Jordan Journal of Pharmaceutical Sciences, Volume 17, No. 4, 2024

Design, Synthesis, Molecular docking and Biological Evaluation of Novel Leucine Derived Sulfamoyl Pentanamides as Antimicrobial and Antioxidant Agents

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ABSTRACT

The preponderance of microbial and oxidative stress-mediated diseases is quite alarming. The need for novel drug development is highlighted by the fact that antimicrobial resistance is rising and many current antioxidant drugs only provide little symptomatic alleviation. The aim of this work was to synthesize leucine derived sulfamoyl pentanamides with antioxidant and antimicrobial activities. New leucine-based sulfamoyl pentanamides were synthesized and elemental analysis, 1H-NMR, 13C-NMR, and FTIR were used to elucidate their structures. They underwent molecular docking investigations as well as in vitro antioxidant and antimicrobial activity analyses. Compound 5a (0.60 gm/ml) was the most active compound against *Pseudomonas aeroginosa*, whereas compound 5f (0.30-0.40 mg/ml) was the most effective antibacterial agent against *E. Coli, S. typhi, S. aureus, and B. subtilis*. The compounds with the best antifungal activity against *C. albican* and *A. niger*, respectively, were 5g (0.80 mg/ml) and 5e (0.50 mg/ml). In the in vitro antioxidant assessment, compounds 5g (1.174µg/ml) and 5h (1.172µg/ml) exhibited similar antioxidant activity to ascorbic acid (IC50 1.001µglml). In addition, most of the target compounds have relatively strong antibacterial, antifungal, and antioxidant potentials, according to molecular docking study. Since every target compound complied with Lipinski's rule of five, it is likely that they might be used as therapeutic candidates to treat oxidative stress-related illnesses and microbial infections.

Keywords: pentanamides; leucine; sulfonamides; antimicrobial; antioxidant; synthesis.

INTRODUCTION

The global health sector is seriously threatened by the prevalence of oxidative stress-related diseases and organisms that are resistant to antibiotics. Among the biggest health problems of the twenty-first century are oxidative stress and microbial infections.[1,2] Thus, in order to elicit dual mechanisms of action and minimize drug resistance, this situation highlights the necessity for the development of drugs through hybrid pharmacophoric strategies that allow the linking of two or more bioactive moieties with distinct pharmacological activities into a drug molecule.[3-5] Combining certain amino acids with sulfonamides and

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Received: 08/03/2024 Accepted: 18/05/2024.
DOI: https://doi.org/10.35516/jjps.v17i4.2467

carboxamides has been shown to exhibit excellent inhibitory activities against diseases linked to oxidative stress and microbial infections.[6-8] According to Fox et al.'s [9] research, leucine is a non-polar aliphatic α-amino acid with excellent antimicrobial potential. It was shown to inhibit Lactobacillus arabinosus strains from growing. Similar to this, it was observed that leucine improved the antibiotic action of ramoplanin, a glycolipodepsipeptide obtained by the fermentation of Actaioplanes sp.[10] Like other branched-chain amino acids, leucine is also known to possess antioxidant properties. Jin et al.[11] found that leucine has an inhibitory effect on lipid peroxidation and nitric oxide scavenging activity, and they proposed that leucine could be used to produce antioxidant products for the food or pharmaceutical industries. Numerous studies have demonstrated the antimicrobial[12-15] and antioxidant[16,17] properties of sulfonamide moieties, among other properties. Additionally, it has been documented that sulfonamides not only neutralize free radicals but also trigger nuclear factor erythroid 2-related factor 2 (NRF2), the primary modulator of an organism's endogenous antioxidant responses.[18,19] Carboxamides also display a wide range of biological activity.[20] They have the potential to be used as medications to treat oxidative stress and microbial infections.[13] In view of improving drug potency through synergism, we proposed that integrating leucine, pentanamide, and sulfonamide moieties into a single compound by simple and effective synthesis would be crucial for increasing therapeutic efficacy through synergism. In view of combating health issues linked to oxidative stress and antimicrobial resistance, the goal of this work was to synthesize leucine-based sulfamoyl pentanamides with enhanced antimicrobial and antioxidant properties.

MATERIAL AND METHODS

Reagents and Instrumentation Sigma Aldrich provided the chemicals. The compounds' melting points were obtained using an electrothermal melting point equipment. 8400s Fourier Transform Infrared spectrometer was used to determine the FT-IR spectra of the compounds. In the Department of Chemistry at the Indian Institute of Technology, Kanpur, India, the 1H- and 13C-NMR analyses were conducted at 400MHz using DMSO. Chemical changes were represented in parts per million, with tetramethylsilane serving as the standard. The elemental analyzer (Exeter Analytical Inc. model: CE440) was used to perform the elemental analysis. For all processes that needed inert conditions, nitrogen gas was utilized.

Chemistry

Synthesis of 4-methyl-2-{[(4-methylphenyl)sulphonyl]amino}pentanoic acid. Water (15 ml) and L-leucine (12 mmol) were mixed in a 100 ml beaker. NaOH (26.30 mmol) was then added, and the mixture was swirled until the solutes were completely dissolved. The different sulphonyl chlorides (1a-b) (30 mmol) were added to the solution in five sections over the course of an hour after it had cooled to zero degrees Celsius. After four hours of stirring at room temperature, 2M hydrochloric acid was added to acidify the mixture to pH 2 in order to promote crystallization. TLC (MeOH/DCM, 1:9) was used to track the reaction process. The products were separated using suction filtration after it was let to settle for a full day. After drying and washing with tartaric acid (pH 2.2), the products yielded chemicals (3a-b) in their analytical grade excellent.

Acetylation of the Sulfamoyl Carboxylic Acids (3a-b). In order to guarantee homogeneity, a beaker was filled precisely with the 1 mmol of sulfamoyl carboxylic acids (3a–b), 25 ml of distilled water, and 9 ml of concentrated HCl. The mixture was then rapidly agitated. Then 150.29 mmol of NaCO3 was dissolved in 50 ml of distilled water in a different 100 ml beaker. The sulfamoyl carboxylic acid solution was filled with the sodium acetate solution and 13.5 ml of acetic anhydride was added in three increments over the course of an hour. To extract the N-

acetylated sulfamoyl carboxylic acids (4a-b) in excellent yields, the mixture was mixed, submerged in an ice bath for an hour, and then filtered and rinsed with water.

Chlorination and ammonolysis of 4a-b

Chlorination. When a three-necked flask with a magnetic bar was filled with sulfamoyl carboxylic acids (4a–b) (1 mmol) and acetone (10 ml), it was cooled to 0°C. Excess thionyl chloride was removed from the mixture by stirring it at 80°C under reflux for three hours before transferring it to an 80°C water bath. To achieve complete evaporation of thionyl chloride and produce acid chloride intermediate, 20 ml of acetone was added and the process was repeated twice.

Ammonolysis. After dissolving the aforementioned acid chloride in 20 ml of acetone, the mixture was chilled to zero degrees Celsius. Crystallization occured when 2 ml of ammonia and 1M NaOH were added, and the liquid was then left to settle for 24 hours before being filtered and cleaned with acetone to extract the remaining material.

2{Acetyl[(4-methylphenyl)sulfonyl]amino}-4-methylpentanamide (5a). Yield; 2.95g (90.1%), mp.215-216^{o}C, IR (KBr) cm^{-1}: 3370(N-H), 2061(C-H aliphatic), 2001(C-H aromatic), 1722,1690(C=O), 1694,1646 (C=C), 1326, 1151(2S=O), 1121(SO_2-NH), 1032(C-N), 682(Ar-H). ^{1}HNMR (DMSO, 400 MHz) δ: 7.32 (d, J = 7.5Hz, 2H, Ar), 6.60 (m, 2H, ArH), 5.69 (s, 2H, NH_2), 3.45 (s, 3H, CH_3-C=O), 2.46 (s, 3H, CH_3-Ar), 1.27 (s, 6H, 2CH_3-CH). ^{13}CNMR (DMSO, 400 MHz)δ: 170.11, 169.23(C=O), 137.08, 133.77, 133.59 132.46, 131.92, 129.21 (aromatic carbon), 67.85, 60.65, 53.68, 50.68, 40.02, 39.82, 39.63 (aliphatic carbons). Anal.calcd (%). for $C_{15}H_{22}N_2O_4S$ (326.41): C: 55.15, H: 6.79, N: 8.58, S: 9.80. Found: C: 55.18, H: 6.81, N: 8.60, S: 9.78.

2-[Acetyl(phenylsulfonyl)amino]-4-methylpentanamide (5b). Yield; 3.09g(92.3%), mp.135-136 ^{o}C, IR (KBr)cm^{-1}: 3257(N-H), 2958(C-H aliphatic), 1996(C-H aromatic), 1720, 1689 (C=O), 1640(C=C), 1344, 1307(2S=O), 1162(SO_2-NH), 1092(C-N), 752(Ar-H). ^{1}HNMR (C_6D_6/DMSO/$CDCl_3$, 400MHz)δ: 8.107 (s, 2H, ArH), 7.147 (s, 2H, ArH), 5.689 (s, 2H, NH_2), 2.209(s, 3H, CH_3-C=O). ^{13}CNMR(C_6D_6, 400 MHz)δ: 178.67, 172.42, 2(C=O),138.62, 138.43, 133.52, 132.97, 132.73, 132.49 (aromatic carbons), 84.09, 83.76, 83.42, 44.99, 44.79, 44.58. ^{13}CNMR(C_6D_6, 400 MHz)δ: 171.67, 170.42, 2(C=O), 138.62, 138.43, 133.52, 132.97, 132.73, 132.50 (aromatic carbons), 84.09, 83.76, 83.42, 44.99, 44.79, 44.58. Anal.calcd.(%) for $C_{14}H_{20}N_2O_4S$ (312.38): C: 53.78, H: 6.40, N:8.96, S: 10.24. Found: C: 53.80, H: 6.38, N: 8.99, S: 10.21

Leucine-based Sulfamoyl Pentanamide Synthesis via Nickel-Catalyzed Reaction:

Bis(triphenylphosphine)nickel(ii)chloride Preparation. Using the Venanzi[21] reaction protocol, the coordination compound was made by dissolving 10 mmol of nickel (II) chloride hexahydrate in 2 ml of distilled water, diluting with 50 ml of glacial acetic acid, and then adding 20 mmol of triphenylphosphine ligand dissolved in 25 ml of glacial acetic acid. Overnight interaction between the green precipitate and the glacial acetic acid solution was observed. After filtering, the catalyst complex was recovered as a dark blue crystal, cleaned with glacial acetic acid, and dried in a desiccator.

Procedure for Synthesis. A three-necked flask (50 ml) containing a magnetic bar was filled with 10 mmol of bis(triphenylphosphine)nickel (II) chloride and 30 mmol of triphenylphosphine. In addition, distilled water (2 ml) and t-butanol (4 ml) were added with a syringe. The mixture was then stirred for 10 minutes at room temperature under an inert nitrogen atmosphere. It was refluxed for two minutes at 80°C. Subsequently, *t*-butanol and H_2O were added in a 2:1 ratio under inert conditions, along with sulfamoyl carboxamides (5a-b) (10 mmol), K_2CO_3 (10 mmol), and a variety of aryl and heteroaryl halides, such as 4-chloroaniline (a), 4-amino-3-chloropyridine (b), and 5-chloro-4,6-diaminopyrimidine (c). It was refluxed for an hour at 100 to 110 degrees

Celsius while being stirred. After cooling it down to room temperature, leucine-based carboxamide derivatives (5c-h) were obtained by recrystallizing it with ethyl acetate and washing it with water. The synthetic route for leucine-based sulfamoyl pentanamide derivatives (**5a-h)** is represented in **scheme 1** while the target compounds were shown in **scheme 2.**

2-{acetyl-[(4-methylphenyl)sulfonyl]amino}-*N*-(4-aminophenyl)-4-methylpentanamide(5c). Yield; 3.19g (95.3%), mp.93-94 ^{o}C, IR (KBr) cm^{-1}: 3373, 3260(N-H), 2800(C-H aliphatic), 1982 (C-H aromatic), 1705, 1690 (C=O), 1684, 1680, 1675 (C=C), 1308,1185(2S=O), 1118(SO_2-NH), 1026(C-N), 723 (Ar-H). ^{1}HNMR (DMSO, 400 MHz) δ: 7.53-7.51 (d, J= 8.0H_2 2H, ArH), 7.46-7.44 (d, J= 8.4H_2, 2H, ArH), 7.18-7.16 (d, J= 8.0 H_2, 2H, ArH), 7.05 -7.03 (d, J= 8.0Hz , 2H, Ar) 3.55 (s,2H, NH_2), 3.54-3.52 (m, IH, NH), 2.48 (s, 3H, CH_3–C=O), 2.16 (s, 3H, CH_3-Ar), 1.44-1.40 (m, 2H, CH), 1.28-1.25 (m, CH, 2CH_3-CH). ^{13}(CNMR (DMSO, 400 MHz) δ: 170. 66, 169.08(C=O), 143.39, 142.93, 139.72, 138.40, 129.72, 129.01, 126.85, 125.84, 123.44, 120.23, 118.54, 116.76 (aromatic carbons), 54.31, 41.17, 39.32, 39.10, 38.84, 38.68, 38.47 (aliphatic carbons). Anal.calcd (%). for $C_{12}H_{27}N_3O_4S$ (417.52): C: 34.49, H: 6.52, N:10.06, S: 7.66. Found: C: 34.50, H: 6.50, N; 10.08, S: 7.68.

2-[Acetyl(phenylsulfonyl)amino*]-N-(*4-aminophenyl)-3-hydroxypropanamide(5d). Yield; 3.20g (95.5%), mp.98-99 ^{o}C,IR (KBr)cm^{-1}: 3369, 3264(2N-H), 2952(C-H aliphatic), 1982(C-H aromatic), 1715, 1679(2C=O), 1323, 1250(2S=O), 1155(SO_2-NH), 940(C=C), 1088 (C-N) 741 (Ar-H). ^{I}HNMR (CD_3CN, 400 MHz), 7.84 (m, 2H, ArH), 7.83 - 7.82 (d, J= 5.2Hz, 2H, ArH), 7.82 -7.81 (d, J= 1.2Hz, 2H, ArH), 7.52 -7.52 (d, J= 1.6Hz, 2H, ArH), 5.97 (s, IH, NH), 4.31 -4.29 (d, J= 5.6H_2, 2H, NH_2) 2.81 (s, IH, CH_3-C=O), 1.69-1.61 (m, IH, CH), 1.48-1.45 (m, 2H, CH_2-CH), 0.88-0.86 (d, J= 6.8Hz, 6H, 2CH_3-CH). ^{13}C-NMR (CD_3CN, 400MHz), 171.45, 170.07, 2 (C=O), 140.41, 132.74, 129.07, 126.91, 117.19, 116.45, 113.64, 112.32, 112.21, 110.54, 109.43, 108.44 (aromatic carbon) 78.27, 77.95, 77.62, 54.21, 41.54, 24.19 (aliphatic carbon). Anal.calcd.(%) for $C_{20}H_{25}N_3O_4S$ (403.50): C: 59.48, H: 6.20, N: 10.41, S: 7.93. Found C: 59.52, H: 6.18, N:10.44, S: 7.89.

2-{acetyl-[(4-methylphenyl)sulfonyl]amino}-*N*-(4-aminopyridin-3-yl)-4-methylpentanamide(5e). Yield; 3.16g (93.7%), mp.91-92 ^{o}C, IR (KBr)cm^{-1}: 3309, 3263(N-H), 2922 (C-H aliphatic) 1982 (C-H aromatic),1711,1660(C=O), 1685(C=N), 1676, 1669(C=C) 1367, 1308(S=O,) 1181, 1118(SO_2N), 1025(C-N), 812(Ar-H). ^{1}HNMR (DMSO, 400 MHz) δ: 6.25-6.25 (d, J= 2.8H_2 2H, ArH), 6.24 (m,2H, ArH), 6.23 (m, IH, ArH), 5.23-5.21 (m, IH, NH), 2.13-4.21 (d, J= 4Hz, 2H, NH_2) , 2.67-2. 64 (m, 3H, CH_3 – C=O), 2.20-2.16 (m, 3H, CH_3-Ar), 1.55 (s, 2H, 2CH), 1.49-1.48 (d, J= 4.8H_2, 6H, 2CH_3). ^{13}C-NMR (DMSO, 400 MHz)δ: 171.61, 170.25(C=O), 156.56(C=N), 129.83, 129.73, 129.73, 129.72, 129.65, 129.62, 129. 46, 127.99, 124.23, 120.57, 117.63 (aromatic carbon) 77.49, 77.17, 76.85, 68.80, 61.86, 33.94, 33.78 (Aliphatic carbons). Anal.calcd (%). for $C_{20}H_{26}N_4O_4S$ (418.51): C, 57.35, H: 6.26, N:13.38, S:7.65. Found: C: 57.37, H: 6.29, N: 13.35, S: 7.67.

2-[Acetyl-[(phenylsulfonyl)amino]-*N*-(4-aminopyridin-3-yl)-4-methylpentanamide(5f). Yield; 3.22g (91.8%), mp.83-84 ^{o}C, IR (KBr)cm^{-1}: 3309, 3231(2N-H), 3063(C-H aliphatic), 1982(C-H aromatic), 1701, 1671(2C=O), 1617 (C=N), 1321-1221(2S=O)1025 (C-N), 935 890 (C=C), 741 (Ar-H). ^{I}HNMR ($CDCl_3$/DMSO, 400 MHz) δ: 7.81(m,2H, ArH), 7.43 (m, 2H, ArH), 7.35(m, IH, ArH), 6.17 (s, IH, NH), 3.61 (s, 2H, NH_2) 2.37 (s, 3H, CH_3-C=O), 0.77 (s, 6H, 2CH_3-CH). ^{1}C-NMR ($CDCl_3$/DMSO, 400 MHz) δ: 172.89, 170.76 (C=O), 157.32 (C=N), 140.10, 132.54, 128.91, 127.09, 128.36, 127.42, 125.85, 123.77, 120.52, 118.96 (aromatic carbon), 77.36, 77.04, 76.73, 55.96, 41.47, 24.26, 22.98, 20.78. Anal.calcd.(%) for $C_{19}H_{24}N_4O_4S$ (404.48): C: 4.70, H: 5.93, N: 13.84, S: 7.91.

Found C: 4.68, H: 5.95, N: 13.80, S: 7.89.

2-{acetyl-[(4-methylphenyl)sulfonyl]amino}-*N*-(4,6-diaminopyrimidin-3-yl)-4-methylpentanamide*e*(5g)

Yield; 3.30 g (95.5%), mp.107-108 ^{o}C, IR (KBr)cm^{-1}: 3328, 3130(2N-H), 3003(C-H aliphatic) 1986 (C-H aromatic), 1713, 1660(C=O), 1680, 1678(C=N), 1367, 1278 (S=O), 1118 (SO_2N), 1088(C-N), 970 (C=C), 890 (Ar-H). ^{1}HNMR (DMSO 400 MHz) δ: 7.81 (d, J = 7.3Hz, 2H, ArH), 7.59-7.53 (m, 2H, ArH), 7.36 (d, J=7.0Hz, IH, ArH) 2.48 (S,IH, NH), 2.36 (s, 2H , NH_2), 2.27 (s,3H, CH_3-C=O), 2.23 (s, 3H, CH_3-Ar), 1.34-1.32 (m, 2H, 2CH), 1.30 (s, 6H, $2CH_3$). ^{13}CNMR (DMSO, 400 MHz) δ: 170.96, 169.35 (C=O), 156.88, 158.79, 142.19, 139.75, 138.15, 130.64, 129.43, 129.37, 128.78, 126.95 (aromatic carbons), 78.92, 78.59, 78.27, 54.21, 41.49, 40.05, 39.84 (aliphatic carbons). Anal.calcd (%). for $C_{19}H_{26}N_6O_4S$ (434.51): C, 52.47, H, 6.03, N, 19.33, S, 7.36. Found: C: 52.49, H: 6.05, N:19.30, S:7.35.

2[Acetyl(phenylsulfonyl)amino*]-N-(*4,6-diaminopyrimidin-5-yl)-4-methylpentanamide(5h).

Yield; 3.18 g (94.6%), mp.100-101 ^{o}C, IR (KBr) cm^{-1}: 3341 (N-H), 3063 (C-H aliphatic), 1982 (C-H aromatic), 1711, 1679(2C=O), 1630, 1580 (C=N), 1580 (N-H), 1308, 1155 (2S=O), 1088 (SO_2-NH), 1025 (C-N), 995 (C=C) 894 (Ar-H). ^{I}HNMR(DMSO, 400 MHz)δ: 8.51-8.49(m, 2H, ArH), 7.16-7. 15 (m, 2H, ArH), 7.15-7.14(m, IH, ArH), 4.35 (s, IH, NH), 3.34 (s, 4H, $2NH_2$), 2.48 (s, IH, CH), 2.47-2.47 (m, 2H, CH_2-CH), 2.18 (m, IH, CH), 1.79 (s, 6H, $2CH_3$CH). ^{13}CNMR (DMSO, 400 MHz)δ: 170.33, 170.09, 2(C=O), 166.77, 154.89 (C=N), 146.15, 130.64, 129.43, 129.37, 128.78, 126.95, 125,79, 124.77, 121.99, 119.43 (aromatic carbons), 48.76, 40.55, 40.34, 40.13, 39.93, 39.50 (aliphatic carbon). Anal.calcd.(%) for $C_{18}H_{24}N_6O_4S$ (420.49): C: 51.37, H;5.71, N: 19.98, S: 7.61. Found C: 51.41, H: 5.68, N: 19. 95, S: 7.58

Biological Evaluations

Antimicrobials studies. The antibacterial screening of each compound was conducted using the Agar dilution technique.[22] Clinical isolates from the pharmaceutical microbiology and biotechnology labs at the University of Nigeria, Nsukka, Nigeria, were used to screen them for in vitro antimicrobial activity against microbes, including Salmonella typhi, Aspergillus niger, Pseudomonas aeruginosa, Bacillus subtilis, Candida albicans, and Escherichia coli. Using 0.5 McFarland turbid equivalents, the organisms were standardized. For the antibacterial and antifungal analyses, ofloxacin was the standard, and fluconazole was utilized. **Table 1** lists the different minimum inhibitory concentrations for the standards and tested compounds.

Antioxidant Studies

Antioxidant Activity: The antioxidant assessment was performed using the Blois technique.[23] 2,2-Diphenyl-1-picrylhydrazyl (DPPH) free radical inhibition was used to measure the antioxidant potential of the compounds in vitro.

Physicochemical studies

The compounds' physicochemical characteristics were determined in silico. Topological surface area (TPSA), molecular weight (MW), octanol/water partition coefficient logP(o/w), aqueous solubility (SlogP), number of hydrogen bond acceptors (HBA), number of hydrogen bond donors (HBD), number of rotatable bonds (NRB), and other physicochemical data were obtained. We computed these physicochemical characteristics using the descriptors calculator found at Swiss Dock internet servers. The compounds' potential for use as drugs was evaluated using Lipinski's rule of five.

Molecular Docking Protocol

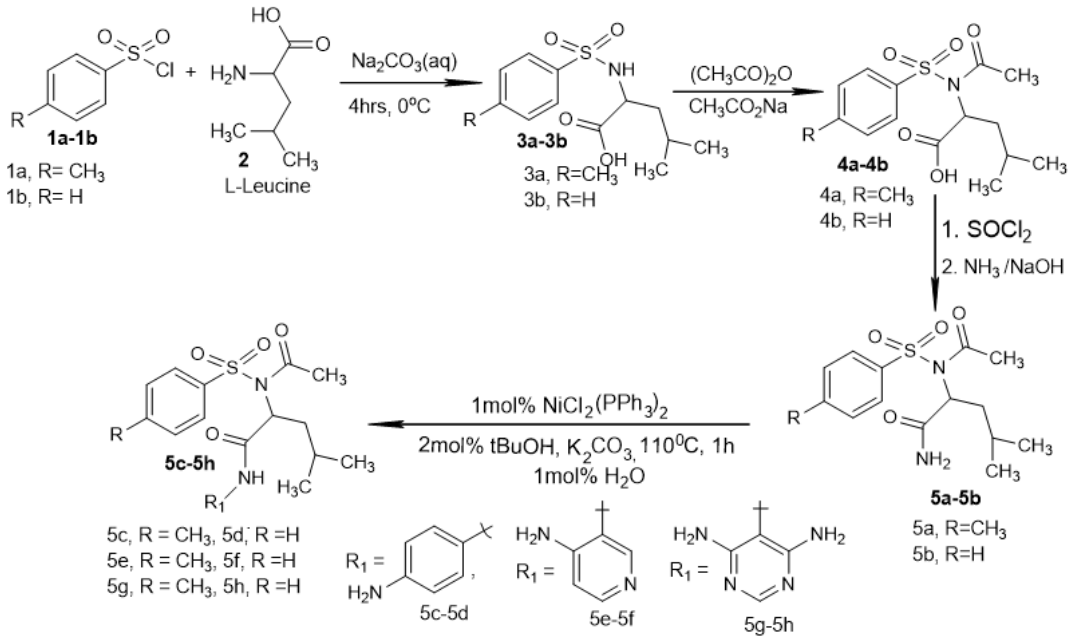
The molecular docking scores of the eight compounds that interact with the target receptors for antifungal (PDB code: 1WS3), antioxidant (PDB code: 1HD2), and antibacterial (PDB code: 5MMN) were investigated.[24,25] To realize this idea, protein preparation was done using Biovia Discovery Studio. This was achieved by extracting the water molecules from the proteins and then identifying

and modifying the binding sites to incorporate a large fraction of the active sites found in the proteins. Moreover, the generated proteins were supplemented with polar hydrogens and saved in PDB format. Additionally, the Autodock Vina program[26,27] was used to carry out the proper molecular docking analysis between the target receptor and the synthesized compounds (5a, 5b, 5c, 5d, 5e, 5f, 5g, and 5h). The PDBQT formatted proteins and ligands, along with the Vina, licensing, and split files, were meticulously transferred into their respective working directories, along with the conf.txt file. In addition, the configuration files were opened, and for every working folder, the receptor, ligand, coordinates, radius, and exhaustiveness were set. As a summary, the vina.exe application was used, the working directories holding the files were copied into the command prompt accordingly, the docking process was completed, and binding affinities were created. To find the ideal position of the ligand-protein interactions, the output files were then divided into sets of exhaustiveness. The Biovia discovery studio was utilized to do further 2D and 3D visualization of the docking score.

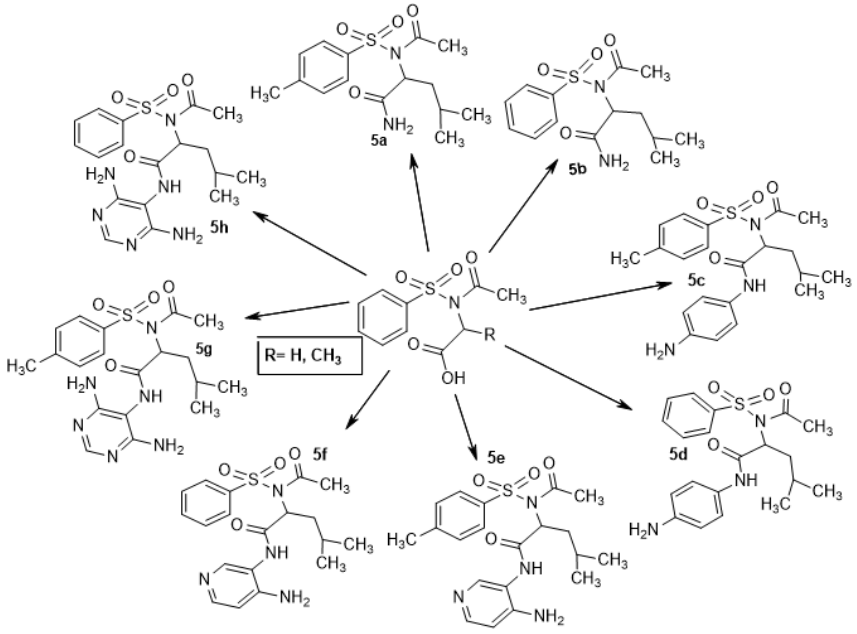
RESULTS AND DISCUSSION

Spectra

The sulfamoyl carboxamides displayed their N-H and S=O bands in the 1367–1151 cm–1 and 3373–3257 cm–1 frequency range, respectively, in their FTIR spectra. Carboxamide bands with a C = O were seen between 1690 and 1660 cm-1; these bands showed that pentanamides and sulfonamides had successfully coupled. The successful synthesis of the target compounds was supported by the 1H-NMR peaks between 6.174 and 2.125 ppm. The synthesis of sulfamoyl pentanamides was indicated by the C=O peaks in the 13C-NMR, which were located between 172.898 and 169.0 ppm. The carbon-13 NMR analysis revealed the presence of all the aromatic and aliphatic carbon peaks. The elemental analysis took the compounds' elemental compositions into consideration.



Scheme 1: Synthetic route for leucine-based sulfamoyl pentanamide derivatives



Scheme 2: Lucine-based Sulfamoyl pentanamide derivatives

Biological Studies

Antimicrobial Activities.

The results in table **1** show that all the target compounds exhibited significant antimicrobial activities. Generally, compounds **5g** exhibited the best antibacterial activities being the only compound that inhibited the growth of all the test bacteria, namely *Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli, Bacillus subtilis* and *Salmonella typhi* while compounds **5c** and **5e** were the best antifungal agents having inhibited the growth of all the test fungi namely *Candida albicans and Aspergillus niger*. Specifically, compounds **5f** (MIC 0.40mg/ml) and **5h** (MIC 0.40gm/ml) were the most potent against *E.coli* while compound **5f**(MIC 0.30mg/ml and 0.40gm/ml) was found to be the most active antibacterial agent against *S.typhi, S.aureus and B.sub* respectively. Novelty was recorded in the antimicrobial studies, it was previously reported that sulfonamides do not inhibit the growth of *Pseudomonas aeruginosa* a recalcitrant bacterium[28-31], however, compounds **5a** (MIC 0.60mg/ml) and **5g**(MIC 0.70mg/ml) exhibited a significant inhibitory activities against *Pseudomonas aeruginosa* and this could be attributed to synergism in microbial antagonism arising from the combination of sulfonamide, carboxamide and leucine moieties[32] in a single drug compound. The antifungal studies revealed that *Aspergillus niger* resisted many of the target compounds because sulfonamides scarcely inhibit the growth of *Aspergillus niger* [33,34], nevertheless, compounds **5c** (MIC 0.70mg/ml) and **5e** (MIC 0.50mg/ml) displayed considerable antifungal activities against the recalcitrant fungus. Similarly, compound **5a**(MIC 0.70mg/ml) was found to be the most potent antifungal agent against *Candida albican.*

The antimicrobial mechanism of sulfonamides has shown that they imitate the substrate para-aminobenzoic acid (PABA), which bacteria utilize to synthesis folic acid, hence engaging in competitive inhibition. Bacteria cannot properly synthesis folic acid when they absorb

sulfonamides in place of PABA, which interferes with vital metabolic processes. Certain amino acids and nucleic acids (DNA and RNA) cannot be produced without folic acid. Consequently, sulfonamides stop bacteria from growing and eventually kill them by blocking the production of folic acid. Interestingly, sulfonamides are known to have selective toxicity, which means that while they primarily affect bacterial cells, they seldom affect human cells at all. This is due to the fact that folic acid is derived from food rather than being synthesized by human body. Thus, sulfonamides have no effect on the synthesis of folic acid in human cells. Furthermore, owing to their broad-spectrum activity, sulfonamides have the ability to effectively combat a broad spectrum of bacteria, which makes them useful in the treatment of a number of diseases. However, the specific type of bacteria and their sensitivity to sulfonamide drugs determine how successful the treatments are.[28,35]

The structure activity relationship (SAR) study of the compounds for antimicrobial activity showed that both *p*-toluenesulfonamide and benzenesulfonamide derivatives possess significant antimicrobial activity. This underscores the potency of sulfonamide moiety as an antimicrobial agent. However, compounds bearing *p*-toluenesulfonamide moiety (**5a**, **5c, 5e** and **5g**) displayed broader spectrum of antimicrobial activity. This may be attributed to the presence of an electron-donating methyl group at position 4 of the phenyl ring of *p*-toluenesulfonamide moiety which gives it a closer structural resemblance to *p*-aminobenzoic acid (PABA), a compound required by bacteria for the synthesis of folic acid, and enables it to mimick PABA better than benzenesulfonamide analogues. Furthermore, the presence of *p*-toluenesulfonamide moiety improved antimicrobial potency of the compounds containing it as this moiety was found to be the only moiety common to the compounds (**5a** and **5g**) that inhibited the recalcitrant bacterium *Pseudomonas aeruginosa* known for its resistance to sulfonamide[28]. Amongst these compounds containing *p*-toluenesulfonamide moiety, the introduction of diaminopyrimidine ring (**5g**) further broadened the antibacterial activity as compound **5g** was the only compound that inhibited the growth of all the bacteria used in the antibacterial evaluation. Amongst the benzenesulfonamide analogues (**5b**, **5d**, **5f** and **5h**), the presence of aminopyridine ring (**5f**) improved the antimicrobial potency as **5f** exhibited the best MIC (≤0.40 mg/ml), almost comparable to ofloxacin.

Table 1: Minimum inhibitory concentration (mg/ml)

Sample no	*E.coli*	*S.typhi*	*S.aureus*	*B. sub*	*Ps.aerug*	*C.albicans*	*A. niger*
5a	0.90	0.80	-	0.80	0.60	0.70	-
5b	0.70	0.70	0.90	0.60	-	-	-
5c	0.70	1.00	0.90	0.60	-	0.90	0.70
5d	0.70	0.60	0.60	0.60	-	-	-
5e	0.80	1.00	0.90	0.60	-	0.90	0.50
5f	0.40	0.30	0.30	0.40	-	-	-
5g	0.80	0.90	0.50	0.50	0.70	0.80	-
5h	0.40	0.50	0.50	0.50	-	-	-
Ofloxacin	0.05	0.05	0.01	0.02	0.03	-	-
Fluconazole	-	-	-	-	-	0.02	0.05

Key: - implies no activity. Ofloxacin was the antibacterial reference drug and Fluconazole was the antifungal standard drug used.

Antioxidant Activities

The antioxidant activity of substances can be classified as weak (IC50 = 250–500 µg/ml), moderate (IC50 = 101–150 µg/ml), extremely strong (IC50 <50 µg/ml), and strong (IC50 = 50–100 µg/ml), according to Setha et al.[36] Table 2 illustrates this concept, demonstrating that every molecule had potent antioxidant properties that allowed it to either stop or slow the development of oxidative stress and the illnesses it causes. The compounds 5g (IC50 1.174µg/ml) and 5h (IC50 1.172µg/ml) demonstrated antioxidant properties at a concentration of 200µg/ml, which was equivalent to ascorbic acid (IC50 1.000µg/ml). It is worthy to note that lower IC_{50} value indicates better antioxidant potential and based on that principle, compound **5h** having the lowest IC_{50} value of 1.172µg/ml was found to be the best antioxidant agent synthesized. Similar compounds exhibited considerable antioxidant activities.[37] The implication is that compound **5h** can serve as an antioxidant agent comparable with ascorbic acid. Stable DPPH free radicals have the ability to react with compounds that donate hydrogen atoms and therefore this assay is always employed in the measurement of the reducing ability of antioxidants towards stable DPPH free radicals. Beyond scavenging of free radicals, sulfonamides have been found to activate NRF2 an endogenous antioxidant[18] and the use of amino acids as precursors are likely to enhance their antioxidant activities.[38]

The SAR study of the compounds (**5a-5h**) as antioxidant agents, revealed that compounds containing benzenesulfonamide moiety (**5b**, **5d, 5f** and **5h**) possess better antioxidant properties that *p*-toluenesulfonamide derivatives based on the IC_{50} values. This may be attributed to the observation that the addition of electron donating group ($-CH_3$) to the benzene ring decreased the antioxidant activities of the compounds. The introduction of aminopyrimidine ring to both *p*-toluenesulfonamide and benzenesulfonamide derivatives resulted in improved antioxidant activity as the analogues bearing aminopyrimidine ring (**5g** and **5h**) exhibited the best antioxidant activities comparable to ascorbic acid.

Table 2: *In vitro* antioxidant (% scavenging activity)

Sample no	% inhibition at 200 µg/ml	% inhibition at 100 µg/ml	% inhibition at 50 µg/ml	IC_{50} (µg/ml)
5a	74.79	72.22	73.44	1.352
5b	52.38	50.12	55.49	1.928
5c	29.67	45.85	15.57	3.939
5d	88.10	40.66	39.68	1.754
5e	56.72	38.83	26.80	2.133
5f	24.91	63.98	83.15	**1.825**
5g	85.60	87.06	80.04	1.174
5h	85.58	87.08	80.06	1.172
Ascorbic acid	96.83	97.68	97.31	1.000

Key: The standard antioxidant drug = ascorbic acid.

Prediction of Drug-likeness and Oral Bioavailability

Table 3 shows the target compounds' physicochemical characteristics. Lipinski's rule of five[39] stipulates that a drug molecule is considered drug-like if it meets specific requirements, including lipophilicity (logP) < 5, molecular weight (MW) ≤ 500, number of hydrogen bond donor (HBD) ≤ 5, and number of hydrogen bond acceptor (HBA)

≤ 10. Furthermore, in accordance with Verber's principle, drug molecules with a topological polar surface area (TPSA) of ≤140 Å2 can enter mammalian cells and demonstrate good oral bioavailability, while TPSA ≤ 90 Å2 indicates that the drug molecule can also enter the blood-brain barrier (BBB) and the central nervous system (CNS). This constitutes a surrogate property for cell permeability. Moreover, it was shown that NRB ≤10 is necessary for adequate oral bioavailability.[40,41] All the compounds demonstrated strong oral bioavailability and outstanding drug-likeness, in accordance with the aforementioned guiding criteria. While compounds 5a–h have high oral bioavailability and can permeate cells, none of the compounds can cross the blood-brain barriers or the central nervous system.

Table 3: Physicochemical properties of compounds

Sample no	HBA	HBD	NRB	logP(o/w)	SlogP	TPSA	MW	Lip violation
5a	4	1	7	1.90	1.43	97.54	326.41	0
5b	4	1	7	1.60	1.12	97.54	312.39	0
5c	4	2	8	3.23	3.17	109.57	417.52	0
5d	4	2	8	2.94	2.86	109.57	403.50	0
5e	5	2	8	2.00	2.56	122.46	418.51	0
5f	5	2	8	1.70	2.25	122.46	404.49	0
5g	6	3	9	0.99	1.54	161.37	434.51	0
5h	6	3	9	0.69	1.23	161.37	420.49	0

Molecular Docking

In recent years, molecular docking has been widely used to investigate the drug's ability of molecules on a global basis, as it seeks to explain several modules underlying Protein-ligand interaction, which corroborate the process of proteins interacting with ligands to form stable complexes with biologically significant functions.[41] Protein-ligand complexes, on the other hand, play an important role in a wide range of biological activities. Ligands are bound to proteins by intermolecular interactions such as ionic bonds, hydrogen bonds, and van der Waals forces. As a result, particular protein-ligand interaction types are essential to understand protein function. As a result, eight synthesized compounds were investigated and compared by docking with three disease conditions namely; bacterial infections (antibacterial activity), fungal infections (antifungal activity) and oxidative stress (antioxidant activity) are to be studied and the following drug targets were selected for molecular docking studies. The target receptor for antibacterial is *Escherichia coli* DNA gyrase in complex with 1-ethyl-3-[8-methyl-5-(2-methyl-pyridin-4-yl)-isoquinolin-3yl]urea (PDB code: **5MMN**); antifungal is urate oxidase from *Aspergillus flavus* complexed with uracil (PDB code: **1WS3**), and for antioxidant is human peroxiredoxin 5 (PDB code: **1HD2).** These target receptors were chosen based on the protein data's predictability in light of being possibly effective for binding to the suggested treatment, as each of the proteins has several active sites. Additionally, examinations between the ligands and proteins were examined in order to suggest or postulate which matches better for compatibility in terms of combating these disease conditions.

Substantially, the antifungal target receptors revealed very important biological properties upon interacting with the eight synthesized compounds, thus implying promising compatibilities. As presented in **table 4** and **figure S1**, the significant binding affinities ranged from -6.9kcal/mol to -

8.0 kcal/mol. As a result, **5g**@1WS3 calculated the best binding affinity of -8.0 kcal/mol, as further validated by the conventional hydrogen bonds incorporated as amino acid residues (ARG C: 108, THR C: 107, CYS C: 103). This was followed by **5f**@1WS3 and **5c**@1WS3, which had a comparable binding affinity of -7.8 kcal/mol, as well as **5e**@1WS3 and **5h**@1WS3, which had a binding affinity of -7.7 kcal/mol. Very interesting information noticed in the said interactions, is the fact that all interactions displayed similar conventional hydrogen bonds embedded as arginine, tryptophan, and threonine. Fascinatingly, the superiority of the investigated interactions can be derived in the following order: **5g**@1WS3 > **5c**@1WS3 > **5f**@1WS3 > **5e**@1WS3 > **5h**@1WS3 > **5d**@1WS3 > **5a**@1WS3 > **5b**@1WS3. On the other hand, the antibacterial potentials of the synthesized compounds were examined to suggest very minimal efficiency upon interaction with the antibacterial target receptors. As evident from **table 4** and **figure S2**, it can be observed that **5h**@5MMN calculated the most significant binding affinity of -6.9 kcal/mol, thus elucidating the conventional hydrogen bonds to be embedded as glutamine and arginine. Additionally, **5g**@5MMN further demonstrated GLY A:77, GLU A:50 and ASN A:46 to be its key pockets for the antibacterial studies, as it also calculated -6.6 kcal/mol as its binding affinity. Interestingly, **5f**@5MMN and **5a**@5MMN revealed similar binding affinity of -6.3 kcal/mol. Overall analysis of the antifungal investigation, shows that the binding affinity ranged from -5.6 kcal/mol to -6.9 kcal/mol. Contrary to the aforementioned disease conditions (fungal and bacterial infections) discussed, the antioxidant potentials of the synthesized molecules as evident in **table 4** and **figure S3**, suggest that only **5a**@1HD2, **5c**@1HD2, **5d**@1HD2, and **5h**@1HD2 revealed favourable conventional hydrogen bonds hence calculating relatively weak binding affinities of -3.9 kcal/mol, -4.2 kcal/mol, -4.0 kcal/mol, and -4.2 kcal/mol.

Summarily, from this investigation, it can be postulated that the eight synthesized compounds were found to elucidate efficient antifungal and antibacterial potentials, as recorded based on their electrostatic forces, electrodynamic forces, and binding affinities, which establishes the interactions formed when atoms of various particles approach into close proximity to one another and alter one another's reactivity. However, most of the compounds were found to possess comparatively significant antibacterial, antifungal and antioxidant potentials. Thus, implying them to be potential compounds for the treatment of both bacterial and fungal infections and less in considering antioxidant potentials. Generally, compounds bearing sulfonamide and carboxamide functionalities have been found to exhibit broad spectrum of biological activities[43,44], and molecular docking has been very useful in ascertaining their suitability as drug candidates [45-49].

CONCLUSION

In this paper, we have reported a facile and efficient approach to the synthesis of leucine-based sulfamoyl pentanamide derivatives. Generally speaking, the *in vitro* biological studies revealed that compounds **5a, 5f, 5g and 5h** were the best antibacterial agents according to their minimum inhibitory concentrations, compounds **5a, 5c, 5e** and **5g** exhibited the best antifungal activities while compounds **5g** and **5h** were found to be the best antioxidants. Furthermore, the molecular docking studies showed the binding affinity of the compounds mentioned above in the order **5h** > 5g > **5f** > 5a for antibacterial potential, 5g > 5c > 5e > 5a for antifungal potential and 5g > 5g for antioxidant potentials. In the next phase of this research, in vitro enzyme assay, in vivo analysis and other relevant assessments would be included for more comprehensive understanding of the biological activities of target compounds. The physicochemical parameters evaluations confirmed all the compounds to be likely drugs that would not pose oral bioavailability problems having satisfied Lipinski's rule of five. All the target compounds are potential antimicrobial and antioxidant agents.

Table 4: Antifungal, antibacterial and antioxidant molecular docking analysis

Compounds	Best pose (Binding affinity (Kcal/mol)			Nature of interactions		
	Antifungal	antibacterial	antioxidant	antifungal	antibacterial	antioxidant
5a	-7.2	-6.3	-3.9	THR C:107, TRP C:106	A:ARG:76, A:GLY770	A:BEZ:201, A:ILE:119
5b	-6.9	-5.6	-0.0	TRP C:106, THR C:107	A:ASN:46, A:ARG:76	Unfavourable bonds
5c	-7.8	-6.0	-4.2	TRP C:106, THR C:107, ARG C:108	A:THR:46	BEZ A:201, PRO A:45, LEU A:116
5d	-7.4	-6.1	-4.0	VAL C:73, MET C:32	A:ARG:76, A:GLU:50, A:ASP:73	A:ILE:119, A:BEZ:201
5e	-7.7	-6.1	-3.8	ARG C:128, GLU C:31, THR C:74	A:GLY:77, A:GLU:50, A:ASN:46	Unfavourable bonds
5f	-7.8	-6.3	-4.2	TRP C:106, VAL C:29, ARG C:108	A:GLY:77, A:GLU:50, A:ASN:46	Unfavourable bonds
5g	-8.0	-6.6	-4.4	ARG C: 108, THR C: 107, CYS C: 103	A:GLU:50, A:ASN:46	Unfavourable bonds
5h	-7.7	-6.9	-4.2	THR A: 143, ARG C:74	A:GLU:50, A:ARG:136,A:ARG:76	A:PHE:43, A:ILE:119

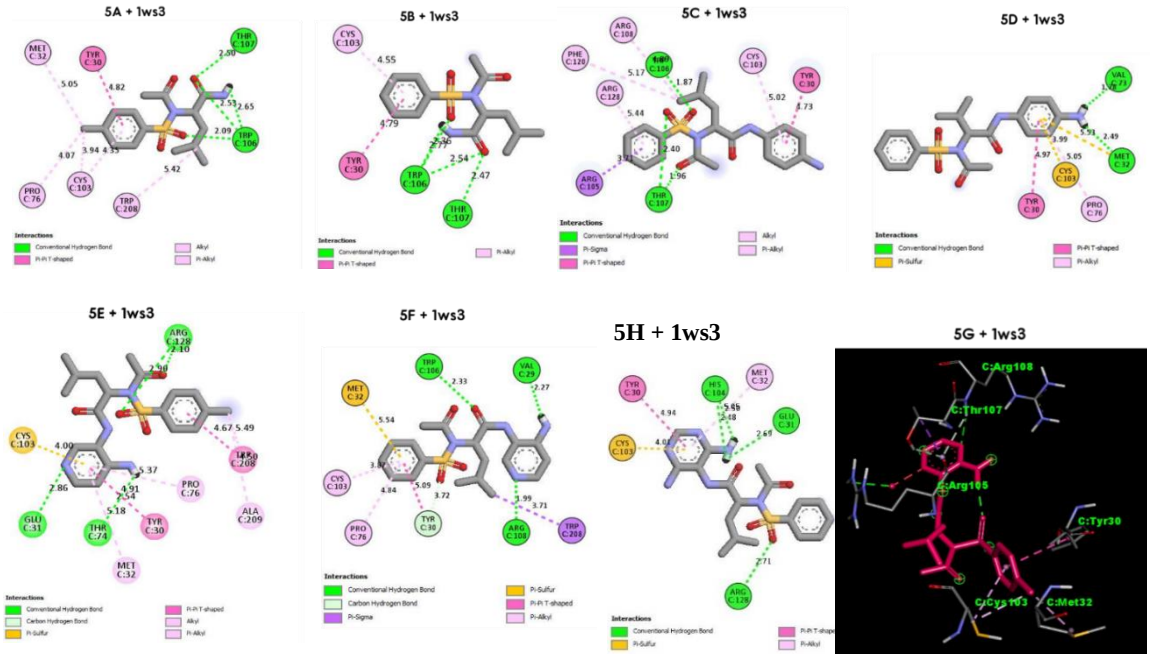


Figure S1: 3D visualization of the antifungal interaction using 1WS3

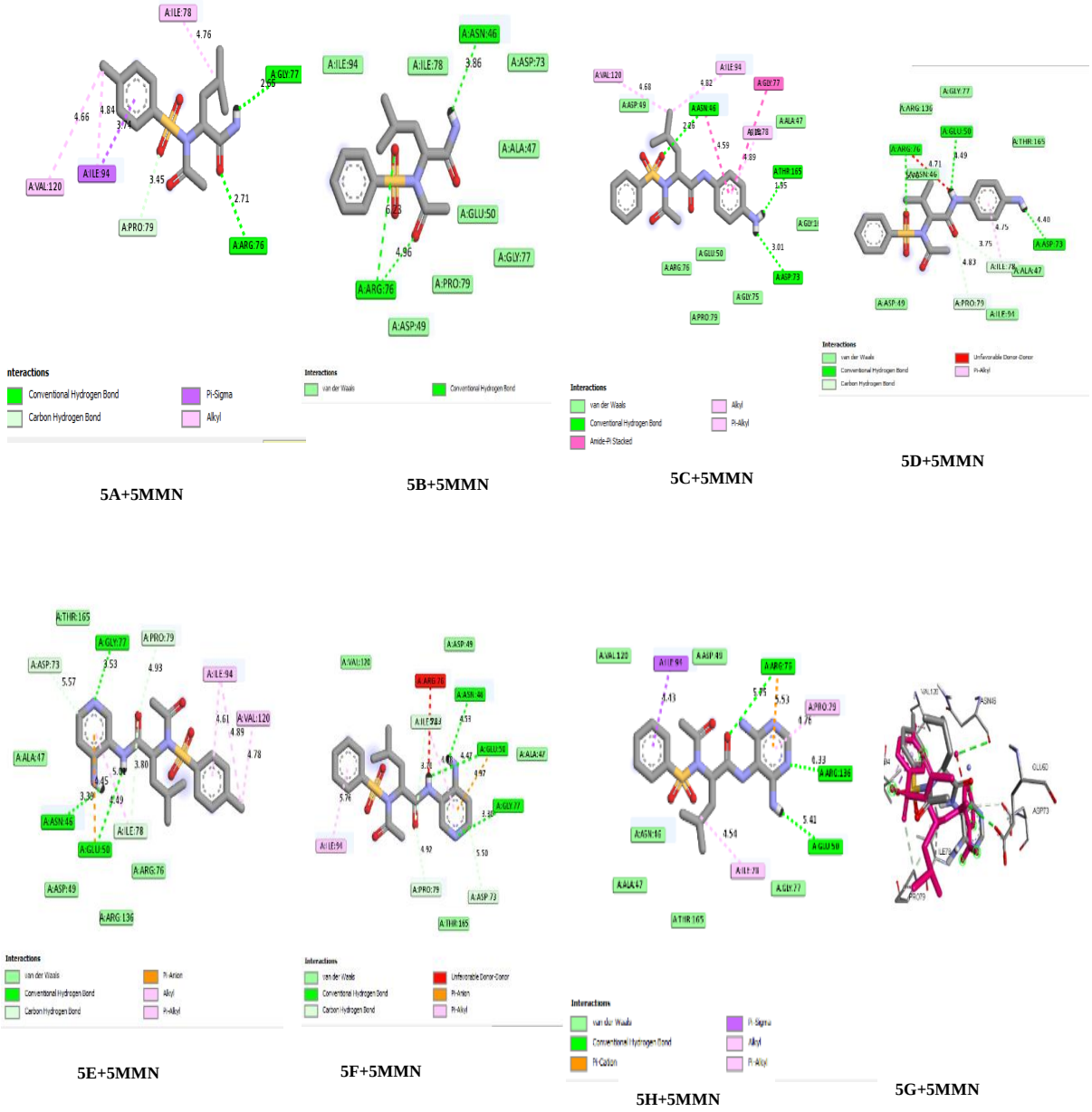


Figure S2: 3D visualization of the antibacterial interactions using 5MMN

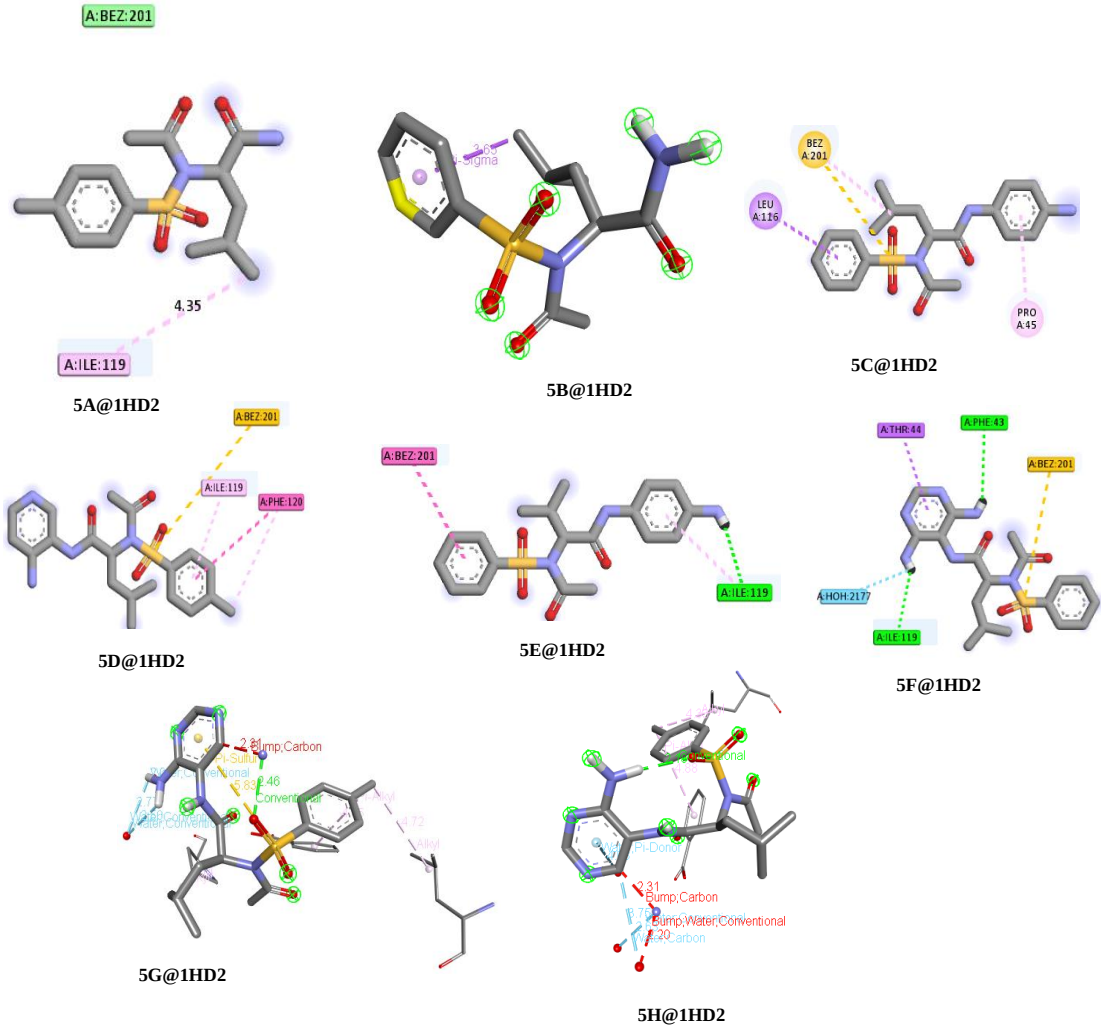


Figure S3: 3D visualization of the antioxidant interactions using 1WS3

ACKNOWLEDGEMENT

Mrs. Ekianinima Okonny-Egbujor is acknowledged for her support during this work.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

FINANCIAL DISCLOSURE

The authors declare that no financial aid was received from any external body.

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تصميم، تخليق، ربط جزيئي وتقييم بيولوجي لمشتقات جديدة من السلفامويل بنتاميدات المستخلصة من الليوسين كعوامل مضادة للميكروبات ومضادة للأكسدة

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ملخص

غالبية الأمراض التي تتوسطها العوامل الميكروبية والإجهاد التأكسدي مقلقة للغاية. تتجلى الحاجة إلى تطوير أدوية جديدة من خلال حقيقة أن مقاومة المضادات الميكروبية في تزايد وأن العديد من الأدوية المضادة للأكسدة الحالية توفر تخفيفًا عرضيًا ضئيلًا فقط. كان الهدف من هذا العمل هو تخليق البنتاميدات السلفامويلية المشتقة من الليوسين ذات الأنشطة المضادة للأكسدة والمضادة للميكروبات. تم تخليق أميدات البنتانامايد السلفامويل القائمة على الليوسين الجديدة وتم استخدام التحليل العنصري، و H-NMR1، و C-NMR13، و FTIRلتوضيح هياكلها. خضعوا لتحقيقات ربط جزيئي بالإضافة إلى تحليلات النشاط المضاد للأكسدة والمضاد للميكروبات في المختبر. المركب 5 a(0.60 جم/مل) كان المركب الأكثر نشاطًا ضد Pseudomonas aeroginosa، بينما كان المركب 5 f(0.30−0.40 ملغ/مل) هو الأكثر فعالية كمضاد للبكتيريا ضد E. Coli و S. typhi و S. aureus و B. subtilis. المركبات ذات أفضل نشاط مضاد للفطريات ضد C. albican و A. niger، على التوالي، كانت 5 0.80) gملغ/مل (و 5 e(0.50 ملغ/مل). في تقييم النشاط المضاد للأكسدة في المختبر، أظهرت المركبات (1.174µg/ml) 5g و5 (1.172µg/ml) hنشاطًا مضادًا للأكسدة مشابهًا لحمض الأسكوربيك (IC50 1.001µg/ml).بالإضافة إلى ذلك، فإن معظم المركبات المستهدفة تتمتع بقدرات قوية نسبيًا مضادة للبكتيريا والفطريات ومضادة للأكسدة، وفقًا لدراسة الربط الجزيئي. نظرًا لأن كل مركب مستهدف امتثل لقواعد ليبينسكي الخمسة، فمن المحتمل أن يتم استخدامه كمرشحين علاجيين لعلاج الأمراض المرتبطة بالإجهاد التأكسدي والعدوى الميكروبية.

الكلمات الدالة: البنتاميدات؛ الليوسين؛ السلفونااميدات؛ مضاد للميكروبات؛ مضاد للأكسدة؛ التخليق.

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تاريخ استلام البحث 2024/03/08 وتاريخ قبوله للنشر 2024/05/18.