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Short communication

10-Benzoyl-1,8-dihydroxy-9(10*H*)-anthracenones: Synthesis and biological properties

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Abstract – The synthesis and biological properties of 10-benzoyl-1,8-dihydroxy-9(10*H*)-anthracenones are described. The compounds were evaluated for their ability to inhibit the growth of the human keratinocyte cell line HaCaT and the 5-lipoxygenase enzyme in bovine polymorphonuclear leukocytes. In addition, generation of hydroxyl radicals was determined as measured by deoxyribose degradation. The results obtained with the new compounds show that substitution with a 4-hydroxy (**4f**) or a 4-benzyloxy group (**4i**) at the phenyl ring of the C-10 substituent resulted in potent antiproliferative agents. No correlation was found between hydroxyl-radical formation and the 5-LO inhibitory or antiproliferative action of the compounds. © Elsevier, Paris

anthracenone / anthralin / antiproliferative activity / dithranol / HaCaT / 5-lipoxygenase / hydroxyl radical

1. Introduction

Anthracenones are important agents in the treatment of psoriasis, a widespread chronic inflammatory and scaling skin disease. Apart from their therapeutic usefulness, side effects such as inflammation of the skin surrounding treated psoriatic plaques reduce their patient acceptability [1]. Several lines of evidence derived from chemical and biological studies have revealed that the mechanism of anthracenone-induced skin inflammation is associated with the formation of reactive oxygen species or anthracenone radicals [2, 3].

We anticipated that substitution with an electron-withdrawing acyl group at the 10-position of dithranol (anthralin, 1,8-dihydroxy-9(10*H*)-anthracenone, **1**), the parent compound, might provide agents with diminished oxygen-radical formation [4]. Indeed, this structural pattern impairs the reduction power of anthracenones [5]. On the other hand, the mere presence of an acyl substituent at C-10 of anthralin does not necessarily lead to enhanced activity, and we demonstrated that a terminal phenyl ring is required [4]. However, a major obstacle encountered in this study was the lack of a convenient and effective method for the preparation of 10-benzoyl derivatives of **1**, the lowest homologs in this series.

Berset et al. reported on the synthesis of a C-10-benzoyl derivative of **1** [6], but we were able to document that their structural assignment was wrong [7]. Rather, the *O*-benzoylated product is formed under their reaction conditions. Nevertheless, we have developed a viable route to 10-benzoyl derivatives of **1** [7].

In a recent paper from our laboratories we reported on 10-aminomethylene-9(10*H*)-anthracenones [8]. Herein, we describe the biological properties of closely related congeners, namely 10-benzoyl-9(10*H*)-anthracenones.

2. Chemistry

We have shown that anthralin diacetate **2**, when treated with benzoyl chloride and sodium hydride in THF, affords an enol ester which can be hydrolyzed to the desired 10-benzoylanthralin [7]. According to this method, introduction of the 10-benzoyl functionality onto the anthracenone nucleus was achieved by reaction of **2** with the appropriate benzoyl chlorides, which were prepared from the corresponding acids

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Abbreviations: LTB_4, leukotriene B_4; 5-LO, 5-lipoxygenase; MDA, malondialdehyde; PMNL, polymorphonuclear leukocytes

according to literature procedures. The primary enol esters **3a–i** thus obtained were then debenzoylated with concomitant hydrolysis of the 1,8-diacetoxy groups using 9% aqueous sodium hydroxide in ethanol to give 10-benzoyl-1,8-dihydroxy-9(10*H*)-anthracenones **4a–i** (*figure 1*). In some instances (**5b,c,e–g,i**), also 1,10-dibenzoylated anthralin derivatives could be isolated. Their formation is rationalized as a process involving nucleophilic attack of the pertinent anthralin phenolates at the benzoic acid methylene esters both generated under the reaction conditions.

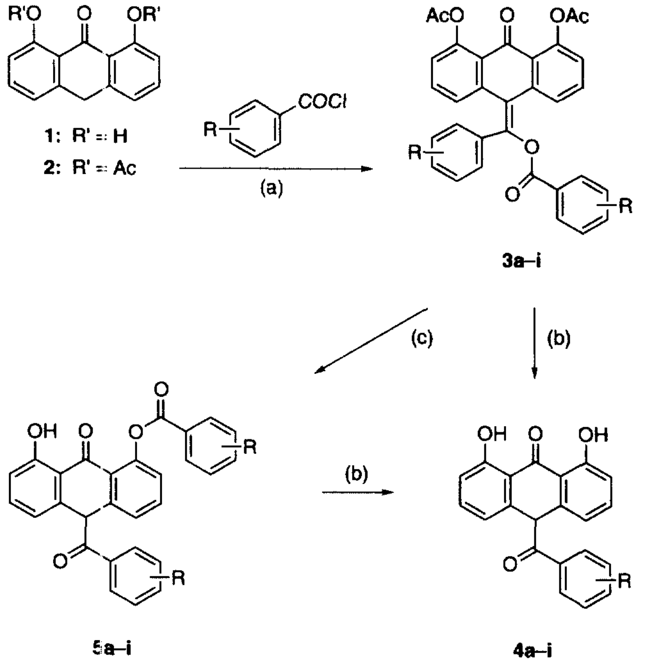


Figure 1. R is defined in *table I*. Reagents: (a) NaH, THF, room temperature, N_2; (b) 9% NaOH, MeOH, room temperature, N_2; (c) 2% NaOH, MeOH, room temperature, N_2.

3. Biological results and discussion

The study of the biological properties of the new anthralin derivatives was performed in vitro using isolated bovine polymorphonuclear leukocytes (PMNL) [4]. Inhibition of the generation of 5-LO products, particularly LTB_4, may be useful to resolve the inflammatory aspects of psoriasis [9, 10]. As shown in *table I*, we found that many compounds of the new series are more potent inhibitors of the 5-LO enzyme than **1**, which is only a moderate inhibitor with an IC_{50} value of 37 μM.

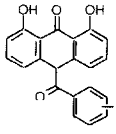
Furthermore, the compounds were evaluated for their ability to inhibit HaCaT cell growth in culture [11], as a model of epidermal hyperproliferation in psoriasis. This rapidly multiplying human keratinocyte line was described as an extremely sensitive target for the antiproliferative action of anthralin [12]. Proliferation of the keratinocytes was determined directly by counting the dispersed cells under a phase-contrast microscope after 48 h of treatment. The IC_{50} value obtained for **1** itself was 0.6 μM demonstrating that its antipsoriatic efficacy is predominantly mediated by this property rather than its 5-LO inhibitory effect. The results obtained with the new compounds show that substitution with a 4-hydroxy (**4f**) or a 4-benzyloxy group (**4i**) at the phenyl ring of the C-10 substituent resulted in potent antiproliferative agents, whereas the esterified analogs **5f** and **5i**, respectively, were less effective. This suggest that the two hydrogen-bonding hydroxyl groups in position 1 and 8 of **1** are both necessary to preserve the potent antiproliferative action of **1**. Also, none of the other analogs retained the full potency of the parent **1**, with the unsubstituted **4a** and the catechol derivative **5g** of the *O*-benzoylated series being inactive within the test range.

Prooxidant properties of the compounds were defined by the deoxyribose assay, which is a sensitive test for the production of hydroxyl radicals [13]. The release of malondialdehyde (MDA) is indicative of oxygen-radical formation. In general, prooxidant properties were substantially reduced by esterification of one of the hydroxyl groups (**5**) as compared to compounds with free hydroxyl groups (**4**) in positions 1 and 8 of the anthracenone nucleus. Also, as already observed in other C-10 substituted series [4], compounds with catechol or pyrogallol structure (**4g,h**) once more increased the release of MDA, indicating enhanced formation of hydroxyl radicals. Finally, there was no straightforward correlation found between hydroxyl-radical formation and the 5-LO inhibitory or antiproliferative action of the compounds.

4. Experimental protocols

Melting points were determined with a Büchi 510 melting point apparatus and are uncorrected. Chromatography refers to column chromatography on silica gel (E. Merck, 70–230 mesh). ^1H NMR spectra were recorded with a Bruker Spectrospin WM 250 spectrometer (250 MHz), using tetramethylsilane as an internal standard. Fourier-transform IR spectra (KBr) were recorded on a Nicolet 510M FTIR spectrometer. Mass spectra (EI, unless otherwise stated) were obtained on a Varian MAT 112S spectrometer (EI-MS, 70 eV). Elemental analyses indicated by the symbols of the elements were within ± 0.4% of theoretical values. HPLC (Kontron 420,

Table I. Deoxyribose degradation, 5-LO inhibition in bovine PMNL, and antiproliferative activity against HaCaT cells by 10-benzoyl-1,8-dihydroxy-9(10*H*)-anthracenones.



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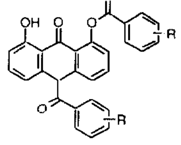

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Compound	R	log *P*	DD (•OH)^a	5-LO IC$_{50}$ (μM)^b	AA IC$_{50}$ (μM)^c
4a	H	3.81	2.31 ± 0.32	4	> 5
4b	4-OCH$_3$	3.74	2.33 ± 0.01	4	2.2
4c	3,4-(OCH$_3$)$_2$	3.45	1.79 ± 0.40	5	2.3
4d	3,4-(OCH$_2$O)	3.68	2.17 ± 0.16	6	1.5
4e	4-OC$_3$H$_7$	3.44	2.53 ± 0.42	4	2.0
4f	4-OH	3.11	2.78 ± 0.72	2	0.8
4g	3,4-(OH)$_2$	2.79	4.87 ± 0.03	3	2.7
4h	3,4,5-(OH)$_3$	2.44	5.68 ± 0.11	2	1.6
4i	4-OCH$_2$Ph	4.22	2.01 ± 0.03	10	0.7
5b	4-OCH$_3$	ND	1.23 ± 0.11	5	1.8
5c	3,4-(OCH$_3$)$_2$	ND	0.91 ± 0.16	12	2.6
5e	4-OC$_3$H$_7$	ND	1.45 ± 0.13	21	3.9
5f	4-OH	ND	0.61 ± 0.09	8	1.9
5g	3,4-(OH)$_2$	ND	1.13 ± 0.01	3	> 5
5i	4-OCH$_2$Ph	ND	0.36 ± 0.10	> 30	4.1
1	Anthralin	4.23	2.89 ± 0.14	37	0.6

^{a}Deoxyribose degradation as a measure of hydroxyl-radical formation. Indicated values are μmol of malondialdehyde/mmol of deoxyribose released by 75 μM test compound (controls < 0.1; values are significantly different with respect to the control; $P < 0.01$). ^{b}Inhibition of 5-HETE and LTB$_4$ biosynthesis in bovine PMNL. Inhibition was significantly different with respect to that of the control; $N = 3$ or more, $P < 0.01$. Nordihydroguaiaretic acid (NDGA) was used as the standard inhibitor for 5-LO (IC$_{50}$ = 0.4 μM). ^{c}Antiproliferative activity against HaCaT cells. Inhibition of cell growth was significantly different with respect to that of the control, $N = 3$, $P < 0.01$.

735 LC UV detector) was performed on a 250 x 4 mm column (4 x 4 mm precolumn) packed with LiChrospher 100 RP18 (5 μm particles; Merck, Darmstadt, Germany). Data were recorded on a MacLab data acquisition system (WissTech, Germany) and analysis was performed with the software Peaks on an Apple Macintosh computer.

4.1. General procedure for the preparation of 1,8-diacetoxy-10-[(benzoyloxy)-phenylmethylene]-9(10H)-anthracenones 3a–i

To a suspension of NaH (3.00 g) in absolute THF (75 mL) was added **2** [14] (3.10 g, 10 mmol) under N$_2$, and the mixture was stirred at room temperature for 15 min. The appropriate benzoyl chloride (30 mmol) in absolute THF (30 mL) was added dropwise, and the mixture was stirred for 1 h. After the reaction was complete, the mixture was poured into water (200 mL) and 37% HCl (20 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phase was washed with water (3 x 100 mL), dried over Na_2SO_4, and then the solvent was evaporated.

4.1.1. 1,8-Diacetoxy-10-[(benzoyloxy)-phenylmethylene]-9-(10H)-anthracenone ***3a***

For this compound, see [7].

4.1.2. 1,8-Diacetoxy-10-[(4-methoxybenzoyloxy)-4-methoxyphenylmethylene]-9(10H)-anthracenone ***3b***

The title compound was obtained from **2** and 4-methoxybenzoyl chloride and was purified by column chromatography using CH_2Cl_2/ether (30:1) to give a pale yellow, crystalline powder: 39% yield; m.p. 267–270 °C; FTIR 1771, 1737, 1661 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.25–6.67 (m, 14H), 3.98 (s, 3H), 3.90 (s, 3H), 1.78 (s, 6H); MS *m/z* = 578 (0.9, M^+), 135 (100). Anal. $C_{34}H_{26}O_9$ (C, H).

4.1.3. 1,8-Diacetoxy-10-[(3,4-dimethoxybenzoyloxy)-3,4-dimethoxyphenylmethylene]-9(10H)-anthracenone ***3c***

The title compound was obtained from **2** and 3,4-dimethoxybenzoyl chloride [15] and was recrystallized from toluene/hexane (3:1) to give a yellow, crystalline powder; 31% yield; m.p. 216–218 °C; FTIR 1769, 1731, 1656 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.80–6.69 (m, 12H), 3.98 (s, 6H), 3.90 (s, 6H), 1.78 (s, 6H); FD-MS *m/z* = 638 (M^+). Anal. $C_{36}H_{30}O_{11}$ (C, H).

4.1.4. 1,8-Diacetoxy-10-[(3,4-methylenedioxybenzoyloxy)-3,4-methylenedioxyphenylmethylene]-9(10H)-anthracenone ***3d***

The title compound was obtained from **2** and 3,4-methylenedioxybenzoyl chloride [16] and was purified by column chromatography using CH_2Cl_2/petroleum ether/ether (25:1:1) to give a pale yellow, crystalline powder; 45% yield; m.p. 205–208 °C; FTIR 1769, 1739, 1661 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.08–6.71 (m, 12H), 6.17 (s, 2H), 6.08 (s, 2H), 1.85 (s, 6H); MS *m/z* = 606 (4, M^+), 149 (100). Anal. $C_{34}H_{22}O_{11}$ (C, H).

4.1.5. 1,8-Diacetoxy-10-[(4-propoxybenzoyloxy)-4-propoxyphenylmethylene]-9(10H)-anthracenone ***3e***

The title compound was obtained from **2** and 4-propoxybenzoyl chloride [17] and was purified by column chromatography using toluene/ethyl acetate (30:1) to give a shiny yellow, crystalline powder; 34% yield; m.p. 208–210 °C; FTIR 1773, 1740, 1656 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.38–6.88 (m, 14H), 4.09–3.95 (m, 4H), 2.04–1.81 (m, 4H), 1.78 (s, 6H), 1.14–1.01 (m, 6H); MS *m/z* = 635 (0.3, M^+), 163 (100). Anal. $C_{38}H_{34}O_9$ (C, H).

4.1.6. 1,8-Diacetoxy-10-[(4-acetoxybenzoyloxy)-4-acetoxyphenylmethylene]-9(10H)-anthracenone ***3f***

The title compound was obtained from **2** and 4-acetoxybenzoyl chloride [18] and was purified by column chromatography using ethyl acetate/petroleum ether (3:2) to give a shiny yellow, crystalline powder; 31% yield; m.p. 231–233 °C; FTIR 1768, 1656 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.66–7.13 (m, 14H), 2.43 (s, 3H), 2.29 (s, 3H), 1.83 (s, 3H), 1.82 (s, 3H); FD-MS *m/z* = 634 (1.1, M^+), 121 (100). Anal. $C_{36}H_{26}O_{11}$ (C, H).

4.1.7. 1,8-Diacetoxy-10-[(3,4-diacetoxybenzoyloxy)-3,4-diacetoxyphenylmethylene]-9(10H)-anthracenone ***3g***

The title compound was obtained from **2** and 3,4-diacetoxybenzoyl chloride [19] and was purified by column chromatography using ethyl acetate/petroleum ether (3:2) to give a shiny yellow, crystalline powder; 37% yield; m.p. 216–219 °C; FTIR 1773, 1673 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.34–7.09 (m, 12H), 2.43–2.29 (m, 12H), 1.83 (s, 3H), 1.82 (s, 3H); FD-MS *m/z* = 750 (M^+). Anal. $C_{40}H_{30}O_{15}$ (C, H).

4.1.8. 1,8-Diacetoxy-10-[(3,4,5-triacetoxybenzoyloxy)-3,4,5-triacetoxyphenylmethylene]-9(10H)-anthracenone ***3h***

The title compound was obtained from **2** and 3,4,5-triacetoxybenzoyl chloride [20] and was purified by column chromatography using ethyl acetate/petroleum ether (3:2) to give a shiny yellow, crystalline powder; 34% yield; m.p. 218–221 °C; FTIR 1775, 1673 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.16–7.10 (m, 10H), 2.43–2.26 (m, 18H), 1.88 (s, 3H), 1.86 (s, 3H); FD-MS *m/z* = 866 (M^+). Anal. $C_{44}H_{34}O_{19}$ (C, H).

4.1.9. 1,8-Diacetoxy-10-[(4-benzyloxybenzoyloxy)-4-benzyloxyphenylmethylene]-9(10H)-anthracenone ***3i***

The title compound was obtained from **2** and 4-benzyloxybenzoyl chloride [21] and was purified by column chromatography using ethyl acetate/petroleum ether (3:2) to give a pale yellow, crystalline powder; 27% yield; m.p. 224–226 °C; FTIR 1771, 1729, 1656 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.39–6.97 (m, 24H), 5.23 (s, 2H), 5.11 (s, 2H), 1.75 (s, 6H); MS *m/z* = 730 (0.1, M^+), 91 (100). Anal. $C_{40}H_{34}O_9$ (C, H).

4.2. General procedure for the preparation of 10-benzoyl-1,8-dihydroxy-9(10H)-anthracenones ***4a–i***

To a solution of the appropriate enol ester **3a–i** (2 mmol) in dry methanol (100 mL) under N_2 was added dropwise a solution of 9% aqueous NaOH (25 mL). The mixture was stirred at room temperature until the reaction was complete (TLC control). Then it was poured into water (200 mL) and 37% HCl (30 mL). In case of the phenolic compounds **4f–h**, the residue was suction-filtered, otherwise extracted with CH_2Cl_2/ethyl acetate (3 x 100 mL). The combined organic phase was washed with water (3 x 100 mL), dried over Na_2SO_4, and evaporated.

4.2.1. 10-Benzoyl-1,8-dihydroxy-9(10H)-anthracenone ***4a***

For this compound, see [7].

4.2.2. 1,8-Dihydroxy-10-(4-methoxybenzoyl)-9(10H)-anthracenone ***4b***

The title compound was obtained from **3b** and was purified by column chromatography using methylene chloride/ethyl acetate (95:5) to give a yellow, crystalline powder; 29% yield; m.p. 218–220 °C; FTIR 1669, 1632, 1611 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.32 (s, 2H), 7.88–6.78 (m, 10H), 6.01 (s, 1H), 3.85 (s, 3H); MS *m/z* = 360 (2.9, M^+), 135 (100). Anal. $C_{22}H_{16}O_5$ (C, H).

4.2.3. 1,8-Dihydroxy-10-(3,4-dimethoxybenzoyl)-9(10H)-anthracenone ***4c***

The title compound was obtained from **3c** and was purified by column chromatography using methylene chloride/ethyl acetate (95:5). Recrystallization from benzene/hexane (2:1) gave a yellow, crystalline powder; 33% yield; m.p. 231–232 °C; FTIR 1669, 1634, 1611 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.32 (s, 2H), 7.71–6.81 (m, 9H), 6.02 (s, 1H), 3.94 (s, 3H), 3.90 (s, 3H); MS *m/z* = 390 (1.3, M^+), 165 (100). Anal. $C_{23}H_{18}O_6$ (C. H).

4.2.4. 1,8-Dihydroxy-10-(3,4-methylenedioxybenzoyl)-9(10H)-anthracenone ***4d***

The title compound was obtained from **3d** and was purified by column chromatography using methylene chloride/ethyl acetate (95:5) to give pale yellow crystals; 68% yield; m.p. 178–180 °C; FTIR 1669, 1632, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.31 (s, 2H), 7.51–6.77 (m, 9H), 6.04 (s, 2H), 5.99 (s, 1H); MS *m/z* = 374 (1.3, M$^+$), 149 (100). Anal. $C_{22}H_{14}O_6$ (C, H).

4.2.5. 1,8-Dihydroxy-10-(4-propoxybenzoyl)-9(10H)-anthracenone **4e**

The title compound was obtained from **3e** and was purified by column chromatography using methylene chloride/ethyl acetate (95:5) to give pale yellow crystals; 78% yield; m.p. 203–206 °C; FTIR 1669, 1629, 1611 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.32 (s, 2H), 7.88–6.79 (m, 10H), 6.02 (s, 1H), 3.98–3.88 (m, 2H), 1.88–1.74 (m, 2H), 1.06–1.00 (m, 3H); FD-MS *m/z* = 388 (M$^+$). Anal. $C_{24}H_{20}O_5$ (C, H).

4.2.6. 1,8-Dihydroxy-10-(4-hydroxybenzoyl)-9(10H)-anthracenone **4f**

The title compound was obtained from **3f** and was purified by column chromatography using methylene chloride/ethyl acetate (7:3) to give yellow crystals; 39% yield; m.p. 231–232 °C; FTIR 1666, 1636, 1613 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.93 (s, 2H), 10.71 (s, br, 1H), 8.17–6.88 (m, 10H), 6.72 (s, 1H); MS *m/z* = 346 (3.3, M$^+$), 121 (100). Anal. $C_{21}H_{14}O_5$ (C, H).

4.2.7. 1,8-Dihydroxy-10-(3,4-dihydroxybenzoyl)-9(10H)-anthracenone **4g**

The title compound was obtained from **3g** and was purified by column chromatography using methylene chloride/ethyl acetate (7:3) to give orange-yellow crystals; 66% yield; m.p. 227–239 °C; FTIR 1665, 1631, 1611 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.94 (s, 2H), 10.25 (s, br, 1H), 9.49 (s, br, 1H), 7.92–6.87 (m, 9H), 6.63 (s, 1H); FD-MS *m/z* = 362 (M$^+$). Anal. $C_{21}H_{14}O_6$ (C, H).

4.2.8. 1,8-Dihydroxy-10-(3,4,5-trihydroxybenzoyl)-9(10H)-anthracenone **4h**

The title compound was obtained from **3h** and was purified by column chromatography using ethyl acetate/petroleum ether (4:2) to give an orange-yellow, crystalline powder; 33% yield; m.p. 215–217 °C; FTIR 1667, 1634, 1617 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.08 (s, 2H), 9.48 (s, br, 2H), 9.16 (s, br, 1H), 7.59–6.86 (m, 8H), 6.26 (s, 1H); MS *m/z* = 378 (2.0, M$^+$), 226 (100). Anal. $C_{21}H_{14}O_7$ (C, H).

4.2.9. 10-(4-Benzyloxybenzoyl)-1,8-dihydroxy-9(10H)-anthracenone **4i**

The title compound was obtained from **3i** and was purified by column chromatography using methylene chloride/ethyl acetate (95:5) to give shiny yellow crystals; 22% yield; m.p. 199–201 °C; FTIR 1685, 1631, 1611 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.32 (s, 2H), 7.88–6.78 (m, 15H), 6.01 (s, 1H), 5.10 (s, 2H); FD-MS *m/z* = 436 (M$^+$). Anal. $C_{28}H_{20}O_5$ (C, H).

4.3. General procedure for the preparation of 10-benzoyl-1-benzoyloxy-8-hydroxy-9(10H)-anthracenones **5b,c,e–g,i**

The title compounds were prepared according to the method described for **4a–i**, but the enol esters **3a,b,c,e–g,i** were hydrolyzed with 2% aqueous NaOH.

4.3.1. 1-Hydroxy-10-(4-methoxybenzoyl)-8-(4-methoxybenzoyloxy)-9(10H)-anthracenone **5b**

The title compound was obtained from **3b** as described for **4b** to give a yellow, crystalline powder; 58% yield; m.p. 219–221 °C; FTIR 1735, 1632, 1604 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.67 (s, 1H), 8.29–6.78 (m, 14H), 6.06 (s, 1H), 3.94 (s, 3H), 3.84 (s, 3H); MS *m/z* = 494 (0.2, M$^+$), 135 (100). Anal. $C_{30}H_{22}O_7$ (C, H).

4.3.2. 1-Hydroxy-10-(3,4-dimethoxybenzoyl)-8-(3,4-dimethoxybenzoyloxy)-9(10H)-anthracenone **5c**

The title compound was obtained from **3c** as described for **4b** to give a yellow, crystalline powder; 30% yield; m.p. 209 °C (dec.); FTIR 1721, 1632, 1599 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.32 (s, 1H), 7.71–6.81 (m, 12H), 6.02 (s, 1H), 3.94–3.90 (m, 12H); FD-MS *m/z* = 554 (M$^+$). Anal. $C_{32}H_{26}O_9$ (C, H).

4.3.3. 1-Hydroxy-10-(4-propoxybenzoyl)-8-(4-propoxybenzoyloxy)-9(10H)-anthracenone **5e**

The title compound was obtained from **3e** as described for **4b** to give yellow crystals; 79% yield; m.p. 194 °C (dec.); FTIR 1733, 1634, 1603 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.66 (s, 1H), 8.27–6.78 (m, 14H), 6.02 (s, 1H), 4.06 (m, 2H), 3.95 (m, 2H), 1.83 (m, 2H), 1.81 (m, 2H), 1.09 (m, 3H), 1.03 (m, 3H); FD-MS *m/z* = 550 (M$^+$). Anal. $C_{34}H_{30}O_7$ (C, H).

4.3.4. 1-Hydroxy-10-(4-hydroxybenzoyl)-8-(4-hydroxybenzoyloxy)-9(10H)-anthracenone **5f**

The title compound was obtained from **3f** as described for **4b** to give a yellow, crystalline powder; 28% yield; m.p. 266–268 °C; FTIR 1706, 1632, 1603 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.11 (s, 1H), 10.78 (s, br, 1H), 10.62 (s, br, 1H), 8.25–6.71 (m, 14H), 6.41 (s, 1H); FD-MS *m/z* = 466 (M$^+$). Anal. $C_{28}H_{18}O_7$ (C, H).

4.3.5. 1-Hydroxy-10-(3,4-dihydroxybenzoyl)-8-(3,4-dihydroxybenzoyloxy)-9(10H)-anthracenone **5g**

The title compound was obtained from **3g** as described for **4b** to give a yellow, crystalline powder; 57% yield; m.p. 223 °C (dec.); FTIR 1706, 1632, 1603 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.11 (s, 1H), 10.78 (s, br, 1H), 10.56 (s, br, 1H), 10.45 (s, br, 1H), 10.41 (s, br, 1H), 8.25–6.71 (m, 12H), 6.41 (s, 1H); FD-MS *m/z* = 498 (M$^+$). Anal. $C_{28}H_{18}O_9$ (C, H).

4.3.6. 10-(4-Benzyloxybenzoyl)-1-(4-benzyloxybenzoyloxy)-8-hydroxy-9(10H)-anthracenone **5i**

The title compound was obtained from **3i** as described for **4b** to give a yellow, crystalline powder; 20% yield; m.p. 213–214 °C; FTIR 1737, 1637, 1611 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.66 (s, 1H), 8.29–6.78 (m, 24H), 6.06 (s, 1H), 5.20 (s, 2H), 5.09 (s, 2H); FD-MS *m/z* = 646 (M$^+$). Anal. $C_{42}H_{30}O_7$ (C, H).

4.4. Biological assay method

The procedures for the biological assays presented in *table I* were described previously in full detail: deoxyribose degradation [22], 5-LO assay [4], and inhibition of HaCaT cell proliferation [11].

4.5. log P determination

A standard reversed-phase HPLC procedure was used. MeOH/water/HOAc (77:23:0.1), adjusted to pH 5.5 with concentrated NH_3, was used as eluant. Calibration was performed as described [4]. log *P* values as a measure of lipophilicity are given in *table I*.

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