Synthesis and Antimalarial Activity of Novel Side Chain Modified Antimalarial Agents Derived from 4-Aminoquinoline

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Abstract: Malaria is one of the foremost public health problems in developing countries affecting nearly 40% of the global population. Apart from this, the past two decade's emergence of drug resistance has severely limited the choice of available antimalarial drugs. Furthermore, the general trend emerging from the SAR-studies is that chloroquine resistance does not involve any change to the target of this class of drugs but involves compound specific efflux mechanism. Based on this premise a number of groups have developed short chain analogues of 4-aminoquinoline, which are active against CQ-resistant strains of P. falciparum in in vitro studies. However, these derivatives undergo biotransformation (de-alklyation) significantly affecting lipid solubility of the drug. In view of this background information, we thought that it would be interesting to study the effect of additional lipophilicity and cationic charge at the lateral side chain of 4-aminoquinoline. This prompted us to explore the cationic amino acid conjugates namely, lysine and ornithine of 4-aminoquinoline with a view to achieve improved antimalarial activity and to the best of our knowledge such amino acid conjugates have not been hitherto reported in the literature in the case of 4-aminoquinolines. In the present study, a new series of side-chain modified 4-aminoquinolines have been synthesized and found active against both susceptible and multidrug resistant strains of P. falciparum in vitro and P. yoelli in vivo. The seminal finding of the present study is that a new series of compounds having significantly more activity against CQ resistant parasites has been identified.

Key Words: 4-Aminoquinoline, amino acid conjugates, antimalarial agents.

1. INTRODUCTION

During the past two decades studies aimed at understanding the mechanism of action as well as drug resistance to the 4-aminoquinoline class of antimalarial compounds has taken centre stage [1-5]. As a result there is compelling evidence to suggest that chloroquine (CQ) interferes with parasite heme detoxification which is essential for the survival of the parasite. In the parasite food vacuole heme is released by the enzymatic degradation of hemoglobin and subsequently oxidized to hematin which is toxic to the parasite. Therefore, the parasite has evolved a *sui generis* mechanism to detoxify hematin by way of biomineralization to a large aggregate of reciprocal heme dimmers called hemozoin. CQ inhibits hemozoin formation by forming association complexes with monomeric hematin [6-9]. In view of this, it is reasonable to assume that the parasite-specific heme detoxification pathway represents a unique target for the development of antimalarial compounds [10,11]. Furthermore, the general trend emerging from the SAR-studies is that CQ resistance does not involve any change to the target of this class of drugs but involves compound specific efflux mechanism [12,13]. Based on this premise a number of groups have developed short chain analogues of 4-aminoquinoline, which are active against CQ-resistant strains of *P. falciparum* in *in vitro* studies [14-16]. However, these derivatives undergo biotransformation (de-alklyation) significantly affecting lipid solubility of the drug. To circumvent these drawbacks, some metabolically stable molecules having *tert*-butyl, morpholinyl, piperazinyl moieties were synthesized and these derivatives are significantly more potent than CQ against a CQ-resistant strain of *P. falciparum in vitro* [17]. Apart from these, Sergherart *et al*. have synthesized a series of 4-anilinoquinolines with two proton accepting side chains of varying length, which help these dicationic moieties in their likely interaction with carboxylate groups of heme. From this study, they concluded that rational modification in the structural features of quinoline, can help in circumventing cross-resistance with CQ [18].

As a part of our ongoing medicinal chemistry program related to the design and synthesis of 4-aminoquinolines as antimalarial agents, we have found that certain modifications on the lateral side chain, particularly those affecting the pK_a2 values [19, 20] namely, guanyl and tetramethylguanyl substitutions (Fig. **1a**), leads to an increase in the pK_a2 values (p*K*a of lateral side chain nitrogen atom) without influencing the pK_a1 values (p*K*a of quinoline nitrogen atom). From this study we have concluded that increased cationic charge as expected enhances hematin binding affinity whereas the antimalarial activity was correlated with alterations in lipophilic character [19]. In a second set of studies short chain analogues of 4-aminoquinoline derivatives were prepared, in which the basicity of the lateral side chain (pK_a2) was completely abolished while lipophilicity was introduced by an-

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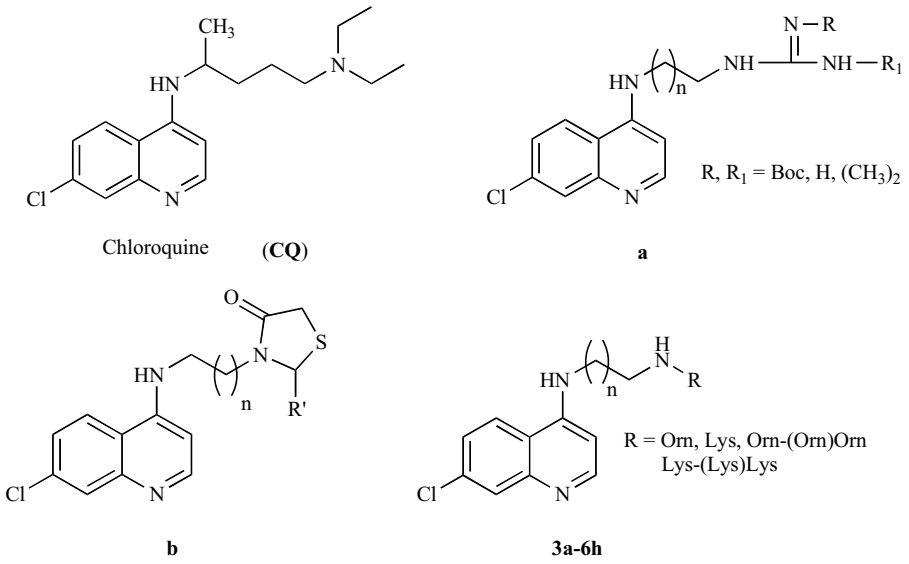


Fig. (1). Structure of 4-aminoquinoline derivatives.

choring a thiazolidin-4-one ring system at the pendant amino group (Fig. **1b**). These compounds were significantly more potent than CQ against NF-54 strain of *P. falciparum* in *in vitro* studies [20]. In view of this background information, we thought that it would be interesting to study the effect of additional lipophilicity and cationic charge at the lateral side chain of 4-aminoquinoline. This prompted us to explore the cationic amino acid conjugates namely, lysine and ornithine of 4-aminoquinoline with a view to achieve improved antimalarial activity and to the best of our knowledge such amino acid conjugates have not been hitherto reported in the literature in the case of 4-aminoquinolines. For the present study we have conjugated lysine and ornithine residues at the lateral side chain amino group. Further, we have also made changes in the carbon chain length as it has been established that the number of carbon atoms in the side chain plays an important role in modulating the antimalarial activity of 4-aminoquinoline class of compounds. In the following text experimental details of the synthesis and antimalarial activity of these conjugates are described.

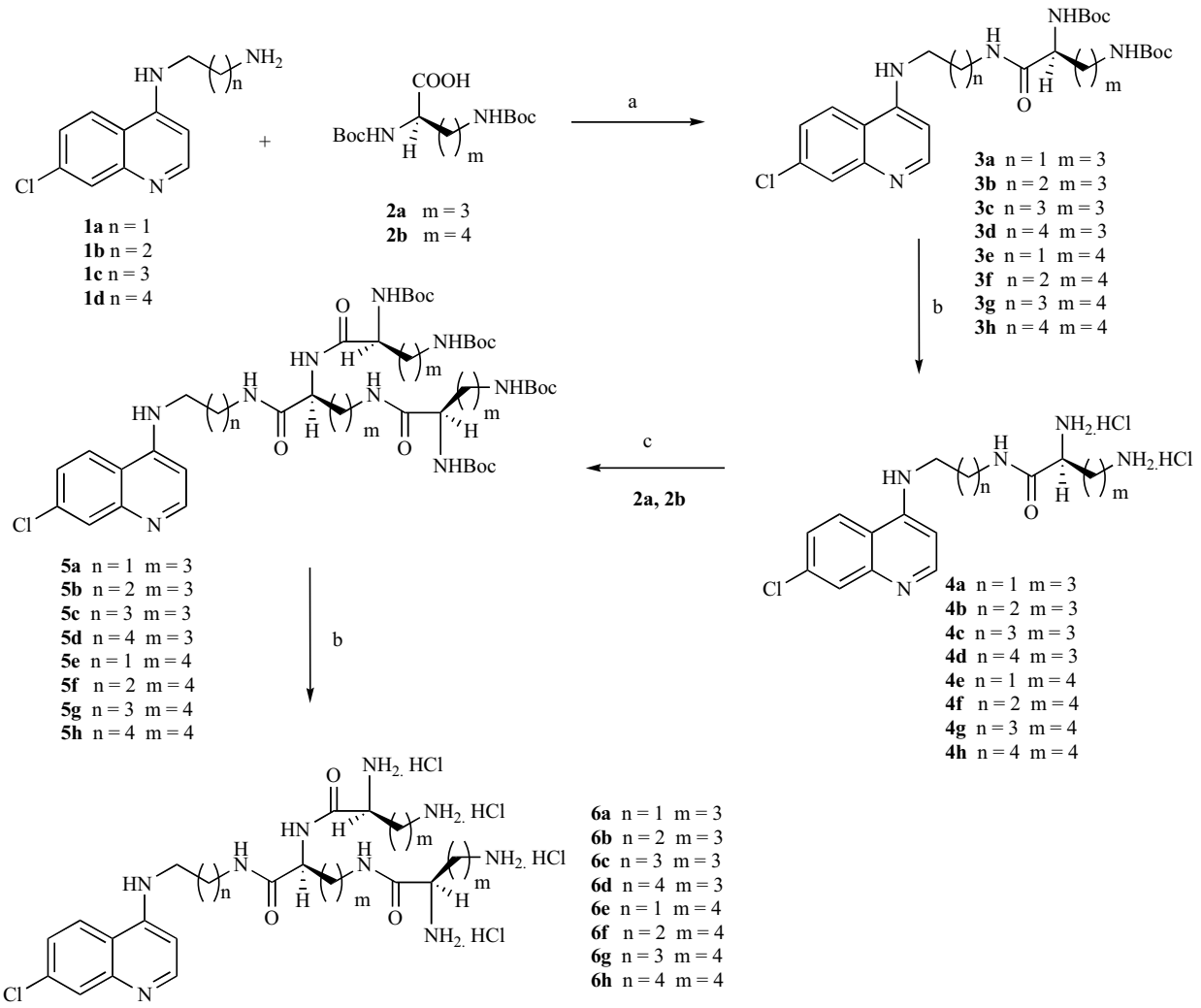
2. CHEMISTRY

Compounds described in this study were prepared as outlined in the Scheme **1**. The synthesis of desired 4-aminoquinoline derivatives (**1a-1d**) were prepared by the aromatic nucleophilic substitution on 4,7-dichloroquinoline with an excess of diaminoalkane without solvent as described earlier [19]. The Boc protected amino acids (**2a-2b**) were prepared using Boc anhydride by the standard protocol. The Boc protected amino acids (**2a-2b**) were coupled to 4-aminoquinoline derivatives (**1a-1d**) using *N*,*N*'-dicyclohexylcarbodiimide (DCC) in combination with 1-hydroxy-benzotriazolehydrate (HOBt), in dry THF at room temperature. The resulting Boc-protected amide derivatives (**3a-3h**) were deprotected by 4*N* HCl/Dioxane to get amino compounds (**4a-4h**). Boc protected derivatives (**5a-5h**) were synthesized by coupling of amino compounds (**4a-4h**) with 2 moles of Boc protected amino acids (**2a-2b**) using (HOBt/DCC) in dry DMF/THF solvent system. These Boc protected derivatives (**5a-5h**) were deprotected by 4*N* HCl/Dioxane to provide the final amino compounds (**6a-6h**). Structures of final compounds were confirmed by elemental analyses and spectroscopic data.

3. RESULTS AND DISCUSSION

All the compounds having modifications at the lateral amino group of the side chain (**4a-4h** and **6a-6h**) were evaluated for their antimalarial activity against the D6-chloroquine sensitive (CQ-S) and Dd2-chloroquine resistant (CQ-R) strains of *P. falciparum* according to the procedure reported by Smilkstein *et al.* [21]. The IC_{50} values are calculated from experiments carried out in triplicate. Some of the selected compounds, which have shown activity superior to CQ, particularly against the resistant strain were also evaluated for *in vivo* activity against the N-67 strain of *P. yoelli* in Swiss mice [22,23]. The *in vitro* activity data (Table **1**) clearly suggest that these derivatives, having amino acid conjugates at the lateral side chain, show significant antimalarial activity. Among the 16 compounds tested, five compounds showed IC_{50} in the range between 0.03 to 0.08 μM and six compounds had IC_{50} ranging between 0.13 to 0.86 μM, while remaining five compounds have shown IC_{50} above >1 μM, but not more than 3.99 μM, against CQ-S strain of *P. falciparum*. In the case of CQ-R strain of *P. falciparum* these derivatives showed *in vitro* activity as follows, four compounds showed IC_{50} range between 0.02 to 0.05 μM, six compounds had IC_{50} range between 0.12 to 0.71 μM, remaining four compounds have shown IC_{50} above 1.03, but not more than 2.89 μM and two compounds were found to be less active having $IC_{50} > 5$ μM.

In the case of ornithine-substituted analogs, compounds (**4a-4d**) having more carbon atoms in the lateral side chain correlates with an increase in the antimalarial activity against CQ-S and CQ-R strains of *P. falciparum*. In the case of compounds having substitution with three ornithine residues (**6a-6d**), activity data for both strains namely, CQ-S and CQ-R indicate that a decrease in the antimalarial activity in comparison to the corresponding mono substituted analogs (**4a-4d**).



Scheme 1. Reagents and conditions : (a) Dry THF, DCC/HOBt, rt, 1 h; (b) 4*N* HCl/Dioxane, rt, 1 h; (c) Dry THF/DMF, DCC/HOBt, Triethyl amine, rt, 2 h.

Whereas in the lysine-substituted analogs, activity data indicate that the compounds (**4e-4h**) with increase in the side chain carbon atoms, leads to an increase in the antimalarial activity against the CQ-S strain of *P. falciparum*. Increased antimalarial activity was observed in compounds (**6e-6h**) due to their lateral side chain length of the carbon atom. In the case of compounds (**6e-6h)** there is reduction of the antimalarial activity (10-20 fold) in both strains of *P. falciparum* in comparison to the corresponding mono substituted analogs (**4e-4h**). Initially mono amino acid conjugation (**4a-4h**) was carried out and resulted significant improvement in antimalarial activity, subsequently additional amino acids (**6a-6h**) were also attached to the two amino functions of cationic amino acid residues. These results provide highly cationic and bulky side chain to the molecules. With the limited data it is difficult to rationalize the discrepancies observed in the biological activities of lysine *vis-a-vis* ornithine analogues. Nevertheless this series of compounds have shown consistently high order of activity particularly against CQ-resistant *P. falciparum*. This is an encouraging finding and deserves further consideration.

It may be appropriate to mention here that resistance factor which is calculated as a ratio of IC_{50} in CQ-S versus CQ-R 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 [17]. Interestingly, all the compounds in this series showed resistance factors between 0.38 to 1.57 as compared to 5.11 for CQ. Against this background the present series of compounds appear to be promising for further lead optimization to obtain compounds active against drug resistant parasites.

Selected compounds (**4e-4h**) having a high degree of activity *in vitro* were evaluated for *in vivo* antimalarial activity in mice infected with the N-67 strain of *P. yoelli* using CQ as positive control [22, 23]. The mice were infected with parasites on day 0 and were treated with compounds (30 mg/kg) intraperitoneally, once daily for 4 consecutive days. The survival times and parasitaemia on day 4 were compared with those of control mice receiving saline (Table **2**). Among these, compound **4f** suppressed parasitaemia on day 4 by

Table 1. Biological and Biophysical Data of the Compounds (4a-4h and 6a-6h))

C. No	IC_{50} (μM)[a]		Resistance factor[d]	Log *P*[e]
	D6[b]	Dd2[c]		
4a	0.35±0.02	0.27±0.02	0.77	-0.06
6a	2.79±0.30	>5	NA	-1.01
4b	0.12±0.07	0.13±0.06	1.08	0.17
6b	1.85±0.25	>5	NA	-0.82
4c	0.13±0.01	0.16±0.04	1.23	0.44
6c	3.99±0.40	2.89±0.31	0.72	-0.62
4d	0.08±0.05	0.12±0.03	1.5	0.74
6d	3.00±0.32	1.14±0.14	0.38	-0.37
4e	0.06±0.01	0.04±0.22	0.67	0.19
6e	0.86±0.11	1.03±0.18	1.20	-0.35
4f	0.03±0.02	0.02±0.01	0.67	0.44
6f	0.45±0.01	0.71±0.14	1.58	-0.13
4g	0.04±0.03	0.05±0.02	1.25	0.74
6g	>1	>1	NA	0.12
4h	0.04±0.02	0.04±0.02	1.0	1.08
6h	0.72±0.17	0.50±0.05	0.69	0.40
CQ	0.01±0.03	0.05±0.02	5.00	4.72

[a]The results are expressed as means ± SD from at least three different experiments in duplicate; [b]D6-chloroquine-senstive strain of *P. falciparum*. [c]Chloroquine-resistant strain of *P. falciparum*; [d]resistance factor calculated from dividing the IC_{50} values of Dd6 by D6; [e]Log *P* values are calculated by Pallas software; NA -Not applicable.

93.85%, compared to 100% suppression displayed by CQ. Although the present series of compounds show promising *in vitro* activity, decreased activity profile in the *in vivo* studies could be attributed to the altered lipophilicity and ionic character of these derivatives as compared to CQ (Table **2**).

Table 2. *In Vivo* Antimalarial Activity Data of Compound (4e-4h) Against N-67 Strain of *P. yoelii* in Swice Mice

C. No	% suppression on day 4[a]	Mean survival time[b] (MST in days)±SE
4e	17.31	17.00±1.67
4f	93.85	17.17±2.82
4g	9.60	15.50±1.34
4h	23.65	15.20±2.13
CQ	99.99	20.00±1.53
Control	-	10.01±0.91

[a]Percent suppression = [(C-T)/C]x100; where C = parasitaemia in control group, and T = parasitaemia in treated group; [b]MST calculated for the mice which died during 28 day observation period.

CONCLUSION

In summary, the synthesis of a new series of 4-aminoquinoline amino acid conjugates has been described. These derivatives exhibit antimalarial activity against CQ-S and CQ-R strains of *P. falciparum in vitro* and N-67 strain of *P. yoelli in vivo*. The potent antimalarial activity of cationic amino acid conjugates of 4-aminoquinolines against both susceptible as well as quinoline resistant strains of *P. falciparum* provides a cautious optimism for the discovery of highly potent and safe antimalarial agents. The seminal finding of the present study is that a new series of compounds having more activity against CQ resistant parasites has been identified.

5. EXPERIMENTAL SECTION

5.1. General

Meting points (mp) were determined on a complab melting point apparatus and are uncorrected. IR spectra (cm^{-1}) were recorded on Perkin-Elmer 621 spectrometer using the KBr disc technique. The ^{1}H-NMR spectra were recorded on a DPX-200 MHz Bruker FT-NMR spectrometer using $CDCl_3$ and DMSO-d_6 as solvent. Tetramethylsilane (δ 0.0 ppm) was used as an internal standard. Fast Atom Bombardment Mass Spectra (FABMS) were obtained on Jeol (Japan)/SX-102 spectrometer using glycerol or *m*-nitrobenzyl

alcohol as matrix. Elemental analysis was performed on a Perkin-Elmer 2400 C, H, N analyzer and values were within the acceptable limits of the calculated values. The progress of the reaction was monitored on ready-made silica gel plates (Merck) using chloroform-methanol (9:1) as a solvent system. Iodine was used as developing agent or by spraying with Dragendorff's reagent. Chromatographic purification was performed over silica gel (100-200 mesh). All chemicals and reagents were obtained from Aldrich (USA), Lancaster (UK) or Spectrochem Pvt.Ltd (India) and were used without further purification.

General Synthetic Procedure for [(7-chloro-quinolin-4-ylamino)-alkyl]-N,N'-di-Boc-Orn-amide (3a-3d)

Di-Boc-Orn OH (**2a**) (1330 mg, 4.0 mmol) was dissolved in dry THF. To this HOBt (540 mg, 4.0 mmol), appropriate 4-aminoquinoline derivatives **1a-1d** (4.0 mmol) and DCC (825 mg, 4.0 mmol) was slowly added to the reaction mixture and resulting mixture was stirred for 30 min at 0ºC and the stirring was continued for 1 hr at room temperature. Dicyclohexylurea (DCU) was removed by filtration and filtrate was evaporated to dryness *in vacuo*. The residue was taken in ethyl acetate and washed with 5% aq. $NaHCO_3$ and brine, dried on anhydrous Na_2SO_4. The crude product was purified by column chromatography over silica gel using chloroform-methanol as eluent.

[2-(7-Chloro-quinolin-4-ylamino)ethyl]-N,N'-Di-Boc-Orn-amide (3a)

This compound was obtained as a yellowish white solid in 74% yield; mp 148-149 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.37 (s, 9H, NHCOOC(CH_3)$_3$), 1.41 (s, 9H, NHCOOC(CH_3)$_3$), 1.57-1.72 (m, 4H, CH_2), 1.81 (br s, 1H, N*H*, D_2O Exchangeable), 3.02-3.21 (m, 4H, CH_2), 3.41 (br s, 1H, N*H*, D_2O Exchangeable), 3.61-3.70 (m, 2H, CH_2), 4.26-4.29 (m, 1H, C*H*), 4.98 (br s, 1H, N*H*, D_2O Exchangeable), 5.55 (br s, 1H, N*H*, D_2O Exchangeable), 6.19-6.23 (d, *J*=6.2 Hz, 1H, Ar-*H* quinoline), 7.33 (s, 1H, Ar-*H* quinoline), 7.85 (s, 1H, Ar-*H* quinoline), 7.95-8.00 (s, 1H, Ar-*H* quinoline), 8.19-8.22 (d, *J*=5.7 Hz, 1H, Ar-*H* quinoline); FAB-MS *m/z* 536 $[M+H]^+$; Anal. Calcd for $C_{26}H_{38}ClN_5O_5$: C, 58.25; H, 7.14; N, 13.06. Found: C, 58.19; H, 7.09; N, 13.09.

[3-(7-Chloro-quinolin-4-ylamino)-propyl]-N,N'-di-Boc-Orn-amide (3b)

This compound was obtained as a pale yellowish white solid in 69 % yield; mp 107-108 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (s, 9H, NHCOOC(CH_3)$_3$), 1.44 (s, 9H, NHCOOC(CH_3)$_3$), 1.52-1.68 (m, 6H, CH_2), 3.09-3.12 (m, 2H, CH_2), 3.31-3.49 (m, 4H, CH_2), 4.28-4.32 (m, 1H, C*H*), 4.75 (br s, 1H, N*H*), 5.19 (br s, 1H, N*H*), 6.37-6.40 (d, *J*=5.5 Hz, 1H, Ar-*H* quinoline), 6.47 (br s, 1H, N*H*), 6.95 (br s, 1H, N*H*), 7.36-7.41 (dd, *J*=9.0, 2.1 Hz, 1H, Ar-*H* quinoline), 7.91-7.96 (m, 2H, Ar-*H* quinoline), 8.47-8.49 (d, *J*=5.5 Hz, 1H, Ar-*H* quinoline); FAB-MS *m/z* 550 $[M+H]^+$; Anal. Calcd for $C_{27}H_{40}ClN_5O_5$: C, 58.95; H, 7.33; N, 12.73. Found: C, 58.97; H, 7.29; N, 12.69.

[4-(7-Chloro-quinolin-4-ylamino)-butyl]-N,N'-di-Boc-Orn-amide (3c)

This compound was obtained as a pale yellowish white solid in 72 % yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.42 (s, 18H, 2-NHCOOC(CH_3)$_3$), 1.54-1.57 (m, 6H, CH_2), 1.65-1.78 (m, 2H, CH_2), 3.06-3.12 (m, 2H, CH_2), 3.30-3.42 (m, 4H, CH_2), 4.24 (br s, 1H, N*H*), 4.74 (br s, 1H, N*H*), 5.20-5.24 (m, 1H, C*H*), 5.67 (br s, 1H, N*H*), 6.37-6.40 (d, *J*=5.4 Hz, 1H, Ar-*H* quinoline), 6.77 (br s, 1H, N*H*), 7.34-7.38 (dd, *J*=9.0, 2.0 Hz, 1H, Ar-*H* quinoline), 7.84-7.89 (d, *J*=9.0 Hz, 1H, Ar-*H* quinoline), 7.94-7.95 (d, *J*=2.0 Hz, 1H, Ar-*H* quinoline), 8.49-8.52 (d, *J*=5.4 Hz, 1H, Ar-*H* quinoline); ^{13}C NMR ($CDCl_3$): δ 24.14, 25.20, 26.35, 27.04 (3C), 27.13 (3C), 28.87, 37.58, 37.97, 41.70, 53.74, 78.11, 78.74, 97.60, 116.06, 120.49, 123.90, 127.10, 133.57, 147.74, 148.81, 150.54, 154.65, 155.33, 171.47; FAB-MS *m/z* 564 $[M+H]^+$; Anal. Calcd for $C_{28}H_{42}ClN_5O_5$: C, 59.62; H, 7.50; N,12.41. Found: C, 59.66; H, 7.48; N, 12.36.

[5-(7-Chloro-quinolin-4-ylamino)-pentyl]-N,N'-di-Boc-Orn-amide (3d)

This compound was obtained as a yellowish white solid in 72 % yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.41 (s, 9H, NHCOOC(CH_3)$_3$), 1.42 (s, 9H, NHCOOC(CH_3)$_3$), 1.48-1.70 (m, 10H, CH_2), 3.02-3.09 (m, 2H, CH_2), 3.28-3.34 (m, 4H, CH_2), 4.25 (br s, 1H, N*H*), 4.72 (br s, 1H, N*H*), 5.19-5.22 (m, 1H, C*H*), 5.46 (br s, 1H, N*H*), 6.36-6.39 (d, *J*=5.5 Hz, 1H, Ar-*H* quinoline), 6.70 (br s, 1H, N*H*), 7.34-7.40 (dd, *J*=9.0, 2.0 Hz, 1H, Ar-*H* quinoline), 7.91 (s, 1H, Ar-*H* quinoline), 7.94-7.95 (d, *J*=2.0 Hz, 1H, Ar-*H* quinoline), 8.49-8.52 (d, *J*=5.4 Hz, 1H, Ar-*H* quinoline); FAB-MS *m/z* 578 $[M+H]^+$; Anal. Calcd for $C_{29}H_{44}ClN_5O_5$: C, 60.25; H, 7.67; N, 12.11. Found: C, 60.21; H, 7.61; N, 12.08.

General synthetic procedure for [(7-chloro-quinolin-4-ylamino)-alkyl]-Orn-amide. 2HCl (4a-4d)

Compounds **3a-3d** were treated with 4*N* HCl/Dioxane solution and kept for 1 h at room temperature. The solvent was evaporated under reduced pressure and the residue was precipitated with anhydrous ether. The precipitate was filtered and thoroughly washed with ether and dried over anhydrous NaOH pellets under high vacuum

[2-(7-Chloro-quinolin-4-ylamino)-ethyl]-Orn-amide. 2HCl (4a)

This compound was obtained as viscous oily in 68% yield; ^{1}H NMR (200 MHz, DMSOd_6 + $CDCl_3$): δ 1.74-1.80 (m, 4H, CH_2), 2.82-2.87 (m, 2H, CH_2), 3.49-3.53 (m, 4H, CH_2), 3.74-3.85 (m, 1H, C*H*), 6.97-7.00 (d, *J*=7.2 Hz, 1H, Ar-*H* quinoline), 7.66-7.70 (d, *J*=9.0 Hz, 1H, Ar-*H* quinoline), 8.08-8.09 (d, *J*=1.8 Hz, 1H, Ar-*H* quinoline), 8.13 (br s, 2H, NH_2, D_2O Exchangeable), 8.42 (br s, 2H, NH_2, D_2O Exchangeable), 8.55-8.59 (d, *J*=7.0 Hz, 1H, Ar-*H* quinoline), 8.87-8.92 (d, *J*=9.2 Hz, 1H, Ar-*H* quinoline), 9.16 (br s, 1H, N*H*, D_2O Exchangeable), 9.86 (br s, 1H, N*H*, D_2O Exchangeable); ^{13}C NMR (DMSO-d_6 + $CDCl_3$): δ 25.79, 29.42, 35.34, 37.93, 52.34, 64.98, 97.89, 114.69, 118.02, 125.24, 125.94, 137.23, 140.98, 149.23, 154.51, 167.60; FAB-MS *m/z* 336 $[M+H]^+$; Anal. Calcd for C16H24Cl3N5O: C, 47.0; H, 5.92; N, 17.13. Found: C, 47.05; H, 5.91, N, 17.16.

[3-(7-Chloro-quinolin-4-ylamino)-propyl]-Orn-amide. 2HCl (4b)

This compound was obtained as viscous oily in 64 % yield; ^{1}H NMR (200 MHz, DMSOd_6 + $CDCl_3$): δ 1.74-1.93

(m, 6H, CH_2), 2.84-2.89 (m, 2H, CH_2), 3.21-3.30 (m, 2H, CH_2), 3.52-3.69 (m, 2H, CH_2), 3.89-3.94 (m, 1H, C*H*), 6.93-6.96 (d, *J*=7.2 Hz, 1H, Ar-*H* quinoline), 7.65-7.70 (dd, *J*=9.0, 1.5 Hz, 1H, Ar-*H* quinoline), 8.04-8.05 (d, *J*=1.9 Hz, 1H, Ar-*H* quinoline), 8.12 (br s, 2H, NH_2), 8.37 (br s, 2H, NH_2), 8.53-8.56 (d, *J*=7.4 Hz, 1H, Ar-*H* quinoline), 8.81-8.86 (d, *J*=9.2 Hz, 1H, Ar-*H* quinoline), 9.09 (br s, 1H, N*H*), 9.78 (br s, 1H, N*H*); FAB-MS *m/z* 350 $[M+H]^+$; Anal. Calcd for $C_{17}H_{26}Cl_3N_5O$: C, 48.3; H, 6.20; N, 16.57. Found: C, 48.35; H, 6.24; N, 16.61.

[4-(7-Chloro-quinolin-4-ylamino)-butyl]-Orn-amide. 2HCl (4c)

This compound was obtained as a pale yellowish white viscous oily in 68 % yield; ^{1}H NMR (200 MHz, DMSOd_6 + $CDCl_3$): δ 1.67-1.82 (m, 6H, CH_2), 2.87-2.92 (m, 2H, CH_2), 3.17-3.29 (m, 2H, CH_2), 3.54-3.59 (m, 2H, CH_2), 3.66-3.71 (m, 2H, CH_2), 3.89-3.95 (m, 1H, C*H*), 6.84-6.87 (d, *J*=7.2 Hz, 1H, Ar-*H* quinoline), 7.58-7.62 (d, *J*=9.0 Hz, 1H, Ar-*H* quinoline), 8.06-8.08 (m, 2H, Ar-*H* quinoline), 8.24 (br s, 2H, NH_2), 8.36 (br s, 2H, NH_2), 8.48 (br s, 1H, N*H*), 8.86-8.91 (d, *J*=9.3 Hz, 1H, Ar-*H* quinoline), 9.75 (br s, 1H, N*H*) ; FAB-MS *m/z* 364 $[M+H]^+$; Anal. Calcd for $C_{18}H_{28}Cl_3N_5O$: C, 49.49; H, 6.46; N,16.03. Found: C, 49.53; H, 6.52; N, 16.00.

[5-(7-Chloro-quinolin-4-ylamino)-pentyl]-Orn-amide. 2HCl (4d)

This compound was obtained as a pale yellowish white solid in 68 % yield; ^{1}H NMR (200 MHz, DMSOd_6 + $CDCl_3$): δ 1.49-1.62 (m, 4H, CH_2), 1.72-1.95 (m, 4H, CH_2), 2.79-2.94 (m, 2H, CH_2), 3.14-3.21 (m, 4H, CH_2), 3.49-3.59 (m, 2H, CH_2), 3.87-3.91 (m, 1H, C*H*), 6.86-6.89 (d, *J*=7.2 Hz, 1H, Ar-*H* quinoline), 7.65-7.89 (d, *J*=9.3 Hz, 1H, Ar-*H* quinoline), 8.06 (s, 1H, Ar-*H* quinoline), 8.17 (br s, 1H, N*H*), 8.20 (br s, 2H, NH_2), 8.33 (br s, 2H, NH_2), 8.49-8.52 (d, *J*=6.4 Hz, 1H, Ar-*H* quinoline), 8.82-8.87 (d, *J*=9.3 Hz, 1H, Ar-*H* quinoline), 9.78 (br s, 1H, N*H*); FAB-MS *m/z* 378 $[M+H]^+$; Anal. Calcd for $C_{19}H_{30}Cl_3N_5O$: C, 50.62; H, 6.71; N, 15.53. Found: C, 50.67; H, 6.75; N, 15.54.

General Synthetic Procedure for (7-chloro-quinolin-4-ylamino)-alkyl-Di-Boc-Orn-(Di-Boc-Orn)-ornithinyl amide (5a-5d)

Di-Boc-Orn OH (**2a**) (996 mg, 3.0 mmol) was dissolved in dry THF. To this HOBt (405 mg, 3.0 mmol), appropriate compounds **4a-4d** (1.5 mmol) were dissolved in 2 ml dry DMF and triethyl amine (0.42 ml, 3.0 mmol). DCC (620 mg, 3.0 mmol) was slowly added to the reaction mixture and resulting mixture was stirred for 30 min at 0ºC and the stirring was continued for 2 hr at room temperature. DCU was removed by filtration and the filtrate was evaporated to dryness in vacuo. The residue was taken in ethyl acetate and washed with 5% aq. $NaHCO_3$ and brine, dried on anhydrous Na_2SO_4. The crude product was purified by column chromatography over silica gel using chloroform-methanol as eluent.

2-(7-Chloro-quinolin-4-ylamino)-ethyl-Di-Boc-Orn-(Di-Boc-Orn)-ornithinyl amide (5a)

This compound was obtained as a pale yellowish white solid in 70 % yield; mp 106-107 ºC; IR (KBr) 3300.4 cm^{-1}; 2977.5 cm^{-1}; 1622.8 cm^{-1}; 1583.1 cm^{-1}; 1529.7 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.39 (s, 18H, 2-NHCOOC(CH_3)$_3$), 1.42 (s, 18H, 2-NHCOOC(CH_3)$_3$), 1.52-1.62 (m, 12H, CH_2), 1.70-1.77 (m, 6H, CH_2), 3.06-3.24 (m, 4H, CH_2), 3.61 (br s, 2H, 2-N*H*, D_2O Exchangeable), 3.98-4.12 (m, 1H, C*H*), 4.16-4.23 (m, 1H, C*H*), 4.45 (br s, 1H, N*H*, D_2O Exchangeable), 4.98 (br s, 1H, N*H*, D_2O Exchangeable), 5.11 (br s, 1H, N*H*), 5.62-5.69 (m, 1H, C*H*), 6.36-6.39 (d, *J*=6.6 Hz, 1H, Ar-*H* quinoline), 7.26-7.33 (m, 2H, Ar-*H* quinoline), 7.85 (br s, 1H, N*H*, D_2O Exchangeable), 8.06-8.09 (d, *J*=6.8 Hz, 1H, Ar-*H* quinoline), 8.28 (br s, 2H, 2-N*H*, D_2O Exchangeable), 8.87-8.92 (d, *J*=9.2 Hz, 1H, Ar-*H* quinoline); FAB-MS *m/z* 964 $[M+H]^+$; Anal. Calcd for C46H74ClN9O11: C, 57.28; H, 7.73; N, 13.07. Found: C, 57.33; H, 7.71; N, 13.09.

3-(7-Chloro-quinolin-4-ylamino)-propyl-Di-Boc-Orn-(Di-Boc-Orn)-ornithinyl amide (5b)

This compound was obtained as a pale yellowish white solid in 70 % yield; mp 104-105 ºC; IR (KBr) 3387.4 cm^{-1}; 2362.9 cm^{-1}; 1589.1 cm^{-1}; 1462.3 cm^{-1}; 1369.6 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.42 (s, 36H, 4-NHCOOC(CH_3)$_3$), 1.50-1.60 (m, 14H, CH_2), 1.74-1.94 (m, 6H, CH_2), 3.12-3.16 (m, 2H, CH_2), 3.24 (br s, 1H, N*H*), 3.36-3.39 (m, 2H, CH_2), 4.15-4.19 (m, 1H, C*H*), 4.24 (br s, 1H, N*H*), 4.42-4.51 (m, 1H, C*H*), 4.82-4.89 (m, 1H, C*H*), 4.96 (br s, 1H, N*H*), 5.32 (br s, 1H, N*H*), 5.56 (br s, 1H, N*H*), 6.37-6.41 (d, *J*=5.6 Hz, 1H, Ar-*H* quinoline), 6.61 (br s, 1H, N*H*), 7.18 (s, 1H, Ar-*H* quinoline), 7.34-7.38 (dd, *J*=9.0, 2.0 Hz, 1H, Ar-*H* quinoline), 7.92-7.93 (d, *J*=2.0 Hz, 1H, Ar-*H* quinoline), 7.99 (br s, 1H, N*H*), 8.45-8.48 (d, *J*=5.5 Hz, 1H, Ar-*H* quinoline), 9.10 (br s, 1H, N*H*); FAB-MS *m/z* 978 $[M+H]^+$; Anal. Calcd for $C_{47}H_{76}ClN_9O_{11}$: C, 57.68; H, 7.83; N, 12.88. Found: C, 57.72; H, 7.86; N, 12.92.

4-(7-Chloro-quinolin-4-ylamino)-butyl-Di-Boc-Orn-(Di-Boc-Orn)-ornithinyl amide (5c)

This compound was obtained as a pale yellow white solid in 70 % yield; mp 104-105 ºC; IR (KBr) 3376.4 cm^{-1}; 2365.9 cm^{-1}; 1591.1 cm^{-1}; 1463.3 cm^{-1}; 1370.6 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.42 (s, 36H, 4-NHCOOC(CH_3)$_3$), 1.58-1.74 (m, 16H, CH_2), 1.74-1.94 (m, 6H, CH_2), 3.12 (br s, 1H, N*H*), 3.34-3.42 (m, 4H, CH_2), 4.16 (br s, 1H, N*H*), 4.21-4.26 (m, 1H, C*H*), 5.19 (br s, 1H, N*H*), 5.22-5.27 (m, 1H, C*H*), 5.69 (br s, 1H, N*H*), 5.71 (br s, 1H, N*H*), 5.74-5.77 (m, 1H, C*H*), 6.28-6.31 (d, *J*=6.3 Hz, 1H, Ar-*H* quinoline), 7.31-7.32 (d, *J*=1.8 Hz, 1H, Ar-*H* quinoline), 7.41 (br s, 1H, N*H*), 7.53 (br s, 1H, N*H*), 7.73 (br s, 1H, N*H*), 7.80 (s, 1H, Ar-*H* quinoline), 8.10-8.15 (d, *J*=9.0 Hz, 1H, Ar-*H* quinoline), 8.26-8.29 (d, *J*=5.9 Hz, 1H, Ar-*H* quinoline); ^{13}C NMR ($CDCl_3$): δ 24.82, 24.92, 25.42, 25.82, 27.92 (6C), 28.82 (6C), 29.12, 30.53, 40.68, 40.94, 40.99, 41.29, 41.54, 42.02, 54.35 (3C), 77.85 (6C), 97.56, 116.54, 121.35, 124.21, 126.21, 131.99, 146.89, 149.10, 150.11, 154.86 (4C), 166.86 (2C), 170.21; FAB-MS *m/z* 992 $[M+H]^+$; Anal. Calcd for $C_{48}H_{78}ClN_9O_{11}$: C, 58.08; H, 7.92; N, 12.70. Found: C, 58.09; H, 7.88; N,12.68.

5-(7-Chloro-quinolin-4-ylamino)-pentyl-Di-Boc-Orn-(Di-Boc-Orn)-ornithinyl amide (5d)

This compound was obtained as a pale yellow white solid in 70 % yield; IR (KBr) 3375.4 cm^{-1}; 2367.9 cm^{-1}; 1592.6

cm^{-1}; 1459.3 cm^{-1}; 1373.9 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.42 (s, 36H, 4-NHCOOC(CH_3)$_3$), 1.52-1.91 (m, 18H, CH_2), 3.10-3.32 (m, 10H, CH_2), 4.09-4.12 (m, 1H, C*H*), 4.40 (br s, 1H, N*H*), 4.90-5.00 (m, 1H, C*H*), 5.41-5.49 (m, 1H, C*H*), 6.03 (br s, 1H, N*H*), 6.36-6.39 (d, *J*=5.5 Hz, 1H, Ar-*H* quinoline), 7.03 (br s, 2H, 2-N*H*), 7.17 (br s, 1H, N*H*), 7.24 (br s, 1H, N*H*), 7.40 (br s, 1H, N*H*), 7.43 (br s, 1H, N*H*), 7.93-7.94 (dd, *J*=2.1 Hz, 1H, Ar-*H* quinoline), 7.99-8.03 (d, *J*=8.7 Hz, 1H, Ar-*H* quinoline), 8.06 (s, 1H, Ar-*H* quinoline), 8.45-8.48 (d, *J*=5.6 Hz, 1H, Ar-*H* quinoline); FAB-MS *m/z* 1006 $[M+H]^+$; Anal. Calcd for $C_{49}H_{80}ClN_9O_{11}$: C, 58.46; H, 8.01; N, 12.52. Found: C, 58.51; H, 8.04; N, 12.53.

General Synthetic Procedure for (7-chloro-quinolin-4-ylamino)-alkyl-Orn-(Orn)-ornithinyl amide. 4HCl (6a-6d)

Compounds **5a-5d** were treated with 4*N* HCl/Dioxane solution and kept for 1 h at room temperature. The solvent was evaporated under reduced pressure and the residue was precipitated with anhydrous ether and the precipitate was filtered, thoroughly washed with ether and dried over anhydrous NaOH pellets under high vacuum.

2-(7-Chloro-quinolin-4-ylamino)-ethyl-Orn-(Orn)-ornithinyl amide. 4HCl (6a)

This compound was obtained as a pale yellowish white oily nature in 66 % yield; ^{1}H NMR (200 MHz, DMSOd_6 + $CDCl_3$): δ 1.57-1.84 (m, 12H, CH_2), 2.85-2.89 (m, 6H, CH_2), 3.09-3.15 (m, 4H, CH_2), 3.71 (br s, 1H, N*H*, D_2O Exchangeable), 3.93-4.00 (m, 2H, 2-C*H*), 4.23-4.28 (m, 1H, C*H*), 6.98-7.02 (d, *J*=7.0 Hz, 1H, Ar-*H* quinoline), 7.52-7.55 (d, *J*=7.0 Hz, 1H, Ar-*H* quinoline), 7.67 (br s, 2H, NH_2, D_2O Exchangeable), 7.71 (br s, 2H, NH_2, D_2O Exchangeable), 8.13-8.27 (m, 2H, Ar-*H* quinoline), 8.42 (br s, 2H, NH_2, D_2O Exchangeable), 8.48 (br s, 2H, NH_2, D_2O Exchangeable), 8.59 (br s, 1H, N*H*, D_2O Exchangeable), 8.79-8.84 (d, *J*=9.0 Hz, 1H, Ar-*H* quinoline), 8.91 (br s, 1H, N*H*, D_2O Exchangeable), 9.82 (br s, 1H, N*H*, D_2O Exchangeable); FAB-MS *m/z* 564 $[M+H]^+$; Anal. Calcd for C26H46Cl5N9O5: C, 43.98; H, 6.53; N, 17.76. Found: C, 44.05; H, 6.59; N,17.81.

3-(7-Chloro-quinolin-4-ylamino)-propyl-Orn-(Orn)-ornithinyl amide. 4HCl (6b)

This compound was obtained as a pale yellowish white viscous oily nature in 66 % yield; IR (neat) 3413.4 cm^{-1}; 2925.9 cm^{-1}; 2858.9 cm^{-1}; 2577.1 cm^{-1}; 2369.1 cm^{-1}; 1715.2 cm^{-1}; 1658.8 cm^{-1}; 1600.0 cm^{-1}; 1458.4 cm^{-1}; 1364.7 cm^{-1}; ^{1}H NMR (200 MHz, DMSOd_6 + $CDCl_3$): δ 1.67-1.92 (m, 16H, CH_2), 2.95-3.00 (m, 4H, CH_2), 3.58-3.70 (m, 4H, CH_2), 3.82-3.87 (m, 1H, C*H*), 4.03 (br s, 1H, N*H*), 4.09-4.11 (m, 1H, C*H*), 4.32-4.39 (m, 1H, C*H*), 6.83-6.86 (d, *J*=6.9 Hz, 1H, Ar-*H* quinoline), 7.59-7.63 (d, *J*=9.4 Hz, 1H, Ar-*H* quinoline), 8.01-8.02 (d, *J*=2.1 Hz, 1H, Ar-*H* quinoline), 8.07 (br s, 1H, N*H*), 8.25 (br s, 4H, 2-NH_2), 8.38 (br s, 4H, 2-NH_2), 8.47 (br s, 1H, N*H*), 8.51 (br s, 1H, N*H*), 8.84-8.88 (d, *J*=9.3 Hz, 1H, Ar-*H* quinoline), 8.93-8.97 (d, *J*=7.1Hz, 1H, Ar-*H* quinoline); FAB-MS *m/z* 578 $[M+H]^+$; Anal. Calcd for $C_{27}H_{48}Cl_5N_9O_3$: C, 44.79; H, 6.68; N, 17.41. Found: C,44.83;, H, 6.72; N, 17.39.

4-(7-Chloro-quinolin-4-ylamino)-butyl-Orn-(Orn)-ornithinyl amide. 4HCl (6c)

This compound was obtained as a pale yellow white sticky nature in 64 % ^{1}H NMR (200 MHz, DMSOd_6 + $CDCl_3$): δ 1.59-1.67 (m, 8H, CH_2), 1.77-1.91 (m, 6H, CH_2), 2.89-2.94 (m, 4H, CH_2), 3.22-3.26 (m, 4H, CH_2), 3.52-3.52 (m, 4H, CH_2), 3.49 (br s, 1H, N*H*), 3.56-3.58 (m, 1H, C*H*), 3.67-3.71 (m, 1H, C*H*), 3.94-4.03 (m, 1H, C*H*), 7.62-7.67 (d, *J*=6.4 Hz, 1H, Ar-*H* quinoline), 8.07-8.08 (d, *J*=1.9 Hz, 1H, Ar-*H* quinoline), 8.16 (br s, 4H, 2-NH_2), 8.28 (br s, 1H, N*H*), 8.46 (br s, 2H, NH_2), 8.64 (br s, 1H, N*H*), 8.57 (br s, 2H, NH_2), 8.66-8.70 (d, *J*=9.3 Hz, 1H, Ar-*H* quinoline), 8.81 (s, 1H, Ar-*H* quinoline), 8.91-8.94 (d, *J*=6.2 Hz, 1H, Ar-*H* quinoline), 9.77 (br s, 1H, N*H*); FAB-MS *m/z* 592 $[M+H]^+$; Anal. Calcd for $C_{28}H_{50}Cl_5N_9O_3$: C, 45.57; H, 6.83; N, 17.08. Found: C, 45.59; H, 6.85; N, 17.06.

5-(7-Chloro-quinolin-4-ylamino)-pentyl-Orn-(Orn)-ornithinyl amide. 4HCl (6d)

This compound was obtained as a pale yellowish white viscous oily in 65 % yield; IR (KBr) 3408.9 cm^{-1}; 3072.3 cm^{-1}; 2934.2 cm^{-1}; 2365.9 cm^{-1}; 2942.0 cm^{-1}; 2047.1 cm^{-1}; 1617.0 1454.1 cm^{-1}; ^{1}H NMR (200 MHz, DMSOd_6 + $CDCl_3$): δ 1.46-1.52 (m, 10H, CH_2), 1.69-1.85 (m, 4H, CH_2), 2.51-2.53 (m, 4H, CH_2), 2.82-2.87 (m, 4H, CH_2), 3.11-3.26 (m, 2H, CH_2), 3.46-3.53 (m, 4H, CH_2), 3.67-3.70 (m, 1H, C*H*), 3.89-3.93 (m, 1H, C*H*), 4.29-4.35 (m, 1H, C*H*), 6.85-6.89 (d, *J*=7.2 Hz, 1H, Ar-*H* quinoline), 7.67-7.72 (dd, *J*=9.0, 2.0 Hz, 1H, Ar-*H* quinoline), 8.04-8.05 (d, *J*=2.0 Hz, 1H, Ar-*H* quinoline), 8.11 (br s, 4H, 2-NH_2), 8.35 (br s, 2H, NH_2), 8.40 (br s, 2H, NH_2), 8.51 (br s, 1H, N*H*), 8.59 (br s, 1H, N*H*), 8.77-8.82 (d, *J*=9.1 Hz, 1H, Ar-*H* quinoline), 8.85-8.88 (d, *J*=7.1 Hz, 1H, Ar-*H* quinoline), 8.91 (br s, 1H, N*H*), 9.70 (br s, 1H, N*H*); ^{13}C NMR (DMSOd_6 + $CDCl_3$): δ 21.42, 22.74, 24.58, 26.23, 27.08, 28.21, 29.45, 37.18, 37.90, 39.57, 41.24, 41.95, 42.22, 42.85, 50.35 (3C), 97.54, 117.54, 118.09, 124.62, 125.75, 137.67, 147.35, 148.42, 150.12, 154.49, 167.27, 170.06; FAB-MS *m/z* 606 $[M+H]^+$; Anal. Calcd for $C_{29}H_{52}Cl_5N_9O_3$: C, 46.32; H, 6.97; N, 16.76. Found: C, 46.36; H, 7.01; N, 16.79.

*General Synthetic Procedure for [(7-chloro-quinolin-4-ylamino)-alkyl]-***N,N'***-di-Boc- Lys-amide (3e-3h)*

Di-Boc-Lys OH (**2b**) (1385 mg, 4.0 mmol) was dissolved in dry THF. To this HOBt (540 mg, 4.0 mmol), appropriate 4-aminoquinoline derivatives **1a-1d** (4.0 mmol) and DCC (825 mg, 4.0 mmol) was slowly added to the reaction mixture and resulting mixture was stirred for 30 min at 0ºC and stirring continued for 1 h at room temperature. DCU was removed by filtration and filtrate was evaporated to dryness *in vacuo*. The residue was taken in ethyl acetate and washed with 5% aq. $NaHCO_3$ and brine, dried on anhydrous Na_2SO_4. The crude product was purified by column chromatography over silica gel using chloroform-methanol as eluent.

*[2-(7-Chloro-quinolin-4-ylamino)-ethyl]-***N,N'***-di-Boc-Lys-amide (3e)*

This compound was obtained as a yellowish white floppy solid in 72 % yield; mp 174-175 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.37 (s, 9H, NHCOOC(CH_3)$_3$), 1.43 (s, 9H,

NHCOOC(CH_3)$_3$), 1.61-1.83 (m, 4H, CH_2), 2.02-2.07 (m, 2H, CH_2), 2.95-3.00 (m, 2H, CH_2), 3.39-3.41 (m, 2H, CH_2), 3.65-3.70 (m, 2H, CH_2), 4.01-4.07 (m, 1H, C*H*), 4.62 (br s, 1H, N*H*), 5.30 (br s, 1H, N*H*), 6.25-6.27 (d, *J*=5.4 Hz, 1H, Ar-*H* quinoline), 6.56 (br s, 1H, N*H*), 7.22 (br s, 1H, N*H*), 7.31-7.38 (dd, *J*=8.9, 2.0 Hz, 1H, Ar-*H* quinoline), 7.79-7.83 (d, *J*=9.0 Hz, 1H, Ar-*H* quinoline), 7.90-7.91 (d, *J*=2.0 Hz, 1H, Ar-*H* quinoline), 8.44-8.47 (d, *J*=5.4 Hz, 1H, Ar-*H* quinoline); FAB-MS *m/z* 550 $[M+H]^+$; Anal. Calcd for $C_{27}H_{40}ClN_5O_5$: C, 58.95; H, 7.33; N, 12.73. Found: C, 58.99; H, 7.35; N, 12.69.

[3-(7-Chloro-quinolin-4-ylamino)-propyl]-N,N'-di-Boc-Lys-amide (3f)

This compound was obtained as a yellowish white sticky matter in 77 % yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (s, 18H, 2-NHCOOC(CH_3)$_3$), 1.66-1.75 (m, 6H, CH_2), 1.83 (br s, 1H, N*H*, D_2O Exchangeable), 3.10-3.13 (m, 2H, CH_2), 3.36-3.42 (m, 4H, CH_2), 4.08-4.10 (m, 2H, CH_2), 4.78 (br s, 1H, N*H*, D_2O Exchangeable), 5.55-5.58 (m, 1H, C*H*), 6.30-6.33 (d, *J*=5.6 Hz, 1H, Ar-*H* quinoline), 6.61 (br s, 1H, N*H*, D_2O Exchangeable), 7.33-7.38 (d, *J*=9.0 Hz, 1H, Ar-*H* quinoline), 7.92 (s, 1H, Ar-*H* quinoline), 8.06-8.11 (d, *J*=9.0 Hz, 1H, Ar-*H* quinoline), 8.16 (br s, 1H, N*H*, D_2O Exchangeable), 8.30-8.33 (d, *J*=5.5 Hz, 1H, Ar-*H* quinoline); FAB-MS *m/z* 564 $[M+H]^+$; Anal. Calcd for $C_{28}H_{42}ClN_5O_5$: C, 59.62; H, 7.50; N, 12.41. Found: C, 59.69; H, 7.52; N, 12.46.

[4-(7-Chloro-quinolin-4-ylamino)-butyl]-N,N'-di-Boc-Lys-amide (3g)

This compound was obtained as a yellowish white thick mass in 76 % yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.41 (s, 9H, NHCOOC(CH_3)$_3$), 1.44 (s, 9H, NHCOOC(CH_3)$_3$), 1.51-1.54 (m, 4H, CH_2), 1.65-1.75 (m, 4H, CH_2), 2.76 (br s, 1H, N*H*), 3.07-3.10 (m, 2H, CH_2), 3.29-3.35 (m, 2H, CH_2), 4.05-4.08 (m, 4H, CH_2), 4.73-4.79 (m, 1H, C*H*), 5.39 (br s, 1H, N*H*), 5.93 (br s, 1H, N*H*), 6.33-6.35 (d, *J*=5.4 Hz, 1H, Ar-*H* quinoline), 6.82 (br s, 1H, N*H*), 7.33-7.38 (dd, *J*=9.0, 2.0 Hz, 1H, Ar-*H* quinoline), 7.79-7.82 (s, 1H, Ar-*H* quinoline), 7.89-7.92 (d, *J*=8.8 Hz, 1H, Ar-*H* quinoline), 8.45-8.48 (d, *J*=5.4 Hz, 1H, Ar-*H* quinoline); FAB-MS *m/z* 578 $[M+H]^+$; Anal. Calcd for $C_{29}H_{44}ClN_5O_5$: C, 60.25; H, 7.67; N, 12.11. Found: C, 60.31; H, 7.71; N, 12.09.

[5-(7-Chloro-quinolin-4-ylamino)-pentyl]-N,N'-di-Boc-Lys-amide (3h)

This compound was obtained as a yellowish white solid in 72 % yield; mp 81-82 ºC; IR (KBr) 3331.3 cm^{-1}; 2932.1 cm^{-1}; 2861.8 cm^{-1}; 1583.7 cm^{-1}; 1452. 0 cm^{-1}; 1363.5 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (s, 9H, NHCOOC(CH_3)$_3$), 1.44 (s, 9H, NHCOOC(CH_3)$_3$), 1.54-1.60 (m, 12H, CH_2), 3.07-3.10 (m, 2H, CH_2), 3.29-3.35 (m, 4H, CH_2), 3.99-4.06 (m, 1H, C*H*), 4.61 (br s, 1H, N*H*), 5.18 (br s, 1H, N*H*), 5.62 (br s, 1H, N*H*), 6.36-6.38 (d, *J*=5.6 Hz, 1H, Ar-*H* quinoline), 6.47 (br s, 1H, N*H*), 7.32-7.38 (d, *J*=9.0 Hz, 1H, Ar-*H* quinoline), 7.95 (s, 1H, Ar-*H* quinoline), 7.99 (s, 1H, Ar-*H* quinoline), 8.47-8.50 (d, *J*=5.3 Hz, 1H, Ar-*H* quinoline); ^{13}C NMR ($CDCl_3$): δ 21.38, 22.73, 26.51, 27.00, 27.16 (3C), 28.21, 28.42 (3C), 30.53, 37.26, 38.52, 41.86, 51.24, 77.94, 78.84, 97.49, 115.88, 120.72, 123.85, 126.67, 133.72, 147.22, 149.13, 150.06, 154.60, 155.01, 171.50; FAB-MS *m/z* 592 $[M+H]^+$; Anal. Calcd for $C_{30}H_{46}ClN_5O_5$: C, 60.85; H, 7.83; N, 11.83. Found: C, 60.83; H, 7.79; N, 11.84.

General Synthetic Procedure for [(7-chloro-quinolin-4-ylamino)-alkyl]-Lys-amide. 2HCl (4e-4h)

Compounds **3e-3h** were treated with 4*N* HCl/Dioxane solution and kept for 1 h at room temperature. The solvent was evaporated under reduced pressure and the residue was precipitated with anhydrous ether, filtered and precipitate was thoroughly washed with ether and dried over anhydrous NaOH pellets under high vacuum.

[2-(7-Chloro-quinolin-4-ylamino)-ethyl]-Lys-amide. 2HCl (4e)

This compound was obtained as a pale yellowish viscous oily in 68 % yield; ^{1}H NMR (200 MHz, DMSOd_6 + $CDCl_3$): δ 1.37-1.40 (m, 2H, CH_2), 1.57-1.72 (m, 4H, CH_2), 2.71-2.77 (m, 2H, CH_2), 3.37-3.47 (m, 4H, CH_2), 3.70-3.71 (m, 1H, C*H*), 6.96-6.99 (d, *J*=6.8 Hz, 1H, Ar-*H* quinoline), 7.67-7.72 (d, *J*=9.0 Hz, 1H, Ar-*H* quinoline), 8.05 (br s, 2H, NH_2), 8.09 (s, 1H, Ar-*H* quinoline), 8.36 (br s, 2H, NH_2), 8.56-8.60 (d, *J*=7.0 Hz, 1H, Ar-*H* quinoline), 8.84-8.88 (d, *J*=8.7 Hz, 1H, Ar-*H* quinoline), 9.07 (br s, 1H, N*H*), 9.84 (br s, 1H, N*H*); FAB-MS *m/z* 351 $[M+H]^+$; Anal. Calcd for $C_{17}H_{26}Cl_3N_5O$: C, 48.30; H, 6.20; N, 16.57. Found: C, 48.36; H, 6.27; N, 16.60.

[3-(7-Chloro-quinolin-4-ylamino)-propyl]-Lys-amide. 2HCl (4f)

This compound was obtained as a pale yellowish white viscous matter in 72 % yield; ^{1}H NMR (200 MHz, DMSOd_6 + $CDCl_3$): δ 1.43-1.46 (m, 2H, CH_2), 1.61-1.65 (m, 2H, CH_2), 1.68-1.79 (m, 2H, CH_2), 1.82-1.94 (m, 2H, CH_2), 2.52-2.56 (m, 2H, CH_2), 2.75-2.82 (m, 2H, CH_2), 3.48-3.53 (m, 2H, CH_2), 3.63-3.69 (m, 1H, C*H*), 6.91-6.96 (d, *J*=7.0 Hz, 1H, Ar-*H* quinoline), 7.67-7.71 (d, *J*=7.71 Hz, 1H, Ar-*H* quinoline), 8.06 (br s, 2H, NH_2, D_2O Exchangeable), 8.25 (s, 1H, Ar-*H* quinoline), 8.32 (br s, 2H, NH_2, D_2O Exchangeable), 8.54-8.57 (d, *J*=6.9 Hz, 1H, Ar-*H* quinoline), 8.81-8.85 (d, *J*=9.1 Hz, 1H, Ar-*H* quinoline), 9.01 (br s, 1H, N*H*, D_2O Exchangeable), 9.77 (br s, 1H, N*H*, D_2O Exchangeable); ^{13}C NMR (DMSOd_6 + $CDCl_3$): δ 20.38, 25.16, 25.99, 29.32, 35.09, 37.60, 51.38, 65.56, 97.46, 114.56, 118.05, 125.05, 125.81, 137.51, 141.22, 148.92, 154.51, 167.60; FAB-MS *m/z* 364 $[M+H]^+$; Anal. Calcd for $C_{18}H_{28}Cl_3N_5O$: C, 49.49; H, 6.46; N, 16.03. Found: C, 49.52; H, 6.49; N, 16.01.

[4-(7-Chloro-quinolin-4-ylamino)-butyl]-Lys-amide. 2HCl (4g)

This compound was obtained as a yellowish white viscous matter in 72 % yield; ^{1}H NMR (200 MHz, DMSOd_6 + $CDCl_3$): δ 1.42-1.45 (m, 2H, CH_2), 1.65-1.79 (m, 4H, CH_2), 2.52-2.54 (m, 2H, CH_2), 2.77-2.84 (m, 2H, CH_2), 3.23-3.26 (m, 2H, CH_2), 3.50-3.59 (m, 4H, CH_2), 3.68 (br s, 1H, N*H*), 3.84-3.92 (m, 1H, C*H*), 6.87-6.90 (d, *J*=7.1 Hz, 1H, Ar-*H* quinoline), 7.64-7.70 (dd, *J*=9.0, 2.0 Hz, 1H, Ar-*H* quinoline), 8.06-8.07 (d, *J*=7.1 Hz, 1H, Ar-*H* quinoline), 8.29 (br s, 2H, NH_2), 8.53 (br s, 2H, 2-N*H*), 8.76-8.79 (d, *J*=5.5 Hz, 1H, Ar-*H* quinoline), 8.80-8.85 (d, *J*=9.1 Hz, 1H, Ar-*H* qui-

noline), 9.73 (br s, 1H, N*H*); FAB-MS *m/z* 377 $[M+H]^+$; Anal. Calcd for $C_{19}H_{30}Cl_3N_5O$: C, 50.62; H, 6.71; N, 15.33.Found: C, 50.63; H, 6.74; N, 15.39.

[5-(7-Chloro-quinolin-4-ylamino)-pentyl]-Lys-amide. 2HCl (4h)

This compound was obtained as a yellowish white solid in 64% yield; ^{1}H NMR (200 MHz, DMSOd_6 + $CDCl_3$): δ 1.37-1.50 (m, 4H, CH_2), 1.67-1.80 (m, 4H, CH_2), 2.51-2.53 (m, 2H, CH_2), 2.76-2.80 (m, 2H, CH_2), 3.14-3.18 (m, 2H, CH_2), 3.48-3.55 (m, 4H, CH_2), 3.78-3.80 (m, 1H, C*H*), 6.86-6.89 (d, *J*=5.4 Hz, 1H, Ar-*H* quinoline), 7.68-7.73 (dd, *J*=9.1, 1.9 Hz, 1H, Ar-*H* quinoline), 8.06-8.07 (d, *J*=2.0 Hz, 1H, Ar-*H* quinoline), 8.26 (s, 1H, Ar-*H* quinoline), 8.52 (br s, 4H, 2-NH_2), 8.73 (br s, 1H, N*H*), 8.78-8.82 (d, *J*=9.1 Hz, 1H, Ar-*H* quinoline), 9.72 (br s, 1H, N*H*); FAB-MS *m/z* 392 $[M+H]^+$; Anal. Calcd for $C_{20}H_{32}Cl_3N_5O$: C, 51.67; H, 6.94; N, 15.07. Found: C, 51.71; H, 6.91; N, 15.05.

General Synthetic Procedure for (7-chloro-quinolin-4-ylamino)-alkyl-di-Boc-Lys-(Di-Boc-Lys)-lysinyl amide (5e-5h)

Di-Boc-Lys OH (**2b**) (1038 mg, 3.0 mmol) was dissolved in dry THF. To this HOBt (405 mg, 3.0 mmol), appropriate compounds **4e-4h** (1.5 mmol) were dissolved in dry DMF and triethyl amine (0.42 ml, 3.0 mmol). DCC (625 mg, 3.0 mmol) was slowly added to the reaction mixture and resulting mixture was stirred for 30 min at 0ºC. The stirring was continued for additional 1 h at room temperature. DCU was removed by filtration and filtrate was evaporated to dryness *in vacuo*. The residue was taken in ethyl acetate and washed with 5% aq. $NaHCO_3$ and brine, dried on anhydrous Na_2SO_4. The crude product was purified by column chromatography over silica gel using chloroform-methanol as eluent.

2-(7-Chloro-quinolin-4-ylamino)-ethyl-Di-Boc-Lys-(Di-Boc-Lys)-lysinyl amide (5e)

This compound was obtained as a pale yellow white solid in 70 % yield; mp 90-91 ºC; IR (KBr) 3300.4 cm^{-1}; 2977.5 cm^{-1}; 1622.8 cm^{-1}; 1583.1 cm^{-1}; 1529.7 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.41 (s, 18H, 2-NHCOOC(CH_3)$_3$), 1.43 (s, 18H, 2-NHCOOC(CH_3)$_3$), 1.44-1.87 (m, 16H, CH_2), 3.04-3.07 (m, 4H, CH_2), 3.39-3.42 (m, 4H, CH_2), 3.60-3.66 (m, 4H, CH_2), 4.02-4.25 (m, 2H, 2-C*H*), 4.77-4.90 (m, 1H, C*H*), 5.59 (br s, 2H, 2-N*H*), 5.85 (br s, 2H, 2-N*H*), 6.29-6.31 (d, *J*=5.5 Hz, 1H, Ar-*H* quinoline), 6.72 (br s, 2H, 2-N*H*), 7.22-7.27 (dd, *J*=9.0, 2.0 Hz, 1H, Ar-*H* quinoline), 7.50 (br s, 2H, 2-N*H*), 7.34-7.38 (d, *J*=8.0 Hz, 1H, Ar-*H* quinoline), 7.92-7.93 (d, *J*=2.0 Hz, 1H, Ar-*H* quinoline), 8.44-8.47 (d, *J*=5.5 Hz, 1H, Ar-*H* quinoline); FAB-MS *m/z* 1007 $[M+H]^+$; Anal. Calcd for $C_{49}H_{80}ClN_9O_{11}$: C, 58.46; H, 8.01; N, 12.52. Found: C, 58.42; H, 7.96; N, 12.49.

3-(7-Chloro-quinolin-4-ylamino)-propyl-Di-Boc-Lys-(Di-Boc-Lys)-lysinyl amide (5f)

This compound was obtained as a yellowish white solid in 68 % yield; mp 83-84 ºC; IR (KBr) 3345.5 cm^{-1}; 2936.5 cm^{-1}; 2362.7 cm^{-1}; 1657.2 cm^{-1}; 1584.1 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (s, 36H, 4-NHCOOC(CH_3)$_3$), 1.74-1.88 (m, 22H, CH_2), 2.97-3.08 (m, 4H, CH_2), 3.16 (br s, 1H, N*H*, D_2O Exchangeable), 3.29-3.44 (m, 4H, CH_2), 4.20-4.26 (m, 1H, C*H*), 4.49-4.57 (m, 2H, 2C*H*), 4.81 (br s, 1H, N*H*, D_2O Exchangeable), 5.07 (br s, 1H, N*H*, D_2O Exchangeable), 6.33-6.37 (d, *J*=6.4 Hz, 1H, Ar-*H* quinoline), 6.69 (br s, 1H, N*H*, D_2O Exchangeable), 7.29-7.32 (d, *J*=9.0 Hz, 1H, Ar-*H* quinoline), 7.36 (br s, 1H, N*H*, D_2O Exchangeable), 7.67 (br s, 2H, 2-N*H*, D_2O Exchangeable), 7.78 (s, 1H, Ar-*H* quinoline), 7.96-8.00 (d, *J*=8.8 Hz, 1H, Ar-*H* quinoline), 8.25 (br s, 1H, N*H*, D_2O Exchangeable), 8.36-8.39 (d, *J*=6.1 Hz, 1H, Ar-*H* quinoline); FAB-MS *m/z* 1021 $[M+H]^+$; Anal. Calcd for $C_{50}H_{82}ClN_9O_{11}$: C, 58.84; H, 8.10; N, 12.35. Found: C, 59.00; H, 8.12; N, 12.33.

4-(7-Chloro-quinolin-4-ylamino)-butyl-Di-Boc-Lys-(Di-Boc-Lys)-lysinyl amide (5g)

This compound was obtained as a yellowish white solid in 62 % yield; mp 105-106 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (s, 36H, 4-NHCOOC(CH_3)$_3$), 1.71-1.79 (m, 16H, CH_2), 2.08-2.18 (m, 6H, CH_2), 3.08 (br s, 1H, N*H*), 3.27-3.38 (m, 10H, CH_2), 4.07 (br s, 1H, 1N*H*), 4.19-4.23 (m, 1H, C*H*), 4.79 (br s, 1H, N*H*), 4.94 (br s, 1H, N*H*), 5.61-5.65 (m, 1H, C*H*), 5.88-6.01 (m, 1H, C*H*), 6.04 (br s, 2H, 2-N*H*), 6.35-6.38 (d, *J*=5.5 Hz, 1H, Ar-*H* quinoline), 6.92 (br s, 1H, N*H*), 7.01 (br s, 1H, N*H*), 7.29-7.35 (dd, *J*=9.0, 1.8 Hz, 1H, Ar-*H* quinoline), 7.93 (s, 1H, Ar-*H* quinoline), 7.96-8.00 (d, *J*=9.0 Hz, 1H, Ar-*H* quinoline), 8.46-8.49 (d, *J*=5.4 Hz, 1H, Ar-*H* quinoline); ^{13}C NMR ($CDCl_3$): δ 20.32, 20.42, 20.98, 21.35, 24.01, 27.16 (6C), 28.42 (6C), 29.12, 29.84, 30.53, 36.54, 37.26, 38.52, 42.34, 43.74, 43.89, 44.64. 44.98, 54.56 (3C), 77.89 (4C), 97.67, 116.45, 121.54, 123.31, 125.98, 132.95, 146.84, 149.10, 150.11, 154.90 (4C), 167.21 (2C), 170.65; FAB-MS *m/z* 1035 $[M+H]^+$; Anal. Calcd for $C_{51}H_{84}ClN_9O_{11}$: C, 59.20; H, 8.18; N, 12.18. Found: C, 59.24; H, 8.21; N, 12.21.

5-(7-Chloro-quinolin-4-ylamino)-pentyl-Di-Boc-Lys-(Di-Boc-Lys)-lysinyl amide (5h)

This compound was obtained as a yellowish white solid in 68 % yield; mp 105-106 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (s, 36H, 4-NHCOOC(CH_3)$_3$), 1.60-1.80 (m, 26H, CH_2), 3.08-3.12 (m, 4H, CH_2), 3.23 (br s, 2H, 2-N*H*), 3.32-3.38 (m, 4H, CH_2), 4.08-4.11 (m, 1H, C*H*), 4.32-4.40 (m, 1H, C*H*), 4.81-4.87 (m, 1H, C*H*), 4.96 (br s, 1H, 1N*H*), 5.67 (br s, 1H, N*H*), 5.94 (br s, 2H, 2-N*H*), 6.35-6.39 (d, *J*=6.1 Hz, 1H, Ar-*H* quinoline), 6.87 (br s, 1H, N*H*), 7.08 (br s, 1H, N*H*), 7.33-7.38 (d, *J*=8.9 Hz, 1H, Ar-*H* quinoline), 7.98 (s, 1H, Ar-*H* quinoline), 8.23-8.29 (d, *J*=9.0 Hz, 1H, Ar-*H* quinoline), 8.38-8.41 (d, *J*=6.1 Hz, 1H, Ar-*H* quinoline) ; FAB-MS *m/z* 1049 $[M+H]^+$; Anal. Calcd for $C_{52}H_{86}ClN_9O_{11}$: C, 59.55; H, 8.27; N, 12.02. Found: C, 59.52; H, 8.24; N, 11.99.

General Synthetic Procedure for (7-chloro-quinolin-4-ylamino)-alkyl-Lys-(Lys)-lysinyl amide. 4HCl (6e-6h)

Compounds **5e-5h** were treated with 4*N* HCl/Dioxane solution and kept for 1 h at room temperature. The solvent was evaporated under reduced pressure and the residue was precipitated with anhydrous ether. The solid was filtered and thoroughly washed with ether and dried over anhydrous NaOH pellets under high vacuum.

2-(7-Chloro-quinolin-4-ylamino)-ethyl-Lys-(Lys)-lysinyl amide. 4HCl (6e)

This compound was obtained as a pale yellowish viscous oily in 66 % yield; ^{1}H NMR (200 MHz, DMSOd_6 + $CDCl_3$): δ 1.24-1.81 (m, 18H, CH_2), 2.78-2.84 (m, 6H, CH_2), 3.10 (br s, 2H, 2-N*H*), 3.39-3.49 (m, 4H, CH_2), 3.89-3.95 (m, 2H, 2-C*H*), 4.21-4.23 (m, 1H, C*H*), 6.97-7.00 (d, *J*=7.0 Hz, 1H, Ar-*H* quinoline), 7.67-7.72 (d, *J*=9.0 Hz, 1H, Ar-*H* quinoline), 8.15 (s, 1H, Ar-*H* quinoline), 8.26 (br s, 1H, N*H*), 8.36 (br s, 4H, 2-NH_2), 8.45 (br s, 4H, 2-NH_2), 8.58-8.61 (d, *J*=6.6 Hz, 1H, Ar-*H* quinoline), 8.79-8.83 (d, *J*=8.72 Hz, 1H, Ar-*H* quinoline), 9.81 (br s, 1H, N*H*); FAB-MS *m/z* 607 $[M+H]^+$; Anal. Calcd for $C_{29}H_{52}Cl_5N_9O_3$: C, 46.32; H, 6.97; N, 16.76. Found: C, 46.35; H, 7.01; N, 16.74.

3-(7-Chloro-quinolin-4-ylamino)-propyl-Lys-(Lys)-lysinyl amide. 4HCl (6f)

This compound was obtained as a yellowish white sticky matter in 64 % yield; ^{1}H NMR (200 MHz, DMSOd_6 + $CDCl_3$): δ 1.45-1.52 (m, 16H, CH_2), 1.64-1.74 (m, 6H, CH_2), 1.79-1.89 (m, 4H, CH_2), 2.79-2.88 (m, 4H, CH_2), 3.53 (br s, 1H, N*H*, D_2O Exchangeable), 3.85-3.97 (m, 2H, 2-C*H*), 4.26-4.31 (m, 1H, C*H*), 6.87-6.91 (d, *J*=6.7 Hz, 1H, Ar-*H* quinoline), 7.61-7.66 (d, *J*=9.6 Hz, 1H, Ar-*H* quinoline), 8.02 (s, 1H, Ar-*H* quinoline), 8.09 (br s, 1H, N*H*, D_2O Exchangeable), 8.13 (br s, 1H, N*H*, D_2O Exchangeable), 8.32 (br s, 4H, 2-NH_2, D_2O Exchangeable), 8.47 (br s, 1H, N*H*, D_2O Exchangeable), 8.84-8.88 (m, 2H, Ar-*H* quinoline), 9.35 (br s, 2H, NH_2, D_2O Exchangeable), 9.84 (br s, 2H, NH_2, D_2O Exchangeable); ^{13}C NMR (DMSOd_6 + $CDCl_3$): δ 20.06, 20.37, 24.35, 25.16, 26.52, 29.30, 30.45, 30.84, 30.96, 31.21, 37.57, 38.76, 38.85, 39.60, 39.98, 51.45 (3C), 97.69, 113.94, 114.70, 118.14, 122.46, 125.84, 137.32, 137.62, 141.67, 154.51, 167.38, 170.67; FAB-MS *m/z* 620 $[M+H]^+$; Anal. Calcd for $C_{30}H_{54}Cl_5N_9O_3$: C, 47.03; H, 7.10; N, 16.46. Found: C, 47.06; H, 7.17; N, 16.49.

4-(7-Chloro-quinolin-4-ylamino)-butyl-Lys-(Lys)-lysinyl amide. 4HCl (6g)

This compound was obtained as a yellowish white viscous oily in 58 % yield; ^{1}H NMR (200 MHz, DMSOd_6 + $CDCl_3$): δ 1.14-1.25 (m, 16H, CH_2), 1.39-1.48 (m, 6H, CH_2), 1.59-1.79 (m, 6H, CH_2), 2.79-2.84 (m, 2H, CH_2), 3.13-3.17 (m, 2H, CH_2), 3.50-3.54 (m, 1H, C*H*), 3.68-3.72 (m, 1H, C*H*), 3.93-3.97 (m, 1H, C*H*), 6.87-6.91 (d, *J*=7.3 Hz, 1H, Ar-*H* quinoline), 7.65-7.70 (d, *J*=8.9 Hz, 1H, Ar-*H* quinoline), 8.07 (s, 1H, Ar-*H* quinoline), 8.18-8.23 (d, *J*=8.9 Hz, 1H, Ar-*H* quinoline), 8.31 (br s, 4H, 2-NH_2), 8.37 (br s, 4H, 2-NH_2), 8.55 (br s, 2H, 2-N*H*), 8.77-8.80 (d, *J*=7.2 Hz, 1H, Ar-*H* quinoline), 8.82 (br s, 1H, N*H*), 9.75 (br s, 1H, N*H*); FAB-MS *m/z* 634 $[M+H]^+$; Anal. Calcd for $C_{31}H_{56}Cl_5N_9O_3$: C, 47.73; H, 7.24; N, 16.16. Found: C, 47.69; H, 7.18; N, 16.18.

5-(7-Chloro-quinolin-4-ylamino)-pentyl-Lys-(Lys)-lysinyl amide. 4HCl (6h)

This compound was obtained as a yellowish white viscous oily in 62 % yield; IR (neat) 3446.7 cm^{-1}; 2364.7 cm^{-1}; 1637.5 cm^{-1}; 1461.4 cm^{-1}; ^{1}H NMR (200 MHz, DMSOd_6 + $CDCl_3$): δ 1.47-1.80 (m, 20H, CH_2), 2.79-2.86 (m, 6H, CH_2), 3.11-3.16 (m, 4H, CH_2), 3.69-3.79 (m, 4H, CH_2), 3.91-3.97 (m, 2H, 2-C*H*), 4.28-4.30 (m, 1H, C*H*), 6.84-6.88 (d, *J*=6.3 Hz, 1H, Ar-*H* quinoline), 7.63-7.69 (d, *J*=8.1 Hz, 1H, Ar-*H* quinoline), 8.10 (s, 1H, Ar-*H* quinoline), 8.17 (br s, 2H, 2-N*H*), 8.35 (br s, 4H, 2-NH_2), 8.44 (br s, 4H, 2-NH_2), 8.79 (s, 1H, Ar-*H* quinoline), 8.84-8.89 (d, *J*=9.5 Hz, 1H, Ar-*H* quinoline), 9.80 (br s, 2H, 2-N*H*); FAB-MS *m/z* 648 $[M+H]^+$; Anal. Calcd for $C_{32}H_{58}Cl_5N_9O_3$: C, 48.40; H, 7.36; N, 15.87. Found: C, 48.46; H, 7.35; N, 15.89.

BIOLOGICAL STUDIES

Measurement of In Vitro Antimalarial Activity

Both CQS (D6) and CQR (Dd2) *P. falciparum* maintained continuously in culture were used. Asynchronous cultures were diluted with uninfected erythrocytes and complete medium (RPMI-1640 with 0.5% Albumax II) to achieve 0.2% parasitemia and 2% hematocrit. In 96-well microplates, chloroquine (positive control) or test compounds diluted in complete medium from 10 mM stock in DMSO were added to the cell mixture to yield triplicate wells with drug concentrations ranging from 0 to 10^{-4} M in a final well volume of 100 μL. After 72 h of incubation under standard culture conditions, plates were harvested and read by the SYBR Green I fluorescence-based method [21] using a 96-well fluorescence plate reader (Gemini-EM, Molecular Devices), with excitation and emission wavelengths at 497 and 520 nm, respectively. The fluorescence readings were plotted against log [drug], and the IC_{50} values were obtained from curve fitting performed by nonlinear regression using Prism [24].

Measurement of *In Vivo* Antimalarial Activity

The *in vivo* drug response was evaluated in Swiss mice infected with *P. yoelii* (N-67 strain). The mice (22±2g) were inoculated with 1x 10^6 parasitised RBC on day 0 and treatment was administered to a group of five mice from day 0 to 3, once daily [22]. The aqueous suspension of compounds were prepared with a few drops of Tween 80. The efficacy of test compounds was evaluated at 30.0 mg/kg/day and required daily dose was administered in 0.2 mL volume *via* intraperitoneal route. Parasitaemia levels were recorded from thin blood smears between days 4 and 28 [23]. The mean value determined for a group of 5 mice was used to calculate the percent suppression of parasitaemia with respect to the untreated control group. Mice treated with CQ served as positive controls.

Determination of Log P

The Log *P* values of 4-aminoquinoline derivatives were calculated by Pallas [25].

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