Research Paper

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Synthesis, Characterisation and Evaluation for Antibacterial Activities of N-Pyridin-2-Yl Substituted-P-Toluene Sulphonamoyl Ethanamides

Chemistry

KEYWORDS : antimicrobial, N-heteroaryl sulphonamides, spectroscopy, sulphonamides.

Ugwu David I — Synthetic Organic Chemistry Division, Department of Pure and Industrial Chemistry, University of Nigeria, Nsukka 410002, Nigeria.

Okoro Uchechukwu C — Synthetic Organic Chemistry Division, Department of Pure and Industrial Chemistry, University of Nigeria, Nsukka 410002, Nigeria.

ABSTRACT

Synthesis of N-pyridin-2-yl-p-totuene sulphonamides 6a-e is reported. This was achieved by first reacting p-toluene sulphonyl chloride 1 with various amino acids in basic medium to afford the p-toluene sulphamides 3a-e. p-Toluene sulphonamides upon refluxing with thionyl chloride were converted to the corresponding acyl chlorides 4a-e which on further reaction with 2-amino pyridine 5 in basic medium of triethylamine gave the N-pyridin-2-yl-p-toluene sulphonamides 6a-e. The structures of the synthesized compounds were confirmed using Fourier transform infrared (FT-IR), proton and carbon-13 Nuclear Magnetic Resonance (1HNMR and 13CNMR). The antimicrobial properties of the sulphonamides were determined on Bacillus subtilis, Bacillus cereus, Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli and Klebsiella pneumoniae using agar diffusion technique. The intermediates 3a-e and the N-pyridin-2-yl derivatives 6a-e were found to be more active than tetracycline against the tested organisms.

1. Introduction

Sulphonamides are class of compounds containing SO_2N functionality. Since the discovery of their applicability as antibacterial agent [1], many useful sulphonamides have been synthesized and found to be effective pharmacologically as antidiuretics [2], anticonvulsant [3], anticancer [4], antiretroviral [5], antihypertensive [6], antibiotics [7], antidiabetic [8], antimalarial [9], antituberculosis agent [10] to mention but a few. Sulphonamides are also ruling as most widely used veterinary medicine [11]. These findings encouraged us to explore the synthesis of different *N*-heteroaryl substituted sulphonamides derived from *p*-toluene sulphonamides with improved and different biological activities.

Bacillus subtilis is known to cause disease in immune-compromised patients [12]. Bacillus cereus is responsible for a minority of food borne illness causing severe nausea, vomiting and diarrhea [13]. Staphylococcus aureus causes a range of illness from minor skin infections to life threatening diseases like meningitis, osteomyelitis and toxic shock syndrome [14]. Pseudomonas aeruginosa typically infects the pulmonary tract, urinary tract and other blood infections [15]; it also causes ventilator-associated pneumonia [16]. Escherichia coli are known to cause serious food poisoning in humans [17], neonatal meningitis, haemolytic-uremic syndrome, peritonitis, septicemia and Gram negative pneumonia [18]. Klebsiella pneumoniae causes Klebsiella pneumonia, lower biliary tract infections [19].

Although there are extensive uses of other antibacterial agents, the emergence of drug resistant strains in clinical applications especially to Gram positive bacteria [20] has created a problem of global proportions [21].

In this work, we report the synthesis and antibacterial activities of novel *N*-heteroaryl substituted *p*-toluene sulphonamides.

2. MATERIALS AND METHODS

GENERAL

All the reagents were purchased from Sigma-Aldrich and used without further purification. The melting points were determined using Fischer Johns melting point apparatus and are uncorrected. Infra-red spectra data were recorded on a FTIR-8400s Fourier transform infrared spectrophotometer using KBr disc and absorption were given in centimeter (cm^{-1}) (NARICT, Zaria). The ^{1}HNMR and ^{13}CNMR spectra were recorded in DMSO-d_6 using Varian NMR 400MHz instrument, Strathclyde Institute of Pharmacy and Biomedical sciences, University of Strathclyde, Glasgow, UK. The chemical shifts (d) were recorded in ppm.

2.1 General Procedure for Synthesis of p-Toluene Sulphonamides (3a-e)

Sodium carbonate, Na_2CO_3 (2.79 g, 26.25 mmol) was added to a solution of amino acid (12.5 mmol) in H_2O (15 mL) at -5°C to 0°C followed by addition of *p*-toluene sulphonyl chloride, *p*-TsCl (2.86 g, 15 mmol) in four portion over a period of 1h. The slurry was then warmed to room temperature and allowed to stir for 4 h. The reaction mixture was acidified with 20% concentrated aqueous HCl solution to pH 2, after which crystallization occurred and the product was obtained via suction filtration. The filtered crude product was washed with 0.1 aqueous tartaric acid solution (pH 2.2) and dried in a vacuum oven at 50°C for 12 h to afford *p*-toluene sulphonamides (**3*a-e***) in good to excellent yield (68.2-85%).

[4-Methylphenylsulphonamido]acetic acid (3a): The reaction of a solution of p-toluene sulphonyl chloride 1 (2.86 g, 15 mmol) in water (15 mL) with glycine 2a (0.94 g, 12.5 mmol) gave the title compound 3a as a white crystal; Yield 2.62 g (76.2%); m.p 122-123°C; IR (KBr) cm^{-1}: 3461 (OH), 3355 (NH), 3042 (C-H Aromatic), 2951(CH, aliphatic), 1714 (C=O of COOH), 1529 (C=C aromatic), 1254, 1140 (SO_2 two bonds), 828 (p-substitutions in benzene), 682 (Ar-H). ^{1}HNMR (DMSO-d_6): d =7.96 (t, J=6.3Hz, 1H), 7.67 (d, J=7.9Hz ,2H), 7.59 (d, J=7.8Hz, 1H), 7.37 (d, J=7.8Hz, 2H), 7.12 (d, J = 7.7Hz, 1H), 3.54 (d, J=4.5Hz, 2H), 2.37 (s, 3H).

2-[4-Methylphenylsulphonamido]propanoic acid (3b) Using a solution of alanine 2b (1.11 g, 12.5 mmol) in water (15 mL) and compound 1 (2.86 g, 15 mmol) as the starting material, compound 3b was obtained as a white crystal; Yield 2.55 g (70.0%); m.p 128-129°C; IR (KBr) cm^{-1}: 3633 (OH), 3273 (NH), 3073 (CH aromatic), 1704 (C=O), 1569 (C=C aromatic), 1369, 1167 (SO_2 two bands), 820 (p-substitution), 658 (Ar-H). ^{1}HNMR (DMSO-d_6): d 12.80 (s, 1H), 7.64 (d, J=7.96Hz, 1H), 7.50 (d, J = 7.7Hz, 2H), 7.33 (d, J = 7.9Hz, 1H), 7.14(d, J = 7.6Hz, 2H), 3.71 (m, 1H), 2.32 (s, 3H), 1.10 (d, J = 7.1Hz, 3H).

2-[4-Methylphenylsuphonamido]-3-phenyl propanoic acid (3c) Using a solution of phenylalanine 2c (2.06 g, 12.5 mmol) in water (15 mL) and compound 1 (2.86 g, 15 mmol) as starting material, compound 3c was obtained as a white crystal; Yield 4.06 g (85.0%); m.p 132-133°C; IR (KBr) cm^{-1}: 3600 (OH), 3313 (NH) 3020 (CH aromatic), 2929 (CH aliphatic), 1704 (C=O of COOH), 1326, 1163 (SO_2 two bands), 684 (Ar-H), 827 (p-substitution in benzene). ^{1}HNMR (DMSO-d_6): d 8.30 (d, J = 9.1Hz, 1H), 7.50 (d, J = 7.9Hz, 1H), 7.45 (d, J = 8.2Hz, 1H), 7.23 (d, J = 7.98Hz, 1H), 7.20 (d, J = 6.9Hz, 1H), 7.12 (m, 5H), 3.85 (td, J = 5.3Hz, 8.8Hz, 1H), 2.93 (dd, J = 5.7Hz, 13.8Hz, 1H), 2.31 (d, J = 18.6Hz, 3H).

2-[(4-Methylphenylsulphonamido)-4-(methylthio)butanoic acid (3d) Using a solution of methionine 2d (1.86 g, 12.5 mmol) in water (15 mL) and compound 1 (2.86 g, 15 mmol) as the starting material, compound 3d as a yellowish oil; Yield 3.80 g (83.5%); IR (KBr) cm^{-1}: 3552 (OH), 3262 (NH), 2931 (CH aliphatic), 1724 (C=O of COOH), 1430 (C=C aromatic), 1320, 1158 (SO_2 two bands), 673 (Ar-H). ^{1}HNMR (DMSO-d_6):d 8.09 (d, J =7.7Hz, 1H), 7.66 (d, J =8.2Hz, 2H), 7.35 (d, J =8.1Hz, 2H), 3.83 (m, 1H), 2.36 (s, 3H), 2.29 (p, J =7.7Hz, 2H), 1.92 (s, 3H), 1.17 (t, J =7.2Hz, 2H).

4-Methyl-2-[4-methylphenylsulphonamido] pentanoic acid (3e) Using a solution of leucine 2e (1.64 g, 12.5 mmol) in water (15 mL) and compound 1 as starting material, compound 3e was obtained as a white crystal; Yield 2.92 g (68.2%); m.p 114-115°C; IR (KBr) cm^{-1}: 3640 (OH), 3276 (NH), 3064 (CH aromatic), 2942 (CH aliphatic), 1710 (CO of COOH), 1579 (C=C aromatic), 1373, 1168 (SO_2 two bands), 662 (Ar-H), ^{1}HNMR (DMSO-d_6):d 8.05 (d, J=8.5Hz, 1H), 7.64 (d, J=8.2Hz, 1H), 7.50 (dd, J =5.7Hz,7.4Hz, 1H), 7.34 (d, J = 8.1Hz, 1H), 7.14 (d, J = 7.96Hz, 1H), 3.62 (q, J = 8.3Hz, 1H), 2.29 (s, 3H), 1.55 (dp, J =6.6Hz, 12.9Hz, 2H), 1.36 (m, 1H), 0.79 (d, J = 6.6Hz, 3H), 0.67 (d, J=6.5Hz, 3H).

2.2 General procedure for synthesis of *N*-pyridin-2-yl substituted p-toluene sulphonamide (6a-e).

A three necked 250 mL flask equipped with magnetic stirring bar was charged with appropriate *p*-toluene sulphonamide (***3a-e***) (10 mmol) and dichloromethane (10 mL)). The flask was stoppered, cooled to 0°C and nitrogen gas was bubbled into it continuously. Thionyl chloride (1.10 mL, 15 mmol) was added via dropping pipette to maintain the temperature below 10°C. The resulting mixture was stirred at 80°C under reflux for 3h. The excess thionyl chloride was evaporated using a water bath at 80°C. Dichloromethane (20 mL) was added to the resulting crude acyl chloride and the solution was concentrated again.

In a separate 250 mL, two-necked round bottom flask equipped with addition funnel was charged with dichloromethane (10 mL), triethylamine (2 mL, 14.3 mmol) and 2-aminopyridine (0.74 g, 10 mmol) and the mixture was cooled to 0°C. The crude acyl chloride was dissolved in dichloromethane (DCM) (10 mL) and this solution was cooled to 0°C and was transferred to the addition funnel. The acyl chloride was then added drop wisely to the 2-aminopyridine solution at such a rate that the internal temperature was maintained below 10°C. Upon completion of the addition of the acyl chloride solution, the mixture was shaked intermittently at 0°C for 3h. The product was filtered by suction and washed with dichloromethane and dried at 50°C to afford the *N*-pyridin-2-yl substituted *p*-toluenesulphonamide (***6a-e***).

2-[4 - Methylphenylsulphonamido] - *N*- (pyridin- 2- yl) acetamide (6a) Using a solution of compound 3a (2.29 g, 10 mmol) in dichloromethane (10 mL), thionyl chloride (1.10 mL, 15 mmol) and compound 5 (0.74 g, 10 mmol) as starting material, compound 6a was obtained as a white crystal; Yield 2.50 g (91.6%); m.p 271-272°C; IR (KBr) cm^{-1}: 3633 (NH of SO_2-NH), 3376 (NH of CO-NH), 3053 (CH aromatic), 2930 (CH aliphatic), 1694 (CO), 1520 (C=C aromatic), 1376 (C=N aromatic), 1291, 1167 (SO_2 two band) 669 (Ar-H). ^{1}HNMR (DMSO-d_6):d 8.01 (d, J =4.6Hz, 1H), 7.87 (d, J =8.3Hz, 2H), 7.76 (d, J =8.2Hz, 2H), 7.70 (m, 4H), 7.45 (d, J =8.2Hz, 1H), 7.33 (d, J =8.1Hz, 2H), 7.14 (d, J=8.6Hz, 1H), 6.86 (m, 4H), 4.55 (s, 1H), 2.41 (s, 3H), 1.19 (t, J = 7.3Hz, 2H). ^{13}CNMR (DMSO-d_6): d 163, 147, 134, 140, 128, 49, 45, 21, 8

2-[4-Methylphenylsulphonamido]-*N*-(Pyridin-2-yl) propanamide (6b) Using a solution of compound 3b (2.43 g, 10 mmol) in dichloromethane (10 mL), thionyl chloride (1.10 mL, 15 mmol) and compound 5 (0.74 g, 10 mmol) as starting material, compound 6b was obtained as a white crystal; Yield 2.20 g (76.7%); m.p 268-269°C; IR (KBr) cm^{-1}: 3433(NH of SO_2-NH), 3360 (NH of CO-NH), 2949 (CH alphatic), 1669 (CO), 1475 (C=C aromatic), 1392 (C=N aromatic), 1184, 1038 (SO_2 two band), 684 (Ar-H).^{1}HNMR (DMSO-d_6):d 8.00 (m, 1H), 7.76 (d, J =8.2Hz, 2H), 7.70 (m, 4H), 7.33 (d, J =8.0Hz, 1H), 7.14 (d, J =8.7Hz, 1H), 6.86 (t, J=6.3Hz, 2H), 3.07 (m, 1H), 2.33 (s, 3H), 1.19 (t, J=7.3Hz, 3H).^{13}CNMR (DMSO-d_6):d 154, 144, 143, 141, 140, 130, 127, 116, 114, 46, 22, 9.

2-[4-Methylphenylsulphonamido]-3-phenyl-N-(pyridin-2-yl) propanamide (6c) Using a solution of compound 3c (3.19 g, 10 mmol) in dichloromethane (10 mL), thionyl chloride (1.10 mL, 15 mmol) and compound 5 (0.74 g, 10 mmol) s starting material, compound 6cb was obtained as a white crystal Yield 3.30 g (90.9%); m.p 196-197°C; IR (KBr) cm^{-1}: 3627 (NH of SO_2 NH), 3275 (NH of CONH), 3054 (CH aromatic), 2881, 2778 (CH aliphatic), 1667 (C=O), 1543, 1445 (C=C aromatic), 1323, 1160 (SO_2 two band).^{1}HNMR (DMSO-d_6):d 8.18 (t, J =8.1Hz 1H), 7.75 (m, 5H), 7.41 (d, J=7.96H_2, 2H), 7.19 (m,4H), 7.08 (dd, J =5.2Hz, 9.2Hz, 2H), 4.30 (td, J =5.2Hz 9.5Hz 1H), 2.94 (dd, J=5.0Hz, 13.7Hz, 1H), 2.21 (s, 3H). ^{13}CNMR(DMSO-d_6): d 173, 146, 142, 138, 137.78, 137, 129, 129.25, 129.12, 128.57, 128.12, 128.08, 127, 126.43, 126.26, 125.94, 125.51, 20.92, 20.76

2-[4-Methylphenylsulphonamido]-4-(methylthio)-N-(pyridin-2-yl) butanamide (6d) Using a solution of compound 3d (3.03 g, 10 mmol) in dichloromethane (10 mL), thionyl chloride (1.10 mL, 15 mmol) and compound 5 (0.74 g, 10 mmol) as starting material, compound 6d was obtained as a brown oil; Yield 3.20 g (92.22%); IR (KBr) cm^{-1}: 3327 (NH of SO_2NH) 3187 (NH of CONH), 2954, 2624 (CH aliphatic), 1663 (C=O), 1162, 1091 (SO_2, two band).^{1}HNMR (DMSO-d_6):d =7.88(m, 4H), 7.64 (t, J =9.1Hz, 2H), 7.48 (m, 4H), 6.56 (m, 4H), 3.05 (q, J =7.3Hz, 1H), 2.50 (m, 2H), 2.30 (m, 3H), 1.93 (d, J=8.3Hz, 3H), 1.18(t, J =7.3Hz, 2H). ^{13}CNMR (DMSO-d_6): d 171, 152, 148, 142, 137.88, 137.83, 129, 127, 119, 113, 55, 45, 24, 23, 21.18, 20.97, 8

4-Methy-2-[4-methylphenylsulphonamido]-N-(pyridin-2-yl) pentanamide (6e) Using a solution of compound 3e (2.43 g, 10 mmol) in dichloromethane (10 mL), thionyl chloride (1.10 mL, 15 mmol) and compound 5 (0.74 g, 10 mmol) as starting material, compound 6e was obtained as a white crystal; Yield 2.90 g (88.15%); m.p 240-241°C; IR (KBr) cm^{-1}: 3425 (NH of SO_2 NH), 3285 (NH of CONH), 3064(CH aromatic), 2937 (CH aliphatic), 2793 (CH methine), 1672 (C=O), 1546 (C=C aromatic), 1323, 1156 (SO_2 two band), 681 (Ar-H). ^{1}HNMR (DMSO-d_6):d 8.29 (d, J = 4.9Hz,1H), 8.01 (d, J= 8.98Hz, 2H), 7.72 (q, J=8.3Hz, 2H), 7.65. (d, J = 8.1Hz, 2H), 7.20 (d, J =8.1Hz, 1H), 7.07 (dd, J =3.2Hz, 8.1Hz, 1H), 4.02 (q, J =8.9Hz 1H), 2.21 (s, 3H), 1.55 (m, 1H), 1.19(t, J =7.3Hz, 2H), 0.82 (d, J =6.6Hz, 3H), 0.71 (d, J =6.5Hz, 3H). ^{13}CNMR (DMSO-d_6):d 171, 152, 148, 143, 138, 130, 127, 120, 114, 56, 46, 25, 22 and 9.

2.3 In-Vitro Antimicrobial Activity

The sensitivity test was achieved using the method described by Adeniyi *et al* [22] Sensitivity test agar plates were seeded with 0.1 ml of overnight culture of microorganism. The seeded 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 sterile pipette, each cup was filled with six drops of their corresponding synthesized compound (2 mg/mL). The solubilizing solvent was DMF. All the plates were incubated at 37°C for 24 h for bacteria. Zones of clearance round each cup means inhibition and the diameter of such zones were measured. The procedure was repeated for tetracycline (standard bacteria) and DMF (solvent). The result of the sensitivity testing is presented in table **2.**

Agar cup diffusion technique as described by Adeniyi *et al* [22] was used to determine the minimum inhibitory concentration (MIC) of the sulphonamides, tetracycline and DMF. Serial dilutions of the sulphonamides were prepared from 2 mg/mL solution of the sulphonamides to give 2, 1, 0.5, 0.25 and 0.125 mg/

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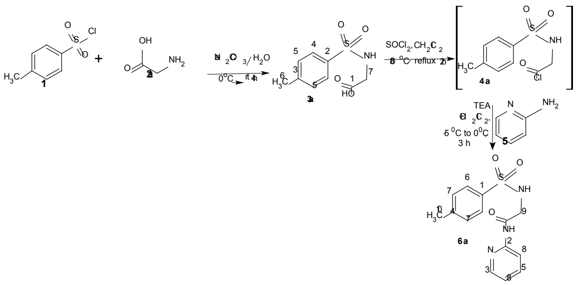
mL. Six drops of each dilution was added to the corresponding cup of seeded microorganisms and the agar previously marked. The cork borer used to make the cup is 8 mm in diameter. The plates were incubated at 37°C for 24 h. The diameter of zone of inhibition was measured and the value subtracted from the diameter of the borer (8mm) to give the inhibition zone diameter (IZD). The graph of IZD^2 against the log of concentration was plotted for each plate containing a specific compound and a microorganism. The anti-log of the intercept on x-axis gives the MIC. The procedure was repeated for tetracycline and DMF (solubilizing agent).

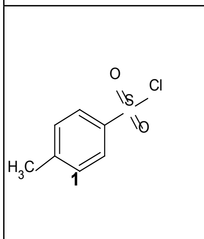
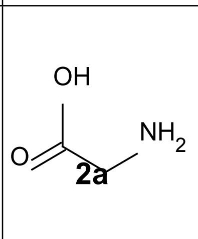
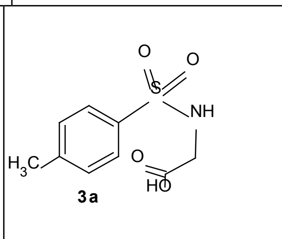
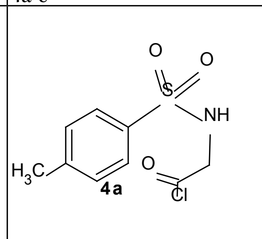
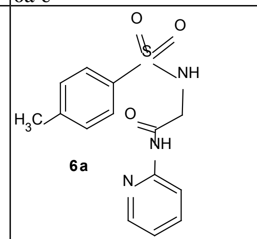
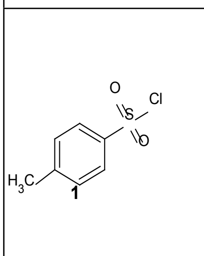
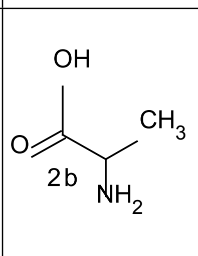
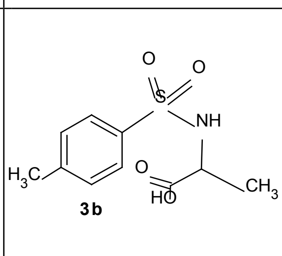
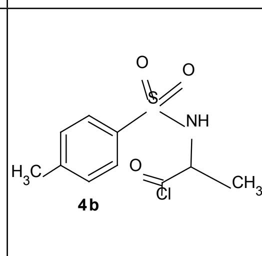
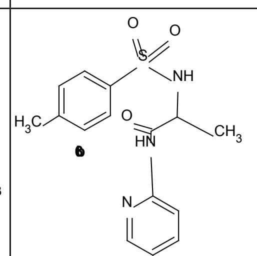
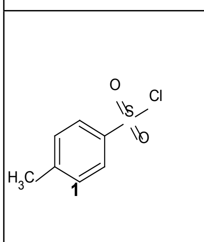
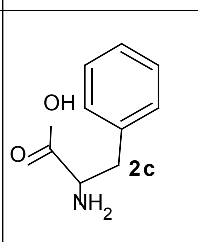
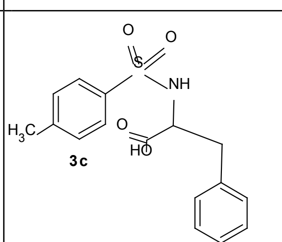
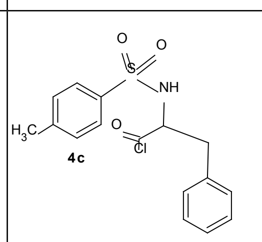
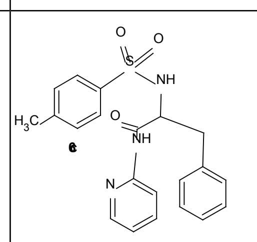
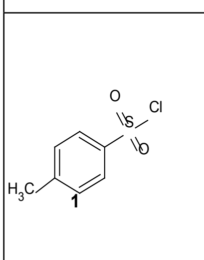
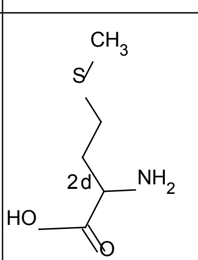
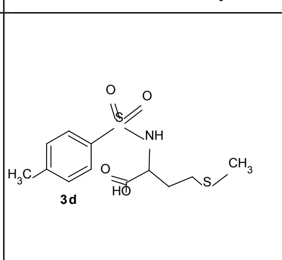
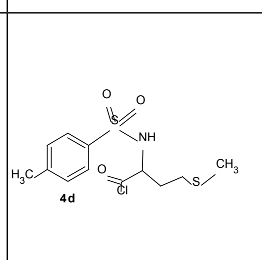
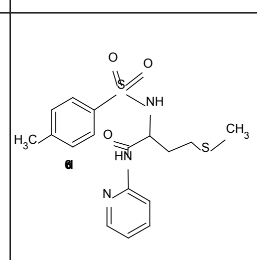
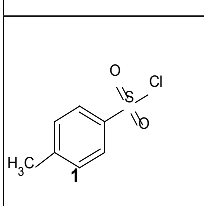
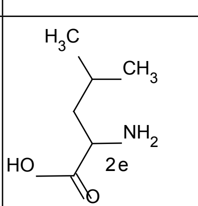
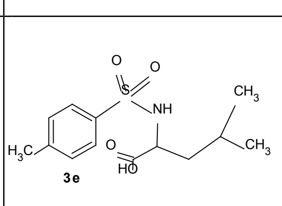
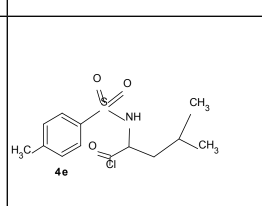
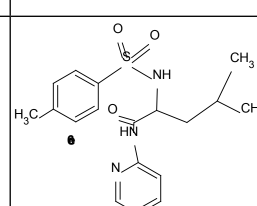
Result and discussion

On stirring amino acids **2*a-e*** in a basic medium of sodium carbonate and *p*-toluene sulphonyl chloride **1** in distilled water at room temperature for 4h, *p*-toluene sulphonamides (**3*a-e***) were obtained as white crystalline solids in exception of **3*d*** that was yellowish oil. Condensation of 2-aminopyridine **5** and acyl chloride derivative of *p*-toluene sulphonamide **4*a-e*** gave *N*-pyridin-2-yl-*p*-toluene sulphonamide **6*a-e*** as white crystalline solids in exception of **6*d*** that was brownish oil.



Scheme 1. Synthesis of *N*-pyridin-2-yl substituted p-toluene sulphonamoyl ethanamides.

Table 1: Table of the derivatives of *N*-pyridin-2-yl substituted p-toluene sulphonamoyl ethanamides.

p-toluene sulphonyl chloride	Amino acids 2a-e	p-toluene sulphonamides 3a-e	Acid derivatives of p-toluene sulphonamides 4a-e	N-pyridin-2-yl-p-toluene sulphonamoyl ethanamides 6a-e
				
				
				
				
				

The *p*-toluene sulphonamides (**3*a-e***) were synthesized as white crystalline solid in exception of methionine derivative **3*d*** that was yellowish oil. The FTIR spectra revealed the presence of a sulphonamide group (1373- 1140 cm^{-1}), -NH group (3640-3461 cm^{-1}), C=O group (1724-1704 cm^{-1}) and OH (3355-3262 cm^{-1}) in the *p*-toluene sulphonamides. The ^{1}HNMR peaks conform to the structures of the compounds. The *N*-pyridin-2-yl-*p*-toluene sulphonamides (**6*a-e***) were all white crystalline in exception of **6*d*** that was oil. The FTIR spectra revealed in addition to other bands in the *p*-toluene sulphonamides (**3*a-e*)** the CONH functional group which appeared at 1694-1663 cm^{-1}showing the successful coupling of the 2-aminopyridine. The ^{1}HNMR and ^{13}CNMR signals agree with the structures of the compounds. Worthy to mention is the appearance of peaks at d6.86 which is assigned to heteroaromatic protons. The stereochemistry of the compounds **3b-e** and **6b-e** are retained since the reaction leading to their synthesis does not involve the stereogenic centers, so, having used L-amino acids, the products were laevo rotatory.

3. In vitro Antibacterial Activity

Five *p*-toluene sulphonamides and their corresponding *N*-heteroaryl substituted derivatives were tested for antibacterial activities in vitro against three Gram positive and three Gram negative bacteria clinical isolate. The minimum inhibitory concentrations are summarized in Table 3.

Table 4.2: Inhibition zone diameter (mm)

	B. subtilis	B. cereus	S. aureus	P. aeruginosa	E. coli	K. pneumonae
3a	3	2	0	4	8	0
3b	0	7	5	7	0	2
3c	0	0	0	12	3	3
3d	3	0	0	12	0	8
3e	0	6	9	0	6	0
6a	0	0	0	0	0	7
6b	0	0	0	10	0	3
6c	9	0	3	6	8	4
6d	8	3	6	11	10	5
6e	0	7	6	0	0	0
TCN	21	18	22	16	29	11
DMF	0	0	0	0	0	0

Table 3: Minimum inhibitory concentration (mg/mL)

	B. subtilis	B. cereus	S. aureus	P. aeruginosa	E. coli	K. pneumonae
3a	1.80	1.90	3.00	0.90	0.36	0
3b	0	0.36	1.70	0.45	3.02	2.0
3c	0	0	2.80	0.224	1.92	1.98
3d	1.90	0	3.00	0.363	2.86	0.170
3e	0	0.97	0.457	0	0.90	0
6a	0	0	0	0	0	0.36
6b	0	0	0	0.240	0	1.50
6c	0.224	0	1.51	0.700	0.407	0.80
6d	0.437	1.80	0.447	0.407	0.389	1.98
6e	0	0.447	0.447	0	0	0
Tetracycline	5.62	11.48	5.31	15.85	3.16	17.78
(DMF)	0	0	0	0	0	0

As is evident from Table 3, were it is active, the sulphonamides had better activity against the bacteria relative to tetracycline, although some of the sulphonamide were inactive against some bacteria. The coupling of the 2-aminopyridine improved the activity of most of the sulphonamide even though some lost their activity as a result of coupling. 2-[4-Methylphenylsulphonamido]-4-(methylthio)-*N*-(pyridin-2-yl) butanamide **(6*d*)** has activity against all the six bacteria whereas 2-[4-Methylphenylsulphonamido]-*N*-(pyridin-2-yl)acetamide **(6*a*)** was only active against *Klebsiella pnemoniae* but it was noticed that the intermediate [4-Methylphenylsulphonamido] acetic acid **(3*a*)** was inactive against *Klebsiella pnemoniae* but active against the rest organisms tested.

4. CONCLUSION

A scrutiny of the results of antibacterial activity of **6a-e** (Table **2)** reveals that bulky nuclear substituents replacing the OH of the intermediates improved the antibacterial activity, though in few cases there was loss or reduction in activity. We have established an efficient synthetic route to novel *N*-heteroaryl substituted *p*-toluene sulphonamoyl ethanamides. Simple condensation of *p*-toluene sulphonyl chloride with various amino acids under basic condition gave *p*-toluene sulphonamides. Functionalization of these sulphonamides and subsequent treatment with 2-aminopyridine gave the *N*-heteroaryl derivatives. The antibacterial activity of both *p*-toluene sulphonamides and the *N*-heteroaryl derivatives were evaluated.

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