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DESIGN, SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF [1,2,4]TRIAZOLO[3,4-*b*][1,3,4] THIADIAZOLE DERIVATIVES

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ABSTRACT:
In order to enhance the antimicrobial properties, a hybrid heterocyclic that contains different pharmacophore, such as benzodioxole and triazolo-thiadiazole has been designed.. We report herein the synthesis of novel *N*-[3-(1,3-benzodioxol-5-yl)[1,2,4]tri-azolo[3,4-*b*][1,3,4]thiadiazol-6-yl]-*N*-aryl/alkylamine 6(a-e):has been synthesized by the reaction of4-amino-5(1,3-benzodioxol-5-yl)-4*H*-1,2,4-triazole-3-ylhydrosul-fide. The *in vitro* antimicrobial activities of newly synthesized compounds were also evaluated
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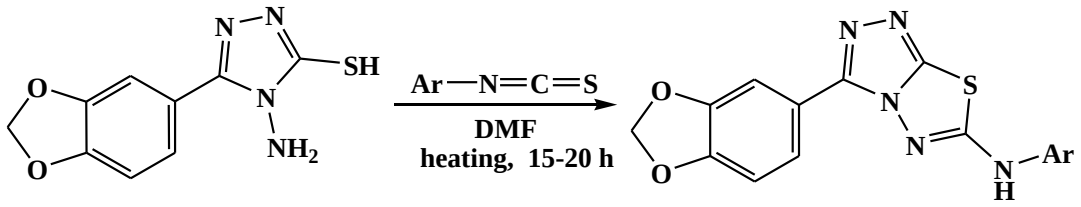


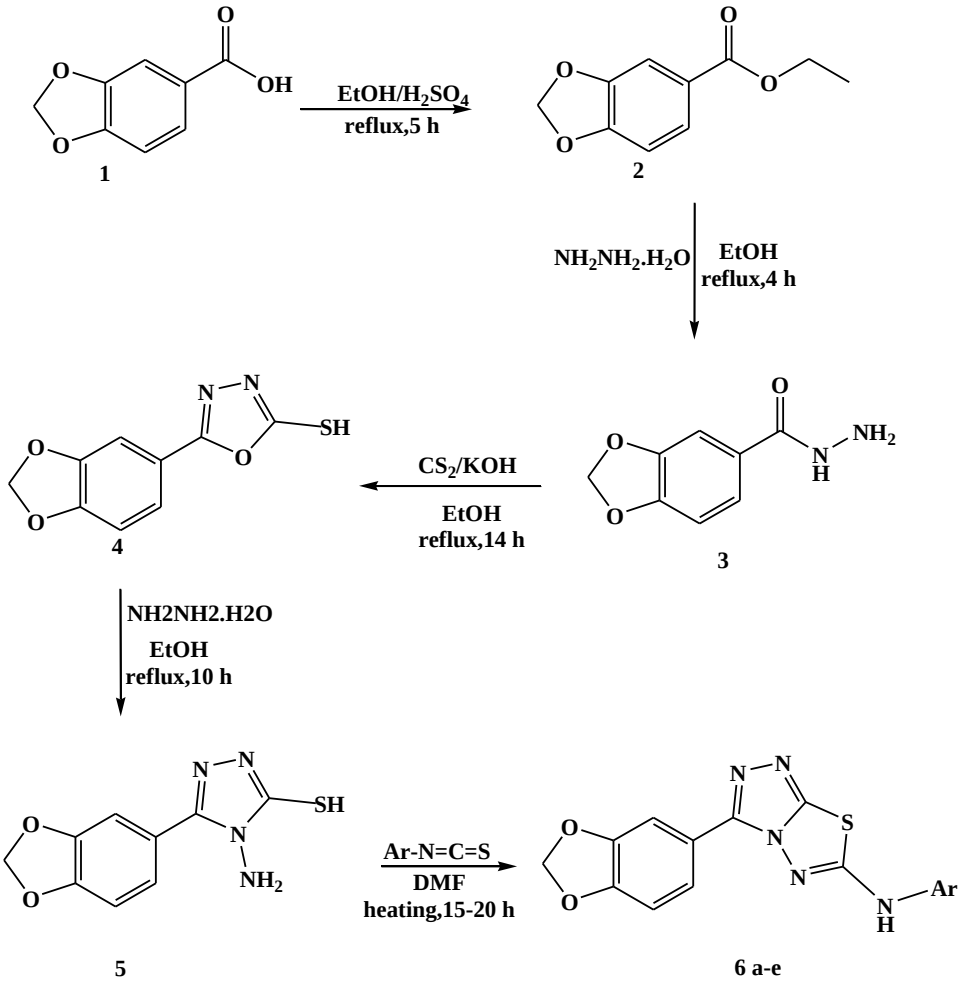
KEYWORDS: Thiadiazole, Triazolo , Antibacterial, Antifungal Agents

INTRODUCTION:

Various 1,2,4-triazole derivatives have been reported to possess diverse types of biological activities such as analgesic, antiinflammatory[I], anticancer[II], antimyco- bacterial[III], antitumor[IV], anticonvulsant[V], diuretic[VI], antimicrobial[VII] and antidiabetic[VIII].
Thiadiazole is a versatile moiety that exhibits a wide variety of biological activities, has attracted much attention since its discovery by Emil Fischer in 1882 on account of its compounds finding applications in agriculture, drugs, dyes and photographic materials. In particular, compounds bearing the 1,3,4-thiadiazole nucleus is known to have unique antibacterial and anti-inflammatory activities. Members of this ring system have found their way into such diverse application as pharmaceuticals, oxidation inhibitors, cyanine dyes and metal complexing agents. The literature review showed that the thiadiazole nuclei have antibacterial[IX], antimicrobial[X], antiinflammatory[XI] and anticonvulsant[XII] activities.

Derivatives of 1,2,4-triazole and 1,3,4-thiadiazole condensed system have been found to possess varying pharmacological activities such as antitumor[XIII], antiinflammatory[XIV], CNS stimulant[XV], anticancer[XVI] and antimicrobial[XVII]. Triazole fused with other heterocyclic rings has also been found to possess diverse application in medicinal field[XVIII].

Asif *et al.*[XIX] reported the synthesis of triazolo-thiadiazole derivatives containing benzimidazole moiety and evaluation of *in vitro* anticancer activity against cancerous cell lines. The activity data of the compounds indicated, compound 1 showed considerable inhibition and high selectivity against the cancerous cell lines.



6: Ar= a)phenyl; b)4-methylphenyl; c)4-fluorophenyl; d)4-methoxyphenyl; e)benzyl

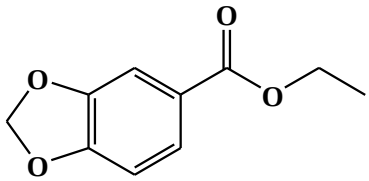
MATERIALS AND METHODS:

All reagents are commercial grade and were used as supplied. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel F254 plates from Merck, and compounds visualized by exposure to UV light. Chromatographic columns 70–230 mesh silica gel for separations were used. IR spectra were recorded using KBr disk on a Perkin–Elmer FTIR spectrometer. The 1H NMR and 13C NMR spectra were recorded on a Varian Gemini spectrometer (300 MHz for 1H and 75 MHz for 13C). Chemical shifts are reported in δ ppm units with respect to TMS as internal standard and coupling constants (J) are reported in Hz units. Mass spectra were recorded on a VG micro mass 7070H spectrometer.

Preparation of ethyl 1,3-benzodioxole-5-carboxylate 2:

To the solution of 1,3-benzodioxole-5-carboxylic acid 1 (0.01 mol) in anhydrous ethyl alcohol

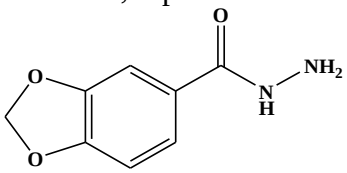
(25 mL), concentrate sulfuric acid (1 mL) was added and heated, the reaction mixture under reflux for 5 hours. The residue obtained on completion of reaction (TLC) was poured over crushed ice, then filtered and recrystallized from ethanol to give the compound 2 as dirty white solid; yield 52%; mp. 245-249 ^{0}C.



IR: 3034 (CH-Ar), 2913 (CH-Ali), 1621 (C=O) 1152 (C-O) cm-1.PMR: 1.28 (t, 3H, CH3), 4.30-4.50 (q, 2H, CH2), 5.74 (s, 2H, CH2), 6.51 (d, J = 8.7Hz, 1H, ArH), 7.30 (s, 1H, ArH), 7.50-7.63 (m, 1H, ArH).MS: m/z 194 (M+).

Preparation of 1,3-benzodioxole-5-carbohydrazide 3:

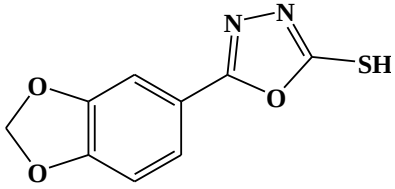
A mixture of 1,3-benzodioxole-5-carboxylate 2 (0.01 mol) and $NH_2NH_2.H_2O$ (0.01 mol) in 20 mL EtOH was heated under stirring for 4-5 hours, then cooled to room temperature to precipitate the product, the residue was filtered, dried and recrystallized from ethanol to give compound 3 as grey color solid; yield 49%; mp. 152-156 ^{o}C.



IR: 3421, 3259 (N-H), 3038 (CH-Ar), 2945 (CH-Ali), 1680 (C=O), 1062 (C-O) cm-1.PMR: 5.53 (s, 2H, NH2), 5.76 (s, 2H, CH2), 6.82 (d, J = 8.6 Hz, 1H, ArH), 7.34- 7.40 (m, 2H, ArH), 9.15 (s, 1H, NH).MS: *m/z* 180 (M+).

Preparation of 5-(1,3-benzodioxol-5-yl)-1,3,4-oxadiazole-2-ylhydroxulfide 4:

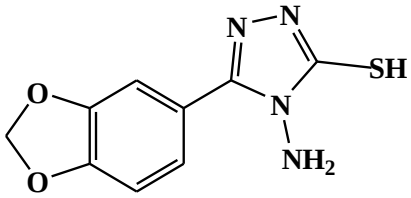
A mixture of compound 3 (0.01 mol), CS2 (0.03 mol) and KOH (0.02 mol) in an RB flask 75 mL of EtOH was added and heated under stirring for 14 h and evaporated the solvent *in vacuum* and the solid obtained was digested in cold water and neutralized with 10% HCl, filtered the product and purified by recrystallization using EtOH to give pure compound 4 as pale yellow color, yield 51%, mp. 262- 266^{o}C.



IR: 3162 (CH-Ar), 2945 (CH-Ali), 2536 (S-H),1600 (C=N), 1152 (C-O) cm-1.PMR: 5.78 (s, 2H, CH2), 6.75 (d, J = 8.4 Hz, 1H, ArH), 7.01-7.18 (m, 2H, ArH),11.40 (s, 1H, NH/SH).CMR: 103.2, 108.7, 109.8, 110.8, 125.4, 148.7, 151.8, 154.5, 169.8.MS: *m/z* 222 (M+).

Preparation of 4-amino-5(1,3-benzodioxol-5-yl)-4*H*-1,2,4-triazole-3-ylhydrosul- fide 5:

A mixture of compound 4 (0.01 mol) and $NH_2NH_2.H_2O$ (0.03 mol) in 50 mL EtOH was heated under stirring for 10 hours, then cooled to room temperature, removed the solvent by distillation, the residue obtained was filtered, dried and recrystallized from chloroform to give compound 5 as yellow color solid; yield 42%, mp. 172-175 ^{o}C.

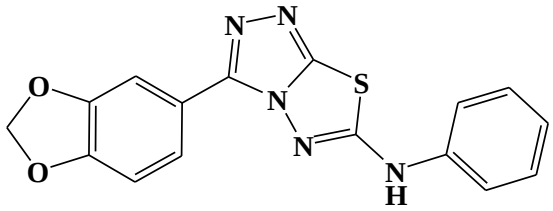


IR:3400,3285(N-H),3036(CH-Ar),2947(CH-Ali),2539(S-H),1632(C=N),1600 (C=C), 1157 (C-O)cm-1.PMR:1.42(s,2H,NH2),5.76(s,2H,CH2),6.73(d,J=8.3Hz,1H,ArH),7.05-7.09 (m, 2H, ArH), 11.80 (s, 1H,NH/SH).CMR: 102.7, 109.8, 110.7, 122.5, 123.1, 147.2, 149.0, 151.5, 155.3.MS: *m/z* 236 (M+).

General procedure for the synthesis of *N*-[3-(1,3-benzodioxol-5-yl)[1,2,4]tri- azolo[3,4-*b*][1,3,4]thiadiazol-6-yl]-*N*-aryl/alkylamine 6(a-e):

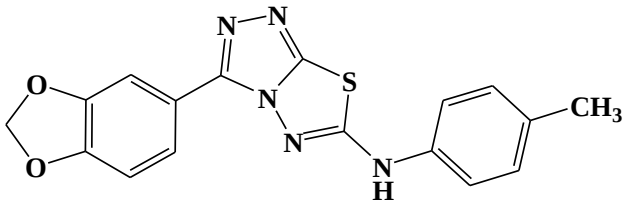
A mixture of compound 5 (0.01 mol), alkylisothiocyanate or arylalkyl isothiocyanate (0.01 mol) and 20 mL of DMF was refluxed for 15-20 h. To the resulted mixture ice water was added the precipitated solid was filtered and purified by the recrystallization using a mixture of solvent chloroform: methyl alcohol (5:1).

***N*-[3-(1,3-benzodioxol-5-yl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl]-*N*-phenyl- amine (6a):**



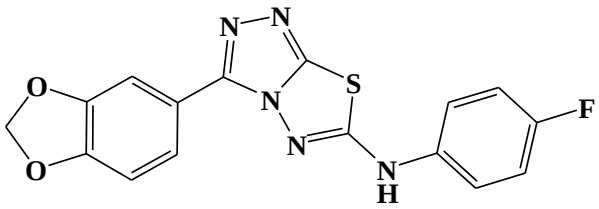
IR: 3432 (N-H), 3073 (CH-Ar), 1631 (C=N), 1155 (C-O) cm-1.PMR: 5.72 (s, 2H, CH2), 6.79 (d, J = 8.6 Hz, 1H, ArH), 7.10-7.20 (m, 5H, ArH), 8.40-8.50 (m, 2H, ArH), 10.52 (s, 1H, NH).CMR: 102.3, 110.2, 111.7, 116.9, 122.4, 122.9, 123.0, 124.0, 129.0, 136.7, 140.2,147.4, 153.6, 159.2.MS: m/z 337 (M+).

***N*[3-(1,3-benzodioxol-5-yl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl]-*N*-(4-meth-ylphenyl)amine (6b):**



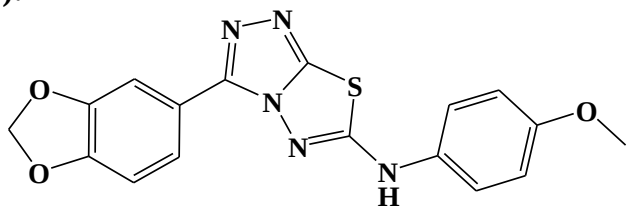
IR: 3434 (N-H), 3078 (CH-Ar), 2955 (CH-Ali), 1632 (C=N), 1156 (C-O) cm-1.PMR: 2.53 (s, 3H, CH3), 5.74 (s, 2H, CH2), 6.72 (d, J = 8.7 Hz, 1H, ArH), 7.30-7.40 (m, 4H, ArH), 8.40-8.50 (m, 2H, ArH), 10.21 (s, 1H, NH).CMR: 31.2, 102.2, 110.7, 111.5, 119.2, 122.9, 123.2, 124.7, 128.8, 130.1, 136.2,140.9, 147.1, 153.2, 159.0.MS: m/z 351 (M+).

***N*[3-(1,3-benzodioxol-5-yl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl]-*N*-(4-fluoro phenyl)amine (6c):**



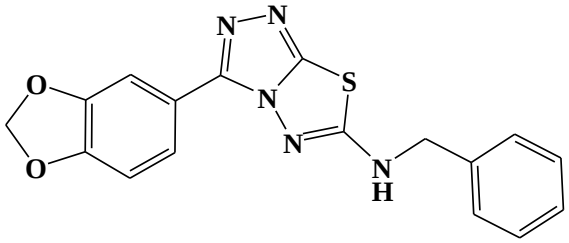
IR: 3439 (N-H), 3068 (CH-Ar), 2977 (CH-Ali), 1629 (C=N), 1378 (C-F), 1151 (C-O)cm-1.PMR: 5.77 (s, 2H, CH2), 6.75 (d, J = 8.4 Hz, 1H, ArH), 7.20-7.30 (m, 4H, ArH), 8.40-8.50 (m, 2H, ArH), 10.24 (s, 1H, NH).CMR: 102.3, 110.2, 111.7, 116.0, 122.4, 123.0, 123.9, 124.0, 136.7, 138.2, 141.2,147.4, 153.6, 159.2.MS: m/z 355 (M+).

***N*[3-(1,3-benzodioxol-5-yl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl]-*N*-(4-methoxyphenyl)amine (6d):**



IR: 3439 (N-H), 3081 (CH-Ar), 2978 (CH-Ali), 1635 (C=N), 1153 (C-O), 1079(C-O)cm-1.PMR: 3.91 (s, 3H, OCH3), 5.74 (s, 2H, CH2), 6.70-6.80 (m, 3H, ArH), 7.10-7.20 (m, 2H, ArH), 8.40-8.50 (m, 2H, ArH), 10.48 (s, 1H, NH).CMR: 59.3, 102.7, 110.4, 111.5, 115.0, 122.3, 123.2, 123.9, 124.0, 134.2,136.7,147.9, 153.5, 155.2, 159.4.MS: m/z 367 (M+).

***N*-[3-(1,3-benzodioxol-5-yl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl]-*N*-benzyl- amine (6e):**



IR: 3438 (N-H), 3078 (CH-Ar), 2967 (CH-Ali), 1629 (C=N), 1154 (C-O) cm-1. PMR: 4.32 (s, 2H, CH2), 5.76 (s, 2H, CH2), 6.72 (d, J = 8.5 Hz, 1H, ArH), 7.20-7.30 (m, 5H, ArH), 8.40-8.50 (m, 2H, ArH), 10.37 (s, 1H, NH).CMR: 52.3, 102.9, 110.7, 111.2, 122.7, 123.3, 124.6, 127.2, 128.0, 129.1, 136.9,140.2, 146.2, 153.2, 159.7.MS: m/z 351 (M+).

RESULTS AND DISCUSSION:

The synthesis of the title compounds was initiated from commercially available 1,3-benzodioxole-5-carboxylic acid 1, which on esterification with anhydrous ethyl alcohol in the presence of catalytic amount of sulfuric acid under reflux temperature for about 5 hours, afforded the 1,3-benzodioxole-5-carboxylate2 in 52% yield. Its structure was confirmed by is IR, ^{1}H NMR and MS spectral data.

The IR spectrum of compound 2 showed the characteristic absorption bands corresponding to carbonyl (C=O) and (C-O) of ester group at 1621 and 1152 cm^{-1}. Its proton NMR spectrum showed a triplet signal at δ 1.28 ppm, a quartet signal at δ 4.30-4.50 ppm were assigned to the methyl and methylene protons of ester, the methylene protons signal appeared as a singlet at δ 5.74 ppm, the other aromatic protons in the range of δ 6.51 and 7.30, 7.50-7.63 ppm as doublet,

singlet and multiplet respectively. Its mass spectrum displayed a molecular ion peak at m/z: 194 which confirmed its molecular weight.

The hydrazinolysis of ethyl 1,3-benzodioxole-5-carboxylate 2 with hydrazine hydrate in ethyl alcohol at reflux temperature under stirring for 4 hours, afforded the 1,3-benzodioxole-5-carbohydrazide 3 in 49% yield. Its structure was confirmed by is IR, ^{1}H NMR and MS spectral data.

The IR spectrum of compound 3 showed the characteristic absorption bands corresponding to amine (N-H) at 3421, 3259, and carbonyl (C=O) at 1680 cm^{-1}. Its proton NMR spectrum showed, the signal at δ 5.76 ppm as singlet is assigned to methylene protons of dioxole ring, the amine protons as broad singlet at δ 5.53 ppm, the aryl protons as multiplets at δ 6.82 as doublet and at δ 7.34-7.40 ppm as multiplet for two protons, the proton of NH group appeared as singlet at δ 9.15 ppm. Its mass spectrum displayed a molecular ion peak at m/z: 180 which confirmed its molecular weight.

The condensation and cyclization of 1,3-benzodioxole-5-carbohydrazide 3 with carbon disulphide in ethyl alcohol in the presence of potassium hydroxide at reflux temperature under stirring for about 14 hours, afforded the 5-(1,3-benzodioxol-5-yl)-1,3,4-oxadiazole-2-ylhydroxulfide 4 in 51% of yield. Its structure was confirmed by is IR, ^{1}H NMR and MS spectral data.

The IR spectrum of compound 4 showed the absorption bands corresponding to C=N at 1600, C-O at 1152 cm^{-1}. The absence of amine absorption band revealed that cyclization involving hydrazinyl group. Its proton NMR spectrum showed, the signal at δ 5.78 ppm as singlet is assigned to methylene protons of dioxole ring, the aryl proton signals appeared at δ 6.75 as doublet and δ 7.10-7.18 ppm as multiplet for two protons, the proton of NH group appeared as singlet at δ 11.40 ppm. Its carbon NMR spectrum showed, the signals of carbons of oxadiazole ring appeared at δ 169.8 (C2) and 154.5 (C5) ppm, the other signals appeared in consistent with the structure. Its mass spectrum displayed a molecular ion peak at m/z: 222 which confirmed its molecular weight.

Further, hydrazinolysis of the 5-(1,3-benzodioxol-5-yl)-1,3,4-oxadiazole-2-ylhydroxulfide 4 with hydrazine hydrate in anhydrous ethyl alcohol at reflux temperature under the stirring for 10 hours, 4-amino-5-(1,3-benzodioxol-5-yl)-4*H*-1,2,4-triazole-3-ylhydrosulfide 5 in 42% of yield. Its structure was confirmed by is IR, ^{1}H NMR and MS spectral data.

The IR spectrum of compound 5 showed the absorption bands corresponding to amine (N-H) at 3400, 3285, thiol (S-H) at 2539 and C=N at 1632 cm^{-1}. The absence of amine absorption band revealed that cyclization involving hydrazinyl group. Its proton NMR spectrum showed, the signal at δ 5.76 ppm as singlet is assigned to methylene protons of dioxole ring, the aryl proton signals appeared at δ 6.73 as doublet and δ 7.05-7.09 ppm as multiplet for two protons, the proton of NH group appeared as singlet at δ 11.80 ppm. Its carbon NMR spectrum showed, the signals of carbons of triazole ring appeared at δ 151.5 (C2) and 149.0 (C5) ppm, the dioxole ring carbon signals appeared at 102.7, 147.2 and 155.3 ppm. Its mass spectrum displayed a molecular ion peak at m/z: 236 which confirmed its molecular weight.

The cyclization of 4-amino-5-(1,3-benzodioxol-5-yl)-4*H*-1,2,4-triazole-3-ylhydro sulfide 5 with corresponding aryl or alkyl isothiocyanate in dimethylformamide under reflux temperature for about 15-20 hours, afforded corresponding *N*-[3-(1,3-benzodioxol-5-yl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl]*N*-aryl/aralkylamine **6(a-e)** in 40-50% of yields (**Scheme 1**).The structures were confirmed by their IR, ^{1}H NMR and MS spectral analyses.

The IR spectrum of compound **6a** showed the absorption bands corresponding to N-H at 3432, C=N at 1631 cm^{-1}. Its proton NMR spectrum showed, the signal at δ 5.72 ppm as singlet is assigned to methylene protons of dioxole ring, the aryl proton signals appeared at δ 6.79 as doublet and δ 7.10-7.20 and δ 8.40-8.50 ppm as multiplet for six protons. Its carbon NMR

spectrum showed, the signals of carbons of triazolo-thiadiazole ring appeared at δ 122.9 (C3), 159.2 (C6) and 136.7 (C8) ppm. Its mass spectrum displayed a molecular ion peak at m/z: 337 which confirmed its molecular weight.

ANTIMICROBIAL ACTIVITY:

N-[3-(1,3-benzodioxol-5-yl)[1,2,4]tri-azolo[3,4-*b*][1,3,4]thiadiazol-6-yl]-*N*-aryl/alkylamine 6(a-e) were evaluated for their *in vitro* antibacterial activity against *Proteus mirabilis*, *Bacillus subtilis* and antifungal activity against*Candida albicans* and *Aspergillus fumigates* using the disc diffusion method[60]. The standard antibacterial drug ciprofloxacin and antifungal drug amphotericin-B were also screened under similar conditions for comparison. The results have been reported in the form of inhibiton zones (mm) at 500 μg/mL and activity index in **Table 1.**

Table 1: Antimicrobial Activity of Compounds 6 (a-e):

Compound	**Zone of inhibition (mm) at 500 µg/ml**			
	Antibacterial Activity		**Antifungal Activity**	
	P.Mirabilis	B.Subtilis	C.Albicans	A.Fumigatus
6a	11(0.44)	12(0.52)	08(0.40)	-
6b	24(0.96)	20(0.86)	19(0.95)	15(093)
6c	13(0.52)	09(0.36)	14(0.70)	-
6d	-	14(0.56)	-	13(0.81)
6e	12(0.48)	10(0.43)	18(0.90)	15(0.93)
Amphotericin	-	-	20	16
Ciprofloxacin	25	23	-	-

The antimicrobial activities of compounds showed that, compound containing 4-methylphenyl group (6b) and compound containing benzyl (6e) good antibacterial and antifungal activity against *C. albicans* (activity index 0.90) and *A. fumigatus* (activity index 0.93).

CONCLUSION:

A series of the *N*-[3-(1,3-benzodioxol-5-yl)[1,2,4]tri-azolo[3,4-*b*][1,3,4]thiadiazol-6-yl]-*N*-aryl/alkylamine 6(a-e) have been synthesized and evaluated their *in vitro* antibacterial and fungal activities and found that, compound 6b effect on bacterial and fungal strains. Compound 6e showed good antifungal activity against both fungal strains.

ACKNOWLEDGEMENT:

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