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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF 5-FLURO-SUBSTITUTED PHENYL - 1, 3, 4-THIADIAZOL-2-AMINE AND THEIR DERIVATIVES

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Abstract

1, 3, 4-Thidiazoles and its derivatives continue to be of a great interest to a large number of researchers owing to their great pharmaceutical and industrial importance It has shown a broad spectrum of activity against various pathogens. Now a day's Microbial infectious diseases are the leading cause of death and disabilities all over the world. Food-borne infections have been one of the major public health problem and raises high cases of sick reports. We wish to report here with synthesis of some novel Fluoro substituted phenyl-1, 3, 4-Thidiazole-2- Amine derivatives and screening of their anti-microbial activity which showed promising results. The antibacterial activity were determined against two gram positive and two gram negative bacterial strains *Staphylococcus aureus, Bacillus subtilis, E. coli* and *Enterobacter aerogenes* by Kirby Bauer Disc diffusion method using ciprofloxacin as a standard bacteria and similarly anti-fungal activity against *Aspergillus niger* and *Penicillium chrysogenum*.

Keywords: Fluoro substituted phenyl-1, 3, 4-Thidiazole-2- Amine derivatives Anti-bacterial and Antifungal activity, Kirby Bauer Disc diffusion method.

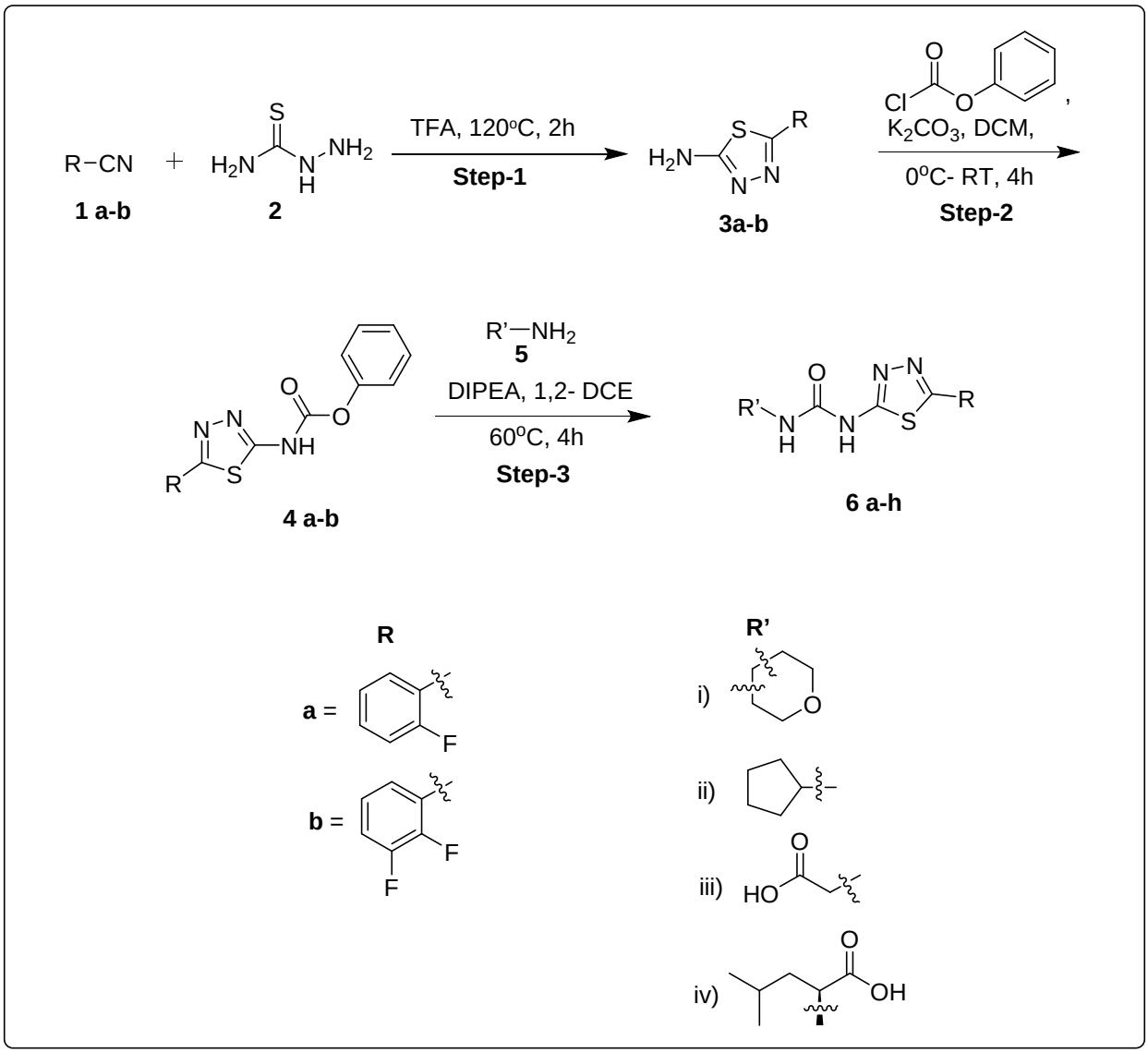
Introduction

Heterocyclic compounds constitute largest and most varied family of organic compounds. They are very widely distributed in nature and essential for life in various ways. They are well known for their pharmacological potential that is exploitable in the synthesis of new bioactive molecules. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic, as are countless additives and modifiers used in industries as varied as cosmetics, reprography, information storage, and plastics. An inspection of the structures of top selling brand-name drugs reveals that 8 of the top 10 and 71 of top 100 drugs contain heterocyclic molecules.(J.A.Joule et al,) 1, 3, 4-Thidiazole are an important class of heterocyclic compounds. 1, 3, 4-Thiadiazole were first described in 1882 by Fischer and further developed by Bush and his co-workers. Thiadiazole are considered to be derived from thiophene by two –CH= (methine) groups by pyridine-type nitrogen (-N=). A lot of research has been carried out with the aim to discover the therapeutic values of 1, 3, 4-Thidiazole. Thidiazoles are important moiety exhibit a variety of activity from antibacterial to antitumor activity (Remer Set et al1982). The Thidiazole drugs were the most first effective chemotherapeutic agents to be employed systematically for the prevention and cure of bacterial infection in human beings as sulphamethazole. In the medical field one of the best known drugs having a 1, 3, 4 - thiadiazole moiety is

acetazolamide, which is a carbonic anhydrase inhibitor launched in 1954. Its indications and usage are many including the treatment of glaucoma, epilepsy and congestive heart failure (Sreenivasa GM et al 2010) - Acetazolamide, antibiotics -Ceftazole antidepressant - Atibeprone (Jumat Salimon et al. 2010) available in the market and sold under their trade mark. The synthesis of 1,3,4-Thidiazole has attracted wide spread attention of researchers due to their diverse application as antimicrobial(Swamy et al,2008) and (Jumat Salimon et al,2010),anticancer (Chu C.H et al, 2002) antifungal (Jun-Chen et al 2007), anti-inflammatory (Sharma S et al,.2002) antiviral(Pandey V.K et al,2003) anticonvulsant (Gupta et al, 2008) anthelmintic (Jain SK et al, 2004) diuretics when 1,3,4-Thidiazole properly substituted in the 2-and 5-position (Mohsen A.et.al,.1986 and Mishra P et.al,. 2006)antidepressant agents (Lumani R.S et.al, 2009) Antidiabetic (Pattan et al, 2009) According to these biological activities and lot of information through literature survey we decided to contribute in this work of research area by using easy, convenient method to synthesis and design various derivatives of 5- Fluro substituted-Phenyl- 1,3,4-Thidiazole-2-Amine and their derivatives. NH_2 group at 2-position of 1,3,4-Thidiazole moiety is synthetically very important. As per literature survey it undergoes various reactions such as Mannich reaction, Schiff base formation and many more reactions to enhance the biologically activity. In this synthesis we converted free NH_2 group of 1,3,4-Thidiazole moiety into carbamate by using phenyl chloroformate and then connected with N-containing compounds by nucleophilic substitution reactions synthetic step. In the hope of having enhancement in antimicriobial activities. Synthesized derivatives showed prominent results and it clears that halogen substituted aryl compound increases the antimicrobial property

Materials and Methods

Scheme for synthesis of 5-(Fluro substituted Phenyl) - 1, 3, 4-Thidiazole-2-Amine and Their Derivatives:-



2.1 General: Chemicals, reagents, synthesis and characterization:

All chemicals used in this study were purchase from Aldrich Chemicals and were used without further purification. Laboratory chemicals were supplied by Vijay Chemicals Ltd. Pune 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 meshes) readymade aluminium plates (E Merck). Products were purified by column chromatography using solvent system Pet Ether: Ethyl Acetate (1:1/ as per requirements) visualized in UV chamber to identify it. Rf values of the synthesised compounds were recorded. FTIR spectra using KBr pallets in the range of 4000-400 cm^{-1} were recorded with Perkin Elmer-838 spectrophotometer. The ^{1}HNMR spectra were determined with Brucker 400 MHz FT-IR spectrometer and mass spectra by HRMS. Elemental analyses of the newly synthesized compounds were performed on Carlo Erba 1108analyzer. Elemental analyses of the entire compounds were in agreement with the calculated values.

2.1a General procedure for the preparation of Synthesis of 5-(Fluro substituted phenyl) -1, 3, 4-Thidiazol-2-amine from Fluro substituted Aryl nitrile (1a-b):

A mixture of Fluro substituted phenyl nitrile (Ia-b) and Thiosemicarbazide (II) in equimolar quantities taken in glass bottle dissolved in Trifluoroacetic acid and sealed it using Teflon tape and make it as glass bomb which kept in oil bath refluxed at 120^{0}C for 2 hours by using Hot Plate with magnetic stirrer apparatus with continuous stirring. The progress of the reaction was monitored by checking TLCs Silica gel 60 $F_{254.}$ The resultant mixture was slowly cooled to room temperature and poured on to crushed ice, stirred for 5 minutes. The solid separates out was filtered, and purified by column chromatography using pet ether: ethyl acetetate (80:20) as mobile phase. Yield was 70%. M.P. 285 ^{0} C confirmed by ^{1}H NMR and FT-IR method.

2.1b General procedure for the preparation of 5-(Fluro substituted phenyl) -1, 3, 4-Thidiazol-2-phenyl acetate (carbamate formation):

5-Substituted-2-Amine 1, 3, 4-Thidiazole (Compound-III 1gm, 0.052 mole) in RB flask and DCM mixed with dry K_2CO_3 (2.2gm 0.155mole) stirred the reaction mixture for 15 min. under Nitrogen atmosphere at 0-5^{o}C. Add Phenyl Chloroformate (1.21gm, 0.077mole) was added slowly with the help of syringe and continue stirring for 4 hour at RT. The progress of reaction was monitored by TLC Silica gel 60 F_{254}. The resultant reaction mixture was extracted with DCM washed with water, brine, concentrated on rotary vacuum evaporator. A solid was separated, dried and purified by column chromatography using pet ether: ethyl acetetate (80:20) as mobile phase. The desired product was obtained confirmed by TLC and directly used for next synthesis.

2.1c General procedure for the preparation of N-(5-(2-fluoro substituted phenyl)-1,3,4-thiadiazol-2-yl)N-containing compound-4-carboxamide (Nucleophilic Substitution) 6a-h:

A mixture of **5-(Fluro substituted phenyl) -1, 3, 4-Thidiazol-2-phenyl acetate** and N- containing compound used molecule such as (morpholine, cyclopentyl amine, Glycine and L-leucine) one by one from 6a-h dissolved in 1, 2- dichloroethane and added DIPEA (N, N-Di-isopropylethylamine) the solution was heated at 60^{0}C for 4 hour. The progress of reaction was monitored by TLC using TLC Silica gel 60 $F_{254.}$ After completion of the reaction, the reaction mixture was concentrated using rotary vacuum evaporator and the white residue solid was purified by column chromatography using pet ether: ethyl acetetate (80:20) as mobile phase. Rf values, melting points, elemental analysis of final target molecules were recorded and analyzed using- IR, H^{1} NMR and HRMS.

Table 1: Physical constants and calculated elemental analysis data

Comp No	M.P ^{0}C	R_f	Yield (%)	Molecular Formula	Molecular Weight (exact mass)	Observed Mass by (HRMS)	Elemental analysis calculated %				
							C	H	F	N	S
6a	280	0.65	55.30	C13H13FN4O2S	308.0743	309.0814 (M+H)	50.64	4.25	6.16	18.17	10.40
6b	285	0.55	52.12	C14H15FN4OS	306.0951	307.1029 (M+H)	54.89	4.94	6.20	18.29	10.46
6c	180	0.75	5406.	C11H9FN4O3S	296.0379	297.0457 (M+H)	44.59	3.06	6.41	18.91	10.82
6d	160	0.80	53.30	C15H17FN4O3S	352.1005	353.1077 (M+H)	51.13	4.86	5.39	15.90	9.10
6e	285	0.62	62.12	C13H12F2N4O2S	326.0649	327.0737 (M+H)	47.85	3.71	11.64	17.17	9.82
6f	290	0.58	55.10	C14H14F2N4OS	324.0856	325.0934 (M+H)	51.84	4.35	11.71	17.27	9.88
6g	185	0.72	63.78	C11H8F2N4O3S	314.0285	315.0368 (M+H)	42.04	2.57	12.09	17.87	10.20
6h	162	0.78	50.15	C15H16F2N4O3S	370.0911	371.0987 (M+H)	48.64	4.35	10.26	15.13	8.66

2.1c The physical and spectral data of the novel synthesized derivatives (6a-h):

(6a) N-(5-(2-fluorophenyl)-1, 3, 4-thiadiazol-2-yl) morpholine-4-carboxamide:

White solid, Yield 55.30%, M.P 280^{0}C, M.F C13H13FN4O2S, Mol. Wt. (expected) 308.0743, Mol .Wt.(observed) 309.0814 (M+H) by HRMS.

IR (KBr pallets): 3380.13 cm^{-1} (-NH-stretch –C=O) 2867 cm^{-1} (C-H stretch , aromatic) 2731 cm^{-1} (=C-H) 1707cm^{-1} (C=O), 1635 cm^{-}1(C=N) 1534 cm^{-1} (C==C, aromatic), 1419 cm^{-1} (C-C stretch Ar), 1328 cm^{-1} (C-N stretch) 1238 cm^{-1} (C-O stretch), 990.44 cm^{-1} (C-H) ,833.76 cm^{-1} (C-F stretch) 761 cm^{-1} (C-H stretch).

^{1}H-NMR (DMSO-d6, 200 MHz): δ 3.57 - 3.60 (m, 8H-morpholine), 7.34 - 7.59 (m, 3H aromatic), 8.15 - 8.22 (m, 1Hp-Ar-H), 11.59 (bs, 1H ,NH)

(6b) 1-cyclopentyl-3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)urea:

White solid, Yield 52.12%, M.P 285^{0}C, M.F C14H15FN4OS, Mol. Wt. (expected) 306.0951, Mol .Wt.(observed) 307.1029 (M+H) by HRMS.

IR (KBr pallets): 3385.18 cm^{-1} (-NH-stretch –C=O) 3190.60 cm^{-1} (C-H stretch, aromatic) 2951.19 cm^{-1} (C-H stretch) 1707cm^{-1} (C=O), 1635 cm^{-}1(C=N) 1534 cm^{-1} (C==C, aromatic), 1419 cm^{-1} (C-C stretch ,aromatic), 1238.34 cm^{-1} (C-N stretch) 1238 cm^{-1} (C-O stretch),1093 cm^{-1}, 990.44 cm^{-1} (C-H) ,831.35 cm^{-1} (C-F stretch) 761 cm^{-1} (C-H stretch).

^{1}H NMR (DMSO-d6, 200 MHz) δ 1.43 - 1.49 (m, 2H-cyclopentyl), 1.54 - 1.72 (m, 4H cyclopentyl), 1.85 - 1.91 (m, 2H-cyclopentyl), 3.93 - 4.03 (m, 1H), 6.69 (d, *J* = 8.1 Hz, 1H NH-cyclopentyl), 7.34 - 7.59 (m, 3H, aromatic), 8.14 - 8.22 (m, 1H-cyclopentyl), 10.73 (bs, 1H, NH)

***(6c):(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl) carbamoyl)glycine* :**

White solid, Yield 52.12%, M.P 180^{0}C, M.F C11H9FN4O3S, Mol. Wt. (expected) 296.0379, Mol .Wt. (observed) 297.0457 (M+H) by HRMS.

IR (KBr pallets): 3315.18 cm^{-1} (-NH-stretch –C=O) 3072.60 cm^{-1} (C-H stretch ,aromatic) 2861.19 cm^{-1} (C-H stretch) 1710cm^{-1} (C=O), 1651 cm^{-}1(C=N) 1522 cm^{-1} (C==C, Ar), 1415 cm^{-1} (C-C stretch ,aromatic), 1218.34 cm^{-1} (C-N stretch) 1230 cm^{-1} (C-O stretch),1090 cm^{-1}, 991.44 cm^{-1} (C-H) ,821.35 cm^{-1} (C-F stretch) 751 cm^{-1} (C-H stretch).

^{1}H NMR (DMSO-d6, 400 MHz): δ 3.88 (d, *J*= 5.6 Hz, 2H, -CH_2), 7.01 (bs, 1H), 7.36 - 7.46 (m, 2H, Ar-H), 7.54 - 7.59 (m, 1H, Ar-H), 8.19 (t, J = 4.8 Hz, 1H), 11.42 (bs, 1H ,NH)

(6d): (5-(2-fluorophenyl)-1, 3, 4-thiadiazol-2-yl) carbamoyl)-L-leucine:

White solid, Yield 53.30%, M.P 160^{0}C, M.F C15H17FN4O3S, Mol. Wt. (expected) 352.1005, Mol .Wt. (observed) 353.1077 (M+H) by HRMS.

IR (KBr pallets): 3325.15 cm^{-1} (-NH-stretch –C=O) 3059.69 cm^{-1} (O-H stretch carboxylic acid) 2871.82 cm^{-1} (C-H stretch),2959.25 cm^{-1}(=C-H), 1712cm^{-1} (C=O), 1651 cm^{-}1(C=N) 1546 cm^{-1} (C==C, aromatic), 1437cm^{-1} (C-H alkane), 1291.34 cm^{-1} (C-N stretch) 1243cm^{-1} (C-O stretch),1090 cm^{-1} (=C-H), 991.44 cm^{-1} (C-H) ,825.35 cm^{-1} (C-F stretch) 751 cm^{-1} (C-H bend). 1H NMR (DMSO-d6, 200 MHz) δ 0.88 - 0.93 (m, 6H 2-methyl), 1.52 - 1.68 (m, 3H), 4.22 - 4.29 (m, 1H), 7.08 (d, *J* = 7.7 Hz, 1H), 7.35 - 7.59 (m, 3H), 8.19 (d, J = 8.0 Hz, 1H)

(6e) N-(5-(2,3 difluorophenyl)-1, 3, 4-thiadiazol-2-yl) morpholine-4-carboxamide

White solid, Yield 62.12%, M.P 285^{0}C, M.F C13H12F2N4O2S, Mol. Wt. (expected) 326.0649, Mol .Wt. (observed) 327.0749 (M+H) by HRMS.

IR (KBr pallets): 3385.13 cm^{-1} (-NH-stretch –C=O) 2860 cm^{-1} (C-H stretch aromatic) 2735 cm^{-1} (=C-H) 1717cm^{-1} (C=O), 1630 cm^{-}1(C=N) 1530 cm^{-1} (C==C, sp^2 aromatic), 1419 cm^{-1} (C-C stretch aromatic), 1318 cm^{-1} (C-N stretch) 1228 cm^{-1} (C-O stretch), 991.44 cm^{-1} (C-H) ,837.76 cm^{-1} (C-F stretch) 765 cm^{-1} (C-H stretch).

^{1}H NMR (DMSO-d6, 200 MHz): δ 3.60 - 3.63 (m, 8H morpholine), 7.35 - 7.41 (m, 1H Ar-H), 7.61 - 7.69 (m, 1H, Ar-H), 7.96 - 8.02 (m, 1H Ar-H), 11.77 (bs, 1H, NH)

(6f) 1-cyclopentyl-3-(5-(2,3-difluorophenyl)-1,3,4-thiadiazol-2-yl)urea:

White solid, Yield 52.12%, M.P 285^{0}C, M.F C14H15FN4OS, Mol. Wt. (expected) 306.0951, Mol .Wt. (observed) 307.1029 (M+H) by HRMS.

IR (KBr pallets): 3392.18 cm^{-1} (-NH-stretch –C=O) 3180.60 cm^{-1} (C-H stretch Ar-H) 2951.19 cm^{-1} (C-H stretch alkane) 1707cm^{-1} (H-C=O), 1635 cm^{-}1(C=N) 1534 cm^{-1} (C==C, Ar), 1419 cm^{-1} (C-C stretch Ar), 1224.34 cm^{-1} (C-N stretch) 1238 cm^{-1} (C-O stretch),1059 cm^{-1} (=C-H bend), 990.44 cm^{-1} (C-H) ,831.35 cm^{-1} (C-F stretch) 761 cm^{-1} (C-H stretch).

^{1}H NMR (CDCl3, 200 MHz): δ 1.57 -1.77 (m, 6H, cyclopentyl), 2.00 - 2.10 (m, 2H ,cyclopentyl), 4.25 - 4.31 (m, 1H-cyclopentyl), 5.90 (d, J = 6.8 Hz, 1H, NH

near to cyclopentyl), 7.15 - 7.34 (m, 2H, aromatic), 7.86 - 7.91 (m, 1H, aromatic), 12.91 (bs, 1H, NH-)

(6g)***((5-(2,3-difluorophenyl)-1,3,4-thiadiazol-2-yl) carbamoyl)glycine:***

White solid, Yield 63.78%, M.P 185^{0}C, M.F C11H8F2N4O3S, Mol. Wt. (expected) 314.0285, Mol .Wt. (observed) 315.0368 (M+H) by HRMS.

IR (KBr pallets): 3310.18 cm^{-1} (-NH-stretch –C=O) 3070.60 cm^{-1} (C-H stretch Ar-H) 2851.19 cm^{-1} (C-H stretch) 1715cm^{-1} (C=O), 1661 cm^{-}1(C=N) 1528 cm^{-1} (C==C, Ar), 1418 cm^{-1} (C-C stretch Ar), 1228.34 cm^{-1} (C-N stretch) 1235 cm^{-1} (C-O stretch),1090 cm^{-1}, 991.44 cm^{-1} (C-H) ,831.35 cm^{-1} (C-F stretch) 755 cm^{-1} (C-H stretch).

^{1}H NMR (DMSO-d6, 200 MHz): δ 3.88 (s, 2H,-CH2), 7.16 (bs, 1H, NH), 7.37 - 7.39 (m, 1H, aromatic), 7.53 - 7.66 (m, 1H, aromatic), 7.93 - 8.00 (m, 1H, aromatic), 11.62 (bs, 1H, OH)

(6h) *((5-(2, 3-difluorophenyl)-1, 3, 4-thiadiazol-2-yl) carbamoyl)-L-leucine:*

White solid, Yield 63.78%, M.P 162^{0}C, M.F C15H17FN4O3S, Mol. Wt. (expected) 379.0911, Mol .Wt. (observed) 371.0987 (M+H) by HRMS.

IR (KBr pallets): 3325.15 cm^{-1} (-NH-stretch –C=O) 3059.69 cm^{-1} (O-H stretch carboxylic acid) 2956.82 cm^{-1} (C-H stretch),2959.25 cm^{-1}(=C-H), 1701cm^{-1} (C=O), 1651 cm^{-}1(C=N) 1537 cm^{-1} (C==C, Ar), 1437cm^{-1} (C-H alkane), 1220.99 cm^{-1} (C-N stretch) 1313cm^{-1} (C-O stretch),1057 cm^{-1} (=C-H), 991.44 cm^{-1} (C-H) ,881.35 cm^{-1} (C-F stretch) 751 cm^{-1} (C-H bend).

^{1}H NMR (DMSO-d6, 400 MHz): δ 0.88 - 0.93 (m, 6H, 2 CH_3), 1.62 - 1.68 (m, 3H), 4.21 (bs, 1H), 7.38 (m, 2H), 7.59 - 7.61 (m, 1H), 7.97 - 7.99 (m, 1H), 11.42 (bs, 1H, OH)

3. Results and Discussion

3.1 Biological Evaluation:

Assessment of antimicrobial activity of newly eight synthesized derivatives(6a-h) of 5- Fluro substituted Phenyl -1, 3, 4-Thiadiazoles-2-Amine were done by using Kirby Bauer Disc Diffusion method using antibiotic chloroamphenicol as a standard antibiotic. The medium used for the maintenance of bacterial culture was Nutrient agar and for Fungal cultivation Potato Dextrose Agar. For zone inhibition experiment the culture medium used was Muller Hinton Medium. All medium were of HI-Media. The Antibacterial activity tested against microorganism used as *Staphylococcuc aureus, Bacillus subtilis, E. coli and Enterobacter aerogenes* Gram positive ,Gram negative bacteria respectively. Antifungal activity screened against *Aspergillus niger* and *Penicillium chrysogenum*.5-Fluro substituted-Phenyl-2-Amine 1, 3, 4-Thidiazole acts as parent molecule and its antibacterial and antifungal activity also tested to compare with all the newly synthesized compounds.

The bacterial and fungal cultures are denoted by alphabets A*, B*.C*.D*, E*, F* where A*,B*,C*,D* assigned for microorganism bacteria and E*,F* for fungi microorganism.

3.1a) Antimicrobial Activity: - 1, 3, 4-Thidiazole were exhibited a broad spectrum of antimicrobial activities. (Lumani R.S et.al 2009 and Joseph et al 2009)

The results in Table 2 show that antimicrobial properties of the synthesized derivatives are excellent comparable with standard and moiety. All synthesized derivatives (6a-h) showed best antibacterial activity against ***S. aureus.*** *While 6a, 6b, 6d, 6g* showed inactive property against ***B. subtilis*** (Gram +Ve) pathogens. 6a is completely inactive against ***E. aerogenes***. 2, 3, di- fluro Phenyl group connected to 1, 3, 4-Thidiazole -2-Amine may enhance the antimicrobial property compare to 2-fluro – Phenyl-connected to 1, 3, 4-Thidiazole-2-Amine based on the structure activity relationship.

Table 2: Antimicrobial activity of 6a-h

Comp. No.	Antimicrobial data in zone of inhibition(mm)				Antimicrobial data in zone of inhibition (mm)	
	Gram + ve Bacteria		Gram-ve Bacteria			
	S. aureus **A***	***B. subtilis*** **B***	***E. coli*** **C***	***E.aerogenes*** **D***	***A.niger*** **E***	***P.chrysogenum*** **F***
6a	11.7	--	12.2	--	7.5	*7*
6b	13.4	---	9.6	13.2	7	*8.25*
6c	10.6	8	10.6	14.6	8.7	*11.5*
6d	13.2	--	14.6	16.4	8	--
6e	12.8	10.6	15.2	16	12.5	*8.25*
6f	10.6	12.6	14	16	14	*7*
6g	12.4	12.4	14.2	11.6	12.5	*9.75*
6h	11.2	---	12	16.6	10	--
STD	10	10	10	10	10	10

According to result table 2 all of the precursors of target molecule shows excellent antimicrobial activity compare to 1, 3, 4-Thidiazole moiety.

3.1b)Antifungal Activity- Among azoles 1, 3, 4-thidiazoles is an interesting group of fungicidal compounds (Sun Y et al 2006 and Hai-Tang et al 2010) Many heterocyclic compounds containing 2, 4, dihydroxy phenyl moiety was reported with good antifungal property. (Legocki J et al 2003 and Niewiadomy A et al 2006) Compare to antibacterial activity 6a-6h synthesized derivatives shows excellent antifungal activity against *Aspergillus niger* (E*) only 6d and 6h inactive against *Penicillium chrysogenum* (F *) Activity of this molecule may enhance due to additional fluro substituent.

4. Conclusion

Antibacterial and antifungal activity of all compounds from above results can be concluded that the compounds bearing halogen (i.e Fluorine) group and connecting N-bearing substituent are more potent than the remaining compounds. They showed comparatively good antibacterial as well as antifungal activity. It was also observed that the potent antimicrobials activity leads to application of synthesized derivatives in the treatment of infectious diseases in future. The biological activities that were observed by the above results because of the modification in the lead molecule via different stages changes the structural variation gave the new ideas for the further investigation on 5-Fluro-substituted Phenyl-1, 3, 4- Thiadiazole -2-Amine and their derivatives.

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