



Copper catalysis in the synthesis of functionalized glycine-based sulphonamides: in silico and in vitro antibacterial studies

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ABSTRACT

The synthesis of functionalized glycine-based sulphonamides via copper catalyzed *N*-arylation reaction and the in silico, in vitro antibacterial studies is reported. The procedure involved the initial synthesis of substituted *p*-toluenesulphonamides and substituted benzenesulphonamides by the reaction of glycine with *p*-toluenesulphonyl chloride and benzenesulphonyl chloride respectively in aqueous basic medium. The synthesized compounds were acetylated by reacting them with acetic anhydride and sodium acetate followed by acylation and amidation to yield amidated *p*-toluenesulphonamides and benzenesulphonamides respectively. Copper catalyzed *N*-arylation of the amidated products with aryltriolborates resulted in the synthesis of benzene, and 2-chlorophenyl derivatives of the amidated products. The synthesized compounds were characterized using FTIR, HNMR and elemental analysis and the spectra were in agreement with the assigned structures. The in silico antibacterial studies revealed that the compounds possess significant antibacterial potency in the respective bacteria cells and could be further employed as potential anti-bacterial agents. The in vitro antimicrobial study revealed that most of the synthesized compounds possess antibacterial activities.

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1. INTRODUCTION

The development of sulphonamides is a fascinating and informative area in medicinal chemistry [1–4]. Its functional group has a long and rich history in organic chemistry and drug discovery [5]. The *p*-toluenesulphonamide and benzenesulphonamides have been widely explored in synthetic chemistry [6–10].

The use of sulphonamides today is limited to specific disease treatment in human medicine such as urinary tract infections, however, sulphonamides are more often encountered in

animal medicine. The widespread use of sulphonamides as a result of their availability and low cost has resulted in considerable increase in resistant bacteria strains for these compounds [11, 12]. Also the extensive application of this antimicrobial agent in chicken production have resulted in residues being detected in poultry products (eggs and meat) when adequate withdrawal periods have not been observed [13]. It is well established that consumption of animal products containing sulphonamide residues poses potential human health risks which include hypersensitivity or anaphylactic shock, cancer and induction of bacterial resistance to the antimicrobials, amongst other risks. This is a good reason for the intensive research into Sulphonamides, its

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synthesis, chemistry, applications, reactions and biological importance.

A copper catalyzed reaction is that reaction that proceeds with the aid of copper catalyst. The copper catalyst refers to a general term for elemental copper, copper oxide and copper salt having catalytic properties. Metal-catalysis have been widely utilized in academics, pharmaceutical industry and for several synthetic purposes. In recent times, several expensive metals have been employed in the reaction protocol for C-F moiety formation in organic synthesis [14, 15]. Despite the fact that copper catalysts are efficient and relatively less expensive when compared to materials of the platinum and palladium groups [16]; copper catalysts are widely used in organic catalytic reactions due to their good catalytic performance, low cost and low toxicity [17], and are useful in several coupling reactions [18–26].

In the present study, functionalized aryl/heteroaryl sulphonamides were synthesized via Copper catalyzed *N*-arylation reaction using benzenesulphonyl chloride, *p*-toluenesulphonyl chloride, and glycine.

2. MATERIALS AND METHODS

Figure 1 shows a scheme of the tandem synthesis of the substituted glycine-based sulphonamide, with arylsulphonylchloride a and glycine b as the precursors and c, d and e as the tandem compounds leading to the synthesis of f(i-iv) as the products; and the procedure for these syntheses are described in section 2.1 – 2.4.

2.1. SYNTHESIS OF (ARYLSULPHONYL)GLYCINE C

Glycine a (12.5 mmol) was dissolved in water (15 mL), sodium carbonate (26.25 mmol) was then added, in a beaker, the beaker was then inserted into an ice bath containing few gram of NaCl, (in a magnetic stirred). The solution was cooled to zero degree, and then benzenesulphonyl chloride b (15 mmol) was added in portions for an interval of 1 hour. At the end of 1 hour, the reaction mixture was stirred for about 4 hours at room temperature. The mixture was acidified to pH level of 2 with 20 % HCl, then filtered and washed with tartaric acid (15 g tartaric acid in 1 litre of water) and dried to obtain the arylsulphonamides in good to excellent yields. It was kept for 24 hours before filtering.

2.2. *N*-ACETYL-*N*-(ARYLSULPHONYL)GLYCINE D

(Arylsulphonyl)glycine c (0.05 mmol) was transferred into a beaker (100mL), concentrated HCl (2.25 mL) and distilled water (6.25 mL) were added, it was stirred to dissolve the sulphonamide. In a separate beaker (100 mL), dissolve sodium acetate (4.13 g) and acetic anhydride (3.25 mL) was added in small proportion at an interval into the sulphonamide solution. Sodium acetate solution was poured into the solution obtained and the content was stirred thoroughly with a glass rod and with the beaker containing the reactant immersed into an ice bath, it was then filtered and dried to afford the desired product.

2.3. 2-(*N*-(ARYLSULPHONYL)ACETAMIDE)PROPANAMIDE E

N-acetyl-*N*-(arylsulphonyl)alanine d (1mmol) was dissolved in acetone (20 mL), thionylchloride (2 mL) was then carefully added inside a round bottom flask in the absence of air that is fixed with condenser and refluxed stand. The solution was then placed on a magnetic stirrer and was left to stir and reflux at 80

Table 1. The binding Affinity of compound f(i).

Interaction	Binding affinity (Kcal/mol)	No of hydrogen bonds
5MMN+ 1	-7.3	5
6HP5+ 1	-7.4	5
6XG5+ 1	-9.7	7
7BGE+ 1	-7.0	3

Table 2. The binding Affinity of compound f(ii).

Interaction	Binding affinity (Kcal/mol)	No of hydrogen bonds
5MMN+ 2	-7.1	5
6HP5+ 2	-7.3	5
6XG5+ 2	-8.7	7
7BGE+ 2	-8.0	3

Table 3. The binding Affinity of compound f(iii)

Interaction	Binding affinity (Kcal/mol)	No of hydrogen bonds
5MMN+ 3	-7.0	5
6HP5+ 3	-7.1	5
6XG5+ 3	-9.2	7
7BGE+ 3	-8.3	3

Table 4. The binding Affinity of compound f(iv)

Interaction	Binding affinity (Kcal/mol)	No of hydrogen bonds
5MMN+ 4	-7.2	5
6HP5+ 4	-8.0	5
6XG5+ 4	-9.1	7
7BGE+ 4	-7.7	3

°C for about 3 hours. After 3 hours, the solution was poured into a beaker (100 ml) then placed on hot plate, addition of acetone and evaporation was repeated severally. The solution was cooled between 0 to 5 °C, then ammonia (1.5 mL) was added in portion at an interval of 3 hours. At the end of 3 hours it was then filtered, and the residue was dried at room temperature to afford the appropriate amidated products.

2.4. COPPER CATALYSIS

Figure 2 shows a scheme for the copper catalyzed *N*-arylation of the substituted glycine-based sulphonamide, where compound e reacts with various aryltriorborates, in methanol, catalyzed by copper (I) oxide. f(i) is formed from the reaction between phenyltriorborate and phenylsulphonyl derivative, f(ii) is formed from the reaction between phenyltriorborate and 4-phenylsulphonyl derivative, f(iii) is formed from the reaction between 2-chlorophenyltriorborate and phenylsulpho-

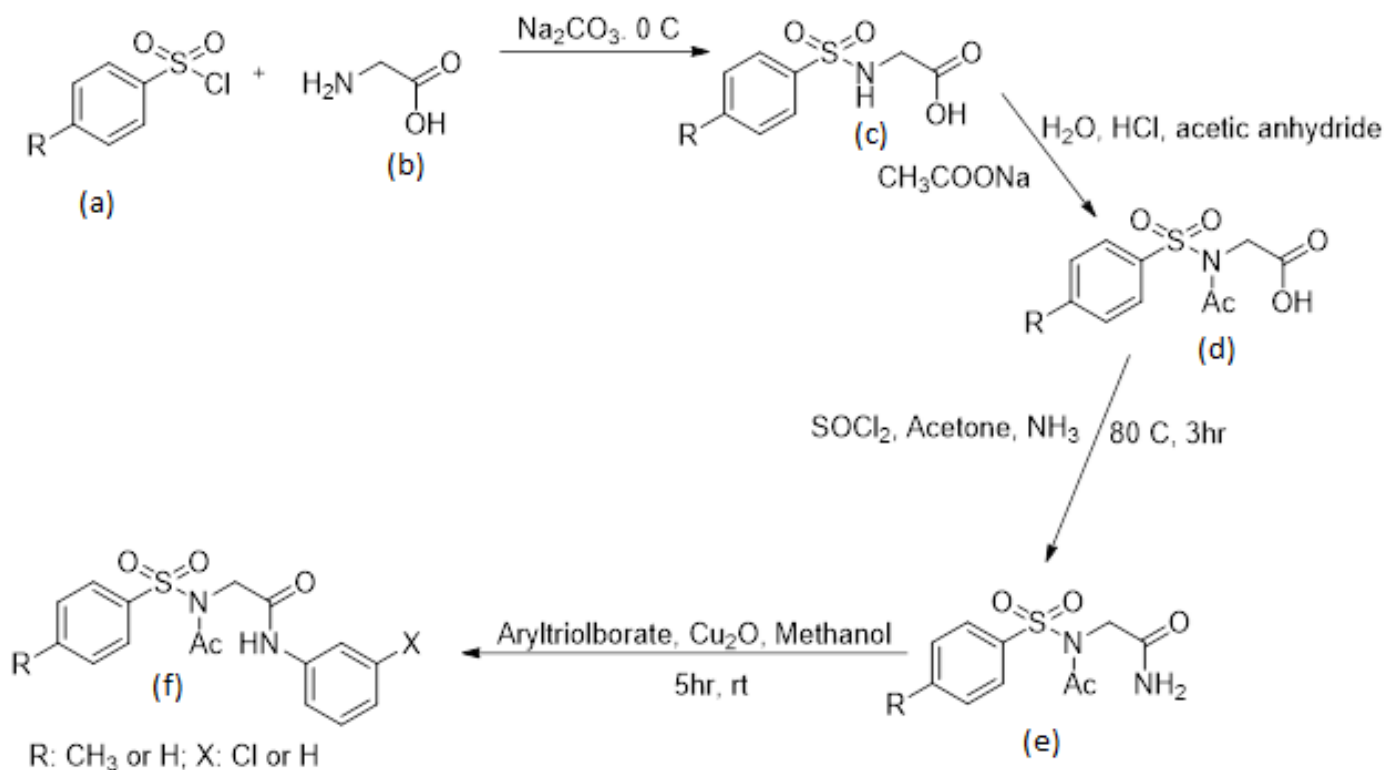


Figure 1. Tandem synthesis of substituted glycine-based sulphonamides. (a): arylsulphonylchloride, (b): glycine, (c): arylsulphonamide, (d): *N*-acetylated arylsulphonamide, (e): amidated arylsulphonamide, (f): several derivatives of the copper catalyzed substituted arylsulphonamides.

Table 5. The antimicrobial activity of various concentrations of compound f(i) in methanol, on the test organisms.

S/N	Test Organisms	50 mg/mL	100 mg/mL	150 mg/mL	200 mg/mL	Positive control	Negative control
1	<i>Staphylococcus aureus</i>	7 mm	8 mm	10 mm	21 mm	31 mm	0
2	<i>Bacillus subtilis</i>	6 mm	6 mm	6 mm	7 mm	22 mm	0
3	<i>Escherichia coli</i>	8 mm	8 mm	11 mm	22 mm	25 mm	0
4	<i>Pseudomonas aeruginosa</i>	6 mm	6 mm	10 mm	20 mm	32 mm	0

Table 6. The minimum inhibitory concentration (MIC) of compound f(i) in methanol against the test organisms.

S/N	Test Organisms	50 mg/mL	100 mg/mL	150 mg/mL	200 mg/mL	Positive control	Negative control
1	<i>Staphylococcus aureus</i>	G	G	G	NG	NG	G
2	<i>Bacillus subtilis</i>	G	G	G	G	NG	G
3	<i>Escherichia coli</i>	G	G	G	NG	NG	G
4	<i>Pseudomonas aeruginosa</i>	G	G	G	NG	NG	G

Key: NG = No growth, G = Growth.

Table 7. The antimicrobial activity of various concentrations of the compound f(ii) in methanol, on the test organisms.

S/N	Test Organisms	50 mg/mL	100 mg/mL	150 mg/mL	200 mg/mL	Positive control	Negative control
1	<i>Staphylococcus aureus</i>	7 mm	8 mm	10 mm	20 mm	31 mm	0
2	<i>Bacillus subtilis</i>	6 mm	6 mm	7 mm	7 mm	22 mm	0
3	<i>Escherichia coli</i>	8 mm	8 mm	13 mm	23 mm	25 mm	0
4	<i>Pseudomonas aeruginosa</i>	6 mm	7 mm	10 mm	20 mm	32 mm	0

nyl derivative while f(iv) is formed from the reaction between 2-chlorophenyltriolborate and 4-methylphenylsulphonyl deriva-

tive. The procedure for these syntheses is described below: Phenyltriolborate (0.1 mmol) was transferred into a three naked

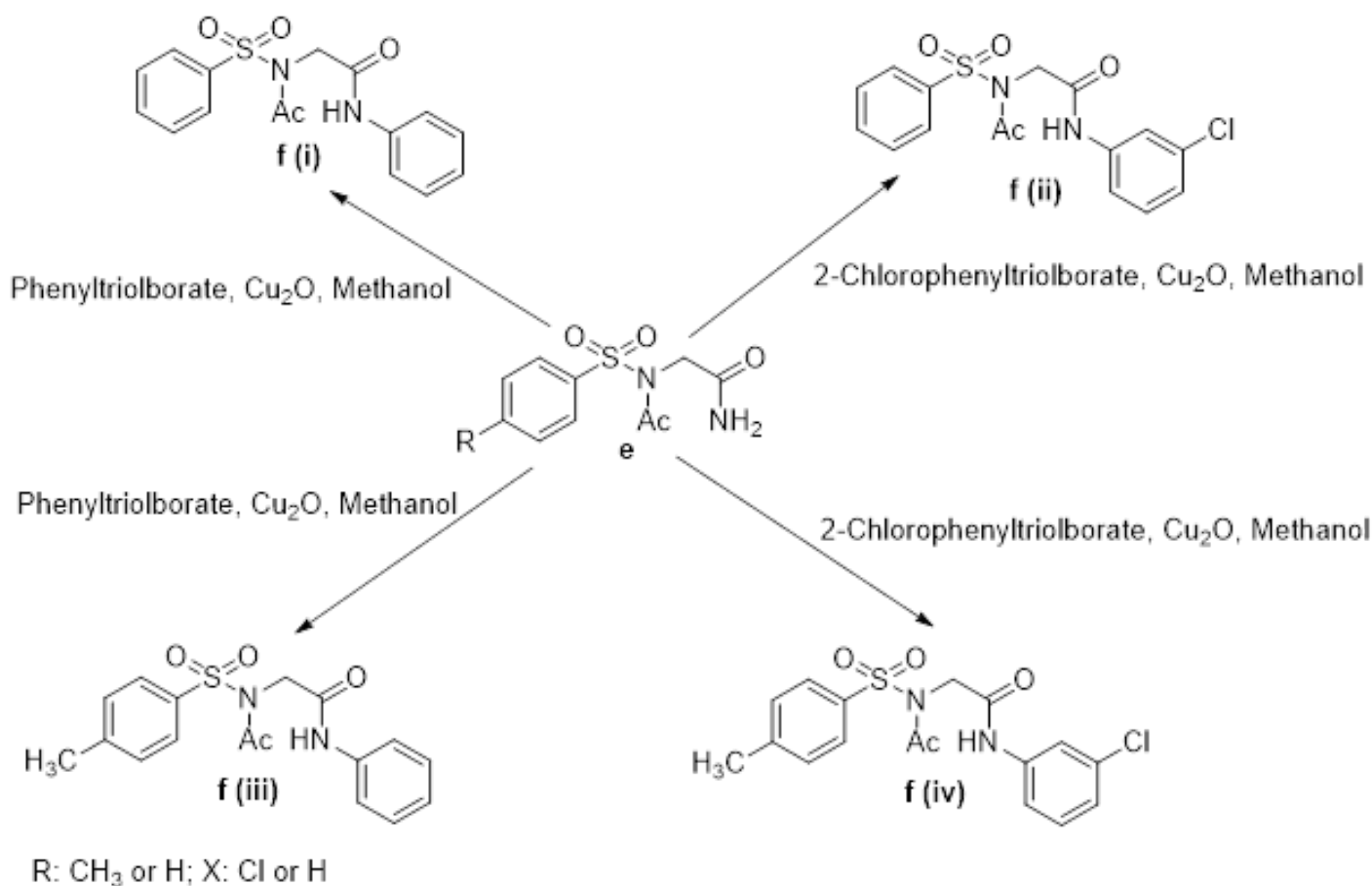


Figure 2. Cu₂O catalysis in the synthesis of substituted arylsulphonamide.

Table 8. The minimum inhibitory concentration (MIC) of compound f(ii) in methanol against the test organisms.

S/N	Test Organisms	50 mg/mL	100 mg/mL	150 mg/mL	200 mg/mL	Positive control	Negative control
1	<i>Staphylococcus aureus</i>	G	G	G	G	NG	G
2	<i>Bacillus subtilis</i>	G	G	G	G	NG	G
3	<i>Escherichia coli</i>	G	G	G	NG	NG	G
4	<i>Pseudomonas aeruginosa</i>	G	G	G	NG	NG	G

Key: NG = No growth, G = Growth.

round bottom flask placed on a hot plate fixed with a triple stand containing methanol (10 mL), copper(I)oxide (1 g) was added and then the amide **e** (1 mmol) was added and stir with magnetic stirrer in the presence of air for about 5 hours. Then the solution obtained was poured into a beaker (200 mL) for proper evaporation at room temperature. The product was then purified and dried. The products obtained from the four different aryltriolborates afforded four different products as seen in Figure 2.

2.5. MOLECULAR DOCKING

Figure 3 outlines the two-dimensional visualization of the interactions between protein and the ligand, in a docking analysis. It outlines the highly hydrophobic cavity consisted of a number of proximate hydrophobic residues (shown in green circles).

Figure 4 outlines the three-dimensional visualization of the interactions between protein and the ligand, in a docking analysis. It shows the highly hydrophobic cavity consisted of a number of

proximate hydrophobic residue.

2.5.1. Molecular docking procedures

The proteins used for molecular docking were downloaded from the protein data bank and prepared with the biovia discovery studio. The receptors were prepared by defining reactive sites, adding explicit hydrogens and removing water molecules that were not necessary during the docking experiments. The receptor cavity was defined with X, Y, Z coordinates of 13.368000, 30.583000, 45.659312 respectively and a boundary size of 36 Å, then converted to pdbqt format with the aid of Autodock 4.0 [27]. The ligands were prepared by conducting energy minimization at the DFT/(B3lyp functional and 6-311++G(d,p)); then, the respective proteins were docked with the studied compounds using Autodock vina, and the result output were visualized with PyMol and biovia discovery studio visualizer (The Pymol Molecular graphics system) and represented in both 2-D (Figure 3) and

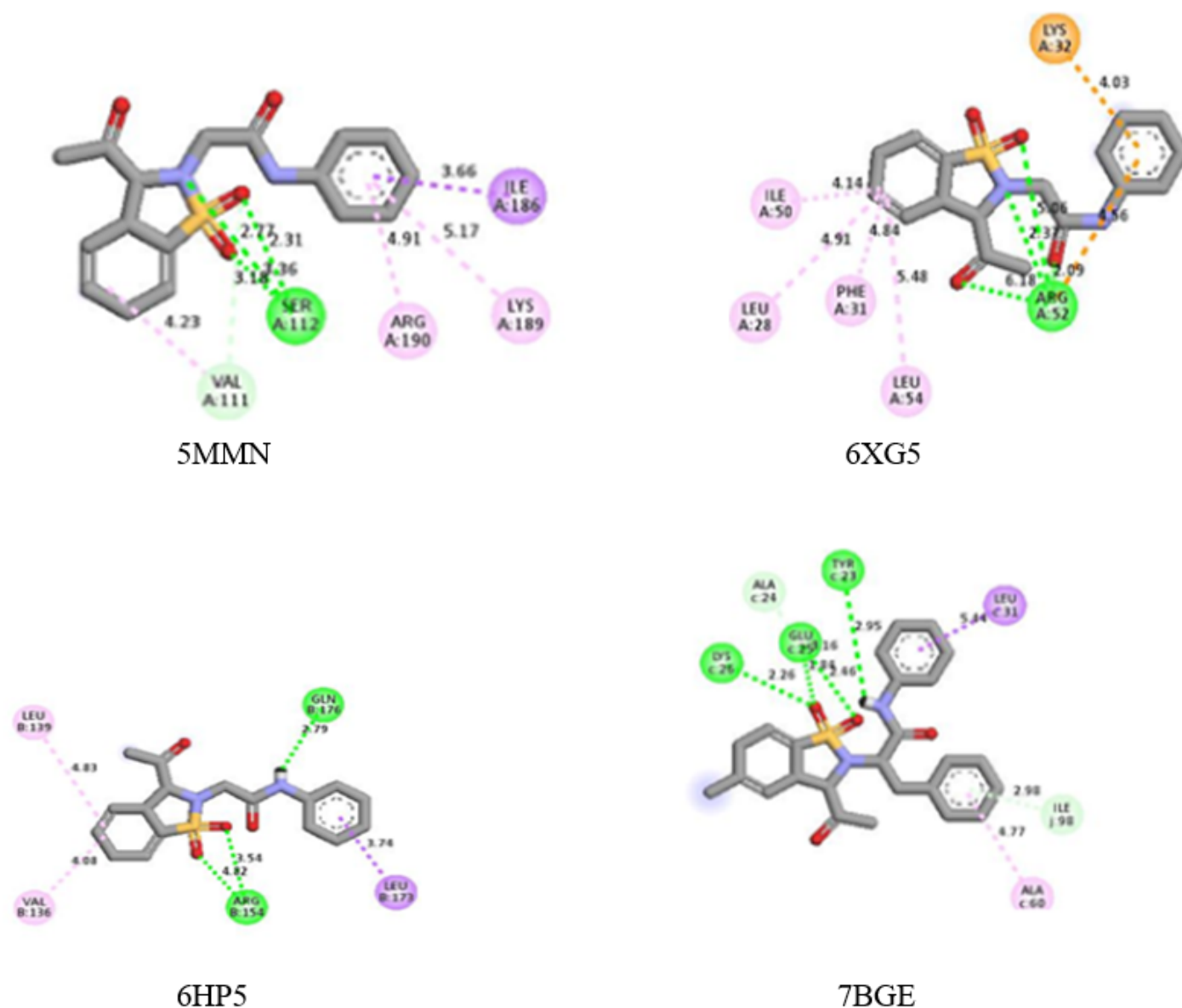


Figure 3. 2D visualization of protein ligand interaction.

Table 9. The antimicrobial activity of various concentrations of the compound f(iii) in methanol, on the test organisms.

S/N	Test Organisms	50 mg/mL	100 mg/mL	150 mg/mL	200 mg/mL	Positive control	Negative control
1	<i>Staphylococcus aureus</i>	0 mm	4 mm	8 mm	20 mm	31 mm	0
2	<i>Bacillus subtilis</i>	6 mm	6 mm	6 mm	7 mm	22 mm	0
3	<i>Escherichia coli</i>	8 mm	8 mm	12 mm	20 mm	25 mm	0
4	<i>Pseudomonas aeruginosa</i>	6 mm	7 mm	10 mm	21 mm	32 mm	0

and 3-D (Figure 4) visualizations. The docking investigations and preparation of pdbqt files were accomplished by autodock 4.0 and autodock tools (ADT) through the Lamarckian Genetic Algorithm (LGA) search. The scoring function in autoDock is primarily based on hydrogen bonding, van der waals interaction, electrostatic interaction, entropy change upon the binding of the compound to the receptor and solvation energy. These were utilized to rank the generated conformations and output respectively. Therefore, the grid parameters (GPF) were set to 20×20×20Å, 20×20×20, and 20×20×20 along the X, Y, Z coor-

dinate axes.

2.5.2. Docking validation and active site selection

Suitable bacteria proteins from *Escherichia coli*, *Bacillus subtilis*, *staphylococcus aureus* and *Pseudomonas aeruginosa* were obtained from the protein data bank (www.RSCB.org) based on literature survey. To predict the active site of the receptor, two distinct approaches were employed; first the chosen receptor proteins were visualized with the online 3D visualization model in the RCSB repository to check the binding conformation and in-

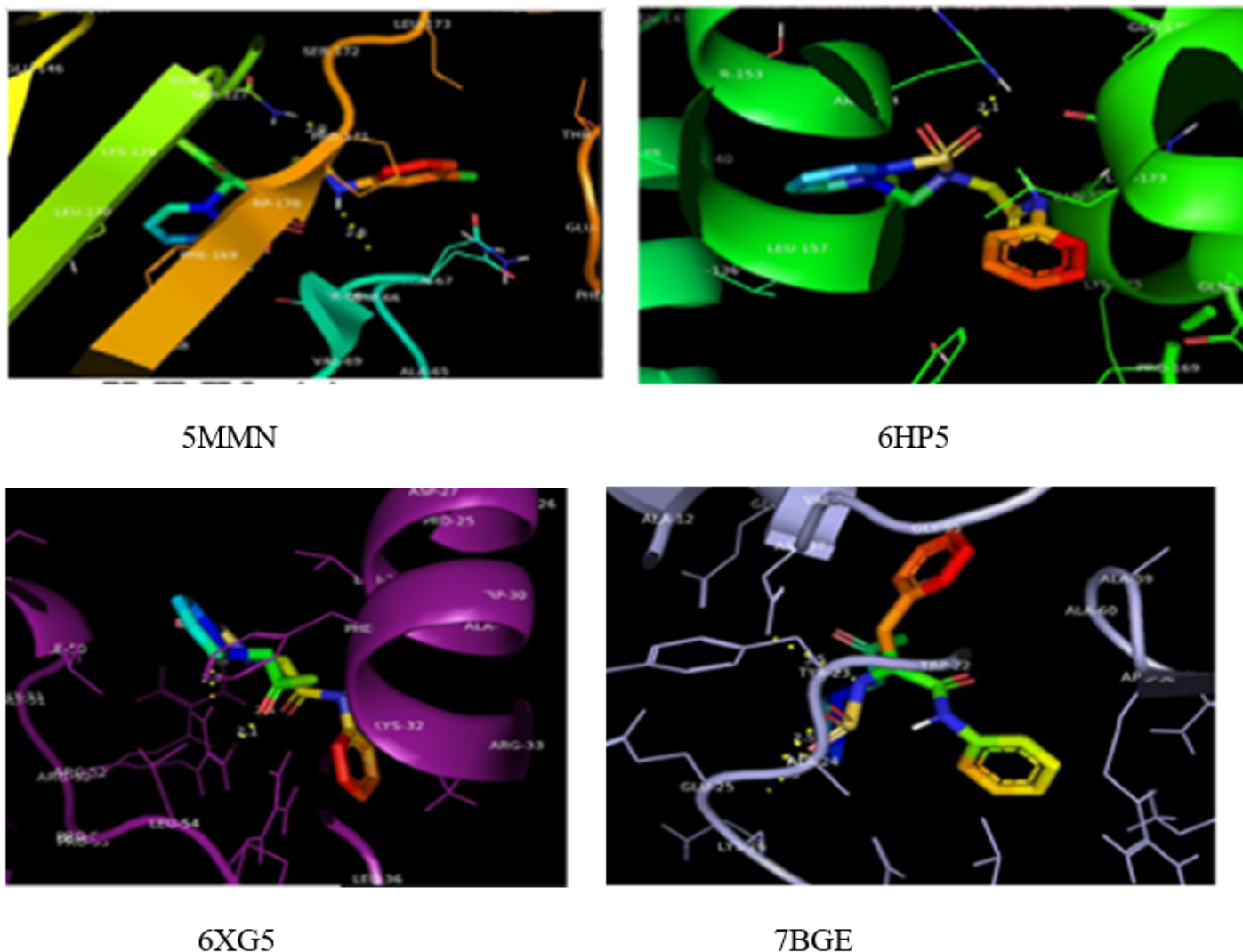


Figure 4. 3D Visualization of protein ligand interaction.

interacting amino acids of the co-crystallized ligand with the receptor proteins. Then the pdb files were downloaded and re-docked directly to affirm that the co-crystallized ligand fits back into the active pocket previously visualized. To further confirm the active site, the p2rank online server (<https://prankweb.cz>) was used to predict the active sites of the chosen pdb files. The proteins active site constitutes an enzymes catalytic or inhibition site. The predicted active sites based on the z-score was then compared with the amino acid residues in the active site of the respective co-crystallized receptor complex. The close similarity of the predicted active site and the co-crystallized ligand site was used as the basis for docking the studied compound against the chosen bacterial proteins.

2.6. BIOLOGICAL ACTIVITIES

The determination the antibacterial activity of the substituted sulphonamides solutions were carried out using the Agar well diffusion method as described. For each of the respective Mueller Hinton Agar plates, a sterile cork borer of 6mm in diameter was used to create wells in the solidified Agar plates. Each of the wells was filled with 0.1 mL of the sample concentrations of

50 mg/mL, 100 mg/L, 150 mg/mL and 200 mg/mL and are labeled appropriately. Distilled sterile water was used to fill one of the wells to serve as negative control, while cephalexin was used to fill the other well and it serves as the positive control. They were allowed to diffuse into the Agar at room temperature for one hour, and then incubated at 37 °C for 18-24 hours. The plates were observed for zone of inhibition or clear after 18-24 hours incubation.

2.6.1. Collection of Test Organisms

The test organisms were collected from the Microbiology laboratory of Prince Abubakar Audu University, Anyigba Nigeria. The organisms include: *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa*.

2.6.2. Determination of Minimum Inhibitory Concentration (MIC)

The estimation of MIC of the complex was carried out using 0.5 mL of varying concentrations of the samples in mg/mL (200, 150, 100 and 50) were dispensed into each test tubes containing nutrient broth, inoculated with a loopful of each test organisms,

Table 10. The minimum inhibitory concentration (MIC) of compound f(iii) in methanol against the test organisms.

S/N	Test Organisms	50 mg/mL	100 mg/mL	150 mg/mL	200 mg/mL	Positive control	Negative control
1	<i>Staphylococcus aureus</i>	G	G	G	NG	NG	G
2	<i>Bacillus subtilis</i>	G	G	G	NG	NG	G
3	<i>Escherichia coli</i>	G	G	G	NG	NG	G
4	<i>Pseudomonas aeruginosa</i>	G	G	NG	NG	NG	G

Key: NG = No growth, G = Growth.

Table 11. The antimicrobial activity of various concentrations of the compound f(iv) in methanol, on the test organisms.

S/N	Test Organisms	50 mg/mL	100 mg/mL	150 mg/mL	200 mg/mL	Positive control	Negative control
1	<i>Staphylococcus aureus</i>	7mm	8mm	10mm	21mm	31mm	0
2	<i>Bacillus subtilis</i>	6mm	6mm	7mm	7mm	22mm	0
3	<i>Escherichia coli</i>	8mm	8mm	10mm	20mm	25mm	0
4	<i>Pseudomonas aeruginosa</i>	6mm	6mm	10mm	20mm	32mm	0

0.5 Mcfarland turbidity standard was adopted. A tube containing nutrients broth with test organism, but no complex served as control. The MIC was taken as the tube with least concentration with no visible turbidity after 24 hrs incubation at 37°C for 24 hrs and then examine for growth by observing for turbidity.

3. RESULTS AND DISCUSSION

3.1. N-(2-OXO-2-(PHENYLAMINO)ETHYL)-N-(PHENYLSULPHONYL)ACETAMIDE F(I)

The synthesis of f(i) yielded 3.03 g (91.4 %), mp.155-156 °C, the structure is supported by spectral analyses. The most diagnostic vibrational bands in the FTIR are (KBr) cm^{-1} : 693.3 (Monosubstituted benzene), 1386.6 (-SO₂-NH₂), 2855.1 (R₃N-C), 1580.4 (C=O), 3332.2 (R₂-NH). In the ¹H-NMR spectrum, the peaks at ppm. 7.27 (1H, s) due to NH of 2° amine, ppm. 7.4-7.35 (10H, m) due to 2(mono substituted benzene), ppm 7.25 (2H, s) due to C₁ proton and ppm 7.29 (3H, s) due to CH₃-CO. Anal.calcd. for C₁₆H₁₆N₂O₄S (332.37): C, 57.82; H, 4.85; N, 8.43 Found: C, 58.12; H, 4.37; N, 8.31.

3.2. N-(3-CHLOROPHENYL)-2-(N-(PHENYLSULPHONYL)ACETAMIDO)ACETAMIDE F(II)

The synthesis of f(ii) yielded 3.01 g (89.4 %), mp.150-151 °C, the structure is supported by spectral analyses. The most diagnostic vibrational bands in the FTIR are (KBr) cm^{-1} : 849.8 (m-disubstituted benzene), 1386.6 (-SO₂-NH₂), 2370.6 (R₃N-C), 1580.4 (C=O), 3336.0 (R₂-NH). In the ¹H-NMR spectrum, the peaks at ppm. 2.5 (1H, s) due to NH of 2° amine, ppm.7.50 (5H, m) due to mono substituted benzene, ppm 2.0-1.8 (1H, s; 3H, s) due to m-disubstituted benzene, ppm. 2.0 (2H, s) due to C₁ proton and ppm 1.2 (3H, s) due to CH₃-CO. Anal.calcd. for C₁₆H₁₅ClN₂O₄S (366.82): C, 52.39; H, 4.12; N, 7.68. Found: C, 52.12; H, 4.37; N, 7.31.

3.3. N-(2-OXO-2-(PHENYLAMINO)ETHYL)-N-TOSYLACETAMIDE F(III)

The synthesis of F(iii) yielded 3.00 g (86.4 %), mp.159-160 °C, the structure is supported by spectral analyses. The most diagnostic vibrational bands in the FTIR are (KBr) cm^{-1} : 693.3 (Monosubstituted benzene), 1386.6 (-SO₂-NH₂), 2855.1 (R₃N-C), 1580.4 (C=O), 3332.2 (R₂-NH). In the ¹H-NMR spectrum,

the peaks at ppm. 1o.02 (1H, s) due to NH of 2° amine, ppm. 7.4-7.35 (5H, m) due to (mono substituted benzene), ppm 7.25 (2H, s) due to C₁ proton, ppm 4.5 (2H, d; 2H, d) due to p-disubstituted benzene and ppm 7.29 (3H, s) due to CH₃-CO. Anal.calcd. for C₁₇H₁₈N₂O₄S (346.40): C, 58.95; H, 5.24; N, 8.09 Found: C, 58.12; H, 5.37; N, 8.11.

3.4. N-(3-CHLOROPHENYL)-2-(N-TOSYLACETAMIDO)ACETAMIDE F(IV)

The synthesis of f(iv) yielded 3.07 g (92.5 %), mp.165-166 °C, the structure is supported by spectral analyses. The most diagnostic vibrational bands in the FTIR are (KBr) cm^{-1} : 849.8 (m-disubstituted benzene), 1386.6 (-SO₂-NH₂), 2370.6 (R₃N-C), 1580.4 (C=O), 3336.0 (R₂-NH). In the ¹H-NMR spectrum, the peaks at ppm. 10.7 (1H, s) due to NH of 2° amine, ppm.7.50 (2H, d; 2H, d) due to p-substituted benzene, ppm 2.0-1.8 (1H, s; 3H, s) due to m-disubstituted benzene, ppm. 2.0 (2H, s) due to C₁ proton and ppm 1.2 (3H, s) due to CH₃-CO. Anal.calcd. for C₁₇H₁₇ClN₂O₄S (380.84): C, 53.61; H, 4.50; N, 7.36. Found: C, 52.92; H, 5.37; N, 7.31.

3.5. DOCKING RESULTS

The effectiveness of antibiotics, which have revolutionized medicine and saved millions of lives, is in jeopardy because of the rapid emergence of bacteria that are resistant to them all over the world. Bacterial infections are still a threat, decades after the first successful treatment with antibiotics. The overuse and misuse of antibiotics, as well as the lack of new drug development due to reduced economic incentives and difficult regulatory requirements, are among the established factors accountable for antibiotic resistance crisis. Most microorganisms known for causing a variety of human diseases, including diarrhea, pneumonia, toxic shock syndrome, and mild wound inflammation, are *Staphylococcus aureus*, *Bacillus subtilis*, *E. coli* and *Pseudomonas aeruginosa*. These microbes' strains have developed resistance to virtually all known antibiotics, including the most effective methicillin variant. Thus, there is an increasing need for more effective therapeutic targets. The efficacy of newly synthesized Sulphonamide derivatives to inhibit these anti-bacteria-resistant microbes is tested herein via *in-silico* approach. Suitable proteins PDB ID: 5 mm, 6hp5, 6xg5 and 7bge

Table 12. The minimum inhibitory concentration (MIC) of compound f(iv) in methanol against the test organisms.

S/N	Test Organisms	50 mg/mL	100 mg/mL	150 mg/mL	200 mg/mL	Positive control	Negative control
1	<i>Staphylococcus aureus</i>	G	G	G	NG	NG	G
2	<i>Bacillus subtilis</i>	G	G	G	G	NG	G
3	<i>Escherichia coli</i>	G	G	G	NG	NG	G
4	<i>Pseudomonas aeruginosa</i>	G	G	G	G	NG	G

Key: NG = No growth, G = Growth.

from *Escherichia coli*, *Bacillus subtilis*, *staphylococcus aureus* and *Pseudomonas aeruginosa* were selected for docking experiments. The obtained results including the binding affinities, binding conformation, and number of interacting amino acids is presented in Table 1 – 4. Numerous important interactions such as hydrogen bond interactions, electrostatic interactions, etc. were observed between the ligand and the respective proteins. In all cases, the results disclosed that the ligands interacted more favorably with the 6xg5 receptor of the *staphylococcus* variant than other microorganisms studied. The highest average binding affinities were observed for the interaction with the *staphylococcus* receptor. These binding affinities were observed between the ranges of -7.0 to -9.7 kcal/mol. This shows that all the studied ligands exhibit maximum inhibitory activity on the respective micro-bacteria. Docking experiments are often assessed by the number of hydrogen bonds, binding affinity, and other stabilizing interactions. Based on this factor, the respective compounds can be concluded to possess significant antibacterial potency in the respective bacteria cells and could be further employed as potential anti-bacterial agents.

3.6. ANTIBACTERIA RESULT

The zone of clearance or inhibition expressed by the various concentration on the test organisms range from 6-22 mm. *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* were the most sensitive at the highest concentration, as seen in Table 5. Table 6 showed that, compound f(i) inhibited growth at 200 mg/mL, and did not show any sign of turbidity or growth for *staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*. Thus, the concentration (200 mg/mL) was taken as the MIC value. The zone of clearance or inhibition expressed by the various concentration on the test organisms range from 6-23 mm. *Escherichia coli* was the most sensitive at the highest concentration, while others show resistance, as seen in Table 7.

Table 8 showed that compound f(ii) inhibited growth at 200 mg/mL, and did not show any sign of turbidity or growth for *Staphylococcus aureus* and *Bacillus subtilis*. Thus, the concentration was taken as the MIC value. The zone of clearance or inhibition expressed by the various concentration on the test organisms range from 0-21mm. *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* were the most sensitive while *Bacillus subtilis* show low resistance, as seen in Table 9.

Table 10 showed that compound f(iii) inhibited growth at 150 mg/mL, and did not show any sign of turbidity or growth for *Pseudomonas aeruginosa*. Hence, the concentration was taken as the MIC value. The zone of clearance or inhibition expressed by the various concentrations on the test organisms range from 6-21 mm. *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas*

aeruginosa were the most sensitive at the highest concentration, as seen in Table 11. Table 12 showed that compound f(iv) inhibited growth at 200 mg/mL, and did not show any sign of turbidity or growth for *Staphylococcus aureus* and *Escherichia coli*. Thus, the concentration (200mg/mL) was taken as the MIC value.

4. CONCLUSION

There is the urgent need to find ambient methodologies for the incorporation of carboxamide functionality in biologically active molecules, hence the need to synthesize novel biological agents to combat enduring challenges of drug resistance using environmentally friendly reagents and hybrids of biologically active compounds with biological activities.

The research is a fulfilment of the aforementioned objectives. The results of the in silico and the in vitro antimicrobial studies agree with the antimicrobial assay. This indicates that the products synthesized are potential drug candidates.

References

- [1] A. K. Gadad, C. S. Mahajanshetti, S. Nimbalkar & A. Raichurkar, "Synthesis and antibacterial activity of some 5-guanylhydrazone/thiocyanato-6-arylimidazo[2,1-*b*]- 1,3,4-thiadiazole-2-sulfon amide derivatives", *European Journal of Medicinal Chemistry* **35** (2000) 853. [https://doi.org/10.1016/S0223-5234\(00\)00166-5](https://doi.org/10.1016/S0223-5234(00)00166-5)
- [2] G. Barbaro, A. Scozzafava, A. Mastrolorenzo & C. T. Supuran, "Highly active antiretroviral therapy: current state of the art, new agents and their pharmacological interactions useful for improving therapeutic outcome", *Current pharmaceutical design* **11** (2005) 1805. <https://doi.org/10.2174/1381612053764869>
- [3] M. A. Bhat, M. Imran, S. A. Khan & N. Siddiqui, "Biological activities of sulfonamides", *Indian Journal of Pharmaceutical Sciences* **67** (2005) 151. <https://ksascholar.dri.sa/en/publications/biological-activities-of-sulfonamides-2>
- [4] M. Khanusiya & Z. Gadhawala, "Chalcones-sulphonamide hybrids: synthesis, characterization and anticancer evaluation", *Journal of the Korean Chemical Society* **63** (2019) 85. <https://doi.org/10.5012/jkcs.2019.63.2.85>
- [5] H. Eshghi, M. R. Rahimizadeh, M. Zokaei, S. Eshghi, Z. Faghihi, E. Tabasi & M. Kihanyan, "Synthesis and antimicrobial activity of some new macrocyclic bisulfonamide and disulphides", *European Journal of Chemistry* **2** (2011) 47. <https://doi.org/10.5155/eurjchem.2.1.47-50.260>
- [6] M. C. Egbujor, U. C. Okoro, S. Okafor & N. E. Nwankwo, "Design, synthesis and molecular docking of novel serine-based sulphonamide bioactive compounds as potential antioxidant and antimicrobial agents", *Indonesian American Journal of Physical Sciences* **06** (2019) 12232. <https://doi.org/10.5281/zenodo.3250306>
- [7] E. A. Onoabedje, A. Ibezim, U. C. Okoro & S. Batra, "New sulphonamide pyrrolidine carboxamide derivatives: Synthesis, molecular docking, antiparasmodial and antioxidant activities" *PLoS ONE* **16** (2021) e0243305. <https://doi.org/10.1371/journal.pone.0243305>
- [8] K. J. Orie, R. U. Duru & R. I. Ngochindo, "Metal complexes of heterocyclic sulphonamide: synthesis, characterization and biological activity", *Science Journal of Analytical Chemistry* **9** (2021) 104. <https://doi.org/10.11648/j.sjac.20210904.14>
- [9] K. J. Orie, R. U. Duru & R. I. Ngochindo, "Synthesis and spectroscopic studies of zinc (II) ion and copper (II) ion complexes of 4-Methyl-N-(pyridin-2-yl)benzene sulphonamide", *World Journal of Applied Chemistry* **6** (2021) 19. <https://doi.org/10.11648/j.wjac.20210602.12>

- [10] K. J. Orié, C. D. Ike & J. U. Nzeneri, "Synthesis and characterization of metal complexes with 4-Methyl-*N*-(*p*-methylphenylsulphonyl)-*N*-(pyridin-2-yl)benzene sulphonamide", *Modern Chemistry* **9** (2021) 46. <https://doi.org/10.11648/j.mc.20210903.11>
- [11] A. Van den Bogaard, N. London, C. Driessen & E. Stobberingh, "Antibiotic resistance of faecal *Escherichia coli* in poultry, poultry farmers and poultry slaughterers", *Journal of Antimicrobial Chemotherapy* **47** (2001) 763. <https://doi.org/10.1093/jac/47.6.763>
- [12] M. C. Egbujor & U. C. Okoro, "New methionine-based *p*-toluenesulphonamoylcarboxamide derivatives as antimicrobial and antioxidant agents: design, synthesis, and molecular docking", *Journal of Pharmacy and Research International* **28** (2019) 1. <https://doi.org/10.9734/jpri/2019/v28i130192>
- [13] M. M. Sirdar, J. Picard, S. Bisschop, A. R. Jambalang & B. Gummow, "A survey of antimicrobial residues in table eggs in Khartoum State, Sudan", *Journal of Veterinary Research Onderstepoort* **79** (2012) 9. <https://doi.org/10.4102/ojvr.v79i1.360>
- [14] S. P. Fier, J. Luo & J. F. Hartwig, "Copper-mediated fluorination of aryl iodides", *Journal of American Chemical Society* **134** (2012) 10795. <https://doi.org/10.1021/ja304410x>
- [15] S. P. Fier, J. Luo & J. F. Hartwig, "Copper-mediated fluorination of arylboronate esters. Identification of a copper (III) fluoride complex", *Journal of American Chemical Society* **135** (2013) 2552. <https://doi.org/10.1021/ja310909q>
- [16] E. A. Standley & T. G. Jamison, "Simplifying nickel (0) catalysis: An air-stable Nickel precatalyst for the internally selective Benzylation of terminal Alkenes", *Journal of American Chemical Society* **135** (2013) 1585. <https://doi.org/10.1021/ja3116718>
- [17] D. Yoshii, "Selective dehydrogenative mono- or diborylation of styrenes by supported Copper catalysts", *ACS Catalysis* **9** (2019) 3011. <https://doi.org/10.1021/acscatal.9b00761>
- [18] E. W. Alison & S. S. Shannon, "Copper(ii)-mediated oxidative cyclization of enamides to oxazoles", *Organic Biomolecule Chemistry* **10** (2012) 3866. <https://doi.org/10.1039/C2OB25310K>
- [19] R. Bernini, S. Cacchi, G. Fabrizi, E. Filisti & A. Sferazza, "3-aryloindoles via Copper-catalyzed cyclization of *N*-(2-Iodoaryl)enaminones", *Synlett* **9** (2009) 1480. <https://doi.org/10.1055/s-0029-1216742>
- [20] J. Yan, J. Li & D. Cheng, "Mild and efficient Indium metal catalyzed synthesis of sulfonamides and sulfonic esters", *Synlett* **16** (2007) 2501. <https://doi.org/10.1055/s-2007-986632>
- [21] H. Liangbin, J. Huanfeng, Q. Chaorongi & L. Xiaohang, "Copper-catalyzed intermolecular oxidative [3 + 2] cycloaddition between Alkenes and Anhydrides: A new synthetic approach to γ -lactones", *Journal of the American Chemical Society* **132** (2010) 17652. <https://doi.org/10.1021/ja108073k>
- [22] C. Wan, J. Zhang, S. Wang, J. Fan & Z. Wang, "Facile synthesis of poly-substituted oxazoles via a copper-catalyzed tandem oxidative cyclization", *Organic Letters* **12** (2010) 2338. <https://doi.org/10.1021/ol100688c>
- [23] M. Jithunsa, M. Ueda & O. Miyata, "Copper(II)chloride-mediated cyclization reaction of *N*-alkoxy-ortho-alkynylbenzamides", *Organic Letters* **13** (2011) 518. <https://doi.org/10.1021/ol1029035>
- [24] C. W. Cheung & L. B. Stephen, "Room temperature copper(II)-catalyzed oxidative cyclization of enamides to 2,5-disubstituted oxazoles via vinylic C-H functionalization", *The Journal of Organic Chemistry* **77** (2012) 7526. <https://doi.org/10.1021/jo301332s>
- [25] U. Satoshi & N. Hideko, "Facile synthesis of 1,2,4-triazoles via a Copper-catalyzed tandem addition-oxidative cyclization", *Journal of American Chemical Society* **131** (2009) 15080. <https://doi.org/10.1021/ja905056z>
- [26] J. Ma & D. Cahard, "Copper(II) triflate-bis(oxazoline)-catalysed enantioselective electrophilic fluorination of β -ketoesters", *Tetrahedron: Asymmetry* **15** (2004) 1007. <https://doi.org/10.1016/j.tetasy.2004.01.014>
- [27] O. Trott & A. J. Olson, "AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading", *Journal of Computational Chemistry* **31** (2010) 455. <https://doi.org/10.1002/jcc.21334>