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Original article

Design, synthesis and biological evaluation of novel nitrogen and sulfur containing hetero-1,4-naphthoquinones as potent antifungal and antibacterial agents

Vishnu K. Tandon [a,*], Hardesh K. Maurya [a], Nripendra N. Mishra [b], Praveen K. Shukla [b]

[a] Department of Chemistry, University of Lucknow, Lucknow 226007, India
[b] Division of Fermentation Technology, Central Drug Research Institute, Lucknow 226001, India

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ABSTRACT

A series of 2-Arylamino-3-chloro-1,4-naphthoquinones (**3**), 2-Amino-3-arylsulfanyl-1,4-naphthoquinones (**5**), 2-Arylamino-3-arylsulfanyl-1,4-naphthoquinones (**6**), Dihydrobenzo[*f*]naphtho[2,3-*b*][1,4]thiazepine-6,11-diones (**9**) (via Pictet–Spengler cyclization), Isoindoline-1,3-dione derivatives of 1,4-naphthoquinone (**13**), 2,2′-(1,4-Dioxo-1,4-dihydronaphthalene-2,3-diyl)bis(methylene)dibenzonitrile (**14**), 13-Amino-12-substituted-6*H*-benzo[*e*]naphtho [2,3-*b*][1,4]diazepine-6,11(12*H*)-diones (**15**–**16**), 2-Chloro-3-arylsulfanyl-1,4-naphthoquinones (**17**–**18**) and 3-Methyl-6*H*-benzo[*b*]phenothiazine-6,11(12*H*)-dione (**19**) were synthesized and studied for their antifungal and antibacterial activities. The results indicate that compounds **3b**, **5a** and **5b** have potent antifungal activity. Amongst the most promising antifungal compounds, **3b** showed better antifungal activity than clinically prevalent antifungal drug Fluconazole ($MIC_{50} = 2.0$ μg/mL) against *Sporothrix schenckii* ($MIC_{50} = 1.56$ μg/mL), significant profile against *Candida albicans* ($MIC_{50} = 1.56$ μg/mL), *Cryptococcus neoformans* ($MIC_{50} = 0.78$ μg/mL) and *Trichophyton mentagraphytes* ($MIC_{50} = 1.56$ μg/mL) and same antifungal activity when compared with Amphotericin-B against *C. neoformans* ($MIC_{50} = 0.78$ μg/mL). Compounds **3b**, **5a** and **5b** also showed promising antibacterial activity.

1. Introduction

The incidence of fungal and bacterial infections has increased dramatically in recent years [1,2]. The widespread use of antifungal and antibacterial drugs and their resistance against fungal and bacterial infections has led to serious health hazards. The resistance of wide spectrum antifungal and antibacterial agents has initiated discovery and modification of the new antifungal and antibacterial drugs [3,4,29].

The amino and thioether derivatives of 1,4-naphthoquinones have extremely rich biological activities because of their redox potentials [5,6]. These derivatives have been found to possess marked antiviral [7], molluscidal [8], antimalarial [9], antileishmanial [10], antiproliferative [11], antibacterial and antifungal activities [11–17].

We have earlier reported the synthesis of novel nitrogen and sulfur containing 1,4-naphthoquinones and studied their antiviral, anticancer, antiproliferative, antibacterial and antifungal activities. The profound antibacterial and antifungal activities exhibited by compounds (**I**–**IV**) indicated that nitrogen and sulfur play significant role in enhancement of biological activity (Fig. 1) [12,15–17]. This prompted us to synthesize and study biological activities of some new analogs of **I**–**IV** containing nitrogen and sulfur substituted at 2- and 3- positions of 1,4-naphthoquinone. We report herein a facile and efficient route to synthesis of 2-Arylamino-3-chloro-1,4-naphthoquinones (**3**), 2-Amino-3-arylsulfanyl-1,4-naphthoquinones (**5**) and 2-Arylamino-3-arylsulfanyl-1,4-naphthoquinones (**6**). Novel Dihydrobenzo[*f*]naphtho[2,3-*b*][1,4]thiazepine-6,11-diones (**9**) have been synthesized via Pictet–Spengler cyclization of **5**. Isoindoline-1,3-dione derivatives of 1,4-naphthoquinone (**13**), 2,2′-(1,4-dioxo-1,4-dihydronaphthalene-2,3-diyl)bis(methylene)dibenzonitrile (**14**), 13-amino-12-substituted-6*H*-benzo[*e*]naphtho[2,3-*b*][1,4]diazepine-6,11(12*H*)-diones (**15** and **16**), 2-Chloro-3-arylsulfanyl-1,4-naphthoquinones (**17** and **18**) and 3-methyl-6*H*-benzo[*b*]phenothiazine-6,11(12*H*)-dione (**19**) were synthesized for structure–activity relationship, compounds **3**–**19** have been studied for their detailed antifungal and antibacterial activities.

* Corresponding author. Tel.: +91 9415066847; fax: +91 522 26848.
E-mail address: vishnutandon@yahoo.co.in (V.K. Tandon).

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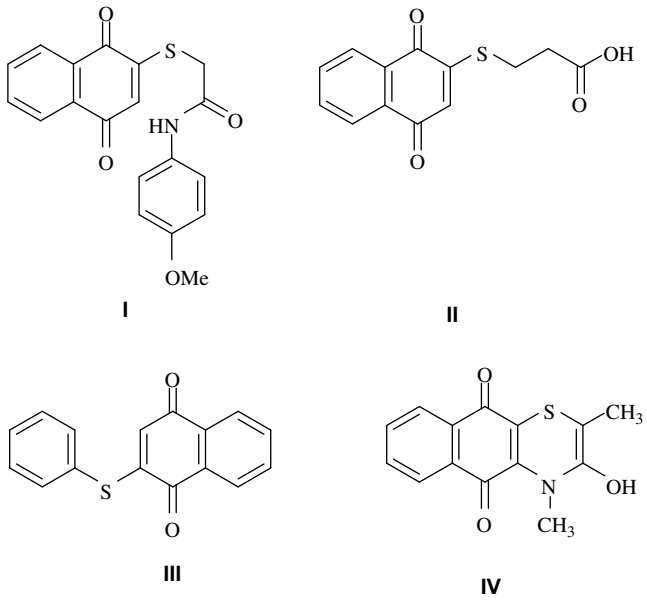


Fig. 1. Lead antifungal and antibacterial agents **I** [15], **II** [16], **III** [14] and **IV** [12].

Table 1
Reaction condition for the synthesis of compounds **3**–**13**.

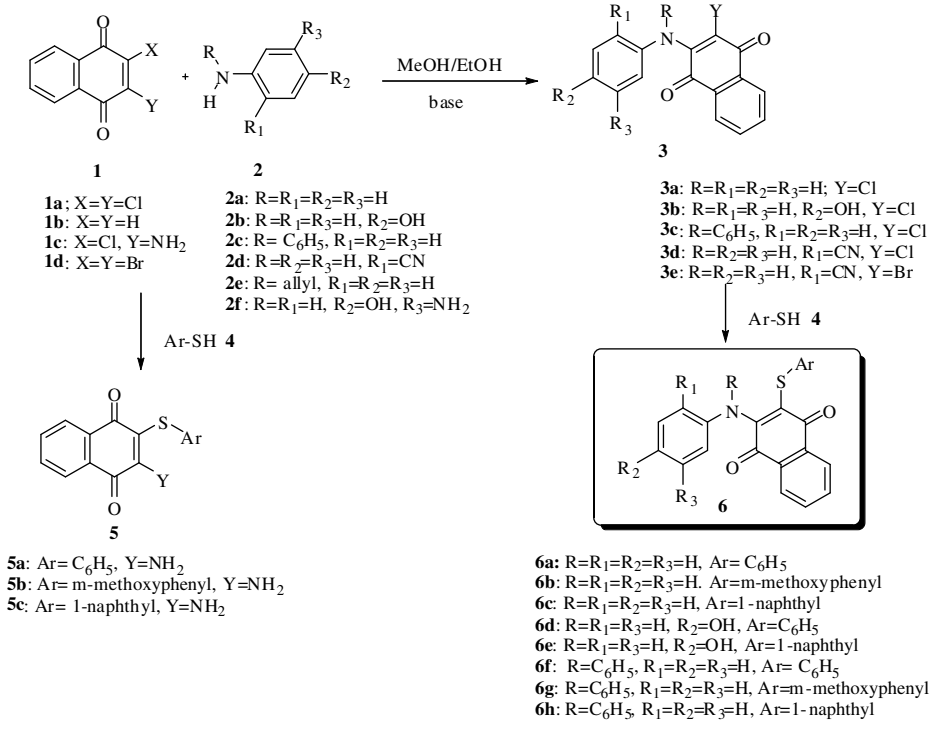
C[b]	B[b]	S[b]	T[b]	t°C[b]	Y[b]	mp[b]
3a	[a]	MeOH	01	RT[b]	98	210 [25]
3b	[a]	MeOH	10	RT	97	181
3c	Et_3N	MeOH	20	70	98	130
3d	Et_3N	MeOH	15	45	65	233
3e	Et_3N	MeOH	07	45	51	109
5a	K_2CO_3	EtOH	30	90	80	160
5b	K_2CO_3	EtOH	35	90	71	186
5c	K_2CO_3	EtOH	40	90	66	140
6a	Et_3N	MeOH	03	80	99	70
6b	Et_3N	MeOH	04	70	99	143
6c	Et_3N	MeOH	03	60	95	119
6d	Et_3N	MeOH	10	70	86	220
6e	Et_3N	MeOH	03	70	83	Oil
6f	Et_3N	MeOH	0.5	60	80	Oil
6g	Et_3N	MeOH	03	70	89	Oil
6h	Et_3N	MeOH	02	60	97	120
9a	BF_3Et_2O	CH_3CN	03	RT	60	183
9b	BF_3Et_2O	CH_3CN	03	RT	80	>290
12	[a]	AcOH	01	100	95	192
13a	K_2CO_3	EtOH	24	120	51	212
13b	K_2CO_3	EtOH	24	120	70	220

[a] Base not required.
[b] C = Compound, B = Base, S = Solvent, T = Reaction time (h), t°C = Reaction temperature, Y = Product yield (%), mp = product melting point (°C), RT = Room temperature.

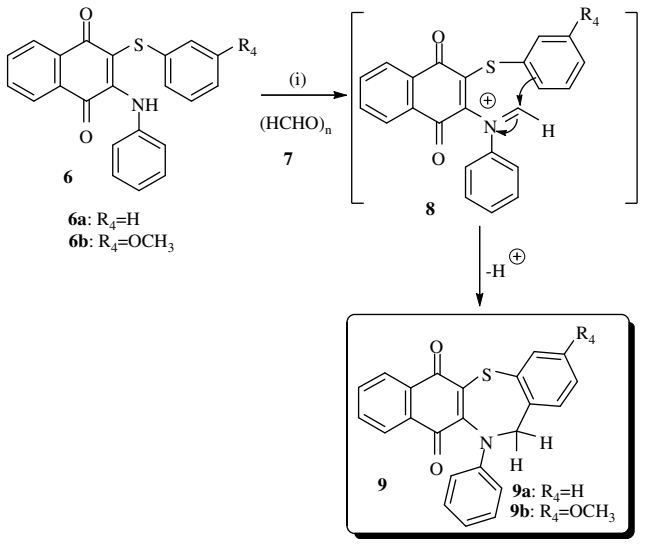
2. Results and discussion

2.1. Chemistry

It is well known that 2,3-Dichloro-1,4-naphthoquinone (**1a**) reacts with nucleophiles and depending on their nucleophilicity, it may undergo substitution of one or both chlorine atoms [11,18]. The aryl amines of enhanced nucleophilicity when react with 2,3-dichloro-1,4-naphthoquinone (**1a**), substitute only one chlorine atom due to electronic enrichment of the quinone system. For second substitution of chlorine atom, it is required that an electron withdrawing effect must be imposed on quinone ring [19] or a catalyst be used [20]. Based on the reactivity and biological activity of 2,3-dichloro-1,4-naphthoquinones [11–18], we studied its reaction with different aryl amines (**2**) in the presence or absence of a base as reported in Table 1 and synthesized 2-Arylamino-3-halo-1,4-naphthoquinones (**3**). However, the reaction of **1a** with *N*-allyl aniline (**2e**) with **1a**, desired product 2-(*N*-allylanilino)-3-chloro-1,4-naphthoquinone was not obtained instead



Scheme 1. For regents and condition refer to Table 1.



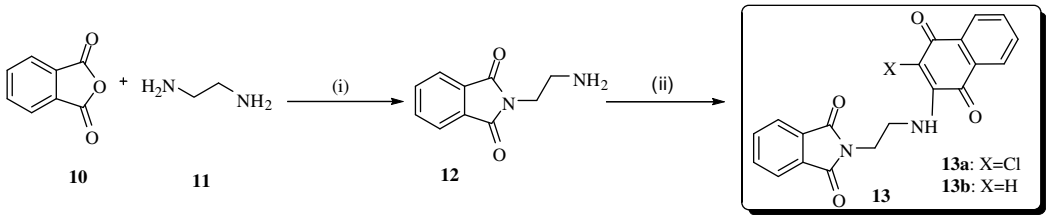
Scheme 2. (i) $BF_3 \cdot Et_2O$, CH_3CN, 3 h, room temperature, stirred [18].

product **3a** was isolated which was characterized by IR, ^1H NMR, mass and analytical data. In order to study structure–activity relationship (SAR) of different substituents in 2-arylamino-3-halo-1, 4-naphthoquinone (**3**), we carried out the reaction of **1a** with 2,4-diamino phenol (**2f**) using different bases such as Et_3N, K_2CO_3 and $NaHCO_3$ in methyl alcohol. The desirable product was not detected. The inertness of compound **2f** to undergo nucleophilic substitution is probably due to the presence of hydroxyl group at ortho or para position leading to nucleophilc nitrogen redundant due to hydrogen bonding and mesomeric effect in **2f** (Scheme 1).

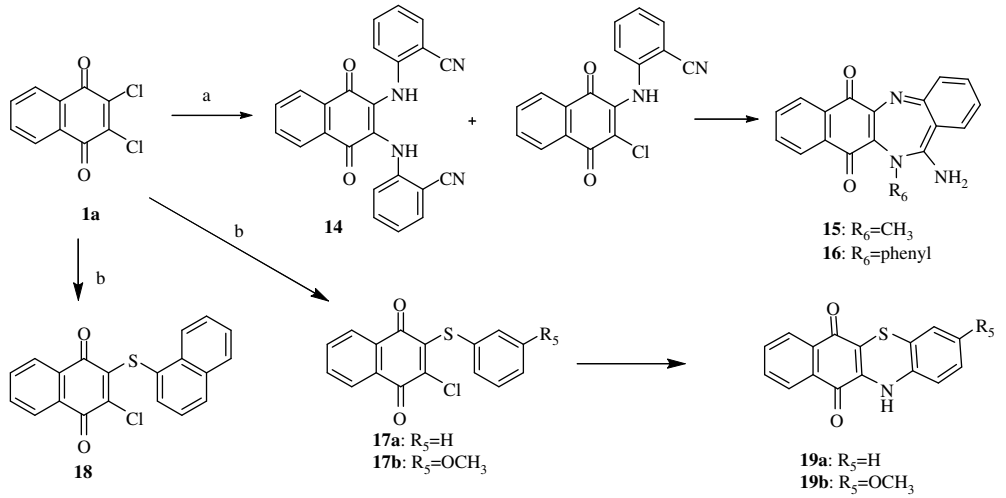
The reaction of **1a** with aryl thiols has already been studied by us [11]. 2-Amino-3-arylsulfanyl-1,4-naphthoquinones (**5**) were synthesized by the reaction of **1c** with aryl thiols as exhibited in Scheme 1 (Table 1). Aryl thiols react with quinone **1a** to yield dithioethers more easily compared to aryl amines which result in the formation of mono-arylamino-1,4-naphthoquinones as major product [19]. On the basis of these results, we have successfully carried out the synthesis of novel 2-Arylamino-3-arylsulfanyl-1,4-naphthoquinones (**6**) by the reaction of 2-arylamino-3-chloro-1,4-naphthoquinones (**3a–d**) with aryl thiols (**4**) and explored a new route for the synthesis of **6** leading to disubstituted product using an inexpensive base triethylamine and methanol as solvent in high yields as shown in Table 1 (Scheme 1).

Recently synthesis of naphthoquinon[*b*]benzo[*e*][1,4]diazepines [21] and naphtha[2,3-*b*]-thiazine-5,10-dione (**IV**) [12] has been reported. The potent biological activity exhibited by six membered thiazine analog (**IV**) [12] prompted us to synthesize seven membered thiazepine analog (**9**). The homolog of **IV**, Dihydrobenzo[*f*]naphtho[2,3-*b*][1,4]thiazepine-6,11-diones (**9**) was synthesized by the reaction of **6** with paraformaldehyde using $BF_3 \cdot Et_2O$, a novel reagent as a catalyst as shown in Scheme 2 (Table 1).

In order to study the structure–activity relationship (SAR) of mono and disubstituted derivatives of 1,4-naphthoquinone (**3**,**5**,**6**), 2-[2-(3-substituted-1,3-dioxo-1,4-dihydronaphthalen-2-ylamino)ethyl]isoindoline-1,3-dione (**13**) were synthesized by the reaction of 2-(2-aminoethyl)isoindoline-1,3-dione **12** with 1,4-naphthoquinones (**1a–b**) resulting in the formation of **13** as shown in Scheme 3.



Scheme 3. Reagents and condition: (i) AcOH, 100 °C, 1 h, stirring. (ii) **1a–b**, K_2CO_3, EtOH, reflux.



Scheme 4. a = Method of synthesis refer to reference [15] and b = method of synthesis refer to reference [8].

Table 2
Structures and in vitro antifungal activity for compounds **3**–**16** (MIC: μg/mL).

Compounds	MIC (μg/mL)					
	C. albicans	*C. neoformans*	*S. schenckii*	*T. mentagraphytes*	*A. fumigatus*	*C. parapsilosis*
3a	>50	>50	>50	>50	>50	>50
3b	**1.56**[b]	**0.78**[b]	**1.56**[b]	**1.56**[b]	**3.12**[b]	6.25
3c	12.5	25	6.25	50	50	12.5
3d	50	50	>50	>50	>50	25
3e	25	12.5	>50	6.25	>50	12.5
5a	12.5	25	25	12.5	6.25	12.5
5b	12.5	12.5	25	12.5	6.25	25
5c	25	50	>50	25	25	50
6c	50	>50	>50	>50	>50	>50
6h	25	>50	>50	50	50	>50
14	>50	25	>50	>50	>50	50
15	>50	50	25	25	25	50
16	25	25	>50	12.5	>50	25
Miconazole [14]	25	12.5	[a]	<0.78	12.5	[a]
Nystatin [14]	7.8	3.5	13.2	[a]	[a]	[a]
Fluconazole [14]	1.0	0.5	2.0	1.56	2.0	1.0
Amphotericin-B [14]	0.39	0.78	[a]	**1.56**	[a]	[a]

[a] Activity not reported.
[b] Entries in bold font indicate better activity than reference drugs Miconazole and Nystatin.

2,2′-(1,4-Dioxo-1,4-dihydronaphthalene-2,3-diyl)bis(methylene)dibenzonitrile (**14**), 13-amino-12-substituted-6*H*-benzo[*e*]naphtho[2,3-*b*][1,4]diazepine-6,11(12*H*)-diones (**15** and **16**), 2-Chloro-3-arylsulfanyl-1,4-naphthoquinones (**17** and **18**) and 3-methyl-6*H*-benzo[*b*]phenothiazine-6,11(12*H*)-dione (**19**) [11,18] were synthesized for structure–activity relationship as shown in Scheme 4.

2.2. Antifungal activity

In our laboratory nearly five year ago, work was initiated on the synthesis and screening of a variety of structurally diverse synthetic 1,4-quinones with a view to developing a therapeutic agent with a broad spectrum of antifungal and antibacterial activities [11–18]. These studies led to the identification of potent antifungal and antibacterial agents (Fig. 1) as lead molecules. Subsequently using a structure–activity relationship approach of antifungal activity of the lead quinones, we further synthesized and screened antifungal assay of **3**–**16** as shown in Table 2 (Schemes 1–4).

Comparison of antifungal activity of compounds **3**–**16** with that of antifungal drug Miconazole ($MIC_{50} = 25.0$ μg/mL), showed that compound **3b** ($MIC_{50} = 1.56$ μg/mL), **3c**, **5a**, **5b** ($MIC_{50} = 12.50$ μg/mL) had better activity and compounds **3e**, **5c**, **6h**, **16** ($MIC_{50} = 25.0$ μg/mL) had same antifungal profile against *Candida albicans*. Compound **3b** ($MIC_{50} = 0.78$ μg/mL) had shown extreme potent activity when compared with Miconazole ($MIC_{50} = 12.5$ μg/mL) and compound **5b** had same antifungal profile against *Cryptococcus neoformans*. Compounds **3b** ($MIC_{50} = 3.12$ μg/mL) and **5a**, **5b** ($MIC_{50} = 6.25$ μg/mL) had shown promising antifungal activity on comparison with antifungal drug Miconazole against *Aspergillus fumigatus* (Fig. 2, see Supporting information).

On comparison of antifungal activity with that of antifungal drug Nystatin ($MIC_{50} = 7.8$ μg/mL), compound **3b** ($MIC_{50} = 1.56$ μg/mL) was found to exhibit better activity against *C. albicans*. Compound **3b** ($MIC_{50} = 0.78$ μg/mL) also had better activity against *C. neoformans* when compared with Nystatin ($MIC_{50} = 3.50$ μg/mL) and compounds **3b** ($MIC_{50} = 1.56$ μg/mL) and **3c** ($MIC_{50} = 6.25$ μg/mL) had better profile against *Sporothrix schenckii* on comparison with Nystatin ($MIC_{50} = 13.20$ μg/mL) as exhibited in Fig. 3 (see Supporting information).

Compound **3b** ($MIC_{50} = 1.56$ μg/mL) exhibited better activity than clinically prevalent antifungal drug Fluconazole ($MIC_{50} = 2.0$ μg/mL) against *S. schenckii* and significant profile of **3b** against *C. albicans* ($MIC_{50} = 1.56$ μg/mL), *C. neoformans* ($MIC_{50} = 0.78$ μg/mL), *Trichophyton mentagraphytes* ($MIC_{50} = 1.56$ μg/mL) and *A. fumigatus* ($MIC_{50} = 3..12$ μg/mL) (Fig. 4, Supporting information). Compound **3b** also exhibited similar antifungal activity when compared with Amphotericin-B against *C. neoformans* ($MIC_{50} = 0.78$ μg/mL) and *T. mentagraphytes* ($MIC_{50} = 1.56$ μg/mL).

Structure–activity relationship of **3**–**16** revealed that mono-substituted arylthio and arylamino substituted-1,4-naphthoquinones posses potent antifungal activity when 3-position is replaced by Cl or NH_2 group (**3b**) and (**5a**–**c**). The derivative **3b** revealed that –OH group is an additional important functionality to enhance the antifungal activity. Antifungal activity decreased considerably when both 2- and 3-positions were replaced by phenyl group (**6a**–**h**).

2.3. Antibacterial activity

Based on the mechanism of the antibacterial action of quinones [22–24], antibacterial activity of **3**–**19** was elucidated as shown in Table 3.

Table 3
Structures and in vitro antibacterial activity for compounds **3**–**19** (MIC: μg/mL).

Compounds	MIC (μg/mL)		
	E. coli	*S. aureus*	*K. pneumoniae*
3a	>50	>50	>50
3b	>50	6.25	6.25
3c	>50	25	25
5a	>50	6.25	1.56
5b	>50	25	12.5
5c	>50	12.5	12.5
6a	>50	>50	25
6d	>50	50	>50
6f	>50	50	50
6g	>50	25	50
13a	6.25	6.25	50
15	25	>50	50
17a	12.5	25	>50
17b	12.5	25	>50
18	25	>50	>50
19a	25	25	>50
19b	25	12.5	>50
Kanamycin [14]	16	2.0	32
Amikacin [14]	1.0	16	1.0
Tobramicin [14]	0.5	0.25	1.0
Gentamycin [14]	0.18	0.78	0.39

Comparison of antibacterial activity with that of antibacterial drug Kanamycin ($MIC_{50} = 16$ μg/mL) showed that compounds **13a** ($MIC_{50} = 6.25$ μg/mL) and **17a–b** ($MIC_{50} = 12.5$ μg/mL) had better activity against *Escherichia coli*. Compound **3b**, **5a**, **13a** ($MIC_{50} = 6.25$ μg/mL) and **5c**, **19** ($MIC_{50} = 12.5$ μg/mL) exhibited better activity against *Staphylococcus aureus* (ATCC25923) when compared with antibacterial drug Amikacin ($MIC_{50} = 16.0$ μg/mL) and compound **3b**, **3c**, **5a**, **5c** and **6a** also exhibited better activity against *Klebsiella pneumoniae* (ATCC 27736) when compared with antibacterial drug Kanamycin as shown in Fig. 5 (see Supporting information). Compounds **3**–**19** were also screened against *Pseudomonas aeruginosa* at $MIC_{50} = 50.0$ μg/mL but did not exhibit significant antibacterial activity.

3. Conclusion

In conclusion, we have synthesized a series of novel 2-Arylamino-3-chloro-1,4-naphthoquinones (**3**), 2-Amino-3-arylsulfanyl-1,4-naphthoquinones (**5**), 2-Arylamino-3-arylsulfanyl-1,4-naphthoquinones (**6**), Dihydrobenzo[*f*]naphtho[2,3-*b*][1,4]thiazepine-6,11-diones (**9**) (via Pictet–Spengler cyclization) and isoindoline-1,3-dione derivatives of 1,4-naphthoquinone (**13**) as well as 2,2′-(1,4-dioxo-1,4-dihydronaphthalene-2,3-diyl)bis(methylene)dibenzonitrile (**14**), 13-amino-12-substituted-6*H*-benzo[*e*]naphtho[2,3-*b*][1,4]diazepine-6,11(12*H*)-diones (**15** and **16**), 2-Chloro-3-arylsulfanyl-1,4-naphthoquinones (**17** and **18**) and 3-methyl-6*H*-benzo[*b*]phenothiazine-6,11(12*H*)-dione (**19**). The antifungal profile of **3**–**19** indicated that compounds **3b**, **5a** and **5b** have potent antifungal activity. Amongst the most promising antifungal compounds, 2-Chloro-3-(4-hydroxyphenylamino)naphthalene-1,4-dione (**3b**) showed better antifungal activity than clinically prevalent antifungal drug Fluconazole ($MIC_{50} = 2.0$ μg/mL) against *S. schenckii* ($MIC_{50} = 1.56$ μg/mL), significant profile against *C. albicans* ($MIC_{50} = 1.56$ μg/mL), *C. neoformans* ($MIC_{50} = 0.78$ μg/mL), *T. mentagraphytes* ($MIC_{50} = 1.56$ μg/mL) and *A. fumigatus* ($MIC_{50} = 3..12$ μg/mL) and same antifungal activity when compared with Amphotericin-B against *C. neoformans* ($MIC_{50} = 0.78$ μg/mL) and *T. mentagraphytes* ($MIC_{50} = 1.56$ μg/mL). Compounds **3a**, **5a**, **5b** also showed promising antibacterial activity against *S. aureus* (ATCC25923) and *K. pneumoniae* (ATCC 27736). Thus 2-Chloro-3-(4-hydroxyphenylamino)naphthalene-1,4-dione (**3b**) is the lead drug candidate and further work is being carryout at Central Drug Research Institute, Lucknow, India concerning its toxicological evaluation.

4. Experimental

4.1. Materials and methods

The reagents and the solvents used in this study were of analytical grade and were used without further purification. The melting points were determined on an electrically heated Townson Mercer melting point apparatus and are uncorrected. IR spectra were recorded on FTIR 8201 PC, Schimadzu Spectrophotometers on KBr discs. Nuclear Magnetic Resonance (NMR) spectra were recorded on Perkin–Elmer model R.32 spectrometers using TMS as an internal reference. All compounds showed satisfactory elemental analysis for C, H, N and S. Progress of reactions and purity of compounds were monitored by thin layer chromatography (TLC), which was performed on silica gel G and compounds were detected with UV Chamber, where required. Spectral facilities and elemental micro-analyses were carried out by SAIF Division of Central Drug Research Institute, Lucknow, India. Most reagents were purchased from Lancaster, Sigma–Aldrich and Merck.

4.2. General procedure for the synthesis of 2-arylamino-3-chloro-1,4-naphthoquinones (*3*), 2-amino-3-arylsulfanyl-1,4-naphthoquinones (*5*)

A mixture of 1,4-naphthoquinones (**1a** or **1c**) (10 mmol) and arylamine or aryl thiols (10.5 mmol) in abs. MeOH/EtOH (50 mL) were stirred at different temperatures using base, where required (Table 1). The resulting solution was concentrated *in vacuo* and the residue was subjected to column chromatography on silica gel using EtOAc/hexane, if required and the product was crystallized with suitable solvent to give **3** and **5** in excellent yield (Table 1).

4.2.1. 2-Chloro-3-(phenylamino)naphthalene-1,4-dione (*3a*) [25]

Red powder from methanol; IR (KBr): 1597 and 1675 (>C=O of quinone), 3243 (N–H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, $J = 8.0$ Hz, 1H), 8.12 (d, $J = 8.0$ Hz, 1H), 7.77 (t, $J = 8.0$ Hz, 1H), 7.69 (t, $J = 8.0$, 1H), 7.35 (m, 3H), 7.22 (t, $J = 7.6$, 1H), 7.09 (d, $J = 7.6$, 2H). Anal. Calcd. for $C_{16}H_{10}ClNO_2$ (284): C, 67.74; H, 3.55; N, 4.94. Found: C, 67.10; H, 3.53; N, 4.91; Beilstein test: [26] Cl positive.

4.2.2. 2-Chloro-3-(4-hydroxyphenylamino)naphthalene-1,4-dione (*3b*)

Violet powder from methanol; IR (KBr): 1593 and 1678 (>C=O of quinone) 3269 (N–H), 3468 (O–H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, $J = 7.6$, 1H), 8.12 (d, $J = 7.6$, 1H), 7.90 (s, 1H), 7.75 (t, $J = 7.6$, 1H), 7.69 (t, $J = 7.6$, 1H), 7.35 (d, 2H), 7.05 (d, 2H), 4.75 (s, 1H). Anal. Calcd. for $C_{16}H_{10}ClNO_3$ (300): C, 64.12; H, 3.36; N, 4.67; Found: C, 63.92; H, 3.42; N, 4.72; Beilstein test: [26] Cl positive.

4.2.3. 2-Chloro-3-(diphenylamino)naphthalene-1,4-dione (*3c*)

Fine needle shaped yellow crystals from methanol which on exposure to air yellowish colour to fluorescent light green; IR (KBr): 1592 and 1678 (>C=O of quinone) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (m, 1H), 8.15 (m, 3H), 8.09 (m, 3H), 7.81 (m, 1H), 7.75 (m, 6H); $M^+ = 360$. Anal. Calcd. For $C_{22}H_{14}ClNO_2$ (360): C, 73.44; H, 3.92; N, 3.89 Found: C, 72.96; H, 3.98; N, 3.92; Beilstein test: [26] Cl positive.

4.2.4. 2-3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-ylaminobenzonitrile (*3d*)

It was synthesized according to the procedure reported by Tandon and Maurya [18].

4.2.5. 2-3-Bromo-1,4-dioxo-1,4-dihydronaphthalen-2-ylaminobenzonitrile (*3e*)

Dark orange crystals after column chromatography on silica gel using EtOAc/hexane; IR (KBr): 1592 and 1675 (>C=O of quinone), 3448 (N–H) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.05–8.25 (m, 8H, Ar-H), 1.22 (bs, 1H, NH); Anal. Calcd. for $C_{17}H_9BrN_2O_2$ (353): C, 57.81; H, 2.57; N, 7.93; Found: C, 57.54; H, 2.68; N, 8.12. Beilstein test: [26] Br positive.

4.2.6. 2-Amino-3-phenylsulfanyl-[1,4]naphthoquinone (*5a*)

Red crystals after crystallization with methanol; IR (KBr): 1598 and 1676 (>C=O of quinone), 3243 and 3462 (NH_2) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.08 (m, 2H), 7.65 (m, 2H), 7.38 (m, 2H), 7.26 (s, 3H), 7.09 (bs, 2H). Anal. Calcd. for $C_{16}H_{11}NO_2S$ (281): C, 68.31; H, 3.94; N, 4.98; S, 11.40; Found: C, 67.98; H, 3.88; N, 4.93; S, 11.35.

4.2.7. 2-Amino-3-(3-methoxyphenylsulfanyl)-[1,4]naphthoquinone (*5b*)

Red crystals after crystallization with methanol; IR (KBr): 1589 and 1665 (>C=O of quinone), 3253 and 3432 (NH_2) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.15 (m, 2H), 7.73 (m, 2H), 6.85–7.21 (m, 6H), 3.78 (s, 3H). Anal. Calcd. for $C_{17}H_{13}NO_3S$ (311): C, 65.58; H, 4.21; N, 4.50; S, 10.30; Found: C, 65.08; H, 4.26; N, 4.46; S, 10.26.

*4.2.8. 2-Amino-3-(naphthalen-1-ylsulfanyl)-[1,4]naphthoquinone (**5c**)*

Brown powder from methanol; IR (KBr): 1585 and 1662 (>C=O of quinone), 3270 and 3440 (NH_2) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.17 (m, 2H), 7.98 (m, 2H), 7.77 (m, 4H), 7.50 (m, 3H), 7.30 (bs, NH_2). Anal. Calcd. for $C_{20}H_{13}NO_2S$ (331): C, 72.49; H, 3.95; N, 4.23; S, 9.68; Found: C, 71.92; H, 3.92; N, 4.27; S, 9.60.

*4.3. General procedure for the synthesis of novel 2-arylamino-3-arylsulfanyl-1,4-naphthoquinones (**6**)*

A mixture of compounds (**3a**–**c**) (5 mmol) and aryl thiols (5.2 mmol) in abs. MeOH (50 mL) was refluxed at different temperatures using triethylamine (5 mmol) as base. The resulting solution was concentrated *in vacuo* and the residue was subjected to column chromatography on silica gel using EtOAc/hexane. The product was crystallized with suitable solvent to give **6** in excellent yields (Table 1).

*4.3.1. 2-Phenylamino-3-(phenylthio)naphthalene-1,4-dione (**6a**)*

Brown solid from methanol; IR (KBr): 1589 and 1664 (>C=O of quinone), 3265 (N–H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, $J = 7.6$, 1H), 8.13 (d, $J = 7.6$, 1H), 7.93 (bs s, 1H), 7.76 (t, $J = 7.6$, 1H), 7.69 (t, $J = 7.6$, 1H), 7.17–7.15 (t, 2H), 7.13–6.98 (m, 4H), 6.75–6.68 (m, 4H); Anal. Calcd. for $C_{22}H_{15}NO_2S$ (357): C, 73.93; H, 4.23; N, 3.92; S, 8.97; Found: C, 74.22; H, 4.21; N, 3.98; S, 9.03.

*4.3.2. 2-(3-Methoxyphenylthio)-3-(phenylamino)naphthalene-1,4-dione (**6b**)*

Shining brown solid from methanol; IR (KBr): 1587 and 1662 (>C=O of quinone), 2359 and 2925 (OMe), 3310 (N–H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, $J = 7.6$, 1H), 8.13 (d, $J = 7.6$, 1H), 7.96 (bs, 1H), 7.77 (t, $J = 7.6$, 1H), 7.69 (t, $J = 7.6$, 1H), 7.19–7.17 (t, 2H, Ar-H), 7.15–7.09 (t, 1H, Ar-H), 6.96–6.92 (t, 1H, Ar-H), 6.73–6.71 (d, 2H, Ar-H), 6.60–6.58 (d, 1H, Ar-H), 6.38–6.39 (d, 1H), 6.22 (s, 1H, Ar-H), 3.63 (s, 3H, OCH_3), Mass (Fab): $M^+ = 387$, $M^+ + 1 = 388$, $M^+ + 2 = 389$; ^{13}C NMR (400 MHz, $CDCl_3$): δ 54, 112 (2C) 113, 114, 120, 122, 124, 126 (2C), 127, 128, 130, 132, 133, 134 (2C), 136, 142, 159, 180 (2C). Anal. Calcd. for $C_{23}H_{17}NO_3S$ (387): C, 71.30; H, 4.42; N, 3.62; S, 8.28; Found: C, 71.24; H, 4.39; N, 3.58; S, 8.32.

*4.3.3. 2-(Naphthalene-1-ylthio)-3-(phenylamino)naphthalene-1,4-dione (**6c**)*

Light brown solid from methanol; IR (KBr): 1590 and 1662 (>C=O of quinone), 3329 (N–H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.04–8.08 (m, 4H), 7.94–7.98 (m, 2H), 7.68–7.80 (m, 4H), 7.43–7.49 (m, 3H) 7.32–7.26 (m, 2H), 6.62–6.56 (m, 2H). Anal. Calcd. for $C_{26}H_{17}NO_2S$ (407): C, 76.64; H, 4.21; N, 3.44; S, 7.87; Found: C, 75.92; H, 4.19; N, 3.41; S, 7.91.

*4.3.4. 2-(4-Hydroxyphenylamino)-3-(phenylthio)naphthalene-1,4-dione (**6d**)*

Shining brown solid from methanol; IR (KBr): 1546 and 1624 (>C=O of quinone), 3315 (N–H), 3375 (O–H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, $J = 7.2$, 1H), 8.12 (d, $J = 7.2$, 1H), 7.90 (bs, 1H), 7.68–7.76 (m, 3H) 7.31 (m, 1H), 7.03–7.05 (m, 3H), 6.77–6.80 (m, 2H), 6.62 (m, 3H); Anal. Calcd. for $C_{22}H_{15}NO_3S$ (373): C, 70.76; H, 4.05; N, 3.75; S, 8.59; Found: C, 70.02; H, 4.01; N, 3.70; S, 8.63.

*4.3.5. 2-(4-Hydroxyphenylamino)-3-(naphthalene-1-ylthio)naphthalene-1,4-dione (**6e**)*

Red oil; IR (KBr): 1593 and 1678 (>C=O of quinone), 3230 (N–H), 3469 (O–H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.05–8.08 (m, 4H), 7.92–7.97 (m, 2H), 6.58–6.64 (m, 2H) 7.69–7.85 (m, 4H), 7.45–7.50 (m, 3H), 7.33–7.27 (m, 2H); Anal. Calcd. for $C_{26}H_{17}NO_3S$ (423): C, 73.74; H, 4.05; N, 3.31; S, 7.57; Found: C, 74.21; H, 4.08; N, 3.28; S, 7.68.

*4.3.6. 2-(Diphenylamino)-3-(phenylthio)naphthalene-1,4-dione (**6f**)*

Red oil; IR (KBr): 1590 and 1678 (>C=O of quinone) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.04–8.08 (m, 4H), 7.94–7.98 (m, 2H), 7.60–7.80 (m, 4H), 7.43–7.49 (m, 3H), 7.02–7.11 (m, 3H), 6.60–6.69 (m, 3H); Anal. Calcd. for $C_{28}H_{19}NO_2S$ (434): C, 77.57; H, 4.42; N, 3.23; S, 7.40; Found: C, 77.42; H, 4.38; N, 3.18; S, 7.45.

*4.3.7. 2-(Diphenylamino)-3-(3-methoxyphenylthio)naphthalene-1,4-dione (**6g**)*

Red oil; IR (KBr): 1588 and 1662 (>C=O of quinone), 2359 and 2925 (OCH_3) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.03–8.07 (m, 4H), 7.92–7.96 (m, 2H), 7.59–7.78 (m, 4H), 7.43–7.45 (m, 2H), 7.02–7.11 (m, 3H), 6.62–6.70 (m, 3H), 3.73 (s, 3H, OCH_3). Anal. Calcd. for $C_{29}H_{21}NO_3S$ (464): C, 75.14; H, 4.57; N, 3.02; S, 6.92; Found: C, 75.42; H, 4.58; N, 3.08; S, 7.00.

*4.3.8. 2-(Diphenylamino)-3-(naphthalene-1-ylthio)naphthalene-1,4-dione (**6h**)*

Yellow powder from methanol; IR (KBr): 1590 and 1678 (>C=O of quinone) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.04–8.08 (m, 4H), 7.94–7.7.98 (m, 2H), 7.60–7.80 (m, 9H), 7.43–7.49 (m, 6H). Anal. Calcd. for $C_{32}H_{21}NO_2S$ (484): C, 79.48; H, 4.38; N, 2.90; S, 6.63; Found: C, 78.98; H, 4.34; N, 2.92; S, 6.58.

*4.4. General procedure for the synthesis of dihydrobenzo[f]naphtho[2,3-b][1,4]thiazepine-6,11-diones (**9**)*

It was synthesized according to the procedure reported by Wang et al. [21].

*4.4.1. 12-Phenyl-12,13-dihydrobenzo[f]naphtho[2,3-b][1,4]thiazepine-6,11-dione (**9a**)*

Dark red solid after column chromatography on silica gel G using ethyl acetate in hexane as solvent (10–50%); IR (KBr): 1654, 1723, 2961 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.04–8.11 (m, 3H), 7.61–7.68 (m, 3H), 6.62–7.05 (m, 7H), 4.50 (s, 2H). Mass (Fab): $M^+ + 1 = 370$. Anal. Calcd. for $C_{23}H_{15}NO_2S$ (369): C, 74.78; H, 4.09; N, 3.79; S, 8.68; Found: C, 75.12; H, 4.12; N, 3.82; S, 8.70.

*4.4.2. 3-Methoxy-12-phenyl-12,13-dihydrobenzo[f]naphtho[2,3-b][1,4]thiazepine-6,11-dione (**9b**)*

Dark brown solid after column chromatography on silica gel G using ethyl acetate in hexane as solvent (10–50%); IR (KBr): 1650, 1726, 2370, 2961 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.98–8.10 (m, 3H), 7.64–7.66 (m, 3H), 6.70–6.98 (m, 6H), 4.52 (s, 2H), 3.81 (s, 3H); Anal. Calcd. for $C_{24}H_{17}NO_3S$ (399): C, 72.16; H, 4.29; N, 3.51; S, 8.03; Found: C, 71.88; H, 4.04; N, 3.48; S, 7.92.

*4.5. General procedure for the synthesis of isoindoline-1,3-dione derivatives of 1,4-naphthoquinone (**13**)*

A mixture of phthalic anhydride (10) (130 mmole) and ethylenediamine (**11**) (200 mmole) in acetic acid (10 mL) was stirred at 100 °C for 1h. 2-(2-aminoethyl)isoindoline-1,3-dione (**12**) was obtained as colorless crystals. A mixture of naphthoquinone (**1a**–**b**) (5 mmol) and compound **12** (5 mmol), K_2CO_3 (5 mmol) and abs. EtOH (50 mL) was refluxed at 90 °C for 24 h . The resulting solution was concentrated in vacuo and the residue was subjected to column chromatography on silica gel using EtOAc/hexane. The product was crystallized with EtOAc/hexane to give **13** (Table 1).

4.5.1. 2-[2-(3-Chloro-1,3-dioxo-1,4-dihydronaphthalen-2-ylamino)ethyl]isoindoline-1,3-dione (**13a**)

Red solid after column chromatography on Silica gel G using ethyl acetate in hexane as solvent (5–40%); IR (KBr): 1553, 1590, 1668, 2820, 2928, 3302 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 7.92–8.16 (m, 4H), 7.68–7.82 (m, 4H), 3.93 (t, $J = 4.0$, 2H), 3.21 (t, $J = 4.0$, 2H), 2.51 (bs, 1H). Anal. Calcd. for $C_{20}H_{13}ClN_2O_4$ (381): C, 63.08; H, 3.44; N, 7.36; Found: C, 62.88; H, 4.38; N, 7.40; Beilstein test: [26] Cl positive.

4.5.2. 2-[2-(1,4-Dioxo-1,4-dihydronaphthalen-2-ylamino)ethyl]isoindoline-1,3-dione (**13b**)

Brown solid after column chromatography on Silica gel G using ethyl acetate in hexane as solvent (5–40%); IR (KBr): 1598, 1709, 2827, 2927, 3427 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 7.95–8.18 (m, 4H), 7.71–7.83 (m, 4H), 6.61 (s, 1H), 3.98 (t, $J = 4.0$, 2H), 3.35 (t, $J = 4.0$, 2H), 2.54 (bs, 1H). Anal. Calcd. for $C_{20}H_{14}N_2O_4$ (346): C, 69.36; H, 4.07; N, 8.09; Found: C, 68.98; H, 4.02; N, 7.98.

4.6. General procedure for the synthesis of **15**–**17**

Anhydrous K_2CO_3 (2.20 mmol) was added to a stirred reaction mixture of 2,3-dihalo-1, 4-napthoquinone **1** (2.20 mmol) and 2-aminobenzonitrile (2.75 mmol) in abs. EtOH (25 mL). The reaction mixture was vigorously stirred at 50 °C for 24 h and filtered while hot. The filtrate was concentrated *in vacuo* to yield a mixture of **14** and mono-derivative which was separated by column chromatography. Primary aliphatic and aromatic amines (1.2 mmol) were added to a stirred solution of mono-derivative (1.0 mmol) in abs. EtOH (90 mL) and Et_3N (1.2 mmol). The reaction mixture was stirred first at room temperature for 0.5 h and then at 90 °C for 12–15 h. The resulting solution was concentrated *in vacuo* and the residue was purified by column chromatography [18].

4.6.1. 13-Amino-12-methyl-12H-5,12-diazabenzo[4,5]cyclohepta[1,2-b]naphthalene-6,11-dione (**15**)

The general procedure was followed for 12 h to give red crystals on crystallization with EtOAc/hexane; 90% yield; mp: 90 °C; IR (KBr): 1599, 1681, 2942, 3452 cm^{-1}; ^1H NMR ($CDCl_3$): 1.25 (bs, 2H), 3.47 (s, 3H), 6.39 (d, $J = 7.5$ Hz, 1H), 6.72 (t, $J = 7.5$ Hz, 1H), 7.29 (t, $J = 7.5$, 1H), 7.60 (d, $J = 7.5$ Hz, 1H), 7.62–7.75 (m, 2H), 8.10 (d, $J = 7.5$ Hz, 2H); ^{13}C NMR ($CDCl_3$): 35.05, 68.92, 105.22, 116.71, 123.28, 123.52, 126.54, 131.80, 132.58, 133.22, 134.53, 135.88, 140,38, 147.62, 156.02, 180.40, 182.02; MS: $M^+(M^+ + 1)$: 304; Anal. Calcd. ($C_{18}H_{13}N_3O_2$): C, 71.28; H, 4.32; N, 13.85; Found: C, 71.52; H, 4.50; N, 13.98 [18].

4.6.2. 13-Amino-12-phenyl-12H-5,12-diazabenzo[4,5]cyclohepta[1,2-b]naphthalene-6,11-dione (**14**)

The general procedure was followed for 15 h to give red solid on crystallization with Benzene/hexane; 80% yield; mp: 60–62 °C; IR (KBr): 1603, 1665, 2932, 3471 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.25 (bs, 2H), 6.72–6.76 (m, 1H), 7.28–7.38 (m, 2H), 7.66–7.72 (m, 6H), 8.02–8.05 (m, 4H); Anal. Calcd. ($C_{23}H_{15}N_3O_2$): C, 75.60; H, 4.14; N, 11.50; Found: C, 75.82; H, 4.30; N, 11.72 [18].

4.7. General procedure for the synthesis **18**–**19**

A mixture of 2,3-dichloro-1,4-naphthoquinone (**1**) (10 mmol) and aryl thiols (12 mmol) in abs. EtOH (50 mL) was stirred with vigorous stirring for 3–8 h at 40 °C. After separation by column chromatography compound **17**–**18** were obtained. Further reaction of Sodium azide (30 mmol) with **17** in DMF (15 mL) and H_2O (1.5 mL) at 100 °C for 4 h and adding onto crushed ice (50 g), a solid precipitate was obtained which was purified by column chromatography gave **19** [11].

4.7.1. 2-Chloro-3-phenylsulfanyl-[1,4]naphthoquinones (**17a**)

Orange needles after crystallization with EtOAc/hexane; 80% yield; mp 124 °C; IR (KBr): 1590 and 1666 (>C=O of quinone) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.27 (s, 3H, Ar-H), 7.40 (m, 2H, Ar-H), 7.65 (m, 2H, C_6-H and C_7-H), 8.08 (m, 2H, C_5-H and C_8-H) Anal. Calcd. for $C_{16}H_9ClO_2S$ (300.76): C, 63.90; H, 3.02; S, 10.66. Found: C, 63.68; H, 2.98; S, 10.58 [11].

4.7.2. 2-Chloro-3-(3-methoxy)phenylsulfanyl-[1,4]naphthoquinones (**17b**)

Orange needles after crystallization with EtOAc/hexane; 63% yield; mp 108 °C; IR (KBr): 1589 and 1665 (>C=O of quinone) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.79 (s, 3H, OCH_3), 6.85–7.20 (m, 4H, Ar-H), 7.73 (m, 2H, C_6-H and C_7-H), 8.15 (m, 2H, C_5-H and C_8-H). Anal. Calcd. for $C_{17}H_{11}ClO_3S$ (330.79): C, 61.73; H, 3.35; S, 9.69; Found: C, 61.92; H, 3.52; S, 9.80 [11].

4.7.3. 2-Chloro-3-(naphthalen-1-ylthio)naphthalene-1,4-dione (**18**)

Orange crystals after crystallization with EtOAc/hexane; 65% yield; mp 180 °C; IR (KBr): 1586 and 1662 (>C=O of quinone) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.50 (m, 3H, Ar-H), 7.77 (m, 4H, Ar-H), 7.98 (m, 2H, C_6-H and C_7-H), 8.17 (m, 2H, C_5-H and C_8-H); Anal. Calcd. For $C_{20}H_{11}ClO_2S$ (350.82): C, 68.47; H, 3.16; S, 9.14; Found: C, 68.50; H, 3.14; S, 9.10 [11].

4.7.4. 6H-Benzo[b]phenothiazine-6,11(12H)-dione (**19a**)

Red crystals after crystallization with EtOAc/hexane; 85% yield; mp 110 °C; IR (KBr): 1592 and 1665 (>C=O of quinone), 3305 (N–H) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.00 (bh, 1H, NH), 7.32 (m, 2H, Ar-H), 7.49 (m, 2H, Ar-H), 7.71 (m, 2H, C_6-H and C_7-H), 8.15 (m, 2H, C_5-H and C_8-H); Anal. Calcd. for $C_{16}H_9NO_2S$ (279.31): C, 68.80; H, 3.25; N, 5.01; S, 11.48; Found: C, 68.78; H, 3.22; N, 4.97; S, 11.51 [11].

4.7.5. 3-Methoxy-6H-benzo[b]phenothiazine-6,11(12H)-dione (**19b**)

Red crystals after crystallization with EtOAc/hexane; 79% yield; mp 145–147 °C; IR (KBr): 1594 and 1662 (>C=O of quinone), 3310 (N–H) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.00 (bh, 1H, NH), 6.77 (d, 1H, $J = 6.5$ Hz, C_1–H), 7.08 (m, 1H, C_3–H), 7.38 (m, 1H, C_2–H), 7.63 (m, 2H, C_6–H and C_7–H), 8.09 (m, 2H, C_5–H and C_8–H); Anal. Calcd. for $C_{17}H_{11}NO_3S$ (309.34): C, 66.01; H, 3.58; N, 4.53; S, 10.37; Found: C, 59.98; H, 3.60; N, 4.50; S, 10.40 [11].

4.8. In vitro antifungal and antibacterial activities' evaluation by MIC assay

The compounds **3**–**19** were evaluated for their *in vitro* antifungal activity against *C. albicans*, *C. neoformans*, *S. schenckii*, *T. mentagraphytes*, *A. fumigatus* and *Candida parapsilosis* (ATCC 22019) and antibacterial activity *E. coli*, *S. aureus* (ATCC25923), *K. pneumoniae* (ATCC 27736) and *P. aeruginosa* against at the Division of Fermentation Technology of Central Drug Research Institute, Lucknow, India. In this process minimum inhibitory concentration of compounds **3**–**19** was tested according to standard micro-broth dilution as per NCCLS [27,28] protocol. Briefly, testing was performed in flat-bottomed 96-well tissue culture plates (CELLSTAR® Greiner bio-one GmbH, Germany) in RPMI 1640 medium buffered with MOPS (3-[*N*-Morpholino]propane sulfonic acid) (Sigma Chemical Co., MO, USA) for fungal strains and in Muller Hinton broth (Titan Biotech Ltd. India) for bacterial

strains. The concentration range of tested compounds was 50–0.36 μg/mL for standard compounds. Initial inocula of fungal and bacterial strains were maintained at $1–5 \times 10^3$ cells/mL. These plates were incubated in a moist chamber at 35 °C and absorbance at 492 nm was recorded on Versa Max micro-plate reader (Molecular devices, Sunnyvale, USA) after 48 h for *C. albicans* and *C. parapsilosis*, 72 h for *A. fumigatus, S. schenckii* and *C. neoformans* and 96 h for *T. mentagraphytes* while bacterial strains were incubated for 24 h. MIC was determined as 90% inhibition of growth with respect to the growth control was observed by using SOFTmax Pro 4.3 Software (Molecular Devices, Sunnyvale, USA).

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Appendix. Supporting information

Supplementary data associated with this article can also be found in the online version, at doi: 10.1016/j.ejmech.2009.03.006.

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