Chapter 1

Design, synthesis and antimalarial activity of 4-aminoquinoline derivatives
Chapter-1

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1.1 Introduction

Malaria, one of the most infectious diseases of mankind in the world, is widespread in more than 90 countries and affecting around 40% of the world’s population. There are some 300-500 million cases and between 1.5-2.7 million deaths each year from malaria. It is a hematoprotozoan parasitic disease transmitted to humans by a particular species of Anopheles mosquitoes. These insects inoculate Plasmodium sporozoites to humans via a blood feeding process. The genus Plasmodium can be classified into nine subgenera. Plasmodium falciparum, P. vivax, P. ovale and P. malariae are the species that infect humans. Malaria caused by P. falciparum is most critical and lethal. It accounts for 80% of all malaria infections and 90% of malaria related deaths. Infection with this parasite can lead to death within hours to days.

The increasing resistance of malaria parasites particularly in P. falciparum is an important factor in the persistence of this disease as a major worldwide public health menace. The existing chemotherapy is not satisfactory in terms of lack of effectiveness and also due to the side effects associated to long-term treatments. Drug resistance and strain sensitivity to the existing drugs are other shortcomings for the clinically accessible chemotherapy. The drug discovery costs for the pharmaceutical industry to introduce new compounds into the market have risen dramatically from the last decades. In 1998, the World Health Organization, UNICEF, UNDP and the World Bank launched the Roll Back Malaria (RBM) initiative to offer a coordinated approach to fight against malaria but with little success so far. Artemisinin based drugs are the only affordable treatment for malaria. However, some parasites isolated from French Guiana and Senegal recently showed diminished in vitro sensitivity to artemether. Therefore, it is an urgent need to find new natural or synthetic drugs before malaria parasite gets resistance against artemisinin and its derivatives. Early discovery of potent drug is highly required to help in the prevention and control of this parasitic disease.
Quinoline and its derivatives represent a very important class of antimalarial drugs that function by parasite hemoglobin breakdown pathway.\cite{12-14} Quinoline-containing antimalarials have long been used to combat malaria. In 1940s, synthetic quinoline compound chloroquine was introduced (Loeb et al., 1946)\cite{15} and proved invaluable in the fight against the disease. However, only limited number of quinolines have evaluated for their antimalarial activity against malaria parasites. Thus, it is meaningful to re-look the antimalarial activity of existing quinoline libraries or synthesize some different quinoline derivatives with enhanced activity. A systematic and extensive study is required to discover effective antimalarial compound form 4-aminoquinoline based scaffold. In this chapter we have synthesized different analogs of 4,7-dichloroquinoline and screened against malaria parasite.

1.1.1 Life cycle of malaria parasite

The human malaria parasite requires both human and insect hosts to complete its life cycle. In anopheles mosquito, the *Plasmodium* parasite reproduces sexually *i.e.*, by combining sex cells, while in human parasite reproduces asexually, first in liver cells and then repeatedly in blood cells. Malaria infection in human host starts when the sporozoites injects into the blood during an infected mosquito bite. The mosquito takes meal to nourish her eggs. At the same time, she injects saliva that contains infectious sporozoites. Although it is assumed that one single sporozoite is capable of initiating the infection in men, the number of sporozoites injected by a mosquito bite is supposed to vary from dozens to thousands. It is likely that this number strongly affects the clinical picture: the greatest the sporozoite load, the shortest the incubation period and the most serious the symptoms. The sporozoites remain into the circulation for a short period, calculated as 60 minutes at maximum, before they actively enter the liver of the host (Lopez-Antunano, 1980).\cite{16} The Kupffer cells in the liver may be invaded (or the parasite may be phagocititated) but the sporozoites are not able to develop in those cells and die shortly after invasion. Most parasites however invade the hepatocytes and start the asexual exo-erythrocytic schizogonic cycle. The cycle has been studied in details in liver sections from a rodent model for malaria infection, but observations from liver biopsy in human volunteers are also available for *P. falciparum* and *P. vivax*. The liver
trophozoite initially appears as a mononucleated round body into the cytoplasm of the host cell; subsequently it begins to develop and multiply asexually, a mature schizont (the multinucleated stage of the parasite) is formed, and finally a large number of merozoites are released. The mature schizont is 30-70 µm large, has no pigment (there is no hemoglobin into the hepatocyte), and occupies the entire cell cytoplasm. The length of the schizogonic liver cycle is constant for each *Plasmodium* species to the extent that it can be considered a taxonomic character: this is the above mentioned prepatent period (5.5, 8, 9, and 15 days for *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*, respectively). The number of merozoites produced at the end of the cycle is also species dependant: it is estimated as 2,000 for *P. malariae*, 10,000 for *P. vivax/P. ovale*, and up to 30,000 for *P. falciparum* (Garnham, 1966).[17] The liver cycle ends when the mature schizont ruptures and releases the merozoites into the sinusoids of the liver. Released merozoites can only invade a red blood cell: the theory of the continuation of the liver cycle by invasion of a new hepatocyte by the merozoite, is not any more accepted at present (figure-1.1).[18, 19]

![Life cycle of malaria parasite](http://www.merckmanuals.com)

*Figure-1.1: Life cycle of malaria parasite (http://www.merckmanuals.com).*
1.1.2 History of quinoline antimalarial drugs

1.1.2.A Quinine

The first quinoline antimalarial drug quinine was alkaloid extracted from the cinchona tree. The cinchona tree is named after the Countess of Chinchon, who according to legend was cured of malaria in 1630 by a powder made from its bark. The powdered bark of the “fever tree” was widely distributed in Europe by the Jesuits during the 17\textsuperscript{th} century (Wallace, 1996).\textsuperscript{[20]} A crude mixture of crystalline alkaloids was extracted from cinchona bark in 1810 by Gomes in Portugal and quinine & cinchonine subsequently were isolated by Pelletier and Caventou in 1820 (Hofheinz and Merkli, 1984) (figure-1.2).\textsuperscript{[21]} A pathway for the synthesis of quinine was described by Woodward and Von Doering in 1944. Quinidine a stereoisomer of quinine is also used as antimalarial drug. After World War II, chloroquine and pyrimethamine largely replaced quinine for prophylaxis and routine treatment.

![Figure-1.2](image)

1.1.2.B 8-Aminoquinoline

The discovery of 8-aminoquinoline drugs came from the mild antimalarial activity of methylene blue. Various analogs of methylene blue were synthesized by replacing one methyl group with basic alkyl side chain to enhance activity. The first analog which was synthesized in this series was plasmoquine which was also known as pamaquine (figure-1.3).\textsuperscript{[22]} This compound was found too toxic to use therefore, to overcome this
problem primaquine was synthesized. Primaquine was comparatively much less toxic analog of 8-aminoquinoline. Primaquine is still used to eradicate the hypnozoites of *P. ovale* and *P. vivax*.

![Figure-1.3: Structure of some 8-amino and 4-aminoquinoline antimalarial drugs](image)

### 1.1.2.C 4-Aminoquinoline

Scientist at Bayer Institute in Germany synthesized 4-aminoquinoline, Resochin by altering the basic side chain.\[^{[15, 23]}\] Resochin was found to be safe for malaria treatment and renamed as chloroquine. Chloroquine (figure-1.3) became popular for clinical use due to its effectiveness and low risk of side effects. Unfortunately, chloroquine has not been used wisely and in early 1960s the cases of chloroquine resistance emerged.\[^{[24, 25]}\] Amodiaquine (figure-1.3) was introduced as an alternative and has been used for the prophylaxis of *P. falciparum* for almost 40 years.

### 1.1.2.D Quinoline methanol

The most promising compounds in this group were 4-aminoquinoline methanol structurally analogous to quinine.\[^{[21]}\] These compounds were very effective for both *P. falciparum* and *P. vivax* but exhibited strong photosensitizing actions. Mefloquine (figure-1.4) was synthesized afterwards which was more potent with no appreciable photosensitizing effects.\[^{[26]}\] Mefloquine was used in fields for almost 30 years especially for chloroquine resistant strains. But due to its resistance and toxicity associated these are now limiting in use.\[^{[27-29]}\] Another major class of compounds emerged by replacing quinoline basic scaffolds of 4-aminoquinoline to various aromatic rings. Halofantrine
(figure-1.4) synthesized in this class and used to treat chloroquine resistant malaria.\textsuperscript{[30-32]} However, its use has been restricted due to serious cardiotoxic effects.\textsuperscript{[33, 34]}

![Mefloquine and Halofantrine Structures](image)

**Figure-1.4:** Structure of some quinoline methanol antimalarial drugs

### 1.1.3 Quinoline and its derivatives: structure-activity relationship (SAR)

Quinine has been used for centuries in the treatment of malaria. It is a low-cost drug but has become limited due to a decrease in its sensitivity by parasites. However, it is still used parenteral to control acute cerebral malaria. The structure-activity relationships of chloroquine and related quinoline antimalarial compounds have been reviewed extensively.\textsuperscript{[35-38]} Other derivatives of quinine include chloroquine, amodiaquine, mefloquine and halofantrine. These drugs act by decreasing the rate of hemozoin formation, rather than irreversibly blocking its formation.\textsuperscript{[39-41]} An alternative mechanism of action of chloroquine has also been hypothesized. It is believed that it works through the generation of highly reactive radicals due to an electron transfer between the redox couple Fe [II] heme/Fe [III] heme and the quinoline ring may be responsible for antimalarial action of chloroquine.\textsuperscript{[42]}

The 7-halosubstituted compounds are the most active antimalarials in the 4-aminoquinoline series. Change of the halogen or dissubstitution on the quinoline nucleus generally lowers activity as in 9-aminoacridine series. The inter-nitrogen separation (the molecular distance between the quinoline N and the alkylamino N) affects the level of activity of 4-aminoquinolines\textsuperscript{[43]} and is important in defining the ability of drugs to bind
Structure-activity relationship studies of quinine analogs suggested that a hydroxyl group on C-9 is necessary for activity. *Erythro* configurations at the C-8 and C-9 positions of quinine analogs are more active than the *threo* isomers but not in all cases. The orientations of the hydroxyl and amine groups of mefloquine are critical to antimalarial activity. 4-Aminoquinoline nucleus of chloroquine and related antimalarials is responsible for complexing free heme and the group at the 7-position of the quinoline ring appears to be vital in determining the antimalarial ability of 4-aminoquinolines to inhibit the formation of hemozoin. The aminoalkyl side chain of quinoline drugs is also accountable for strong antiplasmodial activity. However, change in the length of amino alkyl side chain has little influence on activity against chloroquine-sensitive strain of *P. falciparum* but has an intense influence on the activity especially against chloroquine-resistant strains.

Quinoline drugs lacking 7-chloro group do not inhibit hemozoin formation although forming complexes with heme. Replacing 7-chloro group with a bromo or nitro group shows the inhibition of hemozoin formation. If a chloro atom is introduced at the 6-position on the quinoline ring, the interaction with hematin is completely disrupted. If 7-chloro is replaced by 7-amino and 7-chloro derivatives, hemozoin formation is not inhibited. Aminoquinolines inhibiting hemozoin formation must have aminoalkyl side chain for its strong antimalarial activity. Replacement of aminoalkyl side chain to hydroxyl or other group causes severe reduction in activity. 4-Aminoquinolinedialkylamino side groups are liable for ideal activity.

### 1.1.4 Heme detoxification pathway

The characteristic clinical symptoms produced during the intra-erythrocytic phase of the parasite life cycle within host. During this phase, hemoglobin is employed as a major source of amino acids to stimulate the parasite growth. When hemoglobin is degraded, potentially toxic iron containing heme group is released. Though, *Plasmodium* parasites develop a particular heme detoxification mechanism where heme is altered into a dimeric form and finally converted into polymeric non-toxic hemozoin (malaria pigment) through the formation of hydrogen bonds between dimeric heme units.
The quinoline containing antimalarial drugs like chloroquine kills the parasite, causing swelling of the food vacuole, increasing granularity of the cell and ultimately cell death. Chloroquine is effective against the erythrocytic stages of malaria parasite but shows no effect against liver stages like pre erythrocytic or hypnozoite stage. The sensitivity of the parasite towards chloroquine is much higher than the host cells. Chloroquine is a diprotic weak base ($\text{pK}_{a1}=8.1$, $\text{pK}_{a2}=10.2$) and its unprotonated from it diffuses through the membrane of parasitised erythrocyte and gets accumulated in the acidic food vacuole ($\text{pH}=5-5.2$). Acidic compartment in *P. falciparum* also known as the digestive vacuole (DV) helps the function of digesting hemoglobin from the infected erythrocyte. A by-product hemozoin is produced after the degradation of haemoglobin. Free heme (ferriprotoporphyrin IX, Fp IX; Free FP) can lyse the cell and affect the function of lysosomal enzymes. Detoxification of FP is performed by the food vacuole, which converts it into hemozoin and an enzyme heme polymerase appears to be involved in this process (figure-1.4 & 1.5). This pigment is not incorporated into the merozoites and is left behind with the shell of the parasitized red cell. Early studies implicated the
importance of FP in the mechanism of action of chloroquine because it was noted that quinine was not effective against malaria which did not make pigment.\textsuperscript{[40-51]}

1.1.5 Drug Resistance in malaria parasite

The ability of an organism to resist the action of drugs is known as drug resistance. The development of resistance is one of the greatest threats to malaria control. Generally, drug resistance occurs through spontaneous mutations in genus that confer reduced sensitivity to a given drug or class of drugs. Drug resistance by malaria parasites has been defined as the ability of a parasite strain to survive or multiply despite the administration and absorption of a drug when given in doses equal to or higher than those normally recommended and within the limits of tolerance of the subject. Two of the four species of malaria parasite that naturally infect humans are \textit{P. falciparum} and \textit{P. vivax}. \textit{P. falciparum} has developed resistance to nearly all antimalarials in current use.\textsuperscript{[52]}

Almost 80\% malarial parasites are chloroquine resistant and spread all over world at present. Because of the digestion of hemoglobin, large amount of a toxic by-product are formed. The parasite polymerizes this by-product in its food vacuole, producing non-toxic hemozoin (malaria pigment). It is believed that resistance of \textit{P. falciparum} to chloroquine is related to an increased capacity for the parasite to expel chloroquine at a rate that does not allow chloroquine to reach levels required for inhibition of heme polymerization.\textsuperscript{[53]} The drug resistance against the antifolates has also been reported due to specific gene mutations encoding for resistance to both dihydropteroate synthase (DHPS) and dihydrofolate reductase (DHFR).\textsuperscript{[54]} Recent reports on drug resistant malaria showed that malaria parasite had developed resistance against all class of drugs. Unfortunately, the emergence of malaria parasite strain resistant against effective and cheap chloroquine has eroded its efficacy.

1.1.6 Combination therapy

Combination therapy or polytherapy is the use of more than one medication or therapy. Foremost benefit of combination therapies is that it decreases the development of drug
resistance, since a pathogen is less likely to have resistance to multiple drugs concurrently.\textsuperscript{[55]} Due to resistance of malaria parasites to commonly accessible antimalarial drugs in market, combination therapy is promoted by world health organisation for malaria treatment with remarkable success.\textsuperscript{[56,57]} Sulfadoxine-pyrimethamine, an antifolate combination has been used all over the world, especially in areas where chloroquine has futile. It inhibits folate synthesis that is a key factor for parasite persistence. Pyrimethamine inhibits DHFR\textsuperscript{[58]} and sulfadoxine prevents dihydropteroate synthase (DHPS).\textsuperscript{[59, 60]} Although, the combination of sulfadoxine and pyrimethamine (SP) (figure-1.6) is still being used in Africa as first line treatment for non-severe \textit{falciparum} malaria, however, increasing resistance has been reported in Africa.\textsuperscript{[61, 62]} Several efforts are being made to get most effective combination from current or newly demonstrated drugs. A number of combination have been conveyed, out of which artemisinin based combination therapy is most effective.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{sulfadoxine_pyrimethamine.png}
\caption{Sulfadoxine and Pyrimethamine}
\end{figure}

Artemisinin-based combination therapy (ACT) is being widely promoted to counteract the increase in \textit{P. falciparum} antimalarial drug resistance.\textsuperscript{[63, 64]} Artemisinin derivatives are potent, rapidly acting antimalarials which can reduce gametocyte carriage and patient infectivity. The most common artemisinin derivatives used in ACT are artesunate and artemether as shown in figure-1.7. The drugs used in combination with the artemisinin derivative are called the partner drugs (mefloquine, lumefantrine, amodiaquine etc.). ACTs are now accepted by the scientific community and WHO as the best strategy for the treatment of malaria caused by \textit{Plasmodium falciparum}.\textsuperscript{[65]} Various combinations of
artemisinin and other drugs e.g. artemether + lumefantrine (A/L),\cite{66} artesunate + sulfamethoxypyrazine + pyrimethamine,\cite{67-71} dihydro-artemisinin + piperaquine and artesunate + mefloquine have been reported. The combination of artesunate + amodiaquine is therapeutically superior to a combination of chloroquine + pyrimethamine-sulfadoxine.\cite{72}

![Figure-1.7](attachment:figure17.png)

Various classes of antibiotics also exhibit antimalarial activity. Sulphonamide and sulphones are well known scaffolds exhibiting antimalarial activity. They are very effective when used in combination with pyrimethamine. It is well established fact that antibiotics such as erythromycin, clindamycin, tetracycline, rifampin and chloramphenicol (figure-1.8) displays antimalarial activity in vivo either alone or in combination with other commonly used antimalarial drugs.\cite{73-76}
Despite of slow antimalarial activity against malaria parasite, antibiotics such as doxycycline are used for antimalarial prophylaxis along with more efficient antimalarial drugs.[77] The fluoroquinolones are antimicrobial agents that are similar in structure to quinoline antimalarial drugs also exhibits antimalarial activity. Fluoroquinolones e.g. ciprofloxacin, norfloxacin and pefloxacin (figure-1.9) have been evaluated previously for antimalarial activity against \textit{P. falciparum} in vitro.[78-80]
1.2 Present work

Malaria is not just a disease commonly associated with poverty but also a cause of poverty and a major hindrance to economic development. In last few decades, WHO has made sincere efforts to control malaria globally. However, development of drug resistance by malaria parasites make things more complicated and is proving to be a challenging task in malaria control in most parts of the world.\[81\] Newer antimalarials were discovered in an effort to tackle this problem, but all these drugs are either expensive or have undesirable side effects. To overcome the problem of drug resistance, combination therapy has been used with limited success. Presently, artemisinin and its derivatives are the only drugs to cure all forms of malaria without any known resistance.\[82\] Consequently, there is an urgent need to find new potent antimalarial agent before malaria parasite get resistance against artemisinin and its derivatives.

Our present work is an attempt to find new lead molecules exhibiting good antimalarial activity. A systematic study is needed to find effective leading compounds using 4-aminoquinoline as basic skeleton.\[83-86\] These quinoline derivatives had previously shown promising antimalarial activity with lesser side effects. In literature it is quite well reported that aliphatic 2-3 carbon linker chain, planner quinoline ring and free amino group at position 4 exhibits encouraging antimalarial activity because of the complexion of free heme. There are several drugs like mefloquine or amodiaquine available which neither have aliphatic chain nor free amino group at position 4 of quinoline ring but are very effective against chloroquine resistant strains. Amodiaquine is still clinically useful due to the effectiveness but it has some serious side effects like heptatotoxicity and agranulocytosis. To prevent the formation of toxic metabolite, amodiaquine quinoneimine was developed having potent in vitro activity against CQ-resistant parasites. Unfortunately, the unacceptable high first pass metabolism of isoquine to dealkylated metabolites did not allow further drug development process. Modification of isoquine directed the discovery of drug candidate N-tert-butyl isoquine. In addition, 4-fluoro-N-tert-butylamodiaquine was also identified as a back-up compound for N-tertbutyl isoquine based on potent activity against CQ-sensitive and resistant parasites. Thus, these findings manifest considerable scope for developing new
antimalarial with quinoline nucleus. After analysing all the facts we have designed the analogs under scheme-I. In continuation of our research programme devoted to synthesis of various class of heterocycles as antimalarial agents, we identified trisubstituted triazines, as potential antimalarials.\cite{87a} The 4-anilinoquinoline moiety has been shown to be responsible for CQ-sensitive and CQ-resistant activity in *P. falciparum*. We predicted that combining two intrinsically active antimalarial moiety 4-anilinoquinoline and triazine would lead to develop more potent antimalarials. After surveying all these literature materials, we have used susbtituted triazines on series-I analogs to synthesize triazine-quinoline scaffolds under series-II. This study will be useful to understand the effect of triazine on antimalarial activity and crystallization pattern on the analogs of series-I.

Further, in scheme-III and IV, we liked 4-aminoquinoline and aromatic aldehydes together via flexible linear chained diaminoalkanes likers so that molecule has enough flexibility to fit in the binding site of the target, and as a result, this kind of hybrid molecules may show better antimalarial activity. Chauhan *et al.*, 2009\cite{87b} already reported the synthesis of 4-aminoquinolinepyrimidine conjugates in which 4-aminoquinoline and pyrimidine moieties were linked through an aromatic ring and some of these compounds have shown moderate activity. These compounds are synthesized to study the structure-activity relationship of quinoline derivatives. Among all synthetic molecules 4-amino-7-chloroquinoline is kept constant as a basic scaffold.

Under scheme-I we have synthesized 22 compounds using different aromatic anilines. Briefly, equimolar amount of 4,7-dichloroquinoline and desired aniline were reflux in dry ethanol in basic condition (K$_2$CO$_3$, 1.2 eq.). Compounds were purified by crystallization in methanol/methanol+acetone. These compounds were further used in scheme-II. 11 compounds were synthesized under this scheme using (7-chloroquinolin-4-yl-phenyl)-amine derivatives and cyanuric chloride. In short, 7-chloroquinolin-4-yl-phenyl-amine derivatives (12.0 mmol) and K$_2$CO$_3$ (24 mmol) were placed in a 50 mL round bottom flask with constant stirring. Dry THF (20 mL) was injected with the help of syringe into the flask under nitrogen atmosphere. After that the solution was cooled in an ice bath and stirred for 10 minutes. The mixture was stirred for another 30 min at
room temperature, and its colour became yellow. Then, the yellow solution was slowly dropped into a stirred solution of 2,4,6-trichloro-1,3,5-triazine (1.98 g, 10.8 mmol) in dry THF (20 mL) at 0 °C for 30 min. Afterwards the reaction mixture was stirred for 2 h at room temperature. The solvent was subsequently removed under reduced pressure. The residue was poured into ice water. The precipitate was collected through filtration, washed with chloroform, ethanol and dried under vacuum to get the desired compounds.

All the compound of series-III and series-IV are synthesized using N\(^1\)-(7-chloroquinolin-4-yl)-ethane-1,2-diamine (2) as starting material. Compound 2 was synthesized by a well-known procedure. In general a mixture of 4,7-dichloroquinoline (1 g, 5.1 mmol) and ethylenediamine (1.7 mL, 25.3 mmol) was heated 110 °C for 6 h under inert atmosphere continuously stirring to drive the reaction to completion and then cooled at room temperature. Then, NaOH (1 N, 10 mL) was added and organic product was extracted with ethyl acetate, washed with brine and dried over Na\(_2\)SO\(_4\). Solvent was removed under reduced pressure.

12 compounds were synthesized under scheme-III consuming N\(^1\)-(7-chloroquinolin-4-yl)-ethane-1,2-diamine. Briefly, in a round bottom flask, added N\(^1\)-(7-chloroquinolin-4-yl)-ethane-1,2-diamine (13-15 mmol) and aldehydes (10 mmol) under nitrogen atmosphere in dry acetonitrile (30-40 mL). Allow the reaction mixture at stirring for 2-4 h at room temperature. Progress of reaction was monitored by thin layer chromatography. When the spot of aldehyde and amine get disappeared in TLC, 15-17 mmol of sodium triacetoxyborohydride in dry CH\(_3\)CN (5 mL) was added into the reaction mixture under a nitrogen atmosphere at room temperature. The reaction mixture was extracted with ether (3 x 10 mL). The combined ether extracts were concentrated under reduced pressure. The crude product thus obtained was purified by column chromatography (silica gel 60-120 mesh) using ethyl acetate-hexane as eluent.

Under scheme-IV, 12 compounds were synthesized using N\(^1\)-(7-chloroquinolin-4-yl)-ethane-1,2-diamine (2) and aromatic aldehydes as a starting material. Concisely, ethanolic solution (10 ml) of N\(^1\)-(7-chloroquinolin-4-yl)-ethane-1,2-diamine (221 mg,
1 mmol), ethanol (10 mL) solution of desired aldehyde (1 mmol) was added dropwise and the mixture was refluxed for 2-4 h depending upon the completion of reaction. After completion of reaction, the reaction mixture was poured into ice cold water. The crude obtained was filtered and dried purified by crystallization in ethanol, CHCl₃/methanol or acetone.

All 58 compounds synthesized by above given procedure were purified either by crystallization or by column chromatography and characterized by different spectroscopic techniques e.g., FT-IR, ¹H & ¹³C-NMR, MASS and elemental analysis. X-ray crystallographic studies of compounds are discussed in chapter-2A and chapter-2B in detail. Compounds under scheme-I, II, III and IV are summarised in table-1.I-IV and their inhibitory concentration (IC₅₀) values against *P. falciparum* FCR3 strain are summarised in table-1.V-VII. Cytotoxicity and in vivo screening of compounds are under progress.
Table-1.I: List of compounds synthesized using scheme-I.

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<tr>
<td>38</td>
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<tr>
<td>41</td>
<td><img src="image" alt="Structure 41" /></td>
<td>47</td>
<td><img src="image" alt="Structure 47" /></td>
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Table-1.IV: List of compounds synthesized using scheme-IV.

<table>
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<tr>
<th>S. No.</th>
<th>Structure</th>
<th>S. No.</th>
<th>Structure</th>
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<td><img src="image22.png" alt="Structure" /></td>
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<tr>
<td></td>
<td><img src="image23.png" alt="Structure" /></td>
<td></td>
<td><img src="image24.png" alt="Structure" /></td>
</tr>
</tbody>
</table>
Table-1.V: Comparison of inhibitory concentration values of various quinoline analogs (Series-I) against *P. falciparum* FCR3 strain with Lumefantrine/Desbutyl-lumifantrine.

<table>
<thead>
<tr>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (µg/mL ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>0.098 ± 1.45</td>
</tr>
<tr>
<td>2,5-(OCH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0.013 ± 0.60</td>
</tr>
<tr>
<td>3,4,5-(OCH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0.159 ± 0.44</td>
</tr>
<tr>
<td>4-F</td>
<td>0.018 ± 0.82</td>
</tr>
<tr>
<td>O-Br</td>
<td>0.113 ± 0.35</td>
</tr>
<tr>
<td>2,4-Difluoro</td>
<td>0.087 ± 0.37</td>
</tr>
<tr>
<td>3,4-Difluoro</td>
<td>0.317 ± 0.81</td>
</tr>
<tr>
<td>3,5-Dichloro</td>
<td>0.043 ± 1.48</td>
</tr>
<tr>
<td>2,5-Dichloro</td>
<td>3.161 ± 0.30</td>
</tr>
<tr>
<td>2,3-Dichloro</td>
<td>0.275 ± 0.37</td>
</tr>
<tr>
<td>2,4-(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0.019 ± 0.20</td>
</tr>
<tr>
<td>2,3-(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1.173 ± 0.39</td>
</tr>
<tr>
<td>3,5-(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0.879 ± 0.39</td>
</tr>
<tr>
<td>3,4-(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1.311 ± 1.08</td>
</tr>
<tr>
<td>2-Cl-4-F</td>
<td>0.053 ± 0.11</td>
</tr>
<tr>
<td>3-Cl-4-F</td>
<td>0.038 ± 0.32</td>
</tr>
<tr>
<td>2-CH&lt;sub&gt;3&lt;/sub&gt;-4-F</td>
<td>0.015 ± 0.97</td>
</tr>
<tr>
<td>2-Cl-4-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>0.113 ± 0.72</td>
</tr>
</tbody>
</table>

Figure-1.10: Concentration response graph of compounds of series-I.
Table-1.VI: Comparison of inhibitory concentration values of various quinoline analogs (Series-III) against *P. falciparum* FCR3 strain with Lumefantrine/Desbutyl-lumifantrine.

<table>
<thead>
<tr>
<th>R²</th>
<th>IC₅₀ (µg/mL ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Cl</td>
<td>0.091 ± 0.84</td>
</tr>
<tr>
<td>4-F</td>
<td>0.055 ± 2.01</td>
</tr>
<tr>
<td>4-Cl</td>
<td>0.056 ± 0.97</td>
</tr>
<tr>
<td>4-Br</td>
<td>0.032 ± 0.35</td>
</tr>
<tr>
<td>4-CN</td>
<td>4.307 ± 0.37</td>
</tr>
<tr>
<td>2,4-Difluoro</td>
<td>0.027 ± 0.38</td>
</tr>
<tr>
<td>2,4-Dichloro</td>
<td>1.171 ± 1.30</td>
</tr>
<tr>
<td>3,4-(OCH₃)₂</td>
<td>1.163 ± 0.51</td>
</tr>
</tbody>
</table>

Figure-1.11: Concentration response graph of compounds of series-III.
Table-1.VII: Comparison of inhibitory concentration values of various quinoline analogs (Series-IV) against *P. falciparum* FCR3 strain with Lumefantrine/Desbutyl-lumifantrine.

<table>
<thead>
<tr>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (µg/mL ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-F</td>
<td>0.018 ± 1.25</td>
</tr>
<tr>
<td>4-Cl</td>
<td>0.037 ± 0.91</td>
</tr>
<tr>
<td>4-Br</td>
<td>0.066 ± 0.81</td>
</tr>
<tr>
<td>4-OH</td>
<td>0.711 ± 0.11</td>
</tr>
<tr>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1.581 ± 1.19</td>
</tr>
<tr>
<td>4-N-(CH&lt;sub&gt;3&lt;/sub&gt;)</td>
<td>0.077 ± 0.31</td>
</tr>
<tr>
<td>3,4-Dihydroxy</td>
<td>0.033 ± 0.21</td>
</tr>
<tr>
<td>2-Br-4-OH-3-OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>0.021 ± 0.36</td>
</tr>
</tbody>
</table>

Figure-1.12: Concentration response graph of compounds of series-IV.
1.3 Results and discussion

1.3.1 Design criteria

Quinine, member of cinchona alkaloid family was the first antimalarial drug followed by discovery of widely used drug chloroquine.\cite{20,21} Chloroquine, one of the most extensively used antimalarial drug has lost its utility due to the development of drug resistance. Several new modifications were introduced in basic chloroquine to overcome the problem of drug resistance. Various 4-aminoquinoline compounds were designed and analysed which includes amodiaquine, tebuquine, amopyroquine etc.\cite{42} Amodiaquine, a short-chain aminoquinoline antimalarials underwent phase I clinical trials. Its mechanism of action is thought to be similar to chloroquine but it is a matter of some controversy.\cite{88a} AQ retains antimalarial activity against many CQ-resistant parasites has low bioavailability and is considered as a pro-drug for desethylamodiaquine (DEAQ).\cite{88b} Phenyl ring of amodiaquine enhances activity vs. chloroquine resistant strains. In contrast to CQ, AQ produces a toxic quinoneimine metabolite.\cite{88c} To eliminate this problem, fluoro group was introduced replacing hydroxyl group at position 4 of the phenyl ring. Fluorine blocks the formation of toxic metabolite by P 450 mediated process and retains substantial antimalarial activity in chloroquine-resistant strains (Figure-1.13 & 1.14).\cite{44a} On careful analysis of all these compounds we found that there is still some scope for modification of basic scaffolds to improve antimalarial activity. Till now no systematic study was carried out using different electron releasing and donating groups on phenyl rings were used to synthesize amodiaquine derivatives. Assuming that these combinations might have significant impact on malaria life cycle by inhibiting hemoglobin formation, we have synthesized 22 compounds by direct nucleophilic substitution reaction using anilines with different functionalities at position 2, 3 or 4 of phenyl ring.

The dihydrofolate reductase (DHFR) enzyme is one of the well-defined and successfully exploited targets in malarial chemotherapy. Heterocyclic containing antimalarials like cycloguanil, is one of the important therapeutic drugs commonly employed for the prophylaxis and treatment of malaria target the DHFR.\cite{87c,87d} However, in the recent years, rapid spread of antifolate resistant \textit{P. falciparum} seriously conceded the clinical utilities of these drugs and consequently necessitates the need to search for new potent antifolate antimalarials. Apart from this, structurally similar to
cycloguanil, triazines have also been reported to possess promising antimalarial activity.\[88c\] As part of our research programme devoted to synthesis of various class of heterocycles as antimalarial agents we used cyanuric chloride to determine the effect of trisubstituted triazine on antimalarial analogs. Further, we studied the pattern, nature and type of hydrogen and hydrogen bonding on amodiaquine based derivatives of series I. These triazine analogs will also be very useful to relook the effect of free -NH group at position 4 and their effect on crystallization pattern.

![Figure-1.13: Metabolism of amodiaquine to toxic quinonemine and DEAQ metabolite.](image)

The introduction of a flexible linear chain between the two amino functions in CQ and the replacement of the terminal diethylamino group by different substituents like alkyl, phenyl with electron donating and electron withdrawing groups were screened and well reported. It is found that 4-aminoquinoline derivatives having 2 or 3 carbon linear chain between two terminal amino groups exhibited promising antimalarial activity in nano molar range. These modifications were expected to enhance the lifetime of chloroquine analogs and interesting activity against CQ resistant strains. It is found that 2 or 3 linear carbon chain linker between two terminal amino groups have enough flexibility to fit in the binding site of target. On the basis of these observations we propose to link 4-aminoquinoline and different substituted aldehydes using two carbon linker chain. In third series we have synthesized 4-aminoquinoline based Mannich bases. The length of four carbon linker chain is similar to that chloroquine except that one carbon is replaced by NH group. Different electron donating and electron releasing groups were used to
determine the structure activity relationship. In series IV, we followed the similar designing criteria as we did in series III. Here we did not follow reduction thus, restricted free rotation between two amino terminal groups.

**Figure-1.14:** Structure-activity relationship (SAR) of chloroquine, amodiaquine and designing of new analogs under scheme I-IV.
1.3.2 In vitro antimalarial activity of compounds

All synthetic compounds were evaluated against a Gambian (West Africa) CQ (100 ng/mL), pyrimethamine (15 nM) and cycloguanil resistant FCR3 strain of *P. falciparum*. In vitro activity results are summarized in Table 1.V-VII. Most of compounds of series-I exhibited very promising activity ranges from 3.161-0.013 µg/mL. By going through activity, we found that most of the compounds showed very good in vitro activity. Presence of single methoxy group at position 4 in compound 24 exhibited encouraging in vitro antimalarial activity with IC₅₀=0.098 µg/mL. Further, addition of one more methoxy group in compound 17 had significant improvement in activity with IC₅₀=0.013 µg/mL.

Compound 7 having three methoxy groups at 3,4,5 positions of the phenyl ring showed significant loss of activity with IC₅₀ (0.159 µg/mL) as compared to two methoxy groups. This could be steric hindrance caused by three methoxy group on binding to malaria parasite. There are four compounds which contains two methyl groups at different position in the benzene ring. Among them the compound 4 contains 2,4-dimethyl (IC₅₀=0.019 µg/mL). Interestingly, we did not observe activity in 2,5 & 2,6-dimethyl derivatives. There is no explanation why there is change of single methyl group at position 5 or 6 lost complete loss of activity. Again, compound 22 contained 3,5-dimethyl group also showed significant activity with IC₅₀ 0.879 µg/ml. The change of position of one methyl group from 5 to 6 in benzene ring showed slight decrease in activity with IC₅₀=1.311 µg/mL as seen in compound 16. This suggested that position of methyl group with respect to second has synergistic effect and this is why the same methyl group enhances activity while decrease with shift of position. This could be due to binding of parasite enzyme. However, exact mode of interaction of these compound can be ascertain only by crystallographic analysis and docking studies of compounds bound with parasite enzyme.

This study also reveals that halogen atom has also significant effect activity. Compound 21 and 8 having fluoro group at ortho and meta position did not exhibited promising activity, while compound 32 having fluoro group at para position of phenyl ring exhibited IC₅₀=0.018 µg/mL. Difluoro derivatives like 2,4-difluoro derivative showed good activity with IC₅₀=0.087 µg/mL while its isomer 3,4-difluoro derivative
showed lesser mean inhibitory activity value 0.317 µg/mL. On the other hand, compound 3 and 23 having dichloro groups were found inactive while its isomer compound 13 having 2,5-dichloro group was active with IC$_{50}$=3.161 µg/mL. Combinations of different halogen atoms like chloro and fluoro groups are also found very active. Compound 5 and 18 having Cl and F group at 3,4 and 2,4 position of phenyl ring was found highly active with IC$_{50}$=0.038 and 0.053 µg/mL, respectively. Compound 13 having chloro group at 2,5 position at phenyl ring was found least active with IC$_{50}$=3.161 µg/mL. However, compound having chloro group at 2,6 position lost its activity.

Compounds (36-47) were synthesized in series-III by reductive amination reaction exhibited interesting inhibitory activity value in the range of 4.307-0.027 µg/mL. Electron withdrawing halogen atoms were highly active compounds. The compound 39 with 4-F and 40 with 4-Cl showed similar activity with IC$_{50}$=0.055 and 0.056 µg/mL. Compound 38 with 4-Br at phenyl ring was most active with IC$_{50}$=0.032 µg/mL. Thus, in this series we found the Br>F>Cl activity order of para halogens on phenyl ring. Compound 45 having fluoro group at 2 and 4 position of phenyl ring showed highest activity with IC$_{50}$ value 0.027 µg/mL while dichloro substituents at 2,4-position of compound 37 showed reduced activity with IC$_{50}$=1.171 µg/mL. Thus we can conclude that fluoro group was more potent and increased antimalarial activity when placed at ortho & para position of the phenyl ring. Another compound 41 having 4-CN group at para position on phenyl ring exhibited least inhibitory value 4.307 µg/mL. Electron donating methoxy and methyl groups were not at all active except compound 46 having 3,4-dimethoxy group with IC$_{50}$=1.163 µg/mL. Biological activity screening of other derivatives is under progress.

In vitro antimalarial activity of 12 compounds (48-59) of series-IV are summarised in table-1.VII. These novel quinoline Schiff bases exhibited inhibitory value in the range of 1.581-0.018 µg/mL. Derivatives having halogen atoms at position 4 of phenyl ring were found highly active. Compound having 4-F group at phenyl ring showed IC$_{50}$=0.018 µg/mL, while 4-Cl group at phenyl ring exhibited IC$_{50}$=0.037 µg/mL. Bromo group at para position of phenyl ring was also active with IC$_{50}$=0.066 µg/mL. In this 4-halogen series we found activity order 4-F>4-Cl>4Br with IC$_{50}$=0.018, 0.037 and 0.066 µg/mL, respectively. This decreasing activity may be due to the size
and electron withdrawing nature of the halogen. Compound 55 having 4-F group was found most active followed by chloro and bromo. Another derivative 49 having N,N-dimethyl group at position 4 of phenyl ring exhibited promising activity with IC₅₀=0.077 µg/mL. Compound 52 having methyl group at para position of aryl ring was lesser active with IC₅₀=1.581 µg/mL. This effect may be due to the electron donating nature of methyl group. Another derivative compound 50 having 3,4-dihydroxy group at phenyl ring showed improved activity with IC₅₀=0.033 µg/mL. This enhanced activity could be attributed to the electron donating nature of the hydroxyl group. The compound having 2-bromo-3-hydroxy-4-methoxy was highly active with IC₅₀=0.021 µg/mL. Biological activity of other derivatives is under progress.

1.4 Experimental details

Various chemicals and solvents used in this study were purchased from E. Merk (India) and Sigma-Aldrich chemicals. Melting points were determined by using open capillary method and are uncorrected. \(^1\)H-NMR spectral data were recorded on Brucker Avance spectrometer at 300 MHz and Jeol JNM spectrometer at 400 MHz, respectively, using TMS as an internal standard. The chemical shift values were recorded on δ scale and the coupling constants (\(J\)) in hertz. The following abbreviations were used in reporting spectra: s = singlet, d = doublet, t = triplet, q = quartet, m = multiple. IR spectra were obtained on a Perkin Elmer Fourier-transform infrared (FT-IR) Spectrophotometer (Spectrum 2000) in potassium bromide disk. ESI-MS spectra were obtained on a Waters micromass LCT Mass spectrometer. Elemental analysis was done on Elementar GmbH VarioEl analyser.

**General procedure for the synthesis of N\(^1\)-(7-chloro-quinolin-4-yl)-ethane-1,2-diamine (2)\)**

A mixture of 4,7-dichloroquinoline (1 g, 5.1 mmol) and ethylenediamine (1.7 mL, 25.3 mmol) was heated 110 °C for 6 h under inert atmosphere continuously stirring to drive the reaction to completion and then cooled at room temperature. Then, NaOH (1 N, 10 mL) was added and organic product was extracted with ethylacetate, washed with brine and dried over Na₂SO₄. Solvent was removed under reduced pressure. The compound was used directly in reactions without further purification.\[^{[89, 90]}\]
Compound 2: N-1-(7-chloroquinolin-4-yl)-ethane-1,2-diamine
Pale yellow solid; Yield=79%; Ms: m/z 221 [M⁺]; Rf=0.30 (MeOH:CHCl₃ 2:8); Anal. Calcd. (%) for C₁₁H₁₂ClN₃: C, 59.60; H, 5.46; N, 18.95; Cl, 15.99. ¹H-NMR (300 MHz, CDCl₃, ppm); δ 4.50 (br, s, 1H, NH), δ 1.20 (s, 2H, NH₂), δ 8.84 (d, H₂, J=9.03 Hz), δ 8.41 (s, 1H), δ 7.67 (d, H₅, J= 8.3 Hz), δ 7.50 (d, H₆, J=7.7 Hz), δ 6.44 (d, H₃, J=7.1 Hz). ¹³C-NMR (300 MHz, CDCl₃, ppm); δ 152.1, 147.5, 147.8, 128.3, 126.7, 122.9, 117.3, 110.4, 104.1, 34.6, 32.2.

I. General procedure for synthesis of various 7-chloroquinolin-4-yl-phenylamine (3-24)
Compounds (3-24) were synthesized using 4,7-dichloroquinoline and suitable substituted anilines. Briefly, equimolar quantities of anilines (1 mmol) and 4,7-dichloroquinoline (1 mmol) refluxed in dry ethanol in basic medium (1.2 mmol K₂CO₃) for 2-16 h depending upon the completion of the reaction. Progress of reaction was monitored by thin layer chromatography. After completion of reaction, reaction mixture was neutralised by NaOH solution and extracted with 3 x 50 mL of CHCl₃, washed with NaHCO₃ and brine. The organic layer was dried over anhydrous Na₂SO₄. The solvent was again evaporated under reduced pressure. The ligands were purified by successive recrystallization.[91]

Compound 3: (7-Chloroquinolin-4-yl)-(2,4-dichlorophenyl)-amine
White solid; Yield=79%; mp=274-278 °C; Ms: m/z 323 [M⁺]; Rf=0.65 (MeOH:CHCl₃ 2:8); Anal. Calcd. (%) for C₁₅H₉Cl₂N₂: C, 54.98; H, 2.78; N, 5.15; Cl, 37.09. IR (KBr, cm⁻¹): 3448.63, 2593.15, 1608.33, 1369.54, 1207.25, 1093.78. ¹H-NMR (300 MHz, CD₃OD, ppm); δ 3.62 (s, 1H, NH), δ 8.84 (d, H₂, J=9.03 Hz), δ 8.41 (s, 1H), δ 7.67 (d, H₅, J=8.3 Hz), δ 7.50 (d, H₆, J=7.7 Hz), δ 6.44 (d, H₃, J=7.1 Hz), δ 7.56 (s, 1H), δ 6.80 (d, H₁₅, J=8.7 Hz), δ 6.70 (d, H₁₆, J=7.2 Hz). ¹³C-NMR (300 MHz, CD₃OD, ppm); δ 152.1, 147.5, 147.8, 134.6, 133.0, 128.3, 126.7, 122.9, 117.3, 115.2, 110.4, 138.2, 117.2, 115.2, 109.1.

Compound 4: (7-Chloroquinolin-4-yl)-(2,4-dimethylphenyl)-amine
Light yellow solid; Yield=80%; mp=308-312 °C; Ms: m/z 283 [M⁺]; Rf=0.69 (MeOH:CHCl₃ 2:8); Anal. Calcd. (%) for C₁₇H₁₅ClN₂: C, 72.35; H, 5.22; N, 9.93; Cl,
12.54. IR (KBr, cm\(^{-1}\)): 3184.15, 2870.07, 1653.93, 1450.62, 1329.59. \(^1\)H-NMR (300 MHz, CD\(_3\)OD, ppm): \(\delta\) 2.55 (s, 6H, CH\(_3\)), \(\delta\) 4.04 (s, 1H, NH), \(\delta\) 8.85 (d, H\(_2\), \(J=7.7\) Hz), \(\delta\) 8.31 (s, 1H\(_8\)), \(\delta\) 7.67 (d, 1H\(_5\), \(J=7.8\) Hz), \(\delta\) 7.50 (d, 1H\(_6\), \(J=7.6\) Hz), \(\delta\) 6.42 (d, 1H\(_3\), \(J=7.5\) Hz), \(\delta\) 6.02 (s, 1H\(_12\)), \(\delta\) 6.52 (d, 1H\(_{15}\), \(J=7.9\) Hz), \(\delta\) 6.73 (d, 1H\(_{16}\), \(J=7.2\) Hz). \(^{13}\)C-NMR (300 MHz, CD\(_3\)OD, ppm): \(\delta\) 153.1, 151.5, 150.8, 134.6, 133.0, 128.3, 126.7, 122.9, 117.3, 115.2, 110.4, 138.2, 117.2, 115.2, 103.1, 21.2, 12.6.

**Compound 5:** (7-Chloroquinolin-4-yl)-(3-chloro-4-fluorophenyl)-amine

Yellow solid; Yield=71%; mp=308-311 °C; Ms: m/z 307 [M\(^+\)]; \(R_f=0.62\) (MeOH:CHCl\(_3\) 2:8); Anal. Calcd. (%) for C\(_{15}\)H\(_9\)Cl\(_2\)FN\(_2\): C, 58.95; H, 2.66; N, 9.19; Cl, 23.09; F, 6.12. IR (KBr, cm\(^{-1}\)): 3115.37, 3052.15, 2879.07, 2585.09, 1420.19, 1231.56. \(^1\)H-NMR (300 MHz, CD\(_3\)OD, ppm): \(\delta\) 3.64 (s, 1H, NH), \(\delta\) 8.85 (d, H\(_2\), \(J=8.05\) Hz), \(\delta\) 8.32 (s, 1H\(_8\)), \(\delta\) 7.67 (d, 1H\(_5\), \(J=8.3\) Hz), \(\delta\) 6.50 (d, 1H\(_6\), \(J=7.7\) Hz), \(\delta\) 6.45 (d, 1H\(_3\), \(J=7.5\) Hz), \(\delta\) 6.52 (s, 1H\(_12\)), \(\delta\) 6.77 (d, 1H\(_{15}\), \(J=7.7\) Hz), \(\delta\) 6.80 (d, 1H\(_{16}\), \(J=8.2\) Hz). \(^{13}\)C-NMR (300 MHz, CD\(_3\)OD, ppm): \(\delta\) 153.1, 151.5, 150.8, 149.4, 134.6, 133.0, 128.3, 126.7, 122.9, 117.3, 115.2, 110.4, 138.2, 117.2, 115.2, 103.1.

**Compound 6:** (7-Chloroquinolin-4-yl)-(2,5-dimethylphenyl)-amine

White solid; Yield=78%; mp=310-313 °C; Ms: m/z 282 [M\(^+\)]; \(R_f=0.69\) (MeOH:CHCl\(_3\) 2:8); Anal. Calcd. (%) for C\(_{17}\)H\(_{15}\)ClN\(_2\): C, 72.21; H, 5.35; N, 9.91; Cl, 12.54. IR (KBr, cm\(^{-1}\)): 3180.15, 3004.73, 1540.87, 1231.56, 1056.85. \(^1\)H-NMR (300 MHz, CD\(_3\)OD, ppm): \(\delta\) 2.35 (s, 6H, CH\(_3\)), \(\delta\) 4.00 (s, 1H, NH), \(\delta\) 8.85 (d, H\(_2\), \(J=8.05\) Hz), \(\delta\) 8.32 (s, 1H\(_8\)), \(\delta\) 7.67 (d, 1H\(_5\), \(J=8.3\) Hz), \(\delta\) 6.50 (d, 1H\(_6\), \(J=7.7\) Hz), \(\delta\) 6.45 (d, 1H\(_3\), \(J=7.5\) Hz), \(\delta\) 6.52 (s, 1H\(_12\)), \(\delta\) 6.77 (d, 1H\(_{15}\), \(J=7.7\) Hz), \(\delta\) 6.80 (d, 1H\(_{16}\), \(J=8.2\) Hz). \(^{13}\)C-NMR (300 MHz, CD\(_3\)OD, ppm): \(\delta\) 153.0, 151.9, 150.8, 149.4, 134.6, 133.0, 128.3, 126.7, 122.9, 117.3, 115.2, 110.4, 138.2, 117.2, 115.2, 103.1.

**Compound 7:** (7-Chloroquinolin-4-yl)-(3,4,5-trimethoxylphenyl)-amine

Bright yellow solid; Yield=75%; mp=313-317 °C; Ms: m/z 344 [M\(^+\)]; \(R_f=0.62\) (MeOH:CHCl\(_3\) 2:8); Anal. Calcd. (%) for C\(_{18}\)H\(_{17}\)ClN\(_2\)O\(_3\): C, 62.28; H, 4.12; N, 8.70; Cl, 10.97; O, 13.92. IR (KBr, cm\(^{-1}\)): 3006.19, 2901.43, 1607.65, 1560.24, 1330.02, 1242.00. \(^1\)H-NMR (300 MHz, CD\(_3\)OD, ppm): \(\delta\) 3.85 (s, 9H, OCH\(_3\)), \(\delta\) 4.35 (s, 1H, NH), \(\delta\) 8.85 (d, H\(_2\), \(J=8.50\) Hz), \(\delta\) 8.3 (s, 1H\(_8\)), \(\delta\) 7.67 (d, 1H\(_5\), \(J=7.3\) Hz), \(\delta\) 7.50 (d, 1H\(_6\), \(J=7.5\) Hz), \(\delta\) 6.56 (d, 1H\(_3\), \(J=7.7\) Hz), \(\delta\) 6.77 (d, 1H\(_{15}\), \(J=7.7\) Hz), \(\delta\) 6.80 (d, 1H\(_{16}\), \(J=8.2\) Hz). \(^{13}\)C-NMR (300 MHz, CD\(_3\)OD, ppm): \(\delta\) 153.0, 151.9, 149.8, 134.6, 133.0, 128.4, 124.5, 123.9, 127.3, 115.2, 110.4, 128.2, 117.2, 115.2, 103.1, 20.2, 12.4.
\( J=6.7 \text{ Hz} \), \( \delta 6.42 \) (d, 1H, \( J=6.7 \text{ Hz} \)), \( \delta 5.44 \) (s, 2H). \^13C-NMR (300 MHz, CD\(_3\)OD, ppm): \( \delta 153.1, 151.5, 149.8, 134.6, 133.0, 128.3, 126.7, 123.9, 127.3, 115.2, 110.4, 128.2, 117.2, 115.2, 103.1, 57.8.

**Compound 8: (7-Chloroquinolin-4-yl)-(2-methyl-4-fluorophenyl)-amine**

Light orange; Yield=65\%; mp=314-316 °C; Ms: m/z 286 [M\(^+\)]; \( R_f=0.64 \) (MeOH:CHCl\(_3\) 2:8); Anal. Calcd. (%) for C\(_{16}\)H\(_{12}\)ClFN\(_2\): C, 67.02; H, 9.77; N, 8.70; Cl, 12.46. IR (KBr, cm\(^{-1}\)): 3279.75, 2809.57, 2036.49, 1615.49, 1337.05, 1239.84, 1164.43. \(^1\)H-NMR (300 MHz, CD\(_3\)OD, ppm): \( \delta 2.55 \) (s, 3H, CH\(_3\)), \( \delta 4.50 \) (s, 1H, NH), \( \delta 8.85 \) (d, H\(_2\), \( J=8.01 \text{ Hz} \)), \( \delta 8.31 \) (s, 1 H\(_8\)), \( \delta 7.67 \) (d, 1H\(_5\), \( J=7.3 \text{ Hz} \)), \( \delta 7.50 \) (d, 1H\(_6\), \( J=7.2 \text{ Hz} \)), \( \delta 6.40 \) (d, 1H\(_3\), \( J=7.1 \text{ Hz} \)), \( \delta 6.44 \) (s, 1H\(_{13}\)), \( \delta 6.55 \) (d, 1H\(_{15}\)), \( \delta 6.35 \) (d, 1H\(_{16}\)). \(^{13}\)C-NMR (300 MHz, CD\(_3\)OD, ppm): \( \delta 153.1, 151.5, 149.8, 134.6, 133.0, 128.3, 126.7, 123.9, 127.3, 115.2, 110.4, 128.2, 117.2, 115.2, 103.1, 13.3.

**Compound 9: (7-Chloroquinolin-4-yl)-(2-bromophenyl)-amine**

White solid; Yield=67\%; mp=298-302 °C; Ms: m/z 334 [M\(^+\)]; \( R_f=0.66 \) (MeOH:CHCl\(_3\) 2:8); Anal. Calcd. (%) for C\(_{15}\)H\(_{10}\)BrClN\(_2\): C, 54.00; H, 3.02; N, 23.95; Br, 8.63. IR (KBr, cm\(^{-1}\)): 3185.38, 2880.13, 2845.73, 1660.02, 1551.02, 1329.89, 1291.91. \(^1\)H-NMR (300 MHz, CD\(_3\)OD, ppm): \( \delta 4.80 \) (s, 1H, NH), \( \delta 8.85 \) (d, H\(_2\), \( J=9.03 \text{ Hz} \)), \( \delta 8.31 \) (s, 1 H\(_8\)), \( \delta 7.67 \) (d, 1H\(_5\), \( J=8.3 \text{ Hz} \)), \( \delta 7.50 \) (d, 1H\(_6\), \( J=7.7 \text{ Hz} \)), \( \delta 6.41 \) (d, 1H\(_3\), \( J=7.1 \text{ Hz} \)), \( \delta 7.74-7.65 \) (m, 4H, Ar-H). \(^{13}\)C-NMR (300 MHz, CD\(_3\)OD, ppm): \( \delta 153.1, 151.5, 149.8, 134.6, 133.0, 128.3, 126.7, 123.9, 127.3, 115.2, 110.4, 128.2, 117.2, 115.2, 103.1.

**Compound 10: (7-Chloroquinolin-4-yl)-(3-fluorophenyl)-amine**

Pale yellow solid; Yield=77\%; mp=317-319 °C; Ms: m/z 272 [M\(^+\)]; \( R_f=0.52 \) (MeOH:CHCl\(_3\) 2:8); Anal. Calcd. (%) for C\(_{15}\)H\(_{10}\)ClFN\(_2\): C, 66.70; H, 3.06; N, 10.27; Cl, 10.27; F, 6.97. IR (KBr, cm\(^{-1}\)): 3445.09, 3004.97, 1587.72, 1542.37, 1331.71, 1255.52. \(^1\)H-NMR (300 MHz, CD\(_3\)OD, ppm): \( \delta 5.20 \) (s, 1H, NH), \( \delta 8.82 \) (d, H\(_2\), \( J=8.1 \text{ Hz} \)), \( \delta 8.27 \) (s, 1 H\(_8\)), \( \delta 7.32 \) (d, 1H\(_5\), \( J=7.3 \text{ Hz} \)), \( \delta 7.32 \) (d, 1H\(_5\), \( J=7.3 \text{ Hz} \)), \( \delta 6.41 \) (d, 1H\(_3\), \( J=7.1 \text{ Hz} \)), \( \delta 7.74-7.65 \) (m, 4H, Ar-H). \(^{13}\)C-NMR (300 MHz, CD\(_3\)OD, ppm): \( \delta 153.1, 151.5, 149.8, 134.6, 133.0, 128.3, 126.7, 123.9, 127.3, 115.2, 110.4, 128.2, 117.2, 115.2, 103.5.
**Compound 11: (7-Chloroquinolin-4-yl)-(2,3-dimethylphenyl)-amine**

White solid; Yield=65%; mp=281-284 °C; Ms: m/z 283 [M⁺]; Rf=0.62 (MeOH:CHCl₃ 2:8); Anal. Calcd. (%) for C₁₇H₁₅ClN₂: C, 72.24; H, 5.60; N, 9.76; Cl, 12.41. IR (KBr, cm⁻¹): 348.63, 1578.07, 1455.69, 1207.25, 1093.78. ¹H-NMR (300 MHz, CD₃OD, ppm): δ 2.35 (s, 6H, CH₃), δ 4.15 (s, 1H, NH), δ 8.83 (d, J=8.7 Hz), δ 7.32 (s, 1 H₈), δ 6.60 (d, 1H₅, J=8.3 Hz), δ 6.40 (d, 1H₆, J=7.6 Hz), δ 6.38 (d, 1H₃, J=7.1 Hz), δ 7.50-6.65 (m, 3H, Ar-H). ¹³C-NMR (300 MHz, CD₃OD, ppm): δ 149.1, 148.5, 146.8, 133.6, 133.0, 128.3, 126.7, 125.9, 121.3, 115.9, 120.4, 119.2, 118.3, 115.2, 103.1, 12.4, 10.4.

**Compound 12: (7-Chloroquinolin-4-yl)-(2,6-dimethylphenyl)-amine**

White solid; Yield=62%; mp=277-280 °C; Ms: m/z 283 [M⁺]; Rf=0.65 (MeOH:CHCl₃ 2:8); Anal. Calcd. (%) for C₁₇H₁₅ClN₂: C, 72.44; H, 5.65; N, 9.96; Cl, 12.46. IR (KBr, cm⁻¹): 3279.75, 2036.49, 1587.58, 1497.98, 1367.03, 1239.84. ¹H-NMR (300 MHz, CD₃OD, ppm): δ 2.30 (s, 6H, CH₃), δ 4.25 (s, 1H, NH), δ 8.81 (d, J=8.0 Hz), δ 7.32 (s, 1 H₈), δ 6.62 (d, 1H₅, J=8.1 Hz), δ 6.40 (d, 1H₆, J=7.4 Hz), δ 6.38 (d, 1H₃, J=7.1 Hz), δ 7.50-6.65 (m, 3H, Ar-H). ¹³C-NMR (300 MHz, CD₃OD, ppm): δ 149.1, 148.5, 146.8, 133.6, 133.0, 128.3, 126.7, 125.9, 121.3, 115.9, 119.9, 118.4, 119.2, 118.3, 115.2, 105.1, 12.4, 12.4.

**Compound 13: (7-Chloroquinolin-4-yl)-(2,5-dichlorophenyl)-amine**

White solid; Yield=71%; mp=281-283 °C; Ms: m/z 322 [M⁺]; Rf=0.60 (MeOH:CHCl₃ 2:8); Anal. Calcd. (%) for C₁₅H₉Cl₃N₂: C, 55.77; H, 2.70; N, 8.56; Cl, 32.97. IR (KBr, cm⁻¹): 3006.19, 2676.07, 1607.65, 1542.56, 1459.16, 1330.02. ¹H-NMR (300 MHz, CD₃OD, ppm): δ 4.80 (s, 1H, NH), δ 8.80 (d, J=8.85 Hz), δ 8.30 (s, 1 H₈), δ 6.75 (d, 1H₅, J=8.3 Hz), δ 6.50 (d, 1H₆, J=7.7 Hz), δ 6.50 (d, 1H₃, J=7.1 Hz), δ 6.45 (d, 1H₄, J=7.5), δ 6.50 (d, 1H₁₄, J=8.8 Hz), δ 6.72 (s, 1H₁₆, J= 7.8 Hz). ¹³C-NMR (300 MHz, CD₃OD, ppm): δ 149.5, 151.4, 148.8, 135.6, 133.0, 128.3, 126.7, 122.9, 117.3, 115.2, 110.4, 138.2, 117.2, 115.2, 103.1.

**Compound 14: (7-Chloroquinolin-4-yl)-(2,4-difluorophenyl)-amine**

White solid; Yield=75%; mp=210-213 °C; Ms: m/z 290 [M⁺]; Rf=0.60 (MeOH:CHCl₃ 2:8); Anal. Calcd. (%) for C₁₅H₉ClF₂N₂: C, 61.88; H, 3.22; N, 9.07; Cl, 12.20; F, 13.64.
IR (KBr, cm$^{-1}$): 3006.54, 2886.07, 1605.65, 1512.52, 1451.13, 1330.22. $^1$H-NMR (300 MHz, CD$_3$OD, ppm): $\delta$ 4.0 (s, 1H, NH), $\delta$ 8.85 (d, $H_2$, $J$=9.03 Hz), $\delta$ 8.30 (d, 1H$_6$, $J$=7.6 Hz), $\delta$ 6.94 (d, 1H$_3$, $J$=7.1 Hz), $\delta$ 6.42 (s, 1H$_{13}$), $\delta$ 6.50 (d, 1H$_{15}$, $J$=8.7 Hz), $\delta$ 6.81 (d, 1H$_{16}$, $J$=7.5 Hz). $^{13}$C-NMR (300 MHz, CD$_3$OD, ppm): $\delta$ 153.1, 151.5, 150.8, 134.6, 133.0, 128.3, 126.7, 122.9, 117.3, 115.2, 110.4, 138.2, 117.2, 115.2, 103.1.

**Compound 15: (7-Chloroquinolin-4-yl)-(4-fluorophenyl)-amine**

Light brown solid; Yield=77%; mp=314-316 °C; Ms: m/z 272 [M$^+$]; R$_f$=0.54 (MeOH:CHCl$_3$ 2:8); Anal. Calcd. (%) for C$_{15}$H$_{10}$ClFN$_2$: C, 66.75; H, 3.06; N, 10.22; Cl, 10.37; F, 6.87. IR (KBr, cm$^{-1}$): 3184.15, 3115.37, 2649.47, 1585.09, 1540.87, 1291.49. $^1$H-NMR (300 MHz, CD$_3$OD, ppm): $\delta$ 4.50 (s, 1H, NH), $\delta$ 8.85 (d, $H_2$, $J$=8.3 Hz), $\delta$ 8.27 (s, 1H$_8$), $\delta$ 7.35 (d, 1H$_5$, $J$=7.3 Hz), $\delta$ 6.34 (d, 1H$_6$, $J$=7.7 Hz), $\delta$ 6.50 (d, 1H$_3$, $J$=7.5 Hz), $\delta$ 6.45 (d, 2H$_{12}$ & 16), 6.74 (d, 2H$_{13}$ & 15). $^{13}$C-NMR (300 MHz, CD$_3$OD, ppm): $\delta$ 154.2, 151.5, 148.8, 134.6, 132.8, 128.3, 126.7, 125.8, 123.9, 127.3, 115.2, 110.4, 128.2, 117.2, 115.2, 103.5.

**Compound 16: (7-Chloroquinolin-4-yl)-(3,4-dimethylphenyl)-amine**

White solid; Yield=72%; mp=314-316 °C; Ms: m/z 282 [M$^+$]; R$_f$=0.67 (MeOH:CHCl$_3$ 2:8); Anal. Calcd. (%) for C$_{17}$H$_{15}$ClN$_2$: C, 72.20; H, 5.45; N, 9.82; Cl, 12.54. IR (KBr, cm$^{-1}$): 3370.21, 2834.24, 1612.59, 1408.51, 1365.66, 1229.94. $^1$H-NMR (300 MHz, CD$_3$OD, ppm): $\delta$ 2.40 (s, 6H, CH$_3$), $\delta$ 4.00 (s, 1H, NH), $\delta$ 8.81 (d, $H_2$, $J$=8.14 Hz), $\delta$ 8.32 (s, 1H$_8$), $\delta$ 7.63 (d, 1H$_5$, $J$=8.4 Hz), $\delta$ 7.50 (d, 1H$_6$, $J$=8.7 Hz), $\delta$ 7.12 (d, 1H$_3$, $J$=7.20 Hz), $\delta$ 6.20 (s, 1H$_{12}$), $\delta$ 6.15 (d, 1H$_{16}$, $J$=7.8 Hz), $\delta$ 6.67 (d, 1H$_{15}$, $J$=7.9 Hz). $^{13}$C-NMR (300 MHz, CD$_3$OD, ppm): $\delta$ 151.8, 148.8, 147.8, 134.6, 132.8, 128.3, 126.7, 125.8, 127.3, 115.2, 110.4, 128.2, 117.2, 115.2, 103.5.

**Compound 17: (7-Chloroquinolin-4-yl)-(2,5-dimethoxyphenyl)-amine**

White solid; Yield=75%; mp=281-283 °C; Ms: m/z 314 [M$^+$]; R$_f$=0.68 (MeOH:CHCl$_3$ 2:8); Anal. Calcd. (%) for C$_{17}$H$_{15}$N$_2$O$_2$: C, 64.77; H, 4.90; N, 8.70; Cl, 11.46; O, 10.17. IR (KBr, cm$^{-1}$): 3370.21, 3057.92, 1612.59, 1560.07, 1365.66, 1313.57. $^1$H-NMR (300 MHz, CD$_3$OD, ppm): $\delta$ 3.75 (s, 6H, OCH$_3$), $\delta$ 4.50 (s, 1H, NH), $\delta$ 8.85 (d, $H_2$, $J$=8.01 Hz), $\delta$ 8.38 (s, 1H$_8$), $\delta$ 7.67 (d, 1H$_5$, $J$=7.3 Hz), $\delta$ 7.50 (d, 1H$_6$, $J$=7.6 Hz), $\delta$ 6.46 (d,
1H, J=7.1 Hz), δ 6.49 (s, 1H), δ 6.05 (d, 1H), δ 5.86 (d, 1H). 13C-NMR (300 MHz, CD3OD, ppm): δ 155.1, 151.5, 149.8, 140.6, 133.0, 128.3, 126.7, 123.9, 127.3, 115.2, 110.4, 128.2, 117.2, 115.2, 101.7, 56.3.

**Compound 18: (7-Chloroquinolin-4-yl)-(2-chloro-4-fluorophenyl)-amine**

Dark brown solid; Yield=71%; mp=277-279 °C; Ms: m/z 306 [M]+; Rf=0.62 (MeOH:CHCl3 2:8); Anal. Calcd. (%) for C15H9Cl2FN2: C, 58.95; H, 2.66; N, 9.19; Cl, 23.09; F, 6.12. IR (KBr, cm⁻¹): 3279.75, 2809.57, 2036.49, 1615.49, 1539.97, 1337.05. 1H-NMR (300 MHz, CD3OD, ppm): δ 4.15 (s, 1H, NH), δ 8.80 (d, H2, J=8.08 Hz), δ 8.32 (s, 1H), δ 6.60 (d, 1H, J=8.4 Hz), δ 6.50 (d, 1H, J=7.4 Hz), δ 6.40 (d, 1H, J=7.5 Hz), δ 6.73 (s, 1H), δ 6.60 (d, 1H, J=7.7 Hz), δ 6.38 (d, 1H, J=8.2 Hz). 13C-NMR (300 MHz, CD3OD, ppm): δ 153.1, 151.5, 150.8, 144.1, 134.6, 130.4, 128.3, 126.7, 120.3, 118.1, 115.9, 114.4, 138.2, 117.2, 115.2, 103.5.

**Compound 19: (7-Chloroquinolin-4-yl)-(2-chloro-4-methylphenyl)-amine**

White solid; Yield=72%; mp=288-291 °C; Ms: m/z 302 [M]+; Rf=0.68 (MeOH:CHCl3 2:8); Anal. Calcd. (%) for C16H12Cl2N2: C, 63.88; H, 3.49; N, 9.24; Cl, 23.39. IR (KBr, cm⁻¹): 3008.54, 2686.07, 1605.65, 1516.56, 1455.16, 1331.02. 1H-NMR (300 MHz, CD3OD, ppm): δ 2.30 (s, 1H, CH3), δ 4.0 (s, 1H, NH), δ 8.85 (d, H2, J=9.03 Hz), δ 8.30 (s, 1H), δ 7.65 (d, 1H, J=8.1 Hz), δ 7.50 (d, 1H, J=7.6 Hz), δ 6.49 (d, 1H, J=7.1 Hz), δ 6.82 (s, 1H), δ 6.69 (d, 1H, J=8.1 Hz), δ 6.28 (d, 1H, J=7.7 Hz). 13C-NMR (300 MHz, CD3OD, ppm): δ 153.1, 151.5, 150.8, 144.1, 134.6, 130.4, 128.3, 126.7, 120.9, 117.3, 115.2, 110.4, 138.2, 117.2, 115.2, 103.5.

**Compound 20: (7-Chloroquinolin-4-yl)-(3,4-difluorophenyl)-amine**

Yellow solid; Yield=71%; mp=312-314 °C; Ms: m/z 290 [M]+; Rf=0.50 (MeOH:CHCl3 2:8); Anal. Calcd. (%) for C15H9ClF2N2: C, 61.98; H, 3.12; N, 9.54; Cl, 12.30; F, 13.07. IR (KBr, cm⁻¹): 3006.54, 2886.64, 1588.08, 1510.93, 1451.27, 1364.43. 1H-NMR (300 MHz, CD3OD, ppm): δ 4.45 (s, 1H, NH), δ 8.83 (d, H2, J=8.05 Hz), δ 8.30 (s, 1H), δ 7.67 (d, 1H, J=8.7 Hz), δ 6.50 (d, 1H, J=7.6 Hz), δ 6.45 (d, 1H, J=7.5 Hz), δ 6.52 (s, 1H), δ 6.67 (d, 1H, J=7.7 Hz), δ 6.80 (d, 1H, J=8.2 Hz). 13C-NMR (300 MHz, CD3OD, ppm): δ 163.1, 151.5, 150.8, 149.4, 139.6, 133.0, 128.3, 126.7, 122.9, 117.3, 115.9, 112.4, 118.2, 117.2, 105.2, 103.1.
Compound 21: (7-Chloroquinolin-4-yl)-(2-fluorophenyl)-amine

Brown solid; Yield=77%; mp=323-325 °C; Ms: m/z 272 [M⁺]; Rf=0.62 (MeOH:CHCl₃ 2:8); Anal. Calcd. (%) for C₁₅H₁₀ClFN₂: C, 66.70; H, 3.06; N, 10.27; Cl, 10.27; F, 6.97. IR (KBr, cm⁻¹): 3371.21, 2824.22, 1613.59, 1409.51, 1365.66, 1220.94. ¹H-NMR (300 MHz, CD₃OD, ppm): δ 4.50 (s, 1H, NH), δ 8.82 (d, H₂, J=8.1 Hz), δ 8.27 (s, 1H), δ 7.32 (d, 1H, J=7.3 Hz), δ 6.34 (d, 1H, J=6.7 Hz), δ 6.50 (d, 1H, J=7.5 Hz), δ 7.4-7.62 (m, 4H, Ar-H). ¹³C-NMR (300 MHz, CD₃OD, ppm): δ 154.2, 151.5, 148.8, 134.6, 132.8, 128.3, 126.7, 125.8, 127.3, 115.2, 110.4, 128.2, 117.2, 115.2, 103.5.

Compound 22: (7-Chloroquinolin-4-yl)-(3,5-dimethylphenyl)-amine

White solid; Yield=61%; mp=316-319 °C; Ms: m/z 282 [M⁺]; Rf=0.67 (MeOH:CHCl₃ 2:8); Anal. Calcd. (%) for C₁₇H₁₅ClN₂: C, 72.22; H, 5.43; N, 9.62; Cl, 12.64. IR (KBr, cm⁻¹): 3448.63, 2593.15, 1578.07, 1445.69, 1335.49, 1277.35. ¹H-NMR (300 MHz, CD₃OD, ppm): δ 2.35 (s, 6H, CH₃), δ 4.20 (s, 1H, NH), δ 8.80 (d, H₂, J=8.1 Hz), δ 8.52 (s, 1H), δ 7.63 (d, 1H, J=8.2 Hz), δ 7.50 (d, 1H, J=8.1 Hz), δ 7.32 (d, 1H, J=7.24 Hz), δ 6.09 (s, 2H, 1H₁₂ & 1H₁₆), δ 6.25 (2, 1H, J=7.8 Hz), δ 6.67 (d, 1H, J=7.9 Hz). ¹³C-NMR (300 MHz, CD₃OD, ppm): δ 151.8, 148.8, 147.8, 134.6, 133.0, 128.3, 126.7, 123.9, 127.3, 115.2, 110.4, 117.2, 115.2, 103.1, 25.4.

Compound 23: (7-Chloroquinolin-4-yl)-(2,6-dichlorophenyl)-amine

White solid; Yield=72%; mp=266-268 °C; Ms: m/z 322 [M⁺]; Rf=0.61 (MeOH:CHCl₃ 2:8); Anal. Calcd. (%) for C₁₅H₉Cl₃N₂: C, 55.67; H, 2.80; N, 8.66; Cl, 32.87. IR (KBr, cm⁻¹): 3271.75, 2026.49, 1581.58, 1492.98, 1363.03, 1239.84. ¹H-NMR (300 MHz, CD₃OD, ppm): δ 4.22 (s, 1H, NH), δ 8.88 (d, 1H, J=9.03 Hz), δ 8.31 (s, 1H), δ 7.62 (d, 1H, J=8.0 Hz), δ 7.50 (d, 1H, J=7.3 Hz), δ 6.42 (d, 1H, J=7.6 Hz), δ 6.72-6.22 (m, 3H, Ar-H). ¹³C-NMR (300 MHz, CD₃OD, ppm): δ 153.1, 151.5, 150.8, 148.7, 134.6, 133.0, 128.3, 126.7, 125.9, 121.3, 115.2, 110.4, 115.2, 104.1.

Compound 24: (7-Chloroquinolin-4-yl)-(4-methoxyphenyl)-amine

White solid; Yield=71%; mp=268-271 °C; Ms: m/z 284 [M⁺]; Rf=0.65 (MeOH:CHCl₃ 2:8); Anal. Calcd. (%) for C₁₅H₁₀ClFN₂: C, 67.49; H, 4.70; N, 9.74; Cl 12.45; O, 5.62. IR (KBr, cm⁻¹): 3179.55, 2336.69, 1577.18, 1491.98, 1347.43, 1249.81. ¹H-NMR (300 MHz, CD₃OD, ppm): δ 3.72 (d, 3H, J=10.8 Hz), δ 7.37 (d, 2H, J=9.0 Hz), δ 6.50 (d, 1H, J=7.8 Hz), δ 6.82 (d, 1H, J=7.9 Hz), δ 6.25 (d, 1H, J=7.3 Hz), δ 6.67 (d, 1H, J=7.4 Hz), δ 6.72-6.22 (m, 3H, Ar-H). ¹³C-NMR (300 MHz, CD₃OD, ppm): δ 151.8, 151.5, 150.8, 148.7, 134.6, 133.0, 128.3, 126.7, 125.9, 121.3, 115.2, 110.4, 115.2, 104.1.
1H-NMR (400 MHz, CD3OD, ppm): δ 3.80 (s, 3 H, OCH3), δ 4.50 (s, 1 H, NH), δ 8.85 (d, 1 H2, J=8.3 Hz), δ 8.27 (s, 1 H8), δ 7.35 (d, 1 H5, J=7.3 Hz), δ 6.34 (d, 1H6, J=7.7 Hz), δ 6.50 (d, 1 H3, J=7.5 Hz), δ 6.55 (d, 2 H12 & 16), 6.54 (d, 2 H13 & 15). 13C-NMR (300 MHz, CD3OD, ppm): δ 154.2, 151.5, 148.8, 134.6, 132.8, 128.3, 125.8, 115.2, 110.4, 128.2, 117.2, 115.2, 103.5, 57.8

II. General procedure for synthesis of various (7-chloro-quinolin-4-yl)-(4,6-dichloro-[1,3,5]-triazin-2-yl)-phenyl-amine (25-35).

7-Chloroquinolin-4-yl-phenyl-amine derivatives (12.0 mmol) and K2CO3 (24 mmol) were placed in a 50 mL bottom with constant stirring. Dry THF (20 mL) was injected with the help of syringe into the round bottom flask under nitrogen atmosphere. Then the solution was cooled in an ice bath and stirred for 10 minutes. The mixture was stirred for another 30 min at room temperature, and its colour became yellow. Then, the yellow solution was slowly dropped into a stirred solution of 2,4,6-trichloro-1,3,5-triazine (1.98 g, 10.8 mmol) in dry THF (20 mL) at 0 °C for 30 min. After completion of the addition, the reaction mixture was stirred for 2 h at room temperature. The solvent was subsequently removed under reduced pressure. The residue was poured into water ice. The precipitate was collected through filtration, washed with chloroform, ethanol and dried under vacuum to get the desired compounds. If remained impure after washing with organic solvents, the resulting crude was purified by column chromatography using 2% MeOH/CHCl3 as eluents to obtain the titled compounds.[92]

Compound 25: (7-Chloroquinolin-4-yl)-(4,6-dichloro-[1,3,5]-triazin-2-yl)-(2-fluoro phenyl)-amine

Yellow solid; Yield=61%; mp=230-233 °C; Ms m/z 419 [M+]; Rf=0.55 (MeOH:CHCl3 2:8); Anal. Calcd. (%) for C18H9Cl3FN5: C, 51.39; H, 2.16; N, 16.65; Cl 25.28; F, 4.52.

IR (KBr, cm−1): 3035.37, 1718.96, 1610.88, 1508.14, 1351.45, 1240.30. 1H-NMR (400 MHz, DMSO-d6, ppm): δ 8.85 (d, 1 H2, J=8.3 Hz), δ 8.27 (s, 1 H8), δ 7.35 (d, 1 H5, J=7.3 Hz), δ 6.34 (d, 1 H6, J=7.7 Hz), δ 6.50 (d, 1 H3, J=7.5 Hz), δ 7.23-7.36 (m, 4 H, Ar-H). 13C-NMR (400 MHz, DMSO-d6, ppm): δ 175.4, 171.2, 157.0, 155.7, 144.4, 140.1, 139.8, 138.2, 136.1, 135.8, 133.2, 131.0, 127.3, 126.6, 119.3, 116.2, 100.4.
Compound 26: (7-Chloroquinolin-4-yl)-(4,6-dichloro-[1,3,5]-triazin-2-yl)-(3-chloro-4-fluoro phenyl)-amine

Yellow solid; Yield=63%; mp=244-246 °C; Ms: m/z 455 [M⁺]; R_f=0.51 (MeOH:CHCl₃ 2:8); Anal. Calcd. (%) for C₁₈H₈Cl₄FN₅: C, 47.50; H, 1.77; N, 15.39; Cl, 31.16; F, 4.17. IR (KBr, cm⁻¹): 3166.27, 1610.88, 1497.01, 1388.11, 1297.72. ¹H-NMR (400 MHz, DMSO-d₆, ppm): δ 8.83 (d, 1 H, J=8.1 Hz), δ 8.26 (s, 1 H), δ 7.30 (d, 1 H, J=7.8 Hz), δ 6.31 (d, 1 H, J=7.6 Hz), δ 6.51 (d, 1 H, J=7.2 Hz), δ 6.12 (s, 1 H), δ 6.15 (d, 1 H), δ 6.42 (d, 1 H). ¹³C-NMR (400 MHz, DMSO-d₆, ppm): δ 178.4, 172.2, 163.3, 157.0, 144.4, 140.1, 139.8, 138.2, 136.1, 135.8, 133.2, 131.0, 127.3, 126.6, 119.3, 116.2, 100.4.

Compound 27: (7-Chloroquinolin-4-yl)-(4,6-dichloro-[1,3,5]-triazin-2-yl)-(3,4-dimethyl phenyl)-amine

Yellow solid; Yield=64%; mp=228-231 °C; Ms: m/z 429 [M⁺]; R_f=0.56 (MeOH:CHCl₃ 2:8); Anal. Calcd. (%) for C₂₀H₁₄Cl₃N₅: C, 57.69; H, 3.28; N, 16.77; Cl, 24.26. IR (KBr, cm⁻¹): 3016.17, 2911.43, 1627.65, 1561.24, 1332.02, 1241.00. ¹H-NMR (400 MHz, DMSO-d₆, ppm): δ 2.30 (s, 6 H, CH₃), δ 8.81 (d, 1 H, J=8.0 Hz), δ 8.26 (s, 1 H), δ 7.35 (d, 1 H, J=7.2 Hz), δ 6.36 (d, 1 H, J=7.6 Hz), δ 6.50 (d, 1 H, J=7.2 Hz), δ 6.12 (s, 1 H), δ 6.15 (d, 1 H), δ 6.42 (d, 1 H). ¹³C-NMR (400 MHz, DMSO-d₆, ppm): δ 176.4, 171.5, 157.0, 144.4, 140.1, 139.8, 138.2, 136.1, 135.8, 133.2, 131.0, 127.3, 126.6, 122.4, 116.3, 112.2, 100.4, 19.2.

Compound 28: (7-Chloroquinolin-4-yl)-(4,6-dichloro-[1,3,5]-triazin-2-yl)-(3-fluoro phenyl)-amine

Yellow solid; Yield=67%; mp=219-222 °C; Ms: m/z 420.6 [M⁺]; R_f=0.52 (MeOH:CHCl₃ 2:8); Anal. Calcd. (%) for C₁₈H₈Cl₃FN₅: C, 51.38; H, 2.37; N, 14.15; Cl 25.17; F, 4.53. IR (KBr, cm⁻¹): 3185.15, 2840.07, 1656.93, 1550.62, 1431.59. ¹H-NMR (400 MHz, DMSO-d₆, ppm): δ 8.82 (d, 1 H, J=8.6 Hz), δ 8.21 (s, 1 H), δ 7.32 (d, 1 H, J=6.7 Hz), δ 6.34 (d, 1 H, J=7.9 Hz), δ 6.51 (d, 1 H, J=7.7 Hz), δ 6.42 (s, 2 H, Ar-H), δ 6.74-6.32 (m, 3 H, Ar-H). ¹³C-NMR (400 MHz, DMSO-d₆, ppm): δ 175.9, 171.6, 155.2, 152.1, 147.5, 140.1, 139.8, 135.1, 131.2, 131.0, 128.1, 124.3, 119.3, 116.2, 103.4.
Compound 29: (7-Chloroquinolin-4-yl)-(4,6-dichloro-[1,3,5]-triazin-2-yl)-(3,4,5-trimethoxy phenyl)-amine

Yellow solid; Yield=60%; mp=230-233 °C; Ms: m/z 491 [M⁺]; R_f=0.54 (MeOH:CHCl₃ 2:8); Anal. Calcd. (%) for C₂₁H₁₆Cl₃N₅O₃: C, 51.19; H, 3.27; N, 14.25; Cl 21.29; O, 9.70. IR (KBr, cm⁻¹): 3236.19, 2903.43, 1617.65, 1566.24, 1330.02, 1243.00. ¹H-NMR (400 MHz, DMSO-d₆, ppm): δ 3.80 (s, 9 H, OCH₃), δ 8.85 (d, 1 H, J=8.3 Hz), δ 8.27 (s, 1 H), δ 7.30 (d, 1 H, J=7.9 Hz), δ 6.34 (d, 1 H, J=7.7 Hz), δ 6.50 (d, 1 H, J=7.5 Hz), δ 6.42 (s, 2 H, Ar-H). ¹³C-NMR (400 MHz, DMSO-d₆, ppm): δ 175.1, 171.3, 155.7, 144.5, 140.1, 139.8, 136.1, 133.2, 131.0, 128.1, 126.3, 119.3, 116.2, 100.4, 95.0, 57.3.

Compound 30: (7-Chloroquinolin-4-yl)-(4,6-dichloro-[1,3,5]-triazin-2-yl)-(2,4-difluoro phenyl)-amine

Yellow solid; Yield=63%; mp=231-234 °C; Ms: m/z 437 [M⁺]; R_f=0.52 (MeOH:CHCl₃ 2:8); Anal. Calcd. (%) for C₁₈H₈Cl₃F₂N₅: C, 49.29; H, 1.84; N, 15.97; Cl, 24.25; F, 8.66. IR (KBr, cm⁻¹): 3270.21, 2814.24, 1615.59, 1438.51, 1366.66, 1321.94. ¹H-NMR (400 MHz, DMSO-d₆, ppm): δ 8.83 (d, 1 H, J=8.1 Hz), δ 8.26 (s, 1 H), δ 7.30 (d, 1 H, J=7.8 Hz), δ 6.31 (d, 1 H, J=7.6 Hz), δ 6.51 (d, 1 H, J=7.2 Hz), δ 6.42 (s, 1 H), δ 6.45 (d, 1 H₁₆), δ 6.49 (d, 1 H₁₅) . ¹³C-NMR (400 MHz, DMSO-d₆, ppm): δ 175.1, 171.2, 163.3, 157.0, 144.4, 140.1, 139.8, 138.2, 136.1, 135.8, 133.2, 129.3, 126.6, 118.3, 111.2, 104.5, 103.4.

Compound 31: (7-Chloroquinolin-4-yl)-(4,6-dichloro-[1,3,5]-triazin-2-yl)-(3,4-difluoro phenyl)-amine

Yellow solid; Yield=63%; mp=323-335 °C; Ms: m/z 437 [M⁺]; R_f=0.52 (MeOH:CHCl₃ 2:8); Anal. Calcd. (%) for C₁₈H₈Cl₃F₂N₅: C, 49.19; H, 1.84; N, 14.96; Cl, 25.35; F, 8.67. IR (KBr, cm⁻¹): 35348.63, 2773.15, 1570.07, 1441.69, 1231.49, 1220.15. ¹H-NMR (400 MHz, DMSO-d₆, ppm): δ 8.87 (d, 1 H, J=8.1 Hz), δ 8.29 (s, 1 H), δ 7.35 (d, 1 H, J=7.6 Hz), δ 6.35 (d, 1 H, J=7.4 Hz), δ 6.51 (d, 1 H, J=7.1 Hz), δ 6.14 (s, 1 H), δ 6.20 (d, 1 H₁₆), δ 6.69 (d, 1 H₁₅) . ¹³C-NMR (400 MHz, DMSO-d₆, ppm): δ 176.4, 171.2, 151.0, 149.3, 143.9, 139.8, 134.4, 131.1, 130.1, 129.3, 126.6, 125.8, 121.8, 117.3, 111.2, 104.5, 103.4.
**Compound 32: (7-Chloroquinolin-4-yl)-(4,6-dichloro-[1,3,5]-triazin-2-yl)-(4-fluoro phenyl)-amine**

Yellow solid; Yield=67%; mp=242-245 °C; Ms: m/z 420.6 [M⁺]; Rf=0.52 (MeOH:CHCl₃ 2:8); Anal. Calcd. (%) for C₁₈H₉Cl₃FN₅: C, 51.39; H, 2.27; N, 14.25; Cl 25.17; F, 4.52. IR (KBr, cm⁻¹): 3348.62, 2394.15, 1638.07, 1515.67, 1433.49, 1237.35. 

¹H-NMR (400 MHz, DMSO-d₆, ppm): δ 8.84 (d, 1 H₂, J=8.7 Hz), δ 8.21 (s, 1 H₈), δ 7.31 (d, 1 H₅, J=6.9 Hz), δ 6.34 (d, 1 H₆, J=7.5 Hz), δ 6.51 (d, 1 H₃, J=7.4 Hz), δ 6.42 (d, 2 H, Ar-H), δ 6.74 (d, 2 H, Ar-H).

¹³C-NMR (400 MHz, DMSO-d₆, ppm): δ 175.9, 171.6, 155.2, 152.1, 147.5, 140.1, 139.8, 135.1, 131.2, 131.0, 128.1, 126.3, 119.3, 116.2, 104.4.

**Compound 33: (7-Chloroquinolin-4-yl)-(4,6-dichloro-[1,3,5]-triazin-2-yl)-(3,5-dimethylphenyl)-amine**

Yellow solid; Yield=67%; mp=237-239 °C; Ms: m/z 429 [M⁺]; Rf=0.66 (MeOH:CHCl₃ 2:8); Anal. Calcd. (%) for C₂₀H₁₄Cl₃N₅: C, 55.69; H, 3.28; N, 18.76; Cl, 24.27. IR (KBr, cm⁻¹): 3128.54, 2656.07, 1615.65, 1526.56, 1445.16, 1301.02.¹H-NMR (400 MHz, DMSO-d₆, ppm): δ 2.35 (s, 6 H, CH₃), δ 8.80 (d, 1 H₂, J=8.1 Hz), δ 8.23 (s, 1 H₈), δ 7.39 (d, 1 H₅, J=7.1 Hz), δ 6.36 (d, 1 H₆, J=7.8 Hz), δ 6.53 (d, 1 H₃, J=7.2 Hz), δ 6.02 (s, 2 H, Ar-H), δ 6.15 (d, 1 H₁₆), δ 6.42 (2, 1 H₁₄). ¹³C-NMR (400 MHz, DMSO-d₆, ppm): δ 176.4, 171.2, 157.0, 144.4, 140.1, 139.8, 138.2, 136.1, 135.8, 133.2, 131.0, 127.3, 126.6, 122.4, 116.3, 112.2, 100.4, 21.5.

**Compound 34: (7-Chloroquinolin-4-yl)-(4,6-dichloro-[1,3,5]-triazin-2-yl)-(2,5-dimethoxyphenyl)-amine**

Yellow solid; Yield=67%; mp=230-233 °C; Ms: m/z 461 [M⁺]; Rf=0.56 (MeOH:CHCl₃ 2:8); Anal. Calcd. (%) for C₂₀H₁₄Cl₃O₂N₅: C, 51.91; H, 3.05; N, 15.14; Cl, 22.99; O, 6.92. IR (KBr, cm⁻¹): 3238.54, 2685.27, 1565.65, 1506.56, 1435.16, 1251.02.¹H-NMR (400 MHz, DMSO-d₆, ppm): δ 3.75 (s, 6 H, OCH₃), δ 8.83 (d, 1 H₂, J=8.1 Hz), δ 8.26 (s, 1 H₈), δ 7.30 (d, 1 H₅, J=7.8 Hz), δ 6.31 (d, 1 H₆, J=7.6 Hz), δ 6.51 (d, 1 H₃, J=7.2 Hz), δ 6.42 (d, 1 H₁₃), δ 6.15 (d, 1 H₁₄), δ 6.12 (s, 1 H₁₆). ¹³C-NMR (400 MHz, DMSO-d₆, ppm): δ 174.4, 171.4, 163.3, 157.0, 144.4, 140.1, 139.8, 138.2, 136.1, 135.8, 133.2, 131.0, 127.3, 126.6, 122.4, 116.3, 112.2, 100.4, 58.6.
**Compound 35: (7-Chloroquinolin-4-yl)-(4,6-dichloro-[1,3,5]-triazin-2-yl)-(2-chloro-4-methylphenyl)-amine**

Yellow solid; Yield=64%; mp=218-221 °C; Ms: m/z 429 [M⁺]; $R_f=0.56$ (MeOH:CHCl₃ 2:8); Anal. Calcd. (%) for C₁₉H₁₁Cl₄N₅: C, 50.58; H, 2.46; N, 15.52; Cl, 31.43. IR (KBr, cm⁻¹): 3449.63, 2543.15, 1648.33, 1359.54, 1277.25, 1094.78. $^1$H-NMR (400 MHz, DMSO-d₆, ppm): δ 2.30 (s, 3 H, CH₃), δ 8.87 (d, 1 H, J=8.1 Hz), δ 8.29 (s, 1 H, ), δ 7.35 (d, 1 H, J=7.2 Hz), δ 6.35 (d, 1 H, J=7.8 Hz), δ 6.50 (d, 1 H, J=7.5 Hz), δ 6.82-6.28 (m, 3 H, Ar-H), δ 6.15 (d, 1 H, J=7.2 Hz), δ 4.17 (t, 3 H, OCH₂), δ 3.80 (s, 3 H, OCH₃). $^{13}$C-NMR (400 MHz, DMSO-d₆, ppm): 176.4, 171.5, 157.0, 144.4, 140.1, 139.8, 138.2, 136.1, 133.2, 131.0, 127.3, 126.6, 122.4, 116.3, 112.2, 104.0, 20.2.

**III. General procedure for synthesis of various N-benzyl-N’-(7-chloroquinolin-4-yl)-ethane-1, 2-diamine (36-47)**

In a round bottom flask, added N₁-(7-chloroquinolin-4-yl)-ethane-1,2-diamine (13-15 mmol) and aldehydes (10 mmol) under nitrogen atmosphere in dry acetonitrile (30-40 mL). Allow the reaction mixture at stirring for 2-4 h at room temperature. Progress of reaction was monitored by thin layer chromatography. When the spot of aldehyde and amine get disappeared in TLC, 15-17 mmol of sodium triacetoxyborohydride in dry CH₃CN (5 mL) was added into the reaction mixture under a nitrogen atmosphere at room temperature. Imine formation, however, is a reversible reaction and requires long reaction times and the use of a dehydrating agent such as molecular sieves can be used for the reaction to completion. The progress of the reaction was again followed by thin layer chromatography. The reaction mixture was extracted with ether (3 x 10 mL). The combined ether extracts were concentrated under reduced pressure. The crude product thus obtained was purified by column chromatography (silica gel 60-120 mesh) using ethylacetate-hexane as eluent.[93, 94]

**Compound 36: N-(7-chloroquinolin-4-yl)-N’-(4-methoxybenzyl)-ethane-1,2-diamine**

White solid; Yield=64%; mp=144-147 °C; Ms: m/z 341 [M⁺]; $R_f=0.52$ (MeOH:CHCl₃ 1:9); Anal. Calcd. (%) for C₁₉H₂₀Cl₂N₃O: C, 66.56; H, 5.90; N, 12.49; Cl, 10.68; O, 4.37. IR (KBr, cm⁻¹): 3327.34, 2626.07, 1815.65, 1563.56, 1445.32, 1361.03. $^1$H-NMR (400 MHz, CD₃OD, ppm): δ 3.80 (s, 3 H, OCH₃), δ 3.60 (s, 3 H, CH₃), δ 3.17 (t, 3 H,
\[\delta 3.80 \ (t, \ 3 \ H, \ CH_2), \ \delta 4.50 \ (br, \ s, \ 1 \ H, \ NH), \ \delta 1.80 \ (br, \ s, \ 1 \ H, \ NH), \ \delta 8.87 \ (d, \ 1 \ H_2, J=8.1 \ Hz), \ \delta 8.25 \ (s, \ 1 \ H_8), \ \delta 7.38 \ (d, \ 1 \ H_5, J=7.3 \ Hz), \ \delta 6.32 \ (d, \ 1 \ H_6, J=7.1 \ Hz), \ \delta 6.53 \ (d, \ 1 \ H_3, J=7.5 \ Hz), \ \delta 6.92-6.285 \ (m, \ 4 \ H, \ Ar-H).\]

\[^{13}\text{C}-\text{NMR} \ (400 \ MHz, \ CD_3\text{OD}, \ ppm): \ \delta 168.4, \ 160.2, \ 151.5, \ 147.0, \ 144.4, \ 136.1, \ 133.2, \ 131.1, \ 130.8, \ 129.2, \ 121.0, \ 112.2, \ 103.4, \ 57.1, \ 39.7, \ 30.4, \ 24.0.\]

**Compound 37:** N-(7-chloroquinolin-4-yl)-N'-(2,4-dichlorobenzyl)-ethane-1,2-diamine

White solid; Yield=66%; mp=141-143 °C; Ms: m/z 379 [M^+]; Rf=0.53 (MeOH:CHCl_3 1:9); Anal. Calcd. (%) for C_{18}H_{16}Cl_3N_3: C, 56.89; H, 4.24; N, 11.14; Cl, 27.94; IR (KBr, cm\(^{-1}\)): 3236.19, 2903.43, 1617.65, 1566.24, 1330.02, 1243.00. IR (KBr, cm\(^{-1}\)): 3316.19, 2453.43, 1627.55, 1616.24, 1320.02, 1243.45. \(^1\text{H}-\text{NMR} \ (400 \ MHz, \ CDCl_3, \ ppm): \ \delta 3.62 \ (s, \ 3 \ H, \ CH_2), \ \delta 4.15 \ (t, \ 3 \ H, \ CH_2), \ \delta 3.81 \ (t, \ 3 \ H, \ CH_2), \ \delta 4.54 \ (br, \ s, \ 1 \ H, \ NH), \ \delta 1.83 \ (br, \ s, \ 1 \ H, \ NH), \ \delta 8.87 \ (d, \ 1 \ H_2, J=8.1 \ Hz), \ \delta 8.24 \ (s, \ 1 \ H_8), \ \delta 7.36 \ (d, \ 1 \ H_5, J=7.3 \ Hz), \ \delta 6.33 \ (d, \ 1 \ H_6, J=7.1 \ Hz), \ \delta 6.54 \ (d, \ 1 \ H_3, J=7.5 \ Hz), \ \delta 7.16-6.94 \ (m, \ 3 \ H, \ Ar-H). \ ^{13}\text{C}-\text{NMR} \ (400 \ MHz, \ CDCl_3, \ ppm): \ \delta 158.4, \ 150.2, \ 149.5, \ 143.0, \ 141.4, \ 136.1, \ 134.8, \ 130.5, \ 129.2, \ 121.1, \ 120.8, \ 119.2, \ 111.0, \ 110.2, \ 103.4, \ 38.7, \ 30.7, \ 24.4.

**Compound 38:** N-(7-chloroquinolin-4-yl)-N'-(4-bromobenzyl)-ethane-1,2-diamine

White solid; Yield=61%; mp=222-225 °C; Ms: m/z 390 [M^+]; Rf=0.55 (MeOH:CHCl_3 1:9); Anal. Calcd. (%) for C_{18}H_{17}BrClN_3: C, 55.39; H, 4.33; N, 10.07; Cl, 9.75; Br, 20.45. IR (KBr, cm\(^{-1}\)): 3236.19, 2903.43, 1617.65, 1566.24, 1330.02, 1243.00. \(^1\text{H}-\text{NMR} \ (400 \ MHz, \ CDCl_3, \ ppm): \ \delta 3.61 \ (s, \ 3 \ H, \ CH_2), \ \delta 4.15 \ (t, \ 3 \ H, \ CH_2), \ \delta 3.87 \ (t, \ 3 \ H, \ CH_2), \ \delta 4.00 \ (br, \ s, \ 1 \ H, \ NH), \ \delta 1.83 \ (br, \ s, \ 1 \ H, \ NH), \ \delta 8.87 \ (d, \ 1 \ H_2, J=8.0 \ Hz), \ \delta 8.35 \ (s, \ 1 \ H_8), \ \delta 7.35 \ (d, \ 1 \ H_5, J=7.3 \ Hz), \ \delta 6.33 \ (d, \ 1 \ H_6, J=7.2 \ Hz), \ \delta 6.55 \ (d, \ 1 \ H_3, J=7.2 \ Hz), \ \delta 6.95 \ (dd, \ 2 \ H, Ar-H), \ \delta 7.21 \ (dd, \ 2 \ H, Ar-H). \ ^{13}\text{C}-\text{NMR} \ (400 \ MHz, \ CDCl_3, \ ppm): \ \delta 151.5, \ 149.0, \ 147.0, \ 144.4, \ 136.1, \ 133.2, \ 131.1, \ 130.8, \ 129.2, \ 121.7, \ 121.0, \ 112.2, \ 103.4, \ 39.7, \ 30.9, \ 24.5.

**Compound 39:** N-(7-chloroquinolin-4-yl)-N'-(4-fluorobenzyl)-ethane-1,2-diamine

White solid; Yield=67%; mp=132-134 °C; Ms: m/z 329.11 [M^+]; Rf=0.54 (MeOH:CHCl_3 1:9); Anal. Calcd. (%) for C_{18}H_{17}FClN_3: C, 66.55; H, 5.20; N, 12.74; Cl, 10.75; F, 5.76. IR (KBr, cm\(^{-1}\)): 3162.27, 1620.88, 1467.01, 1381.13, 1292.77. \(^1\text{H}-\text{NMR} \ (400 \ MHz, \ CDCl_3, \ ppm): \ \delta 3.62 \ (s, \ 3 \ H, \ CH_2), \ \delta 4.18 \ (t, \ 3 \ H, \ CH_2), \ \delta 3.87 \ (t, \ 3 \ H, \ CH_2), \ \delta 4.00 \ (br, \ s, \ 1 \ H, \ NH), \ \delta 1.83 \ (br, \ s, \ 1 \ H, \ NH), \ \delta 8.85 \ (d, \ 1 \ H_2, J=8.0 \ Hz), \ \delta 8.35 \ (s, \ 1 \ H_8), \ \delta 7.35 \ (d, \ 1 \ H_5, J=7.3 \ Hz), \ \delta 6.33 \ (d, \ 1 \ H_6, J=7.2 \ Hz), \ \delta 6.55 \ (d, \ 1 \ H_3, J=7.2 \ Hz), \ \delta 6.95 \ (dd, \ 2 \ H, Ar-H), \ \delta 7.21 \ (dd, \ 2 \ H, Ar-H). \ ^{13}\text{C}-\text{NMR} \ (400 \ MHz, \ CDCl_3, \ ppm): \ \delta 151.5, \ 149.0, \ 147.0, \ 144.4, \ 136.1, \ 133.2, \ 131.1, \ 130.8, \ 129.2, \ 121.7, \ 121.0, \ 112.2, \ 103.4, \ 39.7, \ 30.9, \ 24.5.
CH$_2$), $\delta$ 4.20 (br, s, 1 H NH), $\delta$ 1.81 (br, s, 1 H NH), $\delta$ 8.89 (d, 1 H J=8.0 Hz), $\delta$ 8.34 (s, 1 H$_8$), $\delta$ 7.35 (d, 1 H$_5$, J=7.3 Hz), $\delta$ 6.31 (d, 1 H$_6$, J=7.2 Hz), $\delta$ 6.55 (d, 1 H$_3$, J=7.2 Hz), $\delta$ 7.08 (dd, 2 H Ar-H), $\delta$ 6.85 (dd, 2 H Ar-H).

$^{13}$C-NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 160.7, 151.5, 149.0, 147.0, 144.4, 136.1, 133.2, 131.1, 130.8, 129.2, 121.0, 112.2, 103.4, 39.1, 30.1, 21.5.

**Compound 40: N-(7-chloroquinolin-4-yl)-N’-(4-chlorobenzyl)-ethane-1,2-diamine**

White solid; Yield=70%; mp=218-220 °C; Ms: m/z 345.08 [M$^+$]; R$_f$=0.53 (MeOH:CHCl$_3$ 1:9); Anal. Calcd. (%) for C$_{18}$H$_{17}$Cl$_2$N$_3$: C, 62.24; H, 4.98; N, 12.34; Cl, 20.45. IR (KBr, cm$^{-1}$): 3143.27, 1667.81, 1462.01, 1392.23, 1207.12. $^1$H-NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 3.67 (s, 3 H CH$_2$), $\delta$ 4.25 (t, 3 H CH$_2$), $\delta$ 3.80 (t, 3 H CH$_2$), $\delta$ 4.10 (br, s, 1 H NH), $\delta$ 1.82 (br, s, 1 H NH), $\delta$ 8.82 (d, 1 H J=8.1 Hz), $\delta$ 8.33 (s, 1 H$_8$), $\delta$ 7.35 (d, 1 H$_5$, J=7.1 Hz), $\delta$ 6.32 (d, 1 H$_6$, J=7.0 Hz), $\delta$ 6.56 (d, 1 H$_3$, J=7.2 Hz), $\delta$ 6.92 (dd, 2 H Ar-H), $\delta$ 7.22 (dd, 2 H Ar-H).

$^{13}$C-NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 151.5, 149.0, 147.0, 144.4, 136.1, 133.2, 131.1, 130.8, 129.2, 121.0, 112.2, 103.4, 38.7, 30.9, 22.5.

**Compound 41: N-(7-chloroquinolin-4-yl)-N’-(4-cyanobenzyl)-ethane-1,2-diamine**

White solid; Yield=68%; mp=219-221 °C; Ms: m/z 336.82 [M$^+$]; R$_f$=0.59 (MeOH:CHCl$_3$ 1:9); Anal. Calcd. (%) for C$_{19}$H$_{17}$ClN$_4$: C, 67.65; H, 5.19; N, 16.53; Cl, 10.63. IR (KBr, cm$^{-1}$): 3108.27, 1621.24, 1462.01, 1341.20, 1307.12. $^1$H-NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 3.62 (s, 3 H CH$_2$), $\delta$ 4.10 (t, 3 H CH$_2$), $\delta$ 3.84 (t, 3 H CH$_2$), $\delta$ 4.45 (br, s, 1 H NH), $\delta$ 1.81 (br, s, 1 H NH), $\delta$ 8.87 (d, 1 H J=8.7 Hz), $\delta$ 8.39 (s, 1 H$_8$), $\delta$ 7.33 (d, 1 H$_5$, J=8.3 Hz), $\delta$ 6.34 (d, 1 H$_6$, J=8.0 Hz), $\delta$ 6.55 (d, 1 H$_3$, J=7.2 Hz), $\delta$ 7.24 (dd, 2 H Ar-H), $\delta$ 7.38 (dd, 2 H Ar-H).

$^{13}$C-NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 151.9, 149.8, 146.0, 142.2, 134.1, 133.5, 132.1, 131.8, 126.2, 120.7, 121.0, 116.5, 112.7, 103.4, 39.8, 35.5, 24.3.

**Compound 42: N-(7-chloroquinolin-4-yl)-N’-(2-chlorobenzyl)-ethane-1,2-diamine**

White solid; Yield=68%; mp=133-136 °C; Ms: m/z 346.25 [M$^+$]; R$_f$=0.56 (MeOH:CHCl$_3$ 1:9); Anal. Calcd. (%) for C$_{18}$H$_{17}$Cl$_2$N$_3$: C, 62.24; H, 4.98; N, 12.34; Cl, 20.45. IR (KBr, cm$^{-1}$): 3125.89, 1786.22, 1542.12, 1299.02, 1297.79. $^1$H-NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 3.60 (s, 3 H CH$_2$), $\delta$ 4.05 (t, 3 H CH$_2$), $\delta$ 3.85 (t, 3 H CH$_2$), $\delta$ 4.20 (br, s, 1 H, CH$_2$), $\delta$ 1.81 (br, s, 1 H NH), $\delta$ 8.89 (d, 1 H J=8.0 Hz), $\delta$ 8.34 (s, 1 H$_8$), $\delta$ 7.35 (d, 1 H$_5$, J=7.3 Hz), $\delta$ 6.31 (d, 1 H$_6$, J=7.2 Hz), $\delta$ 6.55 (d, 1 H$_3$, J=7.2 Hz), $\delta$ 7.08 (dd, 2 H Ar-H), $\delta$ 6.85 (dd, 2 H Ar-H). 

$^{13}$C-NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 160.7, 151.5, 149.0, 147.0, 144.4, 136.1, 133.2, 131.1, 130.8, 129.2, 121.0, 112.2, 103.4, 39.1, 30.1, 21.5.
NH), δ 1.88 (br, s, 1 H NH), δ 8.82 (d, 1 H, J=8.0 Hz), δ 8.31 (s, 1 H 8), δ 7.35 (d, 1 H 5, J=7.6 Hz), δ 6.33 (d, 1 H 6, J=7.2 Hz), δ 6.55 (d, 1 H 3, J=7.6 Hz), δ 7.00-6.83 (m, 4 H Ar-H). 13C-NMR (400 MHz, CDCl3, ppm): δ 151.5, 149.5, 149.0, 147.3, 144.4, 135.4, 133.2, 131.1, 130.8, 127.2, 126.2, 121.9, 121.1, 112.0, 104.1, 39.9, 31.9, 24.4.

**Compound 43:** N-(7-chloroquinolin-4-yl)-N'-(3,5-dimethoxybenzyl)-ethane-1,2-diamine

White solid; Yield=74%; mp=210-212 °C; Ms: m/z 371.86 [M+]; Rf=0.55 (MeOH:CHCl3 1:9); Anal. Calcd. (%) for C20H22ClN3O2: C, 64.56; H, 6.00; N, 11.30; Cl, 9.53; O, 8.61. IR (KBr, cm⁻¹): 3336.27, 1660.83, 1487.66, 1288.61, 1207.12. 1H-NMR (400 MHz, CDCl3, ppm): δ 3.82 (s, 6 H, OCH3), δ 3.85 (s, 3 H, CH2), δ 4.16 (t, 3 H, CH2), δ 2.80 (t, 3 H, CH2), δ 4.22 (br, s, 1 H, NH), δ 1.87 (br, s, 1 H NH), δ 8.87 (d, 1 H 2, J=8.1 Hz), δ 8.22 (s, 1 H 8), δ 7.33 (d, 1 H 5, J=7.1 Hz), δ 6.32 (d, 1 H 6, J=7.1 Hz), δ 6.55 (d, 1 H 3, J=7.5 Hz), δ 6.19 (s, 2 H, Ar-H), δ 6.09 (s, 1 H, Ar-H). 13C-NMR (400 MHz, CDCl3, ppm): δ 163.4, 160.2, 151.5, 147.0, 144.7, 135.1, 133.1, 130.8, 130.2, 124.2, 121.9, 112.2, 103.4, 57.1, 37.7, 31.8, 25.5.

**Compound 44:** N-(7-chloroquinolin-4-yl)-N'-(4-methylbenzyl)-ethane-1,2-diamine

White solid; Yield=75%; mp=217-220 °C; Ms: m/z 326 [M+]; Rf=0.64 (MeOH:CHCl3 1:9); Anal. Calcd. (%) for C19H20ClN3: C, 70.94; H, 6.18; N, 12.00; Cl, 10.89. IR (KBr, cm⁻¹): 3466.57, 1710.88, 1432.01, 1324.87, 1243.12. 1H-NMR (400 MHz, CDCl3, ppm): δ 2.20 (s, 3 H, CH3), δ 4.05 (s, 3 H, CH2), δ 3.72 (t, 3 H, CH2), δ 3.80 (t, 3 H, CH2), δ 4.23 (br, s, 1 H NH), δ 1.83 (br, s, 1 H NH), δ 8.89 (d, 1 H 2, J=8.0 Hz), δ 8.34 (s, 1 H 8), δ 7.35 (dd, 1 H, J=7.3 Hz), δ 6.31 (dd, 1 H, J=7.2 Hz), δ 6.55 (d, 1 H 6, J=7.2 Hz), δ 7.20-6.69 (m, 4 H Ar-H). 13C-NMR (400 MHz, CDCl3, ppm): δ 160.5, 148.1, 147.3, 144.7, 135.1, 133.1, 130.8, 130.2, 124.2, 121.9, 112.2, 103.4, 57.1, 37.7, 31.8, 25.5.

**Compound 45:** N-(7-chloroquinolin-4-yl)-N'-(2,4-difluorobenzyl)-ethane-1,2-diamine

White solid; Yield=48%; mp=222-225 °C; Ms: m/z 347 [M+]; Rf=0.52 (MeOH:CHCl3 1:9); Anal. Calcd. (%) for C18H16ClF2N3: C, 62.64; H, 4.16; N, 12.08; Cl, 10.1; F, 10.93. IR (KBr, cm⁻¹): 3534.61, 2773.12, 1550.07, 1442.69, 1231.41, 1227.65. 1H-NMR (400 MHz, CDCl3, ppm): δ 3.60 (s, 3 H CH2), δ 4.13 (t, 3 H CH2), δ 3.66 (t, 3 H CH2), δ 4.05 (br, s, 1 H NH), δ 1.82 (br, s, 1 H NH), δ 8.85 (d, 1 H 2, J=8.5 Hz), δ 8.39...
(s, 1 H₈), δ 7.35 (d, 1 H₅, J=8.1 Hz), δ 6.33 (d, 1 H₆, J=8.0 Hz), δ 6.55 (d, 1 H₃, J=7.2 Hz), δ 6.56 (s, 1 H, Ar-H), δ 7.38 (d, 2 H, Ar-H). ¹³C-NMR (400 MHz, CDCl₃, ppm): δ 162.07, δ 161.9, 149.8, 146.0, 142.2, 134.1, 133.5, 131.8, 129.3, 126.2, 120.7, 121.0, 116.5, 112.7, 103.4, 39.3, 30.4, 24.5.

**Compound 46: N-(7-chloroquinolin-4-yl)-N'-(3,4-dimethoxybenzyl)-ethane-1,2-diamine**

White solid; Yield=74%; mp=211-213 °C; Ms: m/z 371.14 [M⁺]; Rᵣ=0.55 (MeOH:CHCl₃ 1:9); Anal. Calcd. (%) for C₂₀H₂₂ClN₃O₂: C, 61.53; H, 6.30; N, 14.36; Cl, 9.53; O, 8.31. IR (KBr, cm⁻¹): 3454, 2673, 1570, 1541, 1233, 1247. ¹H-NMR (400 MHz, CDCl₃, ppm): δ 3.82 (s, 6 H, OCH₃), δ 3.65 (s, 3 H, CH₂), δ 4.16 (t, 3 H, CH₂), δ 3.80 (t, 3 H, CH₂), δ 4.22 (br, s, 1 H, NH), δ 1.87 (br, s, 1 H, NH), δ 8.87 (d, 1 H₂, J=8.1 Hz), δ 8.22 (s, 1 H₈), δ 7.33 (d, 1 H₅, J=7.1 Hz), δ 6.32 (d, 1 H₆, J=7.1 Hz), δ 6.53 (d, 1 H₃, J=7.5 Hz), δ 6.19 (s, 2 H, Ar-H), δ 6.09 (s, 1 H, Ar-H). ¹³C-NMR (400 MHz, CDCl₃, ppm): δ 150.5, 149.9, 145.9, 144.7, 135.1, 133.1, 130.8, 130.1, 124.2, 121.9, 115.8, 114.7, 112.2, 103.4, 57.6, 39.3, 30.9, 21.5.

**Compound 47: N-(7-chloroquinolin-4-yl)-N'-(3-chlorobenzyl)-ethane-1,2-diamine**

White solid; Yield=69%; mp=221-223 °C; Ms: m/z 346.21 [M⁺]; Rᵣ=0.53 (MeOH:CHCl₃ 1:9); Anal. Calcd. (%) for C₁₈H₁₇Cl₂N₃: C, 62.22; H, 3.88; N, 12.36; Cl, 21.55. IR (KBr, cm⁻¹): 3435, 2811, 1554, 1440, 1381, 1227. ¹H-NMR (400 MHz, CDCl₃, ppm): δ 3.60 (s, 3 H, CH₂), δ 4.05 (t, 3 H, CH₂), δ 3.85 (t, 3 H, CH₂), δ 4.20 (br, s, 1 H, NH), δ 1.88 (br, s, 1 H, NH), δ 8.82 (d, 1 H₂, J=8.0 Hz), δ 8.31 (s, 1 H₈), δ 7.35 (d, 1 H₅, J=7.6 Hz), δ 6.33 (d, 1 H₆, J=7.2 Hz), δ 6.55 (d, 1 H₃, J=7.6 Hz), δ 7.07-6.93 (m, 4 H, Ar-H). ¹³C-NMR (400 MHz, CDCl₃, ppm): δ 151.5, 149.5, 149.0, 147.3, 144.5, 135.4, 133.3, 131.2, 130.8, 127.1, 126.2, 121.9, 121.7, 112.9, 104.2, 39.4, 30.3, 24.1.

**IV. General procedure for the synthesis various N-benzylidine-N'(7-chloroquinolin-4-yl) ethane-1,2-diamine (48-59)**

To ethanol solution (10 ml) of N¹-(7-chloroquinolin-4-yl)-ethane-1,2-diamine (221 mg, 1mmol), ethanol (10 mL) solution of desired aldehyde (1 mmol) was added drop wise and the mixture was refluxed for 2-4 h depending upon the completion of reaction. The
progress of reaction was followed by thin layer chromatography. After completion of reaction, the reaction mixture was poured into ice cold water. The crude obtained was filtered and dried purified by crystallization in ethanol, CHCl₃/methanol or acetone.⁹⁵,⁹⁶

**Compound 48: N-(4-chlorobenzylidene)-N’-(7-chloroquinolin-4-yl)-ethane-1,2-diamine**

White solid; Yield=67%; mp=177-179 °C; Ms: m/z 344.24 [M⁺]; Rₓ=0.58 (MeOH:CHCl₃ 2:8); Anal. Calcd. (%) for C₁₈H₁₅Cl₂N₃: C, 66.39; H, 4.80; N, 12.41; Cl, 20.40. IR (KBr, cm⁻¹): 3184.11, 2870.37, 1553.90, 1450.32, 1329.59. ¹H-NMR (400 MHz, CDCl₃, ppm): δ 4.17 (t, 3 H, CH₂), δ 3.80 (t, 3 H, CH₂), δ 4.50 (br, s, 1 H, NH), δ 8.62 (s, 1 H, -CH=N-), δ 8.87 (d, 1 H, J=8.1 Hz), δ 8.25 (s, 1 H), δ 7.35 (d, 1 H, J=7.3 Hz), δ 6.31 (d, 1 H, J=7.1 Hz), δ 6.53 (d, 1 H, J=7.5 Hz), δ 6.92-6.285 (m, 4 H, Ar-H). ¹³C-NMR (400 MHz, CDCl₃, ppm): δ 173.2, 151.5, 147.0, 144.4, 135.4, 136.1, 133.2, 131.1, 130.8, 129.2, 115.9, 121.0, 112.2, 103.4, 43.1, 39.7.

**Compound 49: N-(7-chloroquinolin-4-yl)-N’-(4-dimethylamino-benzylidene)-ethane-1,2-diamine**

Yellow solid; Yield=54%; mp=124-126 °C; Ms: m/z 352.86 [M⁺]; Rₓ=0.55 (MeOH:CHCl₃ 2:8); Anal. Calcd. (%) for C₂₀H₂₂ClN₃O₂: C, 68.08; H, 6.30; N, 15.58; Cl, 10.05. IR (KBr, cm⁻¹): 3284.15, 2970.32, 1646.93, 1550.62, 1320.19. ¹H-NMR (400 MHz, CDCl₃, ppm): δ 3.05 (s, 6 H, CH₃), δ 4.16 (t, 3 H, CH₂), δ 3.80 (t, 3 H, CH₂), δ 5.20 (br, s, 1 H, NH), δ 1.82 (br, s, 1 H, NH), δ 8.61 (s, 1 H, -CH=N-), δ 8.87 (d, 1 H, J=8.1 Hz), δ 8.22 (s, 1 H), δ 7.33 (d, 1 H, J=7.1 Hz), δ 6.32 (d, 1 H, J=7.1 Hz), δ 6.53 (d, 1 H, J=7.5 Hz), δ 7.49 (dd, 2 H, Ar-H), δ 7.09 (dd, 2 H, Ar-H). ¹³C-NMR (400 MHz, CDCl₃, ppm): δ 150.5, 149.9, 146.9, 144.7, 135.1, 133.1, 130.8, 130.1, 124.2, 121.9, 115.8, 114.7, 112.2, 103.4, 47.6, 41.3, 38.9.

**Compound 50: 4-[[2-(7-Chloroquinolin-4-ylamino)-ethylimino]-methyl]-benzene-1,2-diol**

Light yellow solid; Yield=66%; mp=190-194 °C; Ms: m/z 341.10 [M⁺]; Rₓ=0.50 (MeOH:CHCl₃ 2:8); Anal. Calcd. (%) for C₁₈H₁₆ClN₃O₂: C, 63.25; H, 4.72; N, 12.29; Cl, 10.37; O, 9.36. IR (KBr, cm⁻¹): 3324.23, 2856.07, 1673.73, 1457.61, 1371.59. ¹H-NMR (400 MHz, DMSO-d₆, ppm): δ 5.22 (s, 2 H, OH), δ 4.16 (t, 3 H, CH₂), δ 3.80 (t, 3
H, 4.22 (br, s, 1 H, NH), δ 4.18 (br, s, 1 H, NH), δ 8.51 (s, 1 H, -CH=N-), δ 8.97 (d, 1 H, J=8.1 Hz), δ 8.22 (s, 1 H), δ 7.37 (d, 1 H, J=7.1 Hz), δ 6.32 (d, 1 H, J=7.1 Hz), δ 6.46 (d, 1 H, J=7.5 Hz), δ 7.19-6.50 (m, 3 H, Ar-H).

\[ ^{13} \text{C-NMR (400 MHz, DMSO-d_6, ppm)}: \delta 165.8, 150.5, 149.9, 146.8, 145.9, 145.2, 135.1, 133.1, 130.8, 130.1, 124.2, 121.9, 115.8, 114.7, 112.2, 103.4, 39.3, 30.9. \]

**Compound 51: N-(7-chloroquinolin-4-yl)-N’-(2,4-dichlorobenzylidene)-ethane-1,2-diamine**

White solid; Yield=53%; mp=168-170 °C, Ms: m/z 379 [M+]; Rf=0.53 (MeOH:CHCl_3 2:8); Anal. Calcd. (%) for C_{18}H_{14}Cl_3N_3: C, 57.09; H, 3.73; N, 11.10; Cl, 28.09. IR (KBr, cm\(^{-1}\)): 3334.15, 2970.23, 1723.93, 1640.61, 1322.59. \(^{1} \text{H-NMR (400 MHz, DMSO-d_6, ppm)}: \delta 4.15 (t, 3 H, CH_2), δ 3.81 (t, 3 H, CH_2), δ 4.50 (br, s, 1 H, NH), δ 1.89 (br, s, 1 H, NH), δ 8.63 (s, 1 H, -CH=N-), δ 8.97 (d, 1 H, J=8.1 Hz), δ 8.24 (s, 1 H), δ 7.36 (d, 1 H, J=7.3 Hz), δ 6.33 (d, 1 H, J=7.1 Hz), δ 6.54 (d, 1 H, J=7.5 Hz), δ 7.56-7.10 (m, 3 H, Ar-H). \(^{13} \text{C-NMR (400 MHz, DMSO-d_6, ppm)}: \delta 167.4, 158.4, 150.2, 149.5, 143.0, 141.4, 136.1, 134.8, 130.5, 129.2, 121.1, 120.8, 119.2, 111.0, 110.2, 103.4, 43.7, 30.7.

**Compound 52: N-(7-chloroquinolin-4-yl)-N’-(4-methylbenzylidene)-ethane-1,2-diamine**

White solid; Yield=72%; mp=128-130 °C; Ms: m/z 323 [M+]; Rf=0.64 (MeOH:CHCl_3 2:8); Anal. Calcd. (%) for C_{19}H_{18}ClN_3: C, 70.47; H, 5.60; N, 12.98; Cl, 10.95. IR (KBr, cm\(^{-1}\)): 3324.75, 2789.07, 1723.93, 1510.62, 1333.51. \(^{1} \text{H-NMR (400 MHz, DMSO-d_6, ppm)}: \delta 2.30 (s, 3 H, CH_3), δ 4.22 (t, 3 H, CH_2), δ 3.80 (t, 3 H, CH_2), δ 4.23 (br, s, 1 H, NH), δ 1.83 (br, s, 1 H, NH), δ 8.61 (s, 1 H, -CH=N-), δ 8.89 (d, 1 H, J=8.0 Hz), δ 8.34 (s, 1 H), δ 7.35 (dd, 1 H, J=7.3 Hz), δ 6.31 (dd, 1 H, J=7.2 Hz), δ 6.55 (d, 1 H, J=7.2 Hz), δ 7.20-6.69 (m, 4 H, Ar-H). \(^{13} \text{C-NMR (400 MHz, DMSO-d_6, ppm)}: \delta 165.1, 150.5, 148.1, 147.3, 144.4, 136.1, 133.4, 131.1, 130.6, 129.2, 121.8, 121.0, 112.2, 103.4, 39.7, 30.7, 21.7.

**Compound 53: N-(3-chlorobenzylidene)-N’-(7-chloroquinolin-4-yl)-ethane-1,2-diamine**

White solid; Yield=64%; mp=131-133 °C; Ms: m/z 344.24 [M+]; Rf=0.56 (MeOH:CHCl_3 2:8); Anal. Calcd. (%) for C_{18}H_{15}Cl_2N_3: C, 66.31; H, 4.40; N, 12.49; Cl,
20.80. IR (KBr, cm\(^{-1}\)): 3284.13, 2871.47, 1653.43 \(1450.65, 1321.50\). \(^1\)H-NMR (400 MHz, CDCl\(_3\), ppm): \(\delta 4.17\) (t, 3 H, CH\(_2\)), \(\delta 3.80\) (t, 3 H, CH\(_2\)), \(\delta 4.50\) (br, s, 1 H, NH), \(\delta 8.62\) (s, 1 H, -CH=N-), \(\delta 8.87\) (d, 1 H, J=8.1 Hz), \(\delta 8.25\) (s, 1 H), \(\delta 7.35\) (d, 1 H, J=7.3 Hz), \(\delta 6.31\) (d, 1 H, J=7.1 Hz), \(\delta 6.53\) (d, 1 H, J=7.5 Hz), \(\delta 6.92-6.65\) (m, 4 H, Ar-H).

\(^13\)C-NMR (400 MHz, CDCl\(_3\), ppm): \(\delta 170.2, 150.5, 147.8, 145.0, 143.4, 135.4, 134.1, 133.2, 131.1, 130.8, 129.2, 122.4, 115.9, 121.2, 112.1, 103.4, 46.6, 37.0.

**Compound 54:** N-(4-bromobenzylidene)-N’-(7-chloroquinolin-4-yl)-ethane-1,2-diamine

White solid; Yield=61%; mp=143-145 °C; Ms: m/z 388.69 [M\(^+\)]; R\(_f\)=0.57 (MeOH:CHCl\(_3\) 2:8); Anal. Calcd. (%) for C\(_{18}\)H\(_{15}\)BrClN\(_3\): C, 55.62; H, 3.89; N, 10.81; Cl, 9.12; Br, 20.56. IR (KBr, cm\(^{-1}\)): 3183.17, 3375.32, 2622.48, 1587.59, 1543.81, 1241.44. \(^1\)H-NMR (400 MHz, CDCl\(_3\), ppm): \(\delta 4.20\) (t, 3 H, CH\(_2\)), \(\delta 3.67\) (t, 3 H, CH\(_2\)), \(\delta 4.25\) (br, s, 1 H, NH), \(\delta 8.61\) (s, 1 H, -CH=N-), \(\delta 8.85\) (d, 1 H, J=8.1 Hz), \(\delta 8.29\) (s, 1 H), \(\delta 7.30\) (d, 1 H, J=7.8 Hz), \(\delta 6.34\) (d, 1 H, J=7.9 Hz), \(\delta 6.55\) (d, 1 H, J=7.4 Hz), \(\delta 6.90-6.25\) (m, 4 H, Ar-H). \(^13\)C-NMR (400 MHz, CDCl\(_3\), ppm): \(\delta 170.2, 151.4, 146.0, 145.4, 136.6, 132.2, 131.0, 130.2, 129.1, 114.9, 121.5, 113.5, 104.7, 49.1, 39.7.

**Compound 55:** N-(4-fluorobenzylidene)-N’-(7-chloroquinolin-4-yl)-ethane-1,2-diamine

White solid; Yield=71%; mp=142-144 °C; Ms: m/z 327.78 [M\(^+\)]; R\(_f\)=0.66 (MeOH:CHCl\(_3\) 2:8); Anal. Calcd. (%) for C\(_{18}\)H\(_{15}\)ClFN\(_3\): C, 65.96; H, 4.61; N, 10.82; Cl, 10.82; F, 5.80. IR (KBr, cm\(^{-1}\)): 3276.15, 3026.49, 1781.58, 1592.98, 1423.03, 1339.14. \(^1\)H-NMR (400 MHz, CDCl\(_3\), ppm): \(\delta 4.12\) (t, 3 H, CH\(_2\)), \(\delta 3.87\) (t, 3 H, CH\(_2\)), \(\delta 4.15\) (br, s, 1 H, NH), \(\delta 8.68\) (s, 1 H, -CH=N-), \(\delta 8.83\) (d, 1 H, J=8.5 Hz), \(\delta 8.22\) (s, 1 H), \(\delta 7.32\) (d, 1 H, J=7.8 Hz), \(\delta 6.34\) (d, 1 H, J=7.9 Hz), \(\delta 6.55\) (d, 1 H, J=7.4 Hz), \(\delta 6.90-6.25\) (m, 4 H, Ar-H). \(^13\)C-NMR (400 MHz, CDCl\(_3\), ppm): \(\delta 170.2, 151.4, 146.0, 145.4, 136.6, 132.2, 131.0, 130.2, 129.1, 114.9, 121.5, 113.5, 104.7, 49.1, 35.7.

**Compound 56:** 5-Bromo-4-{2-(7-chloroquinolin-4-yl-amino)-ethylimino}-methyl}-2-methoxyphenol

White solid; Yield=54%; mp=132-135 °C; Ms: m/z 434.71 [M\(^+\)]; R\(_f\)=0.50 (MeOH:CHCl\(_3\) 2:8); Anal. Calcd. (%) for C\(_{19}\)H\(_{17}\)BrClN\(_3\)O\(_2\): C, 52.50; H, 3.94; N, 9.67; Cl, 8.16; Br,
18.38; O, 7.36. IR (KBr, cm\(^{-1}\)): 3471.75, 2126.49, 1671.28, 1462.98, 1373.03, 1269.84.

\(^1\)H-NMR (400 MHz, DMSO-d\(_6\), ppm): δ 5.65 (s, 1 H, OH), 3.82 (s, 1 H, OCH\(_3\)), δ 4.17 (t, 3 H, CH\(_2\)), δ 3.80 (t, 3 H, CH\(_2\)), δ 4.50 (br, s, 1 H, NH), δ 9.11 (s, 1 H, -CH=N-), δ 8.80 (d, 1 H, J=8.1 Hz), δ 8.22 (s, 1 H, δ 7.37 (d, 1 H, J=7.3 Hz), δ 6.38 (d, 1 H, J=7.1 Hz), δ 6.50 (d, 1 H, δ 7.5 Hz), δ 6.92 (s, 1 H, Ar-H), δ 6.85 (s, 1 H, Ar-H).

\(^1\)C-NMR (400 MHz, DMSO-d\(_6\), ppm): δ 168.2, 150.5, 148.3, 147.8, 145.0, 143.4, 135.4, 134.1, 133.2, 131.1, 130.8, 129.2, 121.4, 115.9, 112.1, 103.4, 58.8, 46.1, 39.7.

**Compound 57: 4-{{2-(7-Chloroquinolin-4-ylamino)-ethylimino}-methyl}-phenol**

White solid; Yield=63%; mp=164-166 °C; Ms: m/z 325.79 [M\(^+\)]; R\(_f\)=0.66 (MeOH:CHCl\(_3\) 2:8); Anal. Calcd. (%) for C\(_{18}\)H\(_{16}\)ClN\(_3\)O: C, 66.36; H, 4.95; N, 12.90; Cl, 10.88; O, 4.91. IR (KBr, cm\(^{-1}\)): 3571.75, 3226.49, 1781.58, 1632.28, 1463.13, 1245.24. \(^1\)H-NMR (400 MHz, DMSO-d\(_6\), ppm): δ 4.15 (t, 3 H, CH\(_2\)), δ 3.85 (t, 3 H, CH\(_2\)), δ 5.25 (s, 1H, OH) δ 4.15 (br, s, 1 H, NH), δ 8.26 (s, 1 H, -CH=N-), δ 8.17(d, 1 H, J=8.9 Hz), δ 8.25 (s, 1 H, δ 7.33 (d, 1 H, J=7.7 Hz), δ 6.39 (d, 1 H, J=7.9 Hz), δ 6.53 (d, 1 H, J=7.5 Hz), δ 7.45-6.65 (m, 4 H, Ar-H). \(^1\)C-NMR (400 MHz, DMSO-d\(_6\), ppm): δ 170.2, 159.5, 147.8, 145.0, 143.4, 134.1, 133.2, 131.1, 130.8, 129.2, 121.4, 115.9, 112.1, 103.4, 44.1, 35.1.

**Compound 58: 4-{{2-(7-Chloroquinolin-4-ylamino)-ethylimino}-methyl}-benzonitrile**

White solid; Yield=65%; mp=126-129 °C; Ms: m/z 334.10 [M\(^+\)]; R\(_f\)=0.53 (MeOH:CHCl\(_3\) 2:8); Anal. Calcd. (%) for C\(_{19}\)H\(_{15}\)ClN\(_4\): C, 68.16; H, 4.59; N, 10.52; Cl, 16.73. IR (KBr, cm\(^{-1}\)): 3271.75, 2126.49, 1571.58, 1452.98, 1373.03, 1236.14. \(^1\)H-NMR (400 MHz, DMSO-d\(_6\), ppm): δ 4.02 (t, 3 H, CH\(_2\)), δ 3.65 (t, 3 H, CH\(_2\)), δ 4.45 (br, s, 1 H, NH), δ 8.88 (s, 1 H, -CH=N-), δ 8.76 (d, 1 H, J=8.9 Hz), δ 8.37 (s, 1 H, δ 7.45 (d, 1 H, J=7.1 Hz), δ 6.54 (d, 1 H, J=7.3 Hz), δ 6.50 (d, 1 H, J=7.3 Hz), δ 7.80-7.46 (m, 4 H, Ar-H). \(^1\)C-NMR (400 MHz, DMSO-d\(_6\), ppm): δ 176.2, 167.2, 150.3, 144.0, 142.8, 135.3, 133.6, 132.14, 130.0, 129.2, 116.9, 114.9, 111.5, 110.7, 104.4, 49.1, 39.7.

**Compound 59: N-(7-chloroquinolin-4-yl)-N'-{(4-methoxybenzylidene)-ethane-1,2-diamine**

White solid; Yield=71%; mp=190-193 °C; Ms: m/z 327.78 [M\(^+\)]; R\(_f\)=0.66 (MeOH:CHCl\(_3\) 2:8); Anal. Calcd. (%) for C\(_{19}\)H\(_{18}\)ClN\(_3\)O: C, 67.15; H, 5.34; N, 12.37; O,
4.71. IR (KBr, cm\(^{-1}\)): 3591.75, 3326.49, 1701.58, 1692.18, 1463.03, 1228.44. \(^1\)H-NMR (400 MHz, DMSO-d\(_6\), ppm): \(\delta\) 3.78 (s, 3 H, OCH\(_3\)), \(\delta\) 4.10 (t, 3 H, CH\(_2\)), \(\delta\) 3.65 (t, 3 H, CH\(_2\)), \(\delta\) 4.45 (br, s, 1 H, NH), \(\delta\) 8.89 (s, 1 H, -CH=N-), \(\delta\) 8.87 (d, 1 H, J=8.5 Hz), \(\delta\) 8.27 (s, 1 H\(_8\)), \(\delta\) 7.34 (d, 1 H\(_5\), J= 7.0 Hz), \(\delta\) 6.35 (d, 1 H\(_6\), J=7.1 Hz), \(\delta\) 6.54 (d, 1 H\(_3\), J=7.5 Hz), \(\delta\) 7.50-6.90 (m, 4 H, Ar-H). \(^{13}\)C-NMR (400 MHz, DMSO-d\(_6\), ppm): \(\delta\) 167.2, 164.4, 151.4, 146.0, 145.4, 133.3, 136.6, 132.2, 129.2, 129.9, 114.9, 121.5, 112.7, 104.4, 58.8, 51.1, 37.7.

1.4.1a In vitro susceptibility assay of *Plasmodium falciparum* to different antimalarial drugs

Reagents

**Lumefantrine or desbutyl-lumefantrine**

1. **Stock solution**: Dissolve 1 mg/mL lumefantrine or desbutyl-lumefantrine (DBL) in 1:1:1 v/v/v linoleic acid, ethanol and Tween 80. If necessary, use sonication for 90 seconds in a water bath in pre-warmed media to facilitate dissolution. Sterilize by ultra-filtration

2. **Intermediate solution**: Dilute the stock solution 1/100 in culture RPMI medium without hypoxanthine (1 mg/ml divided by 100 = 0.01 mg/mL)

3. **Working solution**: Dilute the intermediate solution 1/10 in culture RPMI medium without hypoxanthine (0.01 mg/ml divided by 10 = 0.001 mg/mL = 1000 ng/mL)

4. **Serial solution**: Dilute working solution to two-fold serial dilutions with a final concentration range of 1.65-211.58 ng/mL (3.12-400 nM). Due to 1:1 dilution in the wells with the parasitized RBC, the serial concentrations will have to be 2 times final concentration: 2 x (1.65; 3.31; 6.61; 13.22; 26.45; 52.90; 105.79; 211.58) ng/mL.

Volume needed for each serial concentration in one 96-well plate:

100 \(\mu\)L x 12 wells = 1200 \(\mu\)L \(\rightarrow\) 1500 \(\mu\)L. To be able to make the next diluted concentration in the serial dilution: 1500 \(\mu\)L + 1500 \(\mu\)L \(\rightarrow\) 3000 \(\mu\)L = 3 mL

Strongest serial concentration: 2 x 211.58 ng/mL = 423.16 ng/mL
Volume of working solution needed to make strongest serial concentration: $423.16 \text{ ng/mL} \times 3 \text{ mL} = 1000 \text{ ng/mL} \times V_2 \rightarrow V_2 = 1.269 \text{ mL}$

**Store:** The stock solution can be stored in aliquots in light-proof tubes at -20°C or the 96-well plates can be made in bulk with 100 µl aliquots of the dosed and drug-free medium and stored at -80°C (for up to 3 months).

A. **Materials**

- Parasitized RBC (In vitro cultured field isolates)
- Parasitized RBC (Laboratory-adapted strains)
- Human O+ erythrocytes (RBC, uRBC)
- Parasite Culture RPMI 1640 medium (without hypoxanthine)

B. **Procedure**

Use synchronized parasites. Run all tests twice (triple) in (duplicate) triplicate.

1. In 96-well microtitre plates each parasite line has a column of 8 wells. Set up the parasites with:
   - 100 µL of lumefantrine- or DBL-dosed culture medium (rows B-H) in ascending order of 2 × concentration (twofold dilutions) or 100 µL of drug-free culture medium (row A; control samples),
   - 90 µL of parasitized RBC (0.5% parasitaemia, 1.5% haematocrit) (not in column 12, rows B-H, control samples) and 10 µL of 5 mg/mL tritium-labelled hypoxanthine to a final concentration of 0.5 µCi/well
2. Set up identically wells with 1-2 known laboratory-adapted strains (control samples)
3. Also set up identically wells but without adding parasites (i.e. using uninfected RBC in medium only) as controls for background incorporation of radioactive label.
4. Place the microtitre plate in a box, gas with 5% CO$_2$, 2% O$_2$, 93% N$_2$, and seal. Incubate for 48 h at 37 °C
5. Harvesting: Dilute the contents of each well into 15 mL of distilled water to lyse the cells and parasites, and suction onto a 96-well glass-fibre filter mat. Remove excess label by washing the filters with a further 15 mL of distilled water. Remove residual water with a final wash in 100% ethanol. (Three freeze-thaw cycles for cell lysis using Harvester 96). Air-dry the filtermats.


7. Analyse data using curve-fitting software.

IC\textsubscript{50} values are defined as the concentration of drug at which parasite growth is reduced to half that of the untreated controls, as measured by tritium incorporation.

To get reliable IC\textsubscript{50} measurements >5000 dpm (disintegration per minute) should be seen in the controls.

1.5 Conclusion

Despite of the extensive research efforts directed towards the improvement of new antimalarial drugs, malaria continues to devastate the poorest countries. Therefore, there is a challenge and urgency to develop new affordable, safe and effective drugs with low potential of inducing resistance. In search of new antimalarials, we have successfully synthesized 58 quinoline derivatives using 4,7-dichloroquinoline as a basic scaffold utilizing readily available and inexpensive chemicals. In search of hybrid analogs, new class of 4-anilinoquinoline triazine derivatives were synthesized to explore and compare the crystallographic properties of amodiaquine analogs and determine the possible role of 4-amino group in antimalarial activity as well as in crystallization. All synthesized compounds of series-I, III and IV are well characterized by various spectroscopic techniques including X-ray crystallographic studies. Compounds of series-I, III and IV are screened against malaria parasite FCR3 strain for their antimalarial activity. Assessment of compounds showed that compound 17 [(7- chloroquinolin-4-yl)-(2,5-dimethoxyphenyl)-amine] of series-I, compound 45 [N-(7-chloroquinolin-4-yl)-N’-(2,4-difluorobenzyl)-ethane-1,2-diamine] of series-III and compound 55 [N-(4-fluorobenzylidene)-N’-(7-chloroquinolin-4-yl)-ethane-1,2-diamine] of series-IV was found most active against \textit{P. falciparum} and exhibited promising IC\textsubscript{50} values. The cytotoxicity and in vivo antimalarial activity of synthetic compounds is under progress. In vitro antimalarial activity of compounds of series II is under progress.
1.6 References


IR spectra of (7-chloroquinolin-4-yl)-(2,5-dimethoxyphenyl)-amine
$^1$H-NMR spectra of (7-chloroquinolin-4-yl)-(2,5-dimethoxyphenyl)-amine
C-NMR spectra of (7-chloroquinolin-4-yl)-(2,5-dimethoxyphenyl)-amine
MALDI-TOF Mass spectra of (7-chloroquinolin-4-yl)-(2,5-dimethoxyphenyl)-amine
IR spectra of (7-chloroquinolin-4-yl)-(2,3-dimethylphenyl)-amine
\(^1\)H-NMR spectra of (7-chloroquinolin-4-yl)-(2,3-dimethylphenyl)-amine
$^{13}$C-NMR spectra of (7-chloroquinolin-4-yl)-(2,3-dimethylphenyl)-amine
MALDI-TOF Mass spectra of (7-chloroquinolin-4-yl)-(2,3-dimethylphenyl)-amine
IR spectra of (7-chloroquinolin-4-yl)-(4,6-dichloro-[1,3,5]-triazin-2-yl)-(3-fluorophenyl)-amine
$^1$H-NMR spectra of (7-chloroquinolin-4-yl)-(4,6-dichloro-[1,3,5]-triazin-2-yl)-(3-fluorophenyl)-amine
$^{13}$C-NMR spectra of (7-chloroquinolin-4-yl)-(4,6-dichloro-[1,3,5]-triazin-2-yl)-(3-fluorophenyl)-amine
MALDI-TOF Mass spectra of (7-chloroquinolin-4-yl)-(4,6-dichloro-[1,3,5]-triazin-2-yl)-(3-fluorophenyl)-amine
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$^1$H-NMR spectra of (7-chloroquinolin-4-yl)-(4,6-dichloro-[1,3,5]-triazin-2-yl)-(4-fluorophenyl)-amine
$^{13}$C-NMR spectra of (7-chloroquinolin-4-yl)-(4,6-dichloro-[1,3,5]-triazin-2-yl)-(4-fluorophenyl)-amine
MALDI-TOF Mass spectra of (7-chloroquinolin-4-yl)-(4,6-dichloro-[1,3,5]-triazin-2-yl)-(4-fluorophenyl)-amine
IR spectra of N-(7-chloroquinolin-4-yl)-N'-(2,4-dichlorobenzyl)-ethane-1,2-diamine
H-NMR spectra of N-(7-chloroquinolin-4-yl)-N'-(2,4-dichlorobenzyl)-ethane-1,2-diamine
$^{13}$C-NMR spectra of N-(7-chloroquinolin-4-yl)-N'-(2,4-dichlorobenzyl)-ethane-1,2-diamine
MALDI-TOF Mass spectra of N-(7-chloroquinolin-4-yl)-N’-(2,4-dichlorobenzyl)-ethane-1,2-diamine
IR spectra of N-(7-chloroquinolin-4-yl)-N'-(4-chlorobenzyl)-ethane-1,2-diamine
\(^{1}\)H-NMR spectra of N-(7-chloroquinolin-4-yl)-N'-(4-chlorobenzyl)-ethane-1,2-diamine
$^{13}$C-NMR spectra of N-(7-chloroquinolin-4-yl)-N'-(4-chlorobenzyl)-ethane-1,2-diamine
MALDI-TOF Mass spectra of N-(7-chloroquinolin-4-yl)-N'-(4-chlorobenzyl)-ethane-1,2-diamine
IR spectra of N-(4-fluorobenzylidene)-N'-(7-chloroquinolin-4-yl)-ethane-1,2-diamine
$^1$H-NMR spectra of N-(4-fluorobenzylidene)-N'-(7-chloroquinolin-4-yl)-ethane-1,2-diamine
$^{13}$C-NMR spectra of N-(4-fluorobenzylidene)-N'-(7-chloroquinolin-4-yl)-ethane-1,2-diamine
MALDI-TOF Mass spectra of N-(4-fluorobenzylimidene)-N'-(7-chloroquinolin-4-yl)-ethane-1,2-diamine
IR spectra of 4-[[2-(7-chloroquinolin-4-ylamino)-ethylimino]-methyl]-phenol
$^1$H-NMR spectra of 4-[[2-(7-chloroquinolin-4-ylamino)-ethylimino]-methyl]-phenol
$^{13}$C-NMR spectra of 4-\{2-(7-chloroquinolin-4-ylamino)-ethylimino\}-methyl\}-phenol
MALDI-TOF Mass spectra of 4-\{[2-(7-chloroquinolin-4-ylamino)-ethylimino]-methyl\}-phenol