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RESEARCH ARTICLE

SYNTHESIS, CHARECTERIZATION AND BIOLOGICAL EVALUATION OF SOME NOVEL THIADIAZOLES ANALOGS AS THEIR SCHIFF BASES

Kommana Balaram Kumar[1]*, B. Aparna devi[2], Ch. Jasmitha[3], G. Moulika[4] M. Satya Sri[5], Sk. Sania[6], T. Usha Rani[7] and T. Vinay Siva ram[8]

[1*]Professor, Srinivasarao college of Pharmacy, P.M. Palem, Visakhapatnam-530041, Andhra Pradesh India
[2,3,4,5,6,7,8]Srinivasarao college of Pharmacy, P.M. Palem, Visakhapatnam-530041, Andhra Pradesh India

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**Corresponding author:*
Kommana Balaram Kumar

ABSTRACT

Thiadiazoles and their derivatives demonstrate a broad spectrum of biological activities, including antibacterial, antifungal, antitubercular, antidiabetic, anti-inflammatory, anti-convulsant, and diuretic effects. In this research, several new series of 1,3,4-Thiadiazole Schiff bases were synthesized from benzoic acid reacted with thiosemicarbazide, resulting in the formation of the 5-(3-nitrophenyl)-1,3,4-thiadiazol-2-amine derivative. The free amine group at the second position of this product was altered into various Schiff bases by reacting it with diverse aromatic aldehydes to obtain the target compound. The compounds' purity was determined through TLC and enhanced via recrystallization and column chromatography. The structures were established using IR, 1H NMR, and mass spectral information. 5-(3-nitrophenyl)-1,3,4-thiadiazole -2 -amine-Schiff basesanalogues were evaluated for their antibacterial (Escherichia coli ATCC 25922) properties using the cup plate method and antitubercular activity through MABA (MicroplateAlamar Blue assay) on the H37Rv strain of Mycobacterium tuberculosis

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INTRODUCTION

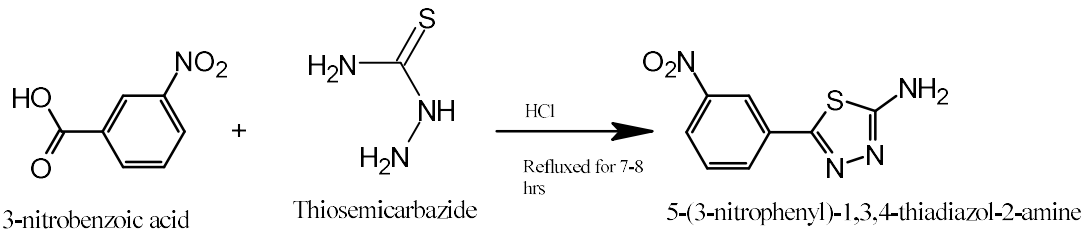
Tuberculosis presents a significant problem in public health due to Mycobacterium tuberculosis strains (1) (2). During the 1980s, tuberculosis was managed through standard treatment provided by the medications available at that time (3) (4). Over time, as HIV (Human Immunodeficiency Virus) developed in various regions globally, a significant rise in concurrent multidrug-resistant tuberculosis has occurred (5)(6)(7)(8). This has resulted in a major surge of extensively drug-resistant TB (9)(10)(11). India is a severe victim of TB, accounting for 27 percent of the globally affected TB-prone areas (12)(13)(14). Various imaging methods, diagnostic evaluations, culture procedures, and drug susceptibility testing (DST) exist to determine the stages of TB (15)(16)(17)(18). Researchers encounter numerous difficulties in discovering various drug combinations or active potential compounds for the prevention and management of TB. Additionally, drug-drug interactions and side effects from these combination medications also present a significant issue. Thiadiazoles have emerged as a key resource for researchers as a possible lead compound for TB management. Thiadiazole is a multifaceted heterocyclic component with various pharmacological effects including antibacterial (19), antifungal (20), antitubercular (21), antidiabetic (22), anti-inflammatory (23), anti-convulsant (24), and diuretic (25), among others. The literature mentioned above has led us to synthesize various aryl substituted thiadiazoles, which are then evaluated for biological activity. Their chemical compositions are validated by IR and 1H NMR

Objective

A collection of oxadiazoles, triazines, esters, and their hydrazide derivatives synthesized from carboxylic acids exhibited notable anti-TB and various antimicrobial properties. The antimicrobial properties of these compound classes prompted us to synthesize thiadiazole Schiff bases, which are derivatives of carboxylic acids. The review of literature shows that thiadiazoles exhibited numerous biological effects, including antiproliferative, antiviral, antimicrobial, anticancer, inactivation of prostaglandin endoperoxide synthase, inhibition of monoglyceride lipase, and antileukemic properties. We synthesized several Thiadiazole Schiff base derivatives from benzoic acid (aryl carboxylic acid) and evaluated their antimicrobial and antitubercular activities

MATERIALS AND METHODS

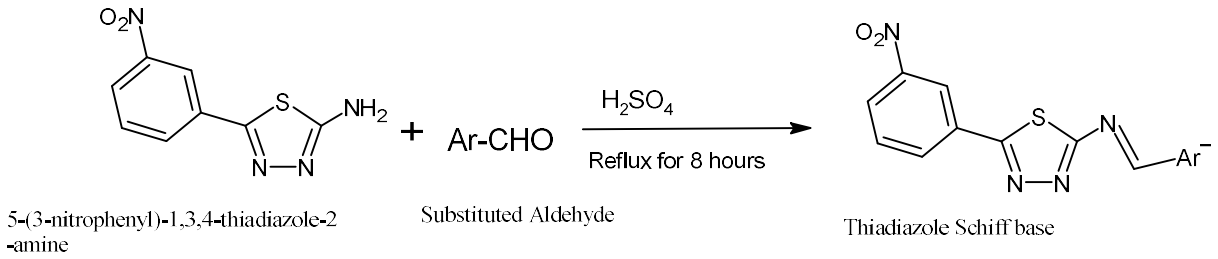
Synthesis of 5-(3-nitrophenyl)-1,3,4-thiadiazol-2-amine: In a round bottomed flask A mixture of equimolar quantities of Thiosemicarbazide (0.01mol,0.91gm) and corresponding 3-nitro benzoic acid (0.01mol,1.22gm) were taken in a clean and dry round bottomed flask in 25 ml methanol to which HCl (8ml) was added drop wise intot he reaction mass with constant stirring and later transferred the reaction mass on to the heating mantle and refluxed for 7-8 hours. The progress of the reaction was monitored through TLC. Excess of methanol was evaporated and the resulting reaction mass was poured on to the crushed ice to obtain yellowish product which is filtered washed with cold water and left for drying and the obtained solid is re-crystallised using ethanol/methanol.



Scheme. General scheme of Synthesis of 5-(3-nitrophenyl)-1,3,4-thiadiazol-2-amine

Synthesis of 5-(3-nitrophenyl)-1,3,4-thiadiazole -2 -amine-Schiff bases

In a round bottomed flask A mixture of equimolar quantities of 5-(3-nitrophenyl)-1,3,4-thiadiazole -2 -amine (0.005mol) and aldehydes (0.005mol) were taken in 25 ml methanol to which 5ml of H_2SO_4 were added and refluxed for 8 hours. The progress of the reaction was monitored through TLC. Excess of methanol was evaporated and the resulting reaction mass was poured on to the crushed ice to obtain dusk to brown colour product which is filtered washed with cold water and left for drying and the obtained solid is re-crystallised using ethanol/methanol.



Scheme. General scheme of Synthesis of5-(3-nitrophenyl)-1,3,4-thiadiazole -2 -amine-Schiff bases

Table I. Different Corresponding Aryl Aldehydes used

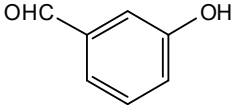
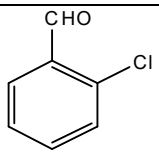
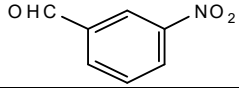
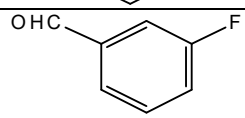
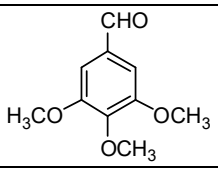
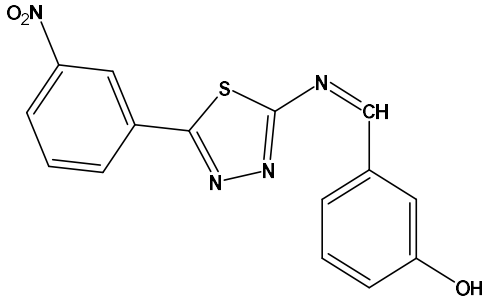
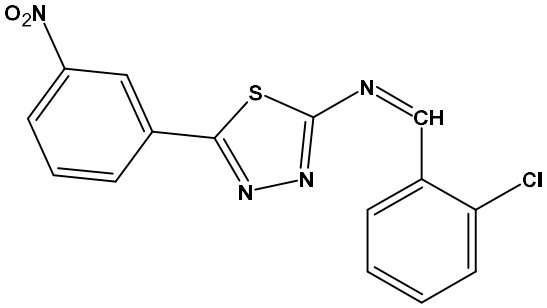
COMPOUND CODE	CORRESPONDING ALDEHYDE	IUPAC NAME OF CORRESPONDING ALDEHYDE
TSB-1		3-hydroxybenzaldehyde
TSB-2		2- Chlorobenzaldehyde
TSB-3		3-Nitrobenzaldehyde
TSB-4		3-fluorobenzaldehyde
TSB-5		3,4,5-trimethoxybenzaldehyde

Table II. List of Thiadiazole Schiff Bases Synthesized

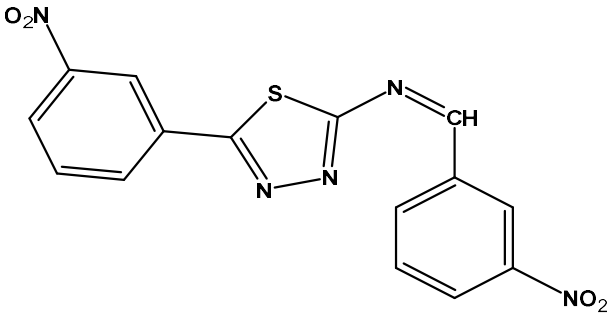
Compound code	IUPAC Name
TSB-1	3-((5-(3-nitrophenyl)-1,3,4-thiadiazol-2-ylimino)methyl)phenol
TSB-2	N-(2-chlorobenzylidene)-5-(3-nitrophenyl)-1,3,4-thiadiazol-2-amine
TSB-3	N-(3-nitrobenzylidene)- 5-(3-nitrophenyl)-1,3,4-thiadiazol-2-amine
TSB-4	N-(3-fluorobenzylidene)- 5-(3-nitrophenyl)-1,3,4-thiadiazol-2-amine
TSB-5	N-(3,4,5-trimethoxybenzylidene)- 5-(3-nitrophenyl)-1,3,4-thiadiazol-2-amine



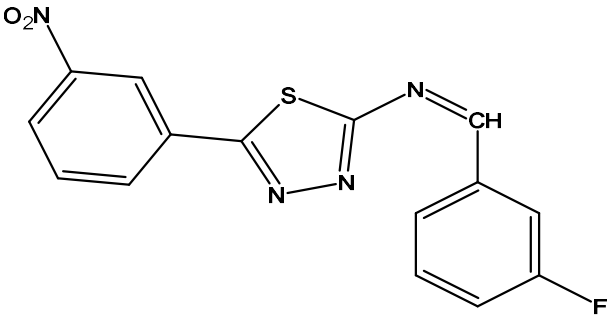
TSB-1



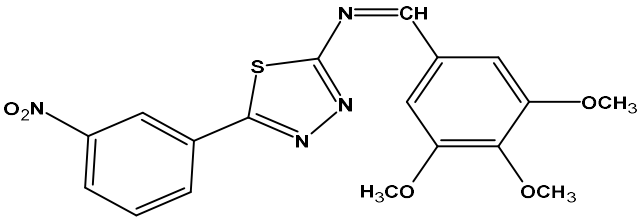
TSB-2



TSB-3



TSB-4



TSB-5

Fig. 1. List of Synthesized Compounds

Table III-Physical characteristics of synthesizedthiadiazoleschiff bases

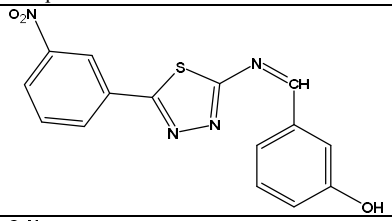
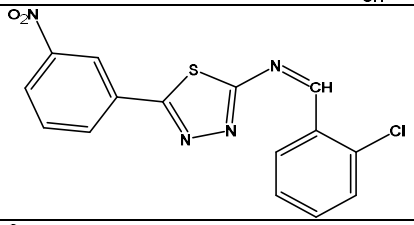
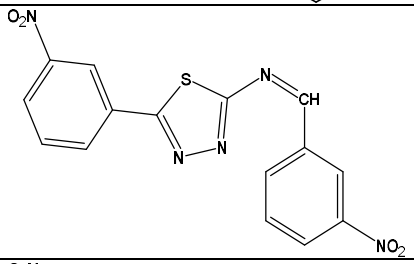
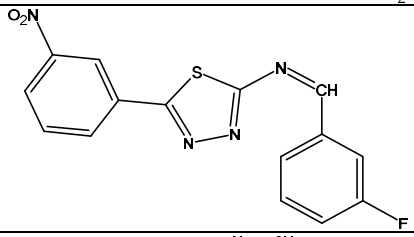
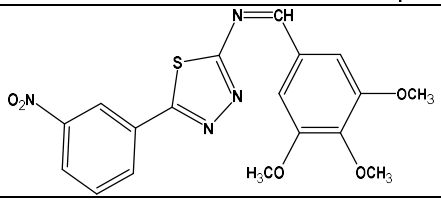
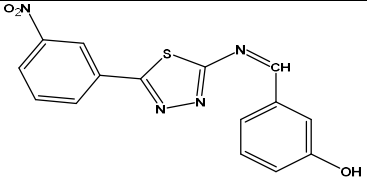
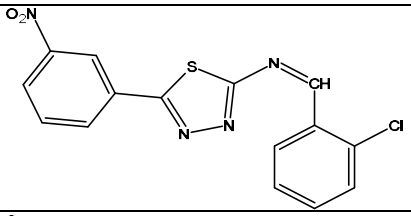
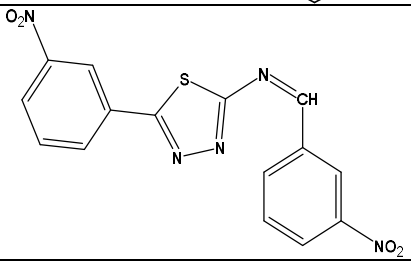
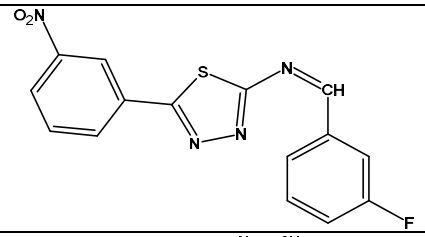
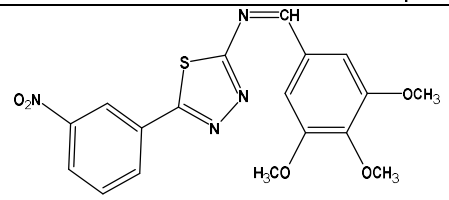
S.No	Compound	Relative molecular mass	Melting point	% Yeild
1		326.3	211ºC	20%
2		344.8	138ºC	33%
3		355.3	193ºC	63%
4		328.3	193ºC	13%
5		400.4	204ºC	55%

Table IV. Spectral Data Of The Synthesized Compounds

S.No	Compound	IR(cm^{-1})	^{1}H NMR(δ ppm) 400 MHz
1		N=O str,Ar-NO_2 1522cm^{-1} (stretch),1353cm^{-1} (stretch); C=N imines1622cm^{-1} ; C-S-C cyclic 730cm^{-1} ; C-H Aromatic 3085;C=C Aromatic 1473cm^{-1}	O-H str (3129); C-O str (1230); C=N (1618); C-S (583.90); C=C (1572); C-H oop bending (782)
2		OH 3129; C-S 782cm^{-1} ; C=N imine1618cm^{-1} ;C-H Ar 2929cm^{-1} ;C=C Ar 1435cm^{-1} ;C=N 1575cm^{-1}	C-Clstr (750); C=N (1684); C=C (1465); C-H (724); C-S (641)
3		C-Cl 750cm^{-1} ; C-S 740cm^{-1} ; C=N imine1652cm^{-1} ;C-H Ar 2929cm^{-1} ;C=C Ar 1435cm^{-1} ;C=N 1614cm^{-1}	N=O (1522.34,1353.17); C=N (1622.91); C-S (670); C=C (1437); C-H str (3085.02) C-H bending (735.03)

Continue ….

4		C-F 1280cm^{-1}, C-S 782cm^{-1}, C=N imine 1702cm^{-1}, C-H Ar3150-3050cm^{-1}, C=C Ar 1451cm^{-1}, C=N Cyclic 1615cm^{-1}	C-F(1268.23); C=N (1615.33); C-S (679.00); C=C (1451.62); C-H str(3066.82) C-H bending(782.94)
5		C=N Imine1652;C-S 753;C=N Cyclic 1595 ;C-H Ar 3102; C=C Ar 1542 ;C-N Ar 1360	C-O str(1329.27,1125.78); C=N (1684.2); C-S (632.62); C=C (1617.89); C-H str (3168.31) C-H bending (834.42)

Biological Evaluation

Antibacterial activity: All synthesized Schiff base derivatives of 5-(3-nitrophenyl)-1,3,4-thiadiazole -2 -amine-Schiff bases were tested for their antibacterial properties. In antibacterial research, the microorganisms used included the Gram positive Staphylococcus aureus (ATCC 9144) and the Gram negative Escherichia coli (ATCC 25922). Both microbial studies were evaluated using the Cup-Plate method. This approach relies on assessing antibiotic efficacy by measuring the diameter of inhibition zones around the cylinders (cups) that hold different dilutions of standard and test substances.

Table V: Antibacterial Activity of the Synthesized compounds.

S.No	Compounds	Zone of inhibition in mm			
		BACTERIA			
		S.aureus (Gram +ve)		*E.coli (Gram -ve)*	
		100 µg	**50 µg**	**100 µg**	**50 µg**
1	TSB-1	12	10	10	9
2	TSB-2	9	2	7	7
3	TSB-3	2	3	2	2
4	TSB-4	3	3	4	2
5	TSB-5	9	2	2	2
6	Rifampacin	20	-	20	-
7	Control	-	-	-	-

Antitubercular activity

Micro plate Alamar Blue Assay (MABA): The MABA method was utilized as the analytical method to assess the antitubercular activity of the synthesized compounds. In summary, 200µl of sterile deionized water was placed in all outer perimeter wells of a sterile 96-well plate to reduce evaporation of the medium in the test wells during incubation. A 96-well plate was provided with 100 µl of Middlebrook 7H9 broth, and serial dilutions of compounds were conducted directly on the plate. The last drug concentrations examined were 100 to 0.2 µg/ml. Plates were covered and sealed with Para film, then incubated at 37ºC for five days. Following this period, 25µl of a freshly made 1:1 blend of Alamar Blue reagent and 10% Tween 80 was added to the plate and incubated for 24 hours. A blue hue in the well signified absence of bacterial growth, while a pink hue indicated growth. The MIC was established as the minimal drug concentration that inhibited the color change from pink to blue. The effectiveness of the compounds was assessed by conducting the procedure again using the standard first-line medications

TABLE VI: AntitubercularActivity Results

S No	Sample	100 µg/ml	50 µg/ml	25 µg/ml	12.5 µg/ml	6.25 µg/ml	3.12 µg/ml	1.6 µg/ml	0.8 µg/ml
1	TSB-1	S	S	S	S	R	R	R	R
2	TSB-1	S	R	R	R	R	R	R	R
3	TSB-1	S	S	R	R	R	R	R	R
4	TSB-1	R	R	R	R	R	R	R	R
5	TSB-1	S	R	R	R	R	R	R	R
10	Pyrazinamide	S	S	S	S	S	S	R	R
11	Streptomycin	S	S	S	S	S	R	R	R
12	Ciprofloxacin	S	S	S	S	S	S	R	R

S: Sensitive
R: Resistance
Strain used: *M.tuberculosis*(H37 RV strain)
Standard valuesfor the Anti-Tb test which was performed.
Pyrazinamide- 3.125µg/ml
Streptomycin- 6.25µg/ml
Ciprofloxacin-3.125µg/ml

RESULTS AND DISCUSSIONS

All the synthesized compounds tested for antibacterial activity (Cup plate method) showed significant activity against gram positive and gram negative bacteria. Among the series of 5schiffs bases synthesized with aryl aldehydesubstitution showed enhanced potency on both gram positive and gram negative bacteria when compared with the standard Rifampicin in the series the potency of the synthesized compounds comparatively less in action. Anti tubercular activity of the above series also showed significant results when compared with that of the standard. Schiffs bases with phenolic OH on the aryl aldehydes showed moderate to potent activity against *mycobacterium.* All the synthesized 5-(3-nitrophenyl)-1,3,4-thiadiazole -2 -amine-Schiff basesshowed activity against antimicrobial and antimycobacterial agents but all the compounds showed less activity than that of the standard used for screening.

CONCLUSION

Thiadiazoleschiff basesshowed moderate to potent activity against bacterial species. The activity may be attributed the cell wall synthesis inhibition. Presence of phenolic hydroxyl group may increase the penetration through some of the specialized channels (polar porin channels) present in gram negative bacteria. So both electron withdrawing and electron donating groups are equally important in these synthesized schiff bases. Compounds with electron withdrawing groups on aryl aldehyde showed challenging activity.Antiotubercular activity of the compound may be attributed to inhibition of cell wall component (Mycolic acid) synthesis.

Future prospective: Pharmacological investigation of the synthesized schiff bases has to be briefly studied. Thiadiazole is a versatile moiety so the free amino group can be modified into various heterocyclic derivatives and explored for their pharmacological actions. Future researchers have to lay an eagles eye on modification of different carboxylic acids into many thiadiazoles and their respective derivatives.

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