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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis of novel 1,4-naphthoquinone derivatives: antibacterial and antifungal agents

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Abstract A novel series of substituted 1,4-naphthoquinone derivatives was synthesized and evaluated for antibacterial and antifungal activity. The structures of the novel products were characterized by spectroscopic methods. Among the tested compounds, **3a** and **9** are the most effective compounds against *M. luteum* as potent antibacterial and *C. tenuis* and *A. niger* as potent antifungal. These two compounds are promising as biologically active compounds.

Keywords Thio and amino substituted · 1,4-naphthoquinones · Antibacterial and antifungal activity

Introduction

The chemistry of quinones has been studied for over a century since this class of compounds exist in many natural products and numerous important synthetic products (Lamourex *et al*., 2008; Eyong *et al*., 2006; Tandon *et al*., 2005; Paramapojin *et al*., 2008; Ibis *et al*., 2011; Ibis and Sahinler Ayla, 2011; Ibis and Deniz, 2010). Addition of sulfur or nitrogen nucleophiles to naphthoquinones represents a common synthetic route to many fused heterocyclic rings which have been used as synthetic intermediates in medicinal chemistry and for dyestuffs (Corral *et al*., 2006; Ibis *et al*., 2011; Voskiene *et al*., 2011; Takagi *et al*., 1998; Matsumoto *et al*., 2002). Structure–activity relationship studies of quinonoid compounds showed that the position and number of nitrogen atoms were considerably important factors to affect the biological activity properties (Shaikh *et al*., 1986; Ryu *et al*., 2004).

The evaluation of electrochemical properties of naphtho- and benzoquinones have also received a considerable attention because of wide range of quinone's biological process from cellular respiration to blood coagulation (Voet and Voet, 1995). The biological activity of quinones results from their ability to accept one or two electrons to form the corresponding radical anion or dianion species. Since many biologic redox reactions including those with quinones take place in hydrophobic membrane, aprotic solvents are used in many electrochemical experiments (Frontana and Gonzalez, 2005; Guin *et al*., 2011).

Due to their redox potentials (Gutierrez, 1989), various hetero-1,4-naphthoquinones have been found to possess potent antiviral (Ganapaty *et al*., 2006), antimolluscidal (Silva *et al*., 2005), antimalarial (Biot *et al*., 2004; Eyong *et al*., 2006), antileishmanial (Mantyla *et al*., 2004), anticancer, antibacterial, and antifungal activity (Ryu *et al*., 2000a, b; Tandon *et al*., 2009).

Results and discussion

We have earlier synthesized various hetero-1,4-naphthoquinones as potent antibacterial and antifungal agents (Ibis

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et al., 2011). In continuation of our previous work for the synthesis of biologically active quinones, we carried out the reactions of 2,3-dichloro-1,4-naphthoquinone **1** with sulfur nucleophiles **2** using Na_2CO_3 or Et_3N (Scheme 1). It is pertinent to note that further nucleophilic substitution reactions with nitrogen nucleophiles **11a**–**11f** did proceed in satisfactory yields. The nucleophilic substitution reaction in the presence of base is highly chemoselective leading to formation of exclusively aminated monosulfanyl products **12a**–**12f** in high yields (Scheme 2).

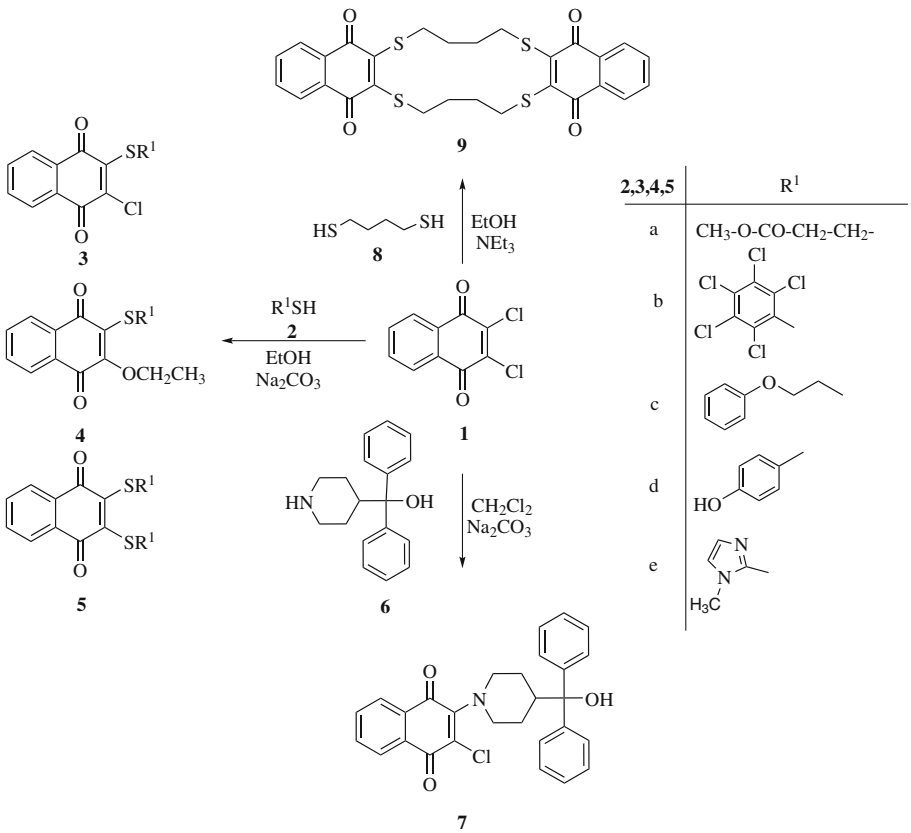
The reactions of 2,3-dichloro-1,4-naphthoquinone (**1**) with different thiols in ethanol in the presence of Na_2CO_3 gave **3a**, **3b**, **4d**, **4e**, **5a**, **5c**, and **5d** compounds (Scheme 1).

While compounds **3a**–**3b** are mono(thio)-substituted naphthoquinone, the naphthoquinones **4d** and **4e** are mono(thio)-substituted ethoxy derivatives. In the mass spectrum of the compounds **4d** and **4e**, the measurement of the molecular ion peak are observed at *m/z* 325 $(M - H)^-$ and 314 $(M)^+$, respectively. In the ^{1}H-NMR spectra of **4d** and **4e**, protons in methylene group (–O–CH_2–) are observed as a multiplet at 4.2 ppm. However, these peaks are not observed in the spectra of mono(thio)-substituted naphthoquinones **3a**–**3b** and bis(thio)-substituted naphthoquinones **5a**, **5c**, and **5d**. In the mass spectra of compounds **5a**, **5c**, and **5d**, the molecular ion peaks were observed at *m/z* 417 $(M + Na)^+$, 462 $(M)^+$, and 405 $(M - H)^-$, respectively.

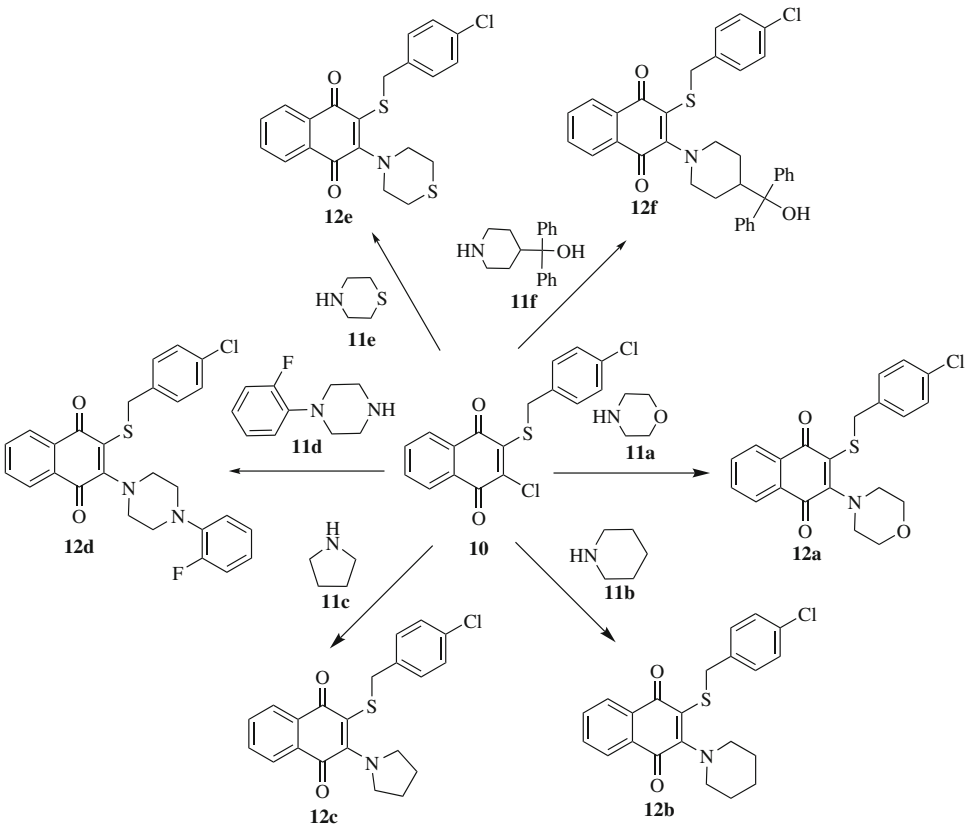
The constitution of compounds **3a**–**3b** is a result of an addition to **1** followed by chloride elimination to afford a quinonyl intermediate that then reacts with a thiol nucleophile to yield the final product. In the absence of thiol nucleophile, the alcohol that is used as reaction media attacks the structure and **4a** and **4e** are formed.

In the ^{13}C NMR spectra of compounds **3a**–**3b**, **4d**, and **4e**, carbon atoms of the carbonyl groups are observed at around 175 and 180 ppm as two peaks while the carbon atom signals of carbonyl groups of **5a**, **5c**, and **5d** are around 179 ppm as one peak only. This data support the structural assignments in Scheme 1.

Furthermore, the reaction of 2,3-dichloro-1,4-naphthoquinone **1** with 1,4-butanedithiol **8** resulted in an intramolecular cyclization to yield novel interesting heterocyclic polythioether compound **9** with diquinone moetiy as shown in Scheme 1. The reaction resulted in the intramolecular cyclization because of the difunctional thiol compound. In the ^{13}C NMR spectra of compound **9**, the carbon atoms of the carbonyl groups are observed at around 180 ppm as one peak only because of the symmetric structure of compound **9**. In the mass spectrum of compound **9**, the measurement of the molecular ion peak was observed at *m/z* 575 $(M + Na)^+$.



Scheme 1 Reaction of 1, 4-naphthoquinones with thiols, 1,4-butandithiol and diphenyl-4-piperidinemethanol



Scheme 2 Reactions of 2-chloro-3-((4-chlorobenzyl) thio) naphthalene-1,4-dione (**10**) with cyclic secondary amines

The amination of 1,4-naphthoquinone was achieved through the substitution of the secondary cyclic amine diphenyl(piperidin-4-yl)methanol **6**, and aminosubstituted 1,4-naphthoquinone derivative **7** was obtained. The IR spectra of compound **7** showed characteristic hydroxyl band (–OH) at 3,520 cm^{-1}. In the ^{13}C NMR spectra of compound **7**, carbon atoms of the carbonyl groups are observed at around 178 and 181 ppm as two peaks.

The reaction of 2,3-dichloro-1,4-naphthoquinone (**1**) with 4-chloro-benzyl thiol in ethanol in the presence of Na_2CO_3 gave 2-chloro-3-((4-chlorobenzyl)thio)naphthalene-1,4-dione **10** (Ibis *et al.*, 2011). The novel N, S-substituted compounds **12a–f** were obtained from the reactions of compound **10** with N-nucleophiles.

The mass spectra of compounds **12a–f** in the positive ion mode for ESI technique confirmed the proposed structure; the molecular ion peaks with sodium adduct were identified at *m/z* 422, 420, 406, 515, and 602, respectively. In the ^1H NMR spectra of compound **12f**, proton in hydroxyl group (–OH) is observed as a singlet at 5.48 ppm.

Some of the novel naphthoquinone derivatives were studied by cyclic voltammetry in aprotic media (DMF) using tetrabutylammonium perchlorate (TBAP) (0.10 M) as supporting electrolyte at 100 mVs^{-1}. Anhydrous DMF was dried overnight with Na_2SO_4. A conventional three-electrode cell was used to carry out the experiments using a glassy carbon disk as a working electrode.

The electrochemical parameters, including cathodic peak potentials (Epc_1 and Epc_2), the half-wave peak potentials ($E_{1,½}$), and the difference between the first oxidation and reduction processes (ΔEp) are given at Table 1.

The cyclic voltammograms are shown in Fig. 1 for DMF + 0.1 M TBAP on Glassy Carbon Electrode at 0.1 V s^{-1}. The compound **9** showed two monoelectronic waves, related with the reversible or quasi-reversible one-electron transfer process to form semiquinone ($Q^{\bullet -}$) and dianion (Q^{2-}) (Frontana and Gonzalez, 2005).

$$Q + e^- \leftrightarrow Q^{\bullet -}$$

$$Q^- + e^- \leftrightarrow Q^{2-}$$

The compound **5a** showed similar cathodic peaks with an intensity decrease of the two quinone reduction waves compared with compound **9**. But the additional peaks were observed in the voltammogram Fig. 1b (Abreu *et al.*, 2004).

In our new endeavors, we have synthesized different (hetero)cyclic naphthoquinones and evaluated their antifungal activity against fungi *Candida tenuis VKM Y-70* and *Aspergillus niger F-1119* by the diffusion method (Murray *et al.*, 1995) and serial dilution method (National Committee for Clinical Laboratory Standard, 1998) with a view to developing therapeutic agents having broad spectrum in antifungal activity. Antibacterial activity of the synthesized

Table 1 Half-wave potentials (for the 1st wave) and electrochemical data for novel naphthoquinone derivatives (10^{-3} M) in DMF/TBAP 0.1 M, $\upsilon = 100$ mV s^{-1}

Compound	E_p (Ic) (V)	E_p (IIc) (V)	ΔEp_1 (mV)	$Ep_{1,1/2}$ (V)
3a	−0.372	−1.057	–	–
3b	−0.272	−1.010	76	−0.2344
5a	−0.459	−1.087	54	−0.4329
5c	−0.486	−1.067	57	−0.4569
9	−0.542	−1.224	102	−0.4908
12a	−0.621	−1.210	90	−0.5767
12b	−0.671	−1.583	145	−0.5985
12c	−0.763	−1.599	147	−0.6573

$\Delta Ep_1 = Epa_1 - Epc_1$

$E_{1,1/2} = (Epa_1 + Epc_1)/2$

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 2 and 3. Their activities were compared with those of the known antibacterial agent Vancomycin and the antifungal agent Nystatin. Afterward, on the basis of structure–activity relationship of antifungal activity of the (hetero)cyclic quinone derivatives, we have further synthesized and screened compounds of **3a–3b** and **12a–12f** for antibacterial and antifungal activity by the diffusion method as shown Table 2.

Data presented in Tables 2, 3, and 4 show that there are substances with antibacterial and fungicidal action among the study compounds. The test-culture *E. coli* appeared not to be sensitive to any compounds. The *S. aureus* was not sensitive to compounds **3b**, **4d**, **4e**, **5c**, **7**, and **12a–12f** and moderately sensitive to compounds **3a**, **5a**, **5d**, and **9** by the diffusion method. The *M. luteum* strain was sensitive to compounds **5a** and **9** at a concentration of 0.5 % (diameter of the inhibition zone was 19.7 and 25.4 mm, respectively).

Antifungal activity against *C. tenuis* was observed for **5a** at concentration of 0.5 % ($d = 15$ mm). *C. tenuis* was sensitive to compounds **3a** and **9** at a concentration of 0.5 % (diameter of the inhibition zone was 13 and 11.4 mm, respectively). Compounds **3b**, **4d**, **5c**, **7**, and **12a–12f** have no antifungal activity against *A. niger* at 0.5 and 0.1 % evaluated concentrations by the diffusion method.

Compounds **3a**, **4e**, and **5d** were found to exhibit low antifungal activity against *A. niger* on comparison with antifungal drug Nystatin evaluated by diffusion method. Compounds **5a** and **9** (at 0.5 % concentration) had better antifungal activity against *A. niger* on comparison with Nystatin Compound **9** was equipotent with Nystatin against A. Niger.

Comparison of antibacterial activity with antibacterial drug Vancomycin (at 0.1 % concentration) showed that **3a** (at 0.5 % concentration), **5a** (at 0.5 and 0.1 %

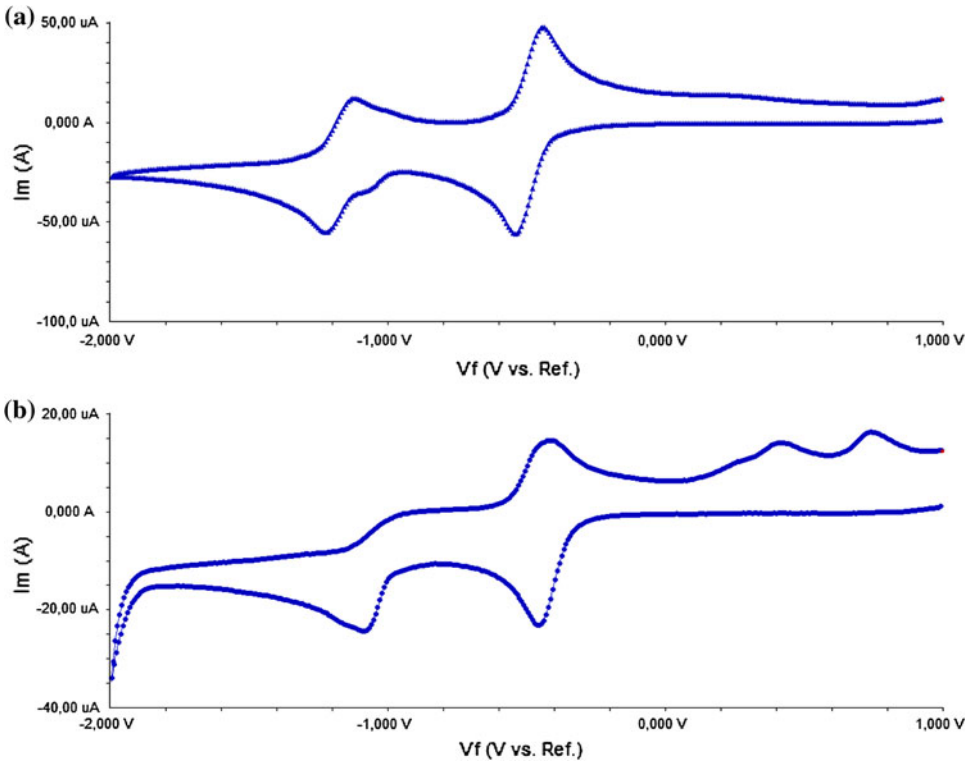


Fig. 1 Cyclic voltammograms of compounds **9** (**a**, Δ) and **5a** (**b**, O) in DMF + 0.1 M TBAP on Glassy Carbon Electrode at 0.1 V s^{-1}

Table 2 Antibacterial and antifungal activities of compounds by diffusion method

Compounds	Concentration (%)	Inhibition diameter of microorganism growth, mm				
		Antibacterial activity			Antifungal activity	
		E. coli	*S. aureus*	*M. luteum*	*C. tenuis*	*A. niger*
3a	0.5	0	8.0	18.0	13.0	10.4
	0.1	0	6.0	9.0	12.4	11.0
3b	0.5	0	0	0	0	0
	0.1	0	0	0	0	0
4d	0.5	0	0	0	0	0
	0.1	0	0	0	0	0
4e	0.5	0	0	0	0	12.0
	0.1	0	0	0	0	0
5a	0.5	0	13.4	19.7	15.0	14.7
	0.1	0	10.0	15.4	10.0	12.4
5c	0.5	0	0	8.0	0	0
	0.1	0	0	0	0	0
5d	0.5	0	9.7	12.7	0	8.0
	0.1	0	6.0	7.0	0	0
7	0.5	0	0	9.0	0	0
	0.1	0	0	7.5	0	0
9	0.5	0	12.0	25.4	11.4	19.4
	0.1	0	10.4	21.4	9.7	16.4
12a	0.5	0	0	8.0	0	0
	0.1	0	0	7.0	0	0
12b	0.5	0	0	9.0	0	0
	0.1	0	0	0	0	0
12c	0.5	0	0	14.4	0	0
	0.1	0	0	8.7	0	0
12d	0.5	0	0	0	0	0
	0.1	0	0	0	0	0
12e	0.5	0	0	13.4	0	0
	0.1	0	0	7.0	0	0
12f	0.5	0	0	0	0	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 of the synthesized compounds, and Nystatin was used in the tests of antifungal activity of the synthesized compounds

concentration), and **9** (at 0.5 and 0.1 % concentration) had better activity against *M. luteum*, with only 5a superior for *S. Aureus.*

The biological results of the compounds were classified as follows: the antibacterial activity was considered as significant when the MIC was 100 μg/mL or less; moderate, when the MIC was 100–500 μg/mL; weak, when the MIC was 500–1,000 μg/mL; and inactive, when the MIC was above 1,000 μg/mL. Evaluation of the antibacterial activity of the synthesized compounds showed that **3a** and **5a** have MIC (minimum inhibition concentration) = 7.8 μg/mL, but **9** was the most potent with MIC = 1.9 μg/mL for *M. luteum* (Table 3).

Notable activity for **3a** and **9** was observed against *C. tenuis* fungi at 1.9 and 3.9 μg/mL concentrations, respectively. Evaluation of antifungal activity of compounds **5d**, **12c**, **12e**, and **12f** showed MIC = 7.8 μg/mL against test-culture *C. tenuis.* MIC of **3a**, **5c**, **5d**, **4d**, **4e**, **5a**, **9**, and **12c** were observed at 7.8–15.6 μg/mL against test-culture *A. niger* (Table 4).

The biological activities of the synthesized compounds can be correlated with their structures. It has been observed that the compounds **3a** and **5a** having the long chain ester group show more significant antibacterial activity among the other compounds. The heterocyclic dinaphthoquinone compound **9** also has a powerful effect on both antibacterial and antifungal activity. It can be related with the cyclic and dinaphthoquinone structure of compound **9**.

We have synthesized compound **10** with a slight antifungal activity in our previous study (Ibis *et al*., 2011). In

Table 3 Antibacterial activities of compounds by serial dilution method

Compounds	MIC (μg/mL)		
	E. coli	*S. aureus*	*M. luteum*
3a	+	+	7.8
3b	+	+	+
4d	+	+	125.0
4e	+	+	+
5a	+	250.0	7.8
5c	+	+	+
5d	+	125.0	250.0
7	+	+	+
9	+	500.0	1.9
12a	+	+	+
12b	+	+	250.0
12c	+	250.0	125.0
12d	+	+	+
12e	+	+	125.0
12f	+	+	+

+: Growth of microorganisms

Table 4 Antifungal activities of compounds by serial dilution method

Compounds	MIC (μg/mL)	
	C. tenuis	*A. niger*
3a	1.9	7.8
3b	125.0	250.0
4d	31.2	15.6
4e	250.0	15.6
5a	15.6	15.6
5c	125.0	7.8
5d	7.8	7.8
7	+	+
9	3.9	15.6
12a	+	+
12b	+	+
12c	7.8	15.6
12d	+	+
12e	7.8	31.2
12f	7.8	31.2

+: Growth of microorganisms

this study, the compound **10**'s antifungal activity significantly increased after the substitution of thiomorpholine and pyrrolidine moiety. For example, compounds **12c** and **12e** show antifungal activities against *C. tenuis*. Piperidine derivative **12b** has no activity for antifungal evaluation. But piperidine derivative with hydroxyl and phenyl group show better antifungal activity with a MIC value of 7.8 μg/mL for *C. tenuis*. The compound **10**'s antifungal activity has decreased after the substitution of morpholine, piperidine, and phenylpiperazine.

Conclusion

In conclusion, compounds especially **3a** and **9** have been discovered as potent antibacterial and antifungal agents. A convenient synthesis route to prepare 2- and 2,3-substituted naphthalene-1,4-diones from 2,3-dichloro-1,4-naphthoquinone has been reported. The synthesized compounds have been employed to prepare new antifungal agents with low MICs against *S. aureus*, *M. luteum* bacteria and *C. tenuis* and *A. niger* fungi in comparison with controls. The results showed that some of the compounds (**9** and **3a**) have strong activity against *M. Luteum*; and **3a**, **9**, **5d**, **12c**, **12e**, and **12f** have strong activity against both *C. tenuis* and *A. niger*. Whereas, the some compounds (**7**, **12a**, **12b**, and **12d**) did not show any significant antifungal and antibacterial activity against fungi and bacteria species. Among the tested compounds, **3a** and **9** are the most effective compounds against *M. luteum* as potent antibacterial and *C. tenuis* and *A. niger* as potent antifungal. These two compounds are promising as biologically active compounds.

Experimental section

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. Infrared (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 CD_3OD, $CDCl_3$, and 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 63–200 μm). Thin-layer chromatography (TLC) was performed on Merck silica gel plates ($60F_{254}$), and detection was carried out with ultraviolet light (254 nm). All chemicals were reagent grade and used without further purification.

Cyclic Voltammetry measurements were performed in a conventional three-electrode cell using a computer-controlled system of a Gamry Reference 600 Model potentiostat/galvanostat. A glassy carbon disk was used as a working electrode. The surface of the working electrode was polished with alumina before each run. A platinum wire served as the counter electrode. The reference electrode was an Ag/AgCl electrode. Electrochemical grade tetrabutylammonium perchlorate (TBAP) in extra pure DMF was employed as the supporting electrolyte at a concentration of 0.10 M. Prior to each run solutions were

purged with nitrogen. Measurements were made over a potential range between 1 and −2 V with a step rate of 0.1 V s^{-1}.

General procedures for the synthesis of 1, 4-naphthoquinones

General procedure 1: for the synthesis of mono-, disulfanyl-1,4-naphthoquinones, and ethoxy sulfanyl-1,4-naphthoquinones

Sodium carbonate (1.52 g) was dissolved in ethanol as reaction media (65 mL). 2,3-Dichloro-1,4-naphthoquinone (**1**) and thiol (**2a**–**2e**) were added to the solution. Without heating, the mixture was stirred for 6–8 h. The color of the solution changed quickly, and the extent of the reaction was monitored by TLC. The reaction mixture was extracted in a Soxhlet extractor with dichloromethane. After recovery of the solvent, the crude product was purified by column chromatography.

*Methyl 3-(2-chloro-1,4-dihydro-1,4-dioxonaphthalen-3-ylthio)propanoate (**3a**)* and *3,3′-((1,4-Dioxo-1,4-dihydronaphthalen-2,3-diyl)di(sulfandiyl)) dipropanoate (**5a**)* were synthesized by the reaction of **1** (1 g, 4.38 mmol) and **2a** (0.49 mL, 4.38 mmol) by general procedure 1.

*(**3a**):* Yellow solid; yield 0.71 g (52 %); 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); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.71 (t, J = 7.32 Hz, 2H, (C=O)–CH_2–), 3.55 (t, J = 7.32 Hz, 2H, S–CH_2), 3.63 (s, 3H, O–CH_3), 7.65–7.69 (m, 2H, CH_{arom}), 8.01–8.08 (m, 2H, CH_{arom});^{13}C NMR (125 MHz, $CDCl_3$): δ 29.33 ((C=O)–CH_2–), 35.55 (S–CH_2), 52.21 (O–CH_2–), 134.44, 134.15, 132.79, 131.42, 127.63, 127.50 (C_{arom}), 148.37, 140.68 (=C–S), 179.99, 175.23, 171.86 (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, 54.06; H, 3.45; S, 12.25 %.

*(**5a**):* Red solid; yield 0.61 g (35 %); 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); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.65 (t, J = 7.32 Hz, 4H, (C=O)–CH_2–), 3.41 (t, J = 7.32 Hz, 4H, S–CH_2), 3.59 (s, 6H, O–CH_3), 7.59–7.63 (m, 2H, CH_{arom}), 7.93–7.97 (m, 2H, CH_{arom}); ^{13}C NMR (125 MHz, $CDCl_3$): δ 30.03 ((C=O)–CH_2–), 35.49 (S–CH_2), 52.09 (O–CH_2–), 133.81, 133.02, 127.14 (C_{arom}), 147.50 (=C–S), 178.92, 171.96 (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, 53.96; H, 4.78; S, 17.54 %.

*2-Chloro-3-(perchlorophenylthio)naphthalene-1,4-dione (**3b**)* was synthesized by the reaction of **1** (1 g, 4.38 mmol) and **2b** (1.24 g, 4.38 mmol) by general procedure 1.

*(**3b**):* Yellow solid; yield 1.62 g (78 %); m.p. 265–266 °C; R_f: 0.57 (PET:$CHCl_3$ = 2:1); IR (KBr): υ (cm^{-1}) 3311 (C–H_{arom}), 1589, 1538 (C=C), 1665 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89–7.91 (d, J = 7.32 Hz, 1H, CH_{arom}), 8.10–8.11 (d, J = 7.32 Hz, 1H, CH_{arom}), 7.64–7.71 (m, 2H, CH_{arom}); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 135.60, 134.02, 133.51, 133.28, 131.47, 130.71, 130.51, 130.13, 126.67, 126.56 (C_{arom}), 144.69, 139.74 (=C–S), 176.75, 174.14 (C=O); Anal. Calcd. for $C_{16}H_4Cl_6O_2S$ (M, 472.98): C, 40.63; H, 0.85; S, 6.78 %. Found C, 40.53; H, 0.90; S, 7.45 %.

*2-(4-Hydroxyphenylthio)-3-ethoxynaphthalene-1,4-dione (**4d**)* and *2,3-bis(4-hydroxyphenylthio)naphthalene-1,4-dione (**5d**)* were synthesized by the reaction of 1 (1 g, 4.38 mmol) and **2d** (0.555 g, 4.38 mmol) by general procedure 1.

*(**4d**):* Black solid, yield 0.51 g (33 %); m.p. 288–289 °C; R_f: 0.85 ($CHCl_3$); IR (KBr): υ (cm^{-1}) 3374 (O–H), 2959 (C–H_{arom}), 2925 (C–H_{aliph}), 1661(C=O), 1593 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.2 (t, J = 6.83, 3H, CH_3), 4.2 (q, 2H, O–CH_2), 5.6 (s, 1H, O–H), 6.6–8 (m, 8H, CH_{arom}); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.57 (CH_3), 69 (O–CH_2), 125.50, 125.73 (–C–S), 129.44, 130.42, 131.15, 132.32, 132.86, 133.12, 134.33 (C_{arom}), 154.98 (C–O), 157.16 (C–OH), 178.74, 181.46 (C=O); MS (–ESI): 325 $(M - H)^-$; Anal. Calcd. for $C_{18}H_{14}O_4S$ (M, 326.37): C, 66.24; H, 4.32; S, 9.82 %. Found C, 66.65; H, 4.54; S, 10.12 %.

*(**5d**):* Black solid; yield 0.47 g (30 %); m.p. 240–241 °C; R_f: 0.75 ($CHCl_3$); IR (KBr): υ (cm^{-1}) 3406 (O–H), 2978 (C–H_{arom}), 2926 (C–H_{aliph}), 1662(C=O), 1587 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.1 (s, 2H, O–H), 6.6–7.4 (m, 12H, CH_{arom}); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 115.12, 115.18, 130.35, 131.86, 132.04, 132.98 (C_{arom}, CH_{arom}), 127.59 (=C–S), 154.94, 176.22 (C=O); MS (–ESI): 405 $(M - H)^-$; Anal. Calcd. for $C_{22}H_{14}O_4S_2$ (M, 406.47): C, 65.01; H, 3.47; S, 15.78 %. Found C, 65.65; H, 3.66; S, 15.21 %.

*2-(1-Methyl-1H-imidazol-2-ylthio)-3-ethoxynaphthalene-1,4-dione (**4e**)* was synthesized by the reaction of **1** (1 g, 4.38 mmol) and **2e** (0.503 g, 4.38 mmol) by general procedure 1.

*(**4e**):* Red solid; yield 0.68 g (45 %); m.p. 152–153 °C; R_f: 0.7 ($CHCl_3$); IR (KBr): υ (cm^{-1}) 2980 (C–H_{arom}), 2929 (C–H_{aliph}), 1679 (C=O), 1620 (–C=N), 1593 (C=C); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.3 (t, J = 7.32, 3H, CH_3), 3.6 (s, 3H, N–CH_3), 4.2 (q, 2H, –OCH_2), 6.6 (d, 1H, C–$H_{imidazole}$), 6.8 (d, 1H, C–$H_{imidazole}$); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.81 (CH_3), 34.43 (N–CH_3), 69.11 (O–CH_2), 125.77, 125.87 (N–C=C), 124.47, 130.05, 130.15, 132.78 (CH_{arom}), 133.60 (=C–S), 155.41 (S–C =), 164.43 (=C–O), 178.62, 179.93 (C=O); MS (+ESI): 314 $(M)^+$; Anal. Calcd. for $C_{16}H_{14}N_2O_3S$ (M, 314.36): C, 61.13; H, 4.49; S, 10.20; N, 8.91 %. Found C, 61.28; H, 4.10; S, 10.01; N, 8.83 %.

*2,3-Bis(2-phenoxyethylthio)naphthalene-1,4-dione (**5c**)* was synthesized by the reaction of **1** (1 g, 4.38 mmol) and **2c** (0.679 g, 4.38 mmol) by general procedure 1.

*(**5c**):* Orange solid; yield 0.51 g (30 %); m.p. 83–84 °C; R_f: 0.75 ($CHCl_3$); IR (KBr): υ (cm^{-1}) 3068 (C–H_{arom}), 2963 (C–H_{aliph}), 1660 (C=O), 1589 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.5(t, $J = 6.35$ Hz, 4H, –S–CH_2), 4.3 (t, $J = 6.34$ Hz, 4H, O–CH_2), 6.7–8.1 (m, 14H, CH_{arom}); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 33.76 (S–CH_2), 76.74 (CH_2–O), 114.45, 114.5, 121.00, 121.01, 126.97, 129.41, 133.02, 133.54 (C_{arom}, CH_{arom}), 147.71 (–C–S), 158.17 (=C–O), 178.82 (C=O); MS (+ESI): 462 $(M)^+$; Anal. Calcd. for $C_{26}H_{22}O_4S_2$ (M, 462.58): C, 67.51; H, 4.79; S, 13.86 %. Found C, 67.25; H, 4.92; S, 13.66 %.

General procedure 2: for the synthesis of cyclic 1,4-naphthoquinone

2,3-Dichloro-1,4-naphthoquinone (1 g, 4.38 mmol) was dissolved in ethanol as reaction media (65 mL). Subsequently, 1,4-butanedithiol (**8**) (0.51 mL, 4.38 mmol) and triethylamine (catalytic amount) were added to the solution. Without heating, the mixture was stirred for 6–8 h. The color of the solution changed quickly, and the extent of the reaction was monitored by TLC. The reaction mixture was extracted in a Soxhlet extractor with dichloromethane. After recovery of the solvent, the crude product was purified by column chromatography.

*7,8,9,10,19,20,21,22-octahydrodinaphtho[2,3-b:2′,3′-j][1,4,9,12]tetrathiacyclohexadecine-5,12,17,24-tetraone (**9**)* was synthesized by the reaction of **1** (1 g, 4.38 mmol) and **8** (0.51 mL, 4.38 mmol) by general procedure 2.

*(**9**):* Red solid; yield 0.22 g (9 %); m.p. 115–116 °C; R_f: 0.59 ($CHCl_3$); IR (KBr): υ (cm^{-1}) 3281, 3068 (C–H_{arom}), 2918, 2896 (C–H_{aliph}), 1587, 1499 (C=C), 1655 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.01 (m, 8H, S–CH_2–CH_2), 3.48 (t, $J = 5.86$ Hz, 8H, S–CH_2), 7.61–7.62 (dd, $J = 3.42$, 5.37 Hz, 2H, CH_{arom}), 7.99–8.01 (dd, $J = 3.41$, 5.37 Hz, 2H, CH_{arom});^{13}C NMR (125 MHz, $CDCl_3$): δ 28.40 (S–CH_2–CH_2), 32.39 (S–CH_2), 133.96, 132.32, 127.32 (C_{arom}), 147.52 (=C–S), 180.73 (C=O); MS (+ESI): 575 $(M + Na)^+$; Anal. Calcd. for $C_{28}H_{24}O_4S_4$ (M, 552.75): C, 60.84; H, 4.38; S, 23.20 %. Found C, 61.16; H, 4.26; S, 22.71 %.

General procedure 3: for amination of 1,4-naphthoquinones

Sodium carbonate (1.52 g) was dissolved in dichloromethane as reaction media (50 mL). 2,3-Dichloro-1,4-naphthoquinone (**1**) or 2-chloro-3-((4-chlorobenzyl)thio) naphthalene-1,4-dione (**10**) and the secondary cyclic amine were added to the solution. Without heating, the mixture was stirred for 4–6 h. The color of the solution changed quickly, and the extent of the reaction was monitored by TLC. The reaction mixture was extracted in a Soxhlet extractor with dichloromethane. After recovery of the solvent, the crude product was purified by column chromatography.

*2-Chloro-3-(4-(hydroxydiphenylmethyl)piperidin-1-yl)naphthalene-1,4-dione (**7**)* was synthesized by the reaction of 1 (1 g, 4.38 mmol) and **6** (4.71 g, 8.76 mmol) by general procedure 3.

*(**7**):* Red solid; yield 1.50 g (74 %); m.p. 151–152 °C; R_f : 0.29 ($CHCl_3$); IR (KBr): υ (cm^{-1}) 3520 (–OH), 3058, 3020 (C–H_{arom}), 2952, 2854 (C–H_{aliph}), 1592, 1553 (C=C), 1672, 1642 (C=O); ^{1}H NMR (500 MHz, CD_3OD): δ 2.81–2.86 (m, 1H, $CH_{piperidine}$), 3.91 (m, 2H, $CH_{2piperidine}$), 3.36 (m, 2H, $CH_{2piperidine}$), 1.76 (m, 2H, $CH_{2piperidine}$), 1.60 (m, 2H, $CH_{2piperidine}$), 5.48 (s, 1H, OH), 7.14–7.17 (m, 2H, CH_{arom}), 7.27–7.31 (m, 4H, CH_{arom}), 7.55–7.57 (m, 4H, CH_{arom}), 7.68–7.74 (m, 4H, CH_{arom}), 7.97–7.99 (d, $J = 7.32$ Hz, 1H, CH_{arom}), 8.01–8.02 (d, $J = 7.32$ Hz, 1H, CH_{arom}); ^{13}C NMR (125 MHz, CD_3OD): δ 27.74, 43.95 ($CH_{2piperidine}$), 52.39 ($CH_{2piperidine}$), 79.37 (($Ph)_2$–C–OH), 133.94, 133.09, 131.88, 131.74, 127.81, 126.73, 126.13, 126.03, 125.99, 125.91, 121.10, 115.45 (C_{arom}), 146.64 (=C–Cl), 151.23 (=C–N), 181.66, 178.38 (C=O); MS (+ESI): 458 $(M + H)^+$; Anal. Calcd. for $C_{28}H_{24}ClNO_3$ (M, 457.95): C, 73.44; H, 5.28; N, 3.06 %. Found C, 73.19; H, 5.31, N, 3.16 %.

*2-(4-Chlorobenzylthio)-3-morpholinonaphthalene-1,4-dione (**12a**)* was synthesized by the reaction of **10** (0.2 g, 0.57 mmol) and **11a** (0.10 g, 1.14 mmol) by general procedure 3.

*(**12a**):* Purple oil; yield 0.198 g (86 %); R_f: 0.3 ($CHCl_3$); IR (KBr): υ (cm^{-1}) 3064 (C–H_{arom}), 2984, 2944 (C–H_{aliph}), 1591, 1494 (C=C), 1661, 1653 (C=O); ^{1}H–NMR (500 MHz, $CDCl_3$): δ 3.68 (t, $J = 4.39$ Hz, 4H, $CH_{2morpholine}$), 3.33 (t, $J = 4.39$ Hz, 4H, $CH_{2morpholine}$), 4.00 (s, 2H, S–CH_2), 7.04–7.03 (d, $J = 8.30$ Hz, 2H, CH_{arom}), 7.08–7.10 (d, $J = 8.30$ Hz, 2H, CH_{arom}), 7.55–7.63 (m, 2H, CH_{arom}), 7.87–7.89 (d, $J = 7.81$ Hz, 1H, CH_{arom}), 8.00–8.02 (d, $J = 8.30$ Hz, 1H, CH_{arom}); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 53.38 ($CH_{2morpholine}$), 67.61 ($CH_{2morpholine}$), 38.61 (S–CH_2), 136.85, 134.09, 133.12, 132.17, 130.49, 128.69, 126.89, 126.55, 123.08 (C_{arom}), 155.70 (=C–S), 181.97, 181.95 (C=O); MS (+ESI): 422 $(M + Na)^+$, 363 $(M\text{-}Cl)^+$; Anal. Calcd. for $C_{21}H_{18}ClNO_3S$ (M, 399.89): C, 63.07; H, 4.54; N, 3.50; S, 8.02 %. Found C, 63.10; H, 4.20, N, 3.45; S, 7.50 %.

*2-(4-Chlorobenzylthio)-3-(piperidin-1-yl)naphthalene-1,4-dione (**12b**)* was synthesized by the reaction of **10** (0.4 g, 1.15 mmol) and **11b** (0.196 g, 2.30 mmol) by general procedure 3.

*(**12b**):* Brown oil; yield 0.41 g (90 %); R_f : 0.67 ($CHCl_3$); IR (KBr): υ (cm^{-1}) 3064 (C–H_{arom}), 2935, 2853 (C–H_{aliph}), 1593, 1533 (C=C), 1669, 1634 (C=O); ^{1}H–NMR (500 MHz, $CDCl_3$): δ 3.25 (t, $J = 5.86$ Hz, 4H,

$CH_{2piperidine}$), 1.57 (m, 6H, $CH_{2piperidine}$), 3.93 (s, 2H, S–CH_2), 7.00–7.02 (d, $J = 8.30$ Hz, 2H, CH_{arom}), 7.04–7.06 (d, $J = 8.30$ Hz, 2H, CH_{arom}), 7.49–7.58 (m, 2H, CH_{arom}), 7.82–7.84 (d, $J = 7.32$ Hz, 1H, CH_{arom}), 7.97–7.99 (d, $J = 7.81$ Hz, 1H, CH_{arom}); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 25.75, 23.08 ($CH_{2piperidine}$), 53.40 ($CH_{2piperidine}$), 37.31 (S–CH_2), 135.81, 132.62, 131.97, 131.66, 131.54, 131.09, 129.24, 127.29, 125,52, 125.11, 119.85 (C_{arom}), 155.77 (=C–S), 181.04, 180.59 (C=O); MS (+ESI): 420 $(M + Na)^+$; Anal. Calcd. for $C_{22}H_{20}ClNO_2S$ (M, 397.92): C, 66.40; H, 5.07; N, 3.52; S, 8.06 %. Found C, 66.07; H, 4.97, N, 3.56; S, 7.56 %.

*2-(4-Chlorobenzylthio)-3-(pyrrolidin-1-yl)naphthalene-1,4-dione (**12c**)* was synthesized by the reaction of **10** (0.4 g, 1.15 mmol) and **11c** (0.163 g, 2.30 mmol) by general procedure 3.

*(**12c**):* Brown oil; yield 0.42 g (95 %); R_f: 0.38 ($CHCl_3$); IR (KBr): υ (cm^{-1}) 3064 (C–H_{arom}), 2973, 2875 (C–H_{aliph}), 1592, 1506 (C=C), 1674, 1621 (C=O); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.74 (m, 4H, $CH_{2pyrrolidine}$), 3.62 (m, 4H, $CH_{2pyrrolidine}$), 3.73 (s, 2H, S–CH_2), 7.00–7.02 (d, $J = 8.79$ Hz, 2H, CH_{arom}), 7.09–7.10 (d, $J = 8.30$ Hz, 2H, CH_{arom}), 7.48–7.61 (m, 2H, CH_{arom}), 7.76–7.78 (d, $J = 7.80$ Hz, 1H, CH_{arom}), 8.00–8.02 (d, $^3J = 6.35$ Hz, 1H, CH_{arom}); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 24.42 ($CH_{2pirolidin}$), 53.37 ($CH_{2pyrrolidine}$), 38.36 (S–CH_2), 135.87, 132.96, 132.64, 131.66, 130.77, 130.72, 129.26, 127,28, 125.06, 124.73, 105.38 (C_{arom}), 155.73 (=C–S), 183.18, 179.61 (C=O); MS (+ESI): 406 $(M + Na)^+$, 348 $(M\text{-}Cl)^+$; Anal. Calcd. for $C_{21}H_{18}ClNO_2S$ (M, 383.89): C, 65.70; H, 4.73; N, 3.65; S, 8.34 %. Found C, 65.50; H, 4.60, N, 3.53; S, 7.35 %.

*2-(4-Chlorobenzylthio)-3-(4-(2-fluorophenyl)piperazin-1-yl)naphthalene-1,4-dione (**12d**)* was synthesized by the reaction of **10** (0.4 g, 1.15 mmol) and **11d** (0.42 g, 2.30 mmol) by general procedure 3.

*(**12d**):* Brown oil; yield 0.50 g (88 %); R_f: 0.59 ($CHCl_3$); IR (KBr): υ (cm^{-1}) 3066, 3015 (C–H_{arom}), 2903, 2839 (C–H_{aliph}), 1592, 1532 (C=C), 1669, 1638 (C=O); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.09 (t, $J = 4.88$ Hz, 4H, $CH_{2piperazin}$), 3.50 (t, $J = 6.35$ Hz, 4H, $CH_{2piperazine}$), 3.99 (s, 2H, S–CH_2), 6.86–7.02 (m, 5H, CH_{arom}), 7.02–7.04 (d, $J = 8.30$ Hz, 2H, CH_{arom}), 7.06–7.08 (d, $J = 8.80$ Hz, 2H, CH_{arom}), 7.54–7.62 (m, 2H, CH_{arom}), 7.87–7.89 (d, $J = 7.80$ Hz, 1H, CH_{arom}), 8.00–8.02 (d, $J = 7.80$ Hz, 1H, CH_{arom}); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 53.05, 51.46 ($CH_{2piperazine}$), 38.66 (S–CH_2), 156.99, 155.03, 136.90, 134.07, 133.11, 132.24, 130.53, 128.70, 126.90, 126.54, 124.79, 124.77, 123.19, 122.90, 119.46, 119.44, 116.39 (C_{arom}), 156.01 (=C–S), 182.07, 181.98 (C=O); MS (+ESI): 515 $(M + Na)^+$; Anal. Calcd. for $C_{27}H_{22}ClFN_2O_2S$ (M, 492.99): C, 65.78; H, 4.50; N, 5.68; S, 6.50 %. Found C, 65.48; H, 4.25, N, 5.38; S, 5.96 %.

*2-((4-Chlorobenzyl)thio)-3-thiomorpholinonaphthalene-1,4-dione (**12e**)* was synthesized by the reaction of **10** (0.45 g, 1.29 mmol) and **11e** (0.27 g, 2.58 mmol) by general procedure 3.

*(**12e**):* Purple oil; yield 0.49 g (91 %); R_f: 0.83 ($CHCl_3$); IR (KBr): υ (cm^{-1}) 3063 (C–H_{arom}), 2958, 2909, 2840 (C–H_{aliph}), 1592, 1537 (C=C), 1667, 1642 (C=O); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.66 (t, $J = 4.88$ Hz, 4H, $CH_{2thiomorpholine}$), 3.47 (t, $J = 4.88$ Hz, 4H, $CH_{2thiomorpholine}$), 4.03 (s, 2H, S–CH_2), 7.03–7.05 (d, $J = 8.29$ Hz, 2H, CH_{arom}), 7.08–7.11 (d, $J = 8.30$ Hz, 2H, CH_{arom}), 7.56–7.64 (m, 2H, CH_{arom}), 7.88–7.89 (d, $J = 7.32$ Hz, 1H, CH_{arom}), 8.00–8.02 (d, $J = 6.83$ Hz, 1H, CH_{arom}); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 55.27 ($CH_{2thiomorpholine}$), 28.27 ($CH_{2thiomorpholine}$), 38.51 (S–CH_2), 136.80, 134.04, 133.28, 133.19, 133.01, 132.21, 130.48, 128.73, 126.92, 126.57, 125.69 (C_{arom}), 156.65 (=C–S), 182.21, 181.88 (C=O); MS (+ESI): 438 $(M + Na)^+$, 379 $(M\text{-}Cl)^+$; Anal. Calcd. for $C_{21}H_{18}ClNO_2S_2$ (M, 415.96): C, 60.64; H, 4.36; N, 3.37; S, 15.42. Found C, 60.33; H, 4.25, N, 3.30; S, 14.95 %.

*2-((4-Chlorobenzyl)thio)-3-(4-(hydroxydiphenylmethyl)piperidin-1-yl)naphthalene-1,4-dione (**12f**)* was synthesized by the reaction of **10** (0.50 g, 1.44 mmol) and **11f** (0.768 g, 2.88 mmol) by general procedure 3.

*(**12f**):* Purple solid; yield 0.75 g (90 %); m.p. 101–102 °C; R_f : 0.15 ($CHCl_3$); IR (KBr): υ (cm^{-1}) 3064 (C–H_{arom}), 2935, 2853 (C–H_{aliph}), 1593, 1533 (C=C), 1669, 1634 (C=O); ^{1}H-NMR (500 MHz, CD_3OD): δ 1.53 (m, 2H, $CH_{2piperidine}$), 1.69 (t, $J = 7.32$ Hz, 2H, $CH_{2piperidine}$), 2.78 (m, 1H, $CH_{piperidine}$), 3.25 (m, 2H, $CH_{2piperidine}$), 3.64 (t, $J = 7.32$ Hz, 2H, $CH_{2piperidine}$), 3.93 (s, 2H, S–CH_2), 5.48 (s, 1H, OH), 7.07–7.11 (m, 4H, CH_{arom}), 7.15–7.18 (m, 2H, CH_{arom}), 7.27–7.31 (m, 4H, CH_{arom}), 7.53–7.55 (m, 4H, CH_{arom}), 7.68–7.72 (m, 2H, CH_{arom}), 7.88–7.87 (d, $J = 7.32$ Hz, 1H, CH_{arom}), 7.97–7.99 (d, $J = 7.32$ Hz, 1H, CH_{arom}); ^{13}C-NMR (125 MHz, CD_3OD): δ 53.82, 43.83, 27.64 ($CH_{2piperidine}$), 37.79 (S–CH_2), 79.38 ($(Ph)_2$–C–OH), 146.56, 137.16, 133.75, 132.97, 132.75, 132.51, 132.28, 130.51, 128.07, 127.80, 126,37, 126.14, 125.73, 119.20 (C_{arom}), 157.53 (=C–S), 182.05, 182.01 (C=O); MS (+ESI): 602 $(M + Na)^+$, 544 $(M\text{-}Cl)^+$; Anal. Calcd. for $C_{35}H_{30}ClNO_3S$ (M, 580.14): C, 72.46; H, 5.21; N, 2.41; S, 5.53 %. Found C, C, 72.10; H, 5.20, N, 2.01; S, 4.65 %.

Antifungal and antibacterial evaluation

Diffusion technique

Antibacterial activity of compounds was evaluated by diffusion in peptone on nutrient medium (meat-extract agar for bacteria; wort agar for fungi). The microbial loading was 10^9 cells (spores)/1 mL. The required incubation periods were as: 24 h at 35 °C for bacteria and 48–72 h at

28–30 °C for fungi. The results were recorded by measuring the zones surrounding the disk. Control disk contained Vancomycin (for bacteria) or Nystatin (for fungi) as a standard.

Serial dilution technique

Testing was performed in a flat-bottomed 96-well tissue culture plate. The tested compounds were dissolved in DMSO, and arriving the necessary concentration. The exact volume of solution of compounds is brought in nutrient medium. The inoculum of bacteria and fungi was inoculated in nutrient medium (meat-extract agar for bacteria; wort agar for fungi). The duration of incubation was at 37 °C for bacteria and 30 °C for fungi during 24–72 h. The results were estimated according to the presence or the absence of microorganism growth.

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