Novel Pyrimidine Associated Thiazolidines: Design, Synthesis, Characterization and Evaluation as Antibacterial Agents

CHANDRA SEKHARA REDDI MADDIREDDI^{1,*}, UMA DEVI PARIMI¹, SREENIVASA REDDY BHIMI REDDY² and V.V.V. SATYANARAYANA KASAPU²

¹Department of Chemistry, GITAM Institute of Science, GITAM University, Rushikonda, Visakhapatnam-530 045, India

²Coastal Chemical Research Society, Visakhapatnam-530 045, India

*Corresponding author: E-mail: csreddimelpl@gmail.com

Received: 7 April 2017;

Accepted: 19 May 2017;

Published online: 15 July 2017;

AJC-18477

Several novel pyrimidine associated thiazolidines (**5a-f**) have been synthesized by using 6-trifluoromethyl-pyrimidine-4-ol (**1**) as starting material and by participating (6-trifluoromethyl-pyrimidine-4-yloxy)acetic acid ethyl ester (**2**) (6-trifluoromethyl-pyrimidine-4-yloxy)acetic acid hydrazide (**3**) and (6-trifluoromethyl-pyrimidine-4-yloxy)acetic acid benzylidene-hydrazides (**4a-f**) as intermediates through substitution, condensation and cyclization. The chemical structures of all the newly synthesized compounds were confirmed by IR, ¹H and ¹³C NMR, mass spectral studies and elemental analysis. Further, the synthesized products were screened for their antibacterial activity and the zone of inhibition was measured.

Keywords: Pyrimidine, Thiazolidines, Antibacterial activity.

INTRODUCTION

The discovery and development of heterocyclic systems of pharmaceutical importance has been of enormous interest to synthetic organic chemists owing to their presence in biological systems. Various heterocycles like thiazolidines constitute an important class and have been under study for various types of activities such as antitumor [1], anticancer [2], anti-inflammatory [3], antimicrobial [4] and antitoxoplasma gondii activities [5]. Consequently, chemists still enthusiastically pursue the syntheses and activity evaluation of thiazolidine derivatives [6]. Nitrogen containing heterocyclic ring such as pyrimidine is a promising structural moiety for drug design and are associated with many biological and therapeutical activities such as antimicrobial [7], analgesic, antiviral, anti-inflammatory [8], anti-HIV [9], antitubercular [10], antitumour [11], antineoplastic [12], antimalarial [13], diuretic [14], cardiovascular [15] agents. On the other hand thiazolo-pyrimidines are important class of compounds with wide range of biological activity [16].

EXPERIMENTAL

All chemicals and reagents were obtained from commercial sources and were used as supplied, without further purification. Melting points were determined with a Fisher-Johns melting point meter in the open glass capillary method and are uncorrected. The reaction progress and purity of the synthesized

compounds were monitored by analytical thin layer chromatography (TLC) using Merck precoated Silica Gel 60F₂₅₄ sheets. IR spectra were recorded on a Perkin-Elmer BX serried FTIR 5000 spectrometer using KBr pellet. ¹H NMR and ¹³C NMR spectra were recorded at room temperature on a Varian spectrometer at 300 and 100 MHz operating frequency using tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a VG-Micromass 7070H spectrometer operating at 70 eV.

General procedure for the synthesis of (6-trifluoromethyl-pyrimidin-4-yloxy)acetic acid ethyl ester (2): An amount of 6-trifluoromethyl-pyrimidine-4-ol (**1**) (0.01 mol) and ethyl chloroacetate (0.01 mol) was dissolved in 20 mL of acetone by adding K₂CO₃ (0.01 mol). The reaction mixture was refluxed for 15 h on a water bath with constant stirring. After completion of the reaction (monitored by the TLC), the mixture was cooled, poured onto a mixture of ice and water. The formed precipitate was filtered, washed with distilled water. The resulting solid was recrystallized from ethanol to give pure (6-trifluoromethyl-pyrimidin-4-yloxy)acetic acid ethyl ester (**2**). Yield: 72 %, m.p.: 115-117 °C, IR (KBr, ν_{max} , cm⁻¹): 3037 (C-H, pyrimidine), 2968 (C-H, CH₃), 1742 (C=O), 1590 (C=C, pyrimidine), 1476 (C=N), 1221 (C-O). ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm: 7.78 (s, 1H, CH, pyrimidine), 7.55 (s, 1H, CH, pyrimidine), 4.14 (q, 2H, *J* = 5.4 Hz, CH₂), 3.46 (s, 2H, CH₂CO), 1.26 (t, 3H, *J* = 5.4 Hz, CH₃). ¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm: δ 171.4, 136.5, 131.7, 122.8,

121.7, 73.1, 68.8, 59.5, 13.6. MS: m/z 250 (M^+). Anal. calcd. (%) for $C_9H_9N_2O_3F_3$: C-43.21, H-3.63, F-22.78, N-11.20, O-19.19. Found (%): C-42.89, H-3.62, F-22.39, N-11.09, O-18.98.

General procedure for the synthesis of (6-trifluoromethyl-pyrimidin-4-yloxy)acetic acid hydrazide (3): To a solution of (6-trifluoromethyl-pyrimidin-4-yloxy)acetic acid ethyl ester (**2**) (0.01 mol) and ethyl alcohol (15 mL) was added hydrazine hydrate (0.02 mol). The resulting reaction mixture was refluxed on a water bath for 5 h with uniform stirring. After realization of the reaction (examined by the TLC), solvent was evaporated, cooled the mixture, washed with distilled water, dried and recrystallized from absolute ethanol to offered (6-trifluoromethyl-pyrimidin-4-yloxy)acetic acid hydrazide (**3**) in pure form. Yield: 70 %, m.p.: 129-131 °C, IR (KBr, ν_{max} , cm^{-1}): 3312 (N-H, NH_2), 3212 (N-H, NH), 3028 (C-H, pyrimidine), 2975 (C-H, CH_2), 1728 (C=O), 1582 (C=C, pyrimidine), 1469 (C=N), 1235 (C-O). 1H NMR (300 MHz, DMSO- d_6) δ ppm: 8.09 (s, 1H, NH), 7.75 (s, 1H, CH, pyrimidine), 7.53 (s, 1H, CH, pyrimidine), 3.42 (s, 2H, CH_2CO), 4.46 (s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO- d_6) δ ppm: 165.2, 133.7, 130.9, 124.3, 119.5, 65.3, 55.3. MS: m/z 236 (M^+). Anal. calcd. (%) for $C_7H_7N_4O_3F_3$: C-35.60, H-2.99, F-24.14, N-23.72, O-13.55. Found (%): C-34.88, H-2.98, F-23.87, N-23.25, O-13.45.

General procedure for the synthesis of (6-trifluoromethyl-pyrimidin-4-yloxy)acetic acid benzylidene-hydrazides (4a-f): To the alcoholic solution of (6-trifluoromethyl-pyrimidin-4-yloxy)acetic acid hydrazide (**3**) (0.01 mol in 20 mL ethanol) was added a suspension of aromatic aldehyde (0.01 mol) and 1 mL of glacial acetic acid. The reaction mixture was stirred steadily while on reflux for 5-7 h. After achievement of the (scanned by the TLC), solvent was removed under reduced pressure to obtain a quantitative precipitation and it is recrystallized from ethanol to acquire (6-trifluoromethyl-pyrimidin-4-yloxy)acetic acid benzylidene-hydrazides (**4a-f**) in pure form.

(6-Trifluoromethyl-pyrimidin-4-yloxy)acetic acid benzylidene-hydrazide (4a): Yield: 67 %, m.p.: 122-124 °C, IR (KBr, ν_{max} , cm^{-1}): 3285 (N-H), 3047 (C-H, Ar), 2981 (C-H, CH_2), 1678 (C=O), 1581 (C=C, Ar), 1442 (C=N), 1232 (C-O). 1H NMR (300 MHz, DMSO- d_6) δ ppm: 8.12 (s, 1H, NH), 7.69 (s, 1H, CH, pyrimidine), 7.62-7.35 (m, 5H, Ar-H), 7.55 (s, 1H, =CH), 7.49 (s, 1H, CH, pyrimidine), 3.47 (s, 2H, CH_2CO). ^{13}C NMR (100 MHz, DMSO- d_6) δ ppm: 163.7, 142.6, 137.5, 134.9, 132.1, 131.0, 129.7, 126.1, 125.2, 120.2, 67.8, 57.2. MS: m/z 324 (M^+). Anal. calcd. (%) for $C_{14}H_{11}N_4O_2F_3$: C-51.86, H-3.42, F-17.58, N-17.28, O-9.87. Found (%): C-50.39, H-3.41, F-17.39, N-17.17, O-9.86.

(6-Trifluoromethyl-pyrimidin-4-yloxy)acetic acid (4-methyl-benzylidene)hydrazide (4b): Yield: 71 %, m.p.: 136-138 °C, IR (KBr, ν_{max} , cm^{-1}): 3265 (N-H), 3055 (C-H, Ar), 2976 (C-H, CH_2), 1672 (C=O), 1588 (C=C, Ar), 1452 (C=N), 1228 (C-O). 1H NMR (300 MHz, DMSO- d_6) δ ppm: 8.23 (s, 1H, NH), 7.75 (s, 1H, CH, pyrimidine), 7.58 (d, 2H, J = 7.4 Hz, Ar-H), 7.51 (s, 1H, =CH), 7.45 (s, 1H, CH, pyrimidine), 7.32 (d, 2H, J = 7.4 Hz, Ar-H), 3.51 (s, 2H, CH_2CO), 3.26 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO- d_6) δ ppm: 165.9,

144.3, 135.1, 132.7, 130.8, 129.7, 128.7, 125.6, 124.8, 122.0, 69.7, 58.1, 22.6. MS: m/z 338 (M^+). Anal. calcd. (%) for $C_{15}H_{13}N_4O_2F_3$: C-53.26, H-3.87, F-16.85, N-16.56, O-9.46. Found (%): C-52.85, H-3.86, F-16.75, N-16.40, O-9.45.

(6-Trifluoromethyl-pyrimidin-4-yloxy)acetic acid (4-methoxy-benzylidene)hydrazide (4c): Yield: 68 %, m.p.: 120-122 °C, IR (KBr, ν_{max} , cm^{-1}): 3252 (N-H), 3042 (C-H, Ar), 2977 (C-H, CH_2), 1670 (C=O), 1582 (C=C, Ar), 1448 (C=N), 1232 (C-O). 1H NMR (300 MHz, DMSO- d_6) δ ppm: 8.18 (s, 1H, NH), 7.79 (s, 1H, CH, pyrimidine), 7.61 (d, 2H, J = 7.4 Hz, Ar-H), 7.53 (s, 1H, =CH), 7.42 (s, 1H, CH, pyrimidine), 7.39 (d, 2H, J = 7.4 Hz, Ar-H), 3.55 (s, 2H, CH_2CO), 3.29 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO- d_6) δ ppm: 162.3, 141.8, 134.3, 131.0, 129.6, 127.2, 126.7, 124.7, 122.0, 121.8, 72.3, 56.7, 45.2. MS: m/z 354 (M^+). Anal. calcd. (%) for $C_{15}H_{13}N_4O_3F_3$: C-50.85, H-3.70, F-16.09, N-15.81, O-13.55. Found (%): C-49.97, H-3.69, F-15.89, N-15.61, O-13.39.

(6-Trifluoromethyl-pyrimidin-4-yloxy)acetic acid (2-chloro-benzylidene)hydrazide (4d): Yield: 75 %, m.p.: 141-143 °C, IR (KBr, ν_{max} , cm^{-1}): 3262 (N-H), 3051 (C-H, Ar), 2981 (C-H, CH_2), 1668 (C=O), 1586 (C=C, Ar), 1456 (C=N), 1242 (C-O). 1H NMR (300 MHz, DMSO- d_6) δ ppm: 8.21 (s, 1H, NH), 7.73 (s, 1H, CH, pyrimidine), 7.66-7.45 (m, 4H, Ar-H), 7.58 (s, 1H, =CH), 7.38 (s, 1H, CH, pyrimidine), 3.61 (s, 2H, CH_2CO). ^{13}C NMR (100 MHz, DMSO- d_6) δ ppm: 164.8, 145.7, 136.5, 133.7, 130.5, 128.5, 126.1, 125.7, 123.8, 121.8, 120.7, 70.8, 57.6, 47.9. MS: m/z 358 (M^+). Anal. calcd. (%) for $C_{14}H_{10}N_4O_2ClF_3$: C-46.88, H-2.81, Cl-9.88, F-15.89, N-15.62, O-8.92. Found (%): C-46.25, H-2.80, Cl-9.87, F-15.65, N-15.29, O-8.90.

(6-Trifluoromethyl-pyrimidin-4-yloxy)acetic acid (2-bromo-benzylidene)hydrazide (4e): Yield: 70 %, m.p.: 112-114 °C, IR (KBr, ν_{max} , cm^{-1}): 3271 (N-H), 3062 (C-H, Ar), 2988 (C-H, CH_2), 1673 (C=O), 1592 (C=C, Ar), 1461 (C=N), 1248 (C-O). 1H NMR (300 MHz, DMSO- d_6) δ ppm: 8.16 (s, 1H, NH), 7.81 (s, 1H, CH, pyrimidine), 7.58-7.32 (m, 4H, Ar-H), 7.48 (s, 1H, =CH), 7.41 (s, 1H, CH, pyrimidine), 3.65 (s, 2H, CH_2CO). ^{13}C NMR (100 MHz, DMSO- d_6) δ ppm: 160.3, 141.8, 134.8, 135.1, 132.9, 127.5, 124.9, 123.0, 121.2, 120.9, 119.7, 76.2, 54.8, 49.2. MS: m/z 402 (M^+). Anal. calcd. (%) for $C_{14}H_{10}N_4O_2BrF_3$: C-41.71, H-2.50, Br-19.82, F-14.14, N-13.90, O-7.94. Found (%): C-41.12, H-2.49, Br-19.73, F-14.02, N-13.75, O-7.92.

(6-Trifluoromethyl-pyrimidin-4-yloxy)acetic acid (2-nitro-benzylidene)hydrazide (4f): Yield: 73 %, m.p.: 130-132 °C, IR (KBr, ν_{max} , cm^{-1}): 3262 (N-H), 3070 (C-H, Ar), 2972 (C-H, CH_2), 1669 (C=O), 1582 (C=C, Ar), 1542 (N=O), 1472 (C=N), 1252 (C-O). 1H NMR (300 MHz, DMSO- d_6) δ ppm: 8.20 (s, 1H, NH), 7.72 (s, 1H, CH, pyrimidine), 7.60-7.38 (m, 4H, Ar-H), 7.46 (s, 1H, =CH), 7.39 (s, 1H, CH, pyrimidine), 3.70 (s, 2H, CH_2CO). ^{13}C NMR (100 MHz, DMSO- d_6) δ ppm: 164.2, 143.7, 136.8, 134.7, 133.0, 129.1, 126.7, 125.0, 123.7, 121.8, 118.6, 78.3, 55.2, 48.2. MS: m/z 369 (M^+). Anal. calcd. (%) for $C_{14}H_{10}N_5O_4F_3$: C-45.54, H-2.73, F-15.44, N-18.97, O-17.33. Found (%): C-45.23, H-2.72, F-15.23, N-18.68, O-17.19.

General procedure for the synthesis of [4-oxo-2-phenyl-3-[2-(6-trifluoromethyl-pyrimidin-4-yloxy)acetyl-amino]-

thiazolidin-5-yl}acetic acids (5a-f): To the solution of (6-trifluoromethyl-pyrimidin-4-yloxy)acetic acid benzylidenehydrazides (**4a-f**) (0.01 mol) and mercaptosuccinic acid (0.01 mol) in THF (15 mL) was added a pinch of anhydrous ZnCl_2 . The reaction mixture was then refluxed on water bath with sustained stirring for 10-12 h. After fulfilment of the reaction (observed by the TLC), the mixture was cooled to obtained crude precipitate and it was recrystallized from absolute ethanol to achieve {4-oxo-2-phenyl-3-[2-(6-trifluoromethyl-pyrimidin-4-yloxy)acetylamino]thiazolidin-5-yl}-acetic acids (**5a-f**) in pure form.

{4-Oxo-2-phenyl-3-[2-(6-trifluoromethyl-pyrimidin-4-yloxy)acetylamino]thiazolidin-5-yl}acetic acid (5a): Yield: 68 %, m.p.: 116-118 °C, IR (KBr, ν_{max} , cm^{-1}): 3326 (N-H), 3058 (C-H, Ar), 2969 (C-H, CH_2), 2855 (O-H, COOH), 1752 (C=O, COOH), 1658 (C=O, CONH_2), 1595 (C=C, Ar), 1466 (C=N), 1265 (C-O). ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ ppm: 10.42 (s, 1H, COOH), 8.55 (s, 1H, NH), 7.68 (s, 1H, CH, pyrimidine), 7.55-7.35 (m, 5H, Ar-H), 7.42 (s, 1H, CH, pyrimidine), 4.75 (s, 2H, CH_2CO), 4.21 (s, 1H, CH), 3.95 (t, 1H, $J = 5.4$ Hz, CH), 3.30 (q, 2H, $J = 5.4$ Hz, CH_2). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ ppm: 175.6, 171.2, 170.3, 169.7, 165.7, 156.5, 137.5, 127.2, 126.2, 125.1, 118.7, 114.3, 77.8, 56.5, 49.7, 36.8. MS: m/z 456 (M^+). Anal. calcd. (%) for $\text{C}_{18}\text{H}_{15}\text{N}_4\text{O}_5\text{SF}_3$: C-47.37, H-3.31, F-12.49, N-12.28, O-17.53, S-7.03. Found (%): C-46.88, H-3.30, F-12.37, N-12.18, O-17.32, S-7.00.

4-Oxo-2-*p*-tolyl-3-[2-(6-trifluoromethyl-pyrimidin-4-yloxy)acetylamino]thiazolidin-5-yl}acetic acid (5b): Yield: 71 %, m.p.: 125-127 °C, IR (KBr, ν_{max} , cm^{-1}): 3332 (N-H), 3065 (C-H, Ar), 2971 (C-H, CH_2), 2848 (O-H, COOH), 1758 (C=O, COOH), 1662 (C=O, CONH_2), 1605 (C=C, Ar), 1473 (C=N), 1255 (C-O). ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ ppm: 10.45 (s, 1H, COOH), 8.52 (s, 1H, NH), 7.71 (s, 1H, CH, pyrimidine), 7.51 (d, 2H, $J = 7.1$ Hz, Ar-H), 7.42 (d, 2H, $J = 7.1$ Hz, Ar-H), 7.48 (s, 1H, CH, pyrimidine), 4.81 (s, 2H, CH_2CO), 4.28 (s, 1H, CH), 3.91 (t, 1H, $J = 5.6$ Hz, CH), 3.37 (q, 2H, $J = 5.6$ Hz, CH_2), 3.35 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ ppm: 173.8, 170.5, 168.7, 167.6, 166.1, 157.9, 139.1, 129.2, 127.5, 126.2, 120.2, 116.1, 79.4, 58.2, 50.3, 37.2, 28.6. MS: m/z 470 (M^+). Anal. calcd. (%) for $\text{C}_{19}\text{H}_{17}\text{N}_4\text{O}_5\text{SF}_3$: C-48.51, H-3.64, F-12.12, N-11.91, O-17.01, S-6.82. Found (%): C-47.98, H-3.63, F-12.11, N-11.90, O-16.981, S-6.81.

{2-(4-Methoxy-phenyl)-4-oxo-3-[2-(6-trifluoromethyl-pyrimidin-4-yloxy)acetylamino]thiazolidin-5-yl}acetic acid (5c): Yield: 67 %, m.p.: 137-139 °C, IR (KBr, ν_{max} , cm^{-1}): 3341 (N-H), 3071 (C-H, Ar), 2967 (C-H, CH_2), 2859 (O-H, COOH), 1765 (C=O, COOH), 1667 (C=O, CONH_2), 1612 (C=C, Ar), 1481 (C=N), 1248 (C-O). ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ ppm: 10.49 (s, 1H, COOH), 8.57 (s, 1H, NH), 7.76 (s, 1H, CH, pyrimidine), 7.49 (d, 2H, $J = 7.5$ Hz, Ar-H), 7.46 (d, 2H, $J = 7.5$ Hz, Ar-H), 7.43 (s, 1H, CH, pyrimidine), 4.88 (s, 2H, CH_2CO), 4.32 (s, 1H, CH), 3.95 (t, 1H, $J = 5.7$ Hz, CH), 3.41 (q, 2H, $J = 5.7$ Hz, CH_2), 3.82 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ ppm: 175.2, 172.7, 169.1, 168.2, 165.6, 155.7, 136.1, 130.2, 128.5, 125.7, 122.3, 118.1, 81.7, 61.5, 52.7, 39.1, 35.7. MS: m/z 486 (M^+). Anal. calcd. (%) for $\text{C}_{19}\text{H}_{17}\text{N}_4\text{O}_6\text{SF}_3$: C-46.91, H-3.52, F-11.72, N-11.52, O-19.74,

S-6.59. Found (%): C-46.12, H-3.51, F-11.70, N-11.50, O-19.68, S-6.58.

{2-(2-Chloro-phenyl)-4-oxo-3-[2-(6-trifluoromethyl-pyrimidin-4-yloxy)acetylamino]thiazolidin-5-yl}acetic acid (5d): Yield: 73 %, m.p.: 110-112 °C, IR (KBr, ν_{max} , cm^{-1}): 3329 (N-H), 3078 (C-H, Ar), 2959 (C-H, CH_2), 2850 (O-H, COOH), 1766 (C=O, COOH), 1671 (C=O, CONH_2), 1623 (C=C, Ar), 1475 (C=N), 1252 (C-O). ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ ppm: 10.41 (s, 1H, COOH), 8.62 (s, 1H, NH), 7.73 (s, 1H, CH, pyrimidine), 7.51-7.41 (m, 4H, Ar-H), 7.36 (s, 1H, CH, pyrimidine), 4.79 (s, 2H, CH_2CO), 4.35 (s, 1H, CH), 3.89 (t, 1H, $J = 5.3$ Hz, CH), 3.43 (q, 2H, $J = 5.3$ Hz, CH_2). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ ppm: 174.6, 171.8, 168.2, 167.3, 164.7, 156.3, 137.8, 132.1, 129.7, 127.3, 125.3, 124.5, 122.8, 120.1, 82.3, 63.2, 53.1, 41.8. MS: m/z 490 (M^+). Anal. calcd. (%) for $\text{C}_{18}\text{H}_{14}\text{N}_4\text{O}_5\text{SClF}_3$: C-44.05, H-2.87, Cl-7.22, F-11.61, N-11.41, O-16.30, S-6.53. Found (%): C-43.79, H-2.86, Cl-7.21, F-11.58, N-11.39, O-16.28, S-6.52.

{2-(2-Bromo-phenyl)-4-oxo-3-[2-(6-trifluoromethyl-pyrimidin-4-yloxy)acetylamino]thiazolidin-5-yl}acetic acid (5e): Yield: 75 %, m.p.: 128-130 °C, IR (KBr, ν_{max} , cm^{-1}): 3337 (N-H), 3072 (C-H, Ar), 2961 (C-H, CH_2), 2862 (O-H, COOH), 1769 (C=O, COOH), 1675 (C=O, CONH_2), 1635 (C=C, Ar), 1471 (C=N), 1258 (C-O). ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ ppm: 10.38 (s, 1H, COOH), 8.59 (s, 1H, NH), 7.69 (s, 1H, CH, pyrimidine), 7.55-7.39 (m, 4H, Ar-H), 7.32 (s, 1H, CH, pyrimidine), 4.72 (s, 2H, CH_2CO), 4.41 (s, 1H, CH), 3.82 (t, 1H, $J = 5.6$ Hz, CH), 3.48 (q, 2H, $J = 5.6$ Hz, CH_2). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ ppm: 176.2, 173.2, 170.2, 167.3, 165.3, 158.6, 137.1, 134.3, 131.0, 128.2, 126.1, 125.2, 123.7, 122.8, 85.1, 66.1, 55.7, 43.7. MS: m/z 534 (M^+). Anal. calcd. (%) for $\text{C}_{18}\text{H}_{14}\text{N}_4\text{O}_5\text{SBrF}_3$: C-40.39, H-2.64, Br-14.93, F-10.65, N-10.47, O-14.94, S-5.99. Found (%): C-39.98, H-2.63, Br-14.87, F-10.63, N-10.45, O-14.90, S-5.98.

{2-(2-Nitro-phenyl)-4-oxo-3-[2-(6-trifluoromethyl-pyrimidin-4-yloxy)acetylamino]thiazolidin-5-yl}acetic acid (5f): Yield: 68 %, m.p.: 130-132 °C, IR (KBr, ν_{max} , cm^{-1}): 3329 (N-H), 3064 (C-H, Ar), 2972 (C-H, CH_2), 2867 (O-H, COOH), 1762 (C=O, COOH), 1670 (C=O, CONH_2), 1642 (C=C, Ar), 1530 (N=O), 1462 (C=N), 1238 (C-O). ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ ppm: 10.28 (s, 1H, COOH), 8.52 (s, 1H, NH), 7.65 (s, 1H, CH, pyrimidine), 7.51-7.36 (m, 4H, Ar-H), 7.35 (s, 1H, CH, pyrimidine), 4.70 (s, 2H, CH_2CO), 4.37 (s, 1H, CH), 3.78 (t, 1H, $J = 5.2$ Hz, CH), 3.45 (q, 2H, $J = 5.2$ Hz, CH_2). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ ppm: 174.8, 171.8, 168.2, 165.3, 163.7, 157.2, 138.7, 136.3, 133.2, 130.2, 128.7, 126.3, 124.2, 123.2, 82.0, 63.8, 52.1, 45.3. MS: m/z 501 (M^+). Anal. calcd. (%) for $\text{C}_{18}\text{H}_{14}\text{N}_5\text{O}_7\text{SF}_3$: C-43.12, H-2.81, F-11.37, N-13.97, O-22.34, S-6.40. Found (%): C-42.87, H-2.80, F-11.31, N-13.88, O-22.02, S-6.39.

RESULTS AND DISCUSSION

In the present study, we have decided to follow a simple and straight forward four-step method to synthesize a novel series of {4-oxo-2-phenyl-3-[2-(6-trifluoromethyl-pyrimidin-4-yloxy)acetylamino]thiazolidin-5-yl}acetic acids (**5a-f**). The synthetic strategies adopted to obtain the target compounds are depicted in **Schemes I-IV**. The spectral and elemental analysis

data of all the synthesized compounds were in accordance with the proposed structures. Thus, the raw material, 6-trifluoromethyl-pyrimidine-4-ol (**1**) through the substitution with ethyl chloroacetate and potassium carbonate in acetone under reflux on uniform stirring for 15 h has been converted into the initial intermediate, (6-trifluoromethyl-pyrimidine-4-yloxy)acetic acid ethyl ester (**2**) (**Scheme-I**). The evidence for the formation of compound **2** can be obtained by different spectroscopic methods. The IR and ^1H NMR spectra of compound **2** showed no signal representing the OH group. In the IR spectrum, the bands at 2968 and 1742 cm^{-1} were obtained due to CH_3 and CO stretching as expected for the formation of compound **2**. The signals derived from ethyl acetate moiety were observed in the corresponding region in the ^1H and ^{13}C NMR spectra. Furthermore, compound **2** gave relatively stable M^+ ion peak at 250.

Further, (6-trifluoromethyl-pyrimidine-4-yloxy)acetic acid hydrazide (**3**) has been prepared from the substitution of compound **2** with hydrazine hydrate in ethanol at reflux temperature on constant stirring for 5 h (**Scheme-II**). The chemical structure of intermediate **3** was established from spectroscopic (IR, ^1H and ^{13}C NMR, MS) and elemental analysis data. The disappearance of stretching band of $\text{CH}_2\text{-CH}_3$ group from the compound **2** and the detection of a broad and a sharp bands from NH_2 and NH stretching vibrations at 3312 cm^{-1} and at 3212 cm^{-1} is evidence for the formation of compound **3**. The ^1H NMR spectrum of compound **3** displayed no signals belonging to the $\text{CH}_2\text{-CH}_3$ group. On the other hand, the NH and NH_2 groups were observed at δ 8.09 ppm and 4.46 ppm. Remaining all protons was seen in the ^1H NMR spectrum with the expected chemical shifts and integral values, which indicated the formation of compound **3**.

In the next step, to prepare the final intermediate, (6-trifluoromethyl-pyrimidine-4-yloxy)acetic acid benzylidenehydrazides (**4a-f**), the condensation was carried out between compound **3** and various aromatic aldehydes in presence of acetic acid at reflux temperature with steady stirring for 5-7 h (**Scheme-III**). The spectral data of this series of compounds **4a-f** was justified the expected chemical structures. The characteristic absorption broad band of NH_2 group of compound **3** around 3300 cm^{-1} was completely disappeared in the IR

spectrum of compound **4a-f**. Moreover, the additional signal due to the CH=N group was observed around 7.50 ppm, while the NH_2 (D_2O exchangeable) signals was disappeared in the ^1H NMR spectrum. The mass spectrum of compound **4a-f** showed M^+ peak in agreement with their molecular weight.

Finally, our strategy for the preparation of target compounds, {4-oxo-2-phenyl-3-[2-(6-trifluoromethyl-pyrimidine-4-yloxy)-acetylamino]thiazolidin-5-yl}-acetic acids (**5a-f**) in quantitative yields (67-75 %) from (6-trifluoromethyl-pyrimidine-4-yloxy)acetic acid benzylidenehydrazides (**4a-f**) on cyclization with mercaptosuccinic acid and zinc chloride in reflux THF with constant stirring for 10-12 h (**Scheme-IV**). Structural assignment of compounds **5a-f** was achieved based on the different spectral data. IR spectra of these compounds showed additional bands for COOH and CO of lactam in addition to CH_2 and CH groups at expected absorption values. In the ^1H NMR spectra, signals were found as singlet (COOH and CH), triplet (CH_2) and doublet (CH) around at anticipated δ -chemical shifts to confirm chemical structures. Further, the synthesized title compounds were used to screen for their antibacterial activity.

Antibacterial activity: The newly synthesized target compounds, {4-oxo-2-phenyl-3-[2-(6-trifluoromethyl-pyrimidine-4-yloxy)acetylamino]thiazolidin-5-yl}acetic acids (**5a-f**) were used to evaluate their antibacterial activity towards four representative gram negative bacteria such as *Escherichia coli*, *Klebsiella pneumonia*, *Shigella dysenteriae* and *Shigella flexneri* in terms of zone of inhibition in mm by applying cup plate method [17] and streptomycin as standard drug. As per the screening results reported in Fig. 1, all tested compounds exhibited moderate to good antibacterial activity with a degree of variation. Among the series of compounds **5a-f**, product **5c** displayed highest activity against all the tested bacterial strains. Compounds **5b** disclosed higher activity averse to *E. coli* and

Fig. 1. Antibacterial activity of compounds **5a-f** (Note: < 17 mm, inactive; 18-20 mm, moderately active; 21-26 mm, highly active)

S. flexneri, product **5d** performed good activity towards *E. coli*, *K. pneumonia* and *S. dysenteriae*. Remaining compounds showed moderate activity against all organisms.

Conclusion

In conclusion, we have developed a conventional access to prepare a novel series of pyrimidine based thiazolidines (**5a-f**) in good yields and the title compounds were screened for their antibacterial activity.

REFERENCES

- J.O. Ban, D.H. Kwak, J.H. Oh, E.J. Park, M.C. Cho, H.S. Song, M.J. Song, S.B. Han, D.C. Moon, K.W. Kang and J.T. Hong, *Chem. Biol. Interact.*, **188**, 75 (2010); <https://doi.org/10.1016/j.cbi.2010.06.001>.
- F.E. Onen-Bayram, I. Durmaz, D. Scherman, J. Herscovici and R.A. Cetin-Atalay, *Bioorg. Med. Chem.*, **20**, 5094 (2012); <https://doi.org/10.1016/j.bmc.2012.07.016>.
- C.D. Barros, A.A. Amato, T.B. Oliveira, K.B.R. Iannini, A.L. Silva, T.G. Silva, E.S. Leite, M.Z. Hernandez, M.C.A. Lima and S.L. Galdino, *Bioorg. Med. Chem.*, **18**, 3805 (2010); <https://doi.org/10.1016/j.bmc.2010.04.045>.
- N.C. Desai, K.M. Rajpara and V.V. Joshi, *J. Fluor. Chem.*, **145**, 102 (2013); <https://doi.org/10.1016/j.jfluchem.2012.10.012>.
- M. D'Ascenzio, B. Bizzarri, C. De Monte, S. Carradori, A. Bolasco, D. Secci, D. Rivanera, N. Faulhaber, C. Bordon and L. Jones-Brando, *Eur. J. Med. Chem.*, **86**, 17 (2014); <https://doi.org/10.1016/j.ejmech.2014.08.046>.
- A.K. Soares e Silva, D. de Oliveira Cipriano Torres, S.W. Santos Rocha, F.O. dos Santos Gomes, B. dos Santos Silva, M.A.M. Donato, C. Raposo, A.C.O. Santos, M.C.A. de Lima, S.L. Galdino, I. da Rocha Pitta, J.R.B. de Souza and C.A. Peixoto, *Cardiovasc. Pathol.*, **22**, 81 (2013); <https://doi.org/10.1016/j.carpath.2012.05.006>.
- R.B. Patel, P.S. Desai, K.R. Desai and K.H. Chikhaliya, *Indian J. Chem.*, **45B**, 773 (2006).
- A.E.-G.E. Amr, N.M. Sabry and M.M. Abdulla, *Monatsh. Chem.*, **138**, 699 (2007); <https://doi.org/10.1007/s00706-007-0651-0>.
- N. Fujiwara, T. Nakajima, Y. Ueda, H. Fujita and H. Kawakami, *Bioorg. Med. Chem.*, **16**, 9804 (2008); <https://doi.org/10.1016/j.bmc.2008.09.059>.
- L. Ballell, R.A. Field, G.A.C. Chung and R.J. Young, *Bioorg. Med. Chem. Lett.*, **17**, 1736 (2007); <https://doi.org/10.1016/j.bmcl.2006.12.066>.
- E. Wagner, K. Al-Kadasi, M. Zimecki and W. Sawka-Dobrowolska, *Eur. J. Med. Chem.*, **43**, 2498 (2008); <https://doi.org/10.1016/j.ejmech.2008.01.035>.
- L. Cordeu, E. Cubedo, E. Bandrés, A. Rebollo, X. Sáenz, H. Chozas, M. Victoria Domínguez, M. Echeverría, B. Mendivil, C. Sanmartín, J.A. Palop, M. Font and J. García-Foncillas, *Bioorg. Med. Chem.*, **15**, 1659 (2007); <https://doi.org/10.1016/j.bmc.2006.12.010>.
- K. Gorlitzer, S. Herbig and R.D. Walter, *Pharmazie*, **52**, 670 (1997).
- I.V. Ukrainets, I.A. Tugaibei, N.L. Berezhnyakova, V.N. Kravchenko and A.V. Turov, *Chem. Heterocycl. Comp.*, **44**, 565 (2008); <https://doi.org/10.1007/s10593-008-0076-7>.
- M. Kurono, M. Hayashi, K. Miura, Y. Isogawa and K. Sawai, *Chem. Abstr.*, **109**, 37832t (1988).
- W.L. Wu, D.A. Burnett, M. Domalski, W.J. Greenlee, C. Li, R. Bertorelli, S. Fredduzzi, G. Lozza, A. Veltri and A. Reggiani, *J. Med. Chem.*, **50**, 5550 (2007); <https://doi.org/10.1021/jm070590c>.
- A.I. Barry, *The Antimicrobial Susceptibility Test, Principles and Practices*, ELBS, edn 4, pp. 80-93 (1976).