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Original Article

Synthesis and antimicrobial evaluation of 5-aryl-1,3,4-thiadiazole-2-ylamine derivatives

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ABSTRACT

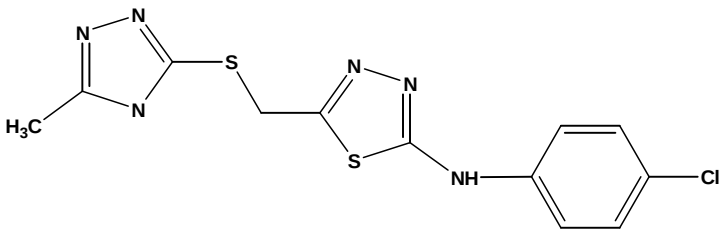
Thiadiazoles occur in nature in four isomeric forms and it contain five membered ring system with two nitrogen and one sulphur atom. In this paper we have synthesized thiadiazole derivatives and confirmed their antimicrobial potential. In literature thiadiazole & their derivatives have been reported as antimicrobial, antiinflammatory, anti-tubercular, antidiabetic, diuretics, antidepressant, and anticonvulsant, anti-HIV & anticancer. Thiadiazoles are prepared with the help of benzoyl chloride and hydrazine and evaluated for antimicrobial activity against gram positive species *Bacillus subtilis, S.pyogenes* and gram negative species *Pseudomonas aeruginosa, Escherichia coli* and for antifungal *Candida albicans, Aspergillus niger* species were used. In synthesized derivatives having substitution with strong electron withdrawing groups has highest activity than electron donating substituted compounds. Trimethoxy and dimethoxy thiadiazole parts have lowest activity than monomethoxy substituted compounds. It may be due to hindrance problem at the binding site. In all cases unsubstituted derivatives have moderate activity due to weak binding with the target site

Keywords: Thiadiazole, antibacterial, antifungal, cytotoxicity.

INTRODUCTION

Thiadiazole is very popular heterocyclic in pharmaceutical field. They occur in nature in four isomeric forms viz. 1, 2, 3- thiadiazole; 1,2,5-thiadiazole; 1,2,4-thiadiazole and 1,3,4-thiadiazole. The Thiadiazole & their derivatives shown the number of pharmacological activity as antimicrobial, antiinflammatory activity, anti-tubercular activity, antidiabetic activity, diuretics, antidepressant & cytotoxic activity. These thiadiazole are the heterocyclic compound which contain the five member ring & nitrogen & sulphur. 1, 3,4-thiadiazoles were conveniently divided into three subclasses**,** one is aromatic systems which include the neutral thiadiazole and constitute a major part of this review. Second is mesoionic systems which is defined as five-membered heterocycles which are not covalent or polar and possess a sextet of electrons in association with the five atoms comprising the ring, and lastly non aromatic systems such as the 1, 3, 4-thiadiazolines and the tetrahydo 1, 3, 4-thiadiazolidines [1].

The synthesis, spectral analysis and antimicrobial evaluation of a novel series of substituted 1,2,4-triazole and 1,3,4-thiadiazole derivatives was carried out by the reaction of acyl thiosemicarbazide derivatives in the presence of alkaline and acidic media. The potential activity of the following compound against Gram-positive bacteria and showed good activity especially against: *Micrococcus luteus*, *Bacillus subtilis* and *Staphylococcus aureus* [2].



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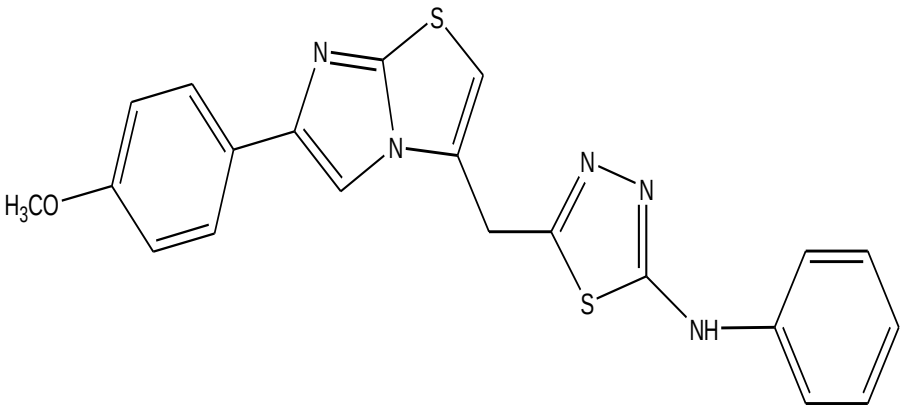
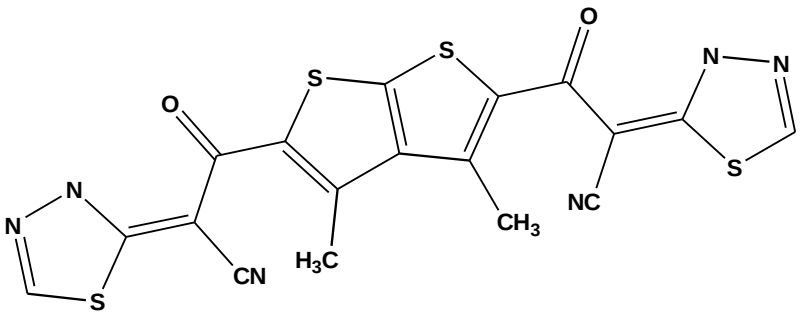
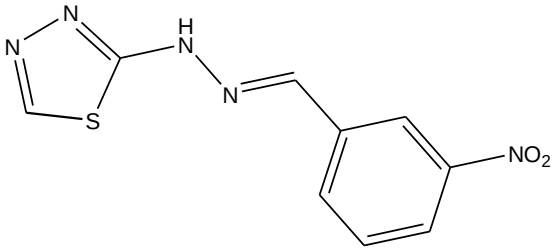
In this work a new compound series of thidiazole was synthesized and evaluated for antibacterial and antifungal activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Candida albicans*, *C. parapsilosis*, *C. krusei*, *Trichophyton mentagrophytes var. erinacei*, *Microsporum gypseum* and *T. tonsurans* [3].



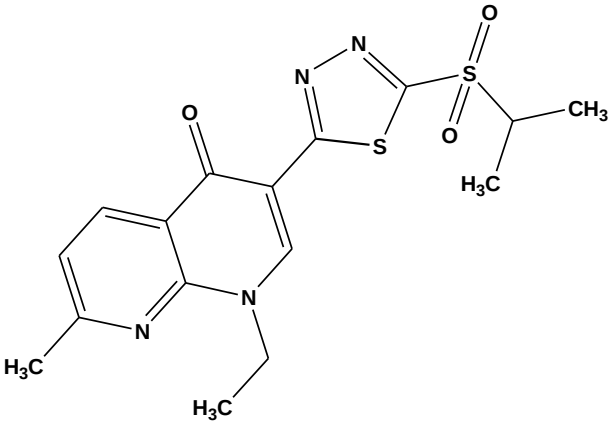
3,3'-(3,4-dimethylthieno[2,3-*b*]thiophene-2,5-diyl) bis (3-oxopropanenitrile) was used as synthetic utility for the synthesis of some novel bis-[1,3,4-thiadiazole] and bis-thiazole and derivatives with thieno[2,3]thiophene moiety was reported with promising results [4].



Synthesis of a series of new hydrazone derivatives of 2-hydrazinyl-1,3,4- thiadiazole was done and screening of the derivatives was done for their potential antimycobacterial activity and the following compound was found to be the most active compound [5].

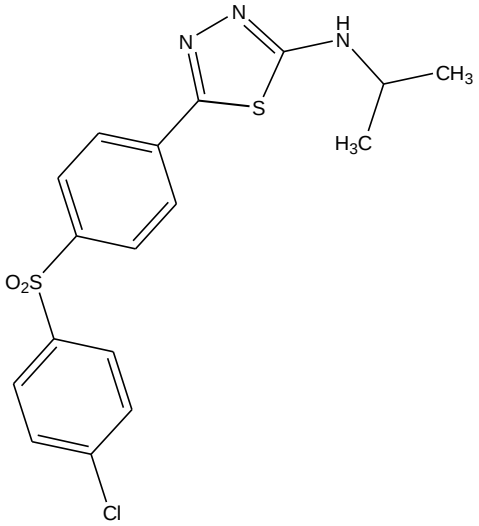


Evalaution of the following synthesized compound was done for their antibacterial activity against two Gram-positive and three Gram-negative bacteria. The most of the compounds had better antibacterial activity than the parent compounds, 1,3,4-thia(oxa)diazoles was shown by preliminary bioassay against *Bacillus subtilis*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* with minimum inhibitory concentration [6].

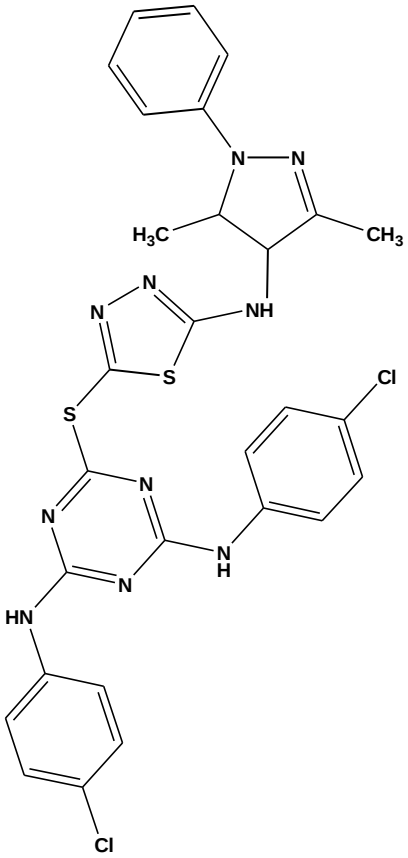


Intramolecular cyclization of acyl thiosemicarbazide synthesize1,2,4- triazoles, in basic media. On contrast, 1,3,4-thiadiazoles were also obtained from same acyl thiosemicarbazides, in acidic media. These novel intermediates from thiosemicarbazide class were obtained by the

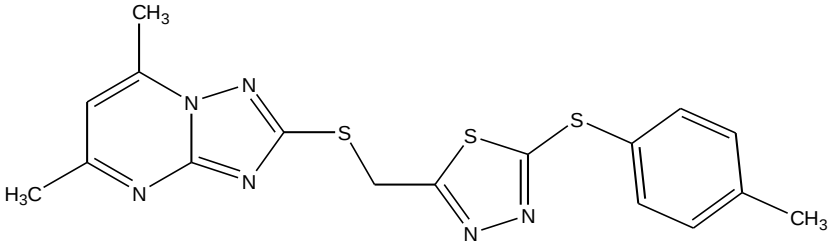
reaction of 4-(4-X-phenylsulfonyl) benzoic acids hydrazides (X, H, Br) with 4-trifluoromethoxyphenyl or 3,4,5- trimethoxyphenyl isothiocyanate. Screening of all the new compounds was done for their antimicrobial activity against some bacteria (*Staphylococcus aureus, Bacillus cereus, Escherichia coli, Enterobacter cloacae, Acinetobacter baumannii and Pseudomonas aeruginosa* and yeasts (*Candida albicans and Candida parapsilosis*) [7].



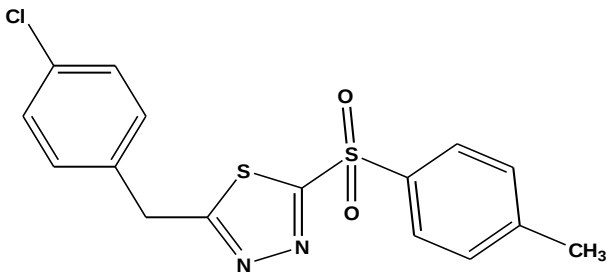
Synthesis and Characterization of some hybrid 1,3,4-thiadiazole-1,3,5-triazine derivatives was done and evaluated for their antibacterial activity against selected Gram-positive and Gram negative bacteria. Terget compounds presented Excellent to moderate antibacterial activity [8].



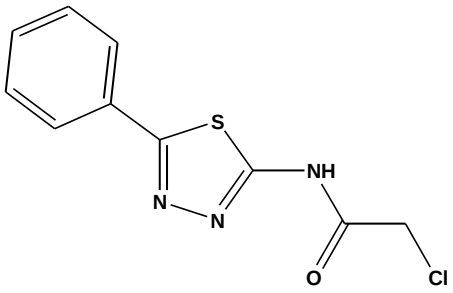
Synthesis of a series of new 1,3,4-thiadiazole derivatives bearing 1,2,4-triazolo pyrimidine moiety was done by the method of splicing active substructures. The following compound was reported highest activity among all the compounds. Assay of all the compounds was performed for antimicrobial activities against five fungi strains and four bacteria strains [9].



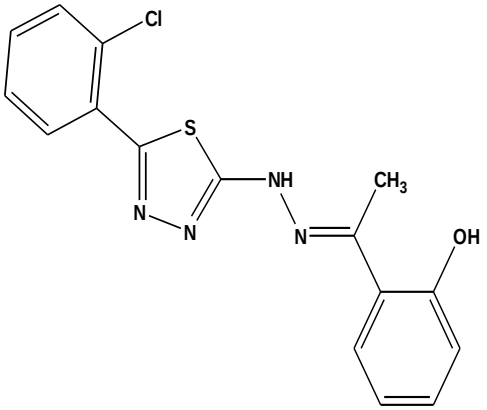
Synthesis of a series of 2,5-substituted-1,3,4-oxadiazole/thiadiazole sulfone derivatives was done and evaluation was done for their antibacterial activities against rice bacterial leaf blight and leaf streak caused by *Xanthomonas oryzae pv. oryzae and Xanthomonas oryzae pv. oryzicolaby* via the turbidimeter test in vitro [10].



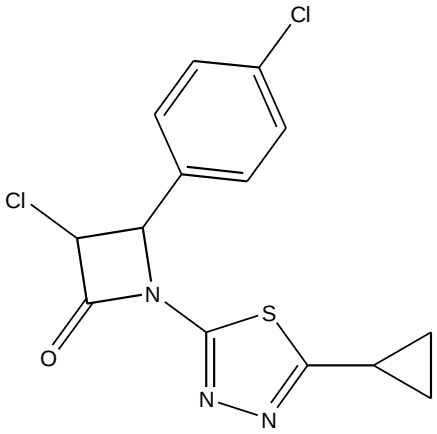
All the synthesized chitosan derivatives, the growth of the tested phytopathogens were inhibited most effectively by the following compound with inhibitory indices against *Colletotrichum lagenarium.* It is hypothesized that obviously better antifungal activity and good solubility in water was possessed by thiadiazole groups enable the synthesized chitosan [10].



Synthesis of Zn (II) complexes have been done by reacting zinc acetate with schiff bases and screening of all these Schiff bases and their complexes have also been done for their antibacterial (Bacillus *subtilis (B. subtilis), Escherichia coli (E. coli*) and antifungal activities (*Colletotrichum falcatum (C. falcatum), Aspergillus niger (A. niger), Fusarium oxysporium (F. oxysporium) Curvularia pallescence (C. pallescence*) [11].



In an attempt to obtain a novel class of antimicrobial agents, synthesis of a series of novel azetidin-2-ones and thiazolidin-4-ones of 2-amino-5-cyclopropyl-1,3,4-thiadiazole was done and this series displayed excellent antibacterial activities against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli, and Pseudomonas aeruginosa* [11].



EXPERIMENTAL

All synthesis reactions were monitored by thin layer chromatography (TLC) using silica gel G and the plates were developed by exposing to iodine chamber. ^{13}C NMR was recorded using DMSO solvent and Proton nuclear magnetic resonance spectra (^{1}H NMR) was recorded with DMSO as a solvent and TMS as an internal standard. ^{1}H NMR spectra was reported as chemical shift in δ values (ppm). IR spectra was recorded using KBr pellets and. Melting points (m.p.) were determined by decibel melting point apparatus and were uncorrected.

Synthesis of 5-aryl-[1,3,4] thiadiazole-2-ylamine derivatives: At the starting sufficient quantity of thionyl chloride was added to substituted benzoic acid and mixture was refluxed for 3 hrs and substituted benzoyl chloride was obtained after recrystallization with ethanol. Then this substituted benzoyl chloride was added in methanol and hydrazine hydrate. This mixture was refluxed for 1 hr, then the reaction mixture was cooled at room temperature and precipitates was collected and washed with distilled water for two to three times. This substituted benzoyl hydrazide, ammonium thiocyanate, hydrochloric acid and ethanol were refluxed for 4 hrs. The white solid appeared on cooling was filtered and recrystallized with ethanol to give pure crystals. These crystals were dissolved in ethanol and conc. sulphuric acid was refluxed for 4 hrs. Then, the solution was filtered and recrystallized with ethanol to give 5-aryl-1,3,4-thiadiazole-2-ylamine.

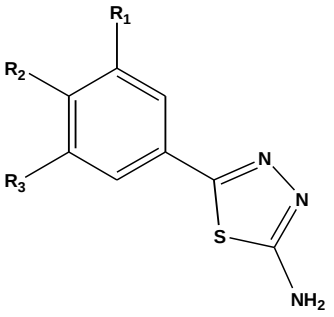


Fig.:5-aryl-1,3,4-thiadiazole-2-ylamine.

Table: Physicochemical properties of synthesized derivatives

Comp.	-R_1	-R_2	-R_3	Mol. Formla	Mol. wt.	IUPAC	M.P. (^{0}C)	R_f	% yield
a	-H	-OCH_3	-H	$C_9H_9N_3OS$	207.25	5-(4-Methoxyphenyl)-1,3,4-thiadiazole-2-ylamine	140-142	0.59	66
b	-OCH_3	-H	-OCH_3	$C_{10}H_{11}N_3O_2S$	225.75	5-(3,5-Dimethoxyphenyl)-1,3,4-thiadiazole-2-ylamine	124-126	0.52	60
c	-OCH_3	-OCH_3	-OCH_3	$C_{11}H_{13}N_3O_3S$	244.15	5-(3,4,5-Trimethoxyphenyl)-1,3,4-thiadiazole-2-ylamine	132-134	0.72	65
d	-H	-OH	-H	$C_8H_7N_3OS$	193.15	5-(4-Hydroxyphenyl)-1,3,4-thiadiazole-2-ylamine	124-126	0.66	78
e	-H	-NH_2	-H	$C_8H_8N_4S$	192.21	5-(4-Aminophenyl)-1,3,4-thiadiazole-2-ylamine	162-164	0.74	60
f	-H	-NO_2	-H	$C_8H_6N_4O_2S$	222.71	5-(4-Nitrophenyl)-1,3,4-thiadiazole-2-ylamine	151-154	0.65	65
g	-NO_2	-H	-NO_2	$C_8H_5N_5O_4S$	268.11	5-(3,5-Dinitrophenyl)-1,3,4-thiadiazole-2-ylamine	126-128	0.58	76
h	-H	-Cl	-H	$C_8H_6ClN_3S$	210.75	5-(4-Chlorophenyl)-1,3,4-thiadiazole-2-ylamine	138-140	0.54	64
i	-Cl	-H	-Cl	$C_8H_5Cl_2N_3S$	244.41	5-(3,5-Dichlorophenyl)-1,3,4-thiadiazole-2-ylamine	130-132	0.70	63
j	-H	-H	-H	$C_8H_7N_3S$	176.52	5-Phenyl-1,3,4-thiadiazole-2-ylamine	124-126	0.64	72

Antimicrobial activity: For antibacterial studies micro-organisms employed were gram positive species *Bacillus subtilis, S.pyogenes* and gram negative species *Pseudomonas aeruginosa, Escherichia coli* and for antifungal *Candida albicans, Aspergillus niger* species were used. Test solutions of synthesized compounds and standard drug amoxicillin (antibacterial) and fluconazole (antifungal) were prepared in DMSO to get a concentration of 100 µg/ml. Antimicrobial activity was done by Agar Diffusion method. For bacterial growth nutrient agar media was used having composition beef extract, 3 g; bacteriological peptones, 5 g; agar, 20 g; the pH was adjusted to 6.2±0.2. For fungal growth Saubaurd Dextrose media was used composed of dextrose, 40 g; bacteriological peptone, 10 g; agar, 15 g, the pH was adjusted to 5.6±0.2. Media was prepared by dissolving the all ingredients in 1L distilled water and heated up to 60-70 °C and was sterilized in an autoclave at 121 °C for 15-20 min. Against the several species the antibacterial and antifungal activity was expressed by the measurement of zone of inhibition by diffusion agar method. The synthesized compounds were dissolved in DMSO to obtain 80 µg/ml concentration of each compound. Controlled holes were filled with only DMSO solvent. Bacterial plates were placed in BOD at 37 °C ± 2 °C and fungal plates were incubated at 28°C ± 2°C for 24-48 hrs. Zone of inhibition created by active compounds were measured after 24-48 hrs. Amoxicillin was used as standard antibacterial agent while fluconazole was used as a standard antifungal agent.

RESULTS AND DISCUSSIONS

All thiadiazole derivatives were synthesized efficiently and purified by appropriate methods. Many derivatives showed antimicrobial potential near to standard drugs as shown in the following table. Amoxicillin drug was used as a standard for antibacterial and Fluconazole for antifungal activity.

Table: *In vitro* antimicrobial activity of synthesized compounds against bacterial and fungal strains

Comp.	Zone of inhibition (mm)					
	Bacterial strain Gram positive		**Bacterial strain Gram negative**		**Fungal strain**	
	***B.subtilis* (MTCC 1133)**	***S.pyogenes* (MTCC 442)**	***P.aeruginosa* (MTCC 1688)**	***E.coli* (MTCC 1575)**	***C.albicans* (MTCC 4748)**	***A.niger* (MTCC 872)**
a	17±0.48	19±0.73	19±0.83	19±0.55	18±0.33	17±0.35
b	20±0.49	21±0.64	20±0.86	19±0.52	20±0.75	18±0.45
c	19±0.41	20±0.41	19±0.64	18±0.64	19±0.37	17±0.45
d	17±0.49	17±0.62	15±0.49	15±0.69	17±0.48	16±0.43
e	17±0.51	18±0.41	16±0.64	16±0.69	19±0.49	17±0.61
f	24±0.50	25±0.49	25±0.59	24±0.54	24±0.47	23±0.68
g	27±0.12	26±0.42	26±0.57	26±0.15	25±0.38	25±0.02
h	27±0.52	27±0.49	27±0.51	26±0.55	25±0.58	25±0.52
i	28±0.62	28±0.57	28±0.57	27±0.43	26±0.54	26±0.54
j	21±0.49	22±0.62	21±0.49	20±0.69	20±0.48	21±0.43
Amoxicillin	29±0.24	29±0.12	30±0.37	29±0.32	-	-
Fluconazole	-	-	-	-	28±0.37	28±0.62
Control	-	-	-	-	-	-

(Values are expressed as mean±S.D.)

Conclusion: In all synthesized thiadiazole derivatives, those derivatives having substitution with strong electron withdrawing groups have highest activity than electron donating substituted compounds. Trimethoxy and dimethoxy thiadiazole parts have lowest activity than monomethoxy substituted compounds. It may be due to hindrance problem at the binding site. In all cases unsubstituted derivatives have moderate activity due to moderate binding with the target site. So in the synthesized derivatives some compounds showed very good activity and in future their toxicity and stability study will be performed.

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