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Original article

Synthesis of a novel series of 2-alkylthio substituted naphthoquinones as potent acyl-CoA: Cholesterol acyltransferase (ACAT) inhibitors

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ABSTRACT

We report a new series of naphthoquinone derivatives as potent ACAT inhibitors, which were obtained through structural variations of previously disclosed lead **1**. Several analogs represented by **3i**–**l**, **4k**–**m**, **6a**–**n**, **7a**, and **7i** demonstrated potent human macrophage ACAT inhibitory activity by a cell-based reporter assay with human HepG2 cell lines. In particular, compounds **4l** and **6j** emerged as highly potent inhibitors, exhibiting significantly high inhibitory potencies with IC_{50} values of 0.44 μM and 0.6 μM, respectively. Moreover, compound **4l** significantly reduced the accumulation of cellular cholesterol in HepG2 cell lines.

1. Introduction

Acyl-CoA: Cholesterol acyltransferase (ACAT, E.C.2.3.1.26) is the primary enzyme responsible for the intracellular esterification of free cholesterol with fatty acyl-CoA to produce cholesterol esters in various tissues [1]. It is believed that ACAT plays a key role in the assembly and secretion of very low density lipoprotein (VLDL) in the liver, as well as in the accumulation of cholesterol esters in macrophages and arterial vascular smooth muscle cells in atherosclerotic lesions. Accumulation of cholesterol ester causes the formation of foam cells from macrophages in the arterial walls, which is a hallmark of atherosclerosis lesions [1,2]. Moreover, hypercholesterolemia is one of the major risk factors for the development of coronary heart disease (CHD) [3,4]. Inhibition of ACAT was expected to reduce plasma lipid levels by inhibiting intestinal cholesterol absorption and to prevent progression of atherosclerotic lesions by inhibiting the accumulation of cholesteryl esters in macrophages [5–7]. Due to these advantages, the therapeutic potential of ACAT inhibitors has been recognized for the treatment of hypercholesterolemia and atherosclerosis. In this regard, considerable efforts have been directed toward the development of potent ACAT inhibitors in recent years [8–19]. As part of our ongoing research into the identification of novel ACAT inhibitors, we have recently reported preliminary structure activity relationship studies of a novel series of imidazo[1,2-α]pyridines and 2-alkyl/aryl-thio/amino naphthoquinones as potent ACAT inhibitors [8,9]. Among the 2-alkylthio-naphthoquinone derivatives, compound **1** having 2-$(CH_2)_{11}CH_3$ thio linked 5,8-dimethoxy-1,4-naphthoquinone exhibited moderate ACAT inhibitory activity with an IC_{50} value of 22.78 μM in a cell-based assay in human HepG2 cell lines. The structure activity relationship studies of naphthoquinone series suggested that the presence of hydrophobic thioalkyl groups is essential for the effective inhibition of ACAT activity and that the replacement of sulfur atom with hydrophilic groups like –NH, –OH and –COOH caused

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significant loss of activity. We hypothesized that the replacement of sulfur in compound **1** (Fig. 1) with S=O and O=S=O while maintaining the 5,8-dimethoxy-1,4-naphthoquinone core structure would modulate the inhibitory activity. On the basis of this strategy, we synthesized a series of 2-alkylsulfinyl and 2-alkylsulfonyl 5,8-dimethoxy naphthoquinone/2-alkylthio and 2-alkylsulfinyl naphthoquinone derivatives and evaluated them *in vitro* for their potential in inhibiting human macrophage ACAT activity using a cell-based assay in human HepG2 cell lines. In addition, the most potent compound among the series **4l** was further evaluated for its efficacy in inhibiting the lipid profile of hepatocytes. Herein, we report the synthesis and biological evaluation of a new structural class of novel naphthoquinone derivatives as potent ACAT inhibitors.

2. Chemistry

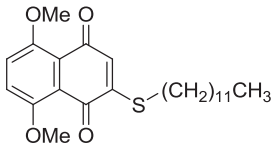
The synthesis of naphthoquinone analogs **3a**–**n**, **4a**–**n**, **6a**–**n**, and **7a**–**n** was accomplished according to the synthetic protocols illustrated in Schemes 1 and 2. As shown in Scheme 1, the synthesis of compounds **3a**–**n** and **4a**–**n** commenced with known compounds **2a**–**n**, which were efficiently prepared in five steps starting from 1,5-dihydroxynaphthalene [8]. Thus, the oxidation of a series of compounds **2a**–**n** was carried-out by reacting with 1.1 equivalent of meta-chloroperbenzoic acid in chloroform at 0 °C to obtain the corresponding 2-alkylsulfinyl-5,8-dimethoxy naphthoquinones **3a**–**n** in good yield. In a separate process, compounds **4a**–**n** were conveniently prepared in a single step starting from **2a**–**n** using 2.2 equivalents of meta-chloroperbenzoic acid at room temperature.

Scheme 2 describes the synthesis of 2-alkylthio and 2-alkylsulfinyl naphthoquinone analogs **6a**–**n** and **7a**–**n**. A single step addition of various alkyl thiols to naphthoquinone **5** afforded the corresponding 2-alkylthio substituted naphthoquinones **6a**–**n** in considerable yield. Subsequent MCPBA mediated oxidation of **6a**–**n** furnished the desired 2-alkylsulfinyl naphthoquinones **7a**–**n**.

3. Biological evaluation

The *in vitro* inhibitory potencies of all the newly synthesized compounds were evaluated for their potential to inhibit human macrophage ACAT activity using a cell-based reporter assay in human HepG2 cell lines and the results are tabulated as IC_{50} values in Tables 1 and 2. All the assays were performed under standard assay conditions by employing the previously described assay protocol [20]. Pipercide [21] and Kurarinone [22], the known ACAT inhibitors, were used as reference standards for comparison, which displayed moderate to potent ACAT inhibitory activity with IC_{50} values of 10.9 μM and 3.7 μM, respectively.

In order to assess the effect of replacement of sulfur with sulfone, we first prepared various 2-alkylsulfinyl-5,8-dimethoxy naphthoquinone derivatives with varying alkyl chain lengths at 2-position, which resulted in the analogs **3a**–**f**. Compounds **3a**–**c** with 1–3 carbon linkers possessing 2-methylsulfinyl, 2-ethylsulfinyl and 2-propylsulfinyl groups respectively, were found to be poor inhibitors. On the other hand, compounds **3d**–**f** having



1: IC_{50} = 22.78 μM

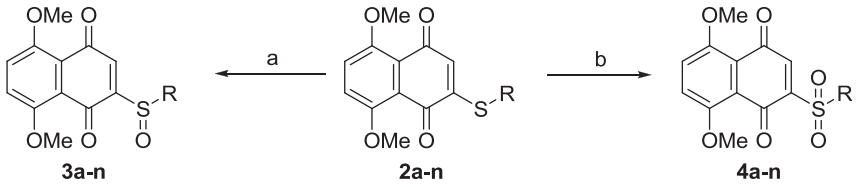
Fig. 1. Compound **1**.

4–6 carbon linkers with 2-butylsulfinyl, 2-pentylsulfinyl, and 2-hexylsulfinyl substitutions demonstrated moderate inhibitory activity comparable to compound **1** (IC_{50} = 23.3 μM, 24.7 μM and 20.5 μM, respectively). Encouraged by these results, we further explored the length of 2-alkylsulfinyl carbon units by preparing compounds **3g**–**l** having 7–12 carbon linkers, and as a result, this modification provided potent inhibitors. Compounds **3k** and **3l** with 11 and 12 carbon units displayed appreciably high inhibitory activity with IC_{50} values of 1.1 μM and 2.4 μM, respectively. It is worth noting that the remaining compounds **3g**–**j** possessing 7–10 carbon linkers also exhibited considerable inhibitory potencies (IC_{50} = 16.5 μM, 14.1 μM, 10.3 μM and 8.4 μM, respectively). In view of high inhibitory activity of **3k** and **3l**, we further extended the analog series by synthesizing compounds **3m** and **3n** with 15 and 18 carbon units, respectively. While compound **3m** having 15 carbon linkers showed good inhibitory activity with an IC_{50} value of 13.7 μM, compound **3n** with 18 carbon units was found to be a poor inhibitor. These results collectively indicate that the potency of these analogs is directly related to the length of the alkyl linker attached to the 2-sulfinyl group, suggesting that the presence of 11–12 carbon units is optimal for potency.

Having established the optimal chain length for potency, we explored the effect of the replacement of the sulfinyl group with the sulfonyl group and this derivatization produced a series of 2-alkylsulfonyl-5,8-dimethoxy naphthoquinone analogs **4a**–**n**. Ccompounds **4k**, **4l**, and **4m** having 11, 12 and 15 carbon units showed potent inhibitory activities against ACAT, and specifically compound **4l** displayed highly potent inhibition with an IC_{50} value of 0.44 μM. Compounds **4i**–**j** and **4n** possessing 9, 10 and 18 carbon units displayed good inhibitory activity (IC_{50} = 21.8 μM, 19.6 μM and 12.9 μM, respectively), whereas all of the other derivatives displayed poor inhibitory activity. To examine the importance of methoxy groups present at 5 and 8-positions of the naphthoquinone moiety, we prepared further series of 2-alkylthio and 2-alkylsulfinyl naphthoquinone analogs **6a**–**n** and **7a**–**n**. Interestingly, this modification resulted in highly potent ACAT inhibitors represented by analogs **6a**–**n** with varying IC_{50} values between 0.44 μM and 11.51 μM. In particular, compound **6j** demonstrated significantly high inhibitory potency with an IC_{50} value of 0.6 μM. On the other hand, 2-alkylsulfinyl naphthoquinone derivatives **7b**–**h** and **7j**–**m** showed moderate to poor inhibitory activity, while compounds **7a** and **7i** potently inhibited ACAT activity with IC_{50} values of 5.66 μM and 5.47 μM.

Hypercholesterolemia is one of the major health problems in many industrialized countries. Therefore, the development of effective drugs to alleviate the risk of this disease has attracted much attention in recent years. Past studies have demonstrated that reduction of cellular cholesterol could be achieved via inhibition of essential enzymes in cholesterol metabolism. Among these enzymes, acetyl-coenzyme A: acetyltransferase (ACAT) has been shown to play an important role in cholesterol homeostasis [23]. It was also reported that the reduced hepatic cholesterol content was correlated with decreased ACAT activity [24]. The authors demonstrated that the incorporation of ACAT inhibitor into the diet of cholesterol-fed rats significantly inhibited hepatic ACAT activity and subsequently led to a substantial reduction in the hepatic cholesterol content. Thus, to evaluate whether the *in vitro* activity of naphthoquinone analogs can be translated into the treatment of hypercholesterolemia, compound **4l**, the most potent inhibitor of the series, was further assayed for its efficacy in inhibiting the accumulation of cellular cholesterol of HepG2 cell lines by employing the previously described assay protocol (Fig. 2) [25].

As shown in Fig. 2A, stimulation of hepatocytes with compound **4l** significantly reduced the accumulation of cellular cholesterol compared with the control. Upon treatment with compound **4l** at

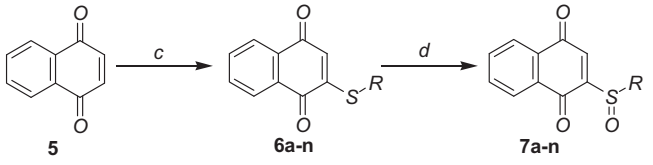


3a : R= -CH_3
3b : R= -CH_2CH_3
3c : R= -$(CH_2)_2CH_3$
3d : R= -$(CH_2)_3CH_3$
3e : R= -$(CH_2)_4CH_3$
3f : R= -$(CH_2)_5CH_3$
3g : R= -$(CH_2)_6CH_3$
3h : R= -$(CH_2)_7CH_3$
3i : R= -$(CH_2)_8CH_3$
3j : R= -$(CH_2)_9CH_3$
3k : R= -$(CH_2)_{10}CH_3$
3l : R= -$(CH_2)_{11}CH_3$
3m: R= -$(CH_2)_{14}CH_3$
3n : R= -$(CH_2)_{17}CH_3$

4a : R= -CH_3
4b : R= -CH_2CH_3
4c : R= -$(CH_2)_2CH_3$
4d : R= -$(CH_2)_3CH_3$
4e : R= -$(CH_2)_4CH_3$
4f : R= -$(CH_2)_5CH_3$
4g : R= -$(CH_2)_6CH_3$
4h : R= -$(CH_2)_7CH_3$
4i : R= -$(CH_2)_8CH_3$
4j : R= -$(CH_2)_9CH_3$
4k : R= -$(CH_2)_{10}CH_3$
4l : R= -$(CH_2)_{11}CH_3$
4m: R= -$(CH_2)_{14}CH_3$
4n : R= -$(CH_2)_{17}CH_3$

Scheme 1. Reagents and conditions: (a) m-CPBA (1.1 eq.), $NaHCO_3$, 0 °C, 4 h; (b) *m*-CPBA (2.2 eq.), $NaHCO_3$, rt, 4 h.

concentrations of 5 and 50 μM, the cellular total cholesterol level was reduced by 25–42% compared to the control. In addition to cellular total cholesterol, the cellular triglyceride concentration was also substantially reduced upon stimulation with compound **4l**. Notably, the cellular triglyceride concentrations in hepatocytes significantly decreased upon treatment with compound **4l** (Fig. 2B). Treatment with compound **4l** (5–50 μM) for 6, 12 and 24 h significantly reduced the TG level by 21–28%, 25–30% and 32–52%, respectively, compared with the control. The reduction of triglycerides by compound **4l** was well supported by our image of Oil Red O staining. Under microscopic visualization, the compound **4l**-stimulated cells displayed fewer and smaller lipid-filled cells compared to the lipid-loaded control (Fig. 2C). This suggested that cells treated with compound **4l** showed marked reductions in cellular lipid accumulation. This observation was then verified by labeling with a lipid specific dye, Vybrant DiI. The control hepatocytes cells were extensively labeled with Vybrant DiI (Fig. 2D). However, the extent of labeling with Vybrant DiI substantially decreased in cells stimulated with compound **4l**, indicating that compound **4l** treatment effectively declines lipid accumulation in hepatocytes compared to the control. This was indeed beneficial as reduction of triglycerides/lipid content in hepatocytes could lead to reduce risk of hepatic steatosis, a disease in which liver lipid (triglycerides) contents exceed 5% of liver weight [26]. Thus, we postulated that compound **4l** used in this study may have partly caused the inhibition of the enzymes related to cholesterol metabolism, leading to reduced cholesterol accumulation. Together with the cholesterol reduction by compound **4l**, our results suggested that this compound might exert hypocholesterolemic and hypotriglycerimic effects.



6a : *R= -CH_3*
6b : *R= -CH_2CH_3*
6c : *R= -$(CH_2)_2CH_3$*
6d : *R= -$(CH_2)_3CH_3$*
6e : *R= -$(CH_2)_4CH_3$*
6f : *R= -$(CH_2)_5CH_3$*
6g : *R= -$(CH_2)_6CH_3$*
6h : *R= -$(CH_2)_7CH_3$*
6i : *R= -$(CH_2)_8CH_3$*
6j : *R= -$(CH_2)_9CH_3$*
6k : *R= -$(CH_2)_{10}CH_3$*
6l : *R= -$(CH_2)_{11}CH_3$*
6m: *R= -$(CH_2)_{14}CH_3$*
6n : *R= -$(CH_2)_{17}CH_3$*

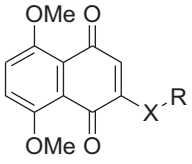
7a : *R= -CH_3*
7b : *R= -CH_2CH_3*
7c : *R= -$(CH_2)_2CH_3$*
7d : *R= -$(CH_2)_3CH_3$*
7e : *R= -$(CH_2)_4CH_3$*
7f : *R= -$(CH_2)_5CH_3$*
7g : *R= -$(CH_2)_6CH_3$*
7h : *R= -$(CH_2)_7CH_3$*
7i : *R= -$(CH_2)_8CH_3$*
7j : *R= -$(CH_2)_9CH_3$*
7k : *R= -$(CH_2)_{10}CH_3$*
7l : *R= -$(CH_2)_{11}CH_3$*
7m: *R= -$(CH_2)_{14}CH_3$*
7n : *R= -$(CH_2)_{17}CH_3$*

Scheme 2. Reagents and conditions: (c) HS-R, rt, 3 h, overnight, MeOH; (d) *m*-CPBA, $NaHCO_3$, 0 °C, 4 h.

4. Conclusion

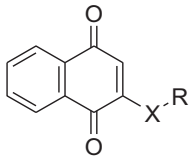
In this study, we disclosed a novel series of potent ACAT inhibitors through structural modification of a previously reported

Table 1
In vitro ACAT inhibitory activities of 2-alkylsulfinyl and 2-alkylsulfonyl-5,8-dimethoxy naphthoquinones **3a**–**n** and **4a**–**n**.



R	Compd	X; S=O	Compd	X; O=S=O
		IC_{50} (μM)		IC_{50} (μM)
$-CH_3$	**3a**	>100	**4a**	>100
$-CH_2CH_3$	**3b**	83.2	**4b**	>100
$-(CH_2)_2CH_3$	**3c**	55.1	**4c**	>100
$-(CH_2)_3CH_3$	**3d**	23.3	**4d**	45
$-(CH_2)_4CH_3$	**3e**	24.7	**4e**	28.7
$-(CH_2)_5CH_3$	**3f**	20.5	**4f**	62.5
$-(CH_2)_6CH_3$	**3g**	16.5	**4g**	53.5
$-(CH_2)_7CH_3$	**3h**	14.1	**4h**	48.4
$-(CH_2)_8CH_3$	**3i**	10.3	**4i**	21.8
$-(CH_2)_9CH_3$	**3j**	8.4	**4j**	19.6
$-(CH_2)_{10}CH_3$	**3k**	1.1	**4k**	3.4
$-(CH_2)_{11}CH_3$	**3l**	2.4	**4l**	0.44
$-(CH_2)_{14}CH_3$	**3m**	13.7	**4m**	5.8
$-(CH_2)_{17}CH_3$	**3n**	>100	**4n**	12.9
Kurarinone [22]		10.9		10.9
Pipercide [21]		3.7		3.7

Table 2
In vitro ACAT inhibitory activities of 2-alkylsulfinyl and 2-alkylsulfonyl naphthoquinones **6a**–**n** and **7a**–**m**.



6a-n, 7a-m

R	Compd	X; S	Compd	X; S=O
		IC_{50} (μM)		IC_{50} (μM)
$-CH_3$	**6a**	2.82	**7a**	5.66
$-CH_2CH_3$	**6b**	7.51	**7b**	17.81
$-(CH_2)_2CH_3$	**6c**	5.08	**7c**	27.55
$-(CH_2)_3CH_3$	**6d**	7.87	**7d**	33.17
$-(CH_2)_4CH_3$	**6e**	8.19	**7e**	27.16
$-(CH_2)_5CH_3$	**6f**	11.51	**7f**	41.47
$-(CH_2)_6CH_3$	**6g**	10.07	**7g**	44.66
$-(CH_2)_7CH_3$	**6h**	6.00	**7h**	46.11
$-(CH_2)_8CH_3$	**6i**	1.63	**7i**	5.47
$-(CH_2)_9CH_3$	**6j**	0.6	**7j**	79.38
$-(CH_2)_{10}CH_3$	**6k**	8.67	**7k**	86.31
$-(CH_2)_{11}CH_3$	**6l**	1.66	**7l**	41.47
$-(CH_2)_{14}CH_3$	**6m**	4.13	**7m**	56.63
$-(CH_2)_{17}CH_3$	**6n**	1.45	**7n**	ND[a]
Kurarinone [22]		10.9		10.9
Pipercide [21]		3.7		3.7

[a] ND: not determined.

naphthoquinone series, in which the sulfinyl/sulfonyl linker was introduced in place of sulfur of lead compound **1**. Several analogs represented by **3i**–**l**, **4k**–**m**, **6a**–**n**, **7a**, and **7i** demonstrated potent ACAT inhibitory activities. In particular, compounds **4l** and **6j** emerged as highly potent inhibitors, which exhibited significantly high inhibitory potencies with IC_{50} values of 0.44 μM and 0.6 μM, respectively. Furthermore, the most potent inhibitor **4l** of the series significantly inhibited the accumulation of cellular cholesterol of HepG2 cell lines. Taken together, the compounds described in this study may serve as valuable leads for the development of therapeutic agents in various ACAT mediated diseases.

5. Experimental

Chemical reagents were obtained from Aldrich Chemical Company. Solvents were of reagent grade and used without further purification. Melting points were determined on an Electrothermal capillary melting point apparatus and were uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a JNM-AL 400 (400 MHz). Chemical shifts (δ) are given in ppm downfield from tetramethylsilan as the internal standard. MS spectra were collected with a AB SCIEX API 2000™ LC/MS/MS (Applied Biosystem) and LCMS-IT-TOF (Shimadzu).

5.1. General procedure for the synthesis of compounds *3a*–*3n*

Under ice-cooling, 77% of *m*-chloroperoxybenzoic acid (0.23 mmol) was added portionwise to a solution of 2-alkylthio-5,8-dimethoxy-1,4-naphthoquinones (**2a**–**2n**, 0.21 mmol) in chloroform (20 ml), stirred, and monitored by TLC. When the starting was disappeared, the chloroform solution was washed with sodium hydrogen carbonate solution, dried over sodium sulfate, and then evaporated. The residue was purified on silica gel column chromatography (HX:EA = 2:1) to give 2-alkylsulfinyl-5,8-diemthoxy-1,4-naphthoquinones (**3a**–**3n**).

5.1.1. Synthesis of 2-methylsulfinyl-5,8-dimethoxy-1,4-naphthoquinone (*3a*)

It was obtained from **2a** as a red solid in 66.7% yield; mp 222 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, J = 9.2 Hz, 1H), 7.37 (d, J = 9.2 Hz, 1H), 7.35 (s, 1H), 3.99 (s, 6H), 2.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.0 (C-1), 181.8 (C-4), 156.1 (C-2), 154.4 (C-5), 154.3 (C-8), 136.2 (C-3), 121.8 (C-6), 121.8 (C-7), 120.4 (C-9), 120.4 (C-10), 56.9 (OCH_3), 56.8 (OCH_3), 41.1 (C-1′); IT-TOF/MS: m/z 303.0279 $(M + Na)^+$.

5.1.2. 2-Ethylsulfinyl-5,8-dimethoxy-1,4-naphthoquinone (*3b*)

It was obtained from **2b** as a red solid in 71.1% yield; mp 145 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, J = 9.6 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 7.29 (s, 1H), 3.99 (s, 6H), 3.27 (td, J = 7.2, 20.8 Hz, 1H), 2.99 (td, J = 7.2, 21.2 Hz, 1H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.0 (C-1), 181.9 (C-4), 156.1 (C-2), 154.4 (C-5), 154.3 (C-8), 136.6 (C-3), 121.7 (C-6), 121.7 (C-7), 120.4 (C-9), 120.4 (C-10), 56.9 (OCH_3), 56.8 (OCH_3), 46.7 (C-1′), 5.9 (C-2′); ESI-MS: m/z 316.9 $(M + Na)^+$.

5.1.3. 2-Propylsulfinyl- 5,8-dimethoxy-1,4-naphthoquinone (*3c*)

It was obtained from **2c** as a red solid in 41.9% yield; mp 120 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, J = 9.2 Hz, 1H), 7.37 (d, J = 9.6 Hz, 1H), 7.29 (s, 1H), 3.99 (s, 3H), 3.91 (s, 3H), 3.14 (m, 1H), 2.82 (m, 1H), 1.88 (m, 1H), 1.66 (m, 1H), 1.01 (t, J = 7.2 Hz, 3H); ^{13}C

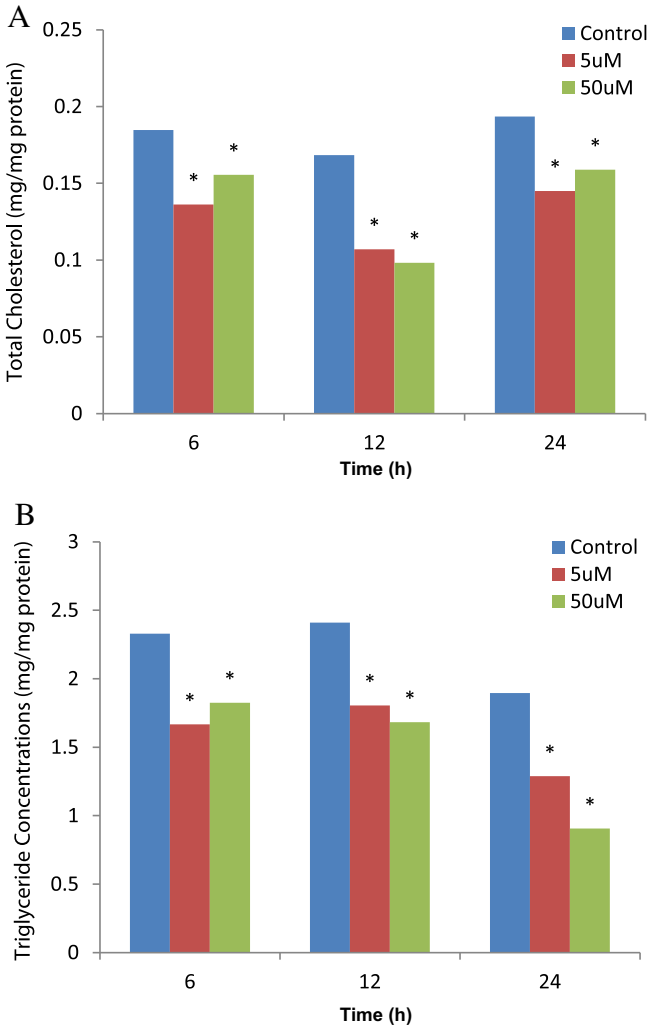


Fig. 2. Lipid profile of HepG2 cells stimulated with compound **4l** (5 μM and 50 μM) for 6, 12 and 24 h. Cellular total cholesterol (A) and triglyceride (B) concentrations as well as Oil Red O (C) staining and DiI staining (D) of HepG2. *Significantly different ($P < 0.05$) between cells treated with compound **4l** and the control.

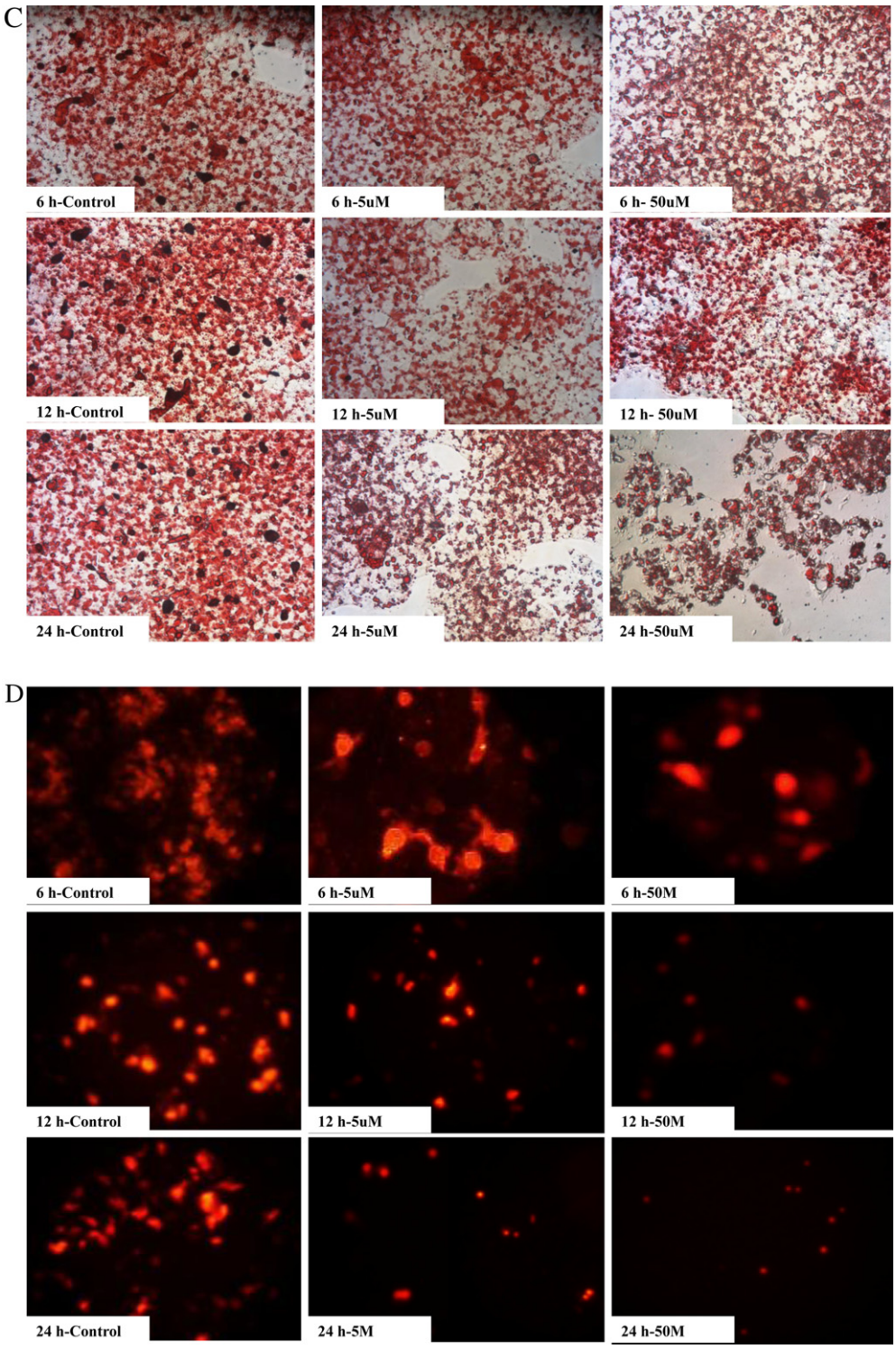


Fig. 2. (*continued*).

NMR ($CDCl_3$, 100 MHz) δ 182.0 (C-1), 181.9 (C-4), 154.4 (C-5), 154.4 (C-8), 154.3 (C-2), 136.9 (C-3), 121.7 (C-7), 120.9 (C-6), 120.3 (C-9), 120.1 (C-10), 56.9 (OCH_3), 56.7 (OCH_3), 55.3 (C-1′), 16.0 (C-2′), 13.1 (C-3′); ESI-MS: m/z 330.9 $(M + Na)^+$.

*5.1.4. 2-Butyllsulfinyl-5,8-dimethoxy-1,4-naphthoquinone (**3d**)*

It was obtained from **2d** as a red solid in 81.6% yield; mp 127 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, J = 9.6 Hz, 1H), 7.36 (d, J = 9.6 Hz, 1H), 7.31 (s, 1H), 3.99 (s, 6H), 3.24 (m, 1H), 2.91 (m, 1H), 1.90 (m, 1H), 1.59 (m, 1H), 1.44 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.0 (C-1), 181.9 (C-4), 154.6 (C-5), 154.4 (C-8), 154.3 (C-2), 136.9 (C-3), 121.7 (C-7), 120.9 (C-6), 120.4 (C-9), 120.1 (C-10), 56.9 (OCH_3), 56.8 (OCH_3), 53.4 (C-1′), 24.1 (C-2′), 22.4 (C-3′), 13.7 (C-4′); ESI-MS: m/z 345.0 $(M + Na)^+$.

*5.1.5. 2-Pentylsulfinyl-5,8-dimethoxy-1,4-naphthoquinone (**3e**)*

It was obtained from **2e** as a red solid in 40.2% yield; mp 125 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, J = 9.2 Hz, 1H), 7.37 (d,

J = 9.6 Hz, 1H), 7.29 (s, 1H), 3.99 (s, 6H), 3.23 (m, 1H), 2.90 (m, 1H), 1.1 (m, 1H), 1.69 (m, 1H), 1.39 (m, 6H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.0 (C-1), 181.8 (C-4), 154.6 (C-5), 154.4 (C-8), 154.2 (C-2), 136.8 (C-3), 121.7 (C-7), 120.8 (C-6), 120.4 (C-9), 120.1 (C-10), 56.9 (OCH_3), 56.7 (OCH_3), 53.7 (C-1′), 30.6 (C-2′), 22.2 (C-3′), 21.8 (C-4′), 13.7 (C-5′); ESI-MS: m/z 358.9 $(M + Na)^+$.

*5.1.6. 2-Hexylsulfinyl-5,8-dimethoxy-1,4-naphthoquinone (**3f**)*

It was obtained from **2f** as a red solid in 76.7% yield; mp 120 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 (d, J = 9.6 Hz, 1H), 7.37 (d, J = 9.6 Hz, 1H), 7.30 (s, 1H), 4.00 (s, 3H), 3.99 (s, 3H), 3.29 (m, 1H), 2.91 (m, 1H), 1.91 (m, 1H), 1.67 (m, 1H), 1.45 (m, 2H), 1.29 (m, 4H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.0 (C-1), 181.9 (C-4), 154.6 (C-5), 154.4 (C-8), 154.3 (C-2), 136.8 (C-3), 121.7 (C-7), 120.8 (C-6), 120.4 (C-9), 120.1 (C-10), 56.9 (OCH_3), 56.7 (OCH_3), 53.7 (C-1′), 31.3 (C-2′), 28.1 (C-3′), 22.3 (C-4′), 22.1 (C-5′), 13.9 (C-6′); ESI-MS: m/z 372.9 $(M + Na)^+$.

*5.1.7. 2-Heptylsulfinyl-5,8-dimethoxy-1,4-naphthoquinine (**3g**)*

It was obtained from **2g** as a red solid in 46.9% yield; mp 106 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, J = 9.6 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 7.29 (s, 1H), 3.99 (s, 6H), 3.23 (m, 1H), 2.90 (m, 1H), 1.90 (m, 1H), 1.67 (m, 1H), 1.44 (m, 2H), 1.36 (m, 2H), 1.27 (m, 4H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.0 (C-1), 181.9 (C-4), 154.5 (C-5), 154.4 (C-8), 154.3 (C-2), 136.9 (C-3), 121.6 (C-7), 120.6 (C-6), 120.3 (C-9), 120.3 (C-10), 56.9 (OCH_3), 56.8 (OCH_3), 53.7 (C-1′), 31.5 (C-2′), 28.8 (C-3′), 28.5 (C-4′), 22.5 (C-5′), 22.2 (C-6′), 14.0 (C-7′); ESI-MS: m/z 386.9 $(M + Na)^+$.

*5.1.8. 2-Octylsulfinyl-5,8-dimethoxy-1,4-naphthoquinone (**3h**)*

It was obtained from **2h** as a red solid in 63.2% yield; mp 110 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, J = 9.2 Hz, 1H), 7.36 (d, J = 9.6 Hz, 1H), 7.30 (s, 1H), 3.99 (s, 6H), 3.23 (m, 1H), 2.90 (m, 1H), 1.90 (m, 1H), 1.64 (m, 1H), 1.45 (m, 2H), 1.25 (m, 8H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 182.0 (C-1), 181.9 (C-4), 154.5 (C-5), 154.4 (C-8), 154.3 (C-2), 136.8 (C-3), 121.6 (C-7), 120.6 (C-6), 120.3 (C-9), 120.3 (C-10), 56.9 (OCH_3), 56.8 (OCH_3), 53.7 (C-1′), 31.7 (C-2′), 29.1 (C-3′), 29.0 (C-4′), 28.5 (C-5′), 22.6 (C-6′), 22.2 (C-7′), 14.1 (C-8′); ESI-MS: m/z 400.8 $(M + Na)^+$.

*5.1.9. 2-Nonylsulfinyl-5,8-dimethoxy-1,4-naphthoquinone (**3i**)*

It was obtained from **2i** as a red solid in 74% yield; mp 100 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 (d, J = 9.6 Hz, 1H), 7.37 (d, J = 9.6 Hz, 1H), 7.31 (s, 1H), 3.99 (s, 6H), 3.23 (m, 1H), 2.90 (m, 1H), 1.90 (m, 1H), 1.61 (m, 1H), 1.43 (m, 2H), 1.24 (m, 10H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.0 (C-1), 181.9 (C-4), 154.6 (C-5), 154.4 (C-8), 154.3 (C-2), 136.8 (C-3), 121.7 (C-7), 120.9 (C-6), 120.4 (C-9), 120.4 (C-10), 56.9 (OCH_3), 56.8 (OCH_3), 53.7 (C-1′), 31.8 (C-2′), 29.3 (C-3′), 29.2 (C-4′), 29.1 (C-5′), 28.5 (C-6′), 22.6 (C-7′), 22.2 (C-8′), 14.1 (C-9′); ESI-MS: m/z 414.8 $(M + Na)^+$.

*5.1.10. 2-Decylsulfinyl-5,8-dimethoxy-1,4-naphthouinone (**3j**)*

It was obtained from **2j** as a red solid in 92.4% yield; mp 127 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, J = 9.6 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 7.30 (s, 1H), 3.99 (s, 6H), 3.22 (m, 1H), 2.90 (m, 1H), 1.89 (m, 1H), 1.62 (m, 1H), 1.43 (m, 2H), 1.24 (m, 12H), 0.87 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.0 (C-1), 181.9 (C-4), 154.6 (C-5), 154.4 (C-8), 154.3 (C-2), 136.9 (C-3), 121.7 (C-7), 120.9 (C-6), 120.3 (C-9), 120.1 (C-10), 56.9 (OCH_3), 56.8 (OCH_3), 53.7 (C-1′), 31.8 (C-2′), 29.4 (C-3′), 29.3 (C-4′), 29.2 (C-5′), 29.2 (C-6′), 28.5 (C-7′), 22.6 (C-8′), 22.2 (C-9′), 14.1 (C-10′); ESI-MS: m/z 429.2 $(M + Na)^+$.

*5.1.11. 2-Undecylsulfinyl-5,8-dimethoxy-1,4-naphthoquinone (**3k**)*

It was obtained from **2k** as a red solid in 76.5% yield; mp 119 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 (d, J = 9.6 Hz, 1H), 7.34 (d, J = 10 Hz, 1H), 7.30 (s, 1H), 3.98 (s, 3H), 3.94 (s, 3H), 3.19 (m, 1H), 2.89 (m, 1H), 1.89 (m, 1H), 1.55 (m, 1H), 1.41 (2H), 1.22 (m, 14H), 0.83 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.0 (C-1), 181.9 (C-4), 154.6 (C-5), 154.4 (C-8), 154.3 (C-2), 136.9 (C-3), 121.6 (C-7), 120.9 (C-6), 120.3 (C-9), 120.1 (C-10), 56.8 (OCH_3), 56.7 (OCH_3), 53.7 (C-1′), 31.9 (C-2′), 29.5 (C-3′), 29.5 (C-4′), 29.3 (C-5′), 29.3 (C-6′), 29.2 (C-7′), 28.5 (C-8′), 22.6 (C-9′), 22.2 (C-10′), 14.1 (C-11′); ESI-MS: m/z 443.0 $(M + Na)^+$.

*5.1.12. 2-Dodecylsulfinyl-5,8-dimethoxy-1,4-naphthoquinone (**3l**)*

It was obtained from **2l** as a red solid in 33% yield; mp 104 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, J = 9.6 Hz, 1H), 7.30 (d, J = 9.6 Hz, 1H), 7.29 (s, 1H), 3.99 (s, 6H), 3.22 (m, 1H), 2.90 (m, 1H), 1.90 (m, 1H), 1.67 (m, 1H), 1.43 (m, 2H), 1.24 (m, 16H), 0.88 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.0 (C-1), 181.9 (C-4), 154.6 (C-5), 154.4 (C-8), 154.3 (C-2), 136.8 (C-3), 121.6 (C-7), 120.9 (C-6), 120.3 (C-9), 120.1 (C-10), 56.8 (OCH_3), 56.7 (OCH_3), 53.7 (C-1′), 31.8 (C-2′), 29.6 (C-3′), 29.5 (C-4′), 29.5 (C-5′), 29.3 (C-6′), 29.3 (C-7′), 29.2 (C-8′), 28.5 (C-9′), 22.7 (C-10′), 22.2 (C-11′), 14.1 (C-12′); ESI-MS: m/z 457.1 $(M + Na)^+$.

*5.1.13. 2-Pentadecansulfinyl-5,8-dimethoxy-1,4-naphthoquinone (**3m**)*

It was obtained from **2m** as an orange solid in 71.6% yield; mp 110 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, J = 9.6 Hz, 1H), 7.36 (d, J = 9.6 Hz, 1H), 7.29 (s, 1H), 3.99 (s, 3H), 3.98 (s, 3H), 3.22 (m, 1H), 2.90 (m, 1H), 1.90 (m, 1H), 1.68 (m, 1H), 1.45 (m, 2H), 1.24 (m, 22H), 0.87 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.9 (C-1), 181.8 (C-4), 154.6 (C-5), 154.4 (C-8), 154.2 (C-2), 136.8 (C-3), 121.7 (C-7), 121.0 (C-6), 120.3 (C-9), 120.2 (C-10), 56.9 (OCH_3), 56.7 (OCH_3), 53.7 (C-1′), 31.9 (C-2′), 29.6 (C-3′), 29.6 (C-4′), 29.6 (C-5′), 29.5 (C-6′), 29.5 (C-7′), 29.4 (C-8′), 29.3 (C-9′), 29.3 (C-10′), 29.1 (C-11′), 28.5 (C-12′), 22.6 (C-13′), 22.2 (C-14′), 14.1 (C-15′); ESI-MS: m/z 499.1 $(M + Na)^+$.

*5.1.14. 2-Octadecansulfinyl-5,8-dimethoxy-1,4-naphthoquinone (**3n**)*

It was obtained from **2n** as an orange solid in 52.3% yield; mp 116 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, J = 9.6 Hz, 1H), 7.36 (d, J = 9.6 Hz, 1H), 7.28 (s, 1H), 3.99 (s, 3H), 3.98 (s, 3H), 3.22 (m, 1H), 2.90 (m, 1H), 1.90 (m, 1H), 1.67 (m, 1H), 1.44 (m, 2H), 1.25 (m, 28H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.9 (C-1), 181.8 (C-4), 154.6 (C-5), 154.4 (C-8), 154.2 (C-2), 136.8 (C-3), 121.7 (C-7), 120.9 (C-6), 120.4 (C-9), 120.2 (C-10), 56.8 (OCH_3), 56.7 (OCH_3), 53.7 (C-1′), 31.8 (C-2′), 29.6 (C-3′), 29.6 (C-4′), 29.6 (C-5′), 29.6 (C-6′), 29.6 (C-7′), 29.5 (C-8′), 29.5 (C-9′), 29.5 (C-10′), 29.4 (C-11′), 29.3 (C-12′), 29.3 (C-13′), 29.1 (C-14′), 28.5 (C-15′), 22.6 (C-16′), 22.2 (C-17′), 14.0 (C-18′); ESI-MS: m/z 541.0 $(M + Na)^+$.

*5.2. General procedure for the synthesis of compounds **4a**–**4n***

To a solution of 2-alkylthio-5,8-dimethoxy1,4-naphthoquinones (**2a**–**2n**, 0.21 mmol) in chloroform (20 ml), 77% *m*-chloroperoxybenzoic acid (0.43 mmol) was added at room temperature, stirred, and monitored by TLC. When the starting was disappeared, the chloroform solution was washed with sodium hydrogen carbonate solution, dried over sodium sulfate, and evaporated. The residue was purified on silica gel column chromatography (HX:EA = 2:1–1:2), to give alkylsulfonyl-5,8-diemthoxy-1,4-naphthoquinones (**4a**–**4n**).

*5.2.1. Synthesis of 2-methylsulfonyl-5,8-dimethoxy-1,4-naphthoquinone (**4a**)*

It was obtained from **2a** as a dark red solid in 46.9% yield; mp 211 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 (s, 1H), 7.41 (s, 2H), 3.99 (s, 6H), 3.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.6 (C-1), 179.6 (C-4), 154.4 (C-5), 154.0 (C-8), 145.5 (C-2), 139.4 (C-3), 121.3 (C-7), 121.3

(C-6), 120.7 (C-10), 120.2 (C-9), 56.9 (OCH_3), 56.9 (OCH_3), 43.8 (C-1′); ESI-MS: *m*/*z* 318.9 $(M + Na)^+$.

*5.2.2. 2-Ethylsulfonyl-5,8-dimethoxy-1,4-naphthoquinone (**4b**)*

It was obtained from **2b** as a dark red solid in 65.9% yield; mp 164 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.49 (s, 1H), 7.41 (s, 2H), 3.98 (s, 6H), 3.57 (q, *J* = 7.2 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.4 (C-1), 179.5 (C-4), 154.3 (C-5), 154.0 (C-8), 144.0 (C-2), 140.6 (C-3), 121.3 (C-7), 121.3 (C-6), 120.6 (C-10), 120.1 (C-9), 56.8 (OCH_3), 56.8 (OCH_3), 49.9 (C-1′), 6.8 (C-2′); ESI-MS: *m*/*z* 332.9 $(M + Na)^+$.

*5.2.3. 2-Propylsulfonyl-5,8-dimethoxy-1,4-naphthoquinone (**4c**)*

It was obtained from **2c** as a dark red solid in 20.7% yield; mp 208 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.50 (s, 1H), 7.41 (s, 2H), 3.99 (s, 6H), 3.53 (t, *J* = 8.4 Hz, 2H), 1.80 (m, 2H), 1.06 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.6 (C-1), 179.7 (C-4), 154.3 (C-5), 154.0 (C-8), 144.7 (C-2), 140.3 (C-3), 121.3 (C-7), 121.3 (C-6), 120.6 (C-10), 120.2 (C-9), 56.8 (OCH_3), 56.8 (OCH_3), 57.1 (C-1′), 16.1 (C-2′), 12.9 (C-3′); IT-TOF/MS: *m*/*z* 347.0533 $(M + Na)^+$.

*5.2.4. 2-Butylsulfonyl-5,8-dimethoxy-1,4-naphthoquinone (**4d**)*

It was obtained from **2d** as a dark red solid in 60.3% yield; mp 112 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.47 (s, 1H), 7.40 (s, 2H), 3.98 (s, 6H), 3.53 (t, *J* = 8.0 Hz, 2H), 1.74 (m, 2H), 1.45 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.6 (C-1), 179.7 (C-4), 154.4 (C-5), 154.0 (C-8), 144.7 (C-2), 140.3 (C-3), 121.3 (C-7), 121.3 (C-6), 120.6 (C-10), 120.2 (C-9), 56.9 (OCH_3), 56.8 (OCH_3), 55.3 (C-1′), 24.1 (C-2′), 21.6 (C-3′), 13.2 (C-4′); ESI-MS: *m*/*z* 360.9 $(M + Na)^+$.

*5.2.5. 2-Pentylsulfonyl-5,8-dimethoxy-1,4-naphthoquinone (**4e**)*

It was obtained from **2e** as a dark red solid in 33.3% yield; mp 42 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.47 (s, 1H), 7.41 (s, 2H), 3.98 (s, 6H), 3.52 (t, *J* = 8.0 Hz, 2H), 1.75 (m, 2H), 1.34 (m, 4H), 0.88 (t, *J* = 7.2 Hz, 3H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.5 (C-1), 179.6 (C-4), 154.3 (C-5), 153.9 (C-8), 144.6 (C-2), 140.2 (C-3), 121.3 (C-7), 121.3 (C-6), 120.6 (C-10), 120.2 (C-9), 56.8 (OCH_3), 56.8 (OCH_3), 55.4 (C-1′), 30.3 (C-2′), 22.0 (C-3′), 21.8 (C-4′), 13.6 (C-5′); IT-TOF/MS: *m*/*z* 353.1050 $(M + H)^+$.

*5.2.6. 2-Hexylsulfonyl-5,8-dimethoxy-1,4-naphthoquinone (**4f**)*

It was obtained from **2f** as a dark red solid in 32% yield; mp 40 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.47 (s, 1H), 7.40 (s, 2H), 3.99 (s, 6H), 3.53 (t, *J* = 8.0 Hz, 2H), 1.75 (m, 2H), 1.42 (m, 2H), 1.28 (m, 4H), 0.86 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.5 (C-1), 179.6 (C-4), 154.3 (C-5), 153.9 (C-8), 144.6 (C-2), 140.2 (C-3), 121.3 (C-7), 121.3 (C-6), 120.6 (C-10), 120.2 (C-9), 56.8 (OCH_3), 56.8 (OCH_3), 55.4 (C-1′), 31.0 (C-2′), 27.8 (C-3′), 22.2 (C-4′), 22.0 (C-5′), 13.8 (C-6′); IT-TOF/MS: *m*/*z* 367.1212 $(M + H)^+$.

*5.2.7. 2-Heptylsulfonyl-5,8-dimethoxy-1,4-naphthoquinone (**4g**)*

It was obtained from **2g** as a dark red solid in 29.7% yield; mp 79 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.49 (s, 1H), 7.40 (s, 2H), 3.98 (s, 6H), 3.55–3.47 (m, 2H), 1.79–1.71 (m, 2H), 1.41–1.39 (m, 2H), 1.30–1.21 (m, 6H), 0.86 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.6 (C-1), 179.7 (C-4), 154.4 (C-5), 154.0 (C-8), 144.7 (C-2), 140.3 (C-3), 121.3 (C-7), 121.3 (C-6), 120.7 (C-10), 120.3 (C-9), 56.9 (OCH_3), 56.8 (OCH_3), 55.5 (C-1′), 31.4 (C-2′), 28.6 (C-3′), 28.2 (C-4′), 22.4 (C-5′), 22.2 (C-6′), 13.9 (C-7′); IT-TOF/MS: *m*/*z* 381.1358 $(M + H)^+$.

*5.2.8. 2-Octylsulfonyl-5,8-dimethoxy-1,4-naphthoquinone(**4h**)*

It was obtained from **2h** as a dark red solid in 32% yield; mp 92 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.49 (s, 1H), 7.41 (s, 2H), 3.99 (s, 6H), 3.53 (t, *J* = 8.0 Hz, 2H), 1.75 (m, 2H), 1.40 (m, 2H), 1.25 (m, 8H), 0.86 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.6 (C-1), 179.7 (C-4), 154.4 (C-5), 154.0 (C-8), 144.7 (C-2), 140.3 (C-3), 121.3 (C-7), 121.3 (C-6), 120.7 (C-10), 120.2 (C-9), 56.9 (OCH_3), 56.8 (OCH_3), 55.5 (C-1′), 31.6 (C-2′), 29.7 (C-3′), 28.9 (C-4′), 28.2 (C-5′), 22.5 (C-6′), 22.2 (C-7′), 14.0 (C-8′); IT-TOF/MS: *m*/*z* 417.1319 $(M + Na)^+$.

*5.2.9. 2-Nonylsulfonyl-5,8-dimethoxy-1,4-naphthoquinone (**4i**)*

It was obtained from **2i** as a dark red solid in 40.1% yield; mp 101 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.49 (s, 1H), 7.40 (s, 2H), 3.99 (s, 6H), 3.53 (t, *J* = 8.4 Hz, 2H), 1.75 (m, 2H), 1.40 (m, 2H), 1.24 (m, 10H), 0.86 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.6 (C-1), 179.7 (C-4), 154.4 (C-5), 154.0 (C-8), 144.7 (C-2), 140.3 (C-3), 121.3 (C-7), 121.3 (C-6), 120.6 (C-10), 120.3 (C-9), 56.9 (OCH_3), 56.8 (OCH_3), 55.5 (C-1′), 31.8 (C-2′), 29.2 (C-3′), 29.1 (C-4′), 28.4 (C-5′), 28.2 (C-6′), 22.6 (C-7′), 22.2 (C-8′), 14.1 (C-9′); ESI-MS: *m*/*z* 430.7 $(M + Na)^+$.

*5.2.10. 2-Decylsulfonyl-5,8-dimethoxy-1,4-naphthoquinone (**4j**)*

It was obtained from **2j** as a dark red solid in 31.4% yield; mp 127 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.47 (s, 1H), 7.40 (s, 2H), 3.98 (s, 6H), 3.52 (t, *J* = 8.4 Hz, 2H), 1.74 (m, 2H), 1.41 (m, 2H), 1.24 (m, 12H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.5 (C-1), 179.6 (C-4), 154.3 (C-5), 153.9 (C-8), 144.6 (C-2), 140.3 (C-3), 121.3 (C-7), 121.3 (C-6), 120.6 (C-10), 120.2 (C-9), 56.8 (OCH_3), 56.8 (OCH_3), 55.5 (C-1′), 31.7 (C-2′), 29.3 (C-3′), 29.1 (C-4′), 29.1 (C-5′), 28.9 (C-6′), 28.2 (C-7′), 22.5 (C-8′), 22.1 (C-9′), 14.0 (C-10′); IT-TOF/MS: *m*/*z* 445.1643 $(M + Na)^+$.

*5.2.11. 2-Undecylsulfonyl-5,8-dimethoxy-1,4-naphthoquinone (**4k**)*

It was obtained from **2k** as a dark red solid in 31.2% yield; mp 84 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.47 (s, 1H), 7.43 (s, 2H), 3.98 (s, 6H), 3.52 (t, *J* = 8.0 Hz, 2H), 1.75 (m, 2H), 1.40 (m, 2H), 1.23 (m, 14H), 0.87 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.6 (C-1), 179.7 (C-4), 154.3 (C-5), 154.0 (C-8), 144.6 (C-2), 140.3 (C-3), 121.3 (C-7), 121.3 (C-6), 120.6 (C-10), 120.2 (C-9), 56.8 (OCH_3), 56.8 (OCH_3), 55.5 (C-1′), 31.7 (C-2′), 29.3 (C-3′), 29.2 (C-4′), 29.1 (C-5′), 29.1 (C-6′), 28.9 (C-7′), 28.2 (C-8′), 22.5 (C-9′), 22.1 (C-10′), 14.1 (C-11′); ESI-MS: *m*/*z* 459.1 $(M + Na)^+$.

*5.2.12. 2-Dodecylsulfonyl-5,8-dimethoxy-1,4-naphthoquinone (**4l**)*

It was obtained from **2l** as a dark red solid in 41.6% yield; mp 78 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.48 (s, 1H), 7.40 (d, *J* = 9.6 Hz, 1H), 3.99 (s, 6H), 3.53 (t, *J* = 8.0 Hz, 2H), 1.74 (m, 2H), 1.41 (m, 2H), 1.23 (m, 16H), 0.87 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.6 (C-1), 179.7 (C-4), 154.3 (C-5), 154.0 (C-8), 144.6 (C-2), 140.3 (C-3), 121.3 (C-7), 121.3 (C-6), 120.6 (C-10), 120.2 (C-9), 56.8 (OCH_3), 56.8 (OCH_3), 55.5 (C-1′), 31.8 (C-2′), 29.5 (C-3′), 29.5 (C-4′), 29.4 (C-5′), 29.3 (C-6′), 29.2 (C-7′), 29.0 (C-8′), 28.2 (C-9′), 22.6 (C-10′), 22.1 (C-11′), 14.1 (C-12′); ESI-MS: *m*/*z* 473.1 $(M + Na)^+$.

*5.2.13. 2-Pentadecansulfonyl-5,8-dimethoxy-1,4-naphthoquinone (**4m**)*

It was obtained from **2m** as a dark red solid in 60.1% yield; mp 90 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.48 (s, 1H), 7.42 (s, 2H), 3.98 (s, 6H), 3.52 (t, *J* = 8.0 Hz, 2H), 1.74 (m, 2H), 1.41 (m, 2H), 1.24 (m, 22H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.5 (C-1), 179.7 (C-4), 154.3 (C-5), 154.0 (C-8), 144.6 (C-2), 140.3 (C-3), 121.3 (C-7), 121.2 (C-6), 120.7 (C-10), 120.2 (C-9), 56.8 (OCH_3), 56.8 (OCH_3), 55.5 (C-1′), 31.8 (C-2′), 29.6 (C-3′), 29.6 (C-4′), 29.6 (C-5′), 29.5 (C-6′), 29.5 (C-7′), 29.4 (C-8′), 29.3 (C-9′), 29.2 (C-10′), 28.9 (C-11′), 28.2 (C-12′), 22.6 (C-13′), 22.1 (C-14′), 14.0 (C-15′); ESI-MS: *m*/*z* 515.1 $(M + Na)^+$.

*5.2.14. 2-Octadecansulfonyl-5,8-dimethoxy-1,4-naphthoquinone (**4n**)*

It was obtained from **2n** as a dark red solid in 14.8% yield; mp 83 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.48 (s, 1H), 7.40 (s, 2H), 3.98 (s,

6H), 3.52 (m, 2H), 1.75 (m, 2H), 1.39 (m, 2H), 1.25 (m, 28H), 0.87 (t, $J = 6.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.5 (C-1), 179.6 (C-4), 154.3 (C-5), 153.9 (C-8), 144.6 (C-2), 140.3 (C-3), 121.3 (C-7), 121.2 (C-6), 120.6 (C-10), 120.2 (C-9), 56.8 (OCH_3), 56.8 (OCH_3), 55.5 (C-1′), 31.8 (C-2′), 29.6 (C-3′), 29.6 (C-4′), 29.6 (C-5′), 29.6 (C-6′), 29.5 (C-7′), 29.5 (C-8′), 29.5 (C-9′), 29.4 (C-10′), 29.3 (C-11′), 29.2 (C-12′), 28.9 (C-13′), 28.3 (C-14′), 28.2 (C-15′), 22.6 (C-16′), 22.1 (C-17′), 14.1 (C-18′); IT-TOF/MS: m/z 557.2942 $(M + Na)^+$.

5.3. General procedure for the synthesis of 2-alkylthio-1,4-napthoquinones **6a**–**6n**

To a solution of 1,4-naphthoquinone (**5**, 0.45 mmol) in MeOH (30 ml), the corresponding sodium thiomethoxide for **6a** or akylthiols for **6b**–**6n** (0.81 mmol) were added. The mixture was stirred at room temperature overnight. Brine (200 ml) was added to the solution and extracted with dichloromethane (200 ml × 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and then concentrated under reduced pressure. The resulting residue was recrystallized with methanol to give 2-alyklthio-1,4-naphthoquinones **6a**–**6n**.

5.3.1. 2-Methylthio-1,4-naphthoquinone (**6a**)

It was obtained from **5** in 14% yield as a yellow solid using sodium thiomethoxide; mp 185 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03 (m, 2H), 7.68 (m, 2H), 6.50 (s, 1H), 2.31 (s, 3H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.0 (C-4), 181.4 (C-1), 156.0 (C-2), 134.3, 133.2 (C-6, C-7), 132.2, 131.8 (C-9, C-10), 126.8 (C-5, C-8), 126.5 (C-3), 13.8 (C-1′); ESI-MS: m/z 205.1 $(M + H)^+$.

5.3.2. 2-Ethylthio-1,4-naphthoquinone (**6b**)

It was obtained from **5** in 40.7% yield as dark yellow solid using 1-ethanethiol; mp 135 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (m, 2H), 7.72 (m, 2H), 6.60 (s, 1H), 2.88 (q, $J = 7.2$ Hz, 2H), 1.44 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.0 (C-4), 181.5 (C-1), 155.0 (C-2), 134.2, 133.2 (C-6, C-7), 132.1, 131.8 (C-9, C-10), 126.9, 126.8 (C-5, C-8), 126.4 (C-3), 24.6 (C-1′), 12.3 (C-2′); ESI-MS: m/z 219.1 $(M + H)^+$.

5.3.3. 2-Propylthylthio-1,4-naphthoquinone (**6c**)

It was obtained from **5** in 33.9% yield as an orange solid using 1-propanethiol; mp 118 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (m, 2H), 7.72 (m, 2H), 6.60 (s, 1H), 2.82 (t, $J = 7.2$ Hz, 3H), 1.81 (m, 2H), 1.11 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.0 (C-4), 181.5 (C-1), 155.2 (C-2), 134.2, 133.1 (C-6, C-7), 132.1, 131.8 (C-9, C-10), 126.9, 126.8 (C-5, C-8), 126.4 (C-3), 32.5 (C-1′), 20.8 (C-2′), 13.6 (C-3′); ESI-MS: m/z 233.0 $(M + H)^+$.

5.3.4. 2-Butylthio-1,4-naphthoquinone (**6d**)

It was obtained from **5** in 33.9% yield as an orange solid using 1-butanethiol; mp 97 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08 (m, 2H), 7.71 (m, 2H), 6.60 (s, 1H), 2.83 (t, $J = 7.32$ Hz, 2H), 1.74 (m, 2H), 1.53 (m, 2H), 0.98 (t, $J = 7.32$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.0 (C-4), 181.4 (C-1), 155.2 (C-2), 134.2, 133.1 (C-6, C-7), 132.1, 131.8 (C-9, C-10), 126.9, 126.7 (C-5, C-8), 126.4 (C-3), 30.3 (C-1′), 29.2 (C-2′), 22.1 (C-3′), 13.5 (C-4′); ESI-MS: m/z 247.1 $(M + H)^+$.

5.3.5. 2-Pentylthio-1,4-naphthoquinone (**6e**)

It was obtained from **5** in 15.3% yield as a dark yellow solid using 1-pentanethiol; mp 111 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (m, 2H), 7.72 (m, 2H), 6.60 (s, 1H), 2.82 (t, $J = 7.2$ Hz, 2H), 1.76 (m, 2H), 1.47 (m, 2H), 1.34 (m, 2H), 0.92 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.0 (C-4), 181.4 (C-1), 155.2 (C-2), 134.2, 133.1 (C-6, C-7), 132.1, 131.8 (C-9, C-10), 126.9, 126.7 (C-5, C-8), 126.4 (C-3), 31.1 (C-1′), 30.6 (C-2′), 26.9 (C-3′), 22.1 (C-4′), 13.8 (C-5′); ESI-MS: m/z 261.0 $(M + H)^+$.

5.3.6. 2-Hexylthio-1,4-naphthoquinone (**6f**)

It was obtained from **5** in 15% yield as a dark yellow solid using 1-hexanethiol; mp: 101 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10 (m, 2H), 7.72 (m, 2H), 6.61 (s, 1H), 2.83 (t, $J = 7.2$ Hz, 2H), 1.77 (m, 2H), 1.49 (m, 2H), 1.34 (m, 4H), 0.90 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.1 (C-4), 181.5 (C-1), 155.3 (C-2), 134.2, 133.2 (C-6, C-7), 132.2, 131.9 (C-9, C-10), 126.9, 126.8 (C-5, C-8), 126.5 (C-3), 31.2 (C-1′), 30.6 (C-2′), 28.7 (C-3′), 27.2 (C-4′), 22.4 (C-5′), 13.9 (C-6′); ESI-MS: m/z 275.3 $(M + H)^+$.

5.3.7. 2-Heptylthio-1,4-naphthoquinone (**6g**)

It was obtained from **5** in 46.4% yield as a dark yellow solid using 1-heptanethiol; mp:118 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08 (m, 2H), 7.74 (m, 2H), 6.59 (s, 1H), 2.82 (t, $J = 7.6$ Hz, 2H), 1.77 (quint, $J = 7.2$ Hz, 2H), 1.48 (m, 2H), 1.32 (m, 6H), 0.89 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.0 (C-4), 181.4 (C-1), 155.2 (C-2), 134.2, 133.1 (C-6, C-7), 132.1, 131.8 (C-9, C-10), 126.9, 126.7 (C-5, C-8), 126.4 (C-3), 31.5 (C-1′), 30.6 (C-2′), 28.9 (C-3′), 28.6 (C-4′), 27.2 (C-5′), 22.4 (C-6′), 13.9 (C-7′); ESI-MS: m/z 289.2 $(M + H)^+$.

5.3.8. 2-Octylthio-1,4-naphthoquinone (**6h**)

It was obtained from **5** in 76.8% yield as a yellow solid % yield using 1-octanethiol; mp 101 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (m, 2H), 7.73 (m, 2H), 6.60 (s, 1H), 2.82 (t, $J = 7.2$ Hz, 2H), 1.77 (quint, $J = 7.2$ Hz, 2H), 1.48 (m, 2H), 1.28 (m, 8H), 0.88 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.1 (C-4), 181.5 (C-1), 155.3 (C-2), 134.2, 133.2 (C-6, C-7), 132.1, 131.8 (C-9, C-10), 126.9, 126.8 (C-5, C-8), 126.4 (C-3), 31.7 (C-1′), 30.6 (C-2′), 29.0 (C-3′), 29.0 (C-4′), 29.0 (C-5′), 27.2 (C-6′), 22.5 (C-7′), 14.1 (C-8′); ESI-MS: m/z 325.2 $(M + Na)^+$.

5.3.9. 2-Nonylthio-1,4-naphthoquinone (**6i**)

It was obtained from **5** in 87.4% yield as a dark yellow solid using 1-nonanethiol; mp: 105 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (m, 2H), 7.74 (m, 2H), 6.61 (s, 1H), 2.83 (t, $J = 7.2$ Hz, 2H), 1.77 (quint, $J = 7.6$ Hz, 2H), 1.48 (m, 2H), 1.27 (m, 10H), 0.88 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.0 (C-4), 181.4 (C-1), 155.2 (C-2), 134.1, 133.1 (C-6, C-7), 132.1, 131.8 (C-9, C-10), 126.8, 126.7 (C-5, C-8), 126.4 (C-3), 31.7 (C-1′), 30.6 (C-2′), 29.3 (C-3′), 29.1 (C-4′), 29.0 (C-5′), 28.9 (C-6′), 27.2 (C-7′), 22.5 (C-8′), 14.0 (C-9′); ESI-MS: m/z 338.5 $(M + Na)^+$.

5.3.10. 2-Decylthio-1,4-naphthoquinone (**6j**)

It was obtained from **5** in 65.8% yield as a yellow solid using 1-decanethiol; mp 101 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (m, 2H), 7.72 (m, 2H), 6.59 (s, 1H), 2.82 (t, $J = 7.2$ Hz, 2H), 1.76 (quint, $J = 7.6$ Hz, 2H), 1.48 (m, 2H), 1.27 (m, 12H), 0.88 (t, $J = 6.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.0 (C-4), 181.4 (C-1), 155.2 (C-2), 134.2, 133.1 (C-6, C-7), 132.1, 131.8 (C-9, C-10), 126.9, 126.7 (C-5, C-8), 126.4 (C-3), 31.8 (C-1′), 30.8 (C-2′), 30.6 (C-3′), 29.4 (C-4′), 29.3 (C-5′), 29.2 (C-6′), 29.0 (C-7′), 27.2 (C-8′), 22.6 (C-9′), 14.0 (C-10′); ESI-MS: m/z 331.1 $(M + H)^+$.

5.3.11. 2-Undecylthio-1,4-naphthoquinone(**6k**)

It was obtained from **5** in 81.8% yield as a dark yellow solid using 1-undecanethiol; mp 111 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10 (m, 2H), 7.63 (m, 2H), 6.50 (s, 1H), 2.82 (t, $J = 7.2$ Hz, 2H), 1.76 (quint, $J = 7.6$ Hz, 2H), 1.48 (m, 2H), 1.29 (m, 14H), 0.88 (t, $J = 6.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.1 (C-4), 181.5 (C-1), 155.3 (C-2), 134.2, 133.1 (C-6, C-7), 132.1, 131.9 (C-9, C-10), 126.9, 126.8 (C-5, C-8), 126.4 (C-3), 31.8 (C-1′), 30.6 (C-2′), 29.5 (C-3′), 29.5 (C-4′), 29.3 (C-5′), 29.2 (C-6′), 29.0 (C-7′), 29.0 (C-8′), 27.3 (C-9′), 22.6 (C-10′), 14.0 (C-11′); ESI-MS: m/z 345.2 $(M + H)^+$.

*5.3.12. 2-Dodecylthio-1,4-naphthoquinone(**6l**)*

It was obtained from **5** in 72.4% yield as a yellow solid using 1-dodecanethiol; mp 113 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (m, 2H), 7.72 (m, 2H), 6.50 (s, 1H), 2.82 (t, J = 7.2 Hz, 2H), 1.77 (quint, J = 7.6 Hz, 2H), 1.46 (m, 2H), 1.27 (m, 12H), 0.88 (t, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.1 (C-4), 181.5 (C-1), 155.2 (C-2), 134.2, 133.2 (C-6, C-7), 132.2, 131.9 (C-9, C-10), 126.9, 126.8 (C-5, C-8), 126.5 (C-3), 31.8 (C-1′), 30.9 (C-2′), 30.6 (C-3′), 29.5 (C-4′), 29.5 (C-5′), 29.4 (C-6′), 29.3 (C-7′), 29.1 (C-8′), 29.0 (C-9′), 27.3 (C-10′), 22.6 (C-11′), 14.0 (C-12′); ESI-MS: m/z 359.2 $(M + H)^+$.

*5.3.13. 2-Pentadecylthio-1,4-naphthoquinone(**6m**)*

It was obtained from **5** in 70.1% yield as a yellow solid using 1-pentadecanethiol; mp 110 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (m, 2H), 7.73 (m, 2H), 6.60 (s, 1H), 2.82 (t, J = 7.2 Hz, 2H), 1.76 (quint, J = 7.2 Hz, 2H), 1.48 (m, 2H), 1.25 (m, 22H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.1 (C-4), 181.5 (C-1), 155.3 (C-2), 134.2, 133.2 (C-6, C-7), 132.2, 131.9 (C-9, C-10), 126.9, 126.8 (C-5, C-8), 126.4 (C-3), 31.8 (C-1′), 30.6 (C-2′), 29.6 (C-3′), 29.6 (C-4′), 29.6 (C-5′), 29.5 (C-6′), 29.5 (C-7′), 29.5 (C-8′), 29.4 (C-9′), 29.3 (C-10′), 29.0 (C-11′), 29.0 (C-12′), 27.3 (C-13′), 22.6 (C-14′), 14.1 (C-15′); ESI-MS: m/z 401.3 $(M + H)^+$.

*5.3.14. 2-Octadecylthio-1,4-naphothoquinone(**6n**)*

It was obtained from **5** in 47.8% yield as a yellow solid using 1-octadecanethiol; mp 114 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10 (m, 2H), 7.70 (m, 2H), 6.61 (s, 1H), 2.82 (t, J = 7.4 Hz, 2H), 1.75 (quint, J = 7.6 Hz, 2H), 1.48 (m, 2H), 1.25 (m, 28H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.1 (C-4), 181.5 (C-1), 155.3 (C-2), 134.2, 133.2 (C-6, C-7), 132.2, 131.9 (C-9, C-10), 126.9, 126.8 (C-5, C-8), 126.5 (C-3), 31.9 (C-1′), 30.6 (C-2′), 29.6 (C-3′), 29.6 (C-4′), 29.6 (C-5′), 29.6 (C-6′), 29.6 (C-7′), 29.6 (C-8′), 29.6 (C-9′), 29.5 (C-10′), 29.5 (C-11′), 29.4 (C-12′), 29.4 (C-13′), 29.3 (C-14′), 29.1 (C-15′), 29.0 (C-15′), 27.3 (C-16′), 22.6 (C-17′), 14.1 (C-18′); ESI-MS: m/z 443.3 $(M + H)^+$.

*5.4. General procedure for the synthesis of compounds **7a**–**7n***

Under ice-cooling, 77% of *m*-chloroperoxybenzoic acid (0.23 mmol) was added portionwise to a solution of 2-alkyl-1,4-naphthoquinones **6a**–**6n** (0.21 mmol) in chloroform (20 ml), stirred, and monitored by TLC. When the starting was disappeared, the chloroform solution was washed with sodium hydrogen carbonate solution, dried over sodium sulfate, and then evaporated. The residue was purified on silica gel column chromatography (HX:EA = 2:1), to give 2-alkylsulfonyl-1,4-naphthoquinones **7a**–**7n**.

*5.4.1. Synthesis of 2-methylsulfinyl-1,4-naphthoquinone (**7a**)*

It was obtained from **6a** in 24.7% yield as a brown solid; mp 83 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (m, 2H), 7.83 (m, 2H), 7.54 (s, 1H), 2.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.2 (C-1), 182.0 (C-4), 157.2 (C-2), 136.2 (C-3), 135.0, 134.3 (C-6, C-7), 132.2, 131.7 (C-9, C-10), 127.1, 126.5 (C-5, C-8), 40.9 (C-1′); IT-TOF/MS: m/z 243.0065 $(M + Na)^+$.

*5.4.2. 2-Ethylsulfinyl-1,4-naphthoquinone (**7b**)*

It was obtained from **6b** in 86.3% yield as a brown solid; mp 81 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (m, 2H), 7.83 (m, 2H), 7.48 (s, 1H), 3.31 (dt, J = 20.8, 7.2 Hz, 1H), 3.01 (dt, J = 20.8, 7.2 Hz, 1H), 1.34 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.2 (C-1), 182.0 (C-4), 155.0 (C-2), 137.5 (C-3), 134.9, 134.2 (C-6, C-7), 132.3, 131.7 (C-9, C-10), 127.1, 126.6 (C-5, C-8), 46.7 (C-1′), 5.8 (C-2′); IT-TOF/MS: m/z 257.0216 $(M + Na)^+$.

*5.4.3. 2-Propylsulfinyl-1,4-naphthoquinone (**7c**)*

It was obtained from **6c** in 77.2% yield as a brown solid; mp 75 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.13 (m, 2H), 7.83 (m, 2H), 7.43 (s, 1H), 3.22 (m, 1H), 2.94 (m, 1H), 1.99 (m, 1H), 1.76 (m, 1H), 1.11 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.2 (C-1), 182.0 (C-4), 155.9 (C-2), 136.9 (C-3), 134.9, 134.2 (C-6, C-7), 132.2, 131.7 (C-9, C-10), 127.1, 126.5 (C-5, C-8), 55.4 (C-1′), 15.9 (C-2′), 13.0 (C-3′); IT-TOF/MS: m/z 271.0375 $(M + Na)^+$.

*5.4.4. 2-Butyllsulfinyl-1,4-naphthoquinone (**7d**)*

It was obtained from **6d** in 63% yield as a brown solid; mp 71 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11 (m, 2H), 7.81 (m, 2H), 7.48 (s, 1H), 3.25 (m, 1H), 2.95 (m, 1H), 1.94 (m, 1H), 1.67 (m, 1H), 1.50 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.1 (C-1), 181.9 (C-4), 155.7 (C-2), 136.8 (C-3), 134.9, 134.2 (C-6, C-7), 132.1, 131.6 (C-9, C-10), 127.0, 126.5 (C-5, C-8), 53.2 (C-1′), 24.0 (C-2′), 21.6 (C-3′), 13.5 (C-4′); IT-TOF/MS: m/z 285.0530 $(M + Na)^+$.

*5.4.5. 2-Pentylsulfinyl-1,4-naphthoquinone (**7e**)*

It was obtained from **6e** in 24.5% yield as a brown solid; mp 91 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16 (m, 2H), 7.83 (m, 2H), 7.49 (s, 1H), 3.24 (m, 1H), 2.94 (m, 1H), 1.97 (m, 1H), 1.70 (m, 1H), 1.40 (m, 4H), 0.90 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.2 (C-1), 182.0 (C-4), 155.8 (C-2), 136.9 (C-3), 134.9, 134.2 (C-6, C-7), 132.2, 131.7 (C-9, C-10), 127.1, 126.5 (C-5, C-8), 53.6 (C-1′), 30.5 (C-2′), 22.1 (C-3′), 21.8 (C-4′), 13.7 (C-5′); IT-TOF/MS: m/z 299.0685 $(M + Na)^+$.

*5.4.6. 2-Hexylsulfinyl-1,4-naphthoquinone (**7f**)*

It was obtained from **6f** in 47.2% yield as a brown solid; mp 67 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (m, 2H), 7.82 (m, 2H), 7.49 (s, 1H), 3.23 (m, 1H), 2.93 (m, 1H), 1.96 (m, 1H), 1.66 (m, 1H), 1.47 (m, 2H), 1.30 (m, 4H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.2 (C-1), 182.0 (C-4), 156.0 (C-2), 136.9 (C-3), 134.9, 134.2 (C-6, C-7), 132.2, 131.7 (C-9, C-10), 127.1, 126.6 (C-5, C-8), 53.6 (C-1′), 31.2 (C-2′), 28.1 (C-3′), 22.3 (C-4′), 22.1 (C-5′), 13.9 (C-6′); IT-TOF/MS: m/z 313.0843 $(M + Na)^+$.

*5.4.7. 2-Heptylsulfinyl-1,4-naphthoquinine (**7g**)*

It was obtained from **6g** in 80% yield as a dark brown solid; mp 48 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (m, 2H), 7.82 (m, 2H), 7.49 (s, 1H), 3.23 (m, 1H), 2.95 (m, 1H), 1.99 (m, 1H), 1.66 (m, 1H), 1.46 (m, 2H), 1.33 (m, 6H), 0.86 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.2 (C-1), 182.0 (C-4), 155.6 (C-2), 136.9 (C-3), 134.9, 134.2 (C-6, C-7), 132.2, 131.7 (C-9, C-10), 127.0, 126.5 (C-5, C-8), 53.5 (C-1′), 31.4 (C-2′), 28.7 (C-3′), 28.4 (C-4′), 22.4 (C-5′), 22.1 (C-6′), 13.9 (C-7′); IT-TOF/MS: m/z 327.1000 $(M + Na)^+$.

*5.4.8. 2-Octylsulfinyl-1,4-naphthoquinone (**7h**)*

It was obtained from **6h** in 95.1% yield as a brown solid; mp 63 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (m, 2H), 7.83 (m, 2H), 7.48 (s, 1H), 3.24 (m, 1H), 2.94 (m, 1H), 1.95 (m, 1H), 1.69 (m, 1H), 1.46 (m, 2H), 1.29 (m, 8H), 0.86 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.2 (C-1), 182.0 (C-4), 155.7 (C-2), 136.8 (C-3), 134.9, 134.2 (C-6, C-7), 132.2, 131.7 (C-9, C-10), 127.0, 126.5 (C-5, C-8), 53.5 (C-1′), 31.5 (C-2′), 28.9 (C-3′), 28.9 (C-4′), 28.4 (C-5′), 22.4 (C-6′), 22.0 (C-7′), 13.9 (C-8′); IT-TOF/MS: m/z 341.1159 $(M + Na)^+$.

*5.4.9. 2-Nonylsulfinyl-1,4-naphthoquinone (**7i**)*

It was obtained from **6i** in 66.8% yield as an orange solid; 66.8%; mp 86 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (m, 2H), 7.83 (m, 2H), 7.48 (s, 1H), 3.23 (m, 1H), 2.92 (m, 1H), 1.95 (m, 1H), 1.68 (m, 1H), 1.46 (m, 2H), 1.30 (m, 10H), 0.86 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.2 (C-1), 182.0 (C-4), 156.0 (C-2), 136.8 (C-3), 134.9, 134.2 (C-6, C-7), 132.2, 131.7 (C-9, C-10), 127.0, 126.5 (C-5, C-8), 53.6 (C-1′), 31.7 (C-2′), 29.2 (C-3′), 29.1 (C-4′), 29.0 (C-5′), 28.4 (C-6′), 22.5 (C-7′), 22.1 (C-8′), 14.0 (C-9′); IT-TOF/MS: m/z 355.1321 $(M + Na)^+$.

*5.4.10. 2-Decylsulfinyl-1,4-naphthouinone (**7j**)*

It was obtained from **6j** in 62.3% yield as an orange solid; mp 82 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.12 (m, 2H), 7.83 (m, 2H), 7.49 (s, 1H), 3.24 (m, 1H), 2.95 (m, 1H), 1.94 (m, 1H), 1.69 (m, 1H), 1.45 (m, 2H), 1.24 (m, 12H), 0.86 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.2 (C-1), 182.0 (C-4), 155.7 (C-2), 136.9 (C-3), 134.9, 134.2 (C-6, C-7), 132.2, 131.7 (C-9, C-10), 127.0, 126.5 (C-5, C-8), 53.5 (C-1′), 31.7 (C-2′), 29.3 (C-3′), 29.2 (C-4′), 29.1 (C-5′), 29.0 (C-6′), 28.4 (C-7′), 22.5 (C-8′), 22.1 (C-9′), 14.0 (C-10′); IT-TOF/MS: m/z 369.1485 $(M + Na)^+$.

*5.4.11. 2-Undecylsulfinyl-1,4-naphthoquinone (**7k**)*

It was obtained from **6k** in 61.6% yield as an orange solid; mp 83 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15 (m, 2H), 7.83 (m, 2H), 7.49 (s, 1H), 3.23 (m, 1H), 2.92 (m, 1H), 1.94 (m, 1H), 1.68 (m, 1H), 1.46 (m, 2H), 1.28 (m, 14H), 0.87 (t, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.3 (C-1), 182.0 (C-4), 156.0 (C-2), 136.9 (C-3), 134.9, 134.2 (C-6, C-7), 132.2, 131.8 (C-9, C-10), 127.1, 126.5 (C-5, C-8), 53.6 (C-1′), 31.8 (C-2′), 29.5 (C-3′), 29.4 (C-4′), 29.3 (C-5′), 29.2 (C-6′), 29.0 (C-7′), 28.5 (C-8′), 22.6 (C-9′), 22.1 (C-10′), 14.0 (C-11′); IT-TOF/MS: m/z 383.1636 $(M + Na)^+$.

*5.4.12. 2-Dodecylsulfinyl-1,4-naphthoquinone (**7l**)*

It was obtained from **6l** in 95.2% yield as an orange solid; mp 68 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (m, 2H), 7.83 (m, 2H), 7.50 (s, 1H), 3.24 (m, 1H), 2.94 (m, 1H), 1.96 (m, 1H), 1.69 (m, 1H), 1.46 (m, 2H), 1.24 (m, 16H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.2 (C-1), 182.0 (C-4), 155.8 (C-2), 136.9 (C-3), 134.9, 134.2 (C-6, C-7), 132.2, 131.7 (C-9, C-10), 127.1, 126.5 (C-5, C-8), 53.5 (C-1′), 31.8 (C-2′), 29.5 (C-3′), 29.5 (C-4′), 29.4 (C-5′), 29.3 (C-6′), 29.2 (C-7′), 29.0 (C-8′), 28.4 (C-9′), 22.6 (C-10′), 22.1 (C-11′), 14.0 (C-12′); IT-TOF/MS: m/z 397.1795 $(M + Na)^+$.

*5.4.13. 2-Pentadecansulfinyl-1,4-naphthoquinone (**7m**)*

It was obtained from **6m** in 42.7% yield as an orange solid; mp 82 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (m, 2H), 7.83 (m, 2H), 7.50 (s, 1H), 3.24 (m, 1H), 2.95 (m, 1H), 1.93 (m, 1H), 1.69 (m, 1H), 1.45 (m, 2H), 1.24 (m, 22H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.2 (C-1), 182.0 (C-4), 155.8 (C-2), 136.9 (C-3), 134.9, 134.2 (C-6, C-7), 132.2, 131.7 (C-9, C-10), 127.1, 126.5 (C-5, C-8), 53.6 (C-1′), 31.8 (C-2′), 29.6 (C-3′), 29.6 (C-4′), 29.6 (C-5′), 29.5 (C-6′), 29.4 (C-7′), 29.3 (C-8′), 29.3 (C-9′), 29.2 (C-10′), 29.0 (C-11′), 28.5 (C-12′), 22.6 (C-13′), 22.1 (C-14′), 14.0 (C-15′); IT-TOF/MS: m/z 439.2273 $(M + Na)^+$.

*5.4.14. 2-Octadecansulfinyl-1,4-naphthoquinone (**7n**)*

It was obtained from **6n** in 67.3% yield as a yellow solid; mp 85 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (m, 2H), 7.83 (m, 2H), 7.50 (s, 1H), 3.24 (m, 1H), 2.93 (m, 1H), 1.95 (m, 1H), 1.69 (m, 1H), 1.48 (m, 2H), 1.24 (m, 28H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.2 (C-1), 182.0 (C-4), 155.4 (C-2), 137.0 (C-3), 134.9, 134.6 (C-6, C-7), 132.2, 131.7 (C-9, C-10), 127.1, 126.5 (C-5, C-8), 53.6 (C-1′), 31.9 (C-2′), 31.5 (C-3′), 29.6 (C-4′), 29.6 (C-5′), 29.6 (C-6′), 29.6 (C-7′), 29.6 (C-8′), 29.6 (C-9′), 29.5 (C-10′), 29.4 (C-11′), 29.3 (C-12′), 29.3 (C-13′), 29.0 (C-14′), 28.5 (C-15′), 22.6 (C-16′), 22.1 (C-17′), 14.1 (C-18′); IT-TOF/MS: m/z 481.2753 $(M + Na)^+$.

5.5. Biological evaluation

5.5.1. Cell culture and treatment

HepG2 cells were grown in Dulbecco's modified Eagle's medium (DMEM; Hyclone, Logan, UT, USA) supplemented with 10% heat-inactivated fetal bovine serum and 1% penicillin/streptomycin for 24 h at 37 °C in 5% CO_2. The cells that reached 90% confluence were seeded into 6-well culture plates. Subsequently, the cells were cultured in serum-free DMEM containing 1% penicillin/streptomycin as well as oleate (400 mmol/L) and palmitate (400 mmol/L), which were conjugated to 0.16% fatty acid-free bovine serum albumin to simulate hyperlipidemic conditions. The lipid-loaded cells were washed with PBS and then incubated with serum-free DMEM with or without compound **4l** (5 and 50 μM) for 6, 12 and 24 h.

5.5.2. DiI staining and Oil Red O staining

HepG2 cells were stained with Vybrant DiI cell labeling solution (Molecular Probes, Carlsbad, CA, USA) according to the manufacturer's instructions. HepG2 cells were also stained with Oil Red O. HepG2 cells were washed with cold PBS prior to fixation with 10% (v/v) formalin for 1 h at room temperature. The fixed cells were washed with distilled water and 60% (v/v) isopropanol. Subsequently, the cells were stained with Oil Red O (0.35%, v/v) for 2 h at room temperature. The stained cells were then rinsed thoroughly and visualized using an Eclipse Ti inverted microscope (Nikon, Tokyo, Japan).

5.5.3. Cellular lipid measurements

The cellular lipids were extracted as described previously [23]. Briefly, HepG2 cells were initially washed with cold PBS. Cellular lipids of HepG2 were then extracted at room temperature with 2 ml of hexane:isopropanol mixture (2:1, v:v). The organic solvent was removed by vacuum centrifugation and the remaining lipids were resuspended in 200 ml of 95% ethanol. Cellular triglycerides and cholesterol were quantified enzymatically using an automatic analyzer (Cobas C111, Roche, Basel, Switzerland) and the concentrations were normalized with total protein concentrations.

5.5.4. ACAT enzyme assay

The reaction mixture, containing 4 μl of rat liver microsomes (10 mg/ml protein), 20 μl of 0.5 M potassium phosphate buffer (pH 7.4, 10 mM, dithiothreitol), 15 μl of BSA (fatty acid free, 40 mg/ml), 2 μl of cholesterol in acetone (20 mg/ml), 41 μl of water and 10 μl of test sample in total volume of 92 μl was pre-incubated for 20 min at 37 °C. The reaction was initiated by the addition of 8 μl of [1-^{14}C] oleoyl-CoA (0.05 μCi; final concentration 10 μM). After 25 min of incubation at 37 °C, the reaction was stopped by addition of 1.0 ml of isopropanol–heptane (4:1, v/v) solution. A mixture of 0.6 ml of heptanes and 0.4 ml of 0.1 M potassium phosphate buffer was then added to the reaction mixture. This was mixed for 2 min and allowed to separate into phases. Cholesterol oleate was recovered in the upper (heptanes) phase. The radioactivity in 100 μl of the upper phase was measured in a 4 ml liquid scintillation vial with 3 ml of scintillation cocktail (Lipoluma, Lumac Co.) using a Perkin–Elmer microbeta liquid scintillation counter (Perkin–Elmer), Background values were obtained using heat inactivated microsomes.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2013.01.020.

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