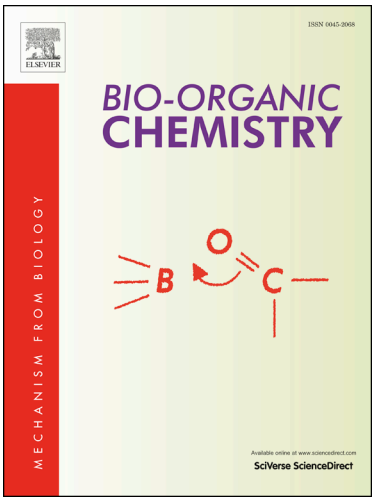


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# Design, Synthesis and Antiplasmodial activity of novel imidazole derivatives based on 7-chloro-4-aminoquinoline.

Srinivasarao Kondaparla[a]*, Ashan Manhas[b], Vasantha Rao Dola[a] ,Kumkum Srivastava[b], Sunil K. Puri[b], S. B. Katti[a]

[a]Medicinal & Process Chemistry Division, CSIR-Central Drug Research Institute Sector-10, Jankipuram Extension, Sitapur Road, Lucknow -226031.

[b]Parasitology Division, CSIR-Central Drug Research Institute, Sector-10, Jankipuram Extension, Sitapur Road, Lucknow-226031, India.

**Keywords:** 4-Aminoquinoline; Antiplasmodial activity; Heme binding; Chloroquine; *Plasmodium falciparum*; *β*-hematin; *in vitro*; Chloroquine sensitive strain; Chloroquine resistant strain.

**Abbreviations:** CQ, chloroquine; DMF, dimethylformamide; TOSMIC, Toluenesulfonylmethyl isocyanide

Corresponding author; Tel: +91-08674-259287, Fax; +91-522-2771941

Email address; srinu086@gmail.com (Srinivasarao Kondaparla*)

**Abstract:**

A series of short chain 4-aminoquinoline-imidazole derivatives have been synthesized in one pot two step multicomponent reaction using van leusen standard protocol. The diethylamine function of chloroquine is replaced by substituted imidazole derivatives containing tertiary terminal nitrogen. All the synthesized compounds were screened against the chloroquine sensitive (3D7) and chloroquine resistant (K1) strains of *Plasmodium falciparum*. Some of the compounds (**6**, **8**, **9** and **17**) in the series exhibited comparable activity to CQ against K1 strain of *P. falciparum*. All the compounds displayed resistance factor between 0.09 and 4.57 as against 51 for CQ. Further, these analogues were found to form a strong complex with hematin and inhibit the *β*-hematin formation, therefore these compounds act *via* heme polymerization target.

## 1. Introduction

Malaria still remains a serious health problem to human beings around the world, mostly sub-Saharan African countries are at much higher risk [1]. As per WHO report 3.2 billion people remain at risk of malaria. In 2015 alone, there were an estimated 212 million new cases of malaria and 429, 000 deaths. Most among them are children younger than 5 years [2]. Among the protozoan parasites (*P. falciparum, vivax, ovale, malariae* and *knowlesi*) of the genus *Plasmodium, P. falciparum* is the most prevalent and virulent in human, and contributes maximum number of deaths compared to other *Plasmodium* species [3]. Over the last 60 years the use of quinine has declined owing to the development of synthetic 4-aminoquinolines such as chloroquine (CQ) (**Figure 1**). Among several quinoline based antimalarials, CQ is the most effective and widely used drug in malaria chemotherapy because of its rapid onset of action, good tolerability and low cost [4]. However, emergence and wide-spread of drug resistance to CQ and many other drugs, including primaquine, pyrimethamine and mefloquine (**Figure 1**) has increased the burden of mortality rate quite abnormally in the last few years [5]. So, there is an urgent need of new chemical entities active against drug resistant parasites. However, despite emergence of drug resistance CQ scaffold still could be a good choice for further chemical modifications, owing to its excellent efficacy, limited host toxicity and affordability [6]. Subsequently, literature survey on 4-aminoquinolines clearly suggested that antimalarial activity, particularly inhibition of *β*-hematin formation and accumulation of the drug at the target site, resides in 4-aminoquinoline core [7]. Accordingly, a number of new 4-aminoquinoline analogues with enhanced activity against CQ-R strain have been developed by conducting synthetic modification of the CQ side chain [8-9]. However, in recent years various strategies have been employed to circumvent the drug resistant. The 4-aminoquinoline hybridization is one quite attractive strategy which has been recently introduced in the medicinal chemistry and

drug discovery process [10-11]. Moreover, chemotherapeutic agents derived from Schiff's base have occupied a unique place in the field of medicinal chemistry [12]. Further, incorporation of bioactive functionalities in the side chain of 4-aminoquinoline emerged as promising strategies to construct the molecules with enhanced activity against drug-resistant *P. falciparum* and also with improved metabolic stability [13]. Recently, Campiani *et al.* synthesized Clotrimazole (CLT) analogues [14] and subsequently prepared hybrid of the 4-aminoquinoline with the clotrimazole-like pharmacophore [15] in which imidazole ring of CLT behaves as a Fe(III) axial ligand and inhibit *β*-hematin formation and reported promising *in vitro* (against both sensitive and resistant strain) and *in vivo* antimalarial activities. On the other hand, various imidazole-based compounds have shown good coordination properties and are able to form stable complexes with several metal ions inhibitors [13].

Previously from our laboratory we introduced biologically privileged thiazolidine-4-one ring system in the side chain in order to enhance the lipophilicity (**Fig. 2, a**). These analogues showed remarkable activity against CQ-sensitive strain (NF-54) of *P. falciparum in vitro* and CQ-resistant strain (N-67) of *P. yoelii in vivo* [16]. Later, we reported the synthesis of chiral chloroquine and its analogues by incorporating different acyclic/cyclic amines in the side chain of CQ (**Fig. 2, a**). These chiral chloroquine analouges exhibited superior activity against both *in vitro* (3D7 & K1 strains) and *in vivo* (N-67 strain) studies [17]. Encouraged by these results, we envisaged that incorporation of biological privileged motif such as imidazole (with ability to coordinate with the heme) in the side chain of 4-aminoquinoline pharmacophore would lead to develop the new antimalarial agents active against CQ-R strain of *P. falciparum*. Based on the above fact and in the continuation of our ongoing antimalarial programme, herein we report the one-pot two step efficient synthesis of 4-aminoquinoline analogues (**Fig. 2, b**) containing imidazole nucleus at lateral part of the

side chain and there evaluation as potentially active compounds against *Plasmodium* malaria parasite. Results are discussed in the present communication.

## 2. Results and Discussion

### 2.1 Chemistry

The designed compounds (**5-22**) were synthesized *via* a two step simple and efficient synthetic protocol. The detailed synthetic route for the synthesis of intermediate **4** and target compounds (**5-22**) is outlined in **Scheme-1**. Initially, treatment of 4, 7-dichloroquinoline with excess of ethylenediamine under solvent free conditions furnished the corresponding $N^1$-(7-chloroquinolin-4-yl)ethane-1,2-diamine (**4**) in quantitative yield. Further, intermediate **4** was utilized as amine input in TOSMIC (Toulene sulfonyl methyl isocyanide) based multi-component cyclisation reaction. Further, condensation of aldehyde with $N^1$-(7-chloroquinolin-4-yl)ethane-1,2-diamine give aldimine followed by TOSMIC induced base ($K_2CO_3$) catalysed cyclisation in DMF at 90 $^{\circ}$C afforded the target compounds (**5-22**) in good yield. All final compounds (**5-22**) were characterized by $^1$H NMR, $^{13}$C NMR, Mass and HRMS respectively.

### 2.2 Antiplasmodial (*P. falciparum*) Activity

A novel series of 4-aminoquinoline-imidazole derivatives (**5-22**) were synthesized and examined for *in vitro* antiplasmodial activity against both CQ-sensitive (3D7) and CQ-resistant (K1) strains of *Plasmodium falciparum.* The results are shown in Table-1. All the compounds exhibited moderate to higher activity with $IC_{50}$ values ranging from 0.079±0.015 -5±0.048 µM against CQ-S strain and 0.291±0.018- 5±0.047 µM against CQ-R strain of *P. falciparum*.

The structure activity relationship (SAR) studies on these compounds clearly suggest that the activity of these compounds is greatly influenced by the type of substitution present on the imidazole ring. The activity data of our compounds suggest that the type of

substitution present on the phenyl ring attached to imidazole markedly influenced the activity of 4-aminoquinoline imidazole derivatives (**Figure 3**). According to our results, compounds (**5**, **6**, **7**, **11** and **14**) with heterocyclic core attached to imidazole had very mild effect on the inhibition of parasite growth against CQ-R strain with $IC_{50}$ values 1.15±0.028, 0.46±0.048, 1.70±0.024, 1.33±0.029 and 0.97±0.025 µM respectively, among them compound **6** ($IC_{50}$ = 0.46±0.048 µM) exhibited comparable activity to CQ ($IC_{50}$ = 0.255±0.049 µM) against CQ-R strain of *P. falciparum*. Moreover, compounds **12** and **20** ($IC_{50}$ values 2.62±0.025 and 0.92±0.031 µM) with phenoxyl and naphthalene substituents on imidazole moiety were found to be inactive against both the strains (3D7 & K1) of *P. falciparum*. This result clearly suggests that bulky aromatic substituents are not suitable on imidazole moiety. However, the activity of compounds was greatly influenced by the type of substitution present on the phenyl ring attached to *N*-(2-(1*H*-imidazol-1-yl)ethyl)-7-chloroquinolin-4-amine pharmacophore. Compounds containing electron withdrawing groups had much better activity against CQ-R strain as compared to those containing electron donating groups. On that account, among the synthesized compounds in the series, compounds **8** and **15** with electron withdrawing group showed better inhibition effect against CQ-R strain compared to compounds **10**, **16**, **19** and **22** which were bearing electron donating group as on phenyl ring. Interestingly, cyclopentyl and cyclohexyl substitutions on *N*-(2-(1*H*-imidazol-1-yl)ethyl)-7-chloroquinolin-4-amine moiety markedly affected the activity profile against both the strains (3D7 & K1) of *P. falciparum*. Consequently, compound **17** with cyclopentyl substitution exhibited much better activity against K1 strain with $IC_{50}$ value 0.34±0.011 µM, than compound **21**($IC_{50}$ = 0.52±0.029 µM) which is having cyclohexyl substitution. Moreover, compound **17** also showed comparable activity to CQ ($IC_{50}$ = 0.255±0.049 µM) against K1 strain. This activity may be due to presence of planar hydrophobic motif in the side chain. Furthermore, despite various substitutions on phenyl ring (**Table-1**) isopropyl group bearing

compound **9** was found to be most active in the series against K1 strain with $IC_{50}$ 0.29±0.018 µM, which was shown all most equal potency with CQ ($IC_{50}$ = 0.255 ±0.049 µM). Furthermore, Compound **13** having tert-butyl group substitution on *N*-(2-(1*H*-imidazol-1-yl)ethyl)-7-chloroquinolin-4-amine pharmacophore showed significant activity with $IC_{50}$ = 0.50±0.023 µM against K1 strain of *P. falciparum*. From the overall results, it is clear that alkyl groups and alkyl substituted phenyl rings are most favourable for the substitution on *N*-(2-(1*H*-imidazol-1-yl)ethyl)-7-chloroquinolin-4-amine pharmacophore, which would lead to compounds having better antimalarial activity against both strains and ultimately opens up a novel strategy to circumvent the drug resistance parasites of *P. falciparum*.

### 2.3 *In vitro* cytotoxicity

The cytotoxicity of all the synthesized compounds **5-22** was determined against VERO cell line using MTT assay (Table-1). 14 compounds in the series showed considerable selectivity index (SI) ranging between 26.12 and 203.82, rest of molecules namely **6**, **7**, **11**, **12**, **16** and **21** showed selectivity index values as >431.03, >117.64, >150.37, >76.33, >112.29 and >383.14 respectively. Compounds **8** and **17** which were exhibited comparable potency against K1 strain also showed good selectivity index 79.54 and 203.82 respectively. Compound **9** which was most potent against resistant strain K1, also showed good selectivity index of >687.2. In the series few compounds exhibited reasonably promising activity against K1 strain, less cytotoxic effect with fairly high selectivity index, and consequently these 4-aminoquinoline imidazole derivatives are promising candidate for further lead optimization.

### 2.4 *In vitro* Inhibition of *β*-hematin Polymerization

The mode of action of new series of 4-aminoquinoline-imidazole derivatives **5-22** was investigated by the reported method [18] and the results are shown in (**Table 1**). Heme binding assay results confirm that all the synthesized compounds interact with the heme. However, compounds **8** and **14** formed strong complex with hematin and log K was found to

be 5.93 and 5.71 respectively. Remaining compounds in the series exhibited the association constants values in the range 5.71-8.73. These results are concurrent with the previous results from our laboratory [19-20] as well as reported literature evidences [21]. These results indicate that, there might be a π-π stacking interaction between quinoline ring and porphyrin ring system.

All the synthesized side chain modified 4-aminoquinoline-imidazole derivatives **5-22** inhibited the *β*-hematin formation in a concentration dependent manner (**Table 1**). However most of the new series of 4-aminoquinoline-imidazole derivatives were good inhibitors of *β*-hematin formation. It is reported that there was no linear correlation between inhibition of *β*-hematin formation and antiplasmodial activity [16]. As reported, some of our compounds showed moderate antiplasmodial activity against CQ-S and CQ-R strains of *P. falciparum*, but showed better affect on inhibition of hemozoin formation (**Table 1**). In this present study most potent inhibitor was compound **9** with an $IC_{50}$ of 0.42 µM in the hemozoin inhibition assay, and also showed comparable activity to CQ against CQ-R strain. These results highlighted the importance of hydrophobic substitution. So, we conclude that this class of compounds act on heme polymerization target.

**3. Conclusion**

In conclusion, we have synthesized novel imidazole derivatives of 4-aminoquinoline by utilizing highly efficient van leusen multicomponent synthetic protocol. A few compounds in the series exhibited moderate antiplasmodial activity against CQ-R strain of *P. falciparum*, and also most of the compounds show fairly high selectivity index. In the present study, substitutions on *N*-(2-(1*H*-imidazol-1-yl)ethyl)-7-chloroquinolin-4-amine moiety has greatly influenced the antiplasmodial activity. Overall results clearly highlight the importance of alkyl substituents on phenyl ring as well as hydrophobic substitutions on *N*-(2-(1*H*-imidazol-1-yl)ethyl)-7-chloroquinolin-4-amine pharmacophore.

## 4. Materials and Methods

### 4.1 General Information

Melting points (mp) were taken in open capillaries on Complab melting point apparatus and are uncorrected. The $^{1}$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded in $CDCl_3$, $CD_3OD$ and DMSO-$d_6$ solvents on DPX-400 Bruker FT-NMR spectrometer. All chemical shifts ($\delta$) are reported in parts per million (ppm) downfield from tetramethylsilane. The splitting pattern abbreviations are as follows: s (singlet), d (doublet), dd (doublet of doublet), t (triplet), and m (multiplet). Coupling constants are given in hertz. Mass Spectra (ESI-MS), high resolution mass spectra HRMS **(**ESI-HRMS) were recorded on Jeol (Japan)/SX-102, Agilent 6520 Q-Tof (ESI-HRMS) spectrometers respectively. Analytical thin-layer chromatography (TLC) was carried out on Merck's pre-coated silica-gel plates 60 $F_{254}$ and spots were visualized by irradiation with UV light (254 nm). Iodine was used as developing agent and/or by spraying with Dragendorff's reagent. Column chromatographic purification was performed over neutral alumina and (silica gel 60-120, 100-200 and 230-400 mesh) using a gradient solvent system (n-hexane/EtoAc, DCM/Hexane or chloroform/methanol as the eluent unless otherwise specified). All chemicals and reagents were obtained from Aldrich (USA), Lancaster (UK) and Spectrochem Pvt. Ltd (India) and were used without further purification**.**

### 4.2. General procedure for the synthesis of $N^1$-(7-Chloroquinolin-4-yl)ethane-1,2-diamine (4)

A mixture of 4,7-dichloroquinoline (1 equiv.) and 1,2-diaminoethane (5 equiv.) was heated slowly from room temperature to 80°C over 1 h with stirring and subsequently at 120–130°C for 6-8 h with continued stirring to drive the reaction to completion. The reaction mixture was cooled to room temperature and taken up in dichloromethane. The organic layer was successively washed with 5% aq $NaHCO_3$ followed by water wash and then finally with brine. The organic layer was dried over anhydrous $Na_2SO_4$ and solvent was removed under

reduced pressure and the residue was precipitated by the addition of 80:20 hexane–chloroform.

Compound **4** was obtained as yellow solid in 85% yield; m.p. 131-132°C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.10-3.16 (m, 2H, $NHCH_2CH_2NH_2$), 3.30-3.45 (m, 2H, $NHCH_2CH_2NH_2$), 4.73 (br s, 2H, $NHCH_2CH_2NH_2$), 5.87 (br s, 1H, $NHCH_2CH_2NH_2$), 6.40 (d, $J$ = 5.4 Hz, 1H, Ar-*H* quinoline), 7.67 (d, $J$ = 9.0 Hz, 1H, Ar-*H* quinoline), 7.70 (d, $J$ = 2.1 Hz, 1H, Ar-*H* quinoline), 7.95-7.99 (dd, $J$ = 2.1, 8.1 Hz, 1H, Ar-*H* quinoline), 8.50 (d, $J$ = 5.1 Hz, 1H, Ar-*H* quinoline); ESI-MS: (*m/z*) 222.3 $(M+H)^+$.

### 4.3 General procedure for the synthesis of (5-22)

Aldehyde (1 equiv. 0.48 mmol) and amine (1 equiv. 0.48 mmol) were dissolved in DMF (10 mL) and heat the reaction mixture at 90°C for 6-8h. Then Potassium carbonate (2 equiv. 0.96 mmol) and TOSMIC (1 equiv. 0.48 mmol) were added to the reaction mixture, continue stirring at 90°C for 12h. The Completion of the reaction was monitored by TLC, then cool the reaction mixture to room temperature, then add 20 mL water and extract with EtOAc (3 X 20 mL). The organic phase was dried over $Na_2SO_4$ and concentrated under reduced pressure. Then obtained crude was purified by column chromatography using 60-120 mesh in Methanol/Chloroform as eluent, afforded the title compounds.

#### 4.3.1 *N*-(2-(5-(1*H*-Pyrrol-2-yl)-1*H*-imidazol-1-yl)ethyl)-7-chloroquinolin-4-amine (5)

Compound **5** was obtained as pale yellow solid in 76% yield; m.p. 168-170°C; $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 3.62-3.66 (m, 2H, $NHCH_2CH_2N$), 4.41 (t, $J$ = 6.2 Hz, 2H, $NHCH_2CH_2N$), 6.20-6.21 (m, 1H, Ar-*H* pyrrole), 6.28 (d, $J$ = 1.4 Hz, 1H, Ar-*H* pyrrole), 6.29 (d, $J$ = 1.4 Hz, 1H, Ar-*H* quinoline), 6.83-6.84 (m, 1H, Ar-*H* pyrrole), 7.00 (d, $J$ = 1.0 Hz, 1H, Ar-*H* Imd), 7.37-7.40 (dd, $J$ = 2.1, 9.0 Hz, 1H, Ar-*H* quinoline), 7.63 (d, $J$ = 0.8 Hz, 1H, Ar-*H* Imd), 7.77 (d, $J$ = 2.0 Hz, 1H, Ar-*H* quinoline), 7.91 (d, $J$ = 9.0 Hz, 1H, Ar-*H* quinoline), 8.27 (d, $J$ = 5.6 Hz, 1H, Ar-*H* quinoline); $^{13}$C NMR (100 MHz, $CD_3OD$): $\delta$ 42.5, 43.5, 98.0, 108.2, 108.5,

117.2, 118.9, 119.0, 122.7, 124.8, 126.0, 126.1, 126.6, 135.0, 137.9, 148.0, 150.8; ESI-MS: (*m/z*): 338.2 $(M+H)^+$; HRMS calcd for $[C_{18}H_{16}ClN_5+H]^+$ 338.1167, found 338.1177.

**4.3.2 7-Chloro-*N*-(2-(5-(3-methylthiophen-2-yl)-1*H*-imidazol-1-yl)ethyl)quinolin-4-amine (6)**

Compound **6** was obtained as yellow solid in 78% yield; m.p. 172-174°C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.08 (s, 3H, C*H*$_3$-thiophene), 3.56 (d, *J* = 5.4 Hz, 2H, NHC*H*$_2$CH$_2$N), 4.21 (t, *J* = 6.1 Hz, 2H, NHCH$_2$C*H*$_2$N), 6.07 (d, *J* = 5.4 Hz, 1H, Ar-*H* quinoline), 6.93 (d, *J* = 5.2 Hz, 1H, Ar-*H* thiophene), 7.07 (s, 1H, Ar-*H* Imd), 7.27-7.30 (dd, *J* = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline), 7.32 (d, *J* = 5.1 Hz, 1H, Ar-*H* thiophene), 7.52 (s, 1H, Ar-*H* Imd), 7.66 (d, *J* = 9.0 Hz, 1H, Ar-*H* quinoline), 7.92 (d, *J* = 2.0 Hz, 1H, Ar-*H* quinoline), 8.40 (d, *J* = 5.3 Hz, 1H, Ar-*H* quinoline); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 14.5, 43.0, 43.4, 98.3, 117.4, 122.1, 123.0, 124.6, 125.4, 126.5, 128.1, 130.1, 130.6, 135.1, 138.4, 138.7, 148.9, 149.5, 151.5; ESI-MS: (*m/z*): 369.2 $(M+H)^+$; HRMS calcd for $[C_{19}H_{17}ClN_4S+H]^+$ 369.0935, found 369.0933.

**4.3.3 *N*-(2-(5-(1*H*-Indol-3-yl)-1*H*-imidazol-1-yl)ethyl)-7-chloroquinolin-4-amine (7)**

Compound **7** was obtained as Pale yellow solid in 76% yield; m.p. 210-212°C; $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 3.52 (t, *J* = 6.2 Hz, 2H, NHC*H*$_2$CH$_2$N), 4.34 (t, *J* = 6.3 Hz, 2H, NHCH$_2$C*H*$_2$N), 6.97-6.98 (m, 1H, Ar-*H* Ind), 6.99 (d, *J* = 8.0 Hz, 1H, Ar-*H* quinoline), 7.11-7.14 (m, 1H, Ar-*H* Ind), 7.21 (s, 1H, Ar-*H* Imd), 7.23-7.26 (dd, *J* = 2.1, 9.0 Hz, 1H, Ar-*H* quinoline), 7.34 (d, *J* = 1.0 Hz, 1H, Ar-*H* quinoline); 7.36 (d, *J* = 0.9 Hz, 1H, Ar-*H* Ind), 7.67 (d, *J* = 2.0 Hz, 1H, Ar-*H* quinoline); 7.72 (d, *J* = 9.0 Hz, 1H, Ar-*H* Ind), 7.79 (s, 1H, Ar-*H* Imd), 7.88 (s, 1H, Ar-*H* Ind), 7.98 (d, *J* = 5.6 Hz, 1H, Ar-*H* quinoline); $^{13}$C NMR (100 MHz, $CD_3OD$): $\delta$ 36.3, 43.0, 97.6, 103.1, 111.3, 117.0, 118.2, 119.7, 121.8, 122.5, 124.4, 124.6, 125.9, 126.8, 126.9, 127.1, 134.9, 136.3, 137.7, 147.7, 150.3, 150.5; ESI-MS: (*m/z*): 388.2 $(M+H)^+$; HRMS calcd for $[C_{22}H_{19}ClN_5+H]^+$ 388.1323, found 388.1325.

#### 4.3.4 7-Chloro-*N*-(2-(5-(4-(trifluoromethyl)phenyl)-1*H*-imidazol-1-yl)ethyl)quinolin-4-amine (8)

Compound **8** was obtained as Pale yellow solid in 71% yield; m.p. 187-189°C; $^{1}$H NMR (400 MHz, $CD_3OD$): $\delta$ 3.57 (t, $J$ = 6.2 Hz, 2H, NHC$H_2$C$H_2$N), 4.80 (t, $J$ = 6.3 Hz, 2H, NHC$H_2$C$H_2$N), 6.58 (d, $J$ = 5.1 Hz, 1H, Ar-*H* quinoline), 7.38 (s, 1H, Ar-*H* Imd), 7.39-7.41 (dd, $J$ = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline), 7.44-7.54 (m, 4H, Ar-*H* Ph), 7.61 (d, $J$ = 7.8 Hz, 1H, Ar-*H* quinoline), 7.64 (s, 1H, Ar-*H* Imd), 7.79 (d, $J$ = 4.7 Hz, 1H, Ar-*H* quinoline), 7.92 (d, $J$ = 8.5 Hz, 1H, Ar-*H* quinoline); $^{13}$C NMR (100 MHz, $CD_3OD$): $\delta$ 43.1, 43.2, 98.2, 117.1, 121.2, 121.9, 124.9, $^{1}J(^{19}F,^{13}C)$ (q, $J_{C\text{-}F}$ = 272.9 Hz, $CF_3$), 125.6, 125.9, $^{3}J(^{19}F,^{13}C)$ (q, $J$ = 7.8 Hz,), 128.0, $^{4}J(^{19}F,^{13}C)$ (q, $J$ = 3.5 Hz,), 128.6, 129.4, 130.7, $^{2}J(^{19}F,^{13}C)$ (q, $J$ = 33.1Hz, ipso), 135.4, 137.4, 137.7, 148.7, 149.6, 150.2, 151.1, 151.5; ESI-MS: (*m/z*): 417.2 $(M+H)^+$; HRMS calcd for $[C_{21}H_{17}ClF_3N_4+H]^+$ 417.1088, found 417.1087.

#### 4.3.5 7-Chloro-*N*-(2-(5-(4-isopropylphenyl)-1*H*-imidazol-1-yl)ethyl)quinolin-4-amine (9)

Compound **9** was obtained as yellow solid in 81% yield; m.p. 175-177°C; $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.23 (d, $J$ = 6.8 Hz, 6H, CH(C$H_3$)$_2$), 2.84-2.91 (sep, 1H, C$H$(CH$_3$)$_2$), 3.47 (t, $J$ = 9.5 Hz, 2H, NHC$H_2$C$H_2$N), 4.26 (t, $J$ = 5.3 Hz, 2H, NHC$H_2$C$H_2$N), 5.95 (d, $J$ = 4.9 Hz, 1H, Ar-*H* quinoline), 6.96 (s, 1H, Ar-*H* Imd), 7.13-7.18 (m, 4H, Ar-*H* Ph), 7.24-7.30 (dd, $J$ = 2.1, 9.0 Hz, 1H, Ar-*H* quinoline), 7.44 (s, 1H, Ar-*H* Imd), 7.77 (d, $J$ = 8.6 Hz, 1H, Ar-*H* quinoline), 7.87 (d, $J$ = 7.5 Hz, 1H, Ar-*H* quinoline), 8.26 (d, $J$ = 5.0 Hz, 1H, Ar-*H* quinoline); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 23.8, 33.7, 43.0, 43.6, 98.2, 117.3, 125.3, 126.2, 126.4, 126.9, 127.6, 129.0, 129.7, 133.4, 135.1, 137.9, 148.4, 149.3, 149.8, 151.0; ESI-MS: (*m/z*): 391.2 $(M+H)^+$; HRMS calcd for $[C_{23}H_{24}ClN_4+H]^+$ 391.1684, found 391.1669.

#### 4.3.6 7-Chloro-*N*-(2-(5-(4-(dimethylamino)phenyl)-1*H*-imidazol-1-yl)ethyl)quinolin-4-amine (10)

Compound **10** was obtained as yellowish white solid in 70% yield; m.p. 192-194°C; $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.99 (s, 6H, N($CH_3$)$_2$), 3.53-3.57 (m, 2H, NHC$H_2$C$H_2$N), 4.33 (t, $J$ = 5.8 Hz, 2H, NHC$H_2$C$H_2$N), 6.05 (d, $J$ = 5.4 Hz, 1H, Ar-*H* quinoline), 6.61-6.64 (m, 2H, Ar-*H* Ph), 7.00 (s, 1H, Ar-*H* Imd), 7.14-7.16 (dd, $J$ = 2.1, 6.7 Hz, 1H, Ar-*H* quinoline), 7.29-7.32 (m, 2H, Ar-*H* Ph), 7.47 (d, $J$ = 8.9 Hz, 1H, Ar-*H* quinoline), 7.51 (s, 1H, Ar-*H* Imd), 7.93 (d, $J$ = 2.1 Hz, 1H, Ar-*H* quinoline), 8.39 (d, $J$ = 5.3 Hz, 1H, Ar-*H* quinoline); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 40.2, 42.8, 43.8, 98.5, 112.1, 116.2, 117.4, 122.0, 125.2, 127.2, 128.3, 130.0, 133.8, 134.9, 137.4, 149.0, 149.2, 150.2, 151.5; ESI-MS: (*m/z*): 392.2 $(M+H)^+$; HRMS calcd for $[C_{22}H_{23}ClN_5+H]^+$ 392.1636, found 392.1638.

#### 4.3.7 7-Chloro-*N*-(2-(5-(quinolin-2-yl)-1*H*-imidazol-1-yl)ethyl)quinolin-4-amine (11)

Compound **11** was obtained as Pale yellow solid in 75% yield; m.p. 203-205°C; $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.43-3.51 (m, 2H, NHC$H_2$C$H_2$N), 4.34 (t, $J$ = 6.2 Hz, 2H, NHC$H_2$C$H_2$N), 6.31 (d, $J$ = 5.0 Hz, 1H, Ar-*H* quinoline), 6.69 (d, $J$ = 8.3 Hz, 1H, Ar-*H* quinoline), 7.11 (s, 1H, Ar-*H* Imd), 7.19-9.21 (dd, $J$ = 2.4, 8.3 Hz, 1H, Ar-*H* quinoline), 7.30 (d, $J$ = 8.9 Hz, 1H, Ar-*H* quinoline), 7.55 (d, $J$ = 7.0 Hz, 1H, Ar-*H* quinoline), 7.60 (d, $J$ = 7.7 Hz, 1H, Ar-*H* quinoline), 7.79 (s, 1H, Ar-*H* Imd), 7.84 (d, $J$ = 7.8 Hz, 1H, Ar-*H* quinoline), 7.91 (d, $J$ = 8.2 Hz, 1H, Ar-*H* quinoline), 7.98 (d, $J$ = 2.4 Hz, 1H, Ar-*H* quinoline), 8.28 (d, $J$ = 6.4 Hz, 1H, Ar-*H* quinoline), 8.43 (d, $J$ = 5.0 Hz, 1H, Ar-*H* quinoline); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 44.7, 45.5, 98.2, 102.9, 116.7, 120.8, 122.3, 123.6, 124.9, 125.0, 126.1, 126.6, 127.2, 128.3, 128.7, 130.2, 135.5, 137.6, 144.8, 146.4, 147.8, 147.9, 149.1; ESI-MS: (*m/z*): 400.2 $(M+H)^+$; HRMS calcd for $[C_{23}H_{19}ClN_5+H]^+$ 400.1323, found 400.1322.

**4.3.8 7-Chloro-*N*-(2-(5-(3-phenoxyphenyl)-1*H*-imidazol-1-yl)ethyl)quinolin-4-amine (12)**

Compound **12** was obtained as Pale yellow solid in 66% yield; m.p. 182-184°C; $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.50-3.61 (m, 2H, NHC$H_2$C$H_2$N), 4.28 (t, $J$ = 5.8 Hz, 2H, NHC$H_2$C$H_2$N), 6.04 (d, $J$ = 5.4 Hz, 1H, Ar-*H* quinoline), 6.87-6.94 (m, 5H, Ar-*H* Ph), 6.95-6.98 (dd, $J$ = 2.0, 8.9 Hz, 1H, Ar-*H* quinoline), 6.98 (s, 1H, Ar-*H* Imd), 7.05-7.08 (m, 3H, Ar-*H* Ph), 7.19 (s, 1H, Ar-*H* Ph), 7.50 (s, 1H, Ar-*H* Imd), 7.69 (d, $J$ = 8.8 Hz, 1H, Ar-*H* quinoline), 7.87 (d, $J$ = 2.0 Hz, 1H, Ar-*H* quinoline), 8.35 (d, $J$ = 5.3 Hz, 1H, Ar-*H* quinoline); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 43.2, 43.6, 98.3, 117.3, 118.0, 118.6, 119.2, 122.0, 123.3, 123.8, 125.3, 128.1, 128.4, 129.6, 129.9, 130.2, 130.7, 131.0, 135.0, 137.6, 138.5, 148.8, 149.4, 151.4, 156.3, 157.8; ESI-MS: (*m/z*): 441.2 $(M+H)^+$; HRMS calcd for $[C_{26}H_{22}ClN_4O+H]^+$ 441.1477, found 441.1474.

**4.3.9 *N*-(2-(5-*Tert*-butyl-1*H*-imidazol-1-yl)ethyl)-7-chloroquinolin-4-amine (13)**

Compound **13** was obtained as white solid in 73% yield; m.p. 166-168°C; $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.38 (s, 9H, C($CH_3$)$_3$), 3.77 (t, $J$ = 6.1 Hz, 2H, NHC$H_2$C$H_2$N), 4.39 (t, $J$ = 6.2 Hz, 2H, NHC$H_2$C$H_2$N), 6.41 (d, $J$ = 5.5 Hz, 1H, Ar-*H* quinoline), 6.72 (s, 1H, Ar-*H* Imd), 7.34-7.36 (dd, $J$ = 2.0, 8.7 Hz, 1H, Ar-*H* quinoline), 7.41 (d, $J$ = 6.7 Hz, 1H, Ar-*H* quinoline), 7.44 (s, 1H, Ar-*H* Imd), 7.93 (d, $J$ = 2.1 Hz, 1H, Ar-*H* quinoline), 8.41 (d, $J$ = 8.2 Hz, 1H, Ar-*H* quinoline); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 29.4, 30.3, 30.8, 43.7, 43.8, 44.8, 99.3, 117.8, 124.3, 124.8, 127.3, 127.8, 134.0, 139.3, 139.6, 149.3, 150.2, 152.3; ESI-MS: (*m/z*): 329.1 $(M+H)^+$; HRMS calcd for $[C_{18}H_{22}ClN_4+H]^+$ 329.1528, found 329.1529.

**4.3.10 7-Chloro-*N*-(2-(5-(furan-2-yl)-1*H*-imidazol-1-yl)ethyl)quinolin-4-amine (14)**

Compound **14** was obtained as white off solid in 65% yield; m.p. 173-175°C; $^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 3.56-3.61 (m, 2H, NHC$H_2$C$H_2$N), 4.36 (t, $J$ = 6.2 Hz, 2H, NHC$H_2$C$H_2$N), 6.40 (d, $J$ = 5.4 Hz, 1H, Ar-*H* quinoline), 6.51-6.52 (m, 1H, Ar-*H* furan), 6.60-6.61 (m, 1H, Ar-*H* furan), 7.14 (d, $J$ = 0.9 Hz, 1H, Ar-*H* Imd), 7.41-7.44 (dd, $J$ = 2.2,

9.0 Hz, 1H, Ar-*H* quinoline), 7.66-7.67 (m, 1H, Ar-*H* furan), 7.75 (d, *J* = 2.2 Hz, 1H, Ar-*H* quinoline), 8.11 (d, *J* = 9.0 Hz, 1H, Ar-*H* quinoline), 8.27 (s, 1H, Ar-*H* Imd), 8.34 (d, *J* = 5.4 Hz, 1H, Ar-*H* quinoline); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 43.1, 44.1, 99.1, 107.8, 111.9, 117.9, 123.7, 124.3, 124.7, 127.8, 128.6, 133.9, 140.0, 143.3, 144.4, 149.3, 150.2, 152.2; ESI-MS: (*m/z*): 339.1 $(M+H)^+$; HRMS calcd for $[C_{18}H_{16}ClN_4O+H]^+$ 339.1007, found 339.1021.

**4.3.11. 4-(1-(2-(7-Chloroquinolin-4-ylamino)ethyl)-1*H*-imidazol-5-yl)benzonitrile (15)**

Compound **15** was obtained as white solid in 77% yield; m.p. 159-161°C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.91-3.96 (m, 2H, NHC$H_2$CH$_2$N), 4.32 (t, *J* = 5.6 Hz, 2H, NHCH$_2$C$H_2$N), 6.46 (d, *J* = 5.3 Hz, 1H, Ar-*H* quinoline), 7.28 (s, 1H, Ar-*H* Imd), 7.45-7.39 (m, 2H, Ar-*H* Ph), 7.53-7.57 (dd, *J* = 2.0, 9.0 Hz, 1H, Ar-*H* quinoline), 7.61-7.63 (m, 2H, Ar-*H* Ph), 7.80 (s, 1H, Ar-*H* Imd), 7.87 (d, *J* = 2.0 Hz, 1H, Ar-*H* quinoline), 7.92 (d, *J* = 8.5 Hz, 1H, Ar-*H* quinoline), 7.99 (d, *J* = 2.0 Hz, 1H, Ar-*H* quinoline); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 43.7, 45.5, 98.9, 116.6, 120.7, 121.6, 123.1, 124.3, 124.6, 124.8, 125.0, 126.1, 127.5 128.9, 132.5, 138.1, 149.5, 151.2, 151.7; ESI-MS: (*m/z*): 374.2 $(M+H)^+$; HRMS calcd for $[C_{21}H_{17}ClN_5+H]^+$ 374.1167, found 374.1169.

**4.3.12 7-Chloro-*N*-(2-(5-(4-methoxyphenyl)-1*H*-imidazol-1-yl)ethyl)quinolin-4-amine(16)**

Compound **16** was obtained as Pale yellow solid in 68% yield; m.p. 160-162°C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 3.45 (t, *J* = 6.4 Hz, 2H, NHC$H_2$CH$_2$N), 3.74 (s, 3H, OC$H_3$), 4.23 (t, *J* = 6.1 Hz, 2H, NHCH$_2$C$H_2$N), 6.08 (d, *J* = 5.0 Hz, 1H, Ar-*H* quinoline), 6.82-6.84 (m, 2H, Ar-*H* Ph), 7.22 (s, 1H, Ar-*H* Imd), 7.23 (d, *J* = 5.1 Hz, 1H, Ar-*H* quinoline), 7.32-7.33 (m, 2H, Ar-*H* Ph), 7.36-7.39 (dd, *J* = 2.1, 9.2 Hz, 1H, Ar-*H* quinoline), 7.74 (s, 1H, Ar-*H* Imd), 8.04 (d, *J* = 9.0 Hz, 1H, Ar-*H* quinoline), 8.23 (d, *J* = 5.2 Hz, 1H, Ar-*H* quinoline); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 42.9, 43.4, 55.4, 98.7, 114.3, 117.8, 122.1, 124.1, 124.5, 127.3,

127.8, 130.4, 132.7, 134.0, 138.7, 149.3, 150.0, 151.8, 159.3; ESI-MS: (*m/z*): 379.2 $(M+H)^+$; HRMS calcd for $[C_{21}H_{20}ClN_4O+H]^+$ 379.1320, found 379.1320.

**4.3.13 7-Chloro-*N*-(2-(5-cyclopentyl-1*H*-imidazol-1-yl)ethyl)quinolin-4-amine (17)**

Compound **17** was obtained as off white solid in 79% yield; m.p. 187-189°C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.51-1.57 (m, 4H, cyclopentane), 1.72-1.76 (m, 2H, cyclopentane), 1.90-1.96 (m, 2H, cyclopentane), 2.77-2.85 (m, 1H, C*H*$(CH_2)_4$), 3.70-3.74 (m, 2H, NHC*H*$_2$CH$_2$N), 4.20 (t, *J* = 5.3 Hz, 2H, NHCH$_2$C*H*$_2$N), 6.41 (d, *J* = 5.3 Hz, 1H, Ar-*H* quinoline), 6.77 (s, 1H, Ar-*H* Imd), 7.26 (s, 1H, Ar-*H* Imd), 7.29-7.32 (dd, *J* = 2.1, 8.8 Hz, 1H, Ar-*H* quinoline), 7.72 (d, *J* = 9.0 Hz, 1H, Ar-*H* quinoline), 7.95 (d, *J* = 2.1 Hz, 1H, Ar-*H* quinoline), 8.54 (d, *J* = 5.3 Hz, 1H, Ar-*H* quinoline); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 25.0, 32.9, 34.8, 42.6, 43.4, 98.4, 117.5, 122.2, 124.0, 125.4, 128.3, 135.1, 136.7, 136.8, 149.2, 149.6, 151.7; ESI-MS: (*m/z*): 341.2 $(M+H)^+$; HRMS calcd for $[C_{19}H_{22}ClN_4+H]^+$ 341.1528, found 341.1534.

**4.3.14 7-Chloro-*N*-(2-(5-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1*H*-imidazol-1-yl)ethyl)quinolin-4-amine (18)**

Compound **18** was obtained as Pale yellow solid in 63% yield; m.p. 201-203°C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.55 (t, *J* = 5.4 Hz, 2H, NHC*H*$_2$CH$_2$N), 4.22 (t, *J* = 4.7 Hz, 2H, dioxane), 4.29 (t, *J* = 4.5 Hz, 2H, dioxane), 4.34 (t, *J* = 5.4 Hz, 2H, NHCH$_2$C*H*$_2$N), 6.09 (d, *J* = 5.3 Hz, 1H, Ar-*H* quinoline), 6.68-6.72 (m, 3H, Ar-*H* Ph), 6.96 (s, 1H, Ar-*H* Imd), 7.29-7.32 (dd, *J* = 2.0, 8.8 Hz, 1H, Ar-*H* quinoline), 7.47 (s, 1H, Ar-*H* Imd), 7.53 (d, *J* = 8.9 Hz, 1H, Ar-*H* quinoline), 7.92 (d, *J* = 1.7 Hz, 1H, Ar-*H* quinoline), 8.39 (d, *J* = 5.2 Hz, 1H, Ar-*H* quinoline); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 42.3, 43.0, 63.8, 98.0, 116.9, 117.2, 121.5, 122.3, 123.3, 123.9, 126.8, 127.2, 132.1, 133.6, 133.7, 138.0, 143.0, 148.6, 148.7, 149.4, 151.2; ESI-MS: (*m/z*): 407.2 $(M+H)^+$; HRMS calcd for $[C_{22}H_{20}ClN_4O_2+H]^+$ 407.1269, found 407.1270.

**4.3.15 7-Chloro-*N*-(2-(5-(4-fluorophenyl)-1*H*-imidazol-1-yl)ethyl)quinolin-4-amine (19)**

Compound **19** was obtained as yellowish white solid in 78% yield; m.p. 161-163°C; $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.52-3.56 (m, 2H, NHC$H_2$C$H_2$N), 4.29 (t, $J$ = 5.8 Hz, 2H, NHC$H_2$C$H_2$N), 6.08 (d, $J$ = 5.3 Hz, 1H, Ar-*H* quinoline), 6.97 (d, $J$ = 8.6 Hz, 2H, Ar-*H* Ph), 7.00 (s, 1H, Ar-*H* Imd), 7.18-7.20 (m, 1H, Ar-*H* Ph), 7.21 (d, $J$ = 2.0 Hz, 1H, Ar-*H* quinoline), 7.30-7.33 (dd, $J$ = 2.0, 8.9 Hz, 1H, Ar-*H* quinoline), 7.49 (s, 1H, Ar-*H* Imd), 7.51-7.53 (m, 1H, Ar-*H* Ph), 7.94 (d, $J$ = 2.0 Hz, 1H, Ar-*H* quinoline), 8.41 (d, $J$ = 7.4 Hz, 1H, Ar-*H* quinoline); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 42.9, 43.4, 98.2, 114.0, 115.6, $^{2}J(^{19}F,^{13}C)$ (d, $J$ = 22.2 Hz), 117.4, 122.3, 125.1, 128.0, 128.7, 130.8, $^{4}J(^{19}F,^{13}C)$ (d, $J$ = 3.0 Hz), 132.1 $^{3}J(^{19}F,^{13}C)$ (d, $J$ = 8.3Hz), 138.2, 139.1, 141.2, 148.9, 149.5, 151.4, 153.4, 167.6, $^{1}J(^{19}F,^{13}C)$ (d, $J$ = 247.6 Hz); ESI-MS: (*m/z*): 367.2 $(M+H)^+$; HRMS calcd for $[C_{20}H_{17}ClFN_4+H]^+$ 367.1120, found 367.1124.

**4.3.16 7-Chloro-*N*-(2-(5-(naphthalen-1-yl)-1*H*-imidazol-1-yl)ethyl)quinolin-4-amine (20)**

Compound **20** was obtained as white solid in 64% yield; m.p. 206-208°C; $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.36 (d, $J$ = 5.0 Hz, 2H, NHC$H_2$C$H_2$N), 3.84 (t, $J$ = 5.4 Hz, 2H, NHC$H_2$C$H_2$N), 6.58 (d, $J$ = 5.3 Hz, 1H, Ar-*H* quinoline), 7.15 (s, 1H, Ar-*H* Imd), 7.23 (d, $J$ = 1.8 Hz, 1H, Ar-*H* quinoline), 7.31 (d, $J$ = 4.7 Hz, 1H, Ar-*H* quinoline), 7.37-7.40 (m, 2H, Ar-*H* naphthalene), 7.47-7.50 (m, 2H, Ar-*H* naphthalene), 7.57 (d, $J$ = 8.2 Hz, 1H, Ar-*H* quinoline), 7.62 (s, 1H, Ar-*H* Imd), 7.87-789 (m, 3H, Ar-*H* naphthalene), 8.13 (d, $J$ = 5.3 Hz, 1H, Ar-*H* quinoline); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 43.1, 43.6, 98.1, 117.1, 121.6, 124.8, 125.1, 125.4, 126.4, 126.5, 127.1, 128.1, 128.5, 129.3, 129.6, 130.9, 132.6, 133.6, 135.0, 136.9, 137.7, 148.6, 149.1, 151.2; ESI-MS: (*m/z*): 399.2 $(M+H)^+$; HRMS calcd for $[C_{24}H_{20}ClN_4+H]^+$ 399.1371, found 399.1372.

**4.3.17 7-Chloro-*N*-(2-(5-cyclohexyl-1*H*-imidazol-1-yl)ethyl)quinolin-4-amine (21)**

Compound **21** was obtained as Pale yellow solid in 73% yield; m.p. 174-176°C; $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.60-1.94 (m, 10H, cyclohexane), 2.17-2.24 (m, 1H, cyclohexane), 3.24 (d, $J$ = 5.3 Hz, 2H, NHC$H_2$CH$_2$N), 3.87 (t, $J$ = 5.1 Hz, 2H, NHCH$_2$C$H_2$N), 6.45 (d, $J$ = 5.3 Hz, 1H, Ar-*H* quinoline), 6.74 (s, 1H, Ar-*H* Imd), 7.28 (s, 1H, Ar-*H* Imd), 7.33-7.35 (dd, $J$ = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline), 7.75 (d, $J$ = 8.9 Hz, 1H, Ar-*H* quinoline), 7.98 (d, $J$ = 2.0 Hz, 1H, Ar-*H* quinoline), 8.59 (d, $J$ = 5.3 Hz, 1H, Ar-*H* quinoline); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 25.6, 26.1, 26.4, 33.5, 33.6, 33.7, 42.0, 43.8, 98.3, 117.5, 122.2, 123.9, 125.4, 128.3, 135.1, 136.1, 138.1, 149.3, 149.6, 151.7; ESI-MS: (*m/z*): 355.6 $(M+H)^+$; HRMS calcd for $[C_{20}H_{24}ClN_4+H]^+$ 355.1684, found 355.1684.

**4.3.18 4-(1-(2-(7-Chloroquinolin-4-ylamino)ethyl)-1*H*-imidazol-5-yl)phenol (22)**

Compound **22** was obtained as off white solid in 65% yield; m.p. 167-169°C; $^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 3.44-3.49 (m, 2H, NHC$H_2$CH$_2$N), 4.20 (t, $J$ = 6.5 Hz, 2H, NHCH$_2$C$H_2$N), 5.75 (s, 1H, Ar-*H* PhO*H*), 6.18 (d, $J$ = 5.4 Hz, 1H, Ar-*H* quinoline), 6.77-6.79 (dd, $J$ = 1.9, 6.6 Hz, 2H, Ar-*H* Ph), 6.85 (s, 1H, Ar-*H* Imd), 7.18-7.20 (dd, $J$ = 1.9, 6.6 Hz, 2H, Ar-*H* Ph ), 7.44-7.47 (dd, $J$ = 2.2, 9.0 Hz, 1H, Ar-*H* quinoline), 7.75 (s, 1H, Ar-*H* Imd), 7.78 (d, $J$ = 2.2 Hz, 1H, Ar-*H* quinoline), 8.13 (d, $J$ = 9.0 Hz, 1H, Ar-*H* quinoline), 8.30 (d, $J$ = 5.4 Hz, 1H, Ar-*H* quinoline); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 43.0, 43.2, 99.0, 116.0, 117.8, 120.6, 124.3, 124.7, 127.1, 127.9, 130.6, 132.9, 133.9, 138.7, 149.4, 150.0, 152.1, 157.8; ESI-MS: (*m/z*): 365.2 $(M+H)^+$; HRMS calcd for $[C_{20}H_{18}ClN_4O+H]^+$ 365.1164, found 365.1164.

**4.4. Biological assay**

**4.4.1 *In vitro* antimalarial assay**

The compounds were evaluated for antimalarial activity against 3D7 (CQ- sensitive) and K1 (CQ-resistant) strains of *Plasmodium falciparum* using Malaria SYBR Green I nucleic acid staining dye based fluorescence (MSF) assay as mentioned by Kondaparla *et al*

[22]. The stock (10 mM) solution was prepared in DMSO and test dilutions were prepared in culture medium (RPMI-1640-FBS). The final concentration of DMSO in *Plasmodium* cultures was < 1%. Chloroquine-diphosphate (SIGMA) was used as reference drug. For assessment of antimalarial activity 50µl of culture medium was dispensed in 96 well plate followed by addition of 50µl of highest concentration (containing less than 0.5% of DMSO) of test compounds (in duplicate wells) in row B. Subsequent two-fold serial dilutions were prepared in culture medium and finally 50 µl of 2.0% parasitized cell suspension containing 0.8% parasitaemia (Asynchronous culture containing more than 80% ring stages) was added to each well except 4 wells in row 'A' received non parasitized erythrocyte suspension. The plates were incubated at 37 °C in $CO_2$ incubator in an atmosphere of 5% $CO_2$ and air mixture and 72 hours later 100 µl of lysis buffer containing 2 x concentration of SYBR Green-I (Invitrogen) was added to each well and incubated for one hour at 37°C [23]. The plates were examined at 485±20nm of excitation and 530±20nm of emission for relative fluorescence units (RFUs) per well using the fluorescence plate reader (FLX800, BIOTEK). Data was transferred into a graphic programme (EXCEL) and $IC_{50}$ values were obtained by Logit regression analysis of dose response curves using pre-programmed Excel spreadsheet.

**4.4.2 *In vitro* assay for evaluation of cytotoxic activity**

Cytotoxicity of the compounds was carried out using Vero cell line (C1008; Monkey kidney fibroblast) following the method as mentioned in Mosmann [24]. The cells were incubated with compound-dilutions for 72 h and MTT was used as reagent for detection of cytotoxicity, 50% cytotoxic concentration ($CC_{50}$) was determined using nonlinear regression analysis of dose response curves using pre-programmed Excel spreadsheet. Selectivity Index (SI) was calculated as $SI = CC_{50} / IC_{50}$

#### 4.4.3 Determination of hematin 4-aminoquinoline derivatives association constant

Association constant for hematin 4-aminoquinoline derivatives complex formation were determined by spectrometric titration procedure in aqueous DMSO at pH-7.5 [25]. In this assay condition, hematin is strictly in monomeric state and interpretation of results is not complicated by the need to consider hematin disaggregation process. Association constant calculated in this technique is a good reflection of the interaction that would occur in the acidic food vacuole of the parasite and pH-7.5 improves the stability of hematin solutions and quality of the data.

#### 4.4.4 *In vitro* inhibition of *β*-hematin formation assay

The ability of the 4-aminoquinoline derivatives to inhibit *β*-hematin formation was induced by 1-oleoyl-rac-glycerol. Spectroscopic measurements were done using UV spectrophotometer wave length 405 nm and at pH 5 [26]. The $IC_{50}$ values obtained from the assay are expressed as percent inhibition relative to *β*-hematin formation in a drug free control. The 50% inhibitory concentration values for the compounds were obtained from the sigmoidal dose-response curves using non-linear regression curve fitting analyses with GraphPad Prism v.3.00 software [27].

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**Conflicts of Interest**

The authors have no conflict of interest to declare.

**Supporting Information available (Appendix S1):** Electronic supplementary information (ESI) available: $^{1}H$ NMR, $^{13}C$ NMR data of selected compounds.

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## Figure Legends

**Table 1** Biological and Biophysical data of the synthesized compounds **5-22**

**Figure 1** Structures of some molecules having antimalarial activity.

**Figure-2** a) Previously reported 4-aminoquinolines from this laboratory b) Designed 4-aminoquinoline imidazole Prototype.

**Figure 3** SAR of the synthesized potent 4-aminoquinoline

**Scheme 1** Synthesis of 4-aminoquinoline-imidazole derivatives

**Table 1** Biological and Biophysical data of the synthesized compounds **5-22**

| Cmpd. no | *In vitro* antiplasmodial activity $IC_{50}$(μM)[a] | | pKa[b] | SI[c] | Log P[d] | Resistance factor[e] | LogK[f] | $IC_{50}$[g] |
|---|---|---|---|---|---|---|---|---|
| | 3D7 | K1 | | | | | | |
| 5 | 5.00±0.038 | 1.15±0.028 | pKa(A)-15.95<br>pKa(B)- 6.01<br>pKa(C)-7.32 | 88.29 | 1.77 | 0.23 | 6.72±0.03 | 0.72±0.02 |
| 6 | 5.00±0.043 | 0.46±0.048 | pKa(A)-5.72<br>pKa(B)-7.31 | >431.03 | 3.70 | 0.09 | 6.32±0.05 | 0.63±0.04 |
| 7 | 5.00±0.046 | 1.70±0.024 | pKa(A)-15.45<br>pKa(B)-5.97<br>pKa(C)-7.32 | >117.64 | 2.77 | 0.34 | 7.20±0.02 | 0.83±0.03 |
| 8 | 0.21±0.021 | 0.45±0.019 | pKa(A)-6.16<br>pKa(B)-7.33 | 79.54 | 4.15 | 2.14 | 5.93±0.04 | 0.62±0.05 |
| 9 | 2.83 ±0.028 | 0.29±0.018 | pKa(A)-6.18<br>pKa(B)-7.33 | >687.2 | 4.46 | 0.10 | 6.12±0.03 | 0.42±0.02 |
| 10 | 5.00±0.047 | 1.09±0.016 | pKa(A)-4.45<br>pKa(B)-6.26<br>pKa(C)-7.36 | 35.56 | 3.51 | 0.21 | 7.43±0.02 | 0.52±0.03 |
| 11 | 5.00±0.039 | 1.33±0.029 | pKa(A)-2.26<br>pKa(B)-5.56<br>pKa(C)-7.30 | >150.37 | 3.74 | 0.26 | 6.86±0.05 | 0.68±0.04 |
| 12 | 5.00±0.044 | 2.62±0.025 | pKa(A)-6.12<br>pKa(B)-7.33 | >76.33 | 4.77 | 0.52 | 7.01±0.02 | 0.73±0.03 |
| 13 | 0.14±0.018 | 0.50±0.023 | pKa(A)-6.69<br>pKa(B)-7.42 | 190.95 | 3.26 | 3.37 | 6.59±0.03 | 0.64±0.02 |
| 14 | 0.29±0.018 | 0.97±0.025 | pKa(A)-5.35<br>pKa(B)-7.30 | 102.76 | 1.85 | 3.29 | 5.71±0.05 | 0.69±0.04 |
| 15 | 5.00±0.048 | 0.73±0.027 | pKa(A)-6.14<br>pKa(B)-7.33 | 160.80 | 3.26 | 0.14 | 7.71±0.04 | 0.71±0.03 |
| 16 | 5.00±0.043 | 1.78±0.021 | pKa(A)-6.20<br>pKa(B)-7.33 | >112.29 | 3.10 | 0.35 | 7.83±0.02 | 0.73±0.04 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 17 | 0.079±0.015 | 0.34±0.011 | pKa(A)-6.72<br>pKa(B)-7.43 | 203.82 | 3.06 | 4.30 | 6.54±0.05 | 0.63±0.03 |
| 18 | 0.52±0.028 | 2.40±0.031 | pKa(A)-6.16<br>pKa(B)-7.33 | 39.21 | 2.73 | 4.57 | 7.88±0.02 | 0.69±0.02 |
| 19 | 5.00±0.045 | 3.04±0.039 | pKa(A)-6.18<br>pKa(B)-7.33 | 26.12 | 3.39 | 0.60 | 8.12±0.03 | 0.79±0.04 |
| 20 | 5.00±0.045 | 0.92±0.031 | pKa(A)-6.15<br>pKa(B)-7.33 | 6.43 | 4.23 | 0.18 | 7.62±0.03 | 0.75±0.03 |
| 21 | 0.19±0.017 | 0.52±0.029 | pKa(A)-6.72<br>pKa(B)-7.43 | >383.14 | 3.47 | 2.67 | 6.70±0.04 | 0.67±0.03 |
| 22 | 3.73±0.038 | 5.00±0.047 | pKa(A)-9.80<br>pKa(B)-6.32<br>pKa(C)-7.23 | 15.13 | 2.84 | 1.34 | 8.73±0.05 | 0.81±0.04 |
| CQ | 0.005±0.002 | 0.255±0.049 | pKa(A)- 9.8<br>pKa(B)- 7.32 | 8983 | 3.73 | 51 | 5.52±0.02 | 0.17±0.02 |

[a] $IC_{50}$ (μM±SD) : Concentration corresponding to 50% growth inhibition of the parasite; [b]Pka value of different compounds was calculated using chemaxon software. [c]Selectivity index (SI): ($CC_{50}$ for cytotoxicity to vero cells /$IC_{50}$(3D7) for antiplasmodial activity);[d]log P values calculated using ChemBioDraw ultra software;[e] Resistance factor (RI): $IC_{50}$(K1)/$IC_{50}$(3D7); [f]1:1 (compound : Hematin) complex formation in 40% aqueous DMSO, 20 mM HEPES buffer, pH 7.5 at 25 °C (data are expressed as means ± SD from at least three different experiments in duplicate); [g]The $IC_{50}$ represents the millimolar equivalents of test compounds, relative to hemin, required to inhibit *β*-hematin formation by 50% (data are expressed as means ± SD from at least three different experiments in duplicate).

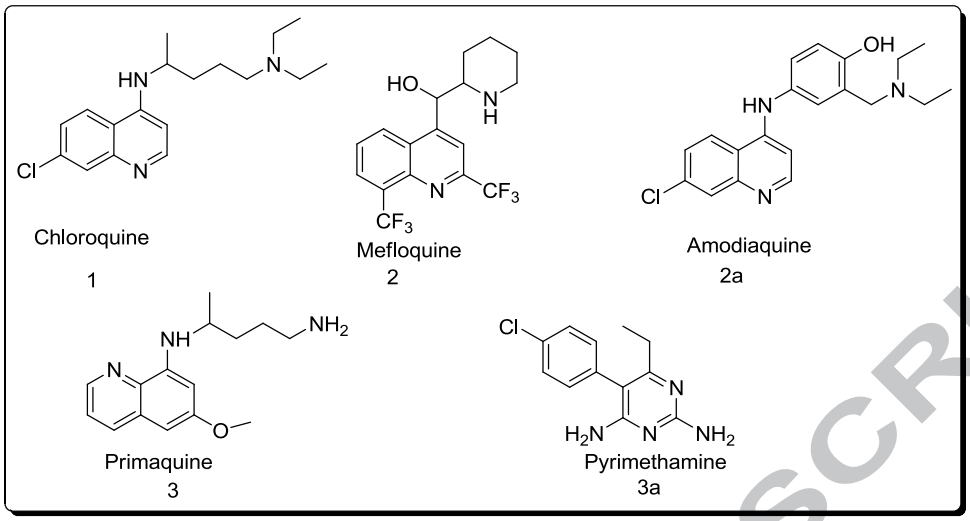



**Figure 1** Structures of some molecules having antimalarial activity.

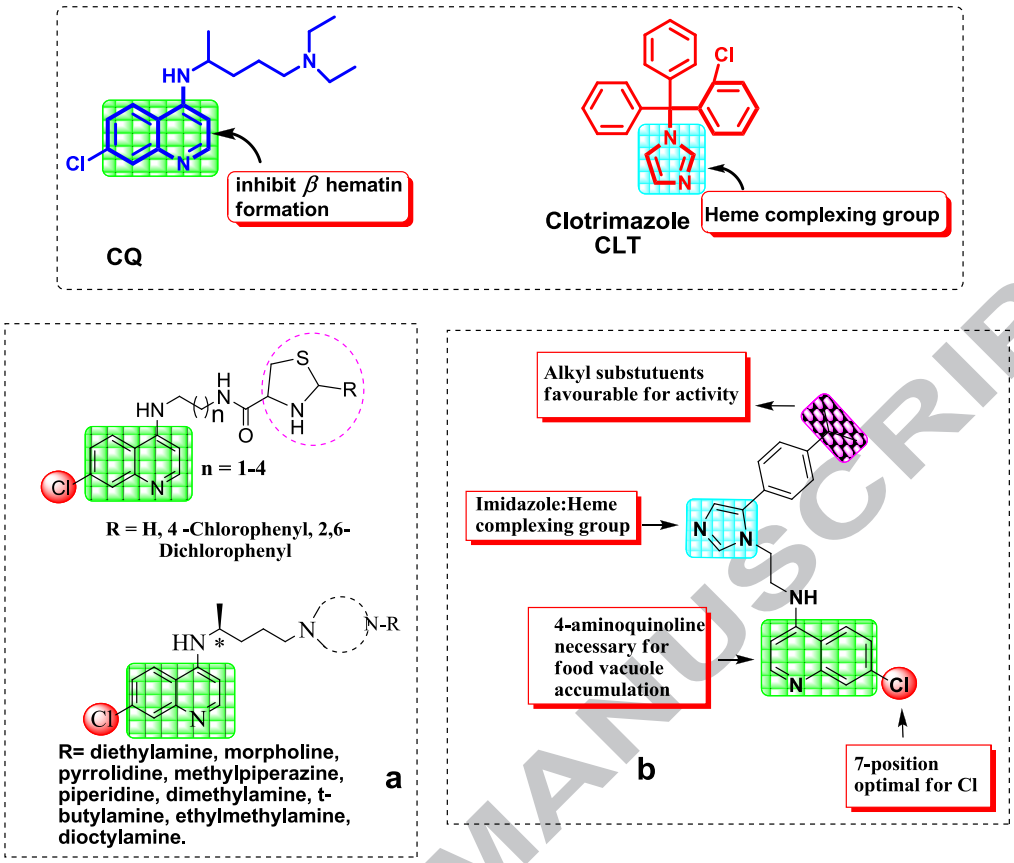



**Figure-2** a) Previously reported 4-aminoquinolines from this laboratory. b) Designed 4-aminoquinoline imidazole Prototype.

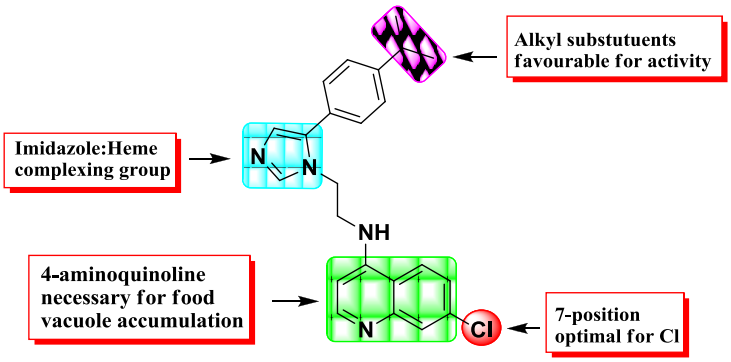
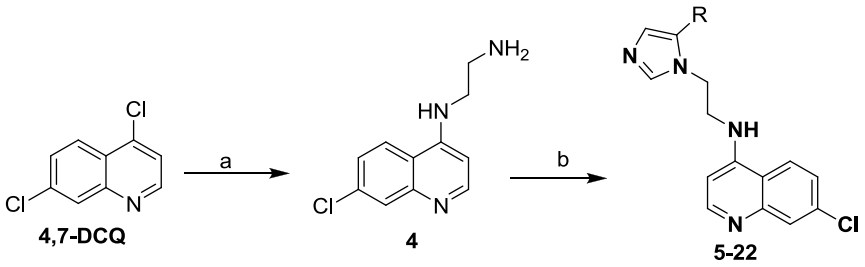



**Figure 3** SAR of the synthesized potent 4-aminoquinoline.




| Compound no | R | Compound no | R |
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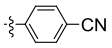
| 6 |  | 15 |  |
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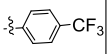
| 8 |  | 17 |  |
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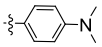
| 10 |  | 19 |  |
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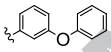
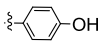
| 12 |  | 21 |  |
| 13 |  | 22 |  |

***Scheme 1 Synthesis of 4-aminoquinoline-imidazole derivatives. Reagents and Conditions:*** *a) ethylenediamine, neat, 80-130 °C, 8h. b) aldehyde, DMF, TOSMIC/$K_2CO_3$, 90 °C, overnight.*

# Design, Synthesis and Antiplasmodial activity of novel imidazole derivatives based on 7-chloro-4-aminoquinoline.

Srinivasarao Kondaparla[a]*, Ashan Manhas[b], Vasantha Rao Dola[a] , Kumkum Srivastava[b], Sunil K. Puri[b], S. B. Katti[a]

## Highlights

1. Novel series of short chain 4-aminoquinoline-imidazole derivatives were designed and synthesized.
2. Assessment of 4-aminoquinolines for *in vitro* antiplasmodial activity.
3. Identified, four compounds (**6**, **8**, **9** and **17**) exhibited comparable activity to CQ against K1 strain of *P. falciparum.*
4. Heme binding studies supported the biological findings.

## *Graphical Abstract*