*Regular Article*

# Cytotoxicity of Synthesized 1,4-Naphthoquinone Oxime Derivatives on Selected Human Cancer Cell Lines

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**In an effort to develop potent and selective antitumor agents, a series of 1,4-naphthoquinone oxime derivatives were designed and synthesized. The cytotoxicity of these compounds were evaluated against five human cancer cell lines (colorectal cancer cell: HCT-15, breast cancer cell: MDA-MB-231, liver cancer cell: BEL-7402, colorectal cancer cell: HCT-116 and ovarian cancer cell: A2780) *in vitro*. Among them, compound 14 was found to be the most potent cytotoxic compound against three cell lines (MDA-MB-231, BEL-7402 and A2780) with $IC_{50}$ values of 0.66±0.05, 5.11±0.12 and 8.26±0.22 $\mu$M, respectively. Additionally, the length of the side chains and the position of the substituent may also affect the cytotoxic activity of the naphthoquinone oxime derivatives. In general, compound 14 effectively inhibited breast cancer cell proliferation and may become a promising anticancer agent.**

**Key words** naphthoquinone; oxime; cytotoxicity; anticancer agent

Naphthoquinone moieties are widely distributed in variety of plants, fungi and some animals. They have received significant attention due to their promising pharmaceutical application. In particular, 1,4-naphthoquinones such as lawsone, shikonin, juglone, phthiocol, lapachol and plumbagin are naturally occurring have become the major of popular research owing to their extensive biological activities (Fig. 1), including antibacterial, antitrypanosome, antiviral, antiparasitic, antiplasmodial, antiinflammatory, antiproliferative and antimalarial.[1–5] As proved by our group[6] and Ahn's team,[7] 6-substituted 5,8-dimethoxy-1,4-naphthoquinone (DMNQ) derivatives display a higher inhibitory efficiency on DNA topoisomerase-I and the cytotoxicity against cancer cells compared with the corresponding 2-substituted derivatives due to less steric hindrance on the naphthalene ring.[8]

The main mechanisms of naphthoquinones acting inhibitory activity are ascribed to the generation of reactive oxygen species (ROS) and bioreductive alkylation.[9] Additionally, some other mechanisms including abduction of DNA double strand breaks, DNA insertion and the suppression of some specific enzymes such as topoisomerases have also been reported.[10] Surprisingly, when the carbonyl groups on the naphthoquinone ring were shielded by oxime, *O*-dimethyl shikonin derivatives showed more considerable cytotoxic activity against cancer cells but to a lower cytotoxicity towards normal cells than their parental compounds.[2,11–13] Nevertheless, the mechanism of their significant inhibitory activity was not attributed to bioreductive alkylation and ROS.[13] Especially, a novel shikonin derivative DMAKO-05, displayed more potential antitumor activity and less toxicity compared to 5-fluorouracil (5-FU) *in vitro* towards K562 and HCT-116 with $IC_{50}$ values of 0.7 and 0.6 $\mu$M, respectively.[2,12]

Existing literatures demonstrate that methylation of some compounds bearing naphthazarin ring could improve their antitumor activity.[6,14–17] Herein, a series of 1,4-naphthoquinone oxime derivatives containing methoxyl and different lengths of alkyl were synthesized through the key intermediates 1,5,8-trimethoxy-2-naphthaldehyde (**2**) and 4,5,8-trimethoxy-2-naphthaldehyde (**9**) and thereafter tested for their cytotoxic activity against colorectal cancer cells (HCT-15, HCT-116), breast cancer cells (MDA-MB-231), liver cancer cells (BEL-7402), ovarian cancer cells (A2780) and human skin fibroblasts (HSF) by the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay.

## Results and Discussion

**Chemistry** The general synthetic routes of key intermediates and target compounds were depicted in Charts 1 and 2, respectively. Juglone was used as the raw material to synthesize **2** initially, but the desired compound 5,8-dimethoxynaphthalen-1-yl acetate was not obtained due to acetyl migration.[18] Herein, *p*-methoxyphenol was considered to be used as the same starting material for the synthesis of **2** and **9**. We obtained **2** by methylation of **1** which was prepared from our laboratory.[19]

An aldehyde group was introduced at the *ortho* position of the phenolic hydroxyl group by the Duff reaction, which was followed by a methylation reaction to produce **4**. The diethyl succinate reacted smoothly with **4** by Stobbe condensation

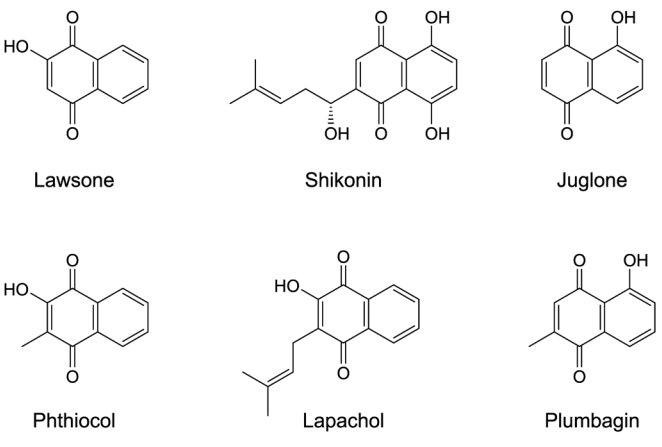


Fig. 1. Chemical Structures of 1,4-Naphthoquinone Derivatives

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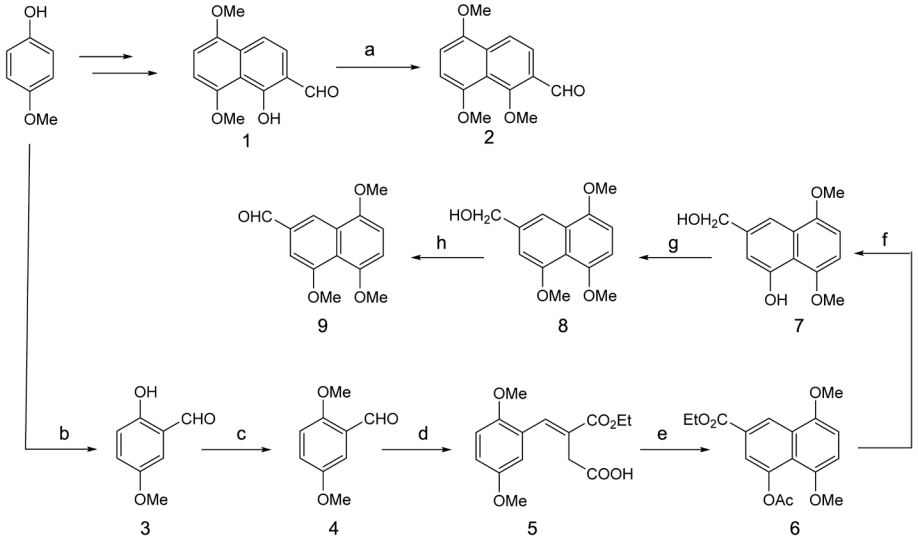
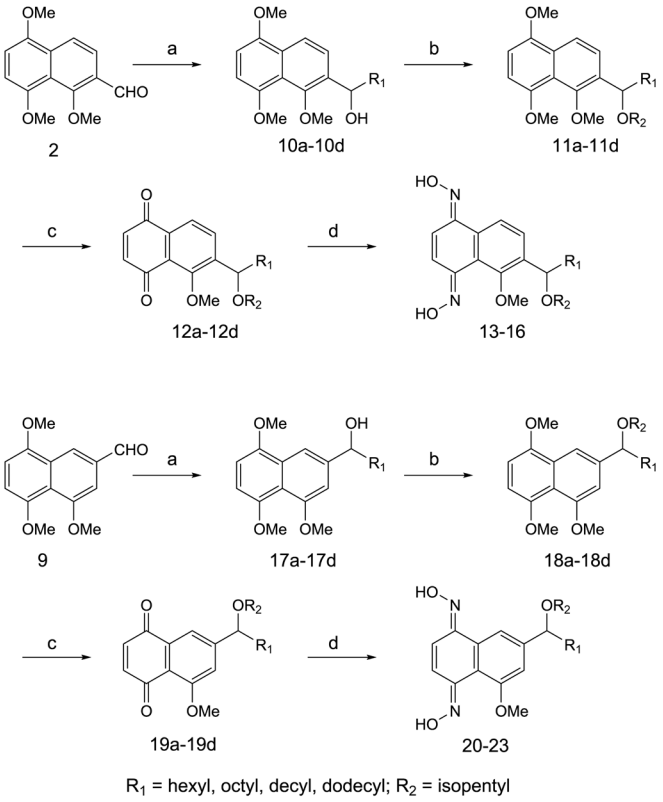


Reagents and conditions: a) MeI, $K_2CO_3$, DMF; b) $TsOH \cdot H_2O$, AcOH, hexamethylenetetramine; c) MeI, $K_2CO_3$, acetone; d) diethyl succinate, NaH, toluene; e) AcONa, AcOH; f) $LiAlH_4$, THF; g) MeI, $K_2CO_3$, DMF; h) $MnO_2$, $CH_2Cl_2$.

Chart 1.



Reagents and conditions: a) $R_1Br$, Mg, THF; b) NaH, $R_2Br$, DMF; c) CAN, EtOAc; d) $NH_2OH \cdot HCl$, Py, EtOH.

Chart 2.

under the alkaline condition[20] and the resulting **6** was reduced to **7** by lithium aluminium hydride, which was methylated to **8** with methyl iodide in good yield. Conversion of **8** into key intermidate **9** was achieved with manganese dioxide.

The Grignard reagent generated by bromoalkane and magnesium was added to the aldehyde **2** and **9** giving **10a**–**10d** and **17a**–**17d**, respectively, which were nucleophilic substituted by bromo isopentane to yield **11a**–**11d** and **18a**–**18d**. And then, they were oxidized by cerium(IV) ammonium nitrate (CAN) to afford the corresponding 1,4-naphthoquinones **12a**–**12d** and **19a**–**19d**. The target compounds 1,4-naphthoquinone dioxime derivatives **13**–**16** and **20**–**23** were gained *via* oximation of their corresponding 1,4-naphthoquinones in the presence of hydroxylamine hydrochloride and pyridine at 50°C.

**Biological Activity** The cytotoxic effects of the target 1,4-naphthoquinone oxime derivatives on five human cancer cell lines were tested *in vitro* using the MTT assay. 5-FU was used as positive control. The concentration (in $\mu$M) of the test compounds which induced $IC_{50}$ is shown in Table 1.

Most of the tested compounds bearing substituents at the *ortho* position of the methoxyl showed higher anti-proliferation activities against five cancer cells than that of substituents at the *meta* position. In particular, 1,4-naphthoquinone oxime derivatives were notably sensitive to MDA-MB-231 cells compared with the other four cancer cell lines. **13**–**15** displayed more superior or comparable cytotoxicity to the positive control (5-FU) against MDA-MB-231, BEL-7402 and A2780 cell lines (Figs. 2–4). In addition, compound **16** was also showed better activity than positive drug against MDA-MB-231. Whereas, compared to 5-FU, the *meta* substituted derivatives displayed almost no cytotoxic activity except **21** showing a moderate activity toward MDA-MB-231 and A2780 with $IC_{50}$ values of $35.01 \pm 2.31$ and $60.36 \pm 2.42\,\mu$M, respectively. Of the note, among the bioactive ones, compound **14** exhibited the highest activity against the human breast cancer cell MDA-MB-231 with an $IC_{50}$ value of $0.66 \pm 0.05\,\mu$M. Meanwhile, the $IC_{50}$ values of **14** against HCT-15, BEL-7402, HCT-116 and A2780 cell lines were found to be $36.40 \pm 2.06$, $5.11 \pm 0.12$, $21.52 \pm 1.41$ and $8.26 \pm 0.22\,\mu$M, separately (Fig. 5). Moreover, none of the target compounds displayed cytotoxicity towards the normal HSF cell line ($IC_{50} > 100\,\mu$M).

Analysis of these data, we can easily conclude that the position of the substituents and the length of the side chains have a significant effect on the cytotoxic activity. The activity of the substituents at the *ortho* position of the methoxy group is obviously better than that at the *meta* position. It is noteworthy that the value of partition coefficient may also affect the

Table 1. The Cytotoxicity of Target Compounds against Five Human Cancer Cell Lines *in Vitro*

| Compound | $c\mathrm{Log}P$[a)] | $IC_{50}$[b)] ($\mu$M) | | | | | |
|---|---|---|---|---|---|---|---|
| | | HCT-15 | MDA-MB-231 | BEL-7402 | HCT-116 | A2780 | HSF |
| **13** | 7.49 | 94.16±2.78 | 7.85±0.21 | 38.93±2.13 | 52.07±3.67 | 68.43±2.33 | >100 |
| **14** | 8.55 | 36.40±2.06 | 0.66±0.05 | 5.11±0.12 | 21.52±1.41 | 8.26±0.22 | >100 |
| **15** | 9.60 | 44.42±3.17 | 9.87±0.08 | 21.08±1.07 | 29.28±1.69 | 33.82±1.71 | >100 |
| **16** | 10.66 | 129.5±5.45 | 11.56±0.33 | 45.98±1.62 | >200 | >200 | >100 |
| **20** | 7.49 | >200 | >200 | 166.7±4.38 | >200 | 168.8±4.37 | >100 |
| **21** | 8.55 | >200 | 35.01±2.31 | 154.5±5.56 | >200 | 60.36±2.42 | >100 |
| **22** | 9.60 | >200 | >200 | >200 | >200 | >200 | >100 |
| **23** | 10.66 | >200 | >200 | >200 | >200 | >200 | >100 |
| 5-FU | −0.58 | 9.89±0.65 | 148.36±4.45 | 37.07±1.81 | 1.73±0.12 | 67.89±2.39 | >100 |

*a*) Calculated log value of partition coefficient by ChemBioDraw 14.0. *b*) $IC_{50}$ values were calculated from at least three independent experiments.

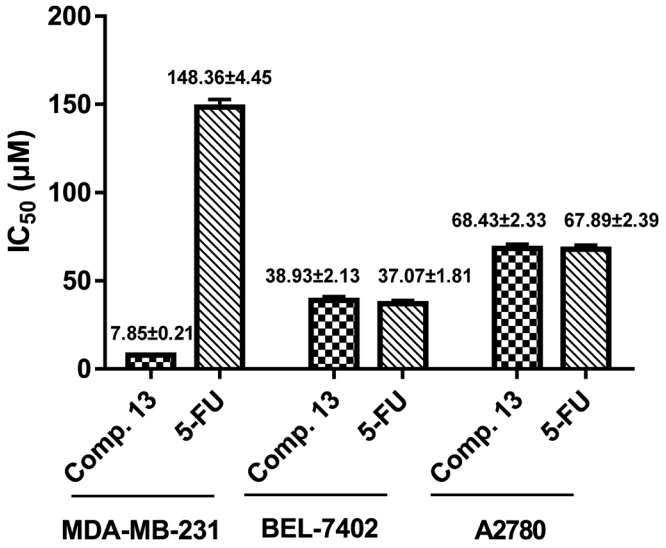



Fig. 2. The Cytotoxicity of Compound **13** against Three Cancer Cell Lines Compared to 5-FU

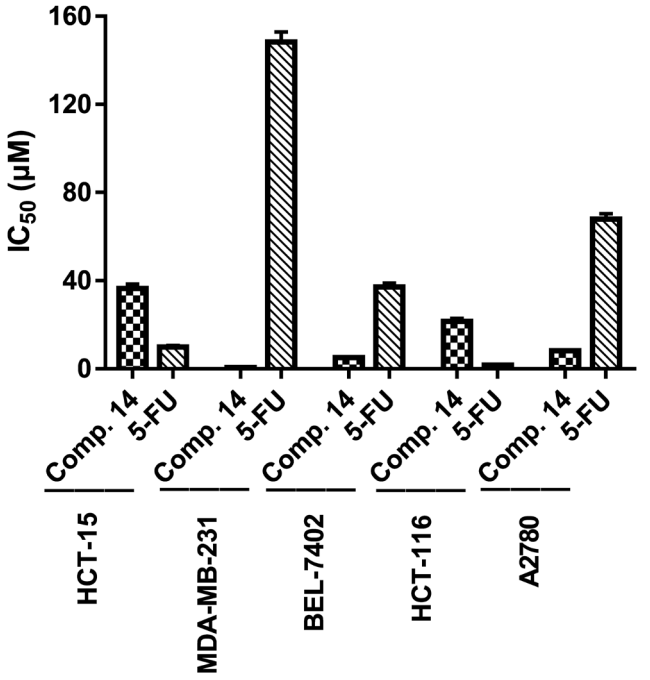



Fig. 3. The Cytotoxicity of Compound **14** against Five Cancer Cell Lines Compared to 5-FU

cytotoxicity. Moreover, the cytotoxic activity was increased by prolongation of the side chain ($R_1$=hexyl, octyl, decyl or dodecyl). The highest activity could be achieved when the length of the side chain was 8 carbon atoms ($R_1$=octyl). However, continuing to extend this side chain could result in a decreased activity. It was suggested that compounds with a suitable length of side chain could enhance their cell membrane permeability and bioavailability, which contribute to their cytotoxic activities.

## Conclusion

In summary, a series of naphthoquinone oxime derivatives (**13**–**16** and **20**–**23**) were designed, synthesized and investigated for their cytotoxic activity against five human cancer cell lines and a normal cell line. Novel anticancer agent such as the most potent compound **14** exhibited a superior cytotoxicity to reference drug against MDA-MB-231, BEL-7402 and A2780 cell lines with $IC_{50}$ values of 0.66±0.05, 5.11±0.12 and 8.26±0.22 $\mu$M, respectively. Meanwhile, all the prepared compounds showed low cytotoxicity towards HSF cells. Furthermore, the cytotoxicity of these compounds was closely associated with the length of the side chains and the position of the substituents. Therefore, these novel 1,4-naphthoquinone oxime derivatives fused with lipophilic side chains may find their pharmaceutical applications after further investigations.

## Experimental

**Chemistry** Reagents and solvents were obtained from commercial suppliers and purified using standard techniques.[21] Column chromatography was conducted on silica gel (100–200 mesh) from Qingdao Ocean Chemical Factory. Melting points (mp) were determined on an SGW X-4 micromelting point apparatus. $^1$H-NMR and $^{13}$C-NMR Spectra were measured on an Agilent 400 spectrometer (400 MHz) and chemical shifts were recorded with tetramethylsilane as the internal standard. Compounds **5** and **7** were prepared according to known procedures.[20]

**1,5,8-Trimethoxy-2-naphthaldehyde (2)** Methyl iodide (0.66 g, 4.7 mmol) was slowly added to a mixture of **1** (0.9 g, 3.9 mmol) and $K_2CO_3$ (2.14 g, 15.6 mmol) in *N*,*N*-dimethylformamide (DMF, 20 mL) under ice bath. The solution was stirred at the room temperature overnight and then diluted with water, extracted with ethyl acetate. The organic layer was washed with brine and then dried over anhydrous $Na_2SO_4$.

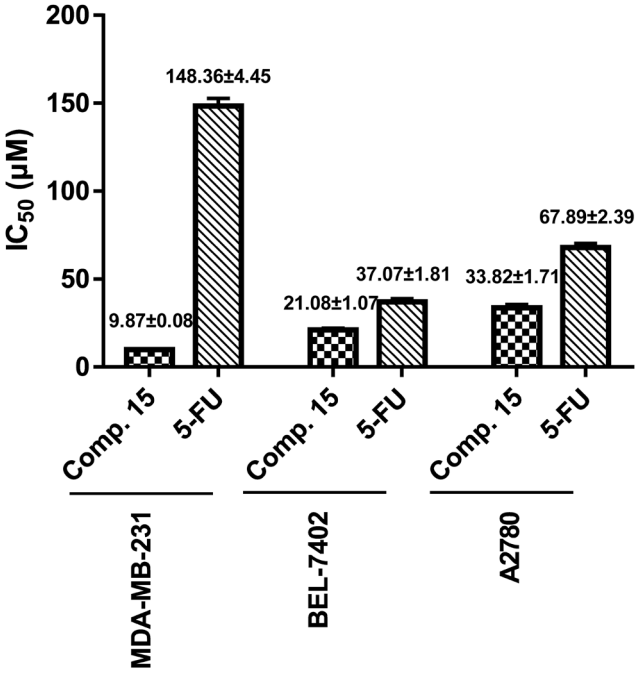



Fig. 4. The Cytotoxicity of Compound **15** against Three Cancer Cell Lines Compared to 5-FU

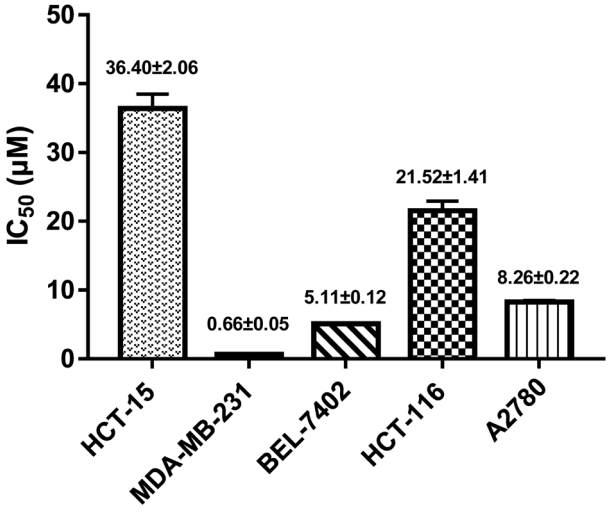



Fig. 5. The Cytotoxicity of Compound **14** against Five Cancer Cell Lines

The solvent was evaporated under reduced pressure and the residue was subjected to flash column chromatography to give **2** as yellow solid. Yield (0.92 g, 96.4%). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 3.95 (s, 3H), 3.97 (s, 3H), 3.98 (s, 3H), 6.84 (d, $J$=8.6 Hz, 1H), 6.89 (d, $J$=8.6 Hz, 1H), 7.84 (d, $J$=9.0 Hz, 1H), 8.07 (dd, $J$=9.0, 0.9 Hz, 1H), 10.60 (d, $J$=0.9 Hz, 1H).

**2,5-Dimethoxybenzaldehyde (4)** *p*-Toluene sulfonic acid monohydrate (5.59 g, 29.4 mmol), hexamethylenetetramine (4.12 g, 29.4 mmol) and *p*-methoxyphenol (1.22 g, 9.8 mmol) were dissolved in acetic acid (30 mL) and the mixture was heated at reflux for 5 h under nitrogen atmosphere. After the completion of the reaction, the solution was cooled to room temperature and poured into ice water, extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ and brine in sequence and then dried over anhydrous $Na_2SO_4$. The solvent was evaporated under reduced pressure to give **3** as colorless oil without further purification which dissolved in acetone (30 mL) containing methyl iodide (1.63 g, 11.5 mmol) and $K_2CO_3$ (3.98 g, 28.8 mmol). The solution was stirred at the room temperature overnight and then diluted with water, extracted with ethyl acetate. The organic layer was washed with brine and then dried over anhydrous $Na_2SO_4$. The solvent was evaporated under reduced pressure and the residue was subjected to flash column chromatography to give **4** as pale green solid. Yield (1.42 g, 87.7%). Mp 49–51°C (lit.[22] 48–50°C). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 3.79 (s, 3H), 3.88 (s, 3H), 6.93 (d, $J$=9.0 Hz, 1H), 7.12 (dd, $J$=9.0, 3.3 Hz, 1H), 7.31 (d, $J$=3.3 Hz, 1H), 10.43 (s, 1H).

**Ethyl 4-Acetoxy-5,8-dimethoxy-2-naphthoate (6)** Sodium acetate (1.23 g, 15 mmol) and **5** (1.47 g, 5 mmol) were dissolved in acetic acid (40 mL) and the mixture was heated at reflux for 3 h under nitrogen atmosphere. After the completion of the reaction, the solution was cooled to room temperature and poured into ice water. The yellow solid was precipitated and then recrystallized from ethanol to give acicular crystals. Yield (1.48 g, 93.1%). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 1.41 (t, $J$=7.1 Hz, 3H), 2.36 (s, 3H), 3.86 (s, 3H), 3.95 (s, 3H), 4.41 (q, $J$=7.1 Hz, 2H), 6.74 (d, $J$=8.6 Hz, 1H), 6.84 (d, $J$=8.6 Hz, 1H), 7.68 (d, $J$=1.7 Hz, 1H), 8.88 (d, $J$=1.7 Hz, 1H). $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$: 14.4, 20.9, 55.8, 56.5, 61.2, 104.8, 108.7, 119.5, 121.8, 123.4, 127.5, 127.7, 146.4, 148.7, 150.5, 165.9, 170.0.

**4,5,8-Trimethoxy-2-naphthaldehyde (9)** Methyl iodide (0.85 g, 6.0 mmol) was slowly added to a mixture of **7** (0.94 g, 4.0 mmol) and $K_2CO_3$ (2.21 g, 16.0 mmol) in DMF (20 mL) under ice bath. The solution was stirred at the room temperature overnight and then diluted with water, extracted with ethyl acetate. The organic layer was washed with brine and then dried over anhydrous $Na_2SO_4$. The solvent was evaporated under reduced pressure and the residue was dissolved in dichloromethane (30 mL) containing manganese dioxide (3.47 g, 39.9 mmol) without further purification. After the completion of the reaction, manganese dioxide was filtered out and the residue was subjected to flash column chromatography to give **9** as yellow solid. Yield (0.88 g, 89.8%). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 3.87 (s, 3H), 3.92 (s, 3H), 3.98 (s, 3H), 6.76 (d, $J$=8.6 Hz, 1H), 6.91 (d, $J$=8.6 Hz, 1H), 7.25 (d, $J$=1.6 Hz, 1H), 8.29 (d, $J$=1.6 Hz, 1H). $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$: 55.8, 56.3, 57.6, 100.9, 105.6, 111.2, 121.2, 123.1, 127.7, 134.0, 150.5, 150.8, 157.7, 192.2.

**General Procedure for the Synthesis of Compounds 10a–10d and 17a–17d** 1-Bromoalkane (10 mmol) was added dropwise to a stirred suspension of magnesium powder (0.25 g, 10.4 mmol) and a catalytic amount of iodine in anhydrous tetrahydrofuran (THF, 10.0 mL) under nitrogen atomosphere. After stirring at 50°C for 2 h, a solution of naphthaldehyde (**2** or **9**, 0.5 g, 2.03 mmol) in anhydrous THF (5.0 mL) was added to the solution of alkylmagnesium bromide prepared above. The solution was stirred at room temperature for 3 h and then quenched with saturated $NH_4Cl$ solution. The mixture was extracted with dichloromethane and washed with brine and then dried over anhydrous $Na_2SO_4$. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography to afford **10a**–**10d** and **17a**–**17d**.

**1-(1,5,8-Trimethoxynaphthalen-2-yl)heptan-1-ol (10a)** Colorless oil; yield 0.63 g (94.0%). $^1$H-NMR (400 MHz,

$CDCl_3$) $\delta$: 0.86 (t, $J$=6.7 Hz, 3H), 1.16–1.39 (m, 8H), 1.71–1. 87 (m, 2H), 2.70–2.90 (m, 1H), 3.79 (s, 3H), 3.89 (s, 1H), 3.91 (s, 3H), 5.22 (dd, $J$=7.9, 5.3 Hz, 1H), 6.65 (d, $J$=8.4 Hz, 1H), 6.72 (d, $J$=8.4 Hz, 1H), 7.51 (d, $J$=8.8 Hz, 1H), 7.99 (d, $J$=8.8 Hz, 1H). $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$: 14.1, 22.6, 26.1, 29.3, 31.8, 38.5, 55.7, 56.6, 63.0, 68.5, 103.7, 106.0, 118.5, 120.5, 124.3, 128.1, 135.1, 149.7, 149.7, 152.6.

**1-(1,5,8-Trimethoxynaphthalen-2-yl)nonan-1-ol (10b)** Colorless oil; yield 0.70 g (95.9%). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 0.86 (t, $J$=6.7 Hz, 3H), 1.19–1.35 (m, 12H), 1.75–1.87 (m, 2H), 2.36–2.39 (m, 1H), 3.82 (s, 3H), 3.93 (s, 3H), 3.94 (s, 3H), 5.23 (dd, $J$=8.0 Hz, $J$=5.4 Hz, 1H), 6.69 (d, $J$=8.4 Hz, 1H), 6.76 (d, $J$=8.4 Hz, 1H), 7.52 (d, $J$=8.8 Hz, 1H), 8.02 (d, $J$=8.7 Hz, 1H).

**1-(1,5,8-Trimethoxynaphthalen-2-yl)undecan-1-ol (10c)** Colorless oil; yield 0.75 g (94.9%). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 0.84–0.87 (m, 3H), 1.21–1.29 (m, 16H), 1.73–1.86 (m, 2H), 2.35–2.45 (m, 1H), 3.82 (s, 3H), 3.92 (s, 3H), 3.94 (s, 3H), 5.22 (dd, $J$=8.0, 5.4 Hz, 1H), 6.69 (d, $J$=8.0 Hz, 1H), 6.76 (d, $J$=8.0 Hz, 1H), 7.52 (d, $J$=8.8 Hz, 1H), 8.02 (d, $J$=8.8 Hz, 1H).

**1-(1,5,8-Trimethoxynaphthalen-2-yl)tridecan-1-ol (10d)** Colorless oil; yield 0.83 g (97.6%). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 0.88 (t, $J$=6.8 Hz, 3H), 1.20–1.36 (m, 20H), 1.74–1.87 (m, 2H), 2.51–2.54 (m, 1H), 3.81 (s, 3H), 3.91 (s, 3H), 3.93 (s, 3H), 5.22 (dd, $J$=8.0, 5.3 Hz, 1H), 6.68 (d, $J$=8.4 Hz, 1H), 6.75 (d, $J$=8.4 Hz, 1H), 7.52 (d, $J$=8.8 Hz, 1H), 8.01 (d, $J$=8.8 Hz, 1H). $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$: 14.1, 22.7, 26.2, 29.4, 29.6, 29.6, 29.6, 29.7, 31.9, 38.4, 55.7, 56.6, 56.6, 63.1, 68.7, 103.7, 103.7, 106.0, 106.1, 118.5, 124.3, 134.9, 149.7, 152.7.

**1-(4,5,8-Trimethoxynaphthalen-2-yl)heptan-1-ol (17a)** Colorless oil; yield 0.64 g (95.5%). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 0.84 (t, $J$=6.8 Hz, 3H), 1.18–1.32 (m, 8H), 1.68–1.80 (m, 2H), 3.87 (s, 3H), 3.88 (s, 3H), 3.91 (s, 3H), 4.69 (dd, $J$=7.5, 5.8 Hz, 1H), 6.65 (d, $J$=8.4 Hz, 1H), 6.69 (d, $J$=8.4 Hz, 1H), 6.83 (d, $J$=1.5 Hz, 1H), 7.65 (d, $J$=1.5 Hz, 1H). $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$: 14.1, 22.6, 25.9, 29.2, 31.8, 38.8, 55.6, 56.3, 57.3, 75.0, 104.3, 104.7, 106.5, 111.4, 117.7, 128.3, 142.8, 149.5, 150.7, 156.9.

**1-(4,5,8-Trimethoxynaphthalen-2-yl)nonan-1-ol (17b)** Colorless oil; yield 0.71 g (97.3%). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 0.85 (t, $J$=6.7 Hz, 3H), 1.19–1.33 (m, 12H), 1.76–1.86 (m, 2H), 3.90 (s, 3H), 3.93 (s, 3H), 3.97 (s, 3H), 4.77 (dd, $J$=7.5, 5.8 Hz, 1H), 6.71 (d, $J$=8.5 Hz, 1H), 6.75 (d, $J$=8.5 Hz, 1H), 6.91 (d, $J$=1.5 Hz, 1H), 7.74 (d, $J$=1.5 Hz, 1H).

**1-(4,5,8-Trimethoxynaphthalen-2-yl)undecan-1-ol (17c)** Colorless oil; yield 0.76 g (96.2%). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 0.85 (t, $J$=6.7 Hz, 3H), 1.17–1.31 (m, 16H), 1.76–1.86 (m, 2H), 3.90 (s, 3H), 3.93 (s, 3H), 3.96 (s, 3H), 4.77 (dd, $J$=7.5, 5.8 Hz, 1H), 6.71 (d, $J$=8.5 Hz, 1H), 6.74 (d, $J$=8.5 Hz, 1H), 6.90 (d, $J$=1.5 Hz, 1H), 7.74 (d, $J$=1.5 Hz, 1H).

**1-(4,5,8-Trimethoxynaphthalen-2-yl)tridecan-1-ol (17d)** Colorless oil; yield 0.82 g (96.5%). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 0.87 (t, $J$=6.8 Hz, 3H), 1.20–1.30 (m, 20H), 1.68–1.84 (m, 2H), 2.48–2.50 (m, 1H), 3.87 (s, 3H), 3.88 (s, 3H), 3.91 (s, 3H), 4.67–4.72 (m, 1H), 6.65 (d, $J$=8.6 Hz, 1H), 6.69 (d, $J$=8.6 Hz, 1H), 6.84 (d, $J$=1.6 Hz, 1H), 7.66 (d, $J$=1.6 Hz, 1H). $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$: 14.1, 22.7, 25.9, 29.4, 29.5, 29.6, 29.6, 29.6, 29.7, 29.7, 31.9, 38.8, 55.6, 56.3, 57.3, 75.0, 104.3, 104.7, 106.5, 111.4, 117.7, 128.3, 142.8, 149.5, 150.7, 156.9.

**General Procedure for the Synthesis of Compounds 11a–11d and 18a–18d** NaH (60%, 0.3 g, 7.5 mmol) was added in portion to a stirred solution of alcohol (**10a**–**10d** or **17a**–**17d**, 1.5 mmol) in anhydrous DMF (15 mL) at 0°C. After stirring for 1 h, a solution of bromo isopentane (0.68g, 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. After cooled to the room temperature, 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 under reduced pressure and the residue was purified by flash column chromatography to afford **11a**–**11d** and **18a**–**18d**.

**2-(1-(Isopentyloxy)heptyl)-1,5,8-trimethoxynaphthalene (11a)** Colorless oil; yield 0.58 g (96.7%). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 0.82–0.90 (m, 9H), 1.25–1.49 (m, 12H), 1.81–1.88 (m, 1H), 3.33 (t, $J$=6.7 Hz, 2H), 3.85 (s, 3H), 3.93 (s, 3H), 3.96 (s, 3H), 4.90 (dd, $J$=8.4 Hz, $J$=4.5 Hz, 1H), 6.70 (d, $J$=8.5 Hz, 1H), 6.77 (d, $J$=8.5 Hz, 1H), 7.57 (d, $J$=8.8 Hz, 1H), 8.09 (d, $J$=8.8 Hz, 1H). $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$: 14,1, 22.6, 22.7, 22.7, 25.0, 26.2, 29.3, 31.8, 38.1, 38.9, 55.7, 56.6, 62.7, 67.3, 75.4, 103.6, 105.8, 118.5, 120.5, 124.5, 128.1, 134.0, 149.7, 149.7, 153.4.

**2-(1-(Isopentyloxy)nonyl)-1,5,8-trimethoxynaphthalene (11b)** Colorless oil; yield 0.62 g (96.0%). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 0.83–0.86 (m, 9H), 1.24–1.27 (m, 16H), 1.69 (d, $J$=3.6 Hz, 1H), 3.29 (t, $J$=6.7 Hz, 2H), 3.82 (s, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 4.86 (dd, $J$=8.5, 4.5 Hz, 1H), 6.70 (d, $J$=8.4 Hz, 1H), 6.77 (d, $J$=8.4 Hz, 1H), 7.54 (d, $J$=8.0 Hz, 1H), 8.05 (d, $J$=8.0 Hz, 1H).

**2-(1-(Isopentyloxy)undecyl)-1,5,8-trimethoxynaphthalene (11c)** Colorless oil; yield 0.65 g (95.9%). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 0.78–0.89 (m, 9H), 1.16–1.26 (m, 16H), 1.44 (q, $J$=6.8 Hz, 2H), 1.64–1.74 (m, 2H), 1.77–1.81 (m, 1H), 3.30 (t, $J$=6.7 Hz, 2H), 3.82 (s, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 4.86 (dd, $J$=8.4, 4.6 Hz, 1H), 6.70 (d, $J$=8.5 Hz, 1H), 6.77 (d, $J$=8.5 Hz, 1H), 7.54 (d, $J$=8.8 Hz, 1H), 8.05 (d, $J$=8.8 Hz, 1H). $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$: 14.1, 22.6, 22.7, 22.7, 25.0, 26.2, 29.3, 29.6, 29.6, 29.6, 29.6, 31.9, 38.1, 38.8, 55.8, 56.6, 62.7, 67.3, 75.4, 103.6, 105.8, 118.4, 120.4, 124.6, 128.1, 134.0, 149.7, 149.7, 153.3.

**2-(1-(Isopentyloxy)tridecyl)-1,5,8-trimethoxynaphthalene (11d)** Colorless oil; yield 0.71 g (97.3%). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 0.80–0.90 (m, 9H), 1.25–1.39 (s, 20H), 1.44 (q, $J$=6.7 Hz, 2H), 1.64–1.75 (m, 2H), 1.78–1.86 (m, 1H), 3.30 (t, $J$=6.7 Hz, 2H), 3.83 (s, 3H), 3.91 (s, 3H), 3.94 (s, 3H), 4.88 (dd, $J$=8.4, 4.5 Hz, 1H), 6.67 (d, $J$=8.5 Hz, 1H), 6.75 (d, $J$=8.5 Hz, 1H), 7.55 (d, $J$=8.8 Hz, 1H), 8.06 (d, $J$=8.8 Hz, 1H). $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$: 14.1, 22.6, 22.7, 22.7, 25.0, 26.2, 29.4, 29.6, 29.6, 29.6, 29.6, 29.7, 29.7, 31.9, 38.1, 38.9, 55.7, 56.5, 62.7, 67.2, 75.4, 103.5, 105.8, 118.5, 120.4, 124.5, 128.1, 133.9, 149.7, 149.7, 153.3.

**3-(1-(Isopentyloxy)heptyl)-1,5,8-trimethoxynaphthalene (18a)** Colorless oil; yield 0.57 g (95.0%). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 0.80–0.88 (m, 9H), 1.16–1.54 (m, 12H), 1.87–1.92 (m, 1H), 3.27–3.38 (m, 2H), 3.90 (s, 3H), 3.92 (s, 3H), 3.98 (s, 3H), 4.30 (dd, $J$=7.7, 5.8 Hz, 1H), 6.70 (d, $J$=8.5 Hz, 1H), 6.70 (d, $J$=8.5 Hz, 1H), 6.94 (d, $J$=1.4 Hz, 1H), 7.73 (d, $J$=1.4 Hz, 1H). $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$: 14,1, 22.5, 22.6, 22.7, 25.0, 26.0, 29.2, 31.8, 38.2, 38.8, 55.6, 56.3, 57.3, 67.1, 82.8, 104.4, 104.7, 106.6, 112.9, 117.9, 128.3, 141.2, 149.5, 150.9, 157.3.

**3-(1-(Isopentyloxy)nonyl)-1,5,8-trimethoxynaphthalene (18b)** Colorless oil; yield 0.63 g (96.9%). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 0.79–0.87 (m, 9H), 1.17–1.33 (m, 14H), 1.43–1.46 (m, 2H), 1.68–1.72 (m, 1H), 3.25–3.35 (m, 2H), 3.90 (s, 3H), 3.94 (s, 3H), 3.97 (s, 3H), 4.28 (dd, $J$=7.6, 5.9 Hz, 1H), 6.72 (d, $J$=8.5 Hz, 1H), 6.75 (d, $J$=8.5 Hz, 1H), 6.91 (d, $J$=1.4 Hz, 1H), 7.69 (d, $J$=1.4 Hz, 1H).

**3-(1-(Isopentyloxy)undecyl)-1,5,8-trimethoxynaphthalene (18c)** Colorless oil; yield 0.66 g (97.3%). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 0.80–0.92 (m, 9H), 1.18–1.38 (m, 16H), 1.45–1.47 (m, 2H), 1.68–1.78 (m, 2H), 1.85–1.93 (m, 1H), 3.27–3.39 (m, 2H), 3.90 (s, 3H), 3.92 (s, 3H), 3.98 (s, 3H), 4.30 (dd, $J$=7.7, 5.9 Hz, 1H), 6.70 (d, $J$=8.5 Hz, 1H), 6.74 (d, $J$=8.5 Hz, 1H), 6.94 (d, $J$=1.5 Hz, 1H) 2, 7 (d, $J$=1.5 Hz, 1H). $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$: 14.1, 22.5, 22.6, 22.7, 22.7, 25.0, 26.0, 29.3, 29.6, 29.6, 29.7, 31.9, 38.2, 38.8 55.6, 56.3, 57.3, 67.1, 82.8, 104.4, 104.7, 106.5, 112.9, 117.9, 128.3, 141.2, 149.5, 150.9, 157.3.

**3-(1-(Isopentyloxy)tridecyl)-1,5,8-trimethoxynaphthalene (18d)** Colorless oil; yield 0.70 g (95.9%). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 0.80–0.91 (m, 9H), 1.18–1.35 (s, 20H), 1.45–1.48 (m, 2H), 1.65–1.75 (m, 2H), 1.89–1.91 (m, 1H), 3.26–3.38 (m, 2H), 3.90 (s, 3H), 3.93 (s, 3H), 3.98 (s, 3H), 4.30 (dd, $J$=7.7, 5.8 Hz, 1H), 6.71 (d, $J$=8.5 Hz, 1H), 6.74 (d, $J$=8.5 Hz, 1H), 6.94 (d, $J$=1.4 Hz, 1H), 7.72 (d, $J$=1.4 Hz, 1H). $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$: 14.1, 22.5, 22.7, 22.7, 25.0, 26.1, 29.4, 29.4, 29.6, 29.6, 29.7, 29.7, 29.7, 31.9, 38.2, 38.9, 55.6, 56.3, 57.3, 67.1, 82.8, 104.4, 104.7, 106.5, 112.9, 117.9, 128.3, 141.2, 149.5, 150.9 157.3.

**General Procedure for the Synthesis of Compounds 12a–12d and 19a–19d** A solution of CAN (1.32 mmol) in water (1 mL) was added dropwise to a solution of trimethoxynaphthalene derivatives (**11a–11d or 18a–18d**, 0.60 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 **12a–12d** and **19a–19d** as yellow oil.

**6-(1-(Isopentyloxy)heptyl)-5-methoxynaphthalene-1,4-dione (12a)** Yellow oil; yield 0.18 g (80.5%). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 0.77–0.83 (m, 9H), 1.14–1.46 (m, 12H), 1.64–1.69 (m, 1H), 3.25 (t, $J$=6.6 Hz, 2H), 3.83 (s, 3H), 4.68 (dd, $J$=8.0, 4.5 Hz, 1H), 6.81 (d, $J$=10.3 Hz, 1H), 6.85 (d, $J$=10.3 Hz, 1H), 7.77 (d, $J$=8.0 Hz, 1H), 7.87 (d, $J$=8.0 Hz, 1H). $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$: 14.0, 22.5, 22.5, 22.5, 22.5, 24.9, 25.8, 29.0, 31.7, 37.6, 38.7, 62.1, 67.8, 75.4, 123.1, 132.6, 132.9, 136.7, 140.2, 146.0, 157.5, 184.5, 184.7.

**6-(1-(Isopentyloxy)nonyl)-5-methoxynaphthalene-1,4-dione (12b)** Yellow oil; yield 0.19 g (79.2%). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 0.81–0.87 (m, 9H), 1.14–1.38 (m, 14H), 1.42–1.46 (m, 2H), 1.67–1.72 (m, 1H), 3.28 (t, $J$=6.7 Hz, 2H), 3.86 (s, 3H), 4.71 (dd, $J$=8.0, 4.4 Hz, 1H), 6.85 (d, $J$=10.3 Hz, 1H), 6.89 (d, $J$=10.3 Hz, 1H), 7.81 (d, $J$=8.0 Hz, 1H), 7.92 (d, $J$=8.0 Hz, 1H). $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$: 14.1, 22.5, 22.6, 22.6, 24.9, 25.8, 29.2, 29.4, 29.5, 31.8, 37.6, 38.7, 62.2, 67.9, 75.5, 123.1, 123.6, 132.7, 132.9, 136.8, 140.3, 146.0, 157.6, 184.6, 184.8.

**6-(1-(Isopentyloxy)undecyl)-5-methoxynaphthalene-1,4-dione (12c)** Yellow oil; yield 0.19 g (73.9%). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 0.79–0.88 (m, 9H), 1.15–1.35 (m, 16H), 1.41–1.44 (m, 2H), 1.56–1.66 (m, 2H), 1.68–1.76 (m, 1H), 3.27 (t, $J$=6.7 Hz, 2H), 3.85 (s, 3H), 4.70 (dd, $J$=8.0, 4.5 Hz, 1H), 6.84 (d, $J$=10.3 Hz, 1H), 6.87 (d, $J$=10.3 Hz, 1H), 7.80 (d, $J$=8.0 Hz, 1H), 7.90 (d, $J$=8.0 Hz, 1H). $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$: 14.1, 22.5, 22.6, 22.6, 24.9, 25.8, 29.3, 29.4, 29.5, 29.5, 29.6, 31.9, 37.6, 38.7, 62.1, 67.9, 75.5, 123.1, 123.5, 132.7, 132.9, 136.8, 140.2, 146.0, 157.6, 184.6, 184.8.

**6-(1-(Isopentyloxy)tridecyl)-5-methoxynaphthalene-1,4-dione (12d)** Yellow oil; yield 0.20 g (73.0%). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 0.75–0.85 (m, 9H), 1.12–1.30 (m, 20H), 1.39–1.45 (m, 2H), 1.52–1.61 (m, 2H), 1.67 (dd, $J$=13.4, 6.7 Hz, 1H), 3.25 (t, $J$=6.6 Hz, 2H), 3.83 (s, 3H), 4.67 (dd, $J$=8.1, 4.4 Hz, 1H), 6.81 (d, $J$=10.2 Hz, 1H), 6.85 (d, $J$=10.2 Hz, 1H), 7.77 (d, $J$=8.0 Hz, 1H), 7.88 (d, $J$=8.0 Hz, 1H). $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$: 14.1, 22.5, 22.5, 22.6, 24.9, 25.8, 29.3, 29.4, 29.5, 29.6, 29.6, 29.6, 29.6, 31.9, 37.6, 38.7, 62.1, 67.8, 75.4, 123.1, 123.5, 132.6, 132.9, 136.7, 140.2, 146.0, 157.5, 184.5, 184.7.

**7-(1-(Isopentyloxy)heptyl)-5-methoxynaphthalene-1,4-dione (19a)** Yellow oil; yield 0.17 g (76.1%). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 0.81–0.88 (m, 9H), 1.21–1.47 (m, 12H), 1.69–1.74 (m, 1H), 3.26–3.34 (m, 2H), 3.99 (s, 3H), 4.25 (dd, $J$=7.9, 5.2 Hz, 1H), 6.83 (d, $J$=8.0 Hz, 1H), 6.80–6.86 (m, 1H), 7.28 (d, $J$=1.5 Hz, 1H), 7.58 (d, $J$=1.5 Hz, 1H). $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$: 14.0, 22.5, 22.5, 22.6, 24.9, 25.7, 29.1, 29.7, 31.7, 38.1, 38.7, 56.5, 67.9, 81.9, 114.9, 117.6, 133.9, 136.1, 141.0, 152.2, 160.1, 184.1, 185.4.

**7-(1-(Isopentyloxy)nonyl)-5-methoxynaphthalene-1,4-dione (19b)** Yellow oil; yield 0.18 g (75.0%). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 0.83–0.88 (m, 9H), 1.20–1.28 (m, 16H), 3.29–3.33 (m, 2H), 4.24–4.28 (m, 3H), 6.83–6.85 (m, 2H), 7.29 (d, $J$=1.5 Hz, 1H), 7.59 (d, $J$=1.5 Hz, 1H).

**7-(1-(Isopentyloxy)undecyl)-5-methoxynaphthalene-1,4-dione (19c)** Yellow oil; yield 0.21 g (81.7%). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 0.79–0.85 (m, 9H), 1.15–1.25 (m, 16H), 1.42–1.45 (m, 2H), 1.52–1.65 (m, 2H), 1.67–1.71 (m, 1H), 3.25–3.32 (m, 2H), 3.97 (s, 3H), 4.24 (dd, $J$=7.9, 5.2 Hz, 1H), 6.79–6.83 (m, 2H), 7.27 (d, $J$=1.4 Hz, 1H), 7.57 (d, $J$=1.4 Hz, 1H). $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$: 14.1, 22.4, 22.5, 22.6, 22.6, 24.9, 25.7, 29.3, 29.4, 29.4, 29.5, 31.8, 38.1, 38.7, 56.4, 67.9, 81.9, 114.9, 117.5, 118.8, 133.9, 136.1, 140.9, 152.2, 160.1, 184.0, 185.3.

**7-(1-(Isopentyloxy)tridecyl)-5-methoxynaphthalene-1,4-dione (19d)** Yellow oil; yield 0.22 g (80.3%). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 0.75–0.82 (m, 9H), 1.10–1.26 (m, 20H), 1.37–1.41 (m, 2H), 1.47–1.64 (m, 2H), 1.65–1.69 (d, $J$=6.6 Hz, 1H), 3.21–3.29 (m, 2H), 3.94 (s, 3H), 4.21 (dd, $J$=7.9, 5.1 Hz, 1H), 6.75–6.80 (m, 2H), 7.25 (d, $J$=1.4 Hz, 1H), 7.53 (d, $J$=1.4 Hz, 1H). $^{13}$C-NMR (100 MHz, $CDCl_3$) $\delta$: 14.1, 22.4, 22.6, 22.6, 24.9, 25.7, 29.3, 29.4, 29.4, 29.5, 29.5, 29.6, 29.6, 31.8, 38.1, 38.6, 56.4, 67.8, 81.8, 114.8, 117.5, 118.7, 133.8, 136.0, 140.9, 152.1, 160.1, 184.0, 185.3.

**General Procedure for the Synthesis of Compounds 13–16 and 20–23** A mixture of 1,4-naphthoquione derivatives (**12a–12d** or **19a–19d**, 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 **13**–**16** and **20**–**23** as yellow solid.

**(1*E*,4*E*)-6-(1-(Isopentyloxy)heptyl)-5-methoxynaphthalene-1,4-dione Dioxime (13)** Yellow solid; yield 0.14 g (70.0%). $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$: 0.76–0.84 (m, 9H), 1.12–1.29 (m, 10H), 1.33–1.37 (m, 2H), 1.62–1.66 (m, 1H), 3.23 (t, $J$=6.5 Hz, 2H), 3.62 (s, 3H), 4.64 (t, $J$=8.1 Hz, 1H), 7.30 (d, $J$=10.7 Hz, 1H), 7.37 (d, $J$=8.4 Hz, 1H), 7.50 (d, $J$=10.7 Hz, 1H), 7.92 (d, $J$=8.4 Hz, 1H), 12.07 (s, 1H), 12.17 (s, 1H). $^{13}$C-NMR (100 MHz, DMSO-$d_6$) $\delta$: 14.3, 22.5, 22.8, 22.9, 24.9, 25.8, 28.9, 31.6, 37.5, 38.8, 61.0, 67.0, 75.1, 118.0, 119.0, 119.8, 122.3, 127.2, 131.1, 138.4, 147.2, 147.5, 155.4.

**(1*E*,4*E*)-6-(1-(Isopentyloxy)nonyl)-5-methoxynaphthalene-1,4-dione Dioxime (14)** Yellow solid; yield 0.16 g (74.4%). $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$: 0.74–0.85 (m, 9H), 1.10–1.48 (m, 16H), 1.62–1.68 (m, 1H), 3.22 (t, $J$=6.4 Hz, 2H), 3.62 (s, 3H), 4.64 (dd, $J$=8.1, 4.6 Hz, 1H), 7.30 (d, $J$=10.7 Hz, 1H), 7.37 (d, $J$=8.4 Hz, 1H), 7.50 (d, $J$=10.7 Hz, 1H), 7.92 (d, $J$=8.4 Hz, 1H), 12.07 (s, 1H), 12.17 (s, 1H). $^{13}$C-NMR (100 MHz, DMSO-$d_6$) $\delta$: 14.4, 22.5, 22.8, 22.9, 24.9, 25.8, 29.1, 29.2, 29.3, 31.7, 37.5, 38.8, 61.0, 67.0, 75.1, 118.0, 119.0, 119.8, 122.3, 127.2, 131.1, 138.4, 147.2, 147.5, 155.4.

**(1*E*,4*E*)-6-(1-(Isopentyloxy)undecyl)-5-methoxynaphthalene-1,4-dione Dioxime (15)** Yellow solid; yield 0.18 g (78.6%). $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$: 0.75–0.87 (m, 9H), 1.13–1.39 (m, 20H), 1.61–1.67 (m, 1H), 3.22 (t, $J$=6.4 Hz, 2H), 3.62 (s, 3H), 4.64 (dd, $J$=8.1, 4.6 Hz, 1H), 7.30 (d, $J$=10.7 Hz, 1H), 7.37 (d, $J$=8.4 Hz, 1H), 7.50 (d, $J$=10.7 Hz, 1H), 7.92 (d, $J$=8.4 Hz, 1H), 12.07 (s, 1H), 12.16 (s, 1H). $^{13}$C-NMR (100 MHz, DMSO-$d_6$) $\delta$: 14.4, 22.5, 22.8, 22.9, 24.9, 25.7, 29.1, 29.2, 29.3, 29.4, 30.2, 31.7, 37.5, 38.8, 61.0, 67.0, 75.1, 118.0, 119.0, 119.8, 122.3, 127.2, 131.1, 138.4, 147.2, 147.5, 155.4

**(1*E*,4*E*)-6-(1-(Isopentyloxy)tridecyl)-5-methoxynaphthalene-1,4-dione Dioxime (16)** Yellow solid; yield 0.20 g (82.3%). $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$: $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$: 0.72–0.79 (m, 9H), 1.09–1.39 (m, 24H), 1.58–1.64 (m, 1H), 3.16–3.22 (m, 2H), 3.58 (s, 3H), 4.62 (dd, $J$=8.1, 4.6 Hz, 1H), 7.26 (d, $J$=10.7 Hz, 1H), 7.33 (d, $J$=8.4 Hz, 1H), 7.47 (d, $J$=10.7 Hz, 1H), 7.89 (d, $J$=8.4 Hz, 1H), 12.05 (s, 1H), 12.15 (s, 1H). $^{13}$C-NMR (100 MHz, DMSO-$d_6$) $\delta$: 14.3, 22.5, 22.8, 22.9, 24.9, 25.7, 29.1, 29.2, 29.3, 29.3, 29.4, 29.4, 29.4, 31.7, 37.5, 38.7, 61.0, 67.0, 75.1, 117.9, 118.9, 119.8, 122.3, 127.1, 131.1, 138.3, 147.2, 147.4, 155.4.

**(1*E*,4*E*)-7-(1-(Isopentyloxy)heptyl)-5-methoxynaphthalene-1,4-dione Dioxime (20)** Yellow solid; yield 0.15 g (75.0%). $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$: 0.76–0.84 (m, 9H), 1.10–1.44 (m, 12H), 1.54–1.57 (m, 1H), 3.22–3.27 (m, 2H), 3.79 (s, 3H), 4.23 (dd, $J$=7.5, 5.5 Hz, 1H), 7.01 (d, $J$=1.6 Hz, 1H), 7.27 (d, $J$=10.7 Hz, 1H), 7.50 (d, $J$=10.7 Hz, 1H), 7.66 (d, $J$=1.6 Hz, 1H), 12.01 (s, 1H), 12.12 (s, 1H). $^{13}$C-NMR (100 MHz, DMSO-$d_6$) $\delta$: 14.3, 22.5, 22.8, 23.0, 24.9, 25.6, 29.0, 31.7, 38.0, 38.8, 56.3, 66.9, 81.5, 110.5, 113.0, 117.3, 117.9, 120.2, 131.8, 144.7, 147.5, 158.0.

**(1*E*,4*E*)-7-(1-(Isopentyloxy)nonyl)-5-methoxynaphthalene-1,4-dione Dioxime (21)** Yellow solid; yield 0.17 g (79.1%). $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$: 0.76–0.84 (m, 9H), 1.15–1.38 (m, 16H), 1.65–1.68 (m, 1H), 3.20–3.27 (m, 2H), 3.79 (s, 3H), 4.23 (t, $J$=6.6 Hz, 1H), 7.02 (d, $J$=1.6 Hz, 1H), 7.27 (d, $J$=10.5 Hz, 1H), 7.51 (d, $J$=10.5 Hz, 1H), 7.65 (d, $J$=1.6 Hz, 1H), 12.01 (s, 1H), 12.13 (s, 1H).

**(1*E*,4*E*)-7-(1-(Isopentyloxy)undecyl)-5-methoxynaphthalene-1,4-dione Dioxime (22)** Yellow solid; yield 0.17 g (74.2%). $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$: 0.70–0.85 (m, 9H), 1.08–1.57 (m, 20H), 1.64–1.66 (m, 1H), 3.18–3.27 (m, 2H), 3.79 (s, 3H), 4.21 (dd, $J$=7.5, 5.4 Hz, 1H), 7.00 (d, $J$=1.6 Hz, 1H), 7.27 (d, $J$=10.7 Hz, 1H), 7.50 (d, $J$=10.7 Hz, 1H), 7.66 (d, $J$=1.6 Hz, 1H), 11.99 (s, 1H), 12.14 (s, 1H). $^{13}$C-NMR (100 MHz, DMSO-$d_6$) $\delta$: 14.4, 22.5, 22.7, 23.0, 24.9, 25.6, 29.1, 29.3, 29.4, 29.4, 31.7, 38.0, 38.8, 56.2, 66.9, 81.5, 110.4, 113.0, 117.3, 117.9, 120.2, 131.8, 144.7, 147.5, 148.1, 158.0.

**(1*E*,4*E*)-7-(1-(Isopentyloxy)tridecyl)-5-methoxynaphthalene-1,4-dione Dioxime (23)** Yellow solid; yield 0.19 g (78.2%). $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$: 0.68–0.78 (m, 9H), 1.03–1.39 (m, 24H), 1.42–1.46 (m, 1H), 3.17–3.23 (m, 2H), 3.75 (s, 3H), 4.17 (t, $J$=6.5 Hz, 1H), 6.97 (d, $J$=1.6 Hz, 1H), 7.23 (d, $J$=10.6 Hz, 1H), 7.45 (d, $J$=10.6 Hz, 1H), 7.61 (d, $J$=1.6 Hz, 1H), 11.97 (s, 1H), 12.13 (s, 1H). $^{13}$C-NMR (100 MHz, DMSO-$d_6$) $\delta$: 14.3, 22.5, 22.7, 22.9, 24.9, 25.6, 29.1, 29.2, 29.3, 29.3, 29.4, 29.4, 29.4, 31.7, 37.9, 38.7, 56.2, 66.8, 81.5, 110.4, 112.9, 117.2, 117.8, 120.1, 131.7, 144.6, 147.4, 148.0, 157.9.

**Cytotoxic Activity** The tested compounds were dissolved in suitable amount of dimethyl sulfoxide (DMSO) prior to the experiment to obtain the known concentration of the solution, and then were diluted to the desired concentrations with culture medium. Cells were planted in 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 the tested compound of serial concentrations for 48 h and control groups were treated with medium containing same concentration of DMSO with the medicated group. The supernatants were removed and replaced by 200 $\mu$L Roswell Park Memorial Institute 1640 (RPMI-1640) medium without serum. After the media was removed and 20 $\mu$L of MTT (5 mg/mL) solution was added to each well and the cells were incubated for an additional 4 h at 37°C. The MTT-containing media was removed and then 100 $\mu$L of DMSO was added into each well for dissolving the formazan crystals. The optical density (OD) was measured by Multiskan MK3 microplate reader (Thermo Scientific, U.S.A.) at 570 nm. Each group was in triplicate samples and each compound was divided into at 6 concentrations. The resulting cytotoxic activities were expressed as $IC_{50}$ values and $IC_{50}$ values were determined by Graphpad Prism 5.

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**Conflict of Interest** The authors declare no conflict of interest.

**Supplementary Materials** The online version of this article contains supplementary materials.

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