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SYNTHESIS OF NEW BIOLOGICALLY ACTIVE COMPOUNDS CONTAINING TRIAZOLE AND TETRAZOLE HETEROCYCLES

G. RAVI*, A. RAVINDER NATH and A. NAGARAJ[a]

Department of Biotechnology and Pharmacy, University College of Technology,
HYDERABAD – 500007, (Telangana) INDIA
[a]Department of Pharmaceutical Chemistry, Telangana University, NIZAMABAD – 503322 (Telangana) INDIA

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ABSTRACT

A new series of novel 5-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-1-aryll-1*H*-1,2,3,4-tetrazole **7(a-j)** in good to excellent yields by the reaction of *N*4,1-diphenyl-5-methyl-1*H*-1,2,3-triazole-4-carboxamide **6(a-j)** with a reaction of phosphorous pentachloride in carbon tetrachloride at reflux to obtain the intermediate imidoyl chloride, which were reacted with sodium azide in DMF at room temperature. The compounds of all the novel new compounds were established by IR, ^{1}H, ^{13}C NMR, MS and elemental data.The compounds **7(a-j)** were evaluated for their antibacterial activity againist four human pathogenic bacteria *viz.* Gram-positive bacteria *viz*. *Bacillus subtilis*, *Bacillus sphaericus* and *Staphylo- coccus aureus* and three Gram-negative bacteria *viz*. *Pseudomonas aeruginosa*, *Klebsiella aerogenes* and *Chromobacterium violaceum*. Amongst them, compounds containing (4-nitrophenyl) moiety **7c**, (4-fluorophenyl) moiety **7f**, (4-bromophenyl) moiety **7g** showed significant antibacterial activity, almost equal/more than the activity activity of the standard drug Sterpomycin and Penicillin. All the compounds displayed significant activity againist *E. coli*. Most of the novel new compounds showed appreciable activity againist test bacteria as potential molecules for further development.

Key words: Synthesis, 5-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-1-aryll-1*H*-1,2,3,4-tetrazole, *N*4, 1-diphenyl-5-methyl-1*H*-1,2,3-triazole-4-carboxamide, Antibacterial activity.

INTRODUCTION

Heterocyclic compounds represent one of the most active classes of compounds possessing a wide spectrum of antimicrobial activities, including antibacterial, antifungal, and other microbial activities[1-7]. Further, the treatment of infectious diseases still remains an important and challenging problem because of a combination of factors including emerging infectious diseases and the increasing number of multi-drug resistant microbial pathogens. In spite of a large number of antibiotics and chemotherapeutics available for medical use, at the same time the emergence of old and new antibiotic resistance created in the last decades revealed a substantial medical need for new classes of antimicrobial agents. There is a real perceived need for the discovery of new compounds endowed with antimicrobial activity. Similarly in recent decades, an increased incidence of fungal infections has been observed as a consequence of the growing number of immuneo compromised patients and the frequent use of antimicrobial and cytotoxic drugs. For many fungal infections, polyenes, such as amphotericin B, represent the standard therapy. Polyenes bind to membrane sterols, leading to membrane permeability, leakage and cell death. However, the clinical use of amphotericin B is limited by a high frequency of renal toxicity, and several adverse effects. Though the

Available online at www.sadgurupublications.com
*Author for correspondence; E-mail: drraviguguloth@gmail.com

various molecules designed and synthesized for the above aim and to reduce the adverse effects, it was demonstrated that thiadiazine and its derivatives offer several advantages in terms of decreased toxicity after oral or intravenous[8]. Administration and are often employed in the treatment of fungal infections, therefore the thiazidine and its derivatives could be considered as possible antimicrobial agents[9].

Further, the thiazidine nucleus appears frequently in the structure of various natural products and biologically active compounds, antibiotics such as penicillin, micrococcin[10] and many metabolic products of fungi and primitive marine animals, Similarly, there has been a considerable interest in the chemistry of thiadiazine ring system, which is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activities. Thiadiazine ring also occurs in nature; thus actithiazic acid isolated from *Streptomyces* strains exhibits highly specific *in vitro* activity against *Mycobacterium tuberculosis*. Thiadiazine derivatives are also known to exhibit diverse bioactivities such as anti-inflammatory[10], anti-nociceptive[11], anti-convulsant activity[12], anticancer[13], anti-diabetic[14], antihypertensive activity[15,16], cyclooxygenase (COX-2) inhibitor[17], hypoglycemic activity[18], antiproliferative activity[19]. The synthesis of heterocycles containing multistructure in a molecule has received much attention in recent years. However, literature survey revealed that linked heterocycles containing triazole and tetrazole have seldom been reported.

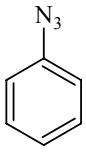
Based on the wide spectrum of biological profile of triazole and tetrazole their increasing importance in pharmaceutical, and biological field, and in continuation of our ongoing research on biologically active heterocycles, it was thought of interest to accommodate triazole and tetrazole moieties in a single molecular frame work to synthesize some new heterocyclic compounds with potential biological activity.

EXPERIMENTAL

Synthesis of phenylazide (3)

To a solution of aniline **1** (10 mol) in hydrochloric acid (25 mL), sodium nitrite solution was added dropwise at 0-5 ^{o}C and stirred for one hour to afford the diazonium chloride **2** and then cooled, stirred solution, a solution of sodium azide (25 mL) was added and stirring was continued for 30 min and the resulting solid was filtered and recrystallized from ethanol as yellow crystals.

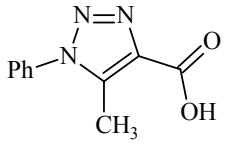
IR (KBr): ν_{max} 3110, 2949, 2230, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.10-7.20 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 117.3, 122.9, 130.1, 140.2; MS: m/z 119 (M^+); Anal. Calcd. for $C_6H_5N_3$: C, 60.50; H, 4.23; N, 35.27. Found: C, 60.45; H, 4.18; N, 35.21.



Synthesis of 5-methyl-1-phenyl-1,2,3-triazole-4-carboxylic acid (5)

A mixture of azide **3** (0.1 mol) and ethyl acetoacetate **4** (0.1 mol) in absolute ethanol (40 mL), and sodium ethoxide solution (20 mL) was refluxed for 4 h, the white solid which formed on heating was filtered and recrystalized from ethanol.

IR (KBr): ν_{max} 3450-3500, 3198, 2980, 2230, 1610 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.47 (s, 3H, CH_3), 7.60-7.60 (m, 5H, ArH), 10.5 (s, 1H, COOH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 126.3, 128.2, 129.6, 131.3, 134.3, 138.1, 168.8; MS: m/z 203 (M^+); Anal. Calcd. for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46; N, 20.68. Found: C, 59.01; H, 4.41; N, 20.62.

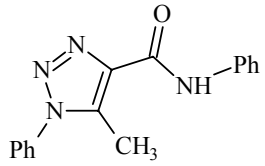


Synthesis of N4,1-phenyl-5-methyl-1H-1,2,3-triazole-4-arylcarboxamide 6(a-j)

To a stirred solution of 5-methyl-1-phenyl-1,2,3-triazole-4-carboxylic acid **5** (0.05 moles) in toluene (50 mL) was added pyridine (0.3 mL) and cooled the contents to 0-5°C. Thionyl chloride (0.06 moles) was added slowly dropwise during 10-15 minutes by maintaining the internal temperature 0-5°C. The reaction mixture was slowly allowed to reach 25-30°C and stirred for 2 hours. After the completion of the reaction, the contents were cooled to 0-5°C and added arylamine (0.055 moles) slowly drop wise during 10-15 minutes. The reaction mixture was allowed to reach 25-30°C and maintained for 4 hours. After completion of the reaction, the solvent was distilled off completely under reduced pressure to afford residue. Added water (100 mL) slowly to the residue and extracted with ethyl acetate (150 + 50 mL). The combined organic layer was washed with saturated $NaHCO_3$ (50 mL) followed by water (50 mL). The organic phase was separated, dried over sodium sulphate (2.0 g) and the solvent was distilled completely. The wet cake was dried under vacuum at 40-45°C for 8 hours to obtain compound **6(a-j)**.

N4,1-diphenyl-5-methyl-1H-1,2,3-triazole-4-carboxamide (6a)

IR (KBr): ν_{max} 3226, 2918, 3010, 1654, 1624 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.42 (s, 3H, CH_3), 7.30-7.40 (m, 8H, ArH), 7.62 (d, J = 8.4 Hz, 2H, ArH); ^{13}C NMR (DMSO-d_6 75 MHz): δ 11.9, 120.7, 122.0. 125.9, 127.0, 128.1, 128.9, 129.5, 137.9, 140.2, 152.5, 158.4; MS: *m/z* 278 (M^+); Anal. Calcd. for $C_{16}H_{14}N_4O$: C, 69.05; H, 5.07; N, 20.13. Found: C, 69.00; H, 5.01; N, 20.08.

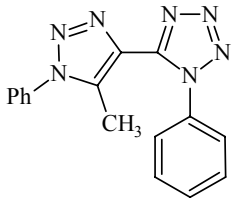


Synthesis of 5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1-aryl-1H-1,2,3,4-tetra- azole 7 (a-j)

To a stirred solution of corresponding compound **6(a-j)** (0.05 moles) in carbon tetrachloride (60 mL) was added phosphorous pentachloride (0.05 moles) under nitrogen atmosphere. The reaction mixture was heated to reflux and maintained for 3 hrs. After completion of the reaction, the solvent was distilled off completely under reduced pressure. The residue was cooled to 0-5°C, added DMF (60 mL) under nitrogen atmosphere and stirred for 10-15 minutes to get clear solution. A suspension of sodium azide (0.07 moles) in DMF (60 mL) was cooled to 0-5°C. The iminoyl chloride solution in DMF was taken into the addition funnel and added to the suspension of sodium azide in DMF at 0-5°C during 1 hr. After the addition, cooling was removed and stirred at 25-30°C for overnight. The reaction mass was cooled to 0-5°C and added water (50 mL) slowly during 20-30 minutes and maintained for 30-45 minutes at same temperature. The separated precipitate was flittered and washed with water.

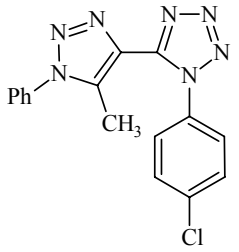
5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-1,2,3,4-tetraazole (7a)

IR (KBr): ν_{max} 3026, 2919, 1653, 1624, 1496, 1331, 1095 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.43 (s, 3H, CH_3), 7.30-7.40 (m, 8H, ArH), 7.67 (d, J = 8.6 Hz, 2H, ArH); ^{13}C NMR (DMSO-d_6 75 MHz): δ 11.7, 121.5, 123.4, 126.1, 128.1, 129.8, 130.4, 131.0, 134.5, 136.2, 137.8, 138.9; MS: *m/z* 303 (M^+); *Anal*. Calcd. for $C_{16}H_{13}N_7$: C, 63.36; H, 4.32; N, 32.32. Found: C, 63.29; H, 4.27; N, 32.26.



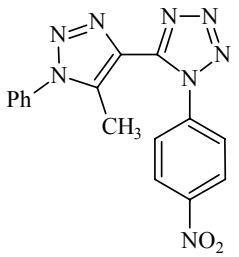
1-(4-chlorophenyl)-5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1H-1,2,3,4-tetra- azole (7b)

IR (KBr): ν_{max} 3047, 2920, 1652, 1493, 1332, 1268, 1095 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.42 (s, 3H, CH_3), 7.30-7.40 (m, 5H, ArH), 7.52 (d, J = 8.2 Hz, 2H, ArH), 7.71 (d, J = 8.2 Hz, 2H, ArH)' ^{13}C NMR (DMSO-d_6 75 MHz): δ 11.7, 121.5, 126.1, 127.1, 128.1, 129.8, 131.0, 133.0, 134.5, 136.4, 137.8, 138.9; MS: *m/z* 337 (M^+); *Anal*. Calcd. for $C_{16}H_{12}ClN_7$: C, 56.90; H, 3.58; N, 29.03. Found: C, 56.82; H, 3.50; N, 28.98.



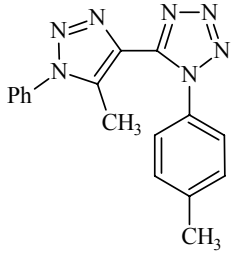
5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1-(4-nitrophenyl)-1H-1,2,3,4-tetraazole (7c)

IR (KBr): ν_{max} 3045, 2920, 1655, 1550, 1492, 1372, 1332, 1268, 1095 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.45 (s, 3H, CH_3), 7.30-7.40 (m, 7H, ArH), 8.22 (d, J = 8.8 Hz, 2H, ArH); ^{13}C NMR (DMSO-d_6 75 MHz): δ 11.7, 121.5, 126.1, 126.9, 127.8, 128.1, 129.8, 134.5, 137.8, 138.9, 140.1, 144.5; MS: m/z 348 (M^+); Anal. Calcd. for $C_{16}H_{12}N_8O_2$: C, 55.17; H, 3.47; N, 32.17. Found: C, 55.11; H, 3.40; N, 32.12.



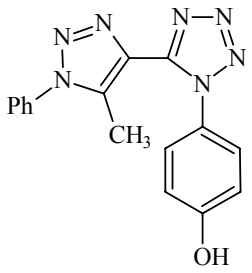
1-(4-methylphenyl)-5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1H-1,2,3,4-tetra- azole (7d)

IR (KBr): ν_{max} 3028, 2921, 1655, 1625, 1497, 1333, 1269, 1094 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2. 28 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 7.30-7.40 (m, 9H, ArH); ^{13}C NMR (DMSO-d_6 75 MHz): δ 11.7, 22.1, 121.5, 126.1, 128.1, 128.8, 129.8, 130.2, 134.5, 136.5, 136.9, 137.8, 138.9; MS: m/z 317 (M^+); Anal. Calcd. for $C_{17}H_{15}N_7$: C, 64.34; H, 4.76; N, 30.90. Found: C, 64.28; H, 4.70; N, 30.82.



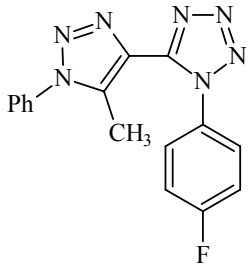
4-[5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1H-1,2,3,4-tetraazol-1-yl]phenol (7e)

IR (KBr): ν_{max} 3330-3400, 3022, 2921, 1655, 1622, 1495, 1330, 1269, 1094 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.45 (s, 3H, CH_3), 4.87 (s, 1H, OH), 7.30-7.40 (m, 7H, ArH), 7.10 (d, J = 8.1 Hz, 2H, ArH); ^{13}C NMR (DMSO-d_6 75 MHz): δ 11.7, 119.2, 121.5, 126.1, 127.6, 128.1, 129.8, 130.1, 134.5, 137.8, 138.9, 154.6; MS: m/z 319 (M^+)' Anal. Calcd. for $C_{16}H_{13}N_7$: C, 60.18; H, 4.10; N, 30.70. Found: C, 60.13; H, 4.05; N, 30.64.



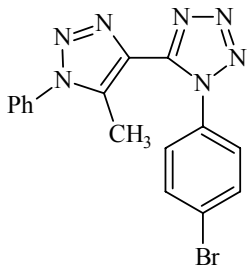
1-(4-fluorophenyl)-5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1H-1,2,3,4-tetra- azole (7f)

IR (KBr): ν_{max} 3037, 2932, 1659, 1626, 1498, 1334, 1269, 1094 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.43 (s, 3H, CH_3), 7.30-7.40 (m, 5H, ArH) 7.50-7.60 (m, 4H, ArH); ^{13}C NMR (DMSO-d_6 75 MHz): δ 11.7, 117.8, 121.5, 126.1, 127.8, 128.1, 129.8, 134.5, 135.2, 137.8, 138.9, 163.5; MS: m/z 321 (M^+); Anal. Calcd. for $C_{16}H_{12}FN_7$: C, 59.81; H, 3.76; N, 30.51. Found: C, 59.76; H, 3.70; N, 30.45.



1-(4-bromophenyl)-5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1H-1,2,3,4-tetra- azole (7g)

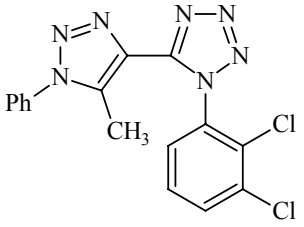
IR (KBr): ν_{max} 3033, 2917, 1651, 1625, 1492, 1333, 1269, 1090, 584 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.47 (s, 3H, CH_3), 7.30-7.40 (m, 5H, ArH), 7.50-7.60 (m, 4H, ArH); ^{13}C NMR (DMSO-d_6 75 MHz): δ 11.7, 121.5, 121.9, 126.1, 128.1, 129.8, 130.1, 133.5, 134.5, 136.8, 137.8, 138.9; MS: m/z 382 (M^+); Anal. Calcd. for $C_{16}H_{12}BrN_7$: C, 50.28; H, 3.16; N, 25.65. Found: C, 50.21; H, 3.10; N, 25.59.



1-(2,3-dichlorophenyl)-5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1H-1,2,3,4-tetraazole (7h)

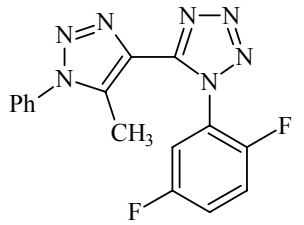
IR (KBr): ν_{max} 3028, 2921, 1655, 1627, 1499, 1329, 1266, 1095, 683 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.45 (s, 3H, CH_3), 7.30-7.40 (m, 6H, ArH), 7.90-8.10 (m, 2H, ArH)); ^{13}C NMR (DMSO-d_6

75 MHz): δ 11.7, 121.5, 123.8, 126.1, 128.1, 129.8, 130.0, 132.1, 132.6, 133.6, 134.5, 137.8, 138.0, 138.9; MS: m/z 372 (M^+); Anal. Calcd. for $C_{16}H_{11}Cl_2N_7$: C, 51.63; H, 2.98; N, 26.34. Found: C, 51.59; H, 2.92; N, 26.28.



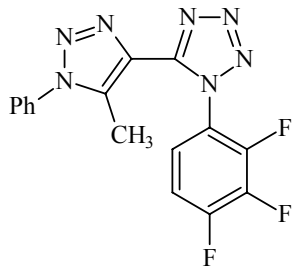
1-(2,5-difluorophenyl)-5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1H-1,2,3,4-tetraazole (7i)

IR (KBr): ν_{max} 3032, 2921, 1654, 1626, 1497, 1327, 1264, 1092 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.44 (s, 3H, CH_3), 6.90 (d, J = 8.1 Hz, 1H, ArH), 7.30-7.40 (m, 6H, ArH), 7.67 (d, J = 8.1 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6 75 MHz): δ 11.7, 109.7, 114.2, 118.9, 121.5, 122.1, 126.1, 128.1, 129.8, 134.5, 137.8, 138.9, 163.4, 164.5; MS: m/z 339 (M^+); Anal. Calcd. for $C_{16}H_{11}F_2N_7$: C, 56.64; H, 3.27; N, 28.90. Found: C, 56.58; H, 3.21; N, 28.84.



5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1-(2,3,4-trifluorophenyl)-1H-1,2,3,4-tetraazole (7j)

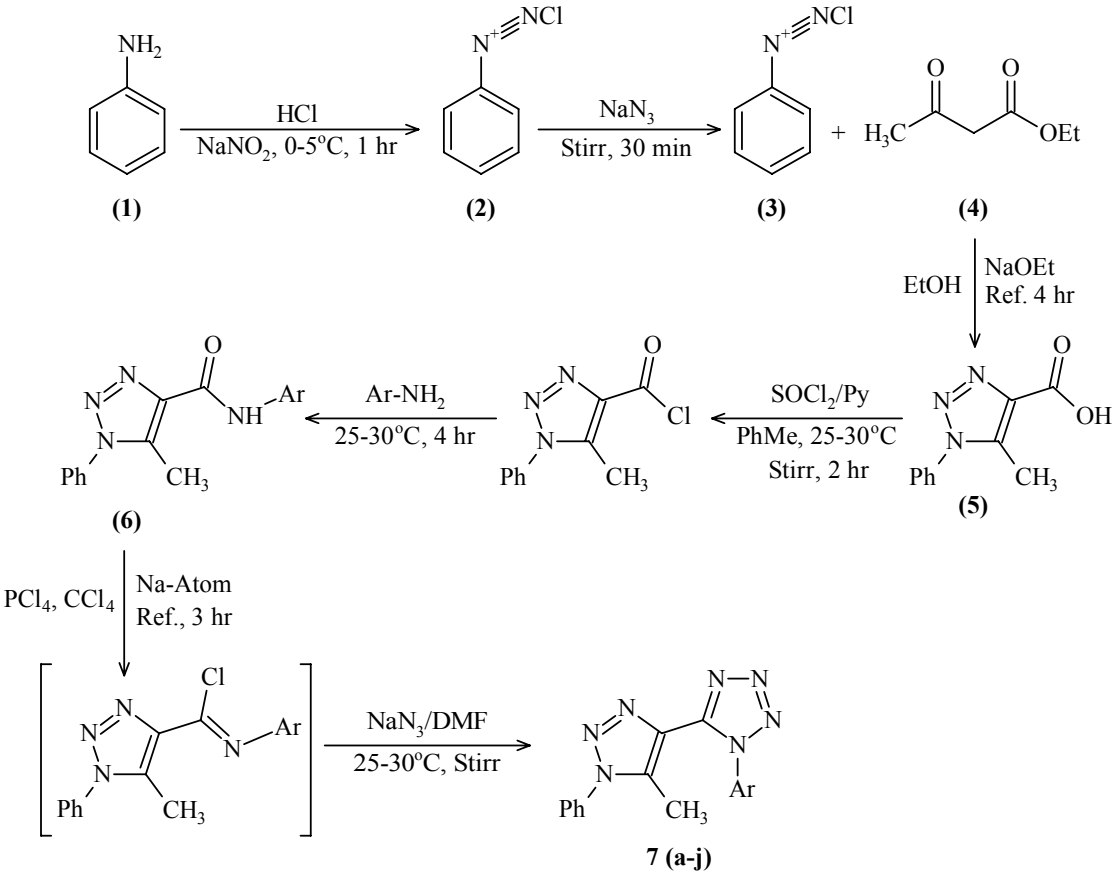
IR (KBr): ν_{max} 3037, 2926, 1659, 1621, 1493, 1324, 1268, 1090 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.47 (s, 3H, CH_3), 7.30-7.40 (m, 6H, ArH), 7.54 (d, J = 8.4 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6 75 MHz): δ 11.7, 117.8, 121.5, 122.1, 126.1, 128.1, 129.0, 129.8, 134.5, 137.8, 138.9, 145.3, 150.3, 153.4; MS: m/z 357 (M^+); Anal. Calcd. for $C_{16}H_{10}F_3N_7$: C, 53.79; H, 2.82; N, 27.44. Found: C, 53.74; H, 2.76; N, 27.38.



RESULTS AND DISCUSSION

The diazotization of aniline **1** by nitrous acid at 0-5^{o}C led to the formation of aryldiazonium chloride **2**, which on reaction with sodium azide produced arylazides **3** in 76% yield. It was reported that the azide compound can be cyclized using ethyl acetoacetate to furnish 1,2,3-triazole derivative.In a similar fashion azide compound **3** was cyclized with ethyl acetoacetate **4** in the presence of sodium ethoxide to afford another intermediate, 5-methyl-1-[aryl]-1,2,3-triazole-4-carboxylic acid **5** in 68% yield. The amide compounds were prepared by reacting 5-methyl-1-(aryl)-1,2,3-triazole-4-carboxylic acid **5** with different

aromatic amines. For this transformation, the acid compound was treated with thionyl chloride in presence of catalytic amount of pyridine in toluene medium to obtain the acid chloride and without isolation is further reacted with appropriate aniline compounds to obtain the *N*4,1-diphenyl-5-methyl-1*H*-1,2,3-triazole-4-carboxamide **6(a-j)**. The reactions proceeded smoothly and gave the expected products in substantial good yields. The amide compounds **6(a-j)** were treated with phosphorous pentachloride in carbon tetrachloride at reflux to obtain the intermediate imidoyl chloride, which were reacted with sodium azide in DMF at room temperature to afford the corresponding 5-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-1-aryll-1*H*-1,2,3,4-tetrazole **7(a-j)**.



Antibacterial activity

The *in vitro* antibacterial activity of 5-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-1-aryll-1*H*-1,2,3,4-tetrazole **7(a-j)** was assessed against three representative Gram-positive bacteria *viz*. *Bacillus subtilis*, *Bacillus sphaericus* and *Staphylo-coccus aureus*, and three Gram-negative bacteria *viz*. *Pseudomonas aeruginosa*, *Klebsiella aerogenes* and *Chromobacterium violaceum* by the broth dilution method recommended by National Committee for Clinical Laboratory Standards. Bacteria were grown overnight in Luria Bertani (LB) broth at 37°C, harvested by centrifugation and then washed twice with sterile distilled water. Stock solutions of the series of compounds were prepared in DMSO. Each stock solution was diluted with standard method broth (Difco) to prepare serial two-fold dilutions in the range of 100 to 0.8 µg/mL. Ten microliters of the broth containing about 10^5 colony-forming units (cfu)/mL of test bacteria were added to each well of a 96-well microtiter plate. Culture plates were incubated for 24 hr at 37°C, and the growth of bacteria was monitored by visually and spectrophotometrically. Penicillin and Streptomycin were also screened under identical conditions for comparison. The obtained data of compounds **7(a-j)** are presented in

Table 1 as the minimal inhibitory concentration (MIC, µg/mL). It has been observed that the compounds exhibit interesting biological activity, however, with a degree of variation.

Table 1: Antibacterial activity of compounds 7(a-j)

Compd.	Minimum inhibitory concentration (MIC) in µg/mL					
	B. subtilis	***B. sphaericus***	***S. aureus***	***P. aeruginosa***	***K. aerogenes***	***C. violaceum***
7a	12.5	12.5	25.0	25.0	50.0	25.0
7b	25.0	12.5	25.0	6.25	25.0	25.0
7c	6.25	6.25	12.5	12.5	6.25	6.25
7d	6.25	6.25	12.5	25.0	12.5	6.25
7e	6.25	6.25	12.5	12.5	6.25	12.5
7f	6.25	6.25	6.25	25.0	6.25	12.5
7g	6.25	6.25	6.25	25.0	12.5	6.25
7h	50.0	50.0	25.0	25.0	12.5	25.0
7i	12.5	6.25	25.0	25.0	25.0	12.5
7j	12.5	25.0	25.0	25.0	12.5	12.5
SM	6.25	12.5	6.25	1.56	1.56	3.12
PN	1.56	3.12	1.56	6.25	6.25	12.5

SM = Streptomycin; PN = Penicillin

In the series of **7(a-j)**, the compounds **7c** and **7g** are found to be the most active against Gram-positive bacteria and the Gram-negative bacteria except *P. aeruginosa*. The compound **7f** is highly active against all the three Gram-positive bacteria and Gram-negative bacteria *K. aerogenes.* The compounds **7d**, **7e, 7f** and **7g** are active against *B. subtilis* and *B. sphaericus*, and **7d**, **7f** and **7i** are active against *B. sphaericus* only. The remaining compounds showed moderate to good activity against all the organisms employed except *P. aeruginosa*.

CONCLUSION

In conclusion, a series of tetrazole 7**(a-j)** was prepared. The antibacterial activity of these compounds was evaluated against various bacteria. The compounds showed variable degree of antimicrobial activity. Among the screened compounds, **7c**, **7f** and **7g** were found to be the most active against all the microorganisms employed both for antibacterial and antifungal activity. With this set of analogues, we are now in a position to investigate the multiple biological activities of these compounds.

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