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Synthesis, biological evaluation, and correlation of cytotoxicity versus redox potential of 1,4-naphthoquinone derivatives

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ABSTRACT

A series of 1,4-naphthoquinone derivatives of lawsone (**1**), 6-hydroxy-1,4-naphthoquinone (**2**), and juglone (**3**) were synthesized by alkylation, acylation, and sulfonylation reactions. The yields of lawsone derivatives **1a-1k** (type **A**), 6-hydroxy-1,4-naphthoquinone derivatives **2a-2j** (type **B**), and juglone derivatives **3a-3h** (type **C**) were 52–99%, 53–96%, and 28–95%, respectively. All compounds were tested *in vitro* for the cytotoxicity against human oral epidermoid carcinoma (KB) and cervix epithelioid carcinoma (HeLa) cells and their structure–activity relationship was studied. Compound **3c** was found to be most potent in KB cell line (IC_{50} = 1.39 μM). Some compounds were evaluated for DNA topoisomerase I inhibition. Compounds **2c**, **3**, **3a**, and **3d** showed topoisomerase inhibition activity with IC_{50} values of 8.3–91 μM. Standard redox potentials (E°) of all naphthoquinones in phosphate buffer at pH 7.2 were examined by means of cyclic voltammetry. A definite correlation has been found between the redox potentials and inhibitory effects of type **A** compounds.

Several kinds of quinonoids like naphthoquinones are widely distributed in nature. Their biological activities have been reported as enzyme inhibition,[1–4] anticancer,[2,5–9] and antivirus etc.[10–14] Betalapachone is an ortho naphthoquinone, originally isolated from the lapacho tree whose extract has been used medicinally for centuries. Isodiospyrin was found from *Diosyros morrisiana* and *Diospyros maritima*, and showed strong DNA topoisomerase I inhibition.[15] The isolation of the stems of *Diospyros maritima* by chromatography yielded plumbagin and isodiospyrin, which possessed potent inhibitory effects against KB, COLO-205, Hepta-3B, and HeLa cancer cell lines.[16,17] The main structures of plumbagin and isodiospyrin are composed of the 1,4-naphthoqunone skeleton. This skeleton is also the basic structure of vitamine K_3, which acts as an anticoagulant agent (Fig. 1). Some polyamine derivatives of naphthoquinone were ever reported by their antiparasitic protozoa properties at trypanothione reductase inhibition effect.[18] This trypanocidal effect acts upon different trypanosomes and is responsible for several human diseases including African sleeping sickness (*Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense*), Chagas' disease, and kala-azar. Naphthoquinone was reported for its anticancer effect on topoisomerase II[1,2] or on the cdk 25A phosphatase in certain type of cancer.[19] Vitamin K, which belongs to naphthoquinones, expresses its dual effect for cells. Vitamin K_1 (phytonadione) is an anti-haemorrhagic agent, while vitamin K_3 (menadione, 2-methyl-1,4-naphthoquinone) led to a 50–75% decrease in gap junctional intercellular communication (GJIC) of WB-F344 rat liver epithelial cells under 50–100 μM.[20] Moreover, vitamin K_3 as an inhibitor of MEK 1/2 counteracted the loss in gap junctional communication. Therefore, menadione could serve as an anticancer quinone for improvement in chemotherapy to decrease intercellular communication, thus diminishing tissue control over the targeted cells and enhancing the hindrance of the formation of uncontrollably growing cancer cell populations.[20] In this study, 29 derivatives of 1,4-naphthoquinone were synthesized and classified into three different subsets by its oxygen replacement at C-2 (as type **A**), C-6 (as type **B**), and C-5 (as type **C**) (Fig. 1). Furthermore, type **A-C** compounds were evaluated for cytotoxicity against oral epidermoid carcinoma (KB) and cervix epithelioid carcinoma (HeLa) cell lines. The tests of DNA type I topoisomerase inhibition were also performed. There are very few reports about the Epstein–Barr virus

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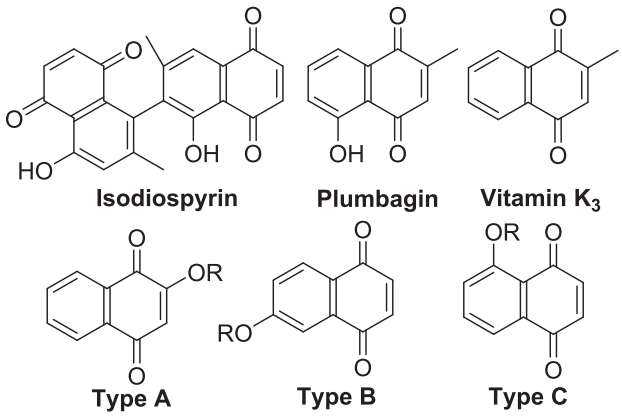


Fig. 1. Selective biological active 1,4-naphthoquinones and classification of the synthesized compounds as type **A–C**.

activation of naphthoquinones and the relationship of cytotoxicity with their redox potentials.[21] Redox potentials of all synthesized compounds were measured by cyclic voltammetry. The relationship between the redox potential values and cytotoxic IC_{50} values[22] of type **A** derivatives was also observed.

We synthesized a series of 1,4-naphthoquinone derivatives, which were classified into three different types, type **A-C** (Fig. 1). Compounds **1a-1k** were prepared by using commercially available lawsone (**1**). Nucleophilic substitution of lawsone with various alcohols at reflux temperature in the presence of catalytic sulfuric acid afforded compounds **1a-1d** in 75–99 yield.[23,24] The results are summarized in Table 1 (entries 1–4). The acetylation of lawsone with Ac_2O in the presence of sulfuric acid at room temperature gave the acetylation product **1e** in 96% yield (Table 1, entry 5).[25] For compounds **1f-1k**, the acylation and sulfonylation of lawsone proceeded at room temperature in moderate to high yields by using dimethylaminopyridine (DMAP) to activate the various acyl chlorides or sulfonyl chlorides (Table 1, entries 6–11). Compounds **1a-1f** and **1k** were known and their structures were identified by comparison of their NMR data with literature data.

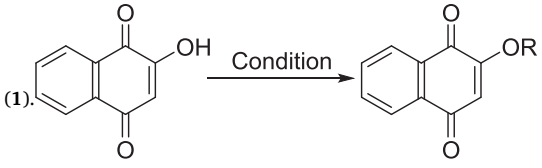
The starting material 6-hydroxy-1,4-naphthoquinone (**2**) for **2a-2j** was prepared by oxidation of 1,6-dihydroxynaphthalene with bis(trifluoroacetoxy)iodobenzene as the oxidizing agent in 97% yield.[29] The alkylation of 6-hydroxy-1,4-naphthoquinone with various alkyl halides was carried out in the presence of Ag_2O to afford **2a-2d** in moderate to good yields (Table 2, entries 1–4). The acylation and sulfonylation of **2** gave the corresponsive products **2e-2j** (Table 2, entries 5–10). The alkylation, acylation, and sulfonation of juglone (**3**) proceeded under similar conditions based on the above reactions and gave products **3a-3h** (Table 3, entries 1–8). Compounds **2a**, **2b**, **2e**, **3a-3d**, and **3h** were known and their structures were confirmed by comparison of their NMR data with those reported in the literature.

Synthesized compounds **1**–**3**, **1a-1k**, **2a-2j**, and **3a-3h** were tested *in vitro* for the cytotoxicity against human tumor cells including oral epidermoid carcinoma (KB) and cervix epithelioid carcinoma (HeLa). The results are summarized in Table 4. The preliminary SAR studies revealed that the prepared 1,4-naphthoquinone analogues possessed significant cytotoxicity against KB and HeLa cells. In addition, some synthesized compounds were tested for topoisomerase I inhibition and the results are summarized in Table 5.

In general, the SAR results for plumbagin and compounds **1**–**3** showed that compounds with a hydroxyl group on the benzene ring exhibited stronger activity than those with a hydroxyl group on the quinone ring. (Table 4, entries 1–4). The presence of methoxy, ethoxy, butoxy, methanesulfonyloxy and toluenesulfonyloxy substituents (compounds **1a**, **1b**, **1d**, **1j**, and **1k**) at C-2 of 1,4-naphthoquinone showed great increase in cytotoxicities against cancer cell lines (Table 4, entries 5, 6, 8, 14, and 15) as compared with lawsone (Table 4, entry 2), while the substitution of propoxy, acetyloxy, benzoyloxy, crotonyloxy, furoyloxy, and thenoyloxy (Table 4, entries 7 and 9–13) at C-2 seemed to be less effective than the former substituents. Among the derivatives of lawsone, compound **1j** with a methanesulfonyloxy group at C-2 exhibited the strongest cytotoxicity, which was comparable to the cytotoxicity of plumbagin (Table 4, entry 1). Synthesized 6-hydroxy-1,4-naphthoquinone (**2**) and commercially available juglone (**3**) (Table 4, entries 3–4) possessed almost the same cytotoxicity as plumbagin. The C-6 substituted 1,4-naphtoquinone derivatives **2a-2j** generally showed slight

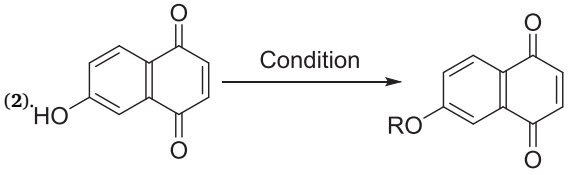
decrease in cytotoxicities (Table 4, entries 16–25) relative to 6-hydroxy-1,4-naphthoquinone (Table 4, entry 3). For C-5 substituted 1,4-naphtoquinone derivatives, **3a**, **3b**, **3d**, **3e**, **3g**, and **3h** showed slight decrease in cytotoxicities (Table 4, entries 26, 27, 29, 30, 32, and 33) compared with that of juglone (Table 4, entry 4). Compound **3f** with a thenoyloxy substituent at C-5 showed cytotoxicity comparable to

Table 1
The alkylation, acylation, and sulfonylation of lawsone



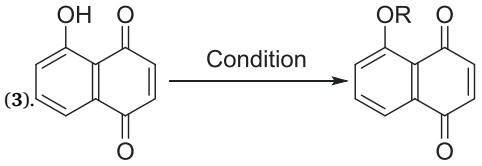
Entry	R	Reagents	Condition	Product	Yield (%)
1	Me	MeOH, cat H_2SO_4	reflux, 5 h	**1a**[23]	99
2	Et	EtOH, cat H_2SO_4	reflux, 5 h	**1b**[23]	96
3	*n*-Pr	*n*-PrOH, cat H_2SO_4	reflux, 8 h	**1c**[24]	75
4	*n*-Bu	*n*-BuOH, cat H_2SO_4	reflux, 8 h	**1d**[24]	90
5	Ac	Ac_2O, cat H_2SO_4	rt, 5 h	**1e**[25]	96
6	Bz	BzCl (2 eq), DMAP (1 eq)	rt, 30 min	**1f**[24,26]	99
7	crotonyl	crotonyl chloride (2 eq), DMAP (1 eq)	rt, 4 h	**1 g**	71
8	2-furoyl	2-furoyl chloride (2 eq), DMAP (1 eq)	rt, 7 h	**1 h**	96
9	2-thenoyl	2-thenoyl chloride (2 eq), DMAP (1 eq)	rt, 5 h	**1i**	81
10	Ms	MsCl (4 eq), DMAP (1 eq)	rt, 3 h	**1j**	52
11	Ts	TsCl (3 eq), DMAP (1 eq)	rt, 2 h	**1 k**[27,28]	68

Table 2
The alkylation, acylation, and sulfonylation of 6-hydroxy-1,4-naphthoquinone



Entry	R	Reagents	Condition	Product	Yield (%)
1	Me	MeI (2 eq), Ag_2O (1 eq)	rt, 24 h	**2a**[30]	79
2	Et	EtBr (4 eq), Ag_2O (1 eq)	rt, 24 h	**2b**[30]	89
3	Bn	BnBr (1.5 eq), Ag_2O (1 eq)	rt, 24 h	**2c**	62
4	allyl	allyl iodide (1.5 eq), Ag_2O (1 eq)	rt, 24 h	**2d**	55
5	Ac	AcCl (2 eq), DMAP (1 eq)	rt, 1 h	**2e**[31]	92
6	Bz	BzCl (2 eq), DMAP (1 eq)	rt, 5 h	**2f**	94
7	2-furoyl	2-furoyl chloride (2 eq), DMAP (1 eq)	rt, 3 h	**2 g**	96
8	2-thenoyl	2-thenoyl chloride (2 eq), DMAP (1 eq)	rt, 3 h	**2 h**	53
9	Ms	MsCl (4 eq), DMAP (1 eq)	rt, 3 h	**2i**	86
10	Ts	TsCl (3 eq), DMAP (1 eq)	rt, 1 h	**2j**	92

Table 3
The alkylation, acylation, and sulfonylation of juglone (**3**).



Entry	R	Reagents	Condition	Product	Yield (%) [a]
1	Me	MeI (4 eq), Ag_2O (1 eq)	rt, 24 h	**3a**[32,33]	46
2	Bn	BnBr (4 eq), Ag_2O (1.5 eq), $CHCl_3$	reflux, 25 h	**3b**[34]	28
3	Ac	AcCl (4 eq), DMAP (1 eq), Et_3N	rt, 1 h	**3c**[35,36]	95
4	Bz	BzBr (4 eq), DMAP (1 eq), Et_3N	rt, 30 min	**3d**[37]	90
5	2-furoyl	2-furoyl chloride (2 eq), DMAP (1 eq), Et_3N	rt, 1 h	**3e**	55
6	2-thenoyl	2-thenoyl chloride (2 eq), DMAP (1 eq), Et_3N	rt, 4 h	**3f**	53
7	Ms	MsCl (4 eq), DMAP (1 eq), Et_3N	rt, 30 min	**3g**	73
8	Ts	TsCl (2 eq), DMAP (1 eq), Et_3N	rt, 20 min	**3h**[26]	35

Table 4
[a]IC_{50} values against human KB and HeLa tumor cells for 1,4-naphthoquinones (type **A**-**C**) and their redox potentials (E°).

Entry	Compound	KB (μM)	HeLa (μM)	Redox potential E° (mV)
1	**Plumbagin**	9.83 ± 2.71	10.20 ± 3.03	−0.346
2	**1**	105.48 ± 21.48	71.26 ± 14.18	−0.431
3	**2**	13.26 ± 2.47	7.06 ± 1.72	−0.192
4	**3**	6.55 ± 0.86	15.73 ± 1.15	−0.204
5	**1a**	17.32 ± 7.60	29.81 ± 4.73	−0.305
6	**1b**	16.91 ± 2.52	23.79 ± 6.82	−0.304
7	**1c**	49.39 ± 11.79	51.61 ± 3.84	−0.320
8	**1d**	26.97 ± 9.68	35.26 ± 7.25	−0.305
9	**1e**	38.76 ± 6.94	62.12 ± 8.88	−0.416
10	**1f**	36.91 ± 8.16	54.95 ± 7.22	−0.368
11	**1 g**	64.20 ± 2.89	37.86 ± 6.11	−0.413
12	**1 h**	53.39 ± 12.38	37.02 ± 11.59	−0.395
13	**1i**	41.54 ± 6.68	35.32 ± 8.86	−0.413
14	**1j**	7.18 ± 0.87	7.61 ± 0.83	−0.146
15	**1 k**	18.76 ± 6.40	12.24 ± 6.55	−0.165
16	**2a**	33.90 ± 1.65	22.69 ± 10.89	−0.196
17	**2b**	21.41 ± 4.25	25.12 ± 4.80	−0.197
18	**2c**	26.18 ± 6.02	16.84 ± 6.17	−0.207
19	**2d**	10.18 ± 1.77	27.17 ± 10.64	−0.194
20	**2e**	22.11 ± 8.46	27.71 ± 8.05	−0.180
21	**2f**	12.08 ± 2.16	19.15 ± 5.97	−0.174
22	**2 g**	15.81 ± 2.35	17.15 ± 4.47	−0.160
23	**2 h**	18.29 ± 5.24	8.86 ± 5.42	−0.166
24	**2i**	11.58 ± 0.83	17.72 ± 3.13	−0.150
25	**2j**	16.35 ± 1.01	15.11 ± 2.50	−0.154
26	**3a**	23.81 ± 10.36	21.68 ± 9.25	−0.165
27	**3b**	8.48 ± 3.63	13.85 ± 1.78	−0.160
28	**3c**	1.39 ± 1.02	6.48 ± 1.43	−0.208
29	**3d**	6.47 ± 2.95	13.01 ± 1.04	−0.208
30	**3e**	13.42 ± 2.72	12.53 ± 3.24	−0.213
31	**3f**	6.23 ± 2.50	5.21 ± 1.34	−0.212
32	**3 g**	27.12 ± 5.87	23.55 ± 2.22	−0.158
33	**3 h**	10.66 ± 5.73	9.47 ± 2.25	−0.151

[a] IC50 values (the concentration of drug required for 50% inhibition). All values are presented as mean ± SD (n = 3).

Table 5
Screening of DNA topoisomerase I inhibition for 1,4-naphthoquinone derivatives.

Entry	Compound	DNA topoisomerase I*IC_{50} (μM)
1	**3**	8.26
2	**2c**	53.66
3	**2e**	>100
4	**2g**	>100
5	**2h**	>100
6	**2j**	>100
7	**3a**	48.00
8	**3d**	90.56
9	**3f**	>100
10	**3g**	>100

* The IC50 values (the concentration of drug required for 50% inhibition) are means from at least two independent experiments.

juglone (6.23 μM). Notably, compound **3c** with an acetyloxy substituent was more potent than juglone against KB (IC_{50} = 1.39 μM) cells. In previous studies Montenegro et al. reported a juglone derivative 5-Methoxy-1,4-naphthoquinone, which exhibits the promising cytotoxic activity against various cell lines.[38] In current research, juglone still remain potent compound than its 5-Methoxy analogue (**3a**). But, gratifyingly **3c** with an acetyloxy substituent is superior in activity than juglone, this was also one of the active analogue in their study. Furthermore, Estevez-Braunc and Felix Machin group investigate the cytotoxic effect of juglone, lawsone and their synthetic derivatives.[39] We observe the similar effect in respect to lawsone, which exhibit poor activity may be due to its membrane-impenetrable nature. Additionally, there may be possibility of **3c** hydrolysis (including other esters) *in vitro* by cell carboxylesterases, to release the parent naphthoquinones and exhibit the activity,[40,41] but, recently S. Fiorito et al. experimentally confirmed that in the endocellular condition **3c** may not be hydrolysed by carboxylesterases/lipases to release the phenolic naphthoquinones and exhibit the cytotoxic activity.[42] Hence, we assume similar observation in current study that **3c** possess cytotoxic property. [42] The cytotoxicity of **3c** *in vitro* is well discussed in earlier reports,[38,39,41] hence further detailed investigations on activity of **3c** was not conducted in current research. Furthermore, detailed investigation and *in vivo* research is required to define the exact mechanism for activity of the **3c**.

One of the antitumor mechanisms also suggests that quinone compounds inhibit DNA topoisomerase I (topo I) by direct binding to topo I, which limits topo I access to the DNA substrates.[15,43] Some of the synthesized derivatives were tested *in vitro* for DNA topoisomerase I inhibition to further explore the antitumor mechanism. The results are summarized in Table 5. The preliminary studies revealed that hydroxynaphthoquinone analogues **3, 2c, 3a**, and **3d** possessed significant inhibition on DNA topoisomerase I, but there was no consistent relation between their cytotoxicities against human tumor cells and DNA topoisomerase I inhibition. Due to the fact that many quinone compounds exhibit the biological activities by their redox cycling, the substituents on quinones could alter the ability of quinones to accept electrons to form the corresponding radical or anion in their redox cycling.[21] The hydroxynaphthoquinone derivatives were further tested for their redox potentials (Table 4) and their correlation with the antitumor activities was examined. We measured redox potentials (E°, mV) of all compounds at pH 7.2 and studied the correlation of redox potential and logIC_{50} (μM) (Figs. 2–5). From the figures it shows that there is apparent linear regression relationship of type **A** and **B** series (except **2a**,**2d** for KB cell line and **2c** for HeLa cell line). The better correlation of cytotoxicity with their redox potentials of type A, maybe a collective process which include, attachment/position (C2-position of 1,4-napthaquinones)[44–47] and nature substituent (electron withdrawing, donating) to produce active/stable intermediate for activity. Such as lawsone (**1**) with free hydroxyl group exhibit poor activity with more negative redox potential value (IC_{50} (KB) = 105.48 μM, IC_{50} (Hela) = 71.26 μM; redox potential

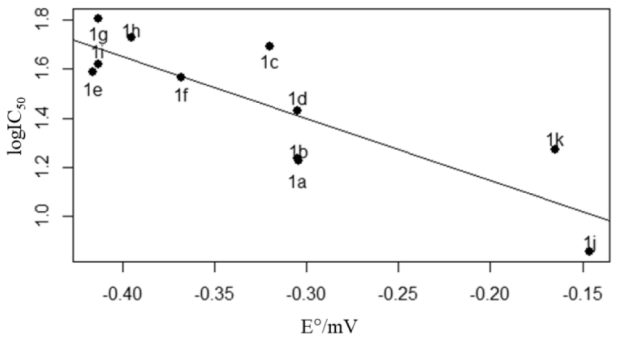


Fig. 2. Semi-log scatter plot of IC_{50} (μM) for KB cell line and redox potential E° (mV) at pH 7.2 by treating with 1,4-naphthoquinone derivatives **1a-k**.

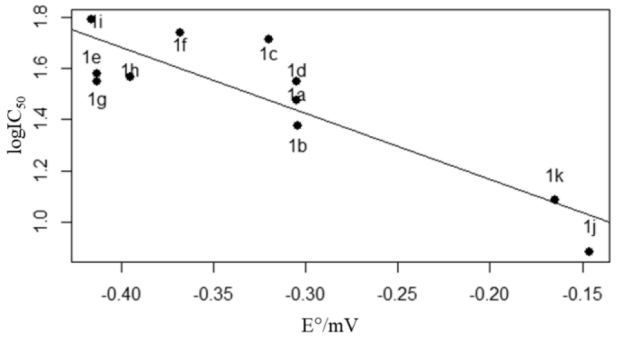


Fig. 3. Semi-log scatter plot of IC_{50} (μM) for HeLa cell line and redox potential E° (mV) at pH 7.2 by treating with 1,4-naphthoquinone derivatives **1a-k**.

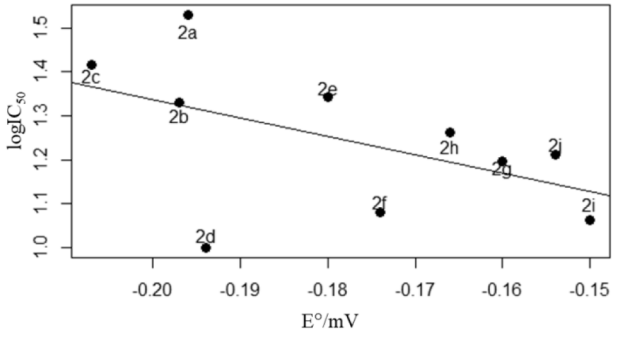


Fig. 4. Semi-log scatter plot of IC_{50} (μM) for KB cell line and redox potential E° (mV) at pH 7.2 by treating with 1,4-naphthoquinone derivatives **2a-j**.

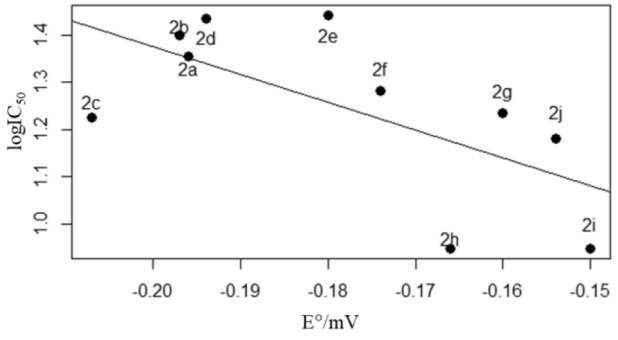


Fig. 5. Semi-log scatter plot of IC_{50} (μM) for HeLa cell line and redox potential E° (mV) at pH 7.2 by treating with 1,4-naphthoquinone derivatives **2a-j**.

E° (mV) = -0.431). Whereas electron donating substituents with more negative redox potential (**1a-d**) possess better activity than lawsone, and strong electron withdrawing group as **1j-k** possess best activity with more positive redox potential, due to their higher reduction ability. [44–47] Overall with few exceptions (Type C, SI, Fig. S1–S2), it is observed that compounds with more positive electrode potential (E°) showed more potent cytotoxicity.

In conclusion, we synthesized a series of 1,4-naphthoquinone derivatives and evaluated their inhibitory activities against KB and HeLa cancer cells as well as DNA topoisomerase I inhibition tests. Generally, type **B** and type **C** compounds showed stronger cytotoxicity than most type **A** compounds, and type **C** compounds show the strongest activity among these 1,4-naphthoquinone derivatives. Compounds **2c, 3, 3a**, and **3d** possessed significant DNA topoisomerase I inhibition between 8.3 and 91 μM. The correlation between the biological activities and redox potentials of type **A** compounds was exhibited by the regression lines of the IC_{50} versus redox potential, which is almost the same as the Epstein–Barr virus inhibition by naphthoquinones. The results indicated that compounds with more positive electrode potentials showed more potent cytotoxicities. However, under complex physiological conditions electrochemical parameters may not give the unambiguous correlation. Further studies on the correlation between redox potential and more biological activities are under investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2021.127976.

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