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Biological activities of [1,2,4]triazolo-[3,4-b],[1,3,4]-thiadiazole-6-yl) (o-tolyamino)methylazetidin-2-one

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ABSTRACT

Synthesis of 4-amino-5-(3-bromophenyl)-4H-1,2,4-triazole-3-thiol (1), 3-(3-bromophenyl) [1,2,4]-triazolo[3,4-b][1,3,4]thiadiazol-6-amine (2), N-substituted benzylidene -3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-amine (3-7),1-(3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-yl)-4-substitutedphenyl azetidin-2-one (8-12), 3-(3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-yl)-2-phenylthia zolidin-4-one (13-17), 1-(3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b],[1,3,4]-thiadiazole-6-yl)-4-substi- tutedphenyl-3-((o-tolyamino)methyl)azetidin-2-one (18-27).Among all the synthesized compounds, Mannich products were found to possess wide spectrum of antibactderial and antifungal activities with lesser potency and among the mannich products, 22 and 26 were found most potent compound of the series.

INTRODUCTION

Indole derivatives are important source of compounds of pharmacological interest as they have shown a wide spectrum of biological activates viz. activities as anti-inflammatory (Wuest *et al.,* 2009;) antibacterial (Prasad *et al.,* 2012;), antiviral (Todoulou *et al.,* 1994;), antifungal (Jianming *et al.,* 2011; Rezaei *et al.,* 2009), and antimicrobial activities (Demirbas *et al.,* 2009;). Among the wide variety of heterocycles that have been explored for developing pharmaceutically important molecules, thiadiazoles (Reddy *et al.,* 2011; Farshori *et al.,* 2010) are played an important role in medicinal chemistry. Some of them have received considerable attention as potential agents. Various derivatives of triazole, thiazolidinone (Rajanarendar *et al.,* 2011; Salvi *et al.,* 2009), azetidinone (Baviskar et al., 2011; Ansari et al., 2009) and thiadazole have also been reported to possess antibacterial activity. In light of above observation it was thought worthwhile to synthesized some new thiadiazole derivations by incorporation of triazole and thiadiazole into a molecular single frame work with the hope to get better antibacterial agents. The structures of these compounds were delineated by elemental analysis, IR, H-1NMR and mass spectroscopy. 4-amino-5-(3-bromophenyl)-4H-1,2,4-triazole-3-thiol. was obtained from subsituted ester hydrazide. Reaction with cyanogen bromide brought further cyclization of compound 1 to obtain 3-(3-bromophenyl)-[1,2,4] triazole [3,4-b] [1,3,4] thiadiazole-6-amine (2), which on further treating with different aromatic aldehydes yielded schiff bases i.e. N-substitutedbenzylidene-3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-amine3-7 by 1,4 dicycol condensation of acetylchloride and thioglycolic acid respectively. 1-(3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-yl)-4-substitutedphenylazetidin-2-one 8-12 underwent Mannich reaction to yield Mannich products i.e.

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1-(3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b],[1,3,4]-thiadiazole-6-yl)-4-ubstitutedphenyl-3 - ((o-tolyamino) methyl) azetidin-2-one 18-27.

MATERIAL & METHOD

The melting points of the compounds were determined in open glass capillaries with the help of thermonic melting point apparatus and are uncorrected. The homogeneity of all the newly synthesized compounds was routinely checked by thin layer chromatography (TLC) on silica gel G plates and spots were located by using iodine chamber.

Elemental analysis (C,H,N) of all the synthesized compounds were determined by Perkin-Elmer 2400 elemental analyzer, and results were found within the $\pm$ 0.4% of theoretical values. Infra red (IR) spectra were recofed in KBr on Perkin Elmer-Spectrum RX-I, spectrometer and V_{max} was recorded in cm^{-1}. ^1H NMR spectra were record by Bruker AC-300 F instrument using a mixture of $CDC1_3$ & DMSO-d_6 as solvent and tetramethylsilane (TMS) as internal reference standard. All chemical shift values were recorded as δ (ppm.) Mass spectra were determined on VG-70-S instrument.

Synthesis of 4-amino-5-(3-bromophenyl)-4H-1,2,4-triazole-3-thiol (1).

In methanolic solution of aromatic acid hydrazides (.001 mole), potassium hydroxide (.005 mole) and carbon di-sulfide (.001 mole) were added and the obtained mixture stirred vigorously for 2-3 hrs. After stirring excess of hydrazine hydrate was added and the mixture further refluxed for 6 h. The completion of the reaction was checked by TLC. The cooled reactionmixture was poured into ice water and neutralized with concentrate HCl. Thus obtained product was filtered, washed with water and recrystallized from appropriate solvents to afford compounds 1. Physical, analytical and spectral analysis are given below-

Compound 1: 4-amino-5-(3-bromophenyl)-4H-1,2,4-triazole-3-thiol.

Yield: 75%; m.p.:145^{o}C; (r.s.) methanol; IR (KBr) (cm^{-1}): 575(C-Br), 1295 (N-N), 1525 (C-N), 1610 (C⋯C of aromatic ring), 1682 (C=N), 2710 (SH), 3140 (C-H aromatic).^{1}H-NMR ($CDCl_3$ + DMSO-d_6 δ (ppm): 5.875 (bs, 2H, NH_2 exchangeable with D_2O), 6.900-7.570 (m, 4H, ArH), 11.435 (bs, 1H, SH exchangeable with D_2O), MS $[M]^+$ at m/z 271, Anal. Calcd. for $C_8H_7BrN_4$: C, 35.44; H, 2.60; N, 20.66: Found: C, 35.55; H, 2.61; N, 20.72%.

Synthesis of 3-(3-bromophenyl) [1,2,4]-triazolo[3,4-b][1,3,4]thiadiazol-6-amine (2).

Ethanolic solution of compounds 1-2 (.001 mole) and cyanogen bromide (.001 mole) was refluxed for 7-8 h. The completion of the reaction was checked by TLC. The excess of ethanol was distilled off. Reaction mixture was poured into ice water, filtered, washed with water, dried and recrystallized from appropriate solvents to yield compounds 2. Physical, analytical and spectral analysis are given as-

Compound 2: 3-(3-bromophenyl) [1,2,4]-triazolo[3,4-b][1,3,4]thiadiazol-6-amine.

Yield: 670%; m.p.: 160^{o}C; (r.s): Ethanol, IR (KBr) (cm^{-1}): 572(C-Br), 685 (C-S-C), 1292 (N-N), 1522 (C-N), 1612 (C⋯C of aromatic ring), 1682 (C=N), 3143 (C-H aromatic), 3320 (NH_2).^{1}H-NMR ($CDCl_3$ + DMSO-d_6 δ (ppm): 5.870 (bs, 2H, NH_2 exchangeable with D_2O), 6.910-7.470 (m, 4H, ArH), MS $[M]^+$ at m/z 296, Anal. Calcd. for $C_9H_6BrN_5S$: C, 36.50; H, 2.04; N, 23.65: Found: C, 36.62; H, 2.05; N, 23.70%.

Synthesis of N-substitutedbenzylidene-3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-amine (3-7).

A methanolic solution of compound 2 (.01 mole) was added with various substituted aromatic aldehydes (.01 mole) in presence of few drops of glacial acetic acid and refluxed for 8 h. Completion of the reaction was checked by TLC. Excess of methanol was distilled off. The reaction mixture was poured in ice water, filtered, dried and recrystallized from suitable solvents. The relevant physical, analytical and spectral data are given as-

Compound 3: N-benzylidene-3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-amine.

Yield: 65%; m.p.: 220^{o}C; (r.s): methanol; IR (KBr) (cm^{-1}): 570(C-Br), 690 (C-S-C), 1290 (N-N), 1520 (C-N), 1610 (C⋯C of aromatic ring), 1685 (C=N), 3142 (C-H aromatic), ^{1}H-NMR ($CDCl_3$ + DMSO-d_6 δ (ppm): 7.250-7.960 (m, 9H, ArH), 8.686 (s, 1H, N=CH-Ar), MS $[M]^+$ at m/z 384, Anal. Calcd. for $C_{16}H_{10}BrN_5S$: C, 50.01; H, 2.62; N, 18.23: Found: C, 50.15; H, 2.63; N, 18.29%.

Compound 4: 3-(3-bromophenyl)-N-(2-chlorobenzylidene)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-amine.

Yield: 63%; m.p.: 118^{o}C, (r.s):Methanol; IR (KBr) (cm^{-1}): 575 (C-Br), 670 (C-Cl), 688 (C-S-C), 1290 (N-N), 1525 (C-N), 1612 (C⋯C of aromatic ring), 1683 (C=N), 3145 (C-H aromatic), ^{1}H-NMR ($CDCl_3$+DMSO-d_6 δ (ppm : 6.918-7.472 (m,4H,ArH), 7.900-8.266 (m, 4H, ArH), 8.689(s,1H,N=CH-Ar), MS $[M]^+$ at m/z 418, Anal. Calcd. for $C_{16}H_9BrClN_5S$.: C, 45.90; H, 2.17; N, 16.73: Found: C, 45.99; H, 2.18; N, 16.79%.

Compound 5: 3-(3-bromophenyl)-N-(4-chlorobenzylidene)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-amine.

Yield: 68%; m.p.: 241^{o}C; (r.s): Methanol; IR (KBr) (cm^{-1}): 570 (C-Br), 672 (C-Cl), 685 (C-S-C), 1295 (N-N), 1522 (C-N), 1610 (C....C of aromatic ring), 1682 (C=N) 3142 (C-H aromatic), ^{1}H-NMR ($CDCl_3$ + DMSO-d_6 δ (ppm) : 7.118-7.260 (m, 4H, ArH), 6.925-7.361 (m, 4H, ArH), 8.680 (s, 1H, N=CH-Ar), MS $[M]^+$ at m/z 418, Anal. Calcd. for $C_{16}H_9BrClN_5S$.: C, 45.90; H, 2.17; N, 16.73: Found: C, 45.82; H, 2.16; N, 16.68%.

Compound 6: 2-(((3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-yl)imino)methyl)phenol.

Yield: 62%; m.p.: 256°C; (r.s): Methanol; IR (KBr) (cm^{-1}): 570 (C-Br), 690 (C-S-C), 1295 (N-N), 1520 (C-N), 1610 (C=C of aromatic ring), 1682 (C=N), 3142 (C-H aromatic 3420 (OH)), ^{1}H-NMR ($CDCl_3$ + DMSO-d_6 δ (ppm): 6.918-7.390 (m, 4H, ArH), 7.618-7.829 (m, 4H, ArH), 8.680 (s, 1H, N=CH-Ar), 12.035 (ss, 1H, Ar-OH exchangeable with D_2O), MS $[M]^+$ at m/z 400, Anal. Calcd. for $C_{16}H_{10}BrN_5OS$: C, 48.01; H, 2.52; N, 17.50: Found: C, 48.14; H, 2.53; N, 17.57%.

Compound 7: 4-(((3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-yl)imino)methyl)phenol.

Yield: 60%; m.p.: 266°C; (r.s): Methanol; IR (KBr) (cm^{-1}): 573 (C-Br), 688 (C-S-C), 1292 (N-N), 1522 (C-N), 1612 (C=C of aromatic ring), 1682 (C=N), 3144 (C-H aromatic 3422 (OH)), ^{1}H-NMR ($CDCl_3$ + DMSO-d_6 δ (ppm) : 6.818-7.220 (m, 4H, ArH), 7.618-7.829 (m, 4H, ArH), 8.120 (s, 1H, N=CH-Ar), 11.935 (ss, 1H, Ar-OH exchangeable with D_2O), MS $[M]^+$ at m/z 400, Anal. Calcd. for $C_{16}H_{10}BrN_5OS$: C, 48.01; H, 2.52; N, 17.50: Found: C, 48.10; H, 2.50; N, 17.55%.

Synthesis of 1-(3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-yl)-4-substitutedphenylazetidin-2-one (8-12).

In DMF (50 ml) solution of compounds 3-7 (.01 mole), triethyl amine (.02 mole) and acetyl chloride (.02 mole) were added dropwise at 0-5°C. The reaction mixture was stirred for about 6-8 h. The completion of the reaction was checked by TLC. The precipitated amino hydrochloride filtered off. The filtrate was concentrated under reduced pressure and poured into cold ice water. The product so obtained was recrystallized from appropriate solvents to obtain compounds 8-12.

Physical, analytical and spectral analysis are given as-

Compound 8: 1-(3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-yl)-4-phenylazetidin-2-one.

Yield: 61%; m.p.: 180°C; (r.s): Methanol; IR (KBr) (cm^{-1}): 575 (C-Br), 687 (C-S-C), 1290 (N-N), 1520 (C-N), 1610 (C=C of aromatic ring), 1680 (C=N), 1720 (C=O of β-lactam ring), 3140 (C-H aromatic), ^{1}H-NMR ($CDCl_3$+DMSO-d_6 δ (ppm) : 4.186-4.216 (d, 2H, CH_2-O), 6.536-6.570 (t, 1H, N-CH-Ar), 7.400-8.108 (m, 9H, ArH), MS $[M]^+$ at m/z 426, Anal. Calcd. for $C_{18}H_{12}BrN_5OS$: C, 50.71; H, 2.84; N, 16.43: Found: C, 50.82; H, 2.85; N,16.48%.

Compound 9: 1-(3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-yl)-4-(2-chlorophenyl)azetidin-2-one.

Yield: 65%; m.p.: 177°C; (r.s0: DMF-water; IR (KBr) (cm^{-1}): 570 (C-Br), 675 (C-Cl), 690 (C-S-C), 1525 (C-N), 1295 (N-N), 1615 (C=C of aromatic ring), 1685 (C=N), 1725 (C=O of β-lactam ring), 3145 (C-H aromatic), 3425 (OH), ^{1}H-NMR ($CDCl_3$ + DMSO-d_6 δ (ppm) : 4.190-4.225 (d, 2H, CH_2-C), 6.547-6.572 (t, 1H, N-CH-Ar), 7.012-7.374 (m, 4H, ArH), 7.650-7.790 (m, 4H, ArH), MS $[M]^+$ at m/z 460, Anal. Calcd. for $C_{18}H_{11}BrClN_5OS$: C, 46.92; H, 2.41; N, 15.20: Found: C, 46.99; H, 2.42; N,15.25%.

Compound 10: 1-(3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-yl)-4-(4-chlorophenyl)azetidin-2-one.

Yield: 58%; m.p.: 220°C; (r.s): Acetic acid; IR (KBr) (cm^{-1}): 572 (C-Br), 673 (C-Cl) 688 (C-S-C), 1522 (C-N), 1292 (N-N), 1612 (C=C of aromatic ring), 1682 (C=N), 1722 (C=O of β-lactam ring), 3142 (C-H aromatic), ^{1}H-NMR ($CDCl_3$ + DMSO-d_6 δ (ppm): 4.158-4.218 (d, 2H, CH_2-C), 6.522-6.564 (t, 1H, N-CH-Ar), 7.012-7.360 (m, 4H, ArH), 7.602-7.792 (m, 4H, ArH), MS $[M]^+$ at m/z 460, Anal. Calcd. for $C_{18}H_{11}BrClN_5OS$: C, 46.92; H, 2.41; N, 15.20: Found: C, 46.80; H, 2.40; N,15.12%.

Compound 11: 1-(3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-yl)-4-(2-hydroxyphenyl)azetidin-2-one.

Yield: 55%; m.p.: 212°C; (r.s): Ethanol, IR (KBr) (cm^{-1}): 575 (C-Br), 690 (C-S-C), 1290 (N-N), 1520 (C-N), 1612 (C=C of aromatic ring), 1682 (C=N), 1722 (C=O of β-lactam ring), 3142 (C-H aromatic), 3420 (OH), ^{1}H-NMR ($CDCl_3$ + DMSO-d_6 δ (ppm):, 4.192-4.230 (d, 2H, CH_2-C), 6.545-6.570 (t, 1H, N-CH-Ar), 7.154-7.265 (m, 4H, ArH), 7.289-7.562 (m, 4H, ArH), 12.096 (ss, 1H, ArOH exchangeable with D_2O), MS $[M]^+$ at m/z 442, Anal. Calcd. for $C_{18}H_{12}BrN_5O_2S$: C, 48.88; H, 2.73; N, 15.83: Found: C, 48.99; H, 2.74; N,15.89%.

Compound 12: 1-(3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-yl)-4-(4-hydroxyphenyl)azetidin-2-one.

Yield: 57%; m.p.: 199°C; (r.s): Methanol, IR (KBr) (cm^{-1}): 572 (C-Br), 690 (C-S-C), 1295 (N-N), 1525 (C-N), 1615 (C=C of aromatic ring), 1685 (C=N), 1725 (C=O of β-lactam ring), 3145 (C-H aromatic), 3425 (OH), ^{1}H-NMR ($CDCl_3$ + DMSO-d_6 δ (ppm):, 4.832-4.230 (d, 2H, CH_2-C), 6.545-6.570 (t, 1H, N-CH-Ar), 7.154-7.265 (m, 4H, ArH), 7.289-7.562 (m, 4H, ArH), 11.960 (ss, 1H, ArOH exchangeable with D_2O), MS $[M]^+$ at m/z 442, Anal. Calcd. for $C_{18}H_{12}BrN_5O_2S$: C, 48.88; H, 2.73; N, 15.83: Found: C, 48.75; H, 2.72; N,15.75%.

Synthesis of-3-(3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b][1,3,4] -thiadiazole-6-yl)-2-phenylthiazolidin-4-one (13-17).

A methanolic solution of compounds 3-7 (.01 mole) and thioglycolic acid (.02 mole) with small amount of anhydrous $ZnCl_2$ was refluxed for 10 h. The completion of the reaction was checked by TLC and excess of methanol distilled off. The cooled residue was poured into ice water, filtered, washed with water and recrystallized from appropriate solvents to afford compounds 13-17. Physical, analytical and spectral analysis are given as-

Compound 13: 3-(3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-yl)-2-phenylthiazolidin-4-one.

Yield: 64%; m.p.: 130°C; (r.s): DMF-water; IR (KBr) (cm^{-1}): 572 (C-Br), 690 (C-S-C), 1295 (N-N), 1525 (C-N), 1615

(C=C of aromatic ring), 1705 (C=O of thialactam), 3155 (C-H aromatic), ^{1}H-NMR ($CDCl_3$ + DMSO-d_6 δ (ppm): 3.876 (s, 2H, CH_2 thialactam), 6.876 (s, 1H, N-CH-Ar), 7.371-8.096 (m, 9H, ArH), MS $[M]^+$ at m/z 458, Anal. Calcd. for $C_{18}H_{12}BrN_5OS_2$: C, 47.17; H, 2.64; N, 15.28: Found: C, 47.29; H, 2.66; N,15.35%.

Compound 14: 3-(3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-yl)-2-(2-chlorophenyl)thiazolidin-4-one.

Yield: 66%; m.p.: 140°C; (r.s): Methanol-water; IR (KBr) (cm^{-1}): 575 (C-Br), 670 (C-Cl), 688 (C-S-C), 1292 (N-N), 1522 (C-N), 1612 (C=C of aromatic ring), 1682 (C=N), 1702 (C=O of thialactam), 3152 (C-H aromatic), ^{1}H-NMR ($CDCl_3$ + DMSO-d_6 δ (ppm): 3.882 (s, 2H, CH_2-S of thialactam), 6.872 (s, 1H, N-CH-Ar), 7.256-7.573 (m, 4H, ArH), 7.600-7.798 (m, 4H, ArH), MS $[M]^+$ at m/z 492, Anal. Calcd. for $C_{18}H_{11}BrClN_5OS_2$: C, 43.87; H, 2.25; N, 14.21: Found: C, 43.98; H, 2.26; N,14.26%.

Compound 15: 3-(3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-yl)-2-(4-chlorophenyl)thiazolidin-4-one.

Yield: 59%; m.p.: 152°C; (r.s): Methanol-water; IR (KBr) (cm^{-1}): 570 (C-Br), 672 (C-Cl), 690 (C-S-C), 1295 (N-N), 1525 (C-N), 1615 (C=C of aromatic ring), 1685 (C=N), 1705 (C=O of thialactam), 3155 (C-H aromatic),^{1}H-NMR ($CDCl_3$ + DMSO-d_6 δ (ppm): 3.912 (s, 2H, CH_2-S of thialactam), 6.932 (s, 1H, N-CH-Ar), 7.256-7.573 (m, 4H, ArH), 7.602-7.790 (m, 4H, ArH), MS $[M]^+$ at m/z 492, Anal. Calcd. for $C_{18}H_{11}BrClN_5OS_2$: C, 43.87; H, 2.25; N, 14.21: Found: C, 43.80; H, 2.27; N,14.15%.

Compound 16: 3-(3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-yl)-2-(2-hydroxyphenyl)thiazolidin-4-one

Yield: 57%; m.p.: 183°C; (r.s): Ethanol-water, IR (KBr) (cm^{-1}): 575 (C-Br), 690 (C-S-C), 1290 (N-N), 1520 (C-N) 1610 (C=C of aromatic ring), 1680 (C=N), 1700 (C=O of thialactam), 3150 (C-H aromatic), 3420 (OH), ^{1}H-NMR ($CDCl_3$ + DMSO-d_6 δ (ppm): 3.882 (s, 2H, CH_2S thialactam), 6.867 (s, 1H, N-CH-Ar) 7.095-7.347(m, 4H, ArH), 7.667-7.985 (m, 4H, ArH), 12.092(ss, 1H, ArOH exchangeable with D_2O), MS $[M]^+$ at m/z 474, Anal. Calcd. for $C_{18}H_{12}BrN_5O_2S_2$: C, 45.58 H, 2.55; N, 14.76: Found: C, 45.66; H, 2.57; N,14.83%.

Compound 17: 3-(3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-yl)-2-(4-hydroxyphenyl)thiazolidin-4-one.

Yield: 78%; m.p.: 195°C; (r.s): Ethanol, IR (KBr) (cm^{-1}): 572 (C-Br), 690 (C-S-C), 1292 (N-N), 1522 (C-N) 1612 (C=C of aromatic ring), 1682 (C=N), 1702 (C=O of thialactam), 3152 (C-H aromatic), 3422 (OH), ^{1}H-NMR ($CDCl_3$ + DMSO-d_6 δ (ppm) : 3.877 (s, 2H, CH_2S thialactam), 6.870 (s, 1H, N-CH-Ar) 7.520-8.078 (m, 8H, ArH), 12.101 (ss, 1H, Ar-OH exchangeable with D_2O), MS $[M]^+$ at m/z 474, Anal. Calcd. for $C_{18}H_{12}BrN_5O_2S_2$: C, 45.58 H, 2.55; N, 14.76: Found: C, 45.68; H, 2.54; N,14.70%.

Synthesis of 1- (3- (3-bromophenyl)- [1,2,4] triazolo- [3,4-b] [1,3,4]- thiadiazole - 6- yl) -4- substitutedpheny l-3- ((o tolyamino)methyl)azetidin-2-one (18-27).

To a mixture of compounds 13-17 (.001 mole) in methanol (20 ml), formaladehyde (.002 mole) and various substituted aromatic amines were added in dropwise manner and obtained mixture was refluxed for 6 h. The completion of the reaction of the reaction was checked by TLC. The excess of methanol was distilled off. The obtained solid residue was washed with petroleum ether (40-60°C) and recrystallized from suitable solvents to give compounds 18-27. Physical, analytical and spectral data are given below-

Compound 18: 1-(3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-yl)-4-phenyl-3-((o-tolyamino)methyl)azetidin-2-one.

Yield: 62%, m.p.: 138°C; (r.s): DMF-water; IR (KBr) (cm^{-1}): 575 (C-Br), 685 (C-S-C), 1295 (N-N), 1522 (C-N), 1615 (C=C of aromatic ring), 1685 (C=N), 1720 (C=O of β-lactam ring], 3145 (C-H aromatic), ^{1}H-NMR ($CDCl_3$ + DMSO-d_6 δ (ppm) : 2.85 (s, 3H, CH_3), 3.620-3.648 (d, 2H, CH_2-NH), 3.784-3.815 (t, IH, CH=O of β-lactam ring), 5.320-5.360 (t, 1H, CH2-NH-Ar exchangeable with D_2O), 6.5 (d, 1H, N-CH-Ar of β-lactam ring), 6.9 (m, 13H, ArH), MS $[M]^+$ at m/z 545, Anal. Calcd. for $C_{26}H_{21}BrN_6OS$: C, 57.25 H, 3.38; N, 15.41: Found: C, 57.38 H, 3.40; N,15.48%.

Compound 19: 1-(3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-yl)-4-(2-chlorophenyl-3-((o-tolyamino)methyl)azetidin-2-one.

Yield: 58%; m.p.: 154°C; (r.s): Methanol; IR (KBr) (cm^{-1}): 570 (C-Br), 672 (C-C1), 690 (C-S-C), 1290 (N-N), 1525 (C-N), 1610 (C=C of aromatic ring), 1680 (C=O), 1725 (C=O of β-lactam ring], 3150 (C-H aromatic), ^{1}H-NMR ($CDCl_3$ + DMSO-d_6 δ (ppm) : 2.90 (s, 3H, CH_3), 3.619-3.650 (d, 2H, CH_2-NH), 3.782-3.819 (t, 1H, CH-C=O of β-lactam ring), 5.315-5.354 (t, 1H, CH_2-NH-Ar exchangeable with D_2O), 6.548-6.584 (d, 1H, N-CH-Ar of β-lactam ring), 6.997-8.000 (m, 12H, ArH), MS $[M]^+$ at m/z 579, Anal. Calcd. for $C_{26}H_{20}BrClN_6OS$: C, 53.85 H, 3.48; N, 14.49: Found: C, 53.98 H, 3.50; N,14.55%.

Compound 20: 1-(3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-yl)-4-(4-chlorophenyl-3-((o-tolyamino)methyl)azetidin-2-one.

Yield: 55%; m.p.: 140°C; (r.s): Methanol; IR (KBr) (cm^{-1}): 572 (C-Br), 675 (C-C1), 688 (C-S-C), 1292 (N-N), 1522 (C-N), 1612 (C=C of aromatic ring), 1682 (C=N), 1722 (C=O of β-lactam ring], 3152 (C-H aromatic), ^{1}H-NMR ($CDCl_3$ + DMSO-d_6 δ (ppm) : 2.86 (s, 3H, CH_3), 3.652-618 (d, 2H, CH_2-NH), 3.790-3.822 (t, 1H, CH-C=O of β-lactam ring), 3.850 (s, 3H, OCH_3), 5.312-5.35 (t, 1H, CH_2-NH-Ar), 6.5426.580 (d, 1H, N-CH-Ar,of β-lactam ring), 6.950-7.680 (m, 12H, ArH), MS $[M]^+$ at m/z 579, Anal. Calcd. for $C_{26}H_{20}BrClN_6OS$: C, 53.85 H, 3.48; N, 14.49: Found: C, 53.75 H, 3.47; N,14.58%.

Compound 21: 1-(3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-yl)-4-(2-hydroxyphenyl-3-((o-tolyamino)methyl)azetidin-2-one.

Yield: 52%; m.p.: 168°C; (r.s): Methanol; IR (KBr) (cm^{-1}): 575 (C-Br), 685 (C-S-C), 1290 (N-N), 1520 (C-N), 1610 (C=C of aromatic ring), 1680 (C-N), 1720 (C=O of β-lactam ring], 3150 (C-H aromatic), 3420 (OH), ^{1}H-NMR ($CDCl_3$+DMSO-d_6 δ (ppm) : 2.88 (s, 3H, CH_3), 3.618-3.646 (d, 2H, CH_2-NH), 3.796.3.827 (t, 1H, CH-C=O of β-lactam ring), 5.310-5.359 (t, 1H, CH_2-NH-Ar exchangeable with D_2O), 6.545-6.579 (d, 1H, N-CH-Ar of β-lactam ring), 6.620-7.578 (m, 12H, ArH). 12.080 (ss, 1H, Ar-OH exchangeable with D_2O), MS $[M]^+$ at m/z 561, Anal. Calcd. for $C_{26}H_{21}BrN_6O_2S$: C, 55.62 H, 3.77; N, 14.97: Found: C, 55.75 H, 3.78; N,14.90%.

Compound 22: 1-(3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]- thiadiazole-6-yl) -4-(4-hydroxyphenyl-3- ((o-tolyamino) methyl) azetidin-2-one.

Yield: 50%; m.p.: 179°C; (r.s): Ethanol; IR (KBr) (cm^{-1}): 570 (C-Br), 688 (C-S-C), 1290 (N-N), 1520 (C-N), 1612 (C=C of aromatic ring), 1722 (C=O), of β- lactam ring), 3152 (C-H aromatic), 3422 (OH),^{1}H-NMR ($CDCl_3$+DMSO-d_6 δ (ppm) : 2.88 (s, 3H, CH_3), 3.611-3.827 (d, 2H, CH_2-NH), 3.796 (t, 1H, CH-C=O of β-lactam ring), 5.310-5.349 (t, 1H, CH_2-NH-Ar exchangeable with D_2O), 6.579 (d, 1H, N-CH-Ar of β-lactam ring), 6.627-7.490 (m, 12H, ArH). 12.080 (ss, 1H, Ar-OH exchangeable with D_2O), MS $[M]^+$ at m/z 561, Anal. Calcd. for $C_{26}H_{21}BrN_6O_2S$: C, 55.62 H, 3.77; N, 14.97: Found: C, 55.50 H, 3.75; N,14.92%.

Compound 23: 1-(3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]- thiadiazole-6-yl) -4-(4- hydroxyphenyl-3- (((2-methoxyphenyl) amino)methyl)4-phenylazetidin-2-one.

Yield: 54%; m.p.: 162°C; (r.s): Ethanol; IR (KBr) (cm^{-1}): 572 (C-Br), 685 (C-S-C), 1292 (N-N), 1522 (C-N), 1612 (C=C of aromatic ring), 1682 (C-N), 1722 (C=O of β-lactam ring), 3152 (C-H aromatic), ^{1}H-NMR ($CDCl_3$ + DMSO-d_6 δ (ppm) : 3.856 (d, 2H, CH_2-NH), 5.349 (t, 1H, CH_2-NH-Ar of β-lactam ring), 3.8 (s, 3H OCH_3), 5.3 (t, 1H, CH_2-NH-Ar exchangeable with D_2O), 6.5 (d, 1H, N-CH-Ar), 6.6 (m, 13H, ArH), MS $[M]^+$ at m/z 561, Anal. Calcd. for $C_{26}H_{21}BrN_6O_2S$: C, 55.62 H, 3.77; N, 14.97: Found: C, 55.47 H, 3.78; N,15.05%.

Compound-24: 1-(3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-yl)-4-(2-chlorophenyl-3-(((2-methoxyphenyl) amino)methyl)4-phenylazetidin-2-one.

Yield: 57%; m.p.: 175°C; (r.s): DMF-water; IR (KBr) (cm^{-1}): 575 (C-Br), 670 (C-C1), 688 (C-S-C), 1290 (N-N), 1520 (C-N), 1610 (C=C of aromatic ring), 1680 (C=N), 1720 (C=O of β-lactam ring), 3150 (C-H aromatic), ^{1}H-NMR ($CDCl_3$ + DMSO-d_6 δ (ppm) : 3.620-3.651 (d, 2H, CH_2-NH), 3.789-3.824 (t, 1H, CH-C=O of β-lactam ring), 3.852 (s, 3H OCH_3), 5.305-5.342 (t, 1H, CH_2-NH-Ar exchangeable with D_2O),6.537-6.564 (d, 1H, N-CH-Ar), 7.012-8.068 (m, 12H, ArH), MS $[M]^+$ at m/z 595, Anal. Calcd. for $C_{26}H_{20}BrClN_6O_2S$: C, 52.40 H, 3.38; N, 14.10: Found: C, 52.52 H, 3.40; N,14.15. %.

Compound-25: 1-(3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-yl)-4-(4-chlorophenyl-3-(((2-methoxyphenyl) amino)methyl)4-phenylazetidin-2-one.

Yield: 60%; m.p.: 185°C; (r.s): Methanol; IR (KBr) (cm^{-1}): 572 (C-Br), 673 (C-C1), 690 (C-S-C), 1292 (N-N), 1522 (C-N), 1612 (C=C of aromatic ring), 16822 (C=N), 172 (C=O of β-lactam ring), 3122 (C-H aromatic), ^{1}H-NMR ($CDCl_3$+DMSO-d_6 δ (ppm) : 3.620.3.644 (d, 2H, CH_2-NH), 3.790-3.832 (t, 1H, CH-C=O of β-lactam ring), 3.856 (s, 3H OCH_3), 5.318-5.351 (t, 1H, CH_2-NH-Ar exchangeable with D_2O), 6.539-6.567 (d, 1H, N-CH-Ar), 7.209-8.015 (m, 12H, ArH), MS $[M]^+$ at m/z 595, Anal. Calcd. for $C_{26}H_{20}BrClN_6O_2S$: C, 52.40 H, 3.38; N, 14.10: Found: C, 52.50, H, 3.36; N,14.06. %.

Compound-26: 1-(3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-yl) -4-(2-hydroxyphenyl-3-(((2-methoxyphenyl)amino)methyl)4-phenylazetidin-2-one.

Yield: 57%; m.p.: 191°C; (r.s): DMF-water; IR (KBr) (cm^{-1}): 570 (C-Br), 688 (C-S-C), 1295 (N-N), 1525 (C-N), 1615 (C=C of aromatic ring), 1685 (C-N), 1725 (C=O of β-lactam ring), 3155 (C-H aromatic), 3420 (OH), ^{1}H-NMR ($CDCl_3$ + DMSO-d_6 δ (ppm) : 3.620-3.644 (d, 2H, CH_2-NH), 3.790-3.832 (t, 1H, CH-C=O of β-lactam ring), 3.856 (s, 3H OCH_3), 5.318-5.351 (t, 1H, CH_2-NH-Ar exchangeable with D_2O), 6.539-6.567 (d, 1H, N-CH-Ar), 7.209-8.015 (m, 12H, ArH), 12.06 (ss, 1H, Ar-OH exchangeable with D_2O), MS $[M]^+$ at m/z 577, Anal. Calcd. for $C_{26}H_{21}BrN_6O_3S$: C, 54.08 H, 3.67; N, 14.55: Found: C, 54.20, H, 3.65; N,14.61. %.

Compound-27: 31-(3-(3-bromophenyl)-[1,2,4]triazolo-[3,4-b] [1,3,4]-thiadiazole-6-yl)-4-(4-hydroxyphenyl-3-(((2-methoxyphenyl)amino)methyl)4-phenylazetidin-2-one.

Yield: 55%; m.p.: 184°C; (r.s): Acetic acid; IR (KBr) (cm^{-1}): 575 (C-Br), 690 (C-S-C), 1290 (N-N), 1520 (C-N), 1610 (C=C of aromatic ring), 1680 (C=N), 1720 (C=O of β-lactam ring], 31520 (C-H aromatic), 3425 (OH), ^{1}H-NMR ($CDCl_3$ + DMSO-d_6 δ (ppm): 3.612 (d, 2H, CH_2-NH), 3.735 (t, 1H, CH-C=O of β-lactam ring), 3.802 (s, 3H, OCH_3), 5.363 (t, 1H, CH_2-NH-Ar exchangeable with D_2O), 6.5 (d, 1H, N-CH-Ar), 6.6 (m, 12H, ArH), 12.08 (ss, 1H, Ar-OH exchangeable with D_2O), MS $[M]^+$ at m/z 577, Anal. Calcd. for $C_{26}H_{21}BrN_6O_3S$: C, 54.08 H, 3.67; N, 14.55: Found: C, 54.18, H, 3.66; N,14.50. %.

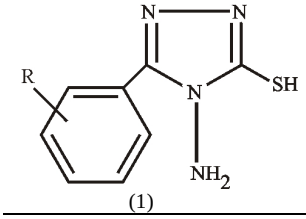
RESULT & DISCUSSION

Antibacterial and antifungal screening, for the synthesized compounds in scheme 1, has been performed against different selected pathogens and result inhibition diameter (mm) are mentioned in table Ia-Ic. Compounds 1 exhibited equipotent antibacterial and antifungal activities. Compound 2 showed i.z. 8

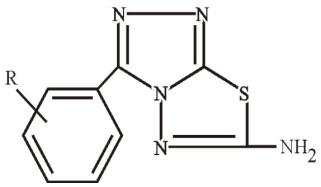
mm against S. aureus, i.z. 10 mm against E.coli, i.z.8mm against P. vulgaris while. Incorporation of different aromatic aldehydes via NH_2 linkage of substituted triazoles 2 yielded N-subsitutetedbenzylidene-3-(3-bromophenyl)-[1,2,4] triazolo [3,4-b] [1,3,4] thiadiazol-6-amine (3-7). Screening results exhibited that among the compounds 3-7, compound 4 possessed both types of activities. This compound exhibited 20 mm inhibition diameter against the fungi A. fumigatus which is maximum. Compounds 3,5 and 6 were found to resistant against the used bacterial and fungal pathogens. Compound 7 gave 14 mm inhibition diameter against S. aureus and 12mm against C. albicans respectively.Compound 7 was found to exhibit equipotent antibacterial as well as antifungal activity. Biological activity results showed that unsubstitued phenyl compound 8, 2-OH substituted phenyl possessing β-lactam (11 & 12) were bacterial resistant. Compounds 9 showed i.z. of 10 mm against S.aureus, 14 mm against P.vulgaris 12mm against *K.pneumoniae*.

The β-thialactam (13-17), which were obtained from the parent compounds 3-7 showed that compound 15 exhibited most potent antifungal activity against C.albicans, which is comparable to standard drug fluconazole. Results revealed that compound 9, 12 devoid of antibacterial as well as antifungal activity. Compound 18-27 are mannich products, obtained from parent compounds 8-12. The screening results exposed mannich products 18-27 possessed wide spectrum of antibacterial as well as antifungal activities but lesser potency. Among the mannich products 18-27, 1-(3-bromophenyl)-[1,2,4] triazolo [3,4-b] [1,3,4] thiadiazol-6-yl-4-methoxyphenyl-3-((o-tolyamino)methyl) azetidin -2-one 22 and 1-(3-bromophenyl)-[1,2,4] triazolo [3,4-b] [1,3,4] thiadiazol-6-yl-4-methoxyphenyl-3-((2-hydroxyphenyl) amino) methyl) 4-phenylazetidin-2-one 26 showed more inhibition diameter of 18 mm and 28 mm against E.coli respectively. The remaining other mannich products showed mild to moderate inhibition zones against various used pathogens.

Table. Ia : Antibacterial and antifungal activity of the compounds: (1), (3) and (3-7).



(1)



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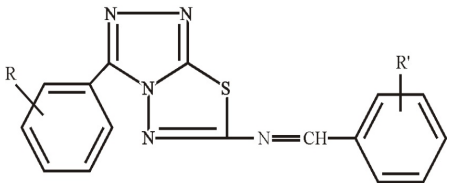
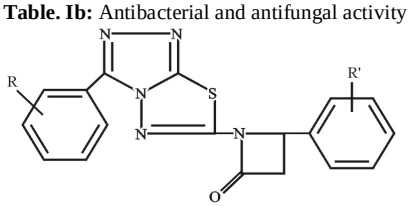


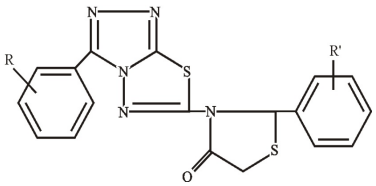
(3-7)

Comp. No.	R	R'	Bacterial growth inhibition (diameter)				Fungal growth inhibition (diameter)			
			S.aureus	*E. coli*	P. vulgaris	*K. pneumoniae*	A. fumigatus	C.albicans	C. albicans *ATCC*	C. Krusei *G03*
1	Br	-	6 mm	7 mm	-	-	-	10 mm	-	-
2	Br	-	8 mm	-	8	-	-	-	-	-
3	Br	H	-	-	-	-	-	-	-	-
4	Br	2-Cl	12 mm	10mm	-	-	20mm	14mm	11 mm	-
5	Br	4-Cl		-	-	-	-	-	10 mm	-
6	Br	2-OH	-	-	-	-	-	-	10 mm	-
7	Br	4-OCH_3	-	9 mm	-	-	16 mm	12 mm	11 mm	12 mm

Table. Ib: Antibacterial and antifungal activity of the compounds: (8-12) and (13-17).

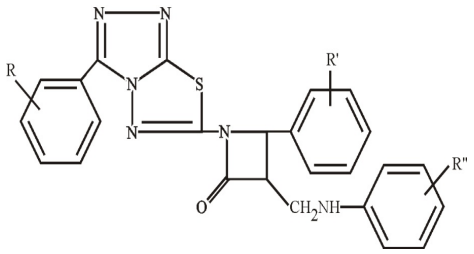


(8-12)



(13-17)

Comp. No.	R	R'	Bacterial growth inhibition (diameter)				Fungal growth inhibition (diameter)			
			S.aureus	*E. coli*	P. vulgaris	*K. pneumoniae*	A. fumigatus	C.albicans	C. albicans *ATCC*	C. Krusei *G03*
8	Br	H	-	-	-	-	-	-	-	-
9	Br	2-Cl	10 mm	-	14 **mm**	12 **mm**	-	-	-	-
10	Br	4-Cl	8 mm	10 mm	-	-	-	-	-	-
11	Br	2-OH	10 **mm**	-	8 **mm**	-	-	-	-	-
12	Br	4-OCH_3	17 mm	16 mm	-	-	-	-	-	-
13	Br	H	-	-	-	-	13 mm	10 mm	10 mm	-
14	Br	2-Cl	6 mm	-	-	-	-	-	-	-
15	Br	4-Cl	10 mm	8 mm	-	-	-	29 mm	26 mm	19 mm
16	Br	2-OH	12 **mm**	-	10 **mm**	10 **mm**	-	-	-	-
17	Br	4-OCH_3	-	12 mm	-	-	-	16 **mm**	-	-

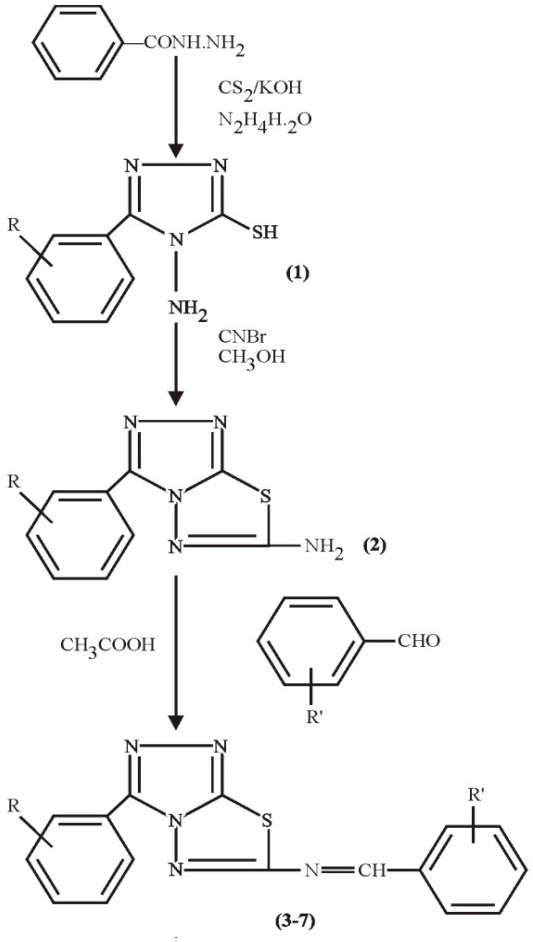


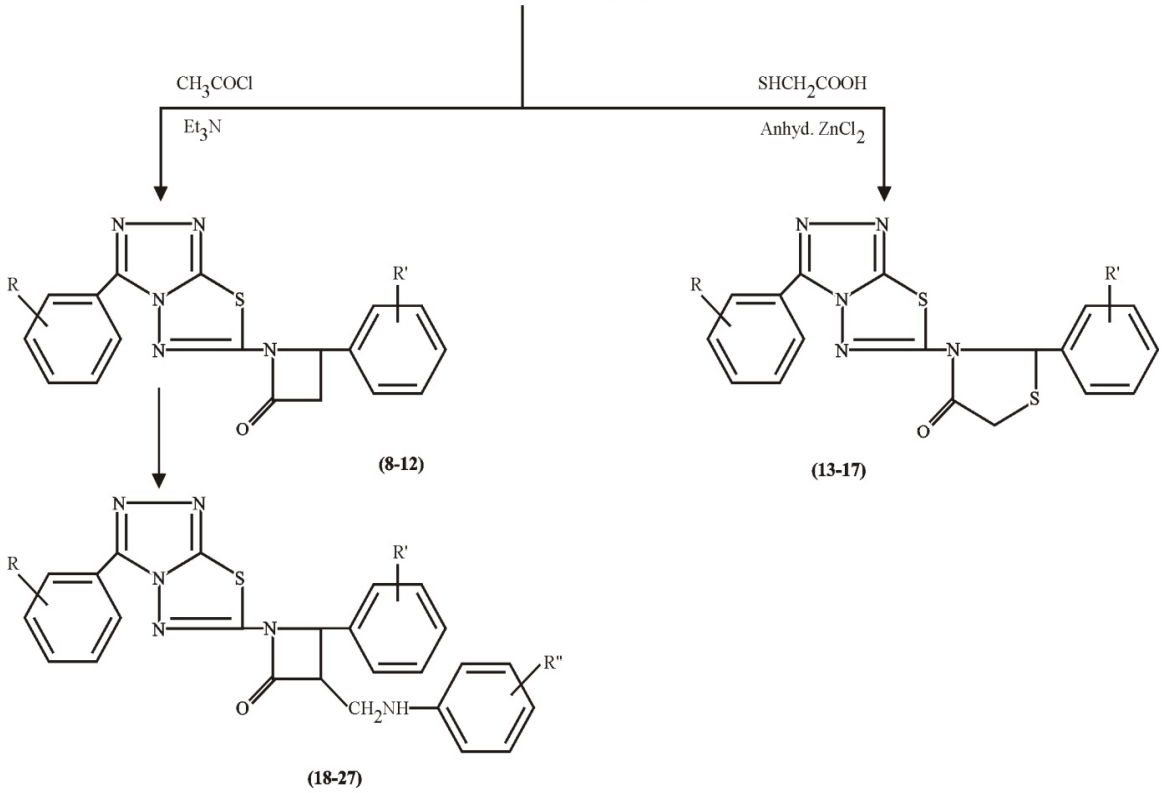
(18-27)

Table. Ic : Antibacterial and antifungal activity of the compounds: (18-27).

Comp. No.	R	R'	R''	Bacterial growth inhibition (diameter)				Fungal growth inhibition (diameter)			
				S.aureus	***E. coli***	**P. vulgaris**	***K. pneumoniae***	**A. fumigatus**	**C.albicans**	**C. albicans *ATCC***	**C. Krusei *G03***
18	Br	H	2-CH_3	-	12 mm	6 mm	-	-	-	-	-
19	Br	2-Cl	2-CH_3	-	14 mm	12 mm	-	-	-	12 mm	-
20	Br	4-Cl	2-CH_3	12 mm	-	6 mm	10 mm	10 mm	12 mm	10 mm	-
21	Br	2-OH	2-CH_3	8 mm	-	-	-	-	-	11 mm	-
22	Br	4-OCH_3	2-CH_3	12 mm	18 mm	-	-	-	-	-	-
23	Br	H	2-OCH_3	10 mm	-	-	-	-	-	-	12 mm
24	Br	2-Cl	2-OCH_3	-	-	-	-	-	-	-	-
25	Br	4-Cl	2-OCH_3	14 mm	15 mm	-	10 mm	-	10 mm	-	-
26	Br	2-OH	2-OCH_3	10 mm	28 mm	-	17 mm	12 mm	16 mm	18 mm	-
27	Br	4-OCH_3	2-OCH_3	6 mm	-	-	-	-	12 mm	-	-
	Ampicillin			20 mm	18 mm	18 mm	14 mm	-	-	-	-
	Gattifloxacin			25 mm	22 mm	20 mm	21 mm	-	-	-	-
	Fluconazole			-	-	-	-	-	29 mm	25 mm	19 mm

* 250 μg/ml. – **Drug concentration**





SCHEME-I

CONCULSION

On the basis of counter study of structural analysis relationship; it is found-

1. 2-hydroxy and 4-methoxy substitution is beneficial from the biological activity point of view.
2. In the series, Mannich product (compound 26) is the most potent compound than all the clinically used chemotherapeutic standard drugs as ampicillin (i.z. 18 mm), gattifloxacin (i.z. 22mm) against E.coli.

Biological activity

Antibacterial activity

The Cup-Plate Method given by Chuinckshank *et al.*[13] Nutrient agar was poured onto the sterlized petri dsihes (20-25 mL each pertri dish). The poured material was allowed to set (1-1.5h) and thereafter the "CUPS" (10 mm diameter) were made by punching into the agar surface with a sterile cork borer and scooping out the punched part of the agar. Into these cups the test compound solution was added with the help of sterile syringe. The plates were incubated at 37°C for 48 h and the results were noted. A solvent control (10% DMSO in methanol) was also run to not the activity of the blank (solvent). The above said standard drugs were also screened under similar conditions for comparison.

Antifungal activity

For antifungal screening, spore suspension (5mL) of each test organisms (72 h culture) was added to sterilised Sabouraud dextrose agar (Himedia Lab. Ltd., Mumbai) medium at 35-40°C by thorough shaking. The petri dishes were seeded with the mixture and the paper discs of the methanolic solution of compound and the reference antibiotic (Fluconazole) as the control was placed in the same manner as in antibacterial activity determination. These petri dishes were incubated at 30°C for 48h. The zone of inhibition was considered as an indicator the antifungal activity.

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