2-Arylnaphthoquinone analogues: potential anti-TB and pro-apoptotic agents

Ivan R Green, a* Sunil Sagar, a Wendell Swigelaar, a Farouk Ameer, a and Mervin Meyer b

a Department of Chemistry, University of the Western Cape, Private Bag X17, Bellville, 7530, South Africa
b Department of Biotechnology, University of the Western Cape, Private Bag X17, Bellville, 7530, South Africa
E-mail: igreen@uwc.ac.za

Abstract
A useful library of substituted 2-arylnaphthoquinones prepared by reaction between the corresponding bromonaphthoquinones and arylboronic acids via Suzuki-Miyaura protocols has been established. Conversion of some of the products into new analogues was effected.

Keywords: Bromonaphthoquinones, naphthylboronic acids, phenylboronic acids, Suzuki-Miyaura coupling, demethylation, oxidation

Introduction
The bisnaphthoquinone disospyrin 1 comprises two 7-methyljuglone units linked between C2 and C6'.1,2 Antimycobacterial activity studies performed on disospyrin 1 alerted the scientific community to the potential importance of this natural product3 which was soon followed by its first published synthesis by Yoshida and Mori in the same year.4 Subsequent studies, which included the synthesis and evaluation of related analogues of disospyrin 1 demonstrated the potential of this basic scaffold to be considered as an integral aspect for good antimycobacterial activity.5-7

In order to gain a better understanding of the structural features and functional parameters that are necessary for such systems to demonstrate activity, we synthesized a number of biquinone molecules in which the two quinone moieties were directly linked viz., 2 and evaluated their pro-apoptotic activities against three human cancer cells lines. In addition the demethylated analogues viz., 3 were also evaluated and demonstrated that the molecules were specific for the available cancer cell lines evaluated.8,9 (Figure 1).
Figure 1. Bisnaphthoquinones of 7-methyljuglone.

All the former studies involved use of the 7-methyljuglone moiety as one component in the quinone-quinone linked systems. It was thus considered necessary to investigate a) whether two quinone-quinone linked moieties are necessary for biological activity, b) whether the 7-methyl group was necessary to enhance any biological activity, c) what, if any, relative reactivities between the peri OMe vs the peri OH groups are detectable and d) what the nature of the substituent attached at C2 of the final juglone moiety should be viz., either phenyl or naphthyl. The latter investigation was prompted by numerous examples reported in the literature.\(^{10}\)

This paper describes the syntheses of a number of families of substituted 2-phenyl- and 2-naphthyl-1,4-naphthoquinones related to the diospyrin type molecules together with a very brief mention of the biological activities of a few of the more active molecules selected to emphasize the importance of this work.

Results and Discussion

In the first series of substituted 2-arylnaphthoquinoidal compounds synthesized, 2-bromo-7-methylnaphthoquinone 4\(^{8,12}\) was selected since this moiety represented the 5-deoxy analogue of the ‘left hand’ juglone moiety in diospyrin 1. Thus treatment of bromoquinone 4 with boronic acid 5 under Suzuki-Miyaura conditions\(^{13a-c}\) afforded the expected naphthoquinone product 6 (90%) while a similar synthetic protocol between bromoquinone 4 and boronic acid 7 afforded the naphthoquinone product 8 (86%). Since one of our major future goals involved the biological evaluation of analogues containing a disulfoxide nucleus to mimic a 9,10-anthraquinoidal moiety, bromoquinone 4 was coupled to the thianthrenyl boronic acid 9 to afford the desired thianthrenyl naphthoquinone 10 (82%). This was in turn was oxidized using meta-chloroperbenzoic acid (m-CPBA) in dichloromethane under stirring to the corresponding disulfoxide 11 (58%) according to the protocol of Nakayama et al.\(^{14}\) The IR spectrum of the product 11 demonstrated clear S=O stretching vibrations at 1328 and 1164 cm\(^{-1}\). Apart from some reasonable variations between the quite complex NMR spectra of the thianthrenyl
naphthoquinone 10 and the corresponding naphthoquinone sulfoxide 11, the molecular formula of 11 viz., C\textsubscript{23}H\textsubscript{14}O\textsubscript{4}S\textsubscript{2} requires M\textsuperscript{+} 418.0334 amu (found M\textsuperscript{+} 418.0330) proved to be the major factor establishing the correct structure (Scheme 1).

Scheme 1. Products from 2-bromo-7-methylnaphthoquinone and naphthyl and thianthrenyl boronic acids.

For the second series of 2-arylnaphthoquinoidal compounds related to the basic skeleton of diospyrin 1, 2-bromo-5-methoxynaphthoquinone 12 was prepared\textsuperscript{15,16} which represented the 7-demethyl analogue of the ‘left hand’ ring. Treatment of quinone 12 with a range of naphthyl boronic acids under Suzuki-Miyaura conditons\textsuperscript{13} afforded the expected coupled products in yields ranging from 79-94% (Scheme 2). Chemoselective peri demethylation was effected in the transformation of quinone 18 to 19 (60%) by treatment with AlCl\textsubscript{3} in dichloromethane.\textsuperscript{8}
Scheme 2. Products from 2-bromo-5-methoxynaphthoquinone and naphthyl and thianthrenyl boronic acids.

Oxidation of the thianthrenyl naphthoquinone 20 to the corresponding disulfoxide 21 was achieved in 68% yield using the protocol described earlier. This was done to investigate the relative activities between disulfoxides 11 and 21 among others.

Literature indicates that introduction of a fluorine atom into a biologically active molecule will lead to an expectation of an increase in its biological activity profile.\textsuperscript{17,18} Treatment of
bromoquinone 12 with the 4-fluoro- and 3,5-difluorophenylboronic acids 22 and 23 respectively under standard Suzuki-Miyaura conditions affording good yields of the corresponding naphthoquinones 25 (81%) and 26 (78%) respectively (Scheme 3).

Scheme 3. Products from 2-bromo-5-methoxynaphthoquinone and fluorinated and aminated phenylboronic acids and naphthyl boronic acids.

Demethylation of the 5-methoxynaphthoquinone 26 to the corresponding 5-hydroxy analogue 27 was effected using AlCl₃ as described earlier and would serve as a comparative model for peri hydrogen bonding influences. An example of a powerful electron-donating substituent in the 2-phenyl analogues was obtained in the form of the dimethylaminophenyl naphthoquinone 28 (78%) derived from the coupling between quinone 12 and boronic acid 24.
Scheme 4. Products from 2-bromo-8-methoxynaphthoquinone and naphthyl and thianthrenyl boronic acids.

The two acetoxy analogues 30 and 31 were prepared from the corresponding acetoxybromonaphthoquinone 29 and boronic acids 7 and 5 respectively (Scheme 3) since we wished to evaluated what comparative electronic effects might operate in these molecules.
compared to their MeO isomers 16 and 13 respectively and how these might be manifested in their biological activities.

Studies by Lall et al.\textsuperscript{5} and Mahapatra et al.\textsuperscript{19} indicated that the peri alkoxy derivatives of diospyrin 1 and 7-methyl-5-hydroxynaphthoquinone exhibited a somewhat reduced activity against the susceptible strain of \textit{M. tuberculosis}, viz., H37Rv. On the other hand, Chakrabarty et al.\textsuperscript{20} reported that the peri alkoxy derivatives were more active compared to their peri hydroxyl analogues when evaluated against four human cancer cell lines.

It is for these reasons that a number of the peri alkoxy compounds were demethylated to serve as comparable test molecules for evaluations.

The isomeric peri methoxynaphthoquinone of 12, viz., 32\textsuperscript{21} was then employed to synthesize the next series of naphthylnaphthoquinones and is shown in Scheme 4. Of note in this series, is the finding that reaction between naphthoquinone 32 and boronic acid 15 produced two products viz., the Suzuki product 34 in addition to a 2,3-disubstituted product 35.

In order to evaluate any variations in activity between the isomeric quinones shown in Schemes 2 and 4 due to the electronic effects of the MeO group of the quinone, the isomeric 2-bromo-7-methoxynaphthoquinone 41 was prepared by reaction between the commercially available diene 39 and 2,5-dibromobenzoquinone 40.\textsuperscript{22} Passage of the crude adduct through a silica gel column produced a mixture of the expected product 42 (18\%) together with the desired naphthoquinone 41 (50\%). Subsequently, the crude adduct obtained from the reaction described above, was methylated by treatment with methyl iodide and Ag(II) oxide in benzene at 24 \textdegree C in which case the desired quinone 41 was isolated in 80\% yield (Scheme 5). Treatment of naphthoquinone 41 with boronic acid 15 also produced two products viz., the expected naphthoquinone 43 in addition to the 2,3-disubstituted product 44 in yields of 61 and 28\% respectively similar to that found for reaction between quinone 32 and boronic acid 15 (Scheme 4). The coupled thianthrenyl naphthoquinone adduct 45, derived between reaction of naphthoquinone 41 and boronic acid 9, could not be oxidized to a stable product in our hands.

Bromoquinone 46\textsuperscript{23} was selected for the final synthesis of a new series of 2-arylnaphthoquinones since it represented the left hand ring of diospyrin 1. A brief series of 2-naphthylnaphthoquinones having the best evaluated activity are illustrated in Scheme 6. Demethylations and oxidation of the thianthrenyl naphthoquinone 54 into the corresponding disulfoxide 55 with \textit{m-CPBA} are also shown.
Scheme 5. Synthesis of 2-bromo-7-methoxynaphthoquinone and its products with arylboronic acids.
Scheme 6. Products from 2-bromo-5-methoxy-7-methylnaphthoquinone and aryl boronic acids and some transformations.
Conclusions

A series of biologically active 2-aryl and 2-naphthyl-naphthoquinones has been prepared via Suzuki Miyaura methodology and subjected to evaluations for their anti-TB and pro-apoptotic behaviour. A comprehensive article on the biological activities will be published elsewhere.

Experimental Section

General. All melting points were obtained on a Fischer Johns melting point stage and are uncorrected. $^1$H NMR/$^{13}$C NMR spectra were obtained on a 200 MHz / 50 MHz Varian Gemini 2000 spectrometer in CDCl$_3$ with $\delta$ 7.26 for $^1$H NMR and $\delta$ 77.11 for $^{13}$C NMR spectra as internal reference. Mass spectra were performed on a Waters GCT Premier 70 eV High Resolution Mass Spectrometer and elemental analyses were performed on a Carlo Erba Strumentazione 1106 apparatus. IR spectra were recorded as nujol mulls for solids and thin films for oils on a Perkin Elmer FT-IR spectrometer Pragon 2000. Column chromatography was carried out on dry-packed columns using Merck silica gel 60 (0.063-0.2 mm) as stationary phase. The term “residue obtained upon work-up” refers to the residue obtained when the organic layer was separated, dried over MgSO$_4$, filtered and the filtrate evaporated under rotatory evaporation. All the boronic acids were purchased from Sigma Aldrich and used without further purification. Dichloromethane (DCM) was dried by distillation from calcium chloride and stored over sodium wire while benzene was dried by distillation and stored over sodium wire.

General procedure for coupling of boronic acids with bromonaphthoquinones e.g. 2-(naphthalen-2-yl)-7-methyl-1,4-naphthoquinone (8)

To a stirred (30 min) mixture of 2-bromo-7-methyl naphthoquinone 4 $^8,^{12}$ (314 mg, 1.25 mmol) and Pd(PPh$_3$)$_4$ (148 mg, 0.11 mmol) in benzene (10 mL) at 25 °C under nitrogen was added an aqueous solution of sodium carbonate (2M, 1.0 mL) followed by 2-naphthaleneboronic acid 7 (203 mg, 1.18 mmol) in benzene (5 mL) drop wise. The mixture was heated under reflux for 16 h with vigorous stirring and after cooling to 25 °C was quenched with water (50 mL) and extracted with dichloromethane. The residue obtained upon work-up was chromatographed using EtOAc: hexane (3:7) as eluent to afford naphthoquinone 8 (319 mg, 86%) as yellow needles, mp 169-170 °C (from EtOAc:hexane), IR ($\nu$$_{max}$, cm$^{-1}$): 1658 and 1652 (C=O). $^1$H NMR (200.1 MHz, CDCl$_3$), $\delta$H 2.53 (3H, s, CH$_3$-7), 7.16 (1H, s, H-3), 7.59 (4H, m, H-1', H-3', H-6' and H-7'), 7.99 (6H, m, H-4', H-5', H-8', H-5, H-6 and H-8). $^{13}$C NMR (50 MHz, CDCl$_3$), $\delta$C 22.0, 126.3, 126.4, 126.7, 127.4, 127.5, 127.8, 128.2, 128.9, 129.8, 130.1, 131.1, 132.6, 133.1, 134.0, 135.6, 145.1, 148.1, 185.0 and 185.1. Anal. Calcd for C$_{21}$H$_{14}$O$_2$: C, 84.54; H, 4.73. Found: C, 84.50; H, 4.82.

2-(4-Methylnaphthalen-2-yl)-7-methyl-1,4-naphthoquinone (6). Condensation between 4$^8,^{12}$ and boronic acid 5 afforded quinone 6 (352 mg, 90%) as red needles, mp 109-111 °C (from EtOAc:hexane), IR ($\nu$$_{max}$, cm$^{-1}$): 1660 and 1652 (C=O). $^1$H NMR (200.1 MHz, CDCl$_3$), $\delta$H 2.53
(3H, s, CH$_3$-7), 2.76 (3H, s, CH$_3$-4'), 7.07 (1H, s, H-3), 7.49 (6H, m, H-2', H-3', H-5', H-6', H-7' and H-8'), 7.97 (1H, d, J = 0.8 Hz, H-8), 8.08 (1H, dd, J = 8.2 and 0.8 Hz, H-6), 8.10 (1H, d, J = 8.2 Hz, H-5). $^{13}$C NMR (50 MHz, CDCl$_3$), δc 19.7, 21.9, 124.6, 125.9, 126.0, 126.1, 126.2, 126.4, 127.0, 127.5, 130.1, 130.3, 131.5, 132.3, 132.7, 134.6, 136.5, 137.9, 145.1, 149.7, 184.8, 185.0. Anal. Calcd for C$_{22}$H$_{16}$O$_3$: C, 84.59; H, 5.16. Found: C, 84.50; H, 5.05.

7-Methyl-2-(thianthren-1-yl)-1,4-napthoquinone (10). Condensation between 4$^{8,12}$ (260 mg, 1.03 mmol) and boronic acid 9 (260 mg, 1.00 mmol) afforded quinone 10 (330 mg, 82%) as yellow crystals, mp 208-209 °C (from EtOAc:hexane), IR (v$_{max}$, cm$^{-1}$): 1671 and 1660 (C=O). $^1$H NMR (200.1 MHz, CDCl$_3$), δH 2.55 (3H, s, CH$_3$-7), 6.93 (1H, s, H-3), 7.27 (5H, m, H-2', H-3', H-4', H-7' and H-8'), 7.51 (1H, dd, J = 8.0 and 1.2 Hz, H-6), 7.61 (2H, m, H-6' and H-9'), 8.01 (1H, d, J = 1.2 Hz, H-8), 8.07 (1H, d, J = 8.0 Hz, H-5), $^{13}$C NMR (50 MHz, CDCl$_3$), δc 21.9, 126.4, 126.6, 127.4, 127.6, 127.8, 127.9, 128.6 (2C), 128.9, 129.9, 130.0, 132.1, 134.1, 134.8, 135.2, 135.8, 136.2, 145.3, 148.8, 183.6, 184.8. Anal. Calcd for C$_{22}$H$_{14}$O$_2$: C, 71.48; H, 3.65. Found: C, 71.62; H, 3.54.

2-(4-Methylnapthalen-1-yl)-5-methoxy-1,4-napthoquinone (13). Condensation between quinone 12$^{15,16}$ (270 mg, 1.00 mmol) and boronic acid 5 (190 mg, 1.00 mmol) afforded the quinone 13 (270 mg, 81%) as an orange powder, mp 203-204 °C, IR (v$_{max}$, cm$^{-1}$): 1693 and 1667 (C=O). $^1$H NMR (200.1 MHz, CDCl$_3$), δH 2.75 (3H, s, CH$_3$-4'), 4.07 (3H, s, OCH$_3$), 7.02 (1H, s, H-3), 7.44 (5H, m, H-6, H-2', H-3', H-6' and H-7'), 7.65 (1H, dd, J = 7.8 and 1.4 Hz, H-5'), 7.70 (1H, t, J = 8.0 Hz, H-7) 7.81 (1H, dd, J = 8.0 and 1.6 Hz, H-8), 8.06 (1H, dd, J = 7.8 and 1.4 Hz, H-8'). $^{13}$C NMR (50 MHz, CDCl$_3$), δc 19.7, 56.6, 117.9, 120.0, 121.0, 124.6, 125.8, 125.9, 126.0, 126.1, 127.0, 129.9, 131.4, 132.6, 134.7, 135.0, 136.4, 139.9, 147.4, 159.6, 184.5, 184.6. Anal. Calcd for C$_{22}$H$_{17}$O$_2$: C, 80.23; H, 5.20. Found: C, 80.15; H, 5.20.

2-(Naphthalen-2-yl)-5-methoxy-1,4-napthoquinone (16). Condensation between quinone 12$^{15,16}$ (270 mg, 1.00 mmol) and boronic acid 7 (170 mg, 1.00 mmol) afforded the quinone 16 (290 mg, 92%) as an orange powder, mp 165-168 °C, IR (v$_{max}$, cm$^{-1}$): 1691 and 1672 (C=O). $^1$H NMR (200.1 MHz, CDCl$_3$), δH 4.05 (3H, s, OCH$_3$), 7.13 (1H, s, H-3), 7.35 (1H, dd, J = 8.0 and 1.5 Hz, H-6), 7.54 (2H, m, H-6' and H-7'), 7.65 (1H, dd, J = 8.8 and 1.6 Hz, H-3'), 7.74 (1H, t, J = 8.0 Hz, H-7), 7.88 (4H, m, H-4', H-5', H-8' and H-8), 8.14 (1H, d, J = 1.4 Hz, H-1'). $^{13}$C NMR (50 MHz, CDCl$_3$), δc 56.6, 117.8, 119.9, 120.0, 126.2, 126.5, 127.2, 127.7, 128.0, 128.7, 129.6, 130.5, 133.0, 133.8, 134.9, 135.0, 137.5, 145.7, 154.9, 184.5, 184.8. Anal. Calcd for C$_{22}$H$_{15}$O$_3$: C, 79.98; H, 4.97. Found: C, 79.84; H, 4.82.

2-(6-Ethoxynaphthalen-2-yl)-5-methoxy-1,4-napthoquinone (17). Condensation between quinone 12$^{15,16}$ (270 mg, 1.00 mmol) and boronic acid 14 (220 mg, 1.00 mmol) afforded the quinone 17 (316 mg, 88%) as a dark red powder, mp 144-147 °C, IR (v$_{max}$, cm$^{-1}$): 1694 and 1679 (C=O). $^1$H NMR (200.1 MHz, CDCl$_3$), δH 1.50 (3H, t, J = 7.0 Hz, OCH$_2$CH$_3$), 4.05 (3H, s, OCH$_3$), 4.18 (2H, q, J = 7.0 Hz, OCH$_2$CH$_3$), 7.10 (1H, s, H-3), 7.18 (2H, m, H-5' and H-7'), 7.33 (1H, dd, J = 7.8 and 1.5 Hz, H-6), 7.61 (1H, dd, J = 8.8 and 1.8 Hz, H-3'), 7.72 (1H, t, J = 7.8 Hz, H-7), 7.78 (1H, d, J = 8.4 Hz, H-8'), 7.80 (1H, d, J = 8.8 Hz, H-4'), 7.86 (1H, dd, J = 7.8 and 1.5 Hz, H-8), 8.07 (1H, br s, H-1'), IR (v$_{max}$, cm$^{-1}$): 1694 and 1679 (C=O). $^{13}$C NMR (50 MHz,
(CDCl₃), δc 14.8, 56.5, 63.8, 106.4, 117.7, 119.7, 119.9, 120.1, 126.6, 126.9, 128.1, 128.5, 129.5, 130.3, 134.8, 135.1, 135.3, 136.8, 145.7, 158.2, 159.4, 184.6, 185.0. Anal. Calcd for C₂₃H₁₉O₄: C, 76.86; H, 5.33. Found: C, 76.72; H, 5.10.

2-(6-Methoxynaphthalen-2-yl)-5-methoxy-1,4-naphthoquinone (18). Condensation between quinone 12¹⁵,¹⁶ (330 mg, 1.24 mmol) and boronic acid 15 (250 mg, 1.25 mmol) afforded the quinone 18 (340 mg, 79%) as orange brown crystals, mp 173-176 °C, IR (vmax, cm⁻¹): 1693 and 1676 (C=O). ¹H NMR (200.1 MHz, CDCl₃), δH 3.94 (3H, s, MeO-6'), 4.04 (3H, s, MeO-5), 7.10 (1H, s, H-3), 7.18 (2H, m, H-5' and H-7'), 7.34 (1H, dd, J = 7.3 and 1.0 Hz, H-6), 7.62 (1H, dd, J = 8.4 and 1.8 Hz, H-3'), 7.72 (1H, t, J = 8.4, H-7), 7.80 (2H, m, H-4' and H-8'), 7.86 (1H, dd, J = 7.8 and 1.0 Hz, H-8), 8.08 (1H, br s, H-1'). ¹³C NMR (50 MHz, CDCl₃), δc 55.4, 56.5, 105.6, 117.7, 119.4, 119.9, 120.0, 126.7, 126.9, 128.2, 128.5, 129.5, 130.3, 134.8, 135.0, 135.2, 136.9, 145.6, 158.8, 159.3, 184.6, 184.9. Anal. Calcd for C₂₂H₁₇O₄: C, 76.51; H, 4.96. Found: C, 76.38; H, 4.86.

5-Methoxy-2-(thianthren-1-yl)-1,4-naphthoquinone (20). Condensation between quinone 12¹⁵,¹⁶ (270 mg, 1.00 mmol) and boronic acid 9 (260 mg, 1.00 mmol) afforded the quinone 20 (380 mg, 94%) as a yellow powder, mp 214-217 °C, IR (vmax, cm⁻¹): 1671 and 1660 (C=O). ¹H NMR (200.1 MHz, CDCl₃), δH 4.07 (3H, s, OMe), 6.87 (1H, s, H-3), 7.25 (6H, m, H-6, H-2', H-3', H-4', H-6', H-7'), 7.51 (1H, dd, J = 7.6 and 1.8 Hz, H-5'), 7.60 (1H, dd, J = 7.6 and 1.8 Hz, H-8'), 7.75 (1H, t, J = 8.4 Hz, H-7), 7.87 (1H, dd, J = 8.4 and 1.8 Hz, H-8). ¹³C NMR (50 MHz, CDCl₃), δc 56.7, 118.0, 120.1, 120.2, 127.5, 127.8, 128.0, 128.7, 128.8, 129.1, 130.0, 134.5, 134.6, 135.2, 135.4, 135.9, 136.3, 137.1, 139.0, 146.7, 159.7, 183.7, 184.3. Anal. Calcd for C₂₃H₁₅O₃S₂: C, 68.47; H, 3.75. Found: C, 68.35; H, 3.60.

2-(4-Fluorophenyl)-5-methoxy-1,4-naphthoquinone (25). Condensation between quinone 12¹⁵,¹⁶ (270 mg, 1.00 mmol) and boronic acid 22 (140 mg, 1.00 mmol) afforded the quinone 25 (230 mg, 81%) as orange needles, mp 184-186 °C (from EtOAc:hexane), IR (vmax, cm⁻¹): 1670 and 1663 (C=O). ¹H NMR (200.1 MHz, CDCl₃), δH 4.04 (3H, s, OMe), 6.97 (1H, s, H-3), 7.13 (1H, d, J = 8.6 Hz, H-2'), 7.17 (1H, d, J = 8.6 Hz, H-6'), 7.34 (1H, dd, J = 7.6 and 1.2 Hz, H-6), 7.57 (1H, s, J = 8.6 Hz, H-3'), 7.59 (1H, d, J = 8.6 Hz, H-5'), 7.71 (1H, t, J = 7.6 Hz, H-7), 7.83 (1H, dd, J = 7.6 and 1.2 Hz, H-8). ¹³C NMR (50 MHz, CDCl₃), δc 56.7, 115.4, 115.8, 117.9, 119.9, 129.0, 129.1, 131.2, 131.4, 134.8, 134.9, 137.1, 144.6, 159.4, 163.8 (d, J = 249.1 Hz, C-4'), 184.3, 185.0. Anal. Calcd for C₁₇H₁₂O₃F: C, 72.08; H, 4.27. Found: C, 72.00; H, 4.40.

2-(3,5-Difluorophenyl)-5-methoxy-1,4-naphthoquinone (26). Condensation between quinone 12¹⁵,¹⁶ (270 mg, 1.00 mmol) and boronic acid 23 (160 mg, 1.00 mmol) afforded the quinone 26 (230 mg, 78%) as yellow needles, mp 221-224 °C (from EtOAc:hexane), IR (vmax, cm⁻¹): 1676 and 1667 (C=O). ¹H NMR (200.1 MHz, CDCl₃), δH 4.04 (3H, s, OMe), 6.91 (1H, dt, J = 8.8 and 2.2 Hz, H-4'), 6.99 (1H, s, H-3), 7.13 (2H, m, H-2' and H-6'), 7.35 (1H, dd, J = 8.4 and 1.2 Hz, H-6), 7.74 (1H, t, J = 8.4 Hz, H-7), 7.84 (1H, dd, J = 8.4 and 1.2 Hz, H-8). ¹³C NMR (50 MHz, CDCl₃), δc 56.6, 105.1 (t, J = 25.1, C-4'), 112.2, 112.7, 118.0, 119.9, 120.0, 134.4, 135.2 (2C), 138.1, 143.5, 159.6, 162.9 (d, J = 247.6 Hz, C-3' and C-5'), 183.7, 183.8. Anal. Calcd for C₁₇H₁₁O₃F₂: C, 67.78; H, 3.68. Found: C, 67.90; H, 3.82.
2-(4'-Dimethylaminophenyl)-5-methoxy-1,4-naphthoquinone (28). Condensation between quinone 1215,16 (270 mg, 1.00 mmol) and boronic acid 24 (170 mg, 1.00 mmol) afforded the quinone 28 (240 mg, 78%) as purple needles, mp 190-192 °C (from EtOAc:hexane), IR (ν_{max}, cm^{-1}): 1671 and 1660 (C=O). 1H NMR (200.1 MHz, CDCl3), δH 3.04 (6H, s, N(CH3)2), 4.02 (3H, s, OMe), 6.75 (2H, d, J = 9.0 Hz, H-3' and H-5'), 6.94 (1H, s, H-3), 7.30 (1H, dd, J = 8.4 and 1.0 Hz, H-6), 7.59 (2H, d, J = 9.0 Hz, H-2' and H-6'), 7.67 (1H, t, J = 7.6 Hz, H-7), 7.82 (1H, dd, J = 8.4 and 1.0 Hz, H-8). 13C NMR (50 MHz, CDCl3), δC 40.1 (2C), 56.5, 111.8 (2C), 117.5, 119.8, 120.2, 130.6 (2C), 133.5, 134.4, 134.5, 135.4, 135.1, 151.6, 159.2, 184.8, 185.6. Anal. Calcd for C19H18NO3: C, 74.01; H, 5.88. Found: C, 74.22; H, 5.73.

5-Acetoxy-2-(naphthalen-2-yl)-1,4-naphthoquinone (30). Condensation between quinone 2915 (150 mg, 0.51 mmol) and boronic acid 7 (86 mg, 0.50 mmol) afforded quinone 30 (137 mg, 79%) as yellow needles, mp 182-183 °C (from ethanol), IR (ν_{max}, cm^{-1}): 1772, 1668 and 1657 (C=O). 1H NMR (200.1 MHz, CDCl3), δH 2.49 (3H, s, CO2CH3), 7.07 (1H, s, H-3), 7.43 (1H, dd, J = 8.2 and 1.0 Hz, H-6), 7.58 (3H, m, H-3', H-6' and H-7'), 7.80 (1H, dd, J = 8.2 and 9.2 Hz, H-7), 7.90 (3H, m, H-4', H-5' and H-8'), 8.11 (1H, d, J = 1.0 Hz, H-1'), 8.18 (1H, dd, J = 9.2 and 1.2 Hz, H-8). 13C NMR (50 MHz, CDCl3), δC 21.1, 123.5, 125.6, 126.1, 126.6, 127.4, 127.7, 128.1, 128.8, 129.5, 129.8, 130.3, 133.0, 133.9, 134.3, 134.7, 136.5, 146.9, 149.2, 169.4, 183.7, 183.8. Anal. Calcd for C22H14O4: C, 77.18; H, 4.12. Found: C, 77.00; H, 4.20.

5-Acetoxy-2-(4-methylnaphthalen-2-yl)-1,4-naphthoquinone (31). Condensation between quinone 29 (150 mg, 0.51 mmol) and boronic acid 5 (93 mg, 0.50 mmol) afforded the quinone 31 (140 mg, 77%) as reddish brown needles, mp 173-174 °C (from ethanol), IR (ν_{max}, cm^{-1}): 1769, 1667 and 1655 (C=O). 1H NMR (200.1 MHz, CDCl3), δH 2.49 (3H, s, CO2CH3), 2.75 (3H, s, CH3-4'), 6.98 (1H, s, H-3), 7.35 (2H, m, H-2' and H-3'), 7.45 (1H, dd, J = 8.0 and 1.0 Hz, H-6), 7.54 (2H, m, H-6' and H-7'), 7.65 (1H, dd, J = 7.4 and 1.4 Hz, H-5'), 7.80 (1H, dd, J = 8.0 and 7.6 Hz, H-7), 8.07 (1H, dd, J = 7.4 and 1.4 Hz, H-8'), 8.15 (1H, dd, J = 7.6 and 1.0 Hz, H-8). 13C NMR (50 MHz, CDCl3), δC 19.6, 21.1, 123.6, 124.6, 125.7, 125.9, 126.0, 126.1, 126.6, 127.1, 129.6, 131.4, 132.7, 134.1, 134.8, 136.7, 138.9, 147.2, 148.6, 149.4, 169.5, 183.7(2C). Anal. Calcd for C23H16O4: C, 77.52; H, 4.53. Found: C, 77.48; H, 4.64.

2-(Naphthalen-2-yl)-8-methoxy-1,4-naphthoquinone (33). Condensation between quinone 3231 (270 mg, 1.00 mmol) and boronic acid 7 (170 mg, 1.00 mmol) afforded the quinone 33 (270 mg, 86%) as a yellow powder, mp 226-229 °C, IR (ν_{max}, cm^{-1}): 1691 and 1672 (C=O). 1H NMR (200.1 MHz, CDCl3), δH 4.03 (3H, s, OMe), 7.17 (1H, s, H-3), 7.35 (2H, m, H-3' and H-7), 7.58 (2H, m, H-6' and H-7'), 7.69 (4H, m, H-1', H-4', H-5' and H-8'), 7.75 (1H, t, J = 7.6 Hz, H-6), 7.89 (1H, dd, J = 7.6 and 1.4 Hz, H-5). 13C NMR (50 MHz, CDCl3), δC 56.7, 110.5, 118.3, 121.7, 123.4, 124.0, 124.3, 124.5, 127.4, 129.0, 130.0, 130.8, 131.6, 133.3, 134.8, 139.9, 143.5, 160.1, 174.4, 180.0. Anal. Calcd for C23H14O3: C, 80.24; H, 4.49. Found: C, 80.10; H, 4.60.

2-(6-Methoxynaphthalen-2-yl)-8-methoxy-1,4-naphthoquinone (34) and 2,3-di-(6-methoxynaphthalen-2-yl)-5-methoxy-1,4-naphthoquinone (35). Condensation between quinone 32 (270 mg, 1.00 mmol) and boronic acid 15 (200 mg, 1.00 mmol) afforded firstly quinone 34 (100 mg, 29%) as orange crystals, mp 160-162 °C (from EtOAc:hexane), IR (ν_{max}, cm^{-1}): 1661 and 1655 (C=O). 1H NMR (200.1 MHz, CDCl3), δH 4.03 (3H, s, OMe), 7.17 (1H, s, H-3), 7.35 (2H, m, H-3' and H-7), 7.58 (2H, m, H-6' and H-7'), 7.69 (4H, m, H-1', H-4', H-5' and H-8'), 7.75 (1H, t, J = 7.6 Hz, H-6), 7.89 (1H, dd, J = 7.6 and 1.4 Hz, H-5). 13C NMR (50 MHz, CDCl3), δC 56.7, 110.5, 118.3, 121.7, 123.4, 124.0, 124.3, 124.5, 127.4, 129.0, 130.0, 130.8, 131.6, 133.3, 134.8, 139.9, 143.5, 160.1, 174.4, 180.0. Anal. Calcd for C23H14O3: C, 80.24; H, 4.49. Found: C, 80.10; H, 4.60.
cm\(^{-1}\): 1663 and 1655 (C=O). \(^1\)H NMR (200.1 MHz, CDCl\(_3\)), \(\delta_H\) 3.95 (3H, s, MeO-6'), 4.05 (3H, s, MeO-8), 7.11 (1H, s, H-3), 7.18 (3H, m, H-3', H-5' and H-7'), 7.35 (1H, dd, \(J = 8.0\) and 1.0 Hz, H-7), 7.62 (1H, dd, \(J = 8.6\) and 1.8 Hz, H-4'), 7.71 (1H, t, \(J = 8.0\) Hz, H-6), 7.80 (2H, m, H-8' and H-5), 8.08 (1H, d, \(J = 1.8\) Hz, H-1'). \(^13\)C NMR (50 MHz, CDCl\(_3\)), \(\delta_C\) 55.5, 56.7, 105.8, 118.1, 118.8, 119.5, 121.0, 126.8, 128.6, 129.1, 130.0, 130.5, 132.5, 134.6, 135.0, 135.4, 149.9, 159.0, 160.1, 184.3, 185.3. Anal. Calcd for C\(_{22}\)H\(_{16}\)O\(_5\): C, 76.73; H, 4.68. Found: C, 76.60; H, 4.80. Further elution gave quinone 35 (210 mg, 42%) as a yellow powder, mp 233-236 °C, IR (\(v_{\text{max}}, \text{cm}^{-1}\)): 1668 and 1658 (C=O). \(^1\)H NMR (200.1 MHz, CDCl\(_3\)), \(\delta_H\) 3.86 (6H, s, MeO-6' and MeO-6''), 4.03 (3H, s, MeO-5), 7.05 (6H, m, H-3', H-3'', H-4', H-4'', H-5' and H-5''), 7.36 (1H, dd, \(J = 8.0\) and 1.4 Hz, H-6), 7.45 (2H, m, H-7' and H-7''), 7.60 (4H, m, H-1', H-1'', H-8' and H-8''), 7.74 (1H, t, \(J = 8.0\), H-7), 7.88 (1H, dd, \(J = 7.6\) and 1.4 Hz, H-8). \(^13\)C NMR (50 MHz, CDCl\(_3\)), \(\delta_C\) 55.4(2C), 56.6, 105.7(2C), 113.1(2C), 118.0, 120.6(2C), 122.6, 124.4(2C), 124.6(2C), 126.1, 127.1(2C), 130.5(2C), 132.9, 134.9, 135.0, 137.0, 137.1, 137.9, 138.0(2C), 154.8(2C), 161.3, 184.4, 185.1. Anal. Calcd for C\(_{33}\)H\(_{24}\)O\(_5\): C, 79.19; H, 4.83. Found: C, 79.00; H, 4.72.

2-(4-Methylnaphthalen-1-yl)-8-methoxy-1,4-naphthoquinone (36). Condensation between quinone 32 (270 mg, 1.00 mmol) and boronic acid 5 (190 mg, 1.00 mmol) afforded the quinone 36 (290 mg, 88%) as an orange powder, mp 157-160 °C, IR (\(v_{\text{max}}, \text{cm}^{-1}\): 1695 and 1673 (C=O). \(^1\)H NMR (200.1 MHz, CDCl\(_3\)), \(\delta_H\) 2.75 (3H, s, CH\(_3\)-4'), 3.97 (3H, s, OMe), 7.02 (1H, s, H-3), 7.40 (5H, m, H-6, H-2', H-3', H-6' and H-7'), 7.68 (1H, dd, \(J = 7.8\) and 1.4 Hz, H-5'), 7.74 (1H, t, \(J = 7.6\) Hz, H-6), 7.84 (1H, dd, \(J = 7.6\) and 1.4 Hz, H-5), 8.05 (1H, dd, \(J = 7.8\) and 1.4 Hz, H-8'). \(^13\)C NMR (50 MHz, CDCl\(_3\)), \(\delta_C\) 19.6, 56.5, 118.1, 118.9, 120.4, 124.5, 125.8, 125.9, 126.1, 126.2, 127.0, 130.7, 131.6, 132.6, 134.5, 134.9, 135.6, 136.2, 151.6, 160.1, 183.6, 185.3. Anal. Calcd for C\(_{22}\)H\(_{16}\)O\(_5\): C, 80.47; H, 4.91. Found: C, 80.33; H, 4.98.

8-Methoxy-2-(thianthren-1-yl)-1,4-naphthoquinone (37). Condensation between quinone 32 (270 mg, 1.00 mmol) and boronic acid 9 (260 mg, 1.00 mmol) afforded the quinone 37 (350 mg, 86%) as a yellow powder, mp 195-198 °C, IR (\(v_{\text{max}}, \text{cm}^{-1}\): 1688 and 1670 (C=O). \(^1\)H NMR (200.1 MHz, CDCl\(_3\)), \(\delta_H\) 4.02 (3H, s, OMe), 6.88 (1H, s, H-3), 7.30 (6H, m, H-7, H-2', H-3', H-4', H-6' and H-7'), 7.50 (1H, dd, \(J = 7.6\) and 1.8 Hz, H-5'), 7.59 (1H, dd, 7.6 and 1.8 Hz, H-8'), 7.74 (1H, t, \(J = 8.0\) Hz, H-6), 7.82 (1H, dd, \(J = 8.0\) and 1.6 Hz, H-5). \(^13\)C NMR (50 MHz, CDCl\(_3\)), \(\delta_C\) 56.5, 118.3, 118.9, 120.5, 127.2, 127.7, 127.8, 127.9, 128.6, 128.7, 129.0, 129.7, 134.4, 134.5, 134.9, 135.2, 135.7, 136.3, 136.8, 150.7, 160.1, 182.6, 185.1. Anal. Calcd for C\(_{33}\)H\(_{24}\)O\(_5\): C, 68.64; H, 3.51. Found: C, 68.58; H, 3.44.

2-Bromo-7-methoxy-1,4-naphthoquinone (41) and 2-bromo-7-hydroxy-1,4-naphthoquinone (42). To a stirred solution of 2,5-dibromobenzoquinone 40 (6.38 g, 24 mmol) in dry benzene (60 mL) at 25 °C was dripped in 1-methoxy-3-trimethylsilyloxybutadiene 39 (5 g, 29.2 mmol) over a period of 30 min and stirring was continued at 50 °C until starting material had been consumed (tlc). The residue obtained upon removal of all solvents was chromatographed and eluted with EtOAc:hexane (3:7) as eluent to yield firstly quinone 41 (1.18 g, 18%) as yellow crystals, mp 134-135 °C (from ethanol), IR (\(v_{\text{max}}, \text{cm}^{-1}\): 1670 (C=O). \(^1\)H NMR (200.1 MHz, CDCl\(_3\)), \(\delta_H\) 3.96
Condensation between quinone 41 (270 mg, 1.00 mmol) and boronic acid 15 (200 mg, 1.00 mmol) afforded firstly the quinone 43 (210 mg, 61%) as a yellow powder, mp 159-162 °C, IR (v_{max}, cm^{-1}): 1663 and 1655 (C=O). $^1$H NMR (200.1 MHz, CDCl$_3$), $\delta_{H}$ 3.95 (3H, s, MeO-6'), 3.98 (3H, s, MeO-7), 7.12 (1H, s, H-3), 7.20 (2H, m, H-5' and H-7'), 7.27 (1H, dd, $J = 8.4$ and 2.6 Hz, H-6), 7.62 (1H, dd, $J = 8.4$ and 1.4 Hz, H-3'), 7.64 (1H, d, $J = 2.6$ Hz, H-8), 7.81 (2H, d, $J = 8.4$ Hz, H-4' and H-8'), 8.06 (1H, d, $J = 1.4$ Hz, H-1'), 8.08 (1H, d, $J = 8.4$ Hz, H-5), $^{13}$C NMR (50 MHz, CDCl$_3$), $\delta_{C}$ 55.4(2C), 55.9, 105.6, 110.5, 119.5, 120.3, 125.9, 126.8, 126.9, 128.4, 128.5, 128.6, 129.6, 130.4, 130.8, 135.3, 147.5, 147.7, 158.9, 164.2, 184.3, 184.9. Anal. Calcd for C$_{22}$H$_{16}$O$_4$: C, 76.73; H, 4.68. Found: C, 76.58; H, 4.56. Further elution afforded quinone 44 (140 mg, 28%) as bright orange crystals, mp 179-181 °C, IR (v_{max}, cm^{-1}): 1668 and 1658 (C=O). $^1$H NMR (200.1 MHz, CDCl$_3$), $\delta_{H}$ 3.87 (6H, s, MeO-6' and MeO-6''), 3.98 (3H, s, MeO-6), 7.10 (6H, m, H-3', H-3'', H-4', H-4'', H-5', H-5''), 7.28 (1H, dd, $J = 8.8$ and 2.6 Hz, H-7), 7.47 (2H, d, $J = 8.2$ Hz, H-7' and H-7''), 7.59 (4H, m, H-1', H-1'', H-8', H-8''), 7.65 (1H, d, $J = 2.6$ Hz, H-5), 8.18 (1H, d, $J = 8.8$ Hz, H-8). $^{13}$C NMR (50 MHz, CDCl$_3$), $\delta_{C}$ 55.4(2C), 56.1, 105.7(2C), 109.8, 118.9(2C), 120.7, 126.0, 126.1, 128.2, 128.3, 128.7(4C), 129.3, 130.0, 130.1, 130.8, 130.9, 134.2(2C), 134.4(2C), 145.3, 145.7, 158.4(2C), 164.3, 184.2, 185.2. Anal. Calcd for C$_{33}$H$_{24}$O$_5$: C, 79.19; H, 4.83. Found: C, 79.10; H, 5.00.

**7-Methoxy-2-(thianthren-1-yl)-1,4-naphthoquinone (45).** Condensation between quinone 41 (270 mg, 1.00 mmol) and boronic acid 9 (260 mg, 1.00 mmol) afforded the quinone 45 (320 mg, 79%) as a yellow powder, mp 184-187 °C, IR (v_{max}, cm^{-1}): 1688 and 1670 (C=O). $^1$H NMR (200.1 MHz, CDCl$_3$), $\delta_{H}$ 3.99 (1H, s, OMe), 6.90 (1H, s, H-3), 7.25 (6H, m, H-6, H-2', H-3', H-4', H-6', H-7'), 7.50 (1H, dd, $J = 7.6$ and 1.4 Hz, H-5'), 7.61 (1H, dd, $J = 7.6$ and 1.4 Hz, H-8'), 7.64 (1H, d, $J = 2.6$ Hz, H-8), 8.12 (1H, d, $J = 8.4$ Hz, H-5). $^{13}$C NMR (50 MHz, CDCl$_3$), $\delta_{C}$ 56.0, 110.6, 120.5, 127.4, 127.8, 128.0, 128.6, 128.8, 129.0, 129.9, 130.3, 134.3, 134.7, 134.8,
2-(6-Methoxynaphthalen-2-yl)-5-methoxy-7-methyl-1,4-naphthoquinone (47). Condensation between quinone 46 (351 mg, 1.25 mmol) and boronic acid 15 (238 mg, 1.18 mmol) afforded the quinone 47 (401 mg, 90%) as orange-red needles, mp 179-181 °C (from ethanol), IR (v_{max}, cm^{-1}): 1663 and 1645 (C=O). ^1H NMR (200.1 MHz, CDCl_3), δ_H 2.51 (3H, s, CH_3-7), 3.95 (3H, s, MeO-6’), 4.03 (3H, s, MeO-5), 7.07 (1H, s, H-3), 7.13 (1H, d, J = 1.2 Hz, H-6), 7.18 (2H, m, H-5’ and H-7’), 7.62 (1H, dd, J = 8.4 and 1.8 Hz, H-3’), 7.67 (1H, d, J = 1.2 Hz, H-8), 7.80 (2H, m, H-4’ and H-8’), 8.07 (1H, d, J = 1.8 Hz, H-1’). ^13C NMR (50 MHz, CDCl_3), δ_c 22.5, 55.5, 56.6, 105.8, 118.3, 119.5, 120.8, 121.9, 126.9, 127.0, 128.4, 128.6, 129.5, 130.4, 135.0, 135.3, 137.2, 145.6, 146.3, 158.9, 159.7, 184.4, 185.3. Anal. Calcd for C_{23}H_{18}O_4: C, 77.08, H, 5.06. Found: C, 77.20, H, 5.22.

2-(Naphthalen-2-yl)-5-methoxy-7-methyl-1,4-naphthoquinone (50). Condensation between quinone 46 (351 mg, 1.25 mmol) and boronic acid 7 (203 mg, 1.18 mmol) afforded the quinone 50 (358 mg, 88%) as a yellow powder, mp 172-173 °C, IR (v_{max}, cm^{-1}): 1658 and 1651 (C=O). ^1H NMR (200.1 MHz, CDCl_3), δ_H 2.54 (3H, s, CH_3-7), 4.03 (3H, s, MeO-5), 7.09 (1H, s, H-3), 7.13 (1H, d, J = 1.4 Hz, H-6), 7.54 (2H, m, H-6’ and H-7’), 7.66 (2H, m, H-5’ and H-8’), 7.89 (3H, m, H-1’, H-3’ and H-4’), 8.13 (1H, d, J = 1.4 Hz, H-8). ^13C NMR (50 MHz, CDCl_3), δ_c 22.5, 56.6, 118.3, 120.8, 126.3, 126.6, 127.3, 127.8, 128.1, 128.8, 129.6, 130.8, 133.2, 133.9, 134.8, 137.8, 145.7, 146.5, 159.7, 184.3, 185.2. Anal. Calcd for C_{22}H_{16}O_5: C, 80.47; H, 4.91. Found: C, 80.70; H, 4.83.

5-Methoxy-7-methyl-2-(4-methynaphthalen-2-yl)-1,4-naphthoquinone (52). Condensation between quinone 46 (351 mg, 1.25 mmol) and boronic acid 5 (220 mg, 1.18 mmol) afforded the quinone 52 (428 mg, 90%) as yellow needles (from EtOAc:hexane), mp 229-230 °C, IR (v_{max}, cm^{-1}): 1659 and 1648 (C=O). ^1H NMR (200.1 MHz, CDCl_3), δ_H 2.51 (3H, s, CH_3-7), 2.74 (3H, s, CH_3-4’), 4.04 (3H, s, MeO-5), 6.98 (1H, s, H-3), 7.15 (1H, d, J = 1.0 Hz, H-6), 7.44 (4H, m, H-2’, H-3’, H-6’ and H-7’), 7.65 (2H, m, H-5’ and H-8), 8.06 (1H, dd, J = 8.0 and 1.0 Hz, H-8’). ^13C NMR (50 MHz, CDCl_3), δ_c 19.7, 22.4, 56.6, 118.1, 118.4, 120.9, 124.7, 126.01, 126.04, 126.1, 126.2, 127.2, 130.2, 131.6, 132.7, 134.5, 136.4, 140.1, 146.5, 147.4, 159.8, 184.3, 185.0. Anal. Calcd for C_{25}H_{18}O_5: C, 80.68; H, 5.30. Found: C, 80.83; H, 5.45.

5-Methoxy-7-methyl-2-(thianthren-1-yl)-1,4-naphthoquinone (54). Condensation between quinone 46 (351 mg, 1.25 mmol) and boronic acid 9 (306 mg, 1.18 mmol) afforded the quinone 54 (420 mg, 86%) as yellow needles, mp 203-204 °C (from EtOAc:Hexane), IR (v_{max}, cm^{-1}): 1670 and 1658 (C=O). ^1H NMR (200.1 MHz, CDCl_3), δ_H 2.52 (3H, s, CH_3-7), 4.04 (3H, s, OMe), 6.83 (1H, d, J = 1.4 Hz, H-6), 7.16 (1H, s, H-3), 7.27 (5H, m, H-2’, H-3’, H-4’, H-7’ and H-8’), 7.49 (1H, dd, J = 7.4 and 1.4 Hz, H-6’), 7.59 (1H, dd, J = 7.6 and 1.6 Hz, H-9’), 7.67 (1H, d, J = 1.4 Hz, H-8). ^13C NMR (50 MHz, CDCl_3), δ 22.3, 56.5, 118.4, 120.8, 127.4, 127.7, 127.9, 128.3, 128.6, 128.7, 129.8, 131.5, 134.2, 134.6, 135.3, 136.2, 136.9, 139.0, 146.4, 146.6, 159.8, 183.8, 183.9. Anal. Calcd for C_{24}H_{16}O_3S_2: C, 69.21; H, 3.87. Found: C, 69.44; H, 3.78.
General procedure for demethylation of the peri-methoxy group in the naphthoquinone products using AlCl₃

To a solution of the naphthoquinone (0.50 mmol) in dry DCM (20 mL) at 25 °C was added AlCl₃ (2.61 g, 19.6 mmol) and the mixture stirred at 25 °C for 24 h and poured into ice/water (100 mL). To this was added 0.1M HCl (100 mL) after which the solution was extracted with DCM (3x60 mL). The residue obtained upon workup was chromatographed using EtOAc:hexane (1:4) as eluent to yield the naphthol product.

2-(6-Methoxynaphthalen-2-yl)-5-hydroxy-1,4-naphthoquinone (19). Demethylation of quinone 18 (170 mg, 0.50 mmol) afforded naphthol 19 (100 mg, 60%) as orange-brown crystals, mp 211-214 °C (from EtOAc:hexane), IR (νmax, cm⁻¹): 3300-2700 (OH), 1687 and 1668 (C=O). ¹H NMR (200.1 MHz, CDCl₃), δH 3.96 (3H, s, MeO-6’), 7.14 (1H, s, H-3), 7.20 (2H, m, H-5’ and H-7’), 7.30 (1H, dd, J = 8.0 and 1.0 Hz, H-6), 7.62 (1H, dd, J = 8.4 and 1.8 Hz, H-3’), 7.66 (1H, t, J = 8.0, H-7), 7.74 (1H, dd, J = 8.0 and 1.0 Hz, H-8), 7.81 (2H, d, J = 8.4 Hz, H-4’ and H-8’), 8.09 (1H, bs, H-1’), 12.09 (1H, s, HO-5). ¹³C NMR (50 MHz, CDCl₃), δC 55.5, 105.6, 115.4, 119.7, 119.9, 124.3, 126.8, 127.1, 128.3, 128.6, 130.1, 130.6, 132.7, 134.5, 135.7, 136.4, 149.2, 159.2, 161.2, 184.2, 190.3. Anal. Calcd for C₂₁H₁₄O₄: C, 76.36; H, 4.27. Found: C, 76.22; H, 4.43.

2-(3,5-Difluorobenzen-1-yl)-5-hydroxy-1,4-naphthoquinone (27). Demethylation of quinone 26 (150 mg, 0.50 mmol) afforded naphthol 27 (80 mg, 56%) as yellow needles, mp 220-220 °C (from EtOAc:hexane), IR (νmax, cm⁻¹): 3430 (OH), 1687 and 1668 (C=O). ¹H NMR (200.1 MHz, CDCl₃), δH 6.95 (3H, s, MeO-6’), 7.14 (1H, s, H-3), 7.13 (2H, m, H-2’ and H-5’), 7.32 (1H, dd, J = 7.2 and 1.0 Hz, H-6), 7.70 (2H, m, H-7 and H-8), 11.92 (1H, s, HO-5). ¹³C NMR (50 MHz, CDCl₃), δC 105.7(t, J = 22.4), 112.4, 113.0, 119.9, 120.1, 124.7, 125.1, 128.3, 132.3, 136.1, 136.8, 137.3, 161.4, 163.7( 2C, d, J = 178.0), 189.7, 191.4. Anal. Calcd for C₁₆H₁₃O₂F₂: C, 67.14; H, 2.82. Found: C, 67.00; H, 2.68.

Demethylation using BB₃

5-Hydroxy-2-(6-methoxynaphthalen-2-yl)-7-methyl-1,4-naphthoquinone (48). To a solution of quinone 47 (250 mg, 0.70 mmol) in dry DCM (20 mL) was added BB₃ (0.9 mL of a 1M solution, 0.9 mmol) dropwise at -78 °C under N₂. The resultant purple mixture was stirred at 25 °C for 3h, poured into ice-water (80 mL), acidified to litmus and extracted into DCM. The residue obtained upon workup was chromatographed using EtOAc:hexane (1:4) as eluent to yield naphthol 48 (122 mg, 51%) as reddish-brown needles, mp 262-263 °C (from ethanol), IR (νmax, cm⁻¹): 3300 (OH), 1665 and 1644 (C=O). ¹H NMR (200.1 MHz, CDCl₃), δH 2.48 (3H, s, CH₃-7), 4.03 (3H, s, MeO-6’), 7.12 (2H, m, H-3 and H-6), 7.26 (1H, d, J = 1.0 Hz, H-5’), 7.33 (1H, dd, J = 8.4 and 1.0 Hz, H-7’), 7.55 (1H, d, J = 1.2 Hz, H-1’), 7.71 (1H, dd, J = 8.8 and 1.2 Hz, H-3’), 7.92 (1H, d, J = 8.4 Hz, H-8’), 8.10 (1H, d, J = 1.0 Hz, H-8), 8.29 (1H, d, J = 8.8 Hz, H-4’), 12.00 (1H, s, HO-5). ¹³C NMR (50 MHz, CDCl₃), δC 22.3, 57.0, 113.2, 114.1, 121.1, 124.0, 126.6, 127.9, 128.9, 129.0, 129.2, 130.1, 130.2, 132.2, 133.9, 135.1, 148.3(2C), 155.1, 161.4, 184.2, 189.5. Anal. Calcd for C₂₂H₁₆O₄: C, 76.73; H, 4.68. Found: C, 76.58; H, 4.75.
5-Hydroxy-2-(6-hydroxynaphthalen-2-yl)-7-methyl-1,4-naphthoquinone (49). To a solution of naphthol 48 (400 mg, 1.11 mmol) in dry DCM (20 mL) was added BBr₃ (2.44 mL of a 1M solution, 2.44 mmol) dropwise at -78 °C under N₂. After stirring at 25 °C for 3h the mixture was poured into ice-water (80 mL), acidified to litmus and extracted into DCM. The residue obtained upon work-up was chromatographed using EtOAc:hexane (1:4) as eluent to afford sulfoxide 49 (178 mg, 46%) as reddish-brown needles, mp 236-238 °C (from EtOAc:hexane), IR (νmax, cm⁻¹): 3300 (OH), 1664 and 1642 (C=O). ¹H NMR (200.1 MHz, CDCl₃), δH 2.47 (3H, s, CH₃-7), 6.05 (1H, bs, HO'6), 7.12 (2H, m, H-3 and H-6), 7.32 (1H, dd, J = 8.8 and 1.0 Hz, H-7'), 7.36 (1H, d, J = 1.0 Hz, H-5'), 7.55 (1H, d, J = 1.2 Hz, H-1'), 7.73 (1H, dd, J = 8.8 and 1.2 Hz, H-3'), 7.83 (1H, d, J = 8.8 Hz, H-8'), 8.12 (2H, m, H-4' and H-8), 12.00 (1H, s, HO-5). ¹³C NMR (50 MHz, CDCl₃), δC 22.3, 117.2, 118.0, 121.1, 124.0, 125.7, 128.1, 128.3, 129.0, 129.2, 130.2, 130.3, 132.2, 133.1, 148.1, 148.2, 152.1, 161.4, 184.1, 189.5. Anal. Calcd for C₂₁H₁₄O₄: C, 76.36; H, 4.27. Found: C, 76.52; H, 4.22.

5-Hydroxy-7-methyl-2-(naphthalene-2-yl)-1,4-naphthoquinone (51). To a solution of quinone 50 (310 mg, 0.94 mmol) in dry DCM (20 mL) was added BBr₃ (1.0 mL of a 1M solution, 1.00 mmol) dropwise at -78 °C under N₂. After stirring at 25 °C for 4h the reaction mixture was worked up as described earlier to afford the naphthol 51 (110 mg, 37%) as orange-red needles, mp 216-218 °C (from EtOAc:hexane), IR (νmax, cm⁻¹): 3340 (OH), 1651 and 1644 (C=O). ¹H NMR (200.1 MHz, CDCl₃), δH 2.58 (3H, s, CH₃-7), 7.15 (1H, s, H-3), 7.26 (1H, d, J = 1.2 Hz, H-6), 7.59 (4H, m, H-1', H-3', H-6' and H-7'), 7.91 (3H, m, H-4', H-5' and H-8'), 8.12 (1H, d, J = 1.2 Hz, H-8), 12.02 (1H, s, HO-5). ¹³C NMR (50 MHz, CDCl₃), δC 24.4, 121.1, 121.6, 126.1, 126.8, 127.6, 127.7, 127.8, 128.3, 129.0, 130.2, 130.3, 130.4, 133.0, 134.1, 134.9, 148.1, 149.3, 158.0, 183.8, 189.5. Anal. Calcd for C₂₁H₁₄O₃: C, 80.24; H, 4.49. Found: C, 80.42; H, 4.41.

5-Hydroxy-7-methyl-2-(4-methylnaphthalen-1-yl)-1,4-naphthoquinone (53). To a solution of quinone 52 (390 mg, 1.13 mmol) in dry DCM (20 mL) was added BBr₃ (1.3 mL of a 1M solution, 1.3 mmol) and after 3h the usual work-up was effected to produce the naphthol 53 (170 mg, 45%) as a red powder, mp 182-183 °C (from EtOAc:hexane), IR (νmax, cm⁻¹): 3433 (OH), 1665 and 1634 (C=O). ¹H NMR (200.1 MHz, CDCl₃), δH 2.58 (3H, s, CH₃-7), 2.76 (3H, s, CH₃-4'), 7.09 (2H, m, H-3 and H-6), 7.43 (4H, m, H-2', H-3', H-6' and H-7'), 7.63 (2H, m, H-5' and H-8), 8.07 (1H, dd, J = 7.6 and 0.8 Hz, H-8'), 12.01 (1H, s, HO-5). ¹³C NMR (50 MHz, CDCl₃), δC 19.7, 24.2, 121.1, 121.6, 124.0, 124.6, 125.9(2C), 126.1, 126.3, 127.2, 129.7, 130.0, 131.3, 132.7, 137.0, 137.3, 148.1, 151.1, 161.6, 183.5, 189.6. Anal. Calcd for C₂₂H₁₆O₃: C, 80.47; H, 4.91. Found: C, 80.32; H, 5.56.

General procedure for the oxidation of thianthrenes to the 5,10-disulfoxides

7-Methyl-2-(5,10-dioxidothianthren-1-yl)-1,4-naphthoquinone (11). To a stirred solution of quinone 10 (150 mg, 0.39 mmol) in dry DCM (20 mL) was added at once m-chloroperbenzoic acid (0.80 mmol) at 25 °C and after stirring 2h, the reaction mixture was washed with aqueous sodium hydrogen carbonate (10 mL of a 5% solution) and the residue obtained was chromatographed using EtOAc:hexane (1:4) as eluent to afford sulfoxide 11 (94 mg, 58%) as
orange needles, mp 115-117 °C (from EtOAc:hexane), IR (νmax, cm⁻¹): 1671 and 1658 (C=O), 1328 and 1164 (S=O). ¹H NMR (200.1 MHz, CDCl₃), δH 2.50 (3H, s, CH₃-7), 6.84 (1H, s, H-3), 7.35 (7H, m, H-5, H-6, H-8, H-6', H-7', H-8' and H-9'), 7.61 (1H, dd, J = 7.6 and 1.4 Hz, H-2'), 7.83 (1H, t, J = 7.6 Hz, H-3'), 8.19 (1H, dd, J = 7.6 and 1.4 Hz, H-4'). ¹³C NMR (50 MHz, CDCl₃), δC 21.1, 123.5, 125.8, 127.4, 127.8, 128.0, 128.7(2C), 129.0, 129.7, 130.1, 134.0, 134.2, 134.9, 135.1, 135.8, 136.2, 137.2, 138.0, 147.7, 149.4, 182.7, 183.5. Anal. Calcd for C₂₅H₁₄O₄S₂: C, 66.01; H, 3.37. Found: C, 66.28; H, 3.54. HREIMS: m/z 418.0330 (calcld. 418.0334).

5-Methoxy-2-(5,10-dioxidothianthren-1-yl)-1,4-napthoquinone (21). Quinone 20 (200 mg, 0.50 mmol) was oxidized in a similar way to the sulfoxide 21 (150 mg, 68%) as yellow needles, mp 142-144 °C (from EtOAc:hexane), IR (νmax, cm⁻¹): 1672 and 1662 (C=O), 1326 and 1164 (S=O). ¹H NMR (200.1 MHz, CDCl₃), δH 4.08 (3H, s, OMe), 6.98 (1H, s, H-3), 7.41 (1H, dd, J = 8.8 and 1.4 Hz, H-6), 7.58 (4H, m, H-2', H-3', H-7' and H-8' ), 7.77 (1H, t, J = 8.0 Hz, H-7), 7.85 (1H, dd, J = 8.0 and 1.4 Hz, H-8), 8.19 (2H, m, H-6' and H-9'), 8.31 (1H, dd, J = 7.6 and 1.4 Hz, H-4'). ¹³C NMR (50 MHz, CDCl₃), δC 56.7, 118.4, 120.1, 121.7, 125.6, 126.5, 127.4, 128.2, 129.1(2C), 132.2, 133.3, 133.4, 135.5, 140.7(2C), 144.2, 147.5, 147.8, 149.5, 159.9, 183.2, 183.6. Anal. Calcd for C₂₅H₁₄O₄S₂: C, 63.58; H, 3.25. Found: C, 63.42; H, 3.38.

8-Methoxy-2-(5,10-dioxidothianthren-1-yl)-1,4-napthoquinone (38). Quinone 37 (200 mg, 0.50 mmol) was oxidized in a similar way to the sulfoxide 38 (130 mg, 60%) as orange needles, mp 134-135 °C (from EtOAc:hexane), IR (νmax, cm⁻¹): 1678 and 1669 (C=O), 1322 and 1163 (S=O). ¹H NMR (200.1 MHz, CDCl₃), δH 3.99 (3H, s, OMe), 7.00 (1H, s, H-3), 7.40 (1H, dd, J = 8.0 and 1.4 Hz, H-7), 7.57 (4H, m, H-2', H-3', H-7' and H-8' ), 7.71 (1H, t, J = 8.0 Hz, H-6), 7.83 (1H, dd, J = 8.0 and 1.4 Hz, H-5), 8.11 (1H, dd, J = 7.0 and 2.0 Hz, H-6'), 8.25 (1H, dd, J = 7.0 and 2.0 Hz, H-9'), 8.37 (1H, dd, J = 7.6 and 1.4 Hz, H-4'). ¹³C NMR (50 MHz, CDCl₃), δC 56.6, 118.5, 119.4, 125.9, 126.6, 128.5, 128.7, 131.6, 132.0(2C), 132.1(2C), 132.2, 132.7, 133.9, 134.7, 135.5, 136.1, 138.7, 140.1, 160.3, 184.1, 184.2. Anal. Calcd for C₂₅H₁₄O₅S₂: C, 63.58; H, 3.25. Found: C, 63.52; H, 3.30.

5-Methoxy-7-methyl-2-(5,10-dioxidothianthren-1-yl)-1,4-napthoquinone (55). Quinone 54 (162 mg, 0.39 mmol) was oxidized in a similar way to the sulfoxide 55 (112 mg, 64%) as orange needles, mp 112-114 °C (from EtOAc:hexane), IR (νmax, cm⁻¹): 1671 and 1660 (C=O), 1326 and 1168 (S=O). ¹H NMR (200.1 MHz, CDCl₃), δH 2.54 (3H, s, CH₃-7), 4.04 (3H, s, OMe), 7.19 (1H, s, H-3), 7.61 (7H, m, H-6, H-8, H-2', H-3', H-7', H-8' and H-9'), 8.24 (1H, dd, J = 7.6 and 1.4 Hz, H-6'), 8.32 (1H, dd, J = 7.6 and 1.2 Hz, H-4'). ¹³C NMR (50 MHz, CDCl₃), δC 22.4, 56.5, 119.0, 120.9, 126.0, 127.1, 128.3, 128.8, 130.3, 131.2, 131.4, 131.8, 132.1, 132.2, 133.1, 133.4, 136.0, 139.1, 140.4, 143.3, 147.0, 160.0, 182.9, 185.0. Anal. Calcd for C₂₄H₁₆O₅S₂: C, 64.27; H, 3.60. Found: C, 64.48; H, 3.50.

Acknowledgements

The authors thank the UWC for their financial support.
References