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Synthesis, Characterisation and Antifungal Activities of [4-Methylphenylsulphonamido]-*N*-(Pyridin-2 Yl) Acetamide Derivatives

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Abstract

In the present study, a series of N-pyridin-2-yl substituted [4-methylphenylsulphonamido] acetamides have been synthesized. The reaction of 4-methylphenyl sulphonyl chloride 1 with various amino acids 2a-e in basic medium yielded [4-methylphenylsulphonamido] alkanoic acids 3a-e which on chlorination with thionyl chloride gave the acid chloride derivatives of [4-methylphenylsulphonamido] alkanoic acid in situ. The acid chloride derivatives on condensation with 2-aminopyridine 4, gave the corresponding acetamides 5a-e in good to excellent yield. The compounds were characterized by FTIR, 1H-NMR and 13C-NMR and screened for antifungal activities against Candida albican and Aspergillus niger. The results revealed that the compounds had better antifungal activity than fluconazole the reference drug. Compound 5d was most active against Candida albicans with MIC of 0.224 mg/mL and compound 2b most active against Aspergillus niger with MIC of 0.190 mg/mL.

Keywords: Antifungal; 2-aminopyridine; 4-Methylphenyl sulphonamide; Sulphonamides; Spectroscopy

Introduction

Sulphonamide antimicrobial agents were the first effective chemotherapeutic agents used but the rapid development of widespread resistance diminished its usefulness [1]. Today, the research for antimicrobial sulphonamides has been revived following the discovery of combinatorial therapy. Sulphonamide-trimethoprin combinations are extensively used today for opportunistic infections in patients with AIDS, in addition to urinary tract infections and burn therapy [2-6]. Sulphonamides has been found useful in the treatment of asthma as reported by Aziz et al. [7] using *N*-pentyl-*N*-(4,5-dibromo-2-methoxyphenyl) benzene sulphonamides and treatment of leukemia as reported by Novotny et al. [8] using arabinosyl cytosine conjugate sulphonamides. Sulphonamides has been applied in the treatment of migrane using avitriptan [9] and almotriptan as recently reported by Ridvan et al. [10] and epilepsy treatment using zonisamide [11]. They are also used as antiretroviral in the treatment of HIV/AIDS e.g fosamprenavir is a prodrug of amprenavir and a non-peptide competitive inhibitor of the HIV protease enzyme [12] and darunavir marketed as prezista [13]. Dorzolamide is used as carbonic acid anhydrase inhibitor in treatment of hypertension [14]. Recently sulphonamide derivatives at C-8 alkyl chain of anarcadic acid mixture isolated from cashew nut shell liquid has been reported to have an outstanding antibacterial activity [15]. Boechat et al.[16] reported the synthesis of new set of 1H-1,2,4-triazol-3-ylbenzene sulphonamides and using docking they identified the new compounds as lead anti-malaria drug. Alexiou et al. [17] reported the synthesis of *N*-(3, 5-difluoro-4-hydroxyphenyl) bezene sulphonamide and its derivatives as putative bioisosteres of the previously reported aldose reductase inhibitors. The in vitro aldose reductase inhibitory activities of the new compounds were found to be higher than that of *N*-benzenesulphonyl glycine derivatives. The new compounds were also found to be potential antioxidants.

Candida albican causes opportunistic oral and genital infections in human. They cause morbidity and mortality in immune comprised patients [18]. *Aspergillus niger* is known to cause aspergillosis which is deadly and frequently found among horticultural workers [19].

In spite of the versatility of sulphonamides in chemotherapy, little is known of its antifungal properties.

In this work, we report for the first time the synthesis and antifungal properties of various *N*-pyridin-2-yl-4-methylphenylsulphonamido acetamides.

Material and Methods

Chemistry

The melting points were determined using Fischer Johns melting point apparatus and are uncorrected. Infrared spectra data were recorded on a FTIR-8400s Fourier transform infrared spectrophotometer using KBr disc and absorption were given in per 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 (δ) were recorded in ppm.

Synthesis

Compounds 5a-e were synthesized by the coupling of compounds 3a-e with 2-aminopyridine in dichloromethane and triethylamine. The main intermediates 3a-e was prepared by condensing 4-methylphenyl sulphonyl chloride with various amino acids 2a-e in the basic medium of Na_2CO_3 at room temperature.

Biology

***In vitro* antifungal testing of synthesized compounds:** Agar cup diffusion technique as described by Adeniyi et al. [20] was used to determine the antimicrobial activity of the compounds. Sensitivity test Muller Hinton 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

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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 48 h. Zones of clearance round each cup means inhibition and the diameter of such zones were measured. The graph of IZD^2 against the log of concentration was plotted for each compound. The anti-log of the intercept on x-axis gives the MIC. The procedure was repeated for fluconazole (standard antifungal agent), and DMF (solvent).

Experimental

General procedure for synthesis of 4-methylphenyl sulphonamides (3a-e): Na_2CO_3 (2.79 g, 26.25 mmol) was added to a solution of amino acid 2a-e (12.5 mmol) in H_2O (15 mL) at -5°C to 0°C followed by addition of 4-methylphenyl sulphonyl chloride, 1 (2.86 g, 15 mmol) in three portion over a period of 1h. The slurry was then warmed to room temperature and allowed to stir for 4h. The reaction mixture was acidified to pH2, after which crystallization occurred and the product was obtained via suction filtration. The filtered crude product was washed with tartaric acid (pH 2.2) and dried in a vacuum oven at 50°C for 12 h to afford 4-methylphenyl sulphonamides (3a-e) in good to excellent yield (68.2-85%).

[4-Methylphenylsulphonamido] acetic acid (3a): To a solution of glycine (0.94 g, 12.5 mmol) in water (15 mL) containing Na_2CO_3 (2.79 g, 26.25 mmol) was added 4-methylphenyl sulphonyl chloride (2.86 g, 15 mmol). The reaction mixture was stirred at room temperature for 4 hours. After separation and purification of the residue, the product 2.62 g was obtained. Yield 2.62 g (76.2%), mp 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) δ: 7.96 (t, J=6.25Hz, 1H), 7.67 (d, J=7.88Hz, 2H), 7.49 (d, J=7.75Hz, 1H), 7.37 (d, J=7.83Hz, 2H), 7.12 (d, J=7.74Hz, IH), 3.54 (d, J=4.51Hz, 2H), 2.37 (s, 3H).

2-[4-Methylphenylsulphonamido] propanoic acid (3b): To a solution of alanine (1.11 g, 12.5 mmol) in water (15 mL) containing Na_2CO_3 (2.79 g, 26.25 mmol) was added 4-methylphenyl sulphonyl chloride (2.86 g, 15 mmol). The reaction mixture was stirred at room temperature for 4 hours. After separation and purification of the residue, the product was obtained. Yield 2.55 g (70.0%), mp 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) δ: 12.8 (s-br, 1H), 7.64 (d, J=7.96Hz, 1H), 7.50 (d, J=7.66Hz, 2H), 7.33 (d, J=7.88Hz, 1H), 7.14(d, J=7.62Hz, 2H), 3.71 (m, 1H), 2.32 (s, 3H), 1.10 (d, J=7.08Hz, 3H).

2-[4-Methylphonylsuphonamido]-3-phenylpropanoic acid (3c): To a solution of phenylalanine (2.06 g, 12.5 mmol) in water (15 mL) containing Na_2CO_3 (2.79 g, 26.25 mmol) was added 4-methylphenyl sulphonyl chloride (2.86 g, 15 mmol). The reaction mixture was stirred at room temperature for 4 hours. After separation and purification of the residue, the product was obtained. Yield 4.06 g (85.0%), mp 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) δ: 8.30 (d, J=9.10Hz, 1H), 7.50 (d, J=7.94Hz, 1H), 7.45 (d, J=8.16Hz, 1H), 7.23 (d, J=7.98Hz, 1H), 7.20 (d, J=6.87Hz, 1H), 7.12 (m, 5H), 3.85 (td, J_1=5.32Hz, J_2=8.80Hz, 1H), 2.93 (dd, J_1=5.68Hz, J_2=13.77Hz, 1H), 2.31 (d, J=18.55Hz, 3H).

2-[(4-Methylphenylsulphonamido)-4-(methylthio)] butanoic acid (3d): To a solution of methionine (1.86 g, 12.5 mmol) in water (15 mL) containing Na_2CO_3 (2.79 g, 26.25 mmol) was added 4-methylphenyl sulphonyl chloride (2.86 g, 15 mmol). The reaction mixture was stirred at room temperature for 4 hours. After separation and purification of the oil, the product was obtained. Yield 3.80g (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) δ: 8.09 (d, J=7.73Hz, 1H), 7.66 (d, J=8.16Hz, 2H), 7.35 (d, J=8.06Hz, 2H), 3.83 (m, 1H), 2.36 (s, 3H), 2.29 (p, J=7.65Hz, 2H), 1.92 (s, 3H), 1.17 (t, J=7.22Hz, 2H).

4-Methyl-2-[4-methylphonylsulphonamido] pentanoic acid (3e): To a solution of leucine (1.64 g, 12.5 mmol) in water (15 mL) containing Na_2CO_3 (2.79 g, 26.25 mmol) was added 4-methylphenyl sulphonyl chloride (2.86 g, 15 mmol). The reaction mixture was stirred at room temperature for 4 hours. After separation and purification of the residue, the product was obtained. Yield 2.92 g (68.2%), mp 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) δ: 8.05 (d, J=8.51Hz, 1H), 7.64 (d, J=8.15Hz, 1H), 7.50 (dd, J_1=5.66Hz, J_2=7.44Hz, 1H), 7.34 (d, J=8.09Hz, 1H), 7.14 (d, J=7.96Hz, 1H), 3.62 (q, J=8.29Hz, 1H), 2.29 (s, 3H), 1.55 (dp, J_1=6.56Hz, J2=12.93Hz, 2H), 1.36 (m, 1H), 0.79 (d, J=6.60Hz, 3H), 0.67 (d, J=6.50Hz, 3H).

General procedure for *N*-pyridin-2-ylsubstituted-4-methylphenyl sulphonamido acetamides (5a-e): A three necked 250mL flask equipped with magnetic stirring bar was charged with appropriate 4-methylphenyl sulphonamides (3a-e) (10 mmol) and dichloromethane (DCM) (10 mL). The flask was stoppered, cooled to 0°C. 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 (DCM) (20 mL) was added to the resulting crude acid 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 acid chloride was dissolved in dichloromethane (DCM) (10 mL) and this solution was cooled to 0°C and was transferred to the addition funnel. The acid chloride was then added drop wisely to the 2-aminopyridine solution at such a rate that the internal temperature was maintained below 5°C. Upon completion of the addition of the acid chloride solution, the mixture was shook 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 4-methylphenylsulphonamide (5a-e).

2-[4-Methylphenylsulphonamido]-*N*-(pyridin-2-yl) acetamide (5a): To a solution of [4-Methylphenylsulphonamido] acetic acid (3a) (2.29 g, 10 mmol) in dichloromethane (10 mL) was added thionyl chloride (1.10 mL, 15 mmol) and refluxed at 80°C for 2 hours. The product was purified to obtain the acid chloride in situ. To a solution of the acid chloride in dichloromethane (10 mL) was added a solution of 2-aminopyridine (0.74 g, 10 mmol) in dichloromethane (10 mL). The reaction mixture was agitated intermittently under ice for 3 hours. After separation and purification of the residue of the reaction, the product was obtained. Yield 2.50 g (91.6%), mp 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) δ: 8.01 (d, J=4.61Hz, 1H), 7.87 (d, J=8.31Hz, 2H), 7.76 (d, J=8.22Hz, 2H), 7.70 (m, 4H), 7.45 (d, J=8.22Hz, 1H), 7.33 (d, J=8.09Hz, 2H), 7.14(d, J=8.64Hz, 1H), 6.86(m, 4H), 4.55(s, 1H), 2.41 (s, 3H), 1.19 (t, J=7.28Hz, 2H).

2-[4-Methylphenylsulphonamido]-*N*-(Pyridin-2-yl) propanamide (5b): To a solution of 2-[4-Methylphenylsulphonamido] propanoic acid (3b) (2.43 g, 10 mmol) in dichloromethane (10 mL) was added thionyl chloride (1.10 mL, 15 mmol) and refluxed at 80^{0}C for 2 hours. The product was purified to obtain the acid chloride in situ. To a solution of the acid chloride in dichloromethane (10 mL) was added a solution of 2-aminopyridine (0.74 g, 10 mmol) in dichloromethane (10 mL). The reaction mixture was agitated intermittently under ice for 3 hours. After separation and purification of the residue of the reaction, the product was obtained. Yield 2.20 g (76.7%) mp 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) δ: 8.00 (m, 1H), 7.76 (d, J=8.21Hz, 2H), 7.70 (m, 4H), 7.33 (d, J=8.02Hz, 1H), 7.14 (d, J=8.68Hz, 1H), 6.86 (t, J=6.32Hz, 2H), 3.07 (m, 1H), 2.33 (s, 3H), 1.19 (t, J=7.27Hz, 3H).^{13}CNMR (DMSO-d_6) δ: 153.57, 144.24, 143.04, 140.75, 139.49, 129.95, 127.18, 116.31, 114.12, 46.01, 21.50, 9.04.

2-[4-Methylphenylsulphonamido]-3-phenyl-*N*-(pyridin-2-yl) propanamide (5c): To a solution of 2-[4-Methylphonylsuphonamido]-3-phenylpropanoic acid (3c) (3.19 g, 10 mmol) in dichloromethane (10 mL) was added thionyl chloride (1.10 mL, 15 mmol) and refluxed at 80°C for 2 hours. The product was purified to obtain the acid chloride in situ. To a solution of the acid chloride in dichloromethane (10 mL) was added a solution of 2-aminopyridine (0.74 g, 10 mmol) in dichloromethane (10 mL). The reaction mixture was agitated intermittently under ice for 3 hours. After separation and purification of the residue of the reaction, the product was obtained. Yield 3.30 g (90.9%), mp 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) δ: 8.18 (t, J=8.12Hz, 1H), 7.75 (m, 5H), 7.41 (d, J=7.96Hz, 2H), 7.19 (m,4H), 7.08 (dd, J_1, 5.23Hz, J_2=9.22Hz, 2H), 4.30 (td, J_1=5.16Hz, J_2=9.50Hz, 1H), 2.94 (dd, J_1=4.99Hz, J_2=13.68Hz, 1H), 2.21 (s, 3H).

2-[4-Methylphenylsulphonamido]-4-(methylthio)-*N*-(pyridin-2-yl) butanamide (5d): To a solution of 2-[(4-Methylphenylsulphonamido)-4-(methylthio)] butanoic acid (3d) (3.03 g, 10 mmol) in dichloromethane (10 mL) was added thionyl chloride (1.10 mL, 15 mmol) and refluxed at 80^{0}C for 2 hours. The product was purified to obtain the acid chloride in situ. To a solution of the acid chloride in dichloromethane (10 mL) was added a solution of 2-aminopyridine (0.74 g, 10 mmol) in dichloromethane (10 mL). The reaction mixture was agitated intermittently under ice for 3 hours. After separation and purification of the oil, the product was obtained. 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) δ: 7.88(m, 4H), 7.64 (t, J=9.07Hz, 2H), 7.48 (m, 4H), 6.56 (m, 4H), 3.05 (q, J=7.30Hz, 1H), 2.50 (m, 2H), 2.30 (m, 3H), 1.93(d, J=8.27Hz, 3H), 1.18(t, J=7.27Hz, 2H).

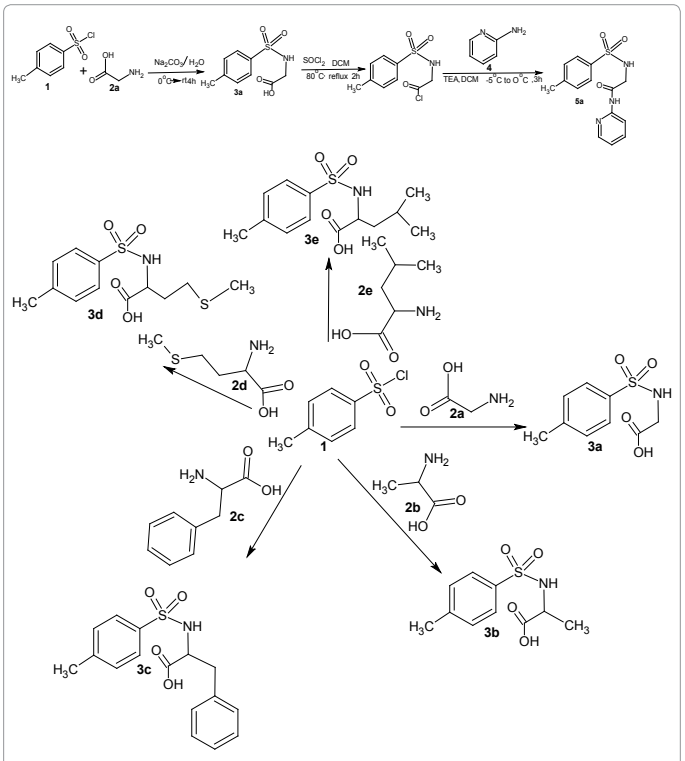
4-Methy-2-[4-methylphenylsulphonamido]-*N*-(pyridin-2-yl) pentanamide (5e): To a solution of 4-Methyl-2-[4-methylphonylsulphonamido] pentanoic acid (3e) (2.86 g, 10 mmol) in dichloromethane (10 mL) was added thionyl chloride (1.10 mL, 15 mmol) and refluxed at 80°C for 2 hours. The product was purified to obtain the acid chloride in situ. To a solution of the acid chloride in dichloromethane (10 mL) was added a solution of 2-aminopyridine (0.74 g, 10 mmol) in dichloromethane (10 mL). The reaction mixture was agitated intermittently under ice for 3 hours. After separation and purification of the oil, the product was obtained. Yield 2.90 g (88.15%), mp 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) δ: 8.29 (d, J=4.85H_2, 1H), 8.01 (d, J=8.98H_2, 2H), 7.72 (q, J=8.34Hz), 7.65. (d, J=8.08 Hz, 2H), 7.20 (d, J=8.05Hz, 1H), 7.07 (dd, J_1=3.23Hz, J_2=8.11Hz, 1H), 4.02 (q, J=8.87Hz, 1H), 2.21 (s, 3H), 1.55 (m,1H), 1.19(t, J=7.28, 2H), 0.82 (d, J=6.59Hz, 3H), 0.71 (d, J=6.50Hz, 3H).^{13}CNMR (DMSO-d_6) δ: 171.43, 152.07, 148.40, 143.00, 138.40, 129.72, 127.22, 120.06, 114.06, 55.82, 45.94, 24.52, 21.77, 9.00

Results and Discussion

Chemistry (synthesis)

The synthesis of [4-methylphenylsulphonamido]-*N*-(pyridin-2 yl) acetamide derivatives was accomplished by stirring amino acid 2a-e in a basic medium of sodium carbonate and 4-methylphenylsulphonyl chloride 1 in distilled water at room temperature for 4 h, to give the intermediates, 4-methylphenylsulphonamides (3a-e) as white crystals in exception of 3d that was oil scheme 1. Condensation of 2-aminopyridine 4 and acid chloride derivative of 4-methylphenyl sulphonamide gave *N*-pyridin-2-yl-4-methylphenyl sulphonamides 5a-e as white crystals in exception of 5d that was oil (Scheme 2).

The 4-methylphenylsulphonamides (3a-e) were synthesized as white crystalline solid in exception of methionine derivative 3d that was yellowish oil. The FTIR spectra revealed the presence of a sulphonamide group 1254 and 1140 cm^{-1}, 1369 and 1167 cm^{-1}, 1326 and 1163 cm^{-1}, 1320 and 1158 cm^{-1}, 1373 and 1168 cm^{-1} respectively for 3a-e. The -NH

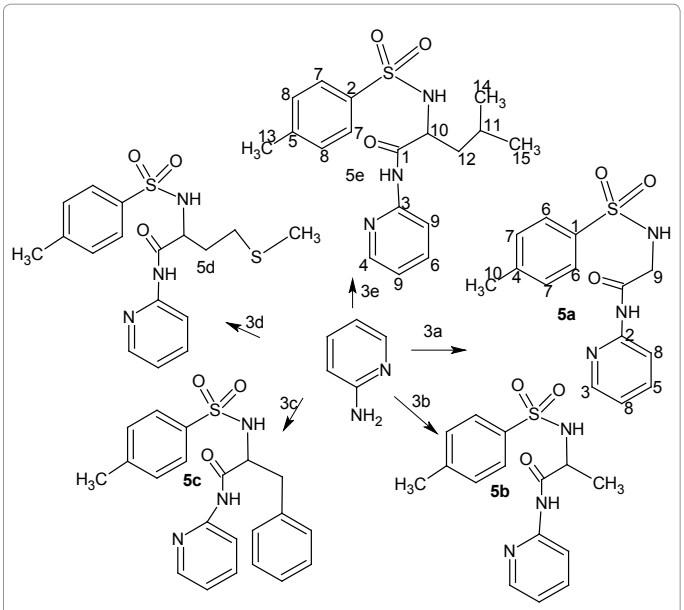


Scheme 1: synthesis of 4-methylphenylsulphonamides 3a-e.

group appeared at 3355 cm^{-1}, 3273 cm^{-1}, 3313 cm^{-1}, 3262 cm^{-1}, 3276 cm^{-1} respectively for 3a-e, the C=O group appeared at (1724-1704 cm^{-1}) and OH (3355-3262 cm^{-1}) in the 4-methylphenylsulphonamides. The ^{1}HNMR peaks agree with the synthesized compounds. The *N*-pyridin-2-yl-4-methylphenylsulphonamides (5a-e) were all white crystalline in exception of 5d that was oil. The FTIR spectra revealed in addition to other bands, the CONH functional group which appeared at 1694-1663 cm^{-1}showing the successful coupling with 2-aminopyridine as the band shifted from that of an acid (above 1700 cm^{-1}) to that of an amide (below 1700 cm^{-1}) [21]. The ^{1}HNMR and ^{13}CNMR signals agree with the structures of the compounds. Worthy to mention in the ^{1}HNMR is the appearance of peaks at δ6.86 which is assigned to heteroaromatic protons given its absence in the 4-methylphenylsulphonamides (3a-e), this is corroborated with the ^{13}CNMR which accounted for all the carbons in the compounds. When compared with fluconazole, the MIC of the sulphonamides was found to possess more antifungal activities even though some of the sulphonamides were inactive against some fungi. The coupling of the 2-aminopyridine does not really show improved antifungal activity except in the case of 5d which could be as a result of increased lipophilicity given the oily nature of the compound according to overtone concept (Table 1).

Conclusion

The synthesis of various 4-methylphenyl sulphonamides and their functionalized analogues of *N*-pyridin-2-yl-4-methylphenyl sulphonamides have been successful. The antifungal activities against some pathogenic microorganisms have also been reported in this work. The compounds were found to have better antifungal properties than fluconazole the clinical reference and therefore establish the fact that sulphonamides could lead the chemotherapeutic world in the fight against fungal infections.



Scheme 2: synthesis of N-pyridin-2-yl-4-methylphenyl sulphonamides 5a-e.

Sample No/Microorganism	*C. albican*	*A. niger*
3a	0.59	0.450
3b	1.50	0.190
3c	1.70	0.234
3d	-	0.234
3e	0.347	0.229
5a	-	-
5b	-	0.240
5c	-	-
5d	0.209	0.200
5e	0.224	0.340
Fluconazole	24.00	27.00

Table 1: Minimum inhibitory concentration (mg/ml).

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