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Synthesis, Antimalarial, Antileishmanial, Antimicrobial, Cytotoxicity and Methemoglobin (MetHb) Formation Activities of New 8-Quinolinamines

Kirandeep Kaur[a], **Sanjay R. Patel**[#a], **Premanand Patil**[#a], **Meenakshi Jain**[a], **Shabana I. Khan**[b], **Melissa R. Jacob**[b], **Babu L. Tekwani**[b], and **Rahul Jain**[*,a]

[a]Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research, Sector 67, S.A.S. Nagar, Punjab, India 160 062, India

[b]National Center for Natural Products Research, School of Pharmacy, University of Mississippi, MS 38677, USA

[#] These authors contributed equally to this work.

Abstract

We report the synthesis, in vitro antiprotozoal (against *Plasmodium* and *Leishmania*), antimicrobial, cytotoxicity (Vero and MetHb-producing properties) and in vivo antimalarial activities of two series of 8-quinolinamines. *N*1-{4-[2-(*tert*-Butyl)-6-methoxy-8-quinolylamino]pentyl}-(2*S*/2*R*)-2-aminosubstitutedamides (**21**–**33**) and *N*1-[4-(4-ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentyl]-(2*S*/2*R*)-2-aminosubstitutedamides (**51**–**63**) were synthesized in six steps from 6-methoxy-8-nitroquinoline and 4-methoxy-2-nitro-5-pentyloxyaniline, respectively. Several analogs displayed promising antimalarial activity in vitro against *P. falciparum* D6 (chloroquine-sensitive) and W2 (chloroquine-resistant) clones with high selectivity indices vs. mammalian cells. The most promising analogs (**21**–**24**) also displayed potent antimalarial activity in vivo in a *P. berghei*-infected mouse model. Most interestingly, many analogs exhibited promising in vitro antileishmanial activity against *L. donovani* promastigotes, and antimicrobial activities against a panel of pathogenic bacteria and fungi. Several analogs, notably **21**–**24**, **26**–**32** and **60,** showed less MetHb formation compared to primaquine indicating the potential of these compounds in 8-quinolinamine-based antimalarial drug development.

[*]**Address for Correspondence:** Dr. Rahul Jain Department of Medicinal Chemistry National Institute of Pharmaceutical Education and Research Sector 67, S.A.S. Nagar, Punjab, 160 062, India rahuljain@niper.ac.in Tel no.: 91-0172-221-4682 Fax: 91-0172-221-4692.

1. Introduction

Protozoan infections remain a major threat to public health especially in the tropical parts of the world. More than a third of world's population is at risk of contracting malaria. It is estimated that approximately 7000 people, mainly children under the age of 5 years and pregnant women in Africa and other parts of world, die of malaria every day.[1] Malaria is one of the main obstacles to socio-economic development in sub-Saharan Africa and other tropical regions of the world.

Leishmaniases is a group of diseases caused by infection with intracellular species of the parasitic protozoan of the genus *Leishmania* with different clinical forms ranging from cutaneous leishmaniasis (CL) with skin lesions to visceral leishmaniasis (VL) with enlargement of liver, spleen and bone marrow dysfunctions.[2] The disease is endemic worldwide with estimated 12 million cases, which are mostly centered in Asia, Mediterranean regions of Europe, Africa, Central America and South America. VL caused due to infection with *Leishmania donovani* is fatal if left untreated.

In the early 1970s, it was believed that virtually any microbial infection could be treated, as a wide range of antimicrobial agents (antibiotics) were available. The belief proved short-lived, when pathogens resistant to the conventional antibiotics routinely used to treat microbial infections emerged. The widespread use of antibiotics allowed many microbial strains to evolve ways to adapt or become resistant to the currently available treatment regimens, resulting in an urgent need for new antimicrobial drugs.[3, 4]

The emergence of *Plasmodium falciparum* strains resistant to almost all the antimalarials currently in use has prompted researchers around the world to search for its effective replacement. This occurrence revitalized research efforts to discover an entirely new structural class of compounds or revisit the existing antimalarials which were earlier considered inactive against *P. falciparum*.[5] 8-Quinolinamines, including primaquine (**1**, PQ, Fig. 1), constitute an interesting and versatile class of drugs,[5] which in addition to antimalarial activity against *P. vivax* and *P. ovale*, also exhibit antileishmanial[6, 7] and anticoccidial activities.[8] PQ has a limited role in current malaria chemotherapy due to its limited activity against asexual blood stages of the malaria parasite, severe hematotoxicities in patients with the glucose-6-phosphate dehydrogenase (G-6-PD) deficiency,[9] and a short half-life due to its rapid metabolism to inactive and toxic metabolites.[10–13] Despite of these negative attributes, PQ is deemed a worthy candidate for additional structural optimization because it is the only antimalarial drug which exhibit a certain degree of activity against almost all the stages in the life cycle of the human malaria parasite.[5] We have already reported two new 8-quinolinamines (**2** and **3**, Fig. 1) with promising blood schizontocidal antimalarial activities. 2-*tert*-Butylprimaquine **2** (suppressive at 10 mg/kg, in vivo against *P. berghei*) was synthesized to eliminate a putative oxidative metabolic pathway known for several quinoline ring-containing antimalarial drugs including quinine by the placement of a bulky metabolically stable *tert*-butyl group at C-2 of the heterocycle.[14] While, 4-ethyl-5-pentyloxyprimaquine **3** (suppressive at 5 mg/kg, in vivo against *P. berghei*) was synthesized to optimize substitution at the C-4 and C-5 position of PQ, known sites of transformation to inactive/toxic metabolites.[15] It is known that approximately 35-83% of PQ is metabolized to

the inactive 4-(6-methoxy-quinolin-8-ylamino)pentanoic acid in a primate model.[11] We have reported antimalarial activities of several L-amino acid conjugates of PQ in which the amino acid residue possibly protects the side-chain amino group of PQ from oxidation to the abovementioned carboxylic acid.[16–18] In continuation of our efforts on the development of 8-quinolinamines as a versatile bioactive class of compounds, we report herein synthesis, of two series of the amino acid conjugated 8-quinolinamines **21**–**33** and **51**–**63** (Fig. 2), in which side-chain amino group of the most promising 8-quinolinamines **2** and **3** was derivatized,[19] and their in vitro and in vivo antimalarial activity, Vero cell cytotoxicity, in vitro MetHb-inducing properties, and in vitro antileishmanial and antimicrobial activity.

2. Chemistry

Commercially available 6-methoxy-8-nitroquinoline **4** upon direct ring-alkylation via a silver catalyzed radical oxidative decarboxylation of trimethylacetic acid by ammonium persulfate in CH_3CN and 10% H_2SO_4 at 70-80 °C for 15 min produced 2-*tert*-butyl-6-methoxy-8-nitroquinoline **5** (Scheme 1).[14] The reaction is highly regiospecific and provides an efficient method for direct ring-alkyl of electron deficient quinoline ring under acidic reaction conditions. Catalytic hydrogenation of the latter compound **5** in 95% ethyl alcohol with wet raney-nickel catalyst (T_1 grade) at 45 psi in a Parr hydrogenator for 45 min gave the highly hygroscopic and light-sensitive 2-*tert*-butyl-6-methoxy-8-quinolinamine **6** which was subjected to the next step without purification. Condensation of **6** with 2-(4-bromopentyl)-1,3-isoindolinedione[20] in the presence of Et_3N at 120 °C for 24 h provided the 2-[4-(2-*tert*-butyl-6-methoxy-8-quinolylamino)pentyl]-1,3-isoindolinedione **7**, which upon hydrazinolysis with hydrazine hydrate in 95% ethyl alcohol at 80 °C for 8 h afforded the *N*8-(4-amino-1-methylbutyl)-2-(*tert*-butyl)-6-methoxy-8-quinolinamine **2** (Scheme 1).[14]

Reaction of 1-chloro-3-pentanone by its addition in two equal portions to the well stirred homogenous mixture of 4-methoxy-2-nitro-5-pentyloxyaniline **34** and *o*-phosphoric acid at 80 °C followed by the addition of As_2O_5 produced the 4-ethyl-6-methoxy-8-nitro-5-pentyloxyquinoline **35**. The latter compound **35** was converted to *N*8-(4-amino-1-methylbutyl)-4-ethyl-6-methoxy-5-pentyloxy-8-quinolinamine **3** in three steps following aforementioned procedure (Scheme 2).[17]

Compounds **2** and **3** upon reaction with suitably side-chain protected Cbz/Boc-L/D- amino acid in the presence of DCC in DCM for 6 h at ambient temperature gave the (*S*/*R*)-{alkoxycarbonylamino-1-[4-(2-*tert*-butyl-6-methoxy-8-quinolylamino)pentylcarbamoyl]-alkyl} carbamic acid benzyl/*tert*-butyl esters **8**–**20** and (*S*/*R*)-{alkoxycarbonylamino-1-[4-(4-ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentylcarbamoyl]alkyl}carbamic acid benzyl/*tert*-butyl esters **38**–**50**, respectively (Scheme 1-2).

Finally, (*S*/*R*)-{alkoxycarbonylamino-1-[4-(2-*tert*-butyl-6-methoxy-8-quinolylamino)-pentylcarbamoyl]alkyl}carbamic acid benzyl/*tert*-butyl esters **8**–**20** and (*S*/*R*)-{alkoxycarbonylamino-1-[4-(4-ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentylcarbamoyl]alkyl}carbamic acid benzyl/*tert*-butyl esters **38**–**50** were deprotected using the procedure(s) described in the experimental section (5.3) to provide *N*1-{4-[2-(*tert*-butyl)-6-methoxy-8-quinolylamino]pentyl}-(2*S*/2*R*)-2-

aminosubstitutedamides **21**–**33** and *N*1-[4-(4-ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentyl]-(2*S*/2*R)*-2-aminosubstitutedamides **51**–**63**, respectively (Scheme 1-2).

3. Biological Activities

3.1.1. Antimalarial, cytotoxicity and MetHb Activities

Determination of in vitro antimalarial activity was based on the plasmodial LDH activity.[21] As shown in Table 1-2, antimalarial activities of analogs **21**–**33** and **51**–**63** are reported as IC_{50} values versus chloroquine-sensitive (D6) and chloroquine-resistant (W2) strains of *P. falciparum*. Analogs **21**–**24** (series 1) were most potent with IC_{50} values in the range of 180 – 300 ng/mL for D6 and 300 – 450 ng/mL for W2 compared to IC_{50} of 2000 and 2800 ng/mL for standard drug primaquine (Table 1). While, remaining analogs **25**–**32** produced modest IC_{50} in the range between 770 – 2800 ng/mL for D6 strain and 600–2300 ng/mL for drug-resistant W2 strain of *P. falciparum.* Analog **33** was found to be inactive. In contrast, analogs **51**–**63** were less active (Table 2). The most active compound **51** of this series exhibited IC_{50} of 580 ng/mL for D6 strain and 730 ng/mL for W2 strain of *P. falciparum*. The remaining analogs produced modest IC_{50} in the range between 700 – 4760 ng/mL for D6 clone and 950 – 3600 ng/mL for W2 clone (Table 2).

The in vitro cytotoxicity of analogs (series 1-2) was determined against mammalian kidney fibroblast (Vero) cell line (obtained from ATCC) up to a highest concentration of 23.8 μg/mL by neutral red assay.[22, 23] None of the compounds were cytotoxic up to the highest test concentration. The selectivity index (ratio of IC_{50} in Vero cells to IC_{50} in *P. falciparum* strain) for all compounds was calculated (Table 1-2). Analogs **21**–**24** (series 1) with highest antimalarial activity were found to exhibit a very high selectivity index to plasmodial strains (>132 – >79.33 for D6 clone and >79 – 53 for W2 clone) compared to 11.9 (D6 clone) and 8.5 (W2 clone) for PQ indicating their better safety profile.

Hematotoxicity by 8-quinolinamines is caused due to their metabolism to the toxic metabolites, which are unstable and difficult to isolate.[24] The analogs of both series were also tested for metabolism-linked methemoglobin toxicity in vitro and % MetHb formation was calculated at 20 μg/mL in comparison to vehicle control.[25] All the analogs of series 1 (**21**–**33**) induced substantially less % MetHb formation (26.8 – 40.6%) compared to PQ (47.9%) as shown in Table 1. All the tested analogs of series 2 produced almost similar MetHb formation as that of PQ except analog **60** which showed significantly lower 34.2% MetHb formation (Table 2).

The most active analogs **21**–**24** (series 1) were selected for in vivo evaluation of the blood-schizontocidal antimalarial activity against *P. berghei* (sensitive strain) in a rodent malaria model as described (Table 3).[14] Briefly; mice (6 mice per group) were dosed orally at 100, 50, 25 and 10 mg/kg/day×4 (oral). Chloroquine was used as a positive control at a suppressive dose of 10 mg/kg/day×4 (oral). The negative consisted of untreated (vehicle only) mice in which 100% mortality was observed within 6–8 days, with a mean survival time of 6.2 days. The compounds/vehicle were administered on days 0 – 3 post infection. All compounds produced 100% cure at the primary test dose of 100 mg/kg. Analogs **21**–**22**

and **24** were also curative at the lower test dose of 50 mg/kg, while **23** was found to show suppressive activity. The most potent compound **21** also produced a 100% cure rate at the lower test dose of 25 mg/kg and was suppressive at the lowest test dose of 10 mg/kg (2/6 cures) (Table 3). These results are in agreement with our earlier observation that attachment of a cationic side-chain amino acid led to a considerable increase in antimalarial activity of 8-quinolinamines.[15] It can be presumed that these side-chain modified ring-substituted PQ analogs have substantially improved therapeutic index (higher blood-schizontocidal antimalarial activity and reduced MetHb toxicity) possibly due to their reduced penetration into the red cells because of steric hindrance that does not allow destabilization of the red cell membrane, inducing hemolysis, which is the source of main toxicity. At the same time, attachment of an amino acid residue may serve to protect the PQ's primary side-chain amino function against metabolic processes discussed earlier.

3.1.2. Antileishmanial Activities

Antileishmanial activity of the compounds was tested in vitro against a culture of *L. donovani* promastigotes by Alamar Blue assay.[26, 27] It was interesting to note that 8-quinolinamine analogs **25**, **27**–**29**, **32**, **57**–**59**, and **62** exhibited stronger antileishmanial activities with IC_{50} values ranging between 2.7 – 4.6 μg/mL (Table 4) in comparison to the activity of PQ (IC_{50} = 19.9 μg/mL). The activity was comparable to the standard drug pentamidine (IC_{50} = 1 μg/mL) used as positive control. Their IC_{90} values ranged from 6.5 – 18 μg/mL as compared to IC_{90} of 3.8 μg/mL for pentamidine. However, they were much less potent than amphotericin B (IC_{50} = 0.19 and IC_{90} = 0.35 μg/mL).

3.1.3. Antimicrobial Activities

The antibacterial activities of the 8-quinolinamines **21**–**33** and **51**–**63** against methicillin-resistant *S. aureus* (MRS) and *Mycobacterium intracellulare* are reported in Table 5 including the positive control Ciprofloxacin. Most of the analogs (e.g. **21**–**32**, **57**–**59)** exhibited promising antibacterial activity against MRS (IC_{50} = 3 – 15 μg/mL and MIC = 5 – 20 μg/mL). Compounds **57** and **27** were bactericidal at 5 and 10 μg/mL, respectively (Table 5). Analogs **22**–**24**, **27**–**29** and **32** also showed activity against *M. intracellulare* (IC_{50} = 4.5 – 15 μg/mL and MIC = 10 – 20 μg/mL). Analogs **27** and **29** were the most potent against both MRS (IC_{50} = 3 μg/mL, MIC = 5 μg/mL, MBC = 10 μg/mL) and *M. intracellulare* (IC_{50} = 7 μg/mL, MIC = 10 μg/mL, MBC = 20 μg/mL) and were bactericidal to both organisms. Analog **57** was the most bactericidal against MRS with an IC_{50} of 3.0 μg/mL, MIC and MBC of 5 μg/mL but was inactive against *M. intracellulare* at the highest test concentration of 20 μg/mL (Table 5).

The antifungal of the 8-quinolinamines **21**–**33** and **51**–**63** against the opportunistic yeast *Candida albicans*, *C. glabrata*, *C. krusei*, and *Cryptococcus neoformans*, along with the positive control Amphotericin B, are summarized in Table 6. All compounds were inactive at 20 μg/mL against the filamentous fungus *Aspergillus fumigatus* (data not shown).

Analog **57** was the most potent of all 8-quinolinamines tested and produced fungicidal activities against *C. albicans* (IC_{50} = 10 μg/mL, MIC = 20 μg/mL, MFC = 20 μg/mL), *C. glabrata* (IC_{50} = 4 μg/mL, MIC = 10 μg/mL, MFC = 10 μg/mL), *C. krusei* (IC_{50} = 7 μg/mL,

MIC = 10 μg/mL, MFC = 10 μg/mL) and *C. neoformans* (IC_{50} = 3.5 μg/mL, MIC = 5 μg/mL, MFC = 5 μg/mL). All analogs (excluding **60**, **61** and **63**) exhibited promising activity against *C. neoformans* with MFCs as low as 5 μg/mL (analogs **21**–**23, 25, 27, 57**–**58, 62**) (Table 6).

4. Conclusions

We have reported synthesis and biological activities of two new series of 8-quinolinamines. Several of the reported analogs have exhibited potent in vitro activity against drug-sensitive and drug-resistant malaria parasites. Analogs **21**–**24** have also displayed promising antimalarial activity in vivo in a *P. berghei*-mouse malaria model. The most potent compound **21** was found curative at 25 mg/kg and suppressive at 10 mg/kg. The potent 8-quinolinamines were also found to exhibit high selectivity index and a significantly reduced methemoglobin toxicity, indicating their better safety profiles than primaquine. Several analogs also displayed high antileishmanial activities comparable to standard drug pentamidine and superior to that of primaquine. The compounds were also evaluated against a panel of pathogenic bacteria and fungi and displayed promising activities. In conclusion, the results of this study confirm that 8-quinolinamines are a versatile class of compounds that exhibit broad-spectrum of activities against parasitic and infectious diseases. The careful structural optimization of this class of compounds could lead to promising agents with utility in treatment of malaria, leishmaniasis and opportunistic infections.

5. Experimental

5.1. Synthesis

Melting points were recorded on Mettler DSC 851 or capillary melting point apparatus and are uncorrected. ^{1}H spectra were recorded on 300 MHz Bruker FT-NMR (Avance DPX300) spectrometer using tetramethylsilane as internal standard and the chemical shifts are reported in δ units. Mass spectra were recorded on HRMS (Finnigan Mat LCQ spectrometer) (APCI/ESI). Elemental analyses were recorded on Elementar Vario EL spectrometer. All chromatographic purification was performed with silica gel 60 (230–400 mesh), whereas all TLC (silica gel) development was performed on silica gel coated (Merck Kiesel 60 F_{254}, 0.2 mm thickness) sheets. All chemicals were purchased from Aldrich Chemical Ltd. (Milwaukee, WI, USA). Solvents used for the chemical synthesis acquired from commercial sources were of analytical grade, and were used without further purification unless otherwise stated.

5.2. General method for the synthesis of *S/R*)-{alkoxycarbonylamino-1-[4-(2-*tert*-butyl-6-methoxy-8-quinolylamino)pentylcarbamoyl]alkyl}carbamic acid benzyl/*tert*-butyl esters (8–20) and (*S/R*-{alkoxycarbonylamino-1-[4-(4-ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentylcarbamoyl]alkyl}carbamic acid benzyl/*tert*-butyl esters (38–50)

To an ice cooled stirred solution of *N*8-(4-amino-1-methylbutyl)-2-(*tert*-butyl)-6-methoxy-8-quinolinamine[14] (**2**, 1 mmol) or *N*8-(4-amino-1-methylbutyl)-4-ethyl-6-methoxy-5-pentyloxy-8-quinolinamine[17] (**3**, 1 mmol) and suitably side-chain protected Cbz/Boc-L/D-amino acid (1.1 mmol) in CH_2Cl_2 (15 mL), DCC (1.1 mmol) was added. Reaction mixture

was allowed to attain ambient temperature and stirring was continued for another 6 h. The solvent was removed under reduced pressure and ethyl acetate (20 mL) was added to the residue. The reaction mixture was kept in refrigerator overnight and the separated 1,3-dicyclohexylurea (DCU) was filtered. Filtrate was washed with saturated sodium bicarbonate solution (3 × 5 mL) followed by water (2 × 5 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude product, which was purified by flash column chromatography on silica gel using EtOAc/hexanes (30:70) to afford the (*S*/*R*)-{alkoxycarbonylamino-1-[4-(2-*tert*-butyl-6-methoxy-8-quinolylamino)pentylcarbamoyl]-alkyl}carbamic acid benzyl/*tert*-butyl esters (**8**–**20**) and (*S*/*R*)-{alkoxycarbonylamino-1-[4-(4-ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentylcarbamoyl]alkyl}carbamic acid benzyl/*tert*-butyl esters (**38**–**50**).

5.2.1. (*R*)-{5-Benzyloxycarbonylamino-1-[4-(2-*tert*-butyl-6-methoxy-8-quinolyl-amino)pentylcarbamoyl]pentyl}carbamic acid benzyl ester (8)—Yield: 85%; oil; IR (neat): 3431, 3019, 2855, 1713, 1675 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.86 (d, 1H, *J* = 8.60 Hz), 7.40 (d, 1H, *J* = 8.55 Hz), 7.31 (m, 10H), 6.30 (d, 1H, *J* = 2.40 Hz), 6.24 (d, 1H, *J* = 2.40 Hz), 5.04 (m, 4H), 4.10 (m, 1H), 3.84 (s, 3H), 3.58 (m, 2H), 3.27 (m, 2H), 3.12 (m, 2H), 1.41 (m, 10H), 1.40 (s, 9H), 0.89 (d, 3H, *J* = 6.50 Hz); APCIMS: *m/z* 712 (M+1); Anal. Calcd for $C_{41}H_{53}N_5O_6$ (711.9): C, 69.17; H, 7.50; N, 9.84. Found: C, 69.34; H, 7.34; N, 9.99.

5.2.2. (*R*)-{4-*tert*-Butoxycarbonylamino-1-[4-(2-*tert*-butyl-6-methoxy-8-quinolyl-amino)pentylcarbamoyl]butyl}carbamic acid *tert*-butyl ester (9)—Yield: 75%; oil; IR (neat): 3362, 2965, 2863, 1715, 1694 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.86 (d, 1H, *J* = 8.60 Hz), 7.40 (d, 1H, *J* = 8.58 Hz), 6.30 (d, 1H, *J* = 2.30 Hz), 6.24 (s, 1H, *J* = 2.30 Hz), 5.14 (brs, 1H), 4.64 (brs, 1H), 4.10 (m, 1H), 3.87 (s, 3H), 3.32 (t, 2H, *J* = 6.60 Hz), 3.05 (m, 1H), 1.65 (m, 4H), 1.59 (m, 6H), 1.42 (m, 18H), 1.40 (s, 9H), 1.29 (d, 3H, *J* = 6.40 Hz); APCIMS: *m/z* 630 (M+1); Anal. Calcd for $C_{34}H_{55}N_5O_6$ (629.8): C, 64.84; H, 8.80; N, 11.12. Found: C, 64.54; H, 8.99; N, 10.99.

5.2.3. (*S*)-{4-(*N,N'*-Bisbenzyloxycarbonylguanidino)-1-[4-(2-*tert*-butyl-6-methoxy-8-quinolylamino)pentylcarbamoyl]butyl}carbamic acid *tert*-butyl ester (10)—Yield: 67%; mp. 113-115 °C; IR (KBr): 3384, 2965, 2843, 1718 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.40 (brs, 2H), 7.86 (d, 1H, *J* = 8.60 Hz), 7.40 (d, 1H, *J* = 8.60 Hz), 7.35 (m, 10H), 6.55 (brs, 1H), 6.30 (s, 1H), 6.21 (s, 1H), 6.08 (brs, 1H), 5.21 (m, 2H), 5.09 (m, 2H), 4.96 (m, 1H), 4.29 (m, 2H), 3.86 (s, 3H), 3.65 (m, 2H), 3.47 (t, 2H, *J* = 6.70 Hz), 2.97 (m, 1H), 1.71 (m, 6H), 1.42 (s, 9H), 1.38 (s, 9H), 1.26 (d, 3H, *J* = 6.0 Hz); APCIMS: *m/z* 841 (M+1); Anal. Calcd for $C_{46}H_{61}N_7O_8$ (840.0): C, 65.77; H, 7.32; N, 11.67. Found: C, 66.03; H, 6.99; N, 11.57.

5.2.4. (*R*)-{4-(*N,N'*-Bisbenzyloxycarbonylguanidino)-1-[4-(2-*tert*-butyl-6-methoxy-8-quinolylamino)pentylcarbamoyl]butyl}carbamic acid *tert*-butyl ester (11)—Yield: 70%; mp. 114-116 °C; IR (KBr): 3390, 2970, 2840, 1688, 1727 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.43 (brs, 1H), 9.40 (brs, 1H), 7.84 (d, 1H, *J* = 8.70 Hz), 7.42 (d, 1H, *J* = 8.70 Hz), 7.33 (m, 10H), 6.51 (brs, 1H), 6.32 (s, 1H), 6.25 (s, 1H), 6.10 (brs, 1H),

5.20 (m, 2H), 5.14 (m, 2H), 4.93 (m, 1H), 4.23 (m, 2H), 3.80 (s, 3H), 3.67 (m, 2H), 3.44 (t, 2H, *J* = 6.70 Hz), 2.99 (m, 1H), 1.73 (m, 6H), 1.42 (s, 9H), 1.40 (s, 9H), 1.25 (d, 3H, *J* = 6.0 Hz); APCIMS: *m/z* 841 (M+1); Anal. Calcd for $C_{46}H_{61}N_7O_8$ (840.0): C, 65.77; H, 7.32; N, 11.67. Found: C, 65.70; H, 7.55; N, 11.41.

5.2.5. (*S*)-{2-(3-Benzyloxymethyl-1*H*-imidazol-4-yl)-1-[4-(2-*tert*-butyl-6-methoxy-8-quinolylamino)pentylcarbamoyl]ethyl}carbamic acid *tert*-butyl ester (12)—Yield: 85%; oil; IR (neat): 3476, 2965, 2863, 1698, 1091 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.86 (d, 1H, *J* = 8.60 Hz), 7.48 (s, 1H), 7.44 (d, 1H, *J* = 8.60 Hz), 7.29 (m, 5H), 6.88 (s, 1H), 6.30 (s, 1H), 6.23 (s, 1H), 6.10 (brs, 1H), 5.98 (m, 2H), 5.33 (brs, 1H), 5.21 (m, 2H), 4.47 (m, 1H), 3.85 (s, 3H), 3.13 (m, 2H), 3.05 (m, 3H), 1.65 (m, 4H), 1.42 (s, 9H), 1.38 (s, 9H), 1.28 (d, 3H, *J* = 6.50 Hz); APCIMS: *m/z* 673 (M+1); Anal. Calcd for $C_{38}H_{52}N_6O_5$ (672.9): C, 67.83; H, 7.79; N, 12.49. Found: C, 67.96; H, 7.51; N, 12.31.

5.2.6. (*R*)-{2-(3-Benzyloxymethyl-1*H*-imidazol-4-yl)-1-[4-(2-*tert*-butyl-6-methoxy-8-quinolylamino)pentylcarbamoyl]ethyl}carbamic acid *tert*-butyl ester (13)—Yield: 90%; oil; IR (neat): 3426, 2965, 2870, 1726 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.90 (d, 1H, *J* = 8.60 Hz), 7.50 (s, 1H), 7.44 (d, 1H, *J* = 8.60 Hz), 7.30 (m, 5H), 6.90 (s, 1H), 6.32 (s, 1H), 6.24 (s, 1H), 6.12 (brs, 1H), 5.95 (m, 2H), 5.34 (brs, 1H), 5.22 (m, 2H), 4.50 (m, 1H), 3.84 (s, 3H), 3.17 (m, 2H), 3.08 (m, 3H), 1.67 (m, 4H), 1.40 (s, 9H), 1.40 (s, 9H), 1.30 (d, 3H, *J* = 6.30 Hz); APCIMS: *m/z* 673 (M+1); Anal. Calcd for $C_{38}H_{52}N_6O_5$ (672.9): C, 67.83; H, 7.79; N, 12.49. Found: C, 67.53; H, 7.88; N, 12.20.

5.2.7. (*S*)-[1-[4-(2-*tert*-Butyl-6-methoxy-8-quinolylamino)pentylcarbamoyl]-2-(1*H*-indol-3-yl)ethyl]carbamic acid *tert*-butyl ester (14)—Yield: 96%; oil; IR (neat): 3384, 2927, 2854, 1694 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.91 (d, 1H, *J* = 8.60 Hz), 7.47 (d, 1H, *J* = 8.60 Hz), 7.10 (m, 5H), 6.89 (d, 1H, *J* = 5.70 Hz), 6.35 (s, 1H), 6.22 (s, 1H), 6.05 (brs, 1H), 5.39 (brs, 1H), 4.36 (m, 1H), 3.90 (s, 3H), 3.46 (m, 2H), 3.28 (m, 2H), 3.03 (m, 1H), 1.55 (m, 4H), 1.42 (s, 9H), 1.25 (s, 9H), 0.88 (d, 3H, *J* = 6.50 Hz); APCIMS: *m/z* 602 (M +1); Anal. Calcd for $C_{35}H_{47}N_5O_4$ (601.8): C, 69.86; H, 7.87; N, 11.64. Found: C, 69.55; H, 7.63; N, 12.03.

5.2.8. (*S*)-{1-[4-(2-*tert*-Butyl-6-methoxy-8-quinolylamino)pentylcarbamoyl]-3-methyl-sulfanylpropyl}carbamic acid *tert*-butyl ester (15)—Yield: 90%; oil; IR (neat): 3345, 2965, 2870, 1694 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.86 (d, 1H, *J* = 8.60 Hz), 7.40 (d, 1H, *J* = 8.60 Hz), 6.30 (d, 1H, *J* = 2.40 Hz), 6.24 (d, 1H, *J* = 2.40 Hz), 6.14 (brs, 1H), 5.18 (brs, 1H), 4.17 (m, 1H), 3.86 (s, 3H), 3.60 (m, 1H), 3.29 (m, 2H), 2.55 (m, 2H), 2.06 (m, 2H), 1.65 (m, 7H), 1.42 (s, 9H), 1.40 (s, 9H), 1.22 (d, 3H, *J* = 6.40 Hz); APCIMS: *m/z* 547 (M+1); Anal. Calcd for $C_{29}H_{46}N_4O_4S$ (546.8): C, 63.70; H, 8.48; N, 10.25. Found: C, 63.31; H, 8.78; N, 10.12.

5.2.9. (*S*)-{1-[4-(2-*tert*-Butyl-6-methoxy-8-quinolylamino)pentylcarbamoyl]-2-phenyl-ethyl}carbamic acid *tert*-butyl ester (16)—Yield: 92%; oil; IR (neat): 3383, 2965, 2875, 1724, 1678 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.86 (d, 1H, *J* = 8.60 Hz), 7.40 (d, 1H, *J* = 8.60 Hz), 7.22 (m, 5H), 6.30 (s, 1H), 6.22 (s, 1H), 6.09 (brs, 1H), 5.68 (brs, 1H,), 4.23 (m,

1H), 3.86 (s, 3H), 3.53 (m, 1H), 3.20 (m, 2H), 2.98 (m, 2H), 1.64 (m, 4H), 1.42 (s, 9H), 1.37 (s, 9H), 1.25 (d, 3H, *J* = 6.50 Hz); APCIMS: *m/z* 563 (M+1); Anal. Calcd for $C_{33}H_{46}N_4O_4$ (562.7): C, 70.43; H, 8.24; N, 9.96. Found: C, 70.79; H, 8.18; N, 10.24.

5.2.10. (*S*)-{2-(4-Benzyloxyphenyl)-1-[4-(2-*tert*-butyl-6-methoxy-8-quinolylamino)-pentylcarbamoyl]ethyl}carbamic acid *tert*-butyl ester (17)— Yield: 97%; oil; IR (neat): 3324, 2929, 2854, 1690, 1124 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.86 (d, 1H, *J* = 8.60 Hz), 7.40 (d, 1H, *J* = 8.60 Hz), 7.24 (m, 5H), 7.10 (d, 2H, *J* = 7.50 Hz), 6.86 (d, 2H, *J* = 7.50 Hz), 6.30 (d, 1H, *J* = 2.30 Hz), 6.22 (d, 1H, *J* = 2.30 Hz), 6.09 (brs, 1H), 5.73 (brs, 1H), 5.03 (m, 1H), 4.93 (m, 2H), 3.86 (s, 3H), 3.55 (m, 2H), 3.20 (m, 2H), 2.98 (m, 1H), 1.64(m, 4H), 1.42 (s, 9H), 1.37 (s, 9H), 1.26 (d, 3H, *J* = 6.48 Hz); APCIMS: *m/z* 669 (M+1); Anal. Calcd for $C_{40}H_{52}N_4O_5$ (668.9): C, 71.83; H, 7.84; N, 8.38. Found: C, 71.66; H, 7.98; N, 8.14.

5.2.11. (*S*)-{2-Benzyloxy-1-[4-(2-*tert*-butyl-6-methoxy-8-quinolylamino)pentyl-carbamoyl]ethyl}carbamic acid *tert*-butyl ester (18)—Yield: 80%; oil; IR (neat): 3372, 2966, 2848, 1707 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.86 (d, 1H, *J* = 8.58 Hz), 7.40 (d, 1H, *J* = 8.56 Hz), 7.33 (m, 5H), 6.44 (brs, 1H), 6.30 (d, 1H, *J* = 2.20 Hz), 6.24 (s, 1H), 6.12 (brs, 1H), 5.40 (brs, 1H), 4.52 (m, 2H), 4.21 (m, 1H), 3.86 (s, 3H), 3.52 (m, 2H), 3.33 (m, 1H), 3.29 (d, 2H, *J* = 6.36 Hz), 1.64 (m, 4H), 1.42 (s, 9H), 1.39 (s, 9H), 1.26 (d, 3H, *J* = 6.48Hz); APCIMS: *m/z* 593 (M+1); Anal. Calcd for $C_{34}H_{48}N_4O_5$ (592.8): C, 68.89; H, 8.16; N, 9.45. Found: C, 69.12; H, 7.99; N, 9.17.

5.2.12. (*R*)-{2-Benzylsulfanyl-1-[4-(2-*tert*-butyl-6-methoxy-8-quinolylamino)pentyl-carbamoyl]ethyl}carbamic acid *tert*-butyl ester (19)— Yield: 95%; oil; IR (neat): 3324, 2959, 2856, 1659 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.86 (d, 1H, *J* = 8.58 Hz), 7.43 (d, 1H, *J* = 8.58 Hz), 7.30 (m, 5H), 6.30 (d, 1H, *J* = 2.28 Hz), 6.25 (d, 1H, *J* = 2.21 Hz), 6.14 (m, 2H), 5.26 (brs, 1H), 4.15 (m, 1H), 3.86 (s, 3H), 3.59 (m, 2H), 3.30 (m, 2H), 2.78 (m, 1H), 1.64 (m, 4H), 1.41 (s, 9H), 1.37 (s, 9H), 1.25 (d, 3H, *J* = 6.48 Hz); APCIMS: *m/z* 609 (M+1); Anal. Calcd for $C_{34}H_{48}N_4O_4S$ (608.9): C, 67.07; H, 7.95; N, 9.20. Found: C, 69.12; H, 7.99; N, 9.17.

5.2.13. (*R*)-{1-[4-(2-*tert*-Butyl-6-methoxy-8-quinolylamino)pentylcarbamoyl]-2-trityl-sulfanylethyl}carbamic acid *tert*-butyl ester (20)—Yield: 90%; oil; IR (neat): 3324, 2929, 2856, 1662 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.86 (d, 1H, *J* = 8.37 Hz), 7.34 (m, 15H), 7.21 (d, 1H, *J* = 8.41 Hz), 6.30 (s, 1H), 6.22 (s, 1H), 6.09 (brs, 1H), 5.98 (brs, 1H), 4.81 (m, 1H), 3.86 (s, 3H), 3.52 (m, 2H), 3.22 (m, 2H), 2.50 (m, 1H), 1.61 (m, 4H), 1.41 (s, 9H), 1.37 (s, 9H), 1.25 (d, 3H, *J* = 5.13 Hz); APCIMS: *m/z* 762 (M+1); Anal. Calcd for $C_{46}H_{56}N_4O_4S$ (761.0): C, 72.60; H, 7.42; N, 7.36. Found: C, 72.51; H, 7.64; N, 7.57.

5.2.14. (*R*)-{5-Benzyloxycarbonylamino-1-[4-(4-ethyl-6-methoxy-5-pentyloxy-8-quinolyl-amino)pentylcarbamoyl]pentyl}carbamic acid benzyl ester (38)— Yield: 84%; oil; IR (neat): 3303, 1684 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.38 (m, 1H), 7.31 (m, 10H), 7.13 (m, 1H), 6.48 (s, 1H), 5.07 (m, 4H), 4.13 (m, 1H), 3.97 (s, 3H), 3.86 (t, 2H, *J* = 7.0 Hz), 3.64 (m, 1H), 3.20 (m, 6H), 1.56 (m, 15H), 1.27 (m, 6H), 0.92 (t, 3H, *J* = 7.2 Hz);

APCIMS: *m/z* 770.4 (M+1); Anal. Calcd for $C_{44}H_{59}N_5O_7$ (769.7): C, 68.64; H, 7.72; N, 9.10. Found: C, 68.95; H, 7.39; N, 9.47.

5.2.15.(*R*)-{4-*tert*-Butoxycarbonylamino-1-[4-(4-ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentylcarbamoyl]butyl}carbamic acid *tert*-butyl ester (39)— Yield: 67%; oil; IR (neat): 3333, 1694 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.38 (d, 1H, *J* = 4.4 Hz), 7.12 (d, 1H, *J* = 4.3 Hz),), 6.51 (brs, 1H), 6.43 (s, 1H), 6.06 (brs, 1H), 5.15 (brs, 1H), 4.67 (brs, 1H), 4.12 (m, 1H), 3.96 (s, 3H), 3.87 (t, 2H, *J* = 6.9 Hz), 3.63 (m, 1H), 3.27-3.20 (m, 6H), 1.70 (m, 14H), 1.39 (s, 18H), 1.28 (m, 6H), 0.94 (t, 3H, *J* = 7.0 Hz); APCIMS: *m/z* 688 (M+1); Anal. Calcd for $C_{37}H_{61}N_5O_7$ (687.9): C, 64.60; H, 8.94; N, 10.18. Found: C, 64.31; H, 8.55; N, 10.37.

5.2.16. (*S*)-{4-(*N*,*N*'-Bisbenzyloxycarbonylguanidino)-1-[4-(4-ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentylcarbamoyl]butyl}carbamic acid benzyl ester (40)—Yield: 77%; mp. 120-122 °C; IR (KBr): 3384, 3292, 1704, 1642 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.42 (brs, 1H), 9.29 (brs, 1H), 8.38 (d, 1H, *J* = 4.0 Hz), 7.34 (m, 15H), 7.11 (d, 1H, *J* = 3.60 Hz), 6.57 (brs, 1H), 6.38 (s, 1H), 6.27 (brs, 1H), 6.01 (brs, 1H), 5.20 (s, 2H), 5.11 (m, 4H), 4.31 (m, 1H), 3.95 (s, 3H), 3.86 (t, 2H, *J* = 6.70 Hz), 3.51 (m, 1H), 3.37 (m, 2H), 2.92 (m, 2H), 1.74 (m, 6H), 1.38 (m, 8H), 1.30 (m, 6H), 1.19 (d, 2H, *J* = 6.0 Hz), 0.92 (t, 3H, *J* = 6.80 Hz); APCIMS: *m/z* 933 (M+1); Anal. Calcd for $C_{52}H_{65}N_7O_9$ (932.1): C, 67.00; H, 7.03; N, 10.50. Found: C, 67.19; H, 7.30; N, 10.32.

5.2.17. (*R*)-{4-(*N*,*N*'-Bisbenzyloxycarbonylguanidino)-1-[4-(4-ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentylcarbamoyl]butyl}carbamic acid benzyl ester (41)—Yield: 75%; mp. 120-122 °C; IR (KBr): 3385, 3292, 1716, 1623 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.41 (brs, 1H), 9.29 (brs, 1H), 8.39 (d, 1H, *J* = 4.30 Hz), 7.35 (m, 15H), 7.11 (d, 1H, *J* = 4.20 Hz), 6.58 (brs, 1H), 6.39 (s, 1H), 6.27 (brs, 1H), 6.02 (brs, 1H), 5.20 (s, 2H), 5.11 (m, 4H), 4.31 (m, 1H), 3.95 (s, 3H), 3.86 (t, 2H, *J* = 7.10 Hz), 3.52 (m, 1H), 3.25 (m, 2H), 2.92 (m, 2H), 1.77 (m, 6H), 1.44-1.36 (m, 8H), 1.31 (m, 6H), 1.19 (d, 2H, *J* = 6.20 Hz), 0.94 (t, 3H, *J* = 7.0 Hz); APCIMS: *m/z* 933 (M+1); Anal. Calcd for $C_{52}H_{65}N_7O_9$ (932.1): C, 67.00; H, 7.03; N, 10.50. Found: C, 66.77; H, 6.88; N, 10.89.

5.2.18. (*S*)-{2-(1-Benzyloxymethyl-1*H*-imidazol-4-yl)-1-[4-(4-ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)-pentylcarbamoyl]ethyl}carbamic acid *tert*-butyl ester (42)—Yield: 73%; oil; IR (neat): 3332, 1662 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.39 (d, 1H, *J* = 4.0 Hz), 7.50 (d, 1H, *J* = 5.0 Hz), 7.30 (m, 5H), 7.12 (d, 1H, *J* = 4.4 Hz), 6.89 (s, 1H), 6.42 (s, 1H), 6.04 (brs, 1H), 5.31 (m, 3H), 4.49 (s, 2H), 4.34 (m, 1H), 3.97 (s, 3H), 3.87 (t, 2H, *J* = 7.0 Hz), 3.57 (m, 1H), 3.22 (m, 2H), 3.14 (m, 2H), 3.06 (d, 2H, *J* = 7.0 Hz), 1.83 (m, 2H), 1.45 (m, 17H), 1.28 (m, 6H), 0.94 (t, 3H, *J* = 7.0 Hz); APCIMS: *m/z* 731 (M+1); Anal. Calcd for $C_{41}H_{58}N_6O_6$ (730.9): C, 67.37; H, 8.00; N, 11.50. Found: C, 67.76; H, 7.77; N, 11.21.

5.2.19. (*R*)-{2-(1-Benzyloxymethyl-1*H*-imidazol-4-yl)-1-[4-(4-ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentylcarbamoyl]ethyl}carbamic acid *tert*-butyl ester (43)—Yield: 67%; oil; IR (neat): 3316, 1675 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.38 (d, 1H,

J = 4.0 Hz), 7.48 (d, 1H, *J* = 5.3 Hz), 7.29 (m, 5H), 7.10 (d, 1H, *J* = 4.2 Hz), 6.89 (s, 1H), 6.42 (s, 1H), 6.06 (brs, 1H), 5.29 (m, 3H), 4.48 (s, 2H), 4.32 (m, 1H), 3.96 (s, 3H), 3.87 (t, 2H, *J* = 7.0 Hz), 3.57 (m, 1H), 3.23 (m, 2H), 3.13 (m, 2H), 3.05 (d, 2H, *J* = 7.1 Hz), 1.83 (t, 2H), 1.46 (m, 17H), 1.27 (m, 6H), 0.94 (t, 3H, *J* = 6.9 Hz); APCIMS: *m/z* 731 (M+1); Anal. Calcd for $C_{41}H_{58}N_6O_6$ (730.9): C, 67.37; H, 8.00; N, 11.50. Found: C, 68.00; H, 8.34; N, 11.75.

5.2.20. (*S*)-[1-[4-(4-Ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentylcarbamoyl]-2-(1*H*-indol-3-yl)ethyl]carbamic acid *tert*-butyl ester (44)—Yield: 76%; mp. 46-48 °C; IR (KBr): 3320, 1701, 1659 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.53 (brs, 1H), 9.05 (brs, 1H), 8.48 (d, 1H, *J* = 4.5 Hz), 7.70 (m, 2H), 7.30-6.98 (m, 5H), 6.42 (s, 1H), 5.85 (s, 1H), 5.53 (brs, 1H), 4.44 (m, 1H), 3.97 (s, 3H), 3.91 (t, 2H, *J* = 6.9 Hz), 3.51 (m, 1H), 3.30 (m, 4H), 3.06 (m, 2H), 1.85 (m, 7H), 1.65 (m, 6H), 1.40 (s, 9H), 1.32 (m, 6H), 0.95 (t, 3H, *J* = 7.0 Hz); APCIMS: *m/z* 660 (M+1); Anal. Calcd for $C_{38}H_{53}N_5O_5$ (659.9): C, 69.17; H, 8.10; N, 10.61. Found: C, 69.45; H, 8.02; N, 10.31.

5.2.21. (*S*)-1-[4-(4-Ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentylcarbamoyl]-2-phenylethyl}carbamic acid *tert*-butyl ester (45)—Yield 73%; oil; IR (neat): 3392, 1718, 1668 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.39 (d, 1H, *J* = 3.4 Hz), 7.18 (m, 6H), 6.41 (s, 1H), 6.03 (brs, 1H), 5.87 (brs, 1H), 5.11 (brs, 1H), 4.25 (m, 1H), 3.96 (s, 3H), 3.87 (t, 2H, *J* = 6.7 Hz), 3.58 (m, 1H), 3.23 (m, 4H), 3.02 (m, 2H), 1.83 (m, 2H), 1.53 (m, 8H), 1.38 (s, 9H), 1.30 (m, 6H), 0.94 (t, 3H, *J* = 6.7 Hz); APCIMS: *m/z* 621 (M+1); Anal. Calcd for $C_{36}H_{52}N_4O_5$ (620.8): C, 69.65; H, 8.44; N, 9.02. Found: C, 69.78; H, 8.23; N, 9.34.

5.2.22. (*S*-{2-(4-Benzyloxyphenyl)-1-[4-(4-ethyl-6-methoxy-5-pentyloxy-8-quinolyl-amino)pentylcarbamoyl]ethyl}carbamic acid *tert*-butyl ester (46)—Yield 97%; mp. 60-62 °C; IR (KBr): 3335, 1684, 1654 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.38 (d, 1H, *J* = 4.2 Hz), 7.35 (m, 5H), 7.09 (m, 3H), 6.87 (m, 2H), 6.42 (s, 1H), 6.02 (brs, 1H), 5.74 (brs, 1H), 5.03 (brs, 1H), 4.96 (m, 2H), 4.19 (m, 1H), 3.95 (s, 3H), 3.86 (t, 2H, *J* = 6.8 Hz), 3.59 (m, 1H), 3.22 (m, 4H), 2.99 (m, 2H), 1.77 (m, 2H), 1.60 (m, 8H), 1.39 (s, 9H), 1.27 (m, 6H), 0.94 (t, 3H, *J* = 7.0 Hz); APCIMS: *m/z* 727 (M+1); Anal. Calcd for $C_{43}H_{58}N_4O_6$ (726.9): C, 71.05; H, 8.04; N, 7.71. Found: C, 71.41; H, 8.21; N, 7.48.

5.2.23. (*S*)-{1-[4-(4-Ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentylcarbamoyl]-3-methylsulfanylpropyl}carbamic acid *tert*-butyl ester (47)—Yield 85%; mp. 46-48 °C; IR (KBr): 3320, 1693, 1660 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.40 (d, 1H, *J* = 4.3 Hz), 7.13 (m, 1H), 6.44 (s, 1H), 6.28 (brs, 1H), 5.17 (brs, 1H), 4.20 (m, 2H), 3.96 (s, 3H), 3.88 (t, 2H, *J* = 7.0 Hz), 3.64 (m, 1H), 3.26 (m, 4H), 2.53 (m, 2H), 2.07 (m, 5H), 1.85 (m, 4H), 1.68 (m, 6H), 1.41 (s, 9H), 1.26 (m, 6H), 0.94 (t, 3H, *J* = 7.0 Hz); APCIMS: *m/z* 605 (M+1); Anal. Calcd for $C_{32}H_{52}N_4O_5S$ (604.8): C, 63.54; H, 8.67; N, 9.26. Found: C, 63.24; H, 8.44; N, 8.91.

5.2.24. (*S*)-{2-Benzyloxy-1-[4-(4-ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentyl-carbamoyl]ethyl}carbamic acid *tert*-butyl ester (48)—Yield 77%; oil; IR (neat): 3401, 1742, 1664 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.38 (d, 1H, *J* = 4.0

Hz), 7.27 (m, 5H), 7.11 (d, 1H, *J* = 4.2 Hz), 6.47 (brs, 1H), 6.42 (s, 1H), 6.07 (brs, 1H), 5.39 (brs, 1H), 4.50 (m, 2H), 4.25 (m, 1H), 3.96 (s, 3H), 3.87 (t, 2H, *J* = 7.18 Hz), 3.60 (m, 1H), 3.55 (m, 2H), 3.26 (m, 4H), 1.80 (m, 2H), 1.65 (m, 8H), 1.39 (s, 9H), 1.27(m, 6H), 0.94 (t, 3H, *J* = 6.9 Hz); APCIMS: *m/z* 651 (M+1); Anal. Calcd for $C_{37}H_{54}N_4O_6$ (650.8): C, 68.28; H, 8.36; N, 8.61. Found: C, 68.56; H, 8.09; N, 8.21.

5.2.25. (*R*)-{2-Benzylsulfanyl-1-[4-(4-ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)-pentylcarbamoyl]ethyl}carbamic acid *tert*-butyl ester (49)—

Yield 97%; oil; IR (neat): 3324, 1652 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.39 (d, 1H, *J* = 4.5 Hz), 7.32-7.21 (m, 5H), 7.12 (d, 1H, *J* = 4.3 Hz), 6.43 (s, 1H), 6.24 (brs, 1H), 6.06 (brs, 1H), 5.25 (brs, 1H), 4.15 (m, 1H), 4.05 (s, 3H), 3.87 (t, 2H, *J* = 6.9 Hz), 3.71 (d, 2H, *J* = 2.9 Hz), 3.63 (m, 1H), 3.25 (m, 4H), 2.82 (m, 2H), 1.80 (m, 2H), 1.64 (m, 8H), 1.37 (s, 9H), 1.29-1.25 (m, 6H), 0.94 (t, 3H, *J* = 7.0 Hz); APCIMS: *m/z* 667 (M+1); Anal. Calcd for $C_{37}H_{54}N_4O_5S$ (666.9): C, 66.63; H, 8.16; N, 8.40. Found: C, 66.33; H, 8.44; N, 8.21.

5.2.26. (*R*)-{{1-[4-(4-Ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentylcarbamoyl]-2-tritylsulfanylethyl}carbamic acid *tert*-butyl ester (50)—

Yield 98%; oil; IR (neat): 3322, 1666 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.37 (m, 1H), 7.40 (m, 5H), 7.24(m, 10H), 7.11 (m, 1H), 6.41 (s, 1H), 6.04 (brs, 2H), 4.80 (brs, 1H), 4.12 (m, 1H), 3.95 (s, 3H), 3.89 (t, 2H, *J* = 6.7 Hz), 3.60 (m, 1H), 3.22 (m, 4H), 2.04 (m, 2H), 1.82 (m, 2H), 1.63 (m, 8H), 1.38 (s, 9H), 1.27 (m, 6H), 0.94 (t, 3H, *J* = 6.70 Hz); APCIMS: *m/z* 820 (M+1); Anal. Calcd for $C_{49}H_{62}N_4O_5S$ (819.1): C, 71.85; H, 7.63; N, 6.84. Found: C, 72.11; H, 7.39; N, 7.02.

5.3. General method for the synthesis of *N*1-{4-[2-(*tert*-butyl)-6-methoxy-8-quinolylamino]pentyl}-(2*S*/2*R*)-2-aminosubstitutedamides (21 –33) and *N*1-[4-(4-ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentyl]-(2 *S*/2 *R)*-2-aminosubstitutedamides (51–63)

In cases where α-amino group was protected with *N*-α-*tert*-butoxycarbonyl (*tert*-Boc) group following protocol was used.

To a solution of *tert*-Boc protected quinoline derivatives (0.5 mmol) was added 4N methanolic HCl solution (5 mL). Reaction mixture was allowed to stir at ambient temperature for 1 h. Solvent was removed under reduced pressure to afford oil, which upon crystallization with anhydrous diethyl ether gave product.

In cases where α-amino group was protected with *N*-α-benzyloxycarbonyl (Cbz) group, following protocol was used.

To a mixture of Cbz protected quinoline derivatives (0.5 mmol), glacial acetic acid (1 mL) and 10% Pd/C (0.1 g) in methanol (20 mL) was bubbled a slow stream of hydrogen gas for 1 h. The catalyst was removed by filtration, and filtrate was concentrated under reduce pressure to afford oil, which upon treatment with a solution of ethereal hydrogen chloride produced product. Recrystallized from diethyl ether.

Alternatively, in cases where amino acid was protected with benzyl (Bzl) and *tert*-Boc groups, following protocol was used.

A mixture of fully protected amino acid conjugates of 8-quinolinamine (0.5 mmol) and 30% HBr in acetic acid (5 ml) was stirred at ambient temperature for 30 min. Solvent was removed under reduced pressure to afford oil, which upon recrystallization with diethyl ether gave desired product.

5.3.1.*N*1-{4-[2-(*tert*-Butyl)-6-methoxy-8-quinolylamino]pentyl}-(2 *R*)-2,6-diaminohexan- amide.3HCl (21)—Yield: 95%; mp. (salt) 108-110 °C; IR (KBr): 3392, 3019, 2856, 1690 cm^{-1}; ^1H NMR (CD_3OD): δ7.72 (m, 2H), 7.60 (m, 2H), 4.22 (brs, 2H), 4.10 (m, 1H), 4.06 (m, 4H), 3.85 (s, 3H), 3.81 (m, 1H), 1.68 (m, 4H), 1.35 (m, 6H), 0.97 (m, 12H); APCIMS: *m/z* 444 (M+1); Anal. Calcd for $C_{25}H_{44}Cl_3N_5O_2$ (553.0): C, 54.30; H, 8.02; N, 12.66. Found: C, 53.94; H, 7.77; N, 12.95.

5.3.2.*N*1-{4-[2-(*tert*-Butyl)-6-methoxy-8-quinolylamino]pentyl}-(2 *R*)-2,6-diaminopentan- amide.3HCl (22)—Yield: 96%; mp. (salt) 100-102 °C; IR (KBr): 3390, 2962, 1673 cm^{-1}; ^1H NMR (D_2O): δ8.22 (d, 1H, *J*=8.81 Hz), 7.72 (m, 2H), 7.26 (s, 1H), 4.71 (m, 1H), 3.90 (s, 3H), 3.18 (t, 2H, *J* = 6.28 Hz), 2.97 (m, 3H), 1.85 (m, 4H), 1.80 (m, 4H), 1.38 (s, 9H), 1.27 (d, 3H, *J* = 6.48 Hz); APCIMS: *m/z* 430 (M+1); Anal. Calcd for $C_{24}H_{42}Cl_3N_5O_2$ (539.0): C, 53.48; H, 7.85; N, 12.99. Found: C, 53.23; H, 7.47; N, 12.76.

5.3.3.*N*1-{4-[2-(*tert*-Butyl)-6-methoxy-8-quinolylamino]pentyl}-(2 *S*)-2-amino-5-amino-(imino)methylaminopentanamide.3HCl (23)—Yield: 67%; mp. (salt) 112-114 °C; IR (KBr): 3407, 2963, 1666 cm^{-1}; ^1H NMR (D_2O): δ8.01 (d, 1H, *J* = 8.80 Hz), 7.49 (d, 1H, *J* = 8.80 Hz), 7.21 (s, 1H), 7.04 (s, 1H), 4.55 (m, 1H), 3.63 (s, 3H), 3.30 (m, 2H), 2.79 (m, 5H), 1.50 (m, 6H), 1.31 (s, 9H), 1.04 (d, 3H, *J* = 6.52 Hz); APCIMS: *m/z* 472 (M+1); Anal. Calcd for $C_{25}H_{44}Cl_3N_7O_2$ (581.0): C, 51.68; H, 7.63; N, 16.87. Found: C, 51.21; H, 7.44; N, 17.09.

5.3.4.*N*1-{4-[2-(*tert*-Butyl)-6-methoxy-8-quinolylamino]pentyl}-(2 *R*)-2-amino-5-amino-(imino)methylaminopentanamide.3HCl (24)—Yield: 83%; mp. (salt) 111-112 °C; IR (KBr): 3355, 2929, 1667 cm^{-1}; ^1H NMR (D_2O): δ8.10 (d, 1H, *J* = 8.70 Hz), 7.53 (d, 1H, *J* = 8.70 Hz), 7.20 (s, 1H), 7.02 (s, 1H), 4.51 (m, 1H), 3.65 (s, 3H), 3.32 (m, 2H), 2.81 (m, 5H), 1.55 (m, 6H), 1.30 (s, 9H), 1.04 (d, 3H, *J* = 6.52 Hz); APCIMS: *m/z* 472 (M+1); Anal. Calcd for $C_{25}H_{44}Cl_3N_7O_2$ (581.0): C, 51.68; H, 7.63; N, 16.87. Found: C, 51.89; H, 7.96; N, 16.68.

5.3.5.*N*1-{4-[2-(*tert*-Butyl)-6-methoxy-8-quinolylamino]pentyl}-(2*S*)-2-amino-3-(1*H*-imidazol-4-yl)propanamide.3HCl (25)—Yield: 70%; mp. (salt) 121-123 °C; IR (KBr): 3418, 2929, 2870, 1679 cm^{-1}; ^1H NMR (D_2O): δ8.62 (s, 1H), 8.39 (d, 1H, *J* = 8.52 Hz), 7.56 (d, 1H, *J* = 8.52 Hz), 7.45 (s, 1H), 7.32 (m, 2H), 4.13 (m, 1H), 3.47 (s, 3H), 3.40 (t, 2H, *J* = 6.28 Hz), 3.23 (m, 1H), 3.04 (m, 2H) 1.50 (m, 4H), 1.24 (s, 9H), 1.12 (d, 3H, *J* = 5.20 Hz); APCIMS: *m/z* 453 (M+1); Anal. Calcd for $C_{25}H_{39}Cl_3N_6O_2$ (562.0): C, 53.43; H, 6.99; N, 14.95. Found: C, 53.72; H, 7.21; N, 14.68.

5.3.6.*N*1-{4-[2-(*tert*-Butyl)-6-methoxy-8-quinolylamino]pentyl}-(2*R*)-2-amino-3-(1*H*-imidazol-4-yl)propanamide.3HCl (26)—Yield: 79%; mp. (salt) 120-122 °C; IR (KBr): 3402, 2931, 2856, 1682 cm^{-1}; ^1H NMR (CD_3OD): δ8.82 (s, 1H), 8.73 (d, 1H, , *J* =

8.76 Hz), 8.49 (brs, 1H), 7.79 (d, 1H, *J* = 8.80 Hz), 7.75 (s, 1H), 7.52 (s, 1H), 7.28 (s, 1H), 4.29 (m, 1H), 4.06 (brs, 1H), 3.88 (s, 3H), 3.48 (m, 2H), 3.34 (m, 2H), 3.24 (m, 1H), 1.45 (m, 4H), 1.31 (s, 9H), 1.14 (d, 3H, *J* = 6.48 Hz); APCI: *m/z* 453 (M+1); Anal. Calcd for $C_{25}H_{39}Cl_3N_6O_2$ (562.0): C, 53.43; H, 6.99; N, 14.95. Found: C, 53.21; H, 6.88; N, 14.88.

5.3.7.*N*1-{4-[2-(*tert*-Butyl)-6-methoxy-8-quinolylamino]pentyl}-(2*S*)-2-amino-3-(1*H*-indol-3-yl)propanamide.2HCl (27)—Yield: 85%; mp. (salt) 117-119 °; IR (KBr): 3387, 2926, 1675 cm^{-1}; ^1H NMR (DMSO-d_6): δ8.26 (brs, 1H), 8.18 (d, 1H, *J* = 8.40 Hz), 7.69 (m, 2H), 7.40 (d, 1H, *J* = 8.0 Hz), 7.25 (s, 1H), 7.11 (m, 1H), 7.00 (m, 1H), 6.86 (m, 2H), 4.27 (m, 1H), 3.94 (s, 3H), 3.22 (m, 2H), 3.04 (m, 2H), 2.54 (m, 1H), 1.64 (m, 4H), 1.43 (s, 9H), 1.26 (d, 3H, *J* = 6.52 Hz); APCIMS: *m/z* 502 (M+1); Anal. Calcd for $C_{30}H_{41}Cl_2N_5O_2$ (574.6): C, 62.71; H, 7.19; N, 12.19. Found: C, 62.98; H, 7.43; N, 12.99.

5.3.8.*N*1-{4-[2-(*tert*-Butyl)-6-methoxy-8-quinolylamino]pentyl}-(2*S*)-2-amino-3-phenyl-propanamide.2HCl (28)—Yield: 84%; mp. (salt) 105-107 °C; IR (KBr): 3413, 2948, 1674 cm^{-1}; ^1H NMR (D_2O): δ8.47 (d, 1H, *J* = 8.70 Hz), 7.93 (d, 1H, *J* = 8.70 Hz), 7.36 (m, 7H), 4.25 (m, 1H), 4.10 (s, 3H), 3.55 (t, 2H, *J* = 7.02 Hz), 3.33 (m, 1H), 3.18 (m, 2H), 1.81 (m, 4H), 1.61 (s, 9H), 1.27 (d, 3H, *J* = 6.52 Hz); APCIMS: *m/z* 463 (M+1); Anal. Calcd for $C_{28}H_{40}Cl_2N_4O_2$ (535.6): C, 62.80; H, 7.53; N, 10.46. Found: C, 62.60; H, 7.26; N, 10.19.

5.3.9.*N*1-{4-[2-(*tert*-Butyl)-6-methoxy-8-quinolylamino]pentyl}-(2*S*)-2-amino-3-(4-hydroxyphenyl)propanamide.2HCl (29)—Yield: 79%; mp. (salt) 85-87 °C; IR (KBr): 3247, 2922, 2856, 1671 cm^{-1}; ^1H NMR (CD_3OD): δ8.30 (d, 1H, *J* = 8.90 Hz), 7.80 (d, 1H, *J* = 8.90 Hz), 7.10 (m, 3H), 6.78 (m, 3H), 6.09 (brs, 1H), 4.01 (m, 1H), 3.95 (s, 3H), 3.49 (t, 2H, *J* = 6.62 Hz), 3.31 (m, 2H), 2.98 (m, 1H), 1.52 (m, 4H), 1.42 (s, 9H), 1.20 (m, 3H); APCIMS: *m/z* 479 (M+1); Anal. Calcd for $C_{28}H_{40}Cl_2N_4O_3$ (551.6): C, 60.97; H, 7.31; N, 10.16. Found: C, 61.28; H, 7.44; N, 10.34.

5.3.10.*N*1-{4-[2-(*tert*-Butyl)-6-methoxy-8-quinolylamino]pentyl}-(2*S*)-2-amino-4-methylsulfanylbutanamide.2HCl (30)—Yield: 62%; mp. (salt) 70-72 °C; IR (KBr): 3402, 2929, 2856, 1679cm^{-1}; ^1H NMR (DMSO-d_6): δ8.69 (brs, 1H), 8.36 (brs, 1H), 8.16 (d, 1H, *J* = 8.60 Hz), 7.63 (d, 1H, *J* = 8.60 Hz), 7.66 (m, 2H), 3.84 (s, 3H), 3.78 (m, 1H), 3.15 (m, 2H), 2.99 (m, 1H), 2.50 (m, 2H), 2.04 (s, 2H), 1.55 (m, 7H), 1.39 (s, 9H), 1.22 (d, 3H, *J* = 6.52 Hz); APCIMS: *m/z* 447 (M+1); Anal. Calcd for $C_{24}H_{40}Cl_2N_4O_2S$ (519.6): C, 55.48; H, 7.76; N, 10.78. Found: C, 55.24; H, 7.97; N, 10.67.

5.3.11.*N*1-{4-[2-(*tert*-Butyl)-6-methoxy-8-quinolylamino]pentyl}-(2*S*)-2-amino-3-hydroxypropanamide.2HBr (31)—Yield: 65%; mp. (salt) 78-80 °C; IR (KBr): 3400, 2890, 1685 cm^{-1}; ^1H NMR (DMSO-d_6): δ8.64 (brs, 1H), 8.27 (d, 1H, *J* = 8.20 Hz), 8.19 (brs, 1H), 7.68 (d, 1H, *J* = 8.60 Hz), 6.83 (s, 1H), 6.71 (s, 1H), 4.01 (m, 1H), 3.86 (s, 3H), 3.84 (m, 2H), 3.70 (m, 1H), 3.20 (m, 2H), 1.75 (brs, 1H), 1.63 (m, 4H), 1.45 (s, 9H), 1.27 (d, 3H, *J* = 5.30 Hz); APCIMS: *m/z* 403 (M+1); Anal. Calcd for $C_{22}H_{36}Br_2N_4O_3$ (564.4): C, 46.82; H, 6.43; N, 9.93. Found: C, 47.09; H, 6.33; N, 9.78.

5.3.12.*N*1-{4-[2-(*tert*-Butyl)-6-methoxy-8-quinolylamino]pentyl}-(2*R*)-2-amino-3-benzylsulfanylpropanamide.2HCl (32)—Yield: 61%; mp. (salt) 94-96 °C; IR (KBr): 3402, 2930, 2870, 1674 cm^{-1}; ^1H NMR (D_2O): δ8.11 (d, 1H, *J* = 8.90 Hz), 7.56 (d, 1H, *J* = 8.90 Hz), 7.01 (m, 7H), 3.86 (m, 1H), 3.74 (s, 3H), 3.51 (m, 2H), 3.12 (m, 2H), 2.97 (m, 1H), 2.67 (d, 2H, *J* = 6.30 Hz), 1.54 (m, 4H), 1.24 (s, 9H), 1.16 (d, 3H, *J* = 6.48 Hz); APCIMS: *m/z* 509 (M+1); Anal. Calcd for $C_{29}H_{42}Cl_2N_4O_2S$ (581.7): C, 59.88; H, 7.28; N, 9.63. Found: C, 60.15; H, 7.33; N, 9.88.

5.3.13.*N*1-{4-[2-(*tert*-Butyl)-6-methoxy-8-quinolylamino]pentyl}-(2*R*)-2-amino-3-sulfanylpropanamide.2HBr (33)—Yield: 76%; mp. (salt) 77-79 °C; IR (KBr): 3402, 2930, 1668 cm^{-1}; ^1H NMR (DMSO-d_6): δ8.57 (brs, 1H), 8.31 (brs, 1H), 8.03 (d, 1H, *J* = 8.80 Hz), 7.56 (d, 1H, *J* = 8.80 Hz), 6.50 (s, 1H), 6.50 (s, 1H), 3.99 (m, 1H), 3.78 (s, 3H), 3.68 (m, 2H), 3.20 (m, 2H), 3.02 (m, 1H), 1.55 (m, 4H), 1.34 (s, 9H), 1.16 (d, 3H, *J* = 6.48 Hz) ; APCIMS: *m/z* 419 (M+1); Anal. Calcd for $C_{22}H_{36}Br_2N_4O_2S$ (580.4): C, 45.52; H, 6.25; N, 9.65. Found: C, 45.33; H, 6.33; N, 9.47.

5.3.14.*N*1-[4-(4-Ethyl-6-methoxy-pentyloxy-8-quinolylamino)pentyl]-(2*R*)-2,6-diamino-hexanamide.3HCl (51)—Yield: 86%; mp. (salt) 119-122 °C (dec.); IR (neat, free base): 3382, 1576 cm^{-1}; ^1H NMR (free base, CD_3OD): δ 8.36 (d, 1H, *J* = 4.40), 7.19 (d, 1H, *J* = 4.40), 6.58 (s, 1H), 3.96 (s, 3H), 3.89 (t, 2H, *J* = 6.80 Hz), 3.71 (m, 2H), 3.30 (m, 4H), 2.87 (m, 2H), 1.50 (m, 18H), 1.30 (m, 6H), 0.96 (t, 3H, *J* = 7.10 Hz); APCIMS: *m/z* 502 (M+1); Anal. Calcd for $C_{28}H_{50}Cl_3N_5O_3$ (611.1): C, 55.03; H, 8.25; N, 11.46. Found: C, 54.77; H, 8.48; N, 11.83.

5.3.15.*N*1[4-(4-Ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentyl]-(2*R*)-2,5-diaminopentanamide.3HCl (52)—Yield: 79%; mp. (salt) 117-120 °C (dec.); IR (KBr): 3402, 1668 cm^{-1}; ^1H NMR (CD_3OD): δ 8.70 (d, 1H, *J* = 5.0 Hz), 7.59 (s, 1H), 7.58 (d, 1H, *J* = 5.0 Hz), 4.13 (t, 2H, *J* = 6.60 Hz), 4.08 (s, 3H) 3.96 (m, 2H), 3.48 (m, 2H), 3.36 (m, 2H), 3.02 (m, 2H), 1.90 (m, 12H), 1.50 (m, 4H), 1.40 (m, 6H), 0.99 (t, 3H, *J* = 7.0 Hz); APCIMS: *m/z* 488 (M+1); Anal. Calcd for $C_{27}H_{48}Cl_3N_5O_3$ (597.1): C, 54.31; H, 8.10; N, 11.73. Found: C, 54.77; H, 8.48; N, 11.83.

5.3.16.*N*1[4-(4-Ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentyl]-(2*S*)-2-amino-5-amino(imino)methylaminopentanamide.3HCl (53)—Yield: 67%; mp. (salt) 101-104 °C (dec.); IR (neat, free base): 3374, 1680 cm^{-1}; ^1H NMR (free base, CD_3OD): δ 8.36 (d, 1H, *J* = 4.30 Hz), 7.19 (d, 1H, *J* = 4.40 Hz), 6.58 (s, 1H), 3.96 (s, 3H), 3.89 (t, 2H, *J* = 6.80 Hz), 3.65 (m, 2H), 3.27 (m, 4H), 3.15 (m, 2H), 1.60 (m, 16H), 1.31-1.26 (m, 6H), 0.96 (t, 3H, *J* = 7.0 Hz); APCIMS: *m/z* 530 (M+1); Anal. Calcd for $C_{28}H_{50}Cl_3N_7O_3$ (639.1): C, 52.62; H, 7.89; N, 15.34. Found: C, 52.86; H, 8.07; N, 15.63.

5.3.17.*N*1[4-(4-Ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentyl]-(2*R*)-2-amino-5-amino(imino)methylaminopentanamide.3HCl (54)—Yield: 84%; mp. (salt) 100-103 °C (dec.); IR (neat, free base): 3369, 1716.1 cm^{-1}; ^1H NMR (free base, $CDCl_3$): δ 8.38 (d, 1H, *J* = 4.30 Hz), 7.11 (d, 1H, *J* = 4.30 Hz), 6.44 (s, 1H), 3.96 (s, 3H), 3.87 (t, 2H, *J* = 6.90 Hz), 3.63 (m, 2H), 3.24 (m, 2H), 2.78 (m, 2H), 2.03 (brs, 1H), 1.83 (m,

2H), 1.47 (m, 16H), 1.26 (m, 6H), 0.94 (t, 3H, *J* = 6.9 Hz); APCIMS: *m/z* 530 (M+1); Anal. Calcd for $C_{28}H_{50}Cl_3N_7O_3$ (639.1): C, 52.62; H, 7.89; N, 15.34. Found: C, 52.34; H, 7.65; N, 15.12.

5.3.18.*N*1-[4-(4-Ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentyl]-(2*S*)-2-amino-3-(1*H*-imidazol-4-yl)propanamide.3HCl (55)—Yield: 96%; mp. (salt) 122-124 °C (dec.); IR (KBr): 3402, 1679 cm^{-1}; ^1H NMR (CD_3OD): δ 9.25 (s, 1H), 8.71 (d, 1H, *J* = 4.90 Hz), 7.60 (m, 3H), 4.53 (m, 1H), 4.08 (m, 5H), 3.97 (m, 1H), 3.42 (m, 6H), 1.85 (m, 2H), 1.63 (m, 10H), 1.36 (m, 6H), 0.97 (t, 3H, *J* = 6.90 Hz); APCIMS: *m/z* 511 (M+1); Anal. Calcd for $C_{28}H_{45}Cl_3N_6O_3$ (620.1): C, 54.24; H, 7.32; N, 13.55. Found: C, 53.90; H, 7.03; N, 13.47.

5.3.19.*N*1-[4-(4-Ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentyl]-(2*R*)-2-amino-3-(1*H*-imidazol-4-yl)propanamide.3HCl (56)—Yield: 87%; mp. (salt) 124-126 °C (dec.); IR (KBr): 3387, 1679 cm^{-1}; ^1H NMR (CD_3OD): δ 9.15 (s, 1H), 8.61 (d, 1H, *J* = 5.0 Hz), 7.50 (m, 3H), 4.35 (m, 1H), 3.99 (m, 5H), 3.85 (m, 1H), 3.38 (m, 6H), 1.77 (m, 8H), 1.43 (m, 4H), 1.30 (m, 6H), 0.88 (t, 3H, *J* = 6.90 Hz); APCIMS: *m/z* 511 (M+1); Anal. Calcd for $C_{28}H_{45}Cl_3N_6O_3$ (620.1): C, 54.24; H, 7.32; N, 13.55. Found: C, 54.55; H, 7.09; N, 13.33.

5.3.20.*N*1-[4-(4-Ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentyl]-(2*S*)-2-amino-3-(1*H*-indol-3-yl)propanamide.2HCl (57)—Yield: 63%; mp. (salt) 114-116 °C (dec.); IR (KBr): 3370, 1668 cm^{-1}; ^1H NMR (CD_3OD): δ 8.66 (d, 1H, *J* = 4.60 Hz), 7.59 (m, 2H), 7.51 (s, 1H), 7.33 (m, 1H), 7.20 (s, 1H), 7.03 (m, 2H), 4.06 (m, 5H), 3.82 (m, 2H), 3.35 (d, 2H, *J* = 6.30 Hz), 3.19 (m, 4H), 1.81 (m, 4H), 1.45 (m, 8H), 1.30 (m, 6H), 0.96 (t, 3H, *J* = 6.80 Hz); APCIMS: *m/z* 560 (M+1); Anal. Calcd for $C_{33}H_{47}Cl_2N_5O_3$ (632.7): C, 62.65; H, 7.49; N, 11.07. Found: C, 62.88; H, 7.75; N, 13.33.

5.3.21.*N*1-[4-(4-Ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentyl]-(2*S*)-2-amino-3-phenylpropanamide.2HCl (58)—Yield: 76%; mp. (salt) 104-106 °C (dec.); IR (KBr): 3414, 1664 cm^{-1}; ^1H NMR (CD_3OD): δ 8.75 (m, 1H), 7.64 (m, 1H), 7.53 (d, 1H, *J* = 6.10 Hz), 7.23 (m, 3H), 7.13 (d, 2H, *J* = 8.10 Hz), 4.11 (s, 3H), 3.93 (m, 2H), 3.87 (m, 2H), 3.37 (m, 2H), 3.00 (m, 4H), 1.85 (m, 2H), 1.52 (m, 10H), 1.30 (m, 6H), 0.97 (t, 3H, *J* = 6.20 Hz); APCIMS: *m/z* 521 (M+1); Anal. Calcd for $C_{31}H_{46}Cl_2N_4O_3$ (593.6): C, 62.72; H, 7.81; N, 9.44. Found: C, 62.97; H, 7.58; N, 9.68.

5.3.22.*N*1-[4-(4-Ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentyl]-(2*S*)-2-amino-3-(4-hydroxyphenyl)propanamide.2HBr (59)—Yield: 80 %; mp. (salt) 130-132 °C (dec.); IR (KBr): 3408, 1667 cm^{-1}; ^1H NMR (CD_3OD): δ 8.69 (d, 1H, *J* = 4.30 Hz), 7.60 (s, 1H), 7.55 (m, 1H), 7.34 (s, 1H), 7.11 (m, 2H), 6.86 (m, 1H), 4.27 (m, 1H), 4.15 (m, 5H), 3.45 (m, 2H), 3.13 (m, 2H), 2.97 (m, 2H), 1.83 (m, 2H), 1.54 (m, 10H), 1.32 (m, 6H), 0.97 (t, 3H, *J* = 7.0 Hz); APCIMS: *m/z* 537 (M+1); Anal. Calcd for $C_{31}H_{46}Cl_2N_4O_4$ (609.7): C, 61.08; H, 7.61; N, 9.19. Found: C, 61.37; H, 7.88; N, 9.23.

5.3.23.*N*1-[4-(4-Ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentyl]-(2*S*)-2-amino-4-methylsulfanylbutanamide.2HCl (60)—Yield: 91 %; mp. (salt) 72-74 °C

(dec.); IR (KBr): 3355, 1668 cm^{-1}; ^1H NMR (CD_3OD): δ 8.68 (d, 1H, *J* = 4.90 Hz), 7.56 (s, 1H), 7.55 (d, 1H, *J* = 4.30 Hz), 4.11 (t, 2H, *J* = 6.50 Hz), 4.06 (s, 3H), 3.98 (m, 2H), 3.47 (m, 2H), 3.27 (m, 2H), 2.54 (t, 2H, *J* = 7.40 Hz), 2.06 (m, 5H), 1.87 (m, 2H), 1.77 (m, 2H), 1.50 (m, 8H), 1.36 (m, 6H), 0.97 (t, 3H, *J* = 7.10 Hz); APCIMS: *m/z* 505 (M+1); Anal. Calcd for $C_{27}H_{46}Cl_2N_4O_3S$ (577.8): C, 56.14; H, 8.03; N, 9.70. Found: C, 56.45; H, 7.87; N, 10.06.

5.3.24.*N*1-[4-(4-Ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentyl]-(2*S*)-2-amino-3-hydroxypropionamide.2HBr(61)—Yield: 96 %; mp. (salt) 88-90 °C (dec.); IR (KBr): 3402, 1672 cm^{-1}; ^1H NMR (CD_3OD): δ 8.61 (d, 1H, *J* = 4.80 Hz), 7.54 (s, 1H), 7.46 (d, 1H, *J* = 4.80 Hz), 4.15 (m, 1H), 4.02 (t, 2H, *J* = 6.10 Hz), 3.98 (s, 3H), 3.84 (m, 2H), 3.37 (m, 2H), 3.21 (m, 2H), 1.97 (m, 2H), 1.78 (m, 4H), 1.65 (m, 4H), 1.44 (m, 4H), 1.28 (m, 6H), 0.88 (t, 3H, *J* = 7.20 Hz); APCIMS: *m/z* 461 (M+1); Anal. Calcd for $C_{25}H_{42}Cl_2N_4O_4$ (533.5): C, 56.28; H, 7.93; N, 10.50. Found: C, 56.55; H, 8.08; N, 10.23.

5.3.25.*N*1-[4-(4-Ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentyl]-(2*R*)-2-amino-3-benzylsulfanylpropanamide.2HCl (62)—Yield 79 %; mp. (salt) 94-96 °C (dec.); IR (KBr): 3321, 1682 cm^{-1}; ^1H NMR (CD_3OD): δ 8.57 (d, 1H, *J* = 4.10 Hz), 7.44 (d, 1H, *J* = 4.70 Hz), 7.43 (s, 1H), 7.18 (m, 5H), 4.00 (t, 2H, *J* = 6.40 Hz), 3.96 (s, 3H), 3.84 (m, 1H), 3.82 (m, 1H), 3.70 (d, 2H, *J* = 4.70 Hz), 3.34 (m, 2H), 3.21 (m, 2H), 2.78 (m, 2H), 1.75 (m, 4H), 1.65 (m, 4H), 1.44 (m, 4H), 1.27 (m, 6H), 0.88 (t, 3H, *J* = 7.0 Hz); APCIMS: *m/z* 567 (M+1); Anal. Calcd for $C_{32}H_{48}Cl_2N_4O_3S$ (639.7): C, 60.08; H, 7.56; N, 8.76. Found: C, 60.35; H, 7.84; N, 8.95.

5.3.26.*N*^{1}-[4-(4-Ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)-pentyl]-(2*R*)-2-amino-3-sulfanylpropanamide.2HBr (63)—Yield 83 %; mp. (salt) 102-104 °C (dec.); IR (KBr): 3402, 1672 cm^{-1}; ^1H NMR (CD_3OD): δ 8.59 (d, 1H, *J* = 4.90 Hz), 7.52 (s, 1H), 7.43 (d, 1H *J* = 4.80 Hz), 4.00 (m, 5H), 3.83 (m, 1H), 3.58 (m, 1H), 3.31 (m, 4H), 3.03 (m, 2H), 1.68 (m, 9H), 1.38 (m, 4H), 1.23 (m, 6H), 0.88 (t, 3H, *J* = 7.0 Hz); APCIMS: *m/z* 477 (M+1); Anal. Calcd for $C_{25}H_{42}Br_2N_4O_3S$ (638.5): C, 47.03; H, 6.63; N, 8.77. Found: C, 47.36; H, 6.47; N, 8.52.

5.4. Assay for methemoglobin (MetHb) toxicity

An in vitro biotransformation-linked assay was used to evaluate methemoglobin toxicity of the analogs at 20 μg/mL. The method involves simultaneous incubation of the test compounds with the mouse liver microsomes and human erythrocytes followed by determination of methemoglobin formation.[25] This allows the unstable metabolites generated in situ to react with the human erythrocytes. The assay mixture (500 μL) contained 100 μL erythrocytes suspension (50% hemtocrit), 100 μL NADPH regenerating co-factors and enzyme mix (0.8 μM NADP, 5 μM Glucose-6-phosphate, 3 μM $MgCl_2$ and 0.2 units Glucose-6-phosphate dehydrogenase), 100 μL KCl (31 μM), 25 μl microsomes (equivalent to 500 μg protein), 5 μL test compound and 170 μL potassium phosphate buffer (100 mM, pH 7.4). The reaction tubes were loosely covered with aluminum foil and maintained at 37 °C in a metabolic water bath with constant shaking at 80 rpm for 1 h. The tubes were chilled on ice and centrifuged at 1000 rpm for 10 min. The supernatants were

discarded and the erythrocyte pellets were hemolyzed with 2 mL of the lysis buffer (0.277% potassium dihydrogen phosphate, 0.289% disodium hydrogen phosphate, and 0.05% Triton X-100; pH 7.8). The methemoglobin levels relative to total hemoglobin in the lysates were measured by the spectrophotometric technique of Evelyn and Malloy adapted to 96 well plates.[28]

5.5. Assay for antimicrobial activity

All organisms are obtained from the American Type Culture Collection (Manassas, VA). They include the fungi *C. albicans* ATCC 90028, *C. glabrata* ATCC 90030, *C. krusei* ATCC 6258, *C. neoformans* ATCC 90113, and *A. fumigatus* ATCC 90906 and the bacteria methicillin-resistant *S. aureus* ATCC 43300 (MRS) and *M. intracellulare* ATCC 23068. Susceptibility testing is performed using a modified version of the CLSI (formerly NCCLS) methods.[29–32]*M. intracellulare* is tested using a modified method of Franzblau, et al.[33] Samples are serially-diluted in 20% DMSO/saline and transferred in duplicate to 96 well flat bottom microplates. Inocula are prepared by correcting the OD_{630} of microbe suspensions in incubation broth [RPMI 1640/2% dextrose/0.03% glutamine/MOPS @ pH 6.0 (Cellgro) for *C. albicans*, Sabouraud Dextrose for *C. neoformans*, cation-adjusted Mueller-Hinton (Difco) @ pH 7.3 for MRS, 5% Alamar Blue™ (BioSource International, Camarillo, CA) in Middlebrook 7H9 broth with OADC enrichment, pH = 7.3 for *M. intracellulare*, and 5% Alamar Blue™/RPMI 1640 broth (2% dextrose, 0.03% glutamine, buffered with 0.165M MOPS at pH 7.3) for *A. fumigatus* to afford final target inocula of: *C. albicans*: 1.0×10^4, *C. neoformans*: 1.0×10^5, *M. intracellulare*: 2.0×10^6, MRS, *C. glabrata*, *C. krusei*: 5.0×10^5 CFU/mL, and *A. fumigatus*: 3.0×10^4 CFU/mL. Drug controls [Ciprofloxacin (ICN Biomedicals, Ohio) for bacteria and Amphotericin B (ICN Biomedicals, Ohio) for fungi] are included in each assay. All organisms are read at either 630 nm using the EL-340 Biokinetics Reader (Bio-Tek Instruments, Vermont) or 544ex/590em, (*M. intracellulare, A. fumigatus*)using the Polarstar Galaxy Plate Reader (BMG LabTechnologies, Germany) prior to and after incubation: *C. albicans*, MRS, *C. glabrata* and *C. krusei* at 37 °C for 18 – 24 h, *C. neoformans* and *A. fumigatus* at 30 °C for 68 – 72 h, and *M. intracellulare* at 37 °C and 10% CO_2 for 68 – 72 h. The MIC is defined as the lowest test concentration that allows no detectable growth (for *M. intracellulare* and *A. fumigatus*, no color change from blue to pink). Minimum fungicidal or bactericidal concentrations are determined by removing 5 μL from each clear (or blue) well, transferring to agar and incubating as previously mentioned. The MFC/MBC is defined as the lowest test concentration that kills the organism (allows no growth on agar).

5.6. Assay for in vitro antimalarial activity

A suspension of red blood cells infected with D6 or W2 strains of *P. falciparum* (200 μL, with 2% parasitemia and 2% hematocrit in RPMI 1640 medium supplemented with 10% human serum and 60 μg/mL amikacin) is added to the wells of a 96-well plate containing 10 μL of test samples diluted in medium at various concentrations. The plate is placed in a modular incubation chamber (Billups-Rothenberg, CA) and flushed with a gas mixture of 90% N_2, 5% O_2, and 5% CO_2 and incubated at 37 °C for 72 h. Parasitic LDH activity, as a measure of growth, is determined by using Malstat™ reagent (Flow Inc., Portland, OR) according to the procedure of Makler, et al.[34] Briefly, 20 μL of the incubation mixture is

mixed with 100 μl of the Malstat™ reagent and incubated at room temperature for 30 min. 20 μL of a 1:1 mixture of NBT/PES (Sigma, St. Louis, MO) is then added, and the plate is further incubated in the dark for 1 h. The reaction is then stopped by the addition of 100 μL of a 5% acetic acid solution. The plate is read at 650 nm using the EL-340 Biokinetics Reader (Bio-Tek Instruments, Vermont). IC_{50} values are computed from the dose response curves. Artemisinin and chloroquine are included in each assay as the drug controls. DMSO (0.25%) is used as vehicle control.

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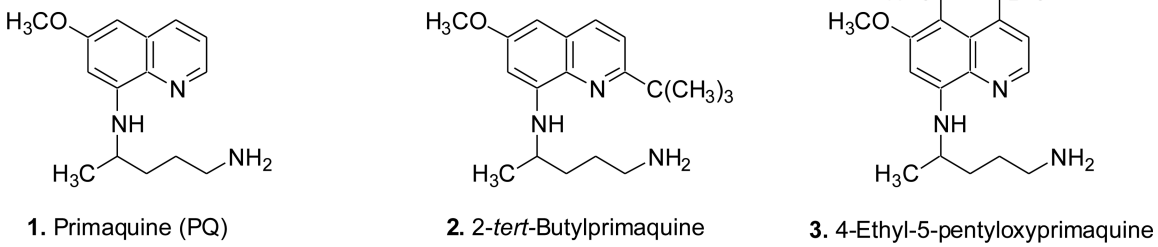


Figure 1.
Structures of primaquine (**1**) and promising 8-quinolinamines **2**–**3**

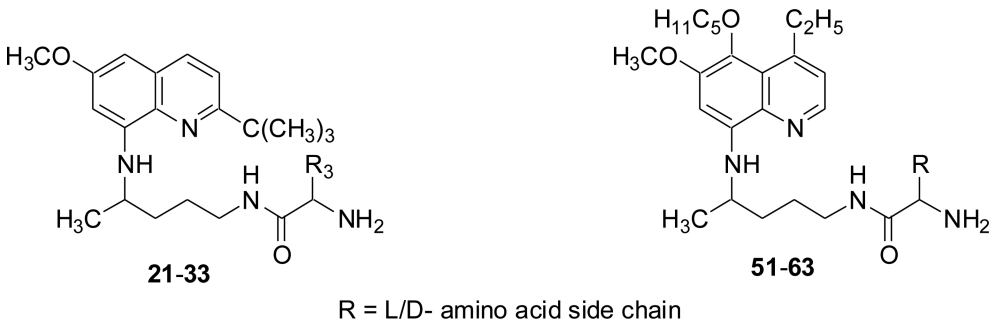
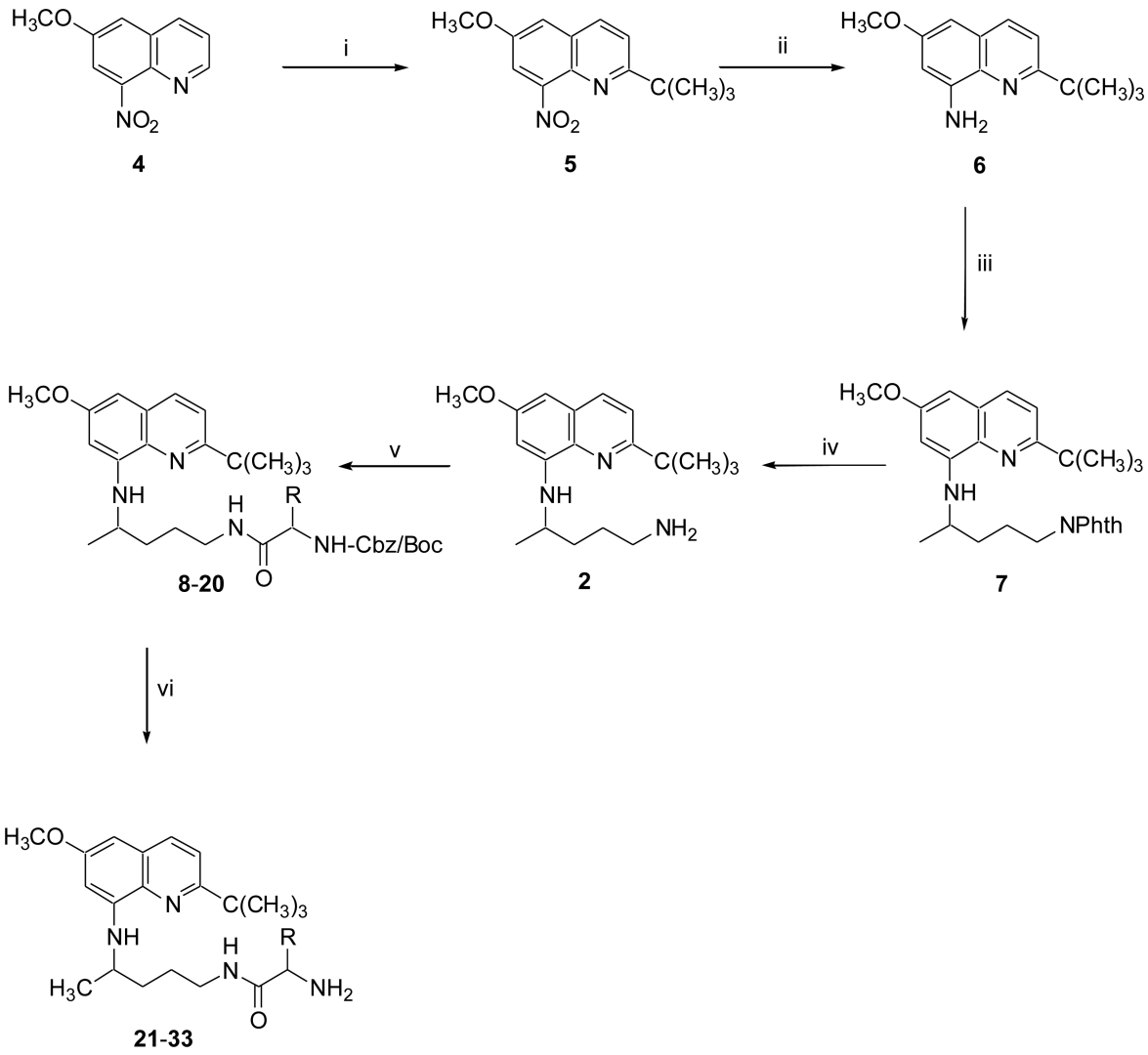
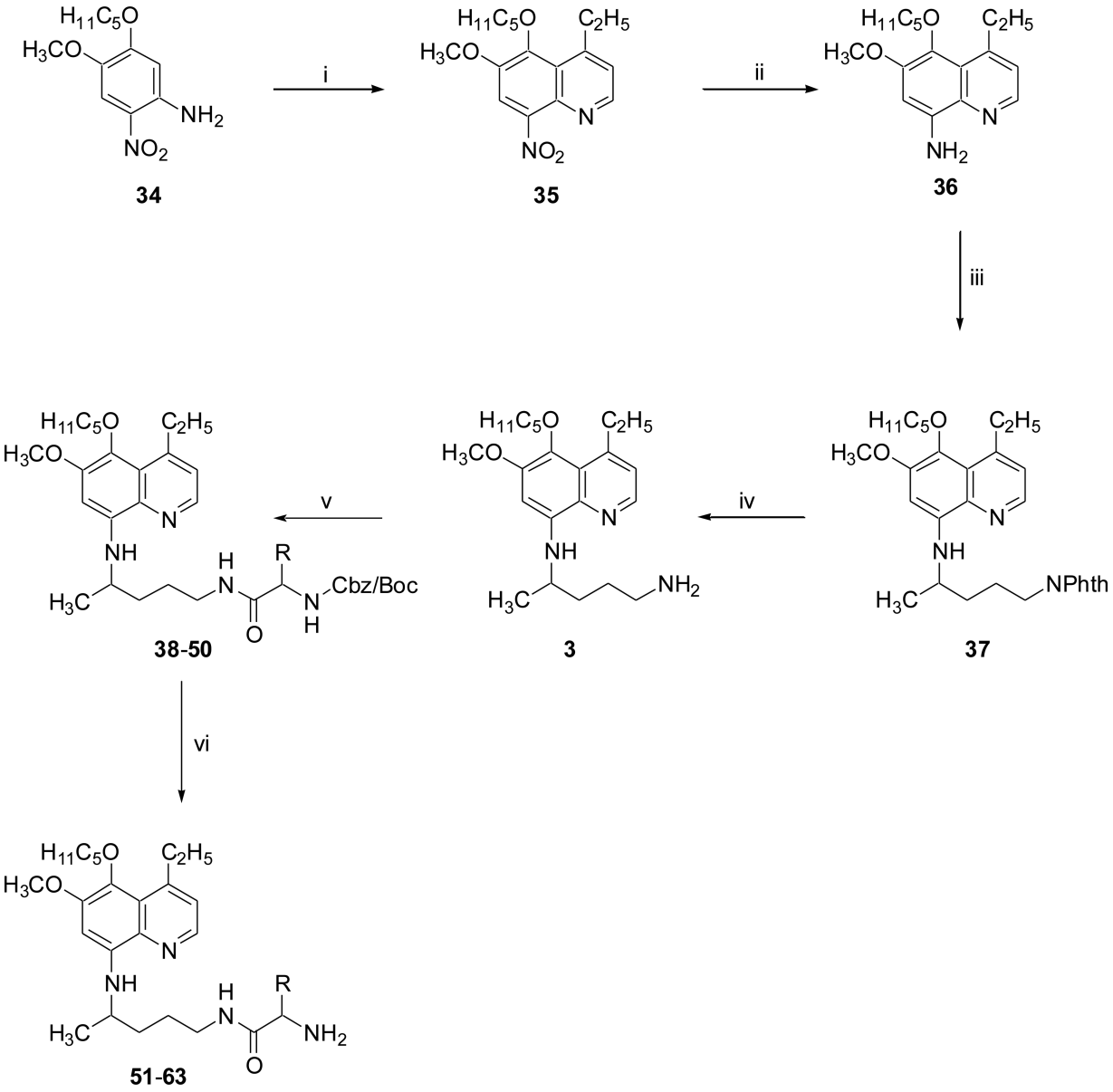


Figure 2.
General structure of the newly synthesized 8-quinolinamines



Scheme 1. Reagents and conditions

(i) $(CH_3)_3CCO_2H$, $AgNO_3$, $(NH_4)_2S_2O_8$, 10% H_2SO_4, CH_3CN, 70 °C; (ii) raney Ni, EtOH, H_2, 45 psi, 45 min; (iii) 2-(4-bromopentyl)-1,3-isoindolinedione, Et_3, 120 °C, 24 h; (iv) $NH_2NH_2.H_2O$, EtOH, reflux, 8 h; (v) suitably *N*- and side-chain protected L/D-amino acid, DCC, DCM, rt, 6 h; (vi) H_2/Pd-C, MeOH, 1h, rt or 4N HCl-MeOH, 1h, rt or 30% HBr-AcOH, 45 min, rt.

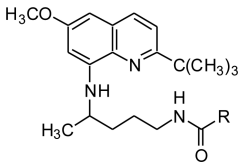


Scheme 2. Reagents and conditions

(i) 1-chloro-3-pentanone, 85% *o*-H_3PO_4, As_2O_5, 80 °C, 3 h; (ii) raney nickel, EtOH, H_2, 45 psi, 45 min; (iii) 2-(4-bromopentyl)-1,3-isoindolinedione, Et_3N, 120 °C, 24 h; (iv) $NH_2NH_2.H_2O$, EtOH, reflux, 8 h; (v) suitably *N*- and side-chain protected L/D-amino acid, DCC, DCM, rt, 6 h; (vi) H_2/Pd-C, MeOH, 1h, rt or 4N HCl-MeOH, 1h, rt or 30% HBr-AcOH, 45 min, rt.

Table 1

In vitro antimalarial activity (*P. falciparum*), cytotoxicity, and MetHb formation activities of the *N*1-{4-[2-(*tert*-butyl)-6-methoxy-8-quinolylamino]pentyl}-(2*S*/2*R*)-2-aminosubstitutedamides **21–33** (series 1).



S. No.	R	*P. falciparum* (D6 clone) IC$_{50}$ (ng/mL)	Sel. Index*	*P. falciparum* (W2 clone) IC$_{50}$ (ng/mL)	Sel. Index*	Vero cell cytotoxicity IC$_{50}$ (ng/mL)	MetHb Toxicity % MetHb formation (20 μg/mL)
21	(*R*)-Lys	180	>132.2	300	>79.3	NC	40.1
22	(*R*)-Orn	190	>125.3	370	>64.3	NC	34.6
23	(*S*)-Arg	300	>79.3	450	>52.9	NC	34.2
24	(*R*)-Arg	280	>85.0	400	>59.5	NC	39.2
25	(*S*)-His	1200	>19.8	1200	>19.8	NC	26.8
26	(*R*)-His	2200	>10.8	2200	>10.8	NC	40.6
27	(*S*)-Trp	2800	>8.5	2300	>10.3	NC	28.2
28	(*S*)-Phe	770	>30.9	920	>25.9	NC	35.7
29	(*S*)-Tyr	870	>27.4	650	>36.6	NC	34.3
30	(*S*)-Met	870	>27.4	600	>39.7	NC	34.5
31	(*S*)-Ser	1000	>23.8	670	>35.5	NC	36.5
32	(*R*)-(Bzl)-Cys	880	>27.0	760	>31.3	NC	35.0
33	(*R*)-Cys	NA	–	NA	–	NC	NT
Primaquine (PQ)		2000	>11.9	2800	>8.5	NC	47.9

NC=not cytotoxic upto 23800 ng/mL (23.8 μg/mL)

NT = not tested

NA = Not active

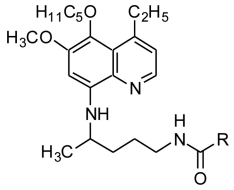
Chloroquine. IC$_{50}$ = 14 ng/mL, Sel. Index = 1700 (D6 clone); IC$_{50}$ = 100 ng/mL, Sel. Index = 238 (W6 clone).

Artemisinin. IC$_{50}$ = 15.2 ng/mL, Sel. Index = 1565 (D6 clone); IC$_{50}$ = 9 ng/mL, Sel. Index = 2644 (W6 clone).

*Selectivity index is the ratio of IC$_{50}$ in Vero cells to IC$_{50}$ in *P. falciparum* (D6 or W2).

Table 2

In vitro antimalarial activity (*P. falciparum*), cytotoxicity and MetHb formation activity of the *N*1-[4-(4-ethyl-6-methoxy-5-pentyloxy-8-quinolylamino)pentyl]-(2*S*/2*R*)-2-aminosubstitutedamides **51–63** (series 2).



		P. falciparum (D6 clone)		*P. falciparum* (W2 clone)		Vero cell cytotoxicity	MetHb toxicity
S. No.	**R**	**IC_{50} (ng/mL)**	**Sel. Index***	**IC_{50} (ng/mL)**	**Sel. Index***	**IC_{50} (ng/mL)**	**% MetHb formation (20 μg/mL)**
51	(*R*)-Lys	580	>41.0	730	>32.6	NC	48.7
52	(*R*)-Orn	700	>34.0	1300	>18.3	NC	43.6
53	(*S*)-Arg	1300	>18.3	1400	>3.4	NC	39.2
54	(*R*)-Arg	1400	>17.0	1700	>2.8	NC	46.1
55	(*S*)-His	NA	–	NA	–	NC	NT
56	(*R*)-His	NA	–	NA	–	NC	NT
57	(*S*)-Trp	860	>20.9	950	>18.9	NC	39.1
58	(*S*)-Phe	3700	>6.4	2200	>10.8	NC	NT
59	(*S*)-Tyr	3800	>6.3	3300	>7.2	NC	NT
60	(*S*)-Met	1900	>12.5	1800	>13.2	NC	34.2
61	(*S*)-Ser	4760	>5.0	3600	>6.6	NC	NT
62	(*R*)-(Bzl)-Cys	2000	>11.9	1200	>19.8	NC	NT
63	(*R*)-Cys	NA	–	NA	–	NC	47.5
Primaquine (PQ)		2000	>11.9	2800	>8.5	NC	47.9

NC=not cytotoxic upto 23800 ng/mL (23.8 μg/mL)

NT = not tested

NA = Not active

Selectivity index is the ratio of IC_{50} in Vero cells to IC_{50} in *P. falciparum* (D6 or W2).

Chloroquine. IC_{50} = 14 ng/mL, Sel. Index = 1700 (D6 clone); IC_{50} = 100 ng/mL, Sel. Index = 238 (W6 clone).

Artemisinin. IC_{50} = 15.2 ng/mL, Sel. Index = 1565 (D6 clone); IC_{50} = 9 ng/mL, Sel. Index = 2644 (W6 clone).

Table 3

In vivo (*P. berghei*) antimalarial activity of the 8-quinolinamine analogs **21–24**

S. No.	*P. berghei* (mg/kg/day×4, oral)			
	10	**25**	**50**	**100**
21	(2/6) Active	(6/6) Curative	(6/6) Curative	(6/6) Curative
22	–	(0/6) Inactive	(6/6) Curative	(6/6) Curative
23	–	–	(3/6) Active	(6/6) Curative
24		(0/6) Inactive	(6/6) Curative	(6/6) Curative
Primaquine (PQ)	–	–	–	(0/6) Inactive

The term “curative” indicates complete elimination of malaria parasites from the body, and animals survive up to day D+60. The term “active” or “suppressive” indicates that all of the treated animals show negative parasitaemia up to D+7. However, by D+60, some mice die, and some survive with complete elimination of parasitaemia as indicated by numbers given in parentheses. The term “inactive” indicates that the treated animals show positive parasitaemia either on D+4 or D+7 and usually die by D+14.

Table 4

In vitro antileishmenial (*L. donovani*) activity of the 8-quinolinamine analogs **21–33** and **51–63**

	Leishmania donovani	
S. No.	**IC_{50} (μg/mL)**	**IC_{90} (μg/mL)**
21	12	37
22	4.6	26
23	7.5	30
24	16	38
25	4	18
26	6.5	30
27	2.9	6.5
28	2.7	6.6
29	3	6.6
30	9.5	32
31	4.5	24
32	4	18
33	15	33
51	17	39
52	17	37
53	18	>40
54	19	>40
55	NA	NA
56	NA	NA
57	3.3	6.7
58	4.2	26
59	4.4	26
60	19	37
61	19	38
62	4.6	23
63	6	29
Primaquine (PQ)	19.9	NA

IC_{50} and IC_{90} are the sample conc that kill 50% and 90% cells compared to vehicle control

NA= no activity

Pentamidine. IC_{50} = 1 μg/mL, IC_{90} = 3.8 μg/mL

Amphotericin B. IC_{50} = 0.19 μg/mL, IC_{90} = 0.35 μg/mL

Table 5

In vitro antibacterial activities of the 8-quinolinamine analogs **21–33** and **51–63**

S. No.	*Methicillin-resistant S. aureus* (MRS)			*M. intracellulare*		
	IC_{50} (μg/mL)	MIC (μg/mL)	MBC (μg/mL)	IC_{50} (μg/mL)	MIC (μg/mL)	MBC (μg/mL)
21	15	20	NA	NA	NA	NA
22	8	20	NA	9	20	NA
23	7	20	20	15	20	NA
24	9	20	20	7	10	NA
25	7	10	20	NA	NA	NA
26	6	10	20	NA	NA	NA
27	3	5	10	7	10	20
28	7	10	NA	10	20	NA
29	3	5	20	4.5	10	20
30	10	20	NA	NA	NA	NA
31	6.5	10	NA	NA	NA	NA
32	4	10	NA	10	20	NA
33	15	NA	NA	NA	NA	NA
51	15	NA	NA	NA	NA	NA
52	15	20	NA	NA	NA	NA
53	15	NA	NA	NA	NA	NA
54	NA	NA	NA	NA	NA	NA
55	NA	NA	NA	NA	NA	NA
56	NA	NA	NA	NA	NA	NA
57	3	5	5	NA	NA	NA
58	6.5	10	NA	NA	NA	NA
59	6	10	NA	NA	NA	NA
60	NA	NA	NA	NA	NA	NA
61	NA	NA	NA	NA	NA	NA
62	6.5	NA	NA	NA	NA	NA
63	NA	NA	NA	NA	NA	NA

IC_{50} = the concentration (μg/mL) that affords 50% growth inhibition

MIC = Minimum Inhibitory Concentration (the lowest concentration in μg/mL that allows no detectable growth)

MBC = Minimum Bactericidal Concentration (the lowest concentration in μg/mL that kills the organism)

NA= no activity at the highest test concentration of 20μg/mL

Ciprofloxacin. IC_{50} = 0.09 μg/mL, MIC = 0.31 μg/mL, MBC = 2.5 μg/mL (*MRS*); IC_{50} = 0.3 μg/mL, MIC = 0.63 μg/mL, MBC = 2.5 μg/mL (*Mi*).

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Table 6

In vitro antifungal activities of the 8-quinolinamine analogs **21–33** and **51–63**

S. NO.	*Candida albicans*			*Candida glabrata*			*Candida krusei*			*Cryptococcus neoformans*		
	IC_{50} (μg/mL)	MIC (μg/mL)	MFC (μg/mL)	IC_{50} (μg/mL)	MIC (μg/mL)	MFC (μg/mL)	IC_{50} (μg/mL)	MIC (μg/mL)	MFC (μg/mL)	IC_{50} (μg/mL)	MIC (μg/mL)	MFC (μg/mL)
21	NA	NA	NA	NA	NA	NA	15	20	20	3.5	5	5
22	NA	NA	NA	15	NA	NA	8	20	20	3.5	5	5
23	NA	NA	NA	15	20	NA	8.5	20	20	3.5	5	5
24	NA	NA	NA	NA	NA	NA	15	20	20	3.5	10	10
25	NA	NA	NA	NA	NA	NA	9.5	20	20	3	5	5
26	15	20	NA	15	NA	NA	7.5	10	20	3.5	5	10
27	15	20	NA	15	20	NA	10	20	20	3.5	5	5
28	NA	NA	NA	NA	NA	NA	15	NA	NA	3.5	10	10
29	15	20	NA	7	20	20	7.5	10	20	3	5	10
30	NA	NA	NA	NA	NA	NA	NA	NA	NA	10	20	20
31	15	20	NA	15	NA	NA	15	20	20	6.5	10	10
32	NA	NA	NA	7.5	20	20	20	NA	NA	3.5	10	10
33	NA	NA	NA	NA	NA	NA	NA	NA	NA	6.5	10	10
51	NA	NA	NA	NA	NA	NA	NA	NA	NA	6	10	20
52	NA	NA	NA	NA	NA	NA	15	NA	NA	4.5	20	20
53	NA	NA	NA	NA	NA	NA	NA	NA	NA	6	10	10
54	NA	NA	NA	NA	NA	NA	NA	NA	NA	15	20	20
55	NA	NA	NA	NA	NA	NA	NA	NA	NA	10	20	20
56	NA	NA	NA	NA	NA	NA	NA	NA	NA	10	20	20
57	10	20	20	4	10	10	7	10	10	3.5	5	5
58	NA	NA	NA	15	NA	NA	15	20	20	3.5	5	5
59	NA	NA	NA	10	20	20	8	20	20	3.5	5	10
60	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
61	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
62	NA	NA	NA	15	NA	NA	NA	NA	NA	3.5	5	5
63	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

IC_{50} = the concentration (μg/mL) that affords 50% growth inhibition

MIC = Minimum Inhibitory Concentration (the lowest concentration in μg/mL that allows no detectable growth)

MFC = Minimum Fungicidal Concentration (the lowest concentration in μg/mL that kills the organism)

NA= no activity at the highest test concentration of 20μg/mL

Amphotericin B. IC_{50} = 0.25 μg/mL, MIC = 0.63 μg/mL, MFC = 1.25 μg/mL (*Ca*); IC_{50} = 0.07 μg/mL, MIC = 0.31 μg/mL, MFC = 0.625 μg/mL (*Cg*); IC_{50} = 0.6 μg/mL, MIC = 1.25 μg/mL, MFC = 1.25 μg/mL (*Ck*); IC_{50} = 0.75 μg/mL, MIC = 1.25 μg/mL, MFC = 1.5 μg/mL (*Cn*).