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Original Article

Synthetic Characterization & Antimicrobial Screening of Some Novel 6-Fluorobenzothiazole Substituted [1, 2, 4] Triazole Analogues

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ABSTRACT

Aim: Benzothiazoles and pyrazoles moieties structurally have better anti inflammatory activity. Therefore various of 8-chloro-7-fluoro-1-[4-methylphenyl] sulphonyl 1,9 dihydro[1,2,4] triazol[3,4-b][1,3] Benzothiazole containing different functional groups have been synthesized by condensing 7- Chloro-6-Fluoro-2-amino-Benzothiazole with hydrazine hydrate in the presence of ethylene glycol and conc. HCl to get 7-chloro-6-fluoro-2-hydrazinyl-1, 3-benzothiazole and then treated with potassium carbonate to get 8-chloro-7-fluoro-1,9a-dihydrol [1,2,4] triazole [3,4-b][1,3] benzothiazole and then treated with *p*-toulene sulphonamide in the presence of pyridine to get 8-chloro-7-fluoro-1-[4-methylphenyl] sulphonyl-1,9a-dihydro[1,2,4]triazolo[3,4-b][1,3]benzothiazole. To the above product different aromatic amines, as well as various primary and secondary amines in presence of DMF and were treated to get newly targeted compounds by replacing chlorine at 7th position. The characterization of the compounds were confirmed on the basis of their spectral (IR, ^{1}H-NMR and MASS) data. Further, they have been screened for their anti-microbial activity. The fungal activity of the compounds was determined by means of the disc-diffusion method. The inhibition zones were measured with a caliper considering the total diameters. The antimicrobial activity of the compounds was determined by means of the disc-diffusion method.

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1. INTRODUCTION

The Benzothiazoles are an interesting group of compounds and biological activities of this class of compounds that are reported in literature are anti-cancer[1], antitumor[2], amyloid-imaging agents[3], anti-microbial[4], anticonvulsant [5], anti-diabetic[6], anti-tubercular [7], muscarinic receptor agonist [8], and antibacterial activity [9]. Fluorine has been incorporated in the drug molecule as a means of increasing therapeutic efficacy, based on considerations such as, its ability to mimic hydrogen with respect to steric requirements, strong electron withdrawing inductive effect which can affect reactivity and stability, inhibition of metabolism because of high C-F bond energy, altered lipid solubility which alters absorption and distribution.

Triazole is one of a class of organic heterocyclic compounds containing a five-membered di unsaturated ring structure composed of three nitrogen atoms and two carbon atoms at non adjacent positions. The simplest member of the triazole family is triazole itself, white to pale yellow crystalline solids with a weak characteristic odour; soluble in water and alcohol, melts at 120^0C, boils at 260^0C. Depending on the character of the substituents, 1, 2, 4-triazole may exhibit different pharmacological activities such as anti-inflammatory, antifungal, antibacterial, and antiviral[10].

Some other 1, 2, 4- and 1, 3, 4-triazole derivatives have been reported to possess tuberculostatic, herbicidal and plant-growth-regulator activities. The triazole antifungal drugs include fluconazole, isavuconazole, itraconazole, voriconazole, pramiconazole, and posaconazole.the triazole plant protection fungicides include epoxiconazole, triadimenol, propiconazole, cyproconazole, tebuconazole, flusilazole and paclobutrazol[11], as well as the potent antiviral *N*-nucleoside ribavirin. Votriconazole is a novel wide spectrum triazole which has potent *invitro* activity against *candida spp* and *aspergillus spps*[12].

2. EXPERIMENTAL

The following experimental methods were used for the characterization of the synthesized compounds. Melting points of the synthesized compounds were determined in open capillary tubes and are uncorrected. The IR spectrum was recorded on ELICIO FTIR spectrometer using potassium bromide pellets. ^{1}H-NMR spectra of the compounds in deutiriated dimethylsulfoxide was recorded on BRUKER Av 400 spectrometer. Mass spectrum was recorded on GCMS QP 5000 shimadzu. Thin layer chromatography was performed using precoated aluminium plates coated with silica gel GF_{254} [E.Merck]. N-hexane: ethylacetate was used as the eluent. The spots were visualized in the ultraviolet light chamber.

2.1. First Step: Synthesis of 2-amino-6-fluoro-7-chloro (1, 3) Benzothiazole:

To glacial acetic acid (20ml) cooled below room temperature were added 8gm (0.08mol) of potassium thiocyanate and 1.45g (0.01 mol) of fluoro chloro aniline. The mixture was placed in a water bath and stirred with magnetic stirrer while 1.6 ml of bromine in 6ml of glacial acetic acid was added from a dropping funnel at such a rate that the temperatures never rise beyond room temperature. After all the bromine was added (105min), the solution was stirred for below room temperature for 10 hours, it was then allowed to stand overnight, during which period an orange precipitate settle at the bottom, water (6ml) was added quickly and slurry was heated at 85^0C and filtered hot. The orange residue was placed in a reaction flask and treated with 10ml of glacial acetic acid heated again to 85^0C and filtered hot. The combined filtrate was cooled and neutralized with ammonia solution to the pH range 6.0 dark yellow precipitate was collected. Recrystalised from benzene & ethanol of (1:1) after

treatment with animal charcoal gave yellow crystals of 2-amino-6-fluoro-7-chloro-(1,3)-benzothiazole. After drying in an oven at 80^0C, the dry material (1gm, 51.02%) melted at 210-212^0C.

***2.2. Second Step: Synthesis of 7- chloro- 6- fluoro-2-hydrazinyl- 1, 3- Benzothiazole*:**

In 500ml of round bottom flask and added 10 ml of concentrated hydrochloric acid was added drop wise with stirring of hydrazine hydrate 12 ml(0.02mol) at 5^o-10^0c drop wise cool the mixture and add 20.2gm (0.1 mol) of 7- chloro- 6- fluoro 2-amino benzothiazole i.e. slowly added then added 40ml to 60ml of ethylene glycol and the resulting mixture refluxed for 3hrs in hot plate, poured into crushed ice then residue settle down to the beaker then filter the product and dry the product and recrystalised from ethanol.

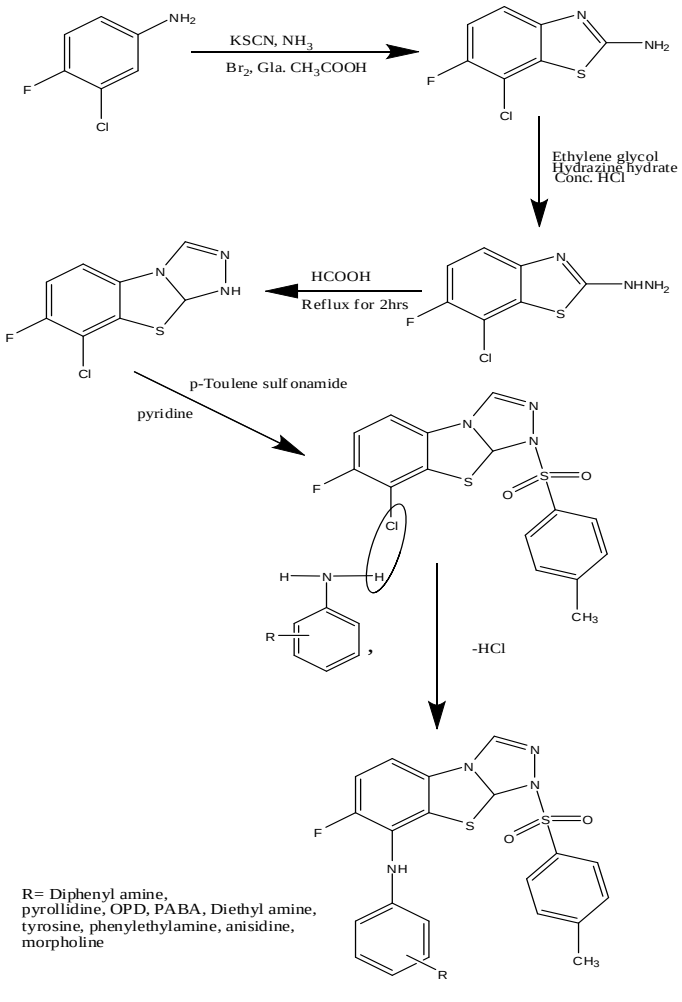
***2.3. Third Step: Synthesis of 8-chloro-7-fluoro-1,9a-dihydrol [1,2,4] triazole [3,4-b][1,3] Benzothiazole*:** In 250"ml of round bottom flask and added the mixture of (0.01mol) ie 2.19gm of 7-chloro-6-fluoro-2-hydrazinyl-1, 3-benzothiazole and, 1gm of anhydrous potassium carbonate add into the 25ml of formic acid, and reflux for 2hrs and the resulting mixture poured into the crushed ice the residue settle down to the beaker then filter the product and dry it recrystalised from ethanol to get the pure final product 8-chloro-7-fluoro-1,9a-dihydrol [1,2,4] triazole [3,4-b][1,3] benzothiazole.

***2.4. Fourth Step: Synthesis of 8-chloro-7-fluoro-1-[4-methylphenyl]sulphonyl-1,9a-dihydro[1,2,4]triazolo[3,4-b][1,3]Benzothiazole*:** In 500ml of round bottom flask added (0.013mol) ie2.2gm of 8-chloro-7-fluoro-1,9a-dihydrol [1,2,4] triazole [3,4-b][1,3] benzothiazole was treated with (0.01mol) ie 1.71gm of p-toluene sulphonamide in the presence of pyridine then reflux for 2hrs and poured into the crushed ice then residue settles product and drained and recrystalised from ethanol to get the final product8-chloro-7-fluoro-1-[4methylphenyl]sulphonyl-1,9a-dihydro[1,2,4]triazolo[3,4-b][1,3]benzothiazole.

***2.5. Fifth Step: Synthesis of 8-chloro-7-fluoro-1-[4-methylphenyl]sulphonyl-1,9a-dihydro[1,2,4] triazolo[3,4-b][1,3]Benzothiazole derivatives (TZ 1-9)*:**

In 100ml of round bottom flask added (0.01mol) i.e. 2.7gm of 8-chloro-7-fluoro-1-[4-methylphenylsulphonyl1,9dihydro[1,2,4]triazolo[3,4b][1,3]benzothiazole was treated with equimolar quantities of various primary and secondary aromatic amines refluxed for 2 hrs in presence of N,N^1-dimethyl form amide (DMF). The mixture was cooled and poured in to crushed ice. The solid separated was filtered off, dried and recrystalized from alcohol and benzene by using the pinch of activated charcoal.

Scheme:



TZ 1-9

2.6. Characterization of Synthesized compounds (TZ 1-9):

2-amino-6-fluoro-7-chloro (1, 3) Benzothiazole:% yield:91%;Yellow solid; m.p. 210-211°C, ; R_f = 0.87 (n-hexane : EtOAc); IR (KBr) V_{max} (cm^{-1}) 678.12,848.02,1067, 1336.58, 1541.38, 1642.89; ^{1}HNMR(400MHz DMSO d_6 (δppm); 7.22 (s, 2H, NH_2), 7.53(m, 4H, aromatic); MS *m/z*: 189 , (100%), 203(M^{+1}) .

Synthesis of 7- chloro- 6- fluoro-2-hydrazinyl- 1, 3-Benzothiazole: :% yield:72%; Off white solid; m.p. 233-234°C; R_f=0.89(n--hexane: EtOAc); IR(KBr) V_{max} (cm^1)712.96,802.80,1072.81,1246.14,1313.91,1547.30, 1640.79;^{1}HNMR(400MHz DMSO d_6 (δppm); 4.0(s, 1H, NH),4.59(s,2H, NH_2), 7.53-8.18(M, 4H, aromatic); *m/z*:172(100%), 219(M^{+2}).

Synthesis of 8-chloro-7-fluoro-1,9a-dihydrol [1,2,4] triazole [3,4-b][1,3] Benzothiazole:%Yield:11%; pale Yellow color;294-296°C; R_f=0.89(n--hexane: EtOAc); IR(KBR) V_{max} (cm^{-1}) 712.87,1074.65,1317.11,1640.98; ^{1}HNMR(400MHz DMSO d_6 (δppm)7.0(s,1H, NH_2), 7.53-8.18(M, 4H, aromatic); MS *m/z*:184(100%),228(M^{-1}),

Synthesis of 8-chloro-7- fluoro- 1-[4-methylphenyl] sulphonyl -1,9a-dihydro [1,2,4]triazolo [3,4-b][1,3] Benzothiazole: :%Yield:82%;Brick Red color;314-316°C; R_f =0.89 (n--hexane: EtOAc); IR(KBR) V_{max}(cm^{-1}) 712.87,1074.65,1317.11,1640.98;2283.19; ^{1}HNMR(400MHz DMSO d_6 (δppm) 7.53-8.18(m, 6H, aromatic).2.34(m, 3H, CH_3); MS *m/z*:279(100%),385(M^{+2}).

6-fluoro-3-[(4-methylphenyl)sulfonyl]-*N*-(2-aminophenylamino)-3,3a dihydro [1,2,4] triazolo [5,1-*b*][1,3]benzothiazol-5-amine(1):

:%Yield:86%;Pale yellow solid; m.p. 110°C; R_f = 0.64 ($CHCl_3$:EtOAc: n-Bu 1:2:1); IR(KBR) V_{max} (cm^{-1})1286,1442,1660,1069,1442,1105,1196;^{1}HNMR(400 MHz DMSO d_6 (δppm) 6.56-7.54(m,11H,aromatic)9.77(s,1H,NH),5.19(s,1H,NH_2)2.34(m,3H,CH_3); MS *m/z*: 412(100%),454(M^{-1}).

6-fluoro-3-[(4-methylphenyl) sulfonyl]-*N*-(4-hydroxypropanoicacid)-3,3a dihydro [1,2,4] triazolo [5,1-*b*][1,3]benzothiazol-5-amine(2):

:%Yield:24% red color; m.p. 122°C; R_f = 0.72 ($CHCl_3$:EtOAc: n-Bu 1:2:1); IR(KBR) V_{max} (cm^{-1}) 1323,1508,1629,1101,1448,1156,1156 ; ^{1}HNMR (400MHz) DMSOd_6 (δppm)6.56 -7.54 (m,10H,aromatic) 9.73(s,1H,NH), 2.34(m,3H,CH_3)3.40(s,2H,CH_2),9.43,12.57(d,2h,OH, *j*=8.4); MS *m/z*: 464(100%),529(M^{+1}).

***N*-(carboxyphenylamino)-6-fluoro-3-[(4-methylphenyl)sulfonyl]-3,3a-dihydro [1,2,4] triazo lo[5,1-*b*][1,3]benzothiazol-5-amine(3):** %Yield:27.4% orange white color; m.p. 158°C; R_f = 0.65 ($CHCl_3$:EtOAc: n-Bu 1:2:1); IR(KBR) V_{max} (cm^{-1}) 1308,1541,1647,1075,1450,1119,1203 ; ^{1}HNMR (400MHz) DMSOd_6 (δppm)6.56 -7.54 (m,9H,aromatic) 9.73(s,1H,NH),2.34(m,3H,CH_3)3.40(s,2H,CH_2),9.43,12.57(d,2h,OH, *j*=8.4)4.0(s,1H,NH); MS *m/z*: 481(100%),530(M^{+2}).

***N*-(4-methoxyphenylamino)-6-fluoro-3-[(4-methylphenyl)sulfonyl]-3,3a-dihydro [1,2,4] triazo lo[5,1-*b*][1,3]benzothiazol-5-amine(4):** %Yield:34.9% ,dark brown color; m.p. 174°C; R_f = 0.84 ($CHCl_3$:EtOAc: n-Bu 1:2:1); IR(KBR) V_{max} (cm^{-1}) 1296,1570,1654,1073,1445,1150,1201 ; ^{1}HNMR (400MHz) DMSOd_6 (δppm)6.56 -7.54 (m,10H,aromatic)9.77(s,1H,NH),2.34(m,3H,CH_3)3.40(s,2H,CH_2),3.84,2.34(s,2H,CH_2); MS *m/z*: 481(100%),469(M^{-1}).

6-fluoro-3-[(4-methylphenyl)sulfonyl]-*N*-morphonyl-3,3a-dihydro[1,2,4]triazolo[5,1-*b*] [1,3] benzothiazol-5-amine(5): %Yield:43.9% ,dark red color ; m.p. 179°C; R_f = 0.92 ($CHCl_3$:EtOAc: n-Bu 1:2:1); IR(KBR) V_{max} (cm^{-1}) 1296,1492,1657,1066,1492,1154,1194 ; ^{1}HNMR

(400MHz) DMSOd_6 (δppm) 6.60 -7.54 (m,5H,aromatic),2.34(m,3H,CH_3)3.40(s,2H,CH_2),3.18-3.65(m,4H,CH_2); MS *m/z*: 347(100%),435(M^{+1}).

6-fluoro-(4-pyrrolidinyl)3-[(4-methylphenyl) sulphonyl]-3,3a-dihydro[1,2,4]triazolo[5,1-b][1,3] benzthiazol-5-amine(6): %Yield:25.6% ,brick red color ; m.p. 172°C; R_f = 0.96 ($CHCl_3$:EtOAc: n-Bu 1:2:1); IR(KBR) V_{max} (cm^{-1}) 1297,1539,1642,1064,1441,1153,1194 ; ^{1}HNMR (400MHz) DMSOd_6 (δppm) 6.60 -7.54 (m,6H,aromatic),2.34(m,3H,CH_3)1.99(m,2H,CH_2),3.18 -3.65(m,4H,CH_2); MS *m/z*: 401(100%),420(M^{+2}).

6-fluoro-*N*-diethylamino-3-[(4-methylphenyl)sulfonyl]-3,3a-dihydro[1,2,4]triazolo[5,1-*b*][1,3]benzothiazol-5-amine(7): %Yield:29.6% ,pale yellow color ; m.p. 108°C; R_f = 0.58 ($CHCl_3$:EtOAc: n-Bu 1:2:1); IR(KBR) V_{max} (cm^{-1}) 1299,1543,1654,1068,1496,1156,1196 ; ^{1}HNMR (400MHz) DMSOd_6 (δppm) 6.60 -7.54 (m,6H,aromatic), 1.15-3.34(m,6H,CH_3)3.41(m,4H,CH_2); MS *m/z*: 386(100%),420(M^+).

1-[6-fluoro-7-(4-phenethylamino)-3-[4-methylphenyl]sulphonyl]-3,3a dihydro [1,2,4] triazo lo[5,1-b][1,3]benzthiazole(8): %Yield:22.1% ,reddish brown color ; m.p. 114°C; R_f = 0.76 ($CHCl_3$:EtOAc: n-Bu1:2:1);IR(KBR)V_{max}(cm^{-1}) 1295,1490,1642,1063,1490,1154,1193 ; ^{1}HNMR (400MHz) DMSOd_6 (δppm) 6.60 -7.54 (m,11H,aromatic),2.93-3.34(m,4H,CH_2) 8.06(s,1H,NH) 2.34(m,3H, CH_3); MS *m/z*: 401(100%),470(M^{+2}).

6-fluoro-3-[(4-methylphenyl)sulfonyl]-5-(naphthylamino)-3,3a-dihydro[1,2,4]triazolo[5,1-*b*][1,3]Benzothiazole(9): %Yield:29.1% ,brown color ; m.p. 165°C; R_f = 0.79 ($CHCl_3$:EtOAc: n-Bu 1:2:1); IR(KBR) V_{max} (cm^{-1}) 1299,1541,1638,1066,1443,1299,1148 ; ^{1}HNMR (400MHz) DMSOd_6 (δppm) 6.60 -7.54 (m,16H,aromatic),2.93-3.34(m,4H,CH_2) 89.77(s,1H,NH) 2.34(m,3H, CH_3); MS *m/z*: 427(100%),489(M^{-1}).

3. RESULTS AND DISCUSSION

3.1. Antibacterial Activity:

The antibacterial activity was determined by the disc diffusion method at the concentration of 50, 100,150 µg/ml . All the synthesized compounds were tested *in vitro* for their antibacterial activity against microorganisms such as *Staphylococcus aureus*, *Bacillus subtilis* (Gram positive), *Escherichia coli*, *Klebsiella pneumonia* (Gram negative), using ciprofloxacin as standard antibacterial. The results of activity, presented in the table-1 suggested that compounds TZ-6 and TZ-4 had shown the potent activity against the standard.Compounds TZ-1, TZ-2, TZ-9 had shown the moderate activity while compound TZ-3 and TZ-8 had shown the poor activity.These compounds increased the permeability of the microbial cell resulting in higher activity . The results were tabulated in the table-1.

3.2. Antifungal Activity:

The antifungal activity was tested against strain such as *A. niger* and *C. albicans*, using fluconazole as standard antifungal. Among the synthesized screened compounds, TZ-4 and TZ-5 had shown the potent activity against the standard.Compounds TZ-1, TZ-2, TZ-3 had shown the moderate activity while compound TZ-8 and TZ-9 had shown the lesser activity. The results were tabulated in the table-2.

3.3 Pharmacology, chemicals and reagents :

Nutrient agar medium, DMSO, Ciprofloxacin, potato dextrose medium, fluconazole, *p*- nitroso dimethyl aniline, ascorbic acid, hydrogen peroxide, phosphate buffer (pH 7.4), EDTA, wlister rats, tween 80.

3.3.1 Antibacterial activity microbial strains

Table 1: Antimicrobial activity of the compounds (TZ 1-9) against the bacterial strains tested.

Microbes	BS			SA			KP			E.coli		
	20	50	100	20	50	100	20	50	100	20	50	100
Compounds		(µg/ml)			(µg/ml)			(µg/ml)			(µg/ml)	
TZ1*	8	7	-	8	9	9	6	7	6	7	9	8
TZ3*	6	7	-	7	-	-	6	8	7	-	-	7
TZ4*	8	9	10	7	10	11	11	12	10	11	12	10
TZ5*	7	8	13	6	9	13	-	7	-	9	16	18
TZ6*	14	11	12	12	7	13	16	11	13	14	9	11
TZ7*	6	8	11	12	14	19	9	8	-	7	8	10
TZ8*	7	9	-	-	-	6	7	8	9	7	9	7
TZ9*	6	-	-	6	-	10	9	7	10	-	-	9
CONTROL	6	8	7.6	6	7	7	7	11	10	7	9	8.6
STANDARD		18			22			19			24	

All the compounds were tested for their antibacterial activity against *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 25923), *Klebsiella pneumonia* (ATCC 13883), *Escheria coli* (ATCC 25922) using disc diffusion method . DMSO was run as a control and test was performed at different concentrations (25,50 and 100 µg/ ml) using a solvent DMSO. Ciprofloxacin was used as a standard drug. All the pyrazolo fluoro benzthiazoles derivatives (4a-l) showed antibacterial activity.

3.3.2 Determination of the in vitro antimicrobial activity bythe disc-diffusion method.

The antimicrobial activity of the compounds was determined by means of the disc-diffusion method. Cultures of each bacteria were inoculated to nutrient agar broth and incubated at 37 ^{0}C for 16 h, then adjusted to OD625 ¼ 0.08–0.1 (approximately 1 x 10^7 –1x 10^8CFU/mL). The bacterial suspensions (100l L) was placed on to agar in a 60-mm Petri dish and spread homogeneously with a Drigalski tip. Discs (6.0-mm diameter) were impregnated with 25, 50 and 100 µg/ ml concentrations in DMSO solution of the compounds (TZ 1-9) and placed on the surface of the agar containing each bacterium, which was incubated at 37 C for 24 h. The inhibition zones were measured with a caliper considering the total diameters. Similarly, each plate carried a blank disc containing 25, 50 and 100 µg/ ml concentrations in DMSO and an anti-biotic disc (100 µg/ml for ciprofloxacin).

3.3.3. Anti fungal activity Microbial Strians: All the compounds were tested for their antifungal activity against A*spergillus flavus* and *Aspergillus niger* (NCCS 1196) by disc diffusion method DMSO was run as a control and test was performed at different concentrations (100 and 150 µg/ml) using a solvent DMSO. Flucoconazole was used as a standard drug. All the compounds (TZ 1-9) showed antifungal activity.

3.3.3. Determination of the in vitro antifungal activity by the disc-diffusion method. The fungal activity of the compounds was determined by means of the disc-diffusion method. Cultures of each bacteria were inoculated to potato dextrose broth and incubated at 37 ^{0}C for 16 h, then adjusted to BOD625 ¼ 0.08–0.1 (approximately 1 x 10^7 –1x 10^8CFU/mL). The Fungal suspensions was placed on to dextrose in a 60-mm Petri dish and spread homogeneously with a Drigalski tip. Discs (6.0-mm diameter) were impregnated with 100 and 150 µg/ ml concentrations in DMSO solution of the compounds (4a-l) and placed on the surface of the dextrose broth containing each fungal strain , which was incubated at 37 C for 24 h.

Table 2:Antifungal activity of synthesized compounds (TZ 1-9) against fungal strains

Microbes	*Aspergillus flavus*		*Aspergillus niger*	
Compounds	**150**	**200**	**150**	**200**
	(µg/ml)		**(µg/ml)**	
TZ1*	**11**	**10**	**9**	**11**
TZ2*	**11**	**12**	**10**	**12**
TZ3*	**8**	**11**	**8**	**12**
TZ4*	**16**	**19**	**17**	**15**
TZ5*	**15**	**12**	**14**	**13**
TZ6*	**6**	**11**	**7**	**9**
TZ7*	**11**	**9**	**9**	**11**
TZ8*	**6**	**--**	**--**	**7**
TZ9*	**7**	**9**	**6**	**8**
CONTROL	**7**	**9**	**8**	**9**
STANDARD	**22**		**18**	

The inhibition zones were measured with a caliper considering the total diameters. Similarly, each plate carried a blank disc containing 100 and 150 µg/ ml concentrations in DMSO and an anti-biotic disc(100µg/ml for Fluconazole).

4. CONCLUSION

From this study, benzothiazole substituted with morpholino, pyrolidine, ansidine on seventh position enhances the anti-microbial, anti-inflammatory, anti-oxidant activities and the synthesized compounds were characterized by solubility, TLC, analytical data, IR, ^{1}HNMR and Mass spectral studies.

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