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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION OF NOVEL COMPOUNDS OF 3-((BENZO[D]THIAZOL-2-YLMETHYL)AMINO)-1-(2,5-DIFLUOROBENZOYL)-4-(2-(4-(SUBSTITUTED)PHENYL)HYDRAZONO)-1H-PYRAZOL-5(4H)-ONE

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Abstract: New novel derivatives of 3-((benzo[d]thiazol-2-ylmethyl)amino)-1-(2,5-difluorobenzoyl)-4-(2-(4-(substituted)phenyl)hydrazono)-1H-pyrazol-5(4H)-one (2a-g) were prepared by refluxing a mixture of ethyl 2-(4-(2-(4-subtituted methyl)phenyl)hydrazono)-1-(2,5-difluoro benzoyl)-4,5-dihydro-5-oxo-1H-pyrazol-3-yl)amino Carboxylic acid. (1a-g) and 2- amino thio phenol

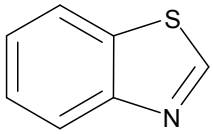
Methods: The newly synthesized compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, mass spectra & Elemental analysis. The newly synthesized compounds were screened for their Biological activity**.**

Keywords: Benzthozole, 2-amino thio phenol, ,Antibacterial and Antifungal activity,spectral data.

INTRODUCTION

BENZOTHIAZOLES

Benzothiazoles are fused membered rings, which contain the heterocycles bearing thiazole. Sulphur and nitrogen atoms constitute the core structure of thiazole and many pharmacologically and biologically active compounds.



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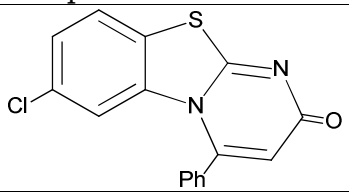
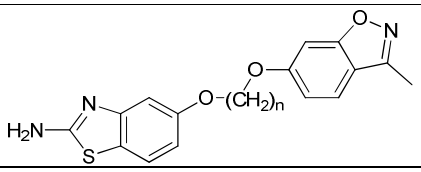
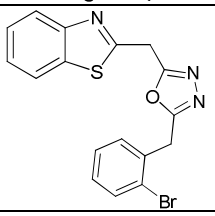
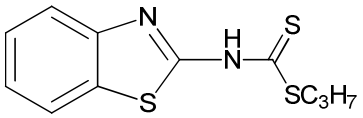
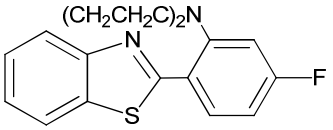
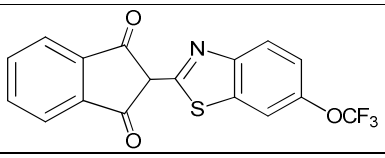
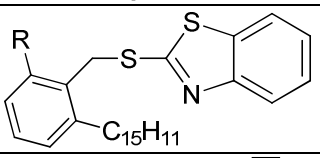
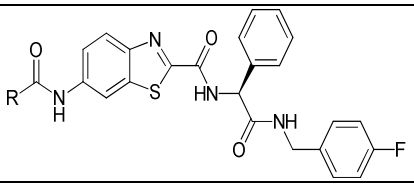
Benzothiazole is a weak base, with broad spectrum of biological activities and still with great scientific interest. They are extensively found in bioorganic and medicinal chemistry with

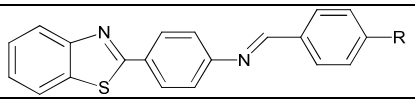
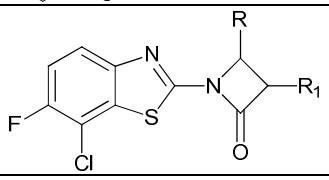
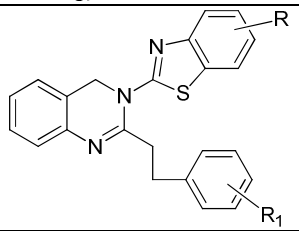
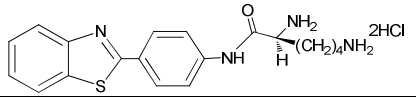
application in drug discovery. Benzothiazoles like 2-aryl benzothiazole received much attention due to unique structure and its uses as radioactive amyloid imagining agents[1], and anticancer agents[2]. Compounds with benzothiazole moiety are found to possess numerous biological activities such as antimicrobial[3-5], anthelmintic[6], anti-diabetic[7], anticancer[8-10]activities. Besides the pharmaceutical applications, they have also found application in industry as anti-oxidants, vulcanisation accelerators.

The review of literatures describes that the benzothiazole derivatives possess a variety of biological activities[11-12]

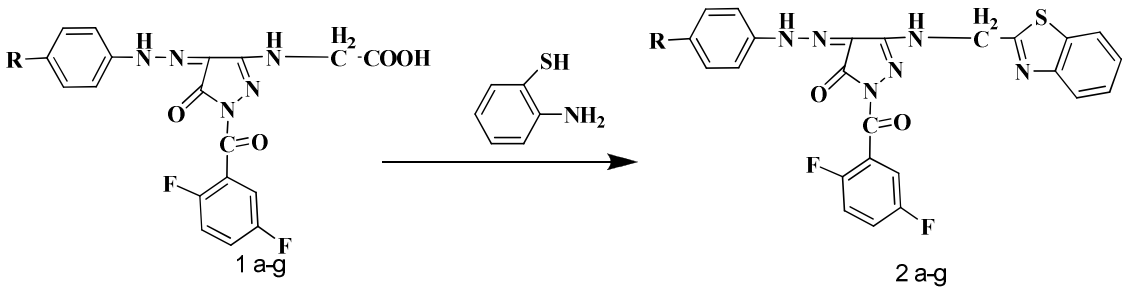
Some biologically potent benzothiazole derivatives with varied structural features were listed

Biologically active benzothiazole derivatives

S.No	Compound	Activity	Reference
1		Antimicrobial	Gupta S *et al* [1]
2		Antifungal	Kumbhare RM *et al* [2]
3		Antimicrobial	Rajeeva B, *et al* [3]
4		Schistosomicidal	Maharan M, *et al* [4]
5		Anticancer	Kini S, *et al* [5]
6		Anti-cancer	Stanton HLK, *et al* [6]
7		Cyclooxygenase inhibitor	Parmshivappa R *et al* [7]
8		MTP inhibiton	Chi B *et al* [8]

9		Antibacterial and antifungal	Nagarajan A *et al* [9]
10		Anti-inflammatory	Gurupadayya B. *et al* [10]
11		Anti-inflammatory	Srivastava N *et al* [11]
12		Anticancer	Hutchinson I *et al* [12]

Scheme I: The synthetic route was depicted in scheme**.** The structure were established by spectral (IR, ^{1}H-NMR, ^{13}C-NMR and mass) and analytical data.



R	-H	-CH3	-OCH_3	-Cl	Br	NO_2	CF_3

MATERIALS & METHODS

All the chemicals used in the present investigation were purchased from Sigma-Aldrich Chemicals Company, Inc.USA. And used without further purification. TLC was performed on aluminum sheet of silica gel 60F254, E-Merk,Germany using iodine as visualizing agent. Melting point was determined in open capillary tubes on Mel-Tempapparatus and is uncorrected. Column chromatography was performed on silica gel with different solvent systems as eluents to afford the pure compound. The IR Spectra were recorded as KBr pellets on Perkin-Elmer 1000 units, instruments. All 1H and 13C-NMR spectra were recorded on a Varian XL-300 spectrometer operating at 400MHzfor 1H -NMR and 75 MHz for ^{13}C-NMR were recorded on a Varian XL-spectrometer operating at161.89MHz. The compounds were dissolved in DMSO-d6 and Chemical shifts were referenced to TMS (1H and^{13}C-NMR) .Mass spectral data were recorded on FAB-MS instrument at 70ev with direct inlet system. Elemental analysis was recorded on a Carlo Erba 1108 elemental Analyzer, Central Drug Research Institute, Lucknow, India.

EXPERIMENTAL

Synthesis of ethyl 2-(4-(2-(4-subtituted methyl)phenyl)hydrazono)-1-(2,5-difluoro benzoyl)-4,5-dihydro-5-oxo-1H-pyrazol-3-yl)amino Carboxylic acid.

To a solution of ester(2a,1eq) in tetra hydro furan/MeOH/H_2O(1:1:1) ratio aq NaOH(2N) was added and stirred (room temp) or reflux for 4-6 hrs.After completion of the reaction as indicated by TLC using mobile phase as cyclo hexane and ehyl acetate (7:3).The a residue was washed with EtOA(removing impurities). The solvent was evaporated under vaccum to affored 3a-g. After the residue was acidified with 1N HCl up to PH-2 to give solid suspension,which filtered extracted with EtOAc(2x30ml) twice. The organic layer was collected washed with water brain dried over anhydrous Na_2SO_4 filtered and evaporated under vacuum to give the crude acid product (4-(2-(4-substituted)phenyl)hydrazono)-1-(2,5-difluorobenzoyl)-4,5-dihydro-5-thioxo-1H-pyrazole-3-yl)amino carboxylic acid(1a).

Synthesis of 3-((benzo[d]thiazol-2-ylmethyl)amino)-1-(2,5-difluorobenzoyl)-4-(2-(4-(substituted)phenyl)hydrazono)-1H-pyrazol-5(4H)-one (2a-g)

A mixture of 2-(4-(phenyl)hydrazono)-1-(2,5-difluoro benzothioyl)-4,5-dihydro-5-oxo-1H-pyrazol-3-yl)amino Carboxylic acid (1a) and 2-aminothio phenol were refluxed for 2h at 150^0C presence of PPSE. . The progress of the reaction was monitored by TLC using 9:1 hexane and ethyl acetate solvent mixture as mobile phase.The reaction mixture was dissolved in dichloro methane and neutralized with aq NaOH(1N).The organic layer was once again extracted with dichloro methane and dried over unhydrous Na_2SO_4. The excess of the solvent in organic layer was evopareted by rotar evoparetor.The crude solid was purified by column chromatography using silica gel(60-120 mesh) as an adsorbed and chloroform as an elutent. The pure product was identified as 3-((benzo[d]thiazol-2-ylmethyl)amino)-1-(2,5-difluorobenzoyl)-4-(2-(4(trifluoromethyl)phenyl) hydrazono) -1H-pyrazol-5(4H)-one(2a). The yield was 75% with mp146-148^0C. was adopt The similar procedure was adopted to synthesise 2 b-g from 1b-g and O-amino thiophenol.

The structure of 3-((benzo[d]thiazol-2-ylmethyl)amino)-1-(2,5-difluorobenzoyl)-4-(2-(4(trifluoromethyl)phenyl)hydrazono)-1H-pyrazol-5(4H)-one (**2a-g)** was established by IR,^{1}H-NMR,^{13}C-NMR and Mass Spectral data.

Physical, analytical and spectral data for the compounds:

IR Spectral data

The IR(KBr) Spectra of **3-((benzo[d] thiazol-2-ylmethyl)amino)-1-(2,5-difluorobenzoyl)-4-(2-(4-(phenyl)hydrazono)-1H-pyrazol-5(4H)-one(2a)**was recorded in the range 4000-400cm-1 in KBr pellets reflect the molecular stracture and showed the characteristic bands around 3384(NH-str),1694(Exocyclic >C=o group),1654(pyrazoline-5-one >C=O),1622(>C=N group),1100(C-F str),and 1158(-C-O-C- of Benzoxazole ring).

IR Spectral data of 3-((benzo[d]thiazol-2-ylmethyl)amino)-1-(2,5-difluorobenzoyl)-4-(2-(4-(trifluoromethyl)phenyl)hydrazono)-1H-pyrazol-5(4H)-one.

Compound	R	υ max in Cm^{-1}				
		C=O cyclic	C=N	C-S	C-F	N-H
2a	-H	1694	1605	1158	1100	3381
2b	CH_3	1698	1608	1140	1107	3390
2c	OCH_3	1697	1609	1145	1109	3389
2d	Cl	1699	1610	1160	1110	3392
2e	Br	1698	1608	1159	1107	3390
2f	NO_2	1699	1610	1165	1110	3392
2g	CF_3	1700	1610	1163	1120	3399

^{1}HNMR Spectral Data:-

The ^{1}H-NMR(400MHz) spectra of **3-((benzo[d]thiazol-2-ylmethyl)amino)-1-(2,5-difluorobenzoyl)-4-(2-(4-(phenyl)hydrazono)-1H-pyrazol-5(4H)-one(2a) was** recorded in DMSO-d_6 showed the following signals at **(δppm)** 2.0(s, H, NH attached to pyrazoline-5-one ring), 3.85(s,2H, -CH_2 attached to benzo [d] oxazole group group) , 10.15 (s,H,Ar-NH—N= Group) 6.81-7.59(m,12H C_6H_5 C_6H_3 and C_6H_3),respectively.

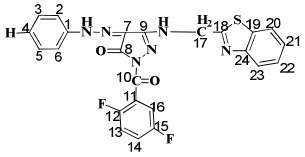
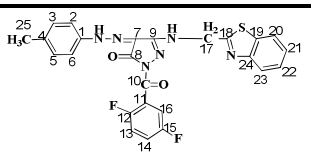
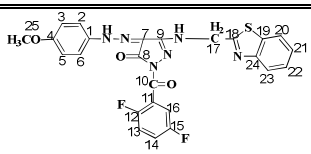
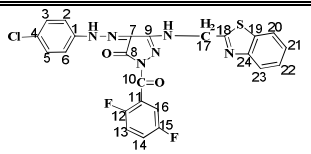
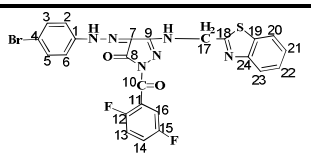
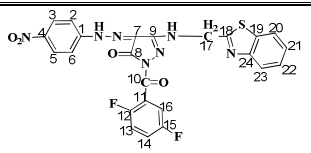
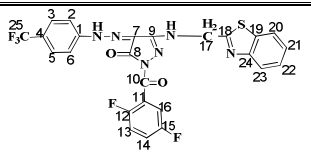
^{1}H-NMR Spectral data:

Table 1.2 ^{1}H- NMR Spectral data of 3-((benzo[d]thiazol-2-ylmethyl)amino)-1-(2,5-difluorobenzoyl)-4-(2-(4-(trifluoromethyl)phenyl)hydrazono)-1H-pyrazol-5(4H)-one (2a-g)

Compound	R	^{1}H- NMR (300 MHz) (DMSO- d6) (δppm)
2a	-H	2.0(t, H, NH attached to pyrazoline-5-one ring), 3.91(t,2H, -CH2 of 1H benzo [d] oxazole group) , 10.15 (s,H,Ar-NH—N= Group) 6.81-7.59(m,12H C_6H_5 C_6H_3 and C_6H_3),
2b	CH_3	2.34 (s,3H,-CH_3 Group),2.0(t, H, NH attached to pyrazoline-5-one ring), 3.91(t,2H, -CH2 of 1H benzo [d] oxazole group) , 10.15 (s,H,Ar-NH—N= Group) 6.81-7.59(m,12H C_6H_5 C_6H_3 and C_6H_3),
2c	OCH_3	3.81 (s,3H,-OCH_3 Group),2.0(t, H, NH attached to pyrazoline-5-one ring), 3.91(t,2H, -CH2 of 1H benzo [d] oxazole group) , 10.15 (s,H,Ar-NH—N= Group) 6.81-7.59(m,12H C_6H_5 C_6H_3 and C_6H_3),
2d	Cl	2.0(t, H, NH attached to pyrazoline-5-one ring), 3.91(t,2H, -CH2 of 1H benzo [d] oxazole group) , 10.15 (s,H,Ar-NH—N= Group) 6.81-7.59(m,12H C_6H_5 C_6H_3 and C_6H_3),
2e	Br	2.0(t, H, NH attached to pyrazoline-5-one ring), 3.91(t,2H, -CH2 of 1H benzo [d] oxazole group) , 10.15 (s,H,Ar-NH—N= Group) 6.81-7.59(m,12H C_6H_5 C_6H_3 and C_6H_3),
2f	NO_2	2.0(t, H, NH attached to pyrazoline-5-one ring), 3.91(t,2H, -CH2 of 1H benzo [d] oxazole group) , 10.15 (s,H,Ar-NH—N= Group) 6.81-7.59(m,12H C_6H_5 C_6H_3 and C_6H_3),
2g	CF_3	2.0(t, H, NH attached to pyrazoline-5-one ring), 3.91(t,2H, -CH2 of 1H benzo [d] oxazole group) , 10.15 (s,H,Ar-NH—N= Group) 6.81-7.59(m,12H C_6H_5 C_6H_3 and C_6H_3),

^{13}C-NMR Spectral data:-

The ^{13}C-NMR spectral data of**3-((benzo[d]thiazol-2-ylmethyl)amino)-1-(2,5-difluorobenzoyl)-4-(2-(4-(trifluoromethyl)phenyl)hydrazono)-1H-pyrazol-5(4H)-one (2a-g)** was recorded in $CDCl_3$ showed the following signals 143.0,113.9,129.5,122.4,142.7,170.2,126.7, 154.9, 118.7, 120.5, 118.6,120.9,117.5,43.3,140.5,123.0,115.2and 128.9 Corresponding to C_1,C_2&C_6,$C_{3\&}C_5$, C_4,C_7, C_8, C_9, C_{10},C_{11}, C_{12},C_{13},C_{14}, C_{15}, C_{16},C_{17},C_{18},C_{19}&C_{24},$C_{20\&}C_{23}$ and $C_{21\&}C_{22}$ .Respectively

S.No	R	STRACTURE	^{13}C-NMR SPECTRA (DMSO-d6(δ,ppm),
2a	**H**		143.0,113.9,129.5,122.4,142.7,170.2,126.7, 154.9, 118.7, 120.5, 118.6,120.9,117.5,43.3,140.5,123.0,115.2and 128.9 Corresponding to C_1,C_2&C_6,C_3&C_5,C_4,C_7, C_8, C_9, C_{10},C_{11}, C_{12},C_{13},C_{14}, C_{15}, C_{16},C_{17},C_{18},C_{19}&C_{24},C_{20}&C_{23} and C_{21}&C_{22}
2b	**CH_3**		143.0,113.9,129.5,122.4,142.7,170.2,126.7, 154.9, 118.7, 120.5, 118.6,120.9,117.5,43.3,140.5,123.0,115.2and 128.9 Corresponding to C_1,C_2&C_6,C_3&C_5,C_4,C_7, C_8, C_9, C_{10},C_{11}, C_{12},C_{13},C_{14}, C_{15}, C_{16},C_{17},C_{18},C_{19}&C_{24},C_{20}&C_{23} and C_{21}&C_{22}
2c	**OCH_3**		143.0,113.9,129.5,122.4,142.7,170.2,126.7, 154.9, 118.7, 120.5, 118.6,120.9,117.5,43.3,140.5,123.0,115.2and 128.9 Corresponding to C_1,C_2&C_6,C_3&C_5,C_4,C_7, C_8, C_9, C_{10},C_{11}, C_{12},C_{13},C_{14}, C_{15}, C_{16},C_{17},C_{18},C_{19}&C_{24},C_{20}&C_{23} and C_{21}&C_{22}
2d	**Cl**		143.0,113.9,129.5,122.4,142.7,170.2,126.7, 154.9, 118.7, 120.5, 118.6,120.9,117.5,43.3,140.5,123.0,115.2and 128.9 Corresponding to C_1,C_2&C_6,C_3&C_5,C_4,C_7, C_8, C_9, C_{10},C_{11}, C_{12},C_{13},C_{14}, C_{15}, C_{16},C_{17},C_{18},C_{19}&C_{24},C_{20}&C_{23} and C_{21}&C_{22}
2e	**Br**		143.0,113.9,129.5,122.4,142.7,170.2,126.7, 154.9, 118.7, 120.5, 118.6,120.9,117.5,43.3,140.5,123.0,115.2and 128.9 Corresponding to C_1,C_2&C_6,C_3&C_5,C_4,C_7, C_8, C_9, C_{10},C_{11}, C_{12},C_{13},C_{14}, C_{15}, C_{16},C_{17},C_{18},C_{19}&C_{24},C_{20}&C_{23} and C_{21}&C_{22}
2f	**NO_2**		143.0,113.9,129.5,122.4,142.7,170.2,126.7, 154.9, 118.7, 120.5, 118.6,120.9,117.5,43.3,140.5,123.0,115.2and 128.9 Corresponding to C_1,C_2&C_6,C_3&C_5,C_4,C_7, C_8, C_9, C_{10},C_{11}, C_{12},C_{13},C_{14}, C_{15}, C_{16},C_{17},C_{18},C_{19}&C_{24},C_{20}&C_{23} and C_{21}&C_{22}
2g	**CF_3**		143.0,113.9,129.5,122.4,142.7,170.2,126.7, 154.9, 118.7, 120.5, 118.6,120.9,117.5,43.3,140.5,123.0,115.2and 128.9 Corresponding to C_1,C_2&C_6,C_3&C_5,C_4,C_7, C_8, C_9, C_{10},C_{11}, C_{12},C_{13},C_{14}, C_{15}, C_{16},C_{17},C_{18},C_{19}&C_{24},C_{20}&C_{23} and C_{21}&C_{22}

Mass Spectra:

The electron impact mass spectrum of **3-((benzo[d]thiazol-2-ylmethyl)amino)-1-(2,5-difluorobenzoyl)-4-(2-(4-(trifluoromethyl)phenyl)hydrazono)-1H-pyrazol-5(4H)-one(2a)**

was recorded and interpreted. The mass spectral data of compound (4a) showed the molecular ion [M^+] ion peak at m/z=490.10(100%) it appeared as a base peak and indicates the presence of odd number of nitrogen atoms.The compound 6a also exhibits a very low intence M+ ion signal at 492.10 with 3.96% relative abundance .This indicates the presence of one sulphar atom in the molecular ion.The m/z value indicates that the presence of even number of nitrozen atom.

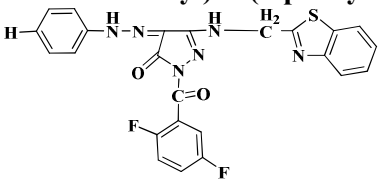
The molecular ion signal was obeying nitrogen rule ,but primary fragmented ions derived from molecular ion may or may not obeying nitrozen rule.The mass data of primary fragmented ions processing sulphar atom fail to exhibit any detectable F+2 ion signal.

Mass spectral data of primary fragmented ions for 3-((benzo[d]thiazol-2-ylmethyl)amino)-1-(2,5-difluorobenzoyl)-4-(2-(4-(trifluoromethyl)phenyl)hydrazono)-1H-pyrazol-5(4H)-one(2a)

Molecular ion	Lost radical	Primary fragmented ion	m/z values	Relative abundance (R.A) (%)
$C_{24}H_{16}F_2N_6O_2S$ m/z=472.13 (100%)	$C_{18}H_{13}N_6O_2\cdot S$	$C_6H_3F_2^+$ (II)	114.02	6.5
	$C_6H_3F_2\cdot$	$C_{18}H_{13}N_6O_2^+S$(III)	378.09	19.7
	$C_{17}H_{14}N_6O\cdot S$	$C_7H_3F_2O^+$(IV)	142.02	7.6
	$C_7H_3F_2O\cdot$	$C_{17}H_{14}N_7OS^+$(V)	351.10	20.7
	$C_6H_6N\cdot$	$C_{18}H_{11}F_2N_5O_2^+S$(VI)	400.06	19.7
	$C_{18}H_{11}F_2N_5O_2\cdot S$	$C_6H_6N^+$(VII)	93.05	6.9
	$C_{16}H_{10}F_2N_5O_2\cdot$	$C_8H_6N\,S^+$(VIII)	149.03	8.8
	$C_8H_6N\,S\cdot$	$C_{16}H_{10}F_2N_5O_2^+$(IX)	343.08	19.2
	$C_{17}H_{12}F_2N_5O_2\cdot$	$C_7H_4N_2S^+$(X)	135.01	8.3
	$C_7H_4N\,S\cdot$	$C_{17}H_{12}F_2N_5O_2^+$(XI)	357.10	18.6

Biological activity

The Antimicrobial profile of 3-(((1H-benzo[d]thiazol-2-yl)methyl)amino)-1-(2,5-difluorobenzoyl)-4-(2-phenylhydrazono)-1H-pyrazol-5(4H)-one (2a-g).



Entry	Bacteria			Fungi	
	Staphylococcus aureus NCCS2079	Bacillus cereus NCCS 2106	Escherichia coli NCCS2065	Aspergillus niger NCCS 1196	Candida albicans NCCS 2106

	25 50	25 50	25 50	25 50	25 50
2a	- 09	- 08	- 07	- 10	- 11
2b	- 07	- 07	- 06	- 09	- 10
2c	- 08	- 10	- 09	- 08	- 12
2d	06 10	09 10	04 08	06 10	08 09
2e	10 14	10 15	07 13	08 13	07 12
2f	09 12	10 14	06 12	07 12	06 15
2g	13 16	13 17	10 15	11 16	12 14
Chloromphenicol (5)	- 25	- 26	- 22	- -	- -
Ketocanazole (50)	- -	- -	- -	- 22	- 24

Each well contains 25 and 50 µg of compounds; Ch=Chloromphenicol 5 µg/mL, Ketocanazole 50 µg/mL

Result and discussion :

The antibacterial activity of **3-(((1H-benzo[d]thiazol-2-yl)methyl)amino)-1-(2,5-difluorobenzoyl)-4-(2-phenylhydrazono)-1H-pyrazol-5(4H)-one (2a-g).**was screened against the gram-positive bacteria *Staphylococcus aureus* NCCS 2079 and *Bacillus cereus* NCCS 2106 The gram negative bacteria used was *Escherichia coli* 2065.The antibacterial results reveals that most of the compounds exhibit good antibacterial activity against both bacteria at the concentration of 50µg/mL.The presence of **nitro (2f),tri fluoro methyl(2g),Chloro (2d) and Bromo(2e**) were showed more activity than other substituted compounds. Here Chloromphenicol was used as reference compound to compare the activity.

The anti-fungal activity of **3-(((1H-benzo[d]thiazol-2-yl)methyl)amino)-1-(2,5-difluorobenzoyl)-4-(2-phenylhydrazono)-1H-pyrazol-5(4H)-one (2 a-g).**was screened against the *Aspergillus niger* NCCS1196 and *Candida albicans* NCCS 2106. The antifungal results reveals that most of the compounds exhibit good anti-fungal activity against both fungi at the concentration of 50µg/mL. The presence of **nitro (2f), tri fluoro methyl (2g), Chloro (2d) and Bromo (2e)** were showed more activity than other substituted compounds. Here Ketocanazole was used as reference compound to Compare the activity

The order of anti microbial activity (50µg/mL) 2f**>2g >2d>2e>2c>2a>2b.**

CONCLUSION:

Heterocyclic compound containing benzothiozole nucleus plays most important role in biological systems. Benzthiazoles and its derivatives are used for biological activities such as antiviral, antibacterial, antifungal and antitubercular. Vast number of benzimidazole derivative compounds have been synthesized and evaluated for their biological activity

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