Bioorganic & Medicinal Chemistry 17 (2009) 270–283

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis and antimalarial activity of new 4-amino-7-chloroquinolyl amides, sulfonamides, ureas and thioureas

Kekeli Ekoue-Kovi [a], Kimberly Yearick [a], Daniel P. Iwaniuk [a], Jayakumar K. Natarajan [a,b], John Alumasa [a], Angel C. de Dios [a,c], Paul D. Roepe [a,b,c,*], Christian Wolf [a,c,*]

[a] Department of Chemistry, Georgetown University, 37th and "O" Streets, Washington, DC 20057, USA
[b] Department of Biochemistry and Cellular and Molecular Biology, Georgetown University, 37th and "O" Streets, Washington, DC 20057, USA
[c] Center for Infectious Diseases, Georgetown University, 37th and "O" Streets, Washington, DC 20057, USA

ARTICLE INFO

Article history:
Received 19 September 2008
Revised 31 October 2008
Accepted 1 November 2008
Available online 12 November 2008

Keywords:
Chloroquine
4-Aminoquinolines
Sulfonamides
Ureas
Thioureas
Amides
Malaria

ABSTRACT

We report the synthesis and in vitro antimalarial activities of more than 50 7-chloro-4-aminoquinolyl-derived sulfonamides **3**–**8** and **11**–**26**, ureas **19**–**22**, thioureas **23**–**26**, and amides **27**–**54**. Many of the CQ analogues prepared for this study showed submicromolar antimalarial activity versus HB3 (chloroquine sensitive) and Dd2 (chloroquine resistant strains of *Plasmodium falciparum*) and low resistance indices were obtained in most cases. Systematic variation of the side chain length and introduction of fluorinated aliphatic and aromatic termini revealed promising leads that overcome CQ resistance. In particular, sulfonamide **3** exhibiting a short side chain with a terminal dansyl moiety combined high antiplasmodial potency with a low resistance index and showed IC_{50}s of 17.5 and 22.7 nM against HB3 and Dd2 parasites.

1. Introduction

Malaria is one of the world's most widespread infectious diseases afflicting approximately 300 million people annually. About 2 million people, mostly young children in tropical and subtropical regions, die of malaria every year which corresponds to more than 5000 casualties per day. Malaria in humans is caused by protozoan parasites of the genus *Plasmodium* and is transmitted by the *Anopheles* mosquito. Although effective antimalarial agents have been known for a long time, the alarming spread of drug resistant strains of *Plasmodium falciparum*, which is the most lethal parasite species, underscores the urgency and continuous need for the discovery of new therapeutics. 7-Chloro-4-aminoquinoline derivatives including chloroquine (CQ), sontoquine, and amodiaquine are among the most potent antimalarial drugs reported to date,[1–3] and new agents with improved activity against CQ resistant (CQR) strains have been introduced via synthetic modifications of the CQ side chain.[4–7]

Chloroquine and other aminoquinolines are commonly believed to inhibit the formation of crystalline hemozoin from free ferriprotoporphyrin IX (FPIX) which is toxic to the parasite and generated during proteolysis of host hemoglobin in the acidic food vacuole in the infected red blood cell.[8] The interaction between the aminoquinoline ring of CQ and FPIX thus interferes with the detoxification mechanism of the parasite and ultimately impedes proliferation.[9–15] The mechanism of CQ resistance is not fully understood but it is known that resistant strains accumulate reduced amounts of CQ in the digestive food vacuole (DV) relative to their CQ sensitive (CQS) counterparts. This has been attributed to mutations in the DV membrane protein Pfcrt (*P. falciparum* chloroquine resistance transporter) which might result in reduced accumulation of CQ in CQR strains.[16–18] Since the trapping of high concentrations of heme-targeted antimalarial drugs in the DV is essential, many efforts have been directed to overcome the resistance mechanism and the drug recognition by Pfcrt via modification of the CQ side chain. Noteworthy, CQR reversal agents[19,20] and new treatments[21] such as artemisinin and related 1,2,4-trioxolanes have been developed.[22–27] A remaining drawback of 1,2,4-trioxolanes is that they are generally less affordable in third world countries while resistance to some organoperoxides has already emerged.[9,28,29] By contrast, 4-aminoquinolines are typically less expensive and have good activity-toxicity profiles.[30] The search for new CQ analogues that are equally effective against CQS and CQR strains has therefore received increasing attention during

* Corresponding authors. Tel.: +1 202 687 3468; fax: +1 202 687 6209 (C.W.); tel.: +1 202 687 7300 (P.D.R.).
E-mail addresses: roepep@georgetown.edu (P.D. Roepe), cw27@georgetown.edu (C. Wolf).

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doi:10.1016/j.bmc.2008.11.009

recent years. Various studies have revealed that structural changes of the 7-chloroquinoline ring in CQ reduces the antimalarial activity,[14,31] whereas modifications of the CQ side chain appears to be more promising. We have prepared several 4-amino-7-chloroquinolyl-derived amides, sulfonamides, ureas and thioureas and discuss the antimalarial activity of these new compounds herein, Figure 1.

2. Results and discussion

Sulfonamides including the protease inhibitor and antiretroviral fosamprenavir, the nonsteroidal anti-inflammatory drug celecoxib, and sumatriptan, which has been used to treat migraine headaches, have found widespread use as pharmaceuticals. Among the few examples of antimalarial sulfonamides reported to date, some exhibit remarkable potency.[32–35] We therefore decided to prepare CQ-derived sulfonamides **3**–**8** and **11**–**18**, Scheme 1. Following a literature procedure, we synthesized **1** in 89% yield from dansyl chloride and aminoethanol.[36] Treatment of **1** with methanesulfonyl chloride gave the corresponding mesylate **2** in 90% yield which allowed formation of sulfonamides **3**–**8** from a series of *N*-(7-chloro-4-quinolyl)-1,n-diaminoalkanes. Reductive amination of *N*-(7-chloro-4-quinolyl)-*N*′-ethyl-1,2-diaminoethane in the presence of *N*-*t*-Boc-glycinal gave chloroquinoline **9** in 54% yield. Deprotection furnished **10** which was then converted to arylsulfonamides **11**–**14** in good yields. Using a similar approach, **15**–**18** were prepared from *N*-(7-chloro-4-quinolyl)-*N*′-propyl-1,3-diaminoethane and an arylsulfonyl chloride in a single step.

The antiplasmodial activity of these compounds was measured versus a CQS (HB3) and a CQR (Dd2) strain using a standardized, inexpensive assay based on SYBR Green I intercalation.[37–39] The IC_{50} values were calculated from experiments carried out in triplicate and compared to CQ (Table 1). Sulfonamides **3**–**8** represent a series of CQ analogues with systematically varied side chain length and a dansyl unit attached to the diethylamino terminus. All compounds within this series showed antimalarial activity against both strains tested and a low resistance index (RI). The RI provides a quantitative measurement of the antiplasmodial activity against CQR strains relative to that against CQS strains and reveals promising drug discovery leads. We found that the RI for **3**–**8** range from 0.5 to 3.6 whereas the resistance index of CQ was determined as 11.8. Most remarkable in this series is that the short chain 7-chloro-4-aminoquinolyl sulfonamide **3** proved significantly more potent against the resistant strain Dd2 relative to CQ. Compound **3** gave IC_{50}s of 17.5 and 22.7 nM against HB3 and Dd2, respectively. It thus retained its potency even when tested against a CQR strain. An increase in the chain length proved detrimental to the antimalarial activity. However, a maximum of the IC_{50}s against the CQS and the CQR strains was obtained for compound **4** exhibiting three methylene units between the 4-aminoquinoline moiety and the tertiary amino function. Krogstad previously reported a somewhat similar trend for the antimalarial potency of CQ derivatives with varying side chain length against Indochina I, a CQR strain, but not against Haiti 135, a CQS strain.[40] Interestingly, comparison of compounds **5** and **6** show that introduction of a methyl group, which perfectly mimics the side chain of CQ, reduces the activity against both strains tested. Exchange of the 6-dimethylaminonaphthyl group in **3** by other aromatic groups furnished sulfonamides **11**–**14**. These compounds gave similar RI values, ranging from 1.4 to 4.1, but showed lower antimalarial activity than **3**, which indicates the significance of the terminal dansyl group. The basic tertiary amino function in the side chain is commonly believed to be crucial for the accumulation of the drug within the acidic food DV. The IC_{50}s of sulfonamides **15**–**18** therefore increased into the micromolar range.

4-Amino-7-chloroquinolyl-derived ureas and thioureas **19**–**26** were prepared in good to high yields from *N*-(7-chloro-4-quinolyl)-1,3-diamine and the corresponding isocyanate and isothiocyanate, respectively, as shown in Scheme 2. Almost all compounds studied showed submicromolar antiplasmodial activity (Table 1). These results compare favorably with the majority of previously reported chloroquine-derived ureas and thioureas.[41,42] However, Chibale et al. found that urea analogues of ferrochloroquine afford superior antiplasmodial activity against a sensitive (D10) and a resistant (K1) strain compared to CQ.[43] In analogy to the sulfonamides discussed above, the low RI values of **19**–**26** are impressive and suggest that incorporation of a rigid urea or thiourea group into the side chain provides new leads that overcome drug resistance to heme-targeted antimalarials.

The incorporation of amide functionalities into the side chain of primaquine,[44] amodiaquine[45,46] and chloroquine[47–51] has led to a remarkable range of promising antimalarial agents. For comparison with the sulfonamides and ureas discussed above, we prepared chloroquine-derived amides **27**–**45**, Scheme 3. Coupling of *N*-(7-chloro-4-quinolyl)-1,n-diaminoalkanes of varying chain length and *N*,*N*-diethylamino-3-propionic acid in the presence of 1-[3-(dimethylaminopropyl]-3-ethylcarbodiimide (EDC) gave **27**–**31**. By contrast, we found that superior results in the syntheses of **32**–**44** are obtained when 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) is used as coupling agent. The anthranilic acids and 2-alkylthio- and 2-arylthiobenzoic acids used in the final coupling step towards **32**–**36** were prepared as reported previously.[52–54] Chloroquine-derived amide **45** was directly prepared from *N*-(7-chloro-4-quinolyl)-1,3-diamine and 5-aminoisatoic anhydride in 64% yield.

The amide series **27**–**31** shows high activity against HB3 (IC_{50}s range from 16.3 to 31.5) but generally less potency against the chlo-

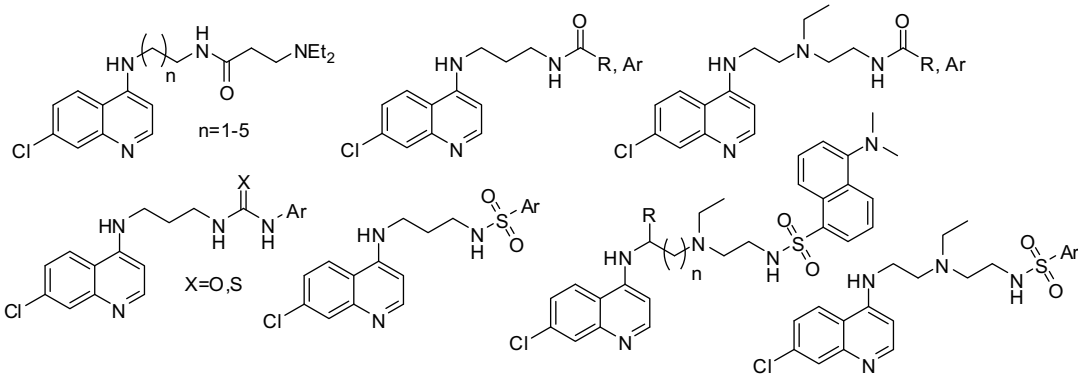
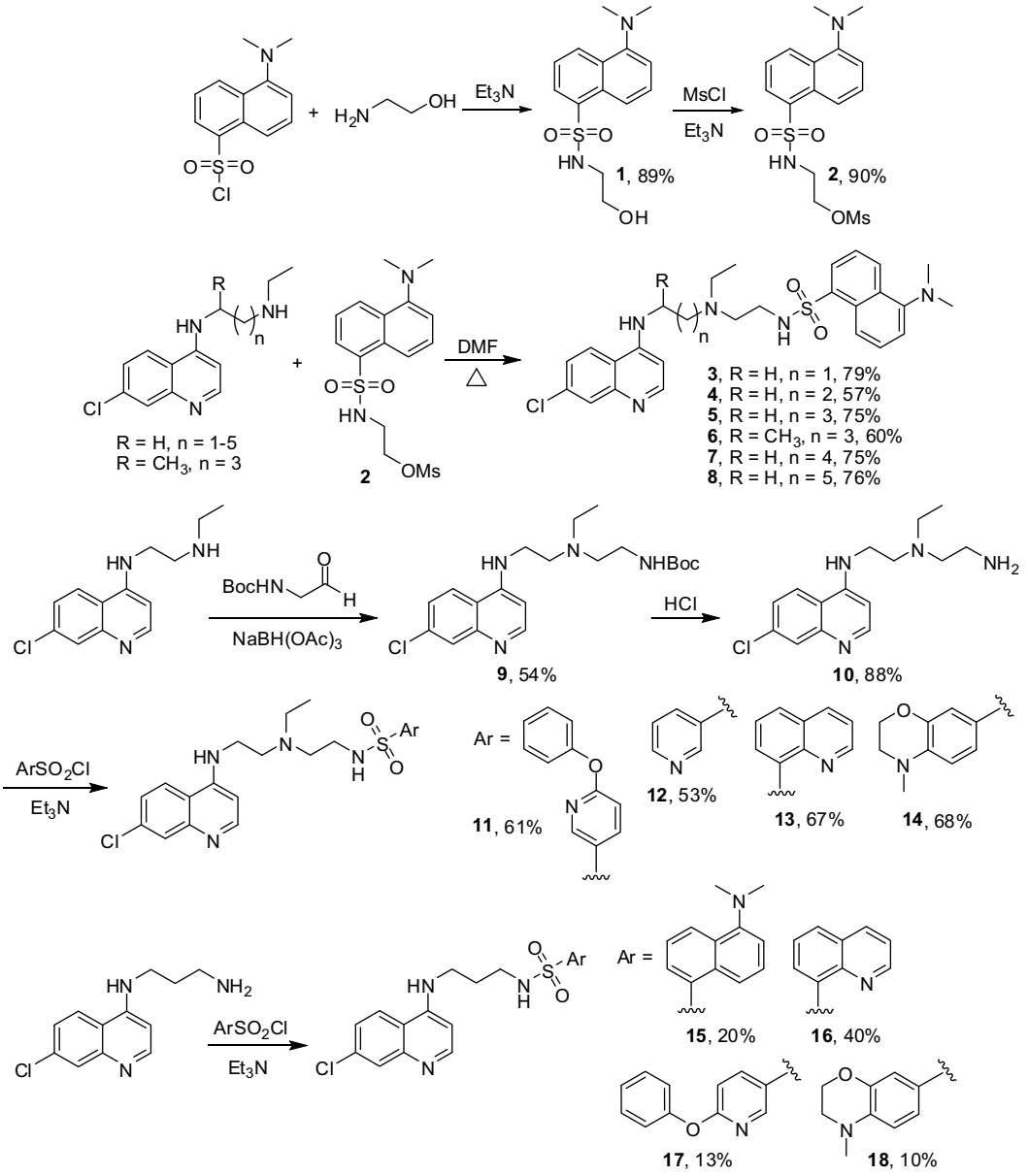


Fig. 1. General structures of tested 4-amino-7-chloroquinolyl-derived amides, sulfonamides, ureas and thioureas.



Scheme 1. Synthesis of sulfonamides **3**–**8**, **11**–**14** and **15**–**18**.

roquine resistant strain Dd2 (Table 2). The IC_{50}s against HB3 do not vary substantially with the chain length. However, comparison of the IC_{50}s obtained with Dd2 reveals a maximum for **29** which has four methylene groups between the 4-aminoquinolyl unit and the amido nitrogen. Apparently, alteration of the chain length again provides an effective tool in the search of new drug candidates that retain their antiplasmodial potency against CQR strains. All other amides prepared proved less effective against both HB3 and Dd2 but we noticed that the 2-benzylamino-4-fluorobenzoyl derivative **33** was significantly more active against Dd2 than HB3. The higher activity against the CQR strain was even more surprising because this was not the case for its defluorinated analogue **34**.

Based on the relatively high activity of **33** against Dd2, we decided to synthesize several additional fluorinated CQ amides (Scheme 4). While amide **46** was prepared via CDMT mediated coupling of **10** with the corresponding benzoic acid derivative, all other amides were obtained using acyl chlorides. We were pleased to find that these fluorinated CQ amides show improved activity compared to **32**–**45** (Table 3). More importantly, fluoro amides **46**–**54** have excellent RI values ranging from 1.2 to 3.1. This compares favorably with the high RIs determined for amides **27**–**31**, and it underscores that incorporation of fluorinated terminal groups into the CQ side chain can possibly provide a means to circumvent the CQR mechanism.

3. Conclusion

More than 50 antiplasmodial 7-chloro-4-aminoquinolyl-derived sulfonamides, ureas, thioureas and amides have been synthesized and tested against CQR and CQS *P. falciparum*. Many of the CQ analogues prepared for this study showed submicromolar antimalarial activity versus HB3 and Dd2 and low resistance indices. The effects of side chain length, the presence of urea, thiourea, amide and sulfonamide functionalites, and the introduction of fluorinated aliphatic and aromatic termini on the potency against CQS and CQR strains of *P. falciparum* was investigated. Although none of the quinolyl antimalarials tested was as active as CQ against HB3, more importantly, sulfonamide **3** showed improved activity against the

Table 1
Antiplasmodial activity of CQ-derived sulfonamides, ureas and thioureas against HB3 and Dd2

Compound	Strain/IC_{50}[a] (nM)		
	HB3	Dd2	RI[b]
CQ	10	127	12.7
3	18	23	1.3
4	115	411	3.6
5	82	125	1.5
6	220	260	1.2
7	70	115	1.7
8	272	147	0.5
11	140	274	2.0
12	124	512	4.1
13	310	443	1.4
14	171	286	1.7
15	754	966	1.3
16	453	607	1.3
17	>1000	>1000	—
18	960	>1000	—
19	316	596	1.9
20	281	>1000	—
21	436	674	1.6
22	365	539	1.5
23	229	353	1.5
24	208	801	3.9
25	272	482	1.8
26	291	606	2.1

[a] IC_{50} values were obtained from an average of two separate determinations each performed in triplicate.
[b] Resistance index (CQR-IC_{50}/CQS-IC_{50}).

CQR strain Dd2. The results revealed interesting SAR principles leading to promising new directions for the design of antimalarials that address CQ resistance. In particular, sulfonamide **3** exhibiting a short side chain with a terminal dansyl moiety proved significantly more potent against the resistant strain Dd2 than CQ, and incorporation of fluorinated termini into the CQ side chain gave desirable RI indices.

4. Experimental

4.1. Cell culture and antimalarial activity measurements

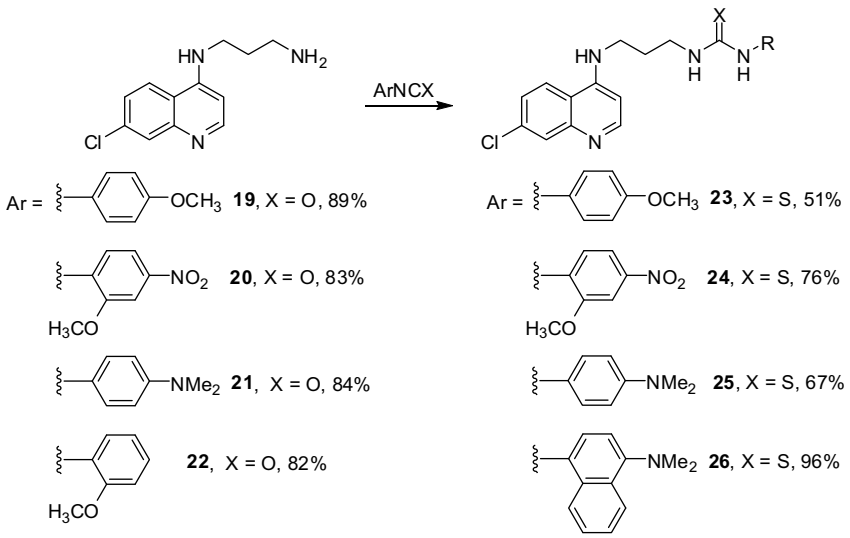
Drug activities were assessed and IC_{50} were quantified essentially as described previously.[37–39] The aminoquinolines were diluted using complete media under sterile conditions and plated in a 96-well plate format. Sorbitol synchronized cultures were utilized with >95% of the parasites at the ring stage. Cultures were diluted to give a working stock of 0.5% parasitemia and 2% hematocrit (final hematocrit 1% and 0.5% Parasitemia). The plates were incubated for 72 h at 37 °C. After 72 h, 50 μL of 10× SYBR green I dye was added to each well, and the plate was incubated for 1 h at 37 °C. Fluorescence was measured at 530 nm (490 nm excitation) using a spectra geminiEM plate reader. Data analysis was performed using Sigma plot 9.0 software after downloading data in Excel format. For each assay, each drug dilution was analyzed in triplicate, and the results from at least two separate assays were averaged in each case (SD < 10% in each case). All drugs were tested against one chloroquine sensitive, and one chloroquine resistant strain of *P. falciparum* (HB3 and Dd2, respectively). Based on NMR spectroscopic and HPLC chromatographic analyses, all compounds were at least of 98% purity.

4.2. Synthesis

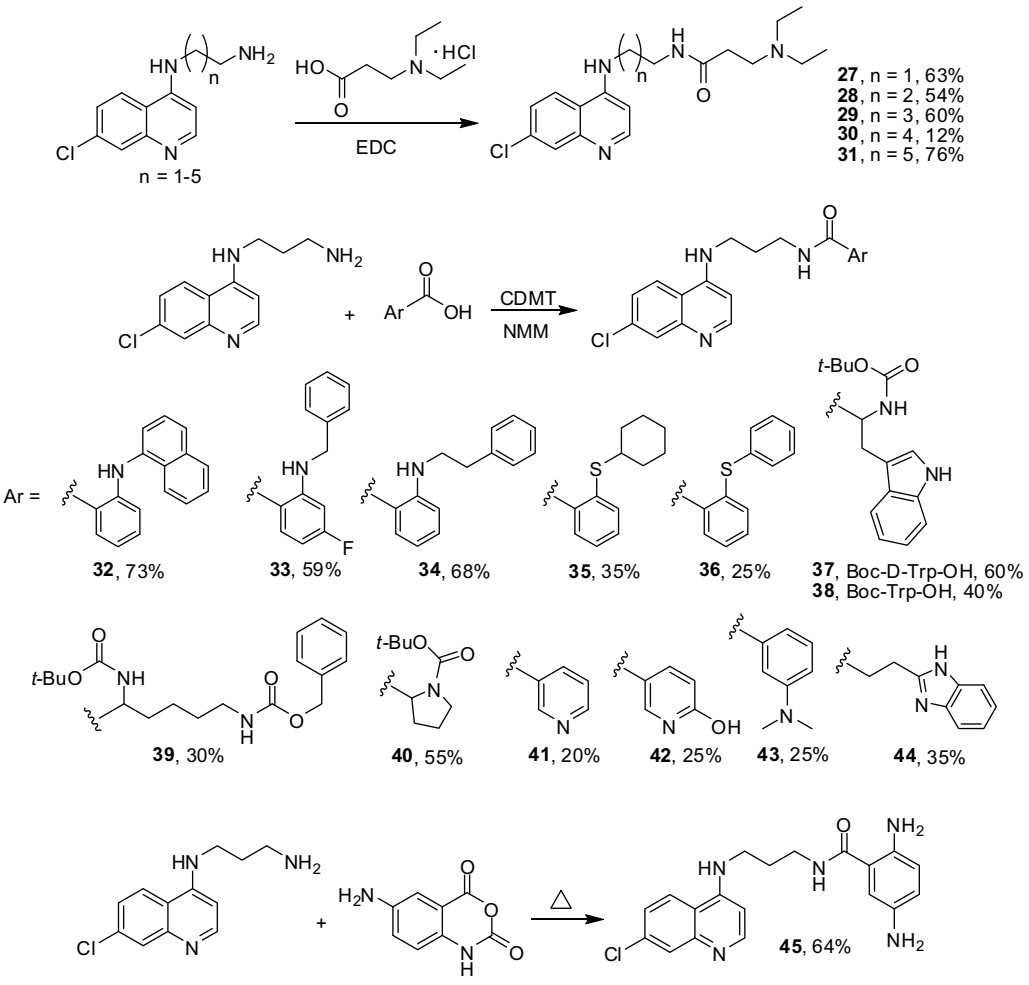
4.2.1. General

All reagents and solvents were commercially available and used without further purification. Flash chromatography was performed on Kieselgel 60, particle size 0.032–0.063 mm. NMR spectra were obtained on a 300 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR) Varian FT-NMR spectrometer using $CDCl_3$ as solvent unless indicated otherwise. *N*-(7-Chloro-4-quinolyl)-1,n-diaminoalkanes and *N*-(7-chloro-4-quinolyl)-*N*′-ethyl-1,n-diaminoalkane derivatives were synthesized following a procedure reported in the literature.[55]

4.2.1.1. 2-(5-Dimethylaminonaphthalene-1-sulfonamido)ethyl methanesulfonate, 2. To a solution of 5-dimethylamino-*N*-(2-hydroxyethyl)naphthalene-1-sulfonamide, **1** (1.5 g, 5.1 mmol) and Et_3N (1.07 mL, 7.64 mmol) in anhydrous CH_2Cl_2, methanesulfonyl chloride (0.44 mL, 5.61 mmol) was added at room temperature and stirred for 1 h. After addition of water, the reaction mixture was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography using EtOAc:hexanes (1:4 v/v) as mobile phase and gradually changing the ratio of EtOAc:hexanes to 1:1.7 (v/v) afforded 1.71 g (4.6 mmol, 90% yield) of a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.86 (s, 3H), 2.89 (s, 6H), 3.27 (m, 2H), 4.17 (t, *J* = 6.0 Hz, 2H), 5.11 (t, *J* = 6.0 Hz, 1H), 7.21 (d, *J* = 7.5 Hz, 1H), 7.50–7.64 (m, 2H), 8.22–8.28 (m, 2H), 8.57



Scheme 2. Preparation of ureas and thioureas **19**–**26**.



Scheme 3. Synthesis of amides **27**–**45**.

Table 2
Antiplasmodial activity of CQ-derived amides against HB3 and Dd2

Compound	Strain/IC_{50}[a] (nM)		
	HB3	Dd2	RI[b]
CQ	10	127	12.7
27	32	760	24.1
28	23	559	24.4
29	29	>1000	–
30	16	672	41.2
31	28	385	12.9
32	>1000	>1000	–
33	>1000	305	–
34	>1000	>1000	–
35	>1000	>1000	–
36	>1000	>1000	–
37	500	764	1.5
38	479	>1000	–
39	902	>1000	–
40	>1000	>1000	–
41	>1000	>1000	–
42	>1000	>1000	–
43	449	792	1.8
44	756	>1000	–
45	179	651	3.6

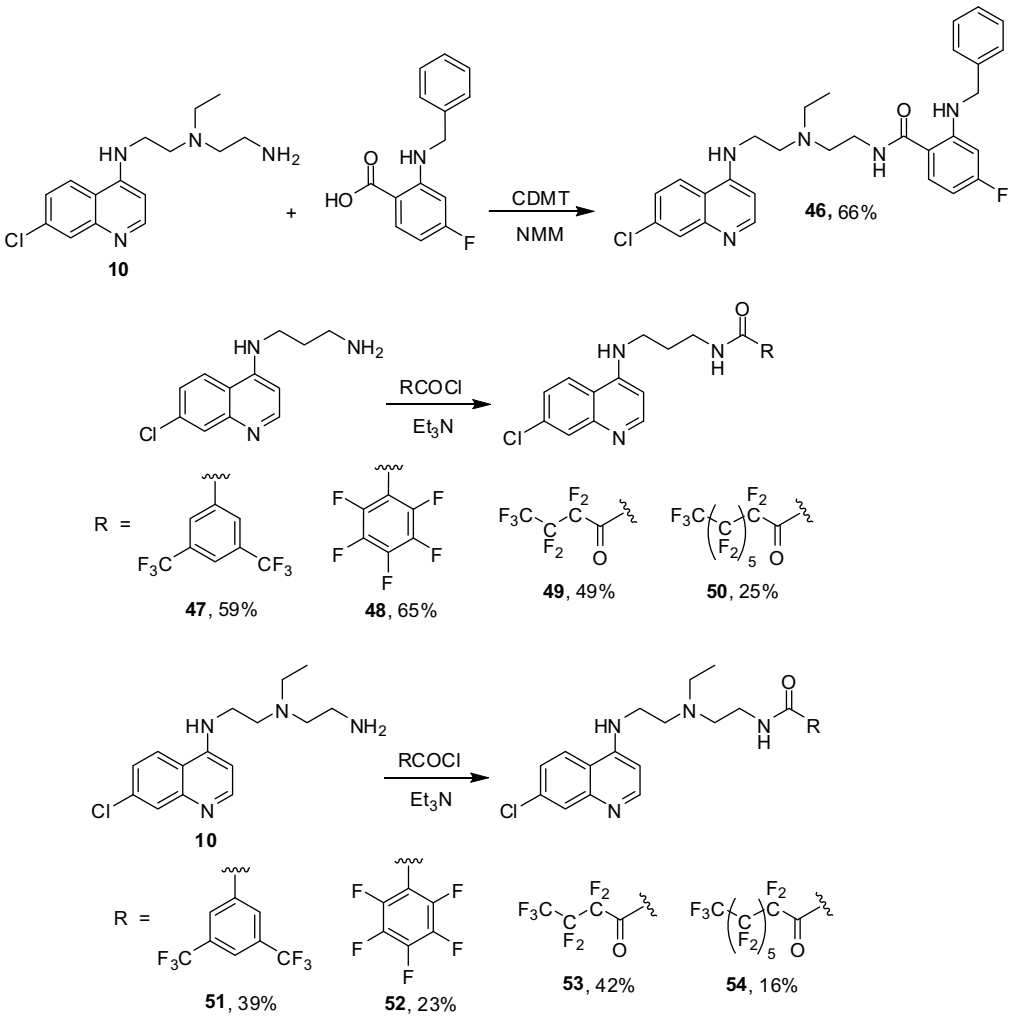
[a] IC_{50} values were obtained from an average of two separate determinations each in triplicate.
[b] Resistance index (CQR-IC_{50}/CQS-IC_{50}).

(d, J = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 37.0, 42.1, 45.2, 68.1, 115.2, 118.5, 123.1, 128.5, 129.2, 129.4, 129.7, 130.6, 134.3, 151.9.

4.2.1.2. Representative procedure for the synthesis of sulfonamide analogs 3–8. A solution of *N*-(7-chloro-4-quinolyl)-*N*′-ethyl-1,4-diaminobutane (0.076 g, 0.27 mmol) and **2** (0.05 g, 0.14 mmol) in anhydrous DMF was heated at 90° C for 3 h. After cooling to room temperature, DMF was removed in vacuo. Saturated $NaHCO_3$ solution was added to the residue, which was then extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography using MeOH:CH_2Cl_2 (1:19 v/v) as the mobile phase gave 0.056 g (0.1 mmol, 75% yield) of **5** as a yellow oil. For the syntheses of **3**, **4** and **7**, the reactions were carried out in anhydrous THF and refluxed for 60 h.

4.2.1.3. *N*-[2-{(*N*′-4-(7-chloro-4-quinolyl)aminobutyl-*N*″-ethyl}-aminoethyl]-5-dimethylaminonaphthalene-1-sulfonamide, 5. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.79 (t, J = 7.2 Hz, 3H), 1.44 (m, 2H), 1.64 (m, 2H), 2.22–2.34 (m, 4H), 2.43 (t, J = 6.0 Hz, 2H), 2.85 (s, 6H), 2.91 (t, J = 6.0 Hz, 2H), 3.24 (q, J = 6.0 Hz, 2H), 5.32 (bs, 1H), 6.37 (d, J = 5.4 Hz, 1H), 7.13 (dd, J = 0.9 Hz, J = 7.5 Hz, 1H), 7.32 (dd, J = 2.1 Hz, J = 8.7 Hz, 1H), 7.46–7.56 (m, 2H), 7.76 (d, J = 9.3 Hz, 1H), 7.94 (d, J = 2.4 Hz, 1H), 8.25 (dd, J = 1.2 Hz, J = 7.5 Hz, 1H), 8.32 (d, J = 8.4 Hz, 1H), 8.50–8.57 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.1, 24.6, 26.4, 40.4, 42.9, 45.3, 46.7, 51.5, 52.1, 98.8, 115.0, 117.1, 118.7, 121.5, 123.0, 125.1, 128.2, 129.5, 129.6, 129.7, 130.3, 134.3, 134.8, 148.7, 149.9, 151.6, 151.9.

4.2.1.4. *N*-[2-{(*N*′-2-(7-chloro-4-quinolyl)aminoethyl-*N*″-ethyl}-aminoethyl]-5-dimethylaminonaphthalene-1-sulfonamide, 3. Employing 0.16 g (0.44 mmol) of **2**, 0.15 g (0.6 mmol) of



Scheme 4. Synthesis of amides **46**–**54**.

Table 3
Antiplasmodial activity of fluorinated CQ-derived amides **46**–**54**

Compound	Strain/IC_{50}[a] (nM)		
	HB3	Dd2	RI[b]
CQ	10	127	12.7
46	80	199	2.5
47	145	236	1.6
48	276	510	1.9
49	234	277	1.2
50	166	197	1.2
51	97	137	1.4
52	118	314	2.7
53	180	556	3.1
54	72	87	1.2

[a] IC_{50} values are an average of two separate determinations each done in triplicate.
[b] Resistance index (IC_{50} CQR)/(IC_{50} CQS).

N-(7-chloro-4-quinolyl)-*N*′-ethyl-1,2-diaminoethane and 0.3 mL (1.7 mmol) of *N*,*N*-diisopropylethylamine in the procedure described above and purification by flash chromatography using MeOH:CH_2Cl_2 (1:19 v/v) as the mobile phase gave 0.18 g (0.33 mmol, 79% yield) of a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.87 (t, *J* = 7.2 Hz, 3H), 2.42 (q, *J* = 7.2 Hz, 2H), 2.55 (t, *J* = 6.0 Hz, 2H), 2.68 (t, *J* = 6.0 Hz, 2H), 2.84 (s, 6H), 2.99 (t, *J* = 5.7 Hz, 2H), 3.19 (q, *J* = 5.7 Hz, 2H), 5.61 (bs, 2H), 6.25 (d, *J* = 5.4 Hz, 1H), 7.10 (d, *J* = 7.5 Hz, 1H), 7.28–7.50 (m, 3H), 7.73 (d, *J* = 9.0 Hz, 1H), 7.92 (d, *J* = 2.1 Hz, 1H), 8.20 (dd, *J* = 1.2 Hz, *J* = 7.2 Hz, 1H), 8.25 (d, *J* = 8.4 Hz, 1H), 8.45–8.56 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 10.9, 39.9, 40.8, 45.1, 46.6, 50.8, 52.0, 98.7, 114.9, 117.0, 118.4, 121.6, 122.9, 125.0, 127.7, 128.1, 129.1, 129.3, 129.6, 130.2, 134.5, 134.6, 148.4, 149.6, 151.5, 151.7.

4.2.1.5. *N*-[2-{(*N*′-3-(7-chloro-4-quinolyl)aminopropyl-*N*′′-ethyl}-aminoethyl]-5-dimethylaminonaphthalene-1-sulfonamide, 4. Employing 0.16 g (0.44 mmol) of **2** , 0.15 g (0.6 mmol) of *N*-(7-chloro-4-quinolyl)-*N*′-ethyl-1,3-diaminopropane and 0.3 mL (1.7 mmol) of *N*,*N*-diisopropylethylamine in the procedure described above and purification by flash chromatography using MeOH:CH_2Cl_2 (1:19 v/v) as the mobile phase furnished 0.133 g (0.25 mmol, 57% yield) of a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.88 (t, *J* = 7.2 Hz, 3H), 1.74 (m, 2H), 2.35–2.49 (m, 4H), 2.52 (t, *J* = 6.0 Hz, 2H), 2.84 (s, 6H), 2.97 (t, *J* = 6.0 Hz, 2H), 3.24 (q, *J* = 6.0 Hz, 2H), 5.48 (bs, 1H), 6.03 (bs, 1H), 6.30 (d, *J* = 5.4 Hz, 1H), 7.10 (d, *J* = 7.5 Hz, 1H), 7.28 (m, 1H), 7.40–7.52 (m, 2H), 7.61 (d, *J* = 8.7 Hz, 1H), 7.93 (t, *J* = 1.8 Hz, 1H), 8.21 (dd, *J* = 1.2 Hz, *J* = 7.5 Hz, 1H), 8.25 (d, *J* = 8.7 Hz, 1H), 8.47–8.55 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.0, 25.1, 40.6, 42.2, 45.2, 47.1, 51.5, 52.2, 98.5, 115.0, 177.1, 118.5, 121.6, 122.9, 124.9, 128.0, 128.2, 129.3, 129.4, 129.6, 130.3, 134.3, 134.5, 148.7, 150.0, 151.6, 151.8.

4.2.1.6. *N*-[2-{(*N*′-4-(7-chloro-4-quinolyl)aminopentyl-*N*″-ethyl}-aminoethyl]-5-dimethylaminonaphthalene-1-sulfonamide, 6. Employing 0.063 g (0.17 mmol) of **2** and 0.1 g (0.34 mmol) of monodesethylchloroquine[56] in the procedure described above and purification by flash chromatography using MeOH:CH_2Cl_2 (1:19 v/v) as the mobile phase afforded 0.058 g (0.10 mmol, 60% yield) of a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.76 (t, J = 7.2 Hz, 3H), 1.31 (d, J = 6.3 Hz, 3H), 1.36–1.72 (m, 4H), 2.16–2.33 (m, 4H), 2.40 (m, 2H), 2.81–2.96 (m, 8H), 3.66 (m, 1H), 4.96 (d, J = 7.8 Hz, 1H), 5.51 (bs, 1H), 6.38 (d, J = 5.4 Hz, 1H), 7.13 (d, J = 7.5 Hz, 1H), 7.34 (m, 1H), 7.46–7.57 (m, 2H), 7.74 (d, J = 9.3 Hz, 1H), 7.95 (d, J = 1.8 Hz, 1H), 8.25 (m, 1H), 8.31 (d, J = 9.0 Hz, 1H), 8.48–8.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.2, 20.2, 23.6, 34.3, 40.3, 45.3, 46.6, 48.2, 51.5, 52.5, 99.0, 115.0, 117.1, 118.7, 121.3, 123.0, 125.0, 128.2, 128.4, 129.5, 129.6, 129.8, 130.5, 134.3, 134.7, 149.0, 149.1, 151.7, 151.9.

4.2.1.7. *N*-[2-{(*N*′-5-(7-chloro-4-quinolyl)aminopentyl-*N*″-ethyl}-aminoethyl]-5-dimethylaminonaphthalene-1-sulfonamide, 7. Employing 0.064 g (0.17 mmol) of **2** and 0.1 g (0.34 mmol) of *N*-(7-chloro-4-quinolyl)-*N*′-ethyl-1,5-diaminopentane in the procedure described above and purification by flash chromatography using MeOH:CH_2Cl_2 (1:19 v/v) as the mobile phase afforded 0.073 g (0.13 mmol, 75% yield) of a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.76 (t, J = 7.2 Hz, 3H), 1.29–1.39 (m, 4H), 1.67 (m, 2H), 2.16–2.28 (m, 4H), 2.39 (t, J = 6.0 Hz, 2H), 2.82–2.93 (m, 8H), 3.28 (q, J = 6.0 Hz, 2H), 5.36 (t, J = 4.8 Hz, 1H), 6.37 (d, J = 5.7 Hz, 1H), 7.14 (d, J = 7.2 Hz, 1H), 7.26 (dd, J = 2.4 Hz, J = 9.0 Hz, 1H), 7.47–7.57 (m, 2H), 7.77 (d, J = 9.0 Hz, 1H), 7.93 (d, J = 2.4 Hz, 1H), 8.25 (dd, J = 1.5 Hz, J = 7.2 Hz, 1H), 8.32 (d, J = 8.4 Hz, 1H), 8.48–8.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.1, 24.9, 26.6, 28.4, 40.3, 43.1, 45.3, 46.6, 51.4, 52.3, 98.8, 115.0, 117.1, 118.7, 121.5, 123.0, 125.0, 128.1, 128.2, 129.5, 129.5, 129.7, 130.2, 134.2, 134.7, 148.8, 149.9, 151.6, 151.8.

4.2.1.8. *N*-[2-{(*N*′-6-(7-chloro-4-quinolyl)aminohexyl-*N*″-ethyl}-aminoethyl]-5-dimethylaminonaphthalene-1-sulfonamide, 8. Employing 0.091 g (0.25 mmol) of **2** and 0.15 g (0.49 mmol) of *N*-(7-chloro-4-quinolyl)-*N*′-ethyl-1,6-diaminohexane in the procedure described above and purification by flash chromatography using MeOH:CH_2Cl_2 (1:19 v/v) as the mobile phase provided 0.108 g (0.19 mmol, 76% yield) of a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.74 (t, J = 7.2 Hz, 3H), 1.20-1.50 (m, 6H), 1.76 (m, 2H), 2.14–2.28 (m, 4H), 2.39 (t, J = 6.0 Hz, 2H), 2.81–2.94 (m, 8H), 3.31 (q, J = 7.2 Hz, 2H), 5.24 (bs, 1H), 6.40 (d, J = 5.4 Hz, 1H), 7.14 (d, J = 7.5 Hz, 1H), 7.28 (dd, J = 2.1 Hz, J = 9.0 Hz, 1H), 7.48–7.58 (m, 2H), 7.74 (d, J = 9.0 Hz, 1H), 7.93 (d, J = 2.1 Hz, 1H), 8.25 (dd, J = 1.2 Hz, J = 7.2 Hz, 1H), 8.32 (d, J = 8.7 Hz, 1H), 8.49–8.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.1, 26.6, 26.8, 26.9, 28.5, 40.3, 43.0, 45.2, 46.5, 51.4, 52.3, 98.7, 115.0, 117.1, 118.6, 121.5, 123.0, 124.9, 128.1, 129.5, 129.7, 130.2, 134.2, 134.6, 148.7, 150.0, 151.6, 151.8.

4.2.1.9. *N*-*t*-Boc *N*′-ethyl-*N*′-[2-(7-chloro-4-quinolyl)aminoethyl]-1,2-diaminoethane, 9. To a solution of *N*-(7-chloro-4-quinolyl)-*N*′-ethyl-1,2-diaminoethane (0.95 g, 3.8 mmol) and *N*-*t*-Boc-glycinal[57] (1.1 g, 6.9 mmol) in anhydrous CH_2Cl_2, sodium triacetoxyborohydride (1.46 g, 6.9 mmol) was added at room temperature and stirred for 24 h. The reaction mixture was quenched with water, basified with 10 N NaOH and extracted with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography using MeOH:CH_2Cl_2 (1:24 v/v) as the mobile phase afforded 0.8 g (2.0 mmol, 54% yield) of a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.05 (t, J = 7.2 Hz, 3H), 1.34 (s, 9H), 2.56–2.70 (m, 4H), 2.81 (t, J = 6.0 Hz, 2H), 3.15–3.36 (m, 4H), 5.25 (bs, 1H), 6.08 (s, 1H), 6.31 (d, J = 5.4 Hz, 1H), 7.30 (dd, J = 2.4 Hz, J = 9.0 Hz, 1H), 7.73 (d, J = 9.0 Hz, 1H), 7.92 (d, J = 2.4 Hz, 1H), 8.47 (d, J = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.6, 28.1, 38.5, 39.8, 47.2, 51.2, 52.6, 78.9, 98.9, 117.1, 121.3, 125.0, 128.0, 134.5, 148.6, 149.7, 151.6, 155.9.

4.2.1.10. *N*-Ethyl-*N*-[2-(7-chloro-4-quinolyl)aminoethyl]-1,2-diaminoethane, 10. To a solution of **9** (0.25 g, 0.62 mmol) in anhydrous methanol, 2 M HCl (3.1 mL, 6.2 mmol) was added at room temperature and stirred overnight. The solvents were removed in vacuo. The reaction mixture was basified with 10 N NaOH, extracted with dichloromethane, dried over anhydrous Na_2SO_4 and concentrated in vacuo to 0.17 g (0.57 mmol, 88% yield) of a brown oil. ^{1}H NMR (300 MHz, CD_3OD) δ = 1.43 (t, J = 7.2 Hz, 3H), 3.40–3.58 (m, 4H), 3.60–3.78 (m, 4H), 4.16 (m, 2H), 7.13 (d, J = 6.9 Hz, 1H), 7.73 (dd, J = 1.8 Hz, J = 9.0 Hz, 1H), 7.92 (d, J = 1.8 Hz, 1H), 8.53 (d, J = 6.9 Hz, 1H), 8.64 (d, J = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.5, 39.6, 40.1, 47.2, 50.9, 55.5, 98.8, 117.2, 121.5, 124.7, 128.1, 134.3, 148.8, 149.8, 151.7.

4.2.1.11. Representative procedure for the synthesis of sulfonamide analogs 11–14. To a solution of *N*-(7-chloro-4-quinolyl)-*N*′-ethyl-*N*′-(2-aminoethyl)-1,2-diaminoethane **10** (0.055 g, 0.21 mmol) and Et_3N (0.06 mL, 0.42 mmol) in anhydrous CH_2Cl_2, 6-phenoxypyridine–3-sulfonyl chloride (0.06 g, 0.21 mmol) was added and the mixture was stirred at room temperature for 1 h. Saturated $NaHCO_3$ solution was added to the reaction mixture, which was then extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Flash chromatography using MeOH:CH_2Cl_2 (1:49 v/v) and gradually changing the ratio of MeOH:CH_2Cl_2 to 1:19 (v/v) gave 0.065 g (0.12 mmol, 61% yield) of a yellow oil.

4.2.1.12. *N*-[2-{(*N*′-2-(7-chloro-4-quinolyl)aminoethyl-*N*″-ethyl}-aminoethyl]-2-phenoxy-5-pyridinesulfonamide, 11. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.00 (t, J = 7.2 Hz, 3H), 2.60 (q, J = 7.2 Hz, 2H), 2.69 (t, J = 6.0 Hz, 2H), 2.79 (t, J = 6.0 Hz, 2H), 3.10 (t, J = 6.0 Hz, 2H), 3.18 (q, J = 6.0 Hz, 2H), 5.92 (bt, 1H), 6.09 (d, J = 5.4 Hz, 1H), 6.89 (d, J = 8.7 Hz, 1H), 7.09–7.16 (m, 1H), 7.21–7.30 (m, 2H), 7.37–7.46 (m, 2H), 7.64 (d, J = 9.0 Hz, 1H), 7.74 (d, J = 2.1 Hz, 1H), 8.02 (dd, J = 2.7 Hz, J = 8.7 Hz, 1H), 8.34 (d, J = 5.4 Hz, 1H), 8.63 (d, J = 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.1, 39.8, 40.9, 46.8, 50.9, 52.0, 98.6, 111.3, 116.8, 121.3, 121.7, 125.3, 125.5, 127.3, 129.7, 131.1, 134.8, 138.1, 147.3, 147.9, 149.6, 151.3, 152.8, 165.8.

4.2.1.13. *N*-[2-{(*N*′-2-(7-chloro-4-quinolyl)aminoethyl-*N*″-ethyl}-aminoethyl]-3-pyridinesulfonamide, 12. Employing 0.045 g (0.26 mmol) of 3-pyridinesulfonyl chloride and 0.075 g (0.26 mmol) of **10** in the procedure described above followed by flash chromatography using MeOH:CH_2Cl_2 (1:19 v/v) and gradually changing the ratio of MeOH:CH_2Cl_2 to 1:9 (v/v) afforded 0.06 g (0.13 mmol, 53% yield) of a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.02 (t, J = 7.2 Hz, 3H), 2.61 (q, J = 7.2 Hz, 2H), 2.70 (t, J = 6.0 Hz, 2H), 2.80 (t, J = 6.0 Hz, 2H), 3.13 (t, J = 6.0 Hz, 2H), 3.19 (q, J = 6.0 Hz, 2H), 5.86 (bt, 1H), 6.11 (d, J = 5.4 Hz, 1H), 7.28 (dd, J = 2.1 Hz, J = 9.0 Hz, 1H), 7.35 (m, 1H), 7.64 (d, J = 9.0 Hz, 1H), 7.75 (d, J = 2.1 Hz, 1H), 8.05 (m, 1H), 8.36 (d, J = 5.4 Hz, 1H), 8.74 (dd, J = 1.8 Hz, J = 5.1 Hz, 1H), 9.06 (dd, J = 0.9 Hz, J = 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.1, 39.8, 40.9, 46.9, 50.9, 52.0, 98.8, 116.9, 121.6, 123.6, 125.3, 127.5, 134.4, 134.8, 136.8, 147.7, 148.1, 149.5, 151.5, 152.9.

4.2.1.14. *N*-[2-{(*N*′-2-(7-chloro-4-quinolyl)aminoethyl-*N*″-ethyl}-aminoethyl]-8-quinolinesulfonamide, 13. Employing 0.04 g (0.17 mmol) of quinoline-8-sulfonyl chloride and 0.05 g (0.17 mmol) of **10** in the procedure described above followed by flash

chromatography using MeOH:CH_2Cl_2 (1:49 v/v) and gradually changing the ratio of MeOH:CH_2Cl_2 to 1:24 (v/v) generated 0.056 g (0.12 mmol, 67% yield) of yellow crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.88 (t, J = 7.2 Hz, 3H), 2.42 (q, J = 7.2 Hz, 2H), 2.62 (t, J = 6.0 Hz, 2H), 2.75 (t, J = 6.0 Hz, 2H), 2.98 (q, J = 6.0 Hz, 2H), 3.22 (q, J = 6.0 Hz, 2H), 5.98 (t, J = 4.2 Hz, 1H), 6.28 (d, J = 5.4 Hz, 1H), 6.72 (t, J = 5.4 Hz, 1H), 7.29 (dd, J = 2.1 Hz, J = 8.7 Hz, 1H), 7.41 (dd, J = 5.2 Hz, J = 8.1 Hz, 1H), 7.59 (dd, J = 7.2 Hz, J = 8.1 Hz, 1H), 7.87 (d, J = 8.7 Hz, 1H), 7.90 (d, J = 2.1 Hz, 1H), 7.99 (dd, J = 1.5 Hz, J = 8.1 Hz, 1H), 8.18 (dd, J = 1.5 Hz, J = 8.1 Hz, 1H), 8.39 (dd, J = 1.5 Hz, J = 7.2 Hz, 1H), 8.48 (d, J = 5.4 Hz, 1H), 8.77 (dd, J = 1.5 Hz, J = 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 10.9, 39.9, 41.2, 46.3, 50.9, 52.1, 61.5, 98.8, 98.9117.1, 121.8, 122.0, 122.1, 125.4, 125.4, 125.5, 128.0, 128.5, 131.1, 133.3, 134.8, 135.2, 136.9, 142.9, 148.6, 149.7, 150.9, 151.5, 151.6.

4.2.1.15. *N*-[2-{(*N*′-2-(7-chloro-4-quinolyl)aminoethyl-*N*′′-ethyl}-aminoethyl]-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-7-sulfonamide, 14. Employing 0.045 g (0.18 mmol) of 4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-7-sulfonyl chloride and 0.053 g (0.18 mmol) of **10** in the procedure described above followed by flash chromatography using MeOH:CH_2Cl_2 (1:16 v/v) as the mobile phase afforded 0.062 g (0.12 mmol, 68% yield) of a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.97 (t, J = 7.2 Hz, 3H), 2.54 (q, J = 7.2 Hz, 2H), 2.64 (t, J = 6.0 Hz, 2H), 2.72–2.81 (m, 5H), 3.04 (t, J = 6.0 Hz, 2H), 3.16–3.30 (m, 4H), 4.27 (t, J = 4.5 Hz, 2H), 5.80 (bs, 1H), 5.91 (bt, 1H), 6.22 (d, J = 5.4 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 2.1 Hz, 1H), 7.10 (dd, J = 2.1 Hz, J = 8.4 Hz, 1H), 7.33 (dd, J = 2.1 Hz, J = 9.0 Hz, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.86 (d, J = 2.1 Hz, 1H), 8.44 (d, J = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.2, 38.4, 40.1, 40.9, 46.9, 48.1, 51.0, 52.1, 64.8, 98.7, 110.3, 115.7, 117.0, 117.2, 121.8, 125.5, 127.6, 131.6, 135.0, 136.7, 147.5, 148.1, 149.8, 151.2.

4.2.1.16. Representative procedure for the synthesis of sulfonamide analogs 15–18. To a mixture of *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane (0.15 g, 0.64 mmol) in 4.5 mL of anhydrous THF under nitrogen at room temperature was added triethylamine (0.084 g, 0.83 mmol) and dansyl chloride (0.21 g, 0.76 mmol). After stirring for 36 h at room temperature, the mixture was quenched with water and extracted with dichloromethane. The combined organic layers were dried over anhydrous $MgSO_4$, concentrated in vacuo, and purified by recrystallization from chloroform to give **15** as a white solid (0.06 g, 0.13 mmol, 20% yield).

4.2.1.17. *N*-(*N*′-3-(7-chloro-4-quinolyl)aminopropyl)-5-dimethylaminonaphthalene-1-sulfonamide, 15. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.69 (tt, J = 6.6 Hz, J = 6.6 Hz, 2H), 2.80 (s, 6H), 2.94 (dt, J = 6.6 Hz, J = 6.1 Hz, 2H), 3.10 (dt, J = 6.6 Hz, J = 5.8 Hz, 2H), 6.16 (d, J = 7.3 Hz, 1H), 7.15 (t, J = 5.8 Hz, 1H), 7.23 (d, J = 7.9 Hz, 1H), 7.41 (dd, J = 2.2 Hz, J = 8.5 Hz, 1H), 7.54 (d, J = 7.9 Hz, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.76 (d, J = 2.2 Hz, 1H), 7.99 (t, J = 6.1 Hz, 1H), 8.09 (dd, J = 1.0 Hz, J = 7.3 Hz, 1H), 8.15 (d, J = 7.3 Hz, 1H), 8.30 (m, 2 H), 8.41 (d, J = 7.3 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 27.8, 45.0, 98.4, 115.0, 117.3, 118.9, 123.43, 123.9, 127.3, 127.8, 128.3, 129.0, 129.3, 133.3, 135.8, 148.8, 149.80, 151.3, 151.6

4.2.1.18. *N*-(*N*′-3-(7-chloro-4-quinolyl)aminopropyl)-8-quinolinesulfonamide, 16. Employing 0.19 g (0.82 mmol) of *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane and 8-quinolinesulfonyl chloride (0.22 g, 0.98 mmol) in the procedure described above gave 0.14 g (0.33 mmol, 40% yield) of white crystals. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.71 (tt, J = 6.5 Hz, J = 6.5 Hz, 2H), 2.95 (dt, J = 6.5 Hz, J = 5.8 Hz, 2H), 3.15 (dt, J = 6.5 Hz, J = 6.2 Hz, 2H), 6.23 (d, J = 5.5 Hz, 1H), 7.17 (t, J = 5.8 Hz, 1H), 7.35 (t, J = 6.2 Hz, 1H), 7.42 (dd, J = 2.2 Hz, J = 9.0 Hz, 1H), 7.65–7.74 (m, 2H), 7.76 (d, J = 2.2 Hz, 1H), 8.12 (d, J = 9.1 Hz, 1H), 8.24 (dd, J = 1.3 Hz, J = 8.3 Hz, 1H), 8.30–8.34 (m, 2H), 8.49 (dd, J = 1.8 Hz, J = 8.4 Hz, 1H), 9.03 (dd, J = 1.8 Hz, J = 4.2 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 27.6, 39.6, 40.7, 98.4, 117.2, 122.4, 124.0, 125.6, 127.1, 128.4, 130.6, 133.4, 133.5, 136.2, 136.9, 142.6, 148.6, 149.9, 151.2, 151.5.

4.2.1.19. *N*-(*N*′-3-(7-chloro-4-quinolyl)aminopropyl)-2-phenoxy-5-pyridinesulfonamide, 17. Employing 0.15 g (0.64 mmol) of *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane and 6-phenoxy-3-pyridinesulfonyl chloride (0.2 g, 0.76 mmol) in the procedure described above gave 0.038 g (0.081 mmol, 13% yield) of white crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.94 (tt, J = 6.2 Hz, J = 6.2 Hz, 2H), 3.16 (t, J = 6.2 Hz, 2H), 3.54 (dt, J = 6.2 Hz, 2H), 5.57 (bs, 1H), 6.32 (d, J = 5.7 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 7.13 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 1H), 7.36 (dd, J = 2.0 Hz, J = 8.9 Hz, 1H), 7.41–7.46 (m, 2H), 7.70 (d, J = 8.9 Hz, 1H), 7.90 (d, J = 1.9 Hz, 1H), 8.08 (dd, J = 2.7 Hz, J = 8.6 Hz, 1 H), 8.46 (d, J = 5.7 Hz, 1H), 8.64 (d, J = 2.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 28.5, 41.2, 99.4, 112.4, 118.1, 122.3, 124.8, 126.1, 128.1, 130.6, 132.4, 134.1, 139.4, 147.1, 149.6, 150.7, 152.5, 153.6, 165.8.

4.2.1.20. *N*-(*N*′-3-(7-chloro-4-quinolyl)aminopropyl)-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-7-sulfonamide, 18. Employing 0.102 g (0.43 mmol) of *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane and 1,4-benzoxazinesulfonyl chloride (0.123 g, 0.49 mmol) in the procedure described above provided 0.02 g (0.04 mmol, 10% yield) of off-white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.79-1.86 (m, 2H), 2.76 (s, 3H), 3.02 (t, J = 4.5 Hz, 2H), 3.19 (t, J = 3.4 Hz, 2H), 3.44 (t, J = 4.5 Hz, 2H), 4.23 (t, J = 3.8 Hz, 2H), 5.79 (bs, 1H), 6.25 (d, J = 4.1 Hz, 1H), 6.72 (d, J = 6.0 Hz, 1H), 6.99 (d, J = 1.5 Hz, 1H), 7.06 (dd, J = 1.8 Hz, J = 6.6 Hz, 1H), 7.28 (dd, J = 1.8 Hz, J = 6.6 Hz, 1H), 7.72 (d, J = 6.6 Hz, 1H), 7.83 (d, J = 1.2 Hz, 1H), 8.37 (d, J = 4.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 26.8, 32.0, 37.5, 38.6, 39.5, 47.3, 63.9, 97.7, 109.3, 115.0, 116.3, 120.5, 124.5, 127.2, 134.2, 135.9, 146.8, 148.7, 150.4, 164.2.

4.2.1.21. Representative procedure for the synthesis of urea (19–22) and thiourea 23–26 analogs. A mixture of *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane (0.15 g, 0.64 mmol) and the appropriate isothiocyanate or isocyanate (0.53 mmol) in anhydrous THF was stirred at room temperature until the reaction was complete. In all cases, the desired urea or thiourea product precipitated from solution. The precipitate was collected via vacuum filtration and dried in vacuo.

4.2.1.22. *N*-(3-(7-chloro-4-quinolyl)aminopropyl)-*N*′-(4-methoxyphenyl)urea, 19. Employing 0.195 g (0.83 mmol) of *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane and 4-methoxyphenyl isocyanate (0.09 mL, 0.69 mmol) in the procedure described above gave 0.244 g (0.64 mmol, 89 % yield) of white crystals. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.81–1.89 (m, 2H), 3.19–3.38 (m, 4H), 3.73 (s, 3H), 6.18 (t, J = 5.6 Hz, 1H), 6.52 (d, J = 5.6 Hz, 2H), 6.85 (dd, J = 2.1 Hz, J = 6.7 Hz, 2H), 7.31–7.37 (m, 3H), 7.49 (dd, J = 3.2 Hz, J = 10.0 Hz, 1H), 7.83 (d, J = 2.2 Hz, 1H), 8.30 (d, J = 2.7 Hz , 1H), 8.32 (s, 1H), 8.44 (d, J = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 25.8, 29.3, 37.8, 55.8, 114.9, 118.2, 120.2, 124.8, 128.2, 134.1, 134.3, 149.8, 150.8, 152.7, 154.7, 156.4.

4.2.1.23. *N*-(3-(7-chloro-4-quinolyl)aminopropyl)-*N*′-(2-methoxy-4-nitrophenyl)urea, 20. Employing 0.146 g (0.65 mmol) of *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane and 2-methoxy-4-nitrophenyl isocyanate (0.1 g, 0.52 mmol) in the procedure described above gave 0.186 g (0.43 mmol, 83 % yield) of yellow crystals. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.85–1.90 (m, 2H), 3.25–3.31 (m,

3H), 3.61 (t, J = 6.4 Hz, 1H), 4.00 (s, 3H), 6.51 (d, J = 5.4 Hz, 1H), 7.32 (t, J = 5.3 Hz, 2H), 7.46 (dd, J = 2.2 Hz, J = 8.8 Hz, 1H), 7.78 (dd, J = 2.2 Hz, J = 10.7 Hz, 2H), 7.88 (dd, J = 2.4 Hz, J = 9.0 Hz, 1H), 8.29 (d, J = 9.3 Hz, 1H), 8.40 (d, J = 3.4 Hz, 1H), 8.43 (s, 1H), 8.57 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 28.9, 57.1, 79.9, 106.1, 116.4, 118.2, 118.4, 124.8, 128.2, 134.1, 137.4, 140.9, 147.2, 149.8, 150.7, 152.6, 155.2.

4.2.1.24. *N*-(3-(7-chloro-4-quinolyl)aminopropyl)-*N′*-(4-dimethylaminophenyl)urea, 21. Employing 0.178 g (0.75 mmol) of *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane and 4-dimethylaminophenyl isocyanate (0.1 g, 0.62 mmol) in the procedure described above furnished 0.208 g (0.52 mmol, 84 % yield) of white crystals. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.81–1.88 (m, 2H), 2.84 (s, 6H), 3.24 (q, J = 6.4 Hz, 2H), 3.31–3.39 (m, 2H), 6.11 (t, J = 5.7 Hz, 1H), 6.52 (d, J = 5.4 Hz, 1H), 6.69 (d, J = 9.0 Hz, 2H), 7.23 (d, J = 9.0 Hz, 2H), 7.37 (t, J = 5.0 Hz, 1H), 7.49 (dd, J = 2.2 Hz, J = 9.0 Hz, 1H), 7.83 (d, J = 2.2 Hz, 1H), 8.12 (s, 1H), 8.30 (d, J = 9.0 Hz, 1H), 8.44 (d, J = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 2.8, 29.4, 37.8, 67.7, 95.2, 99.3, 113.9, 116.2, 118.2, 120.6, 124.8, 128.2, 131.2, 134.1, 135.5, 138.2, 143.7, 146.8, 149.3, 150.7, 152.6, 156.6.

4.2.1.25. *N*-(3-(7-chloro-4-quinolyl)aminopropyl)-*N′*-(2-methoxyphenyl)urea, 22. Employing 0.191 g (0.81 mmol) of *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane and 2-methoxyphenyl isocyanate (0.10 mL, 0.75 mmol) in the procedure described above gave 0.254 g (0.66 mmol, 82 % yield) of white crystals. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.85–1.89 (m, 2H), 3.23–3.39 (m, 4H), 3.86 (s, 3H), 6.53 (d, J = 5.9 Hz, 1H), 6.84–7.02 (m, 4H), 7.36 (t, J = 5.1 Hz, 1H), 7.49 (dd, J = 2.2 Hz, J = 8.8 Hz, 1H), 7.83 (d, J = 2.2 Hz, 1H), 7.94 (s, 1H), 8.14 (dd, J = 2.0 Hz, J = 7.1 Hz, 1H), 8.32 (d, J = 9.0 Hz, 1H), 8.44 (d, J = 5.6 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 25.8, 29.2, 37.7, 67.7, 99.4, 118.2, 118.7, 121.7, 124.7, 128.2, 130.2, 134.1, 148.0, 149.8, 150.8, 152.6, 156.0.

4.2.1.26. *N*-(3-(7-chloro-4-quinolyl)aminopropyl)-*N′*-(4-methoxyphenyl)thiourea, 23. Employing 0.162 g (0.69 mmol) of *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane and 4-methoxyphenyl isothiocyanate (0.08 mL, 0.58 mmol) in the procedure described above gave 0.116 g (0.29 mmol, 51 % yield) of white crystals. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.95–1.99 (m, 2H), 3.35 (q, J = 6.3 Hz, 2H), 3.38 (bs, 2H), 3.77 (s, 3H), 6.52 (d, J = 5.4 Hz, 1H), 6.93 (dd, J = 2.2 Hz, J = 6.8 Hz, 2H), 7.25 (d, J = 9.0 Hz, 2H), 7.40 (t, J = 5.1 Hz, 1H), 7.50 (dd, J = 2.2 Hz, J = 9.0 Hz, 1H), 7.64 (bs, 1H), 7.83 (d, J = 2.2 Hz, 1H), 8.29 (d, J = 9.0 Hz, 1H), 8.44 (d, J = 5.4 Hz, 1H), 9.38 (bs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 25.8, 28.2, 55.9, 67.7, 114.7, 118.2, 124.8, 126.8, 128.0, 132.3, 134.2, 149.6, 150.8, 152.4, 157.3, 181.4.

4.2.1.27. *N*-(3-(7-chloro-4-quinolyl)aminopropyl)-*N′*-(2-methoxy-4-nitrophenyl)thiourea, 24. Employing 0.136 g (0.58 mmol) of *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane and 2-methoxy-4-nitrophenyl isothiocyanate (0.101 g, 0.48 mmol) in the procedure described above afforded 0.144 g (0.33 mmol, 76 % yield) of yellow crystals. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.98–2.03 (m, 2H), 3.36–3.42 (m, 3H), 3.63–3.69 (m, 2H), 4.02 (s, 3H), 6.54 (d, J = 5.4 Hz, 1H), 7.37 (t, J = 5.3 Hz, 1H), 7.49 (dd, J = 2.4 Hz, J = 9.0 Hz, 1H), 7.83 (t, J = 2.4 Hz, 2H), 7.90 (dd, J = 2.7 Hz, J = 9.0 Hz, 3H), 8.31 (d, J = 9.3 Hz, 1H), 8.45 (d, J = 5.4 Hz, 1H), 8.79 (d, J = 9.0 Hz , 1H), 9.13 (bs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 27.7, 42.5, 57.2, 79.9, 106.5, 116.8, 118.2, 124.8, 128.2, 134.1, 136.1, 142.9, 149.8, 150.7, 152.7, 180.5.

4.2.1.28. *N*-(3-(7-chloro-4-quinolyl)aminopropyl)-*N′*-(4-dimethylaminophenyl)thiourea, 25. Employing 0.159 g (0.67 mmol) of *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane and 4-dimethylaminophenyl isothiocyanate (0.101 g, 0.57 mmol) in the procedure described above gave 0.157 g (0.38 mmol, 67 % yield) of white crystals. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.90–1.99 (m, 2H), 2.90 (s, 6H), 3.30–3.38 (m, 2H), 3.61–3.64 (m, 2H), 6.50 (d, J = 5.4 Hz, 1H), 6.71 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 8.8 Hz, 2H), 7.36 (t, J = 5.3 Hz, 1H), 7.49 (dd, J = 2.2 Hz, J = 9.0 Hz, 2H), 7.82 (d, J = 2.2 Hz, 1H), 8.27 (d, J = 9.0 Hz, 1H), 8.44 (d, J = 5.4, 1H), 9.28 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 28.2, 79.9, 113.3, 118.2, 124.7, 126.7, 128.2, 134.0, 149.0, 149.8, 150.7, 152.6, 181.3.

4.2.1.29. *N*-(3-(7-chloro-4-quinolyl)aminopropyl)-*N′*-(4-dimethylaminonaphthyl)thiourea, 26. *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane (0.123 g, 0.52 mmol) and 4-dimethylamino-1-naphthyl isothiocyanate (0.10 g, 0.44 mmol) were employed in the procedure described above. The solution was then cooled to -45 °C and 0.175 g (0.38 mmol, 96 % yield) of white crystals were obtained. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.92 (bs, 2H), 2.87 (s, 6H), 3.28 (bs, 2H), 3.59–3.66 (m, 2H), 6.43 (s, 1H), 7.12 (d, J = 8.1 Hz, 1H), 7.34 (d, J = 8.1 Hz, 2H), 7.48 (dd, J = 2.2 Hz, J = 9.0 Hz, 1H), 7.54–7.57 (m, 2H), 7.81–7.87 (m, 2H), 8.20–8.27 (m, 2H), 8.40 (d, J = 5.6 Hz, 1H), 9.57 (bs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 28.1, 45.6, 79.9, 99.3, 118.2, 124.7, 126.1, 128.2, 129.5, 130.4, 132.1, 134.1, 149.8, 150.6, 151.6, 152.6, 167.4, 182.5.

4.2.1.30. *N*-(7-Chloro-4-quinolyl)-*N′*-(3-diethylaminopropanoyl)-1,2-diaminoethane, 27. A mixture of *N*-(7-chloro-4-quinolyl)-1,2-diaminoethane (0.1 g, 0.45 mmol), *N,N*-diethylamino-3-propionic acid (0.11 g, 0.6 mmol), EDC (0.11 g, 0.6 mmol) and Et_3N (0.19 mL, 1.35 mmol) in 4 mL of anhydrous DMF and $CHCl_3$ (1:1 v/v) was stirred at room temperature for 2 days. Saturated $NaHCO_3$ solution was added to the cooled reaction mixture, which was then extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Flash chromatography using EtOH:Et_3N (1:0.05 v/v) as the mobile phase afforded 0.10 g (0.44 mmol, 63% yield) of yellow crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.05 (t, J = 7.1 Hz, 6H), 2.48 (t, J = 6.1 Hz, 2H), 2.58 (q, J = 7.1 Hz, 4H), 2.69 (t, J = 6.1 Hz, 2H), 3.30–3.45 (m, 2H), 3.64–3.78 (m, 2H), 6.28 (d, J = 5.4 Hz,1H), 7.11 (bs, 1H), 7.40 (dd, J = 2.1 Hz, J = 9.0 Hz, 1H), 7.87 (d, J = 9.0 Hz, 1H), 7.94 (d, J = 2.1 Hz, 1H), 8.50 (d, J = 5.4 Hz, 1H), 9.51 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.6, 32.4, 38.4, 46.3, 46.5, 48.9, 98.2, 117.5, 122.7, 125.7, 128.2, 135.2, 148.9, 150.7, 151.8, 176.2.

4.2.1.31. *N*-(7-Chloro-4-quinolyl)-*N′*-(3-diethylaminopropanoyl)-1,3-diaminopropane, 28. A mixture of *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane (1.0 g, 4.24 mmol), *N,N*-diethylamino-3-propionic acid (0.78 g, 4.3 mmol), EDC (0.98 g, 5.1 mmol) and triethylamine (1.8 mL, 12.9 mmol) in 30 mL of anhydrous DMF and chloroform (1:1 v/v) was stirred at room temperature for 2.5 days. The reaction mixture was concentrated in vacuo, then dissolved in dichloromethane and extracted with aqueous NaOH. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography (ethanol:hexanes:triethylamine 1:1:0.05 v/v) to give 0.83 g of (2.3 mmol, 54% yield) pale yellow crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.02 (t, J = 7.1 Hz, 6H), 1.74–1.83 (m, 2H), 2.41 (t, J = 5.7 Hz, 2H) , 2.53 (q, J = 7.1 Hz, 4H), 2.67 (t, J = 5.9 Hz, 2H), 3.32–3.43 (m, 4H), 6.37 (d, J = 5.6 Hz, 1H), 6.76 (t, J = 5.7 Hz, 1H), 7.36 (dd, J = 2.1 Hz, J = 9.0 Hz, 1H), 7.90 (d, J = 2.1 Hz, 1H), 8.02 (d, J = 9.0 Hz, 1H), 8.45 (d, J = 5.6 Hz, 1H), 9.04 (t, J = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.8, 28.6, 32.7, 35.7, 39.2, 46.5, 49.2, 98.6, 117.9, 122.5, 125.7, 128.5, 135.4, 149.4, 150.5, 151.9, 174.8.

4.2.1.32. *N*-(7-Chloro-4-quinolyl)-*N′*-(3-diethylaminopropanoyl)-1,4-diaminobutane, 29. A mixture of *N*-(7-chloro-4-quinolyl)-1,4-diaminobutane (2.0 g, 8.0 mmol), *N,N*-diethylamino-3-propionic

acid (1.45 g, 8.0 mmol), EDC (1.84 g, 9.6 mmol), and triethylamine (3.35 mL, 24.0 mmol) in 80 mL of anhydrous DMF and chloroform (1:1 v/v) was stirred at room temperature for 2.5 days. The reaction mixture was concentrated in vacuo and partitioned between dichloromethane and 1 N NaOH solution. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (methanol:ammonium hydroxide 1.0:0.005 v/v) to give 1.8 g (4.8 mmol, 60% yield) of colorless crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.02 (t, J = 7.2 Hz, 6H), 1.60–1.88 (m, 4H), 2.36 (t, J = 6.0 Hz, 2H), 2.54 (q, J = 7.2 Hz, 4H), 2.65 (t, J = 6.0 Hz, 2H), 3.28–3.42 (m, 4H), 5.71 (bt, 1H), 6.38 (d, J = 5.7 Hz, 1H), 7.35 (dd, J = 2.4 Hz, J = 9.0 Hz, 1H), 7.86 (d, J = 9.0 Hz, 1H), 7.93 (d, J = 2.4 Hz, 1H), 8.51 (d, J = 5.7 Hz, 1H), 8.85 (bt, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.3, 25.2, 27.8, 32.3, 38.1, 42.9, 45.8, 48.6, 98.6, 117.3, 121.9, 124.7, 128.0, 134.4, 148.9, 150.0, 151.6, 173.1.

4.2.1.33. *N*-(7-Chloro-4-quinolyl)-*N′*-(3-diethylaminopropanoyl)-1,5-diaminopentane, 30. A mixture of *N*-(7-chloro-4-quinolyl)-1,5-diaminopentane (0.25 g, 0.95 mmol), *N,N*-diethylamino-3-propionic acid (0.17 g, 0.93 mmol), EDC (0.22 g, 1.14 mmol), and triethylamine (0.4 mL, 2.9 mmol) in 12 mL of anhydrous DMF and chloroform (1:1 v/v) was stirred at room temperature for 2.5 days. The reaction mixture was concentrated in vacuo, then dissolved in dichloromethane and extracted with aqueous NaOH. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography (methanol:ammonium hydroxide 1.0:0.05 v/v) to afford 0.045 g (0.11 mmol, 12% yield) of colorless crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.01 (t, J = 7.2 Hz, 6H), 1.49–1.59 (m, 4H), 1.82–1.87 (m, 2H) , 2.53 (t, J = 6.0 Hz, 2H), 2.53 (q, J = 7.2 Hz, 4H), 2.64 (t, J = 6.0 Hz, 2H), 3.26–3.33 (m, 4H), 5.46 (bs, 1H), 6.37 (d, J = 5.4 Hz, 1H), 7.35 (dd, J = 2.2 Hz, 8.8 Hz, 1H), 7.94 (d, J = 2.2 Hz, 1H), 7.96 (d, J = 8.8 Hz, 1H), 8.51 (d, J = 5.4 Hz, 1H), 8.80 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.8, 24.3, 28.0, 30.0, 32.8, 37.9, 43.4, 46.3, 49.2, 100.6, 117.6, 122.0, 128.9, 134.9, 149.5, 150.3, 152.3, 173.7.

4.2.1.34. *N*-(7-Chloro-4-quinolyl)-*N′*-(3-diethylaminopropanoyl)-1,6-diaminohexane, 31. A mixture of *N*-(7-chloro-4-quinolyl)-1,6-diaminohexane (0.1 g, 0.36 mmol), *N,N*- diethylamino-3-propionic acid (0.08 g, 0.43 mmol), EDC (0.08 g, 0.43 mmol) and Et_3N (0.19 mL, 1.35 mmol) was stirred at room temperature in 4 mL of DMF:$CHCl_3$ (1:1 v/v) for 2 days. Saturated $NaHCO_3$ was added to the cooled reaction mixture, which was then extracted with CH_2Cl_2 and dried over anhydrous $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography using EtOH:Et_3N (1:0.05 v/v) as the mobile phase gave yellow crystals (0.12 g, 0.27 mmol, 76% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.06 (t, J = 7.1 Hz, 6H), 1.25–1.62 (m, 6H), 1.63–1.82 (m, 2H), 2.40 (t, J = 6.1 Hz, 2H), 2.58 (q, J = 7.1 Hz, 4H), 2.69 (t, J = 6.1 Hz, 2H), 3.20–3.41 (m, 4H), 5.37 (bs, 1H), 6.41 (d, J = 5.4 Hz, 1H), 7.38 (dd, J = 2.1 Hz, J = 9.0 Hz, 1H), 7.80 (d, J = 9.0 Hz, 1H), 7.97 (d, J = 2.1 Hz, 1H), 8.53 (d, J = 5.4 Hz, 1H), 8.67 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.7, 26.7, 28.7, 29.8, 32.7, 38.7, 43.1, 46.3, 49.2, 99.1, 117.5, 121.9, 125.3, 128.6, 135.0, 149.2, 150.3, 152.0, 173.2.

4.2.1.35. Representative procedure for the synthesis of amide analogs 32–36. To a solution of *N*-(1-naphthyl)anthranilic acid (0.15 g, 0.57 mmol) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) (0.1 g, 0.57 mmol) in anhydrous $CHCl_3$, 0.1 mL (0.63 mmol) of *N*-methylmorpholine (NMM) was added dropwise at 0 °C and stirred at room temperature for 2 h. *N*-(7-Chloro-4-quinolyl)-1,3-diaminopropane (0.41 g, 1.7 mmol) in anhydrous DMF was then added. The reaction mixture was stirred for another 2 h and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, extracted with water, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (MeOH:EtOAc 1:32 v/v) allowed the isolation of 0.2 g of **32** (0.41 mmol, 73% yield) as light brown crystals.

4.2.1.36. *N*-(7-Chloro-4-quinolyl)-*N′*-(2-naphthylaminobenzoyl)-1,3-diaminopropane, 32. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.91 (m, 2H), 3.37 (q, J = 5.7 Hz, 2H), 3.58 (q, J = 6.3 Hz, 2H), 6.32 (d, J = 5.7 Hz, 1H), 6.46 (t, J = 5.7 Hz, 1H), 6.71 (m, 1H), 6.97 (bs, 1H), 7.16–7.28 (m, 3H), 7.38–7.56 (m, 5H), 7.62 (d, J = 8.1 Hz, 1H), 7.84–7.95 (m, 3H), 8.17 (m, 1H), 8.42 (d, J = 5.7 Hz, 1H), 9.90 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 27.6, 37.1, 40.2, 98.5, 98.7, 114.8, 115.7, 117.4, 117.8, 118.1, 121.4, 122.6, 124.0, 126.0, 126.2, 127.2, 127.3, 128.4, 128.7, 131.9, 133.4, 134.3, 137.1, 145.4, 148.8, 150.1, 151.6, 169.3.

4.2.1.37. *N*-(7-Chloro-4-quinolyl)-*N′*-(2-benzylamino-4-fluorobenzoyl)-1,3-diaminopropane, 33. Employing 0.15 g (0.6 mmol) of 4-fluoro-*N*-benzylanthranilic acid and *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane (0.43 g, 1.83 mmol) in the procedure described above and purification by flash chromatography (MeOH:EtOAc 1:49 v/v) gave 0.16 g (0.35 mmol, 59% yield) of colorless crystals. ^{1}H NMR (300 MHz, CD_3OD) δ = 2.00 (m, 2H), 3.40–3.54 (m, 4H), 4.31 (s, 2H), 6.23–6.38 (m, 2H), 6.52 (d, J = 5.7 Hz, 1H), 7.18–7.38 (m, 6H), 7.50 (dd, J = 2.1 Hz, 9.0 Hz, 1H), 7.75 (d, J = 2.1 Hz, 1H), 8.05 (d, J = 9.0 Hz, 1H), 8.31 (d, J = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 27.7, 36.8, 36.9, 45.9, 46.0, 97.5, 97.9, 98.6, 100.8, 101.1, 111.8, 117.4, 117.5, 124.0, 126.9, 127.1, 127.4, 128.5, 130.6, 130.8, 133.3, 138.9, 149.0, 149.9, 150.0, 151.1, 151.2, 151.3, 151.4, 151.8, 163.3, 166.5, 168.4, 168.4, 168.5.

4.2.1.38. *N*-(7-Chloro-4-quinolyl)-*N′*-(2-phenylethylaminobenzoyl)-1,3-diaminopropane, 34. Employing 0.15 g (0.6 mmol) of *N*-phenethylanthranilic acid and *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane (0.44 g, 1.86 mmol) in the procedure described above and purification by flash chromatography (MeOH:EtOAc 1:24 v/v) gave 0.19 g (0.42 mmol, 68% yield) of colorless crystals. ^{1}H NMR (300 MHz, CD_3OD) δ = 1.98 (m, 2H), 2.90 (t, J = 7.2 Hz, 2H), 3.36–3.52 (m, 6H), 6.50 (d, J = 5.7 Hz, 1H), 6.59 (m, 1H), 6.74 (d, J = 8.1 Hz, 1H), 7.13 (m, 1H), 7.20–7.48 (m, 7H), 7.78 (d, J = 2.4 Hz, 1H), 8.06 (d, J = 9.0 Hz, 1H), 8.33 (d, J = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 22.7, 34.8, 36.8, 43.8, 43.9, 79.1, 98.6, 111.0, 114.1, 115.0, 115.1, 115.2, 117.4, 117.5, 124.0, 126.0, 127.4, 128.2, 128.8, 132.3, 133.4, 139.4, 148.7, 148.8, 148.9, 149.9, 150.0, 151.7, 169.1, 169.1, 169.2, 169.2.

4.2.1.39. *N*-(7-Chloro-4-quinolyl)-*N′*-(2-cyclohexylthiobenzoyl)-1,3-diaminopropane, 35. Employing 0.12 g (0.51 mmol) of 2-(cyclohexylthio)benzoic acid and *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane (0.1 g, 0.43 mmol) in the procedure described above (this reaction was conducted at 70 °C) and purification by flash chromatography (MeOH:CH_2Cl_2 1:49 v/v and gradually changing the ratio of MeOH:CH_2Cl_2 to 1:11.5 v/v) gave 0.07 g (0.15 mmol, 35% yield) of light yellow crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.12–1.44 (m, 5H), 1.59 (s, 1H), 1.72 (m, 2H), 1.85–2.04 (m, 4H), 3.11 (m, 1H), 3.50–3.70 (m, 4H), 6.41 (d, J = 5.4 Hz, 1H), 6.77 (bt, 1H), 7.29–7.53 (m, 5H), 7.75 (dd, J = 7.5 Hz, J = 2.1 Hz, 1H), 7.90 (d, J = 2.1 Hz, 1H), 8.02 (d, J = 9.0 Hz, 1H), 8.46 (d, J = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 25.2, 25.8, 28.1, 33.1, 36.5, 39.0, 48.0, 98.2, 98.3, 117.5, 122.2, 125.3, 127.4, 127.8, 129.2, 130.5, 132.0, 134.0, 135.0, 138.0, 148.7, 150.2, 151.2, 151.3, 169.6.

4.2.1.40. *N*-(7-Chloro-4-quinolyl)-*N′*-(2-phenylthiobenzoyl)-1,3-diaminopropane, 36. Employing 0.12 g (0.51 mmol) of 2-(phenylthio)benzoic acid and *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane

(0.1 g, 0.43 mmol) in the procedure described above (this reaction was conducted at 70 °C) and purification by flash chromatography ($MeOH:CH_2Cl_2$ 1:24 v/v) gave 0.05 g (0.1 mmol, 25% yield) of light yellow crystals. ^1H NMR (300 MHz, $CDCl_3$) δ = 1.84 (m, 2H), 3.42 (q, J = 6.0 Hz, 2H), 3.54 (q, J = 6.0 Hz, 1H), 6.36 (d, J = 5.4 Hz, 1H), 6.60 (t, J = 6.0 Hz, 1H), 6.89 (t, J = 6.0 Hz, 1H), 7.22–7.39 (m, 9H), 7.66 (m, 1H), 7.89 (d, J = 1.8 Hz, 1H), 7.96 (d, J = 9.0 Hz, 1H), 8.44 (d, J = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 28.0, 36.6, 38.8, 98.2, 98.3, 117.5, 122.1, 125.2, 125.3, 127.3, 127.7, 128.0, 128.1, 128.8, 129.5, 131.0, 131.2, 132.3, 133.7, 134.3, 134.9, 136.5, 148.9, 150.0, 151.4, 151.5, 169.3.

4.2.1.41. Representative procedure for the synthesis of amide analogs (37–44). *N*-(7-Chloro-4-quinolyl)-1,3-diaminopropane (0.1 g, 0.43 mmol), Boc-Trp-OH (0.16 g, 0.52 mmol) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) (0.09 g, 0.52 mmol) were dissolved in 3 mL of acetonitrile and 1 mL of DMF. *N*-Methylmorpholine (NMM) (0.165 g, 0.65 mmol) was added and the reaction was stirred at 40 °C for 24 h. The solvents were removed under reduced pressure and dissolved in 25 mL of CH_2Cl_2 and washed twice with 1 mL of water and brine, respectively. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography using EtOAc:EtOH:Et_3N (4:1:0.02 v/v) as the mobile phase gave 0.134 g of **37** as a colorless oil (0.26 mmol, 60% yield) from Boc-D-Trp-OH. The same procedure gave 0.09 g of **38** as a colorless oil (0.17 mmol, 40% yield) from Boc-Trp-OH.

4.2.1.42. *N*-(7-Chloro-4-quinolyl)-*N′*-1,3-diaminopropan-*N″*-t-Boc-tryptophan amide, 37 and 38. ^1H NMR (300 MHz, $CDCl_3$) δ = 1.40 (s, 9H), 2.74–2.92 (m, 4H), 1.65–1.84 (m, 2H), 3.18–3.36 (m, 6H), 4.34 (t, J = 6.0 Hz, 1H), 6.36 (d, J = 5.6 Hz, 1H), 6.89–7.11 (m, 3H), 7.12 (s, 1H), 7.31 (d, J = 7.5 Hz, 1H), 7.40 (dd, J = 2.0 Hz, J = 7.2 Hz,1H), 7.77 (d, J = 2.0 Hz, 1H), 8.06 (d, J = 9.0 Hz, 1H), 8.31 (d, J = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 27.5, 28.2, 36.6, 39.7, 56.2, 78.3, 79.5, 98.5, 109.8, 111.2, 117.6, 118.3, 118.7, 121.3, 123.1, 123.4, 124.8, 126.4, 127.7, 135.1, 136.9, 148.4, 151.3, 156.4, 174.0.

4.2.1.43. *N*-(7-Chloro-4-quinolyl)-*N′*-1,3-diaminopropan-*N″*-Z-lysine amide, 39. Employing 0.1 g (0.43 mmol) of *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane and Z-Lys(Boc)-OH (0.198 g, 0.52 mmol) in the procedure described above and purification by flash chromatography using EtOAc:EtOH:Et_3N (1:1:0.02 v/v) as the mobile phase gave a colorless oil (0.077 g, 0.13 mmol, 30% yield). ^1H NMR (300 MHz, $CDCl_3$) δ = 1.42 (s, 9H), 1.61–1.98 (m, 6H), 2.95 (m, 1H), 3.01–3.18 (m, 2H), 3.22–3.45 (m, 4H), 4.11–4.25 (m, 1H), 4.83 (t, J = 6.0 Hz, 1H), 5.10 (s, 2H), 6.12 (d, J = 6.3 Hz, 1H), 6.48 (d, J = 5.6 Hz,1H), 7.25–7.40 (m, 5H), 7.92 (d, J = 2.2 Hz, 1H), 7.93 (d, J = 9.0 Hz, 1H), 8.42 (d, J = 5.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 22.8, 28.2, 28.7, 29.9, 31.9, 36.5, 39.3, 39.8, 55.6, 67.5, 79.6, 98.7, 117.8, 122.4, 125.5, 128.3, 128.5, 128.8, 135.1, 136.4, 149.4, 150.3, 152.2, 156.7, 156.8, 162.9, 173.7.

4.2.1.44. *N*-(7-Chloro-4-quinolyl)-*N′*-1,3-diaminopropan-*N″*-t-Boc-proline amide, 40. Employing 0.1 g (0.43 mmol) of *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane and Boc-Pro-OH (0.112 g, 0.52 mmol) in the procedure described above and purification by flash chromatography using EtOH:Et_3N (1:0.02 v/v) as the mobile phase gave a colorless oil (0.092 g, 0.24 mmol, 55% yield). ^1H NMR (300 MHz, $CDCl_3$) δ = 1.45 (s, 9H), 1.82–2.10 (m, 6H), 3.36–3.62 (m, 6H), 4.18–4.22 (m, 1H), 6.62 (d, J = 9.0 Hz, 1H), 7.44 (dd, J = 2.2 Hz, J = 6.8 Hz, 1H), 7.81 (d, J = 2.2 Hz, 1H), 8.17 (d, J = 9.0 Hz, 1H), 8.38 (d, J = 6.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 24.6, 28.1, 28.4, 36.0, 38.9, 47.2, 60.3, 80.6, 98.2, 117.4, 122.2, 125.5, 127.6, 135.3, 148.3, 150.4, 150.9.

4.2.1.45. *N*-(7-Chloro-4-quinolyl)-*N′*-(3-pyridoyl)-1,3-diaminopropane, 41. Employing 0.1 g (0.43 mmol) of *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane and 3-nicotinic acid (0.064 g, 0.52 mmol) in the procedure described above and purification by flash chromatography using EtOH:Et_3N (1:0.02 v/v) as mobile phase afforded a colorless oil (0.032 g, 0.084 mmol, 20% yield). ^1H NMR (300 MHz, $CDCl_3$) δ = 2.01–2.72 (m, 2H), 3.51 (t, J = 6.9 Hz, 2H), 3.75 (t, J = 6.9 Hz, 2H), 6.66 (d, J = 8.4 Hz, 1H), 7.45–7.60 (m, 2H), 7.82 (dd, J = 2.1 Hz, J = 5.8 Hz, 1H), 8.24–8.31 (m, 2H), 8.39 (d, J = 2.1 Hz, 1H), 8.71 (dd, J = 2.1 Hz, J = 5.8 Hz, 1H), 9.10 (d, J = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 28.2, 38.7, 39.5, 98.2, 116.3, 119.4, 123.6, 124.7, 127.3, 129.5, 133.9, 134.1, 134.7, 147.4, 147.8, 151.0, 151.7, 166.4.

4.2.1.46. *N*-(7-Chloro-4-quinolyl)-*N′*-[3-(6-hydroxypyridoyl]-1,3-diaminopropane, 42. Employing 0.1 g (0.43 mmol) of *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane and 6-hydroxynicotinic acid (0.075 g, 0.52 mmol) in the procedure described above and purification by flash chromatography using EtOH:Et_3N (1:0.02 v/v) as mobile phase gave a colorless oil (0.038 g, 0.11 mmol, 25% yield). ^1H NMR (300 MHz, $CDCl_3$) δ = 1.82–1.98 (m, 2H), 3.62 (t, J = 6.7 Hz, 2H), 3.79 (t, J = 6.7 Hz, 2H), 6.42 (d, J = 7.5 Hz, 1H), 7.15 (d, J = 6.8 Hz, 1H), 7.24–7.38 (m, 2H), 8.21 (d, J = 7.5 Hz, 1H), 8.32 (d, J = 6.8 Hz, 1H), 8.42 (dd, J = 2.0 Hz, J = 5.4 Hz, 1H), 8.91 (d, J = 2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 28.4, 38.3, 39.6, 98.2, 110.9, 114.7, 119.4, 116.5, 124.6, 129.5, 134.0, 145.2, 149.8,151.8, 154.1, 154.7, 166.7.

4.2.1.47. *N*-(7-Chloro-4-quinolyl)-*N′*-(3-dimethylaminobenzoyl)-1,3-diaminopropane, 43. Employing 0.1 g (0.43 mmol) of *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane and 3-dimethylaminobenzoic acid (0.086 g, 0.52 mmol) in the procedure described above and purification by flash chromatography using CH_2Cl_2:EtOH:Et_3N (1:1:0.02 v/v) as the mobile phase gave a colorless oil (0.042 g, 0.11 mmol, 25% yield). ^1H NMR (300 MHz, $CDCl_3$) δ = 1.95–2.18 (m, 2H), 3.47 (t, J = 6.8 Hz, 2H), 3.55 (t, J = 6.8 Hz, 2H), 3.96 (s, 6H), 6.55 (d, J = 5.7 Hz, 1H), 7.36–7.42 (m, 2H), 7.53 (dd, J = 6.3 Hz, J = 7.5 Hz, 1H), 7.70 (dd, J = 2.1 Hz, J = 6.3 Hz, 1H), 7.75 (d, J = 2.1 Hz, 2H), 8.12 (d, J = 9 Hz, 1H), 8.32 (d, J = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 27.8, 39.4, 39.6, 40.7, 40.9, 98.7, 108.5, 116.3, 116.9, 120.6, 129.1, 134.4, 134.8, 148.5, 150.9, 151.7, 166.8.

4.2.1.48. *N*-(7-Chloro-4-quinolyl)-*N′*-[3-(2-benzimidazol)propanoyl]-1,3-diaminopropane, 44. Employing 0.1 g (0.43 mmol) of *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane and 2-benzimidazolepropionic acid (0.1 g, 0.52 mmol) in the procedure described above and purification by flash chromatography using EtOH:Et_3N (1:0.01 v/v) as mobile phase gave a colorless oil (0.061 g, 0.15 mmol, 35% yield) . ^1H NMR (300 MHz, MeOD) δ = 1.78–1.95 (m, 2H), 2.27 (t, J = 7.2 Hz, 2H), 3.21 (t, J = 7.5 Hz, 2H), 3.25 (t, J = 7.5 Hz, 2H), 3.27 (t, J = 7.2 Hz, 2H), 6.38 (d, J = 5.7 Hz, 1H), 7.10–7.18 (m, 2H), 7.37 (dd, J = 2.1 Hz, J = 9.0 Hz, 1H), 7.42–7.51 (m, 2H), 8.05 (d, J = 9.0 Hz, 1H), 7.77 (d, J = 2.1 Hz, 1H), 8.28 (d, J = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 24.5, 27.8, 33.5, 36.6, 39.9, 98.4, 117.4, 122.1, 123.3, 125.1, 125.4, 135.4, 135.7, 147.2, 150.1, 152.0, 154.3, 173.3.

4.2.1.49. *N*-(7-Chloro-4-quinolyl)-*N′*-(2,5-diaminobenzoyl)-1,3-diaminopropane, 45. A mixture of 5-aminoisatoic anhydride (0.1 g, 0.56 mmol) and *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane (0.15 g, 0.67 mmol) in ethanol was refluxed for 24 h. After cooling to room temperature, the filtrate was concentrated under reduced pressure. The residue was purified using flash chromatography ($MeOH:CH_2Cl_2$ 3:7 v/v) to afford 0.13 g (0.34 mmol, 64% yield) of brown crystals. ^1H NMR (300 MHz, CD_3OD) δ = 1.95 (m,

2H), 3.36 (t, J = 6.9 Hz, 1H), 3.43 (t, J = 6.9 Hz, 1H), 6.42 (d, J = 6.0 Hz, 1H), 6.65 (d, J = 8.7 Hz, 1H), 6.74 (dd, J = 2.4 Hz, J = 8.7 Hz, 1H), 6.85 (d, J = 2.4 Hz, 1H), 7.29 (dd, J = 2.1 Hz, J = 9.0 Hz, 1H), 7.70 (d, J = 2.1 Hz, 1H), 8.01 (d, J = 9.0 Hz, 1H), 8.26 (d, J = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ = 29.2, 38.1, 41.3, 99.5, 115.9, 118.6, 119.8, 120.0, 122.4, 124.2, 125.9, 127.2, 136.3, 139.0, 141.8, 149.1, 152.0, 152.5, 172.1.

4.2.1.50. *N*-[2-{(*N*′-2-(7-chloro-4-quinolyl)aminoethyl-*N*″-ethyl}-aminoethyl]-2-benzylamino-4-fluorobenzamide, 46. Employing 0.034 g (0.14 mmol) of 4-fluoro-*N*-benzylanthranilic acid and *N*-(7-chloro-4-quinolyl)-*N*′-ethyl-*N*′-(2-aminoethyl)-1,2-diaminoethane **10** (0.04 g, 0.14 mmol) in the procedure described for the syntheses of **32**–**36** followed by flash chromatography using MeOH:CH_2Cl_2 (1:49 to 1:15 v/v) as the mobile phase gave 0.047 g (0.09 mmol, 66% yield) of a light yellow oil. ^{1}H NMR (300 MHz, CD_3OD) δ = 1.10 (t, J = 6.9 Hz, 3H), 2.64–2.78 (m, 4H), 2.85 (t, J = 6.3 Hz, 2H), 3.34–3.47 (m, 4H), 3.55 (t, J = 6.9 Hz, 2H), 6.40 (d, J = 5.7 Hz, 1H), 7.24 (dd, J = 1.8 Hz, J = 9.0 Hz, 1H), 7.66 (d, J = 1.8 Hz, 1H), 7.96 (d, J = 9.0 Hz, 1H), 8.08 (s, 1H), 8.24 (d, J = 5.7 Hz, 1H), 8.38 (s, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ = −62.9; ^{13}C NMR (75 MHz, CD_3OD) δ = 12.2, 38.5, 41.5, 47.8, 52.4, 53.5, 98.8 (m), 99.8, 99.9, 102.5 (m), 113.1, 118.5, 123.9, 126.0, 127.2, 127.3, 128.2, 129.6, 131.2 (dd, $J_{C\text{-}F}$ = 6.8 Hz, $J_{C\text{-}F}$ = 22.6 Hz), 136.4, 136.9, 149.0, 152.0, 152.5, 152.6, 152.7, 165.4, 168.7, 171.3.

4.2.1.51. Representative procedure for the synthesis of amide analogs 47–50. To a solution of *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane (0.11 g, 0.47 mmol) and Et_3N (0.13 mL, 0.94 mmol) in anhydrous DMF and $CHCl_3$ (1:1 v/v), 3,5-bis(trifluoromethyl)benzoyl chloride (0.092 mL, 0.51 mmol) was added at 0 °C. The reaction mixture was stirred for 3 h at room temperature and concentrated under reduced pressure. Saturated $NaHCO_3$ solution was added to the residue, which was then extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Flash chromatography using MeOH:CH_2Cl_2 (1:19 to 1:9 v/v) gave 0.224 g of the *N*-acyl quinolinium salt of **47**. The crystalline residue was hydrolyzed in 1 N NaOH solution, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and concentrated in vacuo to yield 0.13 g (0.27 mmol, 59% yield) of off-white crystals.

4.2.1.52. *N*-(7-Chloro-4-quinolyl)-*N*′-{bis(trifluoromethyl)benzoyl}-1,3-diaminopropane, 47. ^{1}H NMR (300 MHz, CD_3OD) δ = 2.03 (m, 2H), 3.37 (t, J = 6.9 Hz, 2H), 3.55 (t, J = 6.9 Hz, 2H), 6.40 (d, J = 5.7 Hz, 1H), 7.24 (dd, J = 1.8 Hz, J = 9.0 Hz, 1H), 7.66 (d, J = 1.8 Hz, 1H), 7.96 (d, J = 9.0 Hz, 1H), 8.08 (s, 1H), 8.24 (d, J = 5.7 Hz, 1H), 8.38 (s, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ = −62.9 (s, 6F); ^{13}C NMR (75 MHz, CD_3OD) δ = 27.7, 37.9, 40.2, 98.3, 98.4, 117.4, 117.9, 121.5, 122.9, 124.7, 124.8, 125.1, 126.3, 126.4, 127.7, 128.7, 131.8 (q, $J_{C\text{-}F}$ = 126.0 Hz), 135.0, 136.7, 148.3, 151.0, 151.1, 151.2, 165.5.

4.2.1.53. *N*-(7-Chloro-4-quinolyl)-*N*′-(pentafluorobenzoyl)-1,3-diaminopropane, 48. Using 0.11 g (0.47 mmol) of *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane and 2,3,4,5,6-pentafluorobenzoyl chloride (0.07 mL, 0.51 mmol) in the procedure described above and purification by flash chromatography with MeOH:CH_2Cl_2 (1:19 to 1:9 v/v), followed by extraction with 1 N NaOH gave 0.13 g (0.3 mmol, 65% yield) of off-white crystals. ^{1}H NMR (300 MHz, CD_3OD) δ = 2.03 (m, 2H), 3.46 (t, J = 7.2 Hz, 2H), 3.54 (t, J = 6.9 Hz, 2H), 6.53 (d, J = 5.4 Hz, 1H), 7.38 (dd, J = 2.1 Hz, J = 9.0 Hz, 1H), 7.76 (d, J = 2.1 Hz, 1H), 8.08 (d, J = 9.0 Hz, 1H), 8.34 (d, J = 5.4 Hz, 1H); ^{19}F NMR (282 MHz, CD_3OD) δ = −144.4 (m, 2F), −155.5 (tt, J = 2.5 Hz, J = 19.7 Hz, 1F), −164.0 (m, 2F); ^{13}C NMR (75 MHz, CD_3OD) δ = 28.9, 38.7, 41.2, 99.5, 99.6, 113.4 (m), 118.7, 124.2, 126.0, 127.5, 127.6, 136.3, 138.9 (m), 143.3 (m), 145.0 (m), 149.5, 152.3, 152.5, 159.8.

4.2.1.54. *N*-(7-Chloro-4-quinolyl)-*N*′-(heptafluorobutyryl)-1,3-diaminopropane, 49. Using 0.11 g (0.47 mmol) of *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane and perfluorobutyryl chloride (0.08 mL, 0.51 mmol) in the procedure described above and purification by flash chromatography with MeOH:CH_2Cl_2 (1:16 v/v), followed by extraction with 1 N NaOH gave 0.1 g (0.23 mmol, 49% yield) of off-white crystals. ^{1}H NMR (300 MHz, CD_3OD) δ = 1.98 (m, 2H), 3.39 (t, J = 7.2 Hz, 2H), 3.45 (t, J = 7.2 Hz, 2H), 6.50 (d, J = 5.7 Hz, 1H), 7.39 (dd, J = 2.1 Hz, J = 9.0 Hz, 1H), 7.76 (d, J = 2.1 Hz, 1H), 8.06 (d, J = 9.0 Hz, 1H), 8.34 (d, J = 5.7 Hz, 1H); ^{19}F NMR (282 MHz, CD_3OD) δ = −82.6 (t, J = 9.0 Hz, 3F), −122.2 (q, J = 9.0 Hz, 2F), −128.7 (s, 2F); ^{13}C NMR (75 MHz, CD_3OD) δ = 28.6, 38.7, 41.1, 99.5, 99.6, 105.8–114.2 (m), 117.1 (t, $J_{C\text{-}F}$ = 141.0 Hz), 118.7, 120.9 (t, $J_{C\text{-}F}$ = 141.0 Hz), 124.1, 126.0, 126.0, 127.4, 127.5, 136.3, 149.4, 152.2, 152.5, 159.4 (t, $J_{C\text{-}F}$ = 95.9 Hz).

4.2.1.55. *N*-(7-Chloro-4-quinolyl)-*N*′-(pentadecafluorooctanoyl)-1,3-diaminopropane, 50. Employing 0.15 g (0.64 mmol) of *N*-(7-chloro-4-quinolyl)-1,3-diaminopropane and pentadecafluorooctanoyl chloride (0.17 mL, 0.7 mmol) in the procedure described above and purification by flash chromatography using MeOH:CH_2Cl_2 (1:19 to 1:9 v/v), followed by extraction with 1 N NaOH gave 0.1 g (0.16 mmol, 25% yield) of off-white crystals. ^{1}H NMR (300 MHz, CD_3OD) δ = 1.99 (m, 2H), 3.40 (t, J = 7.2 Hz, 2H), 3.45 (t, J = 6.9 Hz, 2H), 6.50 (d, J = 6.0 Hz, 1H), 7.39 (dd, J = 2.1 Hz, J = 9.0 Hz, 1H), 7.77 (d, J = 2.1 Hz, 1H), 8.07 (d, J = 9.0 Hz, 1H), 8.34 (d, J = 6.0 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ = −78.8 (tt, J = 2.5 Hz, J = 9.9 Hz, 3F), −117.1 (t, J = 12.5 Hz, 2F), −118.9 (m, 2F), −119.4 (m, 2F), −120.1 (m, 2F), −123.7 (m, 2F); ^{13}C NMR (75 MHz, CD_3OD) δ = 28.6, 38.8, 41.2, 106.8–117.2 (m), 118.7, 120.3 (t, $J_{C\text{-}F}$ = 112.8 Hz), 124.1, 126.0, 126.1, 127.5, 127.6, 136.3, 149.6, 152.3, 152.4, 159.5 (t, $J_{C\text{-}F}$ = 96.9 Hz).

4.2.1.56. Representative procedure for the synthesis of amide analogs 51–54. To a solution of *N*-(7-chloro-4-quinolyl)-*N*′-ethyl-*N*′-(2-aminoethyl)-1,2-diaminoethane **10** (0.031 g, 0.11 mmol) and Et_3N (0.03 mL, 0.22 mmol) in anhydrous CH_2Cl_2, 3,5-bis(trifluoromethyl)benzoyl chloride (0.02 mL, 0.11 mmol) was added at 0 °C. The reaction mixture was stirred for 1 h at room temperature until saturated 1 N NaOH solution was added. The mixture was extracted with CH_2Cl_2, and the combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuo. Flash chromatography using MeOH:CH_2Cl_2 (1:99 v/v) as the mobile phase gave 0.051 g of the *N*-acyl quinolinium salt. The residue was refluxed in 5 mL of methanol for 6 h and concentrated under reduced pressure. Flash chromatography using MeOH:CH_2Cl_2 (1:49 v/v) gave 0.022 g (0.04 mmol, 39% yield) of a yellow oil.

4.2.1.57. *N*-[2-{(*N*′-2-(7-chloro-4-quinolyl)aminoethyl-*N*″-ethyl}-aminoethyl]-3,5-(bistrifluoromethyl)benzamide, 51. ^{1}H NMR (300 MHz, CD_3OD) δ = 1.13 (t, J = 7.2 Hz, 3H), 2.70–2.85 (m, 4H), 2.88 (t, J = 6.3 Hz, 2H), 3.40 (t, J = 6.0 Hz, 2H), 3.54 (t, J = 6.0 Hz, 2H), 6.49 (d, J = 5.7 Hz, 1H), 7.19 (dd, J = 2.1 Hz, J = 9.0 Hz, 1H), 7.67 (d, J = 2.1 Hz, 1H), 7.82 (d, J = 9.0 Hz, 1H), 7.99 (s, 1H), 8.24 (s, 2H), 8.29 (d, J = 5.7 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ = −63.3 (s, 6F); ^{13}C NMR (75 MHz, CD_3OD) δ = 12.2, 39.2, 41.4, 52.5, 53.4, 99.7, 99.8, 118.3, 119.0, 122.6, 123.7, 126.0 (m), 127.3, 127.4, 128.6, 129.8, 132.8 (q, $J_{C\text{-}F}$ = 126.0 Hz), 136.3, 137.7, 149.1, 152.2, 152.3, 166.4.

4.2.1.58. *N*-[2-{(*N*′-2-(7-chloro-4-quinolyl)aminoethyl-*N*″-ethyl}-aminoethyl]pentafluorobenzamide, 52. Employing 0.047 g (0.16 mmol) of *N*-(7-chloro-4-quinolyl)-*N*′-ethyl-*N*′-(2-aminoethyl)-1,2-

diaminoethane **10** and 2,3,4,5,6-pentafluorobenzoyl chloride (0.023 mL, 0.16 mmol) in the procedure described above and purification by flash chromatography using MeOH:EtOAc (1:24 v/v) as the mobile phase gave 0.018 g (0.04 mmol, 23% yield) of light yellow crystals. ^{1}H NMR (300 MHz, $CD_3OD + CDCl_3$) δ = 1.13 (t, J = 6.9 Hz, 3H), 2.66–2.82 (m, 4H), 2.89 (t, J = 6.3 Hz, 2H), 3.38 (t, J = 5.7 Hz, 2H), 3.52 (t, J = 6.0 Hz, 2H), 6.43 (d, J = 5.7 Hz, 2H), 7.30 (dd, J = 2.1 Hz, J = 9.0 Hz, 1H), 7.82 (d, J = 2.1 Hz, 1H), 7.83 (d, J = 9.0 Hz, 1H), 8.38 (d, J = 5.7 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ = −142.0 (m, 2F), −152.3 (dt, J = 3.1 Hz, J = 20.6 Hz, 1F), −161.4 (m, 2F); ^{13}C NMR (75 MHz, CD_3OD) δ = 11.0, 37.6, 39.9, 47.3, 51.1, 51.8, 98.4, 98.5, 111.0 (m), 116.7, 121.6, 124.8, 126.5, 126.6, 135.1, 136.9 (m, J_{C-F} = 930.6 Hz), 141.6 (m, J_{C-F} = 958.8 Hz), 143.4 (m, J_{C-F} = 958.8 Hz), 147.6, 150.3, 150.7, 157.8.

4.2.1.59. *N*-[2-{(*N*′-2-(7-chloro-4-quinolyl)aminoethyl-*N*″-ethyl}-aminoethyl]heptafluorobutanamide, 53. Using 0.047 g (0.16 mmol) of *N*-(7-chloro-4-quinolyl)-*N*′-ethyl-*N*′-(2-aminoethyl)-1,2-diaminoethane **10** and perfluorobutyryl chloride (0.02 mL, 0.13 mmol) in the procedure described above and purification by flash chromatography with MeOH:EtOAc (1:24 v/v) gave 0.027 g (0.055 mmol, 42% yield) of a light yellow oil. ^{1}H NMR (300 MHz, CD_3OD) δ = 1.06 (t, J = 7.2 Hz, 3H), 2.61–2.75 (m, 4H), 2.85 (t, J = 6.6 Hz, 2H), 3.39–3.49 (m, 4H), 6.56 (d, J = 5.7 Hz, 1H), 7.38 (dd, J = 2.1 Hz, J = 9.0 Hz, 1H), 7.78 (d, J = 2.1 Hz, 1H), 8.09 (d, J = 9.0 Hz, 1H), 8.36 (d, J = 5.7 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ = –82.6 (t, J = 9.0 Hz, 3F), −122.1 (q, J = 9.0 Hz, 2F), −128.7 (s, 2F); ^{13}C NMR (75 MHz, CD_3OD) δ = 12.1, 39.0, 41.8, 48.8, 52.7, 53.5, 99.7, 99.8, 105.2–117.8 (m), 118.7, 120.8 (t, J_{C-F} = 141.0 Hz), 124.2, 126.0, 127.5, 127.4, 136.4, 149.5, 152.3, 152.3, 152.6, 159.3 (t, J_{C-F} = 94.0 Hz).

4.2.1.60. *N*-[2-{(*N*′-2-(7-chloro-4-quinolyl)aminoethyl-*N*″-ethyl}-aminoethyl]pentadecafluorooctanamide, 54. Employing 0.051 g (0.17 mmol) of *N*-(7-chloro-4-quinolyl)-*N*′-ethyl-*N*′-(2-aminoethyl)-1,2-diaminoethane **10** and pentadecafluorooctanoyl chloride (0.04 mL, 0.17 mmol) in the procedure described above and purification by flash chromatography using MeOH:EtOAc (1:24 v/v) gave 0.019 g (0.027 mmol, 16% yield) of a light yellow oil. ^{1}H NMR (300 MHz, CD_3OD) δ = 1.07 (t, J = 7.2 Hz, 3H), 2.61–2.76 (m, 4H), 2.87 (t, J = 6.6 Hz, 2H), 3.45 (q, J = 6.6 Hz, 1H), 6.59 (d, J = 6.0 Hz, 1H), 7.39 (dd, J = 2.4 Hz, J = 9.0 Hz, 1H), 7.79 (d, J = 2.4 Hz, 1H), 8.12 (d, J = 9.0 Hz, 1H), 8.37 (d, J = 5.7 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ = −82.7 (tt, J = 2.3 Hz, J = 9.9 Hz, 3F), −121.0 (t, J = 13.0 Hz, 2F), −122.9 (m, 2F), −123.4 (m, 2F), −123.9 (m, 2F), −124.1 (m, 2F), −127.6 (m, 2F); ^{13}C NMR (75 MHz, CD_3OD) δ = 12.1, 39.0, 41.9, 52.6, 53.5, 99.7, 118.6, 124.3, 126.1, 127.1, 136.6, 149.0, 151.9, 152.9.

Acknowledgment

We thank the NIH (Grant RO1AI060792) for financial support.

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