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Short communication

Synthesis and activity on free radical processes and inflammation of 9,10-dihydro-5,8-dimethoxy-triptycene-quinones

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Abstract

Three triptycene quinones bearing methoxy groups were prepared following a Diels–Alder methodology and were evaluated for antioxidant and anti-inflammatory activity bearing in mind their structural features that could justify intervention with free radical processes. Improved synthetic pathways were achieved for target molecules 9,10-dihydro-5,8-dimethoxy-9,10-[*o*]benzenoanthracene-1,4-dione (**4**), 9,10-dihydro-2-hydroxy-5,8-dimethoxy-9,10-[*o*]benzenoanthracene-1,4-dione (**6**), and 9,10-dihydro-2,5,8-trimethoxy-9,10-[*o*]benzenoanthracene-1,4-dione (**9**). Under our experimental conditions these compounds showed very significant antioxidant activity offering protection against lipid peroxidation of rat hepatic microsomal fraction while inhibiting the reaction completely at very low concentrations (12.5–80 μM). Moreover, compound **6** that was examined, inhibited by 44% (at 120 μM) lipoxygenase acitvity while the anti-inflammatory activity of the compounds, as assessed by the reduction of the mouse paw edema induced by Freund's complete adjuvant, was significant and comparable to that of indomethacin.

Keywords: Antioxidant; Anti-inflammatory; Triptycene; Quinone

1. Introduction

Triptycene quinones combining the rigid structure of triptycene with the redox properties of the quinone ring, find many applications in organic chemistry [1]. Some triptycene quinone derivatives bearing methoxy groups exhibit potent anticancer and antimalarial activities [2,3]. Since their structure may justify a possible intervention in free radical processes, we attempted to explore better the chemistry and other biological activities of such derivatives. Three target molecules, namely 9,10-dihydro-5,8-dimethoxy-9,10-[*o*]benzenoanthracene-1,4-dione (**4**), 9,10-dihydro-2-hydroxy-5,8-dimethoxy-9,10-[*o*]benzenoanthracene-1,4-dione (**6**), and 9,10-dihydro-2,5,8-trimethoxy-9,10-[*o*]benzenoanthracene-1,4-dione (**9**) (Fig. 1) were synthesized in order to investigate structure–activity relationships. Our goal was to improve the synthetic procedures and yields, and explore their antioxidant and anti-inflammatory properties knowing the relationship between these two activities in many compounds.

2. Chemistry

The starting material, 1,4-dimethoxyanthracene (**1**) was prepared from commercially available quinizarin [4]. 9,10-Dihydro-5,8-dimethoxy-9,10-[*o*]benzenoanthracene-1,4-dione (**4**) was prepared by modification of a method from literature [5]. Diels–Alder reaction of 1,4-dimethoxyanthracene with *p*-benzoquinone afforded the dihydro Diels–Alder adduct **2** (68% yield). The latter was almost quantitatively acid-isomerized to the corresponding hydroquinone **3**, which was effectively oxidized to quinone **4**, under mild conditions with (diacetoxyiodo)benzene, $PhI(OAc)_2$ (Fig. 2).

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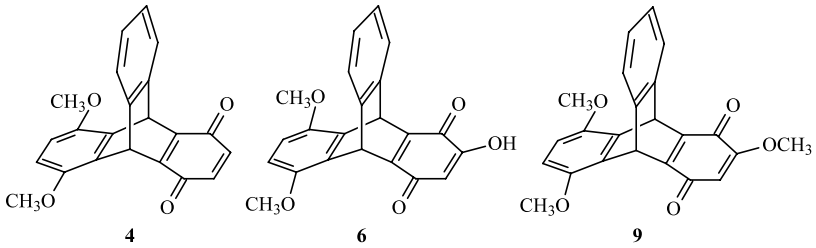

Fig. 1. Structures of the quinones tested for antioxidant and anti-inflammatory properties (compounds **4**, **6**, **9**).

Quinone **4** was one of the three target quinones tested for their antioxidant and anti-inflammatory properties, but also served as a starting material for the preparation of 9,10-dihydro-2-hydroxy-5,8-dimethoxy-9,10-[*o*]benzenoanthracene-1,4-dione (**6**), considering our interest in hydroxyquinones in general [1,6] and triptycene hydroxyquinones more specifically [1]. Quinone **4** was converted to 9,10-dihydro-1,2,4-tris-acetoxy-5,8-dimethoxy-9,10-[*o*]benzenoanthracene (**5**) through a typical Thiele–Winter acetoxylation reaction and the latter was hydrolyzed and oxidized in one step under alkaline conditions to the desired hydroxyquinone **6** in very good overall yield.

9,10-Dihydro-2,5,8-trimethoxy-9,10-[*o*]benzenoanthracene-1,4-dione (**9**) was prepared in very good yield directly from the reaction of 1,4-dimethoxyanthracene (**1**) and 2-methoxy-*p*-benzoquinone (**8**), combining three steps (Diels–Alder reaction, isomerization and oxidation of the intermediate hydroquinone) in one. This methodology is shorter and more effective compared to alternative procedures published lately [3]. Quinone **8** was prepared by oxidation of the corresponding hydroquinone **7** under mild conditions, using $PhI(OAc)_2$ as the oxidant of choice (Fig. 2).

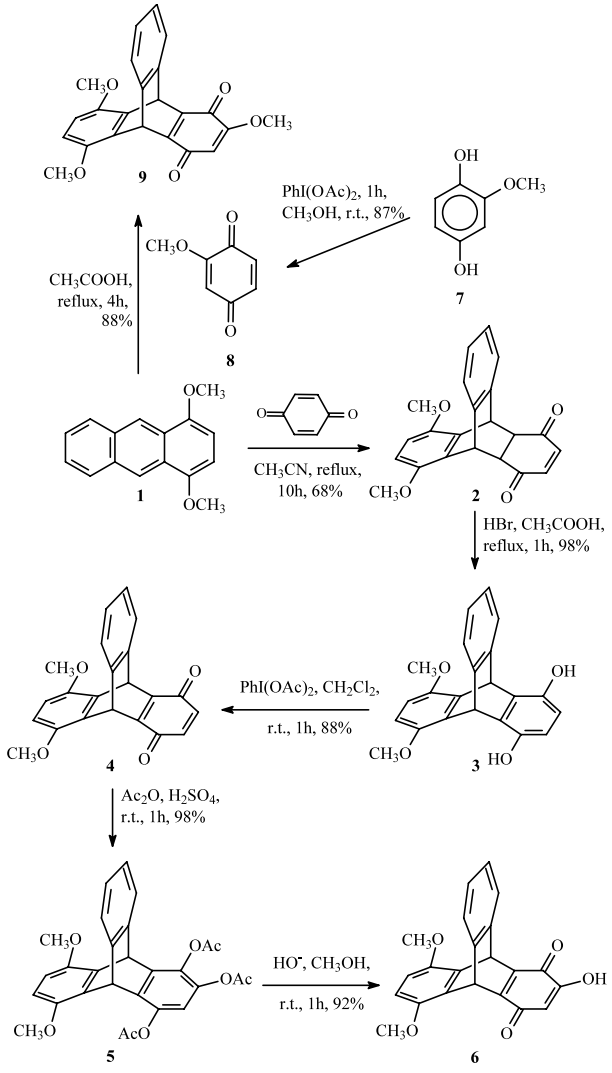

Fig. 2. Synthetic scheme for the preparation of 9,10-dihydro-5,8-dimethoxy-9,10-[*o*]benzenoanthracene-1,4-dione (compound **4**), 9,10-dihydro-5,8-dimethoxy-2-hydroxy-9,10-[*o*]benzenoanthracene-1,4-dione (compound **6**) and 9,10-dihydro-2,5,8-trimethoxy-9,10-[*o*]benzenoanthracene-1,4-dione (compound **9**).

3. Pharmacology

Target compounds (**4**, **6** and **9**) were evaluated for their antioxidant and anti-inflammatory activity using standard and known protocols [7–10]. All examined compounds offered very significant protection against in vitro lipid peroxidation, while for in vivo anti-inflammatory activity the effect of the examined compounds was evaluated on the mouse paw edema assay using FCA (Freund's complete adjuvant) as a flogistic agent. We further investigated the effect of one of the compounds **6** on lipoxygenase activity.

4. Results

All examined compounds (**4**, **6** and **9**) (Fig. 1) offered very significant protection against lipid peroxidation of rat hepatic microsomal fraction: they inhibited the reaction completely (100%) at a concentration ranging from 12.5 to 80 μM. The time course of lipid peroxidation as affected by various concentrations of the test compounds is shown in Fig. 3. From these results IC_{50} values, after 45 min of incubation, were 9, 54 and 11 μM for **4**, **6** and **9**, respectively. D-α-Tocopherol acetate, used as a reference compound, was found to inhibit lipid peroxidation by 100 and 10% at 1 and 0.5 mM,

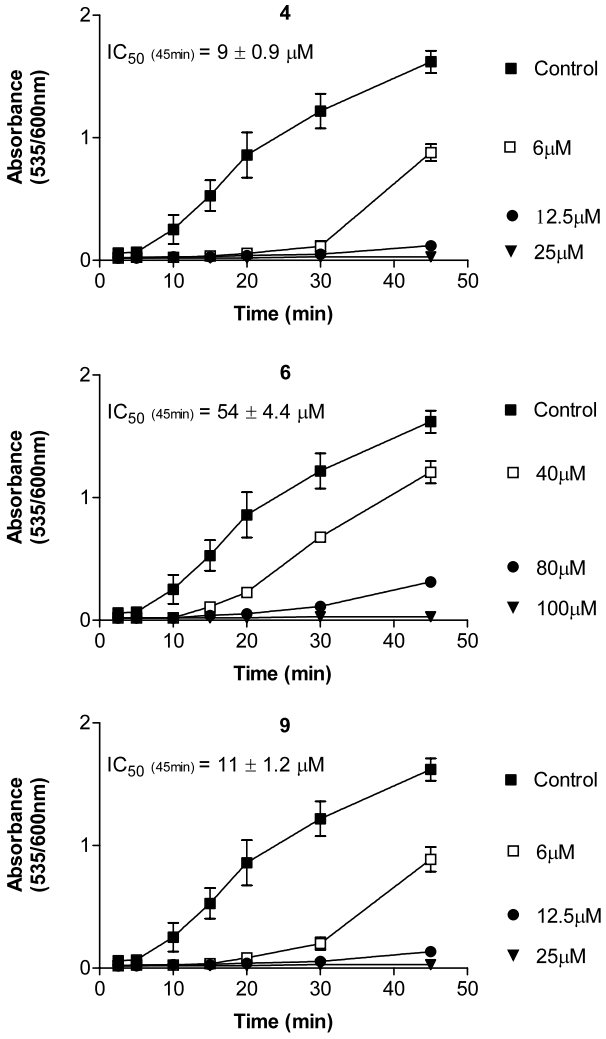

Fig. 3. Time course of lipid peroxidation as affected by various concentrations of compounds **4**, **6** and **9**. Activity of the compounds is expressed as the concentration of compounds that inhibited lipid peroxidation by 50% after 45 min of incubation (IC_{50} values). Results are expressed as a mean (±SEM) of two independent experiments.

respectively, under the same experimental conditions. In the anti-inflammatory assay the examined compounds demonstrated significant reduction of the paw edema produced by FCA. Compound **4**, at a concentration of 0.15 and 0.3 mmol kg^{-1}, presented a 50 and 65% inhibition of paw edema, respectively. Compound **9** at 0.15 and 0.3 mmol kg^{-1}, inhibited paw edema by 63 and 75%, while compound **6** at the same concentrations inhibited paw edema by 40 and 60%, respectively (Fig. 4). Under the same experimental conditions, indomethacin (110 μmol kg^{-1}) exhibited a 67% paw edema inhibition. The effect of compound **6** on lipoxygenase activity at 120 and 60 μM is shown in Fig. 5. It demonstrated a 44 and 23% inhibition of this enzyme, respectively. The other two compounds could not be evaluated in this assay since they showed insufficient solubility in 60% ethanol in water (see methods).

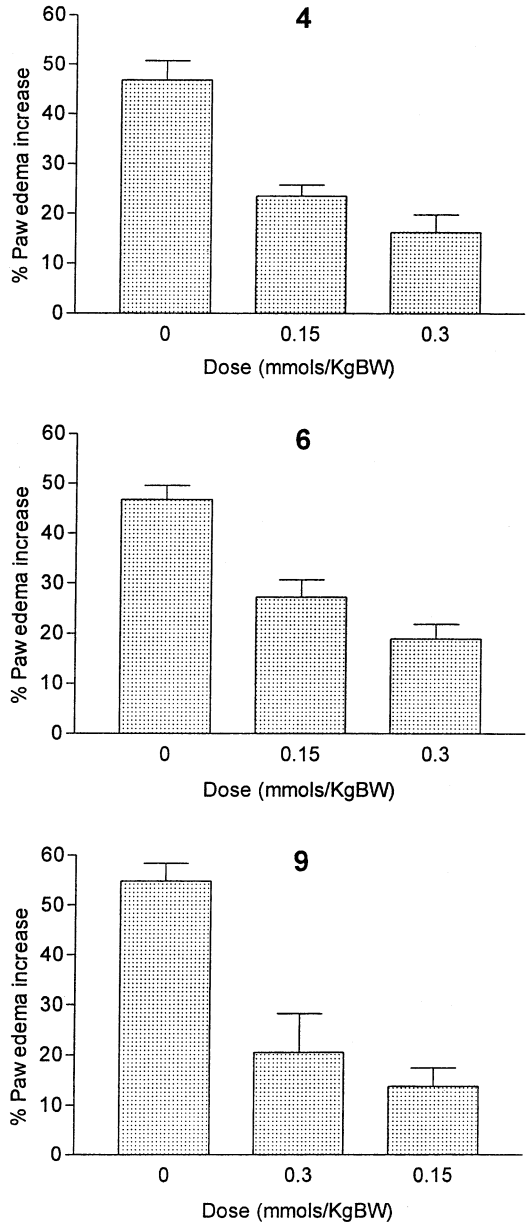

Fig. 4. Effect of **4**, **6** and **9** on the hind paw edema induced by FCA in Balb/C mice. Values are means (±SEM) of two independent experiments ($n = 6$).

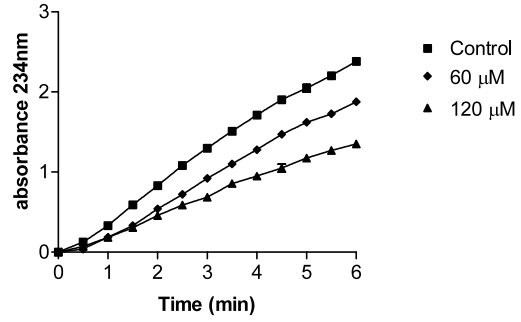

Fig. 5. Effect of **6** on lipoxygenase activity. Values are the mean (± SEM) of two independent experiments.

5. Discussion

Regarding the synthesis of the tested quinones **4**, **6**, **9**, the described methods of preparation offer an easy route to this type of compounds, namely triptycene quinones with methoxy groups.

We examined the protection offered by the three triptycene–quinone derivatives against lipid peroxidation using a standard technique [8–10]. The examined compounds in low concentrations (6–40 μM) protected very efficiently hepatic microsomal membranes from peroxidation. The most active were **4** ($IC_{50} = 9$ μM) and **9** ($IC_{50} = 11$ μM) followed by **6** ($IC_{50} = 54$ μM). This protective action could be mainly attributed to the quinonoid structure common to all tested compounds and could be explained by the abstraction of hydrogen atoms by reaction with ROS [7,11]. Furthermore, the triple allylic hydrogen of these compounds may antagonise those of polyunsaturated fatty acids for ROS. Since lipophilicity has usually a positive influence on antioxidant activity [12,13] we calculated the lipophilicity of the three derivatives to find that compound **4** has a slightly higher lipophilicity ($c\log P$ 3.282 compared to $c\log P$ 3.035 for compound **6** and to $c\log P$ 3.044 for compound **9**). Nevertheless, no correlation between lipophilicity and antioxidant activity could be deduced since compounds **4** and **9** were more or less equipotent.

We also examined the effect of the test compounds on inflammation in an attempt to evaluate their anti-inflammatory actions in conjunction with their antioxidant activity. It is well known that in inflammation oxidative stress plays an important role, both humorally and cellularly, via the action of COX enzymes, lipoxygenase and leukocytes. The anti-inflammatory activity of the compounds was assessed as reduction of the mouse paw edema induced by the FCA, a phlogistic producing an experimental arthritis model quite similar to human rheumatoid arthritis [14]. All examined compounds were quite active anti-inflammatory agents. This also suggests the participation of oxidative processes in inflammation as well as the importance of antioxidant therapy for these conditions.

It is known that the 5-lipoxygenase pathway is the source of a potent group of inflammatory mediators, the leukotrienes, implicated in neutrophil activation, which is associated with the induction of inflammation. Several nonsteroidal anti-inflammatory drugs are moderate lipoxygenase inhibitors, most of them having the ability to participate in redox processes. The synthesised compounds intervene in such reactions, since they inhibit lipid peroxidation, thus, their effect on lipoxygenase activity is of interest for investigation. Compound **6** that was examined offered significant inhibition of this enzyme at a concentration of 120 μM which also confirms the above mentioned relation between lipoxygenase inhibition and inhibition of lipid peroxidation. Further, it offers a possible mechanism of action for the in vivo anti-inflammatory activity of the compounds.

In conclusion, improved synthetic pathways were achieved for compounds **4**, **6** and **9**. In addition, under our experimental conditions these compounds showed very significant antioxidant and anti-inflammatory activity confirming also a relationship between these two activities.

6. Experimental

6.1. Materials

2-Thiobarbituric acid was purchased from Sigma Chemical Co. (St. Louis, MO, USA). All other chemicals were of the highest commercially available purity.

6.2. Chemistry

Melting points were determined on a Stuart Scientific Melting Point Apparatus SMP3 (230 V) and are uncorrected. ^{1}H-NMR spectra were recorded with a Bruker AM 300 (300 and 75 MHz for ^{1}H and ^{13}C, respectively) in ca. 5% solution of $CDCl_3$ using Me_4Si as the internal standard. Mass spectra were recorded with a spectrometer VG-250 in 70 eV, ESI. Elemental analyses were carried out in a Perkin–Elmer 2400-II elemental analyst. Chromatography columns were filled with silica gel No. 60 of Merck A.G. Industry.

6.2.1. 1,4-Dimethoxyanthracene (1)

1,4-Dimethoxyanthracene was prepared from quinizarin, in three steps (methylation and two subsequent reductions with $NaBH_4$) following a procedure from literature [4].

6.2.2. 5,8-Dimethoxy-4a,9,9a,10-tetrahydro-9,10-[o]benzenoanthracene-1,4-dione (2)

To a solution of 1,4-dimethoxy-anthracene (1.95 g, 9.5 mmol) in CH_3CN (40 mL) 1,4-benzoquinone was added (4.2 g, 38.8 mmol) and the mixture was refluxed for 10 h. After cooling, the yellow–green precipitate formed was filtered and dried in a desiccator for 24 h to afford **2** (2.23 g, 68%) m.p. 220 °C (dec.). ^{1}H-NMR: δ 2.17 (s, 2H), 3.80 (s, 6H), 6.54 (s, 2H), 6.58 (s, 2H), 7.00–7.11 (m, 2H), 7.42–7.51 (m, 2H). MS (70 eV); *m/z* (%): 347 (100) [M+1], 239 (77), 224 (70), 208 (31), 180 (48), 152 (68). $C_{22}H_{18}O_4$ (346.38) Anal. Calc.: C, 76.28; H, 5.24; Found: C, 76.01; H, 5.50%.

6.2.3. 9,10-Dihydro-1,4-dihydroxy-5,8-dimethoxy-9,10-[o]benzenoanthracene (3)

A suspension of 5,8-dimethoxy-4a,9,9a,10-tetrahydro-9,10-[*o*]benzenoanthracene-1,4-dione (**2**) (0.75 g, 2.16 mmol) in CH_3COOH (50 mL) was refluxed until the

solid was completely dissolved (20–30 min). Twenty drops of hydrobromic acid (48% solution) were added and the resulting mixture was poured into water (10 mL). The white precipitate formed was filtered and dried in a desiccator for 24 h to yield **3** (0.74 g, 98%): m.p. > 200 °C (dec.). ^{1}H-NMR: ($CDCl_3$+DMSO-d_6) δ 3.80 (s, 6H), 6.27 (s, 2H), 6.34 (s, 2H), 6.55 (s, 2H), 6.96–7.01 (m, 2H), 7.35–7.42 (m, 2H). MS (70 eV); *m/z* (%): 348 (100) [M+2], 330 (36), 316 (94), 298 (34), 284. $C_{22}H_{18}O_4$ (346.38) Anal. Calc.: C, 76.28; H, 5.24; Found: C, 76.68; H, 4.99%.

6.2.4. 9,10-Dihydro-5,8-dimethoxy-9,10-[*o*]benzenoanthracene-1,4-dione (*4*)

To a solution of 9,10-dihydro-1,4-dihydroxy-5,8-dimethoxy-9,10-[*o*]benzenoanthracene (**3**) (0.243 g, 0.70 mmol) in CH_2Cl_2 (8 mL) a solution of (diacetoxyiodo)benzene (0.237 g, 0.73 mmol) in CH_2Cl_2 (8 mL) was added with stirring at room temperature (r.t.). Stirring was continued for 1 h. The solution was concentrated to dryness and purified by column chromatography (silica gel) using a mixture of petroleum ether–ethyl acetate (5:1) as eluant to afford 0.21 g of **4** (yield 88%), m.p.: 271–272 °C. ^{1}H-NMR: δ 3.81 (s, 6H), 6.24 (s, 2H), 6.55 (s, 2H), 6.59 (s, 2H), 7.00–7.05 (m, 2H), 7.42–7.50 (m, 2H). ^{13}C-NMR: δ 41.25, 56.27, 109.34, 124.47, 125.23, 133.41, 135.23, 144.09, 149.48, 152.74, 183.50 (C=O). MS (70 eV); *m/z* (%): 344 (100) [M^+], 330 (40), 286 (25), 176. $C_{22}H_{16}O_4$ (344.37) Anal. Calc.: C, 76.73; H, 4.68; Found: C, 76.41; H, 4.67%.

6.2.5. 9,10-Dihydro-5,8-dimethoxy-1,2,4-tris-acetoxy-9,10-[*o*]benzenoanthracene (*5*)

To a solution 9,10-dihydro-5,8-dimethoxy-9,10-[*o*]benzenoanthracene-1,4-dione (**4**) (0.66 g, 1.91 mmol) in acetic anhydride (33 mL), a catalytic amount of sulphuric acid was added (0.63 g, 0.33 mL, 6.34 mmol) with stirring at r.t. for 1 h. The mixture was poured into ice water (100 mL) and stirring was continued for another half an hour until the product was crystallized. The solid was filtered, washed with water, and dried in a vacuum desiccator overnight to give 0.91 g of **4** (yield 98%), m.p.: 117–120 °C. ^{1}H-NMR: δ 2.27 (s, 3H), 2.41 (s, 3H), 2.43 (s, 3H), 3.76 (s, 3H), 3.77 (s, 3H), 5.87 (s, 1H), 5.89 (s, 1H), 6.49 (s, 2H), 6.71 (s, 1H), 6.99–7.02 (m, 2H), 7.30–7.40 (m, 2H). MS (70 eV); *m/z* (%): 490 (7) [M+2], 432 (10), 348 (20), 316 (8), 244 (10), 205 (12), 180 (25), 150 (20), 135 (22), 122 (46), 111 (66), 91 (80), 81 (100). $C_{28}H_{24}O_8$ (488.49) Anal. Calc.: C, 68.85; H, 4.95; Found: C, 68.62; H, 4.74%.

6.2.6. 9,10-Dihydro-2-hydroxy-5,8-dimethoxy-9,10-[*o*]benzenoanthracene-1,4-dione (*6*)

To a solution of 9,10-dihydro-5,8-dimethoxy-1,2,4-tris-acetoxy-9,10-[*o*]benzenoanthracene (**5**) (0.19 g, 0.39 mmol) in methanol (8 mL), a solution of NaOH (32% w/v) (0.8 mL, 0.256 g, 6.4 mmol) was added with stirring at r.t. The yellow solution turned to green and then purple. Stirring was continued for 30 min and then the solution was acidified with hydrochloric acid (20% v/v) (pH 2) (color changed to orange). The solution was poured onto water (20 mL) and the orange precipitate formed was filtered, washed with water, and dried in a vacuum desiccator for 24 h to afford 0.13 g of orange crystals (yield 92%), m.p.: 174–178 °C. ^{1}H-NMR: δ 3.78 (s, 3H), 3.79 (s, 3H), 5.90 (s, 1H), 6.20 (s, 1H), 6.23 (s, 1H), 6.54 (s, 2H), 7.01–7.19 (m, 2H), 7.30–7.50 (m, 2H). ^{13}C-NMR: δ 41.54, 41.80, 56.32, 56.39, 106.05, 109.51, 124.36, 124.78, 125.42, 126.88, 130.21, 144.02, 183.01 (C=O), 183.98 (C=O). MS (70 eV); *m/z* (%): 361 (100) [M+1], 291 (35), 263 (57), 239 (34), 224. $C_{22}H_{16}O_5$ (360.37) Anal. Calc.: C, 73.32; H, 4.47; Found: C, 73.65; H, 4.23%.

6.2.7. 2-Methoxy-*p*-benzoquinone (*8*)

To a solution of commercially available 1,4-dihydroxy-2-methoxy-benzene (**7**) (2.5 g, 17.8 mmol) in CH_3OH (45 mL) a solution of (diacetoxyiodo)benzene (5.9 g, 18.3 mmol) in CH_3OH (45 mL) was added with stirring at r.t. Stirring continued for 1 h. The solution was concentrated to dryness and purified by column chromatography (silica gel) using a mixture of petroleum ether–ethyl acetate (2:1) as eluant to afford 2.14 g of **8** (yield 87%), m.p.: 145–146 °C. ^{1}H-NMR: δ 6.72 (s, 2H), 5.95 (s, 1H), 3.84 (s, 3H). ^{13}C-NMR: δ 56.2, 107.5, 111.6, 134.2, 137.1, 181.6 (C=O), 187.4 (C=O).

6.2.8. 9,10-Dihydro-2,5,8-trimethoxy-9,10-[*o*]benzenoanthracene-1,4-dione (*9*)

A mixture of 2-methoxy-*p*-benzoquinone (**8**) (0.77 g, 5.6 mmol) and 1,4-dimethoxyanthracene (**1**) (0.5 g, 2.10 mmol) in glacial acetic acid (15 mL) was refluxed for 4 h. After cooling, the solution was poured onto water (15 mL) and the solid was filtered, washed with a small amount of water and purified by column chromatography (silica gel) using a mixture of petroleum ether–ethyl acetate (2:1) as eluant to afford 0.69 g of product **9** (yield 88%), m.p.: 108–110 °C. ^{1}H-NMR: δ 3.74 (s, 3H), 3.79 (s, 6H), 5.72 (s, 1H), 6.23 (s, 1H), 6.25 (s, 1H), 6.53 (s, 2H), 6.97–7.01 (dd, 2H, J = 5.5, 3 Hz), 7.40–7.45 (dd, 2H, J = 5.5, 3 Hz). ^{13}C-NMR: δ 42.34, 42.32, 53.42, 55.28, 55.37, 104.43, 106.59, 108.20, 124.02, 124. 2, 126.14, 126.23, 133.3, 133.5, 144.0, 144.2, 149.6, 149.7, 150.8, 153.64, 158.28, 178.23 (C=O), 183.41 (C=O). MS (70 eV); *m/z* (%): 374 (100) [M^+], 360 (30), 344 (30), 316 (21). $C_{23}H_{18}O_5$ (374.40) Anal. Calc.: C, 73.78; H, 4.84; Found: C, 73.57; H, 4.99%.

6.3. In-vitro lipid peroxidation

Hepatic microsomal fraction from untreated female Fischer-344 rats (180–220 g), was prepared as described

[8]. The incubation mixture contained heat inactivated (90 °C for 90 s) hepatic microsomes corresponding to 2.5 mg protein/mL (final concentration) or 4 mM fatty acid residues [9], ascorbic acid (0.2 mmol L^{-1}) and various concentrations (1–0.05 mmol L^{-1}) of the test compounds dissolved in DMSO. The reaction was started by the addition of a freshly prepared $FeSO_4$ solution (10 μmol L^{-1}), the mixture was incubated at 37 °C for 45 min. Lipid peroxidation was assessed spectrophotometrically (535 against 600 nm) determining the TBA reactive material [10]. Under the above experimental conditions, all compounds, as well as DMSO, were tested and found not to interfere with the assay. Each experiment was performed at least in triplicate.

6.4. Effect of the test compounds on FCA induced inflammation

Edema was induced by i.d. injection of FCA (Freund's Complete Adjuvant, 0.05 mL/paw) into the right hind paw of male Balb/C mice (20–30 g) (the left paw serving as control) [14]. Groups of six animals were used and the test compounds (suspended in water with few drops of Tween-80) were given i.p. (0.15 or 0.3 mmol kg^{-1}) 15 min prior to the FCA injection. Mice were euthanised 3 h later and the produced edema was estimated as paw weight increase 3 h after the FCA administration [15]. Indomethacin a known anti-inflammatory drug was used as reference in addition to the absolute control. Statistical analysis was performed with the student's t-test and differences between treated and non-treated groups were significant at $P < 0.0001$.

6.5. Effect on lipoxygenase activity

The reaction mixture contains (final concentrations) the test compound, dissolved in 60% ethanol (120 or 60 μM), or the solvent, soybean lipoxygenase, dissolved in 2% ethanol in 0.9% NaCl solution (250 u mL^{-1}) and sodium linoleate (100 μM), in Tris–HCl buffer, pH 9.0. The reaction is monitored for 6–7 min at 28 °C, by recording absorbance at 234 nm [16]. The reliability of the method is checked by examining the activity of nordihydroguaiaretic acid (10 μM), used here as a reference under exactly the same experimental conditions.

6.6. c Log P

Hydrophobicity, expressed as $c\log P$ values, of compounds was calculated with the programme CLOGP, v4.62, Daylight Chemical Information Systems Inc.

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