Available online at **www.joac.info**

ISSN: 2278-1862

Journal of Applicable Chemistry

2019, 8 (1): 124-132

(International Peer Reviewed Journal)

In vitro Antimicrobial Activity of Schiff Bases Synthesized from Pyridinamine Derivative and Aryl Aldehydes

Mallupura Veeranna Santhosh[1,2], Lingappa Mallesha[3] and Puttaswamappa Mallu[1]*

1. Department of Chemistry, Sri Jayachamarajendra College of Engineering, JSS Science and Technology University, Mysuru, Karnataka-570 006, **INDIA**
2. Department of Chemistry, GSSS Institute of Engineering and Technology for Women, Mysuru, Karnataka-570 016, **INDIA**
3. PG Department of Chemistry, JSS College of Arts, Commerce and Science, Mysuru, Karnataka570025, **INDIA**

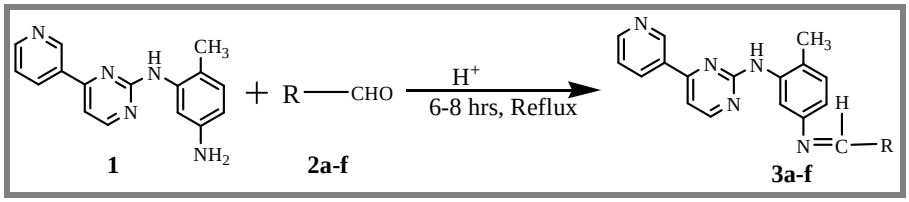
Email: drmallu66@gmail.com

Accepted on 18th January, 2019

ABSTRACT

*A series of new Schiff bases, **3(a-f)** were synthesized by the reaction of pyrimidinamine derivative with various aryl aldehydes in order to determine their in vitro antimicrobial activities against clinically isolated strains. The chemical structures were confirmed by UV-visible, FT-IR and ^{1}H NMR spectral studies. Among the series, compounds **3c** and **3d** showed significant antimicrobial activity compared to other compounds against bacterial and fungal strains tested.*

Graphical Abstract



Keywords: *N*-(5-Amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidinamine, Antimicrobial, Aldehyde.

INTRODUCTION

Compounds containing an azomethine group are known as Schiff bases. It contains a carbon-nitrogen double bond with the nitrogen atom connected to an aryl or alkyl group but not hydrogen. Schiff bases can be synthesized from aromatic amines and carbonyl compounds by nucleophilic addition followed by dehydration to generate an imines [**1, 2**]. Schiff bases are used as substrates in the preparation of a number of industrial and biologically active compounds via ring closure, cycloaddition and replacement reactions [**3**]. Due to the great flexibility and diverse structural aspects of Schiff bases, a wide range of these compounds have been synthesized and their activity have been studied [**4, 5**].

Nitro- and halo- derivatives of Schiff bases are reported to have antimicrobial and antitumor activities [**6**].

Antibacterial, antifungal, antitumor and anticancer activities of Schiff bases have been reported [**7, 8**], and they are active against a wide range of organisms. Antibacterial activity has been studied more than antifungal activity, because bacteria can achieve resistance to antibiotics through biochemical and morphological modifications [**9, 10**]. Some Schiff bases bearing aryl groups or heterocyclic residues possess excellent biological activities have attracted the attention of many researchers in recent years [**11, 12**]. Some acetophenone derivatives have antimicrobial activity against Gram-positive bacteria and fungi [**13**] and others are used as herbicides [**14**].

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. There are currently thirty vaccines that are mainly given prophylactically to prevent or minimize diseases by agents infectious to human. The number of different classes of antibacterial [**15**] and antifungal agents [**16**] has been discovered. The extensive use of antibiotics has led to the appearance of multi-drug resistant microbial pathogens [**17**]. This highlights the incessant need for the development of new classes of antimicrobial agents, and alteration of known drugs in such a way that would allow them to retain their physiological action, but reducing their resistance to the pathogen. The incidence of fungal infections has increased significantly in the past two decades [**18, 19**]. Toxicity problems prevented its use as a systemic agent, but recently developed liposomal delivery technologies have made it an attractive candidate for the treatment of severe systemic fungal infections [**20**].

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) [**21**]. 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 [**22**]. Pyranopyrimidine heterocyclics showed prominent biological activities and are considered required drugs in day to day life [**23**]. One-pot method for the synthesis of 1,3,6-tri substituted pyrimidine-2,4-diones has been reported [**24**]. The Schiff bases were synthesized from the reaction of 3,5-dimethoxyaniline with different aldehydes [**25**].

In connection with such studies, the present paper reporting for the first time on the synthesis of *N*-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidinamine derivatives, **3**(**a-f**) which are formed during the reaction of *N*-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidinamine **(1)** with different aldehydes, **2(a-f)**. The synthesized compounds were characterized by UV-Visible, FT-IR and ^{1}H NMR studies. Antimicrobial activity of compounds was reported and also discussed. On the basis of their activity, these derivatives were identified as viable leads for further studies.

MATERIALS AND METHODS

All solvents and reagents were purchased from Sigma Aldrich Chemicals Pvt Ltd. Melting range was determined by GLNR SELEC apparatus. The UV-Visible spectra were recorded on Agilent Technologies Cary 60 UV-Visible single beam spectrophotometer with quartz cell of 1.0 cm path length in methanol. The FT-IR spectra were recorded using FT-IR Agilent Technologies Cary 630 FT-IR infrared spectrophotometer and were quoted in cm^{-1}. NMR spectra were recorded on Bruker DMX 300 spectrometer (300 MHz for ^{1}H NMR) using DMSO-d_6 as solvent and TMS as an internal standard.

General procedure for the Synthesis of N-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidin amine derivatives, 3(a-f): The starting material, *N*-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-

pyrimidin amine (**1**) was synthesized according to the reported procedure [**26**]. Equimolar concentrations of *N*-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidinamine (**1**, 0.0018 mol) and different aryl aldehydes, **2(a-f)** (0.0018 mol) were stirred for 6-8 h at room temperature using methanol (20 mL) and then 2-3 drops of glacial acetic acid were added to the mixture. 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 methanol.

Synthesis of N^1-(3-methoxybenzylidene)-4-methyl-N^3-(4-(pyridin-3-yl) pyrimidin-2-yl) benzene-1,3-diamine (3a): Equimolar concentrations of *N*-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidinamine (**1**, 0.5 g, 0.0018 mol) and 3-methoxybenzaldehyde (**2a**, 0.25g, 0.0018 mol) and catalytic amount of glacial acetic acid. FT-IR *v*: 3362 (Ar-H), 3117 (N-H), 1606 (HC=N), 1537 (C=C), 1334 (C-N), 1161 (C-O). ^{1}H NMR δ: 9.65 (s, 1H, py-H), 8.90 (d, 1H, py-H), 8.74 (s, 1H, HC=N), 8.70 (d, 1H, pyrimidine-H), 7.42 (d, 1H, py-H), 7.32 (t, 1H, py-H), 7.23 (d, 1H, pyrimidine-H), 7.18-6.95 (3H, m, Ar-H), 6.95 (d, 1H, Ar-H), 6.92 (d, 1H, Ar-H), 6.90 (1H, s, Ar-H), 6.30 (s, 1H, Ar-H), 4.22 (s, 1H, N-H), 3.75 (s, 3H, OCH_3), 2.45 (s, 3H, CH_3).

Synthesis of N^1-(3,4,5-trimethoxybenzylidene)-4-methyl-N^3-(4-(pyridin-3-yl) pyrimidin-2-yl) benzene-1, 3-diamine (3b): Equimolar concentrations of N-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidinamine (**1**, 0.5g, 0.0018 mol) and 3,4,5-trimethoxy benzaldehyde (**2b**, 0.35g, 0.0018 mol). FT-IR *v*: 3200 (Ar-H), 3028 (N-H), 1586 (HC=N), 1511 (C=C), 1332 (C-N), 1280 (C-O). ^{1}H NMR δ: 9.64 (s, 1H, py-H), 8.90 (d, 1H, py-H), 8.70 (s, 1H, HC=N), 8.65 (d, 1H, pyrimidine-H), 7.43 (d, 1H, py-H), 7.30 (t, 1H, py-H), 7.20 (d, 1H, pyrimidine-H), 6.97 (d, 1H, Ar-H), 6.90 (d, 1H, Ar-H), 6.58 (2H, s, Ar-H), 6.25 (s, 1H, Ar-H), 4.20 (s, 1H, N-H), 3.73 (s, 9H, $3OCH_3$), 2.40 (s, 3H, CH_3).

Synthesis of N^1-(2-nitrobenzylidene)-4-methyl-N^3-(4-(pyridin-3-yl) pyrimidin-2-yl) benzene-1,3-diamine (3c): Equimolar concentrations of *N*-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidinamine (**1**, 0.5 g, 0.0018 mol) and 2-nitrobenzaldehyde (**2c**, 0.27 g, 0.0018 mol) and catalytic amount of glacial acetic acid. Grind well and the solid mass was left over 5-6 h. The Product was dried and recrystallized from hot alcohol to obtain the pure product. The progress was monitored by TLC. FT-IR *v*: 2901 (Ar-H), 2816 (N-H), 1587 (HC=N), 1530 (NO_2), 1230 (C-N). ^{1}H NMR δ: 9.80 (s, 1H, py-H), 9.28 (s, 1H, N-H), 8.90 (s, 1H, HC=N), 8.75-8.65 (d, 2H, py-H), 8.55 (d, 1H, pyrimidine-H), 8.40 (s, 1H, Ar-H), 7.70 (d, 2H, Ar-H), 7.55 (d, 1H, pyrimidine-H), 7.45 (t, 1H, py-H),7.38-7.15 (t, 2H, Ar-H), 7.10-6.80 (d, 2H, Ar-H), 2.85 (s, 3H, CH_3).

Synthesis of N^1-(4-(dimethylamino) benzylidene)-4-methyl-N^3-(4-(pyridin-3-yl) pyrimidin-2-yl) benzene-1,3-diamine (3d): Equimolar concentrations of N-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidinamine (**1**, 0.5g, 0.0018 mol) and p-dimethylaminobenzaldehyde (**2d**, 0.35g, 0.0018 mol).). FT-IR *v*: 3451 (Ar-H), 2933 (N-H), 1580 (HC=N), 1524 (C=C), 1285 (C-N). ^{1}H NMR δ: 9.62 (s, 1H, py-H), 8.92 (d, 1H, py-H), 8.72 (s, 1H, HC=N), 8.70 (d, 1H, pyrimidine-H), 7.45 (d, 2H, Ar-H), 7.40 (d, 1H, py-H), 7.30 (t, 1H, py-H), 7.20 (d, 1H, pyrimidine-H), 6.95 (d, 1H, Ar-H), 6.90 (d, 1H, Ar-H), 6.60 (d, 2H, Ar-H), 6.25 (s, 1H, Ar-H), 4.20 (s, 1H, N-H), 2.85 (s, 6H, $2CH_3$), 2.40 (s, 3H, CH_3).

Synthesis of (E)-N^1-(2,3,4-trimethoxybenzylidene)-4-methyl-N^3-(4-(pyridin-3-yl) pyrimidin-2-yl) benzene-1,3-diamine (3e): Equimolar concentrations of *N*-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidinamine (**1**, 0.5g, 0.0018 mol) and 2,3,4-trimethoxybenzaldehyde (**2e**, 0.35g, 0.0018 mol).). FT-IR *v*: 2942 (Ar-H), 2844 (N-H), 1586 (HC=N), 1494 (C=C), 1463 (C-N), 1284 (C-O). ^{1}H NMR δ: 9.64 (s, 1H, py-H), 8.85 (d, 1H, py-H), 8.70 (s, 1H, HC=N), 8.65 (d, 1H, pyrimidine-H), 7.40 (d, 1H, py-H), 7.30 (t, 1H, py-H), 7.20 (d, 1H, pyrimidine-H), 7.10 (d, 1H, Ar-H), 6.90 (d, 1H, Ar-H), 6.85 (d, 1H, Ar-H), 6.25 (s, 1H, Ar-H), 6.10 (d, 1H, Ar-H), 4.20 (s, 1H, N-H), 3.75 (s, 9H, $3CH_3$), 2.45 (s, 3H, CH_3).

Synthesis of (Z)-4-methyl-N^1-((E)-3-phenylallylidene)-N^3-(4-(pyridin-3-yl) pyrimidin-2-yl) benzene-1,3-diamine (3f): Equimolar concentrations of *N*-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-

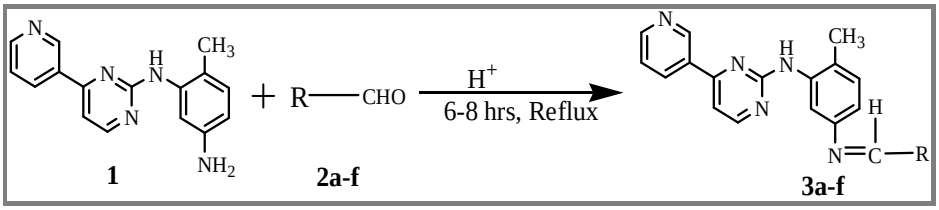
pyrimidinamine (**1**, 0.5g, 0.0018 mol) and cinnamaldehyde (**2f**, 0.24g, 0.0018 mol).). FT-IR *v*: 3024 (N-H), 1572 (HC=N), 1522 (C=C), 1287 (C-N). ^{1}H NMR δ: 9.65 (s, 1H, py-H), 8.84 (d, 1H, py-H), 8.70 (s, 1H, HC=N), 8.62 (d, 1H, pyrimidine-H), 7.40 (d, 1H, py-H), 7.35 (t, 1H, py-H), 7.30-7.28 (m, 5H, Ar-H), 7.22 (d, 1H, pyrimidine-H), 7.10 (d, 1H, Ar-H), 6.84 (d, 1H, Ar-H), 6.60 (d, 1H, CH), 6.24 (s, 1H, Ar-H), 5.50 (d, 1H, CH), 4.25 (s, 1H, N-H), 2.44 (s, 3H, CH_3).

Antibacterial activity: Antibacterial activity of the Schiff bases was determined against gram-positive bacteria (*Bacillus subtilis*, *Staphylococcus aureus*) and gram-negative bacteria (*Xanthomonas malvacearum* and *Escherichia coli*) in DMF by disc diffusion method on nutrient agar medium [27]. The sterile medium (Nutrient Agar medium, 15 mL) in each Petri plates 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 1 mg mL^{-1}, i.e., 50 µg $disc^{-1}$) 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 ± 2ºC and then the inhibition zones were measured in millimeters.

Antifungal activity: The synthesized compounds were screened for their antifungal activity against *Fusarium oxysporum* in DMF by poisoned food technique [28]. Potato Dextrose Agar (PDA) media was prepared and about 15 mL of PDA was poured into each Petri plate 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. All the synthesized compounds were tested (at the dosage of 500 µL of the novel compounds in petriplates, where concentration was 0.1 mg mL^{-1}) by poisoned food technique.

RESULTS AND DISCUSSION

In this work, the novel *N*-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidinamine derivatives **3**(**a-f**) were synthesized by the method summarized in scheme 1. The reactions of *N*-(5-amino-2-methyl phenyl)-4-(3-pyridyl)-2-pyrimidinamine with different aryl aldehydes were carried out in the presence of methanol as a solvent. Synthesized compounds were characterized by UV-Visible, FT-IR and ^{1}H NMR spectral studies. Compounds were purified by recrystalization method using methanol.



Scheme 1. General procedure for the Synthesis of N-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidin amine derivatives, 3(a-f)

Microwave assisted some new pyrazolo (3,4-d) pyrimidines derivatives were synthesized and studied their antimicrobial activity [29]. Green rapid one-pot method for the synthesis of 1,3,6-trisubstituted pyrimidine 2,4-diones has been reported [30]. The electronic absorption spectra of synthesized compounds show new bands and appearance of longer wavelength absorption band in the visible region in UV-visible spectrum owing to confirms the formation of synthesized compounds.

The absence of NH_2 and C=O absorption bands in the IR spectra confirmed that the synthesized compounds **3**(**a-f**) were obtained via condensation. However, the changes in integral intensities and bandwidths, especially of the bands originating from NH_2 stretching vibrations didn't show in products. The absorptions around 3000 cm^{-1} in compounds **3**(**a-f**) confirm the aromatic C-H stretching

vibrations, and the appearance of a medium to strong absorption bands above 1600 cm^{-1} due to a stretching vibration of the azomethine (C=N) bond formation in synthesized compounds. The chemical structures (Table 1) and physical data (Table 2) of all the synthesized compounds are tabulated.

Table 1. Chemical structures of **3a-f**

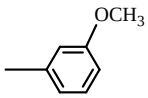
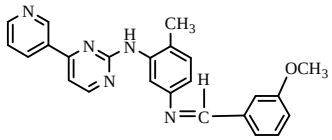
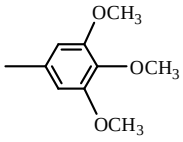
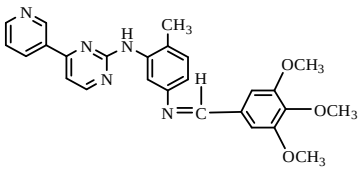
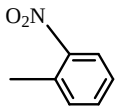
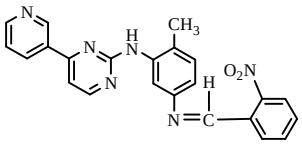
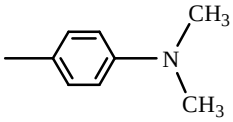
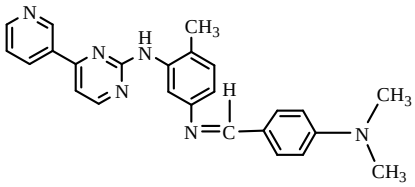
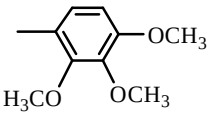
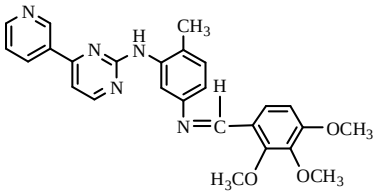
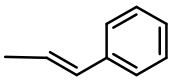
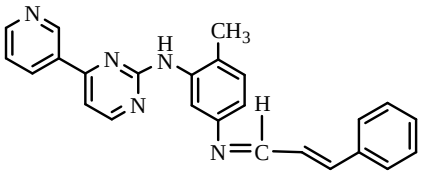
Compound	R	Structure
3a		
3b		
3c		
3d		
3e		
3f		

Table 2. Physical data of **3a-f**

Compound	Molecular Formula	Molecular Weight	Yield (%)	UV-visible (λ_{max})	Melting Point °C	Color	Solubility
3a	$C_{24}H_{21}N_5O$	395.5	60	518	115	Gray	Acetonitrile
3b	$C_{26}H_{25}N_5O_3$	455.5	61	369	108	Brown	Acetonitrile
3c	$C_{23}H_{18}N_6O_2$	410.4	75	320	104	Yellow	Acetonitrile
3d	$C_{25}H_{24}N_6$	408.5	72	348	112	Yellow	Acetonitrile
3e	$C_{26}H_{25}N_5O_3$	455.5	60	380	138	Yellow	Methanol
3f	$C_{25}H_{21}N_5$	391.5	62	345	130	Yellow	Methanol

The IR spectrum of the compound was run using single beam FT-IR. The amine and carbonyl group in the IR spectra confirmed that the synthesized compound **3c** obtained (Figure 1). However, the changes in integral intensities and bandwidths, especially of the bands originating from NH_2

stretching vibrations didn't show in products. The infrared spectrum in the 1606 cm^{-1}, 1586 cm^{-1}, 1587 cm^{-1}, 1580 cm^{-1}, 1580 cm^{-1} and 1572 cm^{-1} region has been determined for C=N in compounds **3a-f**, respectively.

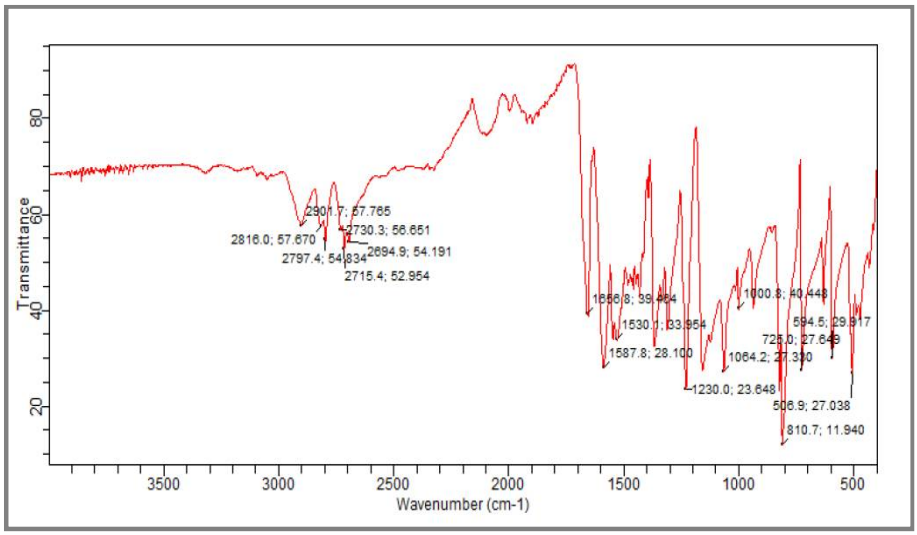


Figure 1. FT-IR Spectra of compound **3c**.

The proposed structures with respect to the number of protons agreed and their chemical shifts with the ^1H spectral data. The proton spectral data of the intermediate, *N*-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidinamine (**1**) shows at δ 5.50 ppm (2H, s, NH_2). The above resonances disappeared in **3**(**a-f**) and additional resonances were observed, which confirmed the Schiff bases. Proton NMR spectral data of compound **3c** has been depicted in figure 2.

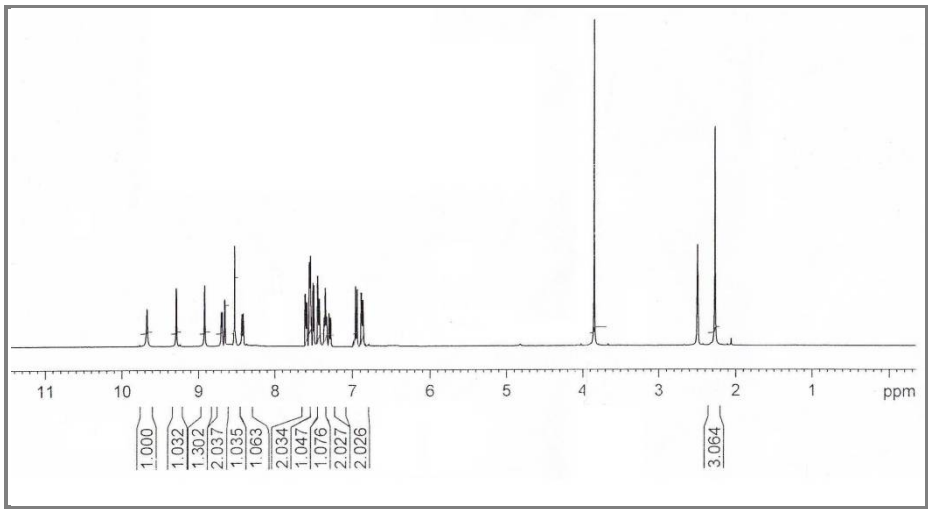


Figure 2. ^1H NMR Spectra of **3c**.

The antibacterial activity of compounds **3**(**a-f**) were evaluated and compared with streptomycin as standard drug (Figure 3). The compounds **3c** and **3d** have shown significant antibacterial activity against four pathogenic bacterial strains among the six compounds screened. Compared with streptomycin the compounds, **3a, 3b, 3e** and **3f** showed less inhibitory activity. Among the compounds **3**(**a-f**) the antibacterial inhibitory activity follows the order **3c** > **3d** > **3f** > **3a** > **3b** > **3e** against tested four pathogenic bacterial strains. Antibacterial and antifungal screening results of the tested compounds are shown in table 3.

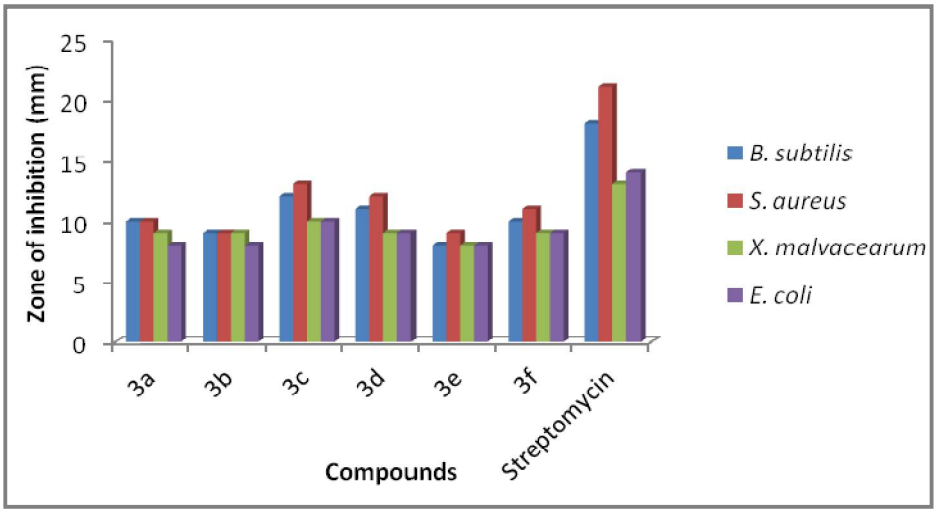


Figure 3. Antibacterial activity of synthesized compounds.

Table 3. Antibacterial and antifungal activity of compounds **3a-f**

Compound	Zone of inhibition in diameter (mm)				Compound	% inhibition
	B. subtilis	*S. aureus*	*X. malvacearum*	*E. coli*		*F. oxysporum*
3a	10	10	09	08	3a	48.0
3b	09	09	09	08	3b	47.6
3c	12	13	10	10	3c	65.7
3d	11	12	09	09	3d	62.0
3e	08	09	08	08	3e	42.2
3f	10	11	09	09	3f	48.9
Streptomycin	18	21	13	14	Nystatin	90.0

The antifungal activity of compounds **3(a-f)** were evaluated and compared with nystatin as standard (Figure 4). The compounds **3c** and **3d** showed significant activity against *F. oxysporum.* Compared with nystatin the compounds, **3a, 3b, 3e** and **3f** showed moderate inhibitory activity against *F. oxysporum*. From the results it is evident that most of the compounds are moderately active. Among the compounds **3(a-f)** showed inhibitory activity in the order **3c** > **3d** > **3f** > **3a** > **3b** > **3e** against *F. oxysporum.*

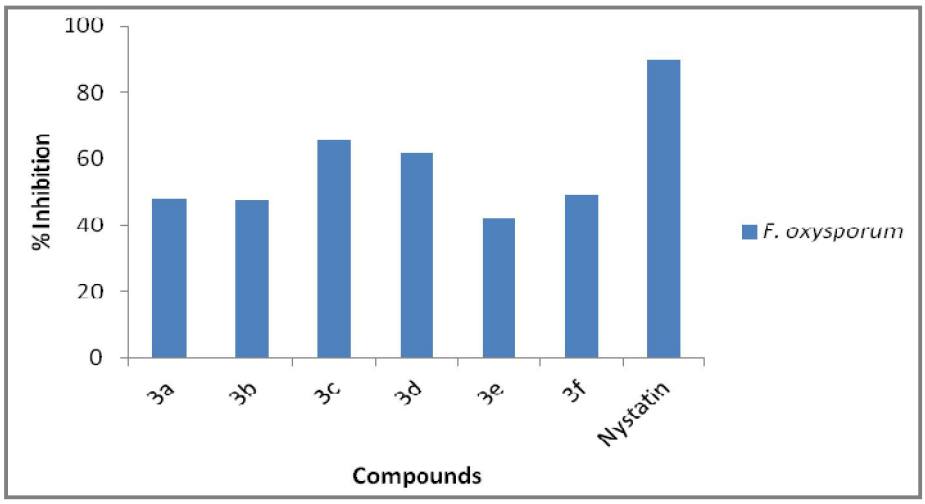


Figure 4. Antifungal activity of synthesized compounds.

APPLICATION

The present study has shown that the selected Schiff bases possess remarkable antimicrobial activity as promising lead molecules for the advance of new medications. This research strongly supports the usefulness of these compounds against different microbial diseases.

CONCLUSION

In conclusion, a series of new pyrimidinamine derivatives **3(a-f)** were synthesized in good yield, characterized by different spectral studies and their antimicrobial activity have been evaluated. Compounds **3c** and **3d** demonstrated significant inhibition against bacterial and fungal strains tested. On the basis of their activity, these derivatives were identified as viable leads for further studies.

ACKNOWLEDGEMENTS

One of the authors (MVS) grateful to GSSS Institute of Engineering and Technology for Women and JSS STU, Mysuru for carrying out the synthetic and characterization work. The authors thank Dr. N. D. Rekha, PG Department of Biotechnology, JSS College, B. N. Road, Mysuru, for carrying out the antimicrobial activity test.

REFERENCES

[1] S. K. Sridhar, S. N. Pandeya, E. De Clercq, Synthesis and anti-HIV activity of some isatin derivatives. *Bollettino Chimico Farmaceutico*, **2001**, 140, 302-305.
[2] S. K. Sridhar, A. Ramesh, Synthesis and pharmacological activities of schiff and hydrazones of isatin derivatives. *Indian Drugs*, **2001**, 38, 174-180.
[3] V. Manjusha, N. P. Surendra, N. S. Krishna, S. P. James, Anticonvulsant activity of Schiff bases of isatin derivatives. *Acta Pharm*., **2004**, 54, 49-56.
[4] M. T. H. Tarafder, A. Kasbollah, N. Saravanan, K. A. Crouse, A. M. Ali, K. T. Oo, S-methyldithiocarbazate and its Schiff bases: evaluation of bondings and biological properties, *J Biochem Mol Biol Biophys*., **2002**, 6, 85-91.
[5] S. B. Desai, P. B. Desai, K. R. Dcsai, Synthesis of some schiff bases, thiazolidinones and azetidinones bisthiazole and their anticancer activities, *Heterocycl Comm*., **2001**, 7, 83-90.
[6] V. E. Kuzmin, V. P. Lozitsky, G. L. Kamalov, R. N. Lozitskaya, A. I. Zheltvay, A. S. Fedtchouk, D. N. Kryzhanovsky, Analysis of the structure-anticancer activity relationship in a set of Schiff bases of macrocyclic 2,6-bis(2- and 4-formylaryloxymethyl)pyridines, *Ada Biochimica Polonica*, **2000**, 47, 867-875.
[7] P. Ball, Quinolone generations: natural history or natural selection, *J. Antimicrob Chemother*., **2000**, 46, 17-24.
[8] V. T. Andriole, In Current Clinical Topics in Infectious Diseases, Blackwell Sciences, Malden, MA, **1999**, 44, 151-162.
[9] J. M. Frere, Beta-lactamases and bacterial resistance to antibiotics, *Mol. Microbiol.*, **1995**, 16, 385-395.
[10] F. W. Diggins, The discovery of penicillin: so many get it wrong, *Biologist*, **2000**, 47, 115-119.
[11] A. Schatz, E. Bugie, S. A. Waksman, S. A. Waksman, Streptomycin reported, *Ann Intern Med*., **1973**, 79, 678-685.
[12] G. F. Brooks, Jawetz, Melnick, Adelbergas, Medical Microbiology, 20th Ed., Appleton and Lange, **1994**.
[13] D. A. Enoch, H. A. Ludlam, N. M. Brown, Invasive fungal infections: a review of epidemiology and management options, *J. Med. Microbiol*., **2006**, 55, 809-818.
[14] A. Chakrabarti, Microbiology of systemic fungal infections, *J. Postgrag Med*., **2005**, 51, S16-S20.

[15] P. C. Appelbaum, P. A. Hunter, The fluoroquinolone antibacterials: past, present and future perspectives, *Int. J. Antimicro.b Agents*, **2000**, 16, 5-15.
[16] Tryphon K. Mazu, Barbara A. Bricker, Hernan Flores-Rozas, Seth Y. Ablordeppey, The Mechanistic Targets of Antifungal Agents: An Overview, *Mini Rev. Med. Chem.*, **2016**, 16, 555–578.
[17] V. T. Andriole, In current clinical topics in infectious diseases, Blackwell Sciences, Malden, MA, **1998**, 19-36.
[18] Felix Bongomin, Sara Gago, Rita O. Oladele, David W. Denning, Global and multi-national prevalence of fungal diseases-estimate precision, *J. Fungi*, **2017**, 3, 1-29.
[19] S. C. A. Chen, T. C. Sorrell, Cryptococcus gattii Infections, *J. Med. Microbiol.*, **2007**, 59, 548-555.
[20] A. H. Groll, V. Petraitis, R. Petraitiene, A. Field-Ridley, M. Calendario, J. Bacher, S. C. Piscitelli, T. J. Walsh, Safety and Efficacy of Multilamellar Liposomal Nystatin against Disseminated Candidiasis in Persistently Neutropenic Rabbits, *Antimicrob Agents Chemother*., **1999**, 43, 2463-2467.
[21] M. Kalaycio, Amyloid-like pulmonary nodules, including localized light-chain deposition: clinicopathologic analysis of three cases, *Cur.r Hematol. Rep.*, **2004**, 3, 37-38.
[22] K. Peggs, S. Mackinnon, Imatinib mesylate--the new gold standard for treatment of chronic myeloid leukemia, N. *Engl. J .Med*., **2003**, 348, 1048-1050.
[23] S. Shabir Bhat, Piyush Masih, M. A.S hah, Tariq Ahmad War, Khursheed Ansari, Rajeev Lohiya, Toyaj Shukla, Synthesis and characterization of Mn_3O_4 nanoparticle: A catalyst for synthesis of tetrahydro-1H-pyrano[2,3-d]pyrimidine derivatives, *J. Applicable Chem*., **2018**, 7, 1636-1643.
[24] Anil Kumar, Punam, Sharwan K Dewan, One pot synthesis and antimicrobial activity of 1, 3, 6-trisubstituted pyrimidine-2,4-diones catalyzed by TsOH, *J. Applicable Chem*., **2018**, 7, 449-452.
[25] L. Mallesha, C. S. Karthik, B. K. Kendagannaswamy, H. M. Viswanatha, Investigation of antioxidant activity of 3, 5-dimethoxyaniline derivatives, *J. Applicable Chem*., **2014**, 3, 2131-2137.
[26] S. Chang, S. L. Yin, J. Wang, Y. K. Jing, J. H. Dong, Design and synthesis of novel 2-phenylaminopyrimidine (PAP) derivatives and their antiproliferative effects in human chronic myeloid leukemia cells, *Molecules*, **2009**, 14, 4166-1479.
[27] A. W. Bauer, W. M. Kirby, J. C. Sherris, M. Turck, Antibiotic susceptibility testing by a standardized single disk method, *Am. J. Clin. Pathol*., **1966**, 45, 493-496.
[28] S. Satish, D. C. Mohana, M. P. Raghavendra, K. A. Raveesha, Antimicrobial activity of some important medicinal plant against plant and human pathogens, *J. Agri. Techn.*, **2007**, 3, 109.
[29] S. Thakur, S. Kaur, M. Bansal, M. Kaur, M. Yusuf, B. Kaur, Microwave assisted facile one pot synthesis and antimicrobial activity of some new pyrazolo [3, 4-d] pyrimidine derivatives, *J. Applicable Chem*., **2016**, 5, 604-611.
[30] Punam, Deepika, Anil Kumar, S. K. Dewan, Sodium chloride catalysed rapid one pot synthesis of 1, 3, 6- trisubstitutedpyrimidine-2,4-diones from ureas and β-ketoesters, *J. Applicable Chem*., **2015**, 4, 624-627.