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SAR: SYNTHESIS AND ANTIMICROBIAL EVALUATION OF NOVEL 5-(2-FLUORO / 2, 3-DI FLUORO PHENYL) - 1, 3, 4-THIADIAZOLE-2-AMINE DERIVATVES AS ANTI-CANCER COMPOUNDS

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ABSTRACT

Structure-activity relationships (SAR) are the traditional practices of medicinal chemistry, which try to modify the effect or the potency (i.e. activity) of bioactive chemical compounds by modifying their chemical structure. Medicinal chemists use the techniques of chemical synthesis to insert new chemical groups into the biomedical compound and test the modifications for their biological effects. The 5(2, 4-dihydroxy phenyl) 1, 3, 4, thiadiazole-2-amine's set are well known compounds with interesting in vitro and in vivo anti-cancer profiles. On the basis of SAR we wish to report here with synthesis of eight novel 5-(2-fluoro and 2, 3-difluoro phenyl)-1, 3, 4-thiadiazole-2-amine and their derivatives.They are evaluated for anti-microbial activity They may have potential anti-cancer activity.

KEY WORDS: Structure-activity relationships (SAR), 1, 3, 4, Thiadiazole derivatives,Anti-microbial activity, Anti-cancer activity

INTRODUCTION

1, 3, 4-Thidiazole derivatives continue to draw the attention of synthetic organic chemists due to their varied biological activity from antimicrobial to antitumor. Literature survey revealed

that 1, 3, 4-Thidiazole has diverse pharmacodynamic and chemotherapeutic activities. [1-10] including antimicrobial [11-14] and antitumor activities. [15-20]Considering these published data and our previous work on 2, 5 disubstituted-1, 3, 4-thidiazole derivatives and their antimicrobial activity which showed potent result force us to synthesize new compounds incorporating substituent at 5 and 2-position of nucleus 1,3,4-thidiazole to explore their antimicrobial activity and SAR study of these synthesized compounds as anticancer drug.

The objects of our scientific interest are aminothiadiazoles as potential anti-cancer substances. It is known that their activity and mechanism of action depend on the type of modification of the thiadiazole ring, which is pharmacophore.

Cancer is one of the most insidious and feared disease. It is a class of diseases in which cell, or a group of cells display uncontrolled growth, invasion, and sometimes metastasis. It affects people at all ages with the risk of most types increasing with age. It caused about 13% (7.6 million) of all human deaths in 2007. [20-21]

Not all cancers is life threatening. Benign tumours are growths that remain localized in a particular part of the body and can grow to the size of football without a fatal result (The word tumour actually means a local swelling). Malignant cancers on the other hand, are life threatening because the cells involved have the ability to break away from the primary tumour, invade a blood vessel or a lymphatic vessel, travel through the circulation and set up tumours elsewhere in the body. Although cancer is difficult to treat, there have been notable successes in treating rapidly growing cancers such as Hodgikin's disease, Burkitt's lymphoma, testicular cancer and several childhood malignancies. Early diagnosis also improves the chances of successful treatment in other cancers. At present, four cancers account for over half of all new cases (lung, breast, colon, and prostate.) [22]

In this research article we mainly emphasis on the structure activity relationships (SAR) of synthesized a series of novel derivatives of 5-(2-fluoro and 2, 3-difluoro phenyl)-1, 3, 4-thiadiazole-2-amine. The aim here is to discover which parts of the molecule are important to biological activity and which are not. Already we studied the antimicrobial activity of these derivatives by using Kirby Bauer Disc diffusion method using standard antibiotic chloroamphenicol. The derivatives are effective against antibacterial agents or antibiotics. Based on the Ehrlich's 'Principle of Chemotherapy' was that chemical could directly interfere with the proliferation of microorganisms, at concentration tolerated by host.

The structures of all synthesized derivates were confirmed by spectral analysis such as UV, IR, ^{1}H NMR, mass spectroscopy and elemental analysis.

MATERIALS AND METHODS

All chemicals used in this study were purchase from Aldrich Chemicals and Loba Chem. It was used without further purification. Laboratory chemicals were supplied by Vijay Chemicals Ltd. and Sharad Agency, Pune.

BIOLOGICAL EVALUATION AS ANTIMICROBIAL ACTIVITY OF SYNTHESIZED DERIVATIVES OF 5- MONO AND DI FLUORO SUBSTITUTED PHENYL -1, 3, 4-THIADIAZOLES-2-AMINE

Assessment of antimicrobial activity of newly eight synthesized derivatives(6ai-iv & 6bi-iv) of 5- mono and di fluoro 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***, (Gram positive bacteria), ***E. coli*** *and* ***Enterobacteraerogenes***, (Gram negative bacteria) respectively. Antifungal activity screened against ***Aspergillus niger*** and ***Penicillium chrysogenum***.

5-(2-fluoro-phenyl)- 1, 3, 4-thidiazole-2-amine acts as parent molecule and its antibacterial and antifungal activity also tested as reference compound of all the newly synthesized derivatives. The bacterial and fungal cultures are denoted by alphabets A*, B*, C*, D*, E*, F* where A*, B*, C*, D* assigned for bacterial microorganism and E*, F* for fungal microorganism.

MINIMUM INHIBITION CONCENTRATION (MIC)

The minimum inhibitory concentrations (MIC) is defined as the lowest concentration of a drug that will inhibit the visible growth of an organism after overnight incubation (this period is extended for organisms such as Anaerobes, which require prolonged incubation for growth).MICs are considered the ‘gold standard’ for determining the susceptibility of organisms to antimicrobials and are therefore used to judge the performance of all other

methods of susceptibility testing. MICs are used in diagnostic laboratories to confirm unusual resistance, to give a definitive answer when a borderline result is obtained by other methods of testing, or when disc diffusion methods are not appropriate.[23]

EXPERIMENTAL

All melting points were taken in open capillary tube method and are uncorrected. The purity of the compounds was checked by TLC on pre-coated SiO_2 gel (HF254, 200 meshes) readymade aluminum 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. R_f values of the synthesized derivatives 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 derivatives were performed on Carlo Erba 1108analyzer. Elemental analyses of the entire compounds were in agreement with the calculated values.

SCHEME FOR SYNTHESIS OF 5-(2-FLUORO/2, 3 DI FLUORO SUBSTITUTED PHENYL) - 1, 3, 4-THIDIAZOLE-2-AMINE AND THEIR DERIVATIVES [25]

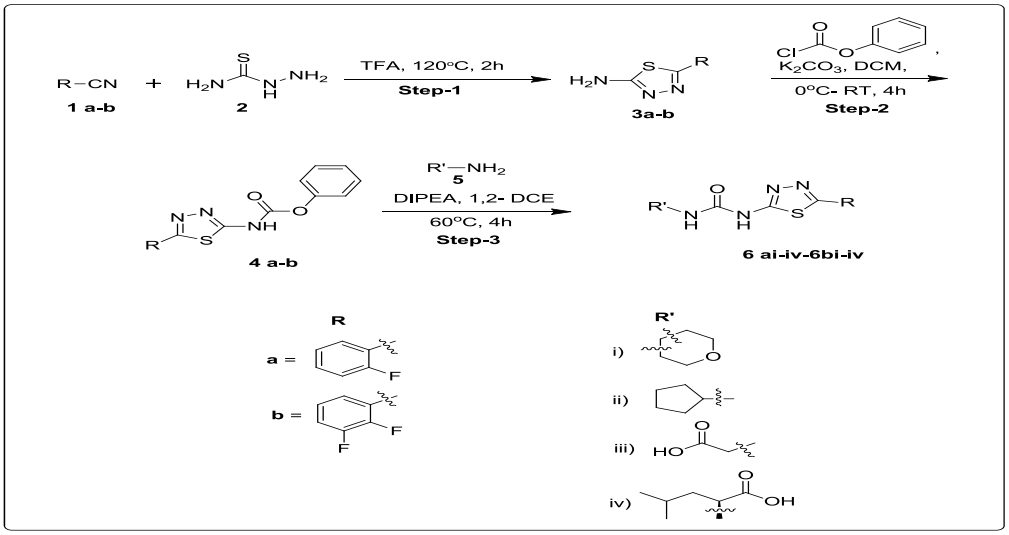
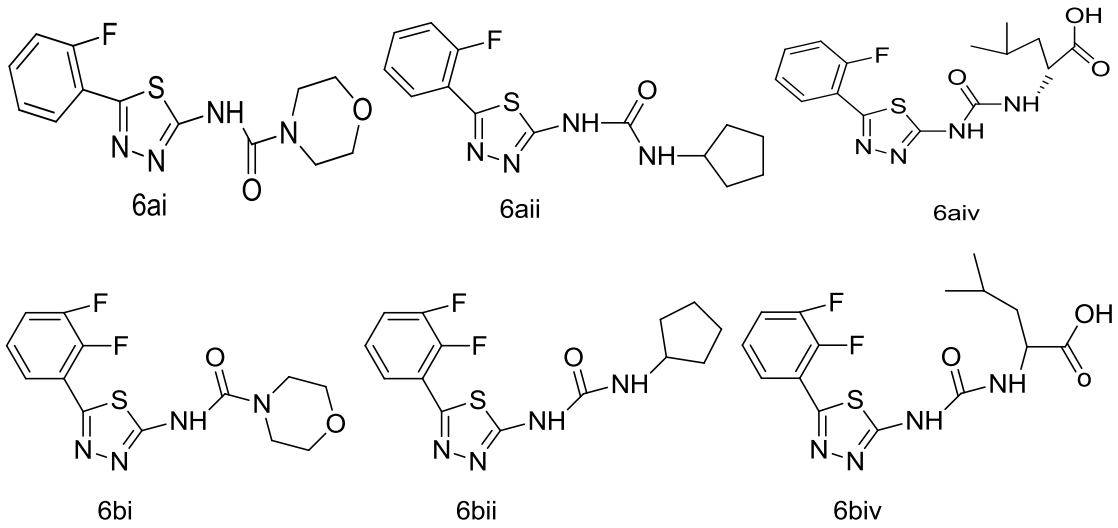


Table no.01-Characterization data of novel synthesized derivatives (6ai-iv & 6bi-iv)

Derivatives	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
6ai	280	0.65	55	$C_{13}H_{13}FN_4O_2S$	308.0743	309.0814 (M+H)	50.64	4.25	6.16	18.17	10.40
6aii	285	0.55	52	$C_{14}H_{15}FN_4OS$	306.0951	307.1029	54.89	4.94	6.20	18.29	10.46

						(M+H)					
6aiii	180	0.75	54	$C_{11}H_9FN_4O_3S$	296.0379	297.0457 (M+H)	44.59	3.06	6.41	18.91	10.82
6aiv	160	0.80	53	$C_{15}H_{17}FN_4O_3S$	352.1005	353.1077 (M+H)	51.13	4.86	5.39	15.90	9.10
6bi	285	0.62	62	$C_{13}H_{12}F_2N_4O_2S$	326.0649	327.0737 (M+H)	47.85	3.71	11.64	17.17	9.82
6bii	290	0.58	55	$C_{14}H_{14}F_2N_4OS$	324.0856	325.0934 (M+H)	51.84	4.35	11.71	17.27	9.88
6biii	185	0.72	63	$C_{11}H_8F_2N_4O_3S$	314.0285	315.0368 (M+H)	42.04	2.57	12.09	17.87	10.20
6biv	162	0.78	50	$C_{15}H_{16}F_2N_4O_3S$	370.0911	371.0987 (M+H)	48.64	4.35	10.26	15.13	8.66

Structure of synthesized Derivatives (6ai-iv & 6bi-iv)



Structures 6aiii and 6biii are shown below table no.04 to explain comparative study of MIC with TM.

Table No.02 IR/ ^{1}H NMR Spectral study of the synthesized derivatives (6ai-iv & 6bi-iv)

Synthesized Derivatives	IR (cm^{-1}, KBr pallets)	^{1}H NMR (ð ppm)
6ai	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 Ar-H str), 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).	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)
6aii	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 tretch),1093 cm^{-1}, 990.44 cm^{-1} (C-H)	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

	,831.35 cm^{-1} (C-F stretch) 761 cm^{-1} (C-H stretch).	Hz, 1H NH-cyclopentyl), 7.34 - 7.59 (m, 3H, aromatic), 8.14 - 8.22 (m, 1H-cyclopentyl), 10.73 (bs, 1H, NH)
6aiii	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).	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)
6aiv	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, Ar-H), 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).	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)
6bi	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 Ar-H), 1419 cm^{-1} (C-C stretch Ar-H), 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).	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)
6bii	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).	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-)
6biii	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).	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)
6biv	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-H), 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).	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)

Table No.03 In vitro antimicrobial activity of synthesized Derivatives (6ai-iv & 6bi-iv)

Derivatives	Antibacterial data in zone of inhibition(mm)				Antifungal data in zone of inhibition (mm)	
	Gram + Ve Bacteria		Gram-Ve Bacteria		Fungi	
	S. aureus *A***	*B. subtilis* *B**	*E. coli* *C**	*E.aerogenus* *D**	*A.niger* *E***	*P.chrysogenum* *F***
6ai	11.7	--	12.2	--	7.5	*7*
6aii	13.4	---	9.6	13.2	7	*8.25*
6aiii	10.6	8	10.6	14.6	8.7	*11.5*
6aiv	13.2	--	14.6	16.4	8	--
6bi	12.8	10.6	15.2	16	12.5	*8.25*
6bii	10.6	12.6	14	16	14	*7*
6biii	12.4	12.4	14.2	11.6	12.5	*9.75*
6biv	11.2	---	12	16.6	10	--
STD	10	10	10	10	10	10
TM	10.8	10.4	9.8	10	15.2	15.25

Highly active = (inhibition zone > 16 mm) moderately active = (inhibition zone 10 - 16mm)

Slightly active = (inhibition zone 6 - 10 mm) Inactive = (inhibition zone < 6 mm)

Table no.04 Minimum inhibition concentration of selected derivatives

Sr. No.	Bacteria	Concentration(ug/ml) MIC FOR TGA				MIC FOR 6biii				MIC FOR 6aiii			
		50	100	150	200	25	50	100	200	25	50	100	200
1	A*	---	++	++	++	+	+	+	+	_	+	+	+
2	B*	__	++	++	++	_	+	+	+	_	_	+	+
3	C*	__	++	++	++	+	+	+	+	_	+	+	+
4	D*	__	++	++	++	+	+	+	+	+	+	+	+
5	E*	++	++	++	++	+	+	+	+	+	+	+	+
6	F*	++	++	++	++	_	+	+	+	_	+	+	+

A* ***Staphylococcus aureus***, ***B**** ***Bacillus subtilis*** (Gram positive bacteria),

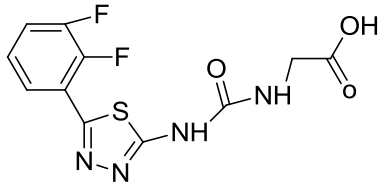
C* ***Escherichia coli*** ***D**** ***Enterobacteraerogenes*** (Gram negative bacteria)

E* - ***Aspergillus niger*** **F*-** ***Penicillium chrysogenum*** (Fungus).

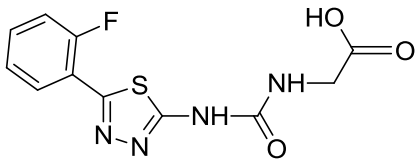
TM- ***5-Phenyl-1, 3, 4-Thidiazole-2-Amine*** **STD-Chloroamphenicol**

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

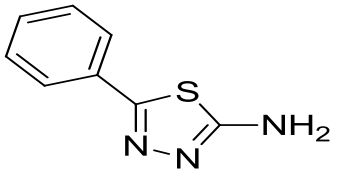
6aiii- ***(5-(2-fluorophenyl)-1, 3, 4-thiadiazol-2-yl) carbamoyl)glycine***



6biii

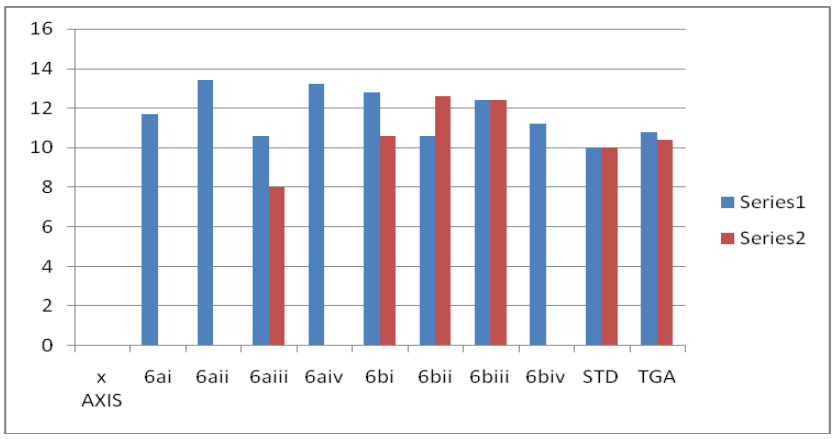


6aiii

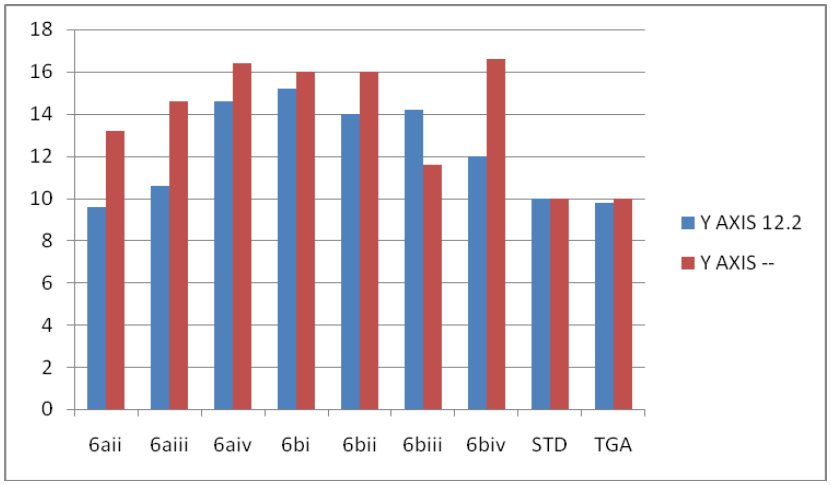


TM

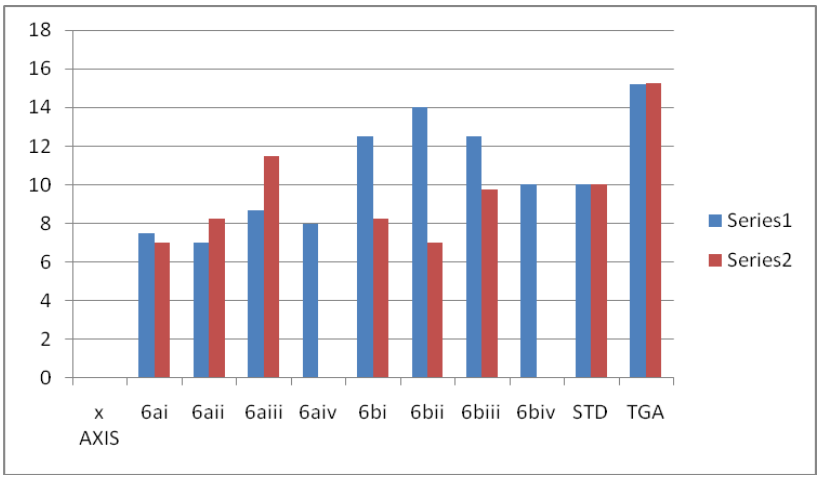
At lower cocentration (50 ug/ml) TM -5-phenyl-1, 3, 4-Thidiazole-2 amine remained inactive against *Staphylococcus aureus, Bacillus subtilis* (Gram positive bacteria), *Escherichia coli Enterobacteraerogenes* (Gram negative bacteria).Against *B.subtilis ,S aureus and E.coli* upto conentration 25-50 ug/ml 6aiii derivatives showed inactive result. 6biii also inactive against *B.subtilis* at 25 ug/ml. At 50-200 ug/ml 6aiii and 6biii synthesized derivatives showed good efficacy. Phenyl ring substituted mono and di fluorine atoms to enhance the antimicrobial activity.i.e antibacterial and antifungal activity. Compare to E* - *Aspergillus niger & F*-*Penicillium chrysogenum* (Fungus) derivatives are more potent towards *A.niger.* TM remained inactive at 50 ug/ml against bacterial strains. i.e derivatives enhance the activity.



Bar graph-1)Inhibition rate of synthesized derivatives against *S.aureus and B.subtilis*

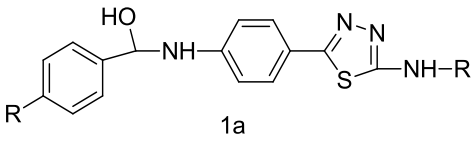


Bar graph-2)Inhibition rate of synthesized derivatives against *E.coli and E.aurogenus*



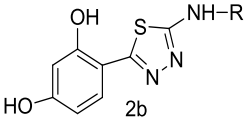
Bar graph Inhibition rate of synthesized derivatives against *A.niger and P.chrysogenum*

ANTICANCER AND ANTIMICROBIAL ACTIVITY:

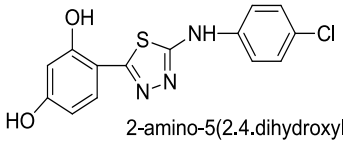


1a

5-[-4-(4Flurobenzyloamino) phenyl]-2-substituted-1,3,4-thidiazole derivatives



2b

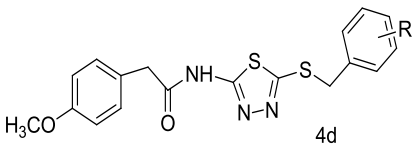


2-amino-5(2.4.dihydroxyl)-1,3,4-thidiazole

3c

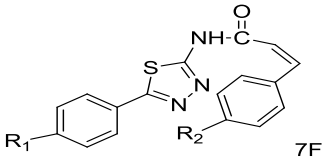
N-substituted -2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thidiazole

R= 2-F,3-F,4-F,OR Cl, NO2 substituents



4d

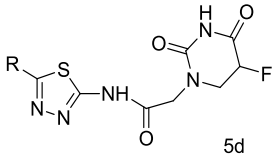
n-(5-mercapto-1,3,4-thidiazole-2-yl)-2-(4-metoxyphenyl acetamide)



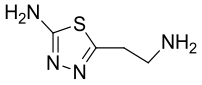
7F

R1=OCH3 &R2=F

potent inhibitory activity in tumor growth may be a potential anticancer agent



5d



6e

5-amino-1,3,4-thidiazole-2-aminoalkyl derivatives

A series of N-substituted 2-amino-5-(2, 4-dihydroxyphenyl)-1, 3, 4-thiadiazoles (1a-3c) were seems to be structural similarity with synthesized and antimicrobial evaluated derivatives 6ai-iv to 6bi-iv. Most antibacterial agents used for the treatment of bacterial infections may be categorized according to their principle mechanism of action : 1) interference with cell wall synthesis.2) inhibition of protein synthesis, 3) interference with nucleic acid synthesis and 4) inhibition of metabolic pathway.[26-27]

Anticancer compounds are evaluated for their antiproliferative activities against human cancer cell lines. The cytotoxicity in vitro against the four human cell lines: SW707 (rectal), HCV29T (bladder), A549 (lung), and T47D (breast) was determined. The highest antiproliferative activity was found for 2-(2, 4-dichlorophenylamino) 5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole, with ID50 two times lower (SW707, T47D) than for cisplatin studied comparatively as the control compound. The panel substitution included alkyl, alkoxy, aryl and hetroaryl derivatives.[28-29]

RESULTS AND DISCUSSION

A series of 5-(2-fluoro/2, 3 di fluoro substituted phenyl) - 1, 3, 4-thidiazole-2-amine and their derivatives (6ai-iv & 6bi-iv) were synthesized and evaluated their antibacterial and antifungal activity in vitro against *S.aureus and B.subtilis* **(**gram positive**)** *E.coli and E.aurogenus(*gram negative) *A.niger and P.chrysogenum* (antifungal) bacterial strains. Bar graph of inhibition activity of these strains against synthesized and evaluated derivatives were explained properly to convinient evaluation.Bioassay activity result showed that the most of synthesized derivatives exhibited significant activity against all the bacterial strains. Amongst all, derivatives 6aii, 6aiii, 6aiv, 6bii, 6biii, 6biv showed comparable activity against to the reference drug. An antifungal drug is medication used to treat fungal infections such as athlete's foot, ring worm,candidiasis (thrush), serious systematic infections such as cryptococcal meningitis and others.[30] Antifungal work by exploiting difference between mammalian and fungal cells to kill the fungal organism without dangerous effect on the host. The SAR studies explain that compound containing electron withdrawing group fluro at phenyl ring increases in 6b synthesized derivatives which resulted into significant antifungal activity against *A.niger and P.chrysogenum* and antibacterial activity against gram positive bacteria *E.coli and E.aurogenus.*Most antibacterial agents used for the treatment of bacterial infections may be categorized according to their principle mechanism of action : Literature

survey of review articles of anticncer activity of 1,3,4-thidiazole opened that chloro,bromo,fluro sunstituted at phenyl group showed better antitumor activity. [31]

The thidiazole ring posseses similar chemical properties to the pyrimidine ring,can be considered as a bioisostere. Given that pyrimidine structure is found in nucleobase component of nucleotide the building block of DNA & RNA, it seems like that thidiazole could readily interact with DNA & RNA potentially explaining the broad and often potential activity. Furthermore this activity against DNA suggest that thidiazole derivatives could be potentially be used for chemical intervention at gene level. Thidiazole are mesoionic and polyheteroatomic system containing a five membered heterocyclic ring associated with a conjugation of ð and π ele.and distinct regions of positive and negative charges leading to highly polarisable derivatives. The distinctive characteristics allows mesoionic compounds to effectively cross cellular membranes and interact with biological molecules in unique ways,further explaining the high potential of this scaffold in medicinal chemistry.The good liposolubility of the sulfur atom in the heterocycle might also have a positive effect on the biological activity and pharmakokinetic properties of thidiazole containing compounds.[32]

CONCLUSION

Mono and di fluro substituted aromatic nitriles reacts with thiosemicarbazide at 120 ^{0}C temperature for 2 hr yielded corresponding 1, 3, 4-thidiazole in excellent yield. Easy to workup and environmental friendly approach. With the help of 1, 3, 4-Thidiazole moiety about eight novel derivatives were synthesized using pharmacophores amino acids leuicine and glycine having carboxylic acid which showed good anti-inflammatory activity and after screening of antimicrobial activity it proved that these derivatives are excellent in antibacterial and antifungal activity compare to chloroamphenicol drug. Structure activity relationship of synthesized and antimicrobial derivatives drug compared with synthesized and screened anticancer activity of compounds through studied referenced articles. There will be always a vital need to discover new chemotherapeutic agents to avert the emergence of resistance and ideally shorten the duration of therapy.

SAR study reveals that a small structural variation may induce an effect of increase in chemotherapeutic activity. We are sure that synthesized novel derivatives of 5-fluro phenyl substituted-1, 3, 4-thidiazole-2-amine moiety will be good in anticancer activity seems like antimicrobial activity of synthesized derivatives. Therefore it is concluded that there exist

ample scope for synthesis, characterization and investigation of in vitro anticancer derivatives.

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