Synthesis and Biological Activity of Esters in the *trans*-1,2-Dihydroxy-1,2-dihydroacronycine Series

Prokopios Magiatis,[†] Sofia Mitaku,[†] Alexios-Leandros Skaltsounis,*[,†] François Tillequin,[‡] Michel Koch,[‡] Alain Pierré,[§] and Ghanem Atassi[§]

Laboratory of Pharmacognosy, University of Athens, Panepistimiopolis, Zografou, GR-15771 Athens, Greece, Laboratoire de Pharmacognosie de l' Université René Descartes, URA au CNRS N° 1310, Faculté des Sciences Pharmaceutiques et Biologiques, 4 avenue de l' Observatoire, F-75006 Paris, France, Institut de recherche SERVIER, 11 rue des Moulineaux, 92150 Suresnes, France

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Permanganate oxidation of acronycine (**1**) led to keto alcohol **4** which could be reduced to *trans*-1,2-dihydroxy-1,2-dihydroacronycine (**3**) using $NaBH_4$. Acylation of **3** afforded **12**, **13**, and **14**. These esters (**12**, **13**, and **14**) were more potent than **1** when tested against L-1210 cells in vitro. Diacetate **12** was evaluated in vivo against murine P-388 leukemia and was markedly active at a dose 16-fold lower than acronycine itself. Comparison of these results with those recently obtained in the *cis*-1,2-dihydroxy-1,2-dihydroacronycine series is discussed.

The acridone alkaloid acronycine (**1**), which was first isolated from *Acronychia baueri* Schott (Rutaceae) in 1948, was then found to be a potent antitumor agent.[1−3] Its main interest lies in its broad spectrum of activity against numerous solid tumors including sarcoma, myeloma, carcinoma, and melanoma.[4,5] Nevertheless, clinical trials only gave poor results,[6] most probably due to the moderate potency of acronycine and its very weak water-solubility, which excludes parenteral formulation of the drug. Despite the interest of acronycine, little chemical investigation has been conducted in order to modify it at the pyran ring.[7] Recently we described the synthesis of *cis*-1,2-dihydroxy-1,2-dihydroacronycine diesters,[8] which exhibit promising antitumor properties, with a broadened spectrum of activity and an increased potency when compared with **1** on several tumor strains in vitro and in vivo. *cis*-1,2-Diacetoxy-1,2-dihydroacronycine (**2**) is of particular interest due to its high activity in vivo against P-388 leukemia and against the highly resistant solid tumor C-38 colon carcinoma. It was, therefore, of interest, in a continuation of our work in the acronycine series, to synthesize various *trans*-1,2-dihydroxy-1,2-dihydroacronycine esters and evaluate their biological activities.

Results and Discussion

The *trans*-1,2-dihydroxy-1,2-dihydroacronycine (**3**) recently isolated from the leaves of *Sarcomelicope glauca*[9] was a suitable candidate for esterification reactions. Treatment of acronycine (**1**) with $KMnO_4$[10,11] in Me_2CO-H_2O solution gave three products: 1-oxo-2-hydroxy-1,2-dihydroacronycine (**4**), *cis*-1,2-dihydroxy-1,2-dihydroacronycine (**5**), and 1-oxo-2-hydroxy-2-acetonyl-1,2-dihydroacronycine (**6**) (Scheme 1). It is interesting to note that the same reaction was explored recently;[11] the same compounds (identical spectral and physical data) were obtained, but the structure elucidation was erroneous for compounds **4** and **6**, which were depicted as **7** and **8**, respectively. We were able to determine unambiguously the position of the carbonyl group for the above compounds on the basis of spectroscopic and chemical methods. Appearance of three-bond correlation between the CH_3 at $\delta_H = 1.69$ and the methine carbon C-2 at $\delta_H = 76.3$ (for compound **4**) and between the CH_3 at $\delta_H = 1.40$ and the methine carbon C-2 at $\delta_H = 78.14$ (for compound **6**), in the C−H HMBC spectrum (heteronuclear multiple bond connectivity), permitted localization of the carbonyl group at position 1 (Figure 1).

On the other hand, treatment of **4** with *N*,*N*-thiocarbonyl diimidazole gave thioester **9**. In a second step, homobenzylic deoxygenation afforded the 1-oxo-1,2-dihydroacronycine (**10**). If the carbonyl group is in the 2 position, the deoxygenation reaction should lead to the known 2-oxo-1,2-dihydroacronycine (**11**).[12] The signals of ^{1}H- and ^{13}C-NMR spectra for compounds **10** and **11** were unambiguously assigned using ^{13}C−^{1}H HETCOR and HMBC experiments (Figure 1).

The desired *trans*-1,2-diacetoxy-1,2-dihydroacronycine (**12**) was obtained in two steps from 1-oxo-2-hydroxy-1,2-dihydroacronycine (**4**). Treatment of **4** with $NaBH_4$ in MeOH led to the trans diol **3** in 50% yield. In a second step, treatment of **3** with excess Ac_2O in pyridine afforded the corresponding diacetate **12** in 92% yield. When 1 equivalent of acylating reagent was used, monoesters at the less-hindered 2 position were obtained, as exemplified by acetate **13** and chloroacetate **14**.

The study of the biological properties of the new acronycine derivatives was carried out first in vitro on L-1210 leukemia. The results (IC_{50}) are reported in Table 1. Compounds **14**, **12**, **13** were more potent (2−3-fold) than **1** in inhibiting L-1210 cell proliferation.

Perturbation of the cell cycle induced by compounds **12**, **13**, and **14** was studied in the same cell line. Compound **13** induced a partial accumulation of cells in the G2 + M phase of the cell cycle, as did acronycine. In contrast, the diester **12** and the monoester **14**

* To whom correspondence should be addressed. Phone: (301) 7284598. Fax: (301) 7238297. E-mail: askalts@atlas.uoa.ariadne-t.gr.
[†] Laboratory of Pharmacognosy, University of Athens.
[‡] Laboratoire de Pharmacognosie de l' Université René Descartes.
[§] Institut de recherche SERVIER.

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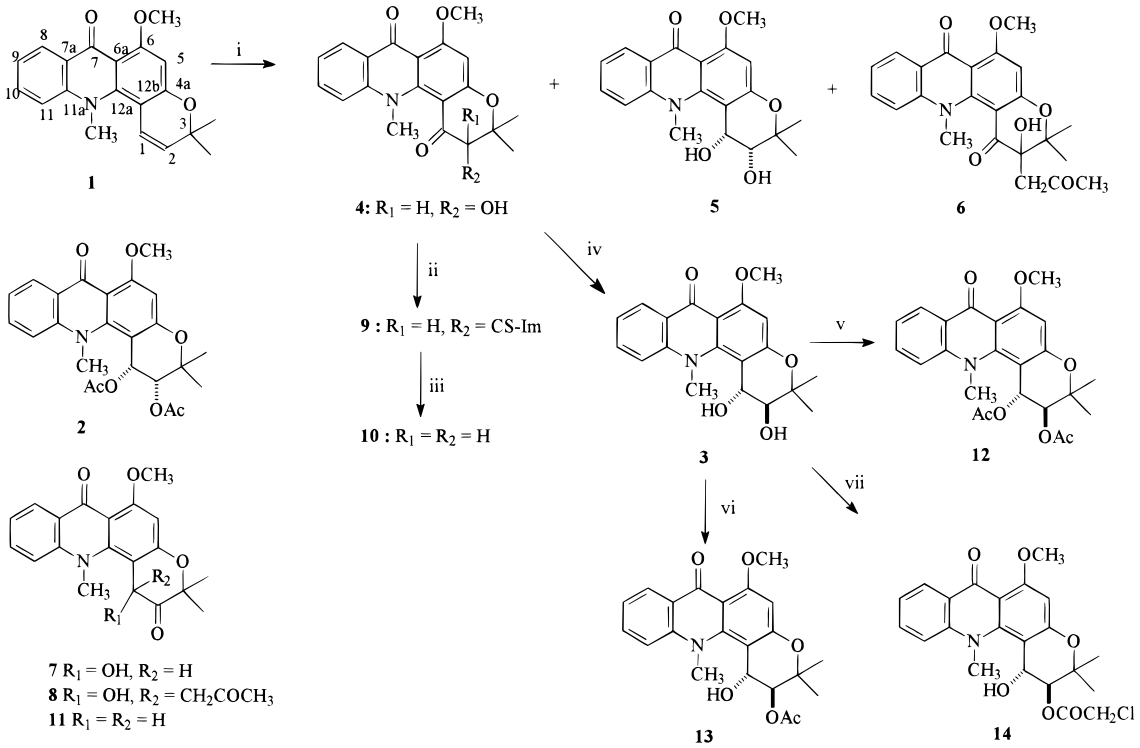
Scheme 1[a]



[a] Key: (i) $KMnO_4$, Me_2CO, H_2O, rt; (ii) 1,1-(thiocarbonyl)diimidazole, 2-butanone, 60 °C; (iii) Bu_3SnH, AIBN, toluene, 110 °C; (iv) $NaBH_4$, MeOH, 0 °C; (v) Ac_2O, Py, rt; (vi) Ac_2O (1 equiv), Py, rt; (vii) $ClCH_2COCl$ (1 equiv), Py, Et_2O, 0 °C.

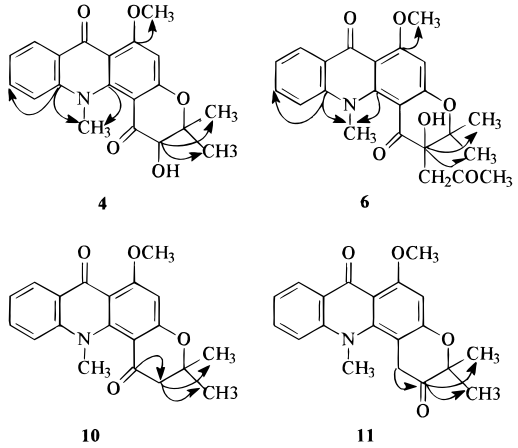


Figure 1. Selected HMBC correlations of compounds **4**, **6**, **10, 11**.

Table 1. Cytotoxic Activity[a]

compound	IC_{50}, μM	compound	IC_{50}, μM
12	8.7	**13**	8.8
4	75.1	**14**	11.0
6	22.5	**1**	25

[a] Inhibition of L-1210 cell proliferation measured by the MMT assay (mean of 2 values obtained in independent experiments).

modified the DNA distribution in a different manner and induced a marked accumulation of cells in the S phase. It is interesting that the recently described[8] and highly active *cis*-1,2-diacetoxy-1,2-dihydroacronycine (**2**) also increased the number of cells in the S phase. The fact that these compounds induced a perturbation of the cell cycle different from that of acronycine suggests some differences in their mechanism of action at the molecular level.

Compound **12** was evaluated in vivo against the ip P-388 leukemia experimental model. Table 2 shows the results in terms of percent T/C in various dosage levels. The best therapeutic effect without toxicity was obtained at 12.5 mg/kg.

Compound **12** was more active in vivo than **1**, at 70−16-fold lower doses, but was less active than *cis*-1,2-dihydroxy-1,2-dihydroacronycine (**2**). At a dose of 25 mg/kg, where **2** gave the optimal therapeutic effect, compound **12** was toxic. One explanation for this toxicity could be the trans stereochemistry of the substituents at positions 1 and 2 of the pyran ring. Indeed, the trans substitution could favor a trans elimination of the acetoxy group in position 1, and the formation of a benzylic carbonium ion. It is known that such benzylic carbonium ions are extremely reactive and are responsible for the alkylation of nucleophiles present in biological matrixes such as cellular proteins and ultimately for irreversible damages and cell death.[13]

Experimental Section

General Experimental Procedures. Spectra were recorded on the following apparatus: MS, Nermag R10−10C in disorption−chemical ionization, using NH_3 as reagent gas; NMR, Bruker AC 200, ^1H NMR (200 MHz) and ^{13}C NMR (50 MHz) and a Bruker DRX400, ^1H NMR (400 MHz). Chemical shifts are given in δ values with TMS as an internal standard. Coupling constants (J) are given in Hz. The signals of ^1H and ^{13}C spectra were unambiguously assigned by using 2D NMR techniques: $^1H-^1H$-COSY, $^{13}C-^1H$ HETCOR, and HMBC. These 2D experiments were performed using standard Bruker microprograms. Column chromatographies were conducted using flash Si gel 60 Merck (40−63 μm), with an overpressure of 300 mbars. All new

Table 2. Antitumor Activity[a]

compound	dose mg/kg ip	median survival time, days (mortality range)	median T/C %
12	0.78	11.8 (11−13)	122
	1.56	13.2 (13−13)	136
	3.125	15.0 (13−16)	155
	6.25	15.5 (13−23)	160
	12.5	17.5 (14−20)	181
	25	7.5 (6−9)	77
2	25	26.0 (20−26)	268
1	200	12 (12−14)	125
control		9.7 (9−12)	100

[a] Mice were inoculated ip on day 0 with 10^6 P-388 cells. Drugs were administered ip on day 1.

compounds gave satisfactory combustion analyses (C, H, N, within ± 0.4% of calcd values). Acronycine was prepared according to the known method of Hlubucek.[14]

Oxidation of Acronycine (1) with $KMnO_4$. A suspension of powdered $KMnO_4$ (8.1 g, 51.26 mmol) in H_2O (30 mL) was added dropwise for 2 h in a solution of **1** (3 g, 9.29 mmol) in Me_2CO (50 mL) at 25 °C. Then the solvents were removed under reduced pressure (with a high vacuum pump), and the remaining residue was mixed with silica. This mixture residue was submitted to flash chromatography on Si gel with CH_2Cl_2−MeOH (99.5:0.5 to 98:2) to give **4** (1 g, 31%), **5**[9] (360 mg, 9.5%), and **6** (300 mg, 9%).

(±)-1-Oxo-2-hydroxy-1,2-dihydroacronycine (4): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.40 (1H, dd, J = 8, 1.5 Hz, H-8), 7.69 (1H, td, J = 8, 1.5 Hz, H-10), 7.48 (1H, d, J = 8 Hz, H-11), 7.32 (1H, t, J = 8 Hz, H-9), 6.27 (1H, s, H-5), 4.36 (1H, d, J = 2 Hz, H-2), 4.05 (3H, s, OMe), 4.00 (1H, d, J = 2 Hz, OH-2), 3.63 (3H, s, NMe), 1.69 (3H, s, Me), 1.33 (3H, s, Me); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 188.70 (C-1), 176.30 (C-7), 168.18 (C-6), 166.66 (C-4a), 148.62 (C-12a), 143.48 (C-11a), 133.09 (C-10), 126.96 (C-8), 125.74 (C-7a), 123.20 (C-9), 117.11 (C-11), 112.38 (C-6a), 101.97 (C-12b), 94.41 (C-5), 84.13 (C-3), 76.30 (C-2), 56.82 (OMe), 45.33 (NMe), 26.97 (Me), 17.81 (Me); MS−DCI m/z 354 $(M + H)^+$.

(±)-1-Oxo-2-hydroxy-2-(2-oxopropyl)-1,2-dihydroacronycine (6): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.41 (1H, dd, J = 8 Hz, 1.5, H-8), 7.65 (1H, td, J = 8 Hz, 1.5, H-10), 7.42 (1H, d, J = 8 Hz, H-11), 7.26 (1H, t, J = 8 Hz, H-9), 6.25 (1H, s, H-5), 5.18 (1H, s, OH-2), 4.01 (3H, s, OMe), 3.50 (3H, s, NMe), 3.11 (1H, d, J = 16 Hz, H-13), 2.88 (1H, d, J = 16 Hz, H-13), 2.29 (3H, s, Me-15), 1.45 (3H, s, Me), 1.40 (3H, s, Me); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 209.25 (C-14), 191.54 (C-1), 176.51 (C-7), 167.01 (C-6), 165.19 (C-4a), 148.66 (C-12a), 143.54 (C-11a), 132.99 (C-10), 126.76 (C-8), 125.47 (C-7a), 122.87 (C-9), 117.03 (C-11), 110.11 (C-6a), 102.86 (C-12b), 94.48 (C-5), 86.29 (C-3), 78.14 (C-2), 56.62 (OMe), 44.63 (C-13), 43.96 (NMe), 32.10 (C-15), 22.39 (Me), 21.10 (Me); MS−DCI m/z 410 $(M + H)^+$.

Reduction of (±)-1-Oxo-2-hydroxy-1,2-dihydroacronycine (4). To a cold solution of **4** (900 mg, 2.55 mmol) in MeOH (30 mL) was added $NaBH_4$ (450 mg, 11.84 mmol). The mixture was stirred for 1 h at 0 °C. The solvent was removed under reduced pressure, and the residue was submitted to flash chromatography with CH_2Cl_2−MeOH (99.5:0.5 to 95:5) to afford compound (±)-**3**[9] (450 mg, 50%).

(±)-*trans*-1-Hydroxy-2-acetoxy-1,2-dihydroacronycine (13). To a solution of **3** (30 mg, 0.084 mmol) in dry pyridine (1 mL) was added 1 equiv of Ac_2O (0.004 mL, 0.084 mmol). The reaction mixture was stirred during 24 h at room temperature, and then the reagents were removed under reduced pressure (with a high vacuum pump). The residue was chromatographed on a flash Si gel column with CH_2Cl_2−MeOH (99:1) to provide **13** (18 mg, 60%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.33 (1H, dd, J = 8, 1.5 Hz, H-8), 7.60 (1H, td, J = 8, 1.5 Hz, H-10), 7.34 (1H, d, J = 8 Hz, H-11), 7.23 (1H, t, J = 8 Hz, H-9), 5.57 (1H, d, J = 8 Hz, H-2), 5.52 (1H, s, H-5), 4.95 (1H, dd, J = 8, 10 Hz, H-1), 4.70 (1H, d, J = 10 Hz, OH-1), 3.84 (3H, s, NMe), 3.52 (3H, s, OMe), 2.27 (3H, s, CH_3CO), 1.52 (3H, s, Me), 1.42 (3H, s, Me); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 176.28 (C-7), 170.46 (2 CH_3CO), 161.64 (C-6), 158.08 (C-4a), 147.96 (C-12a), 144.15 (C-11a), 132.66 (C-10), 127.37 (C-8), 124.38 (C-7a), 121.3 (C-9), 115.71 (C-11), 109.71 (C-6a), 103.73 (C-12b), 93.46 (C-5), 78.68 (C-2), 77.75 (C-3), 68.13 (C-1), 55.48 (OMe), 41.89 (NMe), 21.25 (CH_3CO), 26.43 (Me), 18.42 (Me); MS−DCI m/z 398 $(M + H)^+$.

(±)-*trans*-1-Hydroxy-2-chloroacetoxy-1,2-dihydroacronycine (14). To a solution of **3** (30 mg, 0.084 mmol) in dry Et_2O (3 mL) was added pyridine (0.2 mL) and 1 equiv of chloroacetyl chloride (0.007 mL, 0.084 mmol). The reaction mixture was stirred over 4 h at 0 °C, and then the reagents were removed under reduced pressure. The residue was chromatographed on a flash Si gel column with CH_2Cl_2−MeOH (99:1) to provide **14** (18 mg, 50%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.31 (1H, dd, J = 8, 1.5 Hz, H-8), 7.66 (1H, td, J = 8, 1.5 Hz, H-10), 7.34 (1H, d, J = 8 Hz, H-11), 7.21 (1H, t, J = 8 Hz, H-9), 5.90 (1H, d, J = 8 Hz, H-2), 5.19 (1H, s, H-5), 4.97 (1H, dd J = 8, 10 Hz, H-1), 4.70 (1H, d, J = 10 Hz, OH-1), 4.30 (2H, s, $ClCH_2CO$), 3.85 (3H, s, NMe), 3.30 (3H, s, OMe), 1.40 (3H, s, Me), 1.25 (3H, s, Me); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 176.38 (C-7), 166.80 ($ClCH_2CO$), 161.33 (C-6), 158.03 (C-4a), 147.86 (C-12a), 143.99 (C-11a), 132.74 (C-10), 127.40 (C-8), 124.28 (C-7a), 121.32 (C-9), 115.67 (C-11), 114.15 (C-6a), 103.48 (C-12b), 93.31 (C-5), 78.78 (C-2), 77.70 (C-3), 67.88 (C-1), 55.26 (OMe), 41.88 (NMe), 41.03 ($ClCH_2CO$), 26.41 (Me), 18.36 (Me); MS−DCI m/z 432 $(M + H)^+$.

(±)-*trans*-1,2-Diacetoxy-1,2-dihydroacronycine (12). To a solution of **3** (420 mg, 1.18 mmol) in dry pyridine (5 mL) was added excess Ac_2O (1.5 mL, 15 mmol). The reaction mixture was stirred for 24 h at room temperature, and then the reagents were removed under reduced pressure. The residue was compound **12** (479 mg, 92%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.25 (1H, dd, J = 8, 1.5 Hz, H-8), 7.55 (1H, td, J = 8, 1.5 Hz, H-10), 7.20 (1H, d, J = 8, H-11), 7.15 (1H, t, J = 8 Hz, H-9), 6.40 (1H, d, J = 7 Hz, H-1), 6.25 (1H, s, H-5), 5.20 (1H, d, J = 7 Hz, H-2), 3.95 (3H, s, OMe), 3.65 (3H, s, NMe), 2.10 (3H, s, CH_3CO), 1.85 (3H, s, CH_3CO), 1.45 (3H, s, Me), 1.40 (3H, s, Me); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 177.38 (C-7), 171.03 (CH_3CO), 170.04 (CH_3CO), 162.92 (C-6), 159.52 (C-4a), 149.26 (C-12a), 145.17 (C-11a), 132.82 (C-10), 126.90 (C-8), 125.86 (C-7a), 122.11 (C-9), 116.01 (C-11), 112.15 (C-6a), 99.55 (C-12b), 94.62 (C-5), 77.63 (C-3), 74.77 (C-2), 69.81 (C-1), 56.27 (OMe), 43.24 (NMe), 25.85 (Me), 20.9 (CH_3CO-1, CH_3CO-2), 19.3 (Me); MS−DCI m/z 440 $(M + H)^+$.

1-Oxo-1,2-dihydroacronycine (10). To a solution of **4** (30 mg, 0.085 mmol) in 2-butanone (3 mL) was

added 1,1-thiocarbonyl-diimidazole (100 mg, 0.56 mmol). The reaction mixture was stirred for 20 min at 60 °C under argon. Then the reaction mixture was extracted with EtOAc−$NaHCO_3$ and the organic layer was collected. The solvent was removed under reduced pressure, and the remaining residue was purified by crystallization with a mixture of cyclohexane−EtOAc (8:2). The crystals were dissolved in anhydrous toluene (5 mL), and the solution was refluxed for 15 min under argon. Then 2,2′-azobisisobutyronitrile (AIBN) (5 mg) was added, and, after 5 min, a solution of tributyltin hydride (0.25 mL in 4 mL of toluene) 0.5 mL/5 min for 40 min. The reaction mixture was refluxed for 1 h. The solvent was evaporated, and compound **10** was purified by flash chromatography with a mixture of cyclohexane−EtOAc (1:1): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.37 (1H, dd, J = 8 Hz, 1.5, H-8), 7.65 (1H, td, J = 8, 1.5 Hz, H-10), 7.48 (1H, d, J = 8 Hz, H-11), 7.28 (1H, t, J = 8 Hz, H-9), 6.21 (1H, s, H-5), 4.01 (3H, s, OMe), 3.65 (3H, s, NMe), 2.70 (2H, s, H-2), 1.55 (6H, s, 2Me); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 186.51 (C-1), 176.34 (C-7), 167.88 (C-6), 166.97 (C-4a), 148.57 (C-12a), 143.13 (C-11a), 132.88 (C-10), 126.95 (C-8), 125.69 (C-7a), 122.99 (C-9), 117.01 (C-11), 110.06 (C-6a), 104.45 (C-12b), 93.48 (C-5), 78.63 (C-3), 56.71 (OMe), 49.00 (C-2), 44.89 (NMe), 29.68 (Me), 26.40 (Me); MS−DCI m/z 338 $(M + H)^+$.

2-Oxo-1,2-dihydroacronycine (11). Compound **11** was synthesized according to our previously described method:[12] ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.35 (1H, dd, J = 8 Hz, 1.5, H-8), 7.64 (1H, td, J = 8, 1.5 Hz, H-10), 7.35 (1H, dd, J = 8, 1.5 Hz, H-11), 7.27 (1H, t, J = 8, 1.5 Hz, H-9), 6.50 (1H, s, H-5), 4.00 (3H, s, OMe), 3.78 (2H, s, H-1), 3.76 (3H, s, NMe), 1.47 (6H, s, 2Me); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 208.78 (C-2), 177.98 (C-7), 161.61 (C-6), 158.94 (C-4a), 148.32 (C-12a), 145.27 (C-11a), 132.99 (C-10), 127.05 (C-8), 125.53 (C-7a), 122.14 (C-9), 116.17 (C-11), 109.61 (C-6a), 101.55 (C-12b), 97.17 (C-5), 82.68 (C-3), 56.31 (OMe), 44.44 (NMe), 38.53 (C-1), 26.86 (Me); MS−DCI m/z 338 $(M + H)^+$.

Cell Culture and Cytotoxicity. L-1210 cells were cultivated in RPMI 1640 medium (Gibco) supplemented with 10% fetal calf serum, 2 mM L-glutamine, 100 units/mL penicillin, 100 μg/mL streptomycin, and 10 mM HEPES buffer (pH = 7.4). Cytotoxicity was measured by the microculture tetrazolium assay as described.[15] Cells were exposed to graded concentration of drug (nine serial dilutions in triplicate) for 48 h. Results are expressed as IC_{50}, the concentration that reduced by 50% the optical density of treated cells with respect to the optical density of untreated controls.

For the cell-cycle analysis, L-1210 cells (5×10^5 cells/mL) were incubated for 21 h with various concentrations of drugs. Cells were then fixed by 70% EtOH (v/v), washed, and incubated with PBS containing 100 μg/mL RNAse and 25 μg/mL propidium iodide for 30 min at 20 °C. For each sample, 10 000 cells were analyzed on an ATC3000 flow cytometer (Bruker, Wissenbourg, France).

Antitumor Activity. The antitumor activity was evaluated on P-388 leukemia experimental murine model. P-388 cells (NCI, Frederick) were inoculated ip (10^6 cells/mouse) into B6D2F1 mice (Iffa credo) on day 0. The drugs were suspended in H_2O plus 1% Tween 80 in H_2O and injected ip on day 1. The results are expressed in terms of percent T/C (median survival time of treated animals divided by median survival time of controls, × 100).

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