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Synthesis and antimicrobial evaluation of 8-[{4-(2-substituted phenyl–5-oxo-thiazolidin-1-yl)-5-thiobutyl triazolo} methoxy] quinolines

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ABSTRACT

Several 8-substituted derivatives of quinoline were synthesized. The structure of the prepared compounds were characterezied by elemental and spectral (I.R.,^{1}H-NMR, Mass) analysis. These molecules were evaluated for their efficacy as antimicrobials in vitro by disc diffusion method against some selected pathogenic strains in compare to gatifloxacin and fluconazole.

Key words: Quinolines, antibacterial activity, antifungal activity, toxicity.

INTRODUCTION

In our continual search programme[1] for new biological important molecules, here we have establishment a chemical strategy to find out novel antimicrobial agents. Various workers have been reported that 1,2,4-triazoles are found to possess potent biological activities such as antitumour[2], fungicidal[3], anti-HIV[4], antituberculostatic[5], antimicrobial[6] activities. Furthermore quinolines[7-10] and thiazolidinones[11-12] have also been found associated with different biological activity. These observations prompted us to synthesize some quinoline derivatives bearing 1,2,4-triazole and thiazolidinone with the hope of getting compounds with better antimicrobial property and lesser toxicity in compare to existing chemothereupetic agents.

Chemistry

Synthesis of 3-Substituted aryl-4-amino-5-mercapto-1,2,4-triazoles (1-2) from in a methanolic solution of aromatic acid hydrazines, potassium hydroxide and carbon disulfide. The equimolar mixture of compounds (1-2) and 8-chloro quinoline in methanol formed of 3-Substituted aryl-4-amino-5-(thioquinolin-8'-yl) (1,2,4)-triazolo (3-4). The compounds (3-4) on condensation with acetophenone in presence of a few drops of glacial acetic acids gave of 3-Substituted aryl-[4-N-(a-methyl benzylidene)]-5-(thioquinolin-8'-yl)-(l,2,4)-trizoles (5-6). To the solution of compounds (5-6) was taken in DMF acetyl chloride added dropwise in presence of triethylamine at 0-5ºC were obtained of 3-Substituted aryl-[4-(2'-methyl-2'-phenyl-4'-oxo-azetidin-l'-yl)]-5-thioquinolin-8'-yl-(l,2,4)-triaz0les (7-8). Thioglycolic acid and a pinch of anhydrous $ZnCl_2$ was added to a methanolic solution of compound (7-8) were resulted of 3-Substituted aryl-(4-(2'-methy-2'-phenyl-5'-oxo-thiatolidin-l'-yl)]-5-thioquinolin-8'-yl-(l, 2, 4)-triazoles (9-10). Compounds (9-10) dissolved in methanol and various substituted aromatic amines were added dropwise in presence of glacial acetic acid were carried out to give of 3-Substituted aryl-[4-N-(2'-methyl-2'-phenyl-3'-amino methylene substituted aryl-4'-oxo-azetidm-l'-yl]-5-(thioquinolin-8'-yl)-(1,2, 4)-triazoles[11-16].

EXPERIMENTAL

General

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 TLC on silica gel G plates and spots were located by using iodine chamber. Elemental analysis of all the synthesized compounds were determined by a Perkin-Elmer 2400 elemental analyzer, and results were found within the ± 0.4% of theoretical values. IR spectra were recorded in KBr on a Perkin Elmer-Spectrum RX-I, spectrometer. ^{1}H- NMR spectra were record by Bruker AC-300 F instrument using DMSO–d_6 as solvent and tetramethylsilane (TMS) as internal reference standard. All chemical shift values were recorded as d (ppm). Mass spectra were determined on a VG–70-S instrument.

Synthesis of 3-phenyl-4-amino-5-mercapto-1,2,4-triazoles (1)

In methanolic solution of aromatic acid hydrazides (.01 mole), potassium hydroxide (.015 mole) and carbon disulfide (.01 mole) were added and the obtained mixture stirred vigorously for 2 hrs. After stirring excess of hydrazine hydrate was added and the mixture further refluxed for 3 hrs. The completion of the reaction was checked by TLC. The cooled reaction mixture was poured into ice water and neutralized with concentrate HCl. Thus obtained product was filtered, washed with water, dried and recrystallized from methanol to yield **1** .m.p.142°C; yield: 70%; IR.(KBr) (cm^{-1}): 1295.2 (N-N), 1525 (C-N), 1610 (C┈C of aromatic ring), 1682.1 (C=N), 2710 (SH), 3142 (C-H aromatic), 3230 (NH_2).^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ (ppm): 5.985 (bs, 2H, NH_2-N exchangeable with D_2O), 6.898-7.060 (m, 5H, ArH), 11.380 (bs, 1H, SH). Anal.calcd:for $C_8H_8N_4S$.Calculated: C : 50.00, H : 4.16, N : 29.16; Found: C : 50.38, H : 4.32, N : 29.52. MS [M]$^+$ at m/z 192.

Synthesis of 3-[2'-Hydroxy]pheny-4-amino-5-mercapto-1,2,4-triazole.(2)

m.p., 160°C; yield: 75%; r.s: ethanol; IR (KBr) (cm^{-1}): 1524 (C-N), 1610 (C ┈ C of aromatic ring), 1295 (N-N), 1682.2 (C=N), 2710.1 (SH), 3142.5 (C-H aromatic), 3330.2 (NH_2), 3420 (OH) ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ (ppm) : 5.972 (bs, 2H, NH_2 exchangeable with D_2O), 6.900-7.032 (m, 4H, ArH), 11.372 (bs, 1H, SH) 12.537 (ss, 1H, OH-Ar exchangeable with D_2O). Anal. calcd : for $C_8H_8SN_4O$ C : 46.15, H : 3.84, N : 26.92; Found: C : 46.54, H : 3.60, N : 30.05. MS [M]$^+$ at m/z 208.

Synthesis of 3-phenyl-4-amino-5-(thioquinolin-8'-yl) (1,2,4)-triazolo (3).

The equimolar mixture (.01 mole) of compounds 1-2 and 8-chloro quinoline in methanol (50 ml) was refluxed for 6-8 hrs. The completion of the reaction was checked by TLC and excess of methanol distilled off. Thus obtained residual mass was poured into ice water, filtered, washed, dried and recrystallized from DMF water to yield **3.** m.p.: 180°C; yield: 70%; IR (KBr) (cm^{-1}): 6902 (C-S-C), 1295.1 (N-N), 1524.2 (C-N), 1610.1 (C-C of aromatic ring), 1682 (C=N), 3142.1 (C-H aromatic), 3230.1 (NH_2).'H-NMR ($CDCl_3$ + DMSO-d_6) δ (ppm): 5.964 (bs, 2H, NH_2-N exchangeable with D_20), 6.885-7.055 (m, 5H, ArH), 8.221-8.280 (t, 1H_2, ArH), 8.316-8.354 (t, 1H,, ArH), 8.521-8.562 (d, 1H_3, ArH), 7.790-8.830 (t, 1H_6, ArH), 8.839-8.876 (d, 1H_5, ArH), 9.125 (s, 1H_4, ArH). Anal. calcd : for $C_{17}H_{13}N_5S$ C : 63.94, H : 4.07, N : 21.94; Found: C : 64.10, H : 3.91, N : 22.10. MS: [M]$^+$at m/z 319.

Synthesis of 3-(*o*-Hydroxy) phenyl-4-amino-5-(thioquinolin-8'-yl)-(1,2,4)-triazole (4)

m.p.: 190°C; yield: 72%; r.s: DMF-water; IR (KBr) (cm^{-1}): 690 (C-S-C), 1295.4 (N-N), 1525 (C-N), 1610.2 (C┈C of aromatic ring), 1683.1 (C=N), 3243.1 (NH_2), 3420 **(**OH**).** ^{1}H-NMR ($CDCl_3$-DMSO-d_6) δ(ppm): 5.944 (bs, 2H, NH_2-N exchangeable with D_2O), 6.882-7.041 (m, 4H, ArH), 8,218-8.273 (t, 1H_2, ArH), 8.312-8.355 (t, IH-ArH), 8.520-8.552 (d, 1H_3, ArH), 8.794-8.850 (t, 1H_6, ArH), 8.841-8.876 (d, 1H_6, ArH), 9.129 (s, 1H_4, ArH), 12.527 (ss, 1H, Ar-OH exchangeable with D_20). Anal. calcd : for $C_{17}H_{13}N_5SO$. C : 60.89, H : 3.88, N : 20.89; Found: C : 60.50, H : 3.52, N : 20.68.MS: [M]" atm/z 335.

Synthesis of 3-phenyl -[4-N-(α-methyl benzylidene)]-5-(thioquinolin-8'-yl)-(l,2,4)-trizoles (5).

A methanolic solution, of compounds 3-4 (.01 mole) with acetophenone (01 mole) in presence of a few drops of glacial acetic acid was refluxed for 2-3 hrs. The completion of the reaction was checked by TLC. Excess of methanol was removed by distillation, reacted mixture poured into ice water, filtered, 'washed with water, dried, triturated with petroleum ether (40-60°C) and recrtystallized from DMF water to afford 5.

m.p.: 202°C; yield: 65%; IR (KBr) (cm^{-1}): 690.4 (C-S-C), 1295 (N-N), 1524.2 (C-N), 1610.2 (C⩦C of aromatic ring), 1682 (C=N). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ (ppm): 2.212 (s, 3H,CH_3-C=N), 6.690-7.568 (m, 10H, ArH), 8.236-8.285 (t, 1H_2, ArH), 8.302-8.346 (t, 1H_7, ArH), 8,523-8.560 (d. 1H_3, ArH), 8.826-8.846, (d, 1H_5, ArH), 8.790-8.852 (t, 1H_6, ArH), 9.132 (s, 1H_4, ArH). Anal. calcd : for $C_{25}H_{19}N_5S$: C : 71.25, H : 4.51, N : 16.62; Found: C : 71.57, H : 4.69, N : 16.33.
MS: $[M]^+$ at m/z 421.

Synthesis of 3-(*o*-Hydroxy)phenyl-[4-N-(α-methyl benzylidene)-5-(thioqumolin-8'-yl)]-(l,2,4)-triazole (6)

m.p.: 208°C; yield: 68%; r.s: methanol; IR (KBr) (cm^1): 690.2 (C-S-C), 1295.1 (N-N), 1524.6 (C-N), 1610.4 (C⩦C of aromatic ring), 1682.1 (C=N), 3420.2 (OH). ‘H-NMR ($CDCl_3$+DMSO-d_6) δ (ppm): 2.241 (s, 3H, CH_3-C-), 6.569-7.246 (m, 9H, ArH), 8.241-8.276 (t, 1H, ArH), 8.310-8.342 (t, 1H_7, ArH), 8.536-8.568 (d, 1H, ArH), 8.818-8.851 (d, 1H_5, ArH), 8.798-8.864 (t, 1H_6, ArH), 9.127 (s, 1H_4, ArH), 12.514 (ss, 1H, Ar-OH exchangeable with D_2O). Anal. calcd : for $C;_5H_{19}N_5SO$. C : 68.64, H : 4.34, N : 16.01; Found: C : 68.40, H : 4.58, N : 16.39. MS: $[M]^+$ at m/z 437.

Synthesis of 3-phenyl -[4-(2'-methyl-2'-phenyl-4'-oxo-azetidin-l’-yl)]-5-thioquinolin-8'-yl-(l,2,4)-triazoles (7)

To the solution of compounds 5-6 (.01 mole) was taken in DMF (50 ml), acetyl chloride (.01 mole) added dropsvise in presence of triethylamine at 0-5°C and the reaction mixture stirred constantly for 5-7 hrs. The completion of the reaction was checked by TLC and the precipitated amine hydrochloride filtered out. The filtrate was concentrated under induced pressure and poured in cold water. The solid thus obtained was recrystallized from ethanol water to yield **7**.

m.p.: 215°C; yield: 62%; IR (KBr) (cm^{-1}): 690.1 (C-S-C), 1295.2 (N-N), 1525 (C-N), 1610 (C⩦C of aromatic ring), 1682.1 (C=N), 1760 (C=O of β-lactam ring), 3142 (C-H aromatic). ‘H-NMR ($CDCl_3$+DMSO-d_6) δ (ppm): 2,262 (s, 3H, CH_3), 4.115 (s, 2H, CH_2-C=O), 7.310-6.928 (m, 10H, ArH), 8.217-8.251 (t, 1H_2, ArH), 8.287-8.326 (t, 1H_7, ArH), 8.436-8.468 (d, 1H_3, ArH), 8.728-8.764 (t, 1H_6, ArH), 8.815-8.846 (d, 1H_5, ArH), 9.128 (s, 1H_4, ArH). Anal. calcd : for $C_{27}H_{21}N_5SO$. Calculated: C: 69.97, H : 4.53, N : 15.11; Found: C : 69.60, H : 4.41, N : 15.35 MS:$[M]^+$ at m/z 463.

Synthesis of 3-(*o*-Hydroxy) phenyl-[4-N-(2"-methyl-2"-phenyl-4"-oxo-azetidin-l”-yl)]-5-(thioquinoUn-8'-yl)]-(l,2,4)-triazole (8).

m,p.:212°C; yield: 67%; r.s: methanol-water. IR (KBr) (cm^{-1}): 690.3 (C-S-C), 1295 (N-N), 1524.4 (C-N), 1610.4 (O⩦C of aromatic ring), 1682.2 (C=N), 1760.1 (C=O of β-lactam ring), 3142.1 (C-H aromatic), 3420 (OH). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ (ppm): 2.260 (s, 3H, CH_3), 4.120 (s, 2H, CH_2-C=O), 6.648-7.420 (m, 9H, ArH), 8.215-8.247 (t, 1H_2, ArH), 8.290-8.330 (t, 1H_7, ArH), 8.435-8.460 (d, 1H_3, ArH), 8.718-8.756 (t, 1H_6, ArH), 8.820-8.850 (d, 1H_5, ArH), 9.134 (s, 1H_4, ArH), 12.507 (ss, 1H, Ar-OH exchangeable with D_2O). Anal. calcd : for $C_{27}H_{21}N_5SO_2$. C : 67.64, H : 4.38, N : 14.61; Found: C : 67.32, H : 4.56, N : 14.49. MS: $[M]^+$ at m/z 479.

Synthesis of 3-phenyl-(4-(2'-methy-2'-phenyl-5'-oxo-thiatolidin-l’-$_y$l))-5-thioquinolin-8'-yl-(l, 2, 4)-triazoles (9).

Thioglycolic acid (.01 mole) and a pinch of anhydrous $ZnCl_2$ was added to a methanolic solution of compounds 5-6 (.01 mole). The reaction mixture was refluxed for 8-10 hrs. and completion of the reaction was checked by TLC. Excess of solvent was removed by distilation. The reaction mixture was diluted with cold crushed ice water, filtered, washed, dried and recrystallized from DMF water to afford **9**. m.p.: 190°C; yield; 63%.IR (KBr) (cm^{-1}): 690.2 (C-S-C), 1295.2 (N-N), 1524 (C-N), 1610.4 (C⩦C of aromatic ring), 1682 (C=N), 1733.2 (C=O of β-thialactam ring), 3142 (C-H aromatic). ‘H-NMR ($CDCl_3$+DMSO-d_6) δ (ppm): 2.251 (s, 3H, CH_3), 4.236 (s, 2H, S-CH_2), 6.610-7.387 (m, 10H, ArH), 8.224-8.252 (t, 1H_2, ArH), 8.284-8.326 (t, 1H_7, ArH), 8.438-8.462 (d, 1H_3, ArH), 8.723-8.761 (t, 1H_6, ArH), 8.816-8.847 (d, 1H_5, ArH), 9.121 (s, 1H_4, ArH). Anal. calcd : for $C_{27}H_{21}N_5S_2O$.C : 65.45, H : 4.24, N : 14.14; Found: C : 65.70, H : 4.51, N : 14.38.MS: $[M]^+$ at m/z 495.

Synthesis of 3-(o-hydroxy) phenyl-[4-N-(2"-methyl-2"-phenyl-5"-oxo-thiazolidin-8'-yl)]-5-(thioquinolin-8'-yl)]-(l,2,4)-triazole (10).

m.p.: 200°C; yield. 65%; r.s:DMF-water; IR (KBr) (cm^{-1}): 690 (C-S-C), 1295.2 (N-N), 1525.1 (C-N), 1610 (C⎓C of aromatic ring), 1682 (C=N), 1733 (C=O of β-thialactam), 3142.2 (C-H aromatic ring), 3420 3 (OH). ^{1}H-NMR ($CDCl_3$+DMSOd_6) δ (ppm): 2.251 (s, 3H, CH_3), 4,126 (s, 2H, CH_2-S), 6 695-7.318 (m, 9H, ArH), 8.218-8 250 (t, $1H_2$, ArH), 8.290-8.324 (t, IH_7, ArH), 8 44-8 470 (d, $1H_3$, ArH), 8.725-8.763 (t, 1H, ArH), 8.814-8.842 (d, $1H_5$, ArH), 9.132 (s, IH_4, ArH), 12.524 (ss, 1H, Ar-OH exchangeable with D_2O). Anal. calcd : for $C_{27}H_{21}N_5S_2O_2$ C : 63.40, H : 4.10, N : 13.69; Found: C : 63.63, H : 4.32, N : 13.46 . MS: $[M]^+$ at m/z 511.

Synthesis of 3-phenyl-[4-N-(2'-methyl-2'-phenyl-3'-amino methylene substituted aryl-4'-oxo-azetidm-l'-yl]-5-(thioquinolin-8'-yl)-(1,2, 4)-triazoles (11)

Compounds 7-8 (.01 mole) dissolved in methanol (50ml) and various substituted aromatic amines (.01 mole) were added dropwise in presence of glacial acetic acid. This reaction mixture was allowed to reflux for 4-6 hrs. The completion of the reaction was checked by TLC. Excess of methanol was distilled off, residual mass poured into ice-cold water filtered, washed, dried and re crystallized from methanol to afford **11.** m.p,: 216°C; yield 62%; IR (KBr) (cm^1): 690.1 (C-S-C), 1295.2 (N-N), 1525 (C-N), 1610 (C⎓C of aromatic, 1682.1 (C=N), 1760.3 (C=O of β-lactam ring), 3142.2 (C-H aromatic), 3320 (NH), ^{1}H-NMR ($CDCl_3$+MSO-d_6) δ (ppm): 2.246 (s, 3H, CH_3), 3.702-3.750 (t, 1H, (3-lactam ring), 3.654 (d, 2H, CH_2NH), 4.875 (bs, 1H, NH-Ar exchangeable with D_20), 7.060-8.228 (m, 15H, ArH), 8.234-8.266 (t, $1H_2$, ArH), 8.289-8.320 (t, $1H_7$, ArH), 8.442-8.464 (d, $1H_3$, ArH), 8.723-8.750 (t, $1H_6$, ArH), 8.812-8.840 (d, $1H_5$, ArH), 9.127 (s, $1H_4$, ArH). Anal. calcd : for $C_{34}H_{28}N_6SO$: C : 71.83, H : 4.92, N : 14.78; Found: C : 71.52, H : 4.78, N : 14.56. MS; $[M]^+$ at m/z 568.

Synthesis of 3-Phenyl-[4-N-(2"-methyl-2"-phenyl-3"-amino methylene-(*o*-chloro)phenyl-4"-oxo-azetidin-1'-yl)]-5-(thioquinolin-8'-yl)]-(l,2,4)-triazole. (12)

m.p.:224°C; yield: 63%; r.s:ethanol; Anal. calcd : for $C_{34}H_{27}N_6SOCl$ C : 67.74, H : 4.48, N : 13.95; Found: C : 67.50, H : 4.60, N : 13.67 IR (KBr) (cm^1): 620 (C-C1), 690 (C-S-C), 1295.2 (N-N), 1525.1 (C-N), 1610.1 (C⎓C of aromatic ring), 1682 (C=N), 1760.2 (C=O of p-lactam ring), 3142.2 (C-H aromatic), 3320.2 (NH). ‘H-NMR ($CDCl_3$+DMSO-d_6) δ (ppm): 2.62 (s, 3H, CH_3), 3.628-3.650 (d, 2H, CH_2NH), 3.695-3.748 (t, 1H, β-lactam ring), 4.882 (bs, 1H, NH-Ar exchangeable with D_2O), 6.857-8.194 (m, 14H, ArH), 8.221-8.254 (t, $1H_2$, ArH), 8.296-8.326 (t, $1H_7$, ArH), 8.440-8.463 (d,IH_3,ArH), 8.722-8.750 (t, IH_6, ArH), 8.818-8.843 (d, IH_s, ArH), 9.125 (s, $1H_4$, ArH). Anal. calcd : for $C_{34}H_{27}N_6SOCl$ C : 67.74, H : 4.48, N : 13.95; Found: C : 67.50, H : 4.60, N : 13.67. MS: $[M]^+$ at m/z 602.

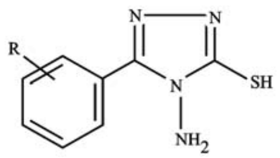
Synthesis of 3-phenyl-[4-N-(2"-methyl-2"-phenyl-3"-amino methylene-(*o*-methoxy)-phenyl-4"-oxo-azetidin-l”-yl)]-5-(thioquinolin-8'-yl)]-(l,2,4)-triazole.(13)

m.p: 238°C; yield 65%; r.s: ethanol-water; IR (KBr) (cm^{-1}): 690 (C-S-C), 1060 (C-0-C), 1295 (N-N), 1524.3 (C-N), 1610 (C⎓C of aromatic ring), 1682.4 (C=N), 1760 (C=O of β-lactam), 3142 (C-H aromatic), 3320 (NH) ‘H-NMR ($CDCl_3$+DMSO-d_6) (ppm): 2.258 (s, 3H, CH_3), 3.521 (s, 3H, Ar-OCH,) 3.627-3.652 (d, 2H, CH_2-NH). 3.700-3,742 (t, 1H, CH of (5-lactam ring) 4.876 (bs, 1H. NH-Ar), 6.862-8.150 (m, 14R, ArH), 8.220-8.254 (t, $1H_2$, ArH), 8.294-8.329 (t, 1H-. ArH), 8.439-8.460 (d, $1H_3$, ArH), 8.718-8.752 (t, $1H_6$, ArH), 8.815-8.840 (d, $1H_5$, .ArH). 9.125 (s, $1H_5$, ArH). Anal. calcd : for $C_{35}H_{30}N_6SO_2$. C : 70.23, H : 5.01, N : 14.04; Found: C : 70.42, H : 4.88, N : 14.36. MS; $[M]^+$ at m/z598.

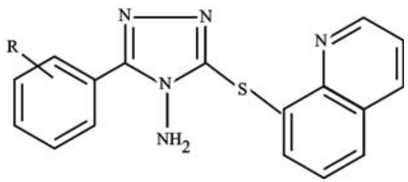
Synthesis of 3-(*o*-hydroxy) phenyl-[4-N-(2"-rnethyl-2"-phenyl-3"-amino methylene-phenyl-4"-oxo-azetidin-1'-yl)]-5-(thioqunolin-8'-yl)]-(l,2,4)-triazole.(14)

m.p.: 220°C; yield 64%; r.s: DMF-water-IR (KBr) (cm^{-1}): 690.1 (C-S-C), 1060.2 (C-O-C), 1295.2 (N-N), 1524.3 (C-N). 1610 (C⎓C of aromatic ring), 1682.2 (C=N), 1760.1 (C=O of β-lactam), 3142.2 (C-N aromatic), 3320.1 (NH), 3420.2 (OH),^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ (ppm): 2.250 (s, 3H, CH_3), 3.664-3.637 (d, 2H, CH_2 NH). 3.746 (s, 1H,CH of β-lactam). 4.870 (bs, IH, NH-Ar exchangeable with D_20), 7.620-7278 (m, 14H, ArH), 8.253-8 224 (t, $1H_2$, ArH), 8.330-8.297 (t, $1H_7$, ArH), 8.462-8.440 (d, $1H_3$, ArH), 8.748-8.712 (t, $1H_6$, ArH), 8.848-8.817 (d, $1H_5$, ArH), 9.120 (s, $1H_4$, ArH), 12,512 (ss, 1H, Ar-OH exchangeable with D_2O). Anal. calcd : for $C_{34}H_{28}N_6SO_2$ C : 69.86, H : 4.79, N : 14.38; Found: C : 69.57, H : 4.50, N : 14.64 MS; $[M]^+$ at m/z 584.

Table 1: Antibacterial and antifungal activity of the compounds: 3-Substituted ary1-4-amino-5-mercapto-1,2,4-triazole (1-2, 3-Subsituted ary1-4-amino-5-(thio quinoline-8'-yl)-(1,2,4)-triazoles (3-4), 3-Substituted ary1-[4N-(a-methyl benzylidene)]-5-(thioquinolin-8'-yl)-(1,2,4)-triazoles (5-6)



(1-2)



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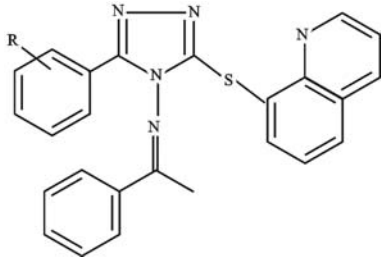
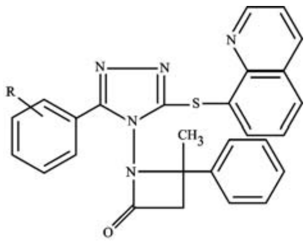


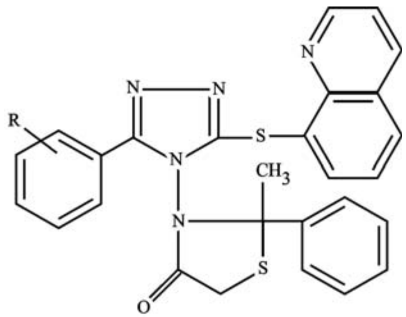
(5-6)

Comp. No.	R	Antibacterial activity				Antifungal activity			
		S.aureus	*E. coli*	*P. vulgaris*	*K. pneumoniae*	*A. fumigatus*	*C.albicans*	*C. albicans ATCC*	*C.Krusei G03*
1	H	-	-	-	5 mm	-	6 mm	-	-
2	o-OH	-	-	-	10 mm	-	8 mm	6 mm	-
3	H	-	-	10 mm	-	-	10 mm	8 mm	-
4	o-OH	6 mm	12 mm	-	-	-	6 mm	12 mm	-
5	H	-	12 mm	-	-	6 mm	-	-	-
6	o-OH	12 mm	25 mm	15 mm	-	-	12 mm	16 mm	8 mm

Table 2: Antibacterial and antifungal activity of the compounds: 3-Substituted aryl-[4-(2'-methyl-2'-phenyl-4'-oxo-agetidin-1'-yl)] -5-thioquinolines-8'-yl-(1,2,4)-triazoles (7-8), 3-Substituted aryl-[4- (2'- methyl-2'- phenyl-5'- oxo-thiazolidin-1'-yl)]- 5-thioquinolin-8'-yl-(1,2,4)-triazoles (9-10)



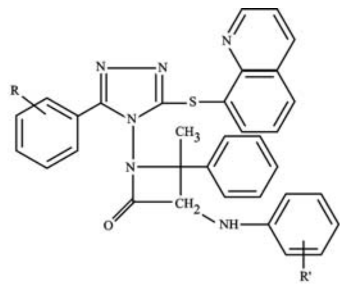
(7-8)



(9-10)

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*
7	H	-	5 mm	14 mm	-	-	-	16 mm	-	8 mm
8	o-OH	-	10 mm	20 mm	28 mm	-	16 mm	15 mm	12 mm	-
9	H	-	5 mm	-	-	-	6 mm	10 mm	12 mm	-
10	o-OH	-	14 mm	18 mm	16 mm	-	-	26 mm	18 mm	17 mm

Table 3: Antibacterial and antifungal activity of the compounds: 3-Substituted aryl-[4-(2'-methyl-2'-phenyl-3'-amino methylene substituted aryl-4'-oxo-zetdin-1'-yl)]-5(thioquinolin-8'-yl)-(1,2,4)-triazoles (11-16)



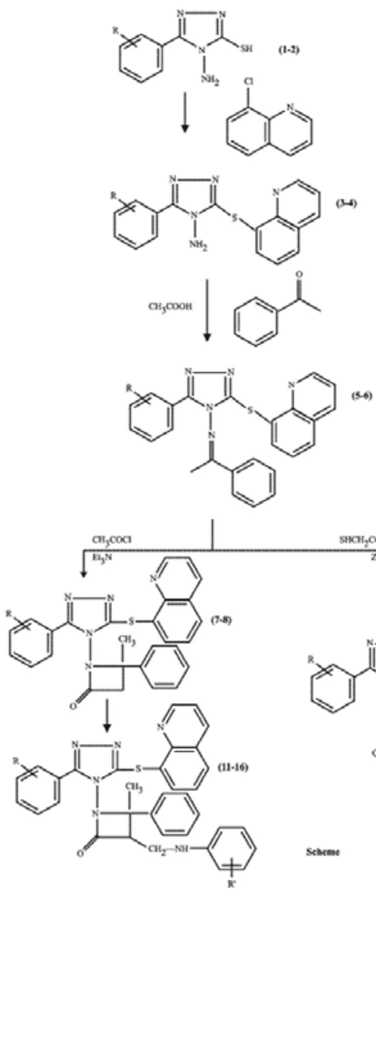
(11-16)

Comp.	R	R'	Bacterial growth inhibition (diameter)				Fungal growth inhibition (diameter)			
No.			***S.aureus***	***E. coli***	***P. vulgaris***	***K. pneumoniae***	***A. fumigatus***	***C.albicans***	***C. albicans ATCC***	***C.Krusei G03***
11	H	H	-	-	-	-	-	-	-	-
12	H	o-C1	20 mm	-	-	16 mm	9 mm	-	-	-
13	H	o-OCH3	15 mm	17 mm	-	-	-	14 mm	10 mm	-
14	o-OH	H	12 mm	-	-	15 mm	-	8 mm	12 mm	12 mm
15	o-OH	o-C1	18 mm	18 mm	-	-	-	-	-	-
16	o-OH	o-OCH3	20 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 g/ml. - Drug concentration

Synthesis of 3-(*o*-hydroxy)phenyl-[4-N-(2"-methyl-2"-phenyl-3"-amino methylene-(*o*-chloro)phenyl-4"-oxo-azetidm-1"-yl)]-5-(thioquinolin-8'-yl)]-(l,2,4)-triazole. (15)

m.p.: 230°C; yield: 62%; r.s.DMF-water; (KBr) (cm^{-1}): 620.1 (C-Cl). 690.2 (C-S-C), 1060.1 (C-O-C), 1295.2 (N-N), 1524.1 (C-N), 1610.1 (C⋯O of aromatic ring), 1682 (C=N), 1760.2 (C=O of β-lactam), 3142.1 (C-H aromatic), 3320.2 (NH). ^{1}H-NMR ($CDCl_6$+DMSO-d_6) δ (ppm): 2.257 (s, 3H, CH_3), 3.638-3,668 (d, 2H, CH_2-NH-Ar), 3.779-3.700 (s, 1H, CH of b-lactam ring), 4.874 (bs, 1H, NH-Ar exchangeable with $D_2$0), 6.892-8.194 (m, 13H, Arh) 8.224-8.255 (t, $1H_2$, ArH), 8.298-8.330 (t, $1H_7$, ArH), 8.441-8.464 (d, $1H_3$, ArH), 8 716-8.751 (t, IHs, ArH), 8.820-8.852 (d, $1H_5$, ArH), 9.124 (s, 1H4, ArH), 12.510 (ss, IR Ar-OH exchangeable with D_2O). Anal. calcd : for $C_{34}H_{27}N_6SO_2Cl$: C : 66.01, H : 4.36, N : 13.59; Found: C : 66.20, H : 4.68, N : 13.40.MS; $[M]^+$ at m/z 618.



Synthesis of 3-(*o*-hydroxy)phenyl-[4-N-(2"-methyl-2"-phenyl-3"-amino methylene-(*o*-ethoxy) phenyl-4"-oxo-azetidin-l”-yl)]-5-(thioquinolin-8'-yl)]-(l,2,4)-triazole. (16)

m.p.; 224°C, yield: 67%; r.s; ethanol; IR (KBr) (cm^{-1}): 690.1 (C-S-C). 1060 (C-O-C), 1295 (N-N), 1524 (C-N), 1610.0 (C-C $_O$f aromatic ring), 1682.1 (C=N), 1760 (C=O of β-lactam ring), 3142 (C-H aromatic), 3320 (NH). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ (ppm): 2.253 (s, 3H, CH_3), 3.521 (s, 3H, Ar-OCH_3) 3.635-3.662 (d, 2H, CH_2-NH), 3 712-3.754 (t, IH, CH of β-iactam ring), 4.877 (bs, IH.NH-Ar exchangeable with $D_2$0). 6.900-8.078 (m, 13H, ArH), 8.225-8.258 (t, $1H_{2;}$ .ArH). 8.300-8.338 (t, $1H_7$, ArH), 8.44S-8 470 (d, $1H_3$, ArH), 8.726-8.762 (s, IH_6, ArH), 8.825-8.856 (d, $1H_5$, ArH), 9.128 (s. $1H_4$, ArH), 12.527 (ss, IH, HO-Ar exchangeable with D_2O). Anal. calcd : for $C_{35}H_{30}N_6SO_3$: C : 68.40, H : 4.88, N : 13.68; Found: C : 68.64, H : 5.02, N : 13.83.MS: $[M]^+$ at m/z 614.

Antimicrobial activity

Preliminary antimicrobial susceptibility tests forall the synthesized quinoline derivatives were performed by using cup plate method[13] at a concentration of 250 mg/mL against some selected pathogenic strains. *S. aureus, E.coli., P.vulgaris, K.pneumoniae* were used for bactericidal activity and *A. fumigatus, C.albicans, C.albicans* ATCC, *C.crusei* G03 for fungicidal activity. Prepared nutrient agar (Qualigen Fine Chem., Mumbai, India) was used to subculture different strains of bacteria while SDA (Sabouraud Dextrose Agar -Himedia Labs., Mumbai) to subculture selected fungal strains. Plates incubated 24 hr for bactricidal and 48 hr for fungicidal activity.

Acute Toxicity

Lethal dose (LD_{50}) of compounds was determined in albino mice. After 24 hr of drug administration, mortality in each group was observed and from the data obtained LD_{50} was calculated by the method of Carrol[14]. Data revealed that compound **9** and **11** do not show any toxicity upto dose of 10.25 mg/kg and 12.50 mg/kg body weight in mice.

RESULT AND DISCUSSION

Various substituted derivatives of triazoles were synthesized and screened for their antibacterial as well as antifungal activity. Screening results are given in Table 1, 2 and3. Compound 3-substituted aryl 4-amino-5-mercapto 1,2,4-triazoles(1-2) on screening was found less active against different bacterial and fungal species.

Substitution with –OH group at 2nd position of phenyl ring in compound 2 enhanced the potency. Substituted triazoles (1 - 2) were incorporated with chloro quinoline via -S- linkage and as a result obtained quinoline moiety bearing triazoles (3-4), exhibited good antibacterial and antifungal activity. The derivatives having -OH group at 2nd position of phenyl ring in compounds 4 and 6 showed more and wide spectrum off antibacterial as well as antifungal activity. Conversion of quinoline moiety bearing triazoles (3-4) into 3-substituted aryl-[4-N-(a-methyl benzylidene)]-5-(thioquinolin-8'-yl)-(l,2,4)-triazoles (5-6) showed more potency against various strains of used pathogens. The compound 6 which have -OH group at o-position of phenyl ring exhibited different range of inhibition zones by ranging as 12 mm for *S. aureus*, 25 mm for *E.coli,* 15 mm for *P. vulgaris*, 12 mm for *C. albicans,* 16 mm for *C. albicans* ATCC, 8 mm for *C. Krusei* respectively. The results on comparing revealed that compound 6 possessed (i.z. 25 mm) maximum efficacy in comparison to gattifloxacin (i.z. 22 mm) as standard drugs against *E.coli.* Incorporation of *p*-lactam ring into compounds (5 and 6) enhanced antibacterial and antifungal activity respectively. But between these two congeners -OH group bearing at 2nd position in phenyl ring (compound 8) is more potent than compound 7. Compound 8 had a high efficacy in P. vulgaris (i.z 28 mm) comparatively to parent compound (6). Thialactam bearing derivatives (Compound 9 and 10) have shown high antifungal activity in comparison to antibacterial activity. As compound (10) having -OH group at 2nd position of phenyl ring showed more potency and a wide range of biological activity against various reported species of bacteria and fungi.

Compounds 11-16 which are mannich products of parent compound (7-8) possessed a high bactericidal property but its wide spectrum reduced in case of bacteria. Among these synthesized derivatives, compounds 13 and 14 showed a moderate wide zone of inhibition as 15 mm for S. aureus. 17 mm for E.coli, 14 mm for C. albicans, 10 mm for C albicans ATCC and 12 mm for S. aureus, 15 mm for K. pneumoniae, 8 mm for C albicans, 12 mm for C. albicans ATCC, 12 mm for C. Krusei respectively. Compounds 12 and 16 bearing -Cl substitution in phenyl ring at o- OCH_3 substitution at *o*-position showed i.z. of 20 mm against S aureus.

CONCLUSION

On the basis of structure activity relationship, it is concluded-

1. *o*-Hydroxy substituted triazcie derivatives showed more efficacy
2. Incorporation of acetophenone is beneficial for antibacterial activity against E.coli and P.vulgaris.
3. Incorporation of p-lactam moiety increases antibacterial and antifungal spectrum,
4. The derivatives bearing 3-thialactam are responsible for regular potent antifungal inhibition.
5. Formation of mannich products exhibited a decrease in antibacterial as well as antifungal activity,
6. Compound 10 was found potent antifungal of this scheme against C.albicans and its efficacy was closer to standard drug fluconazole.
7. It is interesting to mention that compound 6 and 8 possess high efficacy against E.coli in comparison to standard drug cephalexin and gattifloxacin which is further supported by enclosing photographs.

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