Synthesis and Antimicrobial Evaluation of Some New 2-(6-Oxo-5,6-dihydro[1,3]thiazolo[3,2-*b*]-2-aryloxymethyl-1,2,4-triazol-5-yl)-*N*-arylacetamides

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A series of 2-(6-oxo-5,6-dihydro[1,3]thiazolo[3,2-*b*]-2-aryloxymethyl-1,2,4-triazol-5-yl)-*N*-arylacetamides **6** were synthesized in good yield by condensing 5-aryloxymethyl-4*H*-1,2,4-triazole-3-thiol **5** with various substituted *N*-phenyl-maleimides in acetic acid media. The newly synthesized compounds were characterized by spectral data and tested for their *in vitro* antibacterial and antifungal activity against a variety of microorganisms.

Key words: 1,2,4-Triazole-3-thiol, *N*-Aryl-maleimides, Antibacterial, Antifungal

Introduction

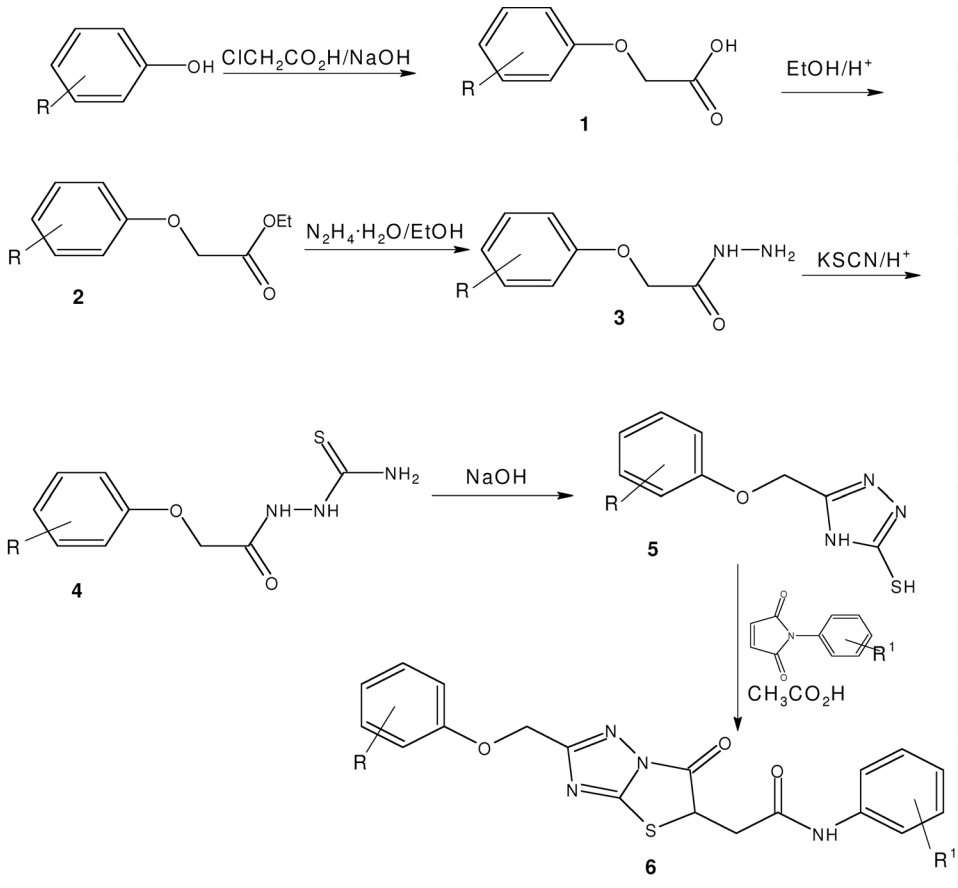
The chemistry of 1,2,4-triazoles and their fused heterocyclic derivatives have received considerable attention due to the synthetic and effective biological importance. Triazoles and in particular 1,2,4-triazole rings have been incorporated into a variety of therapeutically interesting drug candidates including CNS stimulants, sedatives, anti-inflammatory, antianxiety, antimicrobial [1, 2] and antimycotic agents like Fluconazole, Itraconazole and Voriconazole [3, 4]. There are also some drugs containing the 1,2,4-triazole moiety, for example: Triazolam [5], Alprazolam [6], Etizolam [7], Furacyclin [8], Ribavirin [9], Hexaconazole [10], Triadimefon [11], Mycobutanil [12], Rizatriptan [13], Propiconazole [14], and Fluotrimazole [15]. It has been revealed that mercapto- or thione-substituted 1,2,4-triazole ring systems have yielded many biologically active compounds endowed with a wide spectrum of pharmacological activities.

On the other hand thiazoles have attracted continuing interest because of their varied biological activities [16, 17], and have recently found application in drug development for the treatment of allergies [18], hypertension [19], inflammation [20], schizophrenia [21], bacterial infections [22], HIV infections [23], hypnotics [24], and more recently for the treatment of pain [25].

Therefore it was envisaged that the chemical entities with both 1,2,4-triazoles and 1,3- thiazoles containing an aryl ether linkage would result in compounds of interesting biological activities. It was thought to be interesting to synthesize compounds containing a 1,2,4-triazole moiety fused with a 1,3-thiazole ring in addition to having a phenoxy group, and to study their antimicrobial activities. The present report describes the synthesis of the title compounds and the evaluation of their antibacterial and antifungal activities.

Results and Discussion

The reaction sequences employed for the synthesis of the title compounds are shown in Scheme 1. Ethyl (4-aryloxy)acetates **2** were prepared by treating various substituted phenols with chloroacetic acid in water in the presence of sodium hydroxide, followed by esterification in ethanol in the presence of concentrated sulfuric acid. The esters were conveniently converted to 2-(4-aryloxy)-acetohydrazides **3** by refluxing with hydrazine hydrate in ethanol. On reaction with potassium thiocyanate in the presence of conc. hydrochloric acid the compounds yielded 2-(4-aryloxy)-acetothiosemicarbazides **4** in good yield. The required 5-(aryloxymethyl)-4*H*-1,2,4-triazole-3-thiols **5** were synthesized by refluxing **4** with 5 % aqueous sodium hydroxide followed by acidification with hydrochloric acid. Condensation of triazoles with various substituted *N*-phenyl-maleimides in acetic acid medium yielded the title compounds **6**. The formation of N-bridged heterocycles **6a** – **t** is ev-



Comp.	6a	6b	6c	6d	6e	6f	6g	6h	6i	6j
R	4-CH_3	4-CH_3	4-CH_3	4-CH_3	4-Cl	4-Cl	4-Cl	4-Cl	4-Br	4-Br
R^1	4-H	4-Cl	3-Cl-4-F	4-F	4-H	4-Cl	3-Cl-4-F	4-F	4-H	4-Cl
	6k	**6l**	**6m**	**6n**	**6o**	**6p**	**6q**	**6r**	**6s**	**6t**
R	4-Br	4-Br	4-*t*-Bu	4-*t*-Bu	4-*t*-Bu	4-*t*-Bu	4-Cl-5-CH_3	4-Cl-5-CH_3	4-Cl-5-CH_3	4-Cl-5-CH_3
R^1	3-Cl-4-F	4-F	4-H	4-Cl	3-Cl-4-F	4-F	4-H	4-Cl	3-Cl-4-F	4-F

Scheme 1.

idenced by their elemental analysis and spectral data.

In the IR spectra, the absorption bands corresponding to NH and C=O were observed in the region around 3295 and 1713 cm^{-1}, respectively. The absorption band at 1492 cm^{-1} was due to the C=N stretching vibration. Another band at 1235 cm^{-1} was due to the stretching vibration of the C–O bond.

The IR spectrum of triazole **5** showed an absorption band at 3114 cm^{-1} indicating the presence of an NH group. In the IR spectra of triazolothiazole **6**, the bands due to NH were absent thus indicating its formation from **5** through cyclocondensation with *N*-phenylmaleimides.

In the ^{1}H-NMR spectra of compounds **6a – t**, protons of a CH_2-CH fragment showed the characteristic pattern of an ABX system. The chemical shifts of the protons H^A, H^B and H^X are at $\delta \sim 3.40 – 3.60$, 2.8 – 3.00, and 4.50 – 5.50, respectively. Large values of J_{AB} = 17.5 – 19.0 Hz, J_{Ax} = 8.0 – 9.5 Hz and J_{Bx} = 4.5 – 6.0 Hz were observed here like in the structurally related 2-thioxo-4-thiazolidinones earlier referred to a

"carbonyl effect" by Takahashi [32]. The NH proton of compounds **6** appeared at $\delta = 13.0 - 14.5$ ppm. The signal for the SH proton in **5** was observed as a broad singlet at $\delta = 13.71$ ppm. The downfield shift of this signal indicates the thiol-thione tautomerism in the triazole. This downfield signal was absent in the ^{1}H-NMR spectra of the triazolothiazoles **6**, thus confirming their formation.

The investigation of antibacterial and antifungal screening data revealed that all the tested compounds **6a – t** showed moderate to good inhibition at 1.56 – 25 μg mL^{-1} in DMSO. Compounds **6d**, **6f**, **6h**, **6i**, **6l**, **6o**, **6q**, and **6r** showed comparatively good activity against all the bacterial strains. The good activity is attributed to the presence of pharmacologically active Cl or F groups attached to position 4 in either of the phenyl rings. Compounds **6a**, **6c**, **6g**, **6j**, and **6s** exhibited moderate antibacterial activity.

The compounds **6f**, **6h**, **6i**, **6o**, and **6q** showed comparatively good activity against all the fungal strains. The structure of these compounds contains biologically active Cl or F attached to either of the phenyl rings at position 4. The compounds **6a**, **6c**, **6e**, **6j**, **6l**, and **6s** showed moderate activity.

Two of the twenty compounds, namely **6f** and **6h**, were found to be very active against all the tested bacterial and fungal strains which may be due to the presence of Cl or F at *para*-positions of both phenyl rings. Compounds with a disubstituted phenyl ring showed less activity when compared with the monosubstituted analogs.

Conclusion

The successful synthesis and antimicrobial activity of new 2-(6-oxo-5,6-dihydro[1,3]thiazolo[3,2-*b*]-2-(aryloxymethyl)-1,2,4-triazol-5-yl)-*N*-arylacetamides has been reported. The antimicrobial activity study revealed that all the compounds tested showed moderate to good activity against the pathogenic strains. From the structure-biological activity relationship of the title compounds it appears that the presence of groups like Cl or F at 4-position of both the phenyl rings resulted in considerable increase in activity.

Experimental Section

Instruments and starting materials

Melting points were determined in open capillaries and are uncorrected (melting point apparatus: Sewell instruments Inc., India). The purity of the compounds was checked by thin layer chromatography on a silica coated aluminum sheet (silica gel F_{254}) using chloroform and methanol (9 : 1, v/v). IR spectra (KBr pellets) were recorded on a Shimadzu FT-IR 157 spectrophotometer. The ^{1}H-NMR spectra were recorded on a Bruker Avance II 400 (400 MHz) spectrometer using TMS as an internal standard. Mass spectra were determined on a Jeol SX 102/Da-600 mass spectrometer/data system using argon/xenon (6 kV, 10 mA) as the FAB gas. Elemental analyses were carried out using a CHNS elemental analyzer. Solvents and reagents were purchased in the appropriate grade from commercial venders and were used without purification. Aryloxyacetic acids **1** were prepared from phenol [33]. 5-Aryloxymethyl-2-mercapto-1,3,4-triazoles [34] and *N*-aryl-maleimides [35] were prepared according to the literature procedures.

*General procedure for the preparation of 2-(6-oxo-5,6-dihydro[1,3]thiazolo[3,2-b]-2-(substituted phenoxymethyl)-1,2,4-triazol-5-yl)-N-arylacetamides **6a – t***

A mixtures of 1,2,4-trizole-5-thiol (**5**, 10 mmol) and an appropriate *N*-arylmaleimide (10 mmol) was refluxed for 2 h in 10 mL of glacial acetic acid. After cooling to r. t., the reaction mixtures were poured into 50 mL of water. Precipitated colorless crystals were filtered off, washed with methanol and recrystallized from ethanol.

6a: Off-white powder; m. p. 124 °C; yield 79 %. – IR (KBr) ν = 3016 (Ar-H), 2912 (C-H), 1718 (C=O), 1503 (C=N), 3455 (NH), 1237 (C-O) cm^{-1}. – ^{1}H-NMR ([D$_6$]DMSO): δ = 2.27 (s, 3H, CH_3), 2.81 (dd, 1H, J = 17.9, 5.5 Hz), 3.41 (dd, 1H, J = 17.9, 8.3 Hz), 4.51 (dd, 1H, J = 8.3, 5.5 Hz), 4.66 (s, 2H, OCH_2), 6.95 (d, 2H, J = 9.0 Hz, 4-methylphenyl), 7.32 (d, 2H, J = 9.0 Hz, 4-methylphenyl), 7.38 (dd, 3H, J = 9.2, 8.7 Hz, phenyl), 7.56 (d, 2H, J = 9.2 Hz, phenyl), 13.05 (s, 1H, NH). – MS (FAB): m/z (%) = 395 (90) [M+1]$^+$, 394 (60) [M]$^+$, 390 (15), 272 (50), 235 (10), 224 (40), 168 (30), 136 (45). – $C_{20}H_{18}N_4O_3S$ (394.448): calcd. C 60.90, H 4.60, N 14.20; found C 60.87, H 4.62, N 14.17.

6b: Off-white powder; m. p. 102 °C; yield 85 %. – IR (KBr): ν = 3017 (Ar-H), 2912 (C-H), 1717 (C=O), 1512 (C=N), 3457 (NH), 1246 (C-O), 842 (C-Cl) cm^{-1}. – ^{1}H-NMR ([D$_6$]DMSO): δ = 2.21 (s, 3H, CH_3), 2.81 (dd, 1H, J = 17.9, 5.6 Hz), 3.41 (dd,1H, J = 17.9, 8.3 Hz), 4.51 (dd, 1H, J = 8.3, 5.6 Hz), 4.67 (s, 2H, OCH_2), 7.46 (d, 2H, J = 8.8 Hz, 4-chloro- phenyl), 7.24 (d, 2H, J = 8.8 Hz, 4-chlorophenyl), 7.52 (d, 2H, J = 8.3 Hz, 4-methylphenyl), 7.36 (d, 2H, J = 8.3 Hz, 4-methylphenyl), 13.04 (s,1H, NH). – MS (FAB): m/z (%) = 429 (100) [M+1]$^+$, 428 (70) [M]$^+$, 430 (20) [M+2]$^+$, 392 (15), 285 (30), 248 (10), 220 (40), 176 (10), 136 (25). – $C_{20}H_{17}ClN_4O_3S$ (428.893): calcd. C 56.01, H 4.00, N 13.06; found C 56.03, H 4.02, N 13.04.

6c: Off-white powder, m. p. 150 °C; yield 76 %. – IR (KBr): ν = 3020 (Ar-H), 2913 (C-H), 1719 (C=O),

1513 (C=N), 3453 (NH), 1233 (C-O), 846 (C-Cl) cm^{-1}. – ^{1}H-NMR ([D_6] DMSO): δ = 2.22 (s, 3H, CH_3), 2.83 (dd, 1H, J = 17.8, 5.6 Hz), 3.45 (dd, 1H, J = 17.8, 8.5 Hz), 4.57 (dd, 1H, J =8.8, 5.6 Hz), 4.67 (s, 2H, OCH_2), 7.23 (s, 1H, 3-chloro-4-fluorophenyl), 7.46 (d, 1H, J = 8.2 Hz, 3-chloro-4-fluorophenyl), 7.48 (d, 1H, J = 8.2 Hz, 3-chloro-4-fluorophenyl) 7.52 (d, 2H, J = 8.3 Hz, 4-methylphenyl), 7.32 (d, 2H, J = 8.3 Hz, 4-methylphenyl), 13.09 (s,1H, NH). – MS (FAB): m/z (%) = 447 (100) $[M+1]^+$, 446 (70) $[M]^+$, 448 (30) $[M+2]^+$, 376 (60), 315 (40), 257 (60), 228(30). – $C_{20}H_{16}ClFN_4O_3S$ (446.883): calcd. C 53.75, H 3.61, N 12.54; found C 53.72, H 3.60, N 12.57.

6d: Off-white flakes, m. p. 122 °C; yield 60 %. – IR (KBr): ν = 3021 (Ar-H), 2914 (C-H), 1721 (C=O), 1523 (C=N), 3460 (NH), 1253 (C-O) cm^{-1}. – ^{1}H-NMR ([D_6]DMSO): δ = 2.21 (s, 3H, CH_3), 2.83 (dd, 1H, J = 17.8, 5.9 Hz), 3.41 (dd, 1H, J = 17.8, 8.4 Hz), 4.51 (dd, 1H, J = 8.4, 5.9 Hz), 4.67 (s, 2H, OCH_2), 7.58 (d, 2H, J = 8.8 Hz, 4-fluorophenyl), 7.42 (d, 2H, J = 8.8 Hz, 4-fluorophenyl), 7.50 (d, 2H, J = 8.2 Hz, 4-methylphenyl), 7.32 (d, 2H, J = 8.3 Hz, 4-methylphenyl), 13.11 (s, 1H, NH). – MS (FAB): m/z (%) = 413 (100) $[M+1]^+$, 412 (80) $[M]^+$, 414 (35) $[M+2]^+$, 385 (40), 235 (30), 272 (50), 212 (40), 193 (30). – $C_{20}H_{17}FN_4O_3S$ (412.439): calcd. C 58.24, H 4.15, N 13.58; found C 58.26, H 4.14, N 13.53.

6e: Off-white flakes, m. p. 130 °C; yield 75 %. – IR (KBr): ν = 3017 (Ar-H), 2922 (C-H), 1713 (C=O), 1492 (C=N), 3463 (NH), 1235 (C-O), 857 (C-Cl) cm^{-1}. – ^{1}H-NMR ([D_6]DMSO): δ = 2.27 (s, 3H, CH_3), 2.89 (dd, 1H, J =18.5, 4.9 Hz), 3.41 (dd, 1H, J = 18.5, 8.9 Hz), 5.51 (dd, 1H, J = 8.9, 4.9 Hz), 4.65 (s, 2H, OCH_2), 7.38 (dd, 3H, J = 9.0 Hz, 8.7 Hz, phenyl), 7.56 (d, 2H, J = 9.0 Hz, phenyl), 7.31 (d, 2H, J = 8.4 Hz, 4-chlorophenyl), 7.44 (d, 2H, J = 8.4 Hz, 4-chlorophenyl), 13.20 (s, 1H, NH). – MS (FAB): m/z (%) = 415 (100) $[M+1]^+$, 414 (60) $[M]^+$, 416 (25) $[M+2]^+$, 412 (40), 396 (35), 354 (20), 257 (60), 182 (65), 154 (10). – $C_{19}H_{15}ClN_4O_3S$ (414.866): calcd. C 55.01, H 3.64, N 13.50; found C 55.04, H 3.68, N 13.52.

6f: Off-white powder, m. p. 112 °C; yield 87 %. – IR (KBr): ν = 3024 (Ar-H), 2924 (C-H), 1720 (C=O), 1513 (C=N), 3459 (NH), 1244 (C-O), 858 (C-Cl) cm^{-1}. – ^{1}H-NMR ([D_6]DMSO): δ = 2.89 (dd, 1H, J = 18.4, 5.0 Hz), 3.43 (dd, 1H, J = 18.4, 9.0 Hz), 5.53 (dd, 1H, J = 9.0, 5.0 Hz), 4.65 (s, 2H, OCH_2), 7.29 (d, 2H, J = 8.8 Hz, 4-chlorophenyl), 7.33 (d, 2H, J = 8.8 Hz, 4-chlorophenyl), 7.44 (d, 2H, J = 8.6 Hz, 4-chlorophenyl), 7.49 (d, 2H, J = 8.6 Hz, 4-chlorophenyl), 13.17 (s, 1H, NH). – MS (FAB): m/z (%) = 451 (40) $[M+1]^+$, 450 (100) $[M]^+$, 452 (60) $[M+2]^+$, 454 (15) $[M+4]^+$, 444 (65), 377 (30), 312 (40), 264 (20), 214 (10), 188 (25). – $C_{19}H_{14}Cl_2N_4O_3S$ (450.311): calcd. C 50.79, H 3.14, N 12.47; found C 50.76, H 3.16, N 12.44.

6g: Off-white powder, m. p. 144 °C; yield 87 %. – IR (KBr): ν = 3025 (Ar-H), 2937 (C-H), 1715 (C=O), 1517 (C=N), 3448 (NH), 1243 (C-O), 851 (C-Cl) cm^{-1}. – ^{1}H-NMR ([D_6]DMSO): δ = 2.88 (dd, 1H, J = 18.4, 5.6 Hz), 3.42 (dd, 1H, J = 18.4, 9.2 Hz), 5.56 (dd, 1H, J = 9.2, 5.6 Hz), 4.65 (s, 2H, OCH_2), 7.29 (d, 2H, J = 8.8 Hz, 4-chlorophenyl), 7.33 (d, 2H, J = 8.8 Hz, 4-chlorophenyl), 7.21 (s, 1H, 3-Cl-4-F-phenyl), 7.46 (d, 1H, J = 8.6 Hz, 3-chloro-4-fluorophenyl), 7.48 (d, 1H, J = 8.6 Hz, 3-chloro-4-fluorophenyl), 13.03 (s, 1H, NH). – MS (FAB): m/z (%) = 433 (40) $[M+1]^+$, 432 (100) $[M]^+$, 434(40) $[M+2]^+$, 402 (30), 365 (60), 315 (30), 272 (20), 242 (40). – $C_{19}H_{13}Cl_2FN_4O_3S$ (466.301): calcd. C 48.83, H 2.80, N 11.99; found C 48.80, H 2.83, N 11.97.

6h: Off-white powder, m. p. 138 °C; yield 65 %. – IR (KBr): ν = 3028 (Ar-H), 2925 (C-H), 1722 (C=O), 1513 (C=N), 3457 (NH), 1244 (C-O), 848 (C-Cl) cm^{-1}. – ^{1}H-NMR ([D_6]DMSO): δ = 2.80 (dd, 1H, J = 18.2, 5.3 Hz), 3.43 (dd, 1H, J = 18.2, 8.6 Hz), 5.53 (dd, 1H, J = 8.6, 5.3 Hz), 4.66 (s, 2H, OCH_2), 7.34 (d, 2H, J = 8.6 Hz, 4-chlorophenyl), 7.17 (d, 2H, J = 8.6 Hz, 4-chlorophenyl), 7.52 (d, 2H, J = 8.7 Hz, 4-fluorophenyl), 7.47 (d, 2H, J = 8.6 Hz, 4-fluorophenyl), 13.16 (s, 1H, NH). – MS (FAB): m/z (%) = 433 (100) $[M+1]^+$, 432 (75) $[M]^+$, 434 (20) $[M+2]^+$, 397 (45), 368 (80), 338 (50), 282 (20), 248 (30), 202 (15), 172 (40). – $C_{19}H_{14}ClFN_4O_3S$ (432.857): calcd. C 52.72, H 3.26, N 12.94; found C 52.75, H 3.29, N 12.91.

6i: Light-yellow powder, m. p. 137 °C; yield 83 %. – IR (KBr): ν = 3092 (Ar-H), 2916 (C-H), 1707 (C=O), 1487 (C=N), 3454 (NH), 1232 (C-O), 698 (C-Br) cm^{-1}. – ^{1}H-NMR ([D_6]DMSO): δ = 2.88 (dd, 1H, J = 18.2, 5.2 Hz), 3.41 (dd, 1H, J = 18.2, 8.7 Hz), 5.51 (dd, 1H, J = 8.7, 5.2 Hz), 4.65 (s, 2H, OCH_2), 7.37 (dd, 3H, J = 9.1, 8.6 Hz, phenyl), 7.55 (d, 2H, J = 9.1 Hz, phenyl), 7.32 (d, 2H, J = 8.3 Hz, 4-bromophenyl), 7.46 (d, 2H, J = 8.3 Hz, 4-bromophenyl), 13.21 (s, 1H, NH). – MS (FAB): m/z (%) = 460 (90) $[M+1]^+$, 459 (95) $[M]^+$, 461 (100) $[M+2]^+$, 463 (30) $[M^+$+4], 429 (20), 391 (60), 367 (20), 337 (10), 280 (30), 217 (25), 185 (30). – $C_{19}H_{15}BrN_4O_3S$ (459.316): calcd. C 49.68, H 3.29, N 12.20; found C 49.65, H 3.31, N 12.22.

6j: Light-yellow powder, m. p. 142 °C; yield 85 % . – IR (KBr): ν = 3028 (Ar-H), 2927 (C-H), 1712 (C=O), 1497 (C=N), 3468 (NH), 1240 (C-O), 746 (C-Br), 856 (C-Cl) cm^{-1}. – ^{1}H-NMR ([D_6]DMSO): δ = 2.88 (dd, 1H, J = 18.3, 5.1 Hz), 3.41 (dd, 1H, J = 18.3, 8.9 Hz), 5.51 (dd, 1H, J = 8.9, 5.1 Hz), 4.66 (s, 2H, OCH_2), 7.21 (d, 2H, J = 8.2 Hz, 4-bromophenyl), 7.35 (d, 2H, J = 8.5 Hz, 4-chlorophenyl), 7.40 (d, 2H, J = 8.5 Hz, 4-chlorophenyl), 7.47 (d, 2H, J = 8.2 Hz, 4-bromophenyl), 13.21 (s, 1H, NH). – MS (FAB): m/z (%) = 494 (90) $[M+1]^+$, 493 (95) $[M]^+$, 495 (100) $[M+2]^+$, 497 (35) $[M+4]^+$, 453 (30), 419 (40), 372 (50), 332 (30), 297 (40), 266 (20). – $C_{19}H_{14}BrClN_4O_3S$ (493.761): calcd. C 46.22, H 2.86, N 11.35; found C 46.24, H 2.88, N 11.36.

6k: Light-yellow powder, m. p. 148 °C; yield 77 %. – IR (KBr): ν = 3035 (Ar-H), 2932 (C-H), 1713 (C=O), 1497 (C=N), 3458 (NH), 1247 (C-O), 743 (C-Br), 862 (C-Cl) cm^{-1}. – ^{1}H-NMR ([D$_6$]DMSO): δ = 2.88 (dd, 1H, J = 18.4, 5.2 Hz), 3.44 (dd, 1H, J = 18.4, 9.1 Hz), 5.57 (dd, 1H, J = 9.1, 5.2 Hz), 4.67 (s, 2H, OCH_2), 7.21 (d, 2H, J = 8.2 Hz, 4-bromophenyl), 7.23 (s, 1H, 3-chloro-4-fluorophenyl), 7.46 (d, 1H, J = 8.3 Hz, 3-chloro-4-fluorophenyl), 7.48 (d, 1H, J = 8.3 Hz, 3-chloro-4-fluorophenyl), 7.41 (d, 2H, J = 8.2 Hz, 4-bromophenyl), 13.05 (s, 1H, NH). – MS (FAB): m/z (%) = 512 (90) $[M+1]^+$, 511 (95) $[M]^+$, 513 (100) $[M+2]^+$, 515 (35) $[M+4]^+$, 472 (30), 428 (40), 362 (50), 341 (20), 283 (30), 246 (10). – $C_{19}H_{13}$ $BrClFN_4O_3S$ (511.751): calcd. C 44.59, H 2.56, N 10.95; found C 44.59, H 2.54, N 10.91.

6l: Light-yellow powder, m. p. 123 °C; yield 83 %. – IR (KBr): ν = 3037 (Ar-H), 2935 (C-H), 1714 (C=O), 1498 (C=N), 3465 (NH), 1245 (C-O), 746 (C-Br) cm^{-1}. – ^{1}H-NMR ([D$_6$]DMSO): δ = 2.87 (dd, 1H, J = 18.2, 5.7 Hz), 3.45 (dd, 1H, J = 18.2, 9.2 Hz), 5.53 (dd, 1H, J = 9.2, 5.7 Hz), 4.67 (s, 2H, OCH_2), 7.21 (d, 2H, J = 8.2 Hz, 4-bromophenyl), 7.35 (d, 2H, J = 8.4 Hz, 4-fluorophenyl), 7.50 (d, 2H, J = 8.4 Hz, 4-fluororophenyl), 7.47 (d, 2H, J = 8.2 Hz, 4-bromophenyl), 13.15 (s, 1H, NH). – MS (FAB): m/z (%) = 478 (90) $[M+1]^+$, 477 (95) $[M]^+$, 479 (100) $[M+2]^+$, 435 (40), 411 (60), 394 (40), 322 (50), 285 (40), 212 (20). – $C_{19}H_{15}$ $BrFN_4O_3S$ (477.306): calcd. C 47.81, H 2.96, N 11.74; found C 47.85, H 2.98, N 11.77.

6m: Off-white powder, m. p. 138 °C; yield 68 %. – IR (KBr): ν = 3035 (Ar-H), 2943 (C-H), 1714 (C=O), 1502 (C=N), 3457 (NH), 1230 (C-O) cm^{-1}. – ^{1}H-NMR ([D$_6$]DMSO): δ = 2.01 (s, 1H, $C(CH_3)_3$), 2.89 (dd, 1H, J = 18.4, 5.8 Hz), 3.45 (dd, 1H, J = 18.4, 8.8 Hz), 5.51 (dd, 1H, J = 8.8, 5.8 Hz), 4.67 (s, 2H, OCH_2), 7.22 (d, 2H, J = 7.4 Hz, 4-*t*-butylphenyl), 7.28 (dd, 3H, J = 8.8, 8.5 Hz, phenyl), 7.42 (d, 2H, J = 8.8 Hz, 4-chlorophenyl), 7.56 (d, 2H, J = 7.9 Hz, 4-*t*-butylphenyl), 13.20 (s, 1H, NH). – MS (FAB): m/z (%) = 437 (100) $[M+1]^+$, 436 (80) $[M]^+$, 412 (25), 386 (20), 343 (60), 312 (70), 279 (40), 242 (25). – $C_{23}H_{24}N_4O_3S$ (436.528): calcd. C 63.28, H 5.54, N 12.83; found C 63.30, H 5.56, N 12.80.

6n: Off-white powder, m. p. 140 °C; yield 72 %. – IR (KBr): ν = 3028 (Ar-H), 2927 (C-H), 1712 (C=O), 1497 (C=N), 3462 (NH), 1240 (C-O), 825 (C-Cl) cm^{-1}. – ^{1}H-NMR ([D$_6$]DMSO): δ = 2.01 (s, 1H, $C(CH_3)_3$), 2.88 (dd, 1H, J = 18.2, 5.2 Hz), 3.43 (dd, 1H, J = 18.2, 8.8 Hz), 5.51 (dd, 1H, J = 8.8, 5.2 Hz), 4.66 (s, 2H, OCH_2), 7.23 (d, 2H, J = 7.9 Hz, 4-*t*-butylphenyl), 7.28 (d, 2H, J = 8.4 Hz, 4-chlorophenyl), 7.35 (d, 2H, J = 8.4 Hz, 4-chlorophenyl), 7.52 (d, 2H, J = 7.9 Hz, 4-*t*-butylphenyl), 13.20 (s, 1H, NH). – MS (FAB): m/z (%) = 471 (100) $[M+1]^+$, 470 (70) $[M]^+$, 472 (25) $[M+2]^+$, 426 (30), 402 (60), 367 (40), 345 (10), 277 (25), 240 (20), 213 (5), 174 (10). – $C_{23}H_{23}ClN_4O_3S$ (470.973): calcd. C 58.65, H 4.92, N 11.90; found C 58.63, H 4.94, N 11.94.

6o: Off-white powder, m. p. 157 °C; yield 70 %. – IR (KBr): ν = 3037 (Ar-H), 2953 (C-H), 1718 (C=O), 1533 (C=N), 3446 (NH), 1240 (C-O), 851 (C-Cl) cm^{-1}. – ^{1}H-NMR ([D$_6$]DMSO): δ = 2.01 (s, 1H, $C(CH_3)_3$), 2.87 (dd, 1H, J = 18.4, 5.6 Hz), 3.42 (dd, 1H, J = 18.4, 9.2 Hz), 5.56 (dd, 1H, J = 9.2, 5.6 Hz), 4.65 (s, 2H, OCH_2), 7.32 (d, 2H, J = 8.8 Hz, 4-*t*-butylphenyl), 7.48 (d, 2H, J = 8.8 Hz, 4-*t*-butylphenyl), 7.21 (s, 1H, 3-Cl-4-fluorophenyl), 7.46 (d, 1H, J = 8.6 Hz, 3-chloro-4-fluorophenyl), 7.51 (d, 1H, J = 8.6 Hz, 3-chloro-4-fluorophenyl), 13.10 (s, 1H, NH). – MS (FAB): m/z (%) = 489 (60) $[M+1]^+$, 488 (100) $[M]^+$, 490 (30) $[M+2]^+$, 422 (30), 368 (40), 317 (50), 258 (30), 204 (20). – $C_{23}H_{22}ClFN_4O_3S$ (488.963): calcd. C 56.50, H 4.54, N 11.46; found C 56.54, H 4.56, N 11.42.

6p: Off-white powder, m. p. 133 °C; yield 68 %. – IR (KBr): ν = 3028 (Ar-H), 2933 (C-H), 1721 (C=O), 1528 (C=N), 3457 (NH), 1250 (C-O) cm^{-1}. – ^{1}H-NMR ([D$_6$]DMSO): δ = 2.03 (s, 1H, $C(CH_3)_3$), 2.83 (dd, 1H, J = 17.9, 5.9 Hz), 3.41 (dd, 1H, J = 17.9, 8.4 Hz), 4.55 (dd, 1H, J = 8.4, 5.9 Hz), 4.67 (s, 2H, OCH_2), 7.58 (d, 2H, J = 8.8 Hz, 4-fluorophenyl), 7.42 (d, 2H, J = 8.8 Hz, 4-fluorophenyl), 7.27 (d, 2H, J = 8.4 Hz, 4-*t*-butylphenyl), 7.43 (d, 2H, J = 8.4 Hz, 4-*t*-butylphenyl), 13.11 (s, 1H, NH). – MS (FAB): m/z (%) = 455 (100) $[M+1]^+$, 454 (80) $[M]^+$, 416 (50) $[M+2]^+$, 376 (40), 283 (30), 254 (60), 211 (30). – $C_{23}H_{23}FN_4O_3S$ (454.518): calcd. C 60.78, H 5.10, N 12.33; found C 60.75, H 5.74, N 12.36.

6q: Light-brown powder, m. p. 143 °C; yield 81 %. – IR (KBr): ν = 3081 (Ar-H), 2942 (C-H), 1713 (C=O), 1485 (C=N), 3459 (NH), 1237 (C-O), 755 (C-Cl) cm^{-1}. – ^{1}H-NMR ([D$_6$]DMSO): δ = 2.34 (s, 1H, CH_3), 2.88 (dd, 1H, J =18.9, 5.7 Hz), 3.75 (dd, 1H, J = 18.9, 9.1 Hz), 5.18 (dd, 1H, J = 9.1, 5.7 Hz), 4.64 (s, 2H, OCH_2), 6.95 (d, 1H, J = 7.9 Hz, 4-chloro-5-methylphenyl), 7.12 (dd, 3H, J = 8.7, 8.4 Hz, phenyl), 7.29 (d, 2H, J = 8.7 Hz, phenyl), 7.35 (s, 1H, 4-chloro-5-methylphenyl), 7.44 (d, 1H, J = 7.9 Hz, 4-chloro-5-methylphenyl), 13.22 (s, 1H, NH). – MS (FAB): m/z (%): 429 (100) $[M+1]^+$, 428 (90) $[M]^+$, 430 (30) $[M+2]^+$, 410 (50), 372 (30), 351 (40), 292 (25), 252 (10), 237 (20), 166 (20). – $C_{20}H_{17}ClN_4O_3S$ (428.893): calcd. C 56.01, H 4.00, N 13.06; found C 56.03, H 4.03, N 13.02.

6r: Off-white powder, m. p. 167 °C; yield 86 %. – IR (KBr): ν = 3093 (Ar-H), 2921 (C-H), 1710 (C=O), 1476 (C=N), 3456 (NH), 1243 (C-O), 755 (C-Cl) cm^{-1}. – ^{1}H-NMR ([D$_6$]DMSO): δ = 2.34 (s, 1H,CH_3), 2.89 (dd, 1H, J = 18.4, 5.2 Hz), 3.75 (dd, 1H, J = 18.4, 8.6 Hz), 5.15 (dd, 1H, J = 8.6, 5.2 Hz), 4.64 (s, 2H, OCH_2), 6.92 (d, 1H, J = 7.6 Hz, 4-chloro-5-methylphenyl), 7.02 (d, 2H, J = 8.7 Hz, 4-chlorophenyl), 7.21 (d, 2H, J = 8.7 Hz, 4-chlorophenyl), 7.35 (s, 1H, 4-chloro-5-methylphenyl), 7.42 (d, 1H, J = 7.6 Hz, 4-chloro-5-methylphenyl), 13.22 (s, 1H, NH). – MS (FAB):

Table 1. Antibacterial activity of the newly synthesized compounds **6a – t**[a].

Compd.	MIC [μg mL^{-1}] and zone of inhibition [mm] in parentheses			
	S. aureus	*E. coli*	*P. aeruginosa*	*K. pneumoniae*
6a	12.5 (11 – 15)	12.5 (11 – 15)	12.5 (11 – 15)	12.5 (11 – 15)
6b	25 (< 10)	25 (< 10)	25 (< 10)	25 (< 10)
6c	12.5 (11 – 15)	12.5 (11 – 15)	12.5 (11 – 15)	12.5 (11 – 15)
6d	6.25 (16 – 20)	6.25 (18 – 22)	6.25 (16 – 20)	6.25 (16 – 20)
6e	12.5 (11 – 15)	12.5 (11 – 15)	12.5 (11 – 15)	12.5 (11 – 15)
6f	6.25 (18 – 21)	6.25 (18 – 22)	6.25 (18 – 21)	6.25 (18 – 21)
6g	12.5 (11 – 15)	12.5 (11 – 15)	12.5 (11 – 15)	12.5 (11 – 15)
6h	6.25 (18 – 21)	6.25 (18 – 22)	6.25 (18 – 21)	6.25 (18 – 21)
6i	6.25 (16 – 20)	6.25 (18 – 22)	6.25 (16 – 20)	6.25 (16 – 20)
6j	12.5 (11 – 15)	12.5 (11 – 15)	12.5 (11 – 15)	12.5 (11 – 15)
6k	25 (< 10)	25 (< 10)	25 (< 10)	25 (< 10)
6l	6.25 (16 – 20)	25 (< 10)	25 (< 10)	25 (< 10)
6m	25 (< 10)	25 (< 10)	25 (< 10)	25 (< 10)
6n	25 (< 10)	25 (< 10)	25 (< 10)	25 (< 10)
6o	6.25 (16 – 20)	6.25 (18 – 22)	6.25 (16 – 20)	6.25 (16 – 20)
6p	25 (< 10)	25 (< 10)	25 (< 10)	25 (< 10)
6q	6.25 (16 – 20)	6.25 (18 – 22)	6.25 (16 – 20)	6.25 (16 – 20)
6r	6.25 (16 – 20)	6.25 (18 – 22)	6.25 (16 – 20)	6.25 (16 – 20)
6s	12.5 (11 – 15)	12.5 (11 – 15)	12.5 (11 – 15)	12.5 (11 – 15)
6t	25 (< 10)	25 (< 10)	25 (< 10)	25 (< 10)
Standard (Ciprofloxacin)	1.56 (22 – 30)	6.25 (30 – 40)	6.25 (25 – 33)	6.25 (23 – 27)

[a] The MIC values were evaluated at a concentration range 1.56 – 25 μg mL^{-1}.

m/z (%) = 464 (100) $[M+1]^+$, 463 (90) $[M]^+$, 465 (55) $[M+2]^+$, 467 (10) $[M+4]^+$, 425 (70), 372 (30), 337 (30), 286 (25), 212 (10). – $C_{20}H_{16}C_{l2}N_4O_3S$ (463.338): calcd. C 51.84, H 3.48, N 12.09; found C 51.82, H 3.51, N 12.12.

6s: Off-white powder, m. p. 175 °C; yield 78 %. – IR (KBr): ν = 3041 (Ar-H), 2938 (C-H), 1719 (C=O), 1514 (C=N), 3457 (NH), 1232 (C-O), 853 (C-Cl) cm^{-1}. – ^{1}H-NMR ([D$_6$]DMSO): δ = 2.22 (s, 3H, CH_3), 2.83 (dd, 1H, J = 17.8, 5.7 Hz), 3.45 (dd, 1H, J = 17.8, 8.7 Hz), 4.57 (dd, 1H, J = 8.7, 5.7 Hz), 4.67 (s, 2H, OCH_2), 6.95 (d, 1H, J = 8.1 Hz, 4-chloro-5-methylphenyl), 7.23 (s, 1H, 3-chloro-4-fluorophenyl), 7.48 (d, 1H, J = 8.4 Hz, 3-chloro-4-fluorophenyl), 7.51 (d, 1H, J = 8.4 Hz, 3-chloro-4-fluorophenyl), 7.32 (s, 1H, 4-chloro-5-methylphenyl), 7.41 (d, 1H, J = 8.1 Hz, 4-chloro-5-methylphenyl), 13.09 (s, 1H, NH). – MS (FAB): m/z (%) = 481 (80) $[M+1]^+$, 480 (100) $[M]^+$, 482 (60) $[M+2]^+$, 484 (15) $[M+4]^+$, 428 (40), 378 (30), 335 (40), 284 (20). – $C_{20}H_{15}Cl_2FN_4O_3S$ (480.328): calcd. C 49.91, H 3.14, N 11.64; found C 49.94, H 3.18, N 11.67.

6t: Off-white powder, m. p. 174 °C; yield 73 %. – IR (KBr): ν = 3045 (Ar-H), 2922 (C-H), 1721 (C=O), 1532 (C=N), 3462 (NH), 1250 (C-O), 853 (C-Cl) cm^{-1}. – ^{1}H-NMR ([D$_6$]DMSO): δ = 13.12 (s, 1H, NH), 2.21 (s, 3H, CH_3), 2.85 (dd, 1H, J = 18.1, 5.7 Hz), 3.44 (dd, 1H, J = 18.1, 8.7 Hz), 4.56 (dd, 1H, J = 8.7, 5.7 Hz), 4.67 (s, 2H, OCH_2), 7.59 (d, 2H, J = 8.9 Hz, 4-fluorophenyl), 7.44 (d, 2H, J = 8.9 Hz, 4-fluorophenyl), 6.98 (d, 1H, J = 8.5 Hz, 4-chloro-5-methylphenyl), 7.33 (s, 1H, 4-chloro-5-methylphenyl), 7.42 (d, 1H, J = 8.5 Hz, 4-chloro-5-methylphenyl). – MS (FAB): m/z (%) = 447 (100) $[M+1]^+$, 446 (80) $[M]^+$, 448 (30) $[M+2]^+$, 402 (50), 368 (20), 315 (40), 297 (40), 213 (30). – $C_{20}H_{16}ClFN_4O_3S$ (446.883): calcd. C 53.75, H 3.61, N 12.54; found C 53.78, H 3.64, N 12.56.

Antibacterial activity

The newly synthesized compounds were screened for their antibacterial activity against *Escherichia coli* (ATTC-25922), *Staphylococcus aureus* (ATTC-25923), *Pseudomonas aeruginosa* (ATTC-27853), and *Klebsiella pneumoniae* (recultured) bacterial stains by a serial plate dilution method [26, 27]. Serial dilutions of the drug in Muller-Hinton broth were taken in tubes, and their pH was adjusted to 5.0 using a phosphate buffer. A standardized suspension of the test bacterium was inoculated and incubated for 16 – 18 h at 37 °C. The minimum inhibitory concentration (MIC) was noted by seeing the lowest concentration of the drug at which there was no visible growth.

A number of antibacterial discs were placed on the agar for the sole purpose of producing zones of inhibition in the bacterial lawn. Twenty mL of agar media was poured into each Petri dish. The excess of suspension was decanted, and plates were dried by placing in an incubator at 37 °C for 1 h. Using a punch, wells were made on these seeded agar plates, and minimum inhibitory concentrations of the test compounds in dimethyl sulfoxide (DMSO) were added into each labeled well. A control was also prepared for the plates in the same way using DMSO as a solvent. The Petri dishes were prepared in triplicate and maintained at 37 °C for 3 – 4 d. Antibacterial activity was determined by measuring the diameter of the inhibition zone. Activity

Table 2. Antifungal activity of the newly synthesized compounds **6a – t**[a].

Compd.	MIC [μg mL^{-1}] and zone of inhibition [mm] in parentheses			
	P. marneffei	*T. mentagrophytes*	*A. flavus*	*A. fumigatus*
6a	12.5 (11 – 15)	12.5 (11 – 15)	12.5 (11 – 15)	12.5 (11 – 15)
6b	25 (< 10)	25 (< 10)	25 (< 10)	25 (< 10)
6c	12.5 (11 – 15)	12.5 (11 – 15)	12.5 (11 – 15)	12.5 (11 – 15)
6d	25 (< 10)	25 (< 10)	25 (< 10)	25 (< 10)
6e	12.5 (11 – 15)	12.5 (11 – 15)	12.5 (11 – 15)	12.5 (11 – 15)
6f	6.25 (18 – 21)	6.25 (18 – 22)	6.25 (18 – 21)	6.25 (18 – 21)
6g	12.5 (11 – 15)	12.5 (11 – 15)	12.5 (11 – 15)	12.5 (11 – 15)
6h	6.25 (18 – 21)	6.25 (18 – 22)	6.25 (18 – 21)	6.25 (18 – 21)
6i	6.25 (16 – 20)	6.25 (18 – 22)	6.25 (16 – 20)	6.25 (16 – 20)
6j	12.5 (11 – 15)	12.5 (11 – 15)	12.5 (11 – 15)	12.5 (11 – 15)
6k	25 (< 10)	25 (< 10)	25 (< 10)	25 (< 10)
6l	12.5 (11 – 15)	12.5 (11 – 15)	12.5 (11 – 15)	12.5 (11 – 15)
6m	25 (< 10)	25 (< 10)	25 (< 10)	25 (< 10)
6n	25 (< 10)	25 (< 10)	25 (< 10)	25 (< 10)
6o	6.25 (16 – 20)	6.25 (18 – 22)	6.25 (16 – 20)	6.25 (16 – 20)
6p	25 (< 10)	25 (< 10)	25 (< 10)	25 (< 10)
6q	6.25 (16 – 20)	6.25 (18 – 22)	6.25 (16 – 20)	6.25 (16 – 20)
6r	25 (< 10)	25 (< 10)	25 (< 10)	25 (< 10)
6s	12.5 (11 – 15)	12.5 (11 – 15)	12.5 (11 – 15)	12.5 (11 – 15)
6t	25 (< 10)	25 (< 10)	25 (< 10)	25 (< 10)
Standard (Cyclopiroxalamine)	1.56 (22 – 30)	6.25 (30 – 40)	6.25 (25 – 33)	6.25 (23 – 27)

[a] The MIC values were evaluated at a concentration range 1.56 – 25 μg mL^{-1}.

of each compound was compared with ciprofloxacin as standard [28, 29]. The zone of inhibition was determined for **6a – t**, and results are summarized in Table 1.

Antifungal activity

The newly prepared compounds were also screened for their antifungal activity against *Aspergillus flavus* (NCIM No. 524), *Aspergillus fumigatus* (NCIM No. 902), *Penicillium marneffei* (recultured), and *Trichophyton mentagrophytes* (recultured) in DMSO by a serial plate dilution method [30, 31]. Sabourands agar media were prepared by dissolving peptone (1 g), D-glucose (4 g), and agar (2 g) in distilled water (100 mL) and adjusting the pH to 5.7. Normal saline was used to make a suspension of sore of fungal strains for lawning. A loopful of a particular fungal strain was transferred to 3 mL saline to get a suspension of the corresponding species. 20 mL of agar media was poured into each Petri dish. The excess of suspension was decanted, and the plates were dried in an incubator at 37 °C for 1 h. Using a punch, wells were made on these seeded agar plates. Minimum inhibitory concentrations of the test compounds in DMSO were added into each labeled well. A control was also prepared for the plates in the same way using DMSO as solvent. The Petri dishes were prepared in triplicate and maintained at 37 °C for 3 – 4 d. Antifungal activity was determined by measuring the diameter of inhibition zone. The activity of each compound was compared with cyclopiroxolamine as standard. Zones of inhibition were determined for **6a – t**, and results are summarized in Table 2.

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