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SCHOOL OF MATHEMATICAL AND NATURAL SCIENCES
DEPARTMENT OF CHEMISTRY

**COMPUTATIONAL STUDY OF ANTIMALARIAL
ALKALOIDS OF PLANT ORIGIN**

BY

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This thesis is submitted in fulfillment of the requirements for the
degree of Doctor of Philosophy in Chemistry

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Declaration

I, Kabuyi Mireille Bilonda hereby declare that the thesis for the award of a Doctor of Philosophy degree in Chemistry submitted by me has never previously been submitted for a higher degree or diploma at this or any other University. And that to the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

Signature..... Date November 2018

Dedication

To each child's life lost every two minutes due to malaria.

To my dearest husband Tshishimbi Muya, Jules-Christophe for your sacrifice, presence beside me and your continuous encouragement during my study.

I dedicate this work

Mireille, K Bilonda

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Epigraph

A man is not finished when he is defeated. He is finished when he quits.

Richard Nixon

Abstract

This thesis is concerned with the computational study of naphthylisoquinoline alkaloids having antimalarial properties. The study was considered interesting because of the importance of gathering information on antimalarial molecules and because these molecules had not yet been studied computationally.

The alkaloids considered in this study had been isolated from tropical lianas belonging to the Dioncophyllaceae and Ancistrodaceae families. They comprise alkaloids with both monomeric and dimeric structures. The monomeric structures consist of one unit and the dimeric ones of two units, with each unit containing a naphthalene moiety and an isoquinoline moiety. 33 monomeric molecules were studied, which represent a large portion of all the monomeric naphthylisoquinoline alkaloids isolated so far. Two dimeric molecules with antimalarial activity were investigated, namely, jozimine A₂ and mbandakamine A. A third dimeric molecule, with a structure close to that of jozimine A₂ but different activity (michellamine A, anti-HIV) was also calculated for comparison purposes.

This work utilised electronic structures methods and involved the conformational study of all the molecules selected to identify the stabilising factors *in vacuo* and in solution. Two levels of theory (HF/ 6-31G (d,p) and DFT/B3LYP/ 6-31+G(d,p)) were utilised to compare their performance for compounds of this type, also in view of a future study extending to other compounds of the same class. The molecules were firstly studied *in vacuo* and secondly in three different solvents – chloroform, acetonitrile and water – characterized by different polarities and different H-bonding abilities. Quantum chemical calculations in solution were carried out using the Polarizable Continuum Model (PCM).

The main stabilizing factors are the presence and types of intramolecular hydrogen bonds (IHBs), which are the dominant factors, and also the mutual orientation of the moieties. The possible IHBs comprise O–H···O (or O–H···N and N–H···O for mbandakamine A) and other H-bond types interactions such as O–H··· π and C–H···O (or C–H···O and C–H···N for mbandakamine A). The moieties prefer to be perpendicular one to another, which is a common tendency of aromatic

systems. In monomeric structures, there may be only one $\text{O}-\text{H}\cdots\text{O}$ and possibly also one of each of the other two types of IHBs interactions. In dimeric structures, there may be up to four (five in mbandakamine A) $\text{O}-\text{H}\cdots\text{O}$ IHBs simultaneously and also other H-bond type interactions.

The results provide a comprehensive picture of the molecular properties of these compounds, such as conformational preferences, dipole moments, HOMO-LUMO energy gaps, harmonic vibrational frequencies, solvent effect and influence of the solvent on molecular properties which respond to polarisation by the solvent. Altogether, these results may contribute to a better understanding of their biological activity and to the design of molecular structures with enhanced biological activity. This is the reason of focusing the efforts on the investigation of chemical and physical properties of these alkaloids molecules.

Keywords: Alkaloids, Antimalarials, Computable molecular properties, Intramolecular hydrogen bonding, Naphthylisoquinoline alkaloids, Mutual orientation of aromatic moieties, Solute-solvent interactions.

Conference Presentations

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Acronyms

ACE	:	Alternating Conditional Expectation
ACS	:	Apparent Charge Surface
ACT	:	Artemisinin-based Combination Therapy
AM1	:	Austin Method, version 1
AO	:	Atomic Orbital
B3LYP	:	Becke 3-Parameter (Exchange), Lee, Yang and Parr
BHC	:	Boat, Half-Chair
BO	:	Born-Oppenheimer
CAHB	:	Charge-Assisted H-bonds
CAs	:	Cinchona Alkaloids
CAS	:	Complete Active Space
CASPT2	:	Complete Active Space Perturbational theory second order
CASSCF	:	Complete Active Space Self-Consistent Field
CC	:	Chair-Chair
CC	:	Coupled Cluster
CCD	:	coupled cluster doubles
CCSD	:	coupled cluster singles and doubles
CCSDT	:	coupled cluster singles, doubles and triples
CI	:	Configuration Interactions
CNDO/2	:	Complete Neglect of Differential Overlap, version2
COSMO	:	COnductor-like Screening MOdel
CSF	:	Configuration State Function
CTC	:	Chair, Twist-Chair
CQ	:	Chloroquine
DA	:	Daphniphyllum Alkaloids
DFT	:	Density Functional Theory
DPCM	:	Dielectric PCM
EA	:	Erythrina Alkaloids
EPD	:	Electron-Pair-Donor
FP	:	Ferriprotoporphyrin IX
GGA	:	Generalized Gradient Approximation
GTO	:	Gaussian Type Orbital
HF	:	Hartree-Fock
HGGA	:	Hybrid Generalized Gradient Approximation
HOMO	:	Highest Occupied Molecular Orbital
IEF	:	Integral Equation Formalism
IHB	:	Intramolecular Hydrogen Bond
IPCM	:	isodensity PCM
IUPAC	:	International Union of Pure and Applied Chemistry
JZM	:	Jozimine A ₂
KS	:	Kohn-Sham
LCAO	:	Linear Combination of Atomic Orbitals

LDA	:	Local Density Approximation
LSDA	:	Local Spin Density Approximation
LUMO	:	Lowest Unoccupied Molecular Orbital
MBK	:	Mbandakamine A
MCA	:	Michellamine A
MCSCF	:	Multi-Configurations Self Consistent Field
MCSCF	:	Multi-Configurations Self Consistent Field methods
MGGA	:	Meta-Generalized Gradient Approximation
MINDO/3	:	Modified Intermediate Neglect of Differential Overlap
MO	:	Molecular Orbital
MOT	:	Molecular Orbital Theory
MP2	:	Möller-Plesset second perturbation theory
MRAQCC	:	Multi-Reference Averaged Quadratic Coupled Cluster
MRCI	:	The multireference Configuration Interactions
nAChR	:	nicotinic Acetylcholine Receptor
NC	:	Nicotinoids
NHQ	:	Naphthylisoquinoline alkaloid
PA	:	Pyrazole Alkaloids,
PAHB	:	Polarization-Assisted H-Bonds
PCM	:	Polarizable Continuum Model
PES	:	Potential Energy Surface
PfENR	:	<i>P. falciparum</i> Enoyl-ACP Reductase
PGTO	:	Primitive Gaussian functions or primitive Gaussian Type Orbitals
PLS	:	Partial Least Squares
PM3	:	Parameterized Model 3
PM3	:	Parametrization Model, version 3
QCI	:	Quadratic Configuration Interaction
QCISD (T)	:	Quadratic CI Singles, Doubles, triples, with triple excitations
QM)	:	Quantum methods (Electronic structure methods)
QSAR	:	Quantitative Structure Activity Relationships
QSCP	:	Quantum Systems in Chemistry, Physics and Biology
QUITEL	:	International Conference of Theoretical Chemists of Latin Expression
RAHB	:	Resonance-Assisted H-Bonds
RS-PT	:	Rayleigh–Schrödinger perturbation theory
SASA	:	Solvent-Accessible Surface Area
SCF	:	Self-Consistent Field
SCRf	:	Self-Consistent Reaction Field
SI	:	Selectivity Indices
SP	:	Single Point
STO	:	Slater Type Orbital
SVWN	:	Slater exchange plus Vosko, Wilk, Nusair
UAO	:	United Atom Topological Model
UHF	:	Unrestricted Hartree-Fock
WHO	:	World Health Organization
WWARN	:	Worldwide Antimalarial Resistance Network
ZPE	:	Zero Point Energy

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CHAPTER 1

INTRODUCTION

1.1. Malaria disease

Malaria remains a serious world health problem, with huge morbidity and high death rates in tropical regions [1]. Nearly 212 million cases and 429 000 deaths were reported in 2015 [2] and in 2016 [3]. Africa is the continent with the highest number of malaria-endemic countries, and about 90% of the world malaria-related deaths occur in Africa [2]. Pregnant women and children under five years are the most vulnerable to malaria, which is the first cause of morbidity and mortality [2, 3] among them. 303 000 malaria deaths (equivalent to 70% of the global total deaths) are estimated to have occurred in children under 5 years old [2]. There is an estimated decrease of 29% in number of malaria deaths in children since 2010, but malaria remains a main cause of children's death. Every 2 minutes, a child dies as a result of malaria [2]. This high rate of deaths in Africa is due to two factors: the fact that the majority of infections are caused by *Plasmodium falciparum* and the fact that the most effective malaria vector – the *Anopheles gambiae* mosquito – is highly spread in Africa and is the most difficult to control [4].

In the Democratic Republic of Congo, malaria remains the major public health problem. Congo is a malaria-endemic country with 10% of the cases and 11% of the deaths globally [3]. According to a 2013 WHO report, practically 100% (about 63,700 000) of DRC's population live in areas with high risk of contracting malaria [5]. The number of malaria cases in 2012 is estimated to 26,000 000 with about 92,000 deaths, which is the second highest number of deaths in any malaria-endemic country [5].

In South Africa, malaria is present in three provinces, namely, Limpopo, Mpumalanga and KwaZulu-Natal [6]. The transmission of malaria is seasonal, happening from September to May. The maximum transmission rate occurs during the rainfall months, between December and January. In 2017, there was a significant increase in malaria cases compared to the previous year.

In May 2017, nearly 2 783 cases of malaria were reported while 472 cases were reported in May 2016 [6].

Malaria is a tropical and sub-tropical disease caused by a mosquito-borne infection of protozoa parasites of the *Plasmodium* genus [7]. Four species of plasmodia may cause malaria to humans, namely *Plasmodium falciparum*, *Plasmodium ovale*, *Plasmodium vivax* and *Plasmodium malariae* [8]. The most dangerous is *P. falciparum*, mostly found in Sub-Saharan Africa and responsible for most malaria deaths (99% of estimated cases in Africa [3]). Therefore, the search for antimalarials usually targets *P. falciparum*. *P. vivax* is spread worldwide, in tropical and some temperate regions, and accounts for more than half of all malaria cases outside Sub-Saharan Africa. It has a unique property, as a sporozoite injected into the blood stream may stay in hepatocytes as hypnozoites (which are a latent form of parasite) for very long times [9]. In tropical West Africa, malaria is mostly due to *P. ovale* [10]. The *P. malariae* species is found worldwide, but with irregular distribution [11].

In humans, the parasites have a complex life cycle (detailed description in section 3.1). After entering the body through the bite of an infected mosquito, they grow and multiply, first in the liver cells, and then in the red blood cells (erythrocytes). In the liver cells, the parasites have an initial stage of replication called exo-erythrocytic schizogony. After this stage, the parasites move out of the liver and enter the red blood cells, where they feed on haemoglobin and multiply in an asexual form called erythrocytic schizogony stage. When the number of parasites in a red blood cell is high, the cell bursts, releasing daughter parasites called merozoites. The destruction of erythrocytes causes severe anaemia. Two features are peculiar to *P. falciparum* (not present in other human-malaria parasites) and increase its danger: the ability to attack erythrocytes of all ages, resulting in high parasitaemia and fast reproduction-rate of the parasite, and the ability to adhere to vascular endothelium through sequestration [12].

The clinical manifestations of the disease are due to the blood-stage parasites. The manifestations are headache, fever, chills, myalgia, sudoresis, hepatomegalia and splenomegalia, prostration, and the presence of high anaemia in severe malaria cases in children and pregnant women. Severe *P. falciparum* human malaria can cause neurological complications [13] such as cerebral malaria, and others serious complications (severe anaemia, acute renal failure, hypoglycaemia and respiratory

infection). The blood-stage is also a source of infection for mosquitoes, i.e., the mosquito gets infected if it bites a patient in this stage of malaria, because then gametocytes can pass from the human blood to the mosquito [10].

Besides explaining the life cycle of the parasite, chapter 3 provides also an overview of currently used antimalarial drugs, of their mode of action and of the history of resistance to antimalarial drugs.

The greatest challenge for the treatment of malaria is the rapidity with which the *P. falciparum* develops resistance to drugs that are in extensive clinical use. To avoid the onset of a catastrophic situation in the fight against malaria, it is therefore necessary to develop new and affordable viable antimalarial agents at a rate that can at least keep pace with the rate of resistance development. These new antimalarial agents must have original modes of action, different from the ones of the currently used drugs.

1.2. Importance of natural products

This thesis focuses on the computational study of compounds of the same category – alkaloids (section 3.4.1) – from natural origin and having an antimalarial activity. Natural products (molecules produced by living organisms [14]) have diverse molecular geometries and pharmacophores and constitute an immense source of new compounds. They represent a cornerstone of modern pharmaceutical sciences from which several drugs have been developed. Some molecules from plants origin are considered as new leads of antimalarial drugs in drug development.

Most people in developing tropical regions largely use traditional medicine for their treatment, which makes extensive use of plants. About 80% of the population in Africa depend on traditional medicine for their primary health care [15]. This is partly due to the inaccessibility to synthetic drugs for logistic and economic reasons. Various plants used in traditional medicine were experimentally proved to be active against malaria [16]. This implies that they contain biologically active molecules that are effective against malaria and that are probably different from the drugs already in clinical use. New antimalarial leads may certainly come from tropical plant sources [16,

17]. Compounds of natural origin can be new molecules that help fight against resistance because they have new molecular structures and new mechanisms of action. Therefore, compounds of natural origin are seen as the most interesting options for drug development [16, 18].

1.3. Importance of the computational study of biologically active molecules

A molecule has a biological activity when it is able to produce some demonstrable effects on a living organism [19]. The search for new drugs is very important both for diseases for which viable treatments are not yet available and for diseases for which currently used drugs lose their efficacy due to the development of resistance by the pathogen (as is the case of malaria) [20–23].

One the main objectives in drug development is to create new compounds which have improved properties compared to existing drugs. The process of developing a drug is a succession of steps, each step building on the results of previous steps [24–26]. Nowadays, computational studies constitute a powerful source of information for drug development. They provide information about the molecular properties of the compounds considered and may help predict the molecular properties of compounds that have not yet been synthesized. This is important because the biological activity depends on the molecular properties and, therefore, information on molecular properties is fundamental for a better understanding of the molecular aspects involved in the mechanism through which the biological activity is exerted [26]. It is equally fundamental for the development of drugs and in design of new drugs with improved activities, as well as in other molecular designs, such as the design of targeted molecular hosts [27]. Moreover, computational studies may help through other types of information, such as investigating how existing molecules bind to the target site, or how to build new molecules that will fit into that site and inhibit its activities [26]. They can also help identify the pharmacophore (the part of the molecule that is responsible for the given activity [27], which, in turn, is important for the design of new drugs having the desired activity) or can help find the part of the molecule responsible for toxicity (which, in turn, may help design molecules with lower toxicity) [26]. They can also help identify ranges of specific molecular properties within which the molecule may have the activity of interest, thus helping the selection of promising not-yet-synthesised molecular structures. All these aspects

contribute to better focusing research on the desired objectives. Since computational studies are less expensive and less time-consuming than experimental studies, utilising the information provided by computational studies enables substantial time and cost-savings in the experimental components [25], thus helping accelerate the lengthy process of developing new drugs.

1.4. The molecular systems that are the object of this study

Naphthylisoquinoline alkaloids are the molecules that are the object of this study. These alkaloids are exclusively isolated from plants belonging to the Dioncophyllaceae and Ancistrodaceae families [28–31]. The Dioncophyllaceae family has three monotypic genera, *Habropetalum*, *Dioncophyllum*, and *Triphyophyllum* [32], while the Ancistrodaceae family has only one genus, the *Ancistrocladus* [33]. The extracts of plants of these families have been used in traditional medicine in many African and Asian countries to treat dysentery, malaria, elephantiasis, leprosy, fevers, etc. [16, 31].

Pharmacologically, these alkaloids have shown a pronounced growth-inhibition activity *in vitro* and *in vivo* against protozoan parasites causing tropical diseases such as malaria [34, 35], trypanosomiasis [36, 37], and leishmaniasis [38], which make them potential lead structures for anti-parasitic drugs. Naphthylisoquinoline alkaloids show remarkable biological activities such as antimalarial, antileishmanial, antitrypanosomal, fungicidal, molluscicidal, larvicidal, insecticidal, spasmolytic and anti-HIV [36–42]. Some of them have high activity against *Plasmodium* [43–46]. Their half-maximal inhibitory concentration (IC_{50}) value is between 0.0014 and 23.700 μ M [31] (The IC_{50} indicates how much of a particular drug is needed to inhibit 50% of a given biological process or component of a process such as an enzyme, cell, cell receptor or microorganism). Structurally, their molecules may be monomeric (one unit) or dimeric (two units), with each unit consisting of two moieties, a naphthalene moiety and an isoquinoline moiety connected by a C,C– or N,C biaryl axis. In dimeric structures, the naphthalene moieties are bonded to each other, so that the four moieties are connected in the isoquinoline-naphthalene-naphthalene-isoquinoline sequence. This work considers naphthylisoquinoline alkaloids with the moieties connected by a C,C biaryl axis. The large variety of these alkaloid molecules arises from substitution patterns and the absolute configurations at C1 and C3 [47–50]. There are three types of naphthylisoquinoline

alkaloids: the Ancistrocladaceae-type alkaloids, characterized by an S configuration at C3 and an oxygen function at C6; the Dioncophyllaceae-type alkaloid, characterized by an R configuration at C3 and deficient the oxygen function at C6 [51–54]; and the Ancistrocladaceae–Dioncophyllaceae-type alkaloids, which are hybrid-type alkaloids [55–57]. Representative structures of monomeric and dimeric naphthylisoquinoline alkaloids are shown in Fig. 1.1. Computational studies of naphthylisoquinoline alkaloids are still scarce.

1.5. Aim of this study

The present study aims at identifying preferential conformers and computable molecular properties of naphthylisoquinoline alkaloids with antimalarial activity *in vacuo* and in three solvents with different dielectric constants and different types of solute-solvent interactions. The results provide detailed information on molecular properties that can be related to the biological activity of these compounds, including computable properties that can be utilized as QSAR (Quantitative Structure Activity Relationship) descriptors. It is important to consider different media, because biological activity is exerted in a medium and each molecule may be preferably present in one or another type of media in a living organism.

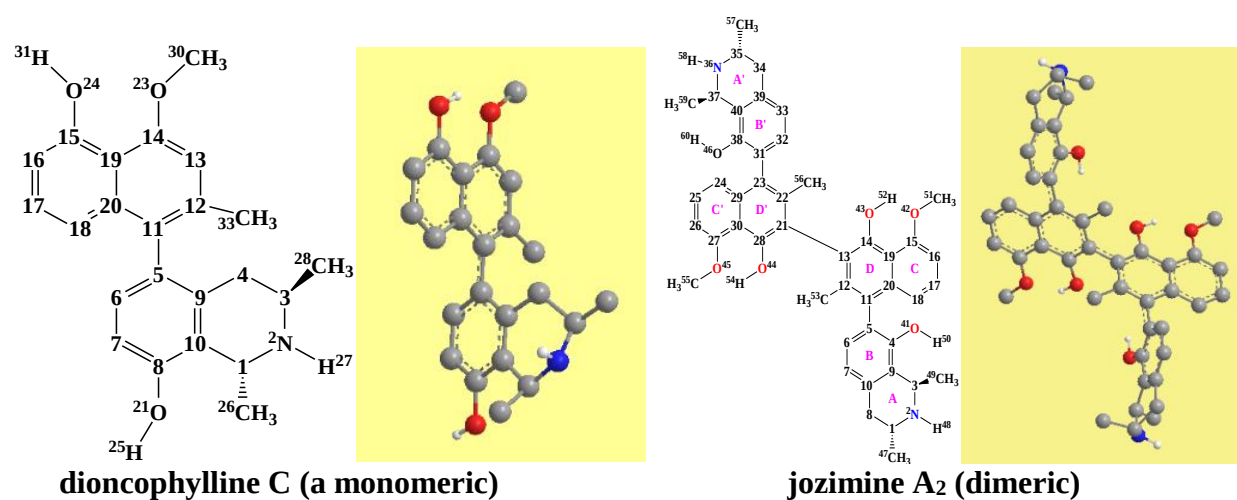


Figure 1.1. Examples of the types of naphthylisoquinoline alkaloids studied in this work

1.6. Organization of the material

The present thesis is divided into eight chapters and two appendices.

The first chapter provides background information about the main issues relevant for this work: the dangers of malaria and the need for the search of new antimalarial drugs, the importance of natural products and the relevance of computational studies of biologically active molecules.

The second chapter gives the theoretical background on the different quantum chemical methods used in the determination of the electronic structures of molecular systems *in vacuo* and in solution and on the calculation of the molecular properties of interest.

Chapter 3 presents the literature review relevant to this work. It starts with an outline of the life cycle of the malaria parasite, and proceeds with a review of the currently used antimalarial drugs and their mode of action, also in relation to the life cycle of the parasite, the history of the development of drug resistance by the plasmodium, an overview on antimalarials drugs of natural origin (including both alkaloids and non-alkaloids) and an overview on the computational study of alkaloids in general.

Chapter 4 deals with the selection of the computational methods suitable for the present study. It also describes the approaches for the preparation of inputs.

Chapter 5–8 present the results obtained, giving all the details. Chapters 5 and 6 present the results of the computational study of the monomeric naphthylisoquinoline alkaloids considered *in vacuo* and in solution, respectively. **Chapters 7 and 8** present the results for two dimeric naphthylisoquinoline alkaloids, namely jozimine A₂ and mbandakamine A respectively; in both cases, calculations were performed *in vacuo* and in solution.

Chapter 9 contains a discussion of the results presented in chapter 5–8 and the main conclusions that can be obtained from them.

Appendix 1 presents the results of a computational study of quinine and quinidine *in vacuo* and in solution highlighting the possibility of intramolecular hydrogen bond (IHB) and appendix 2 presents the results of a computational study of michellamine A, a dimeric naphthylisoquinoline alkaloid with anti-HIV activity, *in vacuo* and in solution.

The results concerning the computational study of the considered monomeric naphthylisoquinoline alkaloids *in vacuo* and the computational study of jozimine A₂ *in vacuo* and in solution have been

published [58, 59]. The results of the computational study of mbandakamine A *in vacuo* and in solution have been submitted for consideration for publication [60] and the other results are being included in articles that are currently in preparation. The results concerning a computational study of quinine and quinidine *in vacuo* and in solution [61] and the computational study of michellamine A, solution have also been published [62]. Results on different molecules have been presented at different conferences (listed on page vii).

CHAPTER 2

THEORETICAL BACKGROUND

This chapter presents various aspects of the theoretical description of molecules and their relevant properties, paying particular attention to the methods that are utilised in the current study.

2.1. The Computational Studies of Molecules

2.1.1. Molecular geometry parameters

From a quantum chemistry point of view, a molecule can be seen as a stable grouping of nuclei and electrons. The molecules are different first of all because of the sequence in which the atoms are bonded to each other. For existing molecules, the sequential arrangement is determined experimentally from spectroscopic data, and gives the nature of the molecule. Atoms inside a molecule have a different behaviour compared to isolated atoms. The properties of its molecules are the basis of the observed physical and chemical properties of a substance [63].

A molecule with single bonds can take different geometries and some of them may be stable. Each stable geometry is an equilibrium geometry which is characterised by the following parameters:

- bond lengths. A bond length is the distance between the nuclei of two consecutive atoms;
- bond angles. A bond angle is the angle between three consecutive atoms or between two related bonds connected at a central atom,
- dihedral angles. A dihedral angle is the angle between the planes identified by the first three of four consecutive atoms and the plane identified by the last three [64, 65].

These parameters, called also *internal coordinates* of the molecule, are spatial coordinates of the molecular system and describe its geometry in space [65].

2.1.2. Potential energy surface and conformational analysis

Rotation about a single bond is free; thus a molecule with single bonds can take a number of different geometries called conformations [65] and those corresponding to minima on the potential energy surface (PES) are called conformers. The study of the possible conformers of a molecule and the corresponding energies is referred to as conformational analysis. Figure 2.1 shows an example of conformers of n-butane considering a rotation around the C2–C3 bond; the calculations of these conformers were performed within the current work.

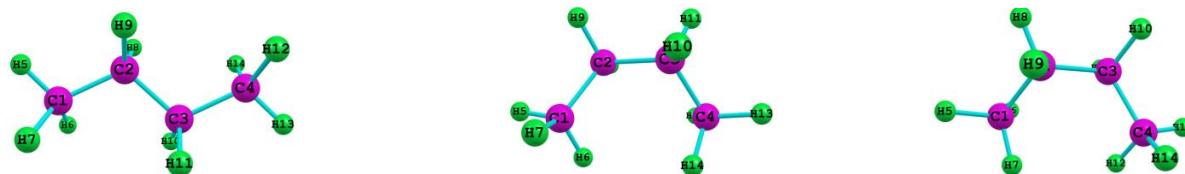


Figure 2.1. Stable conformers of n-butane

A potential energy surface (PES) is a mathematical or graphical relationship between the energy of a given molecule and its geometry [66, 67]. To obtain a PES, one has to see the changes of the energy when a set of geometry parameters are changed. Therefore, a PES involves the parameter/s that is/are changed and the corresponding energy value. When one parameter, q_1 , is being changed, a 2D PES is obtained. When two parameters, q_1 and q_2 , are being changed, a 3D PES is obtained. However, when one wants to change more than two parameters at the same time, it is not possible to visualize the PES because it will have more than three dimensions. When the values of a parameter are changed at a pre-selected pace between two pre-selected values, we say that a “scan” is performed for that parameter.

A potential energy surface contains stationary points, which are points at which the gradient of the electronic energy is zero for all the internal coordinates of the molecule [66].

Mathematically, a stationary point of the PES can be defined by the condition that

$$\frac{\partial E}{\partial q_1} = \frac{\partial E}{\partial q_2} = \dots = 0 \quad . \quad (2.1)$$

where $q_1, q_2, \dots$ are the geometrical parameters

Stationary points on the PES have different meanings, the most relevant of which are:

- minima, corresponding to minimum energy values. Minima can be either a global minimum or a local minimum. The minimum corresponding to the lowest energy on the whole PES is the global minimum, while the other minima are called local minima.
- saddle points correspond to lowest maximum energy points along a path that connects minima on the PES. The first order saddle point is a transition state [66].

The characterization of the PES helps identify all possible geometries for a given molecule. The PES helps visualize and understand the effect of geometry changes on the total molecular energy. It also helps us to understand how computational chemistry programs locate and characterize energy minima [66]. Figure 2.2 shows the 2D potential energy profile of the n-butane molecule and figure 2.3 shows the 3D PES of the n-pentane molecule (calculations performed within the current study). In Fig. 2.3, 'A' is the global minimum; 'B, C, D and E', the local minima; and 'F' and G are examples of saddle points; 'A' is the point that has the lowest energy value on the whole PES; and 'B, C, D and E' are the other minima and their energies are higher than the one of point A; 'F' is a point which connects two minima (a transition state for the change from minimum A to minimum B), whereas 'G' connects B to C.

The most stable geometry of the molecule, also referred to as the equilibrium geometry, is the global minimum. The properties of the molecule are determined by the global minimum and by other geometries corresponding to sufficiently low local minima with non-negligible population. These minima (conformers) are the ones observable experimentally. Therefore, the first step in a computational chemistry study is to find the global minimum and possible low-energy local minima [68, 69]. These equilibrium geometries are identified via a geometry optimization

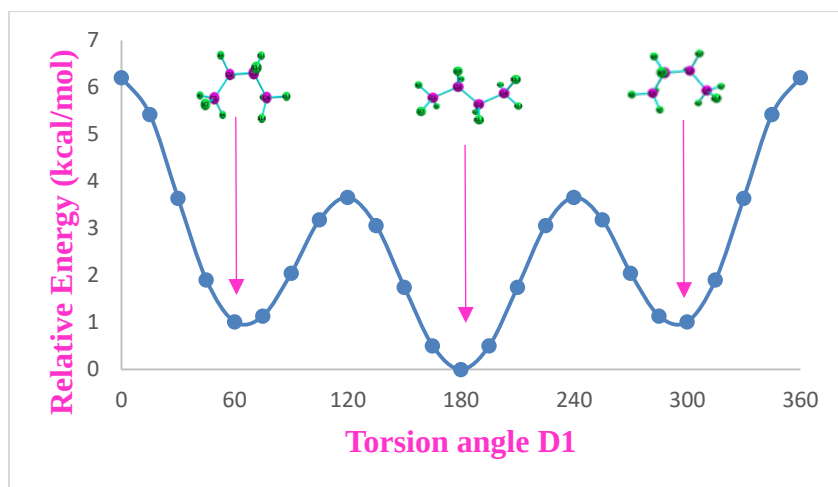


Figure 2.2. 2D potential energy profile of n-butane for the scan of the rotation of the C2–C3 bond (Energy versus D1 being C1–C2–C3–C4). The atom numbering is shown in Fig.2.1.

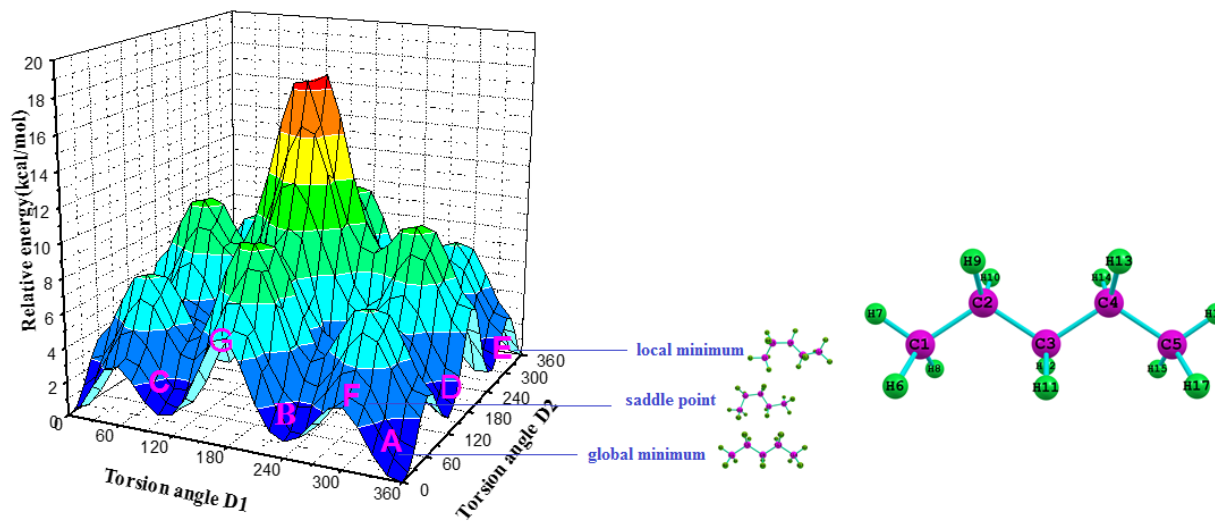


Figure 2.3. 3D potential energy surface of n-pentane for the scan of the rotation of the C2–C3 and C3–C4 bonds (Energy versus D1 and D2, with D1 being the H10–C2–C3–H12 torsion angle and D2 being the H12–C3–C4–H14 torsion angle) and the atom numbering of the molecule.

procedure [66] which is a mathematical algorithm that localizes the stationary points on the PES via energy minimization [66, 67, 70], by varying the molecule's parameters.

Different techniques that attempt to find minima on the PES of the molecule start by approximating the potential energy $E(q)$ in a Taylor series as a function of its cartesian coordinates $\{q_k\}$ [70]:

$$E(q_k) = E(0) + \sum_k \left(\frac{\partial E}{\partial q_k} \right) q_k + \frac{1}{2} \sum_{jk} q_j H_{jk} q_k + \dots \quad (2.2)$$

where $E(0)$ represents the energy at the current geometry, i.e., the current molecular geometry in an iterative process, or a reasonable guess geometry for the minimum or the transition state, $\left(\frac{\partial E}{\partial q_k} \right) = g_k$ is the gradient of the energy along the q_k coordinate, $H_{jk} = \left(\frac{\partial^2}{\partial q_j \partial q_k} \right)$ is the second-derivative of the energy or Hessian matrix, and q_k is the length of the “step” to be taken along this cartesian direction.

The optimization of the molecular geometry can be summarised through the following expression in matrix form [71]:

$$E(\vec{R}_q + \vec{X}) = E(\vec{R}_q) + \vec{G}^t \vec{X} + \frac{1}{2} \vec{X}^t \mathbf{H} \vec{X} \quad , \quad (2.3)$$

where R_q represents the initial geometry; $X(R)$ is the displacement vector of moving R_q geometry towards a new R_{q+1} geometrical position on the molecular potential energy surface (change in atomic coordinates in R_q); $G(R)$ is the energy gradient with respect to the atomic displacement, and $H(R)$ is the second derivative of the energies with respect to the change in the atomic positions given in matrix form (H_{ij}), also called the Hessian matrix [71].

To find a global minimum geometry on the potential energy surface, a computational chemist starts with a guess geometry R_q and submits it to an optimization procedure. The algorithm of the optimization procedure is conceived to find the geometry of the minimum on the PES that is closest to the input geometry. This minimum may not be the global minimum. For this reason, many inputs (R_{q+1}) are made in order to have more chances to get also the global minimum. These inputs are

built considering reasonable geometries for the molecule. It is important to repeat the optimization procedure for different input geometries to get as complete as possible a conformational analysis.

2.2. Electronic structure methods (QM)

There are different methods for the description of the molecule. The current study utilises electronic structure methods to describe the molecules of interest. Electronic structure methods are methods that are used to describe the electron distribution of molecular systems. QM based methods are recommended methods for the detailed description of the electrons in a molecule [63]. Electrons cannot be described even qualitatively correctly by classical mechanics [63]. QM methods give detailed information on molecular systems and can provide different molecular electronic properties in addition to the geometric structure and the corresponding energy. A molecule is considered as a system containing positively and negatively charged particles, namely nuclei and electrons. The electronic structure methods use various mathematical approximations and can be divided into three main groups:

- semi-empirical methods, which include AM1 (Austin Model 1) [63, 72], MINDO/3 (Modified Intermediate Neglect of Differential Overlap) [63, 73] and PM3 (Parameterized Model 3) [63, 74]. They use the parameters derived from experimental data to simplify calculations. They solve an approximate form of the Schrödinger equation which includes the parameters available for the molecule considered. Different semi-empirical methods differ by their parameter sets.
- *ab-initio* methods, which are based on solving the Schrödinger equation mathematically without introducing experimental parameters in the calculations. These methods are employed in the present study to investigate alkaloids molecules, because they are more accurate. More detailed information on these methods is given in next section.
- Methods based on the *Density functional theory* (DFT) which utilises the electron density (ρ) as the key factor of chemical information. DFT is utilised in the present study and more details are given in section 2.2.6.

These three main groups of electronic structure methods differ by the computational cost and the accuracy of the results. Semi-empirical calculations are less time consuming as compared to *ab-*

initio methods and they yield reasonable qualitative descriptions of molecules, whose accuracy depends on the choice of the parameters sets. *Ab-initio* methods give high quality quantitative predictions of the energies and others properties for many molecular systems. DFT gives also high quality quantitative predictions.

2.2.1. The quantum mechanical description of atoms and molecules

For a better description of electrons and nuclei in a molecular system there is no substitution for QM [63]. QM uses the Schrödinger equation as its fundamental equation. Therefore, the electronic structures of molecular systems are obtained as solutions of their corresponding Schrödinger equations [75–77]. The wavefunction solutions of the Schrödinger equation contain useful information on molecular properties (e.g. dipole moments, polarizability, HOMO-LUMO energy, and vibrations).

For a given molecule, the time-independent Schrödinger equation in operator form is written as

$$\hat{H}\psi = E\psi \quad , \quad (2.4)$$

where $\hat{H}$ is the Hamiltonian operator (the energy operator), ψ is the wavefunction describing a given electronic state and E is the total energy of the state.

The Hamiltonian operator is the sum of the kinetic energy $\hat{T}$ and potential energy $\hat{V}$ operators:

$$\hat{H} = \hat{T} + \hat{V} \quad (2.5)$$

In all these equations, uppercase letters are used to denote quantities, coordinates and indexes referred to nuclei, and lowercase letters to denote those referred to electrons. Thus, the uppercase letters “I, J” are the indexes for the nuclei and the lowercase letters “i, j” are the indexes for the electron.

Given that molecules contain electrons and nuclei, the kinetic energy of a molecular system comprises a kinetic energy component for the electron and another for nuclei. Therefore, the kinetic energy component is expressed as

$$\hat{T} = \hat{T}_e(r) + \hat{T}_N(R) \quad , \quad (2.6)$$

where r and R denote the coordinates of electrons and nuclei in the molecular system.

$\hat{T}_e(r)$ is given by

$$\hat{T}_e(r) = -\sum_{i=1}^n \frac{\hbar^2}{2m} \nabla_i^2 \quad (2.7)$$

and $\hat{T}_N(R)$ is given by

$$\hat{T}_N(R) = -\sum_{I=1}^N \frac{\hbar^2}{2M_I} \nabla_I^2 \quad , \quad (2.8)$$

where ∇^2 is the Laplacian operator $\nabla^2 = \frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2}$, M_I is the mass of nucleus I , m is the

mass of the electron and $\hbar$ is equal to the Planck's constant divided by 2π .

Introducing equations (2.7) and (2.8) into (2.6) yields the total kinetic energy of the system

$$\hat{T} = -\sum_{i=1}^n \frac{\hbar^2}{2m} \nabla_i^2 - \sum_{I=1}^N \frac{\hbar^2}{2M_I} \nabla_I^2 \quad . \quad (2.6 \text{ a})$$

The potential energy operator $\hat{V}$ contains the nucleus-nucleus electrostatic repulsion term ($\hat{V}_{NN}$), the nucleus-electron attraction terms ($\hat{V}_{eN}$) and the electron-electron repulsion terms ($\hat{V}_{ee}$)

$$\hat{V} = \hat{V}_{NN} + \hat{V}_{eN} + \hat{V}_{ee} \quad (2.9)$$

with

$$\hat{V}_{NN} = \sum_{I < J}^N \frac{Z_I Z_J e^2}{|R_I - R_J|} \quad , \quad (2.10)$$

$$\hat{V}_{eN} = -\sum_i^n \sum_I^N \frac{Z_I e^2}{|R_I - r_i|} \quad , \quad (2.11)$$

$$\hat{V}_{ee} = \sum_{i < j}^n \frac{e^2}{|r_i - r_j|} \quad , \quad (2.12)$$

where Z_I is the atomic number of nucleus I and $+Z_I e$ is its charge (e is the charge of the electron and is used as atomic unit of electric charge); R_I is the position vector of nucleus I and, therefore, $|R_I - R_J|$ is the distance between nuclei I and J; r_i is the position vector of electron i and, therefore, $|R_I - r_i|$ is the distance between nucleus I and electron i, and $|r_i - r_j|$ is the distance between electron i and electron j. Denoting the distances as $|R_I - R_J| = R_{IJ}$, $|R_I - r_i| = R_{Ii}$ and $|r_i - r_j| = r_{ij}$, the potential energy contributions can be written as

$$\hat{V}_{NN} = \sum_{I < J}^N \frac{Z_I Z_J e^2}{R_{IJ}} \quad , \quad (2.10 \text{ a})$$

$$\hat{V}_{eN} = -\sum_i^n \sum_I^N \frac{Z_I e^2}{R_{Ii}} \quad , \quad (2.11 \text{ a})$$

$$\hat{V}_{ee} = \sum_{i < j}^n \frac{e^2}{r_{ij}} \quad . \quad (2.12 \text{ a})$$

Thus, equation (2.5) can be written as:

$$\hat{H} = \hat{T}_e(r) + \hat{T}_N(R) + \hat{V}_{eN}(r, R) + \hat{V}_{NN}(R) + \hat{V}_{ee}(r) \quad (2.13)$$

Finding the analytical expression of the total wavefunction of a given molecular system and the corresponding energy value requires solving the Schrödinger equation. When this equation is applied to chemical systems like atoms or molecules, its solutions are referred to as atomic orbitals (AOs) or molecular orbitals (MOs), respectively. The molecular orbital (MO) is a fundamental concept in chemistry.

The exact solution of the Schrödinger equation is affordable and accurate only for hydrogenoid systems (one-electron system). The presence of electron-electron repulsion terms in multi-electron systems makes the exact solution of the Schrödinger equation impossible because the expression of the electron-electron repulsion potential depends at the same time on the coordinates of two electrons with a mathematical form that does not allow the separation of the variables. In order to solve the Schrödinger equation for a multi-electron system, several approximations methods have been developed.

The first approximation that is considered in most QM approaches for the study of molecules is the Born–Oppenheimer approximation, which will be described in the next section.

2.2.2. The Born–Oppenheimer approximation

The Born–Oppenheimer (BO) approximation [78] considers that, in a molecule, electrons move much faster (thousands of times faster) than nuclei [79, 80]. Therefore, it is reasonable to consider the nuclei stationary compared to the electrons. Mathematically, this approximation treats electronic and nuclear variables (electronic and nuclear displacements) separately in the Schrödinger equation. The Hamiltonian of the molecular system is thus reduced to the Hamiltonian of the electrons. It is convenient to write the Hamiltonian using atomic units. The atomic units have been chosen in such a way that the fundamental electron properties are all equal to one atomic unit ($m_e=1$, $e=1$, $\hbar = h/2\pi = 1$, $a_0=1$, and the potential energy in the hydrogen atom $e^2/a_0 = 1$, [70]). Therefore, the Hamiltonian of a molecular system consisting of N nuclei and n electrons can be written as [78]

$$\hat{H} = -\sum_{i=1}^n \frac{1}{2} \nabla_i^2 - \sum_{A=1}^N \frac{1}{2M_A} \nabla_A^2 - \sum_{i=1}^n \sum_{A=1}^N \frac{Z_A}{r_{iA}} + \sum_{i=1}^{n-1} \sum_{j>i}^n \frac{1}{r_{ij}} + \sum_{A=1}^{N-1} \sum_{B>A}^N \frac{Z_A Z_B}{R_{AB}} . \quad (2.14)$$

In this expression Z_A represents the charge of nucleus A of M_A mass located at R_{AB} distance from nucleus B and r_{iA} distance from electron i; r_{ij} is the distance between electron i and electron j; Z_B is the charge of nucleus B; ∇^2 represents the Laplacian operator. The first term is the total kinetic energy of n electrons; the second term represents the total kinetic energy of N nuclei; the third one describes the electron-nuclei attraction energy and the two last terms are electron-electron and nuclei-nuclei repulsion energies. To find the electronic energy, the motion of the nuclei is removed from the total Hamiltonian, while the nuclei-nuclei repulsion energy is considered as a constant:

$$\hat{H} = -\sum_{i=1}^n \frac{1}{2} \nabla_i^2 - \sum_{i=1}^N \cancel{\frac{1}{2M_A}} \nabla_A^2 - \sum_{i=1}^n \sum_{A=1}^N \frac{Z_A}{r_{iA}} + \sum_{i=1}^{n-1} \cancel{\sum_{j>1}^n} \frac{1}{r_{ij}} + \sum_{A=1}^{N-1} \sum_{B>A}^N \frac{Z_A Z_B}{R_{AB}} \quad (2.15)$$

The remaining Hamiltonian is the electronic Hamiltonian operator

$$\hat{H}_{el} = -\sum_{i=1}^n \frac{1}{2} \nabla_i^2 - \sum_{i=1}^n \sum_{A=1}^N \frac{Z_A}{r_{iA}} + \sum_{i=1}^{n-1} \sum_{j>i}^n \frac{1}{r_{ij}}. \quad (2.16)$$

This makes it possible to consider, write and solve the Schrödinger equation only for the electrons. The nucleus-nucleus repulsion is more often taken into account by adding it *a posteriori* to the electronic energy (i.e., it is calculated separately and, after finding the electronic energy, the total energy of the molecule is given by the sum of the electronic energy and the nucleus-nucleus repulsion energy). All calculations in the present work are done within the BO approximation.

2.2.3. The Hartree-Fock theory

Approximation methods were developed to solve the Schrödinger equation for molecular systems because the presence of the electron-electron repulsion term does not allow an analytical solution. The Hartree-Fock (HF) method is an approximation method used to solve the electronic Schrödinger equation and it is the starting point for more elaborate theoretical quantum mechanical descriptions (e.g. many-body perturbation theory, single-reference configuration interaction method) [63,67]. The Hartree-Fock theory is used to solve the electronic Schrödinger equation. This theory is based on the independent electron approximation (each electron feels the presence

of the other electrons indirectly through an effective potential) and the linear combination of atomic orbitals (LCAO) approximation (each molecular orbital is expressed as a linear combination of atomic orbitals). The Hamiltonian operator of a molecular system containing n electrons and N_1 nuclei can be written as [81]

$$\hat{H} = \sum_{i=1}^n \hat{h}(i) + \sum_{i=1}^n \sum_{j>i}^n \frac{1}{r_{ij}} \quad (2.17)$$

In this expression, the first part accounts for one electron energy terms (one electron operators, such as $\hat{h}(i)$, give rise to one-electron integrals $\langle \chi_\mu | \hat{h} | \chi_\nu \rangle$), while the second part describes the electron-electron repulsion which is associated to the correlation of the electronic motions. The operator $\hat{h}(i)$ is expressed as the sum of the kinetic energies of individual electrons and the sum of the nuclei-electrons attraction terms [82–84]:

$$\hat{h}(i) = -\frac{1}{2} \nabla_i^2 - \sum_{A=1}^N \frac{Z_A}{r_{iA}} \quad (2.18)$$

These electron-electron repulsion terms make the resolution of the Schrödinger equation impossible because each electron-electron repulsion energy term depends on the coordinates of two particles simultaneously. This prevents the separation of variables that would be necessary to be able to integrate the equation. The term does not depend explicitly on the instantaneous motions of the other electrons. Each of the n electrons feels the presence of an average field made up of all other $(n-1)$ electrons. The HF theory considers the properties of electrons as fermions [85]. Fermions are particles whose behaviour is governed by the stronger condition [86] of Pauli's exclusion principle [70], i.e., the wavefunction of n identical fermions must be antisymmetric. Therefore, a system of electrons is described by an antisymmetric total wavefunction [87].

$$\Phi(\vec{r}_1, \vec{r}_2, \vec{r}_3, \dots, \vec{r}_n) = -\Phi(\vec{r}_2, \vec{r}_1, \vec{r}_3, \dots, \vec{r}_n) \quad (2.19)$$

This is accomplished in practice by assuming that individual electrons are confined to spin-orbitals ψ_o . The spin orbital is the product of the molecular orbital and the spin function. To ensure that

the total spin-orbital wavefunction (Ψ) is anti-symmetric upon any exchange of the coordinates of two electrons, it is constructed as single determinant also called Slater determinant [82, 83]:

$$\Psi = \frac{1}{\sqrt{N!}} \begin{vmatrix} \psi_1(1) & \psi_2(1) & \dots & \psi_N(1) \\ \psi_1(2) & \psi_2(2) & \dots & \psi_N(2) \\ \vdots & \vdots & \ddots & \vdots \\ \psi_1(N) & \psi_2(N) & \dots & \psi_N(N) \end{vmatrix} \quad (2.20)$$

where $\frac{1}{\sqrt{N!}}$ is the normalization factor.

In the Slater determinant, individual electrons are represented by different rows. Interchanging the coordinates of two electrons corresponds to the interchange of two rows in the determinant and to multiplying its value by -1. Only two electrons should occupy a molecular orbital (with α and β spin function). When three electrons are in the same molecular orbital, two rows in the Slater determinant will be identical and the value of the determinant in that case will be zero meaning the wavefunction will vanish or the probability of finding two electrons in the same orbital with same spin is null [84]. This takes into consideration the electron correlation that is intrinsic to the exclusion principle of Pauli.

The approximated Hamiltonian is expressed as

$$\hat{H}^{app} = \sum_i^N (\hat{h}(i) + \hat{V}^{HF}(i)) \quad (2.21)$$

In this equation $\hat{h}(i)$ is the one-electron operator and $\hat{V}^{HF}(i)$ describes the average field perceived by the i^{th} electron due to the presence of the other electrons.

The HF method assumes that electron motions are not correlated and each electron feels an average charge distribution of the remaining $n-1$ electrons. Each electron is thus treated independently and the influence of all remaining electrons is taken into account in an average way. Consequently, the

n-electron Schrödinger equation is reduced to a set of independent one-electron Schrödinger equations. In the one-electron equation the potential is replaced by an effective potential, $\hat{V}_{eff}$.

$$\left[-\frac{1}{2} \nabla^2 + \hat{V}_{eff}(r) \right] \psi_i(r) = \varepsilon_i \psi_i(r) \quad (2.22)$$

The effective potential is spherically symmetric in the so-called central field approximation. Thus the angular part of the wavefunctions has the same solutions as the hydrogen atom. To solve the Schrödinger equation for the electron i (as well as for all the remaining $n-1$ electrons in the molecule), its effective potential $\hat{V}_{eff}(r_i)$ should be known. The latter requires that the other orbitals $\psi_1(r_1), \psi_2(r_2) \dots, \psi_{n-1}(r_{n-1}), \psi_n(r_n)$ must also be known. This means that, to solve the problem, the answer to the problem should be known. One way consists of guessing a reasonable set of orbitals as initial orbitals that should be used to generate an effective potential, allowing energy and orbitals to be calculated in return. These calculations are repeated (with an iterative approach) for all electrons until the solutions of the energies and orbitals for further iteration will not change significantly with respect to the previous ones, indicating that the solutions are self-consistent [66]. The process that the HF method uses to find a set of molecular orbitals leading to the lowest energy is called the self-consistent-field (SCF) procedure [70]. As molecules are made of atoms, the molecular orbital in the HF method is also constructed as a linear combination of a basis set centred at nuclei positions (referred to as atomic orbitals) [63,66,68,88]. The resulting equation is called the linear combination of atomic orbitals (LCAO). This approximation is discussed in detail in Section 2.2.4. The applications of the LCAO to the Schrödinger equation lead to a set of matrix equations known as the Roothaan-Hall equations [66]

$$\mathbf{FC} = \mathbf{SCE} \quad , \quad (2.23)$$

where $\mathbf{C}$ is the matrix of the coefficients in the orbital expansion, $\mathbf{S}$ is the orbital overlap matrix, $\mathbf{F}$ is the Fock operator in matrix form and $\mathbf{E}$ is the diagonal matrix of the energies of the molecular orbitals.

The energy of the molecular orbital is given by the diagonal matrix elements $E_{i,j} = \delta_{i,j} \varepsilon_i$.

The Fock matrix has the following form [25]

$$F_{uv} = H_{uv}^{core} + J_{uv} - K_{uv} , \quad (2.24)$$

with H_{uv}^{core} the core Hamiltonian, J_{uv} the coulomb integral and K_{uv} the exchange integral.

The core Hamiltonian comprises one electron integrals and is expressed by

$$H_{\mu,v}^{core} = \int \chi_{\mu}(r) \left[-\frac{1}{2} \nabla^2 - \sum_A^{nuclei} \frac{Z_A}{r} \right] \chi_{\nu}(r) dr . \quad (2.25)$$

The coulomb elements are computed by

$$J_{\mu, \nu} = \sum_{\lambda}^{basis} \sum_{\sigma}^{basis} P_{\sigma, \lambda} (\mu\nu | \lambda\sigma) , \quad (2.26)$$

where

$$(\mu\nu | \lambda\sigma) = \iint \chi_{\mu}^*(\vec{r}_1) \chi_{\nu}(\vec{r}_1) \left[\frac{1}{r_{12}} \right] \chi_{\lambda}^*(\vec{r}_2) \chi_{\sigma}(\vec{r}_2) d\vec{r}_1 d\vec{r}_2 . \quad (2.27)$$

The exchange elements are calculated by

$$K_{\mu, \nu} = \frac{1}{2} \sum_{\lambda, \sigma}^{basis \ functions} P_{\sigma, \lambda} (\mu\sigma | \lambda\sigma) . \quad (2.28)$$

The Coulomb integrals and exchange integrals contain two electrons integrals elements.

The exchange integrals enter in the Fock operator with a negative sign for the simple reason that when electrons are permuted via antisymmetry, the sign of the wavefunction changes. The J_{uv} Coulomb integrals result from the electron-electron repulsions while the K_{uv} exchange integrals arise if the electrons have the same spin function. The electronic repulsions of unpaired electrons are lowered by exchange integrals.

The term $\mathbf{P}$ found in eqs (2.26) and (2.27) is called the density matrix, whose elements involve a product of two molecular orbital coefficients summed over all occupied molecular orbitals (Occ.MO)

$$P_{\lambda,\sigma} = 2 \sum_i^{\text{Occupied MOs}} C_{\mu,i} C_{\sigma,i}^* \quad (2.29)$$

The expression $(u\lambda | v\sigma)$ (Eq 2.27) represents the two-electron integrals, whose number increases with the fourth power of the number of basis functions. Therefore, the cost of a calculation rises rapidly with the size of the basis set.

Quantitatively, the correlation energy is computed as the energy difference between the Hartree-Fock energy computed using an infinite basis set and the true electronic energy of the molecular system [81]. The main limitation of the HF method is that the correlation of the electronic motions (electron correlation) is taken into account only partially, in an average way, based on the weaker condition of the Pauli Exclusion Principle, which states that two electrons with the same spin cannot be in the same molecular orbital, due to the antisymmetry. Because of this, in several cases the method does not yield satisfactory evaluations of relevant chemical properties. To incorporate this correlation energy into the HF equations, several methods such as Møller Plesset perturbation methods have been developed and are referred to as post-Hartree-Fock methods. Those methods are discussed in detail in Section 2.2.5. Density functional theory (Section 2.2.6) is an alternative method to the wavefunctions, based on the electron density and including electron correlation energy.

2.2.4. The Linear Combination of Atomic Orbitals

Linear Combination of Atomic Orbitals (LCAO) [63, 66, 89] is an approach in the *Molecular Orbital Theory* (MOT) [89, 90] which considers the orbitals within the molecule (molecular orbitals) as delocalised [66]. In this approach, a molecular orbital χ_i is written as a linear combination of atomic orbitals φ_i .

$$\chi_i = \sum_j c_j \varphi_j \quad (2.30)$$

The coefficients c_i are determined by using the variational principle [63, 66] and minimising the energy expectation value. The variational principle states that the expectation value of the energy of a trial wavefunction is always greater than or equal to the true energy. The strength of the LCAO approach is constituted by its general applicability. It can be applied to any molecule with any number of atoms. The molecular orbitals are expressed in more convenient way as a linear combination of other types of basis functions centred on the nuclei of atoms, called basis sets [91–94]. The basis sets assign a group of basis functions to each atom within a molecule to approximate its orbitals. J.C. Slater introduced the first basis set functions, which were different from the actual atomic orbitals. In general, the Slater Type Orbitals (STOs) have the following expression [95, 96],

$$S_{nlm}^{\zeta}(r, \vartheta, \varphi) = Nr^{n-1}e^{-\zeta r}Y_m^l(\vartheta, \varphi) \quad (2.31)$$

This expression is given in spherical coordinates, where N is a normalization factor and ζ is the orbital exponent, that controls the size of the orbital (a large value of ζ gives a tight function, while a small value of ζ gives a diffuse function); n is the principal quantum number for the valence orbital and Y_m^l is the spherical harmonic depending on the angular momentum quantum numbers l and m [70].

In cartesian coordinates, the STOs have the general expression:

$$S_{kmn} = Nx^k y^m z^n e^{-\zeta r} \quad (2.32)$$

where k, m, n are non-negative integers, N is a normalization factor, ζ is an exponent.

For 1s basis functions, the STO can be written as [91, 95]

$$1s \text{ basis function} = Ne^{-\zeta r} \quad (2.33)$$

where r is the distance from the nucleus (in Å). The trend of the STO of 1s is shown in Fig.2.4.

STOs have a number of characteristics that make them attractive, such as the reasonable representations of atomic orbitals: the orbital has the correct exponential decline with increasing r , the angular component is hydrogenic, and the 1s orbital has, as it should, a cusp at the nucleus (i.e., it is not smooth). These features are linked to the degree of which they closely resemble hydrogenic atomic orbitals.

From a practical point of view, overlap integrals between two STOs as a function of interatomic distance are easily calculated. No analytical solution is obtainable for three and four centre integral when the basis functions are STOs, and so numerical methods are required to solve such integrals. This may constitute a limit for the use of STOs for large size molecules [70]. However, high quality STO basis sets have been developed for atomic and diatomic calculations, where such limitations do not arise [80, 97]. As stated above, the STO have a cusp near the nucleus and decay like $e^{-\zeta r}$ when they are far from the nucleus [80, 97].

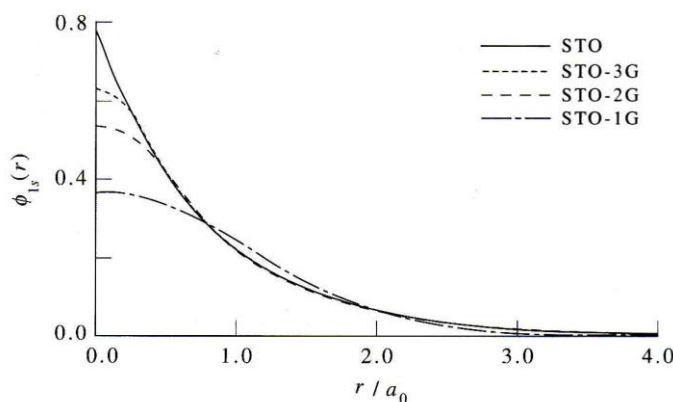


Figure 2.4. Graphical illustration of the variation of 1 (1s) using STO, STO-1G, STO-2G and STO-3G basis sets [80, 96]

The most commonly utilized basis functions in modern calculations are Gaussian Type Orbitals, (GTOs). They are defined by Gaussian functions which can be primitives or contracted. Primitive

Gaussian functions or primitive Gaussian Type Orbitals (PGTO) are single Gaussian functions. The PGTO can be expressed in cartesian or spherical Gaussian atomic.

The cartesian primitive GTOs are

$$g_l(x, y, z) = N x^k y^m z^n e^{-\zeta_l(x^2+y^2+z^2)}, \text{ with } (x^2 + y^2 + z^2) = r^2 \quad (2.34)$$

where l is the angular momentum “quantum number” and the numbers k , m and n are such that $k+m+n=l$

The spherical primitive GTO are expressed as

$$g_l(r, \vartheta, \varphi) = N Y_m^l(\vartheta, \varphi) r^l e^{-\zeta_l r^2} = N Y_m^l(\vartheta, \varphi) r^l e^{-\zeta_l(x^2+y^2+z^2)} \quad (2.35)$$

where l is the angular momentum quantum number and the quantum number $m=-l, \dots, l$ is related to its projection on the Z-axis, in analogy with the atomic case. Spherical and cartesian functions are the same for $l=0$ (s-function) to $l=1$ (p-functions), but differ slightly for $l=2$ (as d-orbitals are described by five spherical functions and by six cartesian function) or higher l (e.g. f-orbitals are described by seven spherical functions versus ten cartesian functions).

A linear combination of primitive functions yields contracted Gaussian functions, also called contracted Gaussian type orbitals and denoted as CGTOs or $G_\alpha(x, y, z)$

$$G_\alpha(x, y, z) = \sum_{l=1}^{N_\alpha} c_l g_l(x, y, z) \quad (2.36)$$

An example of a CGTO is the STO-nG basis sets, where n is a number, which represents the number of GTOs used to approximate the STOs for both core and valence orbitals (where the core orbitals are the orbitals of the completely occupied shell and the valence orbitals are the orbitals of the partially occupied shell). These basis sets are the simplest CGTOs [63, 66, 68, 97]. The figure 2.4 illustrates the trend of STO-1G, STO-2G and STO-3G for the 1s orbital.

GTOs are preferred in practice because they yield integrals that are much easier to compute because they may be evaluated analytically. The main difference between STOs and GTOs is that in the GTOs, the variable “ r ” in the exponential function is squared.

A complete basis set can represent exactly any molecular orbital. Unfortunately, complete basis sets tend to have an infinite number of functions and are therefore not practical for calculations [63, 66, 68, 97]. Many basis sets composed of GTOs are currently used in computational chemistry. They are classified in minimum and extended basis sets.

Minimum basis .The minimum basis sets contain the minimum number of basis functions needed for each atom and utilise fixed size atomic type orbital. The AOs included are the core and valence orbitals. Each AO is expressed in the simplest way, i.e. the STO- n G type. For example, STO-3G is a way of expanding an AO in which each AO is represented by 3 Gaussians (3G). Minimum basis sets give poor results, but they are much cheaper than their larger counterparts. Therefore, a solution to this insufficiency is to increase the number of basis functions representing AOs [66, 97].

Extended basis sets

Extended basis sets can be categorised as follows:

- **Double zeta (DZ)** basis sets and **triple zeta (TZ)** basis sets. In these types of basis sets, two sets of functions (**DZ**) or three sets of functions (**TZ**) are used for each atomic valence orbital. The term zeta refers to the exponent of STO basis functions, often denoted by the Greek letter ζ . This extension allows a better description of spatially different bonds at the same atom [66, 92–94, 98].
- **Split-valence (SV)** basis sets. In this type of basis sets, the number of basis functions per atom is increased for each valence orbital. They are denoted by the number of functions for the core orbitals followed by a combination of numbers that specifies how many primitive GTOs are used for the valence shell. For example, 6-31G denotes a **SV** basis set in which 6 primitives contracted GTOs are required to describe the core atomic orbitals, while three and one primitive functions are used for the valence shell of each atom in a molecule. [66, 91–93].

The quality of a basis set can be further improved not only by increasing the number of basis functions, but also by including polarization and/or diffuse functions [92–94, 97]. The type of functions that can be added are polarization functions or diffuse functions.

- **Polarized basis sets** are another way to increase the size of the basis set by including a polarization function in the basis set. A polarization function is a basis function in which the angular momentum quantum number is greater than the highest angular momentum quantum number in the valence shell. An addition of polarization is the fact that the influence of the neighbouring nuclei distort (polarize) the electron density near a given nucleus. The polarization function improves the description of the mobility of atoms to form chemical bonds in any direction effectively allowing molecular orbitals to be more asymmetric about the nucleus. Polarized basis sets used in this work are (d,p) which means that one set of d -type polarization functions is added to non-hydrogen atoms and one set of p -type polarization functions is added to hydrogens [66, 92–94].
- **Diffuse basis sets:** the size of the basis set can also be increased by adding diffuse functions. These functions consider the electron distribution far away from the nucleus. Thus they have small values of ζ . They are of s -types and p -types. They are added to others functions to have a complete picture. These basis functions are necessary for correct description of anions, excited states and chemical systems characterised by weak chemical bonds (e.g. hydrogen bonds) and are frequently used for calculations of properties related to the polarizability (e.g. dipole moments, polarizabilities, etc.). They are denoted by one ‘+’ if the diffusion function is added only on the heavy atoms and two ‘++’, if the diffuse function is added on the hydrogen atoms as well as heavy atoms. Examples, 6-31+G and 6-31++G [66, 92–94]. It was reported that the addition of diffuse functions to a double zeta basis set is more important than the increasing to a triple zeta basis when calculating relative energies of conformers, above all when molecules contain hydrogen bonds [99].

In this work, basis sets are used in the form of Pople’s basis sets [63, 66, 70, 92–94] as implemented in the Gaussian package.

2.2.5. The Post Hartree-Fock methods (PHF)

2.2.5.1. Need for Post-HF methods

Usually the exact energy of a molecular system is unknown because the Schrödinger equation cannot be solved exactly if a system contains more than one electron. Different approximation methods differ in the way they yield the true energy.

This error in the estimation of the energy in the HF approach is due to the fact that HF replaces the instantaneous repulsion between electrons (electron-electron repulsion) by the repulsion of each electron with an average electron charge cloud [63]. The difference between the HF energy in a complete basis (also called Hartree-Fock limit) and the true energy is referred to as the correlation energy [100].

Post Hartree-Fock methods were developed to correct HF results by introducing some ways of taking into account the correlation energy. They start by computing the HF energy and then correct this energy in one of the following ways:

- by adding either the consideration of electron dynamic correlation energy using various approaches such as Møller-Plesset Perturbation (MP), Configuration Interaction (CI), Coupled-Cluster (CC),
- or by adding the static correlation energy by using a modified HF wavefunction called multireference self-consistent field wavefunction (MCSCF) as starting wavefunction in different methods as for instance multireference configuration interaction (MRCI), multi reference average quadratic coupled cluster (MRAQCC), multireference second order perturbation theory (CASPT2), and averaged coupled pair functional (MRACPF).

Two factors that should be pointed out in connection with post-HF calculations are the questions of whether a method is variational and whether it is size-consistent [63]. The energy computed using variational methods is always greater than the true energy, i.e. the true energy is always a lower limit. Among the methods listed above, CI, MRCI, MCSCF are variational; CC and MRAQCC are not variational, as they are the result of a sort of infinite resummation of MBPT; perturbation methods are also non-variational; therefore, CC, MRAQCC and the methods based on perturbation theory can even yield a total energy which is lower than the true energy.

The quantum chemistry concept of size-extensivity was introduced by Bartlett [101] and refers to a correct scaling of a quantum mechanical method with electron number. Let consider two non-interacting systems denoted as A and B. A quantum mechanical method is size consistent if the energy of A-B complex (denoted as $E(A-B)$) with a sufficiently large distance between A and B is equal to the sum of the energy of the isolated A and B ($E(A)$ and $E(B)$) expressed as: $E(A-B) = E(A)+E(B)$. The MP, CC, CASPT2, MRAQCC and MRACPF methods listed above are size consistent.

2.2.5.2. Configuration Interaction (CI) methods

The CI method is the oldest method (and the easiest one to understand theoretically), but it may be one of the most difficult to implement efficiently on a computer. This method is based on the variational principle as the HF method [63]. The CI takes into account the electron correlation by adding, to the HF wavefunction, terms that represent promotion of electrons from occupied to virtual MOs. Therefore, the HF term and the additional terms represent each a particular electronic configuration. The wavefunction and the electronic structure of the molecular system in the CI approach result from interaction of configurations [66]. The CI expresses the wavefunction as a linear combination of Slater determinants:

$$|\Psi\rangle = \sum_i c_i |\psi_i\rangle \quad (2.37)$$

where the sum can be expanded to include different excited states as follow:

$$|\Psi\rangle = c_o |\phi_o\rangle + \sum_i c_i^a |\phi_i^a\rangle + \sum_{ij} c_{ij}^{ab} |\phi_{ij}^{ab}\rangle + \sum_{ijk} c_{ijk}^{abc} |\phi_{ijk}^{abc}\rangle \dots \quad (2.38)$$

The first four terms in the truncated expansion of the CI wavefunction represent respectively the reference wavefunction (in general the HF wavefunction), single excited state wavefunctions (wave functions obtained after excitation of one electron from the reference orbital to an excited orbital), double excited wavefunctions (if two electrons are excited), and triple excited

wavefunctions (if three electrons are excited). In practice, CI methods are truncated to the following excitations:

- CIS, a CI method including only single excitations
- CISD, a CI method which includes single and double excitations
- CISDT, a CI method that takes in account single, double and triple excitations
- CISDTQ, a CI method that includes single, double, triple and quadruple excitations.

More accurate wavefunctions are found when more terms are added to the expansion, but this is accompanied by a marked increase in computational time.

If one can keep adding more and more terms, the Full CI limit can be reached which is considered to be the exact solution. A full CI calculation with an extremely large basis is difficult to perform, but eventually it will give the exact energies of the ground and all excited states [66]. The coefficients in eqs (2.37) are obtained variationally by solving the Schrödinger equation in its matrix expression. A full CI calculation is computationally so demanding that is not realisable in practice.

Several mathematical approaches have been developed to make the CI calculations improve the correlation energy despite the necessity of truncation of the CI expansion (e.g.: CIS, CISD, CISDT, CISDTQ).

Both CI and MP methods (Section 2.2.5.3) include excited states, which makes it easier for electrons to avoid one another, but the two methods differ in their mathematical approaches [66].

2.2.5.3. Many-Body Perturbation Theory (MBPT)

Møller-Plesset Perturbation (MP) is a many body perturbation theory, which improves the HF method by adding electron correlation effects by means of Rayleigh–Schrödinger perturbation theory (RS-PT) [102]. In the RS-PT theory, a small perturbation V is added to the unperturbed HF Hamiltonian H_0 .

$$H = H_0 + \lambda V' \quad , \quad (2.39)$$

The wavefunction and the energy value are expanded as a Taylor series with λ (which is later set to unity), as

$$E_{\lambda} = E_0 + \lambda E_1 + \lambda^2 E_2 + \dots \quad , \quad (2.40)$$

$$|\psi_{\lambda}\rangle = |\psi_0\rangle + \lambda |\psi_1\rangle + \lambda^2 |\psi_2\rangle + \dots \quad , \quad (2.41)$$

where ψ_0 and E_0 are the HF wavefunction and the HF energy, respectively.

The electron correlation in the MP perturbation method is handled by promoting electrons from occupied MOs to empty MOs giving them more space to move and avoid one another. This leads to the decrease of the electron-electron repulsion and lowers the total electronic energy. The MP theory is typically referred by MP n , where n gives the order of the perturbation included in the calculations, e.g.: MP0, MP1, MP2, MP3, MP4 [103]. In this perturbation expansion, it has shown that the wavefunction experiences some difficulties to converge when n becomes larger. Among MP n methods, MP2 and MP4 are the most commonly used [66]. MP0 uses the electronic energy obtained by summing the one-electron energies from the HF reference wavefunction. MP1 is MP0 corrected with the coulomb and exchange integrals (J and K). The energy in the MP1 approach is equal to the HF electronic energy [104] and is expressed by:

$$E_{MP1} = E_{HF}^{tot} = E_{MP0} + E^{(1)} \quad (2.42)$$

The MP2 approach considers also the third term in expansions (2.40) and (2.41) that is λE_2 and $\lambda^2 |\psi_2\rangle$. Hence, MP2 is considered as the first “real” MP level to go beyond the HF treatment [66].

The MP2 energy is given by

$$E_{MP2} = \sum_{i < j}^{occ} \sum_{a < b}^{virt} \frac{|\langle \psi_a \psi_b | V | \psi_i \psi_j \rangle|^2}{\epsilon_i + \epsilon_j - \epsilon_a - \epsilon_b} \quad , \quad (2.43)$$

$$E_{MP2} = E_{HF}^{tot} + E^{(2)} \quad , \quad (2.44)$$

where $|\psi_i, \psi_j\rangle$ are canonical occupied orbitals and $|\psi_a, \psi_b\rangle$ are virtual (or unoccupied) orbitals with corresponding energies $\varepsilon_i, \varepsilon_j, \varepsilon_a$, and ε_b .

MP2 is the most economical wavefunction-based electronic structure method beyond the HF approximation [104]. MP2 is free from the incorrect electron self-interaction and it represents a significant improvement over approximations based on the electron density, i.e. density functional theory (DFT) for molecular geometries, reaction barriers and hydrogen bonding [104, 105]. MP2 energy is scaled as the fifth power of the molecular size ($O(N^5)$) and recovers almost 80-90% of the correlation energy. Thanks to many theoretical and algorithmic developments [104, 106–108], the applications of MP2 have been extended; therefore, it allows the treatment of relevant biomolecular and nanotechnological systems containing hundreds of atoms. Beside the correlation energy, MP2 includes also the dispersion energy, although it tends to overestimate it [104, 109, 110]. The dispersion energy is fundamental for the description of hydrogen bonds, and this fact explains the reason why it is important to take it in account while studying molecular systems such as protein secondary structure, and DNA double helix (held together by hydrogen bonds).

2.2.5.4. The Coupled-Cluster (CC) method

The CC method is one of the most mathematically sophisticated methods for estimating the electron correlation [70]. This method incorporates both perturbation and configuration interaction approaches [66, 111]. The basic idea behind it is to express the correlated wavefunction as a sum of determinants by allowing a series of operators $\hat{T}_1, \hat{T}_2, \dots, \hat{T}_n \dots$ to act on the HF wavefunction [66]. The wavefunction is written as an exponential ansatz (guess that is verified later by its result)

$$|\Psi\rangle = e^{\hat{T}} |\Psi_{HF}\rangle \quad , \quad (2.45)$$

Where $|\Psi_{HF}\rangle$ is a Slater determinant obtained from HF calculations and $\hat{T}$ is an excitation operator acting on $|\Psi_{HF}\rangle$ to produce a linear combination of excited Slater determinants.

The expression 2.45 is a Taylor series of $\hat{T}$ operators

$$|\Psi\rangle = \left(1 + \hat{T} + \frac{\hat{T}^2}{2!} + \frac{\hat{T}^3}{3!} + \dots \right) |\Psi_{HF}\rangle, \quad (2.46)$$

where $\hat{T} = \hat{T}_1 + \hat{T}_2 + \dots + \hat{T}_n$; with n representing the total number of electrons. The operator $\hat{T}_i$ has the effect of promoting electron i into a virtual spin orbitals.

The first two terms in parenthesis represent the CID method, which is a configuration interaction method limited to double excitations [63]. Based on the number of terms included in the expansion of $\hat{T}$, one can obtain the coupled cluster doubles (CCD), coupled cluster singles and doubles (CCSD) or coupled cluster singles, doubles and triples (CCSDT) methods [66]:

$$\text{in CCD} \quad \hat{T} = \hat{T}_2$$

$$\text{in CCSD} \quad \hat{T} = \hat{T}_1 + \hat{T}_2$$

$$\text{in CCSDT} \quad \hat{T} = \hat{T}_1 + \hat{T}_2 + \hat{T}_3$$

It is easier to use an approximation called CCSD(T) in which the contribution of triple excitations is taken into account in an approximate way. This type of method could be called coupled cluster approximate (or perturbative) triples [66]. Generally speaking, the CCSD(T) calculations are currently the benchmark for practical molecular calculations on molecules of up to moderate size. It is often called the gold standard QM method. It is however computationally highly demanding and it has so far used for small molecules.

Another very similar method to CC is the quadratic configuration interaction method (QCI), with QCISD(T) (quadratic CI singles, doubles, triples, with triple excitations treated in an approximate, non-iterative way) being the most accurate implementation. The CC method is usually slower than QCI, but it is apparently better than QCI [66, 87].

The currently most widely-used implementations of CI are multi-configurational SCF (MCSCF) and its variant complete active space SCF (CASSCF), and the coupled-cluster (CC) and related quadratic CI (QCI) methods [68].

2.2.5.5. Multi-Configurations Self Consistent Field methods (MCSCF)

Multireference configurational self-consistent field methods are usually employed when the single reference methods mentioned above (HF, MP2, CI and CC) fail to provide accurate electronic structures for strongly correlated molecular systems (mostly through static electron correlation) like diradicals and transition metal complexes.

The Complete Active Space Self-Consistent Field (CASSCF) method is a widely-used version of the MCSCF methods, where the linear combination of configuration state functions (CSFs) that includes all CSFs arises from a particular number of electrons in a particular number of orbitals [70].

In CASSCF, the orbitals needed to form the various CI determinants are to be chosen carefully. Molecular orbitals can be divided in three classes: core orbitals (inner orbitals always doubly occupied), active orbitals (partially occupied orbitals) and virtual orbitals (unoccupied orbitals). The complete active molecular orbitals, denoted as CAS, are just a type of MOs, which can be partially occupied by the electrons if the static correlation is strong between electrons, and constitute the so-called active space [66]. The choice of the complete active space (CAS) is very important in MCSCF methods because a bad judgment in the choice of the active orbital space can lead to qualitatively wrong results [66, 108].

The CASSCF wavefunctions, commonly used to take static correlation into account, can be subjected to perturbational calculations to account for dynamic correlation to get better electronic energies, in the same way as HF wavefunctions are usually considered as reference functions for MPn (MP2) calculations [63, 66]. These calculations are usually performed as single point calculations because of affordability reasons.

The CASSCF calculations are widely used in the study of photochemical reactions and in the prediction of electronic spectra [112].

The Complete Active Space Perturbational theory second order (CASPT2), is a kind of analogue of MP2 using MCSCF wavefunctions as reference [63, 66, 70, 87]. It is one of the most reliable and widely used post-CAS methods [70]. Another post-CASSCF method used in computational chemistry is the multireference configuration interaction method that uses the CI approach to include dynamical correlation in the MCSCF wavefunction (MRCI). The multireference CI (MRCI) has a formalism similar to CI methods, with MCSCF wavefunctions used in place of HF wavefunctions [63, 66, 70]. Most multireference methods described to date have been limited to the second order perturbation theory, as is the case of CASPT2 and MRCISD [113].

The coupled-cluster correction to multi-reference CI method [114], as well as the multi-reference averaged quadratic coupled cluster (MRAQCC) method [115] were also suggested.

2.2.6. Density functional theory

2.2.6.1. Generality on the density functional theory

Density Functional Theory (DFT) is an alternative method to the wavefunction based electronic structure methods such as HF and post-HF. This method is computationally less expensive than the post-HF methods. It is not based on the wavefunction, but rather is based upon the Hohenberg-Kohn theorems which state that all the information about the system is contained in the electron density (ρ) [63, 66, 70, 116]. Knowing the exact electron density of the molecular system leads to the knowledge of all the other chemical and physical properties of the molecule. The DFT method is based on two theorems called Hohenberg-Kohn theorems [63, 66, 70, 117–123]. These theorems state that:

1. For a system of n -electrons with a non-degenerate ground state, the external potential (and hence practically everything about the system) is determined up to an additive constant (i.e., the choice of the zero of the energy by the ground-state density).

$$Energy = \frac{\langle \Psi | \hat{H} | \Psi \rangle}{\langle \Psi | \Psi \rangle} \equiv E[\rho] \quad (2.47)$$

2. Given the external potential, there is a universal functional of the charge density $F[\rho]$ such that minimizing $E[\rho] = F[\rho] + \int v_{ext} \rho(r) dr$ will give the exact ground-state energy and charge density.

$$E[\rho] \Rightarrow E[\rho_0], \text{ if } \rho \neq \rho_0 \quad (2.48)$$

If the electron density is known, the total energy is expressed as a sum of functionals of ρ , each corresponding to one of the contributions to the total energy

$$E[\rho] = T[\rho] + V_{ne}[\rho] + J[\rho] + E_{NN}[\rho] + E_{xc}[\rho] \quad , \quad (2.49)$$

where: T is the kinetic energy functional, V_{ne} is the electron–nuclear attraction functional, J is the Coulomb component of the electron–electron repulsion functional, E_{NN} is the nuclear–nuclear functional, E_{xc} is the exchange correlation functional, incorporating correlation and exchange energy.

The expressions of the functions in eq (2.49) are as follows:

the nuclear–nuclear functional

$$E_{NN}[\rho] = \sum_{A>B} \frac{Z_A Z_B}{R_{AB}} \quad (2.50)$$

the nuclear– electron attraction functional

$$V_{Ne}[\rho] = \int \rho(r) V_{ext}(r) dr \quad (2.51)$$

where V_{ext} represents the external potential acting on the interactive system (at minimum, for a molecular system, the electron-nuclei interaction).

The Coulomb component functional (or V_H the Hartree energy) is given by

$$J[\rho] = \frac{1}{2} \iint \frac{\rho(r_1)\rho(r_2)}{r_{12}} dr_1 dr_2 \quad . \quad (2.52)$$

In the energy expression (eq (2.49)) the kinetic energy functional $T[\rho]$ and the exchange-correlation functional $E_{xc}[\rho]$ are the two unknown terms if the exact density is known. Strictly speaking $E_{xc}[\rho]$ is not unknown. Rather it is defined concretely and exactly in the Levy-Lieb constrained variational form. It is only that such a form is too complicated to be used for practical calculations.

This makes the calculations of the $E[\rho]$ difficult. Therefore, to enable to calculate $T[\rho]$, Kohn and Sham introduced the concept of Kohn-Sham orbitals (KS orbitals), which are eigenvectors of the Kohn-Sham equation for a system of non interacting electrons [66].

The KS MO Schrödinger equation is

$$\left(-\frac{1}{2} \nabla^2 + V_{eff}(r) \right) \phi_i(r) = \varepsilon_i \phi_i(r) \quad , \quad (2.53)$$

where ε_i is the orbital energy corresponding KS orbitals ϕ_i , and the electron density for an “N”-particle system is given by

$$\rho(r) = \sum_i^N |\phi_i(r)|^2 \quad , \quad (2.54)$$

Therefore, the Kohn-Sham kinetic energy, T_S , expressed in terms of the KS orbitals is given by

$$T_s[\rho] = \sum_{i=1}^N \int dr \phi_i^*(r) \left(-\frac{1}{2} \nabla^2 \right) \phi_i(r) \quad . \quad (2.55)$$

Therefore, the DFT energy of the molecular system is

$$E[\rho] = T_s[\rho] + \int dr V_{ext}(r)\rho(r) + V_H[\rho] + E_{xc}[\rho] \quad , \quad (2.56)$$

$$E[\rho] = T_s[\rho] + V_{ne}[\rho] + J[\rho] + E_{xc}[\rho] \quad . \quad (2.56.a)$$

The effective Kohn-Sham potential energy is given by

$$V_{eff}(r) = V_{ext}(r) + \int \frac{\rho(r')}{|r-r'|} dr' + \frac{\delta E_{xc}[\rho]}{\delta \rho(r)} \quad , \quad (2.57)$$

where the last term $\frac{\delta E_{xc}[\rho]}{\delta \rho(r)} \equiv V_{xc}(r)$ is the exchange-correlation potential.

Many ways can be used to approximate the exchange correlation functional (E_{xc}). Generally, this functional is divided into two separate terms for non hybrid functional; the first term is the exchange functional $|E_x|$ and the second term is the correlation functional (E_c).

$$E_{xc}[\rho] = E_x[\rho] + E_c[\rho] \quad . \quad (2.58)$$

Both functionals are negative, but E_x is much bigger than $|E_c|$ [63, 66, 70].

Several exchange correlation functionals have been proposed and are classified as local density functionals (LDA), generalized gradient functionals (GGA) and hybrid functionals. These functionals are commonly combined with Gaussian-type basis set functions to describe the Kohn-Sham orbitals [66].

2.2.6.2. Local Density Approximation (LDA)

In mathematics, a function is defined as local if the behaviour of that function depends only on the immediate locality of the point [66, 124]. Local functions cannot access variables that are used by other functions. LDA is the simplest approximation to the exchange correlation functional, $E_{xc}[\rho]$,

and it is developed on the basis of the model of the uniform electron gas. This approximation assumes that the value of E_{xc} depends only on the electron density ρ at the point where it is being evaluated, i.e., E_{xc} depends on the local value of ρ [66, 70]. The local exchange correlation does not depend on the gradient of the electron density. The latter is assumed as being a non local property [63, 66]. The LDA has been modified in the so-called local spin density approximation functionals (LSDA) which is a spin polarized density functional theory using two spin-densities (alpha and beta densities) to treat open shell systems (systems with one or more unpaired electrons, e.g. radicals) [66, 119].

The “spin” in these functionals means that electrons of opposite spin are placed in different KS orbitals, analogously to the unrestricted Hartree–Fock method. The elaboration of LDA method into the LSDA method assigns electrons of α and β spin to different spatial KS orbitals. One of LSDA functionals is SVWN (Slater exchange plus Vosko, Wilk, Nusair) [66, 125].

In reality, the distribution of electrons is not like a uniform gas (jellium model). A way to improve the correlation functional makes it depend not only on the value of the electron density, but rather on the gradient of the density.

2.2.6.3 Generalized Gradient Approximation (GGA)

The GGA functionals are gradient-corrected functionals, i.e. functionals that depend on both the electron density and its gradient ($\nabla\rho(r)$). The GGA functionals can be considered as LDA corrected functional with the correction term. Therefore, the GGA functionals are expressed as

$$\mathcal{E}_{x/c}^{GGA}[\rho] = \mathcal{E}_{x/c}^{LSD}[\rho] + \Delta\mathcal{E}_{x/c} \left[\frac{|\vec{\nabla}\rho(r)|}{\rho^{4/3}(r)} \right] . \quad (2.59)$$

The first widely popular GGA exchange functional was proposed by Becke and denoted as “B” [70]. The B88 [126] functional is an exchange functional [66, 127] introduced into practical DFT calculations by Becke in 1988. The LYP (Lee-Yang-Parr) and the P86 (Perdew 1986) are examples of GGA correlation-energy functionals. The Lee-Yang-Parr correlation functional is computed *in*

toto and does not include any LDA expression. It is one of the most employed GGA functionals. It was found that, among all correlation functionals, the Lee-Yang-Parr functional is the only one that can provide an exact cancellation of the self-interaction error in one-electron systems.

2.2.6.4 Meta-Generalized Gradient Approximation Functionals (meta-GGA, MGGA)

The meta-generalized gradient functionals utilise the second derivative of ρ , the Laplacian of the density ($\nabla^2\rho$). They appear to offer some improvement over LDA functionals, but the SCF from these functionals depending on the Laplacian of the density are more difficult to compute. One way to avoid this consists of including a dependence of the MGGA functional on the kinetic energy density τ calculated from Kohn–Sham orbitals [66]:

$$\tau(r) = \frac{1}{2} \sum_{i=1}^{\text{occupied}} |\nabla \psi_i^{KS}(r)|^2 \quad (2.60)$$

The tHCTH, TPSS, VSXC and M06L are some example of the meta-GGA [128].

2.2.6.5 Hybrid GGA (HGGA) Functionals

Hybrid GGA functionals include the exact Hartree–Fock exchange energy as a functional of the Kohn-Sham molecular orbitals of non interacting electron systems [70], read as

$$E_x^{HF}[\{\psi_i\}] = -\sum_{i=1}^{N/2} \sum_{j=1}^{N/2} \iint \frac{\psi_i^*(r)\psi_j(r)\psi_j^*(r')\psi_i(r')}{|r-r'|} dr dr' \quad (2.61)$$

In this expression N is the number of electrons in the molecular system that can be located at different positions denoted as r or r' . The Hartree-Fock exchange can be considered as the correction energy to the classical coulomb repulsion.

The hybrid GGA exchange correlation functional $E_{xc}[\rho]$ combines as a weighted sum the exchange correlation functional of a pure DFT and that of the exact Hartree-Fock exchange functional as follows

$$E_{xc} = (1-a)E_{xc}^{DFT} + aE_x^{HF} \quad (2.62)$$

The percentage of the Hartree-Fock exchange energy is an important criterion in the classification of hybrid functionals. One of the exchange correlation functionals widely used in the density functional theory framework is B3LYP, a three parameter functional expressed by

$$E_{xc}^{B3LYP} = (1-a)E_x^{LDA} + aE_x^{HF} + b\Delta E_x^B + (1-c)E_c^{LDA} + cE_c^{LYP} \quad (2.63)$$

The three parameters a, b, and c have respectively 0.1161, 0.9262 and 0.8133 values.

Sousa *et al.* [66, 129] show in their 2007 paper that the B3LYP functional has accounted for ca. 80% of the names of functionals in journal articles and abstracts in each year between 2002 and 2006. Furthermore, Zhao and Truhlar use the B3LYP functional for special comparison with their new functionals [66, 130]. More recently (2017), the B3LYP functional has started losing some of its popularity [131]. Besides the B3LYP functional, BHLYP, B3PW91, O3LYP, B3P86 are other hybrid functionals developed in the DFT framework [122, 132, 133]. Compared to DFT, the GGA functionals and HF methods tend respectively to underestimate and overestimate energy barriers between conformers [66].

2.3. Calculation of relevant molecular properties

2.3.1. Dipole moment

When a molecular system interacts with an external field, its electric dipole moment μ can be associated to the molecular energy E and external electric field F through the expression [134]:

$$E = qV - \vec{\mu} \cdot \vec{F} - \frac{1}{2} \vec{F} \cdot (\mathbf{Q} \vec{F}) - \dots \quad (2.64)$$

where V is the electric potential, q is the net charge or monopole, Q is the quadrupole and F' is the electric field gradient. In general, the third term comprising the quadrupole is neglected. The dipole

moment and the electric field are vectors. Thus, the vector product of the dipole moment and the electric field is written as

$$\mu F = \mu_x F_x + \mu_y F_y + \mu_z F_z \quad . \quad (2.65)$$

The dipole moment is computed as the first derivative of the energy with respect to an applied electric field and it is expanded in the Taylor-series as

$$\mu = \mu_0 + \alpha F + \frac{1}{2} \beta F^2 + \frac{1}{3!} \gamma F^3 + \dots, \quad (2.66)$$

where μ_0 , α , β and γ are respectively the permanent dipole, the polarizability tensor, the first hyperpolarizability tensor and the second hyperpolarizability tensor.

In an external field the energy of the molecular system is given by [135]

$$E = E^o - \mu_i F_i - \frac{1}{2} \alpha_{ij} F_i F_j - \frac{1}{6} \beta_{ijk} F_i F_j F_k - \frac{1}{24} \gamma_{ijkl} F_i F_j F_k F_l - \dots, \quad (2.67)$$

with E^o being the unperturbed energy and F_i the component of the field in the i direction.

The dipole moment (μ) is a vector quantity associated with the presence of two opposite charges of magnitude q separated by a distance d . Its magnitude is given by the product of the total positive or negative charge and the distance between the centre of the positive charge and the centre of the negative charge

$$|\mu| = q \times d \quad . \quad (2.68)$$

This quantity is expressed in Debye, defined as $1 \text{ Debye (D)} = 10^{-18} \text{ esu} \cdot \text{cm}$. The direction of the vector is conventionally taken from the centre of the negative charge to the centre of the positive charge.

A dipole moment arises from the difference in atomic electronegativity within a molecule. It can arise between two atoms in a polar covalent bond or between two ions in an ionic bond. The larger

the difference in the electronegativity of the two atoms, the larger the dipole moment [136]. The dipole moment is considered as a measure of the asymmetry of the charge distribution within a molecular system [12].

2.3.2. Frequencies

Atoms in a molecular system are not fixed in space, but have $3N$ degrees of freedom in the gas phase (with N being the number of atoms in the given molecular species). Therefore, they can move through translation (3 degrees of freedom), rotation (2 or 3 degrees of freedom) and vibrational motions (all remaining degrees of freedom). The vibrational motion is the displacement of atoms around their equilibrium positions in a molecular system. In QM, the vibrational motion is usually described by a simple model called harmonic oscillator [66].

Harmonic oscillator is one of the QM models whose corresponding Schrödinger equation can be solved exactly [137]. The vibration in a diatomic molecule is described by an elongation and shortening of the unique bond. In a non-linear triatomic molecule, there are three modes of vibrations described by a symmetric and an anti-symmetric stretching and one bending motion. Polyatomic molecules have complex vibrational motions that result from basic harmonic modes (vibrational modes), in which atoms are moving in phase reaching the maximum and minimum displacements at the same time and passing through the equilibrium position at the same moment [138–140].

The calculations of vibrational frequencies consist of finding these normal modes. The vibrational frequency depends on the nature of the two atoms which are vibrating at the end of the bond and, to a lesser degree, on the presence of other atoms joined to them, which gives origin to the so-called group frequencies [66] commonly used to identify the presence of specific functional groups in organic molecules. Each mode of vibration is characterised by its energy and magnitude and it is treated as an independent harmonic oscillator (normal mode).

A harmonic oscillator has the following parabolic potential:

$$V = \frac{1}{2}kx^2 \quad (2.69)$$

The harmonic vibrational frequencies can be obtained theoretically through the Schrödinger equation of a harmonic oscillator [140–143]:

$$-\frac{h^2}{2\mu} \frac{d^2\psi}{dx^2} + \frac{1}{2}kx^2\psi = E\psi \quad (2.70)$$

where k , μ and x stand for restoring force constant, reduced mass of atoms and atomic displacement respectively. The solutions of this kind of equation are well known in mathematics and are of types [66]:

$$\psi(x) = A_n(x)H_n(\alpha^{0.5}x)e^{-0.5\alpha x^2} \quad (2.71)$$

$$\psi(x) = A_n H_n(\alpha^{0.5}x)e^{-0.5\alpha x^2}. \quad (2.72)$$

In this equation A and H are respectively constant and Hermite polynomials [66].

$$\alpha = (k\mu\hbar^{-2})^{-0.5} \quad (2.73)$$

$$A_n = \frac{1}{\sqrt{2^n n!}} \left(\frac{\alpha}{\pi} \right)^{0.25} \quad (2.74)$$

The Hermite polynomial expressions are well known and are given in Tables [144]

The first few eigenfunction solutions of the Harmonic Schrödinger equation have the following expressions [140, 145, 146]

$$\psi_0(x) = \left(\frac{\alpha}{\pi} \right)^{1/4} e^{-(1/2)\alpha x^2} \quad (2.75)$$

$$\psi_1(x) = \left(\frac{4\alpha^3}{\pi} \right)^{1/4} x e^{-(1/2)\alpha x^2} \quad (2.76)$$

$$\psi_2(x) = \left(\frac{\alpha}{4\pi} \right)^{1/4} (2\alpha x^2 - 1) e^{-(1/2)\alpha x^2} \quad (2.77)$$

$$\psi_3(x) = \left(\frac{\alpha^3}{9\pi} \right)^{1/4} (2\alpha x^3 - 3x) e^{-(1/2)\alpha x^2} . \quad (2.78)$$

The energy values and their associated frequencies of these wavefunctions are [128, 132, 133]

$$\nu = \frac{1}{2\pi} \sqrt{\frac{k}{\mu}} \quad (2.79)$$

$$E_n = h\nu \left(n + \frac{1}{2} \right) , \quad (2.80)$$

where ν is the vibrational frequency (wavenumber in cm^{-1} , i.e. the number of wavelengths that will fit into one cm), k is the force constant for the vibration, and μ is the reduced mass of the molecule. The force constant measures the rigidity of the molecule. The greater the force constant for a given mode, the harder for the molecule to stretch or bend in the manner of that mode. Thus, molecular vibrational frequencies correlate to the force constants of the bonds.

In molecules having many normal modes as the case of polyatomic molecules, the vibrational frequencies are computed from the force constant matrix also called Hessian. The matrix elements of the Hessian can determine the geometry either in the ground state (minimum) or in excited states. A minimum has no imaginary frequencies, a transition state has one imaginary frequency. In general, an n^{th} order saddle point has n *imaginary* frequencies. The energy value is related to the vibrational quantum number n ($n = 0, 1, 2, 3, \dots$). The vibrational energy of a molecular system is quantised and the separation between n and $n+1$ energy levels is kept constant and equals $h\nu$. The energy associated to the vibrational quantum number $n = 0$ is referred as *zero point energy* (ZPE) and cannot be zero because all quantum systems undergo random fluctuations. This ZPE energy is usually summed to the calculated lowest energy to get the energy of the ground state of the molecule. The energy corrected ZPE is necessary for good energy comparison [66].

The use of the same level of theory for the geometry optimisation is recommended for frequency calculations in order to get meaningful frequencies for stationary points. The vibrational analysis is at the basis of IR and Raman spectroscopy for molecules. When a molecule absorbs light at a frequency corresponding to the difference between two energy levels of a vibrational mode, the vibrational energy of the molecule increases.

The frequencies at which the different vibrational modes absorb energy yield the vibrational spectrum [140]. Vibrational spectra are useful in the characterization of molecules because they give information on the energy, magnitude, and force constants of the vibrational modes, which can be correlated to the strength of the different chemical bonds in the molecular system and identification of atoms groups. Therefore, they allow characterising new molecules and also intermediates occurring during a chemical reaction. Despite the fact that molecular vibration energies lie in the infrared (IR) region, it is to be noted that not all vibrational modes are active in IR spectroscopy, but only those that lead to a non-zero transition dipole moment according to selection rules [141, 147].

Actually, vibrational modes in molecules are not harmonic but anharmonic.

The energy of an anharmonic potential for diatomic molecules is written as a series expansion [66]

$$E_n = hv\left(n + \frac{1}{2}\right) - hv\left(n + \frac{1}{2}\right)^2 Xe + hv\left(n + \frac{1}{2}\right)^3 Ye + \dots \quad (2.89)$$

where Xe and Ye are anharmonicity constants.

The calculated spectrum can help experimentalists to identify IR bands for new compounds whose IR bands are not available as in the case of transient species or very reactive molecular systems. It is reported that computed IR frequencies are about 10% higher than the experimental ones, but empirical scaling factors [142] were proposed that can bring the results into a reasonable agreement. In addition, frequency calculations provide useful information that can be used to compute thermodynamic quantities [12, 143, 148].

2.3.3. Highest occupied and lowest unoccupied orbitals (HOMO and LUMO)

The *Molecular Orbital Theory* (section 2.2.4) is widely employed to describe chemical behaviour (e.g. reactivity and kinetics) and other phenomena involving molecular electronic structures (e.g. charge transfer processes, photoexcitation and magnetism) [149]. In a molecular system, molecular orbitals are occupied by electrons in order of increasing orbital energy. The Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital are called the frontier orbitals. They were reported by Kenuchi Fukui in 1952 to play an important role in chemical reactivity [150]. The electrons in the HOMO can leave it more easily than those in the other occupied MOs; thus, HOMO is related to nucleophilic behaviour. LUMO is the lowest-energy orbital available for receiving electrons and therefore it is related to electrophilic behaviour. According to Koopmans' theorem [151], the HOMO and LUMO energies can be associated relatively easily to the first vertical ionization energy and vertical electron affinity respectively [149]. The chemical reactivity between soft electrophile and soft nucleophile reactants is predicted successfully using the frontier molecular orbitals theory [148].

The energy difference between HOMO and LUMO is important because it is correlated to chemical reactivity. It also determines the conductivity abilities of a substance, which has huge implications for organic semiconductors. The HOMO-LUMO energy gaps also help understand why some compounds absorb and emit light in the visible region or why some compounds are coloured as the electrons are constantly shuttling between these orbitals. The energy gap gives an idea of the kind of photons the molecular system absorbs or emits during these jumps. For instance, small HOMO-LUMO gaps in long conjugated molecules can explain why those compounds are coloured. A large HOMO-LUMO energy gap is associated with greater kinetic stability of the molecule, whereas a small HOMO-LUMO energy gap is generally associated with greater tendency to undergo chemical reactions.

The shapes of the HOMO were reported to be useful in interpreting molecular geometry (Walsh's rules) and chemical reactivity (Woodward-Hoffmann rules) [152]. It is to be noted that the HOMO and the LUMO are not always involved in chemical reactivity. The symmetry of a molecule plays a role too. Should the HOMO or LUMO not be of the correct symmetry, it might be the HOMO-1 HOMO-2 or the LUMO+1, LUMO+2 the MO are involved in the reaction.

The energies of all the MOs are listed in the Gaussian outputs. The MOs can also be visualised with the help of the Gauss View program, which also shows their occupancy and lists their energies (in hartrees). The HOMO is easily identified as the last occupied molecular orbital and the LUMO as the first non-occupied molecular orbital in the energy-level diagram of GaussView.

2.4. The computational study of molecules in solution

2.4.1. Importance of studying molecules in a medium

Most chemical reactions take place in a medium. This is particularly important for biologically active molecules because biological activity is exerted within living organisms in a medium. It was demonstrated that solvent is important for protein folding and stability, and it actively participates in catalytic processes in the cell. Water molecules are the principal component that constitute the cellular environment for interactions of biomolecules [153]. It is clearly important to study molecules or molecular ions in solution for a better understanding of their chemical behaviour. The biological activity of a substance depends on the properties of its molecules. The interaction of the molecule (drug) with the target site depends on the properties of the medium and those of the molecule [26]. The solvent influences geometries, energies, electronic structures and spectra (e.g.: IR, UV, NMR) of various molecular species and it is an important factor for the transformations of species in chemical reactions.

In practice, the molecule is first computed in the gas phase, afterwards the result obtained for the isolated molecule is used as starting point for calculations in medium. The difference observed between computed and measured molecular properties such as molecular geometries, activation energies, bond energies, relative energies and spectra gives useful information regarding the effect of the solvent environment on molecules.

2.4.2. Solvent effects on molecular properties

The solvent environment has to be taken into account in modelling chemical reactions. Solvation is defined as an interaction of solvent and solute that leads to the stabilisation of the solute in solution [154]. This interaction may occur in many ways: electrostatic interactions (interactions between polarised areas), lyophilic or lyophobic interactions (hydrophobic or hydrophilic when the solvent is water) and hydrogen bonding interactions (solute and solvent form hydrogen bonds) [155]. The type and strength of the interactions depend on the nature of the solute and on the nature of the solvent. The solute-solvent interactions may affect the geometrical structure, the electronic structure, the relative stability of the solute in solution, the charge distribution, the dipole moment, the polarisabilities, the optical properties, the strength of hydrogen bonds, etc. [156–170]. The presence of a solvent also influences chemical reactions for the aspects such as reaction rates [171, 172], mechanisms of reaction [173], mechanisms of biological activities (including molecular recognition) [174] and interaction with the receptor [175].

In turn, the properties of the solvent are influenced by the presence of the solute (e.g., changes in bulk solvent structure). It is not an easy task to model the interactions between solute and solvent and the changes brought in by the solvent, because a solution is a dynamic ensemble of molecules in continuous motion and with different types of interactions (solvent-solvent and solute-solvent being the most important). Models inevitably introduce simplifications into this dynamic picture. There are several suggested approaches by which the solvent molecules can interact with the solute molecules which can be resumed in two methodologies, the explicit solvation and the continuum solvation [66,176]. In the explicit solvation, the solvent molecules are placed around the solute molecules and interact directly with them, whereas, in the implicit solvation, the solvent molecules do not interact directly with the solute molecules, but the solvent is considered as a parameterised continuous medium which influences the behaviour of the solute molecules [68,176]. The explicit solvation includes the solute and some number of solvent molecules in one large quantum mechanical calculation. To include a large number of explicit solvent molecules, simple classical force fields (classical mechanics methods) are employed. The next section focuses on the continuum model because this approach is used in the present study.

2.4.3. The Polarizable Continuum Model (PCM)

In continuum models, the solvent is treated as a continuous dielectric medium or conductor into which the solute is inserted. Among the continuum models, the Polarizable Continuum Model (PCM, [177–183]) is the most popular of the Self-Consistent Reaction Field (SCRF) models. The SCRF models consider that the solute molecules tend to polarise the continuum solvent and the solvent, in turn, tends to repolarise the solute molecules. Therefore, the entire system is stabilised by the electrostatic interaction between the solute and the solvent [176].

In PCM model, the solvent is considered infinite and defined by an isotropic dielectric into which the solute is inserted. Thus, the solute is modelled as a cavity in the continuum solvent, represented by a distribution of charges on the surface of the cavity. The shape and size of the cavity follow the geometry of the solute molecule, with atomic spheres' intersections smoothed according to the size of the solvent molecules. The shape and size of the cavity depend on the method used and they define the solvent-accessible surface area (SASA), a quantity needed by the method [66]. The simplest shape of the cavity is a spherical one, the next most complex is ellipsoidal [63, 66]. A more accurate shape of the cavity is defined based on the van der Waals radii of the atoms in solute molecule [63, 176, 184]. The cavity surface is generally described in terms of *tesserae* (small finite surface elements); the smaller the size of the *tesserae*, the higher their number and the higher the accuracy of the description. Each *tessera* has an apparent charge surface (ACS) and for each *tessera*, the apparent charge surface is solved iteratively. Several variants of the PCM approach have been developed [70].

Some of these variants are simply technical in nature and are aimed to improve the computational performance of the method such as:

- an integral equation formalism (IEF-PCM [181, 182]) used to solve the relevant SCRF equations, which enables computation of gradients and molecular response properties [176]. The IEFPCM is currently the most commonly utilised in computational software [181, 182],
- an extension to permit application to infinite periodic systems in one and two dimensions [70, 185],
- and an extension to liquid/liquid and liquid/vapour interfaces [70,186],

The other variants show differences in the definition of the molecular cavity. In this group, the cavity can be defined as a surface characterised by a constant value of the electron density (i.e. isodensity surface) [68,187]; the surface can be located from gas-phase density and maintain fixed (IPCM, isodensity PCM) or it can be determined self-consistently (SCIPCM) by adding another iterative level to the SCRF process [68,187]. The two aforementioned PCM methods tend to be significantly less stable in implementation than the original PCM process. They can be subject to unpredictable behaviour in charged systems, which makes their use not recommendable [188].

Two types of PCMs have been popularly used: the dielectric PCM (D-PCM) in which the continuum is polarizable and the conductor-like PCM (C-PCM) in which the continuum is conductor-like [70, 189, 190];

- Dielectric PCM (DPCM), it is an original version of PCM model, the cavity is inserted in a polarisable continuum, this model is no longer recommended
- CPCM (or COSMO, CONductor-like Screening MOdel), where the cavity is inserted in a conductor with an infinite dielectric constant. It may be considered as a limiting case of the PCM model, where the dielectric constant is set to infinity.

The Hamiltonian of the system has two terms, the Hamiltonian operator for the solute, H , considers the energy of the molecule *in vacuo* (unperturbed Hamiltonian, H^0) and a perturbation term, V_R , accounting for the effects of the solvent.

$$\hat{H} = \hat{H}^0 + \hat{V}_R \quad (2.82)$$

The free energy of solvation (ΔG_{solv} – the free energy change accompanying the formation of the solution) is the main energy quantity and it is often called the “solvent effect”. ΔG_{solv} has two major contributions: electrostatic and non-electrostatic. The non-electrostatic term contains the following contributions: cavitation energy, dispersion energy and repulsion energy. These terms do not affect the solute wavefunction, because they do not enter into the Hamiltonian, but have to be taken into consideration to define the total molecular free energy in solution [63].

$$G_{tot} = G_{el} + G_{cav} + G_{dis} + G_{rep} \quad (2.83)$$

For easy understanding of the solvation process and separation of effects of different nature, it is convenient in the continuum theory to split the solvation process in three imaginary steps: creation of the cavity; turning on dispersion-repulsion forces and electrostatic forces as illustrated in Fig.2.5.

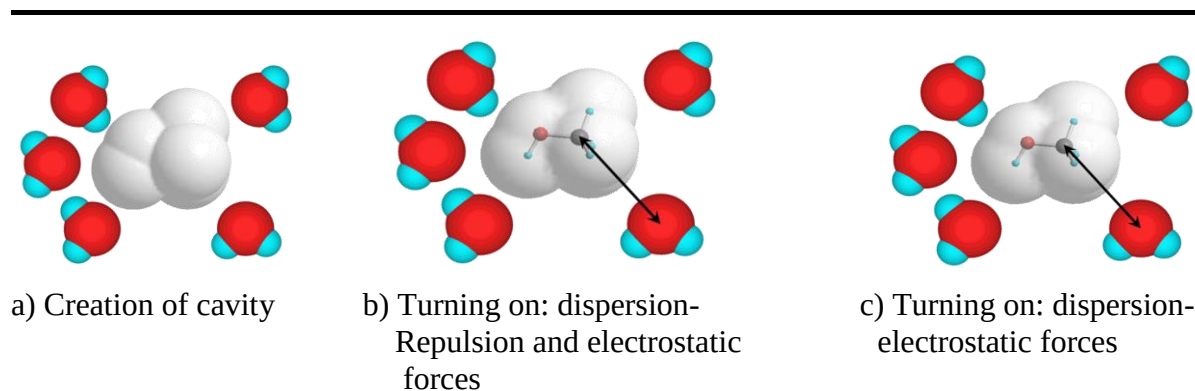


Figure 2.5. Solvation process [191]

Dispersion-repulsion forces and cavitation contribution to the energy normally come with opposite signs. Therefore, they are reducing the total contribution. In many cases, specifically for the case of charged or highly polar solutes, electrostatic forces play a dominant role. Additionally, during the chemical reaction, cavitation and repulsion forces do not change much and therefore, the effect of solvent on reactions. They might be neglected.

To model the solvation effects of the molecules considered in this study, the default settings of PCM calculations as implemented in the Gaussian03 package [192] were used. These comprise the Integral Equation Formalism model (IEF, [180–183]) and Gepol model for building the cavity around the solute molecule [181–183], with simple United Atom Topological Model (UAO) for the atomic radii and $0.200 \text{ \AA}^2$ for the average area of the tesserae into which the cavity surface is

subdivided. Practically, in the initial input for solvation calculations, the PCM default was combined with the SCFVAC and the radii=UAHF keywords, which allow the consideration of the gaseous phase and the application of the united atom topological model on the radii optimised at the HF/6-31G(d) level.

Three solvents were chosen for this study, namely chloroform, acetonitrile and water. They include polar solvents as well as a non-polar solvent, in order to cover a wide range of polarity of the different media and also to mimic the environments present in a living organism. Chloroform is an apolar aprotic solvent, characterized by low relative permittivity ($\epsilon = 4.90$), low dipole moment ($\mu = 1.04$ D), and the inability to act as a hydrogen-bond donor or acceptor; therefore, this solvent does not form specific directional interactions with the solute molecule [193]. Acetonitrile is a dipolar aprotic solvent, which possesses a large relative permittivity ($\epsilon = 36.64$) and a high dipole moment ($\mu = 3.92$ D). This solvent can act as a hydrogen bond acceptor because of the presence of the N atom, whereas it does not act as hydrogen-bond donor, since its C-H bonds are not sufficiently polarised. Because of the presence of the N atom, it is usually a good electron-pair-donor (EPD) solvent, thus having good ability for cation solvation [193]. Acetonitrile is a good model for the medium in cell membranes. Water is a protic solvent, containing two hydrogen atoms bound to an O atom. Since O is electronegative, the O-H bond is polarised and water has the ability to act both as hydrogen-bond donor and as hydrogen-bond acceptor [193]. It is characterised by a high relative permittivity ($\epsilon_r = 78.39$) and a sizeable dipole moment ($\mu = 1.83$ D).

The results *in vacuo* are used as inputs for the PCM calculations in the solvents considered, at the same level of theory of the calculations in *vacuo*. Re-optimisation in solution at the same level of theory as *in vacuo* provides information on geometry changes in the solute molecule brought about by the solvent. Compared to calculations in *vacuo*, the PCM re-optimisation in solution requires more computational time. Therefore, only monomeric structures were re-optimised on the fully optimised *in vacuo* at the same levels of theory, while, for dimeric structures, single point (SP) calculations were done on the *in vacuo*-optimised ones due to the size of the molecules. Although the SP route does not allow the molecular geometry changes which may be caused by the solvent, it provides fairly realistic information on energy features (conformers' relative energies and the free energy of solvation), as well as other properties which are sensitive to the nature of the solvent, such as the dipole moment.

2.5. Hydrogen bonding

2.5.1. Nature and types of hydrogen bonds

According to the *International Union of Pure and Applied Chemistry* (IUPAC), the hydrogen bond is an attractive interaction between a hydrogen atom from a molecule (or a molecular fragment) X–H, in which X is more electronegative than H, and an atom or a group of atoms in the same or a different molecule, in which there is evidence of bond formation [194]. An H-bond can be schematised by X–H···Y, in which X–H and Y represent respectively the donor and acceptor and the three dots describe the H-bond.

Many criteria exist that allow the description of H-bonds. Gilli *et al.* [195] suggested that the easiest and most important [194–196] way of describing H-bonds is the geometric criterion. H-bonds can be categorised in two groups, the conventional and unconventional H-bonds based on the electronegative nature of the Y atom, i.e. H-bond acceptor [196–198]. There is a variety of conventional H-bonds which can be grouped in the following five classes [199]:

- **Negative Charge-Assisted H-Bonds** (–)CAHB sometimes called salt bridges [200], with $[-O\cdots H\cdots O-]^-$ as formula. Not only the acid salts of carboxylic and inorganic acids, but also hydrogen maleate or metal oximes contain this type of H-bond.
- **Positive Charge-Assisted H-Bonds** (+)CAHB, $[=O\cdots H\cdots O=]^+$, emanate from two oxygenated molecules trapping a proton coming from a strong acid.
- **Resonance-Assisted H-Bonds** (RAHB) also called π -cooperative H-bond [201] $-O-H\cdots O=$, where the two oxygens are connected by a π -conjugated system of variable length and are found in β -diketone enols
- **Polarization-Assisted H-Bonds** (PAHB) also called Induction-Assisted H-Bond (IAHB) [200, 202], polarization-enhanced H-bond [200] or σ -cooperative H-bond [200]. $\cdots O-H\cdots O-H\cdots$ found in ice, alcohol and phenol chemistry as well as in some hydroxylated inorganic compounds such as boric acid.
- **Non-charged, non-resonant, non-cooperative** H-bonds or Isolated H-Bonds, $-O-H\cdots O<$

There are also different unconventional H-bond groups such as:

- $\text{O}-\text{H}\cdots\pi$ or $\text{C}-\text{H}\cdots\pi$, where the π -electron systems act as proton acceptors.
- $\text{C}-\text{H}\cdots\text{O}$ or $\text{C}-\text{H}\cdots\text{N}$, where C–H are donors.

Based on the geometric criterion (e.g. $\text{H}\cdots\text{Y}$ bond length, $\text{X}\cdots\text{Y}$ distance and $\text{X}\hat{\text{H}}\text{Y}$ bond angle), an H-bond can be classified as strong, moderate and weak. The strong, moderate and weak H-bonds have the energies in the range of 15–45, 4–15 and 1–4 kcal/mol, respectively [203]. Strong hydrogen bonds resemble covalent bonds in most of their properties, whereas weak hydrogen bonds are essentially electrostatic. The intermediate situation corresponds to moderate hydrogen bonds in between electrostatic and covalent character [194, 203, 204]. The shorter the hydrogen bond length, the stronger the H-bond. This may be used as reference for the classification of H-bonds. According to the classification in [204, 205], the $\text{H}\cdots\text{Y}$ bond length is 1.2–1.5 Å for strong H-bonds, 1.5–2.2 Å for moderate H-bonds and 2.2–3.2 Å for weak H-bonds. Thus the $\text{X}\cdots\text{Y}$ distance is 2.2–2.5 Å for strong H-bonds, 2.5–3.2 Å for moderate H-bonds and more than 3.2–4.0 Å for weak H-bonds. The $\text{X}\hat{\text{H}}\text{Y}$ angle is 170–180° for strong H-bonds, 130–150° for moderate H-bonds and less than 90–120° for weak H-bonds [206].

Besides the geometric classification, the strength of H-bonds can also be classified based on the types of interactions of chemical group species. The negative charge-assisted H-bonds, positive charge-assisted H-bonds and resonance-assisted H-bonds denoted respectively as (–)CAHB, (+)CAHB and RAHB, are considered among strong H-bonds, whereas polarisation-assisted H-bonds (PAHB) are among moderate H-bonds. The non-charged, non-resonant, non-cooperative H-bonds [200], such as $\text{O}-\text{H}\cdots\pi$, $\text{C}-\text{H}\cdots\pi$ and $\text{C}-\text{H}\cdots\text{O}$, are considered as weak H-bonds [196]. $\text{X}-\text{H}\cdots\text{Y}$ bonds can be categorised into intramolecular and intermolecular hydrogen bonds depending on whether X and Y belong to the same or different molecules (Fig.2.6). In condensed phase where intermolecular hydrogen bonds are possible, $\text{X}\hat{\text{H}}\text{Y}$ angles are generally linear [194, 205–211]. Despite the fact that the $\text{X}\hat{\text{H}}\text{Y}$ bond angle is considerably less than 180° for intramolecular H-bonds with respect to the intermolecular H-bond amplitude, intramolecular H-bonds play a crucial role in stabilising chemical geometries (e.g. conformers).

When structures stabilised by intramolecular hydrogen bonds are dissolved in solvents, intermolecular hydrogen bonds can be formed between solute and solvent, which can compete

with intramolecular hydrogen bonds. Conversely it was reported [212] that intramolecular hydrogen bonding interactions present in the solid state remain in solution, as their stabilising effect tends to prevent major changes from an increase in temperature or the addition of a solvent.

2.5.2. Effects of hydrogen bonding and importance in biological systems

H-bond is a specific noncovalent interaction present in a number of chemical systems ranging from organic, inorganic to biological systems [207–216]. Hydrogen bonded network frames have been extensively studied both experimentally and *in silico*. They were reported to be responsible for supramolecular ordering in biological systems and stabilization of molecules in condensed phases (liquid and solid). H-bonding is a crucial factor controlling packing in crystals [196, 217] and it is also one of the main parameters in designing new interesting crystal structures [212–220]. It determines the secondary structure of proteins. It holds together the two strands of DNA [215].

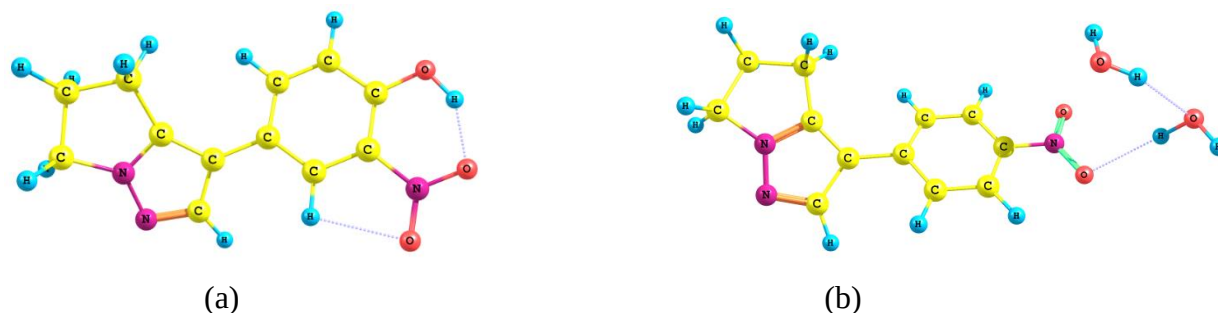


Figure 2.6. Examples of intramolecular hydrogen bonds (a) and intermolecular hydrogen bonds (b)

The hydrogen bonds are represented by dotted segments. Model (a) shows two intramolecular hydrogen bonds in the same molecule. Model (b) shows two intermolecular hydrogen bonds, one between a solute molecule and a water molecule and one between two water molecules.

They influence the melting and boiling points, enthalpies of fusion and enthalpies of vaporization, dielectric constants, surface tension, and some molecular properties such as electronic density distribution, vibrational frequencies, and chemical shifts [221, 222].

H-bonding plays important roles in the mechanism of biological reactions, such as the interactions between a biologically active molecule and its receptor [223–225]. It was reported that H-bonding interactions play also an important role in organic electrically conducting materials related to biology, *e.g.* melanin and indigo [226].

CHAPTER 3

LITERATURE REVIEW

This chapter presents a literature review concerning the life of the malaria parasite, the currently used antimalarial drugs and their mode of action also in relation to the life cycle of the parasite, and the history of the development of drug resistance by the plasmodium. It gives also an overview of antimalarial alkaloids and non-alkaloids of natural origin and an overview of the computational study on alkaloids.

This chapter is adapted from the manuscript entitled: “Overview on computational studies of alkaloids”, by MK Bilonda and L. Mammino, to be submitted.

3.1. Life cycle of the parasite

It is important to understand the mode of action of antimalarial drugs because that issue is essential to improve on them. Different drugs target different stages of the parasite life. The plasmodium has a complex life cycle. It will be described here in some details because it will be relevant for the discussion of the modes of action of currently used antimalarial drugs.

The parasite’s life cycle has five stages, some of each occur in the human body and others in the mosquito body [227]. The stages (outlined in Fig.3.1) are the following:

1. Transmission to human

In this stage, an infected mosquito injects malaria parasites (sporozoites) into the human body through a bite.

2. Liver stage

Once the sporozoites are in the human body, they travel to the liver where they invade the liver cells (hepatocytes). Within the liver cells, the parasites developed into schizonts, where they grow in number via mitotic replication generating the merozoites. Therefore,

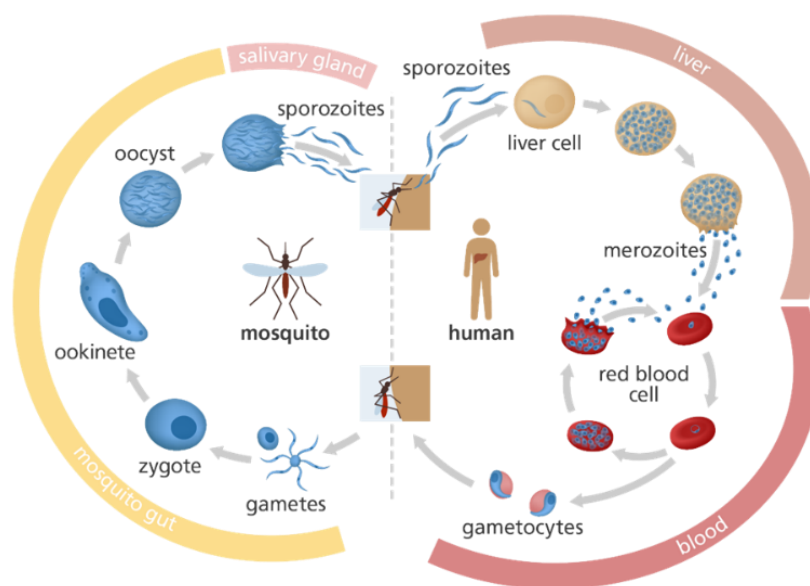


Figure 3.1. Life cycle of the parasite [227]

there is a rupture of the liver cells and a release of the merozoites which invade the red blood cells (erythrocytes). This liver stage is asymptomatic asexual.

3. Red blood cell stage

Once in the blood, the merozoites enter the red blood cells where they feed off the hemoglobin. Within the red blood cells (erythrocytes), the parasite breaks down and digests hemoglobin, releasing heme units into the food vacuoles [228, 229]. The heme units, if released in membranes, can cause the generation of reactive oxygen intermediates which will inhibit other processes vital for the parasite. To prevent this, the parasite detoxifies heme in food vacuoles, by a biocrystallization process in which heme units are sequestered into large insoluble crystals known as hemozoin (pigment of malaria) which is a crystalline form of α -hematin (or ferriprotoporphyrin IX). Inhibiting this biocrystallization process would result in the death of the parasite [229].

The merozoites multiply many times. The red blood cells burst out and they are destroyed. The destruction of the red blood cells causes malaria symptoms such as anaemia and fever.

This stage is an asexual symptomatic stage. Inside some red blood cells, the parasite develops male and female gametocytes.

4. Transmission to mosquito

The gametocytes produced in the red blood cells transfer themselves to a mosquito which bites an human host.

5. Mosquito stage

In the mosquito gut, the gametocytes mature into gametes and they fuse together to reproduce an ookinete. This stage is sexual stage. The ookinete forms an oocyst containing thousands of sporozoites. The bursting of the oocyst releases sporozoites which migrate to the salivary gland of the mosquito and the cycle starts again.

3.2. Currently used antimalarial drugs

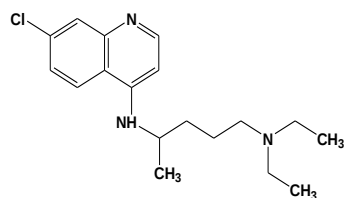
3.2.1. Main classes of antimalarial compounds currently in use [231, 232]

Most antimalarial drugs currently in clinical use belong to the following classes of compounds: aminoquinolines (chloroquine, amodiaquine, primaquine); quinolinomethanol derivatives (quinine, mefloquine, halofantrine); the combination of diaminopyrimidines (pyrimethamine) and sulfonamides (sulfadoxine, sulfalene, dapsone) with respective commercial name fansidar, metakelfin [233] and maloprim [234]; biguanides (proguanil and derivatives); antibiotics (tetracyclines, doxycyclin, clindamycin); sesquiterpenes (artemisinin, dihydroartemisinin, arteether, artemether, artesunate) and naphthoquinones (atovaquone). The schematic structures of the most important drugs are shown in Fig.3.2. The aminoquinolines and the quinolinomethanol derivatives are alkaloids.

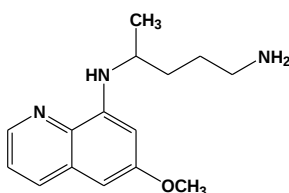
In general, drugs act by interfering with cellular or biochemical processes through interactions with specific molecules involved in those processes and constituting biochemical “targets” for the drug molecules. The best drugs will exhibit selective and possibly high toxicity for the pathogen and, at the same time, should exhibit minimal toxicity to the host. In the case of malaria, the antimalarial drug should lead to the killing of the *P. falciparum* [230, 235].

Figure 3.2. The most commonly used antimalarial drugs, grouped by their classes

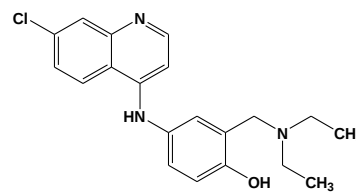
1. Quinolines



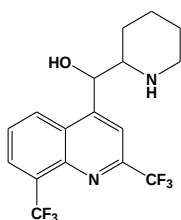
chloroquine



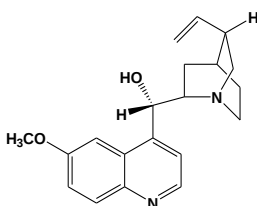
primaquine



amodiaquine

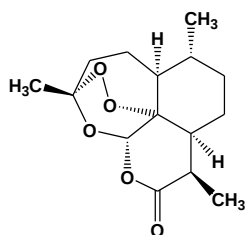


mefloquine

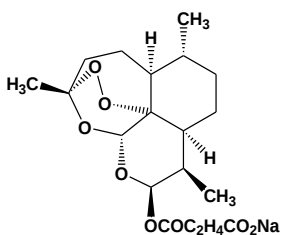


quinine

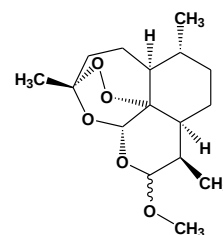
2. Sesquiterpenes: artemisinin and derivatives



artemisinin

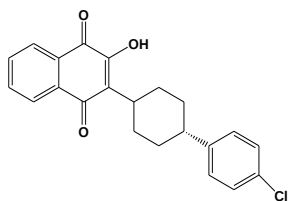


sodium artesunate



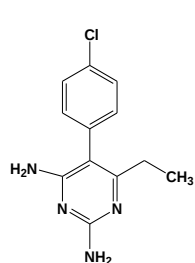
artemether (R=CH₃),
arteether (R = CH₂CH₃)

3. 1,4-Naphthoquinone

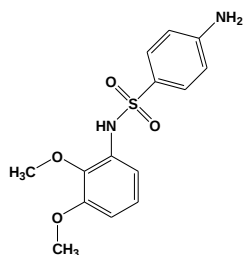


atovaquone

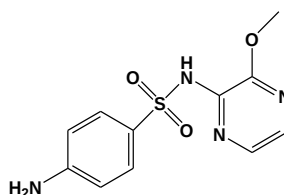
4. diaminopyrimidines and sulfonamides



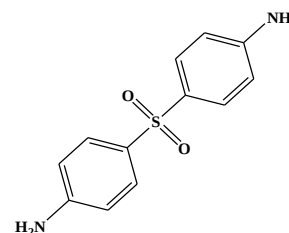
pyrimethamine



sulfadoxine



sulfalene



dapsone

Table 3.1. Target and mode of action of the most common antimalarial drugs [237–240]

Drug	Class of compounds	Target	Mode of action
chloroquine	quinoline	blood stage	Inhibits ferriprotoporphyrin IX(FP) detoxification
amodiaquine	quinoline	blood stage	Inhibits ferriprotoporphyrin IX(FP) detoxification
mefloquine	quinoline	blood stage	Inhibits ferriprotoporphyrin IX (FP) detoxification
quinine	quinoline	blood stage	Inhibits ferriprotoporphyrin IX (FP) detoxification
atovaquone	naphthoquinone	liver and blood stage	Mitochondrial electron transport
sulfadoxine/ pyrimethamine	antifolate	blood stage	Inhibits folate metabolism
artemisinin and derivatives	sesquiterpenes	blood stage and gametocytes	unclear

Different drugs act with different mechanisms. Most of the available drugs (artemisinin and derivatives, quinolines, folate inhibitors and atovaquone) are blood schizonticides, acting on the intraerythrocytic stage of the parasite cycle (the asexual stage and partly also the sexual one). Few drugs, belonging to the classes of 8-aminoquinolines and folate inhibitors, are liver schizonticides, acting on the liver stage of the parasite cycle [231]. Primaquine (an 8-aminoquinoline) is the only

drug which destroys hypnozoites [236]. Hypnozoites are dormant forms in the life cycles of certain parasitic protozoa that belong to the Phylum Apicomplexa (Sporozoa) and are best known for their probable association with latency and relapse in human malarial infections caused by *P. ovale* and *P. vivax*. It is also active against gametocytes, the forms that can be transmitted from a human to a mosquito, infecting the mosquito and initiating the part of the parasite's life cycle that occurs within the mosquito.

The mechanisms with which most of these drugs act are not yet well known. Table 3.1 ([237–240]) summarises what is known about the mode of action of antimalarial drugs, grouping them into classes and indicating the stage of the parasite's life cycle at which the drug exerts its action.

The mechanism of action of chloroquine [228, 230, 235, 240, 241] (a typical example of quinoline drugs), is outlined in section 3.2.2., highlighting what is already known and what still needs to be elucidated.

3.2.2. Mechanism of action of chloroquine

Chloroquine reaches the erythrocytes and accumulates in the parasite's food vacuole, where its concentration can reach up to 400 mM. Three possible mechanisms have been proposed for this chloroquine accumulation in the vacuole, namely:

1. protonation and ion trapping of chloroquine due to the low pH of the food vacuole [228, 241] (the pH of the food vacuole is nearly 4.8).
2. active uptake of chloroquine by a parasite transporter [228].
3. binding of chloroquine to a specific receptor in the food vacuole [228, 241].

The exact contribution of these three mechanisms, or the exact mechanism by which chloroquine inhibits hemozoin formation, is not yet clearly established. Nonetheless, it has been demonstrated that chloroquine exerts its antimalarial effect by interfering with the conversion of free heme into hemozoin. It is known that chloroquine can bind to the heme, resulting in the formation of a complex between chloroquine and hemozoin. This binding may prevent the heme units from being incorporated into the hemozoin crystal; thus, heme, remaining free, would be extremely toxic to the plasmodium [228, 229, 237]. All the quinolines drugs act in the same way as chloroquine and at the same stage of the parasite's life cycle.

3.3. Brief history of drug-resistance to antimalarials

Antimalarial drug resistance is traditionally defined as the persistence of malaria parasites in the body after appropriate drug treatment. *Plasmodium* resistance to antimalarial medicines is one of the major obstacles in the fight against malaria. Of the four malaria species known to affect humans, three of them (*P. falciparum*, *P. vivax* and *P. malariae*) have shown resistance against drugs, and *P. falciparum* is the one showing resistance with a higher frequency [229]. The fast growth of resistance is due to the fast DNA modification of the malaria parasite. The next paragraph gives a brief description of the parasite's genome and how the parasite manages to resist or to survive the human immune system.

The genome of the parasite is known and knowing the DNA gives more possibilities of development of drugs. This genome was sequenced in 2002. A number of genes involved in how the parasite manages to survive and thrive inside its host to cause malaria have been identified and these genes are called the *var* genes. This family of genes is the basis of the encoding of the *Plasmodium falciparum* Erythrocyte Membrane Protein-1s (*PfEMP1s*). The *PfEMP1s* are the sticky proteins which are activated by the parasite and appears on the surface of the red blood cells, after the parasite has made his way into the red blood cell. These proteins are the key in malaria parasite's ability to cause disease. The *PfEMP1s* are encoded by a family of 60 *var* genes. The genes are constantly changing through a recombination process, i.e. they are frequently rearranging their genetic information between each other to create lot of new variations of *var* gene. As consequence, there are lots of variations of *PfEMP1s*. The process of recombination of *var* genes is known, but how the DNA is cut and wedged back together again during recombination is not yet know. So, there is still more works to do to find the mechanism by which the DNA is cut and put back together. This may open new ways for malaria treatment [227].

The following paragraphs give a brief description of resistance to some antimalarial drugs.

Chloroquine (CQ) has been the most commonly used antimalarial drug until recently. However, its effectiveness is decreasing in endemic countries because of resistance [231, 242, 243]. Resistance to it is widely spread in Asia and Africa and, therefore, this molecule is not used nowadays in monotherapy. *P. falciparum* resistance to chloroquine first emerged in the late 1950s

in South East Asia (Thailand, 1957) and spread to other areas in Asia, to the Colombian-Venezuelan border in 1959 and then to Africa (essentially all of Sub-Saharan Africa) in the following three decades; today, chloroquine has lost its efficacy in all but a few areas of the world [241, 244]. Because of the worldwide-spread of resistance to chloroquine, most malaria endemic countries have been forced to abandon chloroquine for treatment of *P. falciparum* malaria.

Almost 30 years after the emergence of chloroquine-resistant *P. falciparum*, the first cases of *P. vivax* resistance to chloroquine were found on the island of New Guinea, which became the epicentre. Nowadays, there is evidence that the efficacy of chloroquine against *P. vivax* is declining in most locations where *P. vivax* malaria is endemic [229]. In areas where it remains effective, chloroquine is still the treatment of choice for *P. vivax* malaria.

The combination of pyrimethamine and sulphonamides (SP) becomes the most used worldwide after the spreading of the chloroquine resistance. These combinations were mostly used as chemoprophylaxis. The resistance to SP also first emerged in the same areas of South East Asia, spreading even more rapidly to – and then across – Africa. In the Amazon region of Latin America, the resistance to chloroquine and to SP emerged independently and subsequently started spreading throughout the sub-continent [229, 244, 245]. These molecules are not used in monotherapy nowadays.

Mefloquine (resistance appeared in Thailand, Cambodia, and Vietnam – countries where it was widely used – within five years of its introduction in the 1990s [240]. One of the brand names of mefloquine is LariamTM.

Artemisinins and atovaquone have come in clinical use as antimalarials more recently. Atovaquone is a 1-4 naphthone with a structure analogue to that of Coenzyme Q involved in the electron transport chain and acts by breaking down the organellar membrane potential, thus arresting the parasite's respiration and the essential (for the parasite) pyrimidine biosynthesis. Resistance emerges rapidly where atovaquone has been used in monotherapy; it appears to be associated with point mutations in the cytochrome b gene, principally affecting Y268 (converted to S, N or C), resulting in drastic reduction of the parasite's susceptibility to the drug both *in vivo* and *in vitro* [244].

Malarone [246] – a combination of atavouone with proguanil – has been successfully in use for some time, especially for prevention purposes for travellers to South East Asia and to parts of Africa where multidrug-resistant parasites are common. Although the mechanism of the synergy between the two components of malarone is not yet fully understood, it seems not to be associated with the role of proguanil as an antifolate precursor, but rather with its ability to sensitize the mitochondrion, possibly by blocking a secondary mechanism for maintaining its membrane potential [244]. Malarone is the only combination without artemisinin as a partner, among recent drugs. Due to the high cost of malarone, its wide-scale use in many malaria- endemic countries is limited.

The artemisinins are sesquiterpene lactones (section 3.5.1) which derive ultimately from the Chinese herb qinghao (*Artemisia annua*), which was used for centuries to treat malaria and other parasitic diseases. The more frequently used arteether, artemether and sodium artesunate are semi-synthetic derivatives of artemisinin [247]. Sodium artesunate is the most effective of these compounds, and can rapidly reduce plasmodium parasite numbers $\sim 10^4$ fold in a single 48 h erythrocytic cycle. Nevertheless, the foreseeable danger of resistance insurgence from using this type of drug in monotherapy – first observed in Chinese field attempts in the 1970s – was emphasized by a recent study reporting that decreased sensitivity was observed in recrudescant parasites after 7 days of treatment with artesunate alone [244].

From 1994 onwards in South East Asia, where it is still used successfully, artesunate was deployed in combination with mefloquine in areas of multidrug-resistance and now, in many other endemic areas, artemisinin derivatives are being evaluated in combinations with other antimalarials, such as lumefantrine, piperaquine, amodiaquine and pyrimethamine-sulfadoxine (so-called artemisinin combination therapy: ACT) [16, 229, 244]. For human malaria, the Artemether-lumefantrine combination (Coartem) is presently the most effective treatment.

The first report of resistance to artemisinin (characterized by slow parasite clearance from the patient's blood following treatment) came from South East Asia, in the border region between Thailand and Cambodia, in 2006 [248, 249]. Recently, parasites resistant to artemisinin-based therapies have also been identified in Vietnam, Eastern Myanmar and Northern Cambodia, and there are signs of emerging resistance in Central Myanmar, Southern Laos and North-eastern

Cambodia [250–252]; however, resistance in these regions remains less spread than in the border area between Thailand and Cambodia.

So far, there are no confirmed reports of artemisinin resistance in Africa or in Latin America. This is due to the increased malaria prevention and control measures which have consequently reduced the burden of the disease in many areas during the last decade. However, these gains are fragile and all the risk factors for resistance emergence exist in both continents [250–252].

Table 3.2.– taken from the WWARN (Worldwide Antimalarial Resistance Network, [253–255])– gives basic information on resistance emergence for the drugs currently in clinical use: the year of introduction of the drug into use, the year when a resistance case was first reported and the time lapse between the introduction and the first observation of resistance.

Table 3.2. Overview of the appearance of antimalarial drug resistance for the most common drugs [253–255]

Drug	Year of introduction into clinical use	First year in which resistance was reported	Time (years) between introduction and resistance emergence
quinine	1632	1910	278
chloroquine	1945	1957	12
proguanil	1948	1949	1
sulfadoxine-pyrimethamine	1967	1967	<1
mefloquine	1977	1982	5
atovaquone	1996	1996	<1
artemisinins	1971	2006?	35

Compounds of plant origin have played important roles in the development of antimalarial drugs. Therefore, it can be anticipated that new antimalarial leads may likely emerge from tropical plant sources [16]. The natural compounds (from plants) possessing antiplasmodial and antimalarial properties belong mainly to the following classes: alkaloids, terpenes, flavonoids, limonoids, chromones, xanthenes and anthraquinones [16, 18]. Among them, a prominent role is played by

alkaloids, because most antimalarial drugs of natural origin, including quinine, belong to that class. The present thesis focus on antimalarial alkaloid molecules and the others classes (non-alkaloids) will be briefly described for the sake of completeness.

3.4. Alkaloid antimalarials

3.4.1. Alkaloids – definition, classification and origin

The term ‘alkaloid’ was mentioned for the first time by W. Meisner (a pharmacist) in 1819 [256]. This term means “alkali-like” and has its origin from the word “alkaline” which means “a water soluble base”. Several authors gave definition of alkaloids. For Winsterstein and Triers (1910), alkaloids are basic compounds containing heterocyclic nitrogen atoms and are synthesized in plants from amino acids or their immediate derivatives [257]. Nowacki and Nowacka (1965) define ‘alkaloids’ as substances with nitrogen atoms in their molecules, connected to at least two carbon atoms, and having at least one ring, but not necessarily a heterocyclic ring. [258].

In general, an alkaloid is an organic compound from natural origin (plants and marine organisms) containing at least one nitrogen atom and one ring in its molecular structure [26]. The presence of a nitrogen atom in their molecular structure is the main criterion for grouping these compounds together. All the other properties (chemical, pharmacological and botanical) must also be taken into account in categorizing compounds as an alkaloid. Based on their structures and origins, alkaloids can be classified into three main groups [26, 258], (Fig.3.3) namely, true alkaloids, protoalkaloids and pseudoalkaloids. True alkaloids derive from aminoacids and are N-heterocyclic; protoalkaloids derive also from aminoacids (mostly from phenylalanine and tyrosine) but the N atom is not part of a heterocyclic ring (although their molecules contain a non heterocyclic aromatic ring); and pseudoalkaloids do not derive from aminoacids, but they are N-heterocyclic compounds [26].

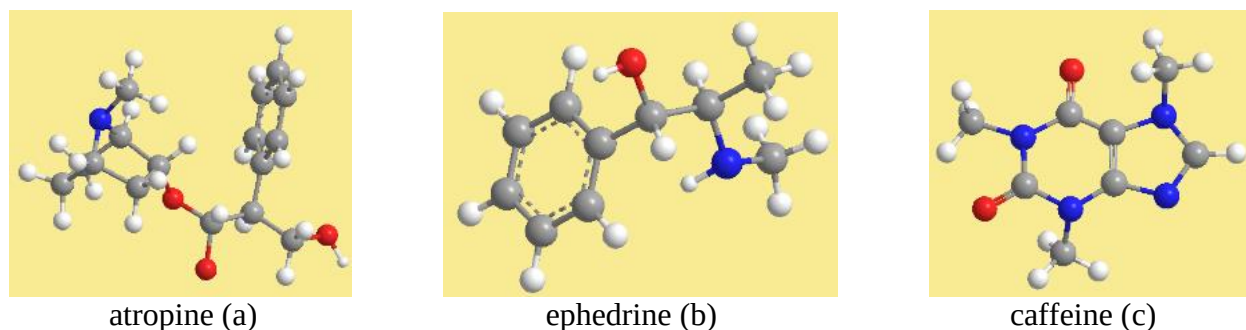


Figure 3.3. Ball-and-stick models of different example of alkaloids' types true alkaloid (a), protoalkaloid (b), pseudoalkaloid (c) [26]

From the point of view of whether the N atom belongs to a heterocyclic ring or not, alkaloids are classified as non-heterocyclic alkaloids and heterocyclic alkaloids, with the latter divided into 14 groups according to the structure of their rings [26, 258] namely: pyrrole, pyrrolidine, pyrrolizidine, pyridine, piperidine, tropane, quinoline, isoquinoline, aporphine, quinolizidine, indole, indolizidine, imidazole, purine [26, 258]. The skeletons of the main rings characterising these 14 groups of heterocyclic alkaloids are shown in Fig.3.4.

Most alkaloids are of natural origin and exhibit a variety of biological activities (antimalarial, anticancer, anaesthetic, vasodilator, antihypertensive, narcotic and analgesic). Some others are synthetic derivatives of natural compounds; for instance, chloroquine is a synthetic alkaloid derived from quinine, which is an alkaloid from natural origin [258]. Therefore, alkaloids are considered as an interesting group of compounds, both for their current pharmacological uses and as potential lead compounds for the development of new drugs [26, 259–261].

The isolation of molecules from natural source, the study of their activity and the investigation of possible derivatives with enhanced activity are essential steps in the search of new more effective antimalarial drugs. The fact that their antimalarial activity is already proved has stimulated great interest for a deeper study of their molecular and chemical properties.

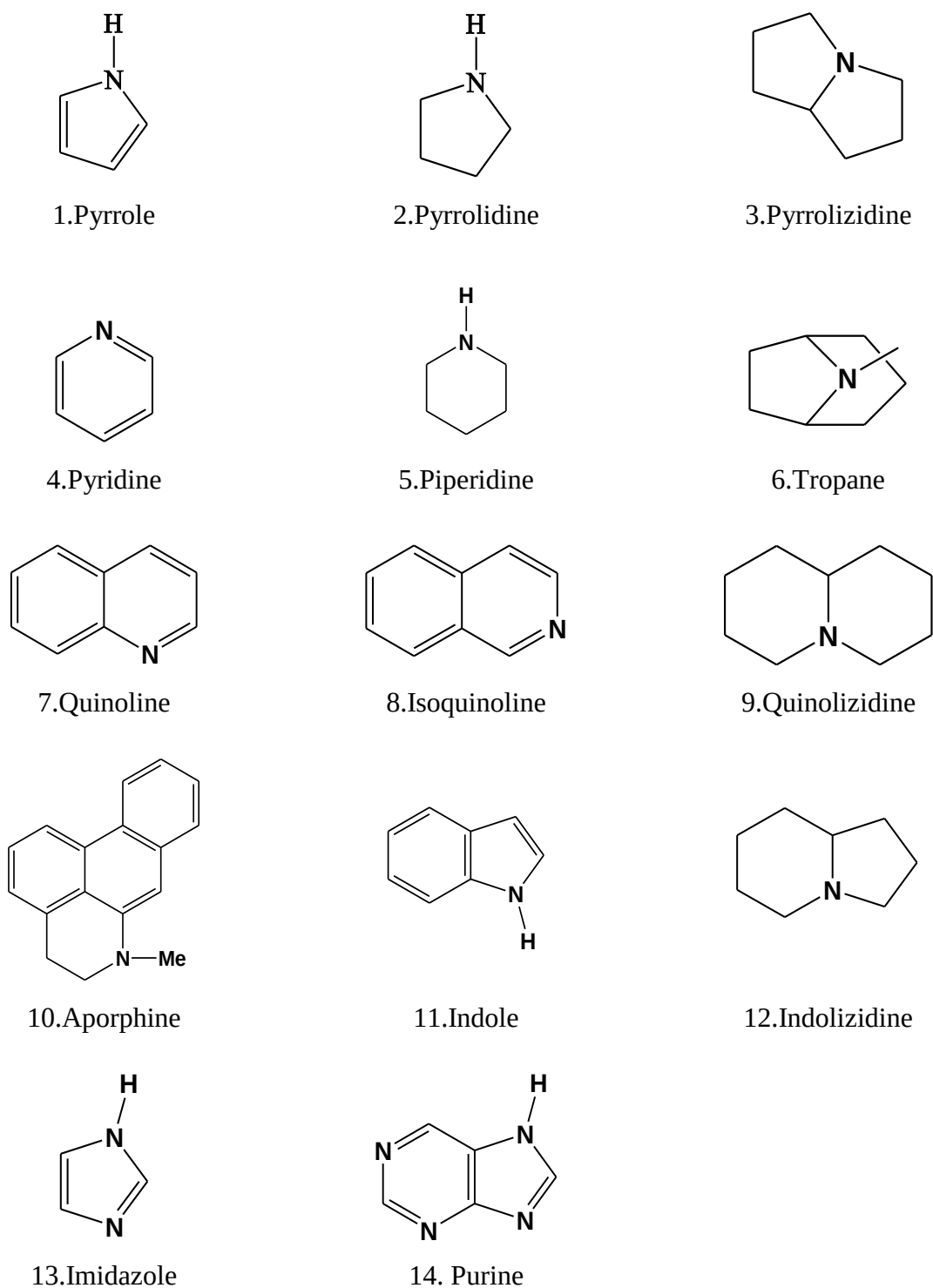


Figure 3.4. Main structural skeletons of alkaloids isolated from plants

Alkaloid molecules have attracted the attention of many research groups for many years, and significant progresses in their knowledge have been achieved. The following section gives a brief overview of the main results reported in literature.

3.4.2. Examples of alkaloid antimalarials of natural origin

Oliveira and co-researchers [16] have done a literature review of investigated alkaloids with antimalarial activity, reporting about 100 different alkaloids. The authors grouped these alkaloids in several classes, according to the origin (plant family) or the structure, namely: phenolic aporphine-benzylisoquinoline, bisbenzylisoquinoline, naphthylisoquinoline, indoloquinoline, indole, mono-indole, bis-indole, indolomonoterpenoid, benzofenantridine, acridone, furoquinoline, acridine and tetrahydroquinoline alkaloids [21, 38–54]. Besides these classes, there is another class – the pyrazole alkaloids – which also showed antimalarial activity [262]. The naphthylisoquinoline alkaloids (section 1.4, Fig.1.1) constitute the object of the current study.

Some of the above-mentioned alkaloids have antiplasmodial activity against *P. falciparum* and some were found to be more bioactive than chloroquine [16]. For example, the phenolic aporphine-benzylisoquinolines alkaloids isolated from the roots of *Thalictrum faberi* Ulbr. (Ranunculaceae) were revealed to be more active against chloroquine resistant (CQR) *P. falciparum* clones (W2; IC₅₀: fifty percent inhibitory concentrations < 25 ng/ml) than against chloroquine sensitive (CQS) clones (D6; IC₅₀ >100 ng/ml) [263]. D6, W2, K1, FcB1 and T9-96 NF54 are clone parasites from different countries used to test the antimalarial activity of different compounds.

Bisbenzylisoquinoline alkaloids are a large class of alkaloids found in many plant species, particularly in members of the Menispermaceae, Berberidaceae, Ranunculaceae, Annonaceae and Monimiaceae. Angerhofer and co-workers [264] studied and tested about 53 bisbenzylisoquinoline alkaloids and evaluated their selectivity in inhibiting the growth of intraerythrocytic malaria parasites. The cytotoxicity of the isolates was tested against KB cells – A cell line derived from a human carcinoma of the nasopharynx, used as an assay for antineoplastic agent– (human oral, epidermoid). These alkaloids were isolated via phytochemical studies and bioassay-directed fractionation.

Benzylisoquinoline alkaloids constitute a novel class of antimalarial drugs with remarkable inhibitory activity against *Plasmodium* hepatic stages [265]. An interesting benzylisoquinoline alkaloid called ‘morphinan’ was isolated from *Strychnopsis thouarssi* (Menispermaceae) and found to possess a weak bioactivity against the FcB1 strain of *P. falciparum* erythrocytic stages *in vitro*, showing an IC_{50} of $34.0 \pm 9.4 \mu\text{g/ml}$ from stem bark decoction.

Cryptolepine is an example of an antimalarial alkaloid belonging to the class of indoloquinoline alkaloids. It is an important constituent and the most potent antiplasmodial compound in *Cryptolepis sanguinolenta*. It has potent effects against CQS (D6 IC_{50} $27.0 \pm 0.3 \text{ ng/ml}$) and CQR *P. falciparum* strains *in vitro* (K1 IC_{50} $33.0 \pm 0.1 \text{ ng/ml}$, W2 IC_{50} $41.0 \pm 0.5 \text{ ng/ml}$). Cytotoxic effects have also been observed [266, 267].

Frederich *et al.* [268] have recently published an article about some mono- and bis-indole alkaloids with high antiplasmodial activities *in vitro* and *in vivo*, and favourable selectivity indices (SI) ($SI = CC_{50}/IC_{50}$, CC: fifty percent cytotoxicity concentration). These alkaloids have been isolated from different plants which are used traditionally in different continents to treat malaria. The compounds isolated from the plants belonging to the Genera *strychnos* (Loganiaceae) and Genera *Alstonia* (Apocynaceae) are the most active.

A large series of antiplasmodial potent effects were observed (IC_{50} expanded from 32 to 500 nM) for the indolomonoterpenoid alkaloids isolated from various *Strychnos* species (Loganiaceae) and have shown antiplasmodial activity against CQR and CQS [269, 270].

Indole alkaloids with antiplasmodial activity have recently been isolated from *Geissospermum* and *Aspidosperma* species (Apocynaceae family) [271]. Four alkaloids were isolated from alkaloidal fractions, which are geissoschizoline, flavopereirine (previously isolated from *Geissospermum vellosii* and *Geissospermum laeve*), geissoschizoline N4-oxide and 1,2-dehydrogeissoschizoline [272–275]. Flavopereirine, a β -carboline alkaloid, was the most active of the four compounds and showed an antiplasmodial activity against K1 (CQR) and T9-96 (CQS) strains of *P. falciparum* ($IC_{50} = 11.53$ and $1.83 \mu\text{M}$, respectively).

Seven benzophenantridine alkaloids, of which nitidine is the most potent against *P. falciparum* ($IC_{50} < 0.27 \mu M$), were isolated by bioassay-guided fractionation from the trunk bark of *Zanthoxylum rhoifolium*, traditionally used in French Guiana to treat and prevent malaria. Five others benzophenantridine alkaloids were isolated from the stem bark of another species of *Zanthoxylum* (*Zanthoxylum tsihamimposa*) used in Madagascar, and showed antiplasmodial activity *in vitro* against *P. falciparum* with the IC_{50} values in the range of 459.1 to 87.7 μM . It was found that the most potent alkaloid was the quinolone γ -fagarine, which had an IC_{50} of 98.4 μM [276–278].

Acridone alkaloids have been isolated from species that belong to the genera *Citrus* (*Glycosmis* and *Severimia*) in the Rutaceae family. These alkaloids were tested for antimalarial activity *in vitro* against *P. yoelli* and *in vivo* against *P. berghei*- and *P. vinckei*-infected mice. About 30 acridone alkaloids were tested at a concentration of 10 $\mu g/ml$ *in vitro* and seven of them inhibited 90% or more of the parasite growth. Against *P. yoelli*, these alkaloids were found to be either equally or more effective than chloroquine *in vitro* ($94 \pm 4\%$ growth inhibition). Among the seven alkaloids which inhibited the parasite, atalaphillinine alkaloid was the only one to be tested for *in vivo* activity [279].

Basco *et al* [280] reported the *in vitro* effect of 23 furoquinoline and acridone alkaloids against CQR (W2) and CQS (HB3) clones of *P. falciparum*. These alkaloids were isolated from plants belonging to the Rutaceae family. Fourteen out of 23 alkaloids presented a $IC_{50} < 10 \mu g/mL$ against the W2 strain. The O-pyranoglycoside derivative of acronycine with an IC_{50} of 0.60 $\mu g/mL$ was the most active among them [280, 281].

Tetrahydroquinoline alkaloids were isolated from the trunk bark of *Galipea officinalis* (Rutaceae). Their IC_{50} values were between 1.8 to 40.0 $\mu g/ml$ against a CQS strain (Nigerian) and 0.09 to 38.0 $\mu g/ml$ against CQR strains (FcB1 and FcM29). Galipinine was the most active among these alkaloids, with an IC_{50} of 0.09 to 0.9 $\mu g/ml$ against CQR strains [282–284].

3.5. Non alkaloid antimalarials of natural origin

Beside alkaloids compounds, there are several other classes from natural origin which have shown activity against plasmodium. In this section, a brief overview of main classes such as terpenes, flavonoids and saponins is given. Review articles concerning these compounds include terpenes, flavonoids, chromones, xanthenes, anthraquinones, chalcones, flavonones, rotenoids, isoflavones, phenolics, polyacetylenes, quinones, coumarines and miscellaneous compounds [18, 285–287]. Batista *et al.* [18] and Ntie-Kang *et al* [287] have done a literature review of investigated non-alkaloids with antimalarial activity grouping them in several classes, according to the origin (plant family) or the structure.

3.5.1. Terpenes (terpenoids)

3.5.1.1. Definition, classification, origin

Terpenes or terpenoids are a large class of natural compounds where the building blocks are isoprene units (units consisting of five carbon atoms, with various degrees of unsaturation, oxidation, functional groups and ring closures). More than 30,000 molecules have been discovered to-date. They have many biological activities such as antimalarial, anti-cancer, anti-inflammatory, antiviral and antibacterial [288].

Terpenes can be classified into 6 classes according to the number of isoprene units, namely:

- Hemiterpenes, constituted by one isoprene unit (C_5H_8). They are the simplest terpenes and have no biological activity. Isoprene itself (Fig.3.5) is a hemiterpene.
- Monoterpenes, containing two isoprene units ($C_{10}H_{16}$). They can be linear (acyclic) or contain rings (cyclic). Cyclic monoterpenes can be monocyclics (one ring) and bicyclics (two rings). Monoterpenes can be simple unsaturated hydrocarbons or may contain functional groups such as alcohols, aldehydes and ketones. They can be found in higher plants, algae, fungi and also in some insects and mammals. Monoterpenes are biologically and pharmacologically active agents. Limonene (Fig.3.5) is a monoterpenoid.

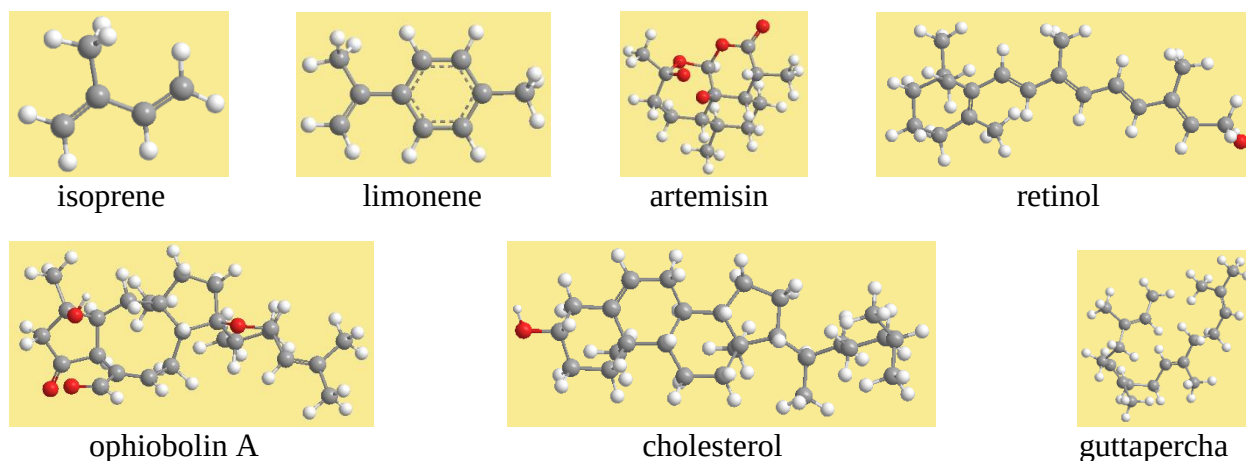


Figure 3.5. The terpenes mentioned in section 3.5.1.1

- sesquiterpenes, constituted by three isoprene units ($C_{15}H_{24}$). They can be found in diverse forms, simple acyclic, simple to macro monocyclic rings, as well as simple and complex bicyclic and tricyclic structures. Sesquiterpenes can be in hydrocarbon forms or oxygenated forms (lactones, alcohols, acids, aldehydes, and ketones). They are found principally in higher plants and in many other living systems such as marine organisms and fungi. The well known antimalarial drug artemisin (Fig.3.5) is sesquiterpene.
- diterpenes, constituted by four isoprene units ($C_{20}H_{32}$), building diverse structures from simple acyclic to complex polycyclic rings (Table 3.3). They are usually found in a polyoxygenated form with keto and hydroxyl groups, which are often esterified by small-sized aliphatic or aromatic acids. Diterpenes are found in plants and also in marine organisms. Retinol (Fig 3.5) is an example of diterpernes.
- sesterterpenes, containing five isoprene units ($C_{25}H_{40}$). They constitute a rare class of terpenes. They are mostly found in marine sponges and terrestrial fungi. Ophiobolin A belongs to this class.
- triterpenes, constituted by six isoprene units. More than 4,000 are known. They can be grouped into more than 40 different carbon skeletons, arising from the cyclisation of an oxidized form of squalene, the linear parent triterperne. They are mostly in cyclic forms (1-5 rings). Cholesterol (Fig. 3.5) is an example.

- polyterpenes, with an open structure consisting of many *cis* or *trans* isoprene units. (e.g. gutta-percha, Fig 3.5.)

The next paragraph gives some examples of terpenes with antimalarial activity. For space reasons they will be given in a sort of list-format, mentioning the compounds, their natural origin and their major activities.

3.5.1.2. Example of terpenes with antimalarial activity, from natural origin

Two cassane furanoditerpenes, deoxycaesaldekarnin C and caesaldekarnin C, were isolated from the chloroform and ethyl acetate extracts of the root bark of *Caesalpinia volkensii* from Kenya [287, 288]. They exhibited antinociceptive and antiplasmodial activities. The antiplasmodial activity was evaluated against chloroquine sensitive (CQS) D6 and chloroquine resistant (CQR)W2, for deoxycaesaldekarnin C, the IC_{50} values were 25.67 and 30.33 $\mu\text{g/mL}$ respectively while for caesaldekarnin C, the values were 34.44 and 30.69 $\mu\text{g/mL}$ respectively [289, 290].

Two cassane diterpenes, namely caesalsappanin R and caesalsappanin S were isolated from *Caesalpinia sappan* (a traditional Chinese herbal medicine) [291]. Caesalsappanin R has an unusual diterpenoid lactone-type skeleton with an N bridge. Caesalsappanin R showed good antiplasmodial activity *in vitro* ($IC_{50} = 3.6 \mu\text{M}$) compared to chloroquine and caesalsappanin S exhibited a weak activity against CQR K1 strain of *P. falciparum*. The presence of the N-bridge may play an important role in enhancing the activity the against CQR K1 strain of *P.falciparum in vitro* [291].

Table 3.3. Different types of diterpenes

Form	Diterpenes types
acyclic	phytanes
bicyclic	abdanes, halimanes, clerodanes
tricyclic	pimaranes, abietanes, cassanes, rosanes, vouacapanes, podocarpanes
tetracyclic	rachylobanes, kauranes, stemodanes, aphidicolanes, stemaranes, atisanes, gibberellanes
macrocyclic	taxanes, cembranes ingenanes, daphnanes, tigianes,

Four diterpenes were isolated from the stem bark of *Ekebergia capensis* (Zingiberaceae). Two of them were new acyclic diterpenoids, namely ekeberin D4 and D5, with D4 having no antimalarial activity while D5 showed activity against CQR K1 strain of *P. falciparum* ($IC_{50} = 137 \mu M$) [290, 292]. The other two were known acyclic diterpenes, 3R,22R)-2,3,22,23-tetrahydroxy-2,6,10,15,19,23-hexamethyl-6,10,14,18-tetracosatetraene and (2R,3R,22R)-2-hydroxymethyl-2,3,22,23-tetrahydroxy-2,6,10,15,19,23-hexamethyl-6,10,14,18-tetracosatetraene, with moderate antimalarial activity against FCR-3 strain of *P. falciparum* with respective IC_{50} values of 55 and 18 μM . They also exhibited good activities against CQR K1 strain of *P. falciparum* with IC_{50} values of 7 and 59 μM respectively [290, 292].

Another acyclic triterpene, (+) S-nerolidol was isolated from the seeds of *Aframomum escapum* [293] and was also found in *Artemisia herba alba* and in lemon grass [294]. This triterpene is the main active constituent of essential oils utilised in the treatment of malaria and it was found to be able to stop the development of the intraerythrocytes stages of the parasite, leading to 100% growth inhibition at the schizont stage.

Sesquiterpenes isolated from *Vernonia* species exhibit interesting antiparasmodial activities [295, 296]. Among them, vernodalin, vernodalol, vernolide and hydroxyvernolide were isolated from the leaves of *Vernonia amygdalina* [295] and 16,17-dihydrobrachycalixolide from the leaves of the sister species, *Vernonia brachycalyx* [296]. They showed moderate activity against the multidrug-resistant K-1 strain of *P. falciparum*, with vernodalin being the most active compound ($IC_{50} = 4 \mu g / mL$) while vernodalol, vernolide and hydroxyvernolide had respective IC_{50} values of 4.2, 8.4 and 11.4 $\mu g / mL$ [295]. 16,17-dihydrobrachycalixolide shows moderate to high

antiplasmodial activity against K39, 3D7, V1/S and Dd2 *P. falciparum* strains, with IC₅₀ values of 4.2, 13.7, 3.0, and 16 µg mL⁻¹, respectively [296].

Vernodalol and vernodalin were also isolated, together with vernangulide A and B and 11,13β-dihydroxyvernodalin, from the dichloromethane/methanol 1:1 and methanol extracts of the aerial part of *Distephanus angulifolius*. They exhibited antiplasmodial activity against CQS D10 and CQR W2 *P. falciparum* strains, with IC₅₀ values in the 1.6–3.8 µM and 2.1–4.9 µM range respectively [297].

Two already known sesquiterpenic lactones, 15-acetoxy-8β-[(2-methylbutyryloxy)]-14-oxo-4,5-cis-acanthospermolide), and 9α-acetoxy-15-hydroxy-8β-(2-methylbutyryloxy)-14-oxo- 4,5-trans-acanthospermolide, were isolated from *Acanthospermum hispidum* garnered in Benin Republic [298]. They exhibited *in vitro* antiplasmodial activity against CQS 3D7 with respective IC₅₀ values of 2.9 and 2.23 µM. Additionally, a weak *in vitro* antimalarial activity against *P. berghei* was observed.

Urospermal A-15-O-acetate was identified as the main active compound responsible for the antiplasmodial activity in *Dicoma tomentosa* (Asteraceae) from Burkina Faso [299]. This compound had an IC₅₀ <1 µg/Ml against both CQS 3D7 and CQR W2 *P. falciparum* strains.

Dehydrobrachylaenolide (an eudesmanolide-type sesquiterpene lactone) was found to be the main active constituent of *Dicoma anomala* subsp. *gerrardii* from the Brits region of North West Province of South Africa [300] and has *in vitro* activity against CQS D10 (IC₅₀ = 1.9 Mm). It is shown that a methylene lactone group must be present in eudesmanolides for them to show any significant antimalarial activity. The fact that this characteristic is absent in the artemisinins (which also are sesquiterpene lactones) suggests that eudesmanolide-type sesquiterpene lactones have a different mode of action from artemisinins, which was further confirmed by microarray gene ontology analysis [300].

3.5.2. Flavonoids

3.5.2.1. Definition, classification, origin

Flavonoids are a large group of polyphenolic compounds present in plants. They can be identified as virtual universal plant pigments. Over 10,000 different flavonoid structures have been reported [301]. In general, the term flavonoid is utilized to define a broad group of natural products that contain a 15-carbon skeleton, consisting of two phenyl rings (A and B) and an heterocyclic ring C (concisely denoted as C6–C3–C6 skeleton, Fig 3.6), or specifically a phenylbenzopyran (phenylchromane) function [301, 302]. Based on the position on the linkage of the aromatic ring to the benzopyrano (chromano) moiety, flavonoids can be divided into three main classes:

1. **True flavonoids** (2-phenylbenzopyrans), e.g., catechin (Fig 3.6)
2. **Isoflavonoids** (3-benzopyrans), e.g., daidzein (Fig 3.6)
3. **Neoflavonoids** (4-benzopyrans), e.g., dalbergin (Fig 3.6)

The three classes have the chalcone precursor in common and, therefore, they are biogenetically and structurally related. Each class can be subdivided in subclasses, which are listed in Table 3.4. Beside these classes, there is a class called ‘minor flavonoids’, which also have a C6–C3–C6 backbone. The compounds of this class are chalcones and aurones [303].

Flavonoids have many pharmacological and biological activities [304, 305], which depend on their chemical structures, degree of hydroxylation and functional groups present. These activities include antiatherosclerotic, anti-inflammatory, antithrombogenic, antitumor, antiosteoporotic, antiviral, antibacterial, antifungal [306, 307] and antimalarial [287]. They also play important roles in plants, such as protection of plants against insects and herbivores [308], UV radiation, heat, and maintain a balanced redox state in plant cells due to their antioxidative properties [309–311].

The following section gives few examples of studies on flavonoids.

Table 3.4. Different classes and sub-class of flavonoids

Class	Sub-class
true flavonoids	Flavones, flavononones, flavonols, dihydroflavonols, flavan-3-ol, flavan-4-ols and flavan-3,4-diols
isoflavonoids	Isoflavans, isoflavones, isoflavonones, isoflav-3-eme, isoflavanols, rotenoids, coumestanes, 3-arylcoumarines, coumestrol, coumaronochromenes, coumaronochromones and pterocarpanes
neoflavonoids	4-arylcoumarins, 3,4-dihydro-4-arylcoumarins and neoflavenes

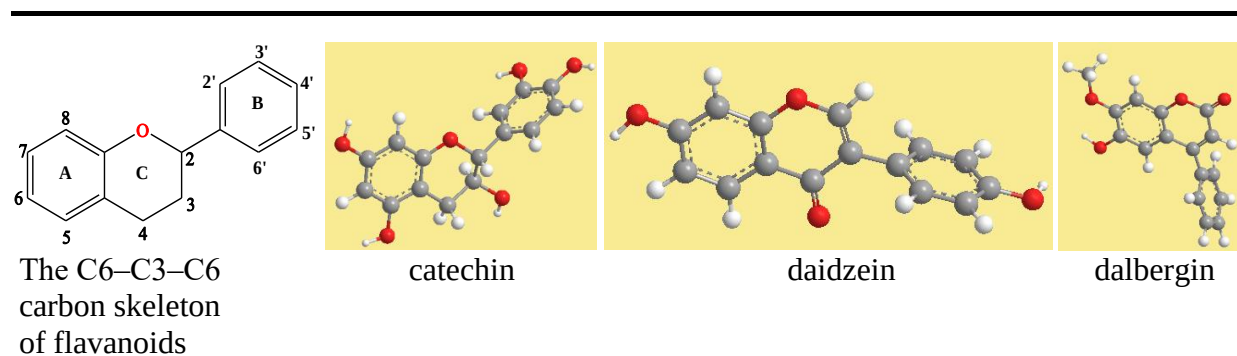


Figure 3.6. Common skeleton of flavonoids and examples of each of the types of flavonoids mentioned in section 3.5.2.1

3.5.2.2. Examples of flavonoids with antimalarial activity.

Artocarpesin, kushenol E, mulberrofuran F, bartericin A and 4-hydroxyronchocarpin were isolated from the root bark of *Morus mesozygia*. Artocarpesin and kushenol E are flavonoids while the three others (mulberrofuran F, bartericin A and 4-hydroxyronchocarpin) are arylbenzofuran derivatives. The isolated compounds and their methanolic extracts were tested for antimalarial activity against CQR FcB1 *P.falciparum* strain and for cytotoxicity on MCF-7 human breast cancer cells. The results showed that all the compounds were active against the FcB1 *P. falciparum*

strain with the two flavonoids and mulberrofuran F showing particular potency ($IC_{50} = 2.5\text{--}2.6\text{ }\mu\text{g/ mL}$) [287].

Mucisoflavone C, a dimeric isoflavonone isolated from the figs of *Ficus mucoso*, showed weak activity ($IC_{50} = 7.69\text{ }\mu\text{M}$) against the validated drug target *P. falciparum* enoyl-ACP reductase (PfENR) [287].

Six flavonoids, lupinifolin, citflavanone, erythrisenegalone, lonchocarpol, liquiritigenin and 8-prenyldaidzein, were isolated from the stem bark of *E. fusca*. Three of them showed *in vitro* activity against the multi-drug-resistant strain (K1) of *P. falciparum* ($IC_{50} < 12.5\text{ }\mu\text{g/ mL}$). Lonchocarpol (diprenylated flavanone) has the most potent activity and a slightly higher cytotoxicity than chloroquine while lupinifolin and erythrisenegalone, as well as diprenylated flavonones, did not show any antimalarial activity and no test on the cytotoxicity was done for them. This result showed that an appropriate introduction of prenyl groups into flavonoids, such as the antimalarial biflavanone [312, 313], may lead to more useful derivatives for designing an antimalarial agent [314].

3.5.3. Saponins

3.5.3.1. Definition, classification, origin

Saponins are plant-derived secondary metabolites with high molecular mass. The term “saponin” originates from Latin 'sapo' (soap) and, traditionally from the plant *Saponaria*, whose roots were used as a soap. Saponins are widely distributed in nature and reported to be present in 500 genera of plants. They possess several biological activities such as anti-inflammatory [315], antiviral [316], immunoregulatory [317], anticancer (as anti-proliferation [318], anti-metastasis [319] and anti-angiogenesis [320, 321]), antioxidant, immunostimulant, antihepatotoxic, antidiarrheal, antiulcerogenic, antioxytotoxic, hypocholesterolemic, anticoagulant, hepatoprotective, hypoglycemic, neuroprotective, inhibition of dental caries and of platelet aggregation [322] and antimalarial activity [287].

Structurally, saponins (Fig 3.7) contain a sugar moiety (glycone which is hydrophilic) glycosidically linked to a non-sugar moiety, aglycone (or sapogenin) which is hydrophobic. The non-sugar moiety may contain one or more unsaturated C–C bonds. The sugar moiety is commonly D-glucose, D-galactose, D-glucuronic acid, D-xylose, L-rhamnose or L-arabinose [323, 324].

On the basis of the number of chains in their structure, saponins can be categorised as:

1. **Monodesmosidic** saponins, which have one single sugar chain attached at C–3,
2. **Bidesmosidic** saponins, which have two sugar chains, one attached at C–3 via an ether linkage and the other one via an ester linkage at C–28 or C–26 [324].

On the basis of the chemical structure of their aglycone (non-sugar) moiety, saponins are divided into two main categories:

1. Steroidal saponins

The steroid skeleton has 27 carbon atoms with a 6-ring spirostane or a 5-ring furostane. They are found in plants belonging to Dioscoreaceae, Liliaceae and Scrophulariaceae families and exhibit various biological activities [321].

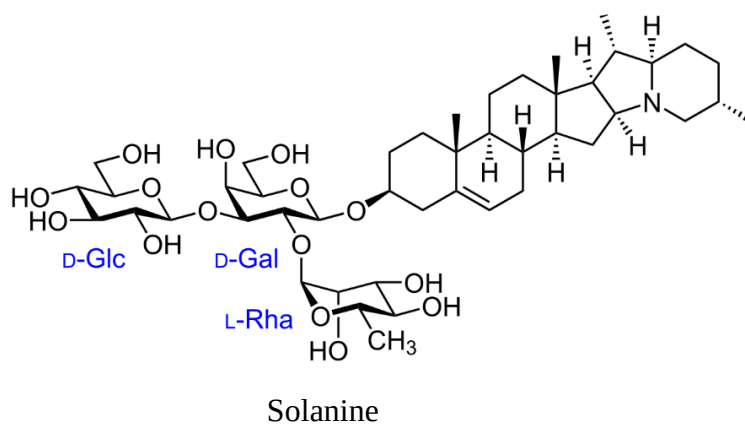


Figure 3.7. Example of saponins

2. Triterpenoid saponins

They are found in plants belonging to Araliaceae, Leguminosae, Polygalaceae and Campanulaceae families. They are triterpene-based glycosidic compounds. Most of the triterpenoid compounds in adaptogenic plants are found as saponin glycosides, which refers to the attachment of various sugar molecules to the triterpene unit [322].

The form of the aglycone structure, the number of sugars added to it, the nature of the side chains and the position of the attachment of the moieties on the aglycone can lead to a large number of saponin structures and those structures, in turn, possess different biological properties. Only few cases of studies on antimalarial saponin molecules are found in literature. The section below gives some examples of saponins.

3.5.3.2. Examples of saponins with antimalarial activity.

Vernonioside A1, A2, A3, A4 and vernonioside B1 are steroidal saponins with antimalarial activity isolated from the leaves of *Vernonia amygdalina* [287]. They showed weak antiplasmodial activity against the multidrug-resistant K-1 strain of *P. falciparum*, with respective IC₅₀ values of values of 139.7, 94.1, 245.1, 81.8 and 46.1 µg/ mL [287, 323].

Sapogenin muzanzagenin, an antimalarial compound, was isolated from *Asparagus africanus* (Asparagaceae) [287, 325] plant and showed antimalarial activity.

Saponin spiroconazole A was isolated from West Africa ‘soap tree’ *Dracaena* sp. (Dracaenaceae) [287, 326] and showed pronounced antimalarial, antileishmanial and molluscicidal activities.

3.6. Overview on computational studies of alkaloids [26]

This section considers the computational studies on all the alkaloids because it is always important to have information of an entire class of compounds even when their biological activities are different. The section provides an overview of the results of computational studies on alkaloids available so far and attempts to identify patterns for the whole class or for some subclasses. This

can contribute to better focusing on the molecular basis of some biological activities and also offer suggestions for finer focusing of future computational studies on the same or other alkaloid molecules. Major attention is therefore given to the results that are relevant for such understanding, thus being important also for the design of viable derivatives. Aspects that have proved important for the classes of alkaloids studied by the authors [58–62, 327], such as the effect – on conformational preferences – of intramolecular hydrogen bonding or of the mutual orientations of ring systems, are given particular attention. Some calculations were also added to elucidate issues that appeared to have remained open in literature for some compounds, such as the possibility that quinine and quinidine form an intramolecular hydrogen bond (IHB) with the heterocyclic N atom as acceptor [61, Appendix 1] or other features for which further elucidation appeared relevant. The studies and results are grouped according to their objectives and main nature, such as conformational investigation of alkaloids' molecules, docking studies investigating the interactions between alkaloid molecules and biological targets, and computational studies performed to confirm experimental results.

3.6.1. Types of alkaloids considered

Computational studies are so far available for alkaloids of the following classes: cinchona alkaloids (CA), nicotinoids (NC), pyrazole alkaloids (PA), Daphniphyllum alkaloids (DA), Erythrina alkaloids (EA), alkaloids from *Peganum harmala* and alkaloids from *Sarcococca saligna*. This section offers an overview of the botanical origin, pharmacological activities and representative compounds of each of these classes. This information is relevant to a meaningful presentation and discussion of computational results, including the significance of these results in view of the practical applications of the compounds.

The cinchona alkaloids are alkaloids isolated from the bark of cinchona trees found in Peru. Their molecules contain two moieties – a quinuclidine moiety and a quinoline moiety. The most abundant compounds in cinchona trees which were found active against malaria are two pairs of erythro diastereoisomers, quinine-quinidine and cinchonidine-cinchonine (their respective threo epimers, epiquininine, epiquinidine, epicinchonidine and epicinchonine are inactive [328]). The

difference in activity among these stereoisomers arises from the absolute stereochemistry of the carbon atoms to which the amine group and the hydroxyl group are attached.

Cinchona alkaloids have found pharmaceutical applications. For instance, quinine (Fig.3.8.) Quinine has been the most powerful known antimalarial for long and is still a resource drug for the treatment of malaria [329]; its use is currently reserved for particularly severe cases in order to prevent the development of resistance by the *plasmodium* parasite [330]. Other compounds (e.g., quinidine) are used for cardiac arrhythmias [331]. Applications in the industry and in chemistry laboratories comprise the use as additives for soft drinks [332], as starting materials for organic synthesis [333], chiral resolving agents in fractional crystallization [334], chiral selectors in chromatographic techniques and also in capillary electrophoresis [335], and agents for promoting enantioselective transformations in both homogeneous and heterogeneous catalysis [336].

Nicotinoids are alkaloids characterized by the presence of a pyridine ring and a second N-containing ring, with the C–C joining a meta C of the pyridine ring to an ortho C of the other ring. They are biochemically relevant compounds, found to be bioactive as agonists of the nicotinic acetylcholine receptor (nAChR). Some of them are utilized in the treatment of numerous neurological diseases such as Alzheimer, schizophrenia, Parkinson disease, Tourette's syndrome, anxiety, cognitive and attention deficits, and smoke addiction [337–346]. Most works on nicotinoids have focused on the nicotine molecule, an alkaloid present in tobacco leaves and responsible for addiction in smokers. Nicotine (Fig.3.9) is a potent agonist of nAChR, thus being promising for the treatment of the just-mentioned nervous system conditions (pain, cognitive and attention deficits, Parkinson's disease, Tourette's syndrome, anxiety, and tobacco addiction [347]). Piperidinic alkaloids have lower presence than pyridinic alkaloids in tobacco leaves. The most representative is (–)-S-anabasine (Fig.3.9), which has shown remarkable biomedical uses [348]; its molecular structure and spectroscopic properties have been widely investigated [349–354].

Pyrazole alkaloids (withasomnine, newbouldine, and their para-hydroxy) are alkaloids isolated from the root bark of *Newbouldia laevis*, (Bignoniaceae), an endemic plant used in various ethnomedicinal preparations in D.R. Congo and across West Africa to treat diarrhoea, dysentery, worms, malaria and sexually transmitted disease and also to reduce dental caries [262]. Figure 3.10 shows the six known pyrazole alkaloids.

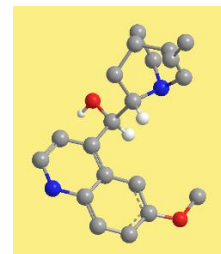
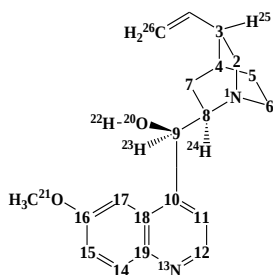
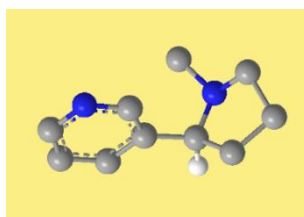
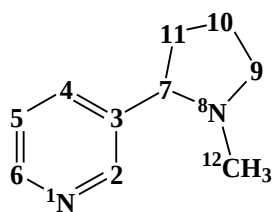
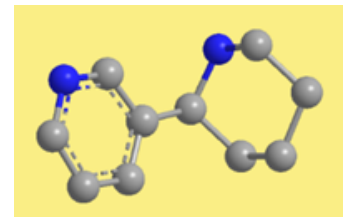
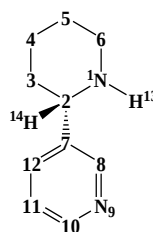


Figure 3.8. Molecular structure and ball-and-stick model of quinine (a representative of cinchona alkaloids) and atom numbering utilized in [26, 61]

The C atoms in the rings are represented only by the numbers denoting their positions. The H atoms attached to C atoms are not shown in the model to better highlight the molecular structures.



Nicotine



(-)-S-anabasine

Figure 3.9. Molecular structure and ball-and-stick models of nicotine and (-) S-anabasine and atom numbering utilized in [26]

The C atoms in the rings are represented only by the numbers denoting their positions. The H atoms attached to C atoms are not shown to better highlight the molecular structures.

Daphniphyllum alkaloids isolated from plants of the *Daphniphyllum* genus [355] are a group of compounds with polycyclic skeletons, always including an N-containing ring. Figure 3.11 shows a representative compound, which also illustrates the unusual polycyclic skeletons of this class of alkaloids. They exhibit cytotoxic, antioxidant, vasorelaxant, and antiplatelet activating factor effects [356].

Erythrina alkaloids (Fig.3.12) are alkaloids with a 1,2,3,4,5,6,8,9-octahydroindolo[7a,1a]isoquinoline skeleton, found only in the plants genera *Erythrina* (*Fabaceae*), *Cocculus* (*Hyperbaena*) and *Pachygone* (*Menispermaceae*) [357]. These alkaloids exhibit many biological activities such as sedative, anxiolytic, anti-inflammatory and antihypertensive [358–369].

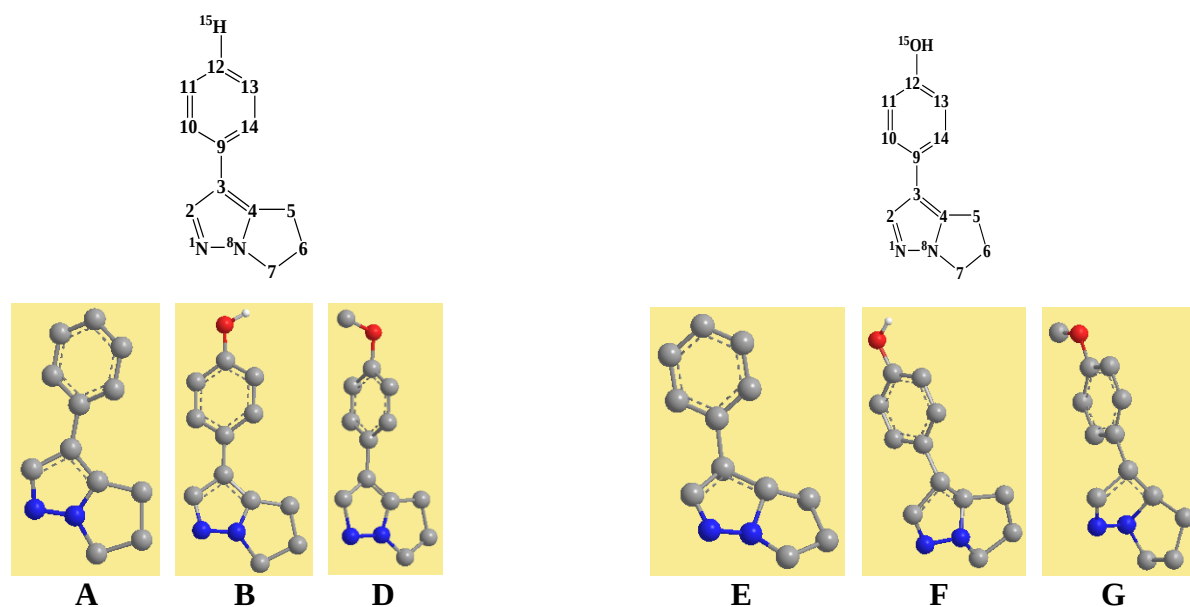


Figure 3.10. Molecular structure and atom numbering of two classes of pyrazole alkaloids (first row) and ball-and-stick models of the six pyrazole alkaloids utilised in [26, 327]

The latter are denoted by letters: **A** withasomnine, **B** p-hydroxy derivative of withasomnine, **D** p-methoxy derivative of withasomnine, **E** newbouldine, **F** p-hydroxy derivative of newbouldine, **G** p-methoxy derivative of newbouldine. The carbon atoms are represented only by their numbers; the symbols of all the other atoms are shown explicitly. The same atom numbering is utilized for atoms in corresponding positions in all the compounds investigated, in order to facilitate comparisons.



Figure 3.11. Molecular structure and ball-and-stick models of calydaephninone (a representative *daphniphyllum* alkaloids) and atom numbering utilized in [26]

In the model the H atom attached to C atoms are removed to better highlight the molecular structures.

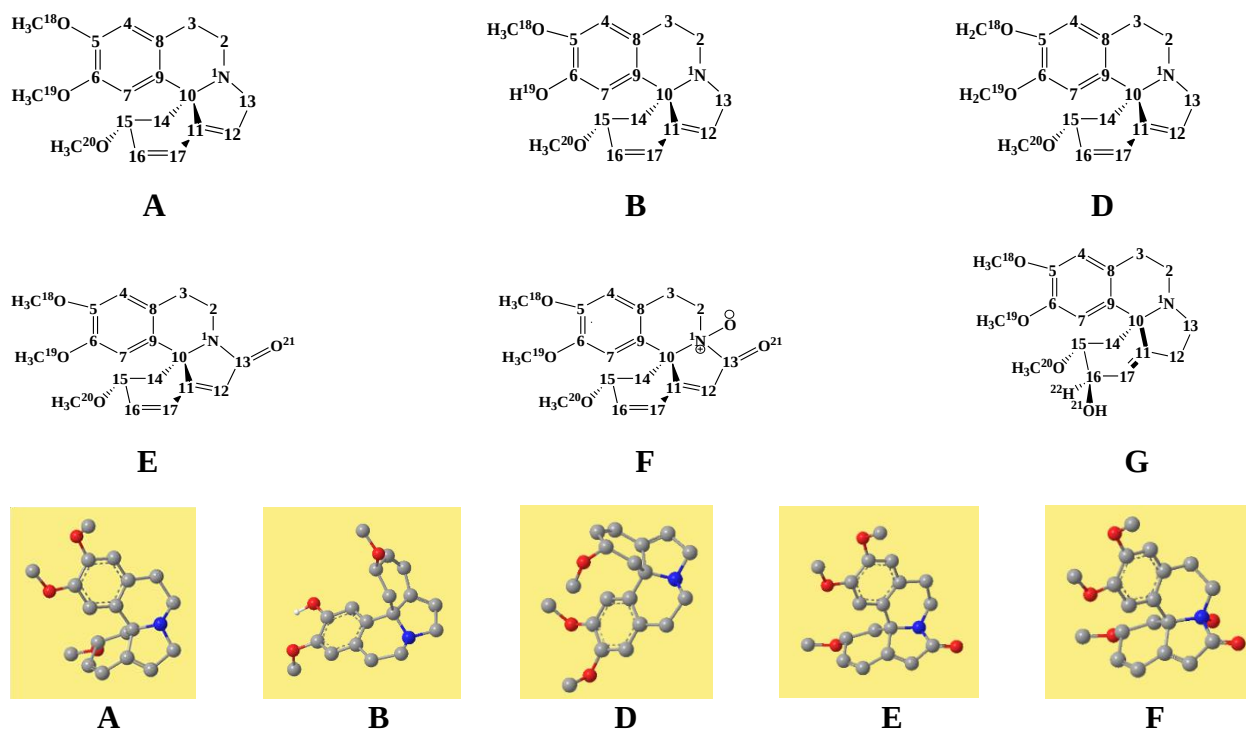


Figure 3.12. Molecular structure of the six erythrina alkaloids isolated from *erythrina fusca* Lour (first two rows) and their ball-and-stick models (third row) utilised in [26]

The molecules are denoted by letters: **A** erysotrine **B** erysodine **D** erythraline **E** erytharbine **F** erysotrine N-oxide **G** epierythratidine. The same atom numbering is here ascribed to atoms in corresponding positions to facilitate comparisons.

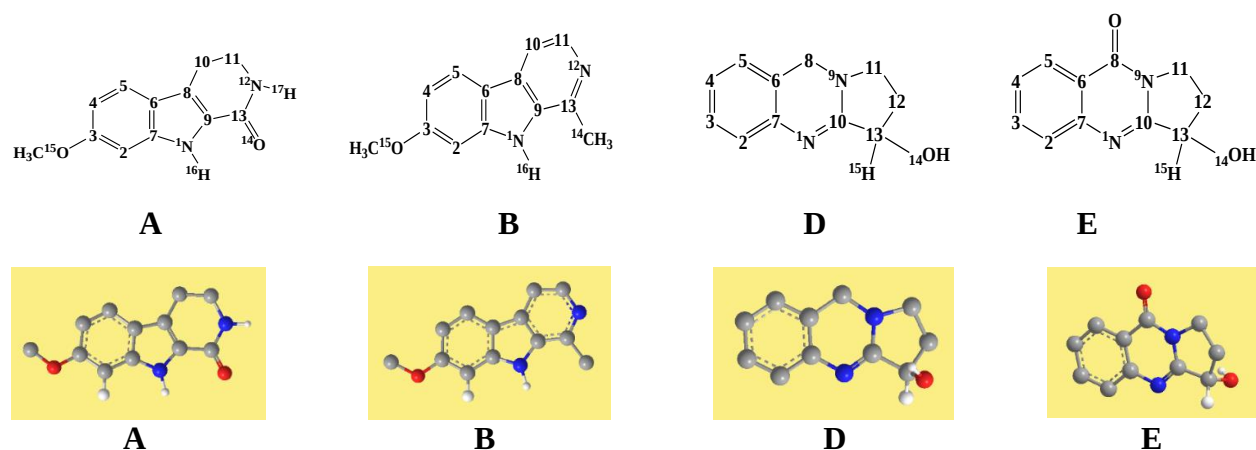


Figure 3.13. Molecular structure of four alkaloids isolated from *Peganum harmala* (first two rows) and their ball-and-stick models (third row)

The molecules are denoted by letters: **A** harmalacidine, **B** harmine, **D** peganine, **E** vasicinone. The same atom numbering is here ascribed to atoms in corresponding positions to facilitate comparisons.

Figure 3.13 shows the alkaloids isolated from *Peganum harmala* – a typical plant of the central Sahara in Morocco, exhibiting antibacterial, antifungal and antiviral activities, analgesic effects on the central nervous system and vasorelaxant effects. The alkaloids have cytotoxic activity on cancerous cell lines and inhibit the synthesis of their DNA [370].

Alkaloids isolated from *Sarcococca saligna* (*Buxaceae*) [371], found in South Asia, exhibit ganglion-blocking activity and are used as acetylcholinesterase (AChE) inhibitors.

3.6.2. Conformational studies of alkaloids from natural sources

The conformational study of a molecule aims at identifying its more stable conformers, and also the factors contributing to their stabilization. An extensive and detailed conformational analysis is important for the understanding of the biological behaviour of bioactive compounds. QSAR analyses require the knowledge of a number of properties, both macroscopical (experimentally determined) and molecular; the latter are mostly obtained through conformational studies. A systematic conformational study (investigating enough conformers to identify patterns and to

include all those with sufficiently low energy) is important to ensure that no feature relevant for QSAR or other structure-activity analyses is overlooked.

Conformational studies have become increasingly sophisticated with the development of computer power and software in the last decades. This has expanded the investigation possibilities to a number of effects. For instance, the early studies did not take into account the solvent effects while more recent studies do. Because of the importance of solvent effect for the study of biologically active molecules, the first investigations considering the solvent effect for each molecule or groups of molecules are mentioned in the next sections, and subsequent relevant applications are also discussed.

Among all the solvents considered, water is the most important because it is of major impact to all living organisms. In human adult body water constitutes up to 70%. It is the major component of most human body parts. Mitchell *et al.* [372], reported that the brain and heart contained about 73% of water, and the lungs are composed of about 83% water. The skin is composed of 64% water, muscles and kidneys contain nearly 79% of water. Even the bones were found to be watery by 31%.

3.6.2.1. Conformational studies of cinchona alkaloids (CAs)

3.6.2.1.1. Studies considering the CAs as a class of compounds

The cinchona alkaloids comprise quinine (Fig.3.8, formula $C_{20}H_{24}N_2O_2$, absolute configuration 1S, 3R,4S,8S,9R and an OCH_3 group at C16); quinidine (formula $C_{20}H_{24}N_2O_2$, absolute configuration 1S,3R,4S,8R,9S and an OCH_3 at C16); cinchonidine (formula $C_{19}H_{22}NO_2$ and absolute configuration 1S,3R,4S,8S,9R); cinchonine (formula $C_{20}H_{24}N_2O_2$ and absolute configuration 1S,3R,4S,8R,9S); epiquinine (formula $C_{20}H_{24}N_2O_2$, absolute configuration 1S,3R,4S,8S,9S and an OCH_3 group at C16); epiquinidine (formula $C_{20}H_{24}N_2O_2$, absolute configuration 1S,3R,4S,8R,9R and an OCH_3 at C16); epicinchonine (formula $C_{20}H_{24}N_2O_2$, absolute configuration 1S,3R,4S,8R,9R); and epicinchonidine (formula $C_{19}H_{22}NO_2$ and absolute configuration 1S,3R,4S,8S,9S). The two relevant rotatable bonds in cinchona alkaloids are those linking the quinuclidine and quinoline moieties, i.e. C8–C9 and C9–C10 (Fig.3.8). The rotation

around these bonds is hindered by protonation of the amine function. The characteristics of these two bonds depend also on the charge state of the molecule, and on the presence of another interacting molecule or a counter-ion [373–375]. A number of early studies combine experimental determinations and molecular mechanics (MM) with empirical potentials, semi-empirical electronic structure methods or *ab initio* methods with small basis sets, which limits the accuracy of computed results [376]. Prelog and Wilhelm suggested a configuration for the Cinchona alkaloids in 1954 on the basis of experimental information [377]. Dijkstra and co-workers investigated “the ground state and conformational behaviour of native and substituted cinchona stereoisomers in different solvents and the states of metal complexation or ionization using NMR spectrometry and X-ray crystallography as well as computational methods” [378–381].

A 1999 study of the molecular electronic properties of CAs using an *ab initio* quantum method with the 3-21G basis set [382] aimed at providing a profile of the electronic characteristics necessary for potent antimalarial activity to be used in the design of new antimalarial and to gain insight into the mechanistic path for antimalarial activity. The authors [382] suggested that, for a good antimalarial activity, “the alkaloids should contain a hydroxyl group of sufficient acidity and quinoline and aliphatic nitrogen atoms that are not too basic”. Furthermore, they suggested that a potent antimalarial CA has a dipole moment of 2.2 D or less, an electric field pointing from the aliphatic nitrogen atom towards the aromatic ring, an acidity equivalent to at least 34.7 kcal/mol of positive potential by the hydroxyl proton, a basicity of negative potential by the aliphatic nitrogen atom no more negative than –64.4 kcal/mol, a proton affinity of the aliphatic quinuclidine nitrogen atom of 200 ± 5 kcal/mol, and a comparatively moderate electron affinity [382]. Having only some of these profile features is insufficient for high antimalarial activity, as showed by the quinine metabolite [382]. The threo alkaloids differ from the erythro alkaloids by a shorter distance between N1 and the hydroxyl oxygen O20 ($N1 \cdots O20$), a larger distance between N1 and the C11 atom of the quinoline ring, and a different orientation of the quinuclidine ring with respect to the quinoline ring as defined by the H24–C9–C10–H23 dihedral angle. For instance, the distance between N1 and O20 is 3.14 – 3.19 Å and 2.82 – 2.89 Å for erythro and threo alkaloids respectively. The distance between N1 and C11 is ~ 3.9 Å for the erythro and ~ 5.3 Å the threo alkaloids. The H24–C8–C9–H23 dihedral angle is either –79.2 to –81.9° or 79.8 to 92.1° for the erythro alkaloids, while it is 169.2 to 174.7° the threo alkaloids. The different electronic features

of O20–H22 and of N1 in different compounds (due to the peculiar molecular environment) seemed to play a key role for antimalarial potency of CAs, mostly by controlling the ability of these groups to form effective intermolecular H-bonds. Both steric and electronic factors seem to be affecting the H-bonding capacity of the inactive epi alkaloids [382]. Many studies focused on specific molecules or pairs of molecules; their approaches and results are summarized in the next subsections.

3.6.2.1.2. Studies on quinine and quinidine

Quinine and its stereoisomer quinidine are the object of most studies on individual CAs. Using Molecular Mechanic (MM2P [377, 383]), Dijkstra and co-workers found three main conformations corresponding to different torsion angles for the rotations around the C8–C9 and C9–C10 bonds; they denoted them as Q1, Q2 and Q3, with Q1 being the most stable [378, 381]. They classified the major types of shapes as “open” and “closed” [380, 381], with Q1 corresponding to the “open” shape and Q2 to the “closed” one. An MM2 [384] conformational study [381, 385] also identified three conformers, corresponding to those reported in [378, 380]. The Q1 conformer was found to correspond to the crystal structure of quinine and to form intermolecular H-bonds with surrounding molecules [381, 386]; the authors presumed that Q1 is the active conformer and it interacts with the receptor site through intermolecular H-bonds. A conformational study of quinine using MM as well as the AM1 [387] and PM3 [388] semi-empirical methods identified six minima on the multidimensional potential energy surface (PES), corresponding to six distinct conformers, and calculated also the transition states (TS) between conformers. The six conformers were denoted with the letters A, B, C, D, E and F. Conformers D, E and F correspond respectively to the conformers Q1, Q2 and Q3 of [377] and are the lowest-energy ones, with energy gaps less than 2kcal/mol. The authors also noticed that the values of some torsion angles from ^1H -NMR spectra did not coincide with the calculated values *in vacuo*, which indicates that the conformation of the quinuclidine ring in solution is somehow halfway between the crystallographic one and the one *in vacuo*; this stresses the necessity of including solvents effects (through calculations in solution) for the conformational study of quinine-like compounds.

Conformational studies of the dihydroquinine molecule are reported in [377] and in [379] with similar results and the same previously described conformers identification (Q1, Q2, Q3). A later study [389] utilizing a combination of variable temperature NMR, circular dichroism spectroscopy and MM calculations identified four conformers that the authors called anti,open (80–90% population), syn,closed (10–20%), syn,open and anti,closed; the energy barrier between anti,open and syn,closed was 8.3 kcal/mol in ether solution. For instance, the model shown in Fig.3.8 would correspond to the open conformer.

A conformational study of CAs using a PM3 semi-empirical method [390] analysed the results in terms of syn/anti, open/closed/hindered and $\alpha/\beta/\gamma$ based on the torsion angles C11–C10–C9–C8, C10–C9–C8–N1 and H22–O20–C9–C8 respectively. It highlighted the importance of the IHB N1...H22 and the quasi-enantiomeric relationships between quinine-quinidine and epiquinine-epiquinidine. The computational results also showed an important structural difference between quinine and epiquinine, and between quinidine and epiquinidine as quinine and quinidine adopt anti-closed- α conformations, while epiquinine and epiquinidine adopt anti-open- β and anti-open- α conformations respectively.

The analysis of the results of a study using the B3LYP/6-31+G(d,p) method to investigate the conformational preferences of quinine and quinidine [375] focused on three dihedral angles (C11–C10–C9–C8, C10–C9–C8–N1 and N1–C8–C9–O20) as main reference. The values of C11–C10–C9–C8 and C10–C9–C8–N1 define the closed or open nature of the conformer [376]. C10–C9–C8–N1 is 50° in the closed conformer and it is close to 150° or 290° in the open one [375]. Information about the *cis* or *trans* orientation of the methoxy group relative to the C10–C9 bond was added to previous nomenclature (for instance, the model shown in Fig.3.8 corresponds to a *cis* conformer). Information about the C8–C9–O20–H22 dihedral angle was also added [375] using the α , β and γ letters for the values of +60°, -60° and 180° respectively. The relative orientation of the O20–H22 with respect to the tertiary amino group is described by the values of N1–C8–C9–O20 and C8–C9–O20–H22 and it indicates whether there can be an IHB or not. The methoxy substituent of the quinoline ring has a *cis* orientation for the most stable conformer. The combinations of all the relevant conformational features for quinine lead to conformers' names

such as *cis* - γ - open, *cis* - α - open, *cis* - γ - closed and *trans*- γ -open, with *cis* - γ -open being the most stable conformer (72% population). Since [375] considered only geometries in which H22 is oriented to the opposite side with respect to N1, with the O and N atoms in an almost gauche position (N1–C8–C9–O20 angle about -83° or 179°), they inferred that there is no possibility of formation of an N1...H22 IHB. The most stable conformer of quinidine is also *cis*- γ -open conformer (78% population) with a C10–C9–C8–N1 angle of -153° . Actually, *cis*- γ -open is the most stable conformer for both quinine and quinidine not only *in vacuo*, but also in chloroform solution [375]. Fewer studies were performed for the others CAs; some of them were calculated together within studies focusing primarily on quinine and quinidine. They are summarized in the next sections.

3.6.2.1.3 Studies on cinchonine and cinchonidine

The first investigation of the behaviour of cinchonidine in different solvents [391] used the HF/6-31G(d,p) and DFT/B3LYP/6-31+G(d) levels and was combined with NMR experiments. The C11–C10–C9–C8 and C10–C9–C8–N1 torsion angles were considered the most important degrees of freedom identifying the relative orientation of the quinoline and quinuclidine moieties. The HF/6-31G(d,p) PES *in vacuo* showed six minima, corresponding to six conformers which were grouped into two sets ‘open’ and ‘closed’. In the minima, C11–C10–C9–C8 is either $-100 \pm 10^\circ$ or $90 \pm 10^\circ$, while C10–C9–C8–N1 can be of $60 \pm 5^\circ$, $150 \pm 5^\circ$, and $-50 \pm 5^\circ$. The dihedral angles were in qualitative agreement with those reported in [392] from MM2 and HF/3-21G calculations. Calculations in solution [391] used the Onsager reaction field model [393], were performed as single point calculations on the *in-vacuo* optimized geometries, considered four solvents – cyclohexane, chloroform, acetone and water – and found that the open form is the most stable conformer of cinchonidine in apolar solvents, while the closed form is considerably more stabilized in polar solvents: this is mostly due to their larger dipole moment. The stabilization of conformations of cinchonidine in solution is influenced by specific interactions such as H-bonding of the solvent to the quinuclidine N. This has a consequence that the open conformers in polar solvents become more stable than the closed conformers. These H-bonds are not feasible in the closed conformers because N1 is not easily accessible to the solvent. A study on the effect of protonation on cinchonidine, using the DFT/B3LYP/6-31G(d,p) combined with NMR experiments

[382] found that the protonation of cinchonidine seemed to obstruct the rotation around the C9–C10 and C8–C9 bonds, thus limiting the number of conformers. The conjugate base anion plays an active role in stabilizing the resulting structures.

3.6.2.1.4. Studies of *epiquinine* and *epiquinidine*

A semi-empirical (PM3) study of *epiquinine* and *epiquinidine* carried out together with a study of *quinine* [390] showed the presence of two conformers for each molecule. The lower energy conformer of *epiquinine* is an anti-open- β conformer having an N1...H22 IHB with 2.60 Å bond length and 108.5° bond angle. The second conformer of *epiquinine* is an anti-open- α conformer without IHB and a relative energy of 0.406 kcal/mol. The lower energy conformer of *epiquinidine* is anti-open- α , also without IHB, while the higher energy conformer is anti-open- β and has N1...H22 IHB (bond length 2.51 Å, bond angle 110.2°) and a relative energy of 0.358 kcal/mol.

3.6.2.2 Nicotinoids

The conformational preferences of nicotinoids have been the object of the several studies [351, 354, 394–409], most of which are on nicotine. H-bonding or cation-contact [345, 410, 411] are the main factor facilitating the interaction between the agonist and the nAChR and the N1...N8 distance plays a key role in establishing this interaction. Many experimental and theoretical studies examined the relative stabilities of different nicotine conformers [394, 396, 412–420]. Most of them focused on the three conformational features of nicotine: (i) the orientation of the methyl at N8 relative to the pyridine ring (*cis* or *trans*), (ii) the relative orientation of the two rings and (iii) the conformation of the pyrrolidine ring.

Like for the other compounds, early computational studies were done at insufficiently sophisticated levels of theory [395–399, 417, 420] and were conducted only *in vacuo*, without considering the possible effects resulting from the interaction with a solvent. The results were similar to the findings from NMR studies [419], with the methyl at N8 having *trans* orientation and the two rings being approximately perpendicular to each other in the most stable conformer.

A 2000 study [399] investigated six “species” of nicotine (the *cis* and *trans* stereoisomers of the unprotonated, monoprotonated and deprotonated forms) using AM1, MM, HF, MP2 and DFT/B3LYP, with the 6-31G(d,p) basis set *in vacuo* and two models available in SPARTAN for water solution. One of them was an explicit model using TIP4P (Planar four-site Interaction Potential) [421] and OPLS (Optimized Potentials for Liquid Simulations) and the other was a continuum method (SM5.42R) [422–425]. The results show that, for all the protonation states, the *trans* species are more stable than the *cis* ones. The monoprotonated species are physiologically important; their N1...N8 distance in the *trans* monoprotonated species resulted 4.7 Å [398] which is close to the value obtained in earlier work (4.8 Å [426]).

Several studies have investigated the molecular structure and spectroscopic properties of (–)-S-anabasine [349, 352–354, 427]. The earlier investigations did not take into account the presence of stereoelectronic effects and the effect of a solvent medium. A 2015 conformational study *in vacuo* and in solution using MM, DFT and vibrational circular dichroism [428] identified eight conformers (m01, m02,..., m08) differing by the piperidine ring conformation, the axial or equatorial arrangement of the N1–H13 and C2–C7 (Pyr) bonds as well as the relative orientation of the two rings. The two most stable conformers were both characterized by the equatorial orientation of N1–H13 and C2–C7 Pyr and differed only by the relative orientation of the two rings. Electronic structure and NBO (Natural Bond Orbitals) of the eight conformers showed that steric and electrostatic factors largely determine the conformational distribution *in vacuo*. Calculations in solutions performed with the Polarizable Continuum Model (PCM, [178–183]) considered two solvents: CCl₄ (carbon tetrachloride) and DMSO (dimethyl sulfoxide). The solvent effect on the calculated molecular geometries or the conformational energy profile are greater for the more polar DMSO. The populations of m03 and m04 increase slightly with respect to the *in vacuo* calculations (whereas they increase more in DMSO); this is consistent with the general trend for which solvents slightly lower the energies of higher-energy conformers. The authors [428] inferred that relative stabilities and abundances of the conformers of (–)-S-anabasine are mostly controlled by electrostatic effects.

3.6.2.3. Pyrazole alkaloids (PA)

Only few pyrazole alkaloids (i.e. alkaloids containing a pyrazole group) exhibit an antimalarial activity [262]. A conformational study of six pyrazole alkaloids (withasomnine, newbouldine and their para-hydroxy and para-methoxy derivatives) was carried out *in vacuo* and in three solvents (chloroform, acetonitrile, and water) at the HF, DFT/B3LYP and MP2 levels using different basis sets [327], and the PCM model for calculation in solution. Adducts with explicit water molecules also were calculated at the HF level, to gain a better understanding of the situation in water solution). The energies of withasomnine and newbouldine were influenced by the mutual orientation of the pyrazole and benzene rings, although with an energy difference of less than 0.3 kcal/mol for all the calculation methods used. The para-hydroxy and para-methoxy derivatives show preference for a coplanar orientation of the OH and OC bonds with the ring to which they are attached. As long as the OH is planar, its orientation toward one or another side does not involve experimentally relevant energy differences in the para-hydroxy derivatives: the energy difference is less than 0.1 kcal/mol, which indicates that the presence of the pyrazole ring does not influence the orientation preferences of the phenol OH. Similarly, the different orientations of the methyl of the OCH₃ group in para-methoxy derivatives do not involve significant energy differences [327]. ΔG_{solv} was negative for all the solvents considered, with a smaller magnitude in acetonitrile, greater in chloroform and greatest in water. In the calculated adducts of withasomnine and newbouldine, the water molecules prefer an arrangement in the vicinity of the N atoms of the pyrazole system. For the derivatives (para-hydroxy and para-methoxy), the water molecules prefer an arrangement in the vicinity of the N atoms as well as in the vicinity of the substituents (OH and OCH₃ respectively). The molecule –water interaction energy increases as the number of water molecules in the adduct increases. The presence of a water molecule bridging two water molecules attached to the central molecule tends to stabilize the adduct. The magnitude of ΔG_{solv} for the adducts decreases as the number of water molecules in the adduct increases [327].

3.6.3. Interaction and docking study

Beside its biological activities, quinine is also used for analytical purposes as a selector in chromatography and also in capillary electrophoresis [429–431].

The Chiral Stationary Phase (CSP) is as quinine-based chiral stationary phase. A study considered CSP as selector and the enantiomeric 3,5-dinitrobenzoyl derivative of leucine as selectand and focused on the type of interactions between the selector and the selectand using MacroModel 5.5 [432]. Three type of interactions were found; the π -stacking interaction between the aromatic ring of quinine and that of the selectand; the electrostatic interaction between the polar part of leucine and the polar part of the quinuclidine moiety; and the steric repulsion for the backyard part of quinine [433]. Quinine can make a π -interaction with the aromatic part of the selectand and electrostatic interaction with the polar part and quinine has also enantioselectivity.

The interaction of alkaloids isolated from *Sarcococca saligna* with the active site of the acetylcholinesterase (AChE) enzyme was investigated by means of a molecular dynamics simulation [371]. The authors of this work tried to understand the interaction of these alkaloids in the active site of AChE from *Torpedo californica*. The hydrophobic interactions inside the aromatic gorge area were identified as the main stabilizing factor in the enzyme-inhibitor complexes of these alkaloids. According to the molecular dynamics simulation of the predicted complex, the enzyme structure was not altered by the ligand binding but its flexibility at the bottleneck was reduced.

3.6.4. Computations to confirm experiments

Ying-Tong Di and co-workers isolated a new hexacyclic alkaloid, calydaphninone, having a 4-azatricyclo [5.2.2.0.^{1,4}] undecan moiety, from the leaves and twigs of *Daphniphyllum calycillum* Benth (Daphniphyllaceae) and elucidated its structure by crystallographic and spectral methods [434]. The conformations of calydaphninone in solution were analysed based on experimental results and DFT/B3LYP/6-31G(d) calculations. The authors found that the conformer of calydaphninone in crystal and in solution was not in agreement with the ROESY spectrum. The

computational study helped in interpreting the experimental information and helped to understand the reasons for the lack of agreement between those two experimental results.

The calculations revealed three low energy conformations of calyphnionone which were distinguished as chair, twist-chair (CTC), chair-chair (CC), and boat, half-chair (BHC) according to conformational differences in seven-membered rings (C1, C2, C5–C8, and N) and (C5, C6, C8–C12). The CTC have a C14 taking R-configuration while the CC conformer had the nitrogen lone pair taking an R-configuration and C14 taking a β -configuration and BHC have both the nitrogen lone pair and C14 taking a β -orientation. The CTC conformer is in good agreement with the X-ray crystal structure of calyphnionone, the CC is the lowest energy conformer and BHC is the highest energy conformer. The calculations also showed two transition states (TS1 and TS2) [435, 436] corresponding to the CTC-CC conversion and to the CC-BHC conversion. The free energies of TS1 and TS2 against the most stable conformer CC were 10.3 and 8.1 kcal/ mol, respectively. Therefore, the incidence of comparatively rapid interconversion of CC to CTC and BHC is a logical process in solution at room temperature, which leads to some broad peaks in NMR spectra.

Six alkaloids, erysotrine (1), erysodine (2), erythraline (3), erytharbine (4), erysotrine Noxide (5) and epierythratidine (6) were isolated from *erythrina fusca* Lour [437]. Their NMR spectra (^1H and ^{13}C) were assigned using 2D experiments (HH COSY, HMQC, HMBC and HH NOESY). The authors found that the structure of alkaloids (1) – (5) were in agreement with the literature [438, 439] but this was not the case for the structure (6). The structural reassignment of this alkaloid, epierythratidine, was done by means of experimental and theoretical NMR studies. A molecular dynamic (MD) conformational search was performed by Chini *and* co-workers [440], followed by a GIAO/DFT (Gauge Invariant Atomic Orbitals) calculation on the minimized energy structures. The computational results provided an excellent agreement with the experimental ^{13}C chemical shifts and a fair agreement with the experimental V coupling constants. The computational results confirmed and supported the experimentally derived assignments and the overall structure of epierythratidine (6).

Four compounds identified as pure– alkaloids; the harmalacidine (1), the harmine (2), the peganine (3) and the vasicinone (4) [370] were isolated from *Peganum harmala* seed and tested against cancer cell lines for antiproliferative and cytotoxic activity [441]. The results showed that vasicinone, harmine and harmalacidine inhibited the proliferation of Jurkat, clone E6-1 cell line with a significant cytotoxic effect. DFT/B3LYP/6-31G(d) calculations were used to analyze the electronic properties such as the HOMO, LUMO, the energy difference gap between E_{HOMO} and E_{LUMO} and the dipole moment for the stable structure of each compound. The results showed that the electronic properties are well correlated with experimental properties.

CHAPTER 4

OVERVIEW OF COMPUTATIONAL METHODS USED

This chapter gives an overview of the different computational methods used in the work presented here to elucidate the electronic structures, conformational structures and relative stabilities, other molecular properties and solvation free energies of 33 monomeric and two dimeric naphthylisoquinoline alkaloids with antimalarial activity. In addition, the practical details regarding inputs preparation, calculations and specific instructions to get desired computational information are highlighted.

4.1. Choice of Computational Methods

On selecting the computational methods for a specific study, one needs to consider computational costs and find the best compromise between affordability in computational costs and desired accuracy of the results. Computational costs are determined by the choice of the theoretical method and the basis set [442], and by the molecule's size. There is no general rule to identify the best choice and, therefore, one tries to search for the best compromise between costs and accuracy according to the characteristics of the molecular system to be studied [443].

The size of the molecules considered in this study enables the use of rather sophisticated electronic structure methods that might be too expensive for bigger molecules. The naphthylisoquinoline alkaloids considered here are between medium and large size. The monomeric structures can be considered as medium size and the dimeric structures are close to large size. The monomeric structures have one unit and the dimeric ones two units, with each unit containing naphthalene and isoquinoline moieties linked by a C,C biaryl axis. The bonds between different moieties are rotatable bonds.

Considering affordability in view of the size of these molecules, this study used the two following

levels of theory: the *ab initio* method, Hartree-Fock (HF) [63, 66, 70, 82–84] and the Density Functional Theory (DFT) [63, 66, 70, 120, 122, 126, 133] with the B3LYP functional [120, 122]. HF is a moderately cheap quantum mechanical method which can yield reasonable information regarding conformational analysis. Previous studies on other molecules [327, 444] showed that HF can successfully handle intramolecular hydrogen bonding (IHB) and yields HOMO–LUMO energy gaps approaching those of experiments. DFT is an alternative method to wavefunction approaches, which is often used in conformational searches because it takes into account part of the correlation effects at a comparatively low cost. Among the numerous functionals available for the DFT framework, B3LYP [120, 122] is the most widely employed [129]. It can provide better quality results in combination with basis sets containing diffuse functions [59–62, 327, 444, 445]. The primary problem with this hybrid density functional is the presence of the self-electron repulsion, which has been identified as a source of errors [133].

The double zeta basis (as 6-31G) is known to bring acceptable flexibility to the molecular wavefunction leading to a good description of bonds between atoms [70, 96, 99]. The p functions added to hydrogen atoms and the incorporation of diffuse functions in the basis set increase the ability of the molecular total wavefunction to describe hydrogen bonds and long range interactions in the molecular system considered. The 6-31G(d,p) basis set is used for HF calculations and the 6-31+G(d,p) basis set for DFT calculations.

The main drawback of the more affordable HF method is that it does not consider electron correlation. Therefore, the electronic energy obtained with HF may be far away from the true energy. This is the reason for using also other methods, as DFT for the current study.

To model the solvation effects of the naphthylisoquinoline alkaloids considered in this work, the polarizable continuum model (PCM) was used, as implemented in the Gaussian 03 program package. In this approach, the solvent is not considered as individual “explicit” solvent molecules, but as a continuum polarizable dielectric (section 2.4.3.). Its dielectric constant is used as the main characteristic property to describe the bulk effect of the solvent. Solvents can be categorized with respect to the magnitude of their dielectric constants. The conformational

preferences of the solute molecule are influenced by the polarity of the solvent molecules and the type of interactions that they establish with the solute molecule.

4.1.1. Computations *in vacuo*

Each molecule was first studied *in vacuo* (gas phase), because a study *in vacuo* is preliminary for any other study. All the molecules have been calculated *in vacuo* with full geometry optimization considering the two levels of theory described previously. The modified GDIIS algorithm (opt=(gdiis) instruction) was used for all the optimisation calculations, because it is more convenient for non-small molecules [446]. All the calculations were performed using the Gaussian03 package [192].

Vibrational frequencies (harmonic approximation) were calculated to verify that the stationary points from optimization results corresponded to true minima, to obtain the zero-point energy (ZPE section 2.3.2) corrections and to evaluate the red shifts caused by the various IHBs (section 2.3.2)

For monomeric naphthylisoquinoline alkaloids, the harmonic vibrational frequencies were calculated for all the conformers of the 33 molecules *in vacuo* at the HF/6-31G(d,p) and DFT/B3LYP/6-31+G(d,p) levels. For the dimeric naphthylisoquinoline alkaloids (jozimine A₂ and mbandakamine A), frequency calculations were calculated *in vacuo* at HF/6-31G(d,p) for all the conformers, because of the large size of the latter molecules.

The *Freq Test* keyword is used for frequency computations. Since frequency calculations are usually performed as single-point calculations on the *in-vacuo*-optimised geometries, the keyword for “single point” is added, namely “test” if the basis set does not contain diffuse functions and the “scf=tight” if the basis set contain diffuse functions. In this work, *Freq Test* is used for HF calculations and *Freq scf=tight* is used for DFT calculations. The vibrational frequencies obtained from frequency calculations need to be scaled by an appropriate factor, for the values to be closer to experimental values. The scaling factor is different for different levels of theory and different basis sets. The frequency values were scaled by 0.9024 [447] and 0.9857 [448], respectively, for HF/6-31G(d,p) and DFT/B3LYP/6-31+G(d,p). The analysis of data focused on the vibrational

frequencies, also because of their importance to evaluate the strength of hydrogen bonds through their red-shifts. ZPE corrections to the energy were also considered.

4.1.2. Computation of solvent effects

Calculations in solution were performed after the calculations *in vacuo* using the results obtained from the calculations *in vacuo* as inputs for calculations in solutions. Since the PCM re-optimisation in solution requires more computational time than the calculation *in vacuo*; the calculations in solution were performed as single point (SP) calculations on the *in vacuo* optimised results at the same levels of theory.

Re-optimisation in solution could provide information on geometry changes in the solute molecule brought about by the solvent [449]. Although SP calculations cannot provide information on these geometry changes, they can provide reasonable information on the energetics, such as the conformers' relative energies in solution and the energy aspects of the solution process (the free energy of solvation, ΔG_{solv} , and its components) [450]. Anyway, the change in the molecular properties (dipole moment and HOMO-LUMO gaps) in solution with respect to *in vacuo* can elucidate the effect of the three solvents considered on the molecules considered.

The default settings of PCM calculations as implemented in the Gaussian03 package [192] were used. These comprise the Integral Equation Formalism model (IEF) [181, 182] and an average tesserae area of $0.200 \text{ \AA}^2$ for the description of the surface of the cavity around the solute. The united atom topological model applied on radii optimized for HF/6-31G(d) level, denoted UAHF radii, were utilized for the interlocking spheres around each atom of the solute molecule (section 2.4.3). The only difference with the PCM default settings was to include the SCFVAC and the radii = UAHF keywords, which allow the consideration of the gaseous phase and the application of the united atom topological model on the radii optimized at HF/6-31G(d). The SCFVAC option was selected to obtain more thermodynamic data in the outputs.

Three solvents were chosen for this study, namely chloroform, acetonitrile and water and they are described in section 2.4.3. They include polar solvents as well as a non-polar solvent, in order to

cover a wide range of polarity of the different media and also to mimic the environments present in a living organism.

4.2. Preparation of Inputs

The inputs for the calculations *in vacuo* were prepared with the help of Gauss View program [192]. In order to gain in computation time, the optimized geometries obtained from HF calculations were used as inputs for DFT calculations. It is well known that HF contributes in the calculation of the exchange correlation in DFT/B3LYP [122, 133].

The rotation scans of relevant rotatable bonds were initially performed to identify potential energy minima. To obtain adequate information, each scan considered 24 steps (15° change of the dihedral angles in each step). The `opt = modredundant` keyword was used in the route section of the input (flexible scan), and the information about the pace and the number of steps was given in the appropriate section, i.e., after the coordinate matrix. The results of the rotation scans for each molecule are given in the respective chapters. The rotations of the hydroxyl groups were also considered in order to find other minima.

According to standard practice, the optimized geometries obtained from calculations *in vacuo* were used as initial geometries for PCM calculations in solution.

4.3. Presentation of Results

The main aspects which need to be mentioned about the presentation of the obtained results are the units of measure and the acronyms used in, above all those that are not standard, but are introduced specifically for this study.

4.3.1. Units used

In the Gaussian outputs, most values are given in atomic units. Thus, most energy values are given in hartrees. The values of ΔG_{solv} and its components (G_{el} and $G_{\text{non-el}}$) from PCM calculations are given in kcal/mol.

On reporting results in this work, all the energy values (conformers' relative energies, HOMO-LUMO energy gaps, ΔG_{solv} , etc.) are given in kcal/mol, because of the wide use of this unit. To convert a value in hartree to a value in kcal/mol, the value in hartree is multiplied by 627.509 kcal/(mol.Ha). For this reason, all the energy values obtained utilising this conversion factor will have a maximum of 3 decimal positions. Energy values from thermodynamic data expressed in kcal/mol in Gaussian outputs maintain the same number of decimal figures (two decimal figures) as in the output.

Bond distances are in angstroms ($1 \text{ \AA} = 10^{-10} \text{ m}$) and all the bond distances values will have a maximum of 3 decimal position. Bond angles are given in degrees and their values will have one decimal position. Dipole moments are given in Debye (D).

4.3.2. Non-Standard Acronyms Utilised

Some non –standard acronyms have been introduced in place of longer standard acronyms, for reason of simplicity and to enable better space organisation in tables and figures. HF/6-31G(d,p) is denoted as HF and DFT/B3LYP/6-31+G(d,p) is denoted as DFT+. For conciseness sake, the media are denoted with the following acronyms on reporting values: 'vac' (vacuum), 'chlrf' (chloroform), 'actn' (acetonitrile), and 'aq' (water). The name of the molecules are also denoted with acronyms to shorten the name for reason of simplicity and the meaning of the acronym for each molecule will be explained in the respective chapter.

For better readability of the text, all the tables and the most bulky figures (such as the shapes of the frontier molecular orbitals) are reported at the end of the chapter. For all the figures that involve more than one page, the captions of the figures are put on top, whereas, for the figures occupying not more than one page, the captions are put at the bottom. Tables and figures are number with two digits system so that the numbering starts for each chapter, for instance the table 5.2 is the table 2 in chapter 5. For the tables and figures that are at the end of chapters, the numbers will be preceded by a K to make their identification easy while reading the text. For example, figure 5K3 is the third figure at the end of chapter 5. The references are numbered in the order, in which they appear throughout the thesis but not for individual chapter.

CHAPTER 5

COMPUTATIONAL STUDY OF MONOMERIC NAPHTHYLISOQUINOLINE ALKALOIDS *IN VACUO*

This chapter presents the results obtained from the calculation of 33 monomeric naphthylisoquinoline alkaloids *in vacuo*. These results were presented at the QUITEL 2015 conference [H] and subsequently published [58].

5.1. Naming of the conformers

The selected 33 naphthylisoquinoline alkaloids in this work have shown good antimalarial activity and they are sufficiently representative for the whole class of naphthylisoquinoline alkaloids. They all have C,C coupling between the naphthalene and isoquinoline moieties, and they differ by aspects such as different positions of the bond linking the two moieties and different positions of OH groups. They are listed in Table 5.1 and their structures are shown in Fig. 5.1.

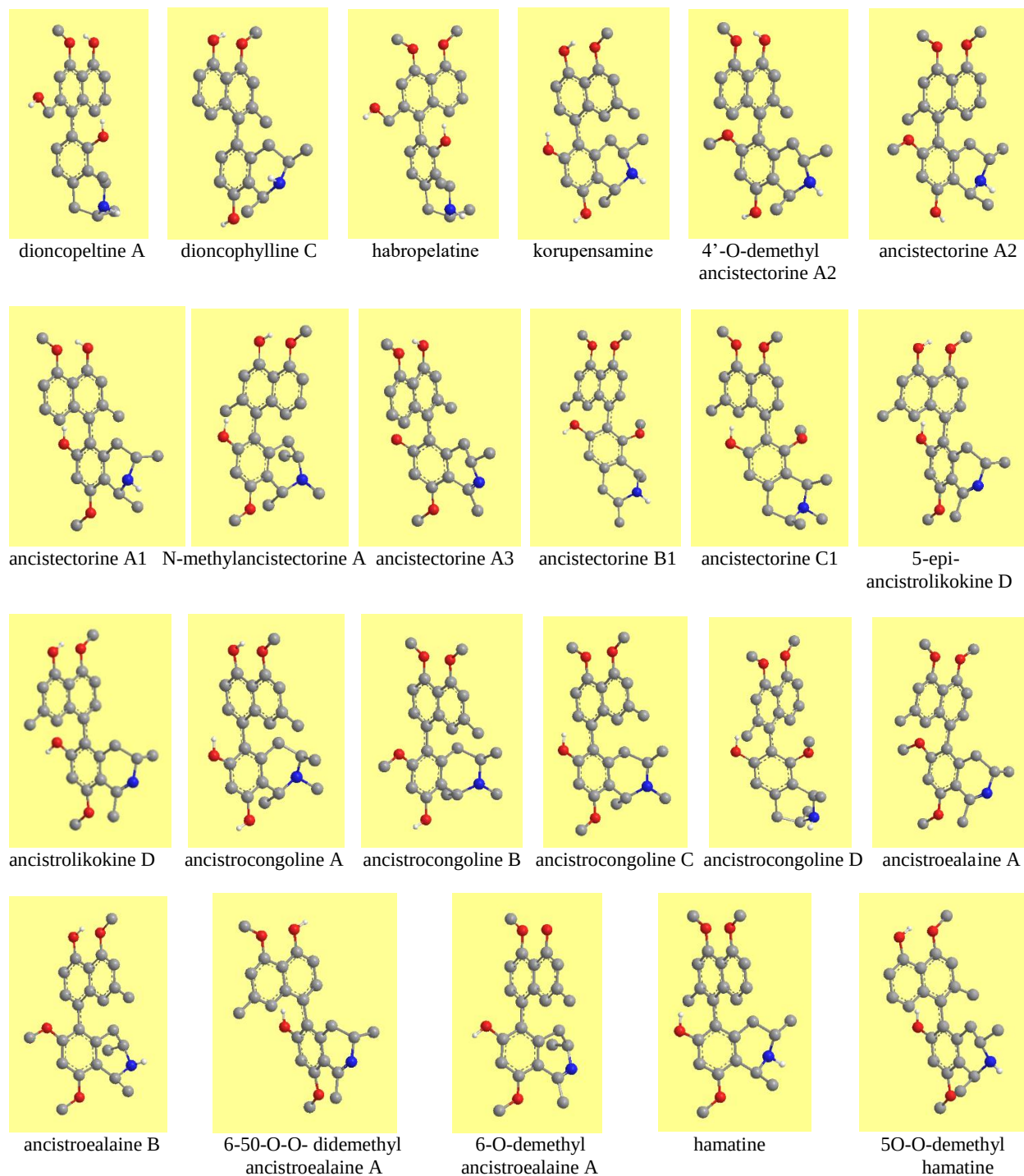
Given the length of the names of the naphthylisoquinoline alkaloids studied in the present work, they are denoted by acronyms in the rest of the text. These compounds are grouped into two categories depending on the atoms involved in the coupling of the naphthalene moiety and the isoquinoline moiety. Figure 5.2 illustrates the two types and shows their atom numbering. The acronyms of the compounds in which the naphthalene moiety is attached at position 5 of the isoquinoline moiety start with “NHQ5,” and the acronyms of the compounds in which the naphthalene moiety is attached at position 7 start with “NHQ7.” NHQ5 or NHQ7 is followed by numbers distinguishing individual compounds, as shown in Table 5.2. Table 5.3 lists different substituents present for each molecule. Acronyms are repeated to facilitate comparison.

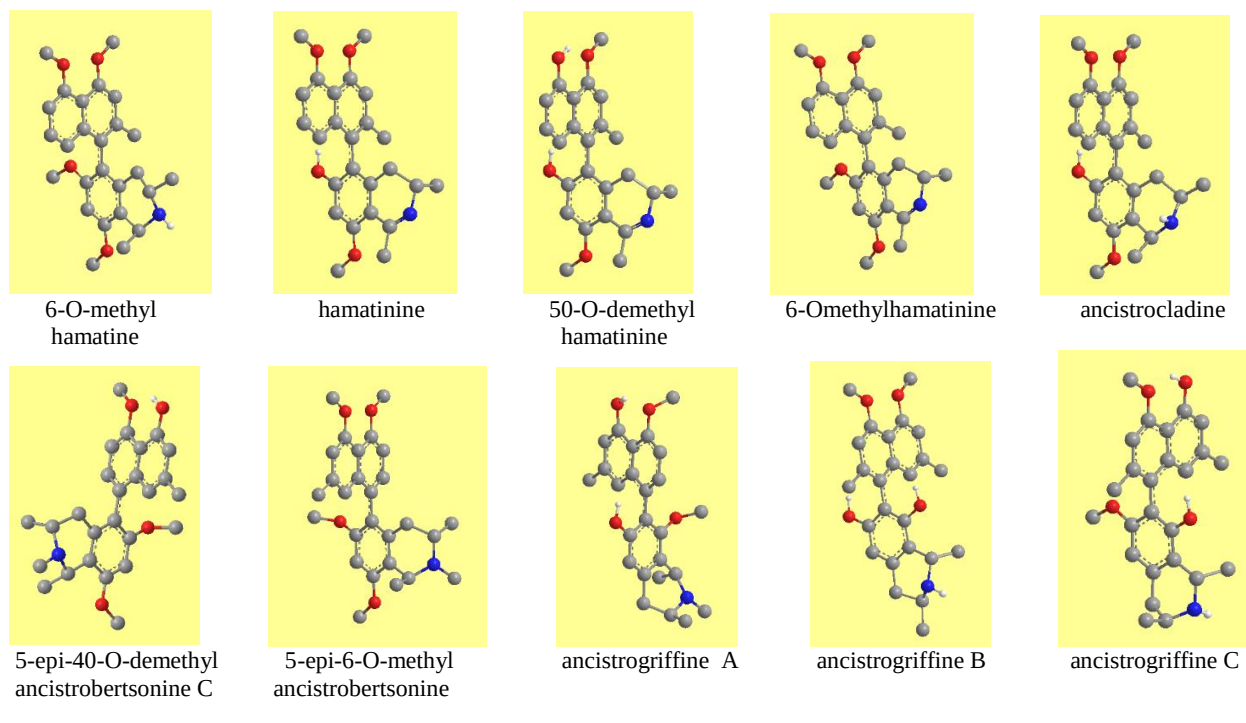
Table 5.1. List of naphthylisoquinoline alkaloids considered in this work, their names and their source. They are listed in alphabetic order and grouped according to the plant source.

Names of naphthylisoquinoline alkaloids	Plant from which they were isolated	reference
hamatinine, 6'-O-methylhamatinine	<i>Ancistrocladus cochinchinensis</i>	[451]
ancistrocongoline A, ancistrocongoline B, ancistrocongoline C, ancistrocongoline D, korupensamine, 5-epi-4'-O-demethylancistrobertsonine C, 5-epi-6'-O-methylancistrobertsonine, 5'-O-demethylhamatinine, 5'-O-demethylhamatine, 6'-O-demethylancistroealaine A, 6,5'-O,O-didemethylancistroealaine A,	<i>Ancistrocladus congolensis</i>	[452,453]
ancistroealaine A, ancistroealaine B	<i>Ancistrocladus ealaensis</i>	[48]
ancistrogriffines A, B, and C	<i>Ancistrocladus griffithii</i>	[454]
hamatine, 6'-O-methylhamatine	<i>Ancistrocladus hamatus</i>	[455, 456]
korupensamine A	<i>Ancistrocladus korupensis</i> ,	[56,57, 457–459],
ancistrolikokine D	<i>Ancistrocladus likoko</i>	[460]
ancistectorine A1, ancistectorine A2, ancistectorine A3, ancistectorine B1, ancistectorine C1, N-methylancistectorine A1, 4'-O-demethylancistectorine A2, 5-epi-ancistrolikokine D,	<i>Ancistrocladus tectorius</i>	[42,461];
dioncopeltine A, dioncopylline C, habropelatine A	<i>Triphyophyllum peltatum</i>	[34, 35]

Figure 5.1. Structures of the monomeric molecules investigated in this study

The H atoms attached to C atoms are not shown to better highlight the molecular structures.





Intramolecular hydrogen bonds (IHBs) of the O–H $\cdots$ O type are the most important interactions stabilizing conformers, but other interactions (O–H $\cdots\pi$, C–H $\cdots$ O) also proved to have significant influence. Individual conformers are denoted with acronyms providing information on the intramolecular interactions present by using different letters for different interactions. The letter/s denoting the interactions follow the part of the acronym denoting the compound (the parts listed in Table 5.2).

The presence of an O–H $\cdots$ O IHB between groups attached to the naphthalene moiety is denoted with the letter “a” if the O–H is attached to C15 and “b” if the O–H is attached to C14. The conformers having O–H $\cdots\pi$ interaction are denoted with the letter “d” if the donor O–H is attached to C6 (O22–H29) in the isoquinoline moiety and with the letter “e” if the donor O–H is attached to C8 (O21–H25). The conformers with C–H $\cdots$ O interactions are denoted with the letter “x” and the conformers without any of these types of interactions are denoted with the letter “z.” The main combinations of interaction types are shown in Fig.5.3. Since, there can be only one IHB of each type in a conformer, the letters also indicate the total number of IHBs.

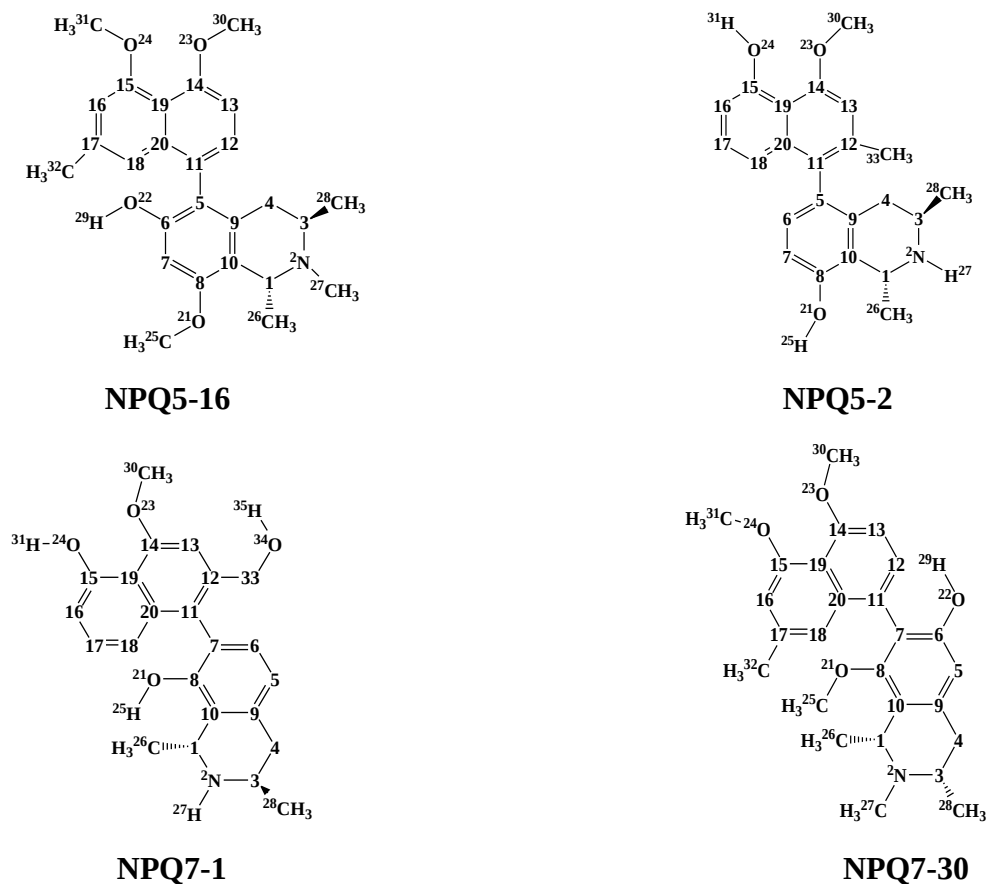


Figure 5.2. Atom numbering utilized in this work

The C atoms in the rings are represented only by the numbers denoting their positions. In order to facilitate comparison, the same atom numbering is utilized for atoms in corresponding positions in all the compounds studied; when needed, some numbers may be skipped for molecules in which some atoms are not present. Two examples for NPQ5 and two examples for NPQ7 are shown in the figure. For each pair, the molecule on the right has more atoms and shows the full numbering, the molecule on the left has less atoms and shows how some numbers may be skipped to maintain the same basic numbering for all compounds. The figures shows the main numbering criteria: e.g., number 26 is assigned to the CH₃ attached to C1; number 27 is assigned to the CH₃ or H attached to N2; number 28 is assigned to the CH₃ attached to C3; number 22 is assigned to the O attached to C6 and number 29 is assigned to the H or CH₃ attached to the O22; and so on. In some compounds, there is a CH₃ attached to C12, and then the number 33 is assigned to that CH₃. Only the H atoms attached to O or N are numbered separately, while the H atoms attached to a C atom are given the same number as the C atom.

Table 5.2. List of naphthylisoquinoline alkaloids studied in this work: their names, the type of naphthylisoquinoline alkaloids and the acronyms used to denote them in this study

Name	Type	Molecular formula	Acronym used in this work
dioncopeltine A	Dioncophyllaceae	C ₂₃ H ₂₅ NO ₄	NPQ7-1
dioncophilline C	Dioncophyllaceae	C ₂₃ H ₂₅ NO ₃	NPQ5-2
habropetaline A	Dioncophyllaceae	C ₂₄ H ₂₇ NO ₄	NPQ7-3
korupensamine A	Ancistrocladaceae-Dioncophyllaceae	C ₂₃ H ₂₅ NO ₄	NPQ5-4
ancistectorine A1	Ancistrocladaceae	C ₂₄ H ₂₇ NO ₄	NPQ5-5
N-methylancistectorine A1	Ancistrocladaceae	C ₂₅ H ₂₉ NO ₄	NPQ5-6
ancistectorine A2	Ancistrocladaceae	C ₂₅ H ₂₉ NO ₄	NPQ5-7
4'-O-demethylancistectorine A2	Ancistrocladaceae	C ₂₄ H ₂₇ NO ₄	NPQ5-8
ancistectorine A3	Ancistrocladaceae	C ₂₄ H ₂₅ NO ₄	NPQ5-9
ancistectorine B1	Ancistrocladaceae	C ₂₅ H ₂₉ NO ₄	NPQ7-10
ancistectorine C1	Ancistrocladaceae	C ₂₆ H ₃₁ NO ₄	NPQ7-11
5-epi-ancistrolikokine D	Ancistrocladaceae	C ₂₄ H ₂₅ NO ₄	NPQ5-12
ancistrolikokine D	Dioncophyllaceae	C ₂₄ H ₂₅ NO ₄	NPQ5-13
ancistrocongoline A	Ancistrocladaceae-Dioncophyllaceae	C ₂₄ H ₂₇ NO ₄	NPQ5-14
ancistrocongoline B	Ancistrocladaceae-Dioncophyllaceae	C ₂₆ H ₃₁ NO ₄	NPQ5-15
ancistrocongoline C	Ancistrocladaceae-Dioncophyllaceae	C ₂₆ H ₃₁ NO ₄	NPQ5-16
ancistrocongoline D	Ancistrocladaceae-Dioncophyllaceae	C ₂₅ H ₂₉ NO ₄	NPQ7-17
ancistroealaine A	Ancistrocladaceae	C ₂₆ H ₂₉ NO ₄	NPQ5-18
6,5'-O,O-didemethylancistroealaine A	Ancistrocladaceae	C ₂₄ H ₂₅ NO ₄	NPQ5-19
6-O-demethylancistroealaine A	Ancistrocladaceae	C ₂₅ H ₂₇ NO ₄	NPQ5-20
ancistroealaine B	Ancistrocladaceae	C ₂₅ H ₂₉ NO ₄	NPQ5-21
hamatine	Ancistrocladaceae	C ₂₅ H ₂₉ NO ₄	NPQ5-22
50-O-demethylhamatine	Ancistrocladaceae	C ₂₄ H ₂₇ NO ₄	NPQ5-23
6-O-methylhamatine	Ancistrocladaceae	C ₂₆ H ₃₁ NO ₄	NPQ5-24
hamatinine	Ancistrocladaceae	C ₂₅ H ₂₇ NO ₄	NPQ5-25
50-O-demethylhamatinine	Ancistrocladaceae	C ₂₄ H ₂₅ NO ₄	NPQ5-26
6-O-methylhamatinine	Ancistrocladaceae	C ₂₆ H ₂₉ NO ₄	NPQ5-27
ancistrocladine		C ₂₅ H ₂₉ NO ₄	NPQ5-28
5-epi-40-O-demethylancistrobertsonine C	Ancistrocladaceae	C ₂₆ H ₃₁ NO ₄	NPQ5-29
5-epi-6-O-methylancistrobertsonine	Ancistrocladaceae	C ₂₇ H ₃₃ NO ₄	NPQ7-30
ancistrogriffine A	Ancistrocladaceae	C ₂₅ H ₂₉ NO ₄	NPQ5-31
ancistrogriffine B	Ancistrocladaceae	C ₂₅ H ₂₉ NO ₄	NPQ7-32
ancistrogriffine C	Ancistrocladaceae	C ₂₅ H ₂₉ NO ₄	NPQ7-33

The same atom numbering is utilized for all the molecules of each group to facilitate comparisons. Figure 5.2 shows the atom numbering schemes for four representative molecules (two molecules for the NHQ5 group and two molecules for the NHQ7 group), and the caption explains the numbering criteria applying to all the molecules of a given group. In order to maintain the correspondence between numbering and positions across molecules, some numbers may be skipped when certain atoms are not present in a given molecule. The atom numbering of other molecules are given in figure 5 K1.

Table 5.3. List of naphthylisoquinoline alkaloids studied in this work: their names, the substituent on the ring skeletons and the acronyms used to denote them in this study

Molecule	Acronym denoting it in this work	Substituents on the ring skeletons
dioncopeltine A	NPQ7-1	OH at C8, C15 and C22, OCH ₃ at C14, CH ₃ at C3 and C1 H at N
dioncophilline C	NPQ5-2	OH at C8 and C15, OCH ₃ at C14, CH ₃ at C1, C3 and C12, H at N
habropetaline A	NPQ7-3	OH at C8 and C22, OCH ₃ at C14 and C15, CH ₃ at C3 and C1 H at N
korupensamine A	NPQ5-4	OH at C8,C6 and C14, OCH ₃ at C15, CH ₃ at C1 and C3, H at N
ancistectorine A1	NPQ5-5	OH at C6 and C14, OCH ₃ at C8 and C15, CH ₃ at C1, C3 and N.
N-methylancistectorine A1	NPQ5-6	OH at C6 and C14, OCH ₃ at C8 and C15, CH ₃ at C1 and C3, H at N
ancistectorine A2	NPQ5-7	OH at C8, OCH ₃ at C6, C14 and C15, CH ₃ at C1, C3and C12, H at N
4'-O-demethylancistectorine A2	NPQ5-8	OH at C8 and C14, OCH ₃ at C6 and C15, CH ₃ at C1, C3and C12, H at N
ancistectorine A3	NPQ5-9	OH at C6 and C14, OCH ₃ at C8 and C15, CH ₃ at C1, C3 and C12.
ancistectorine B1	NPQ7-10	OH at C6 , OCH ₃ at C8, C14 and C15, CH ₃ at C1, C3 and C12, H at N
ancistectorine C1	NPQ7-11	OH at C6, OCH ₃ at C8, C14and C15, CH ₃ at C1, C3, N and C12.
5-epi-ancistrolikokine D	NPQ5-12	OH at C6 and C14, OCH ₃ at C8 and C15, CH ₃ at C1, C3 and C17.
ancistrolikokine D	NPQ5-13	OH at C8 and C14, OCH ₃ at C6 and C15, CH ₃ at C1, C3, N and C17.

ancistrocongoline A	NPQ5-14	OH at C6, C8 and C14, OCH ₃ at C15, CH ₃ at C1, C3, N and C17.
ancistrocongoline B	NPQ5-15	OH at C8, OCH ₃ at C6, C14 and C15, CH ₃ at C1, C3, N and C17.
ancistrocongoline C	NPQ5-16	OH at C6, OCH ₃ at C8, C14 and C15, CH ₃ at C1, C3, N and C17.
ancistrocongoline D	NPQ7-17	OH at C6, OCH ₃ at C8, C14 and C15, CH ₃ at C1, C3, and C12, H at N
ancistroealaine A	NPQ5-18	OCH ₃ at C8, C14 and C15, CH ₃ at C1, C3, C6 and C17
6,5'-O,O-didemethylancistroealaine A	NPQ5-19	OH at C6 and C14, OCH ₃ at C8 and C15, CH ₃ at C1, C3 and C17.
6-O-demethylancistroealaine A	NPQ5-20	OH at C6 and, OCH ₃ at C8, C14 and C15, CH ₃ at C1, C3 and C17.
ancistroealaine B	NPQ5-21	OH at C14, OCH ₃ at C6, C8 and C15, CH ₃ at C1, C3, and C17, H at N
hamatine	NPQ5-22	OH at C6, OCH ₃ at C8, C14 and C15, CH ₃ at C1, C3, and C12, H at N
50-O-demethylhamatine	NPQ5-23	OH at C6 and C14, OCH ₃ at C8 and C15, CH ₃ at C1, C3, and C12, H at N
6-O-methylhamatine	NPQ5-24	OCH ₃ at C6, C8, C14 and C15, CH ₃ at C1, C3, and C12, H at N
hamatinine	NPQ5-25	OH at C6, OCH ₃ at C8, C14 and C15, CH ₃ at C1, C3, and C12.
50-O-demethylhamatinine	NPQ5-26	OH at C6 and C15, OCH ₃ at C8 and C14, CH ₃ at C1, C3, and C12.
6-O-methylhamatinine	NPQ5-27	OCH ₃ at C6, C8, C14 and C15, CH ₃ at C1, C3, and C12.
ancistrocladine	NPQ5-28	OH at C6 and, OCH ₃ at C8, C14 and C15, CH ₃ at C1, C3, and C12, H at N
5-epi-40-O-demethylancistrobertsonine C	NPQ5-29	OH at C15, OCH ₃ at C6, C8 and C14, CH ₃ at C1, N, C3 and C17.
5-epi-6-O-methylancistrobertsonine	NPQ7-30	OCH ₃ at C6, C8, C14 and C15, CH ₃ at C1, N, C3 and C17.
ancistrogriffine A	NPQ5-31	OH at C6 and C14, OCH ₃ at C8 and C15, CH ₃ at C1, C3, N and C17.
ancistrogriffine B	NPQ7-32	OH at C6 and C8, OCH ₃ at C14 and C15, CH ₃ at C1, C3, and C13, H at N
ancistrogriffine C	NPQ7-33	OH at C8 and C15, OCH ₃ at C6 and C14, CH ₃ at C1, C3, and C13, H at N

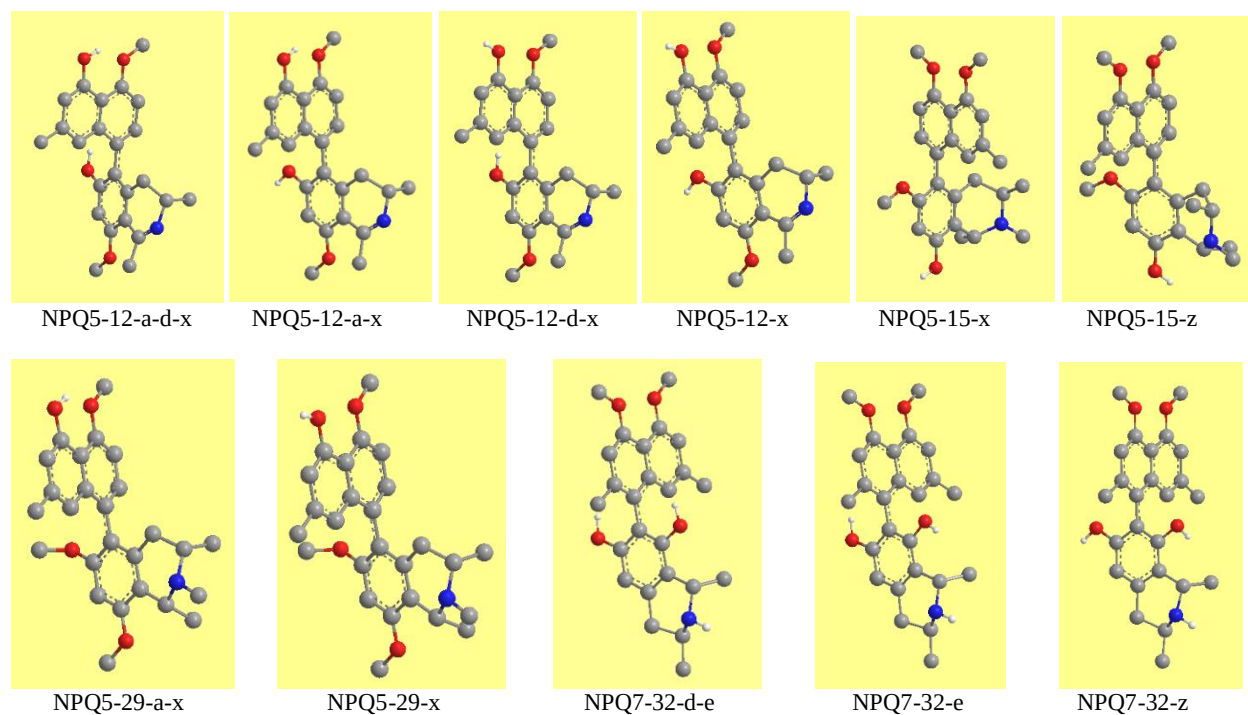


Figure 5.3. Optimized geometries of representative conformers of naphthylisoquinoline alkaloids and acronyms denoting them

The images illustrate the main combinations of interaction types which may be present in the conformers of naphthylisoquinoline alkaloids.

Figure 5.3 shows the geometries corresponding to the main combinations of interaction types and a representative of the optimized geometries. The optimized geometries of all conformers are given in figure 5.K2.

5.2. Conformational Preferences

The conformational preferences of these naphthylisoquinoline alkaloids are influenced by IHB patterns, i.e., the number and type of IHBs present in a conformer, and by the mutual orientation of the two moieties. Three types of IHB interactions may be present: the $\text{O-H}\cdots\text{O}$ IHB between an OH and a neighbouring ether O in the naphthalene moiety ($\text{H30}\cdots\text{O24}$ or $\text{H31}\cdots\text{O23}$); the $\text{O-H}\cdots\pi$ interaction between an O-H in the isoquinoline moiety and the closest π system in the

naphthalene moiety ($\text{O22-H29}\cdots\pi$ or $\text{O21-H25}\cdots\pi$); and $\text{C-H}\cdots\text{O}$ interactions within the isoquinoline moiety ($\text{C8-H26}\cdots\text{O21}$). The $\text{O-H}\cdots\text{O}$ IHBs are the strongest stabilizing factor. Among the weaker interactions, $\text{O-H}\cdots\pi$ interactions have stronger effect than $\text{C-H}\cdots\text{O}$ interactions.

Table 5.4 shows the combinations of different IHBs present simultaneously and the acronyms used to denote them. The naphthalene moiety prefers to be perpendicular to the isoquinoline moiety. This is confirmed by the fact that inputs with different orientations optimize to perpendicular orientation.

Table 5.5 reports the relative energy of the calculated conformers. The relative energy values provide indications on the effects of the different types of interactions. The conformers having all the IHB interactions simultaneously are the lowest energy conformers (e.g., NPQ5-4-a-d-x). The energy of those having only the $\text{O-H}\cdots\text{O}$ and $\text{C-H}\cdots\text{O}$ interaction is ~ 4 kcal/mol higher than the lowest one (4.377 kcal/mol/HF and 4.266 kcal/mol/DFT for NPQ5-4-a-x). The energy of the conformers with simultaneous $\text{O-H}\cdots\pi$ and $\text{C-H}\cdots\text{O}$ interaction is ~ 7 kcal/mol higher than the lowest one (7.303 kcal/mol/HF and 7.574 kcal/mol/DFT for NPQ5-4-d-x), and the energy of conformers where there is only the $\text{C-H}\cdots\text{O}$ interaction is ~ 11 kcal/mol higher than the lowest one (11.590 kcal/mol/HF and 11.770 kcal/mol/DFT for NPQ5-4-x). The energy of the conformers with no interaction at all is ~ 12 kcal/mol higher than conformers with all the interactions.

Information on the relevant molecular properties of naphthylisoquinoline alkaloids is given in Tables 5.6–5.11. Table 5.6 reports the parameters of the IHBs. Table 5.7 lists the calculated harmonic vibrational frequencies of the O-H bonds. Table 5.8 shows the relative energies corrected for ZPE and the ZPE corrections. Table 5.9 gives the relative Gibbs free energies and the thermal corrections to the Gibbs free energy. Table 5.10 lists the values of the dipole moments, and Table 5.11 provides the values of the HOMO–LUMO energy gaps.

The bond lengths of the $\text{H30}\cdots\text{O24}$ and $\text{H31}\cdots\text{O23}$ IHBs are 1.750–1.757 Å /DFT and 1.7956–1.848 Å /HF, which suggests rather strong IHBs. Both calculation methods yield the same $\text{O}\cdots\text{O}$ distance of 2.60 Å. The $\text{O}\hat{\text{H}}\text{O}$ bond angles are estimated around 142.0°/HF and 144.0°/DFT. For

the O22-H29 $\cdots\pi$ interactions, the distance between H29 and the closest C atom of the aromatic system is 2.350–2.280 Å /DFT and 2.271–2.371 Å /HF.

For a further understanding of the IHBs, besides analysing the relative energies of conformers and the geometrical parameters of the IHBs, it is important to analyse the vibrational frequencies of the donor OH. Table 5.7 shows the vibrational frequencies of the O–H bonds for selected molecules. The frequency values of the same OH (O23–H30, O24–H31) are different when it is engaged in an H-bond and when it is free (the lowering of the frequency is called redshift). These frequencies decrease from 3782 to 3735 cm⁻¹/HF for NPQ7-1-b. The same phenomenon is observed for O21–H25 or O22–H29 when they engage in an O–H $\cdots\pi$ interaction with the closest aromatic ring; the frequency of the OH decreases from 3787 to 3750 cm⁻¹/HF for NPQ7-32-d-e. It can be noted that the redshift caused by an O–H $\cdots$ O IHB is greater than the redshift caused by the O–H $\cdots\pi$ interaction. This is expected, because the O–H $\cdots$ O IHB is generally stronger than the O–H $\cdots\pi$ interaction.

The relative energies (ΔE) corrected for ZPE (Table 5.8) have the same trends as the uncorrected relative energies. The ZPE is very close for all the conformers, with values differing only by 3–4 kcal/mol. The relative Gibbs free energy (Table 5.9) has nearly the same trends as the ΔE corrected for ZPE, and the thermal corrections to Gibbs free energy are very close for all the conformers, with values differing only by 1–2 kcal/mol.

The values of the dipole moments (Table 5.10) of the calculated molecular systems range between 0.64 D and 5.97 D. The conformers with IHBs have higher dipole moments in most compounds. Conformers with O–H $\cdots\pi$ interactions have a low dipole moment in most compounds. The orientation of the OH groups is a major factor influencing the dipole moments.

The HOMO–LUMO energy gap is lowest for conformers with IHBs and highest for conformers without IHBs, for all the compounds considered in this study. Thus, the lowest energy conformers are also the conformers with the lowest HOMO–LUMO energy gap. They can be assumed to be the most reactive ones and, therefore, those that may be responsible for the molecules' behaviour. There is a huge difference between HF and DFT estimations of the HOMO–LUMO energy gaps. This is a known phenomenon, as DFT substantially underestimates the values of the gaps [462,

463]. However, the trends highlighted by the two methods are similar, as can be seen by comparing the values in Table 5.11 within each method.

Figures 5.4 and 5.5 show respectively the shapes of the HOMO and LUMO frontier orbitals for selected molecules. Overall, there is a concentration of electrons in the naphthalene part for both HOMO and LUMO, and less concentration in the isoquinoline moiety. The complete HOMO and LUMO orbitals are given respectively in figures 5.K3 and 5.K4.

Another interesting comparison for the naphthylisoquinoline alkaloids studied in this work concerns the structural isomers. There are six sets of structural isomers, having, respectively, the molecular formulas $C_{24}H_{25}NO_4$, $C_{24}H_{27}NO_4$, $C_{25}H_{27}NO_4$, $C_{25}H_{29}NO_4$, $C_{26}H_{29}NO_4$, and $C_{26}H_{31}NO_4$. For compounds having the same molecular formula and belonging to the same group (NPQ5 or NPQ7), the structural difference is due to the positions of the CH_3 , OCH_3 , and OH groups. The CH_3 may be attached to a C atom of the isoquinoline moiety or, in other structures, it can replace an H attached to the N atom. The OCH_3 or the OH groups can change their positions on the C14 and C15 atoms. For compounds having the same molecular formula and belonging to different groups, an additional difference may arise from the position of the naphthalene moiety with respect to the isoquinoline moiety. It is interesting to compare the absolute energies of the lowest energy conformers of structural isomers. For isomers with molecular formulas $C_{24}H_{27}NO_4$ and $C_{26}H_{31}NO_4$ and differing by the position of the naphthalene moiety with respect to the isoquinoline, the NPQ5 isomers are more stable compared to the NPQ7 ones. For those with molecular formula $C_{25}H_{29}NO_4$, the NPQ7 isomers are more stable compared to the NPQ5 isomers.

5.3 Discussion and Conclusions

Three types of IHBs, $O-H\cdots O$ IHBs, $O-H\cdots\pi$ and $C-H\cdots O$ interactions, have a stabilising role in the conformers of these molecules, with the $O-H\cdots O$ IHBs being the dominant factor. The average bond-length ($H\cdots O$) of $O-H\cdots O$ IHBs is 1.8Å/HF and 1.7Å/DFT, which makes them moderate IHBs [464, 465]. For $O-H\cdots\pi$ IHBs, the average distance between the H atom and the closest C atom in the π system involved is 2.3/Å with all the methods.

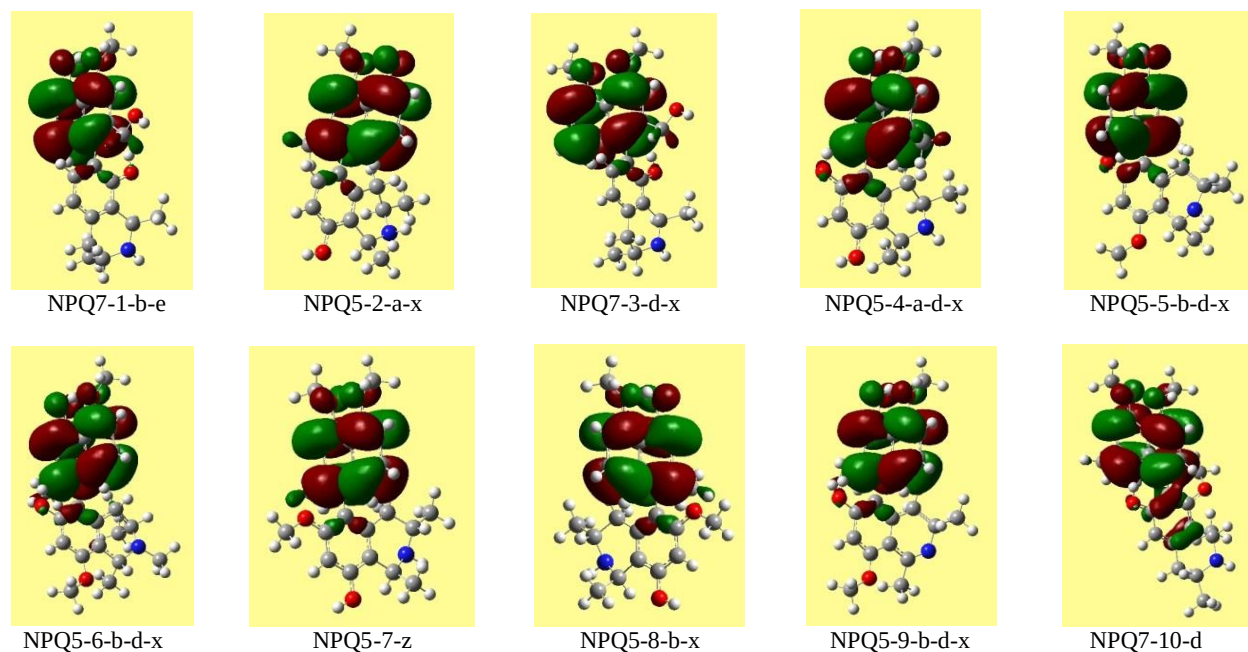


Figure 5.4. Shapes of the HOMO frontiers orbitals for selected conformers of the calculated naphthylisoquinoline alkaloids

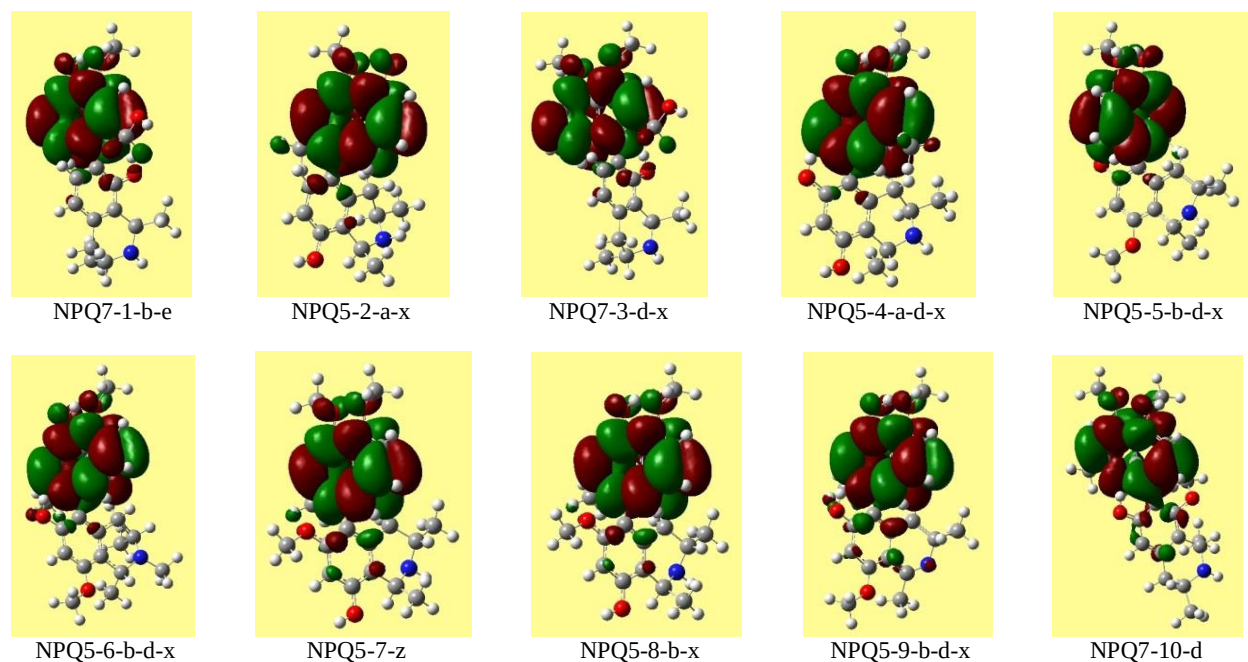


Figure 5.5. Shapes of the LUMO frontiers orbitals for selected conformers of the calculated naphthylisoquinoline alkaloids

This distance is close to the 2.487 Å distance reported by Mohan and co-workers [466] for the comparison of aromatic $\text{NH}\cdots\pi$, $\text{OH}\cdots\pi$, and $\text{CH}\cdots\pi$ interactions in alanine using MP2, CCSD, and DFT methods. For $\text{C-H}\cdots\text{O}$ interactions, the average bond-length ($\text{H}\cdots\text{O}$) is 2.4/Å with all the methods. For instance, the $\text{H26}\cdots\text{O21}$ distance in the $\text{C-H26}\cdots\text{O21}$ interactions is 2.259–2.638 Å /DFT+ and 2.227–2.526 Å /HF. These distances are in the range found by Jones *et al.* [467] in their study of $\text{C-H}\cdots\text{O}$ interactions and their influence on conformations. The same range is also found by Vibhute and co-workers [468] in the study of the conformational divergence between solid and solution states of substituted cyclitols facilitated by $\text{C-H}\cdots\text{O}$ hydrogen bonding, and by Sandoval-Lira *et al.* [469] in the study of the stabilizing role of the intermolecular $\text{C-H}\cdots\text{O}$ hydrogen bond in cyclic amides derived from α -methylbenzylamine.

Another factor influencing the conformational preferences is the mutual orientation of the two moieties. The naphthalene moiety prefers to be perpendicular to the isoquinoline moiety, with the result that only one geometry is possible for the mutual orientation of the two moieties in each molecule. This was verified by trying several inputs with different orientations of the two moieties, and they all converged to the same geometry. In addition, a scan of the complete (360°) rotation around the C5–C11 bond (C6–C5–C11–C12 dihedral angle) was performed for dioncopeltine A to verify orientation preferences through a potential energy profile. The profile (Fig.5.6) shows energy minima in correspondence to 88.95° and -90.02° , i.e., the two options for perpendicular orientation of the moieties. The energy difference is 0.25 kcal/mol, which is below the experimental error.

The same is seen for the other structures. The dihedral angle may be slightly smaller or slightly greater than 90° or -90° . Similar dihedral angles were found by Shockravi *et al.* for the binaphthyl skeleton (two naphthalene moieties connected via a C–C bond), for which they identified two configurations that they called cisoid ($\theta < 90^\circ$) and transoid ($\theta > 90^\circ$) [470]. The preference for mutual perpendicularity is a known tendency of aromatic rings [471–473]. It was confirmed by Jia *et al.*, in a study [474, 475] aimed at elucidating the forces governing the stereochemistry of biphenyl. It is known that biphenyl has a twisted equilibrium geometry, while the planar and perpendicular orientations are transition states of the internal rotation around C–C bond [474, 475].

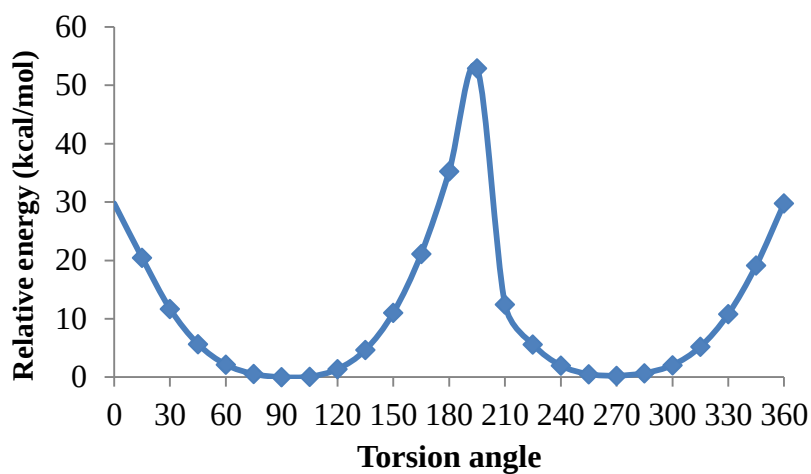
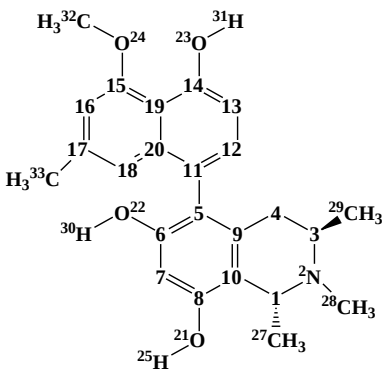
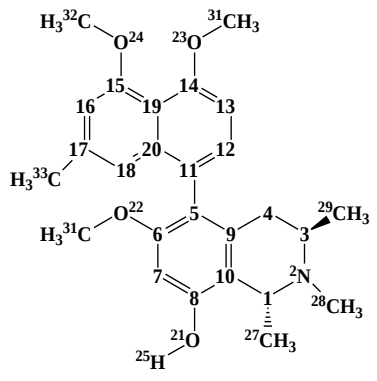
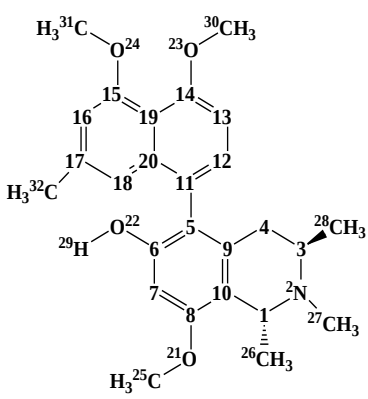
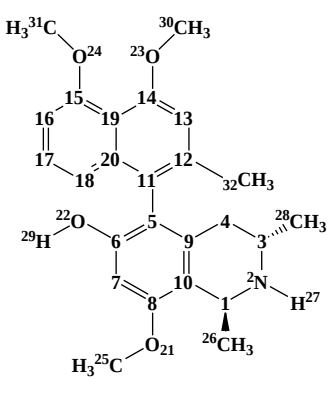
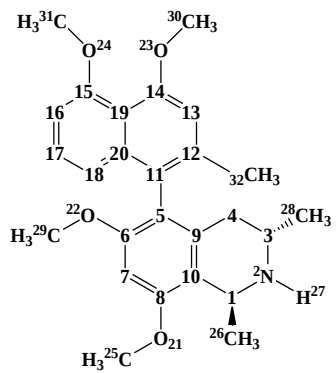
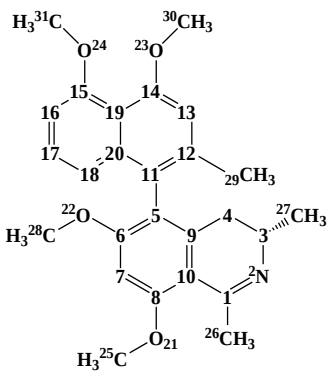
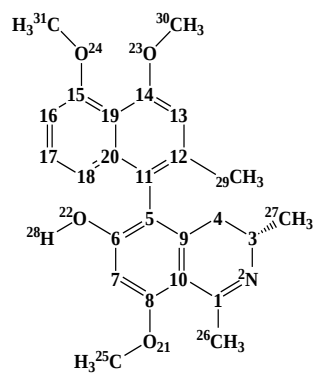
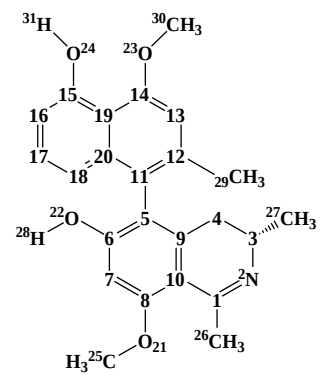
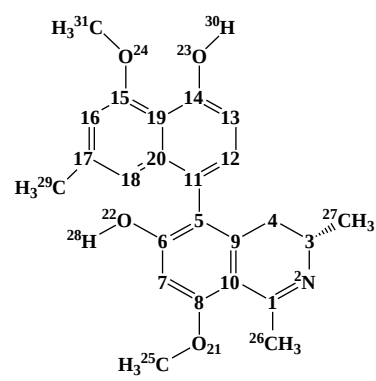
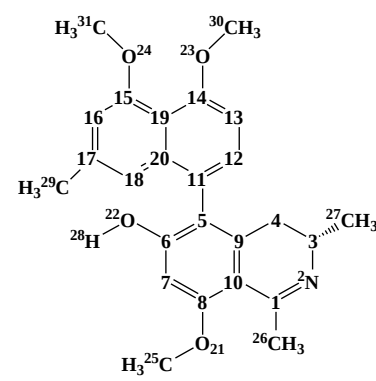
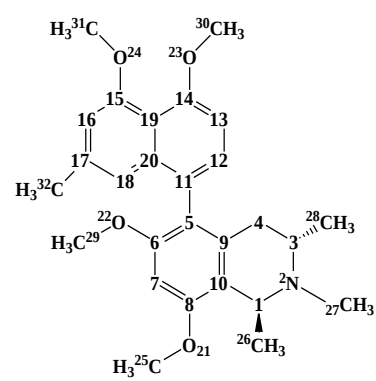
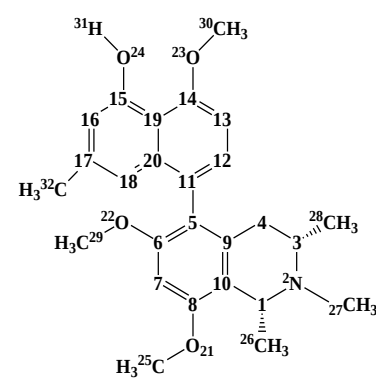


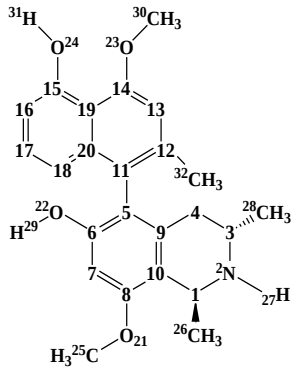
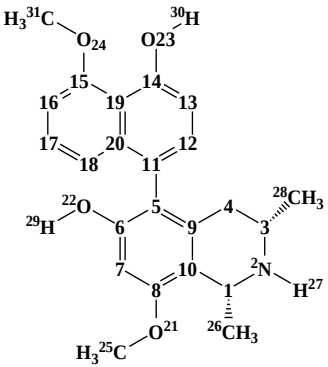
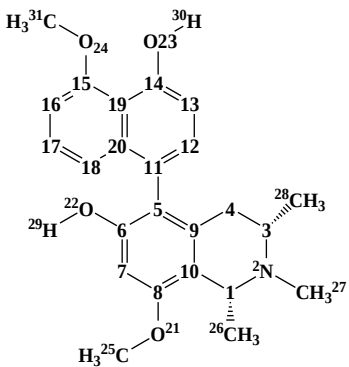
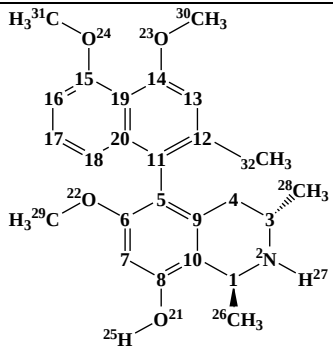
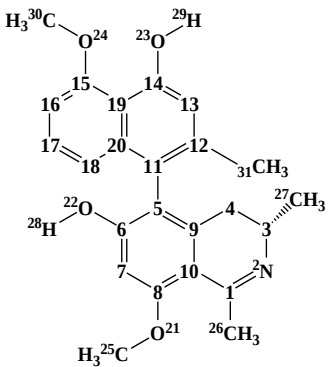
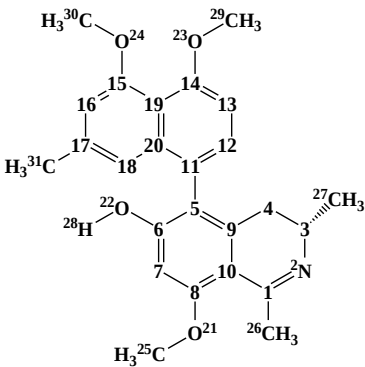
Figure 5.6. Potential energy profile for the rotation scan of the C5–C11 bond (C6–C5–C11–C12 dihedral angle) of dioncopeltine A

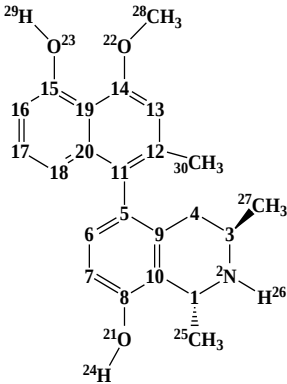
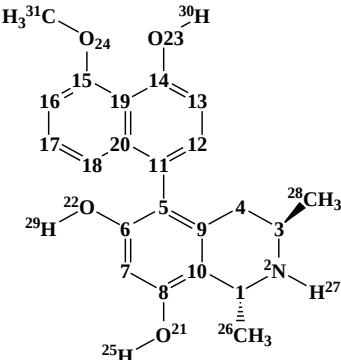
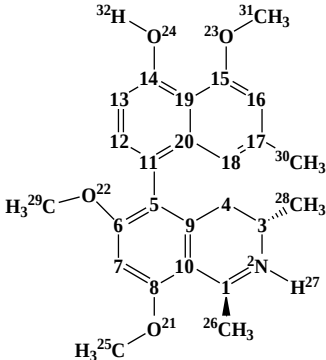
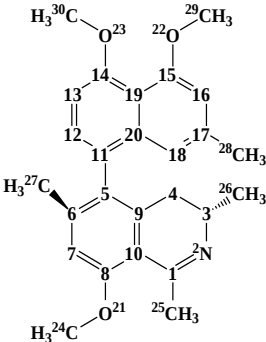
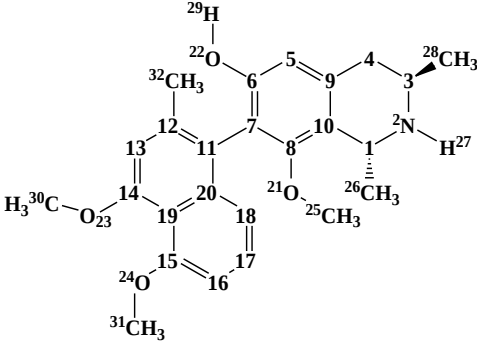
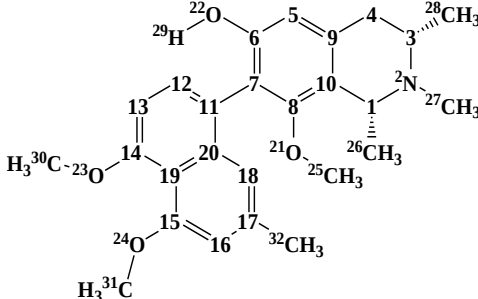
The same authors showed that, due to the absence of steric repulsion and also to hyperconjugation effects, the perpendicular conformation is slightly stable than the planar conformation [474–476]. The mutual orientation of the moieties is thus the same for all the conformers of a given molecule. The conformers of a given molecule differ by the orientation of the substituents (such as the OH groups), which, in turn, determines the presence of absence of IHBs.

Figure 5.K1. Atom numbering utilised for the monomeric naphthylisoquinoline alkaloids considered in this work

	
Ancistrocongoline A	Ancistrocongoline B
	
Ancistrocongoline C	Hamatine
	
6-O-methylhamatine	6-O-methylhamatinine

 Chemical structure of hamatinine, a purine alkaloid. It features a purine core with a methyl group at C-3 (27CH₃), a methyl group at C-1 (26CH₃), a methoxy group at C-6 (O²²CH₃), and a methoxy group at C-7 (O²¹CH₃). The purine ring is numbered 1-10, and the pyrimidine ring is numbered 11-16. The methyl groups are numbered 26, 27, and 29. The methoxy groups are numbered 21 and 22. The oxygen atoms are numbered 23 and 24.	 Chemical structure of 5'-O-demethylhamatinine, a purine alkaloid. It features a purine core with a methyl group at C-3 (27CH₃), a methyl group at C-1 (26CH₃), a methoxy group at C-6 (O²²CH₃), and a methoxy group at C-7 (O²¹CH₃). The purine ring is numbered 1-10, and the pyrimidine ring is numbered 11-16. The methyl groups are numbered 26, 27, and 29. The methoxy groups are numbered 21 and 22. The oxygen atoms are numbered 23 and 24.
hamatinine	5'-O-demethylhamatinine
 Chemical structure of 6,5'-O-O-didemethylancistroealaine A, a purine alkaloid. It features a purine core with a methyl group at C-3 (27CH₃), a methyl group at C-1 (26CH₃), a methoxy group at C-6 (O²²CH₃), and a methoxy group at C-7 (O²¹CH₃). The purine ring is numbered 1-10, and the pyrimidine ring is numbered 11-16. The methyl groups are numbered 26, 27, and 29. The methoxy groups are numbered 21 and 22. The oxygen atoms are numbered 23 and 24.	 Chemical structure of 6-O-demethylancistroealaine A, a purine alkaloid. It features a purine core with a methyl group at C-3 (27CH₃), a methyl group at C-1 (26CH₃), a methoxy group at C-6 (O²²CH₃), and a methoxy group at C-7 (O²¹CH₃). The purine ring is numbered 1-10, and the pyrimidine ring is numbered 11-16. The methyl groups are numbered 26, 27, and 29. The methoxy groups are numbered 21 and 22. The oxygen atoms are numbered 23 and 24.
6,5'-O-O-didemethylancistroealaine A	6-O-demethylancistroealaine A
 Chemical structure of 5-epi-6-O-methylancistrobertsonine A, a purine alkaloid. It features a purine core with a methyl group at C-3 (28CH₃), a methyl group at C-1 (26CH₃), a methoxy group at C-6 (O²²CH₃), and a methoxy group at C-7 (O²¹CH₃). The purine ring is numbered 1-10, and the pyrimidine ring is numbered 11-16. The methyl groups are numbered 26, 27, and 28. The methoxy groups are numbered 21 and 22. The oxygen atoms are numbered 23 and 24.	 Chemical structure of 5-epi-4'-O-demethylancistrobertsonine C, a purine alkaloid. It features a purine core with a methyl group at C-3 (28CH₃), a methyl group at C-1 (26CH₃), a methoxy group at C-6 (O²²CH₃), and a methoxy group at C-7 (O²¹CH₃). The purine ring is numbered 1-10, and the pyrimidine ring is numbered 11-16. The methyl groups are numbered 26, 27, and 28. The methoxy groups are numbered 21 and 22. The oxygen atoms are numbered 23 and 24.
5-epi-6-O-methylancistrobertsonine A	5-epi-4'-O-demethylancistrobertsonine C

	
5'-O-demethylhamatine	Ancistectorine A1
	
N-methylancistectorine A1	4'-O-demethylancistectorine A2
	
Ancistectorine A3	5-epi-ancistrolikokine D

	
Dioncophylline C	Korupensamine A
	
Ancistroealaine B	Ancistroealaine A
	
Ancistrocongoline D	6-O-demethylancistrobrevine A

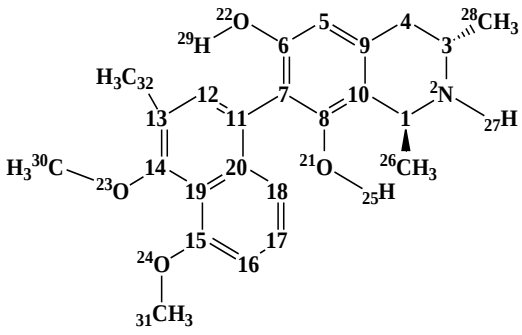
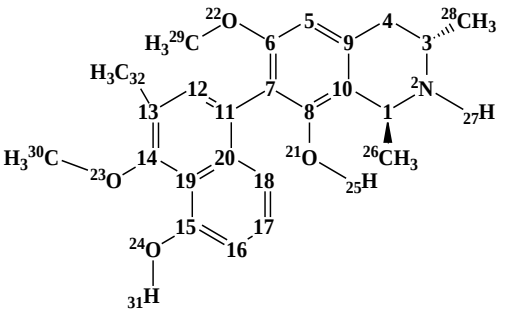
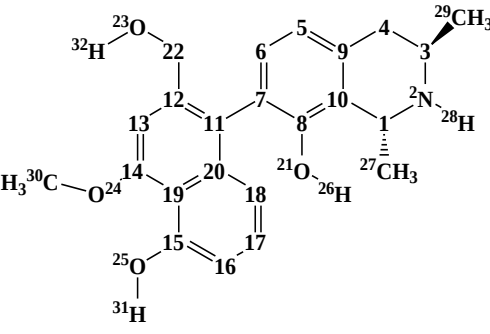
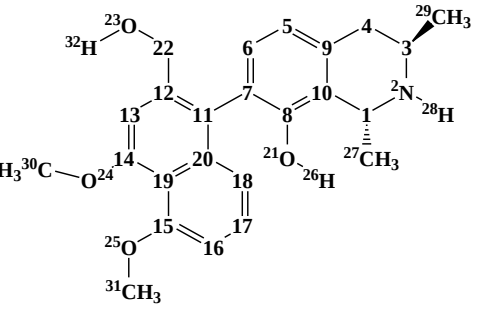
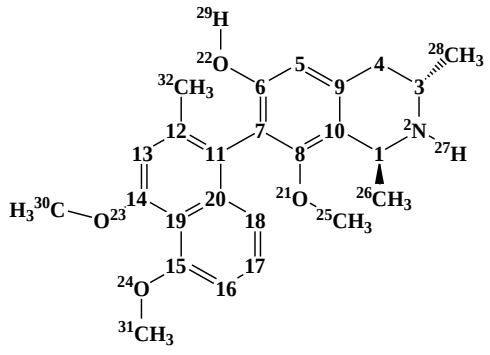
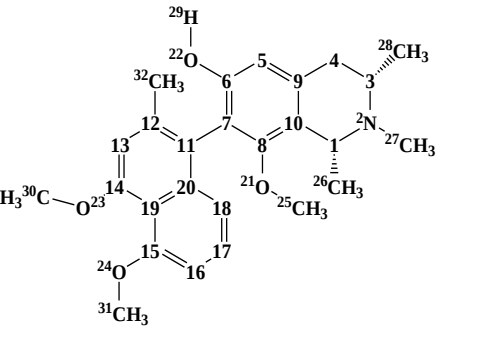
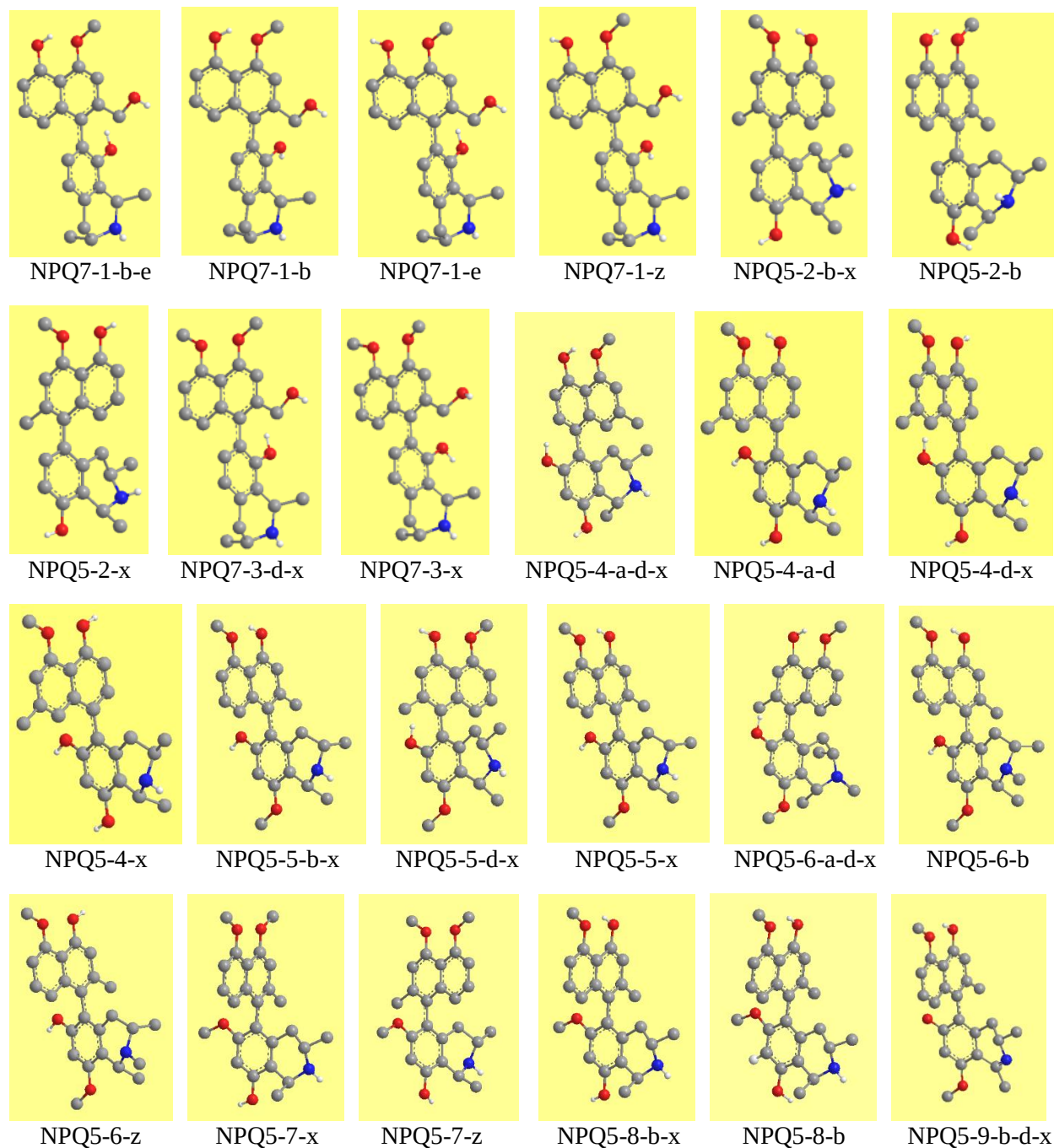
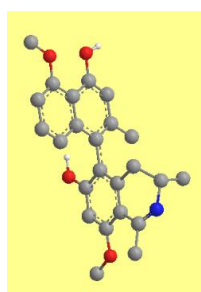
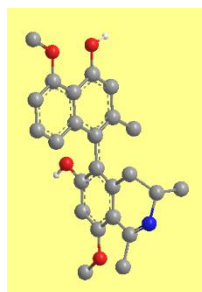
	
Ancistrogriffine B	Ancistrogriffine C
	
Dioncopeltine A	Habropelatine A
	
Ancistectorine B1	Ancistectorine C1

Figure 5.K2. Optimized geometries of the conformers of the monomeric naphthylisoquinoline alkaloids considered in this work and acronyms used to denote them

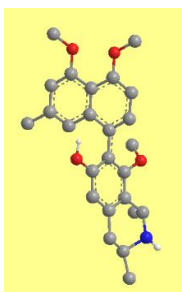




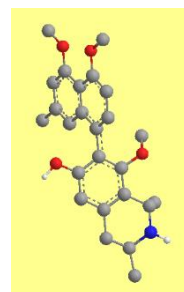
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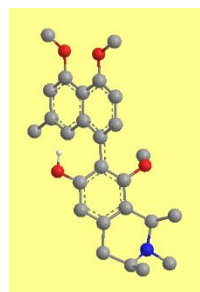
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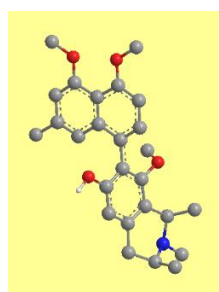
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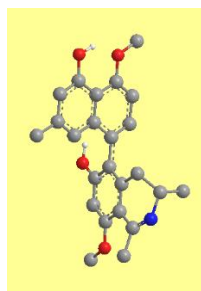
NPQ7-10-z



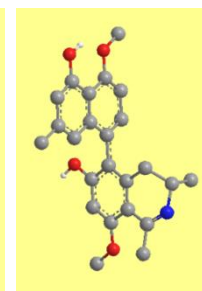
NPQ7-11-d-x



NPQ7-11-x



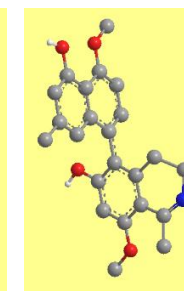
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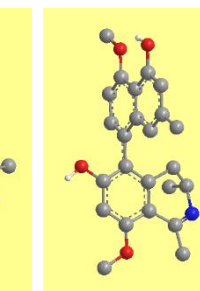
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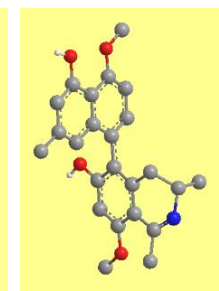
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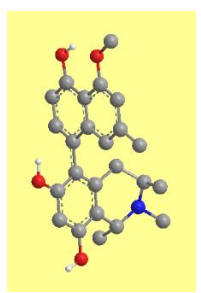
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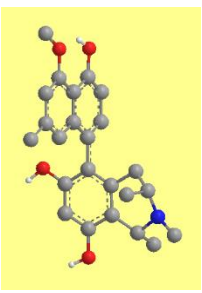
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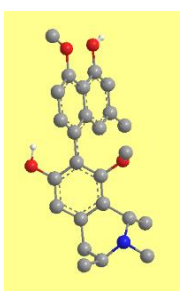
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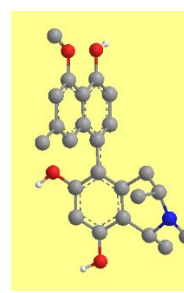
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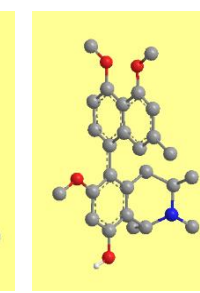
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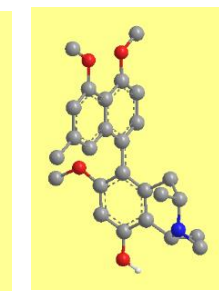
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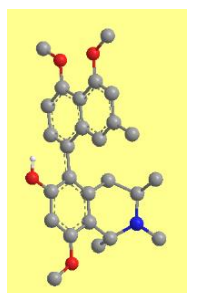
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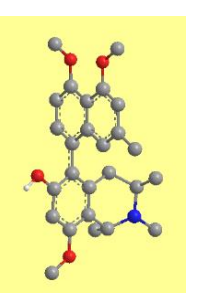
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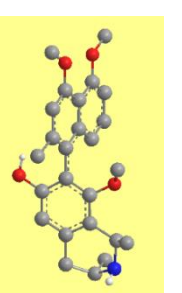
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NPQ5-16-d



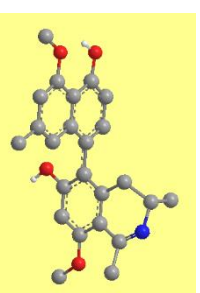
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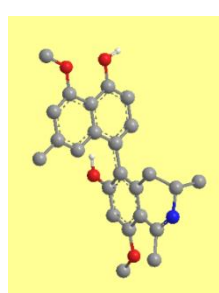
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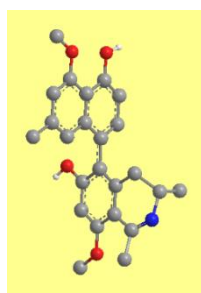
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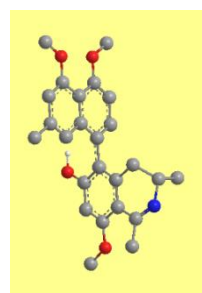
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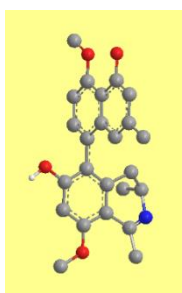
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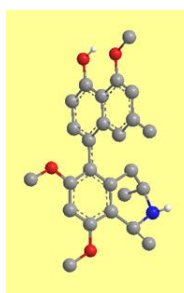
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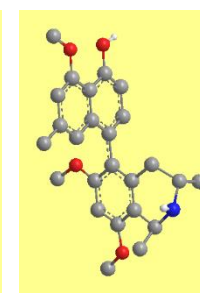
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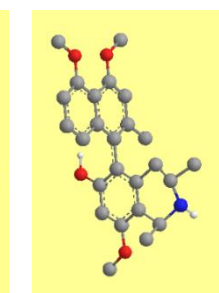
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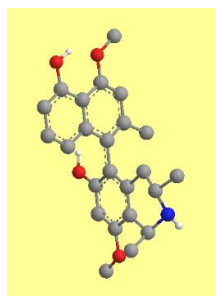
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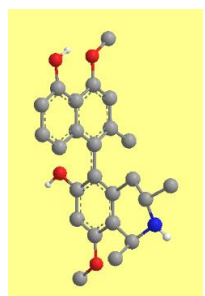
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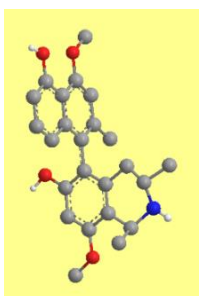
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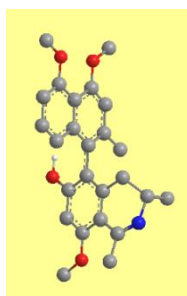
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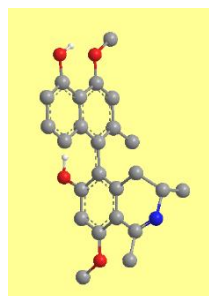
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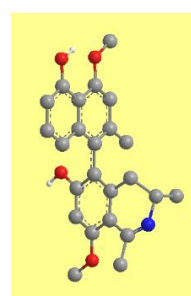
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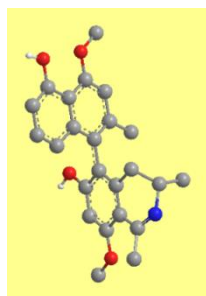
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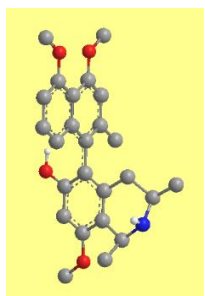
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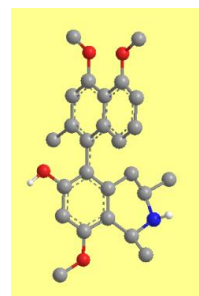
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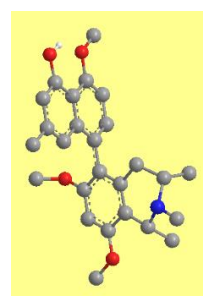
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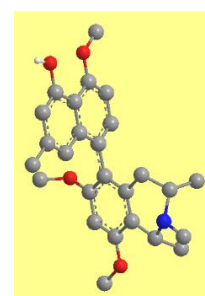
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NPQ7-28-x



NPQ5-29-a-x



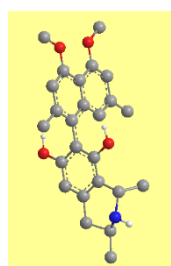
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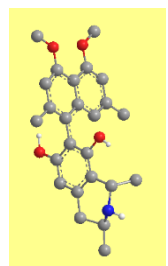
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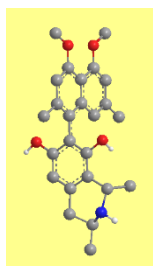
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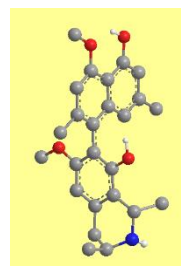
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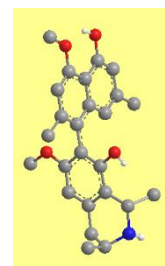
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NPQ7-32-z



NPQ7-33-b-e

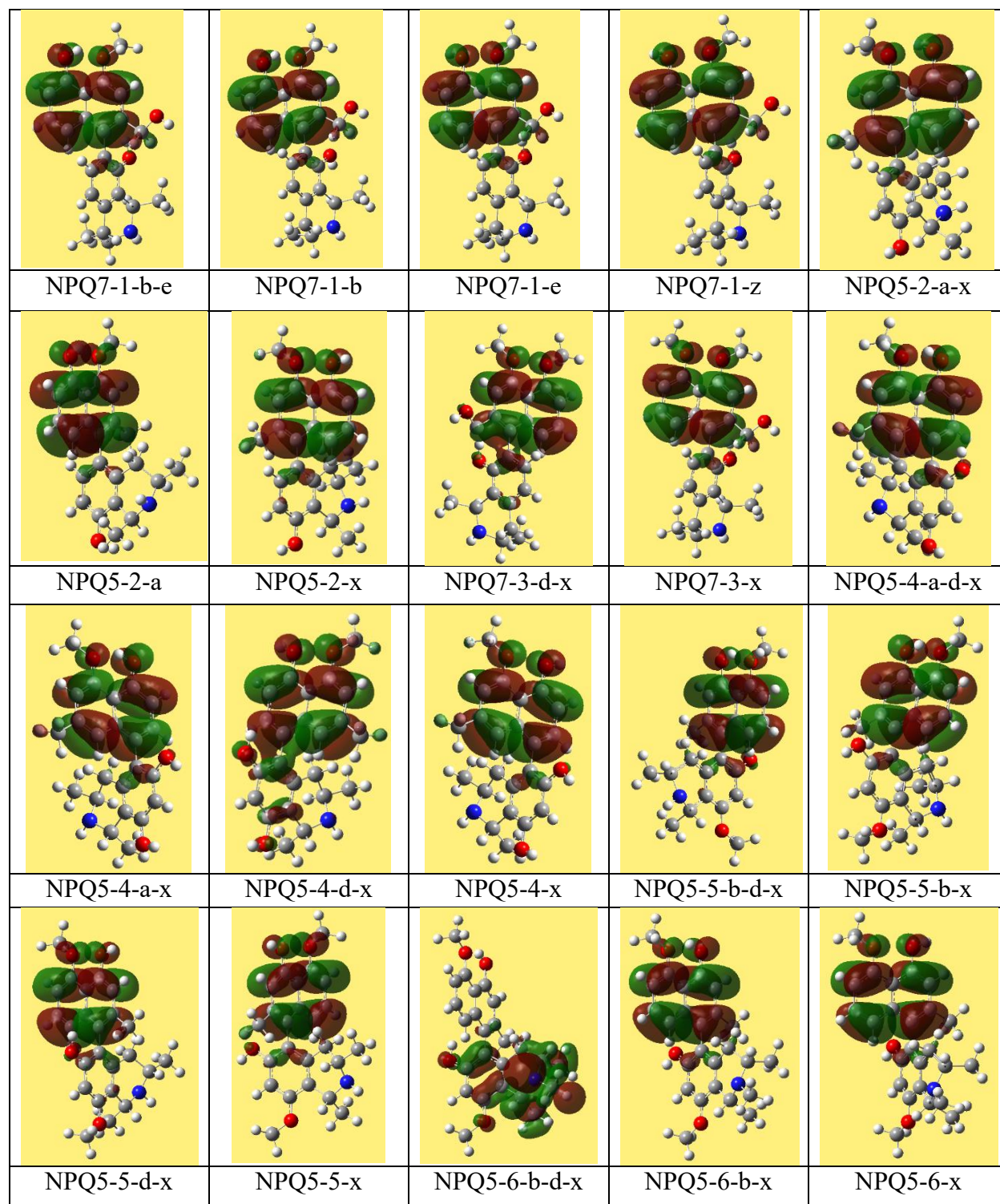


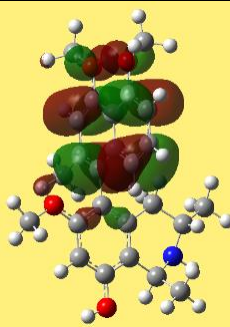
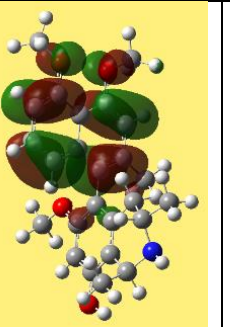
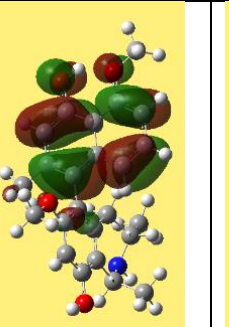
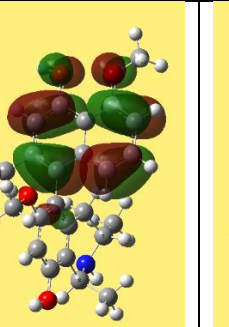
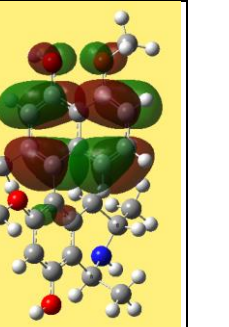
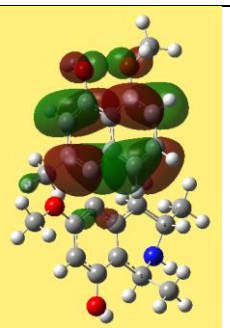
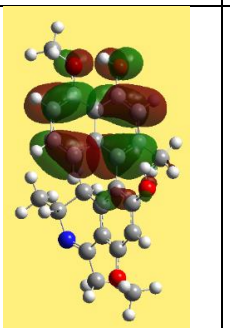
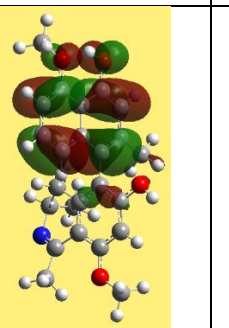
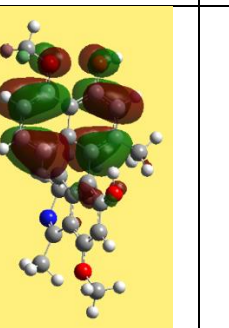
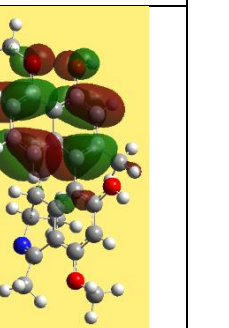
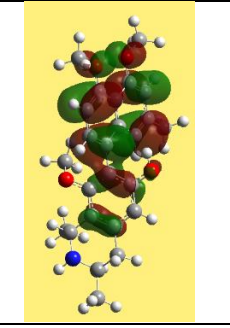
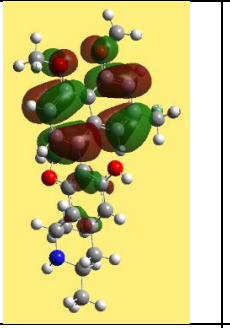
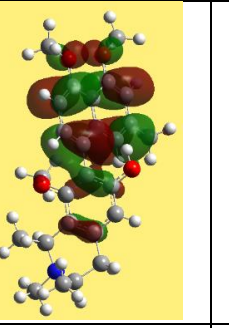
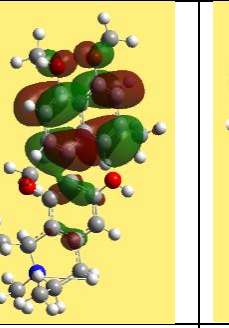
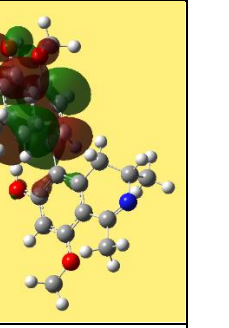
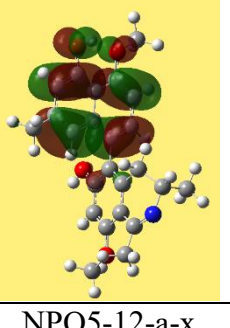
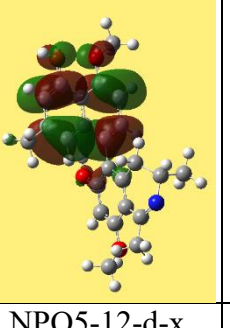
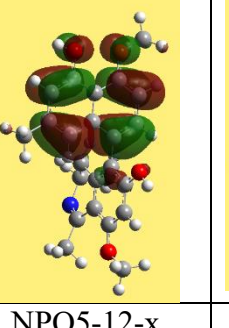
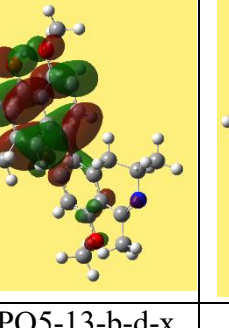
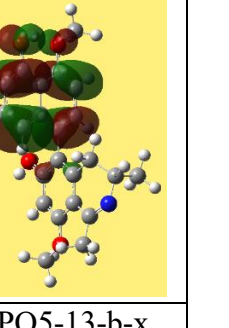
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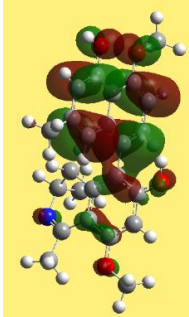
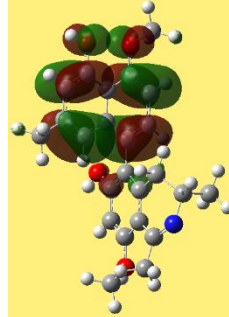
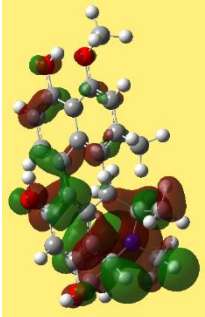
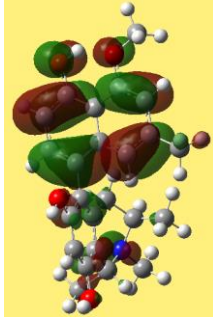
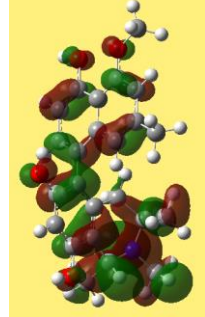
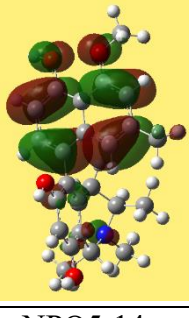
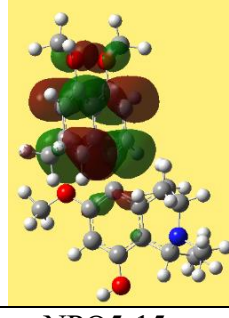
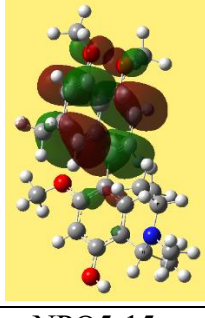
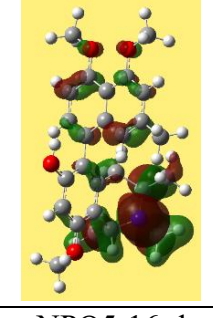
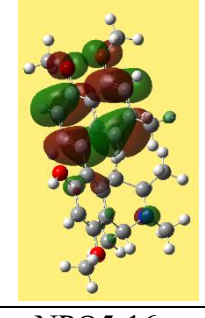
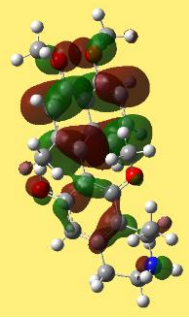
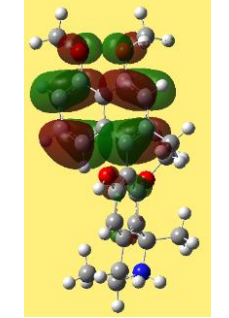
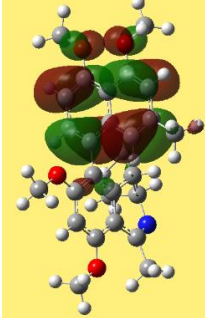
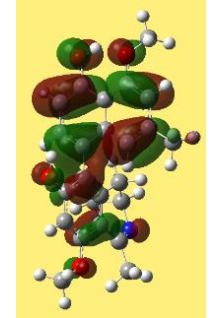
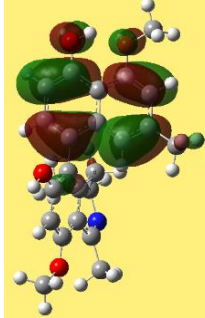
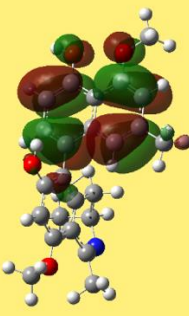
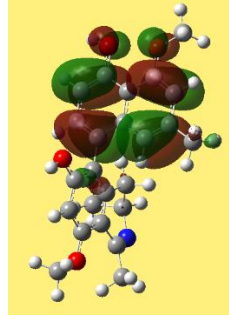
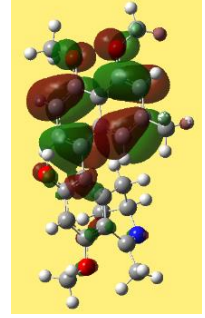
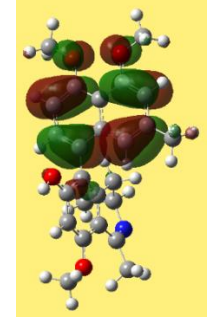
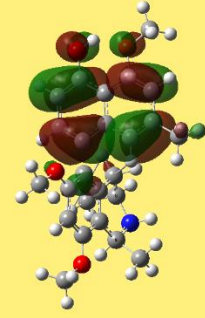


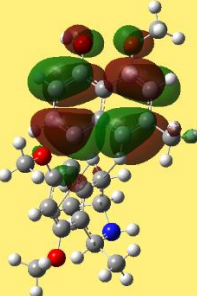
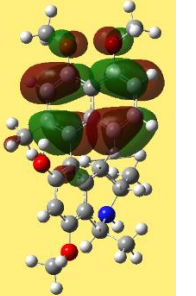
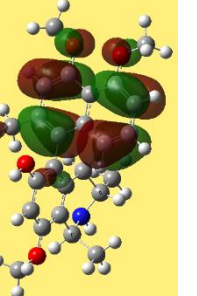
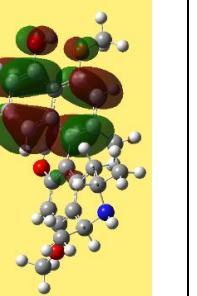
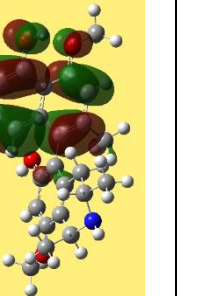
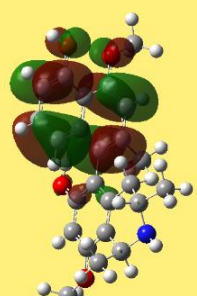
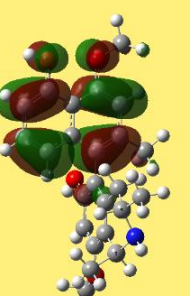
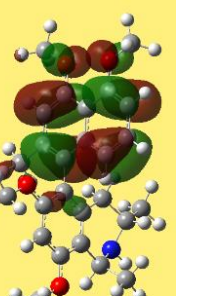
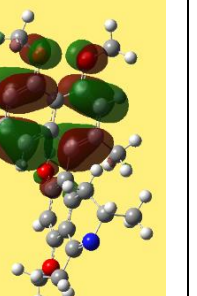
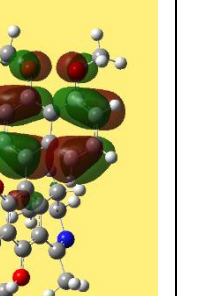
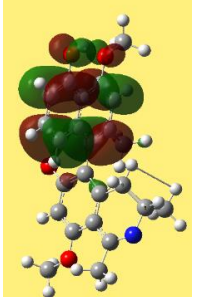
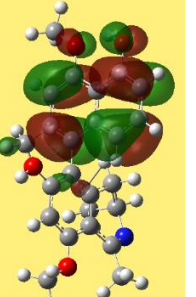
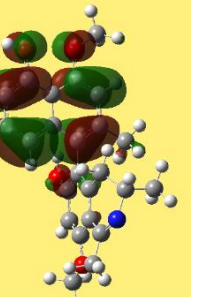
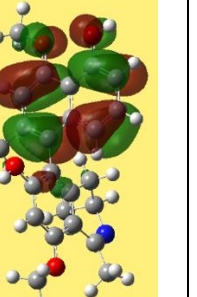
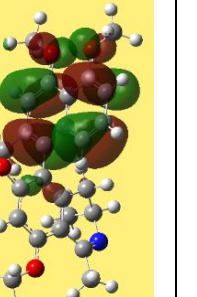
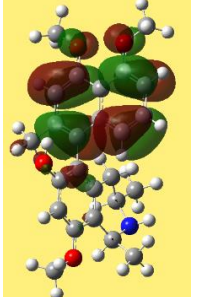
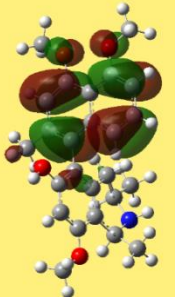
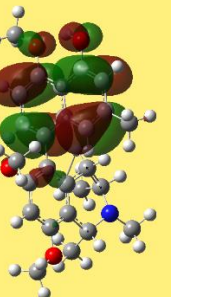
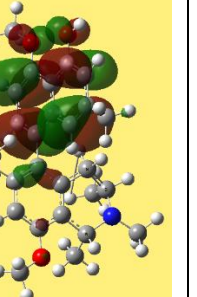
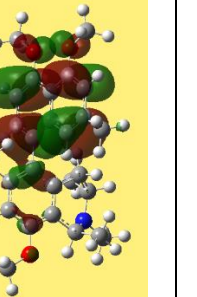
NPQ7-33-z

Figure 5.K3. Shapes of the HOMO frontier orbitals for all conformers of the calculated monomeric naphthylisoquinoline alkaloids. HF results



				
NPQ5-7-x	NPQ5-7-z	NPQ5-8-b-x	NPQ5-8-b	NPQ5-8-x
				
NPQ5-8-z	NPQ5-9-b-d-x	NPQ5-9-b-x	NPQ5-9-d-x	NPQ5-9-x
				
NPQ7-10-d	NPQ7-10-z	NPQ7-11-d-x	NPQ7-11-x	NPQ5-12-a-d-x
				
NPQ5-12-a-x	NPQ5-12-d-x	NPQ5-12-x	NPQ5-13-b-d-x	NPQ5-13-b-x

				
NPQ5-13-d-x	NPQ5-13-x	NPQ5-14-b-d-x	NPQ5-14-b-x	NPQ5-14-d-x
				
NPQ5-14-x	NPQ5-15-x	NPQ5-15-z	NPQ5-16-d	NPQ5-16-z
				
NPQ7-17-d	NPQ7-17-z	NPQ5-18	NPQ5-19-b-d-x	NPQ5-19-b
				
NPQ5-19-d-x	NPQ5-19-x	NPQ5-20-d-x	NPQ5-20-x	NPQ5-21-a-x

				
NPQ5-21-x	NPQ5-22-d-x	NPQ5-22-x	NPQ5-23-a-d-x	NPQ5-23-a-x
				
NPQ5-23-d-x	NPQ5-23-x	NPQ5-24	NPQ5-25-d-x	NPQ5-25-x
				
NPQ5-26-a-d-x	NPQ5-26-a-x	NPQ5-26-d-x	NPQ5-26-x	NPQ5-27
				
NPQ7-28-d-x	NPQ7-28-x	NPQ5-29-a-x	NPQ5-29-x	NPQ7-30

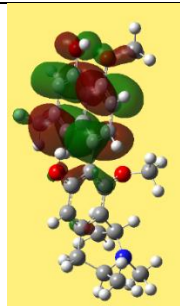
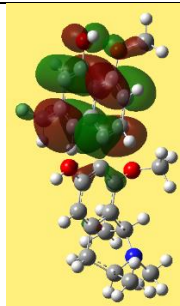
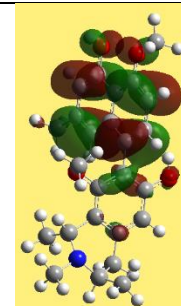
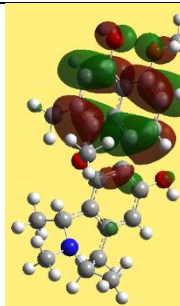
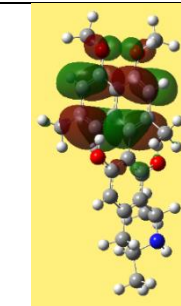
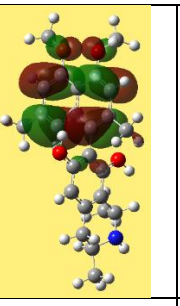
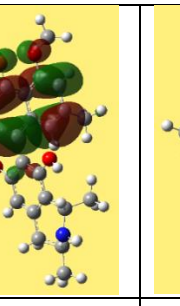
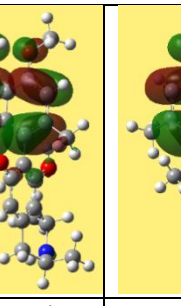
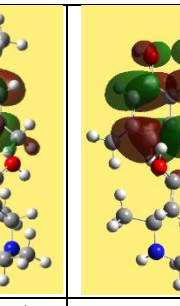
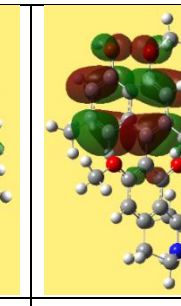
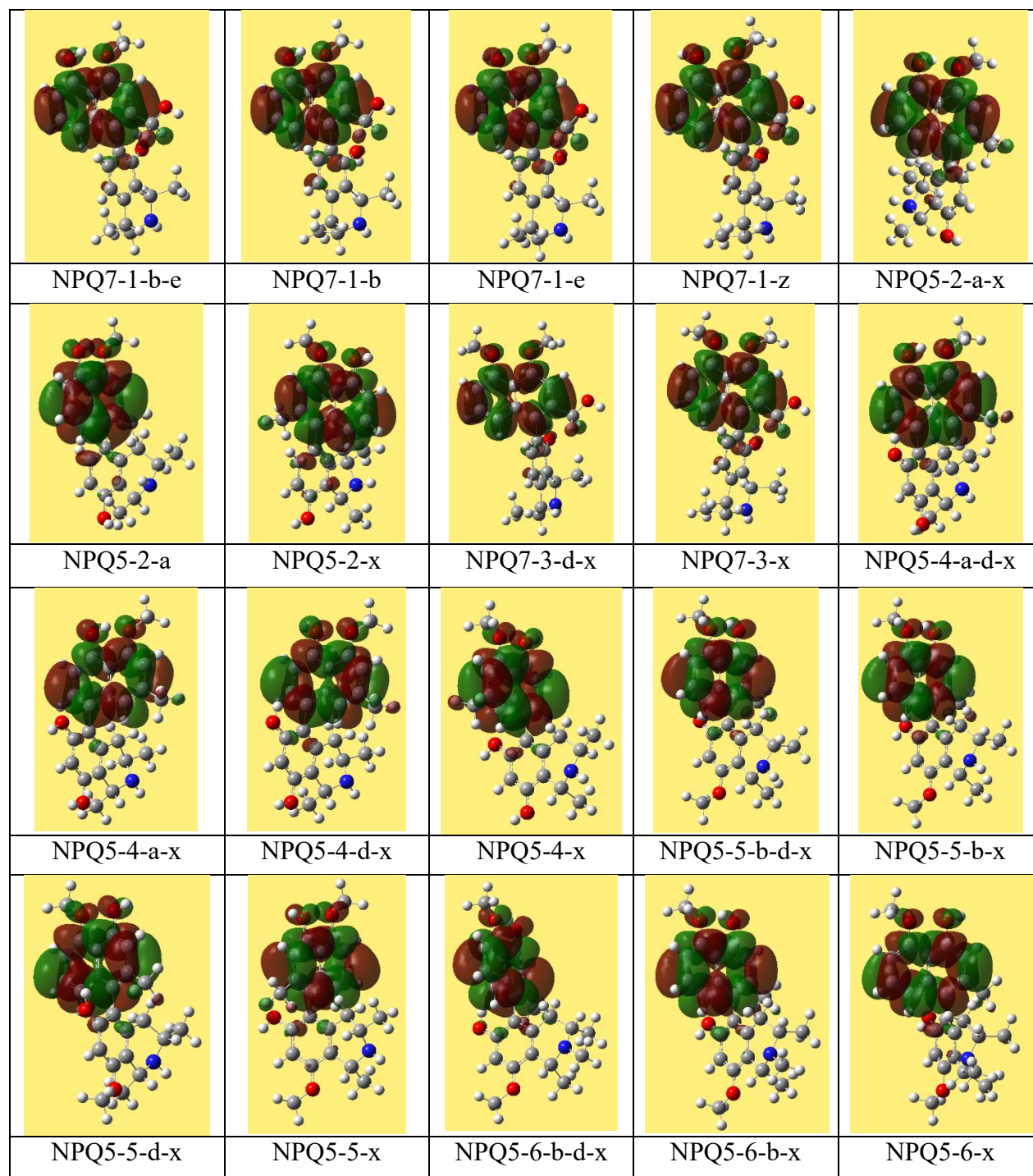
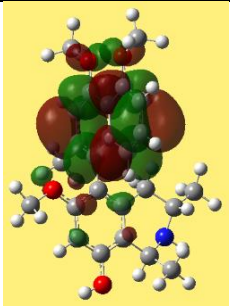
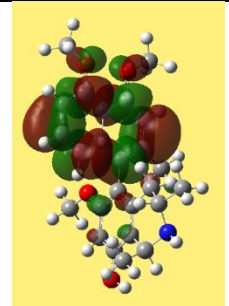
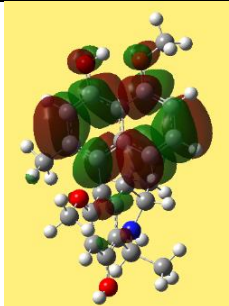
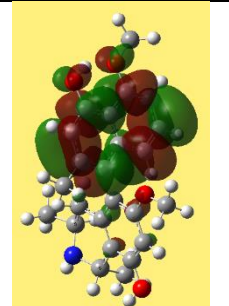
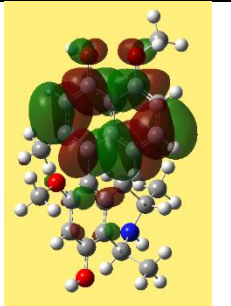
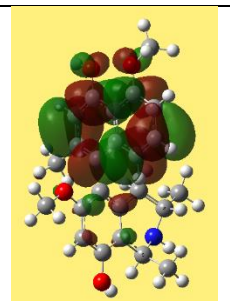
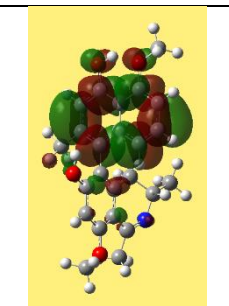
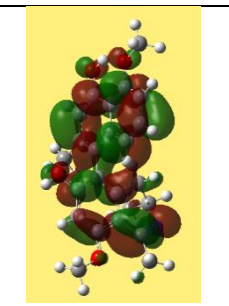
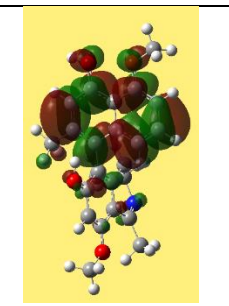
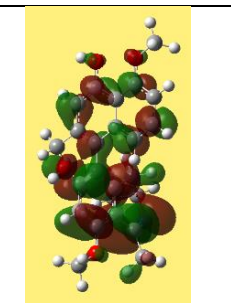
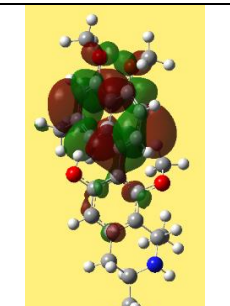
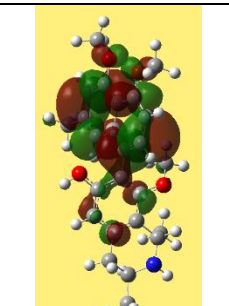
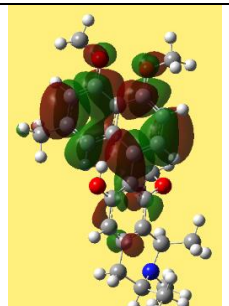
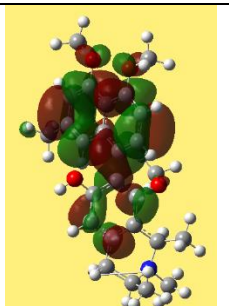
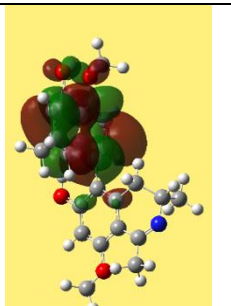
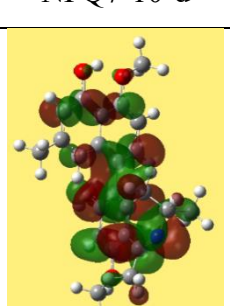
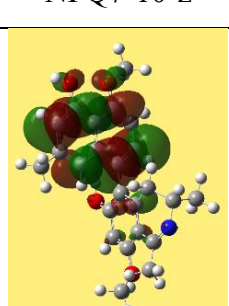
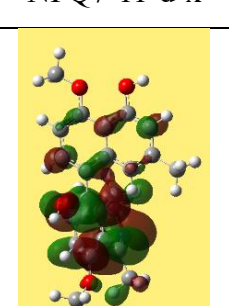
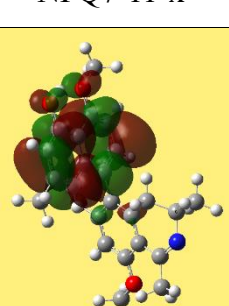
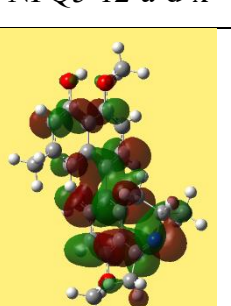
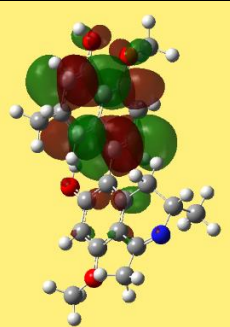
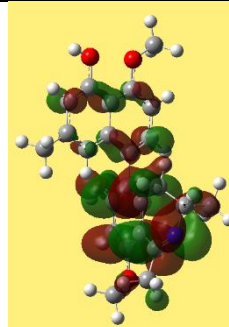
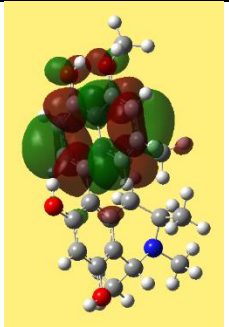
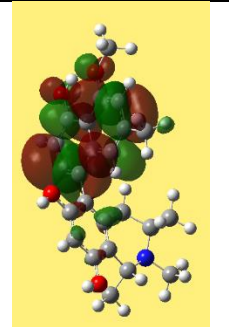
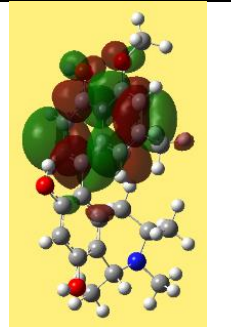
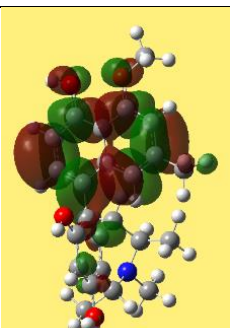
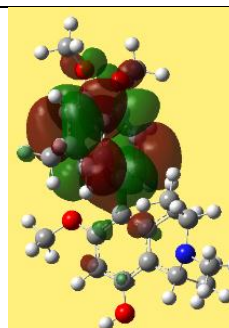
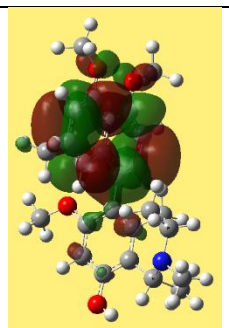
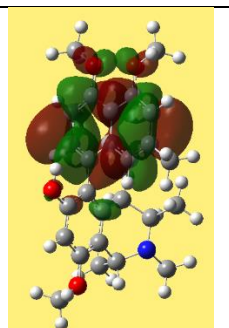
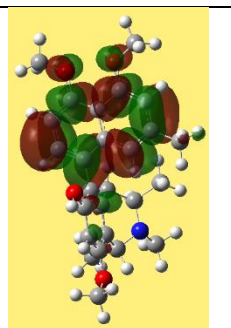
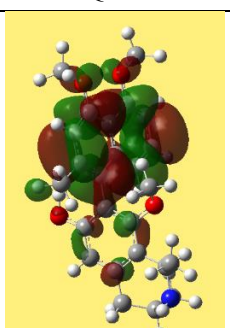
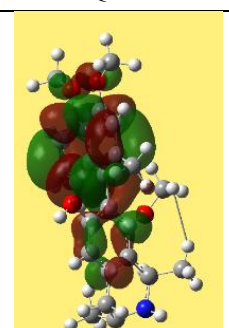
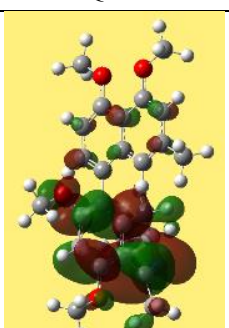
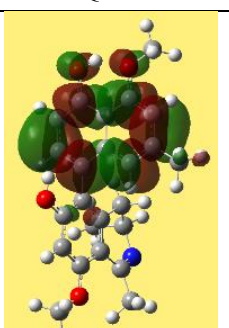
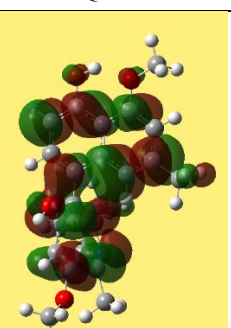
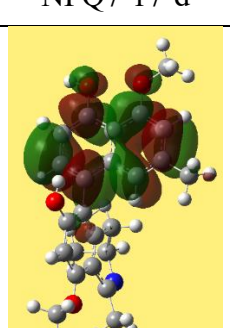
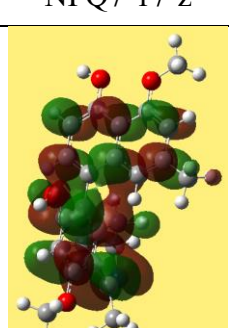
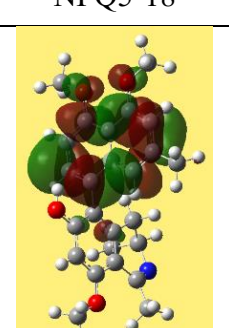
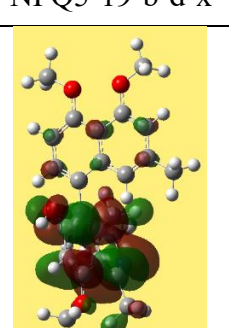
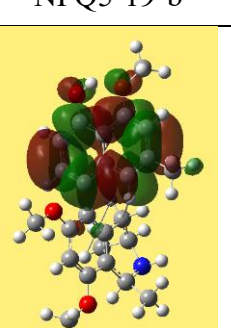
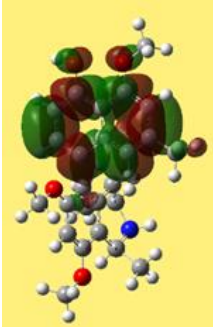
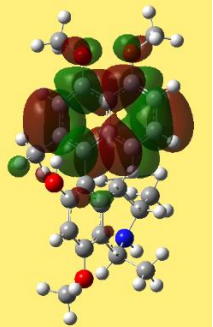
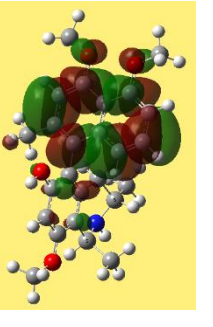
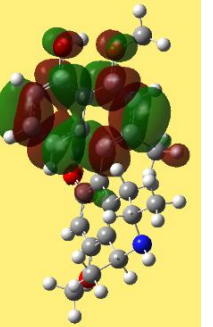
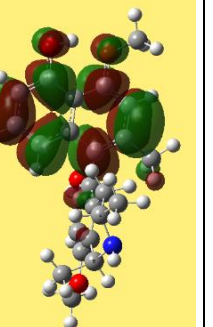
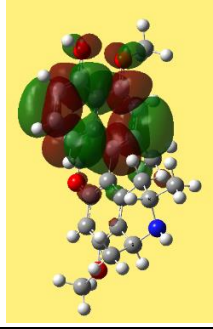
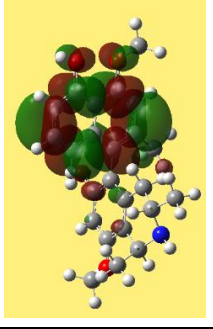
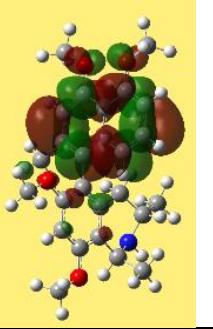
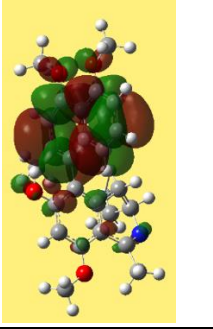
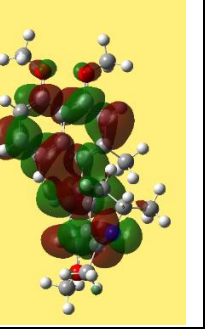
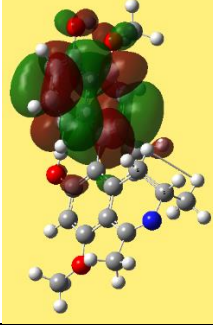
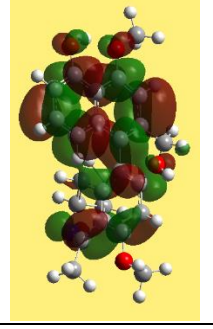
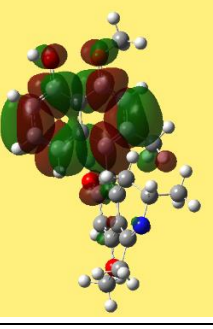
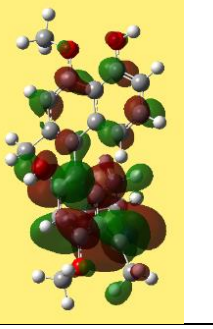
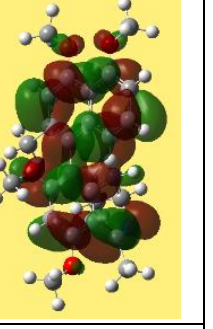
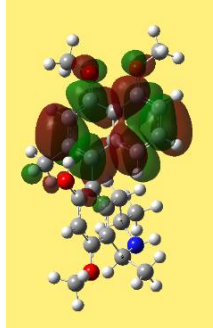
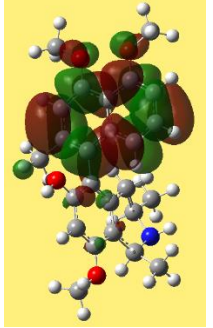
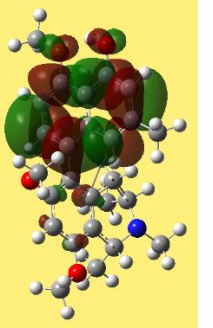
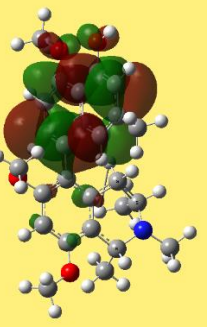
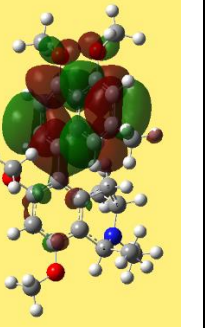
					
NPQ7-31-a-d-x	NPQ7-31-a-x	NPQ7-31-d	NPQ7-31	NPQ7-32-d-e	
					
NPQ7-32-e	NPQ7-32	NPQ7-33-b-e	NPQ7-33-b	NPQ7-33-e	NPQ7-33-z

Figure 5.K4. Shapes of the LUMO frontiers orbitals for all conformers of the calculated monomeric naphthylisoquinoline alkaloids. HF results



				
NPQ5-7-x	NPQ5-7-z	NPQ5-8-b-x	NPQ5-8-b	NPQ5-8-x
				
NPQ5-8-z	NPQ5-9-b-d-x	NPQ5-9-b-x	NPQ5-9-d-x	NPQ5-9-x
				
NPQ7-10-d	NPQ7-10-z	NPQ7-11-d-x	NPQ7-11-x	NPQ5-12-a-d-x
				
NPQ5-12-a-x	NPQ5-12-d-x	NPQ5-12-x	NPQ5-13-b-d-x	NPQ5-13-b-x

				
NPQ5-13-d-x	NPQ5-13-x	NPQ5-14-b-d-x	NPQ5-14-b-x	NPQ5-14-d-x
				
NPQ5-14-x	NPQ5-15-x	NPQ5-15-z	NPQ5-16-d	NPQ5-16-z
				
NPQ7-17-d	NPQ7-17-z	NPQ5-18	NPQ5-19-b-d-x	NPQ5-19-b
				
NPQ5-19-d-x	NPQ5-19-x	NPQ5-20-d-x	NPQ5-20-x	NPQ5-21-a-x

				
NPQ5-21-x	NPQ5-22-d-x	NPQ5-22-x	NPQ5-23-a-d-x	NPQ5-23-a-x
				
NPQ5-23-d-x	NPQ5-23-x	NPQ5-24	NPQ5-25-d-x	NPQ5-25-x
				
NPQ5-26-a-d-x	NPQ5-26-a-x	NPQ5-26-d-x	NPQ5-26-x	NPQ5-27
				
NPQ7-28-d-x	NPQ7-28-x	NPQ5-29-a-x	NPQ5-29-x	NPQ7-30

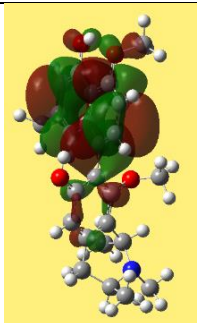
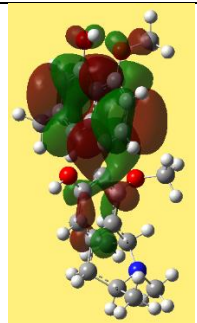
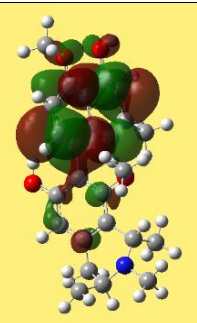
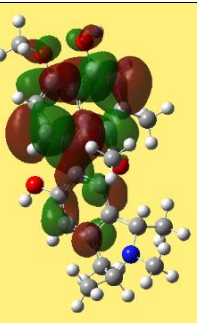
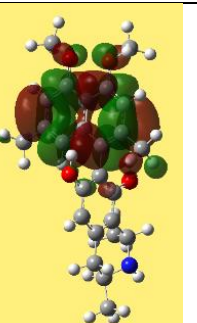
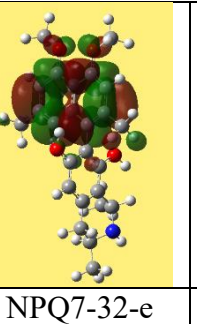
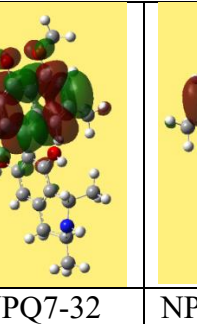
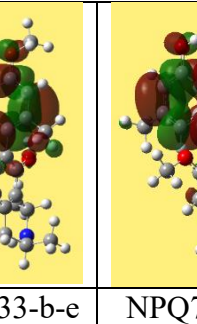
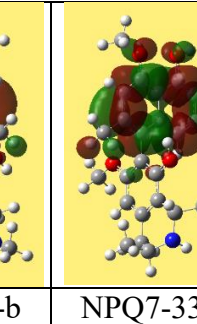
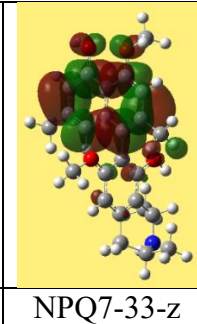
					
NPQ7-31-a-d-x	NPQ7-31-a-x	NPQ7-31-d	NPQ7-31	NPQ7-32-d-e	
					
NPQ7-32-e	NPQ7-32	NPQ7-33-b-e	NPQ7-33-b	NPQ7-33-e	NPQ7-33-z

Table 5.4. Combinations of intramolecular hydrogen bonds and acronyms utilized to denote them

Acronym	a: O–H...O (O–H attached to C15)	b: O–H...O (O–H attached to C14)	d: O–H... π (O–H attached to C6)	e: O–H... π (O–H attached to C8)	x: C–H...O (the C pertaining to a CH ₃)
a	•				
a-b	•	•			
a-d	•		•		
a-e	•			•	
a-x	•				•
a-z	•				
b		•			
b-d		•	•		
b-e		•		•	
b-x		•			•
d			•		
d-x			•		•
d-z			•		
x					•
x-z					
a-b-d	•	•	•		
a-b-e	•	•		•	
a-b-x	•	•			•
a-b-y	•	•			
b-d-e		•	•	•	
b-d-x		•	•		•
b-d-y		•	•		
e-x-y				•	•
d-x-z			•		•
a-b-d-e	•	•	•	•	•
a-b-d-x	•	•	•		•
a-b-d-y	•	•	•		
b-d-e-x		•	•	•	•
b-d-e-y		•	•		

Table 5.5. Relative energies of conformers of the calculated naphthylisoquinoline alkaloids, according to HF/6-31G(d,p) and DFT//6-31G+(d,p) results (respectively denoted as HF and DFT+ in the column headings)

conformers	HF	DFT+	conformers	HF	DFT+
NPQ7-1-b-e	0.000	0.000	NPQ5-14-b-d-x	0.000	0.000
NPQ7-1-b	4.656	4.439	NPQ5-14-b-x	4.218	4.037
NPQ7-1-e	7.212	7.446	NPQ5-14-d-x	7.179	7.438
NPQ7-1-z	12.332	12.348	NPQ5-14-x	11.334	11.414
NPQ5-2-a-x	0.000	0.000	NPQ5-15-x	0.000	0.000
NPQ5-2-a	1.486	1.574	NPQ5-15-z	0.743	0.362
NPQ5-2-x	7.132	7.394	NPQ5-16-d	0.000	0.000
NPQ7-3-d-x	0.000	0.000	NPQ5-16-z	4.073	3.983
NPQ7-3-x	4.526	4.982	NPQ7-17-d	0.000	0.000
NPQ5-4-a-d-x	0.000	0.000	NPQ7-17-z	2.916	2.857
NPQ5-4-a-x	4.377	4.266	NPQ5-19-b-d-x	0.000	0.000
NPQ5-4-d-x	7.303	7.574	NPQ5-19-b	4.383	4.271
NPQ5-4-x	11.597	11.770	NPQ5-19-d-x	7.266	7.540
NPQ5-5-b-d-x	0.000	0.000	NPQ5-19-x	11.569	11.739
NPQ5-5-b-x	4.234	3.925	NPQ5-20-d-x	0.000	0.000
NPQ5-5-d-x	3.272	3.803	NPQ5-20-x	4.406	4.332
NPQ5-5-x	7.424	7.704	NPQ5-21-a-x	0.000	0.000
NPQ5-6-b-d-x	0.000	0.000	NPQ5-21-x	7.170	7.466
NPQ5-6-b-x	4.217	3.903	NPQ5-23-a-d-x	0.000	0.000
NPQ5-6-x	11.523	11.407	NPQ5-23-a- x	3.736	3.397
NPQ5-7-x	0.000	0.000	NPQ5-23-d-x	6.896	7.097
NPQ5-7-z	0.972	0.815	NPQ5-23-x	11.041	10.968
NPQ5-8-b-x	0.000	0.000	NPQ5-26-a-d-x	0.000	0.000
NPQ5-8-b	0.975	0.824	NPQ5-26-a-x	3.736	3.397
NPQ5-8-x	7.205	7.479	NPQ5-26-d-x	6.896	7.097
NPQ5-8-z	8.179	8.302	NPQ5-26-x	11.041	10.968
NPQ5-9-b-d-x	0.000	0.000	NPQ7-28-d-x	0.000	0.000
NPQ5-9-b-x	5.637	5.663	NPQ7-28-x	4.172	3.818
NPQ5-9-d-x	8.768	9.235	NPQ5-29-a-x	0.000	0.000
NPQ5-9-x	12.930	13.217	NPQ5-29-x	7.340	7.613
NPQ7-10-d	0.000	0.000	NPQ7-31-a-d-x	0.000	0.000
NPQ7-10-z	2.888	3.017	NPQ7-31-a-x	2.939	3.128
NPQ7-11-d-x	0.000	0.000	NPQ7-31-d	5.001	7.060
NPQ7-11-x	3.111	3.211	NPQ7-31-z	8.530	10.559
NPQ5-12-a-d-x	0.000	0.000	NPQ7-32-d-e	0.000	0.000
NPQ5-12-a-x	3.902	3.883	NPQ7-32-e	4.665	2.608
NPQ5-12-d-x	6.780	3.883	NPQ7-32	8.495	5.388
NPQ5-12-x	11.111	11.347	NPQ7-33-b-e	0.000	0.000
NPQ5-13-b-d-x	0.000	0.000	NPQ7-33-b	5.470	5.253

NPQ5-13-b-x	3.902	2.646	NPQ7-33-e	6.869	7.209
NPQ5-13-d-x	6.780	5.842	NPQ7-33-z	12.778	12.886
NPQ5-13-x	11.110	10.111			

Table 5.6. Parameters of the intramolecular hydrogen bonds (IHB) of the conformers of the calculated naphthylisoquinoline alkaloids

The table considers all the IHB-type interactions. For the O–H···O IHBs, the length reported is the H···O distance. For the O–H··· π interaction, the length reported is the distance between the H of O–H group and the closest C atom in the aromatic ring. For C–H···O interactions, the length reported is the distance between the H of the CH group and the O atom (the H is given the same number as the C atom to which it is attached). The results are from HF/6-31G(d,p) and DFT/B3LYP/6-31+G(d,p) calculations *in vacuo*.

conformers	IHB considered	Parameters of the IHB					
		HF/6-31G(d,p)			DFT/B3LYP/6-31+G(d,p)		
		H···O (Å)	O···O (Å)	O $\hat{H}$ O (°)	H···O (Å)	O···O (Å)	O $\hat{H}$ O (°)
NPQ7-1-b-e	H30···O24	1.799	2.607	141.6	1.752	2.604	144.1
	O22–H29··· π	2.341			2.305		
NPQ7-1-b	H30···O24	1.794	2.605	142.0	1.747	2.601	144.5
	O22–H29··· π	2.333			2.296		
NPQ5-2-a-x	H31···O23	1.799	2.607	141.7	1.753	2.605	144.1
	C–H26···O21	2.361			2.346		
NPQ5-2-a	H30···O24	1.799	2.607	141.7	1.753	2.605	144.1
	C–H26···O21	2.360			2.345		
NPQ7-3-d-x	O22–H29··· π	2.333			2.292		
	C–H26···O21	2.378			2.344		
NPQ7-3-x	C–H26···O21	2.486			2.534		
	H31···O23	1.798	2.605	141.6	1.751	2.602	144.0
NPQ5-4-a-d-x	O22–H29··· π	2.341			2.318		
	C–H26···O21	2.521			2.514		
NPQ5-4-a-x	H31···O23	1.800	2.608	141.7	1.755	2.606	144.0
	C–H26···O21	2.529			2.518		
NPQ5-4-d-x	O22–H29··· π	2.342			2.319		
	C–H26···O21	2.522			2.513		
NPQ5-4-x	C–H26···O21	2.530			2.519		
	H30···O24	1.797	2.604	141.6	1.752	2.603	144.0
NPQ5-5-b-d-x	O22–H29··· π	2.333			2.307		
	C–H26···O21	2.404			2.399		
NPQ5-5-b-x	H30···O24	1.799	2.607	141.7	1.755	2.606	144.0
	C–H26···O21	2.407			2.396		
NPQ5-5-d-x	O22–H29··· π	2.343			2.320		
	C–H26···O21	2.382			2.341		
NPQ5-5-x	C–H26···O21	2.386			2.343		
	H30···O24	1.797	2.604	141.6	1.751	2.603	144.1
NPQ5-6-b-d-x	O22–H29··· π	2.334			2.312		
	C–H26···O21	2.394			2.395		

NPQ5-6-b-x	H30...O24	1.799	2.607	141.7	1.755	2.606	144.1
	C-H26...O21	2.398			2.403		
NPQ5-6-x	C-H26...O21	2.398			2.404		
NPQ5-7-x	C-H26...O21	2.527			2.520		
NPQ5-8-b-x	H30...O24	1.800	2.607	141.6	1.756	2.606	143.9
	C-H26...O21	2.526			2.517		
NPQ5-8-b	H30...O24	1.800	2.607	141.6	1.756	2.606	143.9
NPQ5-8-x	C-H26...O21	2.526			2.517		
NPQ5-9-b-d-x	H30...O24	1.797	2.604	141.5	1.751	2.602	143.9
	O22-H29... π	2.333			2.310		
	C-H26...O21	2.468			2.453		
NPQ5-9-b-x	H30...O24	1.798	2.605	141.6	1.754	2.604	143.9
	C-H26...O21	2.458			2.446		
NPQ5-9-d-x	O22-H29... π	2.337			2.312		
	C-H26...O21	2.456			2.446		
NPQ5-9-x	C-H26...O21	2.457			2.445		
NPQ7-10-d	O22-H29... π	2.363			2.350		
NPQ7-11-d-x	O22-H29... π	2.382			2.368		
	C-H26...O21	2.409			2.410		
NPQ7-11-x	C-H26...O21	2.402			2.402		
NPQ5-12-a-d-x	H31...O23	1.802	2.608	141.5	1.757	2.607	143.9
	O22-H29... π	2.348			2.326		
	C-H26...O21	2.456			2.447		
NPQ5-12-a-x	H30...O24	1.798	2.607	141.9	1.752	2.605	144.3
	C-H26...O21	2.457			2.447		
NPQ5-12-d-x	O22-H29... π	2.342					
	C-H26...O21	2.456					
NPQ5-12-x	C-H26...O21	2.457			2.448		
NPQ5-13-b-d-x	H30...O24	1.802	2.608	141.5	1.752	2.605	144.3
	O22-H29... π	2.348			2.220		
	C-H26...O21	2.456			2.447		
NPQ5-13-b-x	H30...O24	1.798	2.607	141.9	1.752	2.605	144.3
	C-H26...O21	2.457			2.447		
NPQ5-13-d-x	O22-H29... π	2.342			2.319		
	C-H26...O21	2.456			2.447		
NPQ5-13-x	C-H26...O21	2.457			2.448		
NPQ5-14-b-d-x	H30...O24	1.798	2.605	141.5	1.752	2.603	143.9
	O22-H29... π	2.347			2.329		
	C-H26...O21	2.492			2.431		
NPQ5-14-b-x	H30...O24	1.801	2.608	141.6	1.755	2.606	144.0
	C-H26...O21	2.505			2.427		
NPQ5-14-d-x	O22-H29... π	2.349			2.331		
	C-H26...O21	2.491			2.435		
NPQ5-14-x	C-H26...O21	2.502			2.421		

NPQ5-15-x	C–H1···O21	2.403			2.408		
NPQ5-16-d	O22–H29··· π	2.348			2.326		
NPQ7-17-d	O22–H29··· π	2.334			2.289		
NPQ5-19-b-d-x	H30···O24	1.797	2.604	141.5	1.750	2.602	144.0
	O22–H29··· π	2.341			2.318		
	C–H26···O21	2.456			2.444		
NPQ5-19-b	H30···O24	1.800	2.607	141.6	1.754	2.605	144.0
	C–H26···O21	2.458			2.447		
NPQ5-19-d-x	O22–H29··· π	2.342			2.318		
	C–H26···O21	2.456			2.445		
NPQ5-19-x	C–H26···O21	2.457			2.446		
NPQ5-20-d-x	O22–H29··· π	2.342			2.316		
	C–H26···O21	2.456			2.445		
NPQ5-20-x	C–H26···O21	2.457			2.448		
NPQ5-21-a-x	H31···O23	1.801	2.608	141.6	1.756	2.606	144.0
	C–H26···O21	2.378			2.364		
NPQ5-21-x	C–H26···O21	2.378			2.363		
NPQ5-22-d-x	O22–H29··· π	2.339			2.317		
	C–H26···O21	2.513			2.505		
NPQ5-22-x	C–H26···O21	2.518			2.510		
NPQ5-23-a-d-x	H31···O23	1.801	2.607	141.5	1.755	2.606	143.9
	O22–H29··· π	2.347			2.327		
	C–H26···O21	2.512			2.505		
NPQ5-23-a-x	H31···O23	1.797	2.607	141.9	1.752	2.605	144.3
	C–H26···O21	2.518			2.526		
NPQ5-23-d-x	O22–H29··· π	2.340			2.317		
	C–H26···O21	2.512			2.520		
NPQ5-23-x	C–H26···O21	2.518			2.526		
NPQ5-25-d-x	O22–H29··· π	2.336			2.311		
	C–H26···O21	2.456			2.447		
NPQ5-25-x	C–H26···O21	2.457			2.447		
NPQ5-26-a-d-x	H31···O23	1.788	2.601	142.4			
	O22–H29··· π	2.350					
	C–H26···O21	2.228					
NPQ5-26-a-x	H31···O23	1.798	2.606	141.8	1.753	2.605	144.2
	C–H26···O21	2.458			2.445		
NPQ5-26-d-x	O22–H29··· π	2.336			2.311		
	C–H26···O21	2.456			2.443		
NPQ5-26-x	C–H26···O21	2.457			2.442		
NPQ7-28-d-x	O22–H29··· π	2.343			2.317		
	C–H26···O21	2.367			2.355		
NPQ7-28-x	C–H26···O21	2.369			2.360		
NPQ5-29-a-x	H31···O23	1.796	2.606	142.0	1.750	2.604	144.4
	C–H26···O21	2.383			2.388		

NPQ5-29-x	C–H26···O21	2.382			2.381		
NPQ7-31-a-d-x	H31···O23	1.850	2.648	140.3	1.756	2.606	143.9
	O22–H29··· π	2.381			2.344		
NPQ7-31-a-x	H31···O23	1.848	2.647	140.5	1.752	2.605	144.3
	C–H26···O21	2.463			2.463		
NPQ7-31-d	O22–H29 π	2.368			2.338		
NPQ7-32-d-e	O21–H25··· π	2.332			2.220		
	O22–H29··· π	2.372			2.250	2.628	
NPQ7-32-e	O22–H29··· π	2.352			2.250		
NPQ7-33-b-e	H31···O23	1.803	2.611	141.7	1.760	2.611	144.1
	O22–H29··· π	2.308			2.280		
NPQ7-33-b	H30···O24	1.799	2.610	142.1	1.756	2.610	144.5
NPQ7-33-e	O22–H29··· π	2.272			2.301		

Table 5.7. Vibrational frequencies (harmonic approximation) of the O–H bonds in the naphthylisoquinoline alkaloids

The frequency values have been scaled by 0.9024 and 0.9857 respectively for HF (HF/6-31G (d,p)) [447] and DFT+ (DFT/B3LYP/6-31+G(d,p)) [448] results *in vacuo*.

conformers	Vibrational frequencies			
	HF		DFT+	
	O23–H30 ^(a) O24–H31 ^(b) or	O21–H25... π ^(c) O22–H29... π ^(d)	O23–H30 ^(a) O24–H31 ^(b) or	O21–H25... π ^(c) O22–H29... π ^(d)
NPQ7-1-b-e	3735.07 ^(b)	3788.61 ^(d)	3610.71 ^(b)	3797.02 ^(d)
NPQ7-1-b	3731.27 ^(b)	3795.39 ^(d)	3604.48 ^(b)	3796.46 ^(d)
NPQ7-1-e	3743.73 ^(b)	3788.88 ^(d)	3687.81 ^(b)	3796.39 ^(d)
NPQ7-1-z	3782.57 ^(b)	3797.73 ^(d)	3759.95 ^(b)	3796.21 ^(d)
NPQ5-2-b-x	3739.42 ^(b)		3617.08 ^(b)	
NPQ5-2-b	3739.22 ^(b)		3616.93 ^(b)	
NPQ5-2-x	3782.15 ^(b)		3759.14 ^(b)	
NPQ7-3-d-x		3788.92 ^(d)		3796.80 ^(d)
NPQ7-3-x		3788.91 ^(d)		3796.81 ^(d)
NPQ5-4-a-d-x	3731.79 ^(a)	3750.71 ^(d)	3606.00 ^(a)	3697.94 ^(d)
NPQ5-4-a-x	3739.48 ^(a)	3789.21 ^(d)	3617.09 ^(a)	3777.89 ^(d)
NPQ5-5-b-d-x	3730.03 ^(b)	3746.87 ^(d)	3606.85 ^(b)	3693.03 ^(d)
NPQ5-5-b-x	3737.76 ^(b)	3790.86 ^(d)	3617.35 ^(b)	3777.42 ^(d)
NPQ5-5-d-x	3779.68 ^(b)	3748.34 ^(d)	3756.25 ^(b)	3696.29 ^(d)
NPQ5-5-x	3781.59 ^(b)	3790.89 ^(d)	3758.19 ^(b)	3778.35 ^(d)
NPQ5-6-b-d-x	3730.21 ^(b)	3747.20 ^(d)	3606.04 ^(b)	3694.39 ^(d)
NPQ5-6-b-x	3737.89 ^(b)	3790.96 ^(d)	3616.95 ^(b)	3777.75 ^(d)
NPQ5-6-x	3781.59 ^(b)	3790.95 ^(d)	3758.50 ^(b)	3778.54 ^(d)
NPQ5-8-b-x	3739.30 ^(b)	3790.32 ^(d)	3619.05 ^(b)	3780.25 ^(d)
NPQ5-8-b	3739.19 ^(b)	3807.33 ^(d)	3619.21 ^(b)	3778.52 ^(d)
NPQ5-8-x	3781.41 ^(b)	3790.16 ^(d)	3758.19 ^(b)	3780.29 ^(d)
NPQ5-8-z	3781.39 ^(b)	3807.85 ^(d)	3757.99 ^(b)	3778.90 ^(d)
NPQ5-9-b-d-x	3728.77 ^(b)	3740.46 ^(c)	3758.22 ^(b)	3772.71 ^(c)
NPQ5-9-b-x	3736.15 ^(b)	3786.98 ^(c)	3614.79 ^(b)	3772.67 ^(c)
NPQ5-9-d-x	3778.93 ^(b)	3740.60 ^(c)	3756.33 ^(b)	3684.50 ^(c)
NPQ5-9-x	3781.02 ^(b)	3786.99 ^(c)	3758.22 ^(b)	3772.71 ^(c)
NPQ7-10-d		3764.90 ^(d)		3721.89 ^(d)
NPQ7-10-z		3789.02 ^(d)		3776.78 ^(d)
NPQ7-11-d-x		3763.24 ^(d)		3721.38 ^(d)
NPQ7-11-x		3788.92 ^(d)		3775.86 ^(d)
NPQ5-12-a-d-x	3741.17 ^(a)	3750.60 ^(d)	3621.49 ^(a)	3698.29 ^(d)
NPQ5-12-a-x	3737.67 ^(a)	3787.49 ^(d)	3615.86 ^(a)	3772.87 ^(d)
NPQ5-12-d-x	3780.75 ^(a)	3746.02 ^(d)	3759.61 ^(a)	3691.24 ^(d)

NPQ5-12-x	3781.90 ^(a)	3787.76 ^(d)	3759.94 ^(a)	3772.66 ^(d)
NPQ5-13-b-d-x	3737.60 ^(b)	3787.50 ^(d)	3615.85 ^(b)	3772.86 ^(d)
NPQ5-13-b-x	3781.90 ^(b)	3787.75 ^(d)	3759.90 ^(b)	3772.63 ^(d)
NPQ5-13-d-x	3741.13 ^(b)	3750.61 ^(d)	3621.05 ^(b)	3698.00 ^(d)
NPQ5-13-x	3780.89 ^(b)	3746.03 ^(d)	3759.32 ^(b)	3690.75 ^(d)
NPQ5-14-b-d-x	3732.77 ^(b)	3785.48 ^(d)	3608.64 ^(b)	3706.22 ^(d)
NPQ5-14-b-x	3740.06 ^(b)	3790.57 ^(d)	3616.95 ^(b)	3777.48 ^(d)
NPQ5-14-d-x	3779.56 ^(b)	3753.54 ^(d)	3757.21 ^(b)	3708.83 ^(d)
NPQ5-14-x	3781.51 ^(b)	3790.62 ^(d)	3759.33 ^(b)	3779.64 ^(d)
NPQ5-16-d		3791.86 ^(d)		3779.28 ^(d)
NPQ5-16-z		3755.67 ^(d)		3708.64 ^(d)
NPQ7-17-d		3786.98 ^(d)		3775.41 ^(d)
NPQ7-17-z		3750.59 ^(d)		3691.62 ^(d)
NPQ5-19-b-d-x	3744.93 ^(b)	3730.54 ^(d)	3606.37 ^(b)	3689.07 ^(d)
NPQ5-19-b	3738.45 ^(b)	3787.65 ^(d)	3617.22 ^(b)	3773.99 ^(d)
NPQ5-19-d-x	3746.32 ^(b)	3779.25 ^(d)	3692.02 ^(b)	3757.08 ^(d)
NPQ5-19-x	3787.71 ^(b)	3781.35 ^(d)	3758.07 ^(b)	3773.26 ^(d)
NPQ5-20-d-x		3745.45 ^(d)		3689.73 ^(d)
NPQ5-20-x		3787.85 ^(d)		3773.60 ^(d)
NPQ5-21-a-x	3740.83 ^(a)		3618.57 ^(a)	
NPQ5-22-d-x		3749.24 ^(d)		3697.77 ^(d)
NPQ5-22-x		3791.65 ^(d)		3779.15 ^(d)
NPQ5-23-a-d-x	3741.22 ^(a)	3756.36 ^(d)	3619.13 ^(a)	3707.51 ^(d)
NPQ5-23-a-x	3738.09 ^(a)	3791.26 ^(d)	3615.29 ^(a)	3779.31 ^(d)
NPQ5-23-d-x	3781.48 ^(a)	3749.98 ^(d)	3760.23 ^(a)	3698.69 ^(d)
NPQ5-23-x	3782.63 ^(a)	3791.47 ^(d)	3760.47 ^(a)	3779.04 ^(d)
NPQ5-25-d-x		3739.89 ^(d)		3682.65 ^(d)
NPQ5-25-x		3787.26 ^(d)		3773.21 ^(d)
NPQ5-26-a-d-x	3742.66 ^(a)	3747.54 ^(d)	3622.38 ^(a)	3691.85 ^(d)
NPQ5-26-a-x	3739.33 ^(a)	3786.86 ^(d)	3616.43 ^(a)	3772.17 ^(d)
NPQ5-26-d-x	(a)	(d)	3759.66 ^(a)	3684.08 ^(d)
NPQ5-26-x	3782.22 ^(a)	3787.20 ^(d)	3760.01 ^(a)	3772.47 ^(d)
NPQ7-28-d-x		3748.16 ^(d)		(d)
NPQ7-28-x		3790.91 ^(d)		(d)
NPQ5-29-a-x	3734.36 ^(a)		3611.22 ^(a)	
NPQ5-29-x	3781.63 ^(a)		3758.67 ^(a)	
NPQ7-31-a-d-x	3721.54 ^(a)	3759.89 ^(d)	3624.28 ^(a)	3704.32 ^(d)
NPQ7-31-a-x	3781.53 ^(a)	3754.02 ^(d)	3759.54 ^(a)	3698.66 ^(d)
NPQ7-31-d	3718.54 ^(a)	3788.47 ^(d)	3618.46 ^(a)	3775.64 ^(d)
NPQ7-31	3782.44 ^(a)	3788.74 ^(d)	3759.13 ^(a)	3775.19 ^(d)
NPQ7-32-d-e		3756.01 ^(c)		3711.92 ^(c)
		3750.33 ^(d)		3712.06 ^(d)
NPQ7-32-e		3814.37 ^(c)		3786.17 ^(c)
		3744.70 ^(d)		3692.95 ^(d)
		3815.67 ^(c)		3788.11 ^(c)

NPQ7-32-z		3787.64 ^(d)		3776.15 ^(d)
NPQ7-33-b-e	3742.48 ^(b)	3742.48 ^(d)	3622.51 ^(b)	3686.03 ^(d)
NPQ7-33-b	3738.12 ^(b)	3812.46 ^(d)	3617.20 ^(b)	3792.34 ^(d)
NPQ7-33-e	3781.34 ^(b)	3737.11 ^(d)	3759.54 ^(b)	3676.42 ^(d)
NPQ7-33-z	3782.56 ^(b)	3811.23 ^(d)	3760.91 ^(b)	3791.09 ^(d)

^a is attributed to O23–H30 and ^b to O24–H31

^c Is attributed to O21–H25 and ^d to O22–H29

Table 5.8. Relative energy ($\Delta E_{\text{correct}}$, kcal/mol) corrected for ZPE and ZPE corrections (kcal/mol) of representative conformers of the calculated naphthylisoquinoline alkaloids
Results are from HF/6-31G(d,p) and DFT/6-31+G(d,p) frequency calculations.

conformer	HF		DFT+	
	$\Delta E_{\text{correct}}$	ZPE	$\Delta E_{\text{correct}}$	ZPE
NPQ7-1-b-e	0.000	296.494	0.000	275.673
NPQ7-1-b	4.353	296.194	4.239	275.473
NPQ7-1-e	6.803	296.086	7.017	275.244
NPQ7-1-z	11.590	295.751	11.698	275.022
NPQ5-2-a-x	0.000	292.400	0.000	272.326
NPQ5-2-a	1.477	292.390	1.496	272.249
NPQ5-2-x	6.699	291.966	6.723	271.654
NPQ7-3-d-x	0.000	315.037	0.000	293.120
NPQ7-3-x	4.170	314.681	4.676	292.815
NPQ5-4-a-d-x	0.000	295.781	0.000	275.218
NPQ5-4-a-x	4.014	295.419	3.956	274.907
NPQ5-4-d-x	6.863	295.342	7.118	274.761
NPQ5-4-x	10.796	294.981	10.998	274.444
NPQ5-5-b-d-x	0.000	314.956	0.000	293.195
NPQ5-5-b-x	3.882	314.605	3.541	292.811
NPQ5-5-d-x	2.538	314.222	2.994	292.386
NPQ5-5-x	6.330	313.861	6.601	292.092
NPQ5-6-b-d-x	0.000	333.439	0.000	310.523
NPQ5-6-b-x	3.868	333.089	3.532	310.152
NPQ5-6-x	10.735	332.651	10.607	309.723
NPQ5-7-x	0.000	332.877	0.000	310.061
NPQ5-7-z	0.999	332.904	0.862	310.040
NPQ5-8-b-x	0.000	314.386	0.000	292.677
NPQ5-8-b	0.999	314.410	0.776	292.629
NPQ5-8-x	6.776	313.956	7.053	292.250
NPQ5-8-z	7.776	313.982	7.826	292.200
NPQ5-9-b-d-x	0.000	298.559	0.000	277.772
NPQ5-9-b-x	5.634	298.556	5.631	277.740
NPQ5-9-d-x	8.657	298.448	9.142	277.678
NPQ5-9-x	12.499	298.119	12.751	277.308
NPQ7-10-d	0.000	332.818	0.000	309.836
NPQ7-10-z	2.732	332.661	2.775	309.593
NPQ7-11-d-x	0.000	351.521	0.000	327.324
NPQ7-11-x	2.931	351.340	2.986	327.097
NPQ5-12-a-d-x	0.000	298.721	0.000	278.078
NPQ5-12-a-x	3.635	298.455	3.515	277.710
NPQ5-12-d-x	6.416	298.358	6.694	277.692

NPQ5-12-x	10.444	298.054	10.595	277.326
NPQ5-13-b-d-x	3.635	298.455	3.515	277.710
NPQ5-13-b-x	10.444	298.054	10.596	277.327
NPQ5-13-d-x	0.000	298.721	0.000	278.078
NPQ5-13-x	6.414	298.356	6.695	277.693
NPQ5-14-b-d-x	0.000	314.188	0.000	292.345
NPQ5-14-b-x	3.879	313.849	3.817	292.124
NPQ5-14-d-x	6.750	313.758	7.137	292.044
NPQ5-14-x	10.573	313.426	10.791	291.722
NPQ5-15-x	0.000	351.219	0.000	327.127
NPQ5-15-z	0.695	351.170	0.369	327.133
NPQ5-16-d	3.790	351.243	3.724	327.065
NPQ5-16-z	0.000	351.526	0.000	327.324
NPQ7-17-d	2.732	332.971	2.603	310.176
NPQ7-17-z	0.000	333.156	0.000	310.432
NPQ5-19-b-d-x	0.000	298.804	0.000	278.056
NPQ5-19-b	4.075	298.496	4.008	277.793
NPQ5-19-d-x	6.833	298.370	7.088	277.604
NPQ5-19-x	10.829	298.064	11.017	277.334
NPQ5-20-d-x	0.000	317.306	0.000	295.391
NPQ5-20-x	4.102	317.002	4.037	295.096
NPQ5-21-a-x	0.000	333.534	0.000	310.557
NPQ5-21-x	6.738	333.102	7.000	310.090
NPQ5-22-d-x	0.000	333.283	0.000	310.375
NPQ5-22-x	3.873	332.934	3.672	310.048
NPQ5-23-a-d-x	0.000	314.667	0.000	292.868
NPQ5-23-a-x	3.454	314.385	3.239	292.713
NPQ5-23-d-x	6.554	314.324	6.704	292.477
NPQ5-23-x	10.350	313.975	10.371	292.274
NPQ5-25-d-x	0.000	317.378	0.000	295.404
NPQ5-25-x	3.929	317.045	3.827	295.213
NPQ5-26-a-d-x	0.000	298.729	0.000	278.077
NPQ5-26-a-x	3.477	298.484	3.330	277.835
NPQ5-26-d-x	6.369	298.425	6.667	277.705
NPQ5-26-x	10.213	298.087	10.337	277.415
NPQ7-28-d-x	0.000	333.287	0.000	310.257
NPQ7-28-x	3.817	332.932	3.683	310.122
NPQ5-29-a-x	0.000	351.782	0.000	327.502
NPQ5-29-x	6.939	351.380	7.179	327.066
NPQ7-31-a-d-x	0.000	332.489	0.000	309.765
NPQ7-31-a-x	4.865	332.353	6.662	309.366
NPQ7-31-d	1.352	332.467	2.969	309.606
NPQ7-31	8.104	332.061	9.965	309.172
NPQ7-32-d-e	0.000	332.656	0.000	309.706

NPQ7-32-e	4.468	332.458	4.013	309.542
NPQ7-32	8.053	332.213	7.623	309.306
NPQ7-33-b-e	0.000	333.061	0.000	310.309
NPQ7-33-b	5.229	332.819	4.773	309.829
NPQ7-33-e	6.510	332.702	6.820	309.920
NPQ7-33-z	12.131	332.414	11.992	309.415

Table 5.9. Relative Gibbs free energies (ΔG , sum of electronic and thermal free energies), and thermal corrections to Gibbs free energy, of the calculated conformers of naphthylisoquinoline alkaloids

Results from HF/6-31G(d,p) and DFT/6-31+G(d,p) frequency calculations.

Conformer	ΔG (kcal/mol)		Thermal correction (kcal/mol)	
	HF	DFT+	HF	DFT+
NPQ7-1-b-e	0.000	0.000	262.507	240.345
NPQ7-1-b	4.204	4.352	262.058	240.257
NPQ7-1-e	6.700	6.852	261.995	239.750
NPQ7-1-z	11.315	11.658	261.488	239.654
NPQ5-2-b-x	0.000	0.000	259.149	272.326
NPQ5-2-b	1.497	1.496	259.160	272.249
NPQ5-2-x	6.489	6.723	258.506	271.654
NPQ7-3-d-x	0.000	0.000	279.703	256.834
NPQ7-3-x	4.084	4.480	279.261	256.333
NPQ5-4-a-d-x	0.000	0.000	262.329	240.689
NPQ5-4-a-x	3.813	3.788	261.765	240.210
NPQ5-4-d-x	6.722	6.978	261.747	240.092
NPQ5-4-x	10.478	10.706	261.209	239.624
NPQ5-5-b-d-x	0.000	0.000	280.476	257.702
NPQ5-5-b-x	3.700	2.959	279.943	256.735
NPQ5-5-d-x	2.201	2.555	279.405	256.453
NPQ5-5-x	5.781	6.010	278.833	256.007
NPQ5-6-b-d-x	0.000	0.000	298.063	274.024
NPQ5-6-b-x	3.688	3.236	297.534	273.357
NPQ5-6-x	10.390	10.179	296.929	272.796
NPQ5-7-x	0.000	0.000	296.513	272.870
NPQ5-7-z	1.027	0.862	296.567	272.915
NPQ5-8-b-x	0.000	0.000	279.604	256.839
NPQ5-8-b	1.018	0.819	279.648	256.834
NPQ5-8-x	6.578	6.918	278.977	256.278
NPQ5-8-z	7.602	7.764	279.026	256.301
NPQ5-9-b-d-x	0.000	0.000	263.971	241.748
NPQ5-9-b-x	5.675	5.903	264.008	241.988
NPQ5-9-d-x	8.721	9.661	263.923	242.173
NPQ5-9-x	12.355	12.871	263.387	241.405
NPQ7-10-d	0.000	0.000	296.686	272.402
NPQ7-10-z	2.728	2.587	296.527	271.971
NPQ7-11-d-x	0.000	0.000	314.686	289.057
NPQ7-11-x	2.896	2.848	314.470	288.693
NPQ5-12-a-d-x	0.000	0.000	264.024	242.391
NPQ5-12-a-x	3.436	3.117	263.558	241.624

NPQ5-12-d-x	6.337	6.578	263.582	241.889
NPQ5-12-x	10.147	10.148	263.060	241.192
NPQ5-13-b-d-x	0.000	0.000	264.026	242.391
NPQ5-13-b-x	3.434	3.116	263.558	241.624
NPQ5-13-d-x	6.328	6.579	263.575	241.891
NPQ5-13-x	10.144	10.152	263.060	241.196
NPQ5-14-b-d-x	0.000	0.000	279.641	256.604
NPQ5-14-b-x	3.714	3.518	279.136	256.083
NPQ5-14-d-x	6.615	7.112	279.077	256.278
NPQ5-14-x	10.302	10.620	278.609	255.810
NPQ5-15-x	0.000	0.000	313.748	288.451
NPQ5-15-z	0.665	0.451	313.670	288.539
NPQ5-16-d	0.000	0.000	314.153	288.623
NPQ5-16-z	3.665	3.601	313.743	288.240
NPQ7-17-d	0.000	0.000	296.675	273.536
NPQ7-17-z	3.074	2.487	296.831	273.163
NPQ5-19-b-d-x	0.000	0.000	264.188	242.277
NPQ5-19-b	3.850	3.897	263.655	241.902
NPQ5-19-d-x	6.687	6.929	263.609	241.665
NPQ5-19-x	10.482	10.722	263.100	241.259
NPQ5-20-d-x	0.000	0.000	281.307	258.297
NPQ5-20-x	3.883	3.849	280.784	257.813
NPQ5-21-a-x	0.000	0.000	297.276	273.114
NPQ5-21-x	6.610	6.849	296.716	272.496
NPQ5-22-d-x	0.000	0.000	297.255	273.404
NPQ5-22-x	3.626	3.451	296.659	272.856
NPQ5-23-a-d-x	0.000	0.000	279.781	256.652
NPQ5-23-a-x	3.186	3.714	279.231	256.972
NPQ5-23-d-x	6.621	6.930	279.506	256.487
NPQ5-23-x	10.157	10.700	278.897	256.387
NPQ5-25-d-x	0.000	0.000	281.567	258.386
NPQ5-25-x	3.673	3.914	280.979	258.281
NPQ5-26-a-d-x	0.000	0.000	263.953	242.657
NPQ5-26-a-x	3.356	3.136	263.587	242.222
NPQ5-26-d-x	6.564	6.537	263.846	242.156
NPQ5-26-x	10.127	10.045	263.226	241.705
NPQ7-28-d-x	0.000	0.000	297.236	272.987
NPQ7-28-x	3.584	3.928	296.647	273.097
NPQ5-29-a-x	0.000	0.000	314.801	288.940
NPQ5-29-x	6.863	6.738	314.324	288.064
NPQ7-31-a-d-x	0.000	0.000	296.290	272.432
NPQ7-31-a-x	4.998	6.592	296.287	271.964
NPQ7-31-d	2.605	2.932	295.956	272.236
NPQ7-31-z	8.070	9.822	295.829	271.697

NPQ7-32-d-e	0.000	0.000	296.265	272.212
NPQ7-32-e	4.324	3.994	295.925	272.028
NPQ7-32	7.775	7.477	295.546	271.666
NPQ7-33-b-e	0.000	0.000	296.553	273.118
NPQ7-33-b	5.158	4.209	296.241	272.073
NPQ7-33-e	6.499	6.758	296.182	272.666
NPQ7-33-z	11.999	11.365	295.774	271.596

Table 5.10. Dipole moment of the conformers of the calculated naphthylisoquinoline alkaloids *in vacuo*

HF/6-31G(d,p) and (DFT/B3LYP/6-31+G(d,p) results, respectively denoted as HF and DFT+ in the method columns.

conformers	Method	Dipole moment (Debye)	conformers	Method	Dipole moment (Debye)
NPQ7-1-b-e	HF	2.8098	NPQ5-15-x	HF	2.2033
	DFT+	2.6984		DFT+	2.1893
NPQ7-1-b	HF	4.4267	NPQ5-15-z	HF	0.8518
	DFT+	4.6430		DFT+	1.1092
NPQ7-1-e	HF	0.6474	NPQ5-16-d	HF	2.2120
	DFT+	0.8136		DFT+	2.3844
NPQ7-1-z	HF	3.3598	NPQ5-16-z	HF	1.9082
	DFT+	3.3780		DFT+	1.6656
NPQ5-2-a-x	HF	3.9787	NPQ7-17-d	HF	3.5959
	DFT+	3.9249		DFT+	4.0452
NPQ5-2-a	HF	3.6826	NPQ7-17-z	HF	2.3678
	DFT+	3.3978		DFT+	2.3799
NPQ5-2-x	HF	2.2665	NPQ5-18-z	HF	4.9685
	DFT+	2.1436		DFT+	5.0232
NPQ7-3-d-x	HF	0.9927	NPQ5-19-b-d-x	HF	5.2634
	DFT+	1.2821		DFT+	5.2176
NPQ7-3-x	HF	2.8260	NPQ5-19-b	HF	5.4260
	DFT+	2.7717		DFT+	5.1025
NPQ5-4-a-d-x	HF	3.6062	NPQ5-19-d-x	HF	3.8474
	DFT+	3.7103		DFT+	3.8992
NPQ5-4-a-x	HF	3.2013	NPQ5-19-x	HF	4.4390
	DFT+	2.9972		DFT+	4.2673
NPQ5-4-d-x	HF	1.9137	NPQ5-20-d-x	HF	4.2640
	DFT+	2.3028		DFT+	4.4619
NPQ5-4-x	HF	1.9365	NPQ5-20-x	HF	4.4346
	DFT+	1.7009		DFT+	4.3418
NPQ5-5-b-d-x	HF	2.8173	NPQ5-21-a-x	HF	4.5316
	DFT+	2.7038		DFT+	4.3038
NPQ5-5-b-x	HF	3.2772	NPQ5-21-x	HF	3.0525
	DFT+	2.9688		DFT+	2.9368
NPQ5-5-d-x	HF	1.5066	NPQ5-22-d-x	HF	1.7960
	DFT+	1.6168		DFT+	1.9824
NPQ5-5-x	HF	2.9121	NPQ5-22-x	HF	2.1316
	DFT+	2.6984		DFT+	1.8345
NPQ5-6-b-d-x	HF	3.1770	NPQ5-23-a-d-x	HF	2.8252
	DFT+	3.0734		DFT+	2.7923

NPQ5-6-b-x	HF	3.5166	NPQ5-23-a-x	HF	3.8645
	DFT+	3.1901		DFT+	3.7588
NPQ5-6-x	HF	2.4554	NPQ5-23-d-x	HF	1.2736
	DFT+	2.1795		DFT+	1.3294
NPQ5-7-x	HF	2.2011	NPQ5-23-x	HF	2.4610
	DFT+	2.0855		DFT+	2.2426
NPQ5-7-z	HF	0.7602	NPQ5-24-z	HF	2.3317
	DFT+	0.8811		DFT+	2.1295
NPQ5-8-b-x	HF	4.0759	NPQ5-25-d-x	HF	4.1006
	DFT+	3.8825		DFT+	4.2641
NPQ5-8-b	HF	3.4628	NPQ5-25-x	HF	4.5134
	DFT+	3.4311		DFT+	4.3787
NPQ5-8-x	HF	2.3299	NPQ5-26-a-d-x	HF	4.9493
	DFT+	2.1512		DFT+	4.9000
NPQ5-8-z	HF	0.9964	NPQ5-26-a-x	HF	5.9696
	DFT+	0.8718		DFT+	5.8530
NPQ5-9-b-d-x	HF	4.6984	NPQ5-26-d-x	HF	3.7116
	DFT+	4.7160		DFT+	3.7287
NPQ5-9-b-x	HF	5.0403	NPQ5-26-x	HF	4.5514
	DFT+	4.7637		DFT+	4.4059
NPQ5-9-d-x	HF	3.6649	NPQ5-27-z	HF	5.0163
	DFT+	3.6779		DFT+	4.9815
NPQ5-9-x	HF	4.5334	NPQ7-28-d-x	HF	2.7569
	DFT+	4.3611		DFT+	2.9012
NPQ7-10-d	HF	4.1006	NPQ7-28-x	HF	2.7216
	DFT+	3.8230		DFT+	2.5347
NPQ7-10-z	HF	1.9227	NPQ5-29-a-x	HF	2.2737
	DFT+	1.9402		DFT+	2.0962
NPQ7-11-d-x	HF	2.9812	NPQ5-29-x	HF	1.5754
	DFT+	3.2818		DFT+	1.3732
NPQ7-11-x	HF	1.2729	NPQ5-30-z	HF	2.1712
	DFT+	1.1418		DFT+	2.1136
NPQ5-12-a-d-x	HF	4.5346	NPQ7-31-a-d-x	HF	3.2059
	DFT+	4.5114		DFT+	3.3025
NPQ5-12-a-x	HF	5.4272	NPQ7-31-a-x	HF	3.7245
	DFT+	5.3694		DFT+	3.6717
NPQ5-12-d-x	HF	3.8432	NPQ7-31-d	HF	1.9850
	DFT+	3.9035		DFT+	2.2670
NPQ5-12-x	HF	4.4470	NPQ7-31-z	HF	1.4831
	DFT+	4.2987		DFT+	1.0943
NPQ5-13-b-d-x	HF	4.5348	NPQ7-32-d-e	HF	3.9889
	DFT+	4.3547		DFT+	4.2182
NPQ5-13-b-x	HF	5.4274	NPQ7-32-e	HF	2.2054
	DFT+	5.3692		DFT+	2.4934
NPQ5-13-d-x	HF	3.8432	NPQ7-32	HF	2.6817

	DFT+	3.9041		DFT+	2.0263
NPQ5-13-x	HF	4.4469	NPQ7-33-b-e	HF	3.7911
	DFT+	4.2986		DFT+	3.9069
NPQ5-14-b-d-x	HF	4.8625	NPQ7-33-b	HF	4.0496
	DFT+	4.9802		DFT+	3.6639
NPQ5-14-b-x	HF	4.7055	NPQ7-33-e	HF	3.0650
	DFT+	4.6326		DFT+	2.9479
NPQ5-14-d-x	HF	2.5167	NPQ7-33-z	HF	2.6244
	DFT+	2.7486		DFT+	2.4108
NPQ5-14-x	HF	2.4132			
	DFT+	2.1981			

Table 5.11. HOMO-LUMO energy gaps of the conformers of the calculated naphthylisoquinoline alkaloids *in vacuo*

HF/6-31G(d,p) and (DFT/B3LYP/6-31+G(d,p) results, respectively denoted as HF and DFT+ in the column headings.

Conformers	HOMO-LUMO energy difference (kcal/mol)		Conformers	HOMO-LUMO energy difference (kcal/mol)	
	HF	DFT+		HF	DFT+
NPQ7-1-b-e	234.795	98.951	NPQ5-15-x	241.133	102.516
NPQ7-1-b	236.131	99.579	NPQ5-15-z	241.139	102.673
NPQ7-1-e	237.003	100.113	NPQ5-16-d	241.215	102.692
NPQ7-1-z	237.643	100.144	NPQ5-16-z	240.424	100.771
NPQ5-2-a-x	238.779	100.370	NPQ7-17-d	239.206	100.508
NPQ5-2-a	231.839	100.018	NPQ7-17-z	238.497	136.766
NPQ5-2-x	239.915	100.840	NPQ5-18-z	238.629	100.376
NPQ7-3-d-x	237.399	100.803	NPQ5-19-b	238.547	100.791
NPQ7-3-x	238.014	99.014	NPQ5-19-d-x	240.210	101.687
NPQ5-4-a-d-x	238.829	101.016	NPQ5-19-x	238.240	99.560
NPQ5-4-a-x	238.924	101.110	NPQ5-19-b-d-x	238.779	101.116
NPQ5-4-d-x	240.354	101.631	NPQ5-20-d-x	240.034	102.221
NPQ5-4-x	241.057	102.026	NPQ5-20-x	238.277	99.184
NPQ5-5-b-x	236.245	99.767	NPQ5-21-a-x	238.460	100.370
NPQ5-5-d-x	236.069	99.623	NPQ5-21-x	240.731	101.562
NPQ5-5-x	237.267	100.156	NPQ5-22-d-x	238.302	101.311
NPQ5-5-x	237.681	100.338	NPQ5-23-a-d-x	238.829	99.642
NPQ5-6-b-d-x	236.251	97.351	NPQ5-23-a-x	237.681	100.163
NPQ5-6-b-x	236.063	99.617	NPQ5-23-d-x	238.152	100.753
NPQ5-6-x	237.807	100.483	NPQ5-23-x	238.993	100.897
NPQ5-7-x	238.912	101.361	NPQ5-23-z	238.955	101.431
NPQ5-7-z	238.874	101.418	NPQ5-25-d-x	237.581	101.054
NPQ5-8-b-x	236.012	130.164	NPQ5-26-a-d-x	238.547	99.008
NPQ5-8-b	235.987	99.447	NPQ5-26-a-x	236.200	98.569
NPQ5-8-x	237.869	130.672	NPQ5-26-d-x	237.381	100.564
NPQ5-8-z	237.838	130.704	NPQ5-26-x	237.581	98.431
NPQ5-9-b-d-x	235.856	99.969	NPQ5-27-z	236.752	98.889
NPQ5-9-b-x	235.328	98.820	NPQ7-28-d-x	237.845	101.004
NPQ5-9-d-x	236.979	100.163	NPQ7-28-x	238.435	101.267
NPQ5-9-x	236.169	98.136	NPQ5-29-a-x	238.140	100.740
NPQ7-10-d	238.397	101.010	NPQ5-29-x	239.244	100.997
NPQ7-10-z	238.508	101.450	NPQ5-30-a-x	239.664	101.461
NPQ7-11-d-x	238.246	100.978	NPQ7-31-a-x	235.542	99.315
NPQ7-11-x	238.817	101.004	NPQ7-31	238.535	100.194
NPQ5-12-a-d-x	237.210	88.459	NPQ7-32-d-e	238.892	105.578
NPQ5-12-a-x	238.058	99.993	NPQ7-32-e	239.739	107.292

NPQ5-12-d-x	239.106	101.192	NPQ7-32-z	240.292	107.235
NPQ5-12-x	238.233	99.642	NPQ7-33-b-e	236.803	100.257
NPQ5-13-b-d-x	238.058	99.993	NPQ7-33-b	237.857	100.878
NPQ5-13-b-x	238.227	99.642	NPQ7-33-e	239.206	101.662
NPQ5-13-d-x	237.204	99.974	NPQ7-33-z	239.639	101.650
NPQ5-13-x	239.106	101.192			
NPQ5-14-b-d-x	238.792	97.891			
NPQ5-14-b-x	238.622	100.821			
NPQ5-14-d-x	240.367	99.949			
NPQ5-14-x	240.624	101.800			

Table 5.K1. Absolute energy of the lowest energy conformers of naphthylisoquinoline alkaloids with the same molecular formula

Results from HF/6-31G(d,p) and DFT/ B3LYP /6-31G+(d,p) calculations *in vacuo*.

Molecule's name	Conformers	Molecular formula	Absolute energy (hartree)	
			HF	DFT+
ancistectorine A3-b	NPQ5-9	C ₂₄ H ₂₅ NO ₄	-1277.33397248	-1285.34122170
5-epi-ancistrolikokine D-b	NPQ5-12	C ₂₄ H ₂₅ NO ₄	-1277.33376237	-1285.34010500
ancistrolikokine D-b	NPQ5-13	C ₂₄ H ₂₅ NO ₄	-1277.32754402	-1285.33391608
6,5'-O,O-didemethylancistroealaine A-b	NPQ5-19	C ₂₄ H ₂₅ NO ₄	-1277.334386	-1285.340646
50-O-demethylhamatinine-b	NPQ5-26	C ₂₄ H ₂₅ NO ₄	-1277.33044934	
ancistectorine A1-b	NPQ5-5	C ₂₄ H ₂₇ NO ₄	-1278.49411008	-1286.54348335
4'-O-demethylancistectorine A2-c	NPQ5-8	C ₂₄ H ₂₇ NO ₄	-1278.49496745	-1286.54464935
ancistrocongoline A-b	NPQ5-14	C ₂₄ H ₂₇ NO ₄	-1278.50363193	-1286.55226614
50-O-demethylhamatine-b	NPQ5-23	C ₂₄ H ₂₇ NO ₄	-1278.50092749	-1286.54993940
6-O-demethylancistroealaine A-a	NPQ5-20	C ₂₅ H ₂₇ NO ₄	-1316.34502180	-1324.63102035
hamatinine	NPQ5-25	C ₂₅ H ₂₇ NO ₄	-1316.34197450	-1324.62862381
N-methylancistectorine A1-a	NPQ5-6	C ₂₅ H ₂₉ NO ₄	-1317.52079933	-1325.85086071
ancistectorine A2-a	NPQ5-7	C ₂₅ H ₂₉ NO ₄	-1317.50528858	-1325.83459216
ancistroealaine B-a	NPQ5-21	C ₂₅ H ₂₉ NO ₄	-1317.51544117	-1325.84411558
hamatine	NPQ5-22	C ₂₅ H ₂₉ NO ₄	-1317.51204718	-1325.84086277
ancistrocladine-a	NPQ5-28	C ₂₅ H ₂₉ NO ₄	-1317.51066702	-1325.83942307
ancistroealaine A	NPQ5-18	C ₂₆ H ₂₉ NO ₄	-1355.36066633	-1363.92689183
6-Omethylhamatinine	NPQ5-27	C ₂₆ H ₂₉ NO ₄	-1355.35778836	-1363.92490182
ancistrocongoline B	NPQ5-15	C ₂₆ H ₃₁ NO ₄	-1356.52755536	-1365.13675183
ancistrocongoline C-a	NPQ5-16	C ₂₆ H ₃₁ NO ₄	-1356.533896	-1365.14281077
6-O-methylhamatine	NPQ5-23	C ₂₆ H ₃₁ NO ₄	-1356.52777869	-1365.13704306
5-epi-40-O-demethylancistrobertsonine C-a	NPQ5-29		-1356.53844331	-1365.14582808
habropetaline_A_a	NPQ7-3	C ₂₄ H ₂₇ NO ₄	-1278.47618464	-1286.52403284
ancistectorine B1	NPQ7-10	C ₂₅ H ₂₉ NO ₄	-1317.50840850	-1325.83552794
ancistrocongoline D-a	NPQ7-17	C ₂₅ H ₂₉ NO ₄	-1317.49549920	-1325.82372014
ancistrogriffine A-a	NPQ5-31	C ₂₅ H ₂₉ NO ₄	-1317.51193081	-1325.84195410
ancistrogriffine B-b	NPQ7-32	C ₂₅ H ₂₉ NO ₄	-1317.53512192	-1325.85077860

Table 5.K2. Absolute energy of pairs of NPQ5- and NPQ7-type naphthylisoquinoline alkaloids with same molecular formula for conformers

Results from HF/6-31G(d,p) and DFT/6-31G+(d,p) *in vacuo*.

Molecule's name	Acronym	Molecular formula	Absolute energy (hartree)	
			HF	DFT+
ancistectorine A1-b	NPQ5-5	C ₂₄ H ₂₇ NO ₄	-1278.49411008	-1286.54348335
Habropetaline-A-a	NPQ5-4	C ₂₄ H ₂₇ NO ₄	-1278.47618464	-1286.52403284
N-methylancistectorine A1-a	NPQ5-6	C ₂₅ H ₂₉ NO ₄	-1317.52079933	-1325.85086071
Ancistrogriffine C-b	NPQ7-33	C ₂₅ H ₂₉ NO ₄	-1317.53881992	-1325.86826192
5-epi-40-O-demethylancistrobertsonine C-a	NPQ5-29	C ₂₆ H ₃₁ NO ₄	-1356.53844331	-1365.14582808
ancistectorine C1-a	NPQ7-11	C ₂₆ H ₃₁ NO ₄	-1356.53053997	-1365.13774901

CHAPTER 6

COMPUTATIONAL STUDY OF MONOMERIC NAPHTHYLISOQUINOLINE ALKALOIDS IN SOLUTION

This chapter discusses the influence of the presence of a medium on the conformational preferences and computable properties of the same 33 monomeric naphthylisoquinoline alkaloids with antimalarial activity considered in chapter 5. It follows their computational study *in vacuo* [58] and considers them in three different solvents – chloroform, acetonitrile and water (section 2.4.3). The analysis aims at verifying whether and to what extent the patterns identified *in vacuo* for the conformers' relative energies and for computable molecular properties such as the dipole moment and the HOMO-LUMO energy gap remain valid, or new patterns emerge, under the influence of different types of solute-solvent interactions. The free energy of solvation (ΔG_{solv}) is also taken into account as an important property summarizing the extent of solute-solvent interactions (section 2.4.3). The results were presented at the QUITEL 2016 conference [E] and are the object of a manuscript to be submitted soon [477]. All the tables and figures for this chapter are put at the end of the chapter, starting with the tables and continuing with the figures.

6.1. Introduction

The study in solution is crucial for biologically active molecules because they exert their activity in a medium within living organisms. Nearly all chemistry in the human body occurs in media. The biological activity of a substance depends on the properties of its molecules. The presence of a solvent can influence molecular properties such as the geometry [478, 479], the relative stability of conformers [480] and, therefore, their population [481], the HOMO-LUMO energy gap [482, 483], the spectroscopic properties [484–486], the electric charge distribution, the dipole moment

[487], the polarizabilities [479], the optical properties [479, 488–490], the strength of intramolecular hydrogen bonds (IHBs) [491, 492]. The presence of a solvent also influences chemical reactions for aspects like reaction rates [493, 494], reaction mechanisms [495], and relevant aspects of the molecular mechanism of the biological activity such as the mechanism of biological molecular recognition [496] and the interaction with the receptor [497].

6.2. Results

The same atom numbering (Fig 5.2) and the same acronyms to denote structures and conformers (Table 5.2) are utilised for the study of these molecules *in vacuo* [58] is maintained here for consistency sake.

Conformers with the same type of IHB patterns show similar trends in all the media. It is therefore convenient to categorize the conformers on the basis of the IHBs present, to facilitate comparisons. Seven such categories can be identified; they are denoted with uppercase letters (A, B, C, D, E, F and G), whose meaning is explained in Table 6.1. The trends of the molecular properties, considered according to conformer types, are conveniently illustrated through diagrams, and such diagrams are built for each property. This classification was not important for study *in vacuo* because there is not comparison between molecules in different media, while it is important for the comparison in different media to group together molecules that may have similar trend.

Table 6.2 and 6.3 report the relative energies of the conformers of the calculated molecules for the HF and DFT results respectively. Figure 6.1 shows the trend of the relative energy according to conformer types. Conformers having all types of IHBs are the most stable *in vacuo* [58] and in chloroform. Only one exception to this behaviour appears in acetonitrile, with NPQ5-14-b-x having lower energy than NPQ5-14-b-d-x in the solvent. Seven exceptions appear for water (NPQ7-10, NPQ7-11, NPQ5-12, NPQ5-13, NPQ7-17, NPQ7-31 and NPQ7-32), likely because of its ability to form solute-solvent H-bonds. The relative energy (Table 6.2 and 6.3) of conformers decreases with the solvent polarity – which is consistent with common behaviours and relates to the general tendency for the solvent stabilization to be greater for higher energy conformers and greater for more polar solvents. The decrease is very pronounced in water. The extent of the

decrease depends also on the type of IHB present in the conformers. The only exceptions are structures NPQ5-7 and NPQ5-15, where the relative energy of the only other conformer (besides the lowest energy one) increases in solution with respect to *in vacuo*.

Figure 6.1 shows that conformers with the same IHB types have similar relative energies across structures. Furthermore, there is trend similarity between conformers of categories C and D for corresponding structures. The conformers of these groups have the same types of IHBs with the only difference that the donor of the O–H···O IHB in the naphthalene moiety is attached to C15 (category C) or C14 (category D). Category E contains only the two structures NPQ5-7 and NPQ5-15; their conformers have either only the C–H···O interaction or no IHB interaction at all; the energy of the latter conformer increases in solution.

Table 6.4 and 6.5 report the solvent effect (free energy of solvation, ΔG_{solv}) and its electrostatic components of the calculated molecules for the HF and DFT results respectively. The numbers and types of IHBs have an effect on ΔG_{solv} . ΔG_{solv} is negative in water and positive in acetonitrile for all the conformers, while it may be positive or negative in chloroform. The magnitude (absolute value) of ΔG_{solv} is smaller in chloroform, greater in acetonitrile and greatest in water (where the effect is very pronounced). The electrostatic component (G_{el}) of ΔG_{solv} is negative in all the solvents, with considerably greater magnitude in water. The presence of O–H··· π IHB decreases the magnitude of ΔG_{solv} whereas the presence of the O–H···O IHB increases it.

The values of ΔG_{solv} in a given solvent depend on the type of conformers, with similarities across structures. The next paragraphs compare the magnitude of ΔG_{solv} on the basis of the overall situation in a given conformer (not on the basis of the conformers' categories outlined in Table 6.1). Comparing conformers having all the possible types of IHBs is not the same as comparing conformers containing specific individual IHBs; for instance, both NPQ5-5-b-d-x and NPQ7-11-d-x have the maximum number of IHBs possible for each molecule (NPQ5-5 and NPQ7-11), but they do not belong to the same category because the individual IHBs present are different.

In water, the lowest energy conformers, i.e., conformers with all the types of IHBs present, have smaller magnitude of ΔG_{solv} than the other conformers of the same molecule. Conformers with

only the C–H26···O21 interaction, or no IHBs at all, have the highest ΔG_{solv} magnitude. Conformers with either the O23–H30···O24 or the O24–H31···O23 IHBs and the C–H26···O21 interaction have slightly higher ΔG_{solv} magnitude than conformers having only the O22–H29··· π and C–H26···O21 interactions. In structure NPQ7-32, the conformer with the two O–H··· π interactions (NPQ7-32-d-e) has smaller ΔG_{solv} value than the conformer with only one O–H··· π interaction (NPQ7-32-e). Conformers with only the O23–H30···O24 IHB have smaller ΔG_{solv} magnitude than conformers with only the O21–H25··· π interaction.

Conformers with all the types of IHBs have greater magnitude of ΔG_{solv} than the other conformers of the same molecule, and conformers with only C–H26···O21 have the smallest ΔG_{solv} both in chloroform and in acetonitrile. Also, conformers with the O23–H30···O24 and C–H26···O21 IHBs have smaller ΔG_{solv} values than conformers with the O22–H29··· π and C–H26···O21 IHBs and the NPQ7-32-d-e conformer (with the O21–H25··· π and O22–H29··· π interactions) has greater ΔG_{solv} magnitude than the NPQ7-32-e conformer (with only one O21–H25··· π interaction), both in chloroform and in acetonitrile.

Figure 6.2 shows the trends of ΔG_{solv} in terms of conformers' categories (Table 6.1), i.e., comparing trends for conformers of the same category across structures. Conformers belonging to the same category have similar ΔG_{solv} trends across structures. In the discussion of these diagrams, comparisons in terms of 'greater' or 'smaller' refer to the values as shown in the diagrams; therefore, the smallest values of ΔG_{solv} are the most negative ones, i.e., the ones corresponding to greater solute-solvent stabilization. For category A, conformers with the O–H···O and O–H··· π IHBs have the greatest ΔG_{solv} , conformers with O–H··· π interaction have intermediate values of ΔG_{solv} and conformers with no IHBs have the smallest ΔG_{solv} . In category B, conformers with O–H···O and C–H···O IHBs have greater ΔG_{solv} than conformers with only C–H···O IHB. There is a similar trend between conformers of categories C and D. In these categories, conformers with all types of IHBs (O–H···O, O–H··· π and C–H···O) have the greatest ΔG_{solv} ; conformers with only C–H···O or without any IHB interaction have the smallest ΔG_{solv} ; the other conformers have intermediate values, with conformers with O–H··· π and C–H···O IHBs showing greater ΔG_{solv} than conformers with O–H···O and C–H···O IHBs. In the E category, the behavior is somewhat different, as conformers with the C–H···O IHB have smaller ΔG_{solv} than conformers without any

IHBs; however, the difference between the two is marginal. The F and G categories show similarity of trends: the conformers with both O–H $\cdots\pi$ and C–H $\cdots$ O IHBs or with only the O–H $\cdots\pi$ interaction have smaller ΔG_{solv} than the other conformers.

Table 6.6 and 6.7 report the dipole moments of all the calculated conformers for the HF and DFT results respectively. The dipole moment increases with the solvent polarity, consistently with commonly observed trends. There are few cases where the dipole moment decreases slightly in water with respect to acetonitrile; these exceptions concern some of the conformers having only the O–H $\cdots\pi$ interaction. The same effect of the IHBs and IHB-type interactions as *in vacuo* [58] is also observed in solution: the conformers with O–H $\cdots$ O IHBs have higher dipole moment than the other conformers, and the conformers with only the O–H $\cdots\pi$ interaction have small dipole moments.

Table 6.8 and 6.9 report the HOMO-LUMO energy gap of all the calculated conformers for the HF and DFT results respectively. From the HF results, the HOMO-LUMO energy gap is often smaller in solution than *in vacuo*; in solution, it increases slightly as the solvent polarity increases. The difference between the value in chloroform and the value *in vacuo* is mostly below 0.4 kcal/mol, but in very few cases the gap can be up to 6.8 kcal/mol smaller than *in vacuo*. The increase in different solutions – as the solvent polarity increases – is marginal, mostly remaining well below 0.2 kcal/mol both from chloroform to acetonitrile and from acetonitrile to water. The trends within the same medium are influenced in similar ways by the IHBs present: the presence of an O–H $\cdots$ O IHB tends to increase the value of the HOMO-LUMO energy gap and the presence of the O–H $\cdots\pi$ interaction has a lowering effect on it. The DFT results for the HOMO-LUMO energy gap show a consistent small increase of the gap value as the medium polarity increases (including from *in vacuo* to in chloroform).

Figure 6.3 shows the trends of all the molecular properties (relative energy, ΔG_{solv} , dipole moment and HOMO-LUMO energy gap) of the conformers of category D in the HF and the DFT results. There is a similarity of trends between the two methods, which shows the consistency of the HF and the DFT results and also validates the results.

6.3. Discussion and Conclusions

The results highlight the effect of the solvents on the molecular properties of these molecules.

The conformers' relative energy decreases as the solvent polarity increases. The low relative energy of many conformers in water solution suggests that they might also be involved in the molecules' biological activity. The free energy of solvation has markedly negative values in water, slightly negative values in chloroform and positive values in acetonitrile. The dipole moments increase with the solvent polarity. The values of the HOMO-LUMO energy gap of the same conformer are very close in all the media in the DFT results, whereas the HF results show a difference between the gas phase and the solutions (greater in the gas phase), and only minor differences among the three solvents.

The previous study *in vacuo* had shown that the presence and patterns of IHBs, the other IHB-type interactions ($\text{O}-\text{H}\cdots\pi$ and $\text{C}-\text{H}\cdots\text{O}$) and the mutual orientation of the two moieties are the factors influencing conformational preferences, with the $\text{O}-\text{H}\cdots\text{O}$ IHBs being the dominant factor. The results in solution show that the solvent has an influence on the relative energy of the conformers, the dipole moment and the HOMO-LUMO energy gap. The same conformers' stability trend as *in vacuo* is observed in chloroform and acetonitrile, but may change in water. The free energy of solvation is very pronounced in water. The findings of this work are in good agreements with the effects of solvents observed on other bioactive molecules such as acylphloroglucinols and aspirin.

The solvents have effects on the molecular properties of acylphloroglucinols [450, 498–501] such as conformers' relative energy, dipole moments, HOMO-LUMO gap energies and geometries of the conformers. A significant change was observed for this class in water solution. A study of the effects on solvent polarity on the molecular properties of aspirin [502], in order to understand its reactivity and stability, revealed that the ΔG_{solv} increases with the decrease of the solvent polarity, and that the dipole moment and other molecular properties increase with the solvent polarity except the chemical hardness.

Table 6.1. Different categories of conformers according to the IHB-types present

Category	IHB-type present	Conformers in the given category
A	O23–H30 $\cdots$ O24, O22–H29 $\cdots\pi$ or O21–H25 $\cdots\pi$	NPQ7-1-b-e, NPQ7-1-b, NPQ7-1-e, NPQ7-1-z, NPQ7-32-d-e, NPQ7-32-e, NPQ7-32, NPQ7-33-b-e, NPQ7-33-b, NPQ7-33-e, NPQ7-33-z
B	O24–H31 $\cdots$ O23 C–H26 $\cdots$ O21	NPQ5-2-a-x, NPQ5-2-a, NPQ5-2-x, NPQ5-21-a-x, NPQ5-21-x
C	O24–H31 $\cdots$ O23, O22–H29 $\cdots\pi$ C–H26 $\cdots$ O21	NPQ5-4-a-d-x, NPQ5-4-a-x, NPQ5-4-d-x, NPQ5-4-x, NPQ5-12-a-d-x, NPQ5-12-a-x, NPQ5-12-d-x, NPQ5-12-x, NPQ5-23-a-d-x, NPQ5-23-a-x, NPQ5-23-d-x, NPQ5-23-x, NPQ5-26-a-d-x, NPQ5-26-a-x, NPQ5-26-d-x, NPQ5-26-x, NPQ7-31-a-d-x, NPQ7-31-a-x, NPQ7-31-d, NPQ7-31
D	O23–H30 $\cdots$ O24, O22–H29 $\cdots\pi$ C–H26 $\cdots$ O21	NPQ5-5-b-d-x, NPQ5-5-b-x, NPQ5-5-d-x, NPQ5-5-x, NPQ5-6-b-d-x, NPQ5-6-b-x, NPQ5-6-x, NPQ5-8-b-x, NPQ5-8-b, NPQ5-8-x, NPQ5-8-z, NPQ5-9-b-d-x, NPQ5-9-b-x, NPQ5-9-d-x, NPQ5-9-x, NPQ5-13-b-d-x, NPQ5-13-b-x, NPQ5-13-d-x, NPQ5-13-x, NPQ5-14-b-d-x, NPQ5-14-b-x, NPQ5-14-d-x, NPQ5-14-x, NPQ5-19-b-d-x, NPQ5-19-b, NPQ5-19-d-x, NPQ5-19-x
E	C–H26 $\cdots$ O21	NPQ5-7-x, NPQ5-7-z, NPQ5-15-x, NPQ5-15-z
F	O22–H29 $\cdots\pi$	NPQ7-10-d, NPQ7-10-z, NPQ5-16-d, NPQ5-16-z, NPQ7-17-d, NPQ7-17-z
G	O22–H29 $\cdots\pi$ C–H26 $\cdots$ O21	NPQ7-3-d-x, NPQ7-3-x, NPQ7-11-d-x, NPQ7-11-x, NPQ5-20-d-x, NPQ5-20-x, NPQ5-22-d-x, NPQ5-22-x, NPQ5-25-d-x, NPQ5-25-x

Table 6.2. Relative energies of the conformers of the calculated naphthylisoquinoline alkaloids in the media considered

HF/6-31G(d,p) results. The media are denoted as vac, chlrf, actn and aq in the column headings, for vacuum, chloroform, acetonitrile and water respectively.

Conformers	Relative energy (kcal/mol)				Conformers	Relative energy (kcal/mol)			
	vac	chlrf	actn	aq		vac	chlrf	actn	aq
NPQ7-1-b-e	0.000	0.000	0.000	0.000	NPQ5-15-x	0.000	0.000	0.000	0.000
NPQ7-1-b	4.656	3.491	2.778	1.407	NPQ5-15-z	0.743	1.293	1.522	1.121
NPQ7-1-e	7.212	6.247	5.774	2.977	NPQ5-16-d	0.000	0.000	0.000	0.000
NPQ7-1-z	12.33	4.469	3.406	0.403	NPQ5-16-z	4.073	2.678	1.816	0.130
NPQ5-2-a-x	0.000	0.000	0.000	0.000	NPQ7-17-d	0.000	0.000	0.000	0.008
NPQ5-2-a	1.486	2.027	2.139	2.460	NPQ7-17-z	2.916	1.913	1.232	0.000
NPQ5-2-x	7.132	6.403	5.925	3.145	NPQ5-19-b-d-x	0.000	0.000	0.000	0.000
NPQ7-3-d-x	0.000	0.000	0.000	0.000	NPQ5-19-b	4.383	2.662	1.706	0.052
NPQ7-3-x	4.526	3.830	2.185	0.723	NPQ5-19-d-x	7.266	6.494	5.969	3.584
NPQ5-4-a-d-x	0.000	0.000	0.000	0.000	NPQ5-19-x	11.56	9.214	7.758	3.762
NPQ5-4-a-x	4.377	2.735	1.810	0.113	NPQ5-20-d-x	0.000	0.000	0.000	0.000
NPQ5-4-d-x	7.303	6.545	6.010	3.569	NPQ5-20-x	4.406	2.800	1.777	0.082
NPQ5-4-x	11.59	9.324	7.925	3.887	NPQ5-21-a-x	0.000	0.000	0.000	0.000
NPQ5-5-b-d-x	0.000	0.000	0.000	0.138	NPQ5-21-x	7.170	6.551	6.104	3.970
NPQ5-5-b-x	4.234	2.555	1.964	0.682	NPQ5-22-d-x	0.000	0.000	0.000	0.000
NPQ5-5-d-x	3.272	2.831	2.378	0.000	NPQ5-22-x	4.222	2.752	2.016	0.418
NPQ5-5-x	7.424	5.565	4.427	0.720	NPQ5-23-a-d-x	0.000	0.000	0.000	0.000
NPQ5-6-b-d-x	0.000	0.000	0.000	0.000	NPQ5-23-a-x	3.736	2.476	1.662	0.347
NPQ5-6-b-x	4.217	2.706	1.894	0.262	NPQ5-23-d-x	6.896	6.287	5.844	3.659
NPQ5-6-x	11.52	9.345	8.019	4.080	NPQ5-23-x	11.04	9.021	7.781	4.095
NPQ5-7-x	0.000	0.000	0.000	0.981	NPQ5-25-d-x	0.000	0.000	0.000	0.000
NPQ5-7-z	0.972	1.282	1.524	0.000	NPQ5-25-x	4.262	2.585	1.757	0.191
NPQ5-8-b-x	0.000	0.000	0.000	0.000	NPQ5-26-a-d-x	0.000	0.000	0.000	0.000
NPQ5-8-b	0.975	1.392	1.578	1.405	NPQ5-26-a-x	3.736	2.187	1.472	0.304
NPQ5-8-x	7.205	6.398	6.119	3.768	NPQ5-26-d-x	6.896	6.127	5.838	3.835
NPQ5-8-z	8.179	7.990	7.678	5.164	NPQ5-26-x	11.04	8.697	7.553	4.006
NPQ5-9-b-d-x	0.000	0.000	0.000	0.000	NPQ7-28-d-x	0.000	0.000	0.000	0.000
NPQ5-9-b-x	5.637	3.783	1.080	1.442	NPQ7-28-x	4.172	2.758	1.902	0.489
NPQ5-9-d-x	8.768	7.821	5.417	4.942	NPQ5-29-a-x	0.000	0.000	0.000	0.000
NPQ5-9-x	12.93	10.37	7.222	5.232	NPQ5-29-x	7.340	6.621	6.079	3.798
NPQ7-10-d	0.000	0.000	0.000	0.565	NPQ7-31-a-d-x	0.000	0.000	0.000	0.156
NPQ7-10-z	2.888	1.806	1.130	0.000	NPQ7-31-a-x	3.018	2.139	1.449	0.000
NPQ7-11-d-x	0.000	0.000	0.000	0.383	NPQ7-31-d	5.001	4.127	3.554	1.818
NPQ7-11-x	3.111	1.883	1.184	0.000	NPQ7-31-z	8.530	6.470	5.200	1.909
NPQ5-12-a-d-x	0.000	0.000	0.000	0.061	NPQ7-32-d-e	0.000	0.000	0.000	0.000
NPQ5-12-a-x	3.902	2.376	1.408	0.000	NPQ7-32-e	4.665	3.759	3.295	2.076
NPQ5-12-d-x	6.780	6.161	5.704	3.547	NPQ7-32	8.495	6.113	4.857	2.126

NPQ5-12-x	11.11	8.901	7.478	3.650	NPQ7-33-b-e	0.000	0.000	0.000	0.000
NPQ5-13-b-d-x	0.000	0.000	0.000	0.064	NPQ7-33-b	5.470	4.512	3.836	2.322
NPQ5-13-b-x	3.902	2.382	1.405	0.000	NPQ7-33-e	6.870	6.292	5.816	3.423
NPQ5-13-d-x	6.780	6.163	5.661	3.548	NPQ7-33-z	12.77	10.99	9.948	6.046
NPQ5-13-x	11.11	8.879	7.481	3.650					
NPQ5-14-b-d-x	0.000	0.000	0.000	0.000					
NPQ5-14-b-x	4.218	2.588	1.639	0.004					
NPQ5-14-d-x	7.179	6.454	5.990	3.567					
NPQ5-14-x	11.33	9.098	7.707	3.841					

Table 6.3. Relative energies of the conformers of the calculated naphthylisoquinoline alkaloids in the media considered

DFT/6-31+G(d,p) results. The media are denoted as vac, chlrf, actn and aq in the column headings, for vacuum, chloroform, acetonitrile and water respectively.

Conformers	Relative energy (kcal/mol)				Conformers	Relative energy (kcal/mol)			
	vac	chlrf	actn	aq		vac	chlrf	actn	aq
NPQ7-1-b-e	0.000	0.000	0.000	0.000	NPQ5-15-x	0.000	0.000	0.000	0.000
NPQ7-1-b	4.439	3.349	2.706	1.444	NPQ5-15-z	0.362	0.888	1.095	0.855
NPQ7-1-e	7.446	6.617	6.206	3.532	NPQ5-16-d	0.000	0.000	0.000	0.000
NPQ7-1-z	12.34	10.42	9.238	5.406	NPQ5-16-z	3.983	2.764	2.024	0.289
NPQ5-2-a-x	0.000	0.000	0.000	0.000	NPQ7-17-d	0.000	0.000	0.000	0.008
NPQ5-2-a	1.574	1.891	1.972	2.077	NPQ7-17-z	2.857	1.913	1.232	0.000
NPQ5-2-x	7.394	6.803	6.383	3.877	NPQ5-19-b-d-x	0.000	0.000	0.000	0.000
NPQ7-3-d-x	0.000	0.000	0.000	0.000	NPQ5-19-b	4.271	2.719	1.898	0.052
NPQ7-3-x	4.982	3.884	3.212	2.057	NPQ5-19-d-x	7.540	6.767	6.313	3.809
NPQ5-4-a-d-x	0.000	0.000	0.000	0.000	NPQ5-19-x	11.739	9.575	8.271	3.923
NPQ5-4-a-x	4.266	0.000	0.000	0.000	NPQ5-20-d-x	0.000	0.000	0.000	0.000
NPQ5-4-d-x	7.574	2.797	1.949	0.185	NPQ5-20-x	4.332	2.820	2.032	0.117
NPQ5-4-x	11.77	6.827	6.415	3.853	NPQ5-21-a-x	0.000	0.000	0.000	0.000
NPQ5-5-b-d-x	0.000	0.000	0.000	0.000	NPQ5-21-x	7.466	6.870	6.467	3.921
NPQ5-5-b-x	3.925	2.475	1.872	0.439	NPQ5-22-d-x	0.000	0.000	0.000	0.000
NPQ5-5-d-x	3.803	3.349	2.937	0.425	NPQ5-22-x	4.222	2.731	2.016	0.381
NPQ5-5-x	7.704	5.989	4.893	0.963	NPQ5-23-a-d-x	0.000	0.000	0.000	0.000
NPQ5-6-b-d-x	0.000	0.000	0.000	0.000	NPQ5-23-a-x	3.397	2.147	1.537	0.133
NPQ5-6-b-x	3.903	2.500	1.880	0.178	NPQ5-23-d-x	7.097	6.506	6.108	3.737
NPQ5-6-x	11.40	9.419	8.255	4.001	NPQ5-23-x	10.968	9.069	7.997	4.025
NPQ5-7-x	0.000	0.000	0.000	0.000	NPQ5-25-d-x	0.000	0.000	0.000	0.000
NPQ5-7-z	0.815	1.195	1.354	1.361	NPQ5-25-x	4.262	3.689	2.824	0.972
NPQ5-8-b-x	0.000	0.000	0.000	0.000	NPQ5-26-a-d-x	0.000	0.000	0.000	0.000
NPQ5-8-b	0.824	1.202	1.342	1.335	NPQ5-26-a-x	3.397	2.187	1.472	0.304
NPQ5-8-x	7.479	6.860	6.403	3.859	NPQ5-26-d-x	7.097	6.127	5.838	3.835
NPQ5-8-z	8.302	8.050	7.746	5.200	NPQ5-26-x	10.968	8.697	7.553	4.006
NPQ5-9-b-d-x	0.000	0.000	0.000	0.000	NPQ7-28-d-x	0.000	0.000	0.000	0.000
NPQ5-9-b-x	5.663	3.956	3.150	1.757	NPQ7-28-x	3.818	2.560	1.871	0.335
NPQ5-9-d-x	9.235	8.332	7.795	5.593	NPQ5-29-a-x	0.000	0.000	0.000	0.000
NPQ5-9-x	13.21	10.83	9.546	5.699	NPQ5-29-x	7.613	6.893	6.418	3.992
NPQ7-10-d	0.000	0.000	0.000	0.222	NPQ7-31-a-d-x	0.000	0.000	0.000	0.244
NPQ7-10-z	3.017	2.148	1.472	0.000	NPQ7-31-a-x	3.128	2.089	1.420	0.000
NPQ7-11-d-x	0.000	0.000	0.000	0.236	NPQ7-31-d	7.060	6.496	6.076	3.880
NPQ7-11-x	3.211	2.191	1.464	0.000	NPQ7-31-z	10.559	8.931	7.793	3.918
NPQ5-12-a-d-x	0.000	0.000	0.000	0.067	NPQ7-32-d-e	0.000	0.000	0.000	0.499
NPQ5-12-a-x	3.883	2.478	1.716	0.000	NPQ7-32-e	2.608	1.871	1.403	0.711
NPQ5-12-d-x	7.079	6.425	6.011	3.686	NPQ7-32	5.388	3.407	2.274	0.000

NPQ5-12-x	11.34	9.237	8.007	3.806	NPQ7-33-b-e	0.000	0.000	0.000	0.000
NPQ5-13-b-d-x	0.000	0.000	0.000	1.378	NPQ7-33-b	5.2533	4.418	3.869	2.321
NPQ5-13-b-x	2.646	1.268	0.572	0.000	NPQ7-33-e	7.2093	6.604	6.182	3.449
NPQ5-13-d-x	5.842	5.251	4.822	3.682	NPQ7-33-z	12.886	11.42	10.32	6.271
NPQ5-13-x	10.11	8.083	6.804	3.805					
NPQ5-14-b-d-x	0.000	0.000	0.000	0.000					
NPQ5-14-b-x	4.037	2.606	1.675	0.181					
NPQ5-14-d-x	7.438	6.797	6.297	3.825					
NPQ5-14-x	11.41	9.399	7.980	3.937					

Table 6.4. Free energy of solvation (ΔG_{solv}) and its electrostatic component (ΔG_{el}) of the conformers of the calculated naphthylisoquinoline alkaloids in the three solvents considered (chloroform, acetonitrile and water, respectively denoted as chlrf, actn and aq in the column headings)

HF/6-31G(d,p) results.

Conformers and structures	ΔG_{solv} (kcal/mol)			Conformers and structures	ΔG_{el} (kcal/mol)		
	chlrf	actn	aq		chlrf	actn	aq
NPQ7-1-b-e	-0.45	5.14	-11.07	NPQ7-1-b-e	-5.05	-7.17	-19.76
NPQ7-1-b	-1.72	3.20	-14.35	NPQ7-1-b	-6.31	-9.14	-23.10
NPQ7-1-e	-1.47	3.69	-15.29	NPQ7-1-e	-5.96	-8.55	-23.93
NPQ7-1-z	-2.80	1.71	-17.59	NPQ7-1-z	-6.91	-10.09	-25.69
NPQ5-2-a-x	-0.44	4.78	-9.89	NPQ5-2-a-x	-5.20	-7.43	-18.59
NPQ5-2-a	0.15	5.48	-8.85	NPQ5-2-a	-4.79	-6.91	-17.75
NPQ5-2-x	-1.19	3.58	-13.84	NPQ5-2-x	-5.86	-8.56	-22.51
NPQ7-3-d-x	0.28	6.13	-10.80	NPQ7-3-d-x	-4.35	-6.89	-20.06
NPQ7-3-x	-1.12	4.11	-13.30	NPQ7-3-x	-5.73	-8.49	-22.06
NPQ5-4-a-d-x	-0.34	4.83	-10.60	NPQ5-4-a-d-x	-5.19	-7.47	-18.97
NPQ5-4-a-x	-2.12	2.16	-14.97	NPQ5-4-a-x	-6.83	-10.04	-23.24
NPQ5-4-d-x	-1.60	3.44	-14.42	NPQ5-4-d-x	-6.44	-8.77	-22.71
NPQ5-4-x	-2.87	0.96	-18.49	NPQ5-4-x	-7.47	-11.15	-26.69
NPQ5-5-b-d-x	1.14	7.26	-5.97	NPQ5-5-b-d-x	-4.23	-6.02	-15.57
NPQ5-5-b-x	-0.64	4.90	-9.75	NPQ5-5-b-x	-5.91	-8.28	-19.25
NPQ5-5-d-x	0.76	6.41	-9.38	NPQ5-5-d-x	-4.68	-6.92	-18.98
NPQ5-5-x	-0.80	4.17	-12.95	NPQ5-5-x	-6.10	-9.02	-22.42
NPQ5-6-b-d-x	2.24	8.85	-3.73	NPQ5-6-b-d-x	-3.53	-5.04	-13.73
NPQ5-6-b-x	0.61	6.43	-7.78	NPQ5-6-b-x	-5.05	-7.37	-17.69
NPQ5-6-x	-0.18	5.14	-11.36	NPQ5-6-x	-5.72	-8.55	-21.18
NPQ5-7-x	1.61	7.20	-8.22	NPQ5-7-x	-4.71	-7.20	-18.74
NPQ5-7-z	2.04	7.88	-7.57	NPQ5-7-z	-4.42	-6.66	-18.27
NPQ5-8-b-x	0.43	5.82	-9.10	NPQ5-8-b-x	-5.37	-7.76	-18.90
NPQ5-8-b	0.97	6.55	-8.50	NPQ5-8-b	-4.96	-7.17	-18.48
NPQ5-8-x	-0.50	4.63	-12.61	NPQ5-8-x	-6.18	-8.85	-22.34
NPQ5-8-z	0.25	5.35	-12.02	NPQ5-8-z	-5.57	-8.28	-21.93
NPQ5-9-b-d-x	1.45	7.36	-4.60	NPQ5-9-b-d-x	-4.33	-6.09	-14.17
NPQ5-9-b-x	-0.53	4.49	-8.73	NPQ5-9-b-x	-6.17	-8.88	-18.36
NPQ5-9-d-x	0.38	5.72	-8.32	NPQ5-9-d-x	-5.28	-7.68	-18.00
NPQ5-9-x	-1.33	3.28	-12.27	NPQ5-9-x	-6.89	-10.04	-21.88
NPQ7-10-d	1.51	7.95	-6.04	NPQ7-10-d	-3.92	-5.71	-15.68
NPQ7-10-z	0.27	6.00	-9.63	NPQ7-10-z	-5.08	-7.60	-19.21
NPQ7-11-d-x	3.02	9.97	-2.15	NPQ7-11-d-x	-3.07	-4.52	-12.50
NPQ7-11-x	1.60	7.87	-5.82	NPQ7-11-x	-4.31	-6.45	-15.99
NPQ5-12-a-d-x	0.88	6.70	-5.31	NPQ5-12-a-d-x	-4.71	-6.54	-14.61

NPQ5-12-a-x	-0.76	4.13	-9.35	NPQ5-12-a-x	-6.23	-9.03	-18.57
NPQ5-12-d-x	0.14	5.53	-8.69	NPQ5-12-d-x	-5.33	-7.62	-17.91
NPQ5-12-x	-1.56	2.90	-12.99	NPQ5-12-x	-6.92	-10.17	-22.13
NPQ5-13-b-d-x	0.88	6.70	-5.31	NPQ5-13-b-d-x	-4.71	-6.54	-14.61
NPQ5-13-b-x	-0.75	4.12	-9.35	NPQ5-13-b-x	-6.23	-9.04	-18.57
NPQ5-13-d-x	0.14	5.49	-8.69	NPQ5-13-d-x	-5.33	-7.66	-17.91
NPQ5-13-x	-1.59	2.89	-12.99	NPQ5-13-x	-6.95	-10.17	-22.14
NPQ5-14-b-d-x	0.88	6.73	-7.51	NPQ5-14-b-d-x	-4.66	-6.67	-17.19
NPQ5-14-b-x	-0.90	4.02	-11.86	NPQ5-14-b-x	-6.30	-9.26	-21.41
NPQ5-14-d-x	0.03	5.45	-11.20	NPQ5-14-d-x	-5.39	-7.86	-20.80
NPQ5-14-x	-1.62	2.89	-15.20	NPQ5-14-x	-6.90	-10.30	-24.68
NPQ5-15-x	2.67	8.97	-5.53	NPQ5-15-x	-4.31	-6.44	-16.99
NPQ5-15-z	3.31	9.84	-5.04	NPQ5-15-z	-3.76	-5.66	-16.61
NPQ5-16-d	3.78	10.78	-2.03	NPQ5-16-d	-3.09	-4.55	-13.38
NPQ5-16-z	2.26	8.41	-6.10	NPQ5-16-z	-4.47	-6.80	-17.31
NPQ7-17-d	2.21	8.57	-5.14	NPQ7-17-d	-3.80	-5.63	-15.67
NPQ7-17-z	1.00	6.69	-8.27	NPQ7-17-z	-4.81	-7.32	-18.60
NPQ5-18	3.02	9.36	-2.56	NPQ5-18	-4.25	-6.18	-14.12
NPQ5-19-b-d-x	1.07	6.93	-4.96	NPQ5-19-b-d-x	-4.56	-6.35	-14.30
NPQ5-19-b	-0.76	4.17	-9.37	NPQ5-19-b	-6.28	-9.03	-18.63
NPQ5-19-d-x	0.16	5.52	-8.73	NPQ5-19-d-x	-5.34	-7.66	-17.99
NPQ5-19-x	-1.52	2.93	-12.93	NPQ5-19-x	-6.92	-10.17	-22.11
NPQ5-20-d-x	1.90	8.14	-4.14	NPQ5-20-d-x	-4.17	-5.89	-14.11
NPQ5-20-x	0.17	5.42	-8.54	NPQ5-20-x	-5.78	-8.52	-18.44
NPQ5-21-a-x	2.15	8.35	-4.77	NPQ5-21-a-x	-4.22	-6.07	-15.29
NPQ5-21-x	1.40	7.19	-8.05	NPQ5-21-x	-4.85	-7.15	-18.50
NPQ5-22-d-x	2.59	8.96	-4.85	NPQ5-22-d-x	-3.62	-5.35	-15.23
NPQ5-22-x	1.01	6.67	-8.74	NPQ5-22-x	-5.09	-7.55	-19.03
NPQ5-23-a-d-x	1.65	7.64	-5.91	NPQ5-23-a-d-x	-4.21	-6.00	-15.74
NPQ5-23-a-x	0.25	5.45	-9.41	NPQ5-23-a-x	-5.47	-8.07	-19.13
NPQ5-23-d-x	0.87	6.44	-9.28	NPQ5-23-d-x	-4.82	-7.05	-18.98
NPQ5-23-x	-0.63	4.16	-13.05	NPQ5-23-x	-6.23	-9.25	-22.69
NPQ5-24	3.44	9.94	-3.46	NPQ5-24	-3.64	-5.49	-14.94
NPQ5-25-d-x	2.27	8.47	-3.69	NPQ5-25-d-x	-4.02	-5.84	-14.17
NPQ5-25-x	0.44	5.82	-7.91	NPQ5-25-x	-5.70	-8.35	-18.23
NPQ5-26-a-d-x	1.21	6.92	-5.06	NPQ5-26-a-d-x	-4.74	-6.74	-15.01
NPQ5-26-a-x	-0.52	4.47	-8.70	NPQ5-26-a-x	-6.27	-8.98	-18.43
NPQ5-26-d-x	0.51	5.94	-8.04	NPQ5-26-d-x	-5.27	-7.56	-17.84
NPQ5-26-x	-1.25	3.34	-12.19	NPQ5-26-x	-6.88	-10.02	-21.84
NPQ5-27	2.87	9.16	-2.28	NPQ5-27	-4.29	-6.28	-13.86
NPQ7-28-d-x	2.59	9.09	-4.82	NPQ7-28-d-x	-3.56	-5.20	-15.24
NPQ7-28-x	1.02	6.67	-8.65	NPQ7-28-x	-4.97	-7.47	-18.92
NPQ5-29-a-x	3.34	10.25	-1.99	NPQ5-29-a-x	-3.48	-4.96	-13.22
NPQ5-29-x	2.24	8.57	-5.98	NPQ5-29-x	-4.19	-6.22	-16.76

NPQ7-30	4.93	12.15	0.02	NPQ7-30	-2.96	-4.43	-12.62
NPQ7-31-a-d-x	3.57	10.29	-1.17	NPQ7-31-a-d-x	-3.29	-4.72	-12.45
NPQ7-31-a-x	2.17	8.20	-4.72	NPQ7-31-a-x	-4.53	-6.69	-15.88
NPQ7-31-d	2.22	8.37	-5.41	NPQ7-31-d	-4.16	-6.17	-16.09
NPQ7-31-z	0.85	6.32	-9.00	NPQ7-31-z	-5.37	-8.08	-19.55
NPQ7-32-d-e	1.86	8.14	-6.91	NPQ7-32-d-e	-3.93	-5.87	-16.91
NPQ7-32-e	0.94	6.79	-9.45	NPQ7-32-e	-4.85	-7.25	-19.51
NPQ7-32	-0.66	4.42	-8.05	NPQ7-32	-6.32	-9.52	-18.50
NPQ7-33-b-e	2.25	8.62	-5.29	NPQ7-33-b-e	-4.09	-5.86	-15.95
NPQ7-33-b	1.33	7.05	-8.36	NPQ7-33-b	-5.05	-7.48	-19.09
NPQ7-33-e	1.55	7.48	-8.82	NPQ7-33-e	-4.67	-6.90	-19.39
NPQ7-33-z	0.37	5.74	-12.03	NPQ7-33-z	-5.88	-8.70	-22.69

Table 6.5. Free energy of solvation (ΔG_{solv}) and its electrostatic component (ΔG_{el}) of the conformers of the calculated naphthylisoquinoline alkaloids in the three solvents considered (chloroform, acetonitrile and water, respectively denoted as chlrf, actn and aq in the column headings)

DFT/6-31+G(d,p) results.

Conformers	ΔG_{solv} (kcal/mol)			Conformers	ΔG_{el} (kcal/mol)		
	chlrf	actn	aq		chlrf	actn	aq
NPQ7-1-b-e	-0.32	5.29	-10.89	NPQ7-1-b-e	-4.91	-7.02	-19.57
NPQ7-1-b	-1.41	3.59	-13.81	NPQ7-1-b	-6.00	-8.75	-22.57
NPQ7-1-e	-1.47	3.98	-14.85	NPQ7-1-e	-5.96	-8.26	-23.49
NPQ7-1-z	-2.35	2.14	-17.80	NPQ7-1-z	-6.84	-10.13	-26.52
NPQ5-2-a-x	-0.12	5.20	-9.36	NPQ5-2-a-x	-4.89	-7.01	-18.07
NPQ5-2-a	0.37	5.77	-8.66	NPQ5-2-a	-4.57	-6.61	-17.56
NPQ5-2-x	-0.81	4.12	-12.92	NPQ5-2-x	-5.48	-8.02	-21.58
NPQ7-3-d-x	0.47	6.37	-10.43	NPQ7-3-d-x	-4.50	-6.65	-19.70
NPQ7-3-x	-0.62	4.63	-13.29	NPQ7-3-x	-5.60	-8.42	-22.62
NPQ5-4-a-d-x	-0.10	5.10	-10.94	NPQ5-4-a-d-x	-5.29	-7.63	-19.86
NPQ5-4-a-x	-1.69	2.69	-15.10	NPQ5-4-a-x	-6.76	-9.94	-23.95
NPQ5-4-d-x	-0.96	3.86	-14.73	NPQ5-4-d-x	-6.04	-8.78	-23.58
NPQ5-4-x	-2.43	1.51	-18.71	NPQ5-4-x	-7.38	-11.05	-27.49
NPQ5-5-b-d-x	1.41	7.54	-6.35	NPQ5-5-b-d-x	-4.32	-6.18	-16.52
NPQ5-5-b-x	-0.16	5.37	-9.95	NPQ5-5-b-x	-5.77	-8.24	-20.01
NPQ5-5-d-x	1.00	6.71	-9.73	NPQ5-5-d-x	-4.78	-7.05	-19.90
NPQ5-5-x	-0.43	4.60	-13.27	NPQ5-5-x	-6.04	-8.99	-23.26
NPQ5-6-b-d-x	2.49	9.08	-3.78	NPQ5-6-b-d-x	-3.61	-5.23	-14.33
NPQ5-6-b-x	0.96	6.94	-7.63	NPQ5-6-b-x	-5.02	-7.26	-18.05
NPQ5-6-x	0.25	5.71	-11.39	NPQ5-6-x	-5.60	-8.39	-21.74
NPQ5-7-x	1.89	7.63	-8.29	NPQ5-7-x	-4.75	-7.17	-19.31
NPQ5-7-z	2.42	8.32	-7.56	NPQ5-7-z	-4.37	-6.63	-18.77
NPQ5-8-b-x	0.80	6.24	-9.21	NPQ5-8-b-x	-5.34	-7.76	-19.53
NPQ5-8-b	1.32	6.91	-8.51	NPQ5-8-b	-4.96	-7.24	-19.02
NPQ5-8-x	0.07	5.08	-12.88	NPQ5-8-x	-5.96	-8.83	-23.15
NPQ5-8-z	0.58	5.75	-12.18	NPQ5-8-z	-5.59	-8.31	-22.64
NPQ5-9-b-d-x	1.70	7.59	-4.54	NPQ5-9-b-d-x	-4.42	-6.25	-14.61
NPQ5-9-b-x	0.11	5.32	-8.02	NPQ5-9-b-x	-6.12	-8.76	-18.51
NPQ5-9-d-x	0.68	6.13	-8.04	NPQ5-9-d-x	-5.32	-7.69	-18.25
NPQ5-9-x	-0.70	4.06	-11.71	NPQ5-9-x	-6.80	-9.92	-22.13
NPQ7-10-d	1.83	8.27	-5.98	NPQ7-10-d	-3.95	-5.81	-16.15
NPQ7-10-z	0.77	6.54	-9.40	NPQ7-10-z	-4.82	-7.36	-19.39
NPQ7-11-d-x	3.31	10.28	-1.88	NPQ7-11-d-x	-3.07	-4.59	-12.70
NPQ7-11-x	2.06	8.32	-5.51	NPQ7-11-x	-4.09	-6.33	-16.10
NPQ5-12-a-d-x	1.19	7.00	-4.95	NPQ5-12-a-d-x	-4.71	-6.63	-14.71

NPQ5-12-a-x	-0.33	4.75	-8.96	NPQ5-12-a-x	-6.12	-8.79	-18.66
NPQ5-12-d-x	0.43	5.85	-8.46	NPQ5-12-d-x	-5.37	-7.70	-18.17
NPQ5-12-x	-1.14	3.49	-12.68	NPQ5-12-x	-6.82	-9.97	-22.32
NPQ5-13-b-d-x	1.13	6.89	-4.88	NPQ5-13-b-d-x	-4.75	-6.70	-14.62
NPQ5-13-b-x	-0.36	4.75	-8.96	NPQ5-13-b-x	-6.15	-8.79	-18.66
NPQ5-13-d-x	0.43	5.80	-8.47	NPQ5-13-d-x	-5.36	-7.74	-18.18
NPQ5-13-x	-1.12	3.43	-12.68	NPQ5-13-x	-6.80	-10.03	-22.32
NPQ5-14-b-d-x	1.04	7.04	-7.97	NPQ5-14-b-d-x	-4.74	-6.67	-18.04
NPQ5-14-b-x	-0.54	4.56	-11.96	NPQ5-14-b-x	-6.17	-9.03	-21.90
NPQ5-14-d-x	0.30	5.85	-11.60	NPQ5-14-d-x	-5.38	-7.81	-21.66
NPQ5-14-x	-1.25	3.39	-15.64	NPQ5-14-x	-6.76	-10.10	-25.52
NPQ5-15-x	3.20	9.51	-5.43	NPQ5-15-x	-4.12	-6.30	-17.36
NPQ5-15-z	3.80	10.33	-4.83	NPQ5-15-z	-3.59	-5.57	-16.87
NPQ5-16-d	4.21	11.21	-2.01	NPQ5-16-d	-3.10	-4.65	-13.98
NPQ5-16-z	2.72	8.97	-6.02	NPQ5-16-z	-4.32	-6.61	-17.68
NPQ7-17-d	1.55	8.90	-4.82	NPQ7-17-d	-4.68	-5.70	-15.86
NPQ7-17-z	1.55	7.40	-7.92	NPQ7-17-z	-4.68	-7.13	-18.90
NPQ5-18	3.02	9.36	-2.56	NPQ5-18	-4.19	-6.15	-14.05
NPQ5-19-b-d-x	1.30	7.18	-4.70	NPQ5-19-b-d-x	-4.64	-6.48	-14.51
NPQ5-19-b	-0.37	4.72	-8.99	NPQ5-19-b	-6.19	-8.86	-18.73
NPQ5-19-d-x	0.42	5.87	-8.48	NPQ5-19-d-x	-5.42	-7.71	-18.24
NPQ5-19-x	-1.09	3.54	-12.64	NPQ5-19-x	-6.81	-9.95	-22.32
NPQ5-20-d-x	2.26	8.46	-3.76	NPQ5-20-d-x	-4.11	-5.95	-14.20
NPQ5-20-x	0.64	6.08	-8.04	NPQ5-20-x	-5.63	-8.25	-18.41
NPQ5-21-a-x	2.47	8.66	-4.80	NPQ5-21-a-x	-4.19	-6.14	-15.79
NPQ5-21-x	1.76	7.58	-8.44	NPQ5-21-x	-4.79	-7.14	-19.34
NPQ5-22-d-x	2.85	9.28	-3.27	NPQ5-22-d-x	-3.70	-5.45	-14.23
NPQ5-22-x	1.47	7.17	-8.77	NPQ5-22-x	-4.97	-7.47	-19.59
NPQ5-23-a-d-x	1.97	7.97	-6.03	NPQ5-23-a-d-x	-4.30	-6.18	-16.50
NPQ5-23-a- x	0.50	5.89	-9.52	NPQ5-23-a- x	-5.55	-8.04	-19.77
NPQ5-23-d-x	1.16	6.77	-9.60	NPQ5-23-d-x	-4.89	-7.17	-19.86
NPQ5-23-x	-0.26	4.69	-13.26	NPQ5-23-x	-6.20	-9.15	-23.45
NPQ5-24	3.81	10.39	-3.38	NPQ5-24	-3.59	-5.44	-15.35
NPQ5-25-d-x	2.55	8.85	-3.27	NPQ5-25-d-x	-4.08	-5.86	-14.23
NPQ5-25-x	0.88	6.35	-7.61	NPQ5-25-x	-5.65	-8.30	-18.52
NPQ5-26-a-d-x	1.52	7.35	-4.49	NPQ5-26-a-d-x	-4.72	-6.66	-14.89
NPQ5-26-a-x	-0.12	4.92	-8.33	NPQ5-26-a-x	-6.15	-8.87	-18.49
NPQ5-26-d-x	0.83	6.19	-7.94	NPQ5-26-d-x	-5.29	-7.73	-18.27
NPQ5-26-x	-0.85	3.77	-11.92	NPQ5-26-x	-6.78	-9.95	-22.05
NPQ5-27	3.27	9.57	-1.81	NPQ5-27	-4.19	-6.24	-13.85
NPQ7-28-d-x	2.83	9.31	-5.01	NPQ7-28-d-x	-3.66	-5.40	-15.97
NPQ7-28-x	1.39	7.19	-8.67	NPQ7-28-x	-4.91	-7.35	-19.45
NPQ5-29-a-x	3.59	10.47	-2.16	NPQ5-29-a-x	-3.43	-5.00	-13.73
NPQ5-29-x	2.60	9.00	-6.05	NPQ5-29-x	-4.15	-6.19	-17.35

NPQ7-30	5.31	12.56	0.07	NPQ7-30	-2.83	-4.33	-12.93
NPQ7-31-a-d-x	3.22	9.86	-1.84	NPQ7-31-a-d-x	-3.58	-5.15	-13.06
NPQ7-31-a-x	1.99	7.98	-5.37	NPQ7-31-a-x	-4.62	-6.86	-16.43
NPQ7-31-d	2.52	8.76	-5.35	NPQ7-31-d	-4.15	-6.14	-16.48
NPQ7-31-z	1.27	6.82	-8.97	NPQ7-31-z	-5.21	-7.92	-19.94
NPQ7-32-d-e	2.01	8.42	-6.05	NPQ7-32-d-e	-3.82	-5.65	-16.17
NPQ7-32-e	1.21	7.16	-8.51	NPQ7-32-e	-4.56	-6.86	-18.57
NPQ7-32	-0.14	5.17	-12.09	NPQ7-32	-5.80	-8.77	-22.06
NPQ7-33-b-e	2.55	8.99	-5.03	NPQ7-33-b-e	-4.09	-5.88	-16.19
NPQ7-33-b	1.81	7.71	-7.84	NPQ7-33-b	-4.93	-7.26	-4.93
NPQ7-33-e	1.84	7.89	-8.85	NPQ7-33-e	-4.70	-6.90	-19.95
NPQ7-33-z	1.07	6.45	-11.57	NPQ7-33-z	-5.55	-8.44	-22.81

Table 6.6. Dipole moment of the conformers of the calculated naphthylisoquinoline alkaloids HF/6-31G(d,p) results *in vacuo* and in the three solvents considered

The media are denoted as vac, chlrf, actn and aq in the figures, respectively for vacuum, chloroform, acetonitrile and water.

Conformers and structures	Dipole moment (D)				Conformers and structures	Dipole moment (D)			
	vac	chlrf	actn	aq		vac	chlrf	actn	aq
NPQ7-1-b-e	2.81	3.44	3.62	3.73	NPQ5-15-x	2.20	2.41	2.48	2.46
NPQ7-1-b	4.43	5.85	6.15	6.62	NPQ5-15-z	0.85	1.045	1.20	1.62
NPQ7-1-e	0.65	1.08	1.18	1.34	NPQ5-16-d	2.21	2.43	2.53	2.49
NPQ7-1-z	3.36	4.03	4.35	4.92	NPQ5-16-z	1.91	2.18	2.26	2.38
NPQ5-2-a-x	3.98	4.81	5.05	5.43	NPQ7-17-d	3.60	3.90	4.02	3.93
NPQ5-2-a	3.68	4.04	4.30	4.69	NPQ7-17-z	2.37	2.85	3.12	3.35
NPQ5-2-x	2.27	2.53	2.61	2.69	NPQ5-18	4.97	5.68	5.96	6.18
NPQ7-3-d-x	0.99	1.09	1.08	1.08	NPQ5-19-b-d-x	5.26	5.91	6.19	6.56
NPQ7-3-x	4.39	3.56	3.88	4.55	NPQ5-19-b	5.43	6.37	6.76	7.21
NPQ5-4-a-d-x	3.61	3.82	4.03	4.03	NPQ5-19-d-x	3.85	4.37	4.58	4.89
NPQ5-4-a-x	3.20	3.80	4.04	4.34	NPQ5-19-x	4.44	5.23	5.58	5.93
NPQ5-4-d-x	1.91	2.04	2.09	1.99	NPQ5-20-d-x	4.26	4.75	4.95	5.17
NPQ5-4-x	1.94	2.39	2.60	2.92	NPQ5-20-x	4.43	5.20	5.56	5.91
NPQ5-5-b-d-x	2.82	3.11	3.21	3.44	NPQ5-21-a-x	4.53	5.19	5.48	5.69
NPQ5-5-b-x	3.28	3.81	3.97	4.23	NPQ5-21-x	3.05	3.34	3.44	3.34
NPQ5-5-d-x	1.51	1.82	1.98	2.34	NPQ5-22-d-x	1.80	1.93	1.97	1.85
NPQ5-5-x	2.91	3.44	3.69	4.11	NPQ5-22-x	2.13	2.52	2.68	2.94
NPQ5-6-b-d-x	3.18	3.55	3.67	3.89	NPQ5-23-a-d-x	2.83	3.25	3.42	3.56
NPQ5-6-b-x	3.52	4.06	4.25	4.55	NPQ5-23-a-x	3.86	4.49	4.67	4.89
NPQ5-6-x	2.46	2.85	3.02	3.13	NPQ5-23-d-x	1.27	1.45	1.55	1.59
NPQ5-7-x	2.20	2.53	2.66	2.91	NPQ5-23-x	2.46	2.86	3.03	3.25
NPQ5-7-z	0.76	1.03	1.24	1.77	NPQ5-24	2.33	2.60	2.73	2.84
NPQ5-8-b-x	4.08	4.76	5.07	5.40	NPQ5-25-d-x	4.10	4.60	4.83	5.12
NPQ5-8-b	3.46	4.07	4.36	4.79	NPQ5-25-x	4.51	5.33	5.68	6.06
NPQ5-8-x	2.33	2.70	2.84	2.98	NPQ5-26-a-d-x	4.95	5.75	6.12	6.54
NPQ5-8-z	1.00	1.31	1.53	2.03	NPQ5-26-a-x	5.97	7.03	7.47	7.89
NPQ5-9-b-d-x	4.70	5.29	5.55	5.98	NPQ5-26-d-x	3.71	4.23	4.48	4.83
NPQ5-9-b-x	5.04	5.92	6.31	6.71	NPQ5-26-x	4.55	5.37	5.71	6.07
NPQ5-9-d-x	3.66	4.23	4.48	4.85	NPQ5-27	5.01	5.77	6.08	6.30
NPQ5-9-x	4.53	5.37	5.74	6.12	NPQ7-28-d-x	2.76	3.01	3.10	3.10
NPQ7-10-d	4.10	4.21	4.38	4.39	NPQ7-28-x	2.72	3.16	3.30	3.51
NPQ7-10-z	1.92	2.33	2.60	2.86	NPQ5-29-a-x	2.27	2.57	2.68	2.70
NPQ7-11-d-x	2.98	3.14	3.15	2.96	NPQ5-29-x	1.58	1.81	1.93	2.14
NPQ7-11-x	1.27	1.65	1.86	2.32	NPQ7-30	2.17	2.45	2.62	2.79
NPQ5-12-a-d-x	4.53	5.22	5.56	5.92	NPQ7-31-a-d-x	3.21	3.65	3.83	3.96
NPQ5-12-a-x	5.43	6.37	6.77	7.14	NPQ7-31-a-x	3.72	4.33	4.63	4.96

NPQ5-12-d-x	3.84	4.35	4.59	4.89	NPQ7-31-d	1.99	2.12	2.12	1.95
NPQ5-12-x	4.45	5.24	5.58	5.94	NPQ7-31-z	1.48	1.86	2.06	2.44
NPQ5-13-b-d-x	4.53	5.23	5.56	5.93	NPQ7-32-d-e	3.99	4.32	4.45	4.41
NPQ5-13-b-x	5.43	6.36	6.77	7.14	NPQ7-32-e	2.21	2.62	2.79	3.12
NPQ5-13-d-x	3.84	4.35	4.59	4.90	NPQ7-32	2.68	3.17	3.41	3.34
NPQ5-13-x	4.45	5.23	5.59	5.93	NPQ7-33-b-e	3.79	4.31	4.51	4.61
NPQ5-14-b-d-x	4.86	5.44	5.68	5.97	NPQ7-33-b	4.05	4.73	5.07	5.40
NPQ5-14-b-x	4.71	5.55	5.93	6.42	NPQ7-33-e	3.07	3.28	3.41	3.36
NPQ5-14-d-x	2.52	2.66	2.69	2.63	NPQ7-33-z	2.62	3.13	3.37	3.62
NPQ5-14-x	2.41	2.86	3.08	3.33					

Table 6.7. Dipole moment of the conformers of the calculated naphthylisoquinoline alkaloids DFT/B3LYP/6-31+G(d,p) results *in vacuo* and in the three solvents considered

The media are denoted as vac, chlrf, actn and aq in the figures, respectively for vacuum, chloroform, acetonitrile and water.

Conformers and structures	Dipole moment (Debye)				Conformers and structures	Dipole moment (Debye)			
	vac	chlrf	actn	aq		vac	chlrf	actn	aq
NPQ7-1-b-e	2.70	3.20	3.36	3.45	NPQ5-15-x	2.19	2.41	2.43	2.26
NPQ7-1-b	4.64	5.63	5.99	6.51	NPQ5-15-z	1.11	1.29	1.42	1.76
NPQ7-1-e	0.81	0.90	0.97	1.13	NPQ5-16-d	2.38	2.72	2.86	2.83
NPQ7-1-z	3.38	4.17	4.54	5.22	NPQ5-16-z	1.67	1.92	1.97	2.06
NPQ5-2-a-x	3.92	4.73	5.06	5.48	NPQ7-17-d	4.05	4.48	4.64	4.51
NPQ5-2-a	3.40	4.10	4.41	4.86	NPQ7-17-z	2.38	2.89	3.20	3.37
NPQ5-2-x	2.14	2.45	2.55	2.63	NPQ5-18	5.02	5.97	6.34	6.58
NPQ7-3-d-x	1.28	1.21	1.13	0.93	NPQ5-19-b-d-x	5.22	6.08	6.41	6.85
NPQ7-3-x	2.83	3.59	3.98	4.74	NPQ5-19-b	5.10	6.22	6.68	7.21
NPQ5-4-a-d-x	3.71	4.15	4.26	4.21	NPQ5-19-d-x	3.90	4.60	4.88	5.23
NPQ5-4-a-x	3.00	3.67	3.93	4.24	NPQ5-19-x	4.27	5.24	5.67	6.09
NPQ5-4-d-x	2.30	2.30	2.37	2.25	NPQ5-20-d-x	4.46	5.15	5.42	5.68
NPQ5-4-x	1.70	2.20	2.43	2.83	NPQ5-20-x	4.34	5.30	5.70	6.13
NPQ5-5-b-d-x	2.70	3.06	3.14	3.40	NPQ5-21-a-x	4.30	5.11	5.45	5.68
NPQ5-5-b-x	2.97	3.54	3.71	4.00	NPQ5-21-x	2.94	3.31	3.43	3.28
NPQ5-5-d-x	1.62	2.07	2.33	2.84	NPQ5-22-d-x	1.98	2.21	2.28	5.61
NPQ5-5-x	2.70	3.35	3.69	4.31	NPQ5-22-x	1.83	2.23	2.42	2.69
NPQ5-6-b-d-x	3.07	3.52	3.64	3.90	NPQ5-23-a-d-x	2.79	3.33	3.52	3.70
NPQ5-6-b-x	3.19	3.79	3.98	4.29	NPQ5-23-a-x	3.76	4.50	4.75	4.99
NPQ5-6-x	2.18	2.62	2.84	2.96	NPQ5-23-d-x	1.33	1.61	1.73	1.80
NPQ5-7-x	2.09	2.41	2.53	2.61	NPQ5-23-x	2.24	2.69	2.89	3.15
NPQ5-7-z	0.88	1.08	1.24	1.78	NPQ5-24	2.13	2.42	2.55	2.60
NPQ5-8-b-x	3.88	4.68	5.08	5.47	NPQ5-25-d-x	4.26	5.00	5.28	5.61
NPQ5-8-b	3.43	4.18	4.54	5.08	NPQ5-25-x	4.38	5.16	5.59	6.01
NPQ5-8-x	2.15	2.55	2.72	2.81	NPQ5-26-a-d-x	4.90	5.92	6.37	6.90
NPQ5-8-z	0.87	1.18	1.41	1.99	NPQ5-26-a-x	5.85	7.17	7.76	8.28
NPQ5-9-b-d-x	4.72	5.51	5.84	6.35	NPQ5-26-d-x	3.73	4.45	4.79	5.18
NPQ5-9-b-x	4.76	5.82	6.27	6.76	NPQ5-26-x	4.41	5.41	5.86	6.28
NPQ5-9-d-x	3.68	4.43	4.76	5.20	NPQ7-28-d-x	2.76	3.29	3.41	3.42
NPQ5-9-x	4.36	5.41	5.86	6.31	NPQ5-27	4.98	5.96	6.37	6.61
NPQ7-10-d	3.82	4.67	4.92	4.95	NPQ7-28-x	2.72	3.03	3.21	3.41
NPQ7-10-z	1.94	2.37	2.66	2.88	NPQ5-29-a-x	2.27	2.44	2.56	2.60
NPQ7-11-d-x	3.28	3.57	3.60	3.56	NPQ5-29-x	1.58	1.66	1.82	2.08
NPQ7-11-x	1.14	1.45	1.64	2.08	NPQ7-30	2.11	2.49	2.74	2.99
NPQ5-12-a-d-x	4.51	5.40	5.81	6.25	NPQ7-31-a-d-x	3.21	3.86	4.09	4.14
NPQ5-12-a-x	5.37	6.55	7.06	7.52	NPQ7-31-a-x	3.72	4.50	4.86	5.25
NPQ5-12-d-x	3.90	4.61	4.91	5.26	NPQ7-31-d	1.99	2.50	2.52	2.30

NPQ5-12-x	4.30	5.25	5.69	6.11	NPQ7-31-z	1.48	1.49	1.73	2.22
NPQ5-13-b-d-x	4.98	5.21	5.62	6.02	NPQ7-32-d-e	3.99	4.72	4.89	4.86
NPQ5-13-b-x	4.63	6.55	7.06	7.52	NPQ7-32-e	2.21	3.03	3.23	3.57
NPQ5-13-d-x	2.75	4.61	4.93	5.26	NPQ7-32	2.68	2.50	2.74	3.14
NPQ5-13-x	2.20	5.26	5.70	6.11	NPQ7-33-b-e	3.79	4.61	4.87	5.04
NPQ5-14-b-d-x	4.98	5.76	6.08	6.48	NPQ7-33-b	4.05	4.48	4.85	5.25
NPQ5-14-b-x	4.63	5.66	6.14	6.77	NPQ7-33-e	3.07	3.53	3.69	3.62
NPQ5-14-d-x	2.75	3.00	3.07	2.99	NPQ7-33-z	2.62	3.01	3.30	3.63
NPQ5-14-x	2.20	2.67	2.91	3.19					

Table 6.8. HOMO-LUMO energy gaps of the conformers of the calculated naphthylisoquinoline alkaloids

HF/6-31G(d,p) results *in vacuo* and in the three solvents considered. The media are denoted as vac, chlrf, actn and aq in the figures, respectively for vacuum, chloroform, acetonitrile and water.

Conformers and structures	HOMO-LUMO energy difference (kcal/mol)				Conformers and structures	HOMO-LUMO energy difference (kcal/mol)			
	vac	chlrf	actn	aq		vac	chlrf	actn	aq
NPQ7-1-b-e	234.795	228.727	228.953	229.323	NPQ5-15-x	241.133	240.976	240.901	240.763
NPQ7-1-b	236.131	229.355	229.480	229.668	NPQ5-15-z	241.139	240.976	240.907	240.769
NPQ7-1-e	237.003	230.170	230.133	230.051	NPQ5-16-d	241.215	240.330	240.311	240.279
NPQ7-1-z	237.643	237.619	237.562	237.443	NPQ5-16-z	240.424	241.051	240.963	240.832
NPQ5-2-a-x	238.779	239.232	230.490	230.679	NPQ7-17-d	239.206	239.169	239.169	239.156
NPQ5-2-a	231.839	229.744	229.913	230.114	NPQ7-17-z	238.497	238.541	238.529	238.479
NPQ5-2-x	239.915	230.917	230.835	230.660	NPQ5-18	238.629	238.290	238.353	238.642
NPQ7-3-d-x	237.399	230.528	230.541	230.553	NPQ5-19-b-d-x	238.629	239.056	239.144	239.250
NPQ7-3-x	238.014	237.926	237.920	237.901	NPQ5-19-b	238.547	239.006	239.175	239.282
NPQ5-4-a-d-x	238.829	239.119	239.194	239.307	NPQ5-19-d-x	240.210	240.003	239.922	239.765
NPQ5-4-a-x	238.924	239.257	239.326	239.464	NPQ5-19-x	238.240	238.322	238.472	238.497
NPQ5-4-d-x	240.354	240.192	240.116	239.985	NPQ5-20-d-x	238.779	239.784	239.702	239.740
NPQ5-4-x	241.057	240.807	240.681	240.455	NPQ5-20-x	240.034	238.510	238.792	239.206
NPQ5-5-b-d-x	236.245	236.401	236.427	236.439	NPQ5-21-a-x	238.277	238.836	238.937	239.087
NPQ5-5-b-x	236.069	236.263	236.289	236.376	NPQ5-21-x	238.460	240.487	240.367	240.123
NPQ5-5-d-x	237.267	237.148	237.085	236.922	NPQ5-22-d-x	240.731	238.152	233.628	238.046
NPQ5-5-x	237.681	237.468	237.355	237.167	NPQ5-22-x	238.302	238.767	238.704	238.635
NPQ5-6-b-d-x	236.251	236.408	236.445	236.458	NPQ5-23-a-d-x	238.829	239.382	239.564	239.796
NPQ5-6-b-x	236.063	236.263	236.307	236.395	NPQ5-23-a-x	237.681	238.127	238.209	238.366
NPQ5-6-x	237.807	237.575	237.468	237.286	NPQ5-23-d-x	238.152	237.920	237.820	237.638
NPQ5-7-x	238.912	238.773	238.711	238.635	NPQ5-23-x	238.993	238.767	238.660	238.497
NPQ5-7-z	238.874	238.742	238.679	238.617	NPQ5-24	238.955	236.609	238.742	238.679
NPQ5-8-b-x	236.012	236.314	236.389	236.521	NPQ5-25-d-x	238.955	237.349	237.255	237.111
NPQ5-8-b	235.987	236.301	236.376	236.514	NPQ5-25-x	237.581	236.941	237.092	237.280

NPQ5-8-x	237.869	237.694	237.619	237.475	NPQ5-26-a-d-x	238.547	239.169	239.363	239.583
NPQ5-8-z	237.838	237.669	237.587	237.456	NPQ5-26-a-x	236.200	236.891	237.067	237.242
NPQ5-9-b-d-x	235.856	235.868	235.849	235.768	NPQ5-26-d-x	238.152	237.092	236.966	236.709
NPQ5-9-b-x	235.328	235.655	235.749	235.868	NPQ5-26-x	237.110	237.154	237.186	237.129
NPQ5-9-d-x	236.979	236.721	236.596	236.339	NPQ5-27	236.753	236.609	236.634	236.860
NPQ5-9-x	236.169	236.245	236.289	236.251	NPQ7-28-d-x	236.752	237.738	237.700	237.644
NPQ7-10-d	238.397	238.246	238.158	238.089	NPQ7-28-x	237.845	238.271	238.190	238.071
NPQ7-10-z	238.508	238.548	238.491	238.435	NPQ5-29-a-x	238.435	238.271	238.284	238.284
NPQ7-11-d-x	238.246	238.096	238.027	237.958	NPQ5-29-x	238.140	239.006	238.899	238.679
NPQ7-11-x	238.817	238.842	238.817	238.799	NPQ7-30	239.665	239.464	239.370	239.244
NPQ5-12-a-d-x	237.210	237.663	237.838	238.146	NPQ7-31-a-d-x	239.244	235.347	235.661	236.194
NPQ5-12-a-x	238.058	238.635	238.780	238.880	NPQ7-31-a-x	239.664	236.345	236.596	236.922
NPQ5-12-d-x	239.106	238.842	238.755	238.673	NPQ7-31-d	235.542	238.334	238.340	238.403
NPQ5-12-x	238.233	238.271	238.403	238.428	NPQ7-31-z	238.535	238.629	238.629	238.535
NPQ5-13-b-d-x	238.058	237.663	237.838	238.146	NPQ7-32-d-e	238.892	238.817	238.792	238.836
NPQ5-13-b-x	238.227	238.629	238.786	238.886	NPQ7-32-e	239.739	239.646	239.595	239.558
NPQ5-13-d-x	237.204	238.842	238.748	238.667	NPQ7-32	240.292	240.173	240.104	240.123
NPQ5-13-x	239.106	238.271	238.397	238.422	NPQ7-33-b-e	236.803	237.449	237.650	237.939
NPQ5-14-b-d-x	238.792	239.087	239.169	239.257	NPQ7-33-b	237.857	238.347	238.466	238.629
NPQ5-14-b-x	238.622	239.037	239.144	239.275	NPQ7-33-e	239.206	238.824	238.943	238.824
NPQ5-14-d-x	240.367	240.192	240.116	239.959	NPQ7-33-z	239.639	239.282	239.401	239.282
NPQ5-14-x	240.624	240.530	240.468	240.298					

Table 6.9. HOMO-LUMO energy gaps of the conformers of the calculated naphthylisoquinoline

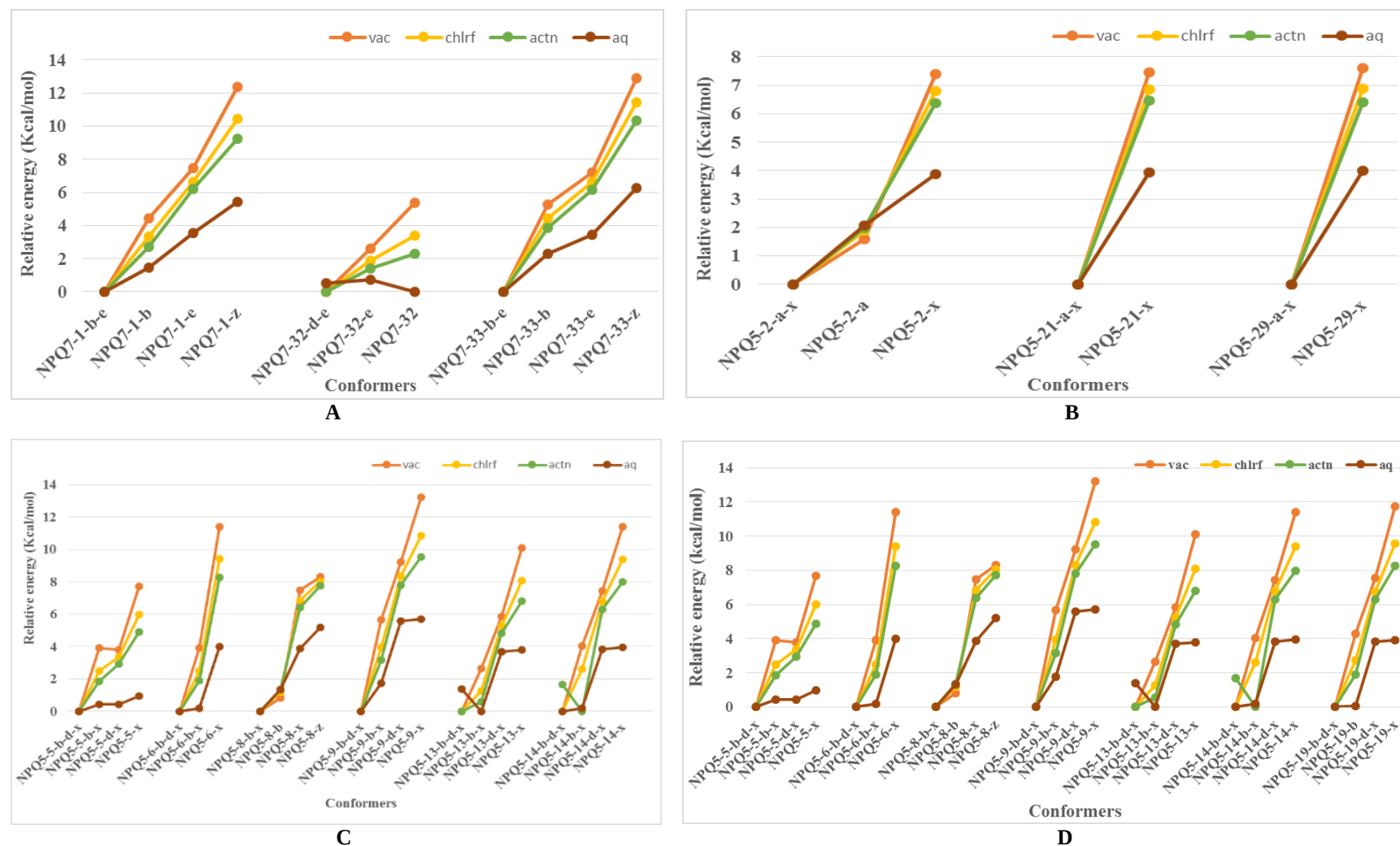
DFT/6-31+G(d,p) results *in vacuo* and in the three solvents considered. The media are denoted as vac, chlrf, actn and aq in the figures, respectively for vacuum, chloroform, acetonitrile and water.

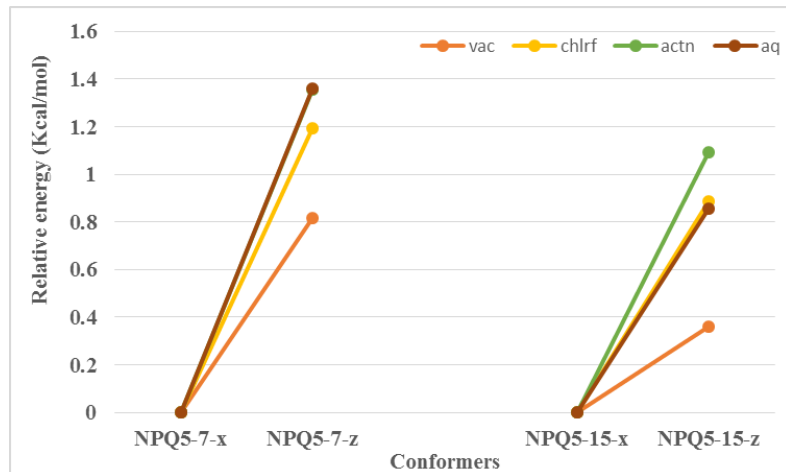
Conformers	HOMO-LUMO energy difference (kcal/mol)				Conformers	HOMO-LUMO energy difference (kcal/mol)			
	vac	chlrf	actn	aq		vac	chlrf	actn	aq
NPQ7-1-b-e	98.951	99.504	99.667	97.101	NPQ5-15-x	102.516	102.497	102.478	102.391
NPQ7-1-b	99.579	100.081	100.176	100.251	NPQ5-15-z	102.673	102.560	102.522	102.428
NPQ7-1-e	100.113	100.107	100.088	100.056	NPQ5-16-d	100.772	101.851	102.046	101.669
NPQ7-1-z	100.144	100.226	100.232	100.188	NPQ5-16-z	102.692	102.573	102.529	102.409
NPQ5-2-a-x	100.370	100.841	100.972	101.098	NPQ7-17-d	100.508	100.885	100.910	100.947
NPQ5-2-a	100.018	100.470	100.596	100.734	NPQ7-17-z	100.571	100.590	100.596	100.583
NPQ5-2-x	100.840	100.772	100.747	100.690	NPQ5-18	100.376	99.109	98.889	99.015
NPQ7-3-d-x	100.803	100.759	100.753	100.778	NPQ5-19-b-d-x	100.376	101.556	101.644	101.744
NPQ7-3-x	99.014	100.910	100.922	100.885	NPQ5-19-b	100.791	100.797	100.866	100.728
NPQ5-4-a-d-x	101.016	101.424	101.518	101.594	NPQ5-19-d-x	101.687	101.675	101.669	101.192
NPQ5-4-a-x	101.110	101.456	101.537	101.644	NPQ5-19-x	99.560	99.046	98.964	98.864
NPQ5-4-d-x	101.631	101.650	101.656	101.644	NPQ5-20-d-x	101.116	102.083	101.933	101.405
NPQ5-4-x	102.026	101.970	101.926	101.826	NPQ5-20-x	102.221	98.732	98.870	99.172
NPQ5-5-b-d-x	99.767	100.150	100.232	100.207	NPQ5-21-a-x	99.184	100.696	100.778	100.853
NPQ5-5-b-x	99.623	99.856	99.906	99.950	NPQ5-21-x	100.370	101.468	101.412	101.305
NPQ5-5-d-x	100.156	100.201	100.219	100.176	NPQ5-22-d-x	101.562	101.186	101.161	100.226
NPQ5-5-x	100.338	100.257	100.207	100.107	NPQ5-22-x	101.311	101.368	101.330	101.305
NPQ5-6-b-d-x	97.351	98.193	98.720	98.506	NPQ5-23-a-d-x	99.642	101.826	101.989	102.202
NPQ5-6-b-x	99.617	99.843	99.899	99.912	NPQ5-23-a-x	100.163	100.571	100.671	100.778
NPQ5-6-x	100.483	100.383	100.332	100.232	NPQ5-23-d-x	100.753	100.652	100.609	100.552
NPQ5-7-x	101.361	101.318	101.318	101.293	NPQ5-23-x	100.897	100.803	100.772	100.709
NPQ5-7-z	101.418	101.324	101.299	101.293	NPQ5-24	101.431	101.324	101.293	101.267
NPQ5-8-b-x	99.423	99.793	99.906	100.050	NPQ5-25-d-x	101.431	100.740	100.514	100.226
NPQ5-8-b	99.448	99.812	99.931	100.056	NPQ5-25-x	101.054	97.452	97.709	98.255

NPQ5-8-x	100.345	100.332	100.320	100.282	NPQ5-26-a-d-x	99.008	99.567	99.743	99.918
NPQ5-8-z	100.389	100.339	100.320	100.276	NPQ5-26-a-x	98.569	99.504	99.724	99.881
NPQ5-9-b-d-x	99.969	100.075	100.031	99.918	NPQ5-26-d-x	98.431	100.351	100.176	99.837
NPQ5-9-b-x	98.820	99.134	99.253	99.347	NPQ5-26-x	98.431	98.249	98.193	98.375
NPQ5-9-d-x	100.163	100.006	99.874	99.567	NPQ5-27	98.889	98.142	97.960	98.356
NPQ5-9-x	98.136	98.067	98.161	98.237	NPQ7-28-d-x	98.889	100.972	100.972	100.947
NPQ7-10-d	101.010	100.897	100.816	100.790	NPQ7-28-x	101.004	101.136	101.085	100.998
NPQ7-10-z	101.450	101.330	101.293	101.318	NPQ5-29-a-x	101.267	100.935	100.947	100.947
NPQ7-11-d-x	100.978	100.866	100.797	100.765	NPQ5-29-x	100.740	100.916	100.872	100.797
NPQ7-11-x	101.004	101.010	101.010	101.054	NPQ7-30	101.462	101.336	101.280	101.192
NPQ5-12-a-d-x	99.906	100.452	100.646	100.916	NPQ7-31-a-d-x	100.997	99.253	98.745	98.437
NPQ5-12-a-x	99.993	100.565	100.784	100.822	NPQ7-31-a-x	101.461	100.107	100.326	100.489
NPQ5-12-d-x	101.192	101.167	101.098	100.853	NPQ7-31-d	99.315	100.470	100.496	100.539
NPQ5-12-x	99.642	99.115	99.015	98.933	NPQ7-31-z	100.194	100.332	100.364	100.370
NPQ5-13-b-d-x	99.993	100.552	100.759	101.067	NPQ7-32-d-e	105.578	106.846	106.827	106.971
NPQ5-13-b-x	99.642	100.533	100.778	100.822	NPQ7-32-e	107.292	107.179	107.147	107.179
NPQ5-13-d-x	99.974	101.161	101.092	100.853	NPQ7-32	107.235	107.222	107.179	107.153
NPQ5-13-x	101.192	99.109	98.964	98.933	NPQ7-33-b-e	100.257	100.860	101.054	101.305
NPQ5-14-b-d-x	97.891	99.592	100.031	99.617	NPQ7-33-b	100.878	101.374	101.500	101.638
NPQ5-14-b-x	100.821	101.136	101.167	100.941	NPQ7-33-e	101.662	101.606	101.581	101.550
NPQ5-14-d-x	99.949	101.305	101.443	101.211	NPQ7-33-z	101.650	101.663	101.656	101.650
NPQ5-14-x	101.800	101.769	101.719	101.562					

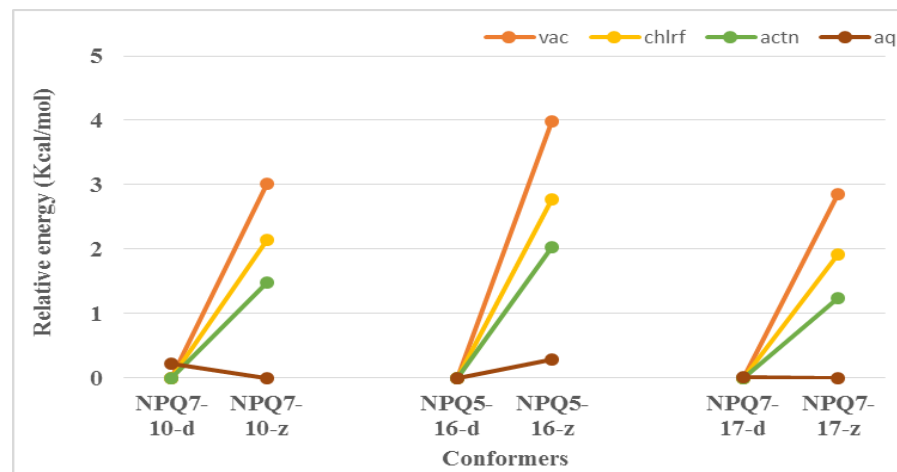
Figure 6.1. Trends of the relative energies for the different categories of conformers of the calculated naphthylisoquinoline alkaloids

DFT results *in vacuo* and in the three solvents considered. The media are denoted as vac, chlrf, actn and aq in the figures, respectively for vacuum, chloroform, acetonitrile and water.

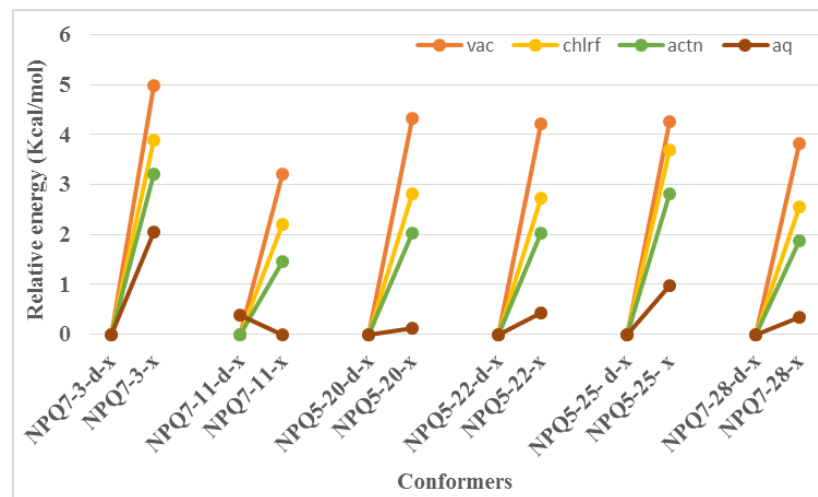




E



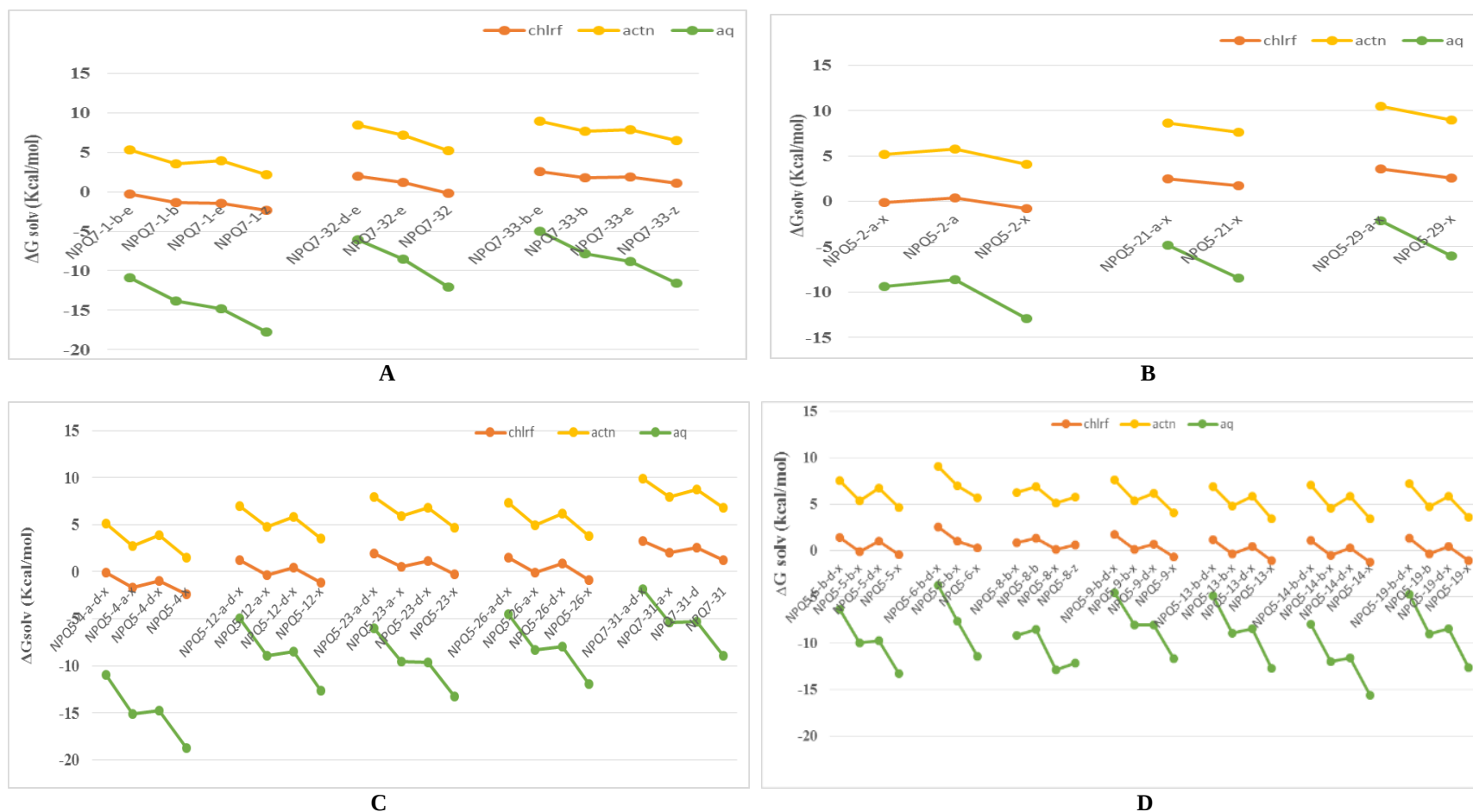
F



G

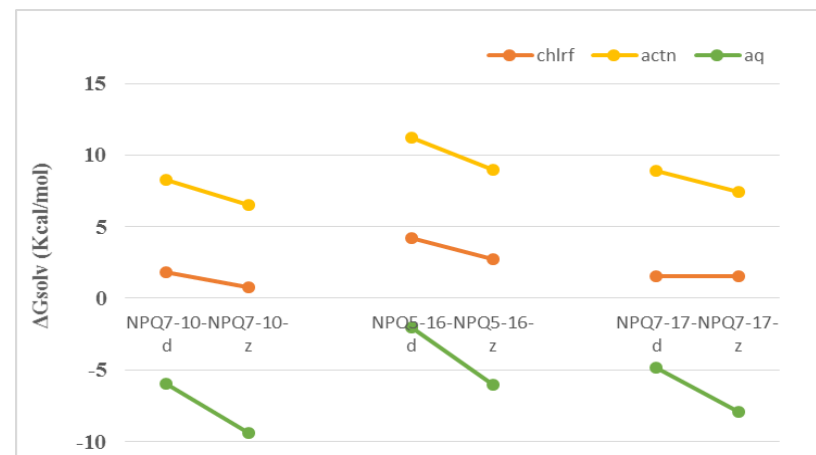
Figure 6.2. Trends of the free energy of solvation (ΔG_{solv}) for the different categories of conformers of the calculated naphthylisoquinoline alkaloids

DFT results in the three solvents considered (chloroform, acetonitrile and water respectively denoted as chlrf, actn and aq in the figures).

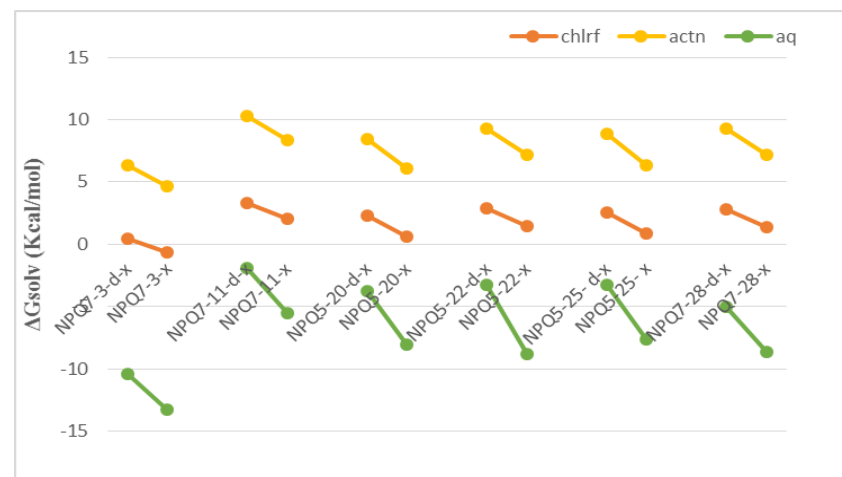




E



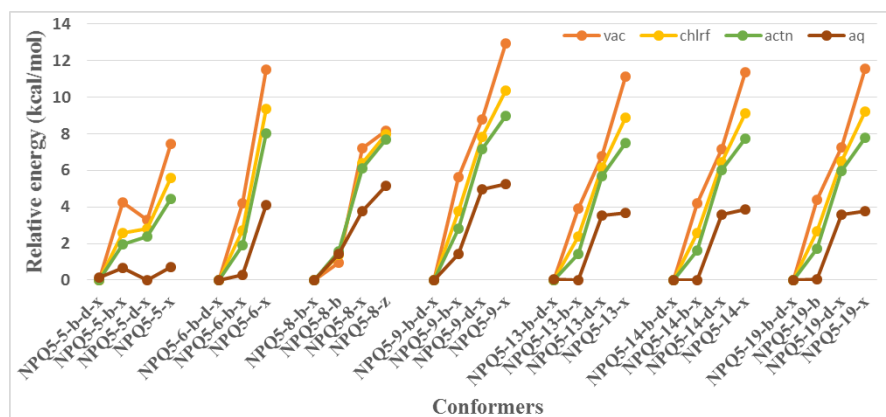
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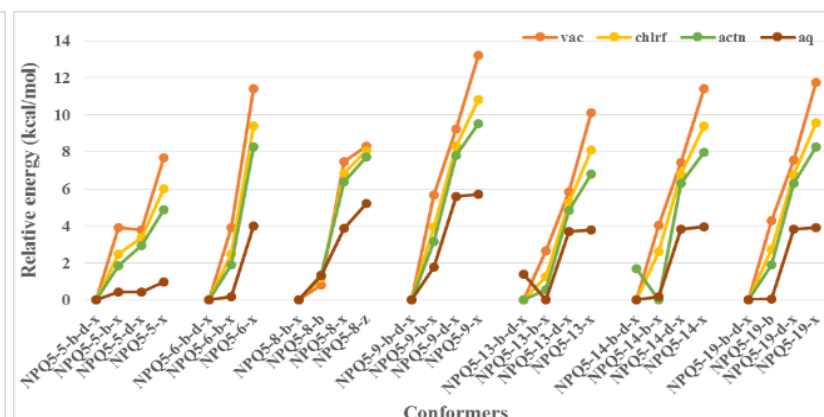
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Figure 6.3. Trends of the different molecular properties of the conformers of category D

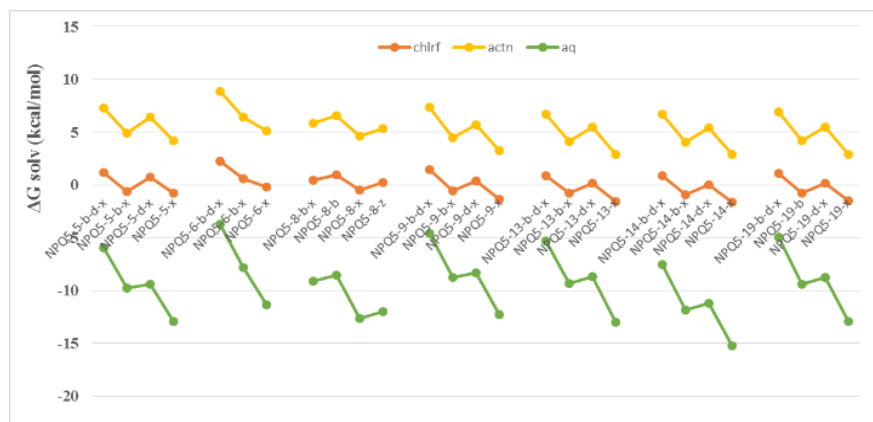
HF and DFT results *in vacuo* and in the three solvents considered. The media are denoted as vac, chlrf, actn and aq in the figures, respectively for vacuum, chloroform, acetonitrile and water.



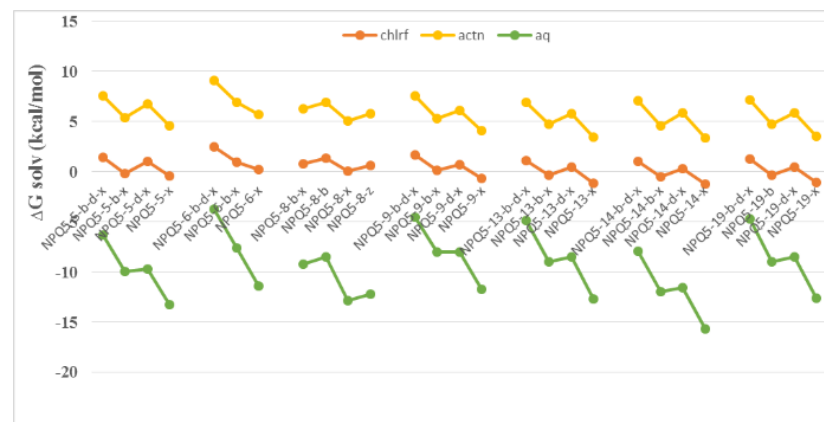
HF relative energy



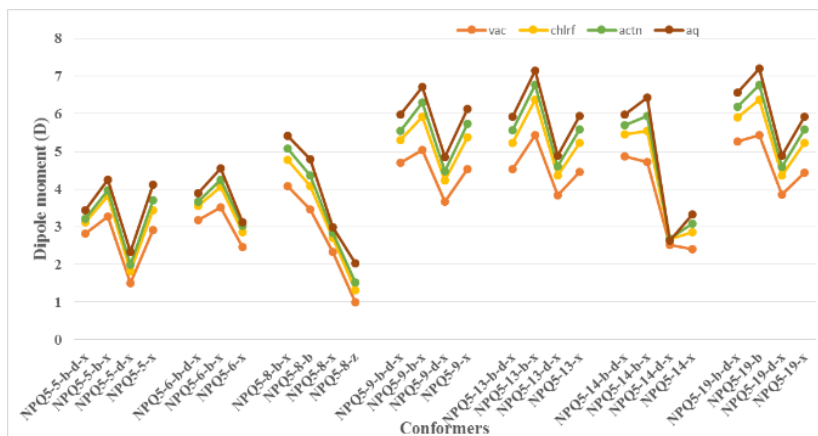
DFT relative energy



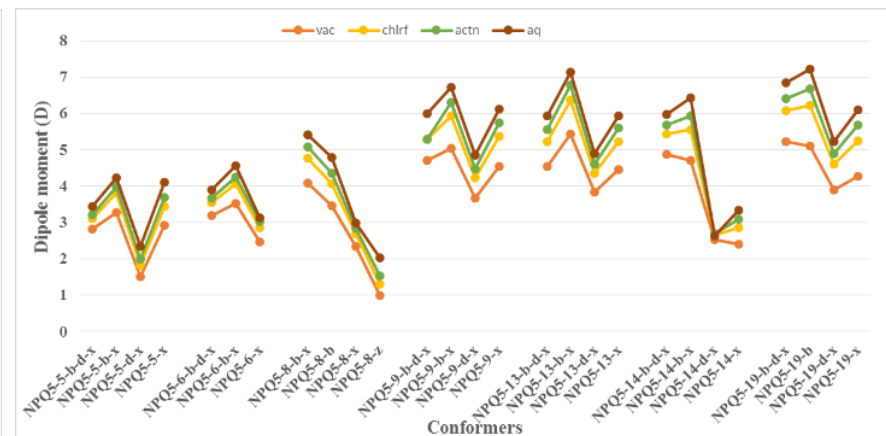
HF ΔG_{solv}



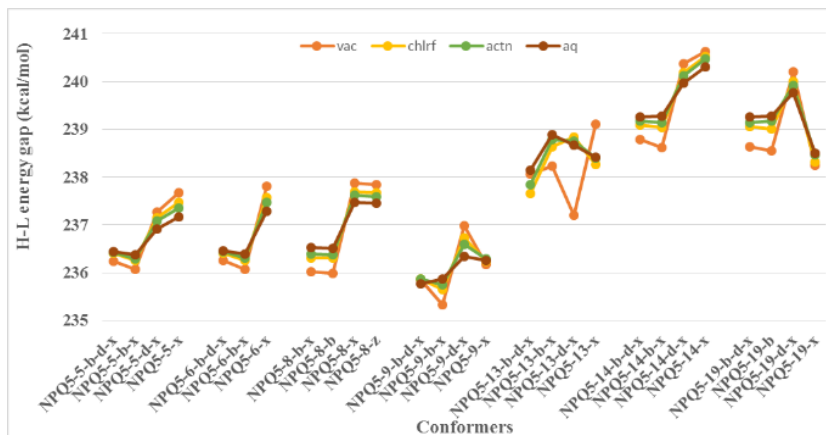
DFT ΔG_{solv}



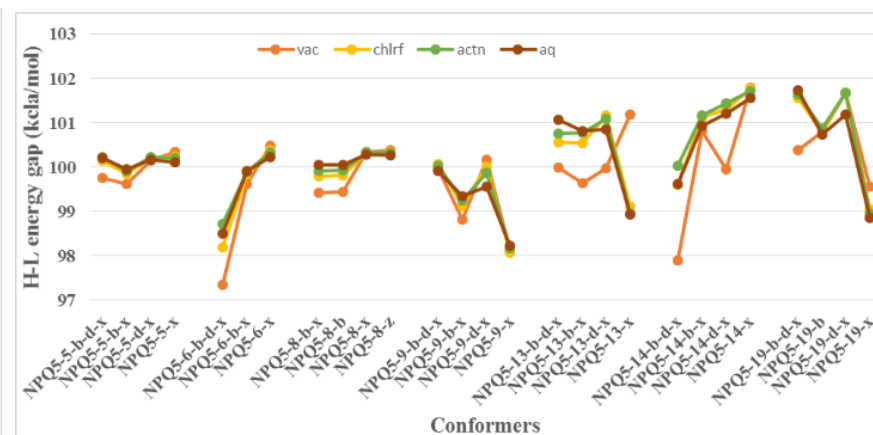
HF dipole moment



DFT dipole moment



HF HOMO-LUMO



DFT HOMO-LUMO

CHAPTER 7

COMPUTATIONAL STUDY OF JOZIMINE A₂, A DIMERIC NAPHTHYLISOQUINOLINE *IN VACUO* AND IN SOLUTION

This chapter presents the results of the conformational study of jozimine A₂ *in vacuo* and in three solvents (chloroform, acetonitrile and water). The results were presented at a QSCP conference in 2016 [F] and subsequently published [59].

7.1. Introduction

Jozimine A₂ (Fig.7.1, denoted by the acronym JZM in the rest of this chapter) is a Dioncophyllaceae-type naphthylisoquinoline alkaloid isolated from a plant belonging to the *ancistrodaceae* family. It has confirmed antimalarial activity, with the lowest IC₅₀ (0.0014 μM) among antimalarial naphthylisoquinoline alkaloids [49]. The molecule has a dimeric structure: it consists of two units, each consisting of a naphthalene moiety and an isoquinoline moiety. The two units are identical (have the same substituents in corresponding positions) making the molecule a C₂ symmetric dimer [49]. These characteristics make the computational study of this molecule particularly interesting. The analysis of the results will give specific attention to symmetry aspects.

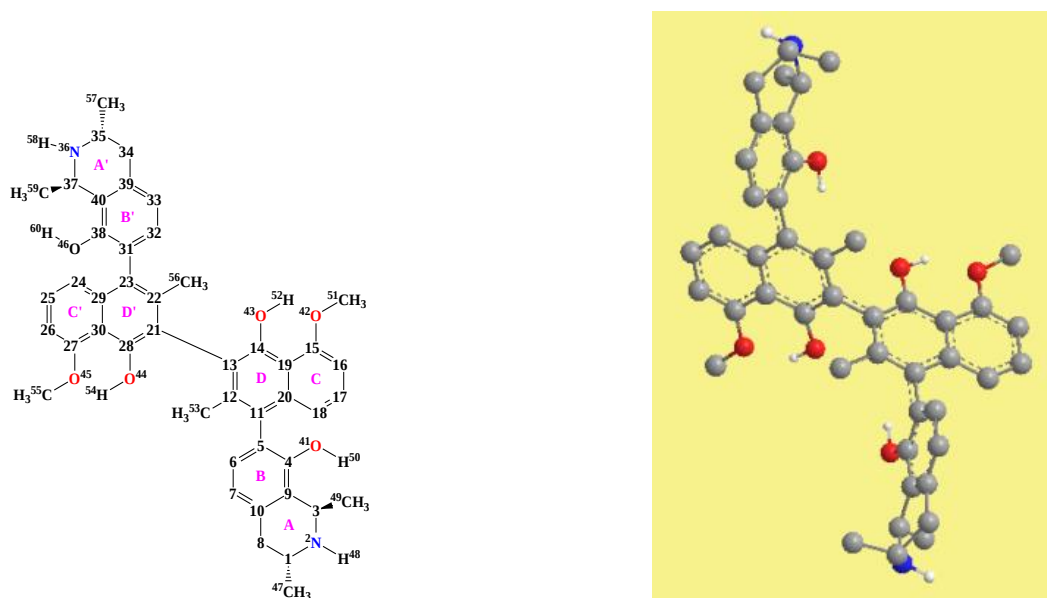


Figure 7.1. Two representations of the jozimine A₂ molecule and atom numbering utilized in this work

In the structure on the left, the C atoms in the rings are represented only by the numbers denoting their positions. Only the H atoms attached to O or N are numbered separately, while the H atoms attached to C atoms are given the same number as the C atom and are not shown in the structure. The two units are identical. Identical rings are denoted by the same letters, primed for one of the units (A, B, C, D and C', D', A' and B').

7.2. Preparation of inputs

For jozimine A₂, a preliminary identification of conformers of interest was carried out by considering the potential energy profiles for the rotation of the C5–C11 bond (showing the minima for the mutual orientation of the two moieties within one unit, Fig.7.2) and for the rotation of the C13–C21 bond (showing the minima for the mutual orientation of the two units).

The rotation of the two bonds was carried out simultaneously, yielding a 3D potential energy profile (Fig.7.2). It was carried out for a complete rotation (360°) about the bond in 15° steps. A conformer without O–H... π interaction between the moieties (a conformer with the

O43–H52...O42 and O44–H54...O45 IHBs) was chosen as input, to avoid the effect of the removal of the interaction during the rotation. The scan highlighted five minima (Fig.7.2, considering that angles differing by 360° are the same). Each of the corresponding geometries was optimized to find the actual geometry corresponding to a given minimum (as the optimization involves fully relaxed geometry).

Since interactions between S and S' were not present in the input, this provides information only on the preferences for the mutual orientations of the moieties and identifies five different combinations of orientations. More conformers were then identified by changing the IHB patterns in each of the five conformers obtained from the potential energy surface.

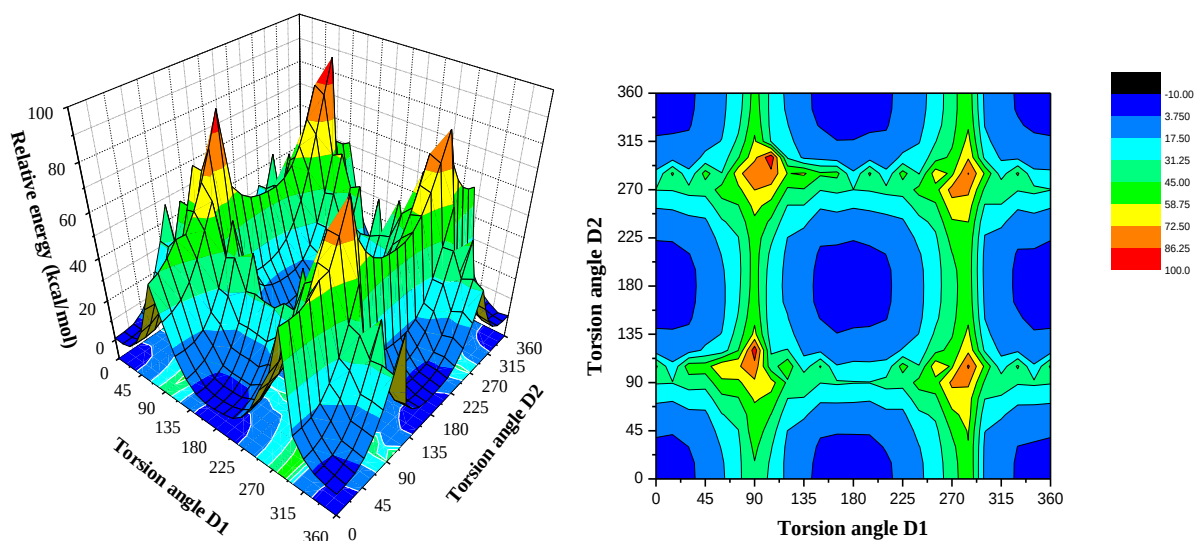


Figure 7.2. 3D potential energy profile for the scan of the rotation of the C5–C11 and C13–C21 bonds (energy versus D1 and D2, with D1 being the C4–C5–C11–C12 torsion angle and D2 being the C14–C13–C21–C28 torsion angle) and 2D potential energy profile for the same rotation scan. The complete 360° rotations were performed in 15° steps.

7.3. Naming of conformers

Given the dimeric nature of this molecule, the system of symbols introduced for the monomeric naphthylisoquinoline alkaloids is not adequate. A new system of symbols is introduced to be able to clearly and easily identify the geometric characteristics of each conformer when analysing the results; thus, each conformer is denoted by an acronym summarising its characterising features. Since it is useful to be able to mention each ring individually and concisely, the rings are denoted by uppercase letters [62]. Since the two units are identical, identical rings are denoted with the same letter, primed for one of the units. Thus, the rings are denoted as A, B, C, D, A', B', C' and D' as shown in Fig.7.1. In order to be able to mention each of the two units of the dimeric molecular structure individually, the whole unit comprising the A, B, C and D rings is called S and the whole unit comprising the A', B', C' and D' rings is called S'.

The O–H···O IHBs and other IHB-type interactions such as O–H··· π and C–H···O are the most important factors stabilizing the conformers. Different conformers have different combinations of these intramolecular interactions and are characterized by them. A specific lowercase letter is used to denote each IHB or IHB-type interaction in the acronyms denoting the conformers. The letters (a – h) and their meanings are listed in Table 7.1. Their use is illustrated by the names of the representative conformers of JZM shown in Fig.7.3. The geometries of all the conformers are shown in Fig. 7.K1 and at the end of the chapter.

The mutual orientations of the four moieties also have significant influence on the energy of the conformers and, therefore, they are also denoted by specific letters. Lowercase letters are utilised to provide information about the torsion angles between moieties, i.e., information about their mutual orientation. The letters 'p' and 'q' refer to the torsion angle within the S unit (angle between the A,B and the D,C rings systems, i.e., C4–C5–C11–C12); the letters 'x' and 'y' refer to the torsion angle within the S' unit (angle between the C',D' and the A',B' rings systems, i.e., C22–C23–C31–C38); the letters 't' and 'v' refer to the torsion angle between the two units S and S' (i.e., C14–C13–C21–C28); the meaning of these letters is explained in Table 7.1. Figure 7.4 highlights the perpendicularity of the moieties through selected examples.

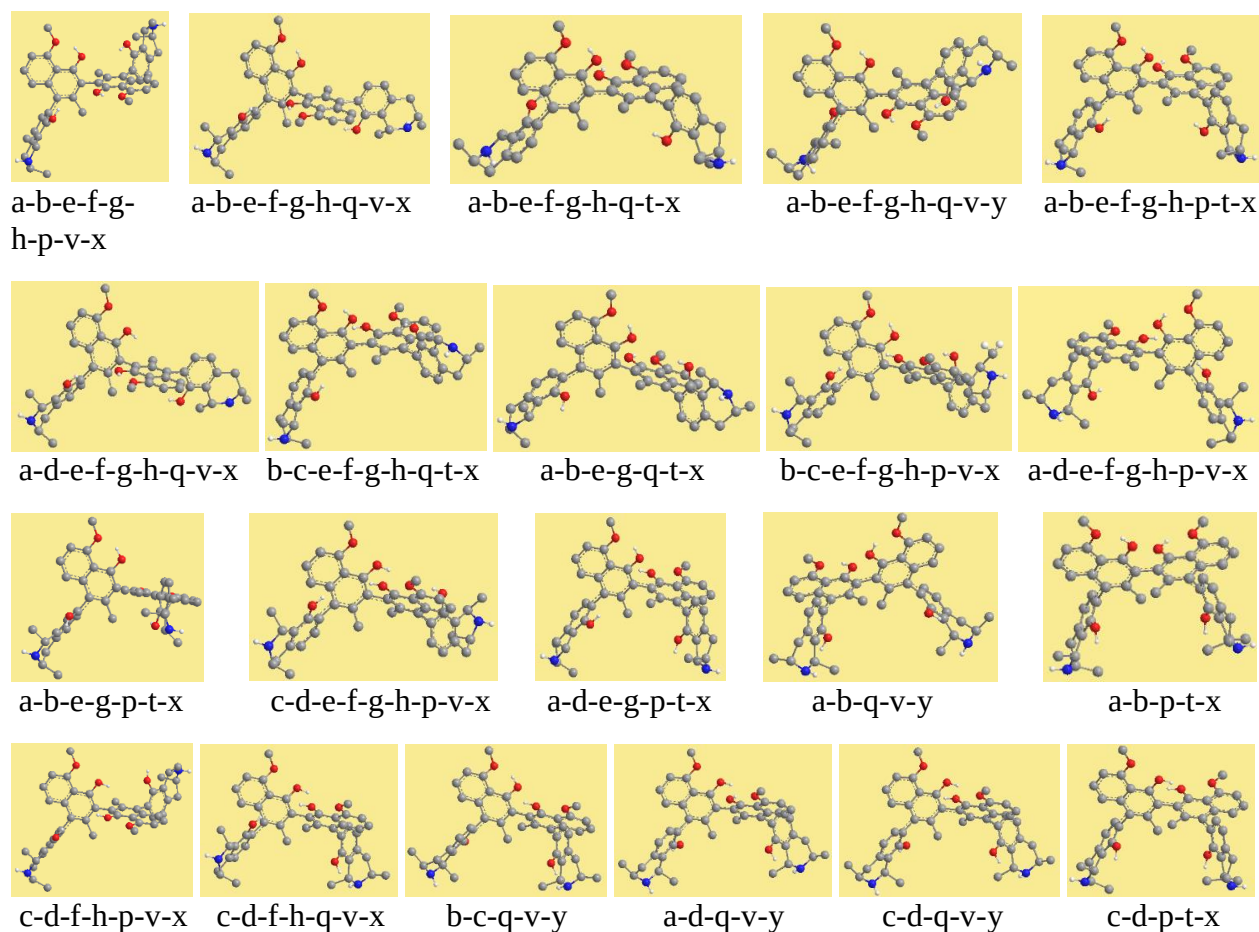


Figure 7.3. Optimized geometries of representative conformers of jozimine A₂ and letter-combinations identifying their characteristics in the acronyms denoting them

Geometries from HF/6-31G(d,p) results. The images show the main combinations of interaction types and moieties' orientations which may be present in the conformers of jozimine A₂. The initial part of the acronyms is not reported under the images, because of space reasons; it is the same for all the conformers (JZM).

Table 7.1. Letters utilized in the acronyms denoting the conformers of jozimine A₂ in this work, and their meanings

Letter	Meaning	Letter	Meaning
a	Presence of the O43–H52...O42	h	Presence of C–H59...O46
b	Presence of the O44–H54...O45	t	C14–C13–C21–C28 torsion angle close to +90°
c	Presence of the O43–H52... π	v	C14–C13–C21–C28 torsion angle close to -90°
d	Presence of the O44–H54... π	p	C4–C5–C11–C12 torsion angle close to +90°
e	Presence of the O41–H50... π	q	C4–C5–C11–C12 torsion angle close to -90°
f	Presence of the O46–H60... π	x	C22–C23–C31–C38 torsion angle close to +90°
g	Presence of C–H49...O41	y	C22–C23–C31–C38 torsion angle close to -90°

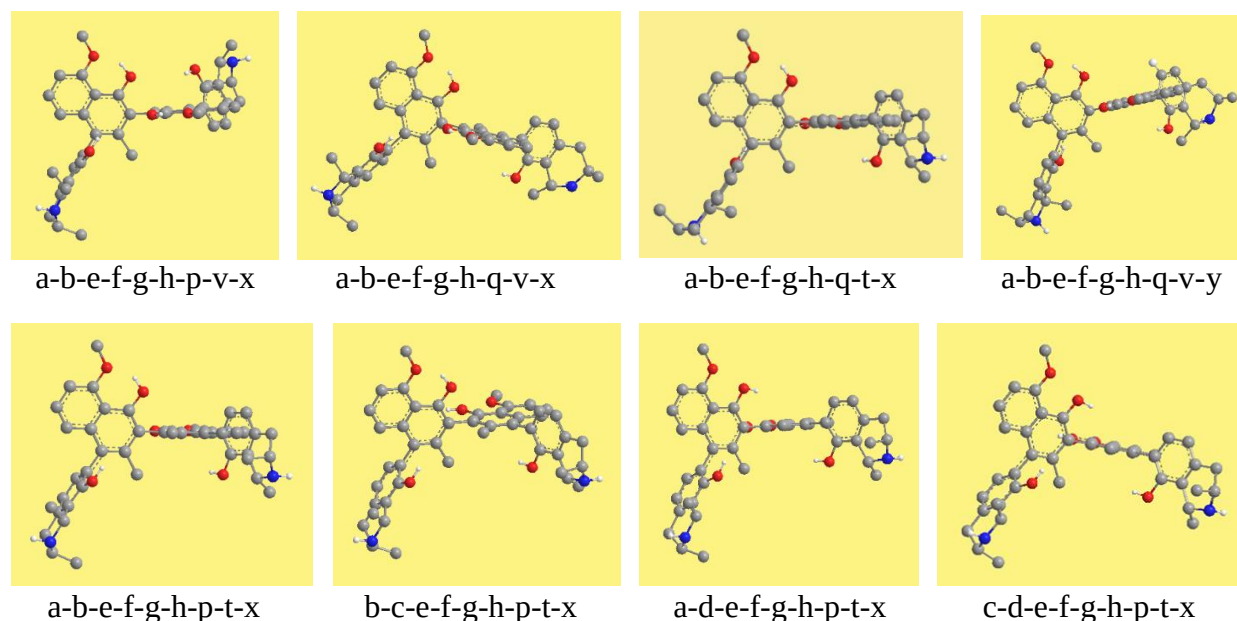


Figure 7.4. Optimized geometries of selected conformers of jozimine A₂ highlighting the perpendicularity of the moieties

Differently from michellamine A [62], there is no specific correspondence between the orientation of the two moieties (within each unit) and the IHB patterns. When the conformers are mentioned in the text, their acronyms start with JZM, followed by the letters denoting their characteristics. In tables and figures, ‘JZM’ is not reported for space-saving reasons. It may be expedient to illustrate how the acronyms describe the characteristics of individual conformers through some examples. JZM-a-b-e-f-g-h-p-v-x is a conformer characterized by the presence of the O43–H52···O42 and O44–H54···O45 IHBs, the O41–H50··· π and O46–H60··· π interactions and the C–H49···O41 and C–H59···O46 interactions, with the C4–C5–C11–C12 torsion angle close to 90°, the C14–C13–C21–C28 torsion angle close to -90° and C22–C23–C31–C38 torsion angle close to 90°; JZM-c-d-e-f-g-h-q-v-y is a conformer with the O43–H52··· π , O44–H54··· π , O41–H50··· π and O46–H60··· π interactions and the C–H49···O41 and C–H59···O46 interactions, with the C4–C5–C11–C12 torsion angle close to -90°, the C14–C13–C21–C28 torsion angle close to -90° and the C22–C23–C31–C38 torsion angle close to -90°; JZM-b-c-q-t-x is a conformer

characterized by the presence of the O44–H54···O45 IHB and the O43–H52··· π interaction, and with the C4–C5–C11–C12 torsion angle close to -90° , the C14–C13–C21–C28 torsion angle close to $+90^\circ$ and the C22–C23–C31–C38 torsion angle close to $+90^\circ$.

7.4. Results *in vacuo*

80 conformers were identified, and the frequency calculations confirm that they correspond to true minima. The relative energies of selected calculated conformers of JZM *in vacuo* and in the three solvents considered are reported in Table 7.2 and Table 7.K1 reports the relative energies of all the calculated conformers. The reported conformers include the first fourteen lower-energy conformers and representative conformers of other types (other combinations of IHBs) not appearing among the first fourteen. The IHB patterns (numbers and types of IHBs present in a conformer) are the dominant stabilizing factors. Other factors influencing conformational preferences are the mutual orientation of the two naphthalene moieties (C,D and C',D' ring systems), which determines the mutual orientation of the two units (S and S') and the orientation of the two moieties (naphthalene and isoquinoline) within each unit. The isoquinoline moiety prefers to be perpendicular to the naphthalene moiety and the two naphthalene moieties (linked by the inter-units biaryl axis) also prefer to be perpendicular to one another; this results in the two units (S and S') preferring to be mutually perpendicular, which excludes the possibility of an IHB between them. As mentioned previously, three types of IHBs interactions may be present: O–H···O IHBs (O43–H52···O42 and O44–H54···O45), O–H··· π interactions between the O–H in an isoquinoline moiety and the closest π system in the naphthalene moiety of the same unit (O41–H50··· π , O46–H60··· π) or between an O–H in the naphthalene moiety of one unit and the closest π system in the naphthalene moiety of the other unit (O43–H52··· π , O44–H54··· π); and C–H···O interactions within an isoquinoline moiety (C–H49···O41 and C–H59···O46). The O–H···O IHBs have the strongest stabilizing effect. The two O–H···O IHBs (O43–H52···O42 and O44–H54···O45) have practically the same geometric parameters in a conformer having both of them simultaneously. The lowest energy conformers are the conformers having all the IHB-type

Table 7.2. Relative energies of the selected conformers of jozimine A₂ shown in Fig.7.3

HF/6-31G(d,p) and DFT/B3LYP/6-31+G(d,p) results *in vacuo* and in the solvents considered, respectively denoted as HF and DFT in the columns' headings. The results *in vacuo* are from full optimization calculations; the results in solution are from single point PCM calculations on the *in vacuo*-optimized geometries. The conformers are listed in order of increasing relative energies in the HF results *in vacuo*.

Conformer	Relative energy (kcal/mol)							
	HF				DFT			
	vac	chlrf	actn	aq	vac	chlrf	actn	aq
a-b-e-f-g-h-p-v-x	0.000	0.000	0.000	0.112	0.000	0.000	0.000	0.095
a-b-e-f-g-h-q-v-x	0.743	0.467	0.278	0.020	0.608	0.404	0.320	0.000
a-b-e-f-g-h-q-t-x	0.793	0.591	0.303	0.243	0.606	0.411	0.290	0.058
a-b-e-f-g-h-q-v-y	1.463	0.637	0.618	0.000	1.202	0.777	0.567	0.005
a-b-e-f-g-h-p-t-x	1.466	0.920	0.707	0.075	1.180	0.825	0.578	0.187
a-b-f-h-q-v-x	5.783	5.411	3.856	1.772	5.634	4.645	3.970	1.860
a-d-e-f-g-h-q-v-x	5.857	5.469	5.429	3.921	5.944	5.799	— ^a	— ^a
b-c-e-f-g-h-q-t-x	5.934	5.759	5.547	3.902	5.990	5.840	5.679	4.132
a-b-e-g-q-t-x	5.962	4.497	4.003	1.987	5.770	4.757	4.121	1.900
b-c-e-f-g-h-p-v-x	6.209	5.756	5.725	4.095	6.267	6.053	5.902	4.341
a-d-e-f-g-h-p-v-x	6.209	5.756	5.725	4.095	6.267	6.053	5.897	4.375
a-b-e-g-p-v-x	6.269	5.549	4.132	2.037	6.028	4.978	4.266	2.160
a-b-f-h-p-v-x	6.269	4.914	4.192	2.096	6.028	5.004	— ^a	2.134
a-b-e-g-v-y	6.476	5.168	4.123	1.625	6.202	— ^a	— ^a	1.819
a-b-f-h-v-y	6.476	5.157	4.037	1.706	6.202	4.917	4.289	1.813
a-b-e-g-p-t-x	6.552	5.316	4.308	1.969	6.204	5.008	4.295	1.999
a-b-f-h-p-t-x	6.552	5.194	4.294	1.945	6.204	5.021	4.278	1.959
c-d-e-f-g-h-p-v-x	11.627	11.590	11.467	8.363	11.508	11.728	11.623	8.798
a-d-e-g-p-t-x	11.682	10.404	9.397	5.723	11.568	10.460	9.692	6.632
a-b-q-v-y	11.899	9.483	7.954	3.038	11.602	— ^a	— ^a	3.878
a-b-p-t-x	12.096	10.142	8.111	3.817	11.684	9.638	8.295	4.437
c-d-f-h-p-v-x	15.532	14.858	14.216	10.362	15.508	15.181	14.688	10.984
c-d-f-h-q-v-x	15.687	14.974	14.302	3.432	15.648	15.128	14.575	— ^a
b-c-q-v-y	16.262	13.764	12.531	6.784	16.266	14.080	12.760	7.637
a-d-q-v-y	16.262	13.982	12.425	6.961	16.266	14.099	12.753	7.714
c-d-q-v-y	20.097	18.547	17.013	11.069	20.169	18.675	17.585	11.609
c-d-p-t-x	20.432	18.889	17.427	11.707	20.216	18.933	18.027	12.417

^a The calculation for this conformer did not converge in the given solvent.

interactions simultaneously. The first five lowest energy conformers have relative energies below 1.5 kcal/mol in both the HF and the DFT results.

They have the same types of IHBs interactions and differ only by the orientations of the moieties. Altogether, they account for 99.95% of the population *in vacuo* (Table 7.K2).

The symmetry of the molecule results in a number of pairs of conformers with the same characteristics (IHBs) in the S moiety of one conformer and in the S' moiety of the other conformer. Pairs of this type will be termed S/S' symmetric pairs in the rest of the text.

The removal of the O43–H52...O42 IHB brings about the O43–H52... π interaction and the removal of the O44–H54...O45 IHB brings about the O44–H54... π interaction. Each of these removals causes an increase in the energy of the conformer. Comparison of the energies of conformers JZM-a-b-e-f-g-h-p-v-x and JZM-b-c-e-f-g-h-p-v-x (removal of O43–H52...O42 and formation of O43–H52... π) shows an energy increase of ≈ 6 kcal/mol. Since the two units are identical, the presence or the absence of a given IHB in only one of the units has the same effects whether it occurs in unit S (O43–H52...O42) or in unit S' (O44–H54...O45). Therefore, the conformers JZM-a-d-e-f-g-h-p-v-x and JZM-b-c-e-f-g-h-p-v-x (or the conformers JZM-a-d-e-f-g-h-q-v-y and JZM-b-c-e-f-g-h-q-v-y, or JZM-a-d-e-f-g-h-p-t-x and JZM-b-c-e-f-g-h-p-t-x, or JZM-a-d-q-t-x and JZM-b-c-q-t-x, or JZM-b-c-q-v-y and JZM-a-d-q-v-y, or JZM-b-c-p-t-x and JZM-a-d-p-t-x, or JZM-b-c-p-v-x and JZM-a-d-p-v-x, or JZM-b-c-q-t-x and JZM-a-d-q-v-x (Table 7.3) have the same relative energy and similar molecular properties such as dipole moment and HOMO-LUMO energy gap, and also rather close values of ΔG_{solv} .

Since the removal of an O–H...O IHB brings about an O–H... π IHB and vice versa, it is not possible to evaluate the energy of an IHB by comparison with a conformer in which it is removed by 180° rotation of the donor [503–511]. It is only possible to compare the strength of the O–H...O and O–H... π IHBs utilizing conformers in which only one or the other is present while the other geometric characteristics are identical, as in the previously considered case of JZM-a-b-e-f-g-h-p-v-x and JZM-b-c-e-f-g-h-p-v-x. Other analogous cases can be considered. For instance, JZM-a-b-e-f-g-h-p-v-x and JZM-c-d-e-f-g-h-p-v-x differ only because the former has two O–H...O IHBs and two O–H... π IHBs and the latter has four O–H... π IHBs. The relative energy of the latter is

Table 7.3. Conformers of S/S' symmetric pairs

S conformer of the pair	S' conformer of the pair
b-c-e-f-g-h-p-v-x	a-d-e-f-g-h-p-v-x
a-b-f-h-p-v-x	a-b-e-g-p-v-x
a-b-e-g-v-y	a-b-f-h-v-y
a-d-e-f-g-h-q-v-y	b-c-e-f-g-h-q-v-y
b-c-e-f-g-h-p-t-x	a-d-e-f-g-h-p-t-x
a-b-e-g-p-t-x	a-b-f-h-p-t-x
b-c-e-g-q-v-y	a-d-f-h-q-v-y
b-c-e-g-p-t-x	a-d-f-h-p-t-x
a-d-e-g-p-v-x	b-c-e-g-p-v-x
c-d-f-h-q-v-y	c-d-e-g-q-v-y
c-d-e-g-p-t-x	c-d-f-h-p-t-x
c-d-f-h-p-v-x	c-d-e-g-p-v-x
a-d-q-t-x	b-c-q-t-x
b-c-q-v-y	a-d-q-v-y
b-c-p-t-x	a-d-p-t-x
b-c-p-v-x	a-d-p-v-x

11.627/HF and 11.508/DFT kcal/mol higher than that of the former, suggesting that in this case the stabilisation brought by an O–H $\cdots\pi$ IHB is $\sim$ 5.8 kcal/mol smaller than that of an O–H $\cdots$ O IHB. Conformers JZM-a-b-e-f-g-h-q-v-x and JZM-c-d-e-f-g-h-q-v-x, JZM-a-b-e-f-g-h-q-t-x and JZM-c-d-e-f-g-h-q-t-x, JZM-a-b-e-f-g-h-q-v-y and JZM-c-d-e-f-g-h-q-v-y, and JZM-a-b-e-f-g-h-p-t-x and JZM-c-d-e-f-g-h-p-t-x are other pairs of this type with the relative energy of the latter in each pair $\sim$ 10 kcal/mol higher than that of the corresponding former, with both HF and DFT.

Table 7.4 reports the ranges of the lengths of all the IHB types present in the conformers. Complete data of the parameters of all the conformers are reported in the Table 7.K3 for the parameters of O–H $\cdots$ O IHBs and C–H $\cdots$ O interactions, and in Table 7.K4 for O–H $\cdots\pi$ interactions. The parameters of the O43–H52 $\cdots$ O42 and O44–H54 $\cdots$ O45 IHBs in the same conformer are very close. For S/S' symmetric pairs, the parameters are identical whether these IHBs are in S or S'. The bond length (Å) is close to 1.73/DFT and 1.77/HF, the O $\cdots$ O distance (Å) is close to 2.58 with both HF and DFT and the O $\hat{H}$ O bond angle is $\sim$ 143°/HF and $\sim$ 145°/DFT for conformers having also other types of IHBs. On the basis of their bond lengths, O $\cdots$ O distances and bond angles,

Table 7.4. Ranges of the length of the IHBs in the conformers of jozimine A₂

For the O–H··· π interaction, the length is taken as distance between the H atom and the closest C atom in the π system, which is indicated in parentheses after the π symbol.

IHB	H···O (Å) or H···C (Å)		IHB	H···O (Å) or H···C (Å)	
	HF	DFT		HF	DFT
H52···O42	1.764–1.770 ^a	1.722–1.731 ^a	H49···O41	2.367–2.372	2.352–2.364
	1.771–1.773 ^b	1.731–1.735 ^b	H59···O46	2.369–2.372	2.355–2.366
H54···O45	1.764–1.770 ^a	1.722–1.732 ^a	H50··· π (C11)	2.323–2.343	2.284–2.312
	1.768–1.773 ^b	1.731–1.735 ^b	H52··· π (C21)	2.222–2.233	2.189–2.203
			H54··· π (C13)	2.221–2.325	2.186–2.288
			H60··· π (C23)	2.324–2.404	2.288–2.315

^a in conformers having other IHBs

^b in conformers having only O–H···O IHBs

the O–H···O IHBs in JZM can be classified in the lower region of moderate H-bonds [464, 465, 512]. For the O–H··· π interactions, a bond length is not defined, as the acceptor is a whole π system and not an individual atom. It may be convenient to consider the distance between the H atom of the donor OH and the C atom in the aromatic system closest to it.

The ranges of the distances thus defined are reported in Table 7.4. It can be inferred from these ranges that the H···C distance is slightly shorter when the interaction involves an O–H in the naphthalene moiety of one unit and the closest π system in the naphthalene moiety of the other unit (O43–H52··· π and O44–H54··· π) than when it involves an O–H in the isoquinoline moiety and the closest π system in the naphthalene moiety of the same unit (O41–H50··· π and O46–H60··· π).

The ranges of the H···O distance for the C–H···O interactions within the isoquinoline moiety (C–H49···O41 and C–H59···O46) are also reported in Table 7.4. This distance is considerably longer than the H···O distance for O–H···O IHBs, consistently with the fact that the C–H···O interaction is considerably weaker. The distance is 2.36 /DFT and 2.37 /HF for both C–H49···O41 and C–H59···O46 interactions. The donor–acceptor C···O distance for C–H49···O41 and C–H59···O46 is $\approx$ 3.0 Å in both the HF and DFT results. The C $\hat{H}$ O bond angle is $\approx$ 115.0°/HF and

$\approx 116.0^\circ/\text{DFT}$ for both C–H49 $\cdots$ O41 and C–H59 $\cdots$ O46. Those values for the parameters show that the C–H $\cdots$ O IHBs are weak H-bonds.

Table 7.5 lists the ranges of the calculated harmonic vibrational frequencies of the O–H bonds and Table 7.K5 reports of these calculated harmonic vibrational frequencies for all the calculated conformers. Only HF frequencies are available in this study because frequency calculations with the DFT method did not complete (which is probably due to the high number of atoms in this molecule). When IHBs are present, it is interesting to consider also the red-shift (lowering of the vibrational frequency of the donor OH) caused by the IHBs. The red shift is evaluated with respect to the frequency of a free OH of the same type. Since the OHs in JZM are never free, two model structures with free OHs and with the other features similar to those of the moieties in JZM (including a CH₃ to mimic the presence of other moieties attached to the one considered) were used to calculate a reference frequency. These structures are shown in Fig.7.5. The ranges of the red shifts of O43–H52 and O44–H54 when engaged in the different types of IHBs are reported in Table 7.5. The values of the red shifts for O–H $\cdots$ O IHBs and the O–H $\cdots$ π interactions are comparable, which is consistent with the stabilizing effect of both types of IHBs (although the strength of the O–H $\cdots$ O IHB is expected to be greater than that of the O–H $\cdots$ π IHB). The complete data are reported in Tables 7.K6 and 7.K7 respectively for the red shifts of O–H $\cdots$ O IHBs and the O–H $\cdots$ π interactions.

Table 7.5. Ranges of the harmonic vibrational frequencies of the OH groups in jozimine A₂ and of the red shifts caused by IHBs

OH	Frequency (cm ⁻¹)	Red shift when engaged in O–H $\cdots$ O IHB	Red shift when engaged in O–H $\cdots$ π interactions
O41–H50	3735.02–3804.55	–	39.08–64.31
O43–H52	3707.53– 3758.99	27.37–60.59	9.13–46.53
O44–H54	3707.73–3759.84	30.03–60.39	8.23–51.28
O46–H60	3736.13–3838.26	–	40.34–65.17

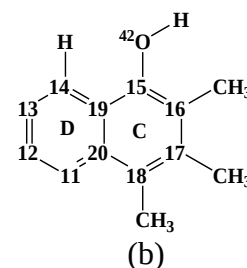
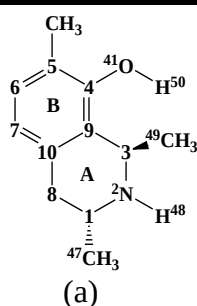


Figure 7.5. Model structures used to calculate a reference frequency for the vibration of the free O41–H50 and O46–H50 (a) or O43–H52 and O44–H54 (b)

Table 7.6 reports the values of the ZPE and of the relative energies corrected for ZPE for the conformers listed in Table 7.2. The ZPE for all the conformers are reported in Table 7.K8. The ZPE corrections are very close for all the conformers. Their values (kcal/mol) are in the 571.572–572.602 kcal/mol range, with the greater values corresponding to lower energy conformers. The relative energies corrected for ZPE have the same trends as the uncorrected ones.

Table 7.6. Relative energy ($\Delta E_{\text{correct}}$, kcal/mol) corrected for ZPE and ZPE corrections (kcal/mol) for conformers of jozimine A₂ selected among those reported in Table 7.2

Results from HF/6-31G(d,p) frequency calculations.

Conformer	$\Delta E_{\text{correct}}$	ZPE correction	Conformer	$\Delta E_{\text{correct}}$	ZPE correction
a-b-e-f-g-h-p-v-x	0.000	572.602	a-b-e-g-p-t-x	6.100	572.150
a-b-e-f-g-h-q-v-x	0.644	572.503	c-d-e-f-g-h-p-v-x	11.036	572.011
a-b-e-f-g-h-q-t-x	0.688	572.497	a-d-e-g-p-t-x	11.053	571.973
a-b-e-f-g-h-q-v-y	1.268	572.407	a-b-q-v-y	11.089	571.791
a-b-e-f-g-h-p-t-x	1.294	572.430	a-b-p-t-x	11.313	571.819
a-d-e-f-g-h-q-v-x	5.545	572.289	c-d-f-h-p-v-x	14.776	571.846
b-c-e-f-g-h-q-t-x	5.616	572.284	c-d-f-h-q-v-x	14.866	571.781
a-b-e-g-q-t-x	5.575	572.215	b-c-q-v-y	15.280	571.621
b-c-e-f-g-h-p-v-x	5.871	572.264	c-d-q-v-y	19.007	571.572
a-d-e-f-g-h-p-v-x	5.872	572.264	c-d-p-t-x	19.433	571.603

Table 7.7 reports the values of the dipole moment for the conformers listed in Table 7.2. The Dipole moment for all the conformers are reported in Table 7.K9. The ranges (Debye) of the values of the dipole moments *in vacuo* are 0.50–7.53/HF and 0.59–7.33/DFT. Both the magnitude and the direction of the dipole moment vector change according to the conformer and are largely influenced by the orientation of the OH groups (although the orientation of the aromatic rings also plays a role). Conformers with O–H···O IHBs have higher dipole moment than conformers with O–H··· π interactions, with few exceptions. Conformers with only O–H··· π interactions (no O–H···O IHBs) are among the conformers with smaller dipole moments. The same phenomenon was observed in the previous study of naphthylisoquinoline alkaloids with antimalarial activity [58] and in the study of michellamine A [62]. The mutual orientation of the moieties also has considerable influence on the dipole moment.

Different orientations of the S and S' units may cause 1–4 D difference in the dipole moments, and different orientations of the isoquinoline and naphthalene moieties within each unit may cause 1–2 D difference in the dipole moments. This trend is reversed with respect to what was observed for the conformers of michellamine A [62], where the orientation of the units caused a 1–2 D difference and the different orientation of the isoquinoline and naphthalene moieties within each unit caused a 1–4 D difference. When two conformers of JZM differ both by the orientation of the S and S' units and by the orientations of the isoquinoline and naphthalene moieties, the dipole moment difference is ≈ 2 D. Conformers of S/S' symmetric pairs have the same dipole moment.

Table 7.8 reports the HOMO-LUMO energy gap for the conformers listed in Table 7.2. Table 7.K10 reports the HOMO-LUMO energy gap for all the conformers. The gap is influenced by the IHB patterns. Conformers with only one O–H···O IHB and other types of IHBs interactions (O–H··· π and C–H···O), such as conformers JZM-b-c-e-g-p-v-x, JZM-c-f-h-q-t-x, JZM-a-d-e-g-p-t-x, JZM-a-d-e-g-q-v-y, have the smallest HOMO-LUMO energy gap.

The gap is slightly greater for conformers with the two O–H···O IHBs and other IHB-type interactions and highest for conformers with only O–H··· π interactions (which are accompanied by C–H···O interactions if they involve the two moieties within the same unit). The presence of the C–H···O interactions in a conformer slightly decreases the HOMO-LUMO energy gap with

Table 7.7. Dipole moment of the conformers of jozimine A₂ listed in Table 7.2, *in vacuo* and in the three solvents considered

HF/6-31G(d,p) and (DFT/B3LYP/6-31+G(d,p) results, respectively denoted as HF and DFT in the column headings. The results *in vacuo* are from full optimization calculations, the results in solution are from single point PCM calculations on the *in-vacuo*-optimized geometries.

Conformer	Dipole moment (Debye)							
	HF				DFT			
	vac	chlrf	actn	aq	vac	chlrf	actn	aq
a-b-e-f-g-h-p-v-x	2.65	2.67	2.55	2.44	2.81	2.87	2.74	2.58
a-b-e-f-g-h-q-v-x	5.46	5.96	6.06	5.97	5.32	5.93	6.09	5.99
a-b-e-f-g-h-q-t-x	5.03	5.41	5.43	5.34	5.01	5.50	5.57	5.45
a-b-e-f-g-h-q-v-y	6.83	7.46	7.55	7.44	6.59	7.36	7.52	7.39
a-b-e-f-g-h-p-t-x	7.53	8.29	8.50	8.43	7.33	8.28	8.57	8.49
a-b-f-h-q-v-x	4.25	4.95	4.51	4.31	4.04	4.36	4.41	4.22
a-d-e-f-g-h-q-v-x	4.56	4.85	4.87	4.73	4.70	5.11	— ^a	— ^a
b-c-e-f-g-h-q-t-x	5.03	6.12	6.29	6.28	5.52	6.22	6.46	6.41
a-b-e-g-q-t-x	4.20	4.45	4.47	4.27	4.10	4.39	4.42	4.21
b-c-e-f-g-h-p-v-x	4.11	4.53	4.63	4.69	4.15	4.65	4.81	4.83
a-d-e-f-g-h-p-v-x	4.11	4.53	4.64	4.69	4.15	4.66	4.80	4.83
a-b-e-g-p-v-x	3.93	4.24	4.29	4.37	4.38	4.79	4.85	4.91
a-b-f-h-p-v-x	3.93	4.23	4.28	4.36	4.38	4.78	— ^a	4.90
a-b-e-g-v-y	4.84	5.08	5.04	4.89	4.36	— ^a	— ^a	4.27
a-b-f-h-v-y	4.84	5.07	5.04	4.89	4.36	4.59	4.55	4.27
a-b-e-g-p-t-x	4.96	5.21	5.18	4.88	4.78	5.12	5.10	4.78
a-b-f-g-p-t-x	4.95	5.22	5.17	4.88	4.77	5.11	5.09	4.78
c-d-e-f-g-h-p-v-x	0.50	0.20	0.02	0.17	0.70	0.40	0.20	0.21
a-d-e-g-p-t-x	4.62	5.10	5.24	5.20	4.03	4.54	4.70	4.62
a-b-q-v-y	1.38	1.13	— ^a	0.65	0.59	— ^a	— ^a	0.41
a-b-p-t-x	1.42	1.19	0.96	0.50	1.08	0.85	0.60	0.15
c-d-f-h-p-v-x	3.83	4.28	4.49	4.65	4.04	4.60	4.82	4.98
c-d-f-h-q-v-x	3.79	4.22	4.39	4.39	3.71	4.56	4.29	— ^a
b-c-q-v-y	3.91	4.40	4.56	4.67	3.97	4.69	5.00	5.25
a-d-q-v-y	3.91	4.40	4.56	4.67	3.97	4.70	5.00	5.24
c-d-q-v-y	1.28	1.81	2.03	2.40	2.07	2.83	3.19	3.70
c-d-p-t-x	1.33	1.86	2.09	2.64	1.84	2.52	2.87	3.48

^aThe calculation for this conformer did not converge in the given solvent

Table 7.8. HOMO-LUMO energy gap of the conformers of jozimine A₂ reported in Table 7.2, *in vacuo* and in the three solvents considered

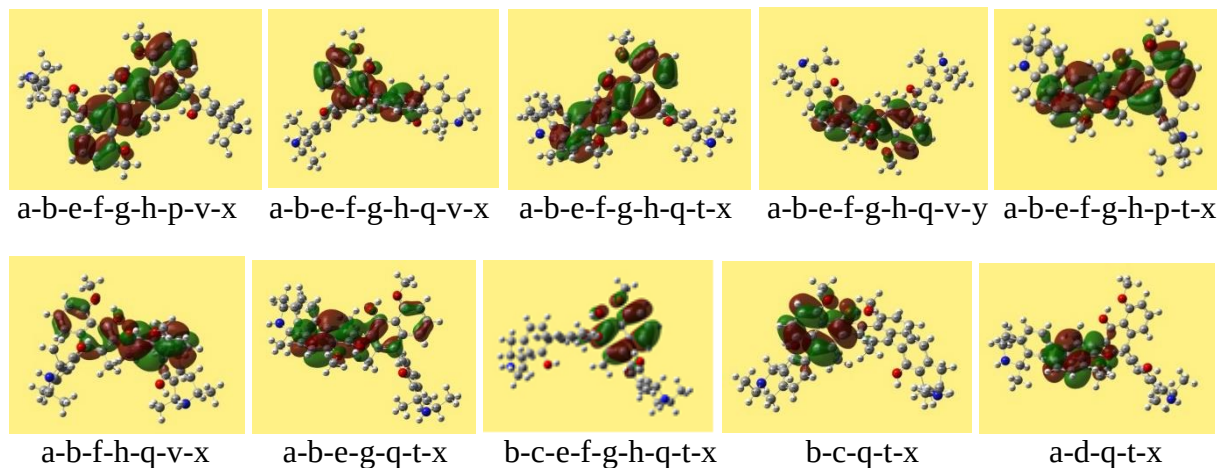
HF/6-31G(d,p) and (DFT/B3LYP/6-31+G(d,p) results, respectively denoted as HF and DFT in the column headings. The results *in vacuo* are from full optimization calculations, the results in solution are from single point PCM calculations on the *in-vacuo*-optimized geometries.

Conformer	HOMO-LUMO energy gap (kcal/mol)							
	HF				DFT			
	vac	chlrf	actn	aq	vac	chlrf	actn	aq
a-b-e-f-g-h-p-v-x	232.762	232.850	232.881	232.919	98.343	98.506	98.563	98.613
a-b-e-f-g-h-q-v-x	253.376	233.929	233.960	234.048	98.908	99.065	99.115	99.203
a-b-e-f-g-h-q-t-x	233.810	233.923	233.967	234.029	98.757	98.946	99.027	99.102
a-b-e-f-g-h-q-v-y	234.921	235.046	235.096	235.159	99.391	99.567	99.642	99.730
a-b-e-f-g-h-p-t-x	234.745	234.883	234.933	234.977	99.579	99.774	99.862	99.931
a-b-f-h-q-v-x	232.341	232.800	232.517	233.007	97.007	97.094	97.389	98.155
a-d-e-f-g-h-q-v-x	224.843	228.733	230.126	231.927	89.031	92.922	— ^a	— ^a
b-c-e-f-g-h-q-t-x	224.661	228.608	230.158	231.896	88.868	92.752	94.327	96.266
a-b-e-g-q-t-x	232.191	232.272	232.505	233.051	96.963	96.982	97.226	97.923
b-c-e-f-g-h-p-v-x	224.912	228.840	230.359	232.166	89.050	92.991	94.515	96.511
a-d-e-f-g-h-p-v-x	225.157	228.859	230.365	232.134	89.044	92.984	94.515	96.505
a-b-e-g-p-v-x	231.846	231.978	232.235	232.749	96.655	96.718	97.025	97.596
a-b-f-h-p-v-x	231.839	231.971	232.241	232.718	96.655	96.718	— ^a	97.615
a-b-e-g-v-y	232.938	232.856	232.969	233.709	96.837	— ^a	— ^a	98.036
a-b-f-h-v-y	232.938	232.850	232.969	233.697	96.843	96.944	97.214	98.036
a-b-e-g-p-t-x	232.498	232.618	232.925	233.640	96.756	96.850	97.163	97.954
a-b-f-h-p-t-x	232.498	232.611	232.900	233.659	96.756	96.850	97.151	97.973
c-d-e-f-g-h-p-v-x	236.558	236.508	236.483	236.433	100.552	100.502	100.489	100.502
a-d-e-g-p-t-x	221.166	225.226	227.064	229.618	85.435	89.257	91.020	93.536
a-b-q-v-y	234.017	234.306	234.506	234.707	98.776	— ^a	— ^a	99.460
a-b-p-t-x	234.237	234.462	234.569	234.776	98.889	99.184	99.335	99.567
c-d-f-h-p-v-x	233.051	233.032	233.239	233.747	97.251	97.088	97.295	97.904
c-d-f-h-q-v-x	234.205	233.873	233.967	234.557	97.760	97.835	97.835	0.000
b-c-q-v-y	225.000	229.028	230.591	232.442	88.999	93.016	94.547	96.442
a-d-q-v-y	225.000	229.041	230.559	232.398	89.006	92.978	94.509	96.448
c-d-q-v-y	236.320	236.307	236.289	236.245	100.407	100.364	100.326	100.282
c-d-p-t-x	236.452	236.401	236.370	236.301	100.307	100.276	100.257	100.213

^aThe calculation for this conformer did not converge in the given solvent

respect to a corresponding conformer where it is absent; for instance, the gap in JZM-c-d-f-h-p-v-x is ≈ 1 kcal/mol less than in JZM-c-d-p-v-x. Conformers of S/S' have the same HOMO-LUMO energy. The estimation of the HOMO-LUMO energy gap shows marked difference between HF

HOMO



LUMO

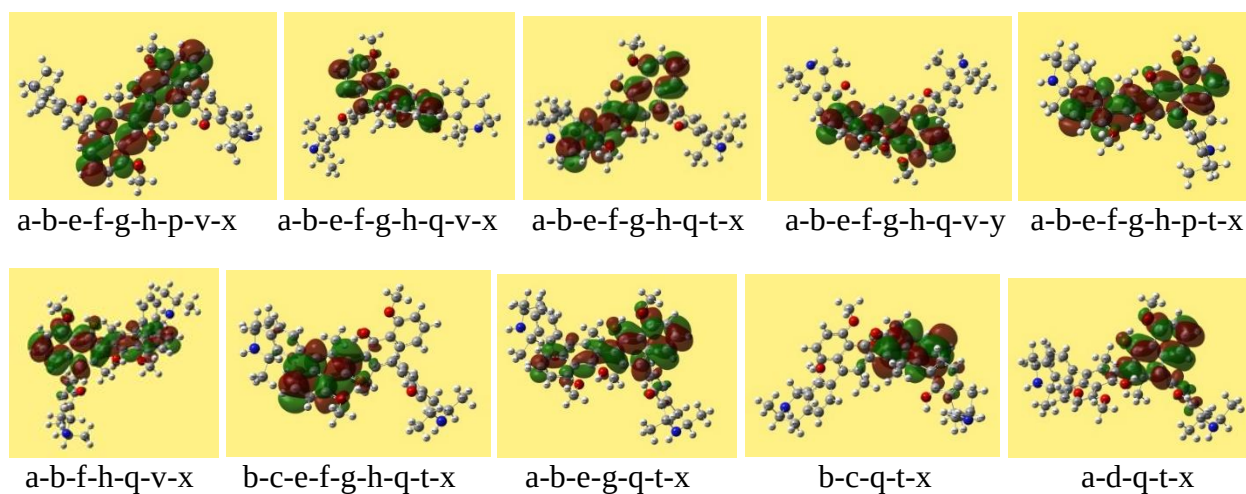


Figure 7.6. Shapes of the HOMO and LUMO frontier orbitals of the lowest energy conformers of jozimine A₂

HF/6-31G(d,p) results. The initial part of the acronyms is not reported under the images, because of space reasons; it is the same for all the conformers (JZM).

and DFT values. This is a known phenomenon, as DFT substantially underestimates the values of the gaps [149, 513]. However, the two methods show similar trends. Figure 7.6 shows the shapes of the HOMO and LUMO orbitals for the five lowest energy conformers, some representative higher energy ones and the conformers of some S/S' symmetric pairs. The shapes indicate greater

electron density and similar distribution in the two naphthalene moieties than in the isoquinoline moieties for the five lowest energy conformers – a phenomenon that was also observed for monomeric naphthylisoquinoline alkaloids with antimalarial activity [58] and for michellamine A [62]. For higher energy conformers, the electron distribution becomes considerably different for the two naphthalene moieties. For conformers of S/S' symmetric pairs, electrons concentrate on one or the other of the naphthalene moieties. The shapes of the HOMO and LUMO orbitals of all the conformers are shown in figures 7.K2 and 7.K3 respectively.

7.5. Results in solution

Table 7.2 shows the relative energy of the conformers in the three solvents considered (chloroform, acetonitrile and water). The relative energy of the conformer decreases with increasing solvent polarity – which is consistent with common behaviours. (Acetonitrile has a greater dipole moment than water, but its effect on solutes is often intermediate between that of chloroform and that of water; therefore, “increasing solvent polarities” refers to the chloroform-acetonitrile-water sequence in this discussion). The first five lowest energy conformers have relative energy below 1 kcal/mol in chloroform and acetonitrile, and below 0.24 kcal/mol in water. The identification of the lowest energy conformer does not change in chloroform and acetonitrile with respect to *in vacuo*, but may be different in water; however, the relative energies of the five lower-energy conformers are so small in water that a different identification of the lowest-energy one among them does not affect the interpretation of the results. Major changes in water occur for some conformers having relative energy *in vacuo* greater than 5 kcal/mol. These cases concern conformers in which O41–H50 or O46–H60 are not engaged in the O–H $\cdots$ π interaction and, therefore, are available to form H-bonds with water molecules. Although PCM does not take into explicit account solute-solvent H-bonds, it appears sometimes to take it into account implicitly through the energetics (possibly as the effect of the point-charge distribution in the areas of the cavity surface corresponding to an H-bond donor or acceptor) [450, 514].

The five lowest energy conformers account for 99.89% of the population in chloroform, 99.66% in acetonitrile and 90.71% in water. The population distribution of the other conformers (besides the five lowest energy ones) is also different. In *vacuo*, no other conformer has a population greater than 0.003%; in chloroform, there are two conformers with population of 0.02 and 0.01%

respectively, and all the other populations are <0.007%; in acetonitrile, ten other conformers have a population between 0.02 and 0.05%; in water, three other conformers have population between 1.0 and 1.3% and seven conformers between 0.1 and 0.9 %. Conformers of with S/S' symmetric pairs may have slightly different relative energy in solution, suggesting that the effect of their symmetric situation may somewhat decrease in solution.

If 3.5 kcal/mol is taken as a cautious threshold value for conformers which might be as potentially responsible for the biological activity, the results in water solution suggest that most conformers of JZM (all those with relative energy ≤ 3.5 kcal/mol in water solution) might be considered as potentially responsible for the antimalarial activity of JZM.

Table 7.9 reports the solvent effect (free energy of solvation, ΔG_{solv}) for the conformers listed in Table 7.2. Table 7.K11 and 7.K12 report respectively the ΔG_{solv} for all the calculated conformers at HF and DFT levels. ΔG_{solv} is positive in chloroform and acetonitrile and negative in water for all the conformers. The values in acetonitrile are considerably greater than those in chloroform. The electrostatic component of ΔG_{solv} (G_{el}) has negative values in all the three solvents, but considerably more negative in water. A quick estimation of the octanol/water partition coefficient of JZM (6.3743, [515]) suggests that JZM could be more soluble in non-polar solvents than in water. This could be due to the presence of many aromatic rings and to the high molecular mass. On the other hand, the negative values of ΔG_{solv} in water suggest the possibility of some (although limited) solubility in water or, at least, the possibility that the molecule may be present also in the water phases of living organisms cannot be excluded. It is likely that the ΔG_{solv} takes into account the presence of OHs, which favour the solubility in water.

The presence and number of O–H $\cdots$ O IHBs, and the O–H $\cdots\pi$ and C–H $\cdots$ O interactions seem to influence ΔG_{solv} and this effect is different for different solvents. The first five lowest energy conformers (with a-b-e-f-g-h in common) have the smallest absolute values of ΔG_{solv} in water. Conformers in which either O41–H50 or O46–H60 is not engaged in the O–H $\cdots\pi$ IHB have the greatest absolute values of ΔG_{solv} in water. Conformers in which only O41–H50 or O46–H60 is engaged in O–H $\cdots\pi$ interaction have greater values of ΔG_{solv} than the conformers in which both O41–H50 and O46–H60 are simultaneously engaged in O–H $\cdots\pi$ interaction.

In acetonitrile, the conformers with all the OHs engaged in IHBs have the greatest values of ΔG_{solv} . The conformers in which neither O41–H50 nor O46–H60 are engaged in O–H $\cdots\pi$ IHBs have the smallest absolute values of ΔG_{solv} and conformers in which only either O41–H50 or O46–H60 is engaged in the O–H $\cdots\pi$ IHB have values of ΔG_{solv} greater than the conformers in which they are not engaged in them. The behaviour in acetonitrile is different with respect to the behaviour in water. The importance of solute-solvent H-bonds for acetonitrile may not be as relevant as in water, both because acetonitrile can only be H-bond acceptor and because N is a weaker acceptor than O. The trend in chloroform is almost similar to the trend in acetonitrile, but the conformers having all the possible O–H $\cdots\pi$ interactions have slightly greater ΔG_{solv} than the other conformers. Conformers with S/S' symmetric pairs may have slightly different ΔG_{solv} values.

The dipole moment (Table 7.7.) increases in chloroform with respect to *in vacuo* and in acetonitrile with respect to chloroform, but decreases slightly in water with respect to acetonitrile. This might be related to the fact that acetonitrile has greater dipole moment than water (although several of its effects on solute molecules appear to be intermediate between those of chloroform and those of water). Conformers with S/S' symmetric pairs have the same value of dipole moment in the solvents considered.

The HOMO-LUMO energy gap increases with the solvent polarity. Conformers with all the O–H $\cdots\pi$ and C–H $\cdots\pi$ interactions (c-d-e-f-g-h) have the highest values of the HOMO-LUMO energy gap in all the media, and conformers with only one O–H $\cdots\pi$ IHB (O43–H52 $\cdots$ O42 or O44–H54 $\cdots$ O45) have the lowest energy gap. The range of the HOMO-LUMO energy gap *in vacuo* is mostly 221.17–236.56/HF and 85.43–100.79/DFT.

Table 7.9. Solvent effect (free energy of solvation, ΔG_{solv}) of selected conformers of jozimine A₂ in the three solvents considered

Results from HF/6-31G(d,p) and DFT/6-31+G(d,p) single point PCM calculations on the *in vacuo*-optimized geometries.

Conformer	ΔG_{solv} (kcal/mol)					
	HF			DFT		
	chlrf	actn	aq	chlrf	actn	aq
a-b-e-f-g-h-p-v-x	7.19	17.60	-4.12	7.37	18.30	-4.12
a-b-e-f-g-h-q-v-x	6.95	17.66	-4.39	7.29	18.16	-4.64
a-b-e-f-g-h-q-t-x	7.15	17.77	-4.04	7.32	18.14	-4.57
a-b-e-f-g-h-q-v-y	6.81	17.67	-4.70	7.19	17.93	-5.09
a-b-e-f-g-h-p-t-x	7.17	17.89	-4.50	7.22	17.96	-4.87
a-b-f-h-q-v-x	5.76	16.21	-7.62	6.65	16.98	-7.54
a-d-e-f-g-h-q-v-x	6.97	17.86	-5.37	7.61	— ^a	— ^a
b-c-e-f-g-h-q-t-x	7.19	17.91	-5.46	7.61	18.44	-5.50
a-b-e-g-q-t-x	5.78	16.21	-7.54	6.57	16.93	-7.72
b-c-e-f-g-h-p-v-x	6.84	18.05	-5.26	7.50	18.36	-5.60
a-d-e-f-g-h-p-v-x	7.17	17.95	-5.55	7.50	18.36	-5.57
a-b-e-g-p-v-x	6.38	15.89	-7.96	6.44	16.72	-7.83
a-b-f-h-p-v-x	5.74	15.95	-7.90	6.47	— ^a	-7.86
a-b-e-g-p-t-x	6.01	15.96	-8.09	6.61	16.94	-7.73
a-b-f-h-p-t-x	5.88	15.94	-8.13	6.62	16.93	-7.76
c-d-e-f-g-h-p-v-x	7.57	18.43	-6.35	7.95	18.87	-6.33
a-d-e-g-p-t-x	6.13	16.10	-9.25	6.68	16.93	-8.49
a-b-q-v-y	4.89	— ^a	-12.31	— ^a	— ^a	-11.36
a-b-p-t-x	5.65	14.61	-11.38	5.61	15.32	-10.92
c-d-f-h-p-v-x	6.74	17.09	-8.42	7.30	17.83	-8.25
c-d-f-h-q-v-x	6.80	17.12	-8.53	7.48	18.00	— ^a
b-c-q-v-y	5.36	15.08	-12.30	5.85	15.53	-11.91
a-d-q-v-y	5.76	15.07	-12.03	5.88	15.54	-11.81
c-d-q-v-y	6.10	15.53	-12.02	6.59	16.50	-11.77
c-d-p-t-x	5.91	15.47	-11.86	6.56	16.70	-11.23

^a The calculation for this conformer did not converge in the given solvent

The gap mostly increases in solution, but it decreases in some cases; the change with respect to *in vacuo* is -0.41–4.34/HF and -0.25–4.15/DFT in chloroform; -0.43–6.04/HF and -3.39–1.84/DFT in acetonitrile and -0.15–8.56/HF and -0.13–8.34/DFT in water. Conformers with S/S' symmetric pairs may have slightly different HOMO-LUMO gaps.

7.6. Discussion and Conclusions

The results highlight the main properties of this molecule. Conformational preferences and other properties are influenced by the presence of O–H $\cdots$ O IHBs (in the naphthalene moieties) and other IHB-type interactions, such as O–H $\cdots$ π (between some OH and a π ring in the same or in another moiety) and C–H $\cdots$ O (between a CH and an OH of the same isoquinoline moiety), and by the mutual orientation of the moieties. The O–H $\cdots$ O IHBs are the dominant factor determining conformational preferences and energetics. All the moieties and the two units prefer perpendicular orientation. This preference of aromatic system has already been discussed in section 5.3.

The low relative energy of many conformers in water solution suggests that a comparatively high number of conformers may be potentially responsible for the molecule's biological activity. The values of the free energy of solvation suggest greater solubility in water than in the other two solvents considered in this study, which would be consistent with the high polarity of the JZM molecule, but not with the octanol/water partition coefficient of JZM or with its high molecular mass.

It is interesting to note that (differently from a number of other molecules), JZM appears to respond to the three solvents considered according to their increasing dipole moment, so that the responses to water are slightly smaller than those to acetonitrile.

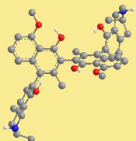
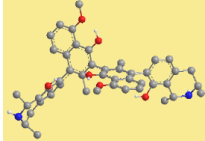
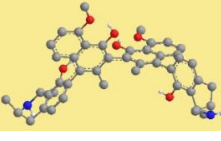
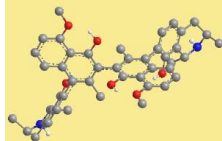
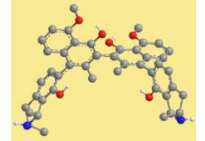
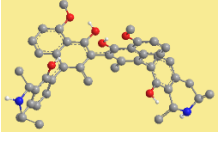
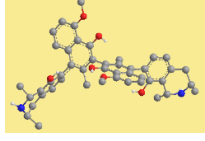
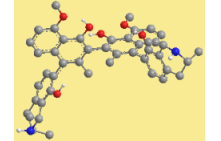
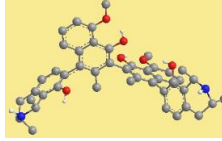
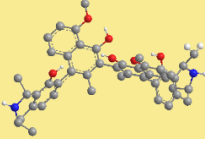
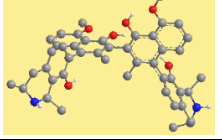
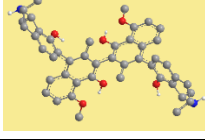
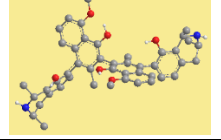
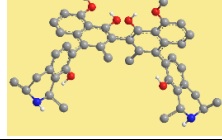
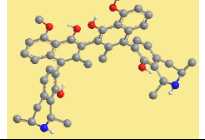
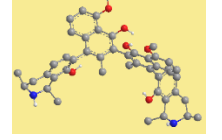
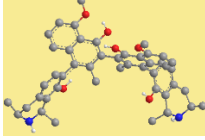
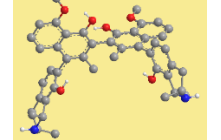
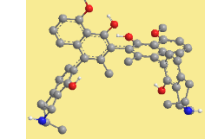
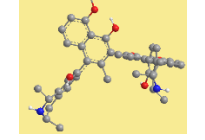
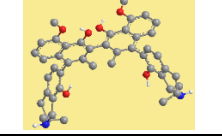
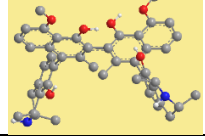
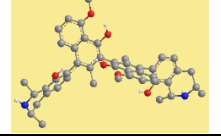
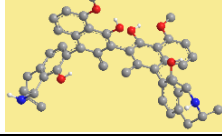
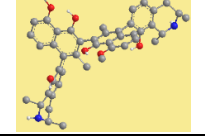
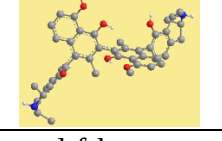
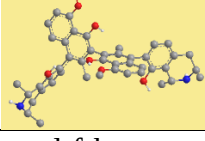
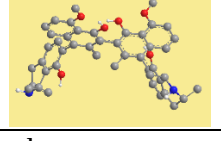
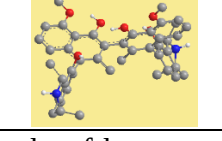
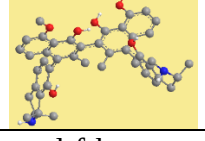
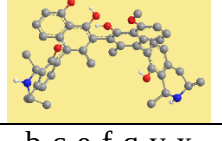
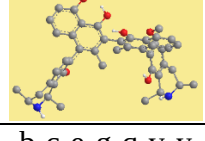
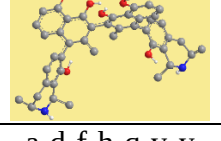
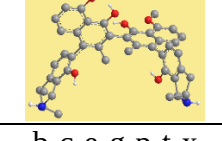
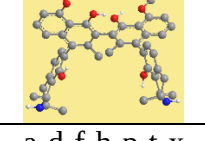
The reported X-ray structure of JZM [49] corresponds to the a-b-f-h-p-v-x conformer, which has 6.269 kcal/mol relative energy and 0.0014 population (Table 7.2). This conformer has the two O–H $\cdots$ O IHBs (O43–H52 $\cdots$ O42 and O44–H54 $\cdots$ O45), one O–H $\cdots$ π interaction and one C–H $\cdots$ O interaction. Compared to the five lowest energy ones (which have all the interactions), this conformer has one O–H $\cdots$ π and C–H $\cdots$ O interaction less, which leaves one OH group free. This phenomenon is observed frequently (e.g., in the case of caespitate [516]): the crystalline structure differs from the geometry *in vacuo* by not having one or more weaker IHBs or other IHB-type interactions that are present in the gas phase. A possible reason is the need, for molecules in the crystal structure, to have some donors or acceptors not engaged in intramolecular interactions, so that they are available for intermolecular interactions with the surrounding molecules.

A typical feature of this molecule is the presence of axial chirality (stereoisomerism resulting from the non-planar arrangement of four groups in pairs about a chirality axis). The presence of axial chirality suggests that rotation about the C13–C21 bond is not free because of steric hindrance. A space-filling visualisation with Chem3D [515] appears to confirm the hindrance, at least for lower energy conformers. On the other hand, the rotation scans about this bond (and about the other two biaryl bonds) were not disrupted (i.e., the steric hindrance did not appear in the bond-rotation model). A possible reason is the fact that the rotation scan input was a conformer with 12.811 kcal/mol relative energy (2.32×10^{-8} population); although expedient to identify minima in the orientation of the moieties, this conformer is poorly populated and, therefore, it does not contribute to the molecule's actual (or experimentally determined) behaviour.

An analysis of the differences with the behaviours and properties of michellamine A may be useful for a better understanding of the difference in the biological activities of these largely similar molecules.

Figure 7. K1. Optimized geometries of the conformers of jozimine A₂ and letters identifying their characteristics in the acronyms denoting them

Geometries from HF/6-31G(d,p) results. The images show the main combinations of interaction types and moieties' orientations which may be present in the conformers of jozimine A₂. The initial part of the acronyms is not reported under the images, because of space reasons; it is the same for all the conformers (JZM).

				
a-b-e-f-g-h-p-v-x	a-b-e-f-g-h-q-v-x	a-b-e-f-g-h-q-t-x	a-b-e-f-g-h-q-v-y	a-b-e-f-g-h-p-t-x
				
a-b-f-g-h-q-v-x	a-d-e-f-g-h-q-v-x	b-c-e-f-g-h-q-t-x	a-b-e-g-q-t-x	b-c-e-f-g-h-p-v-x
				
a-d-e-f-g-h-p-v-x	a-b-f-h-p-v-x	a-b-e-g-p-v-x	a-b-e-v-y	a-b-f-h-v-y
				
a-d-e-f-g-h-q-v-y	b-c-e-f-g-h-q-v-y	b-c-e-f-g-h-p-t-x	a-d-e-f-g-h-p-t-x	a-b-e-g-p-t-x
				
a-b-f-h-p-t-x	a-d-e-f-g-h-q-t-x	b-c-e-f-g-h-q-v-x	a-b-f-h-q-t-x	a-b-e-g-q-v-x
				
a-d-f-h-p-v-x	a-d-f-h-q-v-x	b-c-e-g-q-t-x	b-c-f-h-p-v-x	a-d-f-h-q-t-x
				
b-c-e-f-q-v-x	b-c-e-g-q-v-y	a-d-f-h-q-v-y	b-c-e-g-p-t-x	a-d-f-h-p-t-x

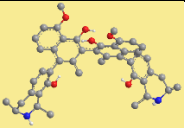
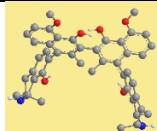
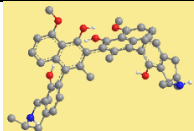
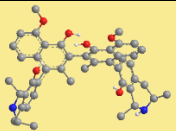
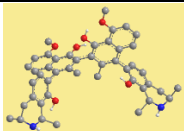
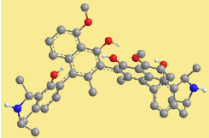
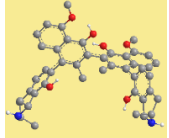
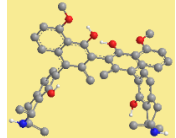
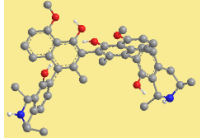
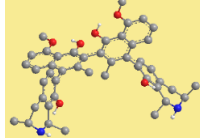
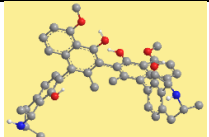
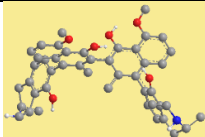
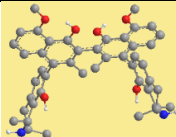
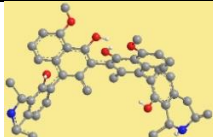
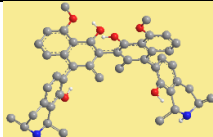
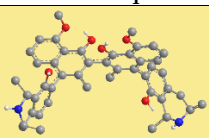
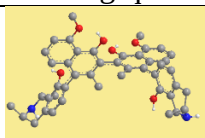
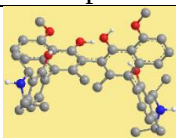
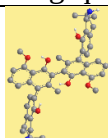
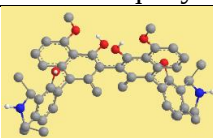
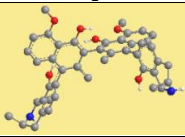
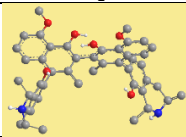
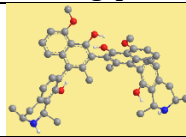
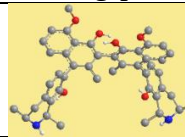
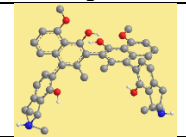
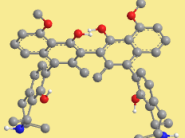
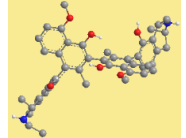
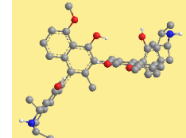
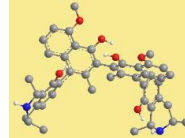
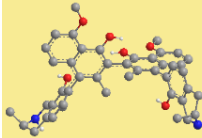
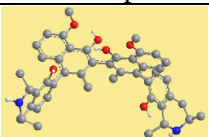
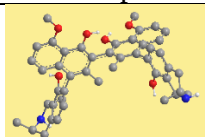
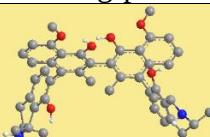
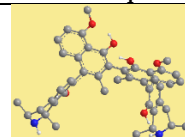
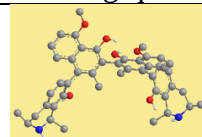
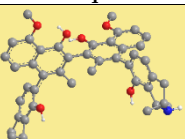
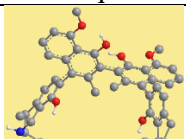
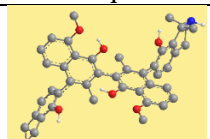
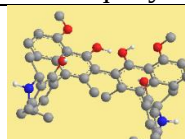
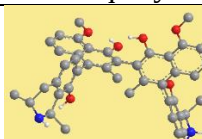
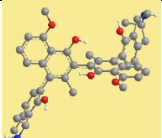
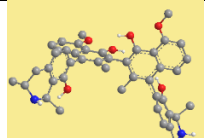
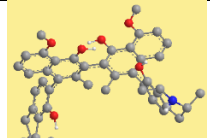
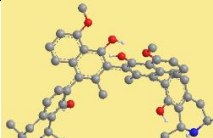
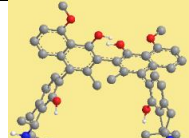
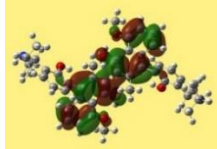
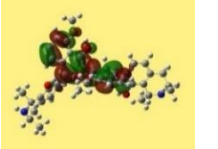
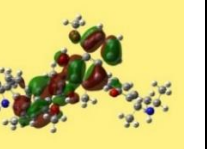
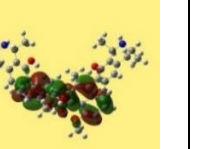
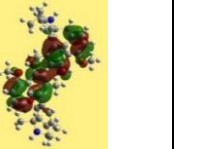
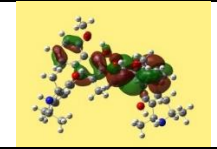
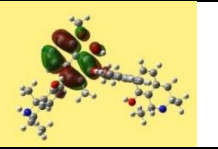
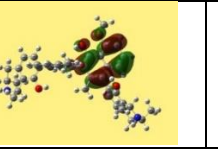
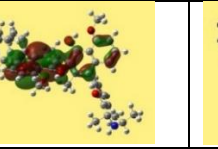
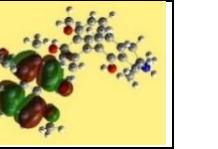
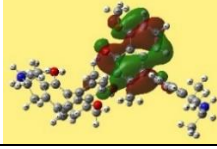
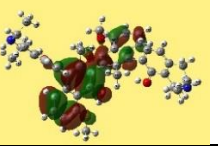
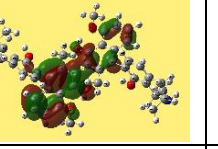
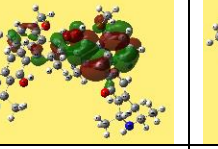
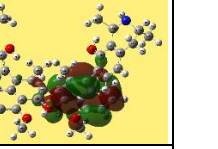
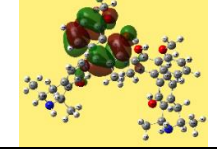
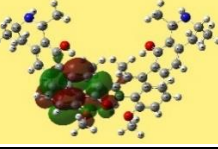
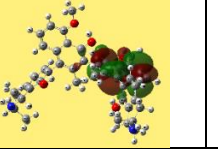
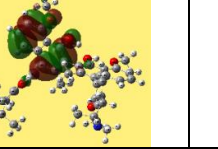
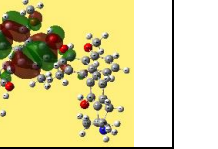
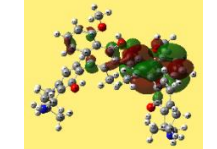
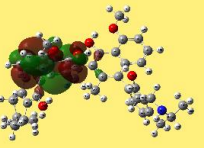
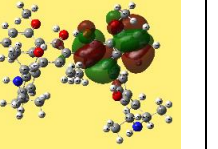
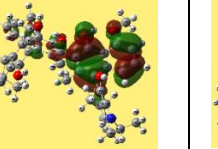
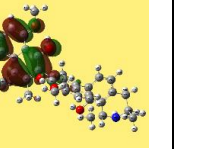
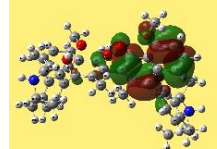
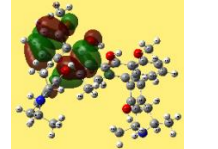
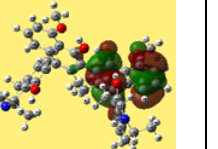
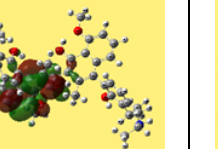
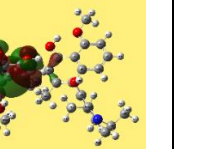
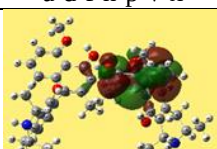
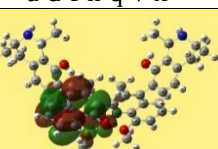
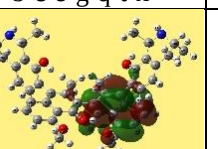
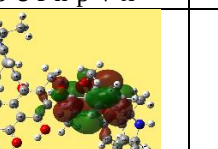
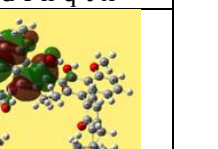
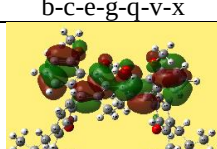
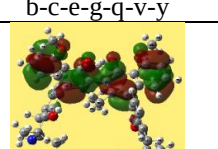
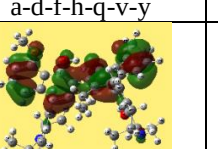
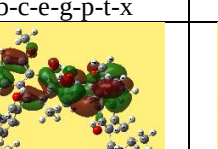
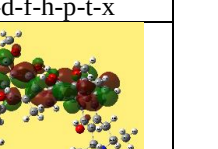
				
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c-d-e-f-g-h-p-v-x	a-d-e-g-p-t-x	b-c-f-h-p-t-x	b-c-f-h-q-v-x	a-b-q-v-y
				
b-c-f-h-q-t-x	a-d-e-g-q-t-x	a-b-p-t-x	a-d-e-g-q-v-x	b-c-f-h-q-v-y
				
a-b-q-v-x	a-b-q-t-x	a-d-e-g-p-v-x	b-c-e-g-p-v-x	a-b-p-v-x
				
c-d-f-h-q-t-x	c-d-e-g-q-v-x	c-d-f-h-q-v-y	c-d-e-g-q-v-y	c-d-e-g-p-t-x
				
c-d-f-h-p-t-x	c-d-f-h-p-v-x	c-d-e-g-p-v-x	c-d-f-h-q-v-x	c-d-e-g-q-t-x
				
b-c-q-v-x	a-d-q-t-x	b-c-q-t-x	b-c-q-v-y	a-d-q-v-y
				
b-c-p-t-x	a-d-p-t-x	b-c-p-v-x	a-d-p-v-x	a-d-q-v-x
				
c-d-p-v-x	c-d-q-v-x	c-d-q-t-x	c-d-q-v-y	c-d-p-t-x

Figure 7.K2. Shapes of the HOMO frontier orbitals of the lowest energy conformers of jozimine A₂

HF/6-31G(d,p) results. The initial part of the acronyms is not reported under the images, because of space reasons; it is the same for all the conformers (JZM).

				
a-b-e-f-g-h-p-v-x	a-b-e-f-g-h-q-v-x	a-b-e-f-g-h-q-t-x	a-b-e-f-g-h-q-v-y	a-b-e-f-g-h-p-t-x
				
a-b-f-h-q-v-x	a-d-e-f-g-h-q-v-x	b-c-e-f-g-h-q-t-x	a-b-e-g-q-t-x	b-c-e-f-g-h-p-v-x
				
a-d-e-f-g-h-p-v-x	a-b-e-g-p-v-x	a-b-f-h-p-v-x	a-b-e-g-v-y	a-b-f-h-v-y
				
a-d-e-f-g-h-q-v-y	b-c-e-f-g-h-q-v-y	b-c-e-f-g-h-p-t-x	a-d-e-f-g-h-p-t-x	a-b-e-g-p-t-x
				
a-b-f-g-p-t-x	a-d-e-f-g-h-q-t-x	b-c-e-f-g-h-q-v-x	a-b-f-h-q-t-x	a-b-e-g-q-v-x
				
a-d-f-h-p-v-x	a-d-f-h-q-v-x	b-c-e-g-q-t-x	b-c-f-h-p-v-x	a-d-f-h-q-t-x
				
b-c-e-g-q-v-x	b-c-e-g-q-v-y	a-d-f-h-q-v-y	b-c-e-g-p-t-x	a-d-f-h-p-t-x
				
c-d-e-f-g-h-q-v-y	c-d-e-f-g-h-p-t-x	c-d-e-f-g-h-q-t-x	c-d-e-f-g-h-q-v-x	a-d-e-g-q-v-y

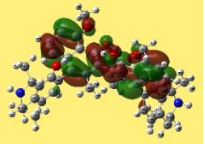
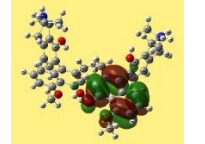
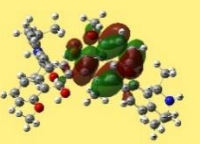
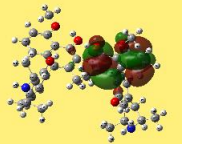
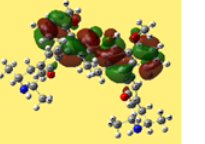
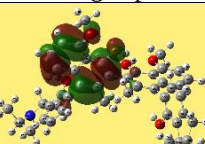
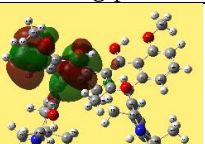
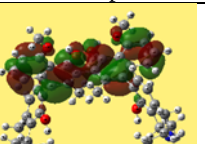
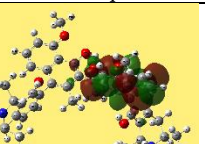
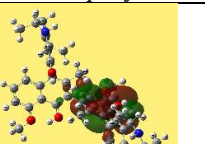
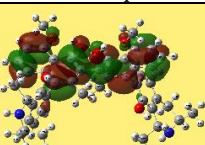
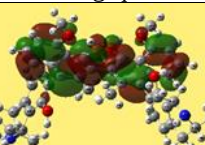
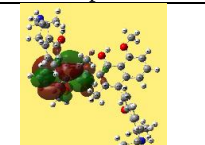
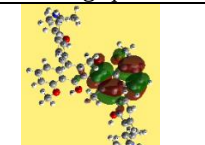
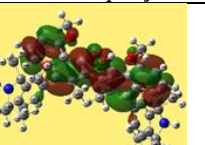
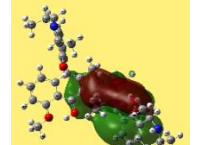
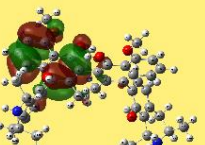
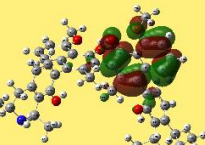
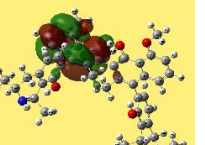
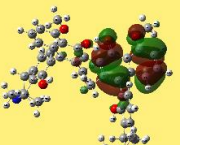
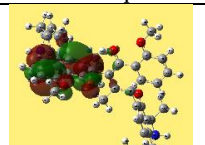
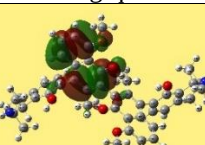
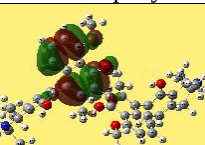
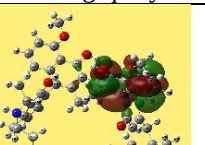
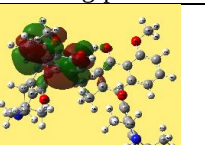
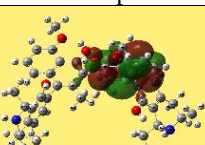
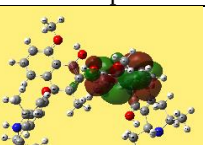
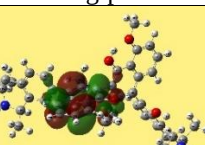
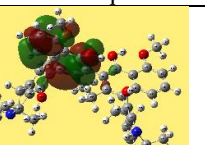
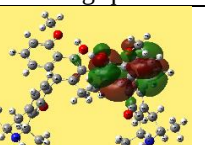
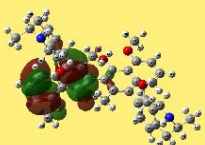
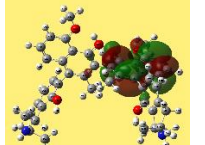
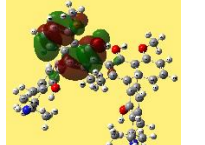
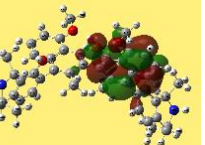
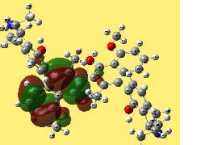
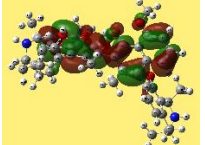
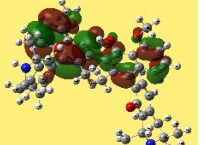
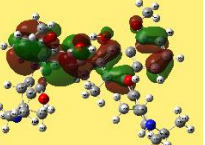
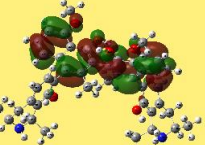
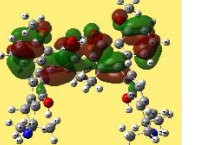
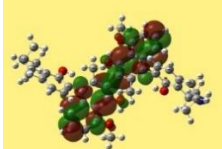
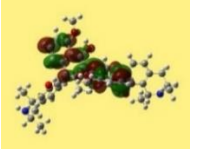
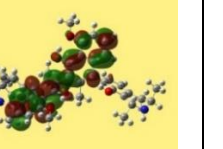
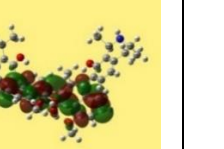
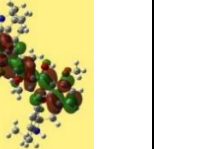
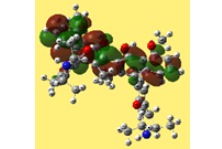
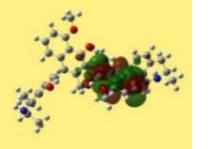
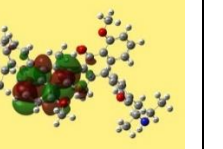
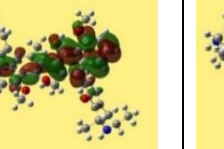
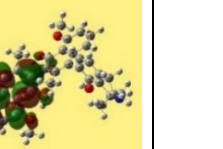
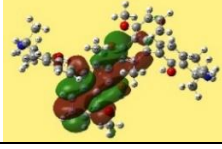
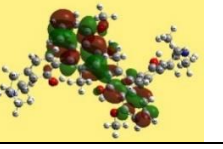
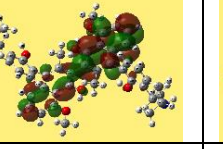
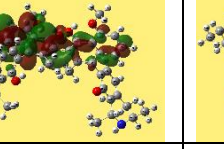
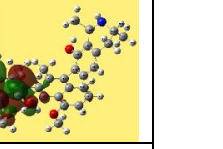
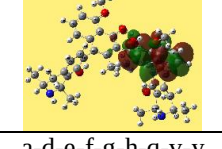
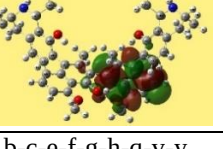
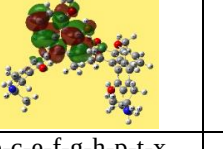
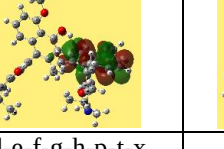
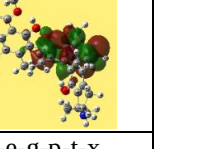
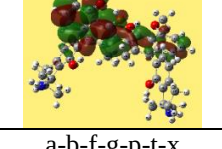
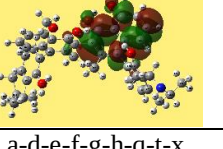
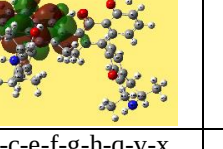
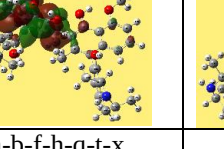
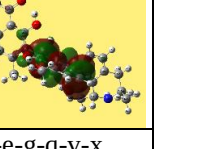
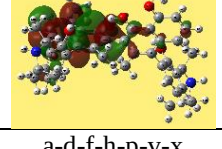
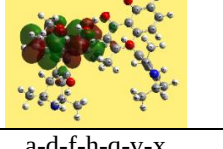
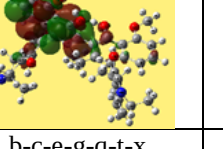
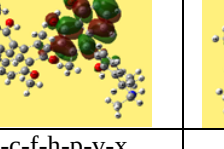
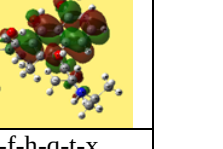
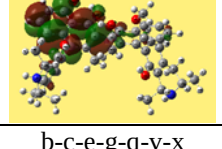
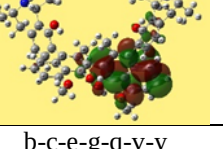
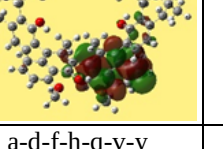
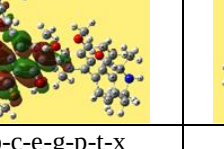
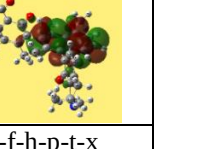
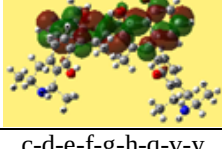
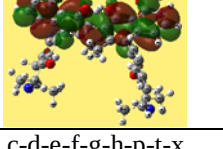
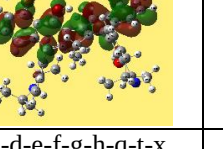
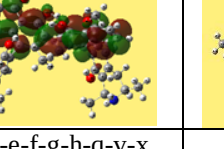
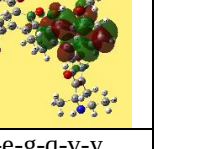
				
c-d-e-f-g-h-p-v-x	a-d-e-g-p-t-x	b-c-f-h-p-t-x	b-c-f-h-q-v-x	a-b-q-v-y
				
b-c-f-h-q-t-x	a-d-e-g-q-t-x	a-b-p-t-x	a-d-e-g-q-v-x	b-c-f-h-q-v-y
				
a-b-q-v-x	a-b-q-t-x	a-d-e-g-p-v-x	b-c-e-g-p-v-x	a-b-p-v-x
				
c-d-f-h-q-t-x	c-d-e-g-q-v-x	c-d-f-h-q-v-y	c-d-e-g-q-v-y	c-d-e-g-p-t-x
				
c-d-h-f-p-t-x	c-d-f-h-p-v-x	c-d-e-g-p-v-x	c-d-f-h-q-v-x	c-d-e-g-q-t-x
				
b-c-q-v-x	a-d-q-v-x	a-d-q-t-x	b-c-q-t-x	b-c-q-v-y
				
a-d-q-v-y	b-c-p-t-x	a-d-p-t-x	b-c-p-v-x	a-d-p-v-x
				
c-d-p-v-x	c-d-q-v-x	c-d-q-t-x	c-d-q-v-y	c-d-p-t-x

Figure 7.K3. Shapes of the LUMO frontier orbitals of the lowest energy conformers of jozimine A₂

HF/6-31G(d,p) results. The initial part of the acronyms is not reported under the images, because of space reasons; it is the same for all the conformers (JZM).

				
a-b-e-f-g-h-p-v-x	a-b-e-f-g-h-q-v-x	a-b-e-f-g-h-q-t-x	a-b-e-f-g-h-q-v-y	a-b-e-f-g-h-p-t-x
				
a-b-f-h-q-v-x	a-d-e-f-g-h-q-v-x	b-c-e-f-g-h-q-t-x	a-b-e-g-q-t-x	b-c-e-f-g-h-p-v-x
				
a-d-e-f-g-h-p-v-x	a-b-e-g-p-v-x	a-b-f-h-p-v-x	a-b-e-g-v-y	a-b-f-h-v-y
				
a-d-e-f-g-h-q-v-y	b-c-e-f-g-h-q-v-y	b-c-e-f-g-h-p-t-x	a-d-e-f-g-h-p-t-x	a-b-e-g-p-t-x
				
a-b-f-g-p-t-x	a-d-e-f-g-h-q-t-x	b-c-e-f-g-h-q-v-x	a-b-f-h-q-t-x	a-b-e-g-q-v-x
				
a-d-f-h-p-v-x	a-d-f-h-q-v-x	b-c-e-g-q-t-x	b-c-f-h-p-v-x	a-d-f-h-q-t-x
				
b-c-e-g-q-v-x	b-c-e-g-q-v-y	a-d-f-h-q-v-y	b-c-e-g-p-t-x	a-d-f-h-p-t-x
				
c-d-e-f-g-h-q-v-y	c-d-e-f-g-h-p-t-x	c-d-e-f-g-h-q-t-x	c-d-e-f-g-h-q-v-x	a-d-e-g-q-v-y

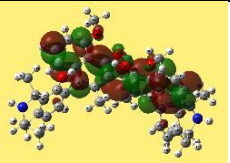
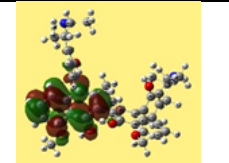
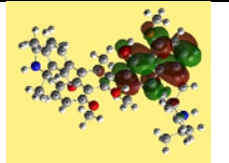
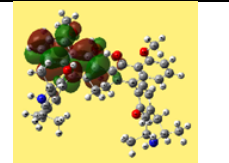
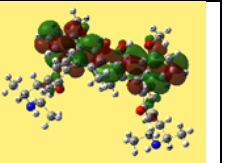
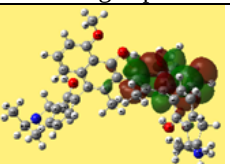
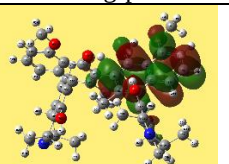
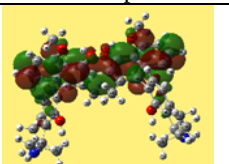
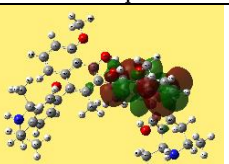
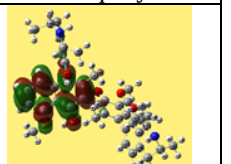
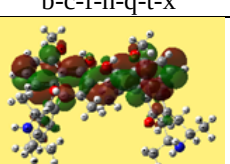
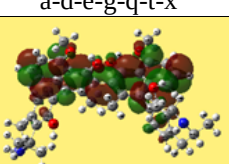
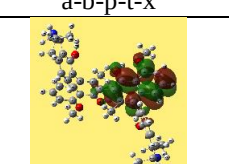
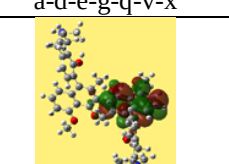
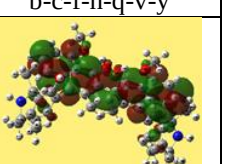
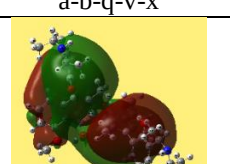
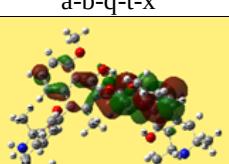
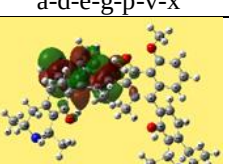
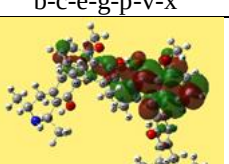
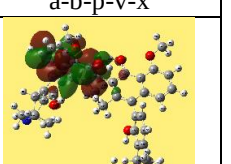
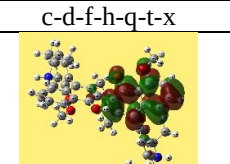
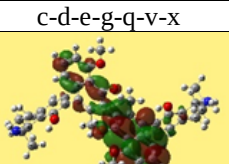
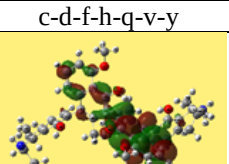
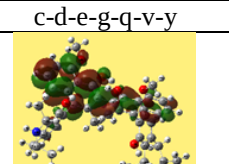
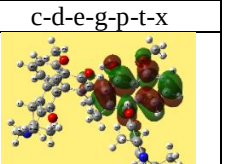
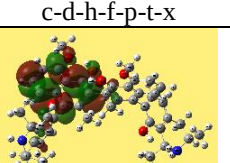
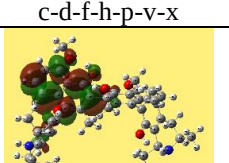
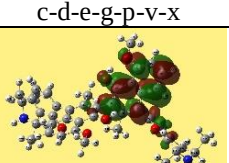
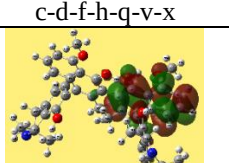
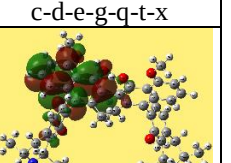
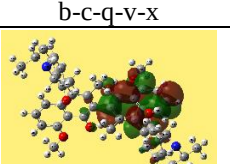
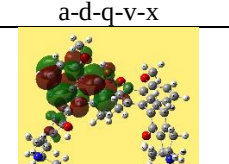
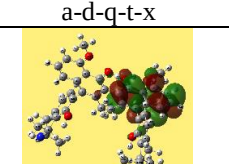
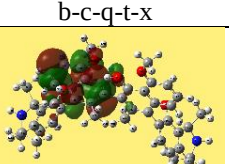
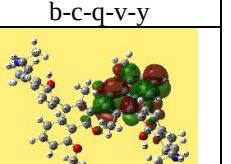
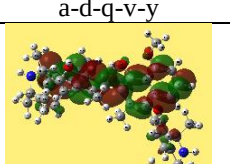
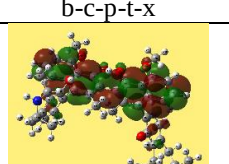
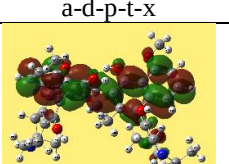
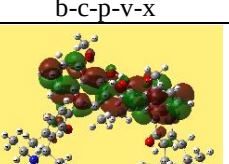
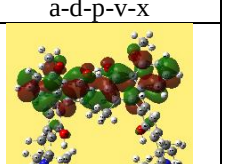
				
c-d-e-f-g-h-p-v-x	a-d-e-g-p-t-x	b-c-f-h-p-t-x	b-c-f-h-q-v-x	a-b-q-v-y
				
b-c-f-h-q-t-x	a-d-e-g-q-t-x	a-b-p-t-x	a-d-e-g-q-v-x	b-c-f-h-q-v-y
				
a-b-q-v-x	a-b-q-t-x	a-d-e-g-p-v-x	b-c-e-g-p-v-x	a-b-p-v-x
				
c-d-f-h-q-t-x	c-d-e-g-q-v-x	c-d-f-h-q-v-y	c-d-e-g-q-v-y	c-d-e-g-p-t-x
				
c-d-h-f-p-t-x	c-d-f-h-p-v-x	c-d-e-g-p-v-x	c-d-f-h-q-v-x	c-d-e-g-q-t-x
				
b-c-q-v-x	a-d-q-v-x	a-d-q-t-x	b-c-q-t-x	b-c-q-v-y
				
a-d-q-v-y	b-c-p-t-x	a-d-p-t-x	b-c-p-v-x	a-d-p-v-x
				
c-d-p-v-x	c-d-q-v-x	c-d-q-t-x	c-d-q-v-y	c-d-p-t-x

Table 7. K1. Relative energies of the calculated conformers of jozimine A₂

HF/6-31G(d,p) and DFT/B3LYP/6-31+G(d,p) results *in vacuo* and in solution, respectively denoted as HF and DFT in the columns' headings. The results *in vacuo* are from full optimization calculations, the results in solution are from single point PCM calculations on the *in-vacuo*-optimized geometries. The conformers are listed in order of increasing relative energies in the HF results *in vacuo*.

Conformer	Relative energy (kcal/mol)							
	HF				DFT			
	vac	chlrf	actn	aq	vac	chlrf	actn	aq
a-b-e-f-g-h-p-v-x	0.000	0.000	0.000	0.112	0.000	0.000	0.000	0.095
a-b-e-f-g-h-q-v-x	0.743	0.467	0.278	0.020	0.608	0.404	0.320	0.000
a-b-e-f-g-h-q-t-x	0.793	0.591	0.303	0.243	0.606	0.411	0.290	0.058
a-b-e-f-g-h-q-v-y	1.463	0.637	0.618	0.000	1.202	0.777	0.567	0.005
a-b-e-f-g-h-p-t-x	1.466	0.920	0.707	0.075	1.180	0.825	0.578	0.187
a-b-f-h-q-v-x	5.783	5.411	3.856	1.772	5.634	4.645	3.970	1.860
a-d-e-f-g-h-q-v-x	5.857	5.469	5.429	3.921	5.944	5.799	— ^a	— ^a
b-c-e-f-g-h-q-t-x	5.934	5.759	5.547	3.902	5.990	5.840	5.679	4.132
a-b-e-g-q-t-x	5.962	4.497	4.003	1.987	5.770	4.757	4.121	1.900
b-c-e-f-g-h-p-v-x	6.209	5.756	5.725	4.095	6.267	6.053	5.902	4.341
a-d-e-f-g-h-p-v-x	6.209	5.756	5.725	4.095	6.267	6.053	5.897	4.375
a-b-e-g-p-v-x	6.269	5.549	4.132	2.037	6.028	4.978	4.266	2.160
a-b-f-h-p-v-x	6.269	4.914	4.192	2.096	6.028	5.004	— ^a	2.134
a-b-e-g-v-y	6.476	5.168	4.123	1.625	6.202	— ^a	— ^a	1.819
a-b-f-h-v-y	6.476	5.157	4.037	1.706	6.202	4.917	4.289	1.813
a-d-e-f-g-h-q-v-y	6.476	5.609	5.722	4.370	6.498	6.181	5.952	— ^a
b-c-e-f-g-h-q-v-y	6.476	5.836	5.705	3.834	6.498	6.171	5.977	4.438
b-c-e-f-g-h-p-t-x	6.494	5.996	5.732	4.017	6.481	6.180	5.975	4.473
a-d-e-f-g-h-p-t-x	6.494	6.083	5.774	4.087	6.481	6.179	5.996	4.471
a-b-e-g-p-t-x	6.552	5.316	4.308	1.969	6.204	5.008	4.295	1.999
a-b-f-h-p-t-x	6.552	5.194	4.294	1.945	6.204	5.021	4.278	1.959
a-d-e-f-g-h-q-t-x	6.751	6.269	5.880	4.161	6.689	6.347	— ^a	4.219
b-c-e-f-g-h-q-v-x	6.802	6.148	5.918	4.333	6.669	6.285	5.970	4.263
a-b-f-h-q-t-x	6.905	5.411	4.297	2.007	6.515	5.284	4.303	2.020
a-b-e-g-q-v-x	6.971	5.505	4.443	1.891	6.596	— ^a	— ^a	2.253
a-d-f-h-p-v-x	9.937	9.042	8.399	5.789	10.038	9.269	8.767	6.294
a-d-f-h-q-v-x	10.218	9.095	8.360	5.460	10.220	9.304	8.679	— ^a
b-c-e-g-q-t-x	10.380	9.197	8.559	5.636	10.331	9.415	8.901	5.912
b-c-f-h-p-v-x	10.380	9.196	8.559	5.409	10.038	9.270	8.767	— ^a
a-d-f-h-q-t-x	10.553	9.288	8.569	5.465	10.485	9.304	8.928	5.921
b-c-e-f-q-v-x	10.565	9.324	8.627	5.548	10.502	9.514	8.955	6.176
b-c-e-g-q-v-y	10.796	9.364	8.673	5.056	10.693	9.398	8.816	5.953
a-d-f-h-q-v-y	10.796	9.619	8.706	4.944	10.693	9.569	8.864	5.904

b-c-e-g-p-t-x	10.830	9.587	8.809	5.294	10.681	11.426	9.050	5.865
a-d-f-h-p-t-x	10.830	9.844	8.816	5.376	10.681	9.620	9.099	5.862
c-d-e-f-g-h-q-v-y	10.930	11.066	11.020	8.399	11.168	11.399	11.380	9.065
c-d-e-f-g-h-p-t-x	10.960	11.085	11.225	8.492	10.991	11.571	11.401	8.766
c-d-e-f-g-h-q-t-x	11.237	11.296	11.151	7.892	11.187	11.491	11.506	— ^a
c-d-e-f-g-h-q-v-x	11.272	11.315	11.209	8.979	11.168	10.266	11.429	8.956
a-d-e-g-q-v-y	11.506	10.076	9.182	5.226	11.562	11.728	9.518	3.869
c-d-e-f-g-h-p-v-x	11.627	11.590	11.467	8.363	11.508	11.728	11.623	8.798
a-d-e-g-p-t-x	11.682	10.404	9.397	5.723	11.568	10.460	9.692	6.632
b-c-f-h-p-t-x	11.682	10.351	9.374	5.770	11.567	— ^a	9.715	6.574
b-c-f-h-q-v-x	11.876	10.314	9.448	5.767	11.864	10.528	9.658	6.178
a-b-q-v-y	11.899	9.483	7.954	3.038	11.602	— ^a	— ^a	3.878
b-c-f-h-q-t-x	11.938	10.453	9.449	5.808	11.949	9.718	8.362	3.869
a-d-e-g-q-t-x	12.055	10.666	9.589	5.944	11.884	10.707	9.844	6.325
a-b-p-t-x	12.096	10.142	8.111	3.817	11.684	9.638	8.295	4.437
a-d-e-g-q-v-x	12.106	10.564	9.570	6.083	11.905	10.663	9.772	— ^a
b-c-f-h-q-v-y	12.106	10.004	9.570	6.083	11.562	— ^a	9.579	6.214
a-b-q-v-x	12.337	9.885	8.161	3.432	11.961	9.670	— ^a	4.098
a-b-q-t-x	12.435	— ^a	7.954	3.552	11.949	9.718	8.362	3.869
a-d-e-g-p-v-x	12.457	10.815	9.820	6.222	12.221	10.911	9.955	9.443
b-c-e-g-p-v-x	12.457	10.813	9.821	6.289	12.221	10.868	9.990	— ^a
a-b-p-v-x	12.811	10.480	8.435	3.814	12.369	10.209	8.641	4.514
c-d-f-h-q-t-x	15.043	14.736	13.976	9.927	15.151	14.721	14.367	10.444
c-d-e-g-q-v-x	15.149	14.417	14.085	9.959	15.145	14.785	14.377	— ^a
c-d-f-h-q-v-y	15.286	14.516	13.860	10.133	15.311	14.864	14.377	10.124
c-d-e-g-q-v-y	15.286	14.567	13.891	9.959	15.311	14.828	14.432	10.192
c-d-e-g-p-t-x	15.420	14.786	14.144	10.142	15.287	14.915	14.569	10.485
c-d-f-h-p-t-x	15.420	14.680	14.163	9.975	15.287	14.929	— ^a	10.552
c-d-f-h-p-v-x	15.532	14.858	14.216	10.362	15.508	15.181	14.688	10.984
c-d-e-g-p-v-x	15.532	14.860	14.263	10.346	15.508	15.147	14.690	10.989
c-d-f-h-q-v-x	15.687	14.974	14.302	3.432	15.648	15.128	14.575	— ^a
c-d-e-g-q-t-x	15.838	14.736	14.308	9.865	15.678	15.233	14.648	10.504
b-c-q-v-x	15.964	13.849	10.987	7.499	15.983	13.999	12.616	8.075
a-d-q-v-x	16.796	14.252	12.751	7.388	16.533	14.363	13.080	8.059
a-d-q-t-x	16.222	13.812	12.557	7.474	16.034	14.149	12.955	8.069
b-c-q-t-x	16.222	13.945	12.179	7.449	16.034	14.149	12.955	8.069
b-c-q-v-y	16.262	13.764	12.531	6.784	16.266	14.080	12.760	7.637
a-d-q-v-y	16.262	13.982	12.425	6.961	16.266	14.099	12.753	7.714
b-c-p-t-x	16.531	14.108	12.709	7.578	16.333	14.328	13.059	8.206
a-d-p-t-x	16.531	14.152	12.689	7.327	16.333	14.270	13.051	8.207
b-c-p-v-x	16.545	14.156	12.633	7.505	16.400	14.446	13.112	8.491
a-d-p-v-x	16.545	14.396	12.608	7.509	16.400	14.408	13.107	8.434
c-d-p-v-x	19.699	18.134	17.130	11.879	19.744	18.577	17.692	13.014
c-d-q-v-x	19.881	18.329	17.001	11.685	19.875	18.622	17.555	12.539

c-d-q-t-x	19.992	18.360	— ^a	11.495	19.936	18.666	17.768	12.375
c-d-q-v-y	20.097	18.547	17.013	11.069	20.169	18.675	17.585	11.609
c-d-p-t-x	20.432	18.889	17.427	11.707	20.216	18.933	18.027	12.417

Table 7.K2. Population distribution of the conformers of jozimine A₂
HF/6-31G(d,p) and DFT/6-31+G(d,p) results.

Conformer	Population (%)							
	HF				DFT			
	vac	chlr	actn	aq	vac	chlr	actn	aq
a-b-e-f-g-h-p-v-x	58.281	42.062	34.612	17.304	50.371	39.616	33.767	17.567
a-b-e-f-g-h-q-v-x	16.610	19.109	21.639	20.214	18.033	20.019	19.665	20.626
a-b-e-f-g-h-q-t-x	15.264	15.497	20.745	13.868	18.094	19.784	20.688	18.701
a-b-e-f-g-h-q-v-y	4.921	14.338	12.184	20.909	6.611	10.660	12.956	20.452
a-b-e-f-g-h-p-t-x	4.896	8.889	10.483	18.420	6.861	9.830	12.717	15.039
a-b-f-h-q-v-x	0.003	0.005	0.051	1.048	0.004	0.015	0.041	0.891
a-d-e-f-g-h-q-v-x	0.003	0.004	0.004	0.028	0.002	0.002	0.000	0.000
b-c-e-f-g-h-q-t-x	0.003	0.003	0.003	0.029	0.002	0.002	0.002	0.019
a-b-e-g-q-t-x	0.002	0.021	0.040	0.728	0.003	0.013	0.032	0.832
b-c-e-f-g-h-p-v-x	0.002	0.003	0.002	0.021	0.001	0.001	0.002	0.013
a-d-e-f-g-h-p-v-x	0.002	0.003	0.002	0.021	0.001	0.001	0.002	0.013
a-b-e-g-p-v-x	0.001	0.004	0.032	0.669	0.002	0.009	0.025	0.536
a-b-f-h-p-v-x	0.001	0.010	0.029	0.606	0.002	0.008	0.000	0.561
a-b-e-g-v-y	0.001	0.007	0.033	1.343	0.001	0.000	0.000	0.954
a-b-f-h-v-y	0.001	0.007	0.038	1.171	0.001	0.010	0.024	0.964
a-d-e-f-g-h-q-v-y	0.001	0.003	0.002	0.013	0.001	0.001	0.001	0.000
b-c-e-f-g-h-q-v-y	0.001	0.002	0.002	0.032	0.001	0.001	0.001	0.011
b-c-e-f-g-h-p-t-x	0.001	0.002	0.002	0.024	0.001	0.001	0.001	0.011
a-d-e-f-g-h-p-t-x	0.001	0.001	0.002	0.021	0.001	0.001	0.001	0.011
a-b-e-g-p-t-x	0.001	0.005	0.024	0.751	0.001	0.008	0.024	0.704
a-b-f-h-p-t-x	0.001	0.006	0.024	0.782	0.001	0.008	0.025	0.753
a-d-e-f-g-h-q-t-x	0.001	0.001	0.002	0.019	0.001	0.001	0.000	0.017
b-c-e-f-g-h-q-v-x	0.001	0.001	0.002	0.014	0.001	0.001	0.001	0.015
a-b-f-h-q-t-x	0.001	0.005	0.024	0.704	0.001	0.005	0.024	0.680
a-b-e-g-q-v-x	0.000	0.004	0.019	0.857	0.001	0.000	0.000	0.458
a-d-f-h-p-v-x	2.98E-06	9.76E-06	2.38E-05	0.001	2.17E-06	6.27E-06	1.25E-05	0.000
a-d-f-h-q-v-x	1.86E-06	8.93E-06	2.54E-05	0.002	1.60E-06	5.91E-06	1.45E-05	0.000
b-c-e-g-q-t-x	1.41E-06	7.51E-06	1.82E-05	0.002	1.32E-06	4.90E-06	9.94E-06	0.001
b-c-f-h-p-v-x	1.41E-06	7.53E-06	1.82E-05	0.002	2.17E-06	6.25E-06	1.25E-05	0.000
a-d-f-h-q-t-x	1.05E-06	6.44E-06	1.79E-05	0.002	1.02E-06	5.91E-06	9.50E-06	0.001
b-c-e-f-q-v-x	1.03E-06	6.06E-06	1.62E-05	0.002	9.92E-07	4.14E-06	9.08E-06	0.001
b-c-e-g-q-v-y	6.99E-07	5.67E-06	1.50E-05	0.004	7.18E-07	5.04E-06	1.15E-05	0.001
a-d-f-h-q-v-y	6.99E-07	3.68E-06	1.42E-05	0.005	7.18E-07	3.77E-06	1.06E-05	0.001
b-c-e-g-p-t-x	6.60E-07	3.89E-06	1.19E-05	0.003	7.33E-07	1.64E-07	7.73E-06	0.001
a-d-f-h-p-t-x	6.60E-07	2.52E-06	1.18E-05	0.002	7.33E-07	3.46E-06	7.12E-06	0.001
c-d-e-f-g-h-q-v-y	5.57E-07	3.20E-07	2.84E-07	1.44E-05	3.22E-07	1.71E-07	1.51E-07	4.60E-06
c-d-e-f-g-h-p-t-x	5.30E-07	3.09E-07	2.01E-07	1.23E-05	4.34E-07	1.28E-07	1.46E-07	7.63E-06
c-d-e-f-g-h-q-t-x	3.32E-07	2.17E-07	2.28E-07	3.39E-05	3.12E-07	1.47E-07	1.22E-07	-

c-d-e-f-g-h-q-v-x	3.13E-07	2.10E-07	2.07E-07	5.40E-06	3.22E-07	1.16E-06	1.39E-07	5.54E-06
a-d-e-g-q-v-y	2.11E-07	1.70E-06	6.34E-06	0.003	1.66E-07	9.83E-08	3.51E-06	0.029896
c-d-e-f-g-h-p-v-x	1.72E-07	1.32E-07	1.34E-07	1.53E-05	1.81E-07	9.83E-08	1.00E-07	7.23E-06
a-d-e-g-p-t-x	1.56E-07	9.78E-07	4.41E-06	0.001	1.64E-07	8.38E-07	2.61E-06	0.0003
b-c-f-h-p-t-x	1.56E-07	1.07E-06	4.58E-06	0.001	1.64E-07	-	2.51E-06	0.0003
b-c-f-h-q-v-x	1.13E-07	1.14E-06	4.05E-06	0.001	9.94E-08	7.47E-07	2.77E-06	0.0006
a-b-q-v-y	1.08E-07	4.63E-06	5.05E-05	0.123	1.55E-07	-	-	0.0294
b-c-f-h-q-t-x	1.02E-07	9.00E-07	4.04E-06	0.001	8.61E-08	2.93E-06	2.47E-05	0.0299
a-d-e-g-q-t-x	8.33E-08	6.28E-07	3.19E-06	0.001	9.61E-08	5.52E-07	2.02E-06	0.0005
a-b-p-t-x	7.77E-08	1.52E-06	3.87E-05	0.033	1.35E-07	3.36E-06	2.77E-05	0.0115
a-d-e-g-q-v-x	7.64E-08	7.46E-07	3.29E-06	0.001	9.27E-08	5.94E-07	2.28E-06	0.0000
b-c-f-h-q-v-y	7.64E-08	1.92E-06	3.29E-06	0.001	1.66E-07	-	3.16E-06	0.0006
a-b-q-v-x	5.17E-08	2.35E-06	3.56E-05	0.063	8.43E-08	3.18E-06	-	0.0203
a-b-q-t-x	4.38E-08	-	5.05E-05	0.052	8.61E-08	2.93E-06	-	0.0299
a-d-e-g-p-v-x	4.22E-08	4.88E-07	2.16E-06	0.001	5.44E-08	3.91E-07	1.68E-06	2.43E-06
b-c-e-g-p-v-x	4.22E-08	4.90E-07	2.15E-06	0.001	5.44E-08	4.20E-07	1.58E-06	-
a-b-p-v-x	2.32E-08	8.60E-07	2.24E-05	0.033	4.23E-08	1.28E-06	1.54E-05	0.010
c-d-f-h-q-t-x	5.35E-10	6.48E-10	1.93E-09	1.09E-06	3.85E-10	6.26E-10	9.71E-10	4.48E-07
c-d-e-g-q-v-x	4.47E-10	1.11E-09	1.60E-09	1.03E-06	3.89E-10	5.62E-10	9.54E-10	-
c-d-f-h-q-v-y	3.55E-10	9.40E-10	2.34E-09	7.68E-07	2.94E-10	4.92E-10	9.54E-10	7.69E-07
c-d-e-g-q-v-y	3.55E-10	8.62E-10	2.22E-09	1.03E-06	2.94E-10	5.23E-10	8.70E-10	6.86E-07
c-d-e-g-p-t-x	2.83E-10	5.96E-10	1.45E-09	7.57E-07	3.06E-10	4.51E-10	6.90E-10	4.18E-07
c-d-f-h-p-t-x	2.83E-10	7.12E-10	1.40E-09	1.00E-06	3.06E-10	4.41E-10	-	3.73E-07
c-d-f-h-p-v-x	2.34E-10	5.27E-10	1.28E-09	5.22E-07	2.11E-10	2.88E-10	5.64E-10	1.80E-07
c-d-e-g-p-v-x	2.34E-10	5.26E-10	1.19E-09	5.36E-07	2.11E-10	3.05E-10	5.62E-10	1.78E-07
c-d-f-h-q-v-x	1.80E-10	4.34E-10	1.11E-09	0.063	1.66E-10	3.15E-10	6.83E-10	-
c-d-e-g-q-t-x	1.40E-10	6.48E-10	1.10E-09	1.21E-06	1.58E-10	2.64E-10	6.04E-10	4.05E-07
b-c-q-v-x	1.13E-10	2.90E-09	3.00E-07	6.58E-05	9.44E-11	2.15E-09	1.87E-08	2.45E-05
a-d-q-v-x	7.29E-11	3.09E-09	2.12E-08	6.86E-05	8.66E-11	1.65E-09	1.05E-08	2.48E-05
a-d-q-t-x	7.29E-11	0.009	4.01E-08	7.16E-05	8.66E-11	1.65E-09	1.05E-08	2.48E-05
b-c-q-t-x	6.82E-11	3.35E-09	2.21E-08	0.00022	5.85E-11	1.85E-09	1.47E-08	5.14E-05
b-c-q-v-y	6.82E-11	2.32E-09	2.65E-08	0.00016	5.85E-11	1.79E-09	1.48E-08	4.51E-05
a-d-q-v-y	4.33E-11	1.87E-09	1.64E-08	5.76E-05	5.23E-11	1.22E-09	8.85E-09	1.97E-05
b-c-p-t-x	4.33E-11	1.74E-09	1.69E-08	8.80E-05	5.23E-11	1.34E-09	8.97E-09	1.96E-05
a-d-p-t-x	4.23E-11	1.73E-09	1.86E-08	6.51E-05	4.67E-11	9.96E-10	8.09E-09	1.21E-05
b-c-p-v-x	4.23E-11	1.15E-09	1.94E-08	6.47E-05	4.67E-11	1.06E-09	8.16E-09	1.34E-05
a-d-p-v-x	3.02E-11	2.47E-09	4.01E-08	7.16E-05	8.66E-11	-	-	-
c-d-p-v-x	2.05E-13	2.08E-12	9.34E-12	4.02E-08	1.64E-13	9.28E-13	3.53E-12	5.83E-09
c-d-q-v-x	1.51E-13	1.50E-12	1.16E-11	5.58E-08	1.32E-13	8.60E-13	4.45E-12	1.30E-08
c-d-q-t-x	1.25E-13	1.42E-12	-	7.69E-08	1.19E-13	7.98E-13	3.10E-12	1.72E-08
c-d-q-v-y	1.05E-13	1.04E-12	1.14E-11	1.58E-07	8.01E-14	7.86E-13	4.23E-12	6.26E-08
c-d-p-t-x	5.94E-14	5.81E-13	5.66E-12	5.38E-08	7.40E-14	5.08E-13	2.00E-12	1.60E-08

Table 7.K3. Parameters of the intramolecular hydrogen bonds (IHB) of the calculated conformers of jozimine A₂ in vacuo

The IHB length refers to the H...O distance for the O–H...O IHBs and C–H...O interactions. The donor-acceptor distance is O...O or C...O for the O–H...O IHBs and C–H...O interactions. Similarly, the hydrogen bond angle is OĤO or CĤO for the O–H...O IHBs and the C–H...O interactions respectively.

conformer	IHB considered	Parameters of the IHB					
		HF/6-31G(d,p)			DFT/B3LYP/6-31+G(d,p)		
		IHB length (Å)	O...O or C...O (Å)	OĤO or CĤO (°)	IHB length (Å)	O...O or C...O (Å)	OĤO or CĤO (°)
a-b-e-f-g-h-p-v-x	H52...O42	1.765	2.585	143.293	1.724	2.586	145.411
	H54...O45	1.764	2.585	143.293	1.724	2.586	145.411
	C–H49...O41	2.370	2.991	115.078	2.362	3.004	116.018
	C–H59...O46	2.370	2.991	115.079	2.362	3.004	116.017
a-b-e-f-g-h-q-v-x	H52...O42	1.765	2.586	143.275	1.724	2.586	145.389
	H54...O45	1.767	2.586	143.197	1.726	2.587	145.383
	C–H49...O41	2.370	2.992	115.084	2.362	3.006	116.149
	C–H59...O46	2.370	2.991	115.084	2.365	3.007	115.943
a-b-e-f-g-h-q-t-x	H52...O42	1.767	2.586	143.207	1.725	2.586	145.361
	H54...O45	1.766	2.586	143.279	1.725	2.586	145.362
	C–H49...O41	2.368	2.990	115.114	2.360	3.003	116.055
	C–H59...O46	2.370	2.992	115.12	2.357	3.001	116.160
a-b-e-f-g-h-q-v-y	H52...O42	1.768	2.587	143.176	1.726	2.587	145.384
	H54...O45	1.768	2.587	143.176	1.726	2.587	145.384
	C–H49...O41	2.371	2.992	115.07	2.366	3.008	116.016
	C–H59...O46	2.371	2.992	115.07	2.366	3.008	116.016
a-b-e-f-g-h-p-t-x	H52...O42	1.767	2.586	143.205	1.726	2.588	145.355
	H54...O45	1.767	2.586	143.205	1.726	2.588	145.355
	C–H49...O41	2.370	2.992	115.108	2.360	3.005	116.182
	C–H59...O46	2.370	2.992	115.108	2.360	3.005	116.182
a-b-f-h-q-v-x	H52...O42	1.769	2.588	143.325	1.729	2.591	145.373
	H54...O45	1.768	2.587	143.235	1.730	2.590	145.244
	C–H59...O46	2.369	2.990	115.111	2.358	3.003	116.193
a-d-e-f-g-h-q-v-x	H52...O42	1.764	2.583	143.032	1.722	2.583	145.192
	C–H49...O41	2.371	2.993	115.089	2.361	3.004	116.020
	C–H59...O46	2.371	2.991	114.999	2.360	3.005	116.232
b-c-e-f-g-h-q-t-x	H54...O45	1.764	2.583	143.043	1.724	2.584	145.111
	C–H49...O41	2.367	2.989	115.157	2.353	2.999	116.312
	C–H59...O46	2.371	2.991	115.026	2.362	3.004	116.061
a-b-e-g-q-t-x	H52...O42	1.768	2.587	143.228	1.729	2.589	145.238
	H54...O45	1.768	2.588	143.335	1.729	2.590	145.309

	C-H49...O41	2.367	2.990	115.126	2.353	2.998	116.218
b-c-e-f-g-h-p-v-x	H54...O45	1.764	2.583	143.032	1.722	2.584	145.183
	C-H49...O41	2.371	2.993	115.089	2.360	3.004	116.155
	C-H59...O46	2.371	2.991	114.999	2.360	3.004	116.092
a-d-e-f-g-h-p-v-x	H52...O42	1.765	2.583	142.978	1.722	2.584	145.180
	C-H49...O41	2.368	2.990	115.131	2.360	3.004	116.092
	C-H59...O46	2.370	2.991	115.005	2.360	3.004	116.155
a-b-e-g-p-v-x	H52...O42	1.768	2.588	143.33	1.728	2.589	145.397
	H54...O45	1.769	2.588	143.13	1.729	2.589	145.284
	C-H49...O41	2.369	2.990	115.112	2.364	3.006	116.006
a-b-f-h-p-v-x	H52...O42	1.769	2.587	143.131	1.728	2.589	145.283
	H54...O45	1.768	2.588	143.329	1.728	2.589	145.398
	C-H59...O46	2.368	2.990	115.107	2.364	3.006	116.006
a-b-e-g-v-y	H52...O42	1.771	2.590	143.219	1.731	2.591	145.315
	H54...O45	1.769	2.588	143.205	1.728	2.589	145.336
	C-H49...O41	2.370	2.992	115.128	2.357	3.002	116.172
a-b-f-h-v-y	H52...O42	1.771	2.590	143.212	1.731	2.590	145.313
	H54...O45	1.768	2.587	143.202	1.729	2.589	145.329
	C-H59...O46	2.370	2.992	115.127	2.358	3.002	116.168
a-d-e-f-g-h-q-v-y	H52...O42	1.765	2.583	142.976	1.723	2.584	145.193
	C-H49...O41	2.372	2.992	114.957	2.360	3.002	115.973
	C-H59...O46	2.369	2.991	115.11	2.357	3.001	116.146
b-c-e-f-g-h-q-v-y	H54...O45	1.764	2.583	143.036	1.723	2.584	145.187
	C-H49...O41	2.372	2.992	114.97	2.357	3.001	116.147
	C-H59...O46	2.371	2.992	115.098	2.360	3.002	115.974
b-c-e-f-g-h-p-t-x	H54...O45	1.765	2.583	142.995	1.723	2.584	145.210
	C-H49...O41	2.371	2.993	115.108	2.359	3.004	116.189
	C-H59...O46	2.370	2.991	115.02	2.359	3.002	116.078
a-d-e-f-g-h-p-t-x	H52...O42	1.765	2.583	142.995	1.723	2.584	145.207
	C-H49...O41	2.370	2.991	115.02	2.359	3.002	116.074
	C-H59...O46	2.371	2.993	115.107	2.360	3.004	116.186
a-b-e-g-p-t-x	H52...O42	1.769	2.588	143.236	1.729	2.590	145.339
	H54...O45	1.770	2.589	143.236	1.731	2.591	145.316
	C-H49...O41	2.370	2.992	115.166	2.360	3.005	116.243
a-b-f-h-p-t-x	H52...O42	1.770	2.589	143.234	1.731	2.591	145.317
	H54...O45	1.768	2.588	143.199	1.728	2.589	145.340
	C-H59...O46	2.290	2.855	116.243	2.360	3.005	116.244
a-d-e-f-g-h-q-t-x	H52...O42	1.765	2.583	142.978	1.725	2.586	145.086
	C-H49...O41	2.372	2.992	114.953	2.364	3.005	115.942
	C-H59...O46	2.372	2.994	115.103	2.364	3.005	115.942
b-c-e-f-g-h-q-v-x	H54...O45	1.765	2.583	142.978	1.725	2.585	145.113
	C-H49...O41	2.368	2.990	115.131	2.358	3.002	116.135
	C-H59...O46	2.370	2.991	115.005	2.358	3.001	116.077
a-b-e-g-q-v-x	H52...O42	1.770	2.588	143.100	1.730	2.590	145.193

	H54...O45	1.770	2.589	143.225	1.732	2.591	145.223
	C-H49...O41	2.369	2.992	115.132	2.358	3.004	116.292
a-d-f-h-q-v-x	H52...O42	1.766	2.585	143.071	1.726	2.586	145.192
	C-H59...O46	2.370	2.992	115.117	2.359	3.005	116.244
a-d-f-h-p-v-x	H54...O45	1.766	2.585	143.075	1.724	2.585	145.246
	C-H59...O46	2.370	2.992	115.117	2.364	3.006	116.010
b-c-f-h-p-v-x	H54...O45	1.765	2.584	143.081	1.724	2.585	145.252
	C-H59...O46	2.288	3.006	116.010	2.364	3.006	116.010
b-c-e-g-q-t-x	H54...O45	1.766	2.585	143.081	1.727	2.586	145.101
	C-H49...O41	2.324	2.989	115.173	2.357	3.003	116.266
a-d-f-h-q-t-x	H52...O42	1.767	2.586	143.022	1.728	2.588	145.068
	C-H59...O46	2.371	2.993	115.151	2.360	3.005	116.230
b-c-e-f-q-v-x	H54...O45	1.767	2.585	143.021	1.728	2.587	145.061
	C-H49...O41	2.368	2.990	115.162	2.358	3.0026	116.207
b-c-e-g-q-v-y	H54...O45	1.768	2.586	143.011	1.726	2.587	145.189
	C-H49...O41	2.368	2.991	115.171	2.356	3.002	116.273
a-d-f-h-q-v-y	H52...O42	1.767	2.586	143.011	1.727	2.586	145.189
	C-H59...O46	2.368	2.991	115.170	2.355	3.002	116.276
b-c-e-g-p-t-x	H54...O45	1.768	2.586	143.023	1.727	2.587	145.163
	C-H49...O41	2.371	2.993	115.156	2.363	3.007	116.192
a-d-f-h-p-t-x	H52...O42	1.767	2.585	143.025	1.727	2.587	145.166
	C-H59...O46	2.371	2.994	115.151	2.363	3.007	116.190
a-d-e-g-q-v-y	H52...O42	1.766	2.585	143.000	1.725	2.585	145.187
	C-H49...O41	2.371	2.992	115.013	2.358	3.002	116.119
a-d-e-g-p-t-x	H52...O42	1.766	2.585	142.988	1.726	2.586	145.173
	C-H49...O41	2.370	2.992	115.07	2.363	3.005	116.056
b-c-f-h-p-t-x	H54...O45	1.766	2.584	142.991	1.726	2.586	145.175
	C-H59...O46	2.371	2.992	115.067	2.362	3.0055	116.054
b-c-f-h-q-v-x	H54...O45	1.766	2.585	143.004	1.727	2.587	145.135
	C-H59...O46	2.369	2.990	115.037	2.357	3.000	116.113
a-b-q-v-y	H52...O42	1.772	2.591	143.27	1.731	2.592	145.439
	H54...O45	1.772	2.591	143.266	1.731	2.592	145.438
b-c-f-h-q-t-x	H54...O45	1.768	2.585	142.841	1.727	2.586	145.021
	C-H59...O46	2.370	2.991	115.06	2.359	3.003	116.173
a-d-e-g-q-t-x	H52...O42	1.766	2.585	142.989	1.727	2.587	145.071
	C-H49...O41	2.366	3.007	115.927	2.366	3.007	115.927
a-b-p-t-x	H52...O42	1.771	2.590	143.279	1.732	2.592	145.382
	H54...O45	1.771	2.590	143.279	1.732	2.592	145.381
a-d-e-g-q-v-x	H52...O42	1.767	2.585	142.913	1.728	2.586	145.024
	C-H49...O41	2.371	2.992	115.014	2.360	3.002	116.00
b-c-f-h-q-v-y	H54...O45	1.766	2.584	142.998	1.725	2.585	145.185
	C-H59...O46	2.372	2.991	115.013	2.358	3.001	116.120
a-b-q-v-x	H52...O42	1.773	2.591	143.156	1.735	2.594	145.162
	H54...O45	1.771	2.590	143.263	1.734	2.594	145.262

a-b-q-t-x	H52...O42	1.772	2.591	143.24	1.734	2.593	145.192
	H54...O45	1.773	2.591	143.09	1.735	2.594	145.105
a-d-e-g-p-v-x	H52...O42	1.767	2.585	142.920	1.726	2.585	145.095
	C-H49...O41	2.369	2.990	115.030	2.352	2.998	116.254
b-c-e-g-p-v-x	H54...O45	1.767	2.585	142.918	1.727	2.586	145.065
	C-H49...O41	2.369	2.990	115.031	2.359	2.866	116.121
a-b-p-v-x	H52...O42	1.772	2.591	143.157	1.733	2.592	145.296
	H54...O45	1.772	2.591	143.157	1.732	2.592	145.299
b-c-q-v-x	H54...O45	1.768	2.587	143.059	1.730	2.589	145.078
a-d-q-v-x	H52...O42	1.770	2.588	142.963	1.731	2.590	145.045
a-d-q-t-x	H52...O42	1.769	2.587	143.042	1.730	2.589	145.070
b-c-q-t-x	H52...O42	1.769	2.587	143.042	1.730	2.589	145.070
b-c-q-v-y	H54...O45	1.769	2.587	143.057	1.729	2.589	145.181
a-d-q-v-y	H52...O42	1.769	2.587	143.057	1.728	2.588	145.204
b-c-p-t-x	H54...O45	1.769	2.587	143.06	1.729	2.588	145.186
a-d-p-t-x	H52...O42	1.769	2.587	143.061	1.729	2.589	145.186
b-c-p-v-x	H54...O45	1.769	2.587	142.962	1.729	2.588	145.104
a-d-p-v-x	H52...O42	1.769	2.587	142.962	1.729	2.588	145.106

Table 7.K4. Parameters of the intramolecular hydrogen bonds (IHB, type O–H $\cdots\pi$ interactions) of calculated conformers of jozimine A₂ *in vacuo*

The IHB length in (Å) refers to the distance between the H atom and the closest C atom in the aromatic ring for the O–H $\cdots\pi$ interactions.

conformer	IHB considered	Parameters of the IHB		conformer	IHB considered	Parameters of the IHB	
		HF	DFT			HF	DFT
		H $\cdots$ O (Å)	H $\cdots$ O (Å)			H $\cdots$ O (Å)	H $\cdots$ O (Å)
a-b-e-f-g-h-p-v-x	O41–H50 $\cdots\pi$ (C11)	2.329	2.299	c-d-e-f-g-h-q-v-x	O41–H50 $\cdots\pi$ (C11)	2.337	2.304
	O46–H60 $\cdots\pi$ (C23)	2.329	2.299		O43–H52 $\cdots\pi$ (C21)	2.225	2.192
a-b-e-f-g-h-q-v-x	O41–H50 $\cdots\pi$ (C11)	2.331	2.301		O44–H54 $\cdots\pi$ (C13)	2.226	2.192
	O46–H60 $\cdots\pi$ (C23)	2.329	2.297		O46–H60 $\cdots\pi$ (C23)	2.339	2.310
a-b-e-f-g-h-q-t-x	O41–H50 $\cdots\pi$ (C11)	2.327	2.298	a-d-e-g-q-v-y	O41–H50 $\cdots\pi$ (C11)	2.334	2.300
	O46–H60 $\cdots\pi$ (C23)	2.329	2.293		O44–H54 $\cdots\pi$ (C13)	2.234	2.206
a-b-e-f-g-h-q-v-y	O41–H50 $\cdots\pi$ (C11)	2.330	2.304	c-d-e-f-g-h-p-v-x	O41–H50 $\cdots\pi$ (C11)	2.339	2.307
	O46–H60 $\cdots\pi$ (C23)	2.330	2.304		O43–H52 $\cdots\pi$ (C21)	2.226	2.196
a-b-e-f-g-h-p-t-x	O41–H50 $\cdots\pi$ (C11)	2.329	2.296		O44–H54 $\cdots\pi$ (C13)	2.226	2.192
	O46–H60 $\cdots\pi$ (C23)	2.329	2.296		O46–H60 $\cdots\pi$ (C23)	2.339	2.308
a-b-f-h-q-v-x	O46–H60 $\cdots\pi$ (C23)	2.328	2.300	a-d-e-g-p-t-x	O41–H50 $\cdots\pi$ (C11)	2.332	2.297
a-d-e-f-g-h-q-v-x	O41–H50 $\cdots\pi$ (C11)	2.326	2.307		O44–H54 $\cdots\pi$ (C13)	2.234	2.204
	O44–H54 $\cdots\pi$ (C13)	2.233	2.201	b-c-f-h-p-t-x	O43–H52 $\cdots\pi$ (C21)	2.233	2.204
	O46–H60 $\cdots\pi$ (C23)	2.342	2.296		O46–H60 $\cdots\pi$ (C23)	2.332	2.297
b-c-e-f-g-h-q-t-x	O41–H50 $\cdots\pi$ (C11)	2.326	2.296	b-c-f-h-q-v-x	O43–H52 $\cdots\pi$ (C21)	2.237	2.203
	O43–H52 $\cdots\pi$ (C21)	2.231	2.199		O46–H60 $\cdots\pi$ (C23)	2.340	2.314
	O46–H60 $\cdots\pi$ (C23)	2.336	2.305	b-c-f-h-q-t-x	O43–H52 $\cdots\pi$ (C21)	2.233	2.200
a-b-e-g-q-t-x	O41–H50 $\cdots\pi$ (C11)	2.327	2.298		O46–H60 $\cdots\pi$ (C23)	2.333	2.302
b-c-e-f-g-h-p-v-x	O41–H50 $\cdots\pi$ (C11)	2.326	2.293	a-d-e-g-q-t-x	O41–H50 $\cdots\pi$ (C11)	2.339	2.313
	O43–H52 $\cdots\pi$ (C21)	2.233	2.199		O44–H54 $\cdots\pi$ (C13)	2.236	2.199
	O46–H60 $\cdots\pi$ (C23)	2.342	2.312	a-d-e-g-q-v-x	O41–H50 $\cdots\pi$ (C11)	2.333	2.299
a-d-e-f-g-h-p-v-x	O41–H50 $\cdots\pi$ (C11)	2.330	2.312		O44–H54 $\cdots\pi$ (C13)	2.233	2.200
	O44–H54 $\cdots\pi$ (C13)	2.232	2.199	b-c-f-h-q-v-y	O43–H52 $\cdots\pi$ (C21)	2.234	2.206
	O46–H60 $\cdots\pi$ (C23)	2.342	2.293		O46–H60 $\cdots\pi$ (C23)	2.333	2.301
a-b-f-h-p-v-x	O46–H60 $\cdots\pi$ (C23)	2.328	2.299	a-d-e-g-p-v-x	O41–H50 $\cdots\pi$ (C11)	2.340	2.309
a-b-e-g-p-v-x	O41–H50 $\cdots\pi$ (C11)	2.328	2.298		O44–H54 $\cdots\pi$ (C13)	2.235	2.202
a-b-e-g-v-y	O41–H50 $\cdots\pi$ (C11)	2.327	2.291	b-c-e-g-p-v-x	O43–H52 $\cdots\pi$ (C21)	2.236	2.202
a-b-f-h-v-y	O46–H60 $\cdots\pi$ (C23)	2.327	2.291		O46–H60 $\cdots\pi$ (C23)	2.341	2.301
a-d-e-f-g-h-q-v-y	O41–H50 $\cdots\pi$ (C11)	2.337	2.306	c-d-f-h-q-t-x	O43–H52 $\cdots\pi$ (C21)	2.226	2.195
	O44–H54 $\cdots\pi$ (C13)	2.230	2.201		O44–H54 $\cdots\pi$ (C13)	2.225	2.192
	O46–H60 $\cdots\pi$ (C23)	2.331	2.296		O46–H60 $\cdots\pi$ (C23)	2.331	2.300
b-c-e-f-g-h-q-v-y	O41–H50 $\cdots\pi$ (C11)	2.337	2.296	c-d-e-g-q-v-x	O41–H50 $\cdots\pi$ (C11)	2.334	2.300
	O43–H52 $\cdots\pi$ (C21)	2.232	2.201		O43–H52 $\cdots\pi$ (C21)	2.222	2.190
	O46–H60 $\cdots\pi$ (C23)	2.326	2.296	c-d-f-h-q-v-y	O43–H52 $\cdots\pi$ (C21)	2.227	2.196

b-c-e-f-g-h-p-t-x	O41-H50... π (C11)	2.328	2.293		O44-H54... π (C13)	2.221	2.186
	O43-H52... π (C21)	2.230	2.198		O46-H60... π (C23)	2.334	2.299
	O46-H60... π (C23)	2.337	2.304	c-d-e-g-q-v-y	O41-H50... π (C11)	2.333	2.299
a-d-e-f-g-h-p-t-x	O41-H50... π (C11)	2.337	2.304		O43-H52... π (C21)	2.186	2.186
	O44-H54... π (C13)	2.230	2.198		O44-H54... π (C13)	2.221	2.196
	O46-H60... π (C23)	2.328	2.293	c-d-e-g-p-t-x	O43-H52... π (C21)	2.227	2.196
a-b-e-g-p-t-x	O41-H50... π (C11)	2.325	2.291		O44-H54... π (C13)	2.222	2.188
a-b-f-h-p-t-x	O46-H60... π (C23)	2.399	2.290		O46-H60... π (C23)	2.330	2.294
a-d-e-f-g-h-q-t-x	O41-H50... π (C11)	2.342	2.311	c-d-f-h-p-t-x	O43-H52... π (C21)	2.222	2.187
	O44-H54... π (C13)	2.232	2.198		O44-H54... π (C13)	2.227	2.195
	O46-H60... π (C23)	2.327	2.291		O46-H60... π (C23)	2.330	2.294
b-c-e-f-g-h-q-v-x	O41-H50... π (C11)	2.330	2.294	c-d-f-h-p-v-x	O43-H52... π (C21)	2.226	2.189
	O43-H52... π (C21)	2.232	2.198		O44-H54... π (C13)	2.224	2.192
	O46-H60... π (C23)	2.342	2.315		O46-H60... π (C23)	2.404	2.305
a-b-f-h-q-t-x	O46-H60... π (C23)	2.326	2.293				
a-b-e-g-q-v-x	O41-H50... π (C11)	2.327	2.293	c-d-e-g-p-v-x	O41-H50... π (C11)	2.304	2.337
a-d-f-h-p-v-x	O43-H52... π (C21)	2.229	2.202		O43-H52... π (C21)	2.192	2.224
	O44-H54... π (C13)	2.325	2.288		O44-H54... π (C13)	2.189	2.225
a-d-f-h-q-v-x	O44-H54... π (C13)	2.228	2.194	c-d-f-h-q-v-x	O43-H52... π (C21)	2.227	2.195
	O46-H60... π (C23)	2.325	2.294		O44-H54... π (C13)	2.223	2.185
b-c-e-g-q-t-x	O41-H50... π (C11)	2.324	2.296		O46-H60... π (C23)	2.337	2.307
	O43-H52... π (C21)	2.227	2.194	c-d-e-g-q-t-x	O41-H50... π (C11)	2.340	2.310
b-c-f-h-p-v-x	O43-H52... π (C21)	2.229	2.201		O43-H52... π (C21)	2.223	2.187
	O46-H60... π (C23)	2.325	2.288		O44-H54... π (C13)	2.227	2.191
a-d-f-h-q-t-x	O44-H54... π (C13)	2.228	2.197	b-c-q-v-x	O43-H52... π (C21)	2.229	2.199
	O46-H60... π (C23)	2.324	2.288	a-d-q-v-x	O44-H54... π (C13)	2.229	2.193
b-c-e-g-q-v-x	O41-H50... π (C11)	2.327	2.291	a-d-q-t-x	O44-H54... π (C13)	2.231	2.201
	O44-H54... π (C13)	2.226	2.196	b-c-q-t-x	O44-H54... π (C13)	2.231	2.201
b-c-e-g-q-v-y	O41-H50... π (C11)	2.327	2.289	b-c-q-v-y	O43-H52... π (C21)	2.229	2.199
	O43-H52... π (C21)	2.226	2.194	a-d-q-v-y	O44-H54... π (C13)	2.229	2.199
a-d-f-h-q-v-y	O44-H54... π (C13)	2.226	2.194	b-c-p-t-x	O43-H52... π (C21)	2.230	2.199
	O46-H60... π (C23)	2.327	2.289	a-d-p-t-x	O44-H54... π (C13)	2.230	2.199
b-c-e-g-p-t-x	O41-H50... π (C11)	2.323	2.284	b-c-p-v-x	O43-H52... π (C21)	2.229	2.198
	O43-H52... π (C21)	2.227	2.195	a-d-p-v-x	O44-H54... π (C13)	2.229	2.198
a-d-f-h-p-t-x	O44-H54... π (C13)	2.227	2.195	c-d-p-v-x	O43-H52... π (C21)	2.225	2.194
	O46-H60... π (C23)	2.323	2.284		O44-H54... π (C13)	2.225	2.194
c-d-e-f-g-h-q-v-y	O41-H50... π (C11)	2.337	2.304	c-d-q-v-x	O43-H52... π (C21)	2.225	2.192
	O43-H52... π (C21)	2.225	2.193		O44-H54... π (C13)	2.222	2.186
	O44-H54... π (C13)	2.225	2.193	c-d-q-t-x	O43-H52... π (C21)	2.222	2.189
	O46-H60... π (C23)	2.337	2.304		O44-H54... π (C13)	2.227	2.194
c-d-e-f-g-h-p-t-x	O41-H50... π (C11)	2.335	2.300	c-d-q-v-y	O43-H52... π (C21)	2.223	2.190
	O43-H52... π (C21)	2.224	2.191		O44-H54... π (C13)	2.223	2.190
	O44-H54... π (C13)	2.224	2.191	c-d-p-t-x	O43-H52... π (C21)	2.224	2.191
	O46-H60... π (C23)	2.335	2.300		O44-H54... π (C13)	2.224	2.191

c-d-e-f-g-h-q-t-x	O41-H50... π (C11)	2.343	2.312				
	O43-H52... π (C21)	2.225	2.191				
	O44-H54... π (C13)	2.225	2.192				
	O46-H60... π (C23)	2.334	2.299				

Table 7.K5. Vibrational frequencies (harmonic approximation) of the O–H bonds in the calculated conformers of jozimine A₂

HF/6-31G(d,p) results *in vacuo*. The frequency values have been scaled by 0.9024, recommended for HF/6-31G(d,p) calculations in [447].

Conformer	Vibrational frequency (cm ⁻¹)			
	O41—H50	O43—H52	O44—H54	O46—H60
a-b-e-f-g-h-p-v-x	3736.68 ^a	3717.84 ^a	3717.84 ^a	3736.68 ^a
	3736.13 ^b	3715.93 ^b	3715.93 ^b	3736.13 ^b
a-b-e-f-g-h-q-v-x	3748.58	3717.10	3722.57	3736.55
a-b-e-f-g-h-q-t-x	3738.05	3722.21	3711.49	3746.98
a-b-e-f-g-h-q-v-y	3748.55 ^a	3723.66 ^a	3723.66 ^a	3748.55 ^a
	3748.32 ^b	3721.63 ^b	3721.63 ^b	3748.32 ^b
a-b-e-f-g-h-p-t-x	3747.18 ^a	3723.45 ^a	3723.45 ^a	3747.18 ^a
	3746.92 ^b	3721.41 ^b	3721.41 ^b	3746.92 ^b
a-b-f-h-q-v-x	3796.70	3727.59	3724.86	3734.19
		3724.86		
a-d-e-f-g-h-q-v-x	3754.12	3707.53	3749.07	3828.26
b-c-e-f-g-h-q-t-x	3748.97 ^a	3748.97 ^a	3711.66	3753.03
	3747.06 ^b	3747.06 ^b		
a-b-e-g-q-t-x	3735.57	3727.24 ^a	3727.24 ^a	3801.36
		3724.61 ^b	3724.61 ^b	
b-c-e-f-g-h-p-v-x	3738.21	3758.99 ^a	3707.73	3758.99 ^a
		3752.62 ^b		3752.62 ^b
a-d-e-f-g-h-p-v-x	3758.99 ^a	3707.74	3758.99 ^a	3738.24
	3752.60 ^b		3752.60 ^b	
a-b-f-h-p-v-x	3799.00	3723.91	3729.63	3734.16
a-b-e-g-p-v-x	3796.70	3724.86	3727.59	3734.19
a-b-e-g-v-y	3797.22	3731.14 ^a	3731.14 ^a	3745.50
		3727.32 ^b	3727.32 ^b	
a-b-f-h-v-y	3797.39	3731.21	3731.21	3745.65
		3727.27	3727.27	
a-d-e-f-g-h-q-v-y	3754.21	3711.79	3749.34 ^a	3749.34 ^a
			3748.34 ^b	3748.34 ^b
b-c-e-f-g-h-q-v-y	3749.33 ^a	3749.33 ^a	3711.79	3754.20
	3748.33 ^b	3748.33 ^b		
b-c-e-f-g-h-p-t-x	3748.97 ^a	3748.97 ^a	3711.66	3753.03
	3747.06 ^b	3747.06 ^b		
a-d-e-f-g-h-p-t-x	3753.05	3711.64	3749.05 ^a	3749.05 ^a
			3747.06 ^b	3749.82 ^b
a-b-e-g-p-t-x	3743.96	3730.23 ^a	3730.23 ^a	3800.86
		3727.22 ^b	3727.22 ^b	
a-b-f-h-p-t-x	3745.65	3731.21 ^a	3731.21 ^a	3797.39

		3727.27 ^b	3727.27 ^b	
a-d-e-f-g-h-q-t-x	3759.84 ^a	3711.65	3759.84 ^a	3746.53
	3752.50 ^b		3752.50 ^b	
b-c-e-f-g-h-q-v-x	3748.37	3758.78 ^a	3711.86	3758.78 ^b
		3752.45 ^b		3752.50 ^b
a-b-f-h-q-t-x	3797.89	3731.51 ^a	3731.51 ^a	3743.93
		3729.48 ^b	3729.48 ^b	
a-b-e-g-q-v-x	3745.78	3730.68 ^a	3730.68 ^a	3799.19 ^a
		3728.70 ^b	3728.70 ^a	
a-d-f-h-p-v-x	3735.02	3740.75	3714.68	3798.44
a-d-f-h-q-v-x	3800.13	3719.96	3744.08 ^a	3744.08 ^a
			3741.15 ^b	3741.15 ^b
b-c-e-g-q-t-x	3737.09	3743.90	3715.50	3801.17
b-c-f-h-p-v-x	3734.97	3740.74	3714.68	3798.47
b-c-e-g-q-v-y	3745.81 ^a	3745.81 ^a	3720.09	3799.34
	3743.80 ^b	3743.80 ^b		
a-d-f-h-q-v-y	3799.37	3720.07	3743.79	3745.80
b-c-e-f-q-v-x	3799.33	3740.34	3719.05	3798.60
b-c-e-g-p-t-x	3744.01 ^a	3744.01 ^a	3719.19	3800.38
	3742.97 ^b	3742.97 ^b		
a-d-f-h-p-t-x	3800.46	3719.17	3744.01	3744.01
c-d-e-f-g-h-q-v-y	3754.53 ^a	3733.09 ^b	3733.09 ^b	3754.53 ^a
	3754.35 ^b	3727.29 ^b	3727.29 ^b	3754.35 ^b
c-d-e-f-g-h-p-t-x	3753.09 ^a	3733.18 ^b	3733.18 ^b	3753.09 ^a
	3752.90 ^b	3727.39 ^b	3727.39 ^b	3752.90 ^a
c-d-e-f-g-h-q-t-x	3760.25	3735.63 ^b	3735.63 ^b	3752.32
		3728.55 ^b	3728.55 ^b	
c-d-e-f-g-h-q-v-x	3754.01	3735.76 ^b	3735.76 ^b	3758.78
		3728.42 ^b	3728.42 ^b	
a-d-e-g-q-v-y	3751.32	3716.84	3753.55	3792.95
c-d-e-f-g-h-p-v-x	3758.56 ^a	3736.80 ^b	3744.92 ^b	3758.56 ^a
	3758.44 ^b	3731.12 ^b	3731.12 ^b	3758.44 ^b
a-d-e-g-p-t-x	3749.70	3716.96	3753.96	3803.98
b-c-f-h-p-t-x	3804.02	3753.99	3716.91	3804.02
b-c-f-h-q-v-x	3792.02	3758.66 ^a	3716.91	3758.66 ^a
		3754.83 ^b		3754.83 ^b
a-b-q-v-y	3796.88 ^a	3736.48 ^a	3736.48 ^a	3796.88 ^a
	3796.82 ^b	3734.52 ^b	3734.52 ^b	3796.82 ^b
b-c-f-h-q-t-x	3792.87	3753.49	3719.35	3749.95
a-d-e-g-q-t-x	3759.18	3716.74	3759.18	3804.73
a-b-p-t-x	3801.04 ^a	3732.74 ^a	3732.74 ^a	3801.04 ^a
	3800.83 ^b	3726.88 ^b	3726.88 ^b	3800.83 ^a
a-d-e-g-q-v-x	3753.88 ^a	3753.88 ^a	3718.91	3802.98
	3751.55 ^b	3751.55 ^b		

b-c-f-h-q-v-y	3802.98	3718.91	3753.88 ^a	3753.88 ^a
			3751.55 ^b	3751.55 ^b
a-b-q-v-x	3796.46	3738.09 ^a	3738.09 ^a	3797.19
		3734.11 ^b	3734.11 ^b	
a-b-q-t-x	3798.12	3737.87 ^a	3737.87 ^a	3800.17
		3734.97 ^b	3734.97 ^b	
a-d-e-g-p-v-x	3759.18 ^a	3759.18 ^a	3719.03	3758.88
	3755.59 ^b	3755.59 ^b		
b-c-e-g-p-v-x	3802.91	3758.88 ^a	3736.10 ^a	3750.06
		3753.98 ^b	3721.61 ^b	
a-b-p-v-x	3797.71 ^a	3737.55 ^a	3737.55 ^a	3797.71
	3797.43 ^b	3738.09 ^b	3738.09 ^b	
c-d-f-h-q-t-x	3795.66	3736.10 ^b	3736.10 ^b	3750.06
		3721.61 ^b	3721.61 ^b	
c-d-e-g-q-v-x	3751.94	4123.15	3736.48	3802.26
c-d-f-h-q-v-y	3795.23	3735.76 ^b	3735.76 ^b	3751.43
		3723.78 ^b	3723.78 ^b	
c-d-e-g-q-v-y	3751.39	3735.71 ^b	3735.71 ^b	3795.08
		3723.73 ^b	3723.73 ^b	
c-d-e-g-p-t-x	3803.54	3736.09 ^b	3736.09 ^b	3749.49
		3723.18 ^b	3723.18 ^b	
c-d-f-h-p-t-x	3803.63	3736.08 ^b	3736.08 ^b	3749.47
		3723.17 ^b	3723.16 ^b	
c-d-f-h-p-v-x	3802.17	3740.45 ^b	3740.45 ^b	3756.64
		3720.60 ^b	3720.60 ^b	
c-d-e-g-p-v-x	4162.9	3740.41 ^b	3740.41 ^b	3802.21
		3720.57 ^b	3720.57 ^b	
c-d-f-h-q-v-x	3794.29	3739.64 ^b	3739.64 ^b	3756.46
		3723.74 ^b	3723.74 ^b	
c-d-e-g-q-t-x	3757.62	3739.85	3739.85	3804.42
		3723.32	3723.32	
b-c-q-v-x	3791.82	3745.30	3723.91	3796.67
a-d-q-v-x	3798.42	3727.24	3749.19	3801.07
a-d-q-t-x	3800.83	3724.89	3746.67	3803.91
b-c-q-t-x	3800.90	3725.04	3746.63	3803.79
b-c-q-v-y	3792.07	3748.89	3724.90	3799.00
a-d-q-v-y	3792.68	3724.90	3748.89	3792.05
b-c-p-t-x	3804.55	3748.96	3723.94	3800.68
a-d-p-t-x	3800.69	3723.92	3748.94	3804.48
c-d-p-v-x	3801.02 ^a	3730.23 ^a	3730.23 ^a	3801.02 ^a
	3800.99 ^b	3724.55 ^b	3724.55 ^b	3800.99 ^b
c-d-q-v-x	3794.25	3732.21 ^a	3732.21 ^a	3800.60
		3725.06 ^b	3725.06 ^b	
c-d-q-t-x	3796.23	3731.79 ^a	3731.79 ^a	3803.51

		3725.77 ^b	3725.77 ^b	
c-d-q-v-y	3794.60 ^a	3732.86 ^a	3732.86 ^a	3794.60 ^a
	3794.55 ^b	3726.99 ^b	3726.99 ^a	3794.55 ^a
c-d-p-t-x	3804.34 ^a	3732.74 ^a	3732.74 ^a	3804.34 ^a
	3804.15 ^b	3726.88 ^b	3726.88 ^b	3804.15 ^b

^a symmetrical stretching

^b asymmetrical stretching

Table 7.K6. Red shift of the vibrational frequencies of the O43–H52 and O44–H54 bonds in the calculated conformers of jozimine A₂ caused when they are engaged in an O–H···O IHB HF/6-31G(d,p) results *in vacuo*.

Conformer	Red shift (cm ⁻¹)		Conformer	Red shift (cm ⁻¹)	
	O43—H52	O44—H54		O43—H52	O44—H54
a-b-e-f-g-h-p-v-x	50.28	50.28	a-d-f-h-p-v-x	27.37	
	52.19	52.19	a-d-f-h-q-v-x	48.16	
a-b-e-f-g-h-q-v-x	51.02	45.55	b-c-e-g-q-t-x	24.22	52.62
			b-c-f-h-p-v-x	27.38	53.44
a-b-e-f-g-h-q-t-x	45.91	56.63	b-c-e-g-q-v-y	48.03	
a-b-e-f-g-h-q-v-y	44.46	44.46	a-d-f-h-q-t-x	48.16	26.97
	46.49	46.49	b-c-e-f-q-v-x	27.78	49.07
a-b-e-f-g-h-p-t-x	44.67	44.67	b-c-e-g-q-v-y		48.03
	46.71	46.71	a-d-f-h-q-v-y	48.05	
a-b-f-h-q-v-x	40.53	40.53	b-c-e-g-p-t-x		48.93
	43.26	43.26	a-d-f-h-p-t-x	48.95	
a-d-e-f-g-h-q-v-x	60.59		a-d-e-g-q-v-y	51.28	
b-c-e-f-g-h-q-t-x		56.46	a-d-e-g-p-t-x	51.16	
a-b-e-g-q-t-x	40.88	40.88	b-c-f-h-p-t-x		51.21
	43.51	43.51	b-c-f-h-q-v-x		51.21
b-c-e-f-g-h-p-v-x		60.39	a-b-q-v-y	31.64	31.64
a-d-e-f-g-h-p-v-x	60.38		b-c-f-h-q-t-x		48.77
a-b-f-h-p-v-x	44.21	38.49	a-d-e-g-q-t-x	51.38	
a-b-e-g-p-v-x	43.26	40.53	a-b-p-t-x	35.38	35.38
	40.53	43.26		41.24	41.24
a-b-e-g-q-v-y	36.98	36.98	a-d-e-g-q-v-x	49.21	
a-b-f-h-v-y			b-c-f-h-q-v-y		49.21
	36.91	36.91	a-b-q-v-x	30.03	30.03
a-d-e-f-g-h-q-v-y	56.33			34.01	34.01
b-c-e-f-g-h-q-v-y		56.33	a-b-q-t-x	30.25	30.25
b-c-e-f-g-h-p-t-x		56.46	a-d-e-g-p-v-x	51.38	
a-d-e-f-g-h-p-t-x	56.48				33.15
a-b-e-g-p-t-x	37.89	37.89	a-b-p-v-x	30.57	30.57
	40.90	40.90		30.03	30.03
a-b-f-h-p-t-x	36.91	36.91	b-c-q-v-x		44.21
	40.85	40.85	a-d-q-v-x	40.88	
a-d-e-f-g-h-q-t-x	56.47		a-d-q-t-x	43.23	
b-c-e-f-g-h-q-v-x		56.26	b-c-q-t-x		43.23
a-b-f-h-q-t-x	36.61	36.61	b-c-q-v-y		43.22
	38.64	38.64	a-d-q-v-y	43.22	
a-b-e-g-q-v-x	37.44	37.44	b-c-p-t-x		44.18
	39.42	39.42	a-d-p-t-x	44.20	
			a-d-p-v-x	41.95	

Table 7.K7. Red shift of vibrational frequency O–H bonds in the calculated conformers of jozimine A₂ having the O43–H52 and O44–H54 when they are engaged in an O–H... π interactions

HF/6-31G(d,p) results *in vacuo*.

conformers	O41–H50	O43–H52	O44–H54	O46–H60
a-b-e-f-g-h-p-v-x	62.65			62.65
	63.20			63.20
a-b-e-f-g-h-q-v-x	50.75			62.78
a-b-e-f-g-h-q-t-x	61.28			52.35
a-b-e-f-g-h-q-v-y	50.78			50.78
	51.01			51.01
a-b-e-f-g-h-p-t-x	52.15			52.15
	52.41			52.41
a-b-f-h-q-v-x	2.63			65.14
a-d-e-f-g-h-q-v-x	45.21	60.59	19.05	-
b-c-e-f-g-h-q-t-x	50.36	19.15	56.46	46.30
	52.27	21.06		
a-b-e-g-q-t-x	63.76	40.88	40.88	
		43.51	43.51	
b-c-e-f-g-h-p-v-x	61.12	9.13	60.39	40.34
		15.50		
a-d-e-f-g-h-p-v-x	40.34	60.38	9.13	61.09
	46.73		15.52	
a-b-f-h-p-v-x	0.33			65.17
a-b-e-g-p-v-x	2.63			65.14
a-b-e-g-v-y	2.11			53.83
a-b-f-h-v-y	1.94			53.68
a-d-e-f-g-h-q-v-y	45.12	56.33	18.78	49.99
			19.78	50.99
b-c-e-f-g-h-q-v-y	50.00	18.79	56.33	45.13
	51.00	19.79		
b-c-e-f-g-h-p-t-x	50.36	19.15	56.46	46.30
	52.27	21.06		
a-d-e-f-g-h-p-t-x	46.28	56.48	19.07	50.28
a-b-e-g-p-t-x	55.37			
a-b-f-h-p-t-x	53.68			1.94
		40.85	40.85	
a-d-e-f-g-h-q-t-x	39.49	56.47	8.28	52.80
	46.83		15.62	
b-c-e-f-g-h-q-v-x	50.96	9.34	56.26	40.55
		15.67		46.83
a-b-f-h-q-t-x	1.44			55.40

		38.64	38.64	
a-b-e-g-q-v-x	53.55			0.14
a-d-f-h-p-v-x	64.31	27.37	53.44	0.89
a-d-f-h-q-v-x		48.16	24.04	55.25
			26.97	58.18
b-c-e-g-q-t-x	62.24	24.22	52.62	-1.84
b-c-f-h-p-v-x	64.36	27.38	53.44	0.86
a-d-f-h-q-t-x		48.16	26.97	55.25
		48.16		55.25
b-c-e-f-q-v-x	62.24	24.22	52.62	-1.84
	64.36	27.38	53.44	0.86
b-c-e-g-q-v-y		48.16	26.97	55.25
		48.16		55.25
a-d-f-h-q-v-y	53.14	27.78	49.07	0.73
b-c-e-g-p-t-x	55.32	24.11	48.93	-1.05
	56.36	25.15		
a-d-f-h-p-t-x		48.95	24.11	55.32
c-d-e-f-g-h-q-v-y	44.80	35.03	35.03	44.80
	44.98	40.83	40.83	44.98
c-d-e-f-g-h-p-t-x	46.24	34.94	34.94	46.24
	46.43	40.73	40.73	46.43
c-d-e-f-g-h-q-t-x	39.08	32.49	32.49	47.01
		39.57	39.57	
c-d-e-f-g-h-q-v-x	45.32	32.36	32.36	40.55
		39.70	39.70	
a-d-e-g-q-v-y	48.01	51.28	14.57	6.38
c-d-e-f-g-h-p-v-x	40.77	31.32	23.20	40.77
	40.89	37.00	37.00	40.89
a-d-e-g-p-t-x	49.63	51.16	14.16	
b-c-f-h-p-t-x		14.13	51.21	
b-c-f-h-q-v-x	7.31	9.46	51.21	40.67
		13.29		44.50
b-c-f-h-q-t-x	6.46	14.63	48.77	49.38
a-d-e-g-q-t-x	40.15	51.38	8.94	
	43.74		12.53	
a-d-e-g-q-v-x	45.45	14.24	49.21	
	47.78	16.57		
b-c-f-h-q-v-y		49.21	14.24	45.45
			16.57	47.78
a-d-e-g-p-v-x	40.15	8.94	51.38	
b-c-e-g-p-v-x	-3.58	9.24	49.09	40.45
		14.14		45.35
c-d-f-h-q-t-x	3.67	32.02	32.02	49.27
		46.51	46.51	

c-d-e-g-q-v-x	47.39	47.39	31.64	
		0.00	0.00	
c-d-f-h-q-v-y	4.10	32.36	32.36	47.90
		44.34	44.34	47.90
c-d-e-g-q-v-y		32.41	32.41	
		44.39	44.39	
c-d-e-g-p-t-x		32.03	32.03	49.84
		44.94	44.94	49.84
c-d-f-h-p-t-x		32.04	32.04	49.86
			44.96	0.00
c-d-f-h-p-v-x		27.67	27.67	42.69
		47.52	47.52	
c-d-e-g-p-v-x	42.73	27.71	27.71	
		47.55	47.55	0.00
c-d-f-h-q-v-x	5.04	28.48	28.48	42.87
		44.38	44.38	
c-d-e-g-q-t-x	41.71	28.27	28.27	
		44.80	44.80	
b-c-q-v-x	7.51	22.82	44.21	2.66
a-d-q-v-x	0.91	40.88	18.93	
a-d-q-t-x		43.23	21.45	
b-c-q-t-x		43.08	21.49	
b-c-q-v-y	7.26	19.23	43.22	0.33
a-d-q-v-y	6.65	43.22	19.23	7.28
b-c-p-t-x		19.16	44.18	
a-d-p-t-x		44.20	19.18	
b-c-p-v-x		22.47	41.95	
a-d-p-v-x		22.47	41.95	
c-d-p-v-x		37.89	37.89	
		43.57	43.57	
c-d-q-v-x	5.08	35.91	35.91	
		43.06	43.06	3799.33
c-d-q-t-x	3.10	36.33	36.33	
		42.35	42.35	
c-d-q-v-y	4.73	35.26	35.26	4.73
	4.78	41.13	41.13	4.78
c-d-p-t-x		35.38	35.38	
		41.24	41.24	
		30.25	30.25	
		33.15	33.15	
a-b-q-t-x	1.21			
a-b-p-v-x	1.62			1.62
	1.90			1.90

a-b-q-v-x	2.87			2.14
a-b-q-v-y	2.45			2.45
	2.51			2.51
a-b-p-t-x				

Table 7.K8. Relative energy ($\Delta E_{\text{correct}}$, kcal/mol) corrected for ZPE and ZPE corrections (kcal/mol) for the calculated conformers of jozimine A₂
Results from HF/6-31G(d,p) frequency calculations

Conformer	$\Delta E_{\text{correct}}$ (kcal/mol)	ZPE (kcal/mol)	Conformer	$\Delta E_{\text{correct}}$ (kcal/mol)	ZPE (kcal/mol)
a-b-e-f-g-h-p-v-x	0.000	572.602	c-d-e-f-g-h-p-v-x	11.036	572.011
a-b-e-f-g-h-q-v-x	0.644	572.503	a-d-e-g-p-t-x	10.224	571.996
a-b-e-f-g-h-q-t-x	0.688	572.497	b-c-f-h-p-t-x	10.225	571.997
a-b-e-f-g-h-q-v-y	1.268	572.407	b-c-f-h-q-v-x	11.139	571.865
a-b-e-f-g-h-p-t-x	1.294	572.430	a-b-q-v-y	11.089	571.791
a-b-f-h-q-v-x	5.397	572.215	b-c-f-h-q-t-x	11.202	571.866
a-d-e-f-g-h-q-v-x	5.545	572.289	a-d-e-g-q-t-x	11.375	571.922
b-c-e-f-g-h-q-t-x	5.616	572.284	a-b-p-t-x	11.313	571.819
a-b-e-g-q-t-x	5.575	572.215	a-d-e-g-q-v-x	11.411	571.907
b-c-e-f-g-h-p-v-x	5.871	572.264	b-c-f-h-q-v-y	10.801	571.896
a-d-e-f-g-h-p-v-x	5.872	572.264	a-b-q-v-x	11.476	571.741
a-b-f-h-p-v-x	5.844	572.177	a-b-q-t-x	11.605	571.772
a-b-e-g-p-v-x	5.845	572.177	a-d-e-g-p-v-x	11.732	571.877
a-b-e-g-v-y	5.997	572.123	b-c-e-g-p-v-x	11.733	571.877
a-b-f-h-v-y	5.997	572.123	a-b-p-v-x	11.907	571.698
a-d-e-f-g-h-q-v-y	6.079	572.204	c-d-f-h-q-t-x	14.270	571.829
b-c-e-f-g-h-q-v-y	6.079	572.204	c-d-e-g-q-v-x	14.419	571.871
b-c-e-f-g-h-p-t-x	6.116	572.225	c-d-f-h-q-v-y	14.492	571.808
a-d-e-f-g-h-p-t-x	6.116	572.225	c-d-e-g-q-v-y	14.491	571.807
a-b-e-g-p-t-x	6.100	572.150	c-d-e-g-p-t-x	14.684	571.867
a-b-f-h-p-t-x	6.100	572.150	c-d-f-h-p-t-x	14.684	571.866
a-d-e-f-g-h-q-t-x	6.330	572.181	c-d-f-h-p-v-x	14.776	571.846
b-c-e-f-g-h-q-v-x	6.381	572.182	c-d-f-h-p-v-x	14.776	571.846
a-b-f-h-q-t-x	6.402	572.099	c-d-f-h-q-v-x	14.866	571.781
a-b-e-g-q-v-x	6.453	572.084	c-d-e-g-q-t-x	15.055	571.818
a-d-f-h-p-v-x	9.435	572.100	b-c-q-v-x	15.008	571.647
a-d-f-h-q-v-x	9.674	572.059	a-d-q-v-x	15.823	571.628
b-c-e-g-q-t-x	9.826	572.048	a-d-q-t-x	15.326	571.706
b-c-f-h-p-v-x	9.436	572.101	b-c-q-t-x	15.326	571.706
a-d-f-h-q-t-x	9.959	572.008	b-c-q-v-y	15.280	571.621
b-c-e-f-q-v-x	9.976	572.012	a-d-q-v-y	15.280	571.621
b-c-e-g-q-v-y	10.173	571.979	b-c-p-t-x	15.616	571.688
a-d-f-h-q-v-y	9.976	572.012	a-d-p-t-x	15.616	571.688
b-c-e-g-p-t-x	10.224	571.996	b-c-p-v-x	15.604	571.661
a-d-f-h-p-t-x	10.173	571.979	a-d-p-v-x	15.604	571.661
c-d-e-f-g-h-q-v-y	10.377	572.049	c-d-p-v-x	18.749	571.652
c-d-e-f-g-h-p-t-x	10.427	572.069	c-d-q-v-x	18.857	571.577
c-d-e-f-g-h-q-t-x	10.663	572.028	c-d-q-t-x	18.962	571.572
c-d-e-f-g-h-q-v-x	10.700	572.030	c-d-q-v-y	19.007	571.572
a-d-e-g-q-v-y	10.801	571.897	c-d-p-t-x	19.433	571.603

Table 7.K9 Dipole moment of the calculated conformers of jozimine A₂ *in vacuo* and in the solvents considered

HF/6-31G(d,p) and (DFT/B3LYP/6-31+G(d,p) results, respectively denoted as HF and DFT in the column headings. The results *in vacuo* are from full optimization calculations, the results in solution are from single point PCM calculations on the *in-vacuo*-optimized geometries.

Conformer	Dipole moment (Debye)							
	HF				DFT			
	vac	chlrf	actn	aq	vac	chlrf	actn	aq
a-b-e-f-g-h-p-v-x	2.65	2.67	2.55	2.44	2.81	2.87	2.74	2.58
a-b-e-f-g-h-q-v-x	5.46	5.96	6.06	5.97	5.32	5.93	6.09	5.99
a-b-e-f-g-h-q-t-x	5.03	5.41	5.43	5.34	5.01	5.50	5.57	5.45
a-b-e-f-g-h-q-v-y	6.83	7.46	7.55	7.44	6.59	7.36	7.52	7.39
a-b-e-f-g-h-p-t-x	7.53	8.29	8.50	8.43	7.33	8.28	8.57	8.49
a-b-f-h-q-v-x	4.25	4.95	4.51	4.31	4.04	4.36	4.41	4.22
a-d-e-f-g-h-q-v-x	4.56	4.85	4.87	4.73	4.70	5.11	— ^a	— ^a
b-c-e-f-g-h-q-t-x	5.03	6.12	6.29	6.28	5.52	6.22	6.46	6.41
a-b-e-g-q-t-x	4.20	4.45	4.47	4.27	4.10	4.39	4.42	4.21
b-c-e-f-g-h-p-v-x	4.11	4.53	4.63	4.69	4.15	4.65	4.81	4.83
a-d-e-f-g-h-p-v-x	4.11	4.53	4.64	4.69	4.15	4.66	4.80	4.83
a-b-e-g-p-v-x	3.93	4.24	4.29	4.37	4.38	4.79	4.85	4.91
a-b-f-h-p-v-x	3.93	4.23	4.28	4.36	4.38	4.78	— ^a	4.90
a-b-e-g-v-y	4.84	5.08	5.04	4.89	4.36	— ^a	— ^a	4.27
a-b-f-h-v-y	4.84	5.07	5.04	4.89	4.36	4.59	4.55	4.27
a-d-e-f-g-h-q-v-y	6.89	7.59	7.75	7.70	6.83	7.72	7.99	— ^a
b-c-e-f-g-h-q-v-y	6.89	7.58	7.76	7.71	6.83	7.72	7.99	7.91
b-c-e-f-g-h-p-t-x	7.43	8.24	8.51	8.46	7.24	8.24	8.59	8.54
a-d-e-f-g-h-p-t-x	7.43	8.25	8.50	8.47	7.25	8.24	8.59	8.54
a-b-e-g-p-t-x	4.96	5.21	5.18	4.88	4.78	5.12	5.10	4.78
a-b-f-g-p-t-x	4.95	5.22	5.17	4.88	4.77	5.11	5.09	4.78
a-d-e-f-g-h-q-t-x	5.67	6.24	6.36	6.37	5.59	6.28	— ^a	6.43
b-c-e-f-g-h-q-v-x	7.02	7.90	8.24	8.31	6.90	7.97	8.42	8.48
a-b-f-h-q-t-x	4.66	4.95	4.96	5.01	4.69	5.08	5.14	5.16
a-b-e-g-q-v-x	4.65	4.95	4.91	4.85	5.03	— ^a	— ^a	5.43
a-d-f-h-p-v-x	5.54	5.91	5.94	5.82	5.98	6.53	6.62	6.51
a-d-f-h-q-v-x	5.46	5.79	5.83	5.82	5.28	5.68	5.74	— ^a
b-c-e-g-q-t-x	6.24	6.77	6.92	6.83	6.45	7.18	7.44	7.40
b-c-f-h-p-v-x	6.24	6.77	6.92	6.83	5.99	6.52	6.62	— ^a
a-d-f-h-q-t-x	6.05	6.48	6.55	6.57	5.88	6.37	6.44	6.42
b-c-e-g-q-v-x	6.79	7.40	7.53	7.42	7.02	7.83	8.06	7.98
b-c-e-g-q-v-y	6.65	7.22	7.39	7.43	6.12	6.73	6.93	6.88
a-d-f-h-q-v-y	6.65	7.22	7.385	7.42	6.12	6.74	6.92	6.88
b-c-e-g-p-t-x	6.22	6.65	6.69	6.48	6.30	6.92	7.05	6.87
a-d-f-h-p-t-x	6.21	6.66	6.69	6.49	6.29	6.92	7.04	6.87
c-d-e-f-g-h-q-v-y	4.29	4.63	4.75	4.57	4.22	4.68	4.84	4.58

c-d-e-f-g-h-p-t-x	4.96	5.46	5.66	5.53	4.71	5.31	5.57	5.36
c-d-e-f-g-h-q-t-x	3.10	3.35	3.47	3.37	2.98	3.29	3.40	— ^a
c-d-e-f-g-h-q-v-x	3.54	3.93	4.10	4.05	3.43	3.89	4.12	4.02
a-d-e-g-q-v-y	3.98	4.27	4.28	4.09	3.89	4.34	4.43	— ^a
c-d-e-f-g-h-p-v-x	0.50	0.20	0.02	0.17	0.70	0.40	0.20	0.21
a-d-e-g-p-t-x	4.62	5.10	5.24	5.20	4.03	4.54	4.70	4.62
b-c-f-h-p-t-x	4.62	5.10	5.25	5.20	4.03	— ^a	4.71	4.62
b-c-f-h-q-v-x	5.43	6.19	6.48	6.48	5.33	6.33	6.79	6.86
a-b-q-v-y	1.38	1.13	— ^a	0.65	0.59	— ^a	— ^a	0.41
b-c-f-h-q-t-x	4.43	4.98	5.15	5.24	1.18	1.19	1.12	1.12
a-d-e-g-q-t-x	4.69	5.33	5.57	5.72	4.32	5.06	5.37	5.51
a-b-p-t-x	1.42	1.19	0.96	0.50	1.08	0.85	0.60	0.15
a-d-e-g-q-v-x	3.64	4.01	4.07	4.24	3.70	4.11	4.17	— ^a
b-c-f-h-q-v-y	3.97	4.26	4.27	4.09	3.89	— ^a	4.44	4.29
a-b-q-v-x	1.16	0.98	0.77	0.62	1.17	1.07	— ^a	0.80
a-b-q-t-x	1.38	1.13	— ^a	0.65	1.18	1.19	1.12	1.12
a-d-e-g-p-v-x	5.14	5.99	6.34	6.68	5.05	6.01	6.44	6.56
b-c-e-g-p-v-x	5.15	5.99	6.35	6.69	5.05	6.01	6.43	— ^a
a-b-p-v-x	0.87	0.74	0.54	0.51	1.43	1.38	1.16	1.12
c-d-f-h-q-t-x	2.62	2.69	2.63	2.63	2.60	2.68	2.61	2.58
c-d-e-g-q-v-x	3.02	3.16	3.15	3.05	3.31	3.55	3.58	— ^a
c-d-f-h-q-v-y	2.90	2.98	2.98	2.87	2.44	2.47	2.44	2.22
c-d-e-g-q-v-y	2.90	2.98	2.98	2.88	2.44	2.47	2.43	2.24
c-d-e-g-p-t-x	2.73	2.74	2.67	2.34	2.57	2.60	2.52	2.19
c-d-h-f-p-t-x	2.72	2.73	2.67	2.34	2.57	2.59	— ^a	2.18
c-d-f-h-p-v-x	3.83	4.28	4.49	4.65	4.04	4.60	4.82	4.98
c-d-e-g-p-v-x	3.83	4.28	4.48	4.65	4.04	4.60	4.82	4.98
c-d-f-h-q-v-x	3.79	4.22	4.39	4.39	3.71	4.56	4.29	— ^a
c-d-e-g-q-t-x	4.01	n.c	4.67	4.74	3.93	4.50	4.79	4.87
b-c-q-v-x	4.03	4.51	4.64	4.45	4.42	5.16	5.42	5.39
a-d-q-v-x	3.83	4.37	4.58	4.96	3.30	3.86	4.10	4.46
a-d-q-t-x	3.77	4.25	4.47	4.66	3.05	3.53	3.76	3.95
b-c-q-t-x	4.00	4.25	4.47	4.67	3.05	3.53	3.76	3.95
b-c-q-v-y	3.91	4.40	4.56	4.67	3.97	4.69	5.00	5.25
a-d-q-v-y	3.91	4.40	4.56	4.67	3.97	4.70	5.00	5.24
b-c-p-t-x	3.93	4.43	4.61	4.79	3.93	4.62	4.90	5.16
a-d-p-t-x	3.93	4.44	4.62	4.78	3.93	4.63	4.90	5.16
b-c-p-v-x	3.93	4.45	4.63	4.71	3.83	4.42	4.64	4.72
a-d-p-v-x	3.93	4.46	4.65	4.72	3.83	4.41	4.64	4.71
c-d-p-v-x	1.46	1.85	2.09	2.18	0.97	1.37	1.64	1.79
c-d-q-v-x	1.39	1.86	2.07	2.33	1.66	2.25	2.55	2.89
c-d-q-t-x	1.48	1.95	— ^a	2.41	2.00	2.64	2.95	3.29
c-d-q-v-y	1.28	1.81	2.03	2.40	2.07	2.83	3.19	3.70
c-d-p-t-x	1.33	1.86	2.09	2.64	1.84	2.52	2.87	3.48

^a The calculation for this conformer did not converge in the given solvent.

Table 7.K10. HOMO-LUMO energy gap of the calculated conformers of jozimine A₂ in vacuo and in the solvents considered

HF/6-31G(d,p) and (DFT/B3LYP/6-31+G(d,p) results, respectively denoted as HF and DFT in the column headings. The results *in vacuo* are from full optimization calculations, the results in solution are from single point PCM calculations on the *in-vacuo*-optimized geometries

Conformer	HOMO-LUMO energy gap (kcal/mol)							
	HF				DFT			
	vac	chlrf	actn	aq	vac	chlrf	actn	aq
a-b-e-f-g-h-p-v-x	232.76	232.85	232.88	232.91	98.343	98.506	98.563	98.613
a-b-e-f-g-h-q-v-x	233.83	233.92	233.96	234.04	98.908	99.065	99.115	99.203
a-b-e-f-g-h-q-t-x	233.81	233.92	233.96	234.02	98.757	98.946	99.027	99.102
a-b-e-f-g-h-q-v-y	234.92	235.04	235.09	235.15	99.391	99.567	99.642	99.730
a-b-e-f-g-h-p-t-x	234.74	234.88	234.93	234.97	99.579	99.774	99.862	99.931
a-b-f-h-q-v-x	232.34	232.80	232.51	233.00	97.007	97.094	97.389	98.155
a-d-e-f-g-h-q-v-x	224.84	228.73	230.12	231.92	89.031	92.922	— ^a	— ^a
b-c-e-f-g-h-q-t-x	224.66	228.60	230.15	231.89	88.868	92.752	94.327	96.266
a-b-e-g-q-t-x	232.19	232.27	232.50	233.05	96.963	96.982	97.226	97.923
b-c-e-f-g-h-p-v-x	224.91	228.84	230.35	232.16	89.050	92.991	94.515	96.511
a-d-e-f-g-h-p-v-x	225.15	228.85	230.36	232.13	89.044	92.984	94.515	96.505
a-b-e-g-p-v-x	231.84	231.97	232.23	232.74	96.655	96.718	97.025	97.596
a-b-f-h-p-v-x	231.83	231.97	232.24	232.71	96.655	96.718	— ^a	97.615
a-b-e-g-v-y	232.93	232.85	232.96	233.70	96.837	— ^a	— ^a	98.036
a-b-f-h-v-y	232.93	232.85	232.96	233.69	96.843	96.944	97.214	98.036
a-d-e-f-g-h-q-v-y	225.09	229.16	230.69	232.54	89.119	93.066	94.610	— ^a
b-c-e-f-g-h-q-v-y	225.09	229.16	230.72	232.53	89.119	93.078	94.610	96.511
b-c-e-f-g-h-p-t-x	225.08	229.16	230.67	232.50	89.144	93.104	94.641	96.567
a-d-e-f-g-h-p-t-x	225.08	229.16	230.69	232.49	89.138	93.110	94.653	96.567
a-b-e-g-p-t-x	232.49	232.61	232.92	233.64	96.756	96.850	97.163	97.954
a-b-f-h-p-t-x	232.49	232.61	232.90	233.65	96.756	96.850	97.151	97.973
a-d-e-f-g-h-q-t-x	225.26	229.31	230.88	232.75	89.207	93.191	— ^a	96.699
b-c-e-f-g-h-q-v-x	225.15	229.32	230.96	232.76	89.219	93.242	94.892	96.793
a-b-f-h-q-t-x	232.86	232.80	232.98	233.67	96.668	96.774	97.032	97.885
a-b-e-g-q-v-x	232.40	232.51	232.77	233.44	96.800	— ^a	— ^a	97.942
a-d-f-h-p-v-x	227.85	231.33	232.29	233.05	92.125	95.965	97.151	98.249
a-d-f-h-q-v-x	227.89	231.91	233.11	234.01	92.394	96.404	97.709	— ^a
b-c-e-g-q-t-x	228.29	232.14	233.25	234.15	92.332	96.436	96.436	98.946
b-c-f-h-p-v-x	228.29	232.14	233.25	234.15	92.125	95.965	97.151	— ^a
a-d-f-h-q-t-x	227.98	232.01	233.28	234.25	92.602	96.567	97.898	99.115
b-c-e-f-q-v-x	228.34	232.12	233.25	234.94	92.432	96.473	97.804	98.983
b-c-e-g-q-v-y	228.26	232.54	233.96	234.96	92.501	96.580	97.992	99.178
a-d-f-h-q-v-y	228.26	232.54	233.94	234.94	92.495	96.574	97.967	99.165
b-c-e-g-p-t-x	228.85	232.87	234.06	235.07	92.620	96.774	98.080	99.341
a-d-f-h-p-t-x	228.86	232.88	234.08	235.05	92.620	96.774	98.124	99.322
c-d-e-f-g-h-q-v-y	236.49	236.42	236.40	236.38	100.43	100.37	100.36	100.389
c-d-e-f-g-h-p-t-x	236.37	236.31	236.28	236.25	100.79	100.72	100.70	100.740

c-d-e-f-g-h-q-t-x	236.42	236.36	236.33	236.27	100.64	100.58	100.55	— ^a
c-d-e-f-g-h-q-v-x	236.50	236.45	236.43	236.37	100.62	100.57	100.54	100.558
a-d-e-g-q-v-y	221.88	225.62	227.25	229.83	85.586	89.414	91.095	— ^a
c-d-e-f-g-h-p-v-x	236.55	236.50	236.48	236.43	100.55	100.50	100.48	100.502
a-d-e-g-p-t-x	221.16	225.22	227.06	229.61	85.435	89.257	91.020	93.536
b-c-f-h-p-t-x	221.17	225.23	227.06	229.64	85.435	— ^a	91.020	93.530
b-c-f-h-q-v-x	222.01	225.84	227.54	230.14	85.705	89.589	91.428	94.045
a-b-q-v-y	234.01	234.30	234.50	234.70	98.776	— ^a	— ^a	99.460
b-c-f-h-q-t-x	221.83	225.61	227.30	229.81	99.115	— ^a	99.573	99.830
a-d-e-g-q-t-x	221.43	225.41	227.27	229.93	85.680	89.451	91.234	93.863
a-b-p-t-x	234.23	234.46	234.56	234.77	98.889	99.184	99.335	99.567
a-d-e-g-q-v-x	221.19	225.22	227.02	229.56	85.486	89.332	91.052	— ^a
b-c-f-h-q-v-y	221.88	225.64	227.25	229.83	85.586	— ^a	91.102	93.662
a-b-q-v-x	233.82	234.13	234.28	234.55	99.058	99.372	— ^a	99.812
a-b-q-t-x	234.00	— ^a	234.50	234.78	99.115	99.410	99.830	99.830
a-d-e-g-p-v-x	221.29	225.38	227.27	229.85	85.592	89.451	91.290	93.417
b-c-e-g-p-v-x	221.29	225.38	227.26	229.85	85.580	89.439	91.277	— ^a
a-b-p-v-x	233.73	233.99	234.13	234.39	98.412	98.720	98.883	99.134
c-d-f-h-q-t-x	233.83	233.48	233.65	234.11	97.515	97.408	97.578	98.224
c-d-e-g-q-v-x	233.17	233.03	233.15	233.62	97.371	97.603	154.47	— ^a
c-d-f-h-q-v-y	234.29	233.88	233.86	234.41	97.546	97.333	97.433	— ^a
c-d-e-g-q-v-y	234.30	233.89	233.87	234.43	97.546	97.327	97.421	97.992
c-d-e-g-p-t-x	233.64	233.48	233.68	234.19	97.427	97.182	97.314	97.873
c-d-f-h-p-t-x	233.64	233.44	233.67	234.21	97.427	97.170	— ^a	97.885
c-d-f-h-p-v-x	233.05	233.03	233.23	233.74	97.251	97.088	97.295	97.904
c-d-e-g-p-v-x	233.05	233.01	233.27	233.72	97.245	97.094	97.276	97.904
c-d-f-h-q-v-x	234.20	233.87	233.96	234.55	97.760	97.835	97.835	0.000
c-d-e-g-q-t-x	233.72	— ^a	233.72	234.37	97.703	97.421	97.603	98.299
b-c-q-v-x	225.16	228.79	230.10	231.94	88.717	97.603	94.214	96.197
a-d-q-v-x	224.22	228.56	230.26	232.09	88.993	92.997	94.572	96.442
a-d-q-t-x	224.05	228.21	229.88	231.85	89.000	92.645	94.227	96.178
b-c-q-t-x	225.52	228.22	229.89	231.84	88.805	92.645	94.227	96.178
b-c-q-v-y	225.00	229.02	230.59	232.44	89.999	93.016	94.547	96.442
a-d-q-v-y	225.00	229.04	230.55	232.39	89.005	92.978	94.509	— ^a
b-c-p-t-x	224.95	229.00	230.54	232.39	88.937	92.953	94.559	96.436
a-d-p-t-x	224.95	229.02	230.56	232.33	88.936	92.965	94.559	96.448
b-c-p-v-x	224.42	228.34	229.80	231.60	88.503	92.451	94.007	95.927
a-d-p-v-x	224.41	228.33	229.82	231.57	88.510	92.457	94.020	95.959
c-d-p-v-x	234.14	234.16	234.11	234.04	99.830	99.799	99.768	99.705
c-d-q-v-x	235.09	235.19	235.20	235.13	100.06	100.04	100.01	99.950
c-d-q-t-x	235.56	235.60	— ^a	235.57	100.48	100.43	100.43	100.401
c-d-q-v-y	236.32	236.30	236.28	236.24	100.40	100.36	100.32	100.282
c-d-p-t-x	236.45	236.40	236.37	236.30	100.30	100.27	100.25	100.213

^a The calculation for this conformer did not converge in the given solvent.

Table 7.K11. Solvent effect (free energy of solvation, ΔG_{solv}) and its electrostatic component (G_{el}) for the calculated conformers of jozimine A₂ in the three solvents considered

Results from HF/6-31G(d,p) single point PCM calculations on the *in-vacuo*-optimized geometries.

conformer	HF/6-31G(d,p)					
	ΔG_{solv} (kcal/mol)			G_{el} (kcal/mol)		
	in chlrf	in actn	in aq	in chlrf	in actn	in aq
a-b-e-f-g-h-p-v-x	7.19	17.60	-4.12	-5.55	-8.65	-24.65
a-b-e-f-g-h-q-v-x	6.95	17.66	-4.39	-5.90	-8.73	-25.08
a-b-e-f-g-h-q-t-x	7.15	17.77	-4.04	-5.87	-8.80	-24.95
a-b-e-f-g-h-q-v-y	6.81	17.67	-4.70	-6.24	-8.90	-25.61
a-b-e-f-g-h-p-t-x	7.17	17.89	-4.50	-5.74	-8.59	-25.31
a-b-f-h-q-v-x	5.76	16.21	-7.62	-7.20	-10.20	-28.38
a-d-e-f-g-h-q-v-x	6.97	17.86	-5.37	-6.07	-8.75	-26.35
b-c-e-f-g-h-q-t-x	7.19	17.91	-5.46	-5.86	-8.71	-26.45
a-b-e-g-q-t-x	5.78	16.21	-7.54	-7.13	-10.27	-28.37
b-c-e-f-g-h-p-v-x	6.84	18.05	-5.26	-6.18	-8.55	-26.24
a-d-e-f-g-h-p-v-x	7.17	17.95	-5.55	-5.86	-8.66	-26.52
a-b-e-g-p-v-x	6.38	15.89	-7.96	-6.43	-10.49	-28.67
a-b-f-h-p-v-x	5.74	15.95	-7.90	-7.06	-10.43	-28.61
a-b-f-h-q-v-y	6.07	15.94	-8.28	-7.01	-10.69	-29.28
a-b-e-g-q-v-y	6.06	15.85	-8.20	-7.01	-10.77	-29.20
a-d-e-f-g-h-q-v-y	6.74	17.74	-5.32	-6.51	-9.03	-26.47
b-c-e-f-g-h-q-v-y	6.97	17.73	-5.84	-6.28	-9.05	-27.01
b-c-e-f-g-h-p-t-x	6.94	17.63	-5.80	-6.13	-9.04	-26.84
a-d-e-f-g-h-p-t-x	7.03	17.67	-5.73	-6.04	-8.99	-26.77
a-b-e-g-p-t-x	6.01	15.96	-8.09	-6.94	-10.59	-29.02
a-b-f-h-p-t-x	5.88	15.94	-8.13	-7.07	-10.61	-29.05
a-d-e-f-g-h-q-t-x	6.97	17.53	-5.88	-6.14	-9.17	-26.98
b-c-e-f-g-h-q-v-x	6.82	17.54	-5.75	-6.31	-9.18	-26.86
a-b-f-h-q-t-x	5.76	15.59	-8.42	-7.20	-10.95	-29.33
a-b-e-g-q-v-x	5.79	15.69	-8.59	-7.16	-10.86	-29.50
a-d-f-h-p-v-x	6.32	16.62	-7.72	-6.56	-9.84	-28.54
a-d-f-h-q-v-x	6.26	16.48	-8.10	-6.78	-10.16	-29.15
b-c-e-g-q-t-x	6.20	16.52	-8.08	-6.86	-10.14	-29.15
b-c-f-h-p-v-x	6.20	16.52	-8.31	-6.87	-10.14	-29.38
a-d-f-h-q-t-x	6.42	16.72	-8.01	-6.95	-10.31	-29.50
b-c-e-g-q-v-x	6.15	16.43	-9.00	-6.92	-10.25	-30.25
b-c-e-g-q-v-y	6.17	16.40	-8.88	-7.10	-10.43	-30.14
a-d-f-h-q-v-y	6.43	16.44	-9.00	-6.85	-10.40	-30.25
b-c-e-g-p-t-x	6.17	16.37	-8.81	-6.93	-10.34	-29.95
a-d-f-h-p-t-x	6.43	16.38	-8.73	-6.67	-10.34	-29.87
c-d-e-f-g-h-q-v-y	7.86	18.72	-5.56	-5.48	-8.17	-26.88
c-d-e-f-g-h-p-t-x	7.76	18.86	-5.59	-5.40	-7.90	-26.77

c-d-e-f-g-h-q-t-x	7.58	18.41	-6.53	-5.58	-8.37	-27.72
c-d-e-f-g-h-q-v-x	7.61	18.46	-5.43	-5.61	-8.36	-26.68
a-d-e-g-q-v-y	6.65	16.68	-9.05	-6.63	-10.16	-30.32
c-d-e-f-g-h-p-v-x	7.57	18.43	-6.35	-5.57	-8.33	-27.53
a-d-e-g-p-t-x	6.13	16.10	-9.25	-6.97	-10.61	-30.38
b-c-f-h-p-t-x	6.08	16.08	-9.20	-7.02	-10.64	-30.33
b-c-f-h-q-v-x	5.99	16.12	-9.20	-7.24	-10.75	-30.52
a-b-q-v-y	4.89	— ^a	-12.31	-8.16	— ^a	-33.34
b-c-f-h-q-t-x	6.27	16.24	-9.44	-6.82	-10.46	-30.56
a-d-e-g-q-t-x	6.05	15.95	-9.36	-7.06	-10.78	-30.52
a-b-p-t-x	5.65	14.61	-11.38	-7.29	-11.96	-32.34
a-d-e-g-q-v-x	5.95	15.94	-9.21	-7.22	-10.86	-30.43
b-c-f-h-q-v-y	6.09	16.13	-9.55	-7.19	-10.71	-30.81
a-b-q-v-x	4.85	14.13	-12.27	-8.19	-12.56	-33.38
a-b-q-t-x	— ^a	13.99	-12.10	— ^a	-12.61	-33.11
a-d-e-g-p-v-x	5.74	15.73	-9.55	-7.33	-10.96	-30.65
a-b-p-v-x	4.94	13.89	-12.42	-7.98	-12.66	-33.37
b-c-e-g-p-v-x	5.73	15.73	-9.48	-7.33	-10.96	-30.58
c-d-f-h-q-t-x	7.16	17.39	-8.30	-5.99	-9.39	-29.53
c-d-e-g-q-v-x	6.73	17.38	-8.02	-6.40	-9.37	-29.20
c-d-f-h-q-v-y	6.98	17.27	-8.08	-6.43	-9.73	-29.55
c-d-e-g-q-v-y	7.03	17.30	-8.25	-6.38	-9.70	-29.72
c-d-e-g-p-t-x	6.86	17.20	-8.43	-6.30	-9.58	-29.67
c-d-f-h-p-t-x	6.75	17.22	-8.60	-6.41	-9.56	-29.84
c-d-f-h-p-v-x	6.74	17.09	-8.42	-6.34	-9.62	-29.56
c-d-e-g-p-v-x	7.16	17.56	-8.02	-5.91	-9.15	-29.16
c-d-f-h-q-v-x	6.80	17.12	-8.53	-6.39	-9.70	-29.82
c-d-e-g-q-t-x	— ^a	16.94	-9.14	— ^a	-9.84	-30.38
b-c-q-v-x	5.21	13.33	-11.80	-7.81	-13.32	-32.90
a-d-q-t-x	5.63	15.43	-11.25	-7.73	-11.63	-32.80
b-c-q-t-x	5.53	14.81	-11.52	-7.84	-12.24	-33.06
b-c-q-v-y	5.36	15.08	-12.30	-7.89	-11.76	-33.60
a-d-q-v-y	5.76	15.07	-12.03	-7.49	-11.78	-33.33
b-c-p-t-x	5.11	14.72	-12.05	-7.99	-12.03	-33.25
a-d-p-t-x	5.51	15.06	-11.95	-7.59	-11.69	-33.14
b-c-p-v-x	4.80	14.28	-12.52	-8.15	-12.31	-33.53
a-d-p-v-x	4.60	13.81	-12.96	-8.36	-12.78	-33.97
a-d-q-v-x	4.86	14.36	-12.65	-8.23	-12.37	-33.83
c-d-p-v-x	5.67	15.66	-11.25	-7.31	-10.95	-32.29
c-d-q-v-x	5.77	15.46	-11.48	-7.33	-11.30	-32.70
c-d-q-t-x	5.78	— ^a	-11.45	-7.35	— ^a	-32.72
c-d-q-v-y	6.10	15.53	-12.02	-7.25	-11.42	-33.45
c-d-p-t-x	5.91	15.47	-11.86	-7.25	-11.35	-33.16

^a The calculation for this conformer did not converge in the given solvent.

Table 7.K12. Solvent effect (free energy of solvation, ΔG_{solv}) and its electrostatic component (G_{el}) for the calculated conformers of jozimine A₂ in the three solvents considered

Results from DFT/6-31G+(d,p) single point PCM calculations on the *in-vacuo*-optimized geometries.

conformer	DFT/B3LYP/6-31G+(d,p)					
	ΔG_{solv} (kcal/mol)			G_{el} (kcal/mol)		
	in chlrf	in actn	in aq	in chlrf	in actn	in aq
a-b-e-f-g-h-p-v-x	7.37	18.30	-4.12	-5.99	-8.74	-25.65
a-b-e-f-g-h-q-v-x	7.29	18.16	-4.64	-6.19	-9.03	-26.35
a-b-e-f-g-h-q-t-x	7.32	18.14	-4.57	-6.19	-9.06	-26.29
a-b-e-f-g-h-q-v-y	7.19	17.93	-5.09	-6.42	-9.37	-26.94
a-b-e-f-g-h-p-t-x	7.22	17.96	-4.87	-6.34	-9.34	-26.74
a-b-f-h-q-v-x	6.65	16.98	-7.54	-6.98	-10.40	-29.52
a-d-e-f-g-h-q-v-x	7.61	— ^a	— ^a	-6.14	— ^a	— ^a
b-c-e-f-g-h-q-t-x	7.61	18.44	-5.50	-6.14	-9.05	-27.60
a-b-e-g-q-t-x	6.57	16.93	-7.72	-7.00	-10.39	-29.61
b-c-e-f-g-h-p-v-x	7.50	18.36	-5.60	-6.20	-9.10	-27.67
a-d-e-f-g-h-p-v-x	7.50	18.36	-5.57	-6.20	-9.11	-27.63
a-b-e-g-p-v-x	6.44	16.72	-7.83	-7.04	-10.50	-29.61
a-b-f-h-p-v-x	6.47	— ^a	-7.86	-7.01	— ^a	-29.64
a-b-f-h-q-v-y	— ^a	— ^a	-8.01	— ^a	— ^a	-30.13
a-d-e-f-g-h-q-v-y	7.84	18.60	— ^a	-6.31	-9.29	— ^a
b-c-e-f-g-h-q-v-y	7.83	18.62	-5.26	-6.32	-9.26	-27.80
b-c-e-f-g-h-p-t-x	8.21	19.15	-4.60	-6.29	-9.24	-27.75
a-d-e-f-g-h-p-t-x	8.21	19.17	-4.60	-6.29	-9.22	-27.75
a-b-e-g-p-t-x	6.61	16.94	-7.73	-7.19	-10.65	-29.95
a-b-f-h-p-t-x	6.62	16.93	-7.76	-7.17	-10.66	-29.99
a-d-e-f-g-h-q-t-x	7.47	— ^a	-6.03	-6.33	— ^a	-28.21
b-c-e-f-g-h-q-v-x	7.45	18.15	-5.94	-6.37	-9.44	-28.15
a-b-f-h-q-t-x	6.41	16.43	-8.26	-7.22	-10.95	-30.24
a-b-e-g-q-v-x	— ^a	— ^a	-8.08	— ^a	— ^a	-30.09
a-d-f-h-p-v-x	6.78	17.28	-7.61	-6.76	-10.01	-29.49
a-d-f-h-q-v-x	6.85	17.25	— ^a	-6.91	-10.28	— ^a
b-c-e-g-q-t-x	6.84	17.36	-7.99	-6.91	-10.17	-30.16
b-c-f-h-p-v-x	6.78	17.28	— ^a	-6.76	-10.01	— ^a
a-d-f-h-q-t-x	6.70	17.26	-8.10	-7.08	-10.30	-30.31
b-c-e-g-q-v-x	6.79	17.26	-7.89	-6.98	-10.29	-30.07
b-c-e-g-q-v-y	6.82	17.09	-8.13	-7.17	-10.62	-30.48
a-d-f-h-q-v-y	6.88	17.13	-8.18	-7.11	-10.57	-30.53
b-c-e-g-p-t-x	6.73	17.17	-8.37	-7.04	-10.37	-30.56
a-d-f-h-p-t-x	6.72	17.22	-8.38	-7.05	-10.32	-30.56
c-d-e-f-g-h-q-v-y	8.43	19.32	-5.36	-5.58	-8.37	-27.69

c-d-e-f-g-h-p-t-x	8.25	19.27	-5.73	-5.58	-8.33	-27.97
c-d-e-f-g-h-q-t-x	8.21	19.16	— ^a	-5.61	-8.42	— ^a
c-d-e-f-g-h-q-v-x	8.28	19.25	-5.55	-5.67	-8.48	-27.95
a-d-e-g-q-v-y	6.73	16.94	— ^a	-7.29	-10.78	— ^a
c-d-e-f-g-h-p-v-x	7.95	18.87	-6.33	-5.77	-8.62	-28.45
a-d-e-g-p-t-x	6.68	16.93	-8.49	-7.10	-10.61	-30.68
b-c-f-h-p-t-x	— ^a	16.96	-8.55	— ^a	-10.59	-30.74
b-c-f-h-q-v-x	6.53	16.70	-9.12	-7.33	-10.95	-31.43
a-b-q-v-y	— ^a	— ^a	-11.36	— ^a	— ^a	-33.47
b-c-f-h-q-t-x	5.48	15.18	-11.68	-8.22	-12.33	-33.82
a-d-e-g-q-t-x	6.60	16.78	-9.10	-7.17	-10.78	-31.30
a-b-p-t-x	5.61	15.32	-10.92	-8.04	-12.13	-32.99
a-d-e-g-q-v-x	6.60	16.75	— ^a	-7.23	-10.87	— ^a
b-c-f-h-q-v-y	— ^a	17.03	-8.69	— ^a	-10.72	-31.09
a-b-q-t-x	5.48	15.18	-11.68	-8.22	-12.33	-33.82
a-b-q-v-x	5.41	— ^a	-11.48	-8.28	— ^a	-33.61
a-d-e-g-p-v-x	6.47	16.57	-9.53	-7.30	-11.01	-31.12
b-c-e-g-p-v-x	6.42	16.60	— ^a	-7.34	-10.97	— ^a
a-b-p-v-x	5.42	14.89	-11.63	-8.15	-12.47	-33.60
c-d-f-h-q-t-x	7.39	18.08	-8.17	-6.42	-9.52	-30.45
c-d-e-g-q-v-x	7.40	18.01	— ^a	-6.35	-9.51	— ^a
c-d-f-h-q-v-y	7.61	18.09	-8.50	-6.44	-9.67	-30.93
c-d-e-g-q-v-y	7.58	18.14	-8.43	-6.47	-9.62	-30.86
c-d-e-g-p-t-x	7.38	18.04	-8.41	-6.36	-9.46	-30.55
c-d-f-h-p-t-x	7.40	— ^a	-8.34	-6.35	— ^a	-30.48
c-d-f-h-p-v-x	7.30	17.83	-8.25	-6.32	-9.56	-30.27
c-d-e-g-p-v-x	7.26	17.84	-8.24	-6.35	-9.56	-30.26
c-d-e-g-q-v-x	7.40	18.01	— ^a	-6.35	-9.51	— ^a
c-d-e-g-q-t-x	7.30	17.75	-8.73	-6.43	-9.77	-30.92
b-c-q-v-x	5.70	15.48	-11.86	-8.16	-12.19	-34.22
a-d-q-t-x	5.93	15.81	-11.40	-7.88	-11.82	-33.71
b-c-q-t-x	5.93	15.81	-11.40	-7.88	-11.82	-33.71
b-c-q-v-y	5.85	15.53	-11.91	-8.18	-12.24	-34.37
a-d-q-v-y	5.88	15.54	-11.81	-8.16	-12.25	-34.29
b-c-p-t-x	5.85	15.64	-11.54	-8.00	-12.01	-33.87
a-d-p-t-x	5.79	15.63	-11.54	-8.05	-12.02	-33.87
b-c-p-v-x	5.58	15.28	-11.73	-7.94	-12.03	-33.65
a-d-p-v-x	5.56	15.30	-11.77	-7.98	-12.03	-33.71
c-d-p-v-x	6.45	16.62	-10.42	-7.16	-10.79	-32.47
c-d-q-v-x	6.44	16.42	-10.93	-7.24	-11.06	-33.08
c-d-q-t-x	6.53	16.71	-10.99	-7.26	-10.91	-33.30
c-d-q-v-y	6.59	16.50	-11.77	-7.48	-11.32	-34.30
c-d-p-t-x	6.56	16.70	-11.23	-7.27	-10.93	-33.54

^a The calculation for this conformer did not converge in the given solvent

CHAPTER 8

COMPUTATIONAL STUDY OF MBANDAKAMINE A, A DIMERIC NAPHTHYLISOQUINOLINE *IN VACUO* AND *IN SOLUTION*

This chapter presents the results of the computational study of mbandakamine A in *vacuo* and in solution. The results were previously presented at the QUITEL conference 2017 [D] and were submitted for consideration for publication [60].

8.1. Introduction

Mbandakamine A (Fig. 8.1, denoted by the acronym MBK in the rest of the text) is one of the naphthylisoquinoline alkaloids isolated from the leaves of Congolese *Ancistrocladus* species and showing good antimalarial activity ($IC_{50} = 0.148 \mu M$, where IC_{50} indicates the amount of a particular drug that is needed to inhibit 50% of a given biological process or component of a process, such as an enzyme, cell, cell receptor or microorganism). It was also one of the first dimeric naphthylisoquinoline alkaloids with an unsymmetrically coupled central biaryl axis to be discovered [48]. It has a peri-peri coupling (Fig.8.2,a), which makes the molecule to have stacking interactions (Fig.8.2.b).

MBK has a dimeric structure, i.e., it contains two units, each consisting of a naphthalene moiety and an isoquinoline moiety. Figure 8.1 shows its structure and the atom numbering utilised in this work. Since it is convenient to be able to mention each ring individually, the rings are denoted by uppercase letters (A, B, C, D, E, F, G and H), as shown in Fig.8.1. In order to be able to mention each of the two units of the dimeric molecular structure individually, the whole unit containing the A, B, C, D rings is called R and the whole unit comprising the E, F, G, H rings is called S.

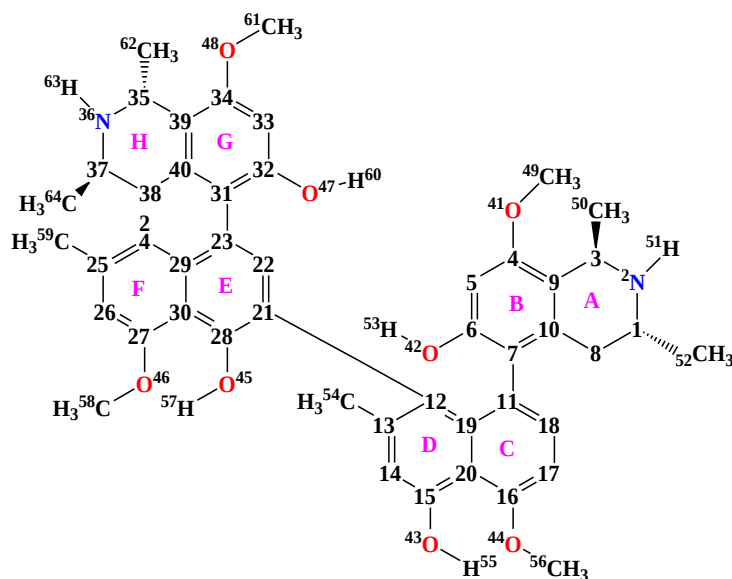


Figure 8.1. Structure of the mbandakamine A molecule and atom numbering utilized in this work

The C atoms in the rings are denoted by the numbers showing their positions. Only the H atoms attached to O or N are numbered separately, while the H atoms attached to a C atom are given the same number as the C atom.

Each moiety has one OH group and one OCH₃ group among its substituents. Each OH group can be H-bond donor, either to the methoxy group in the same moiety or to another OH from another moiety. Beside the H-bonds formed by OH groups, the N36 atom in the isoquinoline (G,H) moiety can be either H-bond donor to an OH and to a methoxy group or H-bond acceptor to an OH from another moiety.

Intramolecular hydrogen bonds (IHBs) are particularly important in the study of biologically active molecules. The MBK molecule can form different types of IHBs. The O–H $\cdots$ O, N–H $\cdots$ O and O–H $\cdots$ N IHBs pertain to the most ‘classical’ type and their importance is widely known [196, 207–226, 517]. Other IHB-type interactions may also be important; for the MBK molecule, these are the O–H $\cdots\pi$, C–H $\cdots$ O and C–H $\cdots$ N interactions. The O–H $\cdots\pi$ interaction is often (but not always) weaker than O–H $\cdots$ O, N–H $\cdots$ O or O–H $\cdots$ N. It has an important influence on the preferred orientation of the portion containing a π system with respect to the rest of the molecule [518–520].

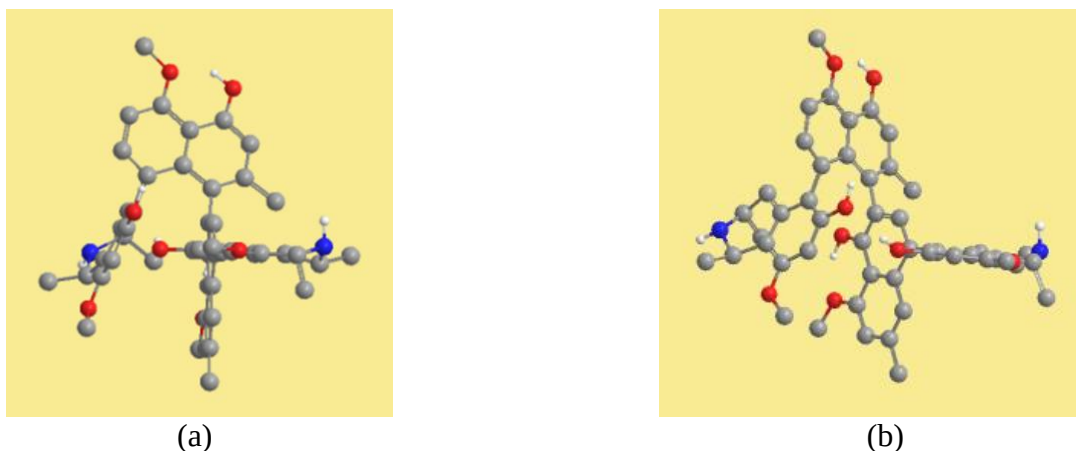


Figure 8.2. Different views of the mbandakamine molecule, to highlight the peri-peri coupling (a) and the stacking interaction between two rings (b).

The comparatively weak C–H $\cdots$ O and C–H $\cdots$ N IHBs were recognised as true H-bonds in 1982 [445, 521–525] and were identified indirectly by IR and NMR spectral data [525 –528]. These bonds play a key role in the structures of biomolecules [445, 528–533]: they determine the direction of protein chain folding [534]; they are partly responsible for the observed registration of α -helices and β -sheets [530, 535, 536]; they help stabilize a chain reversal motif [534, 537] and affect the rotation angles of tryptophan (Trp) residues in proteins [538, 539]; they also contribute to the protein-ligand binding, and play a role in small molecule packing [530]. C–H $\cdots$ O is stronger than the C–H $\cdots$ N [522] and is the dominant force for ligand selectivity [540] into certain hydrophobic pockets.

Conformers of MBK can have up to three O–H $\cdots$ O IHBs simultaneously, and also one or two N–H $\cdots$ O or O–H $\cdots$ N IHBs and some weaker IHBs (O–H $\cdots\pi$, C–H $\cdots$ O and C–H $\cdots$ N). These characteristics make the computational study of this molecule particularly intriguing.

8.2. Preparation of inputs

In the preparation of inputs, a first identification of conformers of interest was done by considering the potential energy profiles for the rotation of three relevant bonds. Each rotation was a complete rotation (360°) about the given bond in 15° steps. The starting input for all the three rotations contained the following IHBs: O43–H53...O44 and O45–H57...O46 within the naphthalene moieties (C,D and E,F), O42–H53...O47 IHB between the two isoquinoline moieties (A,B and H,G) and O42–H50... π and O47–H60... π between the isoquinoline moiety and the naphthalene moiety within each same unit.

The first scan involved the rotation of the C12–C21 bond (C13–C12–C21–C28 torsion angle). It was meant to verify how much the energy changed with the mutual orientation of the two units. Its energy profile (Fig.8.3) shows a minimum for the starting conformer, stabilised by the previously mentioned IHBs and also by stacking interaction between the (E,F) naphthalene moiety and the (B) benzene ring of the (A,B) isoquinoline moiety of the other unit. The O42–H53...O47 IHB is maintained in the first steps of the rotation, while the orientation of (E,F) and (A,B) becomes increasingly less favourable to stacking interaction, as the planes of (E,F) and (A,B) progressively diverge from being parallel. An energy maximum is reached when the C13–C12–C21–C28 torsion angle is 65° ; at this point, the O42–H53...O47 IHB has broken and the (E,F) and (A,B) ring systems have maximum divergence from being parallel. In the next steps, the energy starts decreasing, a new IHB (O47–H60...O43) starts forming and the orientation of the (E,F) and (A,B) rings becomes again more favourable to stacking interaction, until a minimum is reached when the C13–C12–C21–C28 torsion angle is 150° , corresponding to maximum stacking interaction and best geometry of the O47–H60...O43 IHB. Another maximum is reached when C13–C12–C21–C28 is 270° , corresponding to less favourable orientation of the two rings and breaking of the O47–H60...O43 IHB. The geometry when C13–C12–C21–C28 reaches 360° is identical to the starting conformer and corresponds to a minimum. The geometries corresponding to each of the 24 steps of the scan are shown in Fig.8.K.1.

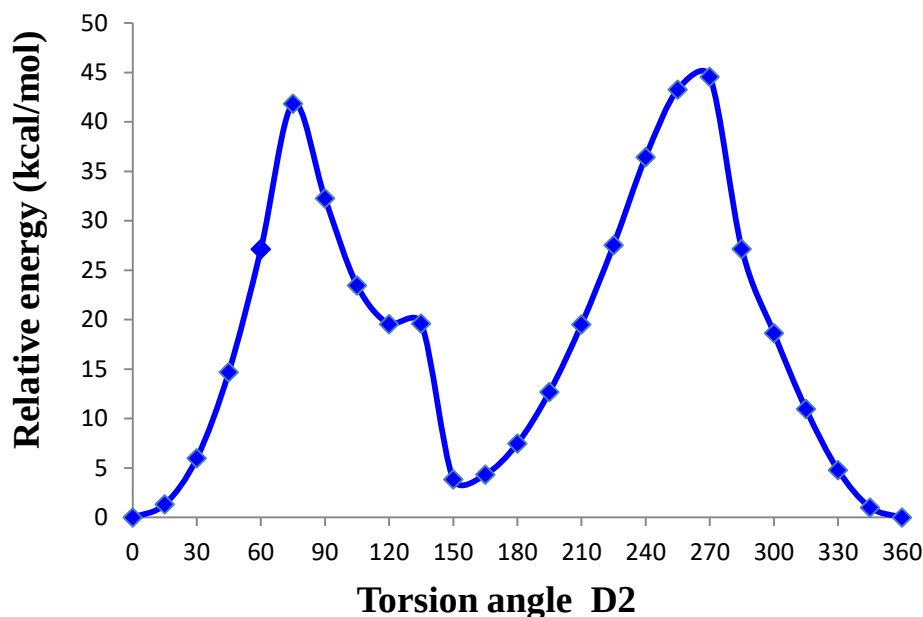


Figure 8.3. Potential energy profile of the scan of the rotation of the C12–C21 bond: energy versus C13–C12–C21–C28 torsion angle (D2)

The second scan involved the simultaneous rotations of the C12–C21 and C7–C11 bonds (C13–C12–C21–C28 and C6–C7–C11–C18 torsion angles respectively). These rotations were performed to evaluate how the energy changes with the mutual orientation of the A,B and C,D naphthalene moieties within one unit (rotation of the C7–C11 bond), and to do it for different orientations of the two units (rotation of the C12–C21 bond). It was also meant to identify how IHB interactions between the moieties may change as their orientation changes. Figure 8.4.a shows the 3D potential energy profile of this scan. Five minima can be identified, corresponding to five conformers, differing mainly by the IHBs between the units: O42–H53...O47 for two minima (as in the starting input); O47–H60...O43 in another minimum; O47–H60...O43 and O42–H53...O48 in still another minimum; and no IHBs between units in the last minimum. These five conformers differ also by the orientation of the moieties. No simultaneous rotation of the C12–C21 and C23–C31 bonds was done because it was assumed that the results will not bring new information with respect to rotating the C12–C21 and C7–C11 bonds.

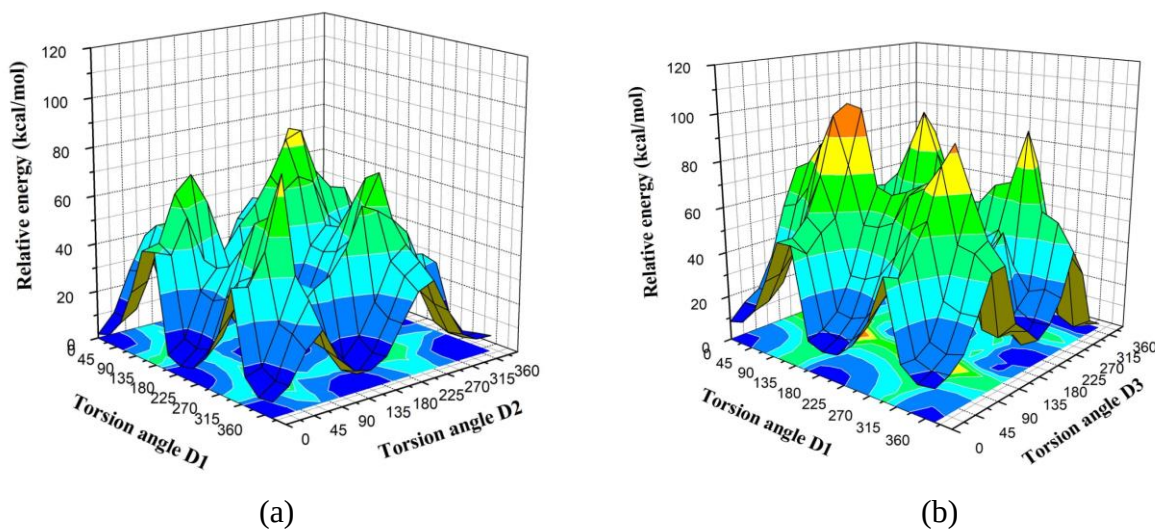


Figure 8.4. Potential energy profiles of the two scans involving simultaneous rotations of two bonds

- (a) Simultaneous scan of the C7–C11 and C21–C12 bonds. Diagram showing the potential energy versus the C6–C7–C11–C18 torsion angle (D1) and C13–C12–C21–C28 torsion angle (D2).
- (b) Simultaneous scan of the C7–C11 and C23–C31 bonds. Diagram showing the potential energy versus the C6–C7–C11–C18 torsion angle (D1) and the C22–C23–C31–C32 torsion angle (D3).

The third scan involved the bonds between the isoquinoline and the naphthalene moieties of each unit (C7–C11 and C23–C31 bonds, corresponding to the C6–C7–C11–C18 and C22–C23–C31–C32 torsion angles respectively). It was performed to check the formation or absence of IHBs for different orientation of the moieties. Figure 8.4.b shows the 3D potential energy profile of this scan. Five conformers were identified, differing by the IHBs between the units: the first conformer has the same IHB as the starting input, the second has the N36–H63···O43 IHB, the third has the O42–H53···N36 IHB, the fourth has the O47–H60···O43, and the last one as no IHB between units. The five conformers also differ by the orientation of the moieties.

The conformers identified with these rotation scans were then utilised as starting conformers to obtain others interesting geometries by rotating the OH groups, thus bringing new IHB patterns.

8.3. Naming of conformers

In order to keep track of the geometric characteristics of each conformer when analysing the results, each conformer is denoted by an acronym summarising its characterising features. The O–H $\cdots$ O, O–H $\cdots$ N and N–H $\cdots$ O IHBs and other IHB-type interactions such as O–H $\cdots\pi$, C–H $\cdots$ O and C–H $\cdots$ N are the most important factors stabilizing the conformers. Different conformers have different IHB patterns. Each IHB or IHB-type interaction is denoted by a specific lowercase letter in the acronym denoting the conformer; the letters and their meanings are listed in Table 8.1. The letters (a–h) maintain the same meanings as in previous studies [59, 62], to denote the same IHBs, while the IHBs present only in MBK are denoted by i–o, r, s, u, w and z. In the acronym denoting the conformer, the sequence of these letters is organised according to the most common strength-scale of the corresponding IHBs (from stronger to weaker: O–H $\cdots$ O, O–H $\cdots$ N or N–H $\cdots$ O, O–H $\cdots\pi$, C–H $\cdots$ O and C–H $\cdots$ N).

Table 8.1. Letters utilized in the acronyms denoting the conformers of mbandakamine A in this work, and their meanings

Letter	Meaning	Letter	Meaning
a	Presence of the O43–H55 $\cdots$ O44 IHB	f	Presence of the O47–H60 $\cdots\pi$ interaction
b	Presence of the O45–H57 $\cdots$ O46 IHB	g	Presence of the C–H50 $\cdots$ O41 interaction
j	Presence of the O43–H55 $\cdots$ O47 IHB	h	Presence of the C–H62 $\cdots$ O48 interaction
k	Presence of the O42–H53 $\cdots$ O47 IHB	i	Presence of the C–H52 $\cdots$ O48 interaction
l	Presence of the O47–H60 $\cdots$ O42 IHB	u	Presence of the C–H59 $\cdots$ O43 interaction
m	Presence of the O47–H60 $\cdots$ O43 IHB	w	Presence of the C–H52 $\cdots$ N36 interaction
n	Presence of the O42–H53 $\cdots$ O48 IHB	t	C13–C12–C21–C28 torsion angle close to +90°
o	Presence of the O47–H60 $\cdots$ O44 IHB	v	C13–C12–C21–C28 torsion angle close to -90°
s	Presence of the O42–H53 $\cdots$ N36 IHB	p	C6–C7–C11–C18 torsion angle close to +90°
r	Presence of the N36–H63 $\cdots$ O43 IHB	q	C6–C7–C11–C18 torsion angle close to -90°
z	Presence of the N36–H63 $\cdots$ O44 IHB	x	C22–C23–C31–C32 torsion angle close to +90°
c	Presence of the O43–H55 $\cdots\pi$ interaction	y	C22–C23–C31–C32 torsion angle close to -90°
e	Presence of the O42–H53 $\cdots\pi$ interaction		

As already mentioned, six types of IHBs may be present: O–H $\cdots$ O, N–H $\cdots$ O, O–H $\cdots$ N, O–H $\cdots\pi$, C–H $\cdots$ O and C–H $\cdots$ N. The O–H $\cdots$ O IHBs comprise the consecutive and sometimes cooperative O47–H60 $\cdots$ O43 and O43–H55 $\cdots$ O44 IHBs, leading to O47–H60 $\cdots$ O43–H55 $\cdots$ O44 sequence; O43–H55 $\cdots$ O44 alone; O45–H57 $\cdots$ O46; O42–H53 $\cdots$ O47; O43–H55 $\cdots$ O47; O47–H60 $\cdots$ O42 alone; and O42–H53 $\cdots$ O48. The N–H $\cdots$ O or O–H $\cdots$ N IHBs comprise O42–H53 $\cdots$ N36, N36–H60 $\cdots$ O43 and N36–H60 $\cdots$ O44. The O–H $\cdots\pi$ interaction may occur between the O–H in an isoquinoline moiety and the closest π system in the naphthalene moiety of the same unit (O42–H53 $\cdots\pi$, O47–H60 $\cdots\pi$) or between an O–H in the naphthalene moiety of one unit and the closest π system in the naphthalene moiety of the other unit (O43–H55 $\cdots\pi$). The C–H $\cdots$ O interactions may occur within an isoquinoline moiety (C–H50 $\cdots$ O41 and C–H62 $\cdots$ O48), between the naphthalene moieties (C–H59 $\cdots$ O43) and between an isoquinoline and a naphthalene moieties of different units (C–H52 $\cdots$ O47). The C–H $\cdots$ N interaction may occur between the two isoquinoline moieties (C–H52 $\cdots$ N36).

The H55 atom can be involved in the O47–H55 $\cdots$ O43 and O47–H55 $\cdots$ O43 IHBs. When they are present simultaneously, O47–H55 $\cdots$ O43 and O47–H55 $\cdots$ O43 IHBs are bifurcated on H55. A similar situation may appear with the N36–H64 $\cdots$ O43 and N36–H64 $\cdots$ O44 IHBs, which are bifurcated on H64. Bifurcation is also observed in the case of the O42–H53 $\cdots\pi$ interaction and the O42–H53 $\cdots$ O47 IHB, which have the H53 atom in common; however, the O42–H53 $\cdots$ O47 IHB has a better directionality (from the orientation of H53), whereas the O42–H53 $\cdots\pi$ interaction is only a weak interaction.

The mutual orientation of the four moieties also have significant influence on the energy of the conformers and, therefore, it is also denoted by specific letters. Lowercase letters are utilised to provide information about the torsion angles between moieties, i. e, information about their mutual orientation; they are the same as in previous studies [59, 62]. The letters ‘p’ and ‘q’ refer to the torsion angle within the R unit (angle between the A,B and the D,C rings systems, i.e., C6–C7–C11–C18); the letters ‘x’ and ‘y’ refer to the torsion angle within the S unit (angle between the E,F and the G,H rings systems, i.e., C32–C31–C23–C22); the letters ‘t’ and ‘v’ refer to the torsion angle between the R and S units (i.e., C28–C21–C12–C13). The meaning of these letters is also

explained in Table 8.1. Figure 8.5 shows representative conformers of MBK and the corresponding acronyms and the geometries of all the conformers are shown in figure 8.K2.

The four moieties tend to be mutually perpendicular, which is a known tendency for aromatic systems bonded to each other [541]. Because of this perpendicular mutual orientation, and due to the peri-peri coupling in this molecule (Fig.8.2a), the E ring tends to be parallel to the B ring, which results in a stacking interaction between the two rings. The interaction is present in nearly all conformers. Its extent– and, therefore, its stabilising effect – is different for different conformers; however, it is not easy to evaluate it and, therefore, it is not specified in the acronyms. Figure 8.6 highlights the stacking interaction through selected examples.

In the text, the acronyms denoting the conformers start with MBK, followed by the letters denoting their characteristics, whereas ‘MBK’ is not reported in tables and figures for the sake of space-saving. The following examples illustrate how the acronyms describe the characteristics of individual conformers. In the acronym MBK-b-r-z-c-e-f-g-h-v-q-y, b represents the O–H $\cdots$ O IHB (O45–H57 $\cdots$ O46); r and z denote the N–H $\cdots$ O IHBs (N36–H63 $\cdots$ O43 and N36–H63 $\cdots$ O44 IHBs respectively); c, e and f represent the O–H $\cdots$ π interactions (O43–H55 $\cdots$ π , O42–H53 $\cdots$ π and O47–H60 $\cdots$ π respectively); g and h denote the C–H $\cdots$ O interactions (C–H50 $\cdots$ O41 and C–H62 $\cdots$ O48) and v, q and y denote the orientations of the moieties, with v (the C13–C12–C21–C28 torsion angle close to -90°), q (C6–C7–C11–C18 torsion angle close to -90°) and y (C22–C23–C31–C32 torsion angle close to -90°). In the acronym MBK-a-b-l-g-h-v-p-y; a, b and l represent the O–H $\cdots$ O IHBs (O43–H51 $\cdots$ O44, O45–H53 $\cdots$ O46 and O47–H55 $\cdots$ O42); g and h represent the C–H $\cdots$ O interactions (C–H50 $\cdots$ O41 and C–H62 $\cdots$ O48) and v, q, p represent the orientation of the moieties with v (the C13–C12–C21–C28 torsion angle close to -90°), q (the C6–C7–C11–C18 torsion angle close to -90°) and y (the C22–C23–C31–C32 torsion angle close to -90°).

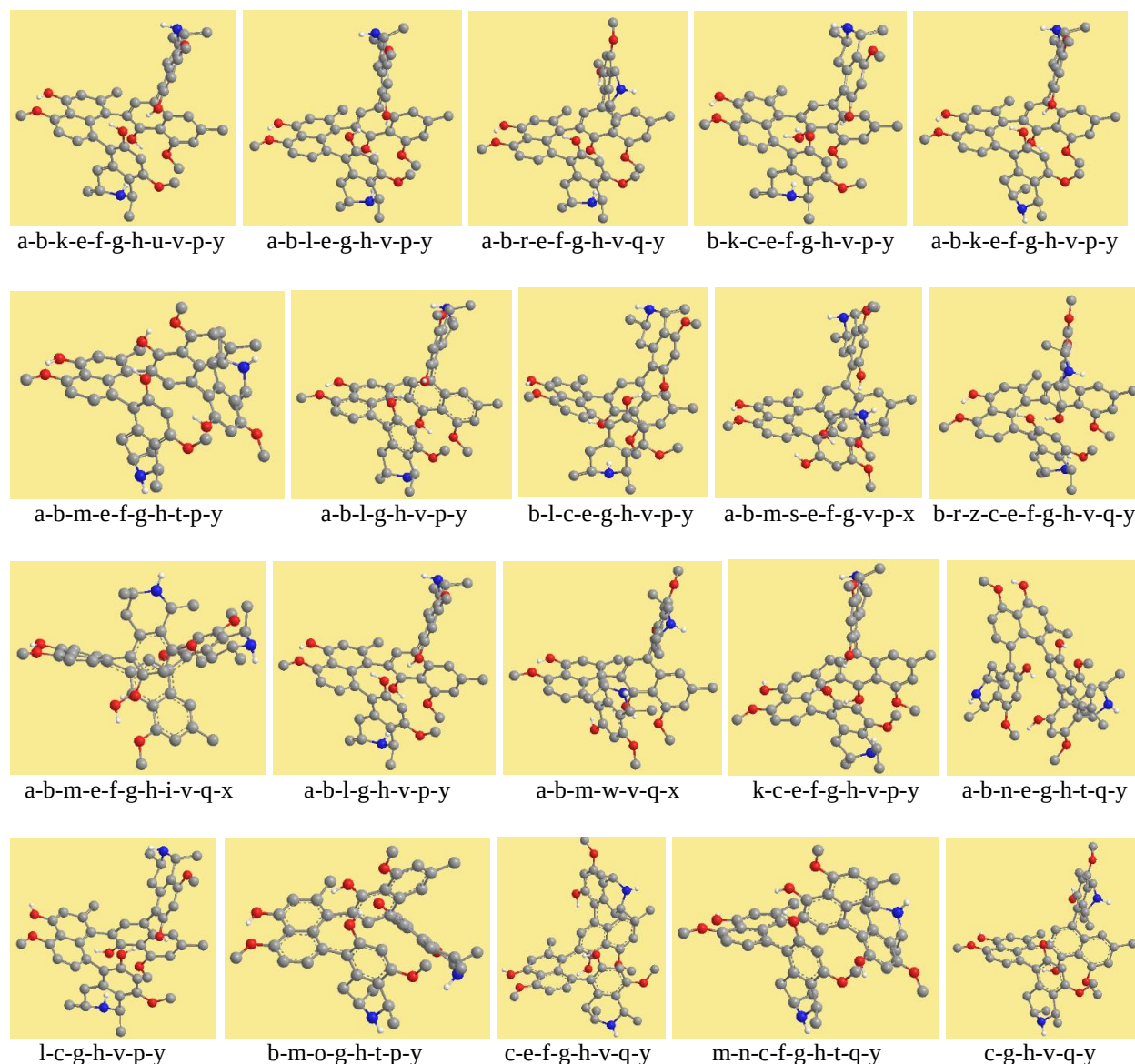


Figure 8.5. Optimized geometries of representative conformers of the mbandakamine A molecule and acronyms denoting them

HF/6-31G(d,p) results. The images show the main combinations of IHBs and different moieties' orientations which may be present in the conformers of mbandakamine A. The initial part of the acronyms is not reported under the images, because of space reasons; it is the same for all the conformers (MBK).

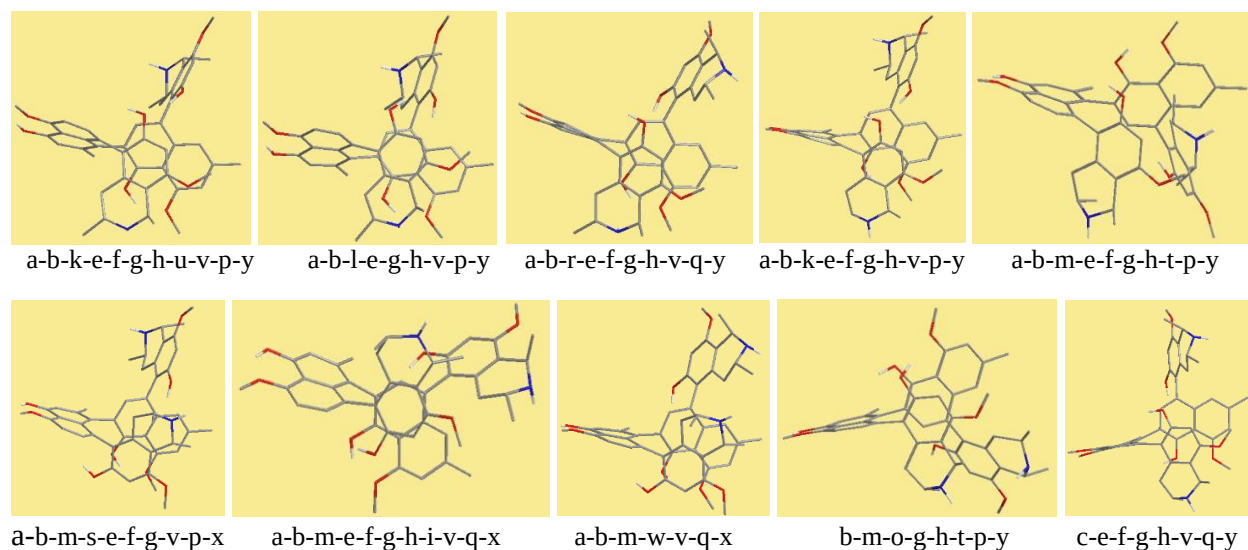


Figure 8.6. Optimized geometries of selected conformers of mbandakamine A highlighting the π - π stacking interaction between the isoquinoline moiety (A,B) and the naphthalene moiety (E,F) in conformers selected among those shown in Fig.8.5

8.4. Results *in vacuo*

107 conformers were identified, and the frequency calculations confirm that they correspond to true minima. Table 8.2 reports the relative energies of selected conformers of MBK *in vacuo* and in the three solvents considered. The reported conformers include the first ten lower-energy ones and representative conformers of other types (other combinations of IHBs) not appearing among the first ten.

The IHB patterns (numbers and types of IHBs present in a conformer) are the dominant stabilizing factors. Others factors influencing conformational preferences are the mutual orientation of the four moieties, which prefer to be perpendicular to one another, and the presence of stacking interaction, as described in the previous section. The relative energies of all the conformers are reported in Table 8.K1.

Table 8.2. Relative energies of the selected conformers of mbandakamine A shown in Fig. 8.5

HF/6-31G(d,p) and DFT/B3LYP/6-31+G(d,p) results *in vacuo* and in the three solvents considered. The methods are respectively denoted as HF and DFT in the columns' headings. The results *in vacuo* are from full optimization calculations; the results in solution are from single point PCM calculations on the *in-vacuo*-optimized geometries. The conformers are listed in order of increasing relative energies in the HF results *in vacuo*.

Conformer	Relative energy (kcal/mol)							
	HF				DFT			
	vac	chlrf	actn	aq	vac	chlrf	actn	aq
a-b-k-e-f-g-h-u-v-p-y	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
a-b-l-e-g-h-u-v-p-y	2.308	3.433	2.538	2.750	2.157	2.384	2.514	2.205
a-b-r-e-f-g-h-v-q-y	3.405	3.584	3.583	4.218	3.155	3.290	3.318	3.497
b-k-c-e-f-g-h-v-p-y	5.101	5.580	5.422	5.530	5.398	5.653	5.682	5.757
a-b-k-e-f-g-h-v-p-y	5.382	4.867	4.858	3.902	5.170	4.868	4.604	3.039
a-b-m-e-f-g-h-t-p-y	5.891	5.849	5.888	4.664	5.968	6.057	5.928	4.013
a-b-l-g-h-v-p-y	5.596	3.856	2.796	1.613	5.331	3.614	2.759	1.004
b-l-c-e-g-h-v-p-y	6.325	8.056	7.832	7.648	6.713	7.694	7.932	8.161
a-b-m-s-e-f-g-v-p-x	6.661	6.968	6.388	5.758	5.639	5.509	5.360	3.804
b-r-z-c-e-f-g-h-v-q-y	8.104	9.662	8.676	8.417	8.329	8.879	9.027	9.096
a-b-m-e-f-g-h-i-v-q-x	9.985	10.063	8.877	7.629	8.584	8.076	7.782	6.176
a-b-l-g-h-v-p-y	10.780	8.495	7.385	4.408	10.303	8.238	7.113	3.809
a-b-m-g-h-w-v-q-x	11.277	11.061	11.321	11.047	10.960	10.800	10.697	9.788
k-c-e-f-g-h-v-p-y	12.258	11.851	11.498	9.434	12.858	12.466	12.047	9.626
a-b-n-e-g-h-t-q-y	16.591	15.044	13.802	10.722	15.949	10.914	10.155	5.736
l-c-g-h-v-p-y	17.443	17.440	15.949	14.073	17.728	15.908	14.676	— ^a
b-m-o-g-h-t-p-y	20.972	20.028	19.245	17.210	20.729	— ^a	19.113	15.720
c-e-f-g-h-v-q-y	21.029	20.280	19.788	16.752	21.142	20.684	20.206	16.634
m-n-c-f-g-h-t-q-y	23.389	22.901	22.100	16.760	23.456	23.049	22.439	16.608
c-g-h-v-q-y	29.358	27.392	26.082	19.821	29.154	27.471	26.224	18.800

^a The calculation for this conformer did not converge in the given solvent.

Different orientations of the moieties give rise to different IHB patterns; the correspondence is listed in Table 8.3 and visualized in Fig. 8.7 and Fig.8.8. The v, p and y orientations enable the O42–H53···O47 and O47–H60···O42 IHBs. The t or v, p or q and y or x orientations enable the O47–H60···O43 IHB. The t, q and y orientations enable the O42–H53···O48 IHB. The t, q or p and y orientations enable the O47–H60···O44 IHB. The v, p and x enable the O42–H53···N36 IHB. The v, q and y orientations enable the N36–H63···O43 and N36–H63···O44 IHBs.

Table 8.3. Different type of IHBs present in mbandakamine A

Category	Sub-categories	IHBs
IHBs between units	IHBs between the two isoquinoline moieties (A,B and H,G)	O42–H53...O47, O47–H60...O42, O42–H53...O48, O42–H53...N36.
	IHBs between an isoquinoline moiety and a naphthalene moiety (G,H and C,D)	O43–H55...O47, O47–H60...O43 O47–H60...O44, N36–H60...O43, N36–H60...O44.
IHBs within the same unit	IHBs within a naphthalene moiety (C,D or E,F)	O43–H55...O44, O45–H57...O46.

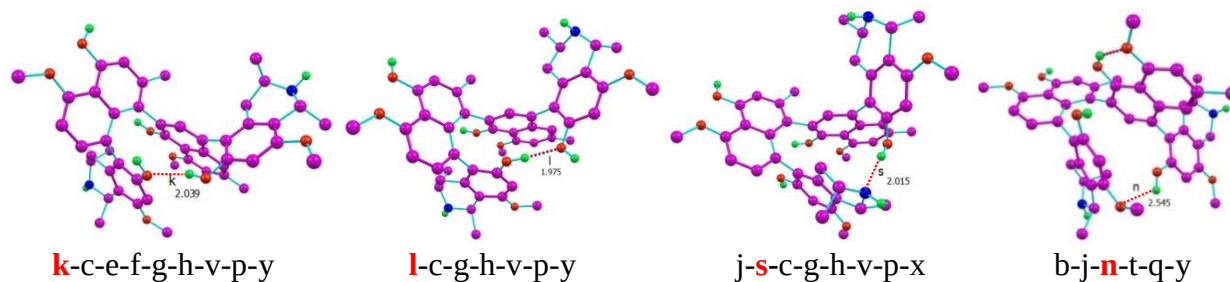
Strictly speaking, there is an H-bond when the IHB length is not greater than the sum of the Van der Waals radii of the H atom and its acceptor; this sum is 2.7 Å both for O and H and for N and H [196, 521]. On the other hand, the directionality of the two atoms may suggest the presence of a weak IHB even when the distance is longer [195, 196]. Some authors consider weaker H-bonds with a length up to 3.2 Å [195, 205, 206, 463].

The number, type and strength of the IHBs are the dominant stabilising factors. However, it is not easy to evaluate the energy of an IHB [514], because its removal causes geometry changes in the molecule and, therefore, the IHB energy is not equal to the energy difference between the conformer in which it is absent and the conformer in which it is present. The easiest criterion that can be used to reliably compare the energy of IHBs of the same type relates to its bond length: the shorter the IHB length, the stronger the IHB. Lower energy conformers of MBK have shorter IHBs than higher energy ones.

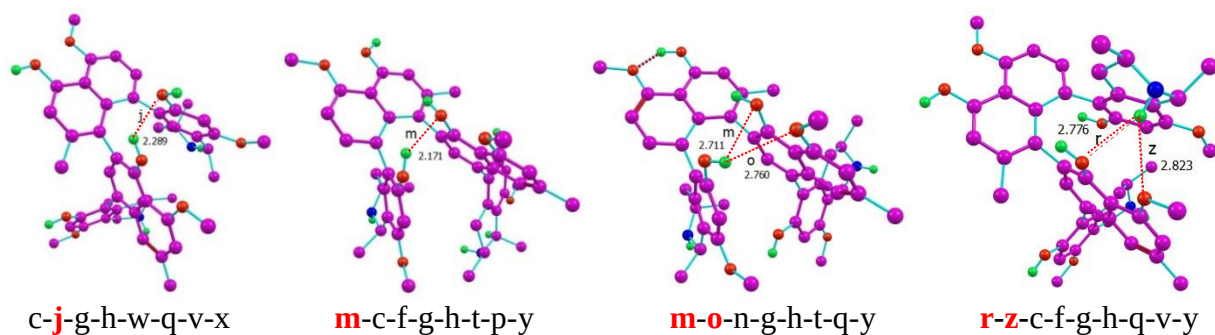
The first three lower-energy conformers have energies less than 3.5 kcal/mol (which is a cautious threshold for a conformer to be considered as potentially responsible for the biological activity of a compound). The first two lowest energy conformers have three O–H...O IHBs (O43–H55...O44, O45–H57...O46 and either O42–H53...O47 or O47–H60...O42), the O–H... π (O42–H53... π) interaction, the C–H...O (C–H52...O41 and C–H61...O47) interactions;

A) IHBs between units

1) IHBs between the two isoquinoline moieties (A,B and H,G)



2) Between an isoquinoline and a naphthalene moieties (C,D and G,H)



B) IHBs within the same unit

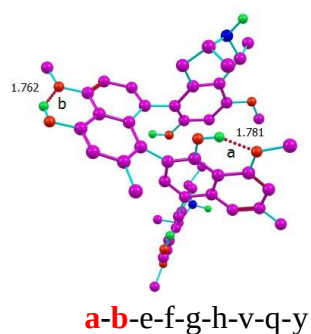
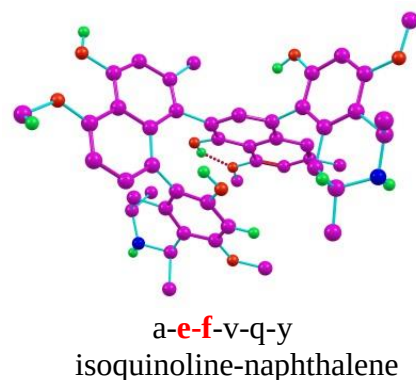
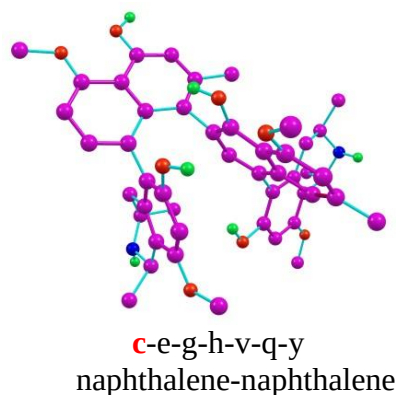


Figure 8.7. Different types of O–H···O (or O–H···N, N–H···O) IHBs that may be present in the conformers of mbandakamine A

The IHBs are represented by dotted lines and their length values (Å) are shown nearby. In the acronym denoting the conformers, the letter/s corresponding to the given H-bond/s are written in red bold.

A) The O—H $\cdots$ π interactions



B) The C—H $\cdots$ O and C—H $\cdots$ N interactions

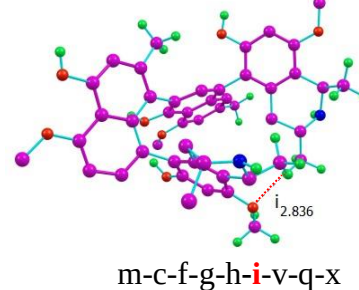
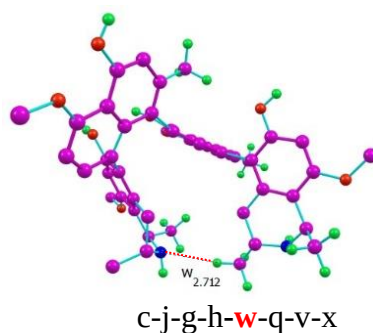
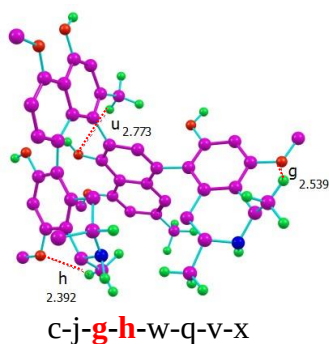


Figure 8.8. Different IHB-type interactions that may be present in the conformers of mbandakamine A

The C—H $\cdots$ O and C—H $\cdots$ N IHBs are represented by dotted lines and their length values ($\text{\AA}$) are shown nearby. In the acronym denoting the conformers, the letter/s corresponding to the given H-bond/s are written in bold.

their moieties are oriented in the same way and, therefore, they have the same stacking interaction. The lowest energy conformer differs from the second-lowest energy one by one of the O—H $\cdots$ O IHBs (O42—H53 $\cdots$ O47 and O47—H60 $\cdots$ O42 respectively) and by having an additional O—H $\cdots$ π interaction (O47—H60 $\cdots$ π). Their energy difference is 2.308 kcal/mol. The third lowest-energy conformer has the O43—H55 $\cdots$ O44, O45—H57 $\cdots$ O46 and N36—H63 $\cdots$ O43 IHBs and the moieties are oriented differently from the two lowest-energy ones. It can also be noted that the

O43–H55...O44 and O45–H57...O46 IHBs have nearly the same length in the two lowest energy conformers (1.76 Å/HF for O43–H55...O44 IHB and 1.75 Å/HF for O45–H57...O46 IHB), while the bond length of the O42–H53...O47 IHB (lowest energy conformer) is shorter than the bond length of the O47–H60...O42 IHB (third conformer) and the N36–H63...O43 IHB (third conformer) is weak (bond length 3.08 Å/HF).

It is not easy to interpret the energy increase in each of the other conformers in terms of the number and types of IHBs, because several high energy conformers have more IHBs than the lower energy ones. It would be necessary to be able to evaluate the energy of each IHB and also the extent of the stacking interaction in different conformers, which is not possible for the already-explained reasons. One can evaluate the energy increase caused by the removal of a certain IHB, but the increase is not equal to the IHB energy, because of the changes in the molecular geometry accompanying the removal. The removal of the O45–H57...O46 IHB causes a 2.199–12.421 kcal/mol energy increase; the increase is smaller in conformers having also the N36–H63...O43 IHB. The removal of the O42–H53... π interaction brings a 1.695–4.527 kcal/mol energy increase, with smaller differences corresponding to conformers in which the O42–H53...N36 IHB is present. The removal of the O47–H60... π interaction brings a 2.038–5.111 kcal/mol energy difference, with smaller differences corresponding to conformers in which the O43–H55...O47 IHB is present. The removal of the O42–H53... π or O47–H60... π interaction brings up a 0.138–3.916 kcal/mol energy increase. The simultaneous removal of O45–H57...O46 and O42–H53...O48 brings a 5.476 kcal/mol energy increase. The removal of O42–H53...O48 brings a 2.333 kcal/mol energy increase. The simultaneous removal of the O45–H57...O46, O47–H60...O44 IHBs and the O47–H60... π interaction brings a 14.004 kcal/mol energy increase; the simultaneous removal of the O47–H60... π interaction and the N36–H63...O43 IHB brings a 7.371 kcal/mol energy increase and the simultaneous removal of O47–H60...O43, O47–H60... π and O42–H53... π brings a 10.818 kcal/mol energy increase. It is also important to note that, in the case of MBK, the removal of some IHBs may cause the formation of some others. For example, the removal of the O43–H55...O44 IHB brings about the O43–H55... π interaction, with a 1.094–5.460/HF kcal/mol energy increase (this phenomenon was also observed in molecules considered in previous studies [52, 53]).

It is also difficult to evaluate the influence of the orientation of the different moieties on the energy of the conformers. One can only check that the energy changes accompanying some orientation changes. For instance, the change from p to q orientation brings a 4.352 kcal/mol energy increase, and the change from t-p to v-q orientation brings a 2–3.6 kcal/mol energy increase.

Table 8.4 shows the ranges of the IHB lengths. On the basis of their bond lengths, O...O distances and bond angles (Table 8.K2), the IHBs present in MBK vary from moderate to weak IHBs. The O43–H55...O44 and O45–H57...O46 IHBs (which form within the same unit) have the shortest IHB length, making them the strongest IHBs in MBK. O42–H53...O47 and O47–H60...O42 IHBs (which form between the two isoquinoline moieties) are moderate IHBs. These two types of IHBs are favoured by the v-p-y orientation of the moieties, and also by a presence or absence of an O–H... π interaction.

In some conformers, the presence of the O42–H53... π interaction favours the presence of O42–H53...O47 IHB and, in some others, the absence of O47–H60... π interaction favours the formation of the O47–H60...O42 IHB. The O47–H60...O43 IHB (which forms between an isoquinoline and a naphthalene in different units) can be consecutive to the O43–H55...O44 IHB; when O43–H55...O44 is moderate, it strengthens the O43–H55...O44 IHB (causing its length to shorten), whereas, when it is weak, it does not influence the length of the O43–H55...O44 IHB; it can be inferred that the O47–H60...O43 and O43–H55...O44 IHBs are cooperative (besides being consecutive) only when O47–H60...O43 is not too weak. Their bond lengths (Table 8.4) suggest that the O42–H53...O48, O43–H55...O47 and O47–H60...O44 IHBs are weak.

The O42–H53...N36 IHB is favoured by the v-p-x orientation. It is moderate in conformers without the O42–H53... π interaction, where O42–H53 can take optimal directionality towards N36. It is weaker in conformers with the O42–H53... π interaction because then O42–H53 is strongly engaged in the H53... π interaction and the directionality for the O42–H53...N36 IHB is less favourable. The N36–H63...O43 and N36–H63...O44 IHBs are weak IHBs.

Table 8.4. Ranges of the length of the IHBs in the calculated conformers of mbandakamine A

HF/6-31G(d,p) and DFT/B3LYP/6-31+G(d,p) results *in vacuo*, respectively denoted as HF and DFT in the column headings. For the O–H $\cdots\pi$ interaction, the length is taken as the distance between the H atom and the closest C atom in the π system, which is indicated in parentheses after the π symbol.

IHB	OH $\cdots$ O (Å) or OH $\cdots$ N(Å) or NH $\cdots$ O (Å) or OH $\cdots$ C (Å)		IHB	OH $\cdots$ O (Å) or OH $\cdots$ N(Å) or NH $\cdots$ O (Å) or OH $\cdots$ C (Å)	
	HF	DFT		HF	DFT
O43–H55 $\cdots$ O44	1.752–1.804	1.700–1.751	C–H50 $\cdots$ O41	2.390–2.547	2.273–2.560
O45–H57 $\cdots$ O46	1.742–1.800	1.694–1.748	C–H62 $\cdots$ O48	2.318–2.567	2.277–2.561
O43–H55 $\cdots$ O47	2.271–2.466	2.095–2.507	C–H52 $\cdots$ O47	2.814–2.856	2.906–3.427
O42–H53 $\cdots$ O47	2.016–2.078	1.934–1.968	C–H59 $\cdots$ O43	2.594–2.773	2.527–2.747
O47–H60 $\cdots$ O42	1.973–2.252	1.880–2.150	C–H52 $\cdots$ N36	2.687–2.728	2.648–2.690
O47–H60 $\cdots$ O43	2.198–2.926	2.041–3.246			
O42–H53 $\cdots$ O48	2.560–3.097	2.354–3.161	H55 $\cdots\pi$ (C21)	2.254–2.445	2.215–2.489
O47–H60 $\cdots$ O44	2.643–3.002	2.300–3.276	H53 $\cdots\pi$ (C11)	2.189–2.580	2.273–2.652
O42–H53 $\cdots$ N36	1.997–2.335	1.776–2.096	H60 $\cdots\pi$ (C23)	2.329–2.715	2.283–2.812
N36–H63 $\cdots$ O43	2.745–3.074	2.711–3.142			
N36–H63 $\cdots$ O44	2.747–2.891	2.782–2.968			

No bond length can be defined for the O–H $\cdots\pi$ interaction, as the acceptor is a whole π system and not an individual atom. It may be convenient to consider the distance between the H atom of the donor OH and the closest C atom in the aromatic system. The ranges of the distances thus defined are reported in Table 8.4 and the complete data are reported in Table 8.K3. The H $\cdots$ C distance is slightly shorter when the interaction involves an O–H in the naphthalene moiety of one unit and the closest π system in the naphthalene moiety of the other unit (O43–H55 $\cdots\pi$ interaction) than when it involves an O–H in the isoquinoline moiety and the closest π system in the naphthalene moiety of the same unit (O42–H53 $\cdots\pi$ and O47–H60 $\cdots\pi$ interactions).

Table 8.4 reports also the ranges of the H $\cdots$ O distance for the C–H $\cdots$ O interactions within the isoquinoline moiety (C–H49 $\cdots$ O41 and C–H62 $\cdots$ O48), between the two naphthalene moieties (C–H59 $\cdots$ O43) and between the two isoquinoline moieties (C–H52 $\cdots$ O47) and the ranges of the H $\cdots$ N distance for the C–H $\cdots$ N interactions between the two isoquinoline moieties (C–H52 $\cdots$ N36). These distances are considerably longer than the H $\cdots$ O distance for O–H $\cdots$ O

IHBs, consistent with the fact that the C–H $\cdots$ O and C–H $\cdots$ N interactions are considerably weaker. The H $\cdots$ O is shorter for the C–H $\cdots$ O interactions within the isoquinoline moiety (C–H₄₉ $\cdots$ O₄₁ and C–H₆₂ $\cdots$ O₄₈) and longer for the C–H $\cdots$ O interactions between isoquinoline moieties. Table 8.K4 reports the C–H $\cdots$ O parameters for all the conformers.

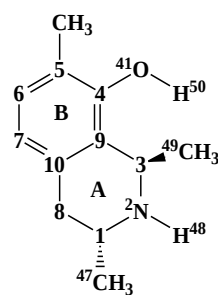
Table 8.5 reports the ranges of the calculated harmonic vibrational frequencies of the O–H and the N–H bonds and the complete data are reported in Table 8.K5. In this study, only the HF frequencies are available, as frequency calculation with the DFT method did not complete, probably due to the size of the molecule. For a molecule having IHBs, it is interesting to consider the red-shift (lowering of the vibrational frequency of the donor OH) caused by the IHBs. The red shift is evaluated with respect to the frequency of a free O–H or N–H of the same type. Since the OHs in MBK are never free, two model structures with free OHs and with the other features similar to those of the moieties in MBK (including a CH₃ to mimic the presence of other moieties attached to the one considered) were used to calculate reference frequencies; they are shown in Fig.8.9. The ranges of the red- shifts of the four OHs (O₄₂–H₅₃, O₄₃–H₅₅, O₄₅–H₅₇ and O₄₇–H₆₀) and of one of the NHs (N₃₆–H₆₃) present in MBK, when they are engaged in the different types of IHBs, are reported in Table 8.5. The values of the red shifts for O–H $\cdots$ O IHBs and the O–H $\cdots$ π interactions are comparable, which is consistent with their stabilizing effect (although the strength of the O–H $\cdots$ O IHB is expected to be greater than that of the O–H $\cdots$ π IHB), while the red shifts for N–H $\cdots$ O is greater than that of the O–H $\cdots$ O and O–H $\cdots$ π IHB. The red shift of O₄₂–H₅₃ is greater than those of the three others OHs when it forms the O₄₂–H₅₃ $\cdots$ N₃₆ IHB. Table 8.K6 reports the complete data of the red shift for the calculated conformers.

Table 8.6 reports the values of the relative energies corrected for ZPE and of the ZPE corrections for the conformers listed in Table 8.2. The ZPE corrections are close for all the conformers. Their range (kcal/mol) is 614.69–616.65 with the greater values corresponding to conformers having shorter IHB bond lengths. The relative energies corrected for ZPE have the same trends as the uncorrected ones, with only few exceptions. Table 8.K7 reports the ZPE for all the conformers. Table 8.7 reports the values of the dipole moment for the conformers listed in Table 8.2. Table 8.K8 reports the dipole moment for all the conformers.

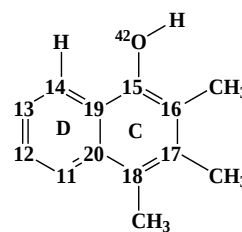
Table 8.5. Ranges of the harmonic vibrational frequencies of the O–H and N–H bonds in mbandakamine A and of the red shifts caused by IHBs

HF results *in vacuo*. The frequencies are scaled by 0.9024 [447]

OH or NH	Frequency (cm ⁻¹)	Red shift when engaged in O–H···O IHB	Red shift when engaged in O–H··· π interactions
O42—H53	3493.75–3795.86	24.99–260.03	20.91–102.77
O43—H55	3696.37–3761.00	8.73–71.75	38.33–81.50
O45—H57	3723.71–3782.44	26.13–44–41	–
O47—H60	3698.79–3804.53	0.99–69.33	24.48–100.54
N36—H63	3373.03 – 3419.47	385.18–401.40	–



(a)



(b)

Figure 8.9. Model structures used to calculate reference frequencies for the vibration of free O41–H50 and O46–H50 (a) or free O43–H52 and O44–H54 (b)

The ranges (Debye) of the values of the dipole moments *in vacuo* are 0.44–7.59/HF and 0.51–7.13/DFT. Both the magnitude and the direction of the dipole moment are largely influenced by the orientation of the OH groups (although the orientation of the aromatic rings also plays a role). The same phenomenon was observed for the alkaloids considered in previous studies [51–53] and is common to all molecules containing OH groups. The number, type and the strength of the IHBs influence the dipole moment of a conformer. The first two lower energy conformers have higher value of the dipole moment than the third lower-energy conformer. In the first two, there are three moderate O–H···O IHBs, while, in the third one, there are two O–H···O IHBs (which are moderate) and one N–H···O IHB (which is weak). Conformers with only O–H···O IHBs have

greater values of the dipole moments (range 5–7D/HF), except the conformers MBK-a-b-g-h-v-q-y, MBK-a-g-h-i-q-v-x and MBK-a-g-h-t-p-y.

Conformers with only O–H $\cdots\pi$ interactions have 4–6D/HF dipole moments, except the conformer MBK-c-e-g-h-v-q-y, whose value is smaller (~ 2 D/HF). Conformers with one or two O–H $\cdots$ O or N–H $\cdots$ O IHBs and all the possible O–H $\cdots\pi$ interactions (O43–H55 $\cdots\pi$, O42–H53 $\cdots\pi$ and O47–H60 $\cdots\pi$) have dipole moments in the 3–4D range, with the exception of MBK-m-c-e-f-g-h-i-v-q-v-x and MBK-b-j-c-e-f-g-h-w-v-q-x, whose dipole moment is ~ 5 D. The conformer with the smallest value of the dipole moment (0.43/HF) is a conformer with the presence of weak IHBs (O47–H60 $\cdots$ O43 and O42–H53 $\cdots$ O48) and one O–H $\cdots\pi$ interaction (O43–H55 $\cdots\pi$), and the conformer with the highest value of the dipole moment (7.59D/HF) has the presence of two moderate IHBs (O43–H55 $\cdots$ O44 and O45–H57 $\cdots$ O46), one weak IHB (O42–H53 $\cdots$ O48) and one O–H $\cdots\pi$ interaction (O42–H53 $\cdots\pi$).

Table 8.8 reports the HOMO-LUMO energy gaps for the conformers listed in Table 8.2. The number, type and strength of the IHBs present in a conformer influence the HOMO-LUMO energy gaps. Table 8.K9 reports the HOMO-LUMO energy gaps for all the conformers.

Table 8.6. Relative energy ($\Delta E_{\text{correct}}$, kcal/mol) corrected for ZPE and ZPE corrections (ZPE_{corr} , kcal/mol) for conformers of mbandakamine A selected among those reported in Table 8.2

Results from HF/6-31G(d,p) frequency calculations.

conformer	$\Delta E_{\text{correct}}$	ZPE_{corr}	conformer	$E_{\text{corrected}}$	ZPE_{corr}
a-b-k-e-f-g-h-u-v-p-y	0.000	616.436	a-b-m-e-f-g-h-i-v-q-x	10.200	616.651
a-b-l-e-g-h-u-v-p-y	2.435	616.563	a-b-l-g-h-v-p-y	10.567	616.223
a-b-r-e-f-g-h-v-q-y	3.333	616.364	a-b-m-w-v-q-x	10.862	616.020
b-k-c-e-f-g-h-v-p-y	5.043	616.378	k-c-e-f-g-h-v-p-y	11.795	615.972
a-b-k-e-f-g-h-v-p-y	5.396	616.450	l-c-g-h-v-p-y	16.760	615.702
a-b-m-e-f-g-h-t-p-y	5.745	616.290	b-m-o-g-h-t-p-y	20.236	615.643
a-b-l-g-h-v-p-y	5.321	616.160	m-n-c-f-g-h-t-q-y	22.150	615.197
b-l-c-e-g-h-v-p-y	6.395	616.506	c-g-h-v-q-y	27.968	615.047
a-b-m-s-e-f-g-v-p-x	6.382	616.158			
b-r-z-c-e-f-g-h-v-q-y	8.035	616.366			

The first three lower energy conformers are among the conformers with greater values of the HOMO-LUMO energy gap. Conformers with only O–H···O IHBs have greater values of the HOMO-LUMO energy gap, except for MBK-a-b-g-g-h-t-p-y, which has a small value.

Table 8.7 Dipole moment of the conformers of mbandakamine A listed in Table 8.2

HF/6-31G(d,p) and (DFT/B3LYP/6-31+G(d,p) results, respectively denoted as HF and DFT in the column headings. The results *in vacuo* are from full optimization calculations, the results in solution are from single point PCM calculations on the *in-vacuo*-optimized geometries.

Conformer	Dipole moment (Debye)							
	HF				DFT			
	vac	chlrf	actn	aq	vac	chlrf	actn	aq
a-b-k-e-f-g-h-u-v-p-y	3.11	3.55	3.74	3.98	3.14	3.68	3.90	4.08
a-b-l-e-g-h-u-v-p-y	4.36	5.18	5.55	5.85	3.97	4.90	5.35	5.70
a-b-r-e-f-g-h-v-q-y	1.76	2.29	2.60	2.79	1.62	2.15	2.46	2.66
b-k-c-e-f-g-h-v-p-y	4.83	5.49	5.75	6.28	5.01	5.79	6.14	6.71
a-b-k-e-f-g-h-v-p-y	3.91	4.56	4.83	5.08	4.20	5.03	5.38	5.67
a-b-m-e-f-g-h-t-p-y	5.63	6.38	6.62	6.69	5.38	6.22	6.51	6.53
a-b-l-g-h-v-p-y	6.71	7.94	8.46	8.93	6.30	7.71	8.38	8.87
b-l-c-e-g-h-v-p-y	3.43	3.91	4.11	4.43	3.25	3.82	4.10	4.52
a-b-m-s-e-f-g-v-p-x	5.51	6.32	6.61	6.91	5.65	6.65	7.07	7.49
b-r-z-c-e-f-g-h-v-q-y	2.83	3.16	3.23	3.36	3.18	3.65	3.81	3.94
a-b-m-e-f-g-h-i-v-q-x	6.40	7.30	7.70	7.80	6.07	7.10	7.58	7.71
a-b-l-g-h-v-p-y	6.24	7.51	8.12	8.53	5.73	7.16	7.88	8.36
a-b-m-w-v-q-x	4.69	5.48	5.84	6.07	4.04	4.84	5.22	5.44
k-c-e-f-g-h-v-p-y	3.32	3.85	4.11	4.55	3.52	4.18	4.46	4.90
a-b-n-e-g-h-t-q-y	7.59	9.03	9.72	10.53	7.14	8.61	9.30	9.75
l-c-g-h-v-p-y	4.50	5.10	5.33	5.44	4.25	4.93	5.19	1.42
b-m-o-g-h-t-p-y	0.54	0.51	0.49	0.69	0.67	^a	0.66	0.97
c-e-f-g-h-v-q-y	3.63	4.12	4.28	4.58	3.82	4.50	4.73	5.08
m-n-c-f-g-h-t-q-y	0.44	0.60	0.92	1.44	0.42	0.37	0.70	
c-g-h-v-q-y	4.33	5.02	5.28	5.59	4.19	5.04	5.37	5.81

^a The calculation for this conformer did not converge in the given solvent.

Conformers with one or two O–H···O or N–H···O IHBs and all the possible O–H··· π interactions (O43–H55··· π , O42–H53··· π and O47–H60··· π) have small values of the HOMO-LUMO energy gap and the few conformers with only the O–H··· π interaction have small value of the HOMO-LUMO energy gaps (with the exception of MBK-c-e-g-h-v-q-y and MBK-c-g-h-v-q). Figure 8.10 shows the shapes of the HOMO and LUMO orbitals for some representative conformers of MBK. Figure 8.K3 and 8.K4 shows respectively the shapes of the HOMO and LUMO orbitals for all the conformers. The shapes indicate greater presence of electron density in the naphthalene moieties in most of the conformers.

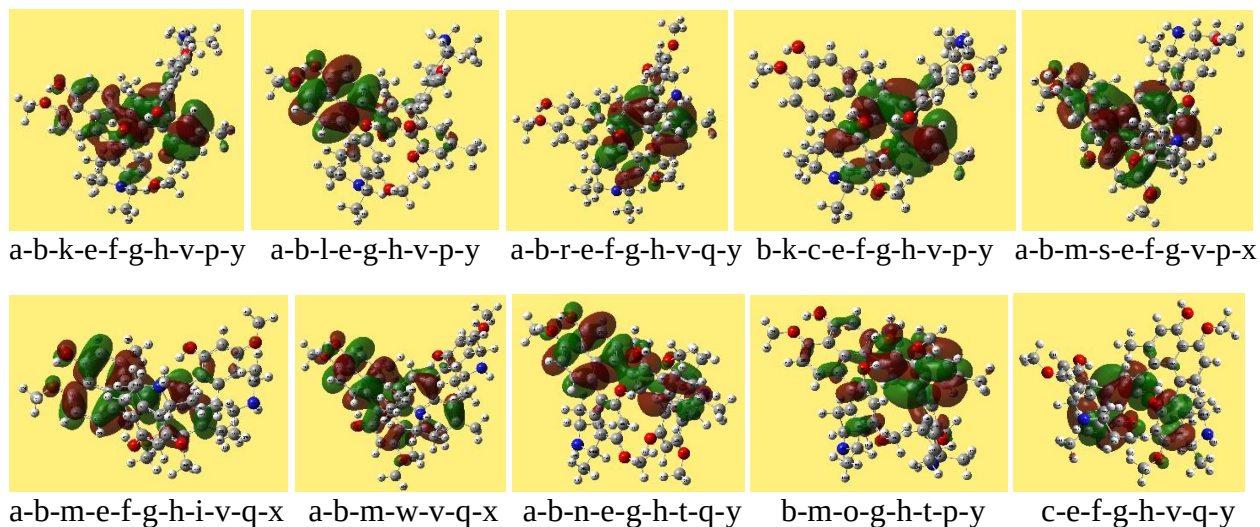
Table 8.8. HOMO-LUMO energy gap of the conformers of mbandakamine A reported in Table 8.2, *in vacuo* and in the three solvents considered

HF/6-31G(d,p) and (DFT/B3LYP/6-31+G(d,p) results, respectively denoted as HF and DFT in the column headings. The results *in vacuo* are from full optimization calculations, the results in solution are from single point PCM calculations on the *in-vacuo*-optimized geometries.

Conformer	HOMO-LUMO energy gap (kcal/mol)							
	HF				DFT			
	vac	chlrf	actn	aq	vac	chlrf	actn	aq
a-b-k-e-f-g-h-u-v-p-y	226.9	226.2	226.8	226.7	91.6	91.7	91.7	91.7
a-b-l-e-g-h-u-v-p-y	223.3	224.9	226.4	227.0	89.4	91.7	92.4	92.9
a-b-r-e-f-g-h-v-q-y	228.8	228.0	228.4	228.1	92.5	92.8	92.7	92.6
b-k-c-e-f-g-h-v-p-y	219.8	221.1	222.7	223.9	84.0	86.2	87.1	88.3
a-b-k-e-f-g-h-v-p-y	227.7	227.5	227.2	227.3	92.2	92.1	92.0	92.0
a-b-m-e-f-g-h-t-p-y	227.3	227.4	227.3	227.4	94.4	94.3	94.0	94.1
a-b-l-g-h-v-p-y	226.1	228.2	228.1	227.4	92.1	93.8	93.4	92.7
b-l-c-e-g-h-v-p-y	228.1	227.6	227.4	227.3	92.4	92.0	91.8	91.9
a-b-m-s-e-f-g-v-p-x	229.1	228.6	228.3	228.2	93.2	92.7	92.5	92.5
b-r-z-c-e-f-g-h-v-q-y	221.9	223.7	224.3	225.1	86.3	88.3	89.0	89.9
a-b-m-e-f-g-h-i-v-q-x	224.0	224.3	224.4	224.5	91.7	92.1	92.2	92.3
a-b-l-g-h-v-p-y	227.4	229.5	229.1	228.4	92.8	94.7	93.9	93.1
a-b-m-g-h-w-v-q-x	228.7	228.9	228.9	228.8	93.2	92.8	92.7	92.3
k-c-e-f-g-h-v-p-y	222.0	224.1	224.8	225.7	85.7	88.0	88.9	90.0
a-b-n-e-g-h-t-q-y	227.3	227.5	226.9	226.5	95.4	95.0	94.8	94.8
l-c-g-h-v-p-y	228.1	227.2	226.7	226.5	83.6	91.3	91.0	89.4
b-m-o-g-h-t-p-y	227.7	226.5	226.1	226.0	89.1	^a	89.8	89.9
c-e-f-g-h-v-q-y	223.7	225.3	225.6	226.3	87.4	89.3	89.8	90.6
89-m-n-c-f-g-h-t-q-y	222.2	222.8	223.0	223.8	87.1	88.1	88.3	89.3
c-g-h-v-q-y	227.8	226.8	226.3	226.2	91.7	91.0	90.7	90.7

^a The calculation for this conformer did not converge in the given solvent.

HOMO shapes



LUMO shapes

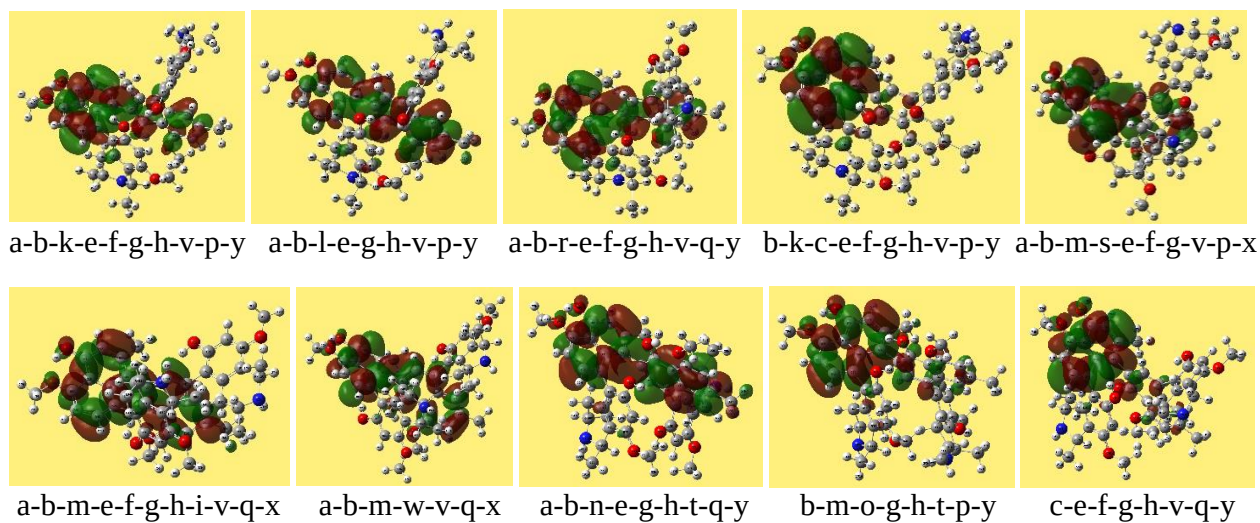


Figure 8.10. Shapes of the HOMO and LUMO frontier orbitals of conformers of mbandakamine A selected from those shown in Fig.8.5
 HF/6-31G(d,p) results

8.5. Results in solution

Table 8.2 reports the relative energy of the conformers in the three solvents considered (chloroform, acetonitrile and water). It has to be noted that acetonitrile has a greater dipole moment than water, but its effect on solutes is often intermediate between that of chloroform and that of water; therefore, in the paragraphs that follow, “increasing solvent polarities” refers to the chloroform-acetonitrile-water sequence. The relative energy trends for the lower energy conformers (up to 11 kcal/mol) are not always in agreement with the common trend for which the relative energy decreases with the increase of the solvent polarity. For some of these conformers, the relative energy decreases with the increase of the solvent polarity; these are the conformers having either O43–H55...O44, O45–H57...O46 and O47–H60...O42 or O43–H55...O44, O45–H57...O46 and N36–H63...O43 IHBs, and no O–H... π interaction (C–H...O interactions may or may not be present). For some other conformers, the relative energy increases in chloroform and acetonitrile with respect to *in vacuo* and decreases in water with respect to acetonitrile; for other conformers, the relative energy increases in chloroform with respect to *in vacuo* and decreases in acetonitrile and water. For the higher energy conformers, the relative energy decreases with the increase of the solvent polarity.

For the first three lower-energy conformers, the relative energy increases with the increase of the solvent polarity with both calculation methods, with the exception of the second lowest-energy conformer, whose relative energy decreases in water with respect to acetonitrile in the DFT results. Their relative energy remains ≤ 3.5 kcal/mol in all the solvents, except the third conformer, whose energy is slightly greater in the HF results water. The relative energy of the conformers with O43–H55...O44, O45–H57...O46 and O47–H60...O42 IHBs or O43–H55...O44 and O47–H60...O42 IHBs decreases significantly in water; this can be explained because, in these conformers, O42–H53 is not engaged in the O–H... π interaction and, therefore, is available to form H-bonds with water molecules. This phenomenon was also observed with the jozimine A₂ molecule [53]. (Although PCM does not take solute-solvent H-bonds into explicit account, it often appears to take it into account implicitly through the energetics [450, 514]). A confirmation could be obtained through the consideration of adducts of MBK with explicit water molecules.

If 3.5 kcal/mol is taken as a cautious energy threshold for conformers which might be potentially responsible for the biological activity of a compound, the results in water solution slightly expand the number of conformers of MBK which might be considered potential responsables for its antimalarial activity, with respects to the results *in vacuo*.

Table 8.9 reports the solvent effect (free energy of solvation, ΔG_{solv}) for the conformers listed in Table 8.2. ΔG_{solv} is positive in chloroform and acetonitrile for all the conformers and may be positive or negative in water.

Table 8.9. Solvent effect (free energy of solvation, ΔG_{solv}) of selected conformers of mbandakamine A in the three solvents considered

Results from HF/6-31G(d,p) and DFT/6-31+G(d,p) single point PCM calculations on the *in vacuo*-optimized geometries.

Conformer	ΔG_{solv} (kcal/mol)					
	HF			DFT		
	chlrf	actn	aq	chlrf	actn	aq
a-b-k-e-f-g-h-u-v-p-y	13.18	24.49	4.48	13.54	24.87	4.80
a-b-l-e-g-h-u-v-p-y	14.16	24.52	4.64	13.41	24.79	4.31
a-b-r-e-f-g-h-v-q-y	14.05	25.45	6.31	14.47	25.88	6.23
b-k-c-e-f-g-h-v-p-y	14.20	25.43	5.66	14.37	25.85	6.05
a-b-k-e-f-g-h-v-p-y	11.72	23.20	2.37	12.47	23.73	2.27
a-b-m-e-f-g-h-t-p-y	13.70	24.78	3.71	13.93	25.17	3.38
a-b-l-g-h-v-p-y	11.50	21.75	0.50	11.45	21.90	0.03
b-l-c-e-g-h-v-p-y	14.96	26.05	5.85	14.32	25.86	6.00
a-b-m-s-e-f-g-v-p-x	13.91	24.84	4.47	13.20	24.58	3.27
b-r-z-c-e-f-g-h-v-q-y	16.40	26.86	6.90	15.16	26.80	7.20
a-b-m-e-f-g-h-i-v-q-x	13.56	23.85	2.93	13.16	24.36	3.07
a-b-l-g-h-v-p-y	10.17	20.55	-2.34	10.31	20.72	-2.51
a-b-m-g-h-w-v-q-x	13.19	25.03	5.24	13.91	25.39	4.99
k-c-e-f-g-h-v-p-y	12.91	23.97	2.02	13.08	24.04	1.67
a-b-n-e-g-h-t-q-y	11.82	22.34	-1.85	13.10	23.83	-0.36
l-c-g-h-v-p-y	11.41	21.52	-2.86	11.29	21.43	-1.70
b-m-o-g-h-t-p-y	12.68	23.30	1.80	^{-a}	23.83	1.04
c-e-f-g-h-v-q-y	12.38	23.61	1.23	13.18	24.34	1.22
m-n-c-f-g-h-t-q-y	12.64	23.18	-1.93	13.13	23.89	-1.70
107-c-g-h-v-q-y	10.63	20.90	-5.04	11.09	21.44	-5.65

The values of ΔG_{solv} in acetonitrile are greater than the values in chloroform. The octanol/water partition coefficient of MBK (7.9868, [515]) suggests that it is more soluble in non-polar solvents than in water. This could be related to the presence of many aromatic rings and to the high molecular mass. On the other hand, the negative values of ΔG_{solv} in water suggest that the possibility that the molecule may be present also in the water phases of living organisms – although in limited amounts – cannot be excluded. It is also probable that the calculation of ΔG_{solv} takes into account the presence of OHs, which favours the solubility in water.

The electrostatic component of ΔG_{solv} (G_{el}) has negative values in all the three solvents, but significantly more negative in water. Tables 8.K10 and 8.K11 report the ΔG_{solv} and G_{el} for all the calculated conformers at HF and DFT respectively.

The dipole moments (Table 8.7) increase with the solvent polarity; some exceptions correspond to conformers with the consecutive O47–H60...O43–H55...O44 IHBs, where the dipole moment decreases slightly in water with respect to acetonitrile.

The HOMO-LUMO energy gap mostly increases with the solvent polarity, but it decreases in some cases. The change with respect to *in vacuo* is -1.79–5.28 kcal/mol/HF and -1.18–2.49 kcal/mol/DFT in chloroform; -2.28–5.33 kcal/mol/HF and -1.776–3.20 kcal/mol/DFT in acetonitrile and -2.291–5.346 kcal/mol/HF and -1.983–4.524 kcal/mol/DFT in water.

8.6. Discussion and Conclusions

A high number of conformers of mbandakamine A (MBK) were calculated, in order to have the possibility of identifying energy-influencing factors and possible patterns in their effects. The results highlight the relative stabilising effects of the various types of IHBs, and also of the mutual orientation of the moieties and of the stacking interaction.

It is interesting to compare MBK with jozimine A₂ because these are the two antimalarial dimeric naphthylisoquinoline alkaloids considered in this study. The two units of MBK are unsymmetrical while in jozimine A₂ they are symmetrical. MBK differs also from jozimine A₂ by the type of coupling; MBK has a particular coupling which enable stacking interaction, that is not evident in jozimine A₂. The types of IHBs present in MBK are different from those present in jozimine A₂.

MBK can make inter-units IHBs ($\text{O}-\text{H}\cdots\text{O}$ or $\text{O}-\text{H}\cdots\text{N}$ or $\text{N}-\text{H}\cdots\text{O}$); these are IHBs between naphthalene and isoquinoline moieties, and IHBs between isoquinoline moieties, which are not present in jozimine A_2 . Beside these IHBs, MBK has also IHBs within naphthalene moieties of the same unit; this type of IHBs is found also in jozimine A_2 . The removal of the $\text{O}-\text{H}\cdots\text{O}$ IHB within a naphthalene moiety brings about the $\text{O}-\text{H}\cdots\pi$ interaction with the π system of the other naphthalene moiety. In jozimine A_2 , the removal of each $\text{O}-\text{H}\cdots\text{O}$ IHBs bring an $\text{O}-\text{H}\cdots\pi$ interaction. Thus allowing two simultaneous $\text{O}-\text{H}\cdots\pi$ interactions. This is not the case for MBK where only one $\text{O}-\text{H}\cdots\pi$ interaction with the π system of the other naphthalene moiety is allowed. This could be due to the coupling of MBK, resulting in dominance of the preference for the mutual orientation of the moieties with respect to a second $\text{O}-\text{H}\cdots\pi$ interaction.

The effect of solvents is more pronounced for jozimine A_2 than in MBK. In MBK, the magnitude of ΔG_{solv} is small; this suggest the possibility that its IHBs do not break to allow H-bonds with water molecules. The stacking interaction may also be a factor contributing to lower solubility in water.

The other computed molecular properties (dipole moments, HOMO-LUMO energy gaps, vibrational frequencies of the OHs, solvent effect) also show some dependence on the IHB patterns.

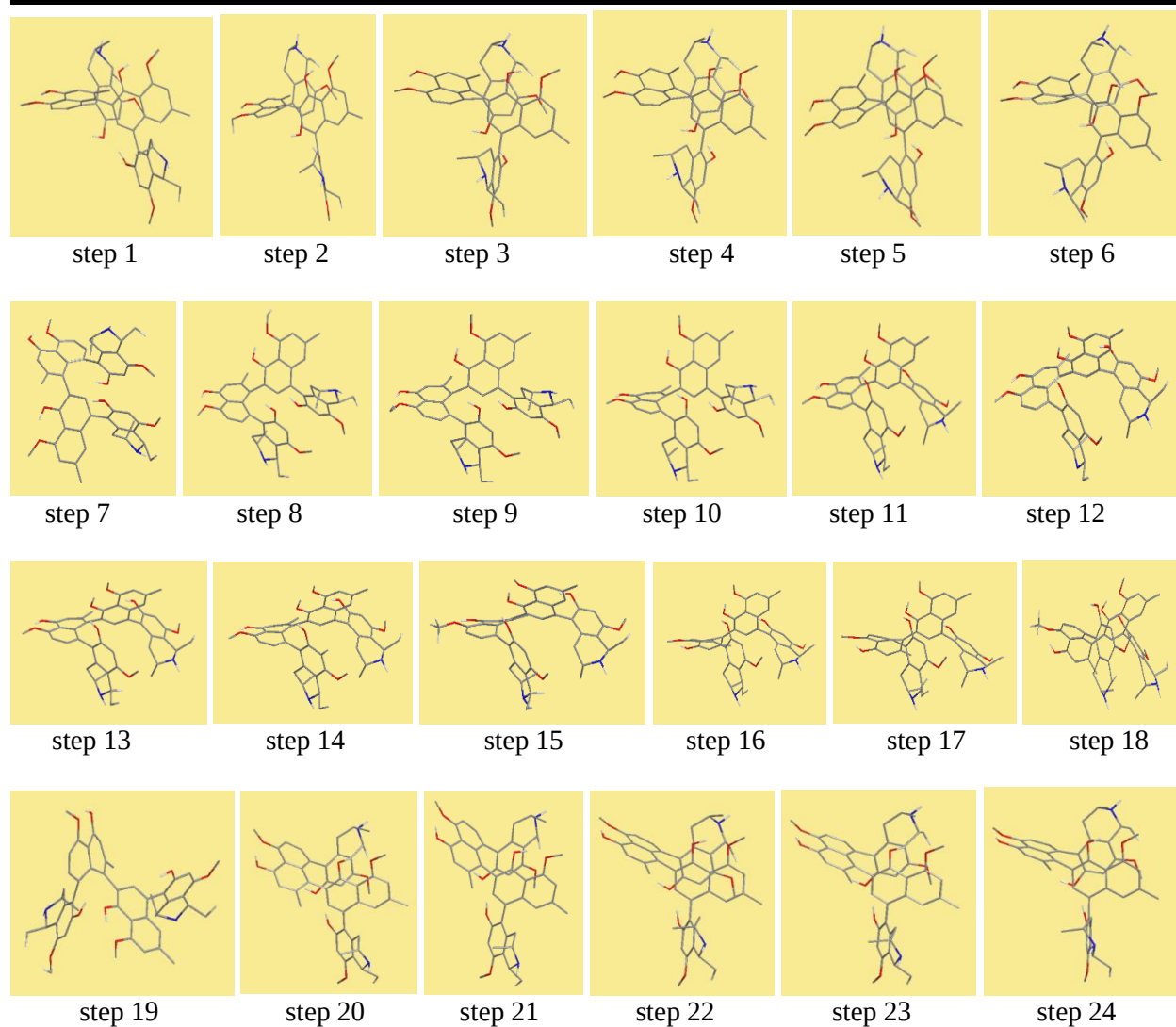
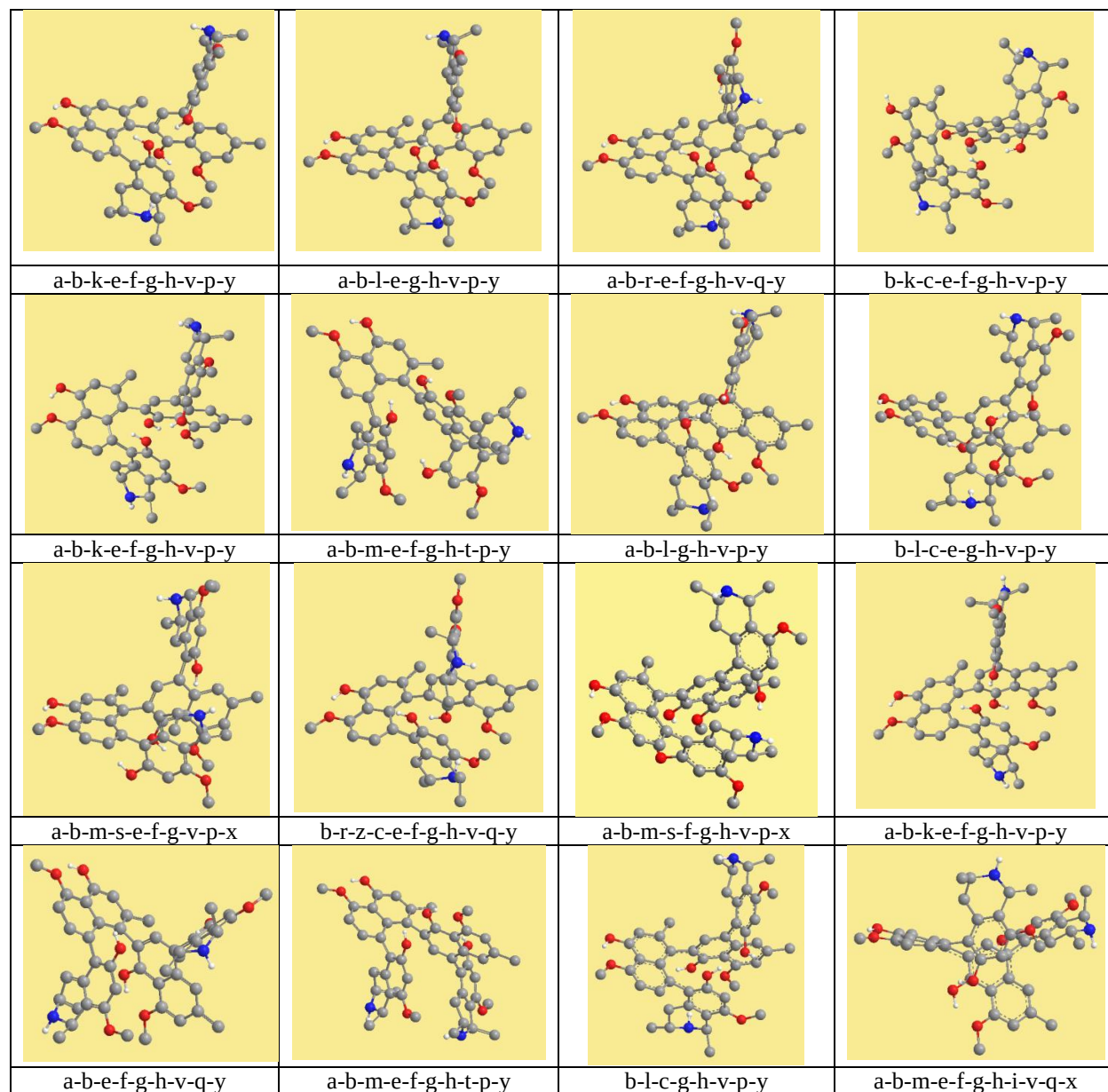
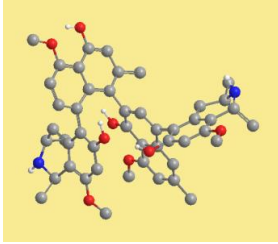
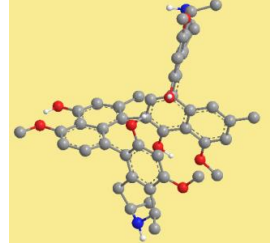
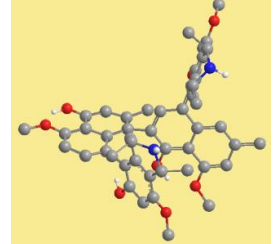
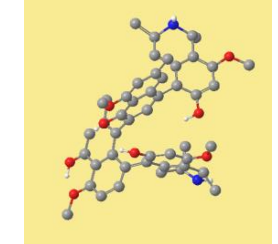
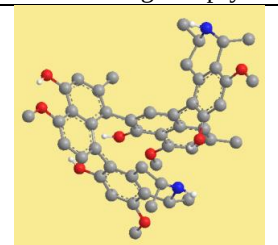
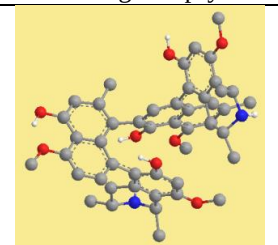
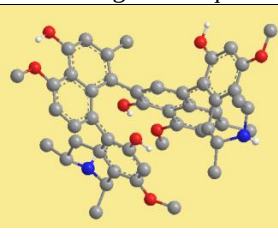
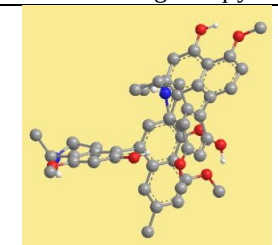
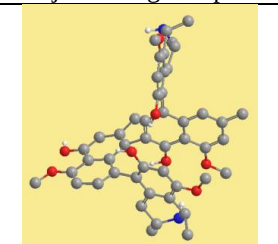
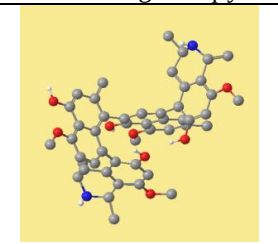
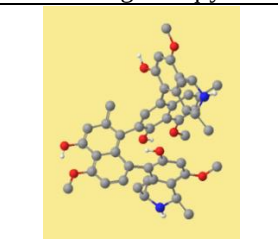
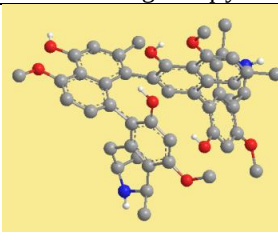
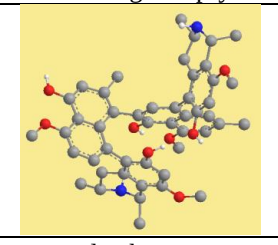
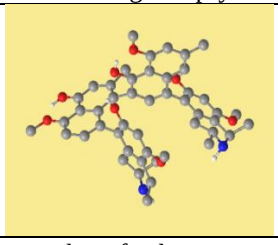
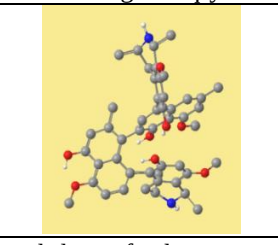
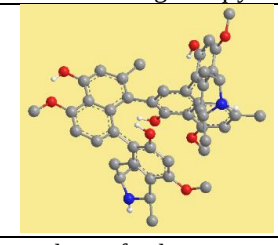
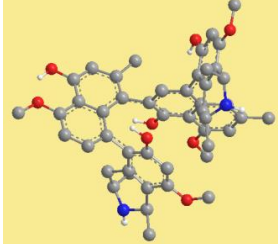
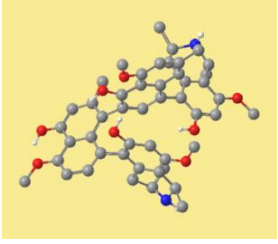
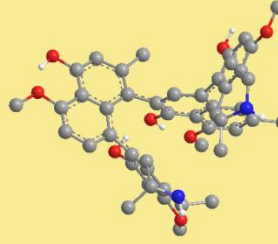
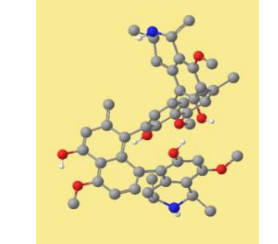
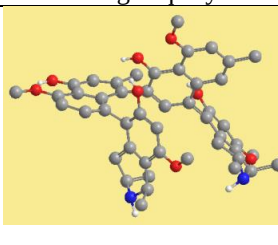
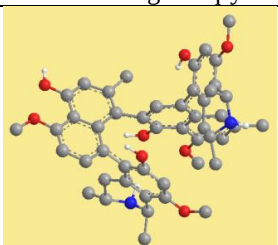
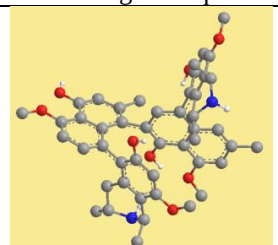
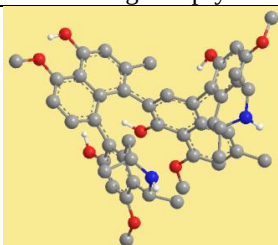


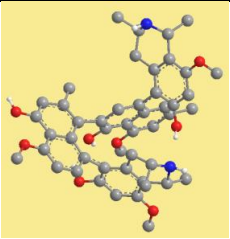
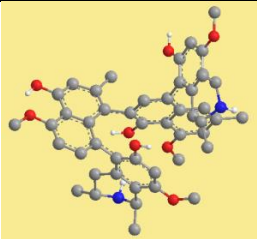
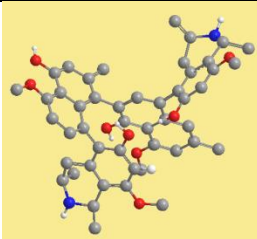
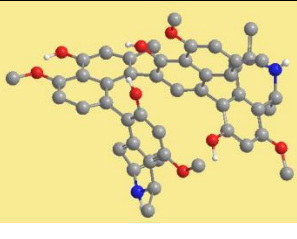
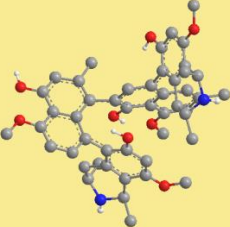
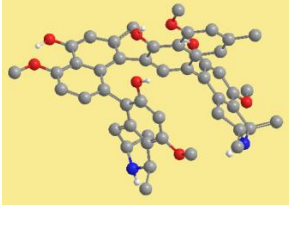
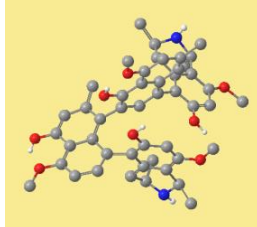
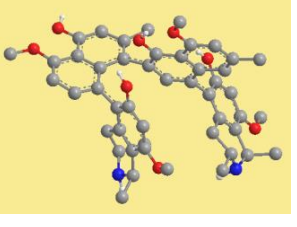
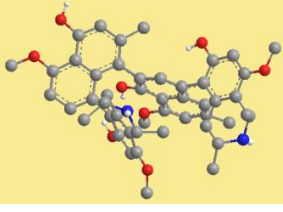
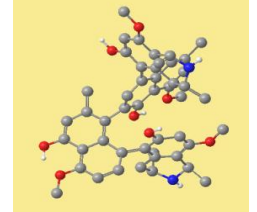
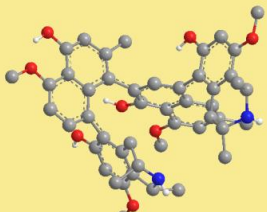
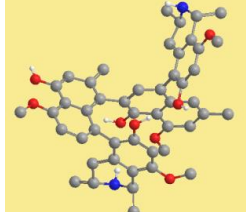
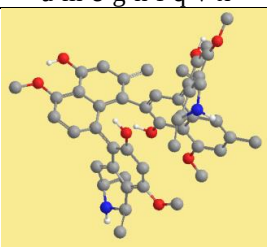
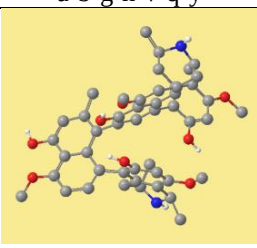
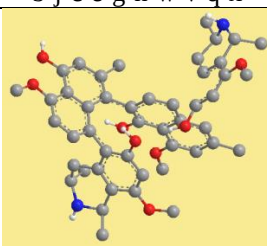
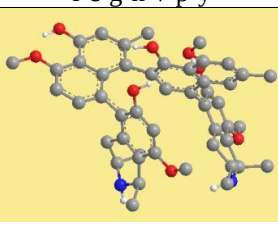
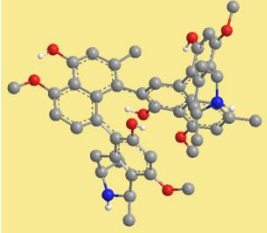
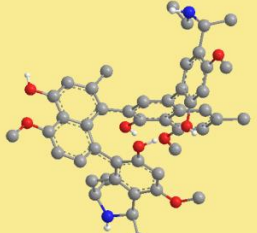
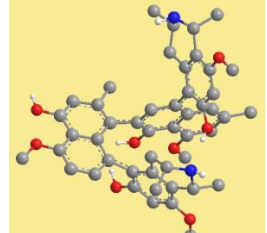
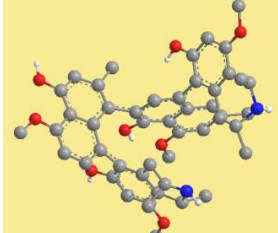
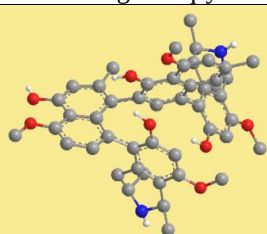
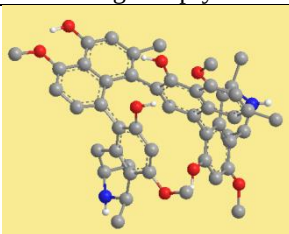
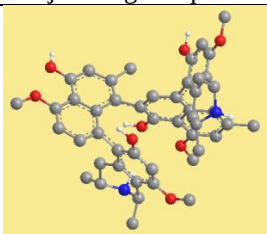
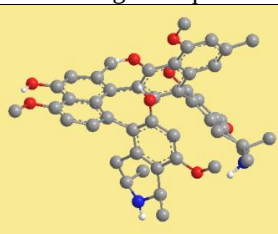
Figure 8.K1. Geometries of the individual steps of the rotation scan of the C12–C21 bond (C28–C21–C12–C13 torsion angle)

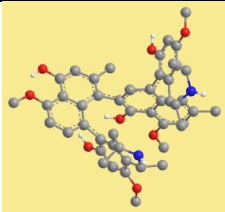
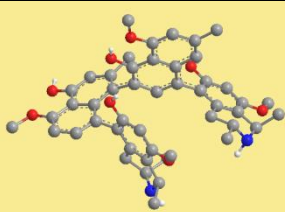
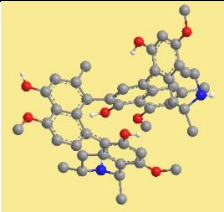
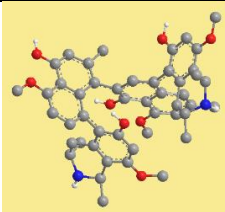
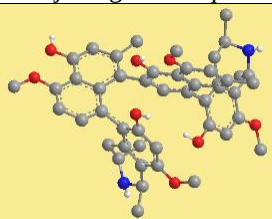
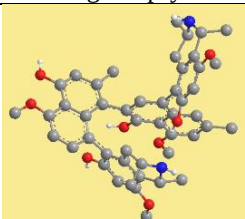
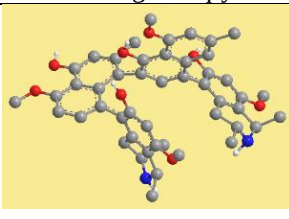
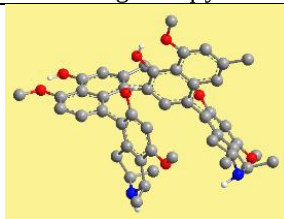
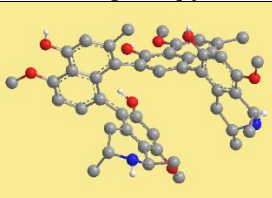
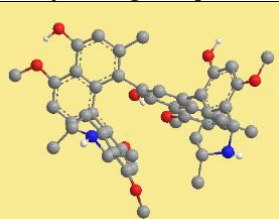
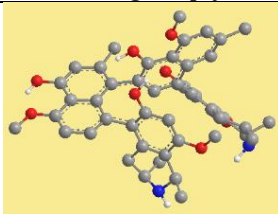
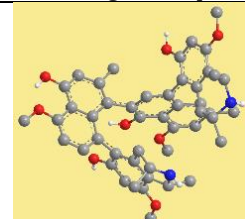
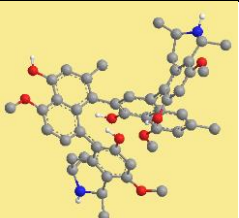
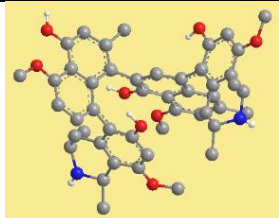
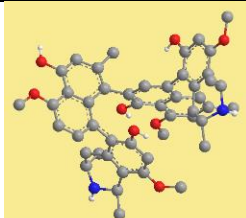
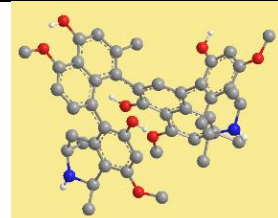
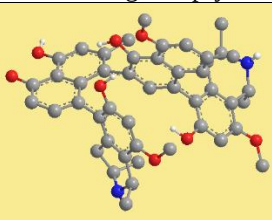
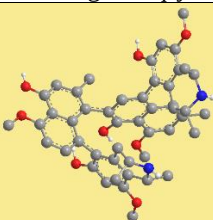
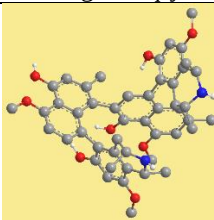
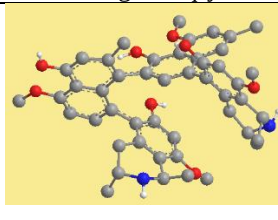
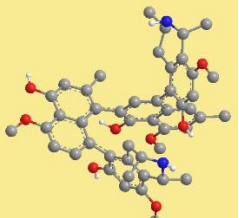
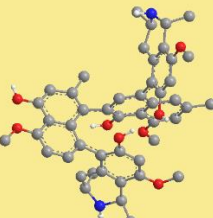
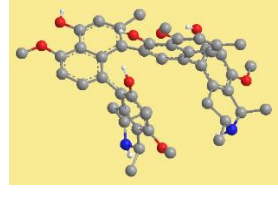
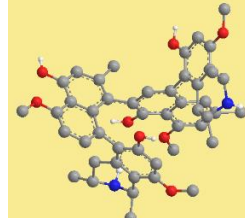
Figure 8.K2. Optimized geometries of conformers of the mbandakamine A molecule and acronyms denoting them

HF/6-31G(d,p) results. The images show the main combinations of IHBs and different moieties' orientations which may be present in the conformers of mbandakamine A. The initial part of the acronyms is not reported under the images, because of space reasons; it is the same for all the conformers (MBK).



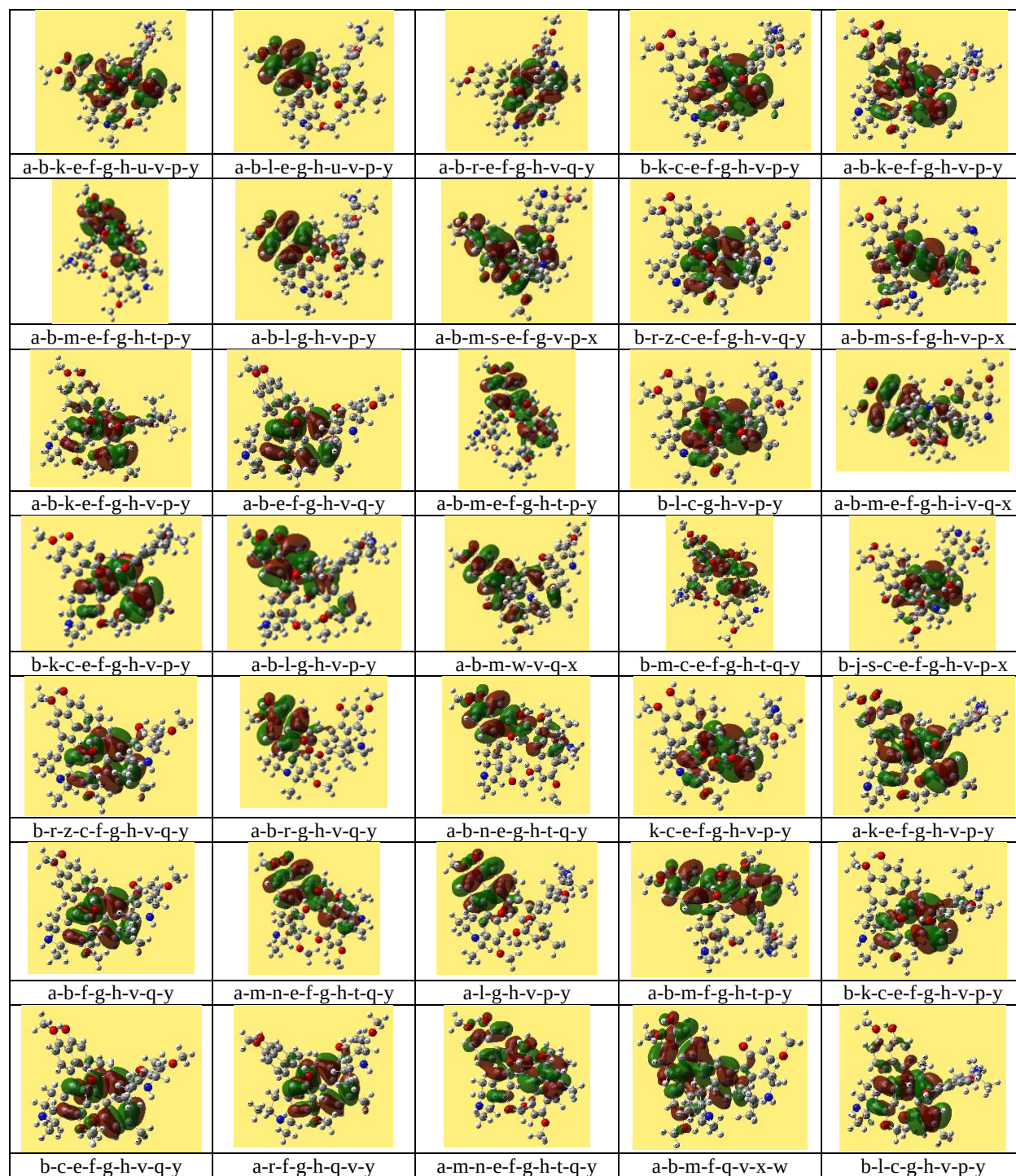
			
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b-j-s-c-e-f-g-h-v-p-x	b-r-z-c-f-g-h-v-q-y	a-b-r-g-h-v-q-y	a-b-n-e-g-h-t-q-y
			
k-c-e-f-g-h-v-p-y	a-k-e-f-g-h-v-p-y	a-b-f-g-h-v-q-y	a-m-n-e-f-g-h-t-q-y
			
a-l-g-h-v-p-y	a-b-m-f-g-h-t-p-y	b-k-c-e-f-g-h-v-p-y	b-c-e-f-g-h-v-q-y
			
a-r-f-g-h-q-v-y	a-m-n-e-f-g-h-t-q-y	a-b-m-f-g-h-w-q-v-x	b-l-c-g-h-v-p-y
			
b-m-c-e-f-g-h-t-p-y	r-z-c-e-f-g-h-v-q-y	a-r-e-g-h-q-v-y	b-j-c-e-f-g-h-w-v-q-x

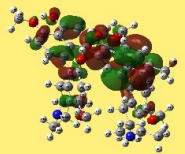
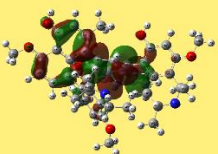
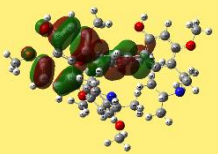
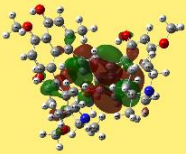
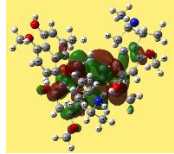
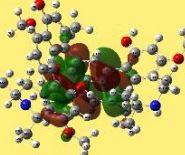
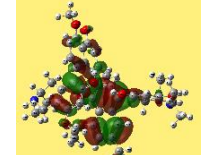
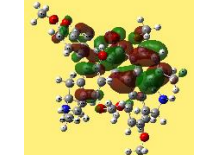
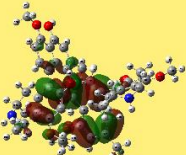
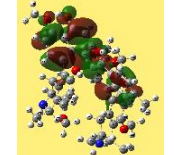
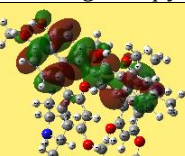
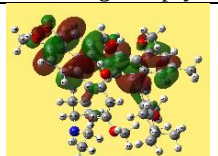
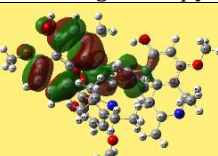
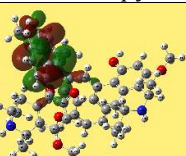
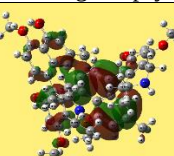
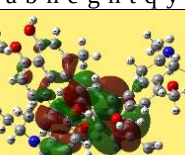
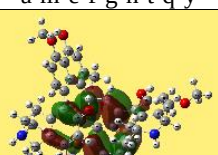
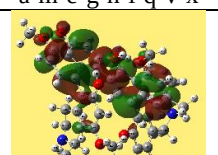
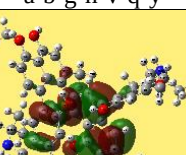
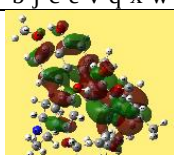
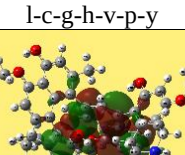
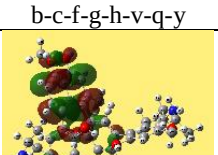
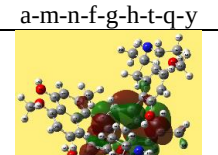
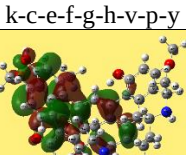
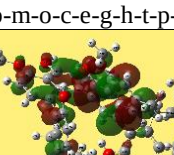
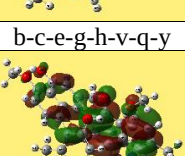
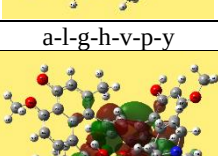
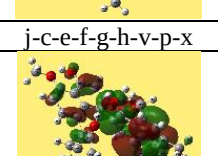
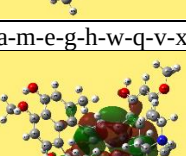
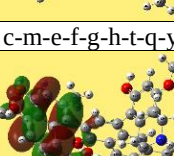
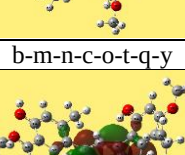
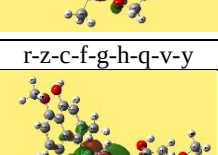
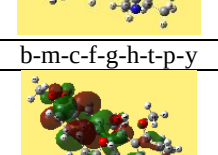
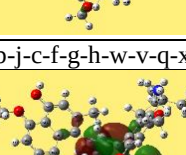
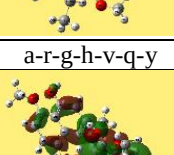
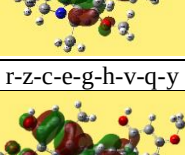
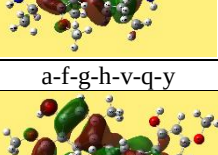
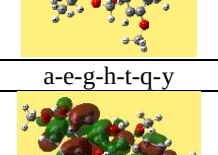
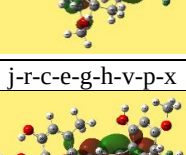
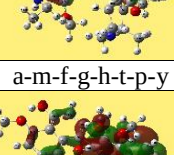
			
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a-e-f-g-h-v-q-y	a-b-e-g-h-t-p-y	a-b-n-e-g-h-t-q-y	a-m-e-f-g-h-t-q-y
			
a-m-e-g-h-i-q-v-x	a-b-g-h-v-q-y	b-j-c-e-g-h-w-v-q-x	l-c-g-h-v-p-y
			
b-c-f-g-h-v-q-y	a-m-n-f-g-h-t-q-y	k-c-e-f-g-h-v-p-y	b-m-o-c-e-g-h-t-p-y
			
b-c-e-g-h-v-q-y	a-l-g-h-v-p-y	j-c-e-f-g-h-v-p-x	a-m-e-g-h-w-q-v-x
			
m-c-e-f-g-h-t-q-y	b-m-n-o-c-g-h-t-q-y	r-z-c-f-g-h-q-v-y	b-m-c-f-g-h-t-p-y

			
b-j-c-f-g-h-w-v-q-x	a-g-h-t-p-y	r-z-c-e-g-h-v-q-y	a-f-g-h-v-q-y
			
a-e-g-h-t-q-y	j-r-c-e-g-h-v-p-x	a-m-f-g-h-t-p-y	a-m-f-g-h-i-v-q-x
			
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j-s-c-g-h-v-p-x	l-c-g-h-v-p-y	m-c-e-f-g-h-t-p-y	r-z-c-g-h-v-q-y

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m-c-g-h-t-p-y	m-n-o-c-g-h-t-q-y	a-g-h-i-v-q-x	a-g-h-t-p-y
j-c-g-h-w-q-v-x	m-n-c-g-h-t-p-y	c-g-h-v-q-y	

Figure 8.K3. Shapes of the HOMO frontier orbitals of conformers of mbandakamine A
HF/6-31G(d,p) results.



				
b-m-c-e-f-g-h-t-p-y	r-z-c-e-f-g-h-v-q-y	a-r-e-g-h-q-v-y	b-j-c-e-f-g-h-w-v-q-x	a-m-r-f-g-h-v-p-x
				
b-r-z-c-g-h-v-q-y	a-e-f-k-g-h-v-p-y	b-m-c-f-g-h-n-t-q-y	a-e-f-v-q-y	a-b-e-g-h-t-p-y
				
a-b-n-e-g-h-t-q-y	a-m-e-f-g-h-t-q-y	a-m-e-g-h-i-q-v-x	a-b-g-h-v-q-y	b-j-c-e-v-q-x-w
				
l-c-g-h-v-p-y	b-c-f-g-h-v-q-y	a-m-n-f-g-h-t-q-y	k-c-e-f-g-h-v-p-y	b-m-o-c-e-g-h-t-p-y
				
b-c-e-g-h-v-q-y	a-l-g-h-v-p-y	j-c-e-f-g-h-v-p-x	a-m-e-g-h-w-q-v-x	c-m-e-f-g-h-t-q-y
				
b-m-n-c-o-t-q-y	r-z-c-f-g-h-q-v-y	b-m-c-f-g-h-t-p-y	b-j-c-f-g-h-w-v-q-x	a-r-g-h-v-q-y
				
r-z-c-e-g-h-v-q-y	a-f-g-h-v-q-y	a-e-g-h-t-q-y	j-r-c-e-g-h-v-p-x	a-m-f-g-h-t-p-y
				
a-m-f-g-h-i-v-q-x	a-b-g-h-i-v-q-x	a-b-g-h-t-p-y	b-j-c-g-h-w-v-q-x	b-m-o-g-h-t-p-y

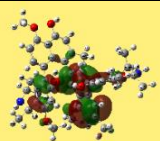
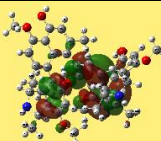
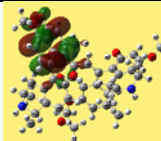
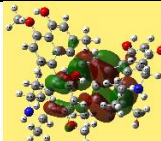
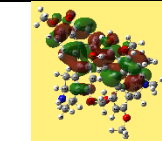
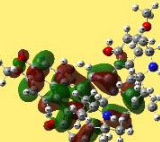
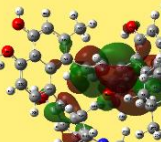
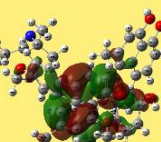
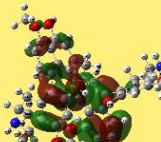
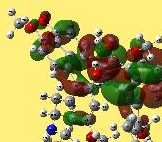
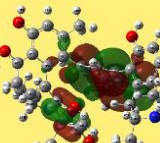
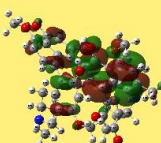
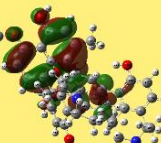
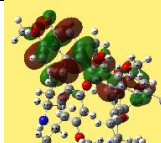
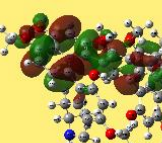
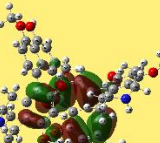
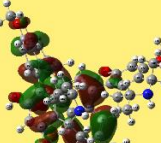
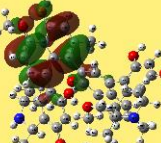
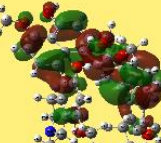
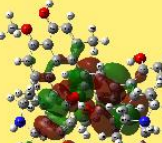
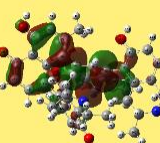
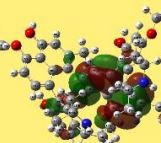
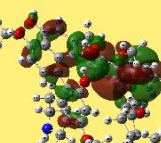
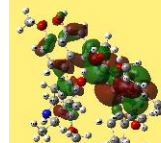
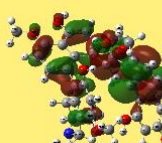
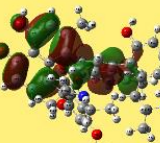
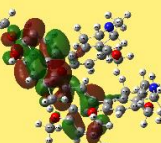
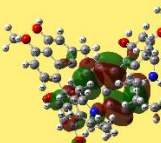
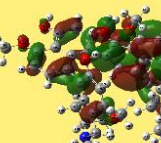
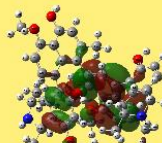
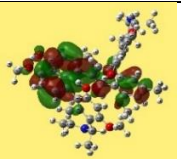
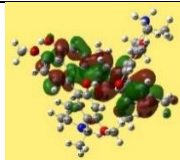
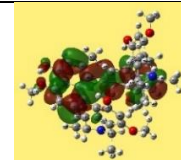
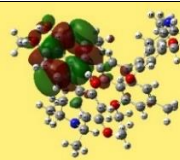
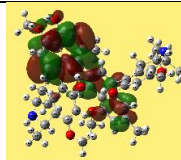
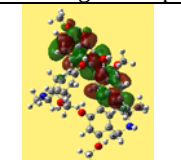
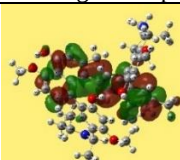
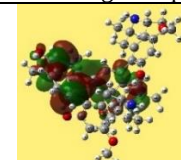
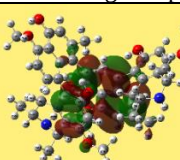
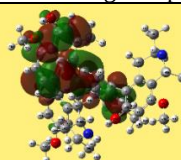
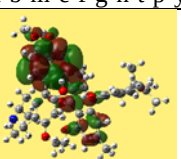
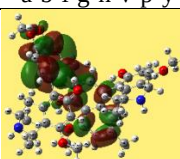
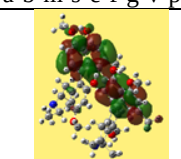
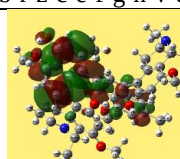
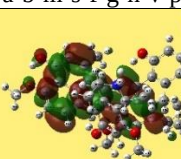
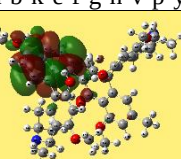
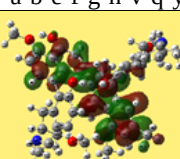
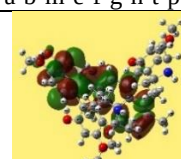
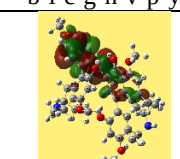
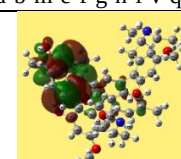
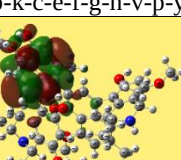
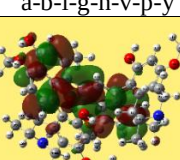
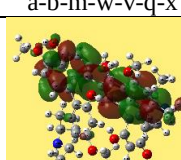
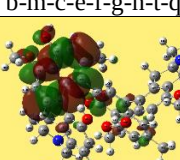
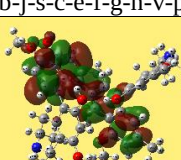
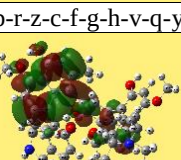
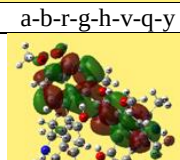
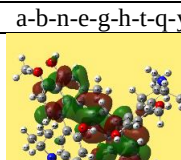
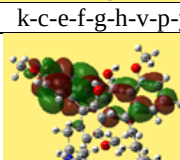
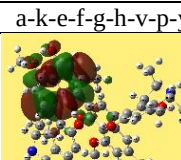
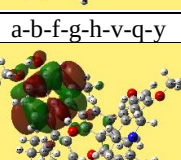
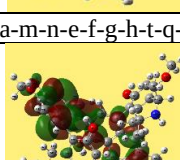
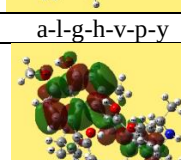
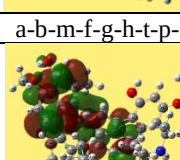
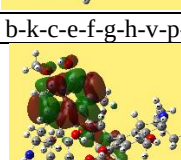
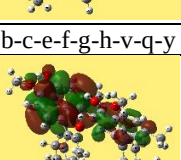
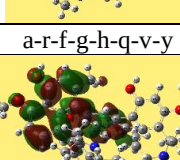
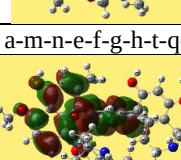
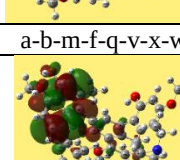
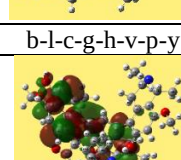
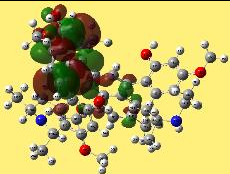
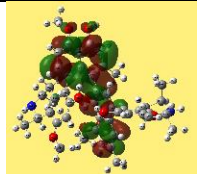
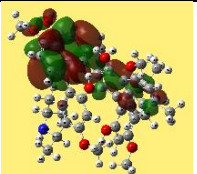
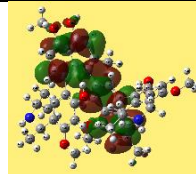
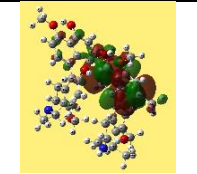
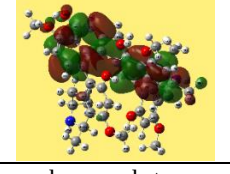
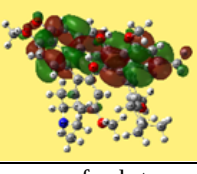
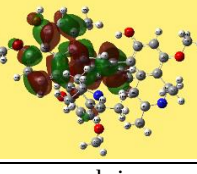
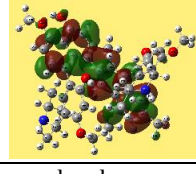
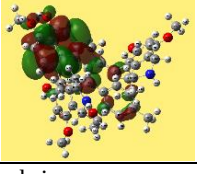
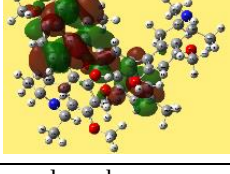
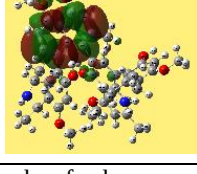
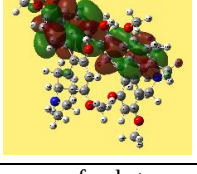
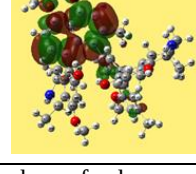
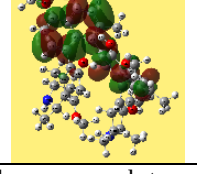
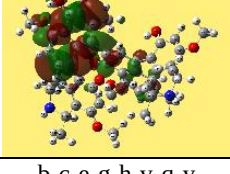
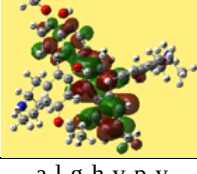
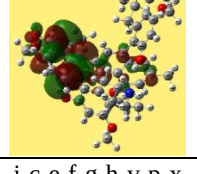
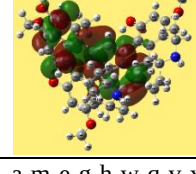
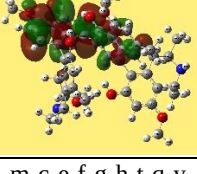
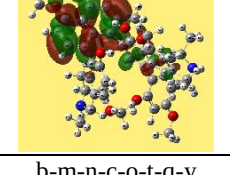
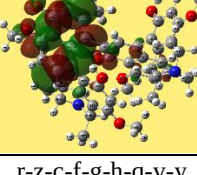
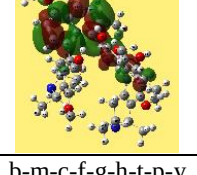
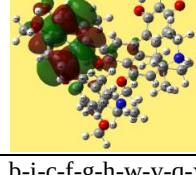
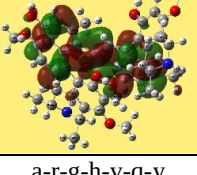
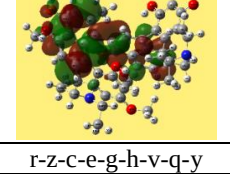
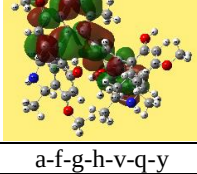
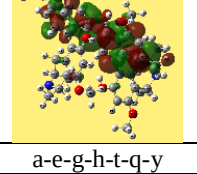
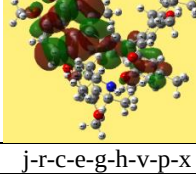
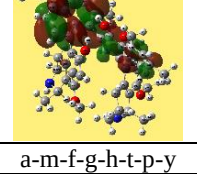
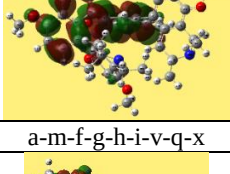
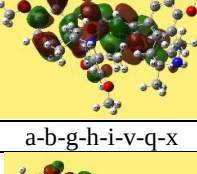
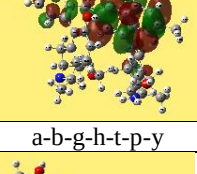
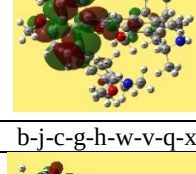
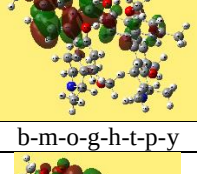
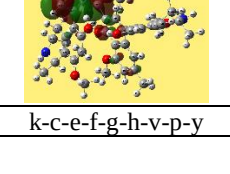
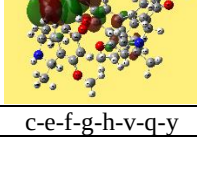
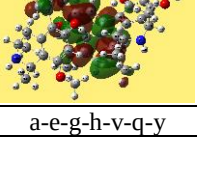
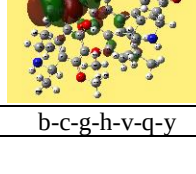
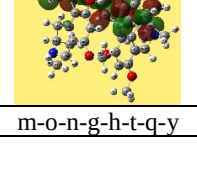
				
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s-z-c-g-h-v-q-y	c-m-n-f-g-h-t-q-y	a-e-g-h-i-v-q-x	a-e-g-h-t-p-y	a-n-t-q-y
				
c-f-g-h-v-q-y	c-e-j-g-h-w-q-v-x	a-g-h-v-q-y	m-o-c-e-g-h-t-p-y	c-e-g-h-v-q-y
				
m-c-f-g-h-i-v-q-x	j-c-f-g-h-w-v-q-x	m-c-f-g-h-t-p-y	m-n-o-c-g-h-t-q-y	m-c-t-p-y
				
a-g-h-i-q-v-x	a-g-h-t-p-y	j-c-g-h-w-q-v-x	m-o-c-g-h-t-p-y	c-g-h-v-q-y

Figure 8.K4. Shapes of the LUMO frontier orbitals of conformers of mbandakamine A
HF/6-31G(d,p) results.

				
a-b-k-e-f-g-h-u-v-p-y	a-b-l-e-g-h-u-v-p-y	a-b-r-e-f-g-h-v-q-y	b-k-c-e-f-g-h-v-p-y	a-b-k-e-f-g-h-v-p-y
				
a-b-m-e-f-g-h-t-p-y	a-b-l-g-h-v-p-y	a-b-m-s-e-f-g-v-p-x	b-r-z-c-e-f-g-h-v-q-y	a-b-m-s-f-g-h-v-p-x
				
a-b-k-e-f-g-h-v-p-y	a-b-e-f-g-h-v-q-y	a-b-m-e-f-g-h-t-p-y	b-l-c-g-h-v-p-y	a-b-m-e-f-g-h-i-v-q-x
				
b-k-c-e-f-g-h-v-p-y	a-b-l-g-h-v-p-y	a-b-m-w-v-q-x	b-m-c-e-f-g-h-t-q-y	b-j-s-c-e-f-g-h-v-p-x
				
b-r-z-c-f-g-h-v-q-y	a-b-r-g-h-v-q-y	a-b-n-e-g-h-t-q-y	k-c-e-f-g-h-v-p-y	a-k-e-f-g-h-v-p-y
				
a-b-f-g-h-v-q-y	a-m-n-e-f-g-h-t-q-y	a-l-g-h-v-p-y	a-b-m-f-g-h-t-p-y	b-k-c-e-f-g-h-v-p-y
				
b-c-e-f-g-h-v-q-y	a-r-f-g-h-q-v-y	a-m-n-e-f-g-h-t-q-y	a-b-m-f-q-v-x-w	b-l-c-g-h-v-p-y
				
b-m-c-e-f-g-h-t-p-y	r-z-c-e-f-g-h-v-q-y	a-r-e-g-h-q-v-y	b-j-c-e-f-g-h-w-v-q-x	a-m-r-f-g-h-v-p-x

				
b-r-z-c-g-h-v-q-y	a-k-e-f-g-h-v-p-y	b-m-c-f-g-h-n-t-q-y	a-e-f-v-q-y	a-b-e-g-h-t-p-y
				
a-b-n-e-g-h-t-q-y	a-m-e-f-g-h-t-q-y	a-m-e-g-h-i-q-v-x	a-b-g-h-v-q-y	b-j-c-e-v-q-x-w
				
l-c-g-h-v-p-y	b-c-f-g-h-v-q-y	a-m-n-f-g-h-t-q-y	k-c-e-f-g-h-v-p-y	b-m-o-c-e-g-h-t-p-y
				
b-c-e-g-h-v-q-y	a-l-g-h-v-p-y	j-c-e-f-g-h-v-p-x	a-m-e-g-h-w-q-v-x	m-c-e-f-g-h-t-q-y
				
b-m-n-c-o-t-q-y	r-z-c-f-g-h-q-v-y	b-m-c-f-g-h-t-p-y	b-j-c-f-g-h-w-v-q-x	a-r-g-h-v-q-y
				
r-z-c-e-g-h-v-q-y	a-f-g-h-v-q-y	a-e-g-h-t-q-y	j-r-c-e-g-h-v-p-x	a-m-f-g-h-t-p-y
				
a-m-f-g-h-i-v-q-x	a-b-g-h-i-v-q-x	a-b-g-h-t-p-y	b-j-c-g-h-w-v-q-x	b-m-o-g-h-t-p-y
				
k-c-e-f-g-h-v-p-y	c-e-f-g-h-v-q-y	a-e-g-h-v-q-y	b-c-g-h-v-q-y	m-o-n-g-h-t-q-y

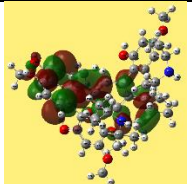
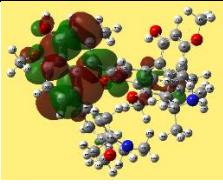
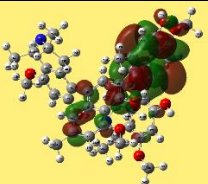
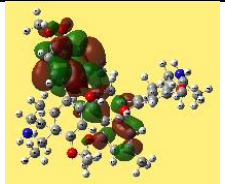
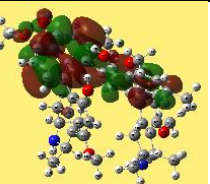
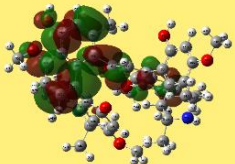
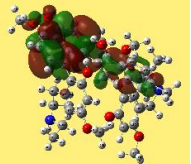
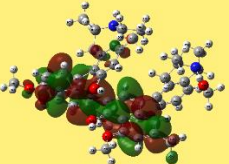
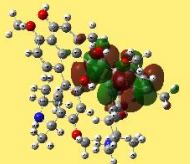
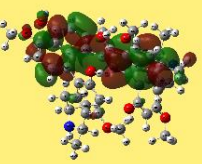
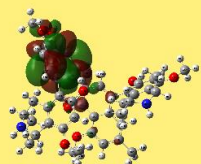
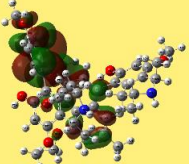
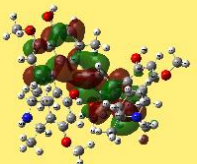
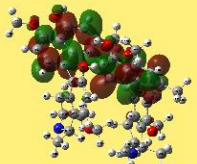
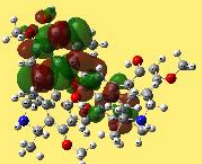
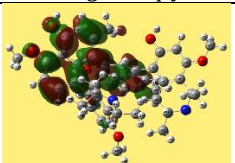
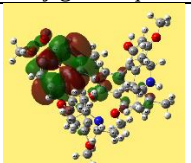
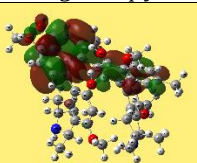
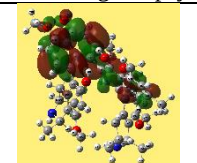
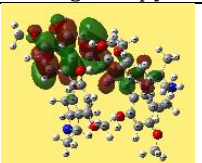
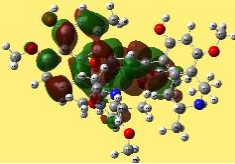
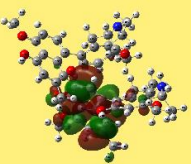
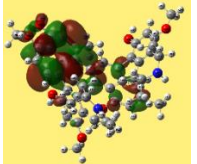
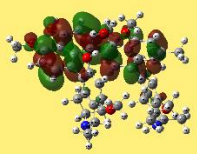
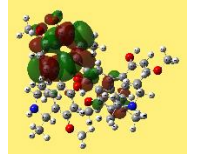
				
a-m-f-g-h-w-v-q-x	j-c-e-f-g-h w-v-q-x	j-s-c-g-h-v-p-x	l-c-g-h-v-p-y	m-c-f-g-h-t-p-y
				
s-z-c-g-h-v-q-y	m-n-c-f-g-h-t-q-y	a-e-g-h-i-v-q-x	a-e-g-h-t-p-y	a-n-t-q-y
				
c-f-g-h-v-q-y	c-e-j-g-h-w-q-v-x	a-g-h-v-q-y	m-o-c-e-g-h-t-p-y	c-e-g-h-v-q-y
				
m-c-f-g-h-i-v-q-x	j-c-f-g-h-w-v-q-x	m-c-f-g-h-t-p-y	m-c-t-p-y	m-n-o-c-g-h-t-q-y
				
a-g-h-i-q-v-x	a-g-h-t-p-y	j-c-g-h-w-q-v-x	m-o-c-g-h-t-p-y	c-g-h-v-q-y

Table 8.K1. Relative energies of the conformers of mbandakamine A

HF/6-31G(d,p) and DFT/B3LYP/6-31+G(d,p) results *in vacuo* and in the three solvents considered. The methods are respectively denoted as HF and DFT in the columns' headings. The results *in vacuo* are from full optimization calculations; the results in solution are from single point PCM calculations on the *in-vacuo*-optimized geometries. The conformers are listed in order of increasing relative energies in the HF results *in vacuo*

Conformer	Relative energy (kcal/mol)							
	HF				DFT			
	vac	chlrf	actn	aq	vac	chlrf	actn	aq
a-b-k-e-f-g-h-u-v-p-y	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
a-b-l-e-g-h-u-v-p-y	2.308	3.433	2.538	2.750	2.157	2.384	2.514	2.205
a-b-r-e-f-g-h-v-q-y	3.405	3.584	3.583	4.218	3.155	3.290	3.318	3.497
b-k-c-e-f-g-h-v-p-y	5.101	5.580	5.422	5.530	5.398	5.653	5.682	5.757
a-b-k-e-f-g-h-v-p-y	5.382	4.867	4.858	3.902	5.170	4.868	4.604	3.039
a-b-m-e-f-g-h-t-p-y	5.891	5.849	5.888	4.664	5.968	6.057	5.928	4.013
a-b-l-g-h-v-p-y	5.596	3.856	2.796	1.613	5.331	3.614	2.759	1.004
b-l-c-e-g-h-v-p-y	6.325	8.056	7.832	7.648	6.713	7.694	7.932	8.161
a-b-m-s-e-f-g-v-p-x	6.661	6.968	6.388	5.758	5.639	5.509	5.360	3.804
b-r-z-c-e-f-g-h-v-q-y	8.104	9.662	8.676	8.417	8.329	8.879	9.027	9.096
a-b-m-s-f-g-h-v-p-x	8.356	8.068	7.795	6.314	6.069	5.822	5.439	3.343
a-b-k-e-f-g-h-v-p-y	8.714	8.135	8.245	7.523	8.273	8.059	7.778	6.250
a-b-e-f-g-h-v-q-y	9.033	9.504	8.683	7.986	8.704	8.512	8.407	6.824
a-b-m-e-f-g-h-t-p-y	9.617	9.158	9.261	9.122	8.971	8.739	8.521	7.744
b-l-c-g-h-v-p-y	9.686	8.991	7.765	5.686	9.645	8.585	7.868	6.274
a-b-m-e-f-g-h-i-v-q-x	9.985	10.063	8.877	7.629	8.584	8.076	7.782	6.176
b-k-c-e-f-g-h-v-p-y	10.519	10.287	10.363	9.603	10.306	10.217	10.116	8.444
a-b-l-g-h-v-p-y	10.780	8.495	7.385	4.408	10.303	8.238	7.113	3.809
a-b-m-w-v-q-x	11.277	11.061	11.321	11.047	10.960	10.800	10.697	9.788
b-m-c-e-f-g-h-t-q-y	11.351	11.938	11.946	9.951	11.470	11.903	— ^a	9.727
b-j-s-c-e-f-g-h-v-p-x	11.159	11.324	11.556	10.032	10.285	10.579	10.631	0.000
b-r-z-c-f-g-h-v-q-y	11.652	11.376	10.621	8.752	11.836	11.429	— ^a	8.998
a-b-r-g-h-v-q-y	11.704	10.279	9.363	8.918	11.287	10.059	9.258	5.858
a-b-n-e-g-h-t-q-y	12.249	11.141	10.449	6.037	11.900	10.906	10.159	5.739
k-c-e-f-g-h-v-p-y	12.258	11.851	11.498	9.434	12.858	12.466	12.047	9.626
a-k-e-f-g-h-v-p-y	12.421	11.573	11.051	7.829	12.538	11.706	11.061	7.197
a-b-f-g-h-v-q-y	12.589	12.005	9.950	7.727	12.205	11.102	10.465	6.517
a-m-n-e-f-g-h-t-q-y	13.131	12.538	12.119	8.457	13.624	13.061	12.522	8.073
a-l-g-h-v-p-y	13.209	10.953	9.269	5.392	13.231	10.880	9.619	4.935
a-b-m-f-g-h-t-p-y	13.281	11.929	11.192	8.925	12.312	11.010	10.198	7.394
b-k-c-e-f-g-h-v-p-y	13.826	20.221	18.584	13.465	13.456	13.444	13.311	11.620
b-c-e-f-g-h-v-q-y	13.868	14.212	14.202	13.129	13.632	13.809	13.835	12.769
a-r-f-g-h-q-v-y	13.903	13.964	14.232	14.167	13.988	12.725	11.783	7.375
a-m-n-e-f-g-h-t-q-y	13.927	12.797	11.562	7.177	13.624	13.061	12.523	8.074

a-b-m-f-g-h-w-q-v-x	14.277	14.417	14.467	13.577	14.058	12.932	12.343	13.910
b-l-c-g-h-v-p-y	14.671	13.183	12.618	9.539	14.341	13.011	12.144	9.066
b-m-c-e-f-g-h-t-p-y	14.792	13.377	12.471	9.046	14.617	14.820	14.842	13.739
r-z-c-e-f-g-h-v-q-y	15.308	15.763	15.544	15.301	15.798	14.820	15.344	13.277
a-r-e-g-h-q-v-y	15.325	15.164	14.882	12.444	15.257	15.682	13.854	10.265
b-j-c-e-f-g-h-w-v-q-x	15.449	14.626	13.864	12.126	14.650	14.504	14.932	13.910
a-m-r-f-g-h-v-p-x	15.703	15.672	16.077	14.983	13.650	14.927	12.257	7.508
b-r-z-c-g-h-v-q-y	15.749	15.117	14.292	11.491	15.695	12.982	14.401	11.759
a-k-e-f-g-h-v-p-y	15.722	15.187	14.073	10.817	15.664	15.079	14.287	10.423
b-m-n-c-f-g-h-t-q-y	15.769	10.064	9.614	7.741	15.671	16.028	15.879	12.068
a-e-f-v-q-y	16.000	16.181	16.537	13.043	16.117	15.476	14.886	10.977
a-b-e-g-h-t-p-y	16.149	15.853	14.969	11.511	15.529	— ^a	— ^a	— ^a
a-b-n-e-g-h-t-q-y	16.591	15.044	13.802	10.722	15.949	10.914	10.155	5.736
a-m-e-f-g-h-t-q-y	16.755	15.297	14.494	10.103	16.723	— ^a	15.264	11.972
a-m-e-g-h-i-q-v-x	16.914	16.031	15.511	13.501	16.115	15.019	14.327	10.222
a-b-g-h-v-q-y	17.100	16.975	15.147	10.910	16.874	15.253	14.220	9.295
b-j-c-e-g-h-w-v-q-x	17.487	16.076	14.118	10.056	16.745	15.815	15.311	12.348
l-c-g-h-v-p-y	17.443	17.440	15.949	14.073	17.728	15.908	14.676	10.442
b-c-f-g-h-v-q-y	17.494	15.416	14.176	9.783	17.196	16.463	15.912	12.671
a-m-n-f-g-h-t-q-y	17.505	17.124	16.044	13.331	17.715	17.133	16.491	12.709
k-c-e-f-g-h-v-p-y	17.665	16.901	16.268	11.167	17.781	17.041	19.876	12.533
b-m-o-c-e-g-h-t-p-y	17.667	18.538	16.398	13.296	17.651	17.727	17.468	16.114
b-c-e-g-h-v-q-y	17.677	17.956	17.790	18.108	17.332	17.534	17.442	15.273
a-l-g-h-v-p-y	17.780	18.227	17.659	16.252	18.319	15.661	14.068	8.131
j-c-e-f-g-h-v-p-x	18.490	15.505	14.838	9.314	17.564	17.316	16.983	12.021
a-m-e-g-h-w-q-v-x	18.087	17.672	17.274	13.672	22.492	20.588	19.295	14.118
m-c-e-f-g-h-t-q-y	18.518	17.670	17.178	14.151	19.183	18.921	18.466	13.369
b-m-n-o-c-g-h-t-q-y	18.686	18.613	18.010	14.352	18.854	14.827	14.723	13.127
r-z-c-f-g-h-q-v-y	18.706	18.612	18.852	15.185	19.324	18.262	17.388	13.134
b-m-c-f-g-h-t-p-y	18.880	17.850	16.717	13.069	18.076	17.173	16.429	13.340
b-j-c-f-g-h-w-v-q-x	18.921	18.148	17.252	14.488	18.081	17.393	16.872	13.513
a-r-g-h-v-q-y	19.069	18.101	17.509	14.629	19.084	17.300	16.054	9.944
r-z-c-e-g-h-v-q-y	19.196	17.208	15.726	11.176	19.851	19.706	19.233	16.360
a-f-g-h-v-q-y	19.471	19.108	18.693	15.688	19.664	18.084	16.983	10.818
a-e-g-h-t-q-y	19.725	17.810	16.874	11.862	19.734	18.088	16.928	9.801
j-r-c-e-g-h-v-p-x	19.726	18.017	16.769	11.143	19.956	18.755	17.767	11.830
a-m-f-g-h-t-p-y	20.642	18.756	17.724	13.614	20.106	18.192	16.865	11.450
a-m-f-g-h-i-v-q-x	20.718	14.397	17.130	12.132	19.566	17.458	16.181	10.065
a-b-g-h-i-v-q-x	20.803	17.978	16.261	11.733	18.678	15.997	14.397	8.532
a-b-g-h-t-p-y	20.676	17.870	16.134	11.710	19.284	16.762	15.204	9.887
b-j-c-g-h-w-v-q-x	21.026	19.569	17.802	12.682	20.122	18.281	17.307	12.058
b-m-o-g-h-t-p-y	20.972	20.028	19.245	17.210	20.729	— ^a	19.113	15.720
k-c-e-f-g-h-v-p-y	21.026	19.569	17.802	12.682	20.956	20.307	19.663	15.826
c-e-f-g-h-v-q-y	21.029	20.280	19.788	16.752	21.142	20.684	20.206	16.634
a-e-g-h-v-q-y	21.111	20.526	20.185	17.446	21.007	19.965	19.066	13.857
b-c-g-h-v-q-y	21.208	19.925	19.134	15.854	21.117	20.134	19.369	14.742

m-o-n-c-g-h-t-q-y	21.668	20.935	19.630	15.886	22.760	22.208	21.538	17.665
a-m-f-g-h-w-v-q-x	22.003	21.476	20.921	16.813	21.605	19.873	18.815	13.331
j-c-e-f-g-h-w-v-q-x	22.045	20.075	19.048	13.855	21.887	21.597	21.191	17.724
m-c-e-f-g-h-i-v-q-x	22.580	22.029	21.693	18.503	26.195	24.748	23.452	17.251
j-s-c-g-h-v-p-x	22.382	21.867	21.135	17.458	20.559	19.160	17.966	10.878
l-c-g-h-v-p-y	22.624	21.044	19.918	13.287	22.469	20.303	18.993	13.089
m-c-f-g-h-t-p-y	22.706	22.094	21.688	18.600	22.405	21.801	21.226	17.467
s-z-c-g-h-v-q-y	23.311	21.638	20.493	16.223	23.632	22.334	21.194	16.267
m-n-c-f-g-h-t-q-y	23.389	22.901	22.100	16.760	23.456	23.049	22.439	16.608
a-e-g-h-i-v-q-x	23.989	21.734	20.952	14.686	22.557	20.429	18.823	12.835
a-e-g-h-t-p-y	24.077	21.893	20.187	16.014	23.412	21.373	19.966	14.327
a-n-t-q-y	24.277	22.383	21.224	14.271	23.831	16.027	15.879	16.559
c-f-g-h-v-q-y	24.726	23.224	22.028	17.383	24.734	23.331	22.316	16.400
c-e-j-g-h-w-q-v-x	24.863	24.021	22.150	17.835	24.428	22.928	21.920	16.559
a-g-h-v-q-y	25.069	22.574	20.984	14.641	24.812	22.633	21.096	13.743
m-o-c-e-g-h-t-p-y	25.377	24.649	24.267	21.431	25.788	25.193	16.439	21.216
c-e-g-h-v-q-y	25.455	24.748	24.073	20.287	25.334	24.818	24.193	19.658
m-c-f-g-h-i-v-q-x	25.860	24.852	22.843	16.362	29.730	27.437	25.737	16.862
j-c-f-g-h-w-v-q-x	26.005	24.599	23.435	17.165	25.369	24.125	23.166	17.451
m-c-f-g-h-t-p-y	26.371	24.784	23.433	18.675	25.871	24.196	23.000	17.176
m-c-t-p-y	26.372	24.462	23.424	18.880	25.872	24.196	22.999	17.244
m-n-o-c-g-h-t-q-y	26.443	25.693	24.816	19.099	26.912	26.329	25.573	19.062
a-g-h-i-q-v-x	28.089	24.793	22.612	15.540	26.295	23.172	21.176	19.062
a-g-h-t-p-y	28.228	24.894	22.432	16.294	27.198	24.108	22.038	14.383
j-c-g-h-w-q-v-x	28.484	25.715	24.141	17.582	27.858	25.475	24.018	16.234
m-o-c-g-h-t-p-y	28.715	26.823	25.871	20.758	28.821	27.251	26.023	19.889
c-g-h-v-q-y	29.358	27.392	26.082	19.821	29.154	27.471	26.224	18.800

Table 8.K2. Parameters of the intramolecular hydrogen bonds (IHB) of the calculated conformers of mbandakamine A *in vacuo*

The IHB length refers to the H...O distance for the O–H...O and N–H...O IHBs and to the H...N distance for the O–H...N IHB. The donor-acceptor distance is O...O for the O–H...O IHB, N...O for the O–H...N IHB and O...N for the N–H...O IHB. The hydrogen bond angle is OĤO for the O–H...O IHB, OĤN for the O–H...N IHB and NĤO for the N–H...O IHB.

Conformers		HF/6-31G(d,p)			DFT/B3LYP/6-31+G(d,p)		
		H...O (Å)	O...O O...N N...O (Å)	OĤO OĤN or NĤO	H...O (Å)	O...O O...N N...O (Å)	OĤO OĤN or NĤO
a-b-k-e-f-g-h-u-v-p-y	H55...O44	1.763	2.586	143.65	1.719	2.585	146.07
	H57...O46	1.771	2.574	141.05	1.730	2.579	143.68
	H53...O47	2.048	2.911	150.73	1.949	2.832	149.44
a-b-l-e-g-h-u-v-p-y	H55...O44	1.763	2.583	143.33	1.718	2.584	146.01
	H57...O46	1.759	2.566	141.56	1.716	2.570	144.18
	H60...O42	2.222	3.021	141.60	2.131	2.965	143.08
a-b-r-e-f-g-h-v-q-y	H55...O44	1.763	2.586	143.58	1.715	2.582	146.12
	H57...O46	1.767	2.571	141.06	1.726	2.576	143.71
	NH63...O4	3.075	3.839	134.04	3.142	3.917	133.79
b-k-c-e-f-g-h-v-p-y	H57...O46	1.759	2.563	141.11	1.717	2.568	143.79
	H53...O47	2.078	2.933	149.45	1.969	2.845	148.46
a-b-k-e-f-g-h-v-p-y	H55...O44	1.779	2.593	142.51	1.735	2.593	144.93
	H57...O46	1.766	2.570	141.10	1.723	2.573	143.76
	H53...O47	2.025	2.898	152.34	1.940	2.831	150.71
a-b-m-e-f-g-h-t-p-y	H55...O44	1.760	2.583	143.47	1.715	2.582	145.96
	H57...O46	1.763	2.568	141.26	1.717	2.569	143.93
	H60...O43	2.299	2.950	125.45	2.256	2.946	127.19
a-b-l-g-h-v-p-y	H55...O44	1.766	2.587	143.55	1.723	2.588	145.92
	H57...O46	1.763	2.572	141.67	1.720	2.574	144.27
	H60...O42	1.980	2.926	176.83	1.889	2.860	174.18
b-l-c-e-g-h-v-p-y	H57...O46	1.750	2.559	141.59	1.707	2.561	144.26
	H60...O42	2.252	3.055	142.26	2.150	2.990	143.83
a-b-m-s-e-f-g-v-p-x	H55...O44	1.787	2.595	141.50	1.719	2.570	144.29
	H57...O46	1.761	2.566	141.30	1.743	2.596	143.82
	H60...O43	2.923	3.084	90.793	3.223	3.203	80.169
	H52...N36	2.295	2.936	124.35	2.062	2.792	129.67
b-r-z-c-e-f-g-h-v-q-y	H57...O46	1.755	2.560	141.13	1.712	2.563	143.80
	NH63...O4	2.799	3.637	141.47	2.756	3.614	141.87
	NH63...O4	2.769	3.616	142.29	2.838	3.702	142.65
a-b-m-s-f-g-h-v-p-x	H55...O44	1.774	2.589	142.53	1.729	2.589	144.91
	H57...O46	1.755	2.562	141.47	1.709	2.562	144.14

	H60...O43	2.268	2.951	128.45	2.098	2.897	138.24
	H53...N36	2.005	2.917	158.67	1.798	2.762	160.92
a-b-k-e-f-g-h-v-p-y	H55...O44	1.779	2.593	142.53	1.735	2.593	148.90
	H57...O46	1.764	2.568	141.11	1.721	2.571	143.78
	H53...O47	2.021	2.870	148.11	1.941	2.811	147.24
a-b-e-f-g-h-v-q-y	H55...O44	1.781	2.594	142.36	1.733	2.591	144.86
	H57...O46	1.762	2.566	141.12	1.721	2.571	143.79
a-b-e-f-m-g-h-t-p-y	H55...O44	1.759	2.582	143.42	1.708	2.577	146.08
	H57...O46	1.759	2.564	141.24	1.712	2.564	143.94
	H60...O43	2.224	2.922	129.90	2.134	2.900	134.50
b-l-c-g-h-p-v-y	H57...O46	1.753	2.563	141.71	1.709	2.564	144.36
	H60...O42	1.987	2.933	176.15	1.881	2.854	176.53
a-b-m-e-f-g-h-q-v-x	H55...O44	1.754	2.576	143.35	1.701	2.572	146.38
	H57...O46	1.769	2.573	141.12	1.722	2.573	143.84
	H60...O43	2.215	2.976	136.74	2.136	2.943	139.33
b-k-c-e-f-g-h-v-p-y	H57...O46	1.761	2.565	141.11	1.716	2.568	143.83
	H53...O47	2.045	2.907	150.39	1.955	2.837	149.24
a-b-l-g-h-p-v-y	H55...O44	1.782	2.595	142.42	1.739	2.596	144.75
	H57...O46	1.757	2.565	141.70	1.712	2.566	144.34
	H60...O42	1.976	2.921	176.52	1.888	2.860	175.54
a-b-m-g-h-w-v-q-x	H55...O44	1.753	2.559	141.34	1.742	2.594	143.98
	H57...O46	1.787	2.593	141.34	1.719	2.570	143.86
	H60...O43	2.568	2.915	102.01	3.001	3.079	85.419
b-m-c-e-f-g-h-t-q-y	H57...O46	1.764	2.569	141.10	1.718	2.570	143.85
	H60...O43	2.243	3.016	138.35	2.123	2.969	144.71
b-j-s-c-e-f-i-g-h-v-p-x	H57...O46	1.768	2.572	141.14	1.724	2.574	143.75
	H55...O47	2.466	3.168	131.02	2.507	3.195	127.76
	H53...N36	2.335	2.962	123.13	2.095	2.810	128.25
b-r-z-c-f-g-h-q-v-y	H57...O46	1.757	2.563	141.22	1.715	2.566	143.88
	NH63...O4	2.769	3.613	142.05	2.735	3.598	142.44
	NH63...O4	2.785	3.628	141.91	2.891	3.754	142.68
a-b-r-g-h-q-v-y	H55...O44	1.768	2.588	143.43	1.720	2.586	144.17
	H57...O46	1.762	2.570	141.58	1.720	2.573	146.12
	NH63...O4	3.007	3.791	135.86	3.093	3.883	135.23
a-b-e-n-g-h-t-q-y	H55...O44	1.796	2.601	141.42	1.747	2.600	144.49
	H57...O46	1.762	2.569	141.57	1.718	2.571	144.21
	H53...O48	2.581	2.997	107.14	3.110	3.234	88.466
k-c-e-f-g-h-p-v-y	H53...O47	2.067	2.926	150.05	1.959	2.839	149.00
a-k-e-f-g-h-v-p-y	H55...O44	1.779	2.593	142.54	1.734	2.593	144.95
	H53...O47	2.019	2.894	152.61	1.935	2.828	151.08
a-b-f-g-h-v-q-y	H55...O44	1.783	2.596	142.39	1.739	2.596	144.83
	H57...O46	1.764	2.568	141.21	1.720	2.571	143.88
a-m-n-e-f-g-h-t-q-y	H55...O44	1.761	2.583	143.49	1.716	2.582	145.94
	H60...O43	2.333	2.960	123.31	2.302	2.966	124.78

	H53...O48	3.097	3.303	94.142	3.161	3.351	92.713
a-l-g-h-p-v-y	H55...O44	1.765	2.587	143.60	1.722	2.587	145.93
	H60...O42	1.981	2.926	176.31	1.893	2.863	173.40
a-b-f-m-g-h-t-p-y	H55...O44	1.763	2.584	143.33	1.714	2.581	145.90
	H57...O46	1.758	2.564	141.35	1.712	2.565	144.02
	H60...O43	2.199	2.919	132.08	2.102	2.886	136.50
b-k-c-e-f-g-h-v-p-y	H57...O46	1.759	2.564	141.13	1.714	2.566	143.86
	H53...O47	2.042	2.880	146.59	1.954	2.818	146.38
b-c-e-f-g-h-v-q-y	H57...O46	1.757	2.562	141.13	1.713	2.565	143.85
a-r-f-g-h-q-v-y	H55...O44	1.766	2.588	143.61	1.720	2.586	146.07
	NH63...O4	3.062	3.833	134.63	3.127	3.905	134.07
a-m-n-e-f-g-h-t-q-y	H55...O44	1.761	2.583	143.48	1.716	2.583	145.94
	H60...O43	2.331	2.960	123.41	2.303	2.966	124.76
	H53...O48	3.098	3.303	94.133	3.161	3.350	92.693
a-b-m-f-g-h-w-v-q-x	H55...O44	1.785	2.594	141.68	1.746	2.598	144.00
	H57...O46	1.759	2.566	141.47	1.721	2.572	143.95
	H60...O43	2.452	2.926	110.99	2.978	3.086	87.202
b-l-c-g-h-v-p-y	H57...O46	1.751	2.561	141.71	1.705	2.561	144.41
	H60...O42	1.973	2.919	176.92	1.880	2.854	176.42
b-m-c-e-f-g-h-t-p-y	H57...O46	1.781	2.594	142.44	1.713	2.565	143.86
	H60...O42	1.977	2.922	175.74	2.391	2.917	118.13
r-z-c-e-f-g-h-v-q-y	NH63...O4	2.804	3.643	141.43	2.775	3.629	141.39
	NH63...O4	2.807	3.648	141.77	2.923	3.777	141.69
a-r-e-g-h-q-v-y	H55...O44	1.763	2.585	143.63	1.714	2.582	146.25
	NH63...O4	3.039	3.812	134.83	3.100	3.890	135.21
b-j-c-e-f-g-h-w-q-v-x	H57...O46	1.765	2.569	141.09	1.727	2.577	143.74
	H55...O47	2.271	3.013	134.89	2.107	2.960	145.38
a-m-s-f-g-h-p-v-x	H55...O44	1.780	2.591	142.01	1.737	2.593	144.67
	H60...O43	2.510	3.005	112.85	2.971	3.163	92.405
	H53...N36	1.997	2.918	160.73	1.777	2.754	164.07
b-r-z-c-g-h-v-q-y	H57...O46	1.752	2.561	141.63	1.708	2.562	144.26
	NH63...O4	2.745	3.594	142.52	2.715	3.585	143.19
	NH63...O4	2.737	3.587	142.66	2.782	3.659	144.30
a-k-e-f-g-h-v-p-y	H55...O44	1.779	2.593	142.55	1.734	2.593	144.95
	H53...O47	2.016	2.866	148.17	1.934	2.807	147.60
b-m-n-c-f-g-h-t-q-y	H57...O46	1.764	2.569	141.20	1.718	2.570	143.91
	H60...O43	2.224	3.014	140.44	2.117	2.975	146.35
	H53...O48	2.636	3.025	105.31	2.576	3.019	108.02
a-e-f-g-h-v-q-y	H55...O44	1.781	2.594	142.35	1.733	2.590	144.87
a-b-e-g-h-t-p-y	H55...O44	1.801	2.604	141.11	1.712	2.566	144.28
	H57...O46	1.758	2.565	141.52	1.748	2.600	144.14
a-b-n-e-g-h-t-q-y	H55...O44	1.798	2.603	141.55	1.751	2.604	144.44
	H57...O46	1.761	2.569	141.63	1.714	2.568	144.26
	H53...O48	2.560	2.952	105.26	2.354	2.889	114.20

a-m-e-f-g-h-t-q-y	H55...O44	1.760	2.582	143.40	1.709	2.577	146.06
	H60...O43	2.259	2.932	127.43	2.176	2.914	131.74
a-m-e-g-h-q-v-x	H55...O44	1.755	2.577	143.38	1.702	2.572	146.33
	H60...O43	2.248	2.990	134.59	2.176	2.963	137.02
a-b-g-h-v-q-y	H55...O44	1.784	2.597	142.43	1.740	2.597	144.81
	H57...O46	1.757	2.565	141.63	1.711	2.565	144.28
b-j-c-e-g-h-w-v-q-x	H57...O46	1.753	2.561	141.47	1.714	2.567	144.08
	H55...O47	2.316	2.913	120.55	2.216	2.918	127.98
l-c-g-h-v-p-y	H60...O42	1.987	2.934	176.12	1.884	2.857	175.95
b-c-f-g-h-v-q-y	H57...O46	1.759	2.565	141.22	1.715	2.567	143.93
a-m-n-f-g-h-t-q-y	H55...O44	1.763	2.586	143.55	1.721	2.587	145.86
	H60...O43	2.337	2.973	124.12	2.319	2.992	125.65
	H53...O48	2.562	2.987	107.66	2.385	2.924	114.67
k-c-e-f-g-h-v-p-y	H53...O47	2.041	2.904	150.54	1.949	2.833	149.51
b-m-o-c-e-g-h-t-p-y	H57...O46	1.744	2.552	141.41	1.694	2.549	144.14
	H60...O43	2.578	2.859	97.452	2.745	2.891	88.788
	H60...O44	2.683	3.565	155.51	3.225	3.995	137.93
b-c-e-g-h-v-q-y	H57...O46	1.749	2.558	141.55	1.703	2.558	144.24
a-l-g-h-v-p-y	H55...O44	1.781	2.594	142.44	1.739	2.595	144.77
	H60...O42	1.977	2.922	175.74	1.891	2.863	174.76
j-s-c-e-f-g-h-v-p-x	H55...O47	2.442	3.165	133.16	2.448	3.176	131.51
	H53...N36	2.334	2.962	123.22	2.084	2.802	128.57
a-m-e-g-h-w-q-v-x	H55...O44	1.719	2.594	140.99	1.719	2.586	146.19
	H60...O43	2.926	2.926	91.545	3.060	3.179	88.156
m-c-e-f-g-h-t-q-y	H60...O43	2.286	3.033	135.53	2.183	3.000	140.96
b-m-n-o-c-g-h-t-q-y	H57...O46	1.746	2.554	141.48	1.699	2.553	144.18
	H60...O43	2.710	2.931	93.940	2.970	3.002	82.550
	H53...O48	2.707	3.007	99.321	2.510	2.928	106.01
	H60...O44	2.760	3.604	149.27	3.276	3.972	130.49
r-z-c-f-g-h-v-q-y	NH63...O4	2.776	3.620	142.01	2.753	3.613	142.05
	NH63...O4	2.823	3.662	141.48	2.968	3.824	141.92
b-m-c-f-g-h-t-p-y	H57...O46	1.761	2.566	141.21	1.713	2.566	143.98
	H60...O43	2.093	2.954	150.57	1.978	2.898	156.67
b-j-c-f-g-h-v-q- x	H57...O46	1.767	2.572	141.19	1.726	2.577	143.83
	H55...O47	2.292	3.046	136.38	2.138	2.972	142.99
a-r-g-h-q-v-y	H55...O44	1.767	2.588	143.56	1.719	2.586	146.17
	NH63...O4	3.014	3.796	135.71	3.084	3.875	135.29
r-z-c-e-g-h-v-q-y	NH63...O4	2.786	3.628	141.87	2.746	3.607	142.21
	NH63...O4	2.747	3.597	142.74	2.892	3.756	142.71
a-f-g-h-v-q-y	H55...O44	1.783	2.596	142.40	1.738	2.595	144.84
a-e-g-h-t-q-y	H55...O44	1.799	2.601	141.08	1.747	2.600	144.38
j-r-c-e-g-h-v-p-x	H55...O47	2.423	3.028	121.59	2.434	3.050	120.85
	H53...N36	2.335	2.962	123.13	2.088	2.806	128.58
a-m-f-g-h-t-p-y	H55...O44	1.764	2.585	143.33	1.715	2.581	145.89

	H60...O43	2.234	2.930	129.61	2.145	2.902	133.51
a-m-f-g-h-i-v-q-x	H55...O44	1.759	2.579	143.23	1.707	2.576	146.19
	H60...O43	2.214	2.978	137.05	2.140	2.943	138.83
a-b-g-h-i-v-q-x	H55...O44	1.795	2.600	141.52	1.741	2.596	144.84
	H57...O46	1.771	2.578	141.53	1.726	2.578	144.15
a-b-g-h-t-p-y	H55...O44	1.798	2.605	141.72	1.751	2.603	144.33
	H57...O46	1.754	2.562	141.61	1.710	2.564	144.23
b-j-c-g-h-w-v-q-x	H55...O44	1.757	2.566	141.56	1.716	2.569	144.16
	H57...O46	2.315	2.941	123.12	2.232	2.929	127.63
b-m-o-g-h-t-p-y	H53...O47	1.743	2.551	141.55	1.695	2.550	144.24
	H60...O43	2.530	2.854	100.25	2.592	2.854	95.582
	H60...O44	3.002	3.872	153.74	3.217	4.048	145.09
k-c-e-f-g-h-v-p-y	H53...O47	2.039	2.877	146.49	1.948	2.814	146.60
a-e-g-h-v-q-y	H55...O44	1.782	2.595	142.39	1.735	2.592	144.85
b-c-g-h-v-q-y	H57...O46	1.752	2.561	141.65	1.704	2.560	144.33
m-o-n-c-g-h-t-q-y	H60...O43	2.755	2.906	89.609	2.669	2.876	92.274
	H53...O48	3.007	3.317	100.80	3.071	3.417	102.62
	H60...O44	2.634	3.458	146.05	2.300	3.204	92.274
a-m-f-g-h-w-q-v-x	H55...O44	1.785	2.594	141.68	1.747	2.598	144.00
	H60...O43	2.452	2.926	110.99	3.139	3.134	80.829
j-c-e-f-g-h-w-v-q-x	H55...O47	2.432	2.926	112.47	2.095	2.955	146.47
m-c-e-f-g-h-q-v-x	H60...O43	2.198	3.041	147.85	3.246	3.243	81.253
j-s-c-g-h-v-p-x	H55...O47	2.368	2.974	121.48	2.284	2.962	125.99
	H53...N36	2.015	2.931	159.79	1.811	2.775	161.50
l-c-g-h-v-p-y	H60...O42	1.974	2.920	176.04	1.884	2.856	175.60
m-c-f-g-h-t-p-y	H60...O43	2.171	2.993	144.68	2.042	2.936	152.08
r-z-c-g-h-v-q-y	NH63...O4	2.749	3.597	142.55	2.712	3.580	142.99
	NH63...O4	2.772	3.618	142.28	2.878	3.744	143.00
m-n-c-f-g-h-t-q-y	H60...O43	2.270	3.033	137.22	2.187	3.012	141.98
	H53...O48	2.616	3.015	105.98	2.542	2.998	108.85
a-e-g-h-i-v-q-x	H55...O44	1.794	2.597	141.11	1.737	2.593	144.75
a-e-g-h-t-p-y	H55...O44	1.804	2.604	140.72	1.750	2.601	144.13
a-n-t-q-y	H55...O44	1.800	2.603	141.20	1.751	2.6031	144.33
	H53...O48	2.546	2.948	106.03	2.327	2.883	115.85
j-c-e-g-h-q-v-x	H55...O47	2.431	2.926	112.47	2.183	2.912	130.57
a-g-h-v-q-y	H55...O44	1.784	2.597	142.44	1.740	2.597	144.81
m-o-c-e-g-h-t-p-y	H60...O43	2.629	2.857	94.105	2.673	2.856	90.790
	H60...O44	2.712	3.570	151.29	2.682	3.541	148.15
m-c-f-g-h-v-q-x	H60...O43	2.156	3.015	150.25	3.169	3.215	83.984
j-c-f-g-h-q-v-x	H55...O47	2.431	2.926	112.47	2.120	2.966	144.43
m-c-f-g-h-t-p-y	H60...O43	2.126	2.970	147.83	2.382	2.917	154.37
m-c-g-h-t-p-y	H60...O43	2.124	2.969	147.91	2.009	2.917	154.38
m-n-o-c-g-h-t-q-y	H60...O43	2.767	2.936	90.809	3.062	3.027	78.801
	H53...O48	2.676	2.994	100.44	2.414	2.902	110.86

	H60...O44	2.819	3.632	144.85	3.393	3.393	125.02
a-g-h-q-v-x	H55...O44	1.797	2.600	141.15	1.741	2.596	144.76
a-g-h-t-p-y	H55...O44	1.801	2.605	141.39	1.752	2.603	144.22
j-c-g-h-v-q-x	H55...O47	2.431	2.926	112.47	2.200	2.923	130.02
m-o-c-g-h-t-p-y	H60...O43	2.587	2.854	96.593	2.697	2.875	90.608
	H60...O44	3.037	3.878	149.31	3.285	4.066	139.10

Table 8.K3. Distance (Å) between the H atom and the closest C atom in the acceptor aromatic ring for the O–H $\cdots\pi$ interactions in selected conformers of mbandakamine A *in vacuo*

conformers	IHB	Closest C atom	H $\cdots$ C distance	
			HF	DFT
a-b-k-e-f-g-h-u-v-p-y	O42–H53 $\cdots\pi$	C11	2.531	2.336
	O47–H60 $\cdots\pi$	C23	2.356	2.550
a-b-l-e-g-h-u-v-p-y	O42–H53 $\cdots\pi$	C11	2.337	2.317
a-b-r-e-f-g-h-v-q-y	O42–H53 $\cdots\pi$	C11	2.316	2.294
	O47–H60 $\cdots\pi$	C23	2.351	2.336
b-k-c-e-f-g-h-v-p-y	O43–H55 $\cdots\pi$	C21	2.295	2.271
	O42–H53 $\cdots\pi$	C11	2.527	2.545
	O47–H60 $\cdots\pi$	C23	2.360	2.344
a-b-k-e-f-g-h-v-p-y	O42–H53 $\cdots\pi$	C11	2.511	2.342
	O47–H60 $\cdots\pi$	C23	2.358	2.525
a-b-m-e-f-g-h-t-p-y	O42–H53 $\cdots\pi$	C11	2.374	2.442
	O47–H60 $\cdots\pi$	C23	2.437	2.363
b-l-c-e-g-h-v-p-y	O43–H55 $\cdots\pi$	C21	2.295	2.343
	O42–H53 $\cdots\pi$	C11	2.332	2.309
a-b-m-s-e-f-g-v-p-x	O42–H53 $\cdots\pi$	C11	2.580	2.652
	O47–H60 $\cdots\pi$	C23	2.429	2.352
b-r-z-c-e-f-g-h-v-q-y	O43–H55 $\cdots\pi$	C21	2.298	2.265
	O42–H53 $\cdots\pi$	C11	2.312	2.285
	O47–H60 $\cdots\pi$	C23	2.355	2.337
a-b-m-s-f-g-h-v-p-x	O47–H60 $\cdots\pi$	C23	2.715	2.813
a-b-k-e-f-g-h-v-p-y	O42–H53 $\cdots\pi$	C11	2.495	2.514
	O47–H60 $\cdots\pi$	C23	2.353	2.334
a-b-e-f-g-h-v-q-y	O42–H53 $\cdots\pi$	C11	2.317	2.294
	O47–H60 $\cdots\pi$	C23	2.351	2.337
a-b-m-e-f-g-h-t-p-y	O42–H53 $\cdots\pi$	C11	2.328	2.306
	O47–H60 $\cdots\pi$	C23	2.461	2.489
b-l-c-g-h-v-p-y	O43–H55 $\cdots\pi$	C21	2.291	2.262
a-b-m-e-f-g-h-i-v-q-x	O42–H53 $\cdots\pi$	C11	2.330	2.304
	O47–H60 $\cdots\pi$	C23	2.444	2.454
b-k-c-e-f-g-h-v-p-y	O43–H55 $\cdots\pi$	C21	2.347	2.276
	O42–H53 $\cdots\pi$	C11	2.493	2.509
	O47–H60 $\cdots\pi$	C23	2.363	2.351
b-m-c-e-f-g-h-t-q-y	O43–H55 $\cdots\pi$	C21	2.254	2.215
	O42–H53 $\cdots\pi$	C11	2.372	2.360
	O47–H60 $\cdots\pi$	C23	2.545	2.596
b-j-s-c-e-f-g-h-v-p-x	O43–H55 $\cdots\pi$	C21	2.328	2.383
	O42–H53 $\cdots\pi$	C11	2.564	2.634
	O47–H60 $\cdots\pi$	C23	2.411	2.304
b-r-z-c-f-g-h-v-q-y	O43–H55 $\cdots\pi$	C21	2.301	2.273

	O47-H60... π	C23	2.357	2.343
a-b-n-e-g-h-t-q-y	O42-H53... π	C11	2.367	2.352
k-c-e-f-g-h-v-p-y	O43-H55... π	C21	2.296	2.273
	O42-H53... π	C11	2.532	2.335
	O47-H60... π	C23	2.353	2.549
a-k-e-f-g-h-v-p-y	O42-H53... π	C11	2.513	2.528
	O47-H60... π	C23	2.351	2.332
a-b-f-g-h-v-q-y	O47-H60... π	C23	2.355	2.341
a-m-n-e-f-g-h-t-q-y	O42-H53... π	C11	2.376	2.416
	O47-H60... π	C23	2.418	2.366
a-b-m-f-g-h-t-p-y	O47-H60... π	C23	2.487	2.520
b-k-c-e-f-g-h-v-p-y	O43-H55... π	C21	2.298	2.269
	O42-H53... π	C11	2.479	2.502
	O47-H60... π	C23	2.359	2.343
b-c-e-f-g-h-v-q-y	O43-H55... π	C21	2.301	2.278
	O42-H53... π	C11	2.315	2.288
	O47-H60... π	C23	2.344	2.345
a-r-f-g-h-q-v-y	O47-H60... π	C23	2.346	2.328
a-m-n-e-f-g-h-t-q-y	O42-H53... π	C11	2.307	2.366
	O47-H60... π	C23	2.369	2.416
a-b-m-f-g-h-w-q-v-x	O47-H60... π	C23	2.619	2.408
b-l-c-g-h-v-p-y	O43-H55... π	C21	2.296	2.265
b-m-c-e-f-g-h-t-p-y	O43-H55... π	C21	2.260	2.221
	O42-H53... π	C11	2.326	2.303
	O47-H60... π	C23	2.605	2.666
r-z-c-e-f-g-h-v-q-y	O43-H55... π	C21	2.298	2.270
	O42-H53... π	C11	2.311	2.283
	O47-H60... π	C23	2.348	2.329
a-r-e-g-h-q-v-y	O42-H53... π	C11	2.315	2.295
b-j-c-e-f-g-h-w-v-q-x	O43-H55... π	C21	2.445	2.486
	O42-H53... π	C11	2.303	2.285
	O47-H60... π	C23	2.335	2.321
a-m-s-f-g-h-v-p-x	O47-H60... π	C23	2.571	2.412
b-r-z-c-g-h-v-q-y	O43-H55... π	C21	2.294	2.257
a-k-e-f-g-h-v-p-y	O42-H53... π	C11	2.345	2.517
	O47-H60... π	C23	2.496	2.323
b-m-n-c-f-g-h-t-q-y	O43-H55... π	C21	2.258	2.220
	O47-H60... π	C23	2.560	2.608
a-e-f-g-h-v-q-y	O42-H53... π	C11	2.315	2.293
	O47-H60... π	C23	2.344	2.326
a-b-e-g-h-t-p-y	O42-H53... π	C11	2.321	2.293
a-b-n-e-g-h-t-q-y	O42-H53... π	C11	2.367	2.352
a-m-e-f-g-h-t-q-y	O42-H53... π	C11	2.325	2.459
	O47-H60... π	C23	2.440	2.301

a-m-e-g-h-i-q-v-x	O42-H53... π	C11	2.326	2.299
	O47-H60... π	C23	2.425	2.432
b-j-c-e-g-h-w-v-q-x	O43-H55... π	C21	2.346	2.349
	O42-H53... π	C11	2.301	2.276
l-c-g-h-v-p-y	O43-H55... π	C21	2.292	2.263
b-c-f-g-h-v-q-y	O43-H55... π	C21	2.304	2.282
	O47-H60... π	C23	2.358	2.350
a-m-n-f-g-h-t-q-y	O47-H60... π	C23	2.422	2.426
k-c-e-f-g-h-v-p-y	O43-H55... π	C21	2.305	2.283
	O42-H53... π	C11	2.493	2.342
	O47-H60... π	C23	2.357	2.283
b-m-o-c-e-g-h-t-p-y	O43-H55... π	C21	2.326	2.283
	O42-H53... π	C11	2.326	2.293
b-c-e-g-h-v-q-y	O43-H55... π	C21	2.291	2.256
	O42-H53... π	C11	2.315	2.285
j-s-c-e-f-g-h-v-p-x	O43-H55... π	C21	2.419	2.402
	O42-H53... π	C11	2.565	2.640
	O47-H60... π	C23	2.327	2.302
a-m-e-g-h-w-v-q-x	O42-H53... π	C11	2.189	2.296
m-c-e-f-g-h-t-q-y	O43-H55... π	C21	2.257	2.224
	O42-H53... π	C11	2.374	2.362
	O47-H60... π	C23	2.519	2.553
b-m-n-o-c-g-h-t-q-y	O43-H55... π	C21	2.303	2.255
r-z-c-f-g-h-v-q-y	O43-H55... π	C21	2.348	2.277
	O47-H60... π	C23	2.350	2.334
b-m-c-f-g-h-t-p-y	O43-H55... π	C21	2.264	2.222
	O47-H60... π	C23	2.626	2.689
b-j-c-f-g-h-w-v-q-x	O43-H55... π	C21	2.446	2.482
	O47-H60... π	C23	2.330	2.310
r-z-c-e-g-h-v-q-y	O43-H55... π	C21	2.292	2.260
	O42-H53... π	C11	2.310	2.282
a-f-g-h-v-q-y	O47-H60... π	C23	2.347	2.330
a-e-g-h-t-q-y	O42-H53... π	C11	2.370	2.355
j-r-c-e-g-h-v-p-x	O43-H55... π	C21	2.339	2.317
	O42-H53... π	C11	2.575	2.652
a-m-f-g-h-t-p-y	O47-H60... π	C23	2.463	2.488
a-m-f-g-h-i-v-q-x	O47-H60... π	C23	2.439	2.453
b-j-c-g-h-w-v-q-x	O43-H55... π	C21	2.347	2.350
k-c-e-f-g-h-v-p-y	O43-H55... π	C21	2.302	2.274
	O42-H53... π	C11	2.479	2.504
	O47-H60... π	C23	2.353	2.334
c-e-f-g-h-v-q-y	O43-H55... π	C21	2.305	2.287
	O42-H53... π	C11	2.316	2.287
	O47-H60... π	C23	2.347	2.335

a-e-g-h-v-q-y	O42-H53... π	C11	2.314	2.292
b-c-g-h-v-q-y	O43-H55... π	C21	2.295	2.260
m-o-n-c-g-h-t-q-y	O43-H55... π	C21	2.321	2.284
a-m-f-g-h-w-v-q-x	O47-H60... π	C23	2.619	2.361
j-c-e-f-g-h-w-v-q-x	O43-H55... π	C21	2.251	2.489
	O42-H53... π	C11	2.189	2.282
	O47-H60... π	C23	2.334	2.319
m-c-e-f-g-h-i-v-q-x	O43-H55... π	C21	2.276	2.283
	O42-H53... π	C11	2.322	2.296
	O47-H60... π	C23	2.551	2.521
m-c-e-f-g-h-t-p-y	O43-H55... π	C21	2.263	2.229
	O42-H53... π	C11	2.324	2.299
	O47-H60... π	C23	2.573	2.632
r-z-c-g-h-v-q-y	O43-H55... π	C21	2.294	2.264
m-n-c-f-g-h-t-q-y	O43-H55... π	C21	2.260	2.224
	O47-H60... π	C23	2.530	2.564
a-e-g-h-i-v-q-x	O42-H53... π	C11	2.321	2.305
a-e-g-h-t-p-y	O42-H53... π	C11	2.318	2.290
c-f-g-h-v-q-y	O43-H55... π	C21	2.308	2.291
	O47-H60... π	C23	2.351	2.340
j-c-e-g-h-w-q-v-x	O43-H55... π	C21	2.251	2.363
	O42-H53... π	C21	2.189	2.273
m-o-c-e-g-h-t-p-y	O43-H55... π	C21	2.348	2.296
	O42-H53... π	C11	2.324	2.289
c-e-g-h-v-q-y	O43-H55... π	C21	2.295	2.262
	O42-H53... π	C11	2.314	2.284
m-c-f-g-h-i-v-q-x	O43-H55... π	C21	2.282	2.289
	O47-H60... π	C23	2.568	2.546
j-c-f-g-h-w-v-q-x	O43-H55... π	C21	2.251	2.488
	O47-H60... π	C23	2.334	2.966
m-c-f-g-h-t-p-y	O43-H55... π	C21	2.267	2.230
	O47-H60... π	C23	2.596	2.654
m-c-f-g-h-t-p-y	O43-H55... π	C21	2.266	2.230
	O47-H60... π	C23	2.598	2.655
m-n-o-c-g-h-t-q-y	O43-H55... π	C21	2.318	2.263
j-c-g-h-w-q-v-x	O43-H55... π	C21	2.251	2.363
m-n-c-g-h-t-p-y	O43-H55... π	C21	2.336	2.301
c-g-h-v-q-y	O43-H55... π	C21	2.297	2.264

Table 8.K4. Parameters of the C–H···O and C–H···N IHB interactions of the calculated conformers mbandakamine A *in vacuo*

The IHB length refers to the H···O distance for the C–H···O IHB and to the H···N distance for the C–H···N IHB. The donor-acceptor distance is C···O for the C–H···O IHB and C···N for the C–H···N IHB. The hydrogen bond angle is C $\hat{H}$ O for the C–H···O IHB and C $\hat{H}$ N for the C–H···N IHB.

Conformer	IHB	HF/6-31G(d,p)			DFT/B3LYP/6-31+G(d,p)		
		H···O (Å)	O·· C	O $\hat{H}$ C	H···O (Å)	O··C (Å)	O $\hat{H}$ C
a-b-k-e-f-g-h-u-v-p-y	C-H50···O41	2.525	3.10	112.49	2.531	3.124	112.968
	C-H62···O48	2.531	3.10	112.46	2.522	3.118	113.165
	C-H59···O43	2.711	3.40	117.85	2.604	3.329	122.989
a-b-l-e-g-h-u-v-p-y	C-H50···O41	2.528	3.10	112.42	2.530	3.122	112.917
	C-H62···O48	2.525	3.10	112.57	2.504	3.105	113.457
	C-H59···O43	2.594	3.27	120.03	2.527	3.224	120.491
a-b-r-e-f-g-h-v-q-y	C-H50···O41	2.520	3.10	112.53	2.526	3.118	112.911
	C-H62···O48	2.526	3.10	112.55	2.511	3.111	113.362
b-k-c-e-f-g-h-v-p-y	C-H50···O41	2.527	3.10	112.45	2.528	3.121	112.981
	C-H62···O48	2.562	3.13	111.95	2.556	3.143	112.611
a-b-k-e-f-g-h-v-p-y	C-H50···O41	2.526	3.10	112.49	2.533	3.126	112.938
	C-H62···O48	2.338	2.94	114.06	2.313	2.942	114.879
	C-H59···O43	2.711	3.40	117.85	2.729	3.437	121.994
a-b-m-e-f-g-h-t-p-y	C-H50···O41	2.536	3.11	112.29	2.539	3.128	112.780
	C-H62···O48	2.339	2.94	114.03	2.313	2.944	115.007
a-b-l-g-h-v-p-y	C-H50···O41	2.529	3.10	112.32	2.529	3.120	112.821
	C-H62···O48	2.538	3.11	112.37	2.529	3.123	112.983
b-l-c-e-g-h-v-p-y	C-H50···O41	2.529	3.10	112.40	2.530	3.123	112.929
	C-H62···O48	2.549	3.12	112.22	2.525	3.121	113.225
a-b-m-s-e-f-g-v-p-x	C-H50···O41	2.526	3.10	112.42	2.519	3.115	113.116
	C-H62···O48	2.324	2.92	113.71	2.302	2.934	115.041
b-r-z-c-e-f-g-h-v-q-y	C-H50···O41	2.521	3.10	112.50	2.516	3.112	112.593
	C-H62···O48	2.567	3.13	111.88	2.558	3.144	113.179
a-b-m-s-f-g-h-v-p-x	C-H50···O41	2.512	3.09	112.64	2.273	2.884	113.222
	C-H62···O48	2.305	2.89	112.48	2.515	3.112	113.434
a-b-k-e-f-g-h-v-p-y	C-H50···O41	2.389	2.98	113.47	2.359	2.984	114.685
	C-H62···O48	2.337	2.94	114.07	2.311	2.942	114.951
a-b-e-f-g-h-v-q-y	C-H50···O41	2.521	3.10	112.51	2.527	3.120	112.922
	C-H62···O48	2.336	2.94	114.05	2.304	2.935	114.928
a-b-m-e-f-g-h-t-p-y	C-H50···O41	2.476	3.06	112.99	2.484	3.085	113.418
	C-H62···O48	2.341	2.94	113.84	2.308	2.937	114.830
b-l-c-g-h-v-p-y	C-H50···O41	2.532	3.10	112.27	2.533	3.123	112.811

	C-H62...048	2.563	3.13	111.94	2.556	3.142	112.571
a-b-m-e-f-g-h-i-v-q-x	C-H50...O41	2.476	2.73	112.04	2.536	3.124	112.688
	C-H62...048	2.383	2.98	113.91	2.354	3.918	114.918
	C-H52...047	2.873	3.91	160.17	2.875	3.918	159.536
b-k-c-e-f-g-h-v-p-y	C-H50...O41	2.527	3.10	112.48	2.532	3.125	112.950
	C-H62...048	2.327	2.93	114.03	2.302	2.930	114.778
a-b-l-g-h-v-p-y	C-H50...O41	2.530	3.10	112.31	2.534	3.124	112.821
	C-H62...048	2.345	2.95	114.10	2.317	2.951	115.197
a-b-m-g-h-w-v-q-x	C-H50...O41	2.409	3.00	111.89	2.541	3.126	112.426
	C-H62...048	2.543	3.11	113.15	2.376	2.996	114.404
	C-H52...N36	2.688	3.75	169.34	2.649	3.718	165.660
b-m-c-e-f-g-h-t-q-y	C-H50...O41	2.535	3.11	112.31	2.530	3.123	112.941
	C-H62...048	2.338	2.94	114.02	2.306	2.938	114.959
b-j-s-c-e-f-g-h-v-p-x	C-H50...O41	2.525	3.10	112.48	2.516	3.113	113.199
	C-H62...048	2.319	2.92	113.45	2.296	2.920	114.492
b-r-z-c-f-g-h-v-q-y	C-H50...O41	2.524	3.10	112.42	2.521	3.115	113.041
	C-H62...048	2.567	3.13	111.88	2.558	3.144	112.623
a-b-r-g-h-v-q-y	C-H50...O41	2.528	3.10	112.37	2.520	3.114	113.046
	C-H62...048	2.528	3.10	112.51	2.510	3.110	113.384
a-b-n-e-g-h-t-q-y	C-H50...O41	2.534	3.11	112.32	2.536	3.127	112.842
	C-H62...048	2.343	2.95	113.97	2.317	2.948	114.938
k-c-e-f-g-h-v-p-y	C-H50...O41	2.527	3.10	112.45	2.529	3.122	112.976
	C-H62...048	2.559	3.13	112.00	2.548	3.137	112.757
a-k-e-f-g-h-v-p-y	C-H50...O41	2.526	3.10	112.50	2.534	3.126	112.942
	C-H62...048	2.339	2.94	114.06	2.312	2.942	114.886
a-b-f-g-h-v-q-y	C-H50...O41	2.523	3.10	112.45	2.529	3.121	112.891
	C-H62...048	2.336	2.94	114.07	2.304	2.935	114.955
a-m-n-e-f-g-h-t-q-y	C-H50...O41	2.535	3.11	112.30	2.538	3.128	112.798
	C-H62...048	2.340	2.94	114.03	2.315	2.946	115.002
a-l-g-h-v-p-y	C-H50...O41	2.528	3.10	112.33	2.531	3.124	112.813
	C-H62...048	2.536	3.11	112.41	2.529	3.120	112.992
a-b-m-f-g-h-t-p-y	C-H50...O41	2.482	3.06	112.84	2.489	3.089	113.312
	C-H62...048	2.341	2.94	113.88	2.310	2.940	114.966
b-k-c-e-f-g-h-v-p-y	C-H50...O41	2.390	2.98	113.46	2.361	2.986	114.661
	C-H62...048	2.327	2.93	114.03	2.300	2.930	114.935
b-c-e-f-g-h-v-q-y	C-H50...O41	2.523	3.10	112.51	2.529	3.121	112.902
	C-H62...048	2.325	2.93	114.03	2.298	2.924	114.606
a-r-f-g-h-q-v-y	C-H50...O41	2.523	3.10	112.44	2.528	3.120	112.874
	C-H62...048	2.525	3.10	112.57	2.513	3.112	113.384
a-m-n-e-f-g-h-t-q-y	C-H50...O41	2.540	3.11	112.20	2.538	3.128	112.798
	C-H62...048	2.337	2.94	114.10	2.314	2.946	115.009
a-b-m-f-g-h- w q-v-x	C-H50...O41	2.540	3.11	111.90	2.538	3.123	112.474
	C-H62...048	2.400	2.99	113.28	2.370	2.993	114.547
	C-H52...N36	2.699	3.76	169.45	2.677	3.739	163.557

b-l-c-g-h-v-p-y	C-H50...O41	2.531	3.10	112.30	2.534	3.125	112.829
	C-H62...048	2.334	2.94	114.09	2.305	2.940	115.248
b-m-c-e-f-g-h-t-p-y	C-H50...O41	2.479	3.06	112.95	2.478	3.082	113.550
	C-H62...048	2.339	2.94	113.82	2.297	2.927	114.836
r-z-c-e-f-g-h-v-q-y	C-H50...O41	2.521	3.10	112.50	2.517	3.113	113.164
	C-H62...048	2.565	3.13	111.91	2.551	3.139	112.732
a-r-e-g-h-q-v-y	C-H50...O41	2.526	3.10	112.43	2.517	3.112	113.094
	C-H62...048	2.524	3.10	112.57	2.507	3.107	113.427
b-j-c-e-f-g-h-w-v-q-x	C-H50...O41	2.544	3.11	111.92	2.530	3.119	112.665
	C-H62...048	2.404	2.99	113.06	2.354	2.977	114.473
	C-H52...N36	2.706	3.77	170.81	2.683	3.747	164.000
a-m-s-f-g-h-v-p-x	C-H50...O41	2.508	3.09	112.70	2.505	3.104	113.311
	C-H62...048	2.307	2.89	112.59	2.275	2.898	114.275
b-r-z-c-g-h-v-q-y	C-H50...O41	2.528	3.10	112.36	2.525	3.118	112.918
	C-H62...048	2.571	3.13	111.81	2.561	3.147	112.570
a-e-f-k-g-h-v-p-y	C-H50...O41	2.389	2.98	113.48	2.359	2.984	114.688
	C-H62...048	2.338	2.94	114.07	2.311	2.942	114.956
b-m-n-c-f-g-h-t-q-y	C-H50...O41	2.541	3.11	112.18	2.540	3.129	112.750
	C-H62...048	2.361	2.96	113.95	2.327	2.958	115.031
a-e-f-g-h-v-q-y	C-H50...O41	2.522	3.10	112.51	2.528	3.120	112.916
	C-H62...048	2.337	2.94	114.05	2.304	2.934	114.912
a-b-e-g-h-t-p-y	C-H50...O41	2.472	3.06	113.02	2.475	3.079	113.561
	C-H62...048	2.348	2.95	113.69	2.313	2.940	114.724
a-b-n-e-g-h-t-q-y	C-H50...O41	2.541	3.11	112.16	2.536	3.126	112.783
	C-H62...048	2.364	2.96	113.84	2.331	2.959	114.844
a-m-e-f-g-h-t-q-y	C-H50...O41	2.476	3.06	112.98	2.483	3.084	113.432
	C-H62...048	2.342	2.94	113.84	2.309	2.938	114.825
a-m-e-g-h-i-q-v-x	C-H50...O41	2.543	3.11	112.03	2.536	3.124	112.677
	C-H62...048	2.383	3.89	113.92	2.354	2.982	114.946
	C-H52...047	2.860	3.89	160.05	2.863	3.905	159.100
a-b-g-h-v-q-y	C-H50...O41	2.524	3.10	112.44	2.513	3.110	113.154
	C-H62...048	2.336	2.94	113.99	2.308	2.938	114.876
b-j-c-e-g-h-w-v-q-x	C-H50...O41	2.543	3.11	111.92	2.536	3.123	112.580
	C-H62...048	2.402	2.99	113.05	2.364	2.983	114.300
	C-H52...N36	2.694	3.76	170.47	2.661	3.736	167.386
l-c-g-h-v-p-y	C-H50...O41	2.531	3.10	112.28	2.533	3.123	112.817
	C-H62...048	2.560	3.13	111.99	2.548	3.136	112.699
b-c-f-g-h-v-q-y	C-H50...O41	2.525	3.10	112.44	2.531	3.122	112.867
	C-H62...048	2.325	2.93	114.08	2.298	2.925	114.644
a-m-n-f-g-h-t-q-y	C-H50...O41	2.542	3.11	112.15	2.539	3.128	114.973
	C-H62...048	2.361	2.96	113.95	2.328	2.958	112.747
k-c-e-f-g-h-v-p-y	C-H50...O41	2.527	3.10	112.48	2.532	3.125	112.956
	C-H62...048	2.328	2.93	114.03	2.303	2.931	114.761
b-m-o-c-e-g-h-t-p-y	C-H50...O41	2.474	3.06	112.99	2.484	3.085	113.368

	C-H62...048	2.346	2.95	113.85	2.320	2.949	114.841
b-c-e-g-h-v-q-y	C-H50...O41	2.524	3.10	112.51	2.516	3.112	113.134
	C-H62...048	2.323	2.93	114.00	2.300	2.928	114.743
a-l-g-h-v-p-y	C-H50...O41	2.530	3.10	112.32	2.533	3.124	112.826
	C-H62...048	2.346	2.95	114.10	2.317	2.951	115.205
j-s-c-e-f-g-h-v-p-x	C-H50...O41	2.525	3.10	112.48	2.512	3.110	113.243
	C-H62...048	2.319	2.92	113.46	2.296	2.918	114.241
a-m-e-g-h-w-q-v-x	C-H50...O41	2.540	3.11	111.87	2.532	3.119	112.566
	C-H62...048	2.400	2.99	113.12	2.369	2.991	114.443
	C-H52...N36	2.699	3.76	168.70	2.657	3.712	161.950
m-c-e-f-g-h-t-q-y	C-H50...O41	2.534	3.11	112.33	2.533	3.124	112.887
	C-H62...048	2.340	2.94	114.01	2.312	2.943	114.951
b-m-n-o-c-g-h-t-q-y	C-H50...O41	2.547	3.11	112.05	2.549	3.135	112.726
	C-H62...048	2.362	2.97	114.02	2.332	2.963	115.032
r-z-c-f-g-h-q-v-y	C-H50...O41	2.524	3.10	112.42	2.522	3.116	113.026
	C-H62...048	2.565	3.13	111.92	2.551	3.140	112.748
b-m-c-f-g-h-t-p-y	C-H50...O41	2.483	3.07	112.86	2.484	3.086	113.404
	C-H62...048	2.339	2.94	113.86	2.298	2.928	114.892
b-j-c-f-g-h-w-v-q-x	C-H50...O41	2.539	3.11	111.97	2.530	3.119	112.686
	C-H62...048	2.394	2.98	113.22	2.358	2.980	114.456
	C-H52...N36	2.728	3.79	168.61	2.686	3.758	166.470
a-r-g-h-v-q-y	C-H50...O41	2.529	3.10	112.36	2.522	3.115	113.018
	C-H62...048	2.525	3.10	112.56	2.509	3.109	113.434
r-z-c-e-g-h-v-q-y	C-H50...O41	2.526	3.10	112.43	2.522	3.116	112.990
	C-H62...048	2.569	3.13	111.85	2.553	3.141	112.706
a-f-g-h-v-q-y	C-H50...O41	2.524	3.10	112.44	2.303	2.934	112.879
	C-H62...048	2.337	2.94	114.08	2.530	3.121	114.963
a-e-g-h-t-q-y	C-H50...O41	2.533	3.11	112.34	2.535	3.126	112.865
	C-H62...048	2.344	2.95	113.96	2.318	2.948	114.937
j-r-c-e-g-h-v-p-x	C-H50...O41	2.527	3.10	112.43	2.522	3.117	113.056
	C-H62...048	2.322	2.92	113.27	2.300	2.927	114.682
a-m-f-g-h-t-p-y	C-H50...O41	2.481	3.06	112.85	2.487	3.088	113.334
	C-H62...048	2.342	2.94	113.88	2.310	2.941	114.952
a-m-f-g-h-i-v-q-x	C-H50...O41	2.477	3.06	112.88	2.473	3.078	113.605
	C-H62...048	2.348	2.95	113.76	2.310	2.941	115.000
a-b-g-h-i-v-q-x	C-H50...O41	2.544	3.11	113.96	2.529	3.119	112.802
	C-H62...048	2.383	3.89	111.99	2.352	2.982	115.028
	C-H52...047	2.866	3.89	159.20	2.907	3.935	156.605
a-b-g-h-t-p-y	C-H50...O41	2.544	3.11	111.97	2.547	3.131	112.414
	C-H62...048	2.381	2.98	114.00	2.354	2.982	114.859
	C-H52...047	2.829	3.84	155.44	3.383	4.136	127.053
b-j-c-g-h-w-v-q-x	C-H50...O41	2.539	3.11	111.94	2.532	3.120	112.631
	C-H62...048	2.391	2.98	113.22	2.356	2.978	114.437
	C-H52...N36	2.711	3.78	169.26	2.693	3.764	166.090
b-m-o-g-h-t-p-y	C-H50...O41	2.486	3.07	112.76	2.497	3.094	113.174

	C-H62...048	2.350	2.95	113.87	2.320	2.951	115.038
k-c-e-f-g-h-v-p-y	C-H50...O41	2.390	2.99	113.46	2.361	2.986	114.666
	C-H62...048	2.328	2.93	114.03	2.300	2.930	114.887
c-e-f-g-h-v-q-y	C-H50...O41	2.523	3.10	112.50	2.513	3.109	113.166
	C-H62...048	2.936	2.32	114.03	2.307	2.937	114.880
a-e-g-h-v-q-y	C-H50...O41	2.524	3.10	112.46	2.514	3.111	113.144
	C-H62...048	2.324	2.93	114.05	2.300	2.929	114.792
b-c-g-h-v-q-y	C-H50...O41	2.524	3.10	112.49	2.535	3.126	112.865
	C-H62...048	2.336	2.94	113.98	2.318	2.948	114.937
m-o-n-c-g-h-t-q-y	C-H50...O41	2.539	3.11	112.23	2.541	3.130	112.709
	C-H62...048	2.338	2.94	114.09	2.314	2.946	115.022
a-m-f-g-h-w-v-q-x	C-H50...O41	2.540	3.11	111.90	2.539	3.124	112.443
	C-H62...048	2.400	2.99	113.28	2.372	2.994	114.542
	C-H52...N36	2.699	3.76	169.45	2.673	3.733	163.130
j-c-e-f-g-h-w-v-q-x	C-H50...O41	2.540	3.11	111.90	2.489	3.119	112.663
	C-H62...048	2.400	2.99	113.28	2.354	2.976	114.501
	C-H52...N36	2.699	3.76	169.45	2.686	3.749	163.785
m-c-e-f-g-h-i-v-q-x	C-H50...O41	2.543	3.11	112.02	2.561	3.142	112.173
	C-H62...048	2.386	2.99	112.02	2.355	2.981	114.781
j-s-c-g-h-v-p-x	C-H50...O41	2.507	3.09	112.72	2.509	3.107	113.269
	C-H62...048	2.307	2.88	111.84	2.277	2.884	113.141
l-c-g-h-v-p-y	C-H50...O41	2.531	3.10	112.31	2.534	3.124	112.839
	C-H62...048	2.334	2.33	114.10	2.305	2.940	115.266
m-c-e-f-g-h-t-p-y	C-H50...O41	2.479	3.06	112.95	2.478	3.082	113.548
	C-H62...048	2.341	2.94	113.82	2.299	2.929	114.826
r-z-c-g-h-v-q-y	C-H50...O41	2.529	3.10	112.34	2.526	3.118	112.644
	C-H62...048	2.568	3.13	111.86	2.557	3.144	112.908
m-n-c-f-g-h-t-q-y	C-H50...O41	2.541	3.11	112.18	2.538	3.128	112.789
	C-H62...048	2.361	2.96	113.95	2.325	2.957	115.062
a-e-g-h-i-v-q-x	C-H50...O41	2.544	3.11	112.02	2.561	3.141	112.209
	C-H62...048	2.382	2.98	113.98	2.358	2.984	114.806
	C-H52...047	2.823	3.83	155.21	3.300	4.092	130.077
a-e-g-h-t-p-y	C-H50...O41	2.473	3.06	113.02	2.475	3.079	113.559
	C-H62...048	2.349	2.95	113.70	2.313	2.940	114.706
a-n-g-h-t-q-y	C-H50...O41	2.540	3.11	112.17	2.540	3.129	112.749
	C-H62...048	2.364	2.96	113.82	2.327	2.958	115.028
c-f-g-h-v-q-y	C-H50...O41	2.525	3.10	112.43	2.531	3.123	112.863
	C-H62...048	2.326	2.93	114.08	2.297	2.925	114.711
j-c-e-g-h-w-q-v-x	C-H50...O41	2.540	3.11	111.90	2.535	3.123	112.589
	C-H62...048	2.400	2.99	113.28	2.364	2.984	114.308
	C-H52...N36	2.699	3.76	169.45	2.664	3.739	167.130
a-g-h-v-q-y	C-H50...O41	2.525	3.10	112.43	2.514	3.110	113.141
	C-H62...048	2.336	2.94	114.00	2.308	2.938	114.875
m-o-c-e-g-h-t-p-y	C-H50...O41	2.475	3.06	112.98	2.484	3.084	113.327

	C-H62...048	2.347	2.95	113.84	2.320	2.951	115.023
c-e-g-h-v-q-y	C-H50...O41	2.524	3.10	112.50	2.516	3.112	113.140
	C-H62...048	2.324	2.93	114.00	2.300	2.927	114.678
m-c-f-g-h-i-t-p-y	C-H50...O41	2.547	3.11	113.80	2.548	3.131	112.369
	C-H62...048	2.388	2.99	113.80	2.353	2.980	114.874
	C-H52...047	2.836	3.89	164.94	2.501	3.522	155.229
j-c-f-g-h-w-v-q-x	C-H50...O41	2.540	3.11	111.90	2.531	3.120	112.669
	C-H62...048	2.400	2.99	113.28	2.358	2.980	114.468
	C-H52...N36	2.699	3.76	169.45	2.683	3.756	166.454
m-c-f-g-h-t-p-y	C-H50...O41	2.483	3.07	112.87	2.485	3.086	113.410
	C-H62...048	2.341	2.94	113.85	2.300	2.930	114.876
m-c-g-h-t-p-y	C-H50...O41	2.483	3.07	112.87	2.485	3.086	113.411
	C-H62...048	2.341	2.94	113.86	2.300	2.930	114.879
m-n-o-c-g-h t-q-y	C-H50...O41	2.546	3.11	112.07	2.541	3.130	112.718
	C-H62...048	2.363	2.97	113.99	2.335	2.966	115.056
a-g-h-i-q-v-x	C-H50...O41	2.546	3.11	117.70	2.546	3.130	112.455
	C-H62...048	2.382	2.98	114.01	2.355	2.982	112.455
	C-H52...047	2.815	3.82	155.55	3.427	4.140	124.038
a-g-h-t-p-y	C-H50...O41	2.477	3.06	112.88	2.473	3.078	144.226
	C-H62...048	2.350	2.95	113.75	2.311	2.942	114.998
j-c-g-h-w-q-v-x	C-H50...O41	2.540	3.11	111.90	2.533	3.121	112.629
	C-H62...048	2.400	2.99	113.28	2.358	2.979	114.426
	C-H52...N36	2.699	3.76	169.45	2.690	3.762	166.254
	C-H59...043	2.773	3.47	122.48	2.748	3.466	122.888
c-m-n-g-h-t-p-y	C-H50...O41	2.486	3.07	112.76	2.495	3.093	113.186
	C-H62...048	2.351	2.95	113.86	2.321	2.951	114.932
c-g-h-v-q-y	C-H50...O41	2.525	3.10	112.44	2.515	3.111	113.135
	C-H62...048	2.325	2.93	114.05	2.300	2.928	114.741

Table 8.K5. Vibrational frequencies (harmonic approximation) of the O–H bonds in the calculated conformers of mbandakamine A

HF/6-31G(d,p) results *in vacuo*. The frequency values have been scaled by 0.9024, recommended for HF/6-31G(d,p) calculations in [447].

Conformer	Vibrational frequency (cm ⁻¹)			
	O43–H55	O45–H57	O42–H53	O47–H60
a-b-k-e-f-g-h-u-v-p-y	3715.47	3741.82	3708.07	3745.93
a-b-l-e-g-h-u-v-p-y	3718.74	3733.87	3720.21 ^a	3720.21 ^a
a-b-r-e-f-g-h-v-q-y	3714.71	3740.29	3761.39	3753.11
b-k-c-e-f-g-h-v-p-y	3744.19	3731.59	3720.49	3753.94
a-b-k-e-f-g-h-v-p-y	3728.53	3741.35	3700.50	3747.26
a-b-m-e-f-g-h-t-p-y	3703.18	3737.41	3740.05 ^b 3739.25 ^a	3740.05 ^b 3739.25 ^a
a-b-l-g-h-v-p-y	3724.26	3734.65	3781.19	3706.66
b-l-c-e-g-h-v-p-y	3736.26	3723.71	3718.19 ^a	3718.19 ^a
a-b-m-s-e-f-g-v-p-x	3727.08	3737.98	3700.07	3773.35
b-r-z-c-e-f-g-h-v-q-y	3743.16	3730.10	3743.87	3759.44
a-b-m-s-f-g-h-v-p-x	3709.51	3738.14 ^b	3508.09	3738.14 ^b
a-b-k-e-f-g-h-v-p-y	3728.19	3741.32	3706.11	3746.37
a-b-e-f-g-h-v-q-y	3729.30	3739.74	3759.93	3755.06
a-b-m-e-f-g-h-t-p-y	3738.42 ^a	3736.32	3767.22	3738.42 ^a
b-l-c-g-h-v-p-y	3737.78	3724.20	3780.98	3704.04
a-b-m-e-f-g-h-i-v-q-x	3696.37	3738.41	3768.97	3728.46
b-k-c-e-f-g-h-v-p-y	3746.00	3731.51	3707.84	3753.22
a-b-l-g-h-v-p-y	3736.95	3734.23	3781.66	3708.57
a-b-m-w-v-q-x	3718.30	3735.70	3766.87	3769.57
b-m-c-e-f-g-h-t-q-y	3754.07 ^b 3738.21 ^a	3728.34	3740.10	3754.07 ^b 3738.21 ^a
b-j-s-c-e-f-g-h-v-p-x	3758.51 ^b 3749.54 ^a	3734.87	3708.39	3758.51 ^b 3749.54 ^a
b-r-z-c-f-g-h-v-q-y	3747.78	3732.63	3791.15	3759.42
a-b-r-g-h-v-q-y	3726.99	3737.26	3791.38	3791.75
a-b-n-e-g-h-t-q-y	3753.28	3735.28	3737.24	3791.56
k-c-e-f-g-h-v-p-y	3749.12	3778.48	3715.83	3746.14
a-k-e-f-g-h-v-p-y	3727.76	3780.90	3696.56	3758.99
a-b-f-g-h-v-q-y	3736.18	3741.99	3791.36	3755.93
a-m-n-e-f-g-h-t-q-y	3704.39	3780.75	3738.90 ^b 3737.60 ^a	3738.90 ^b 3737.60 ^a
a-l-g-h-v-p-y	3723.09	3781.93	3781.25	3709.90
a-b-m-f-g-h-t-p-y	3705.25	3738.14	3790.93	3734.20
b-k-c-e-f-g-h-v-p-y	3745.82	3731.61	3711.83	3752.45
b-c-e-f-g-h-v-q-y	3745.86	3730.12	3759.43	3760.06
a-r-f-g-h-q-v-y	3721.46	3781.32	3791.33	3748.42
a-m-n-e-f-g-h-t-q-y	3754.25 ^b	3724.73	3743.13	3754.25 ^b

a-b-m-f-g-h-w-q-v-x	3721.14	3735.57	3791.58	3757.38
b-l-c-g-h-v-p-y	3739.35	3724.11	3781.90	3703.13
b-m-c-e-f- g-h-t-p-y	3743.49 ^b 3730.67 ^a	3726.87	3767.93	3743.49 ^b 3730.67 ^a
r-z-c-e-f-g- h-v-q-y	3745.28	3778.29	3761.58	3754.96
a-r-e-g-h-q-v-y	3717.83	3781.31	3758.60	3799.51
b-j-c-e-f- g-h-w-v-q-x	3756.92 ^b 3744.86 ^a	3734.94	3763.85	3756.92 ^b 3744.86 ^a
a-m-s-f-g-h-v-p-x	3719.82	3781.23	3493.75	3765.33
b-r-z-c-g-h-v-q-y	3740.99	3727.06	3791.19	3799.52
a-k-e-f-g-h-v-p-y	3745.82	3731.61	3711.83	3752.45
b-m-n-c-f-g-h-t-q-y	3750.92 ^b 3740.76 ^a	3729.13	3792.06	3750.92 ^b 3740.76 ^a
a-e-f-g-h-v-q-y	3728.68	3780.74	3759.54	3749.91
a-b-e-g-h-t-p-y	3755.10	3735.20	3764.96	3792.02
a-m-e-f-g-h-t-q-y	3700.43	3780.52	3766.91	3738.29
a-m-e-g-h-i-v-q-x	3698.03	3780.38	3768.53	3728.64
a-b-g-h-v-q-y	3740.21	3737.13	3791.50	3802.89
b-j-c-e-g-h-w-v-q-x	3724.96	3730.16	3764.46	3785.58
l-c-g-h-v-p-y	3740.05	3779.99	3781.02	3707.29
b-c-f-g-h-v-q-y	3750.06	3732.62	3791.23	3760.87
a-m-n-f-g-h-t-q-y	3710.54	3781.19	3789.51	3738.90
k-c-e-f-g-h-v-p-y	3748.50 ^a 3747.50 ^b	3778.62	3704.15	3748.50 ^a 3747.50 ^b
b-m-o-c-e-g-h-t-p-y	3754.07	3725.20	3734.00	3747.04
b-c-e-g-h-v-q-y	3739.18	3724.55	3756.77	3803.80
a-l-g-h-v-p-y	3735.95	3782.29	3781.67	3711.97
j-s-c-e-f-g-h-v-p-x	3753.77 ^b 3747.75 ^a	3778.80	3707.19	3753.77 ^b 3747.75 ^a
a-m-e-g-h- w-q-v-x	3723.97	3780.34	3765.72	3774.04
m-c-e-f-g-h-t-q-y	3756.64 ^b 3741.58 ^a	3778.67	3738.89	3756.64 ^b 3741.58 ^a
b-m-n-o-c-g-h-t-q-y	3757.59	3726.27	3795.86	3761.40
r-z-c-f-g-h-q-v-y	3749.88	3779.23	3791.14	3754.90
b-m-c-f-g-h-t-p-y	3738.67 ^b 3723.75 ^a	3728.92	3790.53	3738.67 ^b 3723.75 ^a
b-j-c-f-g-h-w-v-q-x	3758.39 ^b 3750.19 ^a	3737.14	3791.81	3758.39 ^b 3750.19 ^a
a-r-g-h-v-q-y	3725.77	3782.02	3791.51	3799.78
r-z-c-e-g-h-v-q-y	3738.36	3779.20	3758.65	3799.17
a-f-g-h-v-q-y	3735.64	3781.56	3791.39	3750.67
a-e-g-h-t-q-y	3753.59	3781.56	3736.68	3791.85
j-r-c-e-g-h-v-p-x	3725.79	3780.13	3709.03	3786.93
a-m-f-g-h-t-p-y	3706.96	3781.43	3790.93	3735.51
a-m-f-g-h-i-v-q-x	3703.84	3781.24	3791.29	3723.39

a-b-g-h-i-v-q-x	3756.79	3739.47	3791.74	3791.22
a-b-g-h-t-p-y	3758.74	3737.38	3791.35	3792.35
b-j-c-g-h-w-v-q-x	3727.56	3732.74	3791.85	3785.84
b-m-o-g-h-t-p-y	3748.97	3727.72	3791.42	3756.80
k-c-e-f-g-h-v-p-y	3748.15 ^a 3746.80 ^b	3778.66	3708.46	3748.15 ^a 3746.80 ^b
a-e-g-h-v-q-y	3733.10	3781.62	3756.81	3802.02
b-c-g-h-v-q-y	3743.36	3727.31	3791.28	3804.53
m-o-n-g-h-t-q-y	3757.13	3779.63	3742.27	3761.44
a-m-f-g-h-w-v-q-x	3730.81	3781.43	3791.64	3774.85
j-c-e-f-g-h-w-v-q-x	3752.04 ^b 3741.49 ^a	3778.47	3763.06	3752.04 ^b 3741.49 ^a
m-c-e-f-g-h-i-v-q-x	3746.52 ^b 3734.83 ^a	3768.37	3778.42	3746.52 ^b 3734.83 ^a
j-s-c-g-h-v-p-x	3733.43	3780.34	3518.76	3784.74
l-c-g-h-v-p-y	3741.72	3780.20	3781.95	3706.55
m-c-e-f-g-h-t-p-y	3749.83 ^b 3734.85 ^a	3778.49	3767.40	3749.83 ^b 3734.85 ^a
r-z-c-g-h-v-q-y	3743.34	3780.16	3791.24	3799.45
m-n-c-f-g-h-t-q-y	3755.19 ^b 3744.35 ^a	3779.20	3791.42	3755.19 ^b 3744.35 ^a
a-e-g-h-i-v-q-x	3750.30	3781.07	3764.49	3791.11
a-e-g-h-t-p-y	3755.55	3781.37	3764.55	3792.23
a-n-g-h-t-q-y	3759.02	3782.01	3790.35	3791.62
c-f-g-h-v-q-y	3752.39	3779.36	3791.22	3755.78
j-c-e-g-h-w-q-v-x	3725.40	3779.73	3763.65	3785.91
a-g-h-v-q-y	3739.67	3782.44	3791.58	3802.48
m-o-c-e-g-h-t-p-y	3757.59	3779.49	3766.23	3752.54
c-e-g-h-v-q-y	3741.89	3779.37	3756.34	3803.40
m-c-f-g-h-i-v-q-x	3724.03	3779.35	3791.11	3748.03
j-c-f-g-h-w-v-q-x	3754.14 ^b 3746.71 ^a	3779.68	3791.90	3754.14 ^b 3746.71 ^a
m-c-f-g-h-t-p-y	3742.88 ^b 3731.24 ^a	3779.45	3790.61	3742.88 ^b 3731.24 ^a
m-c-f-g-h-t-p-y	3742.79 ^b 3731.05 ^a	3779.45	3790.61	3742.79 ^b 3731.05 ^a
m-n-o-c-g-h-t-q-y	3761.00	3780.08	3795.08	3767.13
a-g-h-i-q-v-x	3757.35	3781.90	3791.83	3791.49
a-g-h-t-p-y	3759.39	3782.27	3792.61	3791.34
j-c-g-h-w-q-v-x	3728.07	3780.86	3791.98	3786.18
m-n-c-g-h-t-p-y	3752.90	3780.44	3791.51	3761.50
c-g-h-v-q-y	3746.03	3780.34	3791.34	3804.18

^a symmetrical stretching

^b asymmetrical stretching

Table 8.K6. Red shift of the vibrational frequencies of the O43–H55, O45–H57, O42–H53 and O47–H60 bonds in the calculated conformers of mbandakamine A, when they are engaged in an O–H···O IHB

HF/6-31G(d,p) results *in vacuo*

Conformer	Red shift (cm ⁻¹)			
	O43—H55	O45—H57	O42—H53	O47—H60
a-b-k-e-f-g-h-u-v-p-y	52.65	26.30	60.05	
a-b-l-e-g-h-u-v-p-y	49.38	34.25		23.81
a-b-r-e-f-g-h-v-q-y	53.41	27.83		
b-k-c-e-f-g-h-v-p-y		36.53	47.63	
a-b-k-e-f-g-h-v-p-y	39.59	26.77	67.62	
a-b-m-e-f-g-h-t-p-y	64.94	30.71		28.07
a-b-l-g-h-v-p-y	43.86	33.47		61.46
b-l-c-e-g-h-v-p-y		44.41		26.44
a-b-m-s-e-f-g-v-p-x	41.04	30.14	68.05	
b-r-z-c-e-f-g-h-v-q-y		38.02		
a-b-m-s-f-g-h-v-p-x	58.61	29.98	260.03	29.98
a-b-k-e-f-g-h-v-p-y	39.93	26.80	62.01	
a-b-e-f-g-h-v-q-y	38.82	28.38		
a-b-m-e-f-g-h-t-p-y	69.33	31.80		69.33
b-l-c-g-h-v-p-y		43.92		64.08
a-b-m-e-f-g-h-i-v-q-x	71.75	29.71		39.66
b-k-c-e-f-g-h-v-p-y		36.61	60.28	
a-b-l-g-h-v-p-y	31.17	33.89		59.55
a-b-m-w-v-q-x	49.82	32.42		
b-m-c-e-f-g-h-t-q-y		39.78		29.91
b-j-s-c-e-f-g-h-v-p-x	18.58	33.25	59.73	
b-r-z-c-f-g-h-v-q-y	20.34	35.49		
a-b-r-g-h-v-q-y	41.13	30.86		
a-b-n-e-g-h-t-q-y	14.84	32.84	30.88	
k-c-e-f-g-h-v-p-y			52.29	
a-k-e-f-g-h-v-p-y	40.36		71.56	
a-b-f-g-h-v-q-y	31.94	26.13		
a-m-n-e-f-g-h-t-q-y	63.73		30.52	30.52
a-l-g-h-v-p-y	45.03			58.22
a-b-m-f-g-h-t-p-y	62.87	29.98		33.92
b-k-c-e-f-g-h-v-p-y		36.51	56.29	
b-c-e-f-g-h-v-q-y		38.00		
a-r-f-g-h-q-v-y	46.66			
a-m-n-e-f-g-h-t-q-y	14.42		24.99	14.42
a-b-m-f-g-h-w-q-v-x	46.98	32.55		10.74

b-l-c-g-h-v-p-y		44.01		64.99
b-m-c-e-f-g-h-t-p-y		41.25		37.45
a-r-e-g-h-q-v-y	50.29			
b-j-c-e-f-g-h-w-v-q-x	23.26	33.18		
a-m-r-f-g-h-v-p-x	48.30		274.37	
b-r-z-c-g-h-v-q-y		41.06		
a-k-e-f-g-h-v-p-y	22.30		56.29	
b-m-n-c-f-g-h-t-q-y		38.99		27.36
a-e-f-g-h-v-q-y	39.44			
a-b-e-g-h-t-p-y	13.02	32.92		
a-m-e-f-g-h-t-q-y	67.69			29.83
a-m-e-g-h-i-v-q-x	70.09			39.48
a-b-g-h-v-q-y	27.91	30.99		
b-j-c-e-g-h-w-v-q- x	43.16	37.96		
l-c-g-h-v-p-y				60.83
b-c-f-g-h-v-q-y		35.50		
a-m-n-f-g-h-t-q-y	57.58			29.22
k-c-e-f-g-h-v-p-y			63.97	
b-m-o-c-e-g-h-t-p-y		42.92	34.12	21.08
b-c-e-g-h-v-q-y		43.57		
a-l-g-h-v-p-y	32.17			56.15
j-c-e-f-g-h-v-p-x	20.37			
a-m-e-g-h-w-v-q-x	44.15			
m-c-e-f-g-h-t-q-y	26.54			26.54
b-m-n-o-c-g-h-t-q-y		41.85		6.72
r-z-c-f-g-h-q-v-y				
b-m-c-f- g-h-t-p-y	29.45	39.20		44.37
b-j-c-f-g-h-w-v-q-x	17.93	30.98		
a-r-g-h-v-q-y	42.35			
a-f-g-h-v-q-y	32.48			
a-e-g-h-t-q-y	14.53			
j-r-c-e-g-h-v-p-x	42.33			
a-m-f-g-h-t-p-y	61.16			32.61
a-m-f-g-h-i-v-q-x	64.28			44.73
a-b-g-h-i-v-q-x	11.33	28.65		
a-b-g-h-t-p-y	9.38	30.74		
b-j-c-g-h-w-v-q-x	40.56	35.38		
b-m-o-g-h-t-p-y		40.40		11.32
k-c-e-f-g-h-v-p-y			59.66	
a-e-g-h-v-q-y	35.02			
b-c-g-h-v-q-y		40.81		
m-o-n-g-h-t-q-y			25.85	6.68
a-m-f-g-h-w-v-q-x	37.31			
j-c-e-f-g-h-w-v-q-x	26.63			

m-c-e-f-g-h-i-v-q-x				33.29
j-s-c-g-h-v-p-x	34.69		249.36	
l-c-g-h-v-p-y				61.57
m-c-f-g-h-t-p-y				33.27
m-n-c-f-g-h-t-q-y				23.77
a-e-g-h-i-v-q-x	17.82			
a-e-g-h-t-p-y	12.57			
a-n-g-h-t-q-y	9.10			
j-c-e-g-h-w-q-v-x	42.72			
a-g-h-v-q-y	28.45			
m-o-c-e-g-h-t-p-y				15.58
m-c-f-g-h-i-v-q-x	44.09			20.09
j-c-f-g-h-w-v-q-x	21.41			
m-c-f-g-h-t-p-y				36.88
m-c-t-p-y				37.07
m-n-o-c-g-h t-q-y				0.99
a-g-h-i-q-v-x	10.77			
a-g-h-t-p-y	8.73			
j-c-g-h-w-q-v-x	40.05			
m-o-c-g-h-t-p-y	15.22			6.62

Table 8.K7. Relative energy ($\Delta E_{\text{corrected}}$, kcal/mol) corrected for ZPE and ZPE corrections (ZPE_{corr} , kcal/mol) for calculated conformers of mbandakamine A
Results from HF/6-31G(d,p) frequency calculations.

conformer	$\Delta E_{\text{corrected}}$ (kcal/mol)	ZPE_{corr} (kcal/mol)	conformer	$\Delta E_{\text{corrected}}$ (kcal/mol)	ZPE_{corr} (kcal/mol)
a-b-k-e-f-g-h-u-v-p-y	0.000	616.436	a-m-n-f-g-h-t-q-y	16.748	615.519
a-b-l-e-g-h-u-v-p-y	2.435	616.563	k-c-e-f-g-h-v-p-y	16.974	615.744
a-b-r-e-f-g-h-v-q-y	3.333	616.364	b-m-o-c-e-g-h-t-p-y	16.997	615.756
b-k-c-e-f-g-h-v-p-y	5.043	616.378	b-c-e-g-h-v-q-y	17.163	615.819
a-b-k-e-f-g-h-v-p-y	5.396	616.450	a-l-g-h-v-p-y	17.809	615.755
a-b-m-e-f-g-h-t-p-y	5.745	616.290	j-c-e-f-g-h-v-p-x	17.440	615.789
a-b-l-g-h-v-p-y	5.321	616.160	a-m-e-g-h-w-q-v-x	17.730	615.648
b-l-c-e-g-h-v-p-y	6.395	616.506	m-c-e-f-g-h-t-q-y	17.779	615.529
a-b-m-s-e-f-g-v-p-x	6.382	616.158	b-m-n-o-c-g-h-t-q-y	17.447	615.176
b-r-z-c-e-f-g-h-v-q-y	8.035	616.366	r-z-c-f-g-h-q-v-y	18.119	615.675
a-b-m-s-f-g-h-v-p-x	8.171	616.251	b-m-c-f-g-h-t-p-y	18.220	615.735
a-b-k-e-f-g-h-v-p-y	8.641	616.363	b-j-c-f-g-h-w-v-q-x	18.392	615.760
a-b-e-f-g-h-v-q-y	8.945	616.347	a-r-g-h-v-q-y	18.102	615.343
a-b-m-e-f-g-h-t-p-y	9.713	616.531	r-z-c-e-g-h-v-q-y	18.724	615.688
b-l-c-g-h-v-p-y	9.408	616.157	a-f-g-h-v-q-y	18.920	615.632
a-b-m-e-f-g-h-i-v-q-x	10.200	616.651	a-e-g-h-t-q-y	18.571	615.281
b-k-c-e-f-g-h-v-p-y	10.246	616.162	j-r-c-e-g-h-v-p-x	19.731	615.601
a-b-l-g-h-v-p-y	10.567	616.223	a-m-f-g-h-t-p-y	19.819	615.612
a-b-m-w-v-q-x	10.862	616.020	a-m-f-g-h-i-v-q-x	19.997	615.716
b-m-c-e-f-g-h-t-q-y	10.889	615.974	a-b-g-h-i-v-q-x	19.749	615.382
b-j-s-c-e-f-g-h-v-p-x	10.903	616.180	a-b-g-h-t-p-y	19.699	615.458
b-r-z-c-f-g-h-v-q-y	11.300	616.085	b-j-c-g-h-w-v-q-x	20.256	615.667
a-b-r-g-h-v-q-y	11.061	615.793	b-m-o-g-h-t-p-y	20.011	615.475
a-b-n-e-g-h-t-q-y	11.551	615.737	k-c-e-f-g-h-v-p-y	20.236	615.643
k-c-e-f-g-h-v-p-y	11.795	615.972	a-e-g-h-v-q-y	20.402	615.630
a-k-e-f-g-h-v-p-y	12.010	616.026	b-c-g-h-v-q-y	20.733	615.501
a-b-f-g-h-v-q-y	12.212	616.059	m-o-n-g-h-t-q-y	20.590	615.023
a-m-n-e-f-g-h-t-q-y	12.547	615.852	a-m-f-g-h-w-v-q-x	20.860	615.250
a-l-g-h-v-p-y	12.472	615.699	j-c-e-f-g-h-w-v-q-x	21.759	615.615
a-b-m-f-g-h-t-p-y	12.912	616.068	m-c-e-f-g-h-i-v-q-x	21.839	615.894
b-k-c-e-f-g-h-v-p-y	13.498	616.066	j-s-c-g-h-v-p-x	21.870	615.682
b-c-e-f-g-h-v-q-y	13.506	616.039	l-c-g-h-v-p-y	21.717	615.530
a-r-f-g-h-q-v-y	13.175	615.683	m-c-f-g-h-t-p-y	21.995	615.726
a-m-n-e-f-g-h-t-q-y	13.353	615.512	s-z-c-g-h-v-q-y	22.253	615.379
a-b-m-f-g-h-w-q-v-x	13.865	615.630	m-n-c-f-g-h-t-q-y	22.150	615.197
b-l-c-g-h-v-p-y	14.351	615.995	a-e-g-h-i-v-q-x	23.014	615.461
b-m-c-e-f-g-h-t-p-y	15.056	616.184	a-e-g-h-t-p-y	23.094	615.455
r-z-c-e-f-g-h-v-q-y	14.847	615.958	a-n-g-h-t-q-y	22.795	614.953
a-r-e-g-h-q-v-y	14.624	615.611	c-f-g-h-v-q-y	23.613	615.323

b-j-c-e-f-g-h-w-v-q-x	15.264	615.996	j-c-e-g-h-w-q-v-x	23.934	615.508
a-m-r-f-g-h-v-p-x	15.041	615.728	a-g-h-v-q-y	23.955	615.322
b-r-z-c-g-h-v-q-y	15.012	615.819	m-o-c-e-g-h-t-p-y	24.222	615.279
a-k-e-f-g-h-v-p-y	15.269	615.935	c-e-g-h-v-q-y	24.382	615.362
b-m-n-c-f-g-h-t-q-y	15.216	615.652	m-c-f-g-h-i-v-q-x	24.865	615.441
a-e-f-g-h-v-q-y	15.633	615.921	j-c-f-g-h-w-v-q-x	24.940	615.370
a-b-e-g-h-t-p-y	16.067	615.912	m-c-f-g-h-t-p-y	25.202	615.266
a-b-n-e-g-h-t-q-y	-	-	m-c-t-p-y	25.203	615.268
a-m-e-f-g-h-t-q-y	16.567	616.090	m-n-o-c-g-h-t-q-y	24.696	614.690
a-m-e-g-h-i-v-q-x	16.876	616.212	a-g-h-i-q-v-x	26.574	614.922
a-b-g-h-v-q-y	16.833	615.781	a-g-h-t-p-y	26.778	614.986
b-j-c-e-g-h-w-v-q-x	16.944	615.936	j-c-g-h-w-q-v-x	27.283	615.234
l-c-g-h-v-p-y	16.760	615.702	m-o-c-g-h-t-p-y	26.778	615.022
b-c-f-g-h-v-q-y	16.813	615.744	c-g-h-v-q-y	27.968	615.047

Table 8.K8. Dipole moment of the conformers of mbandakamine A listed in Table 8K1

HF/6-31G(d,p) and (DFT/B3LYP/6-31+G(d,p) results, respectively denoted as HF and DFT in the column headings. The results *in vacuo* are from full optimization calculations, the results in solution are from single point PCM calculations on the *in-vacuo*-optimized geometries

Conformer	Dipole moment (Debye)							
	HF				DFT			
	vac	chlrf	actn	aq	vac	chlrf	actn	aq
a-b-k-e-f-g-h-u-v-p-y	3.11	3.55	3.74	3.98	3.14	3.68	3.90	4.08
a-b-l-e-g-h-u-v-p-y	4.36	5.18	5.55	5.85	3.97	4.90	5.35	5.70
a-b-r-e-f-g-h-v-q-y	1.76	2.29	2.60	2.79	1.62	2.15	2.47	2.66
b-k-c-e-f-g-h-v-p-y	4.83	5.49	5.75	6.28	5.01	5.79	6.14	6.71
a-b-k-e-f-g-h-v-p-y	3.91	4.56	4.83	5.08	4.20	5.03	5.38	5.67
a-b-m-e-f-g-h-t-p-y	5.63	6.38	6.62	6.69	5.38	6.22	6.51	6.54
a-b-l-g-h-v-p-y	6.71	7.94	8.46	8.93	6.30	7.71	8.38	8.87
b-l-c-e-g-h-v-p-y	3.43	3.91	4.11	4.43	3.25	3.83	4.10	4.52
a-b-m-s-e-f-g-v-p-x	5.51	6.32	6.61	6.91	5.65	6.66	7.07	7.49
b-r-z-c-e-f-g-h-v-q-y	2.83	3.16	3.23	3.36	3.18	3.65	3.81	3.94
a-b-m-s-f-g-h-v-p-x	5.69	6.65	7.02	7.56	6.09	7.37	7.94	8.61
a-b-k-e-f-g-h-v-p-y	2.73	3.50	3.71	3.80	2.98	3.56	3.79	3.80
a-b-e-f-g-h-v-q-y	3.51	4.32	4.72	5.15	3.48	4.43	4.92	5.45
a-b-m-e-f-g-h-t-p-y	4.93	5.49	5.67	5.48	4.65	5.27	5.48	5.15
b-l-c-g-h-v-p-y	5.83	6.82	7.25	7.70	5.52	6.66	7.21	7.72
a-b-m-e-f-g-h-i-v-q-x	6.40	7.30	7.70	7.80	6.07	7.10	7.58	7.71
b-k-c-e-f-g-h-v-p-y	4.53	5.10	5.31	5.59	4.69	5.38	5.63	5.94
a-b-l-g-h-v-p-y	6.24	7.51	8.12	8.53	5.73	7.16	7.88	8.36
a-b-m-w-v-q-x	4.69	5.48	5.84	6.07	4.04	4.84	5.22	5.44
b-m-c-e-f-g-h-t-q-y	4.06	4.43	4.49	4.35	3.97	4.39	— ^a	4.23
b-j-s-c-e-f-g-h-v-p-x	6.25	7.02	7.36	7.78	6.31	7.34	7.76	— ^a
b-r-z-c-f-g-h-v-q-y	3.25	3.63	3.70	3.87	3.27	3.77	— ^a	4.19
a-b-r-g-h-v-q-y	4.54	5.31	5.66	4.56	4.17	4.99	5.36	5.78
a-b-n-e-g-h-t-q-y	7.52	8.82	9.36	9.88	7.13	8.62	9.28	9.75
k-c-e-f-g-h-v-p-y	3.32	3.85	4.11	4.55	3.52	4.18	4.46	4.91
a-k-e-f-g-h-v-p-y	2.99	3.62	3.94	4.19	3.38	4.25	4.69	5.06
a-b-f-g-h-v-q-y	2.63	3.11	3.38	3.69	2.41	3.01	3.35	3.79
a-m-n-e-f-g-h-t-q-y	4.52	5.03	5.22	5.29	4.43	5.06	5.28	5.37
a-l-g-h-v-p-y	5.92	6.83	7.23	7.20	5.63	6.68	7.16	7.41
a-b-m-f-g-h-t-p-y	2.72	2.91	2.93	2.67	2.91	3.24	3.32	3.14
b-k-c-e-f-g-h-v-p-y	3.82	4.23	4.37	4.48	3.93	4.45	4.62	4.77
b-c-e-f-g-h-v-q-y	2.92	3.30	3.42	3.54	3.24	3.74	3.89	4.02
a-r-f-g-h-q-v-y	5.12	5.89	6.18	6.46	4.95	5.89	6.28	6.69
a-m-n-e-f-g-h-t-q-y	4.45	5.02	5.21	5.31	4.43	5.06	5.29	5.38
a-b-m-f-g-h-w-q-v-x	1.97	2.33	2.52	2.62	1.18	1.32	1.41	1.41

b-l-c-g-h-v-p-y	4.90	5.75	6.12	6.33	4.42	5.35	5.76	5.97
b-m-c-e-f-g-h-t-p-y	4.26	4.62	4.67	4.47	3.97	4.35	4.37	4.08
r-z-c-e-f-g-h-v-q-y	3.25	3.60	3.68	3.73	3.30	3.77	3.83	3.88
a-r-e-g-h-q-v-y	4.07	4.94	5.46	5.89	3.89	4.90	5.47	6.10
b-j-c-e-f-g-h-w-v-q-x	4.93	5.56	5.81	5.92	4.82	5.58	5.88	6.02
a-m-r-f-g-h-v-p-x	3.36	3.73	3.84	3.98	3.76	4.29	4.50	4.79
b-r-z-c-g-h-v-q-y	3.43	3.86	3.99	4.16	3.26	3.77	3.94	4.21
a-k-e-f-g-h-v-p-y	2.48	3.12	3.46	3.80	2.88	3.76	4.23	4.69
b-m-n-c-f-g-h-t-q-y	3.23	3.64	3.87	4.18	3.20	3.68	3.90	4.24
a-e-f-v-q-y	4.58	5.43	5.84	6.35	4.56	5.62	6.18	6.88
a-b-e-g-h-t-p-y	6.45	7.57	8.13	8.39	6.16	— ^a	— ^a	— ^a
a-b-n-e-g-h-t-q-y	7.59	9.03	9.72	10.53	7.14	8.61	9.30	9.75
a-m-e-f-g-h-t-q-y	4.66	5.11	5.24	5.03	4.66	— ^a	5.42	5.20
a-m-e-g-h-i-q-v-x	5.28	5.88	6.11	6.07	5.09	5.79	6.06	6.00
a-b-g-h-v-q-y	4.32	5.22	5.71	6.13	3.94	4.94	5.51	6.04
b-j-c-e-g-h-w-v-q-x	6.32	7.29	7.68	7.87	6.42	7.62	8.14	8.32
l-c-g-h-v-p-y	4.50	5.10	5.33	5.44	4.25	4.93	5.20	5.31
b-c-f-g-h-v-q-y	2.30	2.46	2.43	2.49	4.78	2.65	2.65	2.76
a-m-n-f-g-h-t-q-y	3.77	4.31	4.59	4.83	3.50	4.07	4.33	4.52
k-c-e-f-g-h-v-p-y	3.13	3.66	3.86	4.22	3.51	4.22	4.51	4.90
b-m-o-c-e-g-h-t-p-y	3.69	4.10	4.25	4.20	3.73	4.28	4.49	4.45
b-c-e-g-h-v-q-y	2.04	2.72	3.13	3.47	1.88	2.64	3.12	3.55
a-l-g-h-v-p-y	5.67	6.67	7.20	7.44	5.23	6.39	7.01	7.29
j-c-e-f-g-h-v-p-x	3.94	4.27	4.39	4.49	4.03	4.51	4.65	4.81
a-m-e-g-h-w-q-v-x	4.35	4.91	5.15	5.23	6.41	7.81	8.52	8.93
c-m-e-f-g-h-t-q-y	2.63	2.85	2.89	2.88	2.61	2.87	2.93	2.88
b-c-m-n-o-t-q-y	4.68	5.57	6.09	6.71	4.78	4.96	5.20	5.27
r-z-c-f-g-h-q-v-y	5.14	5.96	6.19	6.48	4.85	5.82	6.15	6.51
b-m-c-f-g-h-t-p-y	2.61	2.95	3.04	3.25	2.39	2.81	2.96	3.30
b-j-c-f-g-h-w-v-q-x	2.91	3.24	3.37	3.50	2.95	3.42	3.59	3.82
a-r-g-h-v-q-y	5.82	6.72	7.13	7.47	5.52	6.57	7.00	7.51
r-z-c-e-g-h-v-q-y	1.18	1.37	1.46	1.58	2.39	2.81	2.96	3.30
a-f-g-h-v-q-y	5.37	6.28	6.70	7.18	5.09	6.23	6.79	7.47
a-e-g-h-t-q-y	6.00	6.99	7.42	7.86	5.68	6.79	7.32	7.80
j-r-c-e-g-h-v-p-x	5.29	5.94	6.19	6.27	5.50	6.33	6.67	6.75
a-m-f-g-h-t-p-y	4.86	5.58	5.85	6.04	5.09	6.07	6.48	6.83
a-b-g-h-i-v-q-x	4.48	5.26	5.26	5.43	4.36	5.08	5.34	5.53
a-b-g-h-t-p-y	4.90	5.79	6.33	6.69	3.83	4.72	5.27	5.52
a-m-f-g-h-i-v-q-x	3.74	4.39	4.74	4.85	3.57	4.34	4.72	4.84
b-m-o-g-h-t-p-y	2.85	3.21	3.37	3.33	3.00	3.47	3.69	3.62
b-j-c-g-h-w-v-q-x	0.54	0.51	0.49	0.69	0.67	— ^a	0.66	0.97
k-c-e-f-g-h-v-p-y	3.02	3.56	3.80	4.22	3.40	4.20	4.53	5.07
c-e-f-g-h-v-q-y	3.63	4.12	4.28	4.58	3.82	4.50	4.73	5.08
a-e-g-h-v-q-y	5.06	6.18	6.81	7.51	4.88	6.25	7.07	7.96

b-c-g-h-v-q-y	2.35	2.63	2.72	2.72	2.06	2.30	2.39	2.35
m-o-n-c-g-h-t-q-y	2.98	3.31	3.45	3.57	2.80	3.15	3.28	3.33
a-m-f-g-h-w-v-q-x	4.06	4.67	4.94	5.07	3.69	4.37	4.63	4.75
j-c-e-f-g-h w-v-q-x	4.07	4.38	4.42	4.17	3.98	4.37	4.42	4.06
m-c-e-f-g-h-i-v-q-x	4.57	5.08	5.20	5.08	3.84	4.41	4.67	4.46
j-s-c-g-h-v-p-x	5.46	6.06	6.31	6.57	6.11	7.06	7.47	7.85
l-c-g-h-v-p-y	3.53	4.00	4.21	4.05	3.16	3.63	3.84	3.62
m-c-f-g-h-t-p-y	4.06	4.49	4.57	4.56	3.85	4.35	4.43	4.45
r-z-c-g-h-v-q-y	4.71	5.39	5.59	5.83	4.36	5.14	5.37	5.66
m-n-c-f-g-h-t-q-y	0.44	0.60	0.92	1.44	0.42	0.37	0.70	1.42
a-e-g-h-i-v-q-x	5.80	6.74	7.30	7.60	5.23	6.28	6.87	7.06
a-e-g-h-t-p-y	5.17	5.97	6.37	6.49	5.01	5.95	6.37	6.49
a-n-g-h-t-q-y	6.09	7.23	7.84	8.49	3.20	3.68	3.90	4.23
c-f-g-h-v-q-y	4.77	5.55	5.82	6.19	4.63	5.61	5.97	6.47
j-c-e-g-h-w-q-v-x	5.58	6.36	6.69	6.73	5.58	6.52	6.89	6.86
a-g-h-v-q-y	5.97	7.03	7.58	8.11	5.72	7.01	7.68	8.39
m-o-c-e-g-h-t-p-y	3.01	3.25	3.28	3.13	2.96	3.23	3.24	2.99
c-e-g-h-v-q-y	2.13	2.67	3.01	3.45	2.08	2.74	3.19	3.80
m-c-f-g-h-i-v-q-x	4.08	4.83	5.06	5.37	1.23	1.43	1.37	1.45
j-c-f-g-h-w-v-q-x	3.46	3.94	4.02	4.00	3.26	3.80	3.93	3.88
m-c-f-g-h-t-p-y	4.91	5.88	6.26	6.79	4.73	5.93	6.45	7.16
m-c-t-p-y	4.91	5.87	6.27	6.80	4.73	5.93	6.45	7.17
m-n-o-c-g-h-t-q-y	3.08	3.71	4.12	4.67	2.82	3.39	3.78	4.33
a-g-h-i-q-v-x	4.09	4.75	5.14	5.52	3.24	3.88	4.21	4.48
a-g-h-t-p-y	4.46	5.21	5.57	5.78	4.39	5.30	5.70	6.04
j-c-g-h-w-q-v-x	3.57	4.13	4.38	4.40	3.23	3.83	4.05	3.95
m-o-c-g-h-t-p-y	3.31	3.92	4.16	4.40	3.07	3.80	4.07	4.43
c-g-h-v-q-y	4.33	5.02	5.28	5.59	4.19	5.04	5.37	5.81

^a The calculation for this conformer did not converge in the given solvent.

Table 8.K9. HOMO-LUMO energy gap of the conformers of mbandakamine A reported in Table 8K1, *in vacuo* and in the three solvents considered

HF/6-31G(d,p) and DFT/B3LYP/6-31+G(d,p) results, respectively denoted as HF and DFT in the column headings. The results *in vacuo* are from full optimization calculations, the results in solution are from single point PCM calculations on the *in-vacuo*-optimized geometries.

Conformer	HOMO-LUMO energy gap (kcal/mol)							
	HF				DFT			
	vac	chlrf	actn	aq	vac	chlrf	actn	aq
a-b-k-e-f-g-h-u-v-p-y	226.895	226.153	226.801	226.738	91.610	91.704	91.673	91.679
a-b-l-e-g-h-u-v-p-y	223.293	224.914	226.368	226.970	89.401	91.679	92.363	92.858
a-b-r-e-f-g-h-v-q-y	228.809	227.954	228.438	228.118	92.539	92.821	92.708	92.595
b-k-c-e-f-g-h-v-p-y	219.823	221.117	222.665	223.895	84.017	86.163	87.073	88.334
a-b-k-e-f-g-h-v-p-y	227.729	227.466	227.227	227.290	92.194	92.118	91.968	92.005
a-b-m-e-f-g-h-t-p-y	227.321	227.422	227.277	227.403	94.365	94.264	94.013	94.095
a-b-l-g-h-v-p-y	226.060	228.200	228.081	227.422	92.093	93.844	93.405	92.689
b-l-c-e-g-h-v-p-y	228.125	227.635	227.403	227.284	92.388	92.030	91.848	91.943
a-b-m-s-e-f-g-v-p-x	229.129	228.589	228.250	228.194	93.223	92.721	92.482	92.451
b-r-z-c-e-f-g-h-v-q-y	221.944	223.732	224.303	225.050	86.320	88.278	88.962	89.891
a-b-m-s-f-g-h-v-p-x	227.284	226.223	225.734	225.621	93.744	92.683	92.143	91.980
a-b-k-e-f-g-h-v-p-y	227.296	227.259	227.152	227.196	91.146	91.535	91.528	91.698
a-b-e-f-g-h-v-q-y	229.505	229.135	228.727	228.495	93.091	93.022	92.758	92.633
a-b-m-e-f-g-h-t-p-y	226.907	227.127	227.064	227.058	93.518	94.057	93.907	93.718
b-l-c-g-h-v-p-y	226.970	225.621	225.025	224.893	91.001	89.966	89.564	89.640
a-b-m-e-f-g-h-i-v-q-x	224.014	224.341	224.416	224.542	91.660	92.093	92.206	92.313
b-k-c-e-f-g-h-v-p-y	219.528	221.316	222.013	223.236	84.124	85.981	86.703	87.901
a-b-l-g-h-v-p-y	227.422	229.505	229.091	228.357	92.821	94.653	93.894	93.122
a-b-m-w-v-q-x	228.696	228.947	228.859	228.771	93.173	92.846	92.652	92.281
b-m-c-e-f-g-h-t-q-y	222.439	223.211	223.462	224.504	87.801	88.905	— ^a	90.468
b-j-s-c-e-f-g-h-v-p-x	218.869	220.632	221.354	222.728	84.011	85.768	86.490	— ^a
b-r-z-c-f-g-h-v-q-y	219.321	220.513	221.065	222.207	83.885	85.166	— ^a	87.079
a-b-r-g-h-v-q-y	227.949	229.398	228.859	228.878	92.865	93.894	93.380	92.551
a-b-n-e-g-h-t-q-y	226.041	227.390	227.516	227.579	93.016	94.948	94.766	94.748
k-c-e-f-g-h-v-p-y	222.000	224.077	224.786	225.728	85.718	88.046	88.912	90.004
a-k-e-f-g-h-v-p-y	229.104	229.047	228.840	228.784	93.511	93.668	93.574	93.493
a-b-f-g-h-v-q-y	227.384	226.236	225.715	225.715	91.729	90.794	90.324	90.449
a-m-n-e-f-g-h-t-q-y	228.112	228.307	228.238	228.194	94.672	94.980	94.886	94.842
a-l-g-h-v-p-y	225.175	227.767	228.281	228.231	90.794	93.285	93.662	93.373
a-b-m-f-g-h-t-p-y	227.836	227.058	226.562	226.487	94.628	93.587	92.953	92.645
b-k-c-e-f-g-h-v-p-y	218.781	220.889	221.680	222.948	83.045	85.360	86.245	87.569
b-c-e-f-g-h-v-q-y	221.530	223.010	223.431	224.234	85.893	87.569	88.052	0.000
a-r-f-g-h-q-v-y	228.482	227.930	227.579	227.309	92.558	92.288	92.024	91.886
a-m-n-e-f-g-h-t-q-y	229.405	228.984	228.740	228.878	94.672	94.980	94.886	94.842

a-b-m-f-g-h-w-q-v-x	228.357	227.710	227.202	226.895	92.200	91.158	90.713	0.000
b-l-c-g-h-v-p-y	226.826	225.257	224.548	224.535	90.788	89.608	89.012	89.226
b-m-c-e-f-g-h-t-p-y	222.264	223.186	223.425	223.989	88.002	89.131	89.477	90.142
r-z-c-e-f-g-h-v-q-y	224.102	225.972	226.424	227.026	87.851	89.991	90.681	91.478
a-r-e-g-h-q-v-y	224.811	226.706	227.554	228.677	89.282	90.976	91.723	92.545
b-j-c-e-f-g-h-w-v-q-x	220.193	222.063	222.722	223.776	84.833	86.766	87.450	88.516
a-m-r-f-g-h-v-p-x	227.277	226.675	226.393	226.336	90.123	90.048	89.991	90.230
b-r-z-c-g-h-v-q-y	226.236	225.345	225.031	225.012	90.399	89.715	89.533	89.702
a-k-e-f-g-h-v-p-y	228.796	228.890	228.765	228.758	92.721	93.248	93.242	93.292
b-m-n-c-f-g-h-t-q-y	220.563	221.053	221.153	222.151	86.182	86.835	87.010	88.071
a-e-f-g-h-v-q-y	230.308	230.327	230.120	229.938	93.549	93.969	93.907	93.813
a-b-e-g-h-t-p-y	226.161	227.491	227.497	227.491	92.451	— ^a	— ^a	— ^a
a-b-n-e-g-h-t-q-y	227.296	227.466	226.926	226.524	95.369	94.955	94.766	94.754
a-m-e-f-g-h-t-q-y	227.566	227.899	227.924	227.842	93.185	0.000	94.446	94.465
a-m-e-g-h-i-v-q-x	224.924	225.100	225.144	225.138	94.785	95.112	94.089	93.147
a-b-g-h-v-q-y	229.781	230.402	229.398	228.451	91.334	91.729	91.641	91.497
b-j-c-e-g-h-w-v-q-x	227.510	227.347	227.014	226.832	91.798	91.321	91.001	91.064
l-c-g-h-v-p-y	228.100	227.221	226.719	226.474	83.616	84.601	85.009	86.264
b-c-f-g-h-v-q-y	218.831	219.710	220.061	221.260	94.973	94.151	93.637	93.524
a-m-n-f-g-h-t-q-y	228.319	227.736	227.277	227.058	94.980	94.158	93.643	93.536
k-c-e-f-g-h-v-p-y	221.768	223.575	224.184	225.188	85.850	87.864	88.560	89.602
b-m-o-c-e-g-h-t-p-y	228.671	228.482	228.269	228.106	92.714	92.702	92.470	92.545
b-c-e-g-h-v-q-y	228.589	227.980	227.510	227.252	92.489	92.181	91.836	91.767
a-l-g-h-v-p-y	226.374	229.191	229.486	229.229	91.842	94.440	94.553	94.189
j-c-e-f-g-h-v-p-x	221.166	222.872	223.481	224.623	85.693	87.512	88.221	89.451
a-m-e-g-h-w-q-v-x	223.914	229.191	229.248	229.260	88.422	89.658	90.217	90.556
m-c-e-f-g-h-t-q-y	223.958	224.799	225.031	225.759	88.554	90.091	90.543	91.597
b-m-n-o-c-g-h-t-q-y	227.667	226.612	226.022	225.903	90.888	93.762	93.618	93.850
r-z-c-f-g-h-q-v-y	221.661	222.935	223.406	224.366	85.624	87.111	87.676	88.811
b-m-c-f-g-h-t-p-y	220.946	221.360	221.624	222.377	87.324	87.688	87.927	88.623
b-j-c-f-g-h-w-v-q-x	217.131	218.492	219.120	220.513	82.756	84.017	84.670	86.069
a-r-g-h-v-q-y	227.334	229.216	229.656	229.122	91.848	93.574	93.926	93.606
r-z-c-e-g-h-v-q-y	230.045	230.001	229.762	229.436	93.442	93.744	93.681	93.580
a-f-g-h-v-q-y	229.085	228.275	227.736	227.648	93.003	92.482	92.081	92.030
a-e-g-h-t-q-y	225.702	227.372	227.761	227.861	91.918	94.415	94.861	94.879
j-r-c-e-g-h-v-p-x	227.918	227.742	227.535	227.535	92.018	92.081	91.936	92.099
a-m-f-g-h-t-p-y	228.890	228.407	228.012	227.786	95.105	94.867	94.321	94.001
a-b-g-h-i-v-q-x	225.175	227.466	224.780	224.673	92.652	92.859	92.671	92.545
a-b-g-h-t-p-y	223.004	227.899	223.042	223.111	94.704	92.162	91.761	91.736
a-m-f-g-h-i-v-q-x	229.135	227.347	228.627	228.169	92.965	94.829	93.806	93.355
b-m-o-g-h-t-p-y	224.592	224.002	223.720	224.002	91.340	88.799	88.680	89.056
b-j-c-g-h-w-v-q-x	227.710	226.531	226.060	225.966	89.100	— ^a	89.822	89.884
k-c-e-f-g-h-v-p-y	221.097	223.255	223.939	225.006	84.896	87.318	88.178	89.376
c-e-f-g-h-v-q-y	223.738	225.307	225.633	226.267	87.431	89.288	89.797	90.575
a-e-g-h-v-q-y	226.826	229.304	230.402	231.268	91.070	93.191	94.164	94.817

b-c-g-h-v-q-y	225.985	224.736	224.203	224.234	90.411	89.345	88.962	89.094
m-o-n-g-h-t-q-y	230.133	230.082	229.982	230.039	94.785	95.086	95.036	95.231
a-m-f-g-h-w-v-q-x	228.696	228.162	227.779	227.554	92.940	92.413	92.049	91.918
j-c-e-f-g-h-w-v-q-x	222.521	224.322	224.874	225.646	86.709	88.642	89.251	90.110
m-c-e-f-g-h-i-v-q-x	221.649	222.734	222.973	223.280	89.941	91.240	91.541	92.300
j-s-c-g-h-v-p-x	222.521	222.954	223.042	223.575	87.130	87.895	88.077	88.887
l-c-g-h-v-p-y	227.892	226.863	226.255	226.173	91.541	90.945	90.524	90.650
m-c-f-g-h-t-p-y	223.738	224.654	224.836	225.175	88.874	90.393	90.769	91.309
s-z-c-g-h-v-q-y	227.999	227.359	227.026	226.914	91.610	91.265	91.070	91.139
m-n-c-f-g-h-t-q-y	222.176	222.828	223.048	223.776	87.061	88.071	88.334	89.382
a-e-g-h-i-v-q-x	223.155	223.845	224.096	224.284	91.133	92.024	92.194	92.143
a-e-g-h-t-p-y	225.439	227.271	227.648	227.805	91.384	93.436	94.346	94.672
a-n-g-h-t-q-y	227.384	228.112	227.911	227.579	86.182	86.841	87.017	88.071
c-f-g-h-v-q-y	221.209	222.144	222.421	223.425	85.354	86.521	86.935	88.008
j-c-e-g-h-w-q-v-x	229.053	228.834	228.526	228.175	92.821	93.210	93.028	92.627
a-g-h-v-q-y	229.078	231.043	230.616	229.857	93.599	95.601	95.187	94.471
m-o-c-e-g-h-t-p-y	229.424	229.461	229.405	229.612	94.610	94.879	94.779	94.679
c-e-g-h-v-q-y	230.057	229.762	229.329	229.016	93.361	93.398	93.173	93.053
m-c-f-g-h-i-v-q-x	220.456	221.178	221.479	222.069	89.320	89.671	89.734	90.531
j-c-f-g-h-w-v-q-x	219.641	220.902	221.473	222.596	84.776	86.069	86.628	87.826
m-c-f-g-h-t-p-y	222.508	223.029	223.199	223.776	88.353	89.044	89.301	89.947
m-c-t-p-y	222.559	223.092	223.236	223.795	88.353	89.044	89.301	89.941
m-n-o-c-g-h-t-q-y	229.191	228.463	227.943	227.792	92.463	92.056	91.667	92.056
a-g-h-i-q-v-x	223.663	223.914	223.895	223.876	93.041	93.078	92.752	92.752
a-g-h-t-p-y	228.476	229.744	229.455	229.141	93.813	96.065	95.381	94.967
j-c-g-h-w-q-v-x	226.575	226.041	225.759	225.797	90.819	90.612	90.430	90.637
m-o-c-g-h-t-p-y	229.606	228.746	228.294	228.100	93.016	92.256	91.823	91.823
c-g-h-v-q-y	227.786	226.788	226.299	226.192	91.748	91.045	90.675	90.700

^a The calculation for this conformer did not converge in the given solvent.

Table 8.K10. Solvent effect (free energy of solvation, ΔG_{solv}) and its electrostatic component (G_{el}) for the calculated conformers of mbandakamine A in the three solvents considered
Results from HF/6-31G(d,p) single point PCM calculations on the *in-vacuo*-optimized geometries.

conformer	HF					
	ΔG_{solv} (kcal/mol)			G_{el} (kcal/mol)		
	in chlrf	in actn	in aq	in chlrf	in actn	in aq
a-b-k-e-f-g-h-u-v-p-y	13.18	24.49	4.48	-6.37	-9.10	-24.42
a-b-l-e-g-h-u-v-p-y	14.16	24.52	4.64	-5.19	-8.82	-23.93
a-b-r-e-f-g-h-v-q-y	14.05	25.45	6.31	-6.31	-9.04	-23.73
b-k-c-e-f-g-h-v-p-y	14.20	25.43	5.66	-5.68	-8.57	-23.78
a-b-k-e-f-g-h-v-p-y	11.72	23.20	2.37	-7.00	-9.74	-26.01
a-b-m-e-f-g-h-t-p-y	13.70	24.78	3.71	-6.42	-9.12	-25.66
a-b-l-g-h-v-p-y	11.50	21.75	0.50	-7.75	-11.54	-28.04
b-l-c-e-g-h-v-p-y	14.96	26.05	5.85	-4.52	-7.48	-22.98
a-b-m-s-e-f-g-v-p-x	13.91	24.84	4.47	-5.49	-8.80	-24.75
b-r-z-c-e-f-g-h-v-q-y	16.40	26.86	6.90	-3.93	-7.65	-23.23
a-b-m-s-f-g-h-v-p-x	12.15	23.13	1.64	-6.61	-9.62	-26.42
a-b-k-e-f-g-h-v-p-y	11.17	22.49	1.08	-8.07	-11.11	-28.27
a-b-e-f-g-h-v-q-y	14.08	24.83	4.48	-5.36	-8.92	-24.93
a-b-m-e-f-g-h-t-p-y	13.56	25.12	5.49	-6.80	-9.43	-24.89
b-l-c-g-h-v-p-y	12.43	22.55	0.47	-6.92	-10.88	-28.28
a-b-m-e-f-g-h-i-v-q-x	13.56	23.85	2.93	-6.22	-10.14	-26.71
b-k-c-e-f-g-h-v-p-y	12.67	24.24	3.60	-6.06	-8.72	-24.80
a-b-l-g-h-v-p-y	10.17	20.55	-2.34	-8.23	-12.07	-30.37
a-b-m-w-v-q-x	13.19	25.03	5.24	-6.60	-6.60	-24.67
b-m-c-e-f-g-h-t-q-y	15.03	26.40	4.62	-4.97	-7.70	-25.01
b-j-s-c-e-f-g-h-v-p-x	13.95	25.72	4.49	-5.57	-8.07	-24.92
b-r-z-c-f-g-h-v-q-y	13.90	24.65	3.11	-6.46	-9.95	-27.13
a-b-r-g-h-v-q-y	12.92	23.40	3.16	-7.19	-10.84	-26.60
a-b-n-e-g-h-t-q-y	12.54	23.20	-0.93	-7.30	-10.73	-30.37
k-c-e-f-g-h-v-p-y	12.91	23.97	2.02	-6.80	-9.89	-27.27
a-k-e-f-g-h-v-p-y	11.84	22.83	-0.26	-6.75	-10.01	-28.55
a-b-f-g-h-v-q-y	12.34	21.87	-0.02	-6.93	-11.72	-29.26
a-m-n-e-f-g-h-t-q-y	12.75	23.68	0.20	-6.97	-10.12	-29.10
a-l-g-h-v-p-y	11.11	20.75	-3.18	-8.01	-12.43	-31.62
a-b-m-f-g-h-t-p-y	12.19	22.89	1.08	-7.71	-11.18	-28.77
b-k-c-e-f-g-h-v-p-y	13.61	24.44	3.64	-5.15	-8.57	-24.96
b-c-e-f-g-h-v-q-y	13.12	24.94	5.22	-6.29	-8.75	-24.14
a-r-f-g-h-q-v-y	12.61	22.82	-1.33	-7.46	-11.43	-31.13
a-m-n-e-f-g-h-t-q-y	13.43	24.85	4.17	-6.26	-8.95	-25.16
a-b-m-f-g-h-w-q-v-x	12.55	23.55	0.92	-7.06	-10.36	-28.75
b-l-c-g-h-v-p-y	11.60	22.19	-1.15	-6.80	-10.44	-29.19

b-m-c-e-f-g-h-t-p-y	13.94	25.16	5.71	-6.20	-9.16	-24.42
r-z-c-e-f-g-h-v-q-y	13.62	24.81	2.69	-6.59	-9.61	-27.37
a-r-e-g-h-q-v-y	13.14	23.81	2.33	-7.19	-10.68	-27.74
b-j-c-e-f-g-h-w-v-q-x	13.89	25.87	5.27	-6.02	-8.35	-24.76
a-m-r-f-g-h-v-p-x	11.70	22.19	-0.57	-6.99	-10.54	-28.66
b-r-z-c-g-h-v-q-y	13.24	23.57	0.60	-6.87	-10.72	-29.29
a-e-f-k-g-h-v-p-y	11.69	22.77	0.24	-6.99	-10.18	-28.33
b-m-n-c-f-g-h-t-q-y	14.07	25.74	2.46	-5.61	-7.99	-26.80
a-e-f-v-q-y	13.34	24.05	0.96	-6.04	-9.66	-28.43
a-b-e-g-h-t-p-y	13.13	23.42	0.92	-7.38	-11.36	-29.75
a-b-n-e-g-h-t-q-y	11.82	22.34	-1.85	-7.80	-11.34	-31.05
a-m-e-f-g-h-t-q-y	12.91	23.82	2.27	-7.01	-10.26	-27.59
a-m-e-g-h-i-q-v-x	13.24	22.92	-0.95	-6.43	-11.00	-30.55
a-b-g-h-v-q-y	11.33	20.95	-2.81	-7.82	-12.51	-31.89
b-j-c-e-g-h-w-v-q-x	14.22	24.34	-5.58	-27.00	-9.80	-27.00
l-c-g-h-v-p-y	11.41	21.52	-2.86	-7.80	-11.78	-31.49
b-c-f-g-h-v-q-y	12.52	23.01	0.64	-6.74	-10.55	-28.58
a-m-n-f-g-h-t-q-y	13.06	23.75	-1.16	-6.37	-9.73	-30.15
k-c-e-f-g-h-v-p-y	13.43	22.80	-0.16	-5.18	-10.06	-28.48
b-m-o-c-e-g-h-t-p-y	13.98	25.22	6.10	-6.12	-9.02	-24.02
b-c-e-g-h-v-q-y	13.33	24.31	3.21	-5.89	-9.20	-25.92
a-l-g-h-v-p-y	9.45	20.31	-5.12	-8.82	-12.22	-33.06
j-c-e-f-g-h-v-p-x	13.31	24.47	1.18	-6.08	-9.21	-28.13
a-m-e-g-h-w-q-v-x	12.44	23.56	1.05	-7.27	-10.50	-28.85
m-c-e-f-g-h-t-q-y	13.04	23.82	0.39	-6.82	-10.16	-29.14
b-m-n-o-c-g-h-t-q-y	12.74	24.30	0.84	-6.61	-9.11	-28.09
r-z-c-f-g-h-q-v-y	12.85	23.23	-0.07	-7.39	-11.26	-30.22
b-m-c-f-g-h-t-p-y	12.89	23.44	1.14	-6.94	-10.56	-28.65
b-j-c-f-g-h-w-v-q-x	12.76	23.74	1.36	-6.98	-10.31	-28.51
a-r-g-h-v-q-y	12.90	22.86	-1.45	-7.22	-11.43	-31.30
r-z-c-e-g-h-v-q-y	13.49	24.55	1.88	-6.78	-9.93	-28.26
a-f-g-h-v-q-y	11.89	22.56	-2.10	-7.28	-10.95	-31.28
a-e-g-h-t-q-y	12.22	22.35	-3.06	-7.50	-11.48	-32.43
j-r-c-e-g-h-v-p-x	12.83	22.59	-2.80	-6.29	-10.83	-31.83
a-m-f-g-h-t-p-y	12.31	22.82	-0.73	-7.88	-11.64	-31.07
a-m-f-g-h-i-v-q-x	10.93	20.66	-3.26	-8.97	-13.44	-33.18
a-b-g-h-i-v-q-x	21.52	21.52	-3.14	-12.14	-12.14	-32.46
a-b-g-h-t-p-y	9.76	19.57	-4.57	-9.94	-14.39	-34.26
b-j-c-g-h-w-v-q-x	12.68	23.30	1.80	-7.14	-10.66	-28.01
b-m-o-g-h-t-p-y	12.06	21.90	-2.74	-7.47	-11.97	-32.41
k-c-e-f-g-h-v-p-y	12.30	23.35	0.60	-6.36	-9.58	-27.94
c-e-f-g-h-v-q-y	12.38	23.61	1.23	-6.94	-10.01	-28.07
a-e-g-h-v-q-y	11.72	22.54	-0.38	-7.63	-11.16	-29.76
b-c-g-h-v-q-y	12.90	23.14	-0.31	-6.10	-10.14	-29.20

m-o-n-g-h-t-q-y	12.72	23.57	-0.29	-6.97	-10.25	-29.68
a-m-f-g-h-w-v-q-x	11.38	21.96	-2.73	-8.20	-11.96	-32.48
j-c-e-f-g-h w-v-q-x	12.87	24.12	1.45	-6.92	-9.99	-28.50
m-c-e-f-g-h-i-v-q-x	13.16	23.96	0.71	-6.69	-10.16	-29.15
j-s-c-g-h-v-p-x	10.63	20.82	-5.74	-7.89	-11.75	-33.70
l-c-g-h-v-p-y	9.98	19.86	-5.15	-8.30	-12.67	-33.11
m-c-f-g-h-t-p-y	13.06	24.11	1.29	-6.90	-10.04	-28.68
s-z-c-g-h-v-q-y	11.92	22.25	-1.72	-8.07	-11.94	-31.53
m-n-c-f-g-h-t-q-y	12.64	23.18	-1.93	-6.93	-10.47	-31.12
a-e-g-h-i-v-q-x	11.42	22.19	-3.63	-8.40	-11.92	-33.50
a-e-g-h-t-p-y	11.82	21.67	-1.91	-8.54	-12.98	-32.47
a-n-g-h-t-q-y	11.16	21.34	-5.41	-8.24	-12.13	-34.41
c-f-g-h-v-q-y	11.28	21.68	-2.62	-7.86	-11.79	-31.76
c-e-j-g-h-w-q-v-x	13.19	22.94	-0.86	-6.39	-11.00	-30.63
a-g-h-v-q-y	10.24	20.22	-5.82	-8.69	-13.01	-34.67
m-o-c-e-g-h-t-p-y	12.80	23.84	1.56	-7.15	-10.27	-28.42
c-e-g-h-v-q-y	12.05	22.95	-0.51	-7.07	-10.48	-29.59
m-c-f-g-h-i-v-q-x	13.11	22.61	-3.50	-6.34	-11.08	-32.88
j-c-f-g-h-w-v-q-x	12.15	22.65	-3.06	-7.79	-11.69	-33.27
m-c-f-g-h-t-p-y	11.89	22.05	-2.19	-8.00	-12.09	-32.17
m-c-t-p-y	11.63	22.10	-1.93	-8.27	-12.04	-31.91
m-n-o-c-g-h-t-q-y	12.09	22.56	-2.94	-7.19	-10.80	-31.84
a-g-h-i-q-v-x	9.98	19.35	-7.30	-9.58	-14.49	-36.88
a-g-h-t-p-y	10.49	18.72	-6.90	-9.28	-15.29	-36.75
c-j-g-h-w-q-v-x	10.71	20.78	-5.28	-8.82	-13.13	-35.01
m-o-c-g-h-t-p-y	11.37	21.93	-2.63	-8.37	-11.99	-32.42
c-g-h-v-q-y	10.63	20.90	-5.04	-8.33	-12.37	-33.95

Table 8.K11. Solvent effect (free energy of solvation, ΔG_{solv}) and its electrostatic component (G_{el}) for the calculated conformers of mbandakamine A in the three solvents considered
Results from DFT/6-31+G(d,p) single point PCM calculations on the *in-vacuo*-optimized geometries.

conformer	DFT					
	ΔG_{solv} (kcal/mol)			G_{el} (kcal/mol)		
	in chlrf	in actn	in aq	in chlrf	in actn	in aq
a-b-k-e-f-g-h-u-v-p-y	13.54	24.87	4.80	-6.60	-9.44	-24.97
a-b-l-e-g-h-u-v-p-y	13.41	24.79	4.31	-6.38	-9.08	-24.92
a-b-r-e-f-g-h-v-q-y	14.47	25.88	6.23	-6.47	-9.28	-24.62
b-k-c-e-f-g-h-v-p-y	14.37	25.85	6.05	-6.35	-9.16	-24.59
a-b-k-e-f-g-h-v-p-y	12.47	23.73	2.27	-6.91	-10.01	-27.09
a-b-m-e-f-g-h-t-p-y	13.93	25.17	3.38	-6.52	-9.48	-26.92
a-b-l-g-h-v-p-y	11.45	21.90	0.03	-8.32	-12.01	-29.30
b-l-c-e-g-h-v-p-y	14.32	25.86	6.00	-5.62	-8.22	-23.50
a-b-m-s-e-f-g-v-p-x	13.20	24.58	3.27	-6.73	-9.72	-26.80
b-r-z-c-e-f-g-h-v-q-y	15.16	26.80	7.20	-6.06	-8.74	-24.18
a-b-m-s-f-g-h-v-p-x	12.68	23.57	1.40	-6.85	-10.07	-27.69
a-b-k-e-f-g-h-v-p-y	12.43	23.67	2.37	-6.82	-9.94	-26.98
a-b-e-f-g-h-v-q-y	13.38	24.85	3.61	-6.80	-9.74	-26.83
a-b-m-e-f-g-h-t-p-y	13.69	25.00	4.66	-6.84	-9.89	-26.17
b-l-c-g-h-v-p-y	12.19	22.82	1.18	-7.66	-11.22	-28.32
a-b-m-e-f-g-h-i-v-q-x	13.16	24.36	3.07	-7.11	-10.24	-27.36
b-k-c-e-f-g-h-v-p-y	12.66	24.07	2.52	-6.69	-9.63	-26.81
a-b-l-g-h-v-p-y	10.31	20.72	-2.51	-8.67	-12.63	-31.45
a-b-m-w-v-q-x	13.91	25.39	4.99	-6.76	-9.70	-26.11
b-m-c-e-f-g-h-t-q-y	14.42	— ^a	3.84	-6.17	— ^a	-26.68
b-j-s-c-e-f-g-h-v-p-x	13.68	25.26	— ^a	-6.31	-9.09	— ^a
b-r-z-c-f-g-h-v-q-y	13.85	— ^a	3.20	-7.01	— ^a	-27.78
a-b-r-g-h-v-q-y	13.01	23.64	0.43	-7.83	-11.47	-30.38
a-b-n-e-g-h-t-q-y	13.10	23.83	-0.36	-7.60	-11.18	-31.12
k-c-e-f-g-h-v-p-y	13.08	24.04	1.67	-7.00	-10.25	-28.17
a-k-e-f-g-h-v-p-y	11.81	22.71	-1.02	-7.44	-10.92	-30.29
a-b-f-g-h-v-q-y	12.24	23.21	-0.40	-7.71	-11.18	-30.64
a-m-n-e-f-g-h-t-q-y	13.25	24.12	-0.15	-7.17	-10.54	-30.50
a-l-g-h-v-p-y	10.84	20.96	-3.78	-8.96	-13.05	-33.25
a-b-m-f-g-h-t-p-y	12.66	23.35	1.00	-7.91	-11.55	-29.87
b-k-c-e-f-g-h-v-p-y	13.25	24.76	3.44	-6.62	-9.58	-26.77
b-c-e-f-g-h-v-q-y	13.92	25.56	4.92	-6.43	-9.24	-25.80
a-r-f-g-h-q-v-y	12.83	23.35	-0.83	-7.87	-11.65	-31.56
a-m-n-e-f-g-h-t-q-y	13.19	24.05	-0.23	-7.17	-10.54	-30.50
a-b-m-f-q-v-x-w	12.71	23.73	1.14	-7.73	-11.15	-29.72

b-l-c-g-h-v-p-y	11.05	21.71	-1.27	-7.94	-11.64	-30.22
b-m-c-e-f-g-h-t-p-y	14.31	25.81	5.22	-6.40	-9.21	-25.81
r-z-c-e-f-g-h-v-q-y	14.32	25.50	3.78	-6.72	-9.89	-27.45
a-r-e-g-h-q-v-y	13.29	24.01	0.61	-7.36	-10.84	-29.93
b-j-c-e-f-g-h-w-v-q-x	14.09	25.58	4.99	-6.33	-9.16	-25.67
a-m-r-f-g-h-v-p-x	12.01	22.56	-2.19	-7.27	-10.83	-31.09
b-r-z-c-g-h-v-q-y	13.59	24.38	2.03	-7.22	-10.73	-28.87
a-k-e-f-g-h-v-p-y	11.77	22.71	-0.89	-7.37	-10.82	-30.18
b-c-m-f-g-h-n-t-q-y	14.01	25.21	1.60	-6.25	-9.23	-28.54
a-e-f-v-q-y	12.82	23.83	0.30	-7.25	-10.67	-30.08
a-b-e-g-h-t-p-y	— ^a	— ^a	— ^a	— ^a	— ^a	— ^a
a-b-n-e-g-h-t-q-y	13.10	23.83	-0.36	-7.59	-11.19	-31.12
a-m-e-f-g-h-t-q-y	— ^a	23.90	1.09	— ^a	-10.90	-29.69
a-m-e-g-h-i-q-v-x	12.48	23.31	-0.44	-7.70	-11.23	-30.83
a-m-e-g-h-i-q-v-x	11.31	21.85	-2.80	-8.23	-12.09	-32.52
a-b-g-h-v-q-y	12.77	23.84	1.35	-7.54	-10.87	-29.33
b-j-c-e-v-q-x-w	11.29	21.43	-2.82	-8.42	-12.49	-32.23
l-c-g-h-v-p-y	12.57	23.62	0.75	-7.34	-10.72	-29.46
b-c-f-g-h-v-q-y	13.00	23.70	0.09	-7.19	-10.66	-29.94
a-m-n-f-g-h-t-q-y	13.00	23.69	0.09	-7.19	-10.66	-29.94
k-c-e-f-g-h-v-p-y	11.90	22.83	-0.91	-7.35	-10.78	-30.18
b-m-o-c-e-g-h-t-p-y	14.14	25.33	4.55	-6.53	-9.62	-26.46
b-c-e-g-h-v-q-y	13.32	24.78	2.94	-6.40	-9.33	-26.98
a-l-g-h-v-p-y	9.59	19.55	-6.28	-9.26	-13.69	-35.13
j-c-e-f-g-h-v-p-x	12.95	24.15	-0.51	-6.85	-10.02	-30.48
a-m-e-g-h- w-q-v-x	12.02	22.31	-2.30	-8.51	-12.64	-33.30
m-c-e-f-g-h-t-q-y	13.52	24.48	-0.40	-6.87	-10.16	-30.74
b-m-n-c-o-t-q-y	13.90	25.24	3.92	-6.44	-9.38	-26.46
r-z-c-f-g-h-q-v-y	13.09	23.72	-0.22	-7.67	-11.38	-31.12
b-m-c-f-g-h-t-p-y	12.83	23.55	0.95	-7.51	-11.09	-29.67
b-j-c-f-g-h-w-v-q-x	12.97	24.00	1.10	-7.29	-10.65	-29.50
a-r-g-h-v-q-y	12.13	22.30	-3.62	-8.39	-12.47	-34.08
r-z-c-e-g-h-v-q-y	14.00	24.97	2.37	-6.75	-10.06	-28.41
a-f-g-h-v-q-y	11.67	22.21	-3.58	-8.18	-12.12	-33.78
a-e-g-h-t-q-y	12.26	22.55	-4.33	-8.25	-12.25	-34.88
j-r-c-e-g-h-v-p-x	11.81	22.39	-3.24	-7.81	-11.63	-33.06
a-m-f-g-h-t-p-y	11.77	21.98	-2.95	-8.52	-12.68	-33.59
a-m-f-g-h-i-v-q-x	11.25	21.52	-4.24	-8.71	-12.82	-34.44
a-b-g-h-i-v-q-x	11.29	21.26	-4.08	-9.29	-13.72	-35.09
a-b-g-h-t-p-y	11.42	21.39	-3.40	9.13	-13.52	-34.34
b-j-c-g-h-w-v-q-x	11.86	22.53	-2.22	-8.45	-12.25	-33.00
b-m-o-g-h-t-p-y	— ^a	23.83	1.04	— ^a	-11.06	-29.93
k-c-e-f-g-h-v-p-y	11.81	22.71	-0.85	-7.25	-10.73	-30.05
c-e-f-g-h-v-q-y	13.18	24.34	1.22	-7.06	-10.38	-29.43

a-e-g-h-v-q-y	12.04	22.70	-2.18	-7.65	-11.38	-32.08
b-c-g-h-v-q-y	11.88	22.69	-1.64	-7.59	-11.19	-31.30
m-o-n-g-h-t-q-y	13.08	23.87	0.30	-7.16	-10.66	-30.01
a-m-f-g-h-w-v-q-x	12.04	22.62	-2.33	-8.34	-12.23	-33.20
j-c-e-f-g-h-w-v-q-x	13.40	24.51	1.50	-6.89	-10.14	-29.08
m-c-e-f-g-h-i-v-q-x	12.60	22.91	-2.73	-8.05	-12.18	-33.86
j-s-c-g-h-v-p-x	10.97	21.06	-6.04	-8.00	-12.03	-34.62
l-c-g-h-v-p-y	10.10	20.33	-5.44	-8.77	-12.92	-34.31
m-c-f-g-h-t-p-y	13.23	24.14	0.90	-7.21	-10.62	-29.85
s-z-c-g-h-v-q-y	12.74	23.08	-1.53	-11.88	-7.90	-32.29
m-n-c-f-g-h-t-q-y	13.13	23.89	-1.70	-7.01	-10.46	-31.77
a-e-g-h-i-v-q-x	11.88	21.85	-3.59	-8.73	-13.17	-34.65
a-e-g-h-t-p-y	11.89	22.03	-3.04	-8.64	-12.89	-34.01
a-n-g-h-t-q-y	14.01	25.21	1.60	-6.25	-9.23	-28.54
c-f-g-h-v-q-y	11.82	22.42	-3.10	-8.01	-11.86	-33.25
j-c-e-g-h-w-q-v-x	12.07	22.67	-2.19	-8.10	-11.95	-32.79
a-g-h-v-q-y	10.65	20.72	-6.32	-8.78	-13.16	-36.00
m-o-c-e-g-h-t-p-y	13.41	24.29	1.57	-7.20	-10.65	-29.48
c-e-g-h-v-q-y	12.52	23.47	-0.71	-7.12	-10.58	-30.59
m-c-f-g-h-i-v-q-x	12.08	22.42	-2.85	-8.28	-12.31	-33.61
j-c-f-g-h-w-v-q-x	11.60	21.53	-6.76	-8.90	-13.43	-37.79
m-c-f-g-h-t-p-y	12.42	23.07	-2.12	-7.85	-11.64	-32.84
m-c-t-p-y	12.06	22.40	-2.81	-8.28	-12.31	-33.55
m-n-o-c-g-h-t-q-y	12.61	23.22	-3.06	-7.19	-10.78	-32.76
a-g-h-i-q-v-x	10.77	20.37	-7.63	-9.73	-14.56	-38.61
a-g-h-t-p-y	10.71	20.21	-6.88	-9.70	-14.60	-37.74
j-c-g-h-w-q-v-x	11.23	21.45	-5.80	-8.99	-13.28	-36.55
m-o-c-g-h-t-p-y	12.07	22.33	-3.21	-8.17	-12.24	-33.84
c-g-h-v-q-y	11.09	21.44	-5.65	-8.29	-12.37	-35.27

^a The calculation for this conformer did not converge in the given solvent.

CHAPTER 9

DISCUSSION AND CONCLUSION

The previous chapters present the results of the computational study of naphthylisoquinoline alkaloids with antimalarial activity. The objectives were to identify the preferential conformers and computable molecular properties (such as dipole moment, HOMO-LUMO energy gaps) *in vacuo* and in three solvents with different dielectric constants and different types of solute-solvent interactions. It had also the objective of evaluating the solvent effect on the molecular properties. The study in solution is particularly important for the investigation of biologically active molecules. These objectives were stated in the introduction of this thesis.

All the objectives were fulfilled to a satisfactory level of extend and information was obtained about all the properties considered. The obtained results can be used as basis for new studies. The next paragraphs highlight how the objectives were fulfilled and considered their significance. The discussion will concern also michellamine A, even if it biological activity is different because it is also a naphthylisoquinoline alkaloid.

The computational study of naphthylisoquinoline alkaloids as a sub-class of the alkaloids class performed in this work is, to my knowledge, the first of its kind for alkaloids. All the molecular properties that can be derived from geometry optimizations or frequency calculations have been investigated and analysed, and detailed data are reported in the previous chapters and appendix 2.

The naphthylisoquinoline alkaloids studied in this work have monomeric (one unit) or dimeric (two units) structures, with each unit consisting of a naphthalene moiety and isoquinoline moiety connected by a biaryl axis (C,C). The study *in vacuo* focused firstly on the identification of their conformers, obtained by optimising geometries with two levels of theory. The molecules have different number and types of conformers. The monomeric alkaloids have two to four conformers, depending on whether they can form intramolecular hydrogen bonds (IHBs) or not. Dimeric

alkaloids have much higher number of conformers due to the presence of more OHs and the possibilities of other types of IHB interactions; 80 conformers were identified for jozimine A₂ and 107 for mbandakamine A.

The conformers' stability is influenced by the presence and types of IHBs, which have a stabilising effect, and by the mutual orientation of the moieties, with the isoquinoline moiety preferring to be perpendicular to the naphthalene moiety. Additional stabilising factors in dimeric structures are the mutual orientation of the two naphthalene moieties, which prefer to be perpendicular to each other both in jozimine A₂ and in mbandakamine A, and the presence of stacking interactions in mbandakamine A.

The IHBs are particularly important in the study of biologically active molecules. Therefore a particular attention was given to the IHBs. Conformers of these compounds differ by their IHB patterns. Three types of IHBs may be present in these molecules, namely:

- O–H···O within a naphthalene moiety
- O–H··· π between an OH of an isoquinoline moiety and the π system in the naphthalene moiety;
- C–H···O between a C–H and an OH in the same isoquinoline moiety (weaker IHBs).

An additional IHB possible in all the dimeric structures considered is the O–H··· π interaction between the OH of a naphthalene moiety of one unit and the π system of the naphthalene moiety of the other unit. Michellamine A may have the O–H···O between the two naphthalene moieties of different units, which is a consecutive (and cooperative).

The following IHBs are possible only in mbandakamine A:

- O–H···O between the isoquinoline moiety and the naphthalene moiety of different units. It may be consecutive (and cooperative) with the IHB within the naphthalene moiety;
- O–H···N between the isoquinoline moiety and the naphthalene moiety of different units.
- O–H···O between the two isoquinoline moieties;
- O–H···O or N–H···O between the OH (or NH) of an isoquinoline and the O (methoxy) of a naphthalene moiety in the other unit, bifurcated on the H atom;
- C–H···N between the two isoquinoline moieties.

The stabilising effect of the IHBs is related to their strengths which is not easy to evaluate. This strength is evaluated on the basis of the bond lengths and the red-shifts. The bond lengths were evaluated for the O–H $\cdots$ O and the C–H $\cdots$ O IHBs; and the red-shifts were considered for all the IHBs present. On the basis of their bond length and their red-shift, the O–H $\cdots$ O (or also O–H $\cdots$ N in mbandakamine) present in most conformers are moderate IHBs [464, 465], but in some conformers they are weak. The C–H $\cdots$ O (or C–H $\cdots$ N) interactions are weak [464]. On the basis of their red-shifts, the O–H $\cdots\pi$ interactions cause red-shift that is comparable with that of the O–H $\cdots$ O IHBs in several cases. The O–H $\cdots$ O forms between an OH and an O of another OH is more stabilising than the O–H $\cdots$ O between an OH and an O of an OCH₃.

Beside the conformational preferences and IHBs, others molecular properties were calculated and the results will be quickly summarised in the next paragraphs. The dipole moments of monomeric alkaloids are between 0.64–5.97D/HF and 0.81–5.02D/DFT, depending on the number and orientation of the OH groups in each of them. The dipole moments of dimeric structures are rather close, with michellamine A having slightly higher values; the ranges are 0.50–7.53D/HF and 0.59–7.33D/DFT for jozimine A₂, 0.44–7.59D/HF and 0.42–7.53D/DFT for mbandakamine A, and 2.37–8.28D/HF and 2.05–8.28D/DFT for michellamine A. The higher dipole moments of dimeric structures with respect to the monomeric ones are likely due to the presence of a higher number of OH groups (at least four OHs in dimeric structures, and only one or two in the monomeric ones).

The energy difference between HOMO and LUMO (HOMO-LUMO energy gap) is an important molecular property because it is correlated to the chemical reactivity of the molecule. The HOMO-LUMO energy gap is greater for the monomeric alkaloids than for the dimeric ones. This may suggest that the mechanism of action of monomeric alkaloids is different from the dimeric ones. Among the dimeric alkaloids, the gap is greatest for jozimine A₂ and lowest for mbandakamine A.

The shapes of the HOMO and LUMO molecular orbitals show interesting similarity. For both monomeric and dimeric alkaloids, the shapes indicate greater concentration of electron density in the naphthalene moieties than in the isoquinoline moieties with few exceptions among the monomeric structures. For the lower-energy conformers of the dimeric structures, there is a concentration of electron density on the two naphthalene moieties. In the pairs of symmetric

conformers in jozimine A₂, the concentration of electrons is on one of the naphthalene moieties for one conformer and on the other naphthalene moiety for its symmetric conformer. The concentration of electron density is distributed differently for some higher energy conformers of mbandakamine A, the electrons may concentrate on one naphthalene, or on the two naphthalene moieties and a bit less on the isoquinoline moiety, or on the naphthalene moiety and isoquinoline moiety of one unit and a bit less on the other naphthalene moiety. In the higher energy conformers of michellamine A, as the electrons may concentrate mostly on one portion of the naphthalene moieties.

The solvent effect (free energy of solvation, ΔG_{solv}) is positive in chloroform and acetonitrile for all the conformers of all the naphthylisoquinoline alkaloids considered in this work, and negative in water for all the conformers of the monomeric alkaloids, jozimine A₂ and michellamine A, whereas it may be negative or positive in water for the conformers of mbandakamine A. The magnitude of ΔG_{solv} in water is greatest for the monomeric structures and for michellamine A. Thus, ΔG_{solv} (kcal/mol) in water is 0.02–(–18.49)/HF and 0.07–(–17.80)/DFT for the monomeric structures, 6.90–(–7.30)/HF and 6.23–(–7.63) for mbandakamine A, –4.04–(–12.42)/HF and –4.12–(–11.91)/DFT for jozimine A₂, and –11.43–(–22.49)/HF and –13.52–(–22.84)/DFT for michellamine A. The greater magnitude for michellamine might be related to the higher number of OHs in the molecule (six OH groups). Mbandakamine A and jozimine A₂ have both four OHs in their structures; the fact that conformers of jozimine A₂ may have greater ΔG_{solv} magnitude than mbandakamine A is likely due to the higher number of IHBs present in mbandakamine A and also to the presence of stacking interactions.

If 3.5 kcal/mol is taken as a cautious threshold for conformers to be considered as potentially responsible for the biological activity of a substance, then the relative energies in water solution (the medium with a greater number of lower energy conformers) suggest that about 10 conformers of jozimine A₂, 16 of michellamine A and 6 of mbandakamine A might be considered as potentially responsible for their respective activities.

These results enable one to predict the molecular properties of other structurally similar molecules of the same class that may be discovered. For instance, one can predict that the most stable conformers are conformers in which all the IHB-types are present at the same time. To improve

the predictions, one can take also in account the stabilizing effect of the different types of IHBs and consider all their types, including O–H $\cdots\pi$ IHBs when present. The mutual orientation of the moieties (isoquinoline moiety prefer to be perpendicular to the naphthalene moiety) is also an aspect that can be included in the predictions.

Altogether, these results can also be useful for further research on antimalarial naphthylisoquinoline alkaloids, and on antimalarials in general. The obtained information will be important in the study of the ways these molecules may interact with their biological target (e.g. docking calculations with proteins).

An extensive detailed conformational analysis is important to understand the biological behaviour of a class of compounds. Some important structural features of these molecules are relevant for structure-activity relationships [382]. QSAR studies utilise many descriptors. All the data provided on the different molecular properties considered in this study can be used as QSAR descriptors, such as conformational descriptors (the energy of the conformers), electronic descriptors (HOMO, LUMO and dipole moments) and structural descriptors (number of H-bond donors, number of H-bond acceptors and number of rotatable bonds).

Planned future works include the study of the interaction of these molecules with water molecules through the consideration of adducts with explicit water molecules, for a better understanding of these interactions, and the investigations of possible reaction pathways, which might lead to a better understanding of the mechanisms of the molecules' biological activity.

APPENDIX 1

INTRAMOLECULAR HYDROGEN BONDS IN CONFORMERS OF QUININE AND QUINIDINE: AN HF, MP2 AND DFT STUDY

This appendix presents the results of the computational study of quinine and quinidine *in vacuo* and in two solvents (chloroform and water), published in [61]. They are added here as an appendix because quinine is one of the most important antimalarial drugs, and also because this study was prompted by the literature review done for this project.

A1.1. Introduction

Quinine ($C_{20}H_{24}N_2O_2$, Fig.3.8, section 3.6.1) and quinidine are alkaloids isolated from the bark of cinchona trees found in Peru. Quinidine is an erythro diastereoisomer of quinine; the absolute configuration of quinine is 1S,3R,4S,8S,9R and that of quinidine is 1S,3R,4S,8R,9S [388]. Both compounds are active against malaria (section 3.6.2). Because of its pharmaceutical importance, quinine has been the major subject in the studies focusing on cinchona alkaloids.

Figure 3.8 shows the atom numbering utilised in [61]. The most relevant rotatable bonds in cinchona alkaloids are those linking the quinuclidine and quinoline moieties, i.e., C8–C9 and C9–C10, corresponding to the C11–C10–C9–C8, C10–C9–C8–N1 and H22–O20–C9–C8 torsion angles. Their rotations determine the mutual orientations of the two moieties, thus also determining the possibility that the N atom and the OH group come close enough to form an intramolecular hydrogen bond (IHB). The orientations of the hydroxyl group and of the methoxy group may also influence conformers' energies [373, 374].

Because of their importance for the classification of conformers, the values of the C11–C10–C9–C8, C10–C9–C8–N1 and H22–O20–C9–C8 torsion angles from the previous studies are shown in Table A1–1. This work refers mostly to the outcomes of the studies [375–382, 385, 386, 389, 390, section 3.6.2.1] and uses the same terminology of the conformers.

Figure 1 in [375] showed that all the conformers there considered had the OH oriented towards the quinoline moiety. This motivated the current study, based on the assumptions that the opposite orientation of the OH might enable the formation of an IHB with the N atom of the quinuclidine moiety.

Table A1–1. Relevant dihedral angles of the most stable conformer of quinine and quinidine in previous conformational studies

The angles are denoted in the following way in the column headings: A for C11–C10–C9–C8, B for C10–C9–C8–N1, D for O20–C9–C8–N1 and E for H22–O20–C9–C8.

reference	quinine				quinidine			
	A	B	D	E	A	B	D	E
373	-167.6	-114.3		-65.4	-66.2	113.5		-65.4
374	99	152	-83	174	-99	-153	83	-173

A1.2. Computational details

Calculations were performed *in vacuo* at the HF/6-31G(d,p) and DFT/B3LYP/6-31+G(d,p) levels, all with a fully relaxed geometry, similarly to all the other studies considered in the previous chapters. Because of the importance of having a very good description of the possible IHB, MP2/6-31+G(d,p) calculations were added, also with fully relaxed geometry optimisation.

The MP2 [102] method takes into account both the electron correlation and the dispersion energy and is an efficient level of theory for the evaluation of energy differences between minima and for the description of IHBs, because the description of H-bonding is enhanced by the inclusion of dispersion energy contributions [103].

Vibrational frequencies (harmonic approximation) were calculated at the HF and DFT levels, and scaled by the factors recommended for these two methods [446, 447]. They were not calculated with MP2 because of the known difficulties with frequency calculations for this method [99].

Calculations in solution utilized the Polarizable Continuum Model (PCM, [178–183, section 2.4.3]) with the same computational options described in section 4.1.2. Two solvents were considered – chloroform and water – to mimic the most important media within living organisms: the non-polar medium (mostly, lipid phase in the body) and water, which creates a polar medium and is the major component of living organisms. Calculations in solution were performed as single point (SP) calculations on the *in-vacuo* optimised geometries, with the same levels of theory utilized *in vacuo*. It was opted to use SP calculations because the main focus was on the relative energy of the conformers with the IHB in solution, and SP calculations can provide reasonable information on the energetics, with much lower computational costs.

A1.3. Results

A1.3.1. Results *in vacuo*

Besides the conformers expected to have an IHB, the conformer corresponding to cis-open (3) in [375] (the lowest energy conformer of all the previous studies, called Q1 in the earlier studies) was also calculated, as a reference to compare the energy of the conformers with the IHB. Both the cis and trans options, as defined in [375], were calculated for each type of conformer to verify possible influences from the orientation of the methoxy group.

The resulting conformers are shown in Fig.A1–1 for quinine and in Fig.A1–2 for quinidine, and their relative energies are reported in Table A1–2. The conformers are denoted with acronyms starting with ‘quin’ for quinine and ‘quind’ for quinidine. This is followed by a number, increasing according to the relative energy in the DFT results. The relative energy sequence for quinine is considerably different in the results of the different methods utilized. However, the spectroscopic experimental information reported in [375] shows that the lowest energy conformer does not have an IHB. Therefore, it is opted here to choose a relative energy sequence consistent with this, in

assigning numbers to conformers. DFT results are chosen with preference to HF results because DFT takes into account part of the electronic correlation. Furthermore, they are closer to MP2 results, which take into account both electron correlation and dispersion energy. The conformers with the IHB (quin-2-c, quin-2-t, quin-3-c and quin 3-t for quinine and quind-1-t, quind-1-c, quind-3-c and quind-3-t for quinidine) have relative energies only marginally different from those without the IHB in the MP2 results, whereas the difference is not negligible in the DFT results, but also not so large as to exclude them from being potentially responsible for the biological activity. This consistency in the DFT and MP2 results in terms of yielding a low enough relative energy for the conformers with the IHB to include them as potentially responsible for the biological activity can be considered as a clear indication that such conformers need to be included. In the acronym denoting the conformers, the number is followed by ‘c’ for cis or ‘t’ for trans.

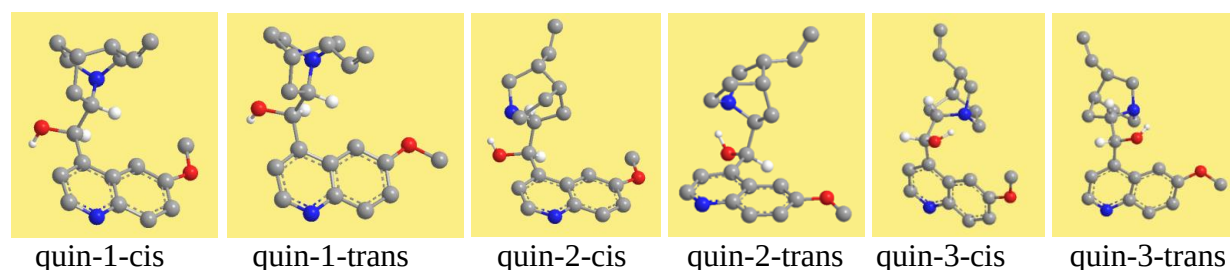


Figure A1–1. Conformers of quinine calculated in [61] .
DFT/6-31+G(d,p) results

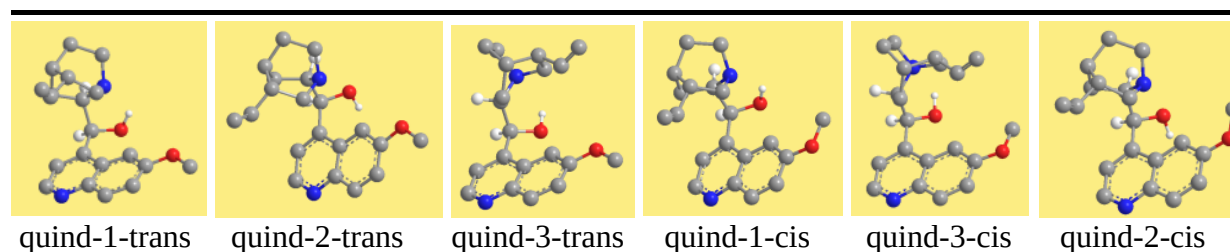


Figure A1–2. Conformers of quinidine calculated in [61] work
DFT/6-31+G(d,p) results

Table A1–2. Relative energy of the conformers of quinine and quinidine calculated within this work.

HF/6-31G(d,p), MP2/6-31+G(d,p) and DFT/B3LYP/6-31+G(d,p) results *in vacuo* and in chloroform and water solutions. The results *in vacuo* are from full optimization calculations, and the results in solution are from single point PCM calculations on the *in vacuo*-optimized geometries, at the same level of theory. The conformers are listed in order of increasing relative energies in the DFT results *in vacuo*.

Conformer	Relative Energy (kcal/mol)								
	HF			MP2			DFT		
	vac	chlrf	aq	vac	chlrf	aq	vac	chlrf	aq
quin-1-c	0.000	0.000	0.000	0.046	0.402	0.264	0.000	0.000	0.000
quin-1-t	2.024	1.569	2.641	2.175	2.061	1.405	1.249	0.995	0.809
quin-2-c	3.702	3.422	3.198	0.000	0.000	0.000	1.734	1.180	1.274
quin-2-t	5.192	4.797	4.712	1.648	1.594	1.434	2.265	1.988	2.266
quin-3-c	5.680	5.431	5.661	1.730	1.926	2.247	3.723	3.294	3.846
quin-3-t	7.837	7.234	6.760	4.337	4.164	3.506	4.599	4.698	4.816
quind-1-t	0.283	2.530	2.931	1.880	2.281	2.289	0.000	1.359	1.927
quind-2-t	0.206	3.342	2.759	0.030	3.355	2.119	0.755	2.863	2.275
quind-3-t	0.000	2.087	1.303	0.000	4.472	4.361	0.810	2.014	1.066
quind-1-c	2.410	0.720	1.856	2.641	0.000	0.824	1.696	0.000	0.989
quind-3-c	2.100	0.000	0.000	4.666	1.979	2.575	2.386	0.390	0.000
quind-2-c	3.331	0.715	1.376	3.684	0.089	0.000	3.125	0.900	1.156

For quinine, *cis* conformers have lower energy than corresponding *trans* conformers, whereas for quinidine, *trans* conformers have lower energy. For both molecules, the difference between corresponding *cis* and *trans* is considerable. For quinine, this energy difference (kcal/mol) is ~2/HF, 1.6–3/MP2 and ~1/DFT; for quinidine, it is 2–3/HF, 1–5/MP2 and 1–3/DFT.

Table A1–3 reports the relative free energies (ΔG , sums of electronic and thermal free energies) of the calculated conformers in the HF and DFT results *in vacuo*. For quinine, the conformer with the lowest relative energy (quin-1-c, not having an IHB) also has the lowest ΔG . For quinidine, the quind-1-c conformer (having the IHB) has the lowest ΔG .

Comparisons with the ΔG values reported in [375] is not easy because only the lowest energy conformer of [375] was calculated in this work, and, therefore, the comparison can refer only to this conformer. For quinine, the conformer with the lowest ΔG coincides in the current results and in [375]; for quinidine, a different conformer (quin-3-c, not present in [375] and with an H $\cdots$ N

Table A1–3. Relative Gibbs free energies (ΔG , sum of electronic and thermal free energies) of the calculated conformers of quinine and quinidine
HF/6-31G(d,p) and DFT/B3LYP/6-31+G(d,p) results *in vacuo*.

Conformer	Sum of Electronic and Thermal Free Energies (kcal/mol)		Conformer	Sum of Electronic and Thermal Free Energies (kcal/mol)	
	HF	DFT		HF	DFT
quin-1-c	0.000	0.000	quind-1-t	2.910	1.882
quin-1-t	5.907	3.666	quind-2-t	3.465	2.727
quin-2-c	4.827	2.937	quind-3-t	1.866	1.709
quin-2-t	1.539	1.787	quind-1-c	1.337	0.398
quin-3-c	6.669	4.895	quind-3-c	0.000	0.000
quin-3-t	8.271	6.305	quind-2-c	1.000	0.508

Distance too long to be considered an IHB but still suggesting a weak interaction between the two atoms) has the lowest ΔG in the current results.

Table A1–4 reports the relevant torsion angles, i.e., the torsion angles indicating the mutual orientations of the ring systems (C11–C10–C9–C8 and C10–C9–C8–N1) and the orientation of the OH group (H22–O20–C9–C8 and O20–C9–C8–N1). The orientation of the methoxy group does not influence the rest of the geometry significantly, and corresponding pairs of cis and Trans conformers have close values for these torsion angles. Conformers 1 and 2 differ for the C10–C9–C8–N1 torsion angle, and conformers 2 and 3 differ for the C11–C10–C9–C8 torsion angle; both angles are associated with the orientation of the two moieties.

Table A1–5 reports the parameters of the IHBs. The H $\cdots$ N bond length would suggest a moderate strength for the IHB [465]. However, the directionality, as shown by the N $\hat{H}$ O angle, is not optimal, which may contribute to decreasing the strength. The parameters indicate a stronger IHB for quinine than for quinidine, and the directionality is also more favorable for quinine. Comparison of the three methods shows that MP2 optimizes for geometries with better IHB parameters.

Frequency calculations confirm that the identified stationary points correspond to true minima. Table A1–6 reports the vibrational frequencies of the OH bond (harmonic approximation) in the HF and DFT results. With reference to the 3650 cm^{–1} experimental frequency value for the ground

state reported in [375], the HF results obtained here are considerably higher, whereas the DFT result obtained here (3766 cm^{-1}), although being 116 cm^{-1} higher than the experimental value, is closer to the experimental value than the calculated result reported in [375]. It is interesting to consider the decrease in the vibrational frequency caused by the formation of the IHB (red shift). The red shift is evaluated with reference to the vibration when the OH is not engaged in the IHB. Although the frequency of quin-1-c and quin-1-t, or quind-2-c and quind-2-t, are very close, it was opted to evaluate the red shifts of the cis conformers with respect to the frequency of the OH in quin-1-c and quind-2-c, and the red shifts of the trans conformers with respect to the frequency in quin-1-t and quind-2-t. The red shifts are reported in Table A1–7. For quinine, the value of the red shift is $67\text{--}98\text{ cm}^{-1}/\text{HF}$ and about $250\text{ cm}^{-1}/\text{DFT}$; for the quind-1-c and quind-1-t conformers of quinidine, it is 63 and $68\text{ cm}^{-1}/\text{HF}$ and 210 and $248\text{ cm}^{-1}/\text{DFT}$, respectively. The quind-3 conformers do not show any red shift with respect to quind-2, and the HF and DFT N...H values are longer than what was normally accepted for an H-bond, although they suggest the presence of a weak interaction between the two atoms (only the MP2 values suggest an IHB).

Table A1–8 reports the dipole moment of the calculated conformers. The dipole moment of the conformers with the IHB is significantly greater than for that of conformers without the IHB for both quinine and quinidine and in the results of all the methods.

A1.3.2. Results in Solution

Table A1–2 also shows the relative energies in chloroform and water solutions. For quinine, the increasing relative-energy sequence remains the same *in vacuo* and in solution. For the lower energy conformers of quinine having the IHB, the relative energy is lower in chloroform than *in vacuo*; in water, it is higher than in chloroform and, for some conformers, it becomes close or slightly higher than *in vacuo*. For quinidine, the increasing relative-energy sequence changes in solution. The lowest energy conformer is a conformer with the IHB both *in vacuo* and in chloroform (quind-1-t and quind-1-c respectively), whereas quind-3-c (with a very weak IHB-type interaction) is the lowest energy conformer in water.

The relative energy increases in solution with respect to *in vacuo* for trans conformers and decreases for cis conformers, up to the point that, differently from *in vacuo*, trans conformers have higher relative energy than the corresponding cis conformers in solution. For conformers quind-1-

t, quind-1-c and quind-2-c, the relative energy is higher in water than in chloroform; for the other three conformers, it is lower in water than in chloroform. The dipole moment (Table A1–8) increases as the medium polarity increases (which is the most common trend). Since calculations in solution were SP calculations, the increase is due only to the polarization of the solute molecule by the solvent (not to a change in the molecular geometry). The dipole moment of the conformers with the IHB remains higher than that of conformers without the IHB in all the media and with all the calculation methods, both for quinine and for quinidine. The cis conformers have higher dipole moment than the trans conformers in all the media and with all the levels of theory, for both quinine and quinidine.

Table A1–9 shows the free energy of solvation (ΔG_{solv}) of the calculated conformers. The presence or absence of the IHB does not appear to influence ΔG_{solv} . The magnitude of ΔG_{solv} is much greater for water than for chloroform. For quinine, ΔG_{solv} is negative for all the conformers and with all the calculation methods. For quinidine, ΔG_{solv} is negative in water for all the conformers; in chloroform, it is negative for most conformers but positive for quind-2-c in the HF and DFT results. For quinine, ΔG_{solv} is smaller for cis conformers than for trans conformers in all the solvents and with all the calculation methods. For quinidine, ΔG_{solv} is greater for quind-3-c and quind-1-c than for their corresponding trans conformers, whereas it is smaller for quind-2-c than for quind-2-t in both solvents and with all the calculation methods. Table A1–10 reports the electrostatic component (G_{el}) of the free energy of solvation (ΔG_{solv}) of the calculated conformers. G_{el} has negative values in both solvents for all the conformers, and its magnitude is considerably greater in water than in chloroform. The non-electrostatic component of ΔG_{solv} can be easily calculated as $G_{\text{non-el}} = \Delta G_{\text{solv}} - G_{\text{el}}$.

A1.4. Discussion

The most important result of this study is to have shown that quinine and quinidine may form an IHB whose strength is likely between weak and moderate (with the IHB length pointing towards ‘moderate’ and the $\text{N}\hat{\text{H}}\text{O}$ angle being closer to the ‘weak’ range). The fact that three different computational methods all show the possibility of the IHB confirms the result. The relative energy values show that the stabilizing effect of the IHB may be comparable to the stabilizing effect of

preferred mutual orientations of the two moieties for the lowest energy conformers in which it is present. The conformer responsible for the biological activity of a compound is not always the lowest energy one. It may be one with higher relative energy, but still with a sufficient population to be able to exert the activity. Different authors often use different threshold values as the maximum energy value beyond which a conformer is not likely to be involved in the biological activity. A very cautious threshold value is 3.5 kcal/mol; thus, conformers whose relative energy is not ≤ 3.5 kcal/mol in at least one of the media can be excluded.

The results of this study (Table A1–2) show that both the lower energy conformer with the IHB and the lower energy conformer without the IHB might be involved in the biological activity. If one considers the MP2 and DFT results, only quin-3-t is excluded from being possibly responsible for the biological activity. Thus, the relative energies of the conformers with the IHB (quin-2 and quin-3) in the various media show that these conformers may be involved in the biological activity of quinine. For quinidine, if one considers the DFT results, no conformer is excluded from being the one possibly responsible for the biological activity; if one considers the MP2 results, only quind-3-t might be excluded because its relative energy in both solvents is too high (and the biological activity is exerted in a medium). It is not possible to predict a priori whether the presence of an IHB hampers or favours the exerting of biological activities by the given conformer (for instance, the antioxidant activity of polyphenols is enhanced by the presence of an IHB between two neighbour OHs [542, 543]).

Besides the relative energies, this study has considered all the properties related to the molecular geometry (relevant torsion angles, parameters of the IHB) as well as other information related to the energetics, i.e. relative Gibbs free energies (sum of electronic and thermal free energies) *in vacuo*, free energy of solvation in chloroform and in water) and the harmonic vibrational frequencies of the O–H bond, in order to sufficiently provide comprehensive information about the conformers having an IHB and how their properties compare with those of the best conformer without IHB.

A1.5. Conclusions

The current study reveals the presence of an intramolecular hydrogen bond in some conformers of quinine and quinidine. This result is confirmed at all the levels of theory utilized. The strength of this IHB is between weak and moderate.

Table A1–4. Relevant dihedral angles of the conformers of quinine and quinidine calculated within this work

HF/6-31G(d,p), MP2/6-31+G(d,p) and DFT/B3LYP/6-31+G(d,p) results *in vacuo*. The angles are denoted in the following way in the column headings: A for C11–C10–C9–C8, B for C10–C9–C8–N1, D for O20–C9–C8–N1 and E for H22–O20–C9–C8.

Conformer	HF				MP2				DFT			
	A	B	D	E	A	B	D	E	A	B	D	E
quin-1-c	101.6	152.1	–84.2	170.9	100.5	155.7	–81.3	169.0	99.3	153.6	–82.4	174.0
quin-1-t	101.2	154.8	–81.7	169.9	99.8	159.8	–77.7	167.5	99.6	155.8	–80.4	172.2
quin-2-c	99.1	–81.5	44.8	–30.0	100.4	–80.7	44.5	–29.4	99.8	–87.5	39.0	–24.1
quin-2-t	99.1	–81.5	44.8	–30.2	100.6	–81.9	43.2	–28.3	100.5	–88.8	37.7	–23.0
quin-3-c	–86.3	–81.6	49.0	–26.0	–89.0	81.1	48.9	–27.2	–81.6	–90.0	41.3	–23.0
quin-3-t	–87.5	–80.6	50.6	–29.0	–90.4	–79.3	50.6	–29.6	–83.4	–87.5	43.8	–25.7
quind-1-t	87.3	81.2	–49.9	27.1	86.7	83.2	–46.7	26.2	82.3	89.3	–41.9	24.3
quind-2-t	98.9	57.2	–71.1	–179.6	101.5	56.8	–70.6	174.0	100.1	56.3	–72.3	178.2
quind-3-t	82.5	–171.3	61.2	–83.0	91.2	159.4	33.6	–53.4	83.1	–169.0	63.8	–82.6
quind-1-c	88.8	80.2	–51.0	29.4	87.7	81.7	–48.2	28.3	84.8	86.9	–44.4	26.7
quind-3-c	84.2	–174.1	58.6	–79.3	91.2	159.4	33.6	–53.4	85.6	–174.7	58.2	–75.7
quind-2-c	98.6	56.2	–71.9	179.1	100.4	54.9	–72.2	173.2	100.4	53.3	–75.0	176.2

Table A1–5. Parameters of the intramolecular hydrogen bond in the the calculated conformers of quinine and quinidine, which have an IHB

HF/6-31G(d,p), MP2/6-31+G(d,p) and DFT/B3LYP/6-31+G(d,p) results *in vacuo*. The distances (N···H and N···O) are in Å and the angle (NĤO) is in degrees.

Conformer	HF			MP2			DFT		
	N···H	N···O	NĤO	N···H	N···O	NĤO	N···H	N···O	NĤO
quin-2-c	2.112	2.726	121.0	1.989	2.677	125.2	1.980	2.675	125.8
quin-2-t	2.102	2.720	121.4	1.977	2.670	125.6	1.967	2.668	126.2
quin-3-c	2.187	2.785	120.0	2.082	2.748	123.6	2.000	2.700	125.9
quin-3-t	2.217	2.801	118.9	2.128	2.772	122.0	2.055	2.727	124.3
quind-1-t	2.194	2.788	119.8	2.039	2.721	124.9	2.010	2.703	125.8
quind-1-c	2.224	2.805	118.7	2.078	2.741	123.4	2.066	2.734	123.9
quind-3-t	2.856	2.979	88.2	2.280	2.740	107.9	2.903	3.044	89.0
quind-3-c	2.794	2.956	90.4	2.280	2.740	107.9	2.772	2.990	93.4

Table A1–6. Vibrational frequencies (harmonic approximation) of the O–H bond in the conformers of quinine and quinidine calculated within this work

HF/6-31G(d,p) and DFT/B3LYP/6-31+G(d,p) results *in vacuo*. The frequency values have been scaled by 0.9024 and 0.9857, respectively, and recommended for HF/6-31G(d,p) [447] and DFT/B3LYP/6-31+G(d,p) [448] calculations.

Quinine			Quinidine		
Conformer	Vibrational Frequencies (cm ⁻¹)		Conformer	Vibrational Frequencies (cm ⁻¹)	
	HF	DFT		HF	DFT
quin-1-c	4177.12	3765.86	quind-1-t	4114.25	3552.36
quin-1-t	4177.86	3766.81	quind-2-t	4176.76	3762.28
quin-2-c	4081.76	3513.87	quind-3-t	4194.83	3775.72
quin-2-t	4079.32	3507.32	quind-1-c	4106.38	3513.52
quin-3-c	4102.45	3513.01	quind-3-c	4197.41	3786.94
quin-3-t	4110.13	3545.42	quind-2-c	4174.45	3761.13

Table A1–7. Red shift of the O–H bonds in the calculated conformers of quinine and quinidine having an IHB

HF/6-31G(d,p) and DFT/B3LYP/6-31+G(d,p) results *in vacuo*.

Conformer	Red Shift of the Frequency of the OH Group (cm ⁻¹)	
	HF	DFT
quin-2-c	95.36	251.99
quin-2-t	98.54	259.49
quin-3-c	74.67	252.85
quin-3-t	67.73	221.39
quind-1-t	62.51	209.92
quind-1-c	68.07	247.61

Table A1–8. Dipole moment of the conformers of quinine and quinidine calculated within this work

HF/6-31G(d,p), MP2/6-31+G(d,p) and DFT/B3LYP/6-31+G(d,p) results *in vacuo* and in solution.

Conformer	Dipole Moment (Debye)								
	HF			MP2			DFT		
	vac	chlrf	aq	vac	chlrf	aq	vac	chlrf	aq
quin-1-c	2.789	3.336	3.999	3.007	3.759	4.679	2.903	3.610	4.423
quin-1-t	1.402	1.473	1.494	1.677	1.529	1.849	1.808	2.059	2.433
quin-2-c	4.459	5.106	5.857	4.707	5.440	6.329	4.733	5.648	6.623
quin-2-t	3.622	4.066	4.376	4.197	4.630	5.050	4.129	4.859	5.412
quin-3-c	4.465	5.113	5.876	4.518	5.473	6.380	4.405	5.258	6.175
quin-3-t	2.975	3.304	3.519	3.337	3.796	4.109	3.210	3.717	4.030
quind-1-t	3.059	3.457	3.882	3.266	3.816	4.417	3.319	3.934	4.542
quind-2-t	0.703	1.010	1.622	1.066	1.341	1.981	1.160	1.472	1.603
quind-3-t	1.987	2.340	2.772	2.837	3.359	4.104	2.325	2.823	3.299
quind-1-c	4.708	5.493	6.501	4.542	5.779	7.032	4.797	5.857	7.116
quind-3-c	4.242	4.979	5.893	4.515	5.161	6.228	4.235	5.771	7.049
quind-2-c	3.310	4.029	5.030	3.657	4.596	5.794	3.355	4.252	5.401

Table A1–9. Solvent effect (free energy of solvation, ΔG_{solv}) for the calculated conformers of quinine and quinidine in chloroform (chlrf) and water (aq)

Results from HF/6-31G(d,p), MP2/6-31+G(d,p) and DFT/B3LYP/6-31+G(d,p) single point PCM calculations on the *in vacuo*-optimized geometries.

Conformers	ΔG_{solv} (kcal/mol)					
	HF		MP2		DFT	
	chlrf	aq	chlrf	aq	chlrf	aq
quin-1-c	−0.95	−9.24	−1.28	−11.38	−0.74	−9.82
quin-1-t	−1.93	−10.94	−2.28	−13.11	−1.71	−11.14
quin-2-c	−0.89	−9.29	−1.87	−11.86	−0.92	−9.76
quin-2-t	−1.49	−9.83	−2.41	−12.63	−1.60	−10.35
quin-3-c	−0.68	−8.37	−1.53	−10.81	−0.71	−8.83
quin-3-t	−1.50	−10.07	−2.42	−13.02	−1.46	−10.19
quind-1-t	−0.79	−9.02	−1.49	−11.09	−0.76	−9.07
quind-2-t	−0.83	−10.04	−1.71	−12.85	−0.57	−10.06
quind-3-t	−0.03	−7.30	−0.64	−9.09	−0.03	−7.73
quind-3-c	−1.24	−9.88	−0.96	−9.70	−1.12	−10.40
quind-2-c	0.20	−7.48	−0.85	−10.47	0.35	−8.02
quind-1-c	−1.73	−11.45	−1.78	−11.60	−1.53	−11.67

Table A1–10. Electrostatic component (G_{el}) of the free energy of solvation for the calculated conformers of quinine and quinidine in chloroform (chlrf) and water (aq)

Results from HF/6-31G(d,p), MP2/6-31+G(d,p) and DFT/B3LYP/6-31+G(d,p) single point PCM calculations on the *in vacuo*-optimized geometries

Conformers	G_{el} (kcal/mol)					
	HF		MP2		DFT	
	chlrf	aq	chlrf	aq	chlrf	aq
quin-1-c	−3.78	−15.42	−4.57	−18.15	−3.82	−16.43
quin-1-t	−4.23	−16.41	−5.04	−19.20	−4.31	−17.10
quin-2-c	−4.06	−15.93	−4.99	−18.48	−4.37	−16.89
quin-2-t	−4.18	−15.90	−2.41	−18.70	−4.52	−16.86
quin-3-c	−4.04	−15.45	−4.84	−17.91	−4.25	−16.30
quin-3-t	−4.38	−16.50	−5.24	−19.42	−4.59	−17.08
quind-3-t	−4.46	−17.53	−4.98	−18.63	−4.60	−18.30
quind-2-t	−4.44	−17.30	−1.71	−20.00	−4.49	−17.83
quind-1-t	−4.33	−16.21	−5.14	−18.62	−4.56	−16.75
quind-1-c	−4.02	−15.16	−4.74	−17.30	−4.23	−15.99
quind-2-c	−3.93	−15.56	−4.75	−18.36	−4.08	−16.58
quind-3-c	−4.45	−16.73	−4.65	−17.51	−4.65	−17.79

APPENDIX 2

COMPUTATIONAL STUDY OF MICHELLAMINES – NAPHTHYLISOQUINOLINE ALKALOIDS WITH ANTI- HIV ACTIVITY

This appendix chapter presents the results of the conformational analysis of michellamine A. The results were presented at a QSCP in 2015 [G] and subsequently published [62]. This is reported separately here as an appendix because michellamine A is not an antimalarial naphthylisoquinoline alkaloids, but it is considered interesting to study because its structure has many similarity to that of jozimine A₂, although their activities are very different.

A2.1. Introduction

Michellamine A (denoted here as MCA) is a naphthylisoquinoline alkaloid isolated from *Ancistrocladus korupensis*, a plant of the Ancistrodaceae family [544]. Michellamines are naphthylisoquinoline alkaloids with a dimeric structure in which each unit consists of a naphthalene and an isoquinoline moiety. The naphthalene moieties of the two units are bonded to each other, (Fig.A2-1).

MCA and its atropisomers (michellamine B, michellamine C and others) show good activity against HIV, with michellamine B having the greatest activity (atropisomers are stereoisomers arising because of hindered rotation about a single bond, where energy differences due to steric strain or other contributors create a barrier to rotation that is high enough to allow for isolation of individual atropisomers).

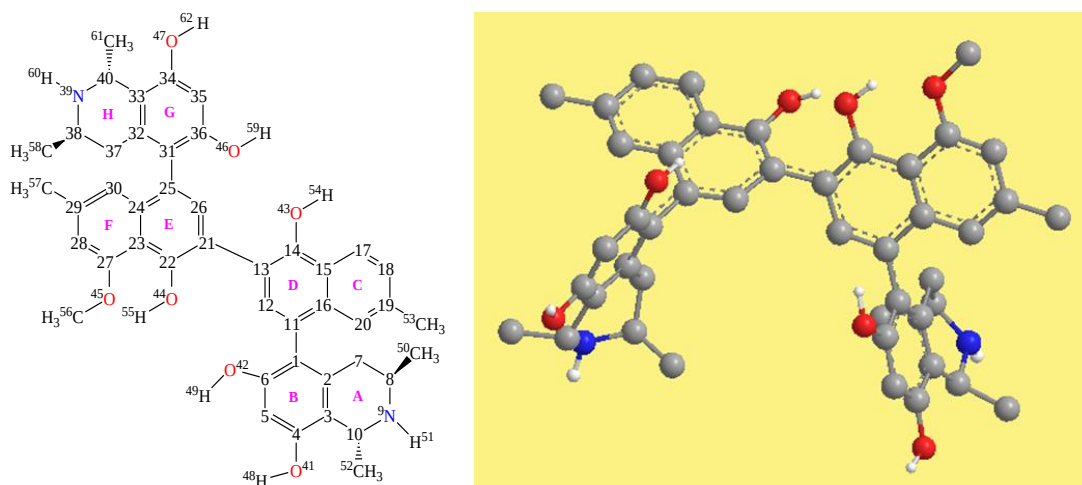


Figure A2–1. Structure of the michellamine A molecule and atom numbering utilized in [62]
The C atoms in the rings are represented only by the numbers denoting their positions. Only the H atoms attached to O or N are numbered separately, while the H atoms attached to a C atom are given the same number as the C atom. The rings are denoted by the letters A, B, C, D, E, F, G and H.

Chemically, michellamines are unique naphthylisoquinoline alkaloids not only because of their ‘dimeric’ structure (which was unprecedented when they were discovered), but also because of their exceptionally high polarity resulting from their three phenolic OH and one secondary amino group per constituent unit [544]. No previous studies have been found on michellamine A or its atropisomers.

A2.2. Naming of conformers

A system of symbols similar for the two others dimeric naphthylisoquinoline alkaloids are used for michellamine as well. Since it is convenient to be able to mention each ring individually, the rings are denoted by uppercase letters (A, B, C, D, E, F, G, H) as illustrated in Fig.A2–1. In order to be able to mention each of the two units of the dimeric molecular structure individually, the whole unit comprising the A, B, C, D rings is called R and the whole unit comprising the E, F, G, H rings is called S.

The most important factors stabilizing the conformers are the O–H···O IHBs and other IHB-type interactions such as O–H··· π and C–H···O. Different conformers often have different combinations of these intramolecular interactions. Each IHB or IHB-type interaction is denoted by a specific lower case letter. The letters and their meanings are kept as similar as possible to those used for jozimine A₂, with the only differences where it is necessary to take into account features or characteristics that are specific for michellamine A such as, C14–C13–C21–C22 torsion angle. The letters (a–h) and their meanings are listed in Table A2–1.

The energy of the conformers is also significantly influenced by the mutual orientations of the four moieties. The mutual orientation of the R and S units is determined by the presence or absence of an IHB between them. When the IHB is present, the C14–C13–C21–C22 torsion angle is close to $\pm 50^\circ$, depending on whether the E,F plane is ‘to the left’ or ‘to the right’ with respect to the D,C plane. When the IHB is absent, the C14–C13–C21–C22 torsion angle is close to $\pm 90^\circ$. These four possibilities for the orientations of the two units are denoted by the letters *t*, *v*, *p* and *q* (Table A2–1). Different combinations of moieties’ orientations correspond to different IHB-type interactions. For instance, the two cooperative (a-b) IHBs are compatible with the *t* and *v* orientations between the R and S units, but not with the *p* and *q* orientations.

Table A2– 1. Letters utilized in the acronyms denoting the conformers of michellamine A in this work, and their meanings

Letter	Meaning	Letter	Meaning
a	Presence of the O43–H54···O44 IHB	h	Presence of C–H61···O47
b	Presence of the O44–H55···O45 IHB	t	C14–C13–C21–C22 torsion angle close to $+50^\circ$
c	Presence of the O42–H50··· π interaction	v	C14–C13–C21–C22 torsion angle close to -50°
d	Presence of the O46–H59··· π interaction	p	C14–C13–C21–C22 torsion angle close to $+90^\circ$
e	Presence of the O43–H54··· π interaction	q	C14–C13–C21–C22 torsion angle close to -90°
f	Presence of the O44–H55··· π interaction	x	C24–C25–C31–C36 torsion angle close to 90°
g	Presence of C–H52···O41	y	C24–C25–C31–C36 torsion angle close to -90°

The potential energy profile for the rotation of the C13–C21 bond between the two units (Fig. A2–2) shows that the minima correspond to the conformers with two consecutive IHBs.

As for the other naphthylisoquinoline alkaloids, the isoquinoline and naphthalene moieties within each unit are approximately perpendicular to each other, with the torsion angle close to $\pm 90^\circ$. Given the high number of possible combinations of different orientations and the comparatively high computational cost per conformer in relation to the size of the molecule, only the mutual orientation of the E,F and G,H moieties in the S unit was varied, whereas the mutual orientation of the A,B and C,D moieties in the R unit was kept the same for all the conformers (C6–C1–C11–C16 torsion angle close to -90°). This is justified by the expected symmetric influence of analogous orientations of the two moieties in the R and S units, and by the potential energy profile for the rotation of the C1–C11 bond (Fig A2–3).

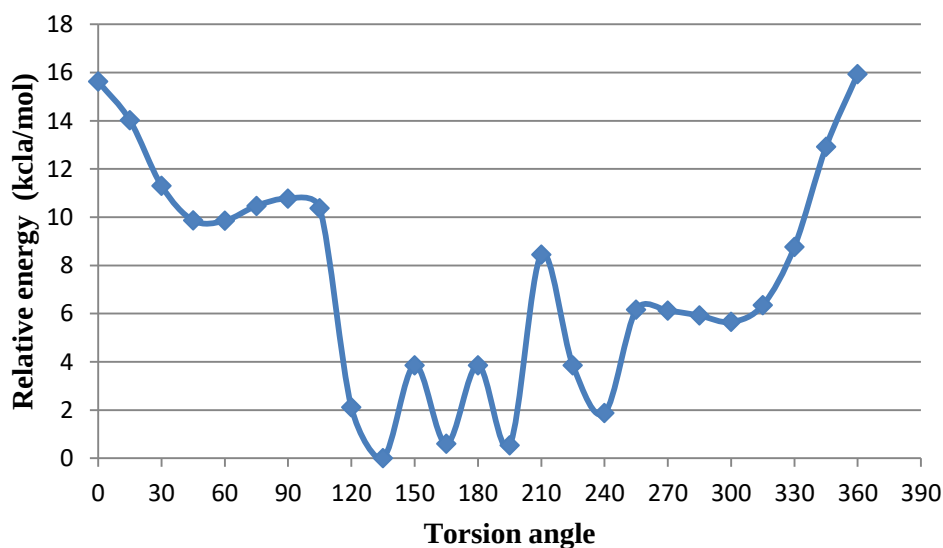


Figure A2– 2. Potential energy profile for the rotation of the C13–C21 bond (C14–C13–C21–C22 torsion angle) between the R and S units (between the C,D naphthalene moiety and the E,F naphthalene moiety)
HF/6-31G(d,p) results

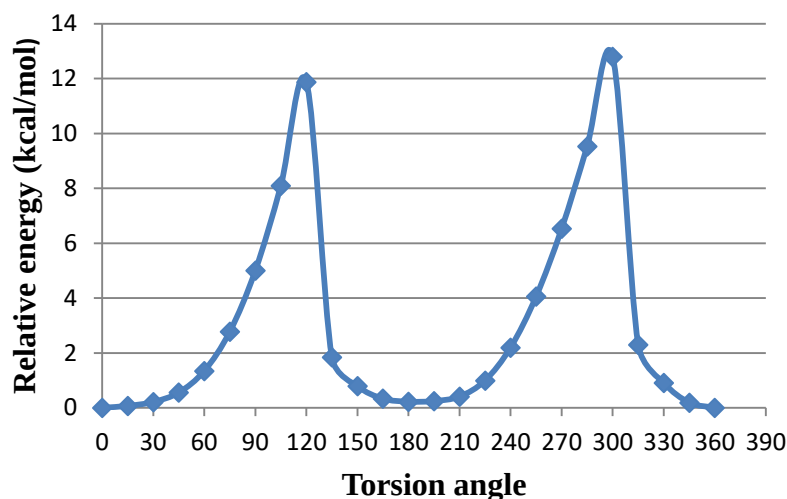


Figure A2–3. Potential energy profile for the rotation of the C1–C11 bond (C6–C1–C11–C16 torsion angle) between the isoquinoline moiety (A,B) and the naphthalene moiety (C,D) within the R unit
HF/6-31G(d,p) results.

The profile shows that the orientation with C6–C1–C11–C16 close to -90° is the lowest energy one and the orientation with C6–C1–C11–C16 close to $+90^\circ$ corresponds to another minimum, with nearly the same energy as the -90° orientation. The two orientations are denoted by the letters x and y (Table A2–1). The orientations with C6–C1–C11–C16 close to $+90^\circ$ or to -90° do not imply different kinds of IHB-types interactions in the conformers, because of the absence of mutual interactions between the isoquinoline moieties of R and S. Thus, the consideration of different orientations of the E,F and G,H moieties in the S unit provides sufficient information on the influence of the orientations of the naphthalene and isoquinoline moiety within the same unit. Geometries involving stacking interactions between different aromatic moieties did not prove viable on optimisation.

Examples of how the acronyms describe the characteristics of individual conformers may be functional. MCA-a-b-c-f-g-h-x-t is a conformer characterised by the presence of the O43–H54...O44 and O44–H55...O45 IHBs (which are consecutive when present simultaneously),

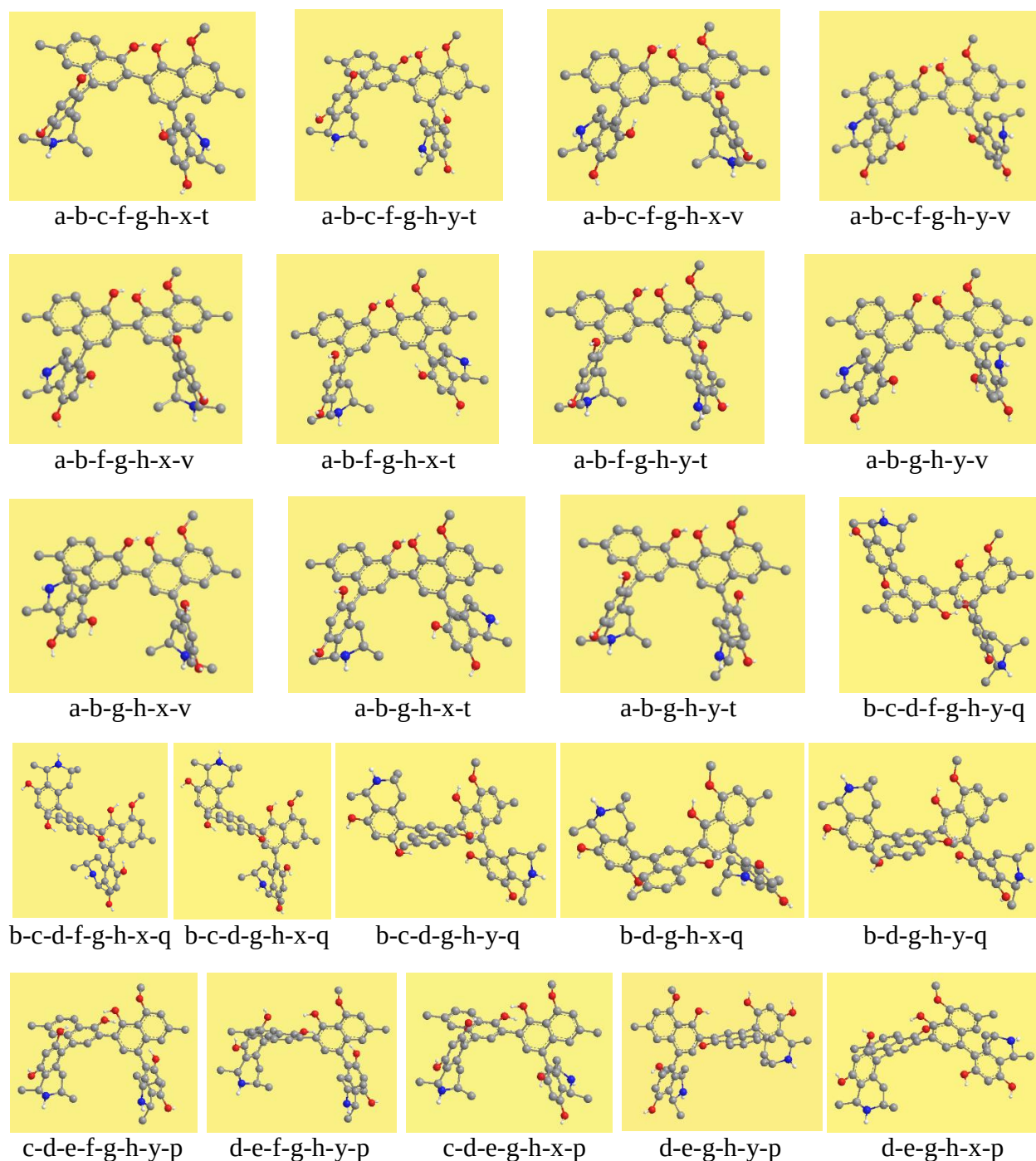


Figure A2–4. Optimized geometries of the conformers of michellamine A and sets of letters identifying their characteristics in the acronyms denoting them

Geometries from HF/6-31G(d,p) results. The images illustrate the main combinations of interaction types and moieties' orientations which may be present in the conformers of michellamine A. The initial part of the acronyms is not reported under the images, because of space reasons; it is the same for all the conformers (MCA).

the O42–H49 $\cdots\pi$ and O46–H59 $\cdots\pi$ interactions and the C–H52 $\cdots$ O41 and C–H61 $\cdots$ O47 interactions, and with the C24–C25–C31–C36 torsion angle close to 90° and the C14–C13–C21–C22 torsion angle close to 50°;

MCA-b-c-d-g-h-y-q is a conformer characterized by the presence of the O44–H55 $\cdots$ O45 IHB, the O42–H49 $\cdots\pi$ and O43–H54 $\cdots\pi$ interactions and the C–H52 $\cdots$ O41 and C–H61 $\cdots$ O47 interactions, and with the C24–C25–C31–C36 torsion angle close to –90° and the C14–C13–C21–C22 torsion angle close to –90°.

Figure A2–4 shows all the calculated conformers of MCA and the corresponding combinations of letters describing their characteristics in the acronyms denoting them.

A2.3. Results

A2.3.1 Results *in vacuo*

Table A2–2 reports the relative energies of the calculated conformers of MCA in *vacuo* and in the three solvents considered. The conformational preferences are influenced by IHB patterns (the number and type of IHBs present in a conformer) and by the mutual orientation of the two units and of the two moieties (naphthalene and isoquinoline) within each unit. Three types of IHB interactions may be present: O–H $\cdots$ O IHBs (the consecutive O43–H54 $\cdots$ O44 and O44–H55 $\cdots$ O45 IHBs, leading to the O43–H54 $\cdots$ O44–H55 $\cdots$ O45 sequence, or O44–H55 $\cdots$ O45 alone); O–H $\cdots\pi$ interactions between the O–H in an isoquinoline moiety and the closest π system in the naphthalene moiety of the same unit (O42–H49 $\cdots\pi$, O46–H59 $\cdots\pi$) or between an O–H in the naphthalene moiety of one unit and the closest π system in the naphthalene moiety of the other unit (O43–H54 $\cdots\pi$, O44–H55 $\cdots\pi$); and C–H $\cdots$ O interactions within an isoquinoline moiety (C–H52 $\cdots$ O41 and C–H61 $\cdots$ O47). The conformers having all the IHB-type interactions simultaneously are the lowest energy conformers. The two consecutive O43–H54 $\cdots$ O44 and O44–H55 $\cdots$ O45 IHBs are cooperative, as each of them strengthens the other. They have the

strongest stabilizing effect, followed by a single O–H $\cdots$ O IHB. The H-bond lengths indicate that the IHB within the E,F naphthalene moiety (O44–H55 $\cdots$ O45) is the strongest IHB.

The removal of the O44–H55 $\cdots$ O45 IHB brings about the O44–H55 $\cdots\pi$ interaction and the removal of the O43–H54 $\cdots$ O44 IHB brings about the O43–H54 $\cdots\pi$ interaction. Each of these removals causes an increase in the energy of the conformer. Comparison of the energies of conformers MCA-a-b-c-f-g-h-x-t and MCA-c-d-e-f-g-h-y-p shows an energy increase of ≈ 8 kcal/mol. In some case, the O–H $\cdots\pi$ interactions can have greater stabilizing effect than an IHB; for instance, conformer MCA-c-d-e-f-g-h-y-p, which has all the O–H $\cdots\pi$ interactions (O42–H49 $\cdots\pi$, O43–H54 $\cdots\pi$, O44–H55 $\cdots\pi$ and O46–H59 $\cdots\pi$), has lower energy than some conformers having O–H $\cdots$ O IHBs, such as MCA-a-b-g-h-y-v. Changes in the mutual orientations of the moieties may cause energy differences of ≈ 1 kcal/mol.

Table A2–3 reports the geometrical parameters of the IHB of the calculated conformers in vacuo. The bond length (Å) of the O43–H54 $\cdots$ O44 IHB is 1.753–1.761/DFT and 1.880–1.891/HF and that of O44–H55 $\cdots$ O45 is 1.688–1.730/DFT and 1.749–1.776/HF. The O $\cdots$ O distance (Å) is 2.660–2.669/DFT and 2.735–2.743/HF for O43–H54 $\cdots$ O44 and 2.560–2.589/DFT and 2.735–2.743/HF for O44–H55 $\cdots$ O45. The O $\hat{H}$ O bond angle is 148.0°/HF and 153.0°/DFT for O43–H54 $\cdots$ O44 and 143.0°/HF and 146.0°/DFT for O44–H55 $\cdots$ O45. For the O–H $\cdots\pi$ interactions, a bond length is not defined, as the acceptor is a whole π system and not an individual atom. It may be convenient to consider the distance between the H atom of the donor and the C atom in the aromatic system closest to it. The H $\cdots$ C distance thus defined is slightly shorter when the interaction involves an O–H in the naphthalene moiety of one unit and the closest π system in the naphthalene moiety of the other unit (O43–H54 $\cdots\pi$ and O44–H55 $\cdots\pi$) than when it involves an O–H in the isoquinoline moiety and the closest π system in the naphthalene moiety of the same unit (O42–H49 $\cdots\pi$ and O46–H59 $\cdots\pi$). The H $\cdots$ C distance (Å) is 2.269–2.381/DFT and 2.302–2.398/HF for O43–H54 $\cdots\pi$ and O44–H55 $\cdots\pi$, and 2.317–2.382/DFT and 2.345–2.401/HF for O42–H49 $\cdots\pi$ and O46–H59 $\cdots\pi$. For the C–H $\cdots$ O interactions within the isoquinoline moiety (C–H52 $\cdots$ O41 and C–H61 $\cdots$ O47), the H $\cdots$ O distance is ~ 2.40 Å in both HF and DFT results. This value is considerably longer than the H $\cdots$ O distance for O–H $\cdots$ O IHBs, consistently with the fact

that the C–H $\cdots$ O interaction is considerably weaker. The C $\cdots$ O distance for C–H52 $\cdots$ O41 and C–H61 $\cdots$ O47 is 3.0 Å in both HF and DFT results. The C $\hat{H}$ O bond angle is $\sim 114.0^\circ$ /HF and $\sim 116.0^\circ$ /DFT for both C–H52 $\cdots$ O41 and C–H61 $\cdots$ O47.

The calculated harmonic vibrational frequencies of the O–H bonds (Table A2–4) highlight the frequency lowering (red shift) in correspondence to IHBs. Interesting enough, the red shift of the frequency of O43–H54 when it acts as donor in the O43–H54 $\cdots$ O44 IHB is smaller than would be expected for an OH engaged in an IHB in which the acceptor O belongs to another OH, and is not dissimilar from the red shift of O44–H55 when engaged in the O44–H55 $\cdots$ O45 IHB although, in this case, the acceptor is an ether O and the IHB might be expected to be weaker than with a phenol O. On the other hand, the red shift of O44–H55 when the O43–H54 $\cdots$ O44 IHB is not present is smaller than when it is present. This can be viewed as a confirmation that the two IHBs (O43–H54 $\cdots$ O44 and O44–H55 $\cdots$ O45) are cooperative. Figure A2–5 shows the calculated IR spectra of selected conformers of MCA (Table A2-5).

The ZPE corrections (Table A2-6). are very close for all the conformers. Their ranges (kcal/mol) are 554.6–556.1/HF and 516.0–517.5/DFT, with the greater values corresponding to lower energy conformers. The relative energies corrected for ZPE have the same trends as the uncorrected ones.

The ranges (Debye, Table A2-7) of the values of the dipole moments in vacuo are 2.37–8.28/HF and between 2.05–8.00/DFT. Conformers with O–H $\cdots$ O IHBs have higher dipole moment than conformers with O–H $\cdots$ π interactions. Conformers with only O–H $\cdots$ π interactions (no O–H $\cdots$ O IHBs) have the smallest dipole moments. For instance, MCA-c-d-e-f-g-h-y-p has all the O–H $\cdots$ π interactions and its dipole moment (HF) is 2.37 D, while MCA-a-b-c-f-g-h-y-v, with O–H $\cdots$ O IHBs, has 7.88 D dipole moment. The orientation of the OH groups is a major factor influencing the dipole

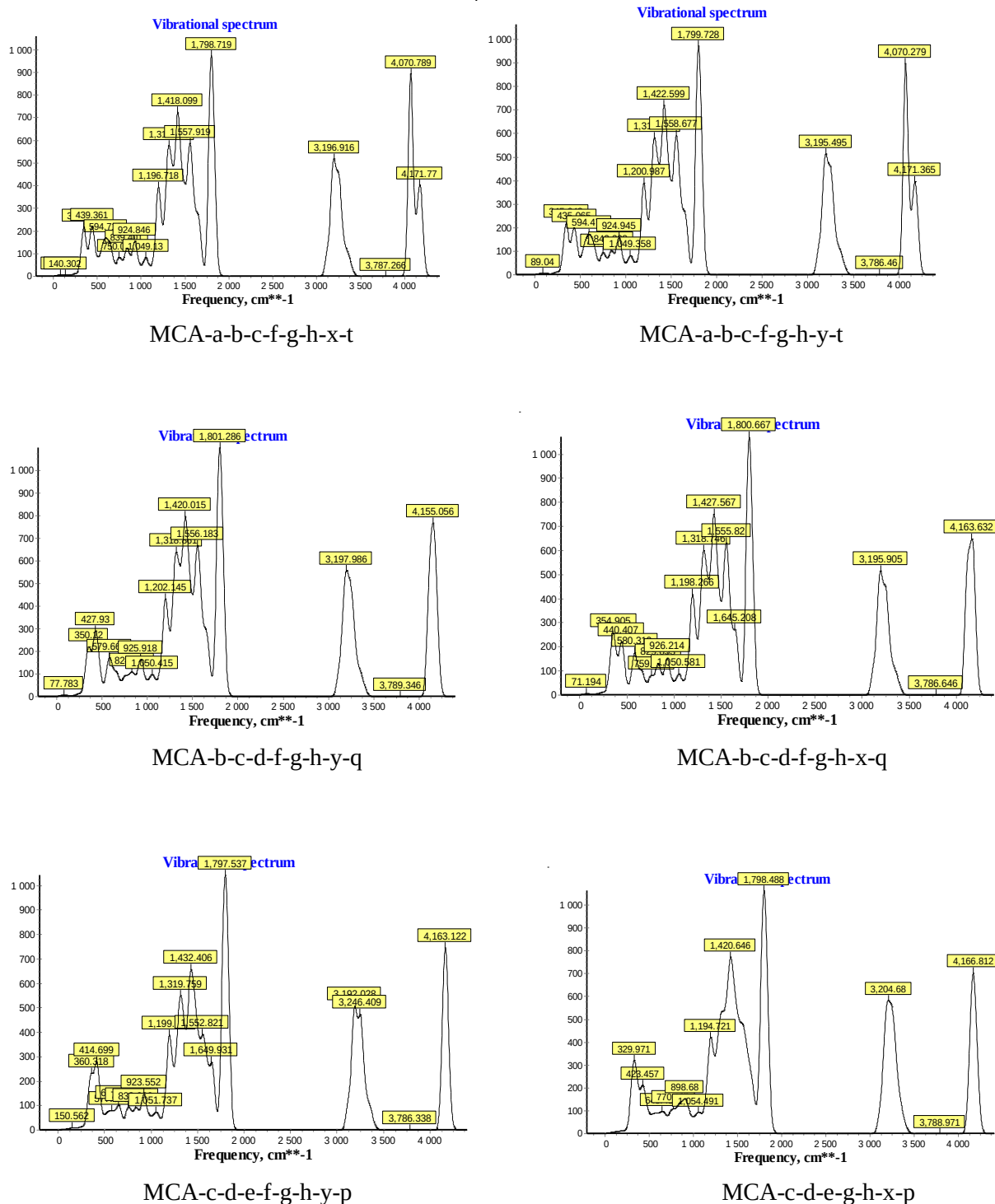


Figure A2–5. Calculated IR spectra of selected conformers of michellamine A
 HF/6-31G(d,p) results.

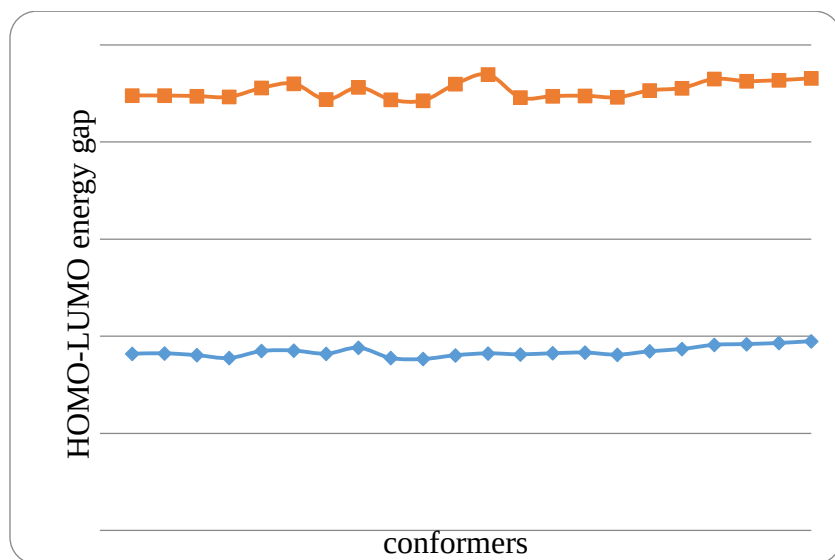


Figure A2–6. Trends of the HOMO-LUMO energy gap (kcal/mol) of the conformers of michellamine A in the DFT (—♦—) and HF (—■—) results *in vacuo*

The conformers are represented by numbers on the x axis, numbering them progressively in the same sequence in which they appear in the first column of Table A2–7.

moments. The same phenomenon is observed for the study of naphthylisoquinoline alkaloids with antimalarial activity [58]. Different orientations of the R and S units may cause 1–2 D difference in the dipole moments, and different orientations of the isoquinoline and naphthalene moieties within each unit may cause 1–4 D difference in the dipole moments.

The energy difference between the frontier orbitals (HOMO, Highest Occupied Molecular Orbital, and LUMO, Lowest Unoccupied Molecular Orbital) is an important molecular descriptor, as it relates to the molecule's reactivity and other properties. The HOMO-LUMO energy gap (Table A2-8) is smallest for conformers with consecutive O–H···O IHBs, slightly greater for conformers with one O–H···O IHB and highest for conformers with only the other types of interactions. Thus, the lower energy conformers also have lower HOMO-LUMO energy gaps. The estimation of the HOMO-LUMO energy gap shows marked difference between HF and DFT values. This is a known phenomenon,

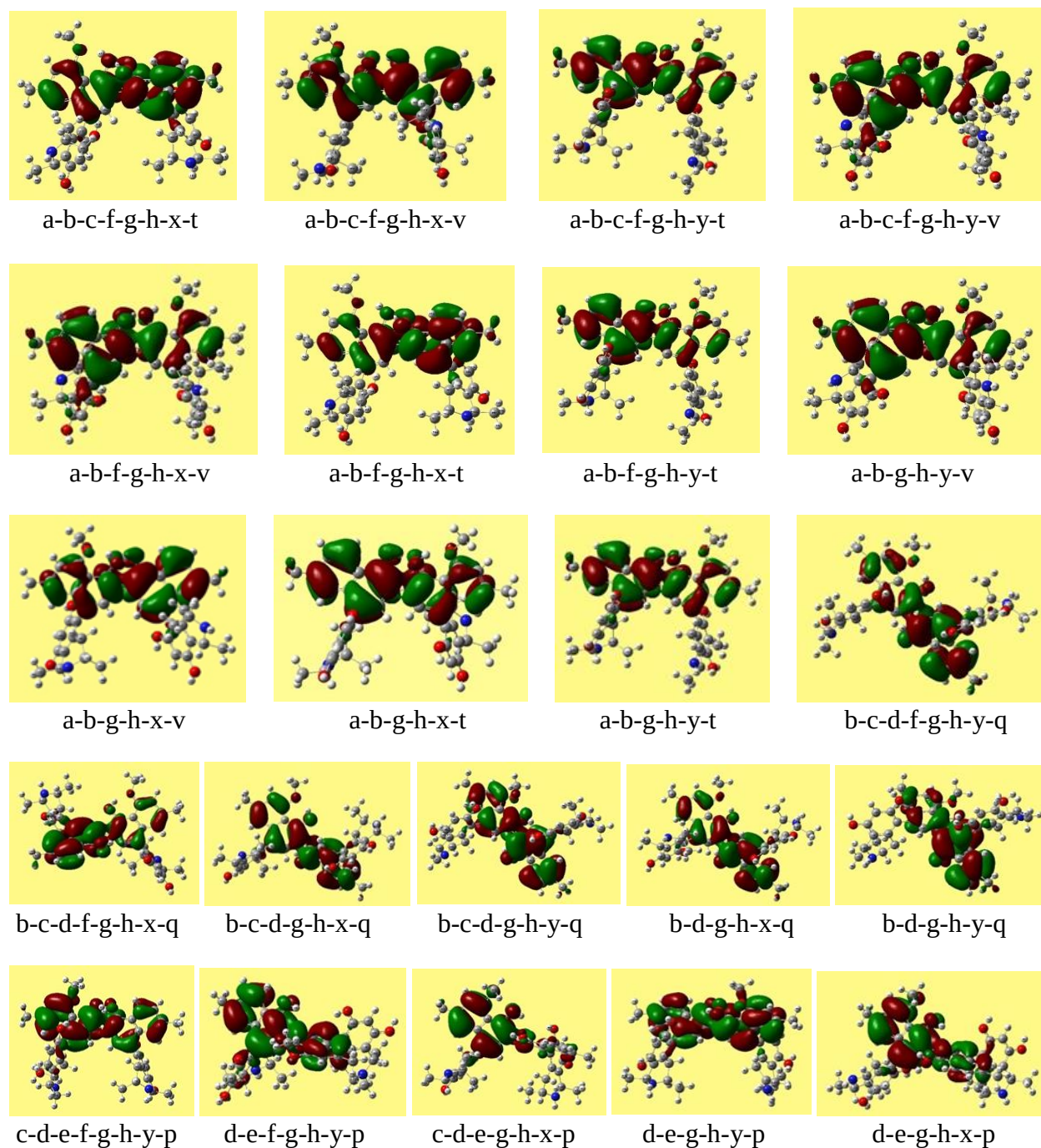


Figure A2– 7. Shapes of the HOMO frontier orbitals of the calculated conformers of michellamine A

HF/6-31G(d,p) results. The initial part of the acronyms is not reported under the images, because of space reasons; it is the same for all the conformers (MCA).

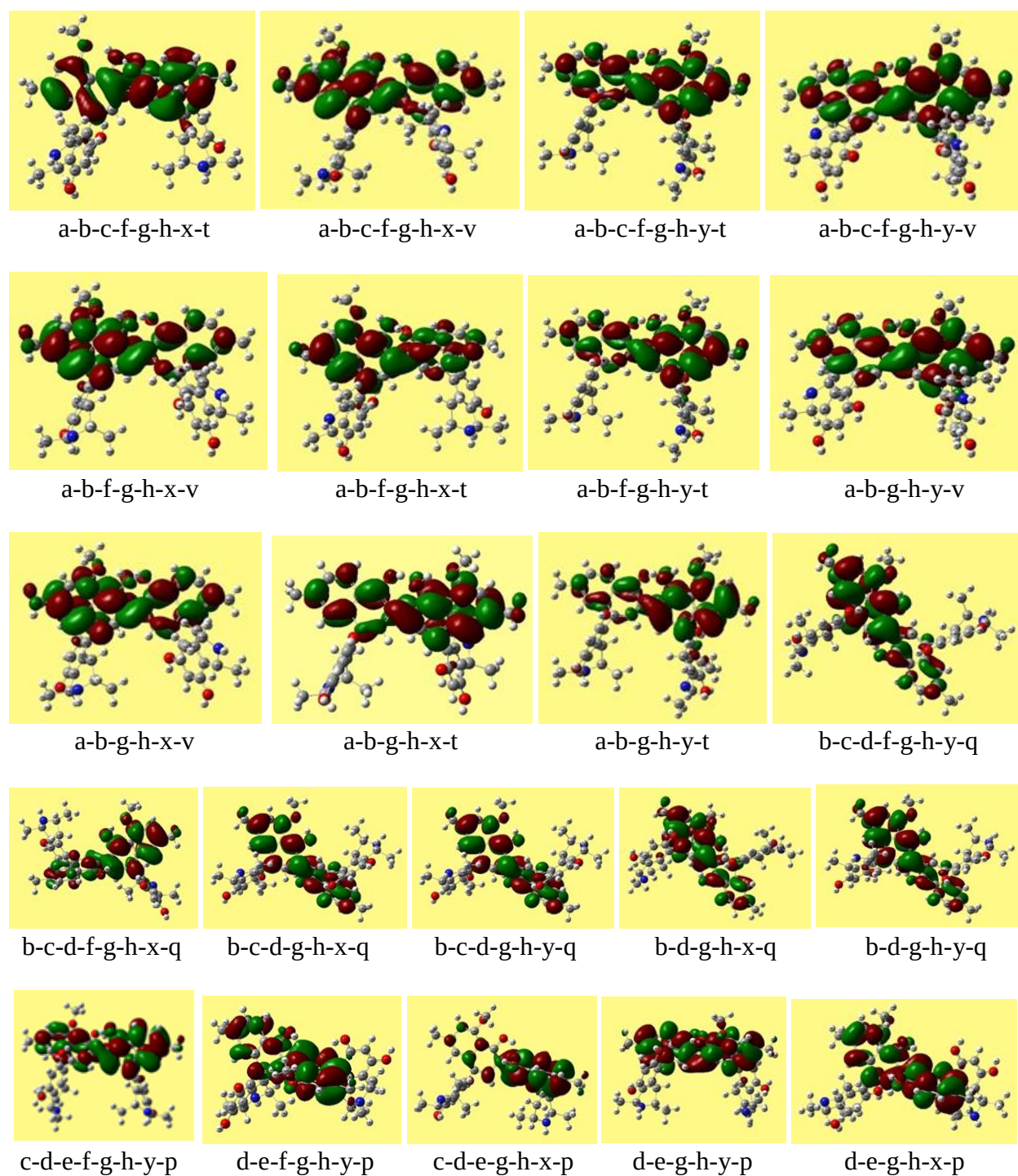


Figure A2–8. Shapes of the LUMO frontier orbitals of the calculated conformers of michellamine A

HF/6-31G(d,p) results. The initial part of the acronyms is not reported under the images, because of space reasons; it is the same for all the conformers (MCA).

as DFT substantially underestimates the values of the gaps [149, 541]. However, the two methods show similar trends, as illustrated in Fig. A2–6. The shapes of the HOMO and LUMO (Fig A2–7 and 8) orbitals indicate greater concentration of electrons in the naphthalene moieties than in the isoquinoline moieties. This phenomenon was also observed for naphthylisoquinoline alkaloids with antimalarial activity [58].

A2.3.2. Results in solution

The relative energies of the conformers (Table A2–2) vary in different ways according to the types of conformers. The four lowest energy conformers are the same in all media, and are conformers with two cooperative IHBs and the same kinds of other IHB-type interactions, and differing only by the mutual orientations of the moieties. Their relative energies remain below 1 kcal/mol in all the media, although the relative energy sequence (including the identification of the lowest energy conformer) may differ from one medium to another. For higher energy conformers, the relative energy decreases as the solvent polarity increases – which is the most common behaviour. If 3.5 kcal/mol is taken as a cautious highest threshold value for conformers which might be responsible for the biological activity, the results in water solution suggest that most conformers (all those with relative energy ≤ 3.5 kcal/mol in water solution) might be considered as potentially responsible for the anti-HIV activity of MCA.

The ranges (kcal/mol) of the solvent effect (free energy of solvation, ΔG_{solv}) are 1.28–6.80/HF and 1.91–5.89/DFT in chloroform, 8.63–15.96/HF and 11.37–16.70./DFT in acetonitrile and -22.08–(-11.43)/HF and -22.84–(-13.52)/DFT in water. Table A2-9 and A2-10 report the HF and DFT results, respectively. ΔG_{solv} is markedly negative in water solution, while it is positive in chloroform and acetonitrile solutions. Similarly, the electrostatic component of ΔG_{solv} (G_{el}) has negative values in all the three solvents, but markedly more negative in water. All this suggests that the molecule might have greater solubility in water than in the other two solvents. The high polarity of this molecule [544] would support this suggestion. A better understanding of the phenomenon may derive from the investigation of adducts with explicit water molecules, considering also the interaction of the water molecules with the π systems of michellamine A; this

study will be the object of a separate work.

The presence and number of O–H $\cdots$ O IHBs and the O–H $\cdots$ π interaction appears to have an effect on ΔG_{solv} . Conformers with two O–H $\cdots$ O IHBs and two O–H $\cdots$ π interactions (a-b-c-f), with one O–H $\cdots$ O IHB and three O–H $\cdots$ π interactions (b-c-d-f), with one O–H $\cdots$ O IHB and two O–H $\cdots$ π interactions (b-c-d) and with three O–H $\cdots$ π interactions (c-d-e or d-e-f) have smaller ΔG_{solv} in all the solvents than conformers without any O–H $\cdots$ π interactions (a-b), with one O–H $\cdots$ O IHB and one O–H $\cdots$ π interaction (b-d) or with two O–H $\cdots$ π interactions (d-e). The conformer with all the O–H $\cdots$ π interactions (MCA-c-d-e-f-g-h-y-p, having four O–H $\cdots$ π interactions) has the smallest ΔG_{solv} in chloroform and acetonitrile and among the smallest in water. The presence or absence of C–H $\cdots$ O interactions does not appear to influence the values of ΔG_{solv} and G_{el} .

Dipole moments and HOMO-LUMO energy gaps in solution are reported in Tables A2-7 and A2-8, besides the results *in vacuo*.

The dipole moment of the conformers increases with the solvent polarity.

The presence of O–H $\cdots$ O IHBs and of other IHB-type interactions has an influence on the changes in the HOMO-LUMO energy gap caused by the solvent. The HOMO-LUMO energy gaps of conformers with the two consecutive O–H $\cdots$ O IHBs (a-b), with one O–H $\cdots$ O IHB and one O–H $\cdots$ π interaction (b-d) and with three O–H $\cdots$ π interactions (c-d-e or d-e-f) increase as the solvent polarity increases. For conformers with one O–H $\cdots$ O IHB and two O–H $\cdots$ π interactions (b-c-d), the gap increases in chloroform and decreases in acetonitrile and water. For conformers with one O–H $\cdots$ O IHB and three O–H $\cdots$ π interactions (b-c-d-f), it increases in chloroform and acetonitrile and decreases in water. For conformers with all the O–H $\cdots$ π interactions (c-d-e-f), it decreases as the solvent polarity increases. The orientation of the moieties does not significantly affect the effect of the solvent on the HOMO-LUMO energy gap.

A2.4. Discussion and Conclusions

The results highlight the main properties of this molecule. Conformational preferences and other properties are influenced by the presence of O–H $\cdots$ O IHBs and other IHB-type interactions, such

as $\text{O}-\text{H}\cdots\pi$ and $\text{C}-\text{H}\cdots\text{O}$, with the $\text{O}-\text{H}\cdots\text{O}$ IHBs being the dominant factor determining conformational preferences and energetics.

Another influencing factor is the mutual orientations of the moieties, the naphthalene moiety prefers to be nearly perpendicular to the isoquinoline moiety. The orientation of the naphthalene moieties of the two units is dictated by the type of IHB present in specific conformers. They prefer a perpendicular orientation in conformers without consecutive IHBs between the two naphthalene moieties and a twist orientation is preferred in conformers with consecutive IHB. This may have the two naphthalene moieties perpendicular to each other, that allows some IHBs. This is different from jozimine A_2 where the perpendicular orientation is preferred to the formation of IHBs between the two naphthalene moieties. It is also interesting to note that this is particular to michellamine and does not happen with jozimine A_2 because in jozimine A_2 , even the inputs with these consecutive IHBs optimise to perpendicular orientation.

It was confirmed that biphenyl groups (prefer a twisted orientation [474]) behave differently to the binaphthyl group because the perpendicular orientation unless there is a stronger interaction and jozimine A_2 is perpendicular even above the interaction, with preference of IHB). The fact that the IHBs in michellamine A have stronger effect than the ones in jozimine A_2 can also be related to the fact that in michellamine A, there is consecutive IHBs. The fact that their stability is higher than the perpendicularity suggest that beside the consecutivity there is cooperativity [545, 546].

The number of calculated conformers, and the fact that other input geometries optimized to one or another of the conformers presented in this work, suggests that the conformational study is sufficiently complete and has identified all the conformers with not-excessively-high energy.

The low relative energy of many conformers in water solution suggests that a comparatively high number of conformers may be involved in the molecule's biological activity. The values of the free energy of solvation suggest greater solubility in water than in the other two solvents considered in this study, which would be consistent with the high polarity of the molecule. A separate study might consider adducts of michellamine A with explicit water molecules, to better understand its behaviour in water solution.

Table A2–2. Relative energies of the calculated conformers of the michellamine A molecule HF/6-31G(d,p) results *in vacuo* and in solution and DFT/B3LYP/6-31+G(d,p) results *in vacuo*, respectively denoted as HF and DFT+ in the columns' headings. The results *in vacuo* are from full optimization calculations, the results in solution are from single point PCM calculations on the *in-vacuo*-optimized geometries. The conformers are listed in order of increasing relative energies in the HF results *in vacuo*.

Conformer	Relative energy (kcal/mol)							
	HF				DFT+			
	vac	chlrf	actn	aq	vac	chlrf	actn	aq
MCA-a-b-c-f-g-h-x-t	0.000	0.000	0.818	0.568	0.036	0.007	0.000	0.146
MCA-a-b-c-f-g-h-x-v	0.029	0.146	0.894	0.590	0.000	0.000	— ^a	0.231
MCA-a-b-c-f-g-h-y-t	0.048	0.046	0.000	0.539	0.272	0.242	0.179	0.000
MCA-a-b-c-f-g-h-y-v	0.315	0.358	0.878	0.000	0.654	2.860	1.988	0.396
MCA-b-c-d-f-g-h-y-q	1.705	1.547	2.287	1.110	2.834	2.814	2.780	2.013
MCA-b-c-d-f-g-h-x-q	2.235	2.128	2.775	0.735	3.131	3.299	3.150	— ^a
MCA-a-b-f-g-h-x-v	4.189	2.570	0.894	— ^a	4.082	0.006	— ^a	0.144
MCA-b-c-d-g-h-x-q	4.455	3.350	3.451	2.219	5.251	— ^a	3.870	2.325
MCA-a-b-f-g-h-x-t	4.578	2.879	2.619	0.766	4.426	2.860	1.989	0.409
MCA-a-b-f-g-h-y-t	4.661	2.839	2.531	0.722	4.707	14.491	13.780	14.027
MCA-b-c-d-g-h-y-q	5.207	3.454	3.615	1.241	6.196	4.936	— ^a	— ^a
MCA-c-d-e-f-g-h-y-p	7.669	8.206	8.829	5.323	10.568	11.375	11.410	— ^a
MCA-a-b-g-h-y-v	8.210	5.021	3.917	0.154	8.142	16.584	15.184	13.598
MCA-a-b-g-h-x-v	8.367	5.113	4.279	0.797	8.118	5.161	3.344	0.216
MCA-a-b-g-h-x-t	8.411	5.165	4.033	0.716	8.193	5.257	3.374	0.295
MCA-a-b-g-h-y-t	8.575	5.096	3.823	0.490	8.485	5.319	3.425	0.060
MCA-b-d-g-h-x-q	9.256	6.460	5.512	0.954	9.979	7.541	5.967	2.659
MCA-b-d-g-h-y-q	10.11	6.913	5.651	1.554	10.924	8.122	6.219	2.176
MCA-d-e-f-g-h-y-p	10.40	10.135	9.900	6.928	12.947	12.569	— ^a	9.174
MCA-c-d-e-g-h-x-p	11.01	10.058	9.999	6.188	13.750	13.077	12.413	8.745
MCA-d-e-g-h-y-p	13.04	10.943	10.381	— ^a	15.758	14.062	12.812	9.126
MCA-d-e-g-h-x-p	14.01	11.757	11.028	6.759	16.486	— ^a	13.291	9.133

—^a The calculation for this conformer did not converge in the given solvent

Table A2– 3. Parameters of the intramolecular hydrogen bonds (IHB) of the calculated conformers of michellamine A *in vacuo*, and parameters suitable to describe the other IHB-type interactions

All the IHB-type interactions present in each conformer are considered. Thus, the IHB length refers to the H $\cdots$ O distance for the O–H $\cdots$ O IHBs and C–H $\cdots$ O interactions, and to the distance between the H atom and the closest C atom in the aromatic ring for the O–H $\cdots\pi$ interactions. The donor-acceptor distance is evaluated only for the O–H $\cdots$ O IHBs and C–H $\cdots$ O interactions, being respectively O $\cdots$ O or C $\cdots$ O. Similarly, the hydrogen bond angle is evaluated only for the O–H $\cdots$ O IHBs and C–H $\cdots$ O interactions, being respectively O $\hat{H}O$ or C $\hat{H}O$.

Conformer	IHB considered	Parameters of the IHB					
		HF			DFT+		
		IHB length (Å)	O $\cdots$ O or C $\cdots$ O (Å)	O $\hat{H}O$ or C $\hat{H}O$	H $\cdots$ O or H $\cdots$ C (Å)	O $\cdots$ O or C $\cdots$ O (Å)	O $\hat{H}O$ or C $\hat{H}O$
MCA-a-b-c-f-g-h-x-t	H54 $\cdots$ O44	1.891	2.740	147.9	1.759	2.664	152.5
	H55 $\cdots$ O45	1.750	2.572	143.2	1.689	2.560	146.1
	O42–H49 $\cdots\pi$	2.346			2.323		
	O46–H59 $\cdots\pi$	2.351			2.332		
	C–H52 $\cdots$ O41	2.387	3.000	114.4	2.347	2.985	115.6
	C–H61 $\cdots$ O47	2.38	2.997	114.4	2.350	2.985	115.5
MCA-a-b-c-f-g-h-x-v	H54 $\cdots$ O44	1.884	2.735	148.1	1.753	2.660	152.8
	H55 $\cdots$ O45	1.749	2.572	143.1	1.688	2.559	146.1
	O42–H49 $\cdots\pi$	2.345			2.321		
	O46–H59 $\cdots\pi$	2.356			2.338		
	C–H52 $\cdots$ O41	2.388	3.000	114.4	2.353	2.991	115.6
	C–H61 $\cdots$ O47	2.385	2.998	114.4	2.346	2.983	115.6
MCA-a-b-c-f-g-h-y-t	H54 $\cdots$ O44	1.891	2.741	148.0	1.759	2.665	152.5
	H55 $\cdots$ O45	1.752	2.573	143.1	1.689	2.561	146.1
	O42–H49 $\cdots\pi$	2.345			2.322		
	O46–H59 $\cdots\pi$	2.356			2.340		
	C–H52 $\cdots$ O41	2.387	3.000	114.4	2.346	2.985	115.6
	C–H61 $\cdots$ O47	2.390	3.001	114.3	2.340	2.983	115.7
MCA-a-b-c-f-g-h-y-v	H54 $\cdots$ O44	1.885	2.735	148.1	1.760	2.665	152.5
	H55 $\cdots$ O45	1.751	2.573	143.1	1.689	2.560	146.1
	O42–H49 $\cdots\pi$	2.346			2.331		
	O46–H59 $\cdots\pi$	2.353			2.323		
	C–H52 $\cdots$ O41	2.388	3.000	114.4	2.347	2.986	115.6
	C–H61 $\cdots$ O47	2.390	3.001	114.3	2.350	2.985	115.5
MCA-b-c-d-f-g-h-y-q	H55 $\cdots$ O45	1.772	2.588	142.6	1.725	2.594	145.1
	O42–H49 $\cdots\pi$	2.397			2.371		

	O43–H54... π	2.346			2.322		
	O46–H59... π	2.353			2.334		
	C–H52...O41	2.389	3.002	114.4	2.348	2.988	115.7
	C–H61...O47	2.390	3.001	114.3	2.349	2.985	115.5
	H55...O45	1.773	2.587	142.6	1.725	2.585	145.1
MCA-b-c-d-f-g-h-x-q	O42–H49... π	2.397			2.382		
	O43–H54... π	2.344			2.323		
	O46–H59... π	2.347			2.321		
	C–H52...O41	2.389	3.002	114.4	2.350	2.988	115.6
	C–H61...O47	2.383	2.996	114.4	2.351	2.988	115.5
MCA-a-b-f-g-h-x-v	H54...O44	1.891	2.743	148.5	1.762	2.669	153.0
	H55...O45	1.751	2.573	143.1	1.691	2.562	146.1
	O46–H59... π	2.357			2.338		
	C–H52...O41	2.387	3.003	114.3	2.358	2.993	115.4
	C–H61...O47	2.392	2.999	114.4	2.347	2.984	115.6
MCA-b-c-d-g-h-x-q	H55...O45	1.772	2.588	142.7	1.725	2.585	145.2
	O42–H49... π	2.401			2.317		
	O43–H54... π	2.341			2.386		
	C–H52...O41	2.389	3.003	114.4	2.347	2.987	115.7
	C–H61...O47	2.389	3.000	114.3	2.357	2.992	115.4
MCA-a-b-f-g-h-x-t	H54...O44	1.887	2.738	148.2	1.759	2.665	152.6
	H55...O45	1.751	2.573	143.1	1.690	2.560	146.1
	O46–H59... π	2.348			2.326		
	C–H52...O41	2.389	3.001	114.3	2.348	2.986	115.5
	C–H61...O47	2.386	2.998	114.4	2.349	2.987	115.6
MCA-a-b-f-g-h-y-t	H54...O44	1.889	2.740	148.2	1.761	2.666	152.7
	H55...O45	1.754	2.573	143.0	1.691	2.562	146.1
	O46–H59... π	2.355			2.338		
	C–H52...O41	2.389	3.000	114.3	2.349	2.985	115.5
	C–H61...O47	2.391	3.003	114.4	2.344	2.983	115.7
MCA-b-c-d-g-h-y-q	H55...O45	1.775	2.590	142.6	1.729	2.589	145.1
	O42–H49... π	2.390			2.319		
	O43–H54... π	2.343			2.357		
	C–H52...O41	2.389	3.002	114.4	2.349	2.988	115.6
	C–H61...O47	2.394	3.003	114.2	2.354	2.985	115.5
MCA-c-d-e-f-g-h-y-p	O42–H49... π	2.354			2.336		
	O43–H54... π	2.398			2.377		
	O44–H55... π	2.324			2.296		
	O46–H59... π	2.350			2.336		
	C–H52...O41	2.386	2.998	114.4	2.349	2.981	115.6
MCA-a-b-g-h-y-v	C–H61...O47	2.389	3.000	114.4	2.342	2.985	115.5
	H55...O45	1.880	2.735	148.8	1.757	2.665	153.1
	H55...O45	1.755	2.575	143.1	1.694	2.564	146.1
	C–H52...O41	2.391	3.002	114.3	2.354	2.991	115.5

	C-H61...O47	2.392	3.003	114.3	2.356	2.991	115.4
MCA-a-b-g-h-x-v	H54...O44	1.887	2.741	148.6	1.758	2.666	153.0
	H55...O45	1.755	2.576	143.2	1.694	2.564	146.1
	C-H52...O41	2.391	3.003	114.3	2.357	2.994	115.5
	C-H61...O47	2.389	2.999	114.3	2.346	2.983	115.6
MCA-a-b-g-h-x-t	H54...O44	1.882	2.735	148.6	1.761	2.669	152.8
	H55...O45	1.755	2.575	143.1	1.696	2.565	146.0
	C-H52...O41	2.391	3.002	114.3	2.679	2.989	115.5
	C-H61...O47	2.389	3.000	114.3	2.351	2.987	115.4
MCA-a-b-g-h-y-t	H54...O44	1.883	2.736	148.5	1.754	2.661	152.8
	H55...O45	1.755	2.576	143.1	1.693	2.564	146.2
	C-H52...O41	2.390	3.002	114.3	2.349	2.986	115.5
	C-H61...O47	2.397	3.006	114.2	2.352	2.999	115.5
MCA-b-d-g-h-x-q	H55...O45	1.774	2.590	142.8	1.726	2.587	145.3
	O43-H54... π	2.400			2.383		
	C-H52...O41	2.391	3.003	114.3	2.352	2.990	115.6
	C-H61...O47	2.391	3.001	114.3	2.359	2.994	115.4
MCA-b-d-g-h-y-q	H55...O4	1.776	2.591	142.7	1.730	2.590	145.1
	O43-H54... π	2.388			2.351		
	C-H52...O41	2.392	3.003	114.3	2.350	2.988	115.6
	C-H61...O47	2.395	3.005	114.2	2.356	2.991	115.4
MCA-d-e-f-g-h-y-p	O43-H54... π	2.388			2.378		
	O44-H54... π	2.300			2.280		
	O46-H59... π	2.350			2.341		
	C-H52...O41	2.390	3.000	114.3	2.351	2.987	115.5
	C-H61...O47	2.390	3.001	114.4	2.347	2.986	115.6
MCA-c-d-e-g-h-x-p	O42-H49... π	2.354			2.334		
	O43-H54... π	2.388			2.347		
	O44-H54... π	2.324			2.282		
	C-H52...O41	2.387	2.999	114.4	2.349	2.987	115.6
	C-H61...O47	2.388	2.998	114.3	2.351	2.987	115.5
MCA-d-e-g-h-y-p	O43-H54... π	2.383			2.366		
	O44-H54... π	2.310			2.286		
	C-H52...O41	2.391	3.001	114.3	2.350	2.987	115.5
	C-H61...O47	2.392	3.002	114.3	2.351	2.986	115.5
MCA-d-e-g-h-x-p	O43-H54... π	2.373			2.343		
	O44-H54... π	2.303			2.269		
	C-H52...O41	2.391	3.002	114.3	2.350	2.986	115.5
	C-H61...O47	2.388	2.999	114.3	2.344	2.981	115.5

Table A2–4. Vibrational frequencies (harmonic approximation) of the O–H bonds in the calculated conformers of michellamine A

HF/6-31G(d,p) results *in vacuo*. The frequency values have been scaled by 0.9024, recommended for HF/6-31G(d,p) calculations in [447].

Conformer	Vibrational frequencies (cm ⁻¹)					
	O41–H48	O42–H49	O43–H54	O44–H55	O46–H59	O47–H62
MCA-a-b-c-f-g-h-x-t	3785.577	3750.149	3700.652	3670.503	3757.792	3784.584
MCA-a-b-c-f-g-h-x-v	3785.306	3751.773	3669.889	3696.817	3756.655	3784.530
MCA-a-b-c-f-g-h-y-t	3785.794	3750.203	3700.363	3672.597	3756.989	3784.873
MCA-a-b-c-f-g-h-y-v	3785.297	3752.125	3700.616	3672.470	3758.622	3784.991
MCA-b-c-d-f-g-h-y-q	3785.550	3749.968	3762.033	3715.939	3757.206	3784.729
MCA-b-c-d-f-g-h-x-q	3785.631	3749.932	3768.594 ^a	3714.540	3768.594 ^a	3784.693
			3762.963 ^b		3762.963 ^b	
MCA-a-b-f-g-h-x-v	3789.963 ^a	3789.963 ^a	3703.468 ^b	3703.468 ^b	3753.470	3784.783
	3788.717 ^b	3788.717 ^b	3676.838 ^a	3676.838 ^a		
MCA-b-c-d-g-h-x-q	3786.100	3749.851 ^b	3749.851 ^b	3721.245	3788.483	3788.483
		3747.360 ^a	3747.360 ^a		3787.634 ^b	3787.634 ^b
MCA-a-b-f-g-h-x-t	3790.856 ^a	3790.856 ^a	3703.314 ^b	3703.314 ^b	3754.733	3785.117
	3789.051 ^b	3789.051 ^b	3677.109 ^a	3677.109 ^a		
MCA-a-b-f-g-h-y-t	3791.037 ^a	3791.037 ^a	3703.522 ^b	3703.522 ^b	3754.697	3785.018
	3789.241 ^b	3789.241 ^b	3679.256 ^a	3679.256 ^a		
MCA-b-c-d-g-h-y-q	3786.082	3747.180	3758.316	3722.905	3789.728 ^a	3789.728 ^a
					3788.266 ^b	3788.266 ^b
MCA-c-d-e-f-g-h-y-p	3784.774	3762.358	3748.561 ^b	3748.561 ^b	3763.811	3784.954
			3740.042 ^a	3740.042 ^a		
MCA-a-b-g-h-y-v	3789.385	3790.775	3703.025 ^b	3703.025 ^b	3790.549	3788.708
			3681.151 ^a	3681.151 ^a		
MCA-a-b-g-h-x-v	3789.295	3790.811	3704.397 ^b	3704.397 ^b	3790.640	3788.474
			3681.702 ^a	3681.702 ^a		
MCA-a-b-g-h-x-t	3789.322	3791.569	3701.347 ^b	3701.347 ^b	3790.071	3788.609
			3679.834 ^a	3679.834 ^a		
MCA-a-b-g-h-y-t	3789.557	3791.506	3704.307 ^b	3704.307 ^b	3790.640	3788.708
			3682.703 ^a	3682.703 ^a		
MCA-b-d-g-h-x-q	3789.313	3790.919	3754.273	3725.513	3788.528 ^a	3788.528 ^a
					3787.797 ^b	3787.797 ^b
MCA-b-d-g-h-y-q	3789.575	3791.470	3762.385	3727.345	3790.658	3788.880
MCA-d-e-f-g-h-y-p	3788.672 ^a	3788.672 ^a	3759.687 ^b	3759.687 ^b	3765.066	3785.180
	3787.950 ^b	3787.950 ^b	3728.816 ^a	3728.816 ^a		
MCA-c-d-e-g-h-x-p	3784.738	3759.976	3738.309	3746.476 ^b	3789.304	3787.977
				3738.309 ^a		
MCA-d-e-g-h-x-p	3788.898 ^a	3788.898 ^a	3749.968	3734.853	3790.026	3788.393
	3788.131 ^b	3788.131 ^b				

Table A2–5. Vibrational frequencies (harmonic approximation) of the O–H bonds in the calculated conformers of michellamine A

DFT/6-31+G(d,p) results *in vacuo*. The frequency values have been scaled by 0.9857, recommended for DFT/6-31+G(d,p) calculations in [448].

Conformer	Vibrational frequencies (cm ⁻¹)					
	O41–H48	O42–H49	O43–H54	O44–H55	O46–H59	O47–H62
MCA-a-b-c-f-g-h-x-v	3775.753	3699.894	3539.590a	3539.590a	3710.372	3774.659
			3492.039a	3492.039a		
MCA-a-b-c-f-g-h-y-t	3775.645	3698.652	3545.277b	3545.277b	3714.058	3774.531
			3496.169a	3496.169a		
MCA-a-b-c-f-g-h-y-v	3774.779 ^a	3774.779 ^a	3553.035 ^a	3553.035 ^a	3703.975	3774.63
	3777.764 ^b	3777.764 ^b	3503.976 ^a	3503.976 ^a		
MCA-b-c-d-f-g-h-y-q	3775.852	3697.39	3718.859	3582.182	3713.94	3774.58
MCA-b-c-d-f-g-h-x-q	3716.799	3775.517	3704.951	3681.107	3722.476	3775.546
MCA-a-b-f-g-h-x-v	3775.241	3699.657	3545.198 ^a	3545.198 ^a	3709.258	3774.354
			3494.681 ^a	3494.681 ^a		
MCA-b-c-d-g-h-x-q	3778.257	3776.581	3714.108	3666.863	3720.032	3774.965
MCA-a-b-f-g-h-y-t	3778.405 ^a	3778.405 ^a	3554.237 ^b	3554.237 ^b	3710.727	3774.630
	3777.577 ^b	3777.577 ^b	3506.509 ^a	3506.509 ^a		
MCA-b-c-d-g-h-y-q	3776.473	3692.767	3710.303	3591.812	3777.932 ^a	3777.932 ^a
					3777.035 ^b	3777.035 ^b
MCA-c-d-e-f-g-h-y-p	3775.832	3700.071	3539.570 ^a	3539.570 ^a	3710.549	3774.748
			3492.099 ^a	3492.099 ^a		
MCA-a-b-g-h-y-v	3778.178a	3778.178 ^a	3550.225 ^b	3550.225 ^b	3778.198 ^a	3778.198 ^a
	3777.370 ^b	3777.370 ^b	3508.353 ^b	3508.353 ^b	3777.212 ^b	3777.212 ^b
MCA-a-b-g-h-x-v	3778.415 ^b	3776.66 ^b	3549.801 ^b	3549.801 ^b	3779.164 ^b	3777.291 ^b
			3507.485a	3507.485a		
MCA-a-b-g-h-x-t	3778.178 ^a	3778.178 ^a	3551.073 ^b	3551.073 ^b	3777.863 ^a	3777.863 ^a
	3777.419 ^b	3777.419 ^b	3509.871 ^a	3509.871 ^a	3777.074 ^b	3777.074 ^b
MCA-a-b-g-h-y-t	3778.504 ^a	3778.504 ^a	3549.723 ^b	3549.723 ^b	3779.036 ^a	3779.036 ^a
	3777.597 ^b	3777.597 ^b	3507.761 ^a	3507.761 ^a	3777.429 ^b	3777.429 ^b
MCA-b-d-g-h-x-q	3778.701 ^a	3778.701 ^a	3709.958	3593.202	3778.218 ^a	3778.218 ^a
	3777.459 ^b	3777.459 ^b			3777.025 ^b	3777.025 ^b
MCA- b-d-g-h-y-q	3779.065 ^a	3779.065 ^a	3716.069	3597.736	3778.326 ^a	3778.326 ^a
	3778.346 ^b	3778.346 ^b			3777.547 ^b	3777.547 ^b
MCA- d-e-f-g-h-y-p	3778.267 ^b	3778.267 ^b	3714.088	3666.853	3719.992	3774.975
	3776.591 ^b	3776.591 ^b				
MCA-c-d-e-g-h-x-p	3775.290	3710.165	3685.030 ^b	3685.030 ^b	3777.794 ^a	3777.794 ^a
			3678.918 ^b	3678.918 ^b	3776.995 ^b	3776.995 ^b
MCA-d-e-g-h-y-p	3778.415 ^a	3778.415 ^a	3697.548	3674.098	3778.809 ^a	3778.809 ^a
	3776.759 ^b	3776.759 ^b			3777.814 ^b	3777.814 ^b
MCA-d-e-g-h-x-p	3778.129 ^a	3778.129 ^a	3697.321	3673.950	3778.218 ^a	3778.218 ^a
	3777.055 ^b	3777.055 ^b			3777.439 ^b	3777.439 ^b

Table A2–6. Relative energy ($\Delta E_{\text{correct}}$, kcal/mol) corrected for ZPE and ZPE corrections (kcal/mol) for the calculated conformers of michellamine A

Results from HF/6-31G(d,p) and DFT/B3LYP/6-31+G(d,p) frequency calculations.

Conformer	HF		DFT+	
	$\Delta E_{\text{correct}}$	ZPE correction	$\Delta E_{\text{correct}}$	ZPE correction
MCA-a-b-c-f-g-h-x-t	0.011	556.059		
MCA-a-b-c-f-g-h-x-v	0.047	556.066	0.099	517.453
MCA-a-b-c-f-g-h-y-t	0.000	555.999	0.294	517.376
MCA-a-b-c-f-g-h-y-v	0.249	555.981	0.000	517.045
MCA-b-c-d-f-g-h-y-q	1.301	555.644	2.337	516.857
MCA-b-c-d-f-g-h-x-q	1.798	555.610	2.736	516.959
MCA-a-b-f-g-h-x-v	3.877	555.735	4.118	517.318
MCA-b-c-d-g-h-x-q	3.889	555.481	4.807	516.911
MCA-a-b-f-g-h-x-t	4.224	555.693		
MCA-a-b-f-g-h-y-t	4.241	555.627	4.410	517.056
MCA-b-c-d-g-h-y-q	4.520	555.359	5.526	516.683
MCA-c-d-e-f-g-h-y-p	6.697	555.076	9.585	516.372
MCA-a-b-g-h-y-v	7.522	555.359	7.447	516.660
MCA-a-b-g-h-x-v	7.677	555.356	7.575	516.811
MCA-a-b-g-h-x-t	7.721	555.358	7.558	516.719
MCA-a-b-g-h-y-t	7.828	555.300	7.906	516.776
MCA-b-d-g-h-x-q	8.279	555.071	9.012	516.387
MCA-b-d-g-h-y-q	9.007	554.939	9.948	516.378
MCA-d-e-f-g-h-y-p	9.173	554.811	11.800	516.207
MCA-c-d-e-g-h-x-p	9.813	554.847	12.516	516.121
MCA-d-e-g-h-y-p	11.649	554.648	14.416	516.012
MCA-d-e-g-h-x-p	12.531	554.568	15.108	515.977

Table A2–7. Dipole moment of the calculated conformers of michellamine A *in vacuo* and in solution

HF/6-31G(d,p) and (DFT/B3LYP/6-31+G(d,p) results, respectively denoted as HF and DFT+ in the column headings. The results *in vacuo* are from full optimization calculations, the results in solution are from single point PCM calculations on the *in-vacuo*-optimized geometries.

Conformer	Dipole moment (Debye)							
	HF				DFT+			
	vac	chlrf	actn	aq	vac	chlrf	actn	aq
MCA-a-b-c-f-g-h-x-t	6.14	6.65	6.77	6.68	6.22	6.89	7.06	6.92
MCA-a-b-c-f-g-h-x-v	6.09	6.74	6.94	7.04	6.37	7.29	— ^a	7.77
MCA-a-b-c-f-g-h-y-t	7.88	8.74	9.06	9.37	8.00	9.17	9.64	10.15
MCA-a-b-c-f-g-h-y-v	7.88	8.86	9.23	9.68	7.61	8.84	9.36	9.93
MCA-b-c-d-f-g-h-y-q	7.59	8.62	9.02	9.56	7.72	9.10	9.71	10.48
MCA-b-c-d-f-g-h-x-q	5.80	6.49	6.70	6.84	5.86	6.79	7.12	— ^a
MCA-a-b-f-g-h-x-v	4.10	4.75	6.94	— ^a	4.33	5.23	5.63	6.14
MCA-b-c-d-g-h-x-q	6.33	6.84	6.98	7.04	6.12	-	6.93	6.92
MCA-a-b-f-g-h-x-t	6.10	6.81	7.09	7.11	5.75	6.60	6.90	6.88
MCA-a-b-f-g-h-y-t	7.54	8.60	9.02	9.50	7.27	8.58	9.11	9.74
MCA-b-c-d-g-h-y-q	8.28	9.32	9.71	10.27	8.28	9.63	— ^a	— ^a
MCA-c-d-e-f-g-h-y-p	2.37	2.55	2.71	2.96	2.05	2.29	2.50	— ^a
MCA-a-b-g-h-y-v	7.59	8.84	9.41	10.10	7.14	8.62	9.32	10.18
MCA-a-b-g-h-x-v	4.75	5.97	6.34	6.63	5.21	6.28	6.76	7.24
MCA-a-b-g-h-x-t	6.80	7.86	8.30	8.61	6.51	7.77	8.32	8.68
MCA-a-b-g-h-y-t	7.13	8.05	8.43	8.99	7.40	8.77	9.34	10.24
MCA-b-d-g-h-x-q	4.71	5.23	5.43	5.54	4.69	5.39	5.68	5.88
MCA-b-d-g-h-y-q	8.10	9.37	9.94	10.49	8.08	9.72	10.47	11.26
MCA-d-e-f-g-h-y-p	3.29	3.78	3.97	4.17	3.35	4.02	— ^a	4.77
MCA-c-d-e-g-h-x-p	3.03	3.73	4.02	4.55	3.11	4.03	4.45	5.21
MCA-d-e-g-h-y-p	2.47	2.84	3.05	— ^a	2.37	2.91	3.22	3.78
MCA-d-e-g-h-x-p	2.48	3.08	3.28	3.52	2.53	— ^a	3.56	3.96

^a The calculation for this conformer did not converge in the given solvent

Table A2–8. HOMO-LUMO energy gaps of the calculated conformers of michellamine A *in vacuo* and in solution

HF/6-31G(d,p) and (DFT/B3LYP/6-31+G(d,p) results, respectively denoted as HF and DFT+ in the column headings. The results *in vacuo* are from full optimization calculations, the results in solution are from single point PCM calculations on the *in-vacuo*-optimized geometries.

Conformer	HOMO-LUMO energy difference (kcal/mol)							
	HF				DFT+			
	<i>vac</i>	<i>chlrf</i>	<i>actn</i>	<i>aq</i>	<i>vac</i>	<i>chlrf</i>	<i>actn</i>	<i>aq</i>
MCA-a-b-c-f-g-h-x-t	223.99	225.32	225.47	225.65	91.00	93.55	93.93	93.89
MCA-a-b-c-f-g-h-x-v	223.93	225.13	225.29	225.33	91.19	93.34	— ^a	93.69
MCA-a-b-c-f-g-h-y-t	223.69	225.44	225.67	225.70	90.24	93.39	93.96	94.01
MCA-a-b-c-f-g-h-y-v	223.22	224.92	225.19	225.30	88.77	93.56	93.63	93.89
MCA-b-c-d-f-g-h-y-q	227.84	230.28	230.68	230.66	92.38	96.05	96.75	96.69
MCA-b-c-d-f-g-h-x-q	230.04	232.29	232.57	232.48	92.63	95.73	96.29	— ^a
MCA-a-b-f-g-h-x-v	221.91	223.91	225.29	— ^a	89.00	91.65	92.46	93.15
MCA-b-c-d-g-h-x-q	228.15	228.33	228.04	227.78	94.08	94.08	94.08	93.53
MCA-a-b-f-g-h-x-t	221.86	224.03	224.59	225.15	88.77	91.67	92.53	93.27
MCA-a-b-f-g-h-y-t	221.38	224.03	224.74	225.36	88.28	98.74	99.00	99.50
MCA-b-c-d-g-h-y-q	229.90	230.55	230.21	229.96	90.22	96.82	— ^a	— ^a
MCA-c-d-e-f-g-h-y-p	234.79	234.72	234.71	234.58	91.18	96.82	96.84	— ^a
MCA-a-b-g-h-y-v	222.94	224.68	224.93	225.09	90.66	99.51	99.56	99.24
MCA-a-b-g-h-x-v	223.66	224.95	225.12	225.26	91.25	93.30	93.63	93.72
MCA-a-b-g-h-x-t	223.83	225.09	225.23	225.30	91.60	93.15	94.06	94.08
MCA-a-b-g-h-y-t	223.04	224.85	225.12	225.23	90.51	93.15	93.61	93.68
MCA-b-d-g-h-x-q	226.59	228.36	228.60	228.63	92.25	94.59	94.90	94.77
MCA-b-d-g-h-y-q	227.81	230.42	230.86	230.95	93.43	96.66	97.15	96.95
MCA-d-e-f-g-h-y-p	232.51	232.37	232.41	232.58	95.56	95.04	— ^a	94.53
MCA-c-d-e-g-h-x-p	231.37	231.51	231.80	232.39	95.98	95.85	95.84	96.05
MCA-d-e-g-h-y-p	231.88	231.61	231.53	— ^a	96.52	96.16	95.95	95.54
MCA-d-e-g-h-x-p	232.81	232.73	232.71	232.64	97.45	97.21	96.98	96.41

^a The calculation for this conformer did not converge in the given solvent

Table A2–9. Solvent effect (free energy of solvation, ΔG_{solv}) and its electrostatic component (G_{el}) for the calculated conformers of michellamine A in the three solvents considered
Results from HF/6-31G(d,p) single point PCM calculations on the *in-vacuo*-optimized geometries.

Conformers	ΔG_{solv} (kcal/mol)			G_{el} (kcal/mol)		
	chlrf	actn	aq	chlrf	actn	aq
MCA-a-b-c-f-g-h-x-t	5.78	14.90	-12.27	-8.70	-12.53	-34.12
MCA-a-b-c-f-g-h-x-v	5.89	14.96	-12.45	-8.64	-12.55	-34.20
MCA-a-b-c-f-g-h-y-t	6.47	14.89	-11.43	-8.25	-12.95	-33.76
MCA-a-b-c-f-g-h-y-v	4.77	13.72	-14.49	-8.68	-12.81	-35.05
MCA-b-c-d-f-g-h-y-q	4.91	14.32	-13.90	-8.90	-12.81	-35.34
MCA-b-c-d-f-g-h-x-q	5.42	14.61	-14.47	-8.84	-12.85	-36.25
MCA-a-b-f-g-h-x-v	3.90	14.96	— ^a	-10.37	-12.55	— ^a
MCA-b-c-d-g-h-x-q	3.81	12.46	-16.48	-9.82	-14.37	-37.49
MCA-a-b-f-g-h-x-t	4.01	12.11	-16.78	-10.40	-15.32	-38.53
MCA-a-b-f-g-h-y-t	4.21	12.41	-16.22	-10.28	-15.24	-38.40
MCA-b-c-d-g-h-y-q	3.19	12.04	-17.38	-10.49	-14.98	-38.71
MCA-c-d-e-f-g-h-y-p	6.80	15.96	-14.28	-8.27	-12.30	-37.17
MCA-a-b-g-h-y-v	1.28	8.63	-22.49	-11.89	-17.66	-42.78
MCA-a-b-g-h-x-v	2.27	9.83	-20.70	-12.00	-17.49	-42.33
MCA-a-b-g-h-x-t	2.33	9.58	-20.75	-11.96	-17.75	-42.43
MCA-a-b-g-h-y-t	2.17	9.43	-20.68	-12.23	-18.16	-42.85
MCA-b-d-g-h-x-q	2.03	9.67	-22.05	-11.53	-17.13	-43.06
MCA-b-d-g-h-y-q	1.61	9.06	-22.08	-11.91	-17.83	-43.29
MCA-d-e-f-g-h-y-p	5.25	13.55	-16.40	-9.00	-13.89	-38.23
MCA-c-d-e-g-h-x-p	5.00	13.41	-17.33	-9.67	-14.38	-39.55
MCA-d-e-g-h-y-p	2.93	10.98	— ^a	-10.80	-16.02	— ^a
MCA-d-e-g-h-x-p	2.97	10.84	-20.45	-10.95	-16.34	-41.97

^a The calculation for this conformer did not converge in the given solvent

Table A2–10. Solvent effect (free energy of solvation, ΔG_{solv}) and its electrostatic component (G_{el}) for the calculated conformers of michellamine A in the three solvents considered

Results from DFT/B3LYP/6-31+G(d,p) single point PCM calculations on the *in-vacuo*-optimized geometries.

Conformers	ΔG_{solv} (kcal/mol)			G_{el} (kcal/mol)		
	chlrf	actn	aq	chlrf	actn	aq
MCA-a-b-c-f-g-h-x-t	5.89	14.90	-13.52	-9.04	-13.11	-35.97
MCA-a-b-c-f-g-h-x-v	5.87	— ^a	-13.52	-9.01	— ^a	-35.85
MCA-a-b-c-f-g-h-y-t	5.91	14.88	-13.82	-9.04	-13.17	-36.35
MCA-a-b-c-f-g-h-y-v	4.82	13.98	-13.59	-8.63	-12.56	-34.15
MCA-b-c-d-f-g-h-y-q	5.37	14.75	-14.52	-9.03	-13.13	-36.90
MCA-b-c-d-f-g-h-x-q	5.76	14.87	— ^a	-8.84	-13.06	— ^a
MCA-a-b-f-g-h-x-v	4.31	12.61	-17.32	-10.44	-15.24	-39.56
MCA-b-c-d-g-h-x-q	— ^a	12.70	-17.55	— ^a	-14.46	-39.01
MCA-a-b-f-g-h-x-t	4.15	12.32	-17.82	-10.58	-15.51	-40.10
MCA-a-b-f-g-h-y-t	4.42	12.68	-15.59	-10.07	-15.02	-37.87
MCA-b-c-d-g-h-y-q	3.83	— ^a	— ^a	-10.27	— ^a	— ^a
MCA-c-d-e-f-g-h-y-p	7.45	16.70	— ^a	-8.21	-12.23	— ^a
MCA-a-b-g-h-y-v	1.91	9.56	-21.03	-11.26	-16.73	-41.32
MCA-a-b-g-h-x-v	2.70	9.99	-21.67	-11.97	-17.85	-43.98
MCA-a-b-g-h-x-t	2.81	10.05	-21.50	-11.95	-17.90	-43.98
MCA-a-b-g-h-y-t	2.58	9.80	-22.00	-12.18	-18.14	-44.51
MCA-b-d-g-h-x-q	2.38	10.12	-21.83	-11.45	-17.09	-43.40
MCA-b-d-g-h-y-q	2.19	9.72	-22.84	-11.81	-17.78	-44.83
MCA-d-e-f-g-h-y-p	4.89	— ^a	-17.85	-9.39	— ^a	-39.85
MCA-c-d-e-g-h-x-p	5.45	14.01	-18.05	-9.68	-14.41	-41.09
MCA-d-e-g-h-y-p	3.33	11.38	-20.86	-10.71	-16.02	-42.71
MCA-d-e-g-h-x-p	3.44	11.37	-21.28	-10.82	-16.27	-43.44

^a The calculation for this conformer did not converge in the given solvent

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