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Original article

Synthesis and antitumor evaluation of analogues of the marine pyrroloiminoquinone tsitsikammamines

Arnaud Rives [a,1], Benjamin Le Calvé [b,1], Tamara Delaine [a], Laurent Legentil [a], Robert Kiss [b], Evelyne Delfourne [a,*]

[a] Université Paul Sabatier, UMR CNRS 5068, Laboratoire de Synthèse et Physicochimie de Molécules d'Intérêt Biologique, 118 route de Narbonne, 31062 Toulouse Cédex 9, France
[b] Université Libre de Bruxelles, Laboratoire de Toxicologie, Institut de Pharmacie, Boulevard du Triomphe, 1050 Bruxelles, Belgium

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ABSTRACT

Two series of analogues of the marine pyrroloiminoquinone alkaloids tsitsikammamine have been synthesized on the basis of a Michael addition between 2′-amino-1-(4-methoxyphenyl)-ethanol and two indolediones. All the compounds were evaluated in vitro for antiproliferative activity against distinct cancer cell lines.

1. Introduction

During the last two decades, an increasing interest has been devoted to pyrroloiminoquinone-based alkaloids including discorhabdins, prianosins or makaluvamines, issued from marine source, due to their diverse and potent biological activities [1]. Also belonging to this group, wakayin **1**, isolated from a Fijian *Clavelina* sp. Ascidian [2], and tsitsikammamine A **2** and B **3**, found in the South African latrunculid sponge *Tsitsikammama favus* [3], are metabolites sharing a unique pyrrolo[4,3,2-*de*]pyrrolo[2,3-*h*]quinoline skeleton Fig. 1.

Many studies have been reported for the synthesis of members of such families [4] or to design analogues of potential value as therapeutic agents [5]. For our part, we recently proposed the first synthetic route to tsitsikammamine A [6].

In this paper, the complete study to prepare this alkaloid and analogues is discussed together with the antitumor evaluation of the different compounds both in terms of growth inhibitory activity and mode of action.

2. Chemistry

The retrosynthetic pathway investigated was based on a Michael addition between 2′-amino-1-(4-methoxyphenyl)-ethanol **4** and the previously described indoledione **5** [5f]. This reaction effected in absolute ethanol gave two regioisomers **6a** and **6b** (57% and 19% respectively, **a** and **b** referring to the order of elution during the purification by silica gel flash-chromatography). The formation of the second five-membered nitrogen-ring was achieved by direct cyclization of the hydroxy-derivatives in a trifluoroacetic acid/CH_2Cl_2 mixture and was concomitant with the cleavage of the Boc protective group leading to compounds **7a** and **7b**. MnO_2 oxidation of these compounds gave the bispyrroloquinone derivatives **8a** and **8b** which were subsequently cyclized into the corresponding iminoquinones **9a** and **9b** by refluxing in ethanol and 4A molecular sieves. The overall yields of these three steps were 16 and 22% respectively. It has to be noted that compounds **9a** and **9b** could also be obtained from **7a** and **7b** respectively by effecting the cyclization step prior to the MnO_2 oxidation (**10a** and **10b** being obtained as intermediates) Scheme 1.

The end of the synthesis consisted in a sequence of two steps, i.e.: (i) removal of the tosyl group of **9a** and **9b** by action of 1 N NaOH in dioxanne leading to compounds **11a** and **11b** (46 and 40% yield respectively), together with secondary compounds **12a** and **12b** (ii) demethylation of compound **11a** and **11b** by BBr_3 affording

* Corresponding author. Tel.: +33 561 55 62 93; fax: +33 561 55 60 11.
E-mail address: delfourn@chimie.ups-tlse.fr (E. Delfourne).
[1] The two first authors contributed equally to the article.

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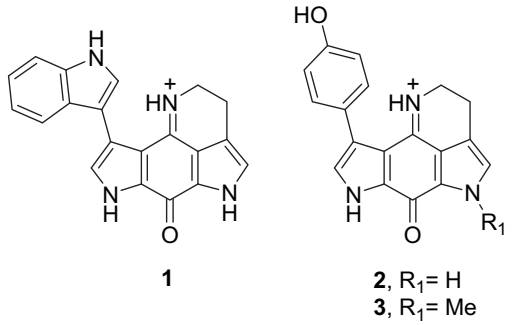
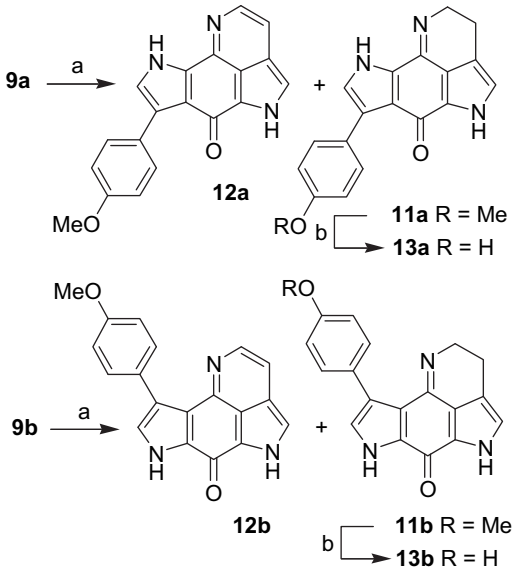


Fig. 1.

the free base of tsitsikammamine A **13b** and its non natural regioisomer **13a** Scheme 2.

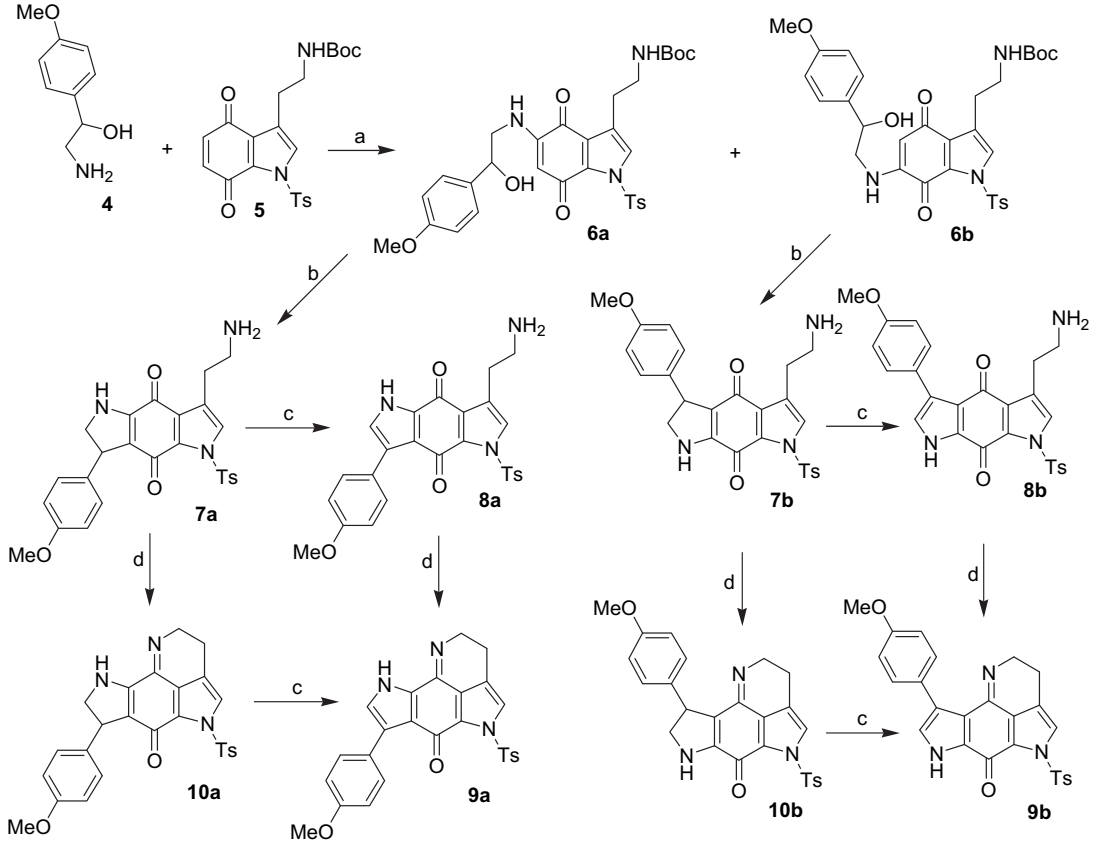
As part of the synthesis of tsitsikammamine, especially focusing on the formation of the second five-membered nitrogen ring, the condensation step involving compounds **4** and **5** was first investigated with the unsubstituted indoledione **14** as a Michael acceptor model. From a structure-activity point of view, the compounds obtained in this series are of interest to check if the iminoquinone moiety has a crucial role in the activity of pyrroloiminoquinone alkaloids. The previous reactional scheme beginning with the condensation reaction of compounds **4** and **14** was applied. As observed before, this step led to two regioisomers **15a** and **15b** in 62 and 16% yield respectively. The cyclization of these compounds by trifluoroacetic acid furnished derivatives **16a** and **16b** (38 and 58% yield) which gave by subsequent MnO_2 oxidation the pyrroloindolediones **17a** and **17b** in 71 and 82% yield. Removal



a- 1N NaOH, dioxanne, rt, overnight. b- BBr_3, CH_2Cl_2, N_2, 4h.

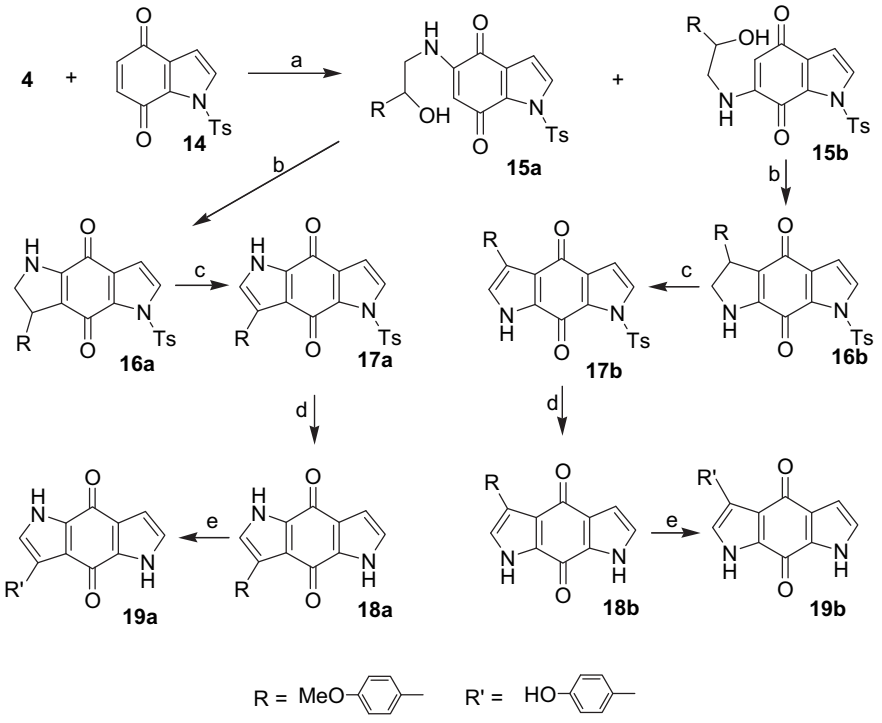
Scheme 2.

of the tosyl group of these compounds by action of 1 N NaOH in dioxanne (93 and 90%) and demethylation of the resulting compounds **18a** and **18b** by BBr_3 gave the final derivatives **19a** and **19b** Scheme 3.



a- abs EtOH, rt, 2h. b- TFA, CH_2Cl_2, rt, 4h. c- MnO_2, CH_2Cl_2, rt, overnight. d- abs EtOH, 4A molecular sieve, reflux, 3h.

Scheme 1.



a- abs EtOH, rt, 2h. b- TFA, CH_2Cl_2, rt, 4h. c- MnO_2, CH_2Cl_2, rt, overnight.d- 1N NaOH, dioxanne, rt, overnight. e- BBr_3, CH_2Cl_2, N_2, 4h.

Scheme 3.

3. Structural assignment

The structure assignment of each isomer in the series leading to the natural product was effected by comparison of the spectroscopic data of the trifluoroacetic salt of **13b** which were proven to be identical with those reported for tsitsikammamine A (**2**) [3]. In the second series (**15**–**19a**,**b**), the structure assignment resulted of the comparison of ^{13}C NMR chemical shift of the C4 carbonyl. Previous work by Qiao et al [7]. have shown that significant chemical shifts occurred at 1,4-benzoquinone units, for instance, in dipyrroloquinones **20a** and **20b**, the ^{13}C NMR chemical shifts of these C4 carbonyl groups being 174 and 179.3 ppm respectively. Furthermore, other data reported both by Lee et al. [8]. and Li et al. [9]. indicated that the presence of substituents on pyrrole rings have no significant influence on the chemical shift of C4. As a result of that, the carbonyl group of compounds **19a** and **19b** are 174.18 and 180.39 ppm respectively Fig. 2.

4. Pharmacology

We evaluated the IC_{50} *in vitro* growth inhibitory values of the 26 compounds under study by means of the MTT colorimetric assay as detailed elsewhere [10,11]. Briefly, the cell lines were incubated for 24 h in 96-microwell plates (at a concentration of 10,000 to 40,000 cells/mL culture medium depending on the cell type) to ensure adequate plating prior to cell growth determination. The assessment of cell population growth by means of the MTT colorimetric assay is based on the capability of living cells to reduce the yellow product MTT (3-(4,5)-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) to a blue product, formazan, by a reduction reaction occurring in the mitochondria. The number of living cells after 72 h of culture in the presence (or absence: control) of the various compounds is directly proportional to the intensity of the blue, which is quantitatively measured by spectrophotometry – in our case using a Biorad Model 680XR (Biorad, Nazareth, Belgium) at a 570 nM wavelength (with a reference of 630 nM). Each experiment was carried out in sextuplicate.

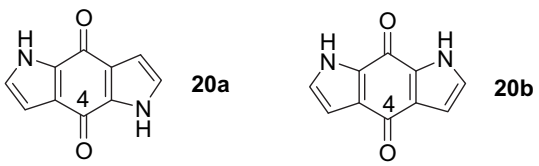


Fig. 2.

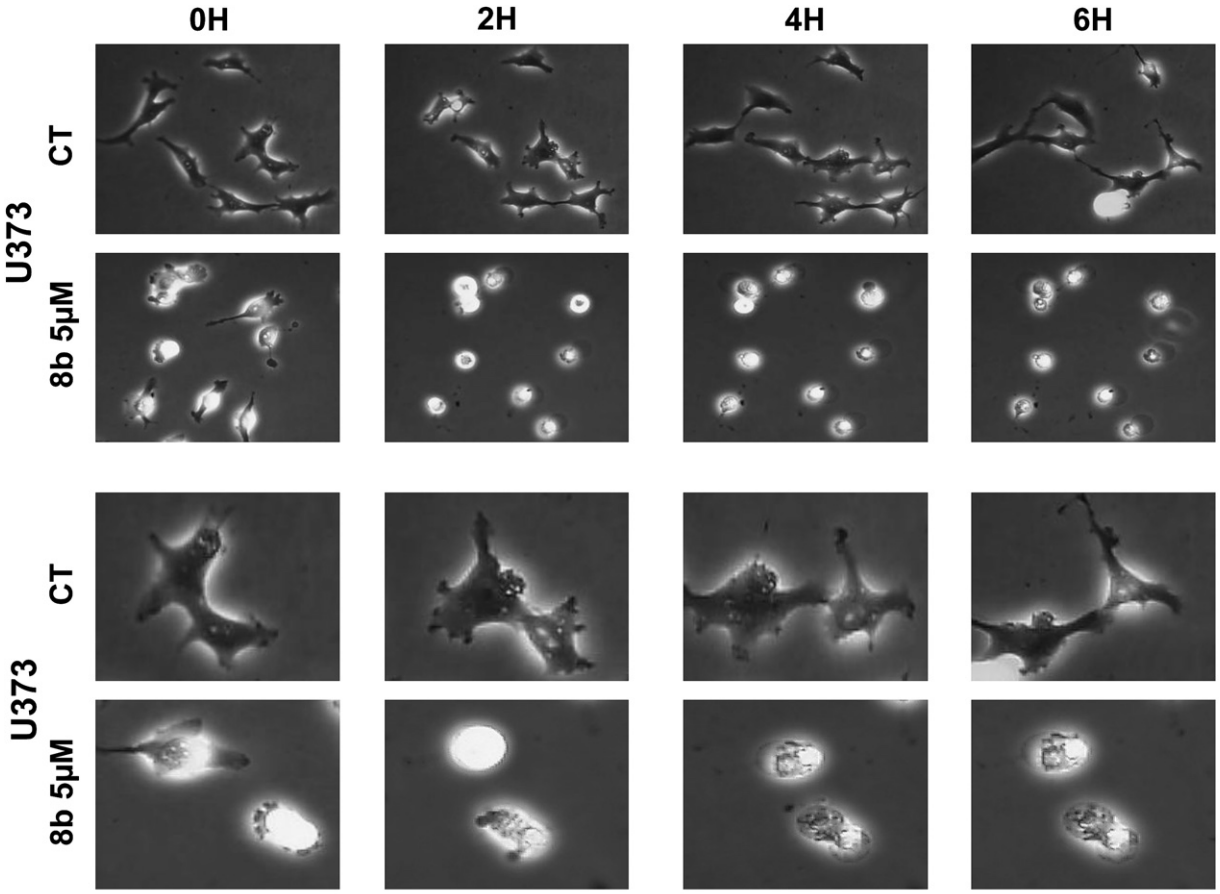
The origin of the cell lines used in the current study and the culture media are also fully detailed in references [10,11]. We made use of three human cancer cell lines, i.e. the U373 glioblastoma (GBM), the A549 non-small-cell-lung cancer (NSCLC) and the PC-3 prostate cancer cell lines. We employed these three cell lines because they display distinct profiles of sensitivity to various cytotoxic and/or cytostatic compounds. Indeed, the U373 GBM cells are resistant to apoptosis [11], but sensitive to autophagy-related cell death [12]. The A549 NSCLC cells are resistant to apoptosis [13] and to autophagy-related cell death [13], but sensitive to lysosomal membrane permeabilization-related cell death [13]. The PC-3 prostate cancer cells are sensitive to apoptosis [14]. These distinct profiles of sensitivity of the three cell lines to various types of cell death is emphasized at best by the data obtained in the current study. Indeed, for example, while being not active against U373 GBM and A549 NSCLC cells, compounds **6a** and **6b** display significant anti-tumor activity against PC-3 prostate cancer cells. The possibility

thus remains that compounds **6a** and **6b** display their anti-tumor activity at least partly though activation of apoptosis. In contrast, compounds **9a**, **9b**, **18b** and **19a** could exert their anti-tumor activity through non-apoptotic cell death processes. We labelled all these compounds as "heterogeneous" in terms of anti-tumor activity (see Table 1 and its legend) and we did not include them in the structure–activity relationship (SAR) analysis we report below. In a general way, compounds of the series leading to the natural product and its regioisomer (**13b** and **13a** respectively) exhibited higher anti-proliferative effects than compounds of the second series missing the functional chain or without the iminoquinone moiety. In almost all couple of products, excepted compounds **11a**/**11b**, regioisomers **b** appeared to display equal or higher *in vitro* antitumor activity than the **a** ones, the natural product tsitsikammamine exhibiting a greater activity than its regioisomer.

Of the 26 compounds under study, compound **8b** displayed IC_{50} *in vitro* growth inhibitory values in the single μM range for the three cell lines under study (Table 1). We thus made use of computer-assisted phase-contrast microscopy (quantitative video-microscopy) to grossly decipher the mechanism of action of compound **8b** when exerting its anti-tumor effects *in vitro*. Quantitative videomicroscopy already made it possible to help in such a gross deciphering of anti-tumor mode of action of various types of compounds including cardiotonic steroids [12,13], naphthalimides [10], alkaloids [11] and platinum derivatives [15].

We made use of the apoptosis-resistant U373 GBM cell line that has been cultured in the absence (control) or the presence of 5 μM of compound **8b**.

The morphological information revealed by this figure clearly indicate that compound **8b** exerts its growth inhibitory activity *in vitro* (as revealed by means of the MTT colorimetric assay; Table 1) through cytotoxic and not cytostatic effects. These effects (analyzed at approximately the compound **8b**'s IC_{50} growth inhibitory concentration; see Table 1) occur very rapidly, i.e. within 2 hrs after the addition of compound **8b** into the culture medium of U373 GBM cells as illustrated in the figure above. The type of cell death induced by compound **8b** remains to be determined and should not relate to a rapid induction of apoptosis according to the fact that: i) U373 GBM cells are apoptosis-resistant [11], and ii) the compound **8b**-induced cytotoxic effects occur too rapidly to be able to actually induce full apoptotic processes. We previously reported on the synthesis of tsitsikammamines A and B aza-analogues and we have observed that one of the final compounds partially inhibits human topoisomerase I, whereas synthetic intermediates inhibit the enzyme DNA cleavage activity at a concentration comparable to that of the control drug camptothecin [5e]. A second larger series of aza-analogues of tsitsikammamines A and B have then been synthesized [5f] and once more some of the compounds inhibited the topoisomerase I and/or II catalyzed relaxation of supercoiled DNA at a concentration comparable to the drugs camptothecin and etoposide. Altogether these data previously reported [5e,5f] and the current ones suggest that those tsitsikammamine analogues, such as compound **8b** under the current study, that display the highest *in vitro* growth inhibitory concentration on various cancer cell types, including apoptosis-resistant ones, kills cancer cell by



*Computer-assisted phase-contrast microscopy analysis of U373 GBM cells treated with 5 μM of compound **8b**. The upper-part of the figure relates to a 100x magnification, while the bottom of the figure relates to a 400x magnification.*

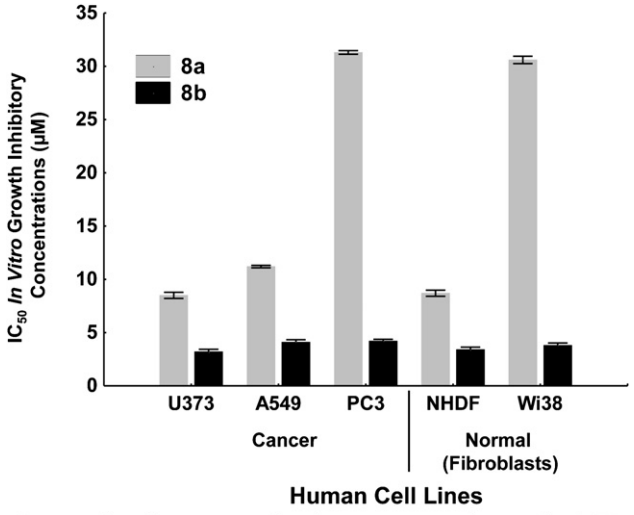
Table 1

Compound	IC_{50} *in vitro* growth inhibitory values (μM)			Profiles of anti-tumor activity[a]
	U373 GBM	A549 NSCLC	PC-3 prostate cancer	
6a	> 100	> 100	9.7	Heterogeneous
6b	> 100	> 100	9.5	Heterogeneous
7a	28.3	35.7	26.1	2
7b	48.5	52.4	33.7	2
8a	8.5	11.2	31.3	1
8b	3.2	4.1	4.2	1
9a	41.4	3.1	> 100	Heterogeneous
9b	57.4	15.4	> 100	Heterogeneous
10a	30.5	25.9	20.5	2
10b	18.3	9.7	20.5	1
11a	4.1	38.1	55.7	2
11b	> 100	> 100	> 100	3
12a	> 100	> 100	> 100	3
12b	97.8	80.6	88.8	2
13a	62.2	35.2	63.7	2
13b	18.1	15.6	23.0	2
15a	56.4	70.2	37.3	2
15b	29.2	> 100	> 100	Heterogeneous
16a	51.9	52.4	33.7	2
16b	47.2	35.4	37.5	2
17a	48.2	41.3	48.2	2
17b	> 100	77.6	24.6	Heterogeneous
18a	> 100	> 100	> 100	3
18b	7.6	7.8	> 100	Heterogeneous
19a	37.0	74.5	> 100	Heterogeneous
19b	> 100	> 100	> 100	3

[a] We labelled as heterogeneous those compounds that display markedly distinct anti-tumor activities against the three cancer cell lines under study. We did not include these compounds in the structure-activity relationship analysis we performed in the Pharmacology section. We labelled as "1" those compounds displaying mean IC_{50} values < 20 μM on the three cell lines under study, as "2" those compounds displaying IC_{50} values in the 21–100 μM range, and as "3" those compounds displaying IC_{50} values > 100 μM.

a yet unknown but very rapid process paralleled by topoisomerase I and II inhibition.

According to the fact that compound **8b** could serve as a lead to develop novel series of anticancer compounds active against cancers associated with dismal prognoses, such as apoptosis-resistant cancers, we analyze its bioselectivity profile along with the one of compound **8a**. We define as bioselective a compound that displays at least 5 fold higher inhibitory effects on cancer cell population growth than on normal cell population growth [14]. In other words, the ratio between the mean IC_{50} *in vitro* growth inhibitory concentrations calculated on cancer cells and normal cells must be >5 [14]. We made use of two human normal fibroblast cell lines (NHDF and Wi38) whose origin and culture conditions are fully detailed in reference [11].



*In vitro bioselectivity profile characterization (using the MTT colorimetric assay) of compounds **8a** and **8b**.*

The data we obtained clearly indicate that neither compound **8a** nor compound **8b** display significant bioselective indices. Indeed, the IC_{50} *in vitro* growth inhibitory concentrations associated with these two compounds in three distinct human cancer cell lines (U373, A549, PC3) are of the same magnitude when compared to two normal human fibroblast cell lines (NHDF, Wi38). However, altogether these data show that while compound **8b** displays similar cytotoxic effects in normal versus cancer cells, compound **8a** displays much higher heterogeneity in its cytotoxic effects towards normal and cancer cells. Thus, while it clearly appears that compound **8b** is definitively not bioselective but cytotoxic, compound **8a** seems to be associated with more or less specific antiproliferative activity when one considers the ranges displayed by its IC_{50} *in vitro* growth inhibitory concentrations in both normal and cancer cell lines. Compound **8a** could therefore be used as an original pharmacophore to design novel bioselective anticancer compounds.

5. Experimental section

^{1}H and ^{13}C NMR spectra were performed on Bruker Avance 300 or Avance 500 (cryoprobe TCI $^{1}H\{^{13}C, ^{31}P\}$) spectrometers with the chemical shifts of the remaining protons of the deuterated solvents serving as internal standards. IR spectra were obtained on a Perkin-Elmer 883 spectrophotometer. High resolution mass spectra (HRMS) were recorded on a micromass LCT mass spectrometer. Reagents were purchased from commercial sources and used as received. Chromatography was performed on silica gel (15–40 μM) by means of the solvent systems indicated below.

*5.1. 6[2-hydroxy-2-(4-methoxyphenyl)-ethylamino]-4,7-dioxo-3-(2-tert-butyloxycarbonylaminoethyl)-1-(toluene-4-sulfonyl)-indole (**6a**) and 5[2-hydroxy-2-(4-methoxyphenyl)-ethylamino]-4,7-dioxo-3-(2-tert-butyloxycarbonylaminoethyl)-1-(toluene-4-sulfonyl)-indole (**6b**)*

To a solution of hydroxylamine **4** (1.6 g, 10.0 mmoL) in ethanol (13 mL) was added dropwise a solution of quinone **5** [5f] (2.1 g, 4.73 mmoL) in ethanol (27 mL). After 4 h of stirring at room temperature, the mixture was concentrated over vacuum and the crude product was purified by flash-chromatography (CH_2Cl_2/MeOH 99:1) to give the two separated isomers.

6a: dark pink solid (1.64 g, 57%), mp 92 °C. HRMS (ESI+) $[M+H]^+$ calcd 610.2223, found 610.2249. ^{1}H NMR ($CDCl_3$) 1.39 (s, 9H); 2.37 (s, 3H); 2.85 (t, 2H, $J = 6.1$ Hz); 3.19 (m, 2H); 3.32 (m, 2H,); 3.75 (s, 3H); 4.83 (m, 1H); 5.09 (s, 1H); 6.18 (m, 1H); 6.83 (d, 2H, $J = 7.9$ Hz); 7.23 (d, 2H, $J = 7.9$ Hz); 7.27 (d, 2H, $J = 8.0$ Hz); 7.46 (s, 1H); 7.93 (d, 2H, $J = 0.8$ Hz). ^{13}C NMR ($CDCl_3$). 21.73; 26.09; 28.37 (3C); 40.01; 49.87; 55.29; 70.95; 79.32; 97.39; 114.10 (2C); 122.06; 124.46; 125.78; 127.05 (2C); 129.03 (2C); 129.41 (2C); 132.89; 133.37; 134.28; 145.73; 147.33; 156.06; 159.50; 174.97; 179.59. IR (KBr) 3400; 3380; 1698; 1676; 1620; 1603 cm^{-1}.

6b: dark pink solid (0.55 g, 19%), mp 88 °C. HRMS (ESI+) $[M+H]^+$ calcd 610.2223, found 610.2235. ^{1}H NMR ($CDCl_3$) 1.36 (s, 9H); 2.34 (s, 3H); 2.87 (t, 2H, $J = 6.1$ Hz); 3.14 (m, 2H); 3.29 (m, 2H,); 3.71 (s, 3H); 4.82 (m, 1H); 5.08 (s, 1H); 6.24 (m 1H); 6.79 (d, 2H, $J = 8.5$ Hz); 7.23 (m, 4H); 7.58 (s, 1H); 7.89 (d, 2H, $J = 8.5$ Hz). ^{13}C NMR ($CDCl_3$). 21.76; 25.69; 28.39 (3C); 40.53; 50.02; 55.33; 71.22; 79.32; 97.49; 114.18 (2C); 120.28; 123.51; 127.09 (2C); 128.88 (2C); 129.74 (2C); 130.09; 130.66; 133.25; 133.98; 146.07;

147.79; 156.10; 159.65; 170.00; 184.11. IR (KBr) 3430, 3362; 1709; 1674; 1599 cm^{-1}.

5.2. 5-(2-aminoethyl)-3-(4-methoxyphenyl)-7-(toluene-4-sulfonyl)-2,3-dihydro-1H,7H-pyrrolo[3,2-f]indole-4,8-dione (**7a**)

To a solution of compound **6a** (600 mg, 0.99 mmoL) in dry $CHCl_3$ (24 mL) was added dropwise TFA (15 mL). The mixture was stirred for 2 h at room temperature and concentrated. 1 N NaOH (10 mL) and CH_2Cl_2 (10 mL) were added to the residue, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuum. The crude product was purified by flash-chromatography (CH_2Cl_2/MeOH 90:10) to give the expected product as a violine solid (248 mg, 51%), mp 159 °C. HRMS (ESI+) $[M+H]^+$ calcd 492.1593, found 492.1591. ^{1}H NMR (DMSO-d_6) 2.39 (s, 3H); 2.98 (m, 2H); 3.13 (t, 2H, $J = 5.4$ Hz); 3.72 (s, 3H); 3.74 (m, 1H); 4.00 (dd, 1H, $J = 11.4$ Hz and 12.6 Hz); 4.26 (dd, 1H, $J = 5.4$ and 11.4 Hz); 6.82 (d, 2H, $J = 8.7$ Hz); 7.05 (d, 2H, $J = 8.7$ Hz); 7.42 (d, 2H, $J = 8.1$ Hz); 7.65 (s, 1H); 7.87 (d, 2H, $J = 8.4$ Hz). ^{13}C NMR (DMSO-d_6) 21.61; 23.73; 38.49; 44.01; 55.50; 56.36; 114.30 (2C); 115.54; 119.59; 125.33; 126.59; 128.37 (2C); 128.77 (2C); 130.06 (2C); 133.43; 134.55; 136.54; 146.15; 154.07; 158.38; 170.48; 178.45. IR ($CHCl_3$) 3337, 3252, 1674, 1610 cm^{-1}.

5.3. 7-(2-aminoethyl)-3-(4-methoxyphenyl)-5-(toluene-4-sulfonyl)-2,3-dihydro-1H,5H-pyrrolo[2,3-f]indole-4,8-dione (**7b**)

The same procedure was used as for compound **7a** involving compound **6b** (580 mg, 0.99 mmoL), dry $CHCl_3$ (24 mL) and TFA (15 mL). Purification by flash-chromatography (CH_2Cl_2/MeOH 95: 5) gave the product as a violine solid (224 mg, 48%), mp 175 °C. HRMS (ESI+) $[M+H]^+$ calcd 492.1593, found 492.1584. ^{1}H NMR (DMSO-d_6) 2.43 (s, 3H); 2.92 (m, 2H); 3.05 (m, 2H); 3.39 (dd, 1H, $J = 6.3$ and 12.6 Hz); 3.70 (s, 3H); 4.02 (dd, 1H, $J = 11.4$ Hz and 12.6 Hz); 4.33 (dd, 1H, $J = 6.0$ and 11.4 Hz); 6.81 (d, 2H, $J = 8.7$ Hz); 7.11 (d, 2H, $J = 8.7$ Hz); 7.51 (d, 2H, $J = 8.7$ Hz); 7.71 (br. s, 2H); 7.89 (s, 1H); 7.99 (d, 2H, $J = 8.7$ Hz). ^{13}C NMR (DMSO-d_6) 21.67; 23.57; 38.70; 44.10; 54.92; 55.49; 114.26 (2C); 115.51; 121.03; 127.85; 128.53 (2C); 128.88 (2C); 130.38 (2C); 131.29; 131.95; 134.02; 136.68; 146.66; 154.32; 158.34; 168.83; 177.95. IR ($CHCl_3$) 3350, 3228, 1672, 1610 cm^{-1}.

5.4. 3-(2-aminoethyl)-5-(4-methoxyphenyl)-1-toluene-4-sulfonyl)-1H,7H-pyrrolo[3,2-f]indole-4,8-dione (**8a**)

A suspension of compound **7a** (200 mg, 0.41 mmoL), MnO_2 (600 mg (6.90 mmoL) in CH_2Cl_2 (32 mL) was stirred at room temperature overnight. After filtration and concentration of the filtrate, the crude product was purified by flash-chromatography (CH_2Cl_2/MeOH 90: 10) to give the product as an orange solid (160 mg, 80%), mp 180 °C. HRMS (ESI+) $[M+H]^+$ calcd 490.1437, found 490.1416. ^{1}H NMR (DMSO-d_6) 2.39 (s, 3H); 3.06 (m, 2H); 3.18 (m, 2H); 3.80 (s, 3H); 6.95 (d, 2H, $J = 8.7$ Hz); 7.33 (s, 1H); 7.48 (dd, 2H, $J = 8.4$ and 2.4 Hz); 7.51 (d, 2H, $J = 8.7$ Hz); 7.81 (s, 1H); 7.95 (d, 2H, $J = 8.4$ Hz). ^{13}C NMR (DMSO-d_6) 21.62; 23.75; 38.58; 55.64; 113.92 (2C); 120.79; 120.63; 125.47; 125.98 (2C); 126.87; 128.07; 128.48 (2C); 128.71; 128.92; 129.99 (2C); 130.20; 133.08; 134.56; 146.33; 159.13; 172.13; 174.41. IR ($CHCl_3$) 3368, 1676, 1631, 1608 cm^{-1}.

5.5. 3-(2-aminoethyl)-7-(4-methoxyphenyl)-1-toluene-4-sulfonyl)-1H,5H-pyrrolo[2,3-f]indole-4,8-dione (**8b**)

The same procedure was used as for compound **8a** involving compound **7b** (200 mg, 0.41 mmoL), MnO_2 (600 mg, 6.90 mmoL) in CH_2Cl_2 (32 mL). Purification of the crude product by flash-chromatography (CH_2Cl_2/MeOH 90: 10) gave the product as an orange solid (164 mg, 82%), mp 203 °C. HRMS (ESI+) $[M+H]^+$ calcd 490.1437, found 490.1429. ^{1}H NMR (DMSO-d_6) 2.43 (s, 3H); 3.07 (m, 2H); 3.12 (m, 2H); 3.80 (s, 3H); 6.95 (d, 2H, $J = 8.7$ Hz); 7.36 (s, 1H); 7.52 (d, 2H, $J = 8.4$ Hz); 7.69 (d, 2H, $J = 8.7$ Hz); 7.85 (s, 1H); 8.02 (d, 2H, $J = 8.4$ Hz). ^{13}C NMR (DMSO-d_6) 21.66; 23.87; 38.72; 55.63; 113.82 (2C); 121.04; 121.33; 125.57; 125.69; 126.79; 128.91 (2C); 129.42; 130.16 (2C); 130.25 (2C); 130.40; 130.69; 133.12; 134.29; 146.55; 159.16; 165.85; 180.42. IR ($CHCl_3$) 3281, 1651, 1610, 1596 cm^{-1}.

5.6. 9-(4-methoxyphenyl)-5-toluene-4-sulfonyl)-2,3,5,7-tetrahydro-1,5,7-triazacyclopenta[e]acenaphthylen-6-one (**9a**)

*From **8a***: a mixture of compound **8a** (120 mg, 0.25 mmoL), 4 A molecular sieves and ethanol (8 mL) was refluxed for 4 h. After filtration and concentration of the filtrate, the crude product was purified by flash-chromatography (CH_2Cl_2/MeOH 99: 1) to give the product as a dark violine solid (46 mg, 39%). *From **10a***: the same procedure was used as for compound **8a** involving compound **10a** (100 mg, 0.21 mmoL), MnO_2 (307 mg, 3.53 mmoL) in CH_2Cl_2 (15 mL). Purification of the crude product by flash-chromatography (CH_2Cl_2/MeOH 99: 1) gave the product (71 mg, 72%), mp 148 °C. HRMS (ESI+) $[M+H]^+$ calcd 472.1331, found 472.1331.^{1}H NMR ($CDCl_3$) 2.43 (s, 3H); 2.86 (t, 2H, $J = 7.5$ Hz); 3.90 (s, 3H); 4.15 (t, 2H, $J = 7.5$ Hz); 6.93 (s, 1H); 6.95 (d, 2H, $J = 8.7$ Hz); 7.32 (d, 2H, $J = 8.7$ Hz); 7.45 (s, 1H); 7.55 (d, 2H, $J = 8.7$ Hz); 8.09 (d, 2H, $J = 8.7$ Hz). ^{13}C NMR ($CDCl_3$) 21.56; 29.72; 55.36; 58.52; 113.46 (2C); 116.50; 123.91; 124.17; 126.49; 128.82; 129.03 (2C); 129.64 (2C); 129.74; 130.13 (2C); 130.91; 132.45; 134.53; 145.77; 149.48; 159.04; 167.80; 171.25. IR ($CHCl_3$) 3261, 1728, 1651, 1598 cm^{-1}.

5.7. 7-(4-methoxyphenyl)-5-toluene-4-sulfonyl)-2,3,5,9-tetrahydro-1,5,9-triazacyclopenta[e]acenaphthylen-6-one (**9b**)

*From **8b***: the same procedure was used as for compound **9a** involving compound **8b** (200 mg, 0.41 mmoL), 4 A molecular sieves and ethanol (14 mL). Purification of the crude product by flash-chromatography (CH_2Cl_2/MeOH 98: 2) gave the product as a brown solid (108 mg, 56%). *From **10b***: the same procedure was used as for compound **8a** involving compound **10b** (100 mg, 0.21 mmoL), MnO_2 (307 mg, 3.53 mmoL) in CH_2Cl_2 (15 mL). Purification of the crude product by flash-chromatography (CH_2Cl_2/MeOH 98: 2) gave the product (87 mg, 88%), mp 158 °C. HRMS (ESI+) $[M+H]^+$ calcd 472.1331, found 472.1378. ^{1}H NMR ($CDCl_3$) 2.44 (s, 3H); 2.78 (t, 2H, $J = 7.5$ Hz); 3.86 (s, 3H); 4.20 (t, 2H, $J = 7.5$ Hz); 6.93 (d, 2H, $J = 8.7$); 7.09 (d, 2H, $J = 2.7$ Hz); 7.36 (d, 2H, $J = 8.4$ Hz); 7.51 (s, 1H); 7.77 (d, 2H, $J = 8.7$ Hz); 8.09 (d, 1H, $J = 8.4$ Hz). ^{13}C NMR ($CDCl_3$) 17.74; 21.76; 49.80; 55.29; 113.48 (2C); 118.94; 122.63; 124.55; 125.16; 125.94; 126.81; 128.21; 128.66 (2C); 129.07; 129.70 (2C); 129.94 (2C); 133.05; 134.93; 145.67; 153.14; 158.92, 165.98. IR ($CHCl_3$) 3279, 1712, 1650, 1613, 1598 cm^{-1}.

5.8. 7-(4-methoxyphenyl)-5-(toluene-4-sulfonyl)-2,3,5,7,8,9-hexahydro-1,5,9-triazacyclopenta[e]acenaphtylen-6-one (**10a**)

The same procedure was used as for compound **9a** involving compound **7a** (200 mg, 0.41 mmoL), 4 A molecular sieve and ethanol (14 mL). Purification of the crude product by flash-chromatography (CH_2Cl_2/MeOH 98: 2) gave the product as a dark blue solid (84 mg, 43%), mp 129 °C. HRMS (ESI+) $[M+H]^+$ calcd 474.1488, found 472.1460. ^{1}H NMR ($CDCl_3$) 2.39 (s, 3H); 2.81 (t, 2H, $J = 7.5$ Hz); 3.63 (dd, 1H, $J = 10.8$ and 4.8 Hz); 3.78 (s, 3H); 4.08 (t, 2H, $J = 7.5$ Hz); 4.14 (m, 1H); 4.38 (dd, 1H, $J = 4.8$ and 11.4 Hz); 6.79 (d, 2H, $J = 8.7$ Hz); 7.15 (d, 2H, $J = 8.4$ Hz); 7.24 (d, 1H, $J = 8.7$ Hz);

7.29 (s, 1H); 8.00 (d, 2H, $J = 8.4$ Hz). ^{13}C NMR ($CDCl_3$) 18.06; 21.71; 44.65; 50.11; 55.28; 56.57; 113.92 (2C); 116.09; 119.64; 122.55; 122.79; 125.92; 128.12 (2C); 128.67 (2C); 129.53 (2C);135.05; 136.09; 145.31; 151.82; 153.6; 158.27; 171.65. IR ($CHCl_3$) 1673, 1609, 1596 cm^{-1}.

5.9. 9-(4-methoxyphenyl)-5-(toluene-4-sulfonyl)-2,3,5,7,8,9-hexahydro-1,5,7-triazacyclopenta[e]acenaphtylen-6-one (**10b**)

The same procedure was used as for compound **9a** involving compound **7b** (100 mg, 0.21 mmoL), 4 A molecular sieves and ethanol (7 mL). Purification of the crude product by flash-chromatography (CH_2Cl_2/MeOH 98: 2) gave the product as a dark blue solid (50 mg, 50%), mp 135 °C. HRMS (ESI+) $[M + H]^+$ calcd 474.1488, found 474.1502. ^{1}H NMR ($CDCl_3$) 2.28 (s, 3H); 2.68 (t, 2H, $J = 7.0$ Hz); 3.51 (dd, 1H, $J = 4.8$ and 10.5 Hz); 3.67 (s, 3H); 3.93-4.05 (m, 1H); 4.05 (t, 2H, $J = 7.0$ Hz); 4.29 (dd, 1H, $J = 3.9$ and 10.5 Hz); 6.68 (d, 2H, $J = 8.7$ Hz); 7.06 (d, 2H, $J = 8.7$ Hz); 7.17 (s, 1H); 7.21 (d, 2H, $J = 8.7$ Hz); 7.89 (d, 2H, $J = 8.7$ Hz). ^{13}C NMR (DMSO-d_6) 21.67; 22.54; 44.11; 55.35; 55.49; 56.31; 114.25 (2C); 115.51; 121.03; 127.82; 128.53 (2C); 128.89 (2C); 130.37 (2C); 131.30; 131.94; 134.02; 136.67; 146.68; 154.32; 158.34; 168.82; 177.95. IR ($CHCl_3$) 3266, 1714, 1660, 1599 cm^{-1}.

5.10. 7-(4-methoxyphenyl)-2,3,5,9-tetrahydro-1,5,9-triazacyclopenta[e]acenaphtylen-6-one (**11a**) and 7-(4-methoxyphenyl)-5,9-dihydro-1,5,9-triazacyclopenta[e]acenaphtylen-6-one (**12a**)

A mixture of compound **9a** (20 mg, 0.042 mmoL) in 1 N NaOH (2 mL) and dioxanne (2 mL) was stirred at room temperature overnight. After concentration, the crude product was purified by flash-chromatography (CH_2Cl_2/MeOH 90:10) to give the expected product **11a** and a side-product **12a**

11a: orange solid (5.3 mg, 40%), mp 128 °C. HRMS (ESI+) $[M + H]^+$ calcd 318.1243, found 318.1281. ^{1}H NMR (DMSO-d_6) 2.76 (t, 2H, $J = 7.8$ Hz); 3.79 (s, 3H); 4.07 (t, 2H, $J = 7.8$ Hz); 6.86 (s, 1H); 6.91 (d, 2H, $J = 8.7$ Hz); 7.06 (s, 1H); 7.61 (d, 2H, $J = 8.7$ Hz). ^{13}C NMR (DMSO-d_6) 18.88; 55.52; 55.91; 113.43 (2C); 114.35; 116.25; 119.85; 123.42; 126.76; 127.13; 130.31 (2C); 131.87; 150.51; 158.47; 163.30; 167.48; 174.38. IR (KBr) 3392, 1640 cm^{-1}.

12a: orange solid (1.3 mg, 10%), mp > 260 °C. HRMS (ESI+) $[M + H]^+$ calcd 316.1086, found 316.1115. ^{1}H NMR (DMSO-d_6) 3.80 (s, 3H); 6.92 (d, 2H, $J = 8.7$ Hz); 7.20 (s, 1H); 7.66 (d, 1H, $J = 6$ Hz); 7.69 (d, 2H, $J = 8.7$ Hz); 7.90 (s, 1H); 8.32 (d, 1H, $J = 6$ Hz). ^{13}C NMR (DMSO-d_6) 55.55; 113.37 (2C); 115.07; 120.18; 122.02; 122.28; 122.67; 123.22; 126.23; 127.55, 130.37; 130.68 (2C); 134.50; 140.79; 142.17; 158.36; 171.49. IR (KBr) 3452, 1635 cm^{-1}.

5.11. 9-(4-methoxyphenyl)-2,3,5,7-tetrahydro-1,5,7-triazacyclopenta[e]acenaphtylen-6-one (**11b**) and 9-(4-methoxyphenyl)-5,7-dihydro-1,5,7-triazacyclopenta[e]acenaphtylen-6-one (**12b**)

The same procedure was used as for compound **11a** involving compound **9b** (50 mg, 0.106 mmoL), 1 N NaOH (5 mL) and dioxanne (5 mL). Purification of the crude product by flash-chromatography (CH_2Cl_2/MeOH 98: 2) gave:

11b: orange solid (16 mg, 46%), mp 140 °C. HRMS (ESI+) $[M + H]^+$ calcd 318.1243, found 318.1210, found 318.1210. ^{1}H NMR (DMSO-d_6) 2.69 (t, 2H, $J = 7.8$ Hz); 3.79 (s, 3H); 3.99 (t, 2H, $J = 7.8$ Hz); 6.91 (d, 2H, $J = 8.7$ Hz); 6.95 (d, 1H, $J = 2.4$ Hz); 7.22 (d, 1H, $J = 2.7$ Hz); 7.87 (d, 2H, $J = 8.7$ Hz); 12.08 (br.s, 1H); 12.39 (br.s, 1H). ^{13}C NMR (DMSO-d_6) 28.18; 51.93; 55.58; 113.46 (2C); 119.70; 120.93; 122.28; 126.07; 126.10; 126.92; 128.00(2C); 128.79; 132.83; 133.10; 161.89; 161.89; 164.60; 167.00. IR (KBr) 3442, 1679, 1630 cm^{-1}.

12b: orange solid (2.7 mg, 8%), mp > 260 °C. HRMS (ESI+) $[M + H]^+$ calcd 316.1086, found 316.1086. ^{1}H NMR (DMSO-d_6) 3.83 (s, 3H); 7.00 (d, 2H, $J = 9.0$ Hz); 7.38 (d, 1H, $J = 3$ Hz); 7.68 (d, 1H, $J = 6$ Hz); 8.07 (s, 1H); 8.09 (d, 2H, $J = 9$ Hz); 8.34 (d, 1H, $J = 6$ Hz); 12.53 (br.s, 1H); 14.25 (br.s, 1H). ^{13}C NMR (DMSO-d_6) 55.54; 113.67; 113.74; 114.69; 121.00; 122.22; 123.55; 123.82; 123.86; 124.87; 127.61; 130.31(2C); 135.39; 140.93; 140.92; 146.81; 158.45; 164.81. IR (KBr) 3415, 3250, 1718, 1648, 1609 cm^{-1}.

5.12. 7-(4-hydroxyphenyl)-2,3,5,9-tetrahydro-1,5,9-triazacyclopenta[e]acenaphtylen-6-one (**13a**)

To a suspension of compound **11a** (5 mg, 0.016 mmoL) in CH_2Cl_2 (2 mL) at 0 °C and under nitrogen atmosphere, was added dropwise a 1 M solution of BBr_3 in CH_2Cl_2 (0.2 mL). The mixture was stirred for 4 h and a saturated $NaHCO_3$ solution (2 mL) was added. After concentration over vacuum, the crude product was purified by flash-chromatography (CH_2Cl_2/MeOH 90:10) to give the product as a dark red solid (2.9 mg, 60%), mp >260 °C. HRMS (ESI+) $[M + H]^+$ calcd 304.1086, found 304.1064. ^{1}H NMR (DMSO-d_6) 2.73 (t, 2H, $J = 8.1$ Hz); 4.05 (t, 2H, $J = 8.1$ Hz); 6.72 (d, 2H, $J = 8.7$ Hz); 6.82 (s, 1H); 6.95 (s, 1H); 7.47 (d, 2H, $J = 8.7$ Hz); 7.6 (br.s, 1H); 7.7 (br.s, 1H); 11.81 (br.s, 1H). ^{13}C NMR (DMSO-d_6) 31.15; 49.05; 114.83 (2C); 115.4; 116.13; 119.85; 120.66; 120.93; 125.57; 126.41; 129.46; 130.36 (2C); 134.26; 150.57; 156.71; 174.49. IR (KBr) 3408, 3148, 1640, 1599 cm^{-1}.

5.13. 9-(4-hydroxyphenyl)-2,3,5,7-tetrahydro-1,5,7-triazacyclopenta[e]acenaphtylen-6-one (**13b**)

The same procedure was used as for compound **13a** involving compound **11b** (5 mg, 0.016 mmoL), CH_2Cl_2 (2 mL) and 1 M solution of BBr_3 in CH_2Cl_2 (0.2 mL). Purification of the crude product by flash-chromatography (CH_2Cl_2/MeOH 90:10) gave the product as a dark red solid (3 mg, 62%), mp > 260 °C. HRMS (ESI+) $[M + H]^+$ calcd 304.1086, found 304.1130. ^{1}H NMR (DMSO-d_6) 2.71 (t, 2H, $J = 7.8$ Hz); 3.97 (t, 2H, $J = 7.8$ Hz); 6.74 (d, 2H, $J = 8.7$ Hz); 6.96 (d, 1H, $J = 2.1$ Hz); 7.16 (d, 1H, $J = 3.0$ Hz); 7.69 (d, 2H, $J = 8.7$ Hz); 12.15 (br.s, 1H); 12.44 (br.s, 1H). ^{13}C NMR (DMSO-d_6) 29.46; 49.07; 115.08 (2C); 118.13; 121.84; 122.17; 123.52; 125.09; 125.28; 125.53; 130.16 (2C); 133.83; 154.95; 156.72; 167.99; 172.45. IR (KBr) 3442, 1679, 1630 cm^{-1}.

5.14. 5-[2-Hydroxy-2-(4-methoxy-phenyl)-ethylamino]-1-(toluene-4-sulfonyl)-1H-indole-4,7-dione (**15a**) and 6-[2-Hydroxy-2-(4-methoxy-phenyl)-ethylamino]-1-(toluene-4-sulfonyl)-1H-indole-4,7-dione (**15b**)

The same procedure was used as for compound **6a** and **6b** involving the hydroxylamine **4** (1.3 g, 7.78 mmoL), ethanol (23 mL) and a solution of quinone **14** (1.2 g, 3.99 mmoL) in ethanol (12 mL). Purification of the crude product by flash-chromatography (CH_2Cl_2/MeOH 99:1) gave the two separated isomers.

15a: dark pink solid (0.33 g, 18%), mp 100 °C. HRMS (ESI+) $[M + Na]^+$ calcd 489.1096, found 489.1085. ^{1}H NMR ($CDCl_3$) 2.36 (s, 3H); 3.20 (m, 2H); 3.74 (s, 3H); 4.80 (dd, 1H, $J = 7.2$ and 9.0 Hz); 5.13 (s, 1H); 6.02 (t, 1H, $J = 4.5$ Hz); 6.60 (d, 1H, $J = 3.3$ Hz); 6.83 (d, 2H, $J = 8.7$ Hz); 7.21 (d, 2H, $J = 8.7$ Hz); 7.26 (d, 2H, $J = 8.4$ Hz); 7.61 (d, 1H, $J = 3.3$ Hz); 7.94 (d, 2H, $J = 8.4$ Hz). ^{13}C NMR ($CDCl_3$) 21.75; 49.84; 55.30; 71.05; 97.62; 107.23; 114.14 (2C); 126.86; 127.07 (2C); 127.80; 129.11 (2C); 129.47 (2C); 132.48; 133.28; 134.16; 145.91; 147.18; 159.55; 175.11; 178.60. IR (KBr) 3364, 1681, 1597 cm^{-1}.

15b: dark pink solid (1.23 g, 66%), mp 128 °C. HRMS (ESI+) $[M + Na]^+$ calcd 489.1096, found 489.1105. ^{1}H NMR ($CDCl_3$) 2.45 (s, 3H); 3.29 (t, 2H, $J = 6.6$ Hz); 3.83 (s, 3H); 4.88 (t, 1H, $J = 6.3$ Hz); 5.33 (s, 1H); 6.23 (t, 1H, $J = 7.2$ Hz); 6.73 (d, 1H, $J = 3.0$ Hz); 6.91 (d, 2H, $J = 8.7$ Hz); 7.30 (d, 2H, $J = 8.7$ Hz); 7.36 (d, 2H, $J = 8.4$ Hz); 7.81 (d, 1H, $J = 3.0$ Hz); 8.01 (d, 2H, $J = 8.4$ Hz). ^{13}C NMR ($CDCl_3$) 21.79; 49.96; 55.36; 71.41; 97.01; 108.56; 114.28 (2C); 126.95; 127.07 (2C); 128.94 (2C); 129.78 (2C); 131.24; 133.00; 133.94; 134.31; 146.20; 148.11; 159.79; 170.05; 181.43. IR (KBr) 3430, 3360, 1701, 1674, 1598 cm^{-1}.

5.15. 3-(4-Methoxy-phenyl)-5-(toluene-4-sulfonyl)-2,3-dihydro-1H,5H-pyrrolo[2,3-f]indole-4,8-dione (**16a**)

To a solution of compound **15a** (170 mg, 0.36 mmoL) in CH_2Cl_2 (6 mL) was added dropwise TFA (6 mL). The mixture was stirred overnight at room temperature and concentrated. 1 N NaOH (5 mL) and CH_2Cl_2 (5 mL) were added to the residue, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated over vacuum. The crude product was purified by flash-chromatography (CH_2Cl_2/MeOH 98:2) to give the expected product as a violine solid (61 mg, 38%), mp 122 °C. HRMS (ESI+) $[M + Na]^+$ calcd 471.0991, found 471.1010. ^{1}H NMR ($CDCl_3$) 2.43 (s, 3H); 3.63 (dd, 1H, $J = 11.1$ and 5.4 Hz); 3.81 (s, 3H); 4.09 (t, 1H, $J = 11.4$ Hz); 4.46 (dd, 1H, $J = 5.4$ and 11.7 Hz); 6.65 (d, 1H, $J = 3.3$ Hz); 6.82 (d, 2H, $J = 8.7$ Hz); 7.14 (d, 2H, $J = 8.7$ Hz); 7.28 (d, 2H, $J = 8.4$ Hz); 7.65 (d, 1H, $J = 3.3$ Hz); 7.97 (d, 2H, $J = 8.4$ Hz). ^{13}C NMR ($CDCl_3$) 21.75; 44.86; 55.30; 56.05; 106.88; 114.03 (2C); 114.17; 126.97; 127.65; 128.10 (2C); 129.04 (2C); 129.43 (2C); 129.98; 134.27; 135.06; 145.68; 152.36; 158.46; 171.65; 177.29. IR (KBr) 3397, 1681, 1609 cm^{-1}.

5.16. 3-(4-Methoxy-phenyl)-7-(toluene-4-sulfonyl)-2,3-dihydro-1H,7H-pyrrolo[3,2-f]indole-4,8-dione (**16b**)

The same procedure was used as for compound **16a** involving compound **15b** (150 mg, 0.31 mmoL), CH_2Cl_2 (5 mL) and TFA (5 mL). Purification of the crude product by flash-chromatography (CH_2Cl_2/MeOH 98:2) gave the product as a violine solid (80 mg, 58%), mp 140 °C. HRMS (ESI+) $[M + H]^+$ calcd 449.1171, found 449.1175. ^{1}H NMR ($CDCl_3$) 2.44 (s, 3H); 3.63 (dd, 1H, $J = 11.1$ and 6.0 Hz); 3.74 (s, 3H); 4.08 (t, 1H, $J = 11.7$ Hz); 4.47 (dd, 1H, $J = 6.0$ and 12.0 Hz); 6.62 (d, 1H, $J = 3.0$ Hz); 6.79 (d, 2H, $J = 8.4$ Hz); 7.16 (d, 2H, $J = 8.4$ Hz); 7.35 (d, 2H, $J = 8.1$ Hz); 7.73 (d, 1H, $J = 3.0$ Hz); 8.01 (d, 2H, $J = 8.1$ Hz). ^{13}C NMR ($CDCl_3$) 21.80; 44.75; 55.23; 55.94; 108.79; 114.09 (2C); 116.71; 126.48; 127.44; 128.14 (2C); 128.97 (2C); 129.79 (2C); 130.80; 134.06; 135.13; 135.81; 146.33; 158.63; 168.94; 177.59. IR (KBr) 3376, 1672, 1611 cm^{-1}.

5.17. 7-(4-Methoxy-phenyl)-1-(toluene-4-sulfonyl)-1H,5H-pyrrolo[2,3-f]indole-4,8-dione (**17a**)

The same procedure was used as for compound **8a** involving compound **16a** (200 mg, 0.45 mmoL), MnO_2 (300 mg, 3.45 mmoL) in CH_2Cl_2 (16 mL). Purification of the crude product by flash-chromatography (CH_2Cl_2) gave the product as an orange solid (143 mg, 71%), mp 199 °C. HRMS (ESI+) $[M + H]^+$ calcd 447.1015, found 447.1049. ^{1}H NMR ($CDCl_3$) 2.45 (s, 3H); 3.91 (s, 3H); 6.76 (d, 1H, $J = 3.3$ Hz); 6.97 (d, 2H, $J = 9.0$ Hz); 7.02 (d, 1H, $J = 2.7$ Hz); 7.35 (d, 2H, $J = 8.4$ Hz); 7.58 (d, 2H, $J = 9.0$ Hz); 7.77 (d, 1H, $J = 3.3$ Hz); 8.07 (d, 2H, $J = 8.4$ Hz). ^{13}C NMR ($CDCl_3$) 21.78; 55.35; 107.26; 113.58(2C); 121.41; 123.21; 124.83; 128.16; 129.06; 129.24; 129.50 (2C); 129.90 (2C); 130.55 (2C); 132.42; 132.95; 134.25; 145.80; 159.26; 171.81; 173.51. IR (KBr) 3378, 1741, 1677, 1626 cm^{-1}.

5.18. 5-(4-Methoxy-phenyl)-1-(toluene-4-sulfonyl)-1H,7H-pyrrolo[3,2-f]indole-4,8-dione (**17b**)

The same procedure was used as for compound **8a** involving compound **16b** (400 mg, 0.90 mmoL), MnO_2 (600 mg, 6.90 mmoL) in CH_2Cl_2 (32 mL). Purification of the crude product by flash-chromatography (CH_2Cl_2) gave the product as an orange solid (330 mg, 82%), mp 236 °C. HRMS (ESI+) $[M + H]^+$ calcd 447.1015, found 447.1030. ^{1}H NMR ($CDCl_3$) 2.45 (s, 3H); 3.86 (s, 3H); 6.80 (d, 1H, $J = 3.3$ Hz); 6.95 (d, 2H, $J = 8.4$ Hz); 7.01 (d, 1H, $J = 3.0$ Hz); 7.37 (d, 2H, $J = 8.4$ Hz); 7.65 (d, 2H, $J = 8.4$ Hz); 7.76 (d, 1H, $J = 3.0$ Hz); 8.04 (d, 2H, $J = 8.4$ Hz). ^{13}C NMR ($CDCl_3$) 21.78; 55.32; 109.12; 113.61 (2C); 114.09; 123.02; 124.76; 127.83; 128.82 (2C); 128.95; 129.63; 129.71 (2C); 129.79 (2C); 133.48; 134.25; 134.82; 146.10; 159.36; 166.35; 178.53. IR (KBr) 3255, 1650, 1610 cm^{-1}.

5.19. 3-(4-Methoxy-phenyl)-1H,5H-pyrrolo[2,3-f]indole-4,8-dione (**18a**)

The same procedure was used as for compound **11a** involving compound **17a** (100 mg, 0.22 mmoL), 1 N NaOH (2 mL) and dioxanne (2 mL). Purification of the crude product by flash-chromatography (CH_2Cl_2/MeOH 98: 2) gave the product as an orange solid (60 mg, 93%), mp > 260 °C. HRMS (ESI+) $[M + Na]^+$ calcd 315.0746, found 315.0762. ^{1}H NMR (DMSO-d_6) 3.80 (s, 3H); 6.49 (d, 1H, $J = 2.4$ Hz); 6.95 (d, 2H, $J = 8.7$ Hz); 7.07 (d, 1H, $J = 2.7$ Hz); 7.24 (s, 1H); 7.75 (d, 2H, $J = 8.7$ Hz); 12.51 (br.s, 2H). ^{13}C NMR (DMSO-d_6) 55.57; 107.36; 113.74 (2C); 120.78; 124.44; 125.25; 125.40; 126.26; 126.47; 130.06 (2C);134.50; 135.31; 158.87; 174.56; 174.83. IR (KBr) 3435, 3196, 1634 cm^{-1}.

5.20. 3-(4-Methoxy-phenyl)-1H,7H-pyrrolo[3,2-f]indole-4,8-dione (**18b**)

The same procedure was used as for compound **11a** involving compound **17b** (180 mg, 0.41 mmoL), 1 N NaOH (5 mL) and dioxanne (5 mL). Purification of the crude product by flash-chromatography (CH_2Cl_2/MeOH 98: 2) gave the product as an orange solid (108 mg, 90%), mp > 260 °C. HRMS (ESI+) $[M + H]^+$ calcd 293.0926, found 293.0955. ^{1}H NMR (DMSO-d_6) 3.77 (s, 3H); 6.45 (d, 1H, $J = 2.7$ Hz); 6.91 (d, 2H, $J = 8.7$ Hz); 7.10 (d, 1H, $J = 2.7$ Hz); 7.23 (s, 1H); 7.68 (d, 2H, $J = 8.7$ Hz); 12.58 (br.s, 2H). ^{13}C NMR (DMSO-d_6) 55.57; 108.59; 113.70 (2C); 122.09; 124.50; 126.14; 126.19; 126.76; 128.85; 130.19 (2C); 131.51; 133.85; 158.92; 168.65; 180.65. IR (KBr) 3377, 3225, 1636 cm^{-1}.

5.21. 3-(4-Hydroxy-phenyl)-1H,5H-pyrrolo[2,3-f]indole-4,8-dione (**19a**)

The same procedure was used as for compound **13a** involving compound **18a** (100 mg, 0.34 mmoL), and 1 M solution of BBr_3 in CH_2Cl_2 (20 mL). Purification of the crude product by flash-chromatography (CH_2Cl_2/MeOH 90:10) gave the product as a dark red solid (61 mg, 65%), mp >260 °C. HRMS (ESI+) $[M + H]^+$ calcd 279.0770, found 279.0764. ^{1}H NMR (DMSO-d_6). ^{13}C NMR (DMSO-d_6) 114.51; 115.14 (2C); 115.77; 121.36; 122.79; 123.63; 125.06; 130.36; 130.99 (2C); 131.65; 133.22; 156.29; 170.45; 174.18. IR (KBr) 3410, 3180, 1640 cm^{-1}.

5.22. 3-(4-Hydroxy-phenyl)-1H,7H-pyrrolo[3,2-f]indole-4,8-dione (**19b**)

The same procedure was used as for compound **13a** involving compound **18b** (50 mg, 0.17 mmoL), and 1 M solution of BBr_3 in CH_2Cl_2

(10 mL). Purification of the crude product by flash-chromatography (CH_2Cl_2/MeOH 90:10) gave the product as a dark red solid (30 mg, 63%), mp >260 °C. HRMS (ESI+) $[M+H]^+$ calcd 279.0770, found 279.0729. ^{1}H NMR (DMSO-d_6) 6.59 (d, 2H, $J = 8.4$ Hz); 7.07 (d, 1H, $J = 2.7$ Hz); 7.37 (d, 1H, $J = 2.7$ Hz); 7.38 (d, 2H, $J = 8.4$ Hz), 12.51 (br. s, 1H); 12.54 (br. s, 1H). ^{13}C NMR (DMSO-d_6) 114.98 (2C); 115.07; 117.90; 122.88; 124.47; 124.66; 127.11; 127.38; 130.19 (2C); 131.97; 132.87; 156.93; 168.45; 180.39. IR (KBr) 3433, 3194, 1634 cm^{-1}.

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