SYNTHESIS AND *In Vitro* ANTIBACTERIAL ACTIVITY OF MORPHOLINE DERIVED BENZENESULPHONAMIDES

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ABSTRACT

This study investigated the synthesis of sulphonamide substituted derivatives of morpholine from appropriate benzenesuphonyl chlorides obtaining excellent yields of oily products. The structural elucidation was confirmed by ^{1}H and ^{13}C NMR spectral analysis. The synthesized compounds; 4(-phenylsulonphonyl)morpholine and N-(4-(4-Methylbenzene-1-sulphonyl)morpholine) were evaluated for their *in vitro* antibacterial activity against bacteria; *B. subtilus*, *S. typhi* and *E. coli*. Both compounds were moderately active against *B. Subtilis*, but had no inhibitive activity against *E. coli.* Whereas, N-(4-(4-Methylbenzene-1-sulphonyl)morpholine) was moderately active against *S. typhi*. The physiochemical properties of the synthesized compounds evaluated, revealed its' potential for drugs.

Keywords: Synthesis; *In Vitro;* Antibacterial Activity; Morpholine

INTRODUCTION

Sulphonamide is the basis of several groups of drugs [1] and paved the way for the antibiotic revolution in medicine. The first sulphonamide, trade-named prontosil (**1**), was a prodrug (a biologically inactive compound which was metabolized in the body to produce a drug). Experiments with prontosil began in 1932 in the laboratories of Bayer AG. The Bayer team believed that coal-tar dyes which are able to bind preferentially to bacteria and parasites might be used to attack harmful organisms in the body. After years of fruitless trial-and-error work on hundreds of dyes, a team led by physician/researcher, Gerhard Domagk [2] finally found one that worked: a red dye that had remarkable effects on stopping some bacterial infections in mice [3]. Prontosil was the first medicine ever discovered that could effectively treat a range of bacterial infections inside the body (*in vivo*). It had a strong protective action against infections caused by streptococci, including blood infections, childbed fever, and erysipelas. However, it had no effect at all in the test tube (*in vitro*), exerting its antibacterial action only in live animals. Later, it was discovered that the drug was metabolized inside the body, releasing from the inactive dye portion a smaller, colorless, active compound called sulphanilamide (**2**) [4].

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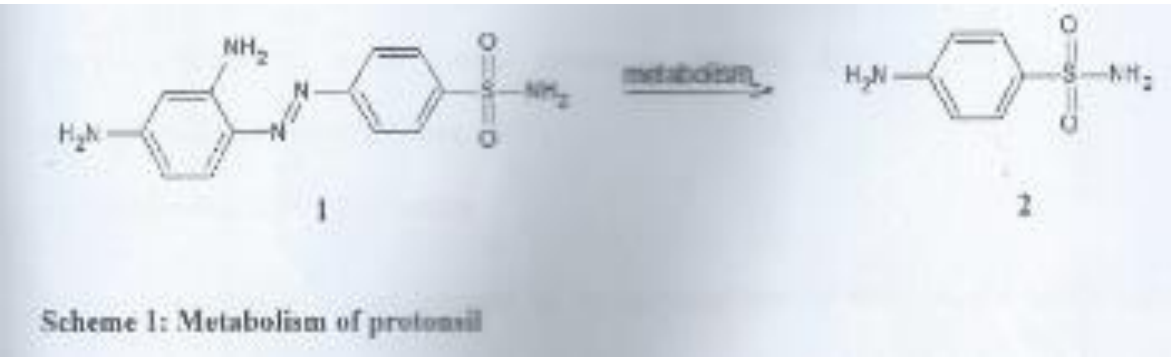
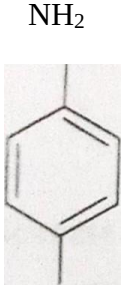


Scheme 1: Metabolism of protonsil

As the first and only effective antibiotic available in the years before penicillin. sulpha drugs continued to thrive through the early years of World War II. Sulphonamides have been the center of drug structures as this group is quite stable and well tolerated inhuman beings. The synthesis of these structures was started in search of new pharmacological active reagents [5].

Antimicrobial Activity of Sulphonamides

Antimicrobial activities of sulphonamides depend on the substituent and their position in the benzene ring [6]. Sulphonamides are bacteriostatic in nature. The sulphonamide sensitive microorganisms require *p-amino* benzoic acid (PABA) (**3**) for the synthesis of folic acid which is essential for the synthesis of DNA and RNA. Due to structural resemblance of suphonamides with PABA, sulphonamides competitively inhibit PABA. This causes folic acid deficiency, resulting in arrest of bacterial growth and cell division [7].



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As antimicrobial agents sulphonamides inhibit Gram-positive and Gram-negative bacteria, *Chlamydia trachomatis* and some Protozoa. Sulphonamides are used in the treatment of tonsillitis, septicemia, meningococcal meningitis, bacillary dysentery and number of infections of urinary tract [7].

Preparation of Sulphonamides

Primarily, sulphonamides are prepared by the sulphonylation of ammonia or primary and secondary amines with sulphonyl chlorides in the presence of a base. Even though many synthetic methods have been reported for the preparation of sulphonamides [8], the sulphonylation of ammonia or primary and secondary amines with sulphonyl chlorides in the presence of a base is still being used as the method of choice because of high efficiency and simplicity of the reaction [9]. Although this method is efficient, it requires the availability of sulphonyl chloride, some of which are difficult to store or handle, In turn, sulphonyl chlorides can be prepared from the corresponding thiols using a number of methods, commonly by bubbling $C1_2$ gas into aqueous acid or a biphasic mixture containing the thiol. Sulphonyl chlorides are prepared also by treating sulphonic acids with chlorinating agents such as $SOC1_2$ [10]. The direct oxidative conversion of thiols into sulphonamides with H_20_2-$SOC1_2$ was reported by Bahrami

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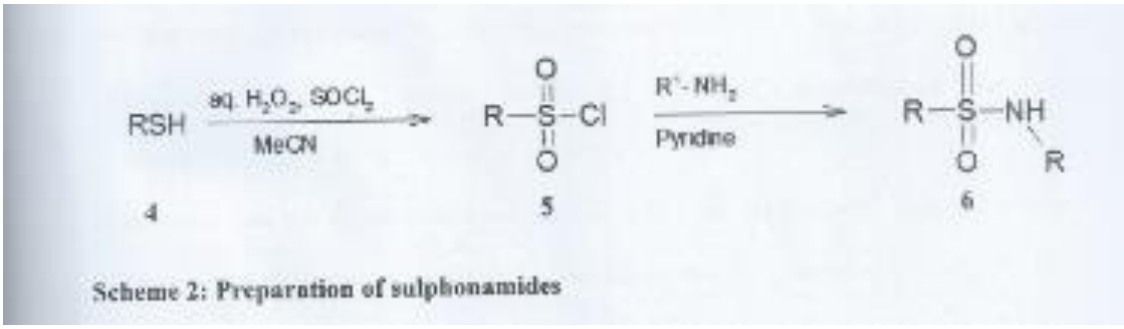
et al. where upon action with amines, the corresponding sulphonamides were obtained in excellent yields in very short reaction times [11].

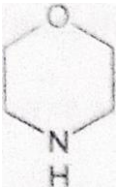


Scheme 2: Preparation of sulphonamides

Sulphonamides function by interfering with the microbial synthesis of folic acid, thereby, inhibiting bacterial growth. More specifically, sulphonamides block the biosynthetic pathway of folic acid synthesis, thus competitively inhibiting the transformation of (PABA) to folic acid which allows them to be considered as antimetabolites.

Morpholine

Morpholine (**7**) is an organiccompound having the chemical formula$O(CH_2CH_2)_2NH$. This heterocycle features both amine and etherfunctional groups. Because of the amine, morpholine is a base; its conjugate acid is called morpholinium. For example, treating morpholine with hydrochloric acid makes the saltmorpholinium chloride. The naming of morpholine is attributed to Ludwig Knorr, who incorrectly believed it to be part of the structure of morphine [12]. Momholine is a six-membered heterocyclic compound [13], It has synonyms tetrahydro-1,4-oxazine; 1-Oxa-4-azaeyclohexane; diethyleneoximide [14].



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Morpholine derivative plays an important role in the treatment of several diseases [15]. Morpholine derivatives have a wide spectrum of antimicrobial activity and insecticidal activity [16]. Morpholine is used as an emulsifier for cosmetics, rubless waxes and polishes, dyes, pharmaceuticals and catalysts [17]. Morpholine and its derivatives (MAID) find a multitude of pharmaceutical application as catalysts, pesticides, personal care, antioxidants, bactericides, analgesics, anesthetics, antidepressants, appetite suppressants, antitumor agents, antibiotics, antifungal, antileismanial and other physiologically active agents [18].

Morpholine and its derivatives have several industrial applications, such as corrosion inhibitor, optical bleaching agent, and in textile solvent to dissolve cellulose, and fruit or vegetable preservation/glazing agent [18]. Apart from that, substituted morpholine derivatives are the core of various natural and biologically active compounds. This class of compounds has found important application in pharmaceutical field [18].

Chemical manipulations on morpholine based molecules through structure-activity relationship strategy could help developing many interesting candidates of therapeutic significance to tackle broad range of

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medical ailments. Feasible physicochemical properties (polarity and solubility), low cost and wide availability make it a suitable candidate for the synthesis of many potent drugs. Being an important substituent, it could profoundly influence parameters of structural activity relationship (SAR) in lead optimization process. In addition, it is very feasible to incorporate morpholine/modified morpholine units in bioactive molecular scaffolds through conventional synthetic approaches. Since several enzymatic targets possess conserved active pocket which could allow ligands to bind through a specific interaction (Vander Waals/ionic/hydrogen bonding) and both the atoms of morpholine could serve as efficient hydrogen bond acceptors and donors, making the moietyideal for improving selectivity during lead optimization process [18]. Apart from this, MAID may pose minimal pharmacokinetic burden due to their polar and water soluble nature. Hence, strategies for synthesis of morpholine based derivatives could set a stage for the development of several interesting therapeutic molecules which may stand promising especially in terms of target selectivity and safety [18].

MATERIALS AND METHODS

General Information

P-toluenesulphonyl chloride, benzenesulphonyl chloride and morpholine were purchased from Aldrich company, Germany and were used without further purification. The ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectroscopic analysis was carried out at IIT, Kanpur, India. The antimicrobial properties were conducted in Microbiology Laboratory in the Department of Veterinary Medicine, University of Nigeria, Nsukka and the melting points were determined with Fisher-John's melting point apparatus and were uncorrected.

General synthesis

Morpholine (0.87g, 10mmol) was dissolved in a mixture of anhydrous acetone (20mL) and dry pyridine (3mL), followed by addition of appropriate benzenesulphonyl chloride. The reaction mixture was warmed to room temperature and allowed to stir for 2 hours. The reaction was left to stand for 24 hours and the product filtered off using suction filtration.

Synthesis of 4(-phenylsulphonyl)morpholine (22)

According to the general procedure described above, compound **22** was synthesized using benzenesuphonyl chloride. Compound **22** had molecular formula $C_{10}H_{13}NO_3S$; yield: (1.79 g, 78.9 %). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.35 (d, J = 8 MHz, 2H, ArH), 8.03 (d, J = 16 MHz, 2H, ArH), 7.72 (s, ^{1}H, ArH), 4.37 - 4.30 (m, 4H, CH_2-O), 3.48 – 3.22 (m, 4H, CH_2-N); ^{13}C NMR (DMSO-d_6 100 MHz) δ: 149.92 (C-S), 147.25, 128.71, 124.78 (5 aromatic carbons), 61.90, 30.79 (4 aliphatic carbons).

Synthesis of N-(4-(4-Methylbenzene-1-sulphonyl)morpholine) (23)

Compound **23** was synthesized according to the general procedure described above, using *p*-toluenesulphonyl chloride. Compound **23** had molecular formula $C_{11}H_{15}NO_3S$; yield (1.95 g, 80.9%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.72 (d, J =

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8 MHz, 2H, ArH), 7.35 (d, J = 20 Hz, 2H, ArH), 3.58 (d, J = 44 MHz, 4H, aliphatic hydrogen) 3.26 (d, J = 12 MHz, 4H, aliphatic hydrogen), 2.87 (s, ^{1}H, CH_3); ^{13}C NMR (DMSO d_6 100 MHz) δ: 150.41 (C-S), 143.78, 129.22, 125.14 (5 aromatic carbons), 61.07, 48.99 (4 aliphatic carbons) 24.74 (CH_3 aliphatic carbons).

In Silico physiochemical properties evaluation

Physiochemical properties which includes molecular weight (MW), LogP, hydrogen bond donor (HBD), hydrogen bond acceptor (HBA), total polar surface area (TPSA), number of rotatable bonds (NoRB), volume and the bioavailability prediction was carried out using Molinspiration Cheminformatics software. The drug likeness was evaluated using the Lipinski's rule which states that; most "drug-like" molecules have logP ≤ 5, molecular weight ≤ 500, number of hydrogen bond acceptors ≤ 10 and number of hydrogen bond donors ≤ 5. [19].

Antimicrobial Study

Standard clinical isolated strains of Gram-positive organism; *Bacillus subtilis* (*B. subtilus*) and Gram-negative organisms; (*Salmonella typhi* (*S. typhi*) and *Escherichia coli* (*E. coli*) were obtained and analysis carried out at Microbiology laboratory, Department of Veterinary Medicine, University of Nigeria, Nsukka. They were maintained on Hinton Agar medium at 4^0C. The isolates were sub-cultured in nutrient broth at 37^0C for at least 8 hrs prior to antibacterial testing.

Agar well diffusion technique was used to determine the antibacterial activity of the synthesized compounds. Culture plates (agar plates) were inoculated with 0.1 mL of an overnight culture of each bacteria strain, allowed to dry and appropriately labeled. Uniformed wells were bored in the inoculated nutrient agar using a 6 mm cork borer. With the aid of a micropipette, 200 µL of 10 mg/ml of each test compound solution was delivered into each well. Ciprofloxacin (CPX) which was used as reference drug was also tested and the plates were left for 30 mins to diffusion of the compound into the agar, after which the plates were incubated at 37^0C for 24 hrs. After incubation, the plates were observed for inhibition zones around the wells and the Minimum Inhibitory Concentration (MIC) evaluated. The procedure was repeated for each bacteria strain at 2.5 mg/mL, 1.25 mg/mL, 0.625 mg/mL, 0.25 mg/mL, 0.125 mg/mL of each test compound solution.

Generation of 3d Structures of the Test Compounds

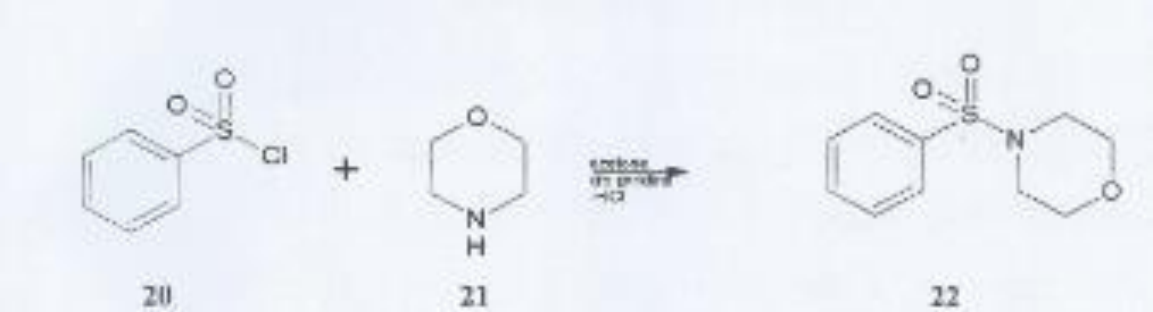
The 3D structures of the sulphonamide derivatives were generated using the molecular builder interface implemented in Chem Draw software.

ISSN 0795 - 22066

RESULTS AND DISCUSSION

Percentage yield and Spectral Analysis

Percentage yield of 4(-Phenylsulphonyl)morpholine (22)



Scheme 8: Synthesis of compound 22

From the equation of reaction;

$C_6H_5SO_2Cl + C_4H_9NO \longrightarrow C_{10}H_{13}NO_3S$

1 mole : 1 mole : 1 mole

176.5 g/mol : 87.1 g/mol : 227.1 g/mol

1.78g : 0.87g : 2.268g (theoretical yield)

Amount of compound **20** = $\frac{\text{Reacted mass}}{\text{MW}} = \frac{1.78\text{g}}{176.5\text{ g/mol}} = 0.010$ mol

Amount of compound **21** = $\frac{\text{Reacted mass}}{\text{MW}} = \frac{0.87\text{g}}{87.1\text{ g/mol}} = 0.0099$ mol

Therefore, compound **21** (0.87, 0.0099mol) was the limiting reactant.

Actual yield of compound **22** = 1.79g

Theoretical yield = $\frac{0.87\text{g}}{87.1\text{ g/mol}} \times 227.1 = 2.268\text{g}$

Percentage yield = $\frac{\text{Actual yield}}{\text{Theoretical yield}} \times \frac{0.87\text{g}}{1} = \frac{1.79\text{g}}{2.268\text{g}} \times \frac{100}{1}$

Percentage yield of N-(4-(4-Methylbenzene-1-sulphonyl)morpholine) (23)

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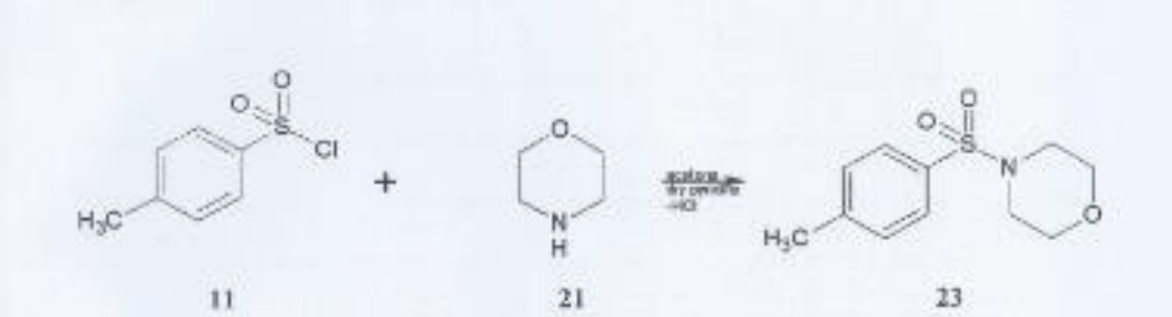


11 21 23

Scheme 9: Synthesis of compound 23

From the equation of reaction;

$C_7H_7SO_2Cl$ + C_4H_9NO ⟶ ClIH15N03S

1 mole : 1 mole : 1 mole

190.65 g/mol : 87.1 g/mol : 241.25 g/mol

1.93 g : 0.87 g : 2.409 g (theoretical yield)

Amount of compound **11** = $\frac{\text{Reacted mass}}{\text{MW}} = \frac{1.93\text{g}}{190.65\ \text{g/mol}} = 0.0101$ mol

Amount of compound **21** = $\frac{\text{Reacted mass}}{\text{MW}} = \frac{0.87\text{g}}{87.1\ \text{g/mol}} = 0.0099$ mol

Therefore, compound **21** (0.87, 0.0099 g) was the limiting reactant.

Actual yield of compound **23** = 1.95 g

Theoretical yield = $\frac{0.87\text{g}}{87.1\ \text{g/mol}}$ x 241.25 = 2.409 g

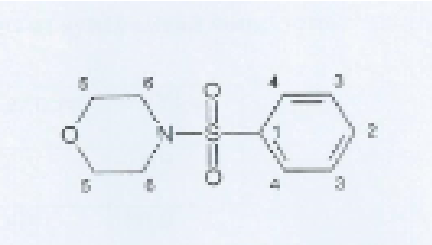
Percentage yield = $\frac{\text{Actual yield}}{\text{Theoretical yield}} \times \frac{100}{1} = \frac{1.95\text{g}}{2.409\ \text{g/m}} \times 100 = 80.9\%$

^{1}H NMR and ^{13}C NMR spectral analysis 4(-phenylsulonphonyl)morpholine (22)

In the proton NMR, four protons of the aromatic ring of which two are in the same chemical environment appeared as a doublet at 8.35 ppm and the other two appeared as a doublet at 8.03 ppm. One proton of the aromatic ring appeared as a singlet at 7.72 ppm. Four aliphatic protons at C_5 which are attached to the oxygen atom and are in the same chemical environment appeared as a multiplet at 4.37 – 4.30 ppm. Four aliphatic protons at C_6 which are attached to the nitrogen atom and are in the same chemical environment appeared as a multiplet at 3.48 – 3.22 ppm. In the Carbon-13 NMR, the C-S carbon (C_1) on the aromatic ring appeared at 149.92 ppm. The aromatic carbon (C_2) appeared at 147.25 ppm. Two carbons of the aromatic ring (C_3) which are in the same chemical environment appeared at 128.71 ppm. Two carbons of the aromatic ring (C_4) which are

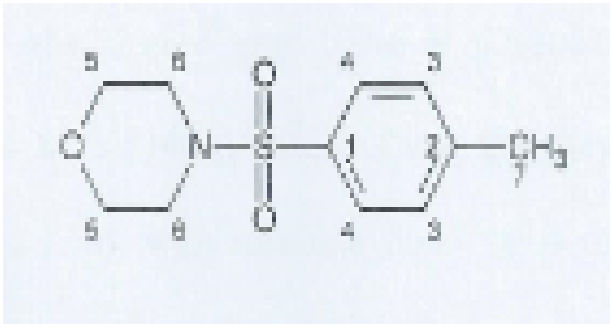
ISSN 0795 - 22066

in the same chemical environment appeared at 124.78 ppm. Four aliphatic carbons of the cyclic ring of which two (C_5) are in the same chemical environment appeared at 61.90 ppm and the other two (C_6) appeared at 30.79.



N-(4-(4-Methylbenzene-1-sulphonyl)morpholine) (23)

In the proton NMR, four protons of the aromatic ring of which two are in the same chemical environment appeared as a doublet at 7.72 ppm and the other two appeared at 7.35 ppm. Four protons of the cyclic aliphatic ring which are in the same chemical appeared environment appeared as a doublet at 3.58 ppm and the other four appeared as a doublet at 3.26 ppm. The protons at the CH_3 appeared as a singlet at 2.87 ppm. In the carbon-13 NMR, the C-S carbon (C_1) on the aromatic ring at 150.41 ppm. The aromatic carbon (C_2) appeared at 143.78 ppm. Two carbons of the aromatic ring (C_3) which are in the same chemical environment appeared at 129.22 ppm and the other two aromatic carbons (C_4) which are in the same chemical environment appeared at 125.14 ppm. Four aliphatic carbons of the cyclic ring (C_5) which are attached to the oxygen atom and are in the same chemical environment appeared at 61.07 and the other two (C_6) which are attached to the nitrogen atom and are in the same chemical environment appeared at 48.99 ppm. The aliphatic CH_3 (C_7) which is attached to the aromatic ring appeared at 24.74 ppm.



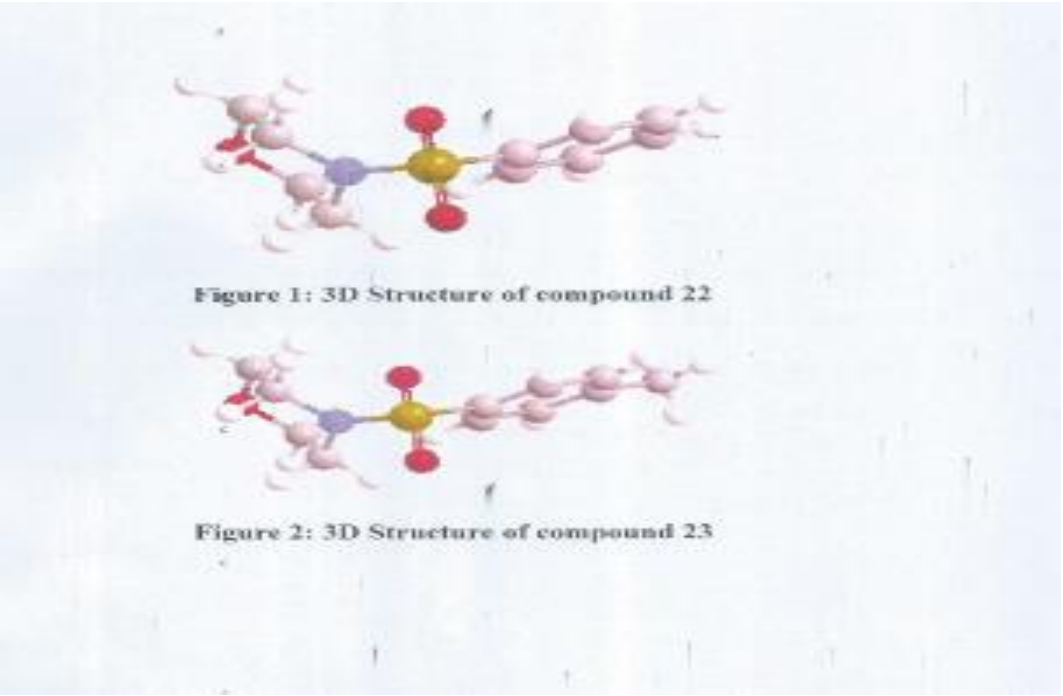


Figure 1: 3D Structure of compound 22

Figure 2: 3D Structure of compound 23

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Properties and evaluation studies

Table 4.1 Physical properties of synthesized compounds

Compound	Colour	Texture	% Yield
22	Light brown	Oily	78.9
23	Colourless	Oily	80.9

***In Silico*physiochemical evaluation**

Table 4.2: Physiochemical properties of synthesized compounds

Compounds	MilogP	TPSA	MW	HBA	HBD	NoRB	Volume	LNV
22	1.10	46.61	227.28	4	0	2	193.61	0
23	1.54	46.61	241.31	4	0	2	210.17	0

In view of the results obtained for compounds **22** and **23** as shown in **table 4.2**, the physiochemical properties; MW, HBD, HBA, TPSA, the volume of ligands and partition coefficient (logP) which indicates lipophilicity, obeyed the principle of drug bioavailability by Lipinski which was stated earlier. Therefore, it was inferred from the results that the synthesized compounds are in agreement with the Lipinski's rule of five since there is no violation of more than one parameter studied. Also, according to Veber *et al*. (2002), the synthesized compounds have their total polar surface areas $\leq$ 140 $Å^2$ which shows that they would have high probability of good oral bioavailability. Also, with rotatable bond value of $\leq$10, they could have high penetration across the central nervous system.

Antibacterial Evaluation

ISSN 0795 - 22066

Table 4.3: Diameter of zone of inhibition of synthesized compounds

	Concentration (mg/M1)														
	2.5			**1.25**			**0.625**			**0.25**			**0.125**		
Compound / Bacteria Strains	**22**	**23**	**CPX**	**22**	**23**	**CPX**	**22**	**23**	**CPX**	**22**	**23**	**CPX**	**22**	**23**	**CPX**
E. coli	R	R	22	R	R	26	R	R	-	R	R	-	R	R	-
B. subtilis	15	10	24	1.8	0.8	22	R	R	-	R	R	-	R	R	-
S. typhi	R	21	28	R	R	26	R	R	-	R	R	-	R	R	-

R = No activity

The results showed that compound **22** had inhibitory effect of 15 mm and 1.8 mm on *B. subtilisat* concentrations of 2.5 mg/mL and 1.25 mg/mL respectively, but no inhibition on *E. coli* and *S. typhi*. It was also observed that an increase in dilution resulted in an increase in the inhibition of compound **22**. Compound **23** had an inhibition of 10 mm and 0.8 mm on *B. subtilis* at concentrations of 2.5 mg/mL and 1.25 mg/mL respectively. Compound **23** also had an inhibition of 21 mm on *S. typhi*, but showed no inhibition on *E coli*. Ciproflaxin (CPX) which was used as reference drug showed inhibition on all three bacteria strains.

Bioactivity Evaluation

Table 4.4: Bioactivity prediction of synthesized compounds

Compounds	Ion channel modulator	Kinase inhibitor	GPCR ligand	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
22	-0.66	-0.85	-0.62	-0.92	-0.42	-0.35
23	-0.71	-0.80	-0.59	-0.83	-0.43	-0.38

For organic molecules if the bioactivity score is (>0), then it is active, if (-5.0 - 0.0) then moderately active, if (<-5.0) then inactive (Chandra *et al.*, 2017). Inferring from the results obtained as shown in **table 4.5**, compound **22** and **23** had values within the range of -5.0 to 0.0 for the bioactivity parameters; protease inhibitor and enzyme inhibitor; therefore, compound **22** and **23** were moderately active. For the bioactivity parameters; ion channel modulator, kinase inhibitor, GPCR ligand and nuclear receptor ligand, compound **22** and **23** had values <-5.0, therefore, showing inactivity.

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CONCLUSION

Two derivatives of substituted benzenesulphonamide were successfully synthesized by the nucleophilic attack of the amine group of morpholine on the electrophilic sulphur of *p*-toluene sulphonyl chloride and benzene sulphonyl chloride. The structures of the synthesized compounds were confirmed by ^{1}H and ^{13}C NMR spectral analysis. The *in vitro* antibacterial activity against target bacteria *B. subtilus*, *S. typhi* and *E. coli* was also evaluated. They both showed no inhibition activity on *E. coli*. Their physiochemical evaluations showed drug-likeness and bioavailability, and hence, these compounds can serve as potential drugs for treating specific diseases, if more research and modifications are being made on them.

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