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Potent Antitumor Activity of Synthetic 1,2-Naphthoquinones and 1,4-Naphthoquinones

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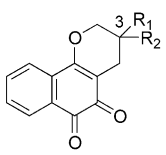
Abstract—Rhinacanthone (**1**) and two 1,2-pyranonaphthoquinones (**2**,**3**) were synthesized and found to show very potent cytotoxicity against three cancer cell lines (KB, HeLa and $HepG_2$) with IC_{50} values of 0.92–9.63 μM, whereas the corresponding hydroxylated derivative **4** had reduced cytotoxicity (IC_{50} values of 7.61–24.13 μM). Three 1,2-furanonaphthoquinone derivatives (**5**–**7**) were also synthesized with similar cytotoxicity as 1,2-pyranonaphthoquinones. In comparison to 1,2-naphthoquinones, six 1,4-naphthoquinones derivatives fused with pyran ring (**8**–**10**) and furan ring (**11**–**13**) were synthesized and they showed less cytotoxicity or inactive to the cancer cell lines. Moreover, compound **13** had significant cytotoxicity against HeLa cell line (IC_{50} value of 9.25 μM) while it showed no toxic to vero cell.

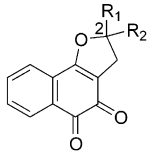
Introduction

Rhinacanthone (**1**)[1–5] (3,4-dihydro-3,3-dimethyl-2*H*-naphtho[1,2-*b*]pyran-5,6-dione) was first isolated from the shrub, *Rhinacanthus nasutus*, which is used in Thai folk medicines for the treatment of cancer, hepatitis, skin diseases such as athletes foot. It has also been reported to has antifungal activity[4] against *Pyricularie oryzae*. Moreover, rhinacanthone (**1**) has been reported antitumor activity[1] against Dalton's ascitic lymphoma. Rhinacanthone (**1**) has 1,2-pyranonaphthoquinone structure. Our group has also done extraction and isolation of cytotoxic constituents from the plant but very limited amounts of active compounds were obtained.

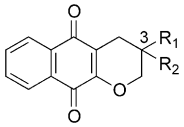
So it was desirable to synthesize more rhinacanthone derivatives, other 1,2-naphthoquinone derivatives related to rhinacanthone and some 1,4-naphthoquinone derivatives in order to compare the bioactivity of the systems. Therefore, rhinacanthone (**1**), three 1,2-pyranonaphtho quinones (**2**–**4**), three 1,2-furanonaphthoquinones (**5**–**7**), three 1,4-pyranonaphthoquinones (**8**–**10**) and three 1,4-furanonaphthoquinones (**11**–**13**) were synthesized, all in high yield for cytotoxicity evaluation.[1–12]



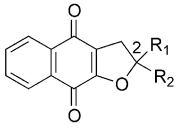
1, $R_1 = CH_3$, $R_2 = CH_3$
2, $R_1 = H$, $R_2 = H$
3, $R_1 = CH_3$, $R_2 = H$
4, $R_1 = OH$, $R_2 = H$



5, $R_1 = CH_3$, $R_2 = CH_3$
6, $R_1 = CH_3$, $R_2 = H$
7, $R_1 = H$, $R_2 = H$



8, $R_1 = CH_3$, $R_2 = CH_3$
9, $R_1 = H$, $R_2 = H$
10, $R_1 = CH_3$, $R_2 = H$



11, $R_1 = CH_3$, $R_2 = CH_3$
12, $R_1 = CH_3$, $R_2 = H$
13, $R_1 = H$, $R_2 = H$

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Synthesis of pyranonaphthoquinones

Synthesis of rhinacanthone (**1**) and compound **8** were achieved starting from 1-hydroxy-2-naphthoic acid (**14**) via 1-naphthol derivative (**20**) (Scheme 1). The yields of all steps involved were very high. Derivatives, compounds **2** and **9** without methyl substitution on C-3 and compounds **3** and **10** with one methyl group on C-3, were also prepared as shown in Scheme 2 via *O*-allylation of 1-naphthol and Claisen rearrangement. Hydroxypyrano-naphthoquinone (**4**) was achieved by *C*-alkylation of lawsone (**35**) and then epoxidation (Scheme 3).

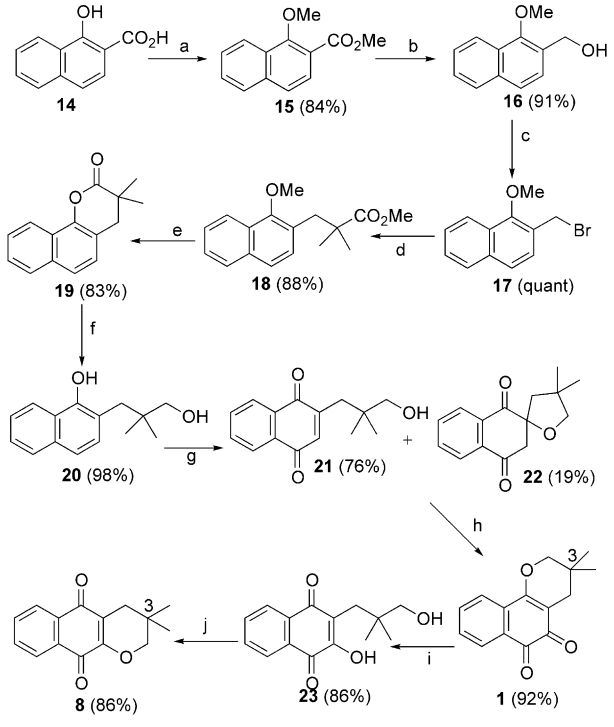
Synthesis of furanonaphthoquinones

Furanonaphthoquinone derivatives (**5**), (**6**), (**11**) and (**12**) were synthesized by *C*-allylation of lawsone and then cyclization by acid (Scheme 3). Also, furanonaphthoquinones (**7**) and (**13**) were accessed from *C*-alkylation of lawsone by α-bromoacetate ethyl ester followed by reduction and then cyclization by concentrated acid as shown in Scheme 4. Variation of acid concentration with water was also used for the cyclization.

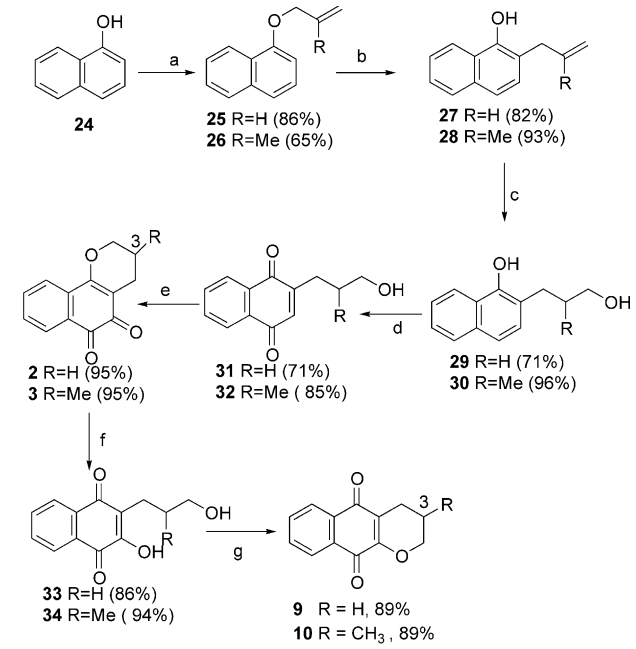
Results and Discussion

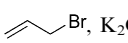
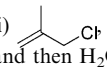
Chemistry

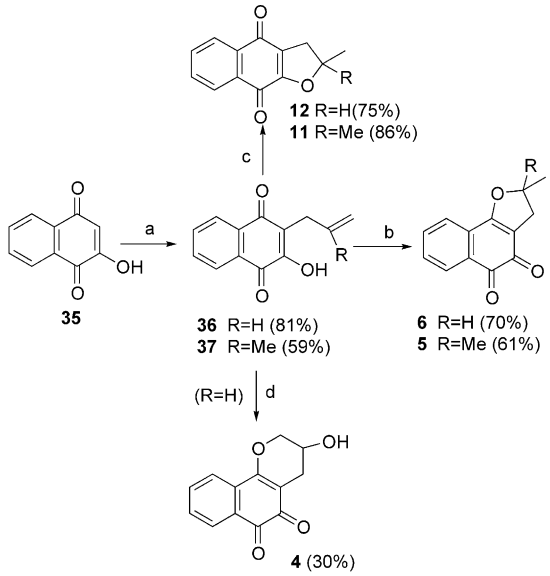
Rhinacanthone (**1**) and compound **8** were prepared starting from 1-hydroxy-2-naphthoic acid (**14**) (Scheme 1). After methylation of compound **14** by methyl iodide and then reduction of the resultant methyl ester (**15**) with lithium aluminium hydride, the hydroxy methyl naphthol ether (**16**) was obtained in 91% yield. Bromination of compound **16** using phosphorous tribromide and then alkylation of the resulting bromide (**17**) by methyl isobutylate gave compound **18**. Demethylation of compound **18** to obtain lactone (**19**) could be done

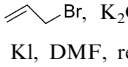
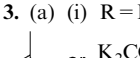


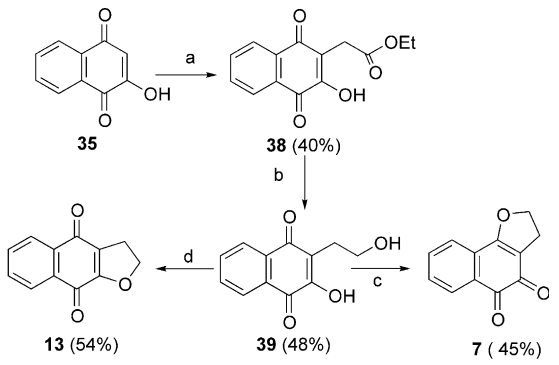
Scheme 1. (a) MeI, K_2CO_3, reflux, 12 h; (b) $LiAlH_4$, dry ether, rt, 1.5 h; (c) PBr_3, dry hexane–CH_2Cl_2 (1:1), rt 6 h; (d) LDA, methyl isobutylate, −78 °C, 2 h; (e) $AlCl_3$, chlorobenzene, reflux, 4 h; (f) $LiAlH_4$, dry ether, rt 2 h; (g) Fremy's salt, MeOH–DMF, 1 M NaOAc, rt 12 h; (h) DDQ, *p*-TsOH, benzene, reflux, 20 min; (i) 1% aq NaOH, reflux, 2 h; (j) 20% aq H_2SO_4, reflux, 5 h.



Scheme 2. (a) (i)  , K_2CO_3, reflux, 3 h; (ii)  K_2CO_3, reflux, 20 h; (b) 180 °C, DMF, 6 h; (c) BH_3·THF and then H_2O_2/OH^-; (d) Fremy's salt, MeOH–DMF, 1 M NaOAc, rt, 12 h; (e) DDQ, *p*-TsOH, benzene, reflux, 20 min; (f) 1% aq NaOH, reflux, 2 h; (g) 20% aq H_2SO_4, reflux.



Scheme 3. (a) (i) R = H;  , K_2CO_3, DMF, reflux, 3 h; (ii) R = Me;  K_2CO_3, Kl, DMF, reflux, 3 h; (b) concd H_2SO_4, 0 °C to rt, 30 min; (c) 20% aq H_2SO_4, reflux 5 h; (d) *m*-CPBA, CH_2Cl_2, 0°–rt, 24 h.



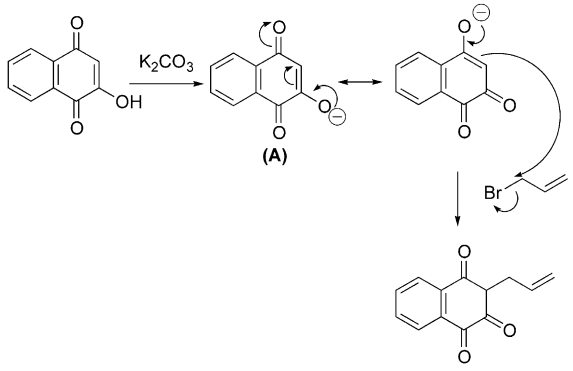
Scheme 4. (a) Br OEt, Li_2CO_3, DMF, reflux, 3 h; (b) $NaBH_4$, MeOH, reflux, 7 h; (c) concd H_2SO_4, 0 °C; (d) 20% aq H_2SO_4, reflux, 5 h.

using trimethyl silyl chloride[13] or aluminium chloride in chlorobenzene.[10] After reduction of the lactone (**19**) by lithium aluminium hydride to give naphthol alcohol (**20**), oxidation of the alcohol (**20**) was done by Fremy's salt[14] to obtain the mixture of naphthoquinones **21** and **22** and then cyclization by dichlorodicyanobenzoquinone (DDQ) to yield rhinacanthone (**1**). Then hydrolysis of compound **1** with base gave 1,4- naphthoquinone (**23**) which was recyclized by acid to afford compound **8**.[12,15]

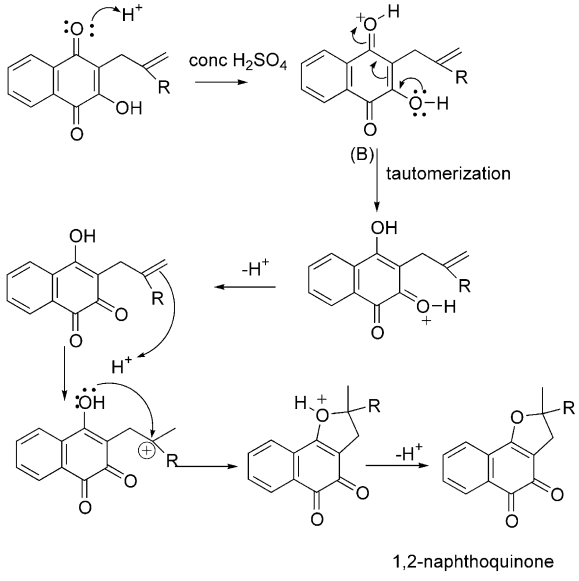
Another four pyranonaphthoquinones[16–20] (**2**), (**3**), (**9**) and (**10**) were accessed from 1-naphthol in five steps (Scheme 2) which are easier, milder and shorter steps than that of the synthesis of rhinacanthone (**1**) and compound **8**. *O*-Allylation of 1-naphthol (CH_2=CH-CH_2–Br, K_2CO_3) gave *O*-allyl-1-naphthol ether (**25**) in 86% yield. Claisen rearrangement of the allyl ether (**25**) (180 °C, DMF) gave 2-allyl-1-naphthol (**27**) (82%). Compound **27** was converted to alcohol (**29**) (71%) by hydroboration and then hydrogen peroxide oxidation in sodium hydroxide solution. Finally, oxidation of the naphthol (**29**) to compound **31** and then cyclization using the same reagent as for the preparation of the rhinacanthone and compound **8**, the pyranonaphthoquinone (**2**) and (**9**) were obtained in 95 and 89% yield, respectively. Similarly, pyrano naphthoquinones (**3**) and (**10**) were prepared by analogous routes in 95 and 89% yield, respectively, and 2-methyl allyl chloride was used for *O*-allylation instead of allyl bromide.

Furanonaphthoquinones[17,21,22] (**5**) and (**6**) were synthesized in only two steps (*C*-allylation and cyclization) from lawsone (**35**) which could be isolated from the shrub, *Lawsonia inermis*.[23] *C*-Allylation of lawsone (allyl bromide, K_2CO_3, DMF) gave allyl lawsone (**36**) in 81% yield (Scheme 3). It was found that solvent effected the *C*-allylation. Firstly, *C*-allylation of lawsone was tried by refluxing with allyl bromide and potassium carbonate in acetone, but no *C*-allylated lawsone was obtained. Only *O*-allylated product (35%) occurred together with the starting material. Use of ethanol gave only 6% of the *C*-allylated product together with *O*-allyated product (32%). However, when *N*,*N*-dimethylformamide (DMF) was used as a solvent the reaction mixture became milky and the *C*-allylated product was obtained in high yield (81%). This may be caused by heterogeneous reaction conditions, where enolates like the anion formed (**A**) was not very soluble in solution (Scheme 5). In Scheme 3, compound **4** was obtained by oxidation of compound **36** using *m*-chloroperbenzoic acid in dichloromethane. Similarly in Scheme 4, *C*-alkylation of lawsone by α-bromoacetate ethyl ester in DMF resulted in compound **38** and reduction of the ester function of **38** provided quinone (**39**) followed by cyclization using 20% aqueous sulfuric acid to afford 1,4-naphthoquinone (**13**) in 54% yield whereas using concentrated sulfuric acid, compound **7** was obtained in 45% yield.

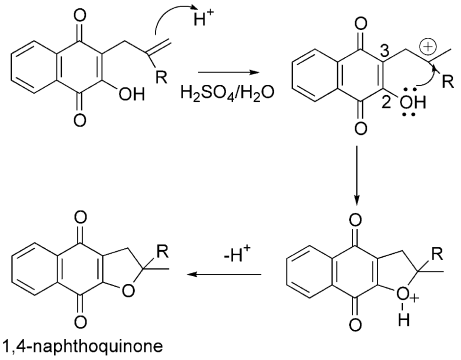
Compounds **36** and **37** were cyclized to furano-1,2-naphthoquinone (**5** and **6**) by concentrated sulfuric acid at 0 °C to room temperature in 61 and 70% yield, respectively[22] (Scheme 3). With respect to cyclization of olefinic alcohols (**36** and **37**), using 20% aqueous sulfuric acid, it was found that the 1,4-naphthoquinone products (**11** and **12**) were obtained instead.[15] It seemed that the mechanism of using concentrated sulfuric acid (H_2SO_4) is different from using aqueous sulfuric acid. The mechanism of concentrated H_2SO_4 action may be mediated by tautomerization of protonated naphthoquinone (**B**) as shown in Scheme 6 whereas using



Scheme 5.



Scheme 6.



Scheme 7.

aqueous H_2SO_4, protonation of the double bond at the side chain may be faster than protonation of the carbonyl group of naphthoquinone and then the hydroxy group at C-3 position attacked the carbocation straight away (Scheme 7).

Bioactivity

There was a report[1] that rhinacanthone showed significant inhibition against Daton's ascitic lymphoma (DAL) in Swiss albino mice. With respect to rhinacanthone activity, all pyranonaphthoquinones (**1–4**, **8–10**) and furanonaphthoquinones (**5–7**, **11–13**) were evaluated against human cancer cell lines which are KB (human epidermoid carcinoma), HeLa (human cervical carcinoma) and $HepG_2$ (human hepatocellular carcinoma) cell lines employing the MTT colorimetric method.[24] The results of their cytotoxicities are shown in Table 1.

From Table 1, compounds **2** and **3** with 1,2-pyrano naphthoquinone skeleton, with one and without methyl group on C-2 of pyran ring, showed better cytotoxicity against KB, HeLa and $HepG_2$ cells with IC_{50} values in the range of 0.92–3.22 μM. Whereas this skeleton with dimethyl groups (**1**) or hydroxy group (**4**) on C-2 of pyran ring instead, reduced the cytotoxicity (IC_{50} value about 6.90–24.13 μM). However, all 1,2-pyranonaphthoquinones (**1–4**) showed potent cytotoxicity against cancer cell lines. This result is in agreement with the report that reduction of lipophilicity by hydroxyl group caused lower cytotoxicity.[25] It means that the 1,2-pyranonaphthoquinone skeleton plays an important role for the activity. In the same way, a similar skeleton with 1,2-furanonaphthoquinone (**5–7**) still showed strong cytotoxicity against all cancer cell lines (KB, HeLa and $HepG_2$). When the 1,2-naphthoquinone was changed to 1,4-naphthoquinone as shown in Table 1 (**8–13**), the cytotoxicity was reduced or was insignificant in accordance with the results reported by De Moura[25] and Goulart[26] groups who observed that the trypanocidal activity of 1,2-quinones is higher than that of the corresponding 1,4-quinones. This means that 1,2-naphthoquinone is an important functional group for bioactivity. Regarding normal cells, it was found as usual that compounds **1–7**, **11–12** showed cytotoxicity to Vero cell similar to that in cancer cell lines. Interestingly, compound **13** was inactive to normal cells with IC_{50} value of 84.15 μM whereas it showed strong cytotoxicity against HeLa cancer cell lines with the IC_{50} values of 9.25 μM. This result suggests that compound **13** might be modified as a cancer drug for treatment of cervical cancers without any harm to normal cells and agrees with Thai folk medicine which recommends the plant (*R. nasutus*) for the treatment of cervical cancer.

Table 1. Cytotoxicity of compounds **1–13** against human carcinoma cell lines (KB, HeLa and $HepG_2$)and vero cell line

Compd	Cancer cell lines IC_{50} (μM)[a]			Vero cell[a]
	KB	HeLa	$HepG_2$	IC_{50} (μM)
1	9.63±1.421	7.15±0.814	6.90±0.620	7.52±0.169
2	3.22±0.224	0.92±0.248	1.07±0.276	2.76±0.117
3	2.37±0.289	1.10±0.254	2.10±0.579	2.37±0.101
4	24.13±1.474	7.83±0.726	7.61±0.600	7.74±0.578
5	2.24±0.241	2.46±0.171	2.41±0.158	2.28±0.509
6	2.71±0.453	2.52±0.477	2.66±0.149	2.48±0.252
7	3.05±0.195	2.85±0.210	3.00±0.040	2.90±0.140
8	38.55±7.235	23.30±1.950	20.83±0.690	55.08±9.661
9	47.52±13.107	9.95±0.920	22.62±0.780	29.44±1.748
10	59.65±6.649	17.89±3.579	24.30±2.228	65.04±3.303
11	10.31±1.202	7.59±0.816	7.59±0.767	7.81±0.329
12	10.89±1.276	7.56±0.748	8.64±0.257	8.50±0.191
13	18.10±3.760	9.25±0.420	26.15±1.435	84.15±7.360
Adriamycin[b]	0.033	0.33	0.40	23.94±6.243

KB, human epidermoid carcinoma; HeLa, human cervical carcinoma; $HepG_2$, human hepatocellular carcinoma; Vero cell line, African green monkey kidney cell.
[a]The results are the average mean of six replicate determinations±SD.
[b]Used as reference.

Furthermore, many chemotherapeutic agents have been reported to exert their antitumor effects by inducing apoptosis of cancer cells.[27] For example, β-lapachone (3,4-dihydro-2,2-dimethyl-2H-naphthol[1,2-*b*]pyran-5,6-dione), a naturally occurring 1,2-naphthoquinone which is structurally related to rhinacanthone was proved to be a novel anticancer drug. It was shown to induce cell-cycle arrest and apoptosis in various human cancer cells by inhibiting the DNA topoisomerase I and II.[27,28] Rhinacanthone (**1**), (3,4-dihydro-2,2-dimethyl-2H-naphtho[1,2-*b*]pyran-5,6-dione) may effect the human cancer cells by the same action as β-lapachone. However, the potential antineoplastic mechanisms of rhinacanthone and its active analogues which were synthesized in this study is still unknown. Apoptosis-inducing mechanisms of these active compounds are being investigated in detail. Since, rhinacanthone has been found to have antitumor activity against Dalton's ascitic lymphoma in mice,[1] the inhibitory effects of active analogues in in vivo tumor models are being further determined.

In addition, we have also done computer docking to simulate how rhinacanthone (**1**) and its analogues (**2–13**) might bind to topoisomerase II, the target enzyme of rhinacanthone, using the AUTODOCK[29] and PASS[30] program (Fig. 1).

First, we used the program PASS to predict the potential binding sites of topoisomerase II (1AB4 obtained from the PDB database). Then the result from PASS program was verified by allowing the known drug, adriamycin (doxorubicin), to dock onto the enzyme

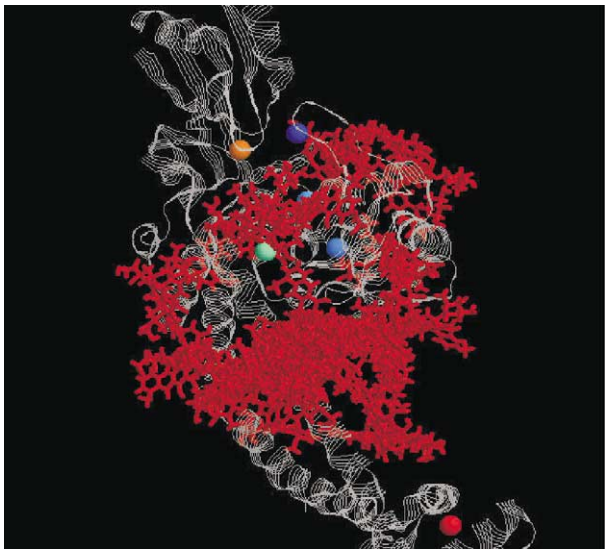


Figure 1. Binding areas of adriamycin (in red wire-framed structures) to 1AB4 (gray spiral) as proposed by AUTODOCK and potential binding sites (colored balls) as predicted by PASS.

using the AUTODOCK program. The area, commonly predicted by the two programs, is our proposed binding site in the green ball area as shown in Figure 1.

The AUTODOCK and PASS were verified using the known drug, adriamycin (doxorubicin), to see how this drug could bind to topoisomerase II. The sites predicted by docking and PASS were used as a guideline for rhinacanthone and other naphthoquinones (Fig. 2). It was found that all compounds (**1**–**13**) showing various activities tended to bind to the same binding site as adriamycin (Fig. 2); however, some compounds with less or no activity at all also bind to the same site in most cases. However, after a close look into the mode of binding, the highly or moderately active and less active compounds appear to bind in a different manner as shown in Figure 2. The two sets of our synthetic compounds which are 1,2-naphthoquinone and

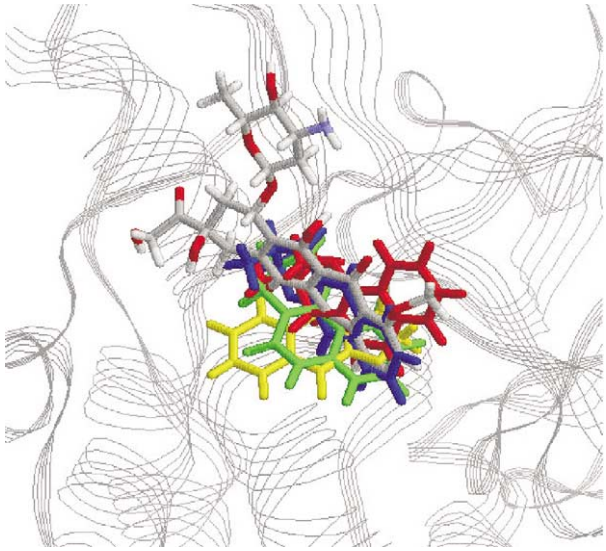


Figure 2. The picture shows how adriamycin (red and grey stick) and test compounds (in colors) dock at the binding site predicted by PASS.

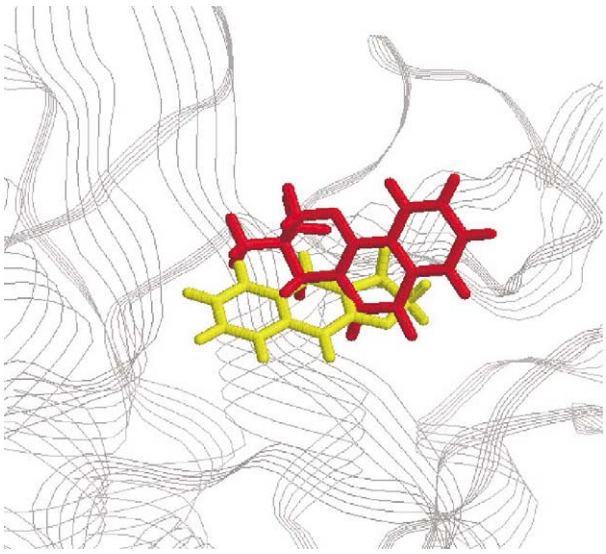


Figure 3. Different manner of binding of rhinacanthone (red) and compound **13** (yellow) as predicted by PASS.

1,4-naphthoquinone, bind in different way. For example, rhinacanthone (**1**), 1,2-naphthoquinone, and compound **13,** 1,4-naphthoquinone, dock at the same binding site but in different manner (Fig. 3).

In conclusion, these preliminary results show that 1,2- and 1,4-naphthoquinones fused with furan or pyran ring are important groups for cytotoxicity to cancer cell lines, with 1,2-naphthoquinones having better activity.

Experimental

General remarks

Melting points were determined on a Fisher-John apparatus and are uncorrected. The IR spectra were recorded on a FTIR Perkin–Elmer System 2000. Mass spectral data were obtained on the GCMS-QP-5050A. Nuclear magnetic resonance spectra were recorded at 400 MHz on a Brucker Advance DPX-400. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane (TMS) as internal standard. Coupling constants are given in Hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet, dd = double doublet, dt = double triplet. Column chromatography was performed with flash silica gel (Merck 9385).

Methyl 1-methoxy-2-naphthoate (15). A mixture of 1-hydroxy-2-naphthoic acid (10 g, 0.053 mol), potassium carbonate (29 g, 0.21 mol), acetone (200 mL) and iodomethane (15 mL, 0.24 mol) were stirred and refluxed for 13 h. Then the reaction mixture was cooled to room temperature, filtered and washed with acetone. The filtrate was concentrated in vacuo, then dichloromethane was added, washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography eluting

with 49:1 v/v hexane–ethyl acetate to afford the product **15** (84%) as a colorless oil.[2] IR (neat) cm^{-1}: 3059, 1720 and 1076. ^1H NMR ($CDCl_3$) δ: 3.98 (s, 3H, CO_2CH_3), 4.07 (s, 3H, OCH_3), 7.57 (m, 2H, ArH), 7.61 (d, 1H, $J=8.7$ Hz, ArH), 7.84 (m, 1H, ArH), 7.86 (d, 1H, $J=8.7$ Hz, ArH) and 8.28 (m, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ: 52.9 (CH_3O), 64.0 (OCH_3), 124.2 (2C), 127.1, 127.3, 128.5, 128.9 (CH arom), 119.8, 129.2, 137.4, 158.9 (C arom) and 167.3 (OC=O). MS *m/z* (%): 216 (M^+, 95), 185 (100), 170 (36), 127 (57) and 114 (74).

2-Hydroxymethyl-(1-methoxynaphthalene) (16). To a stirred and ice-cooled suspension of lithium aluminium hydride (1.7 g, 0.046 mol) in dry diethyl ether (30 mL) was added dropwise a solution of compound **15** (5 g, 0.023 mol) in dry diethyl ether (20 mL). After stirring for 2 h at room temperature, the reaction mixture was quenched with ethyl acetate and water, then extracted with diethyl ether (3×100 mL). The combined organic phase was washed with water and brine, filtered and concentrated in vacuo. The residue was purified by column chromatography eluting with 9:1 v/v hexane–ethyl acetate to afford product **16** (91%) as a colorless amorphous powder, mp 70–71 °C.[2] IR (KBr) cm^{-1}: 3196, 1570, 1365 and 1053. ^1H NMR ($CDCl_3$) δ: 2.20 (br s, 1H, OH), 4.00 (s, 3H, OCH_3), 4.90 (s, 2H, OCH_2), 7.56 (m, 3H, ArH), 7.63 (d, 1H, $J=8.4$ Hz, ArH), 7.83 (dd, 1H, $J=7.5$ Hz, $J=1.3$ Hz, ArH) and 8.10 (dd, 1H, $J=7.9$ Hz, $J=0.9$ Hz, ArH). ^{13}C NMR ($CDCl_3$) δ: 61.4 (OCH_3), 63.3 (OCH_2), 122.7, 125.1, 126.7, 126.8, 127.3, 128.7 (CH arom), 128.4, 129.6, 135.4 and 154.3 (C arom). MS *m/z* (%): 188 (M^+, 71), 156 (39), 127 (100) and 115 (72).

2-Bromomethyl-1-methoxynaphthalene (17). To a stirred solution of compound **16** (2 g, 0.01 mol) in dry hexane–dichloromethane (1:1) (15 mL), phosphorus tribromide (1 M in dichloromethane, 20 mL, 0.02 mol) was added dropwise. After stirring for 6 h at room temperature, water was added, then the mixture was neutralised with saturated sodium hydrogen carbonate and extracted with dichloromethane (3×50 mL). The combined organic phase was washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The product **17** was obtained as a colorless solid in quantitative yield, mp 65–66 °C.[2] IR (KBr) cm^{-1}: 2940, 1570, 1366 and 1078. ^1H NMR ($CDCl_3$) δ: 4.00 (s, 3H, OCH_3), 4.70 (s, 2H, CH_2Br), 7.41 (d, 1H, $J=8.4$ Hz, ArH), 7.47 (m, 2H, ArH), 7.57 (d, 1H, $J=8.4$ Hz, ArH), 7.78 (m, 1H, ArH) and 8.07 (m, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ: 29.1 (CH_2), 63.1 (OCH_3), 123.1, 125.4, 127.0, 127.5, 128.6, 128.8 (CH arom), 128.5, 128.6, 135.8 and 155.0 (C arom). MS *m/z* (%): 252 ($M^+ + 1$, 7), 250 (7), 171 (100), 128 (86) and 115 (47).

2-(2,2-Dimethyl-3-methylpropanoate)-1-methoxy naphthalene (18). To a stirred solution of diisopropylamine (0.56 mL, 4 mmol) and *n*-BuLi (1.6 M in cyclohexane, 2.5 mL, 4 mmol) in dry tetrahydrofuran (THF) (5 mL) at 0 °C, methyl isobutyrate (0.34 mL, 3 mmol) was added dropwise at −78 °C and stirring was continued for 1 h. A solution of compound **17** (0.4 g, 1.6 mmol) in hexamethylphosphoramide (HMPA) (0.6 mL) and dry THF (2 mL) was added dropwise to the reaction mixture at the same temperature. After stirring for 2 h at −78 °C, the reaction mixture was quenched with saturated ammonium chloride solution and then extracted with diethyl ether (3×50 mL). The combined organic phase was washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography eluting with 49:1 v/v hexane–ethyl acetate to afford the product **18** as a colorless solid; mp 99–100 °C.[2] IR (KBr) cm^{-1}: 2965, 1733 and 1193. ^1H NMR ($CDCl_3$) δ: 1.20 (s, 6H, 2×CH_3), 3.08 (s, 2H, CH_2), 3.70 (s, 3H, CO_2CH_3), 3.90 (s, 3H, OCH_3), 7.18 (d, 1H, $J=8.4$ Hz, ArH), 7.4–7.55 (m, 3H, ArH), 7.80 (d, 1H, $J=7.8$ Hz, ArH) and 8.05 (d, 1H, $J=7.8$ Hz, ArH).^{13}C NMR ($CDCl_3$) δ: 24.0 (2×CH_3), 38.9 (CH_2), 42.9 (C), 50.8 (CH_3O), 60.6 (CH_3O), 121.2, 122.4, 124.6, 124.8, 126.9, 128.3 (CH arom), 125.4, 126.9, 133.2, 153.6 (C arom) and 177.3 (OC=O). MS *m/z* (%): 272 (M^+, 17), 171 (100), 128 (34) and 115 (26).

3,4-Dihydro-3,3-dimethyl-2*H*-naphtho[1,2-*b*]pyran-2-one (19). A mixture of compound **18** (0.8 g, 2.9 mmol) and powdered aluminium chloride (0.78 g, 5.8 mmol) in dry redistilled chlorobenzene (20 mL) were refluxed for 4 h. The solution was cooled to room temperature and poured into 10% hydrochloric acid (60 mL), then extracted with diethyl ether (3×30 mL). The combined organic phase was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Then chlorobenzene was removed by distillation under reduced pressure. The resulting residue was purified by column chromatography, eluting with 49:1 v/v hexane–ethyl acetate to afford the product **19** (83%) as a colorless amorphous powder, mp 123–124 °C.[2] IR (KBr) cm^{-1}: 2974, 1759, 1383 and 1111. ^1H NMR ($CDCl_3$) δ: 1.30 (s, 6H, 2×CH_3), 2.90 (s, 2H, CH_2), 7.17 (d, 1H, $J=8.3$ Hz, ArH), 7.46 (m, 2H, ArH), 7.53 (d, 1H, $J=8.3$ Hz, ArH), 7.76 (m, 1H, ArH) and 8.18 (m, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ: 25.5 (2×CH_3), 37.8 (C), 39.4 (CH_2), 121.7, 124.5, 126.5, 127.0, 127.1, 128.2 (CH arom), 117.1, 123.9, 134.1, 146.8 (C arom) and 174.3 (OC=O). MS *m/z* (%): 226 (M^+, 61), 198 (65), 183 (100), 155 (40) and 128 (57).

2-(3-Hydroxy-2,2-dimethylpropyl)-1-hydroxy naphthalene (20). To a stirred and ice-cooled suspension of lithium aluminium hydride (0.34 g, 9 mmol) in dry tetrahydrofuran (10 mL), a solution of compound **19** (0.97 g, 4 mmol) in dry tetrahydrofuran (5 mL) was added dropwise. After stirring for 2 h at room temperature, the reaction mixture was quenched with ethyl acetate and water, then extracted with diethyl ether (3×40 mL). The combined organic phase was washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give the product **20** (98%) as a colorless amorphous powder, mp 123–124 °C.[2] IR (KBr) cm^{-1}: 3363, 2955, 1386 and 1079. ^1H NMR ($CDCl_3$) δ: 1.04 (s, 6H, 2×CH_3), 2.45 (br s, 1H, OH), 2.77 (s, 2H, CH_2), 3.25 (s, 2H, CH_2O), 7.16 (d, 1H, $J=8.4$ Hz, ArH), 7.34 (d, 1H, $J=8.4$ Hz, ArH), 7.46 (m, 2H, ArH), 7.76 (m, 1H, ArH), 8.30 (m, 1H, ArH) and

8.53 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ: 25.8 (2×CH_3), 37.3 (C), 39.0 (CH_2), 69.8 (CH_2O), 119.6, 123.1, 125.6, 126.3, 127.8, 131.4 (CH arom), 118.2, 126.1, 134.3 and 151.5 (C arom). MS *m*/*z* (%): 230 (M^+, 28), 183 (16), 157 (100) and 128 (76).

2-(3-Hydroxy-2,2-dimethylpropyl)-1,4-naphthoquinone (21) and 1,4-naphthoquinone-2-spiro-2′-(4′,4′-dimethyltetrahydrofuran) (22). To a stirred solution of compound **20** (1 g, 4 mmol) in methanol–dimethylformamide (MeOH–DMF) (3:1) (64 mL) was added a solution of Fremy's salt (8 g, 30 mmol) in water (260 mL) and 1 M aqueous sodium acetate solution (6.6 mL). After stirring for 14 h at room temperature, the reaction mixture was extracted with diethyl ether (3×50 mL). The combined organic phase was washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography eluting with 17:3 v/v hexane–ethyl acetate to afford the product **21** (76%) as a yellow solid and product **22** (19%) as a yellow oil.[2] **Compound 21**: mp 81–82 °C. IR (KBr) cm^{-1}: 3420, 1663, 1589 and 1293. ^{1}H NMR ($CDCl_3$) δ: 0.90 (s, 6H, 2×CH_3), 2.50 (s, 2H, CH_2), 3.10 (s, 2H, OCH_2), 6.76 (s, 1H, CH=), 7.69 (m, 2H, ArH), 8.01 (m, 1H, ArH) and 8.05 (m, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ: 25.5 (2×CH_3), 37.7 (CH_2), 38.2 (C), 70.3 (CH_2O), 126.7, 127.7, 134.4, 134.7, 139.0 (CH), 132.6, 132.8, 149.5 (C), 185.3 and 187.3 (C=O). MS *m*/*z* (%) 244 (M^+, 8), 214 (40), 172 (100), 144 (47) and 115 (80). **Compound 22**: IR (nujol) cm^{-1}: 3070, 1700, 1600 and 1300. ^{1}H NMR ($CDCl_3$) δ: 1.10 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.60 and 2.40 (2×d, 2×1H, *J* = 13 Hz, CH_2), 3.20 and 3.30 (2×d, 2×1H, *J* = 16 Hz, CH_2O), 3.60 and 3.70 (2×d, 2×1H, *J* = 8.5 Hz, CH_2CO), 7.76 (m, 2H, ArH), 8.06 (m, 1H, ArH) and 8.12 (m, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ: 26.2 (CH_3), 28.4 (CH_3), 41.4 (C), 47.1 (CH_2), 51.7 (CH_2), 81.3 (CH_2O), 86.8 (C), 127.2, 128.4, 134.7, 135.0 (CH arom), 135.0, 135.8 (C arom), 194.6 and 195.6 (C=O). MS *m*/*z* (%): 244 (M^+, 67), 201 (57), 146 (67), 104 (83) and 76 (100).

3,4-Dihydro-3,3-dimethyl-2*H*-naphtho[1,2-*b*]pyran-5,6-dione (1). A mixture of compound **21** and **22** (0.6 g, 2.6 mmol), dichlorodicyanobenzoquinone (DDQ) (0.87 g, 3.8 mmol) and *p*-toluenesulfonic acid monohydrate (0.05 g, 0.26 mmol) in dry benzene (8 mL) were stirred for 30 min under refluxed, cooled to room temperature and filtered, then washed with dichloromethane and concentrated in vacuo. The residue was filtered through aluminium oxide to afford the product **1** (92%) as an orange amorphous powder, mp 151–152 °C.[2] IR (KBr) cm^{-1}: 1696, 1640, 1599 and 1293. ^{1}H NMR ($CDCl_3$) δ: 1.00 (s, 6H, 2×CH_3), 2.30 (s, 2H, CH_2), 3.90 (s, 2H, CH_2O), 7.45 (dt, 1H, *J* = 7.6 Hz, *J* = 1.1 Hz, ArH), 7.59 (dt, 1H, *J* = 7.6 Hz, *J* = 1.4 Hz, ArH), 7.76 (dd, 1H, *J* = 7.8 Hz, *J* = 0.6 Hz, ArH) and 8.01 (dd, 1H, *J* = 7.6 Hz, *J* = 0.9 Hz, ArH). ^{13}C NMR ($CDCl_3$) δ: 25.5 (2×CH_3), 28.6 (C), 32.6 (CH_2), 77.8 (CH_2O), 124.8, 129.4, 131.4, 135.6 (CH arom), 113.9, 130.5, 132.5, 162.7 (C), 179.7 and 180.3 (C=O). MS *m*/*z* (%): 242 (M^+, 4), 214 (21), 159 (50), and 56 (100). Anal. calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.19; H, 5.86.

2-Hydroxy-3-(3-hydroxy-2,2-dimethylpropyl)-1,4-naphthoquinone (23). The solution of compound **1** (0.5 g, 2.1 mmol) in 1% aqueous sodium hydroxide solution (12 mL, 3.1 mmol) was refluxed for 2 h. Then the reaction mixture was cooled to room temperature and acidified with acetic acid, extracted with dichloromethane (3×50 mL). The combined organic phase was washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was recrystallized from hexane–dichloromethane to give the product **23** (86%) as a yellow amorphous powder, mp 144–145 °C.[4] IR (KBr) cm^{-1}: 3418, 1672, 1482 and 1216. ^{1}H NMR ($CDCl_3$) δ: 1.00 (s, 6H, 2×CH_3), 2.60 (s, 2H, CH_2), 3.10 (s, 2H, CH_2O), 3.70 (br s, 1H, OH), 7.74 (dt, 1H, *J* = 7.5 Hz, *J* = 1.4 Hz, ArH), 7.76 (br s, 1H, OH), 7.8 (dt, 1H, *J* = 7.5 Hz, *J* = 1.4 Hz, ArH), 8.12 (dd, 1H, *J* = 7.5 Hz, *J* = 0.96 Hz, ArH) and 8.16 (dd, 1H, *J* = 7.5 Hz, *J* = 0.96 Hz, ArH). ^{13}C NMR ($CDCl_3$) δ: 25.9 (2×CH_3), 31.3 (CH_2), 39.2 (C), 70.5 (CH_2O), 126.9, 127.8, 133.9, 135.7 (CH arom), 122.5, 130.1, 133.4, 155.8 (C), 181.5 and 187.0 (C=O). MS *m*/*z* (%): 260 (M^+, 2), 230 (77), 188 (100), 160 (35), and 77 (76).

3,4-Dihydro-3,3-dimethyl-2*H*-naphtho[2,3-*b*]pyran-5,10-dione (8). 20% Aqueous sulfuric acid (50 mL) was added to the solution of compound **23** (50 mg, 0.2 mmol) in dichloromethane (1 mL) at room temperature. After the reaction mixture was refluxed for 5 h, cool water was added to the reaction mixture and extracted with chloroform (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 column chromatography eluting with 19:1 v/v hexane–ethyl acetate to afford the product **8** (86%) as yellow needles, mp 146–148 °C.[4] IR (KBr) cm^{-1}: 1683, 1672, 1589 and 1202. ^{1}H NMR ($CDCl_3$) δ: 1.08 (s, 6H, 2×CH_3), 2.41 (s, 2H, CH_2), 3.92 (s, 2H, OCH_2), 7.70 (dt, 1H, *J* = 7.4 Hz, *J* = 1.6 Hz, ArH), 7.76 (dt, 1H, *J* = 7.4 Hz, *J* = 1.6 Hz, ArH), 8.10 (dd, 1H, *J* = 7.0 Hz, *J* = 2.0 Hz, ArH) and 8.13 (dd, 1H, *J* = 7.0 Hz, *J* = 2.0 Hz, ArH). ^{13}C NMR ($CDCl_3$) δ: 25.6 (2×CH_3), 28.6 (C), 33.1 (CH_2), 77.1 (OCH_2), 126.7, 127.0, 133.7, 134.6 (CH arom), 121.6, 131.5, 132.8, 155.0 (C), 180.2 and 185.2 (C=O). MS *m*/*z* (%): 242 (M^+, 88), 214 (44), 102 (52), 76 (100) and 41 (77). HRMS calcd for $C_{15}H_{14}O_3$ (M + H) 243.1021, found 243.1024.

1-Allyloxy-naphthalene (25). A mixture of 1-naphthol (0.5 g, 3.5 mmol), allyl bromide (0.33 mL, 3.9 mmol) and potassium carbonate (0.48 g, 3.5 mmol) in acetone (10 mL) were refluxed for 2 h, the reaction mixture was cooled to room temperature, filtered and washed with acetone. The combined organic phase was concentrated in vacuo, then diethyl ether (50 mL) was added, washed with water (3×20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography eluting with hexane to afford the product **25** (86%) as a colorless oil.[16,18] IR (neat) cm^{-1}: 1580, 1400 and 1269. ^{1}H NMR ($CDCl_3$) δ: 4.73 (d, 2H, *J* = 5.0 Hz, CH_2O), 5.35 (dd, 1H, *J* = 10.0 Hz, *J* = 1.0 Hz, $\underline{CH_2}$=CH), 5.55 (dd, 1H, *J* = 17.0 Hz, *J* = 1.0 Hz, $\underline{CH_2}$=CH), 6.20 (m, 1H,

$-\underline{CH}=CH_2$), 6.82 (d, 1H, $J=7.5$ Hz, ArH), 7.38 (m, 1H, ArH), 7.45 (d, 1H, $J=8.2$ Hz, ArH), 7.50 (m, 2H, ArH), 7.80 (m, 1H, ArH) and 8.35 (m, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ: 69.9 (OCH_2), 105.7 ($CH_2=$), 118.0, 121.0, 122.8, 125.8, 126.4, 127.0, 128.1, 134.0 (CH), 127.0, 135.2, 155.0 (C arom). MS *m*/*z* (%): 184 (M^+, 70), 143 (72) and 113 (100).

1-(2-Methyl-allyloxy)-naphthalene (26). A mixture of 1-naphthol (0.5 g, 3.5 mmol), 3-chloro-2-methyl-1-propene (0.4 mL, 4.2 mmol) and potassium carbonate (0.48 g, 3.5 mmol) in acetone (10 mL) were refluxed for 24 h. The reaction mixture was cooled to room temperature, filtered and washed with acetone. The combined organic phase was concentrated in vacuo, then diethyl ether (50 mL) was added, washed with water (3×20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography eluting with hexane to afford the product **26** (65%) as a colourless oil.[18] IR (neat) cm^{-1}: 3054, 1579, 1398 and 1101. ^{1}H NMR ($CDCl_3$) δ: 2.00 (s, 3H, Me), 4.65 (s, 2H, CH_2O), 5.10 and 5.30 (2×s, 2×1H, $CH_2=$), 6.86 (d, 1H, $J=7.5$ Hz, ArH), 7.40 (m, 1H, ArH), 7.48 (d, 1H, $J=7.6$ Hz, ArH), 7.54 (m, 2H, ArH), 7.85 (m, 1H, ArH) and 8.39 (m, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ: 19.5 (CH_3), 71.7 (OCH_2), 104.9 ($CH_2=$), 112.5, 120.2, 122.0, 125.1, 125.8, 126.3, 127.4 (CH arom), 126.3, 135.3, 154.3 (C arom), 141.7 (C). MS *m*/*z* (%): 198 (M^+, 77), 183 (56), 143 (63) and 115 (100).

2-Allyl-naphthalen-1-ol (27). The allyl ether (**25**) (0.4 g) in *N,N*-dimethylformamide (4 mL) was heated for 6 h at 180 °C. Then the reaction mixture was cooled to room temperature, water was added and extracted with diethyl ether (3×20 mL). The organic phase was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography eluting with 49:1 v/v hexane–dichloromethane to afford the product **27** (82%) as a colorless oil.[16] IR (neat) cm^{-1}: 3509, 1289 and 1265. ^{1}H NMR ($CDCl_3$) δ: 3.56 (d, 2H, $J=6.2$ Hz, CH_2), 5.23 (m, 2H, $\underline{CH_2}=CH$), 5.54 (s, 1H, OH), 6.67 (m, 1H, $CH_2=\underline{CH}$), 7.21 (d, 1H, $J=8.3$ Hz, ArH), 7.40 (d, 1H, $J=8.3$ Hz, ArH), 7.45 (m, 2H, ArH), 7.77 (m, 1H, ArH) and 8.16 (m, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ: 36.4 (CH_2), 117.7 ($CH_2=$), 121.0, 122.0, 126.0, 126.4, 128.2, 129, 136.8 (CH), 118.4, 125.5, 134.4, 150.3 (C arom). MS *m*/*z* (%): 184 (M^+, 100), 169 (32), 141 (45), 128 (63) and 115 (38).

2-(2-Methylallyl)-naphthalen-1-ol (28). The allyl ether (**26**) (0.4 g) in *N,N*-dimethylformamide (4 mL) was heated for 6 h at 180 °C. Then the reaction mixture was cooled to room temperature, water was added and extracted with diethyl ether. The organic phase was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography eluting with 49:1 v/v hexane–dichloromethane to afford the product **28** (93%) as a colorless oil.[20] IR (neat) cm^{-1}: 3489, 1657 and 1266; ^{1}H NMR ($CDCl_3$) δ: 1.80 (s, 3H, Me), 3.58 (s, 2H, CH_2), 5.03 (s, 2H, $CH_2=$), 5.82 (s, 1H, OH), 7.24 (d, 1H, $J=8.3$ Hz, ArH), 7.42 (d, 1H, $J=8.3$ Hz, ArH), 7.50 (m, 2H, ArH), 7.80 (m, 1H, ArH) and 8.22 (m, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ: 22.0 (CH_3), 40.7 (CH_2), 112.8 ($CH_2=$), 120.2, 121.6, 125.2, 125.8, 127.5, 129.0 (CH arom), 117.6, 124.9, 133.8, 150.1 (C arom), 144.7 (C). MS *m*/*z* (%): 198 (M^+, 70), 183 (63), 155 (52) and 128 (100).

2-(3-Hydroxy-propyl)-naphthalen-1-ol (29). A 1 M solution of borane in tetrahydrofuran (7.4 mL, 7.4 mmol) was added dropwise to a stirred solution compound (**27**) (1.36 g, 7.4 mmol) in anhydrous tetrahydrofuran (15 mL) at room temperature under nitrogen. After stirring at room temperature for 4 h, water (0.74 mL) was added dropwise, followed by 3 M sodium hydroxide (1 mL). Then hydrogen peroxide (40%, 1 mL) was added at such a rate that the temperature of the reaction mixture stayed between 30 and 50 °C. Following the addition, stirring was continued for 4 h at room temperature. Diethyl ether (15 mL) was added to the reaction mixture, washed with brine and water. After drying over anhydrous sodium sulfate, filtered and concentrated in vacuo, the residue was purified by column chromatography eluting with 9:1 v/v hexane–ethyl acetate to afford the product **29** (71%) as a colorless amorphous powder, mp 86–87 °C. IR (KBr) cm^{-1}: 3481, 1513 and 1272. ^{1}H NMR ($CDCl_3$) δ: 1.95 (m, 2H, CH_2), 2.95 (t, 2H, $J=6.4$ Hz, CH_2), 3.65 (t, 2H, $J=5.7$ Hz, CH_2O), 7.20 (d, 1H, $J=8.3$ Hz, ArH), 7.37 (d, 1H, $J=8.3$ Hz, ArH), 7.45 (m, 2H, ArH), 7.75 (dd, 1H, $J=7.4$ Hz, $J=1.5$ Hz, ArH) and 8.25 (dd, 1H, $J=8.9$ Hz, $J=1.5$ Hz, ArH). ^{13}C NMR ($CDCl_3$) δ: 25.0 (CH_2), 31.5 (CH_2), 60.5 (CH_2O), 120.2, 122.3, 125.2, 125.7, 127.5, 128.8 (CH arom), 119.8, 125.4, 134.0 and 150.5 (C arom). MS *m*/*z* (%): 202 (M^+, 98), 184 (99), 156 (69) and 128 (100). Anal. calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.41; H, 6.79.

2-(3-Hydroxy-2-methyl-propyl)-naphthalen-1-ol (30). A 1 M solution of borane in tetrahydrofuran (1.3 mL, 1.3 mmol) was added dropwise to a stirred solution of (**28**) (0.25 g, 1.3 mmol) in anhydrous tetrahydrofuran (10 mL) at room temperature under nitrogen. After stirring at room temperature for 4 h, water (0.13 mL) was added dropwise followed by 3 M NaOH (0.2 mL). Then hydrogen peroxide (40%, 0.2 mL) was added at such a rate that the temperature of the reaction mixture stayed between 30 and 50 °C. Following the addition, stirring was continued for 4 h at room temperature. Diethyl ether (15 mL) was added to the reaction mixture, washed with brine and water. After drying over anhydrous sodium sulfate, filtered and concentrated in vacuo, the residue was purified by column chromatography eluting with 9:1 v/v hexane–ethyl acetate to afford the product **30** (96%) as a colorless amorphous powder, mp 89–90 °C. IR (KBr) cm^{-1}: 3376, 1384 and 1016. ^{1}H NMR ($CDCl_3$) δ: 1.08 (d, 3H, $J=7.0$ Hz, CH_3), 2.10 (m, 1H, CH), 2.40 (br s, 1H, OH), 2.90 (m, 2H, CH_2), 3.38 (dd, 1H, $J=10.3$ Hz, $J=6.9$ Hz, CH_2O), 3.60 (dd, 1H, $J=10.3$ Hz, $J=3.9$ Hz, CH_2O), 7.21 (d, 1H, $J=8.3$ Hz, ArH), 7.40 (d, 1H, $J=8.3$ Hz, ArH), 7.48 (m, 2H, ArH), 7.80 (m, 1H, ArH), 8.15 (br s, 1H, OH) and 8.30 (m, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ: 17.5

(CH_3), 32.5 (CH_2), 36.0 (CH), 65.7 (CH_2O), 119.5, 122.2, 125.1, 125.8, 127.5, 129.8 (CH arom), 118.9, 125.7, 133.8 and 150.5 (C arom). MS *m/z* (%): 216 (M^+, 62), 198 (40), 183 (44), 157 (94), 128 (100). Anal. calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.66; H, 7.43.

2-(3-Hydroxy-propyl)-[1,4]-naphthoquinone (31). To a stirred solution of compound (**29**) (0.2 g, 0.99 mmol) in methanol-dimethylformamide (MeOH–DMF) (3:1) (13 mL) was added a solution of Fremy's salt (2.7 g) in water 52 mL and 1 M aqueous sodium acetate solution (1.44 mL). After stirring for 8 h at room temperature, the reaction mixture was extracted with diethyl ether (3×20 mL). The combined organic phase was washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography eluting with 4:1 v/v hexane–ethyl acetate to afford the product **31** (71%) as a yellow solid, mp 66–67 °C. IR (KBr) cm^{-1}: 3249, 1663 and 1305. ^1H NMR ($CDCl_3$) δ: 1.85 (m, 2H, CH_2), 1.95 (br s, 1H, OH), 2.65 (t, 2H, $J=7.6$ Hz, CH_2), 3.70 (t, 2H, $J=6.1$ Hz, CH_2O), 6.80 (s, 1H, CH=), 7.70 (m, 2H, ArH) and 8.05 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ: 26.6 (CH_2), 31.8 (CH_2), 62.3 (CH_2O), 126.7, 127.3, 134.3, 134.4, 135.9 (CH), 132.7, 132.8, 152.0 (C), 185.7 and 186.1 (C=O). MS *m/z* (%): 216 (M^+, 32), 188 (51), 128 (61) and 76 (100). Anal. calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59 Found: C, 72.17; H, 5.59.

2-(3-Hydroxy-2-methyl-propyl)-[1,4]-naphthoquinone (32). To a stirred solution of compound **30** (0.2 g, 0.92 mmol) in MeOH–DMF (3:1) (13 mL) was added a solution of Fremy's salt (2.5 g) in water 50 mL and 1 M aqueous sodium acetate solution (1.3 mL). After stirring for 13 h at room temperature, the reaction mixture was extracted with diethyl ether (3 30 mL). The combined organic phase was washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography eluting with 5:1 v/v hexane–ethyl acetate to afford the product **32** (85%) as a yellow oil. IR (neat) cm^{-1}: 3403, 1662, 1589 and 1029. ^1H NMR ($CDCl_3$) δ: 0.95 (d, 3H, $J=6.8$ Hz, CH_3), 1.99 (m, 1H, CH), 2.09 (br s, 1H, OH), 2.38 and 2.72 (2×m, 2×1H, CH_2), 3.43 and 3.51 (2×m, 2×1H, CH_2O), 6.80 (s, 1H, CH=), 7.71 (m, 2H, ArH) and 8.05 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ: 17.3 (CH_3), 33.8 (CH_2), 36.4 (CH), 67.5 (CH_2O), 126.7, 127.4, 134.3, 134.5, 137.1 (CH), 132.7, 132.8, 150.8 (C), 185.6 and 186.4 (C=O). MS *m/z* (%): 230 (M^+, 18), 212 (64), 197 (100) and 115 (84). HRMS calcd for $C_{14}H_{14}O_3$ (M + Na) 253.0841, found 253.0848.

3,4-Dihydro-2*H*-naphtho-[1,2-*b*]pyran-5,6-dione (2). A mixture of compound **31** (0.2 g, 0.9 mmol), dichlorodicyanobenzoquinone (DDQ) (0.3 g, 1.4 mmol) and *p*-toluenesulfonic acid monohydrate (0.02 g, 0.09 mmol) in dry benzene (4 mL) were stirred for 30 min under refluxed and cooled to room temperature, filtered, washed with dichloromethane and concentrate in vacuo. The residue was filtered through aluminium oxide to afford the product **2** (95%) as an orange amorphous powder, mp 184–185 °C.[6] IR (KBr) cm^{-1}: 1687, 1642, 1564 and 1258. ^1H NMR ($CDCl_3$) δ: 2.05 (m, 2H, CH_2), 2.55 (t, 2H, $J=6.4$ Hz, CH_2), 4.45 (t, 2H, $J=5.2$ Hz, CH_2O), 7.52 (t, 1H, $J=7.7$ Hz, ArH), 7.65 (t, 1H, $J=7.7$ Hz, ArH), 7.80 (d, 1H, $J=7.8$ Hz, ArH) and 8.07 (d, 1H, $J=8.1$ Hz, ArH). ^{13}C NMR ($CDCl_3$) δ: 18.5 (CH_2), 21.4 (CH_2), 69.0 (CH_2O), 124.6, 129.2, 131.3, 135.5 (CH arom), 114.8, 130.6, 132.9, 163.7 (C), 179.2 and 180.2 (C=O). MS *m/z* (%): 214 (M^+, 21), 186 (75), 158 (63), 130(71), 102 (69) and 76 (100). Anal. calcd for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 72.71; H, 4.99.

3-Methyl-3,4-dihydro-2*H*-benzo[*h*]chromene-5,6-dione (3). A mixture of compound **32** (0.2 g, 0.87 mmol), dichlorodicyanobenzoquinone (DDQ) (0.3 g, 1.3 mmol) and *p*-toluenesulfonic acid monohydrate (0.016 g, 0.08 mmol) in dry benzene (4 mL) were stirred for 20 min under refluxed and cooled to room temperature, filtered, washed with dichloromethane and concentrated in vacuo. The residue was filtered through aluminium oxide to afford the product **3** (95%) as an orange amorphous powder, mp 148–149 °C. IR (KBr) cm^{-1}: 1688, 1645, 1256 and 1168. ^1H NMR ($CDCl_3$) δ: 1.03 (d, 3H, $J=6.5$ Hz, CH_3), 2.00 (m, 1H, CH_2), 2.07 (m, 1H, CH), 2.70 (m, 1H, CH_2), 3.81 (m, 1H, CH_2O), 4.37 (m, 1H, CH_2O), 7.43 (m, 1H, ArH), 7.57 (m, 1H, ArH), 7.71 (m, 1H, ArH) and 7.98 (m, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ: 17.3 (CH_3), 26.5 (CH), 26.6 (CH_2), 74.0 (CH_2O), 124.7, 129.3, 131.3, 135.5 (CH arom), 114.2, 130.5, 132.7, 163.3 (C), 179.3 and 180.3 (C=O). MS *m/z* (%): 228 (M^+, 3), 200 (100), 185 (71), 158 (58) and 102 (70). Anal. calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.61; H, 5.40.

3-Hydroxy-2-(3-hydroxypropyl)-1,4-naphthoquinone (33). The solution of compound (**2**) (0.2 g, 0.93 mmol) in 1% aqueous sodium hydroxide solution (6 mL) was refluxed for 2 h. Then the reaction mixture was cooled to room temperature and acidified with acetic acid, extracted with dichloromethane (3×30 mL). The combined organic phase was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was recrystallized from hexane–dichloromethane to give the product **33** (86%) as a yellow amorphous powder, mp 106–107 °C. IR (KBr) cm^{-1}: 3342, 1640, 1638, 1365 and 1272. ^1H NMR ($CDCl_3$) δ: 1.81 (m, 2H, CH_2), 2.70 (t, 2H, $J=7.0$ Hz, CH_2), 3.60 (t, 2H, $J=6.0$ Hz, CH_2O), 7.69 (m, 2H, ArH) and 8.06 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ: 19.6 (CH_2), 31.3 (CH_2), 62.1 (CH_2O), 126.8, 127.5, 133.7, 135.6 (CH arom), 124.3, 130.1, 133.3, 154.4 (C), 181.7 and 186.0 (C=O). MS *m/z* (%): 232 (M^+, 36), 214 (97), 188 (77), 105 (65) and 77 (100). Anal. calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.15; H, 5.27.

3-Hydroxy-2-(3-hydroxy-2-methylpropyl)-1,4-naphthoquinone (34). The solution of compound **3** (0.1 g, 0.44 mmol) was refluxed in 1% aqueous sodium hydroxide solution (2.7 mL) for 2 h. Then the reaction mixture was cooled to room temperature, acidified with acetic acid, extracted with dichloromethane (3×30 mL). The combined organic phase was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was recrystallized from

hexane–dichloromethane to give the product **34** (94%) as a yellow amorphous powder, mp 146–147 °C. IR (KBr) cm^{-1}: 3485, 1656, 1371 and 1215. ^1H NMR ($CDCl_3$) δ: 0.96 (d, 3H, $J=6.8$ Hz, CH_3), 1.60 (br s, 2H, 2×OH), 1.95 (m, 1H, CH), 2.58 (m, 2H, CH_2), 3.36 (m, 2H, CH_2O), 7.67 (m, 2H, ArH) and 8.04 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ: 17.8 (CH_3), 26.7 (CH_2), 36.3 (CH), 67.2 (CH_2O), 126.9, 127.6, 133.8, 135.6 (CH arom), 123.5, 130.1, 133.4, 154.6 (C), 181.7 and 186.3 (C=O). MS *m*/*z* (%): 246 (M^+, 200), 216 (75), 188 (80), 105 (73) and 77 (100). HRMS calcd for $C_{14}H_{14}O_4$ (M + H) 247.0970, found 247.0966.

3,4-Dihydro-2*H*-naphtho[2,3-*b*]pyran-5,10-dione (9). 20% aqueous sulfuric acid (10 mL) was added to the solution of compound **33** (40 mg, 0.17 mmol) in dichloromethane (1 mL) at room temperature. After the reaction mixture was refluxed for 5 h, cool-water (3×30 mL) was added to the reaction mixture and extracted with chloroform. The combined organic phase was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography eluting with 19:1 v/v hexane–ethyl acetate to afford the product **9** (89%) and recrystalized from hexane–dichloromethane to give yellow needles, mp 216–218 °C.[6] IR (KBr) cm^{-1}: 2948, 1672, 1638 and 1187. ^1H NMR ($CDCl_3$) δ: 2.05 (m, 2H, CH_2), 2.63 (t, 2H, $J=6.3$ Hz, CH_2), 4.36 (t, 2H, $J=5.3$ Hz, CH_2O), 7.69 (dt, 1H, $J=7.4$ Hz, $J=1.6$ Hz, ArH), 7.73 (dt, 1H, $J=7.4$ Hz, $J=1.6$ Hz, ArH), 8.09 (dd, 1H, $J=1.1$ Hz, $J=6.8$ Hz, ArH) and 8.11 (dd, 1H, $J=6.8$ Hz, $J=1.1$ Hz, ArH). ^{13}C NMR ($CDCl_3$) δ: 19.0 (CH_2), 21.1 (CH_2), 68.3 (CH_2O), 126.7, 126.9, 133.3, 134.6 (CH arom), 122.3, 131.5, 132.6, 156.1 (C), 180.3, 184.8 (C=O). MS *m*/*z* (%): 214 (M^+, 100), 129 (42), 104 (53) and 76 (99). HRMS calcd for $C_{13}H_{10}O_3$ (M + H) 215.0708, found 215.0705.

3,4-Dihydro-3-methyl-2*H*-naphtho[2,3-*b*]pyran-5,10-dione (10). 20% Aqueous sulfuric acid (70 mL) was added to the solution of compound **34** (500 mg, 0.2 mmol) in dichloromethane (2 mL) at room temperature. After the reaction mixture was refluxed for 5 h, cool-water was added to the reaction mixture and extracted with chloroform (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 column chromatography eluting with 19:1 v/v hexane–ethyl acetate to afford the product **10** (89%) and recrystalized from hexane–dichloromethane to give yellow needles, mp 167–168 °C.[31] IR (KBr) cm^{-1}: 2963, 1675, 1638 and 1239. ^1H NMR ($CDCl_3$) δ: 1.13 (d, 3H, $J=6.4$ Hz, CH_3), 2.15 (m, 2H, CH_2), 2.84 (m, 1H, CH), 3.80 and 4.41 (2×m, 2×1H, OCH_2), 7.70 (dt, 1H, $J=7.5$ Hz, $J=1.6$ Hz, ArH), 7.73 (dt, 1H, $J=7.5$ Hz, $J=1.6$ Hz, ArH), 8.10 (dd, 1H, $J=7.5$ Hz, $J=2.0$ Hz, ArH) and 8.12 (dd, 1H, $J=7.5$ Hz, $J=2.0$ Hz, ArH). ^{13}C NMR ($CDCl_3$) δ: 17.4 (CH_3), 26.2 (CH_2), 28.1 (CH), 73.3 (CH_2O), 126.7, 126.9, 133.7, 134.6 (CH arom), 121.8, 131.6, 132.7, 155.7 (C), 180.3, 184.9 (C=O). MS *m*/*z* (%): 228 (M^+, 60), 200 (49), 102 (51) and 76 (100). HRMS calcd for $C_{14}H_{12}O_3$ ($M+NH_4$) 246.1130, found 246.1128.

2-Allyl-3-hydroxy-1,4-naphthoquinone (36). A solution of lawsone (**35**) (2.0 g, 11.5 mmol) in dimethylformamide (15 mL) was added to the potassium carbonate (1.6 g, 11.5 mmol) in dimethylformamide (50 mL) and stirring for 15 min at room temperature. Allyl bromide (3.5 g, 28.7 mmol) in dimethylformamide (5 mL) was added dropwise over 15 min and stirring was continued for 15 min at the same temperature. After the reaction mixture was refluxed for 3 h, then the reaction mixture was cooled to room temperature, filtered and dichloromethane (30 mL) was added, then washed with water (5×25 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography eluting with 9:1 v/v hexane–ethyl acetate to afford the product **36** (81%) and recrystalized from hexane–dichloromethane to give yellow needles, mp 112–113 °C.[25] IR (KBr) cm^{-1}: 3362, 1648, 1600 and 1227. ^1H NMR ($CDCl_3$) δ: 3.31 (d, 2H, $J=4.5$ Hz, CH_2), 5.00 (dd, 1H, $J=10$ Hz, $J=1.4$ Hz, CH_2=), 5.11 (dd, 1H, $J=17$ Hz, $J=1.4$ Hz, CH_2=), 5.88 (m, 1H, CH=), 7.25 (br s, 1H, OH), 7.64 (dt, 1H, $J=7.5$ Hz, $J=1.0$ Hz, ArH), 7.71 (dt, 1H, $J=7.5$ Hz, $J=1.0$ Hz, ArH), 8.03 (dd, 1H, $J=7.6$ Hz, $J=1.3$ Hz, ArH) and 8.08 (dd, 1H, $J=1.3$ Hz, $J=7.6$ Hz, ArH). ^{13}C NMR ($CDCl_3$) δ: 27.7 (CH_2), 122.0 (CH_2=), 126.4, 127.1, 129.6, 133.0, 133.2 (CH), 116.6, 133.9, 135.2, 153.3 (C), 181.7 and 184.4 (C=O). MS *m*/*z* (%): 214 (M^+, 64), 129 (78), 115 (100) and 77 (95).

2-Hydroxy-3-(2-methyl-2-propenyl)-1,4-naphthoquinone (37). A solution of lawsone (**35**) (2.0 g, 11.5 mmol) in dimethylformamide (15 mL) was added to the potassium carbonate (1.6 g, 11.5 mmol) in dimethylformamide (50 mL) and stirring for 15 min at room temperature. 3-Chloro-2-methyl-1-propene (2.1 g, 23.0 mmol) in dimethylformamide (5 mL) was added dropwise over 15 min and stirring was continued for 15 min at the same temperature. After the reaction mixture was refluxed for 3 h, then the reaction mixture was cooled to room temperature, filtered and added dichloromethane (30 mL), then washed with water (5×25 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography eluting with 9:1 v/v hexane–ethyl acetate to afford the product **37** (59%) and recrystalized from hexane–dichloromethane to give yellow needles, mp 126–126.5 °C.[31] IR (KBr) cm^{-1}: 3351, 1646, 1593 and 1228. ^1H NMR ($CDCl_3$) δ: 1.75 (s, 3H, CH_3), 3.27 (s, 2H, CH_2), 4.68 (d, 1H, $J=1.8$ Hz, CH_2=), 4.73 (d, 1H, $J=1.4$ Hz, CH_2=), 7.35 (s, 1H, OH), 7.64 (dt, 1H, $J=7.5$ Hz, $J=1.4$ Hz, ArH), 7.71 (dt, 1H, $J=7.5$ Hz, $J=1.4$ Hz, ArH), 8.06 (dd, 1H, $J=7.6$ Hz, $J=1.4$ Hz, ArH) and 8.08 (dd, 1H, $J=1.4$ Hz, $J=7.6$ Hz, ArH). ^{13}C NMR ($CDCl_3$) δ: 23.7 (CH_3), 31.7 (CH_2), 112.1 (CH_2=), 126.8, 127.6, 133.6, 135.6 (CH arom), 122.5, 130.5, 133.5, 142.7, 154.2 (C), 182.1 and 185.0 (C=O). MS *m*/*z* (%): 228 (M^+, 100), 213 (75) and 77 (34).

2,3-Dihydro-2-methylnaphthol[1,2-b]furan-4,5-dione 6). A solution of 2-allyl-3-hydroxy-1,4-naphthoquinone (**36**) (1 g, 4.7 mmol) in dichloromethane (5 mL) was added dropwise to concentrated sulfuric acid (25 mL) at 0 °C. After stirring for 30–45 min at 0 °C, the reaction mixture was quenched with ice-water, and extracted

with dichloromethane (3×30 mL). The combined organic phase was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography eluting with 17:3 v/v hexane–ethyl acetate to afford the product **6** (70%) and recrystalized from hexane–dichloromethane to give red needles, mp 126–126.5 °C. IR (KBr) cm^{-1}: 1690, 1645 and 1158. ^1H NMR ($CDCl_3$) δ: 1.52 (d, 3H, $J=3.2$ Hz, CH_3), 2.68 (dd, 1H, $J=7.6$ Hz, $J=7.2$ Hz, CH_2), 3.22 (dd, 1H, $J=7.6$ Hz, $J=9.2$ Hz, CH_2), 5.20 (m, 1H, O–CH), 7.52 (m, 1H, ArH), 7.58 (m, 2H, ArH) and 8.01 (m, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ: 22.2 (CH_3), 33.7 (CH_2), 84.9 (CH), 124.7, 127.9, 129.6, 131.0 (CH arom), 115.4, 132.1, 134.7, 169.9 (C), 175.8 and 181.5 (C=O). MS *m/z* (%): 214 (M^+), 186 (100), 158 (39) and 129 (29). HRMS calcd for $C_{13}H_{10}O_3$ (M) 214.0624, found 214.0630.

2,3-Dihydro-2,2-dimethylnaphtho[1,2-*b*]furan-4,5-dione (5). A solution of compound **37** (1 g, 4.4 mmol) in dichloromethane (5 mL) was added dropwise to concentrated sulfuric acid (25 mL) at 0 °C. After stirring for 30–45 min at 0 °C, the reaction mixture was quenched with ice-water, and extracted with dichloromethane (3×30 mL). The combined organic phase was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography eluting with 17:3 v/v hexane–ethyl acetate to afford the product **5** (61%) and recrystalized from hexane–dichloromethane to give red needles, mp 170–171 °C.[8] IR (KBr) cm^{-1}: 1694, 1642, 1403 and 1276. ^1H NMR ($CDCl_3$) δ: 1.54 (s, 6H, 2×CH_3), 2.89 (s, 2H, CH_2), 7.51 (m, 1H, ArH), 7.57 (m, 2H, ArH) and 8.01 (m, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ: 28.6 (2×CH_3), 39.5 (CH_2), 93.9 (C), 124.8, 128.1, 129.5, 131.1 (CH arom), 115.2, 132.1, 134.6, 169.0 (C), 175.9 and 181.5 (C=O). MS *m/z* (%): 228 (M^+, 83), 186 (100), 158 (38) and 129 (30). Anal. calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.69; H, 5.30.

2,3-Dihydro-2,2-dimethylnaphtho[2,3-*b*]furan-4,9-dione (11). 20% Aqueous sulfuric acid (50 mL) was added to the solution of compound **37** (360 mg, 1.58 mmol) in dichloromethane (2 mL) at room temperature. After the reaction mixture was refluxed for 5 h, cool water was added to the reaction mixture and extracted with chloroform (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 column chromatography eluting with 19:1 v/v hexane–ethyl acetate to afford the product **11** (86%) and recrystalized from hexane–dichloromethane to give yellow needles, mp 184–184.5 °C.[8] IR (KBr) cm^{-1}: 1675, 1634, 1440 and 1206. ^1H NMR ($CDCl_3$) δ: 1.61 (s, 6H, 2×CH_3), 3.02 (s, 2H, CH_2), 7.68 (dt, 1H, $J=6.0$ Hz, $J=1.5$ Hz, ArH), 7.73 (dt, 1H, $J=6.0$ Hz, $J=1.5$ Hz, ArH), 8.08 (dd, 1H, $J=5.6$ Hz, $J=1.4$ Hz, ArH) and 8.10 (dd, 1H, $J=1.4$ Hz, $J=5.6$ Hz, ArH). ^{13}C NMR ($CDCl_3$) δ: 29.0 (2×CH_3), 40.7 (CH_2), 92.6 (C), 126.5, 126.8, 133.4, 134.7 (CH arom), 124.0, 132.2, 133.7, 178.9 (C), 189.5 and 183.1 (C=O). MS *m/z* (%): 228 (M^+, 35), 200 (60), 104 (49) and 76 (100). HRMS calcd for $C_{14}H_{12}O_3$ (M + H) 229.0864, found 229.0864.

2,3-Dihydro-2-methylnaphtho[2,3-*b*]furan-4,9-dione (12). 20% Aqueous sulfuric acid (40 mL) was added to the solution of compound **36** (200 mg, 0.93 mmol) in dichloromethane (2 mL) at room temperature. After the reaction mixture was refluxed for 5 h, cool water was added to the reaction mixture and extracted with chloroform (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 column chromatography eluting with 19:1 v/v hexane–ethyl acetate to afford the product **12** (75%) and recrystalized from hexane–dichloromethane to give yellow needles, mp 166.5–167 °C.[9] IR (KBr) cm^{-1}: 1683, 1645, 1593 and 1194. ^1H NMR ($CDCl_3$) δ: 1.50 (d, 3H, $J=6.4$ Hz, CH_3), 2.74 (dd, 1H, $J=16.9$ Hz, $J=7.8$ Hz, CH_2), 3.28 (dd, 1H, $J=16.9$ Hz, $J=10.2$ Hz, CH_2), 5.13 (m, 1H, CH), 7.60 (dt, 1H, $J=7.4$ Hz, $J=1.5$ Hz, ArH), 7.65 (dt, 1H, $J=7.4$ Hz, $J=1.5$ Hz, ArH), 7.99 (dd, 1H, $J=1.7$ Hz, $J=3.4$ Hz, ArH) and 8.01 (dd, 1H, $J=1.7$ Hz, $J=3.4$ Hz, ArH). ^{13}C NMR ($CDCl_3$) δ: 22.5 (CH_3), 35.0 (CH_2), 83.7 (CH), 126.6, 126.9, 133.5, 134.8 (CH arom), 124.5, 132.1, 133.7, 160.5 (C), 178.7 and 183.0 (C=O). MS *m/z* (%): 214 (M^+, 84), 129 (50), 15 (50), 104 (67) and 76 (100). HRMS calcd for $C_{13}H_{10}O_3$ (M + H) 215.0708, found 215.0704.

3,4-Dihydro-2-hydroxy-2*H*-naphtho[1,2-*b*]pyran-5,6-dione (4). A solution of *m*-chloroperbenzoic acid (0.2 g, 1.1 mmol) in dichloromethane (2 mL) was added dropwise to the solution of 2-allyl-3-hydroxy-1,4-naphthoquinone (**36**) (0.2 g, 0.93 mmol) in dichloromethane (2 mL) at 0 °C. After the reaction mixture was stirred for 24 h, then the reaction mixture was filtered and dichloromethane (50 mL) was added, then washed with water (3×20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography eluting with 7:3 v/v hexane–ethyl acetate to afford the product **4** (30%) and recrystalized from hexane–ethyl acetate to give red needles, mp 197–199 °C. IR (KBr) cm^{-1}: 3470, 1609 and 1277. ^1H NMR ($CDCl_3$) δ: 2.78 (dd, 1H, $J=15.3$ Hz, $J=7.4$ Hz, CH_2), 2.93 (dd, 1H, $J=10.2$ Hz, $J=15.3$ Hz, CH_2), 3.58 (dd, 1H, $J=12.3$ Hz, $J=5.1$ Hz, OCH_2), 3.70 (dd, 1H, $J=12.3$ Hz, $J=3.1$ Hz, OCH_2), 4.66 (br s, 1H, OH), 5.00 (m, 1H, CH), 7.38 (dt, 1H, $J=7.5$ Hz, $J=1.4$ Hz, ArH), 7.46 (dt, 1H, $J=7.5$ Hz, $J=1.4$ Hz, ArH), 7.50 (dd, 1H, $J=7.5$ Hz, $J=1.4$ Hz, ArH), 7.82 (d, 1H, $J=7.6$ Hz, ArH). ^{13}C NMR ($CDCl_3$) δ: 28.3 (CH_2), 63.8 (CHOH), 88.7 (CH_2O), 125.2, 129.5, 132.3, 135.0 (CH arom), 116.0, 127.9, 131.0, 170.7 (C), 175.6 and 181.7 (C=O). LCMS 253 (M^+ + Na). HRMS calcd for $C_{13}H_{10}O_4$ (M + Na) 253.0477, found 253.0477.

2-(Ethylacetylate)-3-hydroxy-1,4-naphthoquinone (38). A solution of 2-hydroxy-1,4-naphthoquinone (**35**) (200 mg, 1.2 mmol) in DMF (1 mL) was added to lithium carbonate (100 mg, 1.2 mmol) in dimethylformamide (5 mL) at room temperature and stirring was continued for 15 min at room temperature, ethyl bromoacetate (380 mg, 2.3 mmol) in DMF (1 mL) was added dropwise over 5 min and stirring was continued for 15 min at room temperature. After the reaction mixture was refluxed for 3 h, then the reaction mixture

was cooled to room temperature, and dichloromethane (3 mL) was added, then washed with water (5×10 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography eluting with 2:1:1 v/v/v hexane–ethyl acetate–chloroform to afford the product **38** (40%) and recrystalized from hexane–ethyl acetate to give brown needles, mp 157–158 °C.[32] IR (KBr) cm^{-1}: 3239, 1731, 1671, 1475 and 1049. ^1H NMR ($CDCl_3$) δ: 1.29 (t, 3H, $J=7.2$ Hz, CH_3), 3.68 (s, 2H, CH_2), 4.20 (q, 2H, $J=7.2$ Hz, CH_2O), 7.73 (dt, 1H, $J=6.1$ Hz, $J=1.4$ Hz, ArH), 7.80 (dt, 1H, $J=6.1$ Hz, $J=1.4$ Hz, ArH), 8.13 (dd, 1H, $J=6.1$ Hz, $J=1.4$ Hz, ArH) and 8.16 (dd, 1H, $J=6.1$ Hz, $J=1.4$ Hz, ArH). ^{13}C NMR ($CDCl_3$) δ: 14.8 (CH_3), 29.6 (CH_2), 61.8 (OCH_2), 126.9, 127.5, 133.7, 135.7 (CH arom), 117.6, 130.1, 133.2, 154.8 (C), 170.7, 181.8 and 184.5 (C=O). MS *m/z* (%): 260 (M^+, 9), 232 (52), 187 (100), 159 (96) and 105 (65).

2-Hydroxy-3-(2-hydroxyethyl)-1,4-naphthoquinone (39). Sodium borohydride (100 mg, 2.6 mmol) was added to the solution of compound **38** (100 mg, 0.38 mmol) in ethanol (5 mL) at 0 °C. After the reaction mixture was refluxed for 7 h, then the reaction mixture was cooled to room temperature, the solution was poured into cool-water (10 mL), acidified with 1% aqueous sulfuric acid and extracted with chloroform (3×5 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography eluting with 1:1 hexane–ethyl acetate to afford the product **39** (48%) and recrystalized from hexane–ethyl acetate to give yellow needles, mp 148–149 °C.[7] IR (KBr) cm^{-1}: 3500, 1672, 1638, 1433 and 1068. ^1H NMR ($CDCl_3$) δ: 2.95 (t, 2H, $J=6.1$ Hz, CH_2), 3.90 (t, 2H, $J=6.1$ Hz, OCH_2), 7.72 (dt, 1H, $J=7.5$ Hz, $J=1.4$ Hz, ArH), 7.79 (dt, 1H, $J=7.5$ Hz, $J=1.4$ Hz, ArH), 8.12 (dd, 1H, $J=7.7$ Hz, $J=1.3$ Hz, ArH) and 8.15 (dd, 1H, $J=7.7$ Hz, $J=1.3$ Hz, ArH). ^{13}C NMR ($CDCl_3$) δ: 27.6 (CH_2), 62.2 (CH_2O), 126.9, 127.5, 133.8, 135.6 (CH arom), 121.9, 130.1, 133.4, 154.8 (C), 181.8 and 186.1 (C=O). MS *m/z* (%): 218 (M^+, 57), 188 (96), 160 (82), 105 (82) and 77 (100).

2,3-Dihydronaphtho[1,2-b]furan-4,5-dione (7). A solution of compound **39** (25 mg, 0.11 mmol) in dichloromethane (0.5 mL) was added dropwise to concentrated sulfuric acid (3 mL) at 0 °C. After stirring for 30–45 min at 0 °C, the reaction mixture was quenched with ice-water, and extracted with dichloromethane (3×3 mL). The combined organic phase was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography eluting with 17:3 v/v hexane–ethyl acetate to afford the product **7** (45%) and recrystalized from hexane–dichloromethane to give red needles, mp 227–229 °C.[7] IR (KBr) cm^{-1}: 1687, 1638, 1407 and 1079. ^1H NMR ($CDCl_3$) δ: 3.18 (t, 2H, $J=9.2$ Hz, CH_2), 4.90 (t, 2H, $J=9.2$ Hz, OCH_2), 7.60 (m, 1H, ArH), 7.68 (m, 2H, ArH) and 8.10 (m, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ: 27.0 (CH_2), 75.4 (CH_2O), 125.1, 130.0, 132.6, 135.2 (CH arom), 116.2, 128.0, 131.2, 171.3 (C), 176.0 and 181.8 (C=O). MS *m/z* (%): 200 (M^+, 12), 172 (100), 144 (36) and 115 (52). HRMS calcd for $C_{12}H_8O_3$ (M) 200.0473, found 200.0465.

2,3-Dihydronaphtho[2,3-*b*]furan-4,9-dione (13). 20% Aqueous sulfuric acid (10 mL) was added to the solution of compound **39** (25 mg, 0.11 mmol) in dichloromethane (0.5 mL) at room temperature. After the reaction mixture was refluxed for 5 h, cool water was added to the reaction mixture and extracted with chloroform (3×10 mL). The combined organic phase was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography eluting with 19:1 v/v hexane–ethyl acetate to afford the product **13** (54%) and recrystalized from hexane–dichloromethane to give yellow needles, mp 214–216 °C.[9] IR (KBr) cm^{-1}: 1675, 1403 and 1052. ^1H NMR ($CDCl_3$) δ: 3.25 (t, 2H, $J=9.9$ Hz, CH_2), 4.83 (t, 2H, $J=9.9$ Hz, OCH_2), 7.70 (dt, 1H, $J=7.5$ Hz, $J=1.5$ Hz, ArH), 7.75 (dt, 1H, $J=7.5$ Hz, $J=1.5$ Hz, ArH) and 8.10 (dd, 2H, $J=7.5$ Hz, $J=1.5$ Hz, ArH). ^{13}C NMR ($CDCl_3$) δ: 28.0 (CH_2), 73.9 (CH_2O), 126.7, 126.9, 133.6, 134.8 (CH arom), 125.1, 132.1, 133.6, 161.4 (C), 178.7 and 183.0 (C=O). LC/MS 223 (M + Na). HRMS calcd for $C_{12}H_8O_3$ (M + Na) 223.0371, found 223.0398.

Cytotoxicity assay

By MTT colorimetric method. Compounds **1**–**13** were subjected to cytotoxic evaluation against KB (human epidermoid carcinoma), HeLa (human cervical carcinoma) and $HepG_2$ (human hepatocellular carcinoma) cell lines employing the colorimetric method.[24] Adriamycin was used as the reference substance which exhibits activity against KB, HeLa and $HepG_2$ cell lines.

3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (Sigma Chemical Co., USA) was dissolved in saline to make the 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, USA) were seeded onto a 96-well culture plate (Costar, Corning Incorporated, NY 14831, USA). After 24 h pre-incubation at 37 °C in a humidified atmosphere of 5% CO_2/95% air to allow cells attachment, various concentrations of test solution (10 μL/well) as listed in Table 1 were added and then incubated for 48 h under the above condition. At the end of the incubation, 10 μL of tetrazolium reagent was added into each well and then incubated at 37 °C for 4 h. 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 average means of six replicates. The 50% inhibition concentration (IC_{50}) was determined by curve fitting.

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