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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SOME NEW 2-AMINO-5-ARYL-1,3,4-THIADIAZOLES AS ANTIBACTERIAL AND ANTIFUNGAL AGENTS.

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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 Thiadiazoles were synthesized from various aryl carboxylic acids with thiosemicarbazide to form various 2-amino-5-aryl-1,3,4-thiadiazole derivatives. The purity of the compounds was identified by TLC and are purified by recrystallization and column chromatography. The structures were determined by IR, ^{1}H NMR and Mass spectral data. The diversified 2-amino-5-aryl-1,3,4-thiadiazoles were screened for their antibacterial (*Escherichia coli* ATCC 25922), antifungal (*Aspergillus niger* ATCC 9029) by cup plate diffusion technique. Based on the results of the antitubercular activity SAR of the synthesized compounds is drawn.

KEY WORDS: Thiadiazole, antibacterial, antifungal.

INTRODUCTION

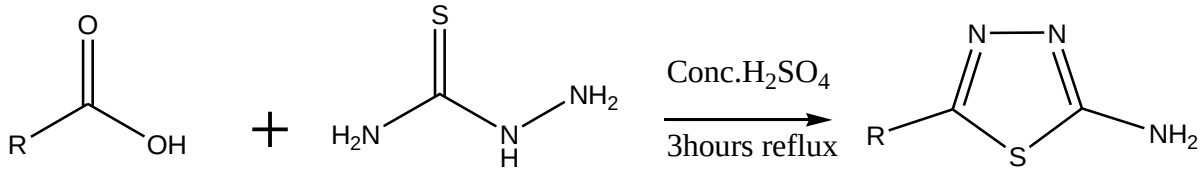
Microbial infection is one of the major alarming disorder around the globe. It is one of the three primary diseases that are closely linked to poverty, the other two being AIDS and malaria.[1, 2,3] It is a solemn health disorder caused by many bacterial strains. The treatment of Bacterial infection is facing lot of hurdles like monodrug therapy and multidrug resistance strains of tuberculosis. According to the MB toll tuberculosis is a serious problem and India is the victim for prone of TB according to WHO statistics. It states that around 2.5 million cases are registered out of 9 million cases at a global level. It also states that around 50% of the people of India are prone to TB[4], so it became indispensable for the emergence of novel synthetic drugs to treat TB efficiently. Tuberculin is being used as a main component in diagnostic test kit for TB.[5, 6] In the recent year the researchers are focusing on the synthesis of 2-amino-5-aryl thiadiazoles as a potent antimicrobial and antimycobacterial agents. 1, 3, 4-thiadiazoles and their derivatives exhibit a wide variety of biological activities like antibacterial[7], antifungal[8], antitubercular[9], antidiabetic[10], anti-inflammatory[11], anti-convulsant[12], diuretic[13] etc.,. The synthesized compounds were evaluated for various biological activities like antimycobacterial and antimicrobial (antibacterial and antifungal) activity. 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.

EXPERIMENTAL

All chemicals used in this study were purchased from Aldrich Chemicals and were used without further purification. All melting points were taken in open capillary tube and are uncorrected. The purity of the compounds was checked by TLC on pre-coated SiO2 gel (HF254, 200 mesh) aluminum plates (E Merk) using Butanol: Acetic acid: water (4:1:5) visualized in iodine chamber. FTIR spectra were recorded with Bruker FTIR. The ^{1}H NMR spectra were determined with Brucker 400 MHz FTNMR spectrometer.

Synthesis of 2-amino- 5-aryl-1, 3,4-thiadiazoles

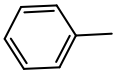
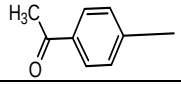
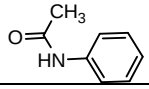
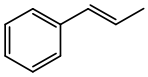
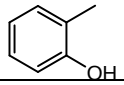
A mixture of thiosemicarbazide (0.1moles), aryl carboxylic acid (0.1 moles), and conc.Sulphuric acid (5 ml) in 50 ml of ethanol was refluxed for 120 minutes and poured onto crushed ice. The solid separated out was filtered, washed with cold water and recrystallized from ethanol **(Scheme-1)**

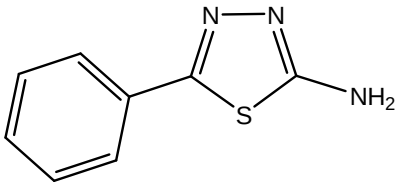


Aryl carboxylic acid Thiosemicarbazide 2 amino 5 aryl 1,3,4-Thiadiazole

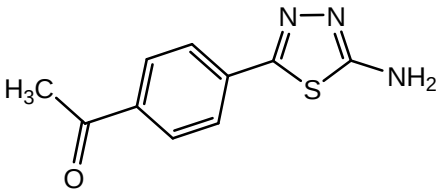
Scheme-1 General scheme of Synthesis of 2-amino-5-aryl-1,3,4-thiadiazoles.

Table 1: List of carboxylic acids used.

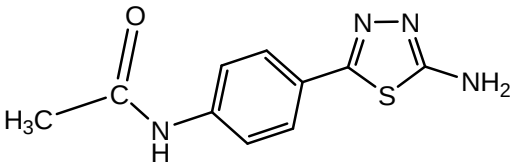
S No	R	Name of the carboxylic acid
1		Benzoic acid
2		4-acetyl benzoic acid
3		4-Acetamido benzoic acid
4		Cinnamic acid
5		Salicylic acid



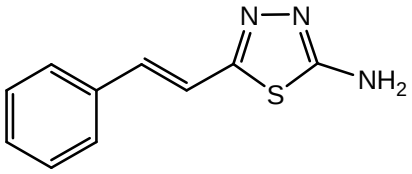
TDZ-1



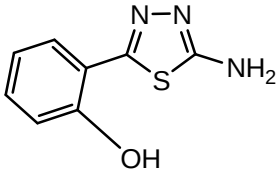
TDZ-2



TDZ-3



TDZ-4



TDZ-5

Fig 1. List of synthesized compounds.

Table 2: IUPAC names of the synthesized compounds.

Code	IUPAC Name of the compounds synthesized
TDZ-1	2-amino-5-phenyl-1,3,4-thiadiazole
TDZ-2	2-amino -5-(*p*-acetylphenyl)-1,3,4-thiadiazole
TDZ-3	2- amino-5-(*p*-acetamidophenyl)-1,3,4-thiadiazole
TDZ-4	2 -amino -5-(styryl)- 1,3,4-thiadiazole
TDZ-5	2-amino -5-(*o*-hydroxyphenyl)-1,3,4-thiadiazole

Table 3: Physico-chemical properties of the synthesized compounds.

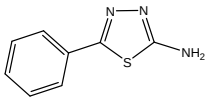
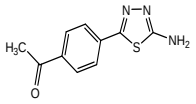
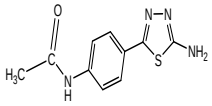
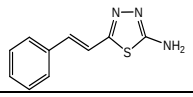
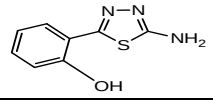
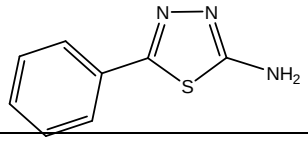
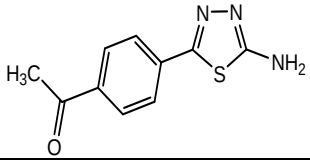
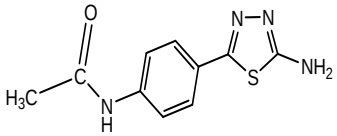
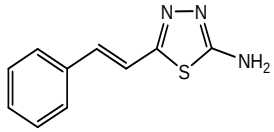
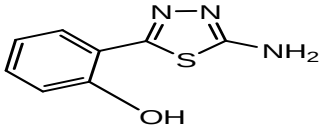
S No	Structure	Molecular weight(gm/mol)	Melting point(°c)	%Yeild
1		177	159	72
2		135	144	69
3		234	183	65
4		203	171	78
5		193	134	65

Table 4: Characterization of the synthesized compounds.

S No	Structure	IR(cm^{-1})	^{1}H NMR(δ ppm)
1		**3397(N-H str), 2925(Ar-C-H), 1428(Ar-C=C), 1108(C=N str), 1028(C-S).**	**7.11-8.09 (5H, m, Ar-H), 5.12 (2H, s, -NH_2)**
2		**3443(N-H str), 2950(Ar-C-H), 1442(ArC=C), 1633(Ar-C=O) 1225 (C=N str), 1018C-S).**	**7.22-8.19 (4H, m, Ar-H), 5.03 (2H, s, -NH_2), 3.43 (3H, s, -$COCH_3$)**
3		**3423(N-H str), 2964(Ar-C-H), 1639(Ar-C=C), 1556(NH-C=O) 1441(C=N str), 1025(C-S).**	**7.25-8.23 (5H, m, Ar-H), 5.15 (2H, s, -NH_2), 3.75 (3H, s, -$COCH_3$), 5.93 (1H, s, -CONH-)**
4		**3391(N-H str), 2950(Ar-C-H), 1628(Ar-C=C), 1450(C=N str), 1055(C-S).**	**7.33-8.20 (5H, m, Ar-H) 6.99 (1H, d, J=17 Hz Ar-CH=C-), 7.24 (1H, d, J=17 Hz Ar-C=CH-), 5.19 (2H, s, -NH_2),**
5		**3550 (N-H str.), 1550 (Ar.C-H str.), 1690 (Ar.C-C str.), 1010 (C-S str.), 1500(C=C str.)**	**6.82-7.96 (4H, m, Ar-H) 5.13 (2H, s, -NH_2) 5.01 (1H, s, Ar-OH)**

S No	Structure	IR(cm^{-1})	^{1}H NMR(δ ppm)
		1250 (C-N str.), 750 (NH str.), 3455 (-OH str.)	

Biological Evaluation

Antibacterial activity

All synthesized 2-amino-5-aryl-1,3,4-thiadiazole 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*), *and Aspergillus niger* (ATCC 9029). Both microbial studies were assessed by Minimum Inhibitory Concentration (MIC) by serial dilution method. For this, the compound whose MIC has to be determined is dissolved in serially diluted DMF. Then a standard drop of the culture prepared for the assay is added to each of the dilutions, and incubated for 16–18 hrs at 37^0c. MIC is the highest dilution of the compound, which shows clear fluid with no development of turbidity. The results are shown below.

Table 5: Zone of inhibition of the synthesized compounds.

S No	Compounds	Bacteria	
		Staphylococcus aureus (Gram +ve)	*Escherichia coli* (Gram -ve)
1	TDZ-1	11	11
2	TDZ-2	16	15
3	TDZ-3	13	12
4	TDZ-4	12	12
5	TDZ-5	09	11
6	Amikacin	20	22

All values given in the table are inhibition zone diameters measured in mm

Results, Discussions And Sar For Antibacterial Activity

All the compounds tested for antibacterial activity exhibited potency against both Gram positive and Gram negative bacteria but are not equivalent compared to standard amikacin. The compound TDZ-2 with 4-acetyl phenyl moiety exhibited more potency against both the bacterial species with a zone of inhibition values of 16mm against Gram positive *S.aureus* and 15mm against Gram negative bacteria *E.coli*. The next to TDZ-2 is TDZ-3 containing acetamido phenyl moiety, which is equipotent against both the bacterial species with the zone of inhibition value of 13mm. This is followed by TDZ-4 and TDZ-1 which are also equipotent against both the bacteria with the zone of inhibition values 12mm and 13mm respectively. The least potent out of all the compounds in the series is TDZ-5 with 2-hydroxy phenyl moiety against *S.aureus* with 09mm zone of inhibition value and 11mm against *E.coli*.

From the above results SAR can be framed and it is clearly evident that compounds containing electron withdrawing groups on the phenyl ring like 4-acetyl group in TDZ-2 and 4-acetamido group in TDZ-3 makes the compounds more potent against both the bacterial strains. The compounds with unsubstituted phenyl rings as in TDZ-4 and TDZ-1 exhibited more potency than the compound TDZ-5 containing electron releasing hydroxyl group. Interestingly, TDZ-5 was found to be equipotent with BT against *E.coli.* This may be due to the fact that presence of polar hydroxyl group on the phenyl ring may enhanced the penetration through the polar porin channel present in the Gram negative bacteria. So different thiadiazoles can be synthesized with different electron withdrawing and releasing substituents on the aromatic and heteroaromatic rings present at 5^{th} position to generate more potent and biologically useful molecules.

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).

Table 6: Zone of inhibition of the synthesized compounds.

S No	Compounds	Fungi
		Aspergillus niger
1	TDZ-1	10
2	TDZ-2	15
3	TDZ-3	13
4	TDZ-4	11
5	TDZ-5	07
6	Fluconazole	18

All figures given in the table are inhibition zone diameters measured in mm

Results, Discussions and SAR for antifungal activity

All the compounds tested for antifungal activity exhibited potency against *Aspergillus niger* but have not shown more or equivalent compared to standard fluconazole. The compound TDZ-2 with 4-acetyl phenyl moiety exhibited more potency with a zone of inhibition values of 16mm.The next to TDZ-2 is TDZ-3 containing acetamido phenyl moiety, which is equipotent with the zone of inhibition value of 14mm. This is followed by TDZ-4 and TDZ-1 with the zone of inhibition values 12mm and 11mm respectively. The least potent out of all the compounds in the series is TDZ-5 with 2-hydroxy phenyl moiety against *A.niger* with 08mm zone of inhibition value.

From the above results SAR can be framed and it is clearly evident that compounds containing electron withdrawing groups on the phenyl ring like 4-acetyl group in TDZ-2 and 4-acetamido group in TDZ-3 makes the compounds more potent against fungal strains. The compounds with unsubstituted phenyl rings as in TDZ-4 and TDZ-1 exhibited more potency than the compound TDZ-5 containing electron releasing hydroxyl group. So different thiadiazoles can be synthesized with different electron withdrawing and releasing substituents on the aromatic and heteroaromatic rings present at 5^{th} position to generate more potent and biologically useful molecules.

FUTURE PROSPECTIVE

The mechanism of antitubercular action of these thiadiazoles is yet to be investigated. Modification of the free amine into different schiff's bases or sulphonyl ureas can be synthesized to give further more thiadiazole derivatives. Different thiadiazoles with electronwith drawing groups have to be tested for Anti TB activity. Modification of the aryl ring to synthesize different thiadiazoles has to be carried out and to investigate their biological activity.

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