Structure−Activity Relationship of Quinoline Derivatives as Potent and Selective α_{2C}-Adrenoceptor Antagonists

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Starting from two acridine compounds identified in a high-throughput screening campaign (**1** and **2**, Table 1), a series of 4-aminoquinolines was synthesized and tested for their properties on the human α_2-adrenoceptor subtypes (α_{2A}, α_{2B}, and α_{2C}). A number of compounds with good antagonist potencies against the α_{2C}-adrenoceptor and excellent subtype selectivities over the other two subtypes were discovered. For example, (*R*)-{4-[4-(3,4-dimethylpiperazin-1-yl)phenylamino]quinolin-3-yl}methanol **6j** had an antagonist potency of 8.5 nM against, and a subtype selectivity of more than 200-fold for, the α_{2C}-adrenoceptor. Investigation of the structure−activity relationship identified a number of structural features, the most critical of which was an absolute need for a substituent in the 3-position of the quinoline ring. The 3-position on the piperazine ring was also found to play an appreciable role, as substitutions in that position exerted a significant and stereospecific beneficial effect on the α_{2C}-adrenoceptor affinity and potency. Replacing the piperazine ring proved difficult, with 1,4-diazepanes representing the only viable alternative.

Introduction

The pleiotropic biological functions exerted in humans by the endogenous catecholamines epinephrine and norepinephrine are mediated by the adrenergic receptor family, which historically has been subdivided into α_1-adrenoceptor, α_2-adrenoceptor and β-adrenoceptor.[1] Each of these three different types of adrenoceptor in turn consists of three separate subtypes. Thus, in total, there are nine distinct human adrenoceptors, encoded by nine individual genes, that belong to the superfamily of G protein-coupled receptors.[1]

Among the three α_2-adrenoceptor subtypes, the α_{2A}-adrenoceptor is the most prevalent one, with expression in a number of peripheral and central tissues.[2] In contrast, the α_{2B} and the α_{2C} subtypes have a more limited distribution, with the α_{2B}-adrenoceptor being present mostly in the periphery[2] and the α_{2C}-adrenoceptor being concentrated in particular central nervous system (CNS) areas, such as olfactory tubercles, the striatum, and the hippocampus.[3,4] This has led to speculation that the α_{2C}-adrenoceptor may have a special role in the CNS,[5] although it has recently been suggested that it may also have a significant role in certain pathologies of the cardiovascular system.[6] In addition, it has been proposed that α_{2C}-adrenoceptor antagonism may play a part in the therapeutically beneficial effects of certain antipsychotic compounds, such as, for example, that of clozapine.[7,8] However, due to the fact that antipsychotic drugs currently in clinical use tend to act on a multiplicity of pharmacological targets, it has so far not been possible to elucidate the contribution of α_{2C}-antagonism to their pharmacodynamic profile in a more precise manner.

Unfortunately, the delineation of the roles of individual α_2-adrenoceptor subtypes is still hampered by the scarcity or outright lack of sufficiently subtype-selective agonists and antagonists.[9] In the absence of such compounds, the assignment of specific physiological and pathological functions towards particular subtypes has relied on the use of genetically modified mice, in which the subtype of interest has either been knocked out or overexpressed.

Evidence from mice with knockout as well as overexpressing mutations of the α_{2C}-adrenoceptor suggests that this subtype may have an important role in the modulation of central monoamine neurotransmission, especially under stressful conditions.[2] Genetic deletion of the α_{2C}-adrenoceptor produced antidepressant-like effects in the forced swimming test,[10] an experimental paradigm in rodents widely used for the screening of antipsychotic compounds,[11] while the overexpression of the α_{2C}-adrenoceptor had the opposite effect. The prepulse inhibition of the startle reflex, an experimental model relating to the so-called sensorimotor gating phenomenon,[12] is being used for the screening of antipsychotic-like compounds. In genetically modified mice, the α_{2C}-adrenoceptor knockout and the α_{2C}-adrenoceptor overexpressing mutations were associated with lower and higher levels of prepulse inhibition of the startle reflex, respectively.[13] On the basis of the studies mentioned above, it has been suggested that α_{2C}-adrenoceptor-specific ligands might have therapeutic use in certain psychiatric disorders such as depression and schizophrenia.[5]

Given the attractive therapeutic potential of α_{2C}-adrenoceptor ligands, we decided to launch a discovery project for such compounds. In this paper we report on the identification of a novel class of α_{2C}-adrenoceptor antagonists in the form of 4-aminoquinoline-based compounds and aspects of their structure−activity relationship on human α_{2C}-adrenoceptors.

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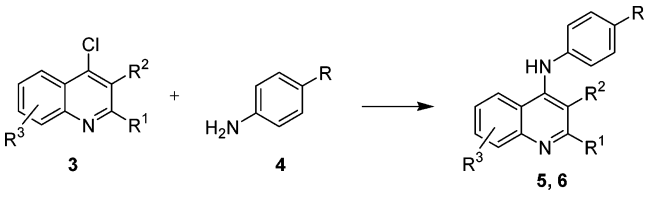
Scheme 1[a]



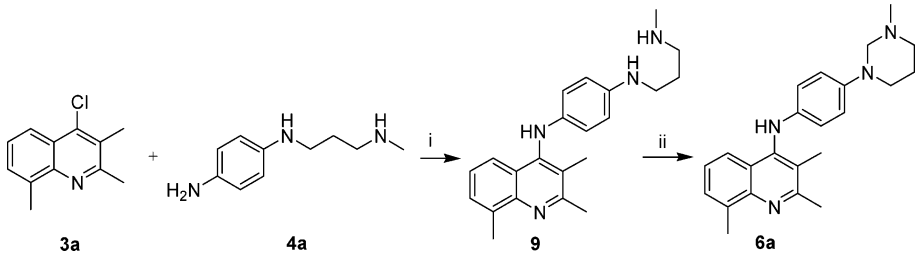
[a] Reagents: HCl or *p*-TsOH·H_2O, MeOH, 60 °C or MW 130 °C.

Chemistry. The quinoline derivatives **5** and **6** in the present study were prepared via a generic reaction that consisted of the condensation of 4-chloroquinolines **3** with *p*-substituted anilines **4** in methanol and in the presence of an acid (Scheme 1). The same scheme was also used for the pyridine compound **7** and the tetrahydroquinoline compound **8**. The majority of reactions were conducted by use of microwave irradiation in a very fast and clean manner. Addition of an acid was important in those reactions where there was an electron-donating alkyl or aryl substituent in the 3-position of the quinoline ring. This coupling reaction yielded the final product for most compounds, except when R was *N*-methylhexahydropyrimidine (**6a**) or when R^1 or R^2 was hydroxymethyl or hydroxyethyl (**6e**−**o**).

To obtain the hexahydropyrimidine derivative **6a** (Scheme 2), the intermediate **9** was cyclized with formaldehyde in formic acid.[15] Building block **4a** has two other possible reactive sites when reacting with **3a**. However, in the presence of an acid, the coupling reaction takes place selectively at the primary aromatic amine.[16] The regioselectivity of this coupling reaction at low pH was also utilized in the synthesis of the unsubstituted piperazine derivative **6k** (Scheme 3). In this case, the reaction of **3b** and **4b** yielded the ester derivative **10**, which was then reduced with lithium aluminum hydride to the intended hydroxymethyl compound **6k**. The same reduction of ester- or ketone-containing substituents on the quinoline ring was also performed as the last step in all cases where hydroxymethyl or 1-hydroxyethyl substituents were desired (**6e**−**o**).

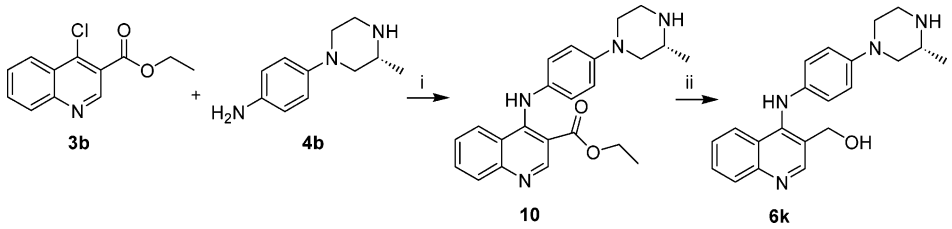
The formation of quinoline rings en route to building blocks **3a** and **3c**−**q** was conducted by modifying the original procedures of Conrad and Limpach[17] and Gould and Jacobs.[18] For this purpose, ethyl acetoacetates **11a**−**e** (Scheme 4) or diethyl oxalopropionate (Scheme 5) were reacted with anilines to afford the corresponding imines, which were then cyclized in diphenyl ether. The obtained 4-hydroxyquinolines **12a**−**p** were subsequently chlorinated to 4-chloroquinolines **3a** and **3c**−**q** with thionyl chloride in the presence of *N*,*N*-dimethylformamide (DMF).[19] To obtain 4-chloro-3-methylquinoline **3r**, the 4-hydroxy-3-methylquinoline-2-carboxylic acid ethyl ester **12p** was hydrolyzed and decarboxylated to **12q** before chlorination with phosphorus oxychloride.[20] The 5,6,7,8-tetrahydroquinoline derivative **13** (Scheme 6) was obtained by selective

Scheme 2[a]



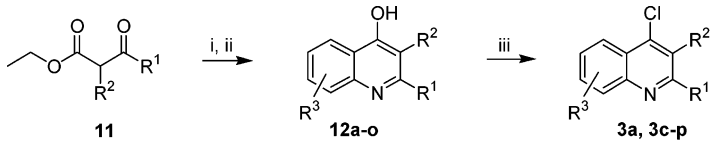
[a] Reagents: (i) HCl, MeOH, MW 120 °C; (ii) formaldehyde, formic acid, 80 °C.

Scheme 3[a]



[a] Reagents: (i) *p*-TsOH·H_2O, MeOH, MW 130 °C; (ii) $LiAlH_4$, THF.

Scheme 4[a]



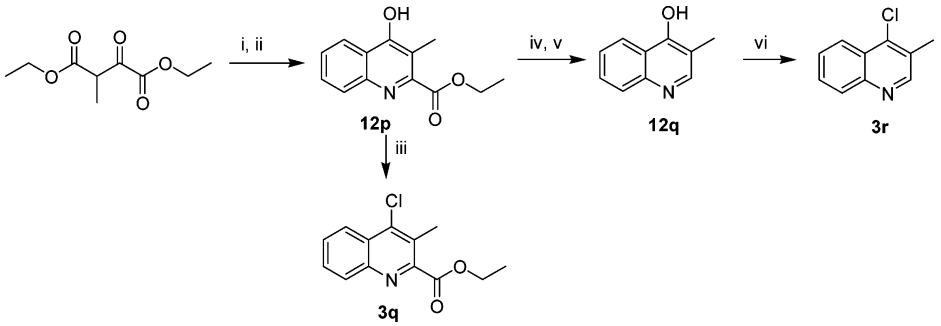
	R^1	R^2
11a	Me	Me
11b	Me	Et
11c	Me	*i*-Pr
11d	Me	Ph
11e	Me	Bn

		R^1	R^2	R^3
12a	**3a**	Me	Me	8-Me
12b	**3c**	Me	Me	H
12c	**3d**	Me	Et	H
12d	**3e**	Me	*i*-Pr	H
12e	**3f**	Me	Ph	H
12f	**3g**	Me	Bn	H
12g	**3h**	Me	Me	7-Me, 8-Me
12h	**3i**	Me	Me	7-Me

		R^1	R^2	R^3
12i	**3j**	Me	Me	5-Me
12j	**3k**	Me	Me	5-Me, 7-Me
12k	**3l**	Me	Me	5-Me, 8-Me
12l	**3m**	Me	Me	7-Cl
12m	**3n**	Me	Me	5-Cl
12n	**3o**	Me	Me	6-F
12o	**3p**	Me	Et	8-Me

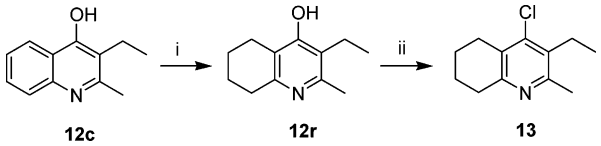
[a] Reagents: (i) (optionally R^3-substituted) aniline, *p*-TsOH·H_2O, toluene; (ii) Ph_2O, 250 °C; (iii) $SOCl_2$, DMF, 80 °C.

Scheme 5[a]



[a] Reagents: (i) aniline, *p*-TsOH·H_2O, toluene; (ii) Ph_2O, 250 °C; (iii) $SOCl_2$, DMF, 80 °C; (iv) 2 M NaOH, 100 °C; (v) Ph_2O, 250 °C; (vi) $POCl_3$, 105 °C.

Scheme 6[a]



[a] Reagents: (i) H_2, Ni, MeOH, 20 bar, 70 °C; (ii) $SOCl_2$, DMF, 80 °C.

hydrogenation of the quinoline **12c** in the presence of a nickel catalyst[21] to produce the corresponding 5,6,7,8-tetrahydroquinoline **12r**, which was then chlorinated.

To obtain building blocks with ester functions in the 3-position of the quinoline ring (Scheme 7), **15a** was reacted with anilines in pyridine to afford 2-phenylaminomethylenemalonic acid diethyl esters, which were cyclized in diphenyl ether. The obtained 4-hydroxyquinolines **12s**−**u** were chlorinated to yield **3b**, **3s**, and **3t**, respectively. The same scheme was applied when combinations of a methyl substituent in the 2-position with an ester (**3u**) or a ketone (**3v**) in the 3-position of the quinoline ring were desired. The starting materials **15b** and **15c** were obtained from triethyl orthoacetate by reacting it with diethyl malonate **14a** and ethyl acetoacetate **14b**, respectively.[22] Compounds **15b** and **15c** were reacted with aniline followed by cyclization to obtain **12v** and **12w**, which were then chlorinated to yield the building blocks **3u** and **3v**, respectively.

The only pyridine intermediate in the present study, 4-chloro-3,5-dimethylpyridine **16**, was obtained in hydrochloric acid salt form by heating 3,5-lutidine in thionyl chloride (Scheme 8).[23]

The building blocks **4b**−**f** (Scheme 9) were obtained by reacting the piperazines **17a**−**d** with 1-chloro-4-nitrobenzene in DMSO in the presence of potassium carbonate.[24] The resulting 4-piperazine-1-nitrophenyl derivatives were optionally methylated to afford **18a**−**f** and then reduced to the corresponding anilines (**4b**−**g**) either with hydrazine or with hydrogen gas in the presence of a palladium on carbon catalyst.

This same strategy was also applied in those cases where the piperazine ring itself was synthesized before being coupled with 1-chloro-4-nitrobenzene (Scheme 10), where the piperazine ring was built after a reaction with 1-chloro-4-nitrobenzene (Scheme 11) or where the piperazine moiety was replaced by an alkyl chain (Schemes 12 and 13).

For the preparation of **4h** (Scheme 10), the starting material hexahydropyrido[1,2-*a*]pyrazin-1-one (**19**) was synthesized via the literature method.[25] Compound **19** was reacted with 1-chloro-4-nitrobenzene and the resulting nitro derivative was reduced with hydrazine.

To obtain the 3,3-dimethylpiperazine derivative **4i** (Scheme 11), 2-methylpropane-1,2-diamine was coupled with 1-chloro-4-nitrobenzene followed by alkylation of the primary amino group with ethyl bromoacetate and cyclization with the aid of trifluoroacetic acid (TFA).[26] The cyclic amide **22** thus prepared was then reduced first with borane−tetrahydrofuran (THF) complex and subsequently with hydrazine.

For the preparation of the chain derivatives **4j** and **4k** (Scheme 12), 2-aminoethanol was coupled with 1-chloro-4-nitrobenzene to obtain 2-(4-nitrophenyl)aminoethanol (**23**). The hydroxy group was mesylated, followed by amination with diethylamine or pyrrolidine, and the resulting nitro derivatives were reduced with hydrazine.

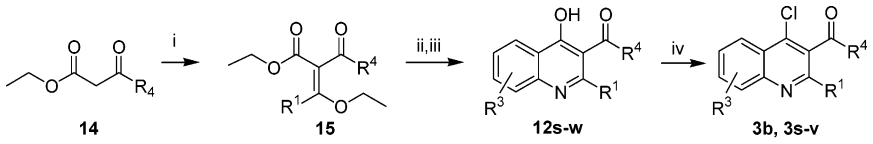
The synthesis of building block **4a** (Scheme 13) was started by coupling propane-1,3-diamine with 1-chloro-4-nitrobenzene, followed by concomitant reductive alkylation[27] of the primary amino function and ring closure. The obtained 1-methylhexahydropyrimidine ring of **25** was inadvertently opened during hydrazine treatment, resulting in formation of **4a**. However, the ring was cyclized again after **4a** was coupled with **3a** (Scheme 2).

Results and Discussion

The starting point for the current study was the two acridine compounds shown in Table 1, which had been identified via a screening campaign as α_{2C}-adrenoceptor selective antagonists and are described in more detail in a patent application.[14] As such, **1** and **2** did already have a sufficiently large (50−100-fold) degree of subtype selectivity and their affinity for the α_{2C}-adrenoceptor was reasonable. However, both hit compounds were acridine-based structures and acridines, while being of interest as antitumor[28] and antiseptic[29] agents, are expected to have genotoxic properties due to their ability to intercalate into DNA strands.[30] In line with this, **1** was found to show activity in the Ames test. The propensity of acridines for DNA intercalation is considered to be due to the size and planar nature of their ring system and its high degree of lipophilicity.[31] The goal of the present study therefore was to find replacements for the screening hits that would retain their α_{2C}-adrenoceptor selectivity but would move away from the acridine 3-ring system toward a less planar and less lipophilic alternative. For this purpose, the acridine ring was replaced with a quinoline, which in addition was endowed with a polar ring substituent. These two structural features led to the identification of novel compounds that, while devoid of mutagenic activity in the Ames test (data not shown), displayed comparable or better antagonist potencies against, and subtype selectivities for, the human α_{2C}-adrenoceptor than the initial hit molecules.

To guide the synthetic efforts, the binding affinities (K_i) and, where warranted, the antagonism potencies (K_B) of the compounds were determined. Both pharmacological properties were found to be in good agreement with each other throughout the

Scheme 7[a]



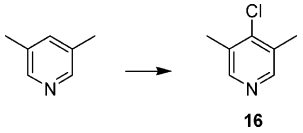
	R^4
14a	OEt
14b	Me

	R^1	R^4
15a	H	OEt
15b	Me	OEt
15c	Me	Me

		R^1	R^3	R^4
12s	**3b**	H	H	OEt
12t	**3s**	H	7-Cl	OEt
12u	**3t**	H	6-F	OEt
12v	**3u**	Me	H	OEt
12w	**3v**	Me	H	Me

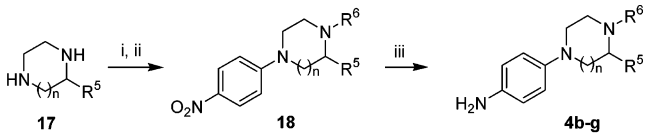
[a] Reagents: (i) triethyl orthoacetate, Ac_2O, $ZnCl_2$, 140 °C; (ii) (optionally R^3-substituted) aniline, pyridine, 115 °C; (iii) Ph_2O, 250 °C; (iv) $SOCl_2$, DMF, 80 °C or $POCl_3$, 105 °C.

Scheme 8[a]



[a] Reagents: $SOCl_2$, 80 °C.

Scheme 9[a]

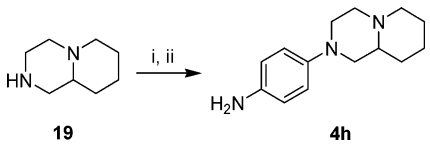


	n	R^5
17a	1	Me (racemic)
17b	1	Me (*R*)
17c	1	Me (*S*)
17d	2	H

		n	R^5	R^6
18a	**4b**	1	Me (*R*)	H
18b	**4c**	1	Me (racemic)	Me
18c	**4d**	1	Me (*R*)	Me
18d	**4e**	1	Me (*S*)	Me
18e	**4f**	2	H	Me
18f	**4g**	1	H	Me

[a] Reagents: (i) 1-chloro-4-nitrobenzene, K_2CO_3, DMSO, 80 °C; (ii) MeI, TBAI, NaOH, toluene, 60 °C; (iii) hydrazine hydrate, 10% Pd/C, EtOH, 90 °C or H_2, 10% Pd/C, EtOH, 20 bar.

Scheme 10[a]



[a] Reagents: (i) 1-chloro-4-nitrobenzene, K_2CO_3, DMSO, 50 °C; (ii) hydrazine hydrate, 10% Pd/C, EtOH, 90 °C.

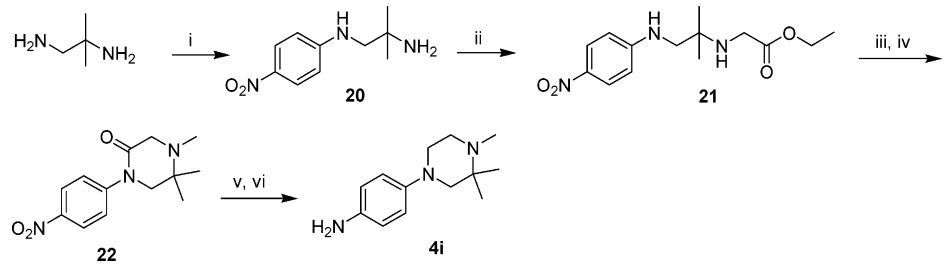
study. More specifically, in the case of the α_{2C}-adrenoceptor subtype a sufficiently large number of 36 K_i and K_B pairs were collected such that a statistical analysis could be attempted. This analysis was used to test whether differences between binding affinities and antagonist potencies were due to typical scattering of experimental values or whether there was any sign of a bias that might indicate more than one type of ligand−receptor interaction. The results of this analysis indicated a normal distribution of experimental scatter (data not shown). While this does not represent definitive proof, it leads us to assume that at least as far as the α_{2C}-adrenoceptor subtype is concerned the compounds most likely interact in a similar manner with the same binding site on the receptor.

The simple removal of one ring from the three-ring system, that is, replacing the acridine with a quinoline, did not prove feasible, as this caused a large drop in binding affinity for the α_{2C}-adrenoceptor accompanied by a complete loss of subtype selectivity (**5a**, Table 2). However, the presence of a three-ring moiety turned out not to be an absolute requirement, as its replacement with a quinoline ring with short alkyl substituents in the 2- and 3-positions (**5b**, **5c**) fully retained the affinity and subtype selectivity for the α_2-adrenoceptor seen in the acridine hit compounds. Even sterically quite large substituents, such as an isopropyl (**5d**), a phenyl (**5e**), or a benzyl (**5f)** in the 3-position of the quinoline ring, were tolerated quite well by the α_{2C}-adrenoceptor. Nonetheless, in the case of the benzyl (**5f**) a significant portion of the α_{2C}-subtype selectivity was lost due to a considerable gain in affinity for the other two α_2-adrenoceptor subtypes, in particular the α_{2B}-adrenoceptor. Of the substituents in the 2- and 3-positions of the quinoline ring, the ones in the 3-position appeared to be much more critical, as the presence of a 2-substituent alone (**5g)** resulted in an affinity profile for the α_2-subtypes that was essentially the same as had been observed for the bare quinoline ring (**5a**). We also tested whether the replacement of both flanking rings in the acridine moiety of **1** by appropriately placed methyl substituents on a pyridine ring would be feasible. However, this turned out not to be the case, as the corresponding compound (**7**) showed rather poor affinity for all the α_2-adrenoceptor subtypes. Somewhat more surprisingly, it was then also observed that replacement of the quinoline by a tetrahydroquinoline ring (**8** versus **5b**) was not possible either. The reason for this result is not clear, but it might indicate a need for an aromatic interaction of the quinoline moiety with the receptor.

After establishing the suitability of quinoline as a substitute for acridine, we started to explore the piperazine component. Compared to the initial hit compounds, **8** had an additional 3-methyl substituent in the piperazine ring. This feature was tested in combination with a number of differently substituted quinoline moieties and systematically resulted in a substantial gain in affinity and selectivity for the α_{2C}-adrenoceptor. A direct example is presented in **5h** (Table 3), which shows 7-fold better affinity for the α_{2C}-adrenoceptor than **5e** (Table 2). The gain in affinity achieved with 3-piperazine substituents was not restricted to the methyl group; it could also be observed by enlarging the 3-and 4-methyl substituents of the piperazine to a fused ring (**5i**, Table 3). In the case of **5i**, gains of 15-fold in affinity for, and 60-fold in antagonist potency against, the α_{2C}-adrenoceptor were obtained relative to **5b** (Table 2). Even introduction of a second methyl substituent in the 3-position of the piperazine ring was possible without negative consequences on the affinity for, or antagonist potency against, the α_{2C}-adrenoceptor (**5j** versus **5k**). The latter two compounds also confirm the notion mentioned earlier that a substitution in the 2-position of the quinoline ring is not necessary to achieve good α_{2C}-adrenoceptor affinity and subtype selectivity.

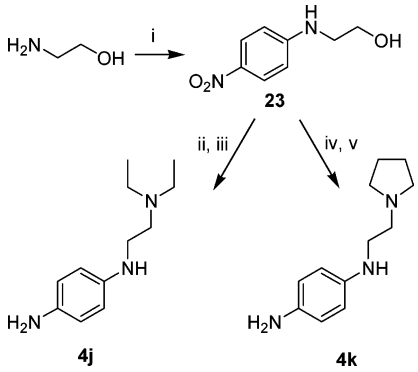
As the addition of a substituent in the 3-position of the piperazine ring introduced a chiral center, the affinity profile

Scheme 11[a]



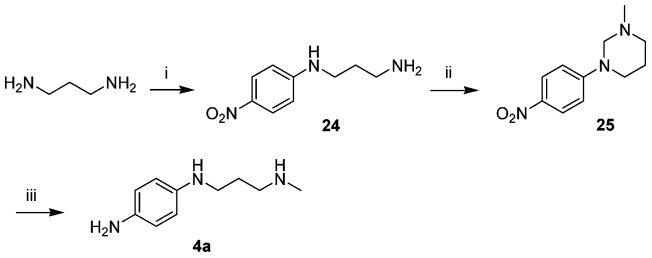
[a] Reagents: (i) 1-chloro-4-nitrobenzene, MW 200 °C; (ii) NaH, ethyl bromoacetate, DMF; (iii) TFA, DCM, 50 °C; (iv) NaH, MeI, DMF; (v) borane−THF complex, THF and then HCl; (vi) hydrazine hydrate, 10% Pd/C, EtOH, 90 °C.

Scheme 12[a]



[a] Reagents: (i) 1-chloro-4-nitrobenzene, 40 °C; (ii) TEA, methanesulfonyl chloride, DCM and then diethylamine, TEA, DBU, DCM; (iii) hydrazine hydrate, 10% Pd/C, EtOH, 90 °C; (iv) TEA, methanesulfonyl chloride, DCM and then pyrrolidine, TEA, DBU, DCM; (v) hydrazine hydrate, 10% Pd/C, EtOH, 90 °C.

Scheme 13[a]



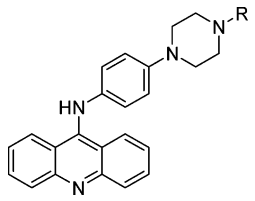
[a] Reagents: (i) 1-chloro-4-nitrobenzene, MW 200 °C; (ii) formaldehyde, formic acid, 80 °C; (iii) hydrazine hydrate, 10% Pd/C, EtOH, 90 °C.

of the two enantiomers for the human α_2-adrenoceptor subtypes was studied. It turned out that there indeed was a difference of about 1 order of magnitude between stereoisomer pairs (**5m** versus **5n** and **5p** versus **5q**) and that the *R*-enantiomer had the higher affinity for, and antagonist potency against, the α_{2C}-adrenoceptor. Interestingly, it also appeared that this effect of the chiral center was limited to the α_{2C}-adrenoceptor subtype, as the outcomes with the optically pure enantiomers on the other two receptor subtypes were either not affected or were clearly much less affected.

To study the role of the piperazine ring, it was replaced with ring systems or acyclic motifs that maintained a basic amino function at roughly the same distance from the central phenyl ring as the aliphatic amino group in the piperazine-containing compounds. The results for these compounds are presented in Table 4.

If the distance was shorter than in piperazine, as was the situation with the hexahydropyrimidine **6a** (Table 4), the affinity was lost. When the distance was kept about the same, but the ring character of piperazine was removed, the affinity was

Table 1. Binding Affinity for α_2-Adrenoceptor of the Initial Acridine Hit Compounds Identified in a HTS Campaign[a]



	R	α_{2A} (K_i, nM)	α_{2B} (K_i, nM)	α_{2C} (K_i, nM)
1	Me	3200 ± 100	1500 ± 100	28 ± 2
2	Et	3600 ± 300	1200 ± 100	37 ± 5

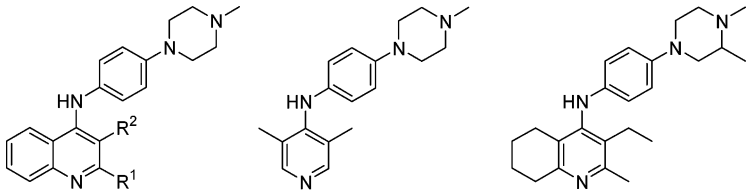
[a] The K_i values (nanomolar) represent the affinities of the compounds for the cloned human α_2-adrenoceptor subtypes. More details on the compounds are provided in a patent application.[14] The K_i numbers (given as mean values ± SEM, $N > 3$ in all cases) were determined in competition binding assays with ^{3}H-rauwolscine and membranes of S115 cells expressing cloned human α_2-adrenoceptor.

significantly decreased but not totally lost (**6b** and **6c**). Compound **6b** can be considered to be an opened *N*-ethyl-substituted piperazine ring. Viewed from this perspective, **6b** can thus be compared to the acridine screening hit **2**, which possesses an ethyl substituent in the 4-piperazine position. The only alternative to a piperazine that resulted in similar affinities and subtype selectivities for the α_{2C}-adrenoceptor was *N*-methyl-1,4-diazepane, as illustrated by compound **6d**.

In a further exploration, the effect of adding small substituents to the phenyl ring side of the quinoline core was tested. As can be seen from the pharmacological results of **5r** (Table 3), a methyl in the 8-position was well tolerated and this substituent gave a reasonable affinity when located in the 7-position (**5o**). However, it extracted a clear toll on the affinity for the α_{2C}-adrenoceptor when placed in the 5-position (**5s**). In accordance with these observations, the combination of two methyl substituents in the 7- and 8-positions (**5l**) was well accepted by the receptor, whereas the combinations of the 5- and 7-positions (**5t**) or the 5- and 8-positions (**5u**) resulted in increasing losses in affinity. The same pattern of tolerability in the 7-position (**5v**) but deterioration in the 5-position (**5w**) was also obtained when a chlorine instead of a methyl was used as the substituent. A fluorine substituent in the 6-position (**5x**) was well accepted by the receptor.

As mentioned above, the propensity of compounds containing structural features such as acridine rings to intercalate into DNA strands and thereby cause genotoxic effects is considered to be driven by the size of the planar ring system and its lipophilic nature. For this reason, the possibility of introducing polar substituents into the quinoline ring was investigated. As can be seen from the data presented in Table 5, introduction of a hydroxymethyl (**6e**, **6f**) or a 1-hydroxyethyl (**6g**) in the 3-position of the quinoline ring was well tolerated by the α_{2C}-

Table 2. Binding and Functional Activities of Compounds **5a**−**g**, **7**, and **8** for α_2-Adrenoceptor Subtypes

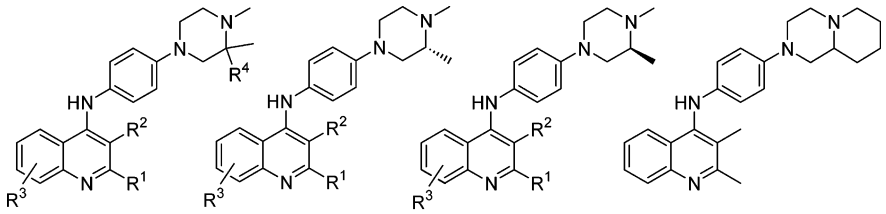


5a-g **7** **8**

			K_i[a] (nM)			K_B[b] (nM)		
no.	R^1	R^2	α_{2A}	α_{2B}	α_{2C}	α_{2A}	α_{2B}	α_{2C}
5a	H	H	720 ± 60	3800 ± 100	1700 ± 600	nt	nt	nt
5b	Me	Me	2210 ± 20	>5000 [3]	35 ± 3	5900 ± 1900	>3000 [3]	61 ± 8
5c	Me	Et	1100 ± 100	>10 000 [3]	25 ± 3	2000 ± 400	16 000 ± 2000	22 ± 10
5d	Me	*i*-Pr	1700 ± 300	3900 ± 300	52 ± 11	3700 ± 800	13 000 ± 3000	87 ± 23
5e	Me	Ph	1700 ± 200	>10 000 [3]	35 ± 3	1600 ± 400	>3000 [3]	48 ± 7
5f	Me	Bn	580 ± 70	96 ± 22	35 ± 3	590 ± 10	220 ± 50	27 ± 3
5g	Me	H	500 ± 60	3700 ± 1300	690 ± 280	nt	nt	nt
7			3600 ± 100	>30 000 [3]	>5000 [3]	nt	nt	nt
8			630 ± 125	2980 ± 390	110 ± 10	1830 ± 160	10 500 ± 670	150 ± 15

[a] The K_i values (nanomolar) were derived from competition binding assays and represent the affinities of the compounds for the cloned human α_2-adrenoceptor subtypes. [b] The K_B values (nanomolar) were determined in ^{35}S-GTPγS binding assays against the agonist epinephrine and represent the antagonist potencies of the compounds against the cloned human α_2-adrenoceptor subtypes. Data are given as mean values ± SEM and, unless indicated otherwise in brackets, are averaged from a minimum of three repeat experiments. Numbers preceded by a greater-than sign mean that the maximal effects of the compound in the corresponding assay were too small to allow determination of their half-maximally effective concentration. In these cases it was therefore only possible to determine that the K_i or K_B value was greater than the given number. nt = not tested.

Table 3. Binding and Functional Activities of Compounds **5h**−**x** for α_2-Adrenoceptor Subtypes[a]



5h, 5j-l, 5o, 5r-x **5m, 5p** **5n, 5q** **5i**

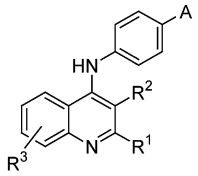
					K_i (nM)			K_B (nM)		
no.	R^1	R^2	R^3	R^4	α_{2A}	α_{2B}	α_{2C}	α_{2A}	α_{2B}	α_{2C}
5h	Me	Ph	H	H	1400 ± 200	1700 ± 220	5.0 ± 0.4	6000 ± 2700	>1000 [3]	4.3 ± 1.1
5i					715 ± 110	1330 ± 125	2.3 ± 0.2	1700 ± 145	>1500 [3]	0.8 ± 0.1
5j	H	Me	H	Me	895 ± 75	1270 ± 20	5.4 ± 1.0	7400 ± 2100	>3000 [3]	7.9 ± 1.1
5k	H	Me	H	H	1400 ± 50	3500 ± 400	8.5 ± 0.8	7700 ± 1900	>3000 [3]	8.9 ± 0.8
5l	Me	Me	7-Me, 8-Me	H	1850 ± 890	580 ± 40	5.0 ± 0.3	>3000 [3]	>3000 [3]	41± 7
5m	Me	Me	7-Me, 8-Me		790 ± 40	600 ± 15	7.7 ± 0.4	2100 ± 80	1750 ± 120	10 ±1
5n	Me	Me	7-Me, 8-Me		850 ± 220	1320 ± 180	84 ± 27	2440 ± 100	3500 ± 140	74 ± 8
5o	Me	Me	7-Me	H	840 ± 110	1280 ± 110	15 ± 3	>3000 [3]	>3000 [3]	51 ± 18
5p	Me	Me	7-Me		910 ± 100	1150 ± 110	8.3 ± 2.4	1500 [2]	>3000 [3]	11 ± 1
5q	Me	Me	7-Me		1050 ± 110	2600 ± 100	76 ± 5	3100 ± 300	9600 ± 400	132 ± 12
5r	Me	Me	8-Me	H	1900 ± 100	1100 ± 60	6.9 ± 0.2	8100 ± 1700	>3000 [5]	22 ± 10
5s	Me	Me	5-Me	H	680 ± 100	2030 ± 250	87 ± 10	1400 [2]	3000 [2]	130 ± 40
5t	Me	Me	5-Me, 7-Me	H	650 ± 30	910 ± 20	132 ± 12	1800 [2]	2100 [2]	130 [2]
5u	Me	Me	5-Me, 8-Me	H	2300 [2]	3600 ± 1900	390 [2]	nt	nt	nt
5v	Me	Me	7-Cl	H	1430 ± 40	880 ± 90	8.3 ± 1.5	>3000 [3]	>3000 [3]	11 ± 2
5w	Me	Me	5-Cl	H	775 ± 95	1120 ± 20	135 ± 6	>3000 [3]	>3000 [3]	115 ± 15
5x	Me	Me	6-F	H	1230 ± 210	3470 ± 700	16 ± 3	3400 ± 160	>3000 [3]	16 ± 1

[a] See Table 2 for footnotes.

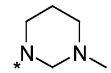
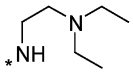
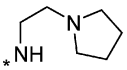
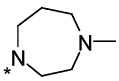
adrenoceptor. The same was also true when a hydroxymethyl substituent was added to the 2-position of the quinoline ring (**6h**), but, as seen before with compounds **5k** and **5j**, the substituent in the 3-position alone was sufficient to provide good α_{2C}-adrenoceptor affinity and selectivity (**6i** and **6j**).

The combination of a hydroxymethyl substituent in the 3-position and a halogen substituent in the 6- or 7-position of the quinoline ring was also studied. In line with the results for **5v**, a chlorine in the 7-position (**6l**) resulted in good α_{2C}-adrenoceptor affinity but was also accompanied by a decrease

Table 4. Binding and Functional Activities of Compounds **6a**−**d** for α_2-Adrenoceptor Subtypes[a]

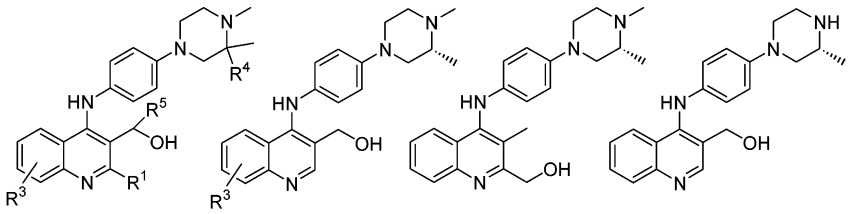


6a-d

					K_i (nM)[a]			K_B (nM)[b]		
No.	A	R^1	R^2	R^3	α_{2A}	α_{2B}	α_{2C}	α_{2A}	α_{2B}	α_{2C}
6a		Me	Me	8-Me	>10000 [3]	2500 [2]	770 ± 90	n.t.	n.t.	n.t.
6b		Me	Et	8-Me	900 ± 260	2900 [2]	82 ± 17	3900 ± 500	>3000 [3]	40 ± 17
6c		Me	Me	H	1000 ± 160	1680 ± 160	100 ± 15	4900 ± 90	7700 ± 450	89 ± 11
6d		Me	Et	8-Me	8000 ± 16	2600 ± 120	8.5 ± 0.9	>3000 [3]	>3000 [3]	9.5 ± 1.2

[a] See Table 2 for footnotes.

Table 5. Binding and Functional Activities of Compounds **6e**−**o** at α_2-Adrenoceptor Subtypes[a]



6e-g, 6i, 6l-n **6j, 6o** **6h** **6k**

					K_i (nM)			K_B (nM)		
no.	R^1	R^3	R^4	R^5	α_{2A}	α_{2B}	α_{2C}	α_{2A}	α_{2B}	α_{2C}
6e	Me	H	H	H	3100 ± 400	>10 000 [3]	7.5 ± 0.9	>3000 [3]	>3000 [3]	7.7 ± 1.2
6f	Me	H	Me	H	1170 ± 60	1470 ± 190	3.8 ± 0.8	6000 ± 1600	>3000 [3]	2.8 ± 0.4
6g	Me	H	H	Me	3100 ± 800	5100 ± 1600	4.9 ± 1.0	>3000 [3]	>3000 [3]	5.0 ± 0.5
6h					1870 ± 90	1800 ± 140	9.0 ± 1.8	8100 ± 1500	>3000 [3]	8.0 ± 0.7
6i	H	H	Me	H	1850 ± 220	1900 ± 240	6.4 ± 0.8	>3000 [3]	>3000 [3]	12 ± 1.6
6j		H			2200 ± 250	2600 ± 300	9.2 ± 2.1	>3000 [3]	>3000 [3]	8.5 ± 0.8
6k					9600 ± 200	17 600 ± 3400	205 ± 17	>3000 [3]	>3000 [3]	655 ± 60
6l	H	7-Cl	Me	H	960 ± 160	420 ± 50	5.9 ± 0.5	1650 [2]	1150 [1]	7.1 ± 0.5
6m	H	6-F	H	H	1380 ± 140	>10 000 [3]	43 ± 10	5400 ± 900	>10 000 [3]	119 ± 7
6n	H	6-F	Me	H	1320 ± 140	1750 ± 100	50 ± 7	5500 ± 1800	8500 ± 1200	122 ± 28
6o		6-F			980 ± 110	3150 ± 240	38 ± 6	6400 ± 1500	11 000 ± 1000	79 ± 8

[a] See Table 2 for footnotes.

in subtype selectivity. The difference in affinities of **6l** toward the α_{2B} and α_{2C} subtypes was only 70-fold, while that of **6i** was 300-fold. In contrast to the 7-chloro substituent, introduction of a 6-fluoro substituent did cause an appreciable deterioration in the affinity for the α_{2C}-adrenoceptor (**6m**−**o**).

In conclusion, we have discovered novel, selective α_{2C}-adrenoceptor antagonists containing a quinoline moiety and have studied their structure−activity relationships. The most essential features of the molecules needed to provide them with good affinity and high selectivity toward the α_{2C}-adrenoceptor were found to be (1) the quinoline ring, (2) the presence of a substituent in the 3-position of the quinoline ring, (3) *N*-methylation of the piperazine ring, and (4) proper balance in the order/degree in which the basic moieties in the molecules are protonated. One of the most promising compounds, on the basis of its primary pharmacology and in vivo properties, was considered to be **6j**. This compound was also found to possess activity in animal models of depression, such as the rat forced swimming assay, in which it statistically significantly extended the active swimming time of the animals by 79% when applied subcutaneously at a dose of 0.3 mg/kg (data not shown).

Experimental Section

Competition Binding Assays. The affinity of test compounds for the three human α_2-adrenoceptor subtypes was determined in competition binding assays with ^{3}H-rauwolscine as the radioligand. The biological material for these assays consisted in membranes from Shionogi S115 cells stably transfected with one of the three

human α_2-adrenoceptor subypes.[32] The membrane suspensions (3−15 μg of total protein per sample, depending on the expression level of individual subtypes) and 1 nM ^{3}H-rauwolscine (specific activity 75−85 Ci/mmol) were incubated with six concentrations of the test compounds in a total volume of 90 μL (50 mM KH_2PO_4, pH 7.5, at room temperature). Nonspecific binding (4−10% of total binding) was defined by 100 μM oxymetazoline. After 30 min at room temperature, the incubations were terminated by rapid filtration (TomTec 96 harvester, Tomtec Inc., Hamden, CT) through presoaked GF/B glass-fiber mats (Wallac Oy, Turku, Finland) which were then immediately washed three times with ice-cold 50 mM KH_2PO_4 (pH 7.5 at room temperature). After they were dried in a microwave oven, a solid scintillate (Meltilex; Wallac Oy) was melted onto the filter mats before the radioactivity contained in them was measured (BetaPlate; Wallac Oy) by scintillation counting. The determination of IC_{50} values from competition binding experiments was carried out by nonlinear least-squares curve fitting analysis. IC_{50}s were then converted to K_is via the Cheng−Prusoff equation.[33]

Functional Activity in Cellular Membranes. The α_2-antagonist properties of test compounds were assessed as their ability to competitively inhibit the epinephrine-stimulated binding of ^{35}S-guanosine 5′-*O*-(3-thio)triphosphate (^{35}S-GTPγS) binding to G proteins[34] in the membranes of CHO cells that had been stably transfected with one of the three human α_2-adrenoceptor subtypes.[35] Membranes (2−6 μg of protein/sample) and six concentrations of test compounds were preincubated for 30 min at room temperature in 50 mM Tris, 5 mM $MgCl_2$, 150 mM NaCl, 1 mM dithiothreitol (DTT), 1 mM ethylenediaminetetraacetic acid (EDTA), 10 μM guanosine diphosphate (GDP), and 30 μM ascorbic acid, pH 7.4, with a fixed concentration of epinephrine (5 μM for α_{2A}, 15 μM for α_{2B}, and 5 μM for α_{2C} adrenoceptor). Then trace amounts of ^{35}S-GTPγS (0.08−0.15 nM, specific activity 1250 Ci/mmol) were added to the incubation mixture. After an additional 30 min at room temperature, the incubations were terminated by rapid vacuum filtration through glass fiber filters. The filters were immediately washed three times with 5 mL of ice-cold wash buffer (20 mM Tris, 5 mM $MgCl_2$, and 1 mM EDTA, pH 7.4), dried, and counted for their radioactivity in a scintillation counter. Experiments were repeated at least three times and analyzed by nonlinear least-squares curve fitting. IC_{50}s were converted to K_Bs by using the equation $K_B = IC_{50}/(1 + [\text{epinephrine}]/EC_{50,\text{epinephrine}})$ with $EC_{50,\text{epinephrine}}$ values for α_{2A}, α_{2B}, and α_{2C} adrenoceptors being 0.76, 2.4, and 0.71 μM, respectively.

Chemistry. NMR spectra were obtained by Bruker DMX NMR spectrometer with ^{1}H and ^{13}C observed at 500 and 125 MHz, respectively. Chemical shifts for NMR spectra were reported in δ (parts per million, ppm) downfield from tetramethylsilane. Liquid chromatographic−mass spectrometric (LC-MS) analyses were performed employing a Waters 2960 Alliance HPLC and a Micromass Micro triple quadrupole mass spectrometer with electrospray (ES) ionization. Exact mass measurements of the final products were carried out with a Micromass LCT time-of-flight (TOF) mass spectrometer. Two diverse high-performance liquid chromatography (HPLC) systems were used for purity determinations (Supporting Information). Hydrogenations under pressure were conducted in a Parr hydrogenation apparatus. A Creator (Biotage) microwave reactor was used for reactions heated by microwave irradiation. Reagents and solvents were purchased from Sigma−Aldrich Finland (Helsinki, Finland) or Acros Organics (Geel, Belgium). Chromatographic purifications were performed on Merck silica gel 60 (0.063−0.200 mm).

[4-(4-Methylpiperazin-1-yl)phenyl]quinolin-4-ylamine (5a). A solution of 4-chloroquinoline (49 mg, 0.30 mmol), **4g** (57 mg, 0.30 mmol), and a drop of concentrated HCl in MeOH (2 mL) was refluxed overnight. The solvent was evaporated in vacuo, and the residue was purified by flash chromatography (CH_2Cl_2/MeOH/TEA = 94:5:1). Salts were removed by partitioning the product between CH_2Cl_2 and brine. The organic phase was dried over Na_2SO_4 and evaporated in vacuo to yield 17 mg (17%) of **5a** as a yellow solid. ^{1}H NMR ($CDCl_3$, δ, ppm): 8.51 (m, 1H), 8.02 (m, 1H), 7.90 (m, 1H), 7.67 (m, 1H), 7.49 (m, 1H), 7.21 (m, 2H), 6.99 (m, 2H), 6.73 (m, 1H), 6.56 (br s, 1H), 3.24 (m, 4H), 2.61 (m, 4H), 2.37 (s, 3H).^{13}C NMR ($CDCl_3$, δ, ppm): 150.96, 149.24, 148.99, 148.80, 131.29, 130.17, 129.22, 125.54, 125.05, 119.37, 119.18, 117.04, 101.29, 55.14, 49.30, 46.18. HRMS *m*/*z* calcd for $C_{20}H_{23}N_4$ $[M + H]^+$ 319.1923, found 319.1913.

(2,3-Dimethylquinolin-4-yl)-[4-(4-methylpiperazin-1-yl)phenyl]amine (5b): Method A. A solution of **3c** (96 mg, 0.50 mmol), **4g** (96 mg, 0.50 mmol), and concentrated HCl (25 μL) in MeOH (500 μL) was heated at 130 °C by microwave irradiation for 15 min. The solvent was evaporated in vacuo and the residue was dissolved in water, which was made alkaline with aqueous saturated $NaHCO_3$ solution and extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and evaporated in vacuo. The product was purified by flash chromatography (CH_2Cl_2/MeOH = 19:1) to obtain 77 mg (44%) of **5b** as a yellow solid. ^{1}H NMR ($CDCl_3$, δ, ppm): 8.04 (m, 1H), 7.80 (m, 1H), 7.59 (m, 1H), 7.34 (m, 1H), 6.85 (m, 2H), 6.71 (m, 2H), 6.00 (br s, 1H), 3.15 (m, 4H), 2.73 (s, 3H), 2.60 (m, 4H), 2.37 (s, 3H), 2.24 (s, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm): 158.94, 147.17, 145.64, 144.61, 139.30, 131.59, 128.56, 128.49, 124.90, 124.31, 124.08, 117.87, 117.59, 55.26, 49.96, 46.09, 28.17, 25.34, 21.16. HRMS: *m*/*z* calcd for $C_{22}H_{27}N_4$ $[M + H]^+$ 347.2236, found 347.2243.

(3-Ethyl-2-methylquinolin-4-yl)-[4-(4-methylpiperazin-1-yl)-phenyl]amine (5c). A solution of **3d** (0.562 g, 3.0 mmol), **4g** (0.574 g, 3.0 mmol), and a couple of drops of concentrated HCl in MeOH (10 mL) was refluxed for 3 h. The reaction mixture was poured into water (100 mL), made acidic with concentrated HCl, and washed with CH_2Cl_2. The water phase was made alkaline with an aqueous saturated $NaHCO_3$ solution and extracted three times with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and evaporated in vacuo. The product was purified by flash chromatography (CH_2Cl_2/MeOH = 9:1) to obtain 0.442 g (41%) of **5c** as a yellow solid. ^{1}H NMR ($CDCl_3$, δ, ppm): 8.00 (m, 1H), 7.71 (m, 1H), 7.55 (m, 1H), 7.25 (m, 1H), 6.80 (m, 2H), 6.69 (m, 2H), 5.81 (br s, 1H), 3.13 (m, 4H), 2.79 (q, J = 7.7 Hz, 2H), 2.78 (s, 3H), 2.58 (m, 4H), 2.35 (s, 3H), 1.17 (t, J = 7.7 Hz, 3H).^{13}C NMR ($CDCl_3$, δ, ppm): 158.56, 146.89, 146.26, 144.46, 138.49, 128.64, 128.36, 126.95, 124.86, 124.13, 122.80, 118.79, 117.53, 55.19, 49.87, 46.04, 23.51, 21.07, 13.50. HRMS *m*/*z* calcd for $C_{23}H_{29}N_4$ $[M + H]^+$ 361.2392, found 361.2408.

(3-Isopropyl-2-methylquinolin-4-yl)-[4-(4-methylpiperazin-1-yl)phenyl]amine (5d). Compound **5d** was synthesized by method A from **3e** (110 mg, 0.50 mmol), **4g** (96 mg, 0.50 mmol), and HCl (25 μL) in MeOH (500 μL). The temperature was 130 °C and the reaction time was 120 min. Yield 95 mg (51%), yellow solid. ^{1}H NMR ($CDCl_3$, δ, ppm) 7.95 (m, 1H), 7.74 (m, 1H), 7.54 (m, 1H), 7.24 (m, 1H), 6.79 (m, 2H), 6.61 (m, 2H), 5.73 (br s, 1H), 3.61 (m, 1H), 3.11 (m, 4H), 2.81 (s, 3H), 2.56 (m, 4H), 2.34 (s, 3H), 1.38 (d, J = 7.3 Hz, 6H). ^{13}C NMR ($CDCl_3$, δ, ppm): 159.27, 146.63, 146.15, 144.28, 137.72, 128.62, 128.41, 125.05, 122.74, 120.84, 118.50, 117.56, 55.18, 49.94, 46.05, 24.22, 14.61. HRMS *m*/*z* calcd for $C_{24}H_{31}N_4$ $[M + H]^+$ 375.2549, found 375.2549.

(2-Methyl-3-phenylquinolin-4-yl)-[4-(4-methylpiperazin-1-yl)-phenyl]amine (5e). Compound **5e** was synthesized by method A from **3f** (127 mg, 0.50 mmol), **4g** (96 mg, 0.50 mmol), and HCl (25 μL) in MeOH (500 μL). The temperature was 130 °C and the reaction time was 120 min. Yield 67 mg (33%), yellow solid. ^{1}H NMR ($CDCl_3$, δ, ppm) 8.01 (m, 1H), 7.64 (m, 1H), 7.58 (m, 1H), 7.47 (m, 2H), 7.41 (m, 1H), 7.28 (m, 2H), 7.20 (m, 1H), 6.75 (m, 4H), 5.57 (br s, 1H), 3.13 (m, 4H), 2.56 (m, 4H), 2.44 (s, 3H), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm): 157.77, 148.29, 147.23, 145.49, 137.67, 136.33, 129.91, 129.50, 129.05, 128.82, 128.19, 125.40, 124.73, 124.31, 121.37, 120.54, 116.98, 55.21, 49.60, 46.12, 24.95. HRMS *m*/*z* calcd for $C_{27}H_{29}N_4$ $[M + H]^+$ 409.2392, found 409.2401.

(3-Benzyl-2-methylquinolin-4-yl)-[4-(4-methylpiperazin-1-yl)-phenyl]amine (5f). Compound **5f** was synthesized by method A from **3g** (134 mg, 0.50 mmol), **4g** (96 mg, 0.50 mmol), and HCl (25 μL) in MeOH (500 μL). The temperature was 130 °C and the reaction time was 120 min. Yield 34 mg (16%), yellow solid. ^{1}H

NMR ($CDCl_3$, δ, ppm) 8.01 (m, 1H), 7.73 (m, 1H), 7.59 (m, 1H), 7.27 (m, 3H), 7.20 (m, 1H), 7.08 (m, 2H), 6.77 (m, 2H), 6.61 (m, 2H), 5.70 (br s, 1H), 4.18 (s, 2H), 3.10 (m, 4H), 2.71 (s, 3H), 2.56 (m, 4H), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm): 159.67, 147.94, 146.16, 145.36, 138.40, 138.20, 128.93, 128.84, 127.81, 126.60, 124.89, 124.36, 123.46, 123.01, 118.43, 117.54, 55.24, 50.00, 46.12, 33.78, 24.46. HRMS *m*/*z* calcd for $C_{28}H_{31}N_4$ $[M + H]^+$ 423.2549, found 423.2550.

[4-(4-Methylpiperazin-1-yl)phenyl]-(2-methylquinolin-4-yl)-amine (5g). Compound **5g** was synthesized by method A from 4-chloroquinaldine (101 μL, 0.50 mmol), **4g** (96 mg, 0.50 mmol), and HCl (25 μL) in MeOH (500 μL). The temperature was 130 °C and the reaction time was 5 min. Yield 123 mg (74%), yellow solid. ^{1}H NMR ($CDCl_3$, δ, ppm) 8.04 (m, 2H), 7.60 (m, 1H), 7.41 (m, 1H), 7.22 (m, 2H), 6.97 (m, 2H), 6.54 (s, 1H), 3.24 (m, 4H), 2.60 (m, 4H), 2.54 (s, 3H), 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm): 158.14, 150.33, 149.42, 130.65, 130.15, 127.11, 125.79, 124.95, 124.76, 120.19, 117.41, 116.90, 101.01, 55.13, 49.13, 46.17, 24.33. HRMS *m*/*z* calcd for $C_{21}H_{25}N_4$ $[M + H]^+$ 333.2079, found 333.2070.

[4-(3,4-Dimethylpiperazin-1-yl)phenyl]-(2-methyl-3-phenylquinolin-4-yl)amine (5h). Compound **5h** was synthesized by method A from **3f** (1.01 g, 4.0 mmol), **4c** (500 mg, 2.4 mmol), and HCl (a couple of drops) in MeOH (2 mL). The temperature was 145 °C and the reaction time was 60 min. Yield 750 mg (73%), orange solid. ^{1}H NMR ($CDCl_3$, δ, ppm): 8.02 (m, 1H), 7.63 (m, 1H), 7.58 (m, 1H), 7.48 (m, 2H), 7.41 (m, 1H), 7.28 (m, 2H), 7.20 (m, 1H), 6.77 (m, 2H), 6.73 (m, 2H), 5.59 (br s, 1H), 3.42 (m, 1H), 3.35 (m, 1H), 2.88 (m, 2H), 2.50 (m, 1H), 2.44 (s, 3H), 2.41 (m, 1H), 2.34 (s, 3H), 2.25 (m, 1H), 1.12 (d, J = 6.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm): 154.86, 147.07, 136.18, 134.03, 129.90, 129.53, 129.13, 128.67, 128.22, 125.39, 124.33, 121.44, 116.94, 57.78, 56.83, 55.64, 49.67, 42.54, 24.87, 17.22. HRMS *m*/*z* calcd for $C_{28}H_{31}N_4$ $[M + H]^+$ 423.2549, found 423.2550.

(2,3-Dimethylquinolin-4-yl)-[4-(octahydro-2*H*-pyrido[1,2-*a*]-pyrazin-2-yl)phenyl]amine (5i). Compound **5i** was synthesized by method A from **3c** (56 mg, 0.29 mmol), **4h** (56 mg, 0.24 mmol), and HCl (a couple of drops) in MeOH (750 μL). The temperature was 145 °C and the reaction time was 15 min. Yield 19 mg (21%), yellow oil. ^{1}H NMR ($CDCl_3$, δ, ppm): 8.02 (m, 1H), 7.81 (m, 1H), 7.56 (m, 1H), 7.32 (m, 1H), 6.82 (m, 2H), 6.72 (m, 2H), 5.92 (br s, 1H), 3.42 (m, 1H), 3.33 (m, 1H), 2.92 (m, 3H), 2.70 (s, 3H), 2.49 (m, 2H), 2.18 (s, 3H), 2.12 (m, 3H), 1.81 (m, 1H), 1.69 (m, 1H), 1.60 (m, 1H), 1.34 (m, 2H), 1.17 (m, 2H). ^{13}C NMR ($CDCl_3$, δ, ppm): 159.38, 147.67, 146.74, 137.91, 129.83, 129.18, 126.87, 125.18, 122.96, 120.43, 117.55, 61.32, 56.00, 55.55, 55.00, 49.68, 29.52, 23.76, 14.66. HRMS *m*/*z* calcd for $C_{25}H_{31}N_4$ $[M + H]^+$ 387.2549, found 387.2538.

(3-Methylquinolin-4-yl)-[4-(3,3,4-trimethylpiperazin-1-yl)phenyl]amine (5j). Compound **5j** was synthesized by method A from **3r** (45 mg, 0.25 mmol), **4i** (50 mg, 0.23 mmol), and HCl (1 drop) in MeOH (500 μL). The temperature was 130 °C and the reaction time was 15 min. Yield 53 mg (64%), red solid. ^{1}H NMR ($CDCl_3$, δ, ppm): 8.63 (s, 1H), 8.05 (m, 1H), 7.85 (m, 1H), 7.59 (m, 1H), 7.36 (m, 1H), 6.78 (m, 4H), 6.30 (br s, 1H), 3.23 (m, 2H), 2.98 (s, 2H), 2.86 (m, 2H), 2.42 (s, 3H), 2.25 (s, 3H), 1.24 (s, 6H). ^{13}C NMR ($CDCl_3$, δ, ppm): 152.83, 147.84, 146.51, 144.87, 137.25, 129.20, 128.61, 125.56, 123.04, 122.88, 120.07, 119.68, 117.99, 62.47, 50.28, 49.43, 36.93, 20.17, 16.18. HRMS *m*/*z* calcd for $C_{23}H_{29}N_4$ $[M + H]^+$ 361.2392, found 361.2410.

[4-(3,4-Dimethylpiperazin-1-yl)phenyl]-(3-methylquinolin-4-yl)amine (5k). Compound **5k** was synthesized by method A from **3r** (100 mg, 0.56 mmol), **4c** (102 mg, 0.50 mmol), and HCl (1 drop) in MeOH (500 μL). The temperature was 145 °C and the reaction time was 20 min. Yield 50 mg (29%), red solid. ^{1}H NMR ($CDCl_3$, δ, ppm): 8.66 (s, 1H), 8.04 (m, 1H), 7.81 (m, 1H), 7.59 (m, 1H), 7.35 (m, 1H), 6.84 (m, 2H), 6.76 (m, 2H), 5.97 (br s, 1H), 3.42 (m, 1H), 3.36 (m, 1H), 2.90 (m, 2H), 2.53 (m, 1H), 2.45 (m, 1H), 2.35 (s, 3H), 2.29 (m, 1H), 2.27 (s, 3H), 1.14 (d, J = 6.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm): 153.35, 148.36, 146.50, 144.56, 136.95, 129.67, 128.41, 125.46, 122.86, 120.00, 119.77, 117.37, 57.85, 57.12, 55.65, 49.95, 42.50, 17.19, 16.05. HRMS *m*/*z* calcd for $C_{22}H_{27}N_4$ $[M + H]^+$ 347.2236, found 347.2232.

[4-(3,4-Dimethylpiperazin-1-yl)phenyl]-(2,3,7,8-tetramethylquinolin-4-yl)amine (5l). Compound **5l** was synthesized by method A from **3h** (214 mg, 1.0 mmol), **4c** (103 mg, 0.50 mmol), and HCl (a couple of drops) in MeOH (500 μL). The temperature was 130 °C and the reaction time was 5 min. Yield 174 mg (90%), red solid. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.55 (d, J = 8.6 Hz, 1H), 7.15 (d, J = 8.6 Hz, 1H), 6.80 (m, 2H), 6.62 (m, 2H), 5.74 (br s, 1H), 3.36 (m, 1H), 3.31 (m, 1H), 2.90 (m, 2H), 2.76 (s, 3H), 2.72 (s, 3H), 2.51 (m, 2H), 2.44 (s, 3H), 2.35 (s, 3H), 2.30 (m, 1H), 2.21 (s, 3H), 1.13 (d, J = 6.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm): 158.29, 145.33, 143.50, 138.74, 135.94, 134.04, 127.79, 121.57, 119.45, 117.81, 117.55, 57.92, 57.44, 55.68, 50.22, 42.44, 24.96, 20.56, 17.11, 14.56, 13.37. HRMS *m*/*z* calcd for $C_{25}H_{33}N_4$ $[M + H]^+$ 389.2705, found 389.2690.

(*R*)-[4-(3,4-Dimethylpiperazin-1-yl)phenyl]-(2,3,7,8-tetramethylquinolin-4-yl)amine (5m). Compound **5m** was synthesized by method A from **3h** (68 mg, 0.31 mmol), **4d** (52 mg, 0.25 mmol), and HCl (a couple of drops) in MeOH (500 μL). The temperature was 145 °C and the reaction time was 30 min. Yield 57 mg (58%), red solid. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.64 (d, J = 8.5 Hz, 1H), 7.17 (d, J = 8.5 Hz, 1H), 6.80 (m, 2H), 6.70 (m, 2H), 3.39 (m, 2H), 3.16 (m, 2H), 2.84 (m, 1H), 2.79 (s, 3H), 2.77 (s, 3H), 2.72 (m 2H), 2.55 (s, 3H), 2.44 (s, 3H), 2.13 (s, 3H), 1.31 (d, J = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm): 157.74, 146.51, 144.95, 138.34, 132.18, 128.10, 121.11, 120.03, 119.96, 118.26, 58.74, 56.22, 54.89, 49.06, 41.53, 24.19, 20.66, 15.83, 14.72, 13.69. HRMS *m*/*z* calcd for $C_{25}H_{33}N_4$ $[M + H]^+$ 389.2705, found 389.2722.

(*S*)-[4-(3,4-Dimethylpiperazin-1-yl)phenyl]-(2,3,7,8-tetramethylquinolin-4-yl)amine (5n). Compound **5n** was synthesized by method A from **3h** (68 mg, 0.31 mmol), **4e** (53 mg, 0.26 mmol), and HCl (a couple of drops) in MeOH (500 μL). The temperature was 145 °C and the reaction time was 20 min. Yield 75 mg (75%), red solid. ^{1}H NMR ($CDCl_3$, CD_3OD, δ, ppm): 7.78 (d, J = 8.9 Hz, 1H), 7.29 (d, J = 8.9 Hz, 1H), 7.02 (m 2H), 6.96 (m, 2H), 3.58 (m, 2H), 3.10 (m, 2H), 2.83 (s, 3H), 2.73 (m, 2H), 2.67 (s, 3H), 2.55 (s, 3H), 2.52 (s, 3H), 2.49 (m, 1H), 2.17 (s, 3H), 1.29 (d, J = 5.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, CD_3OD, δ, ppm): 158.56, 148.57, 143.86, 137.34, 129.34, 126.72, 124.25, 122.19, 117.75, 59.02, 55.94, 55.43, 48.90, 41.90, 20.92, 16.18, 14.65, 13.37. HRMS *m*/*z* calcd for $C_{25}H_{33}N_4$ $[M + H]^+$ 389.2705, found 389.2683.

[4-(3,4-Dimethylpiperazin-1-yl)phenyl]-(2,3,7-trimethylquinolin-4-yl)amine (5o) and [4-(3,4-Dimethylpiperazin-1-yl)phenyl]-(2,3,5-trimethylquinolin-4-yl)amine (5s). Compounds **5o** and **5s** were synthesized by method A from a mixture of isomers **3i** and **3j** (206 mg, 1.0 mmol), **4c** (103 mg, 0.50 mmol), and HCl (a couple of drops) in MeOH (2.0 mL). The temperature was 130 °C and the reaction time was 10 min. Products were separated by flash chromatography (CH_2Cl_2/MeOH = 9:1) to obtain 76 mg (41%) of **5s** and 27 mg (14%) of **5o** in pure form, both as orange solids. The 5-methyl isomer eluted first from the column. Analytical data for **5o**: ^{1}H NMR ($CDCl_3$, δ, ppm) 7.82 (s, 1H), 7.65 (d, J = 8.6 Hz, 1H), 7.15 (d, J = 8.6 Hz, 1H), 6.82 (m, 2H), 6.69 (m, 2H), 5.94 (br s, 1H), 3.40 (m, 1H), 3.34 (m, 1H), 2.89 (m, 2H), 2.71 (s, 3H), 2.50 (m, 1H), 2.49 (s, 3H), 2.43 (m, 1H), 2.34 (s, 3H), 2.27 (m, 1H), 2.21 (s, 3H), 1.13 (d, J = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm) 159.09, 146.68, 146.06, 144.30, 138.88, 127.50, 127.24, 122.54, 120.58, 119.80, 118.65, 117.54, 57.81, 57.33, 55.72, 50.13, 42.56, 24.16, 21.61, 17.27, 14.49. HRMS *m*/*z* calcd for $C_{24}H_{31}N_4$ $[M + H]^+$ 375.2549, found 375.2534. Analytical data for **5s**: ^{1}H NMR ($CDCl_3$, δ, ppm) 7.84 (d, J = 8.2 Hz, 1H), 7.24 (dd, J = 8.2, 7.0 Hz, 1H), 7.13 (d, J = 7.0 Hz, 1H), 6.79 (m, 2H), 6.47 (m, 2H), 5.80 (br s, 1H), 3.33 (m, 1H), 3.28 (m, 1H), 2.85 (m, 2H), 2.72 (s, 3H), 2.66 (s, 3H), 2.43 (m, 2H), 2.31 (s, 3H), 2.24 (m, 1H), 2.18 (s, 3H), 1.09 (d, J = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm) 159.07, 148.72, 144.98, 144.54, 138.80, 133.26, 129.10, 128.02, 127.83, 125.46, 124.63, 118.08, 116.18, 57.89, 57.62, 55.79, 50.35, 42.55, 24.37, 24.08, 17.25, 14.78. HRMS *m*/*z* calcd for $C_{24}H_{31}N_4$ $[M + H]^+$ 375.2549, found 375.2538.

(*R*)-[4-(3,4-Dimethylpiperazin-1-yl)phenyl]-(2,3,7-trimethylquinolin-4-yl)amine (5p). Compound **5p** was synthesized by method A from a mixture of isomers **3i** and **3j** (206 mg, 1.0 mmol), **4d** (103 mg, 0.50 mmol), and HCl (a couple of drops) in MeOH (1.0 mL). The temperature was 130 °C and the reaction time was 10 min. The desired 7-methyl isomer **5p** was separated from the 5-methyl isomer by flash chromatography (CH_2Cl_2/MeOH = 9:1). Yield 46 mg (25%), yellow solid. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.77 (s, 1H), 7.65 (d, J = 8.6 Hz, 1H), 7.15 (dd, J = 8.6, 1.5 Hz, 1H), 6.82 (m, 2H), 6.67 (m, 2H), 5.82 (br s, 1H), 3.38 (m, 1H), 3.33 (m, 1H), 2.87 (m, 2H), 2.69 (s, 3H), 2.49 (m, 1H), 2.49 (s, 3H), 2.43 (m, 1H), 2.33 (s, 3H), 2.25 (m, 1H), 2.22 (s, 3H), 1.12 (d, J = 6.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm): 159.52, 147.35, 145.84, 143.80, 138.55, 138.05, 127.97, 127.15, 122.47, 120.92, 120.32, 118.24, 117.60, 57.80, 57.46, 55.76, 50.24, 42.59, 24.53, 21.60, 17.31, 14.55. HRMS *m*/*z* calcd for $C_{24}H_{31}N_4$ $[M + H]^+$ 375.2549, found 375.2531.

(*S*)-[4-(3,4-Dimethylpiperazin-1-yl)phenyl]-(2,3,7-trimethylquinolin-4-yl)amine (5q). Compound **5q** was synthesized by method A from a mixture of isomers **3i** and **3j** (206 mg, 1.0 mmol), **4e** (103 mg, 0.50 mmol), and HCl (a couple of drops) in MeOH (1.0 mL). The temperature was 130 °C and the reaction time was 10 min. The desired 7-methyl isomer **5q** was separated from the 5-methyl isomer by flash chromatography (CH_2Cl_2/MeOH = 9:1). Yield 40 mg (21%), yellow solid. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.88 (s, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.15 (dd, J = 8.5, 1.5 Hz, 1H), 6.83 (m, 2H), 6.75 (m, 2H), 6.25 (br s, 1H), 3.41 (m, 1H), 3.35 (m, 1H), 2.90 (m, 2H), 2.72 (s, 3H), 2.52 (m, 1H), 2.48 (s, 3H), 2.44 (m, 1H), 2.35 (s, 3H), 2.29 (m, 1H), 2.18 (s, 3H), 1.14 (d, J = 6.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm): 158.16, 146.45, 145.59, 144.05, 139.53, 136.96, 127.39, 126.38, 122.74, 120.16, 119.43, 118.75, 117.39, 57.82, 57.09, 55.63, 49.92, 42.51, 23.41, 21.62, 17.20, 14.43. HRMS *m*/*z* calcd for $C_{24}H_{31}N_4$ $[M + H]^+$ 375.2549, found 375.2562.

[4-(3,4-Dimethylpiperazin-1-yl)phenyl]-(2,3,8-trimethylquinolin-4-yl)amine (5r). Compound **5r** was synthesized by method A from **3a** (137 mg, 0.67 mmol), **4c** (153 mg, 0.74 mmol), and HCl (a couple of drops) in MeOH (500 μL). The temperature was 130 °C and the reaction time was 5 min. Yield 133 mg (53%), yellow solid. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.65 (m, 1H), 7.43 (m, 1H), 7.22 (m, 1H), 6.81 (m, 2H), 6.63 (m, 2H), 5.76 (br s, 1H), 3.36 (m, 1H), 3.31 (m, 1H), 2.86 (m, 2H), 2.80 (s, 3H), 2.73 (s, 3H), 2.45 (m, 2H), 2.33 (s, 3H), 2.26 (m, 1H), 2.23 (s, 3H), 1.12 (d, J = 6.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm): 157.19, 146.53, 144.63, 136.39, 134.19, 129.26, 129.18, 126.42, 125.21, 121.21, 121.15, 118.65, 117.31, 55.46, 55.28, 54.54, 48.20, 45.86, 24.05, 18.66, 14.96, 8.66. HRMS *m*/*z* calcd for $C_{24}H_{31}N_4$ $[M + H]^+$ 375.2549, found 375.2547.

[4-(3,4-Dimethylpiperazin-1-yl)phenyl]-(2,3,5,7-tetramethylquinolin-4-yl)amine (5t). Compound **5t** was synthesized by method A from **3k** (220 mg, 1.0 mmol), **4c** (60 mg, 0.30 mmol), and HCl (a couple of drops) in MeOH (500 μL). The temperature was 130 °C and the reaction time was 5 min. Yield 92 mg (78%), yellow solid. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.69 (s, 1H), 7.00 (s, 1H), 6.81 (m, 2H), 6.50 (m, 2H), 5.87 (br s, 1H), 3.36 (m, 1H), 3.31 (m, 1H), 2.87 (m, 2H), 2.71 (s, 3H), 2.67 (s, 3H), 2.47 (m, 2H), 2.44 (s, 3H), 2.34 (s, 3H), 2.27 (m, 1H), 2.18 (s, 3H), 1.12 (d, J = 6.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm): 158.78, 148.75, 145.02, 138.74, 138.13, 132.92, 131.43, 126.62, 124.33, 122.43, 118.05, 116.35, 57.90, 57.59, 55.78, 50.32, 42.54, 24.13, 23.92, 21.26, 17.24, 14.67. HRMS *m*/*z* calcd for $C_{25}H_{33}N_4$ $[M + H]^+$ 389.2705, found 389.2696.

[4-(3,4-Dimethylpiperazin-1-yl)phenyl]-(2,3,5,8-tetramethylquinolin-4-yl)amine (5u). Compound **5u** was synthesized by method A from **3l** (220 mg, 1.0 mmol), **4c** (103 mg, 0.50 mmol), and HCl (a couple of drops) in MeOH (750 μL). The temperature was 130 °C and the reaction time was 5 min. Yield 152 mg (78%), brown solid. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.31 (d, J = 7.3 Hz, 1H), 7.04 (d, J = 7.3 Hz, 1H), 6.80 (m, 2H), 6.47 (m, 2H), 5.76 (br s, 1H), 3.34 (m, 1H), 3.29 (m, 1H), 2.86 (m, 2H), 2.74 (s, 3H), 2.70 (s, 6H), 2.46 (m, 2H), 2.34 (s, 3H), 2.27 (m, 1H), 2.21 (s, 3H), 1.12 (d, J = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm): 157.80, 147.67, 144.66, 144.21, 139.19, 135.10, 130.79, 128.56, 128.12, 125.41, 124.63, 118.15, 115.86, 57.92, 57.67, 55.79, 50.39, 42.52, 24.79, 24.16, 18.54, 17.20, 14.69. HRMS *m*/*z* calcd for $C_{25}H_{33}N_4$ $[M + H]^+$ 389.2705, found 389.2721.

(7-Chloro-2,3-dimethylquinolin-4-yl)-[4-(3,4-dimethylpiperazin-1-yl)phenyl]amine (5v) and (5-Chloro-2,3-dimethylquinolin-4-yl)-[4-(3,4-dimethylpiperazin-1-yl)phenyl]a mine (5w). Compounds **5v** and **5w** were synthesized by method A from a mixture of isomers **3m** and **3n** (226 mg, 1.0 mmol), **4c** (103 mg, 0.50 mmol), and HCl (a couple of drops) in MeOH (1.0 mL). The temperature was 130 °C and the reaction time was 10 min. Products were separated by flash chromatography (CH_2Cl_2/MeOH = 9:1) to obtain 25 mg (25%) of **5w** and 14 mg (14%) of **5v** in pure form, both as orange solids. The 5-chloro isomer eluted first from the column. Analytical data for **5v**: ^{1}H NMR ($CDCl_3$, δ, ppm) 7.97 (d, J = 2.0 Hz, 1H), 7.69 (d, J = 8.9 Hz, 1H), 7.24 (dd, J = 8.9, 2.0 Hz, 1H), 6.82 (m, 2H), 6.67 (m, 2H), 5.79 (br s, 1H), 3.39 (m, 1H), 3.34 (m, 1H), 2.89 (m, 2H), 2.70 (s, 3H), 2.52 (m, 1H), 2.45 (m, 1H), 2.35 (s, 3H), 2.29 (m, 1H), 2.24 (s, 3H), 1.13 (d, J = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm) 160.89, 147.72, 146.12, 144.05, 137.64, 134.20, 127.84, 125.72, 124.56, 121.23, 121.05, 118.62, 117.62, 57.87, 57.21, 55.64, 50.01, 42.48, 24.64, 17.17, 14.47. HRMS *m*/*z* calcd for $C_{23}H_{28}N_4Cl$ $[M + H]^+$ 395.2002, found 395.1998. Analytical data for **5w**: ^{1}H NMR ($CDCl_3$, δ, ppm) 7.92 (dd, J = 7.9, 1.5 Hz, 1H), 7.44 (dd, J = 7.9, 7.6 Hz, 1H), 7.42 (dd, J = 7.6, 1.5 Hz, 1H), 6.85 (m, 2H), 6.64 (m, 2H), 3.40 (m, 1H), 3.34 (m, 1H), 2.89 (m, 2H), 2.67 (s, 3H), 2.51 (m, 1H), 2.44 (m, 1H), 2.35 (s, 3H), 2.28 (m, 1H), 2.11 (s, 3H), 1.13 (d, J = 6.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm) 160.48, 149.02, 145.80, 144.28, 137.21, 129.25, 128.33, 127.74, 127.57, 123.92, 120.57, 118.37, 117.57, 57.87, 57.37, 55.74, 50.13, 42.54, 24.44, 17.23, 15.96. HRMS *m*/*z* calcd for $C_{23}H_{28}N_4Cl$ $[M + H]^+$ 395.2002, found 395.2014.

[4-(3,4-Dimethylpiperazin-1-yl)phenyl]-(6-fluoro-2,3-dimethylquinolin-4-yl)amine (5x). Compound **5x** was synthesized by method A from **3o** (210 mg, 1.0 mmol), **4c** (102 mg, 0.50 mmol), and HCl (a couple of drops) in MeOH (1.0 mL). The temperature was 130 °C and the reaction time was 10 min. Yield 104 mg (55%), yellow solid. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.97 (m, 1H), 7.38 (m, 1H), 7.33 (m, 1H), 6.83 (m, 2H), 6.64 (m, 2H), 5.70 (br s, 1H), 3.39 (m, 1H), 3.33 (m, 1H), 2.88 (m, 2H), 2.70 (s, 3H), 2.50 (m, 1H), 2.44 (m, 1H), 2.34 (s, 3H), 2.28 (m, 1H), 2.26 (s, 3H), 1.13 (d, J = 6.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm): 160.77, 158.97, 158.82, 145.96, 144.28, 143.45, 137.69, 131.33, 131.26, 118.48, 118.28, 118.06, 117.74, 106.84, 106.65, 57.82, 57.39, 55.71, 50.18, 42.54, 24.48, 17.24, 14.62. HRMS *m*/*z* calcd for $C_{23}H_{28}N_4F$ $[M + H]^+$ 379.2298, found 379.2278.

[4-(3-Methyltetrahydropyrimidin-1(2*H*)-yl)phenyl]-(2,3,8-trimethylquinolin-4-yl)amine (6a). A solution of **9** (185 mg, 0.53 mmol) and aqueous 40% formaldehyde (100 μL, 1.3 mmol) in formic acid (5 mL) was heated at 80 °C for 1 h. The reaction mixture was poured into water (100 mL), made alkaline with 10 M NaOH, and extracted twice with CH_2Cl_2. Combined organic phases were dried over Na_2SO_4 and evaporated in vacuo. The product was purified by flash chromatography (CH_2Cl_2/MeOH = 9:1). Yield 48 mg (25%), yellow oil. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.66 (d, J = 8.2 Hz, 1H), 7.43 (d, J = 6.9 Hz, 1H), 7.23 (dd, J = 8.2, 6.9 Hz, 1H), 6.85 (m, 2H), 6.63 (m, 2H), 5.82 (br s, 1H), 3.76 (s, 2H), 3.17 (t, J = 5.5 Hz, 2H), 2.81 (s, 3H), 2.74 (s, 3H), 2.63 (t, J = 5.5 Hz, 2H), 2.34 (s, 3H), 2.27 (s, 3H), 1.78 (m, 2H). ^{13}C NMR ($CDCl_3$, δ, ppm): 158.40, 146.20, 144.11, 138.69, 136.68, 128.72, 124.77, 123.28, 121.58, 120.58, 118.98, 117.69, 74.99, 54.48, 49.52, 42.24, 24.84, 23.31, 18.22, 14.71. HRMS *m*/*z* calcd for $C_{23}H_{29}N_4$ $[M + H]^+$ 361.2392, found 361.2395.

***N*-(2-Diethylaminoethyl)-*N*′-(3-ethyl-2,8-dimethylquinolin-4-yl)benzene-1,4-diamine (6b).** Compound **6b** was synthesized by method A from **3p** (88 mg, 0.40 mmol), **4j** (59 mg, 0.29 mmol), and HCl (a couple of drops) in MeOH (750 μL). The temperature was 100 °C and the reaction time was 20 min. Yield 45 mg (28%), yellow solid. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.63 (d, J = 8.6 Hz, 1H),

7.41 (d, $J = 7.0$ Hz, 1H), 7.11 (dd, $J = 8.6$, 7.0 Hz, 1H), 6.79 (m, 2H), 6.61 (m, 2H), 3.54 (m, 2H), 3.24 (m, 3H), 3.17 (s, 3H), 3.00 (m, 3H), 2.92 (s, 3H), 2.78 (q, $J = 7.6$ Hz, 2H), 1.39 (t, $J = 7.3$ 6H), 1.15 (t, $J = 7.6$ Hz, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm): 159.06, 153.10, 146.41, 144.57, 138.02, 132.65, 129.85, 126.42, 124.86, 124.33, 122.68, 119.48, 117.85, 113.72, 56.51, 51.30, 47.37, 39.04, 32.78, 24.95, 12.81, 8.72. HRMS *m*/*z* calcd for $C_{25}H_{35}N_4$ $[M + H]^+$ 391.2862, found 391.2864.

***N*-(2,3-Dimethylquinolin-4-yl)-*N*′-(2-pyrrolidin-1-ylethyl)benzene-1,4-diamine (6c).** Compound **6c** was synthesized by method A from **3c** (115 mg, 0.60 mmol), **4k** (95 mg, 0.46 mmol), and HCl (a couple of drops) in MeOH (750 μL). The temperature was 120 °C and the reaction time was 15 min. Yield 160 mg (96%), red solid. ^{1}H NMR (CD_3OD, δ, ppm): 7.97 (m, 1H), 7.92 (m, 1H), 7.76 (m, 1H), 7.40 (m, 1H), 7.01 (m, 2H), 7.76 (m, 2H), 3.59 (t, $J = 6.1$ Hz, 2H), 3.45−3.37 (m, 6H), 2.76 (s, 3H), 2.18 (s, 3H), 2.14 (m, 4H). ^{13}C NMR ($CDCl_3$, CD_3OD, δ, ppm): 153.97, 152.93, 146.74, 138.99, 132.85, 131.50, 126.32, 125.74, 125.13, 120.31, 118.37, 113.88, 113.34, 54.66, 54.52, 40.45, 23.46, 19.68, 14.31. HRMS *m*/*z* calcd for $C_{23}H_{29}N_4$ $[M + H]^+$ 361.2392, found 361.2391.

(3-Ethyl-2,8-dimethylquinolin-4-yl)-[4-(4-methyl-[1,4]diazepan-1-yl)phenyl]amine (6d). Compound **6d** was synthesized by method A from **3p** (1.20 g, 5.5 mmol), **4f** (808 mg, 3.9 mmol), and HCl (a couple of drops) in MeOH (3.0 mL). The temperature was 120 °C and the reaction time was 70 min. Yield 320 mg (21%), yellow solid. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.60 (d, $J = 8.5$ Hz, 1H), 7.38 (d, $J = 6.9$ Hz, 1H), 7.13 (dd, $J = 8.5$, 6.9 Hz, 1H), 6.66 (m, 2H), 6.54 (m, 2H), 5.62 (br s, 1H), 3.52 (m, 2H), 3.40 (m, 2H), 2.78 (m, 2H), 2.78 (s, 3H), 2.77 (s, 3H), 2.71 (m, 2H), 2.61 (m, 2H), 2.40 (s, 3H), 2.01 (m, 2H), 1.16 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm): 157.61, 146.53, 144.76, 144.76, 136.54, 135.95, 128.44, 126.37, 124.20, 122.84, 122.08, 119.56, 112.60, 58.36, 57.10, 48.44, 46.53, 27.67, 24.33, 21.15, 18.20, 13.60. HRMS *m*/*z* calcd for $C_{25}H_{33}N_4$ $[M + H]^+$ 389.2705, found 389.2710.

{4-[4-(3,4-Dimethylpiperazin-1-yl)phenylamino]-2-methylquinolin-3-yl}methanol (6e): Method B. A solution of **3u** (81 mg, 0.32 mmol), **4c** (60 mg, 0.29 mmol), and *p*-TsOH·H_2O (1 mg, cat.) in MeOH (500 μL) were heated at 125 °C by microwave irradiation for 20 min. Solvent was evaporated in vacuo and the residue was dissolved in water, made alkaline with aqueoue saturated $NaHCO_3$ solution, and extracted twice with CH_2Cl_2. Combined organic phases were dried over Na_2SO_4 and evaporated in vacuo. The product was purified by flash chromatography (CH_2Cl_2/MeOH = 19:1) to obtain 75 mg (62%) of 4-[4-(3,4-dimethylpiperazin-1-yl)phenylamino]-2-methylquinoline-3-carboxylic acid ethyl ester as a yellow oil.

To a cooled (0 °C) mixture of $LiAlH_4$ (34 mg, 0.90 mmol) in THF (1.5 mL) under argon atmosphere, a solution of 4-[4-(3,4-dimethylpiperazin-1-yl)phenylamino]-2-methylquinoline-3-carboxylic acid ethyl ester (75 mg, 0.18 mmol) in THF (1.5 mL) was added dropwise with the help of a syringe. After 30 min of reaction time at 0 °C, the reaction mixture was allowed to warm to room temperature and stirring was continued for 2 h. The reaction was cooled (0 °C) and quenched by adding water. The mixture was diluted with THF and filtered. The precipitate was washed a few times with THF and the filtrate was evaporated in vacuo. The product was purified by flash chromatography (CH_2Cl_2/MeOH = 9:1) to obtain 42 mg (62%) of **6e** as a yellow solid. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.92 (m, 1H), 7.63 (m, 1H), 7.52 (m, 1H), 7.51 (br s, 1H), 7.15 (m, 1H), 6.78 (m, 4H), 4.82 (s, 2H), 3.40 (m, 1H), 3.34 (m, 1H), 2.86 (m, 2H), 2.57 (s, 3H), 2.49 (m, 1H), 2.42 (m, 1H), 2.33 (s, 3H), 2.26 (m, 1H), 1.12 (d, $J = 6.1$ Hz, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm): 157.26, 148.37, 147.42, 146.64, 137.23, 129.55, 127.77, 124.92, 124.41, 121.43, 120.97, 120.14, 117.25, 58.87, 57.77, 57.05, 55.65, 49.88, 42.54, 22.97, 17.25. HRMS *m*/*z* calcd for $C_{23}H_{29}N_4O$ $[M + H]^+$ 377.2341, found 377.2325.

{2-Methyl-4-[4-(3,3,4-trimethylpiperazin-1-yl)phenylamino]-quinolin-3-yl}methanol (6f). Compound **6f** was synthesized by method B starting from **3u** (167 mg, 0.67 mmol), **4i** (96 mg, 0.44 mmol), and *p*-TsOH·H_2O (1 mg) in MeOH (750 μL). The thus-obtained 2-methyl-4-[4-(3,3,4-trimethylpiperazin-1-yl)phenylamino]-quinoline-3-carboxylic acid ethyl ester (119 mg, 0.28 mmol) was treated with $LiAlH_4$ (56 mg, 1.48 mmol) in THF to yield 24 mg (22%) of **6f** as a yellow solid. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.94 (m, 1H), 7.65 (m, 1H), 7.54 (m, 1H), 7.41 (br s, 1H), 7.18 (m, 1H), 6.77 (m, 4H), 4.83 (s, 2H), 3.12 (m, 2H), 2.85 (s, 2H), 2.69 (m, 2H), 2.63 (s, 3H), 2.29 (s, 3H), 1.12 (s, 6H). ^{13}C NMR ($CDCl_3$, δ, ppm): 157.18, 148.42, 147.33, 137.06, 129.60, 127.73, 124.90, 124.46, 121.42, 120.93, 120.11, 117.51, 63.15, 58.92, 53.80, 50.20, 49.98, 37.23, 23.43, 22.97, 20.07. HRMS *m*/*z* calcd for $C_{24}H_{31}N_4O$ $[M + H]^+$ 391.2498, found 391.2488.

1-{4-[4-(3,4-Dimethylpiperazin-1-yl)phenylamino]-2-methylquinolin-3-yl}ethanol (6g). Compound **6g** was synthesized by method B starting from **3v** (138 mg, 0.62 mmol), **4c** (119 mg, 0.58 mmol), and *p*-TsOH·H_2O (1 mg) in MeOH (500 μL). The thus obtained 1-{4-[4-(3,4-dimethylpiperazin-1-yl)phenylamino]-2-methylquinolin-3-yl}ethanone (82 mg, 0.22 mmol) was treated with $LiAlH_4$ (20 mg, 0.44 mmol) in THF to yield 56 mg (65%) of **6g** as a yellow solid. ^{1}H NMR ($CDCl_3$, δ, ppm): 8.62 (br s, 1H), 7.91 (m, 1H), 7.56 (m, 1H), 7.48 (m, 1H), 7.08 (m, 1H), 6.78 (m, 2H), 6.73 (m, 2H), 5.34 (q, $J = 6.7$ Hz, 1H), 3.37 (m, 2H), 2.87 (m, 2H), 2.50 (s, 3H), 2.49 (m, 1H), 2.41 (m, 1H), 2.32 (s, 3H), 2.26 (m, 1H), 1.48 (d, $J = 6.7$ Hz, 3H), 1.11 (d, $J = 6.1$ Hz, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm): 155.07, 148.65, 146.57, 137.59, 129.46, 127.00, 125.33, 124.18, 124.07, 122.12, 121.58, 120.50, 117.17, 116.92, 66.93, 57.82, 56.88, 55.66, 49.68, 42.52, 22.66, 21.08, 17.20. HRMS *m*/*z* calcd for $C_{24}H_{31}N_4O$ $[M + H]^+$ 391.2498, found 391.2488.

(*R*)-{4-[4-(3,4-Dimethylpiperazin-1-yl)phenylamino]-3-methylquinolin-2-yl}methanol (6h). Compound **6h** was synthesized by method B starting from **3q** (467 mg, 1.87 mmol), **4d** (297 mg, 1.45 mmol), and *p*-TsOH·H_2O (5 mg) in MeOH (600 μL). The thus-obtained (*R*)-4-[4-(3,4-dimethylpiperazin-1-yl)phenylamino]-3-methylquinoline-2-carboxylic acid ethyl ester (170 mg, 0.41 mmol) was treated with $LiAlH_4$ (76 mg, 2.03 mmol) in THF to yield 97 mg (63%) of **6h** as a yellow solid. ^{1}H NMR ($CDCl_3$, δ, ppm): 8.03 (m, 1H), 7.82 (m, 1H), 7.62 (m, 1H), 7.37 (m, 1H), 6.83 (m, 2H), 6.71 (m, 2H), 5.92 (br s, 1H), 4.82 (s, 2H), 3.40 (m, 1H), 3.34 (m, 1H), 2.90 (m, 2H), 2.51 (m, 1H), 2.44 (m, 1H), 2.35 (s, 3H), 2.28 (m, 1H), 2.11 (s, 3H), 1.14 (d, $J = 6.1$ Hz, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm): 158.14, 146.23, 145.92, 144.65, 137.49, 128.90, 128.78, 125.45, 123.15, 122.83, 118.91, 117.73, 117.53, 62.22, 57.84, 57.21, 55.66, 50.03, 42.51, 17.21, 11.82. HRMS *m*/*z* calcd for $C_{23}H_{29}N_4O$ $[M + H]^+$ 377.2341, found 377.2350.

{4-[4-(3,3,4-Trimethylpiperazin-1-yl)phenylamino]quinolin-3-yl}methanol (6i). Compound **6i** was synthesized by method B starting from **3b** (90 mg, 0.38 mmol), **4i** (67 mg, 0.31 mmol), and *p*-TsOH·H_2O (1 mg) in MeOH (700 μL). The thus-obtained 4-[4-(3,3,4-trimethylpiperazin-1-yl)phenylamino]quinoline-3-carboxylic acid ethyl ester (42 mg, 0.10 mmol) was treated with $LiAlH_4$ (26 mg, 0.68 mmol) in THF to yield 18 mg (48%) of **6i** as a yellow solid. ^{1}H NMR ($CDCl_3$, δ, ppm): 8.45 (s, 1H), 7.97 (m, 1H), 7.70 (m, 1H), 7.56 (m, 1H), 7.50 (br s, 1H), 7.22 (m, 1H), 6.82 (m, 2H), 6.78 (m 2H), 4.77 (s, 2H), 3.15 (m, 2H), 2.91 (s, 2H), 2.76 (m, 2H), 2.33 (s, 3H), 1.16 (s, 6H). ^{13}C NMR ($CDCl_3$, δ, ppm): 150.19, 149.05, 148.07, 147.46, 136.61, 129.38, 128.99, 124.95, 124.82, 121.63, 120.80, 120.96, 117.51, 63.49, 62.74, 61.77, 50.09, 49.65, 37.03, 20.10. HRMS *m*/*z* calcd for $C_{23}H_{29}N_4O$ $[M + H]^+$ 377.2341, found 377.2345.

(*R*)-{4-[4-(3,4-Dimethylpiperazin-1-yl)phenylamino]quinolin-3-yl}methanol (6j). Compound **6j** was synthesized by method B starting from **3b** (0.744 g, 3.16 mmol), **4d** (0.588 g, 2.87 mmol), and *p*-TsOH·H_2O (3 mg) in MeOH (2.0 mL). The thus-obtained (*R*)-4-[4-(3,4-dimethylpiperazin-1-yl)phenylamino]quinoline-3-carboxylic acid ethyl ester (0.875 g, 2.10 mmol) was treated with $LiAlH_4$ (0.431 g, 10.8 mmol) in THF to yield 0.635 g (85%) of **6j** as a yellow solid.^{1}H NMR ($CDCl_3$, δ, ppm): 8.34 (s, 1H), 7.94 (m, 1H), 7.70 (m, 1H), 7.53 (m, 1H), 7.47 (br s, 1H), 7.20 (m, 1H), 6.80 (m, 4H), 4.73 (s, 2H), 3.40 (m, 1H), 3.35 (m, 1H), 2.86 (m, 2H), 2.49 (m, 1H), 2.41 (m, 1H), 2.32 (s, 3H), 2.26 (m, 1H), 1.12 (d, $J = 6.1$ Hz, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm): 150.52, 149.42, 147.85, 146.89, 136.72, 129.26, 129.18, 124.96, 124.70,

121.71, 121.11, 120.77, 117.12, 61.73, 57.77, 56.99, 55.63, 49.82, 42.53, 17.23. HRMS *m/z* calcd for $C_{22}H_{27}N_4O$ $[M + H]^+$ 363.2185, found 363.2181.

(*R*)-{4-[4-(3-Methylpiperazin-1-yl)phenylamino]quinolin-3-yl}methanol (6k). To a cooled (0 °C) mixture of $LiAlH_4$ (0.645 g, 17.3 mmol) in THF (1.5 mL) under argon atmosphere, a solution of **10** (0.933 g, 2.39 mmol) in THF (1.5 mL) was added dropwise with the aid of a syringe. After 30 min of reaction time at 0 °C, the reaction mixture was allowed to warm to room temperature and stirring was continued for 2 h. The reaction was cooled (0 °C) and quenched by adding water. The mixture was diluted with THF and filtered. The precipitate was washed a few times with THF and the filtrate was evaporated in vacuo. The product was purified by flash chromatography (CH_2Cl_2/MeOH = 9:1) to obtain 295 mg (35%) of **6k** as a yellow solid. ^{1}H NMR ($CDCl_3$, δ, ppm): 8.47 (s, 1H), 7.98 (m, 1H), 7.72 (m, 1H), 7.57 (m, 1H), 7.33 (br s, 1H), 7.23 (m, 1H), 6.82 (m, 4H), 4.78 (s, 2H), 3.42 (m, 2H), 3.09 (m, 1H), 3.04 (m, 1H), 2.98 (m, 1H), 2.66 (m, 1H), 2.31 (m, 1H), 1.11 (d, J = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm): 150.47, 149.34, 147.88, 147.31, 136.77, 129.20, 124.98, 124.69, 121.69, 121.15, 120.78, 117.32, 61.67, 57.60, 50.70, 50.02, 45.85, 19.70. HRMS *m/z* calcd for $C_{21}H_{25}N_4O$ $[M + H]^+$ 349.2028, found 349.2040.

{7-Chloro-4-[4-(3,3,4-trimethylpiperazin-1-yl)phenylamino]-quinolin-3-yl}methanol (6l). Compound **6l** was synthesized by method B starting from **3s** (79 mg, 0.29 mmol), **4i** (55 mg, 0.25 mmol), and *p*-TsOH·H_2O (9 mg, 0.05 mmol) in MeOH (500 μL). The thus-obtained 7-chloro-4-[4-(3,3,4-trimethylpiperazin-1-yl)-phenylamino]quinoline-3-carboxylic acid ethyl ester (77 mg, 0.17 mmol) was treated with $LiAlH_4$ (36 mg, 0.94 mmol) in THF to yield 39 mg (53%) of **6l** as a yellow solid.^{1}H NMR ($CDCl_3$, δ, ppm): 8.37 (s, 1H), 7.91 (d, J = 1.8 Hz, 1H), 7.57 (d, J = 9.2 Hz, 1H), 7.53 (br s, 1H), 7.11 (dd, J = 9.2, 1.8 Hz, 1H), 6.78 (m, 4H), 4.76 (s, 2H), 3.15 (m, 2H), 2.89 (s, 2H), 2.73 (m, 2H), 2.31 (s, 3H), 1.15 (s, 6H). ^{13}C NMR ($CDCl_3$, δ, ppm): 151.50, 150.10, 148.11, 147.74, 136.17, 135.04, 128.12, 126.49, 125.44, 121.12, 120.79, 119.81, 117.44, 62.77, 61.75, 54.26, 50.15, 49.65, 37.15, 20.17. HRMS *m/z* calcd for $C_{23}H_{28}N_4OCl$ $[M + H]^+$ 411.1952, found 411.1954.

{4-[4-(3,4-Dimethylpiperazin-1-yl)phenylamino]-6-fluoroquinolin-3-yl}methanol (6m). Compound **6m** was synthesized by method B starting from **3t** (100 mg, 0.39 mmol), **4c** (72 mg, 0.35 mmol), and *p*-TsOH·H_2O (1 mg) in MeOH (500 μL). The thus-obtained 4-[4-(3,4-dimethylpiperazin-1-yl)phenylamino]-6-fluoroquinoline-3-carboxylic acid ethyl ester (123 mg, 0.29 mmol) was treated with $LiAlH_4$ (54 mg, 1.45 mmol) in THF to yield 30 mg (27%) of **6m** as a yellow solid. ^{1}H NMR ($CDCl_3$, δ, ppm): 8.34 (s, 1H), 7.91 (m, 1H), 7.39 (br s, 1H), 7.26 (m, 2H), 6.76 (m, 4H), 4.73 (s, 2H), 3.38 (m, 1H), 3.33 (m, 1H), 2.85 (m, 2H), 2.49 (m, 1H), 2.41 (m, 1H), 2.31 (s, 3H), 2.27 (m, 1H), 1.10 (d, J = 6.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm): 160.01, 158.05, 149.91, 147.44, 146.53, 136.14, 131.76, 122.63, 121.67, 120.79, 119.53, 119.33, 117.32, 108.73, 108.54, 61.63, 57.82, 56.86, 55.53, 49.71, 42.45, 17.11. HRMS *m/z* calcd for $C_{22}H_{26}N_4OF$ $[M + H]^+$ 381.2091, found 381.2095.

{6-Fluoro-4-[4-(3,3,4-trimethylpiperazin-1-yl)phenylamino]-quinolin-3-yl}methanol (6n). Compound **6n** was synthesized by method B starting from **3t** (97 mg, 0.38 mmol), **4i** (73 mg, 0.33 mmol), and *p*-TsOH·H_2O (7 mg, 0.04 mmol) in MeOH (500 μL). The thus-obtained 6-fluoro-4-[4-(3,3,4-trimethylpiperazin-1-yl)-phenylamino]quinoline-3-carboxylic acid ethyl ester (111 mg, 0.25 mmol) was treated with $LiAlH_4$ (52 mg, 1.37 mmol) in THF to yield 57 mg (57%) of **6n** as a yellow solid. ^{1}H NMR ($CDCl_3$, δ, ppm): 8.35 (s, 1H), 7.92 (m, 1H), 7.48 (br s, 1H), 7.29 (m, 2H), 6.76 (m, 4H), 4.75 (s, 2H), 3.13 (m, 2H), 2.88 (s, 2H), 2.72 (m, 2H), 2.30 (s, 3H), 1.15 (s, 6H). ^{13}C NMR ($CDCl_3$, δ, ppm): 159.99, 158.04, 149.97, 147.42, 146.47, 136.20, 131.70, 122.62, 121.92, 120.64, 119.48, 119.27, 117.65, 108.75, 108.56, 62.88, 61.50, 54.33, 50.17, 49.72, 37.13, 20.08. HRMS *m/z* calcd for $C_{23}H_{28}N_4OF$ $[M + H]^+$ 395.2247, found 395.2270.

(*R*)-{4-[4-(3,4-Dimethylpiperazin-1-yl)phenylamino]-6-fluoroquinolin-3-yl}methanol (6o). A solution of **3t** (0.613 g, 2.41 mmol), **4d** (0.455 g, 2.21 mmol), and *p*-TsOH·H_2O (1 mg) in MeOH (3.0 mL) was stirred at room temperature overnight. The reaction mixture was diluted with water (100 mL), made alkaline with aqueoue saturated $NaHCO_3$ solution, and extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by flash chromatography (CH_2Cl_2/MeOH = 19:1) to obtain 0.586 g (63%, 1.39 mmol) of (*R*)-4-[4-(3,4-dimethylpiperazin-1-yl)phenylamino]-6-fluoroquinoline-3-carboxylic acid ethyl ester, which was treated with $LiAlH_4$ (0.487 g, 13.1 mmol) in THF according to method B to yield 386 mg (73%) of **6o** as a yellow solid. ^{1}H NMR ($CDCl_3$, δ, ppm): 8.36 (s, 1H), 7.91 (m, 1H), 7.37 (br s, 1H), 7.26 (m, 2H), 6.77 (m, 4H), 4.74 (s, 2H), 3.39 (m, 1H), 3.33 (m, 1H), 2.86 (m, 2H), 2.49 (m, 1H), 2.42 (m, 1H), 2.31 (s, 3H), 2.27 (m, 1H), 1.11 (d, J = 6.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm): 160.02, 158.06, 149.94, 147.42, 146.56, 136.14, 131.79, 122.56, 121.64, 120.79, 119.54, 119.33, 117.32, 108.72, 108.53, 61.66, 57.83, 56.86, 55.54, 49.71, 42.45, 17.11. HRMS *m/z* calcd for $C_{22}H_{26}N_4OF$ $[M + H]^+$ 381.2091, found 381.2093.

(3,5-Dimethyl-pyridin-4-yl)-[4-(4-methylpiperazin-1-yl)phenyl]amine (7). Compounds **16** (179 mg, 1.0 mmol) and **4g** (97 mg, 0.51 mmol) were mixed and heated in an open reaction vessel by an electric mantle until they melted. The heating and stirring was continued at that temperature for 1 h. The reaction mixture was cooled and dissolved in water. The solution was made alkaline with a saturated aqueous $NaHCO_3$ solution and extracted with $CHCl_3$. The organic phase was dried over Na_2SO_4, evaporated in vacuo, and purified by flash chromatography (CH_2Cl_2/MeOH = 9:1) to obtain 22 mg (15%) of the desired compound as a red solid. ^{1}H NMR ($CDCl_3$, δ, ppm): 8.14 (m, 2H), 6.87 (m, 2H), 6.78 (m, 2H), 5.71 (br s, 1H), 3.22 (m, 4H), 2.67 (m, 4H), 2.42 (s, 3H), 2.01 (s, 6H). ^{13}C NMR ($CDCl_3$, δ, ppm): 149.15, 147.51, 147.27, 135.01, 121.46, 117.14, 54.98, 49.39, 45.82, 15.97. HRMS *m/z* calcd for $C_{18}H_{25}N_4$ $[M + H]^+$ 297.2079, found 297.2079.

[4-(3,4-Dimethylpiperazin-1-yl)phenyl]-(3-ethyl-2-methyl-5,6,7,8-tetrahydroquinolin-4-yl)amine (8). Compound **8** was synthesized by method A from **13** (169 mg, 0.81 mmol), **4c** (82 mg, 0.40 mmol), and HCl (a couple of drops) in MeOH (1.5 mL). The temperature was 145 °C and the reaction time was 60 min. Yield 54 mg (36%), yellow solid. ^{1}H NMR ($CDCl_3$, δ, ppm): 6.79 (m, 2H), 6.60 (m, 2H), 5.25 (br s, 1H), 3.33 (m, 2H), 2.85 (m, 4H), 2.53 (q, J = 7.6 Hz, 2H), 2.50 (s, 3H), 2.48−1.37 (m, 2H), 2.32 (t, J = 6.1 Hz, 2H), 2.31 (s, 3H), 2.22 (m, 1H), 1.77 (m, 2H), 1.62 (m, 2H), 1.10 (d, J = 6.1 Hz, 3H), 1.02 (t, J = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm): 145.86, 137.74, 127.79, 124.16, 118.51, 117.47, 57.83, 57.44, 55.79, 50.22, 42.60, 32.51, 25.31, 22.90, 22.72, 22.16, 20.82, 17.32, 13.64. HRMS *m/z* calcd for $C_{24}H_{35}N_4$ $[M + H]^+$ 379.2862, found 379.2861.

***N*-(3-Methylaminopropyl)-*N*′-(2,3,8-trimethylquinolin-4-yl)-benzene-1,4-diamine (9).** Compound **9** was synthesized by method B from **3a** (223 mg, 1.08 mmol), **4a** (187 mg, 1.04 mmol), and HCl (a couple of drops) in MeOH (750 μL). The temperature was 120 °C and the reaction time was 15 min. Yield 187 mg (52%), red solid. MS (ESI) *m/z* 349 $[M + H]^+$.

(*R*)-4-[4-(3-Methylpiperazin-1-yl)phenylamino]quinoline-3-carboxylic Acid Ethyl Ester (10). Compound **10** was synthesized by method B starting from five batches of **3b** (0.293 g each, total amount 1.464 g, 5.54 mmol), **4b** (163 mg each, total amount 0.815 g, 4.26 mmol), and *p*-TsOH·H_2O (10 mg each, total amount 50 mg, 0.26 mmol) in MeOH (1.5 mL in each). Yield 0.933 g (56%), yellow solid. MS (ESI) *m/z* 391 $[M + H]^+$.

2-(1-Ethoxyethylidene)malonic Acid Diethyl Ester (15b): Method C. A solution of **14a** (1.59 mL, 10.5 mmol), triethyl orthoacetate (5.61 mL, 30.8 mmol), Ac_2O (35 μL, 0.32 mmol), and $ZnCl_2$ (0.4 mg, cat.) was heated in a reaction vessel equipped with a distillation bridge and a thermometer. At a vapor temperature of 70 °C, side products formed in the reaction and started to distill out. Ac_2O (35 μL) was added three times every 30 min. After 4 h of heating, the reaction mixture was allowed to cool to room temperature. The reaction mixture was evaporated gently under reduced pressure to remove low-volatile starting materials and side

products. The residue was purified by flash chromatography (hexane/EtOAc = 3:1) to obtain 1.70 g (70%) of **15b** as a yellowish oil. MS (ESI) *m*/*z* 231 $[M + H]^+$.

2-(1-Ethoxyethylidene)malonic Acid Diethyl Ester (15c). Compound **15c** was synthesized by method C from **14b** (2.68 mL, 21 mmol), triethyl orthoacetate (11.2 mL, 61 mmol), Ac_2O (420 μL, 4.4 mmol), and $ZnCl_2$ (1 mg, cat.). Ac_2O was added in six portions every 30 min. Yield 1.20 g (29%), yellowish oil. MS (ESI) *m*/*z* 201 $[M + H]^+$.

4-Chloro-3,5-dimethylpyridine Hydrochloric Acid Salt (16). A solution of 3,5-lutidine (5.76 mL, 50 mmol) in thionyl chloride (30 mL, 0.41 mol) was refluxed for 100 h. The reaction mixture was cooled to room temperature. The formed precipitate was filtered and washed with toluene. Yield 2.82 g (32%), brown solid. ^{1}H NMR (CD_3OD, δ, ppm) 8.71 (s, 2 H), 2.58 (s, 6 H).

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Supporting Information Available: ^{1}H NMR spectra and LC−MS data of compounds **5a**−**x**, **6a**−**o**, **7**, and **8**; experimental data for **3a**−**v**, **4a**−**k**, **12a**−**w**, **13**, **18a**−**e**, and **19**−**25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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