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ISSN: 0975-7538
Research Article

Synthesis, characterization and antimicrobial activity of some novel thiadiazole and imidazo (2, 1-b) 1, 3, 4-thiadiazole derivatives

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ABSTRACT

Infections caused by bacteria and fungi are the leading cause for the death of millions of people in the world. To combat these infections there is a need to develop some novel and potent antimicrobial agents. With this aim we have synthesized some novel series of thiadiazoles and imidazo (2,1-b) 1,3,4-thiadiazole derivatives. The title compounds, thiadiazoles 5(a-b) and imidazo(2,1-*b*)-1,3,4-thiadiazoles 6(a-j) were synthesized by the reaction between Schiff bases of 1,3,4-thiadiazoles with thioglycollic acid in the presence of ethanol and 2-amino-5-(substituted phenyl)-1,3,4-thiadiazoles with different substituted aryl**/** heteroaryl α-bromoketones in dry ethanol respectively. Structure of the synthesized compounds was confirmed on the bases of spectral data (IR, ^{1}H NMR and Mass). All the synthesized compounds were screened for antibacterial and antifungal activities using Ciprofloxacin and Clotrimazole as standard drugs respectively. The results showed that compounds 6b, 6g, 6h and 6j exhibited good anti-bacterial activity and compounds 6a, 6c, 6h and 6j exhibited good antifungal activity.

Keywords: Thiadiazole; imidazo (2,1-b)1,3,4-thiadiazole; Clotrimazole; Ciprofloxacin

INTRODUCTION

Microbial infections are one of the leading causes for millions of death in the world. Antimicrobial agents are used in the treatment of microbial infections. But due to the development of resistance in the microorganisms, these are found to be less effective. Thus there is a need to develop potent and novel antimicrobial agents.

Along with globalization many new diseases are arising in the world, infection caused by the microorganisms render a major contribution to it. Some of the infections are acute and some are chronic which may be air born, water born or food born. Unhygienic conditions are determined to be the root cause for these infections. In addition to it the development of resistance in microorganisms against current antimicrobial therapy continues to drive the search for more effective antibacterial agents (Sharma S.D and Bandari S, 2002).

Both Gram positive and Gram negative bacteria pose serious threat to human beings. *S.aureus B.substilis, S.pyogenes* are primarily nosocomial pathogens, they are mainly responsible for majority of nosocomial diseases. Gram negative bacteria such as *E.coli, P.aeruginosa* also cause severe diseases in human beings. *S.aureus* causes nosocomial bacteremia, skin infections and also responsible for lower respiratory tract infection. *E.coli* also causes nosocomial septicemia, endocarditis, infection of wounds and UTI. *S.pneumoniae* causes life threatening disease.

The Infectious Disease Society of America (IDSA) reported in 2004 that in US hospitals alone, around 2 million people acquire bacterial infections each year. *S. aureus* is responsible for half of the hospital-associated infections and takes the lives of approximately 1,00,000 patients each year in the USA alone (Arnold L.D and Sergio S, 2009). Annual mortality from *S.pneumoniae* induced disease is estimated to be 50,000 in USA alone and 3-5 million globally. Development of resistance in the micro-organisms against the existing antimicrobial agents is still worsening the situation. The so-called 'super bugs' (organisms that are resistant to most of the clinically used antibiotics) are emerging at a rapid rate. *S. aureus*, which is resistant to methicillin, is responsible for many cases of infections. Similar to bacterial infections fungal infections also cause severe infections.

Heterocyclic compounds have been extensively used in the field of medicinal chemistry for the development of new and potent therapeutic agents. In the present research we have concentrated on the synthesis of two heterocyclic compound derivatives i.e thiazolidine and imidazo (2,1-b) 1,3,4-thiadiazole.

Thiadiazole derivatives show versatile biological and pharmacological activities like anti-cancer [Zhenhua

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Received on: 11-09-2014
Revised on: 05-10-2014
Accepted on: 07-10-2014

Luo et al, 2012], antimicrobial [Tarik El-Sayed Ali, et al], antitubercular [Oruc E.E, et al 2004], anti-inflammatory [Kadi a.a, et al], analgesic [Khazi I.A, et al, 1996], antiviral [Chen Z et al, 2010] and anticonvulsant [Michael R.S, et al, 1986] activities.

Literature review depicts the importance of imidazo(2,1-*b*)-1,3,4-thiadiazole ring system as a pharmacophore having diverse pharmacological and biological properties like anti-oxidant (Pradeep Kumar M.R and Honnalli S.S, 2014), antibacterial [Anshu Jakhar and J.K.Makrandi, 2010], antitubercular [Oruc E.E, et al 2004], anti-cancer [Noolvi M.N, et al, 2011] and anti-inflammatory [Pradeep Kumar M.R et al, 2013] activities.

In this research work we have synthesized some novel thiadiazole and imidazo(2,1-b)1,3,4-thiadiazole derivatives and screened them for antimicrobial activity.

MATERIALS AND METHODS

Chemicals used in the synthesis of the titled compounds were purchased from, Sigma-Aldrich Pvt Ltd, S.D. Fine Chem Pvt Ltd and Spectrochem Pvt. Ltd. They were p-methyl benzoic acid, p-chloro benzoic acid, phosphoryl oxytrichloride, different aromatic aldehydes, thioglycollic acid, p-bromo acetophenone, p-chloro acetophenone, p-nitro acetophenone, p-methoxy acetophenone, Salicylaldehyde, 7-diethylamino salicylaldehyde, dibromo salicylaldehyde etc. Absolute ethanol was prepared as per the literature.

Melting points of synthesized compounds were determined on Thermonik melting point apparatus and are uncorrected; FT-IR spectra were recorded on Thermo Nicolet spectrophotometer by using KBr pellets. The ^{1}HNMR were recorded on Bruker Avance II NMR 400 MHz instruments using $CDCl_3$ / DMSO as solvent and TMS as internal standard, chemical shifts are expressed as δ values (ppm).

Evaluation of Antibacterial activity

For antibacterial activity the MIC determination of synthesized compounds was carried out simultaneously in comparison with ciprofloxacin, norfloxacin against Gram-positive (*Staphylococcus aureus, Streptococuus faecalis, Bacillus subtilis*) and Gram-negative bacteria (*Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa*) by broth microdilution method (Sunil J., et al 2012: National committee ., 1985). Serial dilutions of the all synthesized compounds and standard drug were prepared in Mueller-Hinton broth. Standard drugs (10 mg) were dissolved in dimethylsulfoxide (DMSO, 1 ml). Further progressive dilutions were done to obtain final concentrations of 1.56, 3.125, 6.25, 12.5, 25, 50 and 100 µg ml^{-1}. The tubes were inoculated with 10^5 cfu ml^{-1} (colony forming unit/ml) and incubated at 37 °C for 18 h. The MIC was the lowest concentration of the compounds that yield no visible growth on the plate. To ensure that the solvent had no effect on the bacterial growth, a control was performed with the test medium supplemented with DMSO at the same dilutions as used in the experiments and DMSO had no effect on the micro-organisms in the concentrations studied. The MIC values are given in µg/ml. Ciprofloxacin and norfloxacin were used as standard drugs. The preliminary results of antibacterial activities are shown in Table-2.

Evaluation of Antifungal activity

For antifungal activity the MIC determination of different synthesized compounds was carried out simultaneously in comparison with Clotrimazole against by broth microdilution method. Serial dilutions of the all synthesized compounds and standard drug were prepared in Mueller-Hinton broth. Standard drug (10 mg) was dissolved in dimethylsulfoxide (DMSO, 1 ml). Further progressive dilutions were done to obtain final concentrations of 1.56, 3.125, 6.25, 12.5, 25, 50 and 100 µg ml^{-1}. The tubes were inoculated with 10^5 cfu ml^{-1} (colony forming unit/ml) and incubated at 37 °C for 18 h. The MIC was the lowest concentration of the compound that yield no visible growth on the plate. To ensure that the solvent had no effect on the bacterial growth, a control was performed with the test medium supplemented with DMSO at the same dilutions as used in the experiments and DMSO had no effect on the micro-organisms in the concentrations studied. The MIC values are given in µg/ml. Clotrimazole was used as standard drug. The preliminary results of antifungal activities are shown in Table-3

EXPERIMENTAL

General procedure for synthesis of [2-(substituted aryl)-3-{5-(substituted phenyl)1,3,4-thiadiazole }]-4-oxo-thiazolidines 5(a-b).

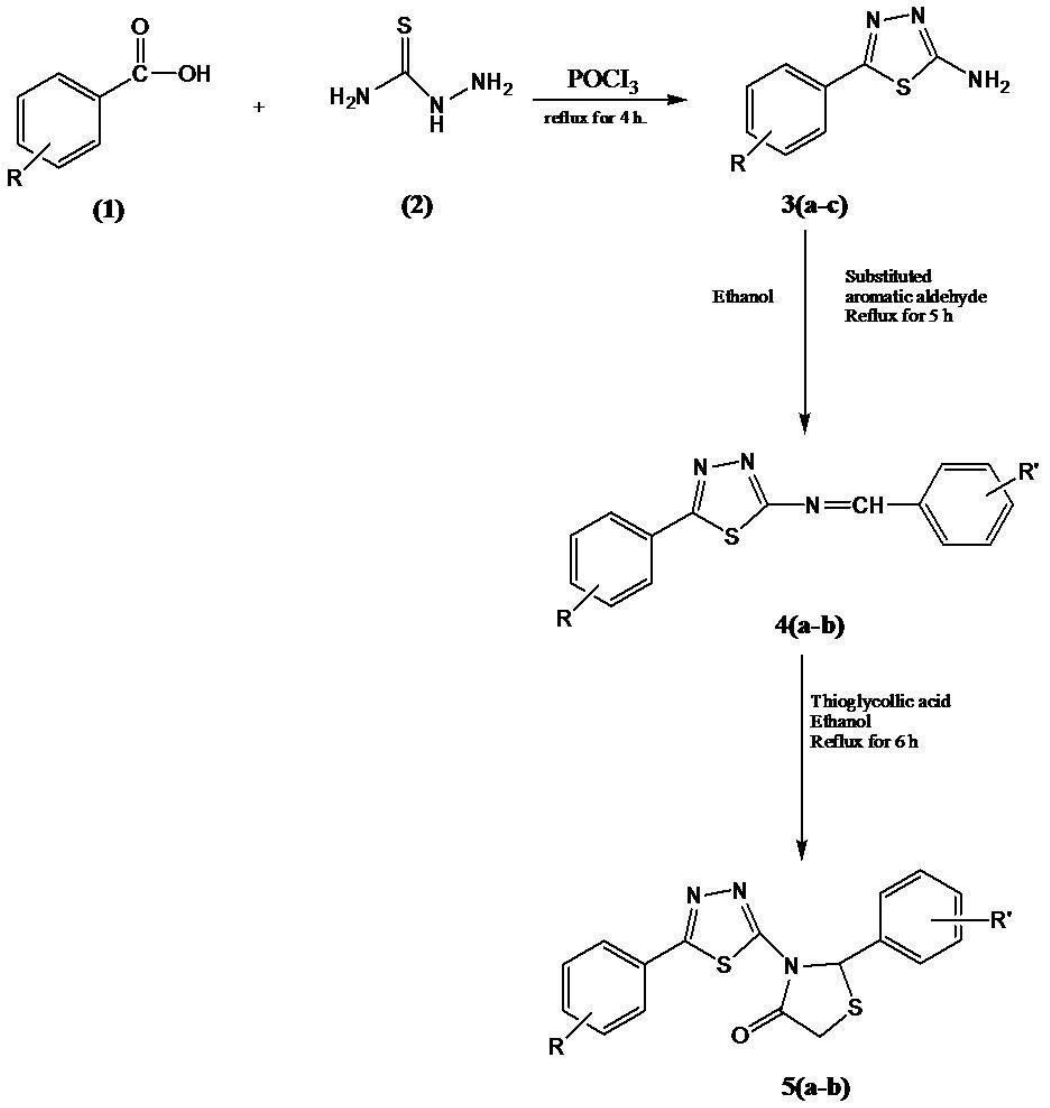
A mixture of thioglycollic acid (0.01 mole) and Schiff bases (0.01mole) in ethanol (25 ml) were refluxed on a water bath for about 4-6 h. and cooled. The solid thus obtained was separated out and was recrystallised from methanol.

5a: IR (KBr) cm^{-1}: 1716 (C=O), 16633 (C=N), 1567 (C=C), 682 (C-S). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 3.73 (s, 3H, OCH_3), 3.20-2.30 (m, 2H, thiazolidinone), 4.42 (s, 1H, thiazolidinone), 6.83 (d, 2H , Ar-H), 7.06 (d, 2H, Ar-H), 7.22 (d, 2H, Ar-H), 7.37 (d, 2H, Ar-H).

5b: IR (KBr) cm^{-1}: 1716 (C=O), 1661 (C=N), 1567 (C=C), 682 (C-S). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 3.79 (s, 3H, OCH_3), 3.22-3.34 (m, 2H, thiazolidinone), 4.56 (s, 1H, thiazolidinone), 6.85 (d, 2H, Ar-H), 6.93 (d, 1H, Ar-H). 7.09 (d, 1H, Ar-H), 7.17 (s, 1H, Ar-H), 7.43 (d, 2H, Ar-H).

General procedure for the synthesis of 2-(substituted phenyl)-5-substituted aryl/heteroaryl imidazo(2,1-*b*)-1,3,4-thiadiazoles 6(a-j).

A mixture of 2-amino-5-[substituted phenyl]-1,3,4-thiadiazoles **(3a-c)** (0.03 mole) and α-bromoketones (0.03 mole) in ethanol (150 ml) was refluxed on a wa-



	R	R'
a.	4-OCH_3-C_6H_4	4-Cl-C_6H_4
b.	4-OCH_3-C_6H_4	2,4-Cl-C_6H_4

Scheme-I

ter bath for 10-12 h. Excess of solvent was removed under reduced pressure and the solid hydrobromide separated was filtered, washed with cold ethanol and dried. Neutralization of hydrobromide salts with cold aqueous solution of Na_2CO_3 yielded the corresponding free bases, which was purified by recrystallization from ethanol.

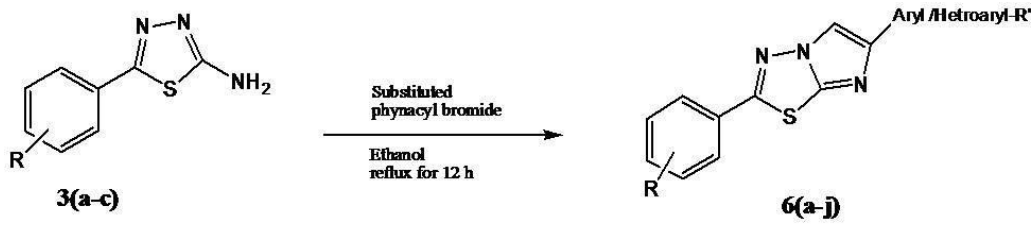
6a: IR (KBr) cm^{-1}: 1725 (C=O), 1605 (C=N), 1558 (C=C). ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 2.35 (s, 3H, CH_3 of tolyl), 7.03 (s, 1H, imidazothiadiazole), 7.1-7.13 (m, 3H, Ar-H), 7.04 (d, 2H, Ar-H), 7.27 (d, 1H, Ar-H), 7.52 (d, 2H, Ar-H), 7.79 (s, 1H, coumarinyl).

6b: IR (KBr) cm^{-1}: 1730 (C=O), 1606 (C=N), 1562 (C=C). ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 7.08 (s, 1H, imidazothiadiazole), 7.1-7.18 (m, 3H, Ar-H), 7.06 (d, 2H, Ar-H), 7.25 (d, 1H, Ar-H), 7.58 (d, 2H, Ar-H), 7.78 (s, 1H, coumarinyl).

6c: IR (KBr) cm^{-1}: 1731 (C=O), 1600 (C=N), 1553 (C=C). ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 6.94 (d, 1H, coumarinyl), 7.11 (s. 1H, imidazothiadiazole), 7.28-7.3 (t, 3H, Ar-H), 7.48 (s, 1H, Ar-H), 7.56 (d, 2H, Ar-H), 7.74 (s, 1H, coumarinyl).

6d: IR (KBr) cm^{-1}: 1594 (C=N), 1567 (C=C), 1513 (C=C). ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 7.11 (s, 1H, imidazothiadiazole), 7.24 (t, 1H, Ar-H), 7.3-7.32 (m, 4H, Ar-H), 7.46 (d, 2H, Ar-H), 7.58 (d, 2H, Ar-H).

6e: IR (KBr) cm^{-1}: 1663 (C=N), 1567 (C=C), 682 (C-S). ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 7.19 (s, 1H, imida-



R	R'
a. 4-CH_3-C_6H_4	$C_9H_5O_2$
b. 4-Cl-C_6H_4	$C_9H_5O_2$
c. 4-Cl-C_6H_4	6-Br-$C_9H_4O_2$
d. 4-Cl-C_6H_4	C_6H_5
e. 4-Cl-C_6H_4	6-Cl-C_6H_4
f. 4-Cl-C_6H_4	6-NO_2- C_6H_4
g. 4-Cl-C_6H_4	7-N(C_2H_5)2-$C_9H_4O_2$
h. 4-Cl-C_6H_4	6,7-Br-$C_9H_3O_2$
i. 4- OCH_3-C_6H_4	$C_9H_5O_2$
j. 4- OCH_3-C_6H_4	6-Br-$C_9H_4O_2$

Scheme-II

Table 1: Physico-chemical data of the synthesized compounds 5(a-b) and 6(a-j)

Compound	Molecular formula	M.P in °C	%Yield	Elemental Analysis Found (Calcd) %		
				C	H	N
5 a	$C_{17}H_{15}OS_2N_2Cl$	204-206	65	50.00 (49.99)	2.72 (2.70)	10.29 (10.27)
5 b	$C_{17}H_{14}S_2N_2Cl_2$	238-240	66	46.11 (46.09)	2.28 (2.26)	9.49 (9.48)
6 a	$C_{20}H_{13}O_2N_3S$	228-230	66	66.84 (66.83)	3.65 (3.63)	11.69 (11.67)
6 b	$C_{19}H_{10}O_2N_3SCl$	242-244	61	60.08 (60.07)	2.65 (2.63)	11.06 (11.04)
6 c	$C_{19}H_9O_2N_3SBrCl$	234-236	68	49.75 (49.73)	1.98 (1.96)	9.16 (9.15)
6 d	$C_{16}H_{10}N_3SCl$	230-232	74	61.64 (61.62)	3.23 (3.22)	13.48 (13.46)
6 e	$C_{16}H_9N_3SCl_2$	246-248	65	55.50 (55.48)	2.62 (2.61)	12.14 (12.13)
6 f	$C_{16}H_9O_2N_4SCl$	274-276	62	53.86 (53.84)	2.54 (2.53)	15.70 (15.68)
6 g	$C_{23}H_{19}O_2N_4SCl$	266-268	78	61.26 (61.24)	4.25 (4.23)	12.42 (12.41)
6 h	$C_{19}H_8O_2N_3SBr_2Cl$	230-232	59	42.45 (42.44)	1.50 (1.48)	7.82 (7.80)
6 i	$C_{20}H_{13}O_3N_3S$	262-264	76	63.99 (63.97)	3.49 (3.47)	11.19 (11.18)
6 j	$C_{20}H_{12}O_3N_3SBr$	216-218	71	52.88 (52.86)	2.66 (2.64)	9.25 (9.24)

zothiadiazole), 7.3- 7.33 (m, 4H, Ar-H), 7.46 (d, 2H, Ar-H), 7.64 (d, 2H, Ar-H),

6f: IR (KBr) cm^{-1}: 1663 (C=N), 1567 (C=C), 682 (C-S). ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 7.1 (s, 1H, imidazothiadiazole), 7.3 (d, 2H, Ar-H), 7.6 (d, 2H, Ar-H), 7.74 (d, 2H, Ar-H), 8.28 (d, 2H, Ar-H).

6g: IR (KBr) cm^{-1}: 1722 (C=O), 1616 (C=N), 1505 (C=C). ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 1.15 (t, 6H, CH_3), 3.41 (q, 4H, CH_2), 6.35 (d, 2H, coumarinyl), 7.16 (s, 1H, imidazothiadiazole), 7.3 (d, 2H, Ar-H), 7.41 (d, 1H, coumarinyl), 7.56 (d, 2H, Ar-H), 7.78 (s, 1H, coumarinyl). Mass; m/z 450.

Table 2: *In vitro* antibacterial activity data of the synthesized compounds 5(a-b) and 6(a-j)

Compound	MIC values (µg ml^{-1})					
	Gram-positive bacteria[a]			Gram-negative bacteria[b]		
	Sa	Sf	Bs	Kp	Ec	Pa
5a	100	>100	50	>100	50	>100
5b	100	50	>100	>100	50	>100
6a	50	>100	>100	>100	50	100
6b	100	50	>100	50	>100	100
6c	50	>100	>100	>100	100	>100
6d	100	50	>100	>100	50	>100
6e	100	100	>100	50	>100	100
6f	50	>100	100	>100	100	>100
6g	50	>100	100	50	100	100
6h	50	>100	100	50	100	>100
6i	50	100	>100	100	>100	>100
6j	100	50	50	>100	100	>100
Ciprofloxacin	<5	<5	≤1	≤1	≤1	>5

[a]Gram-positive bacteria: *Staphylococcus aureus* ATCC 11632 (Sa), *Streptococuus faecalis* ATCC 14506 (Sf), *Bacillus subtilis* ATCC 60511 (Bs);

[b]Gram-negative bacteria: *Klebsiella pneumoniae* ATCC 10031 (Kp), *Escherichia coli* ATCC 10536 (Ec), *Klebsiella pneumoniae* ATCC 10031 (Kp).

Table 3: *In vitro* antifungal activity data of the synthesized compounds 5(a-b) and 6(a-j)

Compound	MIC values (µg ml^{-1})	
	Aspergillus niger (A.niger)	***Penicillium chrysogenum (P. chrysogenum)***
5a	100	>100
5b	100	>100
6a	50	100
6b	100	>100
6c	50	100
6d	>100	>100
6e	100	>100
6f	50	>100
6g	100	>100
6h	100	50
6i	>100	100
6j	50	50
Clotrimazole	<5	<5

6h: IR (KBr) cm^{-1}: 1723 (C=O), 1595 (C=N), 1549 (C=C). ^{1}H NMR (400 MHz, DMSO-d$_6$, δ ppm): 7.14 (s, 1H, imidazothiadiazole), 7.08 (d, 1H, coumarinyl), 7.3-7.33 (m, 3H, Ar-H), 7.6 (d, 2H, Ar-H), 7.72 (s, 1H, Ar-H).

6i: IR (KBr) cm^{-1}: 1738 (C=O), 1604 (C=N), 1567 (C=C). ^{1}H NMR (400 MHz, DMSO-d$_6$, δ ppm): 3.73 (m, 3H, OCH_3), 6.8 (d, 2H, Ar-H), 7.02 (d, 2H, coumarinyl), 7.11 (m, 2H, imidazothiadiazole & Ar-H), 7.32 (d, 1H, coumarinyl), 7.5 (d, 2H, Ar-H), 7.72 (s, 1H, coumarinyl).

6j: IR (KBr) cm^{-1}: 1733 (C=O), 1603 (C=N), 1552 (C=C). ^{1}H NMR (400 MHz, DMSO-d$_6$, δ ppm): 3.7 (m, 3H, OCH_3), 6.7 (d, 2H, Ar-H), 6.91 (d, 1H, coumarinyl), 7.1 (s, 1H, imidazothiadiazole), 7.28 (d, 1H, coumarinyl), 7.44 (s, 1H, coumarinyl), 7.5 (d. 2H, Ar-H), 7.7 (s, 1H, coumarinyl).

CONCLUSION

The antibacterial and anti-fungal activity results of the synthesized compounds reveal that the compounds which are substituted with coumarin moiety showed better activity. Thus the coumarin scaffold influences the pharmacological activity. These results were very encouraging and extended our research in two directions. The first one is to synthesize other derivatives in order to increase their antimicrobial potency. The second one is to carry out more investigations of the synthesized compounds in terms of any possible CNS depressant, anti-tubercular, antiviral, enzyme inhibiting and even anticancer activities. In summary we have identified a novel series of substituted 1,3,4-thiadiazole and imidazo [2,1-b]-1,3,4-thiadiazole derivatives which may develop as potential class of anti-microbial agents.

ACKNOWLEDGEMENT

The authors are thankful to the management and Principal, KLE's College of Pharmacy, Hubli and SET's College of Pharmacy, Dharwad, Karnataka, for providing necessary facilities to carry out this research work. We are also grateful to The Director, SAIF, Punjab University, Chandigarh and The Chairman, USIC, Karnataka University, Dharwad for providing NMR and Mass spectral data.

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