Synthesis, Spectral Analysis and Antibacterial Activity of Some new N-Substituted Sulfonamide Derivatives of 1,3-Benzodioxol-5-amine


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ABSTRACT
1,3-Benzodioxol-5-amine (1) was used as a precursor to synthesize N-alkyl/aralkyl-N-(1,3-benzodioxol-5-yl)aryl sulfonamide derivatives, 7a-b to 9a-b. The molecule 1 was reacted with ary lsulfonyl chlorides, 2a-b, on stirring in a dilute aqueous sodium carbonate solution to synthesize N-(1,3-benzodioxol-5-yl)aryl sulfonamide, 3a-b. The molecules, 3a-b, were further stirred with alkyl/aralkyl halides, 4-6, in DMF at RT to get the desired final compounds, 7a-b, 8a-b, 9a-b. The synthesized molecules were structurally confirmed by IR, 1H-NMR and EIMS spectral data. The antibacterial activity of these compounds rendered them moderately weak inhibitors relative to ciprofloxacin, the reference standard.

Keywords: 1,3-Benzodioxol-5-amine, antibacterial activity and aryl sulfonyl chlorides.

1. INTRODUCTION
The derivatives of sulfonamides are well known pharmaceutical agents. The stability and tolerance of sulfamoyl functional group rendered it a basic constituent of many pharmaceutical agents employed for the treatment of many infections. The diversity of sulfonamide biological activities in agricultural and pharmaceutical fields gave them much importance in medicinal chemistry. These molecules have a diverse number of biological activities such as antibacterial, carbonic anhydrase inhibition, anti-inflammatory and antitumor activities. There are also many commercially available drugs containing sulfamoyl moiety such as bosentan, amrenavir and sildenafil.

Such type of compounds have been synthesized and evaluated for anti-enzymatic activities by our group and the current project was an attempt to evaluate these molecules for their antibacterial potential and found them moderately low inhibitors.

2. EXPERIMENTAL
2.1 General
The chemical reagents used including 1,3-benzodioxol-5-amine, aryl sulfonyl chlorides and alkyl/aralkyl halides were Merck and Alfa Aesar branded along with analytical grade solvents. The technique used to confirm the purity of the prepared compounds was thin layer chromatography run in solvent systems with varying ratios of EtOAc and n-hexane and visualized under UV at 254 nm. Melting points were determined by using Griffin George apparatus with open capillary tube. The IR spectra were obtained by adopting KBr pellet method on a Jasco-320-A spectrometer. 1H-NMR spectra were recorded in CDCl₃-d₆ on Bruker spectrometers at 400 MHz. Mass spectra (EIMS) were recorded on a JMS-HX-110 spectrometer with data system.

2.2 General procedure for synthesis of N-(1,3-Benzodioxol-5-yl)aryl sulfonamide (3a-b)
1,3-Benzodioxol-5-amine (1; 0.012 mol) was dispersed in 15 mL distilled water in a 100 mL round bottom flask. Then aryl sulfonyl chlorides (2a-b; 0.012 mol) were added and set to stir for 2-4 hours. The solution was basified by aqueous Na₂CO₃ to maintain pH 8-9 during the whole reaction. The reaction was supervised by TLC till single spot. Cold distilled water was added and pH was turned to 4-5 by adding dilute HCl. The obtained precipitates were filtered, washed and dried for further use.

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2.2.1 N-(1,3-Benzodioxol-5-yl)benzenesulfonamide (3a)
Grey amorphous solid; Yield: 78%; M. P.: 143-144 °C; Mol. Formula: C_{13}H_{11}NO_{3}S; Mol. Weight: 277; IR (KBr, cm⁻¹): 3028 (Ar C-H), 2906 (R C-H), 1596 (Ar C=C), 1430 (S=O), 1167 (C-O); ¹H-NMR (CDCl₃, 400 MHz, δ/ppm): 7.85 (d, J = 8.4 Hz, 2H, H-2'), 7.57 (t, J = 8.4 Hz, 1H, H-4'), 7.50 (t, J = 8.0 Hz, 2H, H-3', H-5'), 6.64 (d, J = 2.0 Hz, 1H, H-6), 6.60 (d, J = 8.0 Hz, 1H, H-5), 6.38 (dd, J = 8.4, 2.4 Hz, 1H, H-6), 5.91 (s, 2H, H-7); EIMS (m/z): 277[M]+, 141 [C₆H₅SO₂]+, 121 [C₆H₅]+, 77 [C₆H₃]+, 51 [C₅H₅]+.

2.2.2 N-(1,3-Benzodioxol-5-yl)-4-acetylbenzenesulfonamide (3b)
Creamy white amorphous solid; Yield: 85%; M. P.: 133-135 °C; Mol. Formula: C_{15}H_{13}NO_{3}S; Mol. Weight: 319; IR (KBr, cm⁻¹): 3025 (Ar C-H), 2900 (R C-H), 1716 (Ketone C=O) 1566 (Ar C=C), 1550 (S=O), 1460 (C-O); ¹H-NMR (CDCl₃, 400 MHz, δ/ppm): 8.08 (d, J = 8.0 Hz, 2H, H-2'), 6.96 (d, J = 8.8 Hz, 2H, H-3', H-5'), 6.69 (d, J = 2.4 Hz, 1H, H-6), 6.63 (d, J = 8.8 Hz, 1H, H-5), 6.33 (dd, J = 8.8, 2.0 Hz, 1H, H-6), 5.94 (s, 2H, H-7), 2.62 (s, 3H, CH₃CO-4'); EIMS (m/z): 319 [M]+, 183 [C₆H₅SO₂]+, 121 [C₆H₅]+, 119 [C₅H₅]+, 75 [C₄H₅]+, 51 [C₃H₅]+.

2.3 General procedure for synthesis of N-Alkyl/aralkyl-N-(1,3-benzodioxol-5-yl)aryl sulfonamide (7a-bto 9a-b)
The molecules 3a-b (0.002 mol) and lithium hydride (0.002 mol) were dissolved in 13 mL N,N-dimethyl formamide (DMF) in a 50 mL RB flask by one hour stirring. The electrophiles, alkyl/aralkyl halides (4-6; 0.002 mol) were added to the reaction mixture and further stirred for 3-hours. After single spot on TLC plate, ice cold distilled water was added with hand shaking and left for 15-20 min. The precipitated products, 7a-bto9a-b, were filtered, washed with distilled water and dried for further analysis.

2.3.1 N-Ethyl-N-(1,3-benzodioxol-5-yl)benzenesulfonamide (7a)
Dark pink amorphous solid; Yield: 74%; M. P.: 77-78 °C; Mol. Formula: C_{15}H_{13}NO_{3}S; Mol. Weight: 305; IR (KBr, cm⁻¹): 3032 (Ar C-H), 2940 (R C-H), 1598 (Ar C=C), 1450 (S=O), 1157 (C-O); ¹H-NMR (CDCl₃, 400 MHz, δ/ppm): 7.87 (d, J = 7.6 Hz, 2H, H-2'), 7.55 (t, J = 7.6 Hz, 1H, H-4'), 7.52 (t, J = 8.4 Hz, 2H, H-3', H-5'), 6.68 (d, J = 2.4 Hz, 1H, H-2), 6.66 (d, J = 8.4 Hz, 1H, H-5), 6.35 (dd, J = 8.0, 2.4 Hz, 1H, H-6), 5.94 (s, 2H, H-7), 3.27 (q, J = 7.6 Hz, 2H, H-1'), 0.92 (t, J = 7.6 Hz, 3H, CH₃-2'); EIMS (m/z): 305 [M]+, 141 [C₆H₅SO₂]+, 121 [C₆H₅]+, 77 [C₅H₅]+, 51 [C₄H₅]+, 29 [C₃H₅].
2.3.2 N-Ethyl-N-(1,3-benzodioxol-5-yl)-4-acetylbenzenesulfonamide (7b)
Light orange amorphous solid; Yield: 78%; M. P.: 124-125 °C; Mol. Formula: C_{17}H_{13}NO_{2}S; Mol. Weight: 347; IR (KBr, cm⁻¹)ν_max: 3026 (Ar-C-H), 2930 (R-C-H), 1717 (Ketone C=O), 1556 (Ar C=C), 1461 (S=O), 1198 (C-O); ¹H-NMR (CDCl₃, 400 MHz, δ/ppm): 8.04 (d, J = 8.0 Hz, 2H, H-2', H-6'), 7.92 (d, J = 7.6 Hz, 2H, H-3', H-5'), 6.61 (d, J = 2.4 Hz, 1H, H-2), 6.65 (d, J = 8.0 Hz, 1H, H-5), 6.30 (dd, J = 8.8, 2.4 Hz, 1H, H-6), 5.97 (s, 2H, H-7), 3.26 (q, J = 7.6 Hz, 2H, H-1'''), 2.64 (s, 3H, CH₃-CO-4'), 0.96 (t, J = 7.6 Hz, 3H, CH₃-2'''); EIMS (m/z): 347 [M⁺], 183 [C₆H₄SO₂]⁺, 121 [C₅H₇O²]⁻, 119 [C₆H₅]⁺, 51 [C₅H₇]⁺, 29 [C₄H₃]⁺..

2.3.3 N-Benzyl-N-(1,3-benzodioxol-5-yl)-benzenesulfonamide (8a)
Light pink amorphous solid; Yield: 85%; M. P.: 83-84 °C; Mol. Formula: C_{20}H_{17}NO_{2}S; Mol. Weight: 367; IR (KBr, cm⁻¹)ν_max: 3038 (Ar-C-H), 2936 (R-C-H), 1586 (Ar C=C), 1440 (S=O), 1157 (C-O); ¹H-NMR (CDCl₃, 400 MHz, δ/ppm): 7.82 (d, J = 7.6 Hz, 2H, H-2', H-6'), 7.45 (t, J = 8.0 Hz, 1H, H-4'), 7.52 (t, J = 8.0 Hz, 4H, H-3', H-5'), 7.15-7.07 (m, 5H, H-2'' to H-6''), 6.68 (d, J = 2.4 Hz, 1H, H-2), 6.57 (d, J = 8.4 Hz, 1H, H-5), 6.48 (dd, J = 8.8, 2.4 Hz, 1H, H-6), 5.93 (s, 2H, H-7), 3.46 (s, 2H, H-7''); EIMS (m/z): 367 [M⁺], 141 [C₆H₄SO₂]⁺, 121 [C₅H₇O²]⁻, 91 [C₅H₇]⁺, 77 [C₄H₃]⁺, 75 [C₆H₅]⁺, 51 [C₅H₇]⁺.

2.3.4 N-Benzyl-N-(1,3-benzodioxol-5-yl)-4-acetylbenzenesulfonamide (8b)
Creamy white amorphous solid; Yield: 85%; M. P.: 130-131 °C; Mol. Formula: C_{24}H_{19}NO_{2}S; Mol. Weight: 409; IR (KBr, cm⁻¹)ν_max: 3029 (Ar-C-H), 2930 (R-C-H), 1717 (Ketone C=O), 1546 (Ar C=C), 1450 (S=O), 1196 (C-O); ¹H-NMR (CDCl₃, 400 MHz, δ/ppm): 8.01 (d, J = 8.4 Hz, 2H, H-2', H-6'), 7.89 (d, J = 8.4 Hz, 2H, H-3', H-5'), 7.15-7.06 (m, 5H, H-2'' to H-6''), 6.64 (d, J = 2.8 Hz, 1H, H-2), 6.61 (d, J = 8.4 Hz, 1H, H-5), 6.32 (dd, J = 8.0, 2.4 Hz, 1H, H-6), 5.95 (s, 2H, H-7), 3.44 (s, 2H, H-7''), 2.65 (s, 3H, CH₃-CO-4'); EIMS (m/z): 409 [M⁺], 183 [C₆H₄SO₂]⁺, 121 [C₅H₇O²]⁻, 91 [C₅H₇]⁺, 77 [C₄H₃]⁺, 75 [C₆H₅]⁺, 51 [C₅H₇]⁺.

2.3.5 N-(4-Fluorobenzyl)-N-(1,3-benzodioxol-5-yl)-benzenesulfonamide (9a)
Dark pink amorphous solid; Yield: 82%; M. P.: 84-85 °C; Mol. Formula: C_{23}H_{18}FNO₂S; Mol. Weight: 385; IR (KBr, cm⁻¹)ν_max: 3045 (Ar-C-H), 2936 (R-C-H), 1600 (Ar C=C), 1450 (S=O), 1177 (C-O), 1050 (C-F); ¹H-NMR (CDCl₃, 400 MHz, δ/ppm): 7.80 (d, J = 7.8 Hz, 2H, H-2', H-6'), 7.65 (d, J = 7.6 Hz, 2H, H-2', H-6''), 7.60 (t, J = 8.0 Hz, 1H, H-4'), 7.57 (t, J = 8.4 Hz, 2H, H-3'), 6.89 (d, J = 8.0 Hz, 2H, H-3'), 6.78 (d, J = 2.4 Hz, 1H, H-2), 6.59 (d, J = 8.8 Hz, 1H, H-5), 6.48 (dd, J = 8.8, 2.8 Hz, 1H, H-6), 5.97 (s, 2H, H-7), 3.95 (s, 2H, H-7''); EIMS (m/z): 385 [M⁺], 141 [C₆H₄SO₂]⁺, 121 [C₅H₇O²]⁻, 110 [C₅H₇F]⁺, 77 [C₄H₃]⁺, 75 [C₆H₅]⁺, 51 [C₅H₇]⁺.

2.3.6 N-(4-Fluorobenzyl)-N-(1,3-benzodioxol-5-yl)-4-acetylbenzenesulfonamide (9b)
Light brown amorphous solid; Yield: 95%; M. P.: 133-135 °C; Mol. Formula: C_{24}H_{19}FNO₂S; Mol. Weight: 427; IR (KBr, cm⁻¹)ν_max: 3015 (Ar-C-H), 2920 (R-C-H), 1718 (Ketone C=O), 1536 (Ar C=C), 1455 (S=O), 1167 (C-O), 1050 (C-F); ¹H-NMR (CDCl₃, 400 MHz, δ/ppm): 7.93 (d, J = 8.4 Hz, 2H, H-2', H-6'), 7.89 (d, J = 8.4 Hz, 2H, H-3', H-5'), 7.71 (d, J = 7.6 Hz, 2H, H-2'', H-6''), 6.84 (d, J = 7.6 Hz, 2H, H-3'', H-5''), 6.69 (d, J = 2.8 Hz, 1H, H-2), 6.64 (d, J = 8.8 Hz, 1H, H-5), 6.32 (dd, J = 8.8, 2.4 Hz, 1H, H-6), 5.98 (s, 2H, H-7), 3.95 (s, 2H, H-7''), 2.64 (s, 3H, CH₃-CO-4'); EIMS (m/z): 427 [M⁺], 183 [C₆H₄SO₂]⁺, 121 [C₅H₇O²]⁻, 110 [C₅H₇F]⁺, 119 [C₆H₇O⁻], 75 [C₆H₅]⁺, 51 [C₅H₇]⁺.

2.4 Antibacterial activity
The rule for antibacterial activity is that the microbial cell number depends on the logarithm of growth rate which depends on absorbance of broth medium. As the absorbance of the broth medium increases the logarithm of growth also increases. And as a result microbial cell number increases.13
RESULTS AND DISCUSSION

A comprehensive outline for the synthesis of a series of sulfonamides is given in Scheme 1 along with necessary conditions and reagents required. All the molecules were screened for the antibacterial activity against the bacterial strains of Gram-positive and Gram-negative bacteria taking ciprofloxacin as reference standard.

Chemistry

The synthesized molecule 3a showed the [M]⁺ peak at m/z 277 along with other significant peaks at m/z 141 for benzencesulfonylation, at m/z 121 for the 1,3-benzodioxol-5-yl cation and at m/z 77 for the phenyl cation in EIMS spectrum. The definite absorption bands obtained from IR spectrum supporting the major functionalities in the molecule were 3028 (Ar C-H), 2906 (R C-H), 1596 (Ar C=C), 1430 (S=O) and 1167 (C=O). The signals of ¹H-NMR resonated at δ 7.85 (d, J = 8.4 Hz, 2H, H-2', H-6'), 7.57 (t, J = 8.4 Hz, 1H, H-4'), 7.50 (t, J = 8.0 Hz, 2H, H-3', H-5') for the phenyl group attached to sulfur of sulfamoyl moiety while the signals confirming the 1,3-benzodioxol group appeared at δ 6.64 (d, J = 2.0 Hz, 1H, H-2), 6.60 (d, J = 8.0 Hz, 1H, H-5), 6.38 (dd, J = 8.4, 2.4 Hz, 1H, H-6) and 5.91 (s, 2H, H-7). All the spectral data obtained confirmed the molecular structure of 3a named, N-(1,3-Benzodioxol-5-yl)benzenesulfonylamide. By the same way, all the structures of prepared molecules were affirmed by ¹H-NMR, IR and mass spectral data.

Antibacterial activity (in vitro)

Only two compounds, 9a and 8a were inactive against B. subtilis. The most active one against this strain was 3a with MIC of 10.25 ± 0.44 µmol/L relative to the reference. S. aureus was moderately inhibited by all the compounds except 7b, 9a and 9b. The molecules, 3a and 7a showed inhibition against all the bacterial strains while 9a remained the least active showing MIC only against S. typhi. Among all the bacterial strains, S.typhi was inhibited by all the synthesized molecules. The molecules, 7a and 8b showed the best inhibition results with MIC of 11.28 ± 0.90 µmol/L and 11.55 ± 0.54 µmol/L with reference of 7.83 ± 0.78 µmol/L, the MIC of ciprofloxacin. Against E. coli only 7a and 3a remained active with moderate MIC values relative to ciprofloxacin. Half of the synthesised molecules remained inactive and half were moderately active against P. aeruginosa.

CONCLUSION

The synthesized molecules were obtained unreasonable yields and were structurally corroborated by spectral analysis. The antibacterial activity evaluation rendered them moderate inhibitors.

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