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SYNTHESIS, CHARACTERIZATION AND IN-VITRO ANTI-MICROBIAL ACTIVITY OF SUBSTITUTED 1,3,4-THIADIAZOLE DERIVATIVES

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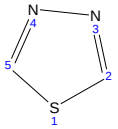
Abstract

Heterocyclic compounds possessing thiazole, thiadiazole or oxadiazole ring system show antifungal, bacteriostatic as well as antihelmintic effects. Compounds containing the above rings also exhibit antiinflammatory and antimicrobial properties and the depression effect on the central nervous system. Structure activity studies show that variations in ring system or minor group extend distinct pharmacological effect upon the drug molecules.1,3,4-Thiadiazoles are biologically important group of compounds havingactivities like antibacterial, antifungal, antiinflammatory, diuretic, antiulcer, antihelmintic other biological activities. Melting points of newly synthesized compounds were determined by open capillary method and were uncorrected. Purity of the compounds was routinely checked by micro TLC. All the reactions were carried out under prescribed laboratory conditions. All the reactions were carried out under prescribed laboratory conditions. All the reactions requiring anhydrous conditions were conducted in well dried apparatus.All the synthesized compounds exhibited antibacterial and antifungal activities but at various MIC levels. Compounds Vb, Ve showed potent antibacterial activity against Bacillus subtilis and Pseudomonas aureginosa but have moderate activity on Escherichia coli and Staphylococcus aureus. Compound Vc exhibited moderate activity on all the bacterial strains under study.

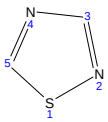
Introduction

Thiadiazoles

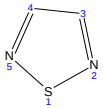
A heterocyclic five membered unsaturated ring possessing a sulfide group and two nitrogen atoms at 1, 3 and 4 positions depending on the position on the position of atom.Thiadiazoles are classified into four types based on the position of sulfur and Nitrogen atoms:



1,3,4-thiadiazoles
(1)



1,2,4-thiadiazoles
(2)



1,2,5-thiadiazoles
(3)

12 ,3-thiadiazoles
(4)

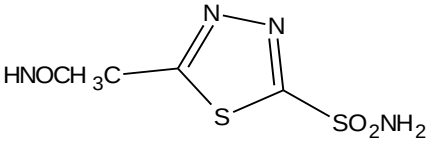
Heterocyclic compounds possessing thiazole, thiadiazole or oxadiazole ring system show antifungal, bacteriostatic as well as antihelmintic effects [1-4]. Compounds containing the above rings also exhibit antiinflammatory and antimicrobial properties and the depression effect on the central nervous system.

- Acetazolamide
- Methazolamide
- Cefazolin
- Sulfamethizole
- Timolol

Acetazolamide

Used as diuretic Acetazolamide **(5)** was the first of the carbonic anhydrase inhibitors to be introduced as an orally effective diuretic with a diuretic effects that lasts about 8-12hrs. Its diuretic action is limited because of the systemic acidosis it produces. Acetazolamide reduces the rate of aq humor formation, and is used primarily in reducing intraocular pressure in the treatment of glaucoma and absence seizures. The dose is 250mg to 1g per day.

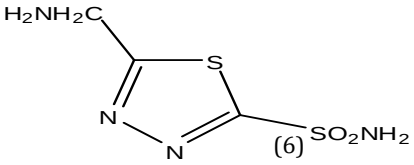
Trade Name: DIAMOX, ZAC



(5)

Methazolamide

Used as diuretic, Methazolamide **(6)** is a derivative of acetazolamide in which one of the active hydrogen has been replaced by a methyl group. This decreases the polarity and permits a greater penetration into the occular fluid, where it acts as a carbonic anhydrase inhibitor, reducing intraocular pressure. Its dose for glaucoma is 50-100mg two to three times a day. It is used orally.

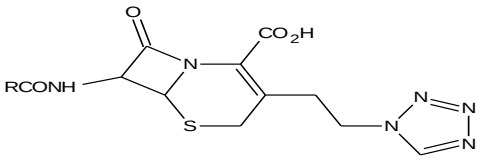


(6)

Cefazolin

Used as a Antibiotic., Cefazolin **(7)** has the natural acetyl side chain at C-3 replaced by a thio-linked thiadiazole ring, while this group is an activating leaving group, the moiety is not subject to the inactivating host hydrolysis reaction that characterizes cephapirin. At C-7 it possesses a tetrazoyl methylene unit. Cefazolin is less irritating on injection than its cohort in this generation of drugs and has a longer half-life than cephapirin. Its dosing should be reduced in the presence of kidney damage. It is comparatively unstable and should be protected from heat and light [5-6].

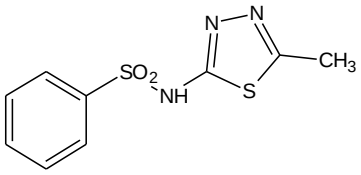
Trade Names: ANCEF, KEFZOL, ZOLICEF



(7)

Sulfamethizole

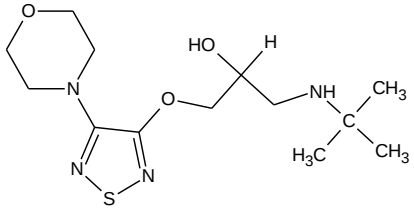
Used as a sulfonamide (8).



(8)

Timolol

Used as a non selective β-adrenergic blocker. Timolol **(9)** is a non selective β-adrenergic receptor antagoniste without intrinsic sympathomimetic activity. They act by decreasing the production of aqueous humor.

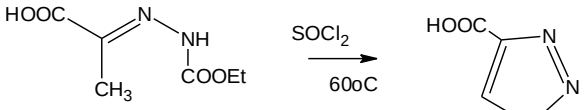


(9)

Trade Name: BLOCADREN

Synthesis

1(a). 1,2,3-thiadiazoles[1] **(4)** are prepared by the reaction of a hydrazine containing an acidic methylene group with thionylchloride.

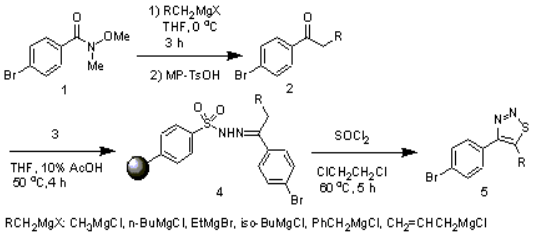


(9) (10)

(b). 1,2,3-thiadiazoles **(4)** were synthesized in parallel using a polymer sulfonyl hydrazide resin (PS-TsNHNH$_2$) and employing a "catch and release" synthesis strategy. Resin capture of ketones synthesized from Weinreb amides and Grignard reagents afforded resin-bound sulfonylhydrazones. Cyclizative cleavage of support-bound sulfonylhydrazones with thionyl chloride afforded 1,2,3-thiadiazoles. Excess thionyl chloride was neutralized using liquid-liquid extraction cartridges.

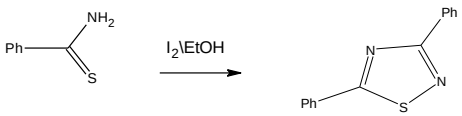
Scheme

1. Thiadiazoles Prepared *via* "Resin capture" of Ketones



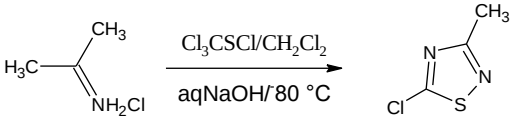
RCH$_2$MgX: CH$_3$MgCl, n-BuMgCl, EtMgBr, iso-BuMgCl, PhCH$_2$MgCl, CH$_2$=CHCH$_2$MgCl

2(a)(i). 1,2,4-thiadiazoles **(2)** carrying identical groups at three and fifth position can be obtained by the oxidation of thioamides **(11)**.



(11) (12)

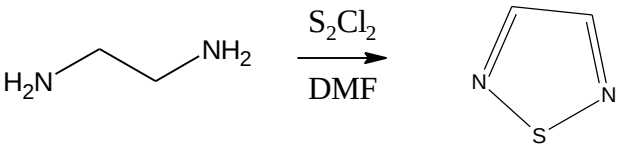
(ii).5-chloro-1,2,4-thiadiazoles result from the reaction of amidines **(13)** with perchlormethyl mercaptan.



(13) (14)

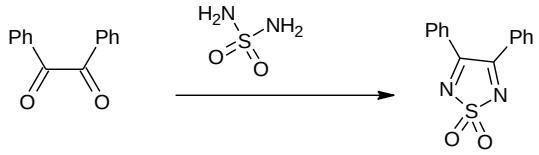
(b).1,2,4-Thiadiazole is a distinctive class of small heterocyclic thiol trapping agents that serve as an interesting pharmacophore in the design of inhibitors targeting the cysteine residues of proteins. X-Ray crystal structures of enzyme-inhibitor complex indicate that the cysteine thiol reacts with the N-S bond of the thiadiazole moiety to form a disulfide bond resulting in the inactivation of the enzymes.

3(a).1,2,5-thiadiazoles **(3)** can be prepared by the oxidative cyclization of 1,2-diamines **(15)**. or aminocaboxmides.



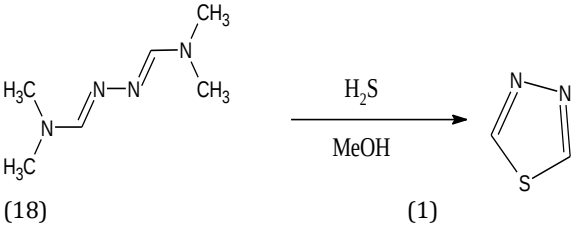
(15) (3)

3(b).Condensation of sulfumide ($SO_2(NH_2)_2$) with1,2-diketones **(16)** gives 1,2,5-thiadiazole 1,1-dioxides **(17)**.

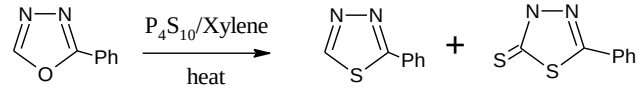


(16) (17)

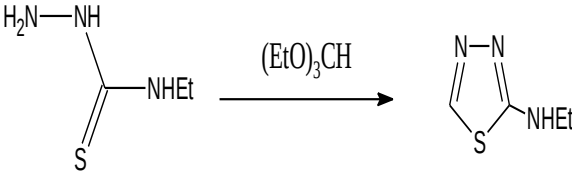
4(a). 1,3,4-thiadiazoles **(1)** are available by a number of convenient general routes including cyclization of N,N*-diacylhydrazines **(18)**, or 1,3,4 oxadiazoles **(19)**, with phosphorous sulfides. 3-Amino-1.3.4-thiadiazoles **(23)** are prepared via acylation of thiosemicarbazides **(22)** and the parent compound is easily obtained from hydrogensulfide and dimethylformamide azine.



(18) (1)



(19) (20) (21)

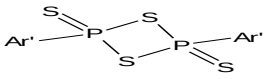


(22) (23)

(b).Thionation of amides[2], 1,4-diketones, N-(2-ozoalkyl)amides (24), and N,N'-acylhydrazines with the use of a fluorous lawesson's reagent {phosphorous pentasulfide (P_2S_5)} leads to thioamides, thiophenes, 1,3-thiazoles and 1,3,4-thiadiazoles in high yields. Reactions using the comparable reagent P_4S_{10} normally need higher temperature and a large excess of the thionating agent.

(24) (25)

lawesson's reagent =



(26)

Hundreds of thousands of new heterocyclic compounds are prepared annually throughout the world, and many of them are entering into pharmacological screens to determine if they have useful biological activity. This process of random screening is inefficient, but it has resulted in identification of new compounds not produced naturally or imagined by chemists. Such lead compounds form the basis of a series of analogues intended to optimize the therapeutic activity. The antitubercular drug, ethambutol, was developed in this way. More recently emphasis has been placed on rational design of new pharmaceuticals.

Aim and Objectives

Chemical modifications of drug molecules of a series having optimal activity is widely used and continue to be an important factor in new drug discovery studies.

In order to obtain new, effective and safe drugs has led today's researchers to improve the existing drugs by increasing their potency, duration of action and by decreasing the toxic side effects. Structure activity studies show that variations in ring system or minor group extend distinct pharmacological effect upon the drug molecules.

1,3,4-Thiadiazoles are biologically important group of compounds havingactivities like antibacterial, antifungal, antiinflammatory, diuretic, antiulcer, antihelmintic other biological activities.

Prompted by these reports, it was contemplated to synthesize new 1,3,4-thiadiazoles. Thus an attempt was made to synthesize 2-(5-{[(1Z)-substituted methylene]amino}-1,3,4-thiadiazol-2-yl)phenol derivatives in this present study.

The reaction, reagents and the condition of the reaction system are given in the following scheme.

A study of the antimicrobial activity of the synthesized compounds was done, after confirming the structure in term of their IR, ^{1}H NMR and Mass spectral analysis.

Scheme

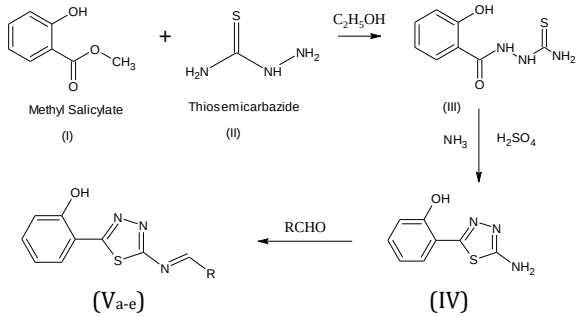
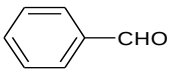
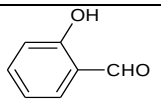
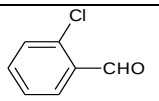
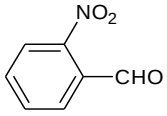
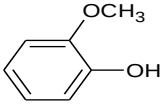


Table 01

Compound	R
V_a	
V_b	
V_c	
V_d	
V_e	

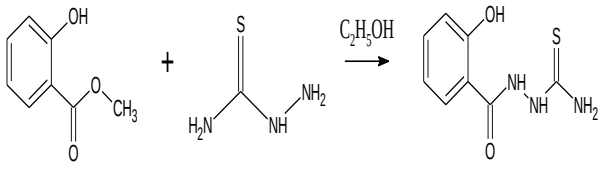
Materials and Methods

The solvents and reagents used in the synthetic work were of laboratory reagent grade and were purified by distillation and crystallization techniques wherever necessary and their melting points were checked with the available literature. Melting points of newly synthesized compounds were determined by open capillary method and were uncorrected. Purity of the compounds was routinely checked by micro TLC. All the reactions were carried out under prescribed laboratory conditions. All the reactions requiring anhydrous conditions were conducted in well dried apparatus. The IR spectra of the compounds were recorded on THERMONICOLET NEXUS-670spectrometer using KBr pellet. 1H NMR spectra were recorded in a ADVANCE-300MHz spectrometer using TMS as internal standard. Mass spectra were recorded in NCMS-spectrometer. The present work deals with the reaction between reduced Schiff's base with five different aldehydes such as benzaldehyde/ salicylaldehyde/ chlorobenzaldehyde/ nitrobenzaldehyde/ vanillin. The reaction was performed as follows [7-9].

Methyl salicylate was treated with thiosemicarbazide. Later it is cyclized using conH2SO4 and ammonia to form Schiff's base, which is then reduced with five different aldehydes such as benzaldehyde/ salicylaldehyde/ chlorobenzaldehyde/ nitrobenzaldehyde/ vanillin.

Synthesis

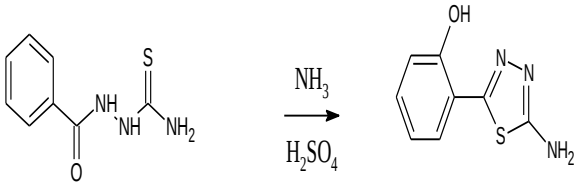
Synthesis of 2-benzoyl hydrazine carbothioamide (III).



(I) (II) (III)

A mixture of methyl salicylate **(I)** (15ml, 0.01mol) and thiosemicarbazide **(II)** (15.2gms, 0.01mol) in ethanol was refluxed for 3hrs. The resultant solution was cooled to room temperature and poured into crushed ice. A solid separates out and it is allowed to settle down during 0.5hrs. It is filtered and washed with water. The crude product thus obtained was recrystallized from chloroform.

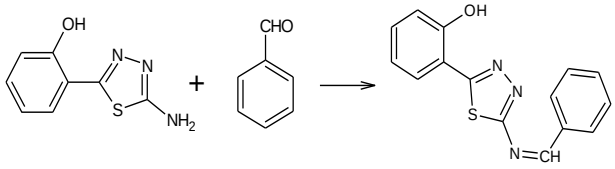
Synthesis of 2-(5-amino-1,3,4-thiadiazol-2-yl)phenol (IV).



(III) (IV)

Compound (III) (0.01mol) was added slowly to concH_2SO_4 with stirring Maintaining the temperature below 0^0C. The temperature was maintained at 0^0C for another 1hr and the reaction mixture was allowed to stand at room temperature overnight. The contents were warmed to 50, cooled and poured over crushed ice. The solid, thus obtained was washed with water and treated with a solution of ammonia. The solid thus obtained was collected washed with water, dried and crystallized from ethanol.

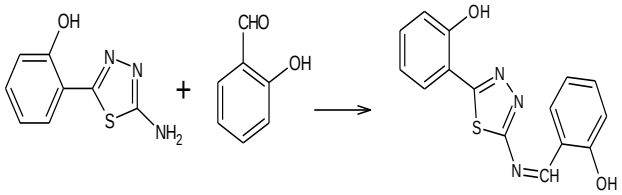
Synthesis of 2-(5-{(1Z)-methyleneamino}-1, 3, 4-thiadiazol-2-yl) phenol (V_a).



(IV) Benzaldehyde (V_a)

A mixture of compound **(IV)** (19.3gms, 0.01mol) and benzaldehyde in equimolar quantity using ethanol as solvent was refluxed for 3hrs. The resultant solution was cooled to room temperature and poured into crushed ice. A solid separates out and it is allowed to settle down during 0.5hrs. It is filtered and washed with water. The crude product thus obtained was recrystallized from water.

Synthesis of 2-(5-{[(1Z)-(2-hydroxyphenyl) methylene] amino}-1, 3, 4-thiadiazol-2-yl) phenol (V_b).

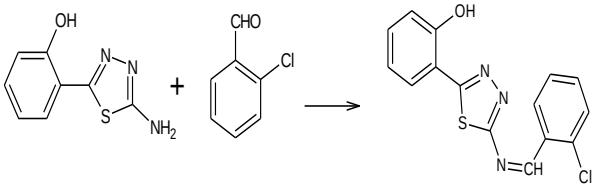


(IV) Salicylaldehyde (V_b)

A mixture of compound **(IV)** (19.3gms, 0.01mol) and salicylaldehyde in equimolar quantity using ethanol as solvent was refluxed for 3hrs. The resultant solution was cooled to room temperature and poured into crushed ice. A solid separates out and it is allowed to settle down

during 0.5hrs. It is filtered and washed with water. The crude product thus obtained was recrystallized from water.

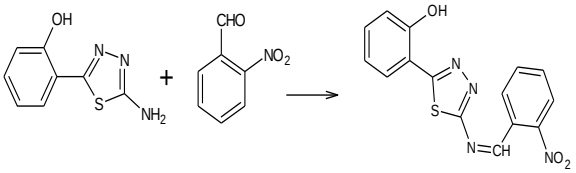
Synthesis of 2-(5-{[(1Z)-(2-chlorophenyl) methylene] amino}-1,3,4-thiadiazol-2-yl)phenol (V_c).



(IV) Chlorobenzaldehyde (V_c)

A mixture of compound **(IV)** (19.3gms, 0.01mol) and chlorobenzaldehyde in equimolar quantity using ethanol as solvent was refluxed for 3hrs. The resultant solution was cooled to room temperature and poured into crushed ice. A solid separates out and it is allowed to settle down during 0.5hrs. It is filtered and washed with water. The crude product thus obtained was recrystallized from water.

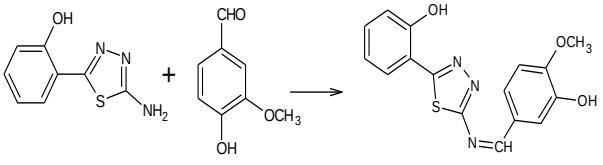
Synthesis of 2-(5-{[(1Z)-(2-nitrophenyl) methylene] amino}-1,3,4-thiadiazol-2-yl)phenol (V_d).



(IV) Nitrobenzaldehyde (V_d)

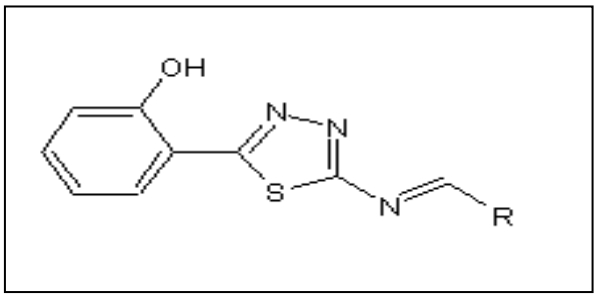
A mixture of compound **(IV)** (19.3gms, 0.01mol) and nitrobenzaldehyde in equimolar quantity using ethanol as solvent was refluxed for 3hrs. The resultant solution was cooled to room temperature and poured into crushed ice. A solid separates out and it is allowed to settle down during 0.5hrs. It is filtered and washed with water. The crude product thus obtained was recrystallized from water.

Synthesis of 2-[(Z)-{[5-(2-hydroxyphenyl)-1,3,4-thiadiazol-2-yl]amino}methyl]2-methoxyphenol (V_e).



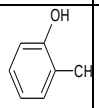
(IV) Vanillin (V_e)

A mixture of compound (IV) (19.3gms, 0.01mol) and vanillin in equimolar quantity using ethanol as solvent was refluxed for 3hrs. The resultant solution was cooled to room temperature and poured into crushed ice. A solid separates out and it is allowed to settle down during 0.5hrs. It is filtered and washed with water. The crude product thus obtained was recrystallized from water.



Physical Data of Synthesized Compounds

Table 02

Compound no	Molecular Formula	R	Molecular wt	% Yield	Melting point ^{0}c
Va	$C_{15}H_{11}N_3OS$		281	76.5 %	179-180
V_b	$C_{15}H_{11}N_3O_2S$		297	81.4 %	209-210
V_c	$C_{15}H_{10}N_3OSCl$		315.7	31 %	219-220
V_d	$C_{15}H_{10}N_4O_3S$		326.3	47 %	264-265
V_e	$C_{16}H_{13}N_3O_3S$		327.3	63 %	277-278

Antimicrobial Activity

Evaluation of antimicrobial activity

The antimicrobial activity can be evaluated by serial dilution test and disc diffusion test. Diffusion test used to determine the sensitivity of organism by measuring zone of inhibition. Serial dilution test is used to determine the minimum inhibitory concentration (MIC). MIC is the lowest concentration of a drug that inhibits the growth of particular organism under specified conditions. Initially the zone of inhibition carried out to evaluate the sensitivity of the organism towards the compounds. From the zone of inhibition data the organisms were selected for determination of MIC.

Disc Diffusion Test

- Modified Kirby-Bauer method[51] was used for the evaluation of microbial sensitivity of the synthesized compounds. Circular paper disks were impregnated with the specific amount of test compounds and were

placed on suitable agar medium (Muller Hinton agar), which was inoculated with the test organism.

- After incubation, the Petri dishes were observed for growth of inhibition zone around the disk. A "halo" or Zone of inhibition forms, where concentration of the diffused molecule is sufficient to inhibit microbial growth. The diameter of zone of inhibition is directly proportional to antimicrobial activity of the compound. The diameter of zone of inhibition was compared with that of standard antibiotics.
- The size of zone of inhibition depends on rate of antibiotic diffusion, rate of bacterial growth and incubation condition, concentration of organism.

Cultivation of microorganism

The following bacterial cultures were used for the study.

1. *Bacillus subtilis* - Gram positive bacteria
2. *Staphylococcus aureous* - Gram positive bacteria
3. *Escherichia coli* - Gram negative bacteria
4. *Pseudomonas aeruginosa* - Gram negative bacteria

The following fungal cultures were used for the study.

- Aspergillus niger
- Candida albicans

Table 03

Dilutions	1	2	3	4	5	6
Con.µg/ml	1000	500	250	125	62.5	31.25

Drugs control

Ampicillin (antibacterial)

Clotrimazole (antifungal)

Concentration All the test compounds were tested at 100 µg/ml.

Solvent: Dimethylformamide (DMF)

Preparation of paper discs

Paper disk of 6 mm diameter and 2 mm thickness was used for the test. These disks were found to absorb 0.02 ml of the solvent (DMF). These disks were sterilized by autoclaving at 121°C (15lbs psig) for 15 minutes.

Preparation of culture medium

It provides all essential nutrients for the growth of microorganism. Muller Hinton agar medium was used to incolate bacterial strains and Sabourands medium used for fungal strains

Composition of Mueller Hinton agar medium

Table 04

Beef infusion	300ml
Casein hydrolysate	16gm
Starch	1.5gm
Agar	15gm
Distilled water	1000ml
Ph	7.2 ± 0.2

The medium was prepared by dissolving the specified quantity of the dehydrated medium in purified water and was dispersed in 20ml volumes in to test tubes. The test tubes were closed with cotton plugs and were sterilized by autoclaving at 121°C (15 lb psig) for 15 minutes. The contents of tubes were poured aseptically in to sterile Petri plates (90mm diameter) and allowed to solidify.

Determination of MIC by serial dilution method

MIC of the synthesized compounds were determined by tube dilution techniques. Serial dilution of the substance under examination was placed into culture tubes containing suitable medium and inoculated with the test organism. After incubation, the minimum concentration of test compound that inhibited the growth of the organism was observed.

Cultivation of microorganism

The following bacterial cultures were used for the study.

- Bacillus subtilis - Gram positive bacteria
- Staphylococcus aureous - Gram positive bacteria
- Escherichia coli - Gram negative bacteria
- Pseudomonas aeruginosa - Gram negative bacteria

The following fungal cultures were used for the study

Aspergillus niger, · Candida albicans

Drugs control: Ampicillin (antibacterial), Griseofulvin (antifungal)

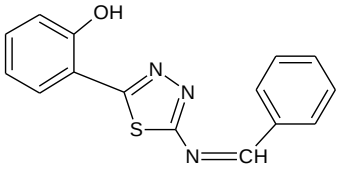
Concentrations: Solvent: Dimethylformamide (DMF)

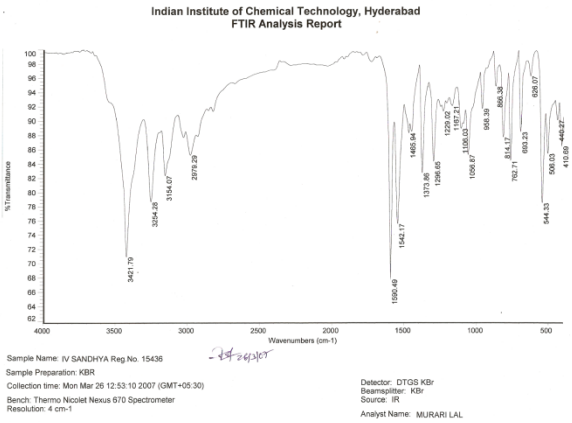
The media were prepared by dissolving the specified quantity of dehydrated medium (Hi-medium) in purified water. The medium was distributed 4 ml quantities into test tubes. The tubes were closed with cotton plug and sterilized by autoclaving at 121° C (15lbs psig) 15 min.

Results and Discussion

Spectral data of synthesized compounds

1. Spectral data of 2-(5-{(1Z)-methyleneamino}-1, 3, 4-thiadiazol-2-yl) phenol (Va).





Proton Magnetic Resonance Spectrum

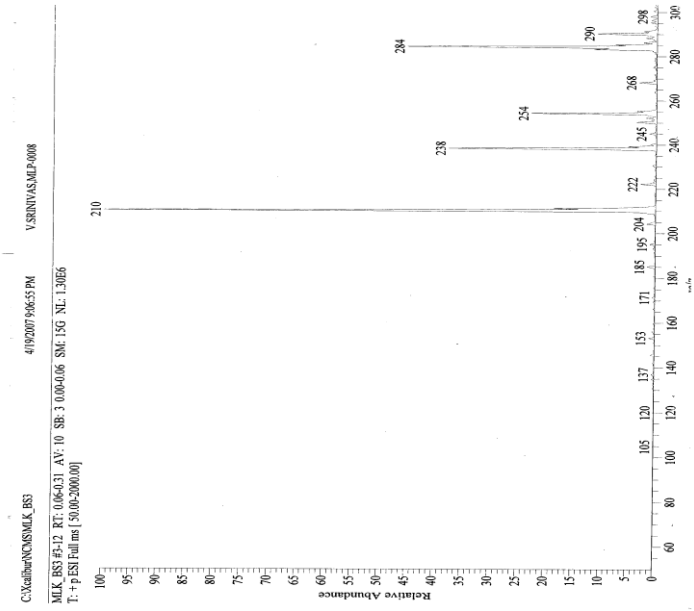
The H^1NMR spectrum was recorded on ADVANCE-300MHz spectrometer using TMS as internal standard and $CDCl_3$ as solvent is represented in figure 02:

Mass Spectrum:

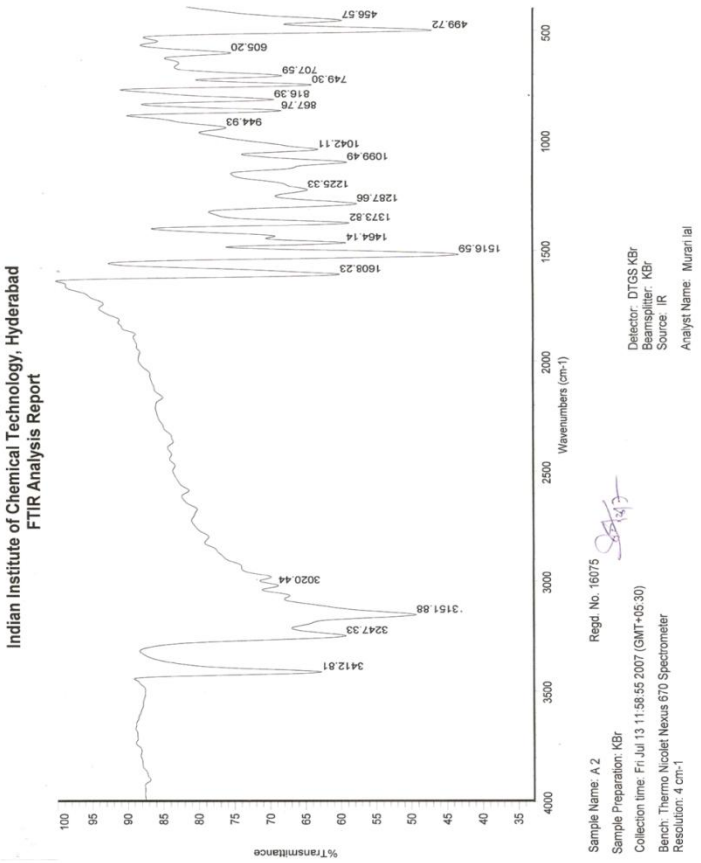
The mass spectrum Showed base peak at 210 corresponding to M peak indicating molecular weight of the compound 281.

2. Spectral data of 2-(5-{[(1Z)-(2-hydroxyphenyl)methylene]amino}-1, 3, 4-thiadiazol-2-yl) phenol (Vb).

Proton Magnetic Resonance Spectrum:

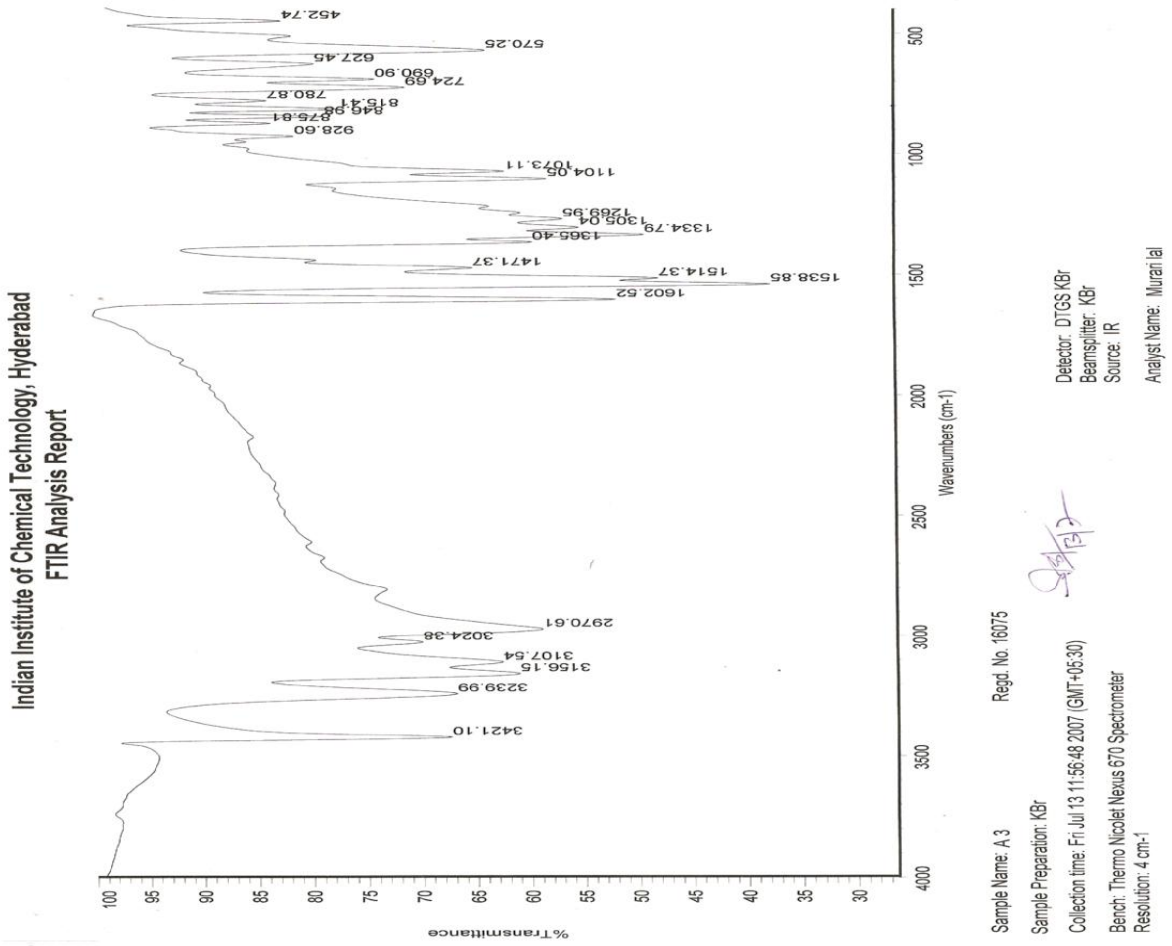


3. Spectral data of 2-(5-{[(1Z)-(2-chlorophenyl)methylene]amino}-1, 3, 4-thiadiazol-2-yl) phenol (Vc).



Proton Magnetic Resonance Spectrum

Spectral data of 2-(5-{[(1Z)-(2-nitrophenyl)methylene]amino}-1, 3, 4-thiadiazol-2-yl) phenol (Vd).



Antibacterial Activity

All the synthesized compounds have shown potent to weak antibacterial activity. Compounds Vb, Ve showed potent antibacterial activity against B.substilis and P.aureginosa. Vc, Vd showed moderate antibacterial activity when compared to the standard [10-15].

Table 05

S.No	Compounds	Diameter of zone of inhibition (mm)			
		B.substilis	S.aureus	P.aeruginosa	E.coli
1.	Va	11	13	12	8
2.	Vb	17	15	16	12
3.	Vc	11	10	13	10
4.	Vd	12	13	14	9
5.	Ve	14	16	18	12
6.	Standard Ampicillin (1mg/ml)	16	14	17	13
7.	DMF	-	-	-	-

Antifungal activity

From the above results it is evident that all the compounds showed potent to weak antifungal activity. Vc and Vd are having more potent antifungal activity against C.albicans and A.niger. Va and Ve showed moderate antifungal activity compared to the standard. Vb showed weak antifungal activity when compared to the standard drug [16-22].

Table 06: Data for Minimum Inhibitary Concentration for Antifungal activity

No.	Compound No.	Candida albicans						Aspergillus niger					
		Concentration (µg/ml)						Concentration (µg/ml)					
		1000	500	250	125	62.5	31.25	1000	500	250	125	62.5	31.25
1	Va	-	-	+	+	+	+	-	-	-	+	+	+
2	Vb	-	-	+	+	+	+	-	-	-	+	+	+
3	Vc	-	-	-	+	+	+	-	-	-	-	+	+
4	Vd	-	-	-	+	+	+	-	-	-	-	+	+
5	Ve	-	-	-	-	+	+	-	-	-	-	+	+
6	+ve control	+	+	+	+	+	+	+	+	+	+	+	+
7	-ve control	-	-	-	-	-	-	-	-	-	-	-	-
8	Griseofulvin	-	-	-	-	-	-	-	-	-	-	-	-

Conclusion

This thesis deals with the synthesis, characterization and anti microbial screening of 2-(5-{[(1Z)-substituted methylene] amino}-1, 3, 4-thiadiazol-2-yl) phenol derivatives. In particular, it explains how Thiadiazoles are an important structural feature for biologically active compounds and the structure of five novel compounds proposed to be synthesized and investigated in the present work for their antimicrobial activity[19-21]. Thiadiazole derivatives prepared in good yields. All the synthesized compounds exhibited antibacterial and antifungal activities but at various MIC levels. Compounds Vb, Ve showed potent antibacterial activity against Bacillus subtilis and Pseudomonas aureginosa but have moderate activity on Escherichia coli and Staphylococcus aureus. Compound Vc exhibited moderate activity on all the bacterial strains under study. Compound Vb and Vc exhibited less activity on all the bacterial and fungal strains under study. Compounds Vd and Ve showed good antifungal activity[22]. The synthesized compounds along with the antimicrobial activity are believed to exhibit various other activities such as antibacterial, antifungal, antiinflammatory, diuretic, antiulcer, antihelmintic other biological activities. Apart from all of these several investigations are going on with Thiadiazole moiety in the field of drug discovery against diuretic activity.

Author Contributions

All authors are contributed equally

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None

Declaration of Competing Interest

The Authors have no Conflicts of Interest to Declare.

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None

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