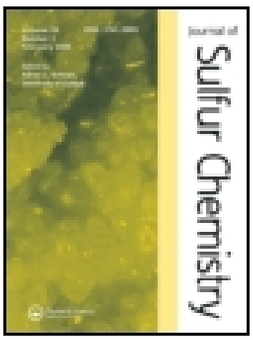

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Synthesis, antibacterial and antifungal evaluation of thio- or piperazinyl-substituted 1,4-naphthoquinone derivatives

Cemil Ibis[a], Zeliha Ozsoy-Gunes[b], Amac Fatih Tuyun[c], Sibel Sahinler Ayla[a], Hakan Bahar[a], Maryna V. Stasevych[d], Rostyslav Ya. Musyanovych[d], Olena Komarovska-Porokhnyavets[c] and Volodymyr Novikov[d]

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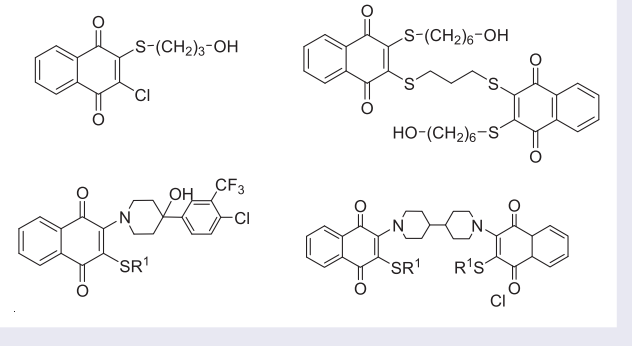
ABSTRACT

A series of S-, S,S-, S,O-, N- and N,S-derivatives from 2,3-dichloro-1,4-naphthoquinone compound **1** were synthesized in different reaction media and evaluated for their antibacterial and antifungal activities. The structures of the novel products were characterized by spectroscopic methods, such as microanalysis, ^{1}H NMR, ^{13}C NMR and MS. Among the tested compounds **9**, **12** and **18** are the most effective compounds against *Candida tenuis* as potent antifungal compounds. Compound **9** is also the most effective compound against *Staphylococcus aureus* as a potent antifungal compound.



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Piperazine; thiol; bipiperidine; 1; 4-naphthoquinone; antibacterial; antifungal activity

1. Introduction

The number of incidence of fungal and bacterial infections has increased dramatically in recent years.[1,2] The widespread use of antifungal and antibacterial drugs and their growing resistance against fungal and bacterial infections has led to serious health hazards.

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Naphthoquinones are important natural substances that are commonly found in different families of plants or animals.[3,4] The biological importance of synthetic or natural organic compounds with a quinone moiety has prompted many scientist to synthesize novel derivatives of 2,3-dichloro-1,4-naphthoquinone **1**.[5–7] Plenty of antibacterial and antifungal agents from **1** have been designed and synthesized in the literature.[8–10]

The structure of nucleophiles in Michael-type reactions affects the biological activity properties.[11] Depending on the nucleophile structure many of quinone derivatives show anti-tuberculosis, anticancer, antimicrobial and antispasmodic activities.[12–15]

In this present work we synthesized new thio- or amino-derivatives as biologically active agents by nucleophilic additions of thiols or amines to the quinone structure and characterized them by spectral methods.

2. Results and discussion

2.1. Chemistry

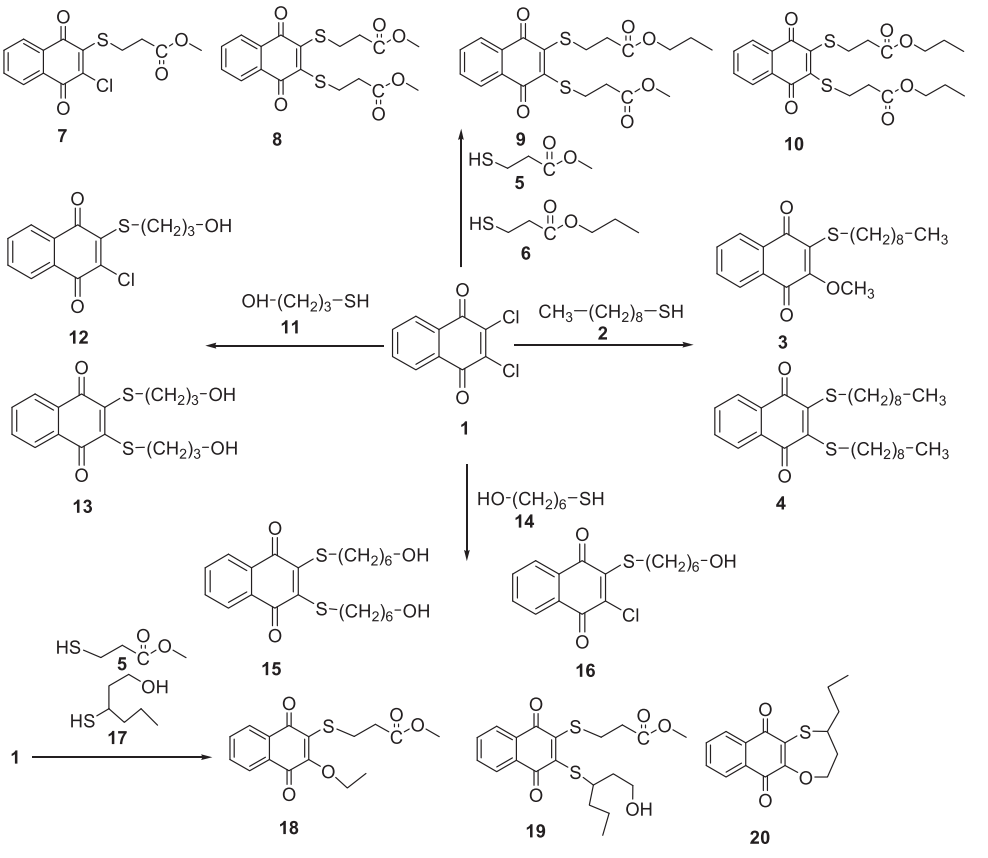
In continuation of our previous work for the synthesis of biologically active quinones, the reaction of 2,3-dichloro-1,4-naphthoquinone **1** with **2** in methanol gave S,O-substituted compound **3** and S,S-substituted compound **4**[9] In the ^{1}H NMR spectra of **3**, protons in ($-OCH_3$) were observed as a singlet at 4.08 ppm. Carbons of the carbonyl groups (C=O) were observed at 177.9 in the ^{13}C NMR spectra of compound **4** [9] as a result of the symmetric structure of molecule (Scheme 1).

Known compounds **7**,[6] **8**,[6] **10** [17] and novel compound **9** were obtained by the reaction of 2,3-dichloro-1,4-naphthoquinone **1** and the mixture of thiols **5** and **6** in ethanol solution of Na_2CO_3. The carbonyl groups in naphthoquinone unit were observed at 177.74 and 177.72 ppm as two peaks in the ^{13}C NMR spectra of **9**.

The characteristic ester carbonyl band and the quinone carbonyl band were seen at 1732 and 1659 cm^{-1}, respectively. Mono(thio)substituted compound **12** and known compound **13** [9] were synthesized from the reaction of **1** and **11**. In the mass spectra of compound **13**, the molecular ion peak was observed at *m/z* 282 $(M)^-$. The reaction of **1** and thioalcohol **14** gave known mono and bis(thio)substituted **15** [17] and **16**.[16] S,O-substituted **18**, S,S-substituted **19** and known cyclic compound **20** [9] were obtained from the reactions of **1** and the mixture of compounds **5** and **17**. The two peaks in the ^{13}C NMR spectra of compound **18** were seen at 177.87 and 181.63 ppm. In the infrared (IR) spectra, the characteristic –OH and ester band were seen at 3516 cm^{-1} for **19**.

Known compound **16** [17] was treated with **6** and S,S-substituted **21** was obtained. The reactions of morpholine **22** and piperazine derivative **24** with **16** in chloroform with Na_2CO_3 gave N,S-substituted compounds **23** and **25**. In the mass spectra of **23** and **25** the molecular ion peaks were observed at *m/z* 376.4 $(M)^+$ and 419.5 $(M)^+$, respectively (Scheme 2).

Interesting compound **27** was synthesized from the reaction of **1** and propanedithiol **26**. In the mass spectra of **27**, the molecular ion peak was observed at *m/z* 684.4 $(M)^+$. N-substituted novel compound **28** was synthesized from the reaction of **1** and **27**. In the mass spectra of **29**, the molecular ion peak was observed at *m/z* 470 $(M+H)^+$. Novel compound **29** was treated with **30a**–**30c** and novel N,S-substituted compounds **31a**–**31c** were obtained in ethanol with Na_2CO_3. In the same way the piperazine-substituted compound **33**[8] was



Scheme 1. Synthesis of novel quinone derivatives.

achieved from the reaction of **1** and **32** in dichloromethane in the presence of Na_2CO_3 (Scheme 3).

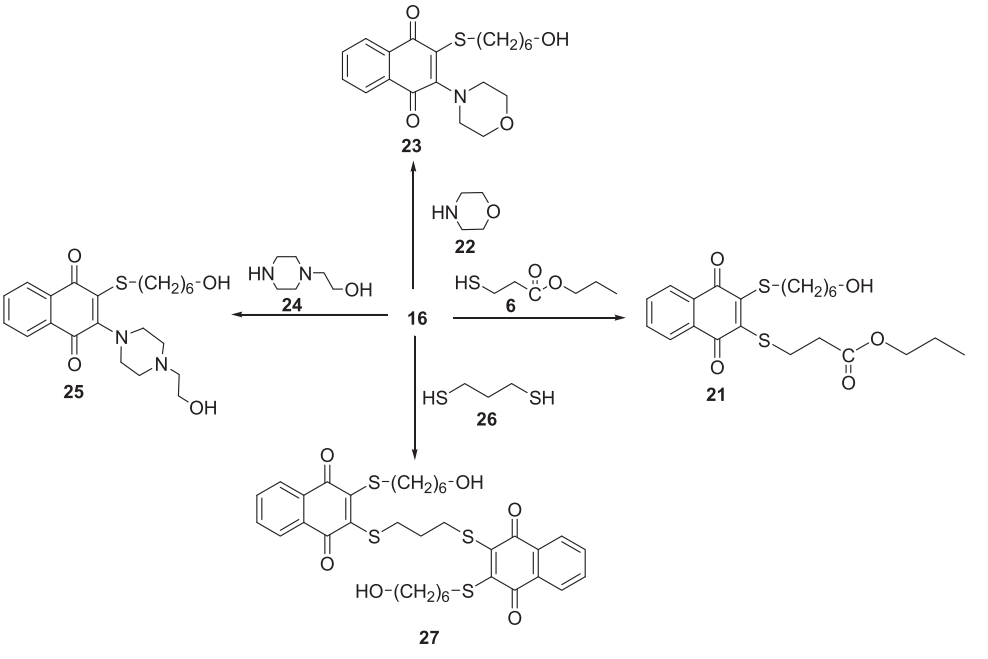
The treatment of **33**[8] with **30b** and **30e** gave N,S-substituted compounds **34b** and **34e**. Novel compound **36** was synthesized from the reaction of **1** and **35** in dichloromethane in the presence of Na_2CO_3. Novel compound **36** was treated with some thiols **30a** and **30b** and gave N,S-substituted compounds **37a** and **37b**.

The reaction of **1** and diamine **38** gave interesting stable compound **39**. Novel compounds **40d** and **40f** were synthesized from the reactions of **39** and **30d–30f**. These compounds are stable and colored compounds and obtained with high yields.

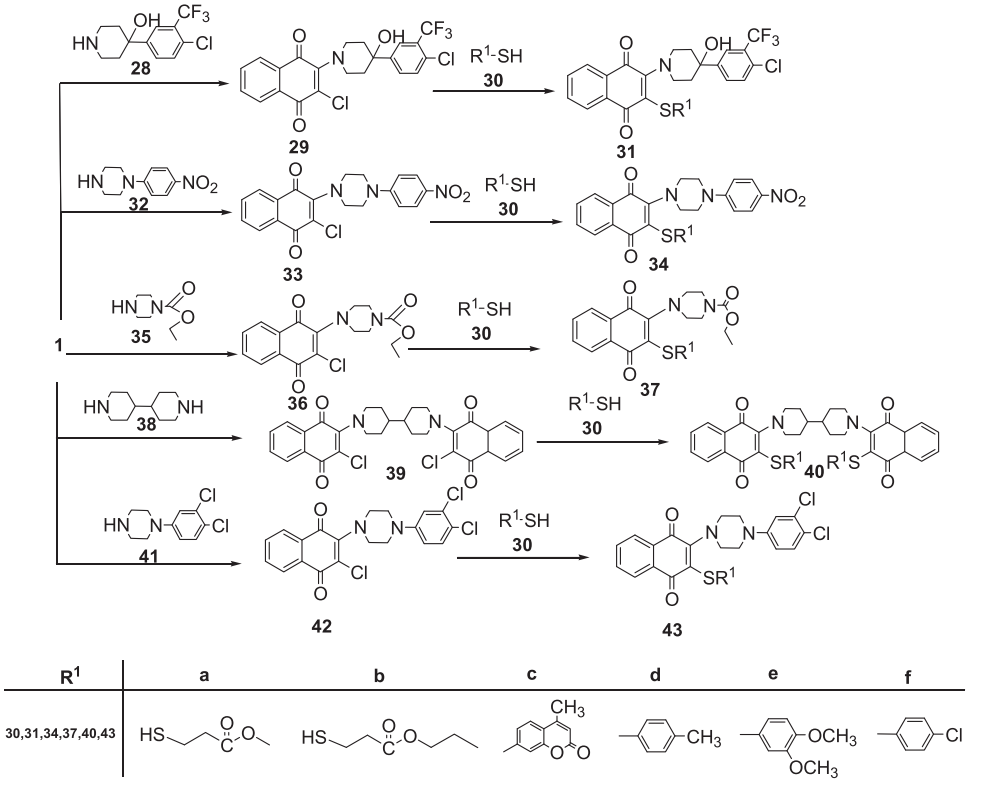
The reactions of 2,3-dichloro-1,4-naphthoquinone **1** with **41** in dichloromethane in the presence of Na_2CO_3 gave compound **42**.[19] Compound **42** was treated with **30b** and N,S-substituted compound **43b** was obtained.

2.2. Pharmacology

The novel naphthoquinone derivatives were evaluated for their antifungal activity against fungi *Candida tenuis VKM Y-70* and *Aspergillus niger F-1119* by the diffusion method [20] and serial dilution method [21] with a view to developing therapeutic agents having



Scheme 2. Synthesis of S,S- and N,S- substituted naphthoquinone derivatives.



R^1	a	b	c	d	e	f
30,31,34,37,40,43	HS–(C=O)–O–	HS–(C=O)–O–	4-methylcoumarin-7-yl	4-methylphenyl	3,4-dimethoxyphenyl	4-chlorophenyl

Scheme 3. Synthesis of novel piperazinyl and N,S- substituted quinones.

broad spectrum in antifungal activity. The antibacterial activity of synthesized compounds was elucidated against *Escherichia coli B-906*, *Staphylococcus aureus 209-P* and *Mycobacterium luteum B-917* by the diffusion method and serial dilution method, as shown in Tables 1 and 2. Their activities were compared with those of the known antibacterial agent Vancomycine and the antifungal agent Nystatin.

Table 1. Antibacterial and antifungal activities of compounds by the diffusion method.

		Inhibition diameter of microorganism growth, mm				
		Antibacterial activity			Antifungal activity	
Compounds	Concentration (%)	*E. coli*	*S. aureus*	*M. luteum*	*C. tenuis*	*A. niger*
3	0.5	0	15.0	9.0	0	16.0
	0.1	0	10.0	7.0	0	10.0
9	0.5	0	9.0	10.7	10.0	13,7
	0.1	0	0	8.0	8.0	7.7
12	0.5	0	22.4	21.4	36.0	17.4
	0.1	0	14.4	12.7	25.0	7.0
15 [18]	0.5	0	13.4	16.0	0	0
	0.1	0	10.0	14.0	0	0
18	0.5	0	12.0	13.7	12.0	14.7
	0.1	0	0	0	10.0	7.0
19	0.5	0	11.7	10.7	11.7	14.4
	0.1	0	8.0	0	9.0	12.0
21	0.5	0	0	12.0	0	0
	0.1	0	0	10.0	0	0
23	0.5	0	0	12.0	0	13.0
	0.1	0	0	0	0	10.0
25	0.5	0	15.0	13.0	0	7.0
	0.1	0	7.0	0	0	0
27	0.5	0	10.4	17.0	0	0
	0.1	0	8.0	10.0	0	0
29	0.5	0	25.0	16.4	0	12.0
	0.1	0	6.0	10.7	0	0
31a	0.5	0	0	12.0	0	15.4
	0.1	0	0	0	0	10.0
31b	0.5	0	0	0	0	10.0
	0.1	0	0	0	0	0
31c	0.5	0	0	0	0	18.7
	0.1	0	0	0	0	0
34b	0.5	0	0	0	0	0
	0.1	0	0	0	0	0
34e	0.5	0	0	10.0	0	15.0
	0.1	0	0	0	0	10.0
36	0.5	0	12.7	12.0	0	16.0
	0.1	0	10.4	0	0	12.0
37a	0.5	0	0	10.7	0	0
	0.1	0	0	0	0	0
37b	0.5	0	0	0	0	0
	0.1	0	0	0	0	0
39	0.5	0	10.0	11.0	25.0	19.4
	0.1	0	0	0	17.0	16.7
40c	0.5	0	0	0	0	0
	0.1	0	0	0	0	0
40f	0.5	0	0	8.0	0	10.0
	0.1	0	0	0	0	0
43b	0.5	0	0	0	0	10.0
	0.1	0	0	0	0	0
C[a]	0.1	14.0	15.0	18.0	19.0	20.0

[a]Vancomycine was used as a control in the tests of antibacterial activity and Nystatin was used in the tests of antifungal activity of the synthesized compounds.

Table 2. Antibacterial and antifungal activities of compounds by the serial dilution method.

	Antibacterial activity			Antifungal activity	
	MIC (μg/mL)			MIC (μg/mL)	
Compound	*E. coli*	*S. aureus*	*M. luteum*	*C. tenuis*	*A. niger*
3	+	250.0	125.0	250.0	62.5
9	+	250.0	62.5	3.9	1.9
12	+	7.8	31.2	0.9	3.9
15 [18]	+	125.0	31.2	+	125.0
18	+	500.0	500.0	3.9	15.6
19	+	250.0	125.0	15.6	0.9
21	+	+	15.6	+	500.0
23	+	+	250.0	62.5	250.0
25	+	500.0	125.0	31.2	250.0
27	+	125.0	62.5	+	250.0
29	+	250.0	250.0	+	62.5
31a	+	+	125.0	+	125.0
31b	+	+	+	+	62.5
31c	+	+	+	250.0	500.0
34b	+	+	+	+	+
34e	+	+	125.0	+	31.2
36	+	125.0	62.5	+	31.2
37a	+	+	500.0	+	250.0
37b	+	+	+	+	+
39	+	62.5	62.5	62.5	7.8
40d	+	+	+	+	+
40f	+	+	62.5	+	125.0
43b	+	+	+	+	125.0

Note: «+» – growth of microorganisms.

As seen from the data presented in Table 1 none of the compounds have showed any sensitivity for *E. coli*. *S. aureus* was sensitive for compounds **9**, **15**, **18**, **19**, **27**, **36**, **39** and most sensitive for compounds **3**, **12**, **25** and **29** for which the diameters of inhibition zones at 0.5% concentration of the investigated compounds were 15.00, 22.4, 15.00, 25.00 mm, respectively. *S. aureus* was not active for other compounds, namely **21**, **23**, **31a–31c**, **34b**, **34e**, **37a**, **40c**, **40f** and **43b**. *M. luteum* was sensitive for compounds **3**, **9**, **15**, **18**, **19**, **21**, **23**, **25**, **29**, **31a**, **37a**, **34e**, **36**, **39** and **40f** for the inhibition zones at 0.5% concentration. In comparison to antibacterial activity with antibacterial drug and our test compound Vancomycine compounds **12** and **27** were active against *M. luteum* having diameter of the inhibition zones 21.4 and 17.00 mm, respectively.

Compounds **31b**, **31c**, **34b**, **37b**, **40c** and **43b** were not sensitive for *M. luteum*. *C. tenuis* and *A. niger* were used to determine the antifungal activity using by the diffusion method. Compounds **3**, **15**, **21**, **23**, **25**, **27**, **29**, **31a–31c**, **34b**, **34e**, **36**, **37a–37b**, **40c**, **40f** and **43b** have no antifungal activity against *C. tenuis* at 0.1% and 0.5% evaluated concentrations by the diffusion method. Furthermore compounds **12** and **39** exhibited high antifungal activity for which the diameters of inhibition zones at 0.5% concentration of the investigated compounds were 36.00 and 25.00 mm, respectively. Other synthesized compounds have moderate activity against *C. tenuis*.

The biological results of the compounds were classified as follows: the antibacterial activity was considered as significant when the minimum inhibition concentration (MIC) was 100 μg/mL or less; moderate, when the MIC was 100–500 μg/mL; weak, when the MIC was 500–1000 μg/mL; and inactive, when the MIC was above 1000 μg/mL.

Evaluation of the antibacterial activity of synthesized compounds showed that compound **12** has a good MIC value at 7.8 μg/mL for *S. aureus*, and compound **39** inhibited growth of *S. aureus at* 62.5 μg/mL (Table 2).

Notable activity for **12** was observed against *C. tenuis* fungi at 0.9 μg/mL concentration. Evaluations of antifungal activity of compounds **9** and **18** showed MIC = 3.9 μg/mL against test-culture *C. tenuis.* MIC values of compounds **23** and **25** were observed at 31.2 and 62.5 μg/mL against test-culture *C. tenuis*, respectively (Table 2). The antifungal activity for *A. niger* for compounds **9** and **19** were seen at 1.9 and 0.9 μg/mL concentrations, respectively. The synthesized naphthoquinone derivatives have no antibacterial activity against *E. coli*.

3. Conclusion

In this study, some of the novel substituted naphthoquinone compounds were synthesized and characterized by using spectral methods. The available compounds were also evaluated for their antifungal and antibacterial activities. Among the tested compounds **12** and **27** were active against *M. luteum* having diameters of the inhibition zones 21.4 and 17.00 mm, for their antibacterial activity. Furthermore compounds **12** and **39** exhibited high antifungal activity for which the diameters of inhibition zones at 0.5% concentration of the investigated compounds were 36.00 and 25.00 mm, respectively. Compounds especially **12** and **25** have been discovered as antibacterial agents. Compound **9** is also the most effective compound against *S. aureus* as a potent antifungal compound.

4. Experimental protocols

4.1. General

Melting points were measured using a Buchi B-540 melting point apparatus and are uncorrected. Elemental analyses were performed on a Thermo Finnigan Flash EA 1112 elemental analyzer. IR spectra were recorded in KBr pellets in Nujol mulls on a Perkin Elmer Precisely Spectrum One FTIR spectrometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded in $CDCl_3$ or DMSO on a Varian Unity INOVA spectrometer. Mass spectra were obtained on a Thermo Finnigan LCQ Advantage MAX LC/MS/MS spectrometer using the ESI technique. Products were isolated by column chromatography on silica gel (Fluka silica gel 60, particle size 63e200 mm). Thin-layer chromatography (TLC) was performed on Merck silica gel plates (60F254), and detection was carried out with ultraviolet light (254 nm). All chemicals were of reagent grade and used without further purification.

4.2. General procedures

4.2.1. General procedure 1: for the synthesis compounds 3, 4

Appropriate amount of 2,3-dichloro-1,4-naphthoquinone **1** and corresponding nucleophile were stirred in methanol (30 mL) with Na_2CO_3 (1.56 g) solution for 2–3 h at room temperature. The color of the solution quickly changed and the reaction was monitored by TLC. Chloroform (30 mL) was added to the reaction mixture. The organic layer was

washed with water (4 × 30 mL), and dried over Na_2SO_4. After the solvent was evaporated the residue was purified by column chromatography on silica gel.

2-Methoxy-3-(nonylthio)naphthalene-1,4-dione ***(3)*** *and 2,3-bis-(nonylthio)naphthalene-1,4-dione* ***(4)*** [9] were synthesized from the reaction of **1** (0.5 g, 2.2 mmol) with **2** (0.35 g, 2.2 mmol) according to the general procedure 1.

(3): Red oil. Yield: 0.08 g (11%). R_f: 0.60 [Petroleum ether/CH_2Cl_2(1:1)]. IR (KBr): ν = 2925, 2854 (C–H), 1660 (C=O), 1591 cm^{-1} (C= C). ^{1}H NMR (499.74 MHz, $CDCl_3$): δ = 0.78 (t, J = 7.32 Hz, 3H, CH_3), 1.16–1.21 (m, 10H, CH_2), 1.30–1.35 (m, 2H, CH_2), 1.51–1.57 (m, 2H, CH_2), 3.08 (t, J = 7.32 Hz, 2H, S–CH_2), 4.08 (s, 3H, O–CH_3), 7.59–7.61 (m, 2H, CH_{arom}), 7.94–7.97 ppm (m, 2H, CH_{arom}). ^{13}C NMR (125.66 MHz, $CDCl_3$): δ = 13.1, 21.6, 27.7, 28.1, 28.2, 28.4, 29.2, 30.8 (CH_2, CH_3), 32.1 (S–CH_2), 60.1 (O–CH_3), 125.3, 125.6, 130.5, 131.3, 132.5, 132.6 (CH_{arom}, C_{arom}), 133.4 (S–C–C=O), 157.0 (O–C–C=O), 177.7, 181.8 ppm (C=O). MS (+ESI): *m/z* 369.09 $(M+Na)^+$. Microanalysis: $C_{20}H_{26}O_3S$ (M, 346.49) = Calculated C, 69.33%; H, 7.56%; S, 9.25%. Found C, 69.41%; H, 7.54%; S, 9.27%.

(4) [9]: Red oil. Yield: 0.12 g (12%). R_f: 0.70 [Petroleum ether/CH_2Cl_2(1:1)]. IR (KBr): ν = 2954, 2925, 2853 (C–H), 1657 (C=O), 1592 cm^{-1} (C=C). ^{1}H NMR (499.74 MHz, $CDCl_3$): δ = 0.79 (t, J = 7.32 Hz 6H, CH_3), 1.17–1.20 (m, 20H, CH_2), 1.31–1.36 (m, 4H, CH_2), 1.52–1.57 (m, 4H, CH_2), 3.19 (t, J = 7.32 Hz, 4H, S–CH_2), 7.58–7.60 (m, 2H, CH_{arom}), 7.95–7.97 ppm (m, 2H, CH_{arom}). ^{13}C NMR (125.66 MHz, $CDCl_3$): δ = 13.1, 21.6, 27.7, 28.1, 28.2, 28.4, 29.5, 30.8 (CH_2, CH_3), 33.9 (S–CH_2), 125.8, 132.1, 132.3 (CH_{arom}, C_{arom}), 146.8 (S–C–C=O), 177.9 ppm (C=O). MS (–ESI): *m/z* 474.22 $(M)^-$. Microanalysis: $C_{28}H_{42}O_2S_2$ (M, 474.77) = Calculated C, 70.84%; H, 8.92%; S, 13.51%. Found C, 70.88%; H, 8.90%; S, 13.48%.

4.2.2. General procedure 2: for the synthesis compounds 7, 8, 9, 10, 18, 19, 20, 30a, 30b, 30c, 33b, 33e, 36a, 36b and 42

An appropriate amount of 2,3-dichloro-1,4-naphthoquinone **1** and corresponding nucleophile were stirred in ethanol (30 mL) with Na_2CO_3 (1.56 g) solution for 2–3 h at room temperature. The color of the solution quickly changed and the reaction was monitored by TLC. Chloroform (30 mL) was added to the reaction mixture. The organic layer was washed with water (4 × 30 mL), and dried over Na_2SO_4. After the solvent was evaporated the residue was purified by column chromatography on silica gel.

Methyl 3-(2-chloro-1,4-dihydro-1,4-dioxonaphthalen-3-ylthio)propanoate ***(7)*** [6], *3,3′-((1,4-Dioxo-1,4-dihydronaphthalen-2,3-diyl)di(sulfandiyl)) dipropanoate* ***(8)*** [6], *Methyl 3-(2-(3-oxoheptilthio)-1,4-dihyhdro-1,4-dioxonaphthalene-3-iltiyo)propanoate* ***(9)*** *and Dibutyl 3,3′-((1,4-dioxo-1,4-dihydronaphthalene-2,3-diyl)bis(sulfanediyl))dipropanoate* ***(10)*** [17] were synthesized by the reaction of **1** (0.6 g, 2.64 mmol) and mixture of **5** and **6** (0.29 mL, 2.64 mmol: 0.43 mL, 2.64 mmol) according to the general procedure 2.

(7) [6]: Yellow solid. Yield: 0.10 g (9%); m.p. 126–127°C; R_f: 0.44 ($CHCl_3$); IR (KBr): υ (cm^{-1}) 3310, 3032 (C–H_{arom}), 2953 (C–H_{aliph}), 1588, 1512 (C=C), 1670, 1727 (C=O); MS (+ESI): 333 $(M+Na)^+$; Anal. Calcd. for $C_{14}H_{11}ClO_4S$ (M, 310.75): C, 54.11%; H, 3.57%; S, 10.32%. Found C, 54.08%; H, 3.56%; S, 10.34%.

(8) [6]: Red solid. Yield: 0.24 g (21%); m. p. 85–86°C; R_f: 0.16 ($CHCl_3$); IR (KBr): υ (cm^{-1}) 3298, 3021 (C–H_{arom}), 2955 (C–H_{aliph}), 1589 (C=C), 1658, 1732 (C=O); MS

(+ESI): 417 $(M+Na)^+$; Anal. Calcd. for $C_{18}H_{18}O_6S_2$ (M, 394.46): C, 54.81%; H, 4.60%; S, 16.26%. Found C, 54.75%; H, 4.61%; S, 16.29%.

(9): Red oil. Yield: 0.45 g (39%). R_f ($CHCl_3$): 0.36. IR (KBr): υ (cm^{-1}) = 3302 ($C–H_{aromatic}$), 2958, 2873 ($C–H_{aliphatic}$), 1591(C=C), 1659 ($C=O_{quinone}$). 1732 ($C=O_{ester}$). ^1H NMR (499.74 MHz, $CDCl_3$): $\delta = 0.84$ (t, $J = 7.32$ Hz, 3H, CH_3), 1.28 (m, 2H, CH_2), 1.52 (m, 2H, CH_2), 2.65 (t, $J = 7.32$ Hz, 4H, (C=O)–CH_2), 3.42 (t, $J = 7.32$ Hz, 4H, S–CH_2), 3.61 (s, 3H, O–CH_3), 4.00 (t, $J = 7.32$ Hz, 2H, O–CH_2), 7.61–7.63 (m, 2H, $CH_{aromatic}$), 7.95–7.97 (m, 2H, $CH_{aromatic}$). ^{13}C NMR (125.66 MHz, $CDCl_3$): $\delta = 12.68$ (CH_3), 28.80, 28.66, 18.09 ($3CH_2$), 28.87, 29.58 (C=O)–CH_2–, 34.28, 34.50 (S–CH_2–), 50.88 (O–CH_3), 63.72 (O–CH_2–), 132.61, 131.80, 125.95 ($C_{aromatic}$), 146.29, 146.37 (=C–S), 170.41, 170.78 ($C=O_{ester}$), 177.74, 177.72 ($C=O_{naphaquinone}$). MS [ESI]: $m/z = 459$ $[M+Na]^+$. Microanalysis: $C_{21}H_{24}O_6S_2$ (M = 436.542 g/mol) = Calculated C, 57.78; H, 5.54; S, 14.69. Found C, 57.55%; H, 5.52%; N, 14.65%.

(10) [17]: Red oil. Yield: 0.17 g (15%); R_f: 0.24 with $CHCl_3$ as an eluent; IR(KBr, cm^{-1}): 2959, 2933, 2873 (C–H), 1659 (quinone C=O), 1734 (ester C=O), 1591 (C=C); MS (+ESI): m/z 479 $(M+H)^+$; $C_{24}H_{30}O_6S_2$ (M, 478.62). Calcd. C, 60.23; H, 6.32; S, 13.40. Found C, 60.15%; H, 6.29%; S, 13.36%.

*Methyl 3-(2-ethoxy-1,4-dihydro-1,4-dioxonaphthalene-3-ylthio)propanoate **(18)**, Methyl 3-(2-(1-hydroxyhexane-3-ylthio)-1,4-dihydro-1,4-dioxonaphthalene-3-ylthio)propanoate **(19)** and 4-propyl-3,4-dihydro-2H-naphtho[2,3-b]* [1,4]*oxathiepine-6,11-dione **(20)*** [9] were synthesized from the reaction of **1** (0.6 g, 2.64 mmol) with mixture of the **5** and **17** (0.29 mL, 2.64 mmol, 0.33 mL, 2.64 mmol) according to the general procedure 2.

(18): Red solid. Yield: 0.32 g (38%). m.p.: 56–57°C. R_f: 0.38 ($CHCl_3$). IR (KBr): υ (cm^{-1}) = 2953, 2983 ($C–H_{aliphatic}$), 1590(C=C), 1660 ($C=O_{quinone}$). 1735 ($C=O_{ester}$). ^1H NMR (499.74 MHz, $CDCl_3$): $\delta = 1.38$ (t, $J = 6.83$ Hz, 3H, CH_3), 2.62 (t, $J = 7.32$ Hz, 2H, (C=O)–CH_2–), 3.35 (t, $J = 7.32$ Hz, 2H, S–CH_2), 3.61 (s, 3H, O–CH_3), 4.43 (q, $J = 10.60$ Hz, 2H, O–CH_2), 7.61–7.64 (m, 2H, $CH_{aromatic}$), 7.96–8.00 (m, 2H, $CH_{aromatic}$). ^{13}C NMR (125.66 MHz, $CDCl_3$): $\delta = 14.88$ (CH_3), 26.83 ((C=O)–CH_2–), 34.18 (S–CH_2), 50.82 (O–CH_3), 69.19 (O–CH_2), 132.71, 132.59, 131.27, 130.37, 125.60 and 125.43 ($C_{aromatic}$), 131.97 (=C–S), 157.01 (=C–N), 170.91 ($C=O_{ester}$), 181.63, 177.87 (C=O). MS [ESI]: $m/z = 343$ $[M+Na]^+$, 321 $[M+H]^+$. Microanalysis: $C_{16}H_{16}O_5S$ (M = 320.36 g/mol) = Calculated C, 59.99; H, 5.03; S, 10.01. Found C, 59.88%; H, 5.01%; S, 10.03%.

(19): Dark red oil. Yield: 0.22 g (20%). R_f: 0.13 (CH_2Cl_2). IR (KBr): υ (cm^{-1}) = 3516 (–OH), 2957, 2931 ($C–H_{aliphatic}$), 1591 (C=C), 1659 ($C=O_{quinone}$). 1736 ($C=O_{ester}$). ^1H NMR (499.74 MHz, $CDCl_3$): $\delta = 0.81$ (t, $J = 7.32$ Hz, 3H, CH_3), 1.18 (s, 1H, OH), 1.90, 1.58, 1.38 (m, 6H, $3CH_2$), 2.67 (t, $J = 7.32$ Hz, 2H, (C=O)–CH_2–), 3.49 (m, 2H, S–CH_2), 3.61 (s, 3H, O–CH_3), 3.71 (m, 1H, S–CH), 3.94 (m, 2H, HO–CH_2), 7.62–7.65 (m, 2H, $CH_{aromatic}$), 7.96–7.99 (m, 2H, $CH_{aromatic}$). ^{13}C NMR (125.66 MHz, $CDCl_3$): $\delta = 12.92$ (CH_3), 46.28, 37.23, 38.57, 19.06 ($4CH_2$), 28.84 ((C=O)–CH_2–), 34.35 (S–CH_2), 50.93 (O–CH_3), 59.00 (HO–CH_2), 132.64, 126.08 and 125.97 ($C_{aromatic}$), 148.81, 145.91 (=C–S), 170.88 ($C=O_{ester}$), 177.70, 178.02 (C=O). MS [ESI]: $m/z = 431$ $[M+Na]^+$. Microanalysis: $C_{20}H_{24}O_5S_2$ (M = 408.532 g/mol) = Calculated C, 58.80; H, 5.92; S, 15.70. Found C, 58.68%; H, 5.90%; S, 15.67%.

(20) [9]: Orange solid. Yield: 0.51 g (40%). m.p. 146.5–148°C. R_f: 0.71 ($CHCl_3$). IR (KBr): υ (cm^{-1}) = 3307, 3068 cm^{-1} (C–H_{arom}), 1587, 1551 (C=C), 1663 (C=O). MS [+ESI]: m/z = 311 $[M+Na]^+$. Anal. Calcd for $C_{16}H_{16}O_3S$ (M, 288.361): C, 66.64%; H, 5.59%; S, 11.12%. Found C, 66.71%; H, 5.61%; S, 11.14%.

Disclosure statement

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