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## RESEARCH ARTICLE

# SYNTHESIS, CHARECTERIZATION AND BIOLOGICAL EVALUATION OF SOME 1, 3 and 4-THIADIAZOLES SCHIFF BASES

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**ABSTRACT**

Thiadiazoles and their analogues exhibit a wide variety of biological activities like antibacterial, antifungal, antitubercular, antidiabetic, anti-inflammatory, anti-convulsant, diuretic etc., In the present research work, some new series of 1,3,4- Thiadiazoles Schiffs bases were synthesized from Benzoic acid treated with thiosemicarbazide to form 2-amino-5-phenyl-1,3,4-thiadiazole derivative, the free amine group at the second position of the formed product was modified into various Schiffs bases by treating with different aromatic aldehydes to obtain the desired entity. The purity of the compounds was identified by TLC and purified by recrystallization and column chromatography. The structures were determined by IR, $^1$H NMR and Mass spectral data. 2-amino-5-phenyl-1, 3, 4-thiadiazole Schiff base analogues were screened for their antibacterial (*Escherichia coli* ATCC 25922), antifungal (*Aspergillus niger* ATCC 9029) by disc plate technique and antitubercular activity by use of MABA (Microplate Alamar Blue assay) analytical method on H37Rv strain of *Mycobacterium tuberculosis*. Based on the results shown by the synthesized compounds, all showed significant antimicrobial and antifungal activity activity. The mechanism of action of the compounds can be implicated for their cell wall disruption by inhibiting the peptidoglycon synthesis as potential antimicrobial agent or inhibiting the synthesis of mycolic acid as potential antitubercular agent.



**Citation: Siddhanadham Arun Satyadev, Sowmya Mantha, Surendra Babu and Prashanth Varanasi, 2016.** "Synthesis, charecterization and biological evaluation of some 1, 3 and 4- Thiadiazoles schiff bases", *International Journal of Current Research*, 8, (08), 36100-36106.

## INTRODUCTION

Tuberculosis is a major issue in the public health sector caused by *Mycobacterium tuberculosis* isolates (Dubos and Dubos, 1952; Waksman, 1964). In the past 1980s tuberculosis was controlled with help of standard therapy carried out by the drugs at that time (Keers, 1978; Sakula and Robert Koch, 1982). During the course of time as HIV (Human Immunodeficiency Virus) evolved in many parts of the world leading to wide spread of concurrent multidrug resistant tuberculosis has emerged (Sharma *et al*., 2005; Padmapriyadarsini *et al*., 2011; Paw *et al*., 2012; Whalen *et al*., 1995). Which caused a major outbreak of extensive drug resistant TB (WHO, 2012; Chadha *et al*., 2005; Chadha *et al*., 2013). India is also a brutal victim to TB contributing to 27 per cent to the globally effected TB prone zones (Seibert *et al*., 1991; Escudero Bueno *et al*., 1990; Gopi *et al*., 2007).

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There are several imaging techniques, diagnostic tests, culture techniques and drug susceptibility testing (DST) to find out stages of TB (Sharma *et al*., 2001; Bhusari *et al*., 2008; Basawaraj *et al*., 2005; Om Prakash *et al*., 2009). Scientists face a lot of challenges in finding out different drug combinations or active potential moiety to the prevention and control of TB. Moreover drug- drug interactions, side effects caused by these combinational drugs also cause a major problem. Thaidiazoles has become one of the major tools for researchers as a potential lead molecule for the control of TB. Thiadiazole is a versatile heterocyclic moiety with diversified pharmacological actions such as antibacterial (Kumar *et al*., 2009), antifungal (Kittur *et al*., 2009), antitubercular (El-Hamouly *et al*., 2006), antidiabetic (Shikha and Anjali, 2009), anti-inflammatory (Bhuva *et al*., 2011), anti-convulsant (Gupta *et al*., 2010), diuretic (Collins *et al*., 1997) etc., The above stated literature have provoked us to synthesize different aryl substituted thiadiazoles and which are screened for biological activity. Their chemical structures are confirmed by IR, $^1$H NMR. These synthesized compounds are tested for their antimicrobial, antifungal (by the use of Disc diffusion method) and antimycobacterial activity (Microplate Alamar Blue Assay)

(Collins *et al*., 1997) Analytical method on H37Rv strain of *M.tuberculosis.*

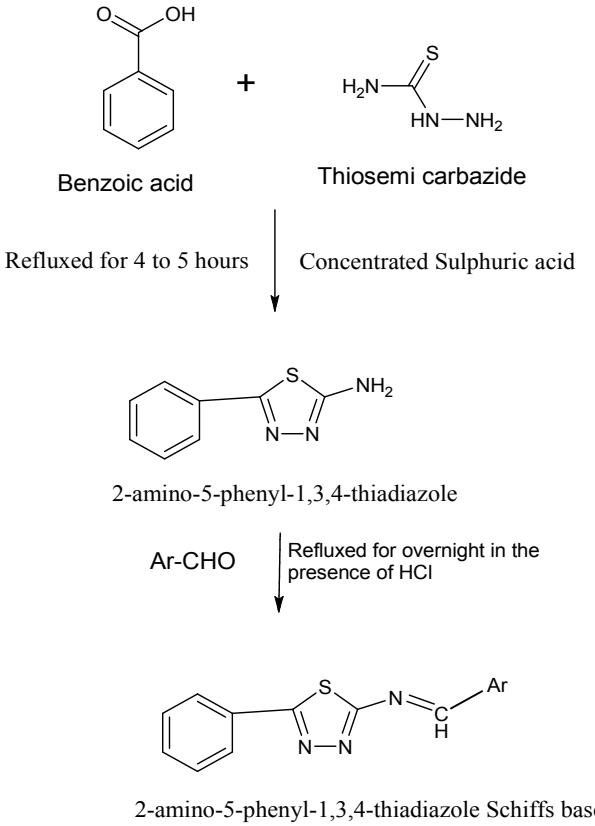
**Objective**

A series of oxadiazoles, triazines, esters and their hydrazide derivatives which were synthesized from carboxylic acids, interestingly possessed anti-TB and other antimicrobial activities. All these antimicrobial potential of these classes of compounds led us to synthesize thiadiazole Schiffs bases, which are derivatives of carboxylic acids. The literature survey reveals that thiadiazoles possessed various biological activities such as antiproliferative, antiviral, antimicrobial, anticancer, prostaglandin endoperoxide synthase inactivation, monoglyceride lipase inhibition and antileukemic activity. So we synthesized a number of Thiadiazole Schiff base derivatives from benzoic acid (aryl carboxylic acid) and tested for antimicrobial and antitubercular activity.

## MATERIALS AND METHODS

**Synthesis of 2-amino-5-phenyl-1, 3, 4-thiadiazole**

In a round bottomed flask a mixture of thiosemicarbazide (0.05 mol) and benzoic acid (0.05 mol) are taken. To the above mixture conc.sulphuric acid (5 ml) in 50 ml of ethanol was added. The resulting solution was heated to reflux for 4-5 hours poured onto crushed ice. The solid separated out was filtered, washed with cold water. The resulting colorless solid was recrystallized from ethanol.




**Scheme:** General scheme of Synthesis of 2-amino-5-phenyl-1,3,4-thiadiazole Schiff base

**Synthesis of 2-amino-5-phenyl-1, 3, 4-thiadiazole Schiff base**

To 2-amine-5-phenyl-1, 3, 4-thiadiazole obtained in the first step (0.05 mol) was taken in a round bottomed flask and 0.05 mol of aryl aldehyde was added and heated at reflux overnight in the presence of few drops of HCl. After completion of the reaction the mixture was poured into ice cold water and the solid separated was filtered and dried to obtain 2-amine5-phenyl-1, 3, 4-thiadiazole Schiff bases and recrystallized with ethanol.

**Table I. Different Corresponding Aryl Aldehydes used**

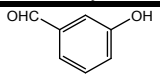
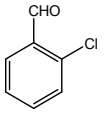
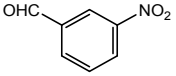
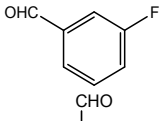
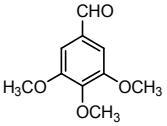
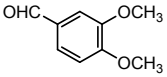
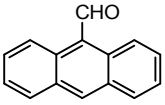
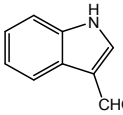
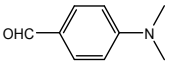
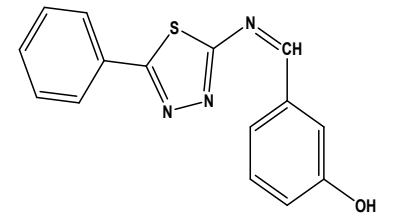
| Compound code | Corresponding Aldehyde | IUPAC name of corresponding aldehyde |
|---|---|---|
| TDAZ-1 |  | 3-hydroxybenzaldehyde |
| TDAZ-2 |  | 2- Chlorobenzaldehyde |
| TDAZ-3 |  | 3-Nitrobenzaldehyde |
| TDAZ-4 |  | 3-fluorobenzaldehyde |
| TDAZ-5 |  | 3,4,5-trimethoxybenzaldehyde |
| TDAZ-6 |  | 3,4-Dimethoxybenzaldehyde |
| TDAZ-7 |  | 9-Anthracenecarboxaldehyde |
| TDAZ-8 |  | Indolecarboxaldehyde |
| TDAZ-9 |  | N,N-dimethylcarboxaldehyde |

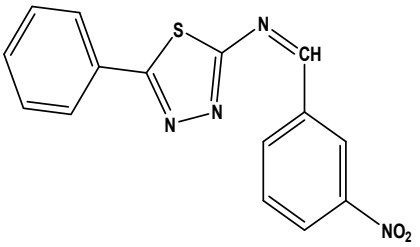
**Table II. List of thiadiazole schiff bases synthesized**

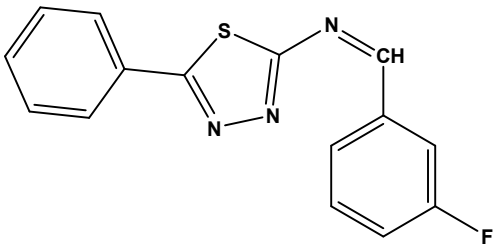
| Compound code | IUPAC Name |
|---|---|
| TDAZ-1 | 3-((*Z*)-(5-phenyl-1,3,4-thiadiazol-2-ylimino)methyl)phenol |
| TDAZ-2 | (*Z*)-*N*-(2-chlorobenzylidene)-5-phenyl-1,3,4-thiadiazol-2-amine |
| TDAZ-3 | (*Z*)-*N*-(3-nitrobenzylidene)-5-phenyl-1,3,4-thiadiazol-2-amine |
| TDAZ-4 | (Z)-*N*-(3-fluorobenzylidene)-5-phenyl-1,3,4-thiadiazol-2-amine |
| TDAZ-5 | (*Z*)-*N*-(3,4,5-trimethoxybenzylidene)-5-phenyl-1,3,4-thiadiazol-2-amine |
| TDAZ-6 | (*Z*)-*N*-(3,4-dimethoxybenzylidene)-5-phenyl-1,3,4-thiadiazol-2-amine |
| TDAZ-7 | (*E*)-*N*-((anthracen-9-yl)methylene)-5-phenyl-1,3,4-thiadiazol-2-amine |
| TDAZ-8 | (*E*)-*N*-((1H-indol-3-yl)methylene)-5-phenyl-1,3,4-thiadiazol-2-amine |
| TDAZ-9 | (*Z*)-*N*-(4-(dimethylamino)benzylidene)-5-phenyl-1,3,4-thiadiazol-2-amine |

**Fig.1. List of Synthesized Compounds**

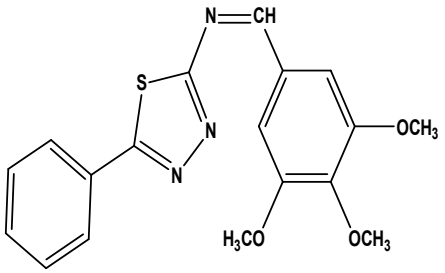


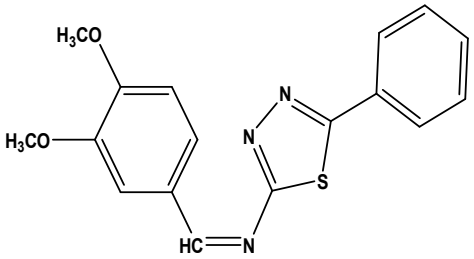
**TDAZ-1TDAZ-2**



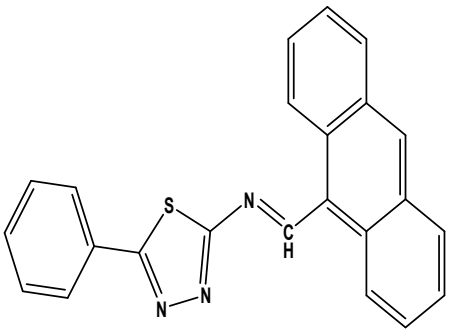


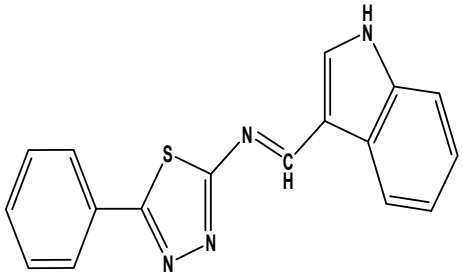
**TDAZ-3TDAZ-4**



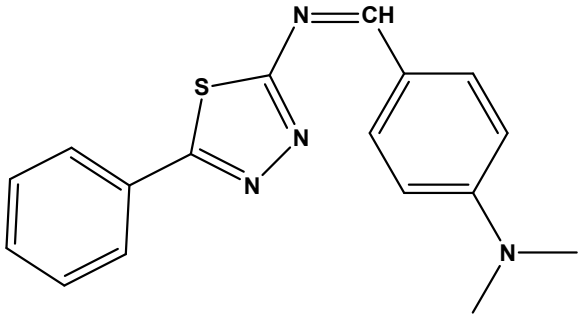


**TDAZ-5TDAZ-6**





**TDAZ-7TDAZ-8**



**TDAZ-9**

## Biological evaluation

### Antibacterial activity

All synthesized 2-amino-5-phenyl-1,3,4-thiadiazole schiff base derivatives were screened for their antibacterial and antifungal activity. For antibacterial studies microorganisms employed were Gram positive *Staphylococcus aureus* (ATCC 9144), Gram negative *Escherichia coli* (*ATCC 25922*. Both microbial studies were assessed by Cup-Plate method. : In this method, assay of antibiotic potency is based on measurement of the diameter of zones of inhibition surrounding the cylinders (cups) containing various dilutions of standard and test compounds, which are poured into the cups of the nutrient agar medium previously inoculated with culture of suitable test organism, Inhibition produced by the test compound is compared (in mm) with that produced by known concentration of a standard.

**Table III- Physical characteristics of synthesized thiadiazole schiff bases**

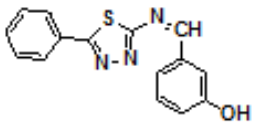
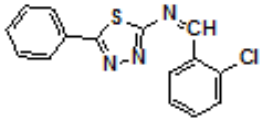
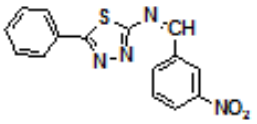
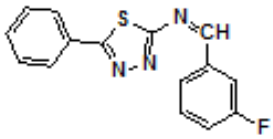
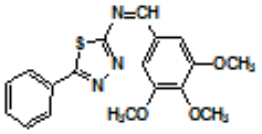
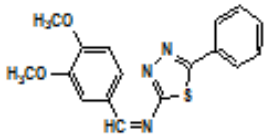
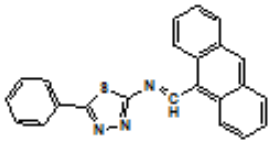
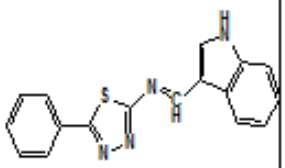
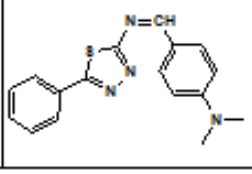
| S.No | Compound | Relative molecular mass | Melting point | % Yeild |
|---|---|---|---|---|
| 1 |  | 281.3 | 198°C | 60% |
| 2 |  | 299.7 | 211°C | 30% |
| 3 |  | 310.3 | 138°C | 65% |
| 4 |  | 288.3 | 162°C | 40% |
| 5 |  | 355.4 | 205°C | 60% |
| 6 |  | 325.3 | 180°C | 75% |
| 7 |  | 364.4 | 175°C | 70% |
| 8 |  | 304.3 | 210°C | 65% |
| 9 |  | 308.4 | 265°C | 40% |

**Table IV: Spectral Data of the synthesized compounds**

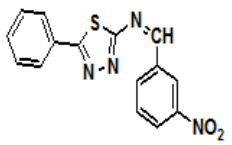
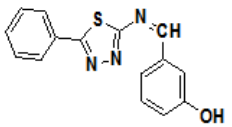
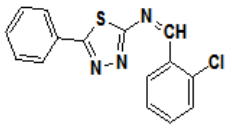
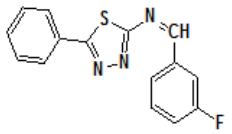
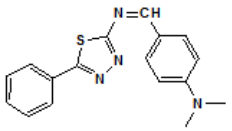
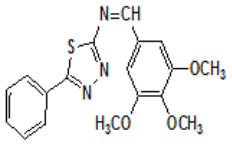
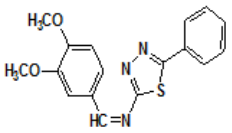
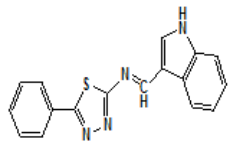
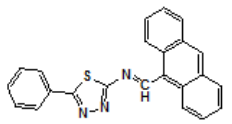
| S.No | Compound | IR($cm^{-1}$) | $^1$H NMR(δ ppm) 400 MHz |
|---|---|---|---|
| 1 |  | N=O str, Ar-$NO_2$ 1522$cm^{-1}$ (stretch),1353$cm^{-1}$ (stretch); C=N imines1622$cm^{-1}$ ; C-S-C cyclic 730$cm^{-1}$; C-H Aromatic 3085;C=C Aromatic 1473$cm^{-1}$ | 7.10-7.68(m,5H,Ar-H); 8.10(s,1H,CH=N); 7.15-6.90(m,4H,$H_{aromatic}$); 5.14(s,1H,OH) |
| 2 |  | OH 3129; C-S 782$cm^{-1}$; C=N imine1618$cm^{-1}$;C-H Ar 2929$cm^{-1}$;C=C Ar 1435$cm^{-1}$;C=N 1575$cm^{-1}$ | 7.02-7.51(m,5H,Ar-H); 7.98(s,1H,CH=N); 7.04-7.68(m,4H,$H_{aromatic}$) |
| 3 |  | C-Cl 750$cm^{-1}$; C-S 740$cm^{-1}$; C=N imine1652$cm^{-1}$;C-H Ar 2929$cm^{-1}$;C=C Ar 1435$cm^{-1}$;C=N 1614$cm^{-1}$ | 8.04-7.47(m,5H,Ar-H); 7.89.(s,1H,CH=N); 8.70-7.56(m,4H,$H_{aromatic}$) |
| 4 |  | C-F 1280$cm^{-1}$, C-S 782$cm^{-1}$, C=N imine 1702$cm^{-1}$, C-H Ar3150-3050$cm^{-1}$, C=C Ar 1451$cm^{-1}$, C=N Cyclic 1615$cm^{-1}$ | 7.15-7.55(m,5H,Ar-H); 8.04(s,1H,CH=N); 7.56-6.98(m,4H,$H_{aromatic}$) |
| 5 |  | C=N Imine1652;C-S 753;C=N Cyclic 1595 ;C-H Ar 3102; C=C Ar 1542 ;C-N Ar 1360 | 8.21-7.48(m,5H,Ar-H); 8.17(s,1H,CH=N); 7.1-6.67 (m,2H,$H_{aromatic}$); 3.75(s,9H,$CH_3$) |
| 6 |  | 2842(C–H str., Ar–OCH3), C=N Imine1684cm;C-S 843, ;C=N Cyclic 1617 ;C-H Ar 3102; C=C Ar 1542C-H Aliphatic 1300 | 7.09-7.44(m,5H,Ar-H); 8.18(s,1H,CH=N); 7.1-6.66(m,2H,$H_{aromatic}$); 3.62(s,6H,$CH_3$) |
| 7 |  | 2843(C–H str., Ar–OCH3),C=N Imine1652;C-S 753;C=N Cyclic 1595 ;C-H Ar 3102; C=C Ar 1542 C-H Aiphatic 1377 | 7.12-7.48(m,5H,Ar-H); 8.21(s,1H,CH=N); 7.30-7.95(m,9H,$H_{aromatic}$) |
| 8 |  | C-Cl 750$cm^{-1}$; C-S 740$cm^{-1}$; C=N imine1652$cm^{-1}$;C-H Ar 2929$cm^{-1}$;C=C Ar 1435$cm^{-1}$;C=N 1614$cm^{-1}$ | 8.14-7.84(m,5H,Ar-H); 7.90(s,1H,CH=N); 10.0(s,1H,NH); 7.00-7.65(m,5H,$H_{aromatic}$) |
| 9 |  | C-Cl 750$cm^{-1}$; C-S 740$cm^{-1}$; C=N imine1652$cm^{-1}$;C-H Ar 2929$cm^{-1}$;C=C Ar 1435$cm^{-1}$;C=N 1614$cm^{-1}$ | 7.15-7.66(m,5H,Ar-H); 8.18(s,1H,CH=N); 6.45-7.55(m,4H,$H_{aromatic}$); 2.85(s,6H,$CH_3$) |

**Table V: Antibacterial and Antifungal Activity of the Synthesized compounds**

| S. No | Compound (Code) | Zone Of Inhibition in mm | | |
|---|---|---|---|---|
| | | Bacteria | | fungi |
| | | *Staphylococcus aureus* (Gram +ve) | *Escherichia coli* (Gram -ve) | *Aspergillus niger* |
| 1 | TDAZ1 | 12 | 10 | 11 |
| 2 | TDAZ 2 | 9 | 7 | 15 |
| 3 | TDAZ 3 | 2 | 2 | 18 |
| 4 | TDAZ 4 | 3 | 4 | 16 |
| 5 | TDAZ 5 | 10 | 12 | 11 |
| 6 | TDAZ 6 | 15 | 13 | -- |
| 7 | TDAZ 7 | 14 | 11 | -- |
| 8 | TDAZ 8 | 13 | 16 | -- |
| 9 | TDAZ 9 | 10 | 12 | 20 |
| 10 | Amikacin (100µg/ml) | 20 | 22 | -- |
| 11 | Fluconazole (100µg/ml) | -- | -- | 26 |

**Table VI: Antitubercular Activity 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 | TDAZ1 | S | S | S | S | R | R | R | R |
| 2 | TDAZ 2 | S | R | R | R | R | R | R | R |
| 3 | TDAZ 3 | S | S | R | R | R | R | R | R |
| 4 | TDAZ 4 | R | R | R | R | R | R | R | R |
| 5 | TDAZ 5 | S | R | R | R | R | R | R | R |
| 6 | TDAZ 6 | R | R | R | R | R | R | R | R |
| 7 | TDAZ 7 | S | S | S | R | R | R | R | R |
| 8 | TDAZ 8 | S | S | S | S | S | R | R | R |
| 9 | TDAZ 9 | R | 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 values for the Anti-Tb test which was performed.
- Pyrazinamide- 3.125µg/ml
- Streptomycin- 6.25µg/ml
- Ciprofloxacin-3.125µg/ml

**Antifungal activity**

All the synthesized compounds which were screened for antibacterial activity are also tested for their Antifungal activity. For antifungal activity the micro organism employed *Aspergillus niger* (ATCC 9029).

**Antitubercular activity**

**Micro plate Alamar Blue Assay (MABA)**

The antitubercular activity of the synthesized compounds was determined using the MABA method as analytical method. Briefly, 200µl of sterile deionzed water was added to all outer perimeter wells of sterile 96 wells plate to minimized evaporation of medium in the test wells during incubation. The 96 wells plate received 100 µl of the Middle brook 7H9 broth and serial dilutions of compounds were made directly on plate. The final drug concentrations tested were 100 to 0.2 µg/ml. plates were covered and sealed with Para film and incubated at 37ºC for five days. After this time, 25µl of freshly prepared 1:1 mixture of Alamar Blue reagent and 10% tween 80 was added to the plate and incubated for 24 hrs. A blue color in the well was interpreted as no bacterial growth, and pink color was scored as growth. The MIC was defined as lowest drug concentration which prevented the color change from pink to blue. The efficacy of the compounds was compared by repeating the procedure with the standard first line drugs.

## RESULTS AND DISCUSSION

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 9 schiffs bases synthesized aryl aldehyde with phenolic OH, dimethoxy, trimethoxy, indole and anthracene substitution showed enhanced potency on both gram positive and gram negative bacteria when compared with the standard amikacin in the series the potency of the synthesized compounds comparatively less in action.. When tested for antifungal activity (Cup plate diffusion technique) all schiffs bases with electron withdrawing groups such as chlorine, fluorine, nitro, N,N dimethyl substitution on aryl aldehydes showed enhanced potency with an inhibition of 15-20 mm diameter when compared with the standard fluconazole in the series. Anti tubercular activity of the above series also showed significant results when compared with that of the standard. Schiffs bases with phenolic OH, nitro, anthracene and indole on the aryl aldehydes showed moderate to potent activity against *mycobacterium.* All the synthesized 2-amine5-phenyl-1, 3, 4-thiadiazole schiff bases showed activity against antimicrobial and antimycobacterial agents but all the compounds showed less activity than that of the standard used for screening.

**Conclusion**

Thiadiazole schiff bases showed moderate to potent activity against bacterial and fungal 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 as antifungal agents. Antitubercular 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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