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

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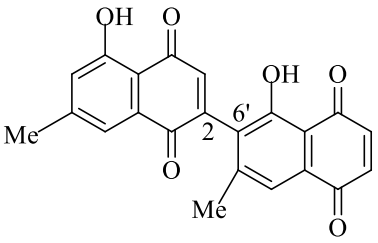
Abstract
A useful library of substituted 2-arylnaphthoquinones prepared by reaction between the corresponding bromonaphthoquinones and arylboronic acids via Suzuki-Miyaura protocols has been established. Conversion of some of the products into new analogues was effected.

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 diospyrin **1** alerted the scientific community to the potential importance of this natural product[3] 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 diospyrin **1** demonstrated the potential of this basic scaffold to be considered as an integral aspect for good antimycrobacterial 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).



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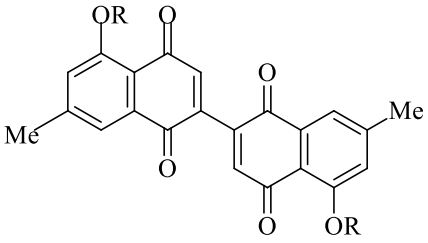


2 R = Me

3 R = H

Figure 1. Bisnaphthoquinones of 7-methyljuglone.

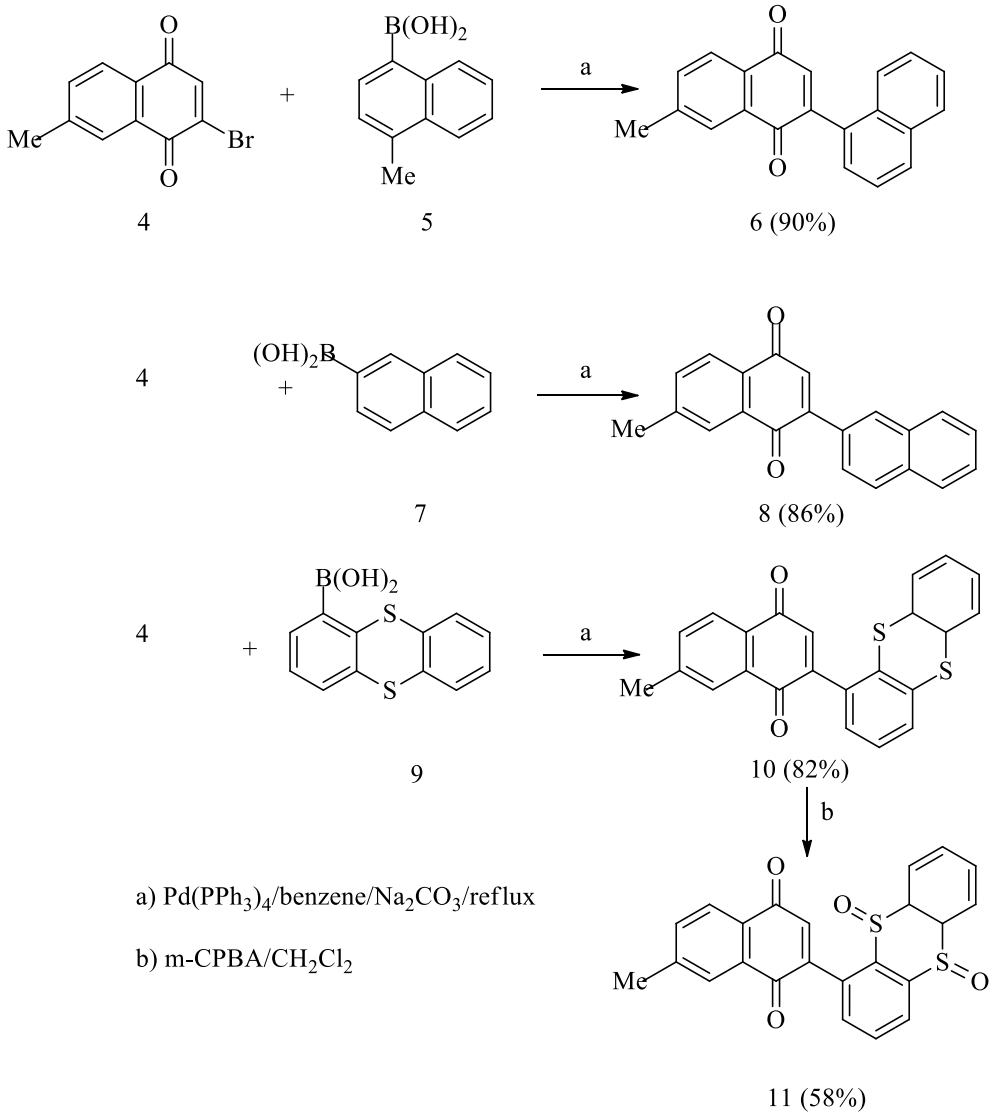
All the former studies involved use of the 7-methyljuglone moiety as one component in the quinone-quinone linked systems. It was thus considered necessary to investigate a) whether two quinone-quinone linked moieties are necessary for biological activity, b) whether the 7-methyl group was necessary to 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

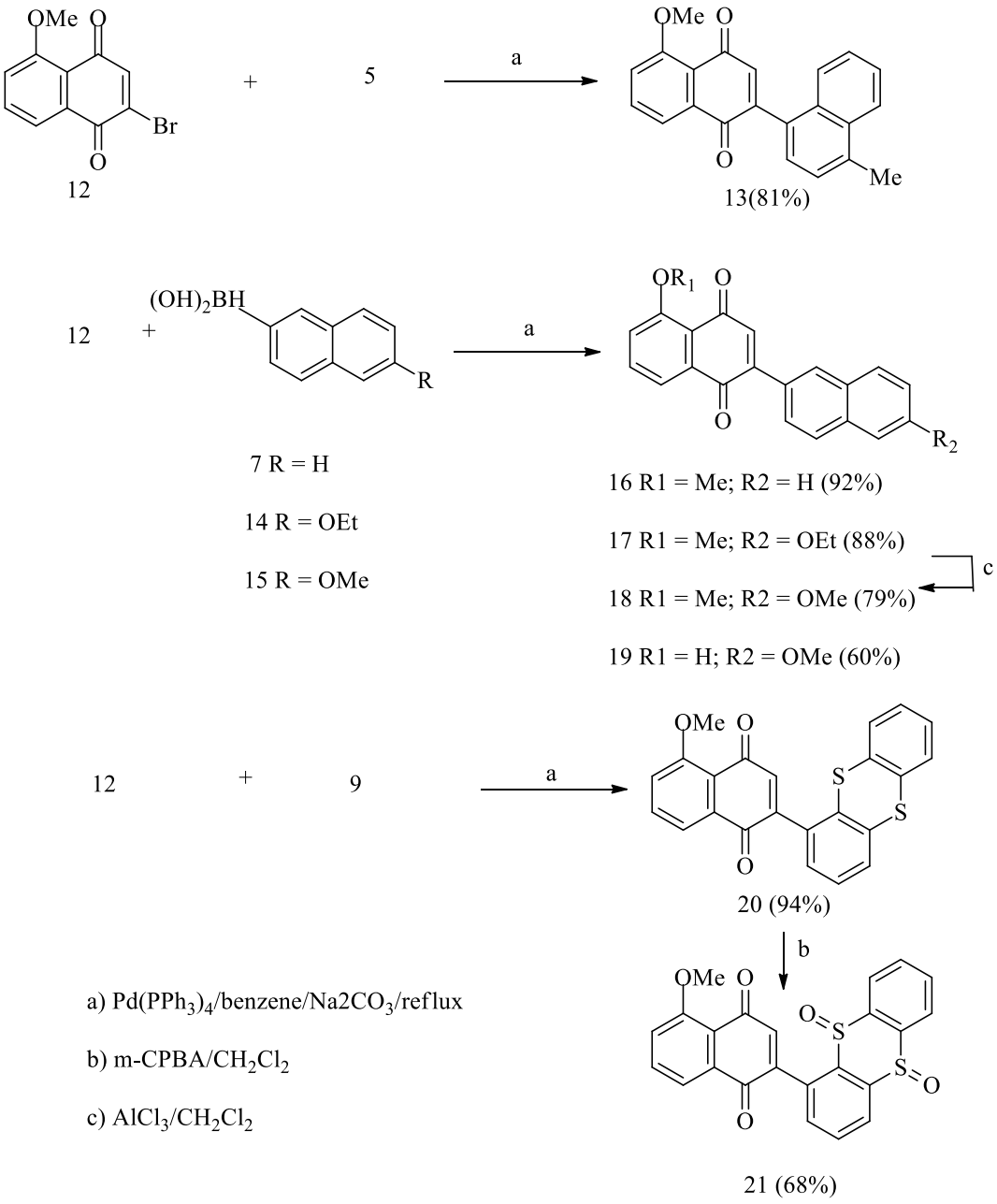
In the first series of substituted 2-arylnapthoquinoidal compounds synthesized, 2-bromo-7-methylnaphthoquinone **4** [8,12] was selected since this moiety represented the 5-deoxy analogue of the 'left hand' juglone moiety in diospyrin **1**. Thus treatment of bromoquinone **4** with boronic acid **5** 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., $C_{23}H_{14}O_4S_2$ requires M^+ 418.0334 amu (found M^+ 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[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[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 $AlCl_3$ in dichloromethane.[8]

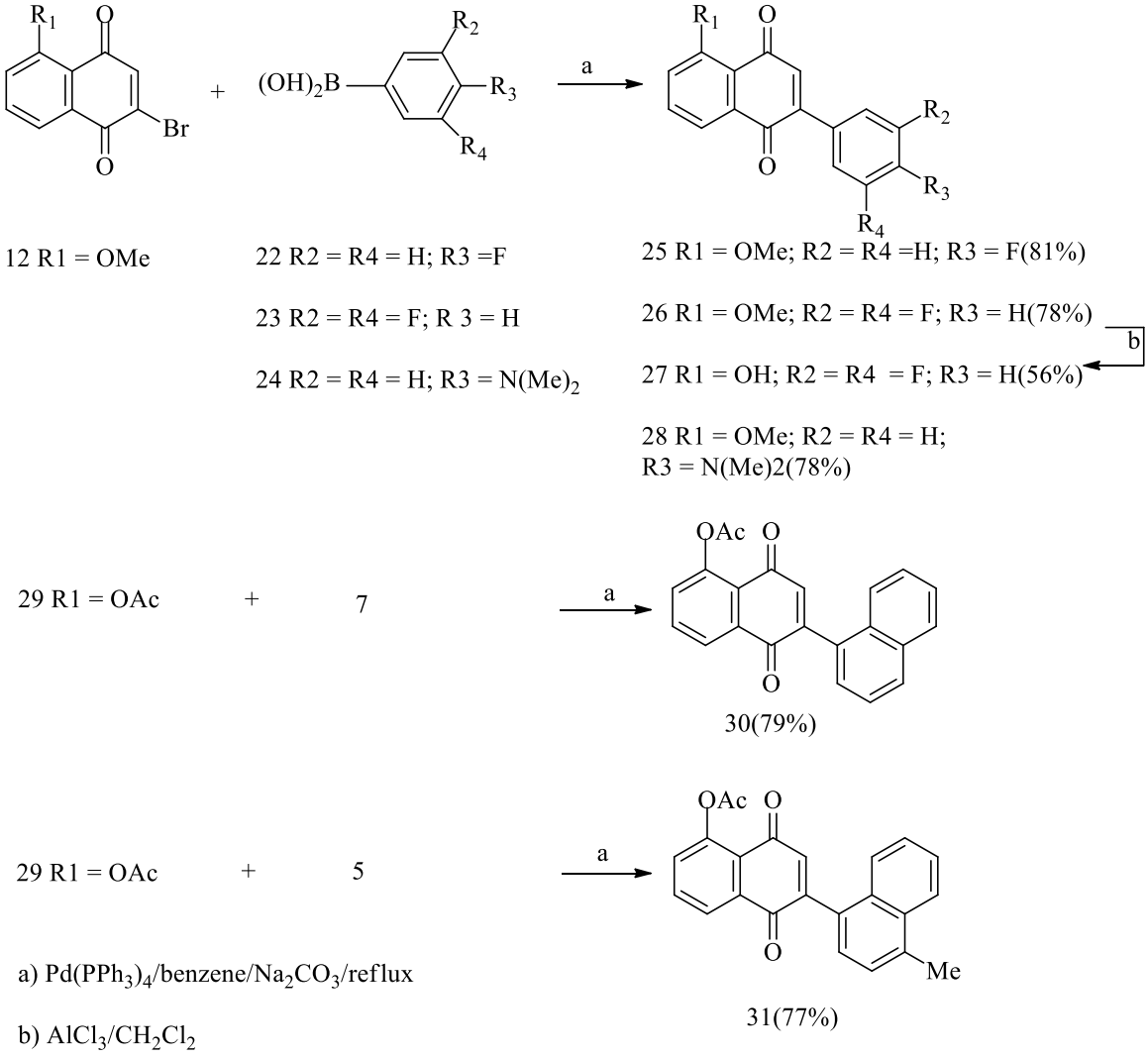


Scheme 2. Products from 2-bromo-5-methoxynaphthoquinone and naphthyl and thianthrenyl boronic acids.

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.

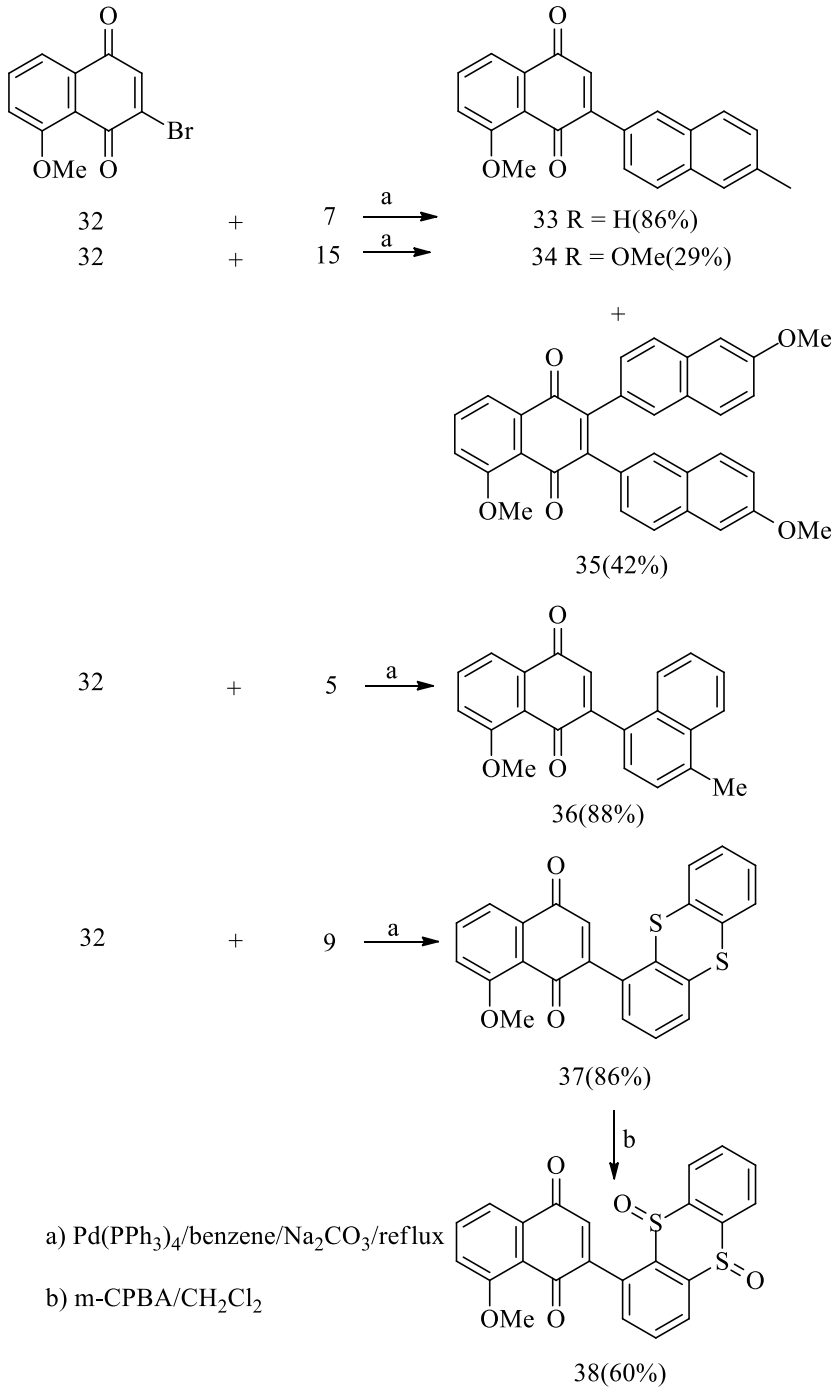
Literature indicates that introduction of a fluorine atom into a biologically active molecule will lead to an expectation of an increase in its biological activity profile.[17,18] Treatment of

bromoquinone **12** with the 4-fluoro- and 3,5-difluorophenylboronic acids **22** and **23** respectively under standard Suzuki-Miyaura conditions[13] 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 $AlCl_3$ 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-methoxynaphthoquinoneand naphthyl and thianthrenyl boronic acids.

The two acetoxy analogues **30** and **31** were prepared from the corresponding acetoxybromonaphthoquinone **29** [15] 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.

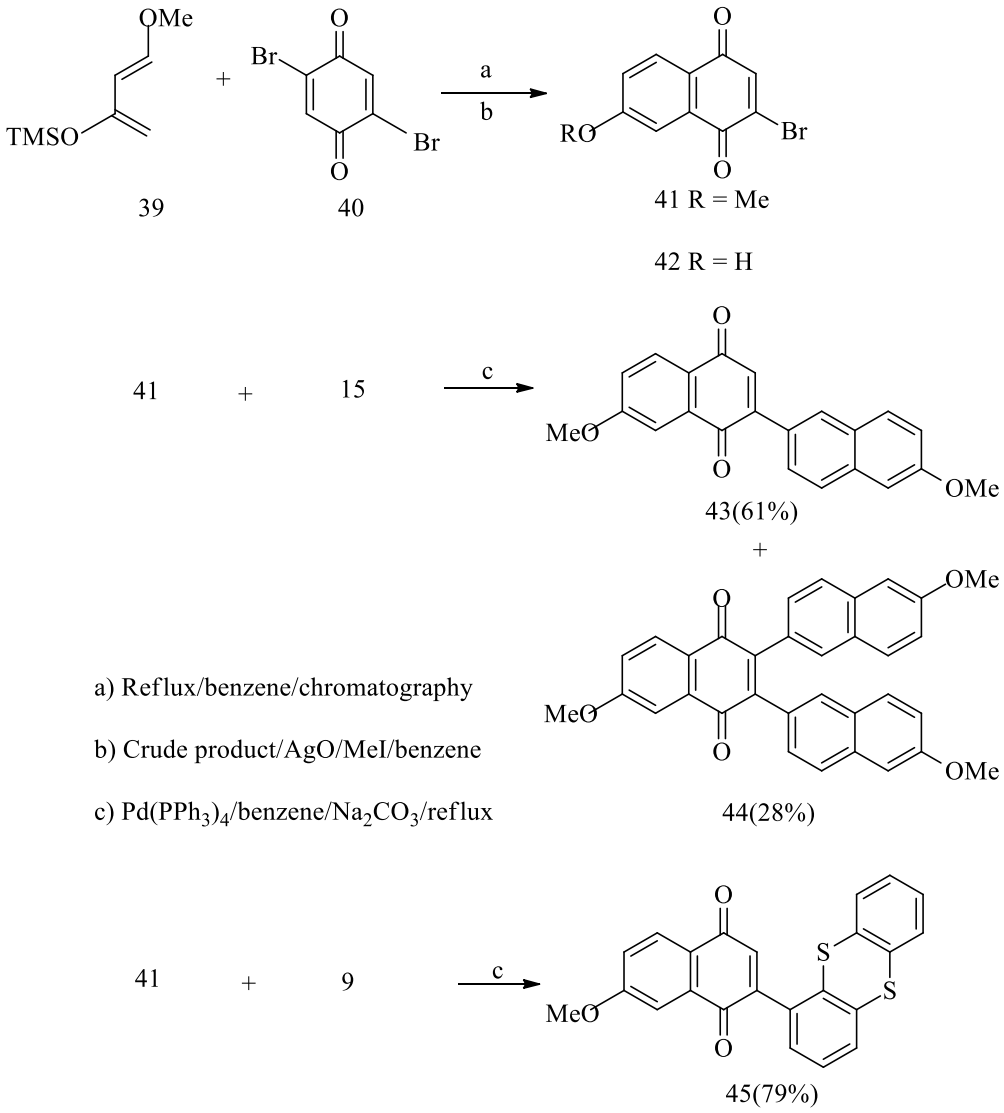
Studies by Lall *et al*.[5] and Mahapatra *et al*.[19] indicated that the *peri* alkoxy derivatives of diospyrin **1** and 7-methyl-5-hydroxynaphthoquinone exhibited a somewhat reduced activity against the susceptible strain of *M. tuberculosis*, viz., H37Rv. On the other hand, Chakrabarty *et al.*[20] 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.

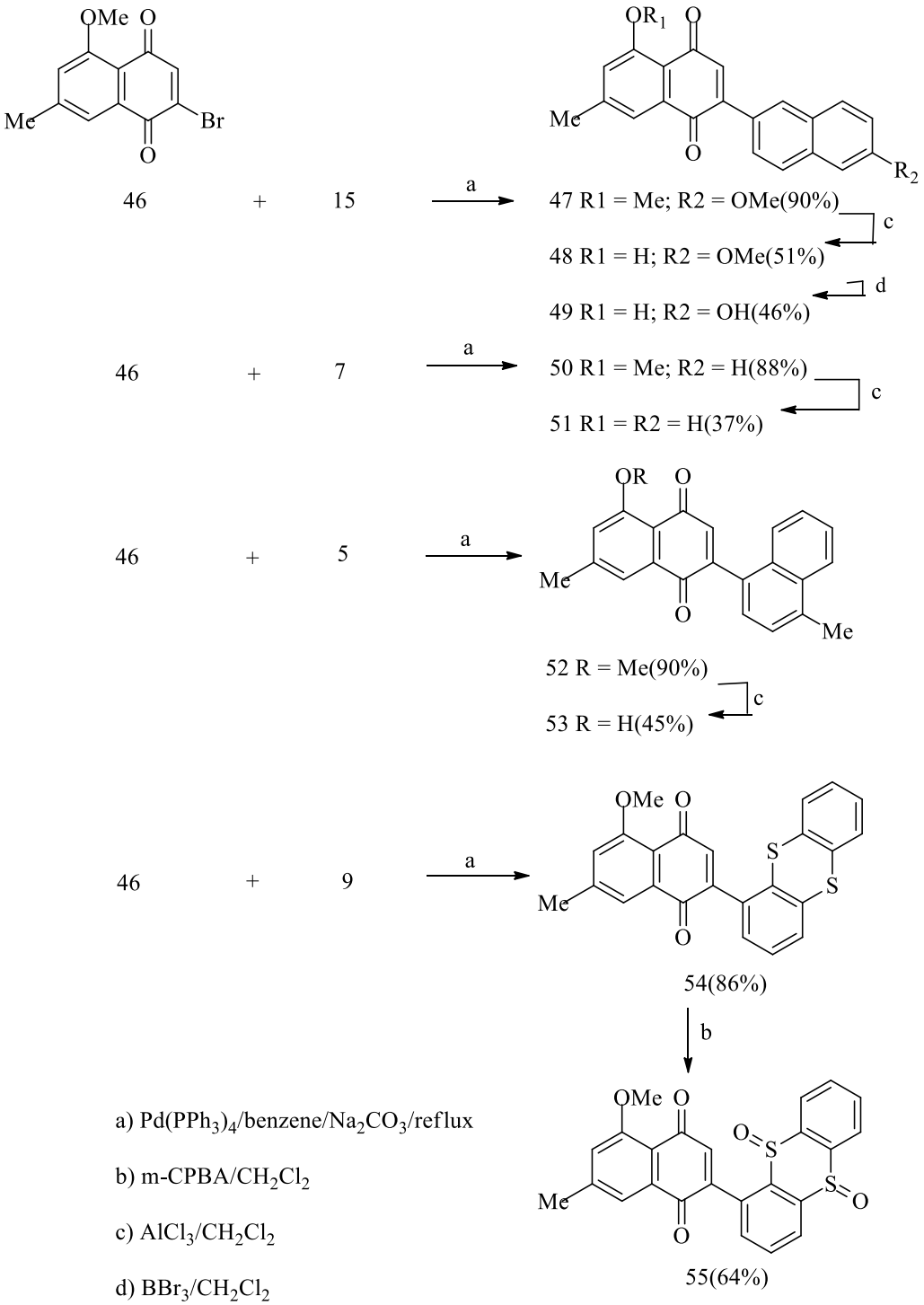
The isomeric *peri* methoxynaphthoquinone of **12**, viz., **32** [21] was then employed to synthesize the next series of naphthylnaphthoquinones and is shown in Scheme 4. Of note in this series, is the finding that reaction between naphthoquinone **32** and boronic acid **15** produced two products 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**.[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 ºC 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-disubstitued 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**[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 *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-naphthylnaphthoquinones 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 δ 7.26 for ^{1}H NMR and δ 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-methylnaphthoquinone **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 (ν_{max}, cm^{-1}): 1658 and 1652 (C=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_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, $CDCl_3$), δ_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, 148.0, 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 (ν_{max}, cm^{-1}): 1660 and 1652 (C=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_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, $CDCl_3$), δ_C 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 $C_{22}H_{16}O_2$: 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 ºC (from EtOAc:hexane), IR (ν_{max}, cm^{-1}): 1671 and 1660 (C=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_H 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, $CDCl_3$), δ_C 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 $C_{23}H_{14}O_2S_2$: C, 71.48; H, 3.65. Found: C, 71.62; H, 3.54.

2-(4-Methylnaphthalen-1-yl)-5-methoxy-1,4-naphthoquinone (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 ºC, IR (ν_{max}, cm^{-1}): 1693 and 1667 (C=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_H 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, $CDCl_3$), δ_C 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 $C_{22}H_{17}O_3$: C, 80.23; H, 5.20. Found: C, 80.15; H, 5.20.

2-(Naphthalen-2-yl)-5-methoxy-1,4-naphthoquinone (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 ºC, IR (ν_{max}, cm^{-1}): 1691 and 1672 (C=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_H 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, $CDCl_3$), δ_C 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 $C_{21}H_{15}O_3$: C, 79.98; H, 4.97. Found: C, 79.84; H, 4.82.

2-(6-Ethoxynaphthalen-2-yl)-5-methoxy-1,4-naphthoquinone (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 ºC, IR (ν_{max}, cm^{-1}): 1694 and 1679 (C=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_H 1.50 (3H, t, *J* = 7.0 Hz, $OCH_2C\mathit{H}_3$), 4.05 (3H, s, OCH_3), 4.18 (2H, q, *J* = 7.0 Hz, $OC\mathit{H}_2CH_3$), 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 (ν_{max}, cm^{-1}): 1694 and 1679 (C=O). ^{13}C NMR (50 MHz,

$CDCl_3$), δ_C 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 $C_{23}H_{19}O_4$: 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 **12**[15,16] (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 ºC, IR (ν_{max}, cm^{-1}): 1693 and 1676 (C=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_H 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′). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C 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 $C_{22}H_{17}O_4$: 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 **12**[15,16] (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 ºC, IR (ν_{max}, cm^{-1}): 1671 and 1660 (C=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_H 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). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C 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 $C_{23}H_{15}O_3S_2$: 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 **12**[15,16] (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 ºC (from EtOAc:hexane), IR (ν_{max}, cm^{-1}): 1670 and 1663 (C=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_H 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). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C 56.6, 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 $C_{17}H_{12}O_3F$: 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 **12**[15,16] (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 ºC (from EtOAc:hexane), IR (ν_{max}, cm^{-1}): 1676 and 1667 (C=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_H 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). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C 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 $C_{17}H_{11}O_3F_2$: 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 **12**[15,16] (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 ºC (from EtOAc:hexane), IR (ν_{max}, cm^{-1}): 1671 and 1660 (C=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_H 3.04 (6H, s, N(C*H*$_3$)$_2$), 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). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C 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, 145.1, 151.6, 159.2, 184.8, 185.6. Anal. Calcd for $C_{19}H_{18}NO_3$: 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 **29**[15] (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 ºC (from ethanol), IR (ν_{max}, cm^{-1}): 1772, 1668 and 1657 (C=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_H 2.49 (3H, s, CO_2C*H*$_3$), 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). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C 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 $C_{22}H_{14}O_4$: 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) affprded the quinone **31** (140 mg, 77%) as reddish brown needles, mp 173-174 ºC (from ethanol), IR (ν_{max}, cm^{-1}): 1769, 1667 and 1655 (C=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_H 2.49 (3H, s, CO_2C*H*$_3$), 2.75 (3H, s, CH_3-4′), 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). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C 19.6, 21.1, 123.6, 124.6, 125.7, 125.9, 126.0, 126.1, 126.3, 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 $C_{23}H_{16}O_4$: 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 **32**[31] (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 ºC, IR (ν_{max}, cm^{-1}): 1691 and 1672 (C=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_H 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). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C 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, 134.9, 138.9, 143.5, 160.1, 174.4, 180.0. Anal. Calcd for $C_{21}H_{14}O_3$: 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 ºC (from EtOAc:hexane), IR (ν_{max},

cm^{-1}): 1663 and 1655 (C=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_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, $CDCl_3$), δ_C 55.5, 56.7, 105.8, 118.1, 118.8, 119.5, 121.0, 126.8, 127.2, 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 $C_{22}H_{16}O_4$: 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 ^{o}C, IR (ν_{max}, cm^{-1}): 1668 and 1658 (C=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_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, $CDCl_3$), δ_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 ^{o}C, IR (ν_{max}, cm^{-1}): 1695 and 1673 (C=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_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, $CDCl_3$), δ_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 $C_{22}H_{16}O_3$: 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 ^{o}C, IR (ν_{max}, cm^{-1}): 1688 and 1670 (C=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_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, $CDCl_3$), δ_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 $C_{23}H_{14}O_3S_2$: 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 ^{o}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 ^{o}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 ^{o} C (from ethanol), IR (ν_{max}, cm^{-1}): 1670 (C=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_H 3.96

(3H, s, OMe), 7.23 (1H, dd, *J* = 8.6 and 2.6 Hz, H-6), 7.26 (2H, s, H-3), 7.60 (1H, d, *J* = 2.6 Hz, H-8), 8.12 (1H, d, *J* = 8.6 Hz, H-5). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C 56.2, 111.9, 121.0, 129.4, 130.8, 133.0, 140.7, 141.7, 164.7, 174.9, 176.1. Anal. Calcd for $C_{11}H_7BrO_3$: C, 49.47; H, 2.64. Found: C, 49.64; H, 2.53. Further elution of the column yielded the quinone **42** (3.06 g, 50%) as dark orange crystals, mp 233-235 ºC (from EtOAc:hexane), IR (ν_{max}, cm^{-1}): 3320 (OH) and 1690 (C=O). ^{1}H NMR (200.1 MHz, Acetone-d_6), δ_H 7.16 (1H, s, H-3), 7.28 (1H, dd, *J* = 8.8 and 2.4 Hz, H-6), 7.51 (1H, d, *J* = 2.4 Hz, H-8), 8.03 (1H, t, *J* = 8.8 Hz, H-5), 10.00 (1H, s, OH). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C 114.6, 122.2, 124.3, 131.6, 134.2, 142.1, 143.7, 163.9, 175.4, 176.7. Anal. Calcd for $C_{10}H_5BrO_3$: C, 47.46; H, 1.99. Found: C, 47.76; H, 2.20.

In a repeat experiment based on the same quantities, the crude product was dissolved in benzene (100 mL) containing AgO (10 g) and methyl iodide (13.63 g, 96 mmol) and stirred at 25 ºC for 24h, filtered and the residue chromatographed using EtOAc:hexane (3:7) as eluent to yield the quinone product **41** (5.13 g, 80%).

2-(6-Methoxynaphthalen-2-yl)-7-methoxy-1,4-naphthoquinone (43) and 2,3-di(6-methoxynaphthalen-2-yl)-6-methoxy-1,4-naphthoquinone (44). 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 ºC, IR (ν_{max}, cm^{-1}): 1663 and 1655 (C=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_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, $CDCl_3$), δ_C 55.4, 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, 135.1, 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 ºC, IR (ν_{max}, cm^{-1}): 1668 and 1658 (C=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_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, $CDCl_3$), δ_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 ºC, IR (ν_{max}, cm^{-1}): 1688 and 1670 (C=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_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, $CDCl_3$), δ_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,

135.0, 135.1, 135.2, 136.2, 137.2, 148.6, 164.4, 183.5,184.0. Anal. Calcd for $C_{23}H_{14}O_3S_2$: C, 68.64; H, 3.51. Found: C, 68.50; H, 3.50.

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 ºC (from ethanol), IR (ν_{max}, cm^{-1}): 1663 and 1645 (C=O). ^{1}H 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′). ^{13}C 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 ºC, IR (ν_{max}, cm^{-1}): 1658 and 1651 (C=O). ^{1}H 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). ^{13}C 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 $C_{22}H_{16}O_3$: C, 80.47; H, 4.91. Found: C, 80.70; H, 4.83.

5-Methoxy-7-methyl-2-(4-methylnaphthalen-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 ºC, IR (ν_{max}, cm^{-1}): 1659 and 1648 (C=O). ^{1}H 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′). ^{13}C 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 $C_{23}H_{18}O_3$: 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 ºC (from EtOAc:Hexane), IR (ν_{max}, cm^{-1}): 1670 and 1658 (C=O). ^{1}H 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). ^{13}C 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, 128.9, 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 $AlCl_3$

To a solution of the naphthoquinone (0.50 mmol) in dry DCM (20 mL) at 25 ^oC was added $AlCl_3$ (2.61 g, 19.6 mmol) and the mixture stirred at 25 ^oC 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 on silica gel using EtOAc:hexane (3:7) as eluent to provide 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 ^oC (from EtOAc:hexane), IR (ν_{max}, cm^{-1}): 3300-2700 (OH), 1687 and 1668 (C=O). ^1H NMR (200.1 MHz, $CDCl_3$), δ_H 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). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C 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 $C_{21}H_{14}O_4$: 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 ^oC (from EtOAc:hexane), IR (ν_{max}, cm^{-1}): 3430 (OH), 1687 and 1668 (C=O). ^1H NMR (200.1 MHz, $CDCl_3$), δ_H 6.95 (1H, dt, *J* = 8.8 and 2.6 Hz, H-4′), 7.04 (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). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C 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 $C_{16}H_8O_3F_2$: C, 67.14; H, 2.82. Found: C, 67.00; H, 2.68.

Demethylations using BBr_3

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 BBr_3 (0.9 mL of a 1M solution, 0.9 mmol) dropwise at -78 ^oC under N_2. The resultant purple mixture was stirred at 25 ^oC 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 ^oC (from ethanol), IR (ν_{max}, cm^{-1}): 3300 (OH), 1665 and 1644 (C=O). ^1H NMR (200.1 MHz, $CDCl_3$), δ_H 2.48 (3H, s, CH_3-7), 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). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C 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 $C_{22}H_{16}O_4$: 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 BBr_3 (2.44 mL of a 1M solution, 2.44 mmol) dropwise at -78 ºC under N_2. After stirring at 25 ºC 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:hexan (1:4) as eluent to yield naphthol **49** (178 mg, 46%) as reddish-brown needles, mp 236-238 ºC (from EtOAc:hexane), IR (ν_{max}, cm^{-1}): 3300 (OH), 1664 and 1642 (C=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_H 2.47 (3H, s, CH_3-7), 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). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C 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, 135.1, 148.1, 148.2, 152.1, 161.4, 184.1, 189.5. Anal. Calcd for $C_{21}H_{14}O_4$: 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 BBr_3 (1.0 mL of a 1M solution, 1.00 mmol) dropwise at -78 ºC under N_2. After stirring at 25 ºC 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 ºC (from EtOAc:hexane), IR (ν_{max}, cm^{-1}): 3340 (OH), 1651 and 1644 (C=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_H 2.58 (3H, s, CH_3-7), 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). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C 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 $C_{21}H_{14}O_3$: 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 BBr_3 (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 ºC (from EtOAc:hexane), IR (ν_{max}, cm^{-1}): 3433 (OH), 1665 and 1634 (C=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_H 2.58 (3H, s, CH_3-7), 2.76 (3H, s, CH_3-4′), 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). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C 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 $C_{22}H_{16}O_3$: 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 ºC 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 ºC (from EtOAc:hexane), IR (ν_{max}, cm^{-1}): 1671 and 1658 (C=O), 1328 and1164 (S=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_H 2.50 (3H, s, CH_3-7), 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′). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C 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 $C_{23}H_{14}O_4S_2$: C, 66.01; H, 3.37. Found: C, 66.28; H, 3.54. HREIMS: *m/z* 418.0330 (calcd. 418.0334).

5-Methoxy-2-(5,10-dioxidothianthren-1-yl)-1,4-naphthoquinone (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 ºC (from EtOAc:hexane), IR (ν_{max}, cm^{-1}): 1672 and 1662 (C=O), 1326 and 1164 (S=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_H 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′).^{13}C NMR (50 MHz, $CDCl_3$), δ_C 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 $C_{23}H_{14}O_5S_2$: C, 63.58; H, 3.25. Found: C, 63.42; H, 3.38.

8-Methoxy-2-(5,10-dioxidothianthren-1-yl)-1,4-naphthoquinone (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 ºC (from EtOAc:hexane), IR (ν_{max}, cm^{-1}): 1678 and 1669 (C=O), 1322 and 1163 (S=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_H 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′). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C 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 $C_{23}H_{14}O_5S_2$: 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-naphthoquinone (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 ºC (from EtOAc:hexane), IR (ν_{max}, cm^{-1}): 1671 and 1660 (C=O), 1326 and 1168 (S=O). ^{1}H NMR (200.1 MHz, $CDCl_3$), δ_H 2.54 (3H, s, CH_3-7), 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′). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C 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 $C_{24}H_{16}O_5S_2$: C, 64.27; H, 3.60. Found: C, 64.48; H, 3.50.

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