Synthesis and Cytotoxic Evaluation of Some 4-Anilinofuro[2,3-*b*]quinoline Derivatives

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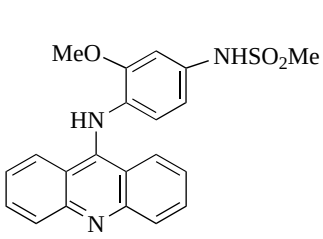
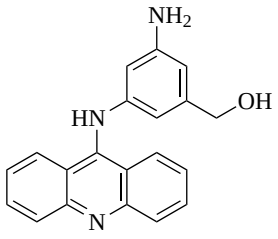
Some 4-anilinofuro[2,3-*b*]quinoline derivatives were synthesized from dictamnine, a natural alkaloid, and evaluated for their cytotoxicity in the NCI's full panel of 60 human cancer cell lines derived from nine cancer cell types, including leukemia, non-small-cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer. 1-[4-(Furo[2,3-*b*]quinolin-4-ylamino)phenyl]ethanone (**5**) (mean $GI_{50} = 0.025$ μM), bearing an 4-acetylanilino substituent at C(4) of furo[2,3-*b*]quinoline, was more active than its 3-acetylanilino counterpart **7** (mean $GI_{50} = 5.27$ μM), and both clinically used anticancer drugs, *N*-[4-(acridin-9-ylamino)-3-methoxyphenyl]methanesulfonamide (*m*-AMSA; mean $GI_{50} = 0.44$ μM) and daunomycin (mean $GI_{50} = 0.044$ μM). Compound **5** was capable of inhibiting all types of cancer cells tested with a mean GI_{50} of less than 0.04 μM in each case except for the non-small-cell lung cancer (average $GI_{50} = 1.75$ μM). Although non-small-cell lung cancer is resistant to compound **5**, the sensitivity within this type of cancer cells varies: HOP-62 ($GI_{50} < 0.01$ μM), NCI-H460 ($GI_{50} = 0.01$ μM), and NCI-H522 ($GI_{50} < 0.01$ μM) are very sensitive, while HOP-92 ($GI_{50} = 12.4$ μM) is resistant. Among these non-small-cell lung cancers, NCI-H522 was found to be very sensitive to **5**, **8a**, and **8b** with a GI_{50} values of < 0.01, 0.074, and < 0.01 μM, respectively.

Introduction. – Acridine derivatives, especially 9-anilinoacridines, have been extensively studied as potential chemotherapeutic agents due to their ability to intercalate in DNA, leading to the inhibition of mammalian topoisomerase II [1–5]. Among them, *N*-[4-(acridin-9-ylamino)-3-methoxyphenyl]methanesulfonamide (amsacrine, *m*-AMSA) has been specifically relevant, and has become a useful clinical drug for the treatment of leukemia and lymphoma [1]. Since then, tremendous effort has been directed toward the design and preparation of new amsacrine analogues with the aim of developing new drug candidates with an improved broad spectrum of antitumor activity [6–10]. Among them, 3-(acridin-9-ylamino)-5-(hydroxymethyl)aniline (AHMA) was found to be superior to *m*-AMSA against the growth of certain solid tumors such as mammary adenocarcinoma, melanoma, and *Lewis* lung carcinoma in mice [9]. Unlike *m*-AMSA, AHMA, which has a 3,5-disubstituted anilino moiety, was resistant to oxidative metabolism and, therefore, was expected to have longer half-life in plasma [9].

These studies, however, were focused only on the 9-anilinoacridine skeleton, with a wide variety of substituents on the anilino and/or acridine chromophore. No attempt has been carried out concerning the replacement of acridine with its bioisosteric furo[2,3-*b*]-quinoline ring system, which is a constituent of an important group of bioactive natural products such as dictamnine, robustine, and haplopine [11][12]. The furo[2,3-*b*]quino-



m-AMSA



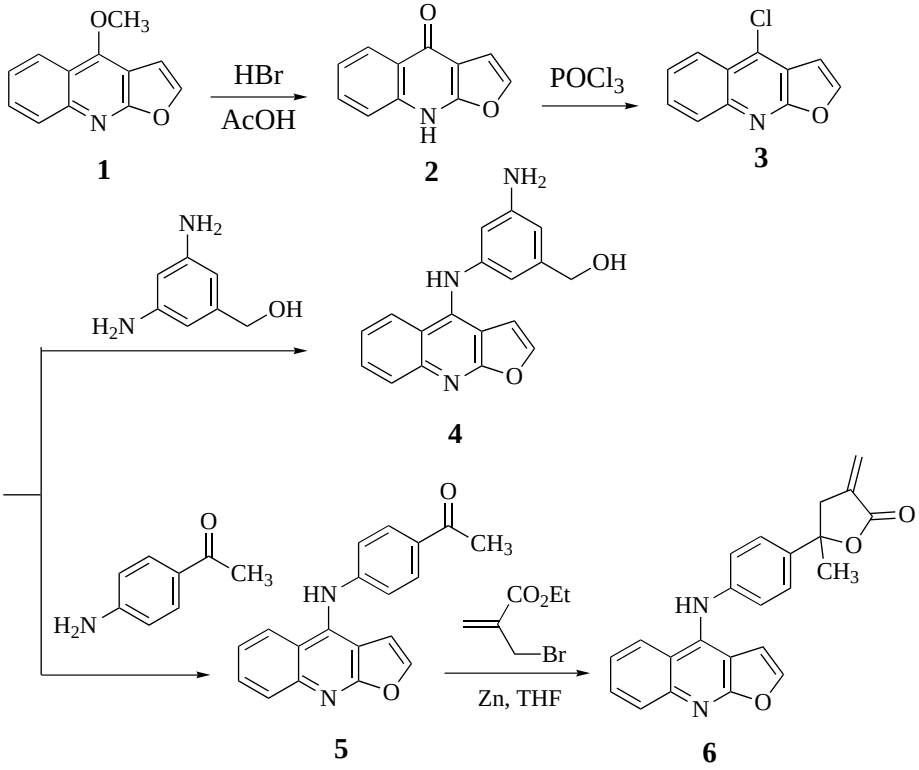
AHMA

line system possesses a higher electron density than that of acridine and, therefore, is advantageous, since the major route of breakdown for *m*-AMSA *in vivo* is a nonenzymatically mediated attack of thiol at C(9), resulting eventually in loss of the side chain and the formation of inactive products [13–15]. Here, we describe the preparation of 3-(furo[2,3-*b*]quinolin-4-ylamino)-5-(hydroxymethyl)aniline (**4**; *c.f. Scheme 1*), the bioisosteric isomer of AHMA, in which acridine was replaced with the furo[2,3-*b*]quinoline moiety. Certain monosubstituted 4-anilinofuro[2,3-*b*]quinoline derivatives, in which the anilino moiety was substituted with an Ac group and its corresponding oxime and methyloxime at either C(3′) or C(4′) were also prepared. We expect these substituents to form H-bonds with DNA molecule during the intercalation process of the tricyclic furo[2,3-*b*]quinoline moiety. Recently, we have synthesized certain α-methylidene-γ-butyrolactone-bearing quinolones and evaluated their cytotoxicities on the grounds that, through the intercalation of quinolone, the α-methylidene-γ-butyrolactone can specifically alkylate the DNA molecule [16–18]. This versatile α-methylidene-γ-butyrolactone moiety has also been appended onto the 9-anilino group (*cf.* **6**) in an attempt to prepare a bifunctional compound in which furo[2,3-*b*]quinoline moiety acts as an intercalator while the lactone ring plays the role of an alkylating unit.

Results and Discussion. – The known alkaloid, dictamnine (4-methoxyfuro[2,3-*b*]-quinoline; **1**) was isolated from the root wood of *Zanthoxylum simulans* [11] and was used as the starting material (*Scheme 1*). Its hydrolysis with HBr in AcOH at 110° for 1 h gave furo[2,3-*b*]quinolin-4-one (**2**) in 36% yield [19]. The yield was increased up to 91% by refluxing the reaction mixture for 8 h. This improvement is crucial because the supply of starting dictamnine is limited. Compound **2** was chlorinated with $POCl_3$ to give 4-chlorofuro[2,3-*b*]quinoline (**3**) [20]. Treatment of **3** with 3,5-diaminobenzyl alcohol in a boiling solution of EtOH/H_2O 2:1 gave the desired 3-(furo[2,3-*b*]quinolin-4-ylamino)-5-(hydroxymethyl)aniline (**4**) in 64% yield. Accordingly, 1-[4-(furo[2,3-*b*]-quinolin-4-ylamino)phenyl]ethanone (**5**) was synthesized from **3** and 4-aminoacetophenone in the boiling EtOH/H_2O 2:1 solution. *Reformatsky*-type condensation of **5** with 2-(bromomethyl)acrylate and Zn powder in THF afforded 5-[4-(furo[2,3-*b*]-quinolin-4-ylamino)phenyl]-2,3,4,5-tetrahydro-5-methyl-3-methylidenefuran-2-one (**6**) in 78% yield.

Preparation of monosubstituted anilino-furo[2,3-*b*]quinoline derivatives is outlined in *Scheme 2*. Reaction of **5** with NH_2OH gave exclusively (*E*)-1-[4-(furo

Scheme 1



[2,3-*b*]quinolin-4-ylamino)phenyl]ethanone oxime (**8a**). The configuration of the oxime moiety was determined by through-space nuclear *Overhauser* effect spectroscopy (NOESY), which revealed coupling connectivity to Me protons. Accordingly, (*E*)-1-[4-(furo[2,3-*b*]quinolin-4-ylamino)phenyl]ethanone *O*-methyloxime (**8b**) was obtained from the reaction of **5** and NH_2OMe. Reaction of **3** with 3-aminoacetophenone gave 1-[3-(furo[2,3-*b*]quinolin-4-ylamino)phenyl]ethanone (**7**), which was then treated with either NH_2OH or NH_2OMe to afford (*E*)-1-[3-(furo[2,3-*b*]quinolin-4-ylamino)phenyl]ethanone oxime (**9a**) and its Me congener **9b**.

All compounds were evaluated in the NCI's full panel of 60 human cancer cell lines derived from nine cancer cell types including 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, and the concentrations causing 50% cell-growth inhibition (GI_{50}) compared with the control were calculated [21] and listed in *Table 1*. Compound **5** (mean $GI_{50} = 0.025$ μM), which bears an 4-acetylanilino substituent at C(4) of furo[2,3-*b*]quinoline, was more active than its 3-acetylanilino counterpart **7** (mean $GI_{50} = 5.27$ μM), and both clinically used anticancer drugs, *m*-AMSA (mean $GI_{50} = 0.44$ μM) and daunomycin (mean $GI_{50} = 0.044$ μM). The

Scheme 2

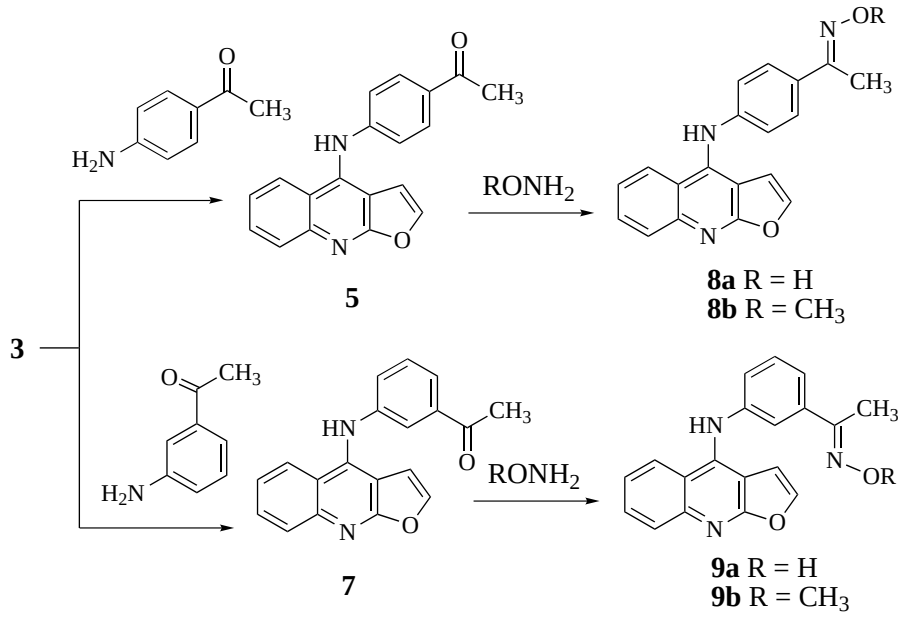


Table 1. *Inhibition of* in Vitro *Cancer Cell Lines by Some 4-Anilinofuro[2,3-*b*]quinoline Derivatives* (GI_{50} [μM])[a])

	4	**5**	**6**	**7**	**8a**	**8b**	**9a**	**9b**	*m*-AMSA	DAM[b])
Leukemia	23.02	< 0.01	0.90	3.22	0.14	0.36	3.64	4.23	0.10	< 0.01
Non-small-cell lung cancer	40.86	1.75	5.59	14.48	4.44	2.58	8.01	10.87	0.35	0.043
Colon cancer	25.16	0.011	1.56	5.11	0.17	0.32	5.35	6.67	1.07	0.083
CNS cancer	45.94	0.016	5.30	7.63	0.35	0.57	10.48	11.48	0.42	0.020
Melanoma	38.61	0.018	1.71	6.09	0.95	1.27	4.81	8.50	0.58	0.047
Ovarian	47.72	0.039	1.92	11.32	0.53	0.66	13.57	11.57	1.05	0.062
Renal cancer	37.66	0.035	4.76	10.61	2.68	1.63	9.90	12.58	0.87	0.048
Prostate cancer	53.60	0.021	1.32	12.00	0.53	0.58	16.20	17.85	0.16	0.032
Breast cancer	23.85	0.017	3.27	5.32	0.42	0.41	3.62	8.68	0.58	0.11
MG_MID[c])	31.10	0.025	1.77	5.27	0.35	0.48	5.60	7.56	0.44	0.044

[a]) Data obtained from NCI's *in vitro* disease-oriented tumor-cell screen. GI_{50}: Drug molar concentration causing 50% cell-growth inhibition. [b]) Daunomycin. [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, NCI-H460, 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 (MCF7, MCF7/ADR-RES, MDA-MB-231/ATCC, HS 578T, MDA-MB-435, MDA-N and T-47D).

cytotoxicity was decreased by converting the Ac group of **5** to the corresponding 1-(hydroxyimino)ethyl **8a** (a mean GI_{50} value of 0.35 μM) or 1-(methoxyimino)ethyl derivative **8b** (0.48 μM). The same order was obtained for 3-substituted anilinofuro-[2,3-*b*]quinoline, in which 1-(hydroxyimino)ethyl and 1-(methoxyimino)ethyl derivatives were less active than their Ac precursor (a mean GI_{50} of 5.27 μM for **7**, 5.60 for **9a**, and 7.56 for **9b**). Compound **4** (mean $GI_{50} = 31.10$ μM) was inactive even though its acridine counterpart, AHMA, was proved to be a potent anticancer agent [9]. The present results also show that compound **6** (mean $GI_{50} = 1.77$ μM), with both intercalating tricyclic furo[2,3-*b*]quinoline and alkylating α-methylidene-γ-butyrolactone moieties, was less active than **5**, **8a**, and **8b**. Compound **5** was capable of inhibiting all types of cancer cells tested with a mean GI_{50} of less than 0.04 μM in each case except for the non-small-cell lung cancer (average $GI_{50} = 1.75$ μM). Most of non-small-cell lung cancer cells are also resistant to compounds **8a** and **8b**. Therefore, the inhibitory activities of **5**, **8a**, and **8b** against the individual non-small-cell lung cancer cells are given in *Table 2*. Although non-small-cell lung cancer is resistant to compound **5** with an average GI_{50} value of 1.75 μM, the sensitivity within this type of cancer cells varies; HOP-62 ($GI_{50} < 0.01$ μM), NCI-H460 ($GI_{50} = 0.01$ μM), and NCI-H522 ($GI_{50} < 0.01$ μM) are very sensitive, while HOP-92 ($GI_{50} = 12.4$ μM) is resistant. Among these cancer cells, NCI-H522 was found to be very sensitive to **5**, **8a**, and **8b** with GI_{50} values of < 0.01, 0.074, and < 0.01 μM, respectively.

Table 2. *Growth Inhibition of Non-Small-Cell Lung Cancer Subpanels by* **5**, **8a**, *and* **8b** (GI_{50} [μM])

	A549/ATCC	EKVX	HOP-62	HOP-92	NCI-H226	NCI-H23	NCI-H322M	NCI-H460	NCI-H522
5	0.57	n.d.[a])	< 0.01	12.4	0.31	0.037	0.68	0.01	< 0.01
8a	0.45	4.03	0.18	10.9	11.5	0.38	12.2	0.21	0.074
8b	0.72	3.78	0.35	12.1	3.88	0.57	1.22	0.56	< 0.01

[a]) n.d.: Not determined.

Conclusions. – Some 4-anilinofuro[2,3-*b*]quinoline derivatives were synthesized from dictamnine and evaluated for their cytotoxicity in the NCI's full panel of 60 human cancer cell lines. Compound **5**, bearing an 4-acetylanilino substituent at C(4) of furo[2,3-*b*]quinoline, was more active than its 3-acetylanilino counterpart **7**, and both clinically used anticancer drugs, *m*-AMSA and daunomycin. The cytotoxicity was decreased by converting the Ac group of **5** to the corresponding 1-(hydroxyimino)ethyl **8a** or 1-(methoxyimino)ethyl derivative **8b**. Among nine cancer cell types tested, non-small-cell lung cancer is the most resistant to compound **5** with an average GI_{50} of 1.75 μM. However, the sensitivity within this type of cancer cells varies; HOP-62, NCI-H460, and NCI-H522 are very sensitive, while HOP-92 is the most resistant. Further *in vivo* anticancer evaluation of **5** is ongoing.

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 or *Varian Gemini-200* spectrometer, chemical shifts δ in ppm with Me_4Si as an

internal standard (=0 ppm), coupling constants J in Hz. Elemental analyses were carried out on a *Heraeus CHN-O-Rapid* elemental analyzer, and results were within ±0.4% of calc. values.

*Furo[2,3-*b*]quinolin-4(9*H*)-one* (**2**) [19]. A mixture of *4-methoxyfuro[2,3-*b*]quinoline* (**1**; 0.20 g, 1 mmol), 48% HBr (10 ml), and AcOH (20 ml) was refluxed for 8 h. After cooling, the mixture was poured into an ice-cold sat. $NaHCO_3$ soln. (60 ml), and extracted with AcOEt (3 × 60 ml). The AcOEt extracts were combined, washed with H_2O, dried ($MgSO_4$), and evaporated to give a residual solid, which was purified by flash column chromatography (FC; silica gel; AcOEt). The proper fractions were combined and evaporated to afford **2** (0.17 g, 91%). M.p. 236–237°. ^{1}H-NMR (200 MHz, DMSO): 7.06 (*d*, *J* = 2.4, H–C(3)); 7.29 (*m*, H–C(6)); 7.56–7.68 (*m*, H–C(2), H–C(7), H–C(8)); 8.28 (*d*, *J* = 7.6, H–C(5)). ^{13}C-NMR (50 MHz, DMSO): 104.85; 105.84; 121.60; 122.12; 123.08; 124.60; 130.06; 140.04; 142.53; 160.70; 166.69.

*4-Chlorofuro[2,3-*b*]quinoline* (**3**) [20]. A mixture of **2** (0.56 g, 3 mmol), $POCl_3$ (20 ml), and Et_3N (2 ml) was heated at 110° for 8 h. The mixture was cooled to r.t. and poured into ice-H_2O (100 ml). NaOH soln. (6N) was added until a pH of 6 resulted. The brown precipitate thus obtained was collected and purified by FC (silica gel; CH_2Cl_2) to give **3** (0.45 g, 73%). M.p. 112–113°. ^{1}H-NMR (200 MHz, DMSO): 6.99 (*d*, *J* = 2.6, H–C(3)); 7.63 (*m*, H–C(6)); 7.77 (*m*, H–C(7)); 7.83 (*d*, *J* = 2.6, H–C(2)); 8.15 (*d*, *J* = 9.8, H–C(8)); 8.32 (*m*, H–C(5)). ^{13}C-NMR (50 MHz, DMSO): 104.74; 119.29; 123.82; 124.06; 125.81; 128.80; 129.76; 134.56; 145.26; 147.37; 160.72.

*3-(Furo[2,3-*b*]quinolin-4-ylamino)-5-(hydroxymethyl)aniline* (**4**). Compound **3** (45 mg, 0.22 mmol) and 3,5-diaminobenzyl alcohol dihydrochloride (47 mg, 0.22 mmol) were dissolved in a boiling soln. of EtOH/H_2O 2:1 (10 ml). Conc. HCl was added until a pH of 6 resulted, while the reflux was continued for 40 min (TLC monitoring). The solvent was evaporated *in vacuo* to give a residue, to which was added ice-H_2O (20 ml), and was neutralized with 2N NaOH soln. The resulting precipitate was collected and chromatographed (silica gel; CH_2Cl_2/MeOH 10:1) to give **4** (43 mg, 64%). M.p. 236–237°. ^{1}H-NMR (400 MHz, DMSO): 4.38 (*d*, *J* = 5.2, CH_2); 5.09 (*t*, *J* = 5.2, OH); 5.18 (*s*, NH_2); 5.99 (*d*, *J* = 2.4, H–C(3)); 6.33 (*s*, 1 arom. H); 6.40 (*s*, 1 arom. H); 6.45 (*s*, 1 arom. H); 7.44 (*t*, *J* = 8.0, H–C(6)); 7.67 (*t*, *J* = 8.0, H–C(7)); 7.70 (*d*, *J* = 2.4, H–C(2)); 7.84 (*d*, *J* = 8.4, H–C(8)); 8.42 (*d*, *J* = 8.4, H–C(5)); 9.19 (*s*, NH). ^{13}C-NMR (100 MHz, DMSO): 62.89; 102.87; 105.98; 107.48; 108.57; 109.53; 117.16; 122.41; 122.88; 127.90; 128.81; 141.44; 141.68; 143.44; 144.05; 145.53; 149.21; 163.03. Anal. calc. for $C_{18}H_{15}N_3O_2 \cdot 0.45\ H_2O$: C 68.97, H 5.11, N 13.40; found: C 69.48, H 5.10, N 13.03.

*1-[4-(Furo[2,3-*b*]quinolin-4-ylamino)phenyl]ethanone* (**5**). From **3** and 4-aminoacetophenone as described for **4**. Compound **5** was obtained by FC (silica gel; hexane/AcOEt acetate 2:1) in 77% yield. M.p. 220–221°. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.59 (*s*, Me); 6.35 (*d*, *J* = 2.6, H–C(3)); 7.11 (*d*, *J* = 8.8, 2 arom. H); 7.31 (br. *s*, NH); 7.48 (*t*, *J* = 7.4, H–C(6)); 7.57 (*d*, *J* = 2.6, H–C(2)); 7.71 (*t*, *J* = 8.4, H–C(7)); 7.95 (*d*, *J* = 8.4, H–C(5), H–C(8)); 8.10 (*d*, *J* = 8.8, 2 arom. H). ^{13}C-NMR (50 MHz, $CDCl_3$): 26.34; 105.53; 108.73; 118.04; 119.59; 121.27; 124.37; 128.99; 129.45; 130.20; 131.36; 138.75; 143.92; 145.81; 146.15; 162.82; 196.64. Anal. calc. for $C_{19}H_{14}N_2O_2$: C 75.48, H 4.69, N 9.27; found: C 75.35, H 4.72, N 9.15.

*5-[4-(Furo[2,3-*b*]quinolin-4-ylamino)phenyl]-2,3,4,5-tetrahydro-5-methyl-3-methylidenefuran-2-one* (**6**). To a soln. of **5** (76 mg, 0.25 mmol) in dry THF (10 ml), activated Zn powder (22 mg, 0.32 mmol), hydroquinone (1 mg), and ethyl 2-(bromomethyl)acrylate (65 mg, 0.32 mmol) were added. The mixture was refluxed under N_2 for 2 h (TLC monitoring). After cooling, it was poured into an ice-cold 5% HCl soln. (60 ml) and extracted with CH_2Cl_2 (3 × 60 ml). The combined CH_2Cl_2 extracts were washed with H_2O, dried ($MgSO_4$), and evaporated to give a residual solid, which was purified by FC (silica gel; hexane/AcOEt 2:1). The proper fractions were combined and evaporated to furnish a residual solid, which was recrystallized from AcOEt to afford **6** (72 mg, 78%). M.p. 85–87°. ^{1}H-NMR (400 MHz, DMSO): 1.73 (*s*, Me); 3.24 (*m*, CH_2(4)); 5.79 (*s*, 1 H, CH_2=C(3)); 5.88 (*d*, *J* = 2.0, H–C(3′)); 6.12 (*s*, 1 H, CH_2=C(3)); 7.29 (*d*, *J* = 8.0, 2 arom. H); 7.46 (*d*, *J* = 8.0, 2 arom. H); 7.54 (*m*, H–C(6′)); 7.77 (*m*, H–C(2′), H–C(7′)); 7.92 (*d*, *J* = 8.4, H–C(8′)); 8.47 (*d*, *J* = 8.4, H–C(5′)); 9.80 (br. *s*, NH). ^{13}C-NMR (100 MHz, DMSO): 29.12; 41.84; 83.77; 103.66; 105.76; 115.61; 117.35; 122.28; 122.75; 123.21; 123.37; 125.24; 126.47; 129.93; 135.50; 140.26; 140.47; 142.76; 143.70; 161.65; 169.10. Anal. calc. for $C_{23}H_{18}N_2O_3 \cdot 1.2\ H_2O$: C 70.46, H 5.24, N 7.14; found: C 70.51, H 5.31, N 6.91.

*1-[3-(Furo[2,3-*b*]quinolin-4-ylamino)phenyl]ethanone* (**7**). From **3** and 3-aminoacetophenone as described for **4**. The crude product was recrystallized from AcOEt to give **7** in 91% yield. M.p. 158–159°. ^{1}H-NMR (400 MHz, DMSO): 2.57 (*s*, Me); 6.03 (*d*, *J* = 2.4, H–C(3)); 7.49 (*m*, 2 arom. H, H–C(6)); 7.74 (*m*, 2 arom. H, H–C(7)); 7.82 (*d*, *J* = 2.4, H–C(2)); 7.92 (*d*, *J* = 8.8, H–C(8)); 8.41 (*d*, *J* = 8.4, H–C(5)); 9.58 (*s*, NH). ^{13}C-NMR (100 MHz, DMSO): 26.78; 104.72; 105.45; 118.23; 120.38; 122.95; 123.05; 123.16; 125.78; 128.17; 129.17; 129.47; 137.62; 141.50; 142.06; 143.20; 145.57; 162.88; 197.68. Anal. calc. for $C_{19}H_{14}N_2O_2 \cdot 0.3\ H_2O$: C 74.16, H 4.78, N 9.10; found: C 74.40, H 4.85, N 8.95.

*(*E*)-1-[4-Furo[2,3-*b*]quinolin-4-ylamino)phenyl]ethanone Oxime* (**8a**). To a suspension of **5** (61 mg, 0.20 mmol) in EtOH (5 ml) was added $NH_2OH \cdot HCl$ (28 mg, 0.40 mmol). The mixture was heated at reflux for 30 min and allowed to cool to r.t. The solvent was removed *in vacuo*, and the residue was suspended in H_2O (20 ml). The precipitate obtained was collected and recrystallized from MeOH to give **8a** (63 mg, 99%). M.p. 264–265°. ^{1}H-NMR (200 MHz, DMSO): 2.18 (*s*, Me); 6.09 (*d*, *J* = 2.6, H–C(3)); 7.21 (*d*, *J* = 8.8, 2 arom. H); 7.49 (*m*, H–C(6)); 7.71 (*m*, 2 arom. H, H–C(7)); 7.81 (*d*, *J* = 2.6, H–C(2)); 7.91 (*m*, H–C(8)); 8.44 (*d*, *J* = 7.6, H–C(5)); 9.60 (*s*, NH); 11.12 (*s*, NOH). ^{13}C-NMR (50 MHz, DMSO): 11.39; 104.76; 105.73; 118.24; 121.28; 123.10; 123.21; 126.24; 128.11; 129.13; 131.74; 141.81; 142.11; 142.97; 145.62; 152.40; 162.95. Anal. calc. for $C_{19}H_{15}N_3O_2 \cdot 0.5\ H_2O$: C 69.98, H 4.94, N 12.88; found: C 70.36, H 4.97, N 12.66.

*(*E*)-1-[4-(Furo[2,3-*b*]quinolin-4-ylamino)phenyl]ethanone* O-*Methyloxime* (**8b**). From **5** and 40% NH_2O-Me · HCl as described for **8a**: 99% yield: M.p. 167–168°. ^{1}H-NMR (400 MHz, DMSO): 2.19 (*s*, Me); 3.92 (*s*, MeO); 6.09 (*d*, *J* = 2.8, H–C(3)); 7.19 (*d*, *J* = 8.8, 2 arom. H); 7.50 (*m*, H–C(6)); 7.69 (*m*, 2 arom. H, H–C(7)); 7.83 (*d*, *J* = 2.8, H–C(2)); 7.91 (*dd*, *J* = 8.4, 0.8, H–C(8)); 8.38 (*d*, *J* = 8.4, H–C(5)); 9.52 (*s*, NH). ^{13}C-NMR (100 MHz, DMSO): 12.05; 61.46; 105.12; 105.65; 118.35; 120.81; 123.02; 123.10; 126.57; 128.12; 129.12; 130.26; 141.38; 142.67; 143.14; 145.57; 153.48; 162.85. Anal. calc. for $C_{20}H_{17}N_3O_2$: C 72.49, H 5.17, N 12.68; found: C 72.33, H 5.24, N 12.53.

*(*E*)-1-[3-(Furo[2,3-*b*]quinolin-4-ylamino)phenyl]ethanone Oxime* (**9a**). From **7** and $NH_2OH \cdot HCl$ as described for **8a**: 97% yield. M.p. 248–249°. ^{1}H-NMR (200 MHz, DMSO): 2.14 (*s*, Me); 5.97 (*d*, *J* = 2.6, H–C(3)); 7.21 (*m*, 1 arom. H); 7.45 (*m*, 3 arom. H, H–C(6)); 7.70 (*m*, H–C(7)); 7.77 (*d*, *J* = 2.6, H–C(2)); 7.89 (*dd*, *J* = 8.4, 1.0, H–C(8)); 8.42 (*d*, *J* = 8.4, H–C(5)); 9.47 (*s*, NH); 11.22 (br. *s*, NOH). ^{13}C-NMR (50 MHz, DMSO): 11.46; 103.98; 105.57; 117.87; 119.05; 120.99; 122.46; 122.95; 128.10; 129.10; 137.77; 141.50; 142.22; 142.70; 145.58; 152.51; 162.95. Anal. calc. for $C_{19}H_{15}N_3O_2 \cdot 0.2\ H_2O$: C 71.15, H 4.84, N 13.10; found: C 71.25, H 4.89, N 12.80.

*(*E*)-1-[3-(Furo[2,3-*b*]quinolin-4-ylamino)phenyl]ethanone* O-*Methyloxime* (**9b**). From **7** and 40% NH_2O-Me · HCl as described for **8a**: 95% yield. M.p. 137–138°. ^{1}H-NMR (400 MHz, DMSO): 2.18 (*s*, Me); 3.90 (*s*, MeO); 5.97 (*d*, *J* = 2.8, H–C(3)); 7.23 (*m*, 1 arom. H); 7.48 (*m*, 2 arom. H, H–C(6)); 7.56 (*m*, 1 arom. H); 7.71 (*m*, H–C(7)); 7.78 (*d*, *J* = 2.8, H–C(2)); 7.90 (*d*, *J* = 8.4, H–C(8)); 8.42 (*d*, *J* = 8.4, H–C(5)); 9.49 (*s*, NH). ^{13}C-NMR (100 MHz, DMSO): 12.27; 61.59; 104.03; 105.53; 117.88; 119.40; 121.25; 122.86; 122.93; 122.96; 128.09; 129.09; 129.15; 136.76; 141.60; 142.13; 142.75; 145.57; 153.70; 162.96. Anal. calc. for $C_{20}H_{17}N_2O_2$: C 72.49, H 5.17, N 12.68; found: C 72.36, H 5.23, N 12.60.

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