Synthesis and Cytotoxic Evaluation of Certain 4-(Phenylamino)furo-[2,3-*b*]quinoline and 2-(Furan-2-yl)-4-(phenylamino)quinoline Derivatives

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Certain 4-(phenylamino)furo[2,3-*b*]quinoline and 2-(furan-2-yl)-4-(phenylamino)quinoline derivatives were synthesized and evaluated *in vitro* against the full panel of NCIs 60 cancer cell lines. The preliminary results indicated these tricyclic 4-(phenylamino)furo[2,3-*b*]quinolines were more cytotoxic than their corresponding 2-(furan-2-yl)-4-(phenylamino)quinoline isomers. For the 4-(phenylamino)furo[2,3-*b*]quinolines, compounds **2a** and **3d** are two of the most potent with a mean GI_{50} value of 0.025 μM in each case. Inactivity of **2b** and **2c** (positional isomers of **2a**) indicated that both electronic environment, and the distance between intercalating pharmacophore and H-bond-donating MeO group are important. For the 2-(furan-2-yl)-4-(phenylamino)-quinoline isomers, compound **12** (a mean GI_{50} of 4.36 μM), which bears a *para*-COMe substituent, is more active than its *meta*-substituted counterpart **13** (10.5 μM). However, the electron-donating MeO substituent is preferred at the *meta*-position, and the cytotoxicity for the *meta*-substituted derivatives decreased in the order: MeO derivative **14b** (3.05 μM) > oxime **16** (6.85 μM) > ketone **13** (10.5 μM) > methyl oxime **18** (20.6 μM).

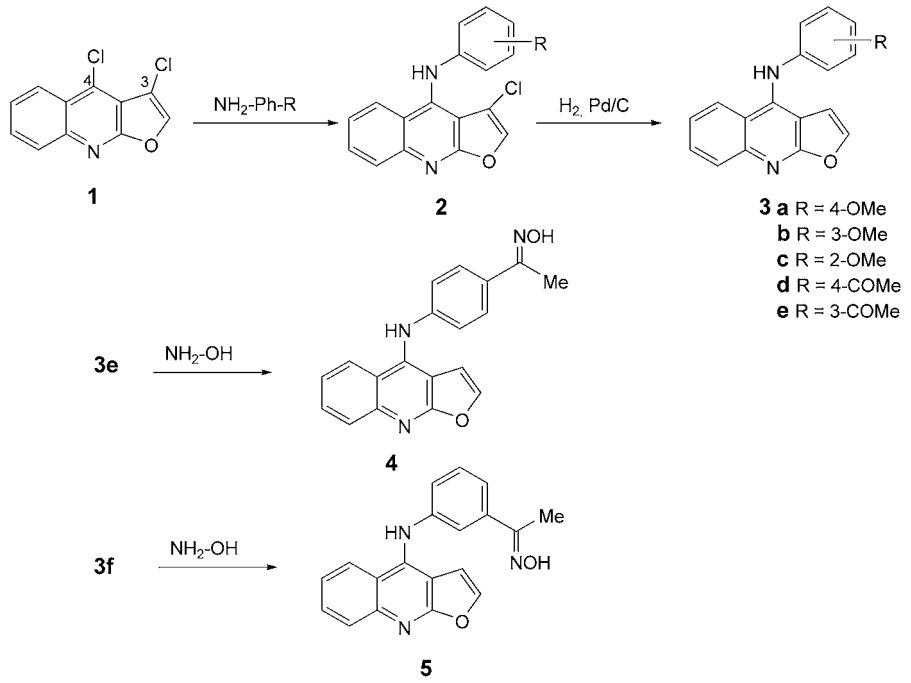
Introduction. – Acridine derivatives, especially 9-(phenylamino)acridines have been extensively studied as potential chemotherapeutic agents due to their capability of intercalating DNA, leading to the inhibition of mammalian topoisomerase II [1–5]. These studies, however, were focused only on the 9-(phenylamino)acridine skeleton, with wide varieties of substituents on the phenylamino and/or acridine chromophores. No attempt has been carried out concerning the replacement of acridine with its bioisosteric furo[2,3-*b*]quinoline ring, which constitutes an important group of bioactive natural products such as dictamnine, robustine, and haplopine [6][7]. Recently, we have synthesized certain 4-(phenylamino)furo[2,3-*b*]quinoline derivatives for cytotoxic evaluation [8][9]. Among them, 1-{4-[(furo[2,3-*b*]quinolin-4-yl)amino]phenyl}ethanone (**3d**) (a mean GI_{50} value of 0.025 μM) exhibited potent and broad spectrum of cytotoxicity [8]. To establish the structure–activity relationships, we describe herein the synthesis and cytotoxic evaluation of **3a**–**3c**, analogues of **3d**. In addition, we have prepared and evaluated 1-(4-{2-[(furan-2-yl])quinolin-4-

yl]amino}phenyl)ethanone (**12**), a structural isomer of **3d**, whose structure belongs to 2-(furan-2-yl)-4-(phenylamino)quinoline skeleton as well as certain congeners of **12**. Although the 2-(furan-2-yl)-4-(phenylamino)quinoline skeleton is not a system with three fused aromatic rings required for a minimal DNA-intercalating ligand, its third furan ring is appended at C(2), which can accommodate itself in a virtually coplanar fashion to the chromophore [10]. The current study was especially encouraged because α-methylidene-β-butyrolactone-bearing flavones were found to be more cytotoxic than their respective tricyclic xanthone counterparts [11].

The oxime, methyl-oxime, and 3-carboxylate derivatives were also synthesized for evaluation. We expect oxime (H-bonding donor) and methyl oxime (H-bonding acceptor) to form H-bonding with DNA molecule during the intercalation process of 2-(furan-2-yl)-4-(phenylamino)quinoline, while 3-carboxylate improves water solubility.

Results and Discussion. – *Chemistry.* Preparation of the 4-(phenylamino)furo[2,3-*b*]quinoline derivatives is outlined in *Scheme 1*. The known 3,4-dichlorofuro[2,3-*b*]quinoline (**1**) [12] was treated with *p*-, *m*-, and *o*-anisidine, respectively, in EtOH/H_2O 2:1 to give *N*-(3-chlorofuro[2,3-*b*]quinolin-4-yl)methoxybenzenamines **2a**–**2c**, which were hydrogenated to afford the respective *N*-(furo[2,3-*b*]quinolin-4-yl)methoxybenzenamines **3a**–**3c** in a good overall yield. Preparation of compounds **3d**, **3e**, **4**, and **5** had been previously described [8][9].

Scheme 1



Synthesis of 2-(furan-2-yl)-4-(phenylamino)quinoline and its 3-carboxylates derivatives is illustrated in the *Scheme 2*. Chlorination of ethyl 2-(furan-2-yl)-1,4-dihydro-4-oxoquinolin-3-carboxylate (**6**) [13] with $POCl_3$ gave ethyl 4-chloro-2-(furan-2-yl)quinoline-3-carboxylate (**7**), which was then treated with substituted anilines to afford ethyl 4-[(4-acetylphenyl)amino]-2-(furan-2-yl)quinoline-3-carboxylate (**10a**) and its 3-substituted isomer **10b**. Hydrolysis of **10a** and **10b** with 1N NaOH gave the 3-carboxylic acid **11a** and **11b**, respectively. Treatment of **6** with 1N NaOH, followed by 20% HCl at reflux, provided 2-(furan-2-yl)quinolin-4(1*H*)-one (**8**) [14], which was chlorinated to give 4-chloro-2-(furan-2-yl)quinoline (**9**). Reaction of **9** with substituted anilines afforded 4-(phenylamino)quinoline derivatives **12**, **13**, and **14a**–**14c** in fairly good yields. Reaction of 1-(4-{[2-(furan-2-yl)quinolin-4-yl]amino}phenyl)ethanone (**12**) with NH_2OH gave exclusively (*E*)-oxime **15** in 72% yield. The configuration of the oxime moiety was determined by through-space nuclear *Overhauser* effect spectroscopy (NOESY), which revealed coupling connectivity to Me H-atoms. Accordingly, compound **16** was obtained from **13** by the treatment with NH_2OH. Reaction of **12** and **13** with NH_2OMe provided (*E*)-methyl oximes **17** and **18**, respectively.

Cytotoxicity. All compounds were evaluated *in vitro* against a 3-cell line panel consisting of MCF 7 (breast), NCI-H460 (lung), and SF-268 (CNS) [15]. Results from the *Table* indicate that most of the 3-chloro-4-(phenylamino)furo[2,3-*b*]quinoline derivatives **2a**–**2e** are inactive with the exception of **2a**, which bears an electron-donating MeO group in the *para*-position of the 4-phenylamino substituent. All the reduced 4-(phenylamino)furo[2,3-*b*]quinoline derivatives **3a**–**3e**, **4**, and **5** are active (compounds that reduce the growth of any one of the three cell lines to 32% or less). For the 2-(furan-2-yl)-4-(phenylamino)quinolines, all the 3-carboxylic acid derivatives **10b**, **11a**, and **11b** are inactive with the exception of **10a**, which exhibits marginal inhibitory activity against NCI-H460. The steric hindrance exerted by the 3-carboxylate of the quinoline moiety may prevent the adjacent furan ring to lie coplanar with bicyclic chromophore, leading to decreased cytotoxicity.

Those active compounds were evaluated in the full panel of 60 human tumor cell lines derived from nine cancer cell types (leukemia, non-small-cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer). For each compound, dose-response curves for each cell line were measured with five different drug concentrations, the concentrations causing 50% cell-growth inhibition (GI_{50}) compared with the control were calculated [16]. For 3-Cl-substituted 4-(phenylamino)furo[2,3-*b*]quinoline derivatives, compounds **2d** and **2e**, which bear electron-withdrawing COMe substituents, were devoid of cytotoxicity, while **2a** (a mean GI_{50} value of 0.025 μM), which bears electron-donating *para*-MeO group, was cytotoxic, implying that the electronic environment is important. Inactivity of its positional isomers **2b** and **2c** indicated that the distance between intercalating pharmacophore and H-bond-donating MeO group also plays an important role. In contrary, the electron-withdrawing COMe moiety (**3d**, 0.025 μM) led to higher cytotoxicity than the electron-donating MeO substituent (**3a**, 1.58 μM) for the reduced 4-(phenylamino)furo[2,3-*b*]quinoline ring. Due to the inductive effect of the Cl-substituent at C(3), the electron density for the 3-chloro-4-(phenylamino)furo[2,3-*b*]quinoline derivatives **2a**–**2e** is less then their reduced 4-(phenylamino)furo[2,3-*b*]quinoline counterparts **3a**–**3e**, and, therefore, the phenylamino moiety prefers to be

Scheme 2

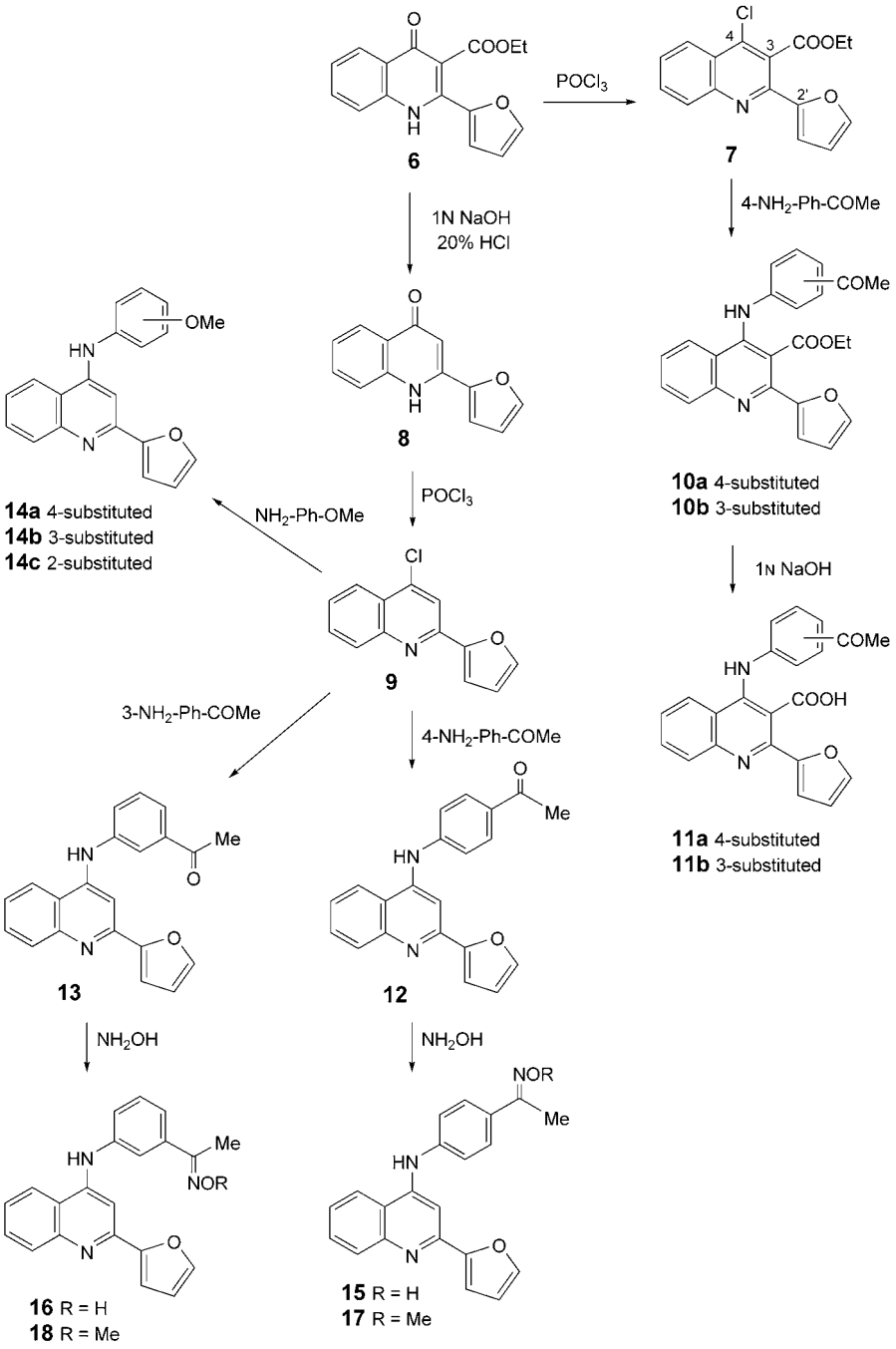

6
7
8
9
10a 4-substituted
10b 3-substituted
11a 4-substituted
11b 3-substituted
12
13
14a 4-substituted
14b 3-substituted
14c 2-substituted
15 R = H
16 R = H
17 R = Me
18 R = Me
POCl3
1N NaOH
20% HCl
4-NH2-Ph-COMe
1N NaOH
NH2-Ph-OMe
3-NH2-Ph-COMe
NH2OH

Table. In Vitro *Cytotoxicity of 4-(Phenylamino)furo[2,3-*b*]quinoline and 2-(Furan-2-yl)quinoline Derivatives*

Compound	Growth percentages[a])			Mean GI_{50} (range) [μM][b])[c])
	NCI-H460 (Lung)	MCF 7 (CNS)	SF-268 (Breast)	
2a	13	12	33	0.025 (0.01 – 25.1)
2b	45	66	72	n.d.[d])
2c	58	66	91	n.d.
2d	53	57	52	n.d.
2e	94	77	101	n.d.
3a	67	25	58	1.58 (0.01 – 70.5)
3b	0	4	6	0.65 (0.01 – 11.0)
3c	1	11	15	5.07 (0.36 – 20.2)
3d	5	13	19	0.025 (0.01 – 20.0)
3e	3	8	29	5.27 (0.09 – 37.2)
4	1	11	24	0.35 (0.01 – 12.2)
5	70	4	5	5.60 (1.74 – 48.0)
10a	13	95	101	20.6 (8.68 – 100)
10b	54	100	103	n.d.
11a	127	105	112	n.d.
11b	118	108	113	n.d.
12	1	2	19	4.36 (0.33 – 32.4)
13	1	11	17	10.5 (1.21 – 34.3)
14a	2	7	5	5.98 (1.70 – 31.9)
14b	1	3	3	3.05 (0.48 – 16.5)
14c	5	18	15	7.45 (1.13 – 24.7)
15	1	88	81	5.54 (1.64 – 28.7)
16	0	25	26	6.85 (1.02 – 38.9)
17	17	83	111	5.99 (0.31 – 74.0)
18	17	50	98	20.6 (4.60 – 67.5)

[a]) In this protocol, each cell line is inoculated and preincubated on a microtiter plate. Test agents are then added at a single concentration (100 μM), and the culture was incubated for 48 h. End-point determinations are made with alamar blue [15]. Results for each test agent are reported as the percent of growth of the treated cells when compared to the untreated control cells. Compounds that reduced the growth of any one of the cell lines to 32% or less are passed on for evaluation in the full panel of 60 cell lines over a 5-log dose range. [b]) Data obtained from *NCIs in vitro* disease-oriented tumor cell screen [16]. GI_{50}: Drug molar concentration causing 50% cell growth inhibition. [c]) Mean values over all cell lines tested. These cell lines are: leukemia (CCRF-CEM, HL-60 (TB), K-562, MOLT-4, PRMI-8226, and SR), non-small-cell lung cancer (A549/ATCC, EKVX, HOP-62, HOP-92, NCI-H226, NCI-H23, NCI-H322M, and NCI-H522), colon cancer (COLC 205, HCC-2998, HCT-116, HCT-15, HT29, KM12, and SW-620), CNS cancer (SF-268, SF-295, SF-539, SNB-19, SNB-75, and U251), melanoma (LOX IMVI, MALME-3M, M14, SK-MEL-2, SK-MEL-28, SK-MEL-5, and UACC-257), ovarian cancer (IGROV1, OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, and SK-OV-3), renal cancer (786-0, A498, ACHN, CAKI-1, RXF 393, SN12C, TK-10, and UO-31), prostate cancer (PC-3 and DU-145), and breast cancer (MCF 7, MCF 7/ADR-RES, MDA-MB-231/ ATCC, HS 578T, MDA-MB-435, MDA-N, and T-47D). [d]) Not determined.

substituted with an electron-donating group for **2a**–**2e** and an electron-withdrawing group for **3a**–**3e** to maintain an optimal electronic environment.

For the 2-(furan-2-yl)-4-(phenylamino)quinoline derivatives, compound **12** (a mean GI_{50} value of 4.36 μM), which bears a *para*-COMe substituent, is more active than its *meta*-substituented counterpart **13** (10.5 μM). The same cytotoxic SAR was observed for the oxime (**15**, 5.54 μM *vs.* **16**, 6.85 μM) and methyl-oxime derivatives (**17**, 5.99 μM *vs.*

18, 20.6 μM). However, the electron-donating MeO group is preferrentially substituted in the *meta*-position, indicating that both electronic environment and the distance between intercalating pharmacophore and H-bonding group are important. Although *para*-substituted 2-(furan-2-yl)-4-(phenylamino)quinoline derivatives **12**, **14a**, and **15**, and **17** exhibited comparable cytotoxicities, the cytotoxicity for the *meta*-substituted derivatives decreased in the order: MeO derivative (**14b** (3.05 μM) > oxime **16** (6.85 μM) > ketone **13** (10.5 μM) > methyl oxime **18** (20.6 μM).

Ac-Substituted tricyclic 4-(phenylamino)furo[2,3-*b*]quinolines **3d** (0.025 μM) and **3e** (5.27 μM) were more cytotoxic than their respective 2-(furan-2-yl)-4-(phenylamino)quinoline isomers **12** (4.36 μM) and **13** (10.5 μM). The same cytotoxic SAR was observed for MeO (**3a**, 1.58 μM *vs.* **14a**, 5.98 μM; **3b**, 0.65 μM *vs.* **14b**, 3.05 μM; **3c**, 5.07 μM *vs.* **14c**, 7.45 μM) and oxime derivatives (**4**, 0.35 μM *vs.* **15**, 5.54 μM; **5**, 5.60 μM *vs.* **16**, 6.85 μM).

Conclusions. – A number of tricyclic 4-(phenylamino)furo[2,3-*b*]quinolines and their 2-(furan-2-yl)-4-(phenylamino)quinoline isomers were synthesized and evaluated for their cytotoxicity. The preliminary results indicated these 4-(phenylamino)furo[2,3-*b*]quinolines were more cytotoxic than their respective 2-(furan-2-yl)-4-(phenylamino)quinoline isomers. For the 4-(phenylamino)furo[2,3-*b*]quinoline derivatives, **2a** and **3d** are two of the most cytotoxic compounds with a mean GI_{50} value of 0.025 μM in each case. For the 2-(furan-2-yl)-4-(phenylamino)quinoline isomers, **14b** is the most cytotoxic compound with a mean GI_{50} value of 3.05 μM.

Experimental Part

General. TLC: Precoated (0.2 mm) silica-gel *60 F_{254}* plates from *EM Laboratories, Inc.*; detection by UV light (254 nm). M.p.: *Electrothermal IA9100* digital melting-point apparatus; uncorrected. ^{1}H-NMR spectra: *Varian Unity-400* spectrometer at 400 MHz or *Varian Gemini-200* spectrometer at 200 MHz, chemical shifts δ in ppm with Me_4Si as an internal standard (= 0 ppm), coupling constants J in Hz. High-resolution (HR) EI-MS: *Bruker APEX II* mass spectrometer. Elemental analyses: *Heraeus CHN-O-Rapid* elemental analyzer; results within ± 0.4% of calc. values.

*3-Chloro-4-[(4-methoxyphenyl)amino]furo[2,3-*b*]quinoline* (**2a**). *3,4-Dichlorofuro[2,3-*b*]quinoline* (**1**; 0.30 g, 1.26 mmol) [12] and *p*-anisidine (0.23 g, 1.87 mmol) were dissolved in boiling EtOH/H_2O 2 : 1 (15 ml). Conc. HCl was added until a pH value of 6, while the reflux was continued overnight (TLC monitoring). The solvent was evaporated *in vacuo* to give a residue, ice-water (80 ml), was added and the mixture was neutralized with 1N NaOH. The resulting precipitate was collected, purified by flash column chromatography (FC; silica gel; CH_2Cl_2), and recrystallized from EtOH to give **2a** (0.34 g, 84%). M.p. 131–132°. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.81 (*s*, MeO); 6.85 (*m*, 2 arom. H); 7.01 (*m*, 2 arom. H); 7.21 (*ddd*, J = 8.2, 7.0, 1.0, H–C(6)); 7.38 (br. *s*, NH); 7.61 (*m*, H–C(2), H–C(7)); 7.72 (*d*, J = 8.4, H–C(8)); 8.04 (*d*, J = 8.2, H–C(5)). ^{13}C-NMR (50 MHz, $CDCl_3$): 55.53; 105.07; 110.18; 114.71 (2 C); 118.26; 122.82 (2 C); 123.22; 124.75; 128.41; 128.85; 136.28; 139.48; 144.52; 146.45; 156.62; 160.38. Anal. calc. for $C_{18}H_{13}ClN_2O_2$: C 66.57, H 4.03, N 8.63; found: C 66.48, H 4.12, N 8.50.

*3-Chloro-4-[(3-methoxyphenyl)amino]furo[2,3-*b*]quinoline* (**2b**). From **1** and *m*-anisidine as described for **2a**: 85% yield. M.p. 181–183°. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.71 (*s*, MeO); 6.54 (*m*, 3 arom. H); 7.17 (*m*, 1 arom. H, NH); 7.30 (*ddd*, J = 8.4, 6.8, 1.4, H–C(6)); 7.66 (*m*, H–C(2), H–C(7)); 7.84 (*dd*, J = 8.4, 1.0, H–C(8)); 8.05 (*d*, J = 8.4, H–C(5)). ^{13}C-NMR (50 MHz, $CDCl_3$): 55.21; 105.09; 107.35; 108.29; 110.17; 111.61; 119.77; 123.70; 124.60; 128.82; 129.86; 130.05; 140.32; 142.34; 144.92; 146.65; 160.58; 160.65. Anal. calc. for $C_{18}H_{13}ClN_2O_2 \cdot 0.3\ H_2O$: C 64.40, H 3.99, N 8.34; found: C 64.35, H 4.05, N 7.99.

*3-Chloro-4-[(2-methoxyphenyl)amino]furo[2,3-*b*]quinoline* (**2c**). From **1** and *o*-anisidine as described for **2a**, **2c** was obtained by FC (CH_2Cl_2) in 94% yield. M.p. 162–164°. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.00 (*s*, MeO); 6.61 (*d*, J = 7.6, 1 arom. H); 6.74 (*ddd*, J = 8.4, 5.6, 2.4, 1 arom. H); 6.97 (*m*, 2 arom. H); 7.33 (*ddd*, J = 8.4, 6.8, 1.2,

H–C(6)); 7.38 (br. *s*, NH); 7.65 (*s*, H–C(2)); 7.68 (*ddd*, *J* = 8.4, 6.8, 1.4, H–C(6)); 7.91 (*d*, *J* = 8.4, H–C(8)); 8.07 (*d*, *J* = 8.4, H–C(5)). ^{13}C-NMR (100 MHz, $CDCl_3$): 55.87; 108.03; 110.41; 110.67; 116.19; 120.35; 120.55; 121.94; 123.70; 124.54; 128.93; 129.85; 133.14; 140.35; 142.26; 146.51; 148.72; 160.72. Anal. calc. for $C_{18}H_{13}ClN_2O_2$: C 66.57, H 4.03, N 8.63; found: C 66.61, H 4.11, N 8.40.

*4-[(4-Methoxyphenyl)amino]furo[2,3-*b*]quinoline* (**3a**). A soln. of **2a** (0.31 g, 0.94 mmol) in MeOH/CH_2Cl_2 1:1 (100 ml) was hydrogenated with 10% Pd/C (20 mg) under H_2 for 1 h (TLC monitoring). The mixture was filtered, and the filtrate was concentrated in *vacuo* to give a residual solid, which was purified by FC (CH_2Cl_2) and recrystallized from EtOH to give **3a** (0.17 g, 61%). M.p. 177–179°. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.87(*s*, MeO); 5.70 (*d*, *J* = 2.6, H–C(3)); 6.96 (*m*, 2 arom. H, NH); 7.23 (*m*, 2 arom. H); 7.30 (*d*, *J* = 2.6, H–C(2)); 7.43 (*ddd*, *J* = 8.4, 7.2, 1.2, H–C(6)); 7.66 (*ddd*, *J* = 8.4, 7.0, 1.2, H–C(6)); 8.02 (*m*, H–C(5), H–C(8)). ^{13}C-NMR (50 MHz, $CDCl_3$): 55.56; 102.95; 105.48; 114.69 (2 C); 116.48; 120.14; 123.23; 126.91 (2 C); 128.68; 129.03; 133.11; 141.61; 143.43; 145.77; 157.98; 163.53. Anal. calc. for $C_{18}H_{14}N_2O_2$: C 74.47, H 4.86, N 9.65; found: C 74.10, H 4.95, N 9.50.

Hydrogenation of **2b**–**2d** as described for **2a** gave **3b**–**3d** resp.

*4-[(3-Methoxyphenyl)amino]furo[2,3-*b*]quinoline* (**3b**). Yield 73%. M.p. 148–149°. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.78 (*s*, MeO); 6.11 (*d*, *J* = 2.8, H–C(3)); 6.78 (*m*, 3 arom. H); 7.00 (br. *s*, NH); 7.27 (*m*, 1 arom. H); 7.43 (*d*, *J* = 2.8, H–C(2)); 7.46 (*ddd*, *J* = 8.4, 6.8, 1.2, H–C(6)); 7.69 (*ddd*, *J* = 8.4, 6.8, 1.2, H–C(7)); 8.03 (*dd*, *J* = 8.4, 0.8, H–C(8)); 8.07 (*dd*, *J* = 8.4, 0.8, H–C(5)). ^{13}C-NMR (50 MHz, $CDCl_3$): 55.32; 105.37; 105.74; 107.89; 110.15; 114.66; 117.92; 120.61; 123.63; 129.03; 129.14; 130.11; 141.23; 142.06; 142.43; 145.87; 160.55; 163.32. Anal. calc. for $C_{18}H_{14}N_2O_2 \cdot 0.4\ H_2O$: C 72.66, H 5.01, N 9.41; found: C 72.73, H 5.02, N 9.20.

*4-[(2-Methoxyphenyl)amino]furo[2,3-*b*]quinoline* (**3c**). Yield 75% . M.p. 124–125°. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.92 (*s*, MeO); 6.21 (*d*, *J* = 2.8, H–C(3)); 7.04 (*m*, NH, 4 arom. H); 7.45 (*d*, *J* = 2.8, H–C(2)); 7.47 (*ddd*, *J* = 8.2, 6.8, 1.4, H–C(6)); 7.70 (*ddd*, *J* = 8.2, 6.8, 1.4, H–C(7)); 8.08 (*dd*, *J* = 8.2, 0.8, H–C(8)); 8.11 (*dd*, *J* = 8.2, 0.8, H–C(5)). ^{13}C-NMR (50 MHz, $CDCl_3$): 55.65; 105.69; 105.85; 110.88; 118.61; 120.44; 120.55; 121.05; 123.63; 123.90; 128.85; 129.12; 130.05; 141.02; 142.34; 145.77; 150.71; 163.18. Anal. calc. for $C_{18}H_{14}N_2O_2$: C 74.47, H 4.86, N 9.65; found: C 74.46, H 4.93, N 9.68.

Ethyl 4-Chloro-2-(furan-2-yl)quinoline-3-carboxylate (**7**). A mixture of *ethyl 2-(furan-2-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylate* (**6**; 2.83 g, 10 mmol) and $POCl_3$ (30 ml) was refluxed for 12 h (TLC monitoring). The soln. was cooled to r.t. and slowly poured into ice-water and then neutralized with NH_4OH (ice bath). The residue was extracted with CH_2Cl_2 (3 × 100 ml), and the extracts were combined, dried ($MgSO_4$), and then concentrated *in vacuo* to give a white solid, which was purified by FC (CH_2Cl_2). The proper fractions were combined and evaporated to afford **7** (2.35 g, 78%). M.p. 71–72°. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.42 (*t*, *J* = 7.2, *M*eCH_2O); 4.48 (*q*, *J* = 7.2, MeC*H*$_2$O); 6.57 (*dd*, *J* = 3.4, 1.8, H–C(4′)); 7.24 (*dd*, *J* = 3.4, 0.8, H–C(3′)); 7.61 (*m*, H–C(5), H–C(6)); 7.78 (*m*, H–C(7)); 8.10 (*m*, H–C(5)); 8.21 (*dd*, *J* = 8.4, 1.6, H–C(8)). ^{13}C-NMR (50 MHz, $CDCl_3$): 14.03; 62.34; 112.32; 112.37; 117.46; 124.20; 124.31; 127.07; 127.89; 129.62; 131.43; 140.52; 144.39; 144.81; 147.97; 151.71. Anal. calc. for $C_{16}H_{12}ClNO_3$: C 63.69, H 4.01, N 4.64; found: C 63.73, H 4.04, N 4.63.

*2-(Furan-2-yl)-1*H*-quinolin-4-one* (**8**). A mixture of **6** (2.83 g, 10 mmol), EtOH (20 ml), and 1N NaOH (200 ml) was refluxed for 6 h. After cooling, EtOH was evaporated, and the soln. was acidified with 20% HCl. The precipitate thus formed was collected and refluxed with 20% HCl for 6 h (TLC monitoring). The precipitate was collected and crystallized from MeOH to give **8** (1.79 g, 85%). M.p. 246–248°. ^{1}H-NMR (200 MHz, TFA): 6.46 (*dd*, *J* = 3.4, 1.6, H–C(4′)); 7.22 (*s*, H–C(3)); 7.28 (*d*, *J* = 3.4, H–C(3′)); 7.46 (*m*, H–C(6), H–C(5′)); 7.75 (*m*, H–C(5), H–C(7)); 8.12 (*d*, *J* = 8.2, H–C(8)). ^{13}C-NMR (50 MHz, TFA): 101.88; 116.16; 120.48; 121.12; 121.36; 125.93; 130.62; 137.96; 140.98; 146.19; 146.33; 151.06; 171.13. HR-EI-MS: 211.0631 ($C_{13}H_9NO_2^+$; calc. 211.0633).

4-Chloro-2-(furan-2-yl)quinoline (**9**). A mixture of **8** (2.11 g, 10 mmol) and $POCl_3$ (30 ml) was refluxed for 12 h (TLC monitoring). The soln. was cooled to r.t. and slowly poured into ice-water, and then neutralized with NH_4OH (ice bath). The soln. was extracted with CH_2Cl_2 (3 × 100 ml) and extracts combined, dried ($MgSO_4$), and then concentrated *in vacuo* to give a brown solid, which was purified by FC (CH_2Cl_2). The proper fractions were combined and evaporated to afford **9** (1.79 g, 78%). M.p. 70–71°. ^{1}H-NMR (200 MHz, $CDCl_3$): 6.58 (*dd*, *J* = 3.4, 1.8, H–C(4′)); 7.24 (*dd*, *J* = 3.4, 0.8, H–C(3′)); 7.57 (*m*, H–C(6)); 7.62 (*dd*, *J* = 1.8, 0.8, H–C(5′)); 7.74 (*m*, H–C(7)); 7.91 (*s*, H–C(3)); 8.15 (*m*, H–C(5), H–C(8)). ^{13}C-NMR ($CDCl_3$): 110.85; 112.38; 117.45; 123.99; 125.27; 127.06; 129.58; 130.71; 143.02; 144.43; 148.76; 148.85; 152.66. Anal. calc. for $C_{16}H_{12}ClNO_3$: C 67.99, H 3.51, N 6.10; found: C 67.65, H 3.53, N 6.11.

Ethyl 4-[(4-Acetylphenyl)amino]-2-(furan-2-yl)quinoline-3-carboxylate (**10a**). From **7** and 4-aminoacetophenone as described for **2a**. Compound **10a** was obtained by FC (CH_2Cl_2) in 85% yield. M.p. 166–168°.

^{1}H-NMR (200 MHz, $CDCl_3$): 1.09 (*t*, *J* = 7.2, *M*eCH$_2$O); 2.53 (*s*, MeCO); 4.21 (*q*, *J* = 7.2, MeC*H*$_2$O); 6.58 (*dd*, *J* = 3.4, 1.8, H–C(4′)); 6.80 (*m*, 2 arom. H); 7.17 (*d*, *J* = 3.4, H–C(3′)); 7.32 (*m*, H–C(6)); 7.56 (*d*, *J* = 1.8, H–C(5′)); 7.71 (*m*, H–C(7), NH); 7.82 (*m*, H–C(5), 2 arom, H); 8.10 (*dd*, *J* = 8.6, 1.4, H–C(8)). ^{13}C-NMR (50 MHz, $CDCl_3$): 13.85; 26.20; 62.02; 111.14; 112.11; 116.92 (2 C); 121.02; 125.12; 126.13; 130.09 (2 C); 130.24; 130.74; 131.20; 143.66; 143.81; 145.14; 147.10; 148.21; 149.07; 153.03; 168.19; 196.49. Anal. calc. for $C_{24}H_{20}N_2O_4$: C 71.99, H 5.03, N 7.00; found: C 71.69, H 5.07, N 7.00.

Ethyl 4-[(3-Acetylphenyl)amino]-2-(furan-2-yl)quinoline-3-carboxylate (**10b**). From **7** and 3-aminoacetophenone as described for **2a**: 82% yield. M.p. 213–215°. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.89 (*t*, *J* = 7.2, *M*eCH$_2$O); 2.57 (*s*, MeCO); 3.39 (*q*, *J* = 7.2, MeC*H*$_2$O); 6.83 (*dd*, *J* = 3.6, 1.6, H–C(4′)); 7.56 (*m*, H–C(3′), 2 arom. H); 7.82 (*m*, H–C(6), 2 arom. H); 8.04 (*m*, H–C(5′), H–C(7)); 8.44 (*d*, *J* = 7.8, H–C(5)); 8.80 (*d*, *J* = 8.4, H–C(8)); 10.96 (br. *s*, NH). ^{13}C-NMR (50 MHz, $CDCl_3$): 12.81; 26.33; 61.11; 109.10; 112.44; 116.45; 118.58; 121.56; 123.00; 124.00; 125.40; 127.02; 128.54; 128.98; 133.71; 136.81; 139.02; 139.31; 141.66; 144.61; 146.97; 150.92; 163.79; 196.89. Anal. calc. for $C_{24}H_{21}ClN_2O_4 \cdot 0.2\ H_2O$: C 65.42, H 5.27, N 6.36; found: C 65.50, H 4.98; N 6.43.

4-[(4-Acetylphenyl)amino]-2-(furan-2-yl)quinoline-3-carboxylic Acid (**11a**). A mixture of **10a** (0.40 g, 1 mmol) in EtOH (20 ml) and 1N NaOH (50 ml) was refluxed for 2 h (TLC monitoring). After cooling, EtOH was evaporated, and the soln. was acidified with 20% HCl. The precipitate thus formed was collected and crystallized from MeOH to give **11a** (0.32 g, 85%). M.p. 255–257°. ^{1}H-NMR (400 MHz, DMSO): 2.38 (*s*, MeCO); 6.61 (*m*, H–C(4′), 2 arom. H); 7.29 (*m*, H–C(3′), H–C(5′), H–C(6)); 7.62 (*m*, H–C(7), 2 arom. H); 7.83 (*m*, H–C(5)); 7.97 (*d*, *J* = 7.6, H–C(8)); 8.86 (br. *s*, NH). ^{13}C-NMR (100 MHz, DMSO): 26.11; 111.85; 112.36; 114.85 (2 C); 122.57; 124.15; 125.58; 127.74; 129.05; 129.19; 129.40; 129.68 (2 C); 139.98; 144.03; 145.87; 146.97; 150.49; 152.49; 169.93; 195.66. HR-EI-MS: 373.1186 ($C_{22}H_{17}N_2O_4$; calc. 373.1183).

4-[(3-Acetylphenyl)amino]-2-(furan-2-yl)quinoline-3-carboxylic Acid (**11b**). From **10b** as described for **11a**: 86% yield. M.p. 231–232°. ^{1}H-NMR (400 MHz, DMSO): 2.41 (*s*, MeCO); 6.59 (*m*, H–C(4′)); 6.86 (*d*, *J* = 8.0, 1 arom. H); 7.32 (*m*, H–C(3′), H–C(6), 3 arom. H); 7.52 (*d*, *J* = 8.4, H–C(5)); 7.66 (*m*, H–C(7)); 7.81 (*m*, H–C(5′)); 7.98 (*d*, *J* = 8.8, H–C(8)); 8.56 (br. *s*, NH). ^{13}C-NMR (100 MHz, DMSO): 26.64; 111.89; 111.95; 115.86; 120.03; 121.31; 121.93; 124.49; 125.46; 129.06; 129.23; 129.45; 129.54; 137.38; 142.19; 144.09; 144.24; 145.90; 147.40; 152.59; 169.93; 197.87. Anal. calc. for $C_{22}H_{16}N_2O_4 \cdot 0.2\ H_2O$: C 64.05, H 4.65, N 6.79; found: C 63.68, H 5.04, N 6.81.

1-(4-{[(2-Furan-2-yl)quinolin-4-yl]amino}phenyl)ethanone Hydrochloride (**12**). From **9** and 4-aminoacetophenone as described for **2a**: 84% yield. M.p. 216–217°. ^{1}H-NMR (200 MHz, DMSO): 2.65 (*s*, MeCO); 6.86 (*dd*, *J* = 3.4, 1.6, H–C(4′)); 7.28 (*s*, H–C(3)); 7.75 (*m*, H–C(6), 2 arom. H); 8.01 (*m*, H–C(7)); 8.14 (*m*, H–C(5′), 2 arom. H); 8.21 (*d*, *J* = 3.4, H–C(3′)); 8.51 (*d*, *J* = 7.8, H–C(5)); 8.82 (*d*, J = 7.8, H–C(8)); 11.17 (br. *s*, NH). ^{13}C-NMR (50 MHz, DMSO): 26.72; 95.81; 113.67; 117.04; 117.25; 120.60; 123.68; 124.24 (2 C); 126.76; 130.02 (2 C); 134.00; 134.70; 139.22; 142.06; 142.16; 145.20; 148.10; 153.66; 196.91. Anal. calc. for $C_{21}H_{17}ClN_2O_2 \cdot H_2O$: C 65.69, H 4.99, N 7.30; found: C 65.60, H 4.96, N 7.34.

1-(3-{[(2-Furan-2-yl)quinolin-4-yl]amino}phenyl)ethanone Hydrochloride (**13**). From **9** and 3-aminoacetophenone as described for **2a**. 82% yield. M.p. 270–271°. ^{1}H-NMR (200 MHz, DMSO): 2.65 (*s*, MeCO); 6.82 (*dd*, *J* = 3.4, 1.4, H–C(4′)); 7.13 (*s*, H–C(3)); 7.70–8.07 (*m*, H–C(3′), H–C(5′), H–C(6), H–C(7), 4 arom. H); 8.32 (*d*, *J* = 8.4, H–C(5)); 8.69 (*d*, *J* = 8.2, H–C(8)); 10.80 (br. *s*, NH). ^{13}C-NMR (50 MHz, DMSO): 26.91; 95.25; 113.47; 115.76; 117.05; 121.88; 123.26; 124.20; 126.44; 126.53; 129.33; 130.42; 133.42; 138.40; 140.60; 142.99; 146.52; 147.46; 147.56; 153.45; 197.47. Anal. calc. for $C_{21}H_{17}ClN_2O_2 \cdot 0.5\ H_2O$: C 67.27, H 5.11, N 7.47; found: C 67.08, H 4.90, N 7.44.

4-[(4-Methoxyphenyl)amino]-2-(furan-2-yl)quinoline (**14a**). From **9** and *p*-anisidine as described for **2a**: 81% yield. M.p. 249–250°. ^{1}H-NMR (200 MHz, DMSO): 3.86 (*s*, MeO); 6.83 (*dd*, *J* = 3.6, 1.6, H–C(4′)); 6.89 (*s*, H–C(3)); 7.15 (*m*, 2 arom. H); 7.46 (*m*, 2 arom. H); 7.72 (*m*, H–C(6)); 7.98 (*m*, H–C(7)); 8.07 (*d*, *J* = 1.6, H–C(5′)); 8.20 (*d*, *J* = 3.6, H–C(3′)); 8.50 (*d*, *J* = 8.4, H–C(5)); 8.76 (*d*, *J* = 8.4, H–C(8)); 10.95 (br. *s*, NH). ^{13}C-NMR (50 MHz, DMSO): 55.45; 94.26; 113.39; 115.17 (2 C); 116.20; 116.75; 120.28; 123.33; 126.38; 127.19 (2 C); 129.63; 133.75; 138.87; 141.44; 145.05; 147.73; 155.07; 158.42. Anal. calc. for $C_{20}H_{16}N_2O_2 \cdot 1.8\ H_2O$: C 68.87, H 5.21, N 8.08; found: C 68.70, H 5.12, N 8.02.

4-[(3-Methoxyphenyl)amino]-2-(furan-2-yl)quinoline Hydrochloride (**14b**). From **9** and *m*-anisidine as described for **2a**: 83% yield. M.p. 246–247°. ^{1}H-NMR (200 MHz, DMSO): 3.83 (*s*, MeO); 6.85 (*dd*, *J* = 3.8, 1.8, H–C(4′)); 7.10 (*m*, H–C(3), 3 arom. H); 7.52 (*m*, 1 arom. H); 7.74 (*m*, H–C(6)); 8.00 (*m*, H–C(7)); 8.10 (*d*, *J* = 1.8, H–C(5′)); 8.18 (*d*, *J* = 3.8, H–C(3′)); 8.49 (*d*, *J* = 7.8, H–C(5)); 8.77 (*d*, *J* = 8.0, H–C(8)); 10.98 (br. *s*, NH). ^{13}C-NMR (50 MHz, DMSO): 55.38; 94.85; 111.05; 113.06; 113.48; 116.40; 116.77; 117.29; 120.37; 123.36;

126.50; 130.75; 133.84; 138.38; 138.97; 141.61; 145.10; 147.88; 154.45; 160.35. Anal. calc. for $C_{20}H_{17}ClN_2O_2$: C 68.06, H 4.87, N 7.94; found: C 67.76, H 4.96, N 7.94.

4-[(2-Methoxyphenyl)amino]-2-(furan-2-yl)quinoline Hydrochloride (**14c**). From **9** and *o*-anisidine as described for **2a**. 82% yield. M.p. 188–189°. ^{1}H-NMR (200 MHz, DMSO): 3.82 (*s*, MeO); 6.57 (*s*, H–C(3)); 6.84 (*dd*, *J* = 3.6, 1.6, H–C(4′)); 7.47 (*m*, 4 arom. H); 7.74 (*m*, H–C(6)); 8.01 (*m*, H–C(7)); 8.07 (*d*, *J* = 1.6, H–C(5′)); 8.24 (*d*, *J* = 3.6, H–C(3′)); 8.55 (*d*, *J* = 8.6, H–C(5)); 8.78 (*d*, *J* = 8.4, H–C(8)); 10.80 (br. *s*, NH). ^{13}C-NMR (50 MHz, DMSO): 55.70; 94.74; 113.03; 113.41; 115.99; 116.82; 120.37; 121.27; 123.33; 124.82; 126.46; 128.17; 129.72; 133.75; 138.84; 141.26; 145.03; 147.79; 154.31; 154.95. Anal. calc. for $C_{20}H_{17}ClN_2O_2 \cdot H_2O$: C 64.75, H 5.16, N 7.55; found: C 64.56, H 5.20, N 7.61.

1-(4-{[(2-Furan-2-yl)quinolin-4-yl]amino}phenyl)ethanone Oxime (**15**). To a suspension of **14** (0.16 g, 0.5 mmol) in EtOH (10 ml) was added $NH_2OH \cdot HCl$ (0.18 g, 2.5 mmol) and K_2CO_3 (0.16 g, 1.3 mmol). The mixture was refluxed for 2 h (TLC monitoring). After cooling, the solvent was removed *in vacuo*, and the residue was suspended in ice water (20 ml). The precipitate obtained was collected and crystallized from MeOH to give **15** (0.12 g, 72%). M.p. 283–284°. ^{1}H-NMR (200 MHz, DMSO): 2.19 (*s*, Me); 6.64 (*dd*, *J* = 3.4, 1.6, H–C(4′)); 7.16 (*d*, *J* = 3.4, H–C(3′)); 7.44 (*m*, H–C(3), H–C(6), 2 arom. H); 7.72 (*m*, H–C(3′), H–C(7), 2 arom. H); 7.89 (*d*, *J* = 8.0, H–C(5)); 8.36 (*d*, *J* = 8.0, H–C(8)); 9.14 (br. *s*, NH); 11.16 (*s*, NOH). ^{13}C-NMR (50 MHz, DMSO): 11.43; 97.31; 109.39; 112.38; 119.16; 121.89 (2 C); 122.15; 124.58; 126.73 (2 C); 128.96; 129.98; 132.22; 141.10; 144.18; 148.25; 148.87; 148.96; 152.54; 153.73. Anal. calc. for $C_{21}H_{17}N_3O_2$: C 73.45, H 4.99, N 12.24; found: C 73.49, H 5.03, N 12.13.

1-(3-{[(2-Furan-2-yl)quinolin-4-yl]amino}phenyl)ethanone Oxime (**16**). From **13** and $NH_2OH \cdot HCl$ as described for **15**: 70% yield. M.p. 268–269°. ^{1}H-NMR (200 MHz, DMSO): 2.21 (*s*, Me); 6.66 (*dd*, *J* = 3.2, 1.6, H–C(4′)); 7.16 (*d*, *J* = 3.2, H–C(3′)); 7.41 (*s*, H–C(3)); 7.52 (*m*, H–C(6), 3 arom. H); 7.73 (*m*, H–C(7), 1 arom. H); 7.82 (*d*, *J* = 1.6, H–C(5′)); 7.90 (*d*, *J* = 8.4, H–C(5)); 8.39 (*d*, *J* = 7.8, H–C(8)); 9.14 (br. *s*, NH); 11.31 (*s*, NOH). ^{13}C-NMR (50 MHz, DMSO): 11.51; 96.69; 109.24; 112.32; 118.93; 119.63; 121.25; 122.07; 122.74; 124.46; 128.93; 129.48; 129.89; 138.26; 140.59; 144.15; 148.55; 148.81; 148.92; 152.59; 153.76. Anal. calc. for $C_{21}H_{17}N_3O_2$: C 73.45, H 4.99, N 12.24; found: C 73.28, H 5.08, N 12.12.

1-(4-{[(2-Furan-2-yl)quinolin-4-yl]amino}phenyl)ethanone O-*Methyloxime Hydrochloride* (**17**). From **12** and $NH_2OMe \cdot HCl$ as described for **15**: 76% yield. M.p. 237–238°. ^{1}H-NMR (200 MHz, DMSO): 2.25 (*s*, C(=NOMe)*Me*); 3.96 (*s*, NOMe); 6.83 (*dd*, *J* = 3.6, 1.6, H–C(4′)); 7.15 (*s*, H–C(3)); 7.58 (*m*, 2 arom. H); 7.72 (*m*, H–C(6)); 7.86 (*m*, 2 arom. H); 7.98 (*m*, H–C(7)); 8.08 (*m*, H–C(3′), H–C(5′)); 8.41 (*d*, *J* = 8.0, H–C(5)); 8.76 (*d*, *J* = 8.0, H–C(8)); 10.90 (br. *s*, NH). ^{13}C-NMR (50 MHz, DMSO): 12.23; 61.73; 95.21; 113.53; 116.35; 116.88; 121.21; 123.41; 124.73 (2 C); 126.52; 127.34 (2 C); 133.65; 134.15; 138.51; 139.90; 142.41; 145.88; 147.69; 153.47; 153.65. Anal. calc. for $C_{22}H_{20}ClN_3O_2 \cdot H_2O$: C 64.13, H 5.39, N 10.20; found: C 64.08, H 5.48, N 10.20.

1-(3-{[(2-Furan-2-yl)quinolin-4-yl)amino}phenyl)ethanone O-*Methyloxime Hydrochloride* (**18**). From **13** and $NH_2OMe \cdot HCl$ as described for **15**: 75% yield. M.p. 276–277°. ^{1}H-NMR (200 MHz, DMSO): 2.29 (*s*, C(=NOMe)Me); 4.00 (*s*, NOMe); 6.79 (*dd*, *J* = 3.6, 1.8, H–C(4′)); 7.20 (*s*, H–C(3)); 7.61 (*m*, H–C(3′), 2 arom. H); 7.79 (*m*, H–C(6), 2 arom. H); 7.94 (*d*, *J* = 1.8, H–C(5′)); 8.04 (*m*, H–C(7)); 8.14 (*d*, *J* = 7.8, H–C(5)); 8.57 (*d*, *J* = 8.6, H–C(8)); 10.69 (br. *s*, NH). ^{13}C-NMR (50 MHz, DMSO): 12.54; 62.46; 96.33; 114.64; 116.95; 118.18; 121.29; 123.93; 124.08; 126.63; 127.11; 128.40; 131.42; 135.52; 138.77; 140.13; 140.30; 143.79; 146.76; 149.08; 154.99; 156.82. Anal. calc. for $C_{22}H_{20}ClN_3O_2$: C 67.06, H 5.13, N 10.66; found: C 67.04, H 5.25, N 10.58.

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