

## Research Article

# Synthesis and Antimicrobial Activities of *N*-(Heteroaryl-substituted)-*p*-toluenesulphonamides

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A new class of *N*-(heteroaryl-substituted)-*p*-toluenesulphonamides has been synthesized exhibiting antibacterial and antifungal properties. The condensation reaction of *p*-toluenesulphonyl chloride **1** with appropriate substituted amino pyridines **2a–g** in acetone furnished *N*-(heteroaryl-substituted)-*p*-toluenesulphonamides **3a–g**. These derivatives were characterized by IR, <sup>1</sup>H-, and <sup>13</sup>C-NMR spectroscopy and were screened *in vitro* against gram-positive bacteria, gram-negative bacteria, and fungi organisms using agar-diffusion method. Results indicated improved biological activities over reference drugs such as Tetracycline (TCN) and Fluconazole (FLU).

## 1. Introduction

Sulphonamides are known to represent a class of medicinally important compounds which are extensively used as antimicrobial, antimalarial, and anticancer agents and inhibitors of carbonic anhydrase among others [1, 2]. Before the discovery of antibiotics in the 1940s, sulphonamides were the first efficient compounds used to treat microbial infections [3]. Sulphonamides are the amides of sulphonic acid which contain the basic group –SO<sub>2</sub>NH. They have been used against most gram-positive and many gram-negative organisms, fungi, and certain protozoa [4]. Sulphonamides are used in veterinary medicines to treat infections in livestock, also used in medicinal chemistry as potential therapeutic agents for depression, sleep disorder, pains, and hypertension among others [5–7]. Clinical sulphonamides have been used for the treatment of uncomplicated urinary tract infections [8]. Interest in the pharmacological activities of sulphonamide prompted the synthesis of scaffolds of sulphonamides and their derivatives. The discovery of sulphonamides started in the early 1930s, when Gerhard Domagk [9] discovered one of the dyes, Prontosil. Prontosil's discovery ushered in the era of antibacterial and had a profound impact on pharmaceutical research, drug laws, and medical history. Prontosil is known as prodrug [10] which was reduced to

sulphanilamide. The potency of these clinically useful drugs in treatment of microbial infections and other activities encouraged the development of some more potent and significant compounds.

In spite of recent advances in the development of sulphonamides as drugs, the synthesis and biological evaluation of *N*-heteroaryl derivatives of *p*-toluenesulphonamides remain largely unknown. Hence these led us to the synthesis of such new categories of *p*-toluenesulphonamides for evaluation of the antimicrobial activities.

## 2. Results and Discussion

**2.1. Chemistry (Synthesis).** In this present investigation, a series of *N*-heteroaryl substituted sulphonamides **3a–g** was prepared by condensation reaction of *p*-toluenesulphonyl chloride **1** and amino pyridine **2a–g** in dry pyridine and acetone at room temperature for 24 hours. The structure of the derivatives was confirmed by IR, <sup>1</sup>H-NMR, and <sup>13</sup>C-NMR as described in the experimental section. The compound **3a** was synthesized as white needle-like crystals with the melting point of 205°C–206°C. The IR spectrum revealed the presence of –NH group (3236 cm<sup>-1</sup>), aromatic C–H (3042 cm<sup>-1</sup>), and sulphonyl group (1133 cm<sup>-1</sup>) in the molecule. In <sup>1</sup>H-NMR, the

peaks at  $\delta$ 8.01 are assigned to NH-proton,  $\delta$ 7.76 is assigned to C<sub>7</sub>-proton,  $\delta$ 7.70 and  $\delta$ 6.86 (m, 8H) are due to aromatic protons,  $\delta$ 7.33 is assigned to C<sub>8</sub>-proton,  $\delta$ 7.14 is assigned to C<sub>9</sub>-proton, and  $\delta$ 2.32 is due to C<sub>10</sub>, aliphatic hydrogen. In <sup>13</sup>C-NMR, peaks at  $\delta$ 153.57– $\delta$ 114.10 are due to aromatic carbons (C<sub>1</sub>–C<sub>9</sub>) and  $\delta$ 21.49 is due to aliphatic carbon (CH<sub>3</sub>). The spectrum agrees with the assigned structure. On the basis of similar spectral characterization, the structures of the synthesized derivatives **3b–g** were identified.

### 3. Antimicrobial Screening

The results of *in vitro* antibacterial and antifungal activities of the synthesized compounds against gram-positive bacteria, gram-negative bacteria, and fungi organisms using diffusion method are presented in Tables 2 and 3. The screening of the synthesized compounds showed inactive against gram-negative bacteria organisms. Some of the compounds, **3b**, **3c**, **3e**, and **3g**, showed good gram-positive antibacterial activity and compounds **3c–e** showed moderate to little antifungal activity. Compound **3e** is the most active against both antibacterial and antifungal activities (Table 1) (Scheme 1).

### 4. Conclusion

The synthesis of *N*-(heteroaryl-substituted)-*p*-toluenesulphonamides has been achieved successfully. The assigned structures were supported by spectra analysis. The sulphonamides have good antimicrobial properties against some of the tested organisms.

**4.1. Materials and Methods.** The melting points were determined with Fischer John's melting point apparatus and are uncorrected. IR spectra were recorded on 8400s Fourier transform infrared (FTIR) spectrophotometer and are reported in wave number (cm<sup>-1</sup>). IR analysis was done at National Research Institute for Chemical Technology (NARICT), Zaria, Kaduna State. <sup>1</sup>H and <sup>13</sup>C-NMR were determined using Jeol 400 MHz at Strathclyde University, Scotland. Chemical shifts are reported in  $\delta$  scale. Tests for biological activities were carried in the Laboratories of the Faculty of Pharmacy Sciences, University of Nigeria, Nsukka. All reagents were of technical grade.

**4.2. Synthesis.** Compounds **3a–g** were synthesized by the condensation reaction of compound **1** with different substituted amino pyridines **2a–g** in the presence of acetone and dry pyridine.

**4.3. Antimicrobial Screening.** The antimicrobial properties of the sulphonamides were investigated in form of the general sensitivity testing and minimum inhibitory concentration (MIC) with respect to freshly cultured targeted organisms. The eight organisms used in this present study are gram-positive bacteria (*Bacillus subtilis*, *Bacillus cereus*, and *Staphylococcus aureus*), gram-negative bacteria (*Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Escherichia coli*), and fungal organisms (*Candida albicans* and *Aspergillus niger*).

The microorganisms were clinical isolates from Shanahan General Hospital Nsukka, and the *S. aureus* is of MRSA species. For each biological activity test, three experiments are performed and the average zone of inhibition is reported.

**4.3.1. Sensitivity Test of Compounds.** Agar-diffusion technique method as described by Okorie [11] was used to determine the antimicrobial (antibacterial and antifungal) activities of the synthesized compounds. Sensitivity test agar plates were seeded with 0.1 mL of 24-hour 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. It should be noted that the solubilizing solvent used was dimethyl formamide (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 Tetracycline and Fluconazole drugs (standard).

**4.3.2. Minimum Inhibitory Concentrations (MICs) Test of Compounds 3a–g.** The MIC was determined by further dilution of the test sample 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 into 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 borer (8 mm) to give the inhibition zone diameter (IZD). The MIC was also determined using graph of IZD<sup>2</sup> against logarithm of concentration for each plate containing a specific compound and a microorganism. The antilogarithm of the intercept on *x*-axis gives the MIC.

### 5. Experimental Section

**5.1. General Procedure for the Synthesis of the *N*-Heteroaryl-substituted-*p*-toluenesulphonamides (3a–g).** The preparation of 4-methyl-*N*-(pyridin-2-yl) benzenesulphonamide **3a** described below is a typical procedure for the preparation of these new *p*-toluenesulphonamides. 2-Amino pyridine (0.94 g, 10.0 mmol) was dissolved in a mixture of anhydrous acetone (20 mL) and dry pyridine (2 mL). *p*-Toluenesulphonyl chloride (1.91 g, 10.0 mmol) was then added later. The reaction mixture was warmed to room temperature and allowed to stir. The reaction was left for 24 hours and 1.50 g of 4-methyl-*N*-(pyridin-2-yl) benzenesulphonamide **3a** (product) was filtered off using suction filtration. On diluting

TABLE 1: Reactions of substituted amino pyridines with *p*-toluene sulphonyl chloride.

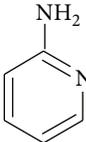
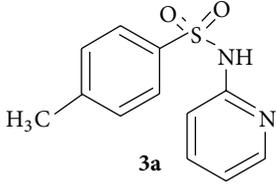
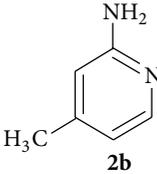
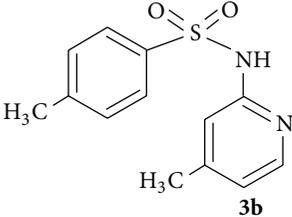
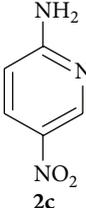
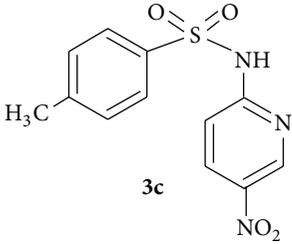
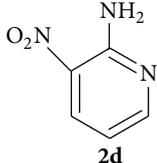
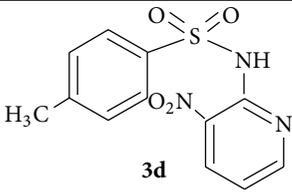
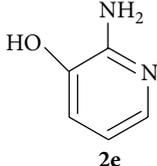
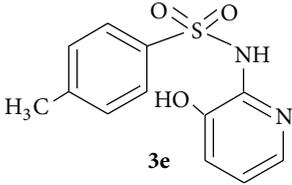
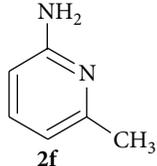
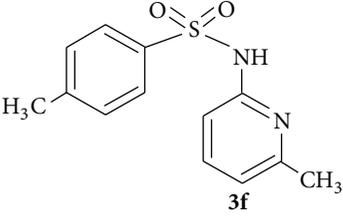
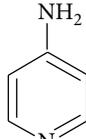
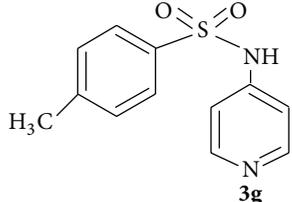
Entry	Substituted amino pyridines <b>2a-g</b>	Reaction time (h)	Product <b>3a-g</b>	Yield (%)
1.	 <b>2a</b>	24	 <b>3a</b>	66.1
2.	 <b>2b</b>	24	 <b>3b</b>	58.0
3.	 <b>2c</b>	24	 <b>3c</b>	53.9
4.	 <b>2d</b>	24	 <b>3d</b>	73.0
5.	 <b>2e</b>	24	 <b>3e</b>	72.7
6.	 <b>2f</b>	24	 <b>3f</b>	63.3
7.	 <b>2g</b>	24	 <b>3g</b>	50.4

TABLE 2: Inhibition zone diameter (IZD in mm) at 2 mg/mL.

Compound numbers	Gram-positive bacteria			Gram-negative bacteria			Fungi organisms	
	<i>B. subtilis</i>	<i>B. cereus</i>	<i>S. aureus</i>	<i>P. aeruginosa</i>	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>C. albicans</i>	<i>Asp. niger</i>
<b>3a</b>	—	—	—	—	—	—	—	—
<b>3b</b>	—	—	19	—	—	—	—	—
<b>3c</b>	—	7	20	—	—	—	7	—
<b>3d</b>	—	—	—	—	—	—	5	—
<b>3e</b>	10	11	13	—	—	—	7	—
<b>3f</b>	—	—	—	—	—	—	—	—
<b>3g</b>	—	7	18	—	—	—	—	—
TCN	21	18	22	16	29	11	—	—
FLU	—	—	—	—	—	—	26	27

Where TCN: Tetracycline clinical reference; FCN: Fluconazole clinical reference.

TABLE 3: Minimum inhibitory concentrations (MICs in mg/mL).

Compound numbers	Gram-positive bacteria			Gram-negative bacteria			Fungi organisms	
	<i>B. subtilis</i>	<i>B. cereus</i>	<i>S. aureus</i>	<i>P. aeruginosa</i>	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>C. albicans</i>	<i>Asp. niger</i>
<b>3b</b>	—	—	0.20	—	—	—	—	—
<b>3c</b>	—	0.23	0.19	—	—	—	0.23	—
<b>3d</b>	—	—	—	—	—	—	0.30	—
<b>3e</b>	0.24	0.13	0.17	—	—	—	0.23	—
<b>3g</b>	—	0.19	0.20	—	—	—	—	—
TCN	5.62	11.48	5.31	15.85	3.16	17.78	—	—
FLU	—	—	—	—	—	—	24.00	27.00

the filtrate with distilled water, a further crop (1.25 g) was obtained. The total product was recrystallized from dimethylformamide (DMF). 4-Methyl-*N*-(5-nitropyridin-2-yl) benzenesulphonamide **3c** and 4-methyl-*N*-(3-nitropyridin-2-yl) benzenesulphonamide **3d** were recrystallized from methanol solvent and *N*-(3-hydroxypyridin-2-yl)-4-methyl benzenesulphonamide **3e** was recrystallized from ethanol solvent. The products were dried in hot air oven under 50°C for 6 hours.

#### 5.1.1. 4-Methyl-*N*-(pyridin-2-yl) Benzenesulphonamide (**3a**).

On condensation reaction of *p*-toluenesulphonyl chloride **1** and 2-amino pyridine **2a** in dry pyridine and acetone at room temperature for 24 hours, 4-methyl-*N*-(pyridin-2-yl) benzenesulphonamide **3a** was obtained as a white needle-like solid with a melting point of 205°C-206°C. IR (KBr)  $\nu_{\text{max}}$ : 3236  $\text{cm}^{-1}$  (N-H stret.), 3042  $\text{cm}^{-1}$  (Ar C-H), 1133  $\text{cm}^{-1}$  ( $\text{SO}_2$ -functional group).  $^1\text{H-NMR}$  [DMSO- $d_6$ ]  $\delta$ : 8.01 (d;  $J = 5.25$  Hz, 1H; NH), 7.76 (d;  $J = 8.14$  Hz, 2H, Ar-H), 7.70 (m; 4H, phenyl-H), 7.33 (d;  $J = 8.14$  Hz, 2H, Ar-H), 7.14 (d;  $J = 8.70$  Hz, 1H, Ar-H), 6.86 (m; 4H, pyridyl-H), 2.32 (s; 3H,  $\text{CH}_3$ -phenyl).  $^{13}\text{C-NMR}$  [DMSO- $d_6$ ]  $\delta$ : 153.57–144.10 ( $\text{C}_1$ – $\text{C}_9$ , Ar-C), 21.49 ( $\text{C}_{10}$ , aliphatic carbon).

#### 5.1.2. 4-Methyl-*N*-(4-methylpyridin-2-yl) Benzenesulphonamide (**3b**).

On condensation reaction of *p*-toluenesulphonyl chloride **1** and 2-amino-4-methyl pyridine **2b** in acetone and dry pyridine at room temperature for 24 hours, 4-methyl-*N*-(4-methylpyridin-2-yl) benzenesulphonamide **3b** was obtained as a white solid with a melting point of 217°C-218°C. IR

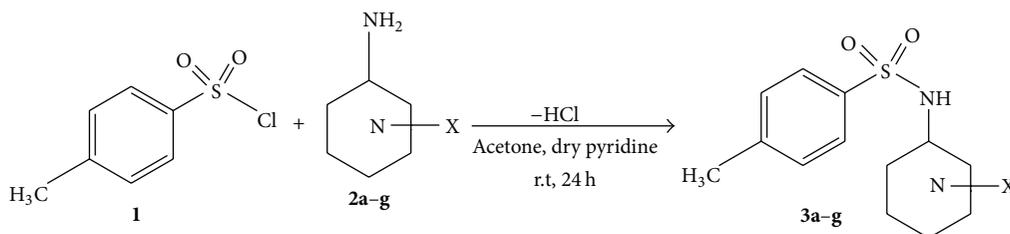
(KBr)  $\nu_{\text{max}}$ : 3229  $\text{cm}^{-1}$  (N-H stret.), 3037  $\text{cm}^{-1}$  (Ar C-H), 1141  $\text{cm}^{-1}$  ( $\text{SO}_2$ -functional group).  $^1\text{H-NMR}$  [DMSO- $d_6$ ]  $\delta$ : 7.81 (d;  $J = 5.87$  Hz, 2H, Ar-H), 7.74 (d;  $J = 8.20$  Hz, 2H, Ar-H), 7.31 (d;  $J = 8.09$  Hz, 1H, Ar-H), 6.99 (s; 1H, Ar-H), 6.67 (d;  $J = 5.86$  Hz, 1H, Ar-H), 3.39 (s; 1H, NH), 2.32 (s; 3H,  $\text{CH}_3$ -pyridyl), 2.22 (s; 3H,  $\text{CH}_3$ -phenyl).

#### 5.1.3. 4-Methyl-*N*-(5-nitropyridin-2-yl) Benzenesulphonamide (**3c**).

On condensation reaction of *p*-toluenesulphonyl chloride **1** and 2-amino-5-nitropyridine **2c** in acetone and dry pyridine at room temperature for 24 hours, 4-methyl-*N*-(5-nitropyridin-2-yl) benzenesulphonamide **3c** was obtained as a milky needle-like solid with a melting point of 183°C-184°C. IR (KBr)  $\nu_{\text{max}}$ : 3259  $\text{cm}^{-1}$  (N-H stret.), 3096  $\text{cm}^{-1}$  (Ar C-H), 1518–1349  $\text{cm}^{-1}$  ( $\text{NO}_2$  stret.), 1198  $\text{cm}^{-1}$  ( $\text{SO}_2$ -functional group).  $^1\text{H-NMR}$  [DMSO- $d_6$ ]  $\delta$ : 8.92 (d;  $J = 2.64$  Hz, 1H, Ar-H), 8.26 (dd;  $J_1 = 2.75$  Hz,  $J_2 = 9.46$  Hz, 1H, Ar-H), 7.50 (d;  $J = 8.05$  Hz, 2H, Ar-H), 7.13 (d;  $J = 7.90$  Hz, 2H, Ar-H), 6.71 (d;  $J = 9.46$  Hz, 1H, Ar-H), 5.30 (s, b; 1H; NH), 2.29 (s; 3H,  $\text{CH}_3$ -phenyl).

#### 5.1.4. 4-Methyl-*N*-(3-nitropyridin-2-yl) Benzenesulphonamide (**3d**).

On condensation reaction of *p*-toluenesulphonyl chloride **1** and 2-amino-3-nitropyridine **2d** in acetone and dry pyridine at room temperature for 24 hours, 4-methyl-*N*-(3-nitropyridin-2-yl) benzenesulphonamide **3d** was obtained as a yellowish needle-like solid with a melting point of 153°C-154°C. IR (KBr)  $\nu_{\text{max}}$ : 3454  $\text{cm}^{-1}$ –3268  $\text{cm}^{-1}$  (N-H stret.),



SCHEME 1

3110  $\text{cm}^{-1}$  (Ar C-H), 1333  $\text{cm}^{-1}$  ( $\text{NO}_2$  stret.), 1162  $\text{cm}^{-1}$  ( $\text{SO}_2$ -functional group).  $^1\text{H-NMR}$  [ $\text{DMSO-d}_6$ ]  $\delta$ : 8.41 (m, 7H, heteroaryl-H), 8.00 (s, b, 1H, NH), 7.51 (dt,  $J = 2.65$  Hz,  $J_1 = 8.07$  Hz,  $J_2 = 8.07$  Hz, 2H, Ar-H), 7.13 (d,  $J = 8.00$  Hz, 1H, Ar-H), 6.77 (dd,  $J_1 = 4.58$  Hz,  $J_2 = 8.31$  Hz, 1H, Ar-H), 2.29 (s, 3H,  $\text{CH}_3$ -phenyl).

**5.1.5. N-(3-Hydroxypyridin-2-yl)-4-methyl Benzenesulphonamide (3e).** On condensation reaction of *p*-toluenesulphonyl chloride **1** and 2-amino-3-hydroxyl pyridine **2e** in acetone/DMF (in mol ratio of 2:1) and dry pyridine at room temperature for 24 hours, *N*-(3-hydroxypyridin-2-yl)-4-methyl benzenesulphonamide **3e** was obtained as a pale white needle-like solid with a melting point of 105°C-106°C. IR (KBr)Vmax: 3474  $\text{cm}^{-1}$  (OH stret.), 3287  $\text{cm}^{-1}$  (N-H stret.), 3138  $\text{cm}^{-1}$  (Ar C-H), 1164  $\text{cm}^{-1}$  ( $\text{SO}_2$ -functional group).  $^1\text{H-NMR}$  [ $\text{DMSO-d}_6$ ]  $\delta$ : 7.82 (m; 7H, heteroaryl-H), 7.43 (d;  $J = 8.15$  Hz, 1H, NH), 7.29 (dd;  $J_1 = 1.39$  Hz,  $J_2 = 7.89$  Hz, 1H, Ar-H), 6.50 (dd,  $J_1 = 4.85$  Hz,  $J_2 = 7.85$  Hz, 1H, Ar-H), 5.97 (s; 1H, OH), 2.40 (s; 3H,  $\text{CH}_3$ -phenyl).  $^{13}\text{C-NMR}$  [ $\text{DMSO-d}_6$ ]  $\delta$ : 153.10–112.40 ( $\text{C}_1$ – $\text{C}_9$ , Ar-C), 21.74 ( $\text{C}_{10}$ , aliphatic carbon).

**5.1.6. 4-Methyl-N-(6-methylpyridin-2-yl) Benzenesulphonamide (3f).** On condensation reaction of *p*-toluenesulphonyl chloride **1** and 2-amino-6-methyl pyridine **2f** in acetone and dry pyridine at room temperature for 24 hours, 4-methyl-*N*-(6-methylpyridin-2-yl) benzenesulphonamide **3f** was obtained as a yellowish liquid (oil). IR (KBr)Vmax: 3311  $\text{cm}^{-1}$  (N-H stret.), 3161  $\text{cm}^{-1}$  (Ar C-H), 1154  $\text{cm}^{-1}$  ( $\text{SO}_2$ -functional group).  $^1\text{H-NMR}$  [ $\text{DMSO-d}_6$ ]  $\delta$ : 8.09 (m; 7H, heteroaryl-H), 8.0 (s,b; 1H, NH), 7.74 (t;  $J = 8.06$  Hz, 1H, Ar-H), 7.52 (d; 8.02 Hz, 1H, Ar-H), 7.25 (d;  $J = 7.84$  Hz, 1H, Ar-H), 7.12 (d;  $J = 7.86$  Hz, 1H, Ar-H), 6.83 (d;  $J = 8.83$  Hz, 1H, Ar-H), 6.62 (d;  $J = 7.03$  Hz, 1H, Ar-H), 2.35 (s; 3H,  $\text{CH}_3$ -pyridyl), 2.24 (s; 3H,  $\text{CH}_3$ -phenyl).

**5.2. 4-Methyl-N-(pyridin-4-yl) Benzenesulphonamide (3g).** On condensation reaction of *p*-toluenesulphonyl chloride **1** and 4-amino pyridine **2g** in acetone and dry pyridine at room temperature for 24 hours, 4-methyl-*N*-(pyridin-4-yl) benzenesulphonamide **3g** was obtained as a white solid with a melting point of 213°C-214°C. IR (KBr) Vmax: 3227  $\text{cm}^{-1}$  (N-H stret.), 3061  $\text{cm}^{-1}$  (Ar C-H), 1164  $\text{cm}^{-1}$  ( $\text{SO}_2$ -functional group).  $^1\text{H-NMR}$  [ $\text{DMSO-d}_6$ ]  $\delta$ : 8.53 (d;  $J = 7.15$  Hz, 2H, Ar-H), 7.87 (d;  $J = 8.31$  Hz, Ar-H), 7.50 (d;  $J = 8.07$  Hz, 2H,

Ar-H), 7.44 (m; 4H, heteroaromatic-H), 7.12 (d;  $J = 7.91$  Hz, NH), 2.28 (s; 3H,  $\text{CH}_3$ -phenyl).

## Conflict of Interests

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

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