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Bis(azolyl)sulfonamidoacetamides: Synthesis and Bioassay

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Abstract. Azole derivatives are valuable precursors in pharmacological arena. In fact, oxazole, thiazole and imidazole containing scaffolds display a variety of biological activities such as antitumor, antibacterial, antiviral, antioxidant, anti-inflammatory and antifungal activities. Azoles are also prominent molecules in various biochemical and synthetic transformations. Based on the importance of these heteroaromatics and also our interest to link the heterocycle molecules with a variety of functional groups we have synthesized a new class of bis(azolyl)sulfonamide acetamides from azolylsulfonylamines and azolylchloroacetamides in the presence of DMAP under ultrasonication and studied their antimicrobial activity. The compounds chloro substituted bis(thiazoles) (6c) and chloro substituted imidazolyl thiazoles (7c) displayed excellent antibacterial activity against B. subtilis greater than the standard drug, Chloramphenicol. Whereas 7c also showed excellent antifungal activity on A. niger higher than the standard drug, Ketoconazole.

INTRODUCTION

Amides, sulfonamides and their derivatives gained importance due to their pharmacological activities such as antibacterial, anti-inflammatory, antifungal, anti-diabetic and hypoglycemic. Amongst different heterocycles, azoles are the core units of many bioactive molecules. Oxazoles occur as subunits in numerous natural products such as Leucamide A and its analogs which are used in the treatment of cancer. Besides these, inthomycin-C, oxapregin, pimolineand bengazole A have oxazole motif. Thiazole containing drugs include sulfathiazole, Ritonavir, Abafungin, Bleomycine, Tiazofurin etc., Moreover, Cimetidine, Etomidate, Ketoconazole, Losartan and metronidazole are some of the drugs having imidazole moiety. Azoles are also valuable precursors in various biochemical and synthetic transformations. Based on the importance of these heteroaromatics and also our interest to link the heterocyclic molecules with a variety of functional groups we have synthesized a new class of bis(azolyl)sulfonamido-acetamides from azolylsulfonylamines and azolylchloroacetamides in the presence of DMAP under ultrasonication and studied their antimicrobial activity.

CHEMISTRY

The synthetic intermediates- N-(5-(aminosulfonyl)-4-aryloxazol-2-yl)benzamide (1), N-(5-(aminosulfonyl)-4-aryltiazol-2-yl) benzamide (2) and N-(5-(aminosulfonyl) -4-aryl-1H-imidazol-2-yl)benzamide (3) were prepared as
per the literature procedures. On the other hand, 2-chloro-N-(4-phenylthiazol-2-yl) acetamide (4) was prepared by N-acylation of phenylthiazol-2-amine with ethyl chloroacetate in the presence of dispersed sodium in THF. The reaction of heteroaryl amines with heteroarylmethyl chlorides was carried out in the presence of DMAP in DCM under ultrasonication. Thus, N-(5-(N-(2-oxo-2-(4-phenylthiazol-2-yl)amino)ethyl)sulfamoyl)-4-phenoxyazol-2-yl) benzamide (5), N-(5-(N-(2-oxo-2-(4-phenylthiazol-2-yl)amino)ethyl)sulfamoyl)-4-phenyl-thiazol-2-yl) benzamide (6), and N-(5-(N-(2-oxo-2-(4-phenylthiazol-2-yl)amino)ethyl)sulfamoyl)-4-phenyl-1H-imidazol-2-yl) benzamide (7) were prepared by the reaction of 1/2/3 with 4 in the presence of DMAP (Scheme 1). The structures of all the new molecules were established by IR, NMR, mass and elemental analyses and the data is incorporated in experimental section.

**EXPERIMENTAL SECTION**

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The purity of the compounds was evaluated by TLC (silica gel H, BDH, ethyl acetate/hexane, 1:3). The IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer as KBr pellets and the wave numbers were given in cm⁻¹. The ¹H and ¹³C NMR spectra were recorded in DMSO-d₆ on a Bruker spectrometer operating at 400 and 100 MHz. The chemical shifts are reported in ppm using TMS as an internal standard. The high-resolution mass spectra are recorded on a Perkin-Elmer 240C elemental analyzer. The progress of the reaction was monitored by TLC using silica gel plates (silica gel 60 F₂₅₄ 0.25 mm), and components were visualized by observation under UV light (254 and 365 nm).

**General procedure for the synthesis of N-(5-(N-(2-oxo-2-(4-phenylthiazol-2-yl)amino)ethyl)sulfamoyl)-4-phenyl azol-2-yl)benzamide (5/6/7)**

N-(4-Phenyl-5-sulfamoyloxazol / thiazol / 1H-imidazol-2-yl) benzamide (1/2/3) (1 mmol) and 2-chloro-N-(4-phenylthiazol-2-yl)acetamide (4) (1 mmol) were dissolved in dichloromethane (15 mL). To this a solution of DMAP (1 mmol) and triethylamine (1 mmol) was added drop wise and sonicated at a frequency of 46 kHz at room temperature for 35–45 min. After the reaction was completed, the contents were poured onto crushed ice and solid obtained was filtered, dried, and recrystallized from ethanol.

N-(5-(N-(2-oxo-2-(4-phenylthiazol-2-yl)amino)ethyl)sulfamoyl)-4-phenylazol-2-yl)benzamide (5a). Yield 66%; mp 139-141 °C. IR (KBr): 3384 (NH), 1688 (C=O), 1639 (C=C), 1579 (C=N), 1340-1135 (SO₂) (cm⁻¹); ¹H NMR (400 MHz, DMSO-d₆): δ 3.48 (s, 2H, CH₂), 7.46-7.72 (m, 16H, Ar-H, C₅'-H), 7.81 (bs, 1H, SO₂NH), 11.71 (bs, 1H, CH₂CONH), 12.15 (bs, 1H, CONH) ppm; ¹³C NMR (100 MHz, DMSO-d₆): δ 123.7 (CH₂-C), 121.9 (CONH), 165.9 (CH₂-C), 161.0 (CH₂CONH), 104.6, 109.3, 115.8, 117.1, 120.0, 121.9, 123.7, 125.1, 127.8, 129.3, 132.1, 134.8, 135.9, 138.5, 140.3, 141.2, 143.6, 145.3 (aromatic carbons, C₂, C₄, C₅, C₆, C₇, C₈, and C₉) ppm. HRMS (m/z): 583.6057 [M+Na]⁺; Anal. Calcd. for C₂₈H₂₃N₅O₅S₂: C, 58.63; H, 4.04; N, 12.21; Found: C, 58.70; H, 4.01, N, 12.25 %.

N-(5-(N-(2-oxo-2-(4-phenylthiazol-2-yl)amino)ethyl)sulfamoyl)-4-(p-tolyl)oxazol-2-yl)benzamide (5b). Yield 61%; mp 135-137 °C. IR (KBr): 3376 (NH), 1675 (C=O), 1632 (C=C), 1566 (C=N), 1334-1139 (SO₂) (cm⁻¹); ¹H NMR (400 MHz, DMSO-d₆): δ 2.32 (s, 3H, CH₃), 3.41 (s, 2H, CH₂), 7.40-7.69 (m, 15H, Ar-H, C₅'-H), 7.75 (br. s, 1H, SO₂NH), 11.66 (br. s, 1H, CH₂CONH), 12.05 (br. s, 1H, CONH) ppm; ¹³C NMR (100 MHz, DMSO-d₆): δ 20.6 (CH₃), 41.5 (CH₂-C), 161.9 (CH₂CONH), 103.3, 108.5, 114.7, 117.8, 129.3, 132.1, 134.8, 135.9, 138.5, 140.3, 141.2, 143.3, 145.3 (aromatic carbons, C₂, C₄, C₅, C₆, C₇, C₈, and C₉) ppm. HRMS (m/z): 596.6312 [M+Na]⁺; Anal. Calcd. for C₂₉H₂₃N₅O₅S₂: C, 58.63; H, 4.04; N, 12.21; Found: C, 58.70; H, 4.01, N, 12.25 %.

**Scheme 1.** Synthesis of N-(5-(N-(2-oxo-2-(4-phenylthiazol-2-yl)amino)ethyl)sulfamoyl)-4-phenylazol-2-yl)benzamide
N-(5-(2-Oxo-2-(4-phenylthiazol-2-yl)amino)ethyl)sulfamoyl) -4-(4-chlorophenyl)-2-oxazolyl)benzamide (6a). Yield 69%; mp 131-133 °C. IR (KBr): 3373 (NH), 1676 (C=O), 1640 (C=C), 1579 (C=N), 1343-1129 (SO2) (cm-1); 1H NMR (400 MHz, DMSO-d6): δ 3.40 (s, 2H, CH2), 7.33-7.62 (m, 15H, Ar-H, C5'-H), 7.70 (br. s, 1H, SO2NH), 11.81 (br. s, 1H, CH2CONH), 12.09 (br. s, 1H, CONH) ppm; 13C NMR (100 MHz, DMSO-d6): δ 43.9 (CH2-C), 164.0 (CONH), 167.9 (CH2CONH), 105.9, 108.0, 110.5, 113.7, 115.5, 117.2, 120.4, 122.9, 124.1, 127.0, 130.5, 131.7, 134.0, 135.8, 138.7, 142.3, 146.5 (aromatic carbons, C2, C4, C5, C2', C4', and C5') ppm. HRMS (m/z): 617.0459 [M+Na]+; Anal. Calcd. for C27H22N6O4S2: C, 58.15; H, 3.30, N, 11.48; Found: C, 58.10; H, 3.36, N, 11.43 %.

N-(5-(2-Oxo-2-(4-phenylthiazol-2-yl)amino)ethyl)sulfamoyl) -4-(4-chlorophenyl)-1H-imidazol-2-ylbenzamide (7a). Yield 63%; mp 145-147 °C. IR (KBr): 3379 (NH), 1681 (C=O), 1635 (C=O), 1572 (C=N), 1338-1132 (SO2) (cm-1); 1H NMR (400 MHz, DMSO-d6): δ 3.45 (s, 2H, CH2), 7.28-7.64 (m, 16H, Ar-H, C5'-H), 7.73 (br. s, 1H, SO2NH), 11.58 (br. s, 1H, CH2CONH), 12.03 (br. s, 1H, CONH), 12.41 (br. s, 1H, Imidazole NH) ppm; 13C NMR (100 MHz, DMSO-d6): δ 43.5 (CH2-C), 163.2 (CONH), 166.1 (CH2CONH), 104.3, 105.1, 112.6, 113.5, 115.7, 119.3, 123.3, 123.5, 126.0, 127.8, 130.0, 132.1, 134.2, 135.8, 139.1, 140.5, 142.3, (aromatic carbons, C2, C4, C5, C2', C4', and C5') ppm. HRMS (m/z): 581.6208 [M+Na]+; Anal. Calcd. for C28H22N6O4S3: C, 58.05; H, 3.97, N, 15.04; Found: C, 58.11; H, 4.04, N, 15.10 %.

N-(5-(2-Oxo-2-(4-phenylthiazol-2-yl)amino)ethyl)sulfamoyl)-4-(4-chlorophenyl)-2-thiazolyl)benzamide (6b). Yield 69%; mp 131-133 °C. IR (KBr): 3370 (NH), 1673 (C=O), 1625 (C=O), 1558 (C=N), 1335-1129 (SO2) (cm-1); 1H NMR (400 MHz, DMSO-d6): δ 3.40 (s, 2H, CH2), 7.33-7.62 (m, 15H, Ar-H, C5'-H), 7.70 (br. s, 1H, SO2NH), 11.81 (br. s, 1H, CH2CONH), 12.09 (br. s, 1H, CONH) ppm; 13C NMR (100 MHz, DMSO-d6): δ 43.9 (CH2-C), 164.0 (CONH), 167.9 (CH2CONH), 105.9, 108.0, 110.5, 113.7, 115.5, 117.2, 120.4, 122.9, 124.1, 127.0, 130.5, 131.7, 134.0, 135.8, 138.7, 142.3, 146.5 (aromatic carbons, C2, C4, C5, C2', C4', and C5') ppm. HRMS (m/z): 617.0459 [M+Na]+; Anal. Calcd. for C27H22N6O4S2: C, 58.15; H, 3.30, N, 11.48; Found: C, 58.10; H, 3.36, N, 11.43 %.

N-(5-(2-Oxo-2-(4-phenylthiazol-2-yl)amino)ethyl)sulfamoyl) -4-(4-chlorophenyl)-1H-imidazol-2-ylbenzamide (7b). Yield 69%; mp 131-133 °C. IR (KBr): 3373 (NH), 1676 (C=O), 1631 (C=O), 1568 (C=N), 1335-1129 (SO2) (cm-1); 1H NMR (400 MHz, DMSO-d6): δ 3.57 (s, 2H, CH2), 7.38-7.67 (m, 15H, Ar-H, C5'-H), 7.85 (br. s, 1H, SO2NH), 11.90 (br. s, 1H, CH2CONH), 12.13 (br. s, 1H, CONH), 12.43 (br. s, 1H, Imidazole NH) ppm; 13C NMR (100 MHz, DMSO-d6): δ 44.5 (CH2-C), 164.9 (CONH), 169.1 (CH2CONH), 105.5, 107.6, 111.3, 113.5, 115.0, 117.7, 120.6, 122.3, 124.6, 127.5, 130.1, 133.3, 134.8, 137.8, 140.2, 142.7, 147.3 (aromatic carbons, C2, C4, C5, C2', C4' and C5') ppm. HRMS (m/z): 595.6483 [M+Na]+; Anal. Calcd. for C28H22N6O4S3: C, 58.73; H, 4.22; N, 14.68; Found: C, 58.80; H, 4.17; N, 14.72 %.

N-(5-(2-Oxo-2-(4-phenylthiazol-2-yl)amino)ethyl)sulfamoyl)-4-(4-chlorophenyl)-2-thiazolyl)benzamide (7c). Yield 73%; mp 146-148 °C. IR (KBr): 3384 (NH), 1687 (C=O), 1643 (C=O), 1581 (C=N), 1344-1141 (SO2) (cm-1); 1H NMR (400 MHz, DMSO-d6): δ 3.57 (s, 2H, CH2), 7.38-7.67 (m, 15H, Ar-H, C5'-H), 7.85 (br. s, 1H, SO2NH), 11.90 (br. s, 1H, CH2CONH), 12.13 (br. s, 1H, CONH), 12.43 (br. s, 1H, Imidazole NH) ppm; 13C NMR (100 MHz, DMSO-d6): δ 44.5 (CH2-C), 164.9 (CONH), 169.1 (CH2CONH), 105.5, 107.6, 111.3, 113.5, 115.0, 117.7, 120.6, 122.3, 124.6, 127.5, 130.1, 133.3, 134.8, 137.8, 140.2, 142.7, 147.3 (aromatic carbons, C2, C4, C5, C2', C4' and C5') ppm. HRMS (m/z): 633.1069 [M+Na]+; Anal. Calcd. for C27H22N6O4S2: C, 54.68; H, 3.57; N, 14.17; Found: C, 54.72; H, 3.55; N, 14.23 %.
ANTIBACTERIAL ACTIVITY

The compounds 5, 6 and 7 were tested for antibacterial activity against Gram +ve bacteria (*Staphylococcus aureus*, *Bacillus subtilis*) and Gram -ve bacteria (*Pseudomonas aeruginosa*, *Klebsiella pneumonia*) at 50, 75 and 100 µg/well. The results revealed that all the compounds except 5b displayed more activity on Gram +ve bacteria than on Gram -ve bacteria. Molecules with bis(thiazole) moiety (6) showed higher activity than those with oxazolyl thiazole (5) and imidazolyl thiazole units (7). Amongst the latter compounds 7 exhibited slightly higher activity than 5. The effect of substituents on aromatic ring indicated that those with electron withdrawing substituent exhibited more activity than the compounds with unsubstituted and electron donating substituents. In fact, 4-chloro substituted compounds showed higher activity than methyl and unsubstituted ones in the respective series. The compounds 6c and 7c displayed excellent antibacterial activity against *B. subtilis* greater than the standard drug, Chloramphenicol.

ANTIFUNGAL ACTIVITY

All the compounds inhibited the spore germination of tested fungi, *Aspergillus niger* and *Penicillium chrysogenum* except 5a and 5b. The tested compounds showed higher activity on *A. niger* than on *P. chrysogenum*. The imidazolyl thiazole derivatives (7) showed greater activity than oxazolyl thiazoles (5) and bis(thiazoles) (6). The compounds 6 showed higher activity than 5. Amongst the compounds with substituents on aromatic ring those with 4-chlorophenyl moiety displayed greater activity in the respective series due to electron withdrawing effect. The compound 7c showed excellent antifungal activity on *A. niger* higher than the standard drug, Ketoconazole.

CONCLUSION

A new class of bis(azolyl)sulfonamidoacetamides were prepared by the reaction of azolylsulfonylamines with azolylchloroacetamides in the presence of DMAP and triethylamine under ultrasonication. The antimicrobial activity of the compounds revealed that N-(4-(4-chlorophenyl)-5-(N-(2-oxo-2-((4-phenylthiazol-2-yl)amino)ethyl)sulfamoyl)thiazol-2-yl)benzamide (6c) and N-(4-(4-chlorophenyl)-5-(N-(2-oxo-2-((4-phenylthiazol-2-yl)amino)ethyl)sulfamoyl)-1H-imidazol-2-yl)benzamide (7c) displayed low MIC against *B. subtilis* equal to standard drug, Chloramphenicol. The compound 7c also showed low MIC against *A. niger* equal to standard drug, Ketoconazole.

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REFERENCES