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Investigation of amination in 4-chloro-2-phenylquinoline derivatives with amide solvents

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ABSTRACT

Novel 4-amino-2-phenylquinoline derivatives were synthesized by reacting various 4-chloro-2-arylquinoline compounds having activated chloro group with the corresponding amide solvents at reflux for overnight. The activity of amination by the amide solvents depended on the competition between the steric and electronic effect of the *N*-substituents on the amino group. Their activities were shown as *N*,*N*-dimethylformamide>*N*,*N*-diethylformamide>*N*-methylformamide>formamide>*N*,*N*-dimethylacetamide>*N*,*N*-dimethylpropionamide. The yields for the amination products seemed proportional to the ease of the dissociation of the amides.

1. Introduction

The preparation of amino-containing heterocyclic and aromatic compounds, such as aminopyrine (antipyretic),[1] ampyzine (central stimulant),[2] 6-dimethylamino-8-azaadenosine (antitumor),[3] dimethirimol (fungicide),[4] diphenhydramine (antihistamine),[2] methadone (narcotic analgesic),[5] and various other drugs,[6] have been extensively studied owing to their importance as biologically active compounds. In addition to their usefulness as drugs, the reactivity of their amino group also makes them popular starting components in organic synthesis.[7]

2-Phenylquinoline derivatives are the effective pharmacophore in medicinal chemistry as illustrated by its application in pharmaceutical agents in fields as novel antitumor promoters,[8] antiplatelet agents,[9] and DNA-intercalator agents[10–12] according to the moderate effective binding ability with DNA. 2-Phenylquinoline containing an additional basic *N*-4-aminoalkyl function would strongly increase the biological activity of immunostimulatory CpG-oligodeoxynucleotides.[13] In 2006, the 4-aminoquinoline derivatives were also explored as the melanin-concentrating hormone 1-receptor (MCH1R) antagonist by DeVita et al.[14] Therefore, we planned to develop a convenient amination methodology using amide solvents to prepare a series of 4-amino-2-arylquinoline for enhancing the biological activities.

In the literature, the structural parameters, and energy barrier for rotational about C–N bond, of a series of amides with varying substituents, have been experimentally determined.[15] They agreed quite well with theoretical values calculated by ab initio calculations (MP2 level with the 6-31+G(d) basis)[16] and hybrid QM/MM calculations (IMOMM method).[17] Thus, it is a great interest to us to relate the amination ability of amides to their dissociation activity and resonance structure parameter.[18] In this work, we also attempted to relate the amination yield of a series of substituted 4-chloro-2-arylquinoline to the ease of dissociation of various substituted amide solvents that were used as amination agents.

2. Results and discussion

2-Phenylquinoline derivatives (**1**) were prepared by following the previous published procedure using condensation and tandem thermal cyclization approaches.[19] 2-Phenylquinoline derivatives (**1a**–**1e**) were efficiently transformed into the corresponding 4-chloro-2-arylquinoline **2a**–**2e** in 77–92% yields by using thionyl chloride in CH_2Cl_2 solution at reflux (see Scheme 1).[20]

For the model amination studies, 4-chloro-2-phenylquinoline (**2a**) was treated with *N*,*N*-dimethylformamide (DMF) or *N*,*N*-diethylformamide (DEF) at reflux. The reaction gave the corresponding amination products in 75% and 51% yield, respectively (**3a**

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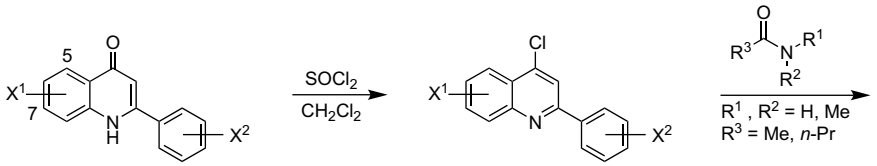
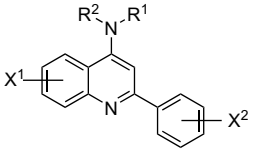


1a. X^1 = H, X^2 = H
1b. X^1 = H, X^2 = *o*-F
1c. X^1 = H, X^2 = *p*-OMe
1d. X^1 = 6-F, X^2 = H
1e. X^1 = 7-F, X^2 = H
1f. X^1 = 8-F, X^2 = H

2a. X^1 = H, X^2 = H, 91%
2b. X^1 = H, X^2 = *o*-F, 92%
2c. X^1 = H, X^2 =*p*-OMe, 88%
2d. X^1 = *6*-F, X^2 = H, 82%
2e. X^1 = *7*-F, X^2 = H, 80%
2f. X^1 = *8*-F, X^2 = H, 77%



3. X^1 = H, X^2 = H
3a. R^1 = R^2 = Me
3b. R^1 = R^2 = Et
3c. R^1 = H, R^2 = Me
3d. R^1 = R^2 = H

4. X^1 = H, X^2 = *o*-F
4a. R^1 = R^2 = Me
4b. R^1 = R^2 = Et
4c. R^1 = H, R^2 = Me
4d. R^1 = R^2 = H

5. X^1 = H, X^2 = *p*-OMe
5a. R^1 = R^2 = Me
5b. R^1 = R^2 = Et
5c. R^1 = H, R^2 = Me
5d. R^1 = R^2 = H

6. X^1 = 6-F, X^2 = H, R^1 = R^2 = Me
7. X^1 = 7-F, X^2 = H, R^1 = R^2 = Me
8. X^1 = 8-F, X^2 = H, R^1 = R^2 = Me

Scheme 1.

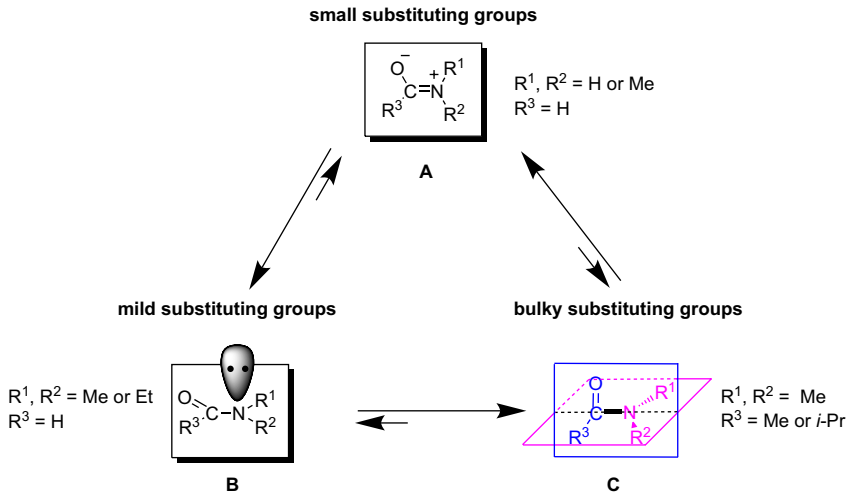
and **3b**, see Scheme 1 and Table 1). Due to the balance of electronic and steric contributions, both *N*,*N*-dimethylformamide (DMF) and *N*,*N*-diethylformamide (DEF) were assumed as planar or nearly planar nitrogen bond configuration to promote the nucleophilicity of lone-pair on nitrogen (**B**, see Scheme 2).[16]

4-Chloro-2-phenylquinoline (**2a**) was treated with other amide solvents, including formamide and *N*-methylformamide under the same condition. Relatively low isolated yields were obtained (**3c** and **3d**, 32–43%, see Table 1). Theoretically, both formamide and *N*-methylformamide favored the $C(O^-)=N^+$ configuration (**A**, see Scheme 2) than *N*,*N*-dimethylformamide (DMF) and *N*,*N*-diethylformamide (DEF). As a consequence, the electron density and nucleophilicity of its nitrogen group were somewhat suppressed.[21,22] In the case of *N*,*N*-dimethylacetamide (DMA) and *N*,*N*-dimethylpropionamide (DMP), large distortions away from planar configuration (**C**, see Scheme 2) caused by repulsion between relatively bulky substituents on carbon and nitrogen groups are expected.[23] The sterical hindrance of substituents on amide likely reduced the nucleophilicity of electron lone-pair on nitrogen group and resulted in poor amination yields (10–11%). Nevertheless, our synthetic yields for amination products seemed to vary with dissociation activity of amides reported in the literatures.[16,17]

For the further demonstration investigation, we applied the various substituents 2-phenylquinolines involving 4-chloro-2-(2-fluorophenyl)quinoline (**2b**), 4-chloro-2-(4-methoxylphenyl)quinoline

Table 1
The results of the amination of 4-chloro-2-arylquinolines with amides

2-Phenylquinolines (**2a**–**2f**)			Amides $R^1R^2NC(=O)R^3$			4-Amino-2-phenylquinolines (**3**–**8**)					
S.M.	X^1	X^2	R^1	R^2	R^3	Products	X^1	X^2	R^1	R^2	Yields (%)
2a	H	H	Me	Me	H	**3a**	H	H	Me	Me	75
			Et	Et	H	**3b**	H	H	Et	Et	51
			Me	H	H	**3c**	H	H	Me	H	43
			H	H	H	**3d**	H	H	H	H	32
			Me	Me	Me	**3a**	H	H	Me	Me	11
			Me	Me	*n*-Pr	**3a**	H	H	Me	Me	10
2b	H	*o*-F	Me	Me	H	**4a**	H	*o*-F	Me	Me	83
			Et	Et	H	**4b**	H	*o*-F	Et	Et	49
			Me	H	H	**4c**	H	*o*-F	Me	H	16
			H	H	H	**4d**	H	*o*-F	H	H	13
2c	H	*p*-OMe	Me	Me	H	**5a**	H	*p*-OMe	Me	Me	58
			Et	Et	H	**5b**	H	*p*-OMe	Et	Et	27
			Me	H	H	**5c**	H	*p*-OMe	Me	H	23
			H	H	H	**5d**	H	*p*-OMe	H	H	14
2d	6-F	H	Me	Me	H	**6**	6-F	H	Me	Me	91
2e	7-F	H	Me	Me	H	**7**	7-F	H	Me	Me	87
2f	8-F	H	Me	Me	H	**8**	8-F	H	Me	Me	56



Scheme 2.

(**2c**), 4-chloro-6-fluoro-2-phenylquinoline (**2d**), 4-chloro-7-fluoro-2-phenylquinoline (**2e**), and 4-chloro-8-fluoro-2-phenylquinoline (**2f**) with a series of amide solvents including *N*,*N*-dimethylformamide, *N*,*N*-diethylformamide, *N*-methylformamide, and formamide under the same condition to obtain the corresponding amination products in 13–91% yields (**4a**–**4d**, **5a**–**5d**, **6**, **7**, and **8** see Table 1). The better isolation yields were obtained by using *N*,*N*-dimethylformamide (DMF) as reaction solvent (58–91%, **4a**, **5a**, **6**, **7**, and **8** see Table 1). However, these experimental results could supported our model conversion studies of 4-chloro-2-phenylquinoline (**2a**) to the corresponding amination products (**3a**–**3f**).

In conclusion, we have developed the newly amination method by treating substituted 4-chloro-2-arylquinoline derivatives (**2a**–**2f**) with various substituent amides, including *N*,*N*-dimethylacetamide, *N*,*N*-dimethylpropionamide, formamide, *N*,*N*-diethylformamide, and *N*-methylformamide. Based on our experimental data, the order of dissociation activity is *N*,*N*-dimethylformamide>*N*,*N*-diethylformamide>*N*-methylformamide>formamide>*N*,*N*-dimethylacetamide>*N*,*N*-dimethylpropionamide. Our experimental results were consistent with the previous literature reported data and theoretical calculations.

3. Experimental section

3.1. General procedure

All chemicals were of reagent grade. Analytical thin-layer chromatography (TLC) was performed on precoated plates (silica gel 60 F-254) purchased from Merck Inc. Purification by gravity column chromatography was carried out by use of Merck Reagents Silica Gel 60 (particle size 0.063–0.200 mm, 70–230 mesh ASTM). Infrared (IR) spectra were measured on a Bomem Michelson Series FT-IR spectrometer. The wave numbers reported are referenced to the polystyrene 1601 cm^{-1} absorption. Absorption intensities are recorded by the following abbreviations: s, strong; m, medium; w, weak. Proton NMR spectra were obtained on a Bruker (200 MHz) spectrometer by use of $CDCl_3$ and DMSO-d_6 as solvent. Carbon-13 NMR spectra were obtained on a Bruker (50 MHz) spectrometer by use of $CDCl_3$ as solvent. Carbon-13 chemical shifts are referenced to the center of the $CDCl_3$ triplet (δ 77.0 ppm). Multiplicities are recorded by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; *J*, coupling constant (Hz). Elemental analyses were carried out on a Heraeus CHN–O RAPID element analyzer.

3.2. Standard procedure for the synthesis of 4-chloro-2-phenylquinoline derivatives (2a–2f)

A solution of 2-phenyl-4-quinolone derivatives (**1a**–**1f**, 15 mmol, 1.0 equiv) and thionyl chloride ($SOCl_2$, 0.15 mol, 10 equiv, ~10 mL) in CH_2Cl_2 solution (100 mL) was reflux for 12 h. When the reaction was completed, the reaction mixture was concentrated, added to water (200 mL), and extracted with ethyl acetate (4×200 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue solution was purified by column chromatography on silica gel or re-crystallization to give the corresponding 4-chloro-2-phenylquinoline products (**2a**–**2g**) in 77–92% yields.

*3.2.1. 4-Chloro-2-phenylquinoline (**2a**)*

^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.49–7.52 (m, 3H, H-3′, 4′, 5′), 7.52 (t, 1H, *J*=6.7 Hz, H-6), 7.84 (t, 1H, *J*=6.7 Hz, H-7), 8.07–8.12 (m, 2H, H-5, 8), 8.23–8.28 (m, 2H, H-2′, 6′), 8.33 (s, 1H, H-3); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 119.31, 123.98, 124.99, 127.82 (C×2), 128.40, 129.37 (C×2), 130.11, 130.62, 131.61, 137.87, 142.78, 148.69, 156.77; IR (KBr) 1613 (C=N) cm^{-1}. Anal. Calcd for $C_{15}H_{10}ClN$: C: 75.16; H: 4.21; N: 5.84. Found: C: 75.21; H: 4.33; N: 5.81.

*3.2.2. 4-Chloro-2-(2-fluorophenyl)quinoline (**2b**)*

^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.35–7.57 (m, 3H, H-4′, 5′, H-3), 7.74–7.78 (dd, 1H, *J*=1.3, 6.9 Hz, H-3′), 7.92 (t, 1H, *J*=8.2 Hz, H-6), 7.80 – 8.05 (m, 2H, H-7, 8), 8.09–8.13 (d, 1H, *J*=8.9, H-6′), 8.16–8.20 (d, 1H, *J*=8.2 Hz, H-5); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 117.10, 122.5, 124.00, 124.91, 125.41, 128.91, 130.20, 131.71 (C×3), 132.50, 142.05, 148.73, 153.75, 162.40; IR (KBr) 1618 (C=N) cm^{-1}. Anal. Calcd for $C_{15}H_9ClFN$: C: 69.91; H: 3.52; N: 5.44. Found: C: 70.12; H: 4.01; N: 5.31.

*3.2.3. 4-Chloro-2-(4-methoxylphenyl)quinoline (**2c**)*

^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.80 (s, 3H, OCH_3), 7.03–7.08 (d, 2H, *J*=8.4 Hz, H-3′, 5′), 7.69 (t, 1H, *J*=8.2 Hz, H-6), 7.82 (t, 1H, *J*=8.2 Hz, H-7), 8.03–8.22 (m, 2H, H-5, 8), 8.26–8.30 (d, 2H, *J*=8.4 Hz, H-2′, 6′), 8.32 (s, 1H, H-3); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 55.8, 114.74 (C×2), 118.82, 123.96, 124.67, 127.91, 129.35 (C×2), 129.91, 130.31, 131.49, 142.55, 148.77, 156.47, 161.50; IR (KBr) 1622 (C=N) cm^{-1}. Anal. Calcd for $C_{16}H_{12}ClNO$: C: 71.25; H: 4.48; N: 5.19. Found: C: 71.14; H: 4.33; N: 5.34.

*3.2.4. 4-Chloro-6-fluoro-2-phenylquinoline (**2d**)*

^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.47–7.51 (m, 3H, H-3′, 4′, 5′), 7.73–7.81 (m, 2H, H-3, 7), 8.12–8.23 (m, 3H, H-2′, 6′, 8), 8.33 (s, 1H,

H-5); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 107.51, 108.00, 119.96, 121.34, 121.85, 125.95, 127.72 (C×2), 129.36 (C×2), 130.62, 133.35, 137.65, 142.11, 145.87; IR (KBr) 1614 (C=N) cm^{-1}. Anal. Calcd for $C_{15}H_9ClFN$: C: 69.91; H: 3.52; N: 5.44. Found: C: 69.95; H: 3.55; N: 5.38.

*3.2.5. 4-Chloro-7-fluoro-2-phenylquinoline (**2e**)*

^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.51–7.54 (m, 3H, H-3′, 4′, 5′), 7.76–7.85 (m, 2H, H-3, 6), 8.11–8.27 (m, 3H, H-2′, 6′, 5), 8.34 (s, 1H, H-8); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 113.42, 113.82, 118.22, 118.86, 122.33, 126.88, 127.08, 127.94 (C×2), 129.39 (C×2), 130.89, 137.59, 142.91, 158.11; IR (KBr) 1622 (C=N) cm^{-1}. Anal. Calcd for $C_{15}H_9ClFN$: C: 69.91; H: 3.52; N: 5.44. Found: C: 70.21; H: 3.64; N: 5.40.

*3.2.6. 4-Chloro-8-fluoro-2-phenylquinoline (**2f**)*

^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.44–7.50 (m, 3H, H-3′, 4′, 5′), 7.69–8.21 (m, 6H, H-3, 5, 6, 7, 2′, 6′); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 111.37, 112.01, 119.17, 120.13, 122.41, 127.15, 127.93 (C×2), 129.33 (C×2), 130.11, 132.45, 137.72, 142.55, 158.21; IR (KBr) 1624 (C=N) cm^{-1}. Anal. Calcd for $C_{15}H_9ClFN$: C: 69.91; H: 3.52; N: 5.44. Found: C: 68.03; H: 3.65; N: 5.58.

3.3. Standard procedure for the synthesis of 4-amino-2-phenylquinoline derivatives (3a–3f, 4a–4d, 5a–5d, 6, 7, and 8)

4-Chloro-2-phenylquinoline derivatives (**2a**–**2f**, 15 mmol, 1.0 equiv) were dissolved in the various amide solutions (100 mL) including *N*,*N*-dimethylformamide, *N*,*N*-diethylformamide, *N*-methylformamide, formamide, *N*,*N*-dimethylacetamide, and *N*,*N*-dimethylpropionamide at reflux for overnight. When the reaction was completed, the reaction mixture was added to water (100 mL) and extracted with ethyl acetate (3×100 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue solution was purified by column chromatography on silica gel to give the corresponding 4-amino-2-phenylquinoline products (**3a**–**3f**, **4a**–**4d**, **5a**–**5d**, **6**, **7**, and **8**) in 11–91% yields.

*3.3.1. N,N-Dimethyl-2-phenylquinoline-4-amine (**3a**)*

^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.05 (s, 6H, NCH_3×2), 7.36 (s, 1H, H-3), 7.47–7.52 (m, 4H, H-3′, 4′, 5′, 6), 7.67 (t, 1H, *J*=8.2 Hz, H-7), 7.95–7.99 (d, 1H, *J*=8.3 Hz, H-5), 8.03–8.08 (d, 1H, *J*=8.3 Hz, H-8), 8.20–8.24 (dd, 2H, *J*=1.8, 6.0 Hz, H-2′, 6′); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 43.84 (C×2), 104.88, 121.67, 124.66, 124.68, 127.47 (C×2), 128.83 (C×2), 129.05, 129.19, 129.96, 139.76, 149.49, 156.56, 158.04; IR (KBr) 1602 (C=N) cm^{-1}. Anal. Calcd for $C_{17}H_{16}N_2$: C: 82.22; H: 6.49; N: 11.28. Found: C: 82.15; H: 6.55; N: 11.14.

*3.3.2. N,N-Diethyl-2-phenylquinolin-4-amine (**3b**)*

^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.05–1.12 (t, 6H, *J*=2.9 Hz, NCH_3×2), 3.31–3.42 (q, 4H, *J*=6.9 Hz, –CH_2×2), 7.41–7.49 (m, 5H, H-3, 6, 3′, 4′, 5′), 7.63 (t, 1H, *J*=7.0 Hz, H-7), 7.92–7.95 (m, 2H, H-5, 8), 8.18–8.19 (m, 2H, H-2′, 6′); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 12.51 (C×2), 46.37 (C×2), 108.13, 123.50, 124.35, 125.26, 127.70 (C×2), 129.11 (C×2), 129.33, 129.68, 130.23, 139.89, 149.84, 156.38, 156.59; IR (KBr) 1621 (C=N) cm^{-1}. Anal. Calcd for $C_{19}H_{20}N_2$: C: 82.57; H: 7.29; N: 10.14. Found: C: 82.42; H: 7.11; N: 10.31.

*3.3.3. N-Methyl-2-phenylquinolin-4-amine (**3c**)*

^{1}H NMR (DMSO-d_6, 200 MHz) δ 2.96–2.98 (d, 3H, *J*=4.4 Hz, NCH_3), 6.87 (1H, s, NH), 7.33–7.47 (m, 6H, H-3, 3′, 4′, 5′, 6, 7), 7.82–7.86 (d, 1H, *J*=9.0 Hz, H-5), 8.15–8.19 (m, 2H, H-2′, 6′); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 29.87, 95.26, 118.54, 121.79, 124.29, 127.58 (C×2), 128.89 (C×2), 129.33, 129.54, 129.77, 140.66, 148.56, 152.17, 157.17; IR (KBr) 1612 (C=N) cm^{-1}. Anal. Calcd for $C_{16}H_{14}N_2$: C: 82.02; H: 6.02; N: 11.96. Found: C: 82.32; H: 6.08; N: 11.54.

*3.3.4. 2-Phenylquinolin-4-amine (**3d**)*

^{1}H NMR (DMSO-d_6, 200 MHz) δ 6.80 (s, 2H, NH_2), 7.07 (s, 1H, H-3), 7.33–7.62 (m, 5H, H-3′, 4′, 5′, 6, 7), 7.76–7.77 (dd, 1H, *J*=1.0, 8.3 Hz, H-5), 8.01–8.05 (m, 2H, H-2′, 6′), 8.06–8.09 (d, 1H, *J*=6.1 Hz, H-8); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 99.51, 118.26, 122.64, 123.96, 127.22 (C×2), 128.99 (C×2), 129.27, 129.62, 129.72, 140.42, 149.22, 152.82, 156.66; IR (KBr) 1633 (C=N) cm^{-1}. Anal. Calcd for $C_{15}H_{12}N_2$: C: 81.79; H: 5.49; N: 12.72. Found: C: 81.35; H: 5.25; N: 12.64.

*3.3.5. 2-(2-Fluorophenyl)-N,N-dimethylquinolin-4-amine (**4a**)*

^{1}H NMR (DMSO-d_6, 200 MHz) δ 2.99 (s, 6H, NCH_3×2), 7.14 (s, 1H, H-3), 7.31–7.35 (m, 2H, H-4′, 5′), 7.44–7.51 (m, 2H, H-3′, 6), 7.65 (t, 1H, *J*=8.3 Hz, H-7), 7.90–7.95 (m, 2H, H-6′, 8), 8.02–8.07 (d, 1H, *J*=8.4 Hz, H-5); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 43.95 (C×2), 108.46, 116.92, 121.69, 124.89, 125.15, 125.29, 128.41, 129.66, 130.15, 131.45, 131.76, 145.85, 149.75, 153.33, 157.60; IR (KBr) 1607 (C=N) cm^{-1}. Anal. Calcd for $C_{17}H_{15}FN_2$: C: 76.67; H: 5.68; N: 10.52. Found: C: 76.87; H: 5.78; N: 10.46.

*3.3.6. N,N-Diethyl-2-(2-fluorophenyl)quinolin-4-amine (**4b**)*

^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.06–1.13 (t, 6H, *J*=7.0 Hz, NCH_3×2), 3.31–3.37 (q, 4H, *J*=7.0 Hz, CH_2×2), 7.22–7.36 (m, 3H, H-3′, 4′, 5′), 7.45–7.50 (m, 2H, H-3, 6), 7.64 (t, 1H, *J*=8.2 Hz, H-7), 7.92–7.97 (m, 3H, H-5, 6′, 8); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 12.43 (C×2), 46.49 (C×2), 111.42, 111.56, 116.49, 116.95, 123.27, 124.33, 125.21, 125.63, 129.72, 130.22, 131.37, 131.69, 149.85, 153.58, 155.53; IR (KBr) 1608 (C=N) cm^{-1}. Anal. Calcd for $C_{19}H_{19}FN_2$: C: 77.52; H: 6.51; N: 9.52. Found: C: 77.53; H: 6.49; N: 9.48.

*3.3.7. N-Methyl-2-(2-fluorophenyl)quinolin-4-amine (**4c**)*

^{1}H NMR (DMSO-d_6, 200 MHz) δ 2.99 (s, 3H, NCH_3), 7.16 (s, 1H, H-3), 7.30–7.36 (m, 3H, H-4′, 5′, NH), 7.45–7.52 (m, 2H, H-3′, 6), 7.66–7.74 (t, 1H, *J*=8.9 Hz, H-7), 7.90–7.95 (m, 2H, H-6′, 8), 8.03–8.04 (d, 1H, *J*=2.2 Hz, H-5); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 30.11, 116.71, 121.33, 123.21, 124.92, 125.17, 125.89, 126.33, 131.82, 132.34, 132.55, 134.41, 147.76, 155.38, 156.72, 158.49; IR (KBr) 1618 (C=N) cm^{-1}. Anal. Calcd for $C_{16}H_{13}FN_2$: C: 76.17; H: 5.19; N: 11.10. Found: C: 76.37; H: 5.02; N: 11.23.

*3.3.8. 2-(2-Fluorophenyl)quinolin-4-amine (**4d**)*

^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.32–7.40 (m, 4H, H-3, 4′, NH_2), 7.62–7.67 (m, 6H, H-3′, 5, 5′, 6, 6′, 7), 8.05–8.11 (d, 1H, *J*=8.6 Hz, H-8); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 100.01, 119.27, 122.73, 123.97, 127.29, 130.52, 133.44, 133.78, 138.25, 140.08, 140.44, 141.42, 157.42, 159.77, 162.31; IR (KBr) 1621 (C=N) cm^{-1}. Anal. Calcd for $C_{15}H_{11}FN_2$: C: 75.62; H: 4.65; N: 11.76. Found: C: 75.21; H: 4.81; N: 11.83.

*3.3.9. 2-(4-Methoxyphenyl)-N,N-dimethylquinolin-4-amine (**5a**)*

^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.01 (s, 6H, NCH_3×2), 3.79 (s, 3H, OCH_3), 7.01–7.05 (d, 2H, *J*=8.0 Hz, H-3′, 5′), 7.29 (s, 1H, H-3), 7.41–7.45 (t, 1H, *J*=7.0 Hz, H-6), 7.61 (dd, 1H, *J*=1.2 Hz, H-7), 7.87–7.91 (d, 1H, *J*=8.6 Hz, H-5), 7.98–8.02 (d, H, *J*=8.4 Hz, H-8), 8.13–8.17 (d, 2H, *J*=8.0 Hz, H-2′, 6′); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 44.08 (C×2), 55.71, 104.66, 114.42 (C×2), 121.71, 124.58, 124.80, 129.06 (C×2), 129.49, 129.97, 132.33, 149.68, 156.41, 158.15, 160.79; IR (KBr) 1623 (C=N) cm^{-1}. Anal. Calcd for $C_{18}H_{18}N_2O$: C: 77.67; H: 6.52; N: 10.06. Found: C: 77.35; H: 6.57; N: 10.37.

*3.3.10. N,N-Diethyl-2-(4-methoxyphenyl)quinolin-4-amine (**5b**)*

^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.05–1.12 (t, 6H, *J*=7.1 Hz, CH_3×2), 3.32–3.42 (q, 4H, *J*=7.1 Hz, CH_2×2), 3.79 (s, 3H, OCH_3), 7.01–7.06 (dd, 2H, *J*=2.0, 8.9 Hz, H-3′, 5′), 7.38 (s, 1H, H-3), 7.41–7.46

(t, 1H, J=8.3 Hz, H-6), 7.61–7.66 (t, 1H, J=8.3 Hz, H-7), 7.88–7.97 (dd, 2H, J=2.1, 8.6 Hz, H-5, 8), 8.12–8.16 (d, 2H, 8.9 Hz, H-2′, 6′); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 12.52 (C×2), 46.35 (C×2), 55.72, 107.71, 114.47 (C×2), 123.30, 124.30, 124.90, 129.08 (C×2), 129.56, 130.00, 132.26, 149.82, 156.22 (C×2), 160.82; IR (KBr) 1610 (C═N) cm^{-1}. Anal. Calcd for $C_{20}H_{22}N_2O$: C: 78.40; H: 7.24; N: 9.14. Found: C: 78.52; H: 7.56; N: 9.18.

*3.3.11. N-Methyl-2-(4-methoxyphenyl)quinolin-4-amine (**5c**)*

^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.10 (s, 3H, NCH_3), 3.77 (s, 3H, OCH_3), 6.68 (s, 1H, H-3), 6.72–6.88 (m, 3H, H-3′, 5′, NH), 7.41–8.03 (m, 2H, H-6, 7), 8.11–8.22 (m, 4H, H-2′, 6′, 5, 8); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 31.15, 55.81, 114.78 (C×2), 117.89, 122.34, 125.81, 128.20, 131.41 (C×2), 132.57, 132.88, 144.12, 149.73, 156.48, 161.52, 161.87; IR (KBr) 1610 (C═N) cm^{-1}. Anal. Calcd for $C_{17}H_{16}N_2O$: C: 77.25; H: 6.10; N: 10.60. Found: C: 77.15; H: 6.19; N:10.24.

*3.3.12. 2-(4-Methoxyphenyl)quinolin-4-amine (**5d**)*

^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.89 (s, 3H, OCH_3), 6.45 (s, 2H, NH_2), 6.99 (s, 1H, H-3), 7.04–7.06 (d, 2H, J=7.8 Hz, H-3′, 5′), 7.64–7.78 (m, 2H, H-6, 7), 8.09–8.13 (m, 2H, H-5, 8), 8.22–8.23 (m, 2H, H-2′, 6′); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 55.91, 114.79 (C×2), 117.22, 124.96, 127.35, 129.41 (C×2), 130.32, 131.05, 141.28, 143.38, 149.66, 154.38, 160.29, 162.39; IR (KBr) 1623 (C═N) cm^{-1}. Anal. Calcd for $C_{16}H_{14}N_2O$: C: 76.78; H: 5.64; N: 11.19. Found: C: 76.75; H: 5.68; N: 11.23.

*3.3.13. 6-Fluoro-N,N-dimethyl-2-phenylquinolin-4-amine (**6**)*

^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.40 (s, 6H, NCH_3×2), 7.13 (s, 1H, H-3), 7.60–7.63 (m, 3H, H-3′, 4′, 5′), 7.82–7.83 (m, 1H, H-7), 8.03–8.09 (m, 3H, H-2′, 6′, 8), 8.25–8.27 (m, 1H, H-5); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 43.77 (C×2), 107.31, 114.30, 121.97, 125.12, 129.92, 130.51 (C×2), 131.28, 134.53 (C×2), 138.76, 149.10, 154.31, 161.38, 162.21; IR (KBr) 1621 (C═N) cm^{-1}. Anal. Calcd for $C_{17}H_{15}FN_2$: C: 76.67; H: 5.68; N: 10.52. Found: C: 76.61; H: 5.69; N: 10.49.

*3.3.14. 7-Fluoro-N,N-dimethyl-2-phenylquinolin-4-amine (**7**)*

^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.43 (s, 6H, NCH_3×2), 7.52 (s, 1H, H-3), 7.63–7.67 (m, 3H, H-3′, 4′, 5′), 7.78–7.80 (m, 1H, H-6), 8.01–8.13 (m, 1H, H-5), 8.32–8.38 (m, 3H, H-2′, 6′, 8); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 43.53 (C×2), 112.31, 114.56, 121.32, 125.47, 125.88, 126.35, 128.01 (C×2), 130.41 (C×2), 136.51, 147.65, 156.34, 159.87, 161.22; IR (KBr) 1620 (C═N) cm^{-1}. Anal. Calcd for $C_{17}H_{15}FN_2$: C: 76.67; H: 5.68; N: 10.52. Found: C: 76.57; H: 5.42; N: 10.68.

*3.3.15. 8-Fluoro-N,N-dimethyl-2-phenylquinolin-4-amine (**8**)*

^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.45 (s, 6H, NCH_3×2), 7.46–7.53 (m, 3H, H-3′, 4′, 5′), 7.66–7.79 (m, 3H, H-3, 6, 7), 8.21–8.23 (m, 3H, H-2′, 6′, 5); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 44.12 (C×2), 111.65, 114.22, 118.53, 126.33, 127.62, 128.01, 129.45 (C×2), 131.94 (C×2), 140.32, 156.65, 158.38, 162.11, 163.04; IR (KBr) 1633 (C═N) cm^{-1}. Anal. Calcd for $C_{17}H_{15}FN_2$: C: 76.67; H: 5.68; N: 10.52. Found: C: 76.72; H: 5.75; N: 10.25.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.09.100.

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