Method 1

A solution of 1,1′-carbonyldiimidazole (CDI) (0.3 mmol) in THF (2 ml) was added to a stirred solution of acid (0.3 mmol) in tetrahydrofuran (THF) (3 ml). After stirring the mixture for 3 hours at room temperature, a solution of quinone alcohol (0.2 mmol) in THF (5 ml) was added. The mixture was stirred for 7 hours at room temperature, quenched with saturated ammonium chloride solution (30 ml) and extracted with dichloromethane (3 x 30 ml). The combined organic layers were washed with brine and water, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography.

Method 2

A solution of naphthoquinone alcohol (0.2 mmol) in dry dichloromethane (2 ml) was added to a stirred solution of acid (0.26 mmol) and 4-dimethylaminopyridine(DMAP) (0.06 mmol) in dry dichloromethane (2 ml). The reaction mixture was stirred at room temperature for 5 minutes, a solution of 1,3-dicyclohexylcarbodiimide (DCC) (0.26 mmol) in dry dichloromethane (3 ml) added and the mixture stirred overnight at room temperature. The precipitate of dicyclohexylurea was filtered off and the organic solution was washed with saturated ammonium chloride solution (2 x 10 ml) and water, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography.

Naphthalene-2-carboxylic acid-3-(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-propyl ester (115)

Flash column chromatography eluting with 17:3 v/v hexane-ethyl acetate provided the product **115** (73% from method 1) as a yellow amorphous powder, m.p. 120-121°C.

FTIR (KBr, cm^{-1}): 3362 (OH), 1714 (C=O), 1645 (C=O), 1590 (C=C), 1278 (C-O), 1226(C-O)

^{1}**H NMR** ($CDCl_3$, 400 MHz) δ: 2.05 (m, 2H, CH_2), 2.77 (t, 2H, J=7.3 Hz, CH_2), 4.38 (t, 2H, J=6.3 Hz, OCH_2), 7.29 (s, 2H, OH), 7.40-7.55 (m, 3H, ArH), 7.61(dt, 1H,

J=7.6 Hz, J=1.4 Hz, ArH), 7.75 (m, 3H, ArH), 7.92 (m, 2H, ArH), 8.00 (m, 1H, ArH), 8.46 (s, 1H, ArH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 20.9 (CH_2), 27.8 (CH_2), 65.5 (OCH_2), 125.8, 126.7, 127.1, 127.4, 128.3, 128.7, 128.8, 130.0, 131.6, 133.5, 135.5 (CH arom), 123.9, 127.0, 128.2, 133.0, 133.5, 136.1, 154.0 (C), 167.4 (OC=O), 181.8 (C=O),
185.2 (C=O)

MS (EI), m/z (%) : 386 (M^+, 4), 214 (63), 155 (100), 127 (60)

HRMS calcd for $C_{24}H_{18}O_5$ [M+H] 387.1232, found 387.1235

1-Methoxy-naphthalene-2-carboxylic acid - 3- (3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-propyl ester (116)

Flash column chromatography eluting with 9:1 v/v hexane-ethyl acetate provided the product **116** (77% from method 1 and 53% from method 2) as a yellow amorphous powder, m.p. 125-126°C.

FTIR (KBr, cm^{-1}): 3356 (OH), 1704 (C=O), 1643 (C=O), 1589 (C=C), 1276(C-O), 1132 (C-O)

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.15 (m, 2H, CH_2), 2.85 (t, 2H, J=7.3 Hz, CH_2), 4.08 (s, 3H, OCH_3), 4.47 (t, 2H, J=6.3 Hz, OCH_2), 7.40 (s, 1H, OH), 7.58 (m, 4H, ArH), 7.70 (dt, 1H, J=7.5 Hz, J=1.3 Hz, ArH), 7.83 (d, 1H, J=7.5 Hz, ArH), 7.86(d, 1H, J=8.6 Hz, ArH), 8.02 (dd, 1H, J=7.6 Hz, J=1.3 Hz, ArH), 8.08 (dd, 1H, J=7.7 Hz, J=1.3 Hz, ArH), 8.24 (dd, 1H, J=7.5 Hz, J=1.5 Hz, ArH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.0 (CH_2), 27.8 (CH_2), 64.1 (OCH_3), 65.6 (OCH_2), 124.1, 124.3, 126.7, 127.0, 127.3 (2C), 128.4, 128.8, 133.4, 135.4 (CH arom), 120.0, 123.9, 129.1, 130.0, 133.4, 137.3, 153.9, 158.7 (C), 166.8 (OC=O),
181.8 (C=O), 185.2 (C=O)

MS (EI), m/z (%) : 416 (M^+, 7), 214 (11), 185 (100), 127 (32), 170 (16)

HRMS calcd for $C_{25}H_{20}O_6$ [M+Na] 439.1158, found 439.1150

1,4-Dimethoxy-naphthalene-2-carboxylic acid – 3 - (3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-propyl ester (117)

Flash column chromatography eluting with 17:3 v/v hexane-ethyl acetate provided the product **117** (58% from method 1) as a yellow amorphous powder, m.p. 146-147°C.

FTIR (KBr, cm^{-1}): 3372 (OH), 1727 (C=O), 1650 (C=O), 1593 (C=C), 1235(C-O), 1097 (C-O)

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.10 (m, 2H, CH_2), 2.80 (t, 2H, J=7.3 Hz, CH_2), 3.98 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 4.44 (t, 2H, J=6.2 Hz, OCH_2), 7.13 (s, 1H, ArH), 7.38 (s, 1H, OH), 7.55 (m, 3H, ArH), 7.64 (dt, 1H, J=7.5 Hz, J=1.1 Hz, ArH), 7.95 (d, 1H, J=6.9 Hz, ArH), 8.02 (d, 1H, J=7.2 Hz, ArH), 8.12 (m, 1H, ArH),
8.19 (m, 1H, ArH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.0 (CH_2), 27.8 (CH_2), 56.3 (OCH_3), 64.0 (OCH_3), 65.6 (OCH_2), 104.2, 122.9, 124.1, 126.6, 127.2, 127.5, 128.2, 133.4, 135.3(CH arom), 119.6, 123.9, 129.3, 129.7, 129.9, 133.4, 151.9, 152.5, 154.0 (C),
167.0 (OC=O), 181.8 (C=O), 185.2 (C=O)

MS (EI), m/z (%) : 446 (M^+, 40), 232 (100), 215 (60), 157 (27), 129 (48)

HRMS calcd for $C_{26}H_{22}O_7$ [M+Na] 469.1263, found 469.1262

Naphthalene-2-carboxylic acid-3(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2- yl)-2-methyl propyl ester (118)

Flash column chromatography eluting with 17:3 v/v hexane-ethyl acetate provided the product **118** (83% from method 1) as a yellow amorphous powder, m.p. 164-166°C.

FTIR (KBr, cm^{-1}): 3363 (OH), 1715 (C=O), 1649 (C=O), 1589 (C=C), 1275(C-O), 1224 (C-O)

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.16 (d, 3H, J=6.9 Hz, CH_3), 2.40 (m, 1H, CH), 2.60 and 2.75 (2xm, 2x1H, CH_2), 4.20 (m, 2H, OCH_2), 7.28 (s, 1H, OH), 7.40-7.60 (m, 4H, ArH), 7.70 (d, 1H, J=8.7 Hz, ArH), 7.75 (m, 2H, ArH), 7.89 (m, 2H, ArH), 7.98 (m, 1H, ArH), 8.42 (s, 1H, ArH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 18.2 (CH_3), 28.5 (CH_2), 33.2 (CH), 70.4 (OCH_2), 125.8, 126.7, 127.1, 127.4, 128.3, 128.7, 128.75, 130.0, 131.5, 133.4, 135.4(CH arom), 123.3, 127.1, 128.2, 133.0, 133.4, 136.0, 154.3 (C), 167.3 (OC=O), 181.7 (C=O), 185.3 (C=O)

MS (EI), m/z (%): 400 (M^+, 2), 228 (44), 172 (55), 155 (100), 127 (98)

HRMS calcd for $C_{25}H_{20}O_5$ [M+H] 401.1389, found 401.1385

1-Methoxy-naphthalene-2-carboxylic acid – 3 -(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-2-methyl-propyl ester (119)

Flash column chromatography eluting with 7:1 v/v hexane-ethyl acetate afforded the product **119** (73% from method 1) as a yellow amorphous powder, m.p. 85-86°C.

FTIR (KBr, cm^{-1}): 3347 (OH), 1728 (C=O), 1646 (C=O), 1589 (C=C), 1276(C-O), 1225 (C-O)

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.16 (d, 3H, J=6.8 Hz, CH_3), 2.49 (m, 1H, CH), 2.69 and 2.84 (2xm, 2x1H, CH_2), 4.05 (s, 3H, OCH_3), 4.30 (m, 2H, OCH_2), 7.43(s, 1H, OH), 7.51 (d, 1H, J=8.8 Hz, ArH), 7.56 (m, 3H, ArH), 7.64 (dt, 1H, J=1.4 Hz, J=7.6 Hz, ArH), 7.81 (d, 1H, J=5.9 Hz, ArH), 7.82 (d, 1H, J=8.8 Hz, ArH), 7.96 (dd, 1H, J=7.6 Hz, J=1.3 Hz, ArH), 8.04 (dd, 1H, J=7.6 Hz, J=1.3 Hz, ArH), 8.21 (m, 1H, ArH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 18.2 (CH_3), 28.5 (CH_2), 33.1 (CH), 64.0(OCH_3), 70.5 (OCH_2), 124.1, 124.2, 126.6, 127.0, 127.3 (2C), 128.4, 128.8, 133.3, 135.3 (CH arom), 120.0, 123.2, 129.1, 130.0, 133.4, 137.3, 154.3, 158.7 (C),
166.7 (OC=O), 181.8 (C=O), 185.4 (C=O)

MS (EI), m/z (%) : 430 (M^+, 16), 228 (14), 185 (100), 170 (16), 127 (21)

HRMS calcd for $C_{26}H_{22}O_6$ [M+Na] 453.1314, found 453.1308

1,4-Dimethoxy-naphthalene-2-carboxylic acid – 3 - (3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-2-methyl-propyl ester (120)

Flash column chromatography eluting with 17:3 v/v hexane-ethyl acetate afforded the product **120** (73% from method 1) as a yellow amorphous powder, m.p. 113-115°C.

FTIR (KBr, cm^{-1}): 3295 (OH), 1727 (C=O), 1648 (C=O), 1592 (C=C), 1276 (C-O), 1223 (C-O)

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.10 (d, 3H, J=6.8 Hz, CH_3), 2.46 (m,1H, CH), 2.65 and 2.80 (m, 2x1H, CH_2), 3.94 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.27 (m, 2H, OCH_2), 7.09 (s, 1H, ArH), 7.38 (s, 1H, OH), 7.44-7.60 (m, 4H, ArH), 7.87 (d, 1H, J=7.5 Hz, ArH), 7.97 (d, 1H, J=7.2 Hz, ArH), 8.05 (m, 1H, ArH), 8.16 (m, 1H, ArH) ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 18.2 (CH_3), 28.5 (CH_2), 33.1 (CH), 56.3(OCH_3), 64.0 (OCH_3), 70.6 (OCH_2), 104.2, 122.8, 124.1, 126.5, 127.1, 127.5, 128.2, 133.3, 135.2 (CH arom), 119.5, 123.2, 129.3, 129.7, 129.9, 133.3, 151.8, 152.4, 154.2(C), 166.9 (OC=O), 181.8 (C=O), 185.4 (C=O)

MS (EI), m/z (%) : 460 (M^+, 41), 232 (100), 215 (69), 159 (31)

Anal. Calcd for $C_{27}H_{24}O_7$: C, 70.42; H, 5.25. Found : C, 70.49; H, 5.45%

Naphthalene-2-carboxylic acid -3-(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-2,2-dimethyl-propyl ester (121)

Flash column chromatography eluting with 9:1 v/v hexane - ethyl acetate afforded the product **121** (87% from method 1 and 73% from method 2) as a yellow amorphous powder, m.p. 114-115°C.

FTIR (KBr, cm^{-1}): 3352 (OH), 1711 (C=O), 1665 (C=O), 1589 (C=C), 1273 (C-O), 1224 (C-O)

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.10 (s, 6H, 2xCH_3), 2.75 (s, 2H, CH_2), 4.10 (s, 2H, OCH_2), 7.40 (s, 1H, OH), 7.50 (m, 4H, ArH), 7.70 (d, 1H, J=8.6 Hz, ArH), 7.76 (m, 2H, ArH), 7.92 (m, 3H, ArH), 8.43 (s, 1H, ArH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 26.1 (2xCH_3), 33.1 (CH_2), 37.8 (C), 74.0(OCH_2), 125.8, 126.6, 127.1, 127.5, 128.3, 128.66, 128.7, 129.9, 131.5, 133.3, 135.4 (CH arom), 122.5, 128.3, 129.9, 133.0, 133.5, 136.0, 154.9 (C), 167.2 (OC=O), 181.8 (C=O), 185.5 (C=O)

MS (EI), m/z (%): 414 (M^+, 5), 242 (12), 155(100), 127 (52)

HRMS calcd for $C_{26}H_{22}O_5$ [M+H] 415.1545, found 415.1550

1-Methoxy-naphthalene-2-carboxylic acid – 3 -(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-2,2-dimethyl-propyl ester (122)

Flash column chromatography eluting with 17:3 v/v hexane - ethyl acetate afforded the product **122** (82% from method 1 and 75% from method 2) as a yellow oil.

FTIR (neat, cm^{-1}): 3363 (OH), 1712 (C=O), 1650 (C=O), 1593 (C=C), 1280 (C-O), 1084 (C-O)

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.15 (s, 6H, 2xCH_3), 2.80 (s, 2H, CH_2), 4.05 (s, 3H, OCH_3), 4.20 (s, 2H, OCH_2), 7.49 (s, 1H, OH), 7.45-7.60 (m, 5H, ArH), 7.81(m, 2H, ArH), 7.93 (dd, 1H, J=7.6 Hz, J=0.9 Hz, ArH), 7.95 (dd, 1H, J=7.6 Hz, J=0.9 Hz, ArH), 8.19 (dd, 1H, J=7.9 Hz, J=1.0 Hz, ArH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 26.1 (2xCH_3), 33.1 (CH_2), 37.7 (C), 64.1(OCH_3), 74.2 (OCH_2), 124.1, 124.2, 126.4, 127.0, 127.2, 127.3, 128.4, 128.8, 133.1, 135.2 (CH arom), 120.0, 122.4, 129.0, 129.8, 133.4, 137.3, 154.7, 158.7 (C),
166.7 (OC=O), 181.8 (C=O), 185.6 (C=O)

MS (EI), m/z (%): 444 (M^+, 5), 185 (100), 170 (21), 127 (30)

HRMS calcd for $C_{27}H_{24}O_6$ [M+Na] 467.1471, found 467.1471

Rhinacanthin-Q (14)

Flash column chromatography eluting with 17:3 v/v hexane - ethyl acetate afforded the product (**14**) (71% from method 1) as an orange amorphous powder; m.p. 117-118°C (Wu, 1998, m.p. 116-117°C).

FTIR (KBr, cm^{-1}): 3374 (OH), 1705 (C=O), 1652 (C=O), 1595 (C=C), 1276 (C-O), 1222 (C-O)

FTIR (KBr, cm^{-1}): 3374 (OH), 1705 (C=O), 1652 (C=O), 1595 (C=C), 1276 (C-O), 1222 (C-O)

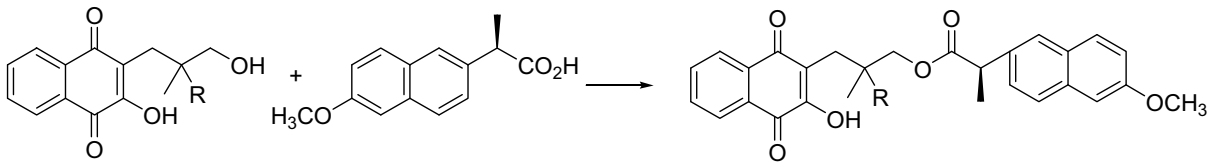
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.18 (s, 6H, 2xCH_3), 2.80 (s, 2H, CH_2), 3.98 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 4.20 (s, 2H, OCH_2), 7.17 (s, 1H, ArH), 7.41 (t, 1H, J=7.6 Hz, ArH), 7.49 (s, 1H, OH), 7.50 (t, 1H, J=7.6 Hz, ArH), 7.58 (m, 2H, ArH), 7.88 (d, 1H, J=7.6 Hz, ArH), 7.91 (d, 1H, J=7.6 Hz, ArH), 8.10 (d, 1H, J=8.7 Hz, ArH), 8.20 (d, 1H, J=8.0 Hz, ArH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 26.2 (2xCH_3), 33.1 (CH_2), 37.7 (C), 56.2 (OCH_3), 64.0 (OCH_3), 74.4 (OCH_2), 104.2, 122.8, 124.1, 126.3, 127.1, 127.5, 128.2, 133.0, 135.0 (CH arom), 119.5, 122.5, 129.3, 129.6, 129.7, 133.4, 151.8, 152.5, 154.7 (C), 166.9 (OC=O), 181.8 (C=O), 185.6 (C=O)

MS (EI), m/z (%): 474 (M^+,65), 215 (100), 187 (32), 159 (40), 129 (57)

HRMS calcd for C28H26O7 [M+H] 475.1757, found 475.1760

General procedure for synthesis of naphthoquinone esters (123, 124)



(**77**): R =H
(**78**): R =Me

(**116**)

(**123**): R =H
(**124**): R =Me

A solution of 1,1′ carbonyldiimidazole (CDI) (0.3 mmol) in THF (2 ml) was added to a stirred solution of acid (0.3 mmol) in tetrahydrofuran (THF) (3 ml). After stirring the mixture for 3 hours at room temperature, a solution of quinone alcohol (0.2 mmol) in THF (5 ml) was added and stirring continued for 7 hours at room temperature. The reaction mixture was quenched with saturated ammonium chloride solution (30 ml) and extracted with dichloromethane (3 x 30 ml). The combined organic phases were washed with brine and water, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography.

2-(6-Methoxy-naphthalen-2-yl)-propionic acid – 3 - (3-hydroxy-1,4-dioxo-1,4-dihydro naphthalen-2-yl)-2-methyl-propyl ester (123)

Flash column chromatography eluting with 9:1 v/v hexane - ethyl acetate afforded the product **123** (86%) as a yellow amorphous powder, m.p. 117°C.

FTIR (KBr, cm^{-1}): 3365 (OH), 1731 (C=O), 1646 (C=O), 1589 (C=C), 1225 (C-O), 1181 (C-O)

^{1}**H NMR** ($CDCl_3$, 400 MHz) δ: 0.92 (d, 3H, J=6.8 Hz, CH_3), 1.60 (d, 3H, J=7.2 Hz, CH_3), 2.20 (m, 1H, CH), 2.51 and 2.64 (2xm, 2x1H, CH_2), 3.87 (q, 1H, J=7.2 Hz, CH), 3.92 (s, 3H, OCH_3), 4.00 (m, 2H, OCH_2), 7.13 (m, 2H, ArH), 7.32 (s, 1H, OH), 7.43 (dd, 1H, J=8.5 Hz, J=1.9 Hz, ArH), 7.69 (m, 4H, ArH), 7.77 (dt, 1H, J=7.5 Hz, J=1.4 Hz, ArH), 8.08 (m, 1H, ArH), 8.12 (m, 1H, ArH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 17.7 (CH_3), 19.1 (CH_3) 27.8 (CH_2), 33.1 (CH), 46.1 (CH), 55.9 (OCH_3), 69.8 (OCH_2), 106.2, 119.5, 126.6, 126.7, 127.0, 127.4, 127.6, 129.9, 133.5, 135.5 (CH arom), 123.0, 129.5, 130.0, 133.4, 134.3, 136.3, 154.3, 158.2 (C), 175.3 (OC=O), 181.7 (C=O), 185.2 (C=O)

MS (EI), m/z (%): 458 (M^+ 13), 212 (43), 185 (100), 170 (29), 141 (30)

HRMS Calcd for C28H26O6 [M+NH4] 476.2068, found 476.2071

2-(6-Methoxy-naphthalen-2-yl)-propionic acid – 3 - (3-hydroxy-1,4-dioxo-1,4-dihydro naphthalen-2-yl)-2,2-dimethyl propyl ester (124)

Flash column chromatography eluting with 9:1 v/v hexane - ethyl acetate afforded the product **124** (94%) as a yellow amorphous powder, m.p. 107-108°C.

FTIR (KBr, cm^{-1}): 3373 (OH), 1738 (C=O), 1645 (C=O), 1602 (C=C), 1270 (C-O), 1169 (C-O)

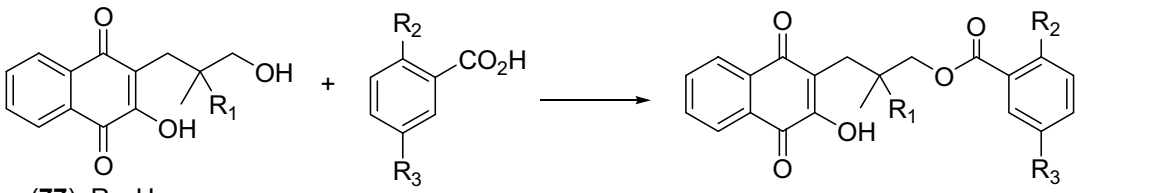
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.90 (s, 3H, CH_3), 0.91 (s, 3H, CH_3), 1.60 (d, 3H, J=7.2 Hz, $\underline{CH_3}$-CH), 2.62 (s, 2H, CH_2), 3.85 (m, 1H, CH), 3.88 (s, 2H, OCH_2), 3.92 (s, 3H, OCH_3), 7.14 (m, 2H, ArH), 7.35 (s, 1H, OH), 7.41 (dd, 1H, J= 8.5 Hz, J=1.8 Hz, ArH), 7.64-7.79 (m, 5H, ArH), 8.08 (dd, 1H, J=1.0 Hz, J=7.8 Hz, ArH), 8.11(dd, 1H, J=1.0 Hz, J=7.7 Hz, ArH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 19.0 (CH_3), 25.5 (CH_3) 25.6 (CH_3), 32.5 (CH_2), 37.6 (C), 46.3 (CH), 55.9 (OCH_3), 73.5 (OCH_2), 106.2, 119.5, 126.6, 126.7, 127.0, 127.6 (2C), 129.9, 133.5, 135.6 (CH arom), 122.2, 129.5, 129.9, 133.5, 134.2, 136.3, 154.8, 158.2 (C), 175.2 (OC=O), 181.7 (C=O), 185.4 (C=O)

MS (EI), m/z (%): 472 (M^+ 16), 212 (52), 185 (100), 69 (59)

HRMS Calcd for C29H28O6 [M+NH4] 490.2224, found 490.2221

General procedure for synthesis of rhinacanthin-M (6) and esters (125-127, 128, 129)



(**77**): R_1=H
(**78**): R_1=Me

(**104**): R_2=R_3=H
(**107**): R_2=OMe, R_3=H
(**115**): R_2=R_3=OMe

(**125**): R_1=R_2=R_3=R_4=H
(**126**): R_1=R_3=H, R_2=OMe
(**127**): R_1=H, R_2=R_3=OMe
(**6**): R_1=Me, R_2=R_3=H
(**128**): R_1=Me,R_2=OMe, R_3=H
(**129**): R_1=Me,R_2=R_3=OMe

Method 1

A solution of 1,1′-carbonyldiimidazole (CDI) (0.3 mmol) in THF (2 ml) was added to a stirred solution of acid (0.3 mmol) in tetrahydrofuran (THF) (3 ml). After stirring the mixture for 3 hours at room temperature, a solution of quinone alcohol (0.2 mmol) in THF 5 ml was added and stirring continued for 7 hours at room temperature. The reaction mixture was quenched with saturated ammonium chloride solution (30 ml) and extracted with dichloromethane (3 x 30 ml). The combined organic phases were washed with brine and water, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography.

Method 2

A solution of naphthoquinone alcohol (0.2 mmol) in dry dichloromethane (2 ml) was added to a stirred solution of acid (0.26 mmol) and 4-dimethylaminopyridine(DMAP) (0.06 mmol) in dry dichloromethane (2 ml). The reaction mixture was stirred at room temperature for 5 minutes and then a solution of 1,3-dicyclohexylcarbodiimide (DCC) (0.26 mmol) in dry dichloromethane (3 ml) was added and stirring continued overnight at room temperature. The precipitate of dicyclohexylurea was filtered off and the filtrate washed with saturated ammonium chloride solution (2 x 10 ml) and water, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography.

Benzoic acid – 3 - (3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-2-methylpropyl ester (125)

Flash column chromatography eluting with 9:1 v/v hexane - ethyl acetate afforded the product **125** (69% from method 2) as a yellow amorphous powder; m.p. 144-145°C.

FTIR (KBr, cm^{-1}): 3351 (OH), 1719 (C=O), 1651 (C=O), 1589 (C=C), 1276 (C-O)

^{1}**H NMR** ($CDCl_3$, 400 MHz) δ: 1.12 (d, 3H, J=6.8 Hz, CH_3), 2.44 (m, 1H, CH), 2.67 and 2.82 (2xm, 2x1H, CH_2), 4.25 (m, 2H, OCH_2), 7.38 (m, 2H, ArH), 7.40(br s, 1H, OH), 7.52 (m, 1H, ArH), 7.69 (dt, 1H, J=7.6 Hz, J=1.6 Hz, ArH), 7.76 (dt, 1H, J=7.6 Hz, J=1.6 Hz, ArH), 8.01 (m, 2H, ArH), 8.07 (dd,1H, J=7.6 Hz, J=1.6 Hz, ArH), 8.12 (dd, 1H, J=7.6 Hz, J=1.6 Hz, ArH)

^{13}**C NMR** ($CDCl_3$, 100 MHz) δ: 18.1 (CH_3), 28.2 (CH) 33.2 (CH_2), 70.2 (OCH_2), 126.7, 127.5, 128.9 (2C), 130.1 (2C), 133.4, 133.6, 135.5 (CH arom), 123.2, 130.0, 130.9, 133.5, 154.3 (C), 167.2 (OC=O), 181.8 (C=O), 185.3 (C=O)

MS (EI), m/z (%): 350 (M^+, 0.5), 228 (32), 213 (17), 105 (100), 77 (80)

HRMS Calcd for $C_{21}H_{18}O_5$ [M+Na] 373.1052, found 373.1056

2-Methoxy-benzoic acid-3-(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-2-methyl-propyl ester (126)

Flash column chromatography eluting with 22:3 v/v hexane - ethyl acetate afforded the product **126** (93% from method 2) as a yellow amorphous powder, m.p. 109-110°C.

FTIR (KBr, cm^{-1}): 3350 (OH), 1730 (C=O), 1657 (C=O), 1242 (C-O), 1085 (C-O)

^{1}**H NMR** (CDCl3, 400 MHz) δ: 1.10 (d, 3H, J=6.8 Hz, CH3), 2.40 (m, 1H, CH), 2.67 and 2.80 (2xm, 2x1H, CH2), 3.90 (s, 3H, OCH3), 4.22 (d, 2H, J=6.0 Hz, OCH2), 6.92 (m, 2H, ArH), 7.41 (s, 1H, OH), 7.43 (m, 1H, ArH), 7.69 (dt, 1H, J=7.5 Hz, J=1.0 Hz,

ArH), 7.75 (dt, 1H, J=7.5 Hz, J=1.0 Hz, ArH), 7.81 (dd, 1H, J=7.6 Hz, J=1.6 Hz, ArH), 8.06 (d, 1H, J=7.6 Hz, ArH), 8.11 (d, 1H, J=7.5 Hz, ArH)

^{13}**C NMR** (CDCl3, 100 MHz) δ: 18.0 (CH3), 28.2 (CH) 33.1 (CH2), 56.5 (OCH3), 70.0 (OCH2), 112.5, 120.6, 126.7, 127.4, 132.3, 133.5, 134.0, 135.5 (CH arom), 120.7, 123.3, 130.0, 133.47, 154.3, 159.8 (C), 166.8 (OC=O), 181.8 (C=O),
185.3 (C=O)

MS (EI), m/z (%): 380 (M^+, 0.5), 228 (12), 135 (100), 92 (18), 77 (82)

HRMS calcd for C22H20O6 [M+Na] 403.1158, found 403.1158

2,5-Dimethoxy-benzoic acid – 3 -(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2yl)-2-methyl propyl ester (127)

Flash column chromatography eluting with 4:1 v/v hexane - ethyl acetate afforded the product **127** (26% from method 1 and 69% from method 2) as a yellow amorphous powder, m.p. 144-145°C.

FTIR (KBr, cm^{-1}): 3343 (OH), 1728 (C=O), 1643 (C=O), 1585 (C=C), 1277 (C-O), 1216 (C-O)

^{1}**H NMR** ($CDCl_3$, 400 MHz) δ: 1.10 (d, 3H, J=6.8 Hz, CH_3), 2.40 (m, 1H, CH), 2.66 and 2.80 (2xm, 2x1H, CH_2), 3.80 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.22(d, 2H, J=6.0 Hz, OCH_2), 6.87 (d, 1H, J=9.0 Hz, ArH), 6.99 (dd, 1H, J=9.0 Hz, J=3.2 Hz, ArH), 7.36 (d, 1H, J=3.2 Hz, ArH), 7.40 (s, 1H, OH), 7.69 (dt, 1H, J=7.5 Hz, J=1.4 Hz, ArH), 7.75 (dt, 1H, J=7.5 Hz, J=1.4 Hz, ArH), 8.06 (dd, 1H, J=7.6 Hz, J=0.8 Hz, ArH), 8.10 (dd, 1H, J=7.6 Hz, J=0.73 Hz, ArH)

^{13}**C NMR** ($CDCl_3$, 100 MHz) δ: 18.0 (CH_3), 28.2 (CH) 33.1 (CH_2), 56.4 (OCH_3), 57.2 (OCH_3), 70.1 (OCH_2), 114.3, 116.6, 119.9, 126.7, 127.4, 133.5, 135.5 (CH arom), 121.2, 123.3, 130.0, 133.5, 153.5, 154.1, 154.3 (C), 166.6 (OC=O), 181.8 (C=O), 185.3 (C=O)

MS (EI), m/z (%): 410 (M^+, 17), 228 (20), 165 (100), 107 (20), 77 (43)

HRMS calcd for $C_{23}H_{22}O_7$ [M+Na] 433.1263, found 433.1279

Rhinacanthin-M (6)

Flash column chromatography eluting with 9:1 v/v hexane - ethyl acetate afforded the product **6** (51% from method 1 and 91% from method 2) as a yellow amorphous powder, m.p. 100-101°C (Wu, 1998).

FTIR (KBr, cm^{-1}): 3240 (OH), 1719 (C=O), 1639 (C=O), 1586 (C=C), 1271 (C-O)

^{1}**H NMR** ($CDCl_3$, 400 MHz) δ: 1.10 (s, 6H, 2xCH_3), 2.80 (s, 2H, CH_2), 4.10 (s, 2H, OCH_2), 7.37 (m, 2H, ArH), 7.47 (br s, 1H, OH), 7.51 (m, 1H, ArH), 7.68 (dt, 1H, J=7.6 Hz, J=1.6 Hz, ArH), 7.73 (dt, 1H, J=7.6 Hz, J=1.6 Hz, ArH), 8.01 (m, 2H, ArH), 8.08(m, 2H, ArH)

^{13}**C NMR** ($CDCl_3$, 100 MHz) δ: 25.9 (2xCH_3), 32.8 (CH_2), 37.7 (C), 73.8 (OCH_2), 126.7, 127.6, 128.9 (2C), 130.1 (2C), 133.4, 133.5, 135.5 (CH arom), 122.3, 129.9, 131.0, 133.5, 154.9 (C), 167.1 (OC=O), 181.8 (C=O), 185.5 (C=O)

MS (EI), m/z (%): 364 (M^+, 3), 242 (9), 105 (100), 77 (45)

HRMS calcd for $C_{22}H_{20}O_5$ [M+Na] 387.1208, found 387.1200

2-Methoxy-benzoic acid – 3 -(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)2,2-dimethyl-propyl ester (128)

Flash column chromatography eluting with 22:3 v/v hexane - ethyl acetate afforded the product **128** (98% from method 2) as a yellow amorphous powder, m.p. 122-123°C.

FTIR (KBr, cm^{-1}): 3243 (OH), 1687 (C=O), 1640 (C=O), 1590 (C=C), 1303 (C-O), 1215 (C-O)

^{1}**H NMR** (CDCl3, 400 MHz) δ: 1.10 (s, 6H, 2xCH3), 2.78 (s, 2H, CH2), 3.86(s, 3H, OCH3), 4.09 (s, 2H, OCH2), 6.90 (m, 2H, ArH), 7.41 (m ,1H, ArH), 7.50 (br s, 1H, OH), 7.66 (dt, 1H, J=7.5 Hz, J=1.5 Hz, ArH), 7.70 (dt, 1H, J=7.5 Hz, J=1.5 Hz, ArH), 7.82 (dd, 1H, J=7.7 Hz, J=1.8 Hz, ArH), 8.05 (m, 2H, ArH)

^{13}C NMR (CDCl3, 100 MHz) δ: 25.9 (2xCH3), 32.9 (CH2), 37.7 (C), 56.4 (OCH3), 73.8 (OCH2), 112.5, 120.6, 126.6, 127.6, 132.4, 133.4, 134.0, 135.4 (CH arom), 120.7, 122.5, 129.9, 133.5, 154.8, 159.8 (C), 166.9 (OC=O), 181.8 (C=O), 185.5 (C=O)

MS (EI), m/z (%): 394 (M^+, 0.4), 242 (6), 135 (100), 92 (12), 77 (41)

HRMS Calcd for C23H22O6 [M+Na] 417.1314, found 417.1313

2,5-Dimethoxy-benzoic acid – 3 -(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2yl)-2,2-dimethyl-propyl ester (129)

Flash column chromatography eluting with 17:3 v/v hexane - ethyl acetate afforded the product **129** (24% from method 1 and 92% from method 2) as a yellow amorphous powder, m.p. 109-110°C.

FTIR (KBr, cm^{-1}): 3269 (OH), 1673 (C=O), 1500 (C=C), 1277 (C-O), 1219(C-O)

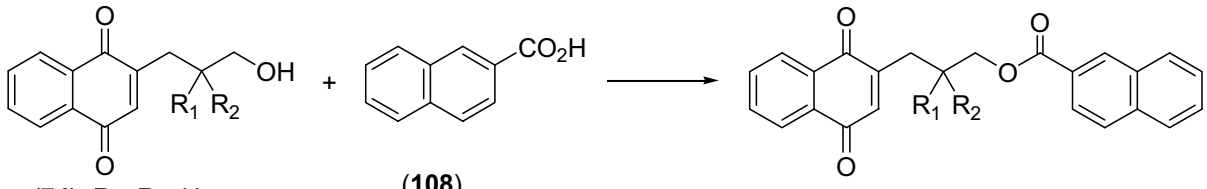
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.10 (s, 6H, 2xCH_3), 2.78 (s, 2H, CH_2), 3.78(s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.08 (s, 2H, OCH_2), 6.82 (d, 1H, J=9.0 Hz, ArH), 6.97 (dd, 1H, J=9.0 Hz, J=3.2 Hz, ArH), 7.39 (d, 1H, J=3.2 Hz, ArH), 7.50 (s, 1H, OH), 7.66 (dt, 1H, J=7.5 Hz, J=1.4 Hz, ArH), 7.71 (dt, 1H, J=7.5 Hz, J=1.4 Hz, ArH), 8.03 (m ,1H, ArH), 8.06 (m, 1H ArH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.9 (2xCH_3), 32.8 (CH_2), 37.7 (C), 56.4 (OCH_3), 57.1 (OCH_3), 73.9 (OCH_2), 114.2, 116.8, 119.9, 126.6, 127.5, 133.4, 135.4 (CH arom), 121.2, 122.5, 129.9, 133.5, 153.5, 154.1, 154.8 (C), 166.7 (OC=O), 181.8 (C=O), 185.5 (C=O)

MS (EI), m/z (%): 424 (M^+, 14), 242 (4), 212 (8), 165 (100), 107 (8), 77 (22)

HRMS calcd for $C_{24}H_{24}O_7$ [M+Na] 447.1420, found 447.1418

General procedure for synthesis of naphthoquinone esters (130-132)



(**74**): R_1=R_2=H
(**75**): R_1=H, R_2=Me
(**85**): R_1=R_2=Me

(**108**)

(**130**): R_1=R_2=H,
(**131**): R_1=H, R_2=Me
(**132**): R_1=R_2=Me

Method 1

A solution of 1,1′-carbonyldiimidazole (CDI) (0.3 mmol) in THF (2 ml). was added to a stirred solution of acid (0.3 mmol) in tetrahydrofuran (THF) (3 ml). After stirring the mixture for 3 hours at room temperature, a solution of quinone alcohol (0.2 mmol) in THF (5 ml) was added and stirring continued for 7 hours at room temperature. The reaction mixture was quenched with saturated ammonium chloride solution (30 ml) and extracted with dichloromethane (3 x 30 ml). The combined organic layers were washed with brine and water, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography.

Method 2

A solution of naphthoquinone alcohol (0.2 mmol) in dry dichloromethane (2 ml) was added to a stirred solution of acid (0.26 mmol) and 4-dimethylaminopyridine(DMAP) (0.06 mmol) in dry dichloromethane (2 ml). The reaction mixture was stirred at room temperature for 5 minutes and then a solution of 1,3-dicyclohexylcarbodiimide (DCC) (0.26 mmol) in dry dichloromethane (3 ml) was added and stirring continued overnight at room temperature. The precipitate of dicyclohexylurea was filtered off, the filtrate washed with saturated ammonium chloride solution (2 x 10 ml) and water, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography.

Naphthalene-2-carboxylic acid-3-(1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-propyl ester (130)

Flash column chromatography eluting with 9:1 v/v hexane - ethyl acetate afforded the product **130** (56% from method 1 and 86% from method 2) as a yellow amorphous powder, m.p. 114-116°C.

FTIR (KBr, cm^{-1}): 1712 (C=O), 1660 (C=O), 1589 (C=C), 1289 (C-O)

^{1}**H NMR** ($CDCl_3$, 400 MHz) δ: 2.30 (m, 2H, CH_2), 2.80 (t, 2H, J=7.4 Hz, CH_2), 4.50 (t, 2H, J= 6.2 Hz, OCH_2), 6.90 (s, 1H, CH=), 7.58 (m, 2H, ArH), 7.69 (m, 2H, ArH), 7.89 (m, 3H, ArH), 8.02 (m, 2H, ArH), 8.09 (m, 1H, ArH), 8.56 (s, 1H, ArH)

^{13}**C NMR** ($CDCl_3$, 100 MHz) δ: 27.4 (CH2), 27.9 (CH2), 64.9 (OCH2), 125.7, 126.6, 127.2, 127.23, 128.3, 128.8, 128.9, 130.0, 131.6, 134.2, 134.3, 135.8 (CH), 127.9, 132.6, 132.8, 133.0, 136.1, 151.3 (C), 167.2 (OC=O), 185.5 (C=O), 185.7 (C=O)

MS (EI), m/z (%): 370 (M^+, 20), 198 (55), 172 (68), 155 (100), 127 (100)

HRMS Calcd for $C_{24}H_{18}O_4$ [M+H] 371.1283, found 371.1285

Naphthalene-2-carboxylic acid-3-(1,4-dioxo-1,4-dihydro naphthalen-2-yl)-2-methyl-propyl ester (131)

Flash column chromatography eluting with 19:1 v/v hexane - ethyl acetate afforded the product **131** (24% from method 1 and 83% from method 2) as a yellow oil.

FTIR (neat, cm^{-1}): 1716 (C=O), 1663 (C=O), 1595 (C=C), 1280 (C-O), 1094 (C-O)

^{1}**H NMR** ($CDCl_3$, 400 MHz) δ: 1.15 (d, 3H, J=6.7 Hz, CH_3), 2.49 (m, 1H, CH), 2.59 and 2.84 (2xm, 2x1H, CH_2), 4.32 (d, 2H, J=6.0 Hz, OCH_2), 6.88 (s, 1H, CH=), 7.51-7.67 (m, 4H, ArH), 7.81 (d, 1H, J=8.6 Hz, ArH), 7.86 (d, 1H, J=8.2 Hz, ArH), 7.89 (d, 1H,

J=8.2 Hz, ArH), 7.96 (m, 1H, ArH), 7.99 (dd, 1H, J=8.2 Hz, J=1.7 Hz, ArH), 8.04 (m, 1H, ArH), 8.51 (s, 1H, ArH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 17.9 (CH_3), 33.2 (CH_2), 35.2 (CH), 69.9 (OCH_2), 125.7, 126.6, 127.16, 127.2, 128.3, 128.8, 128.9, 130.0, 131.6, 134.19, 134.2, 136.7 (CH), 127.8, 132.6, 132.8, 133.0, 136.1, 150.4 (C), 167.2 (OC=O), 185.5 (C=O), 185.8 (C=O)

MS (EI), m/z (%): 384 (M^+, 5), 197 (15), 172 (39), 155 (100), 127 (85)

HRMS calcd for $C_{25}H_{20}O_4$ [M+Na] 407.1259, found 407.1237

Naphthalene-2-carboxylic acid-3-(1,4-dioxo-1,4-dihydro naphthalen-2-yl)-1,2dimethyl propyl ester (132)

Flash column chromatography eluting with 47:3 v/v hexane-ethyl acetate afforded the product **132** (40% from method 1 and 74% from method 2) as a yellow solid, m.p. 93-94°C.

FTIR (KBr, cm^{-1}): 1711 (C=O), 1657 (C=O), 1591 (C=C), 1281 (C-O), 1224 (C-O)

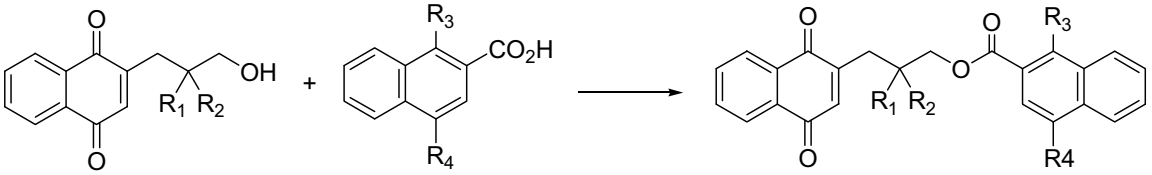
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.17 (s, 6H, 2xCH_3), 2.78 (s, 2H, CH_2), 4.20 (s, 2H, OCH_2), 6.90 (s, 1H, CH=), 7.45-7.61 (m, 4H, ArH), 7.75 (d, 1H, J=8.6 Hz, ArH), 7.83 (m, 2H, ArH), 7.90 (m, 3H, ArH), 8.42 (s, 1H, ArH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.7 (2xCH_3), 36.7 (C), 38.8 (CH_2), 73.2 (OCH_2), 125.5, 126.4, 127.2, 127.24, 128.3, 128.7, 128.8, 130.0, 131.4, 133.9, 134.1, 137.8 (CH), 127.8, 132.6, 132.7, 132.9, 136.0, 149.5 (C), 167.0 (OC=O), 185.5 (C=O), 185.8 (C=O)

MS (EI), m/z (%): 398 (M^+, 10), 226 (3), 211 (5), 155 (100), 127 (3)

HRMS calcd for $C_{26}H_{22}O_4$ [M^+] 398.1518, found 398.1520

General procedure for synthesis of naphthoquinone esters (133-136)



(**74**): R_1=R_2=H
(**75**) R_1=H, R_2=Me
(**85**): R_1=R_2=Me

(**109**): R_3=OMe, R_4=H
(**113**): R_3=R_4=OMe

(**133**): R_1=R_2=H, R_3=OMe, R_4=H
(**134**): R_1=R_2=H, R_3=R_4=OMe
(**135**): R_1=H, R_2=Me,R_3=OMe, R_4=H
(**136**): R_1=R_2=Me,R_3=OMe, R_4=H

A solution of naphthoquinone alcohol (0.2 mmol) in dry dichloromethane (2 ml) was added to a stirred solution of acid (0.26 mmol) and 4-dimethylaminopyridine(DMAP) (0.06 mmol) in dry dichloromethane (2 ml). The reaction mixture was stirred at room temperature for 5 minutes and then a solution of 1,3-dicyclohexylcarbodiimide (DCC) (0.26 mmol) in dry dichloromethane (3 ml) was added and stirring continued overnight at room temperature. The precipitate of dicyclohexylurea was filtered off and the filtrate washed with saturated ammonium chloride solution (2 x 10 ml) and water, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography.

1-Methoxy-naphthalene-2-carboxylic acid-3-(1,4-dioxo-1,4-dihydro-naphthalen2-yl)-propyl ester (133)

Flash column chromatography eluting with 23:2 v/v hexane - ethyl acetate afforded the product **133** (85%) as a yellow amorphous powder, m.p. 95-96°C.

FTIR (KBr, cm^{-1}): 1718 (C=O), 1657 (C=O), 1589 (C=C), 1276 (C-O), 1237 (C-O), 1141 (C-O)

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.16 (m, 2H, CH_2), 2.82 (dt, 2H, J=7.6 Hz, J=1.1 Hz, CH_2), 4.08 (s, 3H, OCH_3), 4.50 (t, 2H, J=6.2 Hz, OCH_2), 6.89 (t,1H, J=1.2 Hz, CH=), 7.59 (m, 3H, ArH), 7.69 (m, 2H, ArH), 7.84 (d, 1H, J=8.6 Hz, ArH), 7.86(dd, 1H, J=6.9 Hz, J=1.8 Hz, ArH), 8.03 (m, 1H, ArH), 8.08 (m, 1H, ArH), 8.26 (m, 1H, ArH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.4 (CH_2), 27.9 (CH_2), 64.1 (OCH_3), 64.9 (OCH_2), 124.3 (2C), 126.6, 127.1, 127.2 (2C), 128.5, 129.0, 134.2, 134.3, 135.8 (CH), 119.8, 129.1, 132.6, 132.8, 137.4, 151.3, 158.9 (C), 166.7 (OC=O), 185.6 (C=O), 185.7 (C=O)

MS (EI), m/z (%): 400 (M^+, 50), 185 (100), 170 (40), 157 (24)

HRMS calcd for $C_{25}H_{20}O_5$ [M+Na] 423.1208, found 423.1205

1,4 - Dimethoxy-naphthalene – 2 - carboxylic acid – 3 - (1,4-dioxo-1,4-dihydro naphthalen-2-yl)-propyl ester (134)

Flash column chromatography eluting with 9:1 v/v hexane - ethyl acetate afforded the product **134** (82%) as a yellow amorphous powder, m.p. 121-122°C.

FTIR (KBr, cm^{-1}): 1698 (C=O), 1662 (C=O), 1594 (C=C), 1242 (C-O), 1104 (C-O)

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.18 (m, 2H, CH_2), 2.82 (dt, 2H, J=7.6 Hz, J=1.1 Hz, CH_2), 4.01 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 4.51 (t, 2H, J=6.2 Hz, OCH_2), 6.89 (t, 1H, J=1.2 Hz, CH=), 7.14 (s, 1H, ArH), 7.60 (m, 2H, ArH), 7.66 (m, 2H, ArH), 8.01 (m, 1H, ArH), 8.06 (m, 1H, ArH), 8.16 (m, 1H, ArH), 8.25 (m, 1H, ArH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.4 (CH_2), 28.0 (CH_2), 56.4 (OCH_3), 64.0 (OCH_3), 65.0 (OCH_2), 104.0, 122.9, 124.1, 126.6, 127.1, 127.7, 128.4, 134.17, 134.2, 135.8 (CH), 119.3, 129.4, 129.7, 132.6, 132.8, 151.3, 152.0, 152.5 (C), 167.0 (OC=O), 185.6 (C=O), 185.7 (C=O)

MS (EI), m/z (%): 430 (M^+, 38), 213 (48), 199 (65), 129 (100), 115 (73), 76 (32)

HRMS calcd for $C_{26}H_{22}O_6$ [M+Na] 453.1314, found 453.1315

1-Methoxy-naphthalene-2-carboxylic acid-3-(1,4-dioxo-1,4-dihydro-naphthalen2-yl)-2-methyl propyl ester (135)

Flash column chromatography eluting with 47:3 v/v hexane - ethyl acetate afforded the product **135** (90%) as a yellow oil.

FTIR (neat, cm^{-1}): 1721 (C=O), 1664 (C=O), 1595 (C=C), 1274 (C-O), 1134(C-O)

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.15 (d, 3H, J=6.7 Hz, CH_3), 2.45 (m, 1H, CH), 2.57 and 2.85 (2xm, 2x1H, CH_2), 4.05 (s, 3H, OCH_3), 4.32 (m, 2H, OCH_2), 6.87 (s, 1H, CH=), 7.57 (m, 5H, ArH), 7.80 (m, 2H, ArH), 7.96 (m, 1H, ArH), 8.02(m, 1H, ArH), 8.22 (d, 1H, J=7.8 Hz, ArH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 17.8 (CH_3), 33.2 (CH_2), 35.1 (CH), 64.1 (OCH_3), 70.0 (OCH_2), 124.2, 124.3, 126.4, 127.09, 127.1 (2C), 128.4, 128.9, 134.1, 134.14, 136.7 (CH), 119.7, 129.1, 132.6, 132.7, 137.4, 150.4, 158.9 (C), 166.6 (OC=O), 185.5 (C=O), 185.8 (C=O)

MS (EI), m/z (%): 414 (M^+, 20), 214 (29), 185 (100), 170 (37), 127 (76)

HRMS calcd for $C_{26}H_{22}O_5$ [M+Na] 437.1365, found 437.1364

1-Methoxy-naphthalene-2-carboxylic acid-3-(1,4-dioxo-1,4-dihydro-naphthalen2-yl)-2,2-dimethyl propyl ester (136)

Flash column chromatography eluting with 47:3 v/v hexane - ethyl acetate afforded the product **136** (98%) as a yellow solid, m.p. 66-68°C.

FTIR (KBr, cm^{-1}): 1706 (C=O), 1662 (C=O), 1597 (C=C), 1275(C-O), 1133 (C-O)

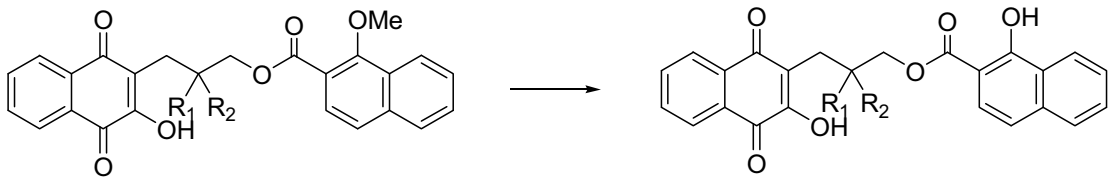
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.20 (s, 6H, 2xCH_3), 2.74 (s, 2H, CH_2), 4.01(s, 3H, OCH_3), 4.19 (s, 2H, OCH_2), 6.87 (s, 1H, CH=), 7.38 (m, 2H, ArH), 7.45 (d, 1H, J=8.7 Hz, ArH), 7.59 (m, 2H, ArH), 7.72 (d, 1H, J=8.7 Hz, ArH), 7.78-7.88 (m, 3H, ArH), 8.17 (dd, 1H, J=8.0 Hz, J=0.9 Hz, ArH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.7 (2xCH_3), 36.6 (C), 38.9 (CH_2), 64.1 (OCH_3), 73.4 (OCH_2), 124.1, 124.2, 126.2, 126.9, 127.0 (2C), 128.3, 128.9, 133.6, 133.7, 137.7 (CH), 119.6, 126.9, 132.5, 132.6, 137.3, 149.5, 158.8 (C), 166.4 (OC=O), 185.6 (C=O), 185.9 (C=O)

MS (EI), m/z (%): 428 (M^+, 8), 227 (10), 185 (100), 170 (28), 129 (27)

HRMS calcd for $C_{27}H_{24}O_5$ [M+Na] 451.1521, found 451.1522

General procedure for synthesis of naphthoquinone esters (137-139)



(**116**): $R_1=R_2=H$
(**119**): $R_1=H$, $R_2=Me$
(**122**): $R_1=R_2=Me$

(**137**): $R_1=R_2=H$
(**138**): $R_1=H$, $R_2=Me$
(**139**): $R_1=R_2=Me$

1M Boron tribromide in dichloromethane (0.2 mmol) was added dropwise at –78°C over 5 minutes to a solution of naphthoquinone ester (0.1 mmol) in dry dichloromethane(5 ml) and the reaction mixture stirred for 15 minutes. Then cold water was added and the mixture extracted with dichloromethane (3 x 30 ml). The combined organic layers were washed with water, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography.

1-Hydroxy-naphthalene-2-carboxylic acid – 3 -(3-hydroxy-1,4-dioxo-1,4-dihydro naphthalen-2-yl)-propyl ester (137)

Flash column chromatography eluting with 23:2 v/v hexane - ethyl acetate afforded the product **137** (85%) as a yellow amorphous powder, m.p. 137-138°C

FTIR (KBr, cm^{-1}): 3350 (OH), 1658 (C=O), 1585 (C=C), 1254(C-O), 1162 (C-O)

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.15 (m, 2H, CH_2), 2.85 (t, 2H, J=7.3 Hz, CH_2), 4.47 (t, 2H, J=6.3 Hz, OCH_2), 7.18 (d, 1H, J=8.8 Hz, ArH), 7.45 (s, 1H, OH), 7.52 (dt, 1H, J=8.2 Hz, J=1.1 Hz, ArH), 7.61 (dt, 1H, J=8.1 Hz, J=1.2 Hz, ArH), 7.65 (dt, 1H, J=7.5 Hz, J=1.2 Hz, ArH), 7.74 (m, 3H, ArH), 8.04 (m, 1H, ArH), 8.11 (m, 1H, ArH), 8.40 (d, 1H, J=8.8 Hz, ArH), 12.0 (s, 1H, OH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 20.8 (CH_2), 27.7 (CH_2), 65.7 (OCH_2), 119.1, 124.5, 124.9, 126.3, 126.7, 127.4, 128.0, 129.9, 133.6, 135.5 (CH arom), 106.3, 123.6, 125.3, 129.9, 133.4, 137.7, 154.0, 161.5 (C), 171.6 (OC=O), 181.8 (C=O), 185.2 (C=O)

MS (EI), m/z (%): 402 (M^+, 2), 215 (100), 170 (78), 115 (74), 77 (44)

HRMS calcd for $C_{24}H_{18}O_6$ [M^+] 402.1098, found 402.1094

1-Hydroxy-naphthalene-2-carboxylic acid – 3 -(3-hydroxy-1,4-dioxo-1,4-dihydro naphthalen-2-yl)-2-methyl-propyl ester (138)

Flash column chromatography eluting with 9:1 v/v hexane - ethyl acetate afforded the product **138** (81%) as a yellow amorphous powder, m.p. 191-192°C

FTIR (KBr, cm^{-1}): 3363 (OH), 1658 (C=O), 1593 (C=C), 1259(C-O), 1166 (C-O)

^{1}**H NMR** (DMSO, 400 MHz) δ: 1.16 (d, 3H, J=6.8 Hz, CH_3), 2.50 (m, 1H, CH), 2.70 and 2.84 (2xm, 2x1H, CH_2), 4.33 (m, 2H, OCH_2), 7.16 (d, 1H, J=8.8 Hz, ArH), 7.42 (s, 1H, OH), 7.53 (m, 1H, ArH), 7.63 (m, 2H, ArH), 7.73 (m, 3H, ArH), 8.03 (dd, 1H, J=7.6 Hz, J=1.2 Hz, ArH), 8.10 (dd, 1H, J=7.6 Hz, J=0.9 Hz, ArH), 8.40 (d, 1H, J=8.3 Hz, ArH), 12.00 (s, 1H, OH)

^{13}**C NMR** (DMSO, 100 MHz) δ: 18.4 (CH_3), 28.2 (CH), 33.0 (CH_2), 71.0 (OCH_2), 119.8, 124.2, 125.0, 126.6, 126.8, 127.3, 128.8, 130.8, 134.1, 135.5 (CH arom), 106.6, 123.1, 125.0, 131.1, 133.0, 137.7, 157.2, 160.6 (C), 171.2 (OC=O), 181.8 (C=O), 185.7 (C=O)

MS (EI), m/z (%): 416 (M^+, 5), 229 (100), 187 (27), 170 (87), 114 (60)

HRMS calcd for $C_{25}H_{20}O_6$ [M+Na] 439.1158, found 439.1161

1-Hydroxy-naphthalene-2-carboxylic acid – 3 -(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-2,2-dimethyl-propyl ester (139)

Flash column chromatography eluting with 9:1 v/v hexane - ethyl acetate afforded the product **139** (80%) as a yellow solid, m.p. 162-163°C.

FTIR (KBr, cm^{-1}): 3327 (OH), 1661 (C=O), 1580 (C=C), 1257 (C-O), 1162 (C-O)

^{1}**H NMR** ($CDCl_3$, 400 MHz) δ: 1.20 (s, 6H, 2xCH_3), 2.80 (s, 2H, CH_2), 4.20 (s, 2H, OCH_2), 7.11 (d, 1H, J=8.8 Hz, ArH), 7.47 (s, 1H, OH), 7.53 (m, 1H, ArH), 7.61 (m, 3H,

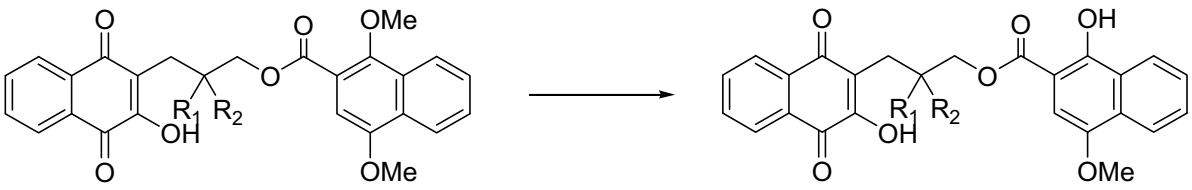
ArH), 7.68 (d, 1H, J=8.8 Hz, ArH), 7.73 (d, 1H, J=8.1 Hz, ArH), 8.04(m, 2H, ArH), 8.40 (d, 1H, J=8.3 Hz, ArH), 12.00 (s, 1H, OH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 26.0 (2xCH_3), 33.0 (CH_2), 37.7 (C), 74.0 (OCH_2), 119.1, 124.4, 124.7, 126.3, 126.6, 127.5, 128.0, 129.9, 133.4, 135.5 (CH arom), 106.4, 122.1, 125.3, 129.9, 133.5, 137.7, 154.9, 161.4 (C), 171.5 (OC=O), 181.8 (C=O), 185.5 (C=O)

MS (EI), m/z (%): 430 (M^+, 6), 243 (100), 187 (52), 170 (83), 115 (44)

HRMS calcd for $C_{26}H_{22}O_6$ [M+Na] 448.1760, found 448.1758

General procedure for synthesis of Rhinacanthin-N (7) and naphthoquinone esters (140, 141)



(**117**): R_1=R_2=H
(**120**): R_1=H, R_2=Me
(**14**): R_1=R_2=Me

(**140**): R_1=R_2=H
(**141**): R_1=H, R_2=Me
(**7**): R_1=R_2=Me

1M Boron tribromide in dichloromethane (0.2 mmol) was added dropwise over 5 minutes at –78°C to a stirred solution of naphthoquinone ester (0.1 mmol) in dry dichloromethane (5 ml) and the reaction mixture was stirred for 15 minutes. Then cold water was added and the mixture extracted with dichloromethane (3 x 30 ml). The combined organic phases were washed with water, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography.

1-Hydroxy -4- methoxy-naphthalene-2-carboxylic acid -3- (3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)- propyl ester (140)

Flash column chromatography eluting with 9:1 v/v hexane - ethyl acetate afforded the product **140** (79%) as an orange solid, m.p. 164-165°C.

FTIR (KBr, cm^{-1}): 3365 (OH), 1663(C=O), 1590 (C=C), 1245 (C-O), 1092 (C-O)

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.18 (m, 2H, CH_2), 2.85 (t, 2H, J=7.3 Hz, CH_2), 3.96 (s, 3H, OCH_3), 4.48 (t, 2H, J=6.3 Hz, OCH_2), 7.05 (s, 1H, ArH), 7.43 (s, 1H, OH), 7.54-7.73 (m, 4H, ArH), 8.00 (dd, 1H, J=7.6 Hz, J=1.3 Hz, ArH), 8.09 (dd, 1H, J=7.7 Hz, J=1.3 Hz, ArH), 8.17 (d, 1H, J=8.2 Hz, ArH), 8.37 (d, 1H, J=8.1 Hz, ArH), 11.6 (s, 1H, OH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 20.7 (CH_2), 27.7 (CH_2), 56.2 (OCH_3), 65.6 (OCH_2), 101.1, 122.5, 124.4, 126.7, 127.0, 127.3, 129.5, 133.5, 135.5 (CH arom), 105.1, 123.6, 126.1, 129.9, 130.4, 133.4, 148.2, 154.0, 156.1 (C), 171.4 (OC=O), 181.8 (C=O), 185.1 (C=O)

MS (EI), m/z (%): 432 (M^+, 9), 215 (80), 200 (100), 144 (28), 129 (41)

HRMS calcd for $C_{25}H_{20}O_7$ [M+NH_4] 450.1553, found 450.1555

<u>1-Hydroxy -4- methoxy-naphthalene -2- carboxylic acid-3- (3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-2-methyl-propyl ester (141)</u>

Flash column chromatography eluting with 23:2 v/v hexane - ethyl acetate afforded the product **141** (80%) as an orange solid, m.p. 149-151°C.

FTIR (KBr, cm^{-1}): 3354 (OH), 1660(C=O), 1592 (C=C), 1234 (C-O), 1152 (C-O)

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.15 (d, 3H, J=6.8 Hz, CH_3), 2.54 (m,1H, CH), 2.65 and 2.85 (2xm, 2x1H, CH_2), 3.93 (s, 3H, OCH_3), 4.27 and 4.38 (m, 2x1H, OCH_2), 7.03 (s, 1H, ArH), 7.43 (s, 1H, OH), 7.54-7.7 (m, 4H, ArH), 7.97 (dd, 1H, J=7.6 Hz, J=1.1 Hz. ArH), 8.07 (dd, 1H, J=7.7 Hz, J=1.0 Hz, ArH), 8.16 (dd, 1H, J=8.3 Hz, J=0.6 Hz, ArH), 8.36 (dd, 1H, J=8.3 Hz, J=0.7 Hz, ArH). 11.56 (s, 1H, OH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 18.1 (CH_3), 28.3 (CH_2), 33.0 (CH), 56.2 (OCH_3), 70.4 (OCH_2), 101.0, 122.5, 124.3, 126.6, 126.9, 127.3, 129.5, 133.5, 135.4 (CH arom),

105.1, 122.9, 126.1, 129.8, 130.4, 133.3, 148.2, 154.3, 156.1 (C), 171.4 (OC=O), 181.7 (C=O), 185.3 (C=O)

MS (EI), m/z (%): 446 (M^+, 8), 229 (84), 200 (100), 187 (33), 129 (50)

Anald. Calcd for $C_{26}H_{22}O_7$: C, 69.95; H, 5.02. Found: C, 69.98; H, 4.95

Rhinacanthin-N (7)

Flash column chromatography eluting with 23:2 v/v hexane - ethyl acetate afforded the product **7** (95%) as an orange amorphous powder, m.p. 124-125°C (Wu, 1998, m.p. 123-124°C).

FTIR (KBr, cm^{-1}): 3235 (OH), 1663(C=O), 1638 (C=O), 1592 (C=C), 1243 (C-O), 1150 (C-O)

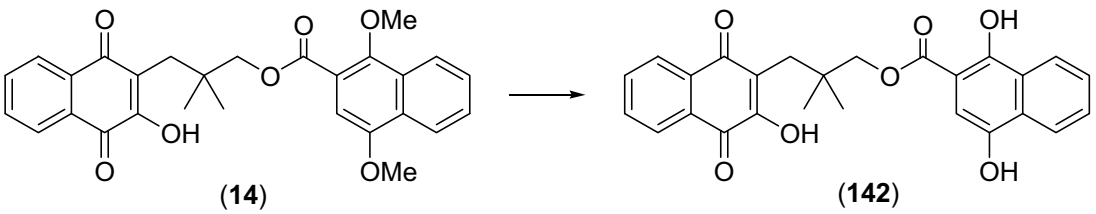
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.15 (s, 6H, 2xCH_3), 2.80 (s, 2H, CH_2), 3.88 (s, 3H, OCH_3), 4.20 (s, 2H, OCH_2), 7.00 (s, 1H, ArH), 7.50 (s, 1H, OH), 7.51-7.65 (m, 4H, ArH), 7.98 (dd, 1H, J=7.3 Hz, J=1.6 Hz, ArH), 8.01 (dd, 1H, J=7.6 Hz, J=1.4 Hz, ArH), 8.14 (d, 1H, J=8.1 Hz, ArH), 8.37 (d, 1H, J=8.3 Hz, ArH), 11.6 (s, 1H, OH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 26.0 (2xCH_3), 32.9 (CH_2), 37.7 (C), 56.0 (OCH_3), 73.9 (OCH_2), 100.9, 122.4, 124.3, 126.5, 126.9, 127.4, 129.5, 133.4, 135.4 (CH arom), 105.2, 122.1, 126.1, 129.8, 130.3, 133.4, 148.1, 154.8, 156.0 (C), 171.2 (OC=O), 181.7 (C=O), 185.5 (C=O)

MS (EI), m/z (%): 460 (M^+, 15), 243 (71), 200 (100), 187 (48), 129 (48).

HRMS calcd for $C_{27}H_{24}O_7$ [M+Na] 483.1420, found 483.1421

1,4 -Dihydroxy-naphthalene – 2 - carboxylic acid – 3 - (3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-2,2-dimethyl-propyl ester (142)



(**14**) (**142**)

Boron tribromide (0.05 ml, 0.5 mmol) was added dropwise over 2 minutes to a stirred solution of Rhinacanthin-Q (**14**) (0.05 g, 0.1 mmol) in dichloromethane (5 ml) at room temperature and the solution stirred for 1 hour at room temperature, then water was added and the mixture extracted with dichloromethane (3 x 30 ml). The combined organic phases were washed with water, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography eluting with 17:3 v/v hexane – ethyl acetate to afford the product **142** (0.034 g, 73%) as an orange amorphous powder, m.p. 160-162 $^{\circ}$C.

FTIR (KBr, cm^{-1}): 3372 (OH), 1662(C=O), 1634 (C=O), 1593 (C=C), 1250 (C-O)

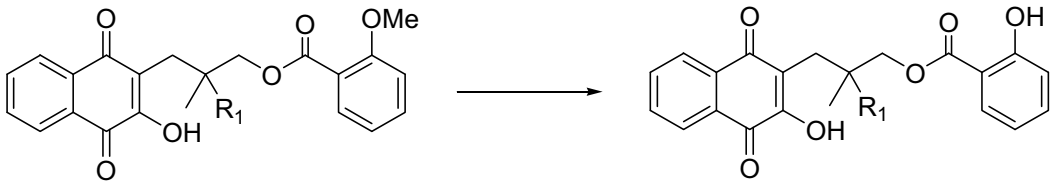
^{1}**H NMR** ($CDCl_3$, 400 MHz) δ: 1.10 (s, 6H, CH_3), 2.80 (s, 2H, CH_2), 4.15 (s, 2H, CH_2O), 5.45 (s, 1H, OH), 7.02 (s, 1H, ArH), 7.50 (s, 1H, OH), 7.53-7.67 (m, 4H, ArH), 8.03 (d, 1H, J=7.6 Hz, ArH), 8.04 (d, 1H, J=7.4 Hz, ArH), 8.10 (d, 1H, J=8.3 Hz, ArH), 8.37 (d, 1H, J=8.3 Hz, ArH), 11.5 (s, 1H, OH)

^{13}**C NMR** ($CDCl_3$, 100 MHz) δ: 25.9 (2xCH_3), 32.6 (CH_2), 37.6 (C), 73.9 (OCH_2), 105.5, 122.4, 124.4, 126.7, 126.9, 127.4, 129.4, 133.6, 135.5 (CH arom), 105.3, 122.2, 126.1, 129.6, 129.8, 133.3, 144.2, 155.1, 155.8 (C), 171.1 (OC=O), 181.7 (C=O), 185.8 (C=O)

MS (EI), m/z (%): 446 (M^+, 14), 243 (100), 186 (93), 159 (39), 77 (65)

HRMS calcd for $C_{26}H_{22}O_7$ [M+NH_4] 464.1709, found 464.1706

General procedure for synthesis of naphthoquinone esters (143, 145)



(**126**): R_1=H
(**128**): R_1=Me

(**143**): R_1=H
(**145**): R_1=Me

1M Boron tribromide in dichloromethane (0.2 mmol) was added dropwise over 5 minutes at –78°C to a stirred solution of naphthoquinone ester (0.1 mmol) in dry

dichloromethane (5 ml) and the reaction mixture was stirred for 15 minutes. Then cold water was added and the mixture extracted with dichloromethane (3 x 30 ml). The combined organic phases were washed with water, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography.

2-Hydroxy-benzoic acid-3-(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-2-methyl-propyl ester (143)

Flash column chromatography eluting with 93:7 v/v hexane - ethyl acetate afforded the product **143** (70%) as a yellow amorphous powder, m.p. 121-122°C.

FTIR (KBr, cm^{-1}): 3354 (OH), 1674(C=O), 1641 (C=O), 1482 (C=C), 1222 (C-O)

^{1}**H NMR** ($CDCl_3$, 400 MHz) δ: 1.11 (d, 3H, J=6.8 Hz, CH_3), 2.45 (m, 1H, CH), 2.67 and 2.82 (2xm, 2x1H, CH_2), 4.26 (m, 2H, OCH_2), 6.79 (dt, 1H, J=7.3 Hz, J=1.1 Hz, ArH), 6.97 (dd, 1H, J=8.4 Hz, J=1.1 Hz, ArH), 7.42 (s, 1H, OH), 7.42 (m, 1H, ArH), 7.75 (m, 3H, ArH), 8.10 (m, 2H, ArH), 10.80 (s, 1H, OH)

^{13}**C NMR** ($CDCl_3$, 100 MHz) δ: 18.0 (CH_3), 28.2 (CH_2), 33.1 (CH), 70.4 (OCH_2), 118.1, 119.7, 126.8, 127.5, 130.4, 133.6, 135.6, 136.2 (CH arom), 113.1, 122.9, 130.0, 133.4, 154.3, 162.2 (C), 170.7 (OC=O), 181.7 (C=O), 185.3 (C=O)

MS (EI), m/z (%): 366 (M^+, 6), 229 (100), 187 (26), 121 (80)

HRMS calcd for $C_{21}H_{18}O_6$ [M+Na] 389.1001, found 389.1007

2-Hydroxy-benzoic acid – 3 - (3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)2,2-dimethyl-propyl ester (145)

Flash column chromatography eluting with 47:3 v/v hexane - ethyl acetate afforded the product **145** (90%) as a yellow amorphous powder, m.p. 110-111°C.

FTIR (KBr, cm^{-1}): 3358 (OH), 1670(C=O), 1641 (C=O), 1589 (C=C), 1363 (C-O), 1275 (C-O)

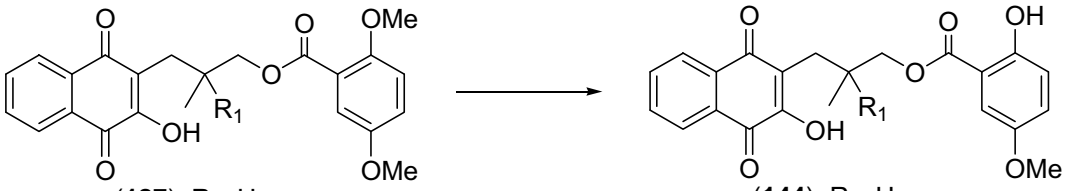
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.13 (s, 6H, 2xCH_3), 2.80 (s, 2H, CH_2), 4.13(s, 2H, OCH_2), 6.74 (t, 1H, J=7.4 Hz, ArH), 6.97 (d, 1H, J=8.3 Hz, ArH), 7.41 (dt, 1H, J=8.5 Hz, J=1.6 Hz, ArH), 7.49 (s, 1H, OH), 7.73 (m, 3H, ArH), 8.09 (m, 2H, ArH), 10.82 (s, 1H, OH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.9 (2xCH_3), 32.9 (CH_2), 37.6 (C), 73.9 (OCH_2), 118.1, 119.6, 126.7, 127.6, 130.3, 133.6, 135.7, 136.1 (CH arom), 113.2, 122.1, 129.9, 133.5, 154.9, 162.1 (C), 170.6 (OC=O), 181.8 (C=O), 185.5 (C=O)

MS (EI), m/z (%): 380 (M^+, 0.3), 243 (55), 187 (29), 121 (100), 65 (49)

HRMS calcd for $C_{22}H_{20}O_6$ [M+Na] 403.1158, found 403.1161

General procedure for synthesis of naphthoquinone esters (144, 146)



(**127**): R_1=H
(**14**): R_1=Me

(**144**): R_1=H
(**146**): R_1=Me

1M Boron tribromide in dichloromethane (0.2 mmol) was added dropwise over 5 minutes at –78°C to a stirred solution of naphthoquinone ester (0.1 mmol) in dry dichloromethane (5 ml) and the reaction mixture was stirred for 15 minutes. Then cold water was added and extracted with dichloromethane (3 x 30 ml). The combined organic phases were washed with water, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography.

2 - Hydroxy – 5 - methoxy-benzoic acid – 3 - (3-hydroxy-1,4-dioxo-1,4-dihydroa phthalen-2-yl)-2-methyl-propyl ester (144)

Flash column chromatography eluting with 22:3 v/v hexane - ethyl acetate afforded the product (**144**) (83%) as a yellow solid, m.p. 142-143°C.

FTIR (KBr, cm^{-1}): 3357 (OH), 1677(C=O), 1645 (C=O), 1492 (C=C), 1273 (C-O),

1224 (C-O)

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.12 (d, 3H, J=6.8 Hz, CH_3), 2.45 (m, 1H, CH), 2.66 and 2.81 (2xm, 2x1H, CH_2), 3.76 (s, 3H, OCH_3), 4.22 and 4.31 (2xm, 2x1H, OCH_2), 6.90 (d, 1H, J=9.0 Hz, ArH), 7.05 (dd, 1H, , J=9.0 Hz, J=3.1 HzArH), 7.32 (d, 1H, J=3.1Hz, ArH), 7.45 (s, 1H, OH), 7.70 (dt, 1H, J=7.5 Hz, J=1.4 Hz, ArH), 7.76 (dt, 1H, J=7.5 Hz, J=1.4 Hz, ArH), 8.08 (m, 1H, ArH), 8.11 (m, 1H, ArH) , 10.37 (s, 1H, OH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 18.0 (CH_3), 28.1 (CH_2), 33.1 (CH), 56.4 (OCH_3), 70.4 (OCH_2), 112.7, 119.1, 124.2, 126.8, 127.4, 133.6, 135.6 (CH arom), 112.7, 122.8, 130.0, 133.4, 152.5, 154.4, 156.6 (C), 170.4 (OC=O), 181.7 (C=O),
185.3 (C=O)

MS (EI), m/z (%): 396 (M^+, 5), 229 (100), 187 (24), 150 (48)

HRMS calcd for $C_{22}H_{20}O_7$ [M+Na] 419.1107, found 419.1107

2 – Hydroxy – 5 - methoxy-benzoic acid – 3 - (3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-2,2-dimethyl-propyl ester (146)

Flash column chromatography eluting with 9:1 v/v hexane - ethyl acetate afforded the product (**146**) (89%) as a yellow amorphous powder, m.p. 92-93°C.

FTIR (KBr, cm^{-1}): 3319 (OH), 1665(C=O), 1612 (C=O), 1492 (C=C), 1283(C-O), 1232 (C-O)

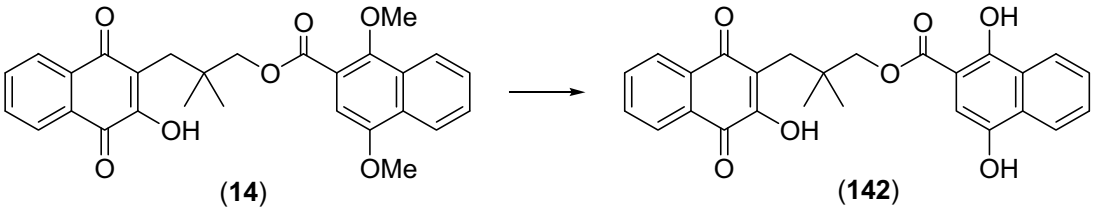
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.13 (s, 6H, 2xCH_3), 2.79 (s, 2H, CH_2), 3.73(s, 3H, OCH_3), 4.13 (s, 2H, OCH_2), 6.90 (d, 1H, J=9.0 Hz, ArH), 7.03 (dd, 1H, J=9.0 Hz, J=3.2 Hz, ArH), 7.28 (s, 1H, OH), 7.29 (d, 1H, J=3.2 Hz, ArH), 7.68 (dt, 1H, J=7.5 Hz, J=1.5 Hz, ArH), 7.73 (dt, 1H, J=7.5 Hz, J=1.5 Hz, ArH), 8.07 (m, 2H, ArH), 10.40 (s, 1H, OH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.9 (2xCH_3), 32.8 (CH_2), 37.6 (C), 56.3 (OCH_3), 74.0 (OCH_2), 112.8, 119.0, 123.8, 126.7, 127.6, 133.5, 135.6 (CH arom), 112.8, 122.0, 129.9, 133.47, 152.4, 154.9, 156.5 (C), 170.3 (OC=O), 181.7 (C=O), 185.5 (C=O)

MS (EI), m/z (%): 410 (M^+, 9), 243 (100), 187 (55), 150 (65), 77 (32)

HRMS calcd for $C_{23}H_{22}O_7$ [M+H] 411.1444, found 411.1440

2,5-Dihydroxy-benzoic acid – 3 -(3-methoxy-1,4-dioxo-1,4-dihydro-naphthalen-2yl)-2,2-dimethyl-propyl ester (142)



1 M Boron tribromide in dichloromethane (0.8 ml, 0.8 mmol) was added dropwise over 5 minutes to a stirred solution of **14** (0.1 g, 0.2 mmol) in dichloromethane (10 ml) at room temperature. The solution was stirred for 2 hour at room temperature, then water was added and the mixture extracted with dichloromethane (3 x 50 ml). The combined organic layers were washed with water, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography eluting with 21:4 v/v hexane – ethyl acetate to afford the product **142** (0.067 g, 72%) as an orange amorphous powder, m.p. 147-149°C.

FTIR (KBr, cm^{-1}): 3365 (OH), 1670 (C=O), 1488 (C=C), 1213 (C-O)

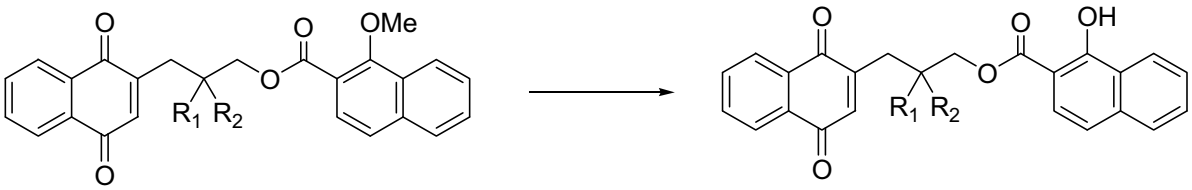
^{1}**H NMR** ($CDCl_3$, 400 MHz) δ: 1.11 (s, 6H, 2xCH_3), 2.79 (s, 2H, CH_2), 4.11(s, 2H, OCH_2), 5.40 (br s, 1H, OH), 6.86 (d, 1H, J=8.9 Hz, ArH), 6.98 (dd, 1H, J=8.9 Hz, J=3.1 Hz, ArH), 7.26 (d, 1H, J=3.1 Hz, ArH), 7.56 (br s, 1H, OH), 7.71 (m, 2H, ArH), 8.09 (m, 2H, ArH), 10.36 (s, 1H, OH)

^{13}**C NMR** ($CDCl_3$, 100 MHz) δ: 26.0 (2xCH_3), 32.7 (CH_2), 37.6 (C), 74.1 (OCH_2), 115.1, 119.0, 121.8, 126.6, 126.8, 134.1, 135.5 (CH arom), 113.4, 124.8, 131.0, 133.1, 150.5, 154.4, 157.8 (C), 170.0 (OC=O), 181.8 (C=O), 186.0 (C=O)

MS (EI), m/z (%): 396 (M^+, 2), 243 (100), 187 (93), 137 (99), 77 (79)

HRMS calcd for $C_{22}H_{20}O_7$ [M+Na] 419.1107, found 419.1103

General Procedure for synthesis of naphthoquinone esters (147, 149, 150)



(**133**): R_1=R_2=H
(**135**): R_1=H, R_2=Me
(**136**): R_1=R_2=Me

(**147**): R_1=R_2=H
(**149**): R_1=H, R_2=Me
(**150**): R_1=R_2=Me

1M Boron tribromide in dichloromethane (0.2 ml, 0.2 mmol) was added dropwise over 5 minutes at –78°C to a stirred solution of naphthoquinone ester (0.1 mmol) in dry dichloromethane (5 ml) and the reaction mixture was stirred for 15 minutes. Then cold water was added and the mixture extracted with dichloromethane (3 x 30 ml). The combined organic layers were washed with water, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography.

1-Hydroxy-naphthalene-2-carboxylic acid - 3-(1,4-dioxo-1,4-dihydro-naphthalen2-yl)-propyl ester (147)

Flash column chromatography eluting with 24:1 v/v hexane - ethyl acetate afforded the product **147** (92%) as a yellow amorphous powder, m.p. 173-175°C.

FTIR (KBr, cm^{-1}): 1662 (C=O), 1593 (C=C), 1254 (C-O), 1165 (C-O)

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.19 (m, 2H, CH_2), 2.82 (dt, 2H, J=7.6 Hz, J=1.2 Hz, CH_2), 4.52 (t, 2H, J=6.2 Hz, OCH_2), 6.90 (t, 1H, J=1.3 Hz, CH=), 7.22 (d, 1H, J=8.0 Hz, ArH), 7.55 (dt, 1H, J=6.9 Hz, J=1.2 Hz, ArH), 7.63 (dt, 1H, J=6.9 Hz, J=1.3 Hz, ArH), 7.72 (m, 3H, ArH), 7.77 (d, 1H, J=8.0 Hz, ArH), 8.05 (m, 1H, ArH), 8.11 (m, 1H, ArH), 8.42 (dd, 1H, J=7.7Hz, J=0.7 Hz, ArH), 12.00 (s, 1H, OH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.3 (CH_2), 27.8 (CH_2), 65.1 (OCH_2), 119.2, 124.5, 124.6, 126.4, 126.7, 127.2, 128.1, 130.0, 134.3, 134.4, 135.9 (CH), 106.1, 125.4, 132.7, 132.8, 137.8, 151.1, 161.7 (C), 171.5 (OC=O), 185.5 (C=O), 185.6 (C=O)

MS (EI), m/z (%): 386(M^+, 5), 199 (100), 170 (62), 114 (40)

HRMS calcd for $C_{24}H_{18}O_5$ [M+Na] 409.1052, found 409.1049

1-Hydroxy-naphthalene-2-carboxylic acid-3-(1,4-dioxo-1,4-dihydro-naphthalen2-yl)-2-methyl-propyl ester (149)

Flash column chromatography eluting with 24:1 v/v hexane - ethyl acetate afforded the product **149** (84%) as a yellow amorphous powder, m.p. 130-131°C.

FTIR (KBr, cm^{-1}): 1662 (C=O), 1461 (C=C), 1273 (C-O), 1133 (C-O)

^{1}**H NMR** ($CDCl_3$, 400 MHz) δ: 1.15 (d, 3H, J=6.7 Hz, CH_3), 2.48 (m, 1H, CH), 2.58 and 2.84 (2xm, 2x1H, CH_2), 4.34 (m, 2H, OCH_2), 6.88 (s, 1H, CH=), 7.17 (d, 1H, J=8.8 Hz, ArH), 7.50-7.80 (m, 6H, ArH), 8.00 (m, 1H, ArH), 8.08 (m, 1H, ArH), 8.40 (d, 1H, J=8.3 Hz, ArH), 11.90 (s, 1H, OH)

^{13}**C NMR** ($CDCl_3$, 100 MHz) δ: 17.8 (CH_3), 33.1 (CH_2), 35.0 (CH), 70.0 (OCH_2), 119.2, 124.5, 124.6, 126.4, 126.6, 127.2, 128.1, 130.1, 134.3, 134.34, 136.8 (CH), 106.0, 125.3, 132.6, 132.8, 137.8, 150.1, 161.6 (C), 171.4 (OC=O), 185.5 (C=O), 185.8 (C=O)

MS (EI), m/z (%): 400 (M^+, 3), 213 (100), 170 (84), 114 (78)

HRMS calcd for $C_{25}H_{20}O_5$ [M+Na] 423.1208, found 423.1205

1-Hydroxy-naphthalene-2-carboxylic acid-3-(1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-2,2-dimethyl-propyl ester (150)

Flash column chromatography eluting with 24:1 v/v hexane - ethyl acetate afforded the product **150** (80%) as a yellow amorphous powder, m.p. 151-152°C.

FTIR (KBr, cm^{-1}): 1663 (C=O), 1589 (C=C), 1251 (C-O), 1161 (C-O)

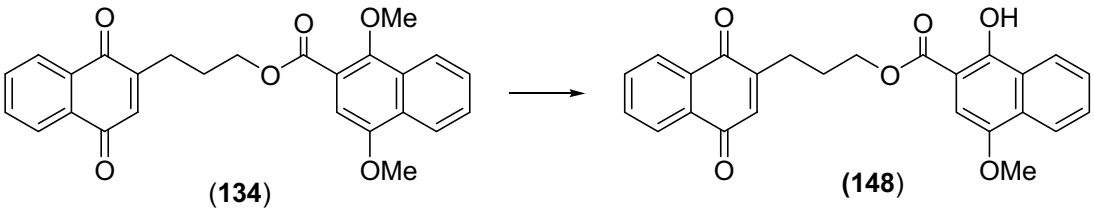
^{1}**H NMR** ($CDCl_3$, 400 MHz) δ: 1.15 (s, 6H, 2xCH_3), 2.72 (s, 2H, CH_2), 4.20 (s, 2H, OCH_2), 6.90 (s, 1H, CH=), 7.06 (d, 1H, J=8.8 Hz, ArH), 7.47-7.63 (m, 5H, ArH), 7.70 (d, 1H, J=8.1 Hz, ArH), 7.95 (m, 1H, ArH), 7.99 (m, 1H, ArH), 8.38 (m, 1H, ArH), 11.90 (s, 1H, OH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.6 (2xCH_3), 36.6 (C), 38.7 (CH_2), 73.2 (OCH_2), 119.2, 124.3, 124.4, 126.4, 126.5, 127.3, 128.0, 130.0, 134.1 (2C), 138.0 (CH), 106.0, 125.3, 132.6, 132.7, 137.7, 149.2, 161.5 (C), 171.2 (OC=O), 185.4 (C=O), 185.8 (C=O)

MS (EI), m/z (%): 414 (M^+, 4), 227 (63), 170 (100), 143 (22), 115 (94)

HRMS calcd for $C_{26}H_{22}O_5$ [M+H] 415.1545, found 415.1547

1-Hydroxy-4-methoxy-naphthalene-2-carboxylic acid – 3-(1,4-dioxo-1,4-dihydro naphthalen-2-yl)-propyl ester (148)



1M Boron tribromide in dichloromethane (0.2 ml, 0.2 mmol) was added dropwise over 5 minutes at –78 ^{o}C to a stirred solution of naphthoquinone ester (**134**) (0.05 g, 0.1 mmol) in dry dichloromethane (5 ml) and the reaction mixture was stirred for 15 minutes. Then cold water was added and the mixture extracted with dichloromethane (3 x 30 ml). The combined organic phases were washed with water, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography eulting with 19:1 v/v hexane-ethyl acetate to afford the product **148** (0.022 g, 46%) as an orange amorphous powder, m.p. 129-130 ^{o}C.

FTIR (KBr, cm^{-1}): 3440 (OH), 1662 (C=O), 1593 (C=C), 1240(C-O)

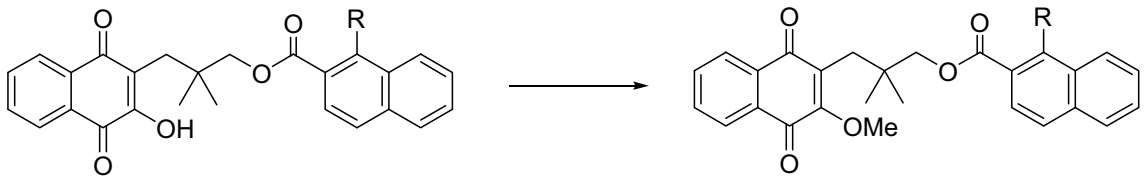
^{1}H NMR ($CDCl_3$, 400 MHz): 2.20 (m, 2H, CH_2), 2.80 (dt, 2H, J=7.6 Hz, J=1.2 Hz, CH_2), 3.97 (s, 3H, OCH_3), 4.52 (t, 2H, J=6.3 Hz, OCH_2), 6.89 (t, 1H, J=1.3 Hz, CH=), 6.99 (s, 1H, ArH), 7.59 (dt, 1H, J=6.9 Hz, J=1.3 Hz, ArH), 7.67 (m, 3H, ArH), 8.00 (m, 1H, ArH), 8.08 (m, 1H, ArH), 8.18 (m, 1H, ArH), 8.39 (m, 1H, ArH), 11.6 (s, 1H, OH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.2 (CH_2), 27.9 (CH_2), 56.3 (OCH_3), 65.0 (OCH_2), 100.8, 122.5, 124.4, 126.6, 127.06, 127.1, 129.7, 134.2, 134.3, 135.8 (CH), 104.8, 126.1, 130.5, 132.5, 132.7, 148.3, 151.0, 156.4 (C), 171.4 (OC=O), 185.5 (C=O), 185.6 (C=O)

MS (EI), m/z (%): 416 (M^+, 11), 199 (100), 157 (27), 129 (56)

HRMS calcd for $C_{25}H_{20}O_6$ [M+Na] 439.1158, found 439.1178

General procedure for synthesis of naphthoquinone esters (151, 152)



(**121**): R=H
(**122**): R=OMe

(**151**): R=H
(**152**): R=OMe

A mixture of naphthoquinone ester (185 or 186) (0.1 mmol), potassium carbonate (0.2 mmol), acetone (3 ml) and iodomethane (1.0 mmol) was stirred and refluxed for 3 hours. Then the reaction mixture was cooled to room temperature, water added and the mixture extracted with dichloromethane, washed with water, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated in vacuo. The residue was purified by flash column
chromatography.

Naphthalene-2-carboxylic acid -3-(3-methoxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-2,2-dimethyl-propyl ester (151)

Flash column chromatography eluting with 19:1 v/v hexane - ethyl acetate afforded the product **151** (75%) as a yellow oil.

FTIR (neat, cm^{-1}): 1715 (C=O), 1667 (C=O), 1597 (C=C), 1462 (C=C), 1275 (C-O), 1222 (C-O)

^{1}**H NMR** ($CDCl_3$, 400 MHz) δ: 1.15 (s, 6H, 2xCH_3), 2.83 (s, 2H, CH_2), 4.14 (s, 3H, OCH_3), 4.16 (s, 2H, OCH_2), 7.53 (m, 3H, ArH), 7.59 (m, 1H, ArH), 7.78 (d, 1H, J=8.6 Hz, ArH), 7.84 (d, 2H, J=8.8 Hz, ArH), 7.94 (m, 2H, ArH), 8.00 (dd, 1H, J=8.6 Hz, J=1.7 Hz, ArH), 8.49 (s, 1H, ArH)

^{13}**C NMR** ($CDCl_3$, 100 MHz) δ: 26.1 (2xCH_3), 33.2 (CH_2), 37.5 (C), 61.6 (OCH_3), 74.0 (OCH_2), 125.7, 126.5, 126.9, 127.1, 128.3, 128.7, 128.75, 129.9, 131.4, 133.5, 134.3

(CH arom), 128.2, 132.0, 132.5, 132.9, 133.0, 136.0, 159.3 (C), 167.2 (OC=O), 182.1 (C=O), 186.2 (C=O)

MS (EI), m/z (%): 428 (M^+, 5), 256 (6), 155 (100), 127 (52)

HRMS calcd for $C_{27}H_{24}O_5$ [M+Na] 451.1521, found 451.1521

1 - Methoxy-naphthalene – 2 - carboxylic acid – 3 - (3-methoxy-1,4-dihydro-naphthalen-2-yl)-2,2-dimethyl-propyl ester (152)

Flash column chromatography eluting with 19:1 v/v hexane - ethyl acetate afforded the product **152** (92%) as a yellow oil.

FTIR (neat, cm^{-1}): 1716 (C=O), 1666 (C=O), 1599 (C=C), 1461 (C=C), 1271 (C-O), 1135 (C-O)

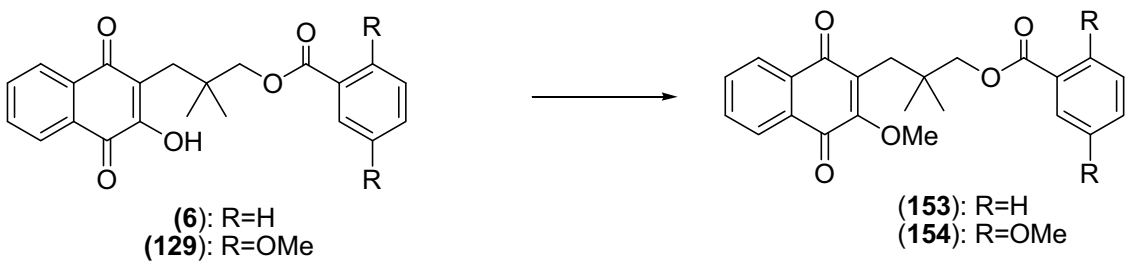
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.13 (s, 6H, 2xCH_3), 2.79 (s, 2H, CH_2), 4.02(s, 3H, OCH_3), 4.14 (s, 3H, OCH_3), 4.15 (s, 2H, OCH_2), 7.44 (m, 3H, ArH), 7.55 (m, 2H, ArH), 7.78 (d, 2H, J=8.7 Hz, ArH), 7.86 (m, 2H, ArH), 8.17 (dd, 1H, J=7.9 Hz, J=1.2 Hz, ArH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 26.1 (2xCH_3), 33.2 (CH_2), 37.4 (C), 61.5 (OCH_3), 64.0 (OCH_3), 74.2 (OCH_2), 124.0, 124.2, 126.3, 126.7, 126.9, 127.2, 128.3, 128.8, 133.3, 134.0 (CH arom), 119.9, 129.0, 132.0, 132.5, 133.0, 137.3, 158.8, 159.2 (C), 166.6 (OC=O), 182.1 (C=O), 186.3 (C=O)

MS (EI), m/z (%): 458 (M^+, 2), 185 (100), 170 (14), 127 (35)

HRMS calcd for $C_{28}H_{26}O_6$ [M+Na] 481.1627, found 481.1627

General procedure for synthesis of naphthoquinone esters (153, 154)



(**6**): R=H
(**129**): R=OMe

(**153**): R=H
(**154**): R=OMe

A mixture of naphthoquinone ester (13 or 195) (0.1 mmol), potassium carbonate (0.2 mmol), acetone (3 ml) and iodomethane (1.0 mmol) was stirred and refluxed for 3 hours. Then the reaction mixture was cooled to room temperature, water added and the mixture extracted with dichloromethane, washed with water, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography.

Benzoic acid-3-(3-methoxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-2,2-dimethyl-propyl ester (153)

Flash column chromatography eluting with 97:3 v/v hexane - ethyl acetate afforded the product **153** (91%) as a yellow oil.

FTIR (neat, cm^{-1}): 1718 (C=O), 1668 (C=O), 1599 (C=C), 1454 (C=C), 1269(C-O), 1114(C-O)

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.10 (s, 6H, 2xCH_3), 2.80 (s, 2H, CH_2), 4.10(s, 2H, OCH_2), 4.13 (s, 3H, OCH_3), 7.36 (m, 2H, ArH), 7.51 (m, 1H, ArH), 7.66 (m, 2H, ArH), 8.01 (m, 4H, ArH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 26.0 (2xCH_3), 33.0 (CH_2), 37.4 (C), 61.5 (OCH_3), 73.8 (OCH_2), 126.6, 127.0, 128.9 (2C), 130.0 (2C), 133.4, 133.7, 134.4 (CH arom), 131.0, 132.1, 132.6, 132.7, 159.3 (C), 167.0 (OC=O), 182.1 (C=O), 186.2 (C=O)

MS (EI), m/z (%): 378 (M^+, 1), 256 (3), 105 (100), 77 (4)

HRMS calcd for $C_{23}H_{22}O_5$ [M+Na] 401.1365, found 401.1369

2,5-Dimethoxy-benzoic acid - 3 -(3-methoxy-1,4-dioxo-1,4-dihydro-naphthalen-2yl)-2,2-dimethyl-propyl ester (154)

Flash column chromatography eluting with 9:1 v/v hexane - ethyl acetate afforded the product **154** (93%) as a yellow oil.

FTIR (neat, cm^{-1}): 1701 (C=O), 1667 (C=O), 1599 (C=C), 1499 (C=C), 1217(C-O), 1046 (C-O)

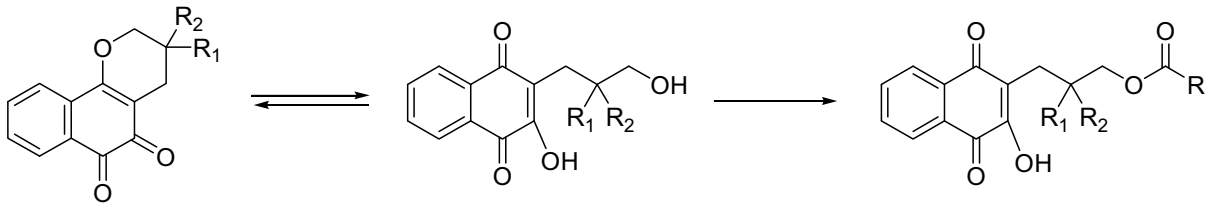
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.06 (s, 6H, 2xCH_3), 2.77 (s, 2H, CH_2), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.05 (s, 2H, OCH_2), 4.13 (s, 3H, OCH_3), 6.78 (d, 1H, J=9.1 Hz, ArH), 6.94 (dd, 1H, J=9.1 Hz, J=3.2 Hz, ArH), 7.35 (d, 1H, J=3.2 Hz, ArH), 7.62 (m, 2H, ArH), 7.97 (m, 2H, ArH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.9 (2xCH_3), 33.0 (CH_2), 37.3 (C), 56.4 (OCH_3), 57.1 (OCH_3), 61.5 (OCH_3), 74.1 (OCH_2), 114.2, 116.8, 119.9, 126.4, 126.9, 133.6, 134.2 (CH arom), 121.2, 132.1, 132.6, 133.0, 153.5, 154.1, 159.2 (C), 166.7 (OC=O), 182.1 (C=O), 186.2 (C=O)

MS (EI), m/z (%): 438 (M^+, 1), 165 (100), 107 (17), 77 (45)

HRMS calcd for $C_{25}H_{26}O_7$ [M+Na] 461.1576, found 461.1570

Synthesis of Naphthoquinone ester derivatives (155-162)



(**92**) R_1, R_2= $(CH_2)_5$
(**98**) R_1, R_2= $(CH_2)_4$

(**92a**) R_1, R_2= $(CH_2)_5$
(**99**) R_1, R_2= $(CH_2)_4$

(**155-158**) R_1, R_2= $(CH_2)_5$
(**159-162**) R^1, R_2= $(CH_2)_4$

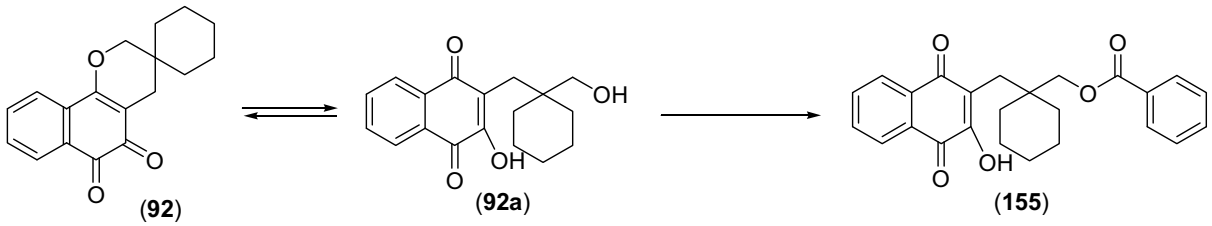
General procedure:

The solution of compound **92** or **98** (0.354 mmol) in 1% aqueous sodium hydroxide solution (0.531 mmol) was refluxed for 1 hour. After completion of the reaction, the reaction mixture was cooled to room temperature and neutralized with acetic acid to pH 7, then extracted with dichloromethane (3×15 mL). The combined organic

phases were washed with water and brine, dried over anhydrous sodium sulfate, then filtered and concentrated in vacuo. After concentration, the intermediate **92a** or **99** was obtained together with a small amount of the cyclized product **92** or **98** (monitoring by TLC).

A solution of carbodiimidazole (CDI)(0.53 mmol) in dry THF (5 mL) was added to a stirred solution of carboxylic acid (0.43 mmol) in THF (2 mL) at room temperature. After 3 hours, a solution of the mixture of compound **92** or **98** and naphthoquinone alcohol intermediate **92a** or **99** in THF (2 mL) was added and then the mixture was stirred at room temperature for 45 hours. The reaction mixture was quenced with saturated ammonium chloride and extracted with dichloromethane (3×15 mL). The combined organic layers were washed with brine and water, dried over anhydrous sodium sulfate, filtered and the fitrate was concentrated in vacuo. The residue was purified by flash column chromatography.

(1-((1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)methyl)cyclohexyl)methyl benzoate (155)



Compound **155** was synthesized by following the general procedure: 3,4-dihydro-3,3-spirocyclohexyl-2H-naphtho[1,2-b]pyran-5,6-dione (**92**) (100 mg, 0.354 mmol), 1% aqueous sodium hydroxide solution (2.12 mL, 0.531 mmol), benzoic acid (64.9 mg, 0.531 mmol) and CDI (86.1 mg, 0.513 mmol) in dry THF (7 mL) was used following the procedure. The reaction mixture was stirred at room temperature for 15h. The crude residue was purified by flash column chromatography eluting with 3% ethyl acetate-hexane to provide the desired product **155** (18.9 mg, 22% yield for 2 steps) as yellow gum and cyclized product **92a** (16.6 mg). The desired product was then recrystallized with hexane–dichloromethane to give the product as a yellow amorphous, m.p. 117.0-118.0 ^{o}C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.40-1.65 (m, 10H, $(CH_2)_5$), 2.83 (s, 2H, CH_2Ar), 4.24 (s, 2H, OCH_2), 7.42 (s, 1H, OH), 7.44 (m, 1H, ArH), 7.64 (m, 2H, ArH), 7.70 (m, 2H, ArH), 7.90 (d, *J*=7.6 Hz, 2H, ArH), 8.00 (m, 2H, ArH).

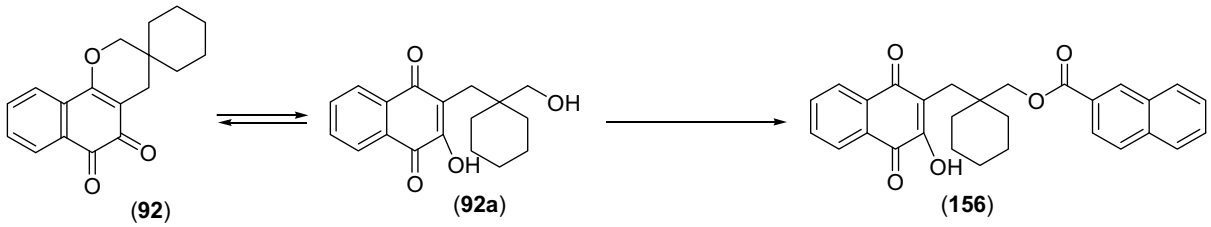
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.72 (2×CH_2), 26.01 (CH_2), 31.76 (CH_2), 33.50 (2×CH_2), 39.42 (C), 69.40 (CH_2), 122.15 (C), 125.93 (CH), 126.97 (CH), 128.12 (2×CH), 129.27 (C), 129.34 (2×CH), 130.37 (C), 132.59 (CH), 132.75 (CH), 133.04 (C), 134.82 (CH), 154.17 (C), 166.52 (C=O), 181.09 (C=O), 185.05 (C=O).

FTIR (neat, cm^{-1}): 3371 (OH), 3067 (CH-aromatic), 2928, 2852 (CH_2), 1715, 1664, 1650 (C=O), 1594, 1451, 1371, 1274 (C=C), 1116, 1025 (C-O).

MS (EI), *m/z* (% relative intensity): 404 (M^+, 100), 296 (22), 284 (76), 257 (42), 175 (9).

Anal. Calcd. for $C_{25}H_{24}O_5$: C, 74.24; H, 5.98. Found: C, 74.44, H, 6.01.

(1-((1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)methyl)cyclohexyl)methyl 2-naphthoate (156)



Compound **156** was synthesized by following the general procedure: 3,4-dihydro-3,3-spirocyclohexyl-2H-naphtho[1,2-b]pyran-5,6-dione (**92**) (100 mg, 0.354 mmol), 1% aqueous sodium hydroxide solution (2.12 mL, 0.531 mmol), 2-naphthoic acid (73.2 mg, 0.425 mmol) and CDI (86.1 mg, 0.513 mmol) in dry THF (6 mL) was used following the procedure. The reaction mixture was stirred at room temperature for 45h. The crude residue was purified by flash column chromatography eluting with 1% ethyl acetate-hexane to provide the desired product **156**(56.0 mg, 43% yield for 2 steps) as yellow gum and cyclized product **92** (19.0 mg). The desired product was then recrystallized with hexane–dichloromethane to give the product as a yellow amorphous, m.p. 179.0-180.0 ^oC.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.40-1.70 (m, 10H, $(CH_2)_5$), 2.86 (s, 2H, CH_2Ar), 4.30 (s, 2H, OCH_2), 7.41 (dt, *J*=1.2 and 7.6 Hz, 1H, ArH), 7.42 (s, 1H, OH), 7.48 (m, 1H, ArH), 7.56 (m, 1H, ArH), 7.69 (d, *J*=8.8 Hz, 1H, ArH), 7.73 (d, *J*=8.0 Hz, 1H, ArH), 7.80 (d, *J*=8.4 Hz, 1H, ArH), 7.85 (dd, *J*=1.2 and 7.6 Hz, 2H, ArH), 7.91 (m, 2H, ArH), 8.37 (s, 1H, ArH).

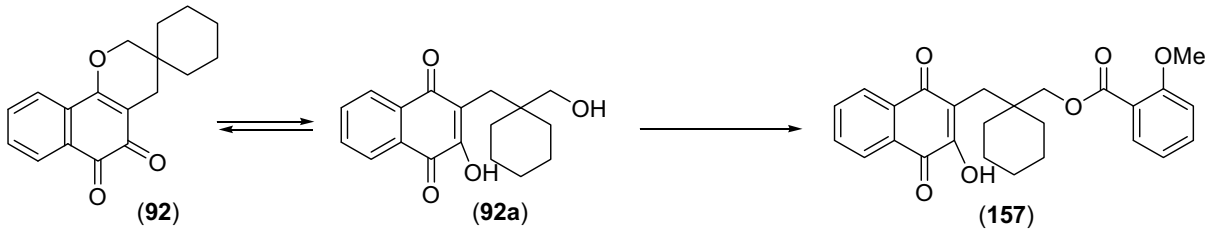
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 22.06 ($2\times CH_2$), 26.38 (CH_2), 32.34 (CH_2), 33.98 ($2\times CH_2$), 39.77 (C), 70.12 (CH_2), 122.61 (C), 125.35 (CH), 126.14 (CH), 126.74 (CH), 127.09 (CH), 127.85 (C), 127.93 (CH), 128.24 (CH), 128.37 (CH), 129.41 (C), 129.58 (CH), 131.01 (CH), 132.55 (C), 132.79 (CH), 133.22 (C), 134.94 (CH), 135.60, 154.41 (C), 166.99 (C=O), 181.41 (C=O), 185.43 (C=O).

FTIR (neat, cm^{-1}): 3383 (OH), 3055 (CH-aromatic), 2931, 2848 (CH_2), 1713, 1651 (C=O), 1594, 1458, 1374, 1275 (C=C), 1196, 1024 (C-O).

MS (EI), *m/z* (% relative intensity): 454 (M^+, 12), 297 (10), 283 (100), 265 (38).

Anal. Calcd. for $C_{29}H_{26}O_5$: C, 76.63; H, 5.77. Found: C, 76.30, H, 5.90.

(1-((1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)methyl)cyclohexyl)methyl 2-methoxybenzoate (157)



(**92**) (**92a**) (**157**)

Compound **157** was synthesized by following the general procedure: 3,4-dihydro-3,3-spirocyclohexyl-2H-naphtho[1,2-b]pyran-5,6-dione (**92**) (140 mg, 0.496 mmol), 1% aqueous sodium hydroxide solution (2.98 mL, 0.744 mmol), 2-methoxybenzoic acid (90.6 mg, 0.595 mmol) and CDI (126.7 mg, 0.744 mmol) in dry THF (8 mL) was used following the general procedure. The reaction mixture was stirred at room temperature for 48h. The

crude residue was purified by flash column chromatography eluting with 1% ethyl acetate-hexane to provide the desired product **157** (109.0 mg, 69% yield for 2 steps) as a yellow gum and cyclized product **92** (37.0 mg).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.25-1.60 (m, 10H, $(CH_2)_5$), 2.73 (s, 2H, CH_2Ar), 3.73 (s, 3H, OCH_3), 4.13 (s, 2H, OCH_2), 6.74 (m, 2H, ArH), 7.26 (m, 1H, ArH), 7.35 (s, 1H, OH), 7.55 (m, 2H, ArH), 7.65 (dd, J=1.8 and 8.0 Hz, 1H, ArH), 7.91 (m, 2H, ArH).

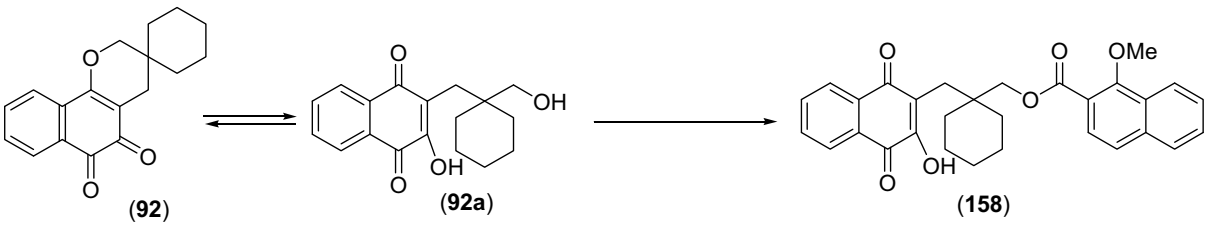
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.74 ($2\times CH_2$), 26.04 (CH_2), 31.72 (CH_2), 33.42 ($2\times CH_2$), 39.41 (C), 55.70 (CH_3), 69.34 (CH_2), 111.77 (CH), 119.90 (CH), 120.09 (C), 122.34 (C), 125.81 (CH), 126.88 (CH), 129.26 (C), 131.71 (CH), 132.64 (CH), 133.01 (C), 133.26 (CH), 134.64 (CH), 154.07 (C), 159.00 (C), 166.22 (C=O), 181.08 (C=O), 185.08 (C=O).

FTIR (neat, cm^{-1}): 3365 (OH), 3062 (CH-aromatic), 2929, 2863 (CH_2), 1716, 1660, 1648 (C=O), 1598, 1460, 1372, 1252 (C=C), 1084, 1024 (C-O).

MS (EI), *m/z* (% relative intensity): 433 ($[M-1]^+$, 7), 297 (12), 265 (8).

Anal. Calcd. for $C_{26}H_{26}O_6$: C, 71.87; H, 6.03. Found: C, 71.75, H, 5.84.

(1-((1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)methyl)cyclohexyl)methyl 1-methoxynaphthalene-2-carboxylate (158)



Compound **158** was synthesized by following the general procedure: 3,4-dihydro-3,3-spirocyclohexyl-2H-naphtho[1,2-b]pyran-5,6-dione (**92**) (140 mg, 0.496 mmol), 1% aqueous sodium hydroxide solution (2.98 mL, 0.744 mmol), 1-methoxy-2-naphthoic acid (120.3 mg, 0.595 mmol) and CDI (120.7 mg, 0.744 mmol) in dry THF (8 mL) was used following the general procedure. The reaction mixture was stirred at room temperature for

48h. The crude residue was purified by flash column chromatography eluting with 1% ethyl acetate-hexane to provide the desired product **158** (67.0 mg, 33% yield for 2 steps) as yellow gum and cyclized product **92** (21.0 mg). The desired product was then recrystallized with hexane–dichloromethane to give the product as a yellow amorphous, m.p. 124.0-125.0 ^{o}C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.25-1.67 (m, 10H, $(CH_2)_5$), 2.73 (s, 2H, CH_2Ar), 3.89 (s, 3H, OCH_3), 4.22 (s, 2H, OCH_2), 7.18 (td, *J*=7.6 and 1.2 Hz, 1H, ArH), 7.29 (d, *J*=8.7 Hz, 1H, ArH), 7.30 (td, *J*=7.6 and 1.2 Hz, 1H, ArH), 7.37 (s, 1H, OH), 7.45 (m, 2H, ArH), 7.63 (d, *J*=8.7 Hz, 1H, ArH), 7.67 (d, *J*=7.7 Hz, 2H, ArH), 7.75 (dd, *J*=8.7 and 1.2 Hz, 1H, ArH), 8.02 (d, *J*=8.2 Hz, 1H, ArH).

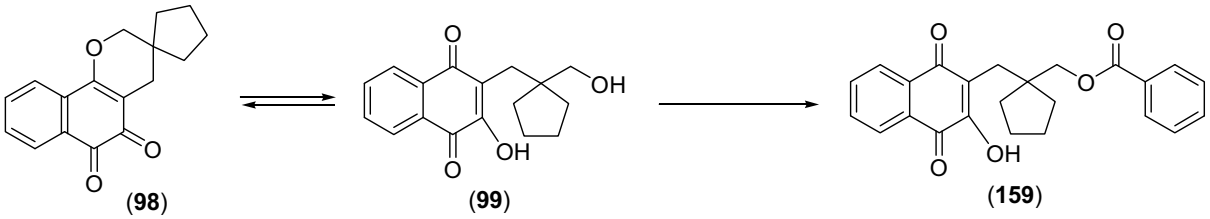
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.75 (2×CH_2), 26.08 (CH_2), 32.01 (CH_2), 33.69 (2×CH_2), 39.39 (C), 63.39 (CH_3), 70.02 (CH_2), 119.36 (C), 122.25 (C), 123.31 (CH), 123.57 (CH), 125.54 (CH), 126.23 (CH), 126.48 (CH), 126.55 (CH), 127.64 (CH), 128.07 (CH), 128.31 (C), 129.04 (C), 132.07 (CH), 132.81 (CH), 134.24 (CH), 136.57 (C), 153.89 (C), 157.92 (C), 166.08 (C=O), 181.13 (C=O), 185.17 (C=O).

FTIR (KBr, cm^{-1}): 3355 (OH), 2970, 2922, 2857 (CH_2), 1709, 1647 (C=O), 1589, 1451, 1371, 1271 (C=C), 1125, 1000 (C-O).

MS (EI), *m/z* (% relative intensity): 484 (M^+, 32), 433 ($[M-1]^+$,100), 297 (12), 283 (71), 265 (7).

Anal. Calcd. for $C_{30}H_{28}O_6$: C, 79.96; H, 8.20. Found: C, 80.00, H, 8

(1-((1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)methyl)cyclopentyl)methyl benzoate (159)



(**98**) (**99**) (**159**)

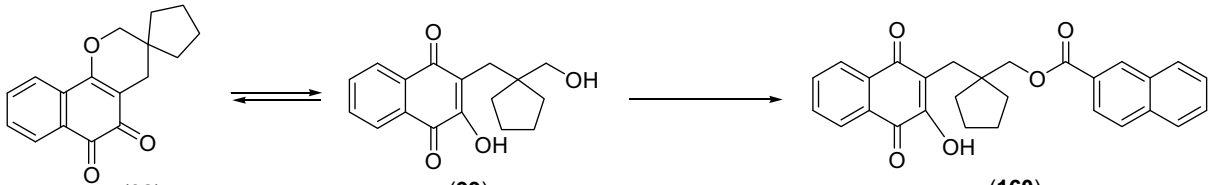
Compound **159** was synthesized by following the general procedure: 3,4-dihydro-3,3-spirocyclopentyl-2H-naphtho[1,2-b]pyran-5,6-dione (**98**) (370 mg, 1.309 mmol), 1% aqueous sodium hydroxide solution (2.24 ml, 0.56 mmol), benzoic acid (77.0 mg, 0.63 mmol) and CDI (137.6 mg, 0.82 mmol) in dry THF (3 mL) was used following the procedure. The reaction mixture was stirred at room temperature for 48 h. The crude residue was purified by flash column chromatography eluting with 5% ethyl acetate-hexane to provide the desired product as yellow oil (69% yield for 2 steps). The desired product was then recrystallized with hexane–dichloromethane to give the product **159** as a yellow needle.

FTIR (KBr, cm^{-1}) : 3407 (OH), 1713, 1664, 1642 (C=O), 1590, 1364 (C=C), 1276, 1224 (C-O)

^{1}H NMR, chemical shift ($CDCl_3$, 400 MHz) : 1.53-1.77 (m, 8H, $(CH_2)_4$), 2.85 (s, 2H, $ArCH_2$), 4.14 (s, 2H, OCH_2), 7.20 (m, 2H, ArH), 7.58 (m, 1H, ArH), 7.60-7.72 (m, 2H, ArH), 7.86 (m, 2H, ArH), 7.94 (m, 2H, ArH). 8.32 (s, 1H, OH)

^{13}C NMR, chemical shift ($CDCl_3$, 100 MHz) : 24.4 ($2xCH_2$), 30.7 (CH_2), 35.0 ($2xCH_2$), 48.2 (C), 70.7 (CH_2), 122.5 (C), 125.9(CH), 127.0 (CH), 128.1 (2xCH), 129.4 (2xCH), 130.4 (C), 132.6 (CH), 132.8 (CH), 133.0 (C), 134.8 (CH), 135.3 (C), 154.2 (C), 166.6 (C=O), 181.2 (C=O), 185.1 (C=O)

(1-((1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)methyl)cyclopentyl)methyl 2-naphthoate (160)



(**98**) (**99**) (**160**)

Compound **160** was synthesized by following the general procedure: 3,4-dihydro-3,3-spirocyclopentyl-2H-naphtho[1,2-b]pyran-5,6-dione (**98**) (370 mg, 1.309 mmol), 1% aqueous sodium hydroxide solution (2.24 ml, 0.56 mmol), benzoic acid (77.0 mg, 0.63 mmol) and CDI (137.6 mg, 0.82 mmol) in dry THF (7 mL) was used following the

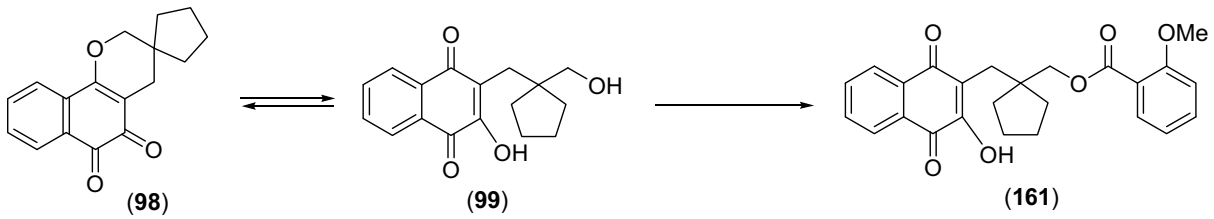
procedure. The reaction mixture was stirred at room temperature for 48 h. The crude residue was purified by flash column chromatography eluting with 5% ethyl acetate-hexane to provide the desired product as yellow oil (66% yield for 2 steps). The desired product was then recrystallized with hexane–dichloromethane to give the product **160** as a yellow needle.

FTIR (KBr, cm^{-1}) : 1715, 1656 (C=O), 1595, 1456, 1371 (C=C), 1276, 1115 (C-O)

^{1}H NMR, chemical shift ($CDCl_3$, 400 MHz) : 1.55-1.74 (m, 8H, $(CH_2)_4$), 2.82 (s, 2H, $ArCH_2$), 4.08 (s, 2H, $OC\underline{H}_2$), 7.20 (m, 2H, ArH), 7.37 (m, 2H, ArH), 7.57 (m, 2H, ArH), 7.85 (m, 2H, ArH), 7.94 (m, 2H, ArH)

^{13}C NMR, chemical shift ($CDCl_3$, 100 MHz) : 24.6 ($2xCH_2$), 30.9 (CH_2), 35.3 ($2xCH_2$), 48.5 (C), 70.9 (CH_2), 122.7 (C), 126.2 (CH), 127.2 (CH), 128.4 (2xCH), 129.5 (C), 129.6 (2xCH), 130.6 (C), 132.9 (CH), 133.0 (CH), 133.2 (C), 135.1 (CH), 154.4 (C), 166.9 (C=O), 181.4 (C=O), 185.4 (C=O)

(1-((1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)methyl)cyclopentyl)methyl 2-methoxybenzoate (161)



(**98**) (**99**) (**161**)

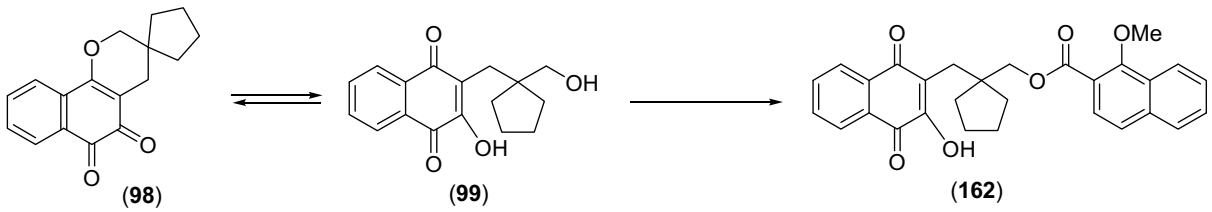
Compound **161** was synthesized by following the general procedure: 3,4-dihydro-3,3-spirocyclopentyl-2H-naphtho[1,2-b]pyran-5,6-dione (**98**) (370 mg, 1.309 mmol), 1% aqueous sodium hydroxide solution (2.24 ml, 0.56 mmol), benzoic acid (77.0 mg, 0.63 mmol) and CDI (137.6 mg, 0.82 mmol) in dry THF (7 mL) was used following the procedure. The reaction mixture was stirred at room temperature for 48 h. The crude residue was purified by flash column chromatography eluting with 5% ethyl acetate-hexane to provide the desired product as yellow oil (40% yield for 2 steps). The desired product was then recrystallized with hexane–dichloromethane to give the product **161** as a yellow needle.

FTIR (KBr, cm^{-1}) : 3369 (OH), 1694, 1649 (C=O), 1595, 1460, 1350, 1305 (C=C), 1265, 1213, 1132 (C-O)

^{1}H NMR, chemical shift ($CDCl_3$, 400 MHz) : 1.16-1.22 (m, 4H, $(CH_2)_4$), 1.52-1.66 (m, 2H, $(CH_2)_4$), 1.66-1.74 (m, 2H, $(CH_2)_4$), 2.80 (s, 2H, ArH), 3.73 (s, 3H,OCH_3), 4.05 (s, 2H, OCH_2), 6.75 m, 2H, ArH), 7.28 (m, 1H, ArH), 7.56 (m, 2H, ArH), 7.67 (m, 1H, ArH), 7.92 (m, 2H, ArH)

^{13}C NMR, chemical shift ($CDCl_3$, 100 MHz) : 24.3 (2xCH_2), 30.7 (CH_2), 35.0 (2xCH_2), 48.2 (C), 55.7 (CH_3), 70.5 (CH_2), 111.8 (CH), 119.9 (CH), 120.1 (C), 122.7 (C), 125.8 (CH), 126.9 (CH), 129.3 (C), 131.7 (CH), 132.7 (CH), 132.9 (C), 133.3 (CH), 134.7 (CH), 154.0 (C), 159.0 (C), 166.3 (C=O), 181.2 (C=O), 185.2 (C=O)

(1-((1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)methyl)cyclopentyl)methyl 1-methoxynaphthalene-2-carboxylate (162)



(**98**) (**99**) (**162**)

Compound **162** was synthesized by following the general procedure: 3,4-dihydro-3,3-spirocyclopentyl-2H-naphtho[1,2-b]pyran-5,6-dione (**98**) (370 mg, 1.309 mmol), 1% aqueous sodium hydroxide solution (2.24 ml, 0.56 mmol), benzoic acid (77.0 mg, 0.63 mmol) and CDI (137.6 mg, 0.82 mmol) in dry THF (7 mL) was used following the procedure. The reaction mixture was stirred at room temperature for 48 h. The crude residue was purified by flash column chromatography eluting with 5% ethyl acetate-hexane to provide the desired product as yellow oil (28% yield for 2 steps). The desired product was then recrystallized with hexane–dichloromethane to give the product **162** as a yellow needle.

FTIR (KBr, cm^{-1}) : 3368 (OH), 1701, 1646 (C=O), 1594, 1457, 1371, 1340, 1278 (C=C), 1242, 1157, 1085 (C-O)

^{1}H NMR, chemical shift ($CDCl_3$, 400 MHz) : 1.63-1.85 (m, 8H, $(CH_2)_4$), 2.88 (s, 2H, $ArCH_2$), 4.00 (s, 3H, OCH_3), 4.21 (s, 2H, OCH_2), 7.33 (m, 1H, ArH), 7.41 (m, 2H, ArH), 7.44 (s, 1H, OH), 7.52 (m, 2H, ArH), 7.74 (m, 1H, ArH), 7.75 (m, 1H, ArH), 7.81 (dd, 1H, *J*=7.66 Hz and *J*=0.96 Hz, ArH), 7.86 (dd, 1H, *J*=7.66 Hz and *J*=0.96 Hz, ArH), 8.11 (m, 1H, ArH)

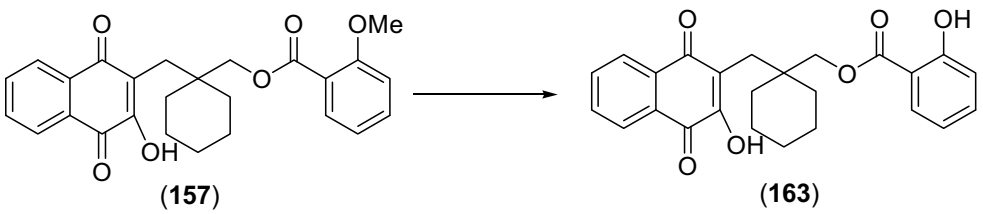
^{13}C NMR, chemical shift ($CDCl_3$, 100 MHz) : 24.6 ($2xCH_2$), 31.1 (CH_2), 35.6 ($2xCH_2$), 48.6 (C), 63.7 (CH_3), 71.5 (CH_2), 119.6 (C), 122.8 (C), 123.6 (CH), 123.8 (CH), 125.9 (CH), 126.5 (CH), 126.78 (CH), 126.83 (CH), 127.9 (CH), 128.3 (CH), 128.6 (C), 129.4 (C), 132.5 (CH), 133.0 (C), 134.6 (CH), 136.8 (C), 154.2 (C), 158.2 (C), 166.4 (C=O), 181.5 (C=O), 185.5 (C=O)

Demethylation of phenyl and naphthyl methyl ether

General procedure:

1 M Boron tribromide (BBr_3) in dichloromethane (0.115 mmol) was added dropwise to a stirred solution of the methyl ether **157**, **158** or **161**,**162** (0.115 mmol) in dry dichloromethane (2.5 mL) at 0 ºC and the solution was stirred for 30 minutes at the same temperature. Then water was added and extracted with dichloromethane (3×10 mL). The organic phases were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford crude residue.

(1-((1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)methyl)cyclohexyl)methyl 2-hydroxybenzoate (163)



Compound **163** was synthesized by following the general procedure: a mixture of methyl ether **157** (50.0 mg, 0.115 mmol) and 1 M BBr_3 (115.0 μL, 0.115 mmol) in dry CH_2Cl_2 (2.5 mL) was stirred at 0 ^oC for 30 minutes. The crude residue was purified by flash column chromatography eluting with 4 % ethyl acetate-hexane. The yellow oil was obtained in 87 %yield (42.0 mg), then it was recrystallized with hexane-dichloromethane to give a yellow amorphous (**163**), m.p. 99.0-100.0 ^oC.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.30-1.70 (m, 10H, $(CH_2)_5$), 2.74 (s, 2H, CH_2Ar), 4.12 (s, 2H, OCH_2), 6.51 (m, 1H, ArH), 6.82 (m, 1H, ArH), 7.24 (m, 1H, ArH), 7.37 (br s, 1H, OH-quinone), 7.55 (m, 3H, ArH), 7.93 (m, 2H, ArH), 10.68 (s, 1H, OH-phenol).

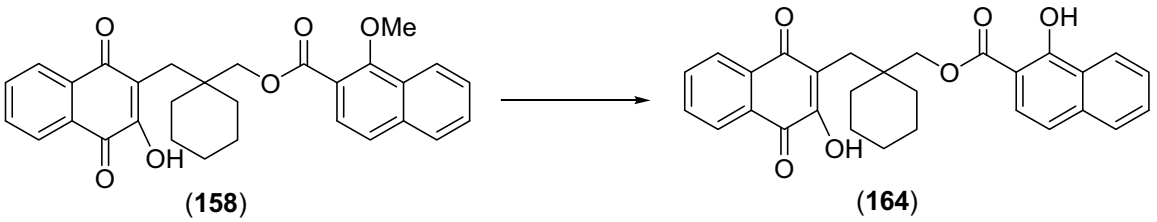
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.65 (2×CH_2), 25.96 (CH_2), 31.67 (CH_2), 33.45 (2×CH_2), 39.30 (C), 69.76 (CH_2), 112.53 (C), 117.43 (CH), 118.84 (CH), 121.84 (C), 125.98 (CH), 126.93 (CH), 129.23 (C), 129.55 (CH), 132.83 (CH), 132.98 (C), 134.92 (CH), 135.34 (C), 154.21 (C), 161.39 (C), 170.01 (C=O), 181.05 (C=O), 185.06 (C=O).

FTIR (KBr, cm^{-1}): 3329 (OH), 2920, 2851 (CH_2), 1675, 1659, 1615 (C=O), 1591, 1487, 1338, 1212 (C=C), 1156, 1090 (C-O).

MS (EI), *m/z* (% relative intensity): 419 ($[M-1]^+$, 2), 297 (3), 283 (100), 265 (11).

Anal. Calcd. for $C_{30}H_{28}O_6$: C, 79.96; H, 8.20. Found: C, 80.00, H, 8.20.

(1-((1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)methyl)cyclohexyl)methyl 1-hydroxynaphthalene-2-carboxylate (164)



Compound **164** was synthesized by following the general procedure: a mixture of methyl ether **158** (30.0 mg, 0.062 mmol) and 1 M BBr_3 (62.0 µL, 0.062 mmol) in dry CH_2Cl_2 (1.5 mL) was stirred at 0 ^oC for 30 minutes. The crude residue was purified by flash column chromatography eluting with 3% ethyl acetate-hexane. The yellow oil was obtained in 68% yield (19.8 mg), then it was recrystallized with hexane-dichloromethane to give a yellow amorphous (164), m.p. 103.0-104.0 ^oC

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.40-1.70 (m, 10H, $(CH_2)_5$), 2.68 (s, 2H, CH_2Ar), 4.22 (s, 2H, CH_2O), 6.87 (m, 1H, Ar), 7.36 (s, 1H, OH-quinone), 7.34-7.44 (m, 3H, ArH), 7.43 (d, *J*=8.8 Hz, 1H, ArH), 7.49 (m, 1H, ArH), 7.58 (m, 1H, ArH), 7.85 (m, 2H, ArH), 8.27 (m, 1H, ArH), 11.84 (s, 1H, OH-naphthol).

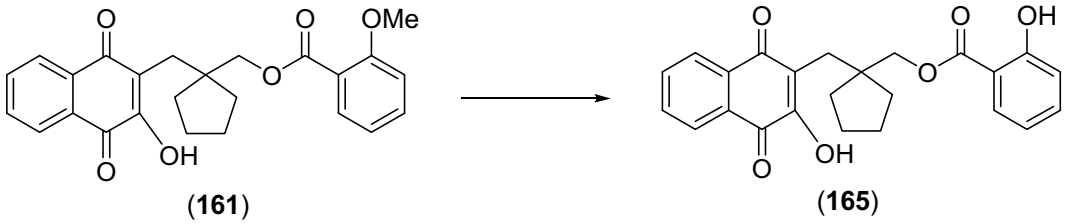
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.71 (2×CH_2), 26.01 (CH_2), 31.76 (CH_2), 33.59 (2×CH_2), 39.38 (C), 69.91 (CH_2), 105.79 (C), 118.30 (CH), 121.95 (C), 123.77 (CH), 123.95 (CH), 124.64 (C), 125.61 (CH), 125.82 (CH), 126.79 (CH), 127.32 (CH), 129.17(C), 129.20 (CH), 132.60 (CH), 132.91(C), 134.63 (CH), 136.97 (C), 154.13 (C), 160.55 (C), 170.82 (C=O), 181.08 (C=O), 185.07 (C=O).

FTIR (KBr, cm^{-1}): 3277 (OH), 2923, 2850 (CH_2), 1668, 1638 (C=O), 1595, 1459, 1394, 1351, 1270 (C=C), 1164, 1089 (C-O).

MS (EI), *m/z* (% relative intensity): 470 (M^+, 32), 415 (100).

Anal. Calcd. for $C_{29}H_{26}O_6$: C, 74.03; H, 5.57. Found: C, 74.08, H, 5.45.

(1-((1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)methyl)cyclopentyl)methyl 2-hydroxybenzoate (165)



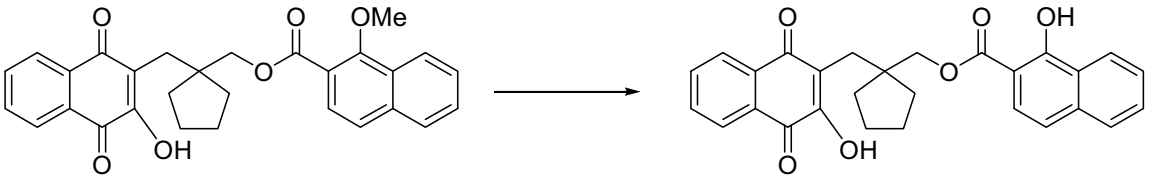
1M Borontribromide in dichloromethane (0.11 mmol) was added dropwise over 5 minutes at roomtemperature to a stirred solution of naphthoquinone ester **161** (0.1 mmol) in dry dichloromethane (5 mL) and the reaction mixture was stirred for 2 hours. Then cold water was added and mixture extracted with dichloromethane (3 x 30 mL). The combined organic phases were washed with water, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 7 % v/v ethyl acetate : hexane to afford the product **165** (86%) as yellow needle.

FTIR (KBr, cm^{-1}) : 3354 (OH), 1666 (C=O), 1593, 1486, 1459, 1365, 1300 (C=C), 1214, 1159, 1090 (C-O)

^{1}H NMR, chemical shift ($CDCl_3$, 400 MHz) : 1.55-1.68 (m, 6H, $(CH_2)_4$), 1.72-1.82 (m, 2H, $(CH_2)_4$), 2.82 (s, 2H, $ArCH_2$), 4.11 (s, 2H, OCH_2), 6.55 (m, 1H, ArH), 6.84 (m, 1H, ArH), 7.27 (m, 1H, ArH), 7.38 (s, 1H, OH), 7.59 (m, 3H, ArH), 7.95 (m, 1H, ArH), 7.97 (m, 1H, ArH), 10.70 (s, 1H, ArOH)

^{13}C NMR, chemical shift ($CDCl_3$, 100 MHz) : 24.6 ($2xCH_2$), 30.9 (CH_2), 35.3 ($2xCH_2$), 48.4 (C), 71.2 (CH_2), 112.8 (C), 117.7 (CH), 119.1 (CH), 122.4 (C), 126.2 (CH), 127.2 (CH), 129.5 (C), 129.8 (CH), 133.1 (CH), 133.2 (C), 135.2 (CH), 135.6 (CH), 154.4 (C), 161.7 (C), 170.3 (C=O), 181.4 (C=O), 185.4 (C=O)

(1-((1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)methyl)cyclopentyl)methyl 1-hydroxynaphthalene-2-carboxylate (166)



1M Borontribromide in dichloromethane (0.174 mmol) was added dropwise over 5 minutes at roomtemperature to a stirred solution of naphthoquinone ester **162** (0.087 mmol) in dry dichloromethane (5 mL) and the reaction mixture was stirred for 2 hours. Then cold water was added and mixture extracted with dichloromethane (3 x 30 mL). The

combined organic phases were washed with water, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 7 % v/v ethyl acetate : hexane to afford the product **166** (70%) as yellow needle.

FTIR (KBr, cm^{-1}) : 3424, 3358 (oh), 1659 (c=o), 1594, 1459, 1395, 1369, 1338 (c=c), 1253, 1214, 1157 (C-O)

^{1}H NMR, chemical shift ($CDCl_3$, 400 MHz) : 1.56-1.83 (m, 8H, $(CH_2)_4$), 2.84 (s, 2H, $ArCH_2$), 4.17 (s, 2H, OCH_2), 6.92 (d, 1H, *J*=8.38 Hz, ArH), 7.37 (s, 1H, OH), 7.41-7.53 (m, 5H, ArH), 7.60 (d, 1H, *J*=8.38 Hz, ArH), 7.89 (m, 2H, ArH), 8.29 (m, 1H, ArH), 11.87 (s, 1H, ArOH)

^{13}C NMR, chemical shift ($CDCl_3$, 100 MHz) : 24.6 ($2xCH_2$), 31.1 (CH_2), 35.4 ($2xCH_2$), 48.5 (C), 71.3 (CH_2), 106.0 (C), 118.5 (CH), 122.5 (C), 124.0 (CH), 124.2 (CH), 124.9 (C), 125.8 (CH), 126.1 (CH), 127.1 (CH), 127.6 (CH), 129.42 (C), 129.43 (CH), 132.9 (CH), 133.1 (C), 134.9 (CH), 137.2 (C), 154.3 (C), 160.8 (C), 171.1 (C=O), 181.4 (C=O), 185.4 (C=O)

Biological Activities

Cytotoxicity assay by the MTT colorimetric method (Skehan *et al.*, 1990)

Rhinacanthins-M (**6**),-N (**7**),-Q (**14**), rhinacanthone (**44**), 1,2-naphthoquinones (**42** and **43**), and naphthoquinone esters (**115-166**) dissolved in dimethyl sulfoxide (DMSO) were subjected to cytotoxic evaluation against KB (human epidermoid carcinoma), HeLa (human cervical carcinoma) and MCF-7 (human breast carcinoma) cell lines employing the colorimetric method. Adriamycin was used as the reference drug which exhibits cytotoxicity against KB, HeLa and MCF-7 cell lines.

3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (Sigma Chemical Co.) was dissolved in saline to make a concentration of 5 mg/mL as a stock solution. Cancer cells (3×10^3 cells) suspended in 100 μg/well of MEM medium containing 10% fetal calf serum (FCS, Gibco BRL, Life Technologies, NY) were seeded onto a 96-well culture

plate (Coster, Corning Incorporated, NY 14831). After 24h of preincubation at 37 ^{o}C in a humidified atmosphere of 5% CO_2/95% air to allow cell attachment, various concentrations of test solution (10 μL/well) as listed in Tables16 and 17 were added and then incubated for 48h under the above conditions. At the end of the incubation, 10 μL of tetrazolium reagent was added to each well and then incubated at 37 ^{o}C for 4h. The supernatant was decanted, and DMSO (100 μL/well) was added to allow Formosan solubilization. The optical density (OD) of each well was detected by a Microplate reader (Bio-Rad, Benchmark Microplate reader) at 550 nm and for correction at 595 nm. Each determination represents the mean of six replicates. The 50% inhibition concentration (IC_{50}) was determined by curve fitting.

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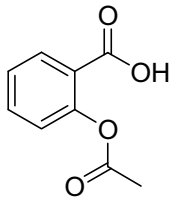
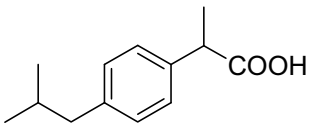
PART II : SYNTHESIS OF NAPHTHOL DERIVATIVES WITH ANTI-INFLAMMATORY ACTIVITY

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are drugs with analgesic (against minor pain and aches), antipyretic (against fever) and anti-inflammatory effects. Prominent members of this group of drugs include aspirin (**167**) and ibuprofen (**168**).

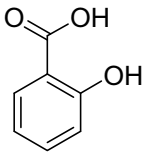


Aspirin, **167**



Ibuprofen, **168**

In 1829, the aspirin precursor, salicylic acid (**169**) was isolated from the folk remedy willow bark and NSAIDs have become an important part of the pharmaceutical treatment of pain at low doses and inflammation at higher doses.



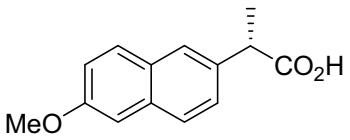
Salicylic acid, **169**

NSAIDs are usually indicated for the treatment of acute or chronic conditions such as pain and inflammation and their widespread has meant that that adverse effects of these relatively safe drugs have become increasingly prevalent. The two main adverse drug reactions (ADRs), associated with NSAIDs are gastrointestinal (GI) effects and renal effects. These effects are dose-dependent, and in many cases severe enough to pose risks of ulcer perforation, upper gastrointestinal bleeding, and death, limiting the use of NSAID therapy.

Most NSAIDs act as non-selective inhibitors of the enzyme, cyclooxygenase, inhibiting to varying degrees both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. Cyclooxygenase catalyses the formation of various types of prostaglandins and thromboxane, from arachidonic acid, promoting inflammation, pain, and fever. However, only COX-1 produces prostaglandins that support platelets and protect the stomach lining. Nonsteroidal anti-inflammatory drugs block the COX enzymes and reduce prostaglandins throughout the body. As a consequence, ongoing inflammation, pain, and fever are reduced. Since the prostaglandins that protect the stomach and support the platelets and blood clotting also are reduced, NSAIDs can cause ulcers in the stomach and promote bleeding. NSAIDs differ in how strongly they inhibit COX-1 and, therefore, in their tendency to cause ulcers and promote bleeding.

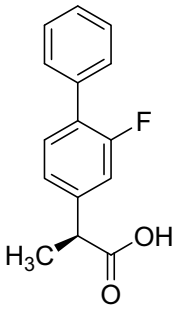
The discovery of COX-2 in 1991 by Xie *et al*. (Xie *et al*., 1991) raised the hope of developing an effective NSAID without the gastric problems, characteristic of these agents. It was thought that selective inhibition of COX-2 would result in anti-inflammatory action without disrupting the COX-1 gastroprotective prostaglandins.

COX-1 is a constitutively expressed enzyme with a "house-keeping" role in regulating many normal physiological processes. One of these is in the stomach lining, where prostaglandins serve a protective role, preventing the stomach mucosa from being eroded by its own acid. When non-selective COX-1/COX-2 inhibitors (such as aspirin, ibuprofen, and naproxen (**170**)) lower stomach prostaglandin levels, these protective effects are lost and ulcers of the stomach or duodenum and internal bleeding can result. COX-2 is an enzyme expressed in inflammation, and it is the inhibition of COX-2 that produces the desirable effects of NSAIDs.

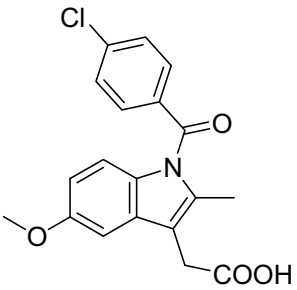


Naproxen, **170**

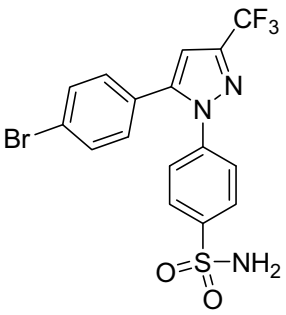
In 1996, Kurumbail *et al*. reported the structural basis for selective inhibition of COX-2 by anti-inflammatory agents such as flurbiprofen (**171**), indomethacin (**172**) and SC-558 (**173**) which is a highly selective COX-2 inhibitor.



Flurbiprofen, **171**

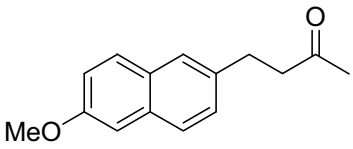


Indomethacin, **172**



SC-558, **173**

As some of NSAIDs such as naproxen and nabumetone (**174**) possess the naphthyl skeleton and naphthol derivatives are intermediates in the synthesis of naphthoquinone ester, it is advantageous to study the anti-inflammatory activity of naphthols.

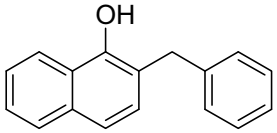


Nabumetone, **174**

(*S*)-Naproxen is a nonsteroidal anti-inflammatory drug introduced to the market by Syntex in 1976. It showed less potent inhibition of COX-1 and COX-2 activity in blood with IC_{50} values of 32.01 and 28.19 μM, respectively. So, the ratio of inhibition concentration (IC_{50}) of naproxen for COX-2/COX-1 is 0.88. Nabumetone (4-(6-methoxy-2-napthalenyl)-2-butanone) is a novel nonacidic broad-spectrum anti-inflammatory, analgesic and antipyretic agent, discovered in 1985. It inhibits COX-1 and COX-2 with IC_{50} values of 33.57 and 20.83 μM, respectively. So, the ratio of inhibition concentration (IC_{50}) of nabumetone for COX-2/COX-1 is 0.62. Thus naproxen and nabumetone are more COX-2 selective (Kolasa *et al*., 1997; Cryer *et al*., 1998).

In 1990, Batt *et al*. reported the synthesis, biological evaluation and structure-activity relationships of a series of 1-naphthol bearing carbon substituents at the 2-position. These compounds were found to be potent inhibitors of 5-lipoxygenase from RBL-1 cells and also inhibited bovine seminal vesicle cyclooxygenases. Especially, 2-benzyl-1-

naphthol (DuP 654, **175**) showed a very attractive profile of topical anti-inflammatory activity (IC50 = 0.019 μM and is currently in clinical trials as a topically applied antipsoriatic agent.

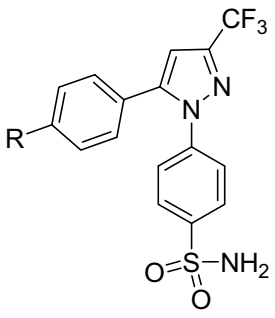


DuP 654, **175**

In 1997, Kolasa and co-workers reported using NSAIDs as orally bioavailable scaffolds to design selective 5-lipoxygenase (5-LO) inhibitors. Replacement of the NSAID carboxylic acid group with a *N*-hydroxyurea group provided congeners with selective 5-LO inhibitory activity. Each new *N*-hydroxyurea congener had individual characteristics which imparted differences in the amount of cyclooxygenase inhibitory activity retained and oral bioavailability observed in the rat.

In 1999, Llorens and co-workers studied molecular modeling on the two cyclooxygenase isozymes suggesting that the cavity at the mouth of the active site on the membrane domain may act as an actual binding site of COX ligands.

In 2000, Plount Price and Jorgensen reported the analysis of the binding affinities for celecoxib analogues (**176**) with COX-1 and COX-2 from docking experiments. The results reveal that steric hindrance restricts access of the ligand's substituents to some regions of the binding pocket and thus affects binding affinity. Furthermore, ligands which contain H-bonding functionality at the 4-position of the 5-aryl ring are poor binders because H-bonds cannot be formed between the substituents and the surrounding protein residues.



Celecoxib analogues, **176**

In the same year, Talanian *et al.* (Talanian *et al.*, 2000) reported using caspases as targets for anti-inflammatory and anti-apoptotic drugs. These enzymes had required roles in both processes and were widely considered promising targets for drug discovery. Much of the emphasis in caspase chemistry had been on development of novel electrophilic aspartic acid derivatives. Electrophilic moieties such as acyloxymethyl, aminomethyl and sulfonylaminomethyl were used in their caspase inhibitors and many of them were effective caspase-1 inhibitors.

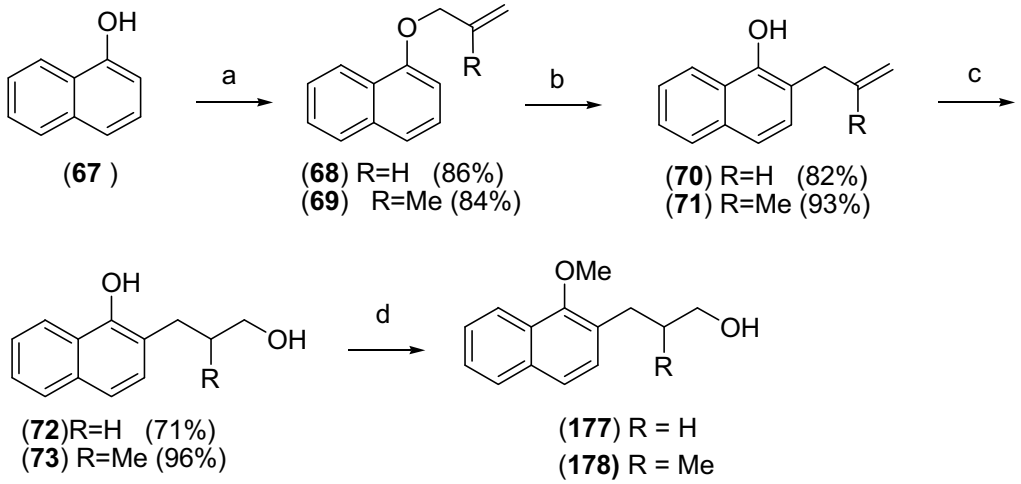
In 2001, Dannhardt and Kiefer discussed the current status and future prospects of cyclooxygenase inhibitors. They described selective cyclooxygenase inhibitors involving inflammatory processes as being agents that inhibit COX-2 but not COX-1 as a new attractive therapeutic development and a major advance in the treatment of rheumatoid arthritis and osteoarthritis. In inflammatory processes, COX-2 seems to play a role in angiogenesis, colon cancer and Alzheimer's disease, based on the fact that it is expressed during these diseases. Moreover, they explained the benefits of specific and selective COX-2 inhibitors which are currently under discussion and offer a new perspective for further use of COX-2 inhibitors.

In 2005, Luo and co-workers discussed the mechanism of COX-2 inhibitor therapy and its role in the development of anti-inflammatory, analgesic and antipyretic drugs.

RESULTS

1. Synthesis of naphthol derivatives

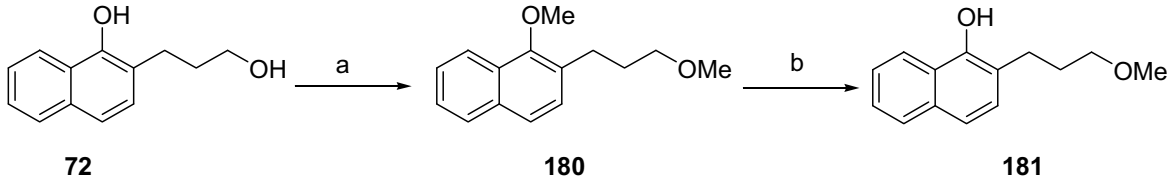
The 2-substituted-1-naphthol derivatives **72** and **73** were synthesized in four steps with high yields from 1-naphthol as shown in **Schemes 26**. While the synthesis of their methyl naphthyl ether derivatives (**177** and **178**) and ether 169 were also obtained in good yield as shown in **Schemes 25** and **26**.



Scheme 25

Reagents and conditions:

a) (i) Allyl bromide, K_2CO_3, reflux, 3h; (ii) 2-chloro-3-methyl-1-propene, K_2CO_3, reflux, 2h, **68** (86%), **69** (84%).
b) 180 °C, DMF, 6h, **70** (82%), **71** (93%).
c) BH_3·THF and then H_2O_2-NaOH, 8h, **72** (71%), **73** (96%).
d) MeI, K_2CO_3, acetone, reflux, 4h, **177** (quant.), **178** (quant.).

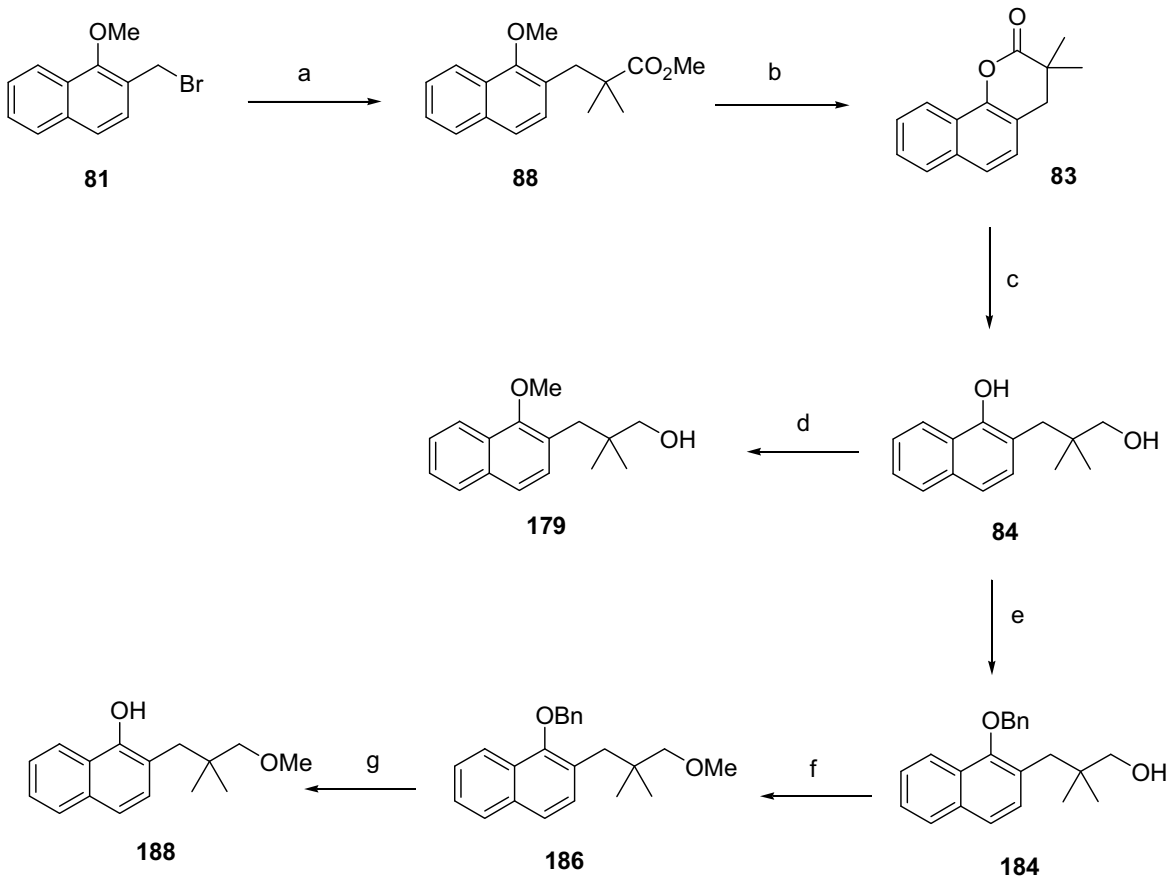


Scheme 26

Reagents and conditions:

a) NaH, MeI, dry THF, reflux, 3h, 93%.
b) BBr_3, dry CH_2Cl_2, 0 °C, 1h, 45%.

The syntheses of 2',2'-dimethylpropyl (**84**, **179**, **184**, **186** and **188**) and 2',2'-cyclohexylpropyl-1-naphthol (**90, 182**, **183**, **184**, **187** and **189**) derivatives were achieved by the same method and are shown in **Schemes 27** and **28**, respectively.



Scheme 27

Reagents and conditions:

a) LDA, methyl isobutylate, HMPA, dry THF, -78 °C, 2h, 89%.
b) $AlCl_3$, chlorobenzene, reflux, 4h, 83%.

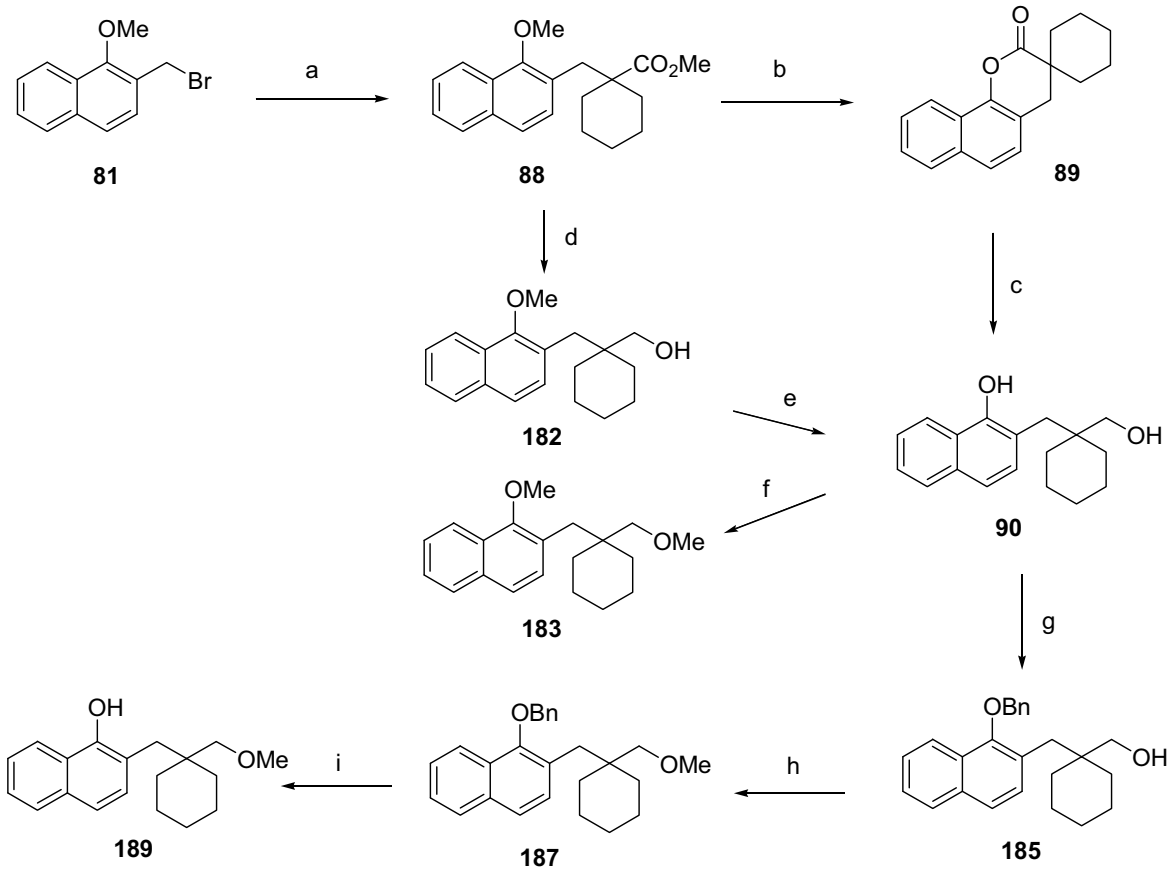
c) $LiAlH_4$, dry ether, rt., 2h, 71%.

d) MeI, K_2CO_3, acetone, reflux, 4h, 98%.

e) BnCl, K_2CO_3, acetone, reflux, 24h, 95%.

f) MeI, NaH, dry THF, reflux, 5h, 94%.

g) TMSCl, KI, CH_3CN, rt., 1h, 87%.



Scheme 28

Reagents and conditions:

a) LDA, methyl cyclohexylcarboxylate, HMPA, dry THF, -78 °C, 2h, 87%.

b) $AlCl_3$, chlorobenzene, reflux, 4h, 81%.

c) $LiAlH_4$, dry THF, rt., 2h, 89%.

d) $LiAlH_4$, dry THF, rt., 2h, 76%.

e) BBr_3, CH_2Cl_2, 0 °C, 1h, 89%.

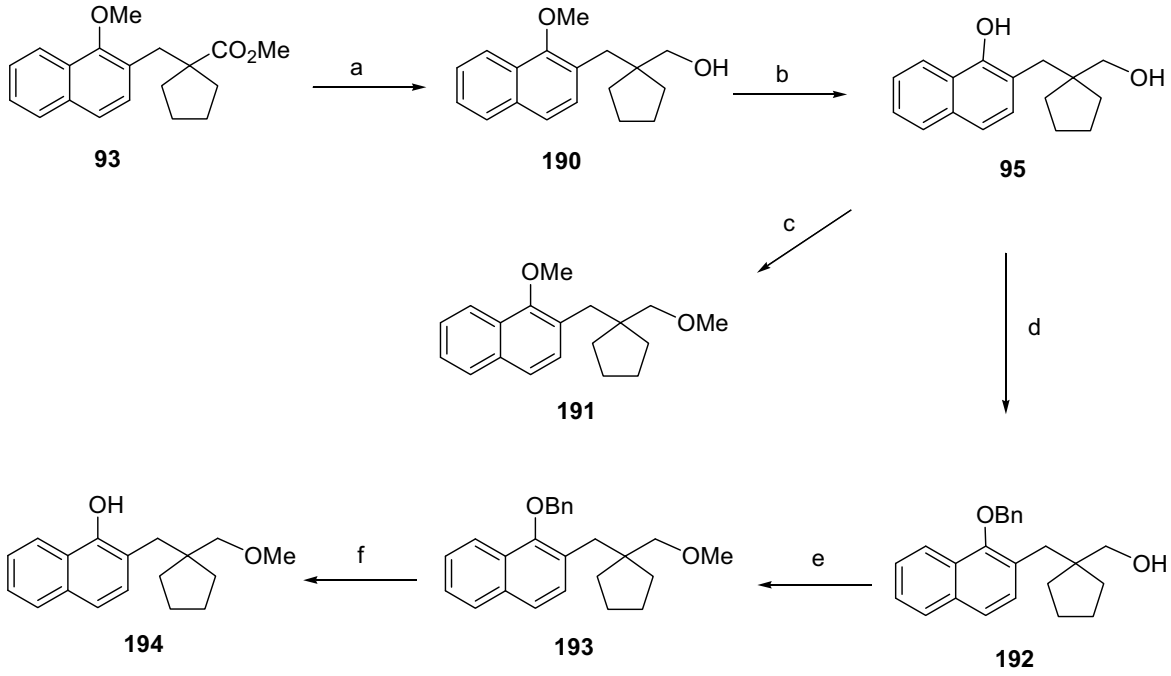
f) MeI, NaH, dry THF, rt., 6h, 82%.

g) BnCl, K_2CO_3, acetone, reflux, 24h, 91%.

h) NaH, MeI, dry THF, reflux, 5h, 68%.

i) H_2, Pd-C, EtOH, rt., 24h, 80%.

The syntheses of 2',2'-cyclopentylpropyl-1-naphthol (**95, 190**, **191**, **192**, **193** and **194**) derivatives were achieved by the method as shown in **Schemes 29**



Schemes 29

Reagents and conditions:

a) $LiAlH_4$, dry Ether, rt., 2h, 90%.

b) BBr_3, CH_2Cl_2, 0 °C, 1h, 95%.

c) MeI, NaH, dry THF, rt., 6h, 78%.

d) BnCl, K_2CO_3, acetone, reflux, 24h, 78%.

e) NaH, MeI, dry THF, reflux, 6h, 82%.

f) H_2, 10%Pd-C, EtOH, rt., 24h, 74%.

Biological Activities

Anti-inflammatory activity of all naphthol derivatives was tested at the BIOTEC as shown in **Table 9**.

Table 9. The experimental activity (IC_{50} values) of naphthol derivatives tested as inhibitors of COX-1 and COX-2.

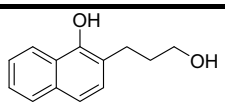
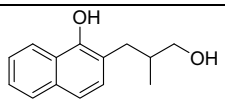
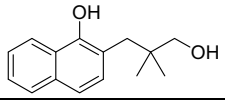
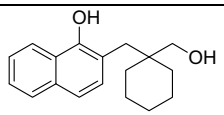
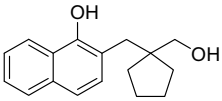
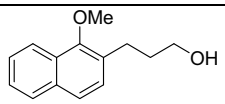
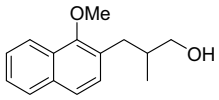
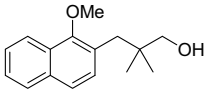
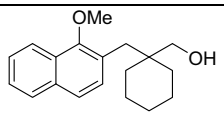
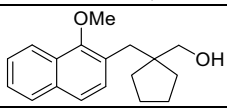
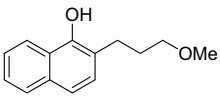
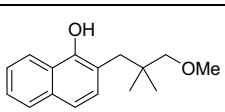
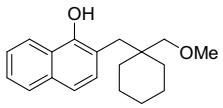
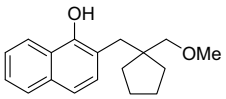
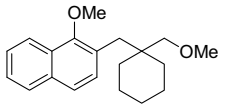
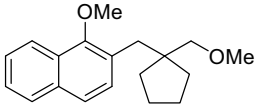
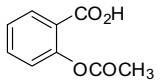
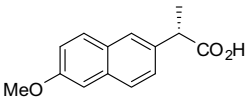
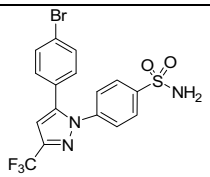
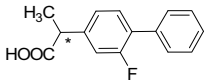
Compound	Structure	IC_{50} of COX-1 (μM)	IC_{50} of COX-2 (μM)
72		93.9	4.20
73		87.8	4.60
84		3.40	1.70
90		5.55	7.77
95		inactive	19.90
177		inactive	inactive
178		inactive	inactive
179		inactive	inactive
182		inactive	inactive
190		inactive	inactive
181		15.7	0.25
188		>40.90	4.10

Table 9. (Continued)

Compound	Structure	IC_{50} of COX-1 (μM)	IC_{50} of COX-2 (μM)
189		inactive	inactive
194		inactive	inactive
183		inactive	inactive
191		inactive	inactive
Aspirin (**165**)*		77.7	321.9
Naproxen (**168**)*		27.8	43.4
SC-558[1]		17.7	0.0093
Flurbiprofen[1]		2.56	0.29

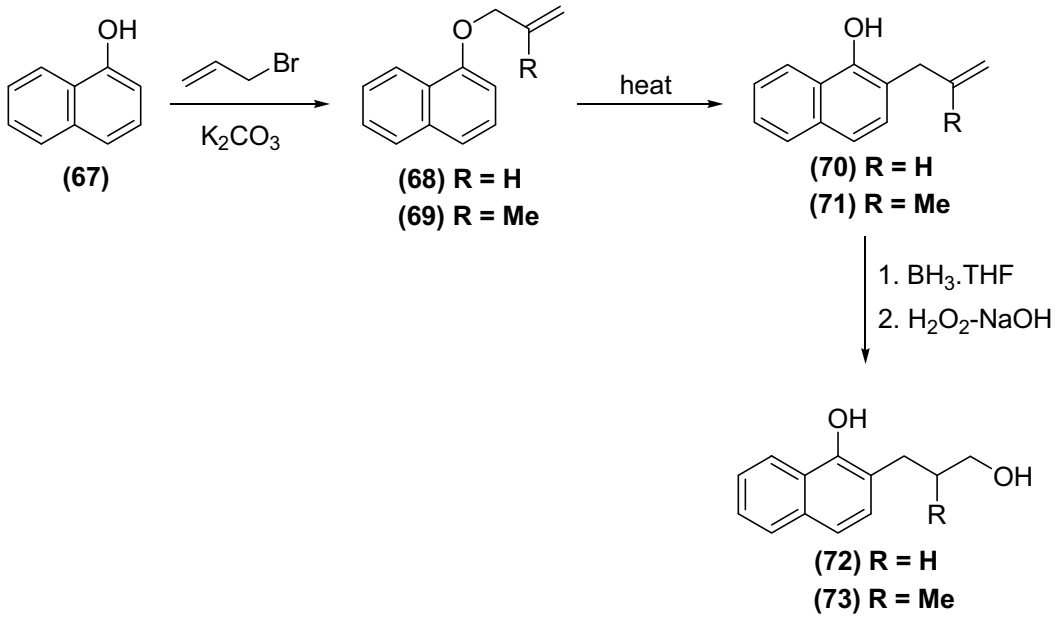
*Used as reference.

[1]Reference no. 11 (Kurumbail *et al.*, 1996)

DISCUSSION

Naphthol derivatives are the intermediates in the process of the syntheses of naphthoquinone ester derivatives and some naphthols such as naproxen have been reported to possess anti-inflammatory activity. So, our synthesized naphthols were also tested for anti-inflammatory activity. It was found that they inhibited cyclooxygenase enzymes (COX) in the inflammation process. therefor it is very interesting to synthesize derivatives of these molecules for evaluation of their anti-inflammatory activity. Methyl substitution of each hydroxyl group and alkyl substituents at the 2'-position of the propyl side chain of the naphthol compound were focused for this study. Docking experiment was also investigated for the structure-activity relationships.

2-Substituted-1-naphthol derivatives (**72** and **73**) were prepared in three steps with high yield. Naphthols **72** without 2'-methyl and **73** with 2'-methyl on the propyl side chain were prepared starting from 1-naphthol (**67**), in three steps involving *O*-allylation, Claisen rearrangement and then hydroboration-oxidation as shown in **Scheme 30**.



(67)

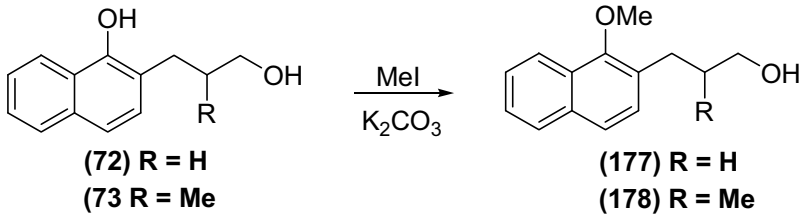
(68) R = H
(69) R = Me

(70) R = H
(71) R = Me

(72) R = H
(73) R = Me

Scheme 30

Treatment of these two naphthol derivatives (**72** and **73**) with methyl iodide (MeI) in the presence of potassium carbonate (K_2CO_3) in acetone provided methyl ether derivatives of naphthol **177** and **178** in quantitative yield as shown in **Scheme 31**.

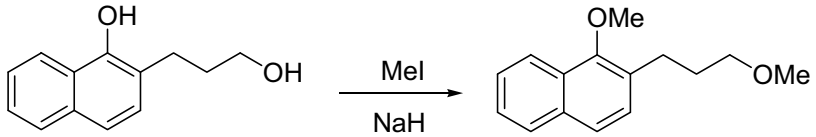


(72) R = H
(73 R = Me

(177) R = H
(178) R = Me

Scheme 31

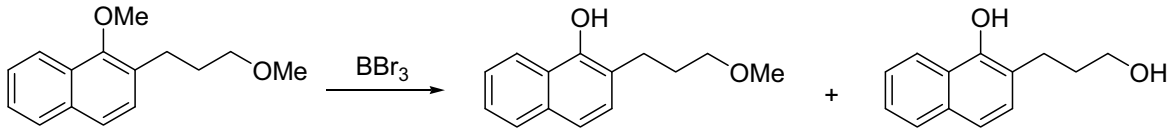
The naphthol **72**, was methylated on both naphthol and hydroxyl groups using MeI in the presence of sodium hydride (NaH) under reflux in dry THF to give dimethyl ether (**180**) in 93% yield (**Scheme 32**).



(72) **(180)**

Scheme 32

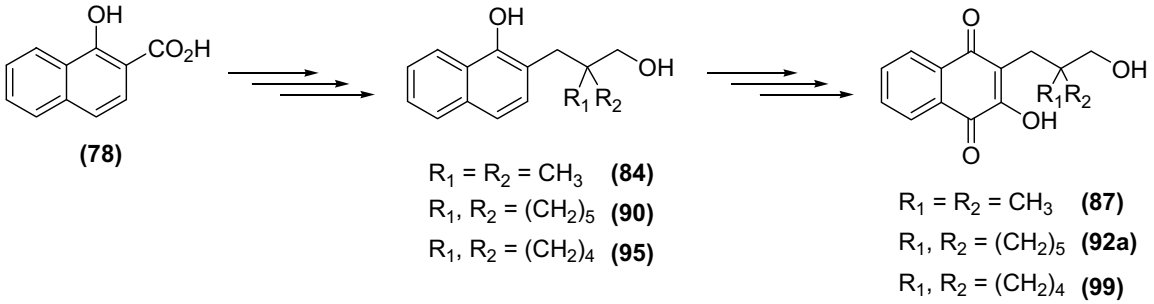
Selective demethylation at the hydroxyl group on the naphthalene ring was achieved by treatment of the methyl ether **180** with BBr_3 in dry CH_2Cl_2. But the desired product (**181**) was obtained in low yield (45%) because the methyl ether of the propyl side chain was also removed to provide compound **72** in 25% yield (**Scheme 33**).



(180) **(181)** **(72)**

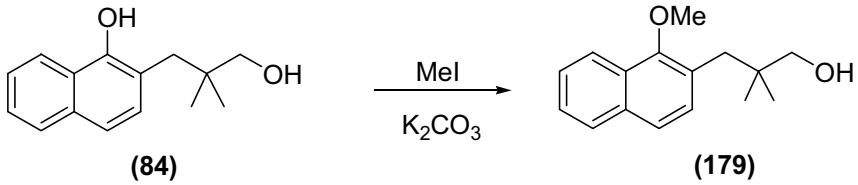
Scheme 33

The naphthol derivatives bearing 2'-dimethyl (**84**), 2'-cyclohexyl substituent (**90**) and 2'-cyclopentyl substituents (**95**) are intermediates in the synthesis of the naphthoquinones alcohols **87, 92a** and **99**, respectively (**Scheme 34**).



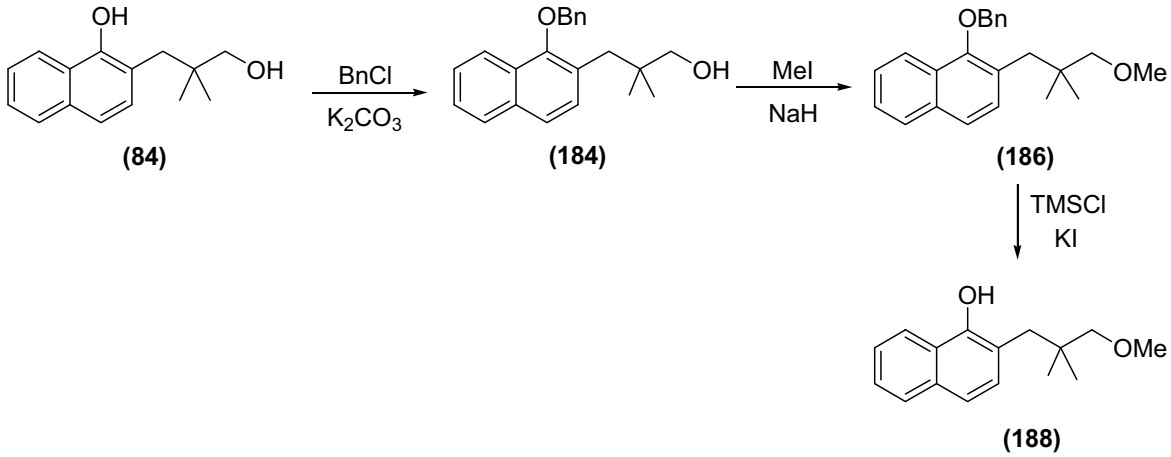
Scheme 34

Naphthol **84** was converted to the monomethyl ether **179** by treatment with methyl iodide (MeI) and K_2CO_3 (**Scheme 35**).



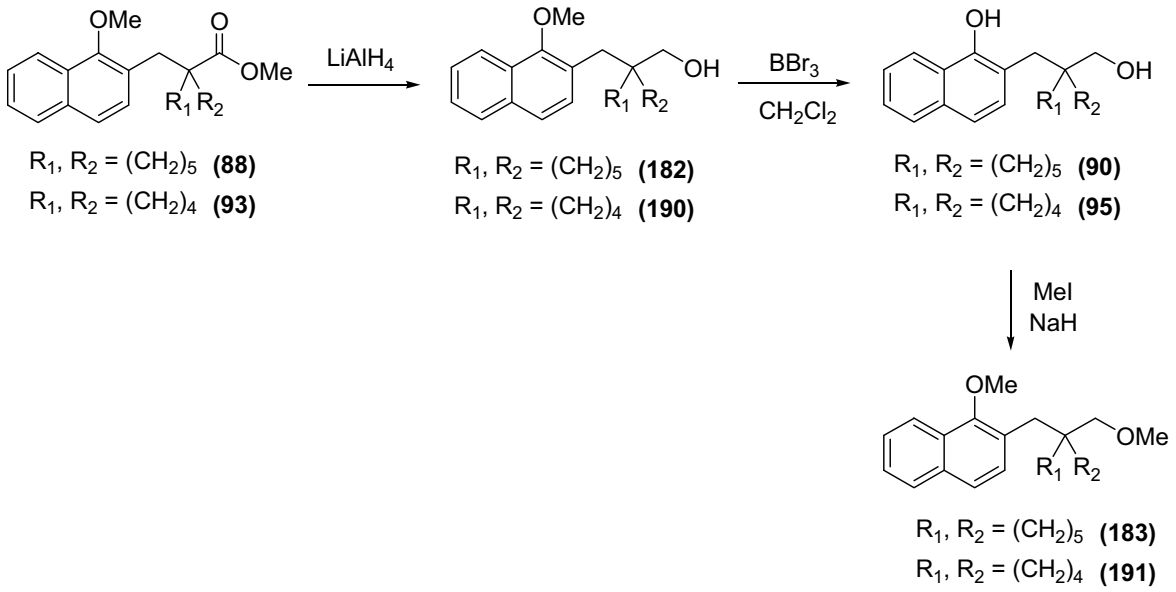
Scheme 35

Since demethylation of methyl naphthyl ether **180** occurred in low yield as previously described, so, 2-(3-methoxy-2,2-dimethyl-propyl)-naphthalen-1-ol (**188**) was synthesized from **84** by a three-step sequence involving selective benzylation of the hydroxyl group of naphthol, methylation of hydroxyl side chain and then debenzylation of benzyl naphthyl ether to solve this problem (**Scheme 36**).



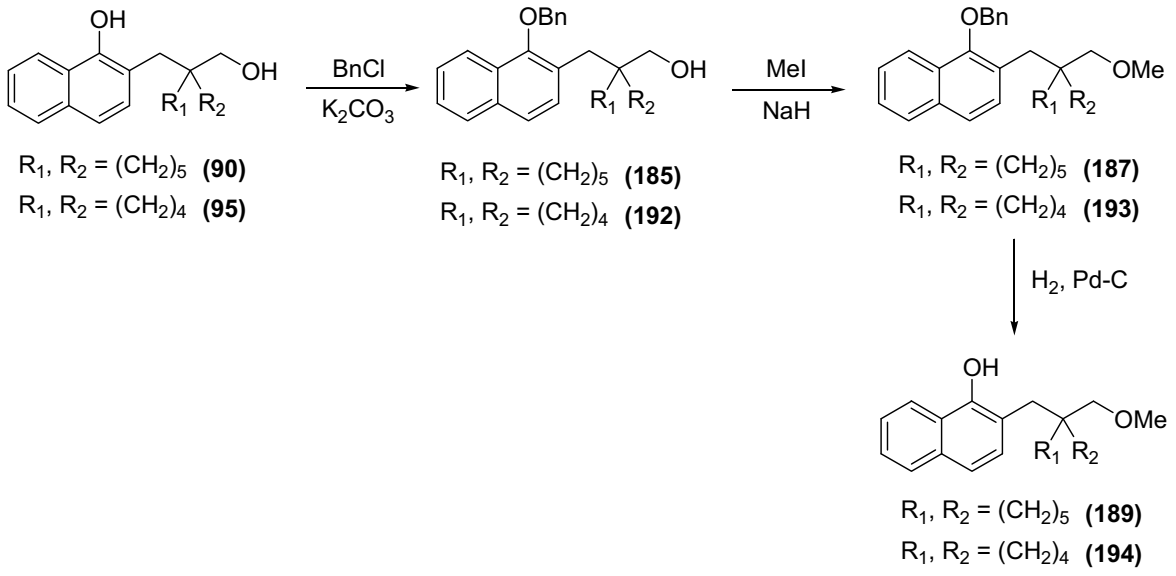
Scheme 36

Naphthol derivatives bearing 2'-cyclohexyl substituent, (**182**) and 2'-cyclopentyl substituent, (**190**) were synthesized from **88** as shown in **Scheme 37**



Scheme 37

In the same manner, 2-((1-(methoxymethyl)cyclohexyl)methyl)naphthalen-1-ol (**189**) and , 2-((1-(methoxymethyl)cyclopentyl)methyl)naphthalen-1-ol (**194**) were synthesized starting from naphthol **90** and **95** by sequential steps of benzylation, methylation and debenzylation. (**Scheme 38**) The desired products (**189**) and (**194**) were obtained in 52% and 47%yield in 3 steps from compound **90** and **95,** respectively.



Scheme 38

Herein, three types of naphthol derivatives were synthesized. **Type I** is comprised of 2-substituted-1-naphthols containing hydroxyl group at the 3′-position of the propyl side chain (**72, 73, 84, 90** and **95**)(**Figure 8**). **Type II** comprises 2-substituted-1-naphthols having methoxy group at the 3′-position of the propyl side chain (**181, 188, 189** and **194**). **Type III** is composed of 2-substituted-methyl naphthyl ethers with hydroxyl group at the 3′-position of the propyl side chain (**177-179, 182** and **190**). There are some reports of naphthol derivatives such as naproxen exerting anti-inflammatory activity (Kolasa *et al*., 1997; Cryer *et al*., 1998). So, our naphthol derivatives were evaluated for anti-inflammatory activity.

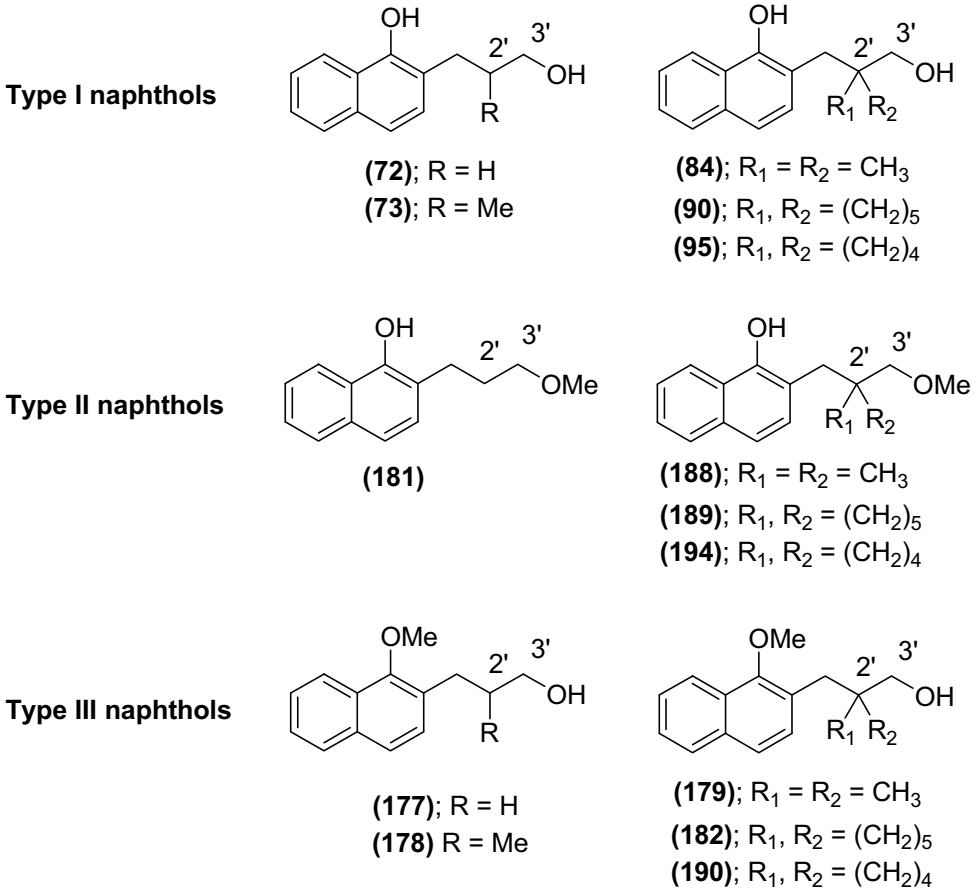


Figure 8. Three types of synthesized naphthol derivatives

These naphthol derivatives were tested for anti-inflammatory activity and aspirin was used as positive control. The results are shown in **Table 9** (page 164). Type I naphthols (**72, 73, 84, 90** and **95**) exhibited potent inhibition of COX-2. Naphthols without methyl and with monomethyl substituent at the 2′-position of the propyl side chain (**72** and **73**) showed similar potency against COX-2 with IC_{50} values of 4.20 and 4.60 μM,

respectively. Naphthols with C-2' dimethyl substituents (**84**) showed more potency against COX-2 (IC_{50} = 1.70 μM) than that with 2'-cyclohexyl substituent (**182**) (IC_{50} = 7.77 μM) and 2'-cyclopentyl substituent (**95**) (IC_{50} = 19.90 μM). Naphthols **72** and **73** showed slightly inhibition of COX-1 with IC_{50} values of 93.9 and 87.8 μM, respectively while the other two naphthols **84** and **127** showed potent inhibition of COX-1 with IC_{50} values of 3.40 and 5.50 μM, respectively. Surprisingly naphthols **95** is ina ctive to COX-1. This means these compounds, with the exception of compound **182**, have selective inhibition of COX-2 over COX-1 because their inhibition of COX-1 are lower than COX-2. C-2' substituents affect cyclooxygenase inhibition. Methyl group is more effective than the cyclohexyl or cyclopentyl group because the latter imparts rigidity or strain to the molecule. Naphthol type II (**181** and **188**) also exhibited potent inhibition of both COX enzymes while 2′-cyclohexyl or cyclopentyl substituent naphthols (**189** and **194**) showed no inhibition. Compounds **181** and **188** also showed strong activity on COX-2 over COX-1. This indicates that the substituent on C-2' effectively inhibits COX enzymes. The structure has more rigidity or strain caused less inhibition of COX isozymes. Naphthol type III (**177-179, 182** and **190**) showed no inhibition of both COX enzymes. Also, 1-methoxy-2-((1-(methoxymethyl)cyclohexyl)methyl)naphthalene (**183**) and 1-methoxy-2-((1-(methoxymethyl)cyclopentyl)methyl)naphthalene (**191**) exhibited no activity on both COXs. Therefore, the hydroxyl group at 1-position of naphthol plays an important role for the anti-inflammatory activity.

From the results of the inhibitory testing, it was found that the presence of the hydroxyl group at 1-position of naphthalene ring (Type I and II naphthols) shows an important role for the activity whereas the presence of methoxy group has no inhibitory effect. Moreover, the substituent at C-2' of the propyl side chain also has inhibitory effect.

There are some reports described about the benchmark descriptions of the cyclooxygenase binding site. This binding domain in both isozymes is a long, narrow hydrophobic channel reaching out from the point of enzyme attachment on the endoplasmic reticulum. At the mount of the channel entrance leading to the active site, the COOH of arachidonic acid interacts with the guanidinium group of Arg120, and the carboxylate group of traditional NSAIDs competes with this linkage, preventing access of arachidonic acid to the channel. (**Figure 9**) At the upper right-hand of the channel amino acid no. 523 is isoleucine (Ile523) in COX-1 and valine (Val523) in COX-2, creating a side pocket which imparts COX-2 selectivity. However, like arachidonic acid or NSAIDs,

naphthol derivatives can occupy the remainder of the channel leading to the active site and might block access of arachidonic acid.

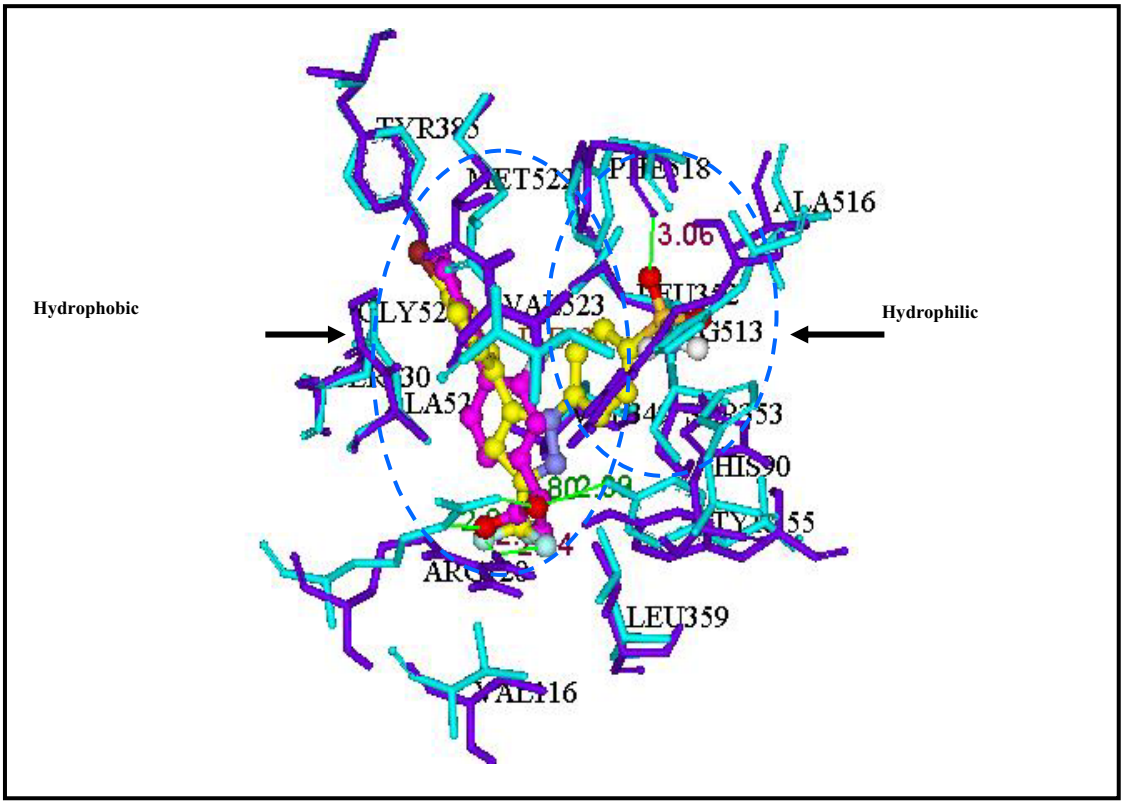


Figure 9. The COX-1 and COX-2 active sites are shown superimposed. Two inhibitors are seen: flurbiprofen (magenta), a nonselective inhibitor, and SC-558 (yellow), a COX-2 selective inhibitor. Note how the COX-2 selective inhibitor projects rightward into a side pocket that is not exploited by the nonselective inhibitor.

Our docking on COX-2, the highly selective inhibitor SC-558 was chosen for comparison with these naphthol derivatives. The presence of hydroxyl group at 1-position of the naphthalene ring (Type I naphthols: **72, 73, 84** and **90**) showed H-bonding with Val523 whereas the hydroxyl group at 3'-position of the propyl side chain revealed H-bond formation with Arg120 and Tyr355 in the COX-2 binding site (**Figure 10**)

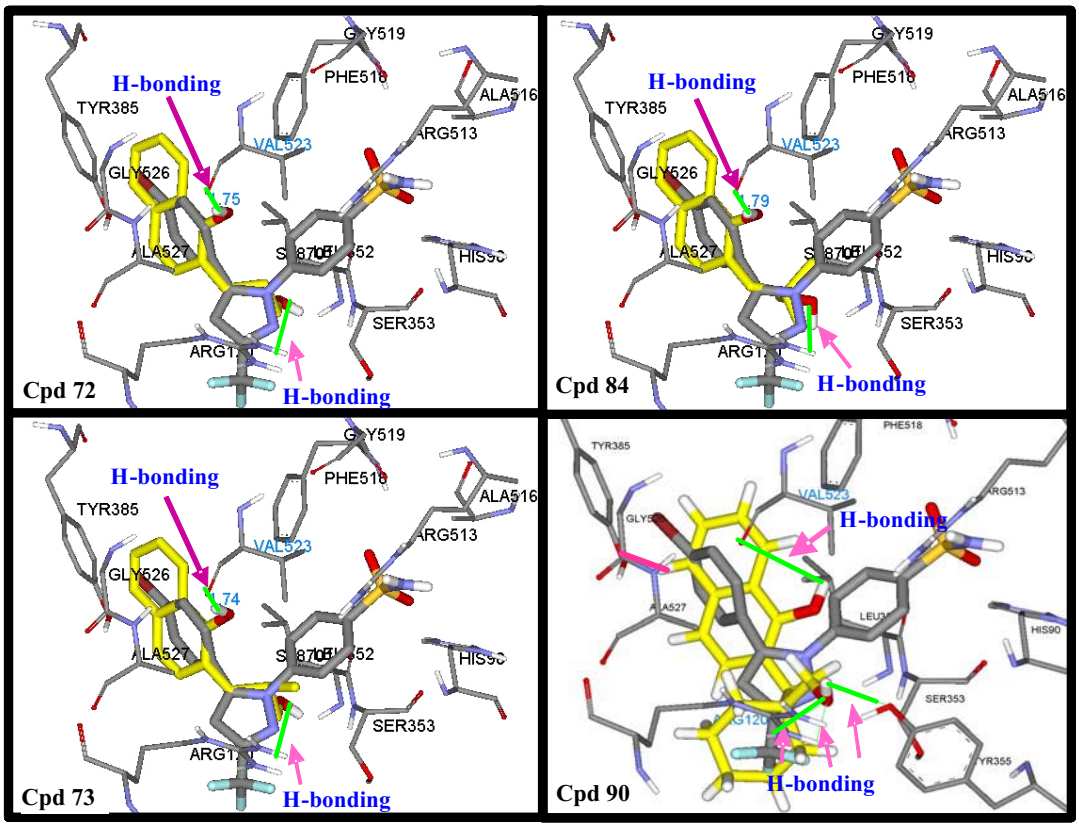


Figure 10. AutoDock binding on COX-2 of naphthol inhibitors **72, 73, 84** and **90** (yellow), superimposed on SC-558 (grey). The H-bonding interactions are shown in green lines. The interaction between the phenolic group of Tyr385 with C-5 hydrogen of naphthalene nucleus (**127**) is shown in pink line.

Furthermore, all active naphthols (**72, 73, 84** and **90**) also showed the orientation of the hydrogen at the C-5 position of naphthalene nucleus to be close to the phenolic group of Tyr385 which interacts by van der Waals interaction. On the other hand, the C-5 hydrogen of the inactive naphthols (**177-179** and **182**) were very far from the phenolic group of Tyr385. (**Figure 10**)

When the substituent at 1-position of naphthalene ring is methoxy group (Type III naphthols: **72, 73, 180** and **186**), the methyl naphthyl ether moiety is oriented downward which is far from the Val523. (**Figure 11**)

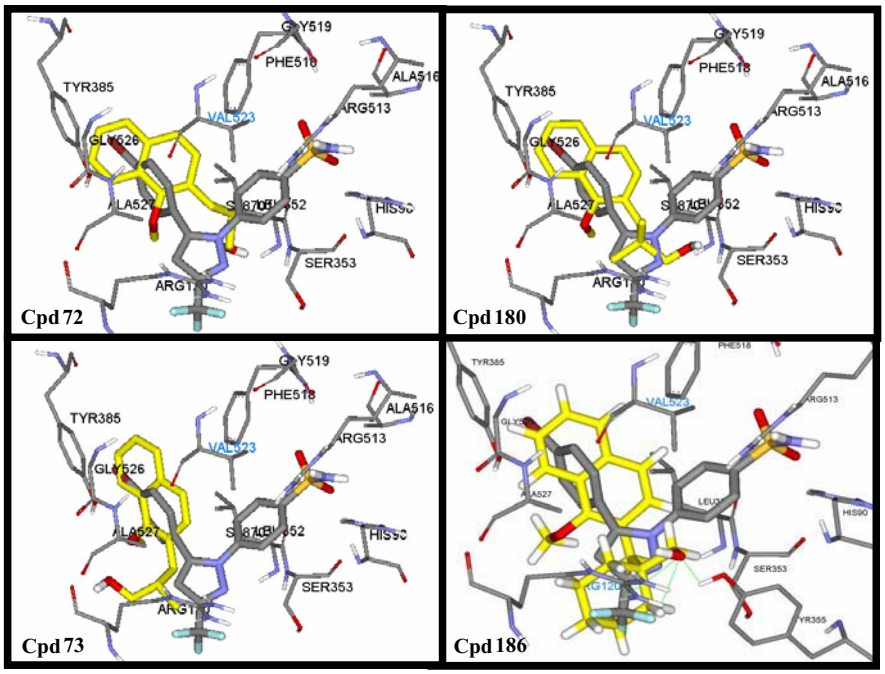


Figure 11. Orientation of inactive naphthols (**72, 73, 180** and **186**) (yellow) on COX-2, superimposed on SC-558 (grey).

From these reasons for active naphthols, the hydroxyl group at 1-position shows an important role for the inhibitory effect. So, type I (**72, 73, 180** and **186**) and type II naphthols (**181, 188, 189** and **194**) contain 1-hydroxyl group which inhibited on COX-2 according to the molecular docking experiment. Exception of naphthol **189** bearing 2'-cyclohexyl ring showed no inhibition on COX-2 because the 1-hydroxyl group oriented downward and very far from Val523. (**Figure 12**)

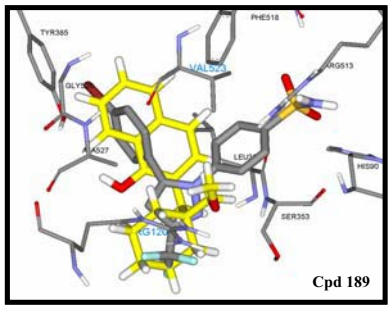


Figure 12. Orientation of inactive naphthols (**189**) (yellow) on COX-2, superimposed on SC-558 (grey).

In COX-1 docking experiments, our synthesized naphthols were also superimposed on flurbiprofen which is one order of magnitude more selective to COX-2 than to COX-1. In the binding site of COX-1, the C-1 hydroxyl group of compounds **72** and **90** formed H-bonding with Ile523, and the C-3′ hydroxyl with Arg120 and Tyr355 whereas compound **182** possesses C-1 methoxy group and C-3′ hydroxyl group, showed H-bonds of C-3′ hydroxyl group with Arg120 and Tyr355 but no H-bond with Ile523. Also the C-1 hydroxyl group of compound **189** formed H-bonding with Ile523 but no H-bond formation with Arg120 and Tyr355 (because they have methoxy group instead of hydroxyl group at C-3′) in the docking and it has no inhibition on COX-1. (**Figure 13**)

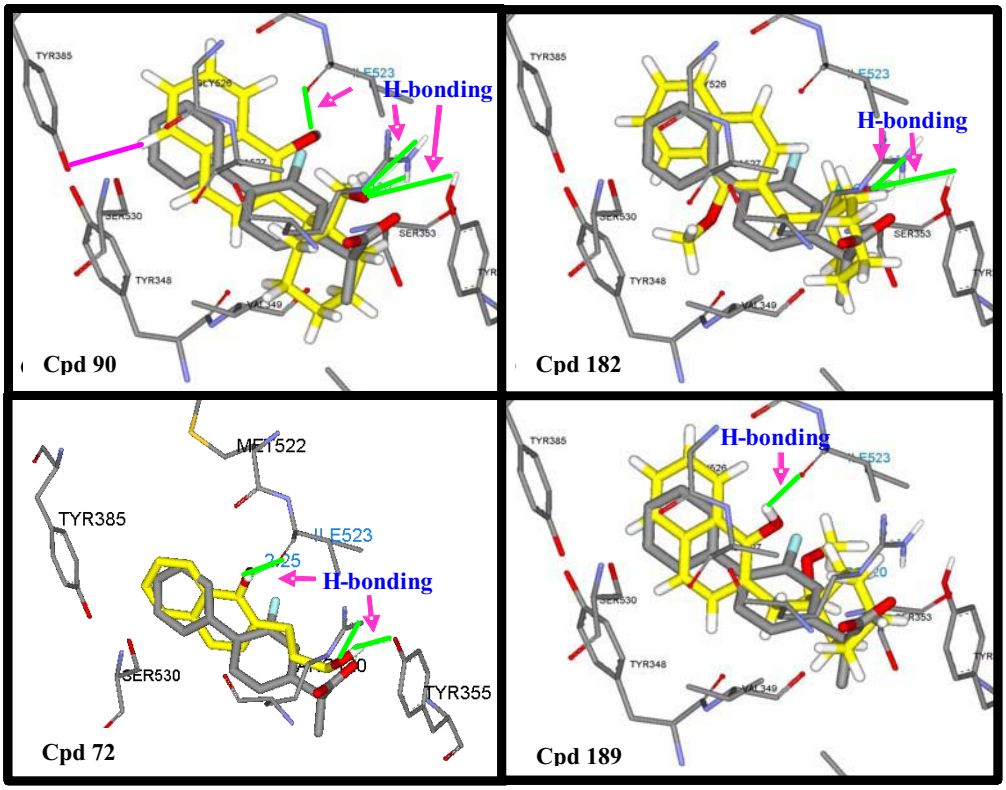


Figure 13. AutoDock binding on COX-1 of active naphthols (**72** and **90**) on the left and inactive naphthols (**182** and **189**) on the right (yellow), superimposed on flurbiprofen (grey). The H-bonding interactions are shown in green lines. The interaction between the phenolic group of Tyr385 with C-5 hydrogen of naphthalene nucleus (**90**) is shown in pink line.

Additionally, the C-5 hydrogen of the naphthalene nucleus of naphthols **90** and **72** are close to the phenolic group of Tyr385, whereas other naphthols **182**, **183** and **189** were

far from Tyr385. (**Figures 9** and **13**) So, the interaction between the C-5 hydrogen and the phenolic group of Tyr385 affected or enhanced the activity.

Another naphthol **183** contain methoxy groups at C-1 and C-3′ showed no H-bond with Ile523, Arg120 and Tyr355, which corresponded to the IC_{50} testing result that no inhibition of COX-1 was observed. (**Figure 14**)

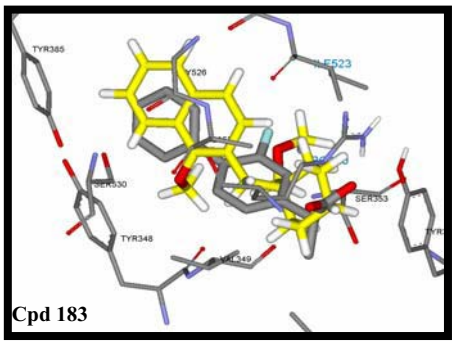


Figure14. AutoDock binding on COX-1 of inactive naphthol **183** (yellow), superimposed on flurbiprofen (grey).

CONCLUSION

Synthesis of 2-substituted-1-naphthol derivatives without 2'-methyl group (**72**) and with 2'-methyl group on the propyl side chain (**73**) were accomplished in three steps involving *O*-allylation, Claisen rearrangement and hydroboration. Their methyl ether derivatives, **165** and **166**, were achieved in quantitative yield by methylation of naphthols **72** and **73**, respectively. Additionally, methyl ether on the propyl side chain (**181**) was synthesized in two steps from naphthol **72** with an overall yield of 42%.

2-Substituted-1-naphthol derivative with C-2' dimethyl groups of the propyl chain (**84**) was synthesized from 1-hydroxy-2-naphthoic acid with an overall yield of 44% in six sequential steps involving methylation, reduction of methyl ester, bromination, alkylation, demethylation and reduction of lactone. Methyl naphthyl ether (**188**) was obtained in 98% yield by methylation and the methyl ether of naphthol **84** (**188**) was synthesized from naphthol **84** in a three-step sequence involving benzylation, methylation and debenzylation.

Synthesis of 2-substituted-1-naphthol derivative bearing cyclohexyl ring at the 2'-position of the propyl chain (**90**) was achieved in six steps with 53% overall yield. Methyl naphthyl ether (**182**) was obtained in 76% yield by reduction of the ester **125** while naphthyl ether (**183**) was synthesized by dimethylation of naphthol **90**. The generation of methyl ether of the naphthol **90** (**189**) from naphthol **90** was accomplished in three-step sequence involving benzylation, methylation and debenzylation.

These synthesized naphthols were evaluated for anti-inflammatory activity. Naphthols type I, 2-substituted-1-naphthols containing hydroxyl group at the 3′-position of the propyl side chain (**84**, **90**, **72** and **73**), exhibited potent inhibition of both COX enzymes and showed selective inhibition of COX-2 over COX-1 except naphthol **90** which has no selectivity. Naphthols type II, 2-substituted-1-naphthol with methoxy group at 3′-position of the propyl side chain (**181** and **188**), inhibited both COX enzymes while that containing 2'-cyclohexyl ring on the side chain has no inhibition. The results showed that more rigidity or strain in the molecule exerts less selectivity. Naphthols type III, 2-substituted-methyl naphthyl ethers with hydroxyl group at the 3′-position of the propyl side chain

(**177**-**179**, **182** and **190**) and the methyl ether derivative (**189** and **194**) exhibited no activity on both COXs. Therefore, the hydroxyl group at 1-position of naphthols and rigidity or strain in the molecule play important roles for the anti-inflammatory activity.

In the molecular modeling experiments on COX-2, it indicated the hydroxyl group at 1-position enhanced inhibition of COX-2 by H-bond formation with Val523 of COX-2. For inactive naphthols, they have no H-bond interaction with Val523 because methyl naphthyl ether moiety oriented downward which far from the Val523. Moreover, the van der Waals interaction between the C-5 hydrogen of the naphthalene nucleus and the phenolic group of Tyr385 was found in the docking which was established for naphthol inhibitors.

In the COX-1 molecular docking, naphthols possess hydroxyl groups at 1-position showed the H-bond formations between 1-hydroxyl group and Ile523. Naphthols with 1- and 3'-hydroxyl groups revealed the H-bonding with Ile523, Arg120 and Tyr355 whereas inactive naphthols did not show the H-bonding with Ile523.

MATERIALS AND METHODS

Materials

Instrumentations

Melting points (m.p.) were determined on a Fisher John apparatus and MEI-TEMP capillary melting point apparatus at the Department of Chemistry, Kasetsart University and are incorrected.

The infrared (IR) spectra were recorded on a Perkin-Elmer 2000 Fourier transform infrared spectrophotometer at the Department of Chemistry, Faculty of Science, Kasetsart University.

Mass spectra (MS) were obtained on the GCMS-QP-5050A at Kasetsart Agricultural and Agro Industrial Product Improvement Institute (KAPI) and on AGILENT 1100 series LC/MSB TRAP at the Faculty of Science, Kasetsart University.

Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 400 MHz on a VARIAN ^{UNITY} INOVA 400 MHz spectrometer at the Department of Chemistry, Kasetsart University. Chemical shifts (δ) are given in parts per million (ppm) downfield from tetramethylsilane (TMS) as internal standard. Coupling constants (J) are given in Hertz (Hz). Unless otherwise specified deuterochloroform ($CDCl_3$) was used as a solvent. The following abbreviations are used: s = singlet, d = doublet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet, br s = broad singlet, dd = doublet of doublet, dt = doublet of triplet, td = triplet of doublet, qd = quartet of doublet, ddd = doublet of doublet of doublet.

High resolution mass spectral data (HRMS) were measured at EPSRC National Mass Spectrometry Service Centre, Department of Chemistry, University of Wales Swansea, UK and by LCP Micromass at the National Science and Technology Development Agency (NSTDA), Bangkok, THAILAND.

Elemental analyses were performed by the LECO CHNS-932 at the Faculty of Science, Kasetsart University.

Chromatographic systems

Thin-layer chromatography (TLC) on aluminum sheets with silica gel 60 F_{254} was used routinely for monitoring reaction progress. The chromatograms were visualized under ultraviolet light (254 nm).

Flash column chromatography was performed on silica gel (230-400 mesh, Merck 9385) according to the method of Still (1978).

Chemical reagents

All reagents and solvents were used as received from Merck, Fluka and Aldrich Chemical. Unless otherwise noted in the case of anhydrous condition, purifications were accomplished according to the standard procedure outlined in Vogel's Text Book of Practical Organic Chemistry (1989).

Dry reagents

Acetone was dried over Type 4A molecular sieves for 24 hours.

Benzene was dried over sodium wire for 24 hours.

Dichloromethane was dried over anhydrous calcium chloride for 24 hours then distilled from calcium hydride and stored over Type 3A molecular sieves.

Diethyl ether and tetrahydrofuran (THF) were dried over sodium metal and benzophenone under nitrogen atmosphere until the dark blue or purple colour persisted. The anhydrous ether was distilled immediately before use.

Dimethylformamide (DMF) was dried over Type 3A molecular sieve for 72 hours, followed by distillation under reduced pressure and stored over Type 3A molecular seives

Tissue culture components

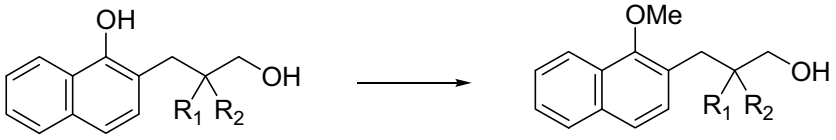
All tissue culture components were purchased from Gibco BRL (Gaithersburg, MD). Aspirin and calcium ionophore A23187 were purchased from Sigma (St. Louis, MO). ^{3}H-PGE$_2$ was from NEN Life Science (Boston, MA) and anti-PGE$_2$ antibody was from the Upstate Biotechnology (Upstate, NY) or Sigma (St. Louis, MO).

Methods

Chemistry

Methylation of naphthol

General procedure:



70: $R_1 = R_2 = H$
73: $R_1 = H$; $R_2 = Me$
84: $R_1 = R_2 = Me$

177: $R_1 = R_2 = H$
178: $R_1 = H$; $R_2 = Me$
179: $R_1 = R_2 = Me$

A mixture of alcohol (**70, 73** or **84**)(1.0 mmol), methyl iodide (2.0 mmol) and potassium carbonate (2.0 mmol) in acetone (5 mL) was refluxed for 4 hours. Then the reaction mixtue was cooled to room temperature, filtered and washed with acetone. The filtrate was concentrated in vacuo, then diethyl ether was added and washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography.

3-(1-Methoxy-naphthalen-2-yl)-propan-1-ol (177)

Compound **177** was synthesized by following the general procedure: a mixture of alcohol **70** (0.2 g, 1.0 mmol), methyl iodide (0.12 mL, 2.0 mmol) and potassium carbonate

(0.27 g, 2.0 mmol) in acetone (5 mL) was refluxed for 4 hours. The residue was purified by flash column chromatography eluting with 10% ethyl acetate-hexane to afford the product (**177**) in quantitative yield (0.22 g) as a colourless oil.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.87 (m, 2H, $CH_2CH_2CH_2$), 2.20 (br s, 1H, OH), 2.87 (t, *J*=7.2 Hz, 2H, CH_2), 3.53 (t, *J*=6.0 Hz, 2H, OCH_2), 3.89 (s, 3H, OCH_3), 7.25 (d, *J*=8.4 Hz, 1H, ArH), 7.43 (m, 2H, ArH), 7.53 (d, *J*=8.4 Hz, 1H, ArH), 7.76 (d, *J*=7.7 Hz, 1H, ArH), 8.02 (d, *J*=8.2 Hz, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 26.12 (CH_2), 33.91 (CH_2), 62.00 (CH_3), 62.84 (CH_2), 122.55 (CH), 125.09 (CH), 126.16 (CH), 126.66 (CH), 128.43 (C), 128.65 (CH), 128.86 (CH), 130.19 (C), 134.47 (C), 153.97 (C).

FTIR (neat, cm^{-1}): 3380 (OH), 2937 (CH_2), 1572, 1446, 1371 (C=C), 1241, 1085, 1056 (C-O).

MS (EI), *m/z* (% relative intensity) : 216 (M^+, 100), 171 (79), 156 (40), 128 (60).

Anal. Calcd for $C_{14}H_{16}O_2$: C,77.75; H, 7.46. Found: C, 77.47; H, 7.64.

3-(1-Methoxy-naphthalen-2-yl)-2-methyl-propan-1-ol (178)

Compound **178** was synthesized by following the general procedure: a mixture of alcohol **73** (0.22 g, 1.0 mmol), methyl iodide (0.23 mL, 2.0 mmol) and potassium carbonate (0.25 g, 2.0 mmol) in acetone (10 mL) was refluxed for 4 hours. The residue was purified by flash column chromatography eluting with 10 % ethyl acetate-hexane provided the product (**178**) in quantitative yield (0.23 g) as a colourless oil.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.93 (d, *J*=6.8 Hz, 3H, CH_3), 1.94 (m, 1H, CH), 2.32 (br s, 1H, OH), 2.65 (m, 1H, CH_2), 2.81 (m, 1H, CH_2), 3.30 (m, 2H, OCH_2), 3.85 (s, 3H, OCH_3), 7.20 (d, *J*=8.4 Hz, 1H, ArH), 7.40 (m, 2H, ArH), 7.49 (d, *J*=8.4 Hz, 1H, ArH), 7.73 (d, *J*=7.8 Hz, 1H, ArH), 7.98 (d, *J*=8.3 Hz, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 17.75 (CH_3), 33.47 (CH_2), 37.75 (CH), 62.79 (CH_3), 66.90 (CH_2), 122.58 (CH), 124.86 (CH), 126.19 (CH), 126.65 (CH), 128.33 (C), 128.64 (CH), 129.57 (C), 129.15 (CH), 134.54 (C), 154.13 (C).

FTIR (neat, cm^{-1}): 3400 (OH), 2952 (CH_2, CH_3), 1462, 1370 (C=C), 1258, 1035 (C-O).

MS (EI), *m/z* (% relative intensity) : 230 (M^+, 50), 171 (100), 156 (44), 128 (69).

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.32; H, 7.92.

3-(1-Methoxy-naphthalen-2-yl)-2,2-dimethyl-propan-1-ol (179)

Compound **179** was synthesized by following the general procedure: a mixture of alcohol **84** (0.22 g, 1.0 mmol), methyl iodide (0.24 mL, 2.0 mmol) and potassium carbonate (0.26 g, 2.0 mmol) in acetone (10 mL) was refluxed for 4 hours. The residue was purified by flash column chromatography eluting with 5 % ethyl acetate-hexane yielded the product (**179**) (0.229 g, 98%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.94 (s, 6H, 2×CH_3), 2.71 (s, 2H, CH_2), 2.99 (s, 2H, OCH_2), 3.11 (br s, 1H, OH), 3.91 (s, 3H, OCH_3), 7.22 (d, *J*=8.4 Hz, 1H, ArH), 7.46 (m, 2H, ArH), 7.53 (d, *J*=8.4 Hz, 1H, ArH), 7.79 (m, 1H, ArH), 8.02 (m, 1H, ArH).

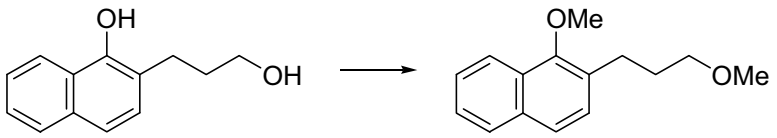
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.77 (2×CH_3), 38.21 (C), 38.75 (CH_2), 62.79 (CH_3), 70.03 (CH_2), 122.62 (CH), 124.41 (CH), 126.32 (CH), 126.68 (CH), 127.82 (C), 128.00 (C), 128.62 (CH), 131.08 (CH), 134.71 (C), 154.31 (C).

FTIR (neat, cm^{-1}): 3437 (OH), 2953 (CH_2, CH_3), 1466, 1371 (C=C), 1080, 1045 (C-O).

MS (EI), *m/z* (% relative intensity): 244 (M^+, 52), 171 (100), 156 (29), 128(47).

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.72, H, 8.09.

1-Methoxy-2-(3-methoxy-propyl)-naphthalene (180)



70 **168**

To a stirred suspension of sodium hydride (0.14 g, 6 mmol) in dry tetrahydrofuran (THF) (5 mL), a solution of alcohol **70** (156) (0.2 g, 1 mmol) in dry THF (5 mL) was added dropwise. After refluxing for 3 hours, the reaction mixture was cooled to room temperature and quenched with water, then extracted with diethyl ether (3×50 mL). The combined organic phase was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography eluting with 2 % ethyl acetate-hexane to afford the dimethoxy product (**180**) (93%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.00 (m, 2H, CH_2), 2.92 (t, J=7.7 Hz, 2H, CH_2), 3.40 (s, 3H, OCH_3), 3.48 (t, J=6.4 Hz, 2H, OCH_2), 3.97 (s, 3H, OCH_3), 7.37 (d, J=8.4 Hz, 1H, ArH), 7.47 (m, 1H, ArH), 7.53 (m, 1H, ArH), 7.61 (d, J=8.4 Hz, 1H, ArH), 7.85 (m, 1H, ArH), 8.12 (m, 1H, ArH).

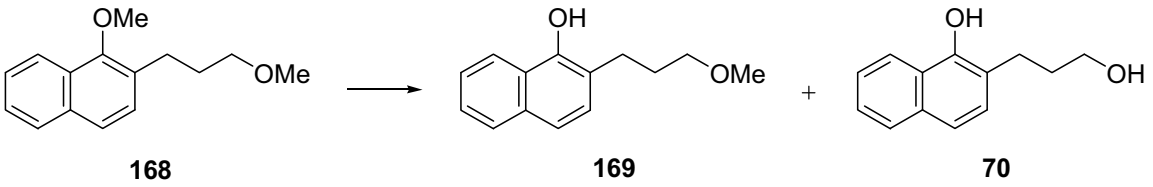
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 26.89 (CH_2), 31.27 (CH_2), 59.21 (CH_2), 62.64 (CH_3), 72.88 (CH_3), 122.62 (CH), 124.62 (CH), 126.03 (CH), 126.49 (CH), 128.58 (CH), 128.72 (C), 128.88 (CH), 130.79 (C), 134.39 (C), 154.04 (C).

FTIR (neat, cm^{-1}): 2931(CH_2), 1572, 1450, 1372 (C=C), 1243, 1116 (C-O).

MS (EI), *m/z* (% relative intensity) : 230 (M^+, 71), 171 (30), 141 (30), 57 (100).

HRMS calcd for $C_{15}H_{18}O_2$ [M+Na] 253.1204, found 253.1201.

2-(3-Methoxy-propyl)-naphthalen-1-ol (181)



168 **169** **70**

To a solution of compound **181** (0.2 g, 0.9 mmol) in dry dichloromethane (20 mL) at 0 ^{o}C, boron tribromide (0.3 mL, 3.5 mmol) was added dropwise and the solution was stirred for 1 hour at 0 °C, then water was added and extracted with dichloromethane (3×50 mL). The organic phase was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography eluting with 2 % ethyl acetate-hexane to afford the desired product (**181**) (84.6 mg, 45%) as major product as a brown oil and the minor product (**70**) (44.0 mg, 25%) as a colourless solid, m.p. 86-87 ^{o}C.

Spectroscopic data for compound **181**

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.00 (m, 2H, CH_2), 2.92 (t, J=6.4 Hz, 2H, CH_2), 3.39 (t, J=6.4 Hz, 2H, OCH_2), 3.49 (s, 3H, OCH_3), 7.22 (d, J=8.3 Hz, 1H, ArH), 7.40 (d, J=8.3 Hz, 1H, ArH), 7.48 (m, 2H, ArH), 7.79 (m, 1H, ArH), 7.94 (s, 1H, OH), 8.33 (m, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 26.00 (CH_2), 29.91 (CH_2), 59.13 (CH_2), 70.40 (CH_3), 120.05(C), 120.48(CH), 122.99(CH), 125.60(CH), 125.94(C), 126.18(CH), 127.90(CH), 129.28 (CH), 134.25(C), 151.07 (C).

FTIR (neat, cm^{-1}): 3290 (OH), 2932 (CH_2, CH_3), 1662, 1574, 1463, 1387 (C=C), 1265, 1105 (C-O).

MS (EI), *m/z* (% relative intensity) : 216 (M^+, 63), 184 (100), 156 (59), 128 (50).

HRMS calcd for $C_{14}H_{16}O_2$ [M+Na] 239.1048, found 239.2046.

Spectroscopic data for compound **70**

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.95 (m, 2H, CH_2), 2.95 (t, J=6.4 Hz, 2H, CH_2), 3.65 (t, J=5.7 Hz, 2H, OCH_2), 7.20 (d, J=8.3 Hz, 1H, ArH), 7.37 (d, 1H, J=8.3 Hz, ArH), 7.45 (m, 2H, ArH), 7.75 (dd, J=7.4 and 1.5 Hz, 1H, ArH), 8.25 (dd, J=8.9 and 1.5 Hz, 1H, ArH).

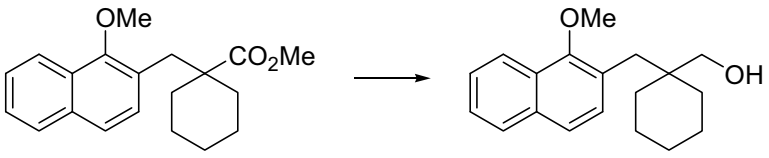
^{13}C NMR ($CDCl_3$, 75 MHz) δ: 25.04 (CH_2), 31.50 (CH_2), 60.49 (CH_2), 119.72 (C), 120.18 (CH), 122.25 (CH), 125.17 (CH), 125.40 (C), 125.61 (CH), 127.54 (CH), 128.82 (CH), 134.00 (C), 150.50 (C).

FTIR (KBr, cm^{-1}): 3481 (OH), 3141 (CH-aromatic), 2940 (CH_2), 1627, 1513, 1323 (C=C), 1272 (C-O).

MS (EI), *m/z* (% relative intensity) : 202 (M^+, 98), 184(99), 156 (69), 128 (100).

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.41; H, 6.79.

1-(1-Methoxynaphthalen-2-yl)methyl)cyclohexyl)methanol (182)



88 **182**

A solution of ester **88**(150 mg, 0.48 mmol) in dry diethyl ether (2 mL) was added dropwise to a stirred and ice-cooled suspension of lithium aluminium hydride (54.0 mg, 0.48 mmol) in dry diethyl ether (3 mL). After stirring for 2 hours at room temperature, the reaction mixture was quenched with ethyl acetate and water, then extracted with diethyl ether (3×30 mL). The combined organic phases were washed with water and brine, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography eluting with 5% ethyl acetate-hexane to afford the desired product **182** (104 mg, 76%) as a colourless solid. M.p. 89-90 ºC.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.28-1.60 (m, 10H, $(CH_2)_5$), 2.73 (s, 2H, CH_2Ar), 3.03 (s, 2H, CH_2OH), 3.88 (s, 3H, $ArOCH_3$), 7.19 (d, 1H, *J*=8.4 Hz, ArH), 7.41 (m, 2H, ArH), 7.48 (d, 1H, *J*=8.4 Hz, ArH), 7.75 (m, 1H, ArH), 7.98 (m, 1H, ArH).

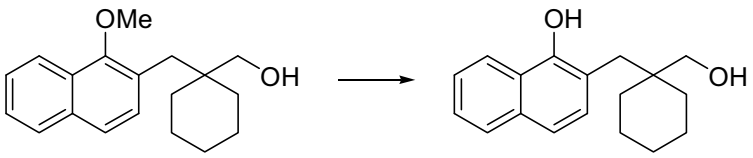
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.81 ($2\times CH_2$), 26.64 (CH_2), 33.26 ($2\times CH_2$), 35.50 (CH_2), 39.78 (C), 62.23 (CH_2), 66.75 (CH_3), 121.96 (CH), 123.79 (CH), 125.67 (CH), 126.05 (CH), 126.96 (C), 127.31 (C), 127.94 (CH), 130.14 (CH), 134.04 (C), 153.75 (C).

FTIR (KBr, cm^{-1}): 3532 (OH), 3051 (CH-aromatic), 2926, 2847 (CH_2, CH_3), 1597, 1455, 1371, 1265, (C=C), 1072, 1038 (C-O).

MS (EI), *m/z* (% relative intensity): 284 (M^+, 21), 172 (100), 157 (26), 141 (25), 142 (9), 128 (30), 115 (22), 95 (32).

HRMS: calcd for $C_{19}H_{24}O_2$ [M+Na] 307.1674, found 307.1669.

2-(1-(Hydroxymethyl)cyclohexyl)methyl)naphthalen-1-ol (90)



182 **90**

1 M Boron tribromide in dichloromethane (141 μL, 0.14 mmol) was added dropwise to a stirred solution of the methyl ether **90** (40 mg, 0.14 mmol) in dry dichloromethane (3 mL) at 0ºC and the solution was stirred for 1 h at the same temperature. Then water was added and extracted with dichloromethane (3×10 mL). The combined organic phases were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography eluting with 5% ethyl acetate-hexane to give the desired product **90** (34 mg, 89%) as a colourless amorphous powder. M.p. 126-127 ºC.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.30-1.65 (m, 10H, $(CH_2)_5$), 2.78 (s, 2H, CH_2Ar), 3.31 (s, 2H, CH_2OH), 7.11 (d, *J*=8.4 Hz, 1H, ArH), 7.26 (d, *J*=8.4Hz, 1H, ArH), 7.38 (m, 2H, ArH), 7.69 (m, 1H, ArH), 8.25 (m, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.64 ($2\times CH_2$), 26.47 (CH_2), 33.16 ($2\times CH_2$), 35.50 (CH_2), 38.81 (C), 67.43 (CH_2), 117.22 (C), 118.84 (CH), 122.52 (CH), 124.85 (CH), 125.54 (C), 125.59 (CH), 127.12 (CH), 130.45 (CH), 133.62 (C), 151.20 (C).

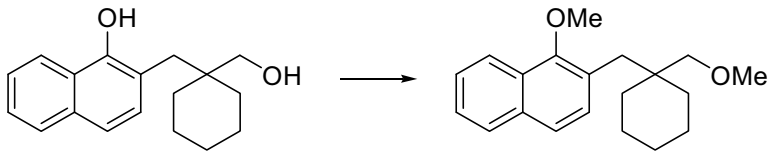
FTIR (KBr, cm^{-1}): 3413 (OH), 3047 (CH-aromatic), 2922, 2856 (CH_2, CH_3), 1570, 1457, 1376, 1273 (C=C), 1072, 1015 (C-O).

MS (EI), *m/z* (% relative intensity): 270 (M^+, 11), 253 (26), 239 (5), 169 (3), 157 (100), 129 (22).

HRMS: calcd for $C_{18}H_{22}O_2$ [M+H] 271.1698, found 271.1699.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.00, H, 8.20.

1-Methoxy-2-((1-(methoxymethyl)cyclohexyl)methyl)naphthalene (184)



90 **184**

A solution of alcohol **90** (50 mg, 0.19 mmol) in dry THF (1mL) was added dropwise to a stirred suspension of sodium hydride (60% in mineral oil)(22.2 mg, 0.56 mmol) in dry THF (2 mL). Then methyl iodide (35 µL, 0.56 mmol) was added dropwise to the reaction mixture. After refluxing for 6 h, the reaction mixture was cooled to room temperature and quenched with water, then extracted with diethyl ether (3×15 mL). The combined organic layers were washed with brine and water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column

chromatography eluting with 5% dichloromethane-hexane to yield the desired product **184** (45 mg, 82%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.30-1.55 (m, 10H, $(CH_2)_5$), 2.76 (s, 2H, CH_2Ar), 3.02 (s, 2H, CH_2OCH_3), 3.29 (s, 2H, CH_2OCH_3), 3.82 (s, 3H, $ArOCH_3$), 7.26 (d, J=8.5 Hz, 1H, ArH), 7.38 (m, 2H, ArH), 7.43 (d, J=8.5 Hz, 1H, ArH), 7.74 (m, 1H, ArH), 8.01 (m, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.94 ($2\times CH_2$), 26.32 (CH_2), 32.97 ($2\times CH_2$), 36.60 (CH_2), 39.20 (C), 58.82 (CH_3), 61.53 (CH_3), 77.00 (CH_2), 122.23 (CH), 122.97 (CH), 125.32 (CH), 125.57 (CH), 127.50 (C), 127.81 (CH), 127.96 (C), 130.83 (CH), 133.92 (C), 154.59 (C).

FTIR (neat, cm^{-1}): 3052 (CH-aromatic), 2926, 2850 (CH_2, CH_3), 1572, 1451, 1370, 1259 (C=C), 1197, 1112 (C-O).

MS (EI), *m/z* (% relative intensity): 298 (M^+, 15), 267 (38), 171 (100), 156 (4), 128 (3).

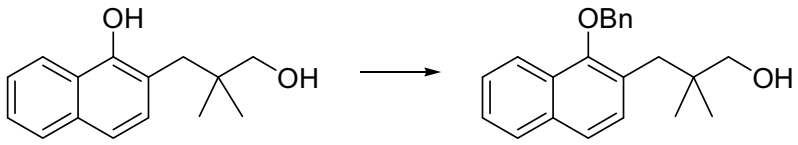
HRMS: calcd for $C_{20}H_{26}O_2$ [M+H] 299.2011, found 299.2013.

Benzylation of naphthol

General procedure:

A mixture of naphthol **84** or **90** (1.0 mmol), potassium carbonate (2.0 mmol) and benzyl chloride (2.0 mmol) in acetone (25 mL) was stirred under refluxing for 5-24 h. After that the reaction mixture was cooled to room temperature, water was added to the mixture and then extracted with diethyl ether (3×25 mL). The combined organic layers were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo.

3-(1-Benzyloxy-naphthalen-2-yl)-2,2-dimethyl-propan-1-ol (185)



84 **185**

Compound **185** was synthesized by following the general procedure: a mixture of naphthol **84** (0.5 g, 2.2 mmol), potassium carbonate (0.6 g, 4.3 mmol) and benzyl chloride (0.5 mL, 4.3 mmol) in acetone (10 mL) was stirred under refluxing for 5 h. The residue was purified by flash column chromatography eluting with 8% ethyl acetate-hexane to afford the product **185** (0.66 g, 95%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.00 (s, 6H, 2×CH_3), 2.78 (s, 2H, CH_2), 3.05 (d, J=7.0 Hz, 2H, OCH_2), 3.41 (t, J=7.0 Hz, 1H, OH), 5.08 (s, 2H, OCH_2Ph), 7.34 (d, J=8.4 Hz, 1H, ArH), 7.43-7.62 (m, 7H, ArH), 7.65 (d, J=8.4 Hz, 1H, ArH), 7.91 (m, 1H, ArH), 8.18 (m, 1H, ArH).

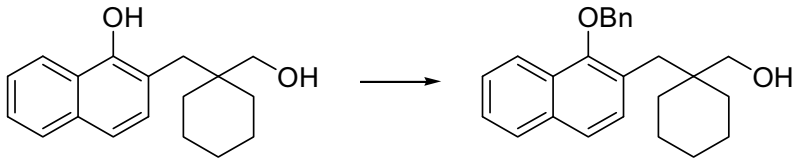
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.75 (2×CH_3), 38.21 (C), 39.05 (CH_2), 69.92 (CH_2), 77.56 (CH_2), 122.64 (CH), 124.57 (CH), 126.38 (CH), 126.79 (CH), 128.17 (C), 128.43 (C), 128.71 (CH), 128.86 (2×CH), 129.31 (CH), 129.55 (2×CH), 131.10 (CH), 134.75 (C), 136.96 (C), 153.04 (C).

FTIR (neat, cm^{-1}): 3447 (OH), 3059 (CH-aromatic), 2956, 2868 (CH_2, CH_3), 1501, 1467, 1361 (C=C), 1231, 1181, 1077, 1044 (C-O).

MS (EI), *m/z* (% relative intensity): 320 (M^+, 4), 212 (5), 157 (16), 128 (11), 91 (100).

HRMS calcd for $C_{22}H_{24}O_2$ [M+H] 321.1849, found 321.1851

(1-((1-(Benzyloxy)naphthalen-2-yl)methyl)cyclohexyl)methanol (186)



90 **186**

Compound **186** was synthesized by following the general procedure: a mixture of naphthol **90** (0.25 g, 0.93 mmol), potassium carbonate (0.19 g, 1.39 mmol) and benzyl chloride (0.16 mL, 1.39 mmol) in acetone (25 mL) was stirred under refluxing for 24 h.The residue was purified by flash column chromatography eluting with 10% CH_2Cl_2-hexane to yield the desired product **186** (0.30 g, 91%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.25-1.46 (m, 10H, $(CH_2)_5$), 2.70 (s, 2H, CH_2Ar), 3.00 (s, 2H, CH_2OH), 4.95 (s, 2H, OCH_2Ph), 7.22 (d, J=8.5 Hz, 1H, ArH), 7.30-7.49 (m, 7H, ArH), 7.51 (d, J=8.5 Hz, 1H, ArH), 7.78 (dd, J=1.0 and 8.4 Hz, 1H, ArH), 8.05 (dd, J=1.0 and 8.4 Hz, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 22.46 (2×CH_2), 27.26 (CH_2), 33.87 (2×CH_2), 36.65 (CH_2), 40.39 (C), 67.01 (CH_2), 77.74 (CH_2), 122.62 (CH), 124.61 (CH), 126.39 (CH), 126.83 (CH), 128.11 (C), 128.20 (C), 128.69 (CH), 128.94 (2×CH), 129.38 (CH), 129.59 (2×CH), 130.81 (CH), 134.69 (C), 136.79 (C), 153.09 (C).

FTIR (neat, cm^{-1}): 3531 (OH), 3049 (CH-aromatic), 2924, 2845 (CH_2, CH_3), 1452, 1384, 1356 (C=C), 1177, 1069, 1041 (C-O).

MS (EI), *m/z* (% relative intensity): 360 (M^+, 44), 359 (97), 343 (22), 341 (59), 247 (100), 169 (10), 128 (5).

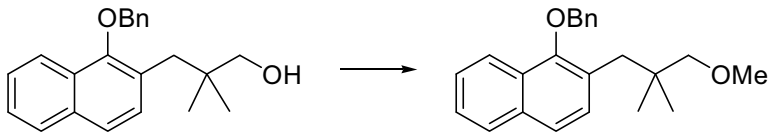
HRMS: calcd for $C_{25}H_{28}O_2$ [M+H] 361.2167, found 361.2168.

Methylation of alkyl alcohol

General procedure:

A solution of alcohol **185** or **186** (1.0 mmol) in dry THF (2 mL) was added dropwise to a stirred suspension of sodium hydride (6.0 mmol) in dry THF (4 mL). Then methyl iodide (6.0 mmol) was added dropwise to the reaction mixture. After refluxing for 5 h, the reaction mixture was cooled to room temperature and quenched with water, then extracted with diethyl ether (3×15 mL). The combined organic layers were washed with brine and water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo.

1-Benzyloxy-2-(3-methoxy-2,2-dimethyl-propyl)-naphthalene (187)



185 **187**

Compound **187** was synthesized by following the general procedure: a solution of alcohol **185** (0.26 g, 0.8 mmol) in dry THF (4 mL) was added dropwise to a stirred suspension of sodium hydride (0.12 g, 4.8 mmol) in dry THF (6 mL). Then methyl iodide (0.31 mL, 4.8 mmol) was added dropwise to the reaction mixture. The mixture was stirred for 5 hours. The residue was purified by flash column chromatography eluting with 10% CH_2Cl_2-hexane to afford the desired product **187** (0.25 g, 94%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.00 (s, 6H, 2×CH_3), 2.85 (s, 2H, CH_2Ar), 3.11 (s, 2H, OCH_2), 3.41 (s, 3H, OCH_3), 5.05 (s, 2H, OCH_2Ph), 7.38 (d, J=8.4 Hz, 1H, ArH), 7.45 (m, 1H, ArH), 7.51 (m, 4H, ArH), 7.64 (m, 3H, ArH), 7.90 (m, 1H, ArH), 8.17 (m, 1H, ArH).

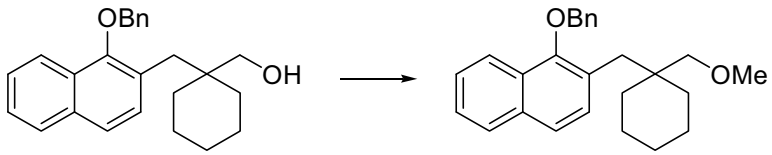
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.54 (2×CH_3), 37.73 (C), 39.31 (CH_2), 59.72 (CH_2), 76.39 (CH_2), 82.06 (CH_3), 122.90 (CH), 123.92 (CH), 126.08 (CH), 126.38 (CH), 128.22 (2×CH), 128.55 (2×CH), 128.79 (2×C), 129.18 (2×CH), 131.17 (CH), 134.63 (C), 138.44 (C), 153.81 (C).

FTIR (neat, cm^{-1}): 3058 (CH-aromatic), 2959, 2868 (CH_2, CH_3), 1457, 1361 (C=C), 1183, 1109 (C-O).

MS (EI), *m/z* (% relative intensity) : 334 (M^+, 4), 212 (22), 157 (20), 128 (13), 91 (100).

HRMS calcd for $C_{23}H_{26}O_2$ [M+H 335.2006, found 335.2006.

1-(Benzyloxy)-2-((1-(methoxymethyl)cyclohexyl)methyl)naphthalene (188)



186 **188**

Compound **188** was synthesized by following the general procedure: a solution of alcohol **186** (0.10 g, 0.28 mmol) in dry THF (2 mL) was added dropwise to a stirred suspension of sodium hydride (67 mg, 1.68 mmol) in dry THF (4 mL). Then methyl iodide (0.10 mL, 1.68 mmol) was added dropwise to the reaction mixture. The mixture was stirred for 5 hours. The residue was purified by flash column chromatography eluting with 3% ethyl acetate-hexane to provide the desired product **188** (71 mg, 68%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.25-1.60 (m, 10H, $(CH_2)_5$), 2.85 (s, 2H, CH_2Ar), 3.13 (s, 2H, CH_2OCH_3), 3.35 (s, 3H, OCH_3), 5.00 (s, 2H, OCH_2Ph), 7.37 (d, *J*=8.4 Hz, 1H, ArH), 7.42 (m, 1H, ArH), 7.42-7.51 (m, 4H, ArH), 7.57-7.60 (m, 3H, ArH), 7.85 (m, 1H, ArH), 8.13 (m, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 22.52 (2×CH_2), 26.90 (CH_2), 30.35(CH_2), 33.48 (2×CH_2), 37.44 (CH_2), 39.89 (C), 59.54 (CH_3), 76.66 (CH_2), 122.93 (CH), 123.81 (CH), 126.04 (CH), 126.33 (CH), 128.55 (3×CH), 128.61(CH), 128.64, (C) 128.71 (C), 129.16 (2×CH), 131.38 (CH), 134.58 (C), 138.31 (C), 153.99 (C).

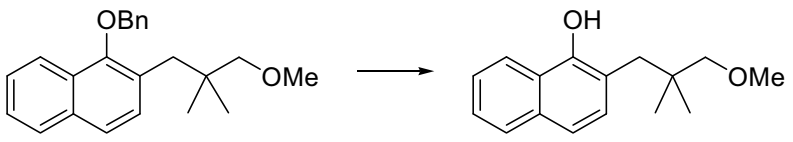
FTIR (neat, cm^{-1}): 3060 (CH-aromatic), 2924, 2852, 2807 (CH_2, CH_3), 1578, 1452, 1359, 1258 (C=C), 1183, 1111 (C-O).

MS (EI), *m/z* (% relative intensity): 374 (M^+, 78), 342 (19), 247 (100), 128 (2), 169 (16).

HRMS: calcd for $C_{26}H_{30}O_2$ [M+H] 375.2324, found 375.2329.

Debenzylation of naphthyl benzyl ether

2-(3-Methoxy-2,2-dimethyl-propyl)-naphthalen-1-ol (189)



187 **189**

To a mixture of compound **187** (0.12 g, 0.37 mmol), potassium iodide (0.18 g, 1.1 mmol) in acetonitrile (6 ml), trimethylsilylchloride (0.14 ml, 1.1 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 1 hour. After that water was added to the reaction mixture and extracted with diethyl ether (3×30 ml). The combined organic phases were washed with saturated sodium hydrogen carbonate and water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography eluting with 5% CH_2Cl_2-hexane to afford the desired product (**189**) (78 mg, 87%) as a colourless solid, m.p. 67-68°C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.10 (s, 6H, 2×CH_3), 2.78 (s, 2H, CH_2Ar), 3.00 (s, 2H, OCH_2), 3.50 (s, 3H, OCH_3), 7.18 (d, *J*=8.3 Hz, 1H, ArH), 7.35 (d, *J*=8.3 Hz, 1H, ArH), 7.48 (m, 2H, ArH), 7.79 (m, 1H, ArH), 8.36 (m, 1H, ArH), 8.55 (s, 1H, OH).

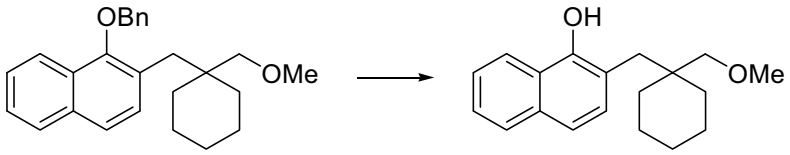
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 26.35 (2×CH_3), 36.84 (C), 39.52 (CH_2), 59.81 (CH_2), 79.96 (CH_3), 117.91 (C), 119.30 (CH), 123.25 (CH), 125.41 (CH), 125.91 (C), 126.25 (CH), 127.79 (CH), 131.43 (CH), 134.28 (C), 151.75 (C).

FTIR (KBr, cm^{-1}): 3229 (OH), 2951 (CH_2, CH_3), 1569, 1456, 1386, 1290 (C=C), 1083 (C-O).

MS (EI), *m/z* (% relative intensity) : 244 (M^+, 35), 212 (35), 157 (100), 128 (78) 87 (46).

HRMS calcd for $C_{16}H_{20}O_2$ [M+Na] 267.1361, found 267.1359.

2-((1-(Methoxymethyl)cyclohexyl)methyl)naphthalen-1-ol (190)



188 **190**

Compound **190** was synthesized by following the general procedure: a mixture of benzyl ether **188** (40 mg, 0.11 mmol) and 10% Palladium-charcoal (11.4 mg, 10 mol%) in ethanol (2 mL) was stirred at room temperature for 24 h. Then the reaction mixture was filtered through celite and washed with ethyl acetate. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 0.5% ethyl acetate-hexane to afford the desired product **190** (24.2 mg, 80%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.40-1.60 (m, 10H, $(CH_2)_5$), 2.81 (s, 2H, CH_2Ar), 3.10 (s, 2H, CH_2OCH_3), 3.48 (s, 3H, OCH_3), 7.17 (d, J=8.4 Hz, 1H, ArH), 7.32 (d, J=8.4 Hz, 1H, ArH), 7.46 (m, 2H, ArH), 7.77 (m, 1H, ArH), 8.35 (m, 1H, ArH), 8.63 (s, 1H, OH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 22.37 (2×CH_2), 27.14 (CH_2), 34.29 (2×CH_2), 36.93 (CH_2), 39.14 (C), 59.91 (CH_3), 78.09 (CH_2), 117.62 (C), 119.22 (CH), 123.28 (CH), 125.38 (CH), 125.99 (C), 126.21 (CH), 127.76 (CH), 131.13 (CH), 134.26 (C), 152.02 (C).

FTIR (neat, cm^{-1}): 3268 (OH), 3047 (CH-aromatic), 2927, 2848 (CH_2, CH_3), 1572, 1454, 1387, 1299 (C=C), 1084 (C-O).

MS (EI), *m/z* (% relative intensity): 284 (M^+, 7), 247 (100), 247 (100), 168 (10), 157 (47), 141 (21).

HRMS calcd for $C_{19}H_{24}O_2$ [M+H] 285.1854, found 285.1857.

Anti-COX (PGHS) assay (Kirtikara *et al.*, 1998, 2001)

Immortalized mouse PGHS-1 (PGHS-$1^{-/-}$) and PGHS-2 (PGHS-$2^{-/-}$) null cells were seeded at 1×10^5 cell/mL in complete Dubelcco's Modified Eagle Medium (DMEM) supplemented with non essential amino acids (0.1 mM), glutamine (292 mg/L), ascorbic acid (50 mg/L) and 10% FCS in 96-well (83 μL/well) flat-bottomed tissue culture plates. The cells were incubated at 37 ^oC in a humidified incubator with 5% CO_2 for 72h. The cells were then washed with DMEM medium without FCS and preincubated for 30 min with 83 μL serum-free DMEM medium containing vehicle or drug. Aspirin or the test compounds were dissolved and serially diluted in ethanol or DMSO before they were added to the medium. The final concentrations of ethanol and DMSO were 1% and 0.1%, respectively. Following the preincubation period, the medium was removed and the cells were immediately treated with serum-free medium containing vehicle or drug and 2 μM A23187 for 30 min. Medium samples were then collected from the wells and analyzed for PGE_2 concentration by RIA as previously described. The test compounds were first screened at 10^{-5} g/mL. IC_{50} values were further determined for samples (10^{-5} g/mL) that show inhibitory effect on PGE_2 production. Aspirin, which was found to have PGHS-1 and PGHS-2 IC_{50} values of 0.014±0.008 and 0.058±0.053 mg/mL, respectively was employed as a nonselective COX-2 inhibitor.

Molecular docking

Crystal structure (1eqh and 1c×2) from Brookhaven Protein Data Bank (http://www.rcsb.org/pdb/) provided enzyme structures and binding site information for COX-2 complexed with SC-588 (Kurumbail *et al.*, 1996) and COX-1 bound to flurbiprofen (Selinsky *et al.*, 2001, Picot *et al.*, 1994) as reference structures. Initial structures of naphthol derivatives were generated by molecular modeling software Sybyl

6.8. (Sybyl version 6.7, 2000) The geometries of these compounds were subsequently optimized using the semi-empirical parameter AM1.

Binding conformations of naphthol derivatives with COX-2 and COX-1 were analyzed by the program AutoDock 3.0.5 using the Lamarckian genetic algorithm (LGA) in conjunction with an empirical force field to calculate ligand free energy of binding. (Morris *et al*., 1998) Kollman-all-atom charges were assigned to enzyme electrostatic contributions whereas Gasteiger-Hückel charges were assigned to all ligands. (Weiner *et al*., 1984, Purcell *et al*., 1967) All calculations were performed by representing the enzyme affinity by a 90×90×90 grid box of 0.25 Å grid spacing.

The conditions applied throughout the docking simulations were those, which reproduced the co-crystals of flurbiprofen and SC-558 bound to COX-1 and COX-2 enzymes with root mean square deviation (RMSD) value of 0.7 Å for both cases using flurbiprofen and SC-558 at the binding sites in 1eqh and 1cx2 as references. The estimated free energy of binding using these docking conditions for SC-558 binding to COX-2 was -11.65 kcal/mol, which was slightly different from the value from the literature (-11.35 kcal/mol). Therefore, the AutoDock method and the parameter set could be extended to search the enzyme binding conformations for other inhibitors accordingly.

Finally, the docked complexes of inhibitor-enzyme were selected according to the criteria of interacting energy combined with geometrical matching quality. All amino acid residues within a 5.0 Å radius of the inhibitor atom were considered and analyzed for their activity contributions.

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APPENDIX