# Synthesis and Cytotoxic Activity of Benzophenanthrolinone Analogues of Acronycine

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**Condensation of either 2-bromobenzoic acid (4) or 2-chloro-3-nitrobenzoic acid (5) with suitable aminoquinolines 6—8 afforded phenylquinolylamines 9—13. Acid mediated cyclization gave the corresponding 12*H*-benzo[*b*][1,7]phenanthrolin-7-ones 14 and 15, and 12*H*-benzo[*b*][1,10]phenanthrolin-7-ones 16—18. Compounds 14, 16, and 17 were subsequently *N*-methylated to 6-demethoxyacronycine and acronycine analogues 19—21, whereas reduction of the aromatic nitro group of 18 gave the amino derivative 22. Unsubstituted 12*H*-benzo[*b*][1,10]phenanthrolin-7-ones 16, 17, 20, and 21 were devoid of significant cytotoxic activity, whereas 18 and 22, bearing a nitrogen substituent at position 11, were significantly active. Unsubstituted 12*H*-benzo[*b*][1,7]phenanthrolin-7-ones 14 and 19, which include a pyridine nitrogen in the same 4-position as the pyran oxygen of acronycine exhibited cytotoxic activities within the same range of magnitude as acronycine itself.**

**Key words** acronycine; benzophenanthrolinone; cytotoxicity

The acridone alkaloid acronycine (**1**), which was first isolated from *Acronychia baueri* SCHOTT (Rutaceae) in 1948, was later found to be a potent anticancer agent.[1—5] It is of interest because of its activity against a broad spectrum of solid tumors, including numerous sarcomas, myelomas, carcinomas, and melanomas.[2—6] Nevertheless, its low water-solubility and moderate potency have severely hampered its clinical trials, which have given so far only poor results.[7] Consequently, the development of structural analogues possessing a basic nitrogen atom able to give water-soluble salts seems highly desirable.[8,9]

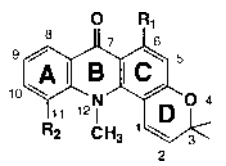
The replacement of the dimethylpyran D ring of acronycine by a pyridine unit, present in numerous tetracyclic antitumor drugs including the linear ellipticines[10—12] and olivacines,[13—15] and their angular 7*H*- and 11*H*-pyridocarbazoles counterparts,[16—19] appeared to us an attractive way to look for new anticancer candidates. In addition, this approach was consistent with the antitumor activities of several recently described benzophenanthrolinones related to amsacrine.[20]

This paper deals with the synthesis and cytotoxic properties of 12*H*-benzo[*b*][1,7] and [1,10]phenanthrolinones related to acronycine, and also to 6-demethoxyacronycine (**2**) and 11-aminoacronycine (**3**), which were shown to exhibit cytotoxic activities within the same range of magnitude as acronycine itself.[9,21]

**Chemistry** The key-step of our approach was an Ullmann condensation[22] of either 2-bromobenzoic acid (**4**) or 2-chloro-3-nitrobenzoic acid (**5**) with suitable aminoquinolines **6**—**8**, to afford the carboxylic phenylquinolylamines **9**—**13**. Cyclization to the corresponding 12*H*-benzo[*b*][1,7]phenanthrolin-7-ones **14** and **15**, and 12*H*-benzo[*b*][1,10]phenanthrolin-7-ones **16**—**18** was obtained by use of trifluoroacetic anhydride[21,23] or concentrated sulfuric acid.[20,24] Methylation at *N*-12 using methyl iodide under classical or phase-transfer catalyzed conditions[21,23] could only be ensured in the cases of compounds **14**, **16**, and **17**, which bear no bulky nitro substitutent at C-11. This reaction gave access to 6-demethoxyacronycine analogues 12-methyl-12*H*-benzo[*b*][1,7]phenanthrolin-7-one (**19**) and 12-methyl-12*H*-benzo[*b*][1,10]phenanthrolin-7-one (**20**), and to acronycine analogue 6-methoxy-12-methyl-12*H*-benzo[*b*][1,10]phenanthrolin-7-one (**21**). Reduction of the nitro group of **18** by catalytic hydrogenation gave 11-amino-12*H*-benzo[*b*][1,10]phenanthrolin-7-one (**22**). In contrast, all attempts towards the reduction of the nitro group of **15** failed, most probably due to the almost complete insolubility of this compound in usual organic solvents.

**Pharmacology** The study of the biological properties of the new benzophenanthrolin-7-one derivatives was carried out *in vitro* on L1210 murine leukemia cell line. The results ($IC_{50}$) are reported in Table 1.

The two 12*H*-benzo[*b*][1,7]phenanthrolin-7-ones **14** and **19** were as potent as acronycine. In the 12*H*-benzo[*b*][1,10]-




**1** $R_1 = OCH_3$, $R_2 = H$
**2** $R_1 = R_2 = H$
**3** $R_1 = OCH_3$, $R_2 = NH_2$

Chart 1

Table 1. Cytotoxic Activities of Benzophenanthrolinones **14**—**22** Compared with Acronycine Derivatives **1**—**3**

| Compound | **1** | **2** | **3** | **14** | **15** | **16** | **17** | **18** | **19** | **20** | **21** | **22** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $IC_{50}$ ($\mu$M) L1210 cells | 10.4 | 29.9 | 18.8 | 15 | ins[a)] | >100 | 33 | 7.7 | 10.7 | 72.1 | 80.8 | 25.4 |

*a*) ins: insoluble.

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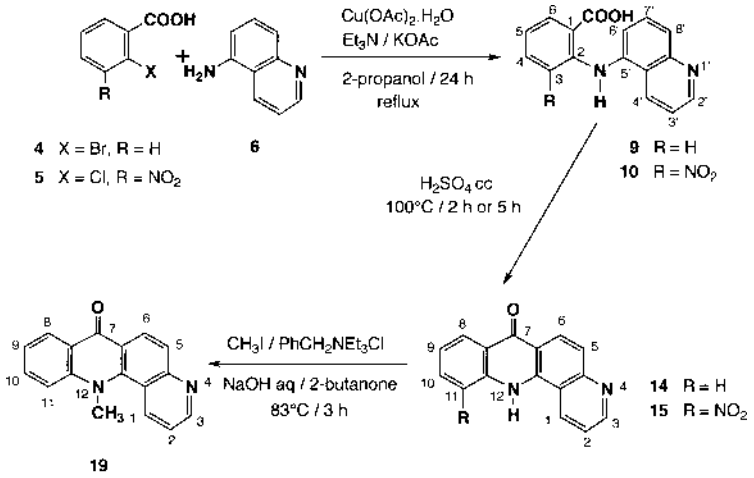


Chart 2

phenanthrolin-7-one series, compounds **18** and **22** were significantly active, whereas **16**, **17**, **20**, and **21** were devoid of antiproliferative activity.

## Results and Discussion

Considering the structure-activity relationships, it appears that in the 12*H*-benzo[*b*][1,10]phenanthrolin-7-one series, only compounds **18** and **22**, bearing a nitrogen substitutent at position 11, exhibited significant cytotoxic activity. Unsubstituted compounds **16**, **17**, **20**, and **21** were devoid of significant activity. Surprisingly, it should be noted that compound **16**, previously prepared as an intermediate in the course of the preparation of amsacrine analogues, was reported to be highly cytotoxic.[20)]

Interestingly, 12*H*-benzo[*b*][1,7]phenanthrolin-7-ones **14** and **19**, which include a pyridine nitrogen in the same 4-position as the pyran oxygen of acronycine exhibited cytotoxic activities within the same range of magnitude as acronycine itself. The position of the heteroatom in the heterocyclic D ring fused onto the A–B–C acridone tricyclic system therefore appears to have a dramatic influence on the cytotoxic activity.

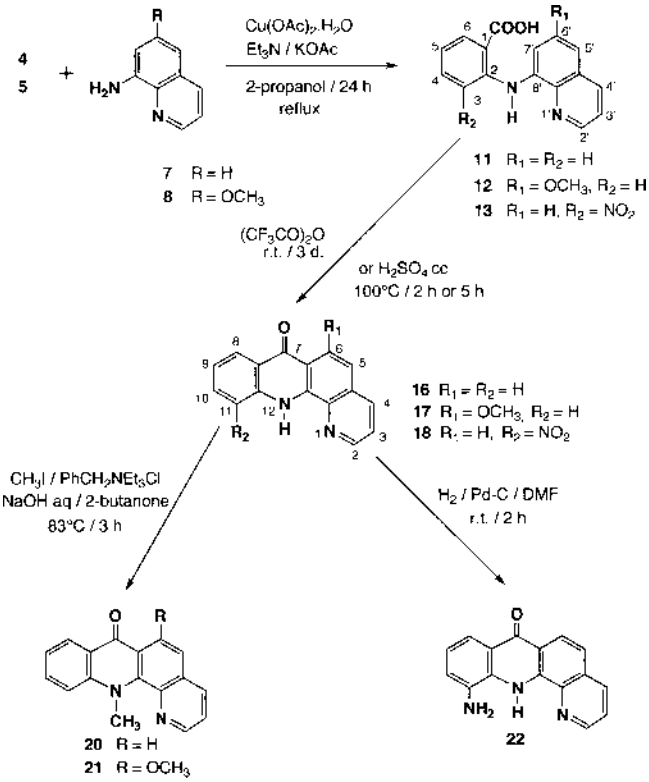


Chart 3

### Experimental

**Chemistry** Mass spectra were recorded with a Nermag R-10-10C spectrometer using electron impact (MS) and/or desorption chemical ionization (DCI-MS; reagent gas: $NH_3$) techniques. UV spectra ($\lambda_{max}$ in nm) were determined in spectroscopic grade MeOH on a Beckman Model 34 spectrophotometer. IR spectra ($\nu_{max}$ in $cm^{-1}$) were obtained in potassium bromide pellets on a Perkin-Elmer 257 instrument. $^1$H-NMR ($\delta$ [ppm], $J$ [Hz]) and $^{13}$C-NMR spectra were recorded at 300 MHz and 75 MHz, respectively, using a Bruker AC-300 spectrometer. Column chromatography was conducted using flash silica gel 60 Merck (40—63 $\mu$m) with an overpressure of 300 mbars.

*N*-(5-Quinolyl)anthranilic Acid (**9**): A mixture containing 5-aminoquinoline (**6**) (216 mg, 1.5 mmol), 2-bromobenzoic acid (**4**) (301.5 mg, 1.5 mmol), potassium acetate (438 mg, 4.47 mmol), copper(II) acetate monohydrate (12 mg, 0.06 mmol), triethylamine (0.25 ml, 1.77 mmol), and 2-propanol (8 ml) was stirred and heated under reflux for 24 h. After cooling and evaporating the solvent, the residue was treated with 1 N HCl (30 ml) and extracted with $CH_2Cl_2$ (3×25 ml). The organic layer was separated, dried over anhydrous $Na_2SO_4$, filtered, and evaporated under reduced pressure. Column chromatography on silica gel ($CH_2Cl_2$/MeOH : 80/20) followed by crystallization from methanol gave **9** (213 mg, 53%) as yellow crystals, mp: 262—263 °C. IR (KBr) $cm^{-1}$: 3240, 3020, 1680, 1600. UV $\lambda_{max}$ (MeOH) nm (log $\varepsilon$): 264 (4.19), 342 (3.65). $^1$H-NMR (300 MHz, DMSO-$d_6$) $\delta$: 6.78 (td, 1H, $J$=8; 2 Hz, C5-H), 6.93 (dd, 1H, $J$=8; 2 Hz, C3-H), 7.32 (td, 1H, $J$=8; 2 Hz, C4-H), 7.53 (dd, 1H, $J$=8; 5 Hz, C3′-H), 7.57 (dd, 1H, $J$=8; 2 Hz, C6′-H), 7.73 (t, 1H, $J$=8 Hz, C7′-H), 7.85 (dd, 1H, $J$=8; 2 Hz, C8′-H), 7.96 (dd, 1H, $J$=8; 2 Hz, C6-H), 8.35 (dd, 1H, $J$=8; 2 Hz, C4′-H), 8.95 (dd, 1H, $J$=5; 2 Hz, C2′-H), 11.20 (br s, 1H, $D_2O$ exch., COOH), 13.10 (br s, 1H, $D_2O$ exch., NH). $^{13}$C-NMR (75 MHz, DMSO-$d_6$) $\delta$: 113.8 (s, C-1), 115.2 (d, C-3), 118.7 (d, C-5), 120.6 (d, C-6′), 124.7 ((s, C-4′a), (d, C-3′)), 126.4 (d, C-8′), 130.7 (d, C-7′) 131.6 (d, C-4′), 132.9 (d, C-6), 135.3 (d, C-4), 137.8 (s, C-5′), 149.2 (s, C-2), 150.0 (s, C-8′a), 151.8 (d, C-2′), 171.4 (s, COOH). MS *m/z*: 264 ($M^+$), 249, 219. *Anal*. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58; N, 10.60. Found: C, 72.88; H, 4.50; N, 10.45.

3-Nitro-*N*-(5-quinolyl)anthranilic Acid (**10**): Treatment of **6** (175 mg, 1.21 mmol) with 2-chloro-3-nitrobenzoic acid (**5**) (246 mg, 1.22 mmol) under the conditions previously described for **9** afforded **10** (226 mg, 60%) as yellow crystals, mp: 205—206 °C. IR (KBr) $cm^{-1}$: 3200—2850, 1630, 1620, 1560, 1350. UV $\lambda_{max}$ (MeOH) nm (log $\varepsilon$): 233 (3.75), 280 (3.68). $^1$H-NMR (300 MHz, DMSO-$d_6$) $\delta$: 6.79 (dd, 1H, $J$=8; 2 Hz, C6′-H), 7.32 (t, 1H, $J$=8, C5-H), 7.56 (dd, 1H, $J$=8; 5 Hz, C3′-H), 7.70 (t, 1H, $J$=8 Hz, C7′-H), 7.82 (dd,

1H, *J*=8; 2 Hz, C8′-H), 7.90 (dd, 1H, *J*=8; 2 Hz, C6-H), 8.35 (dd, 1H, *J*=8; 2 Hz, C4-H), 8.37 (dd, 1H, *J*=8; 2 Hz, C4′-H), 8.94 (dd, 1H, *J*=5; 2 Hz, C2′-H), 12.41 (br s, 1H, $D_2O$ exch., COOH), 13.62 (br s, 1H, $D_2O$ exch., NH). $^{13}$C-NMR (75 MHz, DMSO-$d_6$) $\delta$: 119.3 (d, C-5), 121.0 (d, C-6′), 122.1 (d, C-8′), 123.4 (s, C-1), 123.9 (s, C-4′a), 124.3 (d, C-3′), 124.6 (d, C-7′), 127.1 (d, C-4), 131.9 (s, C-4′), 137.2 (s, C-5′), 137.4 (d, C-6), 139.0 (s, C-2), 140.2 (s, C-3), 149.9 (s, C-8′a), 151.2 (d, C-2′), 170.8 (s, COOH). MS *m/z*: 309 ($M^+$), 264. *Anal*. Calcd for $C_{16}H_{11}N_3O_4$: C, 62.14; H, 3.58; N, 13.59. Found: C, 62.55; H, 3.46; N, 13.42.

*N*-(8-Quinolyl)anthranilic Acid (**11**): 8-Aminoquinoline (**7**) (216 mg, 1.5 mmol) was reacted with **4** under conditions similar to those described for the preparation of **9** to afford **11** (163 mg, 41%) as yellow crystals, mp: 266—267 °C. IR (KBr) cm$^{-1}$: 3200—3000, 1670, 1600. UV $\lambda_{max}$ (MeOH) nm (log $\varepsilon$): 244 (4.08), 261 (4.30), 378 (3.04). $^1$H-NMR (300 MHz, DMSO-$d_6$) $\delta$: 6.95 (td, 1H, *J*=8; 2 Hz, C5-H), 7.51 (m, 2H, C4-H, C7′-H,), 7.54 (t, 1H, *J*=8 Hz, C6′-H), 7.60 (dd, 1H, *J*=8; 5 Hz, C3′-H), 7.75 (dd, 1H, *J*=8; 2 Hz, C5′-H), 7.77 (dd, 1H, *J*=8; 2 Hz, C3-H), 7.79 (dd, 1H, *J*=8; 2 Hz, C6-H), 8.35 (dd, 1H, *J*=8; 2 Hz, C4′-H), 8.90 (dd, 1H, *J*=5; 2 Hz, C2′-H), 11.00 (br s, 1H, $D_2O$ exch., COOH), 13.10 (br s, 1H, $D_2O$ exch., NH). $^{13}$C-NMR (75 MHz, DMSO-$d_6$) $\delta$: 112.7 (d, C-3), 116.8 (d, C-5′), 117.7 (s, C-1), 120.0 (d, C-5), 120.2 (d, C-7′), 123.2 (d, C-3′), 128.0 (d, C-4), 128.7 (s, C-4′a), 133.1 (d, C-6), 134.9 (d, C-6′), 137.4 (d, C-4′), 138.8 (s, C-8′), 140.4 (s, C-8′a), 145.5 (s, C-2), 149.6 (d, C-2′), 170.2 (s, COOH). MS *m/z*: 264 ($M^+$), 249, 219. *Anal*. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58; N, 10.60. Found: C, 72.80; H, 4.37; N, 10.75.

2-(6-Methoxyquinolin-8-ylamino)benzoic Acid (**12**): 6-Methoxy-8-aminoquinoline (**8**) (353 mg, 2.03 mmol) was reacted with **4** under conditions similar to those described for the preparation of **9** to afford **12** (246 mg, 41%) as yellow crystals, mp: 203 °C. IR (KBr) cm$^{-1}$: 3150—3000, 1620, 1280. UV $\lambda_{max}$ (MeOH) nm (log $\varepsilon$): 270 (4.30), 354 (3.76), 375 (3.97). $^1$H-NMR (300 MHz, DMSO-$d_6$) $\delta$: 3.87 (s, 3H, O-$CH_3$), 6.90 (d, 1H, *J*=2 Hz, C7′-H), 6.97 (td, 1H, *J*=8; 2 Hz, C5-H), 7.28 (d, 1H, *J*=2 Hz, C5′-H), 7.53 (td, 1H, *J*=8; 2 Hz, C4-H), 7.54 (dd, 1H, *J*=8; 5 Hz, C3′-H), 7.77 (dd, 1H, *J*=8; 2 Hz, C3-H), 7.98 (dd, 1H, *J*=8; 2 Hz, C6-H), 8.23 (dd, 1H, *J*=8; 2 Hz, C4′-H), 8.72 (dd, 1H, *J*=5; 2 Hz, C2′-H), 10.95 (br s, 1H, $D_2O$ exch., COOH), 13.15 (br s, 1H, $D_2O$ exch., NH). $^{13}$C-NMR (75 MHz, DMSO-$d_6$) $\delta$: 56.5 (q, O–$CH_3$), 98.3 (d, C-7′), 104.1 (d, C-5′), 117.4 (2d, C-1, C-3), 120.5 (d, C-5), 123.7 (d, C-3′), 130.9 (s, C-4′a), 133.1 (d, C-4), 135.1 (d, C-6), 136.3 (d, C-4′), 137.0 (s, C-8′), 139.9 (s, C-8′a), 145.0 (s, C-2), 147.0 (d, C-2′), 158.8 (s, C-6′), 170.1 (s, COOH). MS *m/z*: 294 ($M^+$), 279, 261, 249. *Anal*. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.15; H, 4.62; N, 9.20.

3-Nitro-*N*-(8-quinolyl)anthranilic Acid (**13**): Treatment of **7** (175 mg, 1.21 mmol) with **5** (246 mg, 1.22 mmol) under the conditions previously described for the preparation of **9** afforded **13** (187 mg, 50%) as yellow crystals, mp: 205—206. IR (KBr) cm$^{-1}$: 3200—2900, 1680, 1620, 1560, 1325. UV $\lambda_{max}$ (MeOH) nm (log $\varepsilon$): 221 (3.90), 289 (3.73). mp: 205—206. $^1$H-NMR (300 MHz, DMSO-$d_6$) $\delta$: 6.74 (dd, 1H, *J*=8; 2 Hz, C7′-H), 7.21 (t, 1H, *J*=8, $C_5$-H), 7.32 (t, 1H, *J*=8 Hz, C6′-H), 7.43 (dd, 1H, *J*=8; 2 Hz, C5′-H), 7.57 (dd, 1H, *J*=8; 5 Hz, C3′-H), 7.93 (dd, 1H, *J*=8; 2 Hz, C6-H), 8.31 (dd, 1H, *J*=8; 2 Hz, C4-H), 8.33 (dd, 1H, *J*=8; 2 Hz, C4′-H), 8.87 (dd, 1H, *J*=5; 2 Hz, C2′-H), 12.55 (br s, 1H, $D_2O$ exch., COOH), 13.70 (br s, 1H, $D_2O$ exch., NH). $^{13}$C-NMR (75 MHz, DMSO-$d_6$) $\delta$: 109.8 (d, C-5′), 119.7 (d, C-5), 120.8 (d, C-7′), 123.1 (d, C-3′), 123.8 (s, C-1), 127.5 (d, C-4), 128.6 (d, C-6′), 129.9 (s, C-4′a), 132.6 (s, C-8′a), 137.2 (d, C-6), 137.7 (d, C-4′), 138.5 (s, C-2), 140.1 (s, C-8′), 140.7 (s, C-3), 149.6 (d, C-2′), 171.0 (s, COOH). MS *m/z*: 309 ($M^+$), 264. *Anal*. Calcd for $C_{16}H_{11}N_3O_4$: C, 62.14; H, 3.58; N, 13.59. Found: C, 62.55; H, 3.46; N, 13.42.

12*H*-Benzo[*b*][1,7]phenanthrolin-7-one (**14**): A solution of **9** (213 mg, 0.86 mmol) in concentrated sulfuric acid (5 ml) was heated at 100 °C for 5 h. The cooled solution was poured into ice-water and basified with 30% aqueous NaOH. The solution was extracted with 2-butanone (3×25 ml). The organic layers were dried over anhydrous $Na_2SO_4$, filtered, and evaporated under reduced pressure. Recrystallization from ethanol gave **14** (143 mg, 67%) as a yellow crystalline product, mp: 293 °C. IR (KBr) cm$^{-1}$: 3100—3000, 1620. UV $\lambda_{max}$ (MeOH) nm (log $\varepsilon$): 252 (4.02), 280 (3.75), 303 (3.25), 348 (3.24). $^1$H-NMR (300 MHz, DMSO-$d_6$) $\delta$: 7.15 (td, 1H, *J*=8; 1 Hz, C9-H), 7.41 (d, 1H, *J*=9 Hz, C5-H), 7.67 (m, 2H, C2-H, C10-H), 7.83 (dd, 1H, *J*=8; 1 Hz, C11-H), 8.37 (dd, 1H, *J*=8; 1 Hz, C8-H), 8.40 (d, 1H, *J*=9 Hz, C6-H), 8.88 (dd, 1H, *J*=5; 2 Hz, C3-H), 9.48 (dd, 1H, *J*=8; 2 Hz, C1-H), 12.50 (br s, 1H, $D_2O$ exch., NH). $^{13}$C-NMR (75 MHz, DMSO-$d_6$) $\delta$: 117.6 (s, C-12b), 119.4 (d, C-11), 119.6 (s, C-6a), 122.3 (d, C-2), 122.9 (s, C-7a), 123.5 (d, C-9), 123.6 (d, C-5), 126.7 (d, C-8), 127.3 (d, C-6), 132.7 (d, C-1), 134.2 (d, C-10), 139.4 (s, C-12a), 141.5 (d, C-11a), 151.2 (s, C-4a), 153.4 (d, C-3), 177.0 (s, C-7). MS *m/z*: 246 ($M^+$). *Anal*. Calcd for $C_{16}H_{10}N_2O$: C, 78.03; H, 4.09; N, 11.37. Found: C, 78.20; H, 4.00; N, 11.49.

11-Nitro-12*H*-benzo[*b*][1,7]phenanthrolin-7-one (**15**): Cyclization of **10** (187 mg, 0.60 mmol) under conditions similar to those described for the preparation of **14** afforded **15** (152 mg, 87%) as yellow crystals, mp: 290—291 °C. IR (KBr) cm$^{-1}$: 3200—2900, 1680, 1500, 1290. UV $\lambda_{max}$ (MeOH) nm (log $\varepsilon$): 237 (3.62), 283 (3.49). $^1$H-NMR (300 MHz, DMSO-$d_6$) $\delta$: 7.50 (t, 1H, *J*=8 Hz, C9-H), 7.74 (dd, 1H, *J*=8; 5 Hz, C2-H), 8.04 (d, 1H, *J*=9 Hz, C5-H), 8.67 (d, 1H, *J*=9 Hz, C6-H), 8.71 (dd, 1H, *J*=8; 2 Hz, C3-H), 8.83 (dd, 1H, *J*=8; 2 Hz, C10-H), 8.98 (dd, 1H, *J*=8; 2 Hz, C8-H), 9.18 (dd, 1H, *J*=5; 2 Hz, C1-H), 11.04 (br s, 1H, $D_2O$ exch., NH). $^{13}$C-NMR (75 MHz, DMSO-$d_6$) $\varepsilon$: 116.4 (s, C-12b), 121.1 (d, C-5), 121.9 (d, C-2), 125.6 (d, C-9), 125.7 (s, C-6a), 126.5 (d, C-6), 129.2 (d, C-8), 130.7 (s, C-7a), 131.4 (d, C-1), 136.4 (d, C-10), 141.5 (s, C-12a), 143.9 (s, C-11a), 146.1 (s, C-11), 151.4 (s, C-4a), 153.0 (d, C-3), 174.1 (s, C-7). MS *m/z*: 291 ($M^+$). *Anal*. Calcd for $C_{16}H_9N_3O_3$: C, 65.98; H, 3.11; N, 14.43. Found: C, 65.72; H, 3.02; N, 14.26.

12*H*-Benzo[*b*][1,10]phenanthrolin-7-one (**16**): Cyclization of **11** (140 mg, 0.53 mmol) under conditions similar to those described for the preparation of **14** afforded **16** (80 mg, 61%) as yellow crystals, mp: 271—272°C. IR (KBr) cm$^{-1}$: 3000—2900, 1640. UV $\lambda_{max}$ (MeOH) nm (log $\varepsilon$): 265 (4.11), 295 (3.90), 320 (3.77), 355 (3.52), 383 (3.32). $^1$H-NMR (300 MHz, DMSO-$d_6$) $\delta$: 7.36 (td, 1H, *J*=8; 1 Hz, C9-H), 7.66 (d, 1H, *J*=9 Hz, C5-H), 7.75 (td, 1H, *J*=8; 1 Hz, C10-H), 7.82 (dd, 1H, *J*=8; 5 Hz, C3-H), 8.22 (dd, 1H, *J*=8; 1 Hz, C11-H), 8.26 (d, 1H, *J*=9 Hz, C6-H), 8.28 (dd, 1H, *J*=8; 1 Hz, C8-H), 8.48 (dd, 1H, *J*=8; 2 Hz, C4-H), 9.08 (dd, 1H, *J*=5; 2 Hz, C2-H), 12.00 (br s, 1H, $D_2O$ exch., NH). $^{13}$C-NMR (75 MHz, DMSO-$d_6$) $\delta$: 119.4 (s, C-6a), 120.3 (d, C-11), 120.8 (d, C-5), 123.3 (s, C-7a), 123.4 (d, C-9), 124.2 (d, C-6), 125.5 (d, C-3), 126.7 (d, C-8), 131.1 (s, C-4a), 134.1 (d, C-10), 137.7 (d, C-4), 139.6 (s, C-12a), 140.0 (s, C-12b), 141.4 (s, C-11a), 150.1 (d, C-2), 177.4 (s, C-7). MS *m/z*: 246 ($M^+$). *Anal*. Calcd for $C_{16}H_{10}N_2O$: C, 78.03; H, 4.09; N, 11.37. Found: C, 78.26; H, 4.35; N, 11.14.

6-Methoxy-12*H*-benzo[*b*][1,10]phenanthrolin-7-one (**17**): A solution of **12** (50 mg, 0.17 mmol) and trifluoroacetic anhydride (1 ml, 7.14 mmol) in anhydrous $CH_2Cl_2$ (10 ml) was stirred at room temperature for 3 d. After evaporation of the solvent, the residue was washed with aqueous $NaHCO_3$ (5%). The aqueous layer was further extracted with $CH_2Cl_2$ (2×10 ml). The organic layers were dried and evaporated to give **17** (30 mg, 64%) as yellow prisms, mp: 242—243 °C. IR (KBr) cm$^{-1}$: 3220, 2990, 1630. UV $\lambda_{max}$ (MeOH) nm (log $\varepsilon$): 263 (4.75), 284 (4.47), 349 (3.94). $^1$H-NMR (300 MHz, DMSO-$d_6$) $\delta$: 4.05 (s, 3H, O-$CH_3$), 6.78 (s, 1H, C5-H), 7.33 (td, 1H, *J*=8; 1 Hz, C9-H), 7.48 (dd, 1H, *J*=8; 5 Hz, C3-H), 7.50 (dd, 1H, *J*=8; 1 Hz, C11-H), 7.67 (td, 1H, *J*=8; 1 Hz, C10-H), 8.01 (dd, 1H, *J*=8; 1 Hz, C8-H), 8.52 (dd, 1H, *J*=8; 2 Hz, C4-H), 8.79 (dd, 1H, *J*=5; 2 Hz, C2-H), 9.20 (br s, 1H, $D_2O$ exch., NH). $^{13}$C-NMR (75 MHz, DMSO-$d_6$) $\delta$: 56.0 (q, O–$CH_3$), 95.9 (d, C-5), 111.5 (s, C-6a), 116.7 (d, C-11), 122.5 (d, C-9), 124.3 (d, C-3), 124.7 (s, C-7a), 127.2 (d, C-8), 130.5 (s, C-4a), 132.7 (d, C-10), 134.2 (s, C-12a), 138.0 (s, C-12b), 139.9 (s, C-11a), 145.6 (d, C-2), 158.1 (s, C-6), 177.1 (s, C-7). MS *m/z*: 276 ($M^+$), 261. *Anal*. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.55; H, 4.32; N, 10.25.

11-Nitro-12*H*-benzo[*b*][1,10]phenanthrolin-7-one (**18**): Cyclization of **13** (175 mg, 0.57 mmol) under conditions similar to those described for the preparation of **14** afforded **18** (143 mg, 70%) as orange crystals, mp: 275—276 °C. IR (KBr) cm$^{-1}$: 3100—3000, 1620, 1520, 1330. UV $\lambda_{max}$ (MeOH) nm (log $\varepsilon$): 234 (3.80), 272 (3.56). $^1$H-NMR (300 MHz, DMSO-$d_6$) $\delta$: 7.56 (t, 1H, *J*=8 Hz, C9-H), 7.78 (d, 1H, *J*=9 Hz, C5-H), 7.81 (dd, 1H, *J*=8; 5 Hz, C3-H), 8.41 (dd, 1H, *J*=8; 2 Hz, C4-H), 8.42 (d, 1H, *J*=9 Hz, C6-H), 8.89 (dd, 1H, *J*=8; 2 Hz, C10-H), 8.98 (dd, 1H, *J*=8; 2 Hz, C8-H), 9.14 (dd, 1H, *J*=5; 2 Hz, C2-H), 10.92 (br s, 1H, $D_2O$ exch., NH). $^{13}$C-NMR (75 MHz, DMSO-$d_6$) $\delta$: 119.7 (s, C-6a), 122.4 (d, C-5), 123.2 (d, C-6), 123.4 (d, C-3), 126.3 (d, C-9), 127.9 (s, C-7a), 131.4 (s, C-4a), 132.7 (d, C-8), 136.1 (d, C-10), 136.4 (d, C-11a), 138.1 (d, C-4), 138.2 (s, C-11), 140.7 ((s, C-12a), (s, C-12b)), 151.5 (d, C-2), 176.6 (s, C-7). MS *m/z*: 291 ($M^+$). *Anal*. Calcd for $C_{16}H_9N_3O_3$: C, 65.98; H, 3.11; N, 14.43. Found: C, 65.81; H, 2.94; N, 14.32.

12-Methyl-12*H*-benzo[*b*][1,7]phenanthrolin-7-one (**19**): To a solution of **14** (127 mg, 0.52 mmol), benzyltriethylammonium chloride (330 mg, 1.45 mmol), and 30% aqueous NaOH (3 ml) in 2-butanone (3 ml) was added methyl iodide (0.050 ml, 0.80 mmol). The mixture was stirred and refluxed for 3 h. The cooled solution was diluted with a mixture of $CH_2Cl_2$/$H_2O$ (10 ml/5 ml). The aqueous solution was extracted with $CH_2Cl_2$. The organic layer was dried over anhydrous $Na_2SO_4$, filtered, and evaporated under reduced pressure to afford **19** (54 mg, 40%) as yellow crystals, mp: 290 °C. IR (KBr) cm$^{-1}$: 3000, 2990, 1660, 1280, 750. UV $\lambda_{max}$ (MeOH) nm (log $\varepsilon$): 254 (4.45), 290 (4.71), 332 (3.90), 350 (3.66), 376 (3.84). $^1$H-NMR (300

MHz, DMSO-$d_6$) $\delta$: 4.32 (s, 3H, N-$CH_3$), 7.42 (td, 1H, $J$=8; 1 Hz, C9-H), 7.50 (dd, 1H, $J$=8; 5 Hz, C2-H), 7.66 (d, 1H, $J$=9 Hz, C5-H), 7.82 (td, 1H, $J$=8; 2 Hz, C10-H), 7.91 (dd, 1H, $J$=8; 2 Hz, C11-H), 8.54 (dd, 1H, $J$=8; 2 Hz, C8-H), 8.67 (d, 1H, $J$=9 Hz, C6-H), 8.69 (dd, 1H, $J$=5; 2 Hz, C3-H), 9.02 (dd, 1H, $J$=8; 2 Hz, C1-H). $^{13}$C-NMR (75 MHz, DMSO-$d_6$) $\delta$: 44.6 (q, N–$CH_3$), 117.0 (d, C-11), 118.9 (d, C-2), 119.8 (d, C-12b), 121.3 (s, C-6a), 122.9 (d, C-9), 124.1 (s, C-7a), 124.5 (d, C-5), 126.7 (d, C-8), 127.1 (d, C-6), 133.6 (d, C-1), 135.0 (d, C-10), 143.8 (s, C-12a), 145.7 (s, C-11a), 151.5 (d, C-3), 152.2 (s, C-4a), 177.4 (s, C-7). MS *m/z*: 260 ($M^+$), 245. *Anal*. Calcd for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65; N, 10.76. Found: C, 78.68; H, 4.36; N, 10.80.

12-Methyl-12*H*-benzo[*b*][1,10]phenanthrolin-7-one (**20**): Methylation of **16** (90 mg, 0.36 mmol) under conditions similar to those described for the preparation of **19** afforded **20** (43 mg, 46%) as yellow crystals, mp: 281 °C. IR (KBr) $cm^{-1}$: 3100—3000, 1630, 1290, 750. UV $\lambda_{max}$ (MeOH) nm (log $\varepsilon$): 252 (4.55), 282 (4.65), 344 (4.04), 363 (3.97), 388 (3.99). $^1$H-NMR (300 MHz, DMSO-$d_6$) $\delta$: 4.46 (s, 3H, N-$CH_3$), 7.36 (td, 1H, $J$=8; 1 Hz, C9-H), 7.51 (dd, 1H, $J$=8; 5 Hz, C3-H), 7.65 (d, 1H, $J$=9 Hz, C5-H), 7.73 (td, 1H, $J$=8; 1 Hz, C10-H), 7.76 (dd, 1H, $J$=8; 1 Hz, C11-H), 8.18 (dd, 1H, $J$=8; 1 Hz, C8-H), 8.53 (d, 1H, $J$=9 Hz, C6-H), 8.55 (dd, 1H, $J$=8; 2 Hz, C4-H), 8.93 (dd, 1H, $J$=5; 2 Hz, C2-H). $^{13}$C-NMR (75 MHz, DMSO-$d_6$) $\delta$: 43.6 (q, N–$CH_3$), 117.0 (d, C-11), 121.3 (d, C-5), 122.2 (d, C-9), 122.5 (d, C-6), 122.6 (d, C-6a), 122.8 (d, C-7a), 123.8 (d, C-3), 126.7 (d, C-8), 132.2 (s, C-4a), 133.3 (d, C-10), 136.1 (d, C-4), 141.5 (s, C-12a), 142.3 (s, C-12b), 145.1 (s, C-11a), 146.6 (d, C-2), 177.6 (s, C-7). MS *m/z*: 260 ($M^+$), 245. *Anal*. Calcd for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65; N, 10.76. Found: C, 78.32; H, 4.71; N, 10.51.

6-Methoxy-12-methyl-12*H*-benzo[*b*][1,10]phenanthrolin-7-one (**21**): Methyl iodide (0.4 ml, 6.38 mmol) was added to a solution of **17** (55 mg, 0.2 mmol) and sodium hydride (300 mg, 12.5 mmol) in dimethylformamide (7 ml). The reaction mixture was stirred and refluxed under $N_2$ for 24 h. After dilution with $H_2O$ (15 ml), the solution was extracted with $CH_2Cl_2$ (20 ml). The organic layer was dried over anhydrous $Na_2SO_4$, filtered, and evaporated under reduced pressure to afford **21** (16 mg, 27%) as a yellow crystalline product, mp: 285 °C. IR (KBr) $cm^{-1}$: 3200, 2990, 1595, 1490, 1215, 760. UV $\lambda_{max}$ (MeOH) nm (log $\varepsilon$): 266 (4.41), 283 (4.28), 385 (3.79). $^1$H-NMR (300 MHz, DMSO-$d_6$) $\varepsilon$: 4.13 (s, 3H, N-$CH_3$), 4.37 (s, 3H, O–$CH_3$), 6.85 (s, 1H, C5-H), 7.35 (td, 1H, $J$=8; 1 Hz, C9-H), 7.57 (dd, 1H, $J$=8; 5 Hz, C3-H), 7.68 (dd, 1H, $J$=8; 1 Hz, C11-H), 7.74 (td, 1H, $J$=8; 1 Hz, C10-H), 8.05 (dd, 1H, $J$=8; 1 Hz, C8-H), 8.58 (dd, 1H, $J$=8; 2 Hz, C4-H), 8.80 (dd, 1H, $J$=5; 2 Hz, C2-H). $^{13}$C-NMR (75 MHz, DMSO-$d_6$) $\delta$: 43.2 (q, N–$CH_3$), 56.7 (q, O–$CH_3$), 96.7 (d, C-5), 113.2 (s, C-6a), 114.5 (d, C-11), 122.1 (d, C-9), 123.2 (d, C-3), 123.8 (s, C-7a), 127.3 (d, C-8), 130.9 (s, C-4a), 131.4 (d, C-10), 133.7 (d, C-4), 136.5 (s, C-12a), 141.3 (s, C-12b), 142.1 (d, C-2), 143.2 (s, C-11a), 158.6 (s, C-6), 177.3 (s, C-7). MS *m/z*: 290 ($M^+$), 261. *Anal*. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.59; H, 4.81; N, 9.72.

11-Amino-12*H*-benzo[*b*][1,10]phenanthrolin-7-one (**22**): To a solution of **18** (50 mg, 0.17 mmol) in DMF (15 ml), was added 10% Pd/C (20 mg). The mixture was stirred at room temperature for 2 h under $H_2$ (1 atm.), filtered and evaporated under reduced pressure. Column chromatography of the residue on silica gel (solvent: $CH_2Cl_2$/MeOH : 97/3 : v/v) gave **22** (40 mg, 90%) as yellow crystals, mp: 259—260 °C. IR (KBr) $cm^{-1}$: 3150, 2980, 1590, 1430, 1595. UV $\lambda_{max}$ (MeOH) nm (log $\varepsilon$): 223 (3.56), 245 (3.19). $^1$H-NMR (300 MHz, DMSO-$d_6$) $\delta$: 5.85 (s, 2H, $NH_2$) 7.15 (dd, 1H, $J$=8; 2 Hz, C10-H), 7.17 (t, 1H, $J$=8 Hz, C9-H), 7.66 (dd, 1H, $J$=8; 2 Hz, C8-H), 7.68 (d, 1H, $J$=9 Hz, C5-H), 7.84 (dd, 1H, $J$=8; 5 Hz, C3-H), 8.26 (d, 1H, $J$=9 Hz, C6-H), 8.52 (dd, 1H, $J$=8; 2 Hz, C4-H), 9.10 (dd, 1H, $J$=5; 2 Hz, C2-H), 10.80 (br s, 1H, $D_2O$ exch., NH). $^{13}$C-NMR (75 MHz, DMSO-$d_6$) $\delta$: 115.3 (d, C-9), 118.6 (s, C-6a), 118.8 (d, C-5), 120.6 (d, C-6), 123.7 (d, C-3), 124.0 (d, C-10), 125.3 (d, C-8), 130.5 (s, C-7a), 130.6 (s, C-4a), 137.6 (d, C-4), 138.1 (s, C-11a), 138.8 ((s, C-11), (s, C-12a)), 139.5 (s, C-12b), 150.0 (d, C-2), 177.4 (s, C-7). MS *m/z*: 261 ($M^+$). *Anal*. Calcd for $C_{16}H_{11}N_3O$: C, 73.55; H, 4.24; N, 16.08. Found: C, 73.69; H, 4.33; N, 15.97.

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

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