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ORIGINAL PAPER

6-Substituted 1,4-naphthoquinone oxime derivatives (I): synthesis and evaluation of their cytotoxic activity

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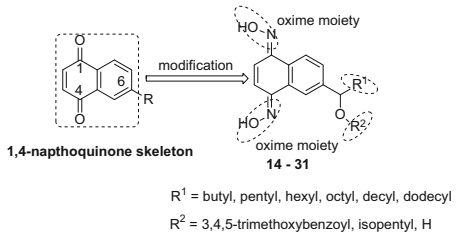
Abstract A series of 6-substituted 1,4-naphthoquinone oxime derivatives were synthesized and evaluated for their in vitro cytotoxicity against four cancer cell lines and one normal cell line. Some compounds exhibited moderate to good cytotoxicity towards cancer cells and meanwhile all the synthesized compounds displayed no apparent cytotoxic activity against normal cells ($IC_{50} > 100$ μM). Among these oxime derivatives, three compounds showed more potent cytotoxicity against human colon cancer cell lines (HCT-15) than adriamycin and 5-fluorouracil, with an IC_{50} value of 2.52, 1.96, and 2.27 μM, respectively. Additionally, structure–activity relationship studies revealed that cytotoxic effects of these oxime derivatives were not only largely dependent upon the size of alkyl chain R^1, but also upon substituents R^2 of the branch chain, indicating that the strong cytotoxicity of these compounds was ascribed to their appropriate lipophilicity. Collectively, this study could provide available strategy for design and synthesis of 6-substituted 1,4-naphthoquinone oxime derivatives as potential anticancer agents.

Graphical abstract



Keywords Naphthoquinone · Cytotoxicity · Anticancer agents · Structure–activity relationship · Aromatization

Introduction

The 1,4-naphthoquinone scaffold is known to confer numerous natural products such as shikonin, lapachol, juglone, and menadione, with diverse biological activities [1–5] including anti-bacterial, antifungal, anticancer, and anti-inflammatory activities. Among the naphthoquione class, 6-substituted 1,4-naphthoquinone derivatives have attracted a great deal of interest from scientific community owing to their excellent antineoplastic activities. Our group and others demonstrated that 6-substituted 5,8-dimethoxy-1,4-naphthoquinone (DMNQ) derivatives exhibited better antitumor activities than the corresponding 2-substituted DMNQ ones due to less steric effects of the quinonoid moiety [6–9]. Meanwhile, Antonini et al. showed that mesylates, tosylates, and *N*-(chloroethyl)carbamates of

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6-methyl-1,4-naphthoquinone derivatives exhibited strong cytotoxic activity against Sarcoma 180 ascites cells [10]. Besides, Gordaliza et al. demonstrated that prenylnaphthoquinones displayed potent cytotoxicity against various cancer cell lines [11]. From the standpoint of pharmacology, the potent antitumor activity of these compounds containing the 1,4-naphthoquinone skeleton was closely associated with the generation of reactive oxygen species (ROS) and bioreductive alkylation [12]. However, the cell damage caused by ROS and alkylation might be nonspecific, indiscriminately leading to the dearth of tumor cells and normal cells.

Interestingly, our recent investigations have shown that *O*-dimethyl shikonin derivatives bearing oxime moiety exhibited more significant cytotoxic activity against cancerous cells as well as lower cytotoxicity towards normal cells than the parent compound [13–17]. Meanwhile, the mechanism of their strong inhibitory actions was demonstrated to be not attributed to bioreductive alkylation and ROS [14, 17]. Specially, shikonin derivative DMAKO-05, a potential candidate compound for colorectal carcinoma, exhibited more excellent anticancer activity against HCT-116 cells both in vitro and in vivo when compared with 5-fluorouracil (5-FU) [16].

In these investigations mentioned above, the modification of shikonin was focused on the 1′-OH at its side chain or the oximation of its carbonyl group. Additionally, taking the 1,4-naphthoquinone oxime moiety with remarkable biological activities into consideration, we suppose that the introduction of various alkyls to the position 6 of 1,4-naphthoquione oxime and modification of the hydroxyl group at the side chain might result in the increase of antitumor activity. Therefore, we herein reported the synthesis of new biologically active 6-substituted 1,4-naphthoquinone oxime derivatives. Furthermore, the preliminary structure–activity relationship was discussed in this article.

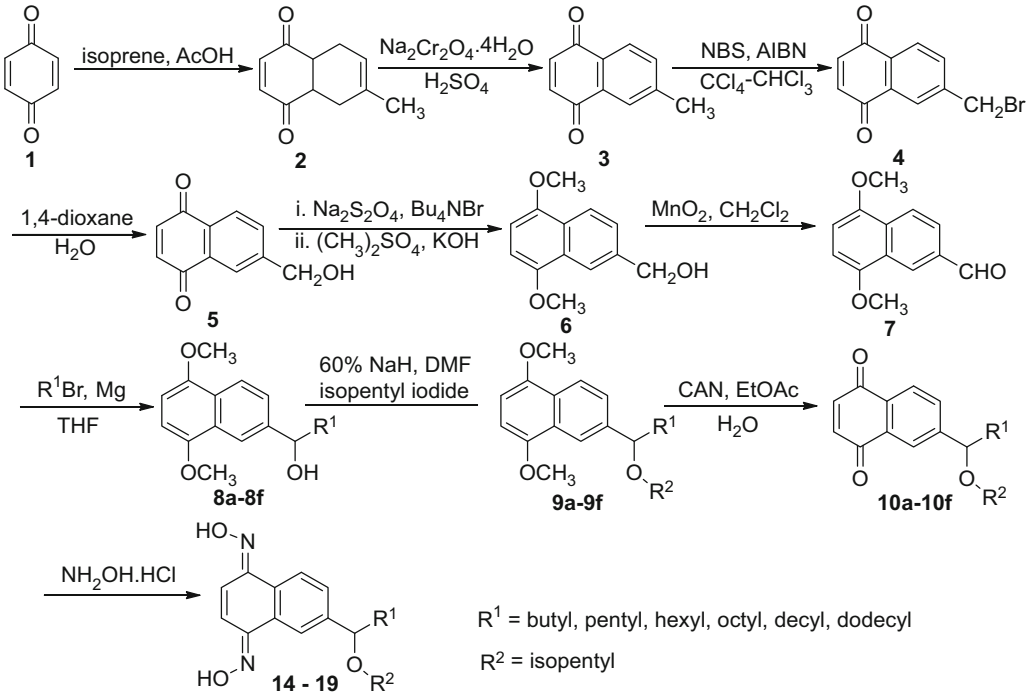
Results and discussion

The general synthetic routes of title compounds were illustrated in Schemes 1 and 2. 6-Methyl-1,4-naphthoquione (**3**) was prepared by the Diels–Alder addition of 1 equivalent of isoprene to 1,4-benzoquinone (**1**), followed by aromatisation of the (±)-6-methyl-γ-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (**2**). However, it was unnecessary to isolate the olefin **2** since extensive decomposition could occur on silica gel column. In addition, many attempts using DDQ [18, 19], active MnO_2 [20], CuBr/LiBr [21], NH_4NO_3/HOAc [22], 35% HNO_3 [23] as oxidative reagents for aromatisation of **2** provided **3** with unsatisfactory yields, but this oxidative reaction could be successfully conducted in the presence of sodium dichromate [24]. Treatment of the intermediate **3** with NBS produced 6-(bromomethy1)-1,4-naphthoquinone (**4**) in 75% yield. A noteworthy observation was that longer reaction time and higher temperature gave rise to 6-(dibromomethyl)naphthalene-1,4-dione as the major by-product. Alcohol **5** was synthesized through hydrolysis of intermediate **4**. The reduction–methylation of **5** in a one-pot strategy and subsequent oxidation of 2-(hydroxymethy1)-5,8-dimethoxynaphthalene (**6**) with active MnO_2 were carried out to afford 2-formyl-5,8-dimethoxynaphthalene (**7**) in 99% isolated yield, whereas another attempt through the straightforward formylation of 1,4-dimethoxynaphthalene for the preparation of **7** via Vilsmeier–Haack reaction was not possible.

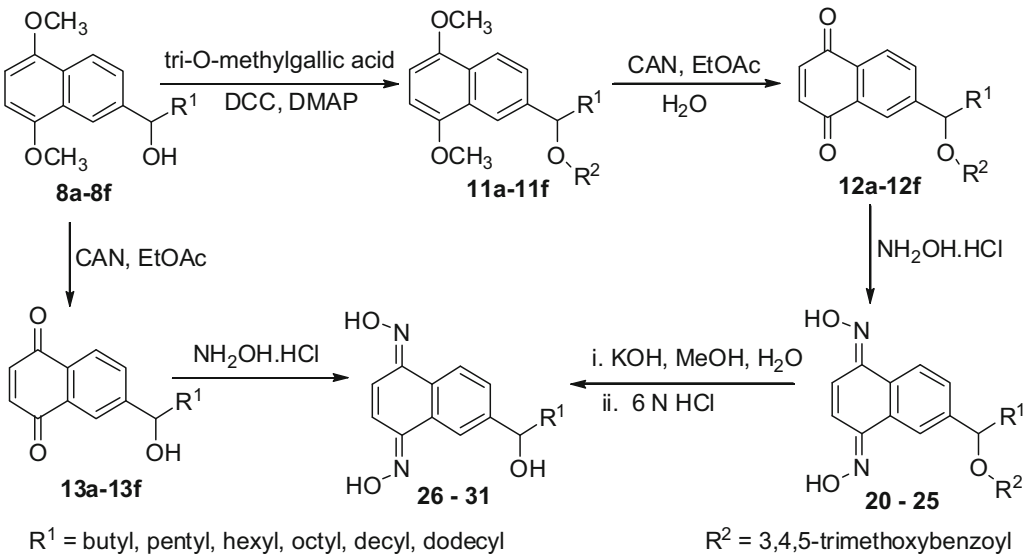
The Grignard addition of alkyl magnesium bromide to aldehyde **7**, followed by nucleophilic substitution reaction gave 6-substituted-1,4-dimethoxynaphthalenes **9a–9f**. Afterward, oxidation of **9a–9f** with cerium(IV) ammonium nitrate (CAN) gave corresponding 6-substituted 1,4-naphthoquinones **10a–10f**. Stirring at 50 °C of compounds **10a–10f** with hydroxylamine hydrochloride [14, 17, 25], respectively, in the presence of pyridine subsequently yielded 1,4-naphthoquinone oxime derivatives **14–19**. Condensation of **8a-8d** with tri-*O*-methylgallic acid afforded **11a–11f** in excellent yield in the presence of DCC and DMAP. Similarly, title compounds **20–25** and **26–31** were provided using the synthetic route as described for compounds **14–19**. In addition, hydrolysis of compounds **20–25** in aqueous alkaline media and successive neutralization with hydrochloric acid provided target compounds **26–31** in relatively good isolated yields.

The cytotoxic activity in vitro of all the synthesized compounds against HCT-15, MGC-803 (gastric carcinoma), Bel7402 (liver cancer), MCF-7 (breast cancer), and HSF (human skin fibroblast) cell lines was evaluated by MTT assay, using adriamycin (ADM) and 5-FU as positive controls. As shown in Table 1, most of oxime derivatives (**14–17**, **20–23**, and **29–31**) displayed more superior or comparative cytotoxicity to the positive reference ADM ($IC_{50} = 2.74$ μM) and 5-FU ($IC_{50} = 8.24$ μM) towards HCT-15 cells and showed moderate cytotoxicity against MGC-803, Bel7402 cell lines, whereas 5-FU showed low cytotoxicity against MGC-803 cells ($IC_{50} > 100$ μM). Among these compounds, the IC_{50} value of the most effective compound **22** against HCT-15 cells was as low as 1.64 μM. Meanwhile, the IC_{50} values of **22** against MGC-803, Bel7402, and MCF-7 cells were found to be 3.28, 4.21, and 6.94 μM, respectively. Importantly, all the prepared compounds displayed no apparent cytotoxicity towards normal cell line HSF ($IC_{50} > 100$ μM), indicating that these oxime derivatives showed good cellular selectivity.

Scheme 1



Scheme 2



Compounds **20**–**25** bearing 3,4,5-trimethoxybenzoyl moiety exhibited much stronger inhibitory action than the corresponding compounds **14**–**19** containing isopentenyl group, which was in good agreement with our previous investigation that introduction of acyl groups at the 1′-OH of shikonin resulted in an increase of its cytotoxic effects [6]. For example, compound **20** showed significant cytotoxicity at lower concentration (IC_{50} = 4.42, 8.23, 9.98, and 16.2 μM), which was superior to the cytotoxicity induced by compound **14** (IC_{50} = 6.71, 15.5, 18.6, and 30.8 μM) in HCT-15 cells, MGC-803 cells, Bel7402 cells, and MCF-7 cells, respectively. Meanwhile, it should be pointed that the

Table 1 In vitro cytotoxicity of target compounds against HCT-15, MGC-803, Bel7402, MCF-7, and HSF cell lines

Compounds	cLogP[a]	IC_{50}^{b}/μM on cell lines				
		HCT-15	MGC-803	Bel-7402	MCF-7	HSF
14	4.69	6.71	15.5	18.6	30.8	>100
15	5.10	4.62	8.43	11.4	19.7	>100
16	5.52	2.52	5.68	9.02	15.3	>100
17	6.35	8.16	12.3	17.8	33.6	>100
18	7.19	20.4	27.1	36.4	62.9	>100
19	8.02	72.8	>100	>100	>100	>100
20	4.50	4.42	8.23	9.98	16.2	>100
21	4.92	2.98	4.45	5.76	10.1	>100
22	5.33	1.64	3.28	4.21	6.94	>100
23	6.17	6.35	9.23	15.3	13.6	>100
24	7.0	11.4	17.8	21.2	29.7	>100
25	7.84	17.3	43.5	39.6	57.2	>100
26	2.75	46.5	56.3	67.4	85.8	>100
27	3.17	30.2	43.6	53.1	59.2	>100
28	3.59	13.4	33.7	32.5	39.4	>100
29	4.42	7.56	14.2	19.7	16.1	>100
30	5.26	2.27	4.21	6.32	8.76	>100
31	6.09	4.96	12.8	8.65	10.5	>100
ADM	−1.34	2.74	1.19	1.32	0.42	4.52
5-FU	–0.90	8.24	>100	21.9	29.5	>100

[a] Indicates that the values of cLogP for all compounds were calculated through ChemDraw 12.0

[b] IC_{50} values were calculated from three independent experiments

cytotoxicities of oxime derivatives seemed to be closely related with their sizes of alkyl chain. The optimal size of alkyl group (R^1) for anticancer activities of oxime derivatives (R^2 = isopentyloxy or 3,4,5-trimethoxybenzoyl) was hexyl because the larger or smaller one would lead to the decline in inhibitory activity. However, the cytotoxicity of some oxime derivatives (R^2 = H) tended to increase with the length of alkyl chain (Table 1, R^1 = butyl, pentyl, hexyl, octyl, or decyl). Obviously, the anticancer activity of these compounds was maximal for compound **30** (R^1 = decyl), which showed IC_{50} values of 2.27 μM against HCT-15 cells.

On the other hand, the cytotoxicity of these oxime derivatives correlated well with their cLogP values (Table 1). For instance, compounds **16**, **22**, and **30** exhibited potent cytotoxicity against HCT-15 cells with cLogP value of 5.52, 5.53, and 5.26, respectively, whereas compounds **18**, **19**, and **25** with higher cLogP value (7.19–8.02) or compounds **26**–**28** with lower cLogP value (2.75–3.59) showed minor anticancer activity. Therefore, cLogP value was commendably responsible for the strong cytotoxicity of oxime derivatives **30** and **31** (R^2 = H), while the corresponding compounds possessing isopentyloxy or 3,4,5-trimethoxybenzoyl group expressed relatively low cytotoxicity against cancer cell lines with higher cLogP values.

Conclusion

In conclusion, eighteen 6-substituted 1,4-naphthoquinone oxime derivatives were synthesized and screened for their cytotoxicity against four cancer cell lines and one normal cells, wherein, compounds **16**, **22**, and **30** exhibited much stronger cytotoxic activity against HCT-15 cells than ADM and 5-FU. Meanwhile, all the prepared compounds showed low cytotoxicity towards HSF cells. Moreover, the cytotoxicity of these compounds was closely associated with their sizes of alkyl chain R^1 and substituents R^2 of branch chain, implying that the appropriate lipophilicity was responsible for their potent cytotoxicity. Thus, the synthesis of 6-substituted 1,4-naphthoquinone oxime derivatives with enhanced antitumor activity and further modification of branch chain (R^1 or R^2) and aromatic ring is suggested in the following work.

Experimental

Reagents and solvents were obtained from commercial suppliers. Column chromatography was conducted on silica gel (100-200 mesh) from Qingdao Ocean Chemical Factory. Melting points were determined on an SGW X-4 micromelting point apparatus. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian MERCURY plus-400 spectrometer with TMS as an internal standard. Mass spectra and HRMS spectra were recorded on a Shimadzu LC–MS-2010EV mass spectrometer and Waters Q-TOF Premier Mass Spectrometer, respectively. Compounds **3**, **4** [24], and **5** [11] were prepared according to known procedures.

5,8-Dimethoxy-2-naphthalenemethanol (**6**, $C_{13}H_{14}O_3$)
To a suspension solution of 2.50 g of **5** (13.3 mmol) and 0.64 g of *N*-butylammonium bromide (2.0 mmol) in 60 cm^3 THF-H_2O (*V*/*V* = 3:1) was added 23.2 g of sodium dithionite (133.0 mmol) in portion. The reaction mixture was stirred at room temperature for 30 min. An aqueous KOH (17.9 g (319.2 mmol) in 20.0 cm^3 H_2O) was added to the reaction mixture at 0 °C. After 20 min, 30.0 cm^3 dimethyl sulfate (319.2 mmol) was added dropwise. The solution was allowed to stir at room temperature for 16 h, which was extracted with dichloromethane and washed with brine, dried, and concentrated to yield yellow oil. The residue was then purified by flash column chromatography to afford compound **6** as white solid. Yield 2.32 g (80%); m.p.: 75–77 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19–8.14 (m, 2H, ArH), 7.49 (dd, J = 8.4, 1.6 Hz, 1H, ArH), 6.70–6.65 (m, 2H, ArH), 4.83 (s, 2H, C$\underline{H}_2$OH), 3.93 (s, 6H, 2× OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.4, 138.4, 126.2, 125.7, 125.1, 122.3, 119.5, 103.6, 103.2, 65.6 (OCH_3), 55.7 (OCH_3) ppm.

5,8-Dimethoxynaphthalene-2-carbaldehyde
(**7**, $C_{13}H_{12}O_3$)
A mixture of 2.18 g of **6** (10.0 mmol) and 13.0 g of activated MnO_2 power (150 mmol) in 40 cm^3 dichloromethane was refluxed for 16 h. After cooling, the resulting precipitate was filtered and evaporation of the filtrate afforded yellow solid. The residue was purified by flash column chromatography to afford compound **7** as light yellow solid. Yield 2.14 g (99%); m.p.: 93–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.13 (s, 1H, CHO), 8.69 (s, 1H, ArH), 8.27 (d, J = 8.4 Hz, 1H, ArH), 7.93 (t, J = 4.0 Hz, 1H, ArH), 6.85 (d, J = 8.4 Hz, 1H, ArH), 6.76 (d, J = 8.4 Hz, 1H, ArH), 3.97 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.6 (CHO), 150.3, 149.3, 133.8, 129.0, 125.5, 123.0, 122.5, 107.0, 104.4, 55.8 (OCH_3), 55.7 (OCH_3) ppm; MS (ESI): *m*/*z* = 275 ([M + H]$^+$).

General procedure for the synthesis of compounds 8a–8f

1-Bromoalkane (14.1 mmol) was added dropwise at 50 °C to a stirred suspension of 0.34 g of magnesium powder (14.3 mmol) and a catalytic amount of iodine in 10.0 cm^3 anhydrous THF. After stirring at 50 °C for 2 h, a solution of 0.61 g of aldehyde **7** (2.82 mmol) in 4.0 cm^3 dry THF was added to the solution of alkylmagnesium bromide prepared above. The solution was stirred for 5 h at room temperature and then quenched with saturated NH_4Cl solution. The mixture was extracted with dichloromethane and washed with brine, dried, and concentrated. The residue was purified by flash column chromatography to afford **8a**–**8f**.

1-(5,8-Dimethoxynaphthalen-2-yl)pentan-1-ol
(**8a**, $C_{17}H_{22}O_3$)
Colorless oil; yield 0.70 g (91%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, J = 8.6 Hz, 1H, ArH), 8.04 (s, 1H, ArH), 7.41 (dd, J = 8.6, 1.6 Hz, 1H, ArH), 6.62–6.57 (m, 2H, ArH), 4.73 (t, J = 6.6 Hz, 1H, C$\underline{H}$OH), 3.87 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 1.81–1.75 (m, 1H, 1/2× (CHC$\underline{H}_2$)), 1.74–1.66 (m, 1H, 1/2× (CHC$\underline{H}_2$)), 1.34–1.20 (m, 4H, CH_2CH_2), 0.78 (t, J = 6.8 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.4, 141.4, 125.1, 124.7, 122.9, 121.2, 117.6, 102.4, 102.1, 74.0, 54.7, 54.6, 37.7, 27.0, 21.6, 13.0 ppm; MS (ESI): *m*/*z* = 289 ([M + H]$^+$).

1-(5,8-Dimethoxynaphthalen-2-yl)hexan-1-ol
(**8b,** $C_{18}H_{24}O_3$)
Colorless oil; yield 0.74 g (90%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, J = 8.6 Hz, 1H, ArH), 8.05 (s, 1H, ArH), 7.42 (dd, J = 8.6, 1.6 Hz, 1H, ArH), 6.63-6.58 (m, 2H, ArH), 4.75 (t, J = 6.6 Hz, 1H, C$\underline{H}$OH), 3.88 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 1.82–1.77 (m, 1H, 1/2× (CHC$\underline{H}_2$)), 1.73–1.67 (m, 1H, 1/2× (CHC$\underline{H}_2$)), 1.39–1.32 (m, 1H, 1/2× CH_2), 1.23–1.18 (m, 5H, 1/2× CH_2 and CH_2CH_2), 0.79 (t, J = 6.8 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.4, 141.4, 125.1, 124.7, 122.9, 121.2, 117.6, 102.4, 102.1, 74.0, 54.7, 54.6, 38.0, 30.7, 24.5, 21.6, 13.0 ppm.

1-(5,8-Dimethoxynaphthalen-2-yl)heptan-1-ol
(**8c**, $C_{19}H_{26}O_3$)
Colorless oil; yield 0.75 g (88%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, J = 8.4 Hz, 1H, ArH), 8.04 (s, 1H, ArH), 7.41 (dd, J = 8.4, 1.6 Hz, 1H, ArH), 6.62–6.57 (m, 2H, ArH), 4.73 (t, J = 6.4 Hz, 1H, C$\underline{H}$OH), 3.87 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 1.81–1.75 (m, 1H, 1/2× (CHC$\underline{H}_2$)), 1.71–1.66 (m, 1H, 1/2× (CHC$\underline{H}_2$)), 1.36–1.29 (m, 1H, 1/2× CH_2), 1.24–1.14 (m, 7H, 1/2× CH_2 and 3× CH_2), 0.77 (t, J = 6.8 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.4, 142.4,

126.1, 125.7, 124.0, 122.2, 118.6, 103.4, 103.0, 75.0, 55.7, 55.6, 39.0, 31.8, 29.2, 25.8, 22.6, 14.1 ppm.

1-(5,8-Dimethoxynaphthalen-2-yl)nonan-1-ol
(**8d**, $C_{21}H_{30}O_3$)
Colorless oil; yield 0.80 g (86%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.08$ (d, $J = 8.4$ Hz, 1H, ArH), 8.02 (s, 1H, ArH), 7.39 (d, $J = 8.4$ Hz, 1H, ArH), 6.61–6.53 (m, 2H, ArH), 4.70 ($J = 6.4$ Hz, 1H, C<u>H</u>OH), 3.84 (s, 6H, 2× OCH_3), 1.75–1.67 (m, 2H, CH(OH)C<u>H</u>$_2$), 1.33-1.29 (m, 1H, 1/2× CH_2), 1.17–1.14 (m, 11H, 1/2× CH_2 and 5× CH_2), 0.77 (t, $J = 6.8$ Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 149.4$, 142.5, 126.1, 125.7, 124.0, 122.2, 118.7, 103.3, 103.0, 74.9, 55.7, 55.6, 39.1, 32.7, 31.9, 29.6, 29.3, 25.9, 22.7, 14.2 ppm.

1-(5,8-Dimethoxynaphthalen-2-yl)undecan-1-ol
(**8e**, $C_{23}H_{34}O_3$)
Colorless oil; yield 0.91 g (90%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.09$ (d, $J = 8.4$ Hz, 1H, ArH), 8.04 (s, 1H, ArH), 7.41 (d, $J = 8.4$ Hz, 1H, ArH), 6.62–6.56 (m, 2H, ArH), 4.72 (t, $J = 6.6$ Hz, 1H, C<u>H</u>OH), 3.86 (s, 6H, 2× OCH_3), 1.76–1.70 (m, 2H, CH(OH)C<u>H</u>$_2$), 1.46-1.41 (m, 2H, CH_2), 1.18–1.15 (m, 14H, 7× CH_2), 0.79 (t, $J = 6.8$ Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 149.4$, 142.5, 126.1, 125.7, 124.0, 122.2, 118.6, 103.4, 103.0, 75.0, 55.7, 55.6, 39.0, 32.8, 31.9, 29.6, 29.6, 29.6, 29.3, 25.7, 22.7, 14.1 ppm.

1-(5,8-Dimethoxynaphthalen-2-yl)tridecan-1-ol
(**8f**, $C_{25}H_{38}O_3$)
Colorless oil; yield 1.0 g (92%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.08$ (d, $J = 8.4$ Hz, 1H, ArH), 8.03 (s, 1H, ArH), 7.40 (d, $J = 8.4$ Hz, 1H, ArH), 6.61–6.54 (m, 2H, ArH), 4.71 (t, $J = 6.6$ Hz, 1H, C<u>H</u>OH), 3.85 (s, 6H, 2× OCH_3), 1.76–1.67 (m, 2H, CH(OH)C<u>H</u>$_2$), 1.47–1.40 (m, 2H, CH_2), 1.17–1.14 (m, 18H, 9× CH_2), 0.80 (t, $J = 6.8$ Hz, 3H) ppm; ^{13}C NMR(100 MHz, $CDCl_3$): $\delta = 149.4$, 142.5, 126.0, 125.7, 124.0, 122.2, 118.6, 103.3, 102.9, 75.0, 55.7, 55.6, 39.0, 32.8, 31.9, 29.7, 29.6, 29.5, 29.4, 25.9, 25.8, 22.7, 14.2 ppm.

General procedure for the synthesis of compounds 9a–9f

NaH (60%; 0.24 g, 6.0 mmol) was added in portion at 0 °C to a stirred solution of alcohol **8** (1.50 mmol) in 10 cm^3 anhydrous DMF. After 45 min, a solution of alkyl iodide (6.0 mmol) in 2.0 cm^3 anhydrous DMF was added to the reaction mixture, which was stirred at 60 °C for 12 h. After cooling, the reaction mixture was quenched with saturated NH_4Cl solution, and then extracted with dichloromethane, washed with brine, dried, and concentrated. The residue was purified by flash column chromatography to afford **9a**–**9f** as colorless oil.

6-[1-(Isopentyloxy)pentyl]-1,4-dimethoxynaphthalene
(**9a**, $C_{22}H_{32}O_3$)
Yield 0.42 g (81%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.12$ (d, $J = 8.6$ Hz, 1H, ArH), 7.98 (s, 1H, ArH), 7.42 (d, $J = 8.6$ Hz, 1H, ArH), 6.64-6.57 (m, 2H, ArH), 4.25 (t, $J = 6.4$ Hz, 1H, C<u>H</u>OH), 3.88 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.27–3.15 (m, 2H, OC<u>H</u>$_2$CH$_2$), 1.85–1.76 (m, 1H, C<u>H</u>$(CH_3)_2$), 1.65–1.60 (m, 1H, 1/2× (CHC<u>H</u>$_2$)), 1.51–1.44 (m, 1H, 1/2× (CHC<u>H</u>$_2$)), 1.39–1.32 (m, 2H, OCH_2C<u>H</u>$_2$), 1.25–1.17 (m, 4H, CH_2CH_2), 0.81–0.71 (m, 9H, 3× CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 148.5$, 148.4, 139.9, 124.9, 124.7, 121.1, 118.8, 102.3, 101.9, 81.8, 66.4, 54.7, 54.6, 37.8, 37.0, 28.6, 27.1, 24.0, 21.6, 21.5, 13.0 ppm; MS (ESI): $m/z = 345$ ($[M + H]^+$).

6-[1-(Isopentyloxy)hexyl]-1,4-dimethoxynaphthalene
(**9b**, $C_{23}H_{34}O_3$)
Yield 0.45 g (83%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.12$ (d, $J = 8.6$ Hz, 1H, ArH), 7.98 (s, 1H, ArH), 7.42 (d, $J = 8.6$ Hz, 1H, ArH), 6.59 (t, $J = 6.0$ Hz, 2H, ArH), 4.25 (t, $J = 6.4$ Hz, 1H, C<u>H</u>OH), 3.88 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.26–3.16 (m, 2H, OCH_2), 1.84–1.77 (m, 1H, C<u>H</u>$(CH_3)_2$), 1.65–1.57 (m, 2H, CHC<u>H</u>$_2$), 1.50–1.44 (m, 1H, 1/2× (OCH_2C<u>H</u>$_2$)), 1.39–1.34 (m, 2H, 1/2× (OCH_2C<u>H</u>$_2$) and 1/2× CH_2), 1.20–1.15 (m, 5H, 1/2× CH_2 and 2× CH_2), 0.78–0.72 (m, 9H, 3× CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.5, 148.4, 141.4, 125.1, 124.7, 122.9, 121.2, 118.8, 102.4, 102.1, 81.8, 67.8, 54.7, 54.6, 38.0, 37.3, 28.6, 27.4, 24.5, 24.0, 21.5, 13.0 ppm; MS (ESI): $m/z = 359$ ($[M + H]^+$).

6-[1-(Isopentyloxy)heptyl]-1,4-dimethoxynaphthalene
(**9c**, $C_{24}H_{36}O_3$)
Yield 0.48 g (86%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.11$ (d, $J = 8.4$ Hz, 1H, ArH), 7.98 (s, 1H, ArH), 7.42 (d, $J = 8.4$ Hz, 1H, ArH), 6.58 (t, $J = 6.4$ Hz, 2H, ArH), 4.25 (t, $J = 6.4$ Hz, 1H, C<u>H</u>OH), 3.87 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.26–3.15 (m, 2H, OCH_2), 1.64–1.58 (m, 2H, C<u>H</u>$(CH_3)_2$ and 1/2× (CHC<u>H</u>$_2$)), 1.38–1.33 (m, 3H, 1/2× (CHC<u>H</u>$_2$) and OCH_2C<u>H</u>$_2$), 1.20–1.16 (m, 8H, 4× CH_2), 0.77–0.72 (m, 9H, 3× CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 149.5$, 149.4, 140.9, 126.0, 125.8, 124.3, 122.2, 119.9, 103.2, 102.8, 82.8, 67.2, 55.7, 55.6, 38.8, 38.4, 31.8, 29.8, 29.3, 26.0, 25.0, 22.7, 22.5, 14.1 ppm.

6-[1-(Isopentyloxy)nonyl]-1,4-dimethoxynaphthalene
(**9d**, $C_{26}H_{40}O_3$)
Yield 0.49 g (82%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.12$ (d, $J = 8.4$ Hz, 1H, ArH), 7.98 (s, 1H, ArH),

7.42 (d, $J = 8.4$ Hz, 1H, ArH), 6.63–6.57 (m, 2H, ArH), 4.25 (t, $J = 6.4$ Hz, 1H, C<u>H</u>OH), 3.87 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.35–3.24 (m, 2H, OCH_2), 1.63–1.58 (m, 2H, C<u>H</u>$(CH_3)_2$ and 1/2× (CHC<u>H</u>$_2$)), 1.39–1.34 (m, 3H, 1/2× (CHC<u>H</u>$_2$) and $OCH_2C\underline{H}_2$), 1.18–1.14 (m, 12H, 6× CH_2), 0.78 (m, 9H, 3× CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 149.5$, 149.4, 140.9, 126.0, 125.8, 124.3, 122.2, 119.9, 103.3, 102.9, 82.8, 67.2, 55.7, 55.6, 38.8, 38.4, 31.9, 29.6, 29.5, 29.3, 26.0, 25.0, 22.7, 22.5, 14.1 ppm.

6-[1-(Isopentyloxy)undecyl]-1,4-dimethoxynaphthalene (**9e**, $C_{28}H_{44}O_3$)
Yield 0.50 g (78%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.12$ (d, $J = 8.4$ Hz, 1H, ArH), 7.98 (s, 1H, ArH), 7.42 (d, $J = 8.4$ Hz, 1H, ArH), 6.64–6.57 (m, 2H, ArH), 4.25 (t, $J = 6.8$ Hz, 1H, CHOH), 3.88 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.36–3.29 (m, 2H, OCH_2), 1.63–1.57 (m, 2H, C<u>H</u>$(CH_3)_2$ and 1/2× (CHC<u>H</u>$_2$)), 1.39–1.34 (m, 3H, 1/2× (CHC<u>H</u>$_2$) and $OCH_2C\underline{H}_2$), 1.18–1.15 (m, 16H, 8× CH_2), 0.83–0.77 (m, 9H, 3× CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 149.5$, 149.4, 140.9, 125.9, 125.7, 124.3, 122.1, 119.9, 103.3, 102.9, 82.8, 67.2, 55.7, 55.6, 38.8, 38.3, 31.9, 29.8, 29.6, 29.5, 29.3, 26.2, 26.0, 25.0, 22.7, 22.7, 14.1 ppm.

6-[1-(Isopentyloxy)tridecyl]-1,4-dimethoxynaphthalene (**9f**, $C_{30}H_{48}O_3$)
Yield 80%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.11$ (d, $J = 8.4$ Hz, 1H, ArH), 7.97 (s, 1H, ArH), 7.41 (d, $J = 8.4$ Hz, 1H, ArH), 6.59–6.54 (m, 2H, ArH), 4.24 (t, $J = 6.4$ Hz, 1H, C<u>H</u>OH), 3.85 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.34–3.23 (m, 2H, OCH_2), 1.63–1.58 (m, 2H, C<u>H</u>$(CH_3)_2$ and 1/2× (CHC<u>H</u>$_2$)), 1.38–1.33 (m, 3H, 1/2× (CHC<u>H</u>$_2$) and $OCH_2C\underline{H}_2$), 1.16–1.13 (m, 20H, 10× CH_2), 0.80–0.74 (m, 9H, 3× CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 149.5$, 149.4, 140.9, 126.0, 125.8, 124.3, 122.2, 119.9, 103.2, 102.8, 82.8, 67.2, 55.7, 55.6, 38.8, 38.4, 32.0, 29.8, 29.7, 29.6, 29.4, 26.0, 25.0, 22.7, 22.5, 14.2 ppm; MS (ESI): $m/z = 457$ ($[M + H]^+$).

General procedure for the synthesis of compounds 11a–11f

To a stirred solution of alcohol **8** (1.0 mmol) and 0.32 g of 3,4,5-trimethoxybenzoic acid (1.5 mmol) in 10.0 cm^3 anhydrous dichloromethane were added 0.31 g of DCC (1.5 mmol) and 61 mg of DMAP (0.5 mmol). After stirring overnight at room temperature, petroleum ether was added to the reaction mixture at 4 °C to facilitate precipitates, and then the solution was filtered and concentrated in vacuo. The residue was purified by flash chromatography to afford **11a–11f** as colorless oil.

1-(5,8-Dimethoxynaphthalen-2-yl)pentyl 3,4,5-trimethoxybenzoate (**11a**, $C_{27}H_{32}O_7$)
Yield 0.44 g (94%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (s, 1H, ArH), 8.12 (d, $J = 8.6$ Hz, 1H, ArH), 7.48 (dd, $J = 8.6$, 1.6 Hz, 1H, ArH), 7.28 (s, 2H, ArH), 6.61 (s, 2H, ArH), 6.06 (t, $J = 7.0$ Hz, 1H, ArC<u>H</u>OCO), 3.87 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.84 (s, 6H, 2× OCH_3), 3.82 (s, 3H, OCH_3), 2.13–2.04 (m, 1H, 1/2× (CHC<u>H</u>$_2$)), 1.98–1.89 (m, 1H, 1/2× (CHC<u>H</u>$_2$)), 1.34–1.24 (m, 4H, CH_2CH_2), 0.81 (t, $J = 7.0$ Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.6$, 151.9, 148.4, 141.1, 137.2, 125.0, 124.9, 124.7, 123.2, 121.3, 118.7, 117.6, 105.9, 102.5, 102.4, 59.9, 55.2, 54.7, 54.6, 35.1, 28.7, 26.7, 21.5, 13.0 ppm; MS (ESI): $m/z = 469$ ($[M + H]^+$).

1-(5,8-Dimethoxynaphthalen-2-yl)hexyl 3,4,5-trimethoxybenzoate (**11b**, $C_{28}H_{34}O_7$)
Yield 0.44 g (92%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.18$ (s, 1H, ArH), 8.12 (d, $J = 8.6$ Hz, 1H, ArH), 7.48 (dd, $J = 8.6$, 1.6 Hz, 1H, ArH), 7.29 (s, 2H, ArH), 6.62 (s, 2H, ArH), 6.06 (t, $J = 7.0$ Hz, 1H, ArC<u>H</u>OCO), 3.87 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.84 (s, 6H, 2× OCH_3), 3.82 (s, 3H, OCH_3), 2.12–2.03 (m, 1H, 1/2× (CHC<u>H</u>$_2$)), 1.97–1.88 (m, 1H, 1/2× (CHC<u>H</u>$_2$)), 1.40–1.33 (m, 1H, 1/2× C<u>H</u>$_2$), 1.28–1.20 (m, 5H, 1/2× C<u>H</u>$_2$ and CH_2CH_2), 0.78 (t, $J = 7.0$ Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.6$, 151.9, 148.4, 141.1, 137.2, 125.0, 124.9, 124.7, 123.2, 121.3, 118.7, 105.9, 102.5, 102.4, 59.9, 55.2, 54.7, 54.6, 35.3, 30.5, 28.7, 24.2, 21.5, 13.0 ppm; MS (ESI): $m/z = 483$ ($[M + H]^+$).

1-(5,8-Dimethoxynaphthalen-2-yl)heptyl 3,4,5-trimethoxybenzoate (**11c**, $C_{29}H_{36}O_7$)
Yield 0.47 g (94%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.18$ (s, 1H, ArH), 8.12 (d, $J = 8.6$ Hz, 1H, ArH), 7.48 (d, $J = 8.6$ Hz, 1H, ArH), 7.28 (s, 2H, ArH), 6.61 (s, 2H, ArH), 6.05 (t, $J = 7.0$ Hz, 1H, ArC<u>H</u>OCO), 3.87 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.84 (s, 6H, 2× OCH_3), 3.82(s, 3H, OCH_3), 2.13–2.04 (m, 1H, 1/2× (CHC<u>H</u>$_2$)), 1.97–1.88 (m, 1H, 1/2× (CHC<u>H</u>$_2$)), 1.38–1.25 (m, 4H, 2× CH_2), 1.21–1.18 (m, 4H, 2× CH_2), 0.77 (t, $J = 7.0$ Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.6$, 151.8, 148.4, 148.3, 141.0, 137.2, 125.0, 124.8, 124.7, 123.2, 121.3, 118.7, 105.8, 102.4, 102.3, 59.9, 55.2, 54.7, 54.6, 35.4, 30.6, 28.0, 24.5, 21.5, 13.0 ppm; MS (ESI): $m/z = 497$ ($[M + H]^+$).

1-(5,8-Dimethoxynaphthalen-2-yl)nonyl 3,4,5-trimethoxybenzoate (**11d**, $C_{31}H_{40}O_7$)
Yield 0.45 g (86%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.18$ (s, 1H, ArH), 8.13 (d, $J = 8.6$ Hz, 1H, ArH), 7.48 (d, $J = 8.6$ Hz, 1H, ArH), 7.18 (s, 1H, ArH), 6.62 (s, 2H, ArH), 6.06 (t, $J = 7.0$ Hz, 1H, ArC<u>H</u>OCO), 3.87 (s, 6H, 2× OCH_3), 3.84 (s, 6H, 2× OCH_3), 3.83 (s, 3H, OCH_3), 2.10–2.03 (m, 1H, 1/2× (CHC<u>H</u>$_2$)), 1.95–1.88 (m,

1H, 1/2× ($CHC\underline{H}_2$)), 1.40–1.34 (m, 1H, 1/2× CH_2), 1.28–1.24 (m, 3H, 1/2× CH_2 and CH_2), 1.18–1.16 (m, 8H, 4× CH_2), 0.78 (t, $J = 7.0$ Hz, 3H, CH_3) ppm; MS (ESI): $m/z = 525$ ($[M + H]^+$).

1-(5,8-Dimethoxynaphthalen-2-yl)undecyl 3,4,5-trimethoxybenzoate (**11e,** $C_{33}H_{44}O_7$)
Yield 0.48 g (87%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.18$ (s, 1H, ArH), 8.13 (d, $J = 8.6$ Hz, 1H, ArH), 7.48 (d, $J = 8.6$ Hz, 1H, ArH), 7.29 (s, 2H, ArH), 6.65–6.59 (m, 2H, ArH), 6.05 (t, $J = 6.8$ Hz, 1H, ArC$\underline{H}$OCO), 3.87 (s, 6H, 2× OCH_3), 3.84 (s, 6H, 2× OCH_3), 3.83 (s, 3H, OCH_3), 2.13–2.05 (m, 1H, 1/2× ($CHC\underline{H}_2$)), 1.97–1.88 (m, 1H, 1/2× ($CHC\underline{H}_2$)), 1.39–1.34 (m, 1H, 1/2× CH_2), 1.28–1.23 (m, 3H, 1/2× CH_2 and CH_2), 1.18–1.15 (m, 12H, 6× CH_2), 0.79 (t, $J = 7.0$ Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.6$, 151.8, 148.4, 141.0, 137.2, 125.0, 124.8, 124.7, 123.2, 121.3, 118.7, 117.6, 105.8, 102.4, 102.3, 59.9, 55.2, 54.7, 54.6, 38.0, 35.4, 30.9, 28.6, 28.5, 28.4, 28.3, 24.6, 21.7, 13.1 ppm.

1-(5,8-Dimethoxynaphthalen-2-yl)tridecyl 3,4,5-trimethoxybenzoate (**11f**, $C_{35}H_{48}O_7$)
Yield 0.52 g (90%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.18$ (s, 1H, ArH), 8.13 (d, $J = 8.6$ Hz, 1H, ArH), 7.49 (d, $J = 8.6$ Hz, 1H, ArH), 7.29 (s, 2H, ArH), 6.63 (d, $J = 8.6$ Hz, 2H, ArH), 6.06 (t, $J = 6.8$ Hz, 1H, ArC$\underline{H}$-OCO), 3.88 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.85 (s, 6H, 2× OCH_3), 3.83 (s, 3H, OCH_3), 2.13–2.03 (m, 1H, 1/2× ($CHC\underline{H}_2$)), 1.98–1.90 (m, 1H, 1/2× ($CHC\underline{H}_2$)), 1.40–1.33 (m, 1H, 1/2× CH_2), 1.29–1.24 (m, 3H, 1/2× CH_2 and CH_2), 1.18–1.15 (m, 16H, 8× CH_2), 0.81 (d, $J = 7.0$ Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.6$, 151.8, 148.4, 141.0, 137.2, 125.0, 124.8, 124.7, 123.2, 121.3, 118.7, 105.8, 102.4, 102.3, 59.9, 55.2, 54.7, 54.6, 35.4, 30.9, 28.6, 28.5, 28.4, 28.3, 24.6, 21.7, 13.1 ppm.

General procedure for the synthesis of compounds 10a–10f and 12a–13f

A solution of 1.15 g of CAN (2.10 mmol) in 1.2 cm^3 water was dropwise added to a solution of 5,8-dimethoxynaphthalene derivatives (0.80 mmol) in 8 cm^3 ethyl acetate at 0 °C. After 8 min, the reaction mixture was diluted with water and extracted with ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate, and then concentrated. The residue was purified by flash column chromatography to afford **10a–10f** and **12a–13f** as yellow oils.

6-[1-(Isopentyloxy)pentyl]-1,4-naphthoquinone (**10a**, $C_{20}H_{26}O_3$)
Yield 0.20 g (80%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.00$ (d, $J = 8.0$ Hz, 1H, ArH), 7.91 (s, 1H, ArH), 7.65 (dd, $J = 8.0$, 1.4 Hz, 1H, ArH), 6.90 (s, 2H, QuinH), 4.24 (t, $J = 6.8$ Hz, 1H, ArC$\underline{H}$$OCH_2$), 3.25–3.18 (m, 2H, OCH_2), 1.76–1.67 (m, 1H, C$\underline{H}$$(CH_3)_2$), 1.65–1.60 (m, 1H, 1/2× ($CHC\underline{H}_2$)), 1.58–1.52 (m, 1H, 1/2× ($CHC\underline{H}_2$)), 1.41–1.34 (m, 2H, OCH_2 $C\underline{H}_2$), 1.26–1.21 (m, 4H, CH_2CH_2), 0.83–0.75 (m, 9H, 3× CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 184.2$ (C=O), 183.8 (C=O), 149.7, 137.7, 137.6, 130.9, 130.7, 130.1, 125.8, 123.6, 109.0, 80.8, 66.8, 37.7, 36.9, 28.5, 26.8, 23.9, 21.6, 21.5, 13.0 ppm; MS (ESI): $m/z = 315$ ($[M + H]^+$).

6-[1-(Isopentyloxy)hexyl]-1,4-naphthoquinone (**10b**, $C_{21}H_{28}O_3$)
Yield 0.22 g (85%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.00$ (d, $J = 8.0$ Hz, 1H, ArH), 7.91 (s, 1H, ArH), 7.64 (d, $J = 8.0$ Hz, 1H, ArH), 6.90 (s, 2H, QuinH), 4.27–4.22 (m, 1H, ArC$\underline{H}$$OCH_2$), 3.25–3.18 (m, 2H, OCH_2), 1.67–1.60 (m, 1H, C$\underline{H}$$(CH_3)_2$), 1.56–1.47 (m, 2H, $CHC\underline{H}_2$), 1.41–1.36 (m, 2H, CH_2), 1.21–1.16 (m, 6H, 3× CH_2), 0.81–0.75 (m, 9H, 3× CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 184.2$ (C=O), 183.9 (C=O), 149.7, 137.7, 137.6, 130.9, 130.7, 130.1, 125.8, 123.6, 80.8, 66.8, 37.7, 37.1, 30.6, 28.5, 24.3, 23.9, 21.6, 21.5, 13.0 ppm; MS (ESI): $m/z = 329$ ($[M + H]^+$).

6-[1-(Isopentyloxy)heptyl]-1,4-naphthoquinone (**10c**, $C_{22}H_{30}O_3$)
Yield 0.21 g (75%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.01$ (d, $J = 8.0$ Hz, 1H, ArH), 7.91 (s, 1H, ArH), 7.65 (d, $J = 8.0$ Hz, 1H, ArH), 6.91 (s, 2H, QuinH), 4.28–4.21 (m, 1H, ArC$\underline{H}$$OCH_2$), 3.23 (t, $J = 6.8$ Hz, 2H, OCH_2), 1.75–1.68 (m, 1H, C$\underline{H}$$(CH_3)_2$), 1.66–1.61 (m, 1H, 1/2× ($CHC\underline{H}_2$)), 1.58–1.51 (m, 1H, 1/2× ($CHC\underline{H}_2$)), 1.41–1.36 (m, 2H, CH_2), 1.22–1.13 (m, 8H, 4× CH_2), 0.81–0.76 (m, 9H, 3× CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 184.2$ (C=O), 183.9 (C=O), 149.7, 137.7, 137.6, 130.8, 130.7, 130.0, 125.8, 123.5, 80.8, 66.8, 37.6, 37.2, 30.7, 28.1, 24.6, 23.9, 21.6, 21.5, 13.1 ppm.

6-[1-(Isopentyloxy)nonyl]-1,4-naphthoquinone (**10d**, $C_{24}H_{34}O_3$)
Yield 0.25 g (83%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.00$ (d, $J = 8.0$ Hz, 1H, ArH), 7.90 (s, 1H, ArH), 7.64 (d, $J = 8.0$ Hz, 1H, ArH), 6.90 (s, 2H, QuinH), 4.26–4.22 (m, 1H, ArC$\underline{H}$$OCH_2$), 3.22 (t, $J = 6.8$ Hz, 2H, OCH_2), 1.75–1.69 (m, 1H, C$\underline{H}$$(CH_3)_2$), 1.68–1.60 (m, 1H, 1/2× ($CHC\underline{H}_2$)), 1.57–1.49 (m, 1H, 1/2 × ($CHC\underline{H}_2$)),

1.41–1.36 (m, 2H, CH_2), 1.16 (m, 12H, 6× CH_2), 0.81–0.75 (m, 9H, 3× CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.2 (C=O), 183.8 (C=O), 149.7, 137.7, 137.6, 130.8, 130.7, 130.0, 125.8, 123.5, 80.8, 66.8, 37.6, 37.2, 30.8, 28.4, 28.2, 24.6, 23.9, 21.6, 21.6, 21.5, 13.1 ppm.

6-[1-(Isopentyloxy)undecyl]-1,4-naphthoquinone (**10e**, $C_{26}H_{38}O_3$)
Yield 0.26 g (81%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, J = 8.0 Hz, 1H, ArH), 7.91 (s, 1H, ArH), 7.65 (d, J = 8.0 Hz, 1H, ArH), 6.90 (s, 2H, QuinH), 4.26–4.22 (m, 1H, ArC<u>H</u>OCH$_2$), 3.22 (t, J = 6.8 Hz, 2H, OCH_2), 1.74–1.67 (m, 1H, C<u>H</u>(CH$_3$)$_2$), 1.66–1.61 (m, 1H, 1/2× (CHC<u>H</u>$_2$)), 1.58–1.49 (m, 1H, 1/2× (CHC<u>H</u>$_2$)), 1.41–1.36 (m, 2H, CH_2), 1.22–1.13 (m, 16H, 8× CH_2), 0.82–0.75 (m, 9H, 3× CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.2 (C=O), 183.9 (C=O), 149.7, 137.7, 137.6, 130.8, 130.7, 130.0, 125.8, 123.5, 80.8, 66.8, 37.6, 37.1, 30.9, 28.5, 28.4, 28.3, 24.6, 23.9, 21.7, 21.6, 21.5, 13.1 ppm.

6-[1-(Isopentyloxy)tridecyl]-1,4-naphthoquinone (**10f**, $C_{28}H_{42}O_3$)
Yield 0.27 g (79%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, J = 8.0 Hz, 1H, ArH), 7.91 (s, 1H, ArH), 7.64 (d, J = 8.0 Hz, 1H, ArH), 6.90 (s, 2H, QuinH), 4.27–4.22 (m, 1H, ArC<u>H</u>OCH$_2$), 3.22 (t, J = 6.8 Hz, 2H, OCH_2), 1.75–1.71 (m, 1H, C<u>H</u>(CH$_3$)$_2$), 1.67–1.61 (m, 1H, 1/2× (CHC<u>H</u>$_2$)), 1.57–1.50 (m, 1H, 1/2× (CHC<u>H</u>$_2$)), 1.41–1.36 (m, 2H, CH_2), 1.16 (m, 20H, 10× CH_2), 0.81–0.75 (m, 9H, 3× CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.2 (C=O), 183.8 (C=O), 149.7, 137.7, 137.6, 130.8, 130.7, 130.0, 125.8, 123.5, 80.8, 66.8, 37.6, 37.2, 30.9, 28.6, 28.5, 28.4, 28.3, 24.6, 23.9, 21.7, 21.6, 21.5, 13.1 ppm; MS (ESI): m/z = 427 ([M + H]$^+$).

6-[1-(3,4,5-Trimethoxybenzoyloxy)pentyl]-1,4-naphthoquinone (**12a**, $C_{25}H_{26}O_3$)
Yield 0.25 g (71%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (s, 1H, ArH), 8.01 (d, J = 8.0 Hz, 1H, ArH), 7.70 (d, J = 8.0 Hz, 1H, ArH), 7.26 (s, 2H, 2ArH), 6.90 (s, 2H, QuinH), 5.95–5.91 (m, 1H, ArC<u>H</u>OCO), 3.86 (s, 6H, 2× OCH_3), 3.84 (s, 3H, OCH_3), 2.07–2.00 (m, 1H, 1/2× (CHC<u>H</u>$_2$)), 1.92–1.84 (m, 1H, 1/2× (CHC<u>H</u>$_2$)), 1.35–1.25 (m, 4H, 2× CH_2), 0.83 (t, J = 7.0 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.9 (C=O), 183.6 (C=O), 164.5, 152.0, 146.7, 141.6, 137.7, 137.6, 131.1, 130.7, 130.3, 125.9, 123.8, 123.0, 105.9, 75.1, 59.9, 55.3, 34.9, 26.6, 21.4, 12.9 ppm; MS (ESI): m/z = 439 ([M + H]$^+$).

6-[1-(3,4,5-Trimethoxybenzoyloxy)hexyl]-1,4-naphthoquinone (**12b**, $C_{26}H_{28}O_3$)
Yield 0.27 g (75%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (s, 1H, ArH), 8.00 (d, J = 8.0 Hz, 1H, ArH), 7.70 (d, J = 8.0 Hz, 1H, ArH), 7.26 (s, 2H, ArH), 6.90 (s, 2H, QuinH), 5.95–5.90 (m, 1H, ArC<u>H</u>OCO), 3.85 (s, 6H, 2× OCH_3), 3.84 (s, 3H, OCH_3), 2.06–1.99 (m, 1H, 1/2× (CHC<u>H</u>$_2$)), 1.91–1.82 (m, 1H, 1/2× (CHC<u>H</u>$_2$)), 1.42–1.35 (m, 1H, 1/2× CH_2), 1.29–1.21 (m, 5H, 1/2× CH_2 and 2× CH_2), 0.80 (t, J = 7.0 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.9 (C=O), 183.6 (C=O), 164.5, 152.0, 146.7, 141.5, 137.7, 137.6, 131.1, 130.7, 130.3, 125.9, 123.8, 123.0, 105.9, 75.1, 59.9, 55.3, 35.2, 30.4, 24.1, 21.4, 12.9 ppm.

6-[1-(3,4,5-Trimethoxybenzoyloxy)heptyl]-1,4-naphthoquinone (**12c**, $C_{27}H_{30}O_3$)
Yield 0.3 g (82%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (s, 1H, ArH), 8.01 (d, J = 8.0 Hz, 1H, ArH), 7.70 (d, J = 8.0 Hz, 1H, ArH), 7.26 (s, 2H, 2ArH), 6.90 (s, 2H, QuinH), 5.95–5.90 (m, 1H, ArC<u>H</u>OCO), 3.86 (s, 6H, 2× OCH_3), 3.84 (s, 3H, OCH_3), 2.08–1.98 (m, 1H, 1/2× (CHC<u>H</u>$_2$)), 1.91–1.82 (m, 1H, 1/2× (CHC<u>H</u>$_2$)), 1.41–1.35 (m, 1H, 1/2× CH_2), 1.32–1.25 (m, 3H, 1/2× CH_2 and CH_2), 1.22–1.17 (m, 4H, CH_2CH_2), 0.79 (t, J = 7.0 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.9 (C=O), 183.6 (C=O), 164.5, 152.0, 146.7, 141.4, 137.7, 137.6, 131.1, 130.7, 130.2, 125.9, 123.7, 123.0, 109.0, 105.8, 75.2, 59.9, 55.2, 35.2, 30.6, 27.9, 24.4, 21.5, 13.0 ppm.

6-[1-(3,4,5-Trimethoxybenzoyloxy)nonyl]-1,4-naphthoquinone (**12d**, $C_{29}H_{34}O_3$)
Yield 0.26 g (65%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (s, 1H, ArH), 8.01 (d, J = 8.0 Hz, 1H, ArH), 7.70 (d, J = 8.0 Hz, 1H, ArH), 7.26 (s, 2H, ArH), 6.91 (s, 2H, QuinH), 5.95–5.90 (m, 1H, ArCHOCO), 3.86 (s, 6H, 2× OCH_3), 3.84 (s, 3H, OCH_3), 2.07–1.98 (m, 1H, 1/2× (CHC<u>H</u>$_2$)), 1.89–1.82 (m, 1H, 1/2× (CHC<u>H</u>$_2$)), 1.41–1.35 (m, 1H, 1/2× CH_2), 1.30–1.26 (m, 2H), 1.22–1.13 (m, 9H), 0.79 (t, J = 7.0 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.9, 183.6, 164.5, 152.0, 146.7, 141.5, 137.7, 137.6, 131.1, 130.7, 130.3, 125.9, 123.7, 123.0, 105.8, 75.2, 60.0, 55.2, 35.2, 30.8, 28.3, 28.2, 28.1, 24.4, 21.6, 13.1 ppm.

6-[1-(3,4,5-Trimethoxybenzoyloxy)undecyl]-1,4-naphthoquinone (**12e**, $C_{31}H_{38}O_3$)
Yield 0.31 g (74%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (s, 1H, ArH), 8.01 (d, J = 8.0 Hz, 1H, ArH), 7.70 (d, J = 8.0 Hz, 1H, ArH), 7.26 (s, 2H, 2ArH), 6.91 (s, 2H, QuinH), 5.95–5.90 (m, 1H, ArCHOCO), 3.86 (s, 6H, 2× OCH_3), 3.84 (s, 3H, OCH_3), 2.08–1.99 (m, 1H, 1/2× (CHC<u>H</u>$_2$)), 1.91–1.82 (m, 1H, 1/2× (CHC<u>H</u>$_2$)), 1.30–1.26 (m, 2H, CH_2), 1.23–1.15 (m, 14H, 7× CH_2), 0.80 (t, J = 7.0 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.9, 183.6, 164.5, 152.0, 146.7, 141.4, 137.7, 137.6, 131.1, 130.7, 130.2, 125.9, 123.7, 123.0,

105.8, 75.2, 59.9, 55.2, 35.2, 30.8, 28.5, 28.4, 28.3, 28.2, 24.4, 21.6, 13.1 ppm.

6-[1-(3,4,5-Trimethoxybenzoyloxy)tridecyl]-1,4-naphthoquinone (**12f**, $C_{33}H_{42}O_3$)
Yield 0.31 g (71%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.06$ (s, 1H, ArH), 8.01 (d, $J = 8.0$ Hz, 1H, ArH), 7.70 (d, $J = 8.0$ Hz, 1H, ArH), 7.26 (s, 2H, ArH), 6.91 (s, 2H, QuinH), 5.95–5.89 (m, 1H, ArC<u>H</u>OCO), 3.86 (s, 6H, 2× OCH_3), 3.84 (s, 3H, OCH_3), 2.07–1.98 (m, 1H, 1/2× (CHC<u>H</u>$_2$)), 1.91–1.82 (m, 1H, 1/2× (CHC<u>H</u>$_2$)), 1.41–1.35 (m, 1H), 1.32–1.25 (m, 3H), 1.21–1.16 (m, 16H), 0.80 (t, $J = 7.0$ Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 183.9$, 183.6, 164.5, 152.0, 146.7, 141.4, 137.7, 137.6, 131.1, 130.7, 130.2, 125.9, 123.7, 123.0, 109.0, 105.8, 75.2, 60.0, 55.2, 35.2, 30.9, 28.6, 28.5, 28.4, 28.3, 28.2, 24.4, 21.7, 13.1 ppm; MS (ESI): *m/z* = 551 ($[M + H]^+$).

6-(1-Hydroxypentyl)-1,4-naphthoquione (**13a**, $C_{15}H_{16}O_3$)
Yield 0.14 g (70%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.99$–7.93 (m, 2H, 2ArH), 7.68 (d, $J = 8.0$ Hz, 1H, ArH), 6.89 (s, 2H, QuinH), 4.78–4.74 (m, 1H, ArC<u>H</u>OH), 1.74–1.65 (m, 2H, CHC<u>H</u>$_2$), 1.36–1.23 (m, 4H, CH_2CH_2), 0.81 (t, $J = 8.0$ Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 184.1$, 183.8, 150.7, 137.7, 137.6, 130.9, 130.2, 130.0, 125.8, 122.7, 72.8, 37.9, 26.6, 21.5, 12.9 ppm; MS (ESI): *m/z* = 245 ($[M + H]^+$).

6-(1-Hydroxyhexyl)-1,4-naphthoquione (**13b**, $C_{16}H_{18}O_3$)
Yield 0.14 g (70%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.97$–7.90 (m, 2H, ArH), 7.67 (dd, $J = 8.0$, 1.6 Hz, 1H, ArH), 6.88 (s, 2H, QuinH), 4.77–4.73 (m, 1H, ArC<u>H</u>OH), 1.73–1.62 (m, 2H, CHC<u>H</u>$_2$), 1.38–1.31 (m, 1H), 1.25–1.17 (m, 5H), 0.79 (t, $J = 7.0$ Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 184.1$, 183.8, 150.8, 137.7, 137.6, 130.8, 130.2, 125.8, 122.7, 105.9, 72.8, 38.1, 30.6, 24.2, 21.5, 13.0 ppm; MS (ESI): *m/z* = 259 ($[M + H]^+$).

6-(1-Hydroxytridecyl)-1,4-naphthoquione (**13f,** $C_{23}H_{32}O_3$)
Yield 0.21 g (72%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.98$–7.94 (m, 2H, ArH), 7.68 (d, $J = 8.0$ Hz, 1H, ArH), 6.89 (s, 2H, QuinH), 4.78–4.73 (m, 1H, ArC<u>H</u>OH), 1.73–1.62 (m, 2H, CHC<u>H</u>$_2$), 1.39–1.29 (m, 1H, 1/2× CH_2), 1.23–1.16 (m, 17H, 1/2× CH_2 and 8× CH_2), 0.80 (t, $J = 7.0$ Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 148.4$, 141.4, 125.0, 124.7, 123.0, 121.1, 117.6, 102.3, 101.9, 73.9, 54.6, 38.0, 31.7, 30.9, 28.6, 28.4, 24.9, 24.7, 21.7, 13.1 ppm.

General procedure for the synthesis of target compounds 14–27

A mixture of 1,4-naphthoquione derivatives (0.50 mmol), 0.24 g of hydroxylamine hydrochloride (3.5 mmol), and 0.28 g of pyridine (3.5 mmol) in 12.0 cm^3 anhydrous ethanol was stirred at 50 °C for 12 h. After cooling, the reaction mixture was extracted with dichloromethane and washed with brine, dried, and concentrated. The residue was purified by flash column chromatography to afford **14**–**27**.

(1E,4E)-6-[1-(Isopentyloxy)pentyl]-1,4-naphthoquinone dioxime (**14**, $C_{20}H_{28}N_2O_3$)
White solid; yield 90.2 mg (54%); m.p.: 171–173 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.03$ (d, $J = 8.2$ Hz, 1H, ArH), 7.96 (s, 1H, ArH), 7.52 (s, 2H, ArH), 7.37 (d, $J = 8.2$ Hz, 1H, ArH), 4.19 (t, $J = 6.8$ Hz, 1H, ArC<u>H</u>OCH_2), 3.33–3.25 (m, 1H, 1/2× OC<u>H</u>$_2$), 3.24–3.17 (m, 1H, 1/2× OC<u>H</u>$_2$), 1.82–1.74 (m, 1H, C<u>H</u>$(CH_3)_2$), 1.66–1.56 (m, 2H, ArCHC<u>H</u>$_2$), 1.43–1.38 (m, 1H, 1/2× (OCH_2C<u>H</u>$_2$)), 1.27–1.18 (m, 7H, 1/2× (OCH_2C<u>H</u>$_2$) and 3× CH_2), 0.80–0.75 (m, 9H, 3× CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 148.1$, 148.0, 144.8, 128.8, 128.0, 127.6, 123.1, 121.0, 119.5, 119.4, 82.3, 67.4, 38.7, 37.8, 29.7, 28.0, 24.9, 22.7, 22.6, 14.0 ppm; HRMS (ESI): *m/z* = 345.2180 ($[M + H]^+$).

(1E,4E)-6-[1-(Isopentyloxy)hexyl]-1,4-naphthoquinone dioxime (**15**, $C_{21}H_{30}N_2O_3$)
White solid; yield 85.7 mg (48%); m.p.: 165–166 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 12.18$ (s, 2H, 2× (= NOH)), 8.07 (d, $J = 8.4$ Hz, 1H, ArH), 8.00 (s, 1H, ArH), 7.43 (s, 2H, ArH), 7.39 (d, $J = 8.4$ Hz, 1H, ArH), 4.28 (t, $J = 6.4$ Hz, 1H, ArC<u>H</u>OCH_2), 3.28–3.21 (m, 2H, OCH_2), 1.73–1.64 (m, 2H, C<u>H</u>$(CH_3)_2$ and 1/2× (ArCHC<u>H</u>$_2$)), 1.59–1.43 (m, 2H, 1/2× (ArCHC<u>H</u>$_2$) and 1/2× (OCH_2C<u>H</u>$_2$)), 1.39–1.33 (m, 2H, 1/2× (OCH_2-C<u>H</u>$_2$) and 1/2× CH_2), 1.29–1.20 (m, 5H, 1/2× CH_2 and CH_2CH_2), 0.86–0.78 (m, 9H, 3× CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 146.8$, 146.7, 144.1, 129.2, 128.5, 127.5, 122.9, 120.4, 118.9, 81.4, 66.8, 38.7, 37.9, 31.5, 25.2, 24.9, 22.9, 22.7, 22.5, 14.3 ppm; HRMS (ESI): *m/z* = 359.2335 ($[M + H]^+$).

(1E,4E)-6-[1-(Isopentyloxy)heptyl]-1,4-naphthoquinone dioxime (**16**, $C_{22}H_{32}N_2O_3$)
White solid; yield 0.14 g (74%); m.p.: 157–159 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 12.15$ (d, $J = 2.2$ Hz, 2H, 2× (= NOH)), 8.03 (d, $J = 8.4$ Hz, 1H, ArH), 7.95 (s, 1H, ArH), 7.38 (s, 2H, 2ArH), 7.32 (d, $J = 8.4$ Hz, 1H,

ArH), 4.20 (t, $J = 6.4$ Hz, 1H, ArC<u>H</u>OCH$_2$), 3.18 (t, $J = 6.4$ Hz, 2H, OCH$_2$), 1.64–1.58 (m, 2H, C<u>H</u>(CH$_3$)$_2$ and 1/2× (ArCHC<u>H</u>$_2$)), 1.52–1.45 (m, 1H, 1/2× (ArCHC<u>H</u>$_2$)), 1.33–1.27 (m, 2H, CH$_2$, OCH$_2$C<u>H</u>$_2$), 1.19–1.13 (m, 8H, 4× CH$_2$), 0.78–0.72 (m, 9H, 3× CH$_3$) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 146.8$, 146.7, 144.1, 129.2, 128.5, 127.4, 122.9, 120.4, 118.9, 81.4, 66.8, 38.7, 38.1, 31.7, 29.0, 25.6, 24.9, 22.9, 22.7, 22.5, 14.3 ppm; HRMS (ESI): $m/z = 373.2489$ ([M + H]$^+$).

(1E,4E)-6-[1-(Isopentyloxy)nonyl]-1,4-naphthoquinone dioxime (**17**, $C_{24}H_{36}N_2O_3$)
White solid; yield 0.13 g (65%); m.p.: 150–152 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 12.14$ (s, 2H, 2× (=NOH)), 8.02 (d, $J = 8.4$ Hz, 1H, ArH), 7.95 (s, 1H, ArH), 7.38 (s, 2H, ArH), 7.32 (d, $J = 8.4$ Hz, 1H, ArH), 4.21 (t, $J = 6.4$ Hz, 1H, ArC<u>H</u>OCH$_2$), 3.19 (t, $J = 6.4$ Hz, 2H, OCH$_2$), 1.65–1.57 (m, 2H, C<u>H</u>(CH$_3$)$_2$ and 1/2× (ArCHC<u>H</u>$_2$)), 1.53–1.44 (m, 1H, 1/2× (ArCHC<u>H</u>$_2$)), 1.34–1.25 (m, 3H, OCH$_2$C<u>H</u>$_2$ and 1/2× CH$_2$), 1.19–1.13 (m, 11H), 0.79–0.73 (m, 9H, 3× CH$_3$) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 146.8$, 146.7, 144.1, 129.2, 128.5, 127.4, 122.8, 120.4, 118.9, 81.4, 66.8, 38.7, 38.0, 31.7, 29.4, 29.3, 29.0, 25.5, 24.9, 22.9, 22.7, 22.5, 14.3 ppm; HRMS (ESI): $m/z = 401.2801$ ([M + H]$^+$).

(1E,4E)-6-[1-(Isopentyloxy)undecyl]-1,4-naphthoquinone dioxime (**18**, $C_{26}H_{40}N_2O_3$)
White solid; yield 76%; m.p.: 147–148 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 12.14$ (d, $J = 4.0$ Hz, 2H, 2× (=NOH)), 8.02 (d, $J = 8.4$ Hz, 1H, ArH), 7.95 (s, 1H, ArH), 7.38 (s, 2H, ArH), 7.31 (d, $J = 8.4$ Hz, 1H, ArH), 4.20 (t, $J = 6.4$ Hz, 1H, ArC<u>H</u>OCH$_2$), 3.18 (t, $J = 6.4$ Hz, 2H, OCH$_2$), 1.66–1.56 (m, 2H, C<u>H</u>(CH$_3$)$_2$ and 1/2× (ArCHC<u>H</u>$_2$)), 1.51–1.46 (m, 1H, 1/2× (ArCHC<u>H</u>$_2$)), 1.33–1.26 (m, 3H, OCH$_2$C<u>H</u>$_2$ and 1/2× CH$_2$), 1.19–1.12 (m, 15H), 0.79–0.72 (m, 9H, 3× CH$_3$) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 146.7$, 146.6, 144.0, 129.2, 128.5, 127.3, 122.8, 120.4, 118.9, 81.5, 66.8, 38.7, 38.0, 31.7, 30.2, 29.4, 29.3, 29.2, 25.5, 24.9, 22.9, 22.7, 22.5, 14.4 ppm; HRMS (ESI): $m/z = 429.3122$ ([M + H]$^+$).

(1E,4E)-6-[1-(Isopentyloxy)tridecyl]-1,4-naphthoquinone dioxime (**19**, $C_{28}H_{44}N_2O_3$)
White solid; yield 0.18 g (78%); m.p.: 144–145 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 12.13$ (d, $J = 4.8$ Hz, 2H, 2× (=NOH)), 8.02 (d, $J = 8.4$ Hz, 1H, ArH), 7.95 (s, 1H, ArH), 7.38 (s, 2H, ArH), 7.30 (d, $J = 8.4$ Hz, 1H, ArH), 4.19 (t, $J = 6.4$ Hz, 1H, ArC<u>H</u>OCH$_2$), 3.18 (t, $J = 6.4$ Hz, 2H, OCH$_2$), 1.66–1.56 (m, 2H, C<u>H</u>(CH$_3$)$_2$ and 1/2× (ArCHC<u>H</u>$_2$)), 1.51–1.44 (m, 1H, 1/2× (ArCHC<u>H</u>$_2$)), 1.33–1.27 (m, 3H, OCH$_2$C<u>H</u>$_2$ and 1/2× CH$_2$), 1.19–1.12 (m, 19H), 0.79–0.72 (m, 9H, 3× CH$_3$) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 146.7$, 146.6, 144.0, 129.3, 128.5, 127.3, 122.8, 120.4, 118.9, 81.5, 66.8, 38.7, 38.1, 31.8, 29.5, 29.4, 29.3, 29.2, 25.6, 24.9, 22.9, 22.7, 22.6, 14.3 ppm; HRMS (ESI): $m/z = 457.3427$ ([M + H]$^+$).

(1E,4E)-6-[1-(3,4,5-Trimethoxybenzoyloxy)pentyl]-1,4-naphthoquinone dioxime (**20**, $C_{25}H_{28}N_2O_7$)
Light-yellow oil; yield 0.17 g (74%); ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 8.08$ (s, 1H, ArH), 7.99 (d, $J = 8.4$ Hz, 1H, ArH), 7.45 (s, 2H, ArH), 7.42 (d, $J = 8.4$ Hz, 1H, ArH), 7.29 (s, 2H, ArH), 5.94 (t, $J = 6.8$ Hz, 1H, ArC<u>H</u>OCO), 3.82 (s, 9H, 3× OCH$_3$), 2.07–2.00 (m, 1H, 1/2× (ArCHC<u>H</u>$_2$)), 1.91–1.84 (m, 1H, 1/2× (ArCHC<u>H</u>$_2$)), 1.34–1.25 (m, 4H, CH$_2$CH$_2$), 0.81 (t, $J = 6.8$ Hz, 3H, CH$_3$) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): $\delta = 164.8$, 151.9, 146.9, 146.7, 141.3, 141.1, 128.0, 127.5, 126.3, 124.2, 122.3, 119.7, 118.5, 118.4, 106.0, 59.9, 55.3, 35.0, 28.7, 26.6, 21.4, 12.9 ppm; HRMS (ESI): $m/z = 469.1977$ ([M + H]$^+$).

(1E,4E)-6-[1-(3,4,5-Trimethoxybenzoyloxy)hexyl]-1,4-naphthoquinone dioxime (**21**, $C_{26}H_{30}N_2O_7$)
Light-yellow oil; yield 0.19 g (79%); ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 8.08$ (s, 1H, ArH), 8.01 (d, $J = 8.4$ Hz, 1H, ArH), 7.45 (s, 2H, ArH), 7.42 (d, $J = 8.4$ Hz, 1H, ArH), 7.28 (s, 2H, ArH), 5.93 (t, $J = 6.8$ Hz, 1H, ArC<u>H</u>OCO), 3.83 (s, 9H, 3× OCH$_3$), 2.04–1.98 (m, 1H, 1/2× (ArCHC<u>H</u>$_2$)), 1.89–1.83 (m, 1H, 1/2× (ArCHC<u>H</u>$_2$)), 1.38–1.33 (m, 1H, 1/2× CH$_2$), 1.26–1.21 (m, 5H), 0.78 (t, $J = 6.8$ Hz, 3H, CH$_3$) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): $\delta = 164.8$, 151.9, 146.9, 146.8, 141.3, 141.1, 128.0, 127.5, 126.3, 124.2, 122.3, 119.7, 118.5, 118.4, 106.0, 59.9, 55.3, 35.2, 30.5, 24.1, 21.4, 13.0 ppm; HRMS (ESI): $m/z = 483.2135$ ([M + H]$^+$).

(1E,4E)-6-[1-(3,4,5-Trimethoxybenzoyloxy)heptyl]-1,4-naphthoquinone dioxime (**22**, $C_{27}H_{32}N_2O_7$)
Light-yellow oil; yield 0.21 g (82%); ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 8.08$ (s, 1H, ArH), 8.00 (d, $J = 8.4$ Hz, 1H, ArH), 7.46 (s, 2H, 2ArH), 7.43 (d, $J = 8.4$ Hz, 1H, ArH), 7.29 (s, 2H, ArH), 5.94 (t, $J = 6.8$ Hz, 1H, ArC<u>H</u>OCO), 3.83 (s, 9H, 3× OCH$_3$), 2.07–1.99 (m, 1H, 1/2× (ArCHC<u>H</u>$_2$)), 1.91–1.84 (m, 1H, 1/2× (ArCHC<u>H</u>$_2$)), 1.31–1.24 (m, 3H), 1.20–1.16 (m, 5H), 0.77 (t, $J = 6.8$ Hz, 3H, CH$_3$) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): $\delta = 165.8$, 152.9, 147.8, 147.7, 142.1, 129.0, 128.4, 127.4, 125.2, 123.3, 120.6, 119.6, 119.5, 106.9, 61.0, 56.3, 36.3, 31.6, 29.7, 29.0, 25.5, 22.5, 14.1 ppm; HRMS (ESI): $m/z = 497.2285$ ([M + H]$^+$).

(1E,4E)-6-[1-(3,4,5-Trimethoxybenzoyloxy)nonyl]-1,4-naphthoquinone dioxime (**23,** $C_{29}H_{36}N_2O_7$)
Light-yellow oil; yield 0.22 g (85%); ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 9.31$ (s, 2H, 2× (= NOH)), 8.08 (s, 1H, ArH), 8.00 (d, $J = 8.4$ Hz, 1H, ArH), 7.46 (s, 2H, ArH), 7.43 (d, $J = 8.4$ Hz, 1H, ArH), 7.29 (s, 2H, ArH), 5.94 (t,

$J = 6.8$ Hz, 1H, ArC<u>H</u>OCO), 3.83 (s, 9H, 3× OCH_3), 2.08–1.97 (m, 1H, 1/2× (ArCHC<u>H</u>$_2$)), 1.91–1.82 (m, 1H, 1/2× (ArCHC<u>H</u>$_2$)), 1.29–1.24 (m, 3H), 1.20–1.15 (m, 9H), 0.78 (t, $J = 6.8$ Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 165.8, 152.9, 147.9, 147.7, 142.3, 142.1, 129.0, 128.4, 127.4, 125.2, 123.3, 120.6, 119.6, 119.5, 106.9, 61.0, 56.3, 36.3, 31.8, 29.4, 29.3, 29.2, 25.5, 22.6, 14.1$ ppm; HRMS (ESI): $m/z = 525.2597$ ($[M + H]^+$).

(1E,4E)-6-[1-(3,4,5-Trimethoxybenzoyloxy)undecyl]-1,4-naphthoquinone dioxime (**24**, $C_{31}H_{40}N_2O_7$)
Light-yellow oil; yield 0.21 g (82%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.59$ (s, 2H, 2× (= NOH)), 8.07 (s, 1H, ArH), 7.98 (d, $J = 8.4$ Hz, 1H, ArH), 7.44 (s, 2H, ArH), 7.41 (d, $J = 8.4$ Hz, 1H, ArH), 7.29 (s, 2H, ArH), 5.95 (t, $J = 6.8$ Hz, 1H, ArC<u>H</u>OCO), 3.83 (s, 9H, 3× OCH_3), 2.07–1.98 (m, 1H, 1/2× (ArCHC<u>H</u>$_2$)), 1.91–1.83 (m, 1H, 1/2× (ArCHC<u>H</u>$_2$)), 1.38–1.33 (m, 1H, 1/2× CH_2), 1.30–1.26 (m, 3H, 1/2× CH_2 and CH_2), 1.20–1.13 (m, 12H, 6× CH_2), 0.76 (t, $J = 6.8$ Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 165.9, 152.9, 147.8, 147.7, 142.2, 142.1, 129.0, 128.4, 127.4, 125.2, 123.3, 120.6, 119.6, 119.5, 106.9, 61.0, 56.3, 36.3, 31.9, 29.6, 29.5, 29.4, 29.3, 25.5, 22.7, 14.1$ ppm; HRMS (ESI): $m/z = 553.2917$ ($[M + H]^+$).

(1E,4E)-6-[1-(3,4,5-Trimethoxybenzoyloxy)tridecyl]-1,4-naphthoquinone dioxime (**25**, $C_{33}H_{44}N_2O_7$)
Light-yellow oil; yield 225.3 mg (78%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.08$ (s, 1H, ArH), 8.00 (d, $J = 8.4$ Hz, 1H, ArH), 7.46 (s, 2H, ArH), 7.43 (d, $J = 8.4$ Hz, 1H, ArH), 7.29 (s, 2H, ArH), 5.94 (t, $J = 6.8$ Hz, 1H, ArC<u>H</u>OCO), 3.84 (s, 9H, 3× OCH_3), 2.07–1.99 (m, 1H, 1/2× (ArCHC<u>H</u>$_2$)), 1.91–1.82 (m, 1H, 1/2× (ArCHC<u>H</u>$_2$)), 1.30–1.26 (m, 3H), 1.21–1.15 (m, 17H), 0.79 (t, $J = 6.8$ Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 165.8, 152.9, 147.9, 147.7, 129.0, 128.4, 127.4, 125.2, 123.3, 120.6, 119.6, 119.5, 106.9, 61.0, 56.2, 36.3, 31.9, 31.5, 31.4, 30.2, 30.1, 29.7, 29.6, 29.5, 29.4, 25.5, 22.7, 14.1$ ppm; HRMS (ESI): $m/z = 581.3232$ ($[M + H]^+$).

(1E,4E)-6-(1-Hydroxypentyl)-1,4-naphthoquinone dioxime (**26**, $C_{15}H_{18}N_2O_3$)
White solid; yield 103.3 mg (75%); m.p.: 187–189 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 12.16$ (d, $J = 9.6$ Hz, 2H, 2× (=NOH)), 8.05 (s, 1H, ArH), 8.03 (d, 1H, $J = 8.4$ Hz, ArH), 7.41 (s, 3H, ArH), 5.26 (d, $J = 4.2$ Hz, 1H, CHO<u>H</u>), 4.57 (dd, $J = 10.6$, 5.4 Hz, 1H, ArC<u>H</u>OH), 1.65–1.57 (m, 2H, ArCHC<u>H</u>$_2$), 1.30–1.57 (m, 4H, CH_2CH_2), 0.84 (t, $J = 6.8$ Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 147.5, 146.9, 146.8, 129.0, 127.9, 127.1, 122.5, 119.7, 118.9, 72.4, 27.9, 22.5, 14.4$ ppm; HRMS (ESI): $m/z = 275.1396$ ($[M + H]^+$).

(1E,4E)-6-(1-Hydroxyhexyl)-1,4-naphthoquinone dioxime (**27**, $C_{16}H_{20}N_2O_3$)
White solid; yield 119.0 mg (83%); m.p.: 182–184 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 12.14$ (d, $J = 7.4$ Hz, 2H, 2× (= NOH)), 8.05 (s, 1H, ArH), 8.03 (d, $J = 8.4$ Hz, 1H, ArH), 7.41 (s, 2H, ArH), 7.40 (s, 1H, ArH), 5.25 (d, $J = 4.2$ Hz, 1H, CHO<u>H</u>), 4.57 (dd, $J = 10.6$, 5.4 Hz, 1H, ArC<u>H</u>OH), 1.64–1.56 (m, 2H, ArCHC<u>H</u>$_2$), 1.37–1.30 (m, 1H), 1.26–1.20 (m, 5H), 0.84 (t, $J = 6.8$ Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 147.5, 146.9, 146.8, 129.0, 127.9, 127.2, 122.5, 119.7, 119.0, 118.9, 72.4, 31.7, 25.3, 22.5, 14.4$ ppm; HRMS (ESI): $m/z = 289.1550$ ($[M + H]^+$).

General procedure for the synthesis of target compounds 28–31

A solution of 5.0 cm^3 sodium hydroxide (10 N) was dropwise added to a solution of ester oxime (0.2 mmol) in 15 cm^3 MeOH. The reaction mixture was stirred at 80 °C for 5 h. After cooling, the solution was brought to acidic pH by careful addition of 6 N HCl and then extracted with dichloromethane and washed with brine, dried, and concentrated. The residue was purified by flash column chromatography to afford **28–31**.

(1E,4E)-6-(1-Hydroxyheptyl)-1,4-naphthoquinone dioxime (**28**, $C_{17}H_{22}N_2O_3$)
White solid; yield 35.4 mg (59%); m.p. 167–169 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 12.14$ (d, $J = 7.4$ Hz, 2H, 2× (=NOH)), 8.05 (s, 1H, ArH), 8.03 (d, $J = 8.4$ Hz, 1H, ArH), 7.42 (s, 2H, 2ArH), 7.40 (s, 1H, ArH), 5.25 (d, $J = 4.2$ Hz, 1H, CHO<u>H</u>), 4.57 (dd, $J = 10.6$, 5.4 Hz, 1H, ArC<u>H</u>OH), 1.64–1.56 (m, 2H, ArCHC<u>H</u>$_2$), 1.35–1.29 (m, 1H), 1.26–1.19 (m, 7H), 0.84 (t, $J = 6.8$ Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 147.5$, 146.9, 146.8, 129.0, 127.9, 127.2, 122.5, 119.7, 119.0, 118.9, 72.4, 31.7, 29.1, 25.6, 22.5, 14.4 ppm; HRMS (ESI): $m/z = 303.1711$ ($[M + H]^+$).

(1E,4E)-6-(1-Hydroxynonyl)-1,4-naphthoquinone dioxime (**29**, $C_{19}H_{26}N_2O_3$)
White solid; yield 42.0 mg (64%); m.p.: 162–164 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 12.14$ (d, $J = 6.2$ Hz, 2H, 2× (= NOH)), 8.05 (s, 1H, ArH), 8.02 (d, $J = 8.4$ Hz, 1H, ArH), 7.41 (s, 2H, ArH), 7.40 (d, $J = 2.0$ Hz, 1H, ArH), 5.25 (d, $J = 4.2$ Hz, 1H, CHO<u>H</u>), 4.57 (dd, $J = 10.6$, 5.4 Hz, 1H, ArC<u>H</u>OH), 1.65–1.56 (m, 2H, ArCHC<u>H</u>$_2$), 1.25–1.19 (m, 12H, 6× CH_2), 0.83 (t, $J = 6.8$ Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 147.5$, 146.9, 146.8, 129.0, 127.9, 127.2, 122.5, 119.7, 119.0, 118.9, 72.5, 31.7, 29.4, 29.1, 25.6, 22.5, 14.4 ppm; HRMS (ESI): $m/z = 331.2023$ ($[M + H]^+$).

(1E,4E)-6-(1-Hydroxyundecyl)-1,4-naphthoquinone dioxime (**30**, $C_{21}H_{30}N_2O_3$)
White solid; yield 46.7 mg (65%); m.p.: 154–157 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 12.13$ (d, $J = 6.2$ Hz, 2H, 2× (=NOH)), 8.05 (s, 1H, ArH), 8.03 (d, $J = 8.4$ Hz, 1H, ArH), 7.42 (s, 2H, ArH), 7.40 (d, $J = 2.0$ Hz, 1H, ArH), 5.24 (d, $J = 4.2$ Hz, 1H, CHOH), 4.57 ($J = 10.6$, 5.4 Hz, 1H, ArCHOH), 1.65–1.56 (m, 2H, ArCHCH_2), 1.26–1.18 (m, 16H, 8× CH_2), 0.84 (t, $J = 6.8$ Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 147.4$, 146.9, 146.8, 129.0, 127.9, 127.1, 122.5, 119.7, 118.9, 118.8, 72.5, 31.7, 29.4, 29.1, 25.6, 22.5, 14.4 ppm; HRMS (ESI): $m/z = 359.2335$ ($[M + H]^+$).

(1E,4E)-6-(1-Hydroxytridecyl)-1,4-naphthoquinone dioxime (**31**, $C_{23}H_{34}N_2O_3$)
White solid; yield 53.4 mg (69%); m.p.: 142–143 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 12.11$ (d, $J = 4.8$ Hz, 2H, 2× (=NOH)), 8.02 (s, 1H, ArH), 7.99 (d, $J = 8.4$ Hz, 1H, ArH), 7.38 (s, 2H, ArH), 7.36 (d, $J = 2.0$ Hz, 1H, ArH), 5.24 (d, $J = 4.2$ Hz, 1H, CHOH), 4.52 (t, $J = 6.2$ Hz, 1H, ArCHOH), 1.60–1.50 (m, 2H, ArCHCH_2), 1.31–1.25 (m, 1H, 1/2× CH_2), 1.19–1.13 (m, 19H, 1/2× CH_2 and 9× CH_2), 0.78 (t, $J = 6.8$ Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 147.4$, 146.8, 146.8, 129.0, 127.9, 127.1, 122.4, 119.7, 118.9, 118.8, 72.5, 31.8, 29.5, 29.2, 25.6, 22.6, 14.4 ppm; HRMS (ESI): $m/z = 387.2651$ ($[M + H]^+$).

Cytotoxic activity

Cells were planted in 96-well plate (5×10^3/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 72 h and control groups were treated with complete medium alone. The supernatants were then removed and replaced by 200 mm^3 Roswell Park Memorial Institute 1640 (RMPI-1640) medium without serum. After the media was removed and 20 mm^3 of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT, 5 mg/cm^3) solution was added, the plates were incubated for 4 h at 37 °C. The MTT-containing media was removed and then 100 mm^3 of DMSO was added to dissolve the dark-blue formazan crystals. The optical density (OD) was measured by Multiskan MK3 microplate reader (Thermo Scientific, USA) at 570 nm. The concentration of each compound was examined in triplicate, and the IC_{50} values were calculated by linear regression analysis using IBM SPSS statistics software (version 21.0).

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