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Short communication

Synthesis and in vitro cytotoxic activity of pyrrolo[2,3-e]indole derivatives and a dihydro benzoindole analogue

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Abstract

The synthesis of pyrrolo[2,3-e]indole derivatives with the structural characteristics of DNA bis- and mono-intercalators are described. A dihydro benzoindol analogue was also synthesised to elucidate the major structural requirements for cytotoxic activity. A biological evaluation of the test compounds was carried out in six different tumoral cell lines. The factors that affect the cytotoxic activity appear to be the substituents on the phenyl group, the presence of an amide group capable of strong interactions such as hydrogen bonding and solubility. © 2002 Éditions scientifiques et médicales Elsevier SAS. All rights reserved.

Keywords: Pyrrolo[2,3-e]indole; Synthesis; Cytotoxic activity

1. Introduction

DNA intercalators are molecules that insert between the base pairs of the DNA without denaturalizing it [1]. This insertion causes conformational changes in the double helix such as increase in the phosphate-sugar angles and the distance between base pairs [2,3]. DNA intercalators have common structural characteristics such as planarity and aromaticity. DNA bis-intercalators are the respective homo- or hetero-dimers bridged by a linker [4,5].

Once the DNA-intercalator complex forms, it is primarily stabilized by hydrogen bonds, van der Waals forces, hydrophobic effects and/or molecular orbital interactions [6–12]. The cytotoxic effect of DNA intercalators is a consequence of the inhibition of topoisomerase I or II through the stabilization of the DNA-intercalator–topo complex [13], as has been for suggested for camptothecin [14]. The stabilization of the DNA-intercalator–topo complex occurs as a result of hydrogen bonding between the intercalator and the amino acids of the enzyme. Finally, cell death takes place, probably due to the intervention of protein p53 as a consequence of the preceding events that cause DNA damage [15,16].

With these considerations in mind, we designed molecules with the structural characteristics of DNA intercalating and bis-intercalating compounds using pyrrolo[2,3-e]indole as the aromatic portion. Compounds of this type were chosen so as to investigate angular chromophores, which have received little attention in the literature. In addition, compounds containing this structure have not been explored in this field, although some studies have been made of compounds of the type of pirroloindole [17].

As mentioned above, it is important that a part of the molecule can form hydrogen bonds in order to achieve enzymatic inhibition. In the present work an amide group was chosen to fulfil this need, because of its additional polar nature. It is important to note that in some acridine derivatives with high cytotoxicity, such as AMSA [18], the phenyl ring plays an essential role in the antitumoral activity. Hence, we decided to incorporate *p*-acetanilide moiety into the structure. A schematic of the homo-dimer resulting from the design process is shown in Fig. 1.

The decision to place eight methylenes in the bis derivative was made taking into consideration the neighbor-exclusion principle, which states that the length of the chain should sufficient to accommodate the torsion necessary for bis-intercalation [19,20]. The

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4-bromophenyl group was incorporated into the structure because it has shown cytotoxic activity in analogues synthesised by our group, and the same observation has been made in some other reported work [21]. Taking into account the factors outlined above, structures **1** and **2** were designed.

To test the importance of the 4′-acetamide portion we designed a structure that replaced the acetanilide in **2** by a phenyl (structure **3**), while to test the importance of one of the *p*-Br-phenylpyrrole segments we replaced the 4-Br-phenylpyrrole by a benzene (structure **5**).

In addition, the previously reported compound **4** [22] was incorporated in the cytotoxic evaluation, because it is known that thiophene is a bioisosteric group of benzene, pyrrole and furane [23]. Compound **4** is considered because its activity reflects the necessity of having a pyrrole substituent instead of another aromatic portion in that region.

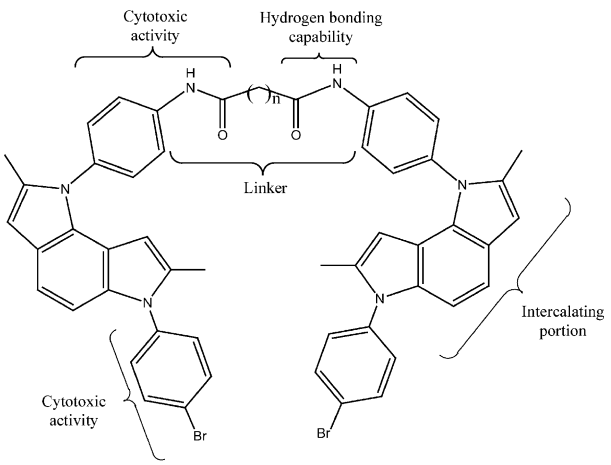

Fig. 1. Schematic representation of the homo-dimer.

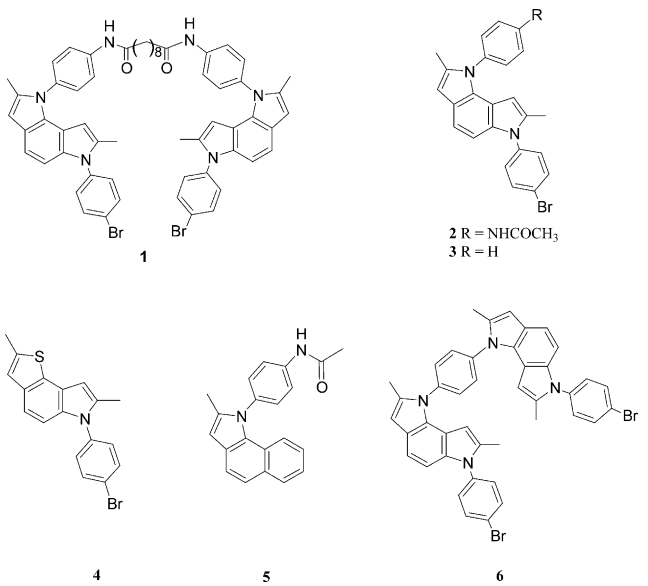

Fig. 2. Structures **1**–**6**.

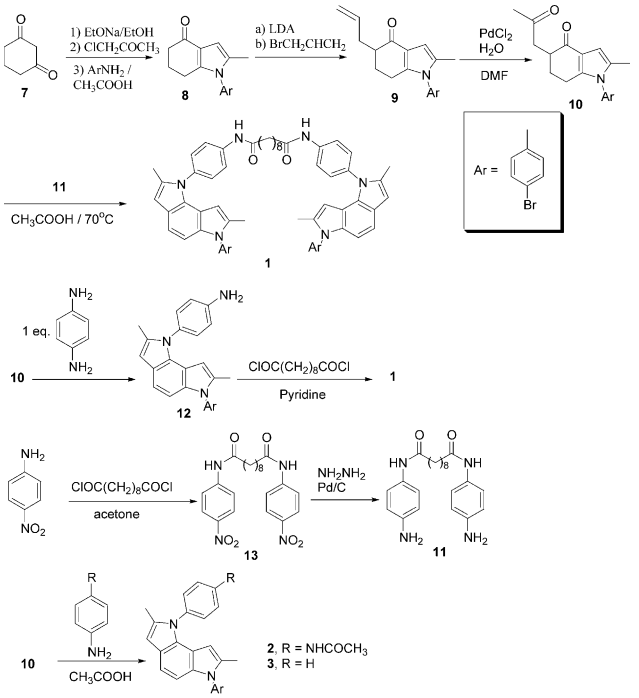

Fig. 3. Synthesis of compounds **1**–**3**.

Structure **6** was designed to test the behaviour of a homo-dimer bridged by only a phenyl group (Fig. 2). While it was expected that bis-intercalation would not occur for this structure, mono intercalation and DNA groove recognition are still possible.

2. Chemistry

Homo-dimer **1** was obtained from 1,3-cyclohexanedione [22] via the steps shown in Fig. 3. In this synthesis pathway, the two pyrrole moieties were constructed in different steps. Although there are two other methodologies described for the synthesis of this skeleton, the method used here is more convenient. One of these methods consists of the cyclization of *m*-phenylenedihydrazones by Fisher's indole synthesis [24], and the other method requires the bis-annulations of arylacetylenes [25]. In both of these reports, pyrroloindoles with the same substitution in both nitrogen atoms are described.

Using our method, the anion of the 1,3-cyclohexanedione (**7**) formed with EtONa in ethanol was reacted with chloroacetone to give the 1,4-dicarbonyl derivatives. This derivative was reacted with 4-bromophenylaniline by a Paal–Knorr reaction to obtain **8** in moderate yield (50%). Reaction of the tetrahydroindolone **8** with LDA, generated in situ, and subsequent addition of an excess of allyl bromide gave **9** with yields corresponding to 80%. Oxidation of **9** with $PdCl_2$ gave **10,** which is the intermediate from which the rest of the

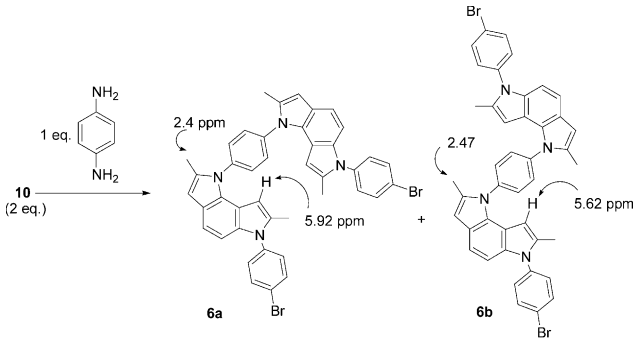

Fig. 4. Synthesis of **6a** and **6b**.

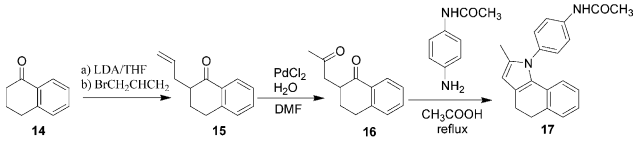

Fig. 5. Synthesis of **17**.

pyrroloindole compounds can be obtained. In another Paal–Knorr reaction, **10** was reacted with decanodioic acid bis-[(4-amino-phenyl)-amide] **11** to give **1**. Diamide **11** was obtained by condensation of 4-nitroaniline with sebacoyl chloride in acetone to give **13**, followed by reduction with NH_2NH_2 and Pd/C in ethanol. The condensation of **10** with 4-aminoacetanilide and aniline yielded compounds **2** and **3**, respectively (Fig. 2).

An alternative synthetic pathway explored for **1** was the reaction of **10** with 1,4-diaminobenzene to give **12**, followed by reaction with sebacoyl chloride in pyridine, as shown in Fig. 3. The primary problem of this synthetic route was the poor yield due to the instability of **12,** which was difficult to separate because of its decomposition in silica and alumina.

To last of the pyrroloindole group of molecules, dimeric compound **6**, was obtained by reaction of 2 equivalents of **10** with 1 equivalents of 1,4-diaminobenzene in acetic acid, as shown in Fig. 4. Two conformers **6a** and **6b** were identified from the duplicity of the ^{1}H-NMR signals detected at 5.92 and 5.62 ppm, corresponding to the '*endo*' pyrrole hydrogen and its respective neighbour methyl groups. Variation of the temperature confirmed the presence of both isomers, which have a diastereoisomeric relationship (Fig. 4).

Benzoindole **5** was tried to be synthesised using the same strategy as that described above for the pyrroloindoles, but with α-tetralone **14** as the starting material. In this synthetic pathway the anion, formed from the reaction of α-tetralone and LDA, reacted with allyl bromide to give the allyl derivative **15** which, under the same conditions used in the oxidation of **9**, results in the 1,4-dicarbonyl derivative **16**. Reaction of **16** with 4-aminoacetanilide, under the conditions described earlier, did not give the expected product **5**, but afforded instead the non-aromatized **17** (Fig. 5). It is interesting that, whereas pyrroloindoles **1**, **2**, **3** and **6** tend to aromatize in the same reaction conditions, **17** did not show any tendency toward aromatisation, even after hours at reflux in acetic acid.

As expected for dihydro benzene derivatives, **17** is not a flat molecule, unlike the other compounds in the series.

Although compound **17** is not absolutely flat, and is not aromatized, it still maintains a structural analogy with the desired adduct. We therefore included it in the panel of compounds to be investigated.

3. Biological results and discussion

The first cytotoxic evaluation was made with **4**. This compound showed inactivity in NCI-H460 (Lung), MCF7 (Breast) or SF-268 (CNS) cell line. Because of its inactivity, no further evaluation was necessary.

Compounds **1**, **2**, **3**, **6** and **17** were evaluated for cytotoxic activity in cultures of PC-3 (prostate), U251 (CNS), K562 (leukemia), Hep-2 (Liver), HeLa (cervix), and HCT-15 (colon) cells. The results are given in Table 1.

The most active compound is **2**, which showed poor activity in all the cell lines probed with the best result in

Table 1
Cytotoxic evaluation of compounds **1**, **2**, **3**, **6** and **17**

Compound	M_W	IG_{50} [μM (± S.D.)]					
		PC3 (prostate)	U251 (CNS)	K562 (leukemia)	Hep-2 (liver)	HCT-15 (colon)	HeLa (cervix)
1	1026.90	>100	N.A.[a]	N.A.	N.A.	N.A.	N.A.
2	472.38	17.7 (2.5)	33.5 (2.4)	17.9 (7.9)	45.1 (4.6)	36.2 (1.6)	36.3 (5.2)
3	415.33	>100	N.A.	N.A.	N.A.	N.A.	N.A.
6	752.54	>100	N.A.	N.A.	N.A.	>100	N.A.
17	316.40	25.3	>100	>100	N.A.	N.A.	>100
Ad[b]	527	5×10^{-5}	1.8×10^{-4}	1.8×10^{-2}	1.5×10^{-2}		5×10^{-5}

[a] N.A., not active.
[b] Ad, adriamycin.

PC-3. All of the compounds listed in Table 1 showed some degree of activity in the PC-3 cell line.

As mentioned above, compound **3** was not expected to show significant activity because it lacks groups capable of interacting strongly with an enzyme. The results are in agreement with this hypothesis.

An unexpected result of the cytotoxicity tests, however, is the remarkable loss of cytotoxicity of dimer **1**. The fact that monomer **2** has a greater activity than its bis analogue could be due to an increase in the molecular weight or moreover to the difference in solubility (dimer **1** was the only compound which showed some problems of insolubility).

Comparison of the results for **2** and **3** makes it clear that the acetamide group is necessary for cytotoxic activity, and moreover comparison of **2** with **4** indicates that the 4-acetanilide portion is also important for activity. In addition, the *N*-(4′-bromophenyl)-pyrryl portion appears to increase activity, as shown by the difference in behaviour between **2** and **17**, which showed only a small amount of activity. In this last instance, however, aromaticity may also play an important role in determining the relative activities. To test this, compound **5** will be synthesised and evaluated.

4. Experimental protocols

4.1. Chemistry

Melting points are uncorrected. The IR spectra were recorded on a Nicolet FT-55X spectrophotometer. The ^{1}H-NMR spectra were determined on a Varian FT-200 and Varian FT-300 instrument in $CDCl_3$ unless other solvent specified. Chemical shift are expressed in δ (ppm) relative to TMS as internal standard and coupling constants (J) in Hz. High resolution mass spectra were recorded using a JEOL SX-102 mass spectrometer using the direct inlet system with an ionization energy of 70 eV, an emission current of 100 μA and ion source temperature of 150 °C.

4.1.1. General procedure for the synthesis of *1–3*, *6* and *17*

4.1.1.1. Decanodioic acid bis-({4-[6-(4-bromo-phenyl)-2,7-dimethyl-6H-1,6-diaza-as-andacen-1-yl]-phenyl}-amide) (1). To a stirred solution of (0.1 g, 0.28 mmol) of **10** in 5 ml of acetic acid at 80 °C, diamine **11** (0.057 g, 0.15 mmol) was added. After 1 h of reflux and magnetic stirring, acetic acid is neutralized with a solution of 5% $NaHCO_3$ in water in a separation funnel with CH_2Cl_2. After reduction of the solvent, previously dried with Na_2SO_4, under reduced pressure, **1** was obtained, by recrystallisation (0.14 g, 50%) or by chromatographic purification in silica gel 1:1 hexane–AcOEt (0.05 g, 17.5%) from the obtained mixture, as a green solid.

M.p. 188–190 °C; IR ν 3436, 3003, 1695, 1517; ^{1}H-NMR δ 1.63 (m, 4 H), 1.77 (m, 2H), 2.12 (s, 3H), 2.24 (s, 3H), 2.43 (t, $J = 7.5$ Hz, 2H), 5.56 (s, 1H), 6.4 (s, 1H), 6.83 (s, $J = 8.4$ Hz, 2H), 7.19 (d, $J = 8.7$ Hz, 2H), 7.25 (d, $J = 8.4$ Hz, 2H), 7.39 (d, $J = 8.7$ Hz, 2H), 7.52 (s, 1H), 7.62 (d, $J = 8.4$ Hz, 2H), 7.74 (d, $J = 8.4$ Hz, 2H); ^{13}C-NMR δ 13.12, 13.21, 28.96, 29.08, 29.69, 37.73, 98.33, 101.78, 104.08, 113.27, 113.95, 120.1, 121.26, 128.3, 129.29, 129.43, 129.75, 130.04, 132.56, 133.66, 133.91, 135.17, 137.62, 137.83, 171.7; HRMS Calc. for $C_{58}H_{54}Br_2N_6O_2$ (FAB^+): 1026.8966. Found: 1026.8962.

4.1.1.2. N-{4-[6-(4-Bromo-phenyl)-2,7-dimethyl-6H-1,6-diaza-as-indacen-1-yl]-phenyl}-acetamide (2). M.p. 130–132 °C (63% yield); IR ν 3437, 2927, 1693, 1516; ^{1}H-NMR δ 2.14 (s, 3H), 2.26 (s, 3H), 2.26 (d, $J = 0.92$ Hz, 3H), 5.54 (s, 1H), 6.41 (q, $J = 0.92$ Hz, 1H), 6.83 (dd, $J = 8.56$, 0.64 Hz, 2H), 7.21 (d, $J = 8.66$ Hz, 2H), 7.26 (d, $J = 8.62$ Hz, 2H), 7.39 (dd, $J = 8.6$, 0.64 Hz, 2H), 7.43 (s, 1H), 7.63 (d, $J = 8.64$ Hz, 2H), 7.72 (d, $J = 8.58$ Hz, 2H); ^{13}C-NMR δ 13.12, 13.21, 24.66, 98.33, 101.78, 104.08, 113.27, 113.95, 120.1, 121.26, 128.3, 129.29, 129.43, 129.75, 130.04, 132.56, 133.66, 133.91, 135.17, 137.62, 137.83, 168; HRMS Calc. for $C_{26}H_{22}BrN_3O$ (FAB^+): 472.3765. Found: 472.3767.

4.1.1.3. 6-(4-Bromo-phenyl)-2,7-dimethyl-1-phenyl-1,6-dihydro-1,6-diaza-as-indacene (3). M.p. 105–107 °C; (70% yield); IR ν 2924, 1595, 1495; ^{1}H-NMR δ 2.13 (s, 3H), 2.28 (s, 3H), 5.48 (s, 1H), 6.43 (s, 1H), 6.84 (dd, $J = 8.52$, 0.81 Hz, 2H), 7.21 (d, $J = 8.5$ Hz, 2H), 7.28 (d, $J = 8.52$ Hz, 2H), 7.46 (dd, $J = 7.95$, 1.78 Hz, 2H), 7.56 (dd, $J = 7.9$, 7.2 Hz, 2H), 7.57 (d, $J = 7.14$ Hz, 1H), 7.63 (d, $J = 8.79$ Hz, 2H); ^{13}C-NMR δ 13.15, 13.24, 98.23, 101.68, 104.03, 112.5, 113.89, 121.22, 128.06, 128.9, 129.18, 129.73, 132.54, 133.61, 133.84, 135.11, 137.59, 139.57; HRMS Calc. for $C_{24}H_{19}N_2Br$ (FAB^+): 414.0732. Found: 414.0734.

4.1.1.4. 1,4-bis-[6-(4-Bromo-phenyl)-2,7-dimethyl-1,6-dihydro-1,6-diaza-as-indacene]-benzene (6). M.p. 97 °C dec.; (45% yield); IR ν 2927, 1515,1493, ^{1}H-NMR δ 2.18 (s, 3H), 2.4 and 2.5 (s, 3H), 5.62 and 5.92 (s br, 1H), 6.5 (s, 1H), 6.89 (d, $J = 8.6$ Hz, 1H), 7.23 (d, $J = 8.52$ Hz, 2H), 7.32 (d, $J = 8.7$ Hz, 1H), 7.65 (d, $J = 8.52$ Hz, 2H), 7.68 (s, 2H); ^{13}C-NMR δ 13.36, 29.69, 98.41, 102.37, 104.3, 113.21, 114, 121.41, 121.44, 129.75, 132.57, 132.64, 133.77, 135.29, 137.5; MS (FAB^+) m/z 752.

4.1.1.5. N-[4-(2-Methyl-4,5-dihydro-benzo[g]indol-1-yl)-phenyl]acetamide (17). M.p. 195–197 °C; (81% yield); IR ν 3437, 2935, 1695, 1516; ^{1}H-NMR δ 2.08 (s, 3H), 2.23 (s, 3H), 2.69 (t, $J = 8$ Hz, 2H), 2.91 (t, $J = 8$ Hz, 2H), 5.94 (s, 1H), 6.29 (dd, $J = 7.46$, 1.56 Hz, 1H),

6.79 (td, $J = 7.42$, 1.56 Hz, 1H), 6.89 (td, $J = 7.42$, 1.5 Hz, 1H), 7.14 (dd, $J = 7$ Hz, 1.56 1H), 7.26 (d, $J = 8.8$ Hz, 2H), 7.35 (s, 1H), 7.63 (d, $J = 8.8$ Hz, 2H); ^{13}C-NMR δ 12.89, 22.46, 24.67, 30.88, 106.4, 120.05, 120.29, 122.48, 123.93, 125.92, 128.06, 128.77, 129.77, 132.06, 135.54, 135.88, 137.49, 168.36; HRMS Calc. for $C_{21}H_{20}ON_2$ (EI^+): 316.1576. Found: 316.1570.

4.1.2. Synthesis of decanodioic acid bis-[(4-amino-phenyl)-amide] (11)

Ethanol (10 ml), Pd/C 5% (0.046 g), hydrazine (0.818 ml, 25.9 mmol), water (0.93 ml) and **13** (2.59 mmol) were mixed in a bottom flask. The mixture was refluxed for 2 h. The resulting solid was dissolved in methanol in heat and filtered at vacuum. Methanol was eliminated up precipitation of a solid that was filtered and crystallized from methanol to afford **11**.

M.p. 199–201 °C, (90% yield); IR ν 3379, 1699; ^{1}H-NMR (dmso-d6) δ 1.25 (s br, 4H), 1.55 (m, 2H), 2.33 (t, $J = 11.13$ Hz, 2H), 4.79 (s br, 2H), 7.77 (d, $J = 13.8$ Hz, 2H), 8.14 (d, $J = 13.86$ Hz, 2H), 10.47 (s, 1H).

4.1.3. Decanodioic acid bis-[(4-nitro-phenyl)-amide (13)

Sebacoyl chloride (0.172 g, 0.72 mmol) was added to a solution of 4-nitroaniline (0.198 g, 1.44 mmol) in 15 ml of acetone at 5 °C. After 2 h stirring, the mixture was filtered and washed with acetone to afford **13**.

M.p. 193–195 °C; (55% yield); IR ν 3398, 3286, 3307, 2929, 1650; ^{1}H-NMR δ (dmso-d6) 1.27 (s br, 4H), 1.54 (m, 2H), 2.19 (t, $J = 11.3$ Hz, 2H), 7.77 (d, $J =$ 13.5Hz, 2H), 8.14 (d, $J = 13.6$ Hz, 2H), 10.47 (s, 1H).

4.1.4. 2-Allyl-3,4-dihydro-2H-naphthalen-1-one (15)

To a solution of diisopropylamine (0.96 mL, 6.8 mM) in 20 mL of THF anhydrous, under nitrogen atmosphere at -78 °C, *n*-butillithium 1.6 M (4.27 mL, 6.84 mM) were added with continues magnetic stirring. After 1 h, α-tetralone (1g, 6.84 mM) was added, and the reaction was maintained at the same temperature with stirring for 2 h more. After this time, allyl bromide (2.35 mL, 27.4 mM) was added and the reaction mixture was raised at room temperature. After 12 h of stirring, reaction flask was putted in a dry ice bath and ammonium chloride was added. Then, excess of THF was evaporated and extractions with water and methylene chloride were performed. The organic phase was dried with anhydrous sodium sulfate and filtered. Solvent reduction gave a viscose material containing **15**. Purification in column chromatography 9:1 hexane–AcOEt, gave **15** as colorless oil, which solidify at low temperature.

M.p. < 25 °C; (80% yield) IR 3072, 2930, 1683; ^{1}H-NMR δ 1.87 (m, 1H), 2.26 (m, 2H), 2.55 (m, 1H), 2.76 (m, 1H), 2.99 (dd, $J = 7.5$, 4.5 Hz, 2H), 5.06 (m, 1H), 5.11 (dq, $J = 15$, 2.1 Hz, 1H) 5.85 (m, 1H), 7.23 (dd, $J = 7.5$, 0.6 Hz, 1H), 7.29 (td, $J = 7.2$, 0.6 Hz, 1H), 7.45 (td, $J = 7.2$, 1.5 Hz, 1H), 8.03 (dd, $J = 7.6$, 1.5 Hz, 1H), ^{13}C-NMR δ 27.96, 28.61, 34.04, 47.19, 116.79, 126.57, 127.45, 128.69, 132.53, 133.17, 136.21, 144.04, 119.40; HRMS Calc. for $C_{13}H_{14}O$ (FAB^+): 186.1045. Found: 186.1052.

4.1.5. 2-(2-Oxo-propyl)-3,4-dihydro-2H-naphthalen-1-one (16)

$PdCl_2$ (0.246 g, 1.38 mM) was added to a magnetically stirred solution of 10 mL of DMF and 1 mL of distilled water. After 5 min, **15** (0.5 g, 1.38 mM) dissolved in 2 mL of DMF was added dropwise. The stirring was maintained for 12 h; the mixture was then percolated in a column packed with cotton using CH_2Cl_2 as solvent. Then DMF was eliminated with consecutive washes with water. Solvent was reduced and purification in column chromatography gave **16** as a green solid.

M.p. 90 °C; (65% yield) IR ν 2933, 1715, 1682; ^{1}H-NMR δ 1.92 (ddd, $J = 25.8$, 12.9, 4.41 Hz, 1H), 2.19 (m, 1H), 2.27 (s, 3H), 2.45 (m, 1H), 2.95 (dt, $J = 16.8$, 2.76 Hz, 1H), 3.11 (m, 1H), 3.15 (m, 1H), 3.18 (dd, $J = 19.5$, 6 Hz, 1H), 7.25 (t, $J = 7.68$ Hz, 1H), 7.29 (t, $J = 7.71$ Hz, 1H), 7.47 (dd, $J = 7.68$, 1.38 Hz, 1H), 8.0 (dd, $J = 7.68$, 1.35 Hz, 1H); ^{13}C-NMR δ 29.35, 29.45, 30.47, 43.82, 44.18, 126.58, 127.36, 128.72, 132.17, 133.35, 144.07, 199, 207.14; MS (EI^+), m/z 202 ([M^+] 19).

4.2. Cytotoxic activity

The IG_{50} for compound **2** was obtained from three different experiments performed in duplicate, whereas for all other compounds it was obtained from one experiment performed in duplicate.

All of the experiments were carried out at four different concentrations (3.1, 10, 31 and 100 μM).

The National Cancer Institute supplied the tumoral cell lines PC-3, U251 and K562. Cytotoxicity assays were carried out at 5000–7500 cells mL^{-1}, as reported by Skehan et al. and Monks et al., who used the sulforhodamine B (SRB) protein assay to estimate cell growth [26,27]. The percentage growth was evaluated spectrophotometrically in a Bio kinetics reader spectrophotometer.

The National Cancer Institute measured cytotoxic activity of **4**, with the same procedure mentioned above.

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