

Original Research Article

Synthesis and Antibacterial Evaluation of 2-(1,3-Benzodioxol-5-ylcarbonyl)arylsulfonohydrazide Derivatives

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Abstract

Purpose: To study the antibacterial activity of various sulfonamides derived from 1,3-benzodioxol-5-carbohydrazide.

Methods: The synthesis involved the conversion of 1,3-benzodioxol-5-carboxylic acid (1) to ethyl 1,3-benzodioxol-5-carboxylate (2) and then to 1,3-benzodioxol-5-carbohydrazide (3). The target molecules, 2-(1,3-benzodioxol-5-ylcarbonyl)arylsulfonohydrazide derivatives (5a-l) were synthesized through a benignant method from aqueous medium by the reaction of 3 and arylsulfonyl chlorides (4a-l). The structural formulae of the synthesized compounds were characterized by infra red spectroscopy (IR), proton nuclear magnetic resonance (¹H-NMR) and electron impact mass spectrometry (EI-MS). The compounds were screened for in vitro antibacterial activity by determining their minimum inhibitory concentration (MIC).

Results: The molecule, 5k, bearing 2-hydroxy-3,5-dichlorophenyl group exhibited the highest activity with MIC of 11.92 ± 3.40 (*S. typhi*), 8.37 ± 2.22 (*E. coli*), 9.28 ± 2.31 (*P. aeruginosa*), 11.76 ± 1.30 (*B. subtilis*) and 10.30 ± 1.63 (*S. aureus*) μmoles/L relative to that of ciprofloxacin with 9.42 ± 1.09, 8.02 ± 2.17, 8.11 ± 1.32, 8.88 ± 2.00 and 9.23 ± 1.87 μmoles/L respectively.

Conclusion: The most potent of the synthesized compounds (5k) possesses moderate activity against all the bacterial strains, while 5g remained completely inactive.

Keywords: 1,3-Benzodioxol-5-carboxylic acid, Antibacterial activity, Sulfonohydrazide, Synthesis

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INTRODUCTION

Most of the biologically active compounds include sulfonamides, and they are an important class of drugs showing various activities such as antimicrobial, antitumor, anticonvulsant, anticancer, anti-inflammatory, antidiuretic, antihydrod, insulin-releasing and hypoglycemic. They also act as inhibitors, e.g., histone deacetylase (HDAC), carbonic anhydrase and HIV protease [1-8]. The chemotherapeutic

derivatives of this class are extensively employed as antibacterial and antiviral agents [4,9] since they are structural analogues of *p*-aminobenzoic acid necessary for the production of folic acid. If they are substituted for *p*-aminobenzoic acid, the production of folic acid stops and ultimately bacterial growth stops [2,10].

In continuation of our earlier work on this class of compounds [11], we sought to synthesize new 2-(1,3-benzodioxol-5-ylcarbonyl)

arylsulfonohydrazide derivatives to evaluate antibacterial activity.

EXPERIMENTAL

General

Melting points of all the synthesized compounds were recorded on Griffin-George apparatus by open capillary tube and were uncorrected. Purity was confirmed Thin Layer Chromatography (TLC) on silica gel G-25-UV254 coated plates, run under varying ratios of solvent system of n-hexane and ethyl acetate. IR spectra were computed by KBr pellet method on a Jasco-320-A spectrophotometer in cm^{-1} . $^1\text{H-NMR}$ spectra were measured in $\text{CHCl}_3\text{-d}_1$ on Bruker spectrometer at 300/400 MHz and $^{13}\text{C-NMR}$ at 100 MHz. Chemical shifts are provided in ppm with tetramethylsilane TMS as internal reference and coupling constant in Hz. Mass spectra were recorded on a JMS-HX-110 spectrometer.

Procedure for the synthesis of ethyl 1,3-benzodioxol-5-carboxylate (2)

The reaction mixture of 1,3-benzodioxol-5-carboxylic acid (1; 6.0 g), ethanol (24 mL, 99 %) and concentrated H_2SO_4 (3.0 mL) was set to reflux in 250 mL round bottom (RB) flask for 3 h till maximum completion, confirmed by TLC. The liquid ester (2) was extracted by solvent extraction at a pH of 8-10.

Procedure for the synthesis of 1,3-benzodioxol-5-carbohydrazide (3)

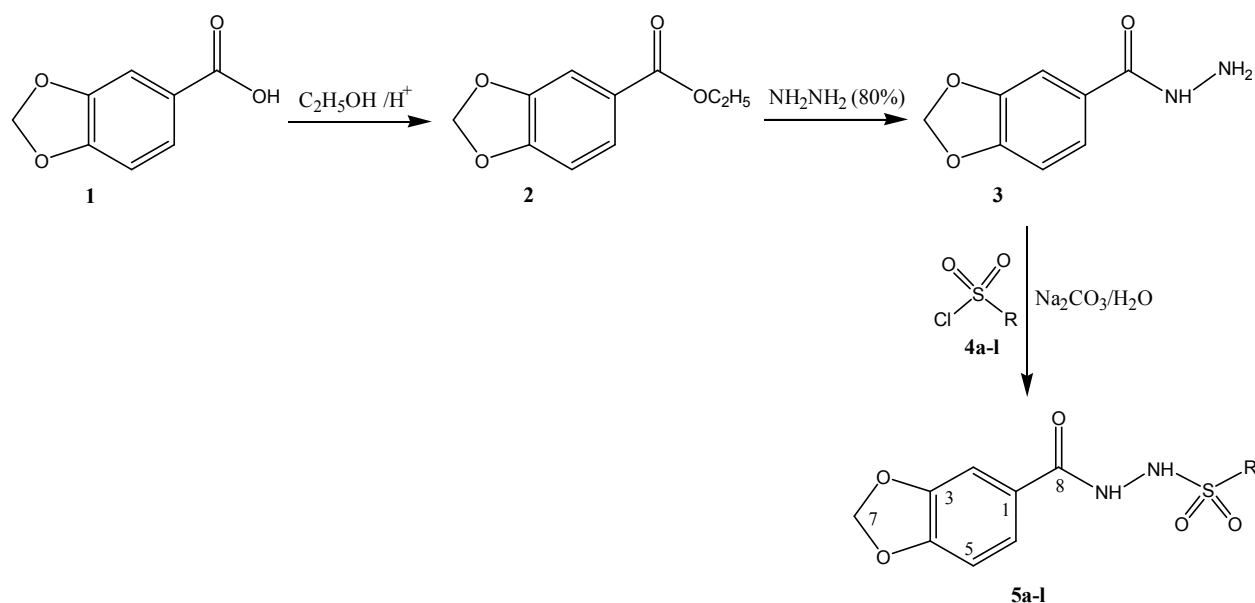
The reaction mixture of ethyl 1,3-benzodioxol-5-carboxylate (2; 0.2 mol), ethanol (150 mL, 99 %) and hydrazine hydrate (15 mL, 80 %) was refluxed in a round bottom flask for 6 h. After completion of the reaction, ice cold distilled water was added to get solid precipitates of 3, which were filtered and washed with distilled water.

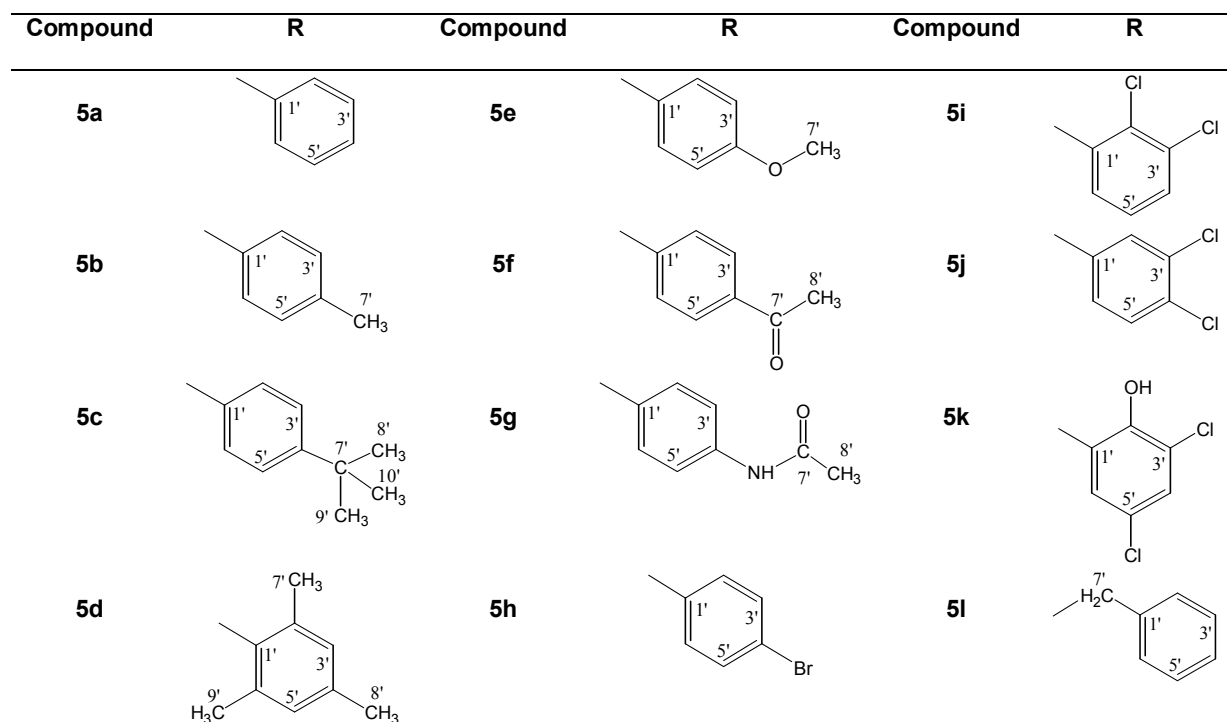
Procedure for the synthesis of 2-(1,3-benzodioxol-5-ylcarbonyl) arylsulfonohydrazide (5a-l)

1,3-Benzodioxol-5-carbohydrazide (3; 0.005 mol) was dispersed in 20 mL distilled water, adjusting the pH at 8-10 with sodium carbonate solution. Arylsulfonyl chlorides (4a-l; 0.005 mol) were added gradually and the reaction mixture was stirred for 2-3 h. After the reaction was completed concentrated HCl (0.5 mL) was added gradually while shaking. Precipitates of the products were obtained which were filtered, washed and dried.

Antibacterial activity assay

Antibacterial test was carried out in sterile 96-well microplates under aseptic conditions. The method was based on the principle that microbial cell number increases as microbial growth proceeds in a log phase of growth, resulting in raised absorbance of broth medium [12,13].





Scheme 1: Outline for synthesis of 2-(1,3-benzodioxol-5-ylcarbonyl)arylsulfonohydrazide derivatives (**5a-l**)

RESULTS

A new series of sulfonamides was synthesized from a facile method by scheme 1. The synthesized 2-(1,3-benzodioxol-5-ylcarbonyl)arylsulfonohydrazide derivatives (**5a-l**) were evaluated for antibacterial activity. The synthesized molecules were well supported by spectral data as follows and also the most of them remained moderately efficient against the bacterial strains taken into account.

Chemistry

The synthesis involved esterification of 1,3-benzodioxol-5-carboxylic acid (**1**) to ethyl 1,3-benzodioxol-5-carboxylate (**2**) by refluxing with ethanol and concentrated sulfuric acid. The ester was isolated using chloroform. The molecule, **2**, was subjected to nucleophilic substitution reaction with hydrazine in ethanol to yield 1,3-benzodioxol-5-carbohydrazide (**3**) which was treated with various arylsulfonyl chlorides in aqueous medium under dynamic pH control. The products were acquired through filtration from a slightly acidic medium. The low acidity of mixture is mandatory for better yields as higher has negative effect. The structures of all the synthesized molecules, **2**, **3** and **5a-l**, were corroborated through spectral data.

Ethyl 1,3-benzodioxol-5-carboxylate (**2**)

Yellowish transparent liquid; Yield: 90 %; Molecular formula: $C_{10}H_{10}O_4$; Molecular mass: 194; IR (NaCl discs): ν_{max} (cm^{-1}): 3006 (aromatic C-H stretching), 1710 (C=O ester stretching), 1605 (Ar C=C stretching), 1110 (C-O ester stretching); 1H -NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.64 (dd, $J = 8.4, 1.6$ Hz, 1H, H-6), 7.44 (d, $J = 1.2$ Hz, 1H, H-2), 6.82 (d, $J = 8.0$ Hz, 1H, H-5), 6.01 (s, 2H, H-7), 4.32 (q, $J = 7.2$ Hz, 2H, -OCH₂CH₃), 1.37 (t, $J = 7.2$ Hz, 3H, -OCH₂CH₃); ^{13}C -NMR ($CDCl_3$, 100 MHz, δ/ppm): 165.4 (C-8), 148.7 (C-4), 145.1 (C-3), 128.6 (C-6), 121.3 (C-1), 109.5 (C-2), 106.9 (C-5), 101.6 (C-7), 62.2 (-OCH₂), 13.9 (CH₃); EIMS (m/z): 194 [M]⁺ (2 %), 165 (23 %), 149 (100 %), 121 (26 %), 119 (6 %), 91 (7 %), 29 (15 %).

1,3-Benzodioxol-5-carbohydrazide (**3**)

White amorphous solid; Yield: 97 %; M.P: 170 °C; Molecular formula: $C_8H_8N_2O_3$; Molecular mass: 180; IR (KBr): ν_{max} (cm^{-1}): 3250 (NH stretching), 3010 (aromatic C-H stretching), 1730 (C=O amide stretching), 1610 (Ar C=C stretching); 1H -NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.66 (dd, $J = 8.4, 1.6$ Hz, 1H, H-6), 7.45 (d, $J = 1.2$ Hz, 1H, H-2), 6.87 (d, $J = 8.0$ Hz, 1H, H-5), 6.06 (s, 2H, H-7); ^{13}C -NMR ($CDCl_3$, 100 MHz, δ/ppm): 170.2 (C-8), 148.9 (C-3), 148.1 (C-4), 124.8 (C-1), 122.3 (C-6), 109.1 (C-5), 107.2 (C-2), 101.9 (C-7); EIMS (m/z): 180 [M]⁺ (1 %), 165

(24 %), 149 (100 %), 121 (25 %), 119 (5 %), 91 (8 %).

2-(1,3-Benzodioxol-5-ylcarbonyl)benzenesulfonylhydrazide (5a)

White amorphous solid; Yield: 92 %; M.P: 209-211 °C; Molecular formula: C₁₄H₁₂N₂O₅S; Molecular mass: 320; IR (KBr): ν_{\max} (cm⁻¹): 3256 (NH stretching), 3018 (aromatic C-H stretching), 1733 (C=O amide stretching), 1612 (Ar C=C stretching), 1413 (S=O stretching); ¹H-NMR (CDCl₃, 400 MHz, δ /ppm): 7.92 (d, J = 7.6 Hz, 2H, H-2' & 6'), 7.58 (t, J = 7.6 Hz, 1H, H-4'), 7.47 (t, J = 7.2 Hz, 2H, H-3', 5'), 7.19 (dd, J = 8.4, 1.6 Hz, 1H, H-6), 7.04 (d, J = 1.2 Hz, 1H, H-2), 6.80 (d, J = 8.0 Hz, 1H, H-5), 6.01 (s, 2H, H-7); ¹³C-NMR (CDCl₃, 100 MHz, δ /ppm): 170.5 (C-8), 148.7 (C-4), 146.4 (C-3), 145.8 (C-1'), 132.4 (C-4'), 127.1 (C-3', C-5'), 125.6 (C-1), 124.8 (C-2', C-6'), 122.6 (C-6), 109.3 (C-2), 107.4 (C-5), 101.6 (C-7); EIMS (*m/z*): 320 [M]⁺ (1 %), 149 (100 %), 121 (27 %), 91 (7 %).

2-(1,3-Benzodioxol-5-ylcarbonyl)-4-methylbenzenesulfonylhydrazide (5b)

White amorphous solid; Yield: 90 %; M.P: 204-206 °C; Molecular formula: C₁₅H₁₄N₂O₅S; Molecular mass: 334; IR (KBr): ν_{\max} (cm⁻¹): 3259 (NH stretching), 3027 (aromatic C-H stretching), 1739 (C=O amide stretching), 1617 (Ar C=C stretching), 1418 (S=O stretching); ¹H-NMR (CDCl₃, 400 MHz, δ /ppm): 7.79 (d, J = 8.0 Hz, 2H, H-2', 6'), 7.42 (d, J = 7.6 Hz, 2H, H-3', 5'), 7.19 (dd, J = 8.4, 1.6 Hz, 1H, H-6), 7.06 (d, J = 1.6 Hz, 1H, H-2), 6.81 (d, J = 8.4 Hz, 1H, H-5), 6.01 (s, 2H, H-7), 2.35 (s, 3H, H-7'); ¹³C-NMR (CDCl₃, 100 MHz, δ /ppm): 170.7 (C-8), 148.4 (C-4), 146.6 (C-3), 145.3 (C-1'), 132.9 (C-4'), 127.8 (C-2' C-6'), 125.2 (C-3' C-5'), 124.6 (C-1), 122.5 (C-6), 109.1 (C-2), 107.6 (C-5), 101.2 (C-7), 20.3 (C-7'); EIMS (*m/z*): 334 [M]⁺ (2 %), 156 (15 %), 149 (100 %), 121 (25 %).

2-(1,3-Benzodioxol-5-ylcarbonyl)-4-terbutylbenzenesulfonylhydrazide (5c)

Brown amorphous solid; Yield: 96 %; M.P: 259-261 °C; Molecular formula: C₁₈H₂₀N₂O₅S; Molecular mass: 376; IR (KBr): ν_{\max} (cm⁻¹): 3272 (NH stretching), 3043 (aromatic C-H stretching), 1733 (C=O amide stretching), 1612 (Ar C=C stretching), 1407 (S=O stretching); ¹H-NMR (CDCl₃, 300 MHz, δ /ppm): 7.82 (d, J = 7.2 Hz, 2H, H-2' & 6'), 7.45 (d, J = 7.2 Hz, 2H, H-3' & 5'), 7.16 (dd, J = 7.2, 1.5 Hz, 1H, H-6), 7.04 (d, J = 1.5 Hz, 1H, H-2), 6.80 (d, J = 7.2 Hz, 1H, H-5), 1.35 (s, 9H, H-8' to 10'); ¹³C-NMR (CDCl₃, 100 MHz, δ /ppm): 170.4 (C-8), 152.8 (C-4'), 148.1

(C-4), 146.7 (C-3), 145.6 (C-1'), 126.9 (C-2' C-6'), 125.3 (C-3' C-5'), 124.9 (C-1), 122.4 (C-6), 109.8 (C-2), 107.2 (C-5), 101.5 (C-7), 32.3 (C-7'), 31.1 (C-8' to C-10'); EIMS (*m/z*): 376 [M]⁺ (1 %), 331 (5 %), 316 (2 %), 198 (20 %), 149 (100 %), 121 (25 %), 119 (6 %).

2-(1,3-Benzodioxol-5-ylcarbonyl)mesitylen-2-ylsulfonylhydrazide (5d)

Creamy white amorphous solid; Yield: 96 %; M.P: 269-271 °C; Molecular formula: C₁₇H₁₈N₂O₅S; Molecular mass: 362; IR (KBr): ν_{\max} (cm⁻¹): 3278 (NH stretching), 3032 (aromatic C-H stretching), 1737 (C=O amide stretching), 1607 (Ar C=C stretching), 1395 (S=O stretching); ¹H-NMR (CDCl₃, 400 MHz, δ /ppm): 7.17 (d, J = 7.6 Hz, 1H, H-6), 7.06 (s, 1H, H-2), 6.89 (s, 2H, H-3' 5'), 6.79 (d, J = 8.0 Hz, 1H, H-5), 6.00 (s, 2H, H-7), 2.71 (s, 6H, H-7' 9'), 2.23 (s, 3H, H-8'); ¹³C-NMR (CDCl₃, 100 MHz, δ /ppm): 170.7 (C-8), 152.3 (C-1'), 149.7 (C-2' & C-6'), 148.2 (C-4), 146.4 (C-3), 140.1 (C-4'), 139.5 (C-3' & C-5'), 124.4 (C-1), 122.7 (C-6), 109.3 (C-2), 107.9 (C-5), 101.1 (C-7), 23.1 (C-7' & C-9'), 20.2 (C-8'); EIMS (*m/z*): 362 [M]⁺ (1 %), 184 (15 %), 165 (30 %), 149 (100 %), 121 (22 %).

2-(1,3-Benzodioxol-5-ylcarbonyl)-4-methoxybenzenesulfonylhydrazide (5e)

White amorphous solid; Yield: 87 %; M.P: 319-321 °C; Molecular formula: C₁₅H₁₄N₂O₆S; Molecular mass: 350; IR (KBr): ν_{\max} (cm⁻¹): 3279 (NH stretching), 3023 (aromatic C-H stretching), 1739 (C=O amide stretching), 1626 (Ar C=C stretching), 1419 (S=O stretching); ¹H-NMR (CDCl₃, 300 MHz, δ /ppm): 7.84 (d, J = 8.7 Hz, 2H, H-2', 6'), 7.21 (dd, J = 9.3, 1.2 Hz, 1H, H-6), 7.07 (d, J = 1.5 Hz, 1H, H-2), 6.90 (d, J = 9.0 Hz, 2H, H-3' & 5'), 6.80 (d, J = 8.1 Hz, 1H, H-5), 6.01 (s, 2H, H-7), 3.80 (s, 3H, H-7'); ¹³C-NMR (CDCl₃, 100 MHz, δ /ppm): 170.5 (C-8), 162.3 (C-4'), 148.7 (C-4), 146.4 (C-3), 144.1 (C-1'), 127.2 (C-2', C-6'), 124.8 (C-1), 123.1 (C-6), 114.7 (C-3', C-5'), 109.4 (C-2), 107.4 (C-5), 101.6 (C-7), 57.8 (C-7'); EIMS (*m/z*): 350 [M]⁺ (50 %), 172 (59 %), 165 (25 %), 149 (100 %), 121 (51 %), 107 (7 %), 91 (9 %).

2-(1,3-Benzodioxol-5-ylcarbonyl)-4-acetylbenzenesulfonylhydrazide (5f)

Light brown amorphous solid; Yield: 97 %; M.P: 199-201 °C; Molecular formula: C₁₆H₁₄N₂O₆S; Molecular mass: 362; IR (KBr): ν_{\max} (cm⁻¹): 3265 (NH stretching), 3019 (aromatic C-H stretching), 1739 (C=O amide stretching), 1629 (Ar C=C stretching), 1417 (S=O stretching); ¹H-NMR

(CDCl₃, 400 MHz, δ /ppm): 8.08 (d, J = 3.6 Hz, 1H, H-2), 7.89 (d, J = 9.6 Hz, 2H, H-2' & 6'), 7.57 (d, J = 8.0 Hz, 2H, H-3, 5'), 7.37 (dd, J = 8.4, 1.6 Hz, 1H, H-6), 6.75 (d, J = 8.4 Hz, 1H, H-5), 5.99 (s, 2H, H-7), 2.60 (s, 3H, H-8'); ¹³C-NMR (CDCl₃, 100 MHz, δ /ppm): 197.3 (C-8'), 170.8 (C-8), 149.5 (C-1'), 148.2 (C-4), 146.9 (C-3), 137.3 (C-4'), 126.6 (C-2', C-6'), 126.2 (C-3', C-5'), 125.7 (C-1), 123.3 (C-6), 109.6 (C-2), 107.7 (C-5), 101.4 (C-7), 25.8 (C-7'); EIMS (*m/z*): 362 [M]⁺ (1 %), 184 (12 %), 165 (28 %), 149 (100 %), 121 (28 %), 119 (6 %).

2-(1,3-Benzodioxol-5-ylcarbonyl)-4-acetamidobenzenesulfonohydrazide (5g)

Creamy white amorphous solid; Yield: 95 %; M.P: 249-251 °C; Molecular formula: C₁₆H₁₅N₃O₆S; Molecular mass: 377; IR (KBr): ν_{\max} (cm⁻¹): 3267 (NH stretching), 3023 (aromatic C-H stretching), 1741 (C=O amide stretching), 1603 (Ar C=C stretching), 1409 (S=O stretching); ¹H-NMR (CDCl₃, 400 MHz, δ /ppm): 7.73 (d, J = 8.8 Hz, 2H, H-2' & 6'), 7.58 (d, J = 8.8 Hz, 2H, H-3' & 5'), 7.17 (dd, J = 8.4, 1.6 Hz, 1H, H-6), 7.03 (d, J = 1.6 Hz, 1H, H-2), 6.72 (d, J = 8.0 Hz, 1H, H-5), 5.93 (s, 2H, H-7), 2.05 (s, 3H, H-8'); ¹³C-NMR (CDCl₃, 100 MHz, δ /ppm): 170.4 (C-8), 167.8 (C-8'), 148.6 (C-4), 146.3 (C-3), 142.8 (C-1'), 138.2 (C-4'), 125.5 (C-1), 124.2 (C-2', C-6'), 123.7 (C-6), 112.4 (C-3', C-5'), 109.4 (C-2), 107.2 (C-5), 101.8 (C-7), 23.7 (C-7'); EIMS (*m/z*): 377 [M]⁺ (1 %), 149 (100 %), 134 (1.2 %), 121 (23 %), 119 (4 %), 91 (8 %).

2-(1,3-Benzodioxol-5-ylcarbonyl)-4-bromobenzenesulfonohydrazide (5h)

Brown liquid; Yield: 89 %; Molecular formula: C₁₄H₁₁BrN₂O₅S; Molecular mass: 398; IR (NaCl discs): ν_{\max} (cm⁻¹): 3264 (NH stretching), 3046 (aromatic C-H stretching), 1730 (C=O amide stretching), 1601 (Ar C=C stretching), 1398 (S=O stretching), 669 (C-Br stretching); ¹H-NMR (CDCl₃, 400 MHz, δ /ppm): 7.77 (d, J = 8.4 Hz, 2H, H-2' & 6'), 7.59 (d, J = 8.8 Hz, 2H, H-3' & 5'), 7.20 (dd, J = 8.4, 1.6 Hz, 1H, H-6), 7.07 (d, J = 1.2 Hz, 1H, H-2), 6.82 (d, J = 8.0 Hz, 1H, H-5), 6.02 (s, 2H, H-7); ¹³C-NMR (CDCl₃, 100 MHz, δ /ppm): 170.3 (C-8), 148.3 (C-4), 146.7 (C-3), 146.1 (C-1'), 130.4 (C-3' & C-5'), 126.9 (C-2' & C-6'), 126.2 (C-4'), 125.5 (C-1), 123.8 (C-6), 109.7 (C-2), 107.3 (C-5), 101.5 (C-7); EIMS (*m/z*): 400 [M+2]⁺ (2 %), 398 [M]⁺ (2 %), 222 (22 %), 220 (22 %), 157 (15 %), 155 (15 %), 149 (100 %), 121 (25 %), 119 (6 %), 91 (7 %).

2-(1,3-Benzodioxol-5-ylcarbonyl)-2,3-dichlorobenzenesulfonohydrazide (5i)

Yellow amorphous solid; Yield: 98 %; M.P: 354-356 °C; Molecular formula: C₁₄H₁₀Cl₂N₂O₅S; Molecular mass: 388; IR (KBr): ν_{\max} (cm⁻¹): 3286 (NH stretching), 3028 (aromatic C-H stretching), 1743 (C=O amide stretching), 1615 (Ar C=C stretching), 1435 (S=O stretching), 703 (C-Cl stretching); ¹H-NMR (CDCl₃, 300 MHz, δ /ppm): 7.97 (d, J = 7.8 Hz, 1H, H-6'), 7.81 (d, J = 7.5 Hz, 1H, H-5'), 7.66 (d, J = 7.5 Hz, 1H, H-4'), 7.18 (dd, J = 7.5, 2.1 Hz, 1H, H-6), 7.06 (d, J = 2.4 Hz, 1H, H-2), 6.79 (d, J = 8.1 Hz, 1H, H-5), 5.99 (s, 2H, H-7); ¹³C-NMR (CDCl₃, 100 MHz, δ /ppm): 170.6 (C-8), 148.7 (C-4), 146.9 (C-3), 143.2 (C-1'), 134.1 (C-2'), 132.8 (C-4'), 131.4 (C-3'), 126.7 (C-5'), 125.4 (C-1), 124.5 (C-6'), 123.6 (C-6), 109.9 (C-2), 107.1 (C-5), 101.6 (C-7); EIMS (*m/z*): 392 [M+4]⁺ (0.7%), 390 [M+2]⁺ (1 %), 388 [M]⁺ (2 %), 213 (5 %), 211 (8 %), 209 (25 %), 165 (25 %), 149 (100 %), 147 (30 %), 145 (60 %), 123 (2 %), 119 (5 %).

2-(1,3-Benzodioxol-5-ylcarbonyl)-3,4-dichlorobenzenesulfonohydrazide (5j)

White amorphous solid; Yield: 98 %; M.P: 399-401 °C; Molecular formula: C₁₄H₁₀Cl₂N₂O₅S; Molecular mass: 388; IR (KBr): ν_{\max} (cm⁻¹): 3275 (NH stretching), 3036 (aromatic C-H stretching), 1741 (C=O amide stretching), 1605 (Ar C=C stretching), 1415 (S=O stretching), 707 (C-Cl stretching); ¹H-NMR (CDCl₃, 300 MHz, δ /ppm): 7.98 (s, 1H, H-2'), 7.73 (d, J = 7.5 Hz, 1H, H-6'), 7.53 (d, J = 8.4 Hz, 1H, H-5'), 7.19 (dd, J = 7.8, 2.1 Hz, 1H, H-6), 7.06 (d, J = 2.4 Hz, 1H, H-2), 6.83 (d, J = 8.1 Hz, 1H, H-5), 6.03 (s, 2H, H-7); ¹³C-NMR (CDCl₃, 100 MHz, δ /ppm): 170.8 (C-8), 148.5 (C-4), 146.8 (C-3), 142.9 (C-1'), 132.2 (C-4'), 128.6 (C-5'), 127.5 (C-3'), 126.2 (C-2'), 125.6 (C-1), 124.6 (C-6'), 123.3 (C-6), 109.7 (C-2), 107.4 (C-5), 101.9 (C-7); EIMS (*m/z*): 392 [M+4]⁺ (0.7 %), 390 [M+2]⁺ (1 %), 388 [M]⁺ (2 %), 213 (9 %), 211 (13 %), 209 (28 %), 165 (30 %), 149 (100 %), 147 (32 %), 145 (63 %), 123 (2 %), 119 (5 %).

2-(1,3-Benzodioxol-5-ylcarbonyl)-3,5-dichloro-2-hydroxybenzenesulfonohydrazide (5k)

Light brown amorphous solid; Yield: 92 %; M.P: 188-190 °C; Molecular formula: C₁₄H₁₀Cl₂N₂O₆S; Molecular mass: 404; IR (KBr): ν_{\max} (cm⁻¹): 3276 (NH stretching), 3016 (aromatic C-H stretching), 1735 (C=O amide stretching), 1608 (Ar C=C stretching), 1401 (S=O stretching), 701 (C-Cl stretching); ¹H-NMR (CDCl₃, 400 MHz, δ /ppm):

7.57 (d, J = 2.8 Hz, 1H, H-6'), 7.41 (d, J = 2.8 Hz, 1H, H-4'), 7.17 (dd, J = 8.4, 1.6 Hz, 1H, H-6), 7.05 (d, J = 1.6 Hz, 1H, H-2), 6.73 (d, J = 8.0 Hz, 1H, H-5), 5.95 (s, 2H, H-7); ¹³C-NMR (CDCl₃, 100 MHz, δ/ppm): 170.4 (C-8), 148.4 (C-4), 146.7 (C-3), 143.2 (C-1'), 133.6 (C-3' C-5'), 129.4 (C-4'), 125.5 (C-1), 124.1 (C-2' C-6'), 123.5 (C-6), 109.4 (C-2), 107.7 (C-5), 101.8 (C-7); EIMS (m/z): 408 [M+4]⁺ (0.7 %), 406 [M+2]⁺ (1 %), 404 [M]⁺ (2 %), 226 (24 %), 165 (25 %), 162 (90 %), 149 (100 %), 119 (5 %).

2-(1,3-Benzodioxol-5-ylcarbonyl)benzylsulfonohydrazide (5l)

White amorphous solid; Yield: 87 %; M.P: 274-276 °C; Molecular formula: C₁₅H₁₄N₂O₅S; Molecular mass: 334; IR (KBr): ν_{max} (cm⁻¹): 3273 (NH stretching), 3024 (aromatic C-H stretching), 1746 (C=O amide stretching), 1614 (Ar C=C stretching), 1411 (S=O stretching); ¹H-NMR (CDCl₃, 400 MHz, δ/ppm): 7.47-7.35 (m, 5H, H-2' to 6'), 7.32 (dd, J = 8.0, 1.6 Hz, 1H, H-6), 7.08 (d, J = 2.4 Hz, 1H, H-2), 6.86 (d, J = 8.0 Hz, 1H, H-

5), 6.05 (s, 2H, H-7), 4.37 (s, 2H, H-7'); ¹³C-NMR (CDCl₃, 100 MHz, δ/ppm): 170.7 (C-8), 148.2 (C-4), 146.5 (C-3), 130.4 (C-2' C-6'), 129.1 (C-4'), 127.9 (C-1'), 127.2 (C-3' C-5'), 125.9 (C-1), 123.6 (C-6), 109.3 (C-2), 107.8 (C-5), 101.5 (C-7), 60.1 (C-7'); EIMS (m/z): 334 [M]⁺ (1 %), 165 (20 %), 156 (18 %), 154 (22 %), 149 (100 %), 121 (26 %), 119 (6 %), 91 (17 %).

Antibacterial activity

The results of the antibacterial screening are displayed in Tables 1 and 2, respectively.

The molecule, **5k**, exhibited the highest activity against all the Gram-bacterial strains. Its MIC values were as 11.92 ± 3.40, 8.37 ± 2.22, 9.28 ± 2.31, 11.76 ± 1.30 and 10.30 ± 1.63 μmoles/L relative to MIC values of ciprofloxacin, the reference standard, as 9.42 ± 1.09, 8.02 ± 2.17, 8.11 ± 1.32, 8.88 ± 2.00 and 9.23 ± 1.87 μmoles/L. The molecules **5c**, **5e** and **5j** showed

Table 1: Antibacterial activity (inhibition) of the synthesized compounds

Compound	Inhibition (%)				
	<i>S. typhi</i> (-)	<i>E. coli</i> (-)	<i>P. aeruginosa</i> (-)	<i>B. subtilis</i> (+)	<i>S. aureus</i> (+)
5a	60.35±1.41	64.31±5.00	60.79±3.04	59.90±5.00	69.30±3.70
5b	61.29±4.94	84.69±1.94	52.46±3.71	65.80±3.30	67.95±3.55
5c	54.47±1.76	81.69±1.09	55.04±4.38	51.55±0.95	59.35±2.92
5d	72.65±1.24	76.50±4.63	58.42±3.42	61.50±1.10	72.85±5.00
5e	57.06±5.00	60.81±1.19	36.63±1.46	53.45±4.55	47.55±3.55
5f	65.59±1.47	69.38±4.38	50.92±2.08	62.20±0.20	65.20±5.00
5g	47.24±5.00	66.50±1.38	35.67±1.25	56.27±2.34	75.60±1.20
5h	61.18±4.71	79.88±0.50	54.71±4.63	68.05±2.85	51.65±4.50
5i	62.24±0.82	84.69±1.06	43.92±1.75	59.10±1.40	66.35±0.35
5j	53.24±5.00	80.38±2.00	46.63±1.46	52.60±3.20	69.05±3.35
5k	70.35±3.06	87.38±1.75	89.33±1.42	72.60±2.20	85.35±1.65
5l	61.76±1.88	69.44±0.44	68.08±2.00	55.30±1.01	74.55±2.45
Ciprofloxacin	91.19±2.10	90.44±1.23	92.00±2.76	89.98±2.07	92.21±1.59

Table 2: MIC values of antibacterial activity

Compound	MIC				
	<i>S. typhi</i> (-)	<i>E. coli</i> (-)	<i>P. aeruginosa</i> (-)	<i>B. subtilis</i> (+)	<i>S. aureus</i> (+)
5a	13.03±2.07	13.54±2.14	14.25±2.44	15.01±2.76	11.58±1.40
5b	12.36±1.68	8.54±4.40	14.58±3.37	12.06±1.15	13.84±2.67
5c	17.08±1.13	10.66±2.06	17.79±1.94	17.11±1.75	13.41±2.97
5d	13.91±1.20	10.86±2.11	16.72±1.75	13.03±1.87	10.59±1.76
5e	16.68±2.40	15.13±1.11	-	15.51±2.98	-
5f	13.78±1.98	11.67± 1.22	17.38±2.69	12.00±2.38	12.53±2.53
5g	-	-	-	-	-
5h	12.68±2.13	10.57±2.83	18.08±2.05	10.72±1.55	16.88±1.55
5i	11.46±3.73	9.23±1.28	-	13.83±1.87	12.44±1.90
5j	17.51±4.80	10.93±1.50	-	15.27±1.38	10.52±1.81
5k	11.92±3.40	8.37±2.22	9.28±2.31	11.76±1.30	10.30±1.63
5l	13.89±2.00	11.98±1.39	11.58±3.25	17.02±2.08	13.83±4.07
Ciprofloxacin	9.42±1.09	8.02±2.17	8.11±1.32	8.88±2.00	9.23±1.87

Note: Minimum inhibitory concentration (MIC) was measured with suitable dilutions (5-30 μg/ well) and results were calculated using EZ-Fit Perrella Scientific Inc. Amherst USA software

50 % inhibitory action, relative to ciprofloxacin, against *S. typhi*; **5e** against *E. coli*; **5a**, **5e** & **5l** against *B. subtilis*; and **5h** against *S. aureus*. The synthesized molecules showed very low activity against *P. aeruginosa* but **5k** and **5l** remained good with MIC values of 9.28 ± 2.31 and 11.58 ± 3.25 $\mu\text{moles/L}$ respectively relative to the reference with MIC value of 8.11 ± 1.32 $\mu\text{moles/L}$.

DISCUSSION

Compound **5a**, was synthesized as white amorphous solid in 92 % yield with melting point of 210 °C. Its molecular formula was $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_5\text{S}$, based on molecular ion peak at m/z 320 in EIMS and integration of protons in $^1\text{H-NMR}$ spectrum. In the IR spectrum, the characteristic stretching absorption bands appeared at 3256 and 1413 cm^{-1} assigned to N-H and S=O respectively. The prominent peaks in EIMS at m/z 149 for 3,4-methylenedioxy benzoyl and 77 for phenyl cations support the structure of **5a**. Mass fragmentation of **5g** is elaborated in Figure 1. The aromatic section of $^1\text{H-NMR}$ spectrum showed three signals, one doublet and two triplets, at δ 7.92 (d, $J = 7.6$ Hz, 2H, H-2' & 6'), 7.58 (t, $J = 7.6$ Hz, 1H, H-4') and 7.47 (t, $J = 7.2$ Hz, 2H, H-3' & 5') for five protons of phenyl group. The three aromatic protons of 1,3-benzodioxol moiety resonated at δ 7.19 (dd, $J = 8.4, 1.6$ Hz, 1H, H-6), 7.04 (d, $J = 1.2$ Hz, 1H, H-2) and 6.80 (d, $J = 8.0$ Hz, 1H, H-5); and two

non-aromatic protons appeared at δ 6.01 (s, 2H, H-7).

The whole molecular structure was also supported by twelve signals resonating in $^{13}\text{C-NMR}$ (BB and DEPT) spectrum for five quaternary, eight methine and one methylene carbon. The four quaternary, three methine and one methylene signals of 1,3-benzodioxol-5-ylcarbonyl moiety resonated at δ 170.5 (C-8), 148.7 (C-4), 146.4 (C-3), 125.6 (C-1), 122.6 (C-6), 109.3 (C-2), 107.4 (C-5) and 101.6 (C-7). The phenyl group attached to electron withdrawing sulfono group was characterized by four signals, one for quaternary and three for methine carbons, two signals resonated with double intensities at δ 127.1 (C-3' & C-5') and 124.8 (C-2' & C-6') and two with single intensities at δ 145.8 (C-1') and 132.4 (C-4'). The above discussion corroborated the structural formula of **5a**, named, 2-(1,3-benzodioxol-5-ylcarbonyl) benzenesulfonohydrazide.

The better activity of **5k** may be attributed to the presence of trisubstituted phenyl ring linked with sulfamoyl group. In addition to **5e**, **5g** remained inactive against *P. aeruginosa* & *S. aureus* and **5i** & **5j** showed no activity against *P. aeruginosa*. Nearly all the synthesized compounds exhibited activity comparable to the reference standard, ciprofloxacin.

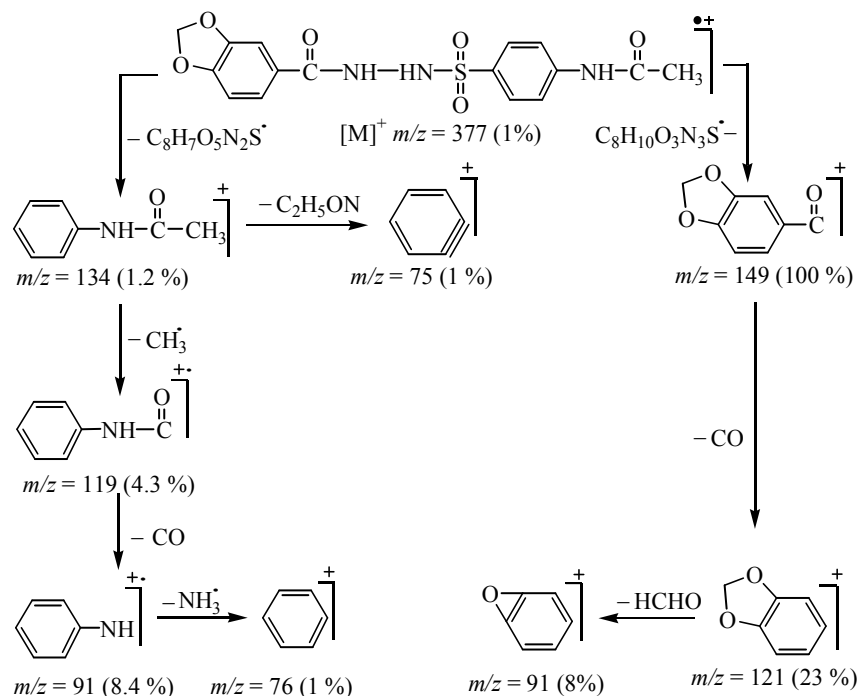


Figure 1: Mass fragmentation of 2-(1,3-Benzodioxol-5-ylcarbonyl)-4-acetamidobenzenesulfonohydrazide (**5g**)

CONCLUSION

The simplicity of the synthesis of the compounds indicates that the compounds can be produced at relatively low cost. The moderate but significant inhibitory activities of the synthesized sulfonamides bearing the heterocyclic moiety are known to be valuable for their pharmaceutical industry. Thus, these molecules should be further evaluated as lead compounds for discovery of new drug candidates.

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REFERENCES

- Ozbek N, Katircioglu H, Karacan N, Baykal T. Synthesis, characterization and antimicrobial activity of new aliphatic sulfonamide. *Bioorgan Med Chem* 2007; 15: 5105-5109.
- Alsughayer A, Elassar AZA, Mustafa S, Al Sagheer F. Synthesis, structural analysis and antibacterial activity of new potent sulfonamide derivatives. *J Biomater Nanobiotechnol* 2011; 2: 144-149.
- Kumar S, Niranjana MS, Chaluvareju KC, Jamakhandi CM, Kadadevar D. Synthesis and antimicrobial study of some schiff bases of sulfonamides. *J Curr Pharm Res* 2010; 1: 39-42.
- Baskin JM, Wang Z. A mild, convenient synthesis of sulfinic acid salts and sulfonamide from alkyl and aryl halides. *Tetrahedron Lett* 2002; 43: 8479-8483.
- Sondhi SM, Dwivedi AD, Singh J, Gupta PP. Synthesis and anti-inflammatory activity evaluation of some sulfonamide and amide derivatives of 4-aryl-3-(2 or 4-picolyl)-2-imino-4-thiazolines. *Indian J Chem* 2010; 49B: 1076-1082.
- Cami GE, Arellano RD, Del MC, Fustero S, Pedregosa JC. Synthesis, growth and characterization of new 1, 3, 4-thiadiazole-5-(N-substituted)-sulfonamides crystals. *J Argent Chem Soc* 2006; 94: 5-17.
- Argyropoulou I, Geronikaki A, Vicini P, Zani F. Synthesis and biological evaluation of sulfonamide thiazole and benzothiazole derivatives as antimicrobial agents. *Arkivoc*. 2009; 6: 89-102.
- Seikwan O, Moon HI, Son IH, Jung JC. Synthesis of sulfonamides and evaluation of their histone deacetylase (HDAC) activity. *Molecules* 2007; 12: 1125-1135.
- Shi F, Tse MK, Zhou S, Pohl MM, Radnik J, Huebner S, Jaehnsch K, Brueckner A, Beller M. Green and efficient synthesis of sulfonamides catalyzed by nano-Ru/Fe₃O₄. *J Am Chem Soc* 2009; 131: 1775-1779.
- Thakur A, Thakur M, Khadikar PV. QSAR study on inhibition of *E. coli* by sulfonamide. *Arkivoc* 2006; 14: 87-102.
- Aziz-ur-Rehman, Siddiqa A, Abbasi MA, Rasool S, Siddiqui SZ, Gul S, Ashraf M, Nasar R. Enzyme inhibition studies on N-substituted sulfonamides derived from m-Phenetidine. *Pak J Chem* 2013; 3(3): 1-7.
- Kaspady M, Narayanaswamy VK, Raju M, Rao GK. Synthesis, antibacterial activity of 2,4-disubstituted oxazoles and thiazoles as bioesters. *Lett Drug Des Discov* 2009; 6: 21-28.
- Yang CR, Zang Y, Jacob MR, Khan SI, Zhang YJ, Li XC. Antifungal activity of C-27 steroidal saponins. *Antimicrob Agents Ch* 2006; 50(5): 1710-1714.