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Synthesis of chiral chloroquine and its analogues as antimalarial agents

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ABSTRACT: In this investigation, we describe a new approach to chiral synthesis of chloroquine and its analogues. All tested compounds displayed potent activity against chloroquine sensitive as well as chloroquine resistant strains of *Plasmodium falciparum in vitro* and *Plasmodium yoelli in vivo*. Compounds **S-13b**, **S-13c**, **S-13d** and **S-13i** displayed excellent *in vitro* antimalarial activity with an IC_{50} value of 56.82, 60.41, 21.82 and 7.94 nM, respectively in the case of resistant strain. Furthermore, compounds **S-13a**, **S-13c** and **S-13d** showed *in vivo* suppression of 100% parasitaemia on day 4 in the mouse model against *Plasmodium yoelii* when administered orally. These results underscore the application of synthetic methodology and need for further lead optimization.

Keywords: 4-Aminoquinolines, chiral chloroquine analogs, chloroquine resistant stain

1. Introduction:

Malaria is a protozoan disease of wide occurrence. It is caused by five species of the genus *Plasmodium*, the most lethal form being *Plasmodium falciparum*. According to World Health Organization, it is estimated that 3.4 billion people are at risk and 90% of all malaria deaths occur in sub-Saharan Africa.[1] Drugs with quinoline scaffold (**Fig.1**) have huge significance as antimalarial agents. However, the emergence of chloroquine resistant parasite strains has led to renewed interest in development of antimalarial agents based on chloroquine.[2] Chloroquine (CQ), a 4-aminoquinoline has been in clinical use for more than five decades and it is administered as racemate. It is generally accepted that stereochemistry of a molecule not only affects the pharmacodynamic profile but changes the pharmacokinetic property of a drug molecule. Although there is no difference in the activity of CQ enantiomers in the case of CQ sensitive strain, *in vitro* studies have indicated that (*S*)-CQ is more active than (*R*)-CQ against CQ resistant strain. The plasma protein binding of chloroquine and hydroxychloroquine in human is enantioselective. The (*S*)-enantiomers of both drugs showed more binding to plasma proteins than their respective enantiomers.[3] The antimalarial activity of the two enantiomers of chloroquine has been studied in mice, and it is observed that (*S*)-CQ is more active than the other isomer and also toxicity (LD_{50}) is lower for the (*S*)-enantiomer in the mouse model.[4,5] Later, Fu

and co-workers[6] studied *in vitro* activity of (*S*)- and (*R*)-enantiomers of chloroquine and found that (*S*)-CQ is more active than (*R*)-CQ in CQ resistant strain. There is little information available in the literature on the activity of chiral chloroquine analogs against the CQ-R strains of *P. falciparum*, possibly because of the non availability of chirally pure chloroquine. This background led us to design new generic methodology for chiral synthesis of chloroquine and its analogues.

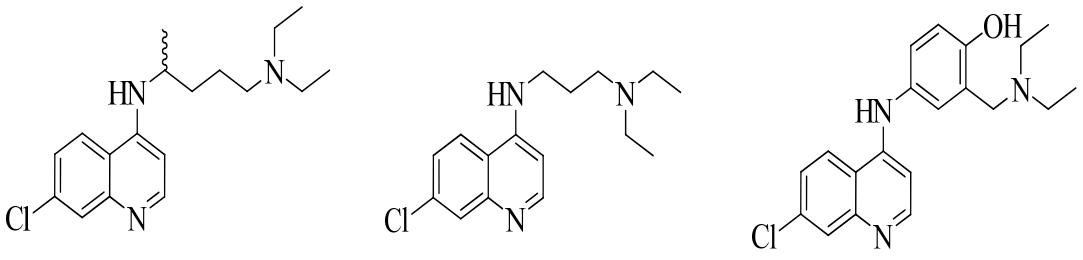


Fig. 1. Structures of some 4-aminoquinoline derivatives with antimalarial activity.

During the literature search, it was observed that there are only two approaches for the synthesis of chiral chloroquine using glutamic acid and pyroglutamic acid as starting materials.[7,8] There are limitations associated with these methods viz., the reaction involves the conversion of carboxylic acid group to methyl which is a low yielding step, secondly, only methyl group could be introduced at the chiral center. In order to optimize substituent group at the chiral carbon, it is important to have a methodology that enables introduction of alkyl/aralkyl substitution at this centre. In the light of these observations, we have developed a new method that involves the homologative olefination for the synthesis of chiral side chain, using L and D-alanine, respectively as shown in Scheme 1. In the present study, we have designed compounds wherein 7-chloro-4-aminoquinoline scaffold as well as carbon chain length was not altered; modifications were carried out only at the pendant amino group (**Fig.2**). The diethylamine function of CQ is replaced by metabolically more stable alkyl amine groups, namely secondary or tertiary terminal nitrogens. The present study describes synthesis, biophysical studies, and antimalarial activity of new series of compounds.

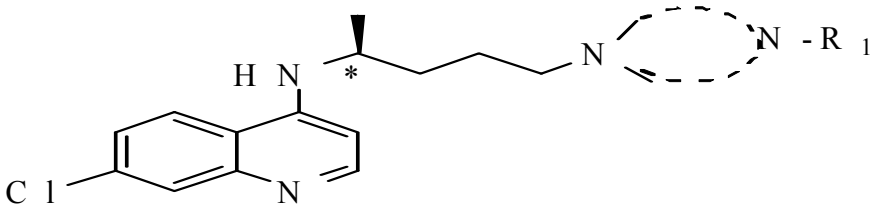
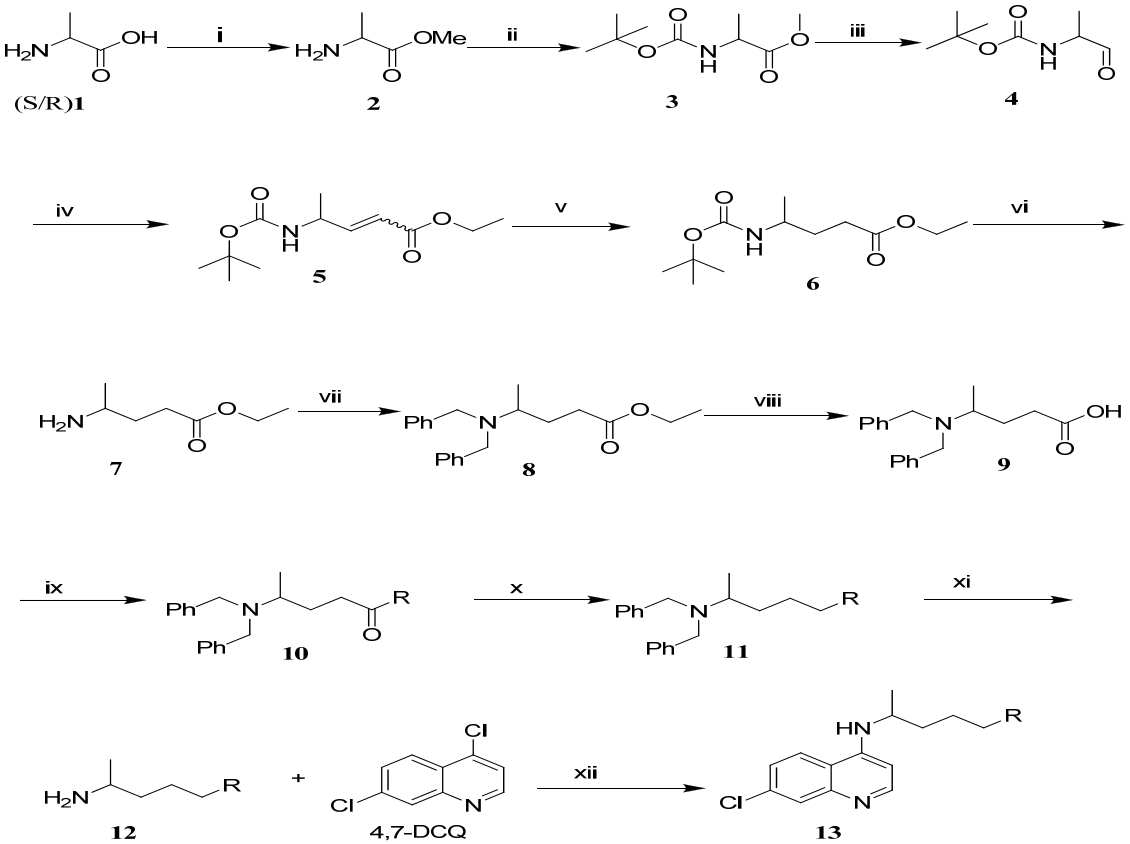


Fig. 2: General structure of compounds synthesized: R= diethylamine, morpholine, pyrrolidine, methylpiperazine, piperidine, dimethylamine, t-butylamine, ethylmethylamine, dioctylamine.

2. Chemistry

The target compounds were prepared as outlined in Scheme 1. The compounds having either (*S*)- or (*R*)-configuration at the chiral carbon in the side chain of chloroquine were synthesized from L- and D-alanine, respectively. The alanine methyl ester (**2**) was prepared by adding thionyl chloride to a suspension of amino acid in methanol and stirring the reaction mixture at 0°C to room temperature.[9] Compound **2** was converted to the corresponding Boc derivative (**3**) by di-*tert*-butylpyrocarbonate in DCM with two equivalents of triethylamine.[10] Boc protected methyl ester was subjected to the DIBAL-H (Diisobutylaluminum hydride) mediated reduction at -78 °C in dry THF to obtain the Boc protected aldehyde (**4**).[11] The aldehyde obtained was highly prone to epimerization and hence, it was used without further purification in the homologation of compound **4** by Wittig reaction to afford olefin (**5**).[12] The olefin (**5**) was hydrogenated at 30 psi, in MeOH 10 % (w/w) Pd/C to get compound **6.** The Boc group of compound (**6**) was deprotected using 15% HCl/Dioxane to obtain the corresponding amine hydrochloride salt (**7**). The amino group was re-protected with dibenzyl group using benzyl bromide in the presence of K_2CO_3 to get compound **8.**[13] Hydrolysis of compound **8** was carried to using LiOH in a 10% water/THF mixture to afford the compound **9**. The dibenzyl protected γ-amino acid (**9**) was converted to the different amides (**10**) by NMM, IBCF protocol.[14] The amides were reduced by using lithium aluminium hydride (LAH) to get the dibenzyl protected diamines (**11**)**.**[8] The dibenzyl protection was removed by catalytic hydrogenation in methanol over 10 % (w/w) Pd/C at 60 psi to get the diamine (**12**)**.** The diamines were fused with 4,7-Dichloroquinoline to get the corresponding chiral chloroquine and its analogues.[15]



R = a. Diethylamine; b. Morpholine; c. Pyrrolidine; d. methyl piperazine; e. Piperidine; f. Dimethylamine; g. t-Butylamine; h. Ethyl methylamine; i. Dioctylamine.

Scheme 1. Synthesis of compounds (**S-13a-i** & **R-14a-i**); Reagents and conditions (i) Thionyl chloride, methanol, 0 ^{o}C, 3h; (ii) $(Boc)_2O$, Triethyl amine, DCM, 0 ^{o}C, 2 h; (iii) DIBAL-H, Dry THF, -78 ^{o}C, 3 h; (iv) $Ph_3PCHCOOEt$, Dry DCM, 0 ^{o}C to rt, 4 h; (v) Pd/C, Methanol, H_2, 30 psi, rt, 2 h; (vi) 15% HCl/Dioxane; (vii) BnBr, K_2CO_3, Acetonitrile, reflux, 4 h; (viii) LiOH, THF/ Water, 0 ^{o}C to rt; (ix) NMM, IBCF, amines a to i, -10 ^{o}C, 3 h; (x) LAH, Dry THF, Reflux, 4 h; (xi) Pd/C, Methanol, H_2, 60 psi, rt, 5 h; (xii) Phenol, 140 ^{o}C, 12 h.

3. Results and Discussion

3.1. *In vitro* antimalarial activity

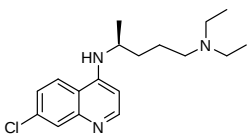
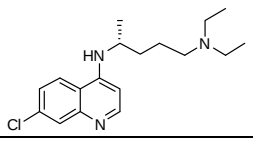
The synthesized compounds were evaluated for *in vitro* antimalarial activity against chloroquine sensitive (3D7) and resistant strains (K1) of *P. falciparum.* A comparative study of antimalarial activities of both the enantiomers of chloroquine and its analogs is presented in Table 1. The obtained results clearly indicate that (*S*)-enantiomers are consistently showing better antimalarial activity than the corresponding (*R*)-enantiomers against K1 strain of *P. falciparum*. However, in case of 3D7 strain, it was found that the antimalarial activity is not enantioselective and this is in consonance with the earlier reports.[6] Majority of the enantiomeric pairs exhibited good to moderate activity against 3D7 strain, with IC_{50} values ranging from 4.66 to 94.76 nM. It is apparent from the activity data presented in Table 1 three compounds **R-13d**, **R-13f** and **R-13g** displayed promising activity 6.92, 6.0 and 4.66 nM respectively, ten compounds displayed moderate activity with IC_{50} values ranging from 7.45 nM to 17.13 nM, and five compounds exhibited IC_{50} values between 28.1 nM to 94.76 nM. Furthermore, In the case of resistance strain, four compounds, namely **S-13b, S-13c, S-13d** and **S-13i** were found to be most active, with IC_{50} values 56.82, 60.41, 21.82, and 7.95 nM respectively, five compounds displayed 105.22 to 126.34 nM range, three compounds showed IC_{50} values between 202.46 to 287.31 nM, four compounds elicited nM range between 357.77 to 535.52 while enantiomeric pairs of **13g** did not exhibit antimalarial activity at the highest concentration tested (IC_{50} > 1563 nM) against K1 strain.

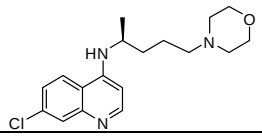
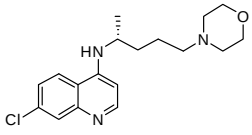
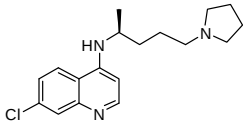
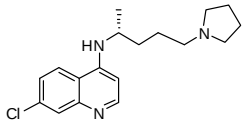
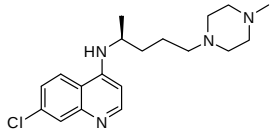
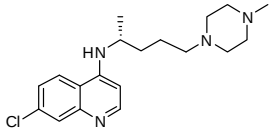
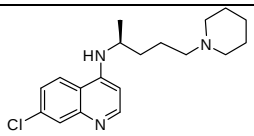
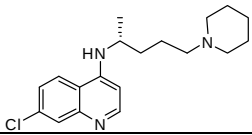
The enantiomeric pairs of chloroquine did not show considerable difference in activity against both 3D7 and K1 strains. Whereas, enantiomeric pairs of chloroquine analogues synthesized in the present study exhibited significant differences in the *in vitro* antimalarial activity against sensitive and resistant strains. More particularly, enantiomeric pairs **13e** and **13i** showed large difference in terms of activity against resistant strain. Overall, compounds **S-13d** and **S-13i** bearing *N*-methylpiperazine and di-octyl amine as pendant side chain emerged as the most active compounds against CQ-R strain. Compounds **R-13f** and **R-13g** containing dimethyl amine and *tert*-butyl amine as pendant side chain respectively emerged as the most active compounds against 3D7 strain. It is believed that smaller the resistance factor, the less likely is the chance of developing resistance to that class of compounds.[16] Based on this observation, it may be inferred from the data presented in Table 1 that a few compounds in the present study are less likely prone to develop resistance and this is a desirable property.

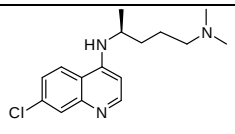
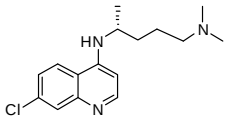
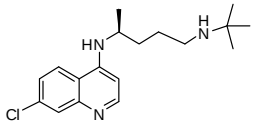
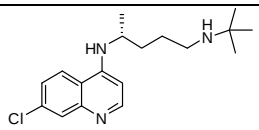
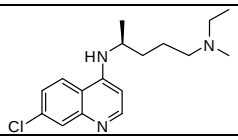
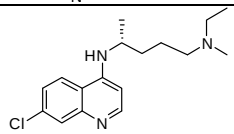
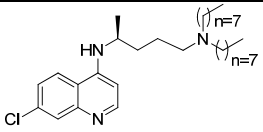
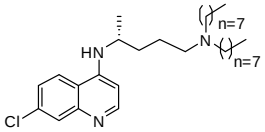
3.2. *In vivo* antimalarial activity

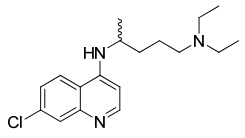
The enantiomeric pairs of chloroquine **13a** and its analogues namely, **13c**, **13d**, **13i,** and only (*S*)-enantiomer of **13b** displayed good potency (Table 1) and were evaluated for *in vivo* activity against innately chloroquine resistant *P. yoelii* (N-67 strain) in Albino mice of Swiss strain. Initially, the *in vivo* activity of selected molecules were determined through oral route at the dose of 100 mg/kg administered once daily for seven consecutive days and monitored for parasitaemia reduction, and survival of mice until day 28 post-infection (Table 2). Enantiomeric pairs of **13a** displayed 100% parasitaemia suppression on day 4 and 60% survival on day 28 of treatment but none of them were cured. Similarly, compound **13b** showed 99.6% parasitaemia suppression on day 4 at a dose of 100mg/kg for 4 days and all mice survived up to day 28 although none of them were cured. A significant result has been observed in the case of enantiomeric pairs of **13c**. (*S*)-enantiomer of **13c** displayed 100% parasitaemia suppression on day 4 and 80% survival on day 28 of post-infection whereas in the case of (*R*)-enantiomer of **13c** 100% parasitaemia suppression on day 4 was observed but none of the mice survived up to day 28. Compound **S-13d** was found the most promising at a dose of 100 mg/kg for 7 days which cured 4 mice out of 5 with 100% inhibition of parasitemia up to day 28. Whereas, the corresponding enantiomer **R-13d** showed lesser activity at a dose of 100 mg/kg for 7 days, which cured 2 mice out of 5 with 100% inhibition of parasitemia on day 4 and all mice survived up to day 28. Surprisingly, the most promising compound **S-13i** as per *in vitro* data showed only 14.5% inhibition on day 4 and its enantiomer **R-13i** suppressed only 9.5% parasitemia on day 4 and none of the mice in both groups survived up to day 28. It may be inferred from the above data that (*S*)-enantiomers of chloroquine analogues exhibited higher antimalarial activity compared to their corresponding (*R*)-enantiomers particularly against resistant strain. Whereas, in the case of chloroquine enantiomers the difference in the activity is minimum. The results discussed in the foregoing paragraph offer unique opportunity to explore the impact of different substituent groups at the chiral carbon, on the biological activity, further, this may lead to design and synthesis of compounds having activity against MDR resistant parasite.

Table 1 Biological and Biophysical data of the synthesized compounds (**S13a-i** and **R13a-i)**

Compound no	Structure	IC_{50}(nM)[a]		Resistance Index[b]	SI[c]	Log K[d]	IC_{50}[e]	LogP[f]
		3D7	K1					
S-13a		10.94	483.63	44.20	2,574	5.28±0.02	0.16±0.03	3.73
R-13a		9.54	517.62	54.25	18,642	5.77±0.04	0.16±0.07	3.73

S-13b		14.02	56.82	4.05	19,256	6.00 ±0.05	0.19±0.03	2.65
R-13b		28.1	105.92	3.76	4,186	5.69±0.02	0.15±0.05	2.65
S-13c		15.76	60.41	3.83	1,469	5.19±0.03	0.18±0.05	3.37
R-13c		10.19	124.71	12.23	14,140	6.02±0.04	0.14±0.06	3.37
S-13d		14.21	21.82	1.53	14,744	4.73±0.05	0.14±0.02	2.81
R-13d		6.92	105.22	15.20	18,245	5.53±0.05	0.18±0.03	2.81
S-13e		14.95	120.95	8.09	20,154	5.4 ±0.02	0.15±0.05	3.78
R-13e		52.85	535.52	10.13	4,257	7.19±0.02	0.13±0.03	3.78

S-13f		17.13	357.77	20.88	12,483	4.95±0.04	0.15±0.04	3.05
R-13f		6	202.46	33.74	28,483	5.77±0.02	0.19±0.04	3.05
S-13g		32.95	>1563	>47.43	7,100	5.04±0.03	0.15±0.81	3.55
R-13g		4.66	>1563	>335	24,459	5.71±0.03	0.17±0.03	3.55
S-13h		12.39	258.44	20.85	26,389	5.61±0.02	0.15±0.03	3.39
R-13h		7.78	287.31	36.92	15,838	3.63±0.01	0.14±0.05	3.39
S-13i		94.76	7.95	11.91	103.94	5.58±0.04	0.20±0.02	8.87
R-13i		78.58	126.34	1.60	44.28	5.02±0.01	0.19±0.04	8.87

CQ		4.75±2.0	287.89±49.7	60.60	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;

Table 2. *In-vivo* antimalarial activity of selected compounds against CQ resistant (N-67) in Albino mice of Swiss strain.

Compound code	Dose	Route of administration	Percent suppression on day 4 postinfection	Survival[a]	Cure[b]
S-13a	100 mg/kg x 7 days	oral	100	3/5	0/5 cured
R-13a	100 mg/kg x 7 days	oral	100	3/5	0/5 cured
S-13b	100 mg/kg x 4 days	oral	99.6	5/5	0/5 cured
S-13c	100 mg/kg x 7 days	oral	100	4/5	0/5 cured
R-13c	100 mg/kg x 7 days	oral	100	0/5	0/5 cured
S-13d	100 mg/kg x 7 days	oral	100	5/5	4/5 cured
R-13d	100 mg/kg x 7 days	oral	100	5/5	2/5 cured
S-13i	100 mg/kg x 7 days	oral	14.5	0/5	0/5 cured
R-13i	100 mg/kg x 7 days	oral	9.5	0/5	0/5 cured
CQ	20 mg/kg x 4 days	oral	99.0	5/5	0/5 cured

[a] Number of mice that survived till day 28 postinfection/total mice in the group.

[b] Number of mice without parasitaemia (cured) till day 28 postinfection.

3.3. In vitro cytotoxicity

The cytotoxicity of all the synthesized molecules was determined against VERO cell line using MTT assay (Table 1). Remarkably, most of the compounds showed high selectivity indices. A few molecules exhibited selectivity index (SI) approximately in the range 45 to 7,000. Whereas, eleven molecules displayed high selectivity index ranging between 12,483 and 28,483, some of the compounds namely, **R-13d**, **R-13f**, and **R-13g** having potent activity against 3D7 strain also showed good selectivity index 18,245, 28,483, 24,459, respectively. Furthermore, compounds **S-13b** and **S-13d** which were most potent against resistance strain K1 also exhibited good SI values 19,256 and 14,744, respectively. In general, most of the compounds of the series exhibited promising activity against K1 strain, less cytotoxic effect with fairly high selectivity index, and as a result these chiral chloroquine derivatives are good candidate for further lead optimization.

3.4. In vitro inhibition of β-hematin polymerization

The results of heme binding assay (Table1) showed that all the synthesized compounds interact with the heme. The association constants for different compounds were obtained in the range of 6.63 to 7.19. These results indicate that the principal interaction might be involving π-π stacking interaction of the quinoline ring with the porphyrin ring system. The results of β-hematin formation inhibition assay showed that these derivatives inhibited β-hematin formation in a concentration dependent manner. The IC_{50} obtained was in the range of 0.13 to 0.20 and the most active compound **S-13d** exhibited IC_{50} (0.14±0.02). Furthermore, data suggest that this class of compounds bind to hematin monomer and inhibit the hemozoin formation by blocking the growing face of the crystal by a capping effect.[16]

4. Conclusion

In summary, we have developed a generic methodology for the synthesis of chiral chloroquine and its analogues. The *in vitro* and *in vivo* data clearly indicate that (*S*)-isomers are more active than (*R*)-isomers against CQ resistant strain of *P. falciparum*. The difference in antimalarial activity between enantiomeric pairs is also noticeable against 3D7 strain. The results offer attractive method for designing of molecules with chirally defined architecture and tailored pendant groups with improved activity against K1 parasite.

5. Biological assay

5.1. *In vitro* antimalarial assay

The compounds were evaluated for antimalarial activity against 3D7 and K1 strains of *P. falciparum* using Malaria SYBR Green I nucleic acid staining dye based fluorescence (MSF) assay as mentioned by Singh et al.[17] The stock (5 mg/mL) solution was prepared in DMSO and test dilutions were prepared in culture medium (RPMI-1640-FBS). Chloroquine diphosphate was used as reference drug.

5.1.1 Test technique:

50mL of culture medium was dispensed in 96 well plate followed by addition of 50mL of highest concentration of test compounds (in duplicate wells) in row B. Subsequent two-fold serial dilutions were prepared and finally 50mL of 1.0% parasitized cell suspension containing 0.8% parasitaemia 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 h later 100µL of lysis buffer containing 2x concentration of SYBR Green-I (in Nitrogen) was added to each well and incubated for 1 h at 37 °C. The plates were examined at 485±20 nm of excitation and 530±20 nm of emission for relative fluorescence units (RFUs) per well using the fluorescence plate reader (FLX800, BIOTEK)

5.1.2. Statistical analysis:
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.

5.1.3. 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 M. Sinha et al.[18] 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 $SI = CC_{50}/IC_{50}$

5.1.4. In vivo antimalarial assay
The *in vivo* drug response was evaluated in Albino mice of Swiss strain infected with *P. yoelii* (N-67 strain) which is innately resistant to CQ.[19] The mice (22±2 g) were inoculated with $1x10^6$ parasitized RBC on day 0 and treatment was administered to a group of five mice from day 0-6, once daily. The aqueous suspensions of compounds were prepared with a few drops of Tween 80. The efficacy of test compounds was evaluated at 100 mg/kg/day and the required daily dose was administered in 0.5mL volume via oral route. Parasitemia levels were recorded from thin blood smears at regular intervals of four days throughout the period of experiment. The mean value determined for a group of five mice was used to calculate the percent suppression of parasitemia with respect to the untreated control group. Mice treated with CQ served as reference controls.

5.1.5. Determination of hematin-4-aminoquinoline derivatives association constant
Association constant for the compounds synthesized in the present study were determined by spectrophotometric titration procedure in aqueous DMSO at pH 7.5.[20] 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.

5.1.6. In vitro Inhibition of β-hematin formation assay
The ability of the 4-aminoquinoline derivatives to inhibit β-Hematin polymerization was induced by 1-oleoyl-rac-glycerol using UV spectrophotometer and measurements were carried out at 405 nm.[21] 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 Graph Pad Prism 30 v.3.00 software.[22] Each IC_{50} value is the result of at least three separate experiments performed in duplicate..

6. Experimental Protocols

6.1. General information

The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ solvent 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 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 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) and Spectrochem Pvt. Ltd (India) and were used without further purification**.**

6.2 Synthesis of compounds 2 to 9:

6.2.1. (*S*)-Methyl-2-aminopropanoate (2): To a suspension of (*S*)-alanine (8.9 g, 0.1 mol) in 100 mL methanol, thionyl chloride (14.6 mL, 0.2 mol) was added slowly at 0 °C and stirred for 4 h. After the completion of reaction (as monitored by TLC), the reaction mixture was concentrated in vacuo and crystallized by dry ether to give the product. (Yield: 13.5g, 97%).

6.2.2. (*S*)-Methyl-2-(*tert*-butoxycarbonylamino)-propanoate (**3**): To a solution of L-alanine methyl ester hydrochloride (13.5 g, 96.7 mmol) in dry dichloromethane (DCM) equimolar amount of triethylamine (14 mL, 96.7 mmol) was added under 0°C. To this solution di-*tert*-butylpyrocarbonate (23.13 g, 106.39 mmol) was added and the stirring was continued for 1h at 0 °C and followed 1h at room temperature. After completion of the reaction organic layer washed with sodium bicarbonate, brine solution and dried over Na_2SO_4 and solvent was concentrated in vacuo. The compound **3** was obtained as gummy residue; yield: 19.9 g, (98%).^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.38 (d, J = 6.3 Hz, 3H, CHCH_3), 1.46 (s, 9H, C(CH_3)$_3$) , 3.76 (s, 3H, OCH_3), 4.32 (br s, 1H, NHC*H*), 5.05 (br. s, 1H, N*H*). ESI-MS: *m/z* 204 $(M+H)^+$.

6.2.3. (*S*)-*Tert*-butyl-1-oxopropan-2-ylcarbamate (4): To a solution of **3** (10.15 g, 50 mmol) in dry THF (100 mL, 100 mmol) of diisobutylaluminum hydride (1 M solution in cyclohexane) was added under -80 °C via needle over a period of 45 minutes while maintaining the internal temperature below -69 °C. The mixture was stirred for 3 h, 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 Na_2SO_4, and concentrated. The crude product thus obtained was kept at -20 °C for next step. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.28 (d, J = 6.5 Hz, 3H, CHCH_3), 1.42 (s, 9H, C(CH_3)$_3$) 4.1 (br. s, 1H, NHC*H*), 5.20 (br. s, 1H, N*H*), 9.52 (s, 1H, C*H*O).

6.2.4. (*S*)-(*E*)-Ethyl-4-(*tert*-butoxycarbonylamino)-pent-2-enoate (5): The crude product **4** dissolved in dry DCM (50 mL) at 0 °C $EtOOCCH{=}PPh_3$ (50 mmol) was added and the solution stirred for 2-3 h. After completion of the reaction (as monitored by TLC), the usual work up was done and the organic layer was dried over Na_2SO_4, and concentrated on a rotary evaporator to give the crude product. This was purified by column chromatography using 11% EtOAc and hexane as eluent. Product was obtained as gummy residue; yield: 6.1 g, (70%), after 2 steps). ^{1}H NMR ($CDCl_3$, 300 MHz) **δ:** (E-isomer) 1.24-1.31 (m, 6H, CHC*H*$_3$, CH_2CH_3), 1.43 (s, 9H, $C(CH_3)_3$), 4.13-4.23 (m, 2H, $COOCH_2CH_3$), 4.39 (br s, 1H, NHC*H*), 4.52 (br s,1H, N*H*), 5.85 (d, *J* = 15.6 Hz, 1H, CH=C*H*), 6.81-6.91 (dd, *J* = 15.5 Hz, 4.0 Hz, 1H, CH-C*H*=CH).

6.2.5. (*S*)-Ethyl-4-(*tert*-butoxycarbonylamino)-pentanoate (6): To a solution of **5** (6.1g, 25.1 mmol) in MeOH 10 % (w/w) Pd/C 0.61 g was added. The apparatus flushed two times with hydrogen gas, and the mixture was agitated at room temperature for 2 h under hydrogen gas, at 30 Psi. The solution was filtered through Celite and concentrated under reduced pressure to afford the **6** as gummy residue. It was used without further purification. (Yield: 6.1 g, quantitative). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.08 (d, *J* = 6.4 Hz, 3H, CHC*H*$_3$), 1.18-125 (t, *J* = 7.0 Hz 3H, CH_2CH3), 1.39 (s, 9H, $C(CH_3)_3$), 1.66-1.76 (m, 2H, CHC*H*$_2$), 2.28-2.35 (t, *J* = 7.4 Hz, 2H, CH_2CH_2), 4.03 (m, 2H, COOC*H*$_2$), 4.27 (br s, 1H, NHC*H*).

6.2.6. (*S*)-Ethyl-4-aminopentanoate hydrochloride (7): Compound **6** was stirred for 1h at 0 °C with 15% HCl/Dioxane. After completion of the reaction, solvent was evaporated and the residue was scratched in diethyl ether. Solid obtained was filtered dried and used for next step. Product obtained as white solid. (Yield: 4.54 g, quantitative). ESI-MS: *m/z* 146 $(M+H)^+$

6.2.7. (*S*)-Ethyl-4-(dibenzylamino)-pentanoate (8): To a solution of **7** (4.54g, 25 mmol) in 50 mL acetonitrile, benzyl bromide (12.8g, 75 mmol) and (13.8g, 100 mmol) of K_2CO_3 were added. Reaction mixture was refluxed for 3 h. After completion of the reaction (as monitored by TLC), acetonitrile was evaporated and water was added to it. Reaction mixture was extracted with ethyl acetate and washed with brine and dried over Na_2SO_4. The crude product was purified by column chromatography using 3% of ethyl acetate and hexane as eluent. Compound **8** was obtained as light yellow gummy residue in (8.12 g) quantitative yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.05 (d, *J* = 6.4 Hz, 3H, CHC*H*$_3$), 1.21-1.26 (t, *J* = 7.0 Hz 3H, CH_2CH_3), 1.62-1.67 (m, 1H, CHCH*H*), 1.87-1.93 (m, 1H, CHCH*H*), 2.26-2.35 (m, 1H, CH_2CH*H*), 2.48-2.56 (m, 1H, CH_2CH*H*), 2.71-2.78 (m, 1H, NHC*H*), 3.37 (d, *J* = 13.7 Hz, 2H, C*H*$_2$Ph), 3.74 (d, *J* = 13.6 Hz, 2H, C*H*$_2$Ph), 4.03-4.10 (m, 2H, COOC*H*$_2$), 7.21-7.39 (m, 10H, Ar-*H*).ESI-MS: *m/z* 326 $(M+H)^+$

6.2.8. (*S*)-4-(Dibenzylamino)-pentanoic acid (9): To a solution of **8** (8.0 g, 24.6 mmol) in 40 mL of THF, LiOH (4.2 g, 100 mmol) in 4.0 mL water was added. The mixture was stirred at rt. for 30 h. THF was evaporated and it was neutralized with citric acid solution to (pH 7) then extracted with ethyl acetate 25 mL (2 x), the organic phases were washed with saturated NaCl solution, dried over sodium sulfate and evaporated. The crude product was purified by column chromatography. Compound **9** was obtained as gummy residue; yield: 7.12 g, (97%).^{1}H NMR ($CDCI_3$, 300 MHz) δ: 1.13 (d, *J* = 6.6 Hz, 3H, CHC*H*$_3$), 1.49-1.55 (m, 1H, CHCH*H*), 1.95-2.08 (m, 1H, CHCH*H*), 2.21-2.31 (m, 1H CH_2CH*H*), 2.40-2.48 (m, 1H, CH_2CH*H*), 2.92-2.94 (m. 1H, NHC*H*), 3.37 (d, *J* = 13.7 Hz, 2H, C*H*$_2$Ph), 3.92 (d, *J* = 13.6 Hz, 2H, C*H*$_2$Ph), 7.30-7.41 (m, 10H, Ar-*H*).

7.0 General procedure for the synthesis of compounds 10a to 10i

To a solution of **9** (2 mmol) in anhydrous THF, NMM (2 mmol) and IBCF (2 mmol) were added successively at -15 ºC under vigorous stirring. The temperature was maintained at -15 ºC for 10 min. Subsequently amine (2.5 mmol) was added to the reaction mixture. The reaction was stirred at -15 ºC for 15 min and then allowed to stirr at rt for additional 2 h. 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.

7.1. (*S*)-4-(Dibenzylamino)-*N,N*-diethylpentanamide (10a): This compound was obtained as gummy residue; yield: 600 mg, (85%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.07-1.18 (m, 9H, CHC*H*$_3$, 2 CH$_2$C*H*$_3$,) 1.63-1.70 (m, 1H, CHCH*H*), 1.88-1.92 (m, 1H, CHCH*H*), 2.06-2.15 (m, 1H, CH$_2$CH*H*), 2.52-2.58 (m, 1H, CH$_2$CH*H*), 2.72-2.79 (m, 1H, NHC*H*), 3.21-3.37 (m, 4H, 2C*H*$_2$CH$_3$), 3.38 (d, *J* = 13.7 Hz, C*H*$_2$Ph), 3.74 (d, *J* = 13.7 Hz, C*H*$_2$Ph), 7.20-7,38 (m, 10H, Ar-*H*): ESI-MS: *m/z* 353 $(M+H)^+$.

7.1.1. (*S*)-4-(Dibenzylamino)-1-morpholinopentan-1-one (10b): This compound was obtained as gummy residue; yield: 622 mg, (85%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.07 (d, *J* = 6.48 Hz, 3H, CHC*H*$_3$), 1.64 (br s, 1H, CHCH*H*), 1.85-1.97 (m, 1H, CHCH*H*), 2.15-2.20 (m, 1H, CH$_2$CH*H*), 2.44-2.50 (m, 1H CH$_2$CH*H*), 2.71-2.74 (m, 1H, NHC*H*), 3.36-3.39 (m, 12H, N(C*H*$_2$)$_2$, 2C*H*$_2$Ph, O(C*H*$_2$)$_2$), 7.22-7.39 (m, 10H. Ar-*H*): ESI-MS: *m/z* 366 $(M+H)^+$.

7.1.2. (*S*)-4-(Dibenzylamino)-1-(pyrrolidin-1-yl)-pentan-1-one (10c): This compound was obtained gummy residue; yield: 598 mg, (85%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.06 (d, *J* = 6.48 Hz, 3H, CHC*H*$_3$), 1.52-1.68 (m, 5H, cycNCH$_2$C*H*$_2$C*H*$_2$CH$_2$, CHCH*H*), 1.84-1.94 (m, 1H, CHCH*H*), 2.08-2.19 (m, 1H, CH$_2$CH*H*), 2.51-2.57 (m, 1H CH$_2$CH*H*), 2.68-2.73 (m, 1H, NHC*H*), 3.32-3.55 (m, 2H, NC*H*$_2$), 3.38 (d, *J* = 13.71 Hz, 2H, C*H*$_2$Ph), 3.45-3.55 (m, 2H, NC*H*$_2$), 3.73 (d, *J* = 13.71 Hz, 2H, C*H*$_2$Ph), 7.20-7.38 (m, 10H, Ar-*H*): ESI-MS: *m/z* 352 $(M+H)^+$.

7.1.3. (*S*)-4-(Dibenzylamino)-1-(4-methylpiperazin-1-yl)-pentan-1-one (10d): The compound was obtained gummy residue; yield: 591 mg, (78%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.09 (d, *J* = 6.51 Hz, 3H, CHC*H*$_3$), 1.27 (br s, 1H, CHCH*H*), 1.59-1.68 (m, 1H, CHCH*H*), 1.88-1.97 (m, 1H, CH$_2$CH*H*), 2.15-2.20 (m, 1H, CH$_2$CH*H*), 2.49 (s, 3H, NC*H*$_3$), 2.53-2.61 (m, 4H, N(C*H*$_2$)$_2$), 2.69 (br s, 1H, NHC*H*), 3.42 (d, *J* = 13.71 Hz, 2H, C*H*$_2$Ph), 3.70-3.90 (m, 6H, C*H*$_2$Ph, N(C*H*$_2$)$_2$), 7.24-7.37 (m, 10H, Ar-*H*): ESI-MS: *m/z* 380 $(M+H)^+$.

7.1.4. (*S*)-4-(Dibenzylamino)-1-(piperidin-1-yl)-pentan-1-one (10e): This compound was obtained gummy residue; yield: 600 mg, (83%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.34 (d, *J* = 6.51 Hz, 3H, CHC*H*$_3$), 1.61-1.77 (m, 8H, CHC*H*$_2$CH$_2$, cycNCH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_2$), 2.08-2.40 (m, 2H, CHCH$_2$C*H*$_2$), 3.11-3.16 (m, 1H, NHC*H*), 3.30-3.33 (m, 2H, NC*H*$_2$), 3.31-3.52 (m, 2H, NC*H*$_2$), 3.85 (d, *J* = 13.65Hz, 2H, C*H*$_2$Ph), 3.05 (d, *J* = 13.71Hz, 2H, C*H*$_2$Ph), 7.28-7.42 (m, 10H, Ar-*H*): ESI-MS: 365 $(M+H)^+$.

7.1.5. (*S*)-4-(Dibenzylamino)-*N,N*-dimethylpentanamide (10f): This compound was obtained gummy residue; yield: 522 mg, (80%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.06 (d, *J* = 6.48 Hz, 3H, CHC*H*$_3$), 1.65-1.70 (m, 1H, CHCH*H*), 1.82-1.94 (m, 1H, CHCH*H*), 2.13-2.23 (m, 1H,

$CH_2CH\mathit{H}$), 2.45-2.55 (m, 1H, $CH_2CH\mathit{H}$), 2.69-2.76 (m, 1H, NHC*H*), 2.89 (d, *J* = 15.51 Hz, 6H, $N(C\mathit{H}_3)_2$), 3.37 (d, *J* = 13.71 Hz, 2H, $C\mathit{H}_2$Ph), 3.74 (d, *J* = 13.71 Hz, 2H, , $C\mathit{H}_2$Ph), 7.19-7.36 (m, 10H, Ar-*H*): ESI-MS: *m/z* 325$(M+H)^+$.

7.1.6. (*S*)-*N*-*Tert*-butyl-4-(dibenzylamino)-pentanamide (10g): This compound was obtained as gummy residue; yield: 602 mg, (85%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.05 (d, *J* = 6.57 Hz, 3H), 1.29 (s, 9H), 1.54-1.68 (m, 1H), 1.84 (m, 1H), 1.97 (m, 1H), 2.24-2.33 (m, 1H), 2.68-75 (m, 1H), 3.41 (d, *J* = 13.71 Hz, 2H), 3.74 (d, *J* = 13.71 Hz, 2H), 7.21-7.40 (m, 10H): ESI-MS: *m/z* 353 $(M+H)^+$.

7.1.7. (*S*)-4-(dibenzylamino)-*N*-ethyl-*N*-methylpentanamide (10h): This compound was obtained gummy residue; yield: 521 mg, (77%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.04 (d, *J* = 6.48 Hz, 3H, $CHC\mathit{H}_3$), 1.08-1.14 (t, *J* = 7.17 Hz, 3H, $NCH_2C\mathit{H}_3$), 1.63 (br s, 1H, CHCH*H*), 1.82-2.01 (m, 1H, CHCH*H*), 2.06-2.19 (m, 1H, $CH_2CH\mathit{H}CH_2$), 2.45-2.68 (m, 1H, $CH_2CH\mathit{H}CH_2$), 2.70-2.75 (m, 1H, NHC*H*), 2.87 (d, *J* = 10.89 Hz, 3H, $NC\mathit{H}_3$), 3.26-3.34 (m, 2H, $NC\mathit{H}_2$), 3.37 (d, *J* = 13.71Hz, 2H, $C\mathit{H}_2$Ph), 3.73 (d, *J* = 13.71 Hz, 2H, $C\mathit{H}_2$Ph), 7.22-7.37 (m, 10H, Ar-*H*): ESI-MS: *m/z* 339 $(M+H)^+$.

7.1.8. (*S*)-4-(Dibenzylamino)-*N,N*-dioctylpentanamide (10i): This compound was obtained as gummy residue; yield: 830 mg, (80%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.91-0.94 (t, *J* = 5.4 Hz, 6H, $N((CH_2)_7C\mathit{H}_3)_2$), 1.07 (d, *J* = 6.48 Hz, 3H, $CHC\mathit{H}_3$), 1.30 (d, *J* = 5.6 Hz, 20H, $(NCH_2CH_2(C\mathit{H}_2)_5)_2$, 1.55 (br s, 4H, $N(CH_2C\mathit{H}_2)_2$, 1.86-2.21 (m, 2H $CHC\mathit{H}_2$), 2.53-2.80 (m, 2H, $CH_2C\mathit{H}_2CH_2$), 3.14-3.33 (m, 5H, $N(C\mathit{H}_2)_2$,NHC*H),* 3.38 (d, *J* = 13.71 Hz, 2H, $C\mathit{H}_2$Ph), 3.75 (d, *J* = 13.71 Hz, 2H, $C\mathit{H}_2$Ph), 7.20-7.41 (m, 10H, Ar-*H*): ESI-MS: *m/z* 521 $(M+H)^+$.

8.0 General procedure for the synthesis of compounds 11a to 11i

To a solution of **10a-10i** (1.7 mmol) in 25 mL of dry THF, LAH (3.06 mmol) was added at 0 °C. The mixture was refluxed for 4 h. After cooling, saturated ammonium chloride was added drop wise with vigorous stirring, precipitate formed was filtered off with suction and washed with diethyl ether. The organic layer was dried over anhydrous Na_2SO_4, evaporated under reduced pressure and purified by column chromatography.

8.1. (*S*)-N^4,N^4-Dibenzyl-N^1,N^1-diethylpentane-1,4-diamine (11a): This compound was obtained as gummy residue; yield: 405 mg, (70%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.02-1.05 (m, 9H, $CHC\mathit{H}_3$, 2 $CH_2C\mathit{H}_3$), 1.36-1.43 (m, 2H, $CH_2C\mathit{H}_2$ CH_2), 1.57-1.66 (m, 2H, $CHC\mathit{H}_2$), 2.31-2.36 (t, *J* = 7.65 Hz, 2H, $CH_2C\mathit{H}_2NEt_2$), 2.48-2.55 (m, 4H, $NC\mathit{H}_2(C\mathit{H}_2)$, 2.69-2.76 (m, 1H, NHC*H*), 3.41 (d, *J* = 13.71 Hz, 2H, $C\mathit{H}_2$Ph), 3.70 (d, *J* = 13.71 Hz, 2H, $C\mathit{H}_2$Ph), 7.19-7.41 (m, 10H, Ar-*H*): ESI-MS: *m/z* 338 $(M+H)^+$.

8.1.1. (*S*)-*N,N*-Dibenzyl-5-morpholinopentan-2-amine (11b): This compound was obtained as gummy residue; yield: 420 mg, (70%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.02 (d, *J* = 6.54 Hz, 3H, $CHC\mathit{H}_3$), 1.24-1.54 (m, 2H, $CH_2C\mathit{H}_2$ CH_2), 1.56-1.69 (m, 2H, $CHC\mathit{H}_2$), 2.19-2.24 (t, *J* = 7.38 Hz, 2H, $CH_2C\mathit{H}_2N(CH_2)_2$), 2.36-2.39 (t, *J* = 4.35 Hz, 4H, $N(C\mathit{H}_2)_2$), 2.69-2.76 (m, 1H, NHC*H*), 3.40 (d, *J* = 13.71 Hz, 2H, $C\mathit{H}_2$Ph), 3.69-3.74 (m, 6H, $C\mathit{H}_2$Ph, $O(C\mathit{H}_2)_2$), 7.19-7.40 (m, 10H, Ar-*H*): ESI-MS: *m/z* 353 $(M+H)^+$.

8.1.2. (*S*)-*N,N*-Dibenzyl-5-(pyrrolidin-1-yl)-pentan-2-amine (11c): This compound was obtained as gummy residue; yield: 401 mg, (70%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.06 (d, *J* = 6.48 Hz, 3H, CHC*H*$_3$), 1.27-1.34 (m, 6H, cycNCH$_2$C*H*$_2$C*H*$_2$CH$_2$, CH$_2$C*H*$_2$ CH$_2$), 1.63-1.72 (m, 2H, CHC*H*$_2$), 1.85-1.91 (m, 2H, CH$_2$C*H*$_2$N(CH$_2$)$_2$), 2.06 (br s, 4H, CH$_2$N(C*H*$_2$)$_2$), 2.65-2.71 (m, 1H, NHC*H*), 3.33 (d, *J* = 13.71 Hz, 2H, C*H*$_2$Ph), 3.69 (d, *J* = 13.71 Hz, 2H, C*H*$_2$Ph), 7.24-7.34 (m, 10H, Ar-*H*): ESI-MS: *m/z* 337 (M+H)$^+$.

8.1.3. (*S*)-*N,N*-Dibenzyl-5-(4-methylpiperazin-1-yl)-pentan-2-amine (11d): This compound was obtained as gummy residue; yield: 450 mg, (79%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.02 (d, *J* = 6.51 Hz, 3H, CHC*H*$_3$), 1.27-1.31 (m, 2H, CH$_2$C*H*$_2$ CH$_2$), 1.43-1.64 (m, 2H, CHC*H*$_2$), 2.22-2.2.27 (t, *J* = 7.38 Hz, 2H, CH2C*H*2cycN(CH$_2$)$_4$NCH$_3$), 2.31 (s, 3H, NC*H*$_3$), 2.47 (br s, 8H, cycN(C*H*$_2$)$_4$NCH$_3$), 2.68-2.74 (br s, 1H, NHC*H*), 3.40 (d, *J* = 13.71Hz, 2H, C*H*$_2$Ph), 3.69-3.73 (m, 2H, C*H*$_2$Ph), 7.21-7.39 (m, 10H, Ar-*H*): ESI-MS: *m/z* 365 (M+H)$^+$.

8.1.4. (*S*)-*N,N*-Dibenzyl-5-(piperidin-1-yl)-pentan-2-amine (11e): This compound was obtained as gummy residue; yield: 398 mg, (69%) ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.03 (d, *J* = 6.51 Hz, 3H, CHC*H*$_3$), 1.27 (br s, 2H, CH$_2$C*H*$_2$ CH$_2$), 1.44-1.69 (m, 8H, CHC*H*$_2$CH$_2$, cycNCH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_2$), 2.18-2.33 (m, 6H, CH$_2$C*H*$_2$N(C*H*$_2$)$_2$), 2.72 (br s, 1H, NHC*H*), 3.40 (d, *J* = 13.65 Hz, 2H, C*H*$_2$Ph), 3.68 (d, *J* = 13.71 Hz, 2H, C*H*$_2$Ph), 7.23-7.37 (m, 10H, Ar-*H*): ESI-MS: *m/z* 352 (M+H)$^+$.

8.1.5 (*S*)-*N*^{4},*N*^{4}-Dibenzyl-*N*^{1},*N*^{1}-dimethylpentane-1,4-diamine (11f): This compound was obtained as gummy residue; yield: 350 mg, (70%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.02 (d, *J* = 6.48 Hz, 3H, CHC*H*$_3$), 1.27 (br s, 2H, CH$_2$C*H*$_2$ CH$_2$), 1.49-1.70 (m, 2H, CHC*H*$_2$), 1.72 (br s, 2H, CH$_2$C*H*$_2$N(CH$_3$)$_2$, 2.24 (s, 6H, N(C*H*$_3$)$_2$), 2.68-1.94 (m, 1H, NHC*H*), 3.39 (d, *J* = 13.71 Hz, 2H, C*H*$_2$Ph)), 3.70 (d, *J* = 13.71 Hz, 2H, C*H*$_2$Ph)), 7.19-7.39 (m, 10H, Ar-*H*): ESI-MS: *m/z* 338 (M+H)$^+$.

8.1.6. (*S*)-*N*^{4},*N*^{4}-Dibenzyl-*N*^{1}-tert-butylpentane-1,4-diamine (**11g**): This compound was obtained as gummy residue; yield: 403 mg, (70%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.02 (d, *J* = 6.57 Hz, 3H, CHC*H*$_3$), 1.10 (s, 9H, C(CH$_3$)$_3$), 1.29-1.34 (m, 2H, CH$_2$C*H*$_2$ CH$_2$), 1.54-1.71 (m, 2H, CHC*H*$_2$CH$_2$), 2.44-2.48 (t, *J* = 7.14 Hz, 2H, C*H*$_2$N), 2.68-2.79 (m, 1H, NHC*H*), 3.42 (d, *J* = 13.71 Hz, 2H, C*H*$_2$Ph), 3.70 (d, *J* = 13.71 Hz, 2H, C*H*$_2$Ph), 7.20-7.42 (m, 10H, Ar-*H*): ESI-MS: *m/z* 339 (M+H)$^+$.

8.1.7. (*S*)-*N*^{4},*N*^{4}-Dibenzyl-*N*^{1}-ethyl-*N*^{1}-methylpentane-1,4-diamine (**11h**): This compound was obtained as gummy residue; yield: 344 mg, (69%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.01-1.06 (m, 6H, CHC*H*$_3$, NCH$_2$C*H*$_3$), 1.23-1.26 (m, 1H, CH$_2$CH*H*CH$_2$), 1.28-1.50 (m, 1H, CH$_2$C*H*HCH$_2$), 1.55-1.67(m, 2H, CHC*H*$_2$), 2.18-2.24 (m, 5H, NC*H*$_3$, CH$_2$C*H*$_2$N), 2.36-2.41 (m, 2H, NC*H*$_2$CH$_3$), 2.69-2.76 (m, 1H, NHC*H*), 3.40 (d, *J* = 13.71 Hz, 2H, C*H*$_2$Ph), 3.70 (d, *J* = 13.71 Hz, 2H, C*H*$_2$Ph), 7.19-7.41 (m, 10H, Ar-*H*): ESI-MS: *m/z* 325 (M+H)$^+$.

8.1.8. (*S*)-*N*^{4},*N*^{4}-Dibenzyl-*N*^{1},*N*^{1}-dioctylpentane-1,4-diamine (11i): This compound was obtained as gummy residue; yield: 575 mg, (71%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.88-0.90 (t, *J* = 5.88 Hz, 6H, N((CH$_2$)$_7$C*H*$_3$)$_2$), 1.02 (d, *J* = 6.48 Hz, 3H, CHC*H*$_3$), 1.29 (s, 20H, (NCH$_2$CH$_2$(C*H*$_2$)$_5$)$_2$), 1.40 (br s, 6H, N(CH$_2$C*H*$_2$)$_2$, CHCH$_2$C*H*$_2$CH$_2$), 1.59 (br s, 2H, CHC*H*$_2$),

2.28-2.39 (m, 6H, N(CH_2)$_3$), 2.68-2.75 (m, 1H, NHC*H*), 3.41 (d, *J* = 13.71 Hz, 2H, CH_2Ph), 3.70 (d, *J* = 13.71 Hz, 2H, CH_2Ph), 7.19-7.41 (m, 10H, Ar-*H*): ESI-MS: *m/z* 506 $(M+H)^+$.

9.0 General procedure for the synthesis of compounds 12a to 12i

To a solution of the **11a-i** (1.2 mmol) in MeOH 10 % (w/w) Pd/C was added. The apparatus flushed 2 times with hydrogen gas, and the mixture was agitated at room temperature for 5 h under hydrogen gas, at 60 Psi. Filtration through Celite and concentration under reduced pressure yielded the free amines **12a-i** were used without further purification.

10. General procedure for the synthesis of compounds S-13a-i & R-13a-i

The diamine **(**1.19 mmol) was heated with 4,7-DCQ (1.55 mmol) in presence of phenol. After completion of the reaction content was dissolved in chloroform. The organic layer was washed with 10% NaOH solution then by water and finally with brine. The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure to get a crude product that was purified by column chromatography on silica gel using methanol-chloroform-triethylamine.

10.1. (*S*)-*N*^{4}-(7-Chloroquinolin-4-yl)-*N*^{1},*N*^{1}-diethylpentane-1,4-diamine (*S*)-Chloroquine) (S-13a): This compound was obtained as white solid; yield: 201 mg, (62%). mp 64-66 °C ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.03-1.08 (t, *J* = 7.1 Hz, 6H, 2CH_2CH_3), 1.32 (d, *J* = 6.3 Hz, 3H, CHCH_3), 1.65-1.82 (m, 4H, CHCH_2, CH_2CH_2), 2.50-2.63 (m, 6H, $CH_2CH_2NEt_2$, NCH_2(CH_2), 3.72-3.76 (m, 1H, NHC*H*), 5.39 (br s, 1H, N*H*), 6.42 (d, *J* = 5.5 Hz, 1H, Ar-*H* quinoline), 7.34-7.38 (dd, *J* = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline), 7.74 (d, *J* = 8.9 Hz, 1H, Ar-*H* quinoline), 7.95 (d, *J* = 2.1 Hz, 1H, Ar-*H* quinoline), 8.50 (d, *J* = 5.4 Hz, 1H, Ar-*H* quinoline); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 11.1, 20.1, 23.6, 34.4, 46.7, 48.2, 52.4, 99. 2, 117.3, 121.3, 124.9, 128.6, 134.7, 149.1, 149.2, 151.9; HRMS calculated for $[C_{18}H_{26}ClN_3+H]^+$ 320.1888, found 320.1875; ESI-MS: *m/z* 320 $(M+H)^+$. $[\alpha]^{r.t}{}_D$ + 100.4° (lit.[8] $[\alpha]^{r.t}{}_D$ +107.5°)

10.1.1. (*S*)-7-Chloro-*N*-(5-morpholinopentan-2-yl)-quinolin-4-amine (S-13b): This compound was obtained as gummy residue; yield: 190 mg, (57%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.33 (d, *J* = 6.3 Hz, 3H, CHCH_3), 1.53-1.80 (m, 4H, CH_2CH_2 CH_2), 2.35-2.44 (m, 6H, CH_2N(CH_2)$_2$), 3.71-3.74 (m, 5H, NHC*H*, O(CH_2)$_2$), 5.05 (br s, 1H, N*H*), 6.43 (d, *J* = 5.5 Hz, 1H, Ar-*H* quinoline), 7.33-7.37 (dd, *J* = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline), 7.66 (d, *J* = 8.9 Hz, 1H, Ar-*H* quinoline), 7.99 (d, *J* = 2.1 Hz, 1H, Ar-*H* quinoline), 8.54 (d, *J* = 5.4 Hz, 1H, Ar-*H* quinoline); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 20.3, 23.1, 29.6, 34.0, 48.3, 53.7, 58.3, 66.8, 99.2, 117.1, 120.9, 125.1, 128.5, 134.9, 149.0, 151.8. HRMS calculated for $[C_{18}H_{24}ClN_3O+H]^+$ 334.1681, found 334.1685; ESI-MS: *m/z* 334 $(M+H)^+$.

10.1.2. (*S*)-7-Chloro-*N*-(5-(pyrrolidin-1-yl)pentan-2-yl)-quinolin-4-amine (S-13c): This compound was obtained as gummy residue; yield: 180 mg, (56%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.31 (d, *J* = 6.3 Hz, 3H, CHCH_3), 1.69-1.81 (m, 8H, cycNC$H_2CH_2CH_2CH_2$, CH_2CH_2 CH_2), 2.42-2.52 (m, 6H, $CH_2CH_2N(CH_2)_2$, $CH_2N(CH_2)_2$), 3.72 (br s, 1H, NHC*H*), 5.56 (br s, 1H, N*H*), 6.41 (d, *J* = 5.5 Hz, 1H, Ar-*H* quinoline), 7.32-7.36 (dd, *J* = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline), 7.68 (d, *J* = 8.9 Hz, 1H, Ar-*H* quinoline), 7.94 (d, *J* = 1.9 Hz, 1H, Ar-*H* quinoline), 8.50 (d, *J* = 5.4 Hz, 1H, Ar-*H* quinoline); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 8.0, 20.1, 23.3, 24.9, 33.8, 48.3, 53.0, 54.1, 55.7, 99.0, 117.4, 121.9, 124.9, 128.3, 134.8, 149.1, 149.4, 151.6. HRMS calculated for $[C_{18}H_{24}ClN_3+H]^+$ 318.1732, found 318.1727; ESI-MS: *m/z* 318 $(M+H)^+$

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10.1.3. (*S*)-7-Chloro-*N*-(5-(4-methylpiperazin-1-yl)pentan-2-yl)-quinolin-4-amine (S-13d): This compound was obtained as gummy residue; yield: 300 mg, (57%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.32 (d, *J* = 6.33 Hz, 3 H, CHC*H*$_3$), 1.65-1.81 (m, 4 H, CHC*H*$_2$C*H*$_2$ CH$_2$), 2.31 (s, 3H, NC*H*$_3$), 2.40-2.50 (m, 10H, C*H*$_2$N, cycNC*H*$_2$C*H*$_2$NC*H*$_2$C*H*$_2$), 3.73-3.75 (m, 1H, NHC*H*), 6.44 (d, *J* = 5.5 Hz, 1H, Ar-*H* quinoline), 7.33-7.37 (dd, *J* = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline), 7.69 (d, *J* = 8.9 Hz, 1H, Ar-*H* quinoline), 7.95 (d, *J* = 2.1 Hz, 1H, Ar-*H* quinoline), 8.49 (d, *J* = 5.4 Hz, 1H, Ar-*H* quinoline). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 20.1, 23.3, 29.6, 33.9, 45.9, 48.4, 52.9, 54.8, 57.7, 99.1, 117.0, 121.6, 125.2, 127.8, 135.1, 148.3,149.5, 150.9; HRMS calculated for $[C_{19}H_{27}ClN_4+H]^+$ 347.1997, found 347.1992; ESI-MS: *m/z* 347 $(M+H)^+$.

10.1.4. (*S*)-7-Chloro-*N*-(5-(piperidin-1-yl)pentan-2-yl)quinolin-4-amine (S-13e): This compound was obtained as gummy residue; yield: 191 mg, (58%) ^{1}H NMR ($CDCl_3$, 300 MHz) δ:1.32 (d, *J* = 6.3 Hz, 3H, CHC*H*$_3$), 1.47-1.48 (m, 2H, CH$_2$C*H*$_2$ CH$_2$), 1.61-1.72 (m, 8H, CHC*H*$_2$, cycNCH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_2$,), 2.39-2.43 (m, 6H, CH$_2$C*H*$_2$N(C*H*$_2$)$_2$), 3.71-3.79 (m, 1H, NHC*H*), 5.21 (br s, 1H, N*H*), 6.43 (d, *J* = 5.5 Hz, 1H, Ar-*H* quinoline), 7.34-7.37 (dd, *J* = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline), 7.74 (d, *J* = 8.9 Hz, 1H, Ar-*H* quinoline), 7.953 (d, *J* = 2.1 Hz, 1H, Ar-*H* quinoline), 8.50 (d, *J* = 5.4 Hz, 1H, Ar-*H* quinoline; ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 20.2, 23.2, 24.1, 25.4, 29.7, 33.9, 48.3, 54.5, 58.5, 99.1, 117.2, 121.3, 125.0, 128.6, 134.8, 149.6, 151.8; HRMS calculated for $[C_{19}H_{26}ClN_3+H]^+$ 332.1888 found 332.2052; ESI-MS: *m/z* 331 $(M+H)^+$.

10.1.5. (*S*)-*N*^{4}-(7-Chloroquinolin-4-yl)-*N*^{1},*N*^{1}-dimethylpentane-1,4-diamine (S-13f): This compound was obtained as gummy residue; yield: 180 mg, (62%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.31 (d, *J* = 6.3 Hz, 3 H, CHC*H*$_3$), 1.62-1.84 (m, 4 H, CHC*H*$_2$C*H*$_2$ CH$_2$), 2.27 (s, 6H, N(C*H*$_3$)$_2$), 2.39 (br s, 2H, C*H*$_2$N), 3.70 (br s, 1H, *NHCH*), 5.96 (s, 1H, N*H*), 6.40 (d, *J* = 5.5 Hz, 1H, Ar-*H* quinoline), 7.34-7.37 (dd, *J* = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline), 7.77 (d, *J* = 8.9 Hz, 1H, Ar-*H* quinoline), 7.95 (d, *J* = 2.1 Hz, 1H, Ar-*H* quinoline), 8.49 (d, *J* = 5.4 Hz, 1H, Ar-*H* quinoline); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 20.0, 23.8, 34.2, 45.2, 48.3, 59.2, 99.0, 117.4, 121.9, 124.9, 128.0, 128.8, 129.0, 134.9, 149.7, 151.4; HRMS calculated for $[C_{16}H_{22}ClN_3+H]^+$ 292.1575, found 292.1574; ESI-MS: 292 $(M+H)^+$.

10.1.6. (*S*)-*N*^{1}-*Tert*-butyl-*N*^{4}-(7-chloroquinolin-4-yl)-pentane-1,4-diamine (S-13g): This compound was obtained as gummy residue; yield: 192 mg, (60%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.26 (d, *J* = 5 Hz, 3 H, CHC*H*$_3$), 1.33 (s, 9H, C(CH$_3$)$_3$), 1.58-1.63 (m, 2H, CHCH$_2$C*H*$_2$ CH$_2$), 1.91-2.08 (m, 2H, CHC*H*$_2$CH$_2$ CH$_2$), 2.76 (br s, 2H, C*H*$_2$N), 3.39 (m, 1H, NHC*H*), 6.02 (br s, 1H, N*H*), 6.32 (d, *J* = 4.9 Hz, 1H, Ar-*H* quinoline), 7.36-7.28 (dd, *J* = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline), 7.92 (br s, 1H, Ar-*H* quinoline), 8.21 (d, *J* = 8.2 Hz, 1H, Ar-*H* quinoline), 8.48 (d, *J* = 5.0 Hz, 1H, Ar-*H* quinoline). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 20.1, 27.4, 28.9, 34.1, 42.1, 48.3, 50.3, 99.0, 117.3, 121.6, 124.8, 128.3, 134.6, 149.2, 151.7. HRMS calculated for $[C_{18}H_{26}ClN_3+H]^+$ 320.1888, found 320.1892; ESI-MS: *m/z* 320 $(M+H)^+$.

10.1.7. (*S*)-*N*^{4}-(7-Chloroquinolin-4-yl)-*N*^{1}-ethyl-*N*^{1}-methylpentane-1,4-diamine (S-13h): This compound was obtained as gummy residue. yield: 180 mg, (59%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.03-1.20 (t, *J* = 7.2 Hz, 3H, NCH$_2$C*H*$_3$), 1.34 (d, *J* = 6.3 Hz, 3H, CHC*H*$_3$), 1.72-1.81 (m, 4H, CHC*H*$_2$C*H*$_2$CH$_2$), 2.31 (s, 3H, NC*H*$_3$), 2.47-2.64 (m, 4H, CH$_2$C*H*$_2$NC*H*$_2$), 3.70-3.81 (m, 1H,

NHC*H*), 5.8 (br s, 1H, N*H*), 6.43 (d, *J* = 5.5 Hz, 1H, Ar-*H* quinoline), 7.36-7.41 (dd, *J* = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline), 7.83 (d, *J* = 8 Hz, 1H, Ar-*H* quinoline), 7.97 (d, *J* = 2.1 Hz, 1H, Ar-*H* quinoline), 8.51 (d, *J* = 5.4 Hz, 1H, Ar-*H* quinoline). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 11.4, 20.1, 23.4, 29.6, 41.2, 48.3, 51.2, 56.5, 99.0, 117.3, 121.6, 125.8, 128.3, 134.6, 149.1, 151.7; HRMS calculated for $[C_{17}H_{24}ClN_3+H]^+$ 306.1732, found 306.1711; ESI-MS: *m/z* 306 $(M+H)^+$.

10.1.8. (*S*)-*N*^{4}-(7-Chloroquinolin-4-yl)-*N*^{1},*N*^{1}-dioctylpentane-1,4-diamine (S-13i): This compound was obtained as gummy residue; yield: 250 mg, (51%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.83-0.88 (t, *J* = 6.9 Hz, 6H, N($(CH_2)_7CH_3)_2$), 1.23 (d, *J* = 4.9 Hz, 20H, $(NCH_2CH_2(CH_2)_5)_2$), 1.38 (d, *J* = 6.2 Hz, 3H, $CHCH_3$), 1.71 (d, *J* = 5.0 Hz, 6H, $N(CH_2CH_2)_2$, $CHCH_2CH_2CH_2$), 1.93-2.06 (m, 1H, CHCH*H*), 2.36-2.39 (m, 1H, CHCH*H*), 2.90-2.95 (m, 4H, $N(CH_2)_2$, 3.02 (br s, 2H CH_2), 3.83 (br s, 1H, NHC*H*), 6.43 (d, *J* = 5.5 Hz, 1H, Ar-*H* quinoline), 7.37 (d, *J* = 7.5 Hz, 1H, Ar-*H* quinoline), 7.80 (br s, 1H, NH), 8.04 (s, 1H, Ar-*H* quinoline), 8.33 (d, *J* = 4.7 Hz, 1H, Ar-*H* quinoline), 8.79 (d, *J* = 8.9 Hz, 1H, Ar-*H* quinoline); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.0, 20.2, 21.8, 22.5, 23.3, 26.8, 29.0, 29.0, 31.6, 32.7, 49.6, 53.1, 53.4, 98.1, 116.6, 125.3, 126.4, 137.5, 153.1; HRMS calculated for $[C_{30}H_{50}ClN_3+H]^+$ 488.3766 found 488.3757; ESI-MS: *m/z* 488 $(M+H)^+$.

10.1.9. (*R*)-*N*^{4}-(7-Chloroquinolin-4-yl)-*N*^{1},*N*^{1}-diethylpentane-1,4-diamine(*(R)*-Chloroquine, (R-13a): This compound was obtained as white solid; yield: 201mg, (62%). mp 64-66 °C ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.03-1.08 (t, *J* = 7.1 Hz, 6H, CH_2CH_3), 1.32 (d, *J* = 6.3 Hz, 3H, $CHCH_3$), 1.65-1.82 (m, 4H, $CHCH_2$, CH_2CH_2), 2.50-2.63 (m, 6H, $CH_2CH_2NEt_2$, $NCH_2(CH_2)$), 3.72-3.76 (m, 1H, NHC*H*), 5.39 (br s, 1H, N*H*), 6.42 (d, *J* = 5.5 Hz, 1H, Ar-*H* quinoline), 7.34-7.38 (dd, *J* = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline), 7.74 (d, *J* = 8.9 Hz, 1H, Ar-*H* quinoline), 7.95 (d, *J* = 2.1 Hz, 1H, Ar-*H* quinoline), 8.50 (d, *J* = 5.4 Hz, 1H, Ar-*H* quinoline); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 11.1, 20.1, 23.6, 34.4, 46.7, 48.2, 52.4, 99.2, 117.3, 121.3, 124.9, 128.6, 134.7, 149.1, 149.2, 151.9; HRMS calculated for $[C_{18}H_{26}ClN_3+H]^+$ 320.1888, found 320.1882; ESI-MS: *m/z* 320 $(M+H)^+$. $[\alpha]^{r.t}{}_D$ - 101.6° (lit.[8] $[\alpha]^{r.t}{}_D$ - 108.7°)

10.1.10. (*R*)-7-Chloro-*N*-(5-morpholinopentan-2-yl)quinolin-4-amine (R-13b): This compound was obtained as gummy residue; yield:190 mg, (57%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.33 (d, *J* = 6.3 Hz, 3H, $CHCH_3$), 1.53-1.80 (m, 4H, CH_2CH_2 CH_2), 2.35-2.44 (m, 6H, $CH_2N(CH_2)_2$), 3.71-3.74 (m, 5H, NHC*H*, $O(CH_2)_2$), 5.05 (br s, 1H, N*H*), 6.43 (d, *J* = 5.5 Hz, 1H, Ar-*H* quinoline), 7.33-7.37 (dd, *J* = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline), 7.66 (d, *J* = 8.9 Hz, 1H, Ar-*H* quinoline), 7.99 (d, *J* = 2.1 Hz, 1H, Ar-*H* quinoline), 8.54 (d, *J* = 5.4 Hz, 1H, Ar-*H* quinoline); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 20.3, 23.1, 29.6, 34.0, 48.3, 53.7, 58.3, 66.8, 99.2, 117.1, 120.9, 125.1, 128.5, 134.9, 149.0, 151.8; HRMS calculated for $[C_{18}H_{26}ClN_3O+H]^+$ 334.1681, found 334.1680; ESI-MS: *m/z* 334 $(M+H)^+$.

10.1.11. (*R*)-7-Chloro-*N*-(5-(pyrrolidin-1-yl)pentan-2-yl)-quinolin-4-amine (R-13c): This compound was obtained as gummy residue; yield: 180 mg, (56%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.31 (d, *J* = 6.3 Hz, 3H, $CHCH_3$), 1.69-1.81 (m, 8H, $cycNCH_2CH_2CH_2CH_2$, CH_2CH_2 CH_2), 2.42-2.52 (m, 6H, $CH_2CH_2N(CH_2)_2$, $CH_2N(CH_2)_2$), 3.72 (br s, 1H, NHC*H*), 5.56 (br s, 1H, N*H*), 6.41 (d, *J* = 5.5 Hz, 1H, Ar-*H* quinoline), 7.32-7.36 (dd, *J* = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline), 7.68 (d, *J* = 8.9 Hz, 1H, Ar-*H* quinoline), 7.94 (d, *J* = 1.98 Hz, 1H, Ar-*H* quinoline), 8.50 (d, *J* = 5.4 Hz, 1H, Ar-*H* quinoline); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 8.0, 20.1, 23.3, 24.9, 33.8, 48.3,

53.0, 54.1, 55.7, 99.0, 117.4, 121.9, 124.9, 128.3, 134.8, 149.1, 149.4, 151.6; HRMS calculated for $[C_{18}H_{24}ClN_3+H]^+$ 318.1732, found 318.1786; ESI-MS: *m/z* 318 $(M+H)^+$.

10.1.12. (*R*)-7-Chloro-*N*-(5-(4-methylpiperazin-1-yl)pentan-2-yl)-quinolin-4-amine (R-13d): This compound was obtained as gummy residue; yield: 300 mg, (57%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.32 (d, *J* = 6.3 Hz, 3 H, CHC*H*$_3$), 1.65-1.81 (m, 4 H, CHC*H*$_2$C*H*$_2$CH$_2$), 2.31 (s, 3H, NC*H*$_3$), 2.40-2.50 (m, 10H, C*H*$_2$N, cycNC*H*$_2$C*H*$_2$NC*H*$_2$C*H*$_2$), 3.73-3.75 (m, 1H, NHC*H*), 6.44 (d, *J* = 5.5 Hz, 1H, Ar-*H* quinoline), 7.33-7.37 (dd, *J* = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline), 7.69 (d, *J* = 8.9 Hz, 1H, Ar-*H* quinoline), 7.95 (d, *J* = 2.1 Hz, 1H, Ar-*H* quinoline), 8.49 (d, *J* = 5.4 Hz, 1H, Ar-*H* quinoline). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 20.1, 23.3, 29.6, 33.9, 45.9, 48.4, 52.9, 54.8, 57.7, 99.1, 117.0, 121.6, 125.2, 127.8, 135.1, 148.3, 149.5, 150.9; HRMS calculated for $[C_{19}H_{27}ClN_4+H]^+$ 347.1997, found 347.1996; ESI-MS: *m/z* 347 $(M+H)^+$.

10.1.13. (*R*)-7-Chloro-*N*-(5-(piperidin-1-yl)-pentan-2-yl)quinolin-4-amine (R-13e): This compound was obtained as gummy residue; yield: 191 mg, (58%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.32 (d, *J* = 6.3 Hz, 3H, CHC*H*$_3$), 1.47-1.48 (m, 2H, CH$_2$C*H*$_2$ CH$_2$), 1.61-1.72 (m, 8H, CHC*H*$_2$, cycNCH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_2$,), 2.39-2.43 (m, 6H, CH$_2$C*H*$_2$N(C*H*$_2$)$_2$), 3.71-3.79 (m, 1H, NHC*H*), 5.21 (br s, 1H, N*H*), 6.43 (d, *J* = 5.5 Hz, 1H, Ar-*H* quinoline), 7.34-7.37 (dd, *J* = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline), 7.74 (d, *J* = 8.9 Hz, 1H, Ar-*H* quinoline), 7.95 (d, *J* = 2.1 Hz, 1H, Ar-*H* quinoline), 8.50 (d, *J* = 5.4 Hz, 1H, Ar-*H* quinoline; ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 20.2, 23.2, 24.1, 25.4, 29.7, 33.9, 48.3, 54.5, 58.5, 99.1, 117.2, 121.3, 125.0, 128.6, 134.8, 149.6, 151.8; HRMS calculated for $[C_{19}H_{26}ClN_3+H]^+$ 332.1888 found 332.1862; ESI-MS: *m/z* 332 $(M+H)^+$.

10.1.14. (*R*)-*N*^{4}-(7-Chloroquinolin-4-yl)-*N*^{1},*N*^{1}-dimethylpentane-1,4-diamine (R-13f): This compound was obtained as gummy residue; yield: 180 mg, (62%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.31 (d, *J* = 6.3 Hz, 3H, CHC*H*$_3$), 1.62-1.84 (m, 4H, CHC*H*$_2$C*H*$_2$ CH$_2$), 2.27 (s, 6H, N(C*H*$_3$)$_2$), 2.39 (br s, 2H, C*H*$_2$N), 3.70 (br s, 1H, *NHCH*), 5.96 (s, 1H, N*H*), 6.40 (d, *J* = 5.5 Hz, 1H, Ar-*H* quinoline), 7.34-7.37 (dd, *J* = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline), 7.77 (d, *J* = 8.9 Hz, 1H, Ar-*H* quinoline), 7.95 (d, *J* = 2.1 Hz, 1H, Ar-*H* quinoline), 8.49 (d, *J* = 5.4 Hz, 1H, Ar-*H* quinoline); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 20.0, 23.8, 34.2, 45.2, 48.3, 59.2, 99.0, 117.4, 121.9, 124.9, 128.0, 128.8, 129.0, 134.9, 149.7, 151.4; HRMS calculated for $[C_{16}H_{22}ClN_3+H]^+$ 292.1575 found 292.1570; ESI-MS: 292 $(M+H)^+$.

10.1.15. (*R*)-*N*^{1}-*Tert*-butyl-*N*^{4}-(7-chloroquinolin-4-yl)pentane-1,4-diamine (R-13g): This compound was obtained as gummy residue; yield: 192 mg, (60%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.26 (d, *J* = 5 Hz, 3 H, CHC*H*$_3$), 1.33 (s, 9H, C(CH$_3$)$_3$), 1.58-1.63 (m, 2H, CHCH$_2$C*H*$_2$ CH$_2$), 1.91-2.08 (m, 2 H, CHC*H*$_2$CH$_2$ CH$_2$), 2.76 (br s, 2H, C*H*$_2$N), 3.39 (m, 1H, NHC*H*), 6.02 (br s, 1H, N*H*), 6.32 (d, *J* = 4.9 Hz, 1H, Ar-*H* quinoline), 7.36-7.28 (dd, *J* = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline), 7.92 (br s, 1H, Ar-*H* quinoline), 8.21 (d, *J* = 8.2 Hz, 1H, Ar-*H* quinoline), 8.48 (d, *J* = 5.04 Hz,1H, Ar-*H* quinoline). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 20.1, 27.4, 28.9, 34.1, 42.1, 48.3, 50.3, 99.0, 117.3, 121.6, 124.8, 128.3, 134.6, 149.2, 151.7; HRMS calculated for $[C_{18}H_{26}ClN_3+H]^+$ 320.1888 found 320.1881; ESI-MS: *m/z* 320 $(M+H)^+$.

10.1.16. (*R*)-*N*^{4}-(7-Chloroquinolin-4-yl)-*N*^{1}-ethyl-*N*^{1}-methylpentane-1,4-diamine (R-13h): This compound was obtained as gummy residue; yield: 180 mg, (59%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.03-1.20 (t, *J* = 7.2 Hz, 3H, NCH$_2$C*H*$_3$), 1.34 (d, *J* = 6.3 Hz, 3H, CHC*H*$_3$), 1.72-1.81

(m, 4H, CHCH_2CH_2CH_2), 2.31 (s, 3H, NCH_3), 2.47-2.64 (m, 4H, CH_2CH_2NCH_2), 3.70-3.81 (m, 1H, NHC*H*), 5.8 (br s, 1H, N*H*), 6.43 (d, *J* = 5.5 Hz, 1H, Ar-*H* quinoline), 7.36-7.41 (dd, *J* = 2.1, 8.9 Hz, 1H, Ar-*H* quinoline), 7.83 (d, *J* = 8. Hz, 1H, Ar-*H* quinoline), 7.97 (d, *J* = 2.1 Hz, 1H, Ar-*H* quinoline), 8.51 (d, *J* = 5.4 Hz, 1H, Ar-*H* quinoline). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 11.4, 20.1, 23.4, 29.6, 41.2, 48.3, 51.2, 56.5, 99.0, 117.3, 121.6, 125.8, 128.3, 134.6, 149.1, 151.7; HRMS calculated for $[C_{17}H_{24}ClN_3+H]^+$ 306.1732 found 306.1731; ESI-MS: *m/z* 306 $(M+H)^+$.

10.1.17. (*R*)-*N*^{4}-(7-Chloroquinolin-4-yl)-*N*^{1},*N*^{1}-dioctylpentane-1,4-diamine (R-13i): This compound was obtained as gummy residue; yield: 250 mg (51%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.83-0.88 (t, *J* = 6.93 Hz, 6H, N((CH_2)$_7$CH_3)$_2$), 1.23 (d, *J* = 4.95 Hz, 20H, (NCH_2CH_2(CH_2)$_5$)$_2$), 1.38 (d, *J* = 6.2 Hz, 3H, CHCH_3), 1.71 (d, *J* = 5.0 Hz, 6H, N(CH$_2$CH_2)$_2$, CHCH$_2$CH_2CH$_2$), 1.93-2.06 (m, 1H, CHCH*H*), 2.36-2.39 (m, 1H, CHCH*H*), 2.90-2.95 (m, 4H, N(CH_2)$_2$, 3.02 (br s, 2H CH_2), 3.83 (br s, 1H, NHC*H*), 6.43 (d, *J* = 5.5 Hz, 1H, Ar-*H* quinoline), 7.37 (d, *J* = 7.5 Hz, 1H, Ar-*H* quinoline), 7.80 (br s, 1H, NH), 8.04 (s, 1H, Ar-*H* quinoline), 8.33 (d, *J* = 4.7 Hz, 1H, Ar-*H* quinoline), 8.79 (d, *J* = 8.9 Hz, 1H, Ar-*H* quinoline); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.0, 20.2, 21.8, 22.5, 23.3, 26.8, 29.0, 29.0, 31.6, 32.7, 49.6, 53.1, 53.4, 98.1, 116.6, 125.3, 126.4, 137.5, 153.1; HRMS calculated for $[C_{30}H_{50}ClN_3+H]^+$ 488.3766 found 488.3764; ESI-MS: *m/z* 488 $(M+H)^+$.

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