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Synthesis of Lakshminine and Antiproliferative Testing of Related Oxoisoaporphines

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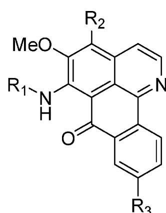
Lakshminine (6-amino-1-aza-5-methoxy-7*H*-dibenzo[*de,h*]quinolin-7-one, **1**) is a recent addition to the small family of oxoisoaporphine alkaloids and a member of an even smaller set bearing an amino group at C-6. This rare natural product has now been synthesized in order to have sufficient amounts for biological testing. Lakshminine, its 4-amino isomer (**2**), their 6- and 4-nitro precursors (**8** and **10**, respectively), the intermediate 5-methoxy-7*H*-dibenzo[*de,h*]quinolin-7-one (**6**), and the unsubstituted skeleton (**11**) were tested against normal human fibroblasts and three human solid tumor cell lines. Only compound **10** showed marginal antiproliferative activity.

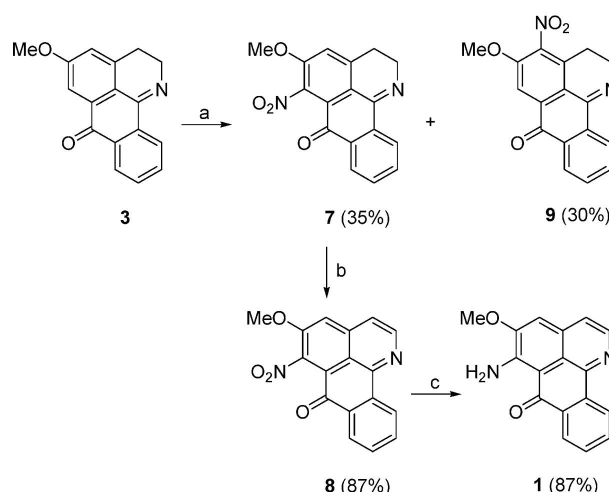
The oxoisoaporphines constitute a small family of alkaloids that are only known to occur in two species of Menispermaceae,[1−8] plants characterized by the accumulation of "regular" isoquinoline alkaloids. Their planar 7*H*-dibenzo[*de,h*]quinolin-7-one skeleton (commonly known as 1-azabenzanthrone, particularly in the dye and pigment industries) could be assumed to intercalate between DNA base pairs. Their redox-active iminoquinone structure could also be expected to interfere with mitochondrial electron transport. Therefore, these compounds might inhibit cell replication and possibly exhibit anticancer properties. In fact, two of these alkaloids isolated from *Menispermum dauricum* DC, bearing a nitrogen substituent at C-6 of the polycyclic scaffold, have demonstrated cytotoxicity and are claimed to be more potent against human mammary cancer cells than the widely used etoposide or VP-16.[7] The cognate daurioxoisoaporphine C does not seem to have been tested, nor is there any report on the antiproliferative or related activity of tyraminoporphine, the first 6-aminooxoisoaporphine reported,[6] or lakshminine (**1**), the most recently described member of this group, isolated from *Sciadotenia toxifera* Krukoff & A.C. Smith.[8] While the literature records no data on the antiproliferative activity of alkaloids of this family lacking a nitrogen substituent at C-6, a number of synthetic 1-aza-9-(substituted amino)benzanthrones have been screened and have been found to be weakly to moderately active.[9]



tyraminoporphine	R_1 = 4-HO-phenethyl; R_2 = OMe; R_3 = OMe
daurioxoisoaporphine A	R_1 = 4-HO-phenethyl; R_2 = H; R_3 = OMe
daurioxoisoaporphine B	R_1 = H; R_2 = R_3 = OMe
daurioxoisoaporphine C	R_1 = Me; R_2 = H; R_3 = OMe
lakshminine (**1**)	R_1 = R_2 = R_3 = H

The scanty biological data on these alkaloids may, at least in part, be a consequence of the small quantities in which they have been isolated. Thus, Sugimoto et al. isolated 20 mg of crude **5** from 20 g of dried, powdered ketoconazole-supplemented *M. dauricum* root culture.[6] Starting from 20 kg of *M. dauricum* roots, Yu et al. were only able to obtain 20, 9, and 10 mg of dauriosoisoaporphines A, B, and C, respectively.[7] Finally, Killmer et al. reported the isolation of 2 mg of **1** from 4.2 kg of *S. toxifera* vines.[8] As we already had experience in the synthesis of 2,3-dihydro-5-methoxy-7*H*-dibenzo[*de,h*]quinolin-7-one (1-aza-2,3-dihydro-5-methoxybenzanthrone), we decided to use this substance as starting material for a straightforward preparation of **1** in sufficient amount to determine its antiproliferative activity against a panel of normal and cancer cell lines.

Scheme 1. Synthesis of Lakshminine (**1**)[a]



[a] Reagents and conditions: (a) H_2SO_4/HNO_3, TFA, rt, 2 h; (b) air, Pd/C, toluene, reflux, 24 h; (c) Na_2S, NaOH, H_2O, reflux, 5 h.

1-Aza-2,3-dihydro-5-methoxybenzanthrone (**3**) and its 6-methoxy (**4**) and 6-hydroxy (**5**) derivatives were obtained by polyphosphoric acid (PPA)-catalyzed cyclization of homoveratrylaminophthalide, which, in spite of its low yield, still appears to be the best available approach to the desired intermediate.[10]

Nitration of 1-aza-2,3-dihydro-5-methoxybenzanthrone in trifluoroacetic acid (TFA) produced a mixture of isomers (**7** and **9**). Subsequent oxidation of **3**, **7**, and **9** with air, over Pd/C in toluene, afforded **6**, **8**, and **10** in approximately 90% yields, and selective reduction of the nitro groups of the latter products with sodium sulfide in alkaline solution gave lakshminine (**1**, Scheme 1) and the isomeric 4-amino-1-aza-5-methoxybenzanthrone (**2**).

Aromatic electrophilic substitution reactions of the 1-azabenzanthrone system and its 2,3-dihydro analogue have been described

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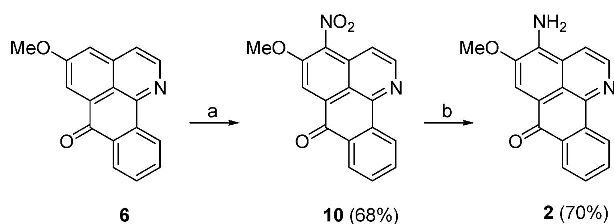
Scheme 2. Synthesis of **2**[a]



[a] Reagents and conditions: (a) H_2SO_4/HNO_3, TFA, rt, 2 h; (b) Na_2S, NaOH, H_2O, reflux, 5 h.

extensively.[11] With regard to nitration of the 5-methoxy-substituted compounds, it is worth pointing out that, although 1-aza-2,3-dihydro-5-methoxybenzanthrone undergoes reaction with similar efficiency at both positions neighboring the OCH_3 group, its aromatized analogue gives the 4-nitro compound (**10**) as the major product. In our hands, the latter reaction occurred in 68% yield. Considering that **10** was reduced to **2**, the regioisomer of **1**, in 70% yield, this alternative route is clearly preferable for the synthesis of **2** (Scheme 2).

The effects of these compounds on cell proliferation were determined in four different human cell lines (MRC-5: normal lung fibroblasts (CCL-171); AGS: gastric adenocarcinoma cells (CRL-1739); SK-MES-1: lung cancer cells (HTB-58); and J82: bladder carcinoma (HTB-1)), using the MTT reduction assay. The concentrations of the compounds inhibiting cell growth by 50% (IC_{50} values) were obtained adjusting the dose−response curves to a sigmoidal model. Only compound **10** was moderately active and slightly more toxic ($IC_{50} = 4.5\ \mu M$) toward gastric adenocarcinoma cells than toward normal fibroblasts.

For comparison, the IC_{50} values obtained for daurioxoisoaporphines A and B, using similar methodology in four different tumor cell lines, were reported to be in the range 3.0 μM to greater than 50 μM.[7] Another similar study, in which 12 synthetic 1-azabenzanthrones were tested against three different tumor cell lines, gave IC_{50} values between 2.09 and >100 μM.[9] Our results, added to the previously published data, suggest that further modification of the 1-azabenzanthrone scaffold might lead to the development of cytotoxic anticancer drugs. Nevertheless, a rational series of compounds with a broader range of substitution patterns would have to be synthesized and tested before any reasonable structure−activity relationships could be discerned.

Experimental Section

General Experimental Procedures. All reagents and solvents were commercially available from Sigma-Aldrich (St. Louis, MO, USA) or Merck (Darmstadt, Germany) and were used without further purification. Melting points are uncorrected and were determined with a Reichert Galen III hot plate microscope equipped with a DUAL JTEK Dig-Sense thermocouple thermometer. ^{1}H and ^{13}C NMR spectra were recorded at 300 or 400 MHz and 75 or 100 MHz, respectively, on Bruker Avance 300 or AMX 400 spectrometers, using $CDCl_3$ or DMSO-d_6 as solvent. The chemical shifts are reported as δ (ppm) downfield from TMS for ^{1}H NMR and relative to the central DMSO-d_6 resonance (39.5 ppm) for ^{13}C NMR. Coupling constants (J) are given in Hz. EIMS were run on a Thermo Finnigan MAT 95XP instrument, with electron impact ionization at 70 eV and with perfluorokerosene as reference. Purities of the compounds subjected to biological testing were >95% in every case (HPLC).

Synthesis of 2,3-dihydro-7*H*-dibenzo[*de*,*h*]quinolin-7-one Derivatives (3, 4, and 5). A solution of phthalaldehydic acid (10 g, 66.6 mmol) in toluene (50 mL) was treated with 3,4-dimethoxyphenethylamine (11.0 mL, 66.6 mmol). The solution was refluxed with stirring under a Dean−Stark trap for 2 h. The solvent was removed in vacuo, and the crude product was heated with polyphosphoric acid (40 g) at 100 °C for 20 min with stirring. The mixture was poured into ice water, made alkaline (pH 8−9) with 10% $NH_{3(aq)}$, and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O and dried over Na_2SO_4, and the solvent was evaporated to a dark brown residue that was chromatographed on silica gel. Elution of the column with EtOAc afforded: **2,3-dihydro-5-methoxy-7*H*-dibenzo[*de*,*h*]quinolin-7-one (1-aza-2,3-dihydro-5-methoxybenzanthrone, 3):** yellow needles, 2.3 g (15%); mp 165 °C (lit.[10] 168−170 °C); ^{1}H NMR ($CDCl_3$) δ 2.89 (2H, t, J = 7.6 Hz, CH_2), 3.92 (3H, s, OCH_3), 4.13 (2H, t, J = 7.6 Hz, CH_2), 6.98 (1H, d, J = 2.5 Hz, ArH), 7.59−7.63 (2H, m, ArH), 7.68 (1H, t, J = 7.3 Hz, ArH), 8.27 (1H, d, J = 7.6 Hz, ArH), 8.38 (1H, d, J = 7.8 Hz, ArH). **2,3-Dihydro-5,6-dimethoxy-7*H*-dibenzo[*de*,*h*]quinolin-7-one (1-aza-2,3-dihydro-5,6-dimethoxybenzanthrone, 4):** yellow needles, 0.086 g (0.5%); mp 156 °C (lit.[11] 154−155 °C); ^{1}H NMR ($CDCl_3$) δ 2.63−2.73 (1H, m, CH_2), 2.84−3.01 (1H, m, CH_2), 3.33−348 (1H, m, CH_2), 3.84 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 4.13−4.23 (1H, m, CH_2), 6.57 (1H, s, ArH), 7.49 (1H, d, J = 7.6 Hz, ArH), 7.66 (2H, m, ArH), 8.00 (1H, d, J = 7.6 Hz, ArH). **2,3-Dihydro-6-hydroxy-5-methoxy-7*H*-dibenzo[*de*,*h*]quinolin-7-one (1-aza-2,3-dihydro-6-hydroxy-5-methoxybenzanthrone, 5):** red needles, 0.935 g (6%); mp 158 °C (lit.[10] 173.5−174.5 °C); ^{1}H NMR ($CDCl_3$) δ 2.80 (2H, t, J = 8.3 Hz, CH_2), 3.97 (3H, s, OCH_3), 4.10 (2H, t, J = 8.3 Hz, CH_2), 6.9 (1H, s, ArH), 7.6 (1H, t, J = 7.6 Hz, ArH), 7.71 (1H, t, J = 7.3 Hz, ArH), 8.27 (1H, d, J = 7.8 Hz, ArH), 8.38 (1H, d, J = 8.1 Hz, ArH), 12.93 (1H, s, OH).

2,3-Dihydro-5-methoxy-6-nitro-7*H*-dibenzo[*de*,*h*]quinolin-7-one (1-aza-5-methoxy-6-nitrobenzanthrone, 7) and 2,3-dihydro-5-methoxy-4-nitro-7*H*-dibenzo[*de*,*h*]quinolin-7-one (1-aza-5-methoxy-4-nitrobenzanthrone, 9). To a solution of **5** (0.5 g, 3.8 mmol) in TFA (10 mL) was added carefully H_2SO_4/HNO_3, 1:1 (10 mL), stirring at room temperature for 2 h. The reaction mixture was poured into water (50 mL), made alkaline with 10% $NH_{3(aq)}$ (pH 8−9), and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with water and dried over Na_2SO_4. The solvent was evaporated to a yellow residue, which was chromatographed on silica gel (AcOEt) to afford **2,3-dihydro-5-methoxy-6-nitro-7*H*-dibenzo[*de*,*h*]quinolin-7-one (1-aza-2,3-dihydro-5-methoxy-6-nitrobenzanthrone, 7):** 0.205 g (35%); mp 209−210 °C; ^{1}H NMR ($CDCl_3$) δ 2.99 (2H, t, J = 7.9 Hz, CH_2), 4.00 (3H, s, OCH_3), 4.20 (2H, t, J = 7.8 Hz, CH_2), 7.19 (1H, s, ArH), 7.64 (1H, t, J = 7.6 Hz, ArH), 7.74 (1H, t, J = 7.4 Hz, ArH), 8.23 (1H, d, J = 7.8 Hz, ArH), 8.38 (1H, d, J = 7.8 Hz, ArH); ^{13}C NMR (DMSO-d_6) δ 25.2, 47.6, 57.9 (CH_3), 109.8, 118.9, 120.6, 121.2, 122.8, 124.9, 126.9, 131.3, 131.7, 134.9, 135.4, 141.3, 152.6, 180.0 (CO); HREIMS m/z 308.0570 (calcd for $C_{17}H_{12}N_2O_4$, 308.0797) and **2,3-dihydro-5-methoxy-4-nitro-7*H*-dibenzo[*de*,*h*]quinolin-7-one (1-aza-2,3-dihydro-5-methoxy-4-nitrobenzanthrone, 9):** 0.178 g (30%); mp 190−191 °C; ^{1}H NMR ($CDCl_3$) δ 2.88 (2H, t, J = 7.8 Hz, CH_2), 4.07 (3H, s, OCH_3), 4.21 (2H, t, J = 7.8 Hz, CH_2), 7.68 (1H, t, J = 7.4 Hz, ArH), 7.77 (1H, t, J = 7.4 Hz, ArH), 7.82 (1H, s, ArH), 8.32 (1H, d, J = 7.6 Hz, ArH), 8.44 (1H, d, J = 7.9 Hz, ArH); ^{13}C NMR (DMSO-d_6) δ 20.5, 47.0, 57.7 (CH_3), 108.5, 114.0, 124.9, 126.9, 127.8, 130.6, 131.3, 131.7, 131.8, 134.7, 135.6, 149.7, 152.6, 182.2 (CO); HREIMS m/z 308.1463 (calcd for $C_{17}H_{12}N_2O_4$, 308.0797).

5-Methoxy-6-nitro-7*H*-dibenzo[*de*,*h*]quinolin-7-one (1-aza-5-methoxy-6-nitrobenzanthrone, 8). To a solution of **7** (1.0 g, 3.2 mmol) in toluene (30 mL) was added Pd/C (0.1 g), and the suspension was refluxed with stirring under air for 24 h. The hot mixture was filtered through Celite and washed several times with hot toluene, and the solvent was evaporated to dryness to leave **8**: brownish-yellow needles (MeOH), 870 mg (87%); mp 277−279 °C; ^{1}H NMR ($CDCl_3$) δ 4.10 (3H, s, OCH_3), 7.59 (1H, s, ArH), 7.66 (1H, t, J = 7.8 Hz, ArH), 7.68 (1H, d, J = 5.5 Hz, ArH), 7.84 (1H, t, J = 7.6 Hz, ArH), 8.34 (1H, d, J = 7.8 Hz, ArH), 8.79 (1H, d, J = 5.6 Hz, ArH), 8.88 (1H, d, J = 7.9 Hz, ArH); ^{13}C NMR (DMSO-d_6) δ 58.5 (CH_3), 115.5, 116.5, 117.3, 119.4, 121.0, 125.5, 127.7, 128.8, 130.1, 131.5, 135.7, 136.1, 146.1, 151.5, 153.5, 183.7 (CO); HREIMS m/z 306.0655 (calcd for $C_{17}H_{10}N_2O_4$, 306.0641).

5-Methoxy-7*H*-dibenzo[*de*,*h*]quinolin-7-one (1-aza-5-methoxybenzanthrone, 6). A solution of **5** (2.0 g, 7.5 mmol) in benzene (10 mL) was treated with Pd/C (400 mg) and refluxed under air for 48 h. The hot mixture was filtered through Celite and washed several times with hot benzene. The solvent was removed to afford **6**: yellow crystals (MeOH), 1.4 g (73%); mp 178−179 °C (lit.[10] 180−181 °C); ^{1}H NMR ($CDCl_3$) δ 4.05 (3H, s, OCH_3), 7.43 (1H, d, J = 2.4 Hz, ArH), 7.65 (1H, t, J = 8.1 Hz, ArH), 7.66 (1H, d, J = 5.6 Hz, ArH), 7.81 (1H, t, J = 7.8 Hz, ArH), 8.29 (1H, d, J = 2.5 Hz, ArH), 8.41 (1H, d, J = 7.8

Hz, ArH), 8.70 (1H, d, $J = 5.6$ Hz, ArH), 8.90 (1H, d, $J = 7.9$ Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 55.9 (CH_3), 112.0, 118.6, 120.2, 120.8, 125.3, 127.1, 129.9, 130.7, 132.2, 134.1, 136.8, 137.3, 143.9, 148.1, 161.0, 183.1 (CO); HREIMS m/z 261.0813 (calcd for $C_{17}H_{11}NO_2$, 261.0790).

5-Methoxy-4-nitro-7*H*-dibenzo[*de*,*h*]quinolin-7-one (1-aza-5-methoxy-4-nitrobenzanthrone, 10). To a solution of **6** (1.0 g, 3.8 mmol) in TFA (50 mL) was added carefully H_2SO_4/HNO_3. 1:1 (10 mL), and the resulting mixture was stirred at room temperature for 6 h. The reaction mixture was poured into water (150 mL), made alkaline with 10% $NH_{3(aq)}$ (pH 8−9), and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O and dried over Na_2SO_4, and the solvent was removed to leave a yellow residue, which was chromatographed on silica gel (AcOEt), giving compound **10**: 0.802 g (68%); mp 232−233 °C (lit.[11] 231−233 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 (3H, s, OCH_3), 7.52 (1H, d, $J = 5.9$ Hz, ArH), 7.68 (1H, t, $J =$ 7.8 Hz, 1H, ArH), 7.84 (1H, t, $J = 7.0$ Hz, ArH), 8.38 (1H, d, $J = 7.8$ Hz, ArH), 8.44 (1H, s, ArH), 8.77 (1H, d, $J = 5.9$ Hz, ArH), 8.87 (1H, d, $J = 7.9$ Hz, ArH); ^{13}C NMR (DMSO-d_6) δ 58.0 (CH_3), 114.4, 115.9, 117.5, 126.3, 128.3, 129.2, 129.5, 131.7, 132.2, 132.6, 135.4, 135.9, 148.1, 150.1, 152.5, 181.9 (CO); HREIMS m/z 306.0781 (calcd for $C_{17}H_{10}N_2O_4$, 306.0641).

6-Amino-5-methoxy-7*H*-dibenzo[*de*,*h*]quinolin-7-one (lakshminine, 1). To a stirred suspension of **8** (1.5 g, 4.8 mmol) in EtOH (50 mL) was added a solution of $Na_2S.9H_2O$ (2.7 g, 11.2 mmol) and NaOH (1.0 g, 25 mmol) in water (50 mL). The mixture was refluxed for 5 h and left to stand overnight. The EtOH was removed in vacuo, and the precipitate formed was collected by filtration, washed with water, and dried to yield compound **1**: red needles (MeOH), 1.18 g (87%); mp 206−207 °C; ^{1}H NMR ($CDCl_3$) δ 3.97 (3H, s, OCH_3), 6.34 (1H, s, NH_2), 6.97 (1H, s, ArH), 7.44 (1H, d, $J = 2.1$ Hz, ArH), 7.66 (1H, t, $J = 7.1$ Hz, ArH), 7.80 (1H, t, $J = 7.1$ Hz, ArH), 8.53 (1H, d, $J = 7.7$ Hz, ArH), 8.60 (1H, d, $J = 2.2$ Hz, ArH), 9.00 (1H, d, $J = 7.9$ Hz, ArH), 10.59 (1H, s, NH_2); ^{13}C NMR ($CDCl_3$) δ 56.0 (CH_3), 104.2, 108.3, 119.4, 120.2, 124.8, 126.4, 128.9, 129.5, 132.3, 132.8, 136.4, 141.9, 143.2, 148.0, 150.5, 183.8 (CO); HREIMS m/z 276.08917 (calcd for $C_{17}H_{12}N_2O_2$, 276.0899).

4-Amino-5-methoxy-7*H*-dibenzo[*de*,*h*]quinolin-7-one (2). Reduction of **10**, following the same procedure used to obtain lakshminine (**1**), yielded **2**: red needles (MeOH), 0.95 g (70%); mp 232−233 °C; ^{1}H NMR (DMSO-d_6) δ 4.05 (3H, s, OCH_3), 7.40 (2H, s, NH_2), 7.69 (1H, t, $J = 7.5$ Hz, ArH), 7.80 (1H, t, $J = 7.3$ Hz, ArH), 8.11 (1H, s, ArH), 8.26 (1H, d, $J = 7.7$ Hz, ArH), 8.29 (1H, d, $J = 5.8$ Hz, ArH), 8.62 (1H, d, $J = 5.7$ Hz, ArH), 8.83 (d, $J =$ 1H, 7.9 Hz, ArH); ^{13}C NMR (DMSO-d_6) δ 56.09 (CH_3), 114.4, 115.4, 116.5, 119.3, 122.4, 124.7, 126.2, 130.0, 132.3, 132.7, 135.6, 141.0, 141.4, 143.5, 146.5, 179.1 (CO); HREIMS m/z 276.0890 (calcd for $C_{17}H_{12}N_2O_2$, 276.0899).

Cell Viability Assay. The MTT reduction assay was used to determine the viability of MRC-5 normal human lung fibroblasts (CCL-171), AGS human gastric adenocarcinoma cells (CRL-1739), SK-MES-1 human lung cancer cells (HTB-58), and J82 human bladder carcinoma cells (HTB-1) from the American Type Culture Collection (ATCC, Manassas, VA, USA), grown in Eagle's minimum essential medium (for MRC-5, AGS, and SK-MES-1 cells) or Ham's F-12 medium (for AGS cells) supplemented with 2 mM L-glutamine and 1.5 g/L $NaHCO_3$. Both media were additionally supplemented with 10% heat-inactivated fetal bovine serum, 100 IU/mL penicillin G, and 10 μg/mL streptomycin. Cells were subcultured once a week, and the medium was changed every two days. The cells were stored in liquid nitrogen in media with 10% glycerol added, and their viability after thawing was higher than 90%, as assessed by the trypan blue exclusion test. For the assay, cells were plated in 96-well plates (100 μL/well) at a density of 5×10^4 cells/mL. One day after seeding, the cells were treated with the medium containing the compounds at concentrations ranging from 0 to 100 μM, first dissolved in DMSO (final concentration of 1%), diluted with complete medium, and incubated for 72 h in a humidified incubator with 5% CO_2 in air at 37 °C, after which the MTT reduction assay was performed as described previously.[12] Etoposide (98% purity, Sigma-Aldrich, St. Louis, MO, USA) was used as a positive control. Each experiment was carried out three times in quadruplicate. The IC_{50} value was obtained adjusting the dose−response curve to a sigmoidal model ($a + (b - a)/1 + 10^{(x-c)}$), where $c = \log IC_{50}$.

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Supporting Information Available: T1: Antiproliferative activity of compounds **1**, **2**, **6**, **8**, **10**, and **11**. Figures S1−S10: ^{1}H and ^{13}C NMR spectra of compounds **1**, **2**, **7**, **8**, and **9**. These materials are available free of charge via the Internet at http://pubs.acs.org.

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