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Synthesis and antimalarial activity of new chloroquine analogues carrying a multifunctional linear side chain

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ABSTRACT

We report the synthesis and in vitro antimalarial activity of several new 4-amino- and 4-alkoxy-7-chloroquinolines carrying a linear dibasic side chain. Many of these chloroquine analogues have submicromolar antimalarial activity versus HB3 (chloroquine sensitive) and Dd2 (chloroquine resistant strain of *Plasmodium falciparum*) and low resistance indices were obtained in most cases. Importantly, compounds 11–15 and **24** proved to be more potent against Dd2 than chloroquine. Branching of the side chain structure proved detrimental to the activity against the CQR strain.

1. Introduction

Malaria remains one of the world's most widespread and devastating infectious diseases and affects approximately 2.4 billion people living in malaria-endemic areas. Recent estimates calculate approximately 600 million annual clinical infections with *Plasmodium falciparum*, 80 million with *Plasmodium vivax* and more than 2 million casualties—malaria kills one child under the age of 5 years every 30 s.[1–3] Among the protozoan parasites of the genus *Plasmodium* causing malaria in humans, *P. falciparum* is the most lethal species while *vivax* is less morbid but carries the problem of severe relapses. Inexpensive and stable antimalarial drugs such as the 7-chloro-4-aminoquinoline derivative chloroquine (CQ) have kept malaria in check in most regions for decades. However, the rising number of malarial deaths is due in part to increased resistance to CQ and other drugs in *P. falciparum*.

Since the discovery of the antimalarial potency of quinine and other cinchona alkaloids, a variety of agents exhibiting a 4-substituted quinoline pharmacophore has been introduced. In particular, chloroquine, quinine and amodiaquine have proved to be among the most effective antimalarial drugs.[4–6] The exact molecular mechanism that describes how quinoline-based antimalarial drugs function is not yet precisely known. Aminoquinolines form a complex with ferriprotoporphyrin IX (FPIX), which is generated in the digestive vacuole (DV) of the intraerythrocytic malaria parasite as a result of proteolysis of host hemoglobin.[7,8] Free FPIX is cytotoxic and it is sequestered in the form of hemozoin, a crystalline Fe–O41 dimer that is structurally identical to synthetic β-hematin.[9,10] Hemozoin is also known as 'malaria pigment' and appears as a dark spot in the DV of the parasite, the organelle in which hemoglobin digestion and hemozoin formation occur. Drug–FPIX interactions inhibit conversion of hematin to hemozoin and hence its detoxification via crystallization, and the accumulation of significant concentrations of toxic FPIX–aminoquinoline adducts is believed to be ultimately responsible for killing the parasite.[11–15] It is widely accepted that the 4-aminoquinoline pharmacophore plays a crucial role in the complexation to FPIX resulting in inhibition of hemozoin formation and parasite growth,[16] while the presence of a basic amino group in the side chain is generally considered essential for trapping high concentrations of the drug in the acidic DV of the parasite.[17]

Previous studies relating the structure of aminoquinoline antimalarial drugs to their function have focused on modifications of the side chain and of the quinoline ring. Various studies have revealed that structural changes of the 7-chloroquinoline ring in CQ reduces the antimalarial activity,[17,18] whereas variation of the CQ side chain appears to be more promising. In a study by Krogstad et al., 7-chloroquinolines with *N*,*N*-diethylaminoalkyl side chains

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exhibiting spacers consisting of two to 12 methylene units were found to be as effective as chloroquine against CQ sensitive (CQS) strains.[19] Importantly, the homologs with either short or very long linkers between the two amino functions showed remarkable activity against CQ resistant (CQR) strains. Analogues of chloroquine with branched and linear side chains containing two and three methylenes between the amino groups were also found to have both in vitro and in vivo antiparasitic activity similar to that of chloroquine in CQS strains of *P. falciparum*, and were more effective than chloroquine against CQR strains.[20,21]

2. Results and discussion

Based on the above findings, we have begun to systematically modify the length and basicity of the CQ side chain.[22–24] In particular, 4-amino-7-chloroquinolines with a linear side chain bearing two aliphatic tertiary amino functions proved to be highly potent antimalarials and were found equally effective against both CQS and CQR strains. In a previous report, we altered the α-portion of the side chain in a series of 4-aminoquinolines and obtained superior antiplasmodial activities when the quinolyl nitrogen and the central amino group were kept in close proximity.[22] We have therefore prepared analogues **1–15** exhibiting a varied β-segment while the α-portion was kept constant at optimized length (Fig. 1).

Our synthetic approach towards heme-targeted antimalarials generally involves inexpensive materials and high-yielding steps in most cases. Treatment of 4,7-dichloroquinoline with excess of 1,2-diaminoethane gave almost quantitative amounts of *N*-(7-chloro-4-quinolyl)diaminoethane, **16**, as described previously.[24] Primary amine **16** then served as the common starting material for the synthesis of β-segment varied amides **1–5**, secondary amines **6–10** and tertiary amines **11–15** (Scheme 1). For example, one-pot amidation of **16** with bromoacetyl chloride followed by peripheral substitution with excess of diethylamine gave **1** in 60% yield. Reduction with borane and subsequent reaction with sodium borohydride in glacial acetic acid then furnished the corresponding amines **6** and **11** in 78% and 37% yield, respectively. The aminoquinolines **2**, **7**, and **12** were available from previous studies.[22] For comparison, we prepared branched aminoquinoline **18** using our established nucleophilic substitution and reductive alkylation protocols.

The antimalarial activity of compounds **1–15** and **18** was measured versus a CQS (HB3) and a CQR (Dd2) strain using a standardized assay based on SYBR Green I intercalation.[25–27] The IC_{50} values were calculated from experiments carried out in triplicate and compared to CQ (Table 1). Several compounds within this series showed promising 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.

It is important to note that several of our aminoquinolines afford antimalarial activity versus HB3 similar to that of CQ and we were pleased to find that some compounds were significantly more potent against the resistant strain Dd2 than CQ. In general, the antiplasmodial activity of tertiary amines **11–15** proved superior over those obtained for the corresponding secondary amines **6–10** and the amides **1–5**. Notably, the amines **11–15** have IC_{50}'s between 19.9 and 53.0 nM for Dd2 (CQ IC_{50} = 122 nM). The resistance index for CQ is about 15 whereas the majority of the heme-targeted antiplasmodials prepared for this study have RI's below 10. Quinolines **12–15** combine high antimalarial activity against HB3 with low RI values ranging from 1.1 to 7.1. These new CQ analogues thus show activity versus a CQS strain similar to that of CQ and, more importantly, they retain their potency against a CQR strain. Our stepwise variation of one chain at a time reveals that small changes in the spacer length can have dramatic effects on the activity versus the two strains tested. For example, a shortening or lengthening of the β-segment in the side chain in compound **12** by only one methylene group increases the RI from 1.1 to 7.1 and 10.5, respectively. But excellent resistance indices are again obtained when the β-chain length is further increased (see compounds **14** and **15**). The data also demonstrate that a linear side chain motif is superior over a branched structure. In analogy to linear amines **11–15**, compound **18** has high potency against HB3 but significantly lower activity against Dd2.

Based on these observations and previous work,[24] we then decided to prepare CQ analogues **19–24** in which the 4-quinolyl amino function is replaced by an ether linker (Fig. 2). As shown in Scheme 2, the amide derivatives can be prepared in two steps from 4,7-dichloroquinoline and an amino alcohol in the presence of strong base followed by EDC-promoted coupling with 3-diethylaminopropionic acid. However, we found that **19** and **22** are not stable to typical amide reduction conditions and we therefore prepared the corresponding amines via mesylation of alcohols **25** and **26** and substitution with either *N,N*-diethyldiaminopropane or *N,N,N′*-triethyldiaminopropane.[24]

The replacement of the 4-quinolyl amino moiety by an ether group is known to significantly reduce the basicity of the quinolyl nitrogen. Based on titration experiments previously performed in our laboratories,[24] the pK_a of the quinolyl *N* in 4-aminoquinolines is approximately 8.5 whereas 4-alkoxyquinolines have a pK_a of 4.5. In contrast to the 4-aminoquinolines **1–15**, ethers **19–24** can therefore be expected to have a free, nonprotonated quinoline ring in the acidic DV. Ethers **19** and **22** are essentially monoprotic bases under physiological conditions and thus less prone to effective bioaccumulation in the DV which explains their relatively low antiplasmodial activity (Table 2). The secondary and tertiary amines **20**, **21**, **23**, and **24** possess two basic groups in the side chain which favors migration into the acidic DV. These compounds therefore show enhanced antimalarial activity versus HB3 and Dd2. Comparison with the screening results obtained for the 4-aminoquinolines **6–15**, reveals that ethers **20**, **21**, **23**, and **24** exhibit lower antimalarial potency but improved RI's. In particular, tertiary amine **24** is a promising new antimalarial lead and more effective against Dd2 than CQ.

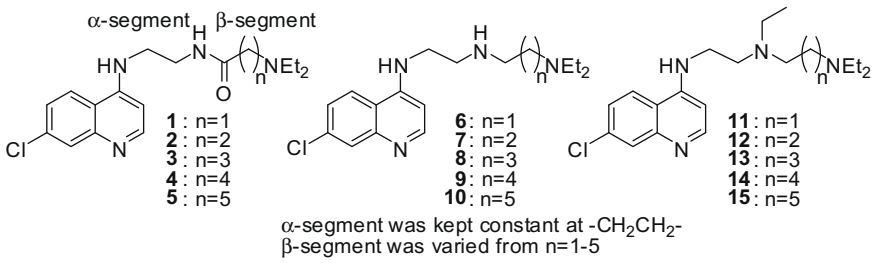
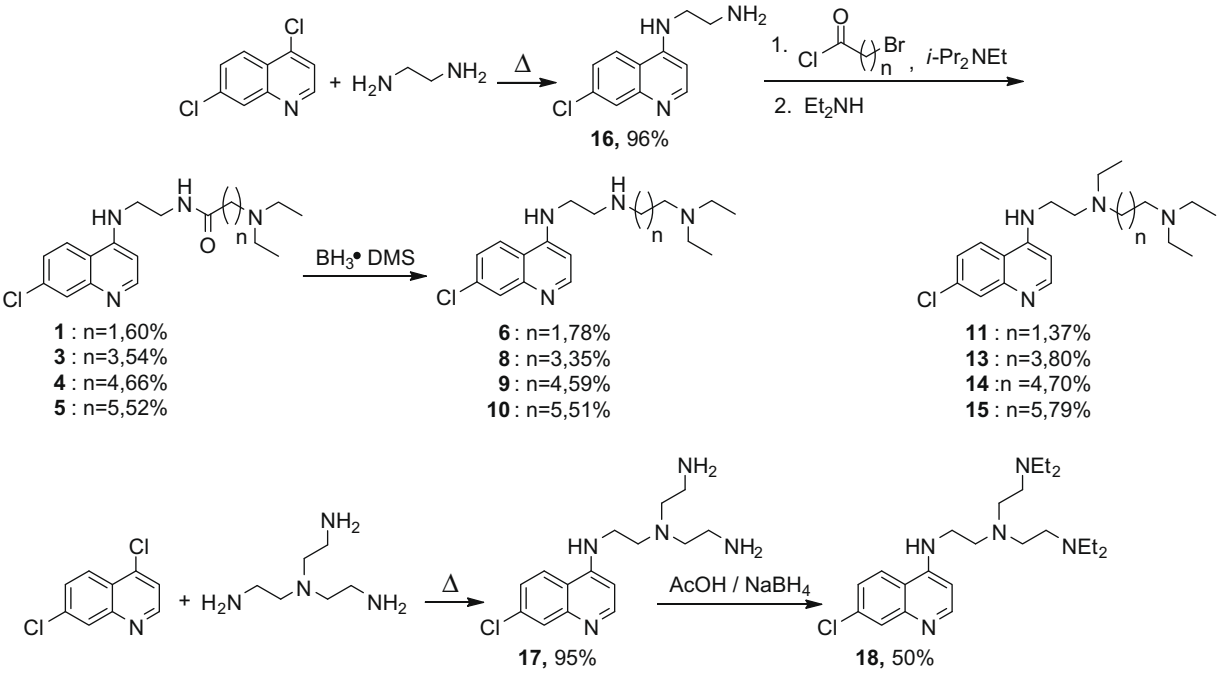


Figure 1. Structures of 4-amino-7-chloroquinolines **1–15** carrying a linear side chain.



Scheme 1. Synthesis of CQ-derived antimalarials carrying a linear side chain and of branched 4-aminoquinoline **18**.

Table 1
Antiplasmodial activities of CQ analogues **1–15**

Compound	Strain/IC_{50} (nM)		
	HB3	Dd2	RI[a]
CQ	8.4	122	14.6
1	715	3362	4.7
2	32	760	24.1
3	225	1187	5.3
4	228	1189	5.2
5	287	2704	9.4
6	10.8	1569	145
7	29.2	129	4.4
8	30.7	1274	41.5
9	28.9	459	15.9
10	68.9	231	3.4
11	5.0	53.0	10.5
12	27.3	31.2	1.1
13	5.1	36.2	7.1
14	8.9	38.7	4.3
15	5.0	19.9	4.0
18	7.0	151	21.5

IC_{50}'s are averages of two separate runs each conducted in triplicate.
[a] The resistance index (RI) is the ratio of the IC_{50} for the resistant versus the sensitive strain (Dd2/HB3).

3. Conclusion

A series of new antiplasmodial 7-chloroquinolyl-derived amines and ethers 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. The impressive activity against Dd2 combined with the low resistance indices values of **11–15** and **24** demonstrate that systematic variations of both the CQ side chain structure and basicity provide new leads that can overcome antimalarial drug resistance.

4. Experimental

4.1. Cell culture and antimalarial activity measurements

Drug activities were assessed and IC_{50} were quantified essentially as described previously.[25–27] 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

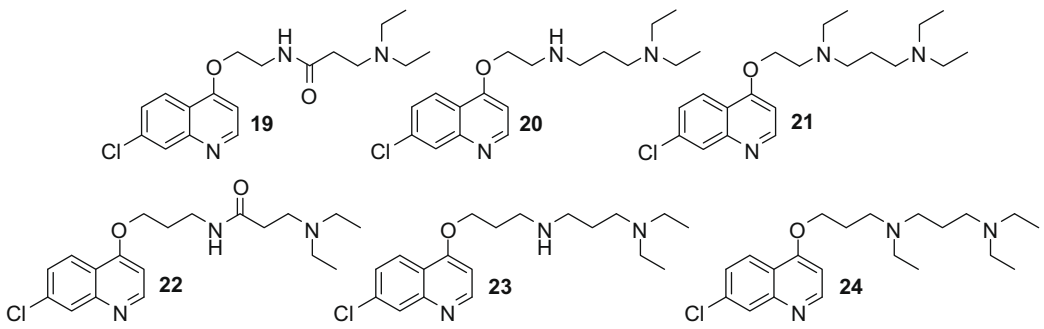
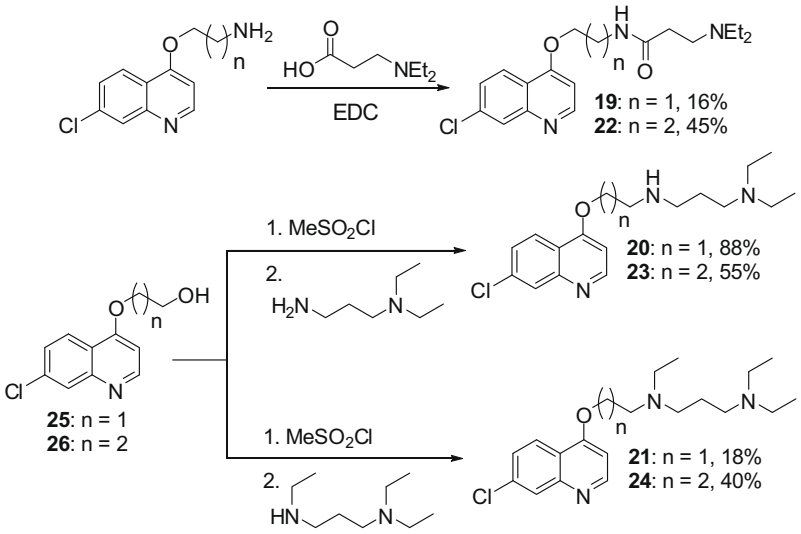


Figure 2. Structures of CQ 4*O* analogues **19–24**.



Scheme 2. Synthesis of 4-alkoxy-derived 7-chloroquinolines **19**–**24**.

Table 2
Antiplasmodial activities of CQ analogues **19**–**24**

Compound	IC_{50} (nM)		
	HB3	Dd2	RI[a]
CQ	9.8	138	14.1
19	1706	1456	0.9
20	94.6	214	2.3
21	321	409	1.3
22	2315	752	0.3
23	19.7	240	12.2
24	77.5	108	1.4

IC_{50}'s are averages of two separate runs each conducted in triplicate.
[a] The resistance index (RI) is the ratio of the IC_{50} for the resistant versus the sensitive strain (Dd2/HB3).

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 (S.D. <10% in each case). All drugs were tested against one chloroquine sensitive, and one chloroquine resistant strain of *P. falciparum* (HB3 and Dd2, respectively).

4.2. Synthesis

All reagents and solvents used 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 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) Varian FT-NMR spectrometer using $CDCl_3$ as solvent. Electrospray mass spectra (ESI-MS) were collected on a Thermo Finnigan LCQ instrument. Samples were dissolved in acetonitrile/water (1:1 v/v) containing 1% acetic acid (1 mg/mL) for MS analysis. Based on NMR spectroscopic and HPLC chromatographic analyses, all compounds were at least of 98% purity.

4.3. Representative procedure for the synthesis of compounds 1–5

A mixture of **16** (0.500 g, 2.26 mmol) and *N*,*N*-diisopropylethylamine (0.91 mL, 5.29 mmol) in anhydrous DMF was stirred vigorously at room temperature under nitrogen atmosphere. Bromoacetyl chloride (0.24 mL, 2.88 mmol) was added dropwise to the mixture and allowed to stir for 1 h. Diethylamine (2.35 mL, 22.62 mmol) was then added and the reaction was stirred at room temperature for 72 h. The mixture was concentrated in vacuo and purified by flash chromatography (1.1:1.0:0.1 hexanes/ethanol/triethylamine). Extraction of a solution in dichloromethane with aqueous $NaHCO_3$ and NaOH solution, dried over $MgSO_4$ and concentrated in vacuo to give **1** as a yellow solid (0.453 g, 1.36 mmol, 60%).

4.3.1. *N*-(7-Chloro-4-quinolyl)-*N*-(2-diethylaminoethanoyl)-1,2-diaminoethane, 1

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.98 (t, J = 7.1 Hz, 6H), 2.54 (q, J = 7.1 Hz, 4H), 3.08 (s, 2H), 3.39 (m, 2H), 3.74 (m, 2H), 6.28 (d, J = 5.4 Hz, 1H), 6.92 (br s, 1H), 7.38 (dd, J = 2.1, 8.9 Hz, 1H), 7.81 (d, J = 8.9 Hz, 1H), 7.93 (d, J = 2.1 Hz, 2H), 8.48 (d, J = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 12.3, 38.5, 46.1, 48.2, 57.4, 98.0, 117.3, 122.1, 125.4, 128.4, 134.8, 149.1, 150.1, 151.9, 175.4; MS (ESI) m/z calcd for $C_{17}H_{23}ClN_4O$ 334.2. Found $(M+H)^+$: 335.2.

4.3.2. *N*-(7-Chloro-4-quinolyl)-*N*-(4-diethylaminobutanoyl)-1,2-diaminoethane, 3

Employing 0.700 g (3.17 mmol) of **16** and 0.48 mL 4-bromobutyryl chloride (4.13 mmol) in the procedure described above gave 0.624 g (1.72 mmol, 54%) of **3** as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.00 (t, J = 7.3 Hz, 6H), 1.76–1.82 (m, 2H), 2.41 (t, J = 6.6 Hz, 2H), 2.47–2.56 (m, 6H), 3.35 (m, 2H), 3.64 (m, 2H), 6.24 (d, J = 5.4 Hz, 1H), 7.11 (br s, 1H), 7.34 (dd, J = 2.1, 8.9 Hz, 1H), 7.88 (d, J = 8.9 Hz, 1H), 7.89 (s, 1H), 8.44 (d, J = 5.4 Hz, 1H), 8.86 (t, J = 5.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 10.9, 22.4, 35.4, 38.4, 46.5, 52.7, 97.8, 117.3, 122.6, 125.1, 125.5, 127.8, 134.8, 148.8, 150.3, 151.7, 176.2; MS (ESI) m/z calcd for $C_{19}H_{27}ClN_4O$ 362.2. Found $(M+H)^+$: 363.7.

4.3.3. *N*-(7-Chloro-4-quinolyl)-*N*-(5-diethylaminopentanoyl)-1,2-diaminoethane, 4

Employing 0.700 g (3.17 mmol) of **16** and 0.55 mL 5-bromovaleryl chloride (4.11 mmol) in the procedure described above gave 0.800 g (2.12 mmol, 67%) of **4** as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.92 (t, J = 7.1 Hz, 6H), 1.38–1.46 (m, 2H), 1.61–1.69 (m, 2H), 2.29 (t, J = 7.3 Hz, 2H), 2.35 (t, J = 7.1 Hz, 2H), 2.41 (q, J = 7.1 Hz, 4H), 3.34 (m, 2H), 3.67 (m, 2H), 6.23 (d,

J = 5.4 Hz, 1H), 7.09 (br s, 1H), 7.32 (dd, J = 2.1, 8.7 Hz, 1H), 7.83 (d, J = 5.3 Hz, 2H), 7.85 (s, 1H), 8.40 (d, J = 5.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.4, 23.8, 26.4, 36.2, 38.7, 46.2, 46.6, 52.4, 98.0, 117.2, 122.1, 125.4, 128.3, 134.8, 149.0, 150.1, 151.9, 176.3; MS (ESI) m/z calcd for $C_{20}H_{29}ClN_4O$ 376.2. Found $(M+H)^+$: 377.3.

4.3.4. *N*-(7-Chloro-4-quinolyl)-*N*-(6-diethylaminohexanoyl)-1,2-diaminoethane, 5

Employing 0.700 g (3.17 mmol) of **16** and 0.62 mL 6-bromohexanoyl chloride (4.14 mmol) in the procedure described above gave 0.642 g (1.65 mmol, 52%) of **5** as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.95 (t, J = 7.1 Hz, 6H), 1.21–1.29 (m, 2H), 1.35–1.42 (m, 2H), 1.62–1.70 (m, 2H), 2.25–2.29 (m, 4H), 2.44 (q, J = 7.1 Hz, 4H), 3.34 (m, 2H), 3.68 (m, 2H), 6.23 (d, J = 5.4 Hz, 1H), 7.07 (br s, 1H), 7.32 (dd, J = 2.0, 9.0 Hz, 1H), 7.76 (t, J = 6.0 Hz, 1H), 7.82 (d, J = 2.0 Hz, 1H), 7.84 (s, 1H), 8.39 (d, J = 5.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.4, 25.5, 26.7, 27.0, 36.4, 38.7, 46.1, 46.7, 52.5, 98.0, 117.3, 122.1, 125.4, 128.3, 134.8, 149.0, 150.1, 151.8, 176.3; MS (ESI) m/z calcd for $C_{21}H_{31}ClN_4O$ 390.2. Found $(M+H)^+$: 391.3.

4.4. Representative procedure for the synthesis of compounds 6–10

A solution of **1** (0.300 g, 0.90 mmol) in 10 mL of THF was heated to reflux and borane–dimethyl sulfide complex (0.45 mL, 5.4 mmol) was added. After 2.5 h, 6 M HCl (1.45 mL, 9.0 mmol) and 2 mL of water were added and the mixture was heated to reflux for 1.5 h. The clear solution was cooled to room temperature, basified with saturated NaOH and extracted with a 1:1 mixture of CH_2Cl_2 and $CHCl_3$. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography using EtOH/hexanes/Et_3N (1:1:0.1 v/v) as the mobile phase gave **6** (0.224 g, 0.70 mmol, 78% yield) as a brown oil.

4.4.1. *N*-(7-Chloro-4-quinolyl)-*N*-(2-diethylaminoethyl)-1,2-diaminoethane, 6

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.01 (t, J = 7.1 Hz, 6H), 2.50–2.58 (m, 6H), 2.70 (t, J = 5.8 Hz, 2H), 3.02 (t, J = 5.8 Hz, 2H), 3.33 (m, 2H), 5.97 (br s, 1H), 6.38 (d, J = 5.4 Hz, 1H), 7.34 (dd, J = 2.1, 8.9 Hz, 1H), 7.73 (d, J = 8.9 Hz, 1H), 7.93 (d, J = 2.1 Hz, 1H), 8.51 (d, J = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.7, 42.0, 46.8, 47.0, 47.4, 52.5, 99.1, 117.4, 121.4, 125.1, 128.6, 134.7, 149.1, 149.9, 152.0; MS (ESI) m/z calcd for $C_{17}H_{25}ClN_4$ 320.2. Found $(M+H)^+$: 321.1.

4.4.2. *N*-(7-Chloro-4-quinolyl)-*N*-(4-diethylaminobutyl)-1,2-diaminoethane, 8

Employing 0.300 g (0.83 mmol) of **3** in the procedure described above gave 0.101 g (0.29 mmol, 35%) of **8** as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.01 (t, J = 7.2 Hz, 6H), 1.53–1.56 (m, 4H), 2.45 (m, 2H), 2.53 (q, J = 7.2 Hz, 4H), 2.68 (m, 2H), 3.03 (m, 2H), 3.34 (m, 2H), 6.10 (br s, 1H), 6.36 (d, J = 5.4 Hz, 1H), 7.34 (dd, J = 2.1, 8.9 Hz, 1H), 7.79 (d, J = 8.9 Hz, 1H), 7.92 (d, J = 2.1 Hz, 1H), 8.50 (d, J = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.4, 24.8, 28.1, 41.8, 46.7, 47.3, 49.2, 52.7, 99.0, 117.5, 121.6, 125.2, 128.6, 134.8, 149.2, 149.9, 152.0; MS (ESI) m/z calcd for $C_{19}H_{29}ClN_4$ 348.2. Found $(M+H)^+$: 349.2.

4.4.3. *N*-(7-Chloro-4-quinolyl)-*N*-(5-diethylaminopentyl)-1,2-diaminoethane, 9

Employing 0.300 g (0.80 mmol) of **4** in the procedure described above gave 0.170 g (0.47 mmol, 59%) of **9** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.07 (t, J = 7.2 Hz, 6H), 1.37 (m, 2H), 1.52–1.57 (m, 4H), 2.48 (m, 2H), 2.61 (q, J = 7.2 Hz, 4H), 2.68 (t, J = 7.0 Hz, 2H), 3.04 (m, 2H), 3.34 (m, 2H), 5.99 (br s, 1H), 6.38 (d, J = 5.4 Hz, 1H), 7.35 (dd, J = 2.1, 8.9 Hz, 1H), 7.76 (d, J = 8.9 Hz, 1H), 7.93 (d, J = 2.1 Hz, 1H), 8.51 (d, J = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.0, 25.2, 26.3, 29.8, 41.7, 46.8, 47.4, 48.9, 99.2, 121.5, 125.2, 128.7, 134.8, 149.2, 150.0, 152.1; MS (ESI) m/z calcd for $C_{20}H_{31}ClN_4$ 362.2. Found $(M+H)^+$: 363.4.

4.4.4. *N*-(7-Chloro-4-quinolyl)-*N*-(6-diethylaminohexyl)-1,2-diaminoethane, 10

Employing 0.300 g (0.77 mmol) of **5** in the procedure described above gave 0.147 g (0.39 mmol, 51%) of **10** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.01 (t, J = 7.2 Hz, 6H), 1.25–1.55 (m, 9H), 2.38 (m, 2H), 2.51 (q, J = 7.2 Hz, 4H), 2.64 (m, 2H), 3.02 (m, 2H), 3.30–3.34 (m, 2H), 5.94 (br s, 1H), 6.37 (d, J = 5.4 Hz, 1H), 7.34 (dd, J = 2.1, 8.9 Hz, 1H), 7.71 (d, J = 8.9 Hz, 1H), 7.93 (d, J = 2.1 Hz, 1H), 8.50 (d, J = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.6, 27.0, 27.3, 27.6, 30.2, 41.9, 46.9, 47.2, 49.2, 52.9, 99.2, 117.4, 121.3, 125.2, 128.8, 134.8, 149.2, 149.9, 152.1; MS (ESI) m/z calcd for $C_{21}H_{33}ClN_4$ 376.2. Found $(M+H)^+$: 377.5.

4.5. Representative procedure for the synthesis of compounds 11–15

To a solution of **6** (0.070 g, 0.22 mmol) in 5 mL of glacial acetic acid, $NaBH_4$ (0.293 g, 7.7 mmol) was added at 0 °C and the reaction temperature was increased to 60 °C. After 48 h, the reaction mixture was cooled, basified with saturated NaOH, extracted with CH_2Cl_2 and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography using CH_2Cl_2/hexanes (1:1 v/v) as the mobile phase gave **11** (0.029 g, 0.080 mmol, 37% yield) as a yellow oil.

4.5.1. *N*-(7-Chloro-4-quinolyl)-*N′*-ethyl-*N′*-(2-diethylaminoethyl)-1,2-diaminoethane, 11

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.99 (t, J = 7.1 Hz, 6H), 1.06 (t, J = 7.1 Hz, 3H), 2.53–2.64 (m, 10H), 2.83 (t, J = 5.5 Hz, 2H), 3.24 (m, 2H), 6.34 (d, J = 5.4 Hz, 1H), 6.36 (br s, 1H), 7.32 (dd, J = 2.1, 8.9 Hz, 1H), 7.77 (d, J = 8.9 Hz, 1H), 7.92 (d, J = 2.1 Hz, 1H), 8.50 (d, J = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.3, 11.9, 40.0, 47.3, 47.5, 50.6, 50.8, 99.1, 117.6, 121.8, 124.8, 134.6, 149.2, 150.0, 152.1; MS (ESI) m/z calcd for $C_{19}H_{29}ClN_4$ 348.2. Found $(M+H)^+$: 349.1.

4.5.2. *N*-(7-Chloro-4-quinolyl)-*N′*-ethyl-*N′*-(4-diethylaminobutyl)-1,2-diaminoethane, 13

Employing 0.100 g (0.29 mmol) of **8** in the procedure described above gave 0.086 g (0.23 mmol, 80%) of **13** as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.99 (t, J = 7.1 Hz, 6H), 1.07 (t, J = 7.1 Hz, 3H), 1.46–1.48 (m, 4H), 2.39 (m, 2H), 2.43–2.48 (m, 4H), 2.52 (m, 2H), 2.59 (m, 2H), 2.81 (t, J = 5.6 Hz, 2H), 3.24 (m, 2H), 6.06 (br s, 1H), 6.35 (d, J = 5.3 Hz, 1H), 7.34 (dd, J = 2.0, 8.9 Hz, 1H), 7.64 (d, J = 8.9 Hz, 1H), 7.93 (d, J = 2.0 Hz, 1H), 8.51 (d, J = 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.6, 11.9, 25.0, 25.4, 39.7, 46.8, 46.9, 51.1, 52.8, 52.9, 99.3, 117.4, 121.0, 125.2, 128.7, 134.7, 149.1, 149.8, 152.1; MS (ESI) m/z calcd for $C_{21}H_{33}ClN_4$ 376.2. Found $(M+H)^+$: 377.4.

4.5.3. *N*-(7-Chloro-4-quinolyl)-*N′*-ethyl-*N′*-(5-diethylaminopentyl)-1,2-diaminoethane, 14

Employing 0.100 g (0.28 mmol) of **9** in the procedure described above gave 0.075 g (0.19 mmol, 70%) of **14** as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.98 (t, J = 7.1 Hz, 6H), 1.07 (t, J = 7.1 Hz, 3H), 1.29 (m, 2H), 1.42–1.54 (m, 4H), 2.33 (m, 2H), 2.45–2.51 (m, 6H), 2.60 (q, J = 7.1 Hz, 4H), 2.81 (t, J = 5.6 Hz, 2H), 3.24 (m, 2H), 6.07 (br s, 1H), 6.36 (d, J = 5.2 Hz, 1H), 7.34 (dd, J = 2.1, 8.9 Hz, 1H), 7.63 (d, J = 8.9 Hz, 1H), 7.93 (d, J = 2.1 Hz, 1H), 8.51 (d,

J = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.5, 12.0, 25.5, 27.0, 27.3, 39.7, 46.8, 46.9, 51.2, 52.8, 52.9, 99.3, 117.5, 121.1, 125.2, 128.8, 134.7, 149.2, 149.8, 152.2; MS (ESI) m/z calcd for $C_{22}H_{35}ClN_4$ 390.2. Found $(M+H)^+$: 391.3.

4.5.4. *N*-(7-Chloro-4-quinolyl)-*N*′-ethyl-*N*′-(6-diethylaminohexyl)-1,2-diaminoethane, 15

Employing 0.100 g (0.27 mmol) of **10** in the procedure described above gave 0.085 g (0.21 mmol, 79%) of **15** as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.04 (t, J = 7.2 Hz, 6H), 1.07 (t, J = 7.1 Hz, 3H), 1.24–1.50 (m, 6H), 2.41 (m, 2H), 2.47–2.50 (m, 4H), 2.53–2.60 (m, 6H), 2.81 (t, J = 5.6 Hz, 2H), 3.24 (m, 2H), 6.12 (br s, 1H), 6.35 (d, J = 5.3 Hz, 1H), 7.34 (dd, J = 2.2, 8.9 Hz, 1H), 7.65 (d, J = 8.9 Hz, 1H), 7.93 (d, J = 2.2 Hz, 1H), 8.51 (d, J = 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.0, 12.0, 26.3, 27.2, 27.4, 27.5, 29.7, 39.7, 46.7, 46.8, 47.0, 51.2, 52.6, 52.7, 99.3, 117.5, 121.2, 125.2, 128.7, 134.7, 149.1, 152.2; MS (ESI) m/z calcd for $C_{23}H_{37}ClN_4$ 403.3. Found $(M+H)^+$: 404.2.

4.5.5. *N*-(7-Chloro-4-quinolyl)-tris(2-aminoethyl)amine, 17

A mixture of 4,7-dichloroquinoline (1.0 g, 5.0 mmol) and tris(2-aminoethyl)amine (8.0 mL, 53.5 mmol) was heated to 90 °C for 30 h under nitrogen atmosphere in a closed vessel with good stirring. The reaction was quenched with 20 mL of concentrated NaOH and extracted between CH_2Cl_2 and brine. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to give a yellow solid (1.47 g, 4.79 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.44 (br s, 4H), 2.61 (t, J = 6.0 Hz, 4H), 2.80–2.83 (m, 4H), 2.85 (m, 2H), 3.28–3.32 (m, 2H), 6.33 (d, J = 5.4 Hz, 1H), 6.62 (br s, 1H), 7.28 (dd, J = 2.1, 8.9 Hz, 1H), 7.89 (dd, J = 2.1 Hz, 1H), 7.93 (d, J = 8.9 Hz, 1H), 8.48 (d, J = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 39.8, 40.8, 52.0, 56.6, 99.1, 117.6, 122.0, 125.0, 128.5, 134.7, 149.2, 150.2, 152.0; MS (ESI) m/z calcd for $C_{15}H_{22}ClN_5$ 307.2. Found $(M+H)^+$: 308.2.

4.5.6. *N*-(7-Chloro-4-quinolyl)-*N*′,*N*″-tetraethyl-tris(2-aminoethyl)amine, 18

To a solution of **17** (0.462 g, 1.5 mmol) in 10 mL of glacial acetic acid, $NaBH_4$ (4.26 g, 112.7 mmol) was added at 5 °C and the reaction was stirred at room temperature for 24 h and then heated to 60 °C for 8 h. The cooled reaction mixture was basified with saturated NaOH, extracted with CH_2Cl_2 and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo to give a yellow solid (0.315 g, 0.75 mmol, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.97 (t, J = 7.2 Hz, 12H), 2.50–2.56 (m, 12H), 2.64–2.68 (m, 4H), 2.86 (m, 2H), 3.25 (m, 2H), 6.33 (d, J = 5.4 Hz, 1H), 6.51 (br s, 1H), 7.31 (dd, J = 2.1, 8.9 Hz, 1H), 7.84 (d, J = 8.9 Hz, 1H), 7.91 (d, J = 2.1 Hz, 1H), 8.49 (d, J = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.1, 40.2, 47.2, 50.7, 51.5, 52.1, 99.1, 117.6, 122.2, 124.6, 128.5, 134.6, 149.2, 150.1, 152.1; MS (ESI) m/z calcd for $C_{23}H_{38}ClN_5$ 419.2. Found $(M+H)^+$: 420.3.

4.5.7. 1-(7-Chloro-4-*O*-quinolyl)-*N*-(3-diethylaminopropanoyl)-2-aminoethane, 19

A mixture of *O-(7-chloro-4-quinolyl)-2-aminoethanol*, (0.300 g, 1.35 mmol), 3-diethylaminopropionic acid (0.270 g, 1.49 mmol), EDC (0.311 g, 1.62 mmol) and Et_3N (0.62 mL, 4.0 mmol) in 6 mL of anhydrous DMF and $CHCl_3$ (1:1 v/v) was stirred at room temperature for 20 h. The reaction was concentrated in vacuo. Flash chromatography using CH_2Cl_2/Et_3N (1:0.2 v/v) as the mobile phase gave 0.045 g (0.13 mmol, 16% yield) of white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.97 (t, J = 7.1 Hz, 6H), 2.47–2.53 (m, 6H), 2.79 (t, J = 7.1 Hz, 2H), 3.57 (m, 2H), 4.49 (t, J = 5.1 Hz, 2H), 5.68 (br s, 1H), 6.39 (d, J = 5.3 Hz, 1H), 7.36 (dd, J = 2.1, 8.9 Hz, 1H), 7.69 (d, J = 8.9 Hz, 1H), 7.94 (d, J = 2.1 Hz, 1H), 8.53 (d, J = 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.7, 32.7, 43.1, 46.8, 48.2, 62.3, 98.9, 117.2, 125.5, 128.8, 135.0, 149.1, 149.5, 152.0, 173.8; MS (ESI) m/z calcd for $C_{18}H_{24}ClN_3O_2$ 349.2. Found $(M+H)^+$: 350.1.

4.5.8. 1-(7-Chloro-4-*O*-quinolyl)-*N*-(3-diethylaminopropyl)-2-aminoethane, 20

To a solution of **25** (0.200 g, 0.90 mmol) and Et_3N (0.39 g, 2.7 mmol) in 4 mL of anhydrous THF at room temperature was added dropwise methanesulfonyl chloride (0.21 mL, 2.7 mmol). The reaction proceeded with good stirring for 15 min and was then quenched with saturated $NaHCO_3$. The mixture was extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was dissolved in anhydrous CH_3CN (3.0 mL) under inert atmosphere and Et_3N (0.62 g, 2.7 mmol) and *N,N*-diethyl diaminopropane (2.9 mL, 18.0 mmol) were added. The reaction mixture was stirred at 40 °C for 21 h and saturated $NaHCO_3$ solution was added. The mixture was extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The product was purified by flash column chromatography using CH_2Cl_2/Et_3N (1:0.2 v/v) as the mobile phase to give a light yellow oil (0.265 g, 0.79 mmol, 88% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.01 (t, J = 7.2 Hz, 6H), 1.76 (m, 2H), 2.37 (t, J = 6.0 Hz, 2H), 2.50 (q, J = 7.2 Hz, 4H), 3.30 (t, J = 5.1 Hz, 2H), 3.48 (t, J = 6.0 Hz, 2H), 3.95 (t, J = 5.1 Hz, 2H), 6.85 (d, J = 5.1 Hz, 1H), 7.36 (dd, J = 2.2, 9.0 Hz, 1H), 7.96 (d, J = 2.2 Hz, 1H), 8.33 (d, J = 9.0 Hz, 1H), 8.61 (d, J = 5.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 10.0, 22.7, 45.7, 49.5, 58.4, 60.0, 109.7, 123.0, 125.8, 125.9, 128.7, 134.8, 150.8, 151.1, 155.5; MS (ESI) m/z calcd for $C_{18}H_{26}ClN_3O$ 335.2. Found $(M+H)^+$: 336.2.

4.5.9. 1-(7-Chloro-4-*O*-quinolyl)-*N*′-ethyl-*N*′-(3-diethylaminopropyl)-2-aminoethane, 21

To a solution of **25** (0.200 g, 0.90 mmol) and Et_3N (0.39 g, 2.7 mmol) in 4 mL of anhydrous THF at room temperature was added dropwise methanesulfonyl chloride (0.21 mL, 2.7 mmol). The reaction proceeded with good stirring for 15 min and was then quenched with saturated $NaHCO_3$. The mixture was extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was dissolved in anhydrous CH_3CN (3.0 mL) under inert atmosphere and Et_3N (0.62 g, 2.7 mmol) and *N,N,N*′-triethyl diaminopropane (0.340 g, 6.75 mmol) were added. The reaction mixture was stirred at 45 °C for 36 h and saturated $NaHCO_3$ solution was added. The mixture was extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The product was purified by flash column chromatography using EtOH/hexanes/Et_3N (1:1.5:0.05 v/v) as the mobile phase to give a light yellow oil (0.035 g, 0.16 mmol, 18% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.01 (t, J = 7.1 Hz, 6H), 1.10 (t, J = 7.1 Hz, 3H), 1.68 (m, 2H), 2.46 (t, J = 7.5 Hz, 2H), 2.52 (q, J = 7.1 Hz, 4H), 2.59 (t, J = 7.5 Hz, 2H), 2.68 (q, J = 7.1 Hz, 2H), 3.02 (t, J = 6.0 Hz, 2H), 4.25 (t, J = 6.0 Hz, 2H), 6.72 (d, J = 5.2 Hz, 1H), 7.42 (dd, J = 2.0, 8.9 Hz, 1H), 8.00 (d, J = 2.0 Hz, 1H), 8.12 (d, J = 8.9 Hz, 1H), 8.72 (d, J = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.5, 12.0, 25.0, 46.8, 48.5, 50.9, 51.9, 52.6, 67.6, 101.0, 119.9, 123.5, 126.4, 127.9, 135.6, 149.7, 152.5, 161.5; MS (ESI) m/z calcd for $C_{20}H_{30}ClN_3O$ 363.2. Found $(M+H)^+$: 364.0.

4.5.10. 1-(7-Chloro-4-*O*-quinolyl)-*N*-(3-diethylaminopropanoyl)-3-aminopropane, 22

A mixture of *O-(7-chloro-4-quinolyl)-3-aminopropanol* (0.100 g, 0.45 mmol), 3-diethylaminopropionic acid (0.110 g, 0.6 mmol), EDC (0.110 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 two 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 0.100 g (0.44 mmol, 55% yield) of yellow crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.99 (t, J = 7.5 Hz, 6H), 2.20 (m, 2H), 2.40 (t, J = 6.5 Hz, 2H), 2.56 (q, J = 7.1 Hz, 4H), 2.70 (t, J = 6.1 Hz, 2H), 3.58 (q, J = 6.5 Hz, 4H), 4.24 (t, J = 6.1 Hz, 2H), 6.74 (d, J = 5.4 Hz, 1H), 7.23 .40 (dd, J = 2.1, 9.0 Hz, 1H), 8.01 (br s, 1H), 8.20 (d, J = 9.0 Hz, 1H), 8.78 (d, J = 2.1 Hz, 1H), 8.90 (d, J = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.7, 29.3, 32.7, 35.8, 46.3, 49.1, 66.4, 101.1, 120.03, 123.6, 126.8, 128.2, 136.0, 150.0, 152.7, 161.7, 173.5; MS (ESI) m/z calcd for $C_{19}H_{26}ClN_3O_2$ 363.2. Found $(M+H)^+$: 364.1.

4.5.11. 1-(7-Chloro-4-*O*-quinolyl)-*N*-(3-diethylaminopropyl)-3-aminopropane, 23

To a solution of **26** (0.1 g, 0.4 mmol) and Et_3N (0.25 g, 2.3 mmol) in 20 mL of anhydrous THF at room temperature was added dropwise methanesulfonyl chloride (0.11 g, 2.3 mmol). The reaction proceeded with good stirring for 10 min and was then quenched with saturated $NaHCO_3$. The mixture was extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was dissolved in anhydrous CH_3CN (3.0 mL) under inert atmosphere and *N,N*-diisopropylethylamine (0.5 g, 4.1 mmol) and *N,N*-diethyl diaminopropane (1.2 g, 15.2 mmol) were added. The reaction mixture was stirred at 40 °C for 48 h and saturated $NaHCO_3$ solution was added. The mixture was extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The product was purified by flash column chromatography using CH_2Cl_2/EtOH/Et_3N (5:1:0.005 v/v) as the mobile phase to give a light yellow oil (0.1 g, 0.32 mmol, 55% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.05 (t, J = 6.6 Hz, 6H), 1.61–1.78 (m, 2H), 2.18 (m, 2H), 2.42–58 (m, 6H), 2.69 (t, J = 6.0 Hz, 2H), 2.90 (t, J = 6.0 Hz, 2H), 4.29 (t, J = 6.0 Hz, 2H), 6.72 (d, J = 5.1 Hz,1H), 7.40 (dd, J = 2.1, 9.0 Hz, 1H), 8.01 (br s, 1H), 8.13 (d, J = 9.0 Hz, 1H), 8.72 (d, J = 5.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.6, 27.03, 29.3, 46.5, 46.8, 48.9, 51.3, 66.8, 100.9, 119.8, 123.4, 126.4, 127.9, 135.6, 149.7, 152.5, 161.5; MS (ESI) m/z calcd for $C_{19}H_{28}ClN_3O$ 349.2. Found $(M+H)^+$: 350.2.

4.5.12. 1-(7-Chloro-4-*O*-quinolyl)-*N*′-ethyl-*N*′-(3-diethylaminopropyl)-3-aminopropane, 24

To a solution of **26** (0.1 g, 0.4 mmol) and Et_3N (0.25 g, 2.3 mmol) in 20 mL of anhydrous THF at room temperature was added dropwise methanesulfonyl chloride (0.11 g, 2.3 mmol). The reaction proceeded with good stirring for 10 min and was then quenched with saturated $NaHCO_3$. The mixture was extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was dissolved in anhydrous CH_3CN (3.0 mL) under inert atmosphere and *N,N*-diisopropylethylamine (0.5 g, 4.1 mmol) and *N,N,N*′-triethyl diaminopropane (1.2 g, 14.3 mmol) were added. The reaction mixture was stirred at 40 °C for 48 h and was quenched with saturated $NaHCO_3$. The mixture was extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The product was purified by flash column chromatography using CH_2Cl_2/EtOH/Et_3N (5:1:0.005 v/v) as the mobile phase to give a light yellow oil (0.03 g, 0.08 mmol, 40% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.05 (t, J = 6.6 Hz, 6H), 1.60 (m, 2H), 2.00–2.18 (m, 2H), 2.40–2.60 (m, 6H), 2.64 (t, J = 6.0 Hz, 2H), 4.23 (t, J = 6.0 Hz, 2H), 6.73 (d, J = 5.1 Hz,1H), 7.44 (dd, J = 2.1, 6.0 Hz, 1H), 8.01 (s, 1H), 8.13 (d, J = 6.0 Hz, 1H), 8.72 (d, J = 5.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.6, 12.4, 27.03, 28.5, 29.3, 46.5, 46.8, 48.9, 51.3, 66.8, 100.9, 119.8, 123.4, 126.4, 127.9, 135.6, 149.7, 152.5, 161.5; MS (ESI) m/z calcd for $C_{21}H_{32}ClN_3O$ 377.2. Found $(M+H)^+$: 378.2.

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Supplementary data

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