Research Article

Synthesis, Characterization, and Evaluation for Antibacterial and Antifungal Activities of *N*-Heteroaryl Substituted Benzene Sulphonamides

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The synthesis and biological activity of *N*-heteroaryl substituted benzene sulphonamides (**3a–h**) were successful. Simple condensation reaction of benzene sulphonyl chloride (**1**) with substituted heteroaromatic compounds (**2a–h**) under dry pyridine and acetone gave the target molecules (**3a–h**) in good to excellent yield. The compounds were characterized using FTIR, ¹HNMR, and ¹³CNMR. The compounds were screened for antibacterial activity against *E. coli*, *Salmonella typhi*, *P. aeruginosa*, *B. cereus*, *K. pneumoniae*, and *Sarcina lutea* and antifungal activity against *C. albicans* and *A. niger*. The results of the antimicrobial activity showed improved biological activity against some tested organisms.

1. Introduction

A large number of sulphonamide derivatives have ultimately been reported to show substantial protease inhibitory properties [1]. Sulphonamides are synthetic antimicrobial agents which act as competitive inhibitors of the enzyme dihydropteroate synthetase (DHPS) [2]. The basic sulphonamide group, SO₂NH, occurs in various biological active compounds widely used as antimicrobial drugs, antithyroid agents, antitumor, antibiotics, and carbonic anhydrase inhibitors [3, 4]. Clinically, sulphonamides are used to treat several urinary tract infections and gastrointestinal infections [5]. Aromatic or heteroaromatic sulphonamides that are used as antitumor agent act by inhibiting carbonic anhydrase. Structurally, sulphonamides are similar to *p*-aminobenzoic acid (PABA) which is a cofactor needed by bacteria for the synthesis of folic acid and therefore could compete for incorporation. Sulphonamide antibiotics are used as veterinary medicines to treat infections in livestock herds [6, 7]. Additionally, sulphonamides are extremely useful pharmaceutical compounds because they exhibit a wide range of biological activities such as anticancer, anti-inflammatory, and antiviral activity [8–12]. The sulphonylation of amines with sulphonyl chlorides in the

presence of a base is still being used as the method of choice because of high efficiency and simplicity of the reaction [13]. However, this approach is limited by the formation of undesired disulphonamides with primary amines and by the need of harsh reaction conditions for less nucleophilic amines such as anilines [14]. Additionally, side reactions take place in the presence of a base. Sulphonamides have been used as protecting groups of OH or NH functionalities for easy removal under mild conditions [15, 16].

Resistance to sulphonamides by bacteria is most likely a result of a compensatory increase in the biosynthesis of *p*-aminobenzoic acid by bacteria although other mechanisms may play a role [17, 18]. Resistance of *E. coli* strains to sulphonamide has been shown due to their containing sulphonamide-resistant dihydropteroate synthase [19]. Research has shown that all things being equal, antibacterial activities of sulphonamides decreases as the length of the carbon chain increases [20]. This work describes the synthesis, spectroscopic characterization of some *N*-heteroaryl substituted benzene sulphonamides (**3a–h**) and evaluation for their antimicrobial activities against *Bacillus cereus*, *Sarcina lutea*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Salmonella typhi*, *Klebsiella pneumoniae*, *Aspergillus niger*, and *Candida albicans*.

2. Experimental

2.1. General Consideration. All the starting materials and reagents were obtained from Sigma-Aldrich and were used without further purification. The melting points were determined with Fischer John's melting point apparatus and are uncorrected. IR spectra were recorded on 8400 s Fourier Transform Infrared (FTIR) spectrophotometer using KBr disc and absorption was reported in wave number (cm^{-1}). IR analysis was done at National Research Institute for Chemical Technology (NARICT), Zaria, Kaduna State. Nuclear Magnetic Resonance (^1H -NMR and ^{13}C -NMR) were determined using Jeol 400 MHz at University of Strathclyde, Scotland. The chemical shifts were reported in (δ).

2.2. General Procedures. The synthesis of *N*-heteroaryl substituted benzene sulphonamide (**3a-h**) is described below. Heteroaromatic compounds (**2a-h**) (10 mmol) were dissolved in anhydrous acetone (10.00 ml) with dry pyridine (3 ml) and benzene sulphonyl chloride (**1**) (1.76 g, 10 mmol) was added at room temperature and allowed to stir for about 5 minutes for dissolution. The reaction mixture was left for 24 hours to give *N*-heteroaryl substituted benzene sulphonamide (**3a-h**) as crystalline solid after suction filtration. The crude product was recrystallized from acetone and dimethylformamide (DMF). The products were dried in a hot air oven at 50°C for 6 hours to give the target molecule in good to excellent yields (67.8% to 85.5%).

N-(Pyridine-2-yl) Benzene Sulphonamide (**3a**). Yield: 1.99 g (85.0%); m.p. $169\text{--}170^\circ\text{C}$; IR (KBr) cm^{-1} 3475 (NH), 3030 (C-H aromatic), 1617 (C=C of aromatic), 1372 (C=N), 1270 (S=O), 1119 (SO_2NH), 972 (C-H deformation), 678 (monosubstitution). ^1H NMR (400 MHz, DMSO-d_6): δ 12.11 (s, 1 H), 7.99 (d, $J = 5.41$ Hz, 1 H), 7.87 (m, 5 H), 7.54 (m, 4 H), 7.17 (d, $J = 8.68$ Hz, 2 H), 6.85 (t, $J = 6.32$ Hz, 2 H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 153.82, 143.49, 142.59, 141.15, 132.70, 129.51, 127.03, 115.93, 114.49.

N-(4 Methylpyridine-2-yl) Benzene Sulphonamide (**3b**). Yield: 1.95 g (85.5%); m.p. $209\text{--}210^\circ\text{C}$; IR (KBr) cm^{-1} 3468 (N-H), 3034 (C-H aromatic), 2911 (C-H aliphatic), 1613 (C=C aromatic), 1274 (S=O), 1385 (C=N), 1148 (SO_2NH), 725 (monosubstitution). ^1H NMR (400 MHz, DMSO-d_6): δ 12.12 (s, 1 H), 7.81 (s, 1 H), 7.51 (m, 1 H), 7.03 (d, $J = 3.40$ Hz, 2 H), 6.66 (d, $J = 5.89$ Hz, 2 H), 2.22 (d, $J = 2.24$ Hz, 3 H).

N-(3 Nitropyridine-2-yl) Benzene Sulphonamide (**3c**). Yield: 1.81 g (65.1%); m.p. $153\text{--}154^\circ\text{C}$. IR (KBr) cm^{-1} 3459 (N-H), 3114 (C-H aromatic), 1642 (C=C aromatic), 1450 (NO_2), 1226 (S=O), 1334 (C=N), 1069 (SO_2NH), 763 (substitution in benzene ring); ^1H NMR (400 MHz, DMSO-d_6): δ 8.38 (m, 5 H), 7.89 (s, 1 H), 6.74 (dt, $J = 3.30$ Hz, 6.48 Hz, 1 H).

N-(5 Nitropyridine-2-yl) Benzene Sulphonamide (**3d**). Yield: 1.96 g (70.5%); m.p. $179\text{--}180^\circ\text{C}$; IR (KBr) cm^{-1} 3484 (N-H), 3057 (C-H aromatic), 1629 (C=C aromatic), 1295 (S=O), 2647 (C-H deformation), 1110 (SO_2NH aromatic), 995 (C-H deformation) 763 (substitution in benzene), ^1H NMR

(400 MHz, DMSO-d_6): δ 8.84 (t, $J = 2.51$ Hz, 1 H), 8.11 (m, 5 H), 7.53 (s, 1 H), 6.49 (d, $J = 9.30$ Hz, 1 H).

N-(3 Hydropyridine-2-yl) Benzene Sulphonamide (**3e**). Yield: 1.76 g (70.7%); m.p. $189\text{--}190^\circ\text{C}$; IR (KBr) cm^{-1} 3483 (N-H), 3289 (O-H), 3143 (C-H aromatic), 1627 (C=C aromatic), 1379 (C=N), 1169 (SO_2NH), 904 (C-H deformation) 797 (substitution in benzene ring). ^1H NMR (400 MHz, DMSO-d_6): δ 7.95 (m, 5 H), 7.81 (m, 1 H), 7.64 (t, 7.86 Hz, 2 H), 7.30 (dt, $J = 1.46$ Hz, 7.86 Hz, 1 H), 6.51 (ddd, $J = 1.27$ Hz, 4.90 Hz, 7.86 Hz, 3 H) 6.05 (s, 1 H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 153.01, 146.70, 135.69, 135.01, 131.39, 130.13, 130.08, 129.08, 112.40.

N-(5 Chloropyridine-2-yl) Benzene Sulphonamide (**3f**). Yield: 1.88 g (74.02%); m.p. $150\text{--}151^\circ\text{C}$. IR (KBr) cm^{-1} 3684 (N-H), 3060 (C-H aromatic), 1695 (C=C aromatic), 1483 (S=O), 1354 (C=N), 1159 (SO_2NH), 937 (C-H deformation), 747 (substitution in benzene ring). ^1H NMR (400 MHz, DMSO-d_6): δ 8.21 (d, $J = 2.65$ Hz, 2 H), 7.91 (m, 5 H), 7.79 (ddd, $J = 2.08$ Hz, 3.45 Hz, 9.12 Hz, 3 H), 7.09 (d, $J = 1.69$ Hz, 2 H).

N-(2,6-Dichloropyridine-4-yl) Benzene Sulphonamide (**3g**). Yield: 2.17 g (71.6%); m.p. $199\text{--}200^\circ\text{C}$; IR (KBr) cm^{-1} 3314 (N-H), 3124 (C-H aromatic), 1657, 1533 (C=C aromatic), 1141 (SO_2NH), 1042 (C-N), 995 (C-H deformation), 797 (substitution in benzene ring). ^1H NMR (400 MHz, DMSO-d_6): δ 7.60 (s, 1 H), 6.86 (m, 5 H).

N-(3,5-Dichloropyridine-2-yl) Benzene Sulphonamide (**3h**). Yield: 2.20 g (72.6%); m.p. $71\text{--}72^\circ\text{C}$. IR (KBr) cm^{-1} 3465 (N-H), 3152 (C-H aromatic), 1621 (C=C aromatic), 1461 (S=O), 1235 (C-S), 1041 (SO_2NH), 732 (substitution in benzene ring). ^1H NMR (400 MHz, DMSO-d_6): δ 7.92 (d, $J = 2.45$ Hz, 2 H), 7.76 (dt, $J = 2.27$ Hz, 7.13 Hz, 2 H), 6.52 (s, 1 H).

2.3. Sensitivity Tests. Agar cup diffusion technique method as described by Vincent (2005) [21] was used to determine the antimicrobial activities of the synthesized compounds. Sensitivity test agar plates were seeded with 0.1 ml of 24 hours culture of each microorganism into its corresponding petri dish previously labeled using the molten agar already prepared. The plates were allowed to set after which cups were made in each sector previously drawn on the backside of the bottom-plate using marker. Using the pipette (sterile), each cup was filled with six drops of their corresponding antimicrobial agent (in appropriate solvent at a concentration of 2 mg/mL). The plates were finally incubated at 37°C for 24 hours for bacteria and 48 hours for fungi. The solubilizing solvent used was dimethylformamide (DMF). Mueller Hinton agar was prepared in 20 mL portions kept molten at 45°C . The zone of inhibition (clearance) produced after 24 hours on incubation at 37°C was measured. The procedure was repeated for ciprofloxacin and ketoconazole drugs (bacteria and fungi standard, resp.).

2.4. Minimum Inhibitory Concentration (MIC) Tests. The MIC was determined by further dilution of the test sample

SCHEME 1: Synthesis of 2-aminopyridine substituted benzene sulphonamides.

SCHEME 2: Synthesis of various biologically active *N*-heteroaryl substituted benzene sulphonamides.

found to be sensitive against a particular organism. Serial dilutions of the sulphonamides were prepared from 2 mg/mL solution of the sulphonamides to give 2.0–0.125 mg/mL. After dilution, the test solutions were added to their corresponding cups previously made in the molten agar starting from the lowest concentration (0.125–1.0 mg/mL). This was followed by incubation at the appropriate incubation temperature

and time. The resultant inhibition zones of diameter (IZD) were measured and the value was subtracted from the diameter of the cork borer (8 mm) to give the inhibition zone diameter (IZD). The MIC was also determined using graph of logarithm of IZD² against concentration for each plate containing a specific compound and a microorganism. The antilogarithm of the intercept on X-axis gives the MIC.

TABLE 1: Result of the sensitivity test against organisms with their inhibition zone diameter (IZD) in mm.

S. number	Antibacterial activity						Antifungal activity	
	<i>B. cereus</i>	<i>S. lutea</i>	<i>P. aeruginosa</i>	<i>E. coli</i>	<i>S. typhi</i>	<i>K. pneumonia</i>	<i>C. albicans</i>	<i>A. niger</i>
3a	10		10	—	10	—	10	10
3b	10	10	12	11	9	10	16	20
3c	9	12	10	10	8	11	16	15
3d	11	17	12	9	12	8	15	9
3e	21	20	20	12	23	21	10	18
3f	—	—	—	—	—	—	—	—
3g	27	28	23	15	24	20	19	22
3h	23	16	25	18	26	24	18	22
Ciprofloxacin	26	26	25	20	28	26	—	—
Ketoconazole	—	—	—	—	—	—	24	23

TABLE 2: Result of the Minimum Inhibition Concentration (MIC) (mg/mL).

Compound	Antimicrobial activity						Antifungal activity	
	<i>B. cereus</i>	<i>S. lutea</i>	<i>P. aeruginosa</i>	<i>S. typhi</i>	<i>E. coli</i>	<i>K. pneumonia</i>	<i>C. albicans</i>	<i>A. niger</i>
3a	0.1175	0.1175	—	0.1585	—	—	0.1230	0.1549
3b	0.1622	0.1584	0.1202	0.1622	0.1514	0.1585	0.1288	0.1549
3c	0.240	0.0603	0.1259	0.1905	0.1259	0.100	0.1148	0.0977
3d	—	0.1175	0.1230	—	0.1905	0.622	—	0.0955
3e	—	0.2399	0.1549	0.1259	0.1950	—	0.1660	0.1259
3g	0.1531		0.1479	0.1585	0.1318	0.1950	0.0870	0.0794
3h	0.1820	0.0977	0.1549	0.1950	0.1585	—	0.1096	0.1202
SD	0.0912	0.0457	0.0468	0.1288	0.0229	0.1023	0.0776	0.0955

SD = standard group.

IZD = inhibition zone diameter.

3. Result and Discussion

We described here the synthesis of various *N*-heteroaryl substituted benzene sulphonamides (**3a–h**) using simple condensation of benzene sulphonyl chloride (**1**) and substituted pyridine (**2a–h**) as starting materials shown in Schemes 1 and 2. The *N*-heteroaryl substituted benzene sulphonamides (**3a–h**) were synthesized as white crystalline solid in exception of 2-amino-5-nitropyridine **3d** and 2-amino-3-nitropyridine **3c** derivatives that were yellowish solid. The FTIR spectra revealed the presence of a sulphonamide group (1373–1140 cm⁻¹), –NH group (3640–3461 cm⁻¹). The ¹HNMR and ¹³CNMR signals agree with the structures of the compounds. Worthy to mention is the appearance of peaks at 6.86 which is assigned to heteroaromatic protons. The *N*-heteroaryl substituted benzene sulphonamide derivatives (**3a–h**) synthesized were screened for their antibacterial activities against some of the pathogenic bacteria, namely, *Bacillus cereus*, *Sarcina lutea*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Salmonella typhi*, and *Escherichia coli*, and antifungal activities against some pathogenic fungi, namely, *Candida albicans* and *Aspergillus niger*. The antimicrobial activity of the analogues was compared with standard drug ciprofloxacin and ketoconazole for antibacterial and

antifungal activities, respectively. The result of inhibition zone diameter IZD as presented in Table 1 indicates that compound **3f** was inactive. The result of the minimum inhibitory concentration MIC as presented in Table 2 shows that compounds **3e**, as against *S. typhi*, **3c**, as against *K. pneumoniae*, and **3g**, as against *A. niger*, have more actives than the standard drugs. A further observation of table indicates that most of the synthesized compounds had comparable antimicrobial property. We used ciprofloxacin and ketoconazole as standards because ciprofloxacin and ketoconazole are antibacterial and antifungal standard drugs that show zone of inhibition like other antimicrobial synthesized compounds. We discuss piperidine/acetone as other base/solvent combination that has been examined other than pyridine/acetone because piperidine/acetone and its derivatives are ubiquitous building blocks in the synthesis of pharmaceuticals compounds like antidepressant drug [22–24] and vasodilators [25]. Piperidine/acetone is also commonly used in sequencing of DNA16 and in solid phase peptide synthesis [26]. This is together with the steric factor which potentiates formation of *p*-nucleophiles (saturated heterocyclic amines) that are added in excess moles to serve as base picking the released HCl and yielding water soluble salt and enhancing the yield of products that were now ready for the next step, that is, acid hydrolysis of amide linkage rather than sulphonamide.

4. Conclusions

The present study describes a convenient and efficient protocol for the synthesis of *N*-heteroaryl substituted benzene sulphonamide derivatives using benzene sulphonyl chloride and heteroaromatic compounds under dry pyridine and acetone conditions. We believe that this procedure is convenient, economic, and user-friendly process for the synthesis of these various sulphonamide compounds. All the synthesized compounds were supported by IR, ¹HNMR, and ¹³CNMR spectral data. The sulphonamide derivatives were screened for their antimicrobial activity against few bacterial and fungal strains and it was observed that some of the compounds showed more biological activity than the standard drug.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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