Synthesis and Cytotoxic Activity of Acronycine Analogues in the Benzo[*c*]pyrano[3,2-*h*]acridin-7-one and Naphtho[1,2-*b*][1,7] and [1,10]-Phenanthrolin-7(14*H*)-one Series

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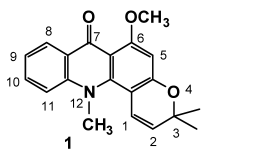
Condensation of 1-bromo-2-naphthalenecarboxylic acid (9) with 7-methoxy-2,2-dimethyl-2*H*-1-benzopyran-5-ylamine (13) followed by acid-mediated cyclization afforded 6-methoxy-3,3-dimethyl-3,14-dihydro-7*H*-benzo[*c*]pyrano[3,2-*h*]acridin-7-one (15), which was further methylated into 6-methoxy-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo[*c*]pyrano[3,2-*h*]acridin-7-one (benzo[*c*]acronycine) (3) and 6,7-dimethoxy-3,3-dimethyl-3*H*-benzo[*c*]pyrano[3,2-*h*]acridine (4). Osmium tetroxide oxidation of 15 gave the (±)-*cis*-diol 16, which afforded the benzopyranoacridine and benzopyranoacridone esters 17—22 upon acylation. Condensation of 9 with suitable aminoquinolines 23—25 afforded the carboxylic naphthylquinolylamines 26—28. Cyclization gave the corresponding naphtho[1,2-*b*][1,10]-phenanthrolin-7(14*H*)-ones 29 and 30, and naphtho[1,2-*b*][1,7]-phenanthrolin-7(14*H*)-one 31, which were subsequently *N*-methylated to the desired 14-methylnaphtho[1,2-*b*][1,10] and [1,7]-phenanthrolinones 6, 7, and 8. Benzo[*c*]pyrano[3,2-*h*]acridin-7-one derivatives 3, 16, and 22 displayed cytotoxic activities within the same range of magnitude as acronycine itself, whereas 7-alkoxybenzo[*c*]pyrano[3,2-*h*]acridine and 7-acyloxybenzo[*c*]pyrano[3,2-*h*]acridine derivatives 4 and 17—21 were less active when tested against L1210 murine leukemia cells *in vitro*. Naphthophenanthrolinones 6—8 were devoid of significant antiproliferative activity, but compounds 29—31 bearing no substituent on the nitrogen atom at position 14 were more potent.

Key words acronycine; benzo[*c*]acronycine; naphthophenanthrolinone; cytotoxicity

The pyranoacridone alkaloid acronycine (**1**), isolated from *Acronychia baueri* Schott (Rutaceae)[1—3] has shown antitumor properties in a panel of murine solid tumor models, including S-180 and AKR sarcomas, X-5563 myeloma, S-115 carcinoma, and S-91 melanoma.[4,5] However, its moderate potency and poor solubility in aqueous solvents severely hampered the subsequent clinical trials, which were rapidly discontinued, due to modest therapeutic effects and dose-limiting gastrointestinal toxicity after oral administration.[6] Consequently, the development of structural analogues with increased potency and/or better water solubility was highly desirable.

Our efforts to design more potent derivatives were guided by the hypothesis of bioactivation of the 1,2-double bond of acronycine into the corresponding epoxide *in vivo*.[7] The high reactivity of acronycine 1,2-epoxide, which readily reacts with water to give the corresponding *cis* and *trans* diols, suggested that this compound could be the active metabolite of acronycine, able to alkylate some nucleophilic target within the tumor cell. Accordingly, significant improvements in terms of potency were obtained with derivatives modified in the pyran ring, which had a similar reactivity toward nucleophilic agents as acronycine epoxide but improved chemical stability. Such compounds are exemplified by diesters of *cis*-1,2-dihydroxy-1,2-dihydroacronycine[8] and diesters of *cis*-1,2-dihydroxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*b*]pyrano[3,2-*h*]acridin-7-one in the related benzo[*b*]acronycine series.[9] A representative of this latter type of compounds, diacetate **2**, developed under the code S23906-1 is currently in phase I clinical trials. The mechanism of its action implies alkylation of the 2-amino group of DNA guanine residues by the carbocation resulting from the elimination of the ester-leaving group at position 1 of the drug.[10—13]

In a continuation of recent studies of the structure–activity relationships in the acronycine series,[14—17] we describe here the synthesis and biological activities of 6-methoxy-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo[*c*]pyrano[3,2-*h*]acridin-7-one (=benzo[*c*]acronycine) (**3**) and 6,7-dimethoxy-3,3-dimethyl-3*H*-benzo[*c*]pyrano[3,2-*h*]acridine (**4**). These isomers **3** and **4** of benzo[*b*]acronycine (**5**) were prepared together with some corresponding derivatives in the *cis*-1,2-dihydroxy-1,2-dihydro series to determine the influence of the position of the additional aromatic ring fused onto the basic tetracyclic pyranoacridone core of acronycine on the cytotoxic activity. Also, the three compounds **6**—**8** in which the dimethylpyran ring present in **3** and **4** is replaced by a pyri-



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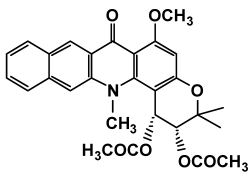
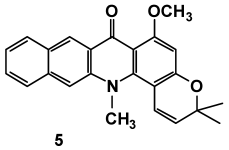


(±)-*cis* **2 = S 23906-1**



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dine, were synthesized with the aim of improving their solubility in biocompatible solvents, which is a critical point in this chemical series. The basic nitrogen atom of the newly introduced pyridine ring was expected to offer the opportunity to prepare water-soluble salts in acidic medium.

Chemistry

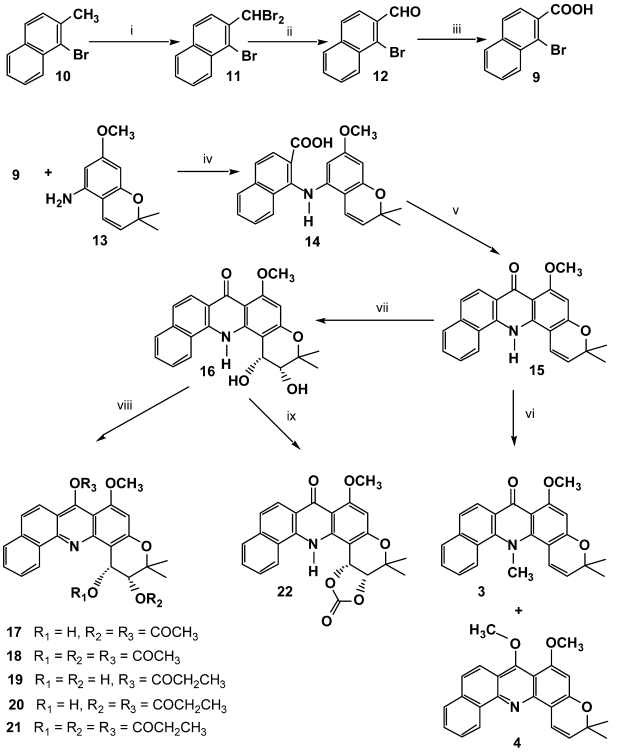
The strategy used to build up the pentacyclic basic core of benzo[*c*]acronycine (**3**) was similar to that previously developed for the syntheses of acronycine,[18] 6-demethoxyacronycine,[19] and 6-demethoxybenzo[*b*]acronycine,[11] through Ullmann condensation[20] of 7-methoxy-2,2-dimethyl-2*H*-1-benzopyran-5-ylamine[21] or 2,2-dimethyl-2*H*-1-benzopyran-5-ylamine[19] with an appropriate *ortho*-haloaromatic acid.

The required 1-bromonaphthalene-2-carboxylic acid (**9**) was prepared in 92% overall yield from commercially available 1-bromo-2-methylnaphthalene (**10**) through a three-step process successively involving benzylic radical dibromination to 1-bromo-2-dibromo-methylnaphthalene (**11**), hydrolysis into the corresponding 1-bromo-2-naphthalene-carbaldehyde (**12**), and oxidation into the corresponding carboxylic acid.[22]

Condensation of **9** and 7-methoxy-2,2-dimethyl-2*H*-1-benzopyran-5-ylamine[21] (**13**) gave the corresponding carboxylic diarylamine **14** in 18% yield. Cyclization to the corresponding acridone **15** was achieved in 27% yield by the use of trifluoroacetic anhydride in dichloromethane, which had previously given good results in the course of related syntheses.[11,18,19] Classic reactions previously developed in the acronycine and benzo[*b*]acronycine series to obtain *N*-methyl derivatives using methyl iodide or dimethyl sulfate, either in the presence of sodium hydride in dimethylformamide or under phase transfer conditions, gave 6,7-dimethoxy-3,3-dimethyl-3*H*-benzo[*c*]pyrano[3,2-*h*]acridine (**4**) as the single reaction product. Formation of the desired benzo[*c*]acronycine (**3**) could only be ensured when the reaction was performed with methyl iodide and potassium carbonate in acetone. Nevertheless, **3** was obtained in a low 5% yield under those mildly alkaline conditions, accompanied by **4**, which was isolated in 11% yield.

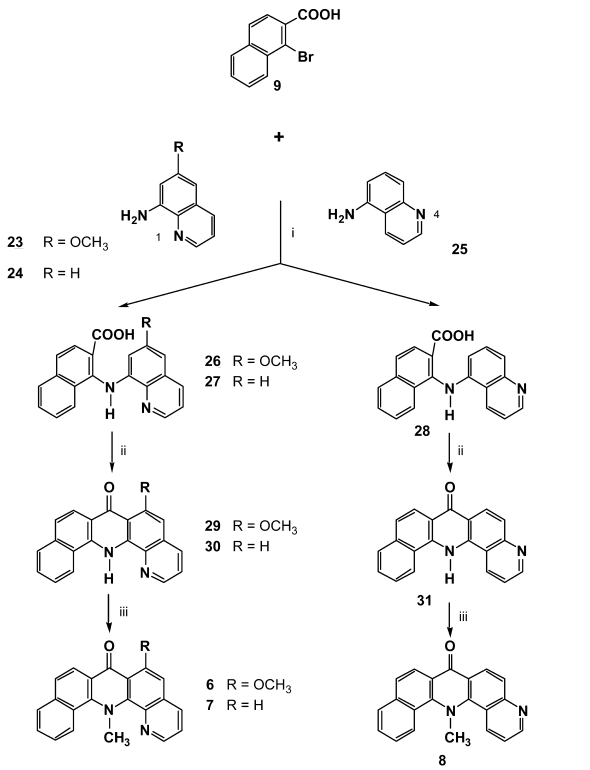
The (±)-*cis*-diol **16** was conveniently obtained in 81% yield by catalytic osmium tetroxide oxidation of **15**, using *N*-methylmorpholine *N*-oxide to regenerate the oxidative agent.[8,9] Treatment of **16** with one equivalent of various acyl anhydrides resulted in the acylation of the tautomeric hydroxyacridine form of the acridone skelton, giving, for example, the corresponding 2,7-diacetate **17** and 1,2,7-triacetate **18** when treated with acetic anhydride, and 7-monopropionate **19**, 2,7-dipropionate **20**, and 1,2,7-tripropionate **21** upon treatment with propionic anhydride. In contrast, acylation of diol **16** with *N*,*N*′-carbonyldiimidazole in 2-butanone under reflux afforded almost quantitatively the acridone cyclic carbonate **22**.

Access to 6-methoxy-14-methylnaphtho[1,2-*b*][1,10]-phenanthrolin-7(14*H*)-one (**6**), 14-methylnaphthro[1,2-*b*]-[1,10]-phenanthrolin-7(14*H*)-one (**7**), and 14-methylnaphtho[1,2-*b*][1,7]-phenanthrolin-7(14*H*)-one (**8**) was suggested by our previous work on related benzophenantholinones.[23] Thus Ullmann condensation[20] of 1-bromonaphthalene-2-carboxylic acid (**9**) with 6-methoxy-8-aminoquinoline (**23**), 8-



Reagents and conditions : (i) NBS, PBO, CCl_4, reflux, 24 h; (ii) 1) AcOK/AcOH, reflux, 24 h, 2) HCl, H_2O, reflux, 24 h; (iii) *t*-butanol, 2-methyl-2-butene, $NaClO_2$, $NaH_2PO_4.H_2O$, rt, 24 h; (iv) $Cu(OAc)_2.H_2O$, KOAc, Et_3N, 2-propanol, reflux, 24 h; (v) $(CF_3CO)_2O$, in dry CH_2Cl_2, N_2, rt, 6 days; (vi) K_2CO_3, ICH_3, in dry acetone, N_2, rt, 8 h; (vii) *t*-butanol, THF, H_2O, OsO_4, 4-methylmorpholine *N*-oxide monohydrate, rt, 8 h; (viii) Ac_2O (1 equiv) or $(EtCO)_2O$ (1 equiv), Py, rt, 24 h; (ix) *N*,*N*′-carbonyldiimidazole, in dry 2-butanone, reflux, 2 h.

Chart 1



Reagents and conditions : (i) $Cu(OAc)_2.H_2O$, KOAc, Et_3N, 2-propanol, reflux, 24 h; (ii) H_2SO_4, at 100°C, 5 h; (iii) ICH_3, 50% $NaOH_{(aq)}$, benzyltriethylammonium chloride, 2-butanone, at 70°C, 3 h

Chart 2

Table 1. Inhibition of L1210 Cell Proliferation by Benzo[*c*]pyrano[3,2-*h*]acridin-7-one Derivatives **3**, **4**, and **15**—**22** in Comparison with Acronycine (**1**) and Benzo[*b*]acronycine (**5**)

Compound	**1**	**5**	**3**	**4**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**
IC_{50} (μM)	23	1.9	12.1	58	49	6.7	15.5	26.2	14.5	11.7	26	10

Table 2. Inhibition of L1210 Cell Proliferation by Naphtho[1,2-*b*][1,7] and [1,10]-phenanthrolin-7(14*H*)-one Derivatives in Comparison with Acronycine (**1**) and Benzo[*b*]acronycine (**5**) and Benzo[*c*]acronycine (**3**)

Compound	**1**	**5**	**3**	**6**	**7**	**8**	**29**	**30**	**31**
IC_{50} (μM)	23	1.9	12.1	>100	30	85	37	9.7	80

aminoquinoline (**24**), and 5-aminoquinoline (**25**) afforded the corresponding carboxylic naphthylquinolylamines **26**—**28** in 41—48% yield. Concentrated sulfuric acid permitted the cyclization of **26**—**28** in 40—46% yield into the corresponding naphtho[1,2-*b*][1,10]-phenanthrolin-7(14*H*)-ones **29** and **30**, and naphtho[1,2-*b*][1,7]-phenanthrolin-7(14*H*)-one **31**, respectively.[23] Finally, methylation at *N*-14 with methyl iodide under phase-transfer catalysis conditions smoothly afforded the desired 14-methylnaphtho[1,2-*b*][1,10] and [1,7]-phenanthrolinones **6**, **7**, and **8**.

Pharmacology

The study of the biological properties of the new derivatives was carried out *in vitro* using the L1210 murine leukemia cell line. The results (IC_{50} values) are reported in Tables 1 and 2, respectively. In contrast with our previous observations on the benzo[*b*]acronycine series, fusion of an additional aromatic ring in position [*c*] onto the acronycine tetracyclic core did not result in an increase in cytotoxicity. The three more potent new compounds **3**, **16**, and **22** displayed cytotoxic activities within the same range of magnitude as acronycine (**1**) itself. All of them belong to the benzo[*c*]pyrano[3,2-*h*]acridin-7-one series, and it should be emphasized that compounds belonging to the isomeric 7-hydroxybenzo[*c*]pyrano[3,2-*h*]acridine series, exemplified by **4** and **17**—**21**, were less active.

Naphtho[1,2-*b*][1,10] and [1,7]-phenanthrolin-7(14*H*)-one **6**—**8** were devoid of significant activity. In both series, the compounds bearing no substituent on the nitrogen atom at position 14, such as **29**—**31**, were more potent than their corresponding *N*-methylated counterparts **6**—**8**.

Results and Discussion

Considering the structure–activity relationships in the acronycine series, introduction of an additional aromatic ring linearly fused in position [*b*] on the natural alkaloid basic skeleton had previously resulted in a dramatic increase in the antiproliferative activity.[9,11,24] In contrast, introduction of an additional aromatic ring angularly fused in position [*c*] on the acronycine tetracyclic system did not lead to a significant increase in the activity. This result is consistent with the mechanism of action postulated for acronycine and benzo[*b*]acronycine, which involves bioactivation into the corresponding 1,2-epoxide able to alkylate nucleophilic DNA sites within the tumor cell.[8—11] In the benzo[*c*]acronycine series, the significant increase in the steric hindrance at the reactive benzylic position 1 implied in the alkylation process should result in a decreased reactivity toward DNA when compared with benzo[*b*]acronycine derivatives.

The reduced potency of 7-alkoxybenzo[*c*]pyrano[3,2-*h*]acridine **4** and 7-acyloxy benzo[*c*]pyrano[3,2-*h*]acridine derivatives **18** and **21** compared with the corresponding benzo[*c*]pyrano[3,2-*h*]acridin-7-ones **3** and **22** is also worth noting. Thus the tricyclic acridin-7-one system appears to be an important structural requirement to observe antiproliferative activity in the acronycine series.

Finally, in the benzo[*c*]acronycine series, the replacement of the dimethylpyran ring by a pyridine resulted in a significant reduction of the cytotoxic activity, in good agreement with our previous work on the comparison of acronycine derivatives with the related 12*H*-benzo[*b*][1,7] and [1,10]-phenanthrolin-7-ones.[23]

Experimental

Chemistry The melting points were determined on a Leica VM apparatus and are not corrected. IR spectra (ν_{max} in cm^{-1}) were obtained in potassium bromide pellets on a Perkin-Elmer 257 instrument. UV spectra (λ_{max} in nm) were determined in spectroscopic-grade MeOH on a Beckman Model 34 spectrophotometer. ^{1}H-NMR [δ (ppm), J (Hz)] and ^{13}C-NMR spectra were recorded at 300 MHz and 75 MHz, respectively, using a Bruker AC-300 spectrometer. When necessary, the signals were unambiguously assigned by 2D NMR techniques: ^{1}H–^{1}H COSY, ^{1}H–^{1}H NOESY, ^{13}C–^{1}H HETCOR, and ^{13}C–^{1}H COLOC. These experiments were performed using standard Bruker microprograms. Mass spectra were recorded with a Nermag R-10-10C spectrometer, using electron impact (EI-MS) and/or chemical ionization (DCI-MS; reagent gas: NH_3) techniques. Flash column chromatography was performed using silica gel 60 Merck (35—70 μm) with an overpressure of 300 mbar.

1-Bromo-2-(dibromomethyl)naphthalene (11) A suspension of 1-bromo-2-methylnaphtalene (**10**) (11.3 g, 51.1 mmol), *N*-bromosuccinimide (21 g, 126.5 mmol), and dibenzoyl peroxide (2.1 g, 126.5 mmol) in dry CCl_4 (250 ml) was refluxed for 24 h. After cooling, the suspension was filtered. The mixture was washed with saturated aqueous $NaHSO_3$ (250 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Flash chromatography of the residue on silica gel (solvent: CH_2Cl_2/cyclohexane 1 : 9) gave **11** (18.70 g, 97%) as yellow crystals, mp 89 °C. IR (KBr) cm^{-1}: 2940, 745. UV λ_{max} (EtOH) nm (log ε): 300 (4.77), 302 (4.65), 312 (3.48), 335 (3.52). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.51 (s, 1H, H-CBr_2), 7.58 (td, 1H, J=8, 2 Hz, C6-H), 7.66 (td, 1H, J=8, 2 Hz, C7-H), 7.84 (dd, 1H, J=8, 2 Hz, C5-H), 7.91 (d, 1H, J=9 Hz, C4-H), 8.08 (d, 1H, J=9 Hz, C3-H), 8.32 (dd, 1H, J=8, 2 Hz, C8-H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 41.2 (d, $CHBr_2$), 119.5 (s, C-2), 126.7 (d, C-4), 127.9 (d, C-6), 128.2 (d, C-5), 128.3 (d, C-3), 128.4 (d, C-8), 129.0 (d, C-7), 131.1 (s, C-1), 134.6 (s, C-8a), 137.9 (s, C-4a). EI-MS *m/z*: 382, 380, 378, 376 $[M]^+$. *Anal.* Calcd for $C_{11}H_7Br_3$: C, 34.87; H, 1.86; Br, 63.27. Found: C, 34.77; H, 1.82; Br, 63.12.

1-Bromo-2-naphthalenecarbaldehyde (12) To a solution of potassium acetate (10 g, 26.4 mmol) in acetic acid (130 ml) was added **11** (10 g, 26.4 mmol). The mixture was refluxed for 24 h. A solution of 2 N HCl (40 ml) was added and the mixture was refluxed for 4 h. After cooling and evaporating the solvent, the residue was partitioned between AcOEt (300 ml) and 2 N HCl (200 ml). The organic layer was washed with saturated aqueous NaCl, treated with charcoal, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give **12** (6.2 g, 99%) as yellow crystals, mp 116 °C. IR (KBr) cm^{-1}: 3010, 2900, 1715. UV λ_{max} (EtOH) nm (log ε): 250 (4.83), 302 (4.64), 312 (3.47), 331 (3.51). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.50 (td, 1H, J=8, 2 Hz, C6-H), 7.78 (d, 1H, J=9 Hz, C4-H), 7.87 (td, 1H, J=8, 2 Hz, C7-H), 7.94 (d, 1H, J=9 Hz, C3-H), 7.97 (dd, 1H, J=8, 2 Hz, C5-H), 8.50 (dd, 1H, J=8, 2 Hz, C8-H), 10.72 (s, 1H, H-CO). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 123.7 (s, C2), 124.0 (d, C-4), 128.0 (d, C-6), 128.1 (d, C-5), 128.2 (d, C-3), 128.3 (d, C-8), 128.4 (d, C-7), 131.2 (s, C-1), 132.0 (s, C-8a), 134.9 (s, C-4a), 192.9 (s, CHO). EI-MS *m/z*: 236, 234 $[M]^+$, 207, 205. *Anal.* Calcd for $C_{11}H_7BrO$: C, 56.20; H, 3.00; Br, 33.99. Found: C, 56.01; H, 3.02; Br, 34.06.

1-Bromo-2-naphthalenecarboxylic Acid (9) To a mixture of **12** (1 g, 4.23 mmol) and *t*-butyl alcohol (70 ml) was added 2-methyl-2-butene (4 ml). A 100 ml aqueous solution of $NaClO_2$ (3.35 g, 39 mmol) and $NaH_2PO_4 \cdot H_2O$ (4.03 g, 29.3 mmol) was added dropwise over a period of 20 min. This resulted in a clear solution, which was stirred for 24 h at room temperature. The *t*-butyl alcohol was removed by rotary evaporation, and the mixture was treated with H_2O (25 ml) and washed with hexane (20 ml). The aqueous layer was then acidified to pH *ca.* 1 and extracted with ether (3×100 ml). The organic extracts were combined, and the solvent was evaporated under reduced pressure. Flash chromatography of the residue on silica gel (solvent: CH_2Cl_2/cyclohexane 1 : 9) gave **9** (1.01 g, 95%) as whitish crystals, mp 177—179 °C. IR (KBr) cm^{-1}: 3450, 2940, 1690, 1662. UV λ_{max} (EtOH) nm (log ε): 245 (4.67), 284 (3.65), 285 (3.62), 304 (4.72). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 7.68 (td, 1H, J=8, 2 Hz, C6-H), 7.70 (d, 1H, J=9 Hz, C4-H), 7.76 (td, 1H, J=8, 2 Hz, C7-H), 8.05 (dd, 1H, J=8, 2 Hz, C5-H), 8.06 (d, 1H, J=9 Hz, C3-H), 8.32 (dd, 1H, J=8, 2 Hz, C8-H), 12.53 (br s, 1H, D_2O exch., COO<u>H</u>). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 120.9 (s, C2), 126.5 (d, C-4), 128.5 (d, C-6), 129.2 (d, C-5), 129.4 (d, C-3), 129.7 (d, C-8), 129.8 (d, C-7), 132.4 (s, C-1), 134.6 (s, C-8a), 135.5 (s, C-4a), 176.6 (s, COOH). EI-MS *m/z*: 252, 250 $[M]^+$, 207, 205. *Anal.* Calcd for $C_{11}H_7BrO_2$: C, 52.62; H, 2.81; Br, 31.82. Found: C, 52.51; H, 2.84; Br, 32.01.

1-[(7-Methoxy-2,2-dimethyl-2*H*-1-benzopyran-5-yl)amino]-2-naphthalenecarboxylic Acid (14) A solution of 7-methoxy-2,2-dimethyl-2*H*-1-benzopyran-5-yl)amine (**13**) (244 mg, 1.19 mmol), 1-bromonaphtalene-2-carboxylic acid (**9**) (300 mg, 1.19 mmol), potassium acetate (234 mg, 2.38 mmol), cupric acetate monohydrate (10 mg), and triethylamine (0.6 ml, 1.19 mmol) in 2-propanol (20 ml) was heated under reflux for 24 h. After cooling, the reaction mixture was evaporated under reduced pressure and the residue was partitioned between CH_2Cl_2 (150 ml) and 1 N HCl (100 ml). The aqueous phase was extracted with CH_2Cl_2 (3×50 ml). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Flash chromatography of the residue on silica gel (solvent: CH_2Cl_2) gave **14** (64 mg, 18%) as yellow crystals, mp 120 °C. IR (KBr) cm^{-1}: 3350, 2950, 1670, 1620, 1240. UV λ_{max} (MeOH) nm (log ε): 283 (4.48), 312 (4.45), 362 (3.58). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.50 (s, 6H, C2′-(C<u>H</u>$_3$)$_2$), 3.51 (s, 3H, O-C<u>H</u>$_3$), 5.61 (d, 1H, J=10 Hz, C3′-H), 5.63 (d, 1H, J=2 Hz, C8′-H), 6.13 (d, 1H, J=2 Hz, C6′-H), 6.89 (d, 1H, J=10 Hz, C4′-H), 7.29 (td, 1H, J=8, 1.5 Hz, C6-H), 7.47 (d, 1H, J=9 Hz, C4-H), 7.51 (td, 1H, J=8, 1.5 Hz, C7-H), 7.78 (dd, 1H, J=8, 1.5 Hz, C5-H), 7.85 (dd, 1H, J=8, 1.5 Hz, C8-H), 8.58 (d, 1H, J=9 Hz, C3-H), 10.41 (br s, 1H, D_2O exch., N<u>H</u>), 11.27 (br s, 1H, D_2O exch., COO<u>H</u>). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 27.7 (q, –C2′-(CH$_3$)$_2$C2′), 55.1 (q, O-<u>C</u>H$_3$), 76.0 (s, C-2′), 96.8 (d, C-6′), 99.8 (d, C-8′), 107.2 (s, C-4′a), 112.9 (s, C-2), 117.4 (d, C-4′), 121.9 (d, C-4), 125.3 (d, C-6), 126.4 (d, C-5), 126.6 (s, C-8a), 127.2 (d, C-3), 127.6 (d, C-8), 128.1 (d, C-3′), 128.7 (d, C-7), 137.3 (s, C-5′), 142.3 (s, C-4a), 147.3 (s, C-1), 154.8 (s, C-8′a), 160.4 (s, C-7′), 173.5 (s, <u>C</u>OOH). DCI-MS *m/z*: 376 $[MH]^+$. *Anal.* Calcd for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.62; H, 5.67; N, 3.76.

6-Methoxy-3,3-dimethyl-3,14-dihydro-7*H*-benzo[*c*]pyrano[3,2-*h*]acridin-7-one (15) Trifluoroacetic anhydride (1.34 ml, 9.71 mmol) was added to a solution of 1-[(7-methoxy-2,2-dimethyl-2*H*-1-benzopyran-5-yl)amino]-naphtalene-2-carboxylic acid (**14**) (728 mg, 1.94 mmol) in CH_2Cl_2 (14 ml). The mixture was stirred at room temperature for 6 d, evaporated under reduced pressure, and taken up by CH_2Cl_2 (150 ml) and saturated aqueous $NaHCO_3$ (150 ml). The aqueous phase was extracted with CH_2Cl_2 (2×100 ml). The combined organic phase was shaken for 5 min with 1 N aqueous NaOH (50 ml), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Flash chromatography of the residue on silica gel (solvent: CH_2Cl_2, then CH_2Cl_2/MeOH 98 : 2) gave **15** (187 mg, 27%) as yellow crystals, mp 226 °C. IR (KBr) cm^{-1}: 3360, 2980, 1632, 1610, 1547, 1473, 1359, 1130, 1075. UV λ_{max} (MeOH) nm (log ε): 263 (4.70), 277 (4.75), 290 (3.41), 383 (3.83). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.51 (s, 6H, C3-(C<u>H</u>$_3$)$_2$), 3.98 (s, 3H, O-C<u>H</u>$_3$), 5.67 (d, 1H, J=10 Hz, C2-H), 6.23 (s, 1H, C5-H), 6.68 (d, 1H, J=10 Hz, C1-H), 7.54 (d, 1H, J=9 Hz, C9-H), 7.59 (td, 1H, J=7, 2 Hz, C11-H), 7.61 (td, 1H, J=7, 2 Hz, C12-H), 7.87 (dd, 1H, J=7, 2 Hz, C10-H), 8.06 (d, 1H, J=9 Hz, C8-H), 8.38 (dd, 1H, J=7, 2 Hz, C13-H), 8.61 (br s, 1H, D_2O exch., NH). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 27.6 (q, C3-(<u>C</u>H$_3$)$_2$), 56.2 (q, O-<u>C</u>H$_3$), 77.2 (s, C-3), 94.5 (d, C-5), 99.7 (s, C-14b), 107.8 (s, C-6a), 114.5 (d, C-1), 119.5 (d, C-8), 121.9 (d, C-9), 123.2 (d, C-13), 126.2 ((s, C-7a)+(d, C-11)), 127.5 (d, C-2), 128.3 (d, C-12), 128.5 (s, C-13a), 129.1 (d, C-9), 135.3 (s, C-9a), 137.9 (s, C-13b), 142.8 (s, C-14a), 157.5 (s, C-4a), 162.6 (s, C-6), 176.7 (s, C7). DCI-MS *m/z*: 358 $[MH]^+$. *Anal.* Calcd for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 77.38; H, 5.31; N, 4.01.

6-Methoxy-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo[*c*]pyrano[3,2-*h*]-acridin-7-one (3) and 6,7-Dimethoxy-3,3-dimethyl-3*H*-benzo[*c*]pyrano-[3,2-*h*]acridine (4) Methyl iodide (800 mg, 1.68 mmol) was added to a mixture of 6-methoxy-3,3-dimethyl-3,14-dihydro-7*H*-benzo[*c*]pyrano[3,2-*h*]-acridin-7-[3,2-*h*]acridin-7-one (**15**) (400 mg, 1.12 mmol) and potassium carbonate (774 mg, 5.6 mmol) in dry acetone (20 ml). The mixture was stirred at room temperature for 24 h and partitioned between CH_2Cl_2 (60 ml) and H_2O (30 ml). The aqueous phase was extracted with CH_2Cl_2 (2×60 ml), and the combined organic phase was dried over anhydrous Na_2CO_3, filtered, and evaporated under reduced pressure. Flash chromatography of the residue on silica gel (solvent: CH_2Cl_2) gave 6-methoxy-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo[*c*]pyrano[3,2-*h*]acridin-7-one (**3**) (22 mg, 5%) as yellow crystals and 6,7-dimethoxy-3,3-dimethyl-3*H*-benzo[*c*]pyrano[3,2-*h*]acridine (**4**) (46 mg, 11%) as a yellow amorphous solid.

6-Methoxy-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo[*c*]pyrano[3,2-*h*]acridin-7-one (**3**): mp 180 °C. IR (KBr) cm^{-1}: 3380, 2945, 1640, 1586, 1490, 1370, 1082, 810. UV λ_{max} (MeOH) nm (log ε): 267 (4.71), 277 (4.78), 285 (3.44), 382 (3.87). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.55 (s, 6H, C3-(C<u>H</u>$_3$)$_2$), 3.70 (s, 3H, N-C<u>H</u>$_3$), 4.00 (s, 3H, O-C<u>H</u>$_3$), 5.68 (d, 1H, J=10 Hz, C2-H), 6.40 (s, 1H, C5-H), 6.86 (d, 1H, J=10 Hz, C1-H), 7.60 (td, 1H, J=7, 2 Hz, C11-H), 7.62 (td, 1H, J=7, 2 Hz, C12-H), 7.68 (d, 1H, J=9 Hz, C9-H), 7.91 (dd, 1H, J=7, 2 Hz, C10-H), 8.29 (d, 1H, J=9 Hz, C8-H), 8.37 (dd, 1H, J=7, 2 Hz, C13-H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 29.2 (q, C3-(<u>C</u>H$_3$)$_2$), 50.5 (q, N-<u>C</u>H$_3$), 56.3 (q, O-<u>C</u>H$_3$), 76.8 (s, C-3), 95.9 (d, C-5), 105.8 (s, C-14b), 112.2 (s, C-6a), 120.5 (d, C-1), 122.7 (d, C-8), 124.2 (d, C-9), 125.6 (d, C-13), 125.7 (d, C-11), 125.8 (s, C-7a), 125.9 (d, C-2), 128.5 (s, C-13a), 128.8 ((d, C-10)+(d, C-12)), 136.2 (s, C-9a), 146.3 (s, C-13b), 150.2 (s, C-14a), 158.8 (s, C-4a), 162.0 (s, C-6), 178.7 (s, C7). DCI-MS *m/z*: 372 $[MH]^+$. *Anal.* Calcd for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.72; H, 5.74; N, 3.72.

6,7-Dimethoxy-3,3-dimethyl-3*H*-benzo[*c*]pyrano[3,2-*h*]acridine (**4**): IR (KBr) cm^{-1}: 3240, 2880, 1596, 1483, 1372, 1140, 1073, 840. UV λ_{max} (MeOH) nm (log ε): 215 (3.73), 242 (3.24), 287 (4.72), 324 (3.50), 342 (3.56), 386 (3.68). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.56 (s, 6H, C3-(C<u>H</u>$_3$)$_2$), 4.04 (s, 3H, C6-O-C<u>H</u>$_3$), 4.05 (s, 3H, C7-O-C<u>H</u>$_3$), 5.56 (d, 1H, J=10 Hz, C2-H), 6.56 (s, 1H, C5-H), 7.63 (d, 1H, J=9 Hz, C9-H), 7.70 (td, 1H, J=8, 2 Hz, C11-H), 7.73 (td, 1H, J=8, 2 Hz, C12-H), 7.85 (d, 1H, J=10 Hz, C1-H), 7.86 (dd, 1H, J=8, 2 Hz, C10-H), 8.08 (d, 1H, J=9 Hz, C8-H), 9.47 (dd, 1H, J=8, 2 Hz, C13-H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 28.2 (q, C3-(<u>C</u>H$_3$)$_2$), 56.2 (q, C6-O-<u>C</u>H$_3$), 63.6 (q, C7-O-<u>C</u>H$_3$), 77.7 (s, C-3), 98.1 (d, C-5), 108.7 (s, C-14b), 110.0 (s, C-6a), 117.7 (s, C-7a), 119.1 (d, C-1), 120.0 (d, C-8), 125.2 ((d, C-9)+(d, C-13), 125.6 (d, C-11), 126.7 (d, C-2), 127.6 (d, C-12), 128.8 (d, C-10), 131.5 (s, C13a), 134.3 (s, C-9a), 146.8 (s, C-13b), 148.8 (s, C-14a), 154.8 (s, C-7), 156.6 (s, C-4a), 161.9 (s, C6). DCI-MS *m/z*: 372 $[MH]^+$. *Anal.* Calcd for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.57; H, 5.62; N, 3.73.

(±)-*cis*-1,2-Dihydroxy-6-methoxy-3,3-dimethyl-2,3-dihydro-1*H*-benzo[*c*]pyrano[3,2-*h*]acridin-7-one (16) To a solution of osmium tetroxide (2.5% in 2-methyl-2-propanol) (0.49 ml) and 4-methylmorpholine *N*-oxide monohydrate (380 mg, 1 mmol) in *t*-BuOHTHF–H_2O (10/3/1: v/v/v, 20 ml) was added **15** (307 mg, 0.86 mmol). The reaction mixture was stirred at room temperature for 2 d. Saturated aqueous $NaHSO_3$ was added, and the mixture was stirred at room temperature for 1 h and extracted with CH_2Cl_2 (3×100 ml). The organic layers were evaporated under reduced pressure to give a yellow solid, which was purified by crystallization in acetone to afford **16** (272 mg, 81%), mp 176 °C. IR (KBr) cm^{-1}: 3385, 3255, 2892, 1595, 1460, 1380, 1144, 1040. UV λ_{max} (MeOH) nm (log ε): 244 (3.72), 290 (4.80), 324 (3.21), 343 (3.28). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.02 (s, 3H, C3-(C<u>H</u>$_3$)$_a$), 1.04 (s, 3H, C3-(C<u>H</u>$_3$)$_b$), 3.72 (dd, 1H, J=6, 4.5 Hz, C2-H), 3.80 (s, 3H, O-C<u>H</u>$_3$), 5.30 (d, 1H, J=6 Hz, HO-C1), 5.52 (d, 1H, J=6 Hz, HO-C2), 6.19 (s, 1H, C5-H), 6.33 (dd, 1H, J=6, 4.5 Hz, C1-H), 7.59 (d, 1H, J=9 Hz, C9-H), 7.72 (td, 1H, J=7, 2 Hz, C11-H), 7.74 (td, 1H, J=7, 2 Hz, C12-H), 8.00 (dd, 1H, J=7, 2 Hz, C10-H), 8.11 (d, 1H, J=9 Hz, C8-H), 8.26 (dd, 1H, J=7, 2 Hz, C13-H), 11.83 (br s, 1H, D_2O exch., N<u>H</u>). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 25.0 (q, C3-(<u>C</u>H$_3$)$_a$), 25.3 (q, C3-(<u>C</u>H$_3$)$_b$), 56.8 (q, O-<u>C</u>H$_3$), 65.3 (d, C-1), 71.2 (d, C-2), 80.3 (s, C-3), 95.2 (d, C-5), 100.3 (s, C-14b), 108.7 (s, C-6a), 119.2 (s, C-7a), 122.1 (d, C-8), 122.3 (d, C-9), 123.5 (d, C-13), 127.8 (d, C-11), 129.9 (d, C-12), 130.0 (d, C-10), 130.2 (d, C-13a), 135.9 (s, C-9a), 137.1 (s, C-13b), 144.9 (s, C-14a), 158.0 (s, C-4a), 162.0 (s, C-6), 176.0 (s, C7). DCI-MS *m/z*: 392 $[MH]^+$. *Anal.* Calcd for $C_{23}H_{21}NO_5$: C, 70.58; H, 5.41; N, 3.58. Found: C, 70.42; H, 5.47; N, 3.56.

(±)-*cis*-1-Hydroxy-6-methoxy-3,3-dimethyl-2,3-dihydro-1*H*-benzo[*c*]pyrano[3,2-*h*]-acridine-2,7-diyle Diacetate (17), and (±)-*cis*-6-Methoxy-3,3-dimethyl-2,3-dihydro-1*H*-benzo[*c*]pyrano-[3,2-*h*]acridine-

1,2,7-triyle Triacetate (18) In a cooled mixture (0 °C) of acetic anhydride (0.059 ml, 0.77 mmol) and dry pyridine (5 ml) was added **16** (180 mg, 0.45 mmol). The mixture was stirred at room temperature for 24 h and poured onto ice-water (10 ml). The precipitate was filtered, washed with water (5×20 ml), and dried under a vacuum over P_2O_5. Column chromatography over silica gel (20—45 μm) (solvent: CH_2Cl_2, then CH_2Cl_2/MeOH 92 : 2) gave **17** (120 mg, 25%) and **18** (142 mg, 33%) as yellow amorphous solids.

(±)-*cis*-1-Hydroxy-6-methoxy-3,3-dimethyl-2,3-dihydro-1*H*-benzo-[*c*]pyrano[3,2-*h*]acridine-2,7-diyle diacetate (**17**): IR (KBr) cm^{-1}: 3250, 2890, 1583, 1476, 1389, 1122, 1040, 815. UV λ_{max} (MeOH) nm (log ε): 214 (3.82), 225 (3.79), 246 (3.32), 292 (4.83), 326 (3.22), 343 (3.29), 400 (3.25). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.45 (s, 3H, C3-(C$\underline{H}_3$)$_a$), 1.56 (s, 3H, C3-(C$\underline{H}_3$)$_b$), 2.15 (s, 3H, C$\underline{H}_3$-CO-O-C2), 2.55 (s, 3H, C$\underline{H}_3$-CO-O-C7), 4.00 (s, 3H, O-C$\underline{H}_3$), 5.59 (d, 1H, *J*=5 Hz, C1-H), 5.82 (d, 1H, *J*=5 Hz, C2-H), 6.52 (s, 1H, C5-H), 7.58 (br s, 1H, D_2O exch., HO-C1), 7.68 (d, 1H, *J*=9 Hz, C9-H), 7.71 (td, 1H, *J*=8, 2 Hz, C11-H), 7.73 (td, 1H, *J*=8, 2 Hz, C12-H), 7.79 (d, 1H, *J*=9 Hz, C8-H), 7.88 (dd, 1H, *J*=8, 2 Hz, C10-H), 9.15 (dd, 1H, *J*=8, 2 Hz, C13-H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 20.8 (q, $\underline{C}H_3$-CO-O-C2), 20.9 (q, $\underline{C}H_3$-CO-O-C7), 23.9 (q, C3-(C$\underline{H}_3$)$_a$), 24.7 (q, C3-(C$\underline{H}_3$)$_b$), 56.3 (q, O-C$\underline{H}_3$), 63.4 (d, C-1), 71.5 (d, C-2), 78.1 (s, C-3), 99.0 (d, C-5), 106.4 (s, C-14b), 109.9 (s, C-6a), 116.7 (s, C-7a), 118.6 (d, C-8), 124.8 (d, C-9), 127.1 (d, C-13), 127.6 (d, C-11), 128.1 (d, C-12), 129.6 (d, C-10), 130.2 (s, C-13a), 134.2 (s, C-9a), 147.6 (s, C-13b), 149.8 (s, C-7), 152.5 (s, C-14a), 154.2 (s, C-4a), 155.7 (s, C-6), 168.8 (s, CH$_3$-$\underline{C}$O-O-C7), 171.1 (s, CH$_3$-$\underline{C}$O-O-C2). DCI-MS *m*/*z*: 476 $[MH]^+$. *Anal.* Calcd for $C_{27}H_{25}NO_7$: C, 68.20; H, 5.30; N, 2.95. Found: C, 68.27; H, 5.23; N, 3.02.

(±)-*cis*-6-Methoxy-3,3-dimethyl-2,3-dihydro-1*H*-benzo[*c*]pyrano-[3,2-*h*]acridine-1,2,7-triyle Triacetate (**18**): IR (KBr) cm^{-1}: 3240, 2894, 1598, 1574, 1480, 1363, 1182, 1057, 810. UV λ_{max} (MeOH) nm (log ε): 218 (3.72), 244 (3.27), 285 (4.66), 325 (3.50), 344 (3.56), 387 (3.59), 407 (3.66). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.46 (s, 3H, C3-(C$\underline{H}_3$)$_a$), 1.53 (s, 3H, C3-(C$\underline{H}_3$)$_b$), 2.09 (s, 3H, C$\underline{H}_3$-CO-O-C2), 2.18 (s, 3H, C$\underline{H}_3$-CO-O-C1), 2.58 (s, 3H, C$\underline{H}_3$-CO-O-C7), 3.97 (s, 3H, O-C$\underline{H}_3$), 5.62 (d, 1H, *J*=5 Hz, C2-H), 6.34 (s, 1H, C5-H), 6.95 (d, 1H, *J*=5 Hz, C1-H), 7.68 (d, 1H, *J*=9 Hz, C9-H), 7.70 (td, 1H, *J*=8, 2 Hz, C11-H), 7.73 (td, 1H, *J*=8, 2 Hz, C12-H), 7.80 (d, 1H, *J*=9 Hz, C8-H), 7.89 (dd, 1H, *J*=8, 2 Hz, C10-H), 9.17 (dd, 1H, *J*=8, 2 Hz, C13-H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 20.8 (q, $\underline{C}H_3$-CO-O-C7), 20.9 (q, $\underline{C}H_3$-CO-O-C1), 21.1 (q, $\underline{C}H_3$-CO-O-C2), 21.3 (q, C3-(C$\underline{H}_3$)$_a$), 26.2 (q, C3-(C$\underline{H}_3$)$_b$), 56.4 (q, O-C$\underline{H}_3$), 63.0 (d, C-1), 72.4 (d, C-2), 78.3 (s, C-3), 99.2 (d, C-5), 104.7 (s, C-14b), 109.8 (s, C-6a), 116.3 (s, C-7a), 118.4 (d, C-8), 124.8 (d, C-9), 127.2 (d, C-13), 127.4 (d, C-11), 128.1 (d, C-12), 129.3 (d, C-10), 130.0 (s, C-13a), 134.2 (s, C-9a), 147.0 (s, C-13b), 149.8 (s, C-7), 154.8 (s, C-14a), 155.8 (s, C-4a), 156.0 (s, C-6), 168.7 (s, CH$_3$-$\underline{C}$O-O-C7), 170.2 (s, CH$_3$-$\underline{C}$O-O-C1), 170.7 (s, CH$_3$-$\underline{C}$O-O-C2). DCI-MS *m*/*z*: 518 $[MH]^+$. *Anal.* Calcd for $C_{29}H_{27}NO_8$: C, 67.30; H, 5.26; N, 2.71. Found: C, 67.41; H, 5.27; N, 2.69.

(±)-*cis*-1,2-Dihydroxy-6-methoxy-3,3-dimethyl-7-propioxy-2,3-dihydro-1*H*-benzo[*c*]pyrano[3,2-*h*]acridine-7-yle Propionate (19), (±)-*cis*-1-Hydroxy-6-methoxy-3,3-dimethyl-2,3-dihydro-1*H*-benzo[*c*]pyrano[3,2-*h*]acridine-2,7-diyle Dipropionate (20), and (±)-*cis*-6-Methoxy-3,3-dimethyl-2,3-dihydro-1*H*-benzo[*c*]pyrano[3,2-*h*]acridine-1,2,7-triyle Tripropionate (21) Propionylation of **16** (180 mg, 0.45 mmol), under conditions similar to those described for the preparation of **17** and **18**, but using propionic anhydride instead of acetic anhydride, afforded **19** (34 mg, 3%), **20** (39 mg, 18%), and **21** (142 mg, 33%) as yellow amorphous solids.

(±)-*cis*-1,2-Dihydroxy-6-methoxy-3,3-dimethyl-7-propioxy-2,3-dihydro-1*H*-benzo[*c*]pyrano[3,2-*h*]acridine-7-yle Propionate (**19**): IR (KBr) cm^{-1}: 3385, 3255, 1595, 1460, 1380, 1144, 1080. UV λ_{max} (MeOH) nm (log ε): 221 (3.80), 225 (3.78), 244 (3.32), 290 (4.80), 324 (3.21), 343 (3.28), 399 (3,24). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.38 (s, 3H, C3-(C$\underline{H}_3$)$_a$), 1.45 (t, 3H, *J*=8 Hz, C$\underline{H}_3$-CH$_2$-CO-O-C7), 1.67 (s, 3H, C3-(C$\underline{H}_3$)$_b$), 2.89 (q, 2H, *J*=8 Hz, C$\underline{H}_3$-CH$_2$-CO-O-C7), 3.43 (dd, 1H, *J*=7, 4.5 Hz, C2-H), 3.96 (s, 3H, O-C$\underline{H}_3$), 4.07 (d, 1H, *J*=7 Hz, HO-C1), 5.68 (d, 1H, *J*=7 Hz, HO-C2), 6.53 (s, 1H, C5-H), 7.75 (m, 3H, C1-H, C11-H, C12-H), 7.81 (d, 1H, *J*=8 Hz, C9-H), 7.89 (dd, 1H, *J*=8, 2 Hz, C10-H), 9.17 (dd, 1H, *J*=8, 2 Hz, C13-H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 9.0 (q, $\underline{C}H_3$-CH$_2$-CO-O-C7), 23.3 (q, C3-(C$\underline{H}_3$)$_a$), 24.4 (q, C3-(C$\underline{H}_3$)$_b$), 27.6 (t, CH$_3$-$\underline{C}$H$_2$-CO-O-C7), 56.2 (q, O-C$\underline{H}_3$), 64.5 (d, C-1), 70.5 (d, C-2), 78.8 (s, C-3), 99.3 (d, C-5), 105.5 (s, C-14b), 110.0 (s, C-6a), 116.8 (s, C-7a), 118.7 (d, C-8), 124.6 (d, C-9), 127.0 (d, C-13), 127.6 (d, C-11), 128.2 (d, C-12), 129.6 (d, C-10), 129.8 (s, C-13a), 134.4 (s, C-9a), 147.5 (s, C-13b), 150.2 (s, C-7), 152.4 (s, C-14a), 154.8 (s, C-4a), 155.8 (s, C-6), 172.1 (s, CH$_3$-CH$_2$-$\underline{C}$O-O-C7). DCI-MS *m*/*z*: 448 $[MH]^+$. *Anal.* Calcd for $C_{26}H_{25}NO_6$: C, 69.79; H, 5.63; N, 3.13. Found: C, 69.91; H, 5.67; N, 3.12.

(±)-*cis*-1-Hydroxy-6-methoxy-3,3-dimethyl-2,3-dihydro-1*H*-benzo-[*c*]pyrano[3,2-*h*]acridine-2,7-diyle Dipropionate (**20**): IR (KBr) cm^{-1}: 3350, 2885, 1595, 1580, 1460, 1390, 1125, 1083, 809. UV λ_{max} (MeOH) nm (log ε): 214 (3.82), 225 (3.81), 245 (3.33), 290 (4.83), 326 (3.21), 343 (3.29), 399 (3.25). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.17 (t, 3H, *J*=8 Hz, C$\underline{H}_3$-CH$_2$-CO-O-C2), 1.43 (t, 3H, *J*=8 Hz, C$\underline{H}_3$-CH$_2$-CO-O-C7), 1.46 (s, 3H, C3-(C$\underline{H}_3$)$_a$), 1.54 (s, 3H, C3-(C$\underline{H}_3$)$_b$), 2.44 (q, 2H, *J*=8 Hz, CH$_3$-C$\underline{H}_2$-CO-O-C2), 2.89 (q, 2H, *J*=8 Hz, CH$_3$-C$\underline{H}_2$-CO-O-C7), 3.98 (s, 3H, O-C$\underline{H}_3$), 5.61 (d, 1H, *J*=5 Hz, C1-H), 5.83 (d, 1H, *J*=5 Hz, C2-H), 6.51 (s, 1H, C5-H), 7.72 (br s, 1H, D_2O exch., HO-C1), 7.67 (d, 1H, *J*=9 Hz, C9-H), 7.70 (td, 1H, *J*=8, 2 Hz, C11-H), 7.73 (td, 1H, *J*=8, 2 Hz, C12-H), 7.78 (d, 1H, *J*=9 Hz, C8-H), 7.86 (dd, 1H, *J*=8, 2 Hz, C10-H), 9.17 (dd, 1H, *J*=8, 2 Hz, C13-H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 9.0 (q, $\underline{C}H_3$-CH$_2$-CO-O-C7), 9.2 (q, $\underline{C}H_3$-CH$_2$-CO-O-C2), 23.9 (q, C3-(C$\underline{H}_3$)$_a$), 24.7 (q, C3-(C$\underline{H}_3$)$_b$), 27.5 (t, CH$_3$-$\underline{C}$H$_2$-CO-O-C7), 27.6 (t, CH$_3$-$\underline{C}$H$_2$-CO-O-C2), 56.2 (q, O-$\underline{C}$H$_3$), 63.4 (d, C-1), 71.3 (d, C-2), 78.1 (s, C-3), 99.0 (d, C-5), 106.5 (s, C-14b), 110.0 (s, C-6a), 116.8 (s, C-7a), 118.6 (d, C-8), 124.9 (d, C-9), 127.1 (d, C-13), 127.5 (d, C-11), 128.1 (d, C-12), 129.5 (d, C-10), 129.9 (s, C-13a), 134.2 (s, C-9a), 147.6 (s, C-13b), 149.8 (s, C-7), 152.1 (s, C-14a), 154.2 (s, C-4a), 155.7 (s, C-6), 172.2 (s, CH$_3$-CH$_2$-$\underline{C}$O-O-C7), 174.5 (s, CH$_3$-CH$_2$-$\underline{C}$O-O-C2). DCI-MS *m*/*z*: 504 $[MH]^+$. *Anal.* Calcd for $C_{29}H_{29}NO_7$: C, 69.17; H, 5.80; N, 2.78. Found: C, 69.12; H, 5.69; N, 2.86.

(±)-*cis*-6-Methoxy-3,3-dimethyl-2,3-dihydro-1*H*-benzo[*c*]pyrano[3,2-*h*]acridine-1,2,7-triyle Tripropionate (**21**): IR (KBr) cm^{-1}: 3245, 2892, 1592, 1575, 1470, 1372, 1174, 1040, 808. UV λ_{max} (MeOH) nm (log ε): 218 (3.72), 244 (3.28), 287 (4.68), 325 (3.52), 342 (3.57), 387 (3.62), 408 (3.65). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.11 (t, 3H, *J*=8 Hz, C$\underline{H}_3$-CH$_2$-CO-O-C2), 1.28 (t, 3H, *J*=8 Hz, C$\underline{H}_3$-CH$_2$-CO-O-C1), 1.33 (t, 3H, *J*=8 Hz, C$\underline{H}_3$-CH$_2$-CO-O-C7), 1.53 (s, 6H, C3-(C$\underline{H}_3$)$_2$), 2.29 (q, 2H, *J*=8 Hz, CH$_3$-C$\underline{H}_2$-CO-O-C2), 2.49 (q, 2H, *J*=8 Hz, CH$_3$-C$\underline{H}_2$-CO-O-C1), 2.51 (q, 2H, *J*=8 Hz, CH$_3$-C$\underline{H}_2$-CO-O-C7), 3.98 (s, 3H, O-C$\underline{H}_3$), 5.51 (d, 1H, *J*=5 Hz, C2-H), 6.40 (s, 1H, C5-H), 7.24 (d, 1H, *J*=5 Hz, C2-H), 7.65 (m, 2H, H-C8, H-C9), 7.69 (td, 1H, *J*=8, 2 Hz, C11-H), 7.75 (td, 1H, *J*=8, 2 Hz, C12-H), 7.83 (dd, 1H, *J*=8, 2 Hz, C10-H), 9.28 (dd, 1H, *J*=8, 2 Hz, C13-H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 8.9 (q, $\underline{C}H_3$-CH$_2$-CO-O-C7), 9.0 (q, $\underline{C}H_3$-CH$_2$-CO-O-C1), 9.2 (q, $\underline{C}H_3$-CH$_2$-CO-O-C2), 21.0 (q, C3-(C$\underline{H}_3$)$_a$), 26.7 (q, C3-(C$\underline{H}_3$)$_b$), 27.4 (t, CH$_3$-$\underline{C}$H$_2$-CO-O-C7), 27.6 (t, CH$_3$-$\underline{C}$H$_2$-CO-O-C1), 27.8 (t, CH$_3$-$\underline{C}$H$_2$-CO-O-C2), 56.1 (q, O-$\underline{C}$H$_3$), 62.1 (d, C-1), 72.1 (d, C-2), 77.0 (s, C-3), 98.4 (d, C-5), 104.9 (s, C-14b), 109.3 (s, C-6a), 116.9 (s, C-7a), 118.7 (d, C-8), 125.9 (d, C-9), 126.9 (d, C-13), 127.3 (d, C-11), 127.5 (d, C-12), 129.1 (d, C-10), 131.3 (s, C-13a), 134.0 (s, C-9a), 148.5 ((s, C-7)+(s, C-13b)), 150.9 (s, C-14a), 155.4 (s, C-4a), 157.0 (s, C-6), 172.3 (s, CH$_3$-CH$_2$-$\underline{C}$O-O-C7), 173.2 (s, CH$_3$-CH$_2$-$\underline{C}$O-O-C1), 174.5 (s, CH$_3$-CH$_2$-$\underline{C}$O-O-C2). DCI-MS *m*/*z*: 560 $[MH]^+$. *Anal.* Calcd for $C_{32}H_{33}NO_8$: C, 68.68; H, 5.94; N, 2.50. Found: C, 68.72; H, 5.97; N, 2.46.

(±)-*cis*-1,2-Di-*O*-carbonyl-6-methoxy-3,3-dimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*c*]pyrano[3,2-*h*]acridin-7-one (22) *N*,*N*′-Carbonyldiimidazole (163 mg, 0.18 mmol) was added to a solution of **16** (65 mg, 0.17 mmol) in dry 2-butanone (5 ml). The reaction mixture was refluxed for 3 h under nitrogen, and then 5% aqueous $NaHCO_3$ (5 ml) was added. The solution was extracted with EtOAc (3×10 ml) and the combined organic layers were dried over anhydrous Na_2CO_3, filtered, and evaporated under reduced pressure. Column chromatography over silica gel (20—45 μm) (solvent: CH_2Cl_2/MeOH 2 : 1) gave **22** (59 mg, 83%) as yellow crystals, mp 240 °C. IR (KBr) cm^{-1}: 3440, 2950, 1810, 1643, 1583, 1487, 1458, 1398, 1210, 1160, 1084, 1032, 975. UV λ_{max} (MeOH) nm (log ε): 223 (4.12), 269 (4.83), 274 (4.87), 294 (3.68), 320 (3.34), 357 (3.31), 368 (3.28), 384 (3.27). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.13 (s, 3H, C3-(C$\underline{H}_3$)$_a$), 1.41 (s, 3H, C3-(C$\underline{H}_3$)$_b$), 3.75 (d, 1H, *J*=5 Hz, C2-H), 3.78 (s, 3H, O-C$\underline{H}_3$), 5.29 (d, 1H, *J*=5 Hz, C1-H), 6.01 (s, 1H, C5-H), 7.33 (d, 1H, *J*=9 Hz, C9-H), 7.57 (td, 1H, *J*=7, 2 Hz, C11-H), 7.59 (td, 1H, *J*=7, 2 Hz, C12-H), 7.86 (dd, 1H, *J*=7, 2 Hz, C10-H), 8.15 (d, 1H, *J*=9 Hz, C8-H), 8.64 (dd, 1H, *J*=7, 2 Hz, C13-H), 12.07 (br s, 1H, D_2O exch., N-$\underline{H}$). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 24.8 (q, C3-(C$\underline{H}_3$)$_a$), 25.6 (q, C3-(C$\underline{H}_3$)$_b$), 56.5 (q, O-C$\underline{H}_3$), 65.6 (d, C-1), 71.2 (s, C-3), 78.8 (d, C-2), 93.4 (d, C-5), 103.4 (s, C-14b), 110.0 (s, C-6a), 119.3 ((s, C-7a)+(d, C-8)), 123.9 (d, C-9), 124.5 (d, C-13), 126.2 (d, C-11), 128.5 (d, C-12), 128.6 (s, C-13a), 128.9 (d, C-10), 135.8 ((s, C-9a)+(s, C-13b)), 143.3 (s, C-14a), 150.8 (s, CO), 155.1 (s, C-4a), 161.5 (s, C-6), 175.7 (s, C7). DCI-MS *m*/*z*: 418 $[MH]^+$. *Anal.* Calcd for $C_{24}H_{19}NO_6$: C, 69.06; H, 4.59; N, 3.36. Found: C, 65.97; H, 4.65; N, 3.46.

1-(6-Methoxyquinolin-8-ylamino)-2-naphthalenecarboxylic Acid (26)

6-Methoxy-8-aminoquinoline (**23**) (280 mg, 1.61 mmol) and 1-bromo-2-naphthalenecarboxylic acid (**9**) (404 mg, 1.61 mmol) were condensed under conditions similar to those described for the preparation of **14**. Purification by flash chromatography (solvent: CH_2Cl_2/MeOH 97 : 3) gave **26** (264 mg, 48%) as yellow crystals from MeOH, mp 246 °C. IR (KBr) cm^{-1}: 3200, 2942, 1620, 1270. UV λ_{max} (MeOH) nm (log ε): 270 (4.82), 313 (4.41), 372 (3.65). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 3.65 (s, 3H, O-C$\underline{H}_3$), 5.79 (d, 1H, J=2 Hz, C7′-H), 6.72 (d, 1H, J=2 Hz, C5′-H), 7.49 (td, 1H, J=8, 1.5 Hz, C6-H), 7.54 (dd, 1H, J=8, 5 Hz, C3′-H), 7.61 (td, 1H, J=8, 1.5 Hz, C7-H), 7.83 (d, 1H, J=9 Hz, C4-H), 7.92 (dd, 1H, J=8, 1.5 Hz, C5-H), 7.98 (d, 1H, J=9 Hz, C3-H), 8.06 (dd, 1H, J=8, 1.5 Hz, C8-H), 8.19 (dd, 1H, J=8, 2 Hz, C4′-H), 8.75 (dd, 1H, J=5, 2 Hz, C2′-H), 8.92 (br s, 1H, D_2O exch., N$\underline{H}$), 10.03 (br s, 1H, D_2O exch., COO$\underline{H}$). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 56.1 (q, O-$\underline{C}H_3$), 96.7 (d, C-7′), 102.5 (d, C-5′), 122.3 (s, C-2), 123.5 (d, C-3′), 125.4 (d, C-4), 126.9 (d, C-6), 127.3 (s, C-8a), 127.6 (d, C-5), 129.3 (d, C-3), 129.6 (d, C-8), 130.3 (d, C-7), 130.6 (s, C-4′a), 136.0 (d, C-4′), 136.3 (s, C-8′), 136.7 (s, C-4a), 141.9 (s, C-8′a), 142.7 (d, C-2′), 144.6 (s, C-1), 158.7 (s, C-6′), 169.6 (s, $\underline{C}$OOH). DCI-MS m/z: 345 $[MH]^+$. *Anal.* Calcd for $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68; N, 8.13. Found: C, 73.22; H, 4.64; N, 8.16.

1-(Quinolin-8-ylamino)-2-naphthalenecarboxylic Acid (27) 8-Aminoquinoline (**24**) (172 mg, 1.19 mmol) and 1-bromo-2-naphthalenecarboxylic acid (**9**) (300 mg, 1.19 mmol) were condensed under conditions similar to those described for the preparation of **14**. Flash chromatography (solvent: CH_2Cl_2/MeOH 97 : 3) afforded **27** (153 mg, 41% yield) as yellow crystals from MeOH, mp 252—253 °C. IR (KBr) cm^{-1}: 3200, 2990, 1670, 1595. UV λ_{max} (MeOH) nm (log ε): 273 (3.21), 344 (4.47), 352 (4.32). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 6.25 (dd, 1H, J=8, 2 Hz, C7′-H), 7.18 (t, 1H, J=8 Hz, C6′-H), 7.33 (dd, 1H, J=8, 2 Hz, C5′-H), 7.55 (td, 1H, J=8, 1.5 Hz, C6-H), 7.61 (dd, 1H, J=8, 5 Hz, C3′-H), 7.64 (td, 1H, J=8, 1.5 Hz, C7-H), 7.80 (d, 1H, J=9 Hz, C4-H), 7.89 (dd, 1H, J=8, 1.5 Hz, C5-H), 7.99 (d, 1H, J=9 Hz, C3-H), 8.06 (dd, 1H, J=8, 1.5 Hz, C8-H), 8.32 (dd, 1H, J=8, 2 Hz, C4′-H), 8.95 (dd, 1H, J=5, 2 Hz, C2′-H), 10.10 (br s, 1H, D_2O exch., N$\underline{H}$), 11.75 (br s, 1H, D_2O exch., COO$\underline{H}$). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 110.6 (d, C-7′), 118.7 (d, C-5′), 121.5 (s, C-2), 123.2 (d, C-3′), 125.0 (d, C4), 127.2 ((d, C-6)+(s, C8a)), 127.3 (d, C-5), 127.7 (d, C-3), 127.8 (d, C-8), 129.2 (s, C-4′a), 129.4 (d, C-6′), 129.6 (d, C-7), 136.8 (s, C-4a), 137.3 (d, C-4′), 139.5 (s, C-8′), 142.6 (s, C-8′a), 143.4 (s, C-1), 149.4 (d, C-2′), 169.8 (s, $\underline{C}$OOH). DCI-MS m/z: 315 $[MH]^+$. *Anal.* Calcd for $C_{20}H_{14}N_2O_2$: C, 76.42; H, 4.49; N, 8.91. Found: C, 76.31; H, 4.43; N, 8.97.

1-(Quinolin-5-ylamino)-2-naphthalenecarboxylic Acid (28) 5-Aminoquinoline (**25**) (172 mg, 1.19 mmol) and 1-bromo-2-naphthalenecarboxylic acid (**9**) (300 mg, 1.19 mmol) were condensed under conditions similar to those described for the preparation of **14**. Flash chromatography (solvent: CH_2Cl_2/MeOH 97 : 3) afforded **28** (183 mg, 49% yield) as yellow crystals from MeOH, mp 237—238 °C. IR (KBr) cm^{-1}: 3260, 3000, 1670, 1600. UV λ_{max} (MeOH) nm (log ε): 269 (3.56), 332 (4.21), 347 (4.67). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 6.24 (dd, 1H, J=8, 1 Hz, C6′-H), 7.34 (t, 1H, J=8 Hz, C7′-H), 7.36 (dd, 1H, J=8, 1 Hz, C5′-H), 7.55 (td, 1H, J=8, 1.5 Hz, C6-H), 7.62 (dd, 1H, J=8, 5 Hz, C3′-H), 7.68 (td, 1H, J=8, 1.5 Hz, C7-H), 7.83 (d, 1H, J=9 Hz, C4-H), 7.90 (dd, 1H, J=8, 1.5 Hz, C5-H), 7.98 (d, 1H, J=9 Hz, C3-H), 8.02 (dd, 1H, J=8, 1.5 Hz, C8-H), 8.37 (dd, 1H, J=8, 2 Hz, C4′-H), 8.91 (dd, 1H, J=5, 2 Hz, C2′-H), 8.95 (br s, 1H, D_2O exch., N$\underline{H}$), 9.62 (br s, 1H, D_2O exch., COO$\underline{H}$). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 113.0 (d, C-6′), 120.5 (s, C-2), 122.0 (s, C-4′a), 122.4 (d, C-8′), 124.7 ((d, C3′)+(d, C-4)), 126.8 (d, C-6), 127.3 (d, C-5), 127.8 (d, C-3), 128.8 (s, C-8a), 129.4 (d, C-8), 129.6 (d, C-7), 130.7 (d, C-7′), 131.8 (d, C-4′), 137.2 (s, C-4a), 144.1 (s, C-8′), 144.4 (s, C-1), 149.8 (s, C-8′a), 151.8 (d, C-2′), 170.7 (s, $\underline{C}$OOH). DCI-MS m/z: 315 $[MH]^+$. *Anal.* Calcd for $C_{20}H_{14}N_2O_2$: C, 76.42; H, 4.49; N, 8.91. Found: C, 76.40; H, 4.53; N, 9.01.

6-Methoxynaphtho[1,2-*b*][1,10]-phenanthrolin-7(14*H*)-one (29) A solution of **26** (200 mg, 0.58 mmol) in concentrated sulfuric acid (5 ml) was heated at 100 °C for 5 h. The cooled solution was poured on ice-water, filtered, and the precipitate was partitioned between CH_2Cl_2 (150 ml) and 10 M aqueous NaOH (100 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Crystallization from EtOH gave **29** (81 mg, 43%) as yellow crystals, mp 270 °C. IR (KBr) cm^{-1}: 3280, 2980, 1642. UV λ_{max} (MeOH) nm (log ε): 263 (4.73), 284 (4.61), 352 (3.74). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 4.09 (s, 3H, O-C$\underline{H}_3$), 6.83 (s, 1H, C5-H), 7.52 (dd, 1H, J=8, 5 Hz, C3-H), 7.67 (d, 1H, J=9 Hz, C9-H), 7.74 (td, 1H, J=8, 2 Hz, C11-H), 7.80 (td, 1H, J=8, 2 Hz, C12-H), 7.98 (dd, 1H, J=8, 2 Hz, C10-H), 8.49 (dd, 1H, J=8, 2 Hz, C13-H), 8.64 (d, 1H, J=9 Hz, C8-H), 8.67 (dd, 1H, J=8, 2 Hz, C4-H), 8.83 (dd, 1H, J=5, 2 Hz, C2-H), 10.93 (br s, 1H, D_2O exch., N$\underline{H}$). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 56.3 (q, O-$\underline{C}H_3$), 95.3 (d, C-6), 110.3 (s, C-6a), 122.3 (s, C-7a), 123.1 (d, C-8), 123.5 (d, C-9), 123.6 (d, C-3), 123.8 (d, C-9), 126.6 (d, C-11), 129.0 (d, C-13), 129.1 (d, C-10), 130.5 (s, C-4a), 135.0 (s, C-13a), 135.8 (d, C-4), 136.7 (s, C-14a), 139.2 (s, C-14b), 142.1 (s, C-9a), 145.6 (s, C-13b), 146.0 (d, C-2), 158.3 (s, C-6), 176.9 (s, C7). DCI-MS m/z: 327 $[MH]^+$. *Anal.* Calcd for $C_{21}H_{14}N_2O_2$: C, 77.29; H, 4.32; N, 8.58. Found: C, 77.22; H, 4.37; N, 8.66.

Naphtho[1,2-*b*][1,10]-phenanthrolin-7(14*H*)-one (30) 1-(Quinolin-8-ylamino)-naphthalene-2-carboxylic acid **27** (400 mg, 1.27 mmol), treated under conditions similar to those described for the preparation of **29** from **26**, gave **30** (150 mg, 40%) which crystallized in MeOH as yellow crystals, mp 287 °C. IR (KBr) cm^{-1}: 3000, 2850, 1670. UV λ_{max} (MeOH) nm (log ε): 263 (3.98), 278 (4.52), 348 (4.39). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 7.59 (d, 1H, J=9 Hz, C5-H), 7.62 (dd, 1H, J=8, 5 Hz, C3-H), 7.70 (d, 1H, J=9 Hz, C9-H), 7.72 (td, 1H, J=8, 2 Hz, C11-H), 7.74 (td, 1H, J=8, 2 Hz, C12-H), 7.98 (dd, 1H, J=8, 2 Hz, C10-H), 8.24 (dd, 1H, J=8, 2 Hz, C4-H), 8.47 dd, 1H, J=8, 2 Hz, C13-H), 8.49 (d, 1H, J=9 Hz, C6-H), 8.52 (d, 1H, J=9 Hz, C8-H), 8.98 (dd, 1H, J=5, 2 Hz, C2-H), 11.25 (br s, 1H, D_2O exch., N$\underline{H}$). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 119.9 (s, C-6a), 120.1 (s, C-7a), 120.4 (d, C-8), 120.6 (d, C-5), 122.9 (d, C-6), 123.0 (d, C-3), 123.4 ((d, C-9)+(d, C-13)), 126.6 (d, C-11), 128.8 (d, C-12), 129.1 (d, C-10), 130.8 (s, C-4a), 135.4 ((d, C-4)+(s, C-13a)), 141.2 (s, C-14a), 142.0 (s, C-9a), 143.8 (s, C-14b), 147.2 (s, C-13b), 148.6 (d, C-2), 177.5 (s, C7). DCI-MS m/z: 297 $[MH]^+$. *Anal.* Calcd for $C_{20}H_{12}N_2O$: C, 81.07; H, 4.08; N, 9.45. Found: C, 80.94; H, 4.07; N, 9.46.

Naphtho[1,2-*b*][1,7]-phenanthrolin-7(14*H*)-one (31) 1-(Quinolin-5-ylamino)-naphthalene-2-carboxylic acid **28** (100 mg, 0.32 mmol), treated under conditions similar to those described for the preparation of **29** from **26**, gave **31** (44 mg, 46%) which crystallized in EtOH as yellow crystals, mp 265 °C. IR (KBr) cm^{-1}: 3150, 2900, 1620. UV λ_{max} (MeOH) nm (log ε): 254 (3.97), 280 (3.43), 347 (4.22). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 7.39 (d, 1H, J=9 Hz, C5-H), 7.64 (dd, 1H, J=8, 5 Hz, C2-H), 7.73 (d, 1H, J=9 Hz, C9-H), 7.76 (td, 1H, J=8, 2 Hz, C11-H), 7.79 (td, 1H, J=8, 2 Hz, C12-H), 8.04 (dd, 1H, J=8, 2 Hz, C10-H), 8.43 (d, 1H, J=9 Hz, C6-H), 8.63 (d, 1H, J=9 Hz, C8-H), 8.55 (dd, 1H, J=8, 2 Hz, C13-H), 8.85 (dd, 1H, J=5, 2 Hz, C3-H), 9.42 (dd, 1H, J=8, 2 Hz, C1-H), 12.63 (br s, 1H, D_2O exch., N$\underline{H}$). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 116.3 (s, C-14b), 117.4 (s, C-6a), 121.4 (s, C-7a), 122.0 (d, C-8), 122.8 (d, C2), 123.6 (d, C-5), 124.2 (d, C-9), 124.7 (d, C-13), 126.3 (d, C-11), 128.1 (d, C-6), 129.1 (d, C-12), 129.8 (d, C-10), 133.0 (d, C-1), 136.0 (s, C-13a), 140.1 (s, C-14a), 142.5 (s, C-9a), 146.7 (s, C-13b), 152.6 (s, C-4a), 154.9 (d, C-3), 177.4 (s, C7). DCI-MS m/z: 297 $[MH]^+$. *Anal.* Calcd for $C_{20}H_{12}N_2O$: C, C, 81.07; H, 4.08; N, 9.45. Found: C, 81.13; H, 4.16; N, 9.37.

6-Methoxy-14-methylnaphtho[1,2-*b*][1,10]-phenanthrolin-7(14*H*)-one (6) Methyl iodide (0.045 ml, 0.72 mmol) was added to a solution of **29** (125 mg, 0.38 mmol), benzyltriethylammonium chloride (330 mg, 1.45 mmol), and 50% aqueous NaOH (3 ml) in 2-butanone (5 ml). The reaction mixture was stirred and refluxed for 3 h. The cooled solution was diluted with a mixture of CH_2Cl_2 (10 ml) and H_2O (5 ml). The aqueous phase was extracted with CH_2Cl_2 (2×20 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Crystallization from EtOAc gave **6** (44 mg, 34%) as a yellow crystals, mp 295—296 °C. IR (KBr) cm^{-1}: 3220, 2990, 1610, 1490, 1250, 760. UV λ_{max} (MeOH) nm (log ε): 266 (3.32), 282 (4.53), 342 (4.61). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 4.27 (s, 3H, N-C$\underline{H}_3$), 4.46 (s, 3H, O-C$\underline{H}_3$), 6.89 (s, 1H, C5-H), 7.60 (dd, 1H, J=8, 5 Hz, C3-H), 7.74 (td, 1H, J=8, 2 Hz, C11-H), 7.81 (td, 1H, J=8, 2 Hz, C12-H), 7.83 (d, 1H, J=9 Hz, C9-H), 8.00 (dd, 1H, J=8, 2 Hz, C10-H), 8.68 (dd, 1H, J=8, 2 Hz, C4-H), 8.70 (d, 1H, J=9 Hz, C8-H), 8.72 (dd, 1H, J=8, 2 Hz, C13-H), 8.96 (dd, 1H, J=5, 2 Hz, C2-H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 43.4 (q, N-$\underline{C}H_3$), 56.5 (q, O-$\underline{C}H_3$), 96.4 (d, C-6), 111.2 (s, C-6a), 123.1 (d, C-3), 124.8 (d, C-8), 125.0 (d, C-9), 125.4 (d, C-13), 126.2 (s, C-7a), 127.2 (d, C-11), 128.6 (d, C-12), 129.1 (d, C-10), 130.7 (s, C-4a), 134.0 (d, C-4), 135.9 (s, C-13a), 138.2 (s, C-14a), 142.2 (s, C-14b), 142.7 (s, C-9a), 143.7 (d, C-2), 148.3 (s, C-13b), 159.8 (s, C-6), 177.1 (s, C7). DCI-MS m/z: 341 $[MH]^+$. *Anal.* Calcd for $C_{22}H_{16}N_2O_2$: C, 77.63; H, 4.74; N, 8.23. Found: C, 77.72; H, 4.79; N, 8.15.

14-Methylnaphtho[1,2-*b*][1,10]-phenanthrolin-7(14*H*)-one (7) Naphtho[1,2-*b*][1,10]-phenanthrolin-7(14*H*)-one (**30**) (113 mg, 0.38 mmol), treated under conditions similar to those described for the preparation of **6** from **29**, afforded **7** (42 mg, 48%) as yellow crystals, mp 291 °C. IR (KBr) cm^{-1}: 3200—2950, 1645, 1300, 750. UV λ_{max} (MeOH) nm (log ε): 252 (4.23), 282 (4.55), 344 (3.97), 367 (3.81). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 4.43 (s, 1H, N-CH_3), 7.58 (dd, 1H, J=8, 5 Hz, C3-H), 7.70 (m, 2H, C11-

H, C12-H), 7.72 (d, 1H, J=9 Hz, C5-H), 7.77 (d, 1H, J=9 Hz, C9-H), 7.98 (dd, 1H, J=8, 2 Hz, C10-H), 8.26 (dd, 1H, J=8, 2 Hz, C4-H), 8.44 (d, 1H, J=9 Hz, C6-H), 8.55 (d, 1H, J=9 Hz, C8-H), 8.74 dd, 1H, J=8, 2 Hz, C13-H), 9.02 (dd, 1H, J=5, 2 Hz, C2-H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 51.9 (q, N-CH_3), 122.7 (d, C-5), 122.0 (d, C-8), 123.0 (d, C-6), 123.4 (d, C-3), 124.4 (d, C-9), 125.2 (s, C-6a), 125.4 (d, C-13), 125.8 (s, C-7a), 127.6 (d, C-11), 128.3 (d, C-12), 128.8 (d, C-10), 131.7 (s, C-4a), 136.4 (d, C-4), 136.9 (s, C-13a)), 142.4 (s, C-9a), 146.6 (s, C-14a), 147.8 (s, C-14b), 147.9 (d, C-2), 150.3 (s, C-13b), 178.3 (s, C7). DCI-MS m/z: 311 $[MH]^+$. *Anal.* Calcd for $C_{21}H_{14}N_2O$: C, 81.27; H, 4.55; N, 9.03. Found: C, 81.34; H, 4.47; N, 9.12.

14-Methylnaphtho[1,2-*b*][1,7]-phenanthrolin-7(14*H*)-one (8) Naphtho[1,2-*b*][1,7]-phenanthrolin-7(14*H*)-one (**31**) (90 mg, 0.30 mmol), treated under conditions similar to those described for the preparation of **6** from **29**, gave **8** (48 mg, 52% yield) as yellow crystals from EtOAc, mp 279—280 °C. IR (KBr) cm^{-1}: 3100, 3000, 1670, 1300, 750. UV λ_{max} (MeOH) nm (log ε): 261 (3.70), 301 (4.21), 352 (4.47). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 4.38 (s, 1H, N-CH_3), 7.52 (dd, 1H, J=8, 5 Hz, C2-H), 7.59 (d, 1H, J=9 Hz, C5-H), 7.69 (td, 1H, J=8, 2 Hz, C11-H), 7.72 (td, 1H, J=8, 2 Hz, C12-H), 7.80 (d, 1H, J=9 Hz, C9-H), 8.02 (dd, 1H, J=8, 2 Hz, C10-H), 8.52 (d, 1H, J=9 Hz, C6-H), 8.71 (dd, 1H, J=8, 2 Hz, C13-H), 8.75 (dd, 1H, J=5, 2 Hz, C3-H), 8.78 (d, 1H, J=9 Hz, C8-H), 9.07 (dd, 1H, J=8, 2 Hz, C1-H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 44.9 (s, N-CH_3), 118.3 (s, C-14b), 120.3 (d, C2), 122.3 (s, C-6a), 123.4 (s, C-7a), 124.9 (d, C-8), 125.1 (d, C-13), 125.5 (d, C-9), 126.1 (d, C-5), 126.3 (d, C-11), 127.8 (d, C-6), 129.0 (d, C-12), 130.1 (d, C-10), 134.2 (d, C-1), 136.8 (s, C-13a), 142.3 (s, C-9a), 145.2 (s, C-14a), 149.9 (s, C-13b), 153.1 (d, C-3), 154.7 (s, C-4a), 177.8 (s, C7). DCI-MS m/z: 311 $[MH]^+$. *Anal.* Calcd for $C_{21}H_{14}N_2O$: C, 81.27; H, 4.55; N, 9.03. Found: C, 81.14; H, 4.51; N, 9.07.

Pharmacology Cytotoxicity: Murine leukemia L1210 cells from the American Type Culture Collection (Rockville Pike, MD, U.S.A.) were grown in RPMI medium 1640 supplemented with 10% fetal calf serum, L-glutamine 2 mM, penicillin 100 U/ml, streptomycin 100 μg/ml, and HEPES buffer 10 mM (pH 7.4). The cytotoxicity was measured using the microculture tetrazolium assay essentially as described.[25] Cells were exposed for 48 h to nine graded concentrations in triplicate of the test drug. Results are expressed as IC_{50} values (mean, n=3), which are defined as the drug concentration inhibiting the absorbance by 50% with respect to that of untreated cells.

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