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# Synthesis and Anti-Inflammatory Evaluation of 9-Phenoxyacridine and 4-Phenoxyfuro[2,3-*b*]quinoline Derivatives. Part 2

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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 9-phenoxyacridine and 4-phenoxyfuro[2,3-*b*]quinoline derivatives and evaluated their anti-inflammatory activities. The title compounds were synthesized by reaction of either 9-chloroacridine or 3,4-dichlorofuro[2,3-*b*]quinoline with appropriate Ar–OH and their anti-inflammatory activities were studied on inhibitory effects on the activation of mast cells, neutrophils and macrophages. Four 9-(4-formylphenoxy)acridine derivatives **2b**–**2e** 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 6.1, 5.9, 13.5, and 4.7 μM, respectively. Compounds **2c**, **3b**, **3c**, and **5a** also showed potent inhibitory activity ($IC_{50}$ = 4.3–18.3 μM) for the secretion of lysosomal enzyme and β-glucuronidase from neutrophils. In addition, **2d**, **3a**, and **4** inhibited TNF-α formation from the N9 cells (the brain resident macrophages) with $IC_{50}$ vales less then 10 μM. These results indicated that acridine derivatives exhibited more potent anti-inflammatory activities than their respective furo[2,3-*b*]quinoline counterparts (**4** vs **9**; **5a** vs **10a**; **5b** vs **10b**).


## Introduction

Mast cells play an important role in anaphylaxis and inflammation. A variety of inflammatory mediators are secreted from mast cell during cell activation. Activated neutrophils release lysosomal enzymes which are capable of proteolytic disruption of healthy tissue in a number of disease states such as pulmonary emphysema, rheumatoid arthritis, arteriosclerosis, and glomerulonephritis.[1,2] Macrophages interact with other immune cells and serves as central regulators of specific immune response.[3] Following the activation of macrophages, tumor necrosis factor-α (TNF-α) was generated which mediated wide variety pathologic states such as lethal septic shock, rheumatoid arthritis, and cachexia.[4] Thus, a therapeutic agent which inhibits the activation of inflammatory cells and the following release of inflammatory mediators may be useful for the treatment of these inflammatory conditions.

9-Aminoacridine has been used clinically as an antiseptic drug. This tricyclic heterocycle may interact with DNA through intercalation, thus disrupting DNA replication.[5,6] A large number of its derivatives have been prepared and evaluated for biological activities.[7–9] Two notable examples are mepacrine (quinacrine), the acridine derivative to be clinically used as an anti-malarial drug which also acts as a calmodulin inhibitor to suppress the histamine secretion process in mast cell[10,11] and amsacrine (*m*-AMSA),[12,13] an antileukemic agent.[14–16] Certain 9-thioacridines have also been synthesized as inhibitors of trypanothione reductase from *Trypanosoma cruzi,* the causative agent of Chagas' disease.[17] Due to the biological versatility of acridine derivatives, we have synthesized certain 9-anilinoacridine and 9-phenoxyacridine derivatives (Fig. 1) and evaluated their anti-inflammatory activities.[18] The present report describes the influence of substituents with respect to anti-inflammatory activities of 9-phenoxyacridine derivatives. To further explore the structure–activity relationships, the acridine skeleton of certain 9-phenoxyacridines was replaced with its bioisosteric furo[2,3-*b*]quinoline ring which constitutes an important group of bioactive natural products such as dictamnine, robustine, and haplopine.[19,20]

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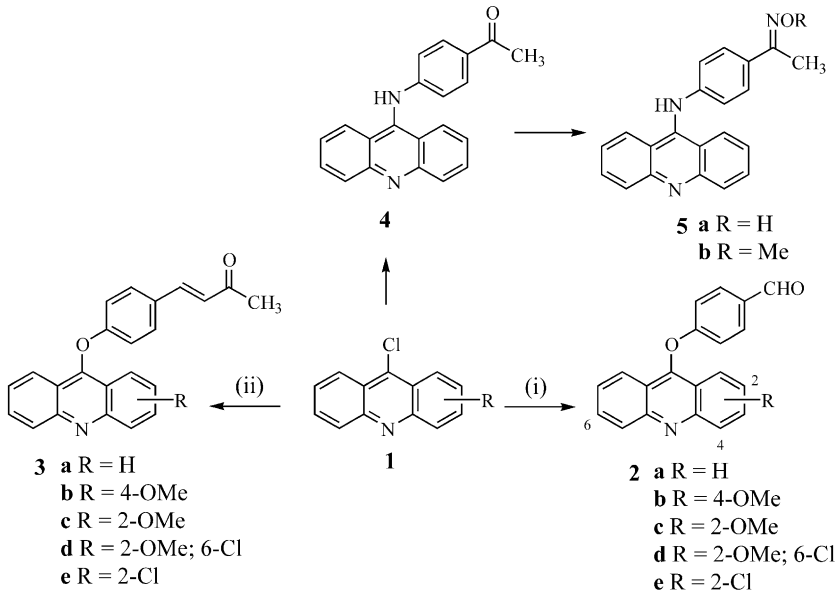
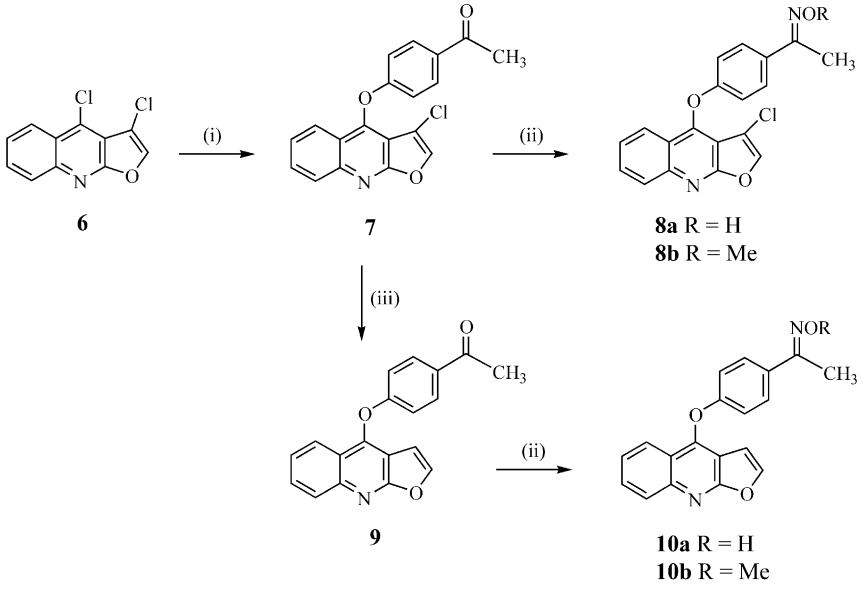



**Scheme 1.** Reagents: (i) 4-hydroxybenzaldehyde, $K_2CO_3$, THF in a sealed bomb; (ii) 4-hydroxybenzylideneacetone, $K_2CO_3$, acetone in a sealed bomb.




**Scheme 2.** Reagents: (i) 4-hydroxyacetophenone, $K_2CO_3$, THF in a sealed bomb; (ii) $NH_2OH$ HCl or 40% $NH_2OMe$ HCl, EtOH; (iii) Lindlar catalyst, $H_2$, MeOH–$CH_2Cl_2$ (1:1).

## Chemistry

9-Phenoxyacridines **2a**–**2e** and **3a**–**3e** were prepared as described in Scheme 1. Reaction of 9-chloro-4-methoxyacridine (**1b**, R = 4-OMe)[21] with 4-hydroxybenzaldehyde afforded 9 - (4 - formylphenoxy) - 4 - methoxyacridine (**2b**) in 57% yield. Accordingly, compounds **2c**–**2e** and **3c**–**3e** were prepared from the respective substituted 9-chloroacridine under the same reaction conditions. Although the synthesis and anti-inflammatory evaluation of **2a**, **3a**, **4**, **5a**, and **5b** had been described in our previously paper,[18] their anti-inflammatory activities are also included in this report for comparison.

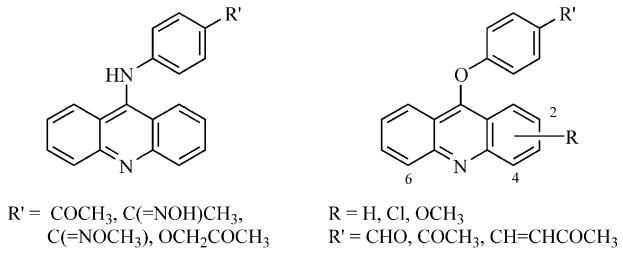



**Figure 1.**

Preparation of 4-phenoxyfuro[2,3-*b*]quinolines **7**–**10** is described in Scheme 2. The known 3,4-dichlorofuro[2,3-*b*]quinoline (**6**)[22] was treated with 4-hydroxyacetophenone to afford 1-[4-(3-chlorofuro[2,3-*b*]quinolin-4yloxy)phenyl]ethanone (**7**) which was then reacted with hydroxylamine or methylhydroxylamine to give (*E*) - 1 - [4 - (3 - chlorofuro[2,3 - *b*]quinolin4 - yloxy)-phenyl]ethanone oxime (**8a**) or its methyl derivative **8b**,

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

| Compd | Mast cell degranulation | Neutrophil degranulation | |
|---|---|---|---|
| | β-glucuronidase[c] | Lysozyme[d] | β-glucuronidase[d] |
| **2a** | 20.7±0.7 | >30.0 (44.8±3.1%)** | >30.0 (49.9±3.9%)** |
| **2b** | 6.1±0.2 | >30.0 (24.6±5.1%) | >30.0 (42.9±0.8%)** |
| **2c** | 5.9±1.1 | 18.3±2.9 | 9.2±0.4 |
| **2d** | 13.5±1.5 | >30.0 (3.5±3.1%) | >30.0 (−1.6±0.8%) |
| **2e** | 4.7±1.0 | >30.0 (6.9±4.0%) | >30.0 (23.6±5.8%)* |
| **3a** | >30.0 (7.7±5.6%) | >30.0 (10.3±11.3%) | >30.0 (32.4±1.5%)** |
| **3b** | >30.0 (33.4±4.5%)* | >30.0 (48.2±3.1%)** | 5.6±0.3 |
| **3c** | >30.0 (17.2±1.2%) | 15.2±2.0 | 4.3±0.8 |
| **3d** | >30.0 (13.4±1.7%) | >30.0 (25.1±6.2%) | >30.0 (33.3±4.8%)** |
| **3e** | >30.0 (48.4±2.9%)** | >30.0 (15.4±6.1%) | >30.0 (42.7±10.5%)** |
| **4** | >30.0 (34.7±4.2%)** | 23.7±0.6 | >30.0 (26.7±0.6%)* |
| **5a** | >30.0 (29.5±7.6%) | 8.2±0.2 | 4.4±0.1 |
| **5b** | 21.0±0.4 | >30.0 (15.4±11.8%) | >30.0 (46.9±0.4%)** |
| **7** | >30.0 (5.9±2.8%) | >30.0 (−0.9±1.1%) | >30.0 (9.6±2.9%) |
| **8a** | >30.0 (33.5±4.0%)* | >30.0 (17.6±0.9%) | >30.0 (32.6±3.2%)** |
| **8b** | >30.0 (−23.3±1.6%) | >30.0 (0.8±2.0%) | >30.0 (17.0±1.6%) |
| **9** | >30.0 (35.9±5.6%)* | >30.0 (9.9±1.4%) | >30.0 (25.8±8.4%)** |
| **10a** | >30.0 (1.5±8.2%) | >30.0 (0.1±3.4%) | >30.0 (18.4±2.2%) |
| **10b** | >30.0 (6.2±4.8%) | >30.0 (27.9±5.0%)* | 28.0±4.4 |
| 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]When 50% inhibition could not be reached at the highest concentration, the % of inhibition is given in parentheses.
[c]Induced by compound 48/80 (10 μg/mL).
[d]Induced by fMLP (1 μM)/cytochalasin B (5 μg/mL). *$p < 0.05$, **$p < 0.01$.

respectively. The configuration of the oxime moiety was determined by through-space nuclear Overhauser effect spectroscopy (NOESY) which revealed coupling connectivity to $CH_3$ protons. Hydrogenative reduction of **7** in the presence of Lindlar catalyst gave 1-[4-(furo[2,3-*b*]quinolin-4-yloxy)phenyl]ethanone (**9**) in 53% yield, which was then reacted with hydroxylamine or methylhydroxylamine to give 1-[4-(furo[2,3-*b*]quinolin-4-yloxy)phenyl]ethanone oxime (**10a**) or its methyl derivative **10b**, respectively.

## Results and Discussion

### 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, 9-(4-formylphenoxy)acridine (**2a–2e**) exhibited a significant inhibition of mast cell activation while its (*E*)-9-[4-(3-oxo-but-1-enyl)phenoxy]acridine counterparts (**3a–3e**) were ineffective. Compounds **2b–2e** ($IC_{50}$ values of 6.1, 5.9, 13.5 and 4.7 μM, respectively) were more potent while **2a** was equipotent to the reference inhibitor, mepacrine. These results also indicated that the substituent such as OMe and Cl at the acridine enhanced inhibitory activity (**2b–2e** vs **2a**). The result that compounds **3a–3e** exerted weak inhibition, suggesting that the distance between acridine and the carbonyl group also play an important role. Although the inhibitory activity of **4** and **9** was comparable, the acridine derivatives are more potent than their respective furo[2,3-*b*]quinoline counterparts (**5a** vs **10a**; **5b** vs **10b**). For the furo[2,3-*b*]quinoline-4-yloxy)phenyl]ethanone derivatives, substituent such as Cl at C-3 position decreased the inhibitory activity (**7** vs **9**; **8b** vs **10b**) with an exception of **8a**, which is more active than its 3-unsubstituted counterpart, **10a**.

### 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. 4-(2-Methoxyacridin-9-yloxy)-benzaldehyde (**2c**), with an $IC_{50}$ value of 18.3 and 9.2 μM against lysozyme and β-glucuronidase release, respectively, was more potent than its 4-methoxy isomer **2b** and was comparable to the calmodulin inhibitor, trifluoperazine which inhibits the degradation and superoxide anion generation in neutrophils.[23,24] The same order was observed for (*E*)-9-[4-(3-oxobut-1-enyl)phenoxy]acridines in which 2-methoxy derivative **3c** with an $IC_{50}$ value of 15.2 and 4.3 μM as compared to its 4-methoxy isomer **3b** with $IC_{50}$ values of near 30 and 5.6 μM against lysozyme and β-glucuronidase release, respectively. In analogy to the inhibition of mast cell degranulation, the acridine derivatives are more active inhibitors than their respective furo[2,3-*b*]quinoline counterparts (**4** vs **9**; **5a** vs **10a**). Compound **5a** showed the most potent activity with $IC_{50}$ values of 4–8 μM for the inhibition of neutrophil degranulation.

### TNF-α release

TNF-α, an early cytokine produced by activated macrophages, plays an essential role in pathological

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

| Compd | $IC_{50}$ (μM)[a,b] | |
|---|---|---|
| | RAW 264.7 | N9 |
| **2a** | >30.0 (17.2±3.3%)* | >3.0 (19.9±3.8%)* |
| **2b** | >10.0 (27.2±2.6%) | >10.0 (34.5±7.1%)** |
| **2c** | >10.0 (18.8±7.9%) | >10.0 (29.9±5.3%)* |
| **2d** | 29.1±1.9 | 9.3±2.8 |
| **2e** | >30.0 (40.5±3.4%)** | >10.0 (22.3±6.9%) |
| **3a** | >30.0 (−15.7±4.1%)** | 8.7±0.3 |
| **3b** | >10.0 (35.2±10.8%)* | >10.0 (44.4±1.4%)** |
| **3c** | >3.0 (33.1±14.2%)* | >3.0 (3.4±12.0%) |
| **3d** | >3.0 (39.0±9.2%)** | >3.0 (9.7±3.9%) |
| **3e** | >30.0 (37.8±7.9%)** | >10.0 (42.8±3.0%)** |
| **4** | >10.0 (47.2±3.1%) | 0.8±0.3 |
| **5a** | >10.0 (44.9±2.0%)** | >3.0 (40.1±3.1%)** |
| **5b** | >30.0 (7.2±0.8%) | >3.0 (39.3±1.2%)** |
| **7** | >30.0 (−46.5±11.9%)* | >30.0 (9.4±7.8%) |
| **8a** | >30.0 (2.4±3.4%) | >10.0 (−19.3±2.0%) |
| **8b** | >30.0 (27.3±2.5%) | >3.0 (−31.1±2.0%)** |
| **9** | >30.0 (−14.1±0.8%) | >3.0 (28.6±11.7%)* |
| **10a** | >30.0 (−11.0±4.3%) | >10.0 (47.7±1.3%)** |
| **10b** | >30.0 (11.1±4.6%) | >3.0 (14.0±2.5%) |
| Dexamethasone | 0.42±0.12 | 0.074±0.01 |

[a]Values are means±SE of at least three separate experiments.
[b]When 50% inhibition could not be reached at the highest concentration, the % of inhibition is given in parentheses. *$p$ <0.05, **$p$ <0.01.

inflammatory reactions. None of compounds **2**–**10** 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, compound **2d** showed weak potency in RAW 264.7 ($IC_{50}$ values of 29.1 μM), and **2d** and **3a** exhibited moderate potency in N9 cells ($IC_{50}$ values of 9.3 and 8.7 μM, respectively). The results also confirm the conclusion above that the acridine derivatives exhibited a better potency for the inhibition of TNF-α formation than their respective furo[2,3-*b*]quinoline counterparts (**4** vs **9**; **5a** vs **10a**; **5b** vs **10b**) (Table 2). Compound **4** was among the most potent inhibitor in N9 cells.

### Preliminary cytotoxic evaluation

Two furo[2,3-*b*]quinoline derivatives, **7** and **9**, 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 sulforhodamine B, a protein-binding dye. 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. The growth percentages over MCF7, NCI-H460, and SF-268 cells are: 91, 74, 96, respectively, for compound **7** and 86, 46, 66, respectively, for compound **9**. These results showed both compounds to be non-cytotoxic.

## Conclusion

These results indicated that the anti-inflammatory effects of acridine and 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.

## Experimental

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 apparatus; uncorrected. $^1H$ 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.

### General procedure for coupling of substituted-phenols with 9-chloroacridine or 4-chlorofuro[2,3-*b*]quinoline derivatives

A mixture of the substituted-phenols (3 mmol), $K_2CO_3$ (0.62 g, 4.5 mmol), and corresponding substituted-9-chloroacridine (1, 3 mmol) or 3,4-dichlorofuro[2,3-*b*]quinoline (6, 3 mmol) in THF (50 mL) or acetone (50 mL) was heated at 150 °C for 20 h in a steel bomb. It was cooled, filtered, concentrated, washed well with water, and purified by flash column chromatography (FC, silica gel).

**4-(4-Methoxyacridin - 9 - yloxy)benzaldehyde (2b).** This compound was obtained from 4-hydroxybenzaldehyde and 9-chloro-4-methoxyacridine, which was purified by FC (hexane/AcOEt 2:1) in 57% yield. Mp 194–196 °C. $^1H$ NMR (200 MHz, DMSO-$d_6$): 4.07 (s, 4-OMe), 7.06 (m, 2H-C(3′, 5′)), 7.24 (m, H-C(3)), 7.50 (m, 2 arom H), 7.62 (m, 1 arom H), 7.91 (m, 2H-C(2′, 6′) and 1 arom H), 8.29 (d, $J$=8.8, H-C(5)), 9.89 (s, CHO). $^{13}C$ NMR (50 MHz, DMSO-$d_6$): 55.78, 107.80, 112.88, 115.96 (2C), 118.27, 119.37, 120.33, 121.51, 127.23, 129.98, 130.63, 131.39, 132.22 (2C), 142.95, 148.57, 152.88, 155.42, 163.12, 191.39. Anal. calcd for $C_{21}H_{15}NO_3 \cdot 0.2H_2O$: C 75.76, H 4.54, N 4.21; found: C 75.90, H 4.65, N 4.19.

**4-(2 - Methoxyacridin - 9 - yloxy)benzaldehyde (2c).** This compound was obtained from 4-hydroxybenzaldehyde and 9-chloro-2-methoxyacridine, which was purified by FC (hexane/AcOEt 3:1) and recrystallized from EtOH in 23% yield. Mp 145–147 °C. $^1H$ NMR (200 MHz, DMSO-$d_6$): 3.78 (s, 2-OMe), 7.06 (m, 2H-C(3′, 5′), and 1 arom H), 7.58 (m, 2 arom H), 7.88 (m, 2H-C(2′, 6′) and 2 arom H), 8.20 (m, 2H-C(4, 5)), 9.90 (s, CHO). $^{13}C$ NMR (50 MHz, DMSO-$d_6$): 55.54, 96.93, 116.08 (2C), 119.33, 120.18, 121.22, 125.90, 126.94, 129.54, 129.72,

131.06, 131.42, 132.24 (2C), 147.11, 148.01, 151.30, 157.37, 162.83, 191.40. Anal. calcd for $C_{21}H_{15}NO_3 \cdot 0.1H_2O$: C 76.17, H 4.57, N 4.23; found: C 76.15, H 4.81, N 4.14.

**4-(6-Chloro - 2 - methoxyacridin - 9 - yloxy)benzaldehyde (2d).** This compound was obtained from 4-hydroxybenzaldehyde and 6,9-dichloro-2-methoxyacridine, which was purified by FC (hexane/AcOEt 3:1) in 54% yield. Mp 148–150 °C. $^1$H NMR (200 MHz, DMSO-$d_6$): 3.79 (s, 2-OMe), 7.11 (m, 2H-C(3′, 5′) and 1 arom H), 7.61 (m, 2 arom H), 7.92 (*m*, 2H-C(2′, 6′) and 1 arom H), 8.15 (d, $J$ = 9.4, H-C(4)), 8.26 (d, $J$ = 1.8, H-C(5)), 9.92 (s, CHO). $^{13}$C NMR (50 MHz, DMSO-$d_6$): 55.61, 97.08, 116.16 (2C), 117.96, 120.37, 123.51, 126.59, 127.21, 127.66, 131.30, 131.54, 132.24 (2C), 134.50, 147.84, 147.90, 151.78, 157.59, 162.70, 191.43. Anal. calcd for $C_{21}H_{14}ClNO_3 \cdot 0.1H_2O$: C 68.99, H 3.91, N 3.83; found: C 68.90, H 4.27, N 3.62.

**4-(2-Chloroacridin-9-yloxy)benzaldehyde (2e).** This compound was obtained from 4-hydroxybenzaldehyde and 2,9-dichloroacridine, which was purified by FC (hexane/AcOEt 3:1) in 53% yield. Mp 172–173 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): 7.12 (m, 2H-C(3′, 5′)), 7.65 (m, 1 arom H), 7.88–7.98 (m, 2H-C(2′, 6′) and 3 arom H), 8.01 (d, $J$ = 2.0, H-C(1)), 8.28 (m, 2H-C(4, 5)), 9.92 (s, CHO). $^{13}$C NMR (100 MHz, DMSO-$d_6$): 116.05 (2C), 119.36, 119.62, 119.98, 121.68, 127.51, 129.60, 131.36, 131.47, 131.53, 131.79, 131.88, 132.21 (2C), 148.04, 150.04, 152.59, 162.91, 191.38. Anal. calcd for $C_{20}H_{12}ClNO_2 \cdot 0.2H_2O$: C 71.20, H 3.65, N 4.15; found: C 71.10, H 3.92, N 3.87.

**4-[4-(4-Methoxyacridin - 9 - yloxy)phenyl]but - 3 - en - 2-one (3b).** This compound was obtained from 4-hydroxybenzylideneacetone and 9-chloro-4-methoxyacridine, which was purified by FC (hexane/AcOEt 1:1) and recrystallized from EtOH in 30% yield. Mp 188–190 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): 2.28 (s, COMe), 4.05 (s, 4-OMe), 6.60 (d, $J$ = 16.4, H-C(3″)), 6.81 (m, 2H-C(2′, 6′)), 7.25 (m, 3 arom H), 7.53 (m, 2H-C(3′, 5′) and H-C(4″)), 7.69 (m, 1 arom H), 7.81 (dd, $J$ = 8.4, 1.2, H-C(8)), 7.94 (dd, $J$ = 8.8, 1.2, H-C(1)), 8.21 (dd, $J$ = 8.0, 1.2, H-C(5)). $^{13}$C NMR (100 MHz, DMSO-$d_6$): 27.12, 56.24, 112.34, 115.86 (2C), 117.15, 118.32, 120.57, 121.13, 121.25, 124.09, 125.35, 125.74, 130.40 (2C), 131.87, 133.10, 140.68, 143.58, 147.85, 159.90, 176.60, 197.82. Anal. calcd for $C_{24}H_{19}NO_3 \cdot 0.3H_2O$: C 76.90, H 5.11, N 3.74; found: C 76.50, H 5.44, N 3.54.

**4-[4-(2-Methoxyacridin - 9 - yloxy)phenyl]but - 3 - en-2-one (3c).** This compound was obtained from 4-hydroxybenzylideneacetone and 9-chloro-2-methoxyacridine, which was purified by FC (hexane/AcOEt 2:1) in 36% yield. Mp 160–161 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): 2.31 (s, COMe), 3.80 (s, 4-OMe), 6.69 (d, $J$ = 16.4, H-C(3″)), 6.96 (m, 2H-C(2′, 6′)), 7.17 (d, $J$ = 2.8, H-C(1)), 7.59 (m, 2 arom H and H-C(4″)), 7.69 (*m*, 2H-C(3′, 5′)), 7.82 (m, 1 arom H), 7.95 (dd, $J$ = 8.4, 1.2, H-C(8)), 8.17 (d, $J$ = 9.6, H-C(4)), 8.21 (d, $J$ = 8.8, 1.2, H-C(5)). $^{13}$C NMR (100 MHz, DMSO-$d_6$): 27.18, 55.52, 97.13, 116.03 (2C), 119.55, 120.35, 121.45, 125.85, 126.32, 126.77, 129.26, 129.53, 129.70, 130.64 (2C), 131.41, 142.38, 147.13, 148.06, 151.84, 157.24, 160.15, 197.98. Anal. calcd for $C_{24}H_{19}NO_3$: C 78.03, H 5.18, N 3.79; found: C 78.20, H 5.18, N 3.63.

**4-[4-(6-Chloro - 2 - methoxyacridin - 9 - yloxy)phenyl]but-3-en-2-one (3d).** This compound was obtained from 4-hydroxybenzylideneacetone and 6,9-dichloro-2-methoxyacridine, which was purified by FC (hexane/AcOEt 3:1) and recrystallized from EtOH in 68% yield. Mp 183–185 °C. $^1$H NMR (200 MHz, DMSO-$d_6$): 2.29 (s, COMe), 3.78 (s, 4-OMe), 6.68 (d, $J$ = 16.4, H-C(3″)), 6.96 (m, 2H-C(2′, 6′)), 7.13 (d, $J$ = 2.4, H-C(1)), 7.54–7.71 (m, 2H-C(3′, 5′), H-C(″) and 2 arom H), 7.95 (d, $J$ = 9.2, H-C(8)), 8.13 (d, $J$ = 9.6, H-C(4)), 8.24 (d, $J$ = 1.8, H-C(5)). $^{13}$C NMR (50 MHz, $CDCl_3$): 27.52, 55.58, 97.29, 116.07 (2C), 118.53, 120.90, 123.28, 126.60, 127.57, 128.21, 129.26, 130.27 (2C), 131.34, 135.54, 142.22, 148.50, 152.67, 157.74, 160.47, 198.16. Anal. calcd for $C_{24}H_{18}ClNO_3 \cdot 0.3H_2O$: C 70.43, H 4.58, N 3.42; found: C 70.48, H 4.60, N 3.18.

**4-[4-(2-Chloroacridin-9-yloxy)phenyl]but-3-en-2-one (3e).** This compound was obtained from 4-hydroxybenzylideneacetone and 2,9-dichloro-2-methoxyacridine, which was purified by FC (hexane/AcOEt 3:1) in 54% yield. Mp 180–182 °C. $^1$H NMR (200 MHz, $CDCl_3$): 2.36 (s, COMe), 6.61 (d, $J$ = 16.2, H-C(3″)), 6.87 (m, 2H-C(2′, 6′)), 7.42–7.54 (m, 2H-C(3′, 5′), H-C(4″) and 1 arom H), 7.71 (dd, $J$ = 9.4, 2.4, H-C(3)), 7.81 (m, 1 arom H), 8.03 (m, 2 arom H), 8.25 (m, 2H-C(4, 5)). $^{13}$C NMR (100 MHz, DMSO-$d_6$): 27.52, 116.04 (2C), 120.68, 122.28, 126.28, 126.80, 129.36, 129.85, 130.30 (2C), 130.96, 131.47, 132.06, 132.29, 142.23, 148.60, 150.50, 153.61, 160.73, 198.19. Anal. calcd for $C_{23}H_{16}ClNO_2 \cdot 0.1H_2O$: C 73.54, H 4.30, N 3.73; found: C 73.32, H 4.38, N 3.69.

**1-[4-(3-Chlorofuro[2,3 - *b*]quinolin - 4 - yloxy)phenyl]ethanone (7).** This compound was obtained from 4-hydroxyacetophenoe and **6**, which was purified by FC (hexane/AcOEt 4:1) in 66% yield. Mp 230–232 °C. $^1$H NMR (400 Hz, $CDCl_3$): 2.57 (*s*, COMe), 6.94 (m, 2H-C(2′, 6′)), 7.53 (ddd, $J$ = 8.8, 6.8, 1.6, H-C(6)), 7.75 (s, H-C(2)), 7.80 (ddd, $J$ = 8.8, 6.8, 1.6, H-C(7)), 7.94 (m, 2H-C(3′, 5′)), 8.06 (ddd, $J$ = 8.8, 1.6, 0.8, H-C(8)), 8.18 (ddd, $J$ = 8.8, 1.6, 0.8, H-C(5)). $^{13}$C NMR (100 MHz, $CDCl_3$): 26.40, 109.91, 110.18, 115.42 (2C), 121.06, 121.91, 125.84, 128.75, 130.71, 130.85 (2C), 132.30, 142.41, 146.76, 151.16, 161.18, 162.63, 196.47. Anal. calcd for $C_{19}H_{12}ClNO_3$: C 67.56, H 3.58, N 4.15; found: C 67.48, H 3.58, N 4.12.

**(*E*)-1 - [4 - (3 - Chlorofuro[2,3 - *b*]quinolin - 4 - yloxy)phenyl]-ethanone oxime (8a).** To a suspension of **7** (50 mg, 0.15 mmol) in ethanol (10 mL) was added $NH_2OH \cdot HCl$ (21 mg, 0.3 mmol). The reaction mixture was stirred at room temperature for 30 min (TLC monitoring), then concentrated in vacuo to give a solid which was washed by $H_2O$ (20 mL) and purified by FC ($CH_2Cl_2$–AcOEt 20:1) to give a white solid (48 mg, 90%). Mp 206–208 °C. $^1$H NMR (200 MHz, DMSO-$d_6$): 2.12 (s, Me), 6.99 (m, 2H-C(2′, 6′)), 7.61 (m, 3H-C(3′, 5′, 6)), 7.88

(ddd, $J=8.6$, 6.8, 1.2, H-C(7)), 8.02 (d, $J=8.6$, H-C(8)), 8.13 (d, $J=8.4$, H-C(5)), 8.55 (s, H-C(2)), 11.14 (s, NOH). $^{13}$C NMR (50 MHz, DMSO-$d_6$): 11.44, 108.57, 110.22, 115.28 (2C), 120.68, 121.80, 125.94, 127.37 (2C), 128.36, 130.72, 131.86, 144.15, 146.11, 150.78, 152.09, 159.28, 160.86. Anal. calcd for $C_{19}H_{13}ClN_2O_3\cdot0.1H_2O$: C 64.36, H 3.75, N 7.90; found: C 64.24, H 3.82, N 7.66.

**(*E*)-1-[4-(3-Chlorofuro[2,3-*b*]quinolin-4-yloxy)phenyl]-ethanone *O*-methyloxime (8b).** To a suspension of **7** (50 mg, 0.15 mmol) in ethanol (10 mL) was added 40% $NH_2OMe\cdot HCl$ aqueous (63 mg, 0.3 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 pale-yellow solid (50 mg, 90%). Mp 140–141 °C. $^1$H NMR (200 MHz, $CDCl_3$): 2.19 (s, Me), 3.97 (s, OMe), 6.88 (m, 2H-C(2′, 6′)), 7.50 (m, H-C(6)), 7.60 (m, 2H-C(3′, 5′)), 7.73 (s, H-C(2)), 7.78 (m, H-C(7)), 8.08 (d, $J=8.4$, H-C(8)), 8.17 (d, $J=8.6$, H-C(5)). $^{13}$C NMR (50 MHz, $CDCl_3$): 12.56, 61.91, 110.16, 110.34, 115.52 (2C), 121.37, 122.31, 125.62, 127.76 (2C), 128.70, 130.61, 131.54, 142.19, 146.80, 151.92, 153.78, 159.99, 161.32. Anal. calcd for $C_{20}H_{15}ClN_2O_3\cdot0.1H_2O$: C 65.17, H 4.15, N 7.59; found: C 65.13, H 4.18, N 7.31.

**1-[4-(Furo[2,3-*b*]quinolin-4-yloxy)phenyl]ethanone (9).** A solution of 1-[4-(3-chlorofuro[2,3-*b*]quinolin-4-yloxy)-phenyl]ethanone (**7**, 0.34 g, 1 mmol) in MeOH–$CH_2Cl_2$ (1/1, 100 mL) was hydrogenated for 3 h (TLC monitoring) under $H_2$ with Lindlar catalyst (0.34 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 **9** (0.16 g, 53%). Mp 195–196 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): 2.59 (s, COMe), 6.21 (d, $J=2.8$, H-C(3)), 7.32 (m, 2H-C(2′, 6′)), 7.62 (ddd, $J=8.4$, 6.8, 1.2, H-C(6)), 7.85 (ddd, $J=8.4$, 6.8, 1.2, H-C(7)), 8.07 (*m*, 4H-C(3′, 5′, 2, 8)), 8.23 (ddd, $J=8.4$, 1.6, 0.4, H-C(5)). $^{13}$C NMR (100 MHz, DMSO-$d_6$): 26.65, 103.29, 108.70, 118.24 (2C), 119.14, 121.69, 125.13, 128.02, 130.05, 130.84 (2C), 133.22, 145.51, 146.97, 151.49, 159.88, 162.90, 196.56. Anal. calcd for $C_{19}H_{13}NO_3\cdot0.1H_2O$: C 74.80, H 4.36, N 4.59; found: C 74.83, H 4.30, N 4.53.

**(*E*)-1-[4-(Furo[2,3-*b*]quinolin-4-yloxy)phenyl]ethanone oxime (10a).** From **9** and $NH_2OH\cdot HCl$ as described for **8a**: 91% yield. Mp 195–197 °C. $^1$H NMR (200 MHz, DMSO-$d_6$): 2.19 (s, Me), 5.91 (d, $J=2.8$, H-C(3)), 7.29 (m, 2H-C(2′, 6′)), 7.62 (m, H-C(6)), 7.77 (m, 2H-C(3′, 5′)), 7.84 (ddd, $J=8.4$, 6.8, 1.4, H-C(7)), 7.99 (d, $J=2.6$, H-C(2)), 8.06 (d, $J=8.4$, H-C(8)), 8.32 (d, $J=8.4$, H-C(5)). $^{13}$C NMR (50 MHz, DMSO-$d_6$): 11.48, 103.41, 107.28, 118.84, 119.19 (2C), 121.88, 124.85, 127.45 (2C), 127.87, 130.01, 133.86, 145.40, 146.21, 152.09, 152.83, 156.26, 62.99. Anal. calcd for $C_{19}H_{14}N_2O_3\cdot0.4H_2O$: C 70.10, H 4.58, N 8.60; found: C 70.24, H 4.73, N 8.41.

**(*E*)-1-[4-(Furo[2,3-*b*]quinolin-4-yloxy-phenyl]ethanone *O*-methyloxime (10b).** From **9** and 40% $NH_2OMe\cdot HCl$ aqueous as described for **8b**: 75% yield. Mp 149–151 °C. $^1$H NMR (200 MHz, $CDCl_3$): 2.26 (s, Me), 4.02 (s, OMe), 5.86 (d, $J=2.8$, H-C(3)), 7.16 (m, 2H-C(2′, 6′)), 7.49 (d, $J=2.6$, H-C(2)), 7.55 (ddd, $J=8.4$, 6.8, 1.0, H-C(6)), 7.74 (m, 2H-C(3′, 5′)), 7.78 (ddd, $J=8.4$, 6.8, 1.0, H-C(7)), 8.16 (d, $J=8.4$, H-C(8)), 8.38 (d, $J=8.4$, H-C(5)). $^{13}$C NMR (50 MHz, $CDCl_3$): 12.56, 62.04, 103.95, 107.28, 119.42 (3C), 122.22, 124.71, 127.84 (2C), 127.88, 130.13, 133.59, 144.57, 145.65, 153.53, 153.92, 156.88, 163.22. Anal. calcd for $C_{20}H_{16}N_2O_3\cdot0.1H_2O$: C 71.89, H 4.89, N 8.38; found: C 71.87, H 5.03, N 8.14.

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