University of Venda

SYNTHESIS of 1, 3, 5-TRIAZINE BASED ANTIMALARIAL DRUGS

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Dissertation for an MSc Degree in Chemistry

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Declaration

I declare that this dissertation is my own, unaided work. It is being submitted for the Degree of Masters of Science to the University of Venda. It has not been submitted before for any degree or examination to any other University.

Signed:…… Date:……

Acknowledgements

I would like to sincerely acknowledge my supervisor Dr SS Mnyakeni Moleele, Prof IDI Ramaite and my mentor Dr Mpelegeng Bvumbi for their guidance, input, support and foremost for giving me the opportunity to work with them and explore the world of pharmaceutical organic chemistry. For that, I am grateful.

Special thanks to my mom Takalani J Mugwena for always being there for me.

Most importantly I would like to thank NRF and Sasol Inzalo Foundation for their financial support.

Not forgetting to appreciate support from Chemistry department, my organic group and NMR "guy" Mr Pandelani.

Abbreviations

^{13}C NMR: Carbon Nuclear Magnetic Resonance

^{1}HNMR: Proton Nuclear Magnetic Resonance

Ar: Aromatic

DCM: Dichloromethane

DMSO: Dimethyl sulfoxide

et al; And Others

EtOAc: Ethyl Acetate

FTIR: Fourier Transform Infrared

h: Hour

HAART: Highly Active Antiretroviral Therapy

Hex: hexane

HIV: Human Immune Virus

Hz: Hertz

IR: Infrared Spectroscopy

IUPAC: International Union of Pure and Applied Chemistry

min: Minutes

MS: Mass Spectrometry

MTOR: Mammalian Target of Rapamycin

NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor

PI3KS: Phosphatidylinositol-3-Kinase

ppm: Part Per Million

rt: Room temperature

THF: Tetrahydrofuran

TLC: Thin Layer Chromatography

USA: United States of America

UV: Ultraviolet

W: Watts

WHO: World Health Organization

Abstract

This dissertation focuses on the application of 1, 3, 5-triazine in a pharmaceutical point of view since it has wide range of uses as described in chapter 1. Malaria is one of the most prevalent and deadly infectious diseases worldwide though there are already many synthesized anti-malarial drugs which are in use presently, drug resistance seems to be one of the major problem and combination therapy seems to be the only solution for now.

Hence in this study we used hybridization as a tool (**Figure 9**) to synthesize new antimalarial drugs using 1, 3, 5-triazine as an intermediate linker, linking known anti-malarial drug, different amine and chloroquine-like amines together using nucleophilic substitution reaction. As explained in chapter four of this dissertation, triazine is used to synthesize mono-, di- and tri-amino-1, 3, 5-triazine substituted products. Using THF as a solvent and K_2CO_3 as a base changing in temperatures, from 0 ^oC 25 ^oC or reflux. Some products were synthesized using microwave irradiation.

The application of triazine as an intermediate linker in the above mentioned condition yielded five mono-amino substituted dichloro-1, 3, 5-triazine (**21-25**) in an average yield of 82%, three amino substitution chloro-1, 3, 5-triazine (**26-28**) in an average yield of 87%, two amino substituted-1, 3, 5-triazine (**29, 30**) in an average of 90%, nine chloroquine-like synthesized compounds (**33-41**) in 84 % average yields respectively.

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1. Introduction

1.1 Malaria

Malaria is one of the most prevalent and deadly infectious diseases worldwide. It is caused by a single-cell parasite from the genus *Plasmodium*.[1] The parasite is characterized into five species that affect humans and are named: *Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, Plasmodium ovale and Plasmodium knowlesi.*[2] Out of these five species, *P. falciparum* and *P. vivax* are the most common and are critical to the public health. *P. falciparum* causes the most deadly form of malaria, whereas *P. vivax* has a wider global distribution.[3] Although efforts to control and eradicate malaria (especially falciparum malaria) through vector control and chemotherapy have provided significant gains, the transmission is still occurring and additional control measures are needed. Malaria has acute symptoms such as fever, headache, chills, muscular aching and weakness, vomiting, cough, diarrhea and abdominal pain.[4]

1.2 Global impact of malaria

According to the World Health Organisation (WHO) malaria report that was released in 2017, 91 countries and territories have ongoing malaria transmission.[5] Globally, an estimated 3.2 billion people are at risk of transmitting malaria of which 1.1 billion are at higher risk. In high-risk areas, more than one malaria case occurs per 1000 population. There has been an estimated 216 million reported cases of malaria worldwide (range 196-263 million) in 2016, of which 90% were from the African region, 7% from the South East Asia region and 2% from the Eastern Mediterranean region.[5] In addition, about 445 000 deaths (range 236 000 - 635 000) were recorded and 91% of malaria deaths occurred in Africa and only 6% occurred in South East Asia and Eastern Mediterranean region combined. In 2016, an estimation of 285 000 African children under the age of five years died due to malaria. Globally, the disease caused an estimated 306 000 deaths in children under the age of five years which is 70% of all reported malaria death related cases.[6] Malaria ranks fourth amongst the major infectious diseases that cause deaths after pneumococcal acute respiratory infections, HIV/AIDS and tuberculosis, and accounts for approximately 2.6% of the total disease burden of the world. Over the past four decades, no new antimalarial classes have been identified.[4]

1.3 Malaria in South Africa

Malaria in South Africa is seasonal. During rainy months like September-May the transmission of these parasites are moderate. However from January-April the transmission is observed to be the highest each year. Stats SA reported in March 2017 that there were 9478 cases of malaria with 76 deaths. These numbers of reported cases were significantly higher as compared to those reported in 2015/16 season (6385).[7] In March 2017 statistics indicated that in Limpopo province there were 4 092 cases of malaria associated with 33 deaths as compared to 1 543 cases and 18 deaths in the 2015/16 season. The 2016/17 malaria season statistics indicated that there was a significant increase in malaria cases and deaths compared to year 2015/16 season when drought conditions prevailed.[7] New malaria cases were reported in April 2017 from Mopani (Greater Giyani) and Vhembe (Thulamela) districts of the Limpopo Province.[7]

1.4 Biological features of malaria

The malaria parasite has a complex life cycle and in order to eradicate the disease, every stage of it should be considered for treatment. The life cycle (**figure 1**) of malaria parasite involves two hosts, namely human and mosquito. When malaria infected female *Anopheles* mosquito bites a human being, it inoculates sporozoites into the human host. Sporozoites enter liver cells and develop into mature schizonts which rupture and release merozoites into the blood stream.[4] This stage is called the pre-erythrocytic stage. At this stage, *P. vivax* and *P. ovale* can remain in a dormant condition known as hypnozoites in the liver and relapses may occur within a week, or even years later. Then merozoites multiply asexually in the erythrocytes and develop into immature ring stage trophozoites, afterwards grow up into schizonts. This stage is called asexual erythrocytic and the parasite at this stage shows clinical symptoms leading to illness and complications of malaria.[4] Finally, Some merozoites differentiate into sexual erythrocytic stages and develop into immature gametocytes, which are the precursors of male and female gametes. These are ingested by an *Anopheles* mosquito through a blood meal where they fuse in the mosquito midgut to form a zygote that furthermore develops to an ookinete, oocyst and finally develops into new sporozoites which then resides in the mosquito's salivary glands and are ready to infect a new human host. [4]

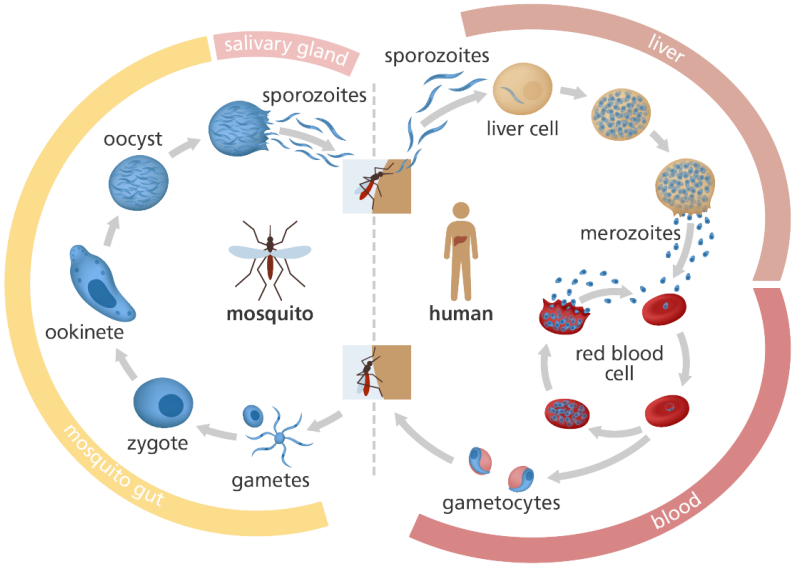


Figure 1: Malarial cycle image.[8]

1.5 Chemistry and clinical features

Antimalarials are used in three different ways namely prophylaxis, treatment of *falciparum* malaria, and treatment of non-*falciparum* malaria. Prophylactic antimalarials are used almost exclusively by travelers from developed countries who are visiting malaria-endemic countries. Residents of malaria-edemic countries rarely use prophylactic medications because of their expensiveness and also because such use might promote drug resistance and impair immunity. Treatment protocols for malaria vary depending on the severity of the disease caused by falciparum malaria, therefore fast-acting parenteral drugs are recommended.[9] The existing antimalarial therapy is broadly categorized into four major drug classes; namely Quinolone derivatives (chloroquine (**6**), quinine, mefloquine (**3**), amodiaquine **(7)**, primaquine), Antifolates, (pyrimethamine **(2)**, proguanil, sulfadoxine (**4**)), Artemisinin derivatives (artemisinin (**1**), artesunate, artemether, arteether, dihydroartemisinin and Antimicrobial (tetracycline, doxycycline, clindamycin, azithromycin).[9] Generally no single drug has been discovered or manufactured that can wipe out all strains of the malaria parasites. Thus to fight malarial infection efficiently, one or more or a combination of antimalarial drugs are frequently given at the same time. Antimalarial dosing therapies depend on the geographical location of infection, the more likely *Plasmodium* species, and the severity of disease presentation. [9]

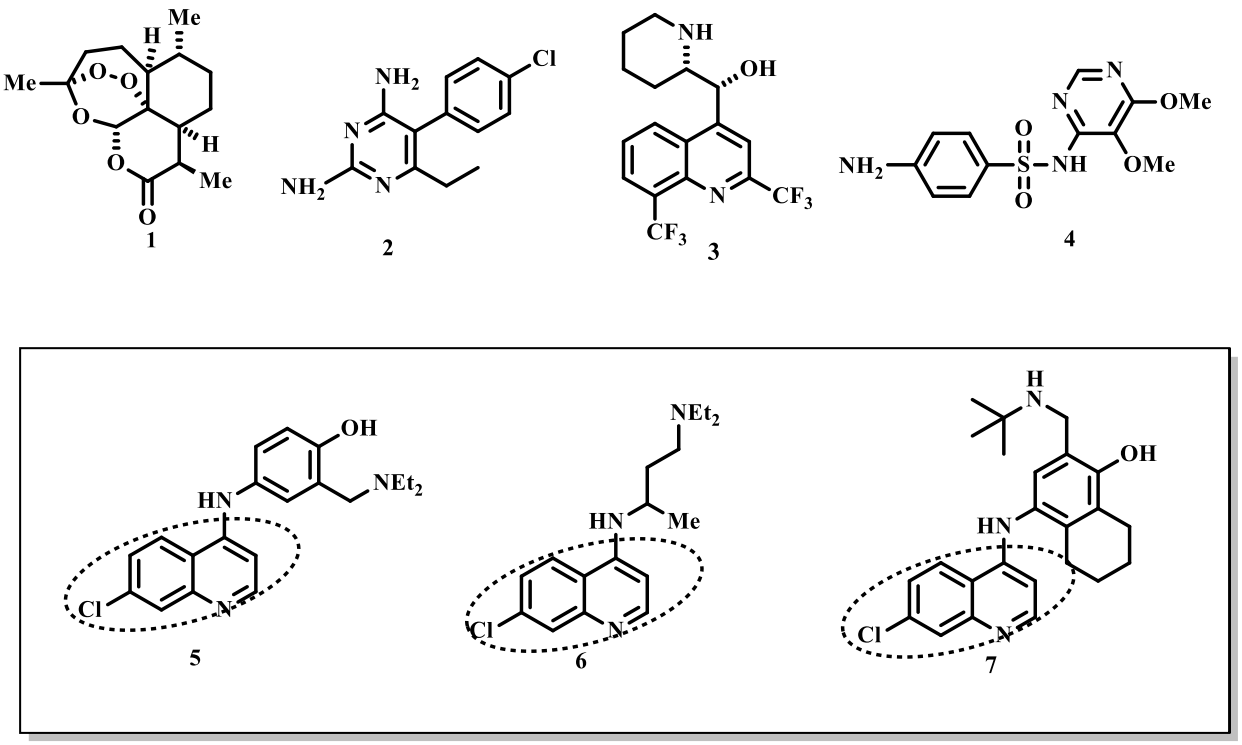


Figure 2: Structure of known antimalarial drugs

1.6 Antimalarial drugs and their mode of action

Artemisinin **(1) [Figure 2]** was isolated from leaves of the plant *Artemisia annua*, english name sweet wormwood. It was discovered by Tu Youyou, a Chinese scientist in 1972.[10] The mode of action of the artemisinin and its derivatives it's not completely elucidated. The present knowledge has been reviewed by Meshnick and co-workers.[11] The structure of artemisinin is unusual, and its activity is thought to depend on the presence of the endo peroxide bond, as molecules without it have no antimalarial activity.[12, 13] The endo peroxide bond may interact with iron or heme, decomposing into free radicals.[14] Unlike many redox reactions, this process is not reversible.[15a-c] Artemisinin acts specifically in the erythrocytic stage. It is currently used as a standard cure for *P. falciparum* malaria and *also P. vivax*.

Pyrimethamine **(2) [Figure 2]** has been available in the market since 1953. It is primarily active against *P. falciparum*, but also against *P. vivax*.[16] It is particularly useful in cases where chloroquine is resistant. Due to the emergence of pyrimethamine-resistant strains of *P. falciparum*, pyrimethamine alone is seldom used, but it is widely used in combination with a long-acting sulfonamide such as sulfadiazine in the blood stage of the malarial cycle.

Mefloquine (**3**) **[Figure 2]** was developed by the United States Army in the 1970s and is chemically related to quinine.[17] It is a very potent blood schizonticide with a long half-life. It is thought to act by forming toxic heme complexes that damage parasitic food vacuoles. Mefloquine is effective when used for prophylaxis treatment and for acute therapy.[17] It is now strictly used for resistant strains of *P. falciparum* and is usually combined with artesunate.

Sulfadoxine **(4)** is a structural analogue of *p*-amino benzoic acid (PABA) and competes with it to block its conversion to dihydrofolic acid. Sulfonamides like sulfodoxine act on the schizont stages of the erythrocytic (asexual) cycle.[18] When administered alone sulfonamides are not efficacious in treating malaria but co-administration with the antifolate pyrimethamine, most commonly as fixed-dose sulfadoxine-pyrimethamine, produces synergistic effects sufficient to cure sensitive strains of malaria. Sulfonamides are not recommended for chemoprophylaxis because of rare but severe skin reactions experienced. However, it is used frequently for clinical episodes of the disease.[18]

Amodiaquine **(5**), chloroquine (**6**) and naphthoquine (**7**) have similar structures as shown by the oval dots and activity profile [figure 2].[19] They all have 7-chloroquinoline moiety which might have been the pharmacophore of these drugs. This is the main reason to revisit this moiety in this project. Amodiaquine is used in partner with sulfadoxine-pyrimethamine combination. It acts by accumulating in the parasite food vacuole and forming a complex with heme that prevents crystallization in the *Plasmodium* food vacuole.[19] Recent studies on the treatment of uncomplicated falciparum malaria conducted over the past ten years in Africa showed a higher therapeutic efficacy of amodiaquine over chloroquine, with a tendency towards faster clinical recovery.[19]

Chloroquine inhibits glutathione-dependent degradation of heme and thereby kills the parasite by allowing toxic heme to accumulate in the cell membrane. Until recently, it was a widely used antimalarial drug until the falciparum malarial strain became resistant to it.[20] It is also the least expensive, best tested and safest of all available antimalarial drugs.

1.7 Triazines

The designing, synthesis and evaluation of molecules with some human therapeutic values remain one of the main objectives of organic and medicinal chemistry. During the past decades, the combination/hybridazation chemistry has provided access to chemical libraries based on privileged heterocyclic compounds with utility in medicinal chemistry.[21] Synthesis of nitrogen containing heterocyclic compounds has been attracting increasing interest because of their utility for various biological receptors with a high degree of binding affinity.[21] The triazine structure is a heterocyclic ring analog to the six-membered benzene ring with three carbon atoms replaced by nitrogen atoms. The isomers of triazine are distinguished from each other by the positions of their nitrogen atoms, and referred to as 1, 2, 3-triazine **(8)**, 1, 2, 4-triazine **(9)** and 1, 3, 5-triazine **(10)** **(figure 3)**.[21]

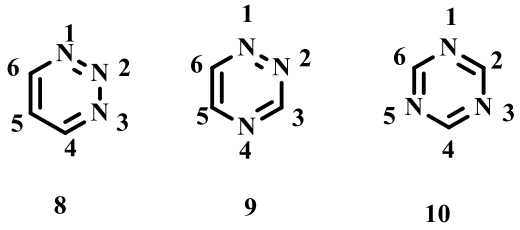


Figure 3: Isomers of triazine

1, 3, 5-Triazine (s-triazine) has been widely used in organic reactions that offer access to a multitude of useful molecules due to its specific structure and electronic properties [22a-g] Increased interests in this compound lie in different reactivity of the chlorine atoms at 2, 4 and 6 positions that are controlled by temperature, allowing the sequential introduction of various substitutuents for the preparation of mono-, di- and tri-substituted triazines.[23, 24] Owing to the immense synthetic importance and varied bioactivities, efforts have been made from time to time to generate libraries of these compounds.

1.8 Biological activity of 1, 3, 5-triazine containing compounds

The triazine containing compounds provide the basis for the design of biologically relevant molecules with widespread applications like antiprotozoal,[25] anticancer,[26a-d] antimalarial,[27] antiviral,[28] and antimicrobial,[29,30], herbicides and resin modifiers like melamine and benzoguanamine.[31, 32]

1.8.1 Herbicides

Herbicides are classified according to selectivity, time of application, translocation in the plant, or mechanism of action. For mechanism of action, there are seven major classes of herbicides namely growth regulators, seedling growth inhibitors, photosynthetic inhibitors, amino acid synthesis inhibitors, lipid synthesis inhibitors, cell membrane disruptors, and pigment inhibitors.[33] For example both the triazine herbicide atrazine (**11**) and prometon (**12**) have been most widely used herbicides in the production of corn, sorghum, and other crops for forty years in the U.S. They are preemergent herbicides used to control broadleaf and grassy weeds. Their mode of action is through selective disruption of photosynthesis to kill weeds, resulting in increased crop production.[34]

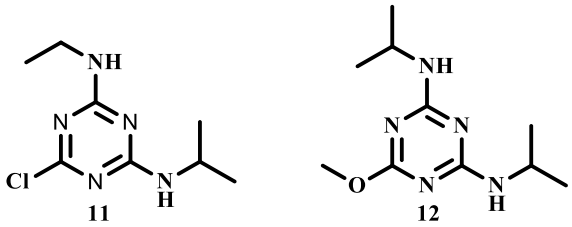


Figure 4: herbicides with triazine nucleus

1.8.2 Antitumor activity

1, 3, 5-Triazine moiety is widely explored for the development of anticancer agents.[35] It has been designed and synthesized as highly selective series of inhibitors of the class I phosphatidylinositol 3-kinases (PI3Ks) that showed the dual PI3K/mTOR inhibitor.[36] When the benzimidazole (**13**) moiety was replaced with methylsulphonyl-piperazine (**14**) group moiety this further improved the potency of the compounds.[36](**Figure 5**)

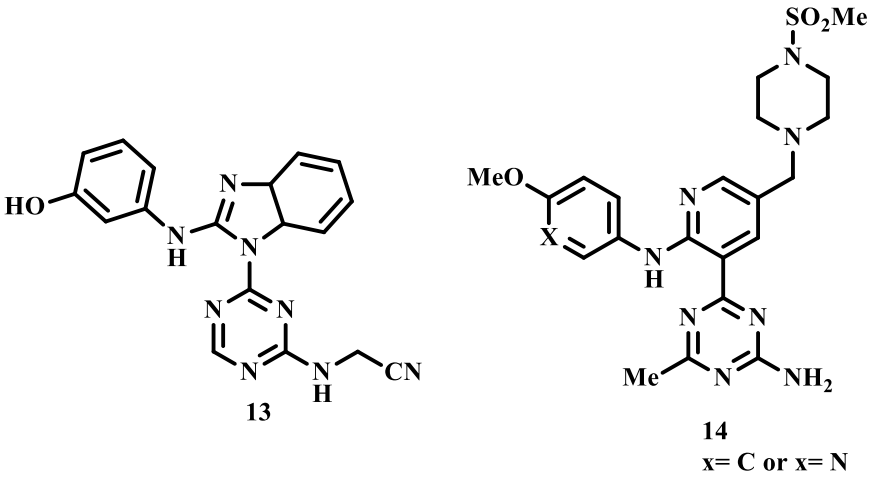


Figure 5: s-triazine containing compounds with anti-tumours activity

1.8.3 Antimicrobial activity

Antimicrobial agents or drugs that kill microorganism can be classified into groups according to microorganisms they primarily act against. For example, antibiotics are used against bacteria and antifungals are used against fungi. Recently, compounds with triazine nucleus and phenylthiazole were found to have antifungal activity.[37, 38] Compound **15** which has phenyl ring attached to the thiazole group and di-substituted diisopropylamine group showed a slight increase in antimicrobial activity while the introduction of di-morpholine fragment (**16**) led to a significant increase in activity.(**Figure 6)**

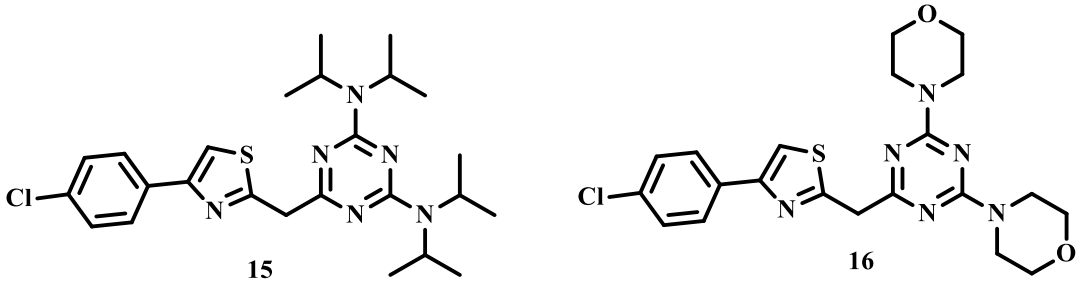


Figure 6: s-triazine compounds with anti-microbial activity

1.8.4 Antiviral activity

Antiviral drugs are a class of medication used specifically for treating viral infections. HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTI) with high antiviral potency, specificity and low cytotoxicity have become an indispensable component in HAART regimen.[39] Studies by Chan *et al* showed the development of novel drugs with piperidine-substituted triazine moiety[40] which

have anti-viral activity. Compounds **17** exhibited a moderate inhibitory activity whilst compounds **18,** which has a carbonyl group compared to compound **17** shows the highest inhibitory activity against HIV-1. (**Figure 7**)

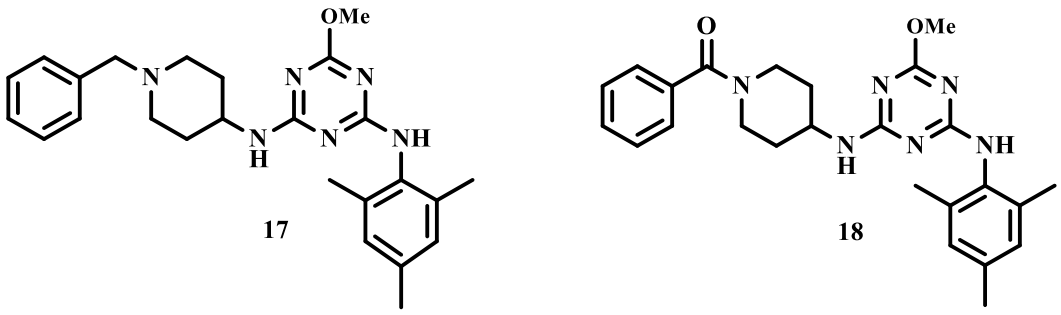


Figure 7: s-triazine compounds with anti-viral activity

1.8.5 Antimalarial activity

Due to development of resistance towards antimalarial drugs, for example resistance of falciparum malaria strain towards chloroquine, there is a need for constant research towards inventing new procedures to synthesize new antimalarial drugs. One of the routes to follow is chemical modification of quinine nucleus which led to the development of other therapeutic agents such as chloroquine, [41] pamaquine and mefloquine. In a study by Sundura *et al* substitution of triazine nucleus with quinoline moiety was incorporated and was tested for antimalarial activity. Triazine and 4, 7-dichloroquine were incorporated together due to chloroquinoline nucleus being essential for antimalarial activity and said to inhibit the β-hematin formation that helps the drug to accumulate in the acidic food vacuole of the parasite.[42a-d] The presence of linker alkyl chain between triazine and quinoline nucleus is said to be an essential antimalarial activity[43,44] and also the substitution of diethyl group by metabolically stable side chain of *tert*-butyl group as well as the heterocyclic functionality such as morpholinyl, piperidinyl or pyrrolidinyl groups led to increase in antimalarial activity.[45] Hence this idea was also adapted as a key point in this project. Triazines derivative **19** and **20** have been found to be the most active against chloroquinoline sensitive strain (**Figure 8**).[46]

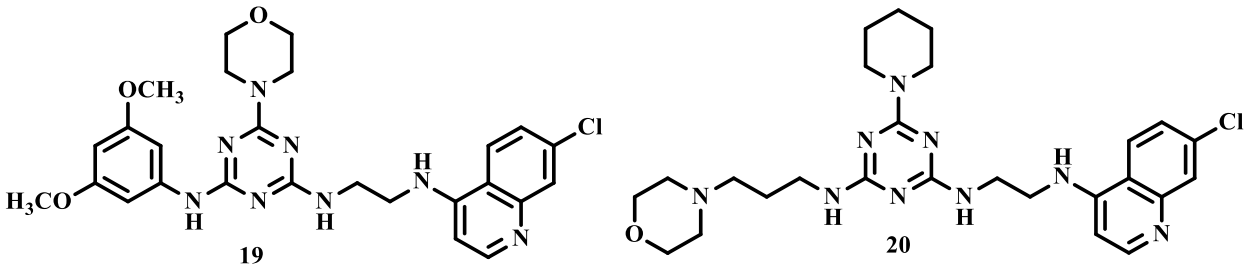


Figure 8: s-triazine compounds with anti-malarial activity

1.9 Aims of the project

Although there are quite a number of synthesized anti-malarial drugs which are in use presently, drug resistance seems to be one of the major problems. Many antimalarial drugs in current usage are closely related chemically and development of resistance to one can facilitate development of resistance to others. Chloroquine and amodiaquine are both 4-aminoquinolines and cross-resistance between these two drugs is well documented.[47,48] Development of resistance to mefloquine may also lead to resistance to halofantrine and quinine. Whilst antifolate combination drugs have similar mode of action and widespread use of sulfadoxine/ pyrimethamine for the treatment of malaria may lead to increased parasitological resistance to other antifolate combination drugs.[49] The use of drug combinations of drugs belonging to different class is less likely to foster resistance or spread of resistant parasites.

Hence in this study we used hybridization as a tool (**Figure 9**) to synthesize novel antimalarial drugs using 1, 3, 5-triazine as an intermediate linker, linking known anti-malarial drugs which belong to different classes (4-aminoquinoline derivatives, artemisinin derivatives, antifolates and antimacrobials) together using nucleophilic substitution reaction. Hoping to also provide breakthrough towards combination therapy, instead of taking two or more drugs for treatment, one can take one hybrid drug which will be synthesized by incorporating two or more known drugs (from different classes) for different stages along with some amines to improve their bioactivity.

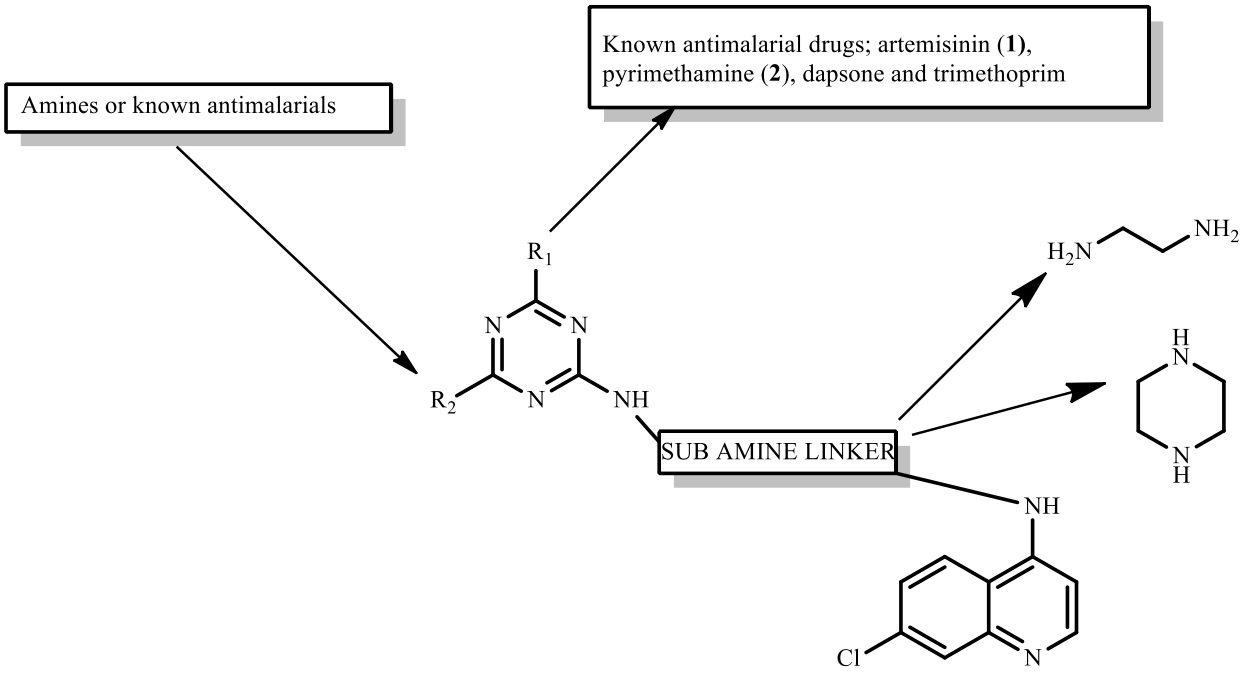


Figure 9: hybridization scheme of study

Sundura *et al*. showed that cyclic amines such as piperidine have greater antimalarial activity.[46] In this project, focus was therefore on the use of other cyclic and also branched alkyl amines. The substitution of antimalarial drugs on the triazine as a linker is as far as we know minimally reported.[46] We therefore thought that, as an opportunity to explore this by hybridization technique with the drugs involve.

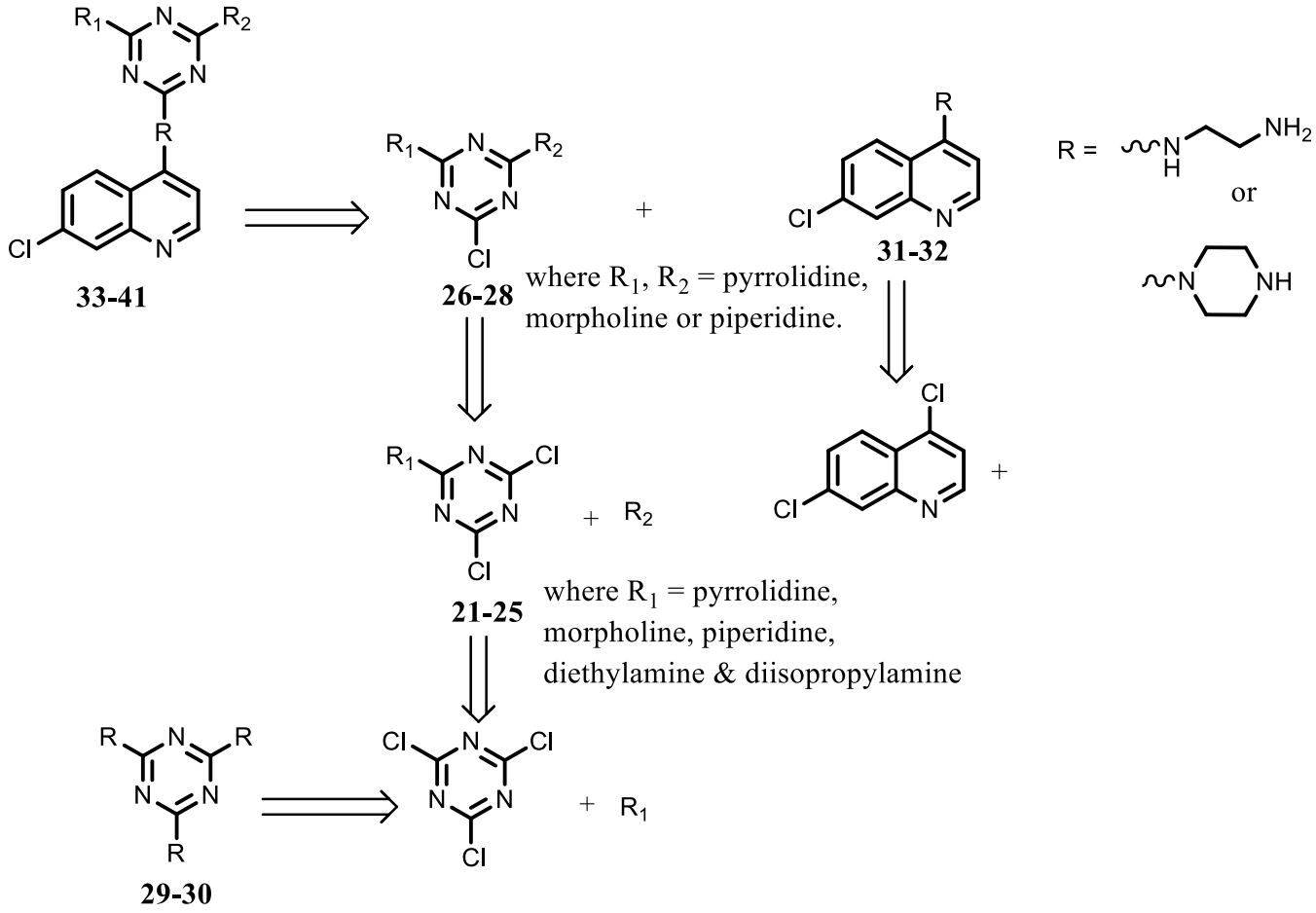
In summary proposed aim and objectives:-

- To synthesize new antimalarial drugs which are more effective by application of hybridization method using 1, 3, 5-triazine as an intermediate linker.
- Synthesize 4, 7-dichloroquine like antimalarial drugs using substitution reactions onto the 1, 3, 5-triazine.
- Linking known anti-malarial drugs for different stages together with some amines to increase their bioactivity.

2. Results and Discussion

This project was aimed at synthesizing 1, 3, 5-triazine based compounds as potential antimalarial drugs using hybridization as a tool to achieve the mentioned objectives. Outlined below (**Scheme 1**) is a retrosynthesis scheme of the project.

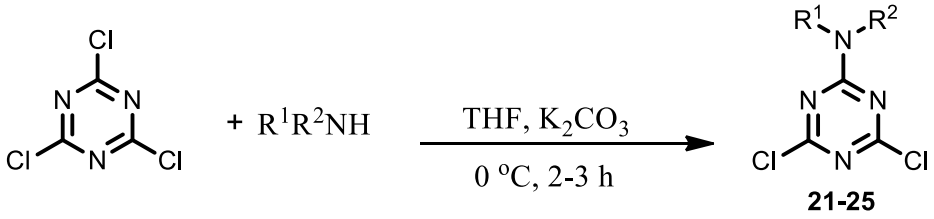
2.1 Project retrosynthesis scheme.



Scheme 2: Retrosynthetic scheme of the project.

Two types of chloroquine-like compounds were targeted in this project. One type used piperazine as a linker whereas the other type used ethylene diamine as a linker. Compounds with piperazine as linker (**33-38**) would be obtained from a reaction of amino chloro-1, 3, 5-triazines (**21-28**) and 4-piperazino-7-chloroquinoline (**32**) which would in turn be obtained from a reaction of 4, 7-dichloroquine and piperazine. On the other hand, compounds with ethylene diamine as a linker (**39-40**) would be obtained from a reaction of aminochloro-1, 3, 5-triazines (**25, 26**) and 7-chloro-4-ethylenediamine (**31**) which would be synthesized from a reaction of 1, 2-diamino ethane and 4, 7-dichloquine. In turn aminochloro-1,3,5-triazines would be synthesized from either a reaction of cyanuric chloride and one molar equivalent of an amine to obtain monoaminodichloro-1,3,5-triazine (**21-25**) or a reaction of cyanuric chloride with two molar equivalents of an amine to obtain diaminochloro-1,3,5-triazines (**26-28**). Finally tri-aminosubstituted-1, 3, 5-triazines (**29, 30**) would be obtained from a reaction of cyanuric chloride with three molar equivalents of either diethyl amine or dapsone.

2.1 Synthesis of mono-substituted 1, 3, 5-triazines



Scheme 2: General reaction scheme for mono substitution reaction.

Aminodichloro-1, 3, 5-triazine derivatives (**21-25**) were obtained from a reaction of cyanuric chloride and one molar equivalent of an amine at 0 ^{o}C for 2-3 hours. Compounds were obtained in good to excellent yield as shown in **table 1** below. Secondary amines of choice were pyrrolidine, piperidine, morpholine, diethylamine and diisopropylamine. Envisaged compounds were confirmed by IR, NMR and MS spectroscopies. IR spectra of all our compounds were characterized by the absence of N-H stretch peak at ~3300 cm^{-1} confirming the consumption of secondary amines used and also characterized by the presence of aryl-halide stretch indicating the presence of C-Cl stretch at ~790 cm^{-1}. ^{1}H NMR spectra of the desired products were characterized by appearance of peaks in the aliphatic to heteroatomic regions. ^{1}H NMR spectrum of compound **21** showed appearance of two triplets accounting for four protons each at 3.57 ppm and 1.91 ppm. The two triplets confirmed the two methylene protons of the pyrrolidine moiety of compound **21**.

Literature has shown that the peaks of the two methylene protons of unreacted pyrrolidine appear at 3.02 ppm and 1.82 ppm respectively.[50] Compound **22** showed appearance of two triplets and a quintet at 3.81 ppm, 1.59 ppm and 1.64 ppm respectively. The two triplets and a quintet indicated the three methylene proton of the piperidine moiety of compound **22**. Research has shown that the peaks of the three methylene protons of unreacted piperidine appear at 2.82 ppm, 1.47 ppm and 1.67 ppm respectively. Compound **23** also showed appearance of two triplets accounting for two protons each at 3.82 ppm and 3.69 ppm. The two triplets confirmed the two methylene proton of the morpholine moiety of compound **23**. Research has shown that the peaks of the two methylene protons of unreacted morpholine appear at 3.64 ppm and 2.65 ppm respectively.[50] Compound **24** showed appearance of a triplet accounting for six protons and a quartet accounting for four protons each at 3.54 ppm and 1.13 ppm respectively. The triplet indicated the methylene protons and a quartet indicated the methyl protons of the diethylamine moiety of compound **24**. Research has shown that the peaks of the two multiplicities of unreacted diethylamine appear at 2.62 ppm and 0.98 ppm respectively. Finally compound **25** showed appearance of a doublet accounting for twelve protons and a septet accounting for two protons each at 4.24 ppm and 1.27 ppm respectively. The doublet indicated the methyl protons and a septet indicated the methine protons of the diisopropylamine moiety of compound **25**. Research has shown that the peaks of the two multiplicities appear at 2.81 ppm and 1.15 ppm respectively.[50]

^{13}C NMR spectra of product **21-25** were more revealing about our envisaged products. An unreacted cyanuric chloride would show one quaternary carbon peak at 153.0 ppm in its ^{13}C NMR spectrum.[50] ^{13}C NMR spectra of all our compounds showed two quaternary carbon peaks at ~169 ppm and at ~163 ppm. This was an indication that all the cyanuric chloride had reacted Moreover this, confirmation that indeed these compounds were mono-amino substituted and not di-amino substituted ones was revealed in the intensities of the peaks observed. Peaks at ~169 ppm (C-Cl) were all roughly double the size of peaks observed at ~163 ppm (C-N). If these were di-amino substituted compounds this order would be reversed. Specific peaks for compounds **21-25** are indicated in table 1 below. Also ^{13}C NMR spectra of our desired compounds showed peaks in the aliphatic to hetero atomic regions. Compound **21** showed two methylene carbon peaks at 47.2 ppm and 25.0 ppm confirming attachment of pyrrolidine onto cyanuric chloride. Research has shown that methylene carbon peaks of unreacted pyrrolidine are observed at 47.3 ppm and 25.7 ppm respectively.[51] Compound **22** showed three methylene carbon peaks at 45.2 ppm, 25.6 ppm and

24.1 ppm confirming attachment of piperadine onto cyanuric chloride. Research has shown that methylene carbon peaks of unreacted piperadine are found at 47.9 ppm, 27.8 ppm and 25.9 ppm respectively. Compound **23** showed two methylene carbon peaks at 66.3 ppm and 44.4 ppm confirming attachment of morpholine onto cyanuric chloride. Research has shown that methylene carbon peaks of unreacted morpholine are observed at 54.9 ppm and at 46.7 ppm respectively. Compound **24** showed one methylene carbon peak at 42.4 ppm and one methyl carbon peak at 12.5 ppm confirming attachment of diisopropylamine onto cyanuric chloride. Research has shown the methylene carbon peaks of unreacted diethylamine is found at 44.5 ppm whereas methyl carbon peak is 15.7 ppm.[51] Compound **25** showed one methine carbon peak at 42.5 ppm and one methyl carbon peak at 15.0 ppm confirming attachment of diisopropylamine onto cyanuric chloride. Research has shown that methine carbon peaks of unreacted diisopropylamine is found at 45.3 ppm whereas the methyl carbon peak is found at 23.7 ppm. The TOF MS (EL+) calculated value corresponded to the found value with a variety between 0.1 – 0.9 m/z of all the mono-amino substituted compounds (**Table 1**).

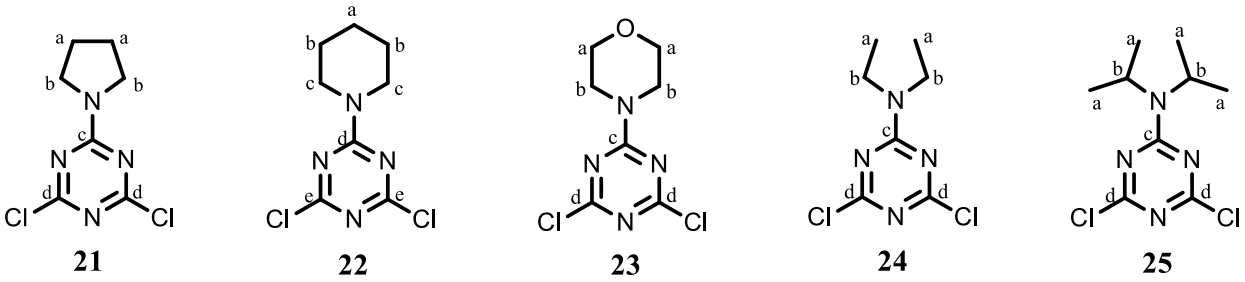
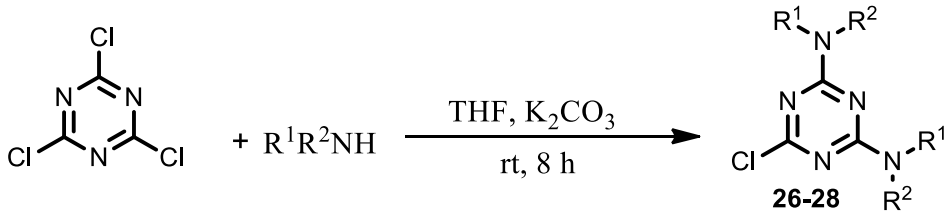


Table 1: Mono-substituted 1, 3, 5-triazine compounds

Compound code	MS Calculated (found) m/z	Percentage Yield (%)	Melting point (literature) (^{o}C)	Distinctive ^{13}Cnmr peak (ppm)
21 R= pyrrolidine	219.0102 (219.0102)	91	86-89 (80-85)[52]	169 (2 x C_d-Cl), 162 (C_c-N)
22 R= piperidine	233.1109 (234.0021)	79	144-146 (142-143)[53]	170 (2 x C_e-Cl), 163 (C_d-N)
23 R= morpholine	238.0706 (138.0007)	87	163-165 (157-158)[54]	170 (2 x C_d-Cl), 164 (C_c-N)
24 R= diethylamine	221.0871 (221.9003)	88	88-90	169 (2 x C_d-Cl), 163 (C_c-N)
25 R=diisopropylamine	249.1413 (248.0023)	90	104-106	169 (2 x C_d-Cl), 164 (C_c-N)

2.2 Synthesis of di-substituted 1, 3, 5-triazine



Scheme 3: General reaction scheme for di substitution reaction.

Di-aminochloro-1, 3, 5-triazine derivatives (**26-28**) were obtained from a reaction of cyanuric chloride and two molar equivalent of an amine at room temperature for 8 hours. Compounds were obtained in good yields as shown in **table 2** below. Secondary amines of choice were pyrrolidine, piperadine and morpholine. Envisaged compounds were confirmed by IR, NMR and MS spectroscopies. IR spectra of the above mentioned compounds were characterized by the absence of N-H stretch peak at ~3300 cm^{-1} confirming the consumption of secondary amines used and an aryl-halide stretch peak that was observed at ~790 cm^{-1} which indicated the presence of C-Cl bond. ^{1}H NMR spectra of our desired products were characterized by appearance of peaks in the aliphatic to heteroatomic regions. ^{1}H NMR spectrum of compound **26** showed appearance of two triplets accounting for eight protons each at 3.44 ppm and 1.93 ppm. The two triplets indicated the presence of two methylene protons of the pyrrolidine moiety of compound **26**. Research has shown that the peaks of the two methylene protons of unreacted pyrrolidine appear at 3.02 ppm and 1.82 ppm respectively.[50] ^{1}H NMR spectrum of Compound **27** showed appearance of one triplet accounting for eight protons at 3.65 ppm and a multiplet accounting for twelve protons between 1.58-1.51 ppm. Both the triplet and the multiplet confirms the three methylene proton of the piperadine moiety of compound **27**. Research has shown that the peaks of the three methylene protons of unreacted piperadine appear at 2.82 ppm, 1.67 ppm and 1.47 ppm respectively. Finally compound **28** showed appearance of two triplets accounting for two protons each at 3.71 ppm and 3.63 ppm. The two triplets indicated the two methylene protons of the morpholine moiety of compound **28**. Research has shown that the peaks for the two methylene protons of unreacted morpholine appear at 3.64 ppm and 2.65 ppm respectively. ^{13}C NMR spectra of all our compounds (**26-28**) showed the intensities of the two quaternary carbon peaks at ~169 ppm and ~164 ppm. They showed a reversed trend compare to those of mono-aminodi-chloro-1, 3, 5-triazine derivatives (**21-25**). Peaks at ~164 ppm (C-N) were roughly double the size of peaks observed at

~169 ppm (C-Cl) confirming that they are now diamichloro-1,3,5-triazine. Specific peaks for compounds **26-28** are indicated in **table 2**. ^{13}C NMR of the synthesized compounds (**26-28**) also showed peaks in the aliphatic to heteroatomic regions. Compound **26** showed two methylene carbon peaks at 46.4 ppm and 25.2 ppm confirming attachment of pyrrolidine onto cyanuric chloride. Research has shown that methylene carbon peaks of unreacted pyrrolidine 47.3 ppm and 25.7 ppm respectively. Compound **27** showed three methylene carbon peaks at 44.4 ppm, 24.6 ppm and 25.8 ppm confirming attachment of piperadine onto cyanuric chloride. Research has shown that methylene carbon peaks of unreacted piperadine are observed at 47.9 ppm, 27.8 ppm and 25.9 ppm respectively. Compound **28** showed two methylene carbon peaks at 66.5 ppm and 44.4 ppm confirming attachment of morpholine onto cyanuric chloride. Research has shown that methylene carbon peaks of unreacted morpholine are observed at 54.9 ppm and 46.7 ppm respectively. The TOF MS (EL+) calculated value for di-amino chloro-1, 3, 5-triazine derivatives (**26** and **28**) corresponded to the found value with a difference between them of 0.1 – 1.6 m/z (**Table 2**).

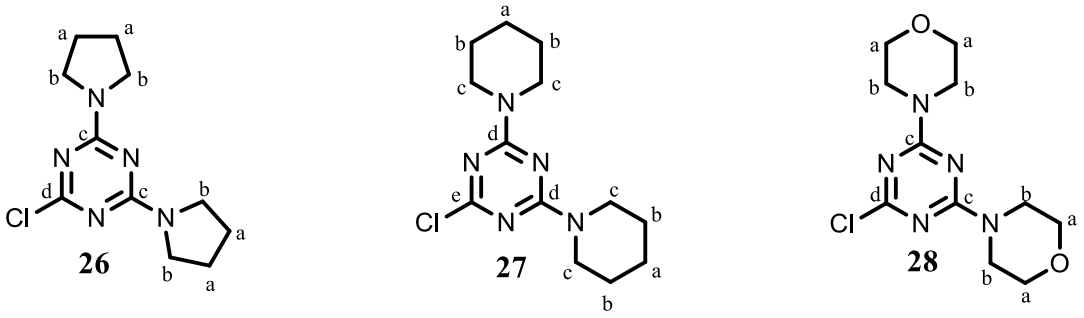
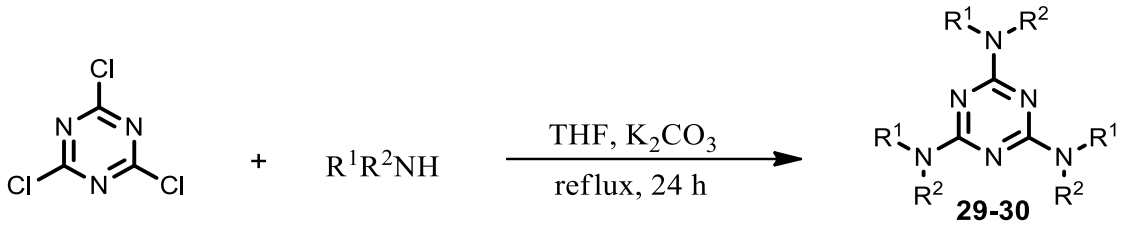


Table 2: Di-substituted 1, 3, 5-triazine compounds

Compound code	MS Calculated (found) m/z	Percentage Yield (%)	Melting point (literature ^{o}C)	Distinctive ^{13}Cnmr peaks (ppm)
26 R= pyrrolidine	253.7312 (254.7001)	78	106-109 (110-112)[55]	168 (C_d-Cl), 162 (2 x C_c-N)
27 R= piperidine	-	78	176-178 (176-178)[56]	169 (C_e-Cl), 164 (2 x C_d-N)
28 R= morpholine	285.7300 (285.0094)	89	156-161 (154-156)[56]	169 (C_d-Cl), 164 (2 x C_c-N)

2.3 Synthesis of tri-substituted 1, 3, 5-triazine



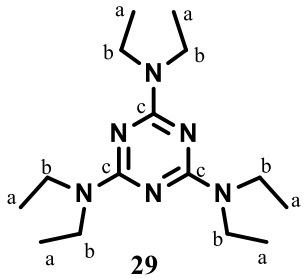
Scheme 4: General reaction scheme for tri substitution reaction.

Tri-substituted amino-1, 3, 5-triazine derivatives (**29** and **30**) were obtained from a reaction of cyanuric chloride and three molar equivalents of an amine for 24 hours (**29**) and 10 min under microwave conditions (**30**). Compounds were obtained in excellent yield as shown in **table 3**. Amines of choice were diethylamine and dapsone, known antimalarial drug. Envisaged compounds were confirmed by IR, NMR and MS only for compound **29** spectroscopies. IR spectra of these compounds were characterized by the absence of aryl-halide stretch peak at ~790 cm^{-1} confirming substitution of all three chlorine atoms. IR spectrum of compound **29** also showed the absence of N-H stretch peak at ~3300 cm^{-1} confirming the consumption of diethylamine used.

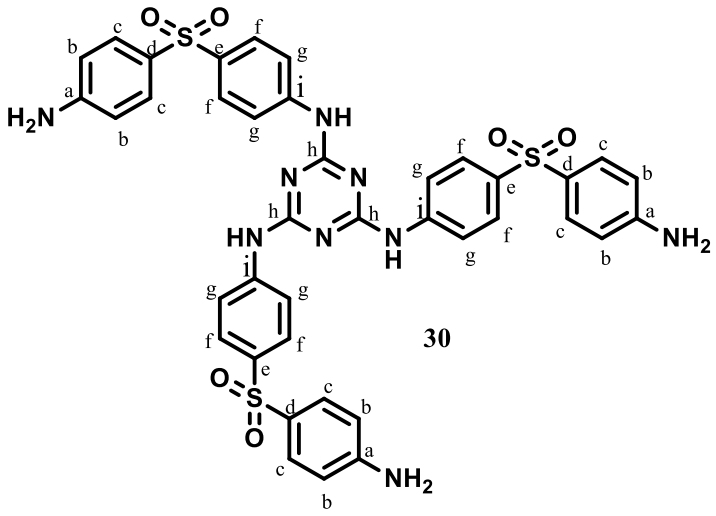
^{1}H NMR spectrum of compounds **29** was characterized by appearance of two peaks in the aliphatic to heteroatomic regions. A triplet accounting for eighteen protons was observed at 3.58 ppm and a quartet accounting for twelve protons was observed at 1.19 ppm. The triplet indicated the methylene protons and a quartet indicated the methyl protons of the diethylamine moiety of compound **29**.

The ^{1}H NMR of Compound **30** was characterized by appearance of six peaks in the heteroatomic-aromatic region. In the aromatic region four doublets accounting to one proton each were observed at 7.98 ppm, 7.77 ppm 7.63 ppm and 6.77 ppm respectively, all due to ortho coupling with neighbouring methine protons. This is a confirmation that one H of the two NH_2 of dapsone has reacted since unreacted dapsone would show only two aromatic C-H peaks due to symmetry. Two broad singlets one accounting for one proton (NH) and the other accounting for two protons (NH_2) were also observed at 5.9 ppm at 4.3 ppm respectively.

^{13}C NMR spectra of both our compounds (**29 and 30**) showed one quaternary carbon peaks at ~160 ppm (C-N) and compared to the one for unreacted cyanuric chloride at ~153 ppm (C-N). ^{13}C NMR of compounds **29** showed two peaks in the aliphatic to hetero atomic regions. One methylene carbon peak at 36.2 ppm and one methyl carbon peak at 8.81 ppm confirming attachment of diethylamine onto cyanuric chloride. ^{13}C NMR spectrum of compounds **30** showed nine carbon peaks in the aromatic regions of these peaks, four are methane carbon peaks were observed at 129.3 ppm, 127.0 ppm, 120.0 ppm and 115.1 ppm confirming the attachment of dapsone onto the cyanuric chloride. An unreacted dapsone would have indicated only two methine carbon peaks. Five quaternary carbon peak were observed 151.0 ppm, 144.0 ppm, 136.1 ppm, 136.1 ppm and 130.0 ppm. Most important quaternary carbon peak is the one observed at 164.0 ppm containing triazine bond to nitrogen since unreacted cyanuric chloride shows its quaternary carbon peak at 153 ppm.



29

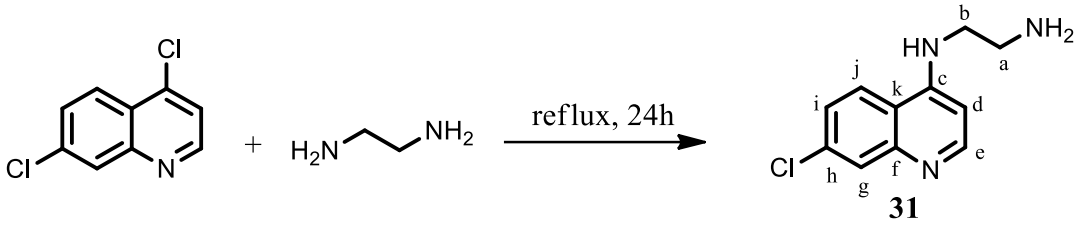


30

Table 3: Tri-substituted 1, 3, 5-triazine compounds

Compound code	MS Calculated (found) m/z	Percentage Yield (%)	Melting point (^{o}C)	Distinctive ^{13}Cnmr peaks (ppm)
29 R=diethylamine	294.4989 (294.0013)	87	_	160 (3 x C_c-N)
30 R= dapsone	-	94	288-290	164 (3 x C_h-N)

2.1.4 **Synthesis of N^1-(7-chloroquinolin-4-yl) ethane-1, 2-diamine**

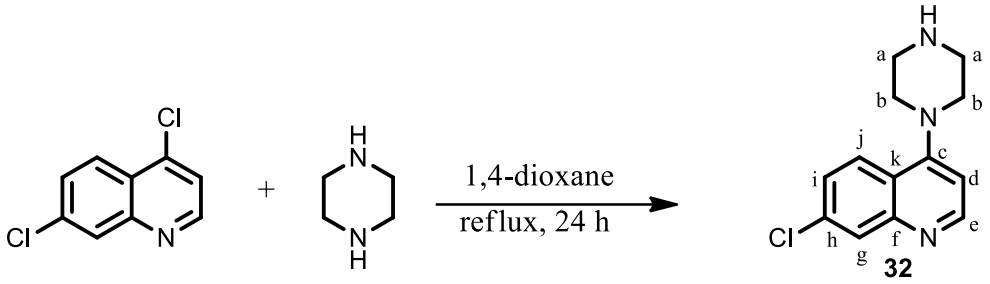


Scheme 5: Synthesis of N^1-(7-chloroquinolin-4-yl) ethane-1, 2-diamine

N^1-(7-chloroquinolin-4-yl) ethane-1, 2-diamine (**31**) was obtained by refluxing 4,7-dichloquinoline in 1, 2-diamino ethane for 24 hours. Compound **31** was obtained in good yield as yellow powder (**Table 4**). It was confirmed by IR and NMR spectroscopies. IR spectrum of compound **31** was characterized by the presence of N-H stretch peak at 3238 cm^{-1} confirming the formation of secondary amine. ^{1}H NMR spectrum of compound **31** was characterized by appearance of two peaks in the aliphatic-hetero atomic region. It showed appearance of two triplets accounting for two protons each at 3.26 ppm and 2.84 ppm and two broad singlets accounting for NH and NH_2 protons each at 3.00 and 2.50 respectively. The two triplets and two broad singlets indicated the two methylene protons and an NH and NH_2 of the 1, 2-diamino ethane moiety of compound **31**. In the aromatic region four doublets and one doublet of a doublet was observed at 8.39 ppm, 8.30 ppm, 7.78 ppm, 6.49 ppm and 7.45 respectively. Literature has shown that the peaks of unreacted ethylene diamine protons appear at 2.64 ppm and five aromatic protons of unreacted 4, 7-dichloroquine appear at 8.74 ppm, 8.24 ppm, 7.9 ppm, 7.70 ppm and 7.50 ppm respectively.[51]

^{13}C NMR spectrum of compound **31** shows two methylene carbon peaks at 46.5 ppm and at 40.5 ppm. Confirming the attachment of ethylene diamine onto the 4, 7-dichloroquinoline. Nine aromatic peaks were observed at 156.0 ppm (C=N), 150.0 ppm (C), 149.1 ppm (C-N), 133.3 ppm (C-Cl), 127.0 ppm (CH), 124.1 ppm (C-H), 124.0 ppm (C-H), 117.0 ppm (C), 99.1 ppm (C-H). Literature has shown that carbon peak of unreacted ethylene diamine are observed at 44.3 ppm and of unreacted 4,7-dichloroquinoline are observed at 149.8 ppm (C=N), 147.3 ppm (C), 142.5 ppm (C-N), 132.8 ppm (C-Cl), 126.7 ppm (C-H), 126.5 ppm (C-H), 125.5 ppm (C-H) , 124.4 ppm (C), 122.4 ppm (C-H) respectively.[51]

2.5 Synthesis of 7-chloro-4-piperazin-1-yl) quinoline



Scheme 6: Synthesis of 7-chloro-4-piperazin-1-yl) quinoline

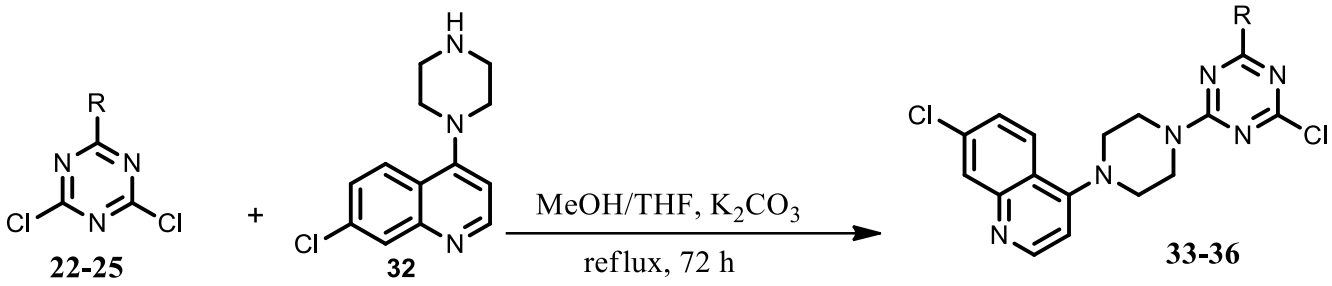
Synthesis of 7-chloro-(4-piperazin-1-yl) quinoline (**32**) was obtained from a reaction of 4, 7-dichloquinoline and five molar equivalent of piperazine in refluxing dioxane for 24 hours, compound **32** was obtained in good yield as shown in **Table 4**. The desired compound was confirmed by NMR spectroscopy. ^{1}H NMR spectrum of compound **32** was characterized by appearance of peaks in the hetero atomic region. Whereby two triplet accounting for two protons each were observed at 3.30 ppm and 3.08 ppm and one broad singlet accounting for one proton (NH) was observed at 2.97. The two triplets indicated the two methylene protons of the piperazine moiety of compound **32**. An unreacted piperazine would show only one peak in its NMR spectrum since it contains all protons are equivalent. Research has shown that the peaks of unreacted piperazine protons appear at 2.66 ppm. Four doublets and one doublet of a doublet was observed in the aromatic region of the spectrum at 8.69 ppm, 8.02 ppm, 7.96 ppm, 6.95 ppm and 7.54 respectively. Literature has shown that the peaks of unreacted 4, 7-dichloroquine protons appear at 8.74 ppm, 8.24 ppm, 7.90 ppm, 7.70 ppm and 7.50 ppm respectively.

^{13}C NMR spectrum of compound **32** showed the appearance of two methylene carbon peaks at 53.5 ppm and 45.9 ppm confirming the attachment of piperazine onto the quinoline. Unreacted piperazine will only show one methylene carbon peak at 47.9 ppm. Nine aromatic carbon peaks were observed at 157.0 ppm (C=N), 152.0 ppm (C), 150.2 ppm (C-N), 133.0 ppm (C-Cl), 128.0 ppm (CH), 126.0 ppm (C-H), 126.0 ppm (C-H), 121.0 ppm (C), 109.0 ppm (C-H) indicating the chloroquinoline moiety. Literature has shown that carbon peaks of unreacted 4,7-dichloroquin are observed at 149.8 ppm (C=N), 147.3 ppm (C), 142.5 ppm (C-N), 132.8 ppm (C-Cl), 126.7 ppm (C-H), 126.5 ppm (C-H), 125.5 ppm (C-H) , 124.4 ppm (C), 122.4 ppm (C-H) respectively.[51]

Table 4: 4-Amino quinoline compounds

Compound code	Percentage Yield (%)	Melting point (literature) (°C)	Distinctive ^{13}C NMR peaks (ppm)
31	77	136-140 (131-132)	109 (C_c-H)
32	94	168-170 (160-162)	99 (C_c-H)

2.6 Addition of 4-piperazinoquinoline unto monoamino-substituted dichloro-1, 3, 5-triazine.



Scheme 7: General reaction scheme for the addition of 4-piperazinoquinoline unto mono-substituted chloro-1, 3, 5-triazine

Compounds with a piperazine as a linker (**33-36**) were obtained from a reaction of mono-amino dichloro-1, 3, 5-triazines (**22-25**) and one molar equivalent of 4-piperazino-7-chloroquinoline (**32**) under reflux by mixture of MeOH and THF 1:1 for 72 hours. Compounds were obtained in good yields as illustrated in **table 5** below. Envisaged compounds **33-36** were confirmed by IR, NMR and MS spectroscopies. IR spectra of all our compounds were characterized by the absence of N-H stretch peak at 3253 cm^{-1} confirming the consumption of 4-piperazino-7-chloroquinoline. ^1H NMR spectra of our desired products were characterized by the disappearance of the NH peaks, which was observed at 2.97 ppm in the in the ^1H NMR spectrum of 4-piperazino-7-chloroquinoline. ^1H NMR spectrum of compound **33** showed two triplets (one at 3.46 ppm accounting for four protons and another at 1.98 ppm accounting for two protons) and a multiplet at 2.87 ppm accounting for four protons. These signals confirm the presence of the piperadine moiety of compound **33**. Two triplets and a multiplet in compound **22** were observed at 3.81 ppm, 1.64 ppm and 1.59 ppm respectively. Moreover this, two more triplets accounting for two protons

each were observed at 3.07 ppm and 2.94 ppm confirming the presence of piperazine moiety in our compound **33**. Piperazine moiety triplets peak of starting material compound **32** were observed at 3.30ppm and 3.08 ppm. Also there was an appearance of five methine protons indicating the 7-chloroquinoline moiety of compound **33** at 8.68 ppm, 8.21 ppm, ppm 8.13 ppm, 7.64 and 7.11 ppm.

Compound **34** showed appearance of two triplets accounting for four protons each at 4.10 ppm and 3.60 ppm. These signals confirm the presence of the morpholine moiety of compound **34.** The two triplets of the methylene protons (accounting for four protons each) in compound **23** were observed at 3.82 ppm and 3.69 ppm respectively. Moreover this, two more triplets accounting for two protons each were observed at 4.18 ppm and 3.66 ppm confirming the presence of piperazine moiety in our compound **34**. Piperazine moiety triplet peaks of starting material compound **32** were observed at 3.30 ppm and 3.08 ppm. Also there was an appearance of four doublets and one doublet of a doublet accounting for one proton indicating the five methine protons of 7-chloroquinoline moiety of compound **34** at 8.68 ppm, 8.21 ppm, ppm 8.16 ppm, 7.65 ppm and 7.19 ppm respectively.

Compound **35** showed one triplet accounting for four protons and a quartet accounting for six protons at 3.16 ppm and 1.13 respectively. These signals confirm the presence of diethylamine moiety of compound **35**. The triplet of the methylene protons (accounting for six protons) and the quartet of the methyl protons (account for four proton) in compound **24** were observed at 3.54 ppm and 1.30 ppm respectively. Moreover this, two more triplets accounting for two protons each were observed at 4.00 ppm and 2.57 ppm confirming the presence of piperazine moiety in our compound **35**. Piperazine moiety triplets' peaks of starting material compound **32** were observed at 3.30 ppm and 3.08 ppm. Also there was an appearance of four doublets and one doublet of a doublet accounting for one proton each indicating the five methine protons of 7-chloroquinoline moiety of compound **35** at 8.65 ppm, 7.97 ppm, ppm 7.90 ppm, 7.40 ppm and 6.81 ppm respectively.

Compound **36** showed appearance of one septet accounting for two protons and a doublet accounting for twelve protons each at 3.24 ppm and 1.26ppm respectively. These signals confirm the presence of diisopropylamine moiety of compound **36**. The septet of the methine proton (accounting for two protons) and the doublet of the two protons (account for twelve protons) in starting material **25** were observed at 4.42 ppm and 1.27 ppm respectively. Moreover this, two

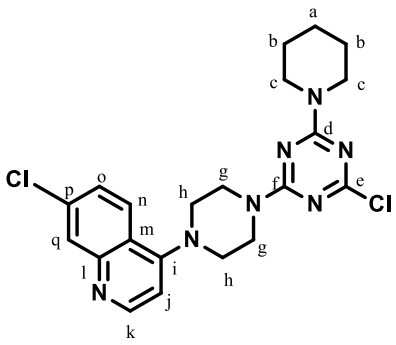
more triplets accounting for two protons each were observed at 4.00 ppm and 2.58 ppm confirming the presence of piperazine moiety in our compound **36**. Piperazine moiety triplets peak of starting material compound **32** were observed at 3.30 ppm and 3.08 ppm. Also there was an appearance of four doublets and one doublet of a doublet accounting for one proton deach indicating the five methine protons of 7-chloroquinoline moiety of compound **36** at 8.67 ppm, 7.99 ppm, ppm 7.93 ppm, 7.40 ppm and 6.78 ppm respectively.

^{13}C NMR spectra were more revealing about our envisage products. ^{13}C NMR spectra of all aminodichloro-1, 3, 5-triazine (**21-25)** used starting material showed two quaternary carbon peaks at ~169 ppm (2x C-Cl) and ~163 ppm (C-N). ^{13}C NMR spectra of all our compounds **33-36** showed three quaternary carbon peaks at ~169 ppm (C-Cl) ~164 ppm (C-N), ~163 ppm (C-N) due to the triazine moiety having three different substituents. All the three observed peaks at ~169 ppm (C-Cl), ~164 ppm (C-N $_{quin}$), ~163 ppm (C-N $_{amines}$) were roughly the same size (equal intensities). Specific peaks observed for compounds **33-36** are indicated in **table 5**. ^{13}C NMR spectra of desired compounds also showed peaks in the aliphatic, heteratomic to aromatic regions. Compound **33** showed seventeen carbon peaks, three methylene carbon peaks at 49.0 ppm, 39.3 ppm and 25.5 ppm confirming attachment of piperadinodichloro-1, 3, 5-triazine (**22)** onto 4-piperazino-7-chloroquinoline **32**. The unreacted piperadinodichloro-1, 3, 5-triazine (**22)** methylene carbon peak were observed at 45.2 ppm, 25.6 ppm and 24.1 ppm**.** eleven peaks were observed at the heteroatomic-aromatic region at 158.0 ppm (C=N), 149.0 ppm (C), 146.0ppm (C-N), 144.0 ppm (C-Cl), 136.0 ppm (CH), 126.0 ppm (C-H), 125.0 ppm (C-H), 120.0 ppm (C), 107.0 ppm (C-H) 51.3 ppm (2 x CH_2), 42.9 ppm (2 x CH_2), indicating the presence of reacted 4-piperazino-7-chloroquinoline moiety. Unreacted 4-piperazino-7-chloroquinoline peaks were observed at 157.0 ppm (C=N), 152.0 ppm (C), 150.2 ppm (C-N), 133.0 ppm (C-Cl), 128.0 ppm (CH), 126.0 ppm (C-H), 126.0 ppm (C-H), 121.0 ppm (C), 109.0 ppm (C-H), 53.5 (2 x CH_2), 45.9 (2 x CH_2). The remaining three quaternary carbon triazine peak were observed at 169.0 (C-Cl), 164.0 (C-N_{amines}) the most important quaternary carbon peaks is the one observed at 164.1 ppm containing triazine bond to nitrogen bonded to quinoline since unreacted aminodichloro-1, 3, 5-triazine (**22)** starting material shows its two quaternary carbon peaks at ~170.0 ppm and ~163.0 ppm

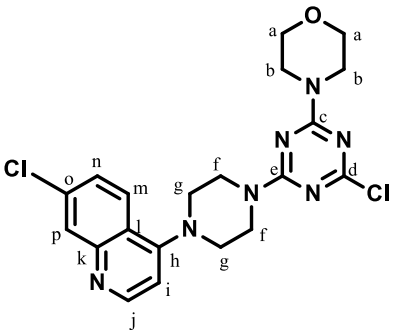
Compound **34** showed sixteen carbon peaks, two methylene carbon peaks on the heteroatomic region at 51.3 ppm and 30.8 ppm confirming attachment of morpholine dichloro-1, 3, 5-triazine (**23)** onto 4-piperazino-7-chloroquinoline **32**. The two methylene carbon peaks of unreacted morpholine dichloro-1, 3, 5-triazine (**23)** were observed at 66.3 ppm and 44.4 ppm**.** Eleven peaks were observed at the heteroatomic-aromatic region each at 158.0 ppm (C=N), 145.0 ppm (C), 143.0 ppm (C-N), 136.0 ppm (C-Cl), 128.0 ppm (CH), 126.0 ppm (C-H), 126.0 ppm (C-H), 122.0 ppm (C), 107.0 ppm (C-H) 67.4 ppm (2 x CH_2), 51.3 ppm (2 x CH_2), indicating the presence of reacted 4-piperazino-7-chloroquinoline moiety. Carbon peaks of unreacted 4-piperazino-7-chloroquinoline was observed at 157.0 ppm (C=N), 152.0 ppm (C), 150.2 ppm (C-N), 133.0 ppm (C-Cl), 128.0 ppm (CH), 126.0 ppm (C-H), 126.0 ppm (C-H), 121.0 ppm (C), 109.0 ppm (C-H), 53.5 (2 x CH_2), 45.9 (2 x CH_2). The remaining three carbon quartenary triazine peak were observed at 169.0 (C-Cl), 164.0 (C-N_{amines}) the most important quaternary carbon peak is the one observed at 164.1 ppm containing triazine bond to nitrogen bonded to quinoline since unreacted aminodichloro-1, 3, 5-triazine **(23)** starting material shows its two quaternary carbon peaks at 170.0 ppm and 164.0 ppm

Compound **35** showed sixteen carbon peaks, one methylene and one methyl carbon peaks on the aliphatic region each at 43.2 ppm and 13.2 ppm respectively confirming attachment of diethylamine dichloro-1, 3, 5-triazine (**24)** onto 4-piperazino-7-chloroquinoline **32**. The unreacted diethylamine dichloro-1, 3, 5-triazine (**24)** were observed at 42.4 ppm and 12.5 ppm**.** eleven peaks were observed at the aliphatic-aromatic region each at 156.0 ppm (C=N), 151.0 ppm (C), 149.0 ppm (C-N), 134.0 ppm (C-Cl), 128.0 ppm (CH), 126.6 ppm (C-H), 124.0 ppm (C-H), 122.0 ppm (C), 107.0 ppm (C-H) 67.4 ppm (2 x CH_2), 52.0 ppm (2 x CH_2), respectively indicating the presence of reacted 4-piperazino-7-chloroquinoline moiety. Unreacted 4-piperazino-7-chloroquinoline was observed at 157.0 ppm (C=N), 152.0 ppm (C), 150.2 ppm (C-N), 133.0 ppm (C-Cl), 128.0 ppm (CH), 126.0 ppm (C-H), 126.0 ppm (C-H), 121.0 ppm (C), 109.0 ppm (C-H), 53.5 (CH_2), 45.9 (CH_2) the remaining three quaternary triazine peak were observed at 169.0(C-Cl), 163.0 (C-N_{amines}) the most important quaternary carbon peak is the one observed at 164.0 ppm containing triazine bond to nitrogen bonded to quinoline since unreacted aminodichloro-1, 3, 5-triazine (**24)** starting material shows its two quaternary carbon peaks at 170 ppm and 163.0 ppm.

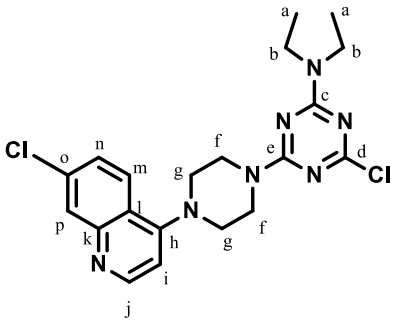
Compound 36 showed sixteen carbon peaks, one methine and one methyl carbon peaks on the aliphatic region each at 45.8 ppm and 20.2 ppm respectively confirming attachment of diethylamine dichloro-1, 3, 5-triazine (**25)** onto 4-piperazino-7-chloroquinoline **32**. The unreacted diethylamine dichloro-1, 3, 5-triazine (**25)** were observed at 42.5 ppm and 15.0 ppm**.** eleven peaks were observed at the aliphatic-aromatic region each at 156.0 ppm (C=N), 151.0 ppm (C), 150.0 ppm (C-N), 135.0 ppm (C-Cl), 128.0 ppm (CH), 126.4 ppm (C-H), 124.0 ppm (C-H), 121.0 ppm (C), 109.0 ppm (C-H) 67.4 ppm (2 x CH_2), 52.0 ppm (2 x CH_2), respectively indicating the presence of reacted 4-piperazino-7-chloroquinoline moiety. Unreacted 4-piperazino-7-chloroquinoline was observed at 157.0 ppm (C=N), 152.0 ppm (C), 150.2 ppm (C-N), 133.0 ppm (C-Cl), 128.0 ppm (CH), 126.0 ppm (C-H), 126.0 ppm (C-H), 121.0 ppm (C), 109.0 ppm (C-H), 53.5 (CH_2), 45.9 (CH_2) the remaining three quaternary triazine peak were observed at 168.7(C-Cl), 163.0 (C-N_{amines}) the most important quaternary carbon peak is the one observed at 164.0 ppm containing triazine bond to nitrogen bonded to quinoline since unreacted aminodichloro-1, 3, 5-triazine (**25)** starting material shows its two quaternary carbon peaks at 169.0 ppm and 164.0 ppm.



33



34



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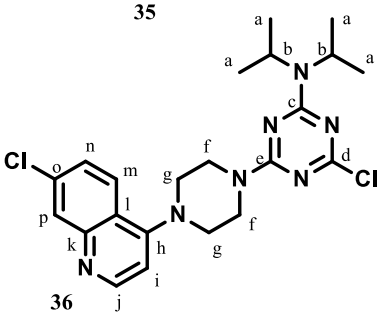
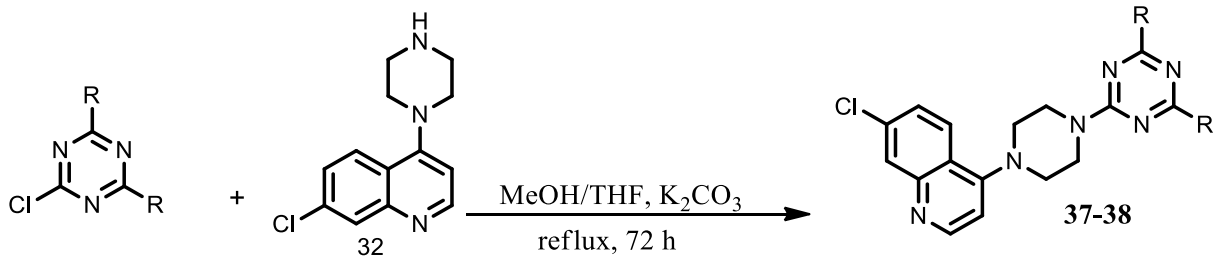


36

Table 5: Addition of 4-aminoquinoline onto mono substituted 1, 3, 5-triazine compounds

Compound code	MS Calculated (found) m/z	Percentage Yield (%)	Melting point (°C)	Distinctive ^{13}Cnmr peaks (ppm)
33 R= piperidine	-	72	125-127	169(C_e-Cl), 164(C_d-N), 164(C_f-Cl),
34 R= morpholine	446.3301 (455.003)	80	136-138	169(C_d-Cl), 164(C_e-N), 163(C_f-Cl),
35 R= diethylamine	432.3501 (432.7001)	65	188-190	169(C_d-Cl), 164(C_e-N), 163(C_f-Cl),
36 R= diisopropylamine	460.4010 (459.0967)	76	184-186	168(C_d-Cl), 164(C_e-N), 163(C_f-Cl),

2.7 Addition of 7-chloro-4-piperazin-1-ly) quinoline unto di-substituted 1, 3, 5-triazine.



Scheme 8: General reaction scheme for the addition of 7-chloro-4-piperazin-1-ly) quinoline unto di-substituted 1, 3, 5-triazine.

Compounds with a piperazine as linker (**37, 38**) were also obtained from a reaction of diamino chloro-1, 3, 5-triazine (**26-27**) and one molar equivalent of 4-piperazino-7-chloroquinoline (**32**) under reflux for 72 hours. Both the desired compounds were obtained in good yield as illustrated in table 6. Envisaged compounds were confirmed by IR, NMR and MS spectroscopies. IR spectra of all our compounds were characterized with the absence of N-H stretch peak at 3253 cm^{-1} confirming the consumption 4-piperazino-7-chloroquinoline. ^{1}H NMR spectra of the desired compounds were characterized by appearance of peaks in the aliphatic-aromatic region. . ^{1}H NMR spectrum of compound **37** showed two triplets one at 3.56 ppm and another at 1.94 ppm both accounting to eight protons respectively. These signals confirm the presence of the pyrrolidine moiety of compound **37**. Two triplets in compound **26** were observed at 3.44 ppm, 1.93 ppm and 1.59 ppm respectively. Moreover this, two more triplets accounting for two protons each were

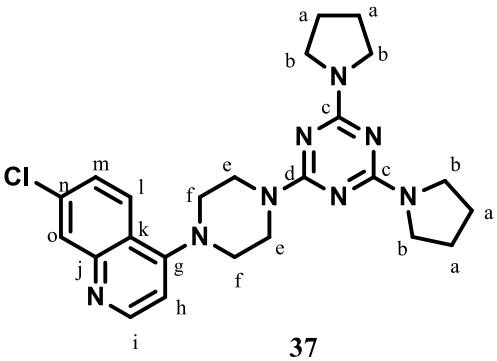
observed at 4.08 ppm and 3.24 ppm confirming the presence of piperazine moiety in our compound **37**. Piperazine moiety triplets peak of starting material compound **32** were observed at 3.30ppm and 3.08 ppm. Also there was an appearance of five methine protons indicating the 7-chloroquinoline moiety of compound **37** each at 8.73 ppm, 8.06 ppm, ppm 8.03 ppm, 7.46 and 6.85 ppm respectively.

^{1}H NMR spectrum of compound **38** showed two triplets (one at 3.68 ppm accounting to eight protons and another at 1.60 ppm accounting to four protons) and a multiplet at 3.08 ppm accounting for eight protons. These signals confirm the presence of the piperadine moiety of compound **38**. Two triplets and a multiplet in compound **27** were observed at 3.65 ppm, 1.58 ppm and 1.51 ppm respectively. Moreover this, two more triplets accounting for two protons each were observed at 3.95 ppm and 3.19 ppm confirming the presence of piperazine moiety in our compound **38**. Piperazine moiety triplets peak of starting material compound **32** were observed at 3.30ppm and 3.08 ppm. Also there was an appearance of five methine protons indicating the 7-chloroquinoline moiety of compound **38** each at 8.76 ppm, 8.12 ppm, ppm 8.00 ppm, 7.56 and 7.02 ppm respectively. Generally for compound 33-36 Research has shown that the proton peaks of unreacted 4-piperazino-7-chloroquinoline each at 3.34 ppm, 2.79 ppm, 8.55 ppm, 8.05 ppm, 7.75 ppm, 7.28 ppm and 6.73 ppm respectively.

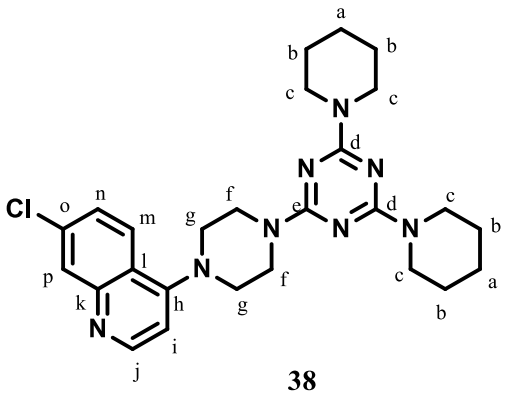
^{13}C NMR spectra of both final compounds were more revealing about our envisage products. An unreacted cyanuric chloride would show one peak at 153 ppm in the ^{13}C NMR spectrum. ^{13}C NMR spectra of all aminodichloro-1, 3, 5-triazine (**21-25)** showed two peaks at ~169 ppm and ~163 ppm. ^{13}C NMR spectra of all 4-amino compound with aminodichloro-1,3,5-triazine showed three peaks at ~169 ppm ~164 ppm , ~163 ppm. Moreover this, desired compounds (37 and 38) ^{13}C NMR spectra showed two peaks at ~165 ppm and ~163 ppm with disappearance of C-Cl signal at ~169. Distinctive peaks for compounds **37-38** are indicated in table 7. Also ^{13}C NMR of compounds **37** and **38** showed peaks in the aliphatic to hetero regions. Compound **37** showed thirteen peaks, four methylene carbon peaks on the aliphatic region each at 52.3 ppm, 45.8 ppm,43,0 ppm and 25.3 ppm confirming attachment of di-pyrrrolidinochloro-1,3,5-triazine (**21-25)** onto 4-piperazino-7-chloroquinoline. The remaining nine peaks were observed at the aromatic region each at 157.0 ppm (C=N), 151.0 ppm (C), 150.0 ppm (C-N), 134.0 ppm (C-Cl), 128.0

ppm(CH) , 126.0 ppm (C-H), 125.0 ppm (C-H), 121.0 ppm (C) and 109.0 ppm (C-H) indicating the presence of 7-chloroquinoline.

Compound **38** showed fourteen peaks, five methylene carbon peaks on the aliphatic region each at 52.1 ppm, 43.9 ppm, 43.1 ppm, 25.8ppm and 24.9 ppm confirming attachment of di-piperadinochloro-1, 3, 5-triazine (**21-25)** onto 4-piperazino-7-chloroquinoline. The remaining nine peaks were observed at the aromatic region each at 156.0 ppm (C=N), 151.0 ppm (C), 150.0 ppm (C-N), 134.0 ppm (C-Cl), 128.0 ppm (CH), 126.0 ppm (C-H), 126.0 ppm (C-H), 121.0 ppm (C) and 109.0 ppm (C-H) indicating the presence of 7-chloroquinoline.



37

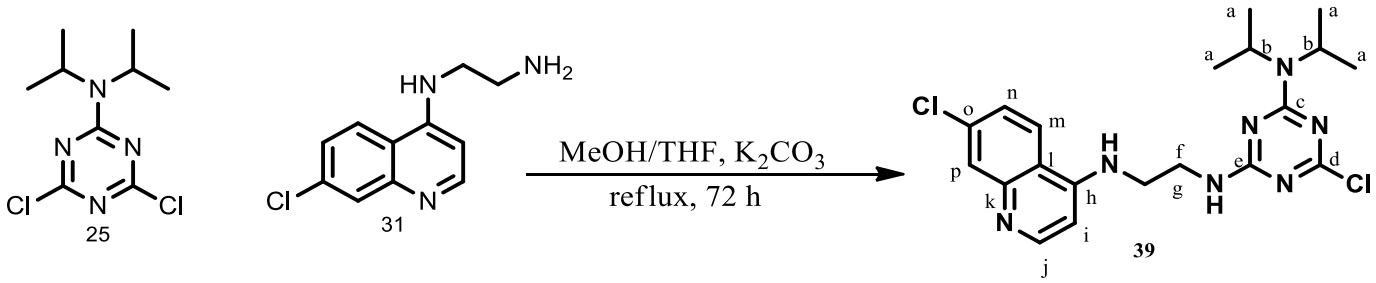


38

Table 6: Addition of 4-piperazinoquinoline unto di-substituted 1, 3, 5-triazine compounds

Compound code	Percentage Yield (%)	Melting point (^{o}C)	Distinctive ^{13}Cnmr peaks (ppm)
37 R= pyrrolidine	76	189-190	165(C_d-Cl), 163(2 x C_c-N)
38 R= piperidine	71	199-201	165.5(C_e-Cl), 165.0(2 x C_d-N)

2.8 Addition of *N*^{1}-(7-chloroquinolin-4-yl) ethane-1, 2-diamine unto mono-substituted 1, 3, 5-triazine



Scheme 9: General reaction scheme for the addition of N^{1}-(7-chloroquinolin-4-yl) ethane-1, 2-diamine unto mono-substituted 1, 3, 5-triazine.

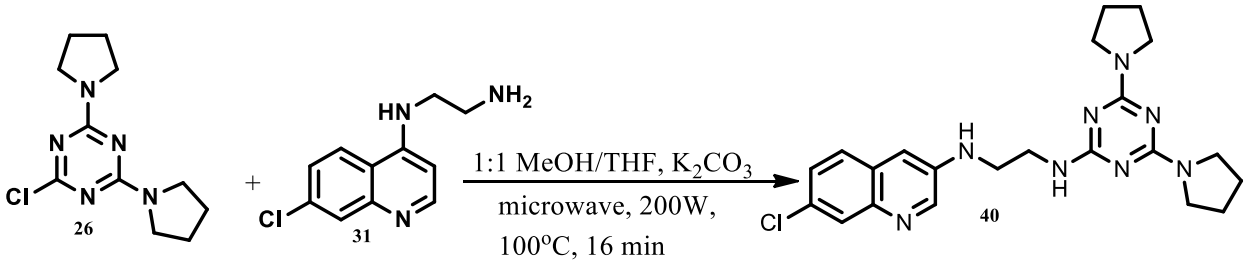
Compound with ethylene diamine as linker was obtained from a reaction of mono-amino chloro-1, 3, 5-triazine compound (**25**) and one molar equivalent 7-chloro-4-ethylenediamine (**31**) under reflux for 72 hours. Compound 39 was obtained in good yield, as illustrated in table 7. It was confirmed by NMR spectroscopies. ^{1}H NMR spectrum of the desired product was characterized by appearance of peaks in the aliphatic-aromatic region.

Compound **39** showed appearance of one septet accounting for two protons and a doublet accounting for twelve protons each at 2.63 ppm and 1.29 ppm respectively. These signals confirms the presence of diisopropylamine moiety of compound **36**. The septet of the methine proton (accounting for two protons) and the doublet of the methyl protons (account for twelve protons) in compound **25** were observed each at 4.42 ppm and 1.27 ppm respectively. Moreover this, two

more triplets accounting for two protons each were observed at 5.00 ppm and 3.26 ppm confirming the presence of ethylenediamine moiety in our compound **39**. ethylenediamine moiety triplets peaks of starting material compound **31** were observed at 3.26 ppm and 2.84 ppm. Also there was an appearance of four doublets and one doublet of a doublet accounting for five protons indicating the methine protons of 7-chloroquinoline moiety of compound **39** each at 9.68 ppm, 8.69 ppm, ppm 8.51 ppm, 8.12 and 6.89 ppm respectively. the unreacted 4-ethylenediamino-7-chloroquinoline each at 8.39 ppm, 8.30 ppm, 7.78 ppm, 7.45 ppm, 6.49 ppm, 3.26 ppm, 2.84 ppm respectively.

Compound 39 showed sixteen peaks, two methylene, one methine and one methyl carbon peaks on the aliphatic region each at 67.9 ppm ppm, 52.0 ppm, 45.8 ppm and 20.2 ppm confirming attachment of diisoproply aminodichloro-1, 3, 5-triazine (**25)** onto 4-ethylenediamine-7-chloroquinoline **31.** The remaining nine peaks were observed at the aromatic region each 156.0 ppm (C-Cl), 143.0 ppm (C-N), 143.0 ppm (C-C), 142.0 ppm(C-C), 139.0 ppm (C-C), 138.4 ppm (CH), 121.0 ppm (CH), 119.0ppm (CH), 98.1 ppm (CH), 42.9 ppm (2 x CH_2) and 20.2 ppm (4 x CH_3).indicating the presence of 7-chloroquinoline.distintive peaks of compound 39 are indicated in table 7. the remaining two quaternary triazine peak were observed at 169.0(C-Cl), 163.0(C-N_{amines}) the most important quaternary carbon peak is the one observed at 165.0 ppm containing triazine bond to nitrogen bonded to quinoline since unreacted aminodichloro-1, 3, 5-triazine (**21-25)** starting material shows its two quaternary carbon peaks at ~169 ppm and ~163 ppm.

2.9 Addition of N^1-(7-chloroquinolin-4-yl) ethane-1, 2-diamine unto di-substituted 1, 3, 5-triazine



Scheme 10: General reaction scheme for the addition of N1-(7-chloroquinolin-4-yl) ethane-1, 2-diamine unto di-substituted 1, 3, 5-triazine.

Compound with ethylene diamine as linker was obtained from a reaction of di-pyrrolidine chloro-1, 3, 5-triazine compound (**25**) and one molar equivalent 7-chloro-4-ethylenediamine (**31**) using the microwave. Compound 40 was obtained in good yield, as illustrated in table 7. 40 was confirmed by NMR spectroscopy. ^{1}H NMR spectra of our desired product was characterized by appearance of peaks in the aliphatic-aromatic region. ^{1}H NMR spectrum of compound 40 showed appearance of two broad singlet peaks, four triplets, accounting for six protons. Each was observed at 4.90 ppm, 4.70 ppm, 3.57 ppm, 3.35 ppm, 3.10 ppm and 1.29 ppm. The two triplets indicated the two protons of pyrrolidine moiety whereas the other remaining four protons indicated the 7-chloro-4-ethylenediamine moiety of compound **40**. Also there was an appearance of five methine protons indicating the 7-chloroquinoline moiety of compound **40**. Each observed at 8.39 ppm, 8.33 ppm, ppm 7.79 ppm, 7.42 and 6.55 ppm respectively.

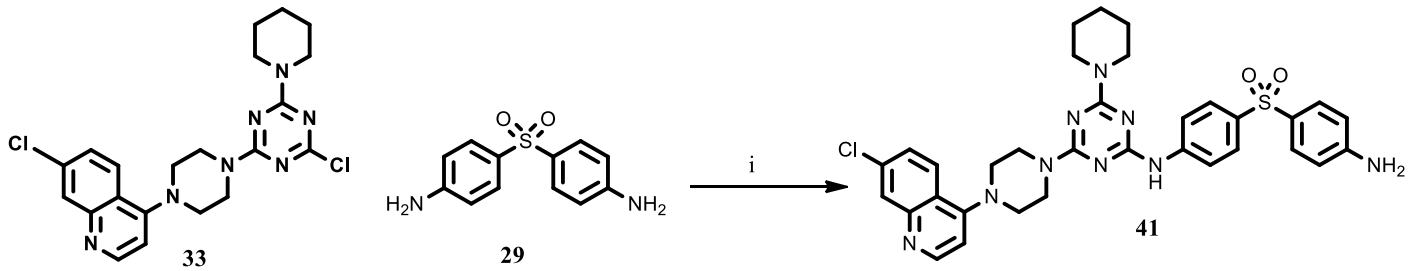
Compound **40** ^{13}CNMR showed sixteen peaks in the aliphatic to aromatic region. In the aliphatic region four methylene carbon peaks were observed each at 46.4 ppm ppm , 39.6 ppm, 37.9 ppm and 25.2 ppm confirming attachment of di-pyrrolidino-chloro-1,3,5-triazine (**26)** onto 4-ethylendiamine-7-chloroquinoline**..** The remaining nine peaks were observed at the aromatic region each at (C=N) 152.0 ppm, (C-H)150.0ppm (C), 149.0 ppm (C-Cl), 136.0 ppm (CH) , 134.0 ppm (CH) , 127.0 ppm (CH), 124 ppm (C), 117 ppm (C) and 99.2 ppm (CH). Unreacted 4-etylenediamine-7-chloroquinoline was found to have eleven peaks each at ~46.5 ppm and ~40.4 ppm. at (C=N) 156.0 ppm, (C)150.0 ppm, (C-N)149.1ppm, (C-Cl)133.3 ppm, (CH) 127.0ppm, (C-H)124.1 ppm, (C-H)124.0 ppm,), 117 (C), (C-H) 99.1.

Proton NMR data of compound **40** showed that there is a disappearance of one proton from NH_2 broad singlet peaks which was initially assigned to two proton in the aliphatic region, now its showed being integrated to one proton at ~ 2-3 ppm which indicates of the presence of NH proton instead of NH_2 ones. The NH peak is also observed to have shifted a bit downfield due to aromatic shielding of the triazine ring moiety. Carbon NMR showed the appearance of new distinctive peak ~165 ppm representing C-N bond. The reduction of C-Cl peak intensity was observed which, therefore confirms the substitution of the second chlorine with 4-aminoquinoline.

Table 7: Addition of 4-ethylenediamino-quinoline unto amino-substituted chloro- 1, 3, 5-triazine compounds

Compound code	Percentage Yield (%)	Melting point (^oC)	Distinctive ^{13}Cnmr peaks (ppm)
39	65	188-190	169(C_c-Cl), 165(C_d-N), 163(C_b-N)
40	93	205-207	165.5(C_d-Cl), 163.0(C_c-N)

2.10 Hybridizing mono-substituted triazine with dapsone



(i) 1:1 MeOH / THF, silica-gel, microwave, 300W, 100 ^oC, 2 min.

Scheme 11: General reaction scheme for hybridizing of mono-piperadino substituted-1,3,5- triazine with dapsone

Compound **41** was obtained from a reaction of 7-chloro-4-(4-4-(chloro-6-(piperadin-1-yl)-1, 3, 5-triazin-2-yl) piperazin-1-yl) quinoline and one molar equivalent dapsone using the microwave. Compound 41 was obtained in good yield 94%. **41** was confirmed by IR and NMR spectroscopies. IR spectra of compound **41** was characterized by the presence of N-H stretch peak at 3221 cm^{-1} confirming the consumption of primary dapsone amine linker to form secondary one ^{1}H NMR spectra of our desired product was characterized by appearance of peaks in the aliphatic-aromatic region. ^{1}H NMR spectra of compound **41** showed appearance of two broad singlet peaks, four triplets, quintet accounting for six aliphatic protons each at 5.5 ppm, 4.70 ppm, 3.46 ppm, 3.07 ppm, 2.94 ppm, 2.88 and 1.99 ppm. The three triplets indicated the two protons of piperadine moiety whereas the other two proton indicated the 7-chloro-4-piperazino moiety and last two are from dapsone NH moiety of compound **41**. Also there was an appearance of nine methine protons in the aromatic region protons indicating the 7-chloroquinoline and dapsone moieties of compound

41. Each was observed at 8.66 ppm, 8.21 ppm, 8.13ppm 7.87 ppm, 7.79, 764 ppm, 7.5 ppm, 7.11 ppm and 6.77 ppm respectively. Compound 41 was formed because instead of obtaining three equivalent dapsone protons, appearance of three extra peaks is observed confirming attachment of dapsone to triazine moiety

Compound **40** ^{13}CNMR showed 25 peaks, in the aliphatic to hetero atomic region. In the aliphatic region five methylene carbon peaks were observed. Each at 56.2 ppm 45.2 ppm, 39.1 ppm, 33.0 ppm and 25.5 ppm confirming attachment of piperadine to cyanuric chloride and another two confirming the attachment of 4-piperazino-7-chloroquinoline unto the cyanuric. The remaining 17 peaks were observed at the aromatic region each at 164.0 ppm (C-N), 163.0 ppm (C-N),162.0 ppm (C-N) 152.0 ppm (C-Cl), 150.0 ppm (C-N), 138.0 ppm (C-C), 135.0 ppm (C-C), 129.0 ppm (CH), 129.0 ppm(CH), 128.0 ppm (CH), 128.0 ppm (CH), 127.0 ppm (CH), 126.0 ppm (2 x CH), 119 ppm (2x CH) 117 ppm (2 x CH) 114 ppm (2x CH) confirming dapsone and 4-piperazino-7-chloroquinoline being attached unto the cyanuric chloride. General information: unreacted 4-piperazino-7-chloroquinoline was found to have eleven peaks each at ~46.5 ppm and ~40.4 ppm. at (C=N) 156.0 ppm, (C)150.0 ppm, (C-N)149.1ppm, (C-Cl)133.3 ppm, (CH) 127.0 ppm, (C-H)124.1 ppm, (C-H)124.0 ppm, General information: unreacted dapsone was found to have peaks each at 154 ppm, 150 ppm, 129.53 and 121 ppm.. Carbon NMR showed the appearance of new distinctive peak at ~165 ppm representing C-N bond and reduction in the C-Cl intensity peak which, therefore confirms the substitution of the second chlorine with 4-aminoquinoline.instead of getting four dapsone equivalent peaks we are getting 8 this confirming the formation of the desired compound **41**.

3. Conclusion and future work

This project was aimed at linking different known antimalarial drugs and secondary amines using 1, 3, 5-triazine in an attempt to synthesize novel drugs.We synthesized five Monoamino-substituted dichloro-1, 3, 5-triazine derivatives (**21-25**) utilizing nucleophilic substitution reaction for both branched and cyclic amines these compounds were synthesized from a reaction of cyanuric chloride and one molar equivalant of an amine at 0 ^{o}C. Products were synthesized in average % yield of 82%. Three diamino-chloro-1, 3, 5-triazine (**26-28**) were synthesized from a reaction of cyanuric chloride and two molar equivalant of pyrrolidine, piperadine and morpholine respectively at room temperature. These compound were synthesized in average yield of 87%. Thirdly two triamino-1, 3, 5-triazines (**29 & 30**) were synthesized from cyanuric chloride and three molar equivalants of diethylamine and dapsone respectively under refluxing THF. The compounds were synthesized in average 90% yield.

Nine compounds which are 4-quinoline-like antimalarial drugs (**33-39** were synthesized from 4-amino-7-chloroquinoline and one molar equivalent of compound **22-27**. These compound were synthesized in average yield of 76%. Only one hybrid compounds was synthesized amongst them that is compound **41** synthesized from compound **33** and one molar equivalent of dapsone known antimalarial drug. These 1, 3, 5-triazine and 4-aminoquinoline compound are promising vehicles for anti-malarial treatment and among other applications with the proper choice of linker. Their synthetic route limits harsh reactions conditions, prolonged reaction times. The possibilities are limitless for incorporation of various groups of choice unto this compound to fulfill the application at hand. **In future** the following will be done.

- Incorporate known antimalarial drug to all synthesized 1, 3, 5-triazine derivatives beside triamino-subtituted ones (artemisinin, pyramithamine and trimethoprime).
- Do malarial biological testing for synthesized compounds.

4. EXPERIMENTAL PROCEDURE

4.0 General Procedure

A Bruker Optics 7.0 Alpha fourier transformed **Infrared (FTIR) spectrophotometer** was used to study the functional group and chemical structure of the materials. The absorptions were reported using the wavenumber (cm^{-1}) scale in the 500-4000 cm^{-1} range. **Proton nuclear magnetic resonance (^{1}H NMR; 400 MHz) and carbon nuclear magnetic resonance (^{13}C NMR; 100 MHz)** spectra were recorded in dimethyl sulfoxide (DMSO-d_6) and chloroform ($CDCl_3$) on a Bruker spectrometer. Chemical shifts were reported in a δ scale in ppm and proton peaks were presented in the following order of multiplicity; s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sept = septet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet and br = broad signal. An **Electrothermal 9200 Büchi LABOTEC melting point (B-5400)** apparatus was used to determine the melting points (M.p) of different pure solid compounds ranging from 24-410 ^{o}C.

Merck **Silica gel 60** (particle size 0.063-0.200 mm) was used as the adsorbent for conventional column chromatography, with a silica to compound ratio of 30:1 by mass. The silica was packed into a suitable size column and products were purified using elution process, using suitable solvent ratio mixtures. An analytical **thin-layer chromatography (TLC)** Pre-coated with silica gel 60 F254 aluminum plates (Merck) was performed to monitor reactions and to ensure separation of compounds after column chromatography. Spectroline American **UV (ENF-240C/FE)** with maximum (230V and 0.17A) was used for detection of compounds at 254 nm and **stains** (6 g vanilin. 100 ml ethanol, 1ml H_2SO_4 conc 98 M). A 2013 Büchi **Rotary Evaporator (B-491)** with 1700W power and 220-240 Hz volts was used for removal of solvents and purification of some solvents via distillation process. The compounds prepared were named in the following experimental sections according to IUPAC systematic nomenclature using **Chem Draw 2010** Cambridge software version 12.0.0. An American **CEM Discorver Microwave (908010)** with maximum power of 300W and 6.3A current was used to synthesize some of compounds.

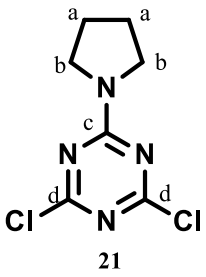
Chemicals used in this project were purchased from the chemical suppliers like Merck and Sigma Aldrich chemical companies. All reagents (cyanuric chloride, diaminodiphenyl sulfone (dapsone), Hünig's base, potassium carbonate, piperazine, morpholine, piperidine, diisopropylamine,

diethylamine, ethylenediamine) were used without further purification. Solvents used were commercial graded materials that were distilled before use. Tetrahydrofuran and *N*, *N*-dimethylformamide were dried from molecular sieves.

4.1 General procedure for mono substitution of 1, 3, 5-triazine.

The amines (1.0 eq) were added drop-wise to a solution of cyanuric chloride (1.0 eq) in dry THF in the presence of K_2CO_3 (1.0 eq) over 5 min at 0 ^oC. The reaction mixture was stirred for a minimum of 2 hours. Progress of the reaction was monitored by TLC analysis using (0.5:9.5) EtOAc/n-Hex as a mobile phase. After the completion of reaction the reaction mixture was poured into ice water then resultant precipitate was obtained and through filtration and filtrate was extracted with ethyl acetate dried over magnesium sulphate before been filtered. Excess solvent was removed on a rotary evaporator to obtain products as solid, which were further purified using silica-gel column chromatography using (0.5:9.5 EtOAc/n-Hex as an eluent.

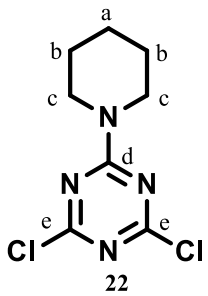
4.1.1 2, 4-dichloro-6-(pyrrolidin-1-yl)-1, 3, 5-triazine



21

Cyanuric chloride (2.09 g, 11.3 mmol), K_2CO_3 (1.57 g, 11.3 mmol) and pyrrolidine (0.89 ml, 11.3 mmol) in THF (30.0 ml) were reacted together to obtain product **21** as a white solid (2.1 g, 91% yield). M.p 86-89 ^oC, literature 80-85 ^oC.[52]IR ν_{max} (cm^{-1}) 2873 (w, C-H stretch), 1448 (s, C=N), 1239 (m, C-N), 788 (m, C-Cl stretch). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm), 3.57 (t, 4H, 2 x C_bH_2, J = 8 Hz), 1.91 (t, 4H, 2 x C_aH_2, J = 9 Hz), ^{13}C NMR (100 MHz, $CDCl_3$): 169 (2 x C_d-Cl), 162 (C_c-N), 47.2 (2 x C_bH_2), 25.0 (2 x C_aH_2). TOF MS (EL+) calculated for $C_7H_8Cl_2N_4$ 219. 0102 found 219.0102

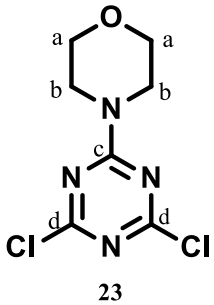
4.1.2 2, 4-dichloro-6-(piperadin-1-yl)-1, 3, 5-triazine



22

Cyanuric chloride (2.03 g, 11.0 mmol), K_2CO_3 (1.52 g, 11.0 mmol) and piperadine (1.07 ml, 11.0 mmol) in THF (30.0 ml) were reacted together to obtain product **22** as a light yellow solid. (2.01g, 79% yield). M.p 144-146 ^oC, literature value 142-143 ^oC.[53] IR ν_{max} (cm^{-1}) 2941 (w, C-H stretch), 1488 (s, C=N stretch), 1257 (m, C-N), 787 (m, C-Cl stretch). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.81 (t, 4H, 2 x C_cH_2, J = 5.4 Hz), 1.64 (t, 4H, 2 x C_bH_2, J = 5.2 Hz), 1.59 (quin, 2H, C_aH_2, J = 6 Hz), ^{13}C NMR (100 MHz, $CDCl_3$); 170 (2 x C_e-Cl), 163 (C_d-N), 45.2 (2 x NC_cH_2), 25.6 (2 x C_bH_2), 24.1 (C_aH_2). TOF MS (EL+) calculated for $C_8H_{10}Cl_2N_4$ 233.1109 found 234.0021

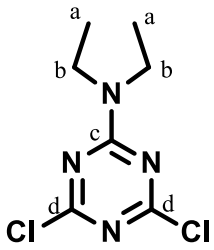
4.1.3 2, 4-dichloro-6-(morpholin -1-yl)-1, 3, 5-triazine



23

Cyanuric chloride (2.00 g, 10.8 mmol), K_2CO_3 (1.49 g, 10.8 mmol) and morpholine (0.93 ml, 10.8mmol) in THF (30.0 ml) were reacted together to obtain product **23** as a white solid that was further washed using hot methanol to obtain a white powder (1.91 g, 87% yield). M.p 163-165 ^oC, literature value 157-158 ^oC [54] IR ν_{max} (cm^{-1}) 2969 (w, C-H stretch), 1456 (s, C=N stretch), 1259 (m, C-N), 787 (s, C-Cl stretch). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.82 (t, 4H, 2 x C_aH_2, J = 4.8 Hz), 3.69 (t, 4H, 2x C_bH_2, J = 4.8 Hz), ^{13}C NMR (100 MHz, $CDCl_3$); 170 (2 x C_d-Cl), 164 (C_c-N), 66.3 (2 x C_aH_2), 44.4 (2 x C_bH_2). TOF MS (EL+) calculated for $C_7H_8Cl_2N_4O$ 235.0706 found 238.0007

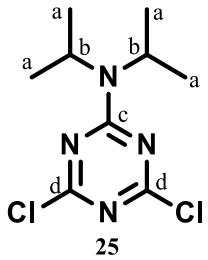
4.1.4 2, 4-dichloro-*N*, *N*-diethyl-1, 3, 5-triazin-2-amine



24

Cyanuric chloride (2.01 g, 10.89 mmol), K_2CO_3 (1.51 g, 10.89 mmol) and diethylamine (1.12 ml, 10.89 mmol) in THF (40 ml) were reacted together to obtain product **24** as a white solid (1.8g, 88% yield). M.p 88-90 ^oC, IR ν_{max} (cm^{-1}) 2985 (w, C-H stretch), 1462 (s, C=N stretch), 1257 (m, C-N), 787 (s, C-Cl stretch).^1H NMR (400 MHz, $CDCl_3$): δ (ppm), 3.54 (q, 4H, 2 x C_bH_2, J = 5.3 Hz), 1.13 (t, 6H, 2 x C_aH_3, J = 5.2 Hz), ^{13}C NMR (100 MHz, $CDCl_3$); 169.0 (2 x C_d-Cl), 163 (C_c-N), 42.4 (2 x C_bH_2), 12.5 (2 x C_aH_3). TOF MS (EL+) calculated for $C_7H_{10}Cl_2N_4$ 221.0871 found 221.9003

4.1.5 2, 4-dichloro-*N*, *N*-diisopropyl-1, 3, 5-triazin-2-amine



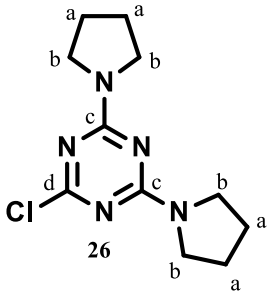
25

Cyanuric chloride (2.03 g, 11.01 mmol), K_2CO_3 (1.52 g, 11.01 mmol) and diisopropylamine (1.50 ml, 11.01 mmol) in THF (40 ml) were reacted together to obtain product **25** as yellow crystals (2.11 g, 90% yield). M.p 104-106 ^oC, IR ν_{max} (cm^{-1}) 2970 (w, C-H stretch), 1380 (s, C=N stretch), 1257 (m, C-N), 787 (s, C-Cl stretch). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm), 4.42 (m, 2H, 2 x C_bH), 1.27 (d, 12H, 4 x C_aH_3, J = 6.8), ^{13}C NMR (100 MHz, $CDCl_3$); 169 (2 x C_d-Cl), 164.0 (C_c-N), 42.5 (2 x C_bH), 15.0 (4 x C_aH_3). TOF MS (EL+) calculated for $C_9H_{14}Cl_2N_4$ 249.1413 found 248.0023

4.2 General procedure for di-substitution of 1, 3, 5-triazine with amines.

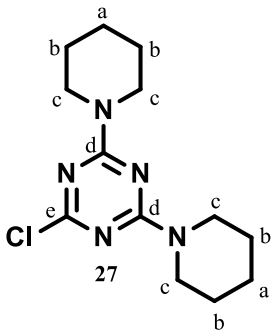
The amines (2.00 eq) were added drop wisely to a solution of cyanuric chloride (1.00 eq) in dry THF in the presence of K_2CO_3 (2.0 eq) over 5 min at 0 ^oC. The reaction mixture was stirred a minimum of 8 hours in room temperature. Progress of the reaction was monitored by TLC analysis using 2:8 MeOH / EtOAc mobile phase. After the completion of reaction the reaction mixture was poured into ice water then resultant precipitate was obtained and through filtration and filtrate was extracted with ethyl acetate dried over magnesium sulphate before been filtered. Excess solvent was removed on a rotary evaporator to obtain products as solid which was purified using silica-gel column chromatography only for those specified.

4.2.1. 2-dichloro-4, 6-di (pyrrolidin-1-yl)-1, 3, 5-triazine



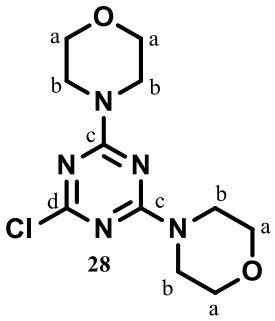
Cyanuric chloride (2.00 g, 10.85 mmol), K_2CO_3 (3.01 g, 21.65 mmol) and pyrrolidine (1.78 ml, 21.65 mmols) in THF(35.0 ml) were reacted together to obtain a solid product that was purified using column chromatograph method (2:8 MeOH / EtOAc) to give product **26** as a creamy white solid (1.50g, 78% yield). M.p 106-109 ^oC, literature value (110-112) ^oC.[55] IR ν_{max} (cm^{-1}) 2868 (w, C-H stretch), 1372 (s, C=N), 1179 (m, C-N), 789 (m, C-Cl stretch). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm), 3.44 (t, 8H, 4 x C_bH_2, J = 8 Hz), 1.93 (t, 8H, 4 x C_aH_2, J = 8 H), ^{13}C NMR (100 MHz, $CDCl_3$); 168.0 (C_d-Cl), 162.6 (2 x C_c-N), 46.4 (4 x C_bH_2), 25.29 (4 x C_aH_2). TOF MS (EL+) calculated for $C_8H_{10}Cl_2N_4$ 253.7312 found 254.7001

4.2.2. 2-dichloro-4, 6-di (piperadin-1-yl)-1, 3, 5-triazine



Cyanuric chloride (2g, 10.85mmol), K_2CO_3 (3.02 g, 21.6 mmol) and piperadine (2.13 ml, 21.6 mmols) in THF (30 ml) were reacted together to obtain a solid product that was purified using column chromatograph method (2:8 MeOH / EtOAc) to give product **27** as a yellow solid (1.5 g, 78 %). M.p 176-178 ^oC, literature value 176-178,[56]IR ν_{max} (cm^{-1}) 2941 (w, C-H stretch), 1488 (s, C=N), 1257 (m, C-N), 787 (m, C-Cl stretch). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm), 3.65 (t, 8H, 4 x C_cH_2, J = 5.4 Hz), 1.58-1.51 (m, 12H, 4 x C_bH_2 +2 x C_aH_2), ^{13}C NMR (100 MHz, $CDCl_3$); 169.0 (C_e-Cl), 164.0 (2 x C_d-N), 44.4 (4 x C_cH_2), 25.8 (4 x C_bH_2), 24.6 (2 x C_aH_2).

4.2.3. 2-dichloro-4, 6-di (morpholine-1-yl)-1, 3, 5-triazine

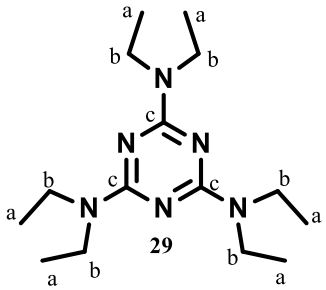


Cyanuric chloride (2.01 g, 10.8 mmol), K_2CO_3 (3.02 g, 21.6 mmol) and morpholine (1.87 ml, 21.6 mmols) in THF (30.0 ml) were reacted together to obtain product **28** as a white solid (1.60 g, 89 % yield). M.p 158-161 ^oC, literature value 154-156,[56] ^oC IR ν_{max} (cm^{-1}) 2918 (w, C-H stretch), 1485 (s, C=N), 1261 (m, C-N), 796 (s, C-Cl stretch). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm), 3.71 (t, 8H, 4 x OC_aH_2, J = 4.7 Hz), 3.63 (t, 8H, 4 x C_bH_2, J = 4.6 Hz), ^{13}C NMR (100 MHz, CDCl3); 169 (C_d-Cl), 164 (2 x C_c-N), 66.5 (4 x C_aH_2), 44.4 (4 x C_bH_2). TOF MS (EL+) calculated for $C_{11}H_{16}ClN_5O$ 285.7300 found 285.0094

4.3 Synthesis of tri-substitution 1, 3, 5-triazine.

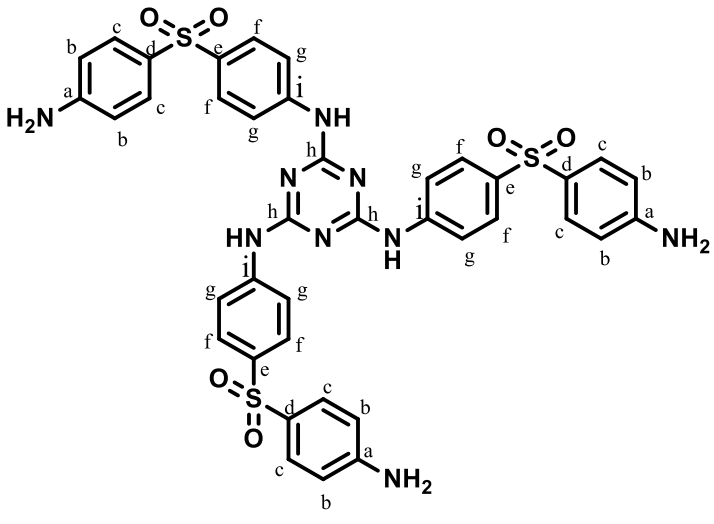
4.3.1. N^2, N^2, N^4, N^4, N^6, N^6-hexaethyl-(2, 4, 6-triamine)-1, 3, 5-triazine

The diethylamine (3 eq) were added drop wisely to a solution of cyanuric chloride (1.0 eq) in dry THF in the presence of K_2CO_3 (3.0 eq) over 5 min at 0 ^oC temperature. The reaction mixture was stirred for a minimum of 24 hours under reflux temperature. Progress of the reaction was monitored by TLC analysis using 2:8 MeOH / EtOAc as a mobile phase After the completion of reaction the reaction mixture was poured into ice water then filtered the solid suspension (if specified) and extracted the liquid suspension with ethyl acetate (2 × 100 ml). Organic extracts were combined and washed with 100 ml water before being dried with magnesium sulphate and filtered. Excess solvent was removed on a rotary evaporator to obtain desired products.



Cyanuric chloride (2.06 g, 11.2 mmol), K_2CO_3 (4.56 g, 33.2 mmol) and diethylamine (2.44 ml, 33. 2 mmol) in THF (45.0 ml) were reacted together to obtain product **29** as a brownish oil (2.80 g, 87 % yield). IR ν_{max} (cm^{-1}) 2929 (w, C-H stretch), 1488 (s, C=N stretch), 787 (s, C-Cl stretch). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.58 (q, 12H, 6 x C_bH_2, J = 6.9 Hz), 1.19 (t, 18H, 6 x C_aH_3, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 160.0 (3 x C_c-N), 36.2 (6 x C_bH_2), 8.8 (6 x C_aH_3). TOF MS (EL+) calculated for $C_{15}H_{30}N_6$ 294.4989 found 295.0013

4.3.2. N^2, N^4, N^6-tris (4-((4-aminophenyl) sulfonyl) phenyl) -2, 4, 6-triamine-1, 3, 5-triazine

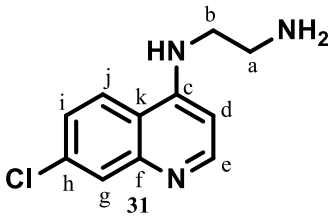


30

Cyanuric chloride (0.51 g, 2.77 mmol), silica-gel (0.51 g) and dapsone (1.90 g, 7.91 mmol) in 50% THF/MeOH were reacted using microwave set at 200W, 81^{o}C for 10 min in a closed reaction vessel condition. Excess solvent was filtered and product **30** was retrieved as a yellow solid (2.2 g, 94 % yield). M.p 288-290 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.87 (d, 6H, 6 x C_fH, J = 8.8 Hz), 7.77 (d, 6H, 6 x C_cH, J = 8.8 Hz), 7.59 (d, 6H, 6 x C_gH, J = 8.4 Hz), 6.77 (d, 6H, 6 x C_bH J = 8 Hz) 5.9 (br s, 3H, NH), 4.3(br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6):164 (3 x C_h-N), 151.0 (3 x C_i-N), 144.0 (3 x C_a-N), 136.1 (3 x C_e-S), 130.0 (3 x C_d-S), 129.0 (6 x C_gH), 127.0 (6 x C_fH), 120.0 (6 x C_cH), 115.0 (6 x C_bH).

4.4 Synthesis of Chloroquinolinyl compounds

4.4.1. Synthesis of N^1-(7-chloroquinolin-4-yl) ethane-1, 2-diamine

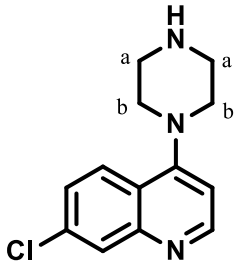


31

4, 7-dichloroquinoline (3.09 g, 15.6 mmol) and ethylenediamine (10.4 ml) were heated under reflux in inert atmosphere for 24 hours. Progress of the reaction was monitored by TLC analysis using 0.5:9.5 MeOH / EtOAc as a mobile phase. The reaction mixture was allowed to cool down to room temperature. The reaction mixture was neutralized by addition of saturated NaOH until

the effervescence disappear. The mixture was extracted with dichloromethane (2× 100 ml, the combined organic layers were washed over water (100 ml) before being dried with magnesium sulphate and then filtered. Excess solvent was removed on a rotary evaporator to obtain a solid product that was further purified with column chromatograph (0.5: 9.5) MeOH / EtOAc), followed by washing using hot methanol. Product **31** was retrieved as a yellow powder (2.65 g, 77% yield). M.p 176-180 ^{o}C, literature 131-132 ^{o}C[56] IR ν_{max} (cm^{-1}) 3238 (w, N-H stretch), 2980 (w, C-H stretch), 114.79 (s, C=N), 1288 (m, C-N), 800 (m, C-Cl stretch). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.39 (d, 1H, C_e-H, *J* = 5.6 Hz), 8.30 (d, 1H, C_h-H, *J* = 9 Hz), 7.78 (d, 1H, C_k-H, *J* = 2 Hz), 7.45 (dd, 1H, C_i-H, *J* = 2, *J* = 9Hz), 6.49 (d, 1H, C_d-H, *J* = 5.6 Hz), 3.26 (t, 2H, C_bH_2, *J* = 5.8 Hz), 3.00 (s, broad, NH) 2.84 (t, 2H, C_aH_2, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, DMSO-d6): 156.0 (C_j-Cl), 150.0 (Cc- N), 149.1 (C_j-C), 133.3 (C_f-C), 127.0 (C_eH), 124.0 (C_kH), 124.0 (C_hH), 117.0 (C_iH), 99.1 (C_dH), 46.5 (C_bH_2), 40.4 (C_aH_2).

4.4.2. Synthesis of 7-chloro-4-(piperazin-1-yl) quinoline



32

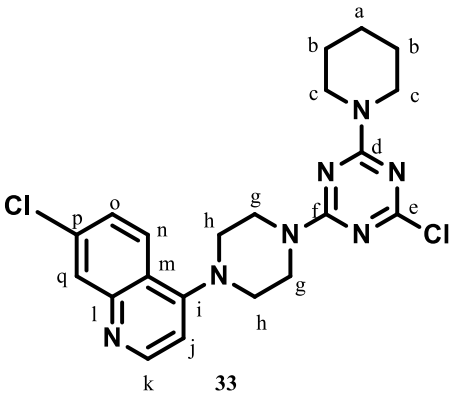
4, 7-dichloroquinoline (5.00 g, 25.2 mmol) and piperazine (10.9 g, 126 mmol) in 1, 4-dioxane were heated under reflux in inert atmosphere for 24 hours. Progress of the reaction was monitored by TLC analysis using 0.5:9.5 MeOH / EtOAc mobile phase. The reaction mixture was allowed to cool down to room temperature. The reaction mixture was neutralized by addition of saturated NaOH until the effervescence disappear. The mixture was extracted with dichloromethane (2× 100 ml, the combined organic layers were washed over water (100 ml) before being dried with magnesium sulphate and then filtered. Excess solvent was removed on a rotary evaporator to obtain a solid product that was purified using column chromatograph (0.5: 9.5) as an eluent MeOH / EtOAc). Product **32** was retrieved as yellow solid (5.30 g, 70% yield). M.p 182-184 ^{o}C, literature 160-162 ^{o}C[56] (IR ν_{max} (cm^{-1}) 3253 (w, N-H stretch), 2993 (w, C-H stretch), 1419 (s, C=N), 1163 (m, C-N), 821 (m, C-Cl stretch). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm), 8.69 (d, 1H, Ce-H, *J* =

4.8 Hz), 8.02 (d, 1H, Ch-H, *J* = 9 Hz), 7.96 (d, 1H, Ck-H, *J* = 2 Hz), 7.54 (dd, 1H, Ci-H, *J* = 2 Hz, *J* = 9 Hz), 6.95 (d, 1H, Cd-H, *J* = 5.2 Hz), 3.30 (t, 4H, 2 x C_bH_2, *J* = 3.6 Hz), 3.08 (t, 4H, 2 x C_aH_2, *J* = 4.8 Hz), 2.97 (s, 1H, NH), ^{13}C NMR (100 MHz, DMSO-d_6); 157 (C_j-Cl,), 152 (C_f-N), 150 (C_c-C), 133 (C_g-C), 128 (C_eH), 126 (C_kH), 126 (C_iH), 121 (C_hH), 109 (C_iH), 53.5 (2 x C_bH_2), 45.9 (2 x C_aH_2).

4.5. General procedure for the synthesis of triazine containing compounds from compound 32

The 7-chloro-4-piperazin-1-ly) quinoline (1eq) was added to a solution of mono-substitued 1, 3, 5-triazine (1eq) with (1:1) MeOH/THF, containing K_2CO_3 (1 eq) the reaction mixture was heated under reflux in an inert atmosphere for 72 hours. After been allowed to cool down to room temperature the mixture was taken up into water and extracted with (2 x 50 ml) of EtOAc organic extract were dried over $MgSO_4$. The organic layer was then filtered excess solvent was removed on a rotary evaporator.

4.5.1 7-chloro-4-(4-(chloro-6-(piperadin-1-yl)-1, 3, 5-triazin-2-yl) piperazin-1-yl) quinoline

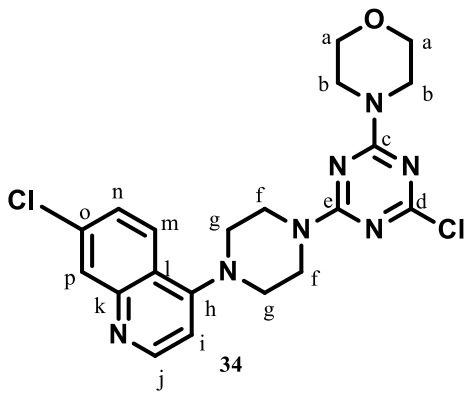


33

7-(chloro-4-piperazin-1-ly) quinoline (**32)** (0.50 g, 1.84 mmols), K_2CO_3 (0.25 g, 1.84 mmol) and 2, 4-dichloro-6-(piperadin-1-yl)-1, 3, 5-triazine **22** (0.43 g, 1.84 mmol) were reacted together in MeOH/THF (10 ml) to obtain product **33** as a yellow solid (0.63 g, 72% yield). M.p 125-127 ^{o}C, IR ν_{max} (cm^{-1}) 2852.72 (w, C-H stretch), 1435 (s, C=N stretch), 1231 (m, C-N), 821 (m, C-Cl stretch). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm), 8.68 (d, 1H, C_k-H, *J* = 6 Hz), 8.21 (d, 1H, Cn-H, *J* = 9.2 Hz), 8.13 (d, 1H, Cq-H, *J* = 4.8 Hz), 7.64 (dd, 1H, Co-H, *J* = 2 Hz, *J* = 9Hz), 7.11 (d, 1H, Cj-H, *J* = 6 Hz), 3.46 (t, 4H, 2 x C_cH_2, *J* = 4.4 Hz), 3.07 (t, 4H, 2 x C_gH_2, *J* = 5.4 Hz), 2.94 (t, 4H, 2 x C_hH_2, *J* = 4.8 Hz), 2.87 (m, 4H, 2 x C_bH_2), 1.98 (t, 2H, C_aH_2, *J* = 4.6 Hz); ^{13}C NMR (100

MHz, DMSO-d_6): 169 (Ce), 164 (Cd), 164 (Cj-N) 158 (Cp), 149 (Cl-N), 146 (Ci), 144 (Cm), 136 (CkH), 126 (CqH), 125 (CoH), 120 (CnH), 107 (CiH), 51.3 (2 x C_hH_2), 49.0 (2 x C_gH_2) 42.9 (2 x C_cH_2), 39.3 (2 x C_bH_2), 25.5 (C_aH_2).

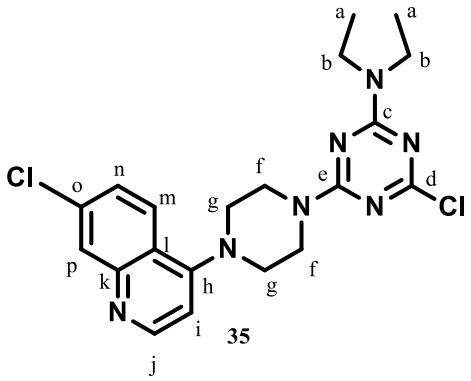
4.5.2 7-chloro-4-(4-4-(chloro-6- (morpholine-1-yl) -1, 3, 5-tirazin-2-yl) piperazin-1-yl) quinoline



34

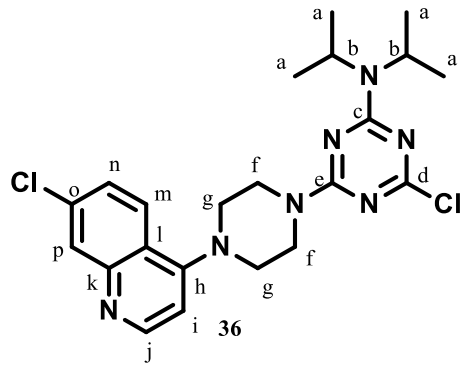
7-(chloro-4-piperazin-1-ly) quinolone **32** (0.50 g, 1.84 mmol), K_2CO_3 (0.24 g, 1.84 mmol) and 2, 4-dichloro-6-(morpholin-1-yl)-1, 3, 5-triazine **23** (0.43 g, 1.84 mmol) were reacted together in MeOH/THF (12 ml) to obtain product **34** as a yellow solid (0.71g, 80% yield). M.p 136-138 ^oC, IR ν_{max} (cm^{-1}) 2852 (w, C-H stretch), 1435 (s, C=N), 1231 (m, C-N), 821 (s, C-Cl stretch). ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.68 (d, 1H, Cj-H, *J* = 6 Hz), 8.21 (d, 1H, Cp-H, *J* = 3 Hz), 8.16 (d, 1H, Cm-H, *J* = 8.4 Hz), 7.65 (dd, 1H, Cn-H, *J* = 2 Hz, *J* = 9 Hz), 7.19 (d, 1H, Ci-H, *J* = 5.6 Hz), 4.10 (t, 4H, 2 x C_bH_2, *J* = 4.2 Hz), 4.18 (t, 4H, 2 x C_fH_2, *J* = 5.3 Hz), 3.66 (t, 4H, 2 x C_aH_2, *J* = 4.4 Hz), 3.60 (t, 4H, 2 x C_gH_2, *J* = 4.8 Hz); ^{13}C NMR (100 MHz, DMSO-d6): 169 (Cd), 164.39 (Ce), 163 (Cc) 158 (Cj-H), 145 (Ch), 143 (Ck), 136 (Co), 128 (Cl), 126 (C p-H), 122 (Cm-H), 119 (Cn-H), 107 (Ci-H), 67.4 (2 x C_aH_2), 51.3 (2 x C_fH_2) 44.3 (2 x C_bH_2), 30.8 (2 x C_gH_2). TOF MS (EL+) calculated for $C_{20}H_{21}Cl_2N_4O$ 446,3301 found 455.0003

4.5.3 4-chloro-*N*, *N*-diethyl-6-(4-(quinolin-4-yl) piperazin-1-yl) -1, 3, 5-triazin-2-amine



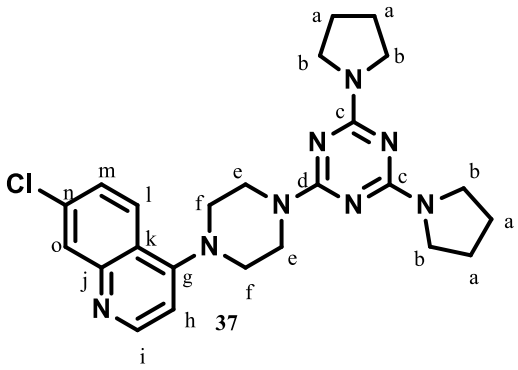
7-(chloro-4-piperazin-1-ly) quinoline **32** (0.51g, 1.85 mmol), K_2CO_3 (0. 26 g, 1.85 mmol) and 2, 4-dichloro-*N*, *N*-diethyl-1, 3, 5-triazin-2-amine **24** (0.41 g, 1.85 mmol) were reacted together in MeOH/THF (10 ml). After consumption of the starting material, the reaction mixture was allowed to cool down to room temperature. Product **35** crashed out as white precipitates and was washed with hot MeOH (10 ml) (0.57g, 65% yield).M.p 188-190 ^oC, IR ν_{max} (cm^{-1}) 2995 (w, C-H stretch), 1441 (s, C=N), 787 (s, C-Cl stretch). ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.65 (d, 1H, Cj-H, *J* = 4 Hz), 7.97 (d, 1H, Cp-H, *J* = 2 Hz), 7.90 (d, 1H, Cm-H, *J* = 9 Hz), 7.40 (dd, 1H, Cn-H, *J* = 2 Hz, J= 9 Hz), 6.81 (d, 1H, Ci-H, *J* = 4 Hz), 4.00 (t, 4H, 2 x C_fH_2, *J* = 4 Hz), 3.16 (t, 4H, 2 x C_gH_2, *J* = 4 Hz), 2.57 (q, 4H, 2 x C_bH_2, *J* = 5 Hz), 1.13 (t, 6H, 2 x C_aH_2, *J* = 5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 169 (Cd), 164 (Ce), 163 (Cc) 156 (Cj-H), 151 (Ch), 149 (Ck), 134 (Co), 128 (Cl), 126.1 (Cp-H), 124.0 (Cm-H), 122.0 (Cn-H), 107 (Ci-H), 67.4 (2 x C_fH_2), 52.0 (2 x C_gH_2) 43.2 (2 x C_bH_2), 13.2 (2 x C_aH_3). TOF MS (EL+) calculated for $C_{20}H_{23}Cl_2N_7$ 432.3501 found 432.7001

4.5.4 4-chloro-*N*, *N*-diisopropyl-6-(4-(quinolin-4-yl) piperazin-1-yl) -1, 3, 5-triazin-2-amine



7-(chloro-4-piperazin-1-ly) quinoline **31** (0.50g, 1.84 mmols), K_2CO_3 (0.24 g, 1.854 mmol) and 2, 4-dichloro-*N*, *N*-diisopropyl-1, 3, 5-triazin-2-amine **25** (0.46 g, 1.84 mmol) were reacted together in MeOH/THF (15.0 ml). After consumption of the starting material, the reaction mixture was allowed to cool down to room temperature. Product **36** crashed out as a white precipitate and was washed with hot MeOH (10 ml) (0.69g, 76% yield). M.p 184-186 ^oC, IR ν_{max} (cm^{-1}) 2995 (w, C-H stretch), 1441 (s, C=N), 1171 (m, C-N), 733 (s, C-Cl stretch). ^1H NMR (400 MHz, DMSO-d6): δ (ppm) 8.67 (d, 1H, Cj-H, *J* = 4 Hz), 7.99 (d, 1H, Cl-H, *J* = 2 Hz), 7.93 (d, 1H, Cm-H, *J* = 9.2 Hz), 7.40 (dd, 1H, Cn-H, *J* = 2 Hz, *J* = 9 Hz), 6.78 (d, 1H, Ci-H, *J* = 4.8 Hz), 4.00 (t, 4H, 2 x C_fH_2, *J* = 4.4 Hz), 3.24 (t, 4H, 2 x C_gH_2, *J* =4.8 Hz), 2.57 (m, 2H, 2 x C_bH), 1.26 (d, 12H, 4 x C_aH_3, *J* = 2.7 Hz), ^{13}C NMR (100 MHz, DMSO-d_6): 168.7 (Cd-Cl), 164.0 (Ce-N), 163.0 (Cc-N) 156.0 (Cj-H), 151.0 (Ch), 150.0 (Ck), 135.0 (Co), 128 (Cl), 126.4 (Cp-H), 124 (Cm-H), 121 (Cn-H), 109 (Ci-H), 67.9 (2 x C_fH_2), 52.0 (2 x C_gH_2), 45.8 (2 x C_bH), 20.2 (4 x C_aH_3). TOF MS (EL+) calculated for $C_{22}H_{27}Cl_2N_7$ 460.4010 found 459.0967

4.5.5 7-chloro-4- (4, 6-di (pyrrolidin-1-yl) -1, 3, 5-triazin-2-yl) piperazin-1-yl) quinoline

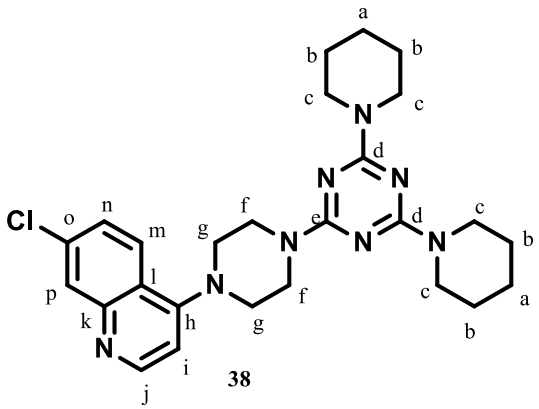


37

Compound **32** (0.50 g, 1.85 mmol), K_2CO_3 (0.26 g, 1.84 mmol) and compound **26** (0.41 g, 1.84 mmol) in THF (20.0 ml) were reacted together to obtain product **37** which was further purified by recrystallized using MeOH to obtain a light yellow crystals (0.59 g, 76% yield). M.p 189-190 ^oC, IR ν_{max} (cm^{-1}) 2992 (w, C-H stretch), 1434 (s, C=N), 1244 (m, C-N), 804 (m, C-Cl stretch) ^1H NMR (400 MHz, DMSO-d_6): δ (ppm), 8.73 (d, 1H, Ci-H, *J* = 4 Hz), 8.06 (d, 1H, Co-H, *J* = 2 Hz), 8.03 (d, 1H, Cl-H, *J* = 9 Hz), 7.46 (dd, 1H, Cm-H, *J* = 2 Hz, *J* = 9 Hz), 6.85 (d, 1H, Ci-H, *J* = 4.8 Hz), 4.08 (t, 4H, 2 x C_eH_2, *J* = 5.2 Hz), 3.56 (t, 8H, 4 x C_bH_2, *J* = 4.4 Hz), 3.24 (t, 4H, 2 x C_fH_2, *J* = 4.8 Hz), 1.94 (t, 8H, 4 x C_aH_2, 4.6 Hz), ^{13}C NMR (100 MHz, DMSO-d_6): 165 (Cd), 163 (Cc),

157 (Cl-H), 151 (Cg), 150 (Cj), 134 (Cn-H), 128 (Ck), 126 (Co-H),125 (Cl-H), 121 (Cm-H), 109 (Ch-H), 52.3 (2 x C_fH_2), 45.8 (4 x C_bH_2) 43.0 (2 x C_eH_2), 25.3 (4 x C_aH_2).

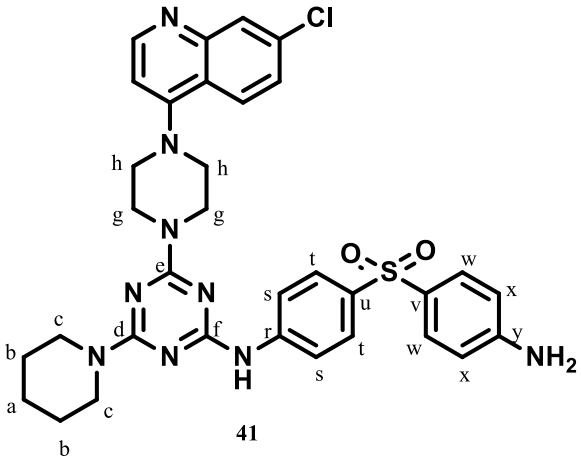
4.5.6 7-chloro-4- (4- 4, 6-di (piperadine-1-yl)-1, 3, 5-triazin-2-yl) piperazin-1-yl) quinoline



38

Compound **32** (0.5g, 1.85 mmols), Hünig's base (0.90 ml) and compound **27** were reacted together in MeOH/ DMF (16.0 ml). After the completion of the reaction, product **38** crashed out as white precipitates and was washed with hot MeOH (40 ml) (0.58 g, 71% yield). M.p 199-201 ^oC, IR ν_{max} (cm^{-1}) 2992.05 (w, C-H stretch), , 1244 (m, C-N), 804 (m, C-Cl stretch) ^1H NMR (400 MHz DMSO-d_6,): δ (ppm), 8.76 (d, 1H, Cj-H, *J* = 4.8 Hz), 8.12 (d, 1H, Cp-H, *J* = 2 Hz), 8.00 (d, 1H, Cm-H, *J* = 9 Hz), 7.56 (dd, 1H, Cn-H, *J* = 2 Hz, *J* = 9 Hz), 7.02 (d, 1H, Ci-H, *J* = 4 Hz), 3.95 (t, 4H, 2 x C_fH_2, *J* = 5 Hz), 3.68 (t, 8H, 4 x C_cH_2, *J* = 5), 3.19 (t, 4H, 2 x C_gH_2, *J* = 4.8 Hz), 3.68 (m, 8H, 4 x C_cH_2,), 1.60 (t, 8H, 4 x C_aH_2, *J* = 4.4 Hz), ^{13}C NMR (100 MHz, DMSO-d_6): 165.5 (Ce), 165.0 (Cd), 156 (Cj-H), 151 (Ch), 150 (Ck), 134 (Co), 128 (Cl), 126 (Cp-H),126 (Cm-H), 121 (Cn-H), 109 (Ci-H), 52.1 (2 x C_fH_2), 43.9 (4 x C_cH_2) 43.1 (2 x C_gH_2), 25.8 (4 x C_bH_2), 24.9 (2 x C_aH_2).

4.5.7 N- (4-((4-aminophenyl) sulfonyl) phenyl)-4-(4-(7-chloroquinolin-4-yl) piperazin-1-yl)-6-(piperidin-1-yl)-1, 3, 5-triazin-2-amine



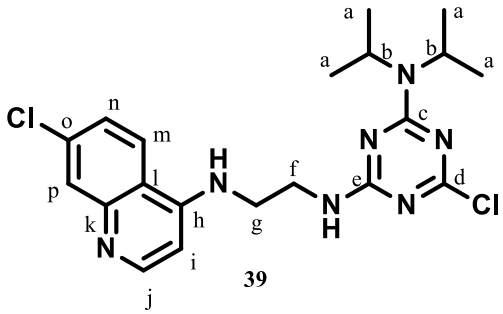
41

Compound **32** (0.21, 0.39 mmol), silica gel (0.20 g) and dapsone (0.09 g, 0.39 mmol) in 1:1 MeOH/THF(6 ml) were reacted together over the microwave set at 300W, 160 ^{o}C for 2 min in a closed vessel condition. Excess solvent was filtered and obtained product **41** as a yellow solid. M.p 288-290 ^{o}C, IR νmax (cm^{-1}) 2995 (w, C-H stretch), 1543 (s, C-C), 1440 (s, C=N), 1370 (m, S=O), ^{1}H NMR (400 MHz, DMSO-d6): δ (ppm), 8.66 (d, 1H, Ar-H, *J* = 4.6 Hz), 8.21 (d, 1H, Ar-H, *J* = 9 Hz), 8.13 (d, 1H, Ar-H, *J* = 3 Hz), 7.87 (d, 1H, Ar-H, *J* = 8.8 Hz), 7.79 (d, 1H, Ar-H, *J* = 8.8 Hz), 7.64 (dd, 1H, Ar-H, *J* = 2.1, Hz *J* = 2.1Hz), 7.59 (d, 1H, Ar-H, *J* = 8.3 Hz), 7.11 (d, 1H, Ar-H, *J* = 6.7), 6.77 (dd, 1H, Ar-H, *J* = 7.8 Hz), 5.5 (br s, 1H, NH) 4.7 (br s, 2H, NH_2), 3.46 (t, 4H, 2 x C_gH_2, *J* = 4.4), 3.07 (t, 4H, 2 x C_cH_2, *J* = 4.2), 2.94 (t, 4H, 2 x C_hH_2, *J* = 5.3 Hz), 2.87 (m, 4H, 2 x C_bH_2), 1.98 (t, 2H, C_aH_2, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, DMSO-d6): 164 (C-N), 163 (C-N), 162 (C-N) 152 (C-Cl), 150 (C-N), 138 (C-C), 135 (C-C), 129 (CH), 129 (CH), 128 (CH), 128.07 (CH), 127 (CH), 126 (2 x CH), 119 (2x CH) 117 (2 x CH) 114 (2x CH) 56.2 (2 x C_gH_2) 45.2 (2 x C_cH_2), 39.1 (2 x C_hH_2) 33.0 (2 x C_bH_2), 25.58 (C_aH_2).

4.6 General procedure for the synthesis of triazine containing compounds from compound 31

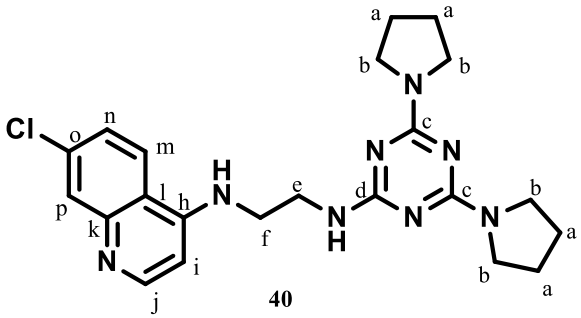
To a solution of N^1-(7-chloroquinolin-4-yl) ethane)-1, 2-diamine (1eq) in MeOH/THF(1:1) in presence of K_2CO_3 (1eq) was added into triazine containing compounds (1eq).The mixture was microwaved at 200W and 100 ºC in a closed reaction vessel. Product were obtained by filtration.

4.6.1 6-chloro-N^2-(2-((7-chloroquinolin-4-yl) amino) ethyl)-N^4, N^4-diisopropyl-2, 4-diamine-1, 3, 5-triazine



Compound **31** (0.52 g, 1.89 mmols), K_2CO_3 (0.26 g, 1.89 mmol) were reacted together and compound **25** (0.43 g, 1.89 mmol) in MeOH/THF (10 ml) to obtain product **39** as a yellow powder (0.57 g, 65% yield). M.p 188-190 ºC, IR ν_{max} (cm^{-1}) 2994 (w, C-H stretch), 1430 (s, C=N), 1240 (m, C-N), 784 (m, C-Cl stretch) ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.68 (d, 1H, Cj-H, *J* = 4 Hz), 8.69 (d, 1H, Cp-H, *J* = 2 Hz), 8.51 (d, 1H, Cm-H, *J* = 9 Hz), 8.12 (dd, 1H, Cn-H, *J* = 9, Hz, *J* = 2.1 Hz), 6.89 (d, 1H, Ci-H, *J* = 5 Hz), 5.0 (t, 2H, C_fH_2, *J* = 5.9 Hz), 4.6 (br s, 1H, Ce-NH), 3.26 (t, 2H, C_gH_2, *J* = 5 Hz), 3.41 (s broad, 1H, C-NH) 2.88 (t, 2H, C_bH_2, *J* = 6 Hz) 1.29 (d, 12H, 4 x C_aH_3, *J* = 2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 169.0 (Cd), 165.0 (Cc), 163.0 (Ce) 156.0 (Cj-H), 143.0 (Ch), 143.0 (Ck), 142.0 (Co), 139.0 (Cl), 138.4 (Cp-H), 121.0 (Cm-H), 119.0 (Cn-H), 98.1 (Ci-H), 46.1 (CfH_2) 42.9 (CgH_2) 31.1 (CbH) 20.2 (4 x CaH_3).

4.6.2 N^1-(7-chloroquinolin-3-yl)-N^2-(4, 6-di (pyrrolidin-1-yl) -1, 3, 5-triazin-2-yl) ethane-1, 2-diamine



40

Compound **31** (0.52g, 2.28 mmol), K_2CO_3 (0.31 g, 2.28 mmol) and compound **26** (0.57g, 2.28 mmol) were reacted together in 1:1 MeOH/THF (6 ml) in the microwave set at 200 W, 100 ^oC for 16 min in a closed vessel condition. Excess solvent was filtered and gave product 40 as a yellow solid (0.71 g, 93 % yield). M.p 205-207 ^oC, IR νmax (cm^{-1}) 2992 (w, C-H stretch), 1436 (s, C=N), 1240 (m, C-N), 787 (m, C-Cl stretch), ^1H NMR (400 MHz, DMSO-d6): δ (ppm), 8.39 (d, 1H, Ci-H, *J* = 8 Hz), 8.33 (d, 1H, Cl-H, *J* = 8 Hz), 7.79 (d, 1H, Cd-H, *J* = 2 Hz), 7.42 (dd, 1H, Cm-H, *J* = 9 Hz, *J* = 2 Hz), 6.55 (d, 1H, Cn-H, *J* = 5.6 Hz), 4.9 (br s, 1H, Cd-NH), 4.7 (br s, H, NH), 3.57 (t, 2H, C_eH_2, *J* = 6 Hz), 3.35 (t , 8H, 4 x C_bH_2, *J* = 6.5), 3.10 (t, 2H, C_fH_2, *J* = 6 Hz), 1.30 (t, 8H, 4 x C_aH_2, *J* = 4.2 Hz), ^{13}C NMR (100 MHz, DMSO-d6): 165 (Cd), 163 (Cc), 162 (Cl), 152 (Cg), 150 (Cj), 149 (Cn), 134 (CK), 127 (CO), 124 (Cl), 117 (Cm), 99.2 (Ch), 46.4 (2 x C_eH_2), 39.6 (4 x C_bH_2) 37.9 (2 x C_fH_2), 25.2 (4 x C_aH_2).

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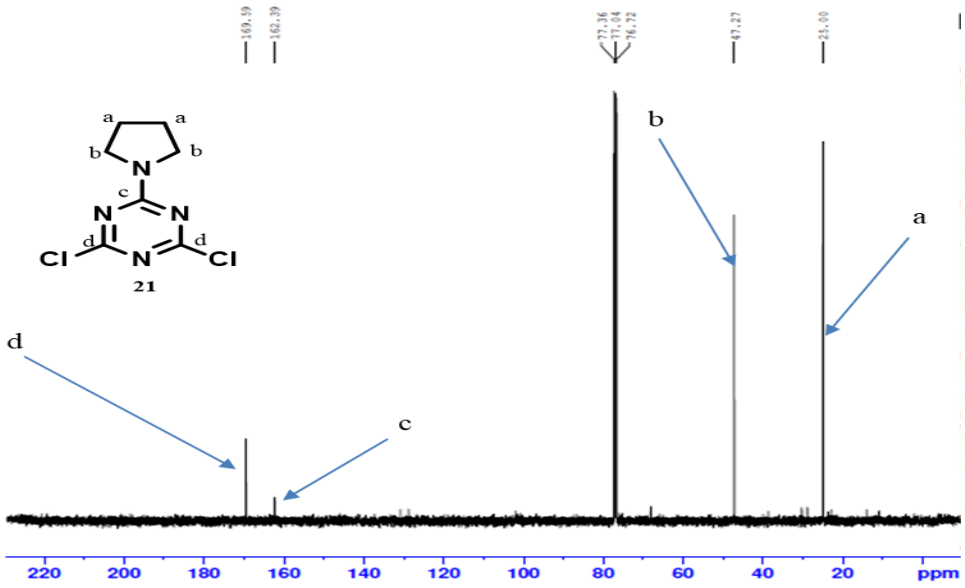
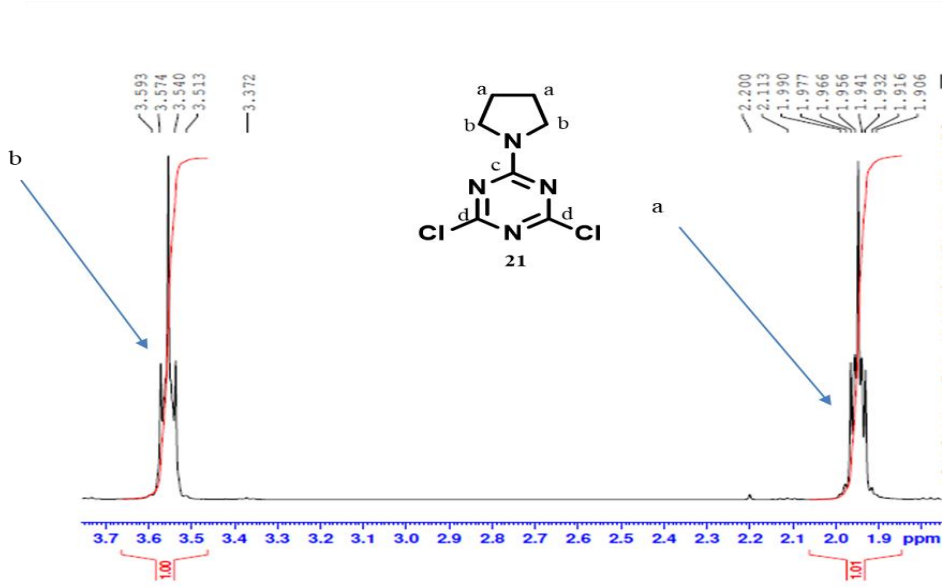
6. APPENDIX

6.1 Mono-substituted 1, 3, 5-triazine compounds (21-25)

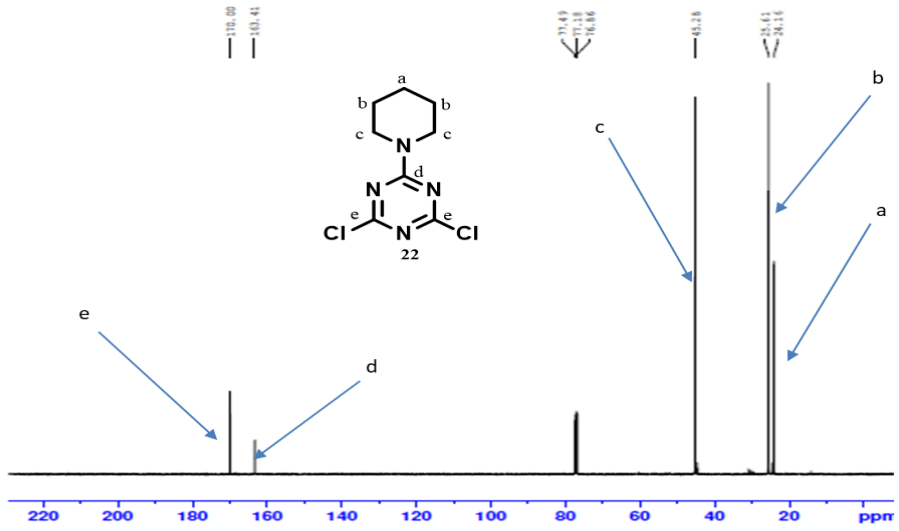
Compound (21) ^{13}C NMR



Proton (21)



Compound (22) ^{13}C NMR



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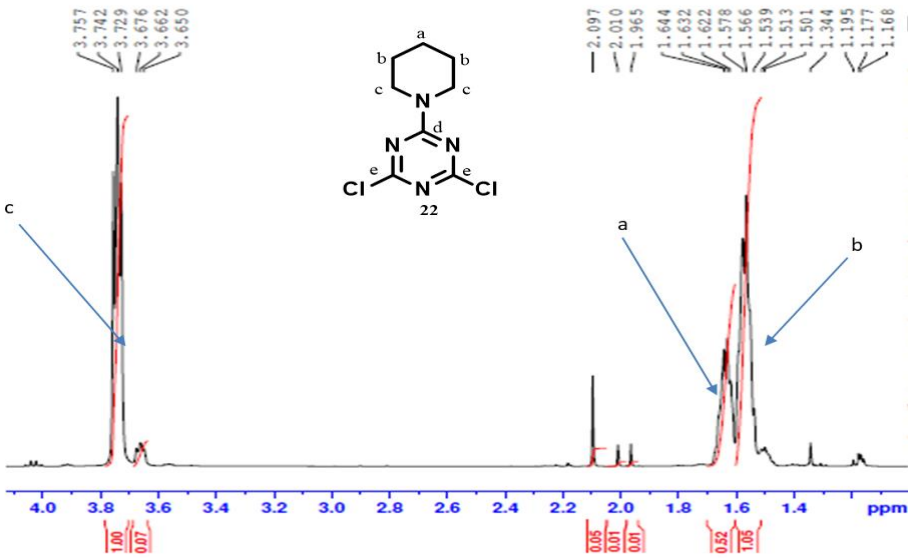
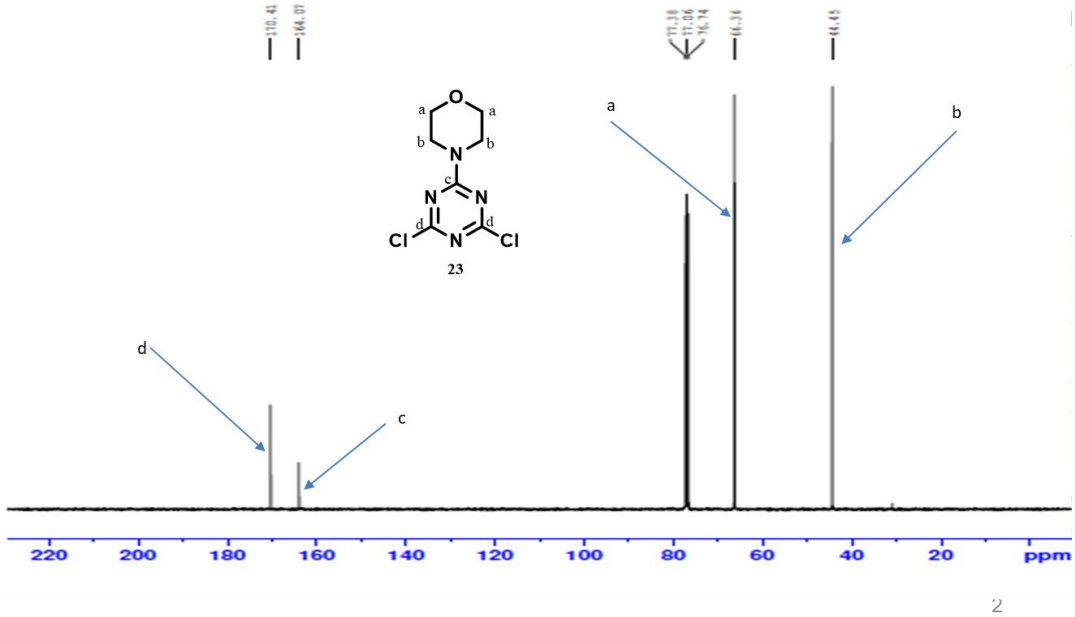
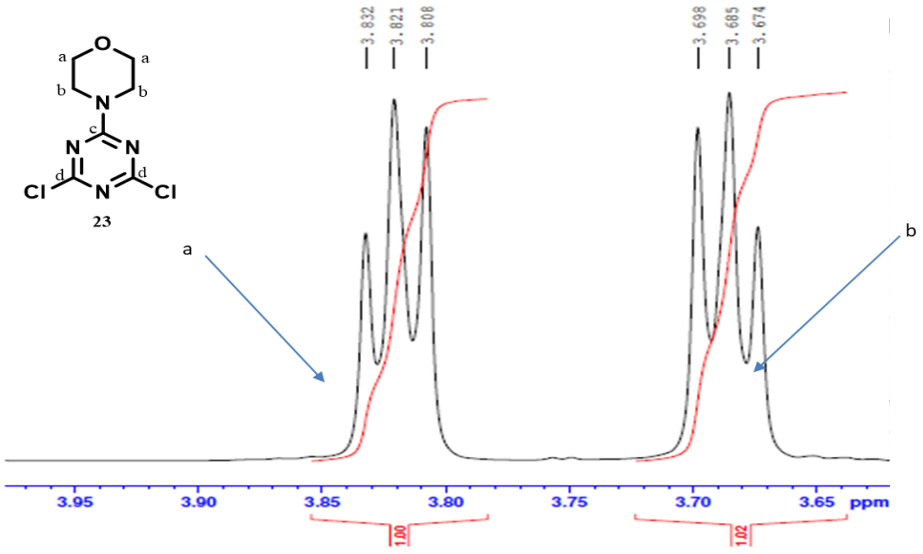


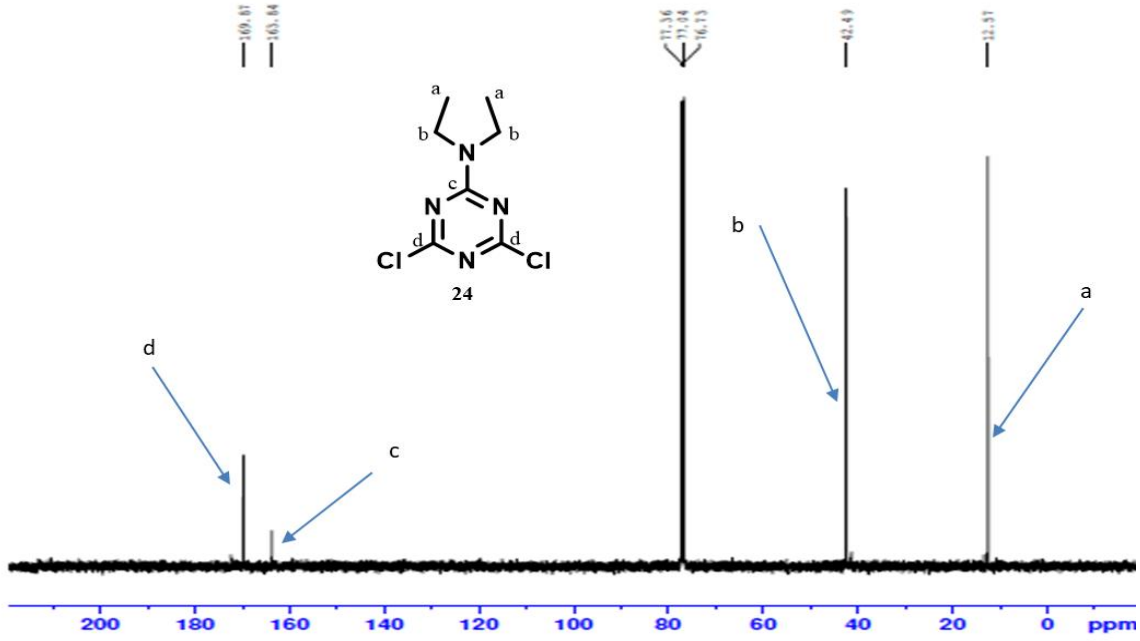
Compound (23) ^{13}C NMR



Proton (23)



Compound (24) ^{13}C NMR



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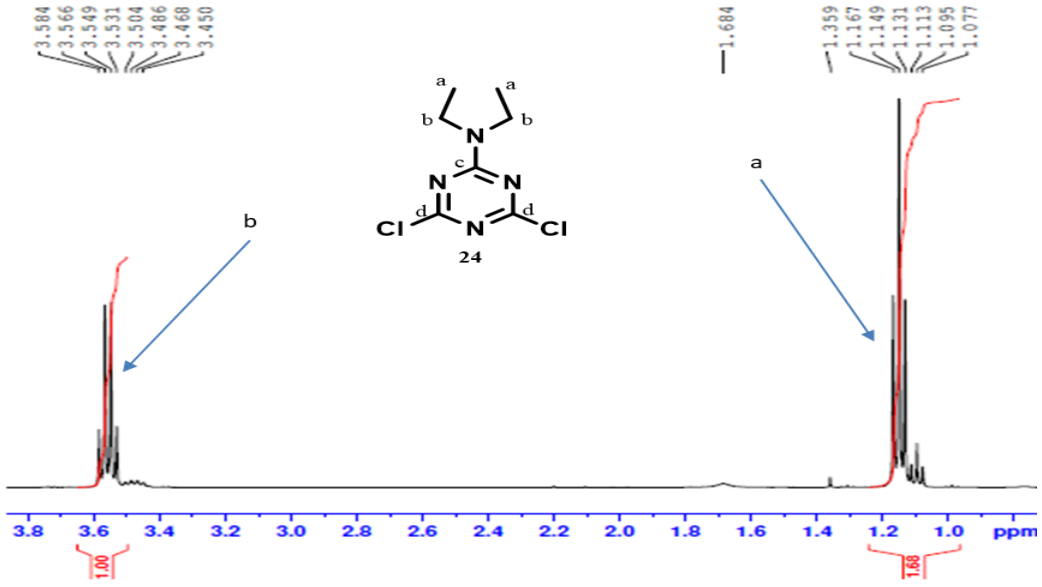
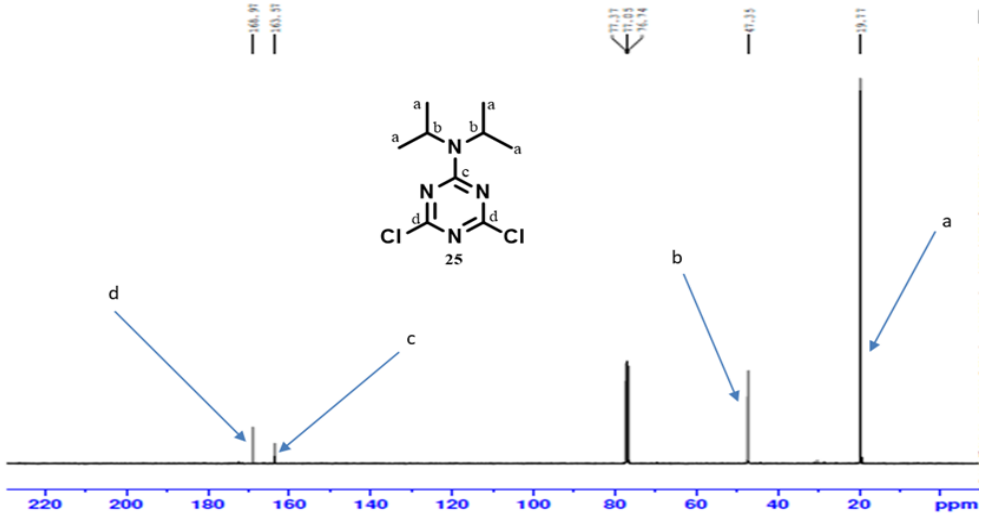


carbon (25)

Compound (25) ^{13}C NMR



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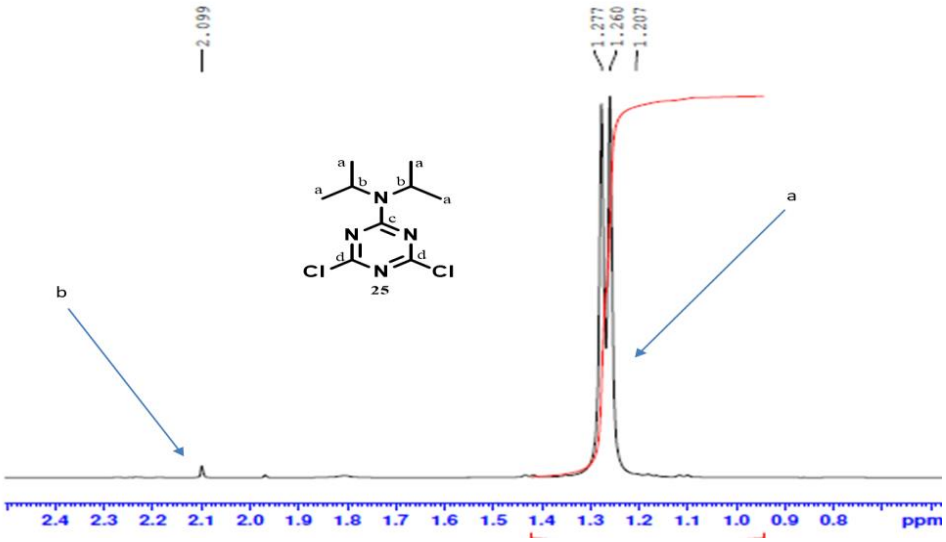
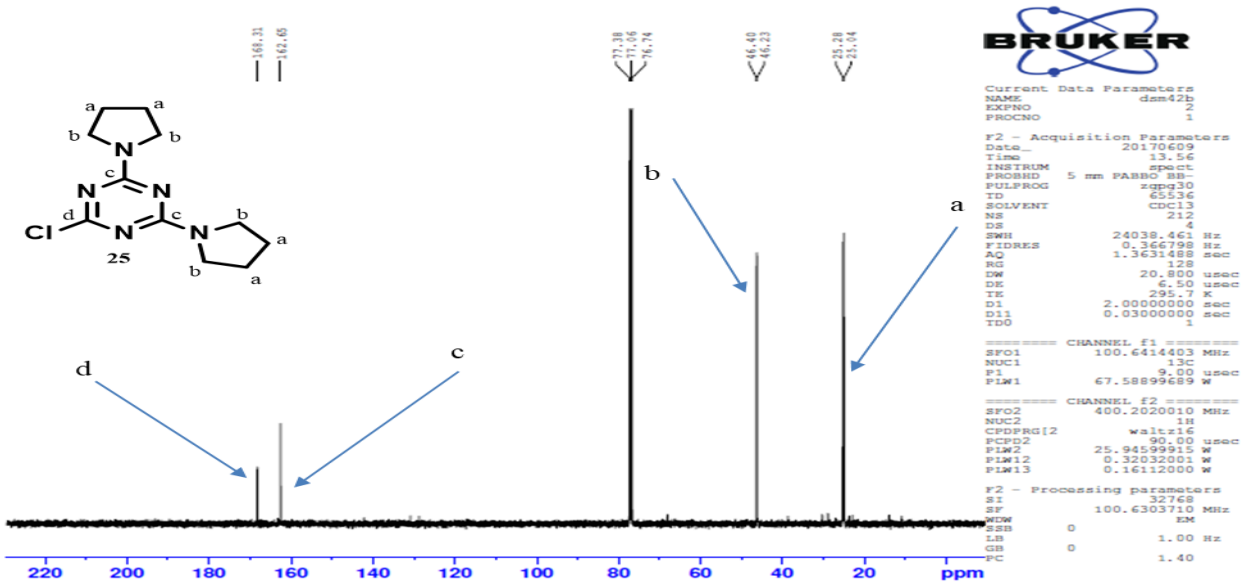
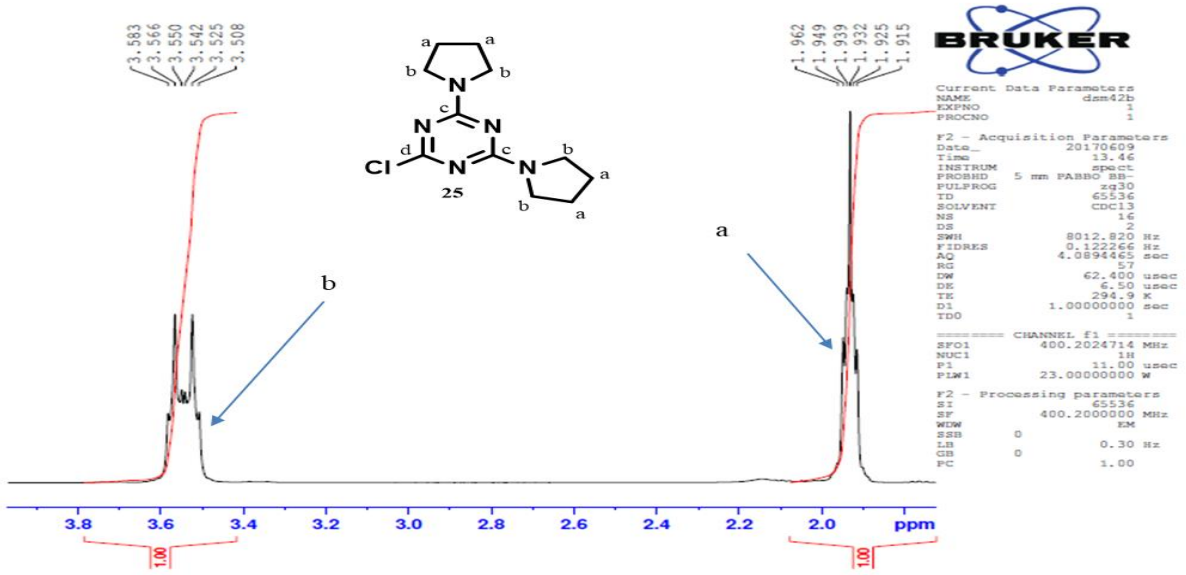


6.2 Di-substituted 1, 3, 5-triazine compounds (26-28)

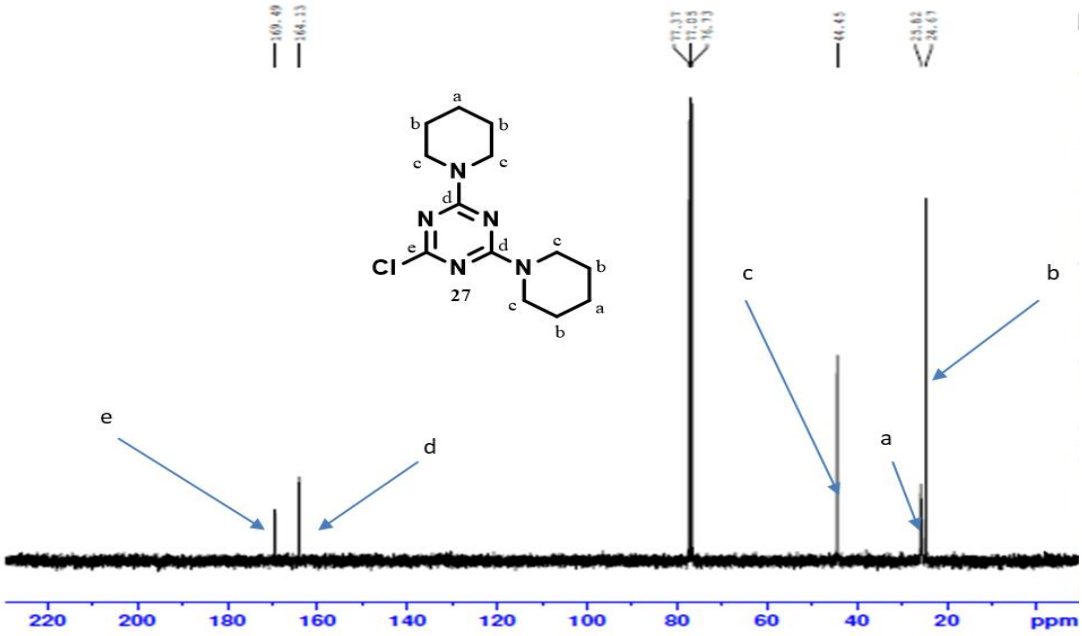
Compound (26) ^{13}C NMR



proton (26)



Compound (27) ^{13}C NMR



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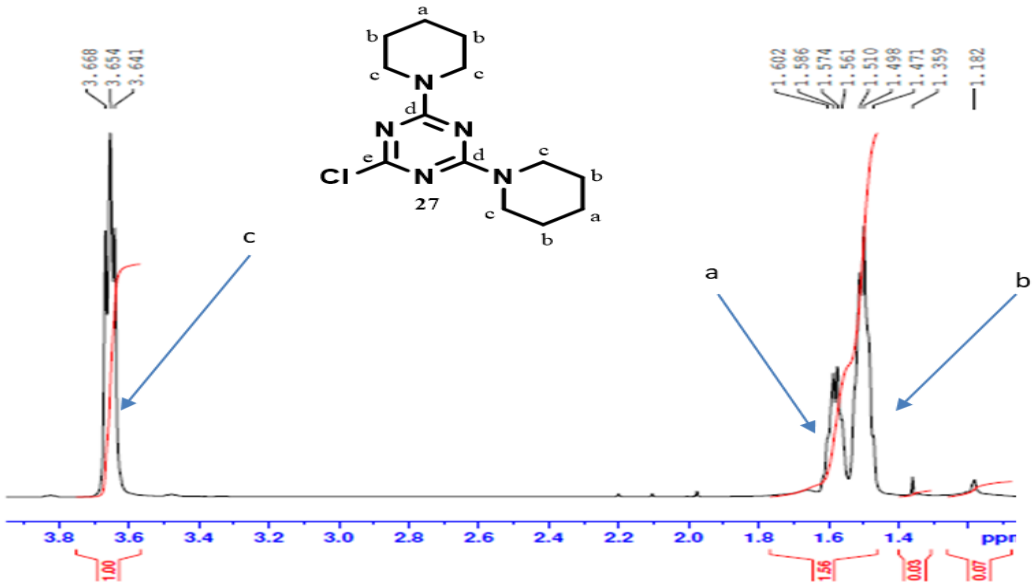
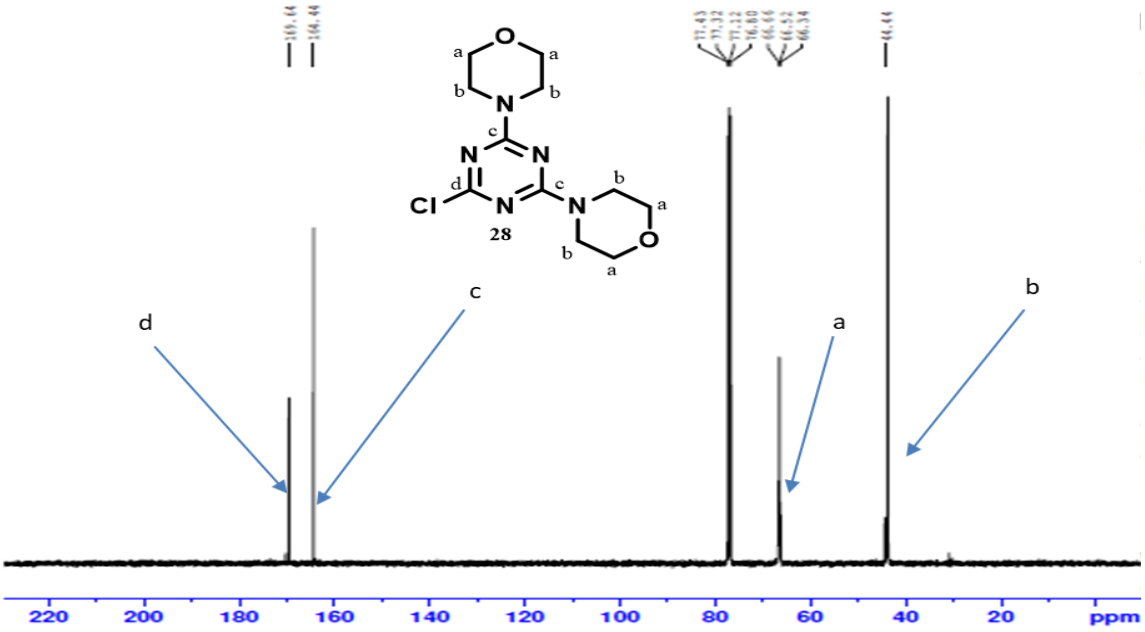


COMPOUND (28) ^{13}C NMR



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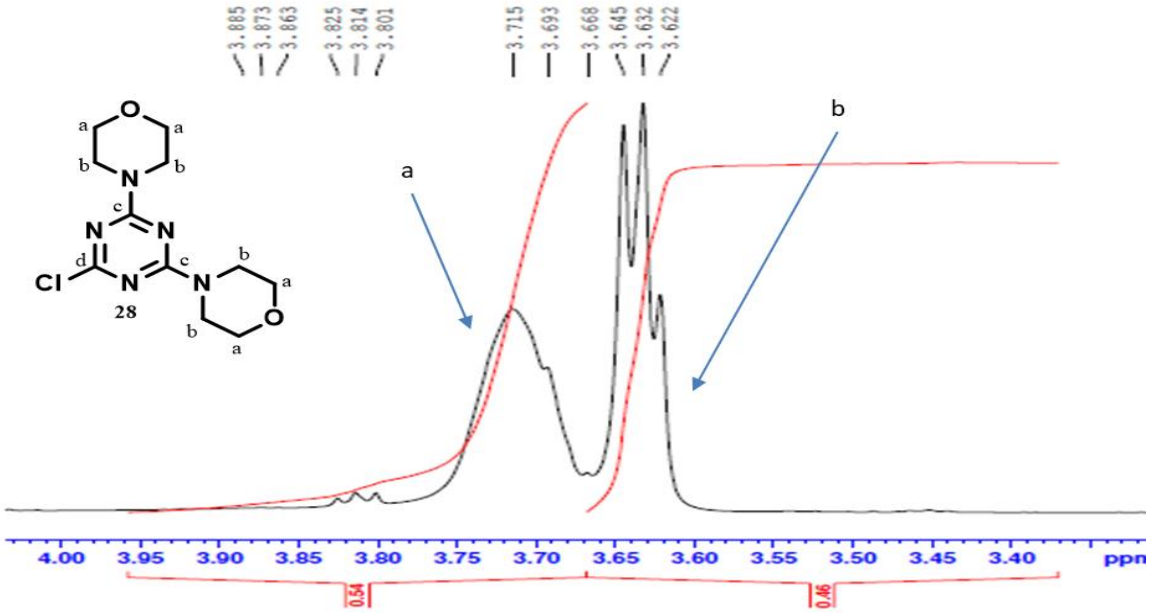
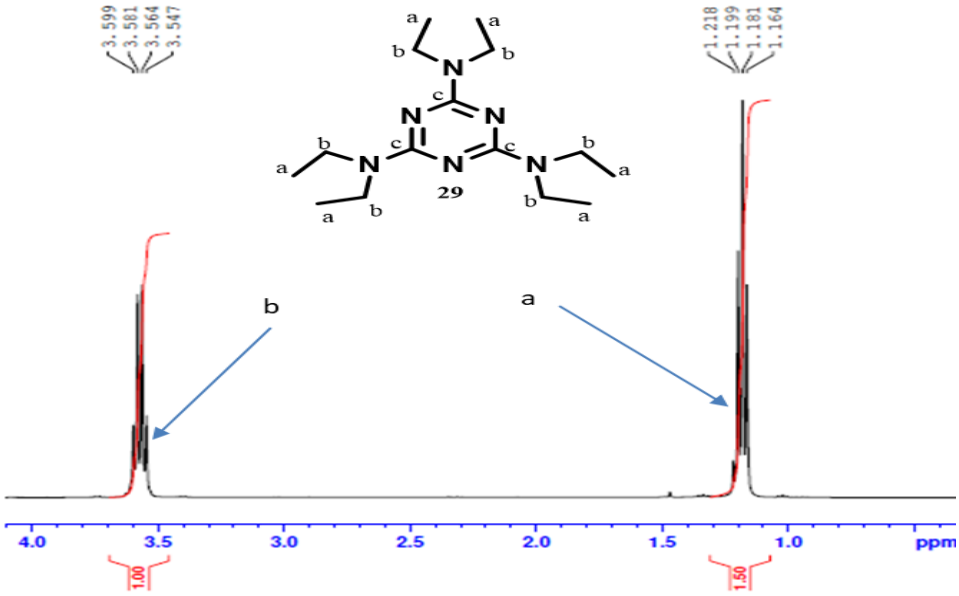


6.3 Triamino-substituted-1,3,5-triazine

Carbon ^{13}C NMR (29)



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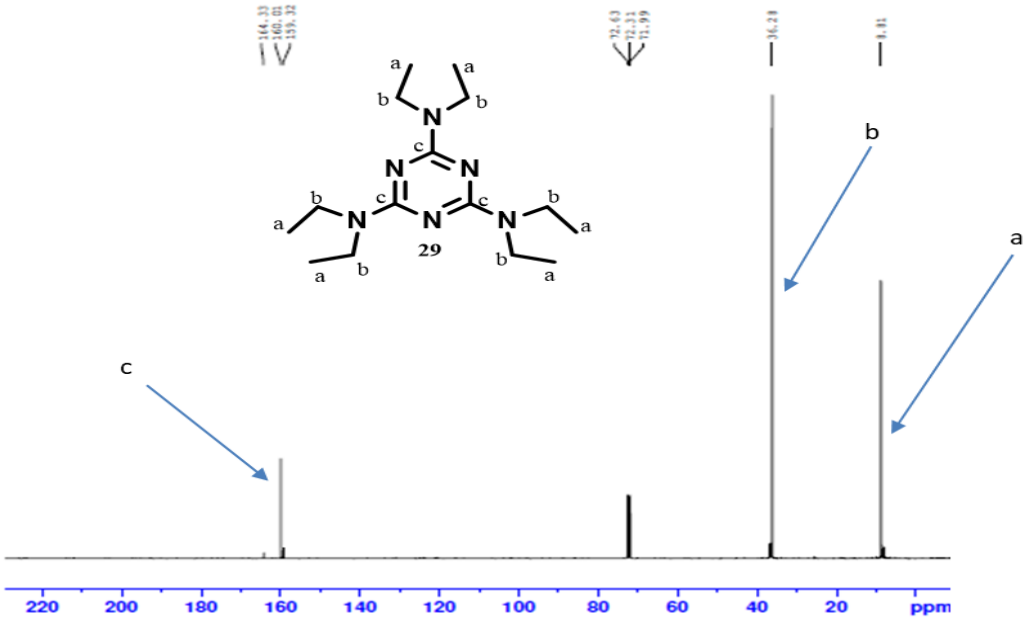
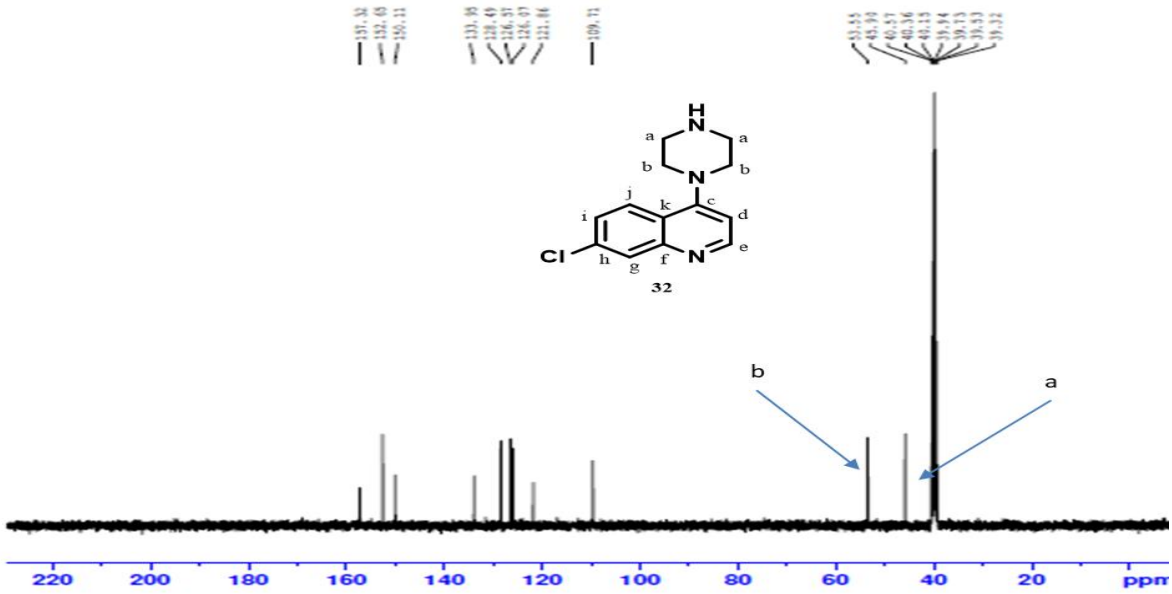
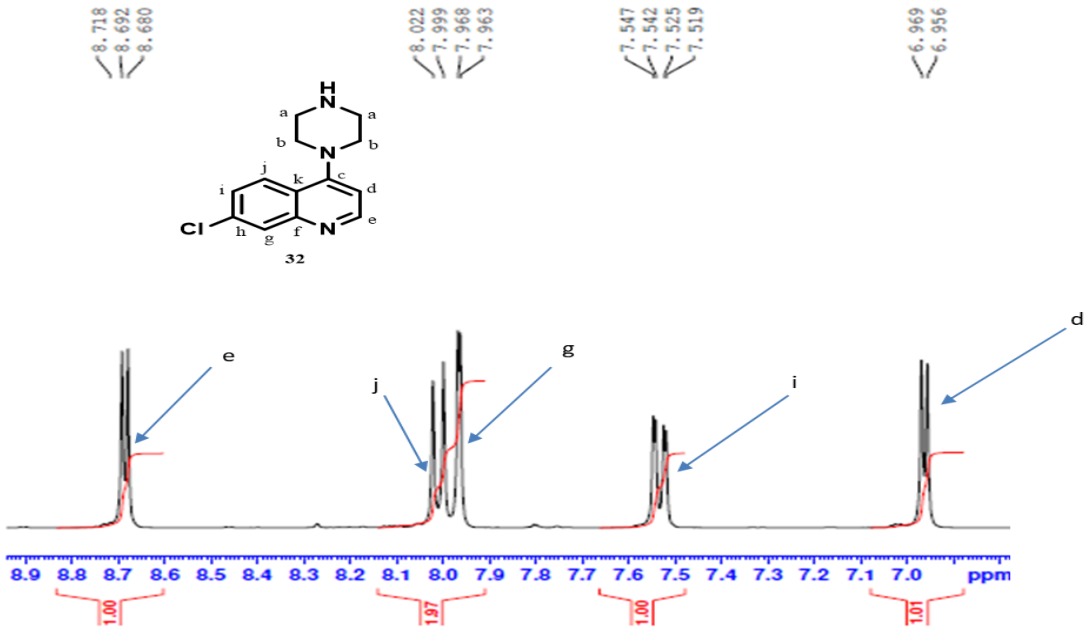


4-amino quinoline linkers

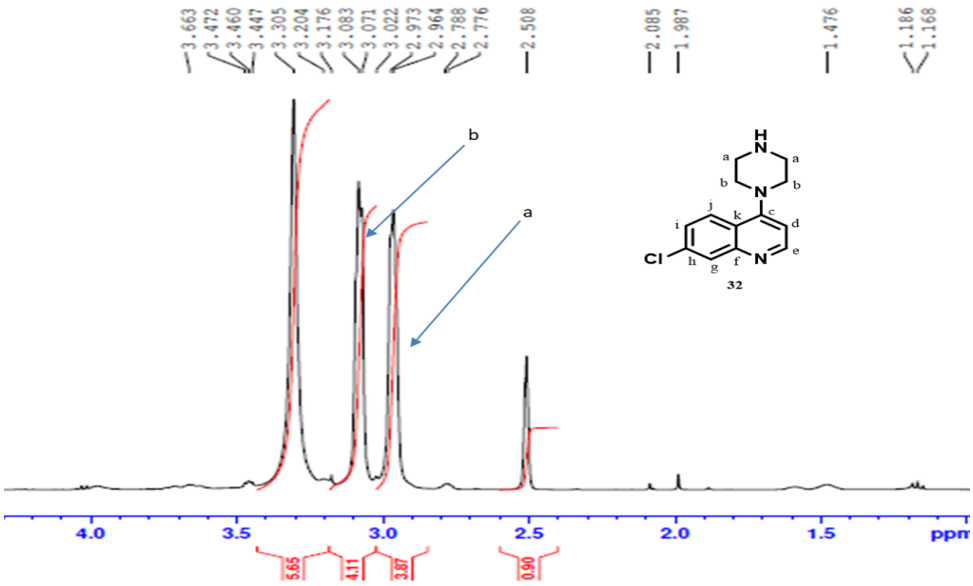
Compound 32 ^{13}CNMR



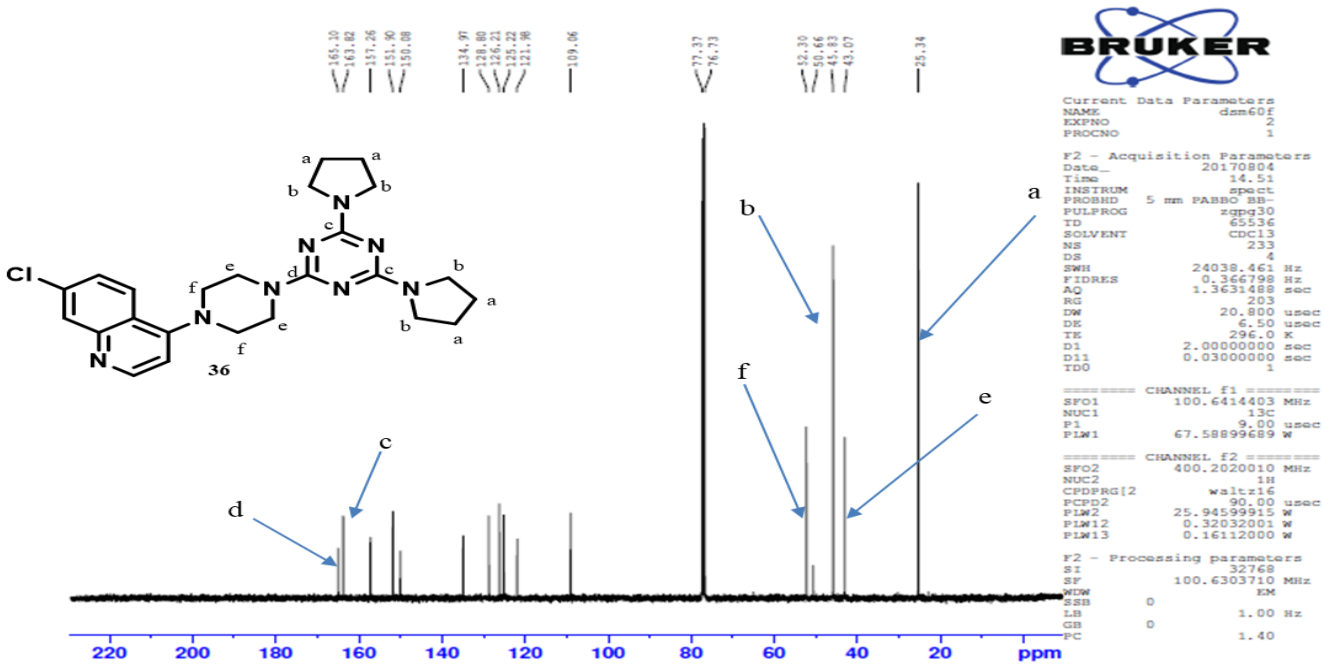
Proton 32 expanded aromatic region



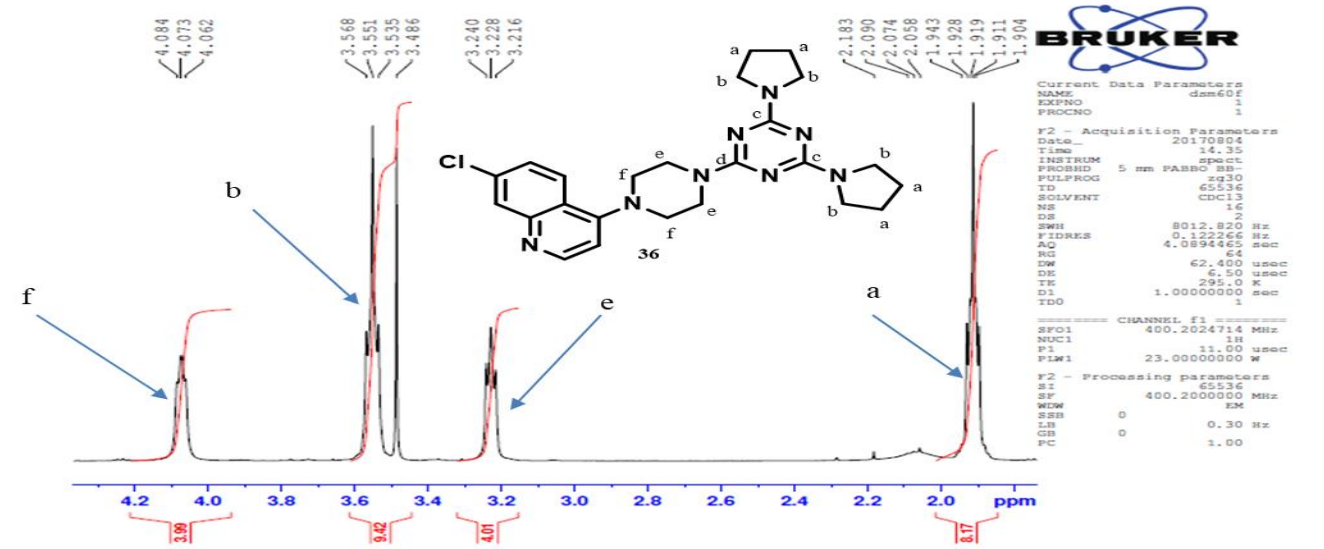
Proton 32 expanded aliphatic region



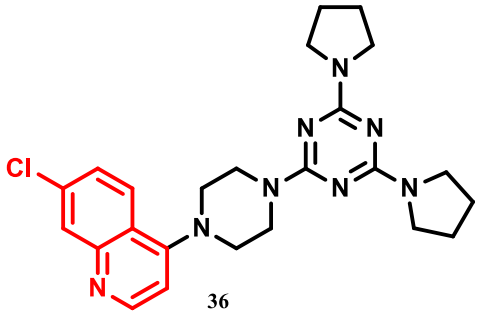
6.4 Addition of 7-chloro-4-piperazin-1-ly) quinoline unto di-substituted 1, 3, 5-triazine



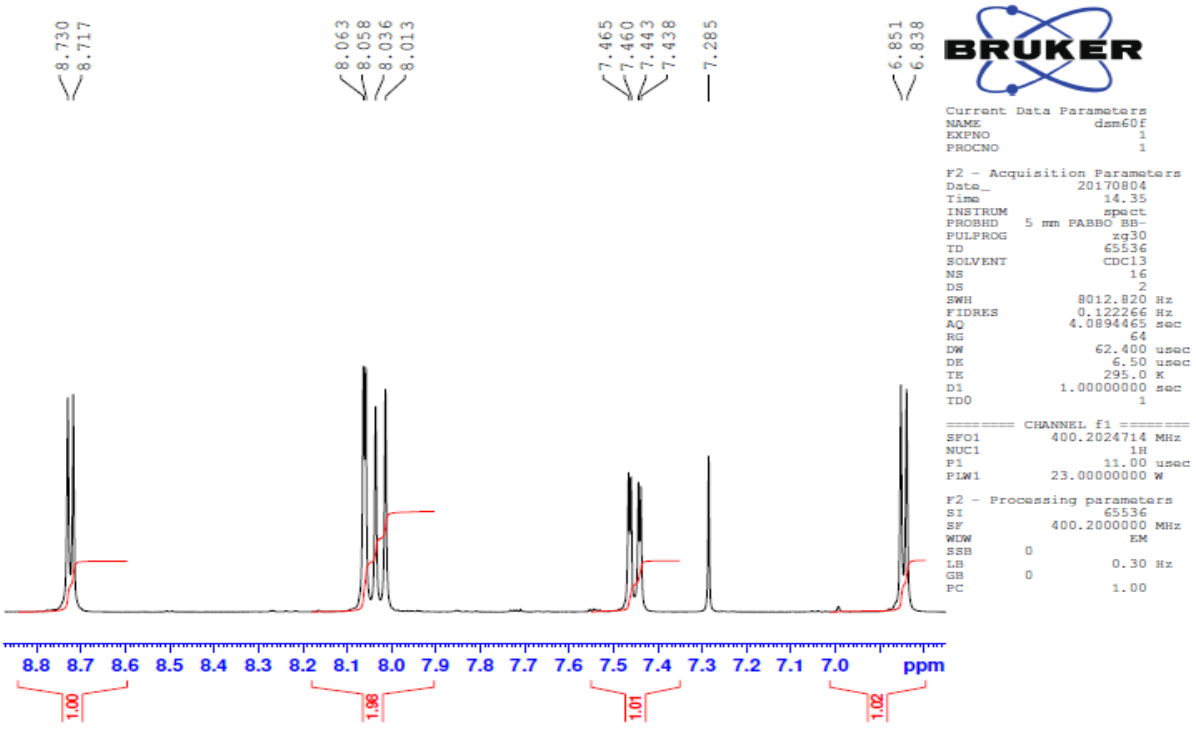
Expanded proton (aliphatic region)



Expanded Proton (aromatic region)



36



BRUKER

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PROCNO                     1

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TD                    65536
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NS                       16
DS                        2
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FIDRES            0.122266 Hz
AQ                4.0894465 sec
RG                       64
DW                   62.400 usec
DE                    6.50 usec
TE                   295.0 K
D1                1.00000000 sec
TD0                        1

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NUC1                      1H
P1                    11.00 usec
PLW1            23.00000000 W

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