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Effect of the Aryl Substituent on Antitumor Activity of 2-Substituted-1,4-dihydroxy-9,10-anthraquinones and 2-Substituted-anthracene-1,4,9,10-tetraones

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2-(1-Aryl-1-hydroxymethyl)- and 2-aroyl-DHAQ derivatives (DHAQ, 1,4-dihydroxy-9,10-anthraquinone), and 2-(1-aryl-1-hydroxymethyl)-ATO derivatives (ATO, anthracene-1,4,9,10-tetraone) were synthesized and their antitumor activities were determined. 2-(1-Aryl-1-hydroxymethyl)-DHAQ derivatives showed a stronger cytotoxicity compared to the series of 2-(1-hydroxyalkyl)-1,4-dihydroxy-9,10-anthraquinone derivatives. It was suggested that the presence of aryl group at the side chain accelerated the bioreductive activation leading to cell death. 2-Aroyl-DHAQ derivatives, despite their higher electrophilicity, revealed smaller cytotoxicity and antitumor activity (expressed by T/C value) than 2-(1-aryl-1-hydroxymethyl)-DHAQ derivatives. Thus, no consistent relationship between the electronic effect on aromatic side chain and the cytotoxicity was observed.

ATO series exhibited a higher antitumor activity (T/C, 125~218%), though their cytotoxicity was not further improved compared to that of 2-(1-aryl-1-hydroxymethyl)-1,4-dihydroxy-9,10-anthraquinones. They manifested no correlation between the cytotoxicity and the antitumor activity. In case of 2-[1-hydroxy-1-(4-propylphenyl)-methyl]-ATO, the most bioactive one *in vivo* among the same series, it showed an ED_{50} value of 10.2 mg/mL and a T/C value of 218%. It is assumed that the anthracene-1,4,9,10-tetraones after uptake into cellular tissues might be transformed to a cytotoxic metabolite(s).

Key words: 1,4-dihydroxy-9,10-anthraquinone, anthracene-1,4,9,10-tetraones, antitumor activity, structure-activity relationship

INTRODUCTION

Anthraquinone is built in the structure of some anticancer agents as a bioactive moiety. For instance, 1,4-dihydroxy-9,10-anthraquinone (quinizarin) is a common structural moiety of adriamycin and mitoxantrone. In a previous study (Jin *et al.*, 1998b) on the structure-activity relationship of 2-substituted-1,4-dihydroxy-9,10-anthra-quinones, it was found that the presence of phenyl group at C-1 of the side chain of these anthraquinones caused a considerable enhancement of the cytotoxic activity of 2-substituted 1,4-dioxy-9,10-anthraquinone derivatives. It was proposed that the presence of aryl group at C-1 might accelerate the bioreductive arylation resulting in the enhancement of the cytotoxicity of the anthra-quinone derivatives. A further study (Jin *et al.*, 1998a) revealed that the anthracene-1,4,9,10-tetraone deriv-tives showed a stronger potency in antitumor activity, supporting the suggestion that enhancement of electro-philicity of quinone moiety potentiated the cytotoxicity (Song *et al.*, 1999a; Song *et al.*, 1999b).

For further investigation of the effects of the aryl groups at C-1 of the side chain and the electrophilicity on the antitumor activity, a series of 2-(1-aryl-1-hydroxymethyl)-1,4-dihydroxy-9,10-anthraquinones,2-(1-aryl-1-hydroxymethyl)-anthracene-1,4,9,10-tetraones and 2-aroyl-1,4-dihydroxy-9,10-anthraquinones were synthesized, and their antitumor activity was evaluated and correlated to the structure.

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MATERIALS AND METHODS

Chemicals and solvents were of reagent grade and used without further purification. L1210 cells were obtained from Korea Institute for Chemical Technology. RPMI 1640, Fetal bovine serum and other reagents used for cell culture were purchased from GIBCO Co. Melting points were determined on an Electrothermal melting point apparatus and are not corrected. IR spectra were recorded on a Jasco Report-100 IR spectrometer. Proton NMR spectra were recorded on a Varian-Gemini 300 MHz, 400 MHz or Jeol-90 MHz spectrometers using tetramethylsilane as an internal standard. Analytical thin layer chromatography was performed on a plastic sheet (0.2 mm) precoated with silica gel 60 F254 (E. Merck). Silica gel 60 (70-230 mesh, E. Merck) was used for column chromatography.

Cytotoxic activity against L1210 cells

Cytotoxicity was measured against L1210 cells *in vitro* as reported previously (Thayer *et al.*, 1971). Fisher's medium supplemented with horse serum in 10% was used for the proliferation of L1210 cells. Cell numbers were counted using a hemocytometer and ED_{50} value was defined as a samples concentration that causes a 50% growth inhibition of cells relative to the control in three independent experiments.

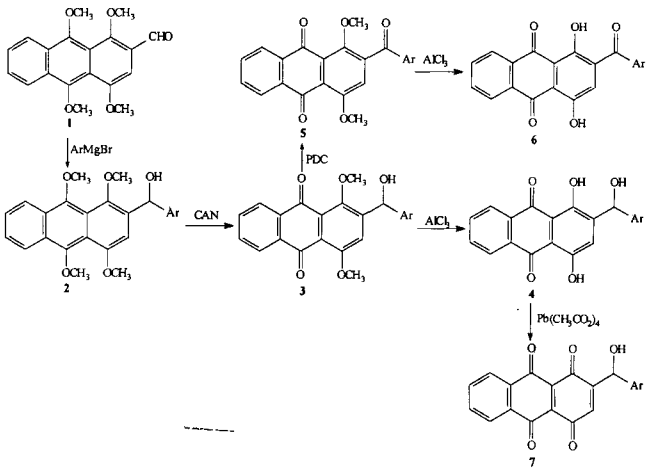
Antitumor activity in ICR mice bearing Sarcoma 180 cells

T/C value for Sarcoma 180 (S 180) system was measured using NCI protocol (National Cancer Institute, 1972); Sarcoma 180 cells suspended in saline (1×10^7 cells/mL) were inoculated intraperitoneally (injection volume; 0.1 mL per mouse). After transplantation, mice were divided so that each group contains 8 mice. The test samples dissolved or emulsified in a predetermined amount of tween 80 4% in injection water were stored at 4°C. The schedule for injection comprised of a total of 7 injections in a manner that 24 hr after the transplantation of S 180, 0.1 mL of the test sample per day was administered for 2 days followed by one day rest. The survival rate (T/C, %) was calculated by the following equation:

$$T/C = \frac{\text{Total survival time of the treated group}}{\text{Total survivial time of the control group}} \times 100$$

Synthesis

General procedure for synthesis of 2-(1-aryl-1-hydroxymethyl)-1,4-di-methoxy-9,10-anthraquinone derivatives (Scheme I)



Scheme 1. Synthesis of 2-(1-aryl-1-hydroxymethyl)-1,4-dimethoxy-9,10-anthraquinone derivatives

Bromophenyl compound (46 mmol) was added to a 250ml two-necked round bottom flask containing magnesium (46 mmol) in 50 ml of tetrahydrofuran and the mixture was stirred for 2 h. To this Grignard reagent, a solution of 2-formyl-1,4,9,10-tetramethoxyanthracene (15 mmol) (Jin *et al.*, 1998b) in 50 mL of tetrahydrofuran was dropwise added under stirring. After 4 h stirring at room temperature, the reaction mixture was treated with 50mL of ammonium chloride 10% in distilled water, stirred for a while and extracted with dichloromethane (3 times × 150 ml). The organic extracts were combined, dried over anhydrous sodium sulfate and evaporated to give a yellowish mass. This was dissolved in 50 ml of acetonitrile and cooled to 0-5°C, to which a solution of 30.5 mmol of cerium diammonium nitrate in 40 ml of distilled water was dropped over 30 min under stirring. After that, the mixture was warmed to room temperature, stirred for 2 h and mixed with 200 ml of distilled water. Then the reaction mixture was extracted with dichloro-methane (3 times × 150 ml), dried over anhydrous sodium sulfate and evaporated to give a crude product which was purified by silica gel column which was eluted with hexane/ethyl acetate (4:1).

2-(1-Hydroxy-1-phenylmethyl)-1,4-dimethoxy-9,10-anthraquinone (3-a)

Yield: 76.7%; Mp: 184.8-185.4°C; Rf=0.41 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3445 (OH), 3050 (CH, aromatic), 1675 (C=O), 1580 (C=C, aromatic), 1455 (C=C, aromatic); 1250 (C-O-C), 1038 (C-OH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.21-8.10 (2H, m), 7.71-7.66 (3H, m), 7.40-7.36 (5H, m), 6.19 (1H, d, *J*=4.14 Hz), 4.04 (3H, s), 3.58 (3H, s), 2.75 (1H, d, *J*=4.14 Hz).

2-[1-(4-Fluorophenyl)-1-hydroxy-methyl]-1,4-dimethoxy-9,10-anthraquinone (3-b)

Yield: 65.6%; Mp: 185.0-186.7°C; Rf=0.42 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3410 (OH), 3060 (CH, aromatic), 1675 (C=O), 1582 (C=C, aromatic), 1458 (C=C), 1248 (C-O-C), 1040 (C-OH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.17-8.13 (2H, m), 7.74-7.70 (2H, m), 7.62 (1H, s), 7.41-7.36 (2H, m), 7.07-7.02 (2H, m), 6.18 (1H, d, *J*=4.17 Hz), 4.09 (3H, s), 3.62 (3H, s), 2.70 (1H, d, *J*=4.16 Hz).

2-[1-(2-Chlorophenyl)-1-hydroxymethyl]-1,4-dimethoxy-9,10-anthraquinone (3-c)

Yield: 51.6%; Mp: 89.2-90.7°C; Rf=0.41 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3450 (OH), 3055 (CH, aromatic), 1675 (C=O), 1580 (C=C, aromatic), 1455 (C=C, aromatic), 1250 (C-O-C), 1038 (C-OH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.15-8.14 (2H, m), 7.76-7.75 (3H, m), 7.45-7.33 (5H, m), 5.91 (1H, d, *J*=4.54 Hz), 4.08 (3H, s), 3.73 (3H, s), 2.94 (1H, d, *J*=3.74 Hz).

2-[1-(3-Chlorophenyl)-1-hydroxymethyl]-1,4-dimethoxy-9,10-anthraquinone (3-d)

Yield: 51.7%; Mp: 125.0-126.5°C; Rf=0.42 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3440 (OH), 3055 (CH, aromatic), 1680 (C=O), 1575 (C=C, aromatic), 1450 (C=C, aromatic), 1240 (C-O-C), 1045 (C-OH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.16-8.30 (2H, m), 7.74-7.70 (2 H, m), 7.59 (1H, s), 7.40 (1H, s), 7.30-7.23 (3H, m), 6.17 (1H, d, *J*=4.38 Hz), 4.04 (3H, s), 3.64 (3H, s), 2.90 (1H, d, *J*=4.56 Hz).

2-[1-(4-Chlorophenyl)-1-hydroxymethyl]-1,4-dimethoxy-9,10-anthraquinone (3-e)

Yield: 57%; Mp: 95.5-97.1°C; Rf=0.41 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3445 (OH), 3045 (CH, aromatic), 1678 (C=O), 1580 (C=C, aromatic), 1445 (C=C, aromatic), 1250 (C-O-C), 1045 (C-OH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.15-8.11 (2H, m), 7.75-7.59 (2H, m), 7.48-7.25 (5H, s), 6.13 (1H, d, *J*=3.92 Hz), 4.00 (3 H, s), 3.60 (3H, s), 2.97 (1H, d, *J* = 4.52 Hz).

2-[1-(2,3-Dichlorophenyl)-1-hydroxymethyl]-1,4-dimethoxy-9,10-anthraquinone (3-f)

Yield: 54.4%; Mp: 105.6-107.1°C; Rf=0.42 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3500 (OH), 3040 (CH, aromatic), 1680 (C=O), 1578 (C=C, aromatic), 1448 (C=C, aromatic), 1245 (C-O-C), 1040 (C-OH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.13-8.07 (2H, m), 7.79-7.68 (3 H,m), 7.56-7.45 (3H, m), 7.35 (1H, s), 6.15 (1H, d, *J* =3.76 Hz), 4.00 (3H, s), 3.66 (3H, s), 3.09 (1H, d, *J* = 4.19 Hz).

2-[1-(3,4-Dichlorophenyl)-1-hydroxymethyl]-1,4-dimethoxy-9,10-anthraquinone (3-g)

Yield: 55.4%; Mp: 95.6-97.1°C; Rf=0.43 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3445 (OH), 3040 (CH, aromatic), 1680 (C=O), 1578 (C=C, aromatic), 1448 (C=C, aromatic), 1245 (C-O-C), 1040 (C-OH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.15-8.10 (2H, m), 7.76-7.65 (3 H,m), 7.56-7.45 (3H, m), 7.35 (1H, s), 6.15 (1H, d, *J* =3.96 Hz), 4.00 (3H, s), 3.66 (3H, s), 3.09 (1H, d, *J*= 4.14 Hz).

2-[1-Hydroxy-1-(2-toluyl)methyl]-1,4-dimethoxy-9,10-anthraquinone (3-h)

Yield: 62.2%; Mp: 156.0-157.0°C; Rf=042 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3445 (OH), 3045 (CH, aromatic), 2945 (CH_3), 1680 (C=O), 1575 (C=C, aromatic), 1475 (C=C, aromatic), 1455 (CH_3), 1245 (C-O-C), 1045 (C-OH); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.20-8.14 (2H, m), 7.74-7.70 (2H, m), 7.59 (1H, s), 7.23-7.18 (4H,m), 6.45 (1H, d, *J*=2.80 Hz), 4.00 (3H, s), 3.54 (3H, s), 2.47 (3H, s), 2.46 (1H, d, *J*=2.00 Hz).

2-[1-Hydroxy-1-(3-toluyl)methyl]-1,4-dimethoxy-9,10-anthraquinone (3-i)

Yield: 75.0%; Mp: 128.2-129.7°C; Rf=0.41 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3445 (OH), 3045 (CH, aromatic), 2945 (CH_3), 1680 (C=O), 1575 (C=C, aromatic), 1465 (CH_3), 1440 (C=C, aromatic), 1250 (C-O-C), 1040 (C-OH); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.20-8.14 (2H, m), 7.76-7.70 (2H, m), 7.67 (1H, s), 7.34-7.11 (4H, m), 6.19 (1H, d, *J*=5.6 Hz), 4.05 (3H, s), 3.58 (3H, s), 2.73 (1H, d, *J*=6.1 Hz), 2.33 (3H, s).

2-[1-Hydroxy-1-(4-toluyl)methyl]-1,4-dimethoxy-9,10-anthraquinone (3-J)

Yield: 80.4%; Mp: 161.5-162.7°C; Rf=0.42 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3450 (OH), 3040 (CH, aromatic), 2945 (CH_3), 1675 (C=O), 1580 (C=C, aromatic), 1445 (C=C, aromatic), 1435 (CH_3), 1245 (C-O-C), 1045 (C-OH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.19-8.14 (2H, m), 7.77-7.73 (2H, m), 7.68 (1H, s), 7.29-7.27 (2H, m), 7.17-7.15 (2H, m), 6.19 (1H, d, *J*=4.0 Hz), 4.06 (3H, s), 3.58 (3H, s), 2.64 (1H, d, *J*=2.8 Hz), 1.58 (3H, s).

2-[1-(4-Ethylphenyl)-1-hydroxymethyl]-1,4-dimethoxy-9,10-anthraquinone (3-k)

Yield: 71.7%; Mp: 122.7-123.5°C; Rf=0.43 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3450 (OH), 3045 (CH, aromatic), 2950 (CH_3), 1678 (C=O), 1580 (C=C, aromatic), 1475 (CH_3), 1445 (C=C, aromatic), 1248 (C-O-C), 1045 (C-OH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.22-

8.09 (2H, m), 7.75-7.69 (3H, m), 7.36-7.12 (4H, s), 6.19 (1H, d, *J*=3.69 Hz), 4.04 (3H, s), 3.58 (3H, s), 2.72-2.67 (1H, d, *J*=4.23Hz), 2.54 (2H, crude quintet, *J*=7.56 Hz), 1.20 (3H, t, *J*=7.38 Hz).

2-[1-Hydroxy-1-(4-n-propylphenyl)methyl]-1,4-dimethoxy-9,10-anthraquinone (3-l)

Yield: 71.6%; Mp: 109.0-110.7°C; Rf=0.43 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3450 (OH), 3055 (CH, aromatic), 2950 (C-H, alkyl), 1658 (C=O), 1580 (C=C, aromatic), 1475 (C-H, alkyl), 1448 (C=C, aromatic), 1252 (C-O-C), 980 (C-OH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.22-8.09 (2H, m), 7.75-7.68 (3H, m), 7.35-7.09 (4H, m), 6.16 (1H, d, *J*=3.06 Hz), 4.03 (3H, s), 3.56 (3H, s), 2.54 (1H, d, *J*=4.12 Hz), 2.61 (2H, t, *J*=7.2 Hz), 1.60 (2H, crude sextet, *J*=7.56 Hz), 0.90 (3 H, t, *J*=7.25 Hz).

2-[1-(4-n-Butylphenyl)-1-hydroxymethyl]-1,4-dimethoxy-9,10-anthraquinone (3-m)

Yield: 66.7%; Mp: 111.4-111.8°C; Rf=0.43 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3452 (OH), 3055 (CH, aromatic), 2950 (C-H, alkyl), 1658 (C=O), 1582 (C=C, aromatic), 1475 (C-H, alkyl), 1445 (C=C, aromatic), 1245 (C-O-C), 980 (C-OH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.20-8.13 (2 H, m), 7.75-7.68 (3H, m), 7.30-7.29 (2H, m), 7.17-7.14 (2H, m), 6.18 (1H, d, *J*=4.79 Hz), 4.05 (3 H, s), 3.57 (3H, s), 2.74 (1H, d, *J*=4.55 Hz), 2.60-2.57 (2H, t, *J*=6.08), 1.60-1.55 (2H, m), 1.38-1.26 (2H, m), 0.90 (3H, t, *J*=7.2 Hz).

2-[1-(4-tert-Butylphenyl)-1-hydroxymethyl]-1,4-dimethoxy-9,10-anthraquinone (3-n)

Yield: 44.8%; Mp: 156.6-156.9°C; Rf=0.42 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3450 (OH), 3050 (CH, aromatic), 2950 (C-H, alkyl), 1656 (C=O), 1582 (C=C, aromatic), 1465 (C-H, alkyl), 1444 (C=C, aromatic), 1242 (C-O-C), 978 (C-OH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.23-8.10 (2H, m), 7.76-7.65 (3H, m), 7.34-7.26 (4H, m), 6.17 (1H, d, *J*=2.70 Hz), 4.05 (3H, s), 3.60 (3H, s), 2.62 (1H, d, *J*=3.96 Hz), 1.29 (9H, s).

2-[1-Hydroxy-1-(1-naphtyl)methyl]-1,4-dimethoxy-9,10-anthraquinone (3-o)

Yield: 42.6%; Mp: 129.0-130.0°C; Rf=0.39 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3400-3200 (OH), 3150-3055 (CH, aromatic), 2940 (CH_3), 1660 (C=O), 1580 (C=C, aromatic), 1475 (CH_3), 1460 (C=C, aromatic), 1240 (C-O-C), 980 (C-OH); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.18-8.12 (3H, m), 7.90-7.81 (2H, m), 7.75-7.68 (2H, m), 7.56-7.42 (5H, m), 7.05 (1H, d, *J*=3.47 Hz), 3.88 (3H, s), 3.64 (3H, s), 2.82 (1H, d, *J*=3.84 Hz).

2-[1-Hydroxy-1-(2-naphtyl)methyl]-1,4-dimethoxy-9,10-anthraquinone (3-p)

Yield: 54.2%; Mp: 117.0-118.0°C; Rf=0.40 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3450 (OH), 3045 (CH, aromatic), 2950 (CH_3), 1662 (C=O), 1580 (C=C, aromatic), 1475 (CH_3), 1455 (C=C, aromatic, 1245 (C-O-C), 980 (C-OH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.17-8.07 (2 H, m), 7.85-7.64 (7H, m), 7.51-7.44 (3H, m), 6.38-6.35 (1H, d, *J*=3.87 Hz), 4.02 (3H, s), 3.56 (3H, s), 2.61-2.58 (1H, d, *J*=4.17 Hz).

2-[1-Hydroxy-1-(4-methoxyphenyl)methyl]-1,4-dimethoxy-9,10-anthraquinone (3-q)

Yield: 69.0%; Mp: 139.0-141.0°C; Rf = 0.39 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3440 (OH), 3055 (CH, aromatic), 2935 (CH_3), 1655 (C=O), 1580 (C=C, aromatic), 1465 (CH_3), 1445 (C=C, aromatic), 1245 (C-O-C), 980 (C-OH); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.22-8.09 (2H, m), 7.75-7.69 (3H, m), 7.35-7.26 (2H, m), 6.91-6.81 (2H, m), 6.16 (1H, d, *J*=2.25 Hz), 4.04 (3H, s), 3.78 (3H, s), 3.57 (3H, s), 2.53 (1H, d, *J*=2.93 Hz).

2-[1-Hydroxy-1-(4-phenylphenyl)methyl]-1,4-dimethoxy-9,10-anthraquinone (3-r)

Yield: 70.0%; Mp: 127.0-129.0°C; Rf=0.29 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3435 (OH), 3060 (CH, aromatic), 2925 (CH_3), 1650 (C=O), 1582 (C=C, aromatic), 1465 (CH_3), 1450 (C=C, aromatic), 124 0 (C-O-C), 978 (C-OH); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.29-8.16 (2H, m), 7.81-7.71 (3H, m), 7.61-7.42 (9H, m), 6.29 (1 H, d, *J*=2.79 Hz), 4.11 (3H, s), 3.69 (3H, s), 1.83 (1H, d, *J*=2.43 Hz).

2-[1-Hydroxy-1-(N-phenylsulfonylindol-2-yl)methyl]-1,4-dimethoxy-9,10-anthraquinone (3-s)

N-phenylsulfonyl-2-lithium-indol generated *in situ* as described previously (Gordon *et al.*, 1992) was employed instead of the arylmagnesium bromide. Yield: 94.9%; Mp: 178-180°C; Rf=0.34 [Hexane: Ethyl acetate (1:1)]; IR (cm^{-1}): 3545 (OH), 3060 (CH, aromatic), 2925 (CH_3), 1650 (C=O), 1582 (C=C, aromatic), 1465 (CH_3), 1450 (C=C, aromatic), 124 0(C-O-C), 978 (C-OH); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.23-8.14 (4H, m), 8.00-7.98 (2H, m), 7.85 (1H, s), 7.76-7.72 (2H, m), 7.64-7.62 (1H, m), 7.56-7.52 (1H, m), 7.35-7.32 (2H, m), 7.23-7.21 (1H, m), 6.78 (1H, s), 5.97 (1H, s), 4.10 (3H, s), 4.02 (1H, broad), 3.34 (3H, s).

2-[1-Hydroxy-1-(N-phenylsulfonylpyrrol-2-yl)methyl]-1,4-dimethoxy-9,10-anthraquinone (3-t)

N-phenylsulfonyl-2-lithium-pyrrol generated *in situ* as described previously (Gordon *et al.*, 1992) was employed instead of the arylmagnesium bromide. Yield: 95%; Mp:

169-171°C; Rf = 0.31 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3550 (OH), 3100 (CH, aromatic), 2915 (CH_3), 1662 (C=O), 1618 (C=C, aromatic), 1465 (CH_3), 1450 (C=C, aromatic), 125 0 (C-O-C), 978 (C-OH); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.23-7.91 (4 H, m), 7.75-7.59 (6H, m), 7.39-7.37 (1H, d, *J*=1.53), 6.42 (1H, d, *J*=3.15 Hz), 5.65 (1H, crude doublet), 4.16 (3H, s), 3.70 (1H, d, *J*=3.6 Hz), 3.09 (3H, s).

2-[1-Hydroxy-1-(2-thienyl)methyl]-1,4-dimethoxy-9,10-anthraquinone (3-u)

2-lithium-thiophene generated in *situ* as described previously (Gordon *et al.*, 1992) was employed instead of the arylmagnesium bromide. Yield: 77.0%; Mp: 113.0-115.0 °C; Rf=0.29 [Hexane: Ethyl acetate (1:1)]; IR (cm^{-1}): 3405 (OH), 3060 (CH, aromatic), 2930 (CH_3), 1668 (C=O), 1585 (C=C, aromatic), 1465 (CH_3), 1458 (C=C, aromatic), 1245 (C-O-C), 980 (C-OH); ^{1}H-NMR ($CDCl_3$) δ: 8.18-8.15 (2H, m), 7.75-7.72 (2H, m), 7.68 (H, s), 7.30-7.28 (1H, m), 6.96 (2H, m), 6.45 (1H, d, *J*=4.15 Hz), 4.06 (3H, s), 3.66 (3H, s), 3.05 (1H, d, *J*=3.97 Hz).

General procedure for synthesis of 2-(1-aryl-1-hydroxymethyl)-1,4-dihydroxy-9,10-anthraquinones(Scheme I)

To a solution of 2-(1-aryl-1-hydroxymethyl)-1,4-dimethoxy-9,10-anthraquinone (20 mmol) dissolved in nitrobenzene (30 ml), anhydrous aluminium chloride (110 mmol) was slowly added. The reaction mixture, after stirred at room temperature for 2 hr, was treated with crushed ice and several drops of concentrated hydrogen chloride under stirring. Nitrobenzene was separated from the aqueous layer using a separatory funnel. The aqueous layer was then stirred for 2 hrs at 50°C. A crude product precipitated was purified using silica gel column chromatography eluted with hexane-ethyl acetate (5:1).

2-(1-Hydroxy-1-phenylmethyl)-1,4-dihydroxy-9,10-anthraquinone (4-a)

Yield: 37.6%; Mp: 221-223°C; Rf=0.20 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3580-3200 (O-H), 3050 (C-H, aromatic), 1620 (C=O), 1580 (C=C, aromatic), 1462 (C=C, aromatic), 1235 (C-O); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 13.43 (1H, s), 12.91 (1H, s), 8.34-8.33 (2H, m), 7.84-7.81 (2H, m), 7.64 (1H, s), 7.49-7.31 (5H, m), 6.15 (1H, d, *J*=4.05 Hz), 2.82 (1H, d, *J*=4.41 Hz).

2-[1-(4-Fluorophenyl)-1-hydroxymethyl]-1,4-dihydroxy-9,10-anthraquinone (4-b)

Yield: 29.0%; Mp: 171-173°C; Rf=0.22 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3600-3200 (O-H), 3045 (C-H, aromatic), 1620 (C=O), 1580 (C=C, aromatic), 1460 (C=C, aromatic), 1240 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 13.42 (1H, s), 12.89 (1H, s), 8.31-8.28 (2H, m), 7.86-7.76 (2H, m), 7.53 (1H, s), 7.44-7.26 (4H, m), 6.14 (1H, d, *J*=4.17 Hz), 2.83 (1H, d, *J*=4.23 Hz).

2-[1-(2-Chlorophenyl)-1-hydroxymethyl]-1,4-dihydroxy-9,10-anthraquinone (4-c)

Yield: 28.4%; Mp: 178.0-179.5°C; Rf=0.22 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3590-3210 (O-H), 3050 (C-H, aromatic), 1620 (C=O), 1580 (C=C, aromatic),1465 (C=C, aromatic), 1235 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 13.51 (1H, s), 12.84 (1H, s), 8.30-8.12 (2H, m), 7.81-7.71 (2H, m), 7.51 (1H, s), 7.41-7.29 (4H, m), 5.74 (1H, d, *J*=4.51 Hz), 3.22 (1H, d, *J*=4.1 Hz).

2-[1-(3-Chlorophenyl)-1-hydroxymethyl]-1,4-dihydroxy-9,10-anthraquinone (4-d)

Yield: 36.3%; Mp: 178.0-179.6°C; Rf=0.23 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3560-3200 (O-H), 3045 (C-H, aromatic), 1618 (C=O), 1578 (C=C, aromatic), 1465 (C=C, aromatic), 1235 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 13.39 (1H, s), 12.89 (1H, s), 8.31-8.17 (2H, m), 7.84-7.74 (2H, m), 7.49 (1H, s), 7.34-7.27 (4H, m), 6.17 (1H, d, *J*=3.67 Hz), 2.98 (1H, d, *J*=4.47 Hz).

2-[1-(4-Chlorophenyl)-1-hydroxymethyl]-1,4-dihydroxy-9,10-anthraquinone (4-e)

Yield: 36.2%; Mp: 192.0-194.0°C; Rf=0.23 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3545-3210 (O-H), 3050 (C-H, aromatic), 1620 (C=O), 1580 (C=C, aromatic), 1465 (C=C, aromatic), 1240 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 13.30 (1H, s), 12.84 (1H, s), 8.30-8.27 (2H, m), 7.85-7.79 (2H, m), 7.47 (1H, s), 7.38-7.26 (4H, m), 6.14 (1H, d, *J*=4.14 Hz), 2.88 (1H, d, *J*=4.41 Hz).

2-[1-(2,3-Dichlorophenyl)-1-hydroxymethyl]-1,4-dihydroxy-9,10-anthraquinone (4-f)

Yield: 28%; Mp: 237.3-238.4°C; Rf=0.23 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3600-3200 (O-H), 3050 (C-H, aromatic), 1620 (C=O), 1582 (C=C, aromatic), 1465 (C=C, aromatic), 1250 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 13.37 (1H, s), 12.87 (1H, s), 8.35-8.29 (2H, m), 7.95-7.82 (2H, m), 7.57 (1H, s), 7.47-7.27 (3H, m), 6.17 (1H, d, *J*=4.39 Hz), 2.94 (1H, d, *J*=4.87 Hz).

2-[1-(3,4-Dichlorophenyl)-1-hydroxymethyl]-1,4-dihydroxy-9,10-anthraquinone (4-g)

Yield: 29%; Mp: 194.6-195.7°C; Rf=0.23 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3590-3200 (O-H), 3050 (C-H, aromatic), 1620 (C=O), 1582 (C=C, aromatic), 1465 (C=C, aromatic), 1250 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 13.39 (1H, s), 12.89 (1H, s), 8.39-8.29 (2H, m), 7.95-7.82 (2H, m), 7.57 (1H, s), 7.47-7.27 (3H, m), 6.17 (1H,

d, J=4.37 Hz), 2.94 (1H, d, J=4.97 Hz).

2-[1-Hydroxy-1-(2-toluyl)methyl]-1,4-dihydroxy-9,10-anthraquinone (4-h)

Yield: 34%; Mp: 140.9-142.1°C; Rf=0.23 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3540-3200 (O-H), 3050 (C-H, aromatic), 2950 (C-H, alkyl), 3050 (C-H, aromatic), 1622 (C=O), 1580 (C=C, aromatic), 1465 (C=C, aromatic), 1250 (C-O); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 13.48 (1H, s), 12.91 (1H, s), 8.36-8.35 (2H, m), 7.85-7.83 (2H, m), 7.41 (1H, s), 7.32 (1H, s), 7.31-7.22 (3H, m), 6.40 (1 H, d, J=3.60 Hz), 2.78 (1H, d, J=3.47 Hz), 2.42 (3H, s).

2-[1-Hydroxy-1-(3-toluyl)methyl]-1,4-dihydroxy-9,10-anthraquinone (4-i)

Yield: 44.6%; Mp: 160.7-163.2°C; Rf=0.23 [Hexane: Ethyl acetate (4:1)], IR (cm^{-1}): 3600-3200 (O-H), 3050 (C-H, aromatic), 2945 (C-H, alkyl), 1620 (C=O), 1580 (C=C, aromatic), 1465 (C=C, aromatic), 1250 (C-O). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 13.39 (1H, s), 12.87 (1H, s), 8.34-8.26 (2H, m), 7.85-7.74 (2H, m), 7.52 (1H, s), 7.28-7.05 (4H, m), 6.13 (1H, d, J=3.96 Hz), 2.84 (1H, d, J=4.14 Hz), 2.35 (3H, s).

2-[1-Hydroxy-1-(4-toluyl)methyl]-1,4-dihydroxy-9,10-anthraquinone (4-J)

Yield: 49.9%; Mp: 177.8-180.0°C; Rf=0.23 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3900-3215 (O-H), 3050 (C-H, aromatic), 2950 (C-H, alkyl), 1622 (C=O), 1580 (C=C, aromatic), 1475 (C=C, aromatic), 1245 (C-O); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 13.37 (1H, s), 12.87 (1H, s), 8.39-8.29 (2H, m), 7.83-7.73 (2H, m), 7.53 (1H, s), 7.47-7.11 (4H, m), 6.12 (1H, d, J=3.69 Hz), 2.81 (1H, d, J=4.23 Hz), 2.33 (3H, s).

2-[1-(4-Ethylphenyl)-1-hydroxymethyl]-1,4-dihydroxy-9,10-anthraquinone (4-k)

Yield: 54.9%; Mp: 180.3-181.5°C; Rf=0.24 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3600-3200 (O-H), 3045 (C-H, aromatic), 2950 (C-H, alkyl), 1625 (C=O), 1580 (C =C, aromatic), 1455 (C=C, aromatic), 1250 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 13.40 (1H, s), 12.90 (1H, s), 8.32-8.27 (2H, m), 7.85-7.75 (2H, m), 7.55 (1H, s), 7.44-7.14 (4H, m), 6.14 (1H, d, J=2.97Hz), 2.73 (1H, d, J=3.65 Hz), 2.60 (2H, quartet, J=7.65 Hz), 1.22 (3H, t, J=7.65 Hz).

2-[1-Hydroxy-1-(4-n-propylphenyl)methyl]-1,4-dihydroxy-9,10-anthraquinone (4-l)

Yield: 64.0%; Mp: 190.6-193.0°C; Rf=0.24 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3580-3210 (O-H), 3050 (C-H, aromatic), 2950-2850 (C-H, alkyl), 1620 (C=O), 1578 (C=C, aromatic), 1445 (C=C, aromatic), 1245 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 13.40 (1 H, s), 12.90 (1H, s), 8.36-8.27 (2H, m), 7.85-7.75 (2H, m), 7.55 (1 H, s), 7.43-7.12 (4H, m), 6.14 (1H, d, J=3.87 Hz), 2.78 (1H, d, J=4.14 Hz), 2.56 (2H, t, J=7.11 Hz), 1.52 (2H, crude sextet, J=7.56 Hz), 0.93 (3H, t, J=7.11 Hz).

2-[1-(4-n-Butylphenyl)-1-hydroxymethyl]-1,4-dihydroxy-9,10-anthraquinone (4-m)

Yield: 48.0%; Mp: 167.8-169.7°C; Rf=0.24 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3580-3220 (O-H), 3050 (C-H, aromatic), 2950-2890-2850 (C-H, alkyl), 1618 (C =O), 1578 (C=C, aromatic), 1454 (C=C, aromatic), 1254 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 13.43 (1H, s), 12.94 (1H, s), 8.39-8.38 (2H, m), 7.83-7.82 (2H, m), 7.56 (1H, s), 7.38-7.36 (2H, m), 7.19-7.17 (2 H, m), 6.18 (1H, d, J=4.17 Hz), 2.79 (1H, d, J=4.44 Hz), 2.59 (2H, t, J = 8.12 Hz), 1.58 (2H, quartet, J=7.89 Hz), 1.40 (2H, crude sextet, J=7.79 Hz), 0.92 (3H, t, J=7.60 Hz).

2-[1-(4-tert-Butylphenyl)-1-hydroxymethyl]-1,4-dihydroxy-9,10-anthraquinone (4-n)

Yield: 65.0%; Mp: 199.1-201.0°C; Rf=0.24 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3600-3200 (O-H), 3045 (C-H, aromatic), 2950-2890-2845 (C-H, alkyl), 1618 (C= O), 1580 (C=C, aromatic), 1450 (C=C, aromatic), 1250 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 13.44 (1H, s), 12.94 (1H, s), 8.39-8.37 (2H, m), 7.84-7.83 (2H, m), 7.57 (1H, s), 7.40-7.39 (4H, m), 6.18 (1H, d, J=4.39 Hz), 2.89 (1H, d, J=3.97 Hz), 1.30 (9H, s).

2-[1-Hydroxy-1-(1-naphtyl)methyl]-1,4-dihydroxy-9,10-anthraquinone (4-o)

Yield: 37.0%; Mp: 221.8-223.0°C; Rf=0.23 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3580-3240 (O-H), 3150-3050 (C-H, aromatic), 1620 (C=O), 1580 (C=C, aromatic), 1465 (C=C, aromatic), 1250 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 13.55 (1H, s), 12.85 (1H, s), 8.43-8.33 (2 H, m), 7.98-7.79 (2H, m), 7.51 (1H, s), 7.40-7.26 (7 H, m), 6.20 (1H, d, J=3.67 Hz), 2.87 (1H, d, J=4.15 Hz).

2-[1-Hydroxy-1-(2-naphtyl)methyl]-1,4-dihydroxy-9,10-anthraquinone (4-p)

Yield: 39.0%; Mp: 231.9-233.4°C; Rf=0.23 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3600-3210 (O-H), 3150-3050 (C-H, aromatic), 1622 (C=O), 1582 (C=C, aromatic), 1470 (C=C, aromatic), 1245 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 13.46 (1H, s), 12.90 (1H, s), 8.39-8.29 (2H, m), 7.95-7.87 (6H, m), 7.52-7.42 (1H, m), 6.36 (1 H, d, J=3.77 Hz), 2.82 (1H, d, J=4.57 Hz).

2-[1-Hydroxy-1-(4-methoxyphenyl)methyl]-1,4-dihydroxy-9,10-anthraquinone (4-q)

Yield: 31%; Mp: 193.6-194.9°C; Rf=0.22 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3590-3210 (O-H), 3050 (C-H, aromatic), 2945 (C-H, alkyl), 1620 (C=O), 1580 (C=C, aromatic), 1450 (C=C, aromatic), 1250 (C-O); ^{1}H -NMR (90 MHz, $CDCl_3$) δ: 13.43 (1H, s), 12.94 (1H, s), 8.39-8.37 (2H, m), 7.83-7.82 (2H, m), 7.56 (1H, s), 7.40-7.38 (2H, m), 6.90-6.88 (2H, m), 6.18 (1H, d, *J* =3.17 Hz), 3.80 (3H, s), 2.87 (1H, d, *J*=3.98 Hz).

2-[1-Hydroxy-1-(4-phenylphenyl)methyl]-1,4-dihydroxy-9,10-anthraquinone (4-r)

Yield: 45%; Mp: 227.4-228.3°C; Rf=0.22 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3600-3200 (O-H), 3100-3045 (C-H, aromatic), 1628 (C=O), 1580 (C=C, aromatic), 1475 (C=C, aromatic), 1250 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 13.47 (1H, s), 12.93 (1H, s), 8.39-8.38 (2H, m), 7.83-7.81 (2H, m), 7.59-7.56 (6H, m), 7.43-7.39 (2 H, m), 7.37-7.35 (2H, m), 6.22 (1H, d, *J*=3.37 Hz), 2.84 (1H, d, *J*=3.98 Hz), 1.30 (9 H, s).

2-[1-Hydroxy-1-(N-phenylsulfonylindol-2-yl)methyl]-1,4-dihydroxy-9,10-anthraquinone (4-s)

Yield: 37%; Mp: 198-200°C; Rf = 0.20 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3545 (O-H), 3100 (C-H, aromatic), 1618 (C=O), 1580 (C=C, aromatic), 1475 (C=C, aromatic), 1250 (C-O); ^{1}H-NMR ($CDCl_3$) δ: 12.97 (1H, s), 12.85 (1H, s), 8.43-8.27 (4H, m), 8.00-7.85 (3H, m), 7.76-7.62 (3H, m), 7.56-7.32 (3H, m), 7.23-7.21 (1H, m), 6.78 (1H, s), 5.97 (1H, s), 3.02 (1H, broad).

2-[1-Hydroxy-1-(N-phenylsulfonylpyrrol-2-yl)methyl]-1,4-dihydroxy-9,10-anthraquinone (4-t)

Yield: 36%; Mp: 218-220°C; Rf=0.19 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3545 (O-H), 3900 (C-H, aromatic), 1618 (C=O), 1580 (C=C, aromatic), 1475 (C=C, aromatic), 1250 (C-O); ^{1}H-NMR ($CDCl_3$) δ: 12.92 (1 H, s), 12.89 (1 H, s), 8.41-8.25 (2H, m), 7.95-7.48 (7 H, m), 7.38-7.32 (2 H, m), 6.39 (1H, crude doublet), 6.20 (1H, t, J=3.42 Hz), 5.85 (1H, crude doublet), 3.44 (1H, d, J =4.14 Hz).

2-[1-Hydroxy-1-(2-thienyl)methyl]-1,4-dihydroxy-9,10-anthraquinone (4-u)

Yield: 37%; Mp: 133.9-135.5°C; Rf=0.22 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3620-3200 (O-H), 3075 (C-H, aromatic), 1628 (C=O), 1580 (C=C, aromatic), 1465 (C=C, aromatic), 1245 (C-O); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 13.47 (1H, s), 12.90 (1H, s), 8.36-8.34 (2H, m), 7.85-7.84 (2H, m), 7.57 (1H, s), 7.31 (1H, dd, J= 3.84/1.20), 6.99-6.98 (2 H, m), 6.42 (1H, d, J=2.79 Hz), 3.11 (1H, d, J=3.18 Hz).

General procedure for synthesis of 2-aroyl-1,4-dimethoxy-9,10-anthraquinones (Scheme I)

Pyridine dichromate (3 mmol) was suspended in dichloromethane (50 ml) in a 250 ml-ground-bottom flask, to which a solution of 2-(1-hydroxy-1-phenylmethyl)-1,4-dimethoxy-9,10-anthraquinone (1 mmol) dissolved in dichloromethane (30 ml) was added dropwise under stirring. The mixture was stirred for further 3 h at room temperature and then filtered. The filter cake was washed twice with dichloromethane. The combined organic solution was sequentially washed with 150 ml of aqueous hydrogen chloride 5%, 150 ml of aqueous sodium hydrogen carbonate (10%), 150 ml of saturated sodium chloride and then evaporated to give a dark brown mass. This mass was purified using sillica gel column which was eluted with hexane-ethyl acetate (4:1) solvent system or crystallized from dichloromethane/ethyl alcohol.

2-Benzoyl-1,4-dimethoxy-9,10-anthraquinone (5-a)

Yield: 58.9%; Mp: 162.4-162.3°C; Rf=0.65 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3050 (CH, aromatic), 2945 (CH_3), 1665 (C=O), 1580 (C=C, aromatic), 1465 (C=C, aromatic), 1235 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$): 8.22-8.17 (2H, m), 7.86-7.84 (2H, m), 7.76-7.75 (2H, m), 7.64-7.60 (1H, m), 7.50-7.48 (2H, m), 7.29 (1H, s), 4.02 (3H, s), 3.77 (3H, s).

2-(4-Fluorobenzoyl)-1,4-dimethoxy-9,10-anthraquinone (5-b)

Yield: 54.0%; Mp: 197.2-198.9°C; Rf=0.66 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3075 (CH, aromatic), 2945 (CH_3), 1675 (C=O), 1590 (C=C, aromatic), 1460 (C=C, aromatic), 1235 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ:8.197-8.196 (2H, m), 7.91-7.81 (2H, m), 7.78-7.75 (2H, m), 7.28 (1H, m), 7.18-7.01 (2H, m), 4.02 (3 H, s), 3.79 (3H, s).

2-(2-Chlorobenzoyl)-1,4-dimethoxy-9,10-anthraquinone (5-c)

Yield: 41.6%; Mp: 77.8-79.0°C; Rf=0.66 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3060 (CH, aromatic), 2950 (CH_3), 1675 (C=O), 1580 (C=C, aromatic), 1455 (C=C, aromatic), 1230 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.15-8.12 (2H, m), 7.91-7.73 (2H, m), 7.67-6.93 (5H, m), 4.05 (3H, s), 3.59 (3H, s).

2-(3-Chlorobenzoyl)-1,4-dimethoxy-9,10-anthraquinone (5-d)

Yield: 46.2%; Mp: 123.5-124.2°C; Rf=0.66 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3055 (CH, aromatic), 2945 (CH_3), 1665 (C=O), 1575 (C=C, aromatic), 1450 (C=C,

aromatic), 1245 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.15-8.12 (2 H, m), 7.91-7.73 (3 H, m), 7.60-7.13 (3 H, m), 7.05 (1H, s), 4.05 (3H, s), 3.59 (3H, s).

2-(4-Chlorobenzoyl)-1,4-dimethoxy-9,10-anthraquinone (5-e)

Yield: 45.0%; Mp: 78.9-90.2°C; Rf=0.67 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3060 (CH, aromatic), 2945 (CH_3), 1662 (C=O), 1578 (C=C, aromatic), 1450 (C=C, aromatic), 1240 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.17-8.05 (2H, m), 7.98-7.75 (3H, m), 7.49-7.20 (4H, m), 4.02 (3H, s), 3.76 (3H, s).

2-(3,4-Dichlorobenzoyl)-1,4-dimethoxy-9,10 anthraquinone (5-f)

Yield: 42.7%; Mp: 86.0-87.0°C; Rf=0.65 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3050 (CH, aromatic), 2950 (CH_3), 1670 (C=O), 1580 (C=C, aromatic), 1450 (C=C, aromatic), 1245 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.20-8.03 (2H, m), 7.97-7.42 (5H, m), 7.35 (1H, s), 4.03 (3H, s), 3.91 (3H, s).

2-(2-Toluoyl)-1,4-dimethoxy-9,10-anthraquinone (5-g)

Yield: 45.3%; Mp: 126.2-127.6°C; Rf=0.64 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3055 (CH, aromatic), 2950 (CH_3), 1675 (C=O), 1580 (C=C, aromatic), 1460 (C=C, aromatic), 1250 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.11-7.93 (2H, m), 7.65-7.55 (2H, m), 7.22-7.05 (5H, m), 3.89 (3H, s), 3.52 (3H, s), 2.50 (3H, s).

2-(3-Toluoyl)-1,4-dimethoxy-9,10-anthraquinone (5-h)

Yield: 67.5%; Mp: 151-152°C; Rf=0.63 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3050 (CH, aromatic), 2945 (CH_3), 1665 (C=O), 1575 (C=C, aromatic), 1460 (C=C, aromatic), 1245 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.19-8.06 (2H, m), 7.73-7.52 (4H, m), 7.34-7.20 (3H, m), 3.94 (3H, s), 3.70 (3H, s), 2.32 (3H, s).

2-(4-Toluoyl)-1,4-dimethoxy-9,10-anthraquinone (5-i)

Yield: 70.9%; Mp: 134.1-135.2°C; Rf=0.64 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3045 (CH, aromatic), 2950 (CH_3), 1670 (C=O), 1570 (C=C, aromatic), 1455 (C=C, aromatic), 1240 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.02-7.93 (2H, m), 7.59-7.50 (3H, m), 7.32-7.01 (4H, m), 3.87 (3H, s), 3.57 (3H, s), 2.22 (3H, s).

2-(4-Ethylbenzoyl)-1,4-dimethoxy-9,10-anthraquinone (5-J)

Yield: 58.8%; Mp: 112.2-112.9°C; Rf=0.64 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3045 (CH, aromatic), 2950 (CH, alkyl), 1665 (C=O), 1575 (C=C, aromatic), 1450 (C=C, aromatic), 1245 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.26-8.13 (2H, m), 7.80-7.73 (3H, m), 7.33-7.26 (4H, m), 3.78 (3H, s), 3.52 (3H, s), 2.73 (2H, quartet, J=7.56 Hz), 1.24 (3H, t, J=7.65 Hz).

2-(4-Propylbenzoyl)-1,4-dimethoxy-9,10-anthraquinone (5-k)

Yield: 55.0%; Mp: 92.9-93.1°C; Rf=0.62 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3050 (CH, aromatic), 2950 (CH, alkyl), 1670 (C=O), 1570 (C=C, aromatic), 1445 (C=C, aromatic), 1240 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.23-8.10 (2H, m), 7.77-7.70 (3 H, m), 7.28-7.19 (4 H, m), 3.97 (3H, s), 3.75 (3H, s), 2.61 (2H, t, J=7.11 Hz), 1.66 (2H, crude sextet, J=7.65 Hz), 095 (3H, t, J= 7.11 Hz).

2-(4-*n*-Butylbenzoy)-1,4-dimethoxy-9,10-anthraquinone (5-l)

Yield: 53.3%; Mp: 69.9-71.2°C; Rf=0.63 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3045 (CH, aromatic), 2950-2800 (CH, alkyl), 1660 (C=O), 1580 (C=C, aromatic), 1450 (C=C, aromatic), 1245 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.23-8.10 (2H, m), 7.77-7.69 (3H, m), 7.38-7.19 (4H, m), 3.97 (3H, s), 3.75 (3H, s), 2.60 (2H, t, J=7.65 Hz), 1.59-1.22 (4H, m), 0.88 (3H, t, J=6.12 Hz).

2-(4-*tert*-Butylbenzoyl)-1,4-dimethoxy-9,10-anthraquinone (5-m)

Yield: 41.0%; Mp: 107-109.1°C; Rf=0.65 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3045 (CH, aromatic), 2950-2900-2850 (CH, alkyl), 1662 (C=O), 1582 (C=C, aromatic), 1458 (C=C, aromatic), 1235 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.26-8.23 (2H, m), 7.84-7.74 (3H, m), 7.52-7.26 (4H, m), 4.00 (3H, s), 3.78 (3H, s), 1.33 (9 H, s).

2-(1-Naphthoyl)-1,4-dimethoxy-9,10-anthraquinone (5-n)

Yield: 46.9%; Mp: 143.7-144.7°C; Rf=0.64 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3150-3045 (CH, aromatic), 2925 (CH_3), 1680-1645 (C=O), 1620-1590 (C=C, aromatic), 1460 (C=C, aromatic), 1250 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.17-8.07 (3H, m), 7.85-7.44 (10H, m), 4.02 (3H, s), 3.56 (3H, s).

2-(2-Naphthoyl)-1,4-dimethoxy-9,10-anthraquinone (5-o)

Yield: 50.7%; Mp: 108.9-109.5°C; Rf=0.63 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3150-3045 (CH, aromatic), 2925 (CH_3), 1675-1640 (C=O), 1618-1590 (C=C, aromatic), 1460 (C=C, aromatic), 1250 (C-O); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.24-8.23 (3H, m), 7.941-7.930 (4

H, m), 7.734-7.720 (2H, m), 7.64-7.61 (2H, m), 7.35 (1H, s), 4.05 (3H, s), 3.83 (3 H, s).

2-(4-Methoxybenzoyl)-1,4-dimethoxy-9,10-anthraquinone (5-p)

Yield: 61.0%; Mp: 171.0-173.0°C; Rf=0.51 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3045 (CH, aromatic), 2930 (CH_3), 1670-1645 (C=O), 1618-1590 (C=C, aromatic), 1455 (C=C, aromatic), 1245 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.18-8.06 (2H, m), 7.80-7.62 (3H, m), 7.00-6.91 (4H, m), 4.02 (3H, s), 3.89 (3H, s), 3.81 (3H, s).

2-(4-Phenylbenzoyl)-1,4-dimethoxy-9,10-anthraquinone (5-q)

Yield: 63.0%; Mp: 149.0-151.0°C; Rf=0.50 [Hexane: Ethyl acetate (5:5)]; IR (cm^{-1}): 3150-3045 (CH, aromatic), 2945 (CH_3), 1675-1650 (C=O), 1620-1590 (C=C, aromatic), 1450 (C=C, aromatic), 1245 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.22-8.07 (2H, m), 7.98-7.37 (12H, m), 4.05 (3H, s), 3.89 (3H, s).

General procedure for synthesis of 2-aroyl-1,4-dihydroxy-9,10-anthraquinones

2-Aroyl-1,4-dihydroxy-9,10-anthraquinones derivative derivatives were obtained by demethylation of the corresponding 2-aroyl-1,4-dimethoxy-9,10 anthraquinones at the positions 9, 10 by aluminium chloride in nitro-benzene using the same procedures described for the synthesis of 2-(1-aryl-1-hydroxymethyl)-1,4-dihydroxy-9,10-anthraquinones.

2-Benzoyl-1,4-dihydroxy-9,10-anthraquinone (6-a)

Yield: 67.7%; Mp: 210-212°C; Rf=0.28 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3050 (C-H, aromatic), 1682 (C=O), 1620 (C=O), 1580 (C=C, aromatic), 1450 (C=C, aromatic), 1235 (C-O), 1060 (C-OH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 13.06 (1H, s), 12.75 (1H, s), 8.35-8.31 (2H, m), 7.91-7.83 (4H, m), 7.65-7.61 (1H, m), 7.51-7.47 (2 H, m), 7.37 (1H, s).

2-(4-Fluorobenzoyl)-1,4-dihydroxy-9,10-anthraquinone (6-b)

Yield: 64.0%; Mp: 244-245°C; Rf=0.31 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3045 (C-H, aromatic), 1680 (C=O), 1620 (C=O), 1580 (C=C, aromatic), 1465 (C=C, aromatic), 1250 (C-O), 1045 (C-OH); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 13.14 (1H, s), 12.95 (1H, s), 8.41-8.39 (2H, m), 7.95-7.87 (4H, m), 7.48-7.25 (3H, m).

2-(2-Chlorobenzoyl)-1,4-dihydroxy-9,10-anthraquinone (6-c)

Yield: 57.0%; Mp: 168-169.5°C; Rf=0.31 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3060 (C-H, aromatic), 1678 (C=O), 1622 (C=O), 1580 (C=C, aromatic), 1445 (C=C, aromatic), 1255 (C-O), 1045 (C-OH); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 13.12 (1H, s), 12.58 (1H, s), 8.34-8.33 (2H, m), 7.87-7.85 (2H, m), 7.65-7.58 (2H, m), 7.39-7.07 (3H, m).

2-(3-Chlorobenzoyl)-1,4-dihydroxy-9,10-anthraquinone (6-d)

Yield: 62.0%; Mp: 186.4-188.0°C; Rf=0.33 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3050 (C-H, aromatic), 1680 (C=O), 1620 (C=O), 1580 (C=C, aromatic), 1465 (C=C, aromatic), 1250 (C-O), 1040 (C-OH); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 13.08 (1H, s), 12.75 (1H, s), 8.38-8.18 (2H, m), 7.93-7.83 (4H, m), 7.72 (1H, s), 7.66-7.40 (1H, m), 7.34 (1 H, s).

2-(4-Chlorobenzoyl)-1,4-dihydroxy-9,10-anthraquinone (6-e)

Yield: 58.3%; Mp: 261.2-262.7°C; Rf=0.33 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3080 (C-H, aromatic), 1680 (C=O), 1622 (C=O), 1580 (C=C, aromatic), 1475 (C=C, aromatic), 1250 (C-O), 1045 (C-OH); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 13.09 (1H, s), 12.77 (1H, s), 8.43-8.33 (2H, m), 7.98-7.79 (4H, m), 7.51-7.40 (3H, m).

2-(3,4-Dichlorobenzoyl)-1,4-dihydroxy-9,10-anthraqinone (6-f)

Yield: 27.0%; Mp: 241.8-243.2°C; Rf=0.34 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3060 (C-H, aromatic), 1682 (C=O), 1623 (C=O), 1575 (C=C, aromatic), 1465 (C=C, aromatic), 1245 (C-O), 1045 (C-OH); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 13.13 (1 H, s), 12.77 (1H, s), 8.41-8.39 (2H, m), 7.97 (1H, s), 7.96-7.89 (2H, m), 7.70 (1H, m), 7.60-7.58 (1H, m), 7.42 (1H, s).

2-(2-Toluoyl)-1,4-dihydroxy-9,10-anthraquinone (6-g)

Yield: 69.0%; Mp: 160.5-162.1°C; Rf=0.34 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3050 (C-H, aromatic), 2950 (C-H, alkyl), 1680 (C=O), 1622 (C=O), 1580 (C=C, aromatic), 1470 (C=C, aromatic), 1430 (C-H, alkyl), 1250 (C-O), 1045 (C-OH); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 13.17 (1H, s), 12.79 (1H, s), 8.39-8.36 (2H, m), 7.89-7.87 (2H, m), 7.48-7.44 (3 H, m), 7.38-7.36 (1H, m), 7.22 (1H, m), 2.63 (3H, s).

2-(3-Toluoyl)-1,4-dihydroxy-9,10-anthraquinone (6-h)

Yield: 71.4%; Mp: 201.6-203.5°C; Rf=0.34 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3045 (C-H, aromatic), 2950 (C-H, alkyl), 1680 (C=O), 1620 (C=O), 1585 (C=C, aromatic), 1475 (C=C, aromatic), 1425 (C-H, alkyl),

1250 (C-O), 1045 (C-OH); ^{1}H-NMR (90 MHz, $CDCl_3$) δ : 13.07 (1H, s), 12.79 (1H, s), 8.37-8.32 (2H, m), 7.92-7.81 (3H, m), 7.73-7.64 (2H, m), 7.43-7.37 (2H, m), 2.41 (3H, s).

2-(4-Toluoyl)-1,4-dihydroxy-9,10-anthraquinone (6-i)

Yield: 75.6%; Mp: 187.1-188.2°C; Rf=0.33 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3050 (C-H, aromatic), 2950 (C-H, alkyl), 1680 (C=O), 1625 (C=O), 1580 (C=C, aromatic), 1450 (C=C, aromatic), 1423 (C-H, alkyl), 1250 (C-O), 1045 (C-OH); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 13.07 (1H, s), 12.79 (1H, s), 8.37-8.32 (2H, m), 7.92-7.81 (4H, m), 7.43-7.37 (3H, m), 2.41 (3H, s).

2-(4-Ethylbenzoyl)-1,4-dihydroxy-9,10-anthraquinone (6-J)

Yield: 41.0%; Mp: 178.0-179.5°C; Rf=0.33 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3090 (C-H, aromatic), 2950-2925 (C-H, alkyl), 1680 (C=O), 1622 (C=O), 1585 (C=C, aromatic), 1475 (C=C, aromatic), 1435 (C-H, alkyl), 1250 (C-O), 1045 (C-OH); ^{1}H-NMR (90 MHz, $CDCl_3$) δ : 13.10 (1H, s), 12.81 (1H, s), 8.42-8.39 (2H, m), 7.92-7.79 (4H, m), 7.38-7.27 (3H, m), 2.77 (2H, quartet, J=7.53 Hz), 1.26 (3H, t, J=7.61 Hz).

2-(4-n-Propylbenzoyl)-1,4-dihydroxy-9,10-anthraquinone (6-k)

Yield: 60.0%; Mp: 165.5-166.9°C; Rf=0.32 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3100-3050 (C-H, aromatic), 2975-2925 (C-H, alkyl), 1680 (C=O), 1620 (C=O), 1580 (C=C, aromatic), 1475 (C=C, aromatic), 1445 (C-H, alkyl), 1250 (C-O), 1045 (C-OH); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 13.09 (1H, s), 12.80 (1H, s), 8.41-8.33 (2H, m), 7.96-7.77 (4H, m), 7.37-7.34 (3H, m), 2.66 (2 H, t, J=7.61 Hz), 1.76 (2H, crude sextet, J=7.38 Hz), 0.96 (3H, t, J=7.11 Hz).

2-(4-n-Butylbenzoyl)-1,4-dihydroxy-9,10-anthraquinone (6-l)

Yield: 45.0%; Mp: 143.0-144.5°C; Rf=0.34 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3120-3060 (C-H, aromatic), 2975-2950-2940 (C-H, alkyl), 1680 (C=O), 1620 (C=O), 1575 (C=C, aromatic), 1475-1465 (C=C, aromatic), 1445 (C-H, alkyl), 1250 (C-O), 1045 (C-OH); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 13.12 (1H, s), 12.83 (1H, s), 8.41-8.34 (2H, m), 7.90-7.81 (4H, m), 7.38 (1H, s), 7.31-7.29 (2H, m), 2.70 (2H, t, J=7.58 Hz), 1.58 (2H, crude quintet, J=7.47 Hz), 1.40 (2H, crude sextet, J=7.11), 0.94 (3H, t, J=7.20 Hz).

2-(4-tert-Butylbenzoyl)-1,4-dihydroxy-9,10-anthraquinone (6-m)

Yield: 55.0%; Mp: 183.4-184.7°C; Rf=0.34 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3090-3050 (C-H, aromatic), 2975-2925 (C-H, alkyl), 1682 (C=O), 1622 (C=O), 1578 (C=C, aromatic), 1460 (C=C, aromatic), 1415 (C-H, alkyl), 1245 (C-O), 1050 (C-OH); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 13.12 (1H, s), 12.82 (1H, s), 8.39-8.37 (2H, m), 7.90-7.83 (4H, m), 7.52-7.50 (2H, m), 7.37 (1 H, m), 1.36 (9 H, s).

2-(1-Naphthoyl)-1,4-dihydroxy-9,10-anthraquinone(6-n)

Yield: 35.0%; Mp: 201-203°C; Rf=0.30 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3120-3060 (C-H, aromatic), 1680 (C=O), 1620 (C=O), 1580 (C=C, aromatic), 1475-1465 (C=C, aromatic), 1250 (C-O), 1045 (C-OH); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 13.16 (1 H, s), 12.82 (1 H, s), 8.93-8.91 (1H, m), 8.41-8.63 (2H, m), 8.10-8.08 (1H, m), 7.90-7.87 (2H, m), 7.76-7.74 (1H, m), 7.72-7.67 (1H, m), 7.53 (1H, s), 7.63-7.59 (1H, m), 7.50-7.46 (1H, m).

2-(2-Naphthoyl)-1,4-dihydroxy-9,10-anthraquinone(6-o)

Yield: 48.0%; Mp: 190.3-193.1°C; Rf=0.31 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3100-3050 (C-H, aromatic), 1682 (C=O), 1622 (C=O), 1578 (C=C, aromatic), 1462-1445 (C=C, aromatic), 1245 (C-O), 1045 (C-OH); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 13.13 (1 H, s), 12.81 (1 H, s), 8.42-8.36 (2 H, m), 8.30 (1H, s), 8.24 (1 H, dd, J=1.84/1.60 Hz), 8.06 (1 H, dd, J=8.80/2.00 Hz), 7.95 (1H, d, J=8.40 Hz), 7.92-7.88 (2H, m), 7.71-7.69 (1H, m), 7.65-7.61 (1H, m), 7.57-7.53 (1H, m).

2-(4-Methoxybenzoyl)-1,4-dihydroxy-9,10-anthraquinone (6-p)

Yield: 69.0%; Mp: 268-269°C; Rf=0.30 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3080-3040 (C-H, aromatic), 2950 (C-H, alkyl), 1680 (C=O), 1620 (C=O), 1580 (C=C, aromatic), 1475-1465 (C=C, aromatic), 1250 (C-O), 1045 (C-OH); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 13.12 (1H, s), 12.93 (1H, s), 8.399-8.395 (2H, m), 7.90-7.87 (4H, m), 7.37 (1H, s), 6.98-6.96 (2H, m), 3.90 (3H, s).

2-(4-Phenylbenzoyl)-1,4-dihydroxy-9,10-anthraquinone (6-q)

Yield: 78.0%; Mp: 264.5-266.0°C; Rf=0.31 [Hexane: Ethyl acetate (4:1)]; IR (cm^{-1}): 3180-3045 (C-H, aromatic), 1680 (C=O), 1622 (C=O), 1580 (C=C, aromatic), 1475-1465 (C=C, aromatic), 1250 (C-O), 1045 (C-OH); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 13.13 (1H, s), 12.81 (1H, s), 8.44-8.30 (2H, m), 8.03-7.76 (4H, m), 7.66-7.62 (2 H, m), 7.54 (1H, s), 7.49-7.44 (5H, m).

General procedure for synthesis of 2-(1-aryl-1-hydroxymethyl)-anthracene-1,4,9,10-tetraones (Scheme I)

2-(1-Aryl-1-hydroxymethyl)-1,4-dihydroxy-9,10-anthraquinone (0.5 mmol) was dissolved in acetic acid (30 ml), to which lead tetra-acetate (1.05 mmol) was added in one portion. After the reaction mixture was stirred for 15 min at room temperature, 20 ml of 5%HCl and 100 ml of water were added. This diluted solution was extracted 3 times with dichloromethane (50 ml). The dichloromethane extract was washed with brine (100 ml), dried over sodium sulfate and evaporated to a brown yellow mass. It was recrystallized from dichloromethane/hexane to give pure products.

2-(1-Hydroxy-1-phenylmethyl)-anthracene-1,4,9,10-tetraone (7-a)

Yield: 93%; Mp: 109-111°C; IR (cm^{-1}): 3490 (OH), 3050 (C-H, aromatic), 1680 (C=O), 1640 (C=C, aromatic), 1580 (C=C, aromatic), 1280 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.09-8.00 (2H, m), 7.89-7.75 (2H, m), 7.47-7.17 (5H, m), 7.04 (1H, s), 5.91 (1H, s), 2.55-2.49 (1H, d, J=2.7).

2-[1-(4-Fluorophenyl)-1-hydroxymethyl]-anthracene-1, 4,9,10-tetraone (7-b)

Yield: 47%; Mp: 151-153°C; IR (cm^{-1}): 3440 (OH), 3060 (C-H, aromatic), 1678 (C=O), 1640 (C=C, aromatic), 1580 (C=C, aromatic), 1280 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.09-8.01 (2H, m), 7.90-7.71 (2H, m), 7.43-7.15 (4 H, m), 6.62 (1H), 5.99 (1H, s), 2.60 (1H, broad).

2-[1-(2-Chlorophenyl)-1-Hydroxymethyl]-anthracene-1, 4,9,10-tetraone (7-c)

Yield: 33%; Mp: 131-133°C; IR (cm^{-1}): 3450 (OH), 3050 (C-H, aromatic), 1680 (C=O), 1640 (C=C, aromatic), 1580 (C=C, aromatic), 1280 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.13-8.05 (2H, m), 7.81-7.71 (2H, m), 7.61-7.28 (4H, m), 6.60 (1H), 6.37-6.32 (1H, s), 2.69 (1H, broad).

2-[1-(3-Chlorophenyl)-1-1-hydroxymethyl]-anthracene-1,4,9,10-tetraone (7-d)

Yield: 46%; Mp: 207.4-209.0°C; IR (cm^{-1}): 3590 (OH), 3045 (C-H, aromatic), 1680 (C=O), 1640 (C=C, aromatic), 1578 (C=C, aromatic), 1280 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.01-7.74 (2H, m), 7.55-7.50 (2H, m), 7.40-7.35 (4H, m), 7.10 (1H, s), 5.90 (H, s), 2.65 (1H, broad).

2-[1-(4-Chlorophenyl)-1-hydroxymethyl]-anthracene-1, 4,9,10-tetraone (7-e)

Yield: 54%; Mp: 221.3-223.7°C; IR (cm^{-1}): 3475 (OH), 3055 (C-H, aromatic), 1680 (C=O), 1640 (C=C, aromatic), 1580 (C=C, aromatic), 1280 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.15-8.11 (2H, m), 7.83-7.76 (2H, m), 7.52-7.27 (4H, m), 7.03 (1H, s), 5.93 (1H, s), 2.52 (1H, broad).

2-[1-(3,4-Dichlorophenyl)-1-hydroxymethyl]-anthracene-1,4,9,10-tetraone (7-f)

Yield: 84%; Mp: 217-219°C; IR (cm^{-1}): 3500 (OH), 3045 (C-H, aromatic), 1680 (C=O), 1640 (C=C, aromatic), 1580 (C=C, aromatic), 1280 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.05-7.97 (2 H, m), 7.86-7.72 (2H, m), 7.57-7.45 (3H, m), 6.79 (1H, s), 5.94 (1H, s), 2.84 (1H, broad).

2-[1-Hydroxy-1-(2-toluyl)methyl]-anthracene-1,4,9,10-tetraone (7-g)

Yield: 81%; Mp: 193.1-195.5°C; IR (cm^{-1}): 3500 (OH), 3050 (C-H, aromatic), 2900 (C-H, alkyl), 1680 (C=O), 1640 (C=C, aromatic), 1580 (C=C, aromatic), 1475 (C-H, alkyl), 1280 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.04-8.00 (2 H, m), 7.85-7.75 (2 H, m), 7.35-7.21 (4 H, m), 6.90 (1 H, s), 6.11 (1 H), 2.56 (3 H, s).

2-[1-Hydroxy-1-(3-toluyl)methyl]-anthracene-1,4,9,10-tetraone (7-h)

Yield: 74%; Mp: 175.7-177.0°C; IR (cm^{-1}): 3500 (OH), 3050 (C-H, aromatic), 2900 (C-H, alkyl), 1678 (C=O), 1640 (C=C, aromatic), 1580 (C=C, aromatic), 1475 (C-H, alkyl), 1280 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.03-8.01 (2H, m), 7.81-7.80 (2H, m), 7.47-7.23 (4H, m), 7.05 (1H, s), 5.90 (1H), 2.35 (3H, s), 2.11 (1H, broad).

2-[1-Hydroxy-1-(4-toluyl)methyl)-anthracene-1,4,9,10-tetraone (7-i)

Yield: 82%; Mp: 184.8-186.2°C; IR (cm^{-1}): 3500 (OH), 3050 (C-H, aromatic), 2900 (C-H, alkyl), 1680 (C=O), 1640 (C=C, aromatic), 1580 (C=C, aromatic), 1475 (C-H, alkyl), 1280 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.09-7.99 (2H, m), 7.89-7.74 (2H, m), 7.50-7.18 (4H, m), 7.04 (1H, s), 5.90 (1H), 2.57 (1H, broad), 2.31 (3H, s).

2-[1-Hydroxy-1-(4-n-propylphenyl)methyl]-anthracene-1,4,9,10-tetraone (7-j)

Yield: 63%; Mp: 159.1-158.0°C; IR (cm^{-1}): 3500 (OH), 3050 (C-H, aromatic), 2950-2900 (C-H, alkyl), 1680 (C=O), 1640 (C=C, aromatic), 1580 (C=C, aromatic), 1475 (C-H, alkyl), 1280 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.10-8.00 (2H, m), 7.89-7.71 (2H, m), 7.41-7.15 (4H, m), 7.05 (1H, s), 5.94 (1H, s), 2.70 (2H, t, J=8.10 Hz), 1.90-1.40 (2H, m), 0.92 (3H, t, J=8.55 Hz).

2-[1-(4-n-Butylphenyl)-1-hydroxymethyl]-anthracene-1,4,9,10-tetraone (7-k)

Yield: 84%; Mp: 132.9-134.7°C; IR (cm^{-1}): 3490 (OH), 3050 (C-H, aromatic), 2940-2850 (C-H, alkyl), 1685 (C=O), 1640 (C=C, aromatic), 1580 (C=C, aromatic), 1475 (C-H, alkyl), 1280 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.09-8.00 (2H, m), 7.85-7.75 (2H, m), 7.39-7.11 (4H, m), 7.07 (1H, s), 5.91 (1H, s), 2.60 (2H, t, J=7.11 Hz), 1.44-1.27 (4H, m), 0.94 (3H, t, J=8.44 Hz).

2-[1-(4-tert-Butylphenyl)-1-hydroxylmethyl]-anthracene-1,4,9,10-tetraone (7-l)

Yield: 77%; Mp: 149.1-151.5°C; IR (cm^{-1}): 3400 (OH), 3050 (C-H, aromatic), 2900-2800 (C-H, alkyl), 1690 (C=O), 1640 (C=C, aromatic), 1580 (C=C, aromatic), 1475 (C-H, alkyl), 1280 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.06-8.00 (2H, m), 7.85-7.75 (2H, m), 7.47-7.38 (4H, m), 7.08 (1H, s), 5.90 (1H, s), 2.14 (1H, broad), 1.30 (9 H, s).

2-[1-Hydroxy-1-(1-naphtyl)methyl]-anthracene-1,4,9,10-tetraone (7-m)

Yield: 84%; Mp: 157-159°C; IR (cm^{-1}): 3450 (OH), 3150-3045 (C-H, aromatic), 1685 (C=O), 1640 (C=C, aromatic), 1580 (C=C, aromatic), 1280 (C-O); ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 8.09-8.00 (2H, m), 7.89-7.67 (2H, m), 7.58-7.21 (8H, m), 6.79 (1H, s), 2.81 (1H, broad).

RESULTS AND DISCUSSION

Chemistry

The previously reported procedure (Jin *et al.*, 1998a) for the synthesis of 2-(1-hydroxyalkyl)-1,4-dimethoxy-9,10-anthraquinone derivatives was employed to synthesize 2-(1-aryl-1-hydroxymethyl)-DMAQ derivatives (DMAQ ;1,4-dimethoxy-9,10-anthraquinone); to 2-formyl-TMA (TMA, 1,4,9,10-tetramethoxyanthacene) were added various arylmagnesium halides to give 2-(1-aryl-1-hydroxymethyl)-TMA derivatives. Oxidation of these compounds with cerium ammonium nitrate produced 2-(1-aryl-1-hydroxymethyl)-1,4-dimethoxy-9,10-anthraquinone derivatives.

The overall yield of 2-(1-aryl-1-hydroxymethyl)-1,4-dimethoxy-9,10-anthraquinone derivatives ranged from 42.6 to 80.4%. The yield was dependent on electronic property of the aryl group; an electron-withdrawing group lowered the yield as manifested with 2-[1-(4-fluorophenyl)-1-hydroxymethyl]-DMNQ (yield, 66%), while an electron-releasing group enhanced it (yield of 2-(1-hydroxy-1-(4-toluyl)-DMAQ, 80.4%). Besides the electronic effect, a steric effect could be observed; the presence of a bulkier group in the aryl moiety such as *tert*-butyl and naphtyl groups reduced the yield.

For the synthesis of 2-(1-heteroaryl-1-hydroxymethyl)-TMA derivatives, lithium salts of heteroarmatics were used. For instance, lithium thiophen was added to 2-formyl-TMA to produce 2-(1-hydroxy-1-thiophenylmethyl)-TMA in good yield. The CAN oxidation of this resulted in formation of 2-(1-hydroxy-1-thiophenylmethyl)-DMAQ in the yield of 77%.

Demethylation at 1,4-positions of the DMAQ derivatives was carried out with aluminum chloride in nitrobenzene to give 2-(1-heteroaryl-1-hydroxymethyl)-DHAQ derivatives (DHAQ, 1,4-dihydroxy-9,10-anthraquinone derivatives in good yield up to 65%.

A series of 2-aroyl-DMAQ derivatives was obtained by oxidizing 1-OH group of the corresponding 2-(1-aryl-1-hydroxymethyl)-DMAQ derivatives with pyridinium dichromate (PDC). The highest yields (42% up to 70%) were observed with 3 equivalent PDC and a reaction time of 3 hr. The lower equivalence of PDC required longer reaction time. The use of PDC in less than 1.5 mol equivalent rendered the reaction incomplete. An attempt to use manganate dioxide to oxidize 1-OH (Jin *et al.*, 1998a) failed to afford the expected products even at 50 molar equivalent of MnO_2 and even after a reaction time prolonged up to 72 hr. Demethylation at 1,4 positions of the aroyl compounds was carried out under the same conditions described above, giving 2-aroyl DMAQ derivatives with a yields up to 78%.

A series of 2-(1-aryl-1-hydroxymethyl)-ATO derivatives (ATO, anthracene-1,4,9,10-tetraone) was synthesized in average yield of 33-93% by selectively oxidizing 1,4-dihydroxyl groups of the DHAQ derivatives using lead tetraacetate. For higher yield, anhydrous condition was pivotal, since the presence of even a trace of water was sufficient to trigger an autoreduction of anthracene-1,4,9,10-tetraones (7) back to 1,4-dihydroxy-9,10-anthraquinones (Jin *et al.*, 1998b). The presence of a bulky group such as isobutyl lowered the yield.

Cytotoxicity and antitumor activity

2-(1-Aryl-1-hydroxymethyl)-and 2-(1-aryl-1-hydroxymethyl)-1,4-dihydroxy-9,10-anthraquinones(4-a to 4-u)

The cytotoxicity and antitumor activity of 2-(1-aryl-1-hydroxymethyl)-DMAQ derivatives (**3-a to 3-u**) were negligible (ED_{50} >12 μg/ml; data not shown), while their demethylated products, 2-(1-aryl-1-hydroxymethyl)-DHAQ derivatives (**4-a to 4-u**), showed a considerable activity (Table I; ED_{50}, 0.042~11.892 μg/mL). The cytoto-xicity of 2-(1-aryl-1-hydroxymethyl)-DHAQ derivatives (**4-a to 4-u**) is generally greater than that (ED_{50}; 1.9~> 80 μg/ml) of 2-(1-hydroxyalkyl)-1,4-dihydroxy-9,10-anthaquinone derivatives reported previously (Jin *et al*, 1998a). As explained in the previous report (Jin *et al.*, 1998a), the higher cytotoxicity of 2-(1-aryl-1-hydroxymethyl)-DHAQ derivatives might be ascribed to their greater binding to

a cellular nucleophile and an accelerated bioreductive activation.

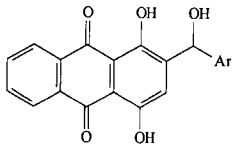
However, the electronic effect could not be correlated to cytotoxicity of the DHAQ derivatives, despite a stronger cytotoxicity and antitumor activity. Rather, a steric factor seemed to be important for the cytotoxicity. For the monochloroaryl-DHAQ derivatives, a sterically crowd-ing substituent at C-2 (**4-c, f**) enhanced cytotoxic activity. For the DHAQ derivatives bearing toluyl or naph-thyl group, a less bulky substituent tended to increase the cytotoxicity as well as the antitumor effect; 2-[1-hydroxy-1-(3-toluyl)-methyl]-DHAQ (**4-i,** ED_{50}, 0.33 μg/ml; T/C, 129%) and 2-[1-hydroxy-1-(2-naphtyl)-methyl]-DHAQ (**4-p**, ED_{50}, 0.025 μg/ml; T/C, 141%) vs. 2-[1-hydroxy-1-(2-toluyl)-methyl]-DHAQ (**4-h**, ED_{50}, 0.82 μg/ml; T/C, 121 %) and 2-[1-hydroxy-1-(1-naphtyl)-methyl]-DHAQ (**4-o**, ED_{50}, 0.32 μg/ml; T/C, 127%). These observations led to a suggestion that a crowded conformation of the aryl side chain may be required for the bioactivity, as reported previously for ar-turmerone derivatives (Baik *et al.*, 1993a, b).

Also, the introduction of a heteroaryl group tended to increase the cytotoxicity; 2-[1-hydroxy-1-(N-phenylsulfonylpyrrol-2-yl)methyl]- and 2-[1-hydroxy-1-(N-phenylsulfonylindol-2-yl)-methyl]-DHAQ (**4-s** and **4-t**) showed a higher cytotoxic activity (ED_{50}, 0.63 and 0.97 μg/ml) than 2-(1-hydroxy-1-phenylmethyl)-DHAQ (**4-a**; ED_{50}, 4.13 μg /ml). This improvement in cytotoxicity could be attributed to the increase in solubility of the hetero-aromatic compounds in aqueous system. Meanwhile, the DHAQ bearing 2-thienyl group, poorly soluble in the medium, showed a weak cytotoxic activity. The intro-duction of a heteroaryl groups as a whole did not improve the T/C value.

2-Aroyl-1,4-dimethoxy- and 2-aroyl-1,4-dihydroxy-9,10-anthraquinones (6-a to 6-q)

While 2-aroyl DMAQ derivatives (**5-a** to **5-q**) showed a negligible cytotoxicity (data not shown), 2-aroyl-DHAQ

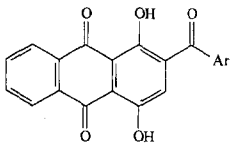
Table I. Cytotoxic and antitumor activity of 2-(1-aryl-1-hydroxymethyl)-1,4-dihydroxy-9,10-anthraquinone derivatives



No	-Ar	ED_{50} against L1210 cell line (μg/ml)	Sarcoma 180	
			μmol/kg/day	T/C (%)
4-a	Phenyl	4.136 ± 0.597	20	109
4-b	4-Fluorophenyl	11.322 ± 0.968		*
4-c	2-chlorophenyl	6.466 ± 1.273		*
4-d	3-chlorophenyl	>20		*
4-e	4-Chlorophenyl	10.445 ± 1.951		*
4-f	2,3-Dichlorophenyl	0.042 ± 0.015	20	138
4-g	3,4-Dichlorophenyl	1.515 ± 0.842	40	<100
			20	119
			10	105
4-h	2-Toluyl	0.823 ± 0.571	20	121
4-i	3-Toluyl	0.330 ± 0.033	20	129
4-*j*	4-Toluyl	2.284 ± 0.358	20	115
4-k	4-Ethylphenyl	11.892 ± 0.797		*
4-l	4-Propylphenyl	11.178 ± 0.896		*
4-m	4-Butylphenyl	7.338 ± 1.619		*
4-n	4-tert-Butylphenyl	3.462 ± 0.231	20	109
4-o	1-Naphtyl	0.325 ± 0.179	20	127
4-p	2-Naphtyl	0.025 ± 0.015	20	141
4-q	4-Methoxyphenyl	7.834 ± 1.375	20	<100
4-r	4-Phenylphenyl	6.218 ± 0.947		*
4-s	N-Phenylsulfonylpyrrol-2-yl	0.635 ± 0.231	20	110
4-t	N-Phenylsulfonylindol-2-yl	0.973 ± 0.697	20	113
4-u	2-Thienyl	5.147 ± 0.695		*

* Not tested

Table II. Cytotoxic and antitumor activity of 2-aroyl-1,4-di-hydroxy-9,10-anthraquinone derivatives



No	-Ar	ED_{50} against L1210 cell line (μg/ml)	Sarcoma 180	
			μmol/kg/day	T/C (%)
6-a	Phenyl	18.652 ± 0.791		*
6-b	4-Fluorophenyl	>20		*
6-c	2-Chlorophenyl	0.512 ± 0.153	40	121
			20	135
			10	105
6-d	3-Chlorophenyl	>20		*
6-e	4-Chlorophenyl	>20		*
6-f	3,4-Dichlorophenyl	>20		*
6-g	2-Toluyl	0.058 ± 0.017	20	137
6-h	3-Toluyl	0.189 ± 0.177	20	128
6-I	4-Toluyl	1.478 ± 0.147	20	119
6-*j*	4-Ethylphenyl	5.076 ± 0.524		*
6-k	4-n-Propylphenyl	>20		*
6-l	4-n-Butylphenyl	8.973 ± 0.107		*
6-m	4-tert-Butylphenyl	1.457 ± 1.399	20	118
6-n	1-Naphtyl	3.998 ± 2.884	20	110
6-o	2-Naphtyl	2.955 ± 0.875	20	123
6-p	4-Methoxyphenyl	>20	20	<100
6-q	4-Phenylphenyl	9.633±1.175		*

* Not tested

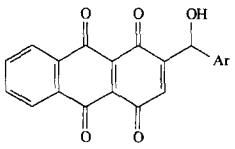
derivatives (**6-q** to **6-q**) exhibited a moderate cytotoxic activity (Table II). The cytotoxicity of the latter was not improved compared to 2-(1-aryl-1-hydroxymethyl)-DHAQ derivatives (**4-a** to **4-q** in Table I). Decrease in the cytotoxicity of the DMAQ derivatives could be explained by low solubility in aqueous system. Contrary to 2-aryl DHAQ derivatives, the 2-aroyl DHAQ bearing 2-toluyl group, for instance 2-(2-toluoylmethyl)-DHAQ (**6-g**, ED_{50}, 0.057 μg/ml; T/C, 137%), exhibited a higher bio-activities than otherwise substituted ones, 2-(3-toluoyl-methyl)-DHAQ (**6-h**, ED_{50}, 0.18 μg/mL; T/C, 128%) and 2-(4-toluoylmethyl)-DHAQ (**6-i**, ED_{50}, 1.47mg/mL; T/C, 119%). The order of the activity among the toluyl isomers; 2-toluyl > 3-toluyl > 4-toluyl. The same effect was observed between 2-(2-chlorobenzoyl)-DHAQ (**6-c**, ED_{50}, 0.51 μg/mL; T/C 135%) and 2-(3-chlorobenzoyl)-DHAQ (**6-d**, ED_{50}, >20 μg/mL; T/C, no activity). Introduction of a naphthyl side chain did not improve the bioactivities of those compounds.

2-[1-Aryl-1-hydroxymethyl)-anthracene-1,4,9,10-tetraones (7-a to 7-m)

Blanz *et al.* (1991) reported that one of the mechanisms for antitumor activity of mitoxantrone was arylation ability of anthracene-1,4,9,10-tetraones, the intermediates produced from its metabolism. Based on this observation, we have synthesized some 2-(1-aryl-1-hydroxymethyl)-ATO (**7-a** to **7-m;** ATO, anthracene-1,4,9,10-tetraone) derivatives and tested their antitumor activity (Table III).

Although the ATO derivatives showed a reduced cytotoxicity, they improved the life prolongation (T/C) of S-180-inoculated mice to a remarkable extent, compared with that of 2-(1-aryl-1-hydroxymethyl)-DHAQ derivatives. The cytotoxicity of the ATO derivatives with a more crowded aromatics showed a better activity; 2-[1-(2-chlorophenyl)-1-hydroxymethyl]-ATO (**7-c**, ED_{50}, 3.34 μg/ml vs. 2-[1-(3-chlorophenyl)-1-hydroxymethyl]-ATO (**7-d**, ED_{50}, 4.87 μg/ml) and 2-[1-(4-chlorophenyl)-1-hydroxyme-thyl]-ATO (**7-b**; ED_{50}, 5.32 mg/mL) and 2-[1-hydroxy-1-(2-toluyl)-methyl)-ATO (**7-g**; ED_{50}, 0.80 μg/ml) vs. 2-[1-hydroxy-1-(3-toluyl)-methyl]-ATO (**7-h**; ED_{50}, 1.53 μg/ml) and 2-[1-hydroxy-1-(4-toluyl)-methyl]-ATO (**7-i**; ED_{50}, 2.32 μg/ml). Despite a relatively low cytotoxic activity of the ATO derivatives, the T/C value was remarkably enhanced. Among the compounds, 2-[1-hydroxy-(4-propyl-phenyl)-methyl]-ATO (**7-j**), showing the lowest cytotoxic activity

Table III. Cytotoxic and anti-tumor activity of 2-(1-aryl-1-hydroxymethyl)-anthracene-1,4,9,10-tetraone derivatives



Compd.	Aryl	ED_{50} against L1210 cell line(μg/ml)	Sarcoma 180		
			μmol/kg/day	T/C (%)	No.of survivors[1]
7-a	Phenyl	4.917 ± 0.204	20	140	1/7
7-b	4-Fluorophenyl	6.231 ± 0.515	20	157	2/7
7-c	2-Chlorophenyl	3.340 ± 0.262	20	170	0/7
7-d	3-Chlorophenyl	4.876 ± 0.656	20	129	3/7
7-e	4-Chlorophenyl	5.327 ± 0.325	20	134	0/7
7-f	3,4-Dichlorophenyl	6.492 ± 0.975	20	126[2]	1/7
7-g	2-Toluyl	0.803 ± 0.067	20	128	1/7
7-h	3-Toluyl	1.532 ± 0.3895	20	151	1/7
7-I	4-Toluyl	2.320 ± 0.340	20	126	1/7
7-*j*	4-n-Propylphenyl	10.257 ± 1.369	8	136	0/7
			20	218	5/7
			32	127	0/7
7-k	4-n-Butylphenyl	9.058 ± 0.872	20	147	2/7
7-l	4-tert-Butylphenyl	6.541 ± 0.346	20	131	1/7
7-m	1-naphtyl	4.120 ± 0.647	20	125[2]	1/7

[1] Number of mice that survived 50 days or longer.
[2] One mouse died of toxicity was excluded from T/C calculation.

(ED_{50}, 10.2 μg/ml), exhibited the highest T/C value of 216 %. Moreover, this compound exhibited a survival rate up to 5/7 on 50th day of the administration. This result suggests the possibility that the ATO **7-j** may be transformed *in vivo* into active metabolite(s) which might be responsible for the high antitumor activity.

One of the mechanisms for the bioactivity of ATO is supposed to be the so-called bioreductive activation of 2-[1-hydroxy-(4-propylphenyl)-methyl]-ATO (**7-j**), which was discussed for 2-(1-hydroxyalkyl)-ATO derivatives (Jin et *al.*, 1998a, b). According to the mechanism, 2-(1-Aryl-1-hydroxymethyl)-ATO derivatives undergoes the bioreductive activation more easily than 2-(1-hydroxyalkyl)-ATO derivatives, because 1-OH of the former anthracenetetraones should be eliminated to form the reactive quinone methide more easily than 2-(1-hydroxyalkyl)-ATO derivatives. The reactive quinone methide then alkylates cellular nucleophiles leading to cell death.

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