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Synthesis and biological evaluation of conformationally constrained analogs of the antitumor agents XK469 and SH80. Part 5

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Abstract—Conformational restriction of bioactive molecules offers the possibility of generating structures of increased potency. To this end, a synthesis has been achieved of (*R*,*S*)-2-[(8-chlorobenzofurano[2,3-*b*]quinolinyl)oxy]propionic acid (**12a**), a highly rigidified, polycyclic analog of 2-{4-[(7-chloro-2-quinoxalinyl)oxy]phenoxy}propionic acid (**2a**, XK469). Efforts to effect the same synthesis of the corresponding 8-bromo-derivative led to a mixture of intermediate, 8-chloro (**9a**), and 8-bromo-2-hydroxybenzofurano[2,3-*b*]quinoline (**9b**), generated by halogen-exchange, via an aromatic $S_{RN}1(A_{RN}1)$ reaction of precursor, **8b**, with pyridine hydrochloride. The presumption that conformational restriction of **1b**–**12a** might enhance the antitumor potency of the latter has not been sustained. In fact, **12a** proved to be significantly less active than **1b**. However, it is apparent that virtually all of the spatial and steric properties of **12a**, necessary for improved activity, including the disposition of the 2-oxypropionic acid side chain remain to be identified.
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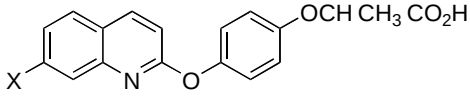
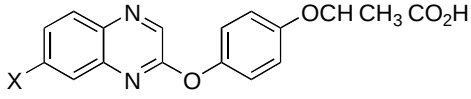
1. Introduction

Our recent studies have shown 2-{4-[(7-bromo-2-quinolinyl)oxy]phenoxy}propionic acid (Fig. 1, **1a**, SH80) to be a highly and broadly active antitumor agent.[1–3] However, the mechanism of action of this agent, as is the case with the closely related 2-{4-[(7-chloro-2-quinoxalinyl)oxy]phenoxy}propionic acid (**2a**, XK469), remains unknown, though several disparate mechanisms of anticancer action have been proposed for the latter.[4a–i]

Lacking knowledge of a molecular target, we turned to the classical pharmacophore approach, which is exemplified[5] in an elegant study leading to the discovery of the novel cholesterol-lowering agent, 'ezetimibe'. In the latter effort, even the existence of the target itself was unknown at the inception of the research. However, as the discovery process continued, the nature of the target was inferred from a consistent pattern of structure–activity relationships (SARs).



1a. X = Br
b. X = Cl
c. X = F
d. X = CH_3O



2a. X = Cl
b. X = Br
c. X = F
d. X = I
e. X = CH_3O

Figure 1.

The 7-halogen derivatives of **1**[1] manifest the following order of antitumor activity in mice: (a) Br > (b) Cl > (c) F, whereas in **2**[6] (a) Cl ≈ (b) Br ≈ (c) F > (d) I. Interestingly, the activities of the former are greater

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than, or at least comparable, to those of the corresponding quinoxaline analogs (Fig. 1: **2a**–**e**). It is also noteworthy that the 7-methoxy analogs of both **1** and **2** exhibit levels of antitumor activity comparable to those of the corresponding halogen derivatives.

The criteria for maximum antitumor activity of both **1** and **2** also include linkage of the 7-halo(methoxy)-2-quinolinyl, or -2-quinoxalinyl-moiety, via a 1,4-hydroquinone bridge, to the 2-carbon atom of an intact (*R*)-propionic acid moiety.

Conformational restriction of bioactive molecules affords an opportunity of gaining valuable insights in to both topographical and chemical features of small molecule-binding sites. Such restriction also offers the possibility of generating structures of increased potency, which may result from a set of more favorable, hydrogen bonding, and hydrophobic interactions with the putative receptor, together with a reduction in the entropic penalty of the precursory flexible structure.[7]

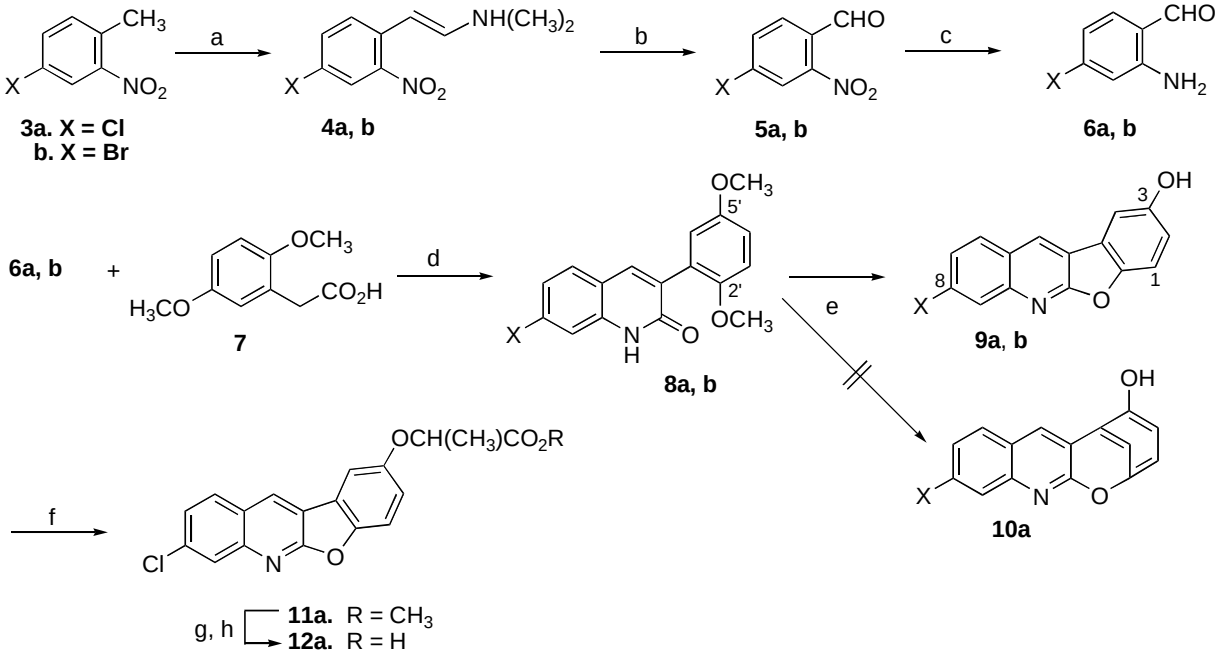
These considerations prompted efforts to introduce restrictions in the mobility of the 2-oxyphenoxypropionic acid moiety of **1a** and **1b** by conversion of the latter to a series of polycyclic derivatives.

2. Results and discussion

2.1. Synthesis

Our approach to the highly rigidified polycyclic analogs of **1a** and **1b**, 8-chloro- and 8-bromo-3-hydroxybenzofuro[2,3-*b*]quinolines (Scheme 1, **9a** and **9b**, respectively), proceeded from the 4-halo-2-nitrotoluenes, **3a** and **3b**. The latter were converted to the enamines, **4a** and **b**, on treatment with *N*,*N*-dimethylformamide dimethyl acetal. Periodate oxidation of the enamines to the corresponding 4-halo-2-nitrobenzaldehydes, **5a** and **5b**, was effected according to procedures described by both Coe[8a] and Caron et al.[8b] Reduction of **5a** and **5b** to amino derivatives, **6a** and **6b**, was readily achieved with $FeSO_4$[9] and NH_3 in aqueous CH_3OH. Friedländer reactions,[10] between (available) 2,5-dimethoxyphenylacetic acid (**7**) and **6a** and **6b**, each in acetic anhydride, containing triethylamine, and in accord with the modified conditions of Bu et al.[11] provided the 7-halo-3-(2,5-dimethoxyphenyl)-2-quinolinols **8a** and **8b**. Fusion of a mixture of **8a** and anhydrous pyridine hydrochloride,[11] followed by a period of reflux for ca. 1.5 h, provided 8-chloro-2-hydroxybenzofuro[2,3-*b*]quinoline (**9a**) in 98% yield. By contrast, the same reaction with **8b** led to an equimolar mixture of the chloro- and bromo-derivatives, **9a** and **9b**, as determined from ^{1}H NMR, ^{13}C NMR, and mass spectra.

The partial exchange of the 7-bromo substituent by chlorine, in the process of cyclization of **8b** in refluxing pyridine hydrochloride leading to **9a**, may be attributed to the occurrence of an $S_{RN}1$ reaction. Indeed, a radical chain mechanism of aromatic nucleophilic substitution by halogen, first recorded by Bunnett,[12] is now well established. The observed order of reactivity of the nucleofuge in these transformations is ArI > ArBr > ArCl > ArF, with the nucleophile, invariably, occupying the position vacated by the leaving group. Of additional relevance is the fact that aromatic $S_{RN}1$ ($A_{RN}1$) reactions occur as well with halogen-substituted heterocyclic structures, including pyridines, quinolines, and aromatic polynuclear systems.



Scheme 1. Reagents and conditions: (a) $(CH_3)_2N(OCH_3)_2$/DMF/120 °C, 18 h; (b) $NaIO_4$/THF-H_2O/rt, 2 h; (c) $FeSO_4/NH_3/CH_3OH$–H_2O/80 °C, 1 h; (d) Ac_2O/Et_3N/100 °C, 4 days; (e) pyridine·HCl/reflux, 1.5 h; (f) $CH_3CHBrCO_2CH_3/K_2CO_3/CH_3CN$/reflux, 18 h; (g) NaOH/THF–H_2O/rt, 18 h; (h) aqueous HCl.

A model of **9a**, as depicted in Figure 2, clearly indicates a structure with planar core geometry. Were ring closure to involve, instead, the distal 5′-methoxy substituent of **8a**, the reaction would lead to the non-planar pyran structure (Fig. 2, **10a**). Clearly, the latter would be energetically much less favorable due to a large increase in steric strain in the formation of bonds that would be forced to assume abnormal angles in order to accommodate closure to the non-planar pyran ring of **12a**.

A 500 MHz NMR spectrum of the putative product (**9a**), wherein aromatic ring proton #5 (Fig. 2) was irradiated concurrently at its exact frequency, produced uncoupling of all aromatic protons, as would be predicted by a Nuclear Overhauser Effect for the planar structure. Etherification of **9a** with (*R*,*S*)-methyl 2-bromopropionate, followed by saponification of the intermediate ester (**11a**), yielded (*R*,*S*)-2-[(8-chlorobenzofurano[2,3-*b*]quinolinyl)oxy]propionic acid (**12a**).

2.2. Cytotoxic activity

All analogs were initially evaluated in our in vitro disk diffusion soft agar colony formation assay, as previously described,[1–3] to determine cytotoxicity against mouse leukemia (L1210) cells, mouse and human solid tumors [Pancreatic Adenocarcinoma 03 (Panc 03), Colon adenocarcinoma 38 (Colon 38), and/or multi-drug-resistant mammary-17/adriamycin-resistant and human colon H15/MDR], in addition to normal-like fibroblast cells. As (*R*,*S*)-**12a** manifested sufficient in vitro cytotoxicity (see Table 1), in vivo studies were then conducted, as previously described.[1,13–19] Tumor selection was based on our prior biological observations and findings that **2a** and the 7-bromoquinoline derivative (**1a**) both exhibited broad antitumor efficacy against several mouse tumor models,[13–17] including mammary adenocarcinoma 16/C, a metastatic, mouse tumor model[18,19] (see Table 2). Although a higher IV total dose was administered, the restricted conformation of **1b**, that is, **12a**, proved to be inactive (63.5% T/C, 0.6 log kill; Table 2). Thus, it is clear that the conformational restriction of **1b** to **12a** generated a product of dramatically reduced antitumor efficacy and potency.

3. Conclusion

Our presumption that conformational restriction of **1b** to **12a** would enhance the antitumor potency of the latter has not been sustained. Indeed, to the contrary, **12a** proved to be significantly less active than **1b**.

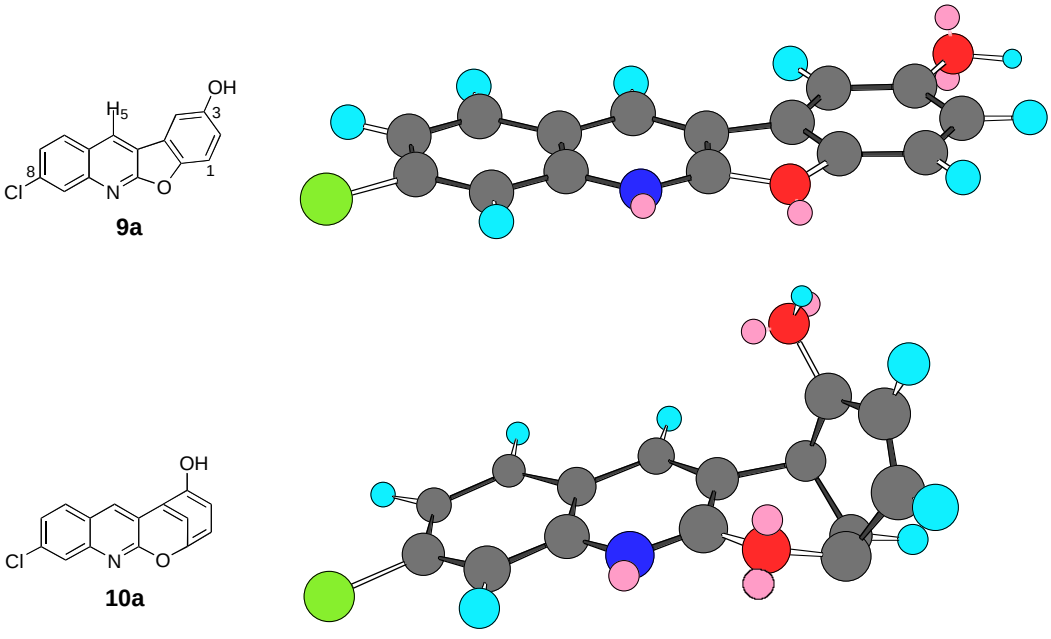


Figure 2.

Table 1. In vitro cytotoxicity of selected racemic analogs of XK469 against leukemic cells, solid tumor cells, and normal cells in the disk-diffusion-soft-agar-colony formation-assay[a]

Compound	μg/disk	Mouse leukemia L1210	Mouse tumors			Human tumors colon H15/MDR	Normal cells fibroblasts
			Colon 38	Panc 03	Mam 17/Adr		
(*R*,*S*)-**1b**	480	0–700		>900	600–800	0–400	0–700
(*R*,*S*)-**2a**	270	0–600	>800		>850	0–500	500–600
(*R*,*S*)-**12a**	480	0–500		500–600	500–600	0–500	0–350

[a] Zone units recorded: 200 U = 6.5 mm.

Table 2. Intravenous treatment of mammary adenocarcinoma 16/C with selected analogs[a]

Compound	No. of iv injections	Total dose (mg/kg)	Drug deaths	% Body wt loss at Nadir	T/C (%)	Log_{10} tumor cell kill[b]	Cures[c]	Activity rating
(*R*,*S*)-**1b**	6	300	0/5	−13.1	0	3.0	1/5	++++
(*R*,*S*)-**12a**	9	698.8	0/5	−3.5	63.5	0.6	0/5	–

A T/C = 0% means no tumor growth (high antitumor activity).

A T/C = 100% means no antitumor activity, that is, the treated and control tumors grew equally.

[a] These agents were soluble in aqueous formulation (0.5% $NaHCO_3$ + PBS; pH 7.4) and injected intravenously (iv) beginning one day after tumor implantation; early stage disease for the rapidly growing Mam 16/C (1.0–1.2 day doubling). Two or three dosages were tested, with the highest nontoxic dosage shown. Treatment was stopped when toxicity or significant weight loss occurred, or the drug supply was exhausted. A dose-escalation schedule[13] was administered for **12a**.

[b] The log_{10} kill values were based on tumors that grew (cures were excluded from the calculation).

[c] All cured mice were re-implanted with 30 mg fragments of Mam 16/C after day 150. These rechallenged mice grew tumor to 1500 mg in the expected fashion, with the expected Td, indicating that immunologic factors were not involved in the original cures.

On one hand, the disparity in molecular weights (~2.0 amu) between **1b** and **12a** is negligible, and each presents an identical number of hydrogen bond acceptors (5), and donors (1), though a comparison of physical parameters, such as log *P* and log *D*, remains to be determined.

It is plausible that the activities of **1b** and **12a** may be attributed to intrinsic differences in such critical pharmacological properties as absorption, distribution, metabolism and excretion (ADME). A comparison of the latter properties along with a comparison of log *P* and log *D*, both of which were beyond the scope of the present investigation, is currently the subject of an ongoing investigation. The latter also includes a quantitative structure–activity relationship (CoMFA) study, that is, currently, in progress.

4. Experimental

All commercially available solvents and reagents were used without further purification. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were measured on a Perkin-Elmer 1330 spectrometer in KBr pellets. Nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were recorded at room temperature, and referenced to a residual solvent signal, on a Varian Mercury 400 or 500 instrument in the Department of Chemistry, Wayne State University, Detroit, MI. Chemical shifts are reported in parts per million downfield from tetramethylsilane (TMS). The splitting pattern abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; b, broad; m, unresolved multiplet. Mass spectra were recorded on instruments in the Department of Chemistry, Wayne State University. Flash column chromatography was carried out with silica gel 200–400 mesh, 60 Å (Aldrich), and the crude product was introduced onto the column as a $CHCl_3$ solution. Thin-layer chromatography was performed on Whatman PE SIL G/UV (250 μm) plates. Compounds were visualized by use of 254 or 366 nm light and I_2 vapor. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ, and are within ± 0.3% of the calculated values.

4.1. 7-Chloro-3-(2,5-dimethoxyphenyl)-2-quinolinol (8a)

A mixture of **6a**[8] (1.80 g, 11.6 mmol), **7** (4.55 g, 23.2 mmol), Et_3N (6 mL), and Ac_2O (60 mL) was heated at 100 °C for 4 days. After cooling, it was concentrated to give a yellow-brown solid to which water (100 mL) and AcOEt (750 mL) were added. The mixture was heated until the solid dissolved and $NaHCO_3$ added until pH 8. The layers were separated and the AcOEt layer was washed several times with dilute $NaHCO_3$ (25 mL) and the combined $NaHCO_3$ layers were extracted with AcOEt (100 mL). Unreacted 2,5-dimethoxyphenylacetic acid was recovered from the combined $NaHCO_3$ layers on acidification with concentrated HCl to pH 3. The combined AcOEt layers were washed with saturated NaCl (25 mL), dried with anhydrous $MgSO_4$, and recrystallized from AcOEt–$CHCl_3$ to give **8a** as pale yellow crystals (1.38 g, 38% yield). Mp 253–254 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.91 (br s, 1H), 7.85 (s, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 1.6 Hz, 1H), 7.20 (dd, J = 8.4, 1.6 Hz, 1H), 6.98 (d, J = 9.2 Hz, 1H), 6.90 (dd, J = 9.2, 3.2 Hz, 1H), 6.86 (d, J = 3.2 Hz, 1H), 3.70 (s, 3H), 3.65 (s, 3H).

4.2. 7-Bromo-3-(2,5-dimethoxyphenyl)-2-quinolinol (8b)

A mixture of **6b**[8] (2.46 g, 12.3 mmol), **7** (4.83 g, 24.5 mmol), Et_3N (6 mL), and Ac_2O (60 mL) was heated at 100 °C for 4 days. It was isolated as in Section 4.1 to give **8b** as off-white crystals (2.45 g, 55%). Mp 252–253 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.87 (br s, 1H), 7.85 (s, 1H), 7.61 (d, J = 8.0 Hz, lH),7.47(d, J = 1.6 Hz, 1H), 7.32 (dd, J = 8.0, 1.6 Hz, 1H), 6.98 (d, J = 9.2 Hz, 1H), 6.90 (dd, J = 9.2, 3.2 Hz, 1H), 6.85 (d, J = 3.2 Hz, 1H), 3.70 (s, 3H), 3.65 (s, 3H).

4.3. 8-Chloro-2-hydroxybenzofuro[2,3-*b*]quinoline (9a)

A mixture of **8a** (1.37 g, 4.39 mmol), anhydrous pyridine hydrochloride (14 g) was heated at gentle reflux for 1.5 h until all the solid had dissolved. After cooling, water was added and after the solid had broken up it was filtered, washed with water, and dried to give **9a** as a yellow-brown solid (1.15 g, 98%). A sample was recrystallized from CH_3OH to give tan crystals. Mp 312–314 °C (dec); ^1H NMR (400 MHz, DMSO-d_6) δ 9.66 (s, 1H),

9.04 (s, 1H), 8.12 (d, $J = 9.2$ Hz, 1H), 8.01 (d, $J = 1.6$ Hz, 1H), 7.58 (dd, $J = 8.8$, 2.0 Hz, 1H), 7.54–7.50 (m, 2H), 7.03 (dd, $J = 8.8$, 2.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.6, 154.8, 149.3, 146.2, 134.8, 130.9, 130.5, 127.0, 126.1, 124.8, 122.7, 118.6, 118.3, 112.8, 108.2. IR (KBr) 3160 (OH) cm^{-1}. ESI-MS m/z 270 $(M+l)^+$.

4.4. Mixture of 8-chloro-(8-bromo-)2-hydroxybenzofuro[2,3-*b*]quinoline (9a and 9b)

A mixture of **8b** (1.01 g, 2.80 mmol), anhydrous pyridine hydrochloride (10 g) was heated at gentle reflux for 1.5 h until all the solid had dissolved. It was isolated as in Section 4.3 to give a yellow-brown solid (0.83 g). This was determined to be an equal mix of the 8-bromo **9b** and 8-chloro **9a** isomers as determined by NMR and MS. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.66 (s, Br + Cl), 8.90 + 8.89 (s, Br + Cl), 8.07 (d, $J = 1.6$ Hz, Br), 8.02 (d, $J = 8.0$ Hz, Cl), 7.95 (d, $J = 8.8$ Hz, Br), 7.90 (d, $J = 1.6$ Hz, Cl), 7.59 (dd, $J = 8.8$, 1.6 Hz, Br + Cl), 7.51–7.43 (m, Br + Cl), 7.00 (dd, $J = 8.8$, 2.4 Hz, Br + Cl). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.6 (Br), 163.5 (Cl), 154.7 (Br + Cl), 149.3 (Br + Cl), 146.4 (Br), 146.2 (Cl), 134.8 (Br + Cl), 130.9 (Br + Cl), 130.5 (Br + Cl), 130.2 (Br), 128.6 (Br), 127.0 (Cl), 126.1 (Cl), 125.0 (Br), 124.8 (Cl), 123.5 (Br), 122.7 (Cl), 118.7 (Br), 118.6 (Cl), 118.3 (Br + Cl), 112.8 (Br + Cl), 108.2 (Br + Cl). ESI-MS m/z 313 (^{79}Br, M)$^+$, 314 (^{79}Br, M+l)$^+$ 316 (^{81}Br, M+1)$^+$, 270 (^{35}Cl, M+1)$^+$, 272 (^{37}Cl, M+1)$^+$.

4.5. Methyl 2-[(8-chloro-2-benzofuro[2,3-*b*]quinolinyl)oxy]propionate (11a)

A mixture of **9a** (0.44 g, 1.6 mmol), methyl 2-bromopropionate (0.27 mL, 0.40 g, 2.4 mmol), anhydrous K_2CO_3 (0.28 g, 2.0 mmol), and CH_3CN (15 mL) was refluxed together overnight. The mixture was filtered hot, washed with hot $CHCl_3$, and the filtrate was purified by filtering through silica gel, washing with 2:1 $CHCl_3$–AcOEt. After concentrating, this mixture was recrystallized from EtOH to give **11a** as tan-yellow crystals (0.51 g, 88% yield). Mp 186–187 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.02 (d, $J = 1.6$ Hz, 1H), 7.81 (d, $J = 9.2$ Hz, 1H), 7.44 (d, $J = 8.8$ Hz, 1H), 7.41 (dd, $J = 8.8$, 1.6 Hz, 1H), 7.39 (d, $J = 2.4$ Hz, 1H), 7.09 (dd, $J = 8.8$, 2.4 Hz, 1H), 4.84 (q, $J = 6.4$ Hz, 1H), 3.79 (s, 3H), 1.68 (d, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 163.6, 154.4, 151.1, 146.5, 135.7, 129.4, 129.0, 127.6, 126.3, 124.4, 122.6, 118.4, 118.2, 113.0, 107.7, 74.0, 52.7, 18.9. IR (KBr) 1765 (C=O) cm^1. ESI-MS m/z 356 $(M+l)^+$. Anal. ($C_{19}H_{14}NO_4C1$): C, 64.14; H, 3.97; N, 3.94. Found: C, 64.12; H, 3.78; N, 3.77.

4.6. 2-[(8-Chloro-2-benzofuro[2,3-*b*]quinolinyl)oxy]propionic acid (12a)

To a solution of **11a** (0.41 g, 1.2 mmol) dissolved in THF (25 mL), 0.1 M NaOH (23 mL, 2.3 mmol) was added in portions and the mixture was stirred overnight. The mixture was concentrated to remove the THF and filtered. The filtrate was cooled and acidified to pH 3–4 with 0.25 M HCl. After recooling, it was filtered and washed with ice water to give a light yellow solid. This was then recrystallized from EtOH to give **12a** as light tan crystals (0.38 g, 96% yield). Mp 261–262 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.06 (br s, 1H), 9.06 (s, 1H), 8.14 (d, $J = 8.0$ Hz, 1H), 8.02 (d, $J = 2.4$ Hz, 1H), 7.72 (d, $J = 2.4$ Hz, 1H), 7.63 (d, $J = 8.8$ Hz, 1H), 7.60 (dd, $J = 8.8$, 2.4 Hz, 1H), 7.16 (dd, $J = 8.8$, 3.2 Hz, 1H), 4.95 (q, $J = 6.4$ Hz, 1H), 1.56 (d, $J = 7.6$ Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.7, 163.5, 154.8, 150.3, 146.2, 134.9, 130.9, 130.7, 127.0, 126.2, 124.8, 122.6, 118.6, 118.3, 113.0, 108.0, 73.0, 19.0. IR (KBr) 3440 (OH), 1715 (C=O) cm^{-1}. ESI-MS m/z 342 $(M+l)^+$. Anal. ($C_{18}H_{12}NO_4Cl$): C, 63.26; H, 3.54; N, 4.10. Found: C, 63.35; H, 3.55; N, 3.91.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2005.11.036.

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