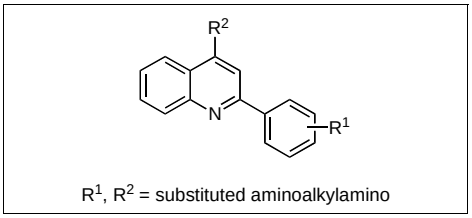
Synthesis of 2-Phenylquinolin-4-amines Substituted with Diverse Amino and Aminoalkyl Groups

Martial Say, Ekaterina Paliakov, Maged Henary and Lucjan Strekowski*

Department of Chemistry, Georgia State University,
Atlanta, Georgia 30302-4098,
e-mail: lucjan@gsu.edu

Received March 10, 2006



Facile synthetic approaches to 2-phenylquinolin-4-amines containing an aminoalkyl group at N^4 of the quinolin-4-amine and amino or aminoalkyl groups at the phenyl moiety are presented.

J. Heterocyclic Chem., **43**, 1613 (2006).

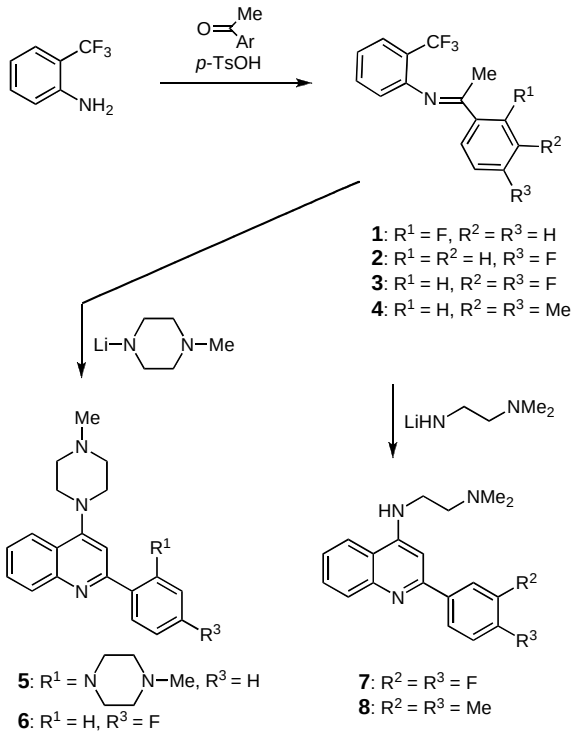
Substituted quinolin-4-amines exhibit a variety of biological activities. Many compounds of this class are important agrochemicals due to their fungicidal, insecticidal, and pesticidal properties [1]. Others are drugs currently in clinical use. Thus, quinolin-4-amines are antimalarial, antiviral, antitumor, anti-inflammatory, analgesic, immunostimulatory, and hypotensive agents [1]. Recently, there has been an immense interest in 2-arylquinolin-4-amines substituted with additional amino groups. Such quinolines can intercalate with poly(dT•dA•dT) and stabilize this triple-helix DNA structure with high selectivity in the presence of duplex DNA of any sequence [2]. This feature has important ramifications for the development of a therapeutic methodology known as antigene strategy [3]. Specifically, it has been suggested that the triple-helix formed from the cellular duplex and an external third strand followed by stabilization of the resultant triplex can be used to directly regulate the expression of a selected gene.

2-Arylquinolin-4-amines functionalized with additional amino groups are also potent antagonists of immunostimulatory bacterial DNA which contains a CpG motif [4]. Extensive research is being conducted to develop such substituted quinolin-4-amines into practical drugs for inducing remission in systemic lupus erythematosus and rheumatoid arthritis [5,6]. It has also been suggested that, due to their immunosuppressive properties, such compounds can be useful in the prevention of graft-versus-host disease in bone transplant patients [7].

This report pertains to the synthesis of new amino derivatives of 2-phenylquinolin-4-amines as potential triple-helix DNA stabilizing and immunosuppressive agents. The goal was to develop simple methodologies for the preparation of a large number of compounds for structure-activity analyses.

Cyclization of ketimines such as **1**-**4** (Scheme 1) by the reactions with lithium dialkylamides is a convenient methodology for the synthesis of *N*-substituted 2-arylquinolin-4-amines [4,8-10]. This is illustrated by cyclization of ketimine **1** in the presence of lithium 4-methylpiperazide that, unexpectedly, also results in nucleophilic displacement of the 2-fluorine atom at the phenyl group to give a dipiperazino derivative **5** in high yield (vide infra) [11]. On the other hand, a similar reaction of a 4-fluorophenyl ketimine gives a 4-piperazinoquinoline as shown in Scheme 1 by the previously unpublished synthesis of **6** from **2**. This cyclization methodology is successful for any lithium reagent derived

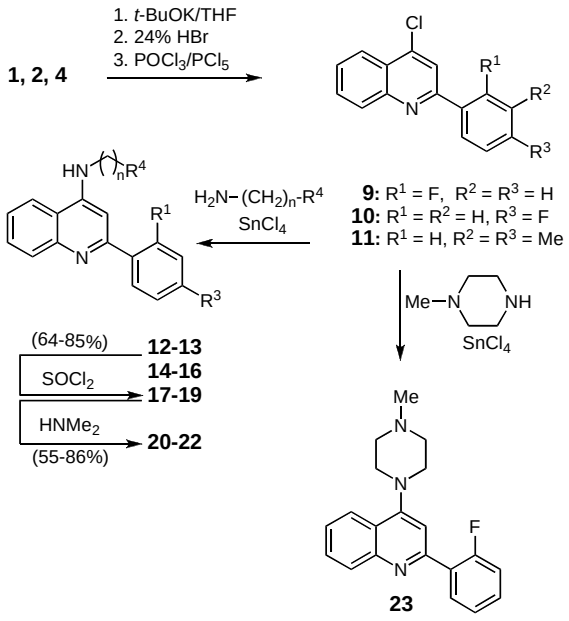
Scheme 1



from a secondary amine and with lithium 2-(dimethylamino)ethylamide as illustrated by a high-yield preparation of new quinolin-4-amines **7** and **8**. Unfortunately, treatment of the ketimines with lithium reagents derived from other primary amines including the simple homolog 3-(dimethylamino)propylamine results in the formation of an amidine as the major or sole product [8,9].

A solution to this problem is provided in Scheme 2 by the synthesis of a 4-chloroquinoline followed by treatment of this intermediate product with an amine. As part of this work it was found that 4-chloroquinolines **9**-**11** are conveniently prepared by cyclization of the respective ketimines **1**, **2**, and **4** with potassium *tert*-butoxide followed by hydrolysis of the resultant 4-*tert*-butoxyquinolines and then treatment of the intermediate 4-hydroxyquinolines with a mixture of phosphorus pentachloride and phosphorus oxychloride. Since the first two steps are highly efficient [12], the previously published procedure was simplified in that the intermediate 4-*tert*-butoxy and 4-hydroxyquinolines were used for the third step without purification. Moreover, the final 4-chloroquinolines are purified by simple crystallization. Our first attempts of a nucleophilic displacement of the C4-chlorine by heating mixtures of **9** or **10** with various amines in the absence of any additive were largely unsuccessful. It was found, however, that *N*-substituted quinolin-4-amines could be obtained in moderate yields by heating the mixtures in the presence of phenol. Similar results were obtained by using boron trifluoride as a catalyst.

Scheme 2



12-22	R^1	R^3	R^4	n
12	F	H	NMe_2	3
13	H	F	NMe_2	3
14	F	H	OH	4
15	H	F	OH	4
16	H	F	OH	6
17	F	H	Cl	4
18	H	F	Cl	4
19	H	F	Cl	6
20	F	H	NMe_2	4
21	H	F	NMe_2	4
22	H	F	NMe_2	6

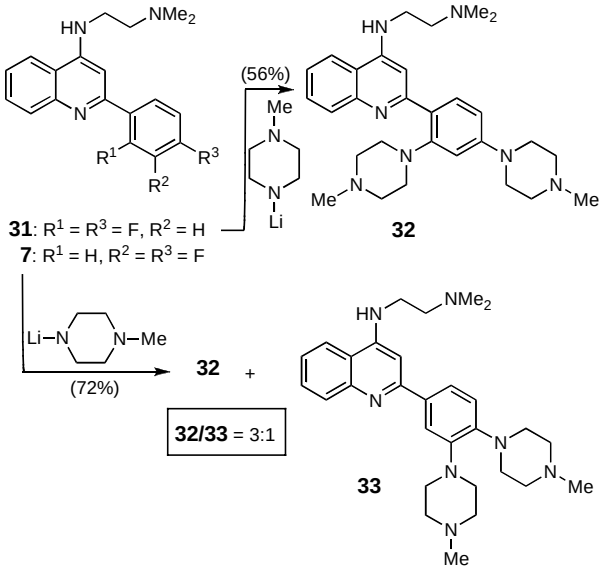
Subsequently, it was found that the substitution reaction proceed with high efficiency and at a relatively low temperature in the presence of a catalytic amount of tin tetrachloride. It can be suggested that complexation of the quinoline N1-atom by this Lewis acid renders the C4-atom more electrophilic, that is, more reactive toward a nucleophilic attack. The intermediate σ-adduct may also be stabilized by the nitrogen-tin interaction.

This methodology for the introduction of an amino group at the position 4 of the quinoline is general, and a large number of compounds were prepared in this fashion. Selected examples are shown in Scheme 2 for illustration. An additional advantage is the possibility to synthesize *N*-substituted quinolin-4-amines for which the amine precursors are not available commercially. Examples are compounds **20**-**22** which were obtained by the reaction of 4-chloroquinolines **9**, **10** with the corresponding ω-hydroxyalkylamines followed by treatment of the resultant alcohols **14**-**16** with thionyl chloride to give alkyl chlorides **17**-**19**, and then the reaction of the alkyl chlorides with dimethylamine.

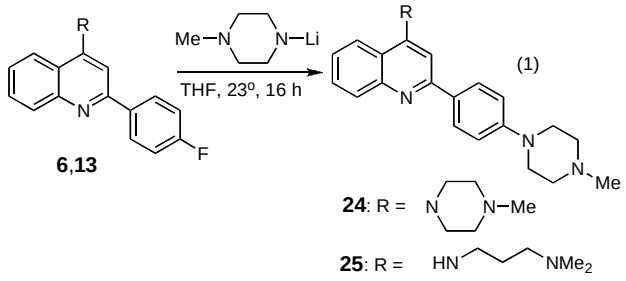
The previous observation of facile nucleophilic displacement of the fluorine atom in the 2-fluorophenyl substituent, as mentioned above, prompted us to study the scope and limitations of the use of other fluorophenyl-substituted quinolines for the synthesis of aminophenyl-substituted derivatives. Previously, it has also been noted that a 2-(2,4-difluorophenyl)quinoline **31** is formed upon cyclization of the corresponding ketimine in the presence of lithium 2-(dimethylamino)ethylamide [11]. Thus, the 2-fluoro substituent at the phenyl group was replaced in the presence of a strongly nucleophilic secondary amide reagent, while the 2-fluorine atom was retained for the reaction conducted with less reactive primary lithium reagent. The quinolines **31** and **7** were used in the initial studies (Scheme 3). As can be seen, a prolonged treatment of the 2,4-difluorophenyl derivative **31** with lithium 4-methylpiperazide resulted in the *ipso* displacement of the two fluorine atoms to give product **32** in good yield. On the other hand, a similar treatment of a 3,4-difluorophenyl derivative **7** gave the same compound **32** and a 2-(3,4-dipiperazino)quinoline **33** as the major and minor product, respectively. In the light of the data already mentioned (see synthesis of **6**, Scheme 1) it can be suggested that the relatively facile displacement of the 2-fluorine atom in **31** is

followed by a slow displacement of the 4-fluorine atom. The presumed initial displacement of the 2-fluorine atom in **31** is consistent with the complex-induced proximity effect (CIPE) [13]. More specifically, it can be suggested that the quinoline N1 atom forms a complex with a lithium reagent resulting in a favorable positioning of this reagent for the nucleophilic displacement of the adjacent fluorine atom at the 2-fluorophenyl group. A similar complexation of **7** may result in lithiation at the unsubstituted adjacent position 2 of the 3,4-difluorophenyl group. It is suggested that the resultant 3,4-difluorophenyl-2-lithio derivative undergoes elimination of fluoride to generate a 2,3-didehydrobenzene (benzyne). Then, addition reaction of this intermediate with amide anion followed by *ipso* displacement of the remaining 4-fluoro substituent by an apparent S_NAr mechanism gives **32** which is the observed major product. Again, the preferential formation of **32** rather than **33** is consistent with the involvement of the CIPE process.

Scheme 3

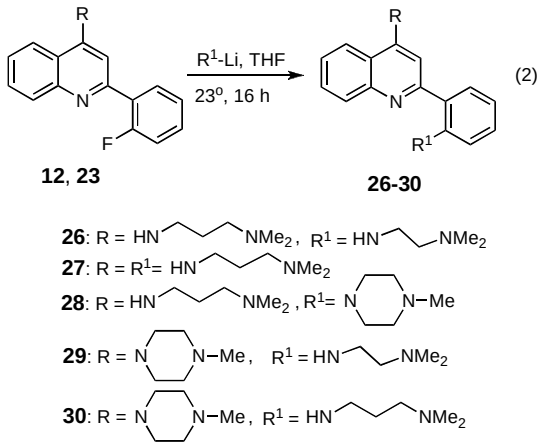


Additional studies were conducted with 2-(4-fluorophenyl)quinolin-4-amines **6**, **13** (Equation 1) and their 2-fluorophenyl analogs **12**, **23** (Equation 2). The expected *ipso* displacement pattern was observed in all cases shown.



However, there are major differences between the reactivities of 4-fluorophenyl and 2-fluorophenyl derivatives toward secondary and primary lithium amides.

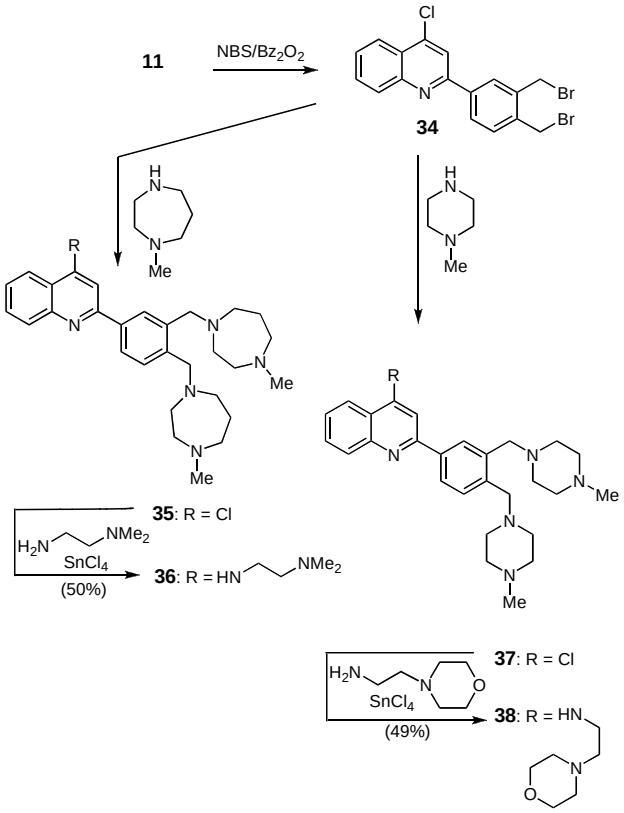
Thus, the facile synthesis of 4-aminophenyl derivatives such as **24** and **25** is restricted to the reactions of secondary lithium amides such as lithium 4-methylpiperazide. Numerous attempts to force the displacement reactions of **6** and **13** by using lithium amides derived from primary amines were all unsuccessful. By contrast, as illustrated in Equation 2, the displacement of the 2-fluorine atom in **12** and **23** to give the corresponding products **26**-**30** was successful by using either an alkylamide or dialkylamide reagent. Also, the synthesis of 2-aminophenyl derivatives required about a four-fold shorter period of time than the preparation of the 4-aminophenyl counterparts conducted under similar conditions.



A different approach to the synthesis of amino functionalized 2-(2-phenyl)quinolines is presented in Scheme 4.

The methodology is based on the efficient preparation of methyl substituted homologs of 4-chloro-2-phenylquinoline, and the chemistry starting with a dimethyl derivative **11** is provided as an example. Compound **11** was brominated at the methyl groups in the presence of *N*-bromosuccinimide and a catalytic amount of dibenzoyl peroxide to give a bis(bromomethyl) derivative **34**. A subsequent reaction of **34** with 4-methylhomopiperazine was selective in that only the bromine atoms were displaced resulting in the formation of a substituted 4-chloroquinoline **35**. The treatment of **35** with 2-(dimethylamino)ethylamine in the presence of a catalytic amount of tin tetrachloride gave a polyamino substituted 2-phenylquinoline **36**. In the synthesis of an analogous product **38** the crude intermediate 4-chloroquinoline **37** was subjected to the reaction with an amine, resulting in simplification of the procedure.

Scheme 4



In summary, several methodologies for the synthesis of polyamino substituted derivatives of 2-phenylquinolin-4-amine were analyzed. The syntheses with 4-chloroquinolines are the most general, as they allow for the preparation of a large number of the desired products starting with a single intermediate 4-chloroquinoline.

EXPERIMENTAL

All commercial reagents were used without purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately before use. Chromatography was conducted on a chromatotron with silica gel-coated rotors. Melting points (Pyrex capillary) are not corrected. Unless reported otherwise, ^{1}H nmr spectra were obtained at 400 MHz at 25° in deuteriochloroform for free bases and in deuterated dimethyl sulfoxide for hydrobromide salts with tetramethylsilane as an internal reference. The ^{19}F nmr spectra were recorded at 282 MHz in the same solvents with hexafluorobenzene as an internal reference.

Ketimines (**1-4**).

The synthesis of ketimines **1** [11] and **2** [10] has been reported previously. Compounds **3** and **4** were prepared in a similar way by condensation of 2-(trifluoromethyl)aniline with the corresponding substituted acetophenone. The oily product **3** was purified by Kugelrohr distillation (100-150°/0.3 mmHg). It was obtained as a mixture of E/Z diastereomers (1:1), as judged by ^{1}H nmr, ^{19}F nmr and TLC analysis (hexanes/ether, 19:1). Compound **4** was crystallized from hexanes, *E*/*Z* = 19:1. The stereochemistry of **4** was determined by nOe studies as described previously [14].

N-[1-(3,4-Difluorophenyl)ethylidene]-2-(trifluoromethyl) aniline (**3**).

This compound was obtained in a 67% yield; ^{1}H nmr (*E*/*Z* mixture): δ 2.15 and 2.56 (2s, 3H), 7.13-7.86 (m, 7H); ^{19}F nmr (*E*/*Z* mixture): δ 24.7, 25.6, 27.3 and 31.9 (4m, 2F), 90.1 and 99.6 (2s, 3F).

Anal. Calcd. for $C_{15}H_{10}F_5N$: C, 60.26; H, 3.36; N, 4.68. Found: C, 60.11; H, 3.40; N, 4.75.

N-[1-(3,4-Dimethylphenyl)ethylidene]-2-(trifluoromethyl)aniline (**4**).

This compound was obtained in an 83% yield; mp 49-51°; ^{1}H nmr (*E* isomer): δ 2.15 (s, 3H), 2.30 (s, 3H), 2.31 (s, 3H), 6.73 (d, J = 8 Hz, 1H), 7.11 (t, J = 8 Hz, 1H), 7.18 (d, J = 8 Hz, 1H), 7.45 (t, J = 8 Hz, 1H), 7.63 (m, 2H), 7.75 (s, 1H); ^{19}F nmr: δ 99.1 (s).

Anal. Calcd. for $C_{17}H_{16}F_3N$: C, 70.09; H, 5.54; N, 4.81. Found: C, 69.76; H, 5.74; N, 4.90.

Substituted 2-Phenylquinolin-4-amines (**5-8**).

Synthesis of **5** from **1** has been reported previously [11]. In the preparation of **6-8** by cyclization of the respective ketimines **2-4** the general procedure [8-10] was modified in that the reactions were conducted in tetrahydrofuran, under otherwise identical conditions. Products **6-8** were purified by chromatography eluting with ethyl acetate/hexanes/tri-ethylamine (10:1:1).

2-(4-Fluorophenyl)-4-(*N*-methylpiperazino)quinoline (**6**).

This compound was obtained in an 80% yield after crystallization from ethyl acetate/hexanes; mp 90-91°; ^{1}H nmr (deuterated dimethyl sulfoxide): δ 2.31 (s, 3H), 2.64 (m, 4H), 3.30 (m, 4H), 7.44 (s, 1H), 7.51 (t, J = 8 Hz, 1H), 7.69 (t, J = 8 Hz, 1H), 7.80 (d, J = 8Hz, 1H), 8.00 (m, 3H), 8.21 (m, 2H); ^{19}F nmr: δ 55.0 (s); hrms: calcd. for $C_{20}H_{20}FN_3$ m/z 321.1641, observed m/z 312.1637.

N-[(2-(Dimethylamino)ethyl]-2-(3,4-difluorophenyl)quinolin-4-amine (**7**).

This compound was obtained in a 73% yield after crystallization from ethyl acetate/hexanes; yellow needles; mp 130-131°; ^{1}H nmr: δ 2.37 (s, 6H), 2.77 (t, J = 6 Hz, 2H), 3.41 (q, J_1 = 6 Hz, J_2 = 7 Hz, 2H), 6.05 (s, exchangeable with D_2O, 1H), 6.77 (s, 1H), 7.29 (m, 1H), 7.47 (m, 1H), 7.69 (m, 1H), 7.87 (m, 2H), 7.99 (m, 1H), 8.07 (m, 1H); ^{19}F nmr: δ 23.71 (m, 1F), 23.95 (m, 1F); ms: m/z 101 (100), 240 (50), 168 (50), 327 (80, M^+).

Anal. Calcd. for $C_{19}H_{19}F_2N_3$: C, 69.70; H, 5.85; N, 12.83. Found: C, 69.70; H, 5.76; N, 12.70.

N-[2-(Dimethylamino)ethyl]-2-(3,4-dimethylphenyl)quinolin-4-amine dihydrobromide (**8**•2HBr•$H_2$0).

The oily free base was transformed into a hydrobromide by using a general procedure [10], and the salt was crystallized from ethanol/hexanes; yield 66%; white solid; mp 299-300°; ^{1}H nmr: δ 2.37 (s, 3H), 2.40 (s, 3H), 2.94 (s, 6H), 3.56 (t, J = 6 Hz, 2H), 4.13 (d, J = 6 Hz, 2H), 7.18 (s, 1H), 7.45 (d, J = 8 Hz, 1H), 7.73 (t, J = 8 Hz, 1H), 7.86 (d, J = 8 Hz, 1H), 7.94 (s, 1H), 7.99

(t, J = 8 Hz, 1H), 8.21 (d, J = 8 Hz, 1H), 8.68 (d, J = 8 Hz, 1H), 9.22 (s, exchangeable with D_2O, 1H), 9.90 (s, exchangeable with D_2O, 1H); ms: m/z 101 (30), 128 (30), 217 (50), 233 (30), 249 (50), 261 (80), 273 (20), 319 (100, M^+).

Anal. Calcd. for $C_{21}H_{25}N_3$•2HBr•H_2O: C, 50.52; H, 5.85; N, 8.42. Found: C, 50.80; H, 5.81; N, 8.44.

4-Chloroquinolines (**9-11**).

Ketimine **1**, **2** or **4** (3 mmoles) was added to a solution of potassium *tert*-butoxide (1.8 g, 16 mmoles) in anhydrous tetrahydrofuran (50 ml), and the mixture was heated under reflux for 2 hours under a nitrogen atmosphere. After cooling the mixture was treated with water (0.5 ml) and the precipitated inorganic material was filtered off. The solution containing a 4-*tert*-butoxyquinoline was treated with 18% hydrochloric acid (2 ml), and the mixture was heated under reflux for 1 hour. Concentration of the mixture on a rotary evaporator to 10 ml followed by treatment with ether (10 ml) and then refrigeration gave a precipitate of a 4-hydroxyquinoline hydrobromide. The precipitate was filtered, washed with ether, and treated with phosphorus oxychloride (5 ml) and phosphorus pentachloride (0.3 g, 1.5 mmoles). The mixture was heated under reflux for 1 hour, then cooled and poured onto ice (50 g). Neutralization of the mixture with a saturated solution of sodium bicarbonate followed by extraction with ether (3 x 15 ml) and then washing of the extract with water (2 x 10 ml), drying (Na_2SO_4) and concentration gave a brown residue of a 4-chloroquinoline **9**, **10** or **11**. Colorless crystals were obtained by crystallization from hexanes.

4-Chloro-2-(2-fluorophenyl)quinoline (**9**).

This compound was obtained in an 82% yield; mp 98-99°; ^{1}H nmr (deuterated dimethyl sulfoxide): δ 7.41 (m, 2H), 7.60 (m, 1H), 7.81 (t, J = 8 Hz, 1H), 7.93 (t, J = 8 Hz, 1H), 8.04 (d, J = 8 Hz, 1H), 8.09 (s, 1H), 8.22 (m, 1H), 8.24 (d, J = 8 Hz, 1H); ^{19}F nmr: δ 49.0 (s).

Anal. Calcd. for $C_{15}H_9ClFN$: C, 69.91; H, 3.52; N, 5.43. Found: C, 69.87; H. 3.35; N, 5.12.

4-Chloro-2-(4-fluorophenyl)quinolines (**10**).

This compound was obtained in an 80% yield; mp 90-92° (reported [4]: yield 66%, mp 90-92°).

4-Chloro-2-(3,4-dimethylphenyl)quinoline (**11**).

This compound was obtained in an 80% yield; mp 100-102°; ^{1}H nmr: δ 2.34 (s, 3H), 2.38 (s, 3H), 7.27 (d, J = 8 Hz, 1H), 7.58 (t, J = 8 Hz, 1H), 7.75 (d, J = 8 Hz, 1H), 7.84 (d, J = 8 Hz, 1H), 7.94 (m, 2H), 8.16 (d, J = 8 Hz, 1H), 8.20 (d, J = 8 Hz, 1H); hr-fab-ms: calcd for $C_{17}H_{15}{}^{35}ClN$ (M^++1) m/z 268.0893, observed m/z 268.0898.

Anal. Calcd. for $C_{17}H_{14}ClN$•0.25H_2O: C, 74.99; H, 5.37; N, 5.14. Found: C, 74.90; H, 5.30; N, 5.18.

Substituted Quinolin-4-amines (**12-16** and **23**).

A mixture of 4-chloroquinoline **9** or **10** (0.21 g, 0.8 mmol), an amine (2.5 mmol) and 2 drops of anhydrous tin tetrachloride was stirred at 130° under a nitrogen atmosphere for 6 hours. The resulting dark oil was allowed to cool and then treated with water (5 ml). Extraction with ethyl acetate (3 x 10 ml) followed by drying of the extract with magnesium sulfate and concentration gave an oil which was further purified by chromatography on silica gel eluting with ethyl acetate/hexanes (1:3) or triethylamine/methanol/ethyl acetate (5:10:85). The solid product **15** and **16** were crystallized from methanol or ethyl acetate. Oily products **12-14** and **23** were converted into hydrobromides by using a general procedure [10], and the salts were crystallized from ethanol/hexanes.

N-[3-(Dimethylamino)propyl]-2-(2-fluorophenyl)quinoline-4-amine Dihydrobromide (**12**•2HBr•0.5H_2O).

This compound was obtained in a 60% yield; mp 152-154°; ^{1}H nmr (deuterated dimethyl sulfoxide): δ 2.10 (m, 2H), 2.80 (s, 6H), 3.22 (m, 2H), 3.71 (m, 2H), 7.20 (s, 1H), 7.55 (m, 2H), 7.90 (t, J = 8 Hz, 1H), 7.95 (m, 2H), 8.00 (m, 2H), 8.65 (d, J = 8 Hz, 1H), 9.50 (s, exchangeable with D_2O, 1H), 9.60 (s, exchangeable with D_2O, 1H); ^{19}F nmr: δ 55.0 (s).

Anal. Calcd. for $C_{20}H_{22}FN_3$•2HBr•0.5H_2O: C, 48.60; H, 5.10; N, 8.50. Found: C, 48.39; H, 5.27; N, 8.21.

N-[3-(Dimethylamino)propyl]-(4-fluorophenyl)quinolin-4-amine Dihydrobromide (**13**•2HBr•2.5 H_2O).

This compound was obtained in a 65% yield; mp 218-220°; ^{1}H nmr (deuterated dimethyl sulfoxide): δ 1.90 (m, 2H), 2.20 (s, 6H), 2.40 (t, J = 7 Hz, 2H), 3.40 (t, J = 7 Hz, 2H), 6.91 (s, 1H), 7.35 (m, 4H), 7.62 (m, 1H), 7.85 (d, J = 8 Hz, 1H), 8.15 (d, J = 8 Hz, 1H), 8.25 (m, 2H); ^{19}F nmr: δ 49.0 (s).

Anal. Calcd. for $C_{20}H_{22}FN_3$•2HBr•1.5H_2O: C, 46.89; H, 5.31; N, 8.20. Found: C, 46.99; H, 5.42; N, 8.19.

N-(4-Hydroxybutyl)-2-(2-fluorophenyl)quinolin-4-amine (**14**).

This compound was used for a further transformation as an oil; yield 61%; ^{1}H nmr (deuterated dimethyl sulfoxide): δ 1.80 (m, 2H), 3.38 (m, 2H), 3.52 (m, 2H), 4.41 (br s, exchangeable with D_2O), 1H), 6.85 (s, 1H), 7.23 (br s, exchangeable with D_2O, 1H), 7.37 (m, 2H), 7.47 (m, 2H), 7.67 (t, J = 8 Hz, 1H), 7.89 (d, J = 8 Hz, 1H), 8.00 (t, J = 8 Hz, 1H), 8.29 (d, J = 8 Hz, 1H); ^{19}F nmr: δ 54.0 (s).

Anal. Calcd. for $C_{19}H_{19}FN_2O$: C, 73.53; H, 6.17; N, 9.02. Found: C, 73.40; H, 6.28; N, 8.80.

N-(4-Hydroxybutyl)-2-(4-fluorophenyl)quinolin-4-amine (**15**).

This compound was obtained in a 76% yield; mp 143-145°; ^{1}H nmr (deuterated dimethyl sulfoxide): δ 1.63 (m, 2H), 1.79 (m, 2H), 3.47 (m, 4H), 6.95 (s, 1H), 7.09 (m, 1H), 7.36, (m, 2H), 7.62 (t, J = 8 Hz, 1H), 7.84 (d, J = 8 Hz, 1H), 8.24 (m, 3H), 9.11 (br s, exchangeable with D_2O, 1H), 1.10 (br s, exchangeable with D_2O, 1H); ^{19}F nmr: δ 54.0 (s).

Anal. Calcd. for $C_{19}H_{19}FN_2O$: C, 73.53; H, 6.17; N, 9.02. Found: C, 73.47; H, 6.34; N, 8.69.

N-(6-Hydroxyhexyl)-2-(4-fluorophenyl)quinolin-4-amine (**16**).

This compound was obtained in a 78% yield; mp 100-102°; ^{1}H nmr (deuterated dimethyl sulfoxide): δ 1.50 (m, 6H), 1.70 (m, 2H), 3.40 (m, 4H), 4.40 (br s, exchangeable with D_2O, 1H), 6.90 (s, 1H), 7.20 (br s, exchangeable with D_2O, 1H), 7.39 (m, 2H), 7.45 (t, J = 8 Hz, 1H), 7.70 (t, J = 8 Hz, 1H), 7.90 (d, J = 8 Hz, 1H), 8.30 (m, 3H); ^{19}F nmr: δ 49.0 (s); hr-ms: calcd for $C_{21}H_{23}FN_2O$ m/z 338.1781, observed m/z 338.1794.

2-(2-Fluorophenyl)-4-(*N*-methylpiperazino)quinoline Dihydrobromide (**23**).

This compound was obtained in a 68% yield; mp 278-279° (dec); ^{1}H nmr: δ 2.92 (s, 3H), 3.49 (s, 2H), 3.63 (s, 2H), 3.78 (s,

2H), 4.27 (s, 2H), 7.55 (m, 2H), 7.74 (m, 2H), 7.95 (m, 2H), 8.03 (t, J = 8 Hz, 1H), 8.16 (d, J = 8 Hz, 1H), 8.23 (d, J = 8 Hz, 1H), 10.27 (s, exchangeable with D_2O, 1H); ms: m/z 101 (30), 222 (50), 306 (80), 321 (100, M^+).

Anal. Calcd. for $C_{20}H_{20}FN_3$•2HBr•H_2O: C, 47.92; H, 4.83; N, 8.38. Found: C, 47.93, H, 4.82, N, 8.30.

N-(-Chloroalkyl)quinolin-4-amines (**17-19**).

A mixture of an *N*-(ω-hydroxyalkyl)quinolin-4-amine **14**, **15** or **16** (3 mmoles) and thionyl chloride (12 ml) in benzene (10 ml) was heated under reflux for 3 hours. After cooling the mixture was poured onto ice (25 g), neutralized with a saturated solution of sodium bicarbonate, and extracted with ethyl acetate (4 x 20 ml). The extract was dried with magnesium sulfate, concentrated, and the residue was subjected to chromatography eluting with pentane/ethyl acetate (7:3).

N-(4-Chlorobutyl)-2-(2-fluorophenyl)quinolin-4-amine (**17**).

This compound was obtained as a yellow solid; yield 80%, mp 107-108°; ^{1}H nmr (deuterated dimethyl sulfoxide); δ 1.86 (m, 4H), 3.38 (t, J = 6 Hz, 2H), 3.72 (t, J = 6 Hz, 2H), 6.83 (s, 1H), 7.24 (s, exchangeable with D_2O, 1H), 7.34 (m, 2H), 7.49 (m, 2H), 7.66 (t, J = 8 Hz, 1H), 7.84 (d, J = 8 Hz, 1H), 7.96 (t, J = 8 Hz, 1H), 8.27 (d, J = 8 Hz, 1H); ^{19}F nmr: δ 54.0 (s); hr-ms: calcd for $C_{19}H_{18}{}^{35}ClFN_2$ m/z 328.1141, observed m/z 328.1150.

N-(4-Chlorobutyl)-2-(4-fluorophenyl)quinolin-4-amine (**18**).

This compound was obtained as an oil; yield 85%; ^{1}H nmr (deuterated dimethyl sulfoxide); δ 1.92 (m, 4H), 3.49 (t, J = 6 Hz, 2H), 3.79 (t, J = 6 Hz, 2H), 7.00 (s, 1H), 7.22 (br s, exchangeable with D_2O, 1H), 7.35 (m, 2H), 7.45 (t, J = 8 Hz, 1H), 7.66 (t, J = 8 Hz, 1H), 7.88 (d, J = 8 Hz, 1H), 8.30 (m, 3H); ^{19}F nmr: δ 54.0 (s); hr-ms: calcd for $C_{19}H_{18}{}^{35}ClFN_2$ m/z 328.1141, observed m/z 328.1145.

N-(6-Chlorohexyl)-2-(4-fluorophenyl)quinolin-4-amine (**19**).

This compound was obtained as an oil; yield 72%; ^{1}H nmr (deuterated dimethyl sulfoxide); δ 1.50 (m, 4H), 1.80 (m, 4H), 3.45 (t, J = 6 Hz, 2H), 3.70 (t, J = 6 Hz, 2H), 6.90 (s, 1H), 7.20 Br s, exchangeable with D_2O, 1H), 7.35 (m, 2H), 7.45 (t, J = 8 Hz, 1H), 7.70 (t, J = 8 Hz, 1H), 7.85 (d, J = 8 Hz, 1H), 8.30 (m, 3H); ^{19}F nmr: δ 50.0 (s); hr-ms: calcd for $C_{21}H_{22}{}^{35}ClFN_2$ m/z 356.1454, observed m/z 356.1464.

N-[ω-(Dimethylamino)alkyl]quinolin-4-amines (**20-22**).

A mixture of an *N*-(ω-chloroalkyl)quinolin-4-amine **17**, **18** or **19** (2 mmoles), dimethylamine hydrochloride (1.65 g, 20 mmoles), sodium carbonate (2.1 g, 20 mmoles), and anhydrous *N*,*N*-dimethylformamide (10 ml) was heated to 70° for 4 hours, then cooled and filtered. The filtrate was concentrated on a rotary evaporator and the residue was subjected to chromatography eluting with ethyl acetate/triethylamine (40:1). The oily products **20** and **21** were converted into hydrobromides by using a general procedure [10], and the salts were crystallized from methanol. The solid free base **22** was crystallized from ethyl acetate.

N-[4-(Dimethylamino)butyl]-2-(2-fluorophenyl)quinolin-4-amine Dihydrobromide (**20**•2HBr•H_2O).

This salt was obtained in a 60% yield; mp 148-150°; ^{1}H nmr: δ 1.80 (m, 4H), 2.80 (s, 6H), 3.18 (m, 2H), 3.61 (m, 2H), 7.01 (s, 1H), 7.52 (m, 2H), 7.78 (m, 2H), 7.90 (t, J = 8 Hz, 1H), 8.00 (m, 2H), 8.66 (d, J = 8 Hz, 1H), 9.50 (br s, exchangeable with D_2O, 2H); ^{19}F nmr: δ 55.0 (s).

Anal. Calcd. for $C_{21}H_{24}FN_3$•2HBr•H_2O: C, 48.76; H, 5.46; N, 8.12. Found: C, 48.79; H, 5.70; N, 8.25.

N-[4-(Dimethylamino)butyl]-2-(4-fluorophenyl)quinolin-4-amine Dihydrobromide (**21**•2HBr•2H_2O).

This salt was obtained in a 63% yield; mp 239-240°;^{1}H nmr: δ 1.81 (m, 4H), 2.78 (s, 6H), 3.17 (t J = 6 Hz, 2H), 3.73 (t, J = 6 Hz, 2H), 7.08 (s, 1H), 7.57 (m, 2H), 7.74 (t, J = 8 Hz, 1H), 8.00 (t, J = 8 Hz, 1H), 8.16 (m, 3H), 8.70 (d, J = 8 Hz, 1H), 9.34 (br s, exchangeable with D_2O, 1H), 9.60 (br s, exchangeable with D_2O, 1H); ^{19}F nmr: δ 55.0 (s).

Anal. Calcd. for $C_{21}H_{24}FN_3$•2HBr•2H_2O: C, 47.12; H, 5.65; N, 7.84. Found: C, 47.34; H, 5.86; N, 7.48.

N-[6-(Dimethylamino)hexyl]-4-(4-fluorophenyl)quinolin-4-amine (**22**).

This compound was obtained in a 65% yield; mp 100-101°; ^{1}H nmr (deuterated dimethyl sulfoxide): δ 1.41 (m, 6H), 1.70 (m, 2H), 2.10 (s, 6H), 2.20 (t, J = 6 Hz, 2H), 3.42 (m, 2H), 6.95 (s, 1H), 7.20 (br s, exchangeable with D_2O, 1H), 7.35 (m, 3H), 7.65 (t, J = 8 Hz, 1H), 7.90 (d, J = 8 Hz, 1H), 8.30 (m, 3H); ^{19}F nmr: δ 49.0 (s); hr-ms: calcd for $C_{23}H_{28}FN_3$ m/z 365.2249, observed m/z 365.2257.

Anal. Calcd. for $C_{23}H_{28}FN_3$: C, 75.58; H, 7.72; N, 11.49. Found: C, 75.64; H, 7.85; N, 11.29.

Substituted 2-(Aminophenyl)quinolin-4-amines (**24-30**, **32**, and **33**).

A solution of the corresponding amine (2.7 mmol) in tetrahydrofuran (3 mL) was treated with a solution of *n*-buthyllithium in cyclohexane (2 *M*, 1.4 mL, 2.7 mmol) at –10° for 30 minutes and then with a solution of **6**, **7**, **12**, **13**, **23** or **31** (0.3 mmol) in tetrahydrofuran (2 ml). The mixture was stirred at room temperature for 4 hours for substitution of *ortho* fluorine atom in **12** and **23**, 24 hours for *para* substitution in **6** and **13**, and 4 days for the reactions of difluorophenyl derivatives **7** and **31**. The mixture was quenched with water (1 mL) and extracted with ethyl acetate (3 x 10 ml). The extract was concentrated and the residue purified by chromatography eluting with triethylamine/methanol/ethyl acetate (1:3:16). Products were transformed into hydrobromide salts according to a general procedure [10], and the salts were crystallized from methanol/ether.

4-(N-Methylpiperazino)-2-[4-(*N*-methylpiperazino)phenyl]-quinoline Trihydrobromide (**24**•3HBr•2.5H_2O).

This salt was obtained in a 74% yield; mp 290-293°; ^{1}H nmr: δ 3.00 (s, 6H), 3.20 (m, 4H), 3.67 (m, 8H), 4.21 (m, 4H), 7.30 (d, J = 8 Hz, 2H), 7.54 (s, 1H), 7.72 (t, J = 8 Hz, 1H), 8.00 (t, J = 8 Hz, 1H), 8.20 (m, 3H), 8.30 (d, J = 8 Hz, 1H), 10.00 (br s, exchangeable with D_2O, 1H), 10.20 (br s, exchangeable with D_2O, 1H); hr-ms for free base: calcd for $C_{25}H_{31}N_5O_2$ m/z 401.2579, observed m/z 401.2579.

Anal. Calcd. for $C_{25}H_{31}N_5$•3HBr•2.5H_2O: C, 43.56; H, 5.70; N, 10.15. Found: C, 43.92; H, 5.53; N, 9.82.

N-[3-(Dimethylamino)propyl]-2-[4-(*N*-methylpiperazino)phenyl]-quinolin-4-amine Trihydrobromide (**25**•3HBr•2H_2O).

This salt was obtained in a 61% yield, mp 313-315°; ^{1}H nmr: δ 2.22 (s, 6H), 2.97 (s, 3H), 2.41 (t, J = 7 Hz, 2H), 2.56

(m, 2H), 3.25 (m, 4H), 3.45 (t, J = 7 Hz, 2H), 6.95 (s, 1H), 7.10 (m, 2H), 7.30 (br s, exchangeable with D_2O, 1H), 7.40 (t, J = 8 Hz, 1H), 7.61 (t, J = 8 Hz, 1H), 7.82 (d, J = 8 Hz, 1H), 8.10 (m, 3H).

Anal. Calcd. for $C_{25}H_{33}N_5$•3HBr•2H_2O: C, 44.00; H, 5.91; N, 10.25. Found: C, 43.92; H, 5.77; N, 9.90.

N-[3-(Dimethylamino)propyl]-2-[2-[[2-(dimethylamino)ethyl]-amino]phenyl]quinolin-4-amine (**26**).

This compound was obtained in a 77% yield, mp 130-131°; ^{1}H nmr (deuterated dimethyl sulfoxide): δ 1.81 (m, 2H), 2.19 (s, 6H), 2.22 (s, 6H), 2.40 (t, J = 6 Hz, 2H), 2.61 (t, J = 6 Hz, 2H), 3.22 (t, J = 6 Hz, 2H), 3.40 (t, J = 6 Hz, 2H), 6.65 (m, 2H), 6.80 (s, 1H), 7.20 (t, J = 8 Hz, 1H), 7.30 (br s, exchangeable with D_2O, 1H), 7.40 (t, J = 8 Hz, 1H), 7.60 (t, J = 8 Hz, 1H), 7.70 (d, J = 8 Hz, 1H), 7.80 (d, J = 8 Hz, 1H), 8.20 (d, J = 8 Hz, 1H), 9.50 (br s, exchangeable with D_2O, 1H).

Anal. Calcd. for C_{24} H_{33} N_5: C, 73.61; H, 8.50; N, 17.88. Found: C, 73.46; H, 8.88; N, 17.55.

N-[3-(Dimethylamino)propyl]-2-[2-[[3-(dimethylamino)propyl]-amino]phenyl]quinolin-4-amine Trihydrobromide (**27**•3HBr•5H_2O).

This salt was obtained in a 72% yield; mp 212-214°; ^{1}H nmr: δ 1.98 (m, 2H), 2.10 (t, J = 6 Hz, 2H), 2.80 (s, 6H), 2.90 (s, 6H), 3.20 (m, 6H), 3.70 (t, J = 6 Hz, 2H), 6.80 (t, J = 8 Hz, 1H), 6.85 (d, J = 8 Hz, 1H), 6.95 (s, 1H), 7.35 (d, J = 8 Hz, 1H), 7.40 (t, J = 8 Hz, 1H), 7.75 (m, 1H), 8.00 (m, 2H), 8.70 (d, J = 8 Hz, 1H), 9.30 (br s, exchangeable with D_2O, 1H), 9.68 (br s, exchangeable with D_2O, 1H).

Anal. Calcd. for $C_{25}H_{35}N_5$•3HBr•5.5H_2O: C, 40.17; H, 6.61; N; 9.37. Found: C, 40.00; H, 6.80; N, 9.25.

N-[3-(Dimethylamino)propyl]-2-[2-(4-methylpiperazino)phenyl]-quinolin-4-amine Trihydrobromide(**28**•3HBr•1.5H_2O).

This salt was obtained in a 75% yield; mp 225-228°; ^{1}H nmr: δ 1.10 (t, J = 6Hz, 2H), 2.15 (t, J = 6 Hz, 2H), 2.80 (s, 9H), 3.20 (m, 4H), 3.31 (t, J = 6 Hz, 2H), 3.50 (m, 2H), 3.81 (t, J = 6 Hz, 2H), 7.10 (s, 1H), 7.40 (m, 2H), 7.65 (t, J = 8 Hz, 1H), 7.75 (m, 2H), 8.00 (t, J = 8 Hz, 1H), 8.10 (d, J = 8 Hz, 1H), 8.70 (d, J = 8 Hz, 1H), 9.40 (br s, exchangeable with D_2O, 1H), 9.80 (br s, exchangeable with D_2O, 1H).

Anal. Calcd. for $C_{25}H_{33}N_5$•3HBr•1.5H_2O: C, 44.60; H, 5.84; N, 10.40. Found: C, 44.75; H, 6.17; N, 10.30.

N-(4-Methylpiperazino)-2-[2-[2-(dimethylamino)ethyl]phenyl]-quinolin-4-amine Trihydrobromide (**29**•3HBr•H_2O).

This salt was obtained in a 69% yield; mp 314-315° (dec); ^{1}H nmr: δ 2.86 (s, 6H), 2.94 (s, 3H), 3.18 (s, 2H), 3.59 (m, 2H), 3.63 (m, 4H), 4.27 (s, 2H), 6.89 (t, J = 7 Hz, 1H), 6.98 (d, J = 8 Hz, 1H), 7.47 (m, 3H), 7.74 (t, J = 7 Hz, 1H) 7.98 (t, J = 7 Hz, 1H), 8.19 (m, 2H), 10.39 (br s, exchangeable with D_2O, 1H); ci-ms: m/z 195.7 (35), 319.4 (100), 390 (M^++1).

Anal. Calcd. for $C_{24}H_{31}N_5$•3HBr•H_2O: C, 44.32; H, 5.58; N, 10.77. Found: C, 43.92; H, 5.58; N, 10.54.

N-(4-Methylpiperazino)-2-[(2-[3-(dimethylamino)propyl)phenyl]-quinolin-4-amine Tetrahydrobromide (**30**•4HBr•H_2O).

This salt was obtained in a 65% yield; mp 187-189° (dec); ^{1}H nmr: δ 2.65 (m, 2H), 2.76 (s, 9H), 2.88 (m, 2H), 2.97 (m, 4H), 3.16 (m, 6H), 6.83 (t, J = 8 Hz, 1H), 6.90 (d, J = 8 Hz, 1H), 7.43 (m, 3H), 7.75 (t, J = 8 Hz, 1H), 8.00 (d, J = 8 Hz, 1H), 8.20 (m, 2H), 9.59 (br s, exchangeable with D_2O, 1H); ci-ms: m/z 202 (75), 319 (100), 404 (M^++1).

Anal. Calcd. for $C_{25}H_{33}N_5$•4HBr•H_2O: C, 40.29; H, 5.27; N, 9.39. Found: C, 40.31; H, 5.57; N, 9.09.

N-[2-(Dimethylamino)ethyl]-2-[2,4-bis(4-methylpiperazino)-phenyl]quinolin-4-amine Tetrahydrobromide(**32**•4HBr•2H_2O).

Reaction of **31** with lithium 4-methylpiperazide followed by treatment of the resultant quinoline **32** with hydrobromic acid gave the salt **32**•4HBr•2H_2O in a 56% yield. The same product was obtained in a 54% yield starting with **7**; mp 239-241° (dec); ^{1}H nmr: δ 2.78 (s, 3H), 2.88 (s, 3H), 2.93 (s, 6H), 2.37 (bs, 4H), 3.21-3.48 (br m, 12H), 3.55 (t, J = 6 Hz, 2H), 4.04 (m, 2H), 6.81 (s, 1H), 6.89 (d, J = 8 Hz, 1H), 7.10 (s, 1H), 7.66 (d, J = 8 Hz, 1H), 7.72 (t, J = 8 Hz, 1H), 7.97 (t, J = 8 Hz, 1H), 8.15 (d, J = 8 Hz, 1H), 6.87 (d, J = 8 Hz, 1H), 9.09 (br s, exchangeable with D_2O, 1H), 9.98 (br s, exchangeable with D_2O, 1H); esi-ms: m/z 244.77 (100), 488.52 (M^++1). The substitution pattern of **32** was derived from proton decoupling and nOe experiments.

Anal. Calcd. for $C_{29}H_{41}N_7$•4HBr•2H_2O: C, 41.11; H, 5.83; N, 11.57. Found: C, 41.16; H, 5.95; N, 11.40.

N-[2-(Dimethylamino)ethyl]-2-[3,4-bis(4-methylpiperazino)-phenyl]quinolin-4-amine Pentahydrobromide (**33**•5HBr).

Quinoline **33** was obtained as a minor product by the reaction of **7** with lithium 4-methylpiperazide. The salt was obtained in an overally yield of 18%; mp >300° (dec.); ^{1}H nmr: δ 2.94 (s, 12H), 3.05 (m, 4 H), 3.36-3.59 (bm, 12H), 4.00 (m, 2H), 4.10 (m, 2H), 7.15 (s, 1H), 7.25 (d, J = 8 Hz, 1H), 7.58 (s, 1H), 7.77 (m, 2H), 8.00 (t, J = 8 Hz, 1H), 8.31 (d, J = 8 Hz, 1H), 8.66 (d, J = 8 Hz, 1H), 9.18 (br s,with D_2O, 1H), 9.95 (br s, exchangeable with D_2O, 1H); esi-ms: m/z 244.8 (100), 488.6 (M^+ +1). The substitution pattern of **33** was derived from proton decoupling and nOe experiments.

Anal. Calcd. for $C_{29}H_{41}N_7$•5HBr: C, 39.04; H, 5.20; N, 10.98. Found: C, 39.34; H, 5.45; N, 10.80.

2-[3,4-Bis(bromomethyl)phenyl]-4-chloroquinoline (**34**).

A mixture of **11** (1.0 g, 3.75 mmoles), *N*-bromosuccinimide (1.47 g, 8.25 mmoles), and benzoyl peroxide (0.15 g) in carbon tetrachloride (50 ml) was heated under reflux for 6 hours. After cooling, a precipitate of succinimide was filtered off, and the solution was concentrated. The resultant yellow residue was crystallized from hexanes to give **34** in a 52% yield; mp104-107° (dec); ^{1}H nmr: δ 4.73 (s, 2H), 4.78 (s, 2H), 7.52 (d, J = 8 Hz, 1H), 7.63 (m, 1H), 7.78 (m, 1H), 7.95 (s, 1H), 8.05 (d, J = 8 Hz, 1H), 8.11 (s, 1H), 8.19 (d, J = 8 Hz, 1H), 8.24 (d, J = 8 Hz, 1H).

Anal. Calcd. for $C_{17}H_{12}Br_2ClN$: C, 47.98; H, 2.84; N, 3.29. Found: C, 47.80; H, 2.75; N, 3.20.

4-Chloro-2-[3,4-bis[*N*-methylhomopiperazino)methyl]phenyl]-quinoline Pentahydrobromide (**35**•5HBr•4H_2O).

A mixture of **34** (85.1 mg, 0.2 mmole) and *N*-methylhomo-piperazine (400 mg, 4 mmoles) was stirred at room temperature for 24 hours and then concentrated on a rotary evaporator. Chromatography of the residue eluting with ethyl acetate/ methanol/triethylamine (5:4:1) gave 37 as an oil. The hydro-bromide salt was obtained in an overall yield of 47%; mp 220-221° (dec); ^{1}H nmr (free base, deuteriochloroform): δ 1.86 (m, 4H), 2.38 (m, 6H), 2.69 (t, J = 5 Hz, 4H), 2.72 (m, 12H), 3.84 (s,

2H), 3.86 (s, 2H), 7.51 (d, J = 8 Hz, 1H), 7.60 (s, 1H), 7.76 (m, 1H), 7.96 (m, 1H), 7.98 (d, J = 8 Hz, 1H), 8.09 (d, J = 8 Hz, 1H), 8.19 (m, 2H).

Anal. Calcd. for $C_{29}H_{38}N_5Cl$•5HBr•4H_2O: C, 35.95; H, 5.31; N, 7.23. Found: C, 35.95; H, 5.30; N, 7.56.

N-[2-(Dimethylamino)ethyl]-2-[3,4-bis[(*N*-methylhomopiperazino)methyl]phenyl]quinolin-4-amine Hexahydrobromide (**36**•6 HBr•6H_2O).

Reaction of **35** with 2-(dimethylamino)ethylamine in the presence of tin tetrachloride was conducted and the product was purified by using a general procedure described above to give a salt of **36** in a yield of 50%; mp 224-225°; ^{1}H nmr: δ 2.25 (m, 4H), 2.89 (s, 6H), 2.94 (s, 6H), 3.39-3.79 (br m, 14H), 3.90 (m, 4H), 4.17 (m, 2H), 4.68 (m, 2H), 4.82 (m, 2H), 7.36 (s, 1H), 7.78 (t, J = 8 Hz, 1H), 8.03 (m, 2H), 8.23 (m, 2H), 8.56 (d, J = 8 Hz, 2H) 8.65 (s, 1H).

Anal. Calcd. for $C_{33}H_{49}N_7$•6HBr•6H_2O: C, 34.84; H, 5.94; N, 8.62. Found: C, 34.82; H, 5.86; N, 8.38.

N-[2-(Morpholino)ethyl]-2-[3,4-bis[(4-methylpiperazino)methyl]-phenyl]quinolin-4-amine Tetrahydrobromide (**38**•4HBr•1.5H_2O).

This salt was obtained by using a modified procedure described above for the synthesis of the salt of **36**. Thus, compound **34** was treated with 4-methylpiperazine and the resultant product **37**, without purification, was subjected to the reaction with 4-(2-aminoethyl)morpholine under otherwise identical conditions. The resultant compound **38** was purified by chromatography eluting with ethyl acetate/methanol/triethylamine and then converted into hydrobromide by using a general procedure. After crystallization from 95% ethanol the overall yield of **38**•4HBr•1.5H_2O was 49%; mp 188-191° (dec); ^{1}H nmr: δ 2.51 (m, 2H), 2.81 (m, 8H), 2.92 (m, 4H), 3.09 (s, 6H), 3.15 (m, 4H), 3.60 (m, 4H), 3.82 (m, 8H), 4.15 (m, 2H), 7.19 (s, 1H), 7.65 (d, J = 8 Hz, 1H), 7.75 (t, J = 8 Hz, 1H), 7.94 (m, 3H), 8.23 (d, J = 8 Hz, 1H), 8.60 (m, 1H), 9.25 (br s, exchangeable with D_2O, 1H), 9.71 (br s, exchangeable with D_2O, 1H), 10.20 (br s, exchangeable with D_2O, 1H); hr-ms (free base): calcd for $C_{33}H_{47}N_7O$ m/z 557.3842, observed m/z 557.3859.

Anal. Calcd. for $C_{33}H_{47}N_7O$•4HBr•1.5H_2O: C, 43.63; H, 5.99; N, 10.79. Found: C, 43.52; H, 6.13; N, 10.39.

REFERENCES

[1] F. Palacios, D. Aparicio, G. Rubiales, A. M. Ochoa de Retana and Martinez de Marigorta in Targets in Heterocyclic Systems. Chemistry and Properties, O. A. Attanasi and D. Spinelli, Eds., Italian Chemical Society, Roma, Italy, 1997, Vol. **1**, p. 187.

[2] J. B. Chaires, J. Ren, M. Henary, O. Zegrocka, G. R. Bishop and L. Strekowski, *J. Am. Chem. Soc*., **125**, 7272 (2003).

[3] C. Helene, *Eur. J. Cancer*, **27**, 1466 (1991).

[4] L. Strekowski, M. Say, M. Henary, P. Ruiz, L. Manzel, D. E. Macfarlane and A. Bojarski, *J. Med. Chem*., **46**, 1242 (2003).

[5] R. Fox, Semin. *Arthritis Rheum*., **23**, 82 (1993).

[6] D. J. Wallace, *Rheum. Dis. Clin. North Amer*., **20**, 243 (1994).

[7] K. R. Schultz and A. L. Gilman, *Leuk. Lymphoma*, **24**, 201 (1997).

[8] L. Strekowski, R. L. Wydra, M. T. Cegla, A. Czarny, D. B. Harden, S. E. Patterson, M. A. Battiste and J. M. Coxon, *J. Org. Chem*., **55**, 4777 (1990).

[9] L. Strekowski, S. E. Patterson, L. Janda, R. L. Wydra, D. B. Harden, M. Lipowska and M. T. Cegla, *J. Org. Chem*., **57**, 196 (1992).

[10] L. Strekowski, J. L. Mokrosz, V. A. Honkan, A. Czarny, M. T. Cegla, R. L. Wydra, S. E. Patterson and R. F. Schinazi, *J. Med. Chem*., **34**, 1739 (1991).

[11] L. Strekowski, L. Janda, S. E. Patterson and J. Nguyen, *Tetrahedron*, **52**, 3273 (1996).

[12] L. Janda, J. Nguyen, S. E. Patterson and L. Strekowski, *J. Heterocyclic Chem*, **29**, 1753 (1992).

[13] P. Beak and A. I. Meyers, *Acc. Chem. Res*., **19**, 356 (1986).

[14] L. Strekowski, M. T. Cegla, D. B. Harden and S.-B. Kong, *J. Org. Chem*., **54**, 2464 (1989).