Synthesis and in Vitro and in Vivo Antimalarial Activity of N^1-(7-Chloro-4-quinolyl)-1,4-bis(3-aminopropyl)piperazine Derivatives

Adina Ryckebusch,[†] Rébecca Deprez-Poulain,[†] Louis Maes,[‡] Marie-Ange Debreu-Fontaine,[†] Elisabeth Mouray,[§] Philippe Grellier,[§] and Christian Sergheraert*[,†]

UMR 8525 CNRS, Université de Lille II, Institut de Biologie et Institut Pasteur de Lille, 1 rue du Professeur Calmette, B.P. 447, 59021 Lille Cedex, France, and Laboratoire de Biologie Parasitaire, IFR CNRS 63, Muséum National d'Histoire Naturelle, 61 rue Buffon, 75005 Paris, France, and Tibotec, B-32800 Mechelen, Belgium

Received June 12, 2002

Three series of monoquinolines consisting of a 1,4-bis(3-aminopropyl)piperazine linker and a large variety of terminal groups were synthesized. Our aim was to prove that in related bisquinoline, it is the second quinoline moiety that is responsible for cytotoxicity and that it is not an absolute requirement for overcoming resistance to chloroquine (CQ). Eleven compounds displayed a higher selectivity index (ratio CC_{50}/IC_{50} activity) than CQ, and one of them cured mice infected by *Plasmodium berghei*.

Introduction

The spread of multidrug-resistant *Plasmodium faciparum* has highlighted the urgent need to develop new antimalarial drugs and preferably those at affordable prices for developing countries where malaria is prevalent.[1,2] Among 4-aminoquinolines, chloroquine (CQ) is believed to exert its activity by inhibiting hemozoin formation in the digestive vacuole of the parasite.[3,4] Discussion about the exclusivity of this mechanism has been recently renewed by Ginsburg and co-workers who proposed that inhibition of ferriprotoporphyrin IX degradation by glutathione-dependent redox processes could be an additional mode of action of CQ and 4-aminoquinolines in general.[5] CQ is also believed to inhibit polymerase and catalase activities of heme.[6] It was recently shown by Wellems and co-workers that chloroquine resistance results from mutations in a new vacuolar transporter, PfCRT.[7] Biochemical studies have clearly indicated that isolates of the CQ-resistant parasites accumulate less drug content than their more sensitive counterparts. However, while opinion remains divided on the mechanistic explanation for this reduction,[8−11] its reversal by molecules such as verapamil, desipramine, and chlorpromazine suggests that an enhanced CQ efflux by a multidrug-resistant protein may be involved.[8,12] A method to overcome CQ efflux consists of designing quinoline-based drugs that are not recognized by the proteins involved in the drug efflux. In this respect, bulky bisquinolines were synthesized and suggested to be extruded with difficulty by a proteinaceous transporter.[13] They were found to inhibit, with equal efficiency, the growth of both CQ-sensitive and CQ-resistant parasites, although it was not proved that steric hindrance was the crucial factor for this.[13−17] With a similar aim, we have studied several series of quinolines and acridines where aromatic rings are joined by a variety of polyamines.[18,19] Among them, the piperazine derivatives **1a**,**b** and **2** (Chart 1) displayed a similarly high antimalarial activity irrespective of the degree of resistance of *P. falciparum* strains to CQ. However, while compounds **1a** and **1b** containing respectively two and one quinoline moieties were cytotoxic at 1 μM on human MRC-5 cells (diploid embryonic lung cell line) and mouse peritoneal macrophages, their bisacridine counterpart **2** was totally devoid of cytotoxicity at 25 μM. These results led us to two issues: (i) whether the steric hindrance introduced by the second aromatic ring and/or the presence of the piperazine linker is an absolute requirement to overcome the resistance to CQ and (ii) whether the replacement of the second quinoline ring in compound **1a** could decrease the cytotoxicity generally reported in bisquinolines.[15,17]

To propose suitable answers, the synthesis and antiparasitic activity study on *Plasmodium falciparum* of three series of monoquinolines with a piperazine linker and a large variety of terminal groups have been undertaken, and the results are reported herein. Cytotoxic effects on human MRC-5 cells are also discussed.

Chemistry

Series A (compounds **4a**−**32a)**, B (**4b**−**23b**), and C (**4c**−**23c**) are derivatives of compound **3** (Scheme 1). Instead of the previously adopted method for bisacridines or bisquinolines employing DMF and K_2CO_3,[18,19] the key intermediate **3** was obtained in 1-pentanol[20] without base by condensation of 4,7-dichloroquinoline with bis(3-aminopropyl)piperazine according to an aromatic nucleophilic substitution mechanism. The excess of amine (3 equiv) led to a satisfactory yield of the N-monosubstituted derivative **3** after purification by chromatography on silica gel column. For all other compounds, thick-layer chromatography was used for purification because the scale of synthesis was about 100 mg per compound.

Compounds **4a**−**27a** and **32a** were prepared by reaction of amine **3** with various carboxylic acids in CH_2Cl_2, using a HBTU as coupling agent and DIEA as a

* To whom correspondence should be addressed. Phone: (33) 3 20 87 12 11. Fax: (33) 3 20 87 12 33. E-mail: christian.sergheraert@pasteur-lille.fr.

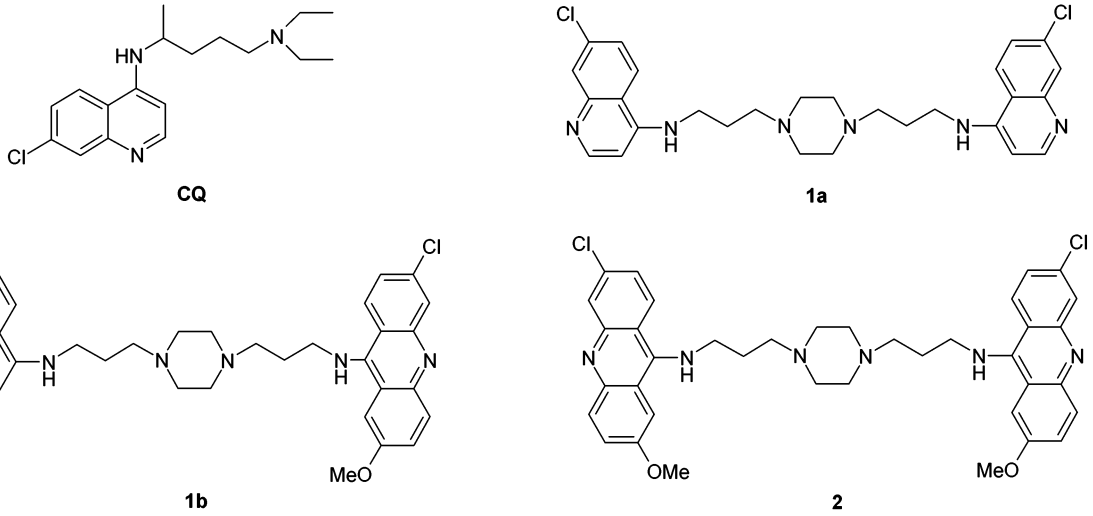
[†] Université de Lille II, Institut de Biologie et Institut Pasteur de Lille.

[‡] Tibotec.

[§] Muséum National d'Histoire Naturelle.

10.1021/jm020960r CCC: $25.00
Published on Web 01/21/2003

Chart 1. Chloroquine (CQ) and Compounds **1a**, **1b**, and **2**



base. *N*-Boc-amino protecting groups of compounds **24a**−**27a** were removed by treatment with a TFA/CH_2Cl_2 (1:1) mixture to give deprotected analogues **28**−**31**, respectively.

Compounds **4b**−**23b** were obtained by a reductive amination between compound **3** and various aldehydes, using sodium borohydride as reducing agent (Scheme 1). The replacement of sodium borohydride by sodium triacetoxyborohydride allowed us to obtain disubstituted compounds **4c**−**23c**.

Each time it was possible, the three compounds corresponding to each series (A, B, or C) and each R group were synthesized.

Biological Evaluation

The antimalarial activities of the compounds of the three series A−C were determined by their inhibition of parasite growth using the CQ-resistant strain FcB1 (IC_{50}(CQ) = 126 nM). These results are given in Tables 1 and 2. In parallel, all the compounds were tested for their cytotoxicity on MRC-5 cells (Tables 3 and 4). Some compounds were also selected for the determination of their activities as inhibitors of β-hematin formation, the commonly accepted mechanism of action of CQ (Table 5). The most interesting compounds were further evaluated in vivo in a murine *Plasmodium berghei* model via an intraperitoneal route (Table 6), and the most potent compound in vitro was tested on several strains (Table 7).

Biological Results

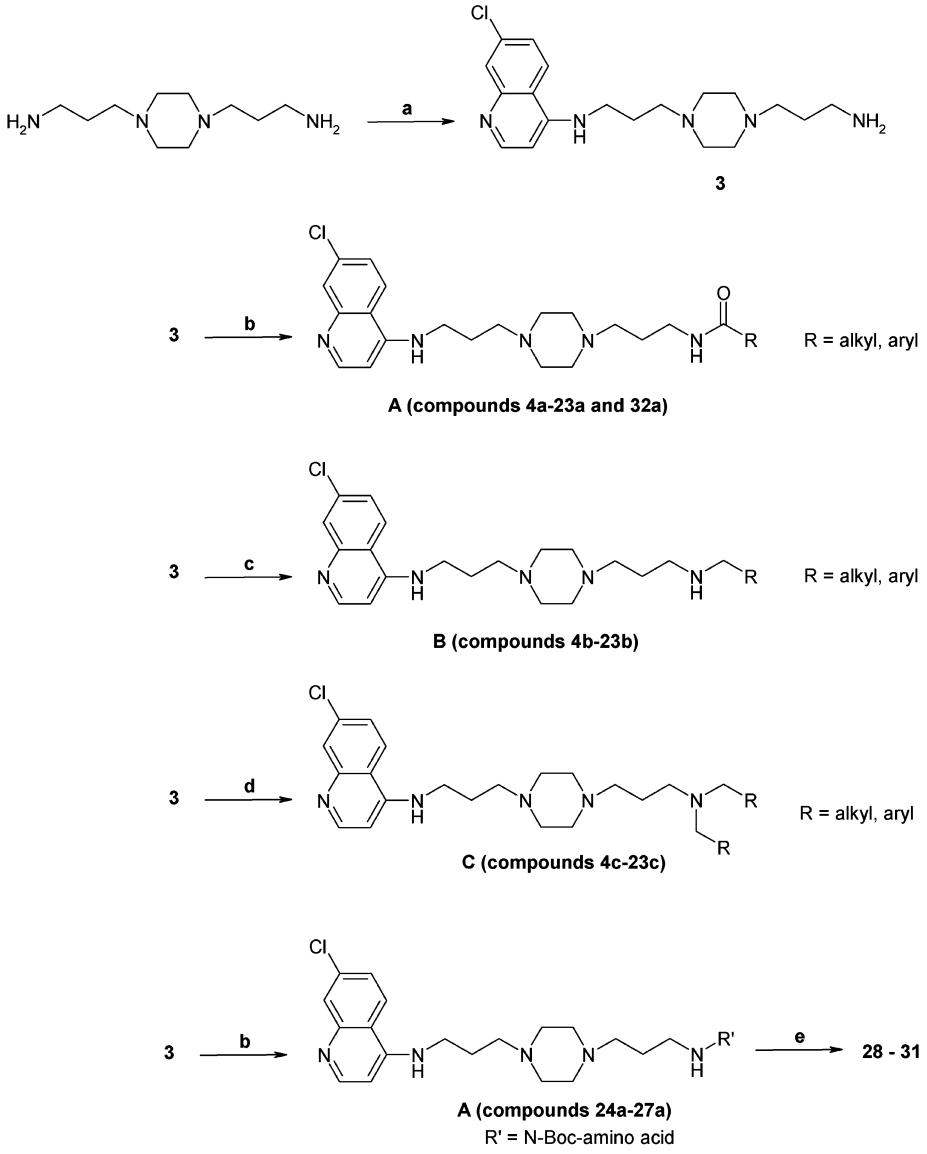
Structure−Activity Relationships on FcB1. The activity of the compounds clearly depends on the chemical link (series A−C) and the nature of the R substituent. Actually, activities vary within a large interval, from 0.9 nM (**23c**) to 416 nM (**13a**).

(1) Aryl Ring Effect in the A Series. A notable difference appears among derivatives corresponding to an aromatic or an aliphatic terminal moiety (Table 1). In the aromatic series, the most potent compound (**12a**) has an IC_{50} of 12.2 nM and all the compounds (except **13a** and **5a**) have an IC_{50} below 126 nM (CQ). As for the aliphatic series, most of them have an IC_{50} greater than 126 nM with the noteworthy exceptions of **18a** and **19a**. Elongation of the chain (**6a**, **14a**, **15a**) maintains the activity. Introducing a constraint via cyclization of the phenethyl group (**15a**) into a tetrahydronaphthyl (**32a**) or a tetrahydroquinoline (isomers **30** and **31**, Table 2) increases the activity. Interestingly, the naphthyl derivative (**5a**) is about 4 times less active than the tetrahydronaphthyl derivative (**32a**), suggesting that methylene groups may play a role in the activity. For other heterocycles (**4a**, **7a**), activity depends on the nature of the cycle. Substitution on the phenyl ring (**8a**−**13a**) is allowed. The presence of either an electron-donating or -withdrawing group is favorable for activity, as noticed in an analogue family of sulfonamides described previously,[21] with the exception of the 4-hydroxyphenyl derivative **13a**. As for the alkyl derivatives, a close correlation is observed between increasing chain length and activity (**18a**−**21a**), but branched or alicyclic derivatives are less active. Cyclohexyl compound **16a** and amino acid derivatives **28** and **29** are rather inactive compared to phenyl (**6a**) and especially tetrahydroquinoline derivatives (**30** and **31**), respectively, suggesting that an aryl ring is essential for attaining activities below 50 nM. Chemical precursors of **28**−**31** (respectively, **24a**−**27a**; see Scheme 1) were also tested. Interestingly, the presence of an amine group is not sufficient to increase the activity except for compounds displaying an aryl moiety (**30** and **31**).

(2) Isosteric Replacement of NHCOR (A Series) by $NHCH_2R$ (B Series). On the whole, secondary amines are more active than their amide counterparts (except **4a**,**b**). This may be due to the introduction of a new basic center, changing both the lipophilicity of the molecules and their ability to be protonated and therefore their subsequent accumulation in the digestive vacuole of the parasite.

(3) Secondary Amines (B Series) versus Symmetrical Tertiary Amines (C Series). Generally, the activity of the tertiary amines is very dependent on the R group, which suggests that steric hindrance and/or basicity of the amine may play a role in the activity of these series. With the exception of **10c** and **13c**, compounds possessing aromatic groups (**4c**−**15c**) proved to be less active than their monosubstituted counterparts. For aliphatic R groups (**16c**−**23c**), an elongation

Scheme 1. Synthesis of Compounds **3**, **4a**−**27a**, **28**−**31**, **32a**, **4b**−**23b**, and **4c**−**23c** (Series A, B, and C)[a]



[a] Reagents: (a) 4,7-dichloroquinoline, 1-pentanol; (b) RCOOH, HBTU, HOBT, DIEA, CH_2Cl_2; (c) RCHO, 3 Å molecular sieves, MeOH, then $NaBH_4$, MeOH; (d) RCHO, $NaHB(OAc)_3$, CH_2Cl_2; (e) CH_2Cl_2/TFA.

of the chain tends to decrease the activity of the compounds. The most potent compounds were obtained in this series (**23c**, **20c**, **21c**, **19c**, **17c**). The second substitution either increases or decreases the activities and thus appears discriminatory for the antimalarial potency of the compounds. In this respect, the study of unsymmetrical amines might be interesting.

Cytotoxic Activity. The following order of cytotoxicity was observed: series A (18 CC_{50} values above 15 μM) < series B (4 CC_{50} values above 15 μM) < series C (no CC_{50} value above 15 μM) (Tables 3 and 4). Aliphatic compounds from C series were more cytotoxic than their secondary amine and amide counterparts. From among the compounds synthesized, 11 of them (**4a**, **18a**, **17b**, **19b**−**22b**, **17c**, **19c**, and **23c**) revealed a selectivity index (ratio CC_{50}/IC_{50}) superior to that of CQ. Hence, it is encouraging to consider those compounds as potent agents for therapy on resistant strains.

In Vitro Inhibition of β-Hematin Formation. Inhibition of β-hematin formation induced by lipids of a few compounds was examined (Table 5). In general, all compounds belonging to the series (A, B, or C) except **8a** are better inhibitors of β-hematin formation than CQ. No difference is observed between groups that displayed an aryl moiety (compounds **4**, **10**, and **12**) and those that did not show such property (compounds **17** and **19**). The higher efficiencies were found with tertiary amines (**12c**, **19c**). Although most of the compounds were good inhibitors of β-hematin formation, some of them displayed poor antimalarial activity (**17a**, for example).

In Vivo Antimalarial Activities. Three amines characterized by fair in vitro antimalarial activity and a variable selectivity index toward MRC-5 cells (compounds **17c**, **20c**, and **23c**) as well as an amide with a good selectivity index (compound **31**) were then studied in a series of assays with the murine *Plasmodium berghei* model (intraperitoneal route). Both compounds **17c** and **20c** at 20 mg/kg provoked a 100% reduction of parasitemia at day 11, but a successful and complete cure was obtained only with compound **17c** (Table 6). The in vivo results also confirmed the toxicity of

Table 1. In Vitro Sensitivity of *P. falciparum* FcB1 Strain to Compounds **4a**−**23a** (Series A), **4b**−**23b** (Series B), and **4c**−**23c** (Series C)

R	series A	IC_{50}[a,b] (nM)	series B	IC_{50}[a] (nM)	series C	IC_{50}[a] (nM)
chloroquine		126 ± 26.0				
4-quinolinyl	**4a**	20.1 ± 2.3	**4b**	74.1 ± 6.1	**4c**	142.1 ± 8.5
1-naphthyl	**5a**	155.0 ± 17.0	**5b**	26.6 ± 5.1	**5c**	215.0 ± 46.4
phenyl	**6a**	80.6 ± 5.8	**6b**	16.5 ± 4.6	**6c**	54.4 ± 10.6
3-thiophenyl	**7a**	112.1 ± 36.0	**7b**	11.4 ± 0.9	**7c**	62.8 ± 8.4
3-phenoxyphenyl	**8a**	20.8 ± 5.9	**8b**	19.8 ± 1.3	**8c**	260.5 ± 16.2
4-chlorophenyl	**9a**	16.7 ± 5.2	**9b**	16.6 ± 3.7	**9c**	nd[c]
4-methoxyphenyl	**10a**	20.2 ± 1.3	**10b**	19.4 ± 0.7	**10c**	9.6 ± 1.0
4-fluorophenyl	**11a**	48.9 ± 11.5	**11b**	18.7 ± 1.2	**11c**	nd[c]
4-nitrophenyl	**12a**	12.2 ± 0.9	**12b**	5.9 ± 1.3	**12c**	46.1 ± 5.7
4-hydroxyphenyl	**13a**	416.0 ± 18.3	**13b**	55.2 ± 12.0	**13c**	45.5 ± 12.6
benzyl	**14a**	67.4 ± 8.4	**14b**	18.5 ± 0.5	**14c**	26.2 ± 5.6
phenethyl	**15a**	82.0 ± 3.1	**15b**	25.9 ± 7.8	**15c**	40.1 ± 2.6
cyclohexyl	**16a**	215.9 ± 15.9	**16b**	43.0 ± 9.8	**16c**	16.0 ± 4.3
cyclopropyl	**17a**	289.2 ± 25.8	**17b**	10.2 ± 7.6	**17c**	8.8 ± 1.7
hexyl	**18a**	34.7 ± 3.1	**18b**	9.5 ± 0.3	**18c**	37.8 ± 12.3
propyl	**19a**	73.4 ± 3.7	**19b**	24.8 ± 4.2	**19c**	7.5 ± 2.8
ethyl	**20a**	276.7 ± 8.1	**20b**	36.1 ± 1.5	**20c**	2.2 ± 1.1
methyl	**21a**	396.0 ± 116.2	**21b**	58.0 ± 13.2	**21c**	5.0 ± 0.8
tert-butyl	**22a**	163.2 ± 4.2	**22b**	9.7 ± 0.4	**22c**	*c*
isopropyl	**23a**	149.0 ± 9.3	**23b**	18.8 ± 0.8	**23c**	0.9 ± 0.1

[a] Mean ± standard deviation calculated on the basis of three experiments. [b] For bisquinoline **1a**, IC_{50} = 23.0 ± 9.0 nM. [c] nd = not determined.

Table 2. In Vitro Sensitivity of *P. falciparum* FcB1 Strain to Compounds **24a**−**27a**, **28**−**31**, and **32a** (Series A)

compd	R	IC_{50} [a] (nM)
	chloroquine	126 ± 26.0
24a	*N*-Boc-Gly	390.0 ± 73.0
25a	*N*-Boc-L-Pro	430.0 ± 57.0
26a	*N*-Boc-(*R*)-1,2,3,4-tetrahydro-3-isoquinolinyl	390.9 ± 41.8
27a	*N*-Boc-(*S*)-1,2,3,4-tetrahydro-3-isoquinolinyl	395.7 ± 95.5
28	Gly	318.0 ± 52.0
29	L-Pro	360.0 ± 68
30	(*R*)-1,2,3,4-tetrahydro-3-isoquinolinyl	19.0 ± 0.9
31	(*S*)−1,2,3,4-tetrahydro-3-isoquinolinyl	27.7 ± 4.5
32a	1,2,3,4-tetrahydronaphthyl	38.2 ± 7.5

[a] Mean ± standard deviation calculated on the basis of three experiments.

compound **20c**, observed on MRC-5 cells, as well as the modest in vitro activity of amide **31**. The appreciable activity of compound **23c** was not confirmed in vivo. In particular, the in vitro antimalarial activity of compound **17c**, when tested against several strains of *P. falciparum* (F32, FCB1, and K1), remained within the same range (Table 7) irrespective of the CQ resistance of the strain.

Discussion

Since the first article describing antimalarial activities of piperaquine and dichloroquinazine, a number of bisquinolines have been reported.[13−17] The results of studies of these molecules have suggested the same mode of action as CQ, leading to the inhibition of hemozoin formation. In contrast to CQ, they inhibit the growth of CQ-sensitive and CQ-resistant parasites with similar efficiency, indicating a possible circumvention of the CQ-resistance mechanism. Unfortunately, in a general manner, they display a cytotoxicity that rules them out as candidates for drug development. In a previous report, we described bisquinolines possessing a piperazine linker, exhibiting notable activity against both CQ-sensitive and CQ-resistant strains of *P. falciparum* but revealing cytotoxicity on diploid embryonic lung cell line.[19] The replacement of a quinoline moiety by different substituents, aromatic and aliphatic, was therefore undertaken in order to explore the influence of the terminal group on the biological properties of new compounds and their cytotoxicity. Three series of compounds were synthesized with amide (A series), secondary amine (B series), and tertiary amine (C series) terminal links and with identical substituents for each family. This enabled us to compare both the influence of the terminal moiety and the nature of the chemical link.

Chloroquine and some quinoline-based drugs (among which bisquinolines) with good antimalarial activity inhibit the crystallization of the heme to form hemozoin (and its synthetic equivalent β-hematin). They accumulate at high concentrations in the parasite's acid food vacuole, which is considered their site of action.[22−24]

It is generally admitted that a stronger basicity of the molecule increases the antimalarial activity due to a better uptake in the vacuole owing to the pH gradient between the cytosol and the acidic vacuole. By taking this into account, series B and C were designed to evaluate the influence of the introduction of a fourth basic nitrogen on the antimalarial activity, while the amide link, being devoid of inherent weak base properties and flexibility, played the role of control.

These series enabled us to consider several compounds as good antimalarial candidates and particularly compounds **17c** and **19c**−**23c**. Studies on the inhibition of β-hematin formation of some selected compounds revealed that they were better inhibitors of β-hematin formation than chloroquine. Differences in the IC_{50} values of β-hematin formation cannot explain the large differences in the in vitro antimalarial activities. Thus, to evaluate the contribution to antimalarial activity of the component accumulation in the food vacuole, lipophilicity measurements (log *D* at vacuolar and cytosolic pHs) and in silico vacuolar accumulation ratios (VAR) based on a weak-base model[25] were carried out.

Compounds of series B and C, as expected, accumulated 4−200 times more than those of series A

Table 3. In Vitro Cytotoxicity of Compounds **4a**−**23a**, **4b**−**23b**, and **4c**−**23c** on MRC-5 Cells (Selectivity Indexes Are Given in Parentheses)

R	series A	CC_{50} [a,b] (μM)	series B	CC_{50} [a] (μM)	series C	CC_{50} [a] (μM)
chloroquine		50.0 (397)				
4-quinolinyl	**4a**	16.4 (816)	**4b**	1.2 (16)	**4c**	5.6 (39)
1-naphthyl	**5a**	4.0 (26)	**5b**	5.5 (224)	**5c**	4.0 (19)
phenyl	**6a**	15.6 (194)	**6b**	5.0 (303)	**6c**	1.0 (18)
3-thiophenyl	**7a**	20.5 (183)	**7b**	1.0 (88)	**7c**	1.0 (16)
3-phenoxyphenyl	**8a**	5.0 (240)	**8b**	1.0 (51)	**8c**	4.0 (15)
4-chlorophenyl	**9a**	1.0 (60)	**9b**	1.0 (60)	**9c**	1.0 (nd[c])
4-methoxyphenyl	**10a**	4.0 (198)	**10b**	4.0 (206)	**10c**	1.0 (104)
4-fluorophenyl	**11a**	6.8 (139)	**11b**	<3.1[d] (<165)	**11c**	<3.1[d] (nd[c])
4-nitrophenyl	**12a**	3.9 (320)	**12b**	<3.1[d] (<525)	**12c**	<3.1[d] (<67)
4-hydroxyphenyl	**13a**	>25 (>60)	**13b**	21 (380)	**13c**	14.0 (308)
benzyl	**14a**	4.0 (59)	**14b**	5.0 (303)	**14c**	1.0 (38)
phenethyl	**15a**	4.0 (49)	**15b**	1.0 (39)	**15c**	1.0 (25)
cyclohexyl	**16a**	4.0 (19)	**16b**	5.5 (128)	**16c**	5.1 (319)
cyclopropyl	**17a**	16.0 (55)	**17b**	16.0 (1569)	**17c**	4.0 (455)
hexyl	**18a**	14.5 (418)	**18b**	<3.1[d] (<326)	**18c**	<3.1[d] (<82)
propyl	**19a**	16.0 (218)	**19b**	16.0 (645)	**19c**	5.1 (864)
ethyl	**20a**	32.0 (116)	**20b**	16.0 (443)	**20c**	0.1 (45)
methyl	**21a**	32.0 (81)	**21b**	32.0 (552)	**21c**	0.1 (20)
tert-butyl	**22a**	20.5 (126)	**22b**	4.1 (423)	**22c**	<3.1[d] (nd[c])
isopropyl	**23a**	17.0 (114)	**23b**	4.0 (213)	**23c**	8.5 (9444)

[a] CC_{50} is the IC_{50} value for cytotoxicity calculated on the basis of three experiments. [b] For bisquinoline **1a**, CC_{50} < 1 μM. [c] nd = not determined. [d] More than 99% cellular death at 3.1 μM.

Table 4. In Vitro Cytotoxicity of Compounds **24a**−**27a**, **28**−**31**, and **32a** (Series A) on MRC-5 Cells (Selectivity Indexes Are Given in Parentheses)

compd	R	CC_{50} [a] (μM)
	chloroquine	50.0 (397)
24a	Boc-Gly	>25.0 (64)
25a	Boc-L-Pro	>25.0 (58)
26a	Boc-(*R*)-1,2,3,4-tetrahydro-3-isoquinolinyl	4.0 (10)
27a	Boc-(*S*)-1,2,3,4-tetrahydro-3-isoquinolinyl	20.0 (51)
28	Gly	25.0 (79)
29	L-Pro	25.0 (69)
30	(*R*)-1,2,3,4-tetrahydro-3-isoquinolinyl	4.0 (211)
31	(*S*)-1,2,3,4-tetrahydro-3-isoquinolinyl	22.0 (815)
32a	1,2,3,4-tetrahydronaphthyl	5.4 (141)

[a] All CC_{50} values are the mean of three experiments.

Table 5. In Vitro Inhibition of β-Hematin Formation of a Few Compounds from Series A−C

compd	R	IC_{50} [a] (μM) β-hematin formation
chloroquine		76.5
4a	4-quinolinyl	50.6
4b	4-quinolinyl	42.5
4c	4-quinolinyl	43.4
8a	3-phenoxyphenyl	79
8b	3-phenoxyphenyl	37.5
8c	3-phenoxyphenyl	74.9
10a	4-methoxyphenyl	34.2
10b	4-methoxyphenyl	61.4
10c	4-methoxyphenyl	47.8
12a	4-nitrophenyl	35.6
12b	4-nitrophenyl	40
12c	4-nitrophenyl	15
17a	cyclopropyl	34
17b	cyclopropyl	23.3
17c	cyclopropyl	27.1
19a	propyl	40.2
19b	propyl	50.9
19c	propyl	6.7
31	(*S*)-1,2,3,4-tetrahydro-3-isoquinolinyl	23.5

[a] All IC_{50} values are the mean of two experiments.

(Table 8). This correlates with an increase of the in vitro antimalarial activity. For example, compound **17c** (VAR = 6062 × 10^3, log D_5 < −2.78, log $D_{7.4}$ = 1.16), displaying a greater accumulation than compound **17a** (VAR = 30 × 10^3, log D_5 = −0.23, log $D_{7.4}$ > 2.78) for a comparable inhibition of β-hematin formation (30 μM), is about 30 times more active. Thus, introduction of the additional amine center considerably increases ion-trapping of molecules.

Interestingly, some aromatic substituted amides (**8a** and **12a**) provide exceptions to this general trend. Indeed, while they inhibit β-hematin formation to a level similar to their series B and C counterparts and theoretically accumulate less in the food vacuole, they

Table 6. Antimalarial Activity of Compounds **17c**, **20c**, **23c,** and **31** on *P. berghei* in Mice

compd	dose (mg/kg)	reduction (%) in parasitemia at day 4	reduction (%) in parasitemia at day 11	excess MST[a] (%)
17c	20	100	100	C[b]
	5	99.99	0	0
20c	40	100	nd[c]	0[d]
	20	100	100	0
23c	40	100	0	0
	20	99.99	nd[c]	61
31	40	100	43	171
	20	99.8	nd[c]	123
	10	88	nd[c]	90

[a] Excess MST is the change in the mean survival time of the treated mice, calculated by comparing the mean survival time of the control mice with the mean survival time of the treated mice. CQ: 10 mg/kg MST = 120%. [b] C for "cured" indicates mice surviving the infection and that can be termed cured definitively. Each entry represents results with each group comprising three animals. [c] nd = not determined. [d] Mice that died on 7th day owing to toxicity.

Table 7. Efficiency of Compound **17c** To Inhibit Growth of Parasites Expressing Different Degrees of Resistance to CQ

	IC_{50} [a] (nM)		
compd	F32	FcB1	K1
CQ	21.0 ± 2.0	126.0 ± 26.0	179.2 ± 21.9
17c	19.3 ± 2.8	7.9 ± 0.9	17.4 ± 6.4

[a] Parasites were considered resistant to CQ for IC_{50} > 100 nM. Mean ± standard deviation was calculated on the basis of three experiments.

Table 8. Vacuolar Accumulation Ratios (VARs)[25] and log *D* Values for Some Selected Compounds at pH 7.4 and pH 5

compd	VAR ($\times 10^3$)	log D_5	log $D_{7.4}$	compd	VAR ($\times 10^3$)	log D_5	log $D_{7.4}$	compd	VAR ($\times 10^3$)	log D_5	log $D_{7.4}$
CQ[a]	53.6	0.51	0.93								
8a	29.5	nd[b]	nd[b]	**8b**	5624.6	nd[b]	nd[b]	**8c**	5319.5	nd[b]	nd[b]
12a	27.7	0.31	>2.78	**12b**	5571.8	nd[b]	nd[b]	**12c**	101.8	nd[b]	nd[b]
17a	29.7	−0.23	>2.78	**17b**	5746.6	nd[b]	nd[b]	**17c**	6061.7	<−2.78	1.16
19a	29.7	−0.96	1.06	**19b**	5746.8	nd[b]	nd[b]	**19c**	5979.1	−1.75	1.92
31	6749.5	−2.20	1.68								

[a] In the case of chloroquine, intraparasitical accumulation (1700-fold[25]) can be obtained by multiplying the VAR coefficient by 3.2% (the vacuolar fractional volume). [b] nd = not determined.

display almost the same antimalarial activity as their B series counterparts and are 4−10 times more active than their series C analogues. These results suggest that additional mechanisms are involved for these aromatic amides derivatives. In the corresponding series C, steric hindrance of the derivatives can argue for the much weaker antimalarial activities that were observed.

We hypothesized that compounds from series B substituted by aliphatic moieties were metabolites of their analogues from series C as discussed previously by Ridley et al.[26] in the case of diethylamines. Bis-alkyl compounds from series C (**16c**−**23c**) displayed high activities, and their presumed metabolites from series B were also active, suggesting that the latter might be capable of contributing to in vivo antimalarial activity of series C compounds. It seemed reasonable to assume that compounds **16c**−**23c** would be promising candidates for in vivo evaluation. This was further supported by encouraging in vivo results obtained for **17c**, **20c**, and **23c** (Table 6) and the fact that compound **17c** cured mice by both intraperitoneal (Table 6) and oral routes (data not shown).

In conclusion, the study of these three series of derivatives shows that (i) in bisquinolines, the second quinoline moiety can be successfully replaced by various aromatic or alkyl groups in terms of activity on CQ-resistant strains (here, FcB1) and (ii) a large number of substitutions lead to compounds of reduced cytotoxicity when compared to bisquinoline **1a**. Among compounds synthesized in this study, 11 compounds (**4a**, **18a**, **17b**, **19b**−**22b**, **17c**, **19c**, **23c**, and **31**) exhibited a selectivity index superior to that of CQ and may be considered as potent agents for therapy. Aliphatic amines in particular reveal good activities and greater selectivity indexes than CQ, leading to in vivo active compounds such as **17c**, a potential therapeutic candidate.

Experimental Section

Abbreviations. CQ, chloroquine; DIEA, diisopropylethylamine; HBTU, 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HOBT, *N*-hydroxybenzotriazole; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (thiazolyl blue); P_{HPLC}, purity determined by HPLC; TkLC, thick-layer chromatography; MALDI-MS, matrix-assisted laser desorption ionization mass spectrometry; TOF-MS, time-of-flight mass spectrometry.

Biological Evaluation. In Vitro *P. falciparum* Culture and Drug Assays. *P. falciparum* strains were maintained continuously in culture on human erythrocytes as described by Trager and Jensen.[27] In vitro antiplasmodial activity was determined using a modification of the semiautomated microdilution technique of Desjardins et al.[28] *Plasmodium falciparum* CQ-sensitive F32 (Tanzania) and CQ-resistant (FcB1/Colombia and K1/Thailand) strains were used in sensitivity testing. Stock solutions of chloroquine diphosphate and test compounds were prepared in sterile distilled water and DMSO, respectively. Drug solutions were serially diluted with culture medium and introduced to asynchronous parasite cultures (0.5% parasitemia and 1% final hematocrite) on 96-well plates for 24 h at 37°C prior to the addition of 0.5 μCi of [^{3}H]-hypoxanthine (1−5 Ci/mmol; Amersham, Les Ulis, France) per well. The growth inhibition of each drug concentration was determined by comparison of the radioactivity incorporated into the treated culture with that in the control culture (without drug) maintained on the same plate. The concentration causing 50% inhibition (IC_{50}) was obtained from the drug concentration−response curve, and the results were expressed as the mean ± standard deviations, determined from several independent experiments. The DMSO concentration never exceeded 0.1% and did not inhibit the parasite growth.

Cytotoxicity Test on MRC-5 Cells. A human diploid embryonic lung cell line (MRC-5, Bio-Whittaker 72211D) was used to assess the cytotoxic effects toward host cells. MRC-5 cells were seeded at 5000 cells per well. After 24 h, the cells were washed and 2-fold dilutions of the drug were added in 200 μL standard culture medium (RPMI + 5% FCS). The final DMSO concentration in the culture remained below 0.5%. The cultures were incubated with several concentrations of compounds (between 32 and 1.6 μM) at 37 °C in 5% CO_2/95% air for 7 days. Untreated cultures were included as controls. Cytotoxicity was determined by using colorimetric MTT assay[29] and scored as a percent reduction of absorption at 540 nm of treated cultures versus untreated control cultures.

In Vivo Drug Assays on *P. Berghei*. Antimalarial activities were determined in mice infected with *Plasmodium berghei* (ANKA 65 strain). Four-week-old female Swiss mice (CD-1, 20−25 g) were intraperitoneally infected with about 10^7 parasitized erythrocytes, collected from the blood of an acutely infected donor animal. At the same time, the animals (three animals per group) were orally treated with the test compound at 40 mg/kg (drug formulation in 100% DMSO). The treatment was continued during the 4 following days by the intraperitoneal route. Untreated control animals generally die between 7 and 10 days following infection. Drug activity was evaluated by the reduction of parasites at days 4 and 11 and by the prolongation of the mean survival time compared to that of untreated controls. Three infected DMSO-dosed mice were used as controls.

Inhibition of β-Hematin Formation.[30,31] A solution of 700 μM hemin in 25 mM NaOH (500 μL) was added to a suspension of 1 mM 1-monooleoylglycerol in 90 mM sodium acetate at pH 5 (500 μL). Drugs were added from stock solutions in DMSO (10 μL). Samples were incubated for 24 h at 37 °C. Controls contained an equal amount of DMSO. Following incubation, the samples were centrifuged at 27000*g* at 4 °C for 15 min. The precipitate of β-hematin was washed several times with 10 mM sodium phosphate, pH 7.4, containing 2.5% SDS, and was vortexed for 10 min at 20 °C before repelleting until the supernatant was colorless. Dissolution of β-hematin was achieved by addition of 900 μL of 10 mM sodium phosphate, pH 7.4, containing 2.5% SDS and 50 μL of 1 M NaOH. Concentration of heme was calculated from absorbance at 405 nm. Experiments were carried out in duplicate.

Partition Coefficients (log *D*, pH 7.4 or pH 5.0). The relative log *D*, at pH 7.4 and 5.0, of each compound in this study was assessed by the classical "shake-flask" method (adapted from Zamora et al.[32]). The compounds were parti-

tioned between 1-octanol (HPLC grade) and phosphate buffer (pH 7.4) or acetate buffer (pH 5.0). Octanol was presaturated with the buffer, and conversely the buffer was presaturated with octanol. The compounds were dissolved at a concentration of 5×10^{-5} M in an equal volume of octanol and buffer. Tubes were shaken continuously for 1 h. The phases were then separated. Each phase was injected into the high-pressure liquid chromatograph, and concentrations were evaluated in with UV (215 nm). The log *D* value was determined by dividing the concentration of drug in 1-octanol by the concentration in the aqueous phase.

Chemistry. All reactions were monitored by thin-layer chromatography carried out on 0.2 mm E. Merck silica gel plates (60F-254) using UV light as a visualizing agent. Chromatography was undertaken using silica gel 60 (230−400 mesh ASTM) from Macherey-Nagel. Thick-layer chromatography (TkLC) was performed using silica gel from Merck, from which the compounds were extracted by the following solvent system: CH_2Cl_2/MeOH/NH_4OH, 75:25:4. All melting points were determined on a Büchi melting point apparatus and were uncorrected. ^1H and ^{13}C NMR spectra were obtained using a Bruker 300 MHz spectrometer. Chemical shifts (δ) were expressed in ppm relative to TMS used as an internal standard. Mass spectra were recorded on a time-of-flight (TOF) plasma desorption spectrometer using a californium source or on a MALDI-TOF Voyager-DE-STR spectrometer. The purity of final compounds was verified by two types of high-pressure liquid chromatography (HPLC) columns: C18 nucleosil (C18N) and X Terra MSC18 (C18XT) (from Waters). Analytical HPLC was performed on a Shimadzu system equipped with a UV detector set at 254 nm. Compounds were dissolved in MeOH/water and injected through a 50 μL loop. For the C18 nucleosil column, the following eluent systems were used: A (H_2O/TFA, 100:0.05) and B (CH_3CN/H_2O/TFA, 80:20:0.05). HPLC retention times (HPLC t_R) were obtained at flow rates of 1 mL/min using the following conditions: a gradient run from 100% eluent A for 1 min, then to 100% eluent B over the next 30 min. For the X Terra MSCC18 column, the following eluent systems were used: A (H_2O/TFA, 100:0.05) and B (CH_3CN/H_2O/TFA, 80:20:0.05). HPLC retention times (HPLC t_R) were obtained at flow rates of 1.5 mL/min using the following conditions: a gradient run from 100% eluent to 100% eluent B over 10 min. 4,7-Dichloroquinoline was obtained from Acros. HBTU and HOBt were obtained from Novabiochem, and other reagents were from Acros, Aldrich, Lancaster, and Avocado.

Procedure for Hydrochloride Salts. To a solution of compound **16c** (1 equiv) in MeOH was added trimethylchlorosilane (1 equiv). After the mixture was stirred for 15 min at room temperature, the solvent was evaporated to yield the desired hydrochloride salt.

Method A: General Procedure for the Synthesis of Compounds 4a−12a, 14a−23a, 24a−27a, and 32a. To a solution of compound **3** (150 mg, 0.41 mmol, 1 equiv) in 3 mL of dry CH_2Cl_2 were added the appropriate carboxylic acid (0.62 mmol, 1.5 equiv), HBTU (314 mg, 0.82 mmol, 2 equiv), HOBt (112 mg, 0.82 mmol, 2 equiv), and *N*,*N*-diisopropylethylamine (361 μL, 2.05 mmol, 5 equiv). After the mixture was stirred at room temperature for 4 h, a total of 15 mL of CH_2Cl_2 was added. Then the mixture was washed with aqueous 1 M $NaHCO_3$ (2 × 25 mL). The organic layer was separated and dried over $MgSO_4$, the solvent was evaporated, and the residue was purified by TkLC to yield the desired product.

Method B: General Procedure for the Synthesis of Compounds 4b−12b and 14b−23b. To a solution of compound **3** (150 mg, 0.41 mmol, 1 equiv) in 3 mL of MeOH were added the appropriate aldehyde (0.45 mmol, 1.1 equiv), TEA (26 μL, 0.16 mmol, 0.4 equiv), and 3 Å molecular sieves. The reaction mixture was stirred at room temperature for 3 h and then cooled to 0 °C. $NaBH_4$ (78 mg, 2.05 mmol, 5 equiv) was added in small portions over 30 min. After the mixture was stirred at 0 °C for 1.5 h, the reaction was quenched by addition of 10 mL of 1 M NaOH. Then the mixture was filtered and the product was extracted from the filtrate into dichloromethane (3 × 20 mL). The organic layers were combined, washed with brine, and dried over $MgSO_4$. The solvent was evaporatedm and the residue was purified by TkLC to yield the desired product.

Method C: General Procedure for the Synthesis of Compounds 4c−12c and 14c−23c. To a solution of compound **3** (150 mg, 0.41 mmol, 1 equiv) in 3 mL of dry CH_2Cl_2 were added the appropriate aldehyde (1.23 mmol, 3 equiv) and $NaHB(OAc)_3$ (263 mg, 1.23 mmol, 3 equiv). After the mixture was stirred at room temperature for 4 h, a total of 5 mL of aqueous 1 M NaOH was introduced. The mixture left for 15 min, the organic layer was separated, and the aqueous layer was washed with CH_2Cl_2. Then the organic layers were mixed and dried over $MgSO_4$, the solvent was evaporated, and the residue was purified by TkLC to yield the desired product.

Method D: General Procedure for the Synthesis of Compounds 28−31. A solution of *N*-Boc-protected compound (200 mg) in 5 mL of a TFA/CH_2Cl_2, 1:1, mixture was stirred at room temperature for 1.5 h. Then the solvents were evaporated and the residue was treated with CH_2Cl_2/2.5 M NaOH. The organic layer was separated and dried over $MgSO_4$, the solvent was evaporated, and the residue was purified by TkLC to yield the desired product.

***N*^{4}-{3-[4-(3-Aminopropyl)piperazino]propyl}-7-chloroquinolin-4-amine (3).** A solution of 4,7-dichloroquinoline (5.0 g, 25.3 mmol, 1 equiv) and 1,4-bis(3-aminopropyl)piperazine (15.5 mL, 75.5 mmol, 3 equiv) in 27.5 mL of 1-pentanol was heated and held at reflux (160 °C) for 18 h. After cooling to room temperature, the mixture was diluted with 50 mL of CH_2Cl_2. The organic layer was washed with 10% NaOH (3 × 50 mL) and dried over $MgSO_4$, the solvents were evaporated, and the residue was purified by flash column chromatography (CH_2Cl_2/MeOH/NH_4OH, 80:20:1) to afford **3** as a yellow oil (7.5 g, 82% yield): $R_f = 0.4$ (acetone/NH_4OH, 9:1); HPLC (C18N) $P_{HPLC} = 100\%$, $t_R = 11.58$ min; HPLC (C18XT) $P_{HPLC} = 98\%$, $t_R = 3.14$ min; ^1H NMR ($CDCl_3$) δ 8.42 (d, $J = 5.4$ Hz, 1 H, Ar−H), 7.86 (d, $J = 2.1$ Hz, 1 H, Ar−H), 7.81 (d, $J = 8.9$ Hz, 1 H, Ar−H), 7.57−7.54 (m, 1 H, NH), 7.26 (dd, $J = 8.9$, 2.1 Hz, 1 H, Ar−H), 6.24 (d, $J = 5.4$ Hz, 1 H, Ar−H), 3.38−3.27 (m, 2 H, CH_2), 2.81−2.79 (m, 2 H, CH_2), 2.66−2.62 (m, 10H, CH_2 + piperazine), 2.53−2.49 (m, 2H, CH_2), 1.98−1.95 (m, 2H, CH_2), 1.72−1.66 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ 151.18, 127.71, 123.60, 121.48, 97.44, 57.77, 55.78, 52.58, 52.40, 43.45, 39.77, 29.51, 22.31; MALDI-MS *m*/*z* 360.5 (M^+).

***N*^{4}-[3-(4-{3-[(7-Chloro-4-quinolyl)amino]propyl}-piperazino)propyl]quinoline-4-carboxamide (4a).** Compound **4a** was prepared from quinoline-4-carboxylic acid (108 mg, 0.62 mmol, 1.5 equiv) by method A and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9) as a yellow solid (142 mg, 66% yield): $R_f = 0.45$ (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); mp 91−92 °C; HPLC (C18N) $P_{HPLC} = 100\%$, $t_R = 12.50$ min; HPLC (C18XT) $P_{HPLC} = 100\%$, $t_R = 3.55$ min; ^1H NMR ($CDCl_3$) δ 8.96 (d, $J = 4.3$ Hz, 1 H, Ar−H), 8.49−8.46 (m, 2 H, NHCO + Ar−H), 8.30 (d, $J = 8.4$ Hz, 1 H, Ar−H), 8.15 (d, $J = 8.5$ Hz, 1 H, Ar−H), 7.92 (d, $J = 2.1$ Hz, 1 H, Ar−H), 7.83 (d, $J = 8.9$ Hz, 1 H, Ar−H), 7.78−7.76 (m, 1 H, Ar−H), 7.63−7.61 (m, 1 H, Ar−H), 7.56−7.53 (m, 2 H, NH and Ar−H), 7.30 (dd, $J = 8.9$, 2.1 Hz, 1 H, Ar−H), 6.30 (d, $J = 5.5$ Hz, 1 H, Ar−H), 3.74−3.68 (m, 2 H, CH_2), 3.40−3.27 (m, 2 H, CH_2), 2.68−1.96 (m, 12 H, CH_2 and piperazine), 1.91−1.83 (m, 2 H, CH_2), 1.81−1.76 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 152.72, 150.76, 131.00, 130.77, 129.21, 128.59, 126.42, 125.73, 123.22, 119.52, 59.15, 54.11, 45.65, 41.84, 25.16, 24.12; TOF-MS *m*/*z* 517.4 (M^+).

***N*^{1}-[3-(4-{3-[(7-Chloro-4-quinolyl)amino]propyl}-piperazino)propyl]-1-naphthamide (5a).** Compound **5a** was prepared from 1-naphthoic acid (107 mg, 0.62 mmol, 1.5 equiv) by method A and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9) as a white solid (151 mg, 71% yield): $R_f = 0.55$ (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); mp 79−81 °C; HPLC (C18N) $P_{HPLC} = 100\%$, $t_R = 15.59$ min; HPLC (C18XT) $P_{HPLC} = 99\%$, $t_R = 3.78$ min; ^1H NMR (DMSO-d_6) δ 8.68−8.63 (m, 1 H, NHCO), 8.47 (d, $J = 5.6$ Hz, 1 H, Ar−H), 8.32 (d, $J = 8.8$ Hz, 1 H, Ar−H), 8.27−8.22 (m, 1 H, Ar−H), 8.04−8.01 (m, 2 H, Ar−H), 7.86 (d, $J = 2.2$ Hz, 1 H, Ar−H), 7.64−7.62 (m, 1 H, NH), 7.61−7.53 (m, 5 H, Ar−H), 6.59 (d, *J*

= 5.7 Hz, 1 H, Ar−H), 3.46−3.37 (m, 4 H, CH_2), 2.61−2.52 (m, 12 H, CH_2 and piperazine), 1.93−1.80 (m, 4 H, CH_2); ^{13}C NMR (DMSO-d_6) δ 151.71, 130.52, 129.05, 127.50, 127.38, 127.06, 126.21, 125.86, 125.23, 125.04, 99.51, 56.12, 53.09, 41.69, 38.36, 26.71, 25.45; MALDI-MS *m*/*z* 516.2 (M^+).

***N*^{1}-[3-(4-{3-[(7-Chloro-4-quinolyl)amino]propyl}-piperazino)propyl]benzamide (6a).** Compound **6a** was prepared from benzoic acid (76 mg, 0.62 mmol, 1.5 equiv) by method A and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4-OH, 80:20:1.4) as a yellow oil (173 mg, 90% yield): R_f = 0.30 (CH_2Cl_2/MeOH/NH_4OH, 8:2:0.14); HPLC (C18N) P_{HPLC} = 100%, t_R = 13.54 min; HPLC (C18XT) P_{HPLC} = 95%, t_R = 3.98 min; ^{1}H NMR ($CDCl_3$) δ 8.40 (d, J = 5.6 Hz, 1 H, Ar−H), 7.97−7.94 (m, 1 H, NHCO), 7.87 (d, J = 2.1 Hz, 1 H, Ar−H), 7.79 (d, J = 8.9 Hz, 1 H, Ar−H), 7.77−7.74 (m, 2 H, Ar−H), 7.57−7.54 (m, 1 H, NH), 7.43−7.34 (m, 3 H, Ar−H), 7.27 (dd, J = 8.9, 2.1 Hz, 1 H, Ar−H), 6.30 (d, J = 5.6 Hz, 1 H, Ar−H), 3.57−3.51 (m, 2 H, CH_2), 3.36−3.32 (m, 2 H, CH_2), 2.62−2.43 (m, 12 H, CH_2 and piperazine), 1.98−1.87 (m, 2 H, CH_2), 1.83−1.77 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 151.44, 131.33, 128.86, 128.04, 127.48, 125.46, 122.83, 98.98, 59.02, 58.81, 53.93, 53.83, 44.73, 40.99, 24.97, 23.80; MALDI-MS *m*/*z* 466.2 (M^+).

***N*^{3}-[3-(4-{3-[(7-Chloro-4-quinolyl)amino]propyl}-piperazino)propyl]thiophene-3-carboxamide (7a).** Compound **7a** was prepared from thiophene-3-carboxylic acid (80 mg, 0.62 mmol, 1.5 equiv) by method A and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9) as a brown oil (153 mg, 79% yield): R_f = 0.40 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); HPLC (C18N) P_{HPLC} = 100%, t_R = 19.38 min; HPLC (C18XT) P_{HPLC} = 98%, t_R = 3.10 min; ^{1}H NMR (DMSO-d_6) δ 8.44 (d, J = 5.5 Hz, 1 H, Ar−H), 8.36−8.33 (m, 1 H, NHCO), 8.29 (d, J = 9.1 Hz, 1 H, Ar−H), 8.13 (dd, J = 3.0, 1.3 Hz, 1 H, Ar−H), 7.83 (d, J = 2.2 Hz, 1 H, Ar−H), 7.62−7.58 (m, 2 H, Ar−H and NH), 7.52 (dd, J = 5.0, 1.3 Hz, 1 H, Ar−H), 7.50 (dd, J = 9.1, 2.2 Hz, 1 H, Ar−H), 6.10 (d, J = 5.6 Hz, 1 H, Ar−H), 3.37−3.27 (m, 4 H, CH_2), 2.55−2.43 (m, 12 H, CH_2 and piperazine), 1.88−1.83 (m, 2 H, CH_2), 1.74−1.71 (m, 2 H, CH_2); ^{13}C NMR (DMSO-d_6) δ 152.14, 129.24, 127.77, 127.60, 127.49, 125.08, 124.98, 99.49, 56.30, 56.22, 53.28, 41.76, 38.13, 27.01, 25.54; MALDI-MS *m*/*z* 472.1 (M^+).

***N*^{1}-[3-(4-{3-[(7-Chloro-4-quinolyl)amino]propyl}-piperazino)propyl]-3-phenoxybenzamide (8a).** Compound **8a** was prepared from 3-phenoxybenzoic acid (133 mg, 0.62 mmol, 1.5 equiv) by method A and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9) as a brown oil (176 mg, 76% yield): R_f = 0.55 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); HPLC (C18N) P_{HPLC} = 100%, t_R = 18.37 min; HPLC (C18XT) P_{HPLC} = 98%, t_R = 4.53 min; ^{1}H NMR (DMSO-d_6) δ 8.49−8.46 (m, 1 H, NHCO), 8.32 (d, J = 5.6 Hz, 1 H, Ar−H), 8.17 (d, J = 9.1 Hz, 1 H, Ar−H), 7.71 (d, J = 2.2 Hz, 1 H, Ar−H), 7.55−7.52 (m, 2 H, Ar−H and NH), 7.42−7.36 (m, 5 H, Ar−H), 7.11−7.06 (m, 2 H, Ar−H), 6.97−6.93 (m, 2 H, Ar−H), 6.43 (d, J = 5.6 Hz, 1 H, Ar−H), 3.27−3.16 (m, 4 H, CH_2), 2.44−2.34 (m, 12 H, CH_2 and piperazine), 1.83−1.70 (m, 2 H, CH_2), 1.66−1.57 (m, 2 H, CH_2); ^{13}C NMR (DMSO-d_6) δ 151.90, 131.02, 127.55, 125.15, 125.01, 124.62, 122.94, 122.10, 119.65, 118.08, 99.49, 56.21, 53.16, 41.72, 38.61, 26.64, 25.51; MALDI-MS *m*/*z* 558.1 (M^+).

***N*^{1}-[3-(4-{3-[(7-Chloro-4-quinolyl)amino]propyl}-piperazino)propyl]-4-chlorobenzamide (9a).** Compound **9a** was prepared from 4-chlorobenzoic acid (97 mg, 0.62 mmol, 1.5 equiv) by method A and was obtained after TkLC (CH_2-Cl_2/MeOH/NH_4OH, 90:10:1.4) as a white solid (151 mg, 73% yield): R_f = 0.50 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.14); mp 175−177 °C; HPLC (C18N) P_{HPLC} = 100%, t_R = 15.30 min; HPLC (C18XT) P_{HPLC} = 100%, t_R = 4.42 min; ^{1}H NMR ($CDCl_3$) δ 8.50 (d, J = 5.4 Hz, 1 H, Ar−H), 8.16−8.13 (m, 1 H, NHCO), 7.93 (d, J = 2.1 Hz, 1 H, Ar−H), 7.83 (d, J = 9.0 Hz, 1 H, Ar−H), 7.79−7.75 (m, 2 H, Ar−H), 7.42−7.38 (m, 3 H, NH and Ar−H), 7.31 (dd, J = 8.9, 2.1 Hz, 1 H, Ar−H), 6.34 (d, J = 5.4 Hz, 1 H, Ar−H), 3.62−3.57 (m, 2 H, CH_2), 3.42−3.37 (m, 2 H, CH_2), 2.69−2.61 (m, 12 H, CH_2 and piperazine), 2.00−1.92 (m, 2 H, CH_2), 1.89−1.80 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 152.41, 129.05, 128.94, 122.61, 117.78, 98.99, 77.87, 77.44, 77.01, 59.03, 54.06, 44.66, 41.28; MALDI-MS *m*/*z* 500.2 (M^+).

***N*^{1}-[3-(4-{3-[(7-Chloro-4-quinolyl)amino]propyl}-piperazino)propyl]-4-methoxybenzamide (10a).** Compound **10a** was prepared from 4-methoxybenzoic acid (95 mg, 0.62 mmol, 1.5 equiv) by method A and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:1.4) as a brown oil (156 mg, 76% yield): R_f = 0.35 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.14); HPLC (C18N) P_{HPLC} = 95%, t_R = 14.29 min; HPLC (C18XT) P_{HPLC} = 95%, t_R = 4.09 min; ^{1}H NMR (DMSO-d_6) δ 8.39−8.32 (m, 2 H, Ar−H and NHCO), 7.82−7.77 (m, 3 H, Ar−H), 7.44−7.41 (m, 2 H, Ar−H and NH), 6.99−6.94 (m, 2 H, Ar−H), 6.46 (d, J = 5.5 Hz, 1 H, Ar−H), 3.78 (s, 3 H, OCH_3), 3.31−3.16 (m, 4 H, CH_2), 2.41−2.30 (m, 12 H, CH_2 and piperazine), 1.84−1.77 (m, 2 H, CH_2), 1.70−1.63 (m, 2 H, CH_2); ^{13}C NMR (DMSO-d_6) δ 152.79, 129.75, 128.37, 124.86, 114.26, 99.47, 56.70, 55.16, 53.77, 41.92, 38.73, 27.17, 25.71; MALDI-MS *m*/*z* 496.3 (M^+).

***N*^{1}-[3-(4-{3-[(7-Chloro-4-quinolyl)amino]propyl}-piperazino)propyl]-4-fluorobenzamide (11a).** Compound **11a** was prepared from 4-fluorobenzoic acid (87 mg, 0.62 mmol, 1.5 equiv) by method A and was obtained after TkLC (CH_2-Cl_2/MeOH/NH_4OH, 80:20:1.8) as a yellow solid (108 mg, 54% yield): R_f = 0.35 (CH_2Cl_2/MeOH/NH_4OH, 8:2:0.14); HPLC (C18N) P_{HPLC} = 98%, t_R = 13.89 min; HPLC (C18XT) P_{HPLC} = 100%, t_R = 4.11 min; ^{1}H NMR ($CDCl_3$) δ 8.41 (d, J = 5.5 Hz, 1 H, Ar−H), 7.99−7.96 (m, 1 H, NHCO), 7.86 (d, J = 2.1 Hz, 1 H, Ar−H), 7.79−7.74 (m, 3 H, Ar−H), 7.38−7.35 (m, 1 H, NH), 7.25 (dd, J = 8.9, 2.1 Hz, 1 H, Ar−H), 7.07−7.01 (m, 2 H, Ar−H), 6.28 (d, J = 5.5 Hz, 1 H, Ar−H), 3.55−3.49 (m, 2 H, CH_2), 3.37−3.32 (m, 2 H, CH_2), 2.61−2.54 (m, 12 H, CH_2 and piperazine), 1.93−1.87 (m, 2 H, CH_2), 1.82−1.76 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 152.59, 130.20, 129.08, 125.77, 123.18, 116.20, 99.50, 59.58, 59.37, 54.53, 54.38, 45.14, 41.63, 25.39, 24.42; MALDI-MS *m*/*z* 484.1 (M^+).

***N*^{1}-[3-(4-{3-[(7-Chloro-4-quinolyl)amino]propyl}-piperazino)propyl]-4-nitrobenzamide (12a).** Compound **12a** was prepared from 4-nitrobenzoic acid (104 mg, 0.62 mmol, 1.5 equiv) by method A and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9) as a yellow oil (208 mg, 98% yield): R_f = 0.85 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.14); HPLC (C18N) P_{HPLC} = 96%, t_R = 14.41 min; HPLC (C18XT) P_{HPLC} = 99%, t_R = 4.20 min; ^{1}H NMR ($CDCl_3$) δ 8.83 (t, J = 5.5 Hz, 1 H, NHCO), 8.40 (d, J = 5.6 Hz, 1 H, Ar−H), 8.33−8.29 (m, 2 H, Ar−H), 8.25 (d, J = 9.1 Hz, 1 H, Ar−H), 8.08−8.03 (m, 2 H, Ar−H), 7.79 (d, J = 2.2 Hz, 1 H, Ar−H), 7.63−7.60 (m, 1 H, NH), 7.47 (dd, J = 9.0, 2.2 Hz, 1 H, Ar−H), 6.52 (d, J = 5.7 Hz, 1 H, Ar−H), 3.33−3.29 (m, 4 H, CH_2), 2.53−2.44 (m, 12 H, CH_2 and piperazine), 1.85−1.70 (m, 4 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 151.78, 129.50, 127.43, 125.19, 125.02, 124.37, 99.50, 56.19, 56.08, 53.14, 41.20, 38.70, 26.64, 25.47; MALDI-MS *m*/*z* 511.1 (M^+).

***N*^{1}-[3-(4-{3-[(7-Chloro-4-quinolyl)amino]propyl}-piperazino)propyl]-4-hydroxybenzamide (13a).** To a solution of compound **3** (150 mg, 0.41 mmol, 1 equiv) in 3 mL of dry CH_2Cl_2 were added 4-hydroxybenzoic acid (86 mg, 0.62 mmol, 1.5 equiv), HBTU (154 mg, 0.49 mmol, 1.2 equiv), HOBt (55 mg, 0.49 mmol, 1.2 equiv), and *N*,*N*-diisopropylethylamine (217 μL, 1.23 mmol, 3 equiv). After the mixture was stirred at room temperature for 2 h, the solvent was evaporated and the residue was purified by TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9) to yield compound **13a** as a yellow oil (64 mg, 32% yield): R_f = 0.65 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); HPLC (C18N) P_{HPLC} = 100%, t_R = 12.44 min; HPLC (C18XT) P_{HPLC} = 95%, t_R = 3.63 min; ^{1}H NMR (DMSO-d_6) δ 8.38 (d, J = 5.4 Hz, 1 H, Ar−H), 8.26−8.21 (m, 2 H, Ar−H and NHCO), 7.78 (d, J = 2.2 Hz, 1 H, Ar−H), 7.72−7.67 (m, 2 H, Ar−H), 7.46−7.42 (m, 2 H, Ar−H and NH), 6.80−6.76 (m, 2 H, Ar−H), 6.48 (d, J = 5.5 Hz, 1 H, Ar−H), 3.36−3.17 (m, 4 H, CH_2), 2.51−2.32 (m, 12 H, CH_2 and piperazine), 1.82−1.79 (m, 2 H, CH_2), 1.67−1.64 (m, 2 H, CH_2); ^{13}C NMR (DMSO-d_6) δ 160.80, 129.84, 128.30, 124.86, 115.57, 95.48, 56.70, 53.70, 41.89, 38.67, 27.14, 25.70; MALDI-MS *m*/*z* 482.1 (M^+).

***N*$^{1-}$[3-(4-{3-[(7-Chloro-4-quinolyl)amino]propyl}-piperazino)propyl]-2-phenylacetamide (14a).** Compound

14a was prepared from 2-phenylacetic acid (85 mg, 0.62 mmol, 1.5 equiv) by method A and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9) as a yellow oil (165 mg, 83% yield): R_f = 0.50 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); HPLC (C18N) P_{HPLC} = 100%, t_R = 23.05 min; HPLC (C18XT) P_{HPLC} = 99%, t_R = 3.29 min; ^{1}H NMR ($CDCl_3$) δ 8.40 (d, J = 5.5 Hz, 1 H, Ar−H), 8.23 (d, J = 9.1 Hz, 1 H, Ar−H), 8.03 (t, J = 5.4 Hz, 1 H, NHCO), 7.78 (d, J = 2.2 Hz, 1 H, Ar−H), 7.55 (t, J = 4.8 Hz, 1 H, NH), 7.46 (dd, J = 9.0, 2.2 Hz, 1 H, Ar−H), 7.31−7.17 (m, 5 H, Ar−H), 6.50 (d, J = 5.6 Hz, 1 H, Ar−H), 3.37 (s, 2 H, CH_2), 3.34−3.28 (m, 2 H, CH_2), 3.16−3.02 (m, 2 H, CH_2), 2.58−2.43 (m, 10 H, CH_2 and piperazine), 2.36−2.31 (m, 2 H, CH_2), 1.85−1.77 (m, 2 H, CH_2), 1.60−1.51 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$), δ 152.08, 129.78, 129.04, 127.72, 127.16, 125.10, 124.98, 99.50, 56.28, 55.99, 53.26, 43.34, 41.75, 37.76, 26.93, 25.54; TOF-MS m/z 480.3 (M^+).

***N*^{1}-[3-(4-{3-[(7-Chloro-4-quinolyl)amino]propyl}-piperazino)propyl]-3-phenylpropanamide (15a).** Compound **15a** was prepared from hydrocinnamic acid (93 mg, 0.62 mmol, 1.5 equiv) by method A and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9) as a yellow oil (166 mg, 82% yield): R_f = 0.50 (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9); HPLC (C18N) P_{HPLC} = 95%, t_R = 14.93 min; HPLC (C18XT) P_{HPLC} = 94%, t_R = 3.59 min; ^{1}H NMR ($CDCl_3$) δ (ppm) 8.37 (d, J = 5.6 Hz, 1 H, Ar−H), 7.94−7.87 (m, 3 H, Ar−H and NHCO), 7.31−7.15 (m, 6 H, Ar−H), 6.97−6.94 (m, 1 H, Ar−NH), 6.34−6.32 (d, J = 5.7 Hz, 1 H, Ar−H), 3.39−3.28 (m, 4 H, CH_2), 3.03−2.94 (m, 2 H, CH_2), 2.66−2.43 (m, 14 H, CH_2 and piperazine), 1.95−1.91 (m, 2 H, CH_2), 1.69−1.61 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ (ppm) 149.22, 128.29, 125.01, 125.15, 122.78, 98.15, 57.51, 58.82, 53.08, 52.65, 43.52, 38.75, 38.54, 31.75, 25.05, 23.28; MALDI-MS m/z 494.1 (M^+).

***N*^{1}-[3-(4-{3-[(7-Chloro-4-quinolyl)amino]propyl}-piperazino)propyl]cyclohexane-1-carboxamide (16a).** Compound **16a** was prepared from cyclohexane-1-carboxylic acid (80 mg, 0.62 mmol, 1.5 equiv) by method A and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9) as a yellow oil (129 mg, 73% yield): R_f = 0.75 (CH_2Cl_2/MeOH/NH_4-OH, 9:1:0.09); HPLC (C18N) P_{HPLC} = 96%, t_R = 14.29 min; HPLC (C18XT) P_{HPLC} = 95%, t_R = 4.18 min; ^{1}H NMR ($CDCl_3$) δ 8.48 (d, J = 5.5 Hz, 1 H, Ar−H), 7.93 (d, J = 2.1 Hz, 1 H, Ar−H), 7.88 (d, J = 9.0 Hz, 1 H, Ar−H), 7.73−7.70 (m, 1 H, NH), 7.41 (dd, J = 8.9, 2.1 Hz, 1 H, Ar−H), 6.86−6.84 (m, 1 H, NHCO), 6.36 (d, J = 5.6 Hz, 1 H, Ar−H), 3.41−3.34 (m, 4 H, CH_2), 2.66−2.54 (m, 12 H, CH_2 and piperazine), 1.98−1.72 (m, 15 H, CH and CH_2); ^{13}C NMR ($CDCl_3$) δ 151.41, 127.88, 124.97, 122.45, 98.58, 58.66, 57.72, 53.64, 53.39, 44.34, 39.26, 29.95, 29.73, 25.85, 25.27, 23.46, 18.56; MALDI-MS m/z 472.2 (M^+).

***N*^{1}-[3-(4-{3-[(7-Chloro-4-quinolyl)amino]propyl}-piperazino)propyl]cyclopropane-1-carboxamide (17a).** Compound **17a** was prepared from cyclopropane-1-carboxylic acid (49 μL, 0.62 mmol, 1.5 equiv) by method A and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 80:20:0.18) as a yellow oil (129 mg, 73% yield): R_f = 0.60 (CH_2Cl_2/MeOH/NH_4-OH, 80:20:1.8); HPLC (C18N) P_{HPLC} = 100%, t_R = 13.18 min; HPLC (C18XT) P_{HPLC} = 100%, t_R = 3.45 min; ^{1}H NMR ($CDCl_3$) δ 8.38 (d, J = 5.7 Hz, 1 H, Ar−H), 7.90 (d, J = 2.0 Hz, 1 H, Ar−H), 7.83 (d, J = 9.0 Hz, 1 H, Ar−H), 7.81−7.78 (m, 1 H, NH), 7.24 (dd, J = 7.2, 2.0 Hz, 1 H, Ar−H), 6.91−6.88 (m, 1 H, NHCO), 6.28 (d, J = 5.6 Hz, 1 H, Ar−H), 3.36−3.28 (m, 4 H, CH_2), 2.73−2.47 (m, 12 H, CH_2 and piperazine), 1.92−1.87 (m, 2 H, CH_2), 1.69−1.65 (m, 2 H, CH_2), 1.32−1.26 (m, 1 H, CH), 0.90−0.87 (m, 2 H, CH_2), 0.67−0.64 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 152.04, 127.13, 125.65, 123.10, 98.76, 58.62, 57.73, 53.93, 53.53, 44.53, 39.61, 25.95, 23.77, 15.27, 7.36; MALDI-MS m/z 430.3 (M^+).

***N*^{1}-[3-(4-{3-[(7-Chloro-4-quinolyl)amino]propyl}-piperazino)propyl]heptanamide (18a).** Compound **18a** was prepared from heptanoic acid (88 μL, 0.62 mmol, 1.5 equiv) by method A and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:1.4) as a yellow oil (153 mg, 78% yield): R_f = 0.30 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.14); HPLC (C18N) P_{HPLC} = 100%, t_R = 15.74 min; HPLC (C18XT) P_{HPLC} = 100%, t_R = 4.68 min; ^{1}H NMR ($CDCl_3$) δ 8.57 (d, J = 5.6 Hz, 1 H, Ar−H), 8.00 (d, J = 2.1 Hz, 1 H, Ar−H), 7.96 (d, J = 8.9 Hz, 1 H, Ar−H), 7.73−7.71 (m, 1 H, NH), 7.44 (dd, J = 8.9, 2.1 Hz, 1 H, Ar−H), 6.91−6.89 (m, 1 H, NHCO), 6.46 (d, J = 5.6 Hz, 1 H, Ar−H), 3.51−3.43 (m, 4 H, CH_2), 2.75−2.64 (m, 12 H, CH_2 and piperazine), 2.28−2.07 (m, 2 H, CH_2), 2.07−2.04 (m, 2 H, CH_2), 1.87−1.81 (m, 2 H, CH_2), 1.74−1.70 (m, 2 H, CH_2), 1.46−1.34 (m, 6 H, CH_2), 0.99−0.94 (m, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 151.45, 127.97, 125.45, 122.91, 99.98, 58.90, 57.92, 54.05, 53.69, 44.73, 39.60, 37.50, 29.46, 26.31, 25.75, 23.82, 22.94, 17.89, 14.46; MALDI-MS m/z 474.1 (M^+).

***N*^{1}-[3-(4-{3-[(7-Chloro-4-quinolyl)amino]propyl}-piperazino)propyl]butanamide (19a).** Compound **19a** was prepared from butyric acid (57 μL, 0.62 mmol, 1.5 equiv) by method A and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4-OH, 80:20:1.4) as a yellow oil (124 mg, 69% yield): R_f = 0.80 (CH_2Cl_2/MeOH/NH_4OH, 8:2:0.14); HPLC (C18N) P_{HPLC} = 100%, t_R = 12.43 min; HPLC (C18XT) P_{HPLC} = 100%, t_R = 3.51 min; ^{1}H NMR ($CDCl_3$) δ 8.40 (d, J = 5.5 Hz, 1 H, Ar−H), 7.85 (d, J = 2.1 Hz, 1 H, Ar−H), 7.79 (d, J = 8.9 Hz, 1 H, Ar−H), 7.56−7.53 (m, 1 H, NH), 7.24 (dd, J = 8.9, 2.1 Hz, 1 H, Ar−H), 6.78−6.75 (m, 1 H, NHCO), 6.28 (d, J = 5.6 Hz, 1 H, Ar−H), 3.35−3.28 (m, 4 H, CH_2), 2.59−2.47 (m, 12 H, CH_2 and piperazine), 2.08 (t, J = 7.2 Hz, 2 H, CH_2), 1.92−1.85 (m, 2 H, CH_2), 1.71−1.55 (m, 4 H, CH_2), 0.89 (t, J = 7.3 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 151.74, 128.25, 125.31, 122.88, 98.94, 58.99, 57.98, 54.10, 53.71, 44.72, 39.58, 39.38, 25.86, 23.81, 19.73, 14.26; MALDI-MS m/z 432.3 (M^+).

***N*^{1}-[3-(4-{3-[(7-Chloro-4-quinolyl)amino]propyl}-piperazino)propyl]propanamide (20a).** Compound **20a** was prepared from heptanoic acid (46 μL, 0.62 mmol, 1.5 equiv) by method A and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 80:20:1.4) as a yellow oil (165 mg, 95% yield): R_f = 0.80 (CH_2Cl_2/MeOH/NH_4OH, 8:2:0.14); HPLC (C18N) P_{HPLC} = 100%, t_R = 11.74 min; HPLC (C18XT) P_{HPLC} = 96%, t_R = 3.36 min; ^{1}H NMR ($CDCl_3$) δ 8.49 (d, J = 5.5 Hz, 1 H, Ar−H), 7.93 (d, J = 2.1 Hz, 1 H, Ar−H), 7.86 (d, J = 8.9 Hz, 1 H, Ar−H), 7.57−7.53 (m, 1 H, NH), 7.32 (dd, J = 8.9, 2.1 Hz, 1 H, Ar−H), 6.82−6.79 (m, 1 H, NHCO), 6.35 (d, J = 5.5 Hz, 1 H, Ar−H), 3.41−3.35 (m, 4 H, CH_2), 2.67−2.54 (m, 12 H, CH_2 and piperazine), 2.24−2.18 (m, 2 H, CH_2), 1.98−1.95 (m, 2 H, CH_2), 1.79−1.72 (m, 2 H, CH_2), 1.20−1.15 (t, J = 7.6 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 152.09, 128.57, 125.23, 122.80, 98.96, 59.03, 58.05, 54.11, 53.76, 44.74, 39.71, 30.36, 25.79, 23.84, 10.51; MALDI-MS m/z 418.2 (M^+).

***N*^{1}-[3-(4-{3-[(7-Chloro-4-quinolyl)amino]propyl}-piperazino)propyl]acetamide (21a).** Compound **21a** was prepared from acetic acid (36 μL, 0.62 mmol, 1.5 equiv) by method A and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4-OH, 80:20:0.9) as a yellow oil (154 mg, 92% yield): R_f = 0.65 (CH_2Cl_2/MeOH/NH_4OH, 8:2:0.09); HPLC (C18N) P_{HPLC} = 100%, t_R = 11.57 min; HPLC (C18XT) P_{HPLC} = 95%, t_R = 3.24 min; ^{1}H NMR (DMSO-d_6) δ 8.37 (d, J = 5.4 Hz, 1 H, Ar−H), 8.23 (d, J = 9.1 Hz, 1 H, Ar−H), 7.83−7.80 (m, 1 H, NH), 7.77 (d, J = 2.2 Hz, 1 H, Ar−H), 7.45−7.41 (m, 2 H, Ar−H and NHCO), 6.46 (d, J = 5.5 Hz, 1 H, Ar−H), 3.31−3.25 (m, 2 H, CH_2), 3.05−2.99 (m, 2 H, CH_2), 2.49−2.35 (m, 10 H, CH_2 and piperazine), 2.28−2.23 (t, J = 7.0 Hz, 2 H, CH_2), 1.84−1.73 (m, 5 H, CH_2 and CH_3), 1.57−1.47 (m, 2 H, CH_2); ^{13}C NMR (DMSO-d_6) δ 152.79, 128.37, 124.83, 99.47, 56.68, 56.40, 53.82, 41.92, 37.84, 27.27, 25.72, 23.50; MALDI-MS m/z 404.1 (M^+).

***N*^{1}-[3-(4-{3-[(7-Chloro-4-quinolyl)amino]propyl}-piperazino)propyl]-2,2-dimethylpropanamide (22a).** Compound **22a** was prepared from trimethylacetic acid (71 μL, 0.62 mmol, 1.5 equiv) by method A and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:1.4) as a yellow oil (183 mg, 99% yield): R_f = 0.30 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.14); HPLC (C18N) P_{HPLC} = 95%, t_R = 12.74 min; HPLC (C18XT) P_{HPLC} = 100%, t_R = 3.76 min; ^{1}H NMR ($CDCl_3$) δ 8.48 (d, J = 5.5 Hz, 1 H, Ar−H), 7.92 (d, J = 2.1 Hz, 1 H, Ar−H), 7.87 (d, J = 9.0 Hz, 1 H, Ar−H), 7.63−7.60 (m, 1 H, NH), 7.33 (dd, J = 8.9, 2.2 Hz, 1 H, Ar−H), 6.88−6.85 (m, 1 H, NHCO), 6.36 (d, J = 5.6 Hz, 1 H, Ar−H), 3.41−3.34 (m, 4 H, CH_2), 2.67−2.54 (m, 12 H, CH_2 and piperazine), 1.98−1.95 (m, 2 H, CH_2), 1.78−

1.74 (m, 2 H, CH_2), 1.21 (s, 9 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 151.35, 127.84, 124.88, 122.44, 98.52, 58.57, 58.00, 53.55, 53.43, 44.34, 39.68, 27.83, 25.07, 23.37; MALDI-MS *m*/*z* 446.1 (M^+).

***N*^{1}-[3-(4-{3-[(7-Chloro-4-quinolyl)amino]propyl}-piperazino)propyl]-2-methylpropanamide (23a).** Compound **23a** was prepared from 2-methylpropionic acid (58 μL, 0.62 mmol, 1.5 equiv) by method A and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 80:20:0.4) as a yellow oil (116 mg, 65% yield): R_f = 0.70 (CH_2Cl_2/MeOH/NH_4OH, 8:2:0.04); HPLC (C18N) P_{HPLC} = 100%, t_R = 12.11 min; HPLC (C18XT) P_{HPLC} = 100%, t_R = 3.55 min; ^1H NMR ($CDCl_3$) δ 8.47 (d, *J* = 5.5 Hz, 1 H, Ar−H), 7.91 (d, *J* = 2.1 Hz, 1 H, Ar−H), 7.86 (d, *J* = 8.9 Hz, 1 H, Ar−H), 7.59−7.56 (m, 1 H, NH), 7.31 (dd, *J* = 8.9, 2.1 Hz, 1 H, Ar−H), 6.82−6.79 (m, 1 H, NHCO), 6.34 (d, *J* = 5.6 Hz, 1 H, Ar−H), 3.40−3.34 (m, 4 H, CH_2), 2.75−2.53 (m, 12 H, CH_2 and piperazine), 2.35 (t, *J* = 6.9 Hz, 1 H, CH), 1.99−1.92 (m, 2 H, CH_2), 1.78−1.70 (m, 2 H, CH_2), 1.16 (d, *J* = 6.9 Hz, 6 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 151.90, 128.38, 125.26, 122.84, 98.94, 58.97, 58.10, 54.03, 53.79, 44.71, 39.64, 36.23, 25.75, 23.84, 20.21; MALDI-MS *m*/*z* 432.3 (M^+).

***tert*-Butyl *N*-(2-[3-(4−3-[(7-Chloro-4-quinolyl)amino]-propylpiperazino)propyl]amino-2-oxoethyl)carbamate (24a).** Compound **24a** was prepared from compound **3** (300 mg, 0.83 mmol, 1equiv) and Boc-glycine (218 mg, 1.24 mmol, 1.5 equiv) by method A and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 80:20:0.9) as a yellow oil (382 mg, 89% yield): R_f = 0.35 (CH_2Cl_2/MeOH/NH_4OH, 8.5:1.5:0.09); HPLC (C18N) P_{HPLC} = 100%, t_R = 14.54 min; HPLC (C18XT) P_{HPLC} = 100%, t_R = 3.20 min; ^1H NMR ($CDCl_3$) δ 8.49 (d, *J* = 5.5 Hz, 1 H, Ar−H), 7.94 (d, *J* = 2.1 Hz, 1 H, Ar−H), 7.87 (d, *J* = 8.9 Hz, 1 H, Ar−H), 7.60−7.57 (m, 1 H, NH), 7.32 (dd, *J* = 8.9, 2.1 Hz, 1 H, Ar−H), 5.29−5.26 (m, 1 H, NHCO), 6.32 (d, *J* = 5.6 Hz, 1 H, Ar−H), 3.78 (d, *J* = 5.5 Hz, 2 H, CH_2), 3.44−3.38 (m, 4 H, CH_2), 2.67−2.58 (m, 12 H, CH_2 and piperazine), 1.99−1.92 (m, 2 H, CH_2), 1.79−1.70 (m, 2 H, CH_2), 1.45 (s, 9 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 152.41, 128.91, 125.87, 123.40, 99.48, 59.47, 58.29, 54.60, 54.28, 45.30, 40.11, 29.32, 26.30, 24.37; MALDI-MS *m*/*z* 518.69 (M^+).

***tert*-Butyl (2*S*)-2-([3-(4-3-[(7-Chloro-4-quinolyl)amino]-propylpiperazino)propyl]aminocarbonyl)tetrahydro-1*H*-pyrrole-1-carboxylate (25a).** Compound **25a** was prepared from compound **3** (300 mg, 0.83 mmol, 1 equiv) and Boc-proline (267 mg, 1.24 mmol, 1.5 equiv) by method A and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9) as a yellow oil (456 mg, 98% yield): R_f = 0.55 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); HPLC (C18N) P_{HPLC} = 97%, t_R = 14.79 min; HPLC (C18XT) P_{HPLC} = 100%, t_R = 3.52 min; ^1H NMR ($CDCl_3$) δ 8.39 (d, *J* = 5.4 Hz, 1 H, Ar−H), 8.23 (d, *J* = 9.1 Hz, 1 H, Ar−H), 7.87−7.83 (m, 1H, Ar−H), 7.78 (d, *J* = 2.2 Hz, 1 H, Ar−H), 7.49−7.43 (m, 2 H, NHCO and Ar−H), 6.48 (d, *J* = 5.5 Hz, 1H, Ar−H), 4.00−3.97 (m, 2 H, CH_3−Pro), 3.37−3.22 (m, 4 H, CH_2), 3.11−3.04 (m, 2 H, CH_2), 2.44−2.39 (m, 12 H, piperazine and CH_2), 2.32−2.28 (m, 2 H, CH_2), 2.10−2.07 (m, 1 H, CH_2), 1.85−1.73 (m, 5 H, CH_2 and CH), 1.58−1.54 (m, 2 H, CH_2), 1.32−1.23 (m, 9 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 152.58, 134.32, 128.19, 124.90, 99.48, 60.88, 56.56, 53.59, 47.44, 41.85, 37.71, 31.95, 30.89, 28.90, 27.25, 25.67; TOF-MS *m*/*z* 574.1 (M^+).

***tert*-Butyl (3*R*)-3-([3-(4−3-[(7-Chloro-4-quinolyl)amino]-propylpiperazino)propyl]aminocarbonyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (26a).** Compound **26a** was prepared from compound **3** (300 mg, 0.83 mmol, 1 equiv) and *N*-Boc-(*R*)-1,2,3,4-tetrahydro-3-isoquinoline-2-carboxylic acid (345 mg, 0.83 mmol, 1.5 equiv) by method A and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9) as a yellow oil (473 mg, 92% yield): R_f = 0.50 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); HPLC (C18N) P_{HPLC} = 100%, t_R = 17.48 min; HPLC (C18XT) P_{HPLC} = 100%, t_R = 5.11 min; ^1H NMR ($CDCl_3$) δ 8.41 (d, *J* = 5.6 Hz, 1 H, Ar−H), 7.87−7.82 (m, 2 H, Ar−H and Ar−NH), 7.79 (d, *J* = 2.2 Hz, 1 H, Ar−H), 7.65−7.62 (m, 1 H, NHCO), 7.48 (dd, *J* = 9.0, 2.2 Hz, 1 H, Ar−H), 7.20−7.16 (m, 4 H, Ar−CH), 6.53 (d, *J* = 5.7 Hz, 1 H, Ar−H), 4.62−4.34 (m, 3 H, CH and CH_2), 3.42−3.33 (m, 2 H, CH_2), 3.17−3.00 (m, 4 H, CH and CH_2), 2.51−2.48 (m, 10 H, CH_2 and piperazine), 2.25−2.23 (m, 2 H, CH_2), 1.87−1.78 (m, 2 H, CH_2), 1.44−1.36 (m, 11 H, CH_2 and CH_3); ^{13}C NMR ($CDCl_3$) δ 151.67, 127.88, 127.33, 126.80, 125.24, 125.04, 99.51, 56.31, 56.04, 54.23, 52.99, 45.04, 37.66, 33.20, 28.90, 26.31, 25.44; MALDI-MS *m*/*z* 621.3 (M^+).

***tert*-Butyl (3*S*)-3-([3-(4-3-[(7-Chloro-4-quinolyl)amino]-propylpiperazino)propyl]aminocarbonyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (27a).** Compound **27a** was prepared from compound **3** (300 mg, 0.83 mmol, 1 equiv) and *N*-Boc-(*S*)-1,2,3,4-tetrahydro-3-isoquinoline-2-carboxylic acid (345 mg, 0.83 mmol, 1.5 equiv) by method A and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9) as a yellow oil (473 mg, 92% yield): R_f = 0.50 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); HPLC (C18N) P_{HPLC} = 100%, t_R = 17.49 min; HPLC (C18XT) P_{HPLC} = 100%, t_R = 5.08 min; ^1H NMR ($CDCl_3$) δ 8.45 (d, *J* = 5.6 Hz, 1 H, Ar−H), 7.91−7.87 (m, 2 H, Ar−H), 7.66−7.63 (m, 1 H, NH), 7.34 (dd, *J* = 8.8, 1.9 Hz, 1 H, Ar−H), 7.26−7.20 (m, 4 H, Ar−H), 6.38 (d, *J* = 5.7 Hz, 1 H, Ar−H), 4.60−4.58 (m, 3 H, CH and CH_2), 3.43−3.40 (m, 2 H, CH_2), 3.02−2.90 (m, 4 H, CH and CH_2), 2.44−2.36 (m, 10 H, CH_2 and piperazine), 2.19−2.15 (m, 2 H, CH_2), 1.76−1.71 (m, 2 H, CH_2), 1.36−1.16 (m, 11 H, CH_2 and CH_3); ^{13}C NMR ($CDCl_3$) δ 152.21, 128.06, 127.62, 126.89, 126.09, 125.23, 122.73, 98.61, 58.49, 57.47, 57.25, 53.37, 44.47, 43.16, 38.12, 32.22, 28.49, 25.86, 23.39; TOF-MS *m*/*z* 621.6 (M^+).

***N*^{1}-[3-(4-3-[(7-Chloro-4-quinolyl)amino]propylpiperazino)propyl]-2-aminoacetamide (28).** Compound **28** was prepared from compound **24a** (200 mg, 0.38 mmol) by method D and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 80:20:0.9) as a yellow oil (42 mg, 27% yield): R_f = 0.29 (CH_2Cl_2/MeOH/NH_4OH, 8.5:1.5:0.09); HPLC (C18N) P_{HPLC} = 100%, t_R = 10.52 min; HPLC (C18XT) P_{HPLC} = 95%, t_R = 3.06 min; ^1H NMR ($CDCl_3$) δ 9.80−9.78 (m, 1 H, Ar−NH), 8.76 (d, *J* = 8.8 Hz, 1 H, Ar−H), 8.66−8.64 (m, 1 H, NHCO), 8.53 (d, *J* = 7.0 Hz, 1 H, Ar−H), 8.19−8.17 (m, 2 H, NH_2), 8.09 (d, *J* = 1.92 Hz, 1 H, Ar−H), 7.71 (dd, *J* = 9.06, 1.84 Hz, 1 H, Ar−H), 6.91 (d, *J* = 7.11 Hz, 1 H, Ar−H), 3.63−3.15 (m, 16 H, piperazine and CH_2), 2.20−2.04 (m, 2 H, CH_2), 1.91−1.78 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 144.06, 128.26, 127.82, 120.58, 100.43, 55.00, 49.63, 41.95, 41.46, 37.31, 25.01, 23.54; MALDI-MS *m*/*z* 419.1 (M^+).

***N*^{2}-[3-(4−3-[(7-Chloro-4-quinolyl)amino]propylpiperazino)propyl]-(2*S*)-tetrahydro-1*H*-pyrrole-2-carboxamide (29).** Compound **29** was prepared from compound **25a** (200 mg, 0.36 mmol) by method D and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 80:20:1.8) as a yellow oil (46 mg, 28% yield): R_f = 0.55 (CH_2Cl_2/MeOH/NH_4OH, 8:2:0.18); HPLC (C18N) P_{HPLC} = 100%, t_R = 12.07 min; ^1H NMR ($CDCl_3$) δ 8.85−8.82 (m, 1 H, Ar−NH), 8.75 (d, *J* = 9.0 Hz, 1 H, Ar−H), 8.59 (d, *J* = 6.7 Hz, 1 H, Ar−H), 8.14−8.11 (m, 1 H, Ar−H), 7.78 (d, *J* = 9.0 Hz, 1 H, Ar−H), 6.96 (d, *J* = 7.1 Hz, 1 H, Ar−H), 4.24−4.44 (m, 1 H, CH), 3.67−3.11 (m, 18 H, CH_2 and piperazine), 2.32−2.23 (m, 2 H, CH_2), 2.15−2.00 (m, 2 H, CH_2), 1.90−1.81 (m, 4 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 143.87, 128.39, 127.58, 121.77, 100.31, 60.24, 54.70, 53.60, 49.39, 46.95, 41.95, 37.43, 30.85, 25.01, 23.66; MALDI-MS *m*/*z* 461.5 (M^+).

***N*^{3}-[3-(4-3-[(7-Chloro-4-quinolyl)amino]propylpiperazino)propyl]-(3*R*)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (30).** Compound **30** was prepared from compound **26a** (200 mg, 0.32 mmol) by method D and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9) as a yellow oil (87 mg, 52% yield): R_f = 0.60 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); HPLC (C18N) P_{HPLC} = 100%, t_R = 12.04 min; HPLC (C18XT) P_{HPLC} = 95%, t_R = 3.63 min; ^1H NMR ($CDCl_3$) δ 8.39 (d, *J* = 5.6 Hz, 1 H, Ar−H), 7.90 (d, *J* = 2.1 Hz, 1 H, Ar−H), 7.83 (d, *J* = 9.0 Hz, 1 H, Ar−H), 7.81−7.74 (m, 2 H, Ar−NH and NHCO), 7.25 (dd, *J* = 8.9, 2.1 Hz, 1 H, Ar−H), 7.11−7.07 (m, 3 H, Ar−H), 6.99−6.96 (m, 1 H, Ar−H), 6.27 (d, *J* = 5.7 Hz, 1 H, Ar−H), 3.95 (s wide, 2 H, CH_2), 3.47 (dd, *J* = 10.7, 5.0 Hz, 1 H, CH), 3.38−3.30 (m, 4 H, CH_2), 3.17 (dd, *J* = 16.5, 5.0 Hz, 1 H, CH_2), 2.81−2.44 (m, 13 H, CH_2 and piperazine), 1.93−1.85 (m, 2 H, CH_2), 1.74−1.65 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 151.18, 129.70, 127.82, 127.02, 125.46, 123.03, 98.80, 58.96,

57.58, 57.20, 53.83, 53.68, 48.22, 44.74, 38.89, 31.71, 26.38, 23.79; MALDI-MS *m/z* 521.1 (M^+).

***N*³-[3-(4−3-[(7-Chloro-4-quinolyl)amino]propylpiperazino)propyl]-(3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (31).** Compound **31** was prepared from compound **27a** (200 mg, 0.32 mmol) by method D and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9) as a yellow oil (92 mg, 55% yield): R_f = 0.60 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); HPLC (C18N) P_{HPLC} = 100%, t_R = 12.10 min; HPLC (C18XT) P_{HPLC} = 100%, t_R = 3.65 min; ^{1}H NMR ($CDCl_3$) δ 8.48 (d, J = 5.4 Hz, 1 H, Ar−H), 7.93 (d, J = 2.1 Hz, 1 H, Ar−H), 7.92−7.89 (m, 1 H, Ar−NH), 7.86 (d, J = 8.9 Hz, 1 H, Ar−H), 7.68−7.65 (m, 1 H, NHCO), 7.30 (dd, J_1 = 8.9, 2.1 Hz, 1 H, Ar−H), 7.18−7.14 (m, 2 H, Ar−H), 7.06−7.03 (m, 2 H, Ar−H), 6.31 (d, J = 5.5 Hz, 1 H, Ar−H), 4.02 (s wide, 2 H, CH_2), 3.53 (dd, J = 10.5, 5.0 Hz, 1 H, CH), 3.46−3.34 (m, 4 H, CH_2), 3.24 (dd, J = 16.5, 4.9 Hz, 1 H, CH_2), 2.82 (dd, J = 16.4, 10.8 Hz, 1 H, CH_2), 2.66−2.51 (m, 12 H, piperazine and CH_2), 1.97−1.92 (m, 2 H, CH_2), 1.81−1.72 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 151.64, 129.21, 128.11, 126.49, 126.10, 125.51, 124.64, 122.44, 99.89, 58.62, 57.21, 56.71, 53.40, 53.30, 47.76, 44.29, 38.42, 31.22, 25.86, 23.26; MALDI-MS *m/z* 521.1 (M^+).

***N*²-[3-(4−3-[(7-Chloro-4-quinolyl)amino]propylpiperazino)propyl]-1,2,3,4-tetrahydronaphthalene-2-carboxamide (32a).** Compound **32a** was prepared from 1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (109 mg, 0.62 mmol, 1.5 equiv) by method A and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9) as a yellow oil (191 mg, 89% yield): R_f = 0.50 (CH_2Cl_2/MeOH/NH_4OH, 8:2:0.04); HPLC (C18N) P_{HPLC} = 100%, t_R = 17.76 min; HPLC (C18XT) P_{HPLC} = 100%, t_R = 4.61 min; ^{1}H NMR (DMSO-d_6) δ 8.51 (d, J = 5.5 Hz, 1 H, Ar−H), 8.36 (d, J = 9.1 Hz, 1 H, Ar−H), 8.06−8.02 (m, 1 H, NHCO), 7.90 (d, J = 2.2 Hz, 1 H, Ar−H), 7.67−7.64 (m, 1 H, Ar−NH), 7.57 (dd, J = 8.9, 2.1 Hz, 1 H, Ar−H), 7.19−7.14 (m, 4 H, Ar−H), 6.61 (d, J = 5.6 Hz, 1 H, Ar−H), 3.46−3.40 (m, 2 H, CH_2), 3.25−3.18 (m, 2 H, CH_2), 2.94−2.83 (m, 4 H, CH_2), 2.62−2.46 (m, 13 H, CH_2 and piperazine and CH), 2.07−2.03 (m, 1 H, CH_2), 1.97−1.89 (m, 2 H, CH_2), 1.83−1.73 (m, 2 H, CH_2), 1.70−1.65 (m, 2 H, CH_2); ^{13}C NMR (DMSO-d_6) δ 152.25, 129.69, 129.44, 127.88, 125.03, 124.95, 99.49, 56.39, 53.38, 41.79, 37.71, 32.69, 29.08, 27.22, 27.02, 25.57; MALDI-MS *m/z* 520.1 (M^+).

***N*⁴-[3-(4-{3-[(4-Quinolylmethyl)amino]propyl}piperazino)propyl]-7-chloroquinolin-4-amine (4b).** Compound **4b** was prepared from 4-quinolinecarboxaldehyde (107 mg, 0.46 mmol, 1.1 equiv) by method B and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:1.4) as a yellow solid (119 mg, 57% yield): R_f = 0.75 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.14); mp 89−91 °C; HPLC (C18N) P_{HPLC} = 100%, t_R = 11.99 min; HPLC (C18XT) P_{HPLC} = 95%, t_R = 3.48 min; ^{1}H NMR ($CDCl_3$) δ 8.89 (d, J = 4.4 Hz, 1 H, Ar−H), 8.50 (d, J = 5.4 Hz, 1 H, Ar−H), 8.16 (dd, J = 8.4, 0.8 Hz, 1 H, Ar−H), 8.10 (dd, J = 8.1, 0.9 Hz, 1 H, Ar−H), 7.92 (d, J = 2.2 Hz, 1 H, Ar−H), 7.88 (d, J = 8.9 Hz, 1 H, Ar−H), 7.75−7.70 (m, 1 H, Ar−H), 7.61−7.58 (m, 2 H, NH and Ar−H), 7.48 (d, J = 4.4 Hz, 1 H, Ar−H), 7.31 (dd, J = 8.9, 2.1 Hz, 1 H, Ar−H), 6.31 (d, J = 5.4 Hz, 1 H, Ar−H), 3.38−3.35 (m, 2 H, CH_2), 2.89−2.84 (m, 2 H, CH_2), 2.62−2.53 (m, 12 H, CH_2 and piperazine), 1.97−1.78 (m, 4 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 151.90, 150.30, 130.26, 129.17, 128.36, 127.04, 124.05, 123.25, 122.50, 119.85, 98.46, 58.70, 57.28, 53.52, 53.36, 50.21, 48.79, 44.45, 26.86, 23.32; TOF-MS *m/z* 503.5 (M^+).

***N*⁴-[3-(4-{3-[(1-Naphthylmethyl)amino]propyl}piperazino)propyl]-7-chloroquinolin-4-amine (5b).** Compound **5b** was prepared from 1-naphthaldehyde (93 μL, 0.46 mmol, 1.1 equiv) by method B and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:1.4) as a yellow oil (127 mg, 61% yield): R_f = 0.45 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); HPLC (C18N) P_{HPLC} = 95%, t_R = 16.54 min; HPLC (C18XT) P_{HPLC} = 96%, t_R = 3.59 min; ^{1}H NMR ($CDCl_3$) δ 8.49 (d, J = 5.4 Hz, 1 H, Ar−H), 8.13 (d, J = 8.8 Hz, 1 H, Ar−H), 7.93 (d, J = 2.1 Hz, 1 H, Ar−H), 7.88−7.84 (m, 2 H, Ar−H), 7.79−7.77 (m, 1 H, Ar−H), 7.57−7.41 (m, 5 H, NH and Ar−H), 7.30 (dd, J = 8.9, 2.2 Hz, 1 H, Ar−H), 6.30 (d, J = 5.4 Hz, 1 H, Ar−H), 4.38 (s, 2 H, CH_2), 3.38−3.28 (m, 2 H, CH_2), 2.89−2.85 (m, 2 H, CH_2), 2.59−2.49 (m, 12 H, CH_2 and piperazine), 1.95−1.87 (m, 2 H, CH_2), 1.88−1.76 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 152.21, 128.85, 128.63, 127.90, 126.24, 126.21, 125.70, 125.47, 124.69, 123.60, 122.50, 98.51, 58.78, 57.42, 53.47, 51.58, 48.76, 44.52, 26.78, 23.37; TOF-MS *m/z* 501.9 (M^+).

***N*⁴-(3-{4-[3-(Benzylamino)propyl]piperazino}propyl)-7-chloroquinolin-4-amine (6b).** Compound **6b** was prepared from benzaldehyde (69 μL, 0.46 mmol, 1.1 equiv) by method B and was obtained after TkLC (acetone/NH_4OH, 90:10) as a yellow oil (103 mg, 55% yield): R_f = 0.30 (acetone/NH_4OH, 9.5:0.5); HPLC (C18N) P_{HPLC} = 95%, t_R = 11.81 min; HPLC (C18XT) P_{HPLC} = 95%, t_R = 3.62 min; ^{1}H NMR ($CDCl_3$) δ 8.49 (d, J = 5.4 Hz, 1 H, Ar−H), 7.93 (d, J = 2.1 Hz, 1 H, Ar−H), 7.86 (d, J = 8.9 Hz, 1 H, Ar−H), 7.61−7.53 (m, 1 H, NH), 7.35−7.24 (m, 6 H, Ar−H), 6.30 (d, J = 5.4 Hz, 1 H, Ar−H), 3.82 (s, 2 H, CH_2), 3.38−3.32 (m, 2 H, CH_2), 2.77−2.72 (m, 2 H, CH_2), 2.63−2.37 (m, 12 H, CH_2 and piperazine), 1.96−1.89 (m, 2 H, CH_2), 1.82−1.72 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 152.06, 128.47, 128.28, 127.97, 126.82, 124.47, 117.35, 98.33, 58.64, 57.16, 53.86, 53.45, 53.25, 47.95, 44.32, 26.79, 23.21; TOF-MS *m/z* 452.7 (M^+).

***N*⁴-[3-(4-{3-[(3-Thienylmethyl)amino]propyl}piperazino)propyl]-7-chloroquinolin-4-amine (7b).** Compound **7b** was prepared from 3-thiophenecarboxaldehyde (60 μL, 0.46 mmol, 1.1 equiv) by method B and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 80:20:1.4) as a yellow oil (82 mg, 43% yield): R_f = 0.75 (CH_2Cl_2/MeOH/NH_4OH, 8:2:0.14); HPLC (C18N) P_{HPLC} = 95%, t_R = 12.04 min; HPLC (C18XT) P_{HPLC} = 98%, t_R = 3.52 min; ^{1}H NMR (DMSO-d_6) δ 8.38 (d, J = 5.4 Hz, 1 H, Ar−H), 8.21 (d, J = 9.1 Hz, 1 H, Ar−H), 7.77 (d, J = 2.2 Hz, 1 H, Ar−H), 7.44−7.41 (m, 2 H, Ar−H and NH), 7.36−7.33 (m, 1 H, Ar−H), 6.95−6.92 (m, 2 H, Ar−H), 6.46 (d, J = 5.5 Hz, 1 H, Ar−H), 3.86 (s, 2 H, CH_2), 3.29−3.25 (m, 2 H, CH_2), 2.56−2.27 (m, 14 H, CH_2 and piperazine), 1.83−1.74 (m, 2 H, CH_2), 1.60−1.51 (m, 2 H, CH_2); ^{13}C NMR (DMSO-d_6) δ 152.79, 128.38, 127.37, 125.27, 124.84, 99.47, 57.07, 56.68, 53.77, 48.55, 47.84, 41.92, 27.24, 25.72; MALDI-MS *m/z* 458.2 (M^+).

***N*⁴-[3-(4-{3-[(3-Phenoxybenzyl)amino]propyl}piperazino)propyl]-7-chloroquinolin-4-amine (8b).** Compound **8b** was prepared from 3-phenoxybenzaldehyde (118 μL, 0.46 mmol, 1.1 equiv) by method B and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:1.4) as a yellow oil (129 mg, 57% yield): R_f = 0.40 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); HPLC (C18N) P_{HPLC} = 100%, t_R = 16.45 min; HPLC (C18XT) P_{HPLC} = 95%, t_R = 4.94 min; ^{1}H NMR ($CDCl_3$) δ 8.42 (d, J = 5.4 Hz, 1 H, Ar−H), 7.87 (d, J = 2.1 Hz, 1 H, Ar−H), 7.78 (d, J = 8.9 Hz, 1 H, Ar−H), 7.48−7.45 (m, 1 H, NH), 7.29−7.19 (m, 4 H, Ar−H), 7.05−7.00 (m, 2 H, Ar−H), 6.96−6.92 (m, 3 H, Ar−H), 6.85−6.82 (m, 1 H, Ar−H), 6.25 (d, J = 5.5 Hz, 1 H, Ar−H), 3.76 (s, 2 H, CH_2), 3.33−3.28 (m, 2 H, CH_2), 2.73−2.43 (m, 14 H, CH_2 and piperazine), 1.90−1.82 (m, 2 H, CH_2), 1.76−1.69 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 152.87, 130.77, 130.67, 129.36, 125.62, 124.19, 124.00, 123.29, 119.74, 119.43, 118.53, 99.36, 59.53, 58.37, 54.40, 52.21, 49.08, 45.27, 26.99, 24.26; MALDI-MS *m/z* 544.2 (M^+).

***N*⁴-[3-(4-{3-[(4-Chlorobenzyl)amino]propyl}piperazino)propyl]-7-chloroquinolin-4-amine (9b).** Compound **9b** was prepared from 4-chlorobenzaldehyde (96 mg, 0.46 mmol, 1.1 equiv) by method B and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:1.4) as a yellow oil (79 mg, 39% yield): R_f = 0.55 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.14); HPLC (C18N) P_{HPLC} = 94%, t_R = 14.96 min; HPLC (C18XT) P_{HPLC} = 95%, t_R = 4.10 min; ^{1}H NMR ($CDCl_3$) δ 8.42 (d, J = 5.4 Hz, 1 H, Ar−H), 7.86 (d, J = 2.1 Hz, 1 H, Ar−H), 7.78 (d, J = 8.9 Hz, 1 H, Ar−H), 7.52−7.49 (m, 1 H, NH), 7.25−7.18 (m, 5 H, Ar−H), 6.23 (d, J = 5.4 Hz, 1 H, Ar−H), 3.71 (s, 2 H, CH_2), 2.67−2.42 (m, 14 H, CH_2 and piperazine), 1.89−1.85 (m, 2 H, CH_2), 1.81−1.67 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 152.53, 129.86, 128.93, 125.04, 122.86, 98.88, 59.16, 57.66, 53.98, 53.78, 53.64, 48.47, 44.85, 27.22, 23.76; MALDI-MS *m/z* 486.2 (M^+).

***N*⁴-[3-(4-{3-[(4-Methoxybenzyl)amino]propyl}piperazino)propyl]-7-chloroquinolin-4-amine (10b).** Com-

pound **10b** was prepared from 4-methoxybenzaldehyde (83 μL, 0.46 mmol, 1.1 equiv) by method B and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 80:20:1.4) as a yellow solid (116 mg, 58% yield): R_f = 0.70 (CH_2Cl_2/MeOH/NH_4OH, 8:2:0.14); HPLC (C18N) P_{HPLC} = 100%, t_R = 12.78 min; HPLC (C18XT) P_{HPLC} = 95%, t_R = 3.83 min; ^{1}H NMR ($CDCl_3$) δ 8.49 (d, *J* = 5.4 Hz, 1 H, Ar−H), 7.92 (d, *J* = 2.1 Hz, 1 H, Ar−H), 7.85 (d, *J* = 8.9 Hz, 1 H, Ar−H), 7.57−7.54 (m, 1 H, NH), 7.31 (dd, *J* = 8.9, 2.2 Hz, 1 H, Ar−H), 7.28−7.24 (m, 3 H, Ar−H and NH), 6.90−6.85 (m, 2 H, Ar−H), 6.32 (d, *J* = 5.4 Hz, 1 H, Ar−H), 3.80 (s, 3 H, CH_3), 3.77 (s, 2 H, CH_2), 3.39−3.33 (m, 2 H, CH_2), 2.77−2.49 (m, 14 H, CH_2 and piperazine), 1.97−1.89 (m, 2 H, CH_2), 1.83−1.74 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 152.56, 129.83, 128.98, 125.04, 122.83, 114.26, 98.87, 59.11, 57.76, 55.69, 53.94, 53.75, 53.57, 48.37, 44.81, 26.88, 23.77; MALDI-MS *m*/*z* 482.1 (M^+).

***N*⁴-[3-(4-{3-[(4-Fluorobenzyl)amino]propyl}piperazino)-propyl]-7-chloroquinolin-4-amine (11b).** Compound **11b** was prepared from 4-fluorobenzaldehyde (73 μL, 0.46 mmol, 1.1 equiv) by method B and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 80:20:1.4) as a yellow oil (107 mg, 55% yield): R_f = 0.65 (CH_2Cl_2/MeOH/NH_4OH, 8:2:0.14); HPLC (C18N) P_{HPLC} = 100%, t_R = 12.79 min; HPLC (C18XT) P_{HPLC} = 99%, t_R = 3.80 min; ^{1}H NMR ($CDCl_3$) δ 8.38 (d, *J* = 5.4 Hz, 1 H, Ar−H), 8.21 (d, *J* = 9.1 Hz, 1 H, Ar−H), 7.77 (d, *J* = 2.2 Hz, 1 H, Ar−H), 7.43−7.40 (m, 4 H, Ar−H and NH), 7.36−7.30 (m, 2 H, Ar−H), 7.13−7.07 (m, 2 H, Ar−H), 6.44 (d, *J* = 5.5 Hz, 1 H, Ar−H), 3.64 (s, 2 H, CH_2), 3.30−3.24 (m, 2 H, CH_2), 2.50−2.26 (m, 14 H, CH_2 and piperazine), 1.82−1.74 (m, 2 H, CH_2), 1.59−1.50 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 152.80, 130.55, 128.41, 124.83, 115.68, 99.46, 57.08, 56.70, 53.82, 53.01, 47.87, 41.92, 27.40, 25.72; MALDI-MS *m*/*z* 470.1 (M^+).

***N*⁴-[3-(4-{3-[(4-Nitrobenzyl)amino]propyl}piperazino)-propyl]-7-chloroquinolin-4-amine (12b).** Compound **12b** was prepared from 4-nitrobenzaldehyde (103 mg, 0.46 mmol, 1.1 equiv) by method B and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 80:20:1.4) as a yellow oil (153 mg, 78% yield): R_f = 0.40 (CH_2Cl_2/MeOH/NH_4OH, 8:2:0.09); HPLC (C18N) P_{HPLC} = 95%, t_R = 13.06 min; HPLC (C18XT) P_{HPLC} = 96%, t_R = 3.87 min; ^{1}H NMR ($CDCl_3$) δ 8.50 (d, *J* = 5.4 Hz, 1 H, Ar−H), 8.22−8.17 (m, 2 H, Ar−H), 7.96 (d, *J* = 2.1 Hz, 1 H, Ar−H), 7.88 (d, *J* = 8.9 Hz, 1 H, Ar−H), 7.65−7.62 (m, 1 H, NH), 7.54−7.51 (m, 2 H, Ar−H), 7.32 (dd, *J* = 8.9, 2.1 Hz, 1 H, Ar−H), 6.32 (d, *J* = 5.5 Hz, 1 H, Ar−H), 3.41−3.36 (m, 2 H, CH_2), 2.76−2.51 (m, 14 H, CH_2 and piperazine), 1.99−1.92 (m, 2 H, CH_2), 1.83−1.74 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 151.81, 128.49, 128.30, 125.09, 124.61, 123.54, 98.38, 58.68, 57.12, 53.52, 53.27, 48.14, 44.39, 26.83, 23.24; MALDI-MS *m*/*z* 497.1 (M^+).

4-({[3-(4-{3-[(7-Chloro-4-quinolyl)amino]propyl}-piperazino)propyl]amino}methyl)phenol (13b). To a solution of compound **3** (150 mg, 0.41 mmol, 1 equiv) in 3 mL of dry CH_2Cl_2 were added 4-hydroxybenzaldehyde (83 mg, 0.45 mmol, 1.1 equiv), TEA (26 μL, 0.16 mmol, 0.4 equiv), and 3 Å molecular sieves. The reaction mixture was stirred at room temperature for 3 h and then cooled to 0 °C. $NaBH_4$ (78 mg, 2.05 mmol, 5 equiv) was added in small portions over 30 min. After the mixture was stirred at 0 °C for 1.5 h, the reaction was quenched by addition of 3 mL of water. Then the solvent was evaporated and the residue was purified by TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:1.4) to yield compound **13b** as a yellow solid (120 mg, 62% yield): R_f = 0.25 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.14); mp 78−80 °C; HPLC (C18N) P_{HPLC} = 100%, t_R = 11.45 min; HPLC (C18XT) P_{HPLC} = 95%, t_R = 3.45 min; ^{1}H NMR ($CDCl_3$) δ 8.44 (d, *J* = 5.4 Hz, 1 H, Ar−H), 8.28 (d, *J* = 9.1 Hz, 1 H, Ar−H), 7.83 (d, *J* = 2.2 Hz, 1 H, Ar−H), 7.51−7.47 (m, 2 H, Ar−H and NH), 7.18−7.15 (m, 2 H, Ar−H), 6.77−6.72 (m, 2 H, Ar−H), 6.52 (d, *J* = 5.5 Hz, 1 H, Ar−H), 3.63 (s, 2 H, CH_2), 3.37−3.31 (m, 2 H, CH_2), 2.58−2.33 (m, 14 H, CH_2 and piperazine), 1.91−1.83 (m, 2 H, CH_2), 1.67−1.60 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 152.79, 130.04, 128.37, 124.85, 115.69, 95.47, 57.08, 56.68, 53.77, 53.23, 47.79, 41.92, 27.05, 25.71; MALDI-MS *m*/*z* 468.3 (M^+).

***N*⁴-(3-{4-[3-(Phenethylamino)propyl]piperazino}-propyl)-7-chloroquinolin-4-amine (14b).** Compound **14b** was prepared from phenylacetaldehyde (80 μL, 0.46 mmol, 1.1 equiv) by method B and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:1.4) as a yellow oil (120 mg, 62% yield): R_f = 0.50 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.14); HPLC (C18N) P_{HPLC} = 100%, t_R = 13.07 min; HPLC (C18XT) P_{HPLC} = 100%, t_R = 4.26 min; ^{1}H NMR ($CDCl_3$) δ 8.42 (d, *J* = 5.4 Hz, 1 H, Ar−H), 7.86 (d, *J* = 2.1 Hz, 1 H, Ar−H), 7.78 (d, *J* = 9.0 Hz, 1 H, Ar−H), 7.51−7.48 (m, 1 H, NH), 7.26−7.14 (m, 6 H, Ar−H), 6.24 (d, *J* = 5.4 Hz, 1 H, Ar−H), 3.32−3.27 (m, 2 H, CH_2), 2.89−2.84 (m, 2 H, CH_2), 2.81−2.76 (m, 2 H, CH_2), 2.68 (t, *J* = 6.8 Hz, 2 H, CH_2), 2.56−2.38 (m, 12 H, CH_2 and piperazine), 1.90−1.82 (m, 2 H, CH_2), 1.73−1.64 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 152.60, 129.13, 128.99, 126.69, 125.04, 122.85, 98.87, 59.14, 57.72, 53.93, 53.77, 51.39, 49.00, 48.88, 36.42, 26.99, 23.77; MALDI-MS *m*/*z* 466.3 (M^+).

***N*⁴-[3-(4-{3-[(3-Phenylpropyl)amino]propyl}piperazino)-propyl]-7-chloroquinolin-4-amine (15b).** Compound **15b** was prepared from hydrocinnamaldehyde (90 μL, 0.46 mmol, 1.1 equiv) by method B and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 80:20:0.9) as a yellow oil (137 mg, 69% yield): R_f = 0.55 (CH_2Cl_2/MeOH/NH_4OH, 8:2:0.09); HPLC (C18N) P_{HPLC} = 99%, t_R = 14.14 min; HPLC (C18XT) P_{HPLC} = 100%, t_R = 4.19 min; ^{1}H NMR ($CDCl_3$) δ 8.47 (d, *J* = 5.4 Hz, 1 H, Ar−H), 7.90 (d, *J* = 2.1 Hz, 1 H, Ar−H), 7.83 (d, *J* = 8.9 Hz, 1 H, Ar−H), 7.53−7.50 (m, 1 H, NH), 7.30−7.24 (m, 3 H, Ar−H), 7.18−7.14 (m, 3 H, Ar−H and NH), 6.28 (d, *J* = 5.5 Hz, 1 H, Ar−H), 3.36−3.30 (m, 2 H, CH_2), 2.75−2.47 (m, 18 H, CH_2 and piperazine), 1.97−1.86 (m, 4 H, CH_2), 1.84−1.71 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 152.27, 128.67, 128.52, 126.02, 124.78, 122.60, 98.61, 58.78, 57.47, 53.71, 53.49, 49.37, 48.76, 44.47, 33.74, 31.33, 26.48, 23.53; MALDI-MS *m*/*z* 480.1 (M^+).

***N*⁴-[3-(4-{3-[(Cyclohexylmethyl)amino]propyl}-piperazino)propyl]-7-chloroquinolin-4-amine (16b).** Compound **16b** was prepared from cyclohexane-1-carboxaldehyde (83 μL, 0.46 mmol, 1.1 equiv) by method B and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 80:20:1.4) as a yellow oil (108 mg, 57% yield): R_f = 0.65 (CH_2Cl_2/MeOH/NH_4OH, 8:2:0.14); HPLC (C18N) P_{HPLC} = 98%, t_R = 17.29 min; HPLC (C18XT) P_{HPLC} = 99%, t_R = 3.94 min; ^{1}H NMR ($CDCl_3$) δ 8.42 (d, *J* = 5.9 Hz, 1 H, Ar−H), 7.94−7.92 (m, 2 H, Ar−H), 7.32 (dd, *J* = 9.0, 2.0 Hz, 1 H, Ar−H), 6.37 (d, *J* = 6.0 Hz, 1 H, Ar−H), 3.48−3.29 (m, 2 H, CH_2), 3.13−3.09 (m, 2 H, CH_2), 2.80−2.78 (d, *J* = 6.8 Hz, 2 H, CH_2), 2.89−2.40 (m, 12 H, CH_2 and piperazine), 2.00−1.96 (m, 4 H, CH_2), 1.83−1.71 (m, 6 H, CH_2 cyclohexyle), 1.46−0.75 (m, 5 H, CH_2 and CH cyclohexyle); ^{13}C NMR ($CDCl_3$) δ 148.98, 125.71, 123.08, 57.91, 57.66, 54.29, 53.37, 53.29, 49.20, 43.93, 35.23, 30.78, 25.45, 23.72, 22.06; TOF-MS *m*/*z* 458.4 (M^+).

***N*⁴-[3-(4-{3-[(Cyclopropylmethyl)amino]propyl}-piperazino)propyl]-7-chloroquinolin-4-amine (17b).** Compound **17b** was prepared from cyclopropane-1-carboxaldehyde (51 μL, 0.46 mmol, 1.1 equiv) by method B and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 80:20:1.8) as a yellow oil (112 mg, 65% yield): R_f = 0.75 (CH_2Cl_2/MeOH/NH_4OH, 8:2:0.18); HPLC (C18N) P_{HPLC} = 100%, t_R = 11.21 min; HPLC (C18XT) P_{HPLC} = 100%, t_R = 5.71 min; ^{1}H NMR ($CDCl_3$) δ 8.49 (d, *J* = 5.4 Hz, 1 H, Ar−H), 7.93 (d, *J* = 2.1 Hz, 1 H, Ar−H), 7.86 (d, *J* = 9.0 Hz, 1 H, Ar−H), 7.54−7.48 (m, 1 H, NH), 7.32 (dd, *J* = 8.9, 2.1 Hz, 1 H, Ar−H), 6.32 (d, *J* = 5.5 Hz, 1 H, Ar−H), 3.40−3.35 (m, 2 H, CH_2), 2.82−2.77 (m, 2 H, CH_2), 2.72−2.52 (m, 14 H, CH_2 and piperazine), 1.98−1.94 (m, 2 H, CH_2), 1.86−1.80 (m, 2 H, CH_2), 1.04−1.01 (m, 1 H, CH), 0.55−0.52 (m, 2 H, CH_2), 0.19−0.17 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 152.15, 128.57, 124.57, 122.40, 98.49, 58.67, 57.47, 54.70, 53.59, 53.36, 48.60, 44.34, 26.18, 23.42, 10.71, 3.56; TOF-MS *m*/*z* 416.2 (M^+).

***N*⁴-(3-{4-[3-(Heptylamino)propyl]piperazino}propyl)-7-chloroquinolin-4-amine (18b).** Compound **18b** was prepared from heptanal (95 μL, 0.46 mmol, 1.1 equiv) by method B and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 80:20:1.4) as a yellow oil (71 mg, 37% yield): R_f = 0.30 (CH_2Cl_2/

MeOH/NH_4OH, 8:2:0.14); HPLC (C18N) P_{HPLC} = 100%, t_R = 15.11 min; HPLC (C18XT) P_{HPLC} = 100%, t_R = 4.48 min; ^1H NMR ($CDCl_3$) δ 8.49 (d, J = 5.4 Hz, 1 H, Ar−H), 7.93 (d, J = 2.1 Hz, 1 H, Ar−H), 7.86 (d, J = 9.0 Hz, 1 H, Ar−H), 7.52−7.49 (m, 1 H, NH), 7.31 (dd, J = 8.9, 2.1 Hz, 1 H, Ar−H), 6.31 (d, J = 5.4 Hz, 1 H, Ar−H), 3.39−3.34 (m, 2 H, CH_2), 2.80−2.76 (m, 2 H, CH_2), 2.69−2.51 (m, 14 H, CH_2 and piperazine), 1.98−1.90 (m, 2 H, CH_2), 1.85−1.76 (m, 2 H, CH_2), 1.58−1.51 (m, 2H, CH_2), 1.32−1.25 (m, 8 H, CH_2), 0.90−0.86 (m, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 152.05, 128.45, 124.55, 122.30, 98.38, 58.54, 57.37, 53.48, 53.26, 49.55, 48.61, 44.24, 31.69, 29.29, 29.07, 27.20, 25.93, 23.34, 22.52, 13.98; MALDI-MS m/z 460.2 (M^+).

***N*⁴-(3-{4-[3-(Butylamino)propyl]piperazino}propyl)-7-chloroquinolin-4-amine (19b).** Compound **19b** was prepared from butyraldehyde (62 μL, 0.46 mmol, 1.1 equiv) by method B and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:1.4) as a yellow oil (90 mg, 52% yield): R_f = 0.30 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); HPLC (C18N) P_{HPLC} = 100%, t_R = 13.13 min; HPLC (C18XT) P_{HPLC} = 100%, t_R = 2.69 min; ^1H NMR ($CDCl_3$) δ 8.41 (d, J = 5.4 Hz, 1 H, Ar−H), 7.86 (d, J = 2.1 Hz, 1 H, Ar−H), 7.78 (d, J = 9.0 Hz, 1 H, Ar−H), 7.36−7.34 (m, 1 H, NH), 7.22 (dd, J = 9.3, 2.1 Hz, 1 H, Ar−H), 6.24 (d, J = 5.5 Hz, 1 H, Ar−H), 3.31−3.26 (m, 2 H, CH_2), 2.85−2.81 (m, 2 H, CH_2), 2.72−2.67 (m, 2 H, H_2), 2.55−2.48 (m, 12 H, CH_2 and piperazine), 1.90−1.82 (m, 4 H, CH_2), 1.61−1.53 (m, 2 H, CH_2), 1.39−1.26 (m, 2 H, CH_2), 0.89−0.83 (m, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 152.48, 128.88, 125.07, 122.76, 98.91, 58.86, 57.76, 53.93, 53.69, 49.12, 48.96, 44.54, 30.73, 24.96, 23.91, 20.73, 14.21; MALDI-MS m/z 418.3 (M^+).

***N*⁴-(3-{4-[3-(Propylamino)propyl]piperazino}propyl)-7-chloroquinolin-4-amine (20b).** Compound **20b** was prepared from propionaldehyde (49 μL, 0.46 mmol, 1.1 equiv) by method B and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:1.4) as a yellow oil (62 mg, 37% yield): R_f = 0.30 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.14); HPLC (C18N) P_{HPLC} = 95%, t_R = 11.41 min; HPLC (C18XT) P_{HPLC} = 95%, t_R = 3.32 min; ^1H NMR ($CDCl_3$) δ 8.47 (d, J = 5.4 Hz, 1 H, Ar−H), 7.93 (d, J = 2.1 Hz, 1 H, Ar−H), 7.87 (d, J = 9.0 Hz, 1 H, Ar−H), 7.59−7.56 (m, 1 H, NH), 7.33 (dd, J = 8.9, 2.1 Hz, 1 H, Ar−H), 6.31 (d, J = 5.4 Hz, 1 H, Ar−H), 3.39−3.34 (m, 2 H, CH_2), 2.72−2.26 (m, 16 H, CH_2 and piperazine), 1.98−1.92 (m, 2 H, CH_2), 1.77−1.70 (m, 2 H, CH_2), 1.57−1.49 (m, 2 H, CH_2), 0.94 (t, J = 7.4 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 152.06, 134.66, 128.40, 122.48, 98.44, 58.63, 57.32, 53.55, 53.36, 51.90, 48.61, 44.31, 26.95, 23.38, 23.08, 11.84; MALDI-MS m/z 404.3 (M^+).

***N*⁴-(3-{4-[3-(Ethylamino)propyl]piperazino}propyl)-7-chloroquinolin-4-amine (21b).** Compound **21b** was prepared from acetaldehyde (35 μL, 0.46 mmol, 1.1 equiv) by method B and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:1.4) as a yellow oil (47 mg, 29% yield): R_f = 0.50 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.14); HPLC (C18N) P_{HPLC} = 95%, t_R = 10.99 min; HPLC (C18XT) P_{HPLC} = 95%, t_R = 3.22 min; ^1H NMR ($CDCl_3$) δ 8.50 (d, J = 5.4 Hz, 1 H, Ar−H), 7.93 (d, J = 2.1 Hz, 1 H, Ar−H), 7.87 (d, J = 8.9 Hz, 1 H, Ar−H), 7.58−7.55 (m, 1 H, NH), 7.32 (dd, J = 8.9, 2.1 Hz, 1 H, Ar−H), 6.31 (d, J = 5.4 Hz, 1 H, Ar−H), 3.39−3.34 (m, 2 H, CH_2), 2.77−2.61 (m, 14 H, CH_2 and piperazine), 2.53 (m, 2 H, CH_2), 1.98−1.91 (m, 2 H, CH_2), 1.82−1.73 (m, 2 H, CH_2), 1.13 (t, J = 7.2 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 152.03, 128.46, 124.46, 122.26, 98.30, 58.60, 57.18, 53.44, 53.20, 48.31, 44.27, 43.89, 26.54, 23.19, 14.87; MALDI-MS m/z 390.0 (M^+).

***N*⁴-(3-{4-[3-(Neopentylamino)propyl]piperazino}propyl)-7-chloroquinolin-4-amine (22b).** Compound **22b** was prepared from trimethylacetaldehyde (74 μL, 0.46 mmol, 1.1 equiv) by method B and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 80:20:1.4) as a yellow oil (79 mg, 44% yield): R_f = 0.30 (CH_2Cl_2/MeOH/NH_4OH, 8:2:0.09); HPLC (C18N) P_{HPLC} = 100%, t_R = 11.97 min; HPLC (C18XT) P_{HPLC} = 100%, t_R = 3.52 min; ^1H NMR ($CDCl_3$) δ 8.43 (d, J = 5.4 Hz, 1 H, Ar−H), 7.86 (d, J = 2.1 Hz, 1 H, Ar−H), 7.80 (d, J = 8.9 Hz, 1 H, Ar−H), 7.54−7.51 (m, 1 H, NH), 7.24 (dd, J = 8.9, 2.1 Hz, 1 H, Ar−H), 6.24 (d, J = 5.5 Hz, 1 H, Ar−H), 3.32−3.27 (m, 2 H, Ar−H), 2.68−2.43 (m, 14 H, CH_2 and piperazine), 2.31 (s, 2 H, CH_2), 1.88−1.85 (m, 2 H, CH_2), 1.73−1.68 (m, 2 H, CH_2), 0.87 (s, 9 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 151.62, 129.05, 125.01, 122.88, 98.87, 62.86, 59.22, 57.99, 54.01, 53.86, 50.31, 44.89, 26.33, 27.04, 23.77; MALDI-MS m/z 432.2 (M^+).

***N*⁴-[3-(4-{3-[(4-Chlorobenzyl)amino]propyl}piperazino)-propyl]-7-chloroquinolin-4-amine (23b).** Compound **23b** was prepared from isobutyraldehyde (62 μL, 0.46 mmol, 1.1 equiv) by method B and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:1.4) as a yellow oil (80 mg, 46% yield): R_f = 0.60 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.14); HPLC (C18N) P_{HPLC} = 100%, t_R = 11.71 min; HPLC (C18XT) P_{HPLC} = 96%, t_R = 3.44 min; ^1H NMR ($CDCl_3$) δ 8.41 (d, J = 5.4 Hz, 1 H, Ar−H), 7.86 (d, J = 2.1 Hz, 1 H, Ar−H), 7.79 (d, J = 8.9 Hz, 1 H, Ar−H), 7.52−7.49 (m, 1 H, NH), 7.24 (dd, J = 8.9, 2.1 Hz, 1 H, Ar−H), 6.23 (d, J = 5.4 Hz, 1 H, Ar−H), 3.32−3.27 (m, 2 H,CH_2), 2.65−2.54 (m, 12 H, CH_2 and piperazine), 2.46−2.41 (m, 2 H, CH_2), 2.36 (d, J = 6.9 Hz, 2 H, CH_2), 1.91−1.85 (m, 2 H, CH_2), 1.76−1.64 (m, 3 H, CH_2 and CH), 0.85 (d, J = 6.7 Hz, 6 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 151.16, 127.56, 123.67, 121.50, 97.47, 57.77, 57.13, 56.47, 52.61, 52.42, 47.88, 43.44, 27.18, 25.91, 22.39, 19.76; MALDI-MS m/z 418.3 (M^+).

***N*⁴-[3-(4-{3-[Di(4-quinolylmethyl)amino]propyl}-piperazino)propyl]-7-chloroquinolin-4-amine (4c).** Compound **4c** was prepared from 4-quinolinecarboxaldehyde (293 mg, 1.24 mmol, 3.0 equiv) by method C and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:1.4) as a yellow oil (176 mg, 66% yield): R_f = 0.45 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); HPLC (C18N) P_{HPLC} = 100%, t_R = 15.06 min; HPLC (C18XT) P_{HPLC} = 96%, t_R = 3.11 min; ^1H NMR ($CDCl_3$) δ 8.87 (d, J = 4.4 Hz, 2 H, Ar−H), 8.51 (d, J = 5.7 Hz, 1 H, Ar−H), 8.12 (d, J = 9.3 Hz, 2 H, Ar−H), 8.03 (d, J = 8.4 Hz, 2 H, Ar−H), 7.99 (d, J = 2.1 Hz, 1 H, Ar−H), 7.91 (d, J = 9.0 Hz, 1 H, Ar−H), 7.72−7.69 (m, 2 H, Ar−H), 7.50 (d, J = 4.4 Hz, 2 H, Ar−H), 7.46−7.40 (m, 1 H, Ar−H), 7.28 (d, J = 8.1 Hz, 2 H, Ar−H), 6.31 (d, J = 5.8 Hz, 1 H, Ar−H), 4.10 (s, 4 H, CH_2), 3.39−3.34 (m, 2 H, CH_2), 2.73−2.29 (m, 14 H, CH_2 and piperazine), 1.96−1.83 (m, 4 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 150.14, 130.01, 129.51, 126.47, 125.35, 124.31, 122.93, 121.88, 117.10, 57.90, 56.67, 56.05, 53.11, 52.77, 52.68, 43.85, 24.30, 23.37; MALDI-MS m/z 642.8 (M^+).

***N*⁴-[3-(4-{3-[Di(1-naphthylmethyl)amino]propyl}-piperazino)propyl]-7-chloroquinolin-4-amine (5c).** To a solution of 1-naphthaldehyde (337 μL, 1.65 mmol, 4.0 equiv) and $NaHB(OAc)_3$ (351 mg, 1.64 mmol, 4 equiv) in 2 mL of dry CH_2Cl_2 on ice, a solution of compound **3** (150 mg, 0.41 mmol, 1 equiv) in 4 mL of dry $CH_2Cl_2$was added dropwise. After the mixture was stirred at room temperature for 4 h, a total of 5 mL of aqueous 1 M NaOH was introduced and the mixture left for 15 min. The organic layer was separated, and the aqueous layer was washed with CH_2Cl_2. Then the organic layers were mixed and dried over $MgSO_4$, the solvent was evaporated, and the residue was purified by TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9) to yield compound **5c** as a yellow oil (120 mg, 45% yield): R_f = 0.50 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); HPLC (C18N) P_{HPLC} = 95%, t_R = 18.88 min; HPLC (C18XT) P_{HPLC} = 95%, t_R = 5.65 min; ^1H NMR ($CDCl_3$) δ 8.41 (d, J = 5.5 Hz, 1 H, Ar−H), 7.97 (d, J = 8.4 Hz, 1 H, Ar−H), 7.91 (d, J = 2.0 Hz, 1 H, Ar−H), 7.80−7.66 (m, 7 H, Ar−H and NH), 7.47−7.30 (m, 8 H, Ar−H), 7.19−7.14 (m, 1 H, Ar−H), 6.23 (d, J = 5.5 Hz, 1 H, Ar−H), 3.97 (s, 4 H, CH_2), 3.30−3.28 (m, 2 H, CH_2), 2.54−2.50 (m, 4 H, CH_2), 2.47−2.23 (m, 8 H, piperazine), 2.10−2.05 (m, 2 H, CH_2), 1.86−1.83 (m, 2 H, CH_2), 1.72−1.67 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 150.70, 127.46, 127.27, 124.80, 124.56, 124.32, 97.73, 57.72, 57.31, 55.87, 52.60, 52.13, 51.36, 43.12, 23.40, 22.39; MALDI-MS m/z 642.08 (M^+).

***N*⁴-(3-{4-[3-(Dibenzylamino)propyl]piperazino}propyl)-7-chloroquinolin-4-amine (6c).** Compound **6c** was prepared from benzaldehyde (190 μL, 1.24 mmol, 3.0 equiv) by method C and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9) as a yellow oil (130 mg, 58% yield): R_f = 0.70 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); HPLC (C18N) P_{HPLC} = 100%, t_R = 12.17 min; HPLC (C18XT) P_{HPLC} = 98%, t_R = 2.87 min; ^1H NMR ($CDCl_3$) δ 8.42 (d, J = 5.7 Hz, 1 H, Ar−H), 8.11−8.08

(m, 1 H, NH), 8.01 (d, $J = 2.1$ Hz, 1 H, Ar−H), 7.97 (d, $J = 9.0$ Hz, 1 H, Ar−H), 7.39−7.21 (m, 11 H, Ar−H), 6.34 (d, $J = 5.8$ Hz, 1 H, Ar−H), 3.58 (s, 4 H, CH_2), 3.48−3.40 (m, 2 H, CH_2), 2.88−2.40 (m, 14 H, CH_2 and piperazine), 2.01−1.95 (m, 2 H, CH_2), 1.79−1.69 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 150.44, 129.74, 129.13, 127.81, 126.24, 123.88, 117.88, 99.16, 59.42, 59.15, 57.53, 54.20, 54.89, 52.22, 45.09, 25.24, 24.07; TOF-MS *m/z* 541.2 (M^+).

***N*⁴-[3-(4-{3-[Di(3-thienylmethyl)amino]propyl}-piperazino)propyl]-7-chloroquinolin-4-amine (7c).** Compound **7c** was prepared from 3-thiophenecarboxaldehyde (163 μL, 1.24 mmol, 3.0 equiv) by method C and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09) as a yellow oil (165 mg, 72% yield): $R_f = 0.50$ (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9); HPLC (C18N) $P_{HPLC} = 100\%$, $t_R = 14.39$ min; HPLC (C18XT) $P_{HPLC} = 95\%$, $t_R = 4.27$min; ^{1}H NMR (DMSO-d_6) δ 8.43 (d, $J = 5.4$ Hz, 1 H, Ar−H), 8.26 (d, $J = 9.1$ Hz, 1 H, Ar−H), 7.83 (d, $J = 2.3$ Hz, 1 H, Ar−H), 7.52−7.46 (m, 4 H, NH and Ar−H), 7.36 (dd, $J = 2.7$, 1.0 Hz, 2 H, Ar−H), 7.10 (dd, $J = 4.9$, 1.2 Hz, 2 H, Ar−H), 6.51 (d, $J = 5.4$ Hz, 1 H, Ar−H), 3.58 (s, 4 H, Ar−H), 3.36−3.30 (m, 2 H, CH_2), 2.56−2.25 (m, 14 H, CH_2 and piperazine), 1.88−1.80 (m, 2 H, CH_2), 1.67−1.58 (m, 2 H, CH_2); ^{13}C NMR (DMSO-d_6) δ 152.79, 129.18, 128.39, 126.66, 124.83, 123.21, 99.47, 56.71, 56.59, 53.76, 53.68, 53.27, 51.36, 41.96, 25.72, 24.67; MALDI-MS *m/z* 554.0 (M^+).

***N*⁴-[3-(4-{3-[Di(3-phenoxybenzyl)amino]propyl}-piperazino)propyl]-7-chloroquinolin-4-amine (8c).** Compound **8c** was prepared from 3-phenoxybenzaldehyde (322 μL, 1.24 mmol, 3.0 equiv) by method C and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9) as a yellow oil (222 mg, 76% yield): $R_f = 0.60$ (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); HPLC (C18N) $P_{HPLC} = 100\%$, $t_R = 17.48$ min; HPLC (C18XT) $P_{HPLC} = 100\%$, $t_R = 6.39$ min; ^{1}H NMR ($CDCl_3$) δ 8.48 (d, $J = 5.4$ Hz, 1 H, Ar−H), 7.93 (d, $J = 2.1$ Hz, 1 H, Ar−H), 7.62−7.59 (m, 1 H, NH), 7.33−7.22 (m, 7 H, Ar−H), 7.09−6.97 (m, 10 H, Ar−H), 6.89−6.86 (m, 2 H, Ar−H), 6.31 (d, $J = 5.5$ Hz, 1 H, Ar−H), 3.54 (s, 4 H, CH_2), 3.37−3.34 (m, 2 H, CH_2), 2.62−2.34 (m, 14 H, CH_2 and piperazine), 1.95−1.92 (m, 2 H, CH_2), 1.73−1.70 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 152.40, 130.13, 129.87, 128.86, 125.13, 123.96, 123.55, 122.90, 119.47, 117.52, 59.11, 58.55, 57.02, 53.94, 53.66, 51.92, 44.48, 24.89, 23.74; MALDI-MS *m/z* 726.2 (M^+).

***N*⁴-[3-(4-{3-[Di(4-chlorobenzyl)amino]propyl}-piperazino)propyl]-7-chloroquinolin-4-amine (9c).** Compound **9c** was prepared from 4-chlorobenzaldehyde (262 mg, 1.24 mmol, 3.0 equiv) by method C and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9) as a yellow oil (187 mg, 74% yield): $R_f = 0.65$ (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); HPLC (C18N) $P_{HPLC} = 100\%$, $t_R = 17.89$ min; HPLC (C18XT) $P_{HPLC} = 97\%$, $t_R = 5.22$ min; ^{1}H NMR ($CDCl_3$) δ 8.40 (d, $J = 5.4$ Hz, 1 H, Ar−H), 7.87 (d, $J = 2.1$ Hz, 1 H, Ar−H), 7.79 (d, $J = 8.9$ Hz, 1 H, Ar−H), 7.58−7.55 (m, 1 H, NH), 7.23−7.18 (m, 9 H, Ar−H), 6.23 (d, $J = 5.5$ Hz, 1 H, Ar−H), 3.44 (s, 4 H, CH_2), 3.31−3.26 (m, 2 H, CH_2), 2.56−2.28 (m, 14 H, CH_2 and piperazine), 1.89−1.82 (m, 2 H, CH_2), 1.69−1.59 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 152.34, 130.44, 128.79, 125.05, 122.94, 98.94, 59.14, 58.11, 56.87, 53.93, 53.61, 51.69, 44.84, 24.82, 23.73; MALDI-MS *m/z* 610.1 (M^+).

***N*⁴-[3-(4-{3-[Di(4-methoxybenzyl)amino]propyl}-piperazino)propyl]-7-chloroquinolin-4-amine (10c).** Compound **10c** was prepared from 4-methoxybenzaldehyde (227 μL, 1.24 mmol, 3.0 equiv) by method C and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9) as a yellow oil (187 mg, 75% yield): $R_f = 0.55$ (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); HPLC (C18N) $P_{HPLC} = 100\%$, $t_R = 16.16$ min; HPLC (C18XT) $P_{HPLC} = 100\%$, $t_R = 4.75$ min; ^{1}H NMR ($CDCl_3$) δ 8.49 (d, $J = 5.4$ Hz, 1 H, Ar−H), 7.94 (d, $J = 2.1$ Hz, 1 H, Ar−H), 7.87 (d, $J = 9.0$ Hz, 1 H, Ar−H), 7.66−7.64 (m, 1 H, NH), 7.33−7.25 (m, 5 H, Ar−H), 6.88−6.83 (m, 4 H, Ar−H), 6.29 (d, $J = 5.4$ Hz, 1 H, Ar−H), 3.78 (s, 6 H, CH_3), 3.49 (s, 4 H, CH_2), 3.38−3.33 (m, 2 H, CH_2), 2.63−2.38 (m, 14 H, CH_2 and piperazine), 1.96−1.91 (m, 2 H, CH_2), 1.78−1.70 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 152.01, 129.84, 128.42, 124.59, 122.54, 113.50, 98.39, 58.71, 57.49, 56.71, 55.20, 53.49, 53.19, 51.01, 44.42, 24.32, 23.24; MALDI-MS *m/z* 602.1 (M^+).

***N*⁴-[3-(4-{3-[Di(4-fluorobenzyl)amino]propyl}-piperazino)propyl]-7-chloroquinolin-4-amine (11c).** Compound **11c** was prepared from 4-fluorobenzaldehyde (200 μL, 1.24 mmol, 3.0 equiv) by method C and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:1.4) as a yellow oil (93 mg, 39% yield): $R_f = 0.80$ (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.14); HPLC (C18N) $P_{HPLC} = 97\%$, $t_R = 15.79$ min; HPLC (C18XT) $P_{HPLC} = 95\%$, $t_R = 4.68$ min; ^{1}H NMR ($CDCl_3$) δ 8.40 (d, $J = 5.4$ Hz, 1 H, Ar−H), 7.87 (d, $J = 2.0$ Hz, 1 H, Ar−H), 7.79 (d, $J = 9.0$ Hz, 1 H, Ar−H), 7.27−7.19 (m, 5 H, Ar−H), 6.96−6.90 (m, 4 H, Ar−H), 6.23 (d, $J = 5.5$ Hz, 1 H, Ar−H), 3.44 (s, 4 H, CH_2), 3.32−3.27 (m, 2 H, CH_2), 2.56−2.38 (m, 12 H, CH_2 and piperazine), 2.34−2.29 (m, 2 H, CH_2), 1.88−1.84 (m, 2 H, CH_2), 1.67−1.62 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 152.20, 130.51, 128.71, 125.08, 122.95, 115.27, 98.83, 59.11, 57.98, 57.01, 53.91, 53.61, 51.62, 44.84, 24.78, 23.69; MALDI-MS *m/z* 578.2 (M^+).

***N*⁴-[3-(4-{3-[Di(4-nitrobenzyl)amino]propyl}piperazino)-propyl]-7-chloroquinolin-4-amine (12c).** Compound **12c** was prepared from 4-nitrobenzaldehyde (282 mg, 1.24 mmol, 3.0 equiv) by method C and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 85:15:0.4) as a yellow oil (58 mg, 22% yield): $R_f = 0.75$ (CH_2Cl_2/MeOH/NH_4OH, 8.5:1.5:0.04); HPLC (C18N) $P_{HPLC} = 100\%$, $t_R = 17.58$ min; HPLC (C18XT) $P_{HPLC} = 98\%$, $t_R = 5.19$ min; ^{1}H NMR ($CDCl_3$) δ 8.42 (d, $J = 5.4$ Hz, 1 H, Ar−H), 8.15−8.12 (m, 4 H, Ar−H), 7.8 (d, $J = 2.1$ Hz, 1H, Ar−H), 7.80 (d, $J = 8.9$ Hz, 1 H, Ar−H), 7.64−7.61 (m, 1H, Ar−NH), 7.50−7.45 (m, 4 H, Ar−H), 7.21 (dd, $J = 8.9$, 2.1 Hz, 1 H, Ar−H), 6.25 (d, $J = 5.4$ Hz, 1 H, Ar−H), 3.63 (s, 4 H, CH_2), 3.34−3.30 (m, 2 H, CH_2), 2.57−2.32 (m, 14 H, CH_2 and piperazine), 1.91−1.86 (m, 2 H, CH_2), 1.75−1.65 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 151.91, 129.58, 128.49, 125.15, 124.10, 122.91, 98.84, 59.04, 58.48, 56.60, 53.87, 53.57, 52.27, 44.80, 24.89, 23.70; MALDI-MS *m/z* 632.0 (M^+).

4-{[[3-(4-{3-[(7-Chloro-4-quinolyl)amino]propyl}-piperazino)propyl](4-hydroxybenzyl)amino]methyl}-phenol (13c). To a solution of compound **3** (150 mg, 0.41 mmol, 1 equiv) in 3 mL of dry CH_2Cl_2 were added 4-hydroxybenzaldehyde (228 mg, 1.24 mmol, 3.0 equiv) and $NaHB(OAc)_3$ (263 mg, 1.23 mmol, 3 equiv). After the mixture was stirred at room temperature for 4 h, a total of 3 mL of aqueous 1 M NaOH was introduced and the mixture was left for 25 min. Then the solvent was evaporated and the residue was purified by TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9) to yield compound **13c** as a yellow solid (105 mg, 44% yield): $R_f = 0.45$ (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); mp 101−103°C; HPLC (C18N) $P_{HPLC} = 100\%$, $t_R = 13.48$ min; HPLC (C18XT) $P_{HPLC} = 95\%$, $t_R = 3.17$ min; ^{1}H NMR (DMSO-d_6) δ 9.30 (broad s, 2 H, OH), 8.44 (d, $J = 5.4$ Hz, 1 H, Ar−H), 8.28 (d, $J = 9.1$ Hz, 1 H, Ar−H), 7.83 (d, $J = 2.2$ Hz, 1 H, Ar−H), 7.50−7.47 (m, 2 H, Ar−H and NH), 7.16−7.13 (m, 4 H, Ar−H), 6.76−6.74 (m, 4 H, Ar−H), 6.51 (d, $J = 5.5$ Hz, 1 H, Ar−H), 3.41 (s, 4 H, CH_2), 3.37−3.30 (m, 2 H, CH_2), 2.45−2.23 (m, 14 H, CH_2 and piperazine), 1.86−1.82 (m, 2 H, CH_2), 1.63−1.59 (m, 2 H, CH_2); ^{13}C NMR (DMSO-d_6) δ 152.75, 130.47, 128.30, 124.85, 115.70, 99.47, 57.74, 56.78, 53.64, 51.15, 41.52, 25.68, 24.44; MALDI-MS *m/z* 574.3 (M^+).

***N*⁴-(3-{4-[3-(Diphenethylamino)propyl]piperazino}-propyl)-7-chloroquinolin-4-amine (14c).** Compound **14c** was prepared from phenylacetaldehyde (218 μL, 1.24 mmol, 3.0 equiv) by method C and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:1.4) as a yellow oil (172 mg, 73% yield): $R_f = 0.55$ (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.14); HPLC (C18N) $P_{HPLC} = 95\%$, $t_R = 16.89$ min; HPLC (C18XT) $P_{HPLC} = 100\%$, $t_R = 4.96$ min; ^{1}H NMR ($CDCl_3$) δ 8.42 (d, $J = 5.4$ Hz, 1 H, Ar−H), 7.88 (d, $J = 2.2$ Hz, 1 H, Ar−H), 7.82 (d, $J = 9.0$ Hz, 1 H, Ar−H), 7.61−7.59 (m, 1 H, NH), 7.28−7.19 (m, 5 H, Ar−H), 7.14−7.09 (m, 6 H, Ar−H), 6.24 (d, $J = 5.5$ Hz, 1 H, Ar−H), 3.32−3.27 (m, 2 H, CH_2), 2.75−2.66 (m, 8 H, CH_2), 2.60−2.55 (m, 12 H, CH_2 and piperazine), 2.37−2.32 (m, 2 H, CH_2), 1.91−1.84 (m, 2 H, CH_2), 1.69−1.61 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 152.31, 129.17, 128.79, 126.39, 125.16, 122.95,

98.84, 59.15, 57.24, 56.40, 53.98, 53.76, 52.25, 44.88, 34.10, 25.73, 25.13; MALDI-MS *m/z* 570.4 (M^+).

***N*⁴-[3-(4-{3-[Di(3-phenylpropyl)amino]propyl}-piperazino)propyl]-7-chloroquinolin-4-amine (15c).** Compound **15c** was prepared from hydrocinnamaldehyde (246 μL, 1.24 mmol, 3.0 equiv) by method C and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9) as a yellow oil (186 mg, 75% yield): R_f = 0.53 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); HPLC (C18N) P_{HPLC} = 100%, t_R = 18.25 min; HPLC (C18XT) P_{HPLC} = 100%, t_R = 5.44 min; ^{1}H NMR ($CDCl_3$) δ 8.49 (d, J = 5.4 Hz, 1 H, Ar−H), 7.94 (d, J = 2.1 Hz, 1 H, Ar−H), 7.87 (d, J = 9.0 Hz, 1 H, Ar−H), 7.64−7.61 (m, 1 H, NH), 7.33−7.25 (m, 5 H, Ar−H), 7.19−7.14 (m, 6 H, Ar−H), 6.30 (d, J = 5.4 Hz, 1 H, Ar−H), 3.39−3.34 (m, 2 H, CH_2), 2.65−2.41 (m, 22 H, CH_2 and piperazine), 1.96−1.92 (m, 2 H, CH_2), 1.83−1.73 (m, 2 H, CH_2), 1.67−1.63 (m, 4 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 152.11, 128.55, 128.37, 128.30, 125.71, 124.66, 122.51, 98.45, 58.79, 56.92, 53.53, 53.36, 51.87, 44.48, 33.75, 28.77, 24.43, 23.31; MALDI-MS *m/z* 598.5 (M^+).

***N*⁴-[3-(4-{3-[Di(cyclohexylmethyl)amino]propyl}-piperazino)propyl]-7-chloroquinolin-4-amine (16c).** Compound **16c** was prepared from cyclohexane-1-carboxaldehyde (226 μL, 1.24 mmol, 3.0 equiv) by method C and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9) as a yellow oil (163 mg, 71% yield): R_f = 0.55 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); HPLC (C18N) P_{HPLC} = 100%, t_R = 18.23 min; HPLC (C18XT) P_{HPLC} = 100%, t_R = 5.18 min; ^{1}H NMR ($CDCl_3$) δ 8.50 (d, J = 5.4 Hz, 1 H, Ar−H), 7.94 (d, J = 2.1 Hz, 1 H, Ar−H), 7.91 (d, J = 9.0 Hz, 1 H, Ar−H), 7.32 (dd, J = 8.9, 2.2 Hz, 1 H, Ar−H), 7.71−7.68 (m, 1 H, NH), 6.31 (d, J = 5.4 Hz, 1 H, Ar−H), 3.40−3.35 (m, 2 H, CH_2), 2.67−2.63 (m, 10 H, CH_2 and piperazine), 2.47 (t, J = 7.4 Hz, 2 H, CH_2), 2.37 (t, J = 16.5 Hz, 2 H, CH_2), 2.10 (d, J = 7.0 Hz, 1 H, CH_2), 1.99−1.93 (m, 2 H, CH_2), 1.93−1.82 (m, 4 H, cyclohexyle), 1.67−1.60 (m, 8 H, cyclohexyle and CH_2), 1.43−1.36 (m, 2 H, cyclohexyle), 1.21−1.16 (m, 6 H, H-cyclohexyl), 0.88−0.75 (m, 4 H, cyclohexyl); ^{13}C NMR ($CDCl_3$) δ 152.15, 128.59, 124.63, 122.56, 98.43, 58.91, 53.68, 53.42, 53.13, 44.60, 36.28, 31.95, 26.98, 24.60, 26.27, 23.29; TOF-MS *m/z* 554.01 (M^+).

***N*⁴-[3-(4-{3-[Di(cyclopropylmethyl)amino]propyl}-piperazino)propyl]-7-chloroquinolin-4-amine (17c).** Compound **17c** was prepared from cyclopropane-1-carboxaldehyde (139 μL, 1.24 mmol, 3.0 equiv) by method C and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9) as a yellow oil (142 mg, 73% yield): R_f = 0.45 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); HPLC (C18N) P_{HPLC} = 100%, t_R = 13.92 min; HPLC (C18XT) P_{HPLC} = 100%, t_R = 3.12 min; ^{1}H NMR ($CDCl_3$) δ 8.50 (d, J = 5.4 Hz, 1 H, Ar−H), 7.95 (d, J = 2.1 Hz, 1 H, Ar−H), 7.89 (d, J = 9.0 Hz, 1 H, Ar−H), 7.63−7.60 (m, 1 H, NH), 7.33 (dd, J = 8.9, 2.1 Hz, 1 H, Ar−H), 6.32 (d, J = 5.5 Hz, 1 H, Ar−H), 3.41−3.36 (m, 2 H, Ar−H), 2.84−2.80 (m, 2 H, CH_2), 2.65−2.56 (m, 12 H, CH_2 and piperazine), 2.51−2.47 (m, 2 H, CH_2), 1.98−1.92 (m, 2 H, CH_2), 1.85−1.80 (m, 2 H, CH_2), 1.02−0.96 (m, 2 H, CH), 0.63−0.58 (m, 4 H, CH_2), 0.25−0.21 (m, 4 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 152.14, 128.61, 124.92, 122.67, 98.64, 58.91, 58.61, 56.83, 53.76, 53.52, 51.40, 44.63, 7.81, 4.44; TOF-MS *m/z* 470.4 (M^+).

***N*⁴-(3-{4-[3-(Diheptylamino)propyl]piperazino}propyl)-7-chloroquinolin-4-amine (18c).** Compound **18c** was prepared from heptanal (260 μL, 1.24 mmol, 3.0 equiv) by method C and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:1.4) as a yellow oil (99 mg, 43% yield): R_f = 0.55 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.14); HPLC (C18N) P_{HPLC} = 100%, t_R = 20.43 min; HPLC (C18XT) P_{HPLC} = 100%, t_R = 6.10 min; ^{1}H NMR ($CDCl_3$) δ 8.43 (d, J = 5.4 Hz, 1 H, Ar−H), 7.87 (d, J = 2.1 Hz, 1 H, Ar−H), 7.81 (d, J = 9.0 Hz, 1 H, Ar−H), 7.55−7.53 (m, 1 H, NH), 7.25 (dd, J = 8.9, 2.1 Hz, 1 H, Ar−H), 6.24 (d, J = 5.4 Hz, 1 H, Ar−H), 3.33−3.27 (m, 2 H, CH_2), 2.58−2.36 (m, 18 H, CH_2 and piperazine), 1.95−1.84 (m, 2 H, CH_2), 1.70−1.60 (m, 2 H, CH_2), 1.45−1.38 (m, 4 H, CH_2), 1.28−1.14 (m, 16 H, CH_2), 0.83−0.78 (m, 6 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 151.32, 127.76, 123.83, 121.68, 97.63, 57.97, 56.09, 53.21, 52.79, 52.57, 51.07, 43.66, 31.04, 28.46, 26.72, 25.81, 23.35, 22.54, 21.81, 13.29; MALDI-MS *m/z* 558.2 (M^+).

***N*⁴-(3-{4-[3-(Dibutylamino)propyl]piperazino}propyl)-7-chloroquinolin-4-amine (19c).** Compound **19c** was prepared from butyraldehyde (168 μL, 1.24 mmol, 3.0 equiv) by method C and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4-OH, 90:10:0.9) as a yellow oil (128 mg, 65% yield): R_f = 0.50 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); HPLC (C18N) P_{HPLC} = 100%, t_R = 13.79 min; HPLC (C18XT) P_{HPLC} = 100%, t_R = 3.24 min; ^{1}H NMR ($CDCl_3$) δ 8.50 (d, J = 5.4 Hz, 1 H, Ar−H), 7.94 (d, J = 2.1 Hz, 1 H, Ar−H), 7.89 (d, J = 8.9 Hz, 1 H, Ar−H), 7.70−7.67 (m, 1 H, NH), 7.32 (dd, J = 8.9, 2.1 Hz, 1 H, Ar−H), 6.32 (d, J = 5.5 Hz, 1 H, Ar−H), 3.41−3.36 (m, 2 H, CH_2), 2.66−2.44 (m, 18 H, CH_2 and piperazine), 1.97−1.93 (m, 2 H, CH_2), 1.78−1.73 (m, 2 H, CH_2), 1.53−1.25 (m, 8 H, CH_2), 0.96−0.91 (m, 6 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 152.07, 134.77, 128.53, 124.75, 98.49, 58.81, 56.73, 53.62, 53.48, 53.38, 51.73, 44.52, 28.33, 23.77, 23.38, 20.69, 14.07; MALDI-MS *m/z* 474.2 (M^+).

***N*⁴-(3-{4-[3-(Dipropylamino)propyl]piperazino}propyl)-7-chloroquinolin-4-amine (20c).** Compound **20c** was prepared from propionaldehyde (135 μL, 1.24 mmol, 3.0 equiv) by method C and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9) as a yellow oil (116 mg, 63% yield): R_f = 0.30 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); HPLC (C18N) P_{HPLC} = 100%, t_R = 12.85 min; HPLC (C18XT) P_{HPLC} = 99%, t_R = 3.53 min; ^{1}H NMR ($CDCl_3$) δ 8.50 (d, J = 5.4 Hz, 1 H, Ar−H), 7.94 (d, J = 2.1 Hz, 1 H, Ar−H), 7.89 (d, J = 9.1 Hz, 1 H, Ar−H), 7.64−7.61 (m, 1 H, NH), 7.32 (dd, J = 9.0, 2.2 Hz, 1 H, Ar−H), 6.31 (d, J = 5.4 Hz, 1 H, Ar−H), 3.39−3.34 (m, 2 H, CH_2), 2.66−2.40 (m, 16 H, CH_2 and piperazine), 1.96−1.93 (m, 2 H, CH_2), 1.74−1.69 (m, 2 H, CH_2), 1.53−1.43 (m, 4 H, CH_2), 0.90 (t, J = 7.3 Hz, 6 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 152.50, 128.91, 125.05, 122.91, 98.83, 59.18, 57.39, 56.43, 53.98, 53.76, 52.37, 44.87, 24.69, 23.73, 20.39, 12.37; MALDI-MS *m/z* 446.2 (M^+).

***N*⁴-(3-{4-[3-(Diethylamino)propyl]piperazino}propyl)-7-chloroquinolin-4-amine (21c).** Compound **21c** was prepared from acetaldehyde (96 μL, 1.24 mmol, 3.0 equiv) by method C and was obtained after TkLC (CH_2Cl_2/MeOH/NH_4-OH, 90:10:1.4) as a yellow oil (50 mg, 78% yield): R_f = 0.20 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); HPLC (C18N) P_{HPLC} = 100%, t_R = 13.22 min; HPLC (C18XT) P_{HPLC} = 100%, t_R = 3.09 min; ^{1}H NMR ($CDCl_3$) δ 8.42 (d, J = 5.4 Hz, 1 H, Ar−H), 7.86 (d, J = 2.1 Hz, 1 H, Ar−H), 7.81 (d, J = 8.9 Hz, 1 H, Ar−H), 7.54−7.21 (m, 1 H, NH), 7.25 (dd, J = 8.9, 2.1 Hz, 1 H, Ar−H), 6.24 (d, J = 5.4 Hz, 1 H, Ar−H), 3.33−3.27 (m, 2 H, CH_2), 2.59−2.48 (m, 16 H, CH_2 and piperazine), 2.48−2.37 (m, 2 H, CH_2), 1.91−1.83 (m, 2 H, CH_2), 1.73−1.63 (m, 2 H, CH_2), 1.02 (t, J = 7.1 Hz, 6 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 152.53, 128.96, 125.06, 122.88, 98.87, 59.18, 57.26, 53.99, 53.74, 51.03, 47.02, 44.87, 24.39, 23.76, 11.67; MALDI-MS *m/z* 418.3 (M^+).

***N*⁴-(3-{4-[3-(Dineopentylamino)propyl]piperazino}-propyl)-7-chloroquinolin-4-amine (22c).** Compound **22c** was prepared from trimethylacetaldehyde (270 μL, 1.65 mmol, 4.0 equiv) by method C and was obtained after TkLC (CH_2-Cl_2/MeOH/NH_4OH, 80:20:1.4) as a yellow solid (38 mg, 18% yield): R_f = 0.80 (CH_2Cl_2/MeOH/NH_4OH, 8:2:0.14); HPLC (C18N) P_{HPLC} = 98%, t_R = 14.30 min; HPLC (C18XT) P_{HPLC} = 100%, t_R = 2.24 min; ^{1}H NMR ($CDCl_3$) δ 8.42 (d, J = 5.4 Hz, 1 H, Ar−H), 7.87 (d, J = 2.1 Hz, 1 H, Ar−H), 7.83 (d, J = 8.9 Hz, 1 H, Ar−H), 7.65−7.62 (m, 1 H, NH), 7.25 (dd, J = 8.9, 2.1 Hz, 1 H, Ar−H), 6.24 (d, J = 5.4 Hz, 1 H, Ar−H), 3.32−3.30 (m, 2 H, CH_2), 2.59−2.34 (m, 14 H, CH_2 and piperazine), 2.16 (s, 4 H, CH_2), 1.91−1.86 (m, 2 H, CH_2), 0.86 (m, 18 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 152.27, 128.75, 125.14, 122.98, 98.80, 70.23, 59.18, 57.39, 56.74, 53.98, 53.75, 44.91, 29.57; MALDI-MS *m/z* 502.3 (M^+).

***N*⁴-(3-{4-[3-(Diisobutylamino)propyl]piperazino}-propyl)-7-chloroquinolin-4-amine (23c).** To a solution of isobutyraldehyde (169 μL, 1.24 mmol, 3.0 equiv) and $NaHB(OAc)_3$ (263 mg, 1.23 mmol, 3 equiv) in 1.5 mL a solution of compound **3** (150 mg, 0.41 mmol, 1 equiv) in 1.5 mL of dry CH_2Cl_2 was added dropwise. After the mixture was stirred at room temperature for 4 h, a total of 5 mL of aqueous 1 M NaOH was introduced. The mixture was left for 15 min, the organic layer was separated, and the aqueous layer was washed with CH_2Cl_2. Then the organic layers were mixed and

dried over $MgSO_4$, the solvent was evaporated, and the residue was purified by TkLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:0.9) to yield compound **23c** as a yellow oil (145 mg, 74% yield): R_f = 0.55 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.09); HPLC (C18N) P_{HPLC} = 100%, t_R = 13.73 min; HPLC (C18XT) P_{HPLC} = 100%, t_R = 3.13 min; ^{1}H NMR ($CDCl_3$) δ 8.49 (d, J = 5.4 Hz, 1 H, Ar−H), 7.93 (d, J = 2.1 Hz, 1 H, Ar−H), 7.89 (d, J = 9.0 Hz, 1 H, Ar−H), 7.70−7.67 (m, 1 H, NH), 7.31 (dd, J = 8.9, 2.1 Hz, 1 H, Ar−H), 6.31 (d, J = 5.4 Hz, 1 H, Ar−H), 3.39−3.35 (m, 2 H, CH_2), 2.66−2.60 (m, 10 H, CH_2 and piperazine), 2.50−2.45 (m, 2 H, CH_2), 2.40−2.35 (m, 2 H, CH_2), 2.06 (d, J = 7.2 Hz, 4 H, CH_2), 1.97−1.93 (m, 2 H, CH_2), 1.72−1.62 (m, 4 H, CH and CH_2), 0.89 (d, J = 6.6 Hz, 12 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 152.29, 128.70, 124.73, 122.64, 98.52, 64.08, 58.99, 57.26, 53.74, 53.52, 53.25, 44.68, 26.70, 24.69, 23.38, 21.07; MALDI-MS m/z 474.2 (M^+).

Acknowledgment. We express our thanks to Gérard Montagne for NMR experiments and to Dr. Steve Brooks for proofreading the manuscript. This work was supported by CNRS (Grants GDR 1077, IFR CNRS 63, UMR CNRS 8525) and Université de Lille II. Adina Ryckebusch is a recipient of fellowships from the Région Nord-Pas de Calais and CNRS.

References

(1) Factsheet No. 94; World Health Organization: Genever, Switzerland, 1998.
(2) White, N. J. Antimalarial drug resistance: the pace quickens. *J. Antimicrob. Chemother.* **1992**, *30*, 571−585.
(3) Dorn, A.; Stoffel, R.; Matile, H.; Bubendorf, A.; Ridley R. G. Malarial haemozoin/β haematin supports haem polymerization in the absence of protein. *Nature* **1995**, *374*, 269−271.
(4) Dorn, A.; Vippagunta, S. R.; Matile, H.; Jaquet, C.; Vennerstrom, J. L.; Ridley, R. G. An assessment of drug−hematin binding as a mechanism for inhibition of hematin polymerization by quinoline antimalarials. *Biochem. Pharmacol.* **1998**, *55*, 727−736.
(5) Ginsburg, H.; Famin, O.; Zhang, J.; Krugliak, M. Inhibition of Glutathione-Dependent Degradation of Heme by Chloroquine and Amodiaquine as a Possible Basis for Their Antimalarial Mode of Action. *Biochem. Pharmacol.* **1998**, *56*, 1305−1313.
(6) Loria, P.; Miller, S.; Foley, M.; Tilley, L. Inhibition of the peroxidative degradation of haem as the basis of action of chloroquine antimalarials. *Biochem. J.* **1999**, *339*, 363−370.
(7) Carlton, J. M.; Fidock, D. A.; Djimde, A.; Plowe, C. V.; Wellems, T. E. Conservation of a novel vacuolar transporter in *Plasmodium* species and its central role in chloroquine resistance of *P. falciparum*. *Curr. Opin. Microbiol.* **2001**, *4*, 415−420 (Review).
(8) Krogstad, D. J.; Gluzman, I. Y.; Kyle, D. E.; Oduola, A. M.; Martin, S. K.; Milhous, W. K.; Schlesinger, P. H. Efflux of chloroquine from *Plasmodium falciparum*: mechanism of chloroquine resistance. *Science* **1987**, *238*, 1283−1285.
(9) Ginsburg, H.; Stein, W. D. Kinetic modeling of chloroquine uptake by malaria-infected erythrocytes. *Biochem. Pharmacol.* **1991**, *41*, 1463−1470.
(10) Wünsch, S.; Sanchez, C. P.; Gekle, M.; GroBe-Wortmann, L.; Wiesner, J.; Lanzer, M. Differential stimulation of the Na^+/H^+ exchanger determines chloroquine uptake in *Plasmodium falciparum*. *J. Cell Biol.* **1998**, *140*, 335−345.
(11) Bray, P. G.; Janneh, O.; Raynes, K. J.; Mungthin, M.; Ginsburg, H.; Ward, S. A. Cellular uptake of chloroquine is dependent on binding to ferriprotoporphyrin IX and is dependent on NHE activity in *Plasmodium falciparum*. *J. Cell. Biol.* **1999**, *145*, 363−376.
(12) Reed, M. B.; Saliba, K. J.; Caruana; S. R.; Kirk, K.; Cowman, A. F. Pgh1 modulates sensitivity and resistance to multiple antimalarials in *Plasmodium falciparum*. *Nature* **2000**, *403*, 906−909.
(13) Vennerstrom, J. L.; Ellis, W. Y.; Ager, A. L., Jr.; Andersen, S. L.; Gerena, L.; Milhous, W. K. Bisquinolines. 1. *N*,*N*-Bis(7-chloroquinolin-4-yl)alkanediamines with potential against chloroquine-resistant malaria. *J. Med. Chem.* **1992**, *35*, 2129−2134.
(14) Raynes, K.; Galatis, D.; Cowman, A. F.; Tilley, L.; Deady, L. W. Synthesis and activity of some antimalarial Bisquinolines. *J. Med. Chem.* **1995**, *38*, 204−206.
(15) Ridley, R. G.; Matile, H.; Jaquet, C.; Dorn, A.; Hofheinz, W.; Leupin, W.; Masciadri, R.; Theil, F.-P.; Richter, W. F.; Girometta, M.-A.; Guenzi, A.; Urwyler, H.; Gocke, E.; Potthast, J.-M.; Csato, M.; Thomas, A.; Peters, W. Antimalarial activity of the bisquinoline *trans*-N^1,N^2-bis(7-chloroquinolin-4-yl)cyclohexane-1,2-diamine: comparison of the two stereoisomers and detailed evaluation of the *S*,*S* enantiomer, Ro 47-7737. *Antimicrob. Agents Chemother.* **1997**, *41*, 677−686.
(16) Cowman, A. F.; Deady, L. W.; Deharo, E.; Desneves, J.; Tilley, L. Synthesis and activity of some antimalarial bisquinolinemethanols. *Aust. J. Chem.* **1997**, *50*, 1091−1096.
(17) Basco, L. K.; Ruggeri, C.; Le Bras, J. *Molécules Antipaludiques* (Antiplasmodial Molecules); Masson: Paris, 1994; pp 115−120.
(18) Girault, S.; Grellier, P.; Berecibar, A.; Maes, L.; Mouray, E.; Lemière, P.; Debreu, M. A.; Davioud-Charvet, E.; Sergheraert, C. Antimalarial, antitrypanosomal, and cytotoxicity of bis(9-amino-6-chloro-2-methoxyacridines): influence of the linker. *J. Med. Chem.* **2000**, *43*, 2646−2654.
(19) Girault, S.; Grellier, P.; Berecibar, A.; Maes, L.; Lemière, P.; Mouray, E.; Davioud-Charvet, E.; Sergheraert, C. Antiplasmodial Activity and Cytotoxicity of Bis-, Tris- and Tetraquinolines with Linear or Cyclic Amino Linkers. *J. Med. Chem.* **2001**, *44*, 1658−1665.
(20) Carlier, P. R.; Chow, E. S.-H.; Han, Y.; Liu, J.; El Yazal, J.; Pang, Y.-P. Heteromeric Tacrine-Based Acetylcholinesterase Inhibitors: Investigating Ligand-Peripheral Site Interactions. *J. Med. Chem.* **1999**, *42*, 4232−4238.
(21) Ryckebusch, A.; Deprez-Poulain, R.; Debreu-Fontaine, M.-A.; Vandaele, R.; Mouray, E.; Grellier, P.; Sergheraert, C. Parallel synthesis and antimalarial activity of a sulfonamide library. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2595−2598.
(22) Yayon, A.; Cabantchik, Z. I.; Ginsburg, H. Identification of the acidic compartment of *Plasmodium falciparum*-infected human erythrocytes as the target of antimalarial drug chloroquine. *EMBO J.* **1984**, *3*, 2695−2700.
(23) Geary, T. G.; Jensen, J. B.; Ginsburg, H. Uptake of [^{3}H]-chloroquine by drug-sensitive and -resistant strains of the human malaria parasite *Plasmodium falciparum*. *Biochem. Pharmacol.* **1986**, *35*, 3805−3812.
(24) Hawley, S.; Bray, P. C.; O'Neill, P. M.; Park, B. K.; Ward, S. A. Amodiaquine accumulation in *Plasmodium falciparum* as a possible explanation for its superior antimalarial activity over chloroquine. *Mol. Biochem. Parasitol.* **1996**, *80*, 15−25.
(25) Vacuolar accumulation ratios (VARs) were calculated mathematically from the equation below: VAR = $[1 + 10^{(pKa1-pHv)} + 10^{(pKa1+pKa2-2pHv)} + 10^{(pKa1+pKa2+pKa3-3pHv)} + 10^{(pKa1+pKa2+pKa3+pKa4-4pHv)}]/[1 + 10^{(pKa1-pHo)} + 10^{(pKa1+pKa2-2pHo)} + 10^{(pKa1+pKa2+pKa3-3pHo)} + 10^{(pKa1+pKa2+pKa3+pKa4-4pHo)}]$, where pHv is the pH inside the vacuole (assumed to be pH 5.0) and pHo is the external pH (assumed to be pH 7.4) This equation is from a derivation of the Henderson−Hasselbach equation, based on predicted values of drug pK_a according to previous studies of Hawley et al. (see reference below). Values of pK_a were calculated using ACD/pKa dB software from Avanced Chemistry Development Inc., Toronto, Canada. Hawley, S.; Bray, P. C.; O'Neill, P. M.; Park, B. K.; Ward, S. A. The role of drug accumulation in 4-aminoquinoline antimalarial potency. The influence of structural substitution and physicochemical properties. *Biochem. Pharmacol.* **1996**, *52*, 723−733.
(26) Ridley, R. G.; Hofheinz, W.; Matile, H.; Jaquet, C.; Dorn, A.; Masciadri, R.; Jolidon, S.; Richter, W. F.; Guenzi, A.; Girometta, M.-A.; Urwyler, H.; Huber, W.; Thithong, S.; Guenzi, A.; Peters, W. 4-Aminoquinoline analogs of chloroquine with shortened side chains retain activity against chloroquine-resistant *Plasmodium falciparum*. *Antimicrob. Agents Chemother.* **1996**, *40*, 1846−1854.
(27) Trager, W.; Jensen, J. B. Human Malarial Parasites in Continuous Culture. *Science* **1976**, *193*, 673−677.
(28) Desjardins, R. E.; Canfield, C. J.; Haynes, J. D.; Chulay, J. D. Quantitative Assessment of Antimalarial Activity in vitro by a Semiautomated Microdilution Technique. *Antimicrob. Agents Chemother.* **1979**, *16*, 710−718.
(29) Mossman, T. Rapid Colorimetric Assay for Cellular Growth and Survival: Application to Proliferation and Cytotoxicity Assays. *J. Immunol. Methods* **1983**, *65*, 55−63.
(30) Fitch, C. D.; Cai, G.; Chen, Y.-F.; Shoemaker, J. D. Involvement of lipids in ferriprotoporphyrin IX polymerization in malaria. *Biochim. Biophys. Acta* **1999**, *1454*, 31−37.
(31) Ayad, F.; Tilley, L.; Deady, L.-W. Synthesis, Antimalarial Activity and Inhibition of Haem Detoxification of Novel Bisquinolines. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2075−2077.
(32) Zamora, J. M.; Pearce, H. L.; Beck, W. T. Physical chemical properties shared by compounds that modulate multidrug resistance in human leukaemic cells. *Mol. Pharmacol.* **1988**, *33*, 454−462.

JM020960R