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Synthesis, Antibacterial and Computational Studies of New Functionalized Sulphonamide Derivatives via Tandem Amidation Catalysis

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ABSTRACT

The development of Sulphonamides is a fascinating and informative area in medicinal chemistry, its functional group has a long and rich history in organic chemistry and drug discovery. The objective of this work is to synthesize and characterize 4-methylbenzenesulphonamides derivatives using 4-methylbenzenesulphonyl chlorides and amino acids (leucine, histidine, phenylalanine, and cysteine) as precursors, then, biological studies were carried out. The FTIR spectroscopic results confirm characteristic functional group, p-disubstituted benzene, $-SO_2-NH_2$, R_3N, C=O, R_2NH, Amide C=O, the ^{1}H-NMR spectrum, the peaks confirm 2^o amine, p- disubstituted benzene), m- disubstituted benzene), CH_3-n and CH_3-CO and the ^{13}CNMR, (acetyl C=O), (C-S=O), amide C=O, (C-H), acetyl CH_3, $-CH_3$, aromatic carbons); the results of the in silico antibacterial studies disclosed that the range of the affinity of binding is between -6.3 to -8.7 kcal/mol, with the ligands interacting more positively than other investigated microbes with the staphylococcus variant's 6xg5 receptor, while the results of the in vitro antibacterials studies showed that at 200 mg/mL, the test organisms exhibit a zone of clearance or inhibition that varies in size from 0 to 28 mm. The spectroscopic results support the proposed structures of the compounds, the synthesized compounds have significant antibacterial potency in the respective bacteria cells, as demonstrated by the in silico antibacterial studies; these findings suggest that the synthesized compounds could be used as future antibacterial agents. According to the in vitro antimicrobial investigation, the majority of the produced compounds had antibacterial properties.

INTRODUCTION

Sulphonamides are organic compounds that contain the $-O_2S-NH_2-$ functional group. The general formula is RSO_2NH_2, where R is an organic group. For example, "methanesu lphonamide" ($CH_3SO_2NH_2$) is a sulphonyl group connected to an amine group; this group is relatively unreactive, as the amine center is no longer basic and the S-N bond is cleaved only with difficulty, because the functional group is rigid. Sulphonamides are typically crystalline. (Apaydin and Torok 2019; Marealle *et al.,* 2018) Sulponamides are extremely valuable medicinal substances. This is because they are capable of displaying a broad variety of biological activity. But their use has decreased over time; this could be related to the rise of resistant bacterial strains and the creation of more potent antibiotics (Deng *et al.,* 2018; Karch, 2011). Sulphonamides are also notable for their broad spectrum antimicrobial activities against many gram-negative and gram-positive microorganisms (Egbujor *et al.,* 2020), and were found to be bacteriostatic and therefore do not kill the bacterium but inhibit their growth and multiplication (Cadena *et al.,* 2018).

Clinically, aliphatic sulphonamides have been extensively utilized in the treatment of chronic urinary tract and gastrointestinal infections (Gaded *et al.,* 2003). Aromatic and heteroaromatic sulphonamides having carbonic anhydrase inhibitory ability are useful antitumor agents (Ahmed *et al.,* 2019; El-sayed *et al.,* 2011; Garcia-Galan *et al.,* 2008). The versatility of sulphonamide as a pharmaceutical compound can be seen in their usefulness in the treatment and prevention of disease syndromes such as occidiosis, toxoplasmosis, actinobaillosis, metritis, respiratory infections and mastitis (Gidden *et al.,* 2019; Reddy *et al.,* 2012).

The synthesis of therapeutic compounds containing carboxamide and sulphonamide separately has advanced significantly in recent years, however there are few reports of molecules with both functions present in one molecule. The synthesis of sulphonamides with carboxamide functionalities is currently of interest due to the class of compounds' promisingly increased biological activity, thus, it is still essential to synthesise novel chemicals. Given the growing resistance to traditional chemotherapeutic drugs, there is a need to synthesise novel classes of molecules with both sulphonamide and carboxamide functional groups that may have pharmacological activity. The objective of the current work is to synthesize 4-methylbenzenesulphonamide

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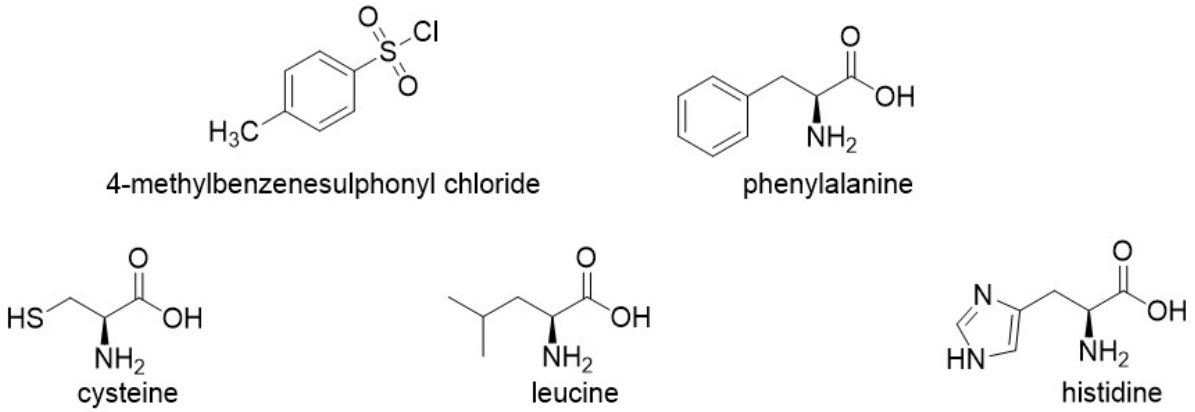
derivatives from 4-methylbenzenesulphonyl chlorides and amino acids, characterize the synthesized sulphonamide derivatives using FTIR, ^{1}HNMR, ^{13}CNMR and elemental analysis and investigate the in silico and in vitro antibacterial acticities of the synthesized compounds, via tandem amidation catalysis.



Figfure 1:

Introduction- Review

In medicinal chemistry, the creation and study of sulphonamides is a significant, engrossing, and educational field (Gadad *et al.,* 2000; Barbaro *et al.,* 2005; Bhat *et al.,* 2005; Khanusiya and Gadhawala, 2019). According to Eshghi *et al.* (2011), its functional group has produced multiple medicinal products with distinguished reputation in organic synthesis and drug development. Synthetic chemistry has extensively investigated 4-methylbenzenenesulphonamides (Egbujor *et al.,* 2019; Onoabedje *et al.,* Orie *et al.,* 2021).

Sulphonamides are more frequently used in animal medicine, but their application in human medicine is currently restricted to treating certain conditions including urinary tract infections. Because sulphonamides are readily available and inexpensive, they are widely used; nonetheless, this has led to a significant rise in the number of bacterial strains that are resistant to sulphonamides (Van den Bogaard *et al.,* 2001; Egbujor and Okoro, 2019). Moreover, residues from the vast use of this medication in the production of chicken have been discovered in poultry products when appropriate withdrawal times have not been observed. (meat and eggs) (Sirdar *et al.,* 2012). It is commonly known that eating animal products that have sulphonamide residues in them can have negative effects on human health. These effects can include cancer, analphylactic shock or hypersensitivity, and the development of bacterial resistance to antibiotics. This justifies the extensive study of sulphonamides, including their manufacture, chemistry, uses, interactions, and biological significance.

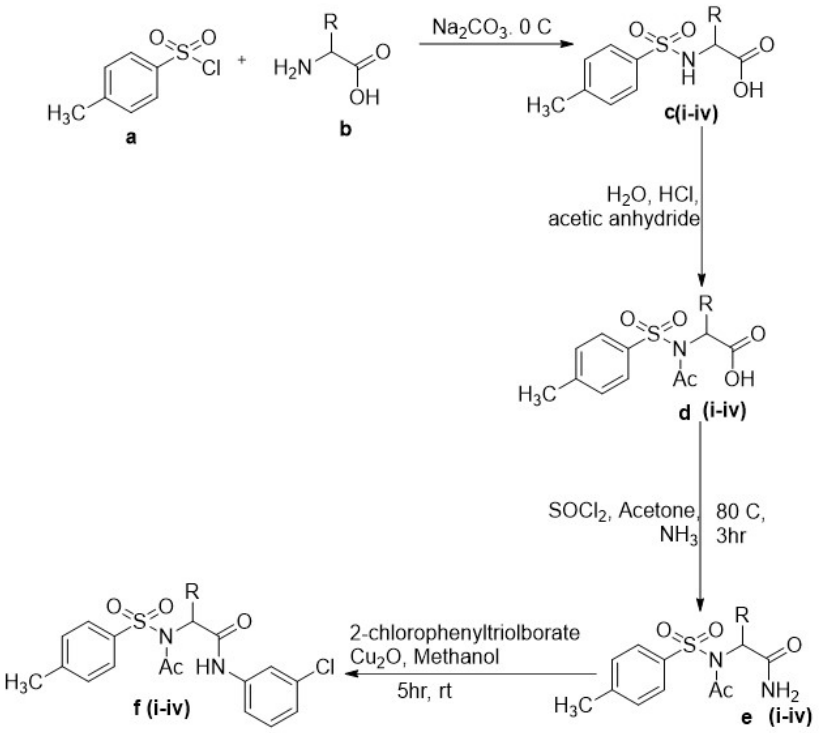
A reaction is considered to be copper-catalyzed if it proceeds by means of a copper catalyst. For elemental copper, copper oxide, and copper salt with catalytic characteristics, the phrase "copper catalyst" is used generally. Numerous synthetic applications, as well as research industries, have made substantial use of metal catalysis.

In recent times, the reaction procedure for the creation of the C-F moiety in organic synthesis has involved the employment of several expensive metals. (Fier *et al.,* 2012). Since they are inexpensive, non-toxic, and have outstanding catalytic activity, copper catalysts are frequently utilized in organic catalytic reactions. (Yoshii, 2019; Jacob and Okoro, 2014; Ihejieto *et al.,* 2015; Jacob *et al.,* 2024). They are also useful in several coupling reactions (Alison and Shannon 2012; Bernini, *et al.,* 2009; Yan *et al.,* 2007; Liangbin, *et al.,* 2010; Wan, *et al.,* 2010; Jithunsa, *et al.,* 2011; Jacob, *et al.,* 2024; Cheung, *et al.,* 2012; Satoshi and Hideko 2009; Ma and Cahard 2004).

In the current work, 4-methylbenzenesulphonyl chloride and amino acids (leucine, histidine, phenylalanine, and cysteine) were used as a precursor to generate functionalized aryl/heteroaryl sulphonamides. Copper (I) oxide was then used to catalyse the N-arylation reaction.

MATERIALS AND METHODS

The procedure for the syntheses of the compounds in figure 2 is described in section 1.1.1.1-1.1.1.4. The illustrations in Fig. 2 shows a scheme of the step-wise synthesis of derivatives of sulphonamides, with 4-methylbenzenesulphonylchloride a and amino acids b (leucine, histidine, phenylalanine, and cysteine) as the starting materials with c - e indicating the compounds formed by the step-wise method of synthesis, giving rise to the formation of the products f(i-iv).



a: 4-methylbenzenesulphonyl chloride, **b**: amino acids (leucine, histidine, phenylalanine and cysteine) **c**: 4-methylbenzenesulphonamide derivatives, **d**: *N*-acylated sulphonamide derivatives, **e**: amidated sulphonamide derivatives, **f**(i-iv): derivatives of the copper catalyzed substituted 4-methylbenzenesulphonamides.

Figfure 2: Tandem synthesis of sulphonamide derivatives

Methylbenzenesulphonamide (c)

The amino acid b (12.5 mmol) was placed in a 100 mL beaker, 15 mL of water and 26.25 mmol of sodium carbonate was added. Next, the beaker was placed in an ice bath with a little amount of NaCl (stirred with a magnetic stirrter). After cooling the mixture to absolute zero, 4-methylbenzenesulphonyl chloride a (15 mmol) was gradually added over the course of an hour. The reaction mixture was then agitated for approximately 4 hours at room temperature. 20% HCl was used to acidify the mixture to a pH of 2, after which it was filtered, cleaned using an acid (tartaric) (15 g/L), and work-up to provide good yields of the benzenesulphonamide. this was filtered after 24 hours.

N-acetyl-N-(4-methylbenzenesulphonamide) (d)

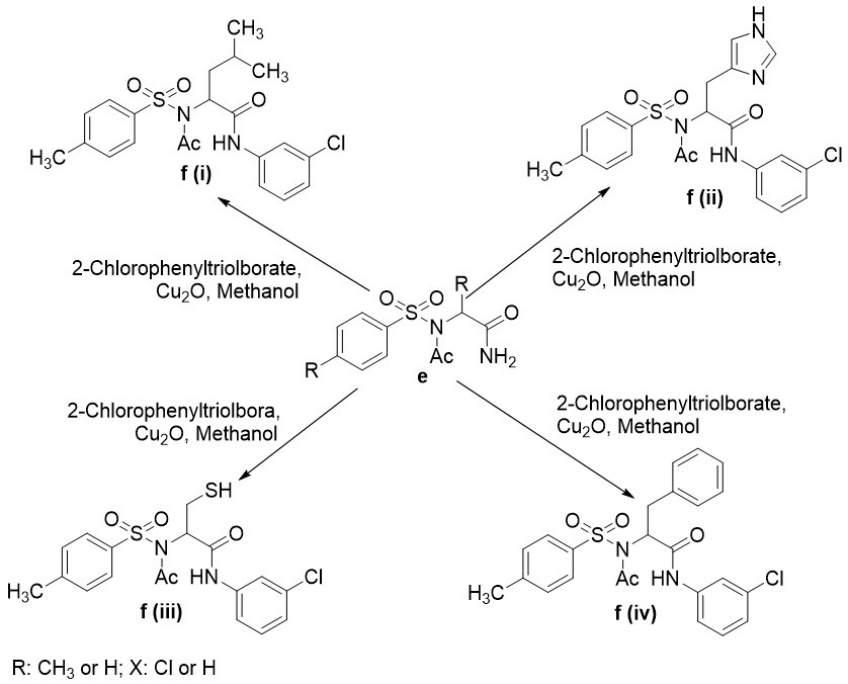
0.05 mmol of the 4-methylsulphonamide was transferred into a 100 mL beaker, the contents were agitated to dissolve. 2.25 mL of conc. HCl and 6.25 mL of distilled water were added. Water (12.5 mL) and sodium acetate (4.13 g) were combined in a different beaker (100 mL). 3.25 mL of acetic anhydride was gradually added to the sulphonamide solution in tiny amounts. After adding the obtained solution to the sodium acetate solution and thoroughly stirring with a glass rod, the reactant-containing beaker was placed in an ice bath for one hour. The resulting N-acetylayed benzenesulphomamide was then obtained by filtration.

(N-(amidated 4-methylsulphonamide)) (e)

N-acetyl-N-(4-methylbenzenesulphonamide d (1 mmol) was dissolved in 20 mL of acetone, and carefully, 2 mL of thionylchloride was then introduced; this was done in the absence of air, in a round bottom flask, attached to a condenser with refluxing apparatus. After that, the magnetic stirrer was switched on with the mixture inside and the refluxing continue for roughly three hours at 80 °C. The solution was transferred to a 100 ml beaker and heated for three hours. Acetone was added and the evaporation process was repeated multiple times. After cooling the mixture to a temperature of between 0 and 5 °C, 1.5 mL of ammonia was gradually added every three hours. After three hours, it was filtered, and dried at 25 °C in order that the products s obtained

Copper Catalysis

Figure 3 depicts a schematic of the N-arylation of substituted 4-methylbenzenesulphonamide, which is catalyzed by copper (I) oxide and involves compounds e reacting with 2-chorophenylltriolborate in methanol. The products that result from the triolborate reacting with leucine-based phenylsulphonyl derivative, histidine-based phenylsulphonyl derivative, cysteine-based phenylsulphonyl derivative and phenylalanine-based phenylsulphonyl derivative are represented by f(i) - f(iv), respectively. Below is the description of the process for the syntheses:



Figfure 3: Cu_2O catalysis in the synthesis of substituted 4-methylbenzenesulphonamide

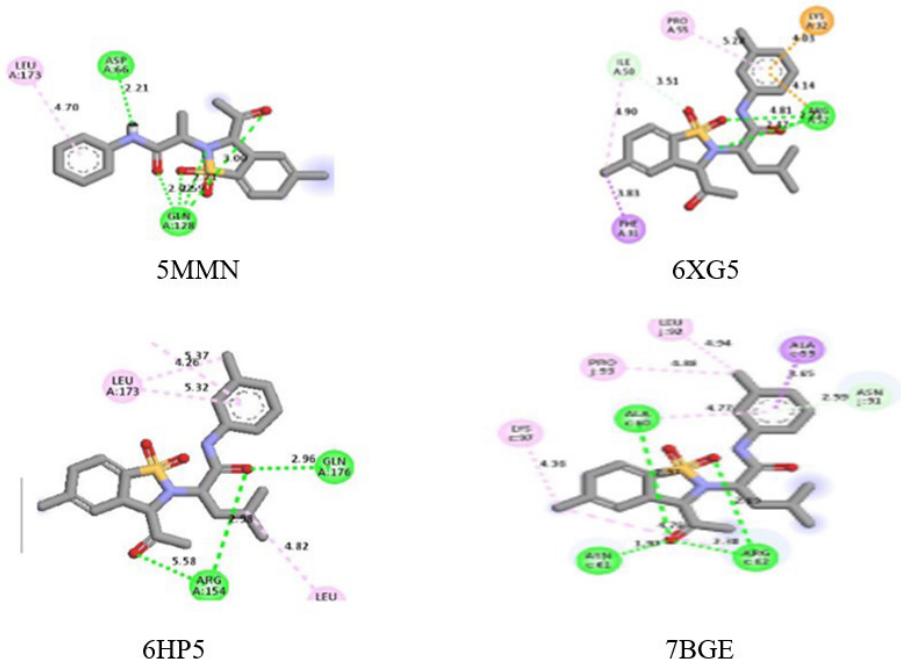
2-After adding 10 mL of CH_3OH and 1 g of Cu_2O, 0.1 mmol of 2-chlorophenyltriolborate was placed into the flask set on a heat source and secured on a stand. Next, the amide e (1 mmol) was added and the mixture was stirred with a magnetic stirrer in the presence of air for approximately five h; then, it was transferred into a 200 mL conical flask to allow appropriate evaporation at ambient temperature, and the product was dried and filtered.

As seen in figure 3 above, four distinct compounds were produced from the four distinct amino acid-based sulphonamides.

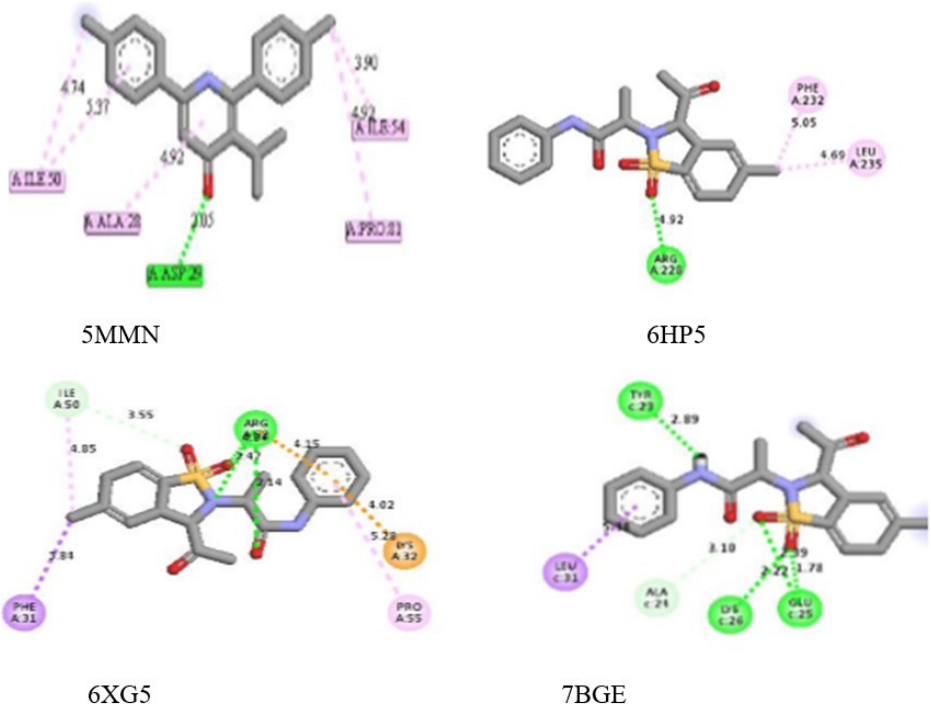
Molecular Docking

Molecular Docking Procedures

The proteins were prepared for molecular docking using Biovia Discovery Studio after being obtained from the protein data library. In order to prepare the receptors for the docking studies, explicit hydrogens were added, reactive sites were defined, and water molecules that weren't required were eliminated, With a border dimension of 36 Å and coordinates X, Y, and Z measuring 13.368000, 30.583000, and 45.659312, respectively, the receptor cavity was established. Autodock 4.0 was then used to convert the data to pdbqt format (Trott and Olson, 2010).



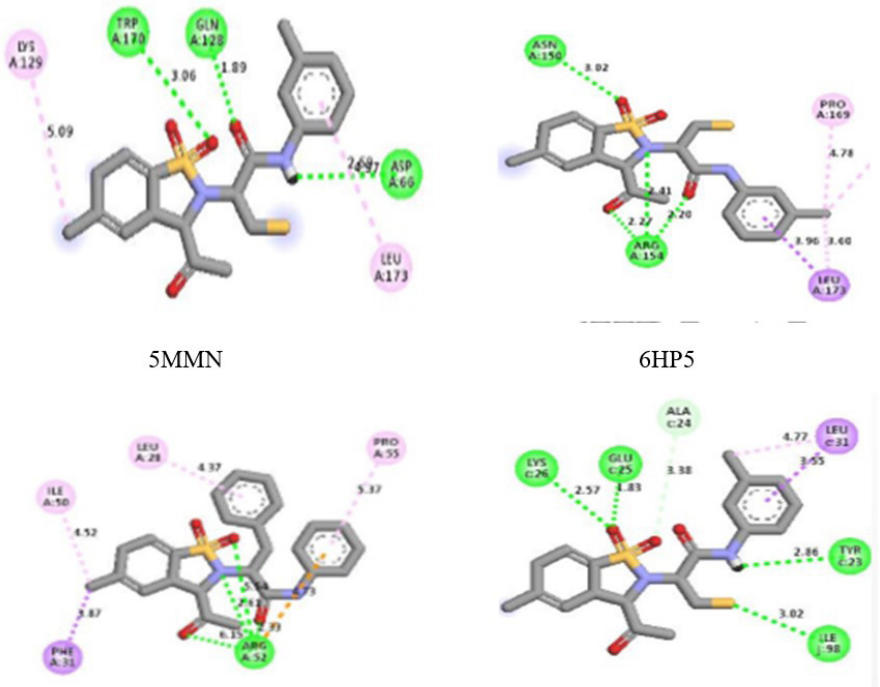
Figfure 4: 2D visualization of protein ligand interaction of compound f(i)



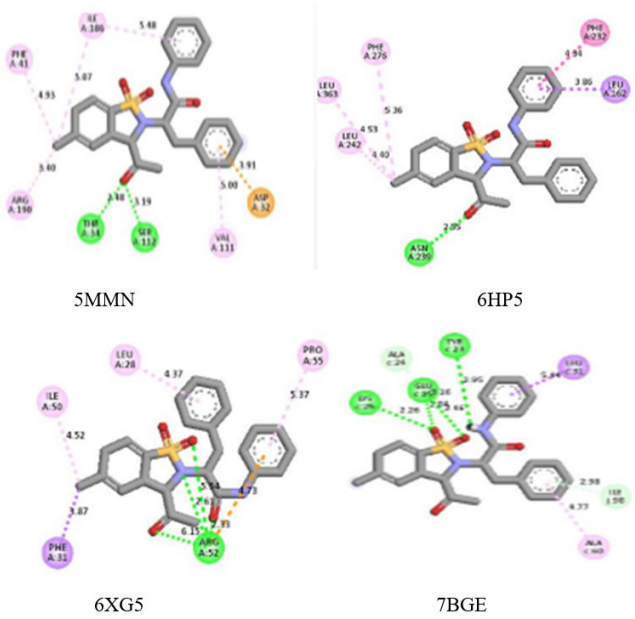
Figfure 5: 2D visualization of protein ligand interaction of compound f(ii)

The ligand was prepare and the Autodock Vina was used to dock the corresponding proteins with the compounds under study, then, the resulting output was visualized and depicted (fig. 4 and 5). Using the Lamarckian Genetic Algorithm (LGA) search, the docking research was completed and the pdbqt files created.

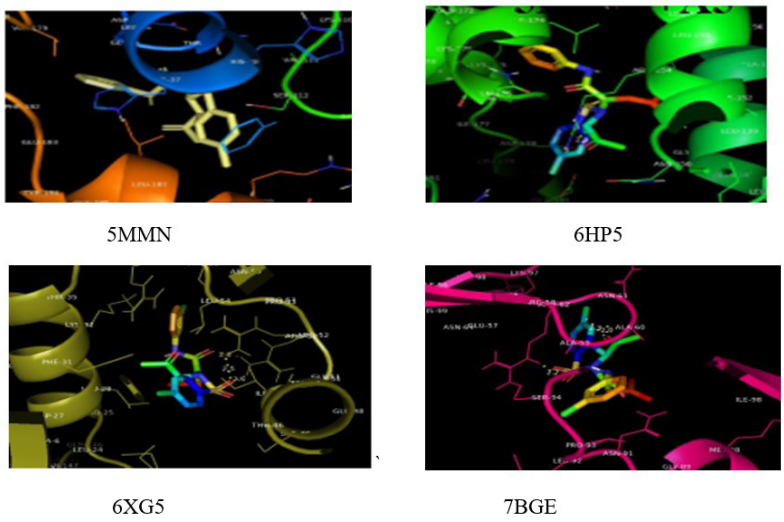
For compounds f(i) through f(iv), a docking analysis's two-dimensional depiction of the interactions between the ligand and protein is shown in Figure 4-7. It depicts the several nearby hydrophobic residues that make up the very hydrophobic cavity (circled in green).



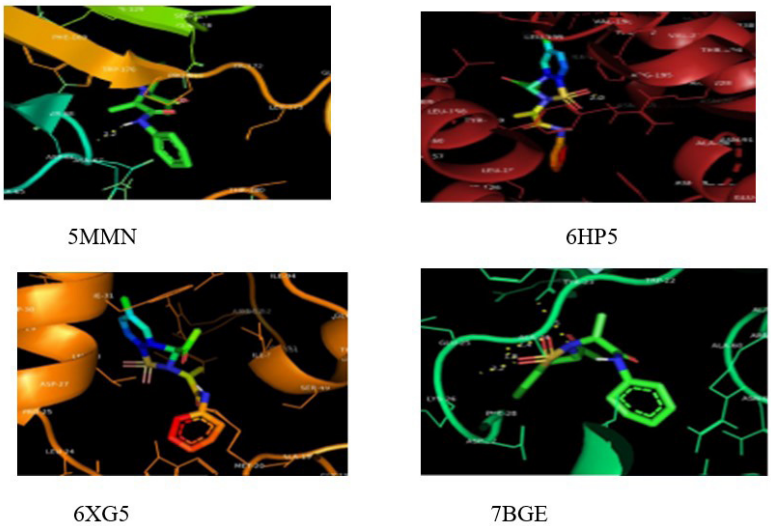
Figfure 6: 2D visualization of protein ligand interaction of compound f(iii)



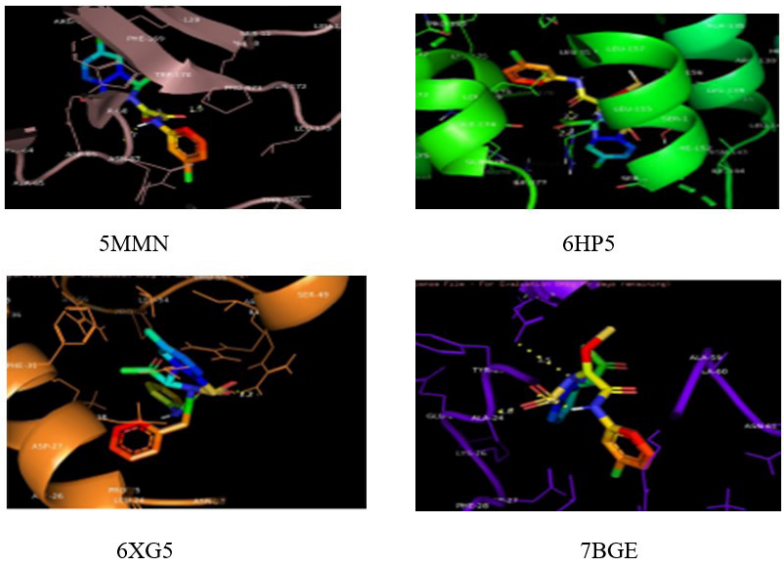
Figfure 7: 2D visualization of protein ligand interaction of compound f(iv)



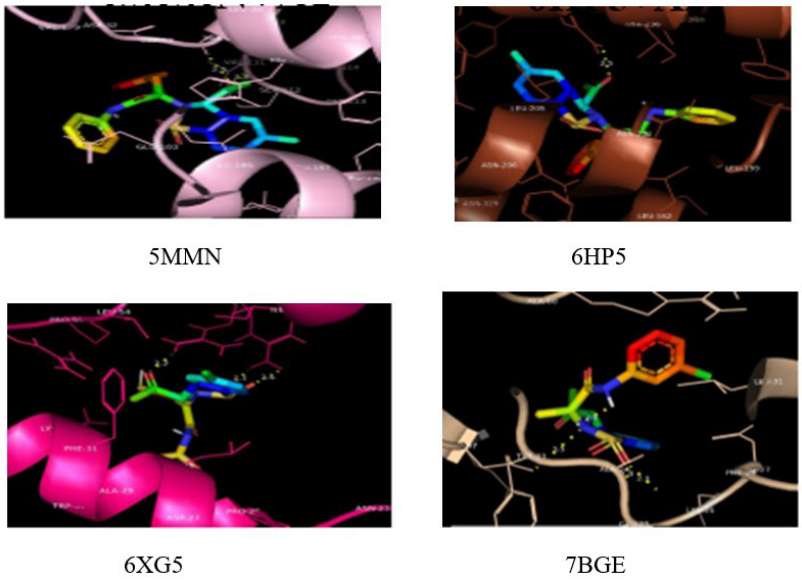
Figfure 8: 3D Visualization of protein ligand interaction of compound f(i)



Figfure 9: 3D Visualization of protein ligand interaction of compound f(ii)



Figfure 10: 3D Visualization of protein ligand interaction of compound f(iii)



Figfure 11: Protein ligand interaction (3D) of compound f(iv)

The docking study of the protein-ligand interactions is illustrated in three dimensions in Figure 8-11. It demonstrates that several proximal hydrophobic residues made up the highly hydrophobic cavity. .

Biological Activities

The agar-well diffusion method was utilized to ascertain the antibacterial activities of the substituted sulphonamide solutions. A sterile cork borer with a diameter of 6 mm diameter was utilized to make wells in each Meuller Hinton agar plate. The added sample were in the concentrations (mg/mL), 50, 100, 150, and 200, and each well was properly labeled. One of the wells was filled with distilled sterile water to act as the negative control, and the other well, which acted as the positive control was filled with cephalexin. After an hour of room temperature diffusion into the agar, there was incubation and the plates were examined for clarity or zones of inhibition.

Test Organisms Collection

They were gathered from Prince Abubakar Audu University's microbiology laboratory in Anyigba, Nigeria. The organisms include P. aeruginosa, B. subtilis, E. coli, and S. aureus..

Determination of Minimum Inhibitory Concentration (MIC)

0.5 mL of samples at different concentrations were distributed into test tubes with nutritional broth and infected with test organism so as to estimate the MIC. The benchmark for McFarland turbidity was set at 0.5. The test organisms were introduced in tubes with nutrients, but no complex was used as a control. After the incubation, the tube with the lowest concentration and no discernible turbidity was designated as the minimum inhibitory concentration (MIC). Turbidity was then observed to check for growth.

RESULTS AND DISCUSSION

N-(3-chlorophenyl)-4-methyl-2-(N-tosylacetamido) pentanamide f(i)

The spectral analyses provide support to the structure. FTIR (KBr) cm-1: 842.4 (para-disubst. benzene), 1344.2 ($-SO_2-NH_2$), 2322.1 R_3N, 2840 (C=O), 3265.1 R_2NH, 1565.1 (Amide C=O). IH-NMR ppm: 4.7 (1H, s) due to NH of 2° amine, ppm. 4.7 (2H, d; 2H, d) due to p-disubstituted benzene), ppm 4.0 (1H, s; 3H, s) due to m- disubstituted benzene), ppm 3.95 (1H, q) due to C1 proton, ppm 2.95 (3H, d) due to C_2 proton, ppm 3.75 (3H, s) due to CH_3-n and ppm 3.3 (3H, s) due to CH_3-CO. ^{13}CNMR (DMSO, 400MHz) δ: 167.154 (acetyl C=O), 136.284 (C-S=O), 172.776 (amide C=O), 53.917 (C-H), 15.221 (acetyl CH_3), 12.153 ($-CH_3$), 127.276, 137.132 (aromatic carbons). Anal.calcd. for $C_{18}H_{19}C_lN_2O_4S$ (394.08): C, 54,75; H, 4.85; N, 7.07. Found: C, 54,44; H, 4.13; N, 7.57

N-(3-chlorophenyl)-3-(1H-imidazol-5-yl)-2-(N-acetamido)propanamide f(ii)

The spectral analyses provide support to the structure. FTIR (KBr) cm-1: 861.0 (para-disubstituted benzene), 1224.2 ($-SO_2-NH_2$), 2322.1 R_3N, 2722 (C=O), 3280.1 R_2NH, 805.7 (meta-disubstituted benzene), 1580.1 (Amide C=O). IH-NMR ppm: 7.7 (1H, s) due to NH of imidazole, ppm 7.2 (1H, s) due to NH of 2o amine, ppm 5.0 (2H, d) due to 2(CH of imidazole), ppm 4.5 (2H, d; 2H, d) due to p-disubstituted benzene, ppm. 4.0 (5H, m) due to mono substituted benzene, ppm. 3.25 (1H, t) due to C1 proton, ppm 2.0 (2H, d) due to C2 proton, ppm 2.5 (3H, s) due to CH_3-n and ppm 1.25 (3H, s) due to CH_3-CO. ^{13}CNMR (DMSO, 400MHz) δ: 168.634 (acetyl C=O), 137.174 (C-S=O), 175.276 (amide C=O), 55.167 (C-H), 19.421 (acetyl CH_3), 127.476, 125.332 (aromatic carbons), 143.954 (C-imidazole). Anal.calcd. for $C_{21}H_{22}N_4O_4S$ (426.14): C, 59.14; H, 5.20; N, 13.14. Found: C, 66.64; H, 5.11; N, 6.56

N-(3-chlorophenyl)-3-phenyl-2-(N-tosylacetamido) propanamide f(iii)

The spectral analyses provide support to the structure. FTIR KBr) cm-1: 857.0 (para-disubstituted benzene), 693.3 (m-disubstitutedbenzene), 1364.2 ($-SO_2-NH_2$), 2866.3 (R_3N-C), 1580.4 (C=O), 3552.2 (R_2-NH), 1552.2 (Amide C=O). IH-NMR ppm: 7.9 (1H, s) due to NH of 2o amine, ppm. 7.5-7.3 (10H, m) due to 2(mono substituted benzene), ppm. 7.1 (1H, s; 3H, s) due to m-disubstituted benzene, ppm 4.7 (1H, t) due to C_2 proton, ppm. 3.9 (2H, d) due to C_3 proton and ppm 2.5 (3H, s) due to CH_3-CO. ^{13}CNMR (DMSO, 400MHz) δ: 168.134 (acetyl C=O), 135.184 (C-S=O), 176.876 (amide C=O), 50.217 (C-H), 19.221 (acetyl CH_3), 33.121 ($-CH_2$), 127.276, 133.142 (aromatic carbons). Anal.calcd. for $C_{23}H_{21}C_lN_2O_4S$ (456.94): C, 60.46; H, 4.63; N, 7.76. Found: C, 69.45; H, 4.15; N, 7.78

N-(3-chlorophenyl)-3-mercapto-2-(N-tosylacetamido) propanamide f(iv)

The spectral analyses provide support to the structure. FTIR (KBr) cm-1: 849.8(para-substituted benzene), 1254.2 ($-SO_2-NH_2$), 2233.8, 2475 (C=O), R_3N, 1509.2 (Amide C=O). IH-NMR ppm: 2.5 (1H, s) due to NH of 2o amine, ppm. 2.2-2.1 (2H, d; 2H, d) due to p- disubstituted benzene), ppm 2.0 (5H, m) due to monosubstituted benzene, ppm 1.85 (1H, t) due to C1 proton, ppm 1.5 (2H, d) due to C_2 proton, ppm 1.19 (3H, s) due to CH_3-n, ppm 1.1 (3H, s) due to CH_3-CO and ppm 1.25 (1H, s) due to SH. ^{13}CNMR (DMSO, 400MHz) δ: 170.134 (acetyl C=O), 133.284 (C-S=O), 173.176 (amide C=O), 56.217 (C-H), 21.321 (acetyl CH_3), 128.176, 134.532 (aromatic carbons), 23.754 (C-SH). Anal.calcd. for $C_{18}H_{20}ClN_2O_4S_2$ (392.49): C, 55.08; H, 5.14; N, 7.14. Found: C, 54.98; H, 5.72; N, 7.44.

Docking Results

For docking tests, the following proteins from Bacillus

Table 1: Compounds' f(i) binding affinity

Interaction	Binding affinity (Kcal/mol)	No of hydrogen bonds
5MMN	-6.3	3
6HP5	-8.1	5
6XG5	-8.7	5
7BGE	-6.9	5

Table 2: Compounds' f(ii) binding affinity

Interaction	Binding affinity (Kcal/mol)	No of hydrogen bonds
5MMN	-6.9	5
6HP5	-8.3	3
6XG5	-9.3	5
7BGE	-7.4	4

Table 3: Compounds' f(ii) binding affinity

Interaction	Binding affinity (Kcal/mol)	No of hydrogen bonds
5MMN	-6.5	4

6HP5	-8.0	4
6XG5	-8.9	4
7BGE	-6.2	4

Table 4: Compounds' f(iv) binding affinity

Interaction	Binding affinity (Kcal/mol)	No of hydrogen bonds
5MMN	-6.7	3
6HP5	-8.7	2
6XG5	-10.0	6
7BGE	-7.1	4

subtilis, Escherichia coli, Staphylococcus aureus, and Pseudomonas aeruginosa were chosen: 5 mm, 6hp5, 6xg5, and 7bge. Tables 1-4 present the collected results, which comprise the amount of interacting amino acids, binding conformation, and binding affinities, which consist of the quantity of interacting amino acids, binding conformation, and binding affinities; between the ligand and the corresponding proteins, a variety of significant interactions, including hydrogen bond and electrostatic interactions, were seen. Overall, the findings showed that the ligands exhibited more favorable interactions with the staphylococcus variant's 6xg5 receptor than with the other microorganisms under investigation. The staphylococcus receptor interaction exhibited the greatest average binding affinities. The range of these binding affinities was found to be between -7.0 and -9.7 kcal/mol. This demonstrates that the highest inhibitory activity of each investigated ligand on the corresponding micro bacteria is displayed. Analyzing the quantity of hydrogen bonds, affinity for binding, and other moderating interactions is a standard method of assessing docking experiments. In light of this, it can be said that each of the compounds has a notable level of antibacterial potency in the corresponding bacterial cells and that they may be used going forward as antibacterial agents.

For docking tests, the following proteins from Bacillus subtilis, Escherichia coli, Staphylococcus aureus, and Pseudomonas aeruginosa were chosen: 5 mm, 6hp5, 6xg5, and 7bge. Tables 1-4 present the collected results, which comprise the amount of interacting amino acids, binding conformation, and binding affinities, which consist of the quantity of interacting amino acids, binding conformation, and binding affinities; between the ligand and the corresponding proteins, a variety of significant interactions, including hydrogen bond and electrostatic interactions, were seen. Overall, the findings showed that the ligands exhibited more favorable interactions with the staphylococcus variant's 6xg5 receptor than with the other microorganisms under investigation.

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Antibacterial Result

Table 5: The antibacterial activities for compound f(i) in methanol

Test Organisms (mg/mL)	50	100	150	200	Positive control	Negative control
Staphylococcus aureus	0 mm	0 mm	0 mm	0 mm	32 mm	0
Bacillus subtilis	10 mm	10 mm	20 mm	28 mm	36 mm	0
Escherichia coli	6 mm	6 mm	10 mm	20 mm	30 mm	0
Pseudomonas aeruginosa	10 mm	10 mm	18 mm	25 mm	33 mm	0

The test organisms' zone of inhibition or clearance, as indicated by the different concentrations, spans from 0 to 28 mm. Table 5 shows which bacteria were most responsive at the greatest concentration: Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa.

For compound f(i), no growth or turbidity was exhibited for B. subtilis, E. coli, or P. aeruginosa, as demonstrated by Table 6, the growth inhibition is at 200 mg/mL. The concentration of 200 mg/mL was therefore determined to be the MIC value.

Table 6: The MIC) for compound f(i)

Test Organisms (mg/mL)	50	100	150	200	Positive control	Negative control
Staphylococcus aureus	G	G	G	G	NG	G

Bacillus subtilis	G	G	NG	NG	NG	G
Escherichia coli	G	G	G	NG	NG	G
Pseudomonas aeruginosa	G	G	NG	NG	NG	G
Key: NG = No growth, G = Growth						

Table 7: The antibacterial activities for compound f(ii) in methanol

Test Organisms (mg/mL)	50	100	150	200	Positive control	Negative control
Staphylococcus aureus	8 mm	8 mm	10 mm	22 mm	33 mm	0
Bacillus subtilis	0 mm	0 mm	0 mm	0 mm	22 mm	0
Escherichia coli	10 mm	10 mm	15 mm	22 mm	26 mm	0
Pseudomonas aeruginosa	mm	10 mm	18 mm	21 mm	32 mm	0

On the test organisms, the different concentrations exhibit a zone of clearance or inhibition ranging from 0 to 22 mm. Bacillus subtilis exhibited no resistance, whereas Escherichia coli, Staphylococcus aureus, and P. aeruginosa shows high sensitivity at the greatest dose.

Compound f(ii) did not exhibit any turbidity or growth for Pseudomonas aeruginosa, Escherichia coli, or Staphylococcus aureus, as demonstrated by Table 8, the growth inhibition is at 200 mg/mL. The concentration was therefore determined to be the MIC value.

Table 8: Table 6: The MIC) for compound f(ii)

Test Organisms (mg/mL)	50	100	150	200	Positive control	Negative control
Staphylococcus aureus	G	G	G	NG	NG	G
Bacillus subtilis	G	G	G	G	NG	G
Escherichia coli	G	G	G	NG	NG	G
Pseudomonas aeruginosa	G	G	NG	NG	NG	G

Key: NG = No growth, G = Growth

Table 9: The antibacterial activities for compound f(iii) in methanol

Test Organisms (mg/mL)	50	100	150	200	Positive control	Negative control
Staphylococcus aureus	15 mm	15 mm	19 mm	26 mm	33 mm	0
Bacillus subtilis	14 mm	14 mm	19 mm	26 mm	34 mm	0
Escherichia coli	10 mm	15 mm	21 mm	25 mm	34 mm	0
Pseudomonas aeruginosa	6 mm	8 mm	10 mm	21 mm	35 mm	0

The test organisms' zones of clearance or inhibition, as indicated by different concentrations, span from 0 to 26 mm. Bacillus subtilis, Escherichia coli, and Staphylococcus aureus were the most susceptible, whilst Pseudomonas aeruginosa exhibited minimal resistance.

For compound f(iii), no growth or turbidity was exhibited for S. aureus, B. subtilis, or E. coli, as demonstrated by Table 10, the growth inhibition is at 150 mg/mL. Thus, the MIC value was determined by taking the concentration.

Table 10: Table 6: The MIC) for compound f(iii)

Test Organisms (mg/mL)	50	100	150	200	Positive control	Negative control
Staphylococcus aureus	G	G	NG	NG	NG	G
Bacillus subtilis	G	G	NG	NG	NG	G
Escherichia coli	G	G	NG	NG	NG	G
Pseudomonas aeruginosa	G	G	G	NG	NG	G

Key: NG = No growth, G = Growth

Table 11: The antibacterial activities for compound f(iv) in methanol

Test Organisms (mg/mL)	50	100	150	200	Positive control	Negative control
Staphylococcus aureus	6mm	10mm	11mm	22mm	30mm	0
Bacillus subtilis	10mm	10mm	15mm	19mm	30mm	0

Escherichia coli	15mm	15mm	21mm	26mm	38mm	0
Pseudomonas aeruginosa	10mm	15mm	20mm	22mm	35mm	0

When applied to test organisms, the different concentrations exhibit a zone of clearance or inhibition that varies from 6 to 26 mm. By using the maximum concentration, every test organism showed sensitivity.
For compound f(iv), no growth or turbidity was exhibited for S. aureus, B. subtilis, or E. coli, as demonstrated by Table 12, the growth inhibition is at 200 mg/mL. The concentration of 200 mg/mL was therefore determined to be the MIC value.

Table 12: Table 6: The MIC) for compound f(iv)

Test Organisms (mg/mL)	50	100	150	200	Positive control	Negative control
Staphylococcus aureus	G	G	G	NG	NG	G
Bacillus subtilis	G	G	G	NG	NG	G
Escherichia coli	G	G	G	NG	NG	G
Pseudomonas aeruginosa	G	G	G	G	NG	G

Key: NG = No growth, G = Growth

Contribution to Knowledge

There have never been any reports on the synthesis of the compounds being studied or on copper(I)oxide being used to catalyze the N-arylation reactions of sulphonamides. New techniques for adding carboxamide functionality to physiologically active compounds are presented in this paper.

CONCLUSION

The results of elemental analysis, IR, 1HNMR, and ^{13}CNMR spectra verified the structures of all the synthesized compounds. The compounds under investigation have strong antibacterial properties, as evidenced by the zones of inhibition and MIC they display in both in vitro and in silico antibacterial studies.
The creation of novel biological agents to address the ongoing problem of drug resistance through the use of environmentally friendly reagents and hybrids of biologically active compounds with biological activities is motivated by the urgent need to find ambient methodologies for the incorporation of carboxamide functionality in biologically active molecules. This work accomplishes the aforementioned goalsThe antibacterial screening and the outcomes of the in vitro and in silico antibacterial investigation agree. This suggests that the compounds that were synthesized have the potentials to be used as medications.

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