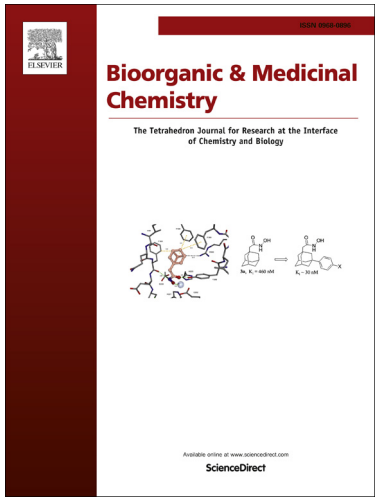

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Antiplasmodial activity of new 4-aminoquinoline derivatives against chloroquine resistant strain.

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Abstract

Emergence and spread of multidrug resistant strains of *P. falciparum* has severely limited the antimalarial chemotherapeutic options. In order to overcome the obstacle, a set of new side-chain modified 4-aminoquinolines were synthesized and screened against chloroquine-sensitive (3D7) and chloroquine-resistant (K1) strains of *P. falciparum*. The key feature of the designed molecules is the use of methylpiperazine linked α, β^3-and γ-amino acids to generate novel side chain modified 4-aminoquinoline analogues. Among the evaluated compounds, **20c** and **30** were found more potent than CQ against K1 and displayed a four-fold and a three-fold higher activity respectively, with a good selectivity index (SI = 5846 & 11350). All synthesized compounds had resistance index between 1.06 and >14.13 as against 47.2 for chloroquine. Biophysical studies suggested that this series of compounds act on heme polymerization target.

Keywords: 4-aminoquinoline; Chloroquine; Malaria; Resistant strains**.**

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1. Introduction

Malaria is a tropical disease caused by Apicomplexan parasite *Plasmodium falciparum* severely affecting human well being. It is estimated that about 1 million deaths occur annually, mostly children under five years of age.[1-2] High morbidity is associated with the failure of the established chemotherapies due to emergence of drug resistant *P. falciparum* against most of the antimalarial drugs.[3] Although, chloroquine (CQ) and other related 4-aminoquinolines (**Fig.1**) have played important role during the past five decades drug resistance to CQ has been a major problem in malaria eradication programme. So, the search for novel, affordable, and structurally diverse drugs has become an urgent need to eradicate this parasitic disease. Early biochemical studies carried out to understand the mechanism of CQ resistance have led to two seminal findings namely, a mutation in the *P. falciparum* CQ-resistance transporter (PfCRT) gene resulting in rapid efflux of CQ from the intracellular loci. Secondly and more importantly study by Ridley *et.al.*[4] has established that drug resistance is compound specific. This has fuelled research activity towards modifying CQ side chain so as to obtain molecules active against CQ-resistant parasite.

Several modifications have been done in the side chain of chloroquine and studied in detail. It has been found that shortening of the chain length or incorporation of intramolecular hydrogen-bonding motif in the side chain significantly increases the antimalrial activity.[4-6] While replacement of 4-position nitrogen atom of the 7-chloro-4-aminoquinoline by oxygen and sulphur significantly decreases the basicity of the quinonyl nitrogen which leads to reduced antimalarial activity.[7] Earlier in our research group we have also explored some specific modifications by introducing, guanidine, tetramethylguandine, and thiazolidin-4-one and substituted thiourea moieties at the side chain. Some of these compounds exhibited superior *in vitro* activity and significant suppression of parasitemia in the *in vivo* assay as

compared to chloroquine. Based on the limited SAR-studies it was inferred that basicity of the quinoline ring nitrogen (pKa1) and side chain nitrogen (pKa2) played an important role for the antimalarial activity.[8] Inspired by these observations, in this study we have synthesized a set of compounds with specific modifications to CQ that are predicated to be relevant for activity against chloroquine resistant parasites. The diversity in the synthesized compounds has been generated through variations in the side chain of CQ. Initially we have selected alanine and synthesized various amides (Scheme 1). Compound having *N*-methylpiperzine as a pendant group showed improved activity against CQ-R strain. We further preferred variety of α-amino acids by keeping the pendant group with *N*-methylpiperzine. We have found that some of them exhibited promising antimalarial activity than CQ in the case of CQ-R strain. Additionally we have also investigated the effect of chain length variation between 2 to 4 carbon atoms via homologation of α-amino acids to get corresponding β^3 and γ- amino acids. The results are described in the present communication.

2. Chemistry

4,7- Dichloroquinoline (**1**), was fused with an excess of alanine (**2**) in the presence of phenol at 140 °C to afford the compound (**6**).[9] The obtained Compound (**6**) was coupled with different amines using DCC, HOBt protocol taking DMF as solvent at 0 °C to afford (**6a-6f**).[10] A similar approach was utilized for some selected α-amino acids *viz.* glycine (**3**), phenylalnine(**4**), methionine (**5**) directly fused to 4,7- Dichloroquinoline to get **7-9** in good yields followed by coupling with N-methylpiperzine to afford **7a, 8a,** and **9a** as shown in Scheme 1. We have observed poor yields in the case of remaining α-amino acids. Therefore, in order to get the desired final products **14a-14j** we have opted for different synthetic strategy. The route is delineated in Scheme-2. Synthesis of compounds **20a-20c** involve prior preparation of β-amino acids followed by their conversion to piperazine amides and after

deprotection they were finally fused with 4,7-Dichloroquinoline as shown in Scheme 3**.** Synthesis of compound **30** involves derivatization of γ-amino acid and its fusion with 4,7-Dichloroquinoline. The synthetic steps involved are shown in Scheme 4. The compounds synthesized in Scheme 1, Scheme 2, Scheme 3 and Scheme 4, essentially comprise of three fragments namely, quinoline, amino acid, and the terminal alkyl amide fragment.

3. Results and Discussion

3.1 Antimalarial *in vitro* evaluation

The antimalarial activity of the targeted compounds **6a-6f** were screened against the 3D7 (CQ-S) and K1 (CQ-R) strains of *P. falciparum in vitro* and the results are presented in Table 1. Amide **6a** was found to exhibit comparable antimalarial activity in the case of resistant strains. Other amides **6b-6f** were noticeably less active against 3D7 strain, no detectable antimalarial activity against K1 strain at the highest concentration tested (IC_{50} > 500 nM). It was inferred from the preliminary screening data that amide **6a** containing *N*-methylpiperzine as a side chain showed comparable activity with reference to CQ against resistant strain. This motivated us to synthesize various analogues of 4-aminoquinolines by using different α-amino acids with methylpiperazine as pendent group. In this study we have also investigated the effect of the chain length variation by homologation of selected α-amino acids to get the corresponding β^3 and γ-amino acids. All compounds exhibited activity in 11.51 nM to > 500 nM range against 3D7 strain and 56.36 nM to > 1378 nM range against K1 strain. Compounds **7a** and **14f** exhibited 1.5 to 1.8 folds activity, whereas **8a** and **9a** displayed 2 fold activities against resistant strain. We also examined the effect of hetroaromatic groups, bulky alkyl groups and polar groups. However, these compounds showed no significant improvements in the *in vitro* antimalarial activity. Another important finding is that antimalarial activity does not improve by adding more basic groups **14i** and **14j**. Increase in the chain length showed positive effects on the antimalarial activity against both 3D7 and K1

strain of *P. falcip*a*rum.* Compounds derived from β^3-isoleucine (**16b**) showed better activity in the case of K1 strain (IC_{50}= 168 nM). The β^3-phenylalanine derivative **(16c)** was found to be 4.6 folds active in the case of K1 strain (IC_{50}= 55.29 nM). Further increase of side chain length of **16c** by one carbon generated the γ-phenylalanine derived 4-aminoquinoline (**30**) and its antimalarial activity against K1 strain was also very good (IC_{50} 71.16 nM) nearly 3.6 folds active than chloroquine. Although both β^3- and γ-phenylalanine derived 4-aminoquinolines exhibited better activity but β^3-compound (**16c**) was found to be the most active in the series. It may be appropriate to reveal here that resistance factor which is calculated as a ratio of IC_{50} in CQ-R vs CQ-S strains has been used as an index to assess chances of parasite developing resistance to a particular class of compounds. Accordingly, it is believed that smaller the resistance factor, the less likely is the chance of developing resistance to that class of compounds. Interestingly, all the compounds in this series showed resistance factors 1.06 and >14.13 as against 47.2 for chloroquine.

3.2 *In vitro* cytotoxicity.

The cytotoxicity of target compounds was determined by making use of standard protocol, MTT assay against VERO cell line (Table-1). Our target compounds showed selectivity index (SI) ranging from 392 to 9772 respectively. Some compounds namely, **6f, 9a, 14g,** and **14h** exhibited moderate activity against sensitive (3D7) strain with good selectivity indices 5834, 3821, 6472, and 4432 respectively. Compounds **20a-20c** and **30** have shown promising antimalarial activity against (3D7) as well as (K1) strain and showed better selectivity indices 6045, 5846, 7613, and 11,350 respectively. Thus these compounds demonstrated the promising safe activity profile.

3.3 *In vitro* inhibition of β-hematin polymerization

The mode of action of this series of 4-aminoquinoline derivatives (**6a-6f, 7a, 8a, 9a, 14a-14j, 20a-20c, 30**) was investigated by the reported method.[11-13] and the results are shown in (Table-1). All the synthesized compounds form complex with hematin and the range of Log K was found to be 5.32-7.34. Among, all the compounds reported in the present study compounds **16c** and **30** have shown very strong binding to hematin. This result is concurrent with the previous results from the reported literature evidences.[14-17] The data suggest that the principle interaction may be hydrophobic as well as electrostatic between the 4-aminoquinoline ring and the porphyrin ring system that plays a role in hematin binding. All the synthesized 4-aminoquinoline derivatives (**6a-6f, 7a, 8a, 9a, 14a-14j, 20a-20c, 30**) inhibited the β-hematin formation in a concentration dependent manner (Table-1). Although most of the synthesized compounds were good inhibitors of β-hematin formation, some of them have shown moderate antimalarial activity against CQ-S and CQ-R strains of *P. falciparum*. The most potent inhibitors were compounds **20c** and **30** with an IC_{50} of 0.17 mM, and 0.19 mM in the hemozoin inhibition assay. It may be inferred from the above data that these compounds bind to hematin monomer or hematin μ-oxo dimer and inhibit the β-hematin formation by blocking the growing face of crystal by a capping effect.[14]

4. Conclusion

In summary, we have prepared a series of new 4-aminoquinoline derivatives by varying the substituents at the pendant group and modifying the trunk of the side chain with different amino acids. Among all, *N*-methylpiperazine moiety as a pendant amino group showing promising *in vitro* antimalarial activity against the chloroquine resistant strains of *P. falciparum.* The most striking feature of this study is consistent antiplasmodial activity of these derivative against both CQ-S and CQ-R strains of parasite. In some cases, the activity against CQ-R strain is superior as compared to their activity against CQ-S strain of parasite. The biophysical studies have suggested that this class of compounds form association

complex with hematin and thereby, inhibit the hemozoin formation. The *N*-methylpiperazine amide functionality on 4-aminoquinoline-pendant amino group provided a promising lead entry for designing the heme polymerization targeted antimalarials. The present 4-aminoquinolines provide new opportunity for the development of potent antimalarials to overcome the emerging problem of drug resistance.

5. Experimental Protocols

5.1 General

Meting points (mp) were determined on a complab melting point apparatus and are uncorrected. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$, CD_3OD, and DMSO-d_6, used as solvents on DPX-300 Bruker FT-NMR spectrometer. Chemical shifts are reported in parts per million δ (ppm) with the residual protons of the solvent as reference. The splitting pattern abbreviations are as follows: s (singlet), d(doublet), dd (doublet of doublet), t (triplet), q (quartet), br s (broad singlet) 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 precoated silica-gel plates 60 F_{254} and spots were visualized by irradiation with UV light (254 nm). Iodine was used as developing agent or by spraying with Dragendorff's reagent. Column chromatographic purification was performed over silica gel (230-400 mesh) using a gradient solvent system (n-hexane/ ethyl acetate or chloroform/ methanol as the eluent unless otherwise specified). All chemicals and reagents were obtained from Aldrich (USA), Lancaster (UK) or Spectrochem Pvt. Ltd (India) and were used without further purification.

5.1.1 General procedure for the synthesis of 6-9:

4,7-Dichloroquinoline (10 mmol) and corresponding amino acid (alanine, glycine, phenylalanine, methionine; 20 mmol) were heated in phenol for one hour at 140 °C. After completion of the reaction as monitored by TLC to the reaction mixture was added a solution of 10% KI 30 mL and diethyl ether 30 mL. The aqueous layer was then washed with ether layer (3x30 mL). The combined ether layer was extracted with 10% KI (30 mL) solution. The pH of the combined aqueous phase was adjusted to 7. The aqueous solution was let uncovered for slow evaporation at room temperature. After 24h, the precipitated solid was filtered and dried under vacuum.

5.1.2 (*S*)-2-(7-Chloroquinolin-4-ylamino)propanoic acid (6): white semi-solid; yield 1.25 g, (55%); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.66 (br s, 3H, CHC*H*$_3$), 4.25 (br s, 1H, NHC*H*), 6.66 (br s, 1H, Ar-H quinoline), 7.53 (d, *J* = 9.5 Hz, 1H, Ar-*H* quinoline), 7.74 (d, *J* = 6.3 Hz,1H, Ar-*H* quinoline), 8.30 (br s, 1H, Ar-*H* quinoline), 8.44 (br s, 1H, Ar-*H* quinoline); ESI-MS: *m/z* 251 $(M+H)^+$.

5.1.3 2-(7-Chloroquinolin-4-ylamino)-acetic acid (7): white semi-solid; yield 1.35 g, (57%); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) : 3.84 (s, 2H, $NHCH_2$), 6.15 (d, *J* = 5.6 Hz, 1H, Ar-H quinoline), 7.24 (dd, *J* = 9.0, 2.1 Hz, 1H, Ar-H quinoline), 7.64 (d, *J* = 9.03 Hz,1H, Ar-H quinoline), 8.19 (d, *J* = 5.6 Hz, 1H, Ar-H quinoline), 8.47 (br s, 1H, Ar-H quinoline).

5.1.4 (S)-2-(7-Chloroquinolin-4-ylamino)-3-phenylpropanoic acid (8): gummy residue; yield 1.25 g, (55%); ^{1}H NMR (300 MHz, DMSO-d_6,) δ (ppm) : 3.55-3.61 (m, 2H, C*H*$_2$Ph), 6.66 (d, *J* = 6.1 Hz, 1H, Ar-*H* quinoline), 7.18-7.33 (m, 5H, 5 Ar-*H* benzene), 7.72 (d, *J* = 3.8 Hz, 1H, Ar-*H* quinoline), 7.85 (d, *J* = 1.7 Hz, 1H, Ar-*H* quinoline), 8.26 (d, *J* = 5.5 Hz, 1H, Ar-*H* quinoline), 8.41 (d, *J* = 8.0 Hz, 1H, Ar-*H* quinoline). ESI-MS: *m/z* 327 $(M+H^+)$

5.1.5 (*S*)-2-(7-Chloroquinolin-4-ylamino)-4-(methylthio)butanoic acid (9): gummy residue; yield 1.3g, (57%); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.03-2.11 (m, 2H, CHC*H*$_2$), 2.14 (s, 3H, SC*H*$_3$), 2.59-2.79 (m, 2H, CHC*H*$_2$CH$_2$), 4.70-4.74 (m, 1H, NHC*H*), 6.88 (d, *J* = 7.0 Hz, 1H, Ar-*H* quinoline), 7.88 (s, 1H, Ar-*H* quinoline), 8.41 (d, *J* = 6.9 Hz, 1H, Ar-*H* quinoline), 8.51 (d, *J* = 9.0 Hz, 1H, Ar-*H* quinoline). ESI-MS: *m/z* 311 (M+H$^+$).

6. General procedure for the synthesis of 6a-6f, 7a, 8a, 9a:

To a solution of (**6-9**, 2 mmol) in dimethylformamide (DMF, 10 mL) at 0 °C, 1-hydroxybenzotriazole (HOBt, 2.2 mmol) was added. The reaction mixture was stirred for 2 minutes and the corresponding amine (3 mmol in 1.0 mL DMF) was added to it followed by the addition of dicyclohexylcarbodimide (DCC, 2.2 mmol in 1.0 mL DMF). The reaction mixture was stirred for next 4 hrs. After completion of reaction the dicyclohexylurea (DCU) was filtered and the filtrate was evaporated under reduced pressure. The oily residue was dissolved in chloroform, washed with 5% aqueous sodium bicarbonate followed by washing with water and finally with brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified over silica gel column to get the pure compound.

6.1 (*S*)-2-(7-Chloroquinolin-4-ylamino)-1-(4-methylpiperazin-1-yl)-propan-1-one (6a): Yellow residue; yield: 410 mg, (62 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm): 1.49 (d, *J* = 6.6, 3H, CHC*H*$_3$), 2.35 (s, 3H, NC*H*$_3$), 2.44-2.52 (m, 4H, N(CH$_2$C*H*$_2$)$_2$), 3.59-3.62 (m, 2H, CONC*H*$_2$), 3.7-3.77 (m, 2H, CONC*H*$_2$), 4.53-4.58 (m, 1H, NHC*H*), 6.30 (d, *J* = 5.4 Hz, 1H, Ar-*H* quinoline), 6.51 (br s, 1H, NH), 7.40 (dd, *J* = 9.0, 2.1 Hz, 1H, Ar-*H* quinoline), 7.80 (d, *J* = 8.97 Hz, 1H, Ar-*H* quinoline), 7.95 (d, *J* = 2.0 Hz, 1H, Ar-*H* quinoline), 8.51 (d, *J* = 5.3, 1H, Ar-*H* quinoline); ^{13}C NMR (75 MHz ,$CDCl_3$,) δ (ppm): 17.8, 42.3, 45.3, 45.9, 47.8, 54.5,

54.9, 98.7, 117.3, 121.5, 125.5, 128.5, 135.1, 147.7, 149.1, 151.6, 170.4; HRMS calculated for [$C_{17}H_{21}ClN_4O$ + H^+] 333.1477, found 333.1418; ESI-MS: *m/z* 333 $(M+H)^+$.

6.1.1 (*S*)-2-(7-Chloroquinolin-4-ylamino)-*N*-(3-(diethylamino)-propyl)-propanamide (6b): white solid; yield: 580 mg, (80 %), mp 150-152 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm): 0.87 (t, *J* = 7.1 Hz, 6H, $N(CH_2)_2(CH_3)_2$), 1.57 (d, *J* = 6.8 Hz, 3H, $CHCH_3$), 2.26-2.48 (m, 8H, $CH_2CH_2N(CH_2)_2$), 3.24-3.49 (m, 2H, $CONHCH_2$), 3.97-4.10 (m, 1H, NHC*H*), 5.72 (d, *J* = 4.9 Hz, 1H, N*H*), 6.31 (d, *J* = 5.3 Hz, 1H, Ar-*H* quinoline, 7.35 (dd, *J* = 9.0, 2.1 Hz, 1H, Ar-*H* quinoline), 7.74 (d, *J* = 9.0 Hz, 1H, Ar-*H* quinoline), 7.95 (d, *J* = 2.1, 1H, Ar-*H* quinoline), 8.3 (br s, 1H, N*H*), 8.50 (d, 5.32 Hz, 1H, Ar-*H* quinoline); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 10.9, 18.2, 25.0, 39.5, 46.4, 46.5, 51.6, 58.2, 99.4, 117.3, 121.8, 125.5, 128.3, 135.1, 148.9, 151.8, 168.5; HRMS calculated for [$C_{19}H_{27}ClN_4O$+ H^+] 363.1946, found 362.1899; ESI-MS: *m/z* 363 $(M+H)^+$.

6.1.2 (*S*)-2-(7-Chloroquinolin-4-ylamino)-1-(4-phenylpiperazin-1-yl)-propan-1-one (6c): brown gummy residue; yield 500 mg, (64 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.54 (d, *J* = 6.6, 3H, $CHCH_3$) 3.24-3.29 (m, 4H, $2CH_2CH_2$), 3.77 (br s, 2H, $CONCH_2$), 3.89 (d, *J* = 9.5 Hz, 2H, $CONCH_2$), 4.58-4.66 (m, H, NHC*H*), 6.34 (br s, 1H, N*H*), 6.48 (d, *J* = 6.3, 1H, Ar-*H* quinoline), 6.96 (d, *J* = 7.47, 3H, Ar-*H*), 7.28-7.35 (m, 2H, Ar-*H*), 7.39 (dd, *J* = 9.0, 2.1 Hz, 1H, Ar-*H* quinoline), 7.82 (d, *J* = 8.9 Hz, 1H, Ar-*H* quinoline), 7.97 (d, *J* = 2.0 Hz, 1H, Ar-*H* quinoline), 8.54 (d, *J* = 5.2 Hz, 1H, Ar-*H* quinoline); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) : 17.9, 42.3, 45.4, 47.8, 49.5, 49.8, 98.7, 116.8, 121.0, 121.4, 125.5, 128.6, 129.3, 135.1, 147.7, 149.2, 150.6, 151.7, 170.6; HRMS calculated for [$C_{22}H_{23}ClN_4O$+ H^+] 395.1633, found 395.1644; ESI-MS: *m/z* 395 $(M+H)^+$.

6.1.3 (*S*)-2-(7-Chloroquinolin-4-ylamino)-*N*-(3-(dimethylamino)-propyl)-propanamide (6d): Brown gummy residue; yield 475 mg, (71 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.6 (d, *J* = 6.9 Hz, 3H, $CHCH_3$), 1.9 (s, 6H, $N(CH_3)_2$, 2.22-2.32 (m, 4H, CH_2CH_2N), 3.4-

3.41 (m, 2H, NHCH_2), 4.05-4.09 (m, 1H NHC*H*), 5.60 (d, *J* = 4.5 Hz, 1H, N*H*), 6.35 (d, *J* = 5.2 Hz, 1H, Ar-*H* quinoline), 7.39 (dd, *J* = 9.0, 2.1 Hz, 1H, Ar-*H* quinoline), 7.78 (d, *J* = 8.9 Hz, 1H, Ar-*H* quinoline) 7.97 (d, *J* = 2.0 Hz, 1H, Ar-*H* quinoline), 8.23 (br s, 1H, N*H*), 8.53 (d, *J* = 5.1, 1H, Ar-*H* quinoline); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) : 19.3, 24.8, 40.2, 45.0, 53.1, 59.0, 99.9, 120.9, 125.7, 128.9, 135.1, 148.3, 149.1, 152.0, 172.0 ; HRMS calculated for [$C_{17}H_{23}ClN_4O+H^+$] 335.1633, found 335.1593; ESI-MS: *m/z* 335 $(M+H)^+$.

6.1.4 (*S*)-2-(7-Chloroquinolin-4-ylamino)-*N*-(2-(piperidin-1-yl)-ethyl)-propanamide (6e): White gummy residue; yield: 420 mg, (62 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.39 (br s, 6H, cycNCH_2(CH_2)$_3$CH_2), 1.64 (d, *J* = 6.9 Hz, 3H, CHCH_3) 2.18-2.51 (m, 6H, CH_2CH_2N(CH_2)$_2$, 3.34-3.39 (m, 2H, CONHCH_2), 4.11-4.20 (m, 1H, NHC*H*), 5.67 (d, *J* = 5.2 Hz, 1H, N*H*), 6.37 (d, *J* = 5.2 Hz, 1H, Ar-*H* quinoline), 7.21 (s, 1H, N*H*), 7.41 (dd, *J* = 9.0, 2.1 Hz, 1H, Ar-*H* quinoline), 7.82 (d, *J* = 8.9, 1H, Ar-*H* quinoline), 7.99 (d, *J* = 2.1 Hz, 1H, Ar-*H* quinoline), 8.53 (d, *J* = 5.2 Hz, 1H, Ar-*H* quinoline); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 19.0, 23.4, 24.7, 24.9, 33.9, 35.4, 49.1, 53.1, 54.0, 56.8, 99.8, 121.5, 125.6, 128.5, 135.2, 148.5, 151.7, 156.8, 172.7; HRMS calculated for [$C_{19}H_{25}ClN_4O+H^+$] 361.1790, found 361.1767; ESI-MS: *m/z* 361 $(M+H)^+$.

6.1.5 (*S*)-2-(7-Chloroquinolin-4-ylamino)-*N*-(2-(diethylamino)-ethyl)-propanamide (6f): white gummy residue ; yield: 467 mg, (67 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) : 0.92 (t, *J* = 7.1 Hz, 6H, 2CH_2CH_3), 1.65 (d, *J* = 6.9 Hz, 3H, CHCH_3), 2.50-2.55 (m, 4H, N(CH_2)$_2$, 2.57-2.65 (m, 2H, CH_2CH_2N), 3.32-3.47 (m, 2H, CONHCH_2), 4.15-4.21 (m, 1H, NHC*H*), 5.81 (d, *J* = 4.1 Hz, 1H, N*H*), 6.37 (d, *J* = 5.37Hz, 1H, Ar-*H* quinoline), 7.40 (dd, *J* = 9.0, 2.1 Hz, 1H, Ar-*H* quinoline), 7.87 (d, *J* = 9.0 Hz, 1H, Ar-*H* quinoline), 7.97 (d, *J* = 2.0 Hz, 1H, Ar-*H* quinoline), 8.52 (d, *J* = 5.3 Hz, 1H, Ar-*H* quinoline); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) : 19.1, 23.9, 25.3, 29.6, 35.8, 53.0, 54.0, 56.8, 99.8, 115.7, 117.2, 119.5, 121,3,

125.6, 128.5, 129.5, 135.1, 148.4, 149.0, 151.7, 172.3; HRMS calculated for $[C_{18}H_{25}ClN_4O+H^+]$ 349.1790, found 349.1721; ESI-MS: *m/z* 349 $(M+H)^+$.

6.1.6 2-(7-Chloroquinolin-4-ylamino)-1-(4-methylpiperazin-1-yl)-ethanone (7a): brown gummy residue; yield 520 mg, (75 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) : 2.22 (br s, 1H, N*H*), 2.35 (s, 3H, NCH_3), 2.46-2.51 (m, 4H, N(CH_2CH_2)$_2$), 3.52 (t, *J* = 5.1 Hz, 2H, CONCH_2), 3.76 (t, *J* = 5.0 Hz, 2H, CONCH_2), 3.98 (d, *J* = 3.5 Hz, 2HNHCH_2CO), 6.26 (d, *J* = 5.3 Hz, 1H, Ar-*H* quinoline), 6.49 (s, 1H, NH), 7.38 (dd, *J* = 9.0, 2.1 Hz, 1H, Ar-*H* quinoline), 7.83 (d, *J* = 8.9 Hz, 1H, Ar-*H* quinoline), 7.96 (d, *J* = 2.0 Hz, 1H, Ar-*H* quinoline), 8.52 (d, *J* = 5.2 Hz, 1H, Ar-*H* quinoline); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) : 42.2, 43.7, 44.2, 46.0, 54.4, 54.7, 99.2, 117.0, 121.5, 125.7, 128.2, 135.3, 148.5, 148.6, 151.5, 165.8 ; HRMS calculated for $C_{16}H_{19}ClN_4O$ 319.1325, found 319.1291; ESI-MS: *m/z* 319 $(M+H)^+$.

6.1.7 (*S*)-2-(7-Chloroquinolin-4-ylamino)-1-(4-methylpiperazin-1-yl)-3-phenylpropan-1-one (8a): Yellow gummy residue; yield 357 mg,(65%); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.25 (s, 3H, NCH_3), 2.34-2.37 (m, 4H, COcycN(CH_2CH_2)$_2$NCH_3), 3.00-3.25 (m , 4H, COcycN(CH_2CH_2)$_2$NCH_3)), 3.56-3.74 (m, 2H, CHCH_2Ph), 4.79-4.81 (m, 1H, NHC*H*), 6.33 (d, *J* = 5.3 Hz, 2H, Ar-*H* quinoline, N*H*), 7.19-7.731 (m, 5H, Ar-*H*), 7.37 (dd, *J* = 1.9, 8.9 Hz, 1H, Ar-*H* quinoline), 7.76 (d, *J* = 8.97 Hz, 1H, Ar-*H* quinoline), 7.99 (d, *J* = 1.8 Hz, 1H, Ar-*H* quinoline), 8.50 (d, *J* = 5.3 Hz, 1H, Ar-*H* quinoline); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 41.5, 45.2, 45.8, 54.4, 54.7, 98.8, 117.3, 121.5, 125.5, 127.3, 128.4, 128.6, 129.3, 129.4, 135.0, 136.3, 148.4, 149.0, 151.6, 170.8; HRMS calculated for $[C_{23}H_{25}ClN_4O+H^+]$ 409.1795, found 409.1762; ESI-MS: *m/z* 409 $(M+H^+)$.

6.1.8 (*S*)-2-(7-Chloroquinolin-4-ylamino)-1-(4-methylpiperazin-1-yl)-4-(methylthio)butan-1-one (9a): Yellow residue; yield: 357 mg, (65%); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) : 1.96-2.05 (m, 2H, CHCH_2), 2.09 (s, 3H, SCH_3), 2.31 (s, 1H, NCH_3), 2.41-

2.48 (m, 4H, COcycN(CH_2CH_2)$_2$NCH_3), 2.58-2.63 (m, 2H, CHCH_2CH_2), 3.59-3.69 (m, 4H, COcycN(CH_2CH_2)$_2$NCH_3), 4.81-4.82 (m, 1H, NHC*H*), 6.34 (br s, 1H, NH), 6.45 (d, *J* = 5.3 Hz, 1H, Ar-*H* quinoline), 7.30 (dd, *J* = 2.5, 9.0 Hz, 1H, Ar-*H* quinoline), 7.81 (d, *J* = 8.4 Hz, 1H, Ar-*H* quinoline), 7.97 (s, 1H, Ar-*H* quinoline), 8.54 (d, *J* = 5.2 Hz, 1H, Ar-*H* quinoline). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) : 15.8, 30.2, 32.1, 42.4, 45.4, 45.9, 50.7, 54.5, 55.0, 99.0, 117.4, 121.5, 125.5, 128.4, 128.5, 135.1, 149.1, 151.7, 151.8, 169.9. HRMS calculated for [$C_{19}H_{25}ClN_4OS+H^+$] 393.1516 found 393.1514; ESI-MS: *m/z* 393 ($M+H^+$).

7. General procedure for the synthesis of 12a-12j: Amino acids (**10a-10j**) were converted to the corresponding Boc derivatives (**11a-11j**) in quantitative yields by using di-*tert*-butylpyrocarbonate. [18] To a solution of (**11a-11j**; 2 mmol) in 10 mL THF, 1-Hydroxybenzotriazole (HOBt; 2.2 mmol) was added. The reaction mixture was stirred for 2 minutes at 0 °C. The *N*-methylpiperazine (3 mmol) was added to above reaction mixture, followed by addition of dicyclohexylcarbodimide (DCC; 2.2 mmol, 1.0 mL THF) at 0 °C.[10] The reaction mixture was allowed to reach at room temperature and was stirred for next 4 hrs. The dicyclohexylurea (DCU) was filtered and the filtrate was evaporated under reduced pressure. The oily residue was dissolved in chloroform, organic layer was washed with 5% aqueous sodium bicarbonate followed by washing with water and finally with brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified over silica gel column to afford compounds (**12a**-**12j**) in good yields.

7.1. (*S*)-*Tert*-butyl 3-methyl-1-(4-methylpiperazin-1-yl)-1-oxobutan-2-ylcarbamate (**12a**): Gummy residue; yield 559 mg, (77 %) ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) : 0.80 (d, *J* = 6.6 Hz, 3H, CHCH(CH_3)C*H*$_3$), 0.87 (d, *J* = 6.6 Hz, 3H, CHCH(C*H*$_3$)CH_3), 1.36 (s, 9H, C(C*H*$_3$)$_3$), 1.80-1.89 (m, 1H, CHC*H*(CH_3)CH_3), 2.23 (s, 3H, NC*H*$_3$), 2.31-2.33 (m, 4H,

COcycN(CH_2CH_2)$_2$NCH_3), 3.49-3.61 (m, 4H, COcycN(CH_2CH_2)$_2$NCH_3), 4.35-4.40 (m, 1H, NHC*H*CH), 5.35 (d, *J* = 8.6 Hz, N*H*).

7.1.1 *Tert*-butyl (2*S*,3*S*)-3-methyl-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-ylcarbamate (**12b**): Gummy residue ; yield 579 mg, (79 %) ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) : 0.82-0.95 (m, 6H, CHCH(CH_3)CH_2CH_3), 1.39 (s, 9H, C(CH_3)$_3$), 1.61-1.71 (m, 2H, CHCH(CH_3)CH_2), 2.26 (s, 3H, NCH_3), 2.35-2.36 (m, 4H, COcycN(CH_2CH_2)$_2$NCH_3), 2.58 (br s, 1H, NHCHC*H*), 3.54-3.65 (m, 4H, COcycN(CH_2CH_2)$_2$NCH_3), 4.40-4.45 (m, 1H, NHC*H*)

7.1.2 (*S*)-*Tert*-butyl 3-*H*ydroxy-1-(4-methylpiperazin-1-yl)-1-oxopropan-2-ylcarbamate (**12c**): Gummy residue; yield 413 mg, (72%) ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) : 1.31 (s, 9H, C(CH_3)$_3$), 2.16 (s, 3H, NCH_3), 2.28-2.30 (m, 4H, COcycN(CH_2CH_2)$_2$NCH_3), 3.50-3.59 (m, 4H, COcycN(CH_2CH_2)$_2$NCH_3), 3.76 (br s, 2H, NHCHCH_2), 4.56-4.57 (s, 1H, NHC*H*), 5.83 (d, *J* = 8.3 Hz, 1H, N*H*).

7.1.3 *Tert*-butyl (2*R*,3*S*) 3-*H*ydroxy-1-(4-methylpiperazin-1-yl)-1-oxobutan-2-ylcarbamate (**12d**): Gummy residue; yield 421 mg, (70%), ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) : 1.04 (d, *J* = 6.2 Hz, 3H, CHCH(OH)CH_3), 1.34 (s, 9H, C(CH_3)$_3$), 2.18 (s, 3H, NCH_3), 2.22-2.38 (m, 4H, COcycN(CH_2CH_2)$_2$NCH_3), 3.47-3.59 (m, 4H, COcycN(CH_2CH_2)$_2$NCH_3), 3.97-3.99 (m, 1H, CHC*H*(CH_3)OH), 4.44 (d, *J* = 5.0 Hz, 1H, NHC*H*CH(CH_3)OH), 5.68 (d, *J* = 8.3 Hz, 1H, N*H*).

7.1.4 (*S*)-*Tert*-butyl-3-(1H-indol-3-yl)-1-(4-methylpiperazin-1-yl)-1-oxopropan-2-ylcarbamate (**12e**): Gummy residue; yield: 557 mg, (72 %) ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm) : 1.34 (s, 9H, C(CH_3)$_3$), 2.01-2.35 (m, 7H, cycN(CH_2CH_2)$_2$NCH_3), 3.04-3.10 (m, 2H, CHCH_2), 3.29-3.59 (m, 4H cycN(CH_2CH_2)$_2$NCH_3), 4.84-4.91 (m, 1H, NHC*H*), 7.05 (d, *J* =

2.0 Hz, 1H, Ar-*H* indole), 7.13-7.28 (m, 2H, Ar-*H* indole), 7.37-7.40 (m, 2H, Ar-*H* indole); ESI-MS: *m/z* 387 ($M+H^+$)

7.1.5 (*S*)-*Tert*-butyl4-methyl-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-ylcarbamate (**12f**): Gummy residue; yield 500 mg, (80 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.91-0.98 (m, 6H, $CH(CH_3)_2$), 1.43(s, 9H, $C(CH_3)_3$), 1.70-1.87 (m, 3H, $CH_2CH(CH_3)_2$), 2.29 (s, 3H, NCH_3), 2.36-2.41 (m, 4H, $COcycN(CH_2CH_2)_2NCH_3$), 2.58 (br s, 1H, NHCHCH), 3.58 (br s, 4H, $COcycN(CH_2CH_2)_2NCH_3$), 4.58 (br s, 1H, NHCH).

7.1.6 *Tert*-butyl 3-(4-methylpiperazin-1-yl)-3-oxopropylcarbamate (12g): Gummy residue; yield 375 mg, (70%) ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm) : 1.37 (s, 9H, $C(CH_3)_3$), 2.25 (s, 6H, $2NCH_3$), 2.31-2.35 (m, 4H, $COcycN(CH_2CH_2)_2NCH_3$), 2.44-2.47 (m, 2H, $NHCH_2CH_2$), 3.33-3.42 (m, 4H, $COcycN(CH_2CH_2)_2NCH_3$), 3.56-3.59 (m, 2H, $NHCH_2$), 5.33 (s, 1H, *NH*).

7.1.7 *Tert*-butyl 4-(4-methylpiperazin-1-yl)-4-oxobutylcarbamate (12h): Gummy residue,yield 407 mg, (71%), ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm): 1.37 (s, 9H, $C(CH_3)_3$), 1.71-1.80 (m, 2H, $NHCH_2CH_2$), 2.25 (s, 3H, NCH_3), 2.27-2.36 (m, 6H, $CH_2COcycN(CH_2CH_2)_2NCH_3$), 3.06-3.13 (m, 2H, $NHCH_2$), 3.40-3.58 (m, 4H, $CH_2COcycN(CH_2CH_2)_2NCH_3$), 4.99 (s, 1H, NH).

7.1.8 (*S*)-*Tert*-butyl 1,5-bis(4-methylpiperazin-1-yl)-1,5-dioxopentan-2-ylcarbamate (**12i**): Gummy residue; yield : 600 mg, (73%) ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) : 1.36 (s, 9H, $C(CH_3)_3$), 1.76-1.79 (m, 2H, $CHCH_2$), 2.09-2.36 (m, 10H, $CH_2COcyc2N(CH_2CH_2)_2NCH_3$), 2.50 (s, 6H, $2NCH_3$), 3.33-3.51 (m, 8H, $COcyc2N(CH_2CH_2)_2NCH_3$), 4.34 (br s, 1H, NHCH).

7.1.9 (*S*)-*Tert*-butyl 1,4-bis(4-methylpiperazin-1-yl)-1,4-dioxobutan-2-ylcarbamate (12j): Gummy residue,yield, 595 mg. (75%) ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.42 (s, 9H, C(CH_3)$_3$), 2.28 (s, 6H, 2NCH_3), 2.30-2.34 (m, 8H, COcyc2N(CH_2CH_2)$_2$NCH_3), 2.57-2.64 (m, 1H, CHCH*H*), 2.86-2.94 (m, 1H, CHC*H*H), 3.36-3.70 (m, 8H, COcyc2N(CH_2CH_2)$_2$NCH_3), 5.01-5.03 (m, 1H, NHC*H*), 5.42 (d, *J* = 8.64 Hz, N*H*).

8. General procedure for the synthesis of 14a-14j: Boc protection of (**12a-12j**) was removed using 15% HCl/Dioxane at 0 °C.[19] Compounds **13a-13j** obtained in quantitative yields as corresponding hydrochloride salts. Hydrochloride salts were converted to free base by triethylamine and fused to the 4,7-Dichloroquinoline in the presence of phenol to obtain compounds **14a**-**14j.**[9]

8.1 (*S*)-2-(7-Chloroquinolin-4-ylamino)-3-methyl-1-(4-methylpiperazin-1-yl)butan-1-one (14a): Gummy residue; yield 164 mg, 45.4%).^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) : 1.04-1.12 (m, 6H, CHCH(CH_3)$_2$, 2.35 (s, 3H, NCH_3), 2.44-2.51 (m, 5H, CHC*H*(CH_3)$_2$, cycN(CH_2CH_2)$_2$NCH_3), 3.71-3.73 (m, 4H, cycN(CH_2CH_2)$_2$NCH_3)), 4.54-4.58 (m, 1H, NHC*H*), 6.50 (d, *J* = 6.1 Hz, 1 H, Ar-*H* quinoline), 7.43 (dd, *J* = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline), 7.88-7.91 (m, 1H, Ar-*H* quinoline), 8.06 (d, *J* = 1.9 Hz, 1H, Ar-*H* quinoline), 8.49 (d, *J* = 4.4 Hz, 1H, Ar-*H* quinoline). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) :18.4, 29.6, 41.5, 45.6, 45.8, 54.4, 54.9, 55.8, 98.6, 117.0, 121.9, 125.5, 127.1, 135.5, 147.7, 150.4, 169.6. HRMS calculated for [$C_{19}H_{25}ClN_4O$+H^+] 361.1795, found 361.1791; ESI-MS: *m/z* 361 ($M+H^+$).

8.1.1 (2*S*,3*S*)-2-(7-Chloroquinolin-4-ylamino)-3-methyl-1-(4-methylpiperazin-1-yl)pentan-1-one (14b): Gummy residue; yield 182 mg, 48 %), ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) : 0.88-1.00 (m, 6H, CHCH_3, CH_2CH_3), 1.48-1.78 (m, 3H, NHCHC*H*CH_2), 2.36 (s, 1H, NCH_3), 2.44-2.55 (m, 4H, cycN(CH_2CH_2)$_2$NCH_3), 3.62-3-78 (m, 4H,

cycN(C*H*$_2$CH$_2$)$_2$NCH$_3$), 4.92-4.97 (m, 1H, NHC*H*), 6.36 (s, 1H, N*H*), 6.55 (d, *J* = 6.2 Hz, 1H, Ar-*H* quinoline), 7.46-7.50 (dd, *J* = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline), 7.88 (d, *J* = 9.1 Hz, 1H, Ar-*H* quinoline), 8.20 (d, *J* = 2.1 Hz, 1H, Ar-*H* quinoline), 8.43 (d, *J* = 5.4 Hz, 1H, Ar-*H* quinoline); ^{13}C NMR (75 MHz; CDCl$_3$+DMSO-d$_6$) δ (ppm) : 16.2, 20.6, 30.0, 41.9, 42.3, 46.8, 50.7, 60.0, 104.3, 122.6, 128.4, 129.4, 132.5, 139.1, 155.0, 156.5, 166.0, 175.1. HRMS calculated for [C$_{20}$H$_{27}$ClN$_4$O+H$^+$] 375.1952, found 375.1946; ESI-MS: *m/z* 375.2 (M+H$^+$).

8.1.2 (*S*)-2-(7-Chloroquinolin-4-ylamino)-3-hydroxy-1-(4-methylpiperazin-1-yl)propan-1-one (**14c**): Gummy residue; yield 178 mg, 51%); ^{1}H NMR (300 MHz, DMSO-d$_6$,) δ (ppm) : 2.20 (s, 3H, NC*H*$_3$), 2.31-2.51 (m, 4H, cycN(CH$_2$C*H*$_2$)$_2$NCH$_3$), 3.33-3.43 (m, 4H, cycN(C*H*$_2$CH$_2$)$_2$NCH$_3$), 3.65-3.79 (m, 2H, CHC*H*$_2$), 4.75-4.78 (m, 1H, NHC*H*), 5.15 (br s, 1H, N*H*), 6.44 (d, *J* = 6.1 Hz, 1H, Ar-*H* quinoline), 7.17 (d, *J* = 7.2 Hz, 1H, Ar-*H* quinoline), 7.47 (dd, *J* = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline), 7.81 (d, *J* = 2.0 Hz, 1H, Ar-*H* quinoline), 8.39 (d, *J* = 4.4 Hz, 1H, Ar-*H* quinoline); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ: 40.2, 45.3, 54.2, 54.8, 61.1, 98.4, 117.3, 122.1, 125.3, 127.4, 135.1, 148.2, 150.2, 151.0, 169.6. HRMS calculated for [C$_{17}$H$_{22}$ClN$_4$O$_2$+H$^+$] 349.1431, found 349.1355; ESI-MS: *m/z* 349 (M+H$^+$).

8.1.3 (2*S*,3*S*)-2-(7-Chloroquinolin-4-ylamino)-3-hydroxy-1-(4-methylpiperazin-1-yl)butan-1-one (**14d**): Gummy residue; yield 168 mg, 46 %); ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) : 1.31 (d, *J* = 6.36 Hz, CHCH(OH)C*H*$_3$), 2.36 (s, NC*H*$_3$), 2.46-2.52 (m, 4H, cycN(CH$_2$C*H*$_2$)$_2$NCH$_3$), 3.51-3.78 (m, 4H, cycN(C*H*$_2$CH$_2$)$_2$NCH$_3$)), 4.26-4.29 (m, NCHC*H*, 1H), 4.61 (m, 1H, NC*H*), 5.15 (br s, 1H, NH), 6.28 (d, *J* = 6.1 Hz, 1 H, Ar-*H* quinoline), 7.40 (dd, *J* = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline), 7.82 (d, *J* = 2.0 Hz, 1H, Ar-*H* quinoline), 7.97 (d, *J* = 1.9 Hz, 1H, Ar-*H* quinoline), 8.52 (d, *J* = 4.4 Hz, 1H, Ar-*H* quinoline). ^{13}C NMR (75

MHz, $CDCl_3$) δ (ppm): 19.3, 42.4, 45.8, 54.3, 55.2, 57.9, 67.5, 99.5, 117.1, 122.1, 125.6, 127.3, 135.5, 147.9, 149.6, 150.8, 168.7; HRMS calculated for [$C_{18}H_{23}ClN_4O_2$+ H^+] 363.1588, found 363.1591; ESI-MS: *m/z* 363.1 ($M+H^+$).

8.1.4 (*S*)-2-(7-Chloroquinolin-4-ylamino)-3-(1H-indol-3-yl)-1-(4-methylpiperazin-1-yl)propan-1-one (**14e**): Gummy residue; yield 197 mg, (44%); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.01-2.35 (m, 7H, cycN(CH_2CH_2)$_2$NCH_3), 3.04-3.10 (m, 2H, CHCH_2), 3.29-3.59 (m, 4H cycN(C$H_2$$CH_2$)$_2NCH_3$), 4.84-4.91 (m, 1H, NHC*H*), 6.33-6.41(m, 2H, N*H*, Ar-*H* quinoline), 7.05 (d, *J* = 2.0 Hz, 1H, Ar-*H* indole), 7.13-7.28 (m, 2H, Ar-*H* indole), 7.37-7.40 (m, 2H, Ar-*H* indole), 7.57 (d, *J* = 7.7 Hz, 1H, Ar-*H* quinoline), 7.77 (d, *J* = 8.9 Hz, 1H, Ar-*H* quinoline), 7.98 (d, *J* = 1.9 Hz, 1H, Ar-*H* quinoline), 8.34 (s, 1H, N*H*), 8.46 (d, *J* = 5.4 Hz, 1H, Ar-*H* quinoline); ^{13}C NMR (75 MHz, DMSO-d_6) δ(ppm) :27.4, 44.2, 44.8, 53.2, 53.6, 57.0, 99.5, 109.2, 111.4, 117.1, 118.1, 118.4, 120.9, 124.3, 126.4, 127.3, 134.1, 135.9, 149.8, 150.9, 158.9, 169.8; HRMS calculated for [$C_{25}H_{26}ClN_5O$+ H^+] 448.1904, found 448.1898; ESI-MS: *m/z* 448 ($M+H^+$).

8.1.5. (*S*)-2-(7-Chloroquinolin-4-ylamino)-4-methyl-1-(4-methylpiperazin-1-yl)pentan-1-one (**14f**)**:** Gummy residue; yield:170 mg, 45 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.99-1.02 (m, 6H, $CH_2CH(CH_3)_2$), 1.71 (m, 1H, CH_2C*H*), 1.87 (m, 2H, NHCHCH_2), 2.33 (s, 1H, NCH_3), 2.43 (m, 4H, COcycN(CH_2CH_2)$_2$NCH_3), 3.56 (m, 4H, COcycN(C$H_2$$CH_2$)2N$CH_3$), 4.58 (m, 1H, NHC*H*), 6.32 (d, *J* = 5.5 Hz, 1H, Ar-*H* quinoline), 7.36 (dd, *J* = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline), 7.82 (d, *J* = 8.9 Hz, 1H, Ar-*H* quinoline), 7.96 (d, *J* = 2.1 Hz, 1H, Ar-*H* quinoline), 8.54(d, *J* = 5.4 Hz, 1H, Ar-*H* quinoline); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 22.3, 23.4, 24.7, 41.5, 42.3, 45.3, 45.9, 54.6, 55.0, 98.7, 117.2, 121.6, 125.5, 127.7, 135.4, 148.2, 149.6, 151.0, 170.6; HRMS calculated for [$C_{20}H_{27}ClN_4O$+H^+] 375.1952, found 375.1946; ESI-MS: *m/z* 375.2 (M+H+).

8.1.6. 3-(7-Chloroquinolin-4-ylamino)-1-(4-methylpiperazin-1-yl)propan-1-one (14g): Gummy residue; yield 164, (45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.28 (s, 3H, NC*H*$_3$), 2.34-2.38 (m, 4H, cycN(CH$_2$C*H*$_2$)$_2$NCH$_3$), 2.69-2.72 (m, 2H, HNCH$_2$C*H*$_2$CO), 3.43-3.48 (m, 2H, HNC*H*$_2$CH$_2$CO), 3.63-3.66 (m, 4H, 2 COcycN(C*H*$_2$CH$_2$)$_2$NCH$_3$), 6.32 (s, 1H, N*H*), 6.40 (d, *J* = 5.4 Hz, 1H, Ar-*H* quinoline), 7.31 (dd, *J* = 8.9, 2.1, Hz, 1H, Ar-*H* quinoline), 7.72 (d, *J* = 9 Hz, 1H, Ar-*H* quinoline), 7.91 (d, *J* = 2.1 Hz, 1H, Ar-*H* quinoline), 8.47 (d, *J* = 5.4 Hz, 1H, Ar-*H* quinoline); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 31.2, 38.7, 41.5, 45.2, 45.8, 54.4, 54.7, 98.4, 117.3, 122.1, 125.3, 127.4, 135.1, 148.2, 150.2, 151.0, 169.6; HRMS calculated for $[C_{17}H_{22}ClN_4O+H]^+$ 333.1482, found 333.1471; ESI-MS: *m/z* 333.2 (M+H$^+$).

8.1.7. 4-(7-Chloroquinolin-4-ylamino)-1-(4-methylpiperazin-1-yl)butan-1-one (14h): Gummy residue; yield:188 mg, (54%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) : 1.84 (br s, 2H, CH$_2$C*H*$_2$), 2.22-2.64 (m, 9H, CH$_2$C*H*$_2$COcycN(CH$_2$C*H*$_2$)$_2$NC*H*$_3$), 3.36-3.51 (m, 4H, COcycN(C*H*$_2$CH$_2$)$_2$NCH$_3$), 3.71 (br s, 2H, NHC*H*$_2$), 6.34 (d, *J* = 5.2 Hz, 1H, Ar-*H* quinoline), 7.38 (d, *J* = 7.4 Hz, 1H, Ar-*H* quinoline), 7.58 (s, 1H, N*H*), 7.92 (d, *J* = 9.0 Hz, 1H, Ar-*H* quinoline), 8.03 (d, *J* = 2.1 Hz, 1H, Ar-*H* quinoline), 8.45 (br s, 1H, Ar-*H* quinoline); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 25.2, 33.0, 43.7, 45.3, 45.8, 45.8, 54.4, 55.1, 98.1, 117.1, 123.1, 125.4, 126.1, 135.6, 146.8, 149.7, 151.4, 171.6; HRMS calculated for $[C_{18}H_{23}ClN_4O+H]^+$ 346.1633, found 346.1639 ; ESI-MS: *m/z* 347 (M+H$^+$).

8.1.8. (*S*)-2-(7-Chloroquinolin-4-ylamino)-1,5-bis(4-methylpiperazin-1-yl)pentane-1,5-dione (14i): Gummy residue; yield 171 mg, (36%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.95 (br s, 4H, CHC*H*$_2$C*H*$_2$), 2.29 (s, 3H, NC*H*$_3$), 2.34 (s, 3H, NC*H*$_3$), 2.39-2.52 (m, 8H, 2 cycN(CH$_2$C*H*$_2$)$_2$NCH$_3$), 3.30-3.90 (m, 8H, 2 cycN(C*H*$_2$CH$_2$)$_2$NCH$_3$), 4.88-4.90 (m, 1H, NHC*H*), 6.35 (d, *J* = 5.4 Hz, 1H, Ar-*H* quinoline), 6.68 (s, 1 H, N*H*), 7.41 (dd, *J* = 2.1, 8.9

Hz, 1H, Ar-*H* quinoline), 7.88 (d, *J* = 9 Hz, 1H, Ar-*H* quinoline), 8.00 (d, *J* = 2.1 Hz, 1H, Ar-*H* quinoline), 8.46 (d, *J* = 5.3 Hz, 1H, Ar-*H* quinoline); HRMS calculated for $[C_{24}H_{34}ClN_6O_2+ H^+]$ 473.2432, found 473.2424; ESI-MS: *m/z* 473 ($M+H^+$).

8.1.9. (*S*)-2-(7-Chloroquinolin-4-ylamino)-1,4-bis(4-methylpiperazin-1-yl)butane-1,4-dione (**14j**): Brown gummy residue; yield 206 mg, (44%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.20 (s, 3H, NC*H*$_3$), 2.30 (s, 3H, NC*H*$_3$), 2.35-2.44 (m, 8H, COcycN(CH_2CH_2)$_2$NCH$_3$), 2.84-2.87 (m, 2H, CHC*H*$_2$), 3.42-3.71 (m, 8H, COcycN(CH_2CH_2)$_2$NCH$_3$), 5.16-5.21 (m, 1H, NHC*H*), 6.20 (d, *J* = 6.1 Hz, 1H, N*H*), 6.58 (d, *J* = 4.1 Hz, 1 H, Ar-*H* quinoline), 7.37 (dd, *J* = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline), 7.76 (d, *J* = 6.7 Hz, 1H, Ar-*H* quinoline), 7.96 (d, *J* = 2.1 Hz, 1H, Ar-*H* quinoline), 8.53 (d, *J* = 5.6 Hz, 1H, Ar-*H* quinoline); HRMS calculated for $[C_{23}H_{31}ClN_6O_2+H]^+$ 459.2275, found 459.2286; ESI-MS: *m/z* 459.1 ($M+H^+$).

9. General procedure for the synthesis of 16a-16c: Boc-protected amino acids of valine, phenylalanine and isoleucine were converted to the corresponding diazoketones .[20]

9.1 Boc-L-valyl-diazoketone (16a): Gummy residue; yield: 1.62 gm, (45%); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.92 (d, *J* = 4.3 Hz, 6H, CH(C*H*$_3$)$_2$, 1.43 (s, 9H, C(C*H*$_3$)$_3$), 1.95-2.10 (m, 1H, CHC*H*(CH$_3$)$_2$), 3.50-3.95 (m, 1H, NHC*H*), 5.13 (s, 1H, COC*H*N$_2$).

9.1.1. Boc-L-phenylalanyl-diazoketone (16b): Gummy residue; yield: 2.9 gm, (68%); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) : 1.42 (s, 9H, C(C*H*$_3$)$_3$), 3.00-3.22 (m, 2H, CHC*H*$_2$Ph), 4.38 (br s, 1H, NHC*H*), 5.12 (s, 1H, COC*H*N$_2$), 5.23 (br, N*H*), 7.16-7.28 (m, 3H, Ar-*H*), 7.29-7.36 (m, 2H, Ar-*H*).

9.1.2. Boc-L-isoleucyl-diazoketone (16c): Gummy residue; yield: 1.79 gm, (47%); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.85-1.38 (m, 8H, CHCH(CH_3)CH_2CH_3), 1.43 (s, 9H, C(CH_3)$_3$), 1.46-1.58 (m, 1H, CHC*H*(CH_3)CH_2CH_3), 4.10-4.25 (m, 1H, NHC*H*), 5.13 (s, 1H, COC*H*N_2).

10. General procedure for the synthesis of 17a-17c: Purified diazoketone derivatives were then stirred in dioxane/water (5:1) at 70 °C in the presence of silver benzoate to get corresponding β-amino acids (**17a-17c**) via wolf rearrangement.[21]

10.1. Boc-L-β^{3}h-valine (17a): Gummy residue; yield: 1.01 gm, (88%); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.90 (d, *J* = 4.4 Hz, 6H, CH(CH_3)$_2$, 1.43 (s, 9H, C (CH_3)$_3$), 1.82-1.98 (m, 1H, NHCH(CH_2)C*H*(CH_3)$_2$), 2.45-2.71(m, 2H, NHCH(CH_2)CH(CH_3)$_2$), 3.45 (s, 1H, NHC*H*).

10.1.1. Boc-L-β^{3}h-phenylalanine (17b): Gummy residue; yield: 1.14 gm, (82%); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.42 (s, 9H, C(CH_3)$_3$), 2.50-2.65 (m, 2H, NHCH(CH_2)CH_2), 2.82-3.12 (m, 2H, NHCH(CH_2)CH_2 Ph)), 4.11-4.23 (m, 1H, NHC*H*), 5.17 (br, N*H*), 7.18-7.26 (m, 3H, Ar-*H*), 7.29-7.36 (m, 2H, Ar-*H*).

10.1.2. Boc-L-β^{3}h-isoleucine (17c): Gummy residue; yield: 1.11 gm, (91%); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.90-1.20 (m, 6H, CH(CH_3)CH_2CH_3), 1.43 (s, 9H, C (CH_3)$_3$), 1.48-1.60 (m, 2H, CH(CH_3)CH_2CH_3), 1.93-2.05 (m, 1H, NHCH(C*H*)CH_2), 2.40-2.73 (m, 2H, , NHCH(CH)CH_2), 3.48 (br s, 1H, NHC*H*).

11. General procedure for the synthesis of 18a-18c: The compounds obtained **17a-17c** were coupled with methylpiperazine using DCC, HOBt protocol in dry THF.[10]

11.1. (*S*)-*Tert*-butyl 4-methyl-1-(4-methylpiperazin-1-yl)-1-oxopentan-3-ylcarbamate (**18a**): Gummy residue; yield 500 mg, (80 %) ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.80 (d, *J* = 6.6 Hz, 3H, CHCH(CH_3)CH_3), 0.87 (d, *J* = 6.6 Hz, 3H, CHCH(CH_3)CH_3), 1.36 (s, 9H,

C(CH_3)$_3$), 1.80-1.89 (m, 1H, CHCH(CH$_3$)CH$_3$), 2.23 (s, 3H, NCH_3), 2.31-2.33 (m, 4H, COcycN(CH$_2$CH_2)$_2$NCH$_3$), 2.45-2.71 (m, 2H, NHCH(CH_2)CH(CH$_3$)$_2$), 3.49-3.61 (m, 4H, COcycN(CH_2CH$_2$)$_2$NCH$_3$), 4.35-4.40 (m, 1H, NHCHCH), 5.35 (d, J = 8.6 Hz, NH).

11.1.1. (*S*)-*Tert*-butyl 4-(4-methylpiperazin-1-yl)-4-oxo-1-phenylbutan-2-ylcarbamate (18b): Gummy residue; yield 575 mg, (80%). ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm): 1.42 (s, 9H, C(CH_3)$_3$), 2.31-2.33 (m, 4H, COcycN(CH$_2$CH_2)$_2$NCH$_3$), 2.52-2.66 (m, 2H, NHCH(CH$_2$)CH_2), 2.83-3.14 (m, 2H, NHCH(CH$_2$)CH_2 Ph), 3.51-3.64 (m, 4H, COcycN(CH_2CH$_2$)$_2$NCH$_3$), 4.14-4.23 (m, 1H, NHCH), 5.13 (br, NH), 7.16-7.27 (m, 3H, Ar-H), 7.28-7.35 (m, 2H, Ar-H).

11.1.2. *Tert*-butyl (3*S*)-4-methyl-1-(4-methylpiperazin-1-yl)-1-oxohexan-3-ylcarbamate (18c): Gummy residue; yield 525 mg, (84%) ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm): 0.82-0.95 (m, 6H, CHCH(CH_3)CH$_2$CH_3), 1.39 (s, 9H, C(CH_3)$_3$), 1.61-1.71 (m, 2H, CHCH(CH$_3$)CH_2 CH$_3$), 1.93-2.05 (m, 1H, NHCH(CH)CH$_2$), 2.26 (s, 3H, NCH_3), 2.34-2.76 (m, 6H, 2.40-2.73 NHCH(CH)CH_2COcycN(CH$_2$CH_2)$_2$NCH$_3$), 3.54-3.65 (m, 4H, COcycN(CH_2CH$_2$)$_2$NCH$_3$), 4.40-4.45 (m, 1H, NHCH)

12. General procedure for the synthesis of 19a-19c:

Boc protection of **18a-18c** was removed using 15% HCl/Dioxane at 0 °C.[19] Compounds **19a-19c** obtained in quantitative yields as corresponding hydrochloride salt. Hydrochloride salts were converted to free base by triethylamine and used for the next step without further purification.

12.1 General procedure for the synthesis of 20a-20c: The compounds **19a-19c** obtained were fused with the 4,7-Dichloroquinoline in the presence of phenol resulting in compounds **20a** -**20c**.[9]

12.1.1 (*S*)-3-(7-Chloroquinolin-4-ylamino)-4-methyl-1-(4-methylpiperazin-1-yl)pentan-1-one (**20a**): Gummy residue; yield 168 mg, (45 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.01-1.06 (m, 6H, CH(C*H*$_3$)$_2$), 2.10 (br s, 1H, CHC*H*(CH$_3$)$_2$), 2.25 (s, 3H, NC*H*$_3$), 2.32-2.37 (m, 4H, cycN(CH$_2$C*H*$_2$)$_2$NCH$_3$), 2.59-2.84 (m, 2H, NHCHC*H*$_2$), 3.49-3.63 (m, 4H, COcycN(C*H*$_2$CH$_2$)$_2$NCH$_3$), 3.84 (br s, 1H, NHC*H*), 6.47 (d, *J* = 5.4 Hz, 1H, Ar-*H* quinoline), 6.58 (d, *J* = 7.8 Hz, 1H, N*H*), 7.36 (dd, *J* = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline),7.76 (d, *J* = 8.9 Hz, Ar-*H* quinoline), 7.96 (d, *J* = 2.1 Hz, 1H, A Ar-*H* quinoline), 8.47 (d, *J* = 5.4, 1H, Ar-*H* quinoline); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 19.4, 31.9, 33.3, 41.5, 45.6, 45.8, 54.4, 54.9, 55.9, 98.8, 117.0, 122.1, 125.5, 126.9, 135.6, 147.7, 150.2, 150.5, 169.6; HRMS calculated for [$C_{20}H_{27}ClN_4O$+H^+] 375.1952, found 375.1946; ESI-MS: *m/z* 375.2 (M+H^+).

12.1.2. (*3R,4S*)-3-(7-Chloroquinolin-4-ylamino)-4-methyl-1-(4-methylpiperazin-1-yl)hexan-1-one (**20b**)**:** Yellow gummy residue; yield 160 mg, (41%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) : 0.94-1.00 (m, 6H, CH(C*H*$_3$)CH$_2$C*H*$_3$), 1.58-1.66 (m, 2H, CH(CH$_3$)C*H*$_2$CH$_3$), 1.93-2.39 (m, 8H, NHCHC*H*, COcycN(CH$_2$C*H*$_2$)$_2$NC*H*$_3$), 2.59-2.89 (m, 2H, NHCHC*H*$_2$), 3.52-3.63 (m, 4H, COcycN(C*H*$_2$CH$_2$)$_2$NCH$_3$), 3.95 (br s, 1H), 6.47 (d, *J* = 5.49, 1H, Ar-*H* quinoline), 6.97 (br s,1H, NH), 7.35 (dd, *J* = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline), 7.82 (d, *J* = 8.9 Hz, 1H, Ar-*H* quinoline), 7.92 (d, *J* = 2.1 Hz, 1H, Ar-*H* quinoline), 8.44 (d, *J* = 5.4 Hz, 1H, Ar-*H* quinoline): ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6) δ (ppm) : 16.2, 20.6, 30.0, 33.2, 41.9, 42.3, 46.8, 50.7, 60.0, 104.3, 122.6, 128.4, 129.4, 132.5, 139.1, 155.0, 156.5, 166.0, 175.1; HRMS calculated for [$C_{21}H_{30}ClN_4O$+H^+] 389.2108, found 389.2139; ESI-MS: *m/z* 389.2 (M+H^+).

12.1.3 (*S*)-3-(7-Chloroquinolin-4-ylamino)-1-(4-methylpiperazin-1-yl)-4-phenylbutan-1-one (**20c**): Brown gummy residue; yield 190 mg, 45 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.29 (s, 3H, NC*H*$_3$), 2.30-2.64 (m, 4H, COcycN(CH$_2$C*H*$_2$)$_2$NCH$_3$), 2.93-3.34 (m, 4H,

NHCHCH_2CO, CHCH_2Ph), 3.63-3.70 (m, 4H, COcycN(CH_2CH_2)$_2$NCH_3), 4.2 (br s, 1H), 6.44 (d, *J* = 5.49 Hz, 1H, Ar-*H* quinoline), 6.99 (d, *J* = 7.86 Hz, 2H, Ar-*H* quinoline), 7.18 (m, 4 H, 3Ar-*H*, 1Ar-*H* quinoline),7.74 (d, *J* = 8.9, 1H, Ar-*H* quinoline), 7.92 (s, 1H, Ar-*H* quinoline), 8.46 (d, *J* = 5.4, 1H, Ar-*H* quinoline). ^{13}C NMR (75 MHz, $CDCl_3$): 33.2, 39.2, 41.5, 45.3, 45.4, 51.4, 54.9, 54.8, 98.5, 117.3, 121.9, 125.4, 126.6, 126.8, 127.8, 128.5, 128.7, 129.1, 135.5, 137.8, 148.5, 148.2, 151.1, 169.5; HRMS calculated for [$C_{24}H_{28}ClN_4O$+H^+] 423.1952, found 423.1947; ESI-MS: *m/z* 423.2 (M+H^+).

13. General procedure for the synthesis of (30): The L- phenylalanine was converted to its methyl ester (**22)** by drop wise addition of thionyl chloride to the methanolic solution of **21** at 0 °C.[22] After completion of the reaction solvent was evaporated and the compound was crystallized by dry ether. The hydrochloride salt obtained was basified by triethylamine and dissolved in dry dichloromethane. Di-*tert*-butylpyrocarbonate was added to the solution at 0 °C and reaction was stirred for next three hours. This afforded the Boc protected methyl ester (**23**) in quantitative yields. A carefully controlled reduction of **23** by DIBAL-H at -78 °C afforded **24** (the N protected amino aldehyde) and the aldehyde was directly used for the Wittig reaction without any purification.[23] The reaction of aldehyde with the stabilized ylide in THF at 0 °C led to α, β-unsaturated esters (**25**). Crude product was purified by the silica gel column chromatography. Compound **25** obtained in 70% yield after 2 steps. Catalytic hydrogenation of the double bond.[23] led to Boc-protected ethyl ester of γ-amino acid (**26**) in quantitative yield. Compound **26** was hydrolyzed in a mixture of THF and water (9:1 ratio) by lithium hydroxide produced the Boc protected γ-amino acid (**27**). Compound **22** was reacted at -15 °C in dry THF with *N*-methylpiperazine using isobutylchloroformate (IBCF) in the presence of N-methylmorpholine (NMM) to afford compound **28** in 90% yield. Deprotection of **28** by 15% HCl/Dioxane at 0 °C gave compound **29** in quantitative yield.[19]

The salt was converted to free amine (**29**) and it was fused with 4,7-DCQ in phenol at 140 °C afforded the final product (**30**).[9]

13.1. (*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-3-phenylpropanoate (23): At 0 °C di-*tert*-butylpyrocarbonate (7 mL, 30 mmol) was added drop wise under a nitrogen atmosphere to a solution of L-phenylalanine methyl ester hydrochloride **22** (5 g, 23 mmol) and triethylamine (5.5 mL, 56 mmol) in CH_2Cl_2, (120 mL). The resulting mixture was stirred at room temperature for 5 h. After completion of the reaction organic layer was washed with 5% citric acid (100 mL), then with 5% $NaHCO_3$, (100 mL) and finally with H_2O (50 mL). The organic layer was dried over Na_2SO_4, and evaporated to give an oily residue (Yield: quantitative). Compound was purified by column chromatography with 5% EtOAc/hexane. ESI-MS: *m/z* 280 ($M+H^+$).

13.1.1. (*S*)-*Tert*-butyl 1-oxo-3-phenylpropan-2-ylcarbamate (24): Protected ester (7.4 g, 26.5 mmol) obtained above was dissolved in dry THF (300 mL) and cooled to -80 °C. To this diisobutylaluminum hydride (52 mL, 1 M solution in cyclohexane, 0.052 mol) was added via needle over a period of 45 minutes while maintaining the internal temperature below -69 °C. The mixture was stirred for 3 hrs, and precooled (-75 °C) methanol (20 mL) was added. During the addition, the reaction mixture was maintained below -69 °C. The mixture was then allowed to warm to 5 °C, and 300 g of ice was added with heavy agitation, the mixture was filtered through sintered funnel and extracted with chloroform. Organic layer was washed with brine (100 mL), dried over $MgSO_4$, and concentrated. The crude product thus obtained stored at -20 °C for next step.

13.1.2. (*S*,*E*)-Ethyl 4-(*tert*-butoxycarbonylamino)-5-phenylpent-2-enoate (25): To a solution of the above N-protected α-amino aldehyde in dry DCM (50 mL) at 0 °C EtOOCCH = PPh_3 (26.5 mmol) was added and the solution stirred for 2-3 h. After completion of the

reaction (as monitored by TLC), the reaction mixture was concentrated on a rotary evaporator to give the crude product. This was purified by column chromatography using a mixture of EtOAc and hexane as eluent. (Yield : 5.5g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): (E-isomer) 1.24-1.29 (t, *J* = 7.11 Hz, 3H, CH_2CH_3), 1.39 (s, 9H, $C(CH_3)_3$), 2.88-2.90 (m, 2H, $CHCH_2Ph$), 4.14-4.21 (m, 2H, $COOCH_2CH_3$), 4.66-4.69 (m, 2H, NHCH), 5.84 (d, *J* = 17.3 Hz, 1H, CH=CH), 6.88 (dd, *J* = 15.6 Hz, 4.89, 1H, CH-CH=CH), 7.18-7.32 (m, 5H, Ar-H).

13.1.3. (*R*)-Ethyl 4-(*tert*-butoxycarbonylamino)-5-phenylpentanoate (26): To a solution of the olefin (5.5g, 16.5mmol) in MeOH 10 % (w/w) Pd/C (10%) was added. The apparatus flushed 2 times with hydrogen gas, and the mixture was agitated at room temperature for 2 h under hydrogen gas at 30 Psi. Filtration through Celite and concentration under reduced pressure yielded the ethyl carboxylate which was used without further purification. (Yield 5.3 g, quantitative). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.20 (t, *J* = 6.4 Hz, 3H, CH_2CH_3), 1.39 (s, 9H, $C(CH_3)_3$), 1.58-1.65 (m, 1H, CHCHH), 1.79-1.89 (m, 1H, CHCHH), 2.32-2.38 (m, 2H, CH_2CH_2), 2.69-2.80 (m, 2H, CH_2Ph), 3.82 (br s 1H, NHCH), 4.06-4.03 (m, 2H, $COOCH_2$), 7.16-7.29 (m, 5H, Ar-H).

13.1.4. (*R*)-4-(*Tert*-butoxycarbonylamino)-5-phenylpentanoic acid (27): Ethyl ester (1g, 3.1 mmol) was dissolved in 20 mL of THF, and LiOH solution (0.51 g, 12 mmol) in water was added to it. The mixture was stirred at room temperature for 30 h. After completion of the reaction the reaction mixture was acidified with citric acid solution to (pH 3) and extracted with chloroform 25 mL (2 x), the organic phases were washed with saturated NaCl solution, dried over sodium sulfate and evaporated to afford oily residue.(Yield: Quantitative). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.32 (s, 9H, $C(CH_3)_3$), 1.54-1.46 (m, 1H, CHCHH), 1.70-1.62 (m, 1H, CHCHH), 2.20 (m, 2H, $CHCH_2CH_2$), 2.65 (m, 2H,

CHC*H*$_2$Ph), 3.60 (m, 1H, NHC*H*), 6.72 (brs, N*H*CH, 1H), 7.29-7.16 (m, 5H), 11.99 (br s, 1H).

13.1.5. (*R*)-*Tert*-butyl 5-(4-methylpiperazin-1-yl)-5-oxo-1-phenylpentan-2-ylcarbamate (28):

To a solution of **27** (586 mg, 2 mmol) in 10 mL THF with 1.0 mL of DMF, NMM (0.22 mL, 2 mmol) and IBCF (0.26 mL, 2 mmol) were added successively at -15 ºC under vigorous stirring. The temperature was maintained at -15 ºC for 10 min. Subsequently *N*-methylpiperazine (0.270 mL, 3 mmol) was added to the reaction mixture. The reaction was stirred at -15 ºC for 15 min and then allowed to stir at room temperature for additional 2 hr. Solvent was evaporated under reduced pressure. The oily residue was taken in EtOAc and washed with 5 % aqueous sodium bicarbonate, water and finally with brine. The organic layer was dried over anhydrous Na_2SO_4, evaporated under reduced pressure and purified by column chromatography (1% methanol chloroform was used as eluent). This compound was obtained as oil (yield 562 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) : 1.31 (s, 9H, C(C*H*$_3$)$_3$), 2.04-2.22 (m, 2H, CHC*H*$_2$CH$_2$), 2.24 (s, 3H, NC*H*$_3$), 2.30-2.62 (m, 4H, CHCH$_2$C*H*$_2$COcycN(CH$_2$C*H*$_2$)$_2$NCH$_3$), 2.83-2.90 (m, 2H, CHC*H*$_2$Ph), 3.11-3.60 (m, 4H, COcycN(C*H*$_2$CH$_2$)$_2$NCH$_3$), 3.82 (br s, 1H, NHC*H*), 7.22-7.35 (m, 5H, Ar-*H*).

13.1.6. (*R*)-4-Amino-1-(4-methylpiperazin-1-yl)-5-phenylpentan-1-one (29): Compound **28** was deprotected by 15 % HCl/Dioxane. After evaporation of solvent the hydrochloride salt was crystallized by dry ether. The hydrochloride salt was converted to free base **29** by triethylamine and used without further purification.

13.1.7. (*R*)-4-(7-Chloroquinolin-4-ylamino)-1-(4-methylpiperazin-1-yl)-5- phenylpentan-1-one (30): To a solution of **29** (412.5 mg, 1.5 mmol) in phenol 4,7-Dichloroquinoline (198 mg, 1mmol) was added. The reaction mixture was stirred at 140 °C for 5 hours. After

completion of the reaction the reaction mixture was dissolved in chloroform and extracted with sodium hydroxide solution and then with water and finally with brine. Organic layer was dried over sodium sulfate and concentrated in vacuo. Compound was purified by column chromatography using chloroform: methanol: triethylamine in 9.5:0.3:0.2 ratio. Compound obtained as dark brown gummy residue. (Yield: 201 mg; 41%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.03-2.22 (m, 2H, CHCH_2CH$_2$), 2.24 (s, 3H, NCH_3), 2.30-2.62 (m, 4H, CHCH$_2$CH_2COcycN(CH$_2$CH_2)$_2$NCH$_3$), 2.83-3.13 (m, 2H, CHCH_2Ph), 3.37-3.62 (m, 4H, COcycN(CH_2CH$_2$)$_2$NCH$_3$), 3.80 (br s, 1H, NHC*H*), 6.42 (d, *J* = 8.9 Hz, 1H, Ar-*H* quinoline), 7.21-7.34 (m, 5H, Ar-*H*), 7.41 (dd, *J* = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline), 7.92 (d, *J* = 9.0 Hz, 1H, Ar-*H* quinoline), 8.02 (d, *J* = 1.9 Hz, 1H, Ar-*H* quinoline), 8.41 (d, *J* = 5.8 Hz, 1H, Ar-*H* quinoline); HRMS calculated for [$C_{25}H_{29}ClN_4O$+H^+] 437.2103, found 437.2098; ESI-MS: *m/z* 437 (M+H^+).

14. Biological testing assay.

14.1 *In vitro* antimalarial assay.

The compounds were dissolved in DMSO to get 10 mM concentration. Two fold serial dilutions of the test samples were made in 96 well plates and incubated with 1.0% parasitized cell suspension containing 0.8% parasitemia (an asynchronous culture with more than 80% ring stages). The plates were incubated at 37 °C in CO_2 incubator in an atmosphere of 5% CO_2 and air mixture. Later (72 h) 100µl of lysis buffer containing 2 x concentration of SYBR Green-1 (Invitrogen) was added to each well and incubated for 1 h at 37 °C. The plates were examined at 485±20 nm of emission for relative fluorescence units (RFUs) per well using the fluorescence plate reader (FLUO star, BMG lab technologies). Data was transferred into a graphic programme (EXCEL) and IC_{50} values were obtained by Logit regression analysis of dose response curve.[24] Chloroquine (CQ) was used as the standard reference drug.

14.1.1. *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 *et al.*[25] 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

$$SI = CC_{50} / IC_{50}$$

14.1.2. Determination of hematin - 4-aminoquinoline derivatives association constant

Association constant for hematin - 4-aminoquinoline derivatives complex formation were determined by spectrophotometric titration procedure in aqueous DMSO at pH-7.5.[26] In this assay condition, hematin is strictly in monomeric state and interpretation of results is not complicated by 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. The pH-7.5 improves the stability of hematin solutions and quality of data.

14.1.3. *In vitro* inhibition of β-Hematin polymerization:

The ability of the 4-aminoquinoline derivatives to inhibit β-*H*ematin polymerization was induced by 1-oleoyl-rac-glycerol using UV spectrophotometer and measurements were carried out at 405 nm.[27] The triplicate values obtained from the assay are expressed as percent inhibition relative to hemozoin formation in a drug free control. The 50% inhibitory concentration (IC_{50}) 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.[28] Each IC_{50} value is the result of at least three separate experiments performed in duplicate.

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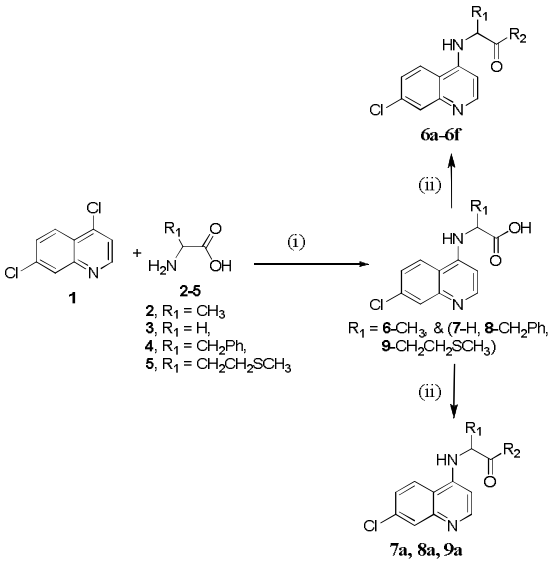
28. GraphPad Prism, version 3.0, GraphPad Software Inc., 10855 Sorrento Valley Rd. #203, San Diego, CA 92121.

Captions

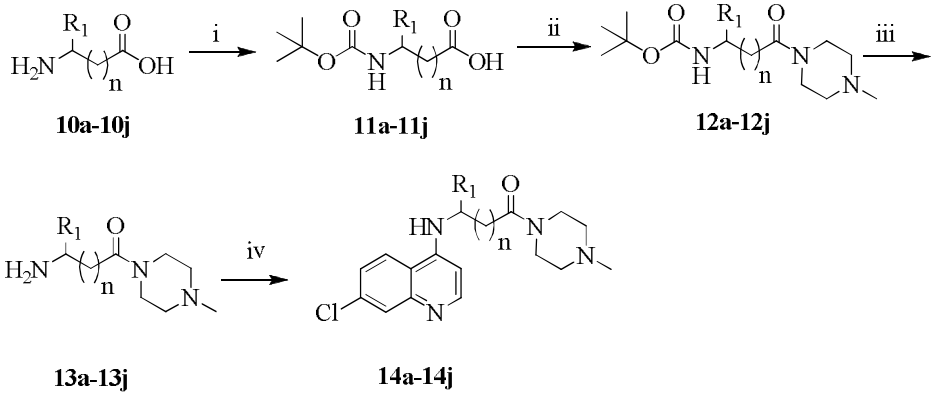
Table 1 Biological and Biophysical data of the synthesized compounds (**6a-6f, 7a, 8a, 9a, 14a- 14j, 20a-20c, 30**).

Figure 1. Structures of CQ and related 4-aminoquinolines having antimalarial activity



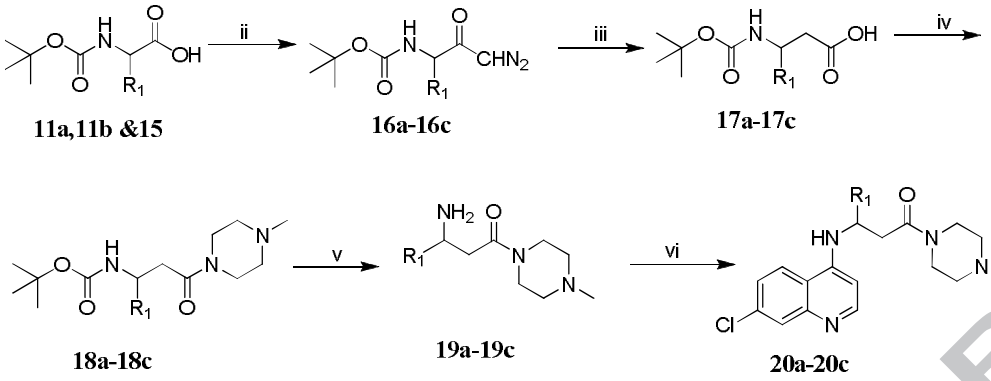
Compound No	R_1	R_2
6a)	CH_3	N-Methylpiperzine
6b)	CH_3	N^1,N^1-diethylpropane-1,3-diamine
6c)	CH_3	1-phenylpiperazine
6d)	CH_3	N^1,N^1-dimethylpropane-1,3-diamine
6e)	CH_3	2-(piperidin-1-yl) ethanamine
6f)	CH_3	N^1,N^1-diethylethane-1,2-diamine
7a)	H	N-Methylpiperzine
8a)	CH_2Ph	N-Methylpiperzine
9a)	$CH_2CH_2SCH_3$	N-Methylpiperzine

Scheme 1. Synthesis of compounds (**6a-6f, 7a, 8a, & 9a**); Reagents and conditions: (i) Phenol, 140 °C; (ii) Amines (a. N-methylpiperazine; b. N^1,N^1-diethylpropane-1,3-diamine; c. 1-phenylpiperazine; d. N^1,N^1-dimethylpropane-1,3-diamine; e. 2-(piperidin-1-yl) ethanamine; f. N^1,N^1-diethylethane-1,2-diamine), DCC; HOBt, DMF, 0 °C.



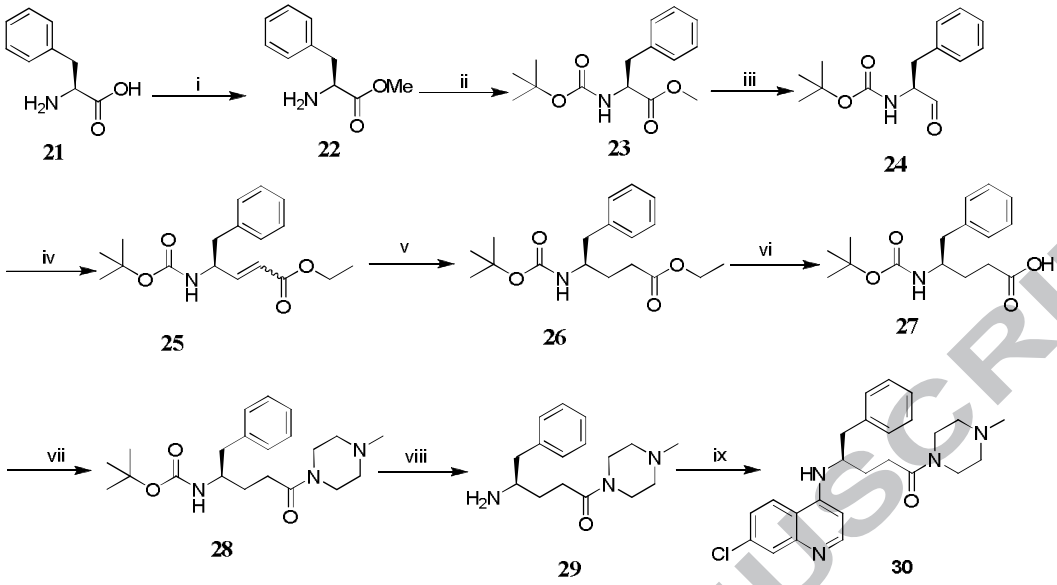
Compound No	n	R_1
14a)	0	$CH(CH_3)_2$
14b)	0	$CH(CH_3)C_2H_5$
14c)	0	CH_2OH
14d)	0	$CH(OH)CH_3$
14e)	0	CH_2-indolyl
14f)	0	$CH_2CH(CH_3)_2$
14g)	1	H
14h)	2	H
14i)	0	$(CH_2)_2CON(CH_2CH_2)_2NCH_3$
14j)	0	$CH_2CON(CH_2CH_2)_2NCH_3$

Scheme 2. Synthesis of compounds (**14a-14j**); Reagents and conditions: (i) amino acids (a to j), $(Boc)_2O$/NaOH, Dioxane/H_2O (1:1), 0 °C; (ii) *N*-methylpiperazine, DCC/ HOBt, THF, 0 °C (iii) 15% HCl/Dioxane; (iv) 4,7-Dichloroquinoline, amines (**13a-13j**), Phenol, 140 °C.



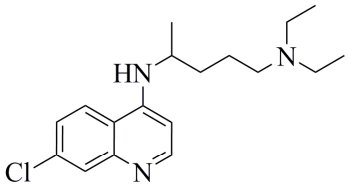
Compound No	R_1
20a)	$CH(CH_3)_2$
20b)	$CH(CH_3)C_2H_5$
20c)	CH_2Ph

Scheme 3. Synthesis of compounds (**20a-20c**); Reagents and conditions: (i) $(Boc)_2O$/NaOH, Dioxane/H_2O, 0 °C; (ii) Mixed anhydride (NMM/ IBCF, -15 °C), CH_2N_2, ether; (iii) Silver benzoate, 1,4-dioxane/H_2O (5:1), refluxing at 70 °C; (iv) *N*-methylpiperazine, DCC/ HOBt, THF, 0 °C; (v) 15% HCl/Dioxane; (iv) 4,7-DCQ, amines (**19a-19c**), Phenol, 140 °C.



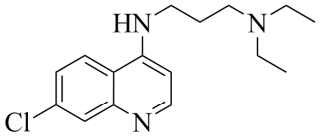
Scheme 4. Synthesis of compound (**30**); Reagents and conditions: (i) Thionyl chloride, methanol, 0 ^{o}C; (ii) $(Boc)_2O$, triethylamine, DCM; (iii) DIBAL-*H*, Dry THF, -78 ^{o}C; (iv) $Ph_3PCHCOOEt$, DCM, 4 h; (v) H_2 , Pd/C, Methanol; (vi) LiOH, THF, H_2O; (vii) NMM, IBCF, *N*-methylpiperazine, -10 °C, 3 h, 95%; (viii) 15% HCl/Dioxane; (ix) 4,7-DCQ, **29**, Phenol, 140 °C.

Fig. 1.



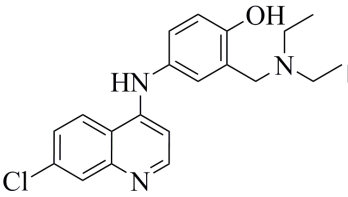
Chloroquine

1



AQ-13

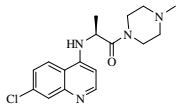
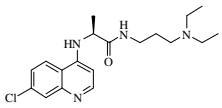
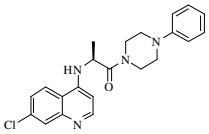
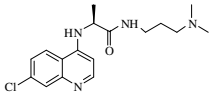
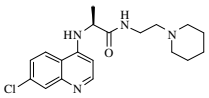
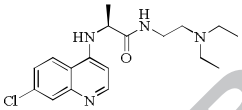
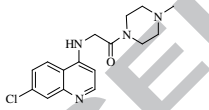
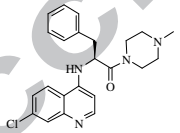
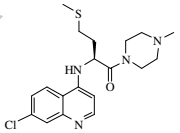
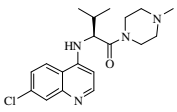
2

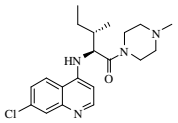
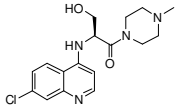
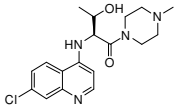
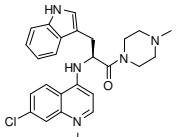
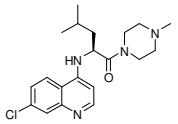
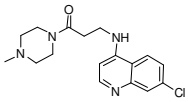
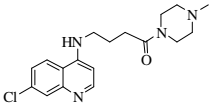
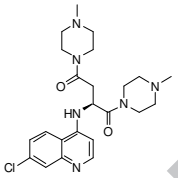
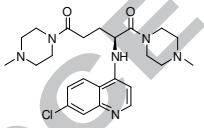
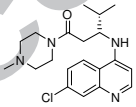
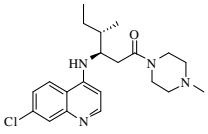
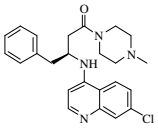


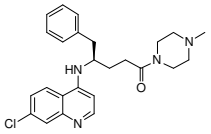
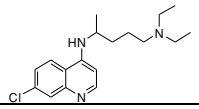
Amodiaquine

3

Table 1 Biological and Biophysical data of the synthesized compounds (**6a-6f, 7a, 8a, 9a, 14a- 14j, 20a-20c, 30**)

Comp no	Structure	IC_{50}(nM)[a]		Resistance Index[b]	SI[c]	Log K[d]	IC_{50}[e]	LogP[f]
		3D7	K1					
6a		73.79	206.6	2.79	2900	5.36±04	0.1677±0.3	1.51
6b		82.64	>500	>6.05	2585	5.27±02	0.2145±0.03	2.3
6c		>500	>500	NA	NA	5.94±03	0.2082±0.05	3.58
6d		142.22	>500	> 3.51	2606	5.34±03	0.1760±0.04	1.62
6e		64.09	>500	> 7.80	3025	5.73±03	0.2166±0.04	2.25
6f		35.37	>500	> 14.13	5834	6.03±03	0.1531±0.01	2.19
7a		149.37	176.69	1.18	1566	7.34±0.02	0.1915±0.03	1.02
8a		108.9	116.4	1.06	429	5.11±0.03	0.6619±0.02	3.18
9a		58.4	128.7	2.20	3821	5.04±02	0.3595±0.03	1.84
14a		270.8	599.3	2.21	1023	6.39±04	0.2349±0.06	2.39

14b		83.82	364.6	4.34	2188	5.72±03	0.2295±0.02	2.81
14c		116.2	925	7.96	1976	5.68±05	0.3604±0.03	0.65
14d		142.5	>1378	> 9.67	1934	6.07±02	0.3837±0.02	0.97
14e		223.1	261.9	1.17	392	6.36±02	0.3302±0.04	2.72
14f		60.16	146.8	2.44	905	5.38±04	0.2283±0.05	2.74
14g		35.89	398.5	11.10	6472	6.43±02	0.3293±0.04	1.31
14h		65.06	780.7	11.99	4432	6.52±03	0.2023±0.06	1.59
14i		47.94	283	5.90	4410	5.62±03	0.2262±0.06	0.30
14j		113.3	712.9	6.29	1923	6.54±03	0.3432±0.05	0.58
20a		44.12	323.5	7.33	6045	5.33±03	0.2286±0.06	2.51
20b		33.03	168	5.08	7613	6.26±04	0.2197±0.05	2.93
20c		19.24	55.29	2.87	5846	5.80±03	0.1739±0.03	3.3

30		11.51	71.16	6.18	11350	5.32±02	0.1961±0.05	3.58
CQ		5.4	255	47.22	8983	5.52±0.02	0.17±0.02	4.5

[a] IC_{50} (nM) : Minimum concentration of compound inducing 50% parasitic cells.

[b]Resistance Index (RI) = IC_{50} K1/IC_{50} 3D7

[c] Selectivity index (SI): (IC_{50} for cytotoxicity to vero cells /IC_{50} for antimalarial activity).

[d] 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).

[e]The IC_{50} represents the milimolar 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).

[f] log P values calculated by using ChemBioDraw ultra software;

NA = Not Applicable

Graphical abstract