Synthesis of Novel Benzofuran-Gathered *C*-2,4,6-substituted Pyrimidine Derivatives Conjugated by Sulfonyl Chlorides: Orally Bioavailable, Selective, Effective Antioxidants and Antimicrobials Drug Candidates

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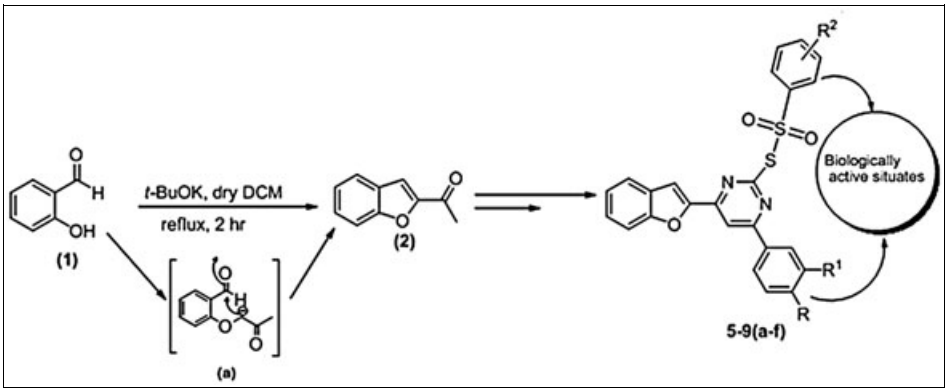

In the present study, we have made an effort to develop the novel synthetic antioxidants and antimicrobials with improved potency. The novel benzofuran-gathered *C*-2,4,6-substituted pyrimidine derivatives **5–9(a–f)** were synthesized by simple and efficient four-step reaction pathway. Initially, *o*-alkyl derivative of salicylaldehyde readily furnish corresponding 2-acetyl benzofuran **2** in good yield, upon the treatment with potassium *tertiary* butoxide in the presence of molecular sieves. Further, Claisen–Schmidt condensation with aromatic aldehydes via treatment with thiourea followed by coupling reaction with different sulfonyl chlorides afforded target compounds. The structures of newly synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass, and elemental analysis and further screened for their antioxidant and antimicrobial activities. The results showed that the synthesized compounds **8b**, **8e**, **9b**, and **9e** produced significant antioxidant activity with 50% inhibitory concentration higher than that of reference, whereas compounds **7d** and **7c** produced dominant antimicrobial activity at concentrations 1.0 and 0.5 mg/mL compared with standard Gentamicin and Nystatin, respectively.

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INTRODUCTION

Heterocyclic compounds play an imperative role in an untiring effort aimed at developing new biological agents with new mechanism of action. Heterocyclic compounds are also well known to possess diverse pharmacological properties. Benzofurans are very interesting heterocycles, which are ubiquitous in nature and show a wide range of biological activities [1]. A wide variety of pharmacological properties has been shown to be associated with benzofuran [2]. The benzofuran ring system itself is a common structural element that appears in a large number of medicinally important compounds [3]. Benzofuran and its heterocyclic systems are known to exhibit a wide range of biological properties such as anti-hyperglycemic, analgesic, anti-inflammatory, antimicrobial, and anti-tumor activities [4–6]. Nitrogen containing heterocycles such as pyrimidine and isoxazole is a promising structural moiety for drug designing. They also play an essential role in several biological processes, found in nucleoside antibiotics, antibacterials, cardiovascular as well as considerable chemical reactions and also occupy a prominent place in the pharmaceutical arena. Pyrimidine derivatives form a component in a number of useful drugs and are associated with many biological, pharmaceutical, and therapeutical activities [7]. Condensed benzofuran-gathered pyrimidine heterocyclic derivatives have been reported as antimicrobial, analgesic, anti-viral, anti-inflammatory, anti-HIV, anti-tubercular, anti-tumor, antioxidant, anti-neoplastic, anti-malarial, and diuretic cardiovascular [8–15] agents. Pyrimidine compounds are also used as hypnotic drugs for the nervous system [16], calcium-sensing receptor antagonists [17]. On the other hand, compounds containing sulfonyl groups have long been a research focus as a result of their biological importance and chemical applications.

It was envisaged that these three active pharmacophores, if linked together would generate novel molecular templates, which are likely to exhibit interesting biological properties. The aforementioned applications prompted us to synthesize a series of new compounds, which are reported in this article. Owing to the importance and in continuation of our research work on synthesis of

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biologically active compounds [18–20], now, we wish to describe the synthesis of new benzofuran-gathered *C*-2, 4,6-substituted pyrimidine derivatives containing sulfonyl chlorides moiety and were screened for their antioxidant and antimicrobial study. Thus, we have created new avenues to explore the potent heterocyclic moieties for the pharmacological activities in medicinal chemistry.

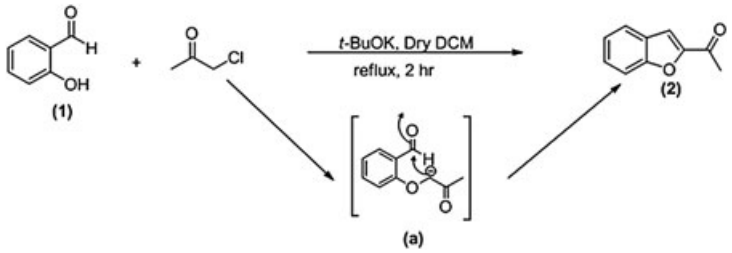
RESULTS AND DISCUSSION

In this present work, a series of 30 new benzofuran-gathered *C*-2,4,6-substituted pyrimidine derivatives **5–9**(**a–f**) were synthesized by a four-step reaction. The desired starting material 2-acetyl benzofuran (**2**) was obtained by cyclocondensation reaction. At present, several general methods for the preparation of 2-acetyl benzofuran are known [21–24]. Very recently, we have reported 1,8-diazabicyclo[5.4.0]undec-7-ene assisted one-pot synthesis of benzofurans [25]. In this manuscript, we described a mild variant potassium *tertiary* butoxide (*t*-BuOK) that aided one-pot synthesis of 2-acetyl benzofuran in the presence of molecular sieves Scheme 1. The synthetic route involves, initially, *o*-alkylation of salicylaldehyde (**1**) with chloroacetone (**i**) in the presence of *t*-BuOK as base-furnished *o*-alkylated salicyaldehyde derivative (**ii**), which subsequently generates enolate anion (**iii**) undergoing intramolecular cyclocondensation reaction that afforded 2-acetyl benzofuran (**2**) with improved yield Scheme 2. The resultant starting material was subjected to Claisen–Schmidt condensation reaction with different aromatic aldehydes in the presence of zirconium chloride as a catalyst [26] afforded corresponding chalcones **3**(**a–e**). Generally, chalcones are considered to be useful intermediates in several cyclisation reactions to produce types of heterocyclic compounds of diverse biological importance, according to the reactants used and the reaction conditions [27]. Further, the compounds **3**(**a–e**) were treated with thiourea in DMF to yield the corresponding pyrimidine derivatives **4**(**a–e**) [28]. In the final step, compounds **4**(**a–e**) were coupled with different substituted sulfonyl chlorides in the presence of triethylamine as base accomplished the desired products **5–9**(**a–f**) Scheme 3, Table 1. The structures of the compounds were elucidated by IR, ^{1}H NMR, ^{13}C NMR, mass, and elemental analysis.

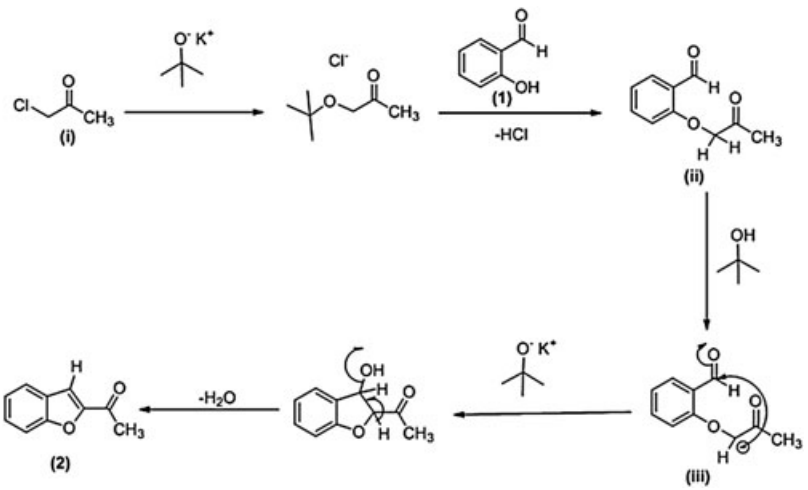
ANTIOXIDANT EVALUATION

Evaluation of antioxidant activity for the newly synthesized analogs **5–9**(**a–f**) was performed by using three *in vitro* assays such as 2,2-diphenyl-1-picryl-hydrazyl

Scheme 1. Reaction lane for the synthesis of 2-acetyl benzofuran.



Scheme 2. Mechanism toward the synthesis of 2-acetyl benzofuran (**2**) by using *t*-BuOK.



Scheme 3. Reaction pathway for the synthesis of benzofuran-gathered *C*-2,4,6-substituted pyrimidine derivatives **5–9** (**a–f**).

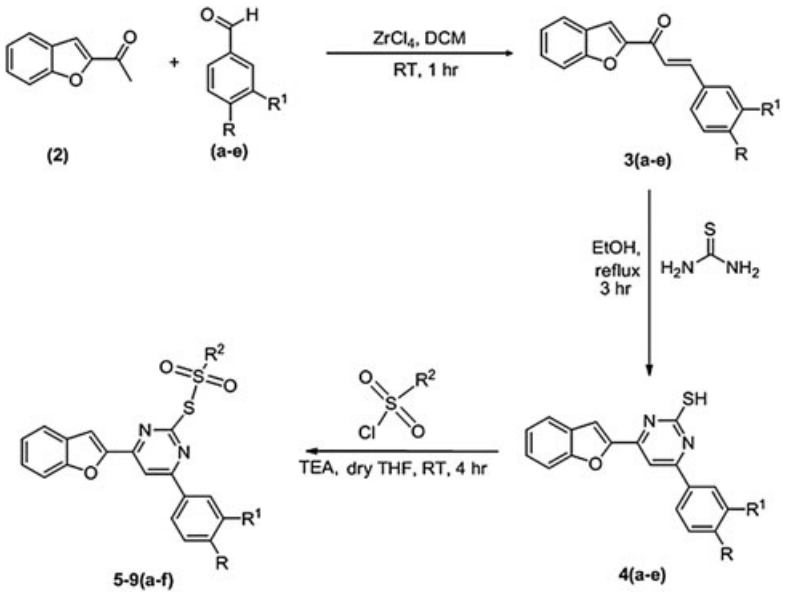
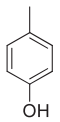
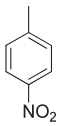
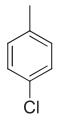
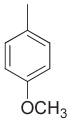
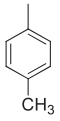


Table 1
Sulfonyl linked phenyl ring (R^2) in compounds **5–6**(**a–f**).

Compounds	Entry R^2
5a, **6a**, **7a**, **8a**, **9a**	
5b, **6b**, **7b**, **8b**, **9b**	
5c, **6c**, **7c**, **8c**, **9c**	
5d, **6d**, **7d**, **8d**, **9d**	
5e, **6e**, **7e**, **8e**, **9e**	
5f, **6f**, **7f**, **8f**, **9f**	

(DPPH) radical scavenging activity (RSA), *N*,*N*-dimethyl-*p*-phenylenediamine (DMPD), and Ferric ion reducing power assay. The antioxidant properties were expressed as 50% inhibitory concentration (IC_{50}) values and optical density (OD) (Table 2).

DPPH radical scavenging activity. The DPPH radical scavenging evaluation is a standard assay in antioxidant activity studies and offers a rapid technique for screening the RSA of specific compounds. The reaction of synthesized compounds with stable DPPH free radical indicates their free radical scavenging ability. In the present study, different electron-withdrawing and electron-donating groups attached to phenyl ring as substituent, which is linked to sulfonyl groups were studied for antioxidant efficacy. Among the synthesized analogs, compounds **8b** and **9b** exhibited dominant antioxidant activity with IC_{50} value when compared with other compounds in the series, this may be due to the presence of methoxy group in addition to hydroxy moiety on *C*-6-substituted phenyl ring and also the presence of hydroxy group at *para* position on *C*-2-substituted phenyl ring in compound **8b**. Compound **9b** has a hydroxy group at *para* position on both *C*-6 and *C*-2-substituted phenyl rings, which are accounted for enhanced activity. Compounds **5b**, **6b**, and **7b** having hydroxy group on the sulfonyl-linked phenyl ring produce better activity but slightly less than that of the standard ascorbic acid (AA). The compounds in the series (**5c–d**, **6c–d**, and **7c–d**) at the *para* position emphasize that the electron-withdrawing group (chloro and nitro) on the sulfonyl-linked phenyl ring decreases the potency of the activity, and compounds **8c–d** and **9c–d** also possess electron-withdrawing group on sulfonyl-linked phenyl ring, showing moderate activity in the presence of hydroxy

Table 2

Concentration required for 50% scavenging (IC_{50}) of DPPH$^{\bullet}$, DMPD radicals inhibition and absorbance of ferric ion reducing by the compounds **5–6(a–f)** and the standard antioxidant AA.

Compounds	DPPH	DMPDx	Ferric re
	IC_{50}[a]		Absorbance[b]
5a	208	350	0.0812
5b	45	65	0.3256
5c	500	500	0.0701
5d	500	500	0.0683
5e	175	225	0.1201
5f	182	295	0.0910
6a	98	275	0.1025
6b	25	32	0.3989
6c	185	293	0.0962
6d	192	386	0.0774
6e	52	75	0.2937
6f	84	98	0.2357
7a	227	>500	—
7b	57	79	0.2645
7c	287	>500	—
7d	344	>500	—
7e	102	118	0.2156
7f	154	203	0.1659
8a	32	43	0.3677
8b	08	15	0.4781
8c	43	91	0.2235
8d	52	74	0.3015
8e	18	29	0.4567
8f	15	42	0.3751
9a	52	74	0.3098
9b	10	18	0.4300
9c	55	76	0.2935
9d	62	89	0.2513
9e	24	22	0.4256
9f	45	33	0.3947
AA	11	20	0.4135

AA, ascorbic acid; DPPH, 2,2-diphenyl-1-picryl-hydrazyl; DMPD, *N*,*N*-dimethyl-*p*-phenylenediamine.

[a]The values are expressed as μM concentration. Lower IC_{50} values indicate higher radical scavenging activity.

[b]Higher absorbance indicates higher reducing power.

group on the *C*-6-substituted phenyl ring; changing the substituent on the $–SO_2–$ linked phenyl ring by electron-donating group such as methyl and methoxy instead of withdrawing group favors for antioxidant activity [29]. Thus, the compounds (**5e–f**, **6e–f**, **7e–f**, **8e–f**, **9e–f**) showed relatively good RSA, respectively. The conjugation of benzene sulfonyl chloride to scaffold (**4a–e**) revealed considerable to moderate radical inhibition activity in compounds **5a**, **6a**, **7a**, **8a**, and **9a**. The aforementioned SAR correlation study reveals that the nature of the functional group present on the $–SO_2–$ linkage phenyl ring as well as *C*-2 linked phenyl ring influences the antioxidant activity.

DMPD radical scavenging activity. All the synthesized benzofuran-gathered *C*-2,4,6-substituted pyrimidine derivatives **5–9(a–f)** were evaluated for their antioxidant activity employed by DMPD radical scavenging assay. The dark color of DMPD$^{\bullet+}$ radical cation solution becomes lighter and absorbance of solution becomes lower in the presence of an antioxidant compound. The DMPD$^{\bullet+}$ radical cation solution shows a maximum absorbance at 505 nm. Antioxidant compounds, which are hydrogen donors to DMPD$^{\bullet+}$, quench the color of DMPD$^{\bullet+}$ solution. AA was used as a standard for comparison. Among the synthesized compounds **8b** and **9b**, possessed maximum radical activity as well as more potent than the standard, and this is because of the presence of 4-hydroxyphenyl pharmacophore at –S-linked *C*-2 and *C*-6 positions of pyrimidine in compound **8b**. Compound **9b** emphasizes with 4-hydroxy 3-methoxyphenyl at *C*-6 position of pyrimidine and as well as 4-hydroxyphenyl at sulfonyl-linked *C*-2 position of pyrimidine nucleus, respectively. The presence of a strong electron-withdrawing group such as nitro, chloro group on the phenyl ring at *para* position did not favor the activity. This might be the reason compounds **5–9(c–d)** showed considerable activity. In general, it appears that the presence of electron-donating groups on the phenyl ring favors the activity. This might be the reason for the enhancement of activity of the other compounds, which showed moderate RSA in compounds **5b**, **6b**, and **7b**. Compounds **5–9(e–f)** showed good activity. The rest of the analogs showed weak radical inhibition activity. The DMPD RSA results were presented in Table 2.

Ferric ion reducing power assay. In the ferric to ferrous reduction assay, the yellow color of the test solution changes to various shades of green and blue depending upon the reducing power of each compound. The presence of reducer (i.e., antioxidant) causes the reduction of the Fe^{+3}/Ferricyanide complex to the ferrous from giving, after the addition of trichloroacetic acid and ferric chloride, the Perls Prussian blue that can be monitored at 700 nm. The synthesized compounds **5–9(a–f)** were screened to reduce power ability, results revealed that the entire tested compounds exhibited a certain degree of activity (Table 2) compared with the reference drug. Compounds **5b**, **6b**, and **7b** having hydroxy group, compounds **5e**, **6e**, and **7e** were possessing methoxy on sulfonyl–phenyl ring that exhibited moderate to good activity. Compounds **8a**, **8f**, **9a**, and **9f** incorporating with aromatic methyl and benzene sulfonyl group linked at *C*-2 position of pyrimidine, produce remarkable activity but less than that of the standard (AA). The presence of hydroxy and methoxy substituents at the *para* position of the phenyl ring, in compounds **8b**, **8e**, **9b**, and **9e** exhibit more absorbance, indicates strong reducing power than the standard, whereas compounds **5c–d**, **6c–d**, and **7c–d** having electron-withdrawing group (nitro and chloro) on the SO_2-linked phenyl ring at *C*-4 position reveal lesser reducing ability. Compounds **5a**, **6a**, **7a** do not have any substituents on the 2-substituted phenyl ring and displayed the weak reducing power compared with other analogs.

ANTIMICROBIAL EVALUATION

Antibacterial activity. The antibacterial activities of newly synthesized compounds **5–9**(**a–f**) were determined by well plate method. In this study, *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 25923, and *Pseudomonas aeruginosa* ATCC 27853 were used as bacterial strains to investigate the activity. The test compounds were dissolved in DMSO at concentrations 1 and 0.5 mg/mL. The investigation of antibacterial screening data revealed that in all tested compounds, some were showed good antibacterial activity against three pathogenic bacterial strains. Among the tested series, compound **5d** exhibited a considerable antibacterial activity against *E. coli* and *P. Aeruginosa* bacteria, this is because of the presence of chloro substituents on the sulfonyl–phenyl ring, and compounds **5a–c** and **5e–f** did not exhibit any antibacterial activity. On the other hand, compounds, **6a–f**, **8a–f**, and **9a–f** demonstrated less activity against all the tested organisms, this could be due to the presence electron-releasing substituents such as methoxy and hydroxy on the 2-substituted sulfonyl–phenyl ring. In general, the significant antibacterial activity attributed to chloroaryl moiety [30]. Thus, compound **7d** showed dominant antibacterial activity against all the tested organisms and even more than that of the standard, this may be due to the presence of electron-withdrawing group such as nitro on 6-substituted phenyl ring and chloro on 2-substituted sulfonyl–phenyl ring. Compound **7c** showed good activity but slightly less than the standard, and other compounds in tested series **7a**, **7b**, **7e**, and **7f** showed moderate inhibitory activity against all tested bacterial strains. The results were compared with standard drug Gentamicin as depicted in Table 3.

Antifungal activity. Newly synthesized compounds **5–9** (**a–f**) were also screened for their antifungal activity against *Aspergillus flavus* MTCC 3306, *Chrysosporium keratinophilum* MTCC 3017, and *Candida albicans*

Table 3

Inhibitory zone (diameter) millimeter of the synthesized compounds **5–6**(**a–f**) against tested bacterial strains by well plate method. Each value represents mean ± SD ($n = 3$).

Compounds no	*Escherichia coli*		*Staphylococcus aureus*		*Pseudomonas aeruginosa*	
Concentration in mg/mL	1	0.5	1	0.5	1	0.5
Control	00	00	00	00	00	00
5a	1 ± 0.03	—	2 ± 0.01	—	1 ± 0.03	—
5b	2 ± 0.33	1 ± 0.17	1 ± 0.15	—	1 ± 0.06	—
5c	1 ± 0.24	—	1 ± 0.43	1 ± 0.10	2 ± 0.24	1 ± 0.25
5d	5 ± 0.10	4 ± 0.21	4 ± 0.20	3 ± 0.23	4 ± 0.34	3 ± 0.14
5e	1 ± 0.12	—	1 ± 0.10	—	2 ± 0.23	1 ± 0.21
5f	2 ± 0.33	1 ± 0.17	1 ± 0.10	—	1 ± 0.21	—
6a	3 ± 0.24	2 ± 0.12	2 ± 0.13	1 ± 0.14	3 ± 0.24	2 ± 0.25
6b	3 ± 0.30	1 ± 0.11	2 ± 0.19	1 ± 0.19	4 ± 0.25	2 ± 0.26
6c	2 ± 0.32	1 ± 0.18	3 ± 0.14	2 ± 0.16	2 ± 0.26	1 ± 0.32
6d	3 ± 0.35	1 ± 0.13	2 ± 0.18	1 ± 0.13	3 ± 0.27	2 ± 0.21
6e	5 ± 0.25	4 ± 0.10	4 ± 0.04	2 ± 0.34	7 ± 0.75	4 ± 0.20
6f	4 ± 0.42	3 ± 0.44	2 ± 0.88	1 ± 0.10	6 ± 0.12	4 ± 0.08
7a	13 ± 0.34	1 ± 0.15	12 ± 0.15	7 ± 0.11	13 ± 0.26	10 ± 0.36
7b	12 ± 0.11	7 ± 0.13	13 ± 0.10	10 ± 0.17	15 ± 0.32	12 ± 0.54
7c	16 ± 0.32	9 ± 0.24	8 ± 0.14	6 ± 0.24	17 ± 0.22	14 ± 0.10
7d	20 ± 0.30	13 ± 0.05	14 ± 0.35	9 ± 0.48	21 ± 0.65	17 ± 0.95
7e	15 ± 0.32	9 ± 0.24	8 ± 0.45	6 ± 0.36	9 ± 0.12	7 ± 0.10
7f	12 ± 0.23	9 ± 0.10	7 ± 0.14	6 ± 0.24	15 ± 0.02	10 ± 0.09
8a	2 ± 0.21	1 ± 0.16	2 ± 0.16	1 ± 0.11	5 ± 0.18	3 ± 0.10
8b	2 ± 0.65	1 ± 0.13	2 ± 0.10	1 ± 0.13	5 ± 0.24	3 ± 0.45
8c	3 ± 0.21	1 ± 0.11	4 ± 0.14	3 ± 0.05	3 ± 0.15	3 ± 0.04
8d	3 ± 0.15	2 ± 0.11	2 ± 0.22	1 ± 0.15	4 ± 0.14	2 ± 0.14
8e	2 ± 0.34	1 ± 0.11	4 ± 0.11	2 ± 0.13	4 ± 0.16	3 ± 0.10
8f	2 ± 0.18	1 ± 0.10	3 ± 0.15	2 ± 0.11	2 ± 0.18	1 ± 0.10
9a	2 ± 0.26	1 ± 0.37	2 ± 0.24	1 ± 0.12	3 ± 0.11	1 ± 0.19
9b	3 ± 0.24	2 ± 0.29	2 ± 0.28	1 ± 0.28	2 ± 0.13	1 ± 0.27
9c	2 ± 0.14	1 ± 0.27	3 ± 0.17	2 ± 0.27	1 ± 0.20	—
9d	4 ± 0.21	3 ± 0.16	4 ± 0.29	2 ± 0.16	5 ± 0.11	3 ± 0.12
9e	3 ± 0.10	2 ± 0.15	3 ± 0.13	1 ± 0.13	3 ± 0.14	1 ± 0.14
9f	3 ± 0.67	2 ± 0.73	2 ± 0.33	1 ± 0.42	2 ± 0.16	1 ± 0.83
Gentamicin	18 ± 0.33	11 ± 0.41	14 ± 0.21	09 ± 0.36	20 ± 0.70	17 ± 0.41

MTCC 2827. The compounds were dissolved in DMSO and antifungal activity was determined by well plate method at concentrations 1 and 0.5 mg/mL. The results indicated that among the tested compounds, **7d** and **7c** produced significant antifungal activity when compared with other compounds in the series against *A. flavus* and the standard, Nystatin (Table 4), this would be possessing of 4-chlorophenylsulfonyl and 4-nitrophenylsulfonyl at *C*-2 position of pyrimidine and 4-nitrophenylsulfonyl at *C*-6 position of pyrimidine. The compounds **5c**, **5d**, **6c**, and **6d** were found to be moderately active against tested *C. albicans* fungal strain. The remaining compounds **5b**, **5e–f**, **5a–b**, **8a–f**, and **9a–f** demonstrated very least activity against the three tested fungal strains compared with other analogs. From the results, it is evident that in both antibacterial and antifungal activities, two compounds showed significant activity and few are moderately active. The activity is considerably affected by halogens and electron-withdrawing substituents present at the *para* position of *C*-2 and *C*-6 pyrimidine-substituted phenyl rings.

In conclusion, a series of novel benzofuran-gathered *C*-2,4,6-substituted pyrimidine derivatives conjugated by sulfonyl chlorides **5–9(a–f)** were synthesized and their antioxidant and antimicrobial activities were evaluated. In DPPH and DMPD assays, the presence of hydroxy and methoxy substituents on both *C*-2 and *C*-6-substituted phenyl rings, in compounds **8b** and **9b**, exhibits more antioxidant activity than the standard. In Ferric ion reducing power assay (FRAP) assay, compounds **8b**, **8e**, **9b**, and **9e** containing hydroxy and methoxy on both phenyl rings produced significant enhancement of reducing ability compared with other compounds in the series and higher than the standard. The antimicrobial activity results indicated that among the tested compounds, **7d** and **7c** displayed significant antimicrobial activity when compared with other analogs in the series. This present studies revealed that the nature of functional linkage –SO_2– and *C*-6 phenyl ring) and substituents (electron-withdrawing and electron-donating groups) on phenyl ring is crucial for enhanced antioxidant and antimicrobial activities. On the basis of their

Table 4

Inhibitory zone (diameter) millimeter of the synthesized compounds **5–9(a–f)** against tested fungal strains by well plate method. Each value represents mean ± SD ($n = 3$).

Compounds no	*Aspergillus flavus*		*Chrysosporium keratinophilum*		*Candida albicans*	
Concentration in mg/mL	1	0.5	1	0.5	1	0.5
Control	00	00	00	00	00	00
5a	1 ± 0.01	—	2 ± 0.06	1 ± 0.13	2 ± 0.27	1 ± 0.01
5b	2 ± 0.06	1 ± 0.45	1 ± 0.71	—	3 ± 0.43	2 ± 0.21
5c	9 ± 0.41	6 ± 0.43	9 ± 0.31	8 ± 0.70	11 ± 0.23	10 ± 0.11
5d	8 ± 0.36	7 ± 0.02	6 ± 0.16	6 ± 0.42	10 ± 0.10	7 ± 0.33
5e	2 ± 0.45	1 ± 0.21	3 ± 0.73	1 ± 0.46	3 ± 0.17	2 ± 0.02
5f	3 ± 0.06	2 ± 0.43	2 ± 0.77	1 ± 0.09	2 ± 0.12	1 ± 0.03
6a	2 ± 0.02	1 ± 0.41	1 ± 0.01	—	3 ± 0.13	2 ± 0.14
6b	2 ± 0.72	1 ± 0.22	2 ± 0.24	2 ± 0.13	3 ± 0.33	2 ± 0.06
6c	6 ± 0.15	5 ± 0.62	7 ± 0.35	5 ± 0.72	9 ± 0.11	8 ± 0.46
6d	9 ± 0.21	8 ± 0.16	8 ± 0.06	6 ± 0.21	7 ± 0.32	5 ± 0.25
6e	2 ± 0.16	1 ± 0.31	2 ± 0.74	2 ± 0.63	3 ± 0.09	2 ± 0.06
6f	2 ± 0.02	1 ± 0.07	3 ± 0.33	1 ± 0.41	4 ± 0.22	2 ± 0.14
7a	2 ± 0.42	1 ± 0.36	1 ± 0.07	—	2 ± 0.63	1 ± 0.17
7b	4 ± 0.11	2 ± 0.13	3 ± 0.02	2 ± 0.07	4 ± 0.16	3 ± 0.01
7c	21 ± 0.45	19 ± 0.65	16 ± 0.43	15 ± 0.09	22 ± 0.78	20 ± 0.88
7d	22 ± 0.13	20 ± 0.15	17 ± 0.37	16 ± 0.06	24 ± 0.05	21 ± 0.43
7e	2 ± 0.05	1 ± 0.47	2 ± 0.36	1 ± 0.08	2 ± 0.23	1 ± 0.76
7f	2 ± 0.43	1 ± 0.65	3 ± 0.12	2 ± 0.38	3 ± 0.01	2 ± 0.09
8a	2 ± 0.03	—	3 ± 0.12	1 ± 0.41	1 ± 0.02	—
8b	2 ± 0.01	1 ± 0.23	2 ± 0.02	—	2 ± 0.05	1 ± 0.41
8c	2 ± 0.43	1 ± 0.05	3 ± 0.08	1 ± 0.70	4 ± 0.04	2 ± 0.02
8d	3 ± 0.11	2 ± 0.24	2 ± 0.35	1 ± 0.42	2 ± 0.74	1 ± 0.01
8e	3 ± 0.42	1 ± 0.61	2 ± 0.01	—	3 ± 0.45	1 ± 0.02
8f	2 ± 0.46	1 ± 0.73	2 ± 0.33	2 ± 0.40	3 ± 0.75	2 ± 0.01
9a	1 ± 0.21	—	2 ± 0.63	1 ± 0.06	—	—
9b	3 ± 0.16	1 ± 0.21	4 ± 0.41	2 ± 0.73	2 ± 0.02	—
9c	4 ± 0.02	2 ± 0.01	4 ± 0.02	3 ± 0.02	4 ± 0.02	3 ± 0.01
9d	3 ± 0.01	2 ± 0.02	2 ± 0.01	—	2 ± 0.21	1 ± 0.11
9e	3 ± 0.49	1 ± 0.17	2 ± 0.13	—	3 ± 0.42	1 ± 0.65
9f	3 ± 0.21	2 ± 0.46	2 ± 0.12	3 ± 0.01	2 ± 0.04	1 ± 0.43
Nystatin	21 ± 0.05	18 ± 0.41	16 ± 0.33	14 ± 0.25	22 ± 0.23	19 ± 0.57

activity, these derivatives were identified as viable leads for further studies.

EXPERIMENTAL

All reagents and solvents were purchased from Merck (Darmstadt, Germany) chemical AR grade and were used as provided. DPPH and AA were purchased from Sigma-Aldrich chemical Co., (St. Louis, MO, USA). TLC analysis was performed on alumina sheets precoated with silica gel 60 F-254 and SiO2, 200-400mesh (Merck, Germany) was used for column chromatography. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were obtained from AC Bruker spectrometer (Karlsruhe, Germany) in the appropriate (DMSO-d_6) solvent. Melting points were obtained on a Reichert Thermopan melting point apparatus (Barnstead International, Dubuque, IO, USA), equipped with a microscope and are uncorrected. Mass spectra were obtained by Water-QTOF ultima spectrometer (Milford, MA, USA). Micro analytical data were obtained by elemental-Vario EL-III (Bombay, India).

Synthesis of 2-acetyl benzofuran (2). A mixture of salicyaldehyde (**1**) (2 mmol), chloroacetone (2 mmol), and *potassium tert-butoxide* (*t*-BuOK) (2 mmol) in 10 mL of dry dichloromethane containing molecular sieves was reflux for 1 h. Progress of the reaction was monitored by TLC using hexane/ethyl acetate (8:2) mixture as mobile phase. After the completion of the reaction, the reaction mixture was washed with 10% HCl solution followed by water. The organics were dried over anhydrous sodium sulfate. The yellow solid was obtained by desolventizing in a rotary evaporator at room temperature affords 2-acetyl benzofuran (**2**). mp 73–75°C [31], Yield 94%, IR (KBr) ν_{max} (cm^{-1}): 1674 (C═O), 1558 (C═C) 3087 (CH furan), 2900 (CH_3). ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 6.80-7.70 (m, 5H, Ar–H), 2.60 (s, 3H, CH_3); MS (ESI) *m/z*: 161 (M^+). *Anal*. Calcd. for $C_{10}H_8O_2$, C, 74.99; H, 5.03; found: C, 74.95; H, 5.07%.

General procedure for synthesis of 3(a–e). Compound (**2**) (1 mmol) in dichloromethane (5 mL) was treated with $ZrCl_4$ (46.6 mg, 20 mol%) followed by addition-substituted benzaldehyde (1 mmol). The solution was stirred at room temperature under an air atmosphere for 1 h. After the completion of the reaction monitored by TLC, the crude mixture was worked up in ice cold brine solution and then extracted with ethyl acetate solution (3 × 10 mL). The combined ethyl acetate extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo, and the resulting products were purified by column chromatography using ethyl acetate/*n*-hexane as mobile phase (7:3) to afford the pure products **3(a–e)** as a solid. The product was recrystallized by methanol.

(E)-1-(benzofuran-2-yl)-3-phenylprop-2-en-1-one (3a). Light yellow solid, yield 82%, mp 178–181°C, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3138–2950 (Ar–CH), 1624 (C═O); ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 7.25–7.89 (m, 10H, Ar–H), 7.71 (d, 1H, J = 3.5 Hz, β–CH), 6.69 (d, 1H, J = 4.3 Hz, α–CH); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 177.6, 160.4, 155.0, 145.5, 135.7, 128.6, 127.8, 124.7, 123.3, 121.3, 120.9, 116.3, 111.2; MS (ESI) *m/z*: 248.04 (M^+); *Anal*. Calcd. for $C_{17}H_{12}O_2$: C, 82.24; H, 4.87; found: C, 82.20; H, 4.90%.

(E)-1-(benzofuran-2-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (3b). Yellow semisolid, yield 73%, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3142–2963 (Ar–CH), 1634 (C═O); ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 6.90–7.85 (m, 9H, Ar–H), 3.82 (s, 3H, OCH_3), 7.68 (d, 1H, J = 3.0 Hz, β–CH), 6.70 (d, 1H, J = 3.4 Hz, α–CH); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 177.5, 160.4, 159.4, 155.0, 145.1, 130.2, 127.6, 124.5, 123.0, 121.6, 116.0, 114.2, 111.4, 55.7; MS (ESI) *m/z*: 278.09 (M^+); *Anal*. Calcd. for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07; found: C, 77.63; H, 5.14%.

(E)-1-(benzofuran-2-yl)-3-(4-nitrophenyl)prop-2-en-1-one (3c). Light brown solid, yield 56%, mp: 205–208°C, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3122–2961 (Ar–CH), 1629 (C═O); ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 7.32–8.20 (m, 9H, Ar–H), 7.84 (d, 1H, J = 2.6 Hz, β–CH), 6.95 (d, 1H, J = 3.5 Hz, α–CH); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 177.3, 160.2, 155.6, 145.1, 147.1, 141.3, 129.0, 127.8, 124.5, 123.6, 123.2, 121.0, 120.8, 116.2, 111.0; MS (ESI) *m/z*: 293.07 (M^+); *Anal*. Calcd. for $C_{17}H_{11}NO_4$: C, 69.62; H, 3.78; N, 4.78; found: C, 69.60; H, 3.82; N, 4.75%.

(E)-1-(benzofuran-2-yl)-3-(4-hydroxy-3-methoxyphenyl)prop-2-en-1-one (3d). Light yellow solid, yield, 78%, mp 192–195°C, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3130–2942 (Ar–CH), 1628 (C═O); 1H NMR (DMSO-d6 400 MHz) δ ppm: 6.70–7.90 (m, 8H, Ar–H), 7.65 (d, 1H, J = 4.5 Hz, β–CH), 6.72 (d, 1H, J = 3.8 Hz, α–CH), 5.32 (s, 1H, –OH), 3.83 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d6 100 MHz) δ ppm: 177.3, 160.5, 156.2, 149.0, 147.6, 145.1, 127.7, 124.7, 123.3, 122.9, 121.3, 120.9, 116.7, 111.9, 111.5, 56.1; MS (ESI) *m/z*: 294.09 (M^+); *Anal*. Calcd. for $C_{18}H_{14}O_4$: C, 73.46; H, 4.79; found: C, 73.42; H, 4.75%.

(E)-1-(benzofuran-2-yl)-3-(4-hydroxyphenyl)prop-2-en-1-one (3e). Dark brown semisolid, yield 65%, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3140–2960 (Ar–CH), 1630 (C═0); ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 6.65–7.88 (m, 9H, Ar–H), 7.70 (d, 1H, J = 3.6 Hz, β–CH), 6.65 (d, 1H, J = 2.6 Hz, α–CH), 5.32 (s, 1H, –OH); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 177.2, 160.5, 157.9, 155.0, 144.9, 130.2, 127.6, 124.7, 123.3, 121.5, 120.5, 116.6, 115.8, 111.6; MS (ESI) *m/z*: 278.09 (M^+); *Anal*. Calcd. for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07; found: C, 77.63; H, 5.14%.

General procedure for synthesis of 4(a–e). Compounds **3** (**a–e**) (0.01 mol) and thiourea (0.01 mol) were dissolved in DMF (20 mL). Few drops of concentrated HCl were added, the reaction mixture was refluxed, and the reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured onto 250 mL of ice cold water and kept aside for some time. The crude solid was filtered and subjected to column chromatography. Elution with solvent system ethyl acetate/hexane (20:80) gave pure compounds (**4a–e**).

4-(benzofuran-2-yl)-6-phenylpyrimidine-2-thiol (4a). Light yellow solid, yield 82%, mp 238–241°C, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3130–2958 (Ar–CH), 1638 (C═N); ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 8.37 (s, 1H, CH of pyrimidin), 7.14–7.92 (m, 10H, Ar–H), 12.3 (s, 1H, SH); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 181.2, 166.0, 164.6, 155.2, 149.9, 135.8, 129.3, 128.7, 127.5, 124.7, 123.2, 120.9, 111.5, 103.4, 101.7; MS (ESI) *m/z*: 304.07 (M^+); *Anal*. Calcd. for $C_{18}H_{12}N_2OS$: C, 71.03; H, 3.97; N, 9.20; found: C, 71.10; H, 3.91; N, 9.23%.

4-(benzofuran-2-yl)-6-(4-methoxyphenyl)pyrimidine-2-thiol (4b). Brown semisolid, yield 55%, mp: 402–405°C, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3148–2952 (Ar–CH), 1639 (C═N); ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 8.39 (s, 1H, CH of pyrimidine), 7.12–8.32 (m, 9H, Ar–H), 12.5 (s, 1H, SH); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 181.0, 166.3, 164.5, 160.6, 155.4, 150.0, 129.3, 128.5, 128.1, 124.7, 123.0, 120.9, 114.8, 111.5, 103.2, 101.5, 55.7; MS (ESI) *m/z*: 334.08 (M^+); *Anal*. Calcd. for $C_{19}H_{14}N_2O_2S$: C, 68.24; H, 4.22; N, 8.38; found C, 68.20; H, 4.27; N, 8.42%.

4-(benzofuran-2-yl)-6-(4-nitrophenyl)pyrimidine-2-thiol (4c). Reddish brown solid, yield 74%, mp: 324–327°C, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3130–2946 (Ar–CH), 1625 (C═N); ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 7.94 (s, 1H, CH of pyrimidin), 7.12–7.96 (m, 9H, Ar–H), 12.5 (s, 1H, SH); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 181.5, 166.2, 164.6, 155.4, 149.8, 147.9, 141.9, 129.3, 126.2, 124.7, 124.1, 123.4, 120.8, 111.2, 103.6, 101.9; MS (ESI) *m/z* : 349.05 (M^+); *Anal*. Calcd. for $C_{18}H_{11}N_3O_3S$: C, 61.88; H, 3.17; N, 12.03; found: C, 61.92; H, 3.22; N, 11.99%.

4-(6-(benzofuran-2-yl)-2-mercaptopyrimidin-4-yl)-2-methoxyphenol (4d). Yellow semisolid, yield 65%, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3140–2958 (Ar-CH), 1664 (C═N); ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 12.40 (s, 1H, SH), 7.98 (s, 1H, CH of pyrimidin), 6.65–7.85 (m, 9H, Ar–H), 5.30 (s,1H, OH), 3.82 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 180.9, 165.8, 164.6, 155.0, 149.9, 148.7, 148.0, 130.5, 129.3, 124.7, 123.0, 121.2, 120.9, 115.8, 111.2, 108.8, 103.4, 101.3, 56.0; MS (ESI) *m/z*: 350.07 (M^+); *Anal*. Calcd. for $C_{19}H_{14}N_2O_3S$: C, 65.13; H, 4.03; N, 7.99; found: C, 65.18; H, 4.00; N, 8.05%.

4-(6-(benzofuran-2-yl)-2-mercaptopyrimidin-4-yl)phenol (4e). Brown solid, yield 72%, mp: 194–197°C, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3138–2975 (Ar–CH), 1634 (C═N) ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 12.50 (s, 1H, SH), 8.24 (s, 1H, CH of pyrimidin), 6.68–7.85 (m, 9H, Ar–H), 5.35 (s, 1H, OH); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 181.3, 166.8, 164.2, 158.5, 155.3, 149.9, 129.3, 128.9, 128.3, 124.7, 123.3, 120.7, 116.2, 111.5, 103.4, 1017; MS (ESI) *m/z*: 320.06 (M^+); *Anal*. Calcd. for $C_{18}H_{12}N_2O_2S$: C, 67.48; H, 3.78; N, 8.74; found: C, 67.45; H, 3.81; N, 8.70%.

General procedure for the synthesis of benzofuran-gathered *C*-2,4,6-substituted pyrimidine derivatives 5–9 (a–f). 4-(Benzofuran-2-yl)-6-phenylpyrimidine-2-thiol (**4a**) (1.2 mmol) was suspended in dry THF (5 mL) in an inert atmosphere (N_2). To this suspension, at room temperature, triethylamine (1.5 mmol) followed by different sulfonyl chlorides (RSO_2Cl) (1 mmol in 3 mL of THF) was added, and reaction mixture was stirred for 3–4 h. The progress of reaction mixture was monitored by TLC using ethyl acetate/hexane (6:4). The reaction mixture was then desolventized in rotary evaporator, and the compound was extracted in ethyl acetate. The ethyl acetate layer was washed with water and dried over anhydrous sodium sulfate. The products were obtained by further desolventation in rotary evaporator at 50°C. The respective products were purified through column chromatography using ethyl acetate/hexane (6:4) to furnish the pure products (**5a–f**) as a solid. The same procedure was adopted for synthesis of **6–9**(**a–f**).

S-4-(benzofuran-2-yl)-6-phenylpyrimidin-2-yl methanesulfonothioate (5a). Dark yellow semisolid; spectroscopic analysis IR (KBr) ν_{max} (cm^{-1}): 3128–2973 (Ar–CH), 1618 (C═N); ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 7.10–7.88 (m, 15H, Ar–H), 8.42 (m, 1H, CH of pyrimidin); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.3, 166.0, 164.6, 155.4, 149.2, 135.8, 129.3, 128.7, 127.4, 124.7, 123.3, 120.7, 111.5, 103.0, 101.6, 52.4; MS (ESI) *m/z*: 460.06(M^+); *Anal*. Calcd. for $C_{19}H_{14}N_2O_3S_2$: C, 59.67; H, 3.69; N, 7.32; found: C, 59.57; H, 3.62; N, 7.31%.

S-4-(benzofuran-2-yl)-6-phenylpyrimidin-2-yl 4-hydroxybenzenesulfonothioate (5b). Brown solid, mp: 231-233°C; spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3131–2970 (Ar–CH), 1625 (C═N); ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 7.12–7.92 (m, 14H, Ar–H), 5.32 (s, 1H, OH), 8.12 (s, 1H, CH of pyrimidin); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.6, 166.2, 164.8, 163.4, 155.2, 150.0, 135.8, 131.0, 130.7, 129.8, 129.2, 128.7, 127.5, 124.8, 123.3, 120.9, 111.8, 103.8, 101.5; MS (ESI) *m/z*: 460.06 (M^+); *Anal*. Calcd. for $C_{24}H_{16}N_2O_4S_2$: C, 62.59; H, 3.50; N, 6.08; found: C, 62.54; H, 3.52; N, 6.12%.

S-4-(benzofuran-2-yl)-6-phenylpyrimidin-2-yl 4-nitrobenzenesulfonothioate (5c). Light yellow solid, mp: 303–305°C, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3135–2943 (Ar–CH), 1619 (C═N); ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 7.07–8.10 (m, 13H, Ar–H), 8.20 (s, 1H, CH of pyrimidin), 3.73 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.0, 166.3, 164.2, 155.2, 152.9, 149.8, 144.8, 135.7, 129.3, 128.7, 127.5, 124.8, 123.3, 120.9, 111.4, 103.5, 101.7; MS (ESI) *m/z*: 489.05 (M^+); *Anal*. Calcd. for $C_{24}H_{15}N_3O_5S_2$: C, 58.89; H, 3.09; N, 8.58; found: C, 58. 91; H, 3.08; N, 8.55%.

S-4-(benzofuran-2-yl)-6-phenylpyrimidin-2-yl 4-chlorobenzenesulfonothioate (5d). Brown solid, mp: 195–198°C, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3135–2963 (Ar–CH), 1643 (C═N); ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 7.20–7.90 (m, 14H, Ar–H), 8.41 (s, 1H, CH of pyrimidin); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.3, 166.0, 164.3, 155.0, 149.8, 139.2, 136.6, 135.8, 129.7, 129.2, 128.7, 127.3, 124.7, 123.0, 120.8, 111.2, 103.3, 101.7; MS (ESI) *m/z*: 478.00 (M^+); *Anal*. Calcd. for $C_{24}H_{15}ClN_2O_3S_2$: C, 60.18; H, 3.16; N, 5.85; found: C, 60.20; H, 3.12; N, 5.82%.

S-4-(benzofuran-2-yl)-6-phenylpyrimidin-2-yl 4-methoxybenzenesulfonothioate (5e). Dark brown solid, mp: 241–243°C, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3133–2975 (Ar–CH), 1628 (C═N, Pyrazole); ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 7.15–7.95 (m, 14H, Ar–H), 7.94 (s, 1H, CH of pyrimidin), 3.83 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.5, 166.2, 165.6, 164.2, 155.5, 149.9, 135.7, 130.7, 129.3, 128.7, 127.5, 124.8, 123.5, 120.8, 115.2, 111.3, 103.4, 101.7, 55.8; MS (ESI) *m/z*: 474.09 (M^+); *Anal*. Calcd. for $C_{25}H_{18}N_2O_4S_2$: C, 63.27; H, 3.82; N, 5.90; found: C, 63.19; H, 3.87; N, 5.85%.

S-4-(benzofuran-2-yl)-6-phenylpyrimidin-2-yl 4-methylbenzenesulfonothioate (5f). Brown semisolid, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3132–2981 (Ar–CH), 1630 (C═N) ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 7.21–7.78 (m, 14H, Ar–H), 8.24 (s, 1H, CH of pyrimidin), 2.34 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.2, 159.8, 164.5, 155.4, 149.8, 139.4, 135.8, 135.5, 130.0, 129.2, 128.7, 128.2, 127.4, 124.5, 123.3, 120.9, 111.4, 103.0, 101.5, 21.3; MS (ESI) *m/z*: 458.10 (M^+); *Anal*. Calcd. for $C_{25}H_{18}N_2O_3S_2$: C, 65.48; H, 3.96; N, 6.11; found: C, 65.39; H, 4.05; N, 6.14%.

S-4-(benzofuran-2-yl)-6-(4-methoxyphenyl)pyrimidin-2-yl benzenesulfonothioate (6a). Reddish brown semisolid, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3130–2971 (Ar–CH), 1626 (C═N, Pyrazole); ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 8.22 (s, 1H, CH of pyrimidin), 7.05–7.79 (m, 14H, Ar–H), 3.88 (s, 3H, OCH_3),; ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.6, 166.3, 164.0, 160.6, 155.4, 149.8, 129.2, 128.5, 126.1, 124.7, 123.3, 120.9, 114.8, 111.3, 103.4, 101.7, 55.8, 52.0; MS (ESI) *m/z*: 412.01 (M^+); *Anal*. Calcd. for $C_{25}H_{18}N_2O_4S_2$: C, 58.24; H, 3.91; N, 6.79; found: C, 58.20; H, 3.90; N, 6.83%.

S-4-(benzofuran-2-yl)-6-(4-methoxyphenyl)pyrimidin-2-yl 4-hydroxybenzenesulfonothioate (6b). Light yellow solid, mp: 282–285°C, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3123–2968 (Ar–CH), 1622 (C═N); ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 8.33 (s, 1H, 1CH of pyrimidin), 7.10–7.93 (m, 13H, Ar–H), 5.35 (s, IH, OH), 3.80 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.0, 166.2, 164.5, 163.4, 160.5, 155.5, 149.8, 131.1, 130.7, 129.6, 129.0, 128.4, 128.1, 124.7, 123.3, 120.9, 114.8, 111.5, 103.4, 101.6, 55.6; MS (ESI) *m/z* :

490.07 (M^+). *Anal*. Calcd. for $C_{25}H_{18}N_2O_5S_2$: C, 61.21; H, 3.70; N, 5.71; found: C, 61.32; H, 3.58; N, 5.65%.

S-4-(benzofuran-2-yl)-6-(4-methoxyphenyl)pyrimidin-2-yl 4-nitrobenzenesulfonothioate (6c). Reddish brown solid, mp: 258–261°C, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3129–2975 (Ar–CH), 1638 (C═N); ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 7.24–8.35 (m, 13H, Ar–H), 8.40 (s, 1H, CH of pyrimidin), 3.78 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 179.9, 165.8, 164.3, 160.6, 155.2, 152.9, 149.8, 144.6, 129.2, 128.5, 128.1, 124.9, 124.7, 123.3, 120.9, 114.8, 111.5, 103.4, 101.7, 55.8; MS (ESI) *m/z*: 519.09 (M^+); *Anal*. Calcd. for $C_{25}H_{17}N_3O_6S_2$: C, 57.79; H, 3.30; N, 8.09; found: C, 57.75; H, 3.27; N, 8.00%.

S-4-(benzofuran-2-yl)-6-(4-methoxyphenyl)pyrimidin-2-yl 4-chlorobenzenesulfonothioate (6d). Brown semisolid, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3123–2982 (Ar–CH), (C═N,); ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 8.39 (s, 1H, CH of pyrimidin), 7.02–7.85 (m, 13H, Ar–H), 3.85 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.4, 166.2, 164.1, 160.4, 155.3, 149.5, 139.2, 136.6, 129.8, 129.3, 128.5, 128.1, 124.7, 123.3, 120.9, 114.8, 111.5, 103.2, 101.7; MS (ESI) *m/z*: 508.03 (M^+); *Anal*. Calcd. for $C_{25}H_{17}ClN_2O_4S_2$: C, 58.99; H, 3.37; N, 5.50; found: C, 58.95; H, 3.30; N, 5.62%.

S-4-(benzofuran-2-yl)-6-(4-methoxyphenyl)pyrimidin-2-yl 4-methoxybenzenesulfonothioate (6e). Brown semisolid, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3122–2985 (Ar–CH), 1655 (C═N); ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 7.02–7.75 (m, 13H, Ar–H), 3.84 (s, 6H, OCH_3), 8.47 (s, 1H, CH of pyrimidin); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.1, 166.2, 164.6, 165.6, 160.5, 155.4, 149.8, 130.8, 129.3, 128.5, 128.1, 124.7, 123.3, 120.9, 115.3, 114.8, 111.5, 103.1, 101.7, 55.8; MS (ESI) *m/z*: 504.08 (M^+); *Anal*. Calcd. for $C_{26}H_{20}N_2O_5S_2$: C, 61.89; H, 4.00; N, 5.55; found: C, 61.80; H, 4.12; N, 5.53%.

S-4-(benzofuran-2-yl)-6-(4-methoxyphenyl)pyrimidin-2-yl 4-methylbenzenesulfonothioate (6f). Light brown semisolid, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3135–2943 (Ar–CH), 1619 (C═N); ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 7.05–7.89 (m, 13H, Ar–H), 7.90 (s, 1H, CH of pyrimidin), 2.82 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.3, 166.0, 164.5, 160.3, 155.4, 149.8, 139.4, 135.5, 130.0, 129.3, 128.5, 128.2, 126.1, 124.7, 123.3, 120.9, 114.8, 111.5, 103.4, 101.7, 55.8, 21.3; MS (ESI) *m/z* : 488.11 (M^+). *Anal*. Calcd. for $C_{26}H_{20}N_2O_4S_2$: C, 63.92; H, 4.13; N, 5.73; found: C, 63.90; H, 4.18; N, 5.68%.

S-4-(benzofuran-2-yl)-6-(4-nitrophenyl)pyrimidin-2-yl benzenesulfonothioate (7a). Brown solid, mp: 325–328°C, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3138–2963 (Ar–CH), 1643 (C═N); ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 8.30 (s, 1H, CH of pyrimidin), 7.09–7.90 (m, 14H, Ar–H); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.4, 166.5, 164.3, 155.5, 149.8, 147.9, 141.8, 129.3, 126.2, 124.7, 124.4, 123.3, 120.9, 111.5, 103.4, 101.6, 52.0; MS (ESI) *m/z*: 427.03 (M^+). *Anal*. Calcd. for $C_{24}H_{15}N_3O_5S_2$: C, 53.39; H, 3.07; N, 9.83; found: C, 53.32; H, 3.10; N, 9.75%.

S-4-(benzofuran-2-yl)-6-(4-nitrophenyl)pyrimidin-2-yl 4-hydroxybenzenesulfonothioate (7b). Dark yellow solid, mp: 238–241°C, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3128–2984 (Ar–CH), 1626 (C═N); ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 8.41 (s, 1H, CH of pyrimidin), 7.12–8.30 (m, 13H, Ar–H), 5.34 (s, 1H, OH); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.4, 166.2, 164.5, 163.3, 153.7, 149.8, 147.9, 141.9, 131.1, 130.7, 129.6, 129.2, 126.2, 124.7, 124.4, 123.2, 120.9, 111.5, 103.4, 101.6; MS (ESI) *m/z*: 505.04 (M^+); *Anal*. Calcd. for $C_{24}H_{15}N_3O_6S_2$: C, 57.02; H, 2.99; N, 8.31; found: C, 57.10; H, 3.02; N, 8.38%.

S-4-(benzofuran-2-yl)-6-(4-nitrophenyl)pyrimidin-2-yl 4-nitrobenzenesulfonothioate (7c). Yellow semisolid, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3261–2933 (Ar-CH), 1637 (C═N); ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 8.41 (s, 1H, CH of pyrimidin), 7.10–8.20 (m, 13H, Ar–H); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.6, 166.4, 164.6, 155.4, 152.9, 149.9, 147.9, 144.6, 141.9, 129.2, 126.2, 124.9, 124.4, 123.1, 120.7, 111.3, 103.3, 101.5; MS (ESI) *m/z*: 534.03 (M^+); *Anal*. Calcd. for $C_{24}H_{14}N_4O_7S_2$: C, 53.93; H, 2.64; N, 10.48; found: C, 53.85; H, 2.71; N, 10.52%.

S-4-(benzofuran-2-yl)-6-(4-nitrophenyl)pyrimidin-2-yl 4-chlorobenzenesulfonothioate (7d). Reddish brown solid, mp: 272–275°C, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3135–2972 (Ar–CH), 1632 (C═N); ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 8.35 (s, 1H, CH of pyrimidin), 7.14–7.98 (m, 13H, Ar–H); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.3, 166.1, 164.3, 155.5, 149.9, 147.9, 139.3, 136.6, 129.8, 129.3, 126.1, 124.5, 123.3, 120.9, 111.5, 103.4, 101.7; MS (ESI) *m/z*: 523.04 (M^+); *Anal*. Calcd. for $C_{24}H_{14}ClN_3O_5S_2$: C, 55.01; H, 2.69; N, 8.02; found: C, 55.09; H, 2.72; N, 8.12%.

S-4-(benzofuran-2-yl)-6-(4-nitrophenyl)pyrimidin-2-yl 4-methoxybenzenesulfonothioate (7e). Brown semisolid, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3133–2964 (Ar–CH), 1634 (C═N); ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 8.35 (s, 1H, CH of pyrimidin), 7.09–8.10 (m, 13H, Ar–H), 3.81 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.4, 166.2, 165.1, 164.6, 155.6, 149.9, 147.9, 141.9, 130.8, 129.3, 126.2, 124.7, 124.4, 123.3, 120.9, 115.3, 111.5, 103.0, 101.6, 55.6; MS (ESI) *m/z*: 519.08 (M^+); *Anal*. Calcd. for $C_{25}H_{17}N_3O_6S_2$: C, 57.79; H, 3.30; N, 8.09; found: C, 57.74; H, 3.8; N, 8.15%.

S-4-(benzofuran-2-yl)-6-(4-nitrophenyl)pyrimidin-2-yl 4-methylbenzenesulfonothioate (7f). Reddish brown semisolid, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3130–2946 (Ar–CH), 1625 (C═N); ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 7.94 (s, 1H, CH of pyrimidin), 7.12–7.96 (m, 13H, Ar–H), 2.84 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.3, 166.0, 164.8, 155.2, 149.8, 147.9, 141.9, 139.4, 135.5, 130.0, 129.3, 128.2, 126.2, 124.7, 124.4, 123.2, 120.9, 111.5, 103.2, 101.7, 21.3; MS (ESI) *m/z*: 503.06 (M^+); *Anal*. Calcd. for $C_{25}H_{17}N_3O_5S_2$: C, 59.63; H, 3.40; N, 8.34; found: C, 59.68; H, 3.34; N, 8.40%.

S-4-(benzofuran-2-yl)-6-(4-hydroxy-3-methoxyphenyl)pyrimidin-2-yl benzenesulfonothioate (8a). Light yellow solid. mp: 302–305°C, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3133–2964 (Ar–CH), 1634 (C═N); ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 8.29 (s, 1H, CH of pyrimidin), 7.05–7.98 (m, 13H, Ar–H), 5.34 (s, 1H, OH), 3.83 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.2, 166.5, 164.3, 155.0, 149.9, 148.7, 148.0, 130.5, 129.3, 124.7, 123.3, 121.2, 120.9, 115.8, 111.5, 108.8, 103.2, 101.6, 56.1, 52.0; MS (ESI) *m/z*: 428.05 (M^+); *Anal*. Calcd. for $C_{25}H_{18}N_2O_5S_2$: C, 56.06; H, 3.76; N, 6.54; found: C, 56.10; H, 3.68; N, 6.50%.

S-4-(benzofuran-2-yl)-6-(4-hydroxy-3-methoxyphenyl)pyrimidin-2-yl 4-hydroxybenzenesulfonothioate (8b). Yellow semisolid, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3128–2958 (Ar–CH), 1644 (C═N); ^{1}H NMR (DMSO-d_6 400 MHz) δ ppm: 8.41 (s, 1H, CH of pyrimidin), 7.10–8.08 (m, 12H, Ar–H), 5.30 (s, 2H, OH),

3.75 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 187.9, 166.1, 164.3, 163.5, 155.4, 149.8, 148.6, 148.0, 131.1, 130.7, 130.5, 129.7, 129.3, 124.7, 123.3, 121.2, 120.7, 115.8, 111.5, 108.7, 103.4, 101.7, 56.1; MS (ESI) *m/z*: 506.06 (M^+); *Anal*. Calcd. for $C_{25}H_{18}N_2O_6S_2$: C, 59.28; H, 3.58; N, 5.53; found: C, 59.35; H, 3.46; N, 5.51%.

S-4-(benzofuran-2-yl)-6-(4-hydroxy-3-methoxyphenyl)pyrimidin-2-yl 4-nitrobenzenesulfonothioate (8c). Light yellow solid. mp: 265–268°C, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3135–2945 (Ar–CH), 1635 (C=N); ^1H NMR (DMSO-d_6 400 MHz) δ ppm: 8.39 (s, 1H, CH of pyrimidin), 7.08–7.85 (m, 12H, Ar–H), 5.31(s,1H, OH), 3.78 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.6, 166.0, 164.6, 155.7, 152.9, 149.7, 148.7, 148.0, 144.6, 130.5, 129.3, 124.9, 124.7, 123.3, 121.2, 120.9, 115.8, 111.5, 108.6, 103.2, 101.6, 56.1; MS (ESI) *m/z*: 535.05 (M^+); *Anal*. Calcd. for $C_{25}H_{17}N_3O_7S_2$: C, 56.07; H, 3.20; N, 7.85; found: C, 56.01; H, 3.28; N, 7.75%.

S-4-(benzofuran-2-yl)-6-(4-hydroxy-3-methoxyphenyl)pyrimidin-2-yl 4-chlorobenzenesulfonothioate (8d). Reddish black semisolid, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3135–2960 (Ar–CH), 1632 (C=N); ^1H NMR (DMSO-d_6 400 MHz) δ ppm: 8.25 (s, 1H, CH of pyrimidin), 7.10–7.90 (m, 12H, Ar–H), 5.28 (s, 1H, OH), 3.73(s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.5, 166.3, 164.0, 155.4, 149.9, 148.6, 148.0, 139.3, 136.6, 130.5, 129.8, 129.2, 124.7, 123.3, 121.2, 120.9, 115.3, 111.2, 109.1, 101.3, 56.0; MS (ESI) *m/z*: 524.03 (M^+); *Anal*. Calcd. for $C_{25}H_{18}N_2O_6S_2$: C, 57.19; H, 3.26; N, 5.34; found C, 57.24; H, 3.20; N, 5.34%.

S-4-(benzofuran-2-yl)-6-(4-hydroxy-3-methoxyphenyl)pyrimidin-2-yl 4-methoxybenzenesulfonothioate (8e). Brown semisolid, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3130–2954 (Ar–CH), 1633 (C=N); ^1H NMR (DMSO-d_6 400 MHz) δ ppm: 8.24 (s, 1H, CH of pyrimidin), 7.05–8.10 (m, 12H, Ar–H), 5.28 (s, 1H, OH), 3.78 (s, 6H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.3, 166.2, 165.3, 164.6, 155.5, 149.3, 148.7, 148.0, 130.8, 130.5, 129.3, 124.7, 123.3, 121.2, 120.9, 115.8, 115.3, 111.5, 108.7, 103.2, 101.7, 56.1, 55.8; MS (ESI) *m/z*: 520.08 (M^+); *Anal*. Calcd. for $C_{26}H_{20}N_2O_6S_2$: C, 59.99; H, 3.87; N, 5.38; O, 18.44; S, 12.32; found: C, 59.95; H, 3.91; N, 5.34; O, 18.49; S, 12.35%.

S-4-(benzofuran-2-yl)-6-(4-hydroxy-3-methoxyphenyl)pyrimidin-2-yl 4-methylbenzenesulfonothioate (8f). Light yellow solid, mp: 358–361°C, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3136–2952 (Ar–CH), 1636 (C=N); ^1H NMR (DMSO-d_6 400 MHz) δ ppm: 8.37 (s, 1H, CH of pyrimidin), 7.10–7.89 (m, 12H, Ar–H), 5.33 (s, 1H, OH), 3.82 (s, 3H, OCH_3), 2.32 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.2, 166.0, 164.6, 155.5, 149.6, 148.5, 148.0, 139.2, 135.5, 130.5, 130.0, 129.3, 128.2, 124.7, 123.3, 121.2, 120.7, 115.6, 108.6, 103.1, 101.2, 56.1, 21.3; MS (ESI) *m/z*: 520.08 (M^+); *Anal*. Calcd. for $C_{26}H_{20}N_2O_6S_2$: C, 59.99; H, 3.87; N, 5.38; O, 18.44; S, 12.32; found: C, 59.95; H, 3.91; N, 5.34; O, 18.49; S, 12.35%.

S-4-(benzofuran-2-yl)-6-(4-hydroxyphenyl)pyrimidin-2-yl benzenesulfonothioate (9a). Light yellow semisolid, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3140–2954 (Ar–CH), 1628 (C=N); ^1H NMR (DMSO-d_6 400 MHz) δ ppm: 8.35 (s, 1H, CH of pyrimidin), 7.10–8.05 (m, 14H, Ar–H), 5.35 (s, 1H, OH); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.0, 166.3, 164.2, 158.5, 155.5, 149.8, 129.4, 128.9, 128.4, 124.7, 123.3, 120.8, 116.4, 111.5, 103.2, 101.9, 52.0; MS (ESI) *m/z*: 398.04 (M^+); *Anal*. Calcd. for $C_{24}H_{16}N_2O_4S_2$: C, 57.27; H, 3.54; N, 7.03; found: C, 57.30; H, 3.60; N, 7.10%.

S-4-(benzofuran-2-yl)-6-(4-hydroxyphenyl)pyrimidin-2-yl 4-hydroxybenzenesulfonothioate (9b). Greenish black solid, mp: 343–3346°C, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3138–2964 (Ar–CH), 1636 (C=N); ^1H NMR (DMSO-d_6 400 MHz) δ ppm: 8.35 (s, 1H, CH of pyrimidin), 7.02–7.95 (m, 12H, Ar–H), 5.29 (s, 2H, OH); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.3, 166.0, 164.5, 163.5, 158.5, 155.4, 149.9, 131.1, 130.7, 129.6, 129.3, 128.7, 128.4, 124.7, 123.3, 120.9, 116.4, 111.5, 103.2, 101.7; MS (ESI,)*m/z*:476.05 (M^+); *Anal*. Calcd. for $C_{24}H_{16}N_2O_5S_2$: C, 60.49; H, 3.38; N, 5.88; found: C, 60.51; H, 3.42; N, 5.84%.

S-4-(benzofuran-2-yl)-6-(4-hydroxyphenyl)pyrimidin-2-yl 4-nitrobenzenesulfonothioate (9c). Yellow semisolid, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3140–2958 (Ar–CH), 1664 (C=N); ^1H NMR (DMSO-d_6 400 MHz) δ ppm: 7.98 (s, 1H, CH of pyrimidin), 6.98–7.85 (m, 12H, Ar–H), 5.30(s,1H, OH); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.3, 166.2, 164.6, 158.4, 155.5, 152.8, 149.9, 144.6, 129.3, 128.9, 128.4, 124.8, 123.3, 120.9, 116.4, 111.5, 103.1, 101.7; MS (ESI) *m/z*: 505.06 (M^+); *Anal*. Calcd. for $C_{24}H_{15}N_3O_6S_2$: C, 57.02; H, 2.99; N, 8.31; found: C, 57.10; H, 2.86; N, 8.36%.

S-4-(benzofuran-2-yl)-6-(4-hydroxyphenyl)pyrimidin-2-yl 4-chlorobenzenesulfonothioate (9d). Brown semisolid, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3152–2948 (Ar–CH), 1639 (C=N); ^1H NMR (DMSO-d_6 400 MHz) δ ppm: 8.10 (s, 1H, CH of pyrimidin), 7.10–7.98 (m, 12H, Ar-H), 5.31 (s, 1H, OH); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.2, 166.3, 164.6, 158.5, 155.5, 149.8, 139.3, 136.3, 129.8, 129.3, 128.9, 128.4, 124.7, 123.3, 120.9, 116.4, 111.5, 103.4, 101.5; MS (ESI) *m/z*: 494.02 (M^+); *Anal*. Calcd. for $C_{24}H_{15}ClN_2O_4S_2$: C, 58.24; H, 3.05; N, 5.66 found C, 58.28; H, 3.12; N, 5.59%.

S-4-(benzofuran-2-yl)-6-(4-hydroxyphenyl)pyrimidin-2-yl 4-methoxybenzenesulfonothioate (9e). Brown semisolid, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3148–2960 (Ar–CH), 1642 (C=N); ^1H NMR (DMSO-d_6 400 MHz) δ ppm: 8.33 (s, 1H, CH of pyrimidin), 7.05–8.10 (m, 12H, Ar-H), 5.28 (s, 1H, OH), 3.83 (s, 6H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.4, 166.2, 165.5, 164.6, 158.7, 155.2, 149.7, 130.8, 129.3, 124.7, 123.3, 120.9, 116.4, 115.3, 111.5, 103.4, 101.7, 55.8; MS (ESI) *m/z*: 490.07 (M^+); *Anal*. Calcd. for $C_{25}H_{18}N_2O_5S_2$: C, 61.21; H, 3.70; N, 5.71; found: C, 61.29; H, 3.62; N, 5.63%.

S-4-(benzofuran-2-yl)-6-(4-hydroxyphenyl)pyrimidin-2-yl 4-methylbenzenesulfonothioate (9f). Light yellow solid. mp: 253–256°C, spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3138–2950 (Ar–CH), 1636 (C=N); ^1H NMR (DMSO-d_6 400 MHz) δ ppm: 7.98 (s, 1H, CH of pyrimidin), 7.05–7.94 (m, 12H, Ar–H), 5.30 (s, 1H, OH), 3.84 (s, 3H, OCH_3), 2.34 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 188.4, 166.0, 164.5, 158.4, 155.5, 149.9, 139.4, 135.5, 130.0, 129.3, 128.9, 128.3, 128.2, 124.7, 123.3, 120.9, 116.4, 111.5, 103.2, 101.6, 21.3; MS (ESI) *m/z*: 474.07 (M^+); *Anal*. Calcd. for $C_{25}H_{18}N_2O_4S_2$: C, 63.27; H, 3.82; N, 5.90; found: C, 63.27; H, 3.82; N, 5.90%.

Antioxidant evaluation.

DPPH free radical scavenging assay. The evaluation of antioxidant activity of newly synthesized compounds **5–9(a–f)** was carried out by DPPH RSA assay [32]. Internal standard Butylated hydroxy anisole (BHA) and the synthesized compounds of different concentrations were prepared in distilled ethanol,

1 mL of each compound solutions having different concentrations (10, 25, 50, 100, 200, and 500 μM) was taken in different test tubes, 4 mL of 0.1 mM ethanol solution of DPPH was added and shaken vigorously. The tubes were then incubated in the dark room at room temperature for 20 min. A DPPH blank was prepared without compound and ethanol was used for the baseline correction. Changes (decrease) in the absorbance at 517 nm were measured using a UV–visible spectrophotometer and the remaining DPPH was calculated. The percent decrease in the absorbance was recorded for each concentration and percent quenching of DPPH was calculated on the basis of the observed decreased in absorbance of the radical. The RSA was expressed as the inhibition percentage and was calculated using the formula

$$\text{Radical scavenging activity } (\%) = [(A_0 - A_1)/A_0 \times 100]$$

where A_0 is the absorbance of the control (blank, without compound) and A_1 is the absorbance of the compound.

DMPD radical scavenging activity. The DMPD radical scavenging ability of bromophenols was determined by the method of Fogliano et al. [33] with slight modifications by Gulcin [34]. This assay is based on the capacity of the extract to inhibit $DMPD^+$ cation radical formation. Briefly, 105 mg of DMPD was dissolved in 5 mL of distilled water. Then, 1 mL of this solution was added to 100 mL of 0.1 M acetate buffer (pH 5.3). $DMPD^+$ was produced by adding 0.3 mL ferric chloride (0.05 M) to this solution. Different concentrations of standard antioxidants or synthesized compounds **5–9(a–f)** (10–500 μM/mL) were added, and the total volume was adjusted to 0.5 mL with distilled water. One milliliter of the $DMPD^+$ solution was directly added to the reaction mixture. The reaction mixtures were vortexed and incubated in the dark for 15 min. The absorbance was measured at 505 nm.

Ferric ion reducing power assay. The reducing power was investigated by the Fe^{3+} to Fe^{2+} transformation in the presence of synthesized compounds **5–9(a–f)** as described by [35]. The Fe^{2+} can be monitored by measuring the formation of Perl's Prussian blue at 700 nm [36]. About 1 mL of the sample (10 μg/mL), 2.5 mL of phosphate buffer (pH 6.6), and 2.5 mL of 1% potassium ferricyanide were incubated at 50°C for 30 min and 2.5 mL of 10% trichloroacetic acid was added to the mixture and centrifuged for 10 min at 3000 rpm. About 2.5 mL of the supernatant was diluted with 2.5 mL of water and shaken with 0.5 mL of freshly prepared 0.1% ferric chloride. The absorbance was measured at 700 nm. BHA was used as the standard. All tests were performed in triplicate.

Antimicrobials evaluation.

Antibacterial activity. The antibacterial activities of newly synthesized compounds **5–9(a–f)** were determined by well plate method in Mueller–Hinton Agar [37]. The antibacterial activity was carried out against 24-h old cultures of bacterial strains. In this work, *E. coli*, *S.aureus*, and *P. aeruginosa* were used to investigate the activity. The test compounds were dissolved in DMSO at concentrations 1 and 0.5 mg/mL. About 20 mL of sterilized agar media was poured into each pre-sterilized Petri dish. Excess of suspension was decanted and plates were dried by placing in an incubator at 37°C for an hour. About 60 mL of 24-h old culture suspension was poured and neatly swabbed with the pre-sterilized cotton swabs. About 6 mL diameter well was then punched carefully using a sterile cork borer and 30 mL of test solutions of different concentrations were added into each labeled well. The plates were incubated for 24 h at 37°C. The inhibition zone that appeared after 24 h around the well in each plate was measured as zone of inhibition in millimeter. Experiments were triplicates and standard deviation was calculated.

Antifungal activity. Antifungal studies of newly synthesized compounds were carried out against *A. flavus, C. keratinophilum*, and *C. albicans*. Sabourands agar media was prepared by dissolving peptone (10 g), D-glucose (40 g), and agar (20 g) in distilled water (1000 mL) and adjusting the pH to 5.7. Normal saline was used to make a suspension of spore of fungal strains for lawning. A loopful of particular fungal strain was transferred to 3 mL saline to get a suspension of corresponding species [38]. About 20 mL of agar media was poured into each petri dish. Excess of suspension was decanted and plates were dried by placing in incubator at 37°C for 1 h. Using sterile cork borer punched carefully, wells were made on these seeded agar plates different concentrations of the test compounds in DMSO were added into each labeled well. A control was also prepared for the plates in the same way using solvent DMSO. The Petri dishes were prepared in triplicate and maintained at 25°C for 72 h. Antifungal activity was determined by measuring the diameter of inhibition zone. Activity of each compound was compared with fluconazole as standard and zones of inhibition were determined for all the synthesized compounds **5–9(a–f)**.

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