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SYNTHESIS, CHARACTERIZATION AND ANTI-INFLAMMATORY ACTIVITIES OF N-ARYL SUBSTITUTED BENZENESULPHONAMIDE DERIVATIVES

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ABSTRACT

The synthesis of these novel N-aryl substituted benzenesulphonamid derivatives was reported using benzenesulphonyl chloride in a mixture of acetone and pyridine as a solvent and base respectively. This was achieved by coupling reaction of benzenesulphonyl chloride with different substituted aromatic amines. Their solubilities in different solvents and anti-inflammatory activity of the products were also reported. The synthesized sulphonamide derivatives were characterized using FTIR, ^{1}HNMR, ^{13}CNMR and UV Spectroscopy. These sulphonamide derivatives reported in this work had been tested and confirmed to have anti-inflammatory activity in comparison with paracetamol as a standard drug.

Keywords: Sulphonamides, anti-inflamatory, spectroscopy, aromatic amines and benzenesulphonyl chlorides.

INTRODUCTION

Sulphonamides are one of the classes of heterocycles containing the functionalaity $\mathbf{R^1\text{-}SO_2\text{-}NR_2}$ where R^1 can be an alkyl or an aryl group and R^2 can be H, an alkyl or an aryl group. These heterocyles have been reported to be the first medicinal compounds widely employed in the area of medicinal chemistry and pharmacology to combact and prevent various kinds of infectious diseases (Hansch *et al*., 1990). Good number of drugs containing this functionality have been proven very effective towards many bacteria and fungi in the treatment of infectious diseases, with an appreciable biological properties such as : antihypertensive agent (Kanda *et al*., 2001), antibacterial (Stokes *et al*., 2012), Antiprotozoal (Chibale *et al*., 2001), antifungal (Rahavi *et al*., 2008), anti-inflammatory (Kennedy and Thorley, 1999), nonpeptidic vasopressin receptor antagonists (Serradeil-Le, 2001) and translation initiation inhibitors (Natarajan *et al*., 2004).

Some derivatives of sulphonamide are also used as carbonic anhydrase inhibitors which is of great commercial significance (Vullo *et al*., 2013). They are also very efficient in the treatment of urinary, intestine, and ophthalmic infections, scalds, ulcerative colitis (Wilson *et al*., 2010), rheumatoid arthritis (Levin *et al*., 2002), male erectile dysfunction and infertility as the phosphodiesterase-5 inhibitor sildenafil also known under its commercial name Viagra (Kim *et al*., 2001; Hu *et al*., 2001). Recent development shows that, sulphonamides are used as an anticancer agent (Ma *et al*., 2012) as the antiviral HIV protease inhibitor amprenavir (Dekker, 2001) and are found very effective in the treatment of Alzheimer's disease (Roush *et al*., 1998).

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MATERIALS AND METHODS

Chemistry

All the synthesis and coupling reactions were carried out under the atmosphere of nitrogen. Reagents used in this synthesis were purchased from Sigma-Aldrich and BDH. Melting points of compounds was determined in open capillary tubes. The synthesized compounds was characterized using spectroscopic methods which include:

Infra-red spectroscopic method: The Fourier Transform IR spectra of the synthesized compounds was measured in KBr discs.

Ultraviolet/Visible spectroscopic method: The UV/ VIS spectra of the synthesized compounds was determined from the analytical HPLC results since the instrument has a routine detection of the chromophores and auxochromes in the synthesized compounds at different mn.

Nuclear Magnetic Resonance Spectroscopic Method: The 1H-NMR and 13C-NMR of the synthesized compounds was done. Thin layer chromatography (TLC) was used to monitor the progress of the reaction which was performed on silica coated aluminum plates as adsorbent and the spots were visualized using ultraviolet light or iodine chamber. The anti-inflammatory activity

was done in Department of Biochemistry, University of Nigeria, Nsukka.

Preparation of dry pyridine

Potassium hydroxide pellet (6g) was discharged into a 1000 mL standard flask containing pyridine. The solution was corked and left for 24 h to facilitate efficient elimination of water, since KOH pellet is a dehydrating agent.

General Procedure for the synthesis of N-aryl substituted benzenesulphonamide derivatives using benzenesulphonyl chloride

This synthesis was reported using benzenesulphonyl chloride in a mixture of acetone and pyridine as a solvent and base, respectively. This was achieved by coupling reaction of benzenesulphonyl chloride with different substituted aromatic amines **(1a-o)** to afford the different benzenesulphonamide derivatives **(2a-o).**

Solubility test

Solubility simply means the ability, pattern and extent to which a substance can dissolve and form a homogenous phase in a solvent. solubility test is conducted by incorporating a little quantity of the sample in a test tube containing the desired solvent and shaking the resulting mixture thouroughly, if the substance does not dissolve, intensive variables as temperature pressure, concentration of solvent etc must be specified and utilized. If it is still not soluble the solvent then might not be a good solvent for dissolution of the substance. Organic solvents as ethanol, *N,N*-dimethylformamide (DMF), dimethylsulphoxide (DMSO) were used in dissolution of the products.

Anti-inflammatory activity

The various sulphonamides synthesized were screened for anti-inflammatory activity as follows: Colony bred healthy Wistar albino rats containing either sex weighing 150–200 g were used. They were acclimatized in standard conditions exposed to 12:12 h, light: dark cycle. They were fed with standard diet and water.

The rats used in this experiment were 18, which were divided into three groups. Each group contains six animals each. Acute inflammation was induced in the rats through intraplantar administration of 0.1 mL of carrageenan (1% solution in normal saline). Group A was treated with paracetamol (10 mL/kg p.o.), Group B received indomethacin (10 mg/kg p.o.), and Group C received the synthesized Sulphonamide derivatives (500 mg/kg p.o.) 1 h before administration of phlogistic agents. The paw volume was measured prior to injection of phlogistic agent at zero hour (immediately after injecting carrageenan). The same procedure was repeated at 1, 2, 3 and 4 hours after carrageenan injection. Actual ooedema volume was recorded as the difference between the initial and subsequent reading. Reduction in paw volume compared to the control animals was considered as anti-inflammatory response (Winter *et al*., 1962). Change in the paw volume was measured, and anti-inflammatory activity was calculated as follows:

$$\% \text{ Inhibition of inflammation} = 1-(Vt/Vc)\times 100$$

Where; Vt = the change in the paw volume in sulphonamide-treated group. Vc = represents the change in the paw volume in the corresponding vehicle-treated control group.

RESULTS

Results of the Synthesis and Characterization of N-aryl substituted benzenesulphonamide derivatives (2a-2o). *N*,*N*'-(6-chloropyrimidine-2,4-diyl)bis(4-methylbenzenesulfonamide (2a)

m.p 155-157C^0, Yield 2.67g,(71%), IR (KBr) cm^{-1} 788(C-Cl), 1268 (C-N stretch aryl), 1378 (SO_2), 1470 (C=N stretch aromatic), 1623 (C=C aromatic), 2839 (C-H), 3351 (N-H). ^{1}H-NMR (400MHz, DMSO-d_6): δ 7.55-7.54 (m, 4H, Ar-H), 7.68(s, 1H Ar-H), 7.41-7.39 (m, 4H, Ar-H), 7.88 (s, 1H, N-H), 2.32 (s, 6H 2CH_3-Ar); ^{13}C-NMR (400MHz, DMSO-d_6) : δ 162.3, 148.4, 143.2, 141.5, 140.8, 139.4, 138.6, 137.1, 135.7, 131.5, 130.6, 129.8, 127.4, 21.9

N-(6-methoxypyridin-3-yl)-4-methylbenzene sulphonamide (2b)

m.p 177-118C^0, Yield 2.09g,(77%), IR (KBr) cm^{-1} 1262 (C-N aromatic amine), 1267 (C-O- diaryl), 1387 (SO_2), 1554 (C=N), 1636 (C=C aromatic), 2839 (C-H), 2929(C-H), 3062 (=C-H aromatic), 3713 (N-H). 1H-NMR (400MHz, DMSO-d_6): δ 8.13(s, 1H-Ar-H),7.95-7.94(d, J=7.32Hz, ^{1}H Ar-H), 7.82-7.81(d, J=7.12Hz, 1H, Ar-H), 7.7-7.5(d, J=7.32Hz, 1H, Ar-H), 7.54-7.53 (d, J=8.80Hz, 2H, Ar-H), 3.41(s, 3H, CH_3-O),2.33 (s, 3H CH_3-Ar); ^{13}C-NMR (400MHz, DMSO-d_6) :150.4, 149.2, 148.4, 145.3, 143.1, 140.6, 137.5, 136.7, 135.4, 50.4, 21.7.

4-methyl-*N*-(pyrimidin-4-yl)benzenesulphonamide (2c)

m.p 125-126C^0, Yield 1.65g,(65%), IR (KBr) cm^{-1} 1362 (SO_2), 1368 (C-H stretch), 1246 (C-N stretch aryl), 1495 (C=N stretch aromatic), 1622 (C=C aromatic), 3175(=C-H aromatic), 3428 (N-H). ^{1}H-NMR (400MHz, DMSO-d_6): δ 8.68 (s 1H, N-H), 8.41(s 1H, Ar-H), 7.99-7.97(d, J=7.11 Hz, 1H Ar-H), 7.82-7.80(d, J=7.13 Hz, 1H Ar-H), 7.43-7.41 (m, 2H Ar-H), 7.22-7.19 (m, 2H Ar-H), 2.33 (s, CH_3-Ar); ^{13}C-NMR (400MHz, DMSO-d_6) : δ 154.3, 150.1, 147.2, 146.5, 141.3, 139.9, 138.6, 136.9, 128.5, 125.2, 21.6.

Synthesis of *N*-(3-hydroxypyridin-2-yl)-4-methylbenzenesulphonamide (2d)

m.p 125-126^{0}C, Yield 1.65g,(65%), IR (KBr) cm^{-1} 801 (C-S), 1063 (SO_2), 1073 (Ar-H), 1621 (C=N), 1246 (C-N stretch aryl), 2416 (C=C aromatic stretch), 3127 (C-H aromatic), 3342 (OH), 3519 (N-H), ^{1}H-NMR (400MHz, DMSO-d_6): 11.23 (s, 1H- 1OH), 7.61(s 1H, Ar-OH), 7.99 (s, 1H, N-H), 7.32-7.31 (d, J=7.82 Hz, 1H, Ar-H), 7.53-7.49 (d, J=7.02, 1H, Ar-H), 6.69-6.67 (d, J= 7.23Hz, 1H, Ar-H), 7.05-7.02 (d, J = 7.10Hz, 2H, Ar-H), 7.43-7.40 (d, J, = 7.13Hz, 2H, Ar-H), 2.42 (s, CH_3-Ar); ^{13}C-NMR (400MHz, DMSO-d_6) : δ 148.1, 145.6, 140.3, 138.1, 134.7, 132.1, 131.2, 130.9,126.3, 27.2

Synthesis of *N*, *N'*-benzene-1,2-diylbis(4-methylbenzenesulphonamide) (2e)

m.p 138-139 ^{0}C, Yield 1.42(55%), IR (KBr) cm^{-1} 772 (C-S), 803 (P-disubstituted benzene), 1146 (C-N stretch), 1147 (SO_2), 2912 (Sp^3 C-H), 3127 (C-H aromatic), 3310 (N-H), ^{1}H-NMR (400MHz, DMSO-d_6): δ8.69 (s, 2H, N-H), 2.5 (s, 6H, CH_3-Ar), 7.89-7.86(d, J=7.21 Hz 2H Ar-H), 7.86-7.84 (d, J=8.22 Hz 2H, Ar-H), 7.22 (d, J= 6.78 Hz, 2H Ar-H),7.71 (d, J=7.0 Hz, 2H Ar-H). ^{13}C-NMR (400MHz, DMSO-d_6) : δ 160.1, 159.2, 155,3,153.2, 148.5, 136.5, 131.6, 22.3.

Synthesis of 4-methyl-*N*-(4-nitrophenyl)benzenesulphonamide (2f)

m.p 116-118^{0}C, Yield 2.05g,(70.1%), IR (KBr) cm^{-1} 801 (C-S), 1063 (Ar-H), 1201 (SO_2), 1322 (C-N stretch aryl), 1527 (NO), 1623 (C=C aromatic stretch), 2918 (C-H aromatic), 3250 (N-H). ^{1}H-NMR(400MHz, DMSO-d_6): δ 7.86 (s, 1H, 2N-H), 8.33-8.31 (d, J=6.91 Hz 2H Ar-H), 8.08-8.01 (d, J =7.15Hz 2H, Ar-H), 7.46 (d,J= 6.81 Hz 2H Ar-H), 7.43-7.41(d, J=7.2Hz 2H Ar-H), 2.36 (s, CH_3-Ar);^{13}C-NMR (400MHz, DMSO-d_6) : δ 148.2, 146.9, 142.2, 141.7, 138.2, 135.7, 132.3, 122.5, 121.8, 119.3, 22.1

Synthesis of 4-methyl-*N*-(4-methylpyridin-2-yl)benzenesulphonamide (2g)

m.p 150-151^{0}C, Yield 1.66 (63.5%), IR (KBr) cm^{-1} 9609 (Ar-H), 1200 (C-N stretch aryl), 1383 (SO_2), 1621 (C=N), 1627 (C=C aromatic stretch), 3301 (C-H aromatic), 3426 (N-H),. ^{1}H-NMR (400MHz, DMSO-d_6): 7.79 (s, 1H, N-H), 7.5 (d, J=8.0 Hz 1H Ar-H), 7.2-7.1 (d,J= 7.5Hz 1H Ar-H), 7.01 (s, 1H, Ar-H), 7.25-7.21(d, J=6.83Hz 2H Ar-H), 6.93-6.91 (d, J=6.83Hz 2H Ar-H), 2.32 (s, CH_3-Ar), 2.51 (s, CH_3-Ar);^{13}C-NMR (400MHz, DMSO-d_6) : δ 161.3, 159.2, 157.3, 141.4, 140.6, 138.5, 125.1, 120.3,22.7,21.6

Synthesis of 4-methyl-*N*-(4-methylpyridin-2-yl)benzenesulphonamide (2h)

m.p 138-140^0, Yield 1.22g,(45%), IR (KBr) cm^{-1} 749 (C-S) , 1063.4 (Ar-H), 1129 (SO_2), 1265 (C-N stretch aryl), 1590 (C=C aromatic stretch), 2807 (Sp^3 C-H), 3068 (C-H Ar), 3100 (C-H aromatic). 3469 (N-H). ^{1}H-NMR (400MHz, DMSO-d_6): δ 6.68-6.66 (d, J=6.92 Hz 1H Ar-H), 7.53-7.51(d, J= 7.3Hz 1H Ar-H), 6.57 (d, J=8.1Hz 2H Ar-H), 7.57-7.31 (t, J=6.83Hz 2H Ar-H), 7.72-7.70 (d, J=6.4 Hz 2H Ar-H),7.12-6.93 (d, J=7.02 Hz 2H Ar-H) 2.21 (s, CH_3-Ar)^{13}C-NMR (400MHz, DMSO-d_6) : δ 148.5, 146.7, 143.2, 138.5, 126.7, 125.4, 122.9, 119.9, 117.6,108.4, 23.7

Synthesis of *N*,*N'*-(4-chloropyridine-2,6-diyl)bis(4-methyldibenzenesulphonamide) (2i)

m.p 138-139^{0}C, Yield 1.42(55%), IR (KBr) cm^{-1} m.p 138-139^{0}C, Yield 1.42(55%), IR (KBr) cm^1 709.94 (mono substituted benzene), 713 (C-S), 935 (Ar-H), 1147 (SO_2), 1304 (C-N), 1318 (C-N), 1353 (Sp^3 C-H), 1424 (C=C aromatic stretch), 3094 (C-H aromatic), 3309 (N-H) ^{1}H-NMR (400MHz, DMSO-d_6): 7.79 (s, 2H N-H), 7.7 (d, J= 7.3Hz 2H Ar-H), 7.64-7.63 (d, J=6.91Hz 2H Ar-H), 7.61 (d, J=6.93, 2H Ar-H), 7.21 (t, J=6.99, 1H Ar-H), 2.4 (s, CH_3-Ar)13C-NMR (400MHz, DMSO-d_6) : δ 156.2, 155.2, 135.4, 122.1, 118.3, 109.6, 107.8,23.9

***N*-(4-nitrophenyl)benzenesulphonamide (2j)**

m.p 123-125^0, Yield 2.01g,(72%), IR (KBr) cm^{-1} 1249 (C-N aromatic amine), 1384 (C-NO_2). 1394 (SO_2), 1475 (C=C aromatic), 2154 (C=N), 2839 (C-H), 3046 (C-H), 3046 (=C-H aromatic), 3545 (N-H), 1H-NMR (400MHz, DMSO-d_6): δ 8.21 (s, 1H, N-H), 8.11-7.49 (d, J=7.02 Hz 2H Ar-H), 7.48-7.46 (d,J= 7.31Hz 2H Ar-H), 7.33-7.31 (d,J= 7.09Hz 2H, Ar-H), 7.06-7.03(d, J=6.83Hz 2H Ar-H), 6.93-6.90 (t, J=6.94 Hz 1H Ar-H); 13C-NMR (400MHz, DMSO-d_6) : δ 148.3, 145.6, 142.9, 139.6, 137.8, 134.6, 133.7, 130.3

Synthesis of 1-(phenylsulphonyl)-1*H*-indole (2k)

m.p 138-139^{0}C, Yield 1.42(55%), IR (KBr) cm^{-1} N-S (524), 759 (C-S), 1281 (SO_2), 1579 (C=C aromatic), 2474 (C=N), 3185 (=C-H aromatic). ^{1}H-NMR (400MHz, DMSO-d_6): δ 7.57-7.44 (d,J=7.10Hz 1H Ar-H), 7.62-7.59 (d, J= 6.98Hz 1H Ar-H), 7.33-7.31 (d, J=7.13Hz 2H Ar-H), 7.19-7.03 (t, J=7.22, 2H, Ar-H), 7.15-7.13 (t, J=7.22, 2H, Ar-H), 7.05-7.03 (t, J=7.22, 1H, Ar-H) 7.61-7.59 (d, J= 7.21 Hz 2H Ar-H) ^{13}C-NMR (400MHz, DMSO-d_6) : δ 145.2, 142.7, 141.6, 140.8, 139.3, 136.8, 122.5,121.0,119.6, 118.9

Synthesis of *N*-(1,3-benzothiazol-2-yl)-4-methylbenzenesulphonamide (2l)

m.p 123-125^0, Yield 2.01g,(72%), IR (KBr) cm^{-1} 749 (C-S), 866(P-disubstituted benzene), 1063 (Ar-H), 1083 (SO_2), 1246 (C-N stretch aryl), 1305 (C-N), 1337 (Sp^3 C-H), 1416 (C=C aromatic stretch), 3126 (C-H aromatic), 3266 (N-H), ^{1}H-NMR (400MHz, DMSO-d_6): δ7.44-7.42 (d ,J=7.02 Hz 2H Ar-H), 7.41-7.38 (d, J= 7.21 Hz 2H Ar-H), 7.43 (t, J=6.38 Hz 1H Ar-H), 6.43 (t, J=6.35 Hz 2H Ar-H), 6.40 (t, J=6.33 Hz 1H Ar-H), 6.35 (t, J=7.38 Hz 1H Ar-H),7.42-7.41 (d, J=6.89, 2H, Ar-H), 7.39-7.36 (d,

J= 7.12 Hz 2H Ar-H) 13C-NMR (400MHz, DMSO-d_6) : 158.2,151.1, 148.4, 136.1, 135.3,134.9,133.7, 125.1, 116.7, 110.2, 106.1

Synthesis of *N*,*N*'-benzene-1,2-diyldibenzenesulphonamide (2m)

m.p 138-139^{0}C, Yield 1.42(55%), IR (KBr) cm^{-1} 721 (C-S), 810 (para substituted benzene), 935 (Ar-H), 1063 (SO_2), 1307 (C-N), 1353 (Sp^3 C-H), 1618 (C-N), 2051 (C=C aromatic stretch), 3126 (C-H aromatic), 3309 (N-H), ^{1}H-NMR (400MHz, DMSO-d_6): δ 7.36 (s, 2H, N-H), 7.73-7.71 (d,J=6.30Hz 2H Ar-H), 7.05 (t, J= 7.1Hz 4H Ar-H), 7.09-6.68 (d, J=7.30Hz 4H Ar-H), 7.24-7.21 (d, J=6.4, 2H, Ar-H), 6.93 (t, J= 7.13 Hz 2H Ar-H) ^{13}C-NMR (400MHz, DMSO-d_6) : 155.8,124.3,120.6,119.8,117.6,114.8,110.4

Synthesis of *N*-(6-methoxypyridin-3-yl)benzenesulphonamide (2n)

m.p 114-116^{0}C, Yield 1.42(55%), IR (KBr) cm^{-1} m.p 138-139^{0}C, Yield 1.42(55%), IR (KBr) cm^1 710 (mono substituted benzene), 713 (C-S), 1255 (C-N), 1304 (C-N), 1378 (SO_2), 1414 (Sp^3 C-H), 1646 (C=C aromatic stretch), 3154 (C-H aromatic), 3454 (N-H). ^{1}H-NMR (400MHz, DMSO-d_6): δ 8.12 (s, 1H N-H), 7.72 (s ,1H Ar-H), 7.01-6.69 (d, J= 6.5Hz 1H Ar-H), 7.05-6.69 (d, J=6.7Hz 2H Ar-H), 7.51 (t, J=7.02, 1H, Ar-H), 7.46 (t, J=7.02, 2H, Ar-H). 7.03-6.67, (d, J=6.7Hz 1H Ar-H); 2.61 (s, 3H O-CH_3), 13C-NMR (400MHz, DMSO-d_6) : δ 162.1, 149.7, 147.6,143.5, 138.9,133.6, 127.5, 125.6,120.9,117.7, 31.3

Synthesis of *N*-(4-methylpyridin-2-yl)benzenesulphonamide (2o)

m.p 209-211^{0}C, Yield 1.7(70%), IR (KBr) cm^{-1} 721 (C-S), 810 (para substituted benzene), 1396 (SO_2), 1281 (C-N), 1524 (C=N), 1625 (C=C aromatic stretch), 2938 (C-H aromatic), 3154 (C-H Ar), 3454 (N-H), ^{1}H-NMR (400MHz, DMSO-d_6): δ 7.37 (s, 1H N-H), 7.25(s ,1H Ar-H), 7.21-7.19 (d, J= 7.23Hz 1H Ar-H), 7.01-6.69 (d, J=6.7Hz 1H Ar-H), 7.32-7.21 (d, J=6.68, 2H, Ar-H), 6.69-6.67 (t, J= 7.17, 2H, Ar-H), 7.57-7.52 (t, J= 6.92Hz, 1H Ar-H), 13C-NMR (400MHz, DMSO-d_6) : 151.3, 150.2, 148.9, 146.7, 145.2, 138.3, 128.9, 126.8, 122.5, 120.8, 119.6, 24.6.

The elucidated structures of the newly synthesized compounds (2a – 2e) were gotten by the coupling reaction of methyl benzenesulphonyl chloride with different substituted aromatic amines as seen in Figure 1, while Figure 2 shows coupling reaction of benzenesulphonyl chloride with different substituted aromatic amines to give compounds (2d- 2o).

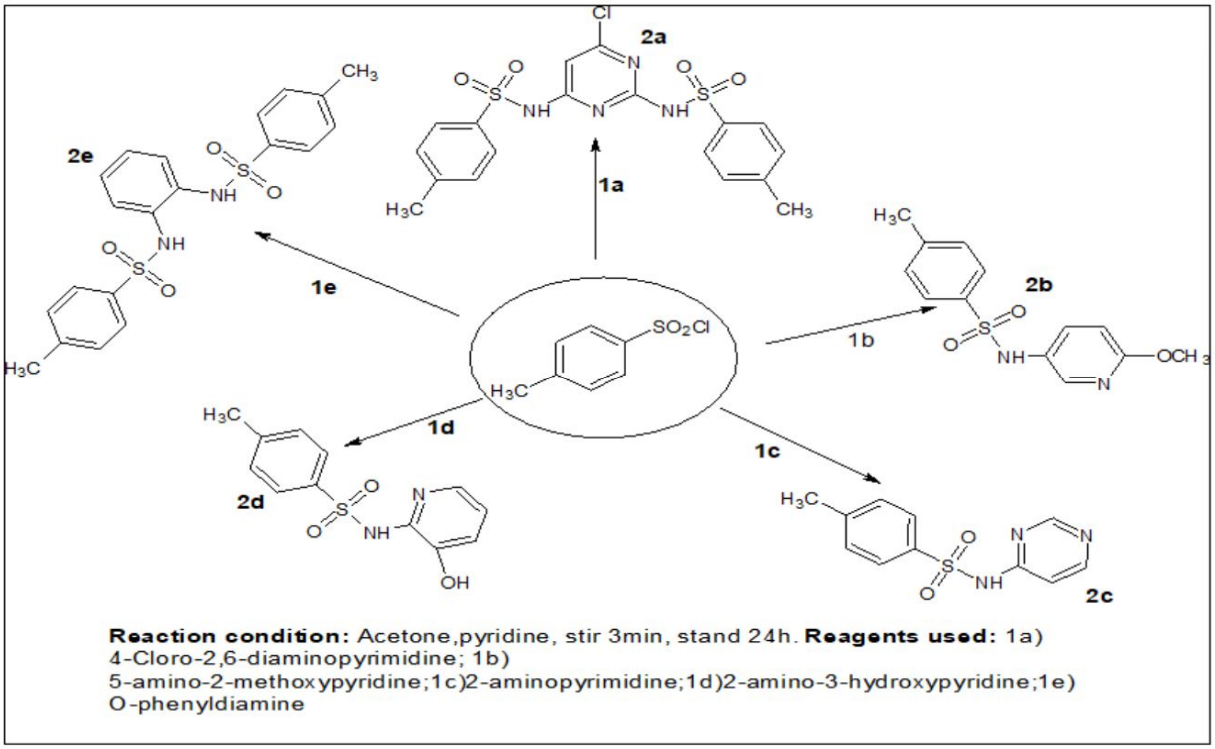

Fig. 1. Coupling reaction of methyl benzenesulphonyl chloride with different substituted aromatic amines.

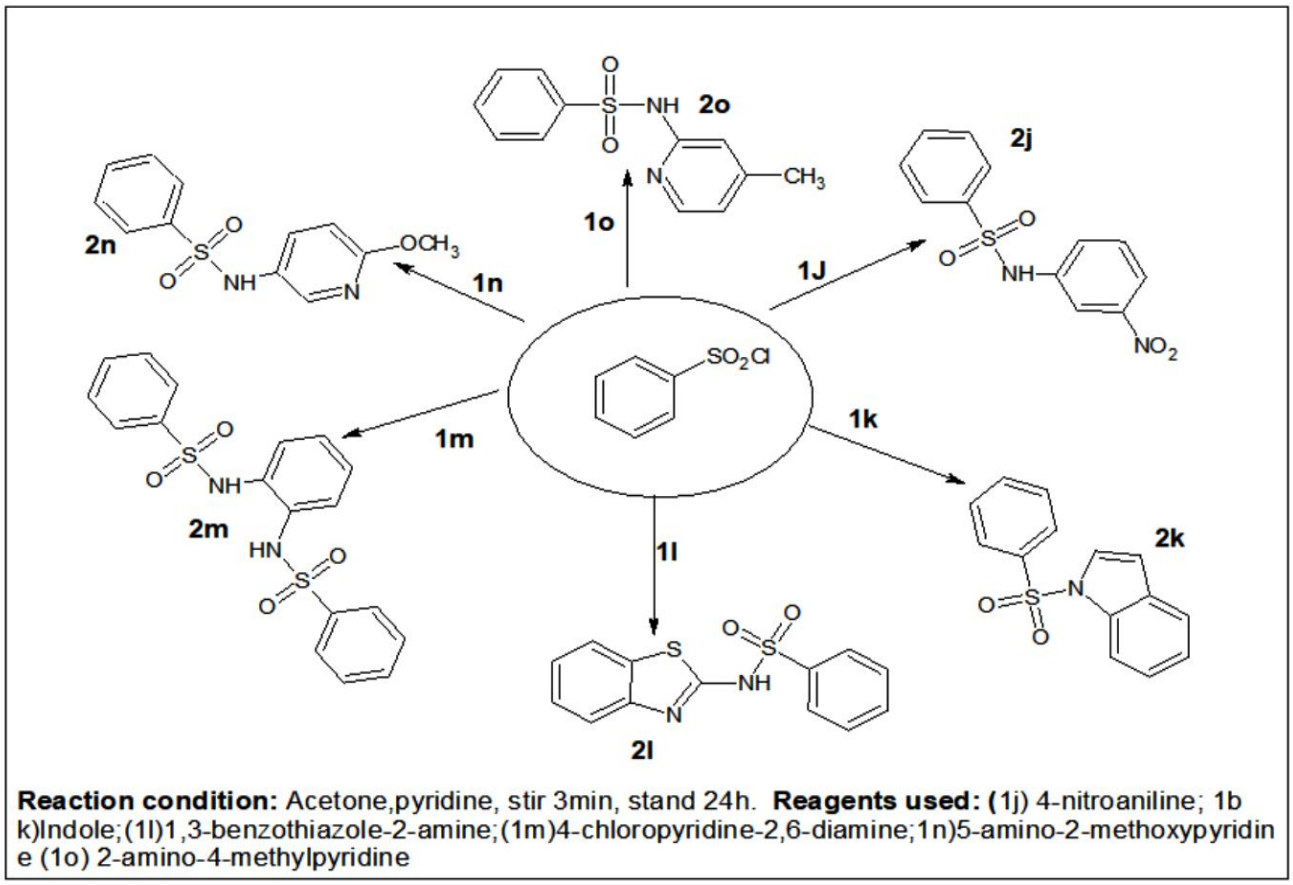

Fig. 2. Coupling reaction of benzenesulphonyl chloride with different substituted aromatic amines.

Table 1. Solubility Test Results.

Samples	DCM	CH_3OH	C_2H_5OH	DMF	DMSO
2a	-	-	-	+	+
2b	+	+	+	+	+
2c	±	±	-	+	+
2d	±	+	+	±	+
2e	±	+	+	+	+
2f	+	+	+	+	+
2g	+	-	-	+	+
2h	+	+	+	+	+
2i	-	-	-	+	+
2j	±	±	-	+	+
2k	+	+	+	+	+
2l	-	-	-	+	+
2m	±	+	+	+	+
2n	+	+	+	+	+
2o	+	-	-	+	+

Key: Soluble = + , Insoluble = - , Sparingly soluble = ±

From the solubility test results, it was found out all the newly synthesized compounds were soluble in polar aprotic solvents used in this experiment ,but not all were soluble in the polar protic solvent as can be seen in Table 1.

Table 2. Results of Anti-Inflammatory Activities.

S/N	Samples	% Inflammatory inhibition of three different induced rat paw edema			Mean % inhibition	Standard deviation
1	**2a**	86	50	60	65	8.00
2	**2b**	43	67	60	57	5.40
3	**2c**	43	17	0	20	10.95
4	**2d**	85.7	50	48	61.23	9.418
5	**2e**	28.57	0.00	0.00	9.52	7.33
6	**2f**	57	66.6	40	54.5	11
7	**2g**	28.5	33.3	60	40.6	13.9
8	**2h**	28.5	16.6	20	21.7	5.0
9	**2i**	40	66.7	40	45.09	8.31
10	**2j**	43	0	4	16	18.14
11	**2k**	57	33	20	37	24.00
12	**2l**	40	48	40	42.67	8.27
13	**2m**	42.8	33.33	40	38.70	2.07
14	**2n**	42.9	33.3	20	32.1	9.4
15	**2o**	71.4	66.6	40	59.3	13.8
16	**Standard Paracetamol**	71.4	66.6	80	72.7	5.5

In view of their biological activity, compound 2a -2o were tested for their anti-inflammatory and anti-pyretic activity as seen in Table 2. Paracetamol was used as a reference drug with mean % inhibition of 72.7.

Compound 2a was observed to possess the highest mean %inhibition of 65, compounds 2d, 2f, 2g 2i, and 2o has a mean % anti-inflammatory and antipyretic inhibition of 61.23, 45.09, 54.5, 40.6 and 59.3 respectively. The data establishes that substitution of an electron donating group e.g. methyl at the *ρ*-position of I greatly increases activity. Compounds 2k, 2m and 2n exhibits moderate activity while compound 2e possesses the least anti-inflammatory and anti-pyretic activity. Thus the order of activity of the newly synthesized compounds are as follows: 2a > 2d >2o > 2b > 2f > 2i > 2l > 2g >2m >2k > 2n > 2h > 2c > 2j > 2e.

CONCLUSION

The present study describes a convenient and efficient protocol for the synthesis of *N*-heteroaryl substituted benzene sulphonamide derivatives using benzene sulphonyl chloride, *p*-toluenesulphonyl chloride and heteroaromatic compounds under dry pyridine and acetone conditions. I believed that this procedure is convenient, economical, and user-friendly process for the synthesis of these various sulphonamide compounds. The synthesized compounds were also supported by NMR, IR and UV spectral data. Finally, the sulphonamide derivatives reported in this work had been tested and confirmed to have anti-inflammatory and antipyretic activities in comparison with paracetamol used as the standard drug and also had affordable synthetic routes. It is therefore encouraged that further research should be conducted to exploit the medicinal potential of sulphonamides in the combat of inflammation disease in Nigeria and the world at large.

REFERENCES

Chibale, K., Haupt, H., Kendrick, H., Yardley, V., Saravanamuthu, A., Fairlamb, AH. and Croft, SL. 2001. Antiprotozoal and cytotoxicity evaluation of sulfonamide and urea analogues of quinacrine. Bioorg. and Med. Chem. Lett. 11:2655.

Dekker, M. 2001. In Protease Inhibitors in AIDS Therapy. Eds. Ogden, RC. and Flexner, CW. New York, NY, USA.

Hansch, C., Sammes, PG. and Taylor, JB. 1990. Comprehensive Medicinal Chemistry. (vol. 2, Chap. 7.1). Pergamon Press, Oxford.

Hu, B., Ellingboe, J., Han, S., Largis, E., Lim, K., Malamas, M., Mulvey, R., Niu, C., Oliphant, A., Pelletier, J., Singanallore, T., Sum, FW., Tillett, J. and Wong, V. 2001. Novel (4-Piperidin-1-yl)-phenyl Sulfonamides as Potent and Selective Human b3 Agonists. Bioorg. & Med. Chem. 8:2045.

Kanda, Y., Kawanishi, Y., Oda, K., Sakata, T., Mihara, S., Asakura, K., Kanemasa, T., Ninomiya, M., Fujimoto, M. and Kanoike, T. 2001. Synthesis and structure-activity relationships of potent and orally active sulfonamide ETB selective antagonists. Bioorg. and Med. Chem. (vol. 9). pp 897.

Kennedy, JF. and Thorley, M. 1999. Pharmaceutical Substances. (3rd edi.). Eds. Kleeman, A., Engel, J., Kutscher, B. and Reichert, D. Thieme, Stuttgart.

Kim, DK., Lee, JY., Lee, N., Ryu, DH., Kim, JS., Lee, S., Choi, JY., Ryu, JH., Kim, NH., Im, GJ., Choi, WS. and Kim, TK. 2001. Synthesis and phosphodiesterase inhibitory activity of new sildenafil analogues containing a carboxylic acid group in the 5'-sulfonamide moiety of a phenyl ring. Bioorg. and Med. Chem. 9:3013.

Levin, JI., Chen, JM., Du, MT., Nelson, FC., Killar, LM., Skala, S., Sung, A., Jin, G., Cowling, R., Barone, D. and March, CJ. 2002. Anthranilate sulfonamide hydroxamate TACE inhibitors. Part 2: SAR of the acetylenic P1' group. Bioorg. and Med. Chem. Lett. 12:1199.

Ma, T., Fuld, AD., Rigas, JR., Hagey, AE., Gordon, GB., Dmitrovsky, E. and Dragnev, KH. 2012. A Phase I Trial and in vitro Studies Combining ABT-751 with Carboplatin in Previously Treated Non-Small Cell Lung Cancer Patients. Chemotherapy. 58:321.

Natarajan, A., Guo, Y., Harbinski, F., Fan, YH., Chen, H., Luus, L., Diercks, J., Aktas, H., Chorev, M. and Halperin, JA. 2004. Novel Arylsulfoanilide−Oxindole Hybrid as an Anticancer Agent That Inhibits Translation Initiation. J. Med. Chem. 47:4979.

Rahavi, EI., Camoutsis, C., Zoumpoulakis, P., Geronikaki, A., Soković, M., Glamočilija, J. and Čirič, A. 2008. Sulfonamide-1,2,4-triazole derivatives as antifungal and antibacterial agents: Synthesis, biological evaluation, lipophilicity, and conformational studies. Bioorg. and Med. Chem. 16:1150.

Roush, WR., Gwaltney, SL., Cheng, J., Scheidt, KA., McKerrow, JH. and Hansell, E. 1998. Vinyl Sulfonate Esters and Vinyl Sulfonamides: Potent, Irreversible Inhibitors of Cysteine Proteases. J. Am. Chem. Soc. 120:10994.

Stokes, SS., Albert, R., Buurman, Ed T., Andrews, B., Shapiro, AB., Green, OM., McKenzie AR. and Otterbein, LR. 2012. Inhibitors of the acetyltransferase domain of N-acetylglucosamine-1-phosphate-uridylyltransferase/glucosamine-1-phosphate acetyltransferase (GlmU). Part 2: Optimization of physical properties leading to antibacterial aryl sulfonamides. Bioorg. and Med. Chem. Lett. 22:7019.

Serradeil-Le Gal, C. 2001. An overview of SR121463, a selective non-peptide vasopressin V2 receptor antagonist. Cardiovascular Drug Rev. 19:201.

Vullo, D., De Luca, V., Scozzafava, A., Carginale, V., Rossi, M., Supuran, CT. and Capasso, C. 2013. The extremo-α-carbonic anhydrase from the thermophilic bacterium Sulfurihydrogenibium azorense is highly inhibited by sulfonamides. Bioorg. and Med. Chem. 21: 4521.

Wilson, CO., Gisvold, O. and Block, JH. 2004. Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry. (11th ed.). Eds. Block, J. and Beale, JM. Lippincott Williams and Wilkins, Philadelphia.

Winter, C., Risley, EA. and Nuss, GW. 1962. Carragennian induced ooedema in hind paw of the rats for anti-inflammatory drugs. Proceedings of the Society for Experimental Biology and Medicine. 3:544-547.

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