Synthesis and Antiproliferative Evaluation of 4-Anilino-*n*-methoxyfuro[2,3-*b*]quinoline Derivatives ($n = 6, 7$)

Part 5[1])

by **Yeh-Long Chen**[a]), **Huan-Chin Lin**[a]), **Chia-Ning Yang**[b]), **Pei-Jung Lu***[c])[d]), and **Cherng-Chyi Tzeng***[a])

[a]) Faculty of Medicinal and Applied Chemistry, College of Life Science, Kaohsiung Medical University, Kaohsiung City 807, Taiwan (phone: +886-7-3121101 ext. 6985; fax: +886-7-3125339; e-mail: tzengch@kmu.edu.tw)

[b]) Department of Medical Imaging and Radiological Sciences, I-Shou University, Kaohsiung 840, Taiwan

[c]) Department of Medical Education and Research, Veteran General Hospital, Kaohsiung City 813, Taiwan (phone: +8867-3422121 ext. 1501; fax: +8867-3468056; e-mail: pjfranklu@isca.vghks.gov.tw)

[d]) Department of Biological Sciences, National Sun Yat-Sen University, Kaohsiung City 804, Taiwan

A series of 27 differently substituted 4-anilinofuro[2,3-*b*]quinolines were synthesized and evaluated for their antiproliferative activities against the HeLa, SKHep1, SAS, AGS, A549, and CE81T cell lines, cancers commonly found in Asian countries. Among the compounds tested, 1-{4-[(3-chloro-7-methoxyfuro[2,3-*b*]quinolin-4-yl)amino]phenyl}ethanone (**1**) was the most potent, with IC_{50} values of 3.1, 3.0, and 4.2 μM, resp., against the growth of HeLa, SKHep, and CE81T cells. Compound **1** was, thus, further evaluated by flow cytometry to evaluate its effect on the cell-cycle distribution of HeLa cells. Our results indicated that **1** readily induces cell-cycle arrest in the G2/M phase, followed by DNA fragmentation and, ultimately, cell death.

Introduction. – Acridine derivatives have been extensively studied as potential anticancer agents due to their capability of intercalating into DNA leading to the inhibition of mammalian topoisomerase II [5–9]. These results prompted us to synthesize and evaluate furo[2,3-*b*]quinoline derivatives, which are structurally related to acridines by isosteric substitution of a benzene moiety for a furan ring [6–9]. Similar approaches to this kind of compounds were also reported where a benzene moiety was isosterically replaced with a thiazole ring [10][11].

Recently, we have reported the preparation of certain 4-anilinofuro[2,3-*b*]quinoline derivatives, which were evaluated for their antiproliferative activities against 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). Among them, 1-{4-[(3-chloro-7-methoxyfuro[2,3-*b*]quinolin-4-yl)amino]phenyl}ethanone (**1**; see *Scheme 1* below) exhibited an excellent antiproliferative activity, with a mean GI_{50} value of 0.27 μM [4].

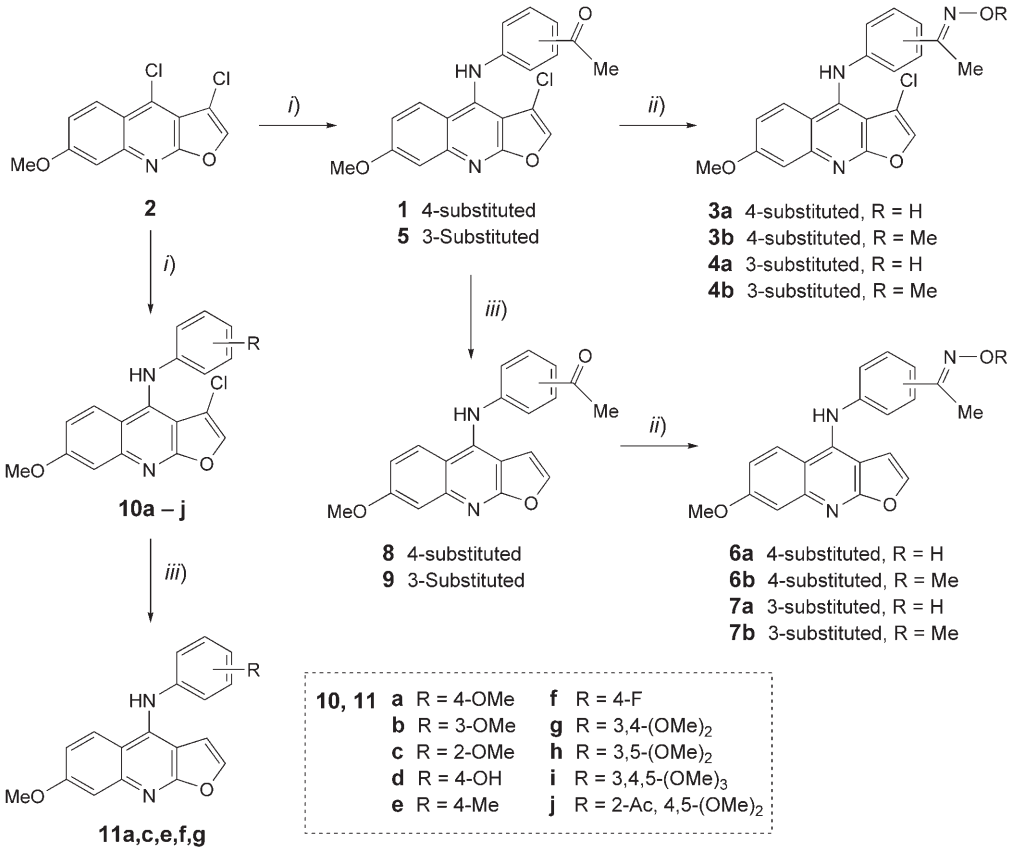
The present study intends to further evaluate compound **1** and its analogous against human cervical epithelioid carcinoma (HeLa), hepatocelluar carcinoma (SKHep1),

[1]) For Parts 1–4, see [1–4].

oral squamous cell carcinoma (SAS), human stomach adenocarcinoma (AGS), non-small-cell lung cancer (A549), and esophageal carcinoma (CE81T) cells, types of cancer commonly found in Asian countries, including Taiwan.

Results and Discussion. – 1. *Synthesis.* The preparation of 4-anilino-7-methoxyfuro[2,3-*b*]quinoline derivatives is illustrated in *Scheme 1*. Compound **1** was obtained by reaction of 3,4-dichloro-7-methoxyfuro[2,3-*b*]quinoline (**2**) with 4-aminoacetophenone, as described previously [4]. Treatment of **1** with NH_2OH or NH_2OMe gave exclusively the (*E*)-oxime **3a** or the (*E*)-configured *O*-methyl oxime **3b**, respectively, in good overall yield. The configuration of the oxime moiety was determined by through-space nuclear-*Overhauser*-effect spectroscopy (NOESY), which revealed coupling between the oxime OH (or MeO) and Me–C(α) groups. The configuration was further confirmed by ^{13}C-NMR spectroscopy. The Me–C(α) group *syn* to the OH moiety is

Scheme 1



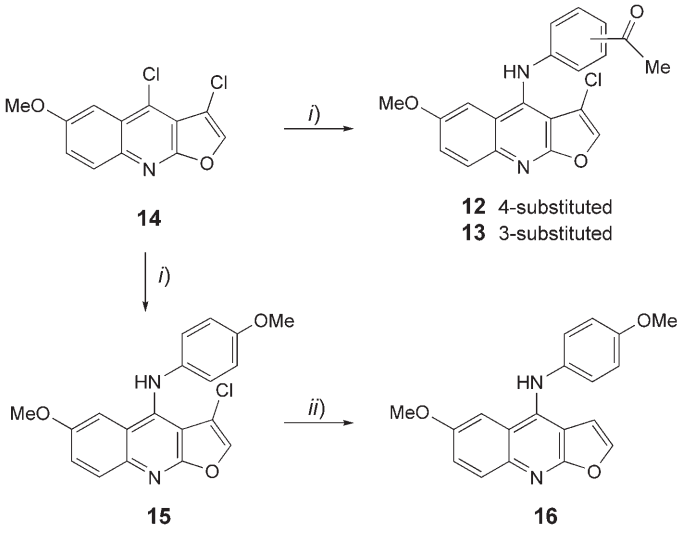
i) Substituted aniline, EtOH/H_2O, HCl, reflux. *ii*) NH_2OH or NH_2OMe, EtOH, reflux. *iii*) H_2, Pd/C, MeOH/CH_2Cl_2.

typically shifted upfield by *ca.* 11.50 ppm ((*E*)-configuration), while that of the *anti* isomer is shifted downfield by *ca.* 18.75 ppm ((*Z*)-configuration) [12].

Accordingly, the corresponding (*E*)-oxime **4a** and (*E*)-methyloxime **4b** were prepared from their 3-substituted precursor **5**, which was obtained by the treatment of **2** with 3-aminoacetophenone. The same synthetic procedures were applied for the synthesis of the (*E*)-oximes **6a** and **7a**, and for the (*E*)-configured *O*-methyl oximes **6b** and **7b**, respectively, from their respective ketone precursors **8** and **9**, which, in turn, were obtained from **1** and **5**, respectively, by hydrogenation with Pd/C. Treatment of **2** with substituted anilines afforded the 4-(arylamino)-3-chloro-7-methoxyfuro[2,3-*b*]quinolines **10a**–**j**, which were hydrogenated to the corresponding Cl-free compounds **11** in good overall yields.

The preparation of 4-anilino-6-methoxyfuro[2,3-*b*]quinoline derivatives is illustrated in *Scheme* 2. Compound **12** and its 3-substituted isomer **13** were obtained by the reaction of 3,4-dichloro-6-methoxyfuro[2,3-*b*]quinoline (**14**) with 4- or 3-aminoacetophenone, respectively. Treatment of **14** with 4-methoxyaniline afforded **15**, which was hydrogenated to afford 6-methoxy-4-[(methoxyphenyl)amino]furo[2,3-*b*]quinoline (**16**) in good overall yield.

Scheme 2



i) Substituted aniline, $EtOH/H_2O$, HCl, reflux. *ii*) H_2, Pd/C, $MeOH/CH_2Cl_2$.

2. *Biological Activity.* Six cell lines, including human cervical epithelioid carcinoma (HeLa), hepatocelluar carcinoma (SKHep1), oral squamous cell carcinoma (SAS), human stomach adenocarcinoma (AGS), non-small-cell lung cancer (A549), and esophageal carcinoma (CE81T) were used for cytotoxicity screening *in vitro*. The cytotoxic potential of all synthesized compounds was evaluated against a panel of

human cancer cell lines using the MTT[2]) assay (see *Exper. Part*) [13]. The concentration that killed 50% of the cells (IC_{50}) was determined from the linear portion of the curve by calculating the concentration of agent that reduced the absorbance of the formazan product in treated cells, compared to control cells, by 50%. The results of these studies are summarized in the *Table*.

Table. *Antiproliferative Activities of Furo[2,3-*b*]quinolines.* Cells tested: SAS, oral squamous cell carcinoma; HeLa, human cervical epithelioid carcinoma; SKHep1, hepatocellular carcinoma; AGS, human stomach adenocarcinoma; A549, non-small-cell lung cancer; CE81T, esophageal carcinoma.

Drug	IC_{50} [μM][a])					
	SAS	HeLa	SKHep	AGS	A549	CE81T
1	18.9±3.3	3.10±1.8	3.00±1.7	9.10±1.4	6.60±1.4	4.20±0.2
3a	16.1±0.7	15.2±2.8	13.1±3.9	1.8±0.1	>30	6.00±2.7
4b	16.6±0.1	>30	20.5±6.2	13.3±1.4	8.90±0.8	>30
5	>30	>30	16.0±1.6	12.2±0.7	>30	10.4±0.1
6a	>30	26.1±4.4	12.4±2.5	9.6±1.8	19.1±2.8	>30
6b	17.2±1.7	15.2±1.8	12.4±0.8	14.2±1.3	8.40±1.3	>30
6a	>30	19.3±2.3	16.4±6.2	10.7±1.3	21.4±1.5	>30
6b	>30	>30	>30	>30	>30	>30
10a	19.2±3.5	4.60±2.4	6.43±4.5	24.7±1.2	8.56±0.6	8.30±2.1
10b	>30	11.9±2.1	14.9±4.4	11.2±0.5	13.0±1.9	9.60±1.5
10c	>30	>30	>30	16.9±3.9	11.4±1.9	9.40±0.8
10d	>30	>30	>30	>30	14.3±2.3	12.2±2.4
10e	>30	>30	>30	16.1±0.7	10.4±2.1	13.4±3.5
10f	>30	21.7±4.5	15.9±2.5	10.2±1.0	20.5±1.4	11.8±2.9
10g	19.1±8.1	19.7±3.4	15.2±2.8	13.6±1.6	17.1±1.2	9.30±1.1
10h	17.4±2.6	15.6±4.7	12.6±4.3	14.1±2.2	12.0±2.5	7.60±2.0
10i	13.7±1.5	7.40±0.6	5.47±4.3	10.8±1.2	7.50±0.4	2.80±1.4
10j	18.9±5.2	7.80±0.9	10.1±2.1	8.7±0.1	17.6±2.6	4.50±3.4
11a	20.6±8.2	>30	24.6±2.4	10.3±0.5	10.8±1.6	>30
11c	>30	24.2±1.7	24.0±5.7	>30	8.60±0.9	>30
11e	>30	>30	>30	>30	9.00±1.6	>30
11f	>30	>30	>30	>30	26.4±1.5	>30
11g	>30	26.2±2.1	29.8±8.2	>30	>30	>30
12	23.2±8.5	14.9±2.7	11.6±4.7	15.1±1.0	20.9±2.1	>30
13	>30	23.2±3.1	>30	15.9±1.3	10.7±1.8	>30
15	18.2±1.1	12.1±4.3	15.2±6.2	18.1±2.0	21.4±1.7	14.6±3.2
16	>30	>30	12.8±5.8	>30	>30	>30
CPT[b])	6.0±2.7	0.3±0.1	0.2±0.1	>30	2.8±0.7	2.8±1.5
Dox[b])	5.7±0.3	0.4±0.1	<0.1	>30	2.2±0.3	0.3±0.1

[a]) Concentration required to kill 50% of the exposed cells ($n=4$). [b]) CPT and Dox refer to (+)-camptothecin and doxorubicin hydrochloride, resp. (positive controls).

For the 7-methoxy-4-anilinofuro[2,3-*b*]quinoline derivatives, the 4-COMe substituted derivative **1** was more active than its oxime derivative **3a**, except for AGS, in

[2]) MTT = 3-(4,5-Dimethyl-1,3-thiazol-2-yl)-2,5-diphenyltetrazolium bromide.

which **3a** was found to be especially active ($IC_{50}=1.8$ μM). Comparison of positional isomers showed that the 4-COMe derivative **1** was more active than its 3-substituted counterpart **5**, while the 4-OMe derivative **10a** was more active than the 3-OMe congener **10b**, which, in turn, was more active than the 2-OMe derivative **10c**, except for AGS, in which **10a** was relatively inactive.

The observation that **10a** is more potent than **10d** implies that a H-bond-accepting MeO group is preferred to a H-bond-donating OH group. For the 4-substituted derivatives, the antiproliferative activity decreased in the order **1** > **10f** > **10e** > **10d**, except for A549, in which **10f** was relatively inactive, which indicated that an electron-withdrawing substituent is more favorable than an electron-donating one.

The antiproliferative activities of the dimethoxy-substituted derivatives **10g** and **10h** were comparable, but the trimethoxy derivatives **10i** generally exhibited higher activities. Esophageal carcinoma (CE81T) was found to be especially susceptible to the 3-chloro substituted derivatives **10**, with IC_{50} values of 2.8 and 4.5 μM for **10i** and **10j**, respectively. In contrast, CE81T was basically resistant to the unsubstituted counterparts **11a**, **11c**, and **11e**–**g** ($IC_{50}>16.0$ μM in each case), indicating that the 3-Cl substituent is crucial for growth inhibition of CE81T cells. The importance of the 3-Cl substituent was further confirmed by comparison of **10a**, **10f**, and **10g** and their respective unsubstituted counterparts **11a**, **11f**, and **11g**, again except for AGS, in which **11a** ($IC_{50}=10.3$ μM) was more active than **10a**. In general, the multiply substituted 4-anilino derivatives **10g**–**j** exhibited broad antiproliferative activities against the growth of all six cell lines, while most of the 3-unsubstituted derivatives **11a**, **11c**, and **11e** demonstrated selective cytotoxicity towards A549 only. Oral squamous cell carcinoma (SAS) was the most resistant against all compounds tested, with IC_{50} values >13.7 μM in each case.

The structure–activity relationship (SAR) for the 7-methoxy-4-anilinofuro[2,3-*b*]quinoline derivatives can also be applied to the 6-methoxy counterparts. Thus, the 4-MeCO derivative **12** was more active than its 3-substituted counterpart **13** (with an exception of A549), and the 3-chloro-substituted derivative **15** was more potent than its unsubstituted isomer **16**. With only a few exceptions, the 7-methoxy-4-anilinofuro[2,3-*b*]quinoline derivatives **1**, **5**, **10a**, and **11a** were more active than their respective 6-methoxy isomers **12**, **13**, **15**, and **16**, indicating that positional isomerism plays an important role.

Among the tested compounds, **1** was the most cytotoxic, with mean IC_{50} values of 3.1, 3.0, and 4.2 μM against the growth of HeLa, SKHep, and CE81T cells, respectively. Therefore, compound **1** was further evaluated by flow-cytometric analysis for its effect on cell-cycle distribution. As shown in the *Figure*, the cell-cycle arrest induced by **1** is time-dependent. The proportion of cells was slightly decreased in the G1 and accumulated in the G2/M phase after 6 h of treatment, but was arrested in the G2/M phase of the cell cycle after 12 h. After 36 h, the accumulation of the cells in the G2/M phase was significantly decreased, while the number of hypodiploid (sub-G0/G1 phase) cells increased. The observation of cells in sub-G0/G1 phase indicates DNA fragmentation and cell death.

Together, compound **1**, thus, inhibits proliferation of HeLa cells by the alteration of cell division, accumulation of cells in the G2/M phase as early as 6 h, which then decreased, followed by cell accumulation in the sub-G1 phase after 36 h of treatment.

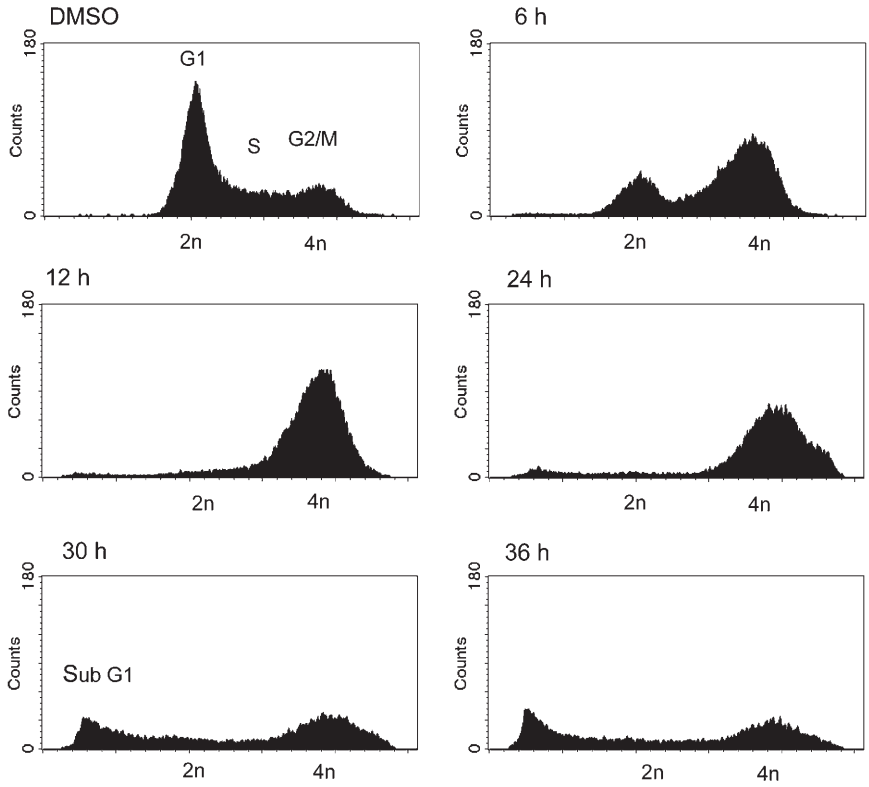


Figure. *Flow-cytometric analysis of the effect of* **1** *on HeLa cells.* The cells were treated with DMSO as control or with 5 μM of **1**. For exposure times, see the *Figure.* DNA was stained with propidium iodide.

Thus, compound **1** induces cell-cycle arrest in the G2/M phase followed by DNA fragmentation, and consequentially cell death.

Conclusions. – A number of 4-anilinofuro[2,3-*b*]quinoline derivatives were synthesized and evaluated for their antiproliferative activities. From the preliminary results it can be concluded that *1*) 7-MeO derivatives are more potent than their respective 6-MeO isomers; *2*) 4-substituted anilino derivatives are more active than their 3-substituted counterparts; *3*) esophageal carcinoma (CE81T) is very susceptible to 3-chloro-substituted 4-anilinofuro[2,3-*b*]quinolines, but resistant to the unsubstituted derivatives; *4*) multiply substituted 4-anilino derivatives exhibit broader antiproliferative activities than mono- and disubstituted derivatives; *5*) most of the 3-unsubstituted derivatives demonstrate selective cytotoxicity on A549 cells, while their respective 3-chloro-substituted counterparts exhibit general antiproliferative activity; and *6*) oral squamous cell carcinoma (SAS) is the most resistant against all compounds tested.

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and the *National Center for High-Performance Computing* for providing computer resources and chemical-database services.

Experimental Part

General. TLC: Precoated (0.2 mm) silica gel *60* F_{254} plates (*EM Laboratories, Inc.*); detection under UV light (254 nm). Column chromatography (CC): silica gel *60* (230–400 mesh; *Merck*). M.p.: *Electrothermal IA9100* melting-point apparatus; uncorrected. UV Spectra: *Hitachi U-3210* spectrophotometer; λ_{max} (log ε) in nm. IR Spectra: *Nicolet Magna-IR 550* spectrophotometer; in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Varian-Unity-400* spectrometer, at 400 and 100 MHz, resp.; chemical shifts δ in ppm rel. to Me_4Si (=0 ppm), coupling constants *J* in Hz. Elemental analyses: *Heraeus CHN-O-Rapid* elemental analyzer; correct within ±0.4% of the calc. values.

*1-{3-[(3-Chloro-7-methoxyfuro[2,3-*b*]quinolin-4-yl)amino]phenyl}ethanone* (**5**). To a soln. of 3,4-dichloro-7-methoxyfuro[2,3-*b*]quinoline (**2**; 268 mg, 1 mmol) and 3-aminoacetophenone (270 mg, 2 mmol) in EtOH/H_2O 2:1 (15 ml) was added conc. HCl until pH 6 resulted. The mixture was heated at reflux for 24 h (TLC monitoring). Then, the solvent was evaporated *in vacuo* to give a residual solid. After addition of ice-water (40 ml), the mixture was neutralized with 1N aq. NaOH soln. The resulting precipitate was collected and purified by CC (SiO_2; CH_2Cl_2). Yield: 194 mg (53%). M.p. 198–201°. UV (MeOH): 212 (4.30), 248 (4.56), 341 (4.09). IR (KBr): 1675, 3330. ^{1}H-NMR ($CDCl_3$): 2.54 (*s*, MeCO); 3.95 (*s*, MeO); 6.96 (*dd*, *J*=2.4, 9.6, H–C(6)); 7.05 (*dd*, *J*=2.0, 8.0, 1 arom. H); 7.21 (br. *s*, NH); 7.33 (*m*, 1 arom. H); 7.38 (*d*, *J*=2.4, H–C(8)); 7.55 (*m*, 1 arom. H); 7.60 (*m*, 1 arom. H); 7.62 (*s*, H–C(2)); 7.65 (*d*, *J*=9.6, H–C(5)). ^{13}C-NMR ($CDCl_3$): 26.7 (MeCO); 55.5 (MeO); 106.2; 106.8; 110.2; 114.7; 117.4 (2 C); 117.8; 122.6; 122.7; 125.3; 129.6; 138.3; 139.6; 141.6; 144.2; 148.8; 161.1; 197.7 (C=O). Anal. calc. for $C_{20}H_{15}ClN_2O_3 \cdot 0.1\ H_2O$ (368.59): C 65.17, H 4.16, N 7.60; found: C 64.95, H 4.08, N 7.53.

*(1*E*)-1-{4-[(3-Chloro-7-methoxyfuro[2,3-*b*]quinolin-4-yl)amino]phenyl}ethanone Oxime* (**3a**). To a suspension of **1** (367 mg, 1.0 mmol) in EtOH (10 ml) was added $NH_2OH \cdot HCl$ (140 mg, 2.0 mmol). The mixture was heated at reflux for 1 h (TLC monitoring), then concentrated *in vacuo* to give a solid, which was crystallized from EtOH. Yield: 347 mg (91%). M.p. 194° (dec). UV (MeOH): 244 (4.51), 346 (4.15), 373 (4.13). IR (KBr): 1570, 3200. ^{1}H-NMR ((D_6)DMSO): 2.10 (*s*, Me); 3.94 (*s*, MeO); 6.88 (*m*, 2 arom. H); 7.20 (*dd*, *J*=2.6, 9.4, H–C(6)); 7.38 (*d*, *J*=2.6, H–C(8)); 7.50 (*m*, 2 arom. H); 8.17 (*d*, *J*=9.4, H–C(5)); 8.24 (*s*, H–C(2)); 9.20 (br. *s*, NH); 11.00 (br. *s*, NOH). ^{13}C-NMR ((D_6)DMSO): 11.3 (Me); 55.6 (MeO); 106.4; 110.0; 116.1 (2 C); 116.4; 117.1; 118.9; 125.0; 126.4 (2 C); 129.0; 141.0; 141.3; 146.4; 147.6; 152.5; 160.9; 161.1. Anal. calc. for $C_{20}H_{16}ClN_3O_3 \cdot 0.3\ H_2O$ (387.20): C 62.04, H 4.32, N 10.85; found: C 61.95, H 4.38, N 10.75.

*(1*E*)-1-{4-[(3-Chloro-7-methoxyfuro[2,3-*b*]quinolin-4-yl)amino]phenyl}ethanone* O*-Methyloxime* (**3b**). To a suspension of **1** (100 mg, 0.28 mmol) in EtOH (5 ml) was added $NH_2OMe \cdot HCl$ (46 mg, 0.54 mmol). The mixture was heated at reflux for 1 h (TLC monitoring), then concentrated *in vacuo* to give a solid, which was crystallized from EtOH. Yield: 80 mg (74%). M.p. 160–161°. UV (MeOH): 246 (4.37), 374 (3.96). IR (KBr): 1589, 3136. ^{1}H-NMR ((D_6)DMSO): 2.11 (*s*, Me); 3.87 (*s*, MeO); 3.94 (*s*, MeO); 6.86 (*m*, 2 arom. H); 7.21 (*dd*, *J*=2.6, 9.6, H–C(6)); 7.38 (*d*, *J*=2.6, H–C(8)); 7.50 (*m*, 2 arom. H); 8.12 (*d*, *J*=9.6, H–C(5)); 8.24 (*s*, H–C(2)); 9.13 (br. *s*, NH). ^{13}C-NMR ((D_6)DMSO): 12.0 (Me); 55.5 (MeO); 61.3 (MeO); 106.7; 109.9; 115.7 (2 C); 116.6; 117.2; 117.4; 124.8; 126.8 (2 C); 129.8; 140.7; 141.1; 147.1; 148.0; 153.6; 160.8; 161.3. Anal. calc. for $C_{21}H_{18}ClN_3O_3 \cdot 0.8\ H_2O$ (410.24): C 61.48, H 4.82, N 10.24; found: C 61.31, H 4.87, N 9.90.

*(1*E*)-1-{3-[(3-Chloro-7-methoxyfuro[2,3-*b*]quinolin-4-yl)amino]phenyl}ethanone Oxime* (**4a**). From **5** and $NH_2OH \cdot HCl$, as described for **3a**. Yield: 95%. M.p. 274° (dec). UV (MeOH): 251 (4.12), 342 (3.58). IR (KBr): 1581, 3386. ^{1}H-NMR ((D_6)DMSO): 2.07 (*s*, Me); 3.94 (*s*, MeO); 6.88 (*m*, 1 arom. H); 7.13–7.24 (*m*, 4 arom. H); 7.36 (*d*, *J*=2.4, H–C(8)); 8.15 (*d*, *J*=9.6, H–C(5)); 8.21 (*s*, H–C(2)); 8.99 (br. *s*, NH); 11.09 (br. *s*, NOH). ^{13}C-NMR ((D_6)DMSO): 11.4 (Me); 55.5 (MeO); 106.7; 110.0; 113.2; 116.3; 117.0; 117.0; 118.1; 124.9; 129.1; 137.7; 140.6; 140.8; 141.3; 145.9; 148.0; 152.7; 160.8; 161.4. Anal. calc. for $C_{20}H_{16}ClN_3O_3 \cdot 0.5\ H_2O$ (390.81): C 61.47, H 4.38, N 10.75; found: C 61.22, H 4.41, N 10.69.

*(1*E*)-1-{3-[(3-Chloro-7-methoxyfuro[2,3-*b*]quinolin-4-yl)amino]phenyl}ethanone* O*-Methyloxime* (**4b**). From **5** and $NH_2OMe \cdot HCl$, as described for **3b**. Yield: 96%. M.p. 181–183°. UV (MeOH): 249

(4.61), 342 (4.09). IR (KBr): 1571, 3384. ^{1}H-NMR ((D$_6$)DMSO): 2.11 (*s*, Me); 3.88 (*s*, MeO); 3.94 (*s*, MeO); 6.86 (*m*, 1 arom. H); 7.15–7.23 (*m*, 3 arom. H); 7.33 (*m*, 1 arom. H); 7.36 (*d*, *J* = 2.4, H–C(8)); 8.20 (*m*, H–C(2,5)); 9.18 (br. *s*, NH). ^{13}C-NMR ((D$_6$)DMSO): 12.8 (Me); 56.0 (MeO); 62.0 (MeO); 106.9; 110.5; 114.8; 116.5; 117.5; 117.8; 119.0; 125.4; 129.6; 137.2; 140.3; 141.3; 142.0; 146.3; 148.1; 154.4; 161.4; 161.7. Anal. calc. for $C_{21}H_{18}ClN_3O_3 \cdot 0.2\ H_2O$ (399.43): C 63.15, H 4.64, N 10.52; found: C 63.01, H 4.72, N 10.53.

3-Chloro-7-methoxy-N-*(4-methoxyphenyl)furo[2,3*-b*]quinolin-4-amine* (**10a**). From **2** and *para*-anisidine (= 4-methoxybenzenamine), as described for **5**. Yield: 73%. M.p. 189–190°. UV (MeOH): 245 (4.54), 342 (4.06). IR (KBr): 1586, 3398. ^{1}H-NMR (CDCl$_3$): 3.80 (*s*, MeO); 3.92 (*s*, MeO); 6.81–6.87 (*m*, 2 arom. H, H–C(6)); 7.98 (*m*, 2 arom. H); 7.20 (br. *s*, NH); 7.31 (*d*, *J* = 2.8, H–C(8)); 7.57 (*m*, H–C(2,5)). ^{13}C-NMR (CDCl$_3$): 55.4 (MeO); 55.5 (MeO); 103.7; 106.9; 110.1; 113.2; 114.7 (2 C); 116.2; 122.7 (2 C); 125.9; 136.5; 138.4; 144.1; 149.4; 156.4; 160.7; 161.4. Anal. calc. for $C_{19}H_{15}ClN_2O_3 \cdot 0.2\ H_2O$ (358.38): C 63.68, H 4.33, N 7.82; found: C 63.58, H 4.22, N 7.76.

3-Chloro-7-methoxy-N-*(3-methoxyphenyl)furo[2,3*-b*]quinolin-4-amine* (**10b**). From **2** and *meta*-anisidine, as described for **5**. Yield: 56%. M.p. 168–169°. UV (MeOH): 212 (4.38), 248 (4.53), 341 (4.06). IR (KBr): 1588, 3417. ^{1}H-NMR (CDCl$_3$): 3.72 (*s*, MeO); 3.94 (*s*, MeO); 6.47 (*m*, 1 arom. H); 6.52 (*m*, 1 arom. H); 6.59 (*dd*, *J* = 2.0, 8.0, 1 arom. H); 6.95 (*dd*, *J* = 2.6, 9.4, H–C(6)); 7.11 (br. *s*, NH); 7.16 (*m*, 1 arom. H); 7.35 (*d*, *J* = 2.6, H–C(8)); 7.59 (*s*, H–C(2)); 7.71 (*d*, *J* = 9.6, H–(5)). ^{13}C-NMR (CDCl$_3$): 55.2 (MeO); 55.5 (MeO); 105.1; 105.3; 105.7; 106.7; 108.2; 110.2; 111.6; 114.6; 116.9; 125.9; 130.1; 139.2; 142.4; 144.9; 149.0; 160.6; 161.0. Anal. calc. for $C_{19}H_{15}ClN_2O_3 \cdot 0.3\ H_2O$ (360.18): C 63.36, H 4.37, N 7.78; found: C 63.38, H 4.30, N 7.75.

3-Chloro-7-methoxy-N-*(2-methoxyphenyl)furo[2,3*-b*]quinolin-4-amine* (**10c**). From **2** and *ortho*-anisidine, as described for **5**. Yield: 62%. M.p. 161–162°. UV (MeOH): 214 (4.37), 246 (4.59), 344 (4.14). IR (KBr): 1587, 3397. ^{1}H-NMR (CDCl$_3$): 3.95 (*s*, MeO); 4.00 (*s*, MeO); 6.62 (*m*, 1 arom. H); 6.74 (*m*, 1 arom. H); 6.93–7.00 (*m*, 3 arom. H); 7.32 (br. *s*, NH); 7.37 (*d*, *J* = 2.4, H–C(8)); 7.59 (*s*, H–C(2)); 7.78 (*d*, *J* = 9.2, H–(5)). ^{13}C-NMR (CDCl$_3$): 55.5 (MeO); 55.9 (MeO); 106.4; 106.7; 110.4; 110.7; 115.2; 116.1; 116.9; 120.6; 121.8; 125.8; 133.2; 139.2; 142.2; 148.7; 148.8; 161.0; 161.4. Anal. calc. for $C_{19}H_{15}ClN_2O_3$ (354.77): C 64.32, H 4.26, N 7.90; found: C 64.28, H 4.39, N 7.70.

4-[(3-Chloro-7-methoxyfuro[2,3-b*]quinolin-4-yl)amino]phenol* (**10d**). From **2** and 4-aminophenol, as described for **5**. Yield: 33%. M.p. 247° (dec). UV (MeOH): 248 (4.49), 340 (3.98). IR (KBr): 1580, 3392. ^{1}H-NMR ((D$_6$)DMSO): 3.91 (*s*, MeO); 6.66 (*m*, 2 arom. H); 6.85 (*m*, 2 arom. H); 7.09 (*dd*, *J* = 2.6, 9.4, H–C(6)); 7.26 (*d*, *J* = 2.6, H–C(8)); 8.06 (*s*, H–C(2)); 8.16 (*d*, *J* = 9.4, H–C(5)); 8.66 (br. *s*, NH); 9.11 (br. *s*, OH). ^{13}C-NMR ((D$_6$)DMSO): 55.4 (MeO); 103.2; 106.7; 110.1; 114.5; 115.7 (2 C); 115.9; 121.0 (2 C); 124.8; 137.0; 139.4; 143.4; 148.1; 153.0; 160.5; 161.8. Anal. calc. for $C_{18}H_{13}ClN_2O_3$ (340.75): C 63.45, H 3.84, N 8.22; found: C 63.41, H 3.92, N 8.29.

3-Chloro-7-methoxy-N-*(4-methylphenyl)furo[2,3*-b*]quinolin-4-amine* (**10e**). From **2** and 4-methylaniline, as described for **5**. Yield: 87%. M.p. 176–177°. UV (MeOH): 246 (4.55), 341 (4.12). IR (KBr): 1588, 3320. ^{1}H-NMR (CDCl$_3$): 2.32 (*s*, Me); 3.93 (*s*, MeO); 6.87–6.90 (*m*, 3 arom. H); 7.08 (*m*, 2 arom. H); 7.18 (br. *s*, NH); 7.34 (*d*, *J* = 2.4, H–C(8)); 7.56 (*s*, H–C(2)); 7.63 (*d*, *J* = 9.2, H–(5)). ^{13}C-NMR (CDCl$_3$): 20.8 (Me); 55.5 (MeO); 104.6; 106.7; 110.2; 113.8; 116.5; 120.0 (2 C); 126.0; 129.9 (2 C); 130.6; 133.0; 138.7; 140.9; 143.4; 149.1; 160.9; 161.3. Anal. calc. for $C_{19}H_{15}ClN_2O_2$ (338.78): C 67.36, H 4.46, N 8.27; found: C 67.17, H 4.47, N 8.10.

3-Chloro-N-*(4-fluorophenyl)-7-methoxyfuro[2,3*-b*]quinolin-4-amine* (**10f**). From **2** and 4-fluoroaniline, as described for **5**. Yield: 66%. M.p. 164–165°. UV (MeOH): 248 (4.53), 340 (4.12). IR (KBr): 1593, 3396. ^{1}H-NMR (CDCl$_3$): 3.93 (*s*, MeO); 6.89–7.00 (*m*, 5 arom. H); 7.16 (br. *s*, NH); 7.34 (*d*, *J* = 2.4, H–C(8)); 7.58 (*s*, H–C(2)); 7.60 (*d*, *J* = 9.6, H–C(5)). ^{13}C-NMR (CDCl$_3$): 55.7 (MeO); 104.9; 106.8; 110.1; 113.8; 116.2 (2 C, *J* = 22.7); 116.9; 121.5 (2 C, *J* = 7.6); 125.6; 139.0; 139.7; 143.1; 149.0; 159.1 (*J* = 241.3); 161.0; 161.2. Anal. calc. for $C_{18}H_{12}ClFN_2O_2$ (342.74): C 63.08, H 3.53, N 8.17; found: C 63.00, H 3.82, N 7.93.

3-Chloro-N-*(3,4-dimethoxyphenyl)-7-methoxyfuro[2,3*-b*]quinolin-4-amine* (**10g**). From **2** and 3,4-dimethoxyaniline, as described for **5**. Yield: 71%. M.p. 195–196°. UV (MeOH): 247 (4.58), 342 (4.08). IR (KBr): 1586, 3379. ^{1}H-NMR (CDCl$_3$): 3.75 (*s*, MeO); 3.88 (*s*, MeO); 3.92 (*s*, MeO); 6.57 (*dd*, *J* = 2.4, 8.8, 1 arom. H); 6.61 (*d*, *J* = 2.4, 1 arom. H); 6.78 (*d*, *J* = 8.8, 1 arom. H); 6.86 (*dd*, *J* = 2.8, 9.2, H–C(6));

7.22 (br. *s*, NH); 7.31 (*d*, *J* = 2.8, H–C(8)); 7.56 (*s*, H–C(2)); 7.60 (*d*, *J* = 9.2, H–C(5)). ^{13}C-NMR ($CDCl_3$): 55.5 (MeO); 56.0 (MeO); 56.2 (MeO); 103.9; 105.8; 106.9; 110.1; 111.8; 113.1; 113.3; 116.2; 126.0; 136.9; 138.5; 143.8; 146.0; 149.5; 149.7; 160.8; 161.5. Anal. calc. for $C_{20}H_{17}ClN_2O_4$ (384.80): C 62.43, H 4.45, N 7.28; found: C 62.39, H 4.53, N 7.21.

3-Chloro-N-*(3,5-dimethoxyphenyl)-7-methoxyfuro[2,3*-b*]quinolin-4-amine* (**10h**). From **2** and 3,5-dimethoxyaniline, as described for **5**. Yield: 57%. M.p. 184–186°. UV (MeOH): 246 (4.56), 342 (4.11). IR (KBr): 1585, 3411. ^{1}H-NMR ($CDCl_3$): 3.69 (*s*, 2 MeO); 3.94 (*s*, MeO); 6.07 (*d*, *J* = 2.0, 2 arom. H); 6.16 (*t*, *J* = 2.0, 1 arom. H); 6.97 (*dd*, *J* = 2.4, 9.6, H–C(6)); 7.05 (br. *s*, NH); 7.34 (*d*, *J* = 2.4, H–C(8)); 7.59 (*s*, H–C(2)); 7.75 (*d*, *J* = 9.6, H–C(5)). ^{13}C-NMR ($CDCl_3$): 55.3 (2 MeO); 55.5 (MeO); 94.8 (2 C); 97.6 (2 C); 105.7; 106.7; 110.4; 114.4; 117.0; 125.9; 139.2; 142.1; 145.6; 149.0; 161.0; 161.5 (2 C). Anal. calc. for $C_{20}H_{17}ClN_2O_4$ (384.80): C 62.43, H 4.45, N 7.28; found: C 62.25, H 4.42, N 7.19.

3-Chloro-7-methoxy-N-*(3,4,5-trimethoxyphenyl)furo[2,3*-b*]quinolin-4-amine* (**10i**). From **2** and 3,4,5-trimethoxyaniline, as described for **5**. Yield: 53%. M.p. 188–189°. UV (MeOH): 220 (4.34), 250 (4.55), 342 (3.99). IR (KBr): 1591, 3411. ^{1}H-NMR ($CDCl_3$): 3.70 (*s*, 2 MeO); 3.83 (*s*, MeO); 3.94 (*s*, MeO); 6.21 (*s*, 2 arom. H); 6.94 (*dd*, *J* = 2.8, 9.6, H–C(6)); 7.16 (br. *s*, NH); 7.33 (*d*, *J* = 2.8, H–C(8)); 7.59 (*s*, H–C(2)); 7.68 (*d*, *J* = 9.6, H–C(5)). ^{13}C-NMR ($CDCl_3$): 55.4 (MeO); 56.1 (2 MeO); 61.0 (MeO); 97.7 (2 C); 104.7; 106.8; 110.1; 113.8; 116.5; 126.0; 134.3; 138.9; 139.5; 142.7; 149.3; 153.8 (2 C); 160.9; 161.4. Anal. calc. for $C_{21}H_{19}ClN_2O_5$ (414.82): C 60.80, H 4.62, N 6.75; found: C 60.52, H 4.66, N 6.81.

1-{2-[(3-Chloro-7-methoxyfuro[2,3-b*]quinolin-4-yl)amino]-4,5-dimethoxyphenyl}ethanone* (**10j**). From **2** and 2-amino-4,5-dimethoxyacetophenone, as described for **5**. Yield: 62%. M.p. 174–175°. UV (MeOH): 245 (4.35), 346 (3.90), 394 (3.84). IR (KBr): 1588, 1619, 3141. ^{1}H-NMR ($CDCl_3$): 2.70 (*s*, Me); 3.48 (*s*, MeO); 3.91 (*s*, MeO); 3.97 (*s*, MeO); 6.11 (*s*, 1 arom. H); 7.09 (*dd*, *J* = 2.8, 9.2, H–C(6)); 7.29 (*s*, 1 arom. H); 7.43 (*d*, *J* = 2.8, H–C(8)); 7.66 (*s*, H–C(2)); 7.87 (*d*, *J* = 9.2, H–C(5)); 11.45 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 28.0 (Me); 55.6 (MeO); 55.8 (MeO); 56.7 (MeO); 98.5; 106.7; 109.4; 111.1; 112.1; 114.2; 117.1; 118.1; 125.4; 139.7; 140.3; 141.7; 144.4; 148.5; 155.1; 161.4; 161.4; 199.5. Anal. calc. for $C_{22}H_{19}ClN_2O_5$ (426.83): C 61.91, H 4.49, N 6.56; found: C 61.89, H 4.57, N 6.62.

1-{3-[(7-Methoxyfuro[2,3-b*]quinolin-4-yl)amino]phenyl}ethanone* (**9**). A soln. of **5** (0.37 mg, 1 mmol) in MeOH/CH_2Cl_2 1:1 (100 ml) was hydrogenated for 3 h (TLC monitoring) under H_2 over 10% Pd/C (0.20 g). The mixture was filtered, and the filtrate was concentrated *in vacuo* to give a residual solid, which was purified by CC (SiO_2; CH_2Cl_2) and recrystallization (EtOH). Yield: 0.13 g (39%). M.p. 125–126°. UV (MeOH): 212 (4.30), 244 (4.61), 335 (4.20). IR (KBr): 1585, 1677, 3347. ^{1}H-NMR ($CDCl_3$): 2.58 (*s*, Me); 3.93 (*s*, MeO); 6.02 (*d*, *J* = 2.6, H–C(3)); 7.08 (*dd*, *J* = 2.4, 9.2, H–C(6)); 7.31 (br. *s*, NH); 7.34–7.50 (*m*, 4 arom. H); 7.75 (*m*, 2 arom. H); 7.97 (*d*, *J* = 9.2, H–C((5)). ^{13}C-NMR ($CDCl_3$): 26.7 (Me); 55.5 (MeO); 104.5; 105.4; 106.7; 113.0; 116.9; 120.7; 122.3; 123.7; 125.6; 129.6; 138.2; 141.0; 141.6; 141.9; 147.5; 160.8; 163.3; 197.7. Anal. calc. for $C_{20}H_{16}N_2O_3 \cdot 0.6\ H_2O$ (343.15): C 70.00, H 5.05, N 8.16; found: C 69.76, H 5.21, N 8.11.

*(1*E*)-1-{4-[(7-Methoxyfuro[2,3*-b*]quinolin-4-yl)amino]phenyl}ethanone Oxime* (**6a**). From **8** and $NH_2OH \cdot HCl$, as described for **3a**. Yield: 86%. M.p. 222–223°. UV (MeOH): 262 (4.35), 305 (3.74), 335 (4.02). IR (KBr): 1507, 1555, 3222. ^{1}H-NMR ((D$_6$)DMSO): 2.22 (*s*, Me); 3.97 (*s*, MeO); 5.73 (*d*, *J* = 2.4, H–C(3)); 7.28 (*dd*, *J* = 2.4, 9.6, H–C(6)); 7.34 (*d*, *J* = 2.4, H–C(8)); 7.38 (*m*, 2 arom. H); 7.76 (*d*, *J* = 2.4, H–C(2)); 7.79 (*m*, 2 arom. H); 8.57 (*d*, *J* = 9.6, H–C(5)); 10.64 (br. *s*, NH); 11.13 (br. *s*, NOH). ^{13}C-NMR ((D$_6$)DMSO): 11.9 (Me); 55.3 (MeO); 101.7; 102.6; 106.9; 110.8; 116.3; 125.1 (2 C); 126.0; 127.0 (2 C); 135.3; 140.0; 141.8; 142.3; 148.1; 152.7; 159.1; 162.5. Anal. calc. for $C_{20}H_{17}N_3O_3 \cdot HCl$ (383.82): C 62.59, H 4.73, N 10.95; found: C 62.66, H 4.88, N 10.64.

*(1*E*)-1-{4-[(7-Methoxyfuro[2,3*-b*]quinolin-4-yl)amino]phenyl}ethanone* O-*Methyloxime* (**6b**). From **8** and $NH_2OMe \cdot HCl$, as described for **3b**. Yield: 88%. M.p. 240–241°. UV (MeOH): 262 (4.55), 305 (3.99), 335 (4.19). IR (KBr): 1531, 1581, 3100. ^{1}H-NMR ((D$_6$)DMSO): 2.23 (*s*, Me); 3.95 (*s*, MeON); 3.96 (*s*, MeO); 5.79 (*d*, *J* = 2.4, H–C(3)); 7.28 (*dd*, *J* = 2.4, 9.6, H–C(6)); 7.37 (*d*, *J* = 2.4, H–C(8)); 7.38 (*m*, 2 arom. H); 7.78–7.80 (*m*, H–C(2), 2 arom. H); 8.56 (*d*, *J* = 9.6, H–C(5)); 10.58 (br. *s*, NH). ^{13}C-NMR ((D$_6$)DMSO): 12.2 (Me); 55.8 (MeO); 61.6 (MeON); 101.7; 102.8; 106.3; 110.8; 115.8; 124.0 (2 C); 125.5; 126.9 (2 C); 133.1; 140.5; 142.0; 146.7; 153.4; 159.2; 161.8. Anal. calc. for $C_{21}H_{19}N_3O_3 \cdot 1.1$ HCl (401.49): C 62.82, H 5.05, N 10.47; found: C 62.73, H 5.18, N 10.30.

*(1*E*)-1-{3-[(7-Methoxyfuro[2,3-*b*]quinolin-4-yl)amino]phenyl}ethanone Oxime* (**7a**). From **9** and $NH_2OH \cdot HCl$, as described for **3a**. Yield: 73%. M.p. 272–273°. UV (MeOH): 258 (4.56), 296 (3.71), 333 (4.16). IR (KBr): 1506, 1573, 3270. ^{1}H-NMR ((D_6)DMSO): 2.15 (*s*, Me); 3.93 (*s*, MeO); 5.90 (*d*, *J* = 2.4, H–C(3)); 7.16 (*dd*, *J* = 2.4, 9.2, H–C(6)); 7.23 (*d*, *J* = 8.0, arom. H); 7.27 (*d*, *J* = 2.4, H–C(8)); 7.41–7.54 (*m*, 3 arom. H); 7.70 (*d*, *J* = 2.4, H–C(2)); 8.34 (*d*, *J* = 9.2, H–C(5)); 9.59 (br. *s*, NH); 11.25 (br. *s*, NOH). ^{13}C-NMR ((D_6)DMSO): 11.5 (Me); 55.4 (MeO); 102.4; 105.7; 106.0; 112.2; 115.3; 119.4; 121.3; 122.8; 124.5; 129.2; 137.8; 141.2; 141.7; 143.2; 146.7; 152.5; 160.4; 162.7. Anal. calc. for $C_{20}H_{17}N_3O_3 \cdot HCl$ (383.82): C 62.59, H 4.73, N 10.95; found: C 62.46, H 4.77, N 10.73.

*(1*E*)-1-{3-[(7-Methoxyfuro[2,3-*b*]quinolin-4-yl)amino]phenyl}ethanone* O*-Methyloxime* (**7b**). From **9** and $NH_2OMe \cdot HCl$, as described for **3b**. Yield: 93%. M.p. 236–237°. UV (MeOH): 258 (4.57), 299 (3.62), 349 (4.06). IR (KBr): 1527, 1618, 3100. ^{1}H-NMR ((D_6)DMSO): 2.20 (*s*, Me); 3.92 (*s*, MeO); 3.96 (*s*, MeON); 5.62 (*d*, *J* = 2.4, H–C(3)); 7.30 (*dd*, *J* = 2.4, 9.6, H–C(6)); 7.30 (*d*, *J* = 2.4, H–C(8)); 7.43 (*d*, *J* = 8.4, 1 arom. H); 7.57 (*m*, 2 arom. H); 7.71 (*d*, *J* = 8.0, 1 arom. H); 7.78 (*d*, *J* = 2.4, H–C(2)); 8.65 (*d*, *J* = 9.6, H–C(5)); 10.82 (br. *s*, NH). ^{13}C-NMR ((D_6)DMSO): 12.3 (Me); 55.8 (MeO); 61.7 (MeON); 100.8; 101.9; 106.3; 110.1; 115.8; 122.5; 124.2; 125.7; 126.0; 129.7; 137.2; 139.3; 141.0; 141.8; 148.2; 153.4; 158.3; 162.1. Anal. calc. for $C_{21}H_{19}N_3O_3 \cdot 0.8$ HCl (390.55): C 64.58, H 5.11, N 10.76; found: C 64.41, H 5.19, N 10.94.

7-Methoxy-N*-(4-methoxyphenyl)furo[2,3-*b*]quinolin-4-amine* (**11a**). Prepared by hydrogenation of **10a**, as described for **9**, and purified by CC (SiO_2; CH_2Cl_2/AcOEt 10:1). Yield: 42%. M.p. 127–128°. UV (MeOH): 258 (4.53), 308 (3.79), 346 (4.01). IR (KBr): 1511, 1584, 3250. ^{1}H-NMR ($CDCl_3$): 3.86 (*s*, MeO); 3.92 (*s*, MeO); 5.66 (*d*, *J* = 2.8, H–C(3)); 6.93–6.97 (*m*, 2 arom. H); 7.04 (*dd*, *J* = 2.4, 9.2, H–C(6)); 7.23–7.25 (*m*, NH, H–C(8), 2 arom. H); 7.34 (*d*, *J* = 2.8, H–C(2)); 7.92 (*d*, *J* = 9.2, H–C(5)). ^{13}C-NMR ($CDCl_3$): 55.5 (MeO); 55.6 (MeO); 101.6; 105.7; 106.5; 111.1; 114.7 (2 C); 116.0; 121.9; 126.8 (2 C); 133.0; 140.6; 144.1; 147.0; 158.0; 160.7; 163.4. Anal. calc. for $C_{19}H_{16}N_2O_3 \cdot 0.6\ H_2O$ (342.21): C 68.92, H 5.24, N 8.46; found: C 68.68, H 5.10, N 8.23.

7-Methoxy-N*-(2-methoxyphenyl)furo[2,3-*b*]quinolin-4-amine* (**11c**). Prepared by hydrogenation of **10c**, as described for **9**, and purified by CC (SiO_2; hexane/CH_2Cl_2 1:1). Yield: 65%. M.p. 126–128°. UV (MeOH): 257 (4.49), 300 (3.62), 335 (4.10). IR (KBr): 1527, 1581, 3350. ^{1}H-NMR ($CDCl_3$): 3.92 (*s*, MeO); 3.96 (*s*, MeO); 6.02 (*d*, *J* = 2.6, H–C(3)); 6.89–7.15 (*m*, H–C(6)); NH, 4 arom. H); 7.40 (*m*, H–C(2,8)); 7.97 (*d*, *J* = 9.2, H–C(5)). ^{13}C-NMR ((D_6)DMSO): 55.5 (MeO); 55.7 (MeO); 104.6; 105.9; 107.2; 110.9; 113.6; 116.5; 120.1; 120.6; 122.4; 123.6; 130.3; 141.0; 141.4; 148.0; 150.5; 160.6; 163.9. Anal. calc. for $C_{19}H_{16}N_2O_3$ (320.33): C 71.24, H 5.03, N 8.74; found: C 71.21, H 5.09, N 8.56.

7-Methoxy-N*-(4-methylyphenyl)furo[2,3-*b*]quinolin-4-amine* (**11e**). Prepared by hydrogenation of **10e**, as described for **9**, and purified by CC (SiO_2; CH_2Cl_2/AcOEt 10:1). Yield: 55%. M.p. 175–177°. UV (MeOH): 257 (4.50), 301 (3.66), 346 (4.12). IR (KBr): 1511, 1582, 3198. ^{1}H-NMR ($CDCl_3$): 2.40 (*s*, Me); 3.91 (*s*, MeO); 5.79 (*d*, *J* = 2.8, H–C(3)); 7.03 (*dd*, *J* = 2.4, 9.2, H–C(6)); 7.14–7.22 (*m*, 4 arom. H); 7.25 (*d*, *J* = 2.8, H–C(2)); 7.28 (*d*, *J* = 2.4, H–C(8)); 7.53 (br. *s*, NH); 7.94 (*d*, *J* = 9.2, H–C(5)). ^{13}C-NMR ($CDCl_3$): 21.0 (Me); 55.5 (MeO); 102.4; 105.9; 109.2; 111.5; 116.2; 122.2; 123.9 (2 C); 130.0 (2 C); 135.3; 137.6; 140.7; 142.2; 146.5; 160.8; 162.1. Anal. calc. for $C_{19}H_{16}N_2O_2$ (304.33): C 74.99, H 5.30, N 9.20; found: C 74.83, H 5.55, N 8.88.

N*-(4-Fluorophenyl)-7-methoxyfuro[2,3-*b*]quinolin-4-amine* (**11f**). Prepared by hydrogenation of **10f**, as described for **9**, and crystallized from EtOH. Yield: 66%. M.p. 167–168°. UV (MOH): 256 (4.48), 298 (3.66), 334 (4.06). IR (KBr): 1507, 1585, 3270. ^{1}H-NMR ($CDCl_3$): 3.94 (*s*, MeO); 5.83 (*d*, *J* = 2.4, H–C(3)); 6.87 (br. *s*, NH); 7.10 (*dd*, *J* = 2.4, 9.2, H–C(6)); 7.11–7.13 (*m*, 2 arom. H); 7.19–7.24 (*m*, 2 arom. H); 7.33 (*d*, *J* = 2.4, H–C(2)); 7.36 (*d*, *J* = 2.4, H–C(8)); 7.88 (*d*, *J* = 9.2, H–C(5)). ^{13}C-NMR ($CDCl_3$): 55.5 (MeO); 102.9; 105.4; 107.3; 112.0; 116.3 (2 C, *J* = 22.0); 116.5; 121.6; 125.4 (2 C, *J* = 7.5); 136.8; 141.3; 142.2; 148.0; 160.1 (*J* = 243.3); 160.6; 164.0. Anal. calc. for $C_{18}H_{13}FN_2O_2$ (308.29): C 70.13, H 4.25, N 9.09; found: C 70.06, H 4.37, N 9.12.

N*-(3,4-Dimethoxyphenyl)-7-methoxyfuro[2,3-*b*]quinolin-4-amine* (**11g**). Prepared by hydrogenation of **10g**, as described for **9**, and crystallized from EtOH. Yield: 56%. M.p. 181–182°. UV (MeOH): 262 (4.41), 304 (3.59), 346 (3.93). IR (KBr): 1516, 1586, 3363. ^{1}H-NMR ($CDCl_3$): 3.81 (*s*, MeO); 3.94 (*s*, 2 MeO); 5.78 (*d*, *J* = 2.8, H–C(3)); 6.83 (*dd*, *J* = 2.4, 8.4, 1 arom. H); 6.86 (*d*, *J* = 2.4, 1 arom. H); 6.89 (br. *s*, NH); 6.90 (*d*, *J* = 8.4, 1 arom. H); 7.08 (*dd*, *J* = 2.4, 9.2, H–C(6)); 7.29 (*d*, *J* = 2.8, H–C(2)); 7.36 (*d*, *J* = 2.4,

H–C(8)); 7.88 (*d*, *J* = 9.2, H–C(5)). ^{13}C-NMR ($CDCl_3$): 55.4, 56.0, 56.1 (3 MeO); 102.0; 105.6; 107.3; 109.1; 111.5; 116.1; 117.0; 121.4; 133.6; 140.8 (2 C); 143.0; 147.2; 148.0; 149.5; 160.4; 164.2. Anal. calc. for $C_{20}H_{18}N_2O_4$ (350.35): C 68.56, H 5.18, N 8.00; found: C 68.50, H 5.25, N 7.93.

*3,4-Dichloro-6-methoxyfuro[2,3-*b*]quinoline* (**14**). To a suspension of 6-methoxy-9*H*-furo[2,3-*b*]quinoline-3,4-dione (1.15 g, 5 mmol) [14] in $POCl_3$ (30 ml) was added H_2O (1 ml). The mixture was heated at reflux for 4 h. After cooling, the volatiles were evaporated *in vacuo* to give a residue, which was poured into ice-water (80 ml). The resulting precipitate was collected, purified by CC (SiO_2; hexane/CH_2Cl_2 1:1), and crystallized from EtOH. Yield: 0.47 g (35%). Colorless solid. M.p. 210–212°. UV (MeOH): 278 (3.14), 320 (4.05), 339 (3.59), 364 (3.67). IR (KBr): 1506, 1626. ^{1}H-NMR ($CDCl_3$): 4.01 (*s*, MeO); 7.45 (*dd*, *J* = 2.4, 9.2, H–C(7)); 7.55 (*d*, *J* = 2.4, H–C(5)); 7.81 (*s*, H–C(2)); 8.00 (*d*, *J* = 9.2, H–C(8)). ^{13}C-NMR ($CDCl_3$): 55.7 (MeO); 101.0; 111.2; 118.4; 123.8; 125.5; 130.2; 141.4; 143.2; 144.2; 157.9; 160.2. Anal. calc. for $C_{12}H_7Cl_2NO_2$ (268.09): C 53.76, H 2.63, N 5.22; found: C 63.80, H 2.63, N 5.19.

*1-{4-[(3-Chloro-6-methoxyfuro[2,3-*b*]quinolin-4-yl)amino]phenyl}ethanone* (**12**). From **14** and 4-aminoacetophenone, as described for **5**. Yield: 78%. M.p. 215–217°. UV (MeOH): 278 (3.80), 307 (4.17), 353 (3.80), 384 (4.02). IR (KBr): 1506, 1670, 3302. ^{1}H-NMR ($CDCl_3$): 2.54 (*s*, Me); 3.68 (*s*, Me); 6.84 (*m*, 2 arom. H); 7.06 (*d*, *J* = 2.8, H–C(5)); 7.26 (br *s*, NH); 7.39 (*dd*, *J* = 2.8, 9.2, H–C(7)); 7.70 (*s*, H–C(2)); 7.88 (*m*, 2 arom. H); 8.02 (*d*, *J* = 9.2, H–C(8)). ^{13}C-NMR ($CDCl_3$): 26.2 (Me); 55.5 (MeO); 101.8; 110.1; 110.2; 116.2; 122.1; 123.5; 130.0; 130.3 (2 C); 130.6; 138.6; 141.5 (2 C); 141.8; 148.2; 156.6; 159.0; 196.5. Anal. calc. for $C_{20}H_{15}ClN_2O_3 \cdot 0.3\ H_2O$ (375.79): C 64.54, H 4.22, N 7.53; found: C 64.28, H 4.26, N 7.49.

*1-{3-[(3-Chloro-6-methoxyfuro[2,3-*b*]quinolin-4-yl)amino]phenyl}ethanone* (**13**). From **14** and 3-aminoacetophenone, as described for **5**. Yield: 72%. M.p. 153–154°. UV (MeOH): 253 (4.48), 303 (3.59), 346 (3.93). IR (KBr): 1506, 1675, 3346. ^{1}H-NMR ($CDCl_3$): 2.55 (*s*, Me); 3.59 (*s*, MeO); 6.97 (*d*, *J* = 2.4, H–C(5)); 6.99 (*dd*, *J* = 2.0, 8.0, 1 arom. H); 7.19 (br. *s*, NH); 7.34 (*m*, 1 arom. H); 7.36 (*dd*, *J* = 2.4, 9.6, H–C(7)); 7.55–7.59 (*m*, 2 arom. H); 7.68 (*s*, H–C(2)); 7.99 (*d*, *J* = 9.6, H–C(8)). ^{13}C-NMR ($CDCl_3$): 26.7 (Me); 55.3 (MeO); 102.1; 108.7; 110.0; 117.6; 120.9; 122.2; 122.4; 123.1; 129.4; 130.3; 138.2; 139.8; 140.9; 142.2; 144.1; 156.1; 159.3; 197.8. Anal. calc. for $C_{20}H_{15}ClN_2O_3$ (366.78): C 65.49, H 4.12, N 7.64; found: C 65.16, H 4.14, N 7.53.

3-Chloro-6-methoxy-N-*(4-methoxyphenyl)furo[2,3-*b*]quinolin-4-amine* (**15**). From **14** and *para*-anisidine, as described for **5**. Yield: 71%. M.p. 174–176°. UV (MeOH): 266 (4.40), 345 (3.63), 382 (3.95). IR (KBr): 1506, 1583, 3220. ^{1}H-NMR ($CDCl_3$): 3.50 (*s*, MeO); 3.79 (*s*, MeO); 6.85 (*m*, 2 arom. H); 6.93 (*d*, *J* = 2.8, H–C(5)); 6.98 (*m*, 2 arom. H); 7.16 (br. *s*, NH); 7.28 (*dd*, *J* = 2.8, 9.2, H–C(7)); 7.62 (*s*, H–C(2)); 7.91 (*d*, *J* = 9.2, H–C(8)). ^{13}C-NMR ($CDCl_3$): 55.0, 55.6 (2 MeO); 103.0; 109.8; 114.6 (2 C); 114.7; 119.2; 122.6; 122.7 (2 C); 130.2; 136.5; 139.7; 142.4; 142.9; 155.1; 156.2; 159.7. Anal. calc. for $C_{19}H_{15}ClN_2O_3 \cdot 0.6\ H_2O$ (377.59): C 62.42, H 4.67, N 7.66; found: C 62.34, H 4.79, N 7.57.

6-Methoxy-N-*(4-methoxyphenyl)furo[2,3-*b*]quinolin-4-amine* (**16**). Prepared by hydrogenation of **15**, as described for **9**, and crystallized from EtOH. Yield: 36%. M.p. 187–188°. UV (MeOH): 263 (4.43), 331 (3.54), 367 (3.88). IR (KBr): 1510, 1583, 3230. ^{1}H-NMR ($CDCl_3$): 3.87 (*s*, MeO); 3.94 (*s*, MeO); 5.76 (*d*, *J* = 2.8, H–C(3)); 6.63 (br. *s*, NH); 6.96 (*m*, 2 arom. H); 7.21 (*m*, 2 arom. H); 7.22 (*d*, *J* = 2.8, H–C(5)); 7.33 (*d*, *J* = 2.8, H–C(2)); 7.37 (*dd*, *J* = 2.8, 9.2, H–C(7)); 7.96 (*d*, *J* = 9.2, H–C(8)). ^{13}C-NMR ($CDCl_3$): 55.6, 55.6 (2 MeO); 99.2; 105.2; 114.6 (2 C); 117.1; 121.1; 126.2 (2 C); 128.8; 130.5; 130.9; 133.6; 141.5; 141.9; 155.8; 157.6; 162.4. Anal. calc. for $C_{19}H_{16}N_2O_3$ (320.33): C 70.06, H 5.14, N 8.60; found: C 69.94, H 5.26, N 8.71.

Determination of Antiproliferative Activity. Cancer cells were purchased from the *Bioresources Collection and Research Center*, Taiwan. The cell lines were maintained in the same standard medium, and grown as a monolayer in *DMEM* (*Gibco*, USA) supplemented with 10% fetal bovine serum (FBS) and the antibiotics penicillin (100 IU/ml), streptomycin (0.1 mg/ml), and amphotericin (0.25 μg/ml). The cultures were maintained at 37° in a humidified atmosphere with 5% CO_2.

The cancer cells were treated for 48 h in medium containing 10% FBS. Then, MTT[2]) soln. (2 mg/ml, 20 ml) was added to the cultures, which were incubated during the final 1.5 h. The resultant tetrazolium salt was dissolved by addition of DMSO (100 μl). The color was measured spectrophotometrically with a microtiter plate reader at 570 nm, and used as a rel. measure of the number of viable cells. This number was compared to solvent and untreated control cells and used to determine the percent of control growth

as $(A_{treated}/A_{control}) \times 100$, where A represents the mean absorbance ($n = 3$). The concentration that killed 50% of the cells (IC_{50}) was determined from the linear portion of the curve by calculating the concentration of agent that reduced the absorbance in treated cells, compared to the control cells, by 50% [13].

Flow-Cytometric Analysis. The HeLa cells treated with DMSO (solvent control) or **1** (drug) at a concentration of 5 μM for the times indicated (see *Figure*), were harvested, rinsed with *PBS*, resuspended, fixed in 80% EtOH, and stored at $-20°$ in fixation buffer until ready for analysis. Then, the pellets were suspended in propidium iodide (PI) soln. containing 20 μg/ml of PI (1 ml), 0.2 mg/ml RNase, and 0.1% (*v*/*v*) *Triton X-100*. Cell samples were incubated at r.t. in the dark for at least 30 min, and analyzed on a *FACScan* flow cytometer (*Becton Dickinson*, Mountain View, CA). Data were recorded with the CELLQuest software (*Becton Dickinson*), and cell-cycle data were analyzed with the ModFitLT software (*Veruty Software House*, USA).

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