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Synthesis and *in vitro* antimicrobial activity of *N*-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidinamine derivatives

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ABSTRACT

*A series of N-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidinamine derivatives **4a-k** were synthesized by the reaction of N-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidinamine with various aldehydes. The newly synthesized compounds were characterized by elemental analyses, UV-visible, FT-IR and ^{1}H NMR spectral studies. All compounds were evaluated their in vitro antimicrobial activity against clinically isolated strains i.e., Bacillus subtilis, Staphylococcus aureus, Xanthomonas campestris, Escherichia coli, Fusarium oxysporum. Compounds **4f**, **4g**, **4h** and **4i** exhibited good antimicrobial activity when compared with other compounds in the series against tested pathogenic bacterial and fungal strains.*

Keywords: *N*-(5-Amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidinamine, aldehydes, antibacterial activity, antifungal activity.

INTRODUCTION

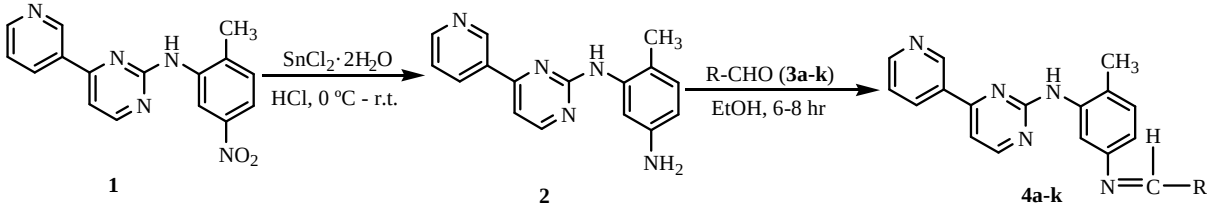
The compounds containing an azomethine group (-CH=N-) are important in elucidating the mechanism of transamination and racemisation reactions in biological systems [1, 2]. Schiff bases have been synthesized from a variety of compounds such as amino thiazoles, 2-hydroxy-1-napthalaniline, amino sugars, aromatic aldehydes, acetophenones, isatin, triazole ring, thiosemicarbazides, amino acids and pyrazolone [3, 4]. Antibacterial, antifungal, antitumor and anticancer activities of some Schiff bases have been reported and they are found to be active against a wide range of organisms [5, 6].

N-(5-Amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidinamine is an intermediate for the preparation of imatinib which is an anti-cancer agent, and it is currently marketed as Gleevec. It has also been found to be effective in the treatment of gastrointestinal stromal tumors (GISTs)

[7]. This selective inhibition of Bcr-Abl kinase by imatinib has been a successful therapeutic strategy for chronic myeloid leukemia because of the high efficacy and mild side effects of this compound [8]. The target key intermediate, *N*-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidinamine (**2**) was synthesized according to the reported procedure [9]. In connection with such studies, the present paper report on the synthesis, antibacterial and antifungal activities of *N*-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidinamine derivatives **4a-k**.

EXPERIMENTAL SECTION

All solvents and reagents were purchased from Sigma Aldrich Chemicals Pvt Ltd. Melting points were determined on an electrically heated VMP-III melting point apparatus. The elemental analyses of the compounds were performed on a Perkin Elmer 2400 Elemental Analyser. The UV-visible spectra were recorded on Analytikjena Specord 50 UV–vis spectrophotometer with quartz cell of 1.0 cm path length in DMSO. The FT-IR spectra were recorded using KBr discs on FT-IR Jasco 4100 infrared spectrophotometer. The ^{1}H NMR spectra were recorded using Bruker DRX 400 spectrometer at 400 MHz with TMS as the internal standard. The reaction sequences are outlined in Scheme 1. The chemical structure and physical data of novel compounds are given in Table 1.



Scheme 1

***General procedure for the Synthesis of N-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidinamine derivatives* 4a-k**

Equimolar concentrations of different aldehydes **3a-k** (0.01 mol) and *N*-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidinamine (0.01 mol) were stirred for 6-8 hr at room temperature using absolute ethanol (25 ml). The progress of the reaction was followed by TLC until the reaction was complete. It was cooled to 0 °C, the precipitate was filtered, washed with diethyl ether and the residue was recrystallized from ethanol.

***4-Methyl-N^1-methylene-N^3-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine* (4a)**

FT-IR (KBr, cm^{-1}) *v*: 3162 (N-H), 3034 (Ar-H), 1630 (HC=N), 1150 (C-N). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.23 (s, 1H, N-H), 8.82 (s, 2H, H_2C=N), 8.77 (s, 1H, pyridine-H), 8.70 (d, 1H, pyridine-H), 8.49 (d, 1H, pyridine-H), 7.55 (t, 1H, pyridine-H), 7.41-731 (d, 2H, pyrimidine-H), 7.11 (s, 1H, Ar-H), 6.98 (d, 1H, Ar-H), 6.58 (d, 1H, Ar-H), 2.13 (s, 3H, CH_3). Anal. calcd. for $C_{17}H_{15}N_5$ (in %): C-70.57, H-5.23, N-24.21. Found C-70.59, H-5.18, N-24.25.

***N^1-Ethylidene-4-methyl-N^3-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine* (4b)**

FT-IR (KBr, cm^{-1}) *v*: 3162 (N-H), 3032 (Ar-H), 1630 (HC=N), 1150 (C-N). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.24 (s, 1H, N-H), 8.78 (q, 1H, HC=N), 8.69 (s, 1H, pyridine-H), 8.48 (d, 1H, pyridine-H), 8.42 (d, 1H, pyridine-H), 7.55 (t, 1H, pyridine-H), 7.39-7.38 (d, 2H, pyrimidine-H), 7.03 (s, 1H, Ar-H), 7.00 (d, 1H, Ar-H), 6.52 (d, 1H, Ar-H), 2.10 (d, 3H, CH_3), 1.94 (s, 3H, CH_3). Anal. Calcd. for $C_{18}H_{17}N_5$ (in %): C-71.27, H-5.65, N-23.09. Found C-71.30, H-5.68, N-23.12.

***N^1-Benzylidene-4-methyl-N^3-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-dia*mine (4c)**
FT-IR (KBr, cm^{-1}) *v*: 3163 (N-H), 3034 (Ar-H), 1632 (HC=N), 1151 (C-N). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.28 (s, 1H, N-H), 9.02 (s, 1H, HC=N), 8.72 (s, 1H, pyridine-H), 8.54 (d, 1H, pyridine -H), 8.47 (d, 1H, pyridine-H), 7.58 (t, 1H, pyridine-H), 7.58-7.47 (m, 3H, Ar-H), 7.29 (d, 1H, pyridine-H), 7.26 (d, 1H, pyrimidine-H), 6.94 (d, 1H, Ar-H), 6.91-6.90 (d, 2H, Ar-H), 6.87 (d, 1H, Ar-H), 6.82 (d, 1H, pyrimidine-H), 2.26 (s, 3H, CH_3). Anal. Calcd. for $C_{23}H_{19}N_5$ (in %): C-75.59, H-5.24, N-19.16. Found C-75.61, H-5.21, N-19.19.

***N^1-(4-Methoxybenzylidene)-4-methyl-N^3-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine* (4d)**
FT-IR (KBr, cm^{-1}) *v*: 3123 (N-H), 3015 (Ar-H), 1637 (HC=N), 1136 (C-O), 1047 (C-N). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.26 (s, 1H, HC=N), 8.97 (s, 1H, N-H), 8.69 (s, 1H, pyridine-H), 8.67 (s, 1H, Ar-H), 8.55 (d, 1H, pyridine-H), 8.50 (d, 1H, pyrimidine-H), 8.42 (d, 1H, Ar-H), 7.87 (d, 1H, pyridine-H), 7.53 (d, 1H, Ar-H), 7.44 (t, 1H, pyridine-H), 7.42 (t, 1H, pyridine-H), 7.25 (t, 1H, Ar-H), 7.06-7.03 (d, 2H, Ar-H), 6.97 (d, 1H, pyrimidine-H), 3.81 (s, 3H, CH_3), 2.25 (s, 3H, CH_3). Anal. Calcd. for $C_{24}H_{21}N_5O$ (in %): C-72.89, H-5.35, N-17.71. Found C-72.93, H-5.31, N-17.69.

2-((3-(4-(Pyridin-3-yl)pyrimidin-2-ylamino)-4-methylphenylimino)methyl)phenol (4e)
FT-IR (KBr, cm^{-1}) *v*: 3367 (O-H), 3164 (N-H), 3034 (Ar-H), 1632 (HC=N), 1153 (C-N). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 13.24 (s, 1H, O-H), 9.27 (s, 1H, HC=N), 9.03 (s, 1H, N-H), 8.97 (s, 1H, pyridine-H), 8.68 (s, 1H, Ar-H), 8.67 (d, 1H, pyridine-H), 8.53 (s, 1H, Ar-H), 8.51 (d, 1H, pyrimidine-H), 8.42 (d, 1H, pyridine-H), 7.63 (d, 1H, Ar-H), 7.60 (d, 1H, Ar-H), 7.53 (t, 1H, pyridine-H), 7.45 (d, 1H, Ar-H), 7.36 (t, 1H, Ar-H), 7.29 (d, 1H, Ar-H), 6.97 (d, 1H, pyrimidine-H), 2.28 (s, 3H, CH_3). Anal. Calcd. for $C_{23}H_{19}N_5O$ (in %): C-72.42, H-5.02, N-18.36. Found C-72.41, H-4.98, N-18.31.

***4-((3-(4-(Pyridin-3-yl)pyrimidin-2-ylamino)-4-methylphenylimino)methyl)-2-methoxyphenol* (4f)**
FT-IR (KBr, cm^{-1}) *v*: 3365 (O-H), 3167 (N-H), 3032 (Ar-H), 1634 (HC=N), 1155 (C-N). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.67 (s, 1H, O-H), 9.29 (s, 1H, HC=N), 8.91 (s, 1H, N-H), 8.69 (s, 1H, pyridine-H), 8.68 (s, 1H, Ar-H), 8.53 (s, 1H, Ar-H), 8.42 (d, 1H, pyridine-H), 7.54 (d, 1H, pyrimidine-H), 7.52 (d, 1H, pyridine-H), 7.51 (d, 1H, Ar-H), 7.44 (d, 1H, Ar-H), 7.33 (t, 1H, pyridine-H), 7.31 (d, 1H, Ar-H), 6.96 (d, 1H, Ar-H), 6.89 (d, 1H, pyrimidine-H), 3.84 (s, 3H, $2CH_3$), 2.27 (s, 3H, $2CH_3$). Anal. Calcd. for $C_{24}H_{21}N_5O_2$ (in %): C-70.06, H-5.14, N-17.02. Found C-70.13, H-5.13, N-16.98.

***N^1-(2-Chloro-6-fluorobenzylidene)-4-methyl-N^3-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine* (4g)**
FT-IR (KBr, cm^{-1}) *v*: 3164 (N-H), 3035 (Ar-H), 1636 (HC=N), 1253 (C-F), 1158 (C-N), 722 (C-Cl). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.28 (s, 1H, HC=N), 9.07 (s, 1H, N-H), 8.73 (s, 1H, pyridine-H), 8.71 (s, 1H, Ar-H), 8.55 (s, 1H, Ar-H), 8.53 (d, 1H, pyridine-H), 8.49 (d, 1H, pyrimidine-H), 7.65 (d, 1H, pyridine-H), 7.61 (t, 1H, pyridine-H), 7.55 (d, 1H, Ar-H), 7.34 (d, 1H, Ar-H), 7.03 (d, 1H, Ar-H), 6.97 (d, 1H, Ar-H), 6.87 (d, 1H, pyrimidine-H), 2.26 (s, 3H, CH_3). Anal. Calcd. for $C_{23}H_{17}ClFN_5$ (in %): C-66.11, H-4.10, N-16.76. Found C-66.09, H-4.15, N-16.71.

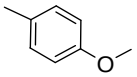
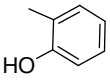
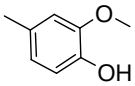
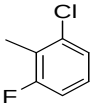
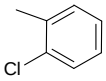
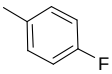
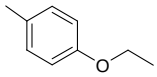
***N^1-(2-Chlorobenzylidene)-4-methyl-N^3-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine* (4h)**

FT-IR (KBr, cm^{-1}) *v*: 3134 (N-H), 3025 (Ar-H), 1631 (HC=N), 1157 (C-N), 722 (C-Cl). ^1H NMR (DMSO-d_6, 400 MHz) δ: 9.29 (s, 1H, HC=N), 9.01 (s, 1H, N-H), 8.69 (s, 1H, pyridine-H), 8.66 (s, 1H, Ar-H), 8.52 (d, 1H, pyridine-H), 8.42 (d, 1H, pyrimidine-H), 7.94-7.91 (d, 2H, Ar-H),7.58 (d, 1H, pyridine-H), 7.55 (t, 1H, pyridine-H), 7.53-7.51 (t, 2H, Ar-H), 7.42 (d, 1H, Ar-H), 7.05 (d, 1H, Ar-H), 7.02 (d, 1H, pyrimidine-H), 2.26 (s, 3H, CH_3). Anal. Calcd. for $C_{23}H_{18}ClN_5$ (in %): C-69.88, H-4.54, N-17.51. Found C-70.01, H-4.51, N-17.48.

***N^1-(4-Fluorobenzylidene)-4-methyl-N^3-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine* (4i)**

FT-IR (KBr, cm^{-1}) *v*: 3135 (N-H), 3035 (Ar-H), 1635 (HC=N), 1284 (C-F), 1153 (C-N). ^1H NMR (DMSO-d_6, 400 MHz) δ: 9.27 (s, 1H, HC=N), 9.03 (s, 1H, N-H), 8.70 (s, 1H, pyridine-H), 8.65 (s, 1H, Ar-H), 8.56 (d, 1H, pyridine-H), 8.44 (d, 1H, pyrimidine-H), 7.94-7.91 (d, 2H, Ar-H),7.58 (d, 1H, pyridine-H), 7.56 (t, 1H, pyridine-H), 7.55-7.52 (d, 2H, Ar-H), 7.42-7.40 (d, 2H, Ar-H), 7.01 (d, 1H, pyrimidine-H), 2.28 (s, 3H, CH_3). Anal. Calcd. for $C_{23}H_{18}FN_5$ (in %): C-72.05, H-4.73, N-18.27. Found C-72.01, H-4.69, N-18.30.

Table 1. Chemical structure and physical data of the synthesized compounds 4a-k

Compound	R	Yield (%)	mp (°C)	UV-visible (λ_{max})
4a	—H	76	142-145	445
4b	—CH_3	74	118-120	450
4c		67	136-137	469
4d		68	140-142	505
4e		74	112-113	516
4f		71	110-112	535
4g		64	158-160	510
4h		61	117-120	488
4i		74	121-123	485
4j		65	142-143	524
4k		68	163-164	512

***N^1-(4-Ethoxybenzylidene)-4-methyl-N^3-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine* (4j)**

FT-IR (KBr, cm^{-1}) *v*: 3134 (N-H), 3036 (Ar-H), 1637 (HC=N), 1152 (C-N). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.26 (s, 1H, HC=N), 8.97 (s, 1H, N-H), 8.69 (s, 1H, pyridine-H), 8.54 (s, 1H, Ar-H), 8.50 (d, 1H, pyridine-H), 8.42 (d, 1H, pyrimidine-H), 7.85-7.82 (d, 2H, Ar-H), 7.53 (t, 1H, pyridine-H), 7.51 (d, 1H, pyridine-H), 7.25-7.03 (d, 2H, Ar-H), 6.99 (d, 1H, Ar-H), 6.96 (d, 1H, Ar-H), 6.95 (d, 1H, pyrimidine-H), 4.09 (q, 2H, CH_2), 2.25 (t, 3H, CH_3), 1.35 (s, 3H, CH_3). Anal. Calcd. for $C_{25}H_{23}N_5O$ (in %): C-73.33, H-5.66, N-17.10. Found C-73.31, H-5.63, N-17.07.

***4-Methyl-N^1-((pyridin-2-yl)methylene)-N^3-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine* (4k)**

FT-IR (KBr, cm^{-1}) *v*: 3135 (N-H), 3037 (Ar-H), 1635 (HC=N), 1155 (C-N). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.28 (s, 1H, HC=N), 9.05 (s, 1H, N-H), 8.72 (s, 1H, pyridine-H), 8.71 (s, 1H, Ar-H), 8.55 (d, 1H, pyridine-H), 8.46 (d, 1H, pyrimidine-H), 7.69-7.55 (t, 2H, Ar-H), 7.55 (d, 1H, pyridine-H), 7.50 (t, 1H, pyridine-H), 7.49-7.31 (d, 2H, Ar-H), 7.28 (d, 1H, Ar-H), 7.23 (d, 1H, Ar-H), 6.97 (d, 1H, pyrimidine-H), 2.25 (s, 3H, CH_3). Anal. Calcd. for $C_{22}H_{18}N_6$ (in %): C-72.11, H-4.95, N-22.94. Found C-72.09, H-4.85, N-22.87.

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 [10]. The sterile medium (Nutrient Agar medium, 15 ml) in each petriplates was uniformly smeared with cultures of gram +ve and gram –ve bacteria. Sterile discs of 6 mm diameter (Hi-Media) were made in each of the petriplates, to which 50 µl (concentration was 1mg/ml, i.e., 50 µg/disc) of the different synthesized compounds were added. The treatments also included 50 µl of DMF and streptomycin as negative and positive control for comparison. Each compound was assessed in triplicate. The plates were incubated overnight at 25 ± 2 ºC and then the inhibition zones were measured in millimeters.

Antifungal activity

The synthesized compounds were screened for their antifungal activity against *Fusarium oxysporum* MTCC 2480 in DMF by poisoned food technique [11]. Potato Dextrose Agar (PDA) media was prepared and about 15 ml of PDA was poured into each petriplate and allowed to solidify. 5 mm disc of seven days old culture of the test fungi was placed at the center of the petri plates 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 drug. All the synthesized compounds were tested (at the dosage of 500 µl of the novel compounds in petriplate, where concentration was 0.1 mg/ml) by poisoned food technique.

RESULTS AND DISCUSSION

The intermediate **2** was reacted with various aldehydes (R-CHO, **3a-k**) in ethanol to obtain *N*-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidinamine derivatives **4a-k** in good yield (61-76 %). The FT-IR spectra of **4a-k** were recorded using KBr pellets in the range of 4000 - 400 cm^{-1}. The absorption bands at 3015 - 3037 cm^{-1} are assigned to the aromatic C-H stretch. The absorption band at 3365 cm^{-1} is due to the N-H stretch in compound **2**. The absence of N-H absorption band in **4a-k** confirmed the synthesized compounds. The appearance of a medium to strong absorption bands above 1630 cm^{-1} due to a stretching vibration of the azomethine (HC=N) bond formation in the synthesized compounds via condensation. New bands appeared at 1253

cm^{-1} (**4g**) and 1284 cm^{-1} (**4i**) corresponding to C-F stretching frequency. The strong bands at 722 cm^{-1} are assigned to the C-Cl stretch in **4g** and **4h**. The characteristic resonance peaks in ^1H NMR for the novel compounds were reported using DMSO. The proton spectral data of the intermediate, *N*-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidinamine (**2**) shows resonance at δ 4.82 ppm (s, 2H, $-NH_2$). In all the synthesized compounds **4a-k** the above resonance disappeared and additional resonances assigned to the –CH=N (δ 9.29 - 9.23 ppm) were observed which confirmed the condensation between the amino group and carbonyl group.

Antibacterial activity

The investigation of antibacterial screening data revealed that all tested compounds showed antibacterial activity against four pathogenic bacterial strains except **2** and **4a-c**. Compounds **4f**, **4g**, **4h** and **4i** showed good antibacterial properties and they were more effective when compared with other compounds in the series and less effective when compared with standard drug. Among the series **4a-k**, the compound **4g** exhibited good antibacterial activity against gram positive (zone of inhibition 16 - 18 mm) and gram negative (zone of inhibition 11 - 12 mm) bacteria. Compounds **4d**, **4e** and **4j** showed no inhibition against *X. Campestris*. The results were compared with standard drug streptomycin as depicted in Table 2. Comparison of zone of inhibition of compounds **4f**, **4g**, **4h** and **4i** with standard against bacterial strains are shown in Fig. 1.

Table 2. *In vitro* antibacterial and antifungal activities of 4a-k

Compound	Zone of inhibition in diameter (mm)				% inhibition
	B. subtilis	*S. aureus*	*X. campestris*	*E. coli*	*F. oxysporum*
2	-·	-·	-·	-·	24.5
4a	-·	-·	-·	-·	24.5
4b	-·	-·	-·	-·	25.7
4c	-·	-·	-·	-·	27.6
4d	07	08	-·	08	31.2
4e	07	08	-·	08	34.1
4f	15	17	11	11	64.0
4g	16	18	11	12	66.5
4h	15	16	10	11	63.3
4i	13	15	10	10	62.1
4j	08	07	-·	08	42.4
4k	07	08	09	09	46.3
Streptomycin	18	21	13	14	-
Nystatin	-	-	-	-	90.0

·No inhibition

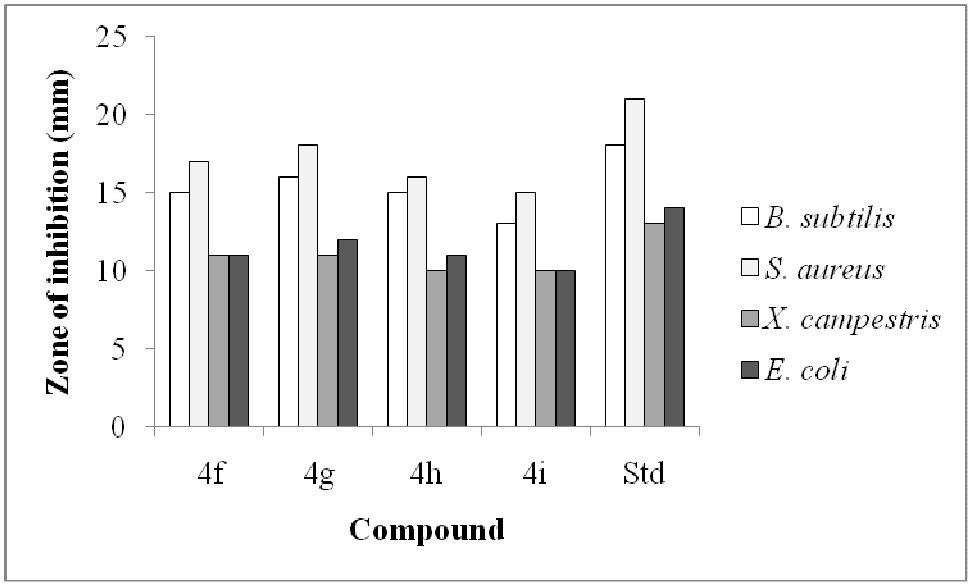


Fig. 1

Antifungal activity

The *in vitro* antifungal activity of the synthesized compounds **4a-k** was studied against *Fusarium oxysporum*. The results were compared with the standard drug nystatin as collected in Table 2. Compounds **4f**, **4g**, **4h** and **4i** have been demonstrated good antifungal activity against *F. oxysporum* when compared with other compounds in the series. Compounds **4j** and **4k** were found to be moderately active against tested fungal strain. From the results it is evident that, most of the compounds showed weak antifungal activity. Comparison of percentage inhibition of compounds **4f**, **4g**, **4h** and **4i** with standard against fungal strain is shown in Fig. 2.

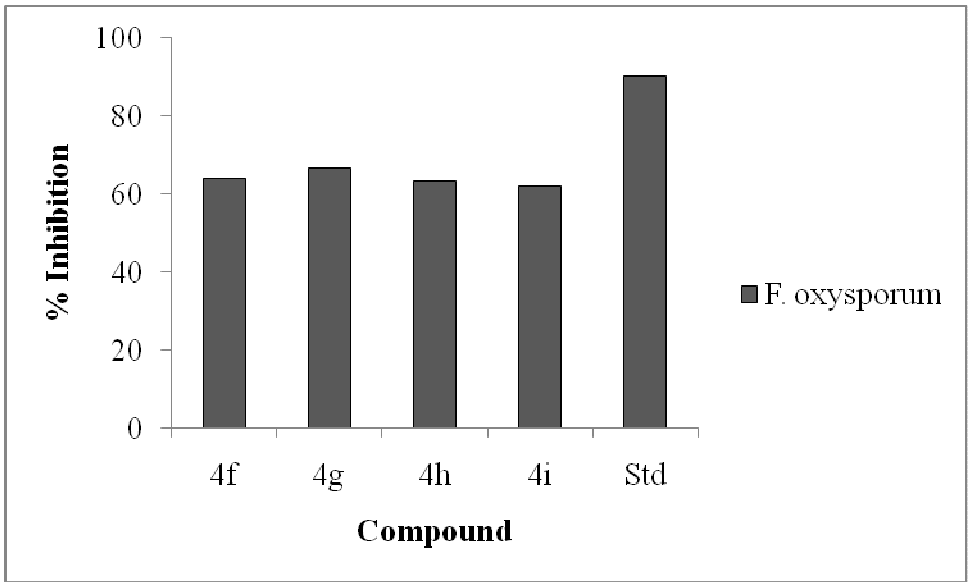


Fig. 2

CONCLUSION

In conclusion, a series of *N*-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidinamine derivatives **4a-k** were synthesized in good yield, characterized by different spectral studies and their antibacterial and antifungal activities have been evaluated. The synthesized compounds **4f**, **4g**, **4h** and **4i** demonstrated good inhibition against all the microbial strains tested. It should be

noted that compound **4g** demonstrated better inhibition compared to other compounds against bacterial and fungal strains tested. On the basis of their activity, these derivatives were identified as viable leads for further studies.

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