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ORIGINAL ARTICLE

Studies on synthesis of pyrimidine derivatives and their antimicrobial activity

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Abstract A series of novel 2-(5-bromo-2-chloro-pyrimidin-4-ylsulfanyl)-4-methoxy-phenylamine derivatives were synthesized by the reaction of 2-(5-bromo-2-chloro-pyrimidin-4-ylsulfanyl)-4-methoxy-phenylamine with various sulfonyl chlorides, and their *in vitro* antimicrobial activity was evaluated. The synthesized compounds were characterized by elemental analyses, FT-IR, ^{1}H NMR and LC–MS spectral studies.

1. Introduction

The growing health problems demand search and synthesis of a new class of antimicrobial compounds which are effective against pathogenic microorganisms, developing resistance to the antibiotics used in the current regime (Koca et al., 2005). The increasing resistance of human pathogens to current antimicrobial agents is a serious medical problem. During the 20th century, vaccines for bacterial toxins and many other common acute viral infections were developed and made widely available. A number of different classes of antibacterial (Appelbaum and Hunter, 2000; Ball, 2000) and antifungal agents (Andriole, 1998) have been discovered. Since the discovery of several synthetic and semi-synthetic antibacterial sulfa drugs, nitrofuranes, penicillins, cephalosporins, tetracyclines, macrolides, oxazolidinones and antifungal agents such as fluconazole, ketoconazole and miconazole, including amphotericin B, there has been much progress in this field. Despite advances in antibacterial and antifungal therapies, many problems remain to be solved for most antimicrobial drugs available. The extensive use of antibiotics has led to the appearance of multi-drug resistant microbial pathogens (Frere, 1995).

As pyrimidine is a basic nucleus in DNA & RNA, it has been found to be associated with diverse biological activities (Ghoneim and Youssef, 1986). The synthesis of substituted pyrimidine and many detailed reviews have appeared (Kenner and Todd, 1957; Brown, 1962). Pyrimidine and its derivatives are considered to be important for drugs and agricultural chemicals. Pyrimidine derivatives possess several interesting biological activities such as antimicrobial (Karale and Gill, 2002), antitumor (Reddy and Sarma Rama, 1993) and antifungal activities (Shingare et al., 1999). Many Pyrimidine

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derivatives are used for thyroid drugs and leukemia. In view of these reports, the present paper reports the synthesis of 2-(5-bromo-2-chloro-pyrimidin-4-ylsulfanyl)-4-methoxy-phenylamine derivatives, **4a–i** characterized by different spectral studies. Antimicrobial activity of all the compounds was also reported.

2. Chemistry

2-(5-Bromo-2-chloro-pyrimidin-4-ylsulfanyl)-4-methoxy-phenylamine derivatives, **4a–i** were prepared by the method summarized in Scheme 1. The target key intermediate, 2-(5-bromo-2-chloro-pyrimidin-4-ylsulfanyl)-4-methoxy-phenylamine (**2**) was synthesized according to the reported procedure (Chang et al., 2009). Compound (**2**) was reacted with various aromatic sulfonyl chlorides, **3a–i** in MDC and the reaction mass was stirred for 2 h at room temperature. The obtained solid was filtered and washed with ethanol. The residue **4a–i** yields 70–78%. These synthesized compounds were characterized by elemental analyses, FT-IR, ^{1}H NMR and LC–MS spectral studies. Antimicrobial activity was reported. The chemical structures, physical data and purity of all the synthesized compounds are given in Table 1.

3. Experimental

3.1. Materials and equipments

All solvents and reagents were purchased from Merck chemicals. Melting range was determined by Veego Melting Point VMP III apparatus. Elemental analyses were recorded on VarioMICRO superuser V1.3.2 Elementar. The FT-IR spectra were recorded using KBr discs on FT-IR Jasco 4100 infrared spectrophotometer. ^{1}H NMR spectra were recorded on Bruker DRX -500 spectrometer at 400 MHz using d_6-DMSO as solvent and TMS as internal standard. Silica gel column chromatography was performed using Merck 7734 silica gel (60–120 mesh) and Merck-made TLC plates.

3.2. General procedure for synthesis of 2-(5-bromo-2-chloro-pyrimidin-4-ylsulfanyl)-4-methoxy-phenylamine derivatives *4a–i*

A solution of 2-(5-bromo-2-chloropyrimidin-4-ylthio)-4-methoxybenzenamine (**2**) (1.0 eq) in dry dichloromethane was taken and cooled to 0–5 °C in an ice bath. Triethylamine (3.0 eq) was added to the cold reaction mixture and stirred for 10 min, then different sulfonyl chlorides (**3a–i**) (1.0 eq) were added, the reaction mixture was stirred at room temperature for 7–8 h. The progress of the reaction was monitored by TLC. Upon completion, the solvent was removed under reduced pressure and residue was taken in water and extracted with ethyl acetate. The organic layer was washed with 10% ammonium chloride solution and finally water wash was given to organic layer and dried with anhydrous sodium sulfate. The solvent was evaporated to get a crude product which was purified by column chromatography over silica gel (60–120 mesh) using hexane:ethyl acetate (8:2) as eluent.

3.2.1. Synthesis of N-[2-(5-bromo-2-chloro-pyrimidin-4-ylsulfanyl)-4-methoxy-phenyl]-2,4,6-trimethyl-benzenesulfonamide (*4a*)

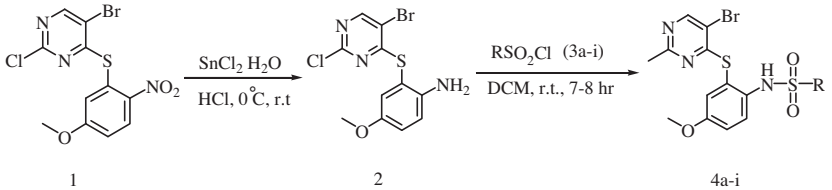
The general experimental procedure described above afforded **4a**, and the product obtained from 2-(5-bromo-2-chloropyrimidin-4-ylthio)-4-methoxybenzenamine (**2**) (3.47 g, 0.01 mol) and 2,4,6-trimethylbenzene-1-sulfonyl chloride (**3a**) (2.19 g, 0.01 mol). FT-IR (KBr, cm^{-1}) *v*: 3176 (N–H), 2924 (C–H), 1698 (C=N), 1463 (C=C), 1376 (C–N), 1151 (C–O), 722 (C–Cl), 521 (C–Br). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.66 (s, 1H, Pyrimidine-H), 8.55 (s, 1H, Ar-H), 7.47 (d, 1H, Ar-H), 7.14 (d, 1H, Ar-H), 7.03 (s, 1H, NH), 6.61 (s, 2H, Ar-H), 3.71 (s, 3H, OCH_3), 2.29–1.99 (s, 9H, CH_3). MS (ESI) *m/z*: 529.0. Anal. calcd. for $C_{20}H_{19}BrClN_3O_3S_2$ (in %): C-45.42, H-3.62, N-7.95. Found C-45.62, H-3.72, N-8.12.

3.2.2. Synthesis of N-[2-(5-bromo-2-chloro-pyrimidin-4-ylsulfanyl)-4-methoxy-phenyl]-4-chloro-benzenesulfonamide (*4b*)

The general experimental procedure described above afforded **4b**, and the product obtained from 2-(5-bromo-2-chloropyrimidin-4-ylthio)-4-methoxybenzenamine (**2**) (3.47 g, 0.01 mol) and 4-chlorobenzene-1-sulfonyl chloride (**3b**) (2.12 g, 0.01 mol). FT-IR (KBr, cm^{-1}) *v*: 3282 (N–H), 2924 (C–H), 1698 (C=N), 1462 (C=C), 1376 (C–N), 1166 (C–O), 722 (C–Cl), 627 (C–Br). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.89 (s, 1H, Pyrimidine-H), 8.65(s, 1H, Ar-H), 7.57 (d, 2H, Ar-H), 7.46 (d, 2H, Ar-H), 7.29 (d, 1H, Ar-H), 7.13 (d, 1H, Ar-H), 7.11 (s, 1H, NH), 3.74 (s, 3H, OCH_3). MS (ESI) *m/z*: 522.3 Anal. calcd. for $C_{17}H_{12}BrCl_2N_3O_3S_2$ (in %): C-39.17, H-2.32, N-8.06. Found C-39.25, H-2.46, N-8.26.

3.2.3. Synthesis of N-[2-(5-bromo-2-chloro-pyrimidin-4-ylsulfanyl)-4-methoxy-phenyl]-4-methyl-benzenesulfonamide (*4c*)

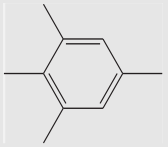
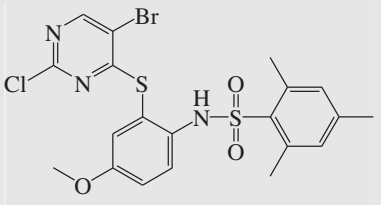
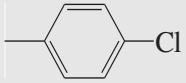
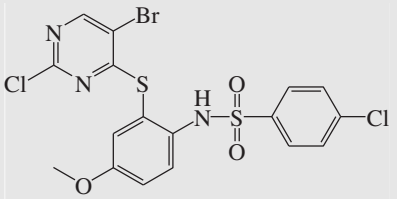
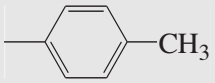
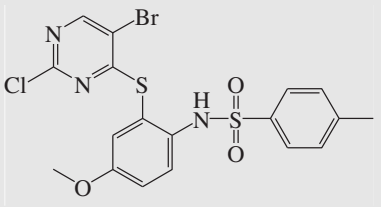
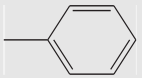
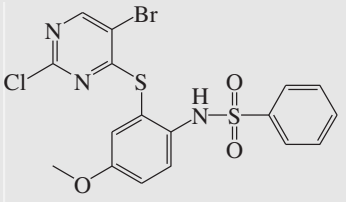
The general experimental procedure described above afforded **4c**, and the product obtained from 2-(5-bromo-2-chloropyrimidin-4-ylthio)-4-methoxybenzenamine (**2**) (3.47 g, 0.01 mol) and 4-methylbenzene-1-sulfonyl chloride (**3c**) (1.91 g, 0.01 mol). FT-IR (KBr, cm^{-1}) *v*: 3275 (N–H), 2925 (C–H), 1698 (C=N), 1463 (C=C), 1376 (C–N), 1165 (C–O), 722 (C–Cl), 561 (C–Br). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.66 (s, 1H, Pyrimidine-H), 8.63 (s, 1H, Ar-H), 7.43 (d, 2H, Ar-H), 7.26 (d, 2H, Ar-H), 7.15 (d, 1H, Ar-H), 7.10 (d, 1H,



1 2 4a-i

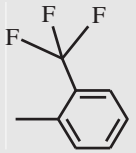
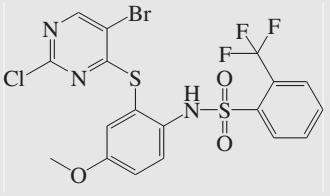
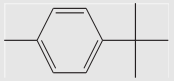
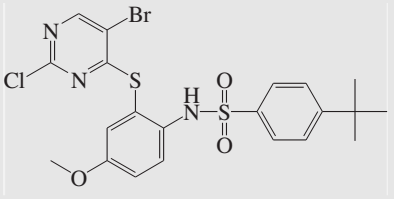
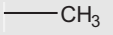
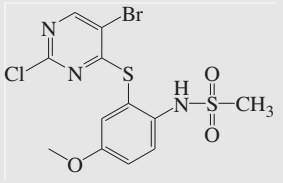
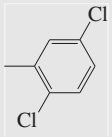
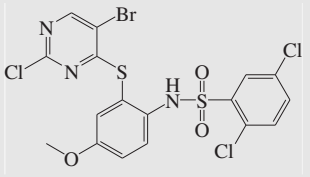
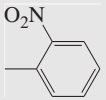
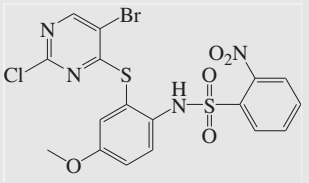
Scheme 1

Table 1 Chemical structure and physical data of 2-(5-bromo-2-chloro-pyrimidin-4-ylsulfanyl)-4-methoxy-phenylamine derivatives **4a**–**i**.

Compound	R	Structure	Yield (%)	Mp (°C)
4a			75	126–128
4b			73	129–131
4c			74	123–124
4d			71	119–121

(*continued on next page*)

Table 1 (*continued*)

4e			78	132–134
4f			81	109–111
4g			74	104–106
4h			71	125–127
4i			84	130–132

Ar-H), 7.06 (s, 1H, NH), 3.72 (s, 3H, OCH_3), 2.23 (s, 3H, CH_3). MS (ESI) *m/z*: 501.1. Anal. calcd. for $C_{18}H_{15}BrClN_3O_3S_2$ (in %): C-43.17, H-3.02, N-8.39. Found C-43.31, H-3.24, N-8.56.

*3.2.4. Synthesis of N-[2-(5-bromo-2-chloro-pyrimidin-4-ylsulfanyl)-4-methoxy-phenyl]-benzene sulfonamide (**4d**)*

The general experimental procedure described above afforded **4d**, and the product obtained from 2-(5-bromo-2-chloropyrimidin-4-ylthio)-4-methoxybenzenamine (**2**) (3.47 g, 0.01 mol) and benzene sulfonyl chloride (**3d**) (1.77 g, 1.2 mmol). FT-IR (KBr, cm^{-1}) *v*: 3272 (N–H), 2924 (C–H), 1698 (C═N), 1458 (C═C), 1376 (C–N), 1165 (C–O), 721 (C–Cl), 577 (C–Br). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.70 (s, 1H, Pyrimidine-H), 8.61 (s, 1H, Ar-H), 7.57 (d, 2H, Ar-H), 7.45 (t, 3H, Ar-H), 7.23 (d, 1H, Ar-H), 7.09 (d, 1H, Ar-H), 7.06 (s, 1H, NH), 3.72 (s, 3H, OCH_3). MS (ESI) *m/z*: 487.0. Anal. calcd. for $C_{17}H_{13}BrClN_3O_3S_2$ (in %): C-41.94, H-2.69, N-8.63. Found C-42.11, H-2.84, N-8.76.

*3.2.5. Synthesis of N-[2-(5-bromo-2-chloro-pyrimidin-4-ylsulfanyl)-4-methoxy-phenyl]-2-tri fluoro methyl-benzene sulfonamide (**4e**)*

The general experimental procedure described above afforded **4e**, and the product obtained from 2-(5-bromo-2-chloropyrimidin-4-ylthio)-4-methoxybenzenamine (**2**) (3.47 g, 0.01 mol) and 2-trifluoromethyl-benzenesulfonyl chloride (**3e**) (2.44 g, 0.01 mol). FT-IR (KBr, cm^{-1}) *v*: 3271 (N–H), 2923 (C–H), 1697 (C═N), 1461 (C═C), 1372 (C–N), 1271 (C-F), 1164 (C–O), 721 (C–Cl), 562 (C–Br). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.72 (s, 1H, Pyrimidine-H), 8.63 (s, 1H, Ar-H), 7.83–7.50 (d, 2H, Ar-H), 7.41 (t, 2H, Ar-H), 7.21 (d, 2H, Ar-H), 7.01 (s, 1H, NH), 3.77 (s, 3H, OCH_3). MS (ESI) *m/z*: 555.0. Anal. calcd. For $C_{18}H_{12}BrClF_3N_3O_3S_2$ (in %): C-38.97, H-2.18, N-7.57. Found C-38.91, H-2.23, N-7.52.

*3.2.6. Synthesis of N-[2-(5-bromo-2-chloro-pyrimidin-4-ylsulfanyl)-4-methoxy-phenyl]-4-tert-butyl-benzenesulfonamide (**4f**)*

The general experimental procedure described above afforded **4f**, and the product obtained from 2-(5-bromo-2-chloropyrimidin-4-ylthio)-4-methoxybenzenamine (**2**) (3.47 g, 0.01 mol) and 4-*tert*-butyl-benzenesulfonyl chloride (**3f**) (2.32 g, 0.01 mol). FT-IR (KBr, cm^{-1}) *v*: 3273 (N–H), 2924 (C–H), 1693 (C═N), 1463 (C═C), 1374 (C–N), 1161 (C–O), 723 (C–Cl), 565 (C–Br). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.65 (s, 1H, Pyrimidine-H), 8.61 (s, 1H, Ar-H), 7.44 (d, 2H, Ar-H), 7.27 (d, 2H, Ar-H), 7.16 (d, 1H, Ar-H), 7.13 (d, 1H, Ar-H), 7.08 (s, 1H, NH), 3.76 (s, 3H, OCH_3), 2.21 (s, 9H, CH_3). MS (ESI) *m/z*: 543.0. Anal. calcd. for $C_{21}H_{21}BrClN_3O_3S_2$ (in %): C- 46.46, H-3.90, N-7.74. Found C-46.49, H-3.96, N-7.77.

*3.2.7. Synthesis of N-[2-(5-bromo-2-chloro-pyrimidin-4-ylsulfanyl)-4-methoxy-phenyl]-4-methyl-benzenesulfonamide (**4g**)*

The general experimental procedure described above afforded **4g**, and the product obtained from 2-(5-bromo-2-chloropyrimidin-4-ylthio)-4-methoxybenzenamine (**2**) (3.47 g, 0.01 mol) and 4-methly-benzenesulfonyl chloride (**3g**) (1.14 g, 0.01 mol). FT-IR (KBr, cm^{-1}) *v*: 3274 (N–H), 2922 (C–H), 1696 (C═N), 1465 (C═C), 1371 (C–N), 1166 (C–O), 725 (C–Cl), 564 (C–Br). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.64 (s, 1H, Pyrimidine-H), 8.63 (s, 1H, Ar-H), 7.43 (d, 2H, Ar-H), 7.06 (s, 1H, NH), 3.72 (s, 3H, OCH_3), 2.23 (s, 3H, CH_3). MS (ESI) *m/z*: 425.0. Anal. calcd. for $C_{12}H_{11}BrClN_3O_3S_2$ (in %): C-33.93, H-2.61, N-9.89. Found C-33.99, H-2.66, N-9.86.

*3.2.8. Synthesis of N-[2-(5-bromo-2-chloro-pyrimidin-4-ylsulfanyl)-4-methoxy-phenyl]-2,5-dichloro-benzenesulfonamide (**4h**)*

The general experimental procedure described above afforded **4h**, and the product obtained from 2-(5-bromo-2-chloropyrimidin-4-ylthio)-4-methoxybenzenamine (**2**) (3.47 g, 0.01 mol) and 2, 5-dichloro-benzenesulfonyl chloride (**3h**) (2.44 g, 0.01 mol). FT-IR (KBr, cm^{-1}) *v*: 3271 (N–H), 2924 (C–H), 1695 (C═N), 1461 (C═C), 1375 (C–N), 1161 (C–O), 723 (C–Cl), 562 (C–Br). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.68 (s, 1H, Pyrimidine-H), 8.63 (s, 1H, Ar-H), 7.43 (d, 2H, Ar-H), 7.26 (d, 2H, Ar-H), 7.15 (d, 1H, Ar-H), 7.06 (s, 1H, NH), 3.72 (s, 3H, OCH_3). MS (ESI) *m/z*: 556.0. Anal. calcd. for $C_{17}H_{11}BrCl_3N_3O_3S_2$ (in %): C-36.74, H-2.00, N-7.56. Found C-36.79, H-2.06, N-7.51.

*3.2.9. Synthesis of N-[2-(5-bromo-2-chloro-pyrimidin-4-ylsulfanyl)-4-methoxy-phenyl]-4-nitro-benzenesulfonamide (**4i**)*

The general experimental procedure described above afforded **4i**, and the product obtained from 2-(5-bromo-2-chloropyrimidin-4-ylthio)-4-methoxybenzenamine (**2**) (3.47 g, 0.01 mol) and 2-nitro-benzenesulfonyl chloride (**3i**) (2.21 g, 0.01 mol). FT-IR (KBr, cm^{-1}) *v*: 3276 (N–H), 2927 (C–H), 1693 (C═N), 1464 (C═C), 1373 (C–N), 1167 (C–O), 721 (C–Cl), 567(C–Br). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.73 (s, 1H, Pyrimidine-H), 8.63 (s, 1H, Ar-H), 7.53 (d, 2H, Ar-H), 7.41 (t, 3H, Ar-H), 7.21 (d, 1H, Ar-H), 7.01 (s, 1H, NH), 3.77 (s, 3H, OCH_3). MS (ESI) *m/z*: 532.0. Anal. calcd. for $C_{17}H_{12}BrClN_4O_5S_2$ (in %): C-38.40, H-2.27, N-10.54. Found C-38.47, H-2.21, N-10.59.

4. Antibacterial activity

Antibacterial activity of the synthesized compounds was determined against Gram-positive bacteria (*Bacillus subtilis* MTCC 121, *Staphylococcus aureus* MTCC 7443) and Gram-negative bacteria (*Xanthomonas campestris* MTCC 7908 and *Escherichia coli* MTCC 7410) in DMF by disc diffusion method on nutrient agar medium (Bauer et al., 1966). The sterile medium (Nutrient Agar Medium, 15 ml) in each petri-plate was uniformly smeared with cultures of Gram positive and Gram negative bacteria. Sterile discs of 10 mm diameter (Hi-Media) were placed in the petriplates, to which 50 µl (1 mg/ml i.e., 50 µg/disc) of different synthesized compounds were added. The treatments also included 50 µl of DMF as negative, bacteriomycin and gentamycin as positive control for comparison. For each treatment, three replicates were maintained. The plates were incubated at 37 ± 2 °C for 24 h and the zone of inhibition was determined.

5. Antifungal activity

The synthesized compounds were screened for their antifungal activity against *Fusarium oxysporum* MTCC 2480 in DMF by

poisoned food technique (Satish et al., 2007). Potato Dextrose Agar (PDA) medium was prepared and about 15 ml of PDA was poured into each petriplate and allowed to solidify. 5 mm disc of seven day old culture of the test fungi was placed at the center of the petriplate and incubated at 26 °C for 7 days. After incubation the percentage inhibition was measured and three replicates were maintained for each treatment. Nystatin was used as standard. All the synthesized compounds were tested (at the dosage of 500 µl of the novel compounds/petriplate, where concentration was 0.1 mg/ml) by poisoned food technique.

6. Results and discussion

Synthesized compounds were characterized by elemental analyses, FT-IR, ^{1}H NMR and Mass spectral studies. Compounds were purified by recrystallization method using ethanol. The elemental analyses of data showed good agreement between the experimentally determined values and the theoretically calculated values within $\pm 0.4\%$.

The absence of NH_2 absorption bands in the IR spectra confirmed that the synthesized compounds were obtained. The absorptions above 2922 cm^{-1} in compounds, **4a–i** confirm the C–H stretching vibrations, and the appearance of a medium to strong absorption bands around 1700 cm^{-1} due to a stretching vibration of the C–N bond formation in the synthesized compounds. The proton spectral data agree with respect to the number of protons and their chemical shifts with the proposed structures. The proton spectral data of compound **3** shows resonance at δ 5.45 ppm (s, 2H, $-NH_2$). In all the synthesized compounds the above resonance peak disappeared, which confirmed the product. The synthesized compounds were further confirmed by the appearance of molecular ion peak in mass spectra. Mass spectra of all the newly synthesized compounds showed M^+ fragmentation peak in agreement with their molecular formula.

The investigation of antibacterial screening data revealed that all tested compounds showed antibacterial activity against four pathogenic bacterial strains. Among the series **4a–i**, compound **4e** exhibited an elevated antibacterial activity against Gram positive (zone of inhibition 29–33 mm) and Gram negative (zone of inhibition 32–33 mm) bacteria. Compounds **4b**, **4h** and **4i** showed good antibacterial activity against all the tested organisms. Compounds **4a**, **4c**, **4d**, **4f** and **4g** showed moderate inhibitory activity. The results were compared with standard drugs bacteriomycin and gentamycin as depicted in Table 2.

Table 2 *In vitro* antibacterial and antifungal activities of **4a–i**.

Compound	Zone of inhibition in diameter (mm)				% Inhibition
	B. subtilis	*S. aureus*	*X. campestris*	*E. coli*	*F. oxysporum*
4a	28	23	28	29	69.5
4b	30	25	30	29	88.5
4c	29	23	27	29	68.6
4d	28	12	27	28	55.4
4e	33	29	32	33	96.9
4f	28	22	26	27	54.7
4g	29	22	25	27	54.3
4h	30	27	30	30	78.4
4i	31	26	29	29	76.7
Bacteriomycin	–	–	34	–	–
Gentamycin	35	30	–	35	–
Nystatin	–	–	–	–	100

The *in vitro* antifungal activity of the synthesized compounds **4a–i** was studied against *Fusarium oxysporum*. The results were compared with the standard drug nystatin as in Table 2. Compound **4e** showed good antifungal activity with 96.9% inhibition when compared with other compounds in the series against *F. oxysporum*. The good inhibition by compound **4e** could be attributed to the presence of an electron withdrawing trifluoromethyl group. Antimicrobial activity of some pyrimidine derivatives has been reported (Keche et al., 2012). Antimicrobial activity of some benzenesulfonyl derivatives has been reported (Mallesha and Mohana, 2011). Compounds **4b**, **4h** and **4i** have demonstrated good antifungal activity against *F. oxysporum*. Compounds **4a**, **4c**, **4d**, **4f** and **4g** were found to be moderately active against tested fungal strain. From the results it is evident that most of the compounds were moderately active and few showed good activity. Compounds **4a–i** showed antimicrobial activity in the order: **4e** > **4b** > **4h** > **4i** > **4a** > **4c** > **4d** > **4f** > **4g** against tested microbial strains.

7. Conclusion

In conclusion, a series of novel 2-(5-bromo-2-chloro-pyrimidin-4-ylsulfanyl)-4-methoxy-phenylamine derivatives, **4a–i** was synthesized and their antimicrobial activities have been evaluated. Compound **4e** produced significant changes in the activity against Gram-positive and Gram-negative bacteria. Therefore, this work presents a novel class of potent, wide-spectrum antimicrobial activity of the compounds.

Conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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