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DEPARTMENT OF CHEMISTRY

COMPUTATIONAL STUDY OF ANTIMALARIAL PYRAZOLE ALKALOIDS FROM *NEWBOULDIA LAEVIS IN VACUO AND IN SOLUTION*

BY

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This thesis is submitted in fulfillment of the requirements for the degree of Master in Chemistry.

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Abstract

This thesis is concerned with the computational study of pyrazole alkaloids having anatimalarial propperties by means of electronic structure methods. The pyrazole alkaloids studied in the present work are the following: withasomnine (3-phenyl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole) and newbouldine (3-phenyl -3a,5,6-tetrahydro-3H-pyrrolo[1,2-b]pyrazole) with their corresponding p-hydroxy and p-methoxy. They were isolated from the root-bark of *Newbouldia laevis* (an endemic plant in DR Congo traditionally used for the treatment of malaria, diarrhoea and other disease). The antimalarial activity of these compounds is intriguing because it appears rarely in alkaloids containing pyrazole groups. This makes their computational study particulary interesting to search for information thay 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.

The molecules were firstly studied *in vacuo* and secondly in three different solvents. These solvents (chloroform, acetonitrile and water) are characterized by different polarities and different H-bonding abilities. The octanol/water partition coefficients of these molecules suggest a non-negligible presence in media with broad polarity-range. Experimental studies on the withasomnine and 4'-hydroxywithasomnine nitro derivatives have shown an enhancement in antimalarial activity of these molecules, therefore the studies were extended on these nitro derivatives.

Wave functions and electron density methods (HF,DFT/B3LYP,MP2) combined with different basis sets (6-31G(d,p), 6-31+G(d,p), 6-31++G(d,p), 6-311G(d,p), 6-311+G(d,p), 6-311++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. Quantum chemical calculations on these molecules in solution were carried out using the polorisable contininuum model (PCM). The study in water solution was complemented by the study of adducts with explicit water molecules, because of the presence of atoms (e.g: O, N) capable of forming hydrogen bonds with water molecules.

The results provide a comprehensive picture of the molecular properties of these compounds, such as conformational preferences in *vacuo* and in solution, bond rotational scans, harmonic

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vibrational frequencies, solvent effects, preferred interactions with explicit water molecules. The results in solution show the influence of the solvent on the molecular structures (including the characteristics of the intramolecular hydrogen bond) and the energy aspects of the solution process. The results of the study of adducts with explicit water molecules show possible preferred arrangements of water molecules around the studied pyrazoles alkaloids moleculeand may facilitate the interpretation of the results in water solution.

Different computational methods (HF, MP2 and DFT) were utilised, depending on the affordability considerations for the structural sizes, in order to allow to obtain an assessment of the performance of less expensive methods like HF or DFT, in view of their utilisation for other classes of alkaloids structures for which more sophisticated methods (like MP2) remain unaffordable.

Keywords: antimalarials of natural origin, conformational preferences of pyrazoles alkaloids, electronic structure methods, *Newbouldia Laevis*, Polarizable Continuum Model (PCM), solute-solvent interactions, withasomnine.

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