ISSN 1070-3632, Russian Journal of General Chemistry, 2018, Vol. 88, No. 11, pp. 2388–2393. © Pleiades Publishing, Ltd., 2018.

Synthesis and Cytotoxicity of 1,4-Naphthoquinone Oxime Derivatives[1,2]

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Received April 27, 2018

Abstract—A series of hydroxylated 1,4-naphthoquinone oximes were designed and synthesized. The *in vitro* cytotoxicity of these compounds was evaluated against five human cancer cell lines and human skin fibroblast cell line. Among them, compounds (1*E*,4*E*)-6-{1-[(5-Hydroxypentyl)oxy]-2,2-dimethylbut-3-en-1-yl}-5,8-dimethoxynaphthalene-1,4-dione dioxime and (1*E*,4*E*)-6-{1-[(6-Hydroxyhexyl)oxy]-2,2-dimethylbut-3-en-1-yl}-5,8-dimethoxynaphthalene-1,4-dione dioxime displayed higher cytotoxicity in three cancer cell lines than the positive drug 5-fluorouracil

Keywords: naphthoquinone, oxime, cytotoxicity, synthesis

DOI: 10.1134/S1070363218110221

1,4-Naphthoquinones, such as lawsone, shikonin, juglone, phthiocol, lapachol, and plumbagin, are naturally occurring and have received significant attention due to their wide spectrum of biological activities, including antiproliferative antiviral, antibacterial, antitrypanosome, antiplasmodial, antiparasitic, antimalarial, and anti-inflammatory[1–5].

When naphthoquinone carbonyls were converted to oxime groups, *O*-dimethyl shikonin derivatives showed a higher cytotoxic activity against cancer cells but a lower cytotoxicity against normal cells than their parent compounds [6, 7]. As a continuation of our previous research [8], we synthesized a series of 1,4-naphthoquinone oxime derivatives and evaluated their cytotoxic activity.

RESULTS AND DISCUSSION

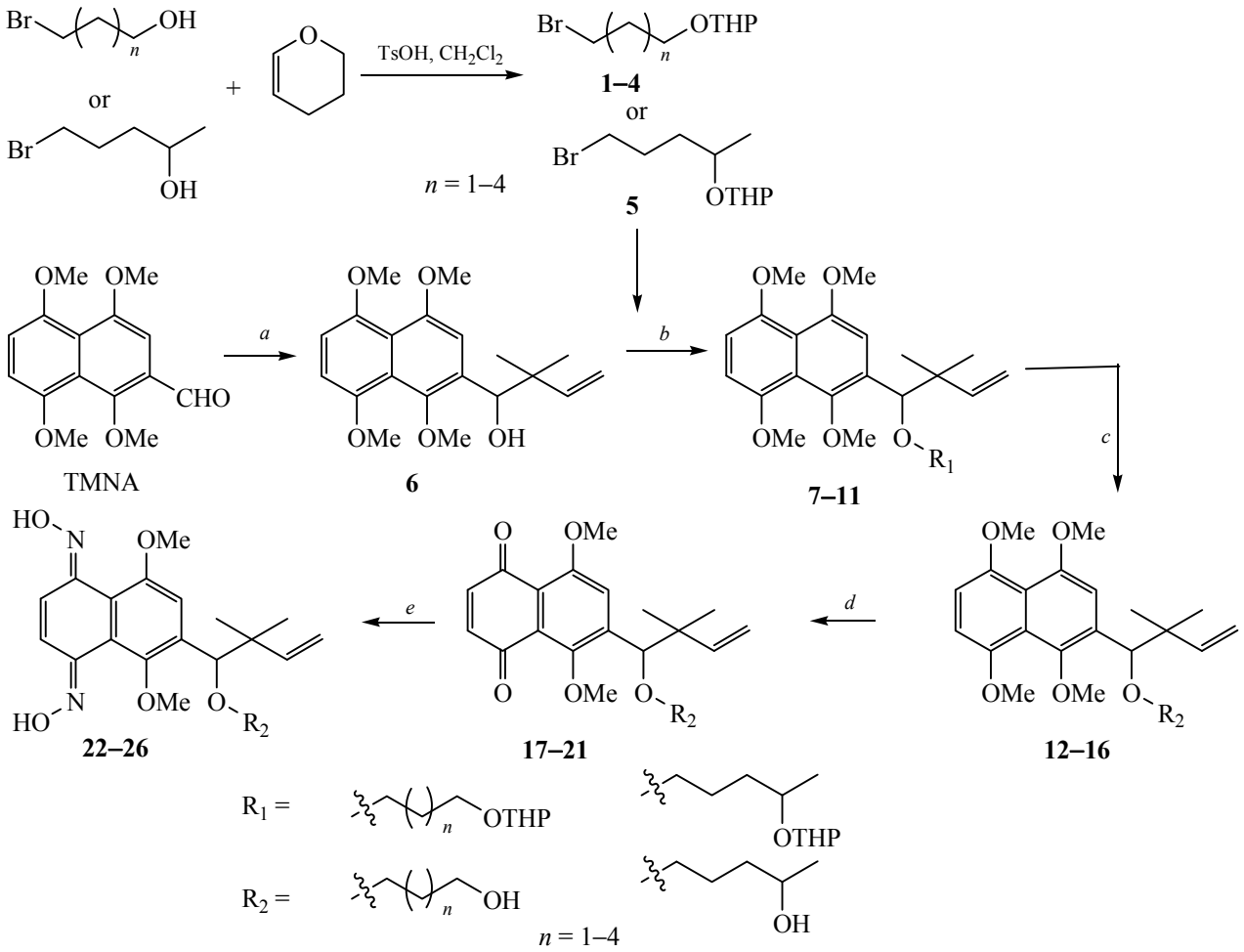
Synthesis. The hydroxyls in compounds **1–5** were protected by 3,4-dihydropyran (DHP) in the presence of *p*-toluenesulfonic acid (TsOH). 1,4,5,8-Tetramethoxy-2-naphthaldehyde (TMNA) was obtained by the procedures previously reported by our research group [9]. Alcohol **8** was prepared by the zinc-mediated γ-regioselective prenylation of TMNA as described in the reference [10]. The nucleophilic substitution of compound **6** with protected alcohols (compounds **1–5**) gives compounds **7–11**, which were then deprotected by treatment of methanolic HCl at room temperature (RT) to afford compounds **12–16.** Subsequent oxidation with cerium(IV) ammonium nitrate (CAN) yields the corresponding 1,4-naphthoquinones **17–21**. The target 1,4-naphthoquinone dioxime derivatives **22–26** were obtained by the oximation of their corresponding 1,4-naphthoquinones in the presence of hydroxylamine hydrochloride and pyridine at 50°C (Scheme 1).

Biological activity. The cytotoxic effects of the synthesized 1,4-naphthoquinone oxime derivatives on colorectal cancer cells (HCT-15 and HCT-116), breast cancer cells (MDA-MB-231, liver cancer cells (BEL-7402), ovarian cancer cells (A2780), and human skin fibroblast (HSF) cell lines were tested in vitro using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The first line drug 5-fluorouracil (5-Fu) was used as positive control. The resulting half-maximal inhibitory concentrations (IC_{50}, μM) are listed in the table.

As seen from the table, compounds **22–26** showed lower cytotoxicity against two colorectal cancer cells but higher cytotoxicity against breast cancer cells than the reference drug 5-Fu. Among these naphthoquinone oxime derivatives, compound **25** exhibited the highest cytotoxicity against BEL-7402 and MDA-MB-231 with IC_{50} values of 6.53 and 8.46 μM, respectively. At the same time, the IC_{50} of compound **25** toward A2780 was found to be 60.59 μM. None of the target compounds displayed cytotoxicity toward the normal HSF cell line (IC_{50}>100 μM).

[1] The text was submitted by the authors in English.
[2] Supporting materials are available from authors.

Scheme 1.



Reagents and conditions: *a*, isopentyl bromide, Zn power, THF, room temperature; *b*, NaH, I_2, DMF, room temperature; *c*, HCl, MeOH, room temperature; *d*, EtOAc/H_2O, CAN, ice bath; *e*, $NH_2OH \cdot HCl$, Py, EtOH, 50°C.

EXPERIMENTAL

Reagents and solvents were obtained from commercial suppliers and purified using standard techniques. Column chromatography was conducted on silica gel (100–200 mesh) from Qingdao Ocean Chemical Factory. The ^1H NMR and ^{13}C NMR spectra were measured on an Agilent 400 spectrometer (400 MHz) using DMSO-d_6 or $CDCl_3$ as solvents, and chemical shifts were measured against internal TMS.

In vitro cytotoxicity of hydroxylated 1,4-naphthoquinone oximes **22**–**26** against five human cancer cell lines

Compound	IC_{50}, μM					
	HCT-15	MDA-MB-231	BEL-7402	HCT-116	A2780	HSF
22	77.59	41.81	31.95	56.38	>100	>100
23	>100	98.56	48.15	>100	>100	>100
24	35.91	24.97	12.92	27.64	85.89	>100
25	30.22	8.46	6.53	23.52	60.59	>100
26	>100	33.63	22.31	48.92	>100	>100
5-Fu	9.89	148.36	37.07	1.73	67.89	>100

Synthesis of compounds 1–5. 3,4-Dihydropyran (DHP, 15 mmol) was added slowly to a stirred solution of bromohydrin (10 mmol) and *p*-toluenesulfonic acid (1 mmol) in dichloromethane (20 mL) on ice bath. After stirring at room temperature overnight, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography to afford **1-5** as a light yellow oil.

2-(3-Bromopropoxy)tetrahydro-2*H*-pyran (1). Yield 94.2%. ^{1}H NMR spectrum, δ, ppm: 1.37–1.55 m (4H), 1.57–1.65 m (1H), 1.70–1.78 m (1H), 2.01–2.10 m (2H), 3.37–3.49 m (4H), 3.73–3.83 m (2H), 4.49–4.55 m (1H). ^{13}C NMR spectrum, δ_C, ppm: 19.4, 25.4, 30.5, 30.6, 32.8, 62.1, 64.8, 98.7.

2-(4-Bromobutoxy)tetrahydro-2*H*-pyran (2). Yield 95.8%. ^{1}H NMR spectrum, δ, ppm: 1.34–1.46 m (4H), 1.54–1.73 m (4H), 1.79–1.89 m (2H), 3.25–2.40 m (4H), 3.59–3.75 m (2H), 4.44 s (1H). ^{13}C NMR spectrum, δ_C, ppm: 19.5, 25.4, 28.3, 29.7, 30.6, 33.6, 62.1, 66.3, 98.6.

2-[(5-Bromopentyl)oxy]tetrahydro-2*H*-pyran (3). Yield 97.3%. ^{1}H NMR spectrum, δ, ppm: 1.42–1.48 m (8H), 1.56–1.64 m (1H), 1.70–1.72 m (1H), 1.73–1.77 m (2H), 3.24–3.43 m (4H), 3.57–3.80 m (2H), 4.45–4.48 m (1H). ^{13}C NMR spectrum, δ_C, ppm: 19.6, 24.9, 25.4, 28.8, 30.6, 32.5, 33.6, 62.2, 67.0, 98.7.

2-[(6-Bromohexyl)oxy]tetrahydro-2*H*-pyran (4). Yield 96.4%. ^{1}H NMR spectrum, δ, ppm: 1.25–1.51 m (10H), 1.54–1.76 m (4H), 3.19–3.30 m (3H), 3.32–3.40 m (1H), 3.56–3.62 m (1H), 3.70–3.74 m (1H), 4.43 t (J = 3.5 Hz, 1H). ^{13}C NMR spectrum, δ_C, ppm: 19.6, 25.4, 25.4, 27.9, 29.5, 30.7, 32.7, 33.8, 62.2, 67.3, 98.8.

2-[(5-Bromopentan-2-yl)oxy]tetrahydro-2*H*-pyran (5). Yield 92.1%. ^{1}H NMR spectrum, δ, ppm: 1.02–1.16 m (3H), 1.37–1.98 m (10H), 3.60–3.85 m (3H), 3.61–3.86 m (2H), 4.46–4.59 m (1H). ^{13}C NMR spectrum, δ_C, ppm: 19.9, 21.5, 25.4, 26.4, 31.1, 34.0, 37.9, 62.7, 73.1, 98.7.

2,2-Dimethyl-1-(1,4,5,8-tetramethoxynaphthalen-2-yl)but-3-en-1-ol (6). Isopentyl bromide (25 mL) was added dropwise to a stirred suspension of zinc powder (30 g, 0.46 mol) in anhydrous THF (100 mL) under nitrogen atmosphere. After stirring for 2 h, zinc powder was removed by centrifugation. A solution of TMNA (2.76 g, 10 mmol) in anhydrous THF (5 mL) was added to the supernatant containing isopentylzinc bromide prepared at the previous step. The solution was stirred at room temperature for 3 h and then quenched with saturated NH_4Cl solution. The mixture was extracted with dichloromethane, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography to afford **6** as a yellow oil (yield 93.7%). ^{1}H NMR spectrum, δ, ppm: 0.97 d (J = 2.5 Hz, 3H), 1.08 d (J = 2.6 Hz, 3H), 2.22–2.32 m (1H), 3.68 s (3H), 3.84–3.90 m (9H), 5.04 d.d (J = 10.1, 7.6 Hz, 2H), 5.11 d (J = 10.9 Hz, 1H), 6.03–6.07 m (1H), 6.74–6.82 m (2H), 6.95 d (J = 2.5 Hz, 1H). ^{13}C NMR spectrum, δ_C, ppm: 21.3, 25.1, 43.2, 57.0, 57.4, 57.7, 62.4, 73.6, 108.0, 108.2, 108.3, 113.6, 120.2, 122.4, 130.7, 145.4, 147.7, 150.3, 151.4, 152.2.

Synthesis of compounds 7–11. NaH (60%, 0.3 g, 7.5 mmol) was added in portion to a stirred solution of **6** (1.04 g, 3 mmol) in anhydrous DMF (20 mL) at 0°C. After stirring for 1 h, a solution of **1–5** (4.5 mmol) dissolved in anhydrous DMF (3 mL) and a catalytic amount of iodine were added to the reaction mixture, which was stirred at 60°C overnight. The reaction mixture was quenched with saturated NH_4Cl solution and then extracted with dichloromethane. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated to give **7–11** as yellow oil and used for the next step without further purification.

Synthesis of compounds 12–16. Hydrochloric acid (1 mL) was added dropwise to a solution of **7–11** (2 mmol) in methanol (10 mL) under ice-bath. After the completion of reaction, the mixture was diluted with dichloromethane, neutralized with saturated sodium bicarbonate. The organic layer was separated, washed with saturated NaCl, dried over Na_2SO_4 and then evaporated under reduced pressure. The residue was purified by flash column chromatography to afford **12–16** as light yellow oil.

3-{[2,2-Dimethyl-1-(1,4,5,8-tetramethoxynaphthalen-2-yl)but-3-en-1-yl]oxy}propan-1-ol (12). Yield 89.6%. ^{1}H NMR spectrum, δ, ppm: 0.96 s (3H), 1.11 s (3H), 1.72–1.85 m (2H), 3.43–3.50 m (2H), 3.70 s (3H), 3.76 t.d (J = 6.3, 4.1 Hz, 2H), 3.86–3.92 m (9H), 4.65 s (1H), 4.91 d.d (J = 17.5, 1.4 Hz, 1H), 5.00 d.d (J = 10.8, 1.4 Hz, 1H), 6.03 d.d (J = 17.5, 10.8 Hz, 1H), 6.79–6.85 m (2H), 6.87 s (1H). ^{13}C NMR spectrum, δ_C, ppm: 22.6, 25.0, 29.7, 31.9, 42.3, 56.9,

57.5, 57.6, 62.1, 62.7, 69.3, 77.3, 82.6, 107.2, 108.2, 108.4, 112.4, 128.9, 145.1, 148.9, 150.2, 151.5, 152.5.

4-{[2,2-Dimethyl-1-(1,4,5,8-tetramethoxynaphthalen-2-yl)but-3-en-1-yl]oxy}butan-1-ol (13). Yield 93.3%. ^{1}H NMR spectrum, δ, ppm: 0.95 d (*J* = 1.9 Hz, 3H), 1.10 d (*J* = 1.9 Hz, 3H), 1.58–1.68 m (4H), 2.38 s (1H), 3.29 q (*J* = 6.6, 5.5 Hz, 2H), 3.61 d (*J* = 5.5 Hz, 2H), 3.69 t (*J* = 1.7 Hz, 3H), 3.83–3.92 m (9H), 4.62 d (*J* = 1.9 Hz, 1H), 4.84 d.d (*J* = 17.6, 2.0 Hz, 1H), 4.94 d.d (*J* = 10.7, 2.0 Hz, 1H), 6.09 d.d (*J* = 17.6, 10.8 Hz, 1H), 6.79 d (*J* = 8.0 Hz, 2H), δ 6.89 s (1H). ^{13}C NMR spectrum, δ_C, ppm: 22.8, 25.0, 26.6, 30.1, 42.4, 56.9, 57.4, 57.6, 62.1, 62.6, 69.3, 82.3, 107.9, 108.0, 108.3, 112.0, 120.2, 122.3, 129.6, 145.2, 148.7, 150.2, 151.5, 152.2.

5-{[2,2-Dimethyl-1-(1,4,5,8-tetramethoxynaphthalen-2-yl)but-3-en-1-yl]oxy}pentan-1-ol (14). Yield 90.5%. ^{1}H NMR spectrum, δ, ppm: 0.94 d (*J* = 1.8 Hz, 3H), 1.09 d (*J* = 1.8 Hz, 3H), 1.36–1.42 m (2H), 1.47–1.57 m (2H), 2.09 s (1H), 3.20–3.26 m (2H), 3.53–3.58 m (2H), 3.67 s (3H), 3.82–3.90 m (9H), 4.57 d (*J* = 1.8 Hz, 1H), 4.79 d (*J* = 17.6 Hz, 1H), 4.90 d (*J* = 10.8 Hz, 1H), 6.11 d.d (*J* = 17.6, 10.8 Hz, 1H), 6.77 d (*J* = 8.0 Hz, 2H), 6.89 s (1H). ^{13}C NMR spectrum, δ_C, ppm: 22.6, 22.8, 25.0, 29.6, 32.4, 42.4, 57.0, 57.4, 57.6, 62.1, 62.7, 69.1, 81.9, 107.9, 108.2, 108.3, 111.6, 120.2, 122.3, 130.1, 145.4, 148.7, 150.2, 151.4, 152.1.

6-{[2,2-Dimethyl-1-(1,4,5,8-tetramethoxynaphthalen-2-yl)but-3-en-1-yl]oxy}hexan-1-ol (15). Yield 94.1%. ^{1}H NMR spectrum, δ, ppm: 0.95 d (*J* = 1.9 Hz, 3H), 1.09 d (*J* = 1.9 Hz, 3H), 1.27–1.42 m (4H), 1.48–1.57 m (4H), 1.85 s (1H), 3.24 (dt, *J* = 7.2, 3.6 Hz, 2H), 3.56 t.d (*J* = 6.7, 1.8 Hz, 2H), 3.69 s (3H), 3.82–3.95 m (9H), 4.58 d (*J* = 1.9 Hz, 1H), 4.80 d (*J* = 17.6 Hz, 1H), 4.91 d (*J* = 10.8 Hz, 1H), 6.12 d.d (*J* = 17.6, 10.8 Hz, 1H), 6.75–6.84 m (2H), 6.90 d (*J* = 2.0 Hz, 1H). ^{13}C NMR spectrum, δ_C, ppm: 22.8, 25.0, 25.6, 26.2, 29.8, 32.7, 42.4, 56.9, 57.5, 57.6, 62.1, 62.8, 69.2, 81.9, 107.9, 108.2, 108.3, 111.6, 120.2, 122.3, 130.2, 125.5, 148.7, 150.2, 151.4, 152.1.

5-{[2,2-Dimethyl-1-(1,4,5,8-tetramethoxynaphthalen-2-yl)but-3-en-1-yl]oxy}pentan-2-ol (16). Yield 90.7%. ^{1}H NMR spectrum, δ, ppm: 0.94 s (3H), 1.08 s (3H), 1.12 d (*J* = 6.2 Hz, 3H), 1.46–1.54 m (2H), 1.62–1.66 m (2H), 2.52 s (1H), 3.24–3.29 m (2H), 3.67 s (3H), 3.73–3.79 m (1H), 3.80–3.90 m (9H), 4.60 d (*J* = 4.2 Hz, 1H), 4.81 d.d (*J* = 17.6, 1.6 Hz, 1H), 4.92 d.d (*J* = 10.8, 1.6 Hz, 1H), 6.07 d.d (*J* = 17.6, 10.8 Hz, 1H), 6.73–6.81 m (2H), 6.88 d (*J* = 3.1 Hz, 1H). ^{13}C NMR spectrum, δ_C, ppm: 22.7, 22.8, 23.4, 25.0, 26.4, 36.7, 42.4, 56.9, 57.5, 62.1, 67.3, 67.7, 69.6, 82.3, 108.0, 108.4, 111.9, 120.2, 122.3, 129.7, 145.2, 148.7, 150.2, 151.5, 152.2.

Synthesis of compounds 17–21. A solution of CAN (2.2 mmol) in water (1 mL) was added dropwise to a solution of **12–16** (1 mmol) in ethyl acetate (6 mL) at 0°C. After 10 min, the reaction mixture was diluted with water and extracted with ethyl acetate, washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography to afford **17–21** as yellow oil.

6-[1-(3-Hydroxypropoxy)-2,2-dimethylbut-3-en-1-yl]-5,8-dimethoxynaphthalene-1,4-dione (17). Yield 36.3%. ^{1}H NMR spectrum, δ, ppm: 0.85 s (3H), 1.04 s (3H), 1.72–1.78 m (2H), 2.47 s (1H), 3.31–3.42 m (2H), 3.64–3.71 m (2H), 3.72 s (3H), 3.87 s (3H), 4.52 s (1H), 4.77 d.d (*J* = 17.6, 1.3 Hz, 1H), 4.93 d.d (*J* = 10.8, 1.3 Hz, 1H), 5.90 d.d (*J* = 17.5, 10.8 Hz, 1H), 6.70 d (*J* = 2.1 Hz, 2H), 7.27 s (1H). ^{13}C NMR spectrum, δ_C, ppm: 22.3, 24.7, 32.2, 42.3, 56.5, 61.3, 61.9, 68.5, 81.9, 113.3, 119.1, 120.1, 124.3, 137.8, 138.7, 143.2, 143.6, 152.6, 155.4, 184.4, 184.9.

6-[1-(4-Hydroxybutoxy)-2,2-dimethylbut-3-en-1-yl]-5,8-dimethoxynaphthalene-1,4-dione (18). Yield 32.4%. ^{1}H NMR spectrum, δ, ppm: 0.84 s (3H), 1.04 s (3H), 1.52–1.65 m (4H), 2.37 s (1H), 3.15–3.29 m (2H), 3.50–3.61 m (2H), 3.71 s (3H), 3.85 s (3H), 4.50 s (1H), 4.71 d.d (*J* = 17.6, 1.4 Hz, 1H), 4.90 d.d (*J* = 10.8, 1.4 Hz, 1H), 5.94 d.d (*J* = 17.6, 10.8 Hz, 1H), 6.69 d (*J* = 8.0 Hz, 2H), 7.27 s (1H). ^{13}C NMR spectrum, δ_C, ppm: 22.5, 24.7, 26.4, 29.7, 42.4, 56.5, 61.9, 62.4, 69.8, 81.7, 113.0, 119.4, 120.0, 124.2, 137.8, 138.7, 143.6, 143.7, 152.5, 155.3, 184.5, 185.0.

6-{1-[(5-Hydroxypentyl)oxy]-2,2-dimethylbut-3-en-1-yl}-5,8-dimethoxynaphthalene-1,4-dione (19). Yield 30.8%. ^{1}H NMR spectrum, δ, ppm: 0.85 s (3H), 1.04 s (3H), 1.30–1.40 m (2H), 1.44–1.54 m (4H), 2.06 s (1H), 3.15–3.25 m (2H), 3.55 t (*J* = 6.5 Hz, 2H), 3.72 s (3H), 3.86 s (3H), 4.47 s (1H), 4.71 d.d (*J* = 17.6, 1.4 Hz, 1H), 4.89 d.d (*J* = 10.8, 1.4 Hz, 1H), 5.97 d.d (*J* = 17.6, 10.8 Hz, 1H), 6.70 d (*J* = 8.0 Hz, 2H), 7.28 s (1H). ^{13}C NMR spectrum, δ_C, ppm: 22.5, 22.6, 24.7, 29.5, 32.3, 42.5, 56.5, 61.9, 62.5, 69.8, 81.5, 112.8, 119.5, 120.0, 124.2, 137.8, 138.7, 143.8, 144.0, 152.6, 155.3, 184.5, 185.0.

6-{1-[(6-Hydroxyhexyl)oxy]-2,2-dimethylbut-3-en-1-yl}-5,8-dimethoxynaphthalene-1,4-dione (20). Yield 35.1%. ^{1}H NMR spectrum, δ, ppm: 0.83 s (3H), 1.02 s (3H), 1.22–1.34 m (4H), 1.42–1.52 m (4H), 2.23 s (1H), 3.11–3.21 m (2H), 3.49–3.56 m (2H), 3.70 s (3H), 3.84 s (3H), 4.45 s (1H), 4.69 d.d (*J* = 17.6, 1.4 Hz, 1H), 4.87 d.d (*J* = 10.8, 1.4 Hz, 1H), 5.96 d.d (*J* = 17.6, 10.8 Hz, 1H), 6.68 d (*J* = 8.0 Hz, 2H), 7.26 s (1H). ^{13}C NMR spectrum, δ_C, ppm: 22.5, 24.6, 25.5, 26.1, 29.7, 32.6, 42.5, 56.4, 61.9, 62.5, 69.8, 81.5, 112.7, 119.4, 120.0, 124.2, 137.8, 138.7, 143.8, 144.1, 152.6, 155.3, 184.5, 185.0.

6-{1-[(4-Hydroxypentyl)oxy]-2,2-dimethylbut-3-en-1-yl}-5,8-dimethoxynaphthalene-1,4-dione (21). Yield 37.1%. ^{1}H NMR spectrum, δ, ppm: 0.83 s (3H), 1.03 s (3H), 1.09 d (*J* = 6.2 Hz, 3H), 1.35–1.46 m (2H), 1.50–1.62 m (2H), 2.29 s (1H), 3.15–3.29 m (2H), 3.70 s (3H), 3.72–3.76 m (1H), 3.85 s (3H), 4.49 d (*J* = 4.0 Hz, 1H), 4.71 d.d (*J* = 17.6, 1.4 Hz, 1H), 4.89 d.d (*J* = 10.8, 1.4 Hz, 1H), 5.93 d.d (*J* = 17.6, 10.8 Hz, 1H), 6.68 d (*J* = 8.0 Hz, 2H), 7.28 s (1H). ^{13}C NMR spectrum, δ_C, ppm: 22.5, 23.5, 24.7, 26.0, 26.3, 36.1, 36.4, 42.4, 56.5, 61.9, 67.6, 70.0, 70.2, 81.8, 113.0, 119.4, 120.0, 124.2, 138.7, 143.7, 155.3, 184.4, 184.9.

Synthesis of compounds 22–26. A mixture of 1,4-naphthoquione derivatives (**17–21** 0.5 mmol), hydroxylamine hydrochloride (4.0 mmol), and pyridine (4.0 mmol) in absolute ethanol (10.0 mL) was stirred at 50°C overnight. After cooled to the room temperature, the ethanol was evaporated under reduced pressure and the mixture was diluted with water and extracted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography to afford **22–26** as yellow solid.

(1*E*,4*E*)-6-[1-(3-Hydroxypropoxy)-2,2-dimethylbut-3-en-1-yl]-5,8-dimethoxynaphthalene-1,4-dione dioxime (22). Yield 89.3%. ^{1}H NMR spectrum, δ, ppm: 0.88 s (3H), 0.99 s (3H), 1.63 t (*J* = 6.9 Hz, 2H), 3.19–3.29 m (2H), 3.40–3.46 m (2H), 3.52 s (3H), 3.72 s (3H), 4.32 s (1H), 4.46 s (1H), 4.77 d (*J* = 17.6 Hz, 1H), 4.88 d (*J* = 10.8 Hz, 1H), 5.99 d.d (*J* = 17.6, 10.8 Hz, 1H), 6.91 s (1H), 7.34 d (*J* = 8.0 Hz, 2H), 12.02 s (2H). ^{13}C NMR spectrum, δ_C, ppm: 23.1, 24.6, 33.3, 42.5, 56.5, 58.3, 60.7, 66.4, 81.6, 109.9, 112.4, 112.9, 119.6, 120.1, 123.9, 134.9, 145.2, 147.7, 150.4, 152.9. HRMS: calculated for $C_{21}H_{29}N_2O_6$ 405.2026, found 405.2049 $[M + H]^+$.

(1*E*,4*E*)-6-[1-(4-Hydroxybutoxy)-2,2-dimethylbut-3-en-1-yl]-5,8-dimethoxynaphthalene-1,4-dione dioxime (23). Yield 91.1%. ^{1}H NMR spectrum, δ, ppm: 0.88 s (3H), 1.00 s (3H), 1.47–1.54 m (4H), 3.23 s (2H), 3.37 s (2H), 3.54 s (3H), 3.72 s (3H), 4.33 s (1H), 4.47 s (1H), 4.78–4.86 m (2H), 6.00 d.d (*J* = 17.5, 10.5 Hz, 1H), 6.94 s (1H), 7.37 d (*J* = 8.0 Hz, 2H), 12.01 s (2H). ^{13}C NMR spectrum, δ_C, ppm: 23.0, 24.6, 26.4, 29.9, 42.5, 56.5, 60.7, 61.0, 69.3, 81.6, 112.3, 112.9, 119.6, 119.7, 120.0, 124.0, 135.0, 145.2, 147.7, 148.0, 150.4, 152.9. HRMS: calculated for $C_{22}H_{31}N_2O_6$. 419.2182, found 419.2204 $[M + H]^+$.

(1*E*,4*E*)-6-{1-[(5-Hydroxypentyl)oxy]-2,2-dimethylbut-3-en-1-yl}-5,8-dimethoxynaphthalene-1,4-dione dioxime (24). Yield 93.5%. ^{1}H NMR spectrum, δ, ppm: 0.88 s (3H), 1.00 s (3H), 1.32–1.40 m (4H), 1.44–1.50 m (2H), 3.21 s (2H), 3.34 d (*J* = 5.6 Hz, 2H), 3.53 s (3H), 3.70 s (3H), 4.30 t (*J* = 5.2 Hz, 1H), 4.46 s (1H), 4.76 d (*J* = 17.6 Hz, 1H), 4.88 d (*J* = 10.8 Hz, 1H), 6.00 d.d (*J* = 17.6, 10.8 Hz, 1H), 6.93 s (1H), 7.36 d (*J* = 8.0 Hz, 2H), 12.01 s (2H). ^{13}C NMR spectrum, δ_C, ppm: 22.9, 23.0, 24.6, 29.7, 32.7, 42.5, 56.5, 60.7, 61.1, 69.4, 81.7, 112.3, 112.9, 119.6, 119.7, 120.1, 124.0, 135.0, 145.2, 147.7, 148.0, 150.4, 152.9. HRMS: calculated for $C_{23}H_{33}N_2O_6$ 433.2339, found 433.2358 $[M + H]^+$.

(1*E*,4*E*)-6-{1-[(6-Hydroxyhexyl)oxy]-2,2-dimethylbut-3-en-1-yl}-5,8-dimethoxynaphthalene-1,4-dione dioxime (25). Yield 92.4%. ^{1}H NMR spectrum, δ, ppm: 0.88 s (3H), 0.99 s (3H), 1.18–1.39 m (6H), 1.42–1.55 m (2H), 3.21 t (*J* = 6.1 Hz, 2H), 3.32 t (*J* = 6.5 Hz, 2H), 3.52 s (3H), 3.70 s (3H), 4.27 s (1H), 4.46 s (1H), 4.77 d.d (*J* = 17.6, 1.6 Hz, 1H), 4.88 d.d (*J* = 10.8, 1.6 Hz, 1H), 6.00 d.d (*J* = 17.6, 10.8 Hz, 1H), 6.92 s (1H), 7.35 d (*J* = 2.4 Hz, 2H), 12.01 s (2H). ^{13}C NMR spectrum, δ_C, ppm: 23.0, 24.6, 25.7, 26.3, 29.8, 33.0, 42.5, 56.5, 60.7, 61.1, 69.3, 81.6, 112.3, 113.0, 119.6, 119.8, 120.1, 124.0, 134.9, 145.2, 147.7, 148.0, 150.4, 152.9. HRMS: calculated for $C_{23}H_{33}N_2O_6$ 433.2339, found 433.2362 $[M + H]^+$.

(1*E*,4*E*)-6-{1-[(4-Hydroxypentyl)oxy]-2,2-dimethylbut-3-en-1-yl}-5,8-dimethoxynaphthalene-1,4-dione dioxime (26). Yield 91.1%. ^{1}H NMR spectrum, δ, ppm: 0.89 s (3H), 1.00 s (3H), 1.29–1.61 m (4H), 3.23 t (*J* = 7.3 Hz, 2H), 3.36 s (1H), 3.51 s (3H), 3.72 s (3H), 4.30 s (1H), 4.47 s (1H), 4.77 d (*J* = 17.7 Hz, 1H), 4.88 d (*J* = 10.8 Hz, 1H), 6.01 d.d (*J* = 17.7, 10.8 Hz, 1H), 6.94 s (1H), 7.28-7.45 m (2H), 12.01 s (2H). ^{13}C NMR spectrum, δ_C, ppm: 23.0, 24.1,

24.6, 26.3, 36.3, 42.5, 56.5, 60.7, 66.0, 69.6, 81.6, 112.3, 113.0, 119.6, 119.8, 120.1, 124.0, 135.0, 145.2, 147.7, 148.0, 150.4, 152.9. HRMS: calculated for $C_{24}H_{35}N_2O_6$ 447.2495, found 447.2521 $[M + H]^+$.

Cytotoxic activity. Cells were planted in a 96-well plate (5000/well) until 70–80% confluence was achieved. After incubation for 24 h at 37°C, 5% CO_2 atmosphere, cells were treated with serial dilutions of the test compound for 48 h, and control groups were treated with a medium containing DMSO in the same concentration as with the medicated group. The supernatants were removed and replaced by 200 μL of RPMI-1640 medium without serum. After that 20 μL of MTT solution (5 mg/mL) was added to each well, and the cells were incubated for an additional 4 h at 37°C. The MTT-containing medium was removed, and 100 μL of DMSO was added into each well to dissolve the formazan crystals. The optical density (OD) was measured by a Thermo Scientific Multiskan MK3 microplate reader at 570 nm.

ACKNOWLEDGMENTS

The research is supported by the National Natural Science Foundation of China (project nos. 81373274 and 81673281) and Hong Kong Scholar Program (project no. XJ2015032). We are grateful to the Instrumental Analysis Center of Shanghai Jiao Tong University for recording the ^{1}H NMR , ^{13}C NMR and HRMS spectra.

CONFLICT OF INTERESTS

No conflict of interests was declared by the authors.

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