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Synthesis and anti-inflammatory evaluation of 4-anilinofuro[2,3-*b*]quinoline and 4-phenoxyfuro[2,3-*b*]quinoline derivatives. Part 3

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Abstract—Mast cells, neutrophils and macrophages are important inflammatory cells that have been implicated in the pathogenesis of acute and chronic inflammatory diseases. To explore a novel anti-inflammatory agent, we have synthesized certain 4-anilinofuro[2,3-*b*]quinoline and 4-phenoxyfuro[2,3-*b*]quinoline derivatives and evaluated their anti-inflammatory activities by reaction of 3,4-dichlorofuro[2,3-*b*]quinoline with appropriate Ar-NH_2 or Ar-OH. Compounds **6a** and **15** were proved to be more potent than the reference inhibitor, mepacrine for the inhibition of rat peritoneal mast cell degranulation with IC_{50} values of 6.5 and 16.4 μM, respectively. Compounds **2b**, **6a**, **10**, and **15** also showed potent inhibitory activity (IC_{50} = 7.2–29.4 μM) for the secretion of lysosomal enzyme and β-glucuronidase from neutrophils. These results also indicated that oxime derivatives are more potent than the respective ketone precursors (**6a** ≥ **2a**; **7a** ≥ **3**), and the substituent such as Me at the oxime decreased inhibitory activity (**6a** ≥ **6b**; **7a** ≥ **7b**). Among these derivatives, compound **6a** showed the most potent activity with IC_{50} values of 6.5–11.6 μM for the inhibition of mast cell degranulation and neutrophil degranulation.

1. Introduction

9-Aminoacridine has been used clinically as an antiseptic drug. This tricyclic heterocycle may interact with DNA through intercalation, thus disrupting DNA replication.[1,2] A large number of its derivatives have been prepared and evaluated for biological activities.[3–5] Two notable examples are mepacrine (quinacrine), the acridine derivative to be clinically used as an antimalarial drug which also acts as a calmodulin inhibitor to suppress the histamine secretion process in mast cell [6–9] and amsacrine (m-AMSA), an antileukemic agent.[10–12] Certain 9-thioacridines have also been synthesized as inhibitors of trypanothione reductase from *Trypanosoma cruzi,* the causative agent of Chagas' disease.[13] Due to the biological versatility of acridine derivatives, we have synthesized certain 9-anilinoacridine, 9-phenoxyacridine, and 4-phenoxyfuro[2,3-*b*]quinoline derivatives and evaluated their anti-inflammatory activities.[14,15] Recently, we have also synthesized certain 4-anilinofuro[2,3-*b*]quinoline derivatives from a natural alkaloid, dictamnine, and evaluated their cytotoxicity.[16,17] We were especially interested in the study of furo[2,3-*b*]quinoline because it constitutes an important group of bioactive natural products such as dictamnine, acrophylline, confusameline, skimmianine, kokusaginine, and haplopine.[18–23] These alkaloids were found to possess wide-ranging biological properties including anti-allergic,[18] anti-inflammatory,[19] cytotoxic,[20] antiplatelet aggregation,[21,22] and the voltage-gated potassium channel blocking activities.[23] Although the 4-anilinofuro[2,3-*b*]quinoline ring belongs to the isosteric isomer of 9-anilinoacridine, comparison on the biological activities between these two rings have not been explored. In continuation of our studies on 9-anilinoacridine derivatives, we report herein the preparation and anti-inflammatory activities of certain 4-anilinofuro[2,3-*b*]quinoline derivatives. We have also synthesized and evaluate a number of 4-phenoxyfuro[2,3-*b*]quinoline derivatives for the establishment of anti-inflammatory structure–activity relationships.

Keywords: Anti-inflammatory; 4-Anilinofuro[2,3-*b*]quinoline; 4-Phenoxyfuro[2,3-*b*]quinoline; Furo[2,3-*b*]quinoline.
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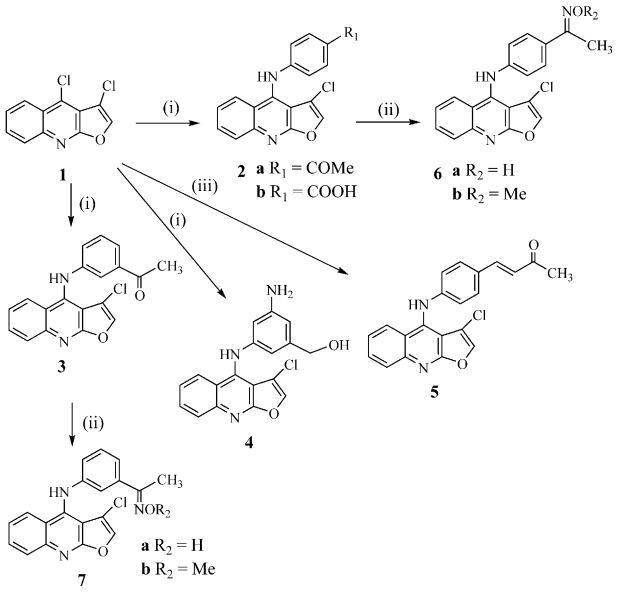
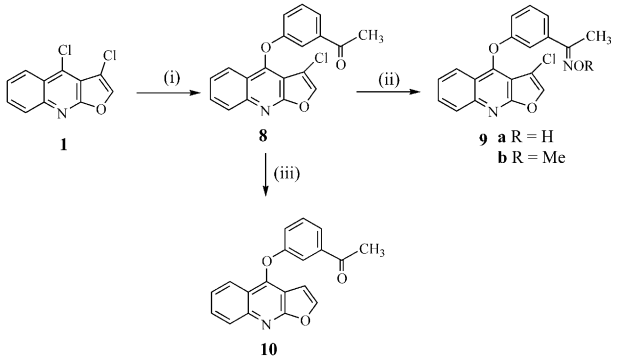
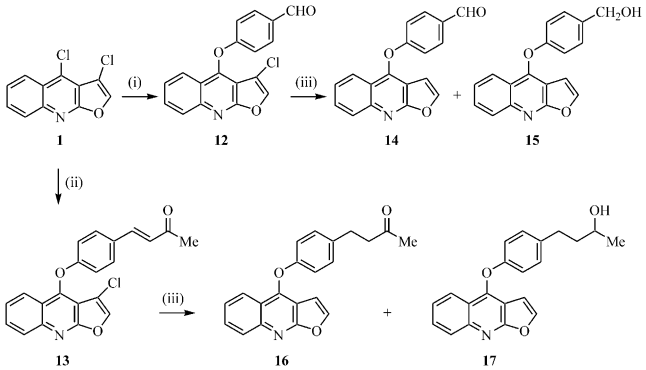


Scheme 1. (i) Substituted-anilines, EtOH-H_2O (2:1 v/v), HCl, reflux; (ii) R′ONH_2, EtOH, reflux; (iii) *N*-[4-(3-oxobut-1-enyl)phenyl]acetamide, EtOH–H_2O (2:1) v/v), HCl, reflux.



Scheme 2. (i) 3-Hydroxyacetophenone, EtOH–H_2O (2:1 v/v), HCl, reflux; (ii) $RONH_2$, EtOH, reflux; (iii) H_2, Lindlar catalyst, EtOH–CH_2Cl_2 (1:1 v/v).



Scheme 3. Reagents (i) 4-Hydroxybenzaldehyde, K_2CO_3, THF in a sealed bomb; (ii) 4-Hydroxybenylideneacetone, K_2CO_3, acetone in a sealed bomb; (iii) Lindlar catalyst, H_2, MeOH-CH_2Cl_2 (1:1 v/v).

2. Chemistry

4-Anilinofuro[2,3-*b*]quinolines 2-7 were prepared as described in Scheme 1. Reaction of the known 3,4-dichlorofuro[2,3-*b*]quinoline (**1**)[24] with 4-aminobenzoic acid in EtOH/H_2O (2:1) afforded 4-(3-chlorofuro[2,3-*b*]quinolin-4-ylaminobenzoic acid (**2b**) in 57% yield. Accordingly, 4-[4-(3-chlorofuro[2,3-*b*]quinolin-4-ylamino)phenyl]- but-3-en-2-one (**5**) was prepared from *N*-[4-(3-oxobut-1-enyl)phenyl]acetamide[25] under the same reaction condition. Preparation of **2a**, **3**, and **4** had been described in our previously paper.[16] Compounds **2a** and **3** were reacted with hydroxylamine or methoxylamine, respectively, in EtOH to give the corresponding oximes **6a**, **7a** and methyloximes **6b**, **7b** in 62–97% yield.

Preparation of 4-phenoxyfuro[2,3-*b*]quinolines **8**–**10** is described in Scheme 2. Compound **1** was treated with 3-hydroxyacetophenone to afford 1-[3-(3-chlorofuro[2,3-*b*]quinolin-4yloxy)phenyl]ethanone (**8**) which was then reduced with H_2 in the presence of Lindlar catalyst to give 1-[3-(furo[2,3-*b*]quinolin-4-yloxy)phenyl]ethanone (**10**) in 69% yield. Reaction of **8** with hydroxylamine or methoxylamine, respectively, in EtOH gave the corresponding oximes **9a** and methyloximes **9b** in 87–90% yield.

4-(3-Chlorofuro[2,3 - *b*]quinolin - 4 - yloxy)benzaldehyde (**11**) was synthesized from **1** and 4-hydroxybenzaldehyde, which was then reduced with Lindlar catalyst and H_2 to give 4-(furo[2,3-*b*]quinolin-4-yloxy)-benzaldehyde (**13**) and [4-(furo[2,3-*b*]quinolin- 4-yloxy)-phenyl]methanol (**14**) (Scheme 3). Accordingly, reaction of **1** and 4-hydroxybenzylideneacetone afforded **12**, which was reduced to give 4-[4-(furo[2,3-*b*]quinolin-4-yloxy)phenyl]butan-2-one (**15**) and 4-[4-(furo[2,3-*b*]-quinolin-4-yloxy)phenyl]butan-2-ol (**16**).

3. Biological results and discussion

3.1. Mast cell degranulation

In the present study, assessment of inhibitory efficacy with respect to mast cell degranulation was performed by measuring the content of β-glucuronidase in supernatant. As shown in Table 1, (*E*)-1-[3-(3-chlorofuro [2,3-*b*]quinolin-4-ylamino)phenyl]ethanone oxime (**7a**) demonstrated only a weak inhibitory activity (IC_{50} value of 35.8 μM) while (*E*)-1-[4-(3-chlorofuro[2,3-*b*]quinolin-4-ylamino)phenyl]ethanone oxime (**6a**) (6.5 μM) and 4-[4-(furo[2,3-*b*]quinolin-4-yloxy)phenyl]butan-2-one (**15**) (16.4 μM) exhibited more potent activity than the reference inhibitor, mepacrine (20.6 μM). These results also indicated that oxime derivatives are more potent than the respective ketone precursors (**6a** ≥ **2a**; **7a** ≥ **3**) and the substituent such as Me at the oxime decreased inhibitory activity (**6a** ≥ **6b**; **7a** ≥ **7b**). The result that compound **15** was more potent than **13** suggested that the distance between furoquinoline and the carbonyl group also play an important role.

3.1.1. Neutrophil degranulation. Activation of neutrophils with 1 μM formyl-methionyl-leucyl-phenylalanine (fMLP) in the presence of cytochalasin B (5 μg/mL) evoked the release of 21.2 and 19.8% of lysozyme and β-glucuronidase, respectively, of the initial cellular content. Compound **6a**, with an IC_{50} value of 11.6 and

Table 1. IC_{50} (μM)[a] values of furo[2,3-*b*]quinoline derivatives against mast cell and neutrophil degranulation

Compd	Mast cell degranulation β-glucuronidase[b]	Neutrophil degranulation	
		Lysozyme[c]	β-glucuronidase[c]
2a	>30.0	>30.0	>30.0
2b	>30.0	23.3±6.9	18.9±5.7
3	>30.0	>30.0	>30.0
4	>30.0	>30.0	>30.0
5	>30.0	>30.0	>30.0
6a	6.5±1.1	11.6±1.7	7.2±0.9
6b	>30.0	>30.0	>30.0
7a	35.8±1.1	>30.0	>30.0
7b	>30.0	>30.0	>30.0
8	>30.0	>30.0	>30.0
9a	>30.0	>30.0	>30.0
9b	>30.0	>30.0	>30.0
10	>30.0	29.4±2.0	26.1±5.9
11	>30.0	>30.0	>30.0
12	>30.0	>30.0	32.0±2.4
13	>30.0	>30.0	13.0±0.5
14	>30.0	>30.0	>30.0
15	16.4±1.8	14.0±1.2	9.3±1.2
Mepacrine	20.6±1.2		
Trifluoperazine		11.9±0.6	10.6±0.9

[a] Values are means±SE of at least three separate experiments.
[b] Induced by compound 48/80 (10 μg/mL).
[c] Induced by fMLP (1 μM)/cytochalasin B (5 μg/mL).

7.2 μM against lysozyme and β-glucuronidase release, respectively, was more potent than its positional isomer **7a** and was comparable to the calmodulin inhibitor, trifluoperazine (11.9 and 10.6 μM, respectively) which inhibits the degradation and superoxide anion generation in neutrophils.[26,27] 4-(3-Chlorofuro[2,3-*b*]quinolin-4-ylaminobenzoic acid (**2b**) with an IC_{50} value of 23.3 and 18.9 μM against lysozyme and β-glucuronidase release, respectively, was more potent than its acetyl analogue **2a**. In analogy to the inhibition of mast cell degranulation, oxime derivatives are more potent than the respective ketone precursors (**6a**≥**2a**), and the substituent such as Me at the oxime decreased inhibitory activity (**6a**≥**6b**) and a longer distance between furoquinoline and the carbonyl group was preferred (**12**≥**11**; **15**≥**13**). In addition, the inhibitory activity was decreased by the reduction of carbonyl group to an alcohol (**13**≥**14**), but was increased by the reduction of Cl at the 3-position (**10**≥**8**). Compound **6a** showed the most potent activity with IC_{50} values of 7–12 μM for the inhibition of neutrophil degranulation.

3.2. TNF-α release

TNF-α, an early cytokine produced by activated macrophages, plays an essential role in pathological inflammatory reactions. None of compounds **2**–**15** had similar IC_{50} value as dexamethasone in the inhibition of TNF-α formation in macrophage-like cell line RAW 264.7 and microglial cell line N9 cells (the brain resident macrophages) (Table 2). However, (*E*)-1-[3-(3-chlorofuro[2,3-*b*]quinolin-4-yloxy)phenyl]ethanone oxime (**9a**) showed weak potency in N9 cells (IC_{50} values of 1.7 μM). The results also confirm the conclusion above that the substituent such as Me at the oxime decreased inhibitory activity (**9a**≥**9b**) (Table 2).

Table 2. IC_{50} values of furo[2,3-*b*]quinoline derivatives on TNF-α formation

Compd	IC_{50} (μM)[a,b]	
	RAW 264.7	N9
2a	>10.0	>0.3
2b	>30.0	>30.0
3	>30.0	>30.0
4	>30.0	>30.0
5	>10.0	>3.0
6a	>10.0	>1.0
6b	>30.0	>3.0
7a	>30.0	>3.0
7b	>30.0	>3.0
8	>30.0	>30.0
9a	>30.0	1.7±0.1
9b	>30.0	>10.0
10	>30.0	>10.0
11	>30.0	>3.0
12	>10.0	>10.0
13	>30.0	>30.0
14	>30.0	>30.0
15	>30.0	>10.0
Dexamethasone	0.42±0.12	0.074±0.01

[a] Values are means±SE of at least three separate experiments.
[b] When compounds exhibited cytotoxicity at 30 μM, a lower concentration was applied.

3.3. Preliminary cytotoxic evaluation

Nine furo[2,3-*b*]quinoline derivatives were selected for evaluation in vitro against a three-cell line panel consisting of MCF7 (Breast), NCI-H460 (Lung), and SF-268 (CNS). 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 incubated for 48 h. End-point determinations are made with alamar blue.[28] Results for each test agent are reported as the percent of growth of the treated cells when compared to the untreated control cells. Compounds which reduced the growth of any one of the cell lines to 32% or less are considered to be cytotoxic. Results indicated all of them, with the exception of compound **5** which exhibited a weak inhibitory activity on MCF7 cancer cell, are non-cytotoxic.

4. Conclusion

These results indicated that the anti-inflammatory effects of furo[2,3-*b*]quinoline derivatives were mediated, at least in part, through the suppression of chemical mediators released from mast cells, neutrophils and macrophages, and the potential of these compounds to be novel anti-inflammatory agents with no significant cytotoxicity.

5. Experimental

5.1. General

TLC: precoated (0.2 mm) silica gel 60 F_{254} plates from EM Laboratories, Inc.; detection by UV light (254 nm). Mp: Electrothermal IA9100 digital melting-point appa-

ratus; uncorrected. ^{1}H and ^{13}C NMR spectra: Varian-Unity-400 spectrometer at 400 and 100 MHz or Varian-Gemini-200 spectrometer at 200 and 50 MHz, chemical shifts δ in ppm with $SiMe_4$ 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 calculated values.

5.1.1. 4-(3-Chlorofuro[2,3-*b*]quinolin-4-ylaminobenzoic acid (2b). To a solution of 3,4-dichlorofuro[2,3-*b*]quinoline (**1**, 1.19 g, 5.00 mmol) and 4-aminobenzoic acid (1.03 g, 7.50 mmol) in EtOH/H_2O 2:1 (50 mL) was added concentrated HCl until pH 6 resulted. The mixture was refluxed for 18 h (TLC monitoring) and then the solvent evaporated in vacuo to give a residual solid, which was suspended in ice-water (250 mL) and neutralized with 1 N NaOH solution. The resulting precipitate was collected by filtration, washed with H_2O, and then purified by flash column chromatography (FC, silica gel CH_2Cl_2/MeOH 20:1) and recrystallized from EtOH to give **2b** (0.96 g, 57%). Mp 262–263°C ^{1}H NMR (200 MHz, DMSO-d_6): 6.86 (m, 2H-C(2′, 6′)), 7.59 (m, H-C(6)), 7.75 (m, 2H-C(3′, 5′)), 7.82 (m, H-C(7)), 8.04 (dd, J=8.4, 0.8, H-C(8)), 8.22 (dd, J=8.6, 0.8, H-C(5)), 8.40 (s, H-C(2)), 9.45 (br s, NH), 12.65 (br s, COOH). ^{13}C NMR (50 MHz, DMSO-d_6): 110.11, 111.05, 114.84, 121.70, 122.61, 123.73, 125.18, 128.65, 130.54, 131.31, 139.98, 143.37, 146.04, 150.73, 160.88, 167.43. HRMS (EI): calcd for $C_{18}H_{11}ClN_2O_3$: 338.0458. Found: 338.0462.

5.1.2. 4-[4-(3-Chlorofuro[2,3-*b*]quinolin-4-ylamino)-phenyl]but-3-en-2-one (5). This compound was obtained from **1** and *N*-[4-(3-oxobut-1-enyl)phenyl]acetamide as described for **2b**, which was purified by FC (CH_2Cl_2/AcOEt 20:1) in 48% yield. Mp 207–208°C. ^{1}H NMR (400 MHz, $CDCl_3$): 2.36 (s, CO<u>Me</u>), 6.62 (d, J=16.4, CH=<u>CH</u>COMe), 6.93 (m, 2H-C(2′, 6′)), 7.31 (m, H-C(6)), 7.46 (m, 2H-C(3′, 6′), <u>CH</u>=CHCOMe and NH), 7.71 (m, 2H-C(2, 7)), 7.89 (d, J=8.0, H-C(8)), 8.13 (d, J=8.4, H-C(5)). ^{13}C NMR (100 MHz, $CDCl_3$): 27.48, 108.36, 110.42, 118.41 (2C), 120.06, 124.25, 124.52, 125.46, 128.25, 128.74, 129.74 (2C), 130.50, 141.00, 141.64, 142.76, 145.55, 145.73, 160.02, 198.27. Anal. calcd for $C_{21}H_{15}ClN_2O_2$: C 69.52, H 4.17, N 7.72; Found: C 69.27, H 4.27, N 7.66.

5.1.3. (*E*)-1-[4-(3-Chlorofuro[2,3-*b*]quinolin-4-ylamino)-phenyl]ethanone oxime (6a). To a suspension of **2a** (216 mg, 0.64 mmole) in ethanol (20 mL) was added NH_2OH·HCl (89 mg, 1.28 mmol). The reaction mixture was stirred at room temperature for 1 h (TLC monitoring), then concentrated in vacuo to give a solid which was washed by H_2O (20 mL), purified by FC (CH_2Cl_2–AcOEt 20:1) and recrystallized from EtOH to give a yellow solid (140 mg, 62%). Mp 219–220°C. ^{1}H NMR (200 MHz, DMSO-d_6): 2.10 (s, Me), 6.90 (m, 2H-C(2′, 6′)), 7.54 (m, 3H-C(6, 3′, and 5′)), 7.80 (m, H-C(7)), 8.01 (d, J=8.6, H-C(8)), 8.26 (d, J=8.4, H-C(5)), 8.34 (s, H-C(2)), 9.16 (br s, NH), 10.93 (br s, NOH). ^{13}C NMR (50 MHz, DMSO-d_6): 11.21, 109.08, 109.90, 115.86 (2C), 121.61, 123.47, 124.36, 126.38 (2C), 128.26, 128.91, 130.01, 140.78, 142.24, 145.74, 146.44, 152.37, 160.72. Anal. calcd for $C_{19}H_{14}ClN_3O_2$·0.2HCl: C 63.55, H 3.99, N 11.70; Found: C 63.94, H 4.28, N 11.33.

5.1.4. (*E*)-1-[4-(3-Chlorofuro[2,3-*b*]quinolin-4-ylamino)-phenyl]ethanone *O*-methyloxime (6b). To a suspension of **2a** (103 mg, 0.30 mmol) in ethanol (16 mL) was added 40% NH_2Ome·HCl aqueous (126 mg, 0.6 mmol). The reaction mixture was stirred at room temperature for 1 h (TLC monitoring), then concentrated in vacuo to give a solid which was washed by H_2O (20 mL) and purified by FC (CH_2Cl_2) to give a white solid (102 mg, 93%). Mp 213–215°C. ^{1}H NMR (200 MHz, $CDCl_3$): 2.20 (s, Me), 3.98 (s, NOMe), 6.89 (m, 2H-C (2′, 6′)), 7.20 (br s, NH), 7.31 (m, H-C(6)), 7.55 (m, 2H-C(3′, 5′)), 7.68 (m, 2H-C(2, 7)), 7.82 (d, J=8.4, H-(8)), 8.08 (d, J=8.4, H-C(5)). ^{13}C NMR (50 MHz, $CDCl_3$): 12.46, 61.86, 107.78, 110.13, 118.28 (2C), 119.88, 123.96, 124.45, 127.10 (2C), 128.92, 129.93, 130.95, 105.55, 141.75, 144.39, 146.58, 153.96, 160.57. Anal. calcd for $C_{20}H_{16}ClN_3O_2$·0.3HCl: C 63.76, H 4.36, N 11.15; Found: C 63.71, H 4.12, N 11.29.

5.1.5. (*E*)-1-[3-(3-Chlorofuro[2,3-*b*]quinolin-4-ylamino)-phenyl]ethanone oxime (7a). This compound was obtained from **3** and NH_2OH·HCl as described for **6a**, which was purified by FC (CH_2Cl_2/MeOH 100:1) in 93% yield. Mp. 250–252°C. ^{1}H NMR (200 MHz, DMSO-d_6): 2.08 (s, Me), 6.90 (m, H-C(6′)), 7.13–7.26 (m, 3H-C(2′, 4′, 5′)), 7.55 (m, H-C(6), 7.80 (m, H-C(7)), 8.01 (d, J=8.4, H-C(8)), 8.30 (m, 2H-C(2, 5)), 9.10 (br s, NH), 11.11 (br s, NOH). ^{13}C NMR (50 MHz, DMSO-d_6): 11.44, 108.51, 109.99, 113.33, 117.02, 118.24, 121.44, 123.53, 124.35, 128.29, 129.10, 130.08, 137.73, 141.27, 142.09, 145.79, 145.88, 152.66, 160.81. Anal. calcd for $C_{19}H_{14}ClN_3O_2$: C 64.87, H 4.01, N 11.94; Found: C 64.83, H 4.09, N 11.73.

5.1.6. (*E*)-1-[3-(3-Chlorofuro[2,3-*b*]quinolin-4-ylamino)-phenyl]ethanone *O*-methyloxime (7b). This compound was obtained from **3** and 40%·NH_2OMe·HCl as described for **6b**, which was purified by FC (CH_2Cl_2) in 97% yield. Mp 151–152°C. ^{1}H NMR (200 MHz, DMSO-d_6): 2.11 (s, Me), 3.87 (s, NOMe), 6.86 (m, H-C(6′)), 7.17–7.34 (m, 3H-C(2′, 4′, 5′)), 7.54 (m, H-C(6)), 7.78 (m, H-C(7)), 7.98 (d, J=8.4, H-C(8)), 8.30 (m, 2H-C(2, 5)), 9.13 (br s, NH). ^{13}C NMR (50 MHz, DMSO-d_6): 12.32, 61.46, 108.36, 109.92, 114.05, 117.06, 118.40, 121.30, 123.44, 124.26, 128.24, 129.08, 130.00, 136.68, 141.05, 142.02, 145.73, 145.84, 153.88, 160.77. Anal. calcd for $C_{20}H_{16}ClN_3O_2$·0.1H_2O: C 65.35, H 4.44, N 11.43; Found: C 65.28, H 4.50, N 11.08.

5.1.7. 1-[3-(3-Chlorofuro[2,3-*b*]quinolin-4-yloxy)phenyl]-ethanone (8). A mixture of **1** (0.72 g, 3.0 mmol), K_2CO_3 (0.62 g, 4.5 mmol), and 3-hydroxyacetophenone (0.49 g, 3.6 mmol) in acetone (50 mL) was heated at 150°C for 20 h in a steel bomb. It was cooled, the solvent evaporated in vacuo to give a residual solid, which was suspended in ice-water (100 mL). The resulting precipitate was collected by filtration, washed with H_2O, and then purified by FC (*n*-hexane/EtOAc 4:1) and recrystallized from EtOH to give a white solid **8** (0.80 g, 79%). Mp

168–169°C. ^{1}H NMR (200 MHz, $CDCl_3$): 2.56 (s, Me), 7.08 (m, H-C(6′)), 7.41 (dd, J = 8.2, 7.8, H-C(5′)), 7.51 (m, 2H-C(2′, 6)), 7.67 (m, H-C(4′)), 7.73 (s, H-C(2)), 7.79 (m, H-C(7)), 8.08 (dd, J = 8.4, 1.2, H-C(8)), 8.17 (d, J = 8.4, H-C(5)). ^{13}C NMR (50 MHz, $CDCl_3$): 26.72, 109.90, 114.82, 120.15, 121.20, 122.04, 123.15, 123.46, 125.70, 128.69, 130.13, 130.62, 138.96, 142.26, 146.75, 151.53, 159.50, 161.22, 197.18. Anal. calcd for $C_{19}H_{12}ClNO_3$: C 67.56, H 3.58, N 4.15; Found: C 67.52, H 3.63, N 4.13.

5.1.8. (*E*)-1-[3-(3-Chlorofuro[2,3-*b*]quinolin-4-yloxy)-phenyl]ethanone oxime (9a). This compound was obtained from **8** and NH_2OH·HCl as described for **6a**, which was purified by FC (CH_2Cl_2/EtoAc 20:1) in 90% yield. Mp 181–183 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 2.11 (s, Me), 7.00 (m, H-C(6′)), 7.23 (m, H-C(2′)), 7.37 (m, 2H-C(4′, 5′)), 7.62 (m, H-C(6)), 7.88 (m, H-C(7)), 8.04 (dd, J = 8.4, 0.8, H-C(8)), 8.13 (d, J = 8.4, H-C(5)), 8.55 (s, H-C(2)), 11.25 (s, NOH). ^{13}C NMR (100 MHz, DMSO-d_6): 11.46, 108.56, 110.16, 111.63, 115.83, 120.57, 120.72, 121.87, 126.01, 128.35, 130.22, 130.81, 138.89, 144.19, 146.07, 150.88, 152.22, 158.89, 160.83. Anal. calcd for $C_{19}H_{13}ClN_2O_3$: C 64.69, H 3.71, N 7.94; Found: C 64.33, H 3.86, N 7.60.

5.1.9. (*E*)-1-[3-(3-Chlorofuro[2,3-*b*]quinolin-4-yloxy)-phenyl]ethanone *O*-methyloxime (9b). This compound was obtained from **8** and 40% NH_2OMe·HCl as described for **6b**, which was purified by FC (CH_2Cl_2) in 87% yield. Mp 137–139°C. ^{1}H NMR (200 MHz, $CDCl_3$): 2.18 (s, Me), 3.97 (s, NOMe), 6.73 (m, H-C(6′)), 7.25 (dd, J = 8.4, 8.0, H-C(5′)), 7.38 (m, 2H-C(2′, 4′)), 7.51 (m, H-C(6)), 7.72 (s, H-C(2)), 7.79 (m, H-C(7)), 8.14 (m, H-C(5, 8)). ^{13}C NMR (50 MHz, $CDCl_3$): 12.67, 62.04, 110.19, 113.63, 115.70, 120.78, 121.42, 122.43, 125.58, 128.62, 129.78, 130.58, 138.78, 142.11, 142.72, 146.79, 152.08, 153.81, 159.38, 161.35. Anal. calcd for $C_{20}H_{15}ClN_2O_3$: C 65.49, H 4.12, N 7.64; Found: C 65.28, H 4.17, N 7.47.

5.1.10. 1-[3-(Furo[2,3-*b*]quinolin-4-yloxy)phenyl]ethanone (10). A solution of **8** (0.23 g, 0.68 mmol) in MeOH–CH_2Cl_2 (1/1, 60 mL) was hydrogenated for 1 h (TLC monitoring) under H_2 with Lindlar catalyst (0.23 g). The reaction mixture was filtered and the filtrate concentrated in vacuo to give a residual solid, which was purified by FC (*n*-hexane–EtOAc 2:1) to give **10** (0.14 g, 69%). Mp 132–133 °C. ^{1}H NMR (200 MHz, $CDCl_3$): 2.60 (s, Me), 5.81 (d, J = 2.6, H-C(3)), 7.36 (m, H-C(6′)), 7.51 (d, J = 2.6, H-C(2)), 7.57 (m, 2H-C(5′, 6)), 7.76–7.89 (m, 3H-C(2′, 4′, 7)), 8.18 (d, J = 8.2, H-C(8)), 8.37 (dd, J = 8.4, 1.2, H-C(5)). ^{13}C NMR (50 MHz, $CDCl_3$): 26.74, 103.53, 107.32, 118.84, 119.31, 122.04, 123.86, 124.84, 127.86, 130.21, 130.40, 139.13, 144.82, 145.57, 152.16, 153.56, 156.56, 163.05, 196.82. Anal. calcd for $C_{19}H_{13}NO_3$·0.1H_2O: C 74.80, H 4.36, N 4.59; Found: C 74.80, H 4.43, N 4.55.

5.1.11. 4-(3-Chlorofuro[2,3-*b*]quinolin-4-yloxy)benzaldehyde (11). This compound was obtained from **1** and 4-hydroxybenzaldehyde in THF as described for **8**, which was purified by FC (CH_2Cl_2) in 72% yield. Mp 194–195°C. ^{1}H NMR (200 MHz, $CDCl_3$): 7.02 (m, 2H-C(2′, 6′)), 7.54 (m, H-C(6)), 7.76 (s, H-C(2)), 7.81 (m, H-C(7)), 7.86 (m, 2H-C(3′, 5′)), 8.05 (dd, J = 8.6, 1.6, H-C(8)), 8.19 (d, J = 8.6, H-C(5)), 9.93 (s, CHO). ^{13}C NMR (50 MHz, $CDCl_3$): 109.85, 110.15, 116.04 (2C), 120.96, 121.81, 125.91,. 128.80, 130.79, 131.78, 132.19 (2C), 142.53, 146.77, 150.58, 161.15, 163,58, 190.51. Anal. calcd for $C_{18}H_{10}ClNO_3$: C 66.78, H 3.11, N 4.33; Found: C 66.63, H 3.14, N 4.34.

5.1.12. 4-[4-(3-Chlorofuro[2,3-*b*]quinolin-4-yloxy)phenyl]-but-3-en-2-one (12). This compound was obtained from **1** and 4-hydroxybenzylideneacetone in acetone as described for **8**, which was purified by FC (CH_2Cl_2) in 87% yield. Mp 185–186°C. ^{1}H NMR (200 MHz, $CDCl_3$): 2.36 (s, Me), 6.61 (d, J = 16.0, CH=<u>CH</u>(C=O)Me), 6.91 (m, 2H-C(2′, 6′)), 7.42–7.56 (m, 3H-C(3′, 5′, 6) and <u>CH</u>=CH(C=O)Me), 7.73 (s, H-C(2)), 7.79 (m, H-C(7)), 8.07 (dd, J = 8.0, 1.0, H-C(8)), 8.17 (d, J = 8.6, H-C(5)). ^{13}C NMR (50 MHz, $CDCl_3$): 27.50, 109.97, 110.17, 116.12 (2C), 121.18, 122.05, 125.75, 126.27, 128.73, 129.39, 130.15 (2C), 130.65, 142.42, 146.78, 151.45, 160.88, 161.24, 198.16. Anal. calcd for $C_{21}H_{14}ClNO_3$·0.1H_2O: C 68.99, H 3.91, N 3.83; Found: C 38.92, H 3.93, N 3.75.

5.1.13. 4-(Furo[2,3-*b*]quinolin-4-yloxy)benzaldehyde (13) and [4-(furo[2,3-*b*]quinolin-4-yloxy)phenyl]methanol (14). Hydrogenation of **11** as described for **10**, which was purified by FC (CH_2Cl_2) to give **13** (23% yield) and **14** (34% yield).

Compound 13. Mp 129–131°C. ^{1}H NMR (200 MHz, $CDCl_3$): 6.16 (d, J = 2.6, H-C(3)), 7.22 (m, 2H-C(2′, 6′)), 7.55 (m, H-C(6)), 7.61 (d, J = 2.6, H-C(2)), 7.79 (m, H-C(7)), 7.94 (m, 2H-C(3′, 5′)), 8.18 (d, J = 8.4, H-C(8)), 8.25 (dd, J = 8.6, 1.0, H-C(5)), 10.00 (s, CHO). ^{13}C NMR (50 MHz, $CDCl_3$): 103.43, 108.97, 118.67 (2C), 119.70, 121.87, 125.19, 128.21, 130.26, 132.08 (2C), 132.82, 145.65, 145.90, 152.11, 161.38, 163.02, 190.45. Anal. calcd for $C_{18}H_{11}NO_3$·0.1H_2O: C 74.28, H 3.88, N 4.81; Found: C 74.32, H 4.23, N 4.76.

Compound 14. Mp 163–164°C. ^{1}H NMR (400 MHz, DMSO-d_6): 4.57 (d, J = 5.6, <u>CH_2</u>OH), 5.32 (t, J = 5.6, OH), 5.66 (d, J = 2.8, H-C(3)), 7.27 (m, 2H-C(2′, 6′)), 7.45 (m, 2H-C(3′, 5′)), 7.62 (m, H-C(6)), 7.83 (m, H-C(7)), 7.93 (d, J = 2.8, H-C(2)), 8.04 (d, J = 8.0, H-C(8)), 8.36 (dd, J = 8.4, 0.8, H-C(5)). ^{13}C NMR (100 MHz, DMSO-d_6): 62.27, 103.44, 106.40, 118.61, 119.52 (2C), 121.95, 124.66, 127.77, 128.27 (2C), 129.96, 139.91, 145.34, 145.66, 153.63, 154.46, 163.06. Anal. calcd for $C_{18}H_{13}NO_3$·0.1H_2O: C 73.76, H 4.54, N 4.78; Found: C 73.63, H 4.61, N 4.74.

5.1.14. 4-[4-(Furo[2,3-*b*]quinolin-4-yloxy)phenyl]butan-2-one (15) and 4-[4-(furo[2,3-*b*]quinolin-4-yloxy)phenyl]-butan-2-ol (16). Hydrogenation of **12** as described for **10**, which was purified by FC to give **15** (eluting with CH_2Cl_2/EtOAc 20:1 and 21% yield) and **16** (eluting with CH_2Cl_2/EtOAc 4:1 and 28% yield).

Compound 15. Mp 113–115°C. ^{1}H NMR (200 MHz, DMSO-d_6): 2.12 (s, Me), 2.84 (br s, $\underline{CH_2CH_2}$(C=O)Me), 5.62 9d, J = 2.6, H-C(3)), 7.21 (m, 2H-C(2′, 6′)), 7.35 (m, 2H-C(3′, 5′)), 7.61 (m, H-C(6)), 7.82 (m, H-C(7)), 7.92 (d, J = 2.6, H-C(2)), 8.03 (d, J = 8.6, H-C(8)), 8.34 (dd, J = 8.4, 0.8, H-C(5)). ^{13}C NMR (50 MHz, DMSO-d_6): 28.38, 29.70, 44.09, 103.32, 106.26, 118.51, 119.66 (2C), 121.87, 124.55, 127.68, 129.87, 129.93 (2C), 138.54, 145.26, 145.55, 153.61, 153.82, 162.99, 207.48. Anal. calcd for $C_{21}H_{17}NO_3$: C 76.12, H 5.17, N 4.23; Found: C 75.92, H 5.30, N 4.20.

Compound 16. Pale-yellow oil. ^{1}H NMR (200 MHz, DMSO-d_6): 1.11 (d, J = 6.0, Me), 1.66 (m, $\underline{CH_2}CH_2CH(OH)Me$), 2.70 (m, $CH_2\underline{CH_2}CH(OH)Me$), 3.63 (m, $-CH_2CH_2\underline{CH}(OH)Me$), 4.51 (d, J = 5.0, OH), 5.61 (d, J = 2.8, H-C(3)), 7.22 (m, 2H-C(2′, 6′)), 7.33 (m, 2H-C(3′, 5′)), 7.61 (m, H-C(6)), 7.82 (m, H-C(7)), 7.92 (d, J = 2.8, H-C(2)), 8.03 (dd, J = 8.4, 1.2, H-C(8)), 8.35 (dd, J = 8.4, 1.4, H-C(5)). ^{13}C NMR (50 MHz, DMSO-d_6): 23.63, 30.88, 40.90, 65.16, 103.36, 106.21, 118.55, 119.77 (2C), 121.95, 124.61, 127.73, 129.63, 129.99 (2C), 139.93, 145.31, 145.56, 153.64, 153.78, 163.06. Anal. calcd for $C_{21}H_{19}NO_3 \cdot 0.2H_2O$: C 74.85, H 5.80, N 4.16; Found: C 75.15, H 6.08, N 3.97.

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