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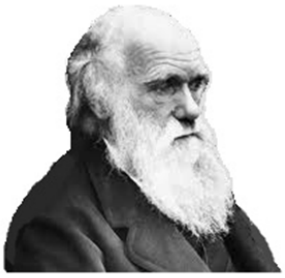

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In silico Prediction of Anti-bacterial Potentials of Some Synthesized Sulfonamide Compounds

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ABSTRACT

Overuse and misuse of antibiotics as well as social and economic factors have accelerated the spread of antibiotic-resistant bacteria, making drug treatment ineffective. This study aimed at screening some sulphonamide compounds in other to recommend new anti-bacteria drugs with better efficacy and lower toxicity. The ten (10) sulfonamide compounds were screened for their antibacterial activities against medically important gram (-) and gram (+) bacterial strains, namely, *Escherichia coli* (*E. coli)*, *Pseudomonas aeruginosa* (*P. aeruginosa*), *Bacillus cereus* (*B. cereus*) and *Staphylococcus aureus (Staph aureus)*. The antibacterial activities have been determined by *in silico* molecular docking of the ten (10) sulphonamide compounds on the targeted site of the organism`s protein. Among the tested compounds, it was found that ciprofloxacin was the most potent against *E. coli* with the highest binding affinity (-13.17 kcal/mol), while compounds; 3-(3*H*-indol-3-yl)-2-[(phenylsulfonyl)amino] propanoic acid (1906; -12.93 kcak/mol), {[(4-methylphenyl)sulfonyl]amino}-3-methylbutanoic acid (1909; -12.83 kcal/mol) and 3-(4-hydroxyphenyl)-2-[(phenylsulfonyl)amino]propanoic acid (1902; -12.48 kcal/mol) gave better binding scores than ciprofloxacin (-12.25 kcal/mol) with *Pseudomonas aeruginosa.* On the binding with *Bacillus aereus* protein, 2-[(phenylsulfonyl)amino]-3-sulfanylpropanoic acid (1904; -15.54 kcal/mol), 3-(4-hydroxyphenyl)-2-[(phenylsulfonyl)amino] propanoic acid (1902; -15.46 kcal/mol) and 3-(4-hydroxyphenyl)-2-{[(4methylphenyl)sulfonyl]anino} propanoic acid (1901; -15.45 kcal/mol), showed better binding affinity than cipro (-15.36 kcal/mol), while ciprofloxacin gave the highest binding affinity (-12.08 kcal/mol) with *Staphylococcus aureus* protein (3G75) when compared to the analysed sulfonamide compounds. The analysed 10 sulfonamide compounds showed potential drug candidates by obeying all the physicochemical parameters that qualifies a compound to be used as drug and therefore, can be clinically use for the treatment of diseases caused by the named organisms.

***Keywords*:** sulphonamide, anti-bacteria, drugs, physicochemical, ciprofloxacin

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1. INTRODUCTION

Sulfonamides, a widely used anti-microbial agents[1] have been in clinical use to treat various kinds of ill health. Sulfonamide has been the basis of several groups of drugs. The original antibacterial drugs called sulfa drugs are synthetic compounds that contain the sulfonamide functionality[2]. They are widely used in medicine because of their low cost, low toxicity and excellent biological activities[3]. Apart from their uses as antibacterial agents, sulfonamides are useful in other medicinal areas as clinical relevant molecules[4]. For instance, recent drugs with sulfonamide structural skeleton are used as anti-tumor[5], anti-thyroid[6] and anti inflammatory agent.[7-8] Other important uses of sulphonamides include as anti-hyperglycemic agents,[9] diuretic agent,[10] anti-convulscant,[11-12] anti-cancer,[13-14] anti-retroviral,[15] anti-oxidant,[16] anti-malaria drugs,[17] anti-tuberculosis,[18] anti-viral[19] among others.

In addition some sulfonamides derived from natural products have been found to contain some relevant biological properties, for instance, a mixture isolated from cashew nuts shell has also been reported to possess fascinating anti-bacterial activities[20]. Also sildenafil a plant preservative isolated from fruits and vegetable was found to be promising agent used in the treatment of erectile dysfunction in man[21].

Apart from medicinal properties, sulfonamide has been reported to possess good herbicidal[22] properties. Another interesting property of sulfonamides is their corrosive inhibitory properties as reported by some reseachers[23-24] that sulfonamides have been found to be effective and harmless inhibitors for the corrosion of mild steel in acidic medium.

Sulfonamides have the potential to cause a variety of allergic reactions, though it has been argued that the terms 'sulfonamide allergy' or 'sulfa allergy' are misleading, and should be replaced by a reference to a specific sulfonamide drug[26]. Antibacterial resistance is a global public health problem that has hampered the effective prevention and treatment of wide range of bacterial diseases.[26]

Antibacterial resistance is aggravated by the misuse or overuse of antibacterial agents in people and animal.[27] Some bacteria are multidrug resistant and the major examples are *Staphylococcus aureus* and *Escherichia coli*.[28] One of the WHO strategies for the control of antimicrobial resistance is to encourage investment in new medicine research and development.[29] In accordance with this recommendation many research team are engrossed in the synthesis of new antimicrobial drug with better efficacy and lower toxicity. Due to the various hazardous effects of some deadly microbes, there have been need for the discovery of new antimicrobial drugs.

2. MATERIALS AND METHODS

2. 1. Sulfonamide compounds for molecular docking

The synthesized sulfonamide compounds were retrieved from published journals and Chem Draw soft ware was used for the drawing of the structures.

2. 2. Prediction of physicochemical properties

The drug likeness properties were predicted using molecular operating environment (MOE). This is a drug discovery software platform used for structure-based design for visualization, modelling and simulations, as well as methodology development.[30]

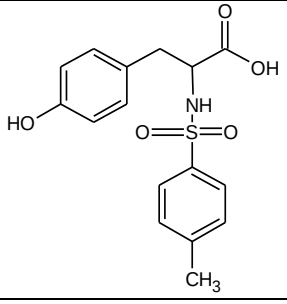
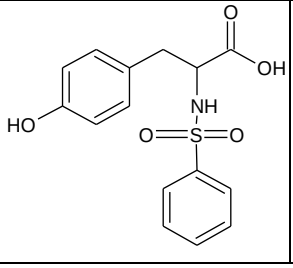
2. 3. Molecular docking studies

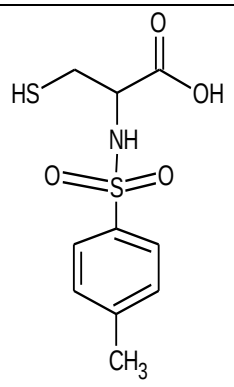
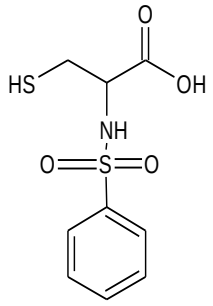
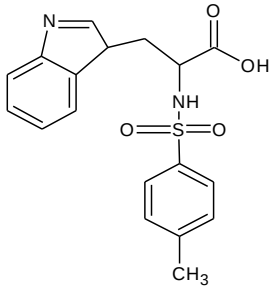
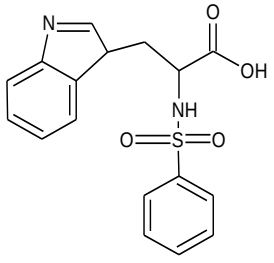
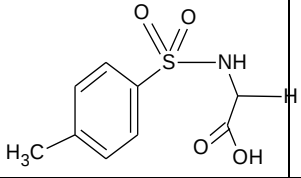
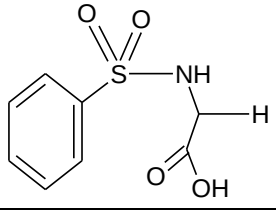
The 3-Dimensional crystal structures of the proteins used in this study include: *Staphylococcus aureus* Gyrase (PDB ID: 3G75);[31] *Bacillus cereus* (PDB ID: 3FCE);[32] *Pseudomonas aeruginosa* (PDB ID: 3P3E[33] and *E. coli*, (PDB ID: 5MMN). They were retrieved from protein databank (http://www.rcsb.org) with their co-crystallized ligands, which were used to validate the docking protocols for the binding sites. The proteins were prepared by removing water of crystallization and unwanted protein chains in Discovery studio. Molecular Operating Environment (MOE, 2014) was employed in the validation of the docking protocols, docking studies and visualization of the docking results. The force field MMFF94x in MOE was used to minimize the energy of the structures.

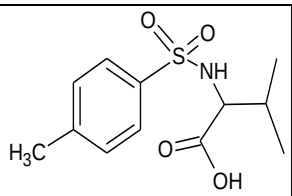
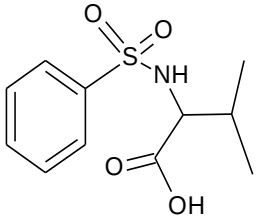
3. RESULTS AND DISCUSSION

The sulfonamide compounds under study were five benzene sulfonamides and five *para* toluene sulfonamides that has been synthesized and published in the references on the table below (Table 1).

Table 1. Synthesized sulfonamides for *in silico* analysis

Compd NO	Name Compounds	Amino Acids Used	MW	Structure	References
1901	3-(4-hydroxyphenyl)-2-{[(4-methylphenyl)sulfonyl]anino} Propanoic acid	Tyrosine	335.37		34, 35
1902	3-(4-hydroxyphenyl)-2-[(phenylsulfonyl)amino] propanoic acid	Tyrosine	321.35		36

1903	2-{[(4-methylphenyl)sulfonyl] amino}-3-sulfanylpropanoic acid	Cystien	275.34		35
1904	2-[(phenylsulfonyl)amino]-3-sulfanylpropanoic acid	Cystien	261.32		35
1905	3-(3*H*-indol-3-yl)-2-{[(4methylphenyl) sulfonyl]amino}propanoc acid	Tryptophan	358.41		37
1906	3-(3*H*-indol-3-yl)-2-[(phenylsulfonyl)amino] propanoic acid	Tryptophan	344.38		37
1907	2-{[(4-methylphenyl)sulfonyl] Amino} acetic acid	Glycine	229.25		34
1908	[(2-phenylsulfonyl)amino] acetic acid	Glycine	215.23		36

1909	{[(4-methylphenyl)sulfonyl] amino}-3-methylbutanoic acid	Valine	271.33		34
1910	[(2-phenylsulfonyl)amino]-3-methylbutanoic acid	Valine	257.31		36

Compd No = compound number, MW = Molecular weight

3. 2. In silico prediction of physicochemical properties of the sulfonamides for drug-likeness

The desirable properties which small molecules were required to possess in order to produce good lead compounds were all observed in the ten analysed sulphonamide compounds. Lipinski's Rule of Five (Ro5) provides the basic assessment for the development of orally bioavailable drug lead. Lipinski Ro5 states that for a drug candidate to be bioavailable in the systemmic circulation after oral administration, octanol-water partition coefficient (log P) ≤ 5; hydrogen bond donor (HBD) ≤ 5 taken as equivalent to the number of –OH and –NH groups; hydrogen bond acceptor (HBA) ≤ 10 taken as equivalent to the number of oxygen and nitrogen atoms and molecular weight (MW) ≤ 500. A violation of more than one of this physicochemical parameter disqualifies a compound from being a potential drug candidate. Lipophilicity (log P) is a property that has a major effect on solubility, absorption, distribution, metabolism, and excretion properties as well as pharmacological activity.[38] When log P is higher than the upper limit, the drug molecule will have low solubility whereas in lower log P, the drug has difficulty to penetrate the lipid membranes.[39] There should be balance between the aqueous solubility of a compound and its ability to diffuse passively through the different biological barriers for a good oral bioavailability.[40] Veber and co-workers also discovered that the number of rotatable bonds is an important parameter with seven seen to be optimal for oral bioavailability.[41] TPSA is another useful parameter, and a molecule with a TPSA < 140 $Å^2$ can easily permeate the cells. From the foregoing, all the compounds seem to have a good oral bioavailability profiles (Table 2) and as such can be use as candidate drugs.

Table 2. Drug-likeness parameters

Compd	MW	#Rotatable bonds	#H-bond acceptors	#H-bond donors	MR	TPSA	iLOGP	Lipinski #violations
1901	335.37	6	6	3	85.2	112.08	1.07	0
1902	321.35	6	6	3	80.23	112.08	0.9	0

1903	275.34	5	5	2	66.62	130.65	0.99	0
1904	261.32	5	5	2	61.65	130.65	1.15	0
1905	358.41	6	6	2	98.4	104.21	1.8	0
1906	344.38	6	6	2	93.44	104.21	1.47	0
1907	229.25	4	5	2	53.88	91.85	0.78	0
1908	215.23	4	5	2	48.92	91.85	0.97	0
1909	271.33	5	5	2	68.3	91.85	1.39	0
1910	257.31	5	5	2	63.34	91.85	1.47	0

Compd: compound; MW: molecular weight; TPSA: topological polar surface area; MR: molar refractivity; iLOGP: Partition coefficient

3. 3. Validation of the docking procedure of the sulphonamides with bacteria organisms

Molecular operating environment (MOE) was used for docking studies. In order to validate the accuracy of MOE-Dock program, the retrieved co-crystallised ligand was docked into the active sites of 3P3E containing the co-crystallized ligand (Fig. 1). The compounds fitted very well in the binding cavity as the co-crystallised ligand. In this study, RMSD value was found as 1.8032 Å showing that our docking method is valid for the studied inhibitors which make the MOE-Dock method reliable for docking of these compounds. In Figure 1, the structure with grey colour represents the co-crystallised ligand while the structures with orange colour represent the docked ligand. The docked ligand (orange) superimposed on the co-crystallized ligand in the same active binding sites.

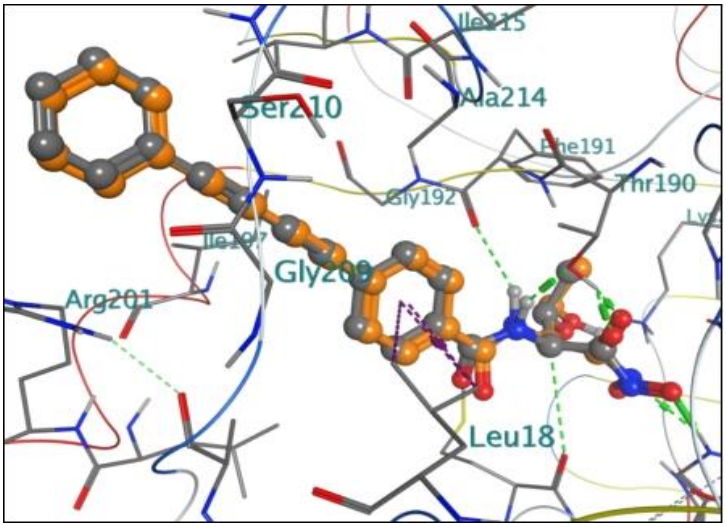


Figure 1. Validation of docking protocol using 3P3E; (grey compound = co-crystalized ligand; orange compound = docked ligand). (RMSD = 0.81Å)

3. 4. Molecular docking results

The 10 synthesized compounds were docked into the active binding sites of; 5MMN, 3P3E, 3FCE and 3G75 with their respective binding affinity in kcal/mol as shown in Table 3. The compounds showed appreciable binding affinity with all the drug targets used comparable to the binding affinity of the standard drug (Table 3).

Table 3. Binding free energy (ΔG, kcal/mol) of the compounds with the bacteria Organisms

	Gram-negative bacteria		Gram-positive bacteria	
Compd	***E. coli*** **5MMN**	***Pseudomonas aeruginosa*** **3P3E**	***Bacillus cereus*** **3FCE**	***Staphylococcu saureus*** **3G75**
1901	-10.81	-12.18	-16.45	-11.22
1902	-11.58	-12.48	-15.46	-11.59
1903	-9.92	-10.90	-13.19	-10.38
1904	-9.89	-10.61	-15.54	-10.18
1905	-10.71	-12.21	-14.27	-11.00
1906	-9.80	-12.93	-13.42	-10.83
1907	-10.24	-10.74	-13.81	-11.85
1908	-10.18	-11.73	-13.05	-10.11
1909	-9.64	-12.83	-13.41	-10.06
1910	-10.15	-10.41	-13.42	-11.23
Ciprofloxacin	-13.17	-12.25	-15.36	-12.08
Native ligand	-10.67	-12.06	ND	-10.94

Compd: compound; ND: No docking.

Compound 1902 gave the highest binding energy with the drug target, 5MMN. Therefore, we further analysed the binding modes of 1902 with the target (Figure 2) with a view to understanding the nature and type of interaction involved in the protein–ligand complexes. Figure 2 is the binding pose in the active binding sites of the receptor, 5MMN. There are various chemical interactions observed. There were various H-bondings through H-donor and H-acceptor interactions. The N-4 atom of 1902, through H-donor interaction, combined with ASN through an intermolecular distance of 3.03Å and energy of -1.9 kcal/mol. Other H-donor interactions include GLU 50 (2.88Å, -6.6 kcal/mol), ASP 73 (3.37Å, -1.0 cal/mol). though H-acceptor, interacted with THR 165 and ALA 47 respectively. The pi electrons of the aromatic 6-membered ring of compound 1902 interacted with the ILE 78 and PRO 79 respectively (Table 4).

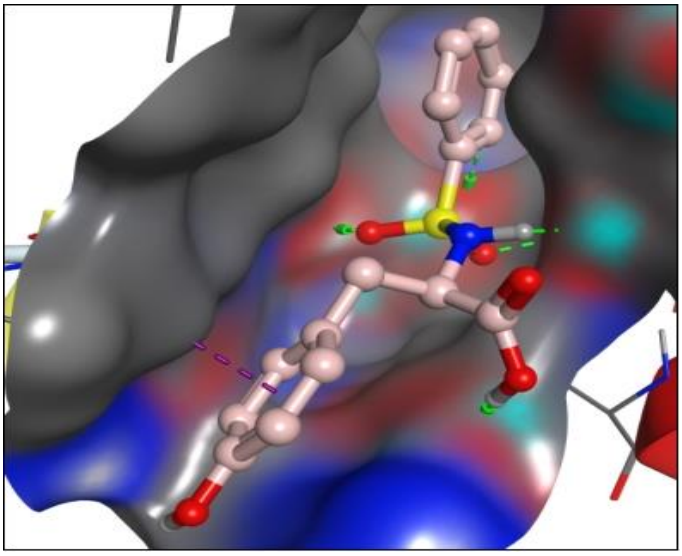


Figure 2. Binding pose of compound 1902 in the binding cavity of 5MMN
(the green dotted lines signify H-bond; purple dotted lines signify H-pi interaction)

Table 4. Chemical interactions of compound 1902 with amino residues of 5MMN

Receptors	Interactions	Distance(Å) E	(kcal/mol)
ASN 46	H-donor	3.03	-1.9
GLU 50	H-donor	2.83	-6.6
ASP 73	H-donor	3.37	-1.0
THR 165	H-acceptor	2.87	-1.3
ALA 47	H-acceptor	3.47	-0.5
ILE 78	pi-H	4.96	-0.2
PRO 79	pi-H	3.92	-0.9

Compound 1907 showed the highest binding affinity with 3G75. The binding pose of this compound in the active binding sites of the receptor is shown in Figure 3. 1907 tightly fitted into the binding cavity of 3G75 where it interacted with the amino acid residues of the receptors. Among these amino acid residues involved in the interactions include THR 173, ASP 81, SER 55 and ILE 86. The detailed interactions are shown in Table 5. Bacterial DNA gyrase is an attractive target for the investigation of new antibacterial agents. ASP 81 has been shown to be a very important amino acid residue in 3G75.[31] 1907 interacted with this important amino acid through H-bonding at a distance of 2.69Å. These effective interactions have potentials of inhibiting the normal biochemical processes of the protein through competitive antagonism.

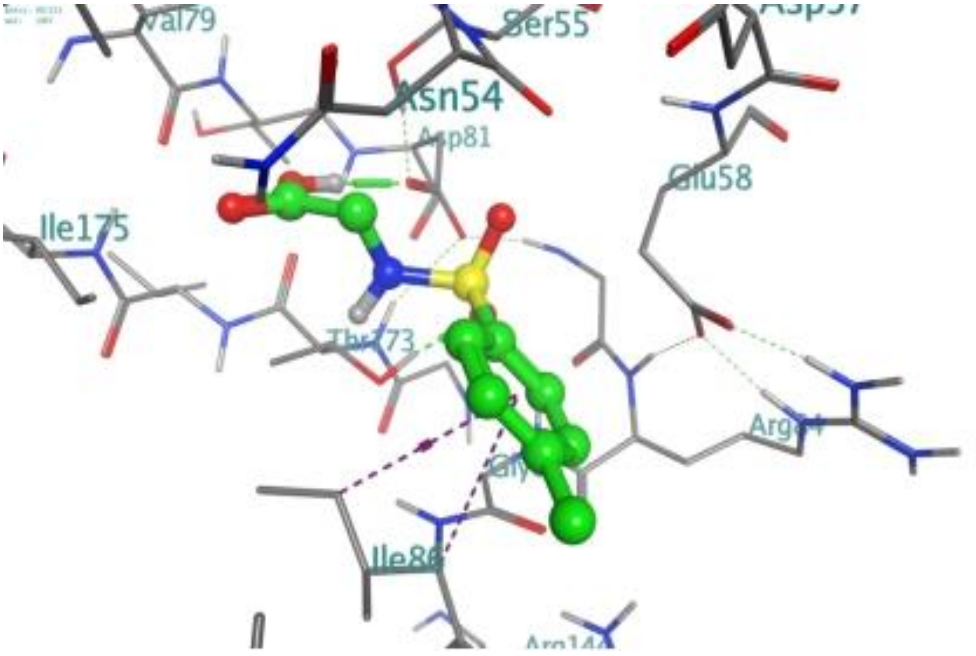


Figure 3. Binding pose of compound 1907 in the binding cavity of 3G75
(the green dotted lines signify H-bond; purple dotted lines signify H-pi interaction)

Table 5. Chemical interactions of compound 1907 with amino acid residues of 3G75

Receptors	Interactions	Distance(Å) E	(kcal/mol)
THR 173	H-donor	3.05	-0.2
ASP 81	H-donor	2.69	-5.9
THR 173	H- acceptor	2.75	-2.1
SER 55	H-acceptor	3.49	-0.3
ILE 86	pi-H	4.25	-0.5
ILE 86	pi-H	4.14	-0.9

Compound 1901 was able to interact with these vital amino acid residues (LYS 492, GLU 298, ARG 397) and others (Fig. 4; Table 6). D-alanylation of lipoteichoic acids modulates the surface charge and ligand binding of the Gram-positive cell wall. Disruption of the bacterial dlt operon involved in teichoic acid alanylation, as well as inhibition of the DltA (D-alanyl carrier protein ligase) protein, has been shown to render the bacterium more susceptible to conventional antibiotics and host defence responses.[32]

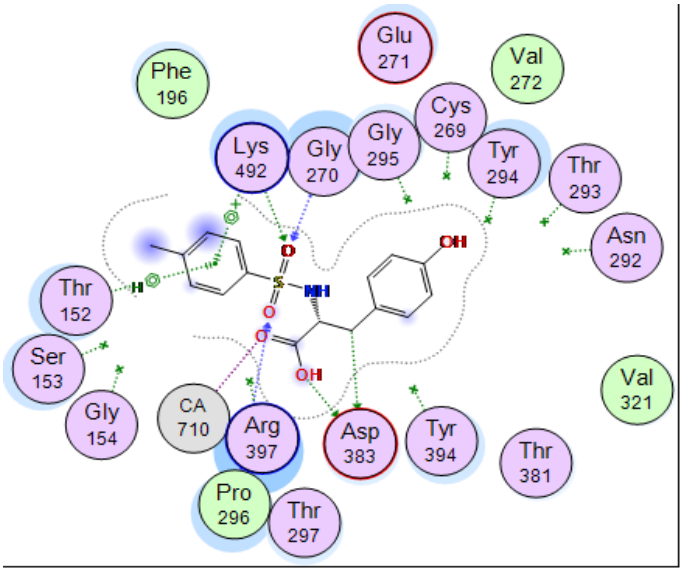


Figure 4. 2D representation of the binding interactions between 1901 and the amino residues of 3FCE

Table 6. Chemical interactions of compound 1901 with amino residues of 3FCE

Receptor	Interaction	Distance (Å)	E (kcal/mol)
ASP 383	H-donor	3.59	-0.4
ASP 383	H-donor	3.65	-0.2
GLY 270	H-acceptor	3.30	-0.2
LYS 492	H-acceptor	2.99	-6.8
PRO 296	H-acceptor	3.37	-0.7
THR 152	pi-H	4.83	-0.3
LYS 492	pi-cation	3.54	-0.3

Figure 5 illustrated the binding pose of 1906 in 3P3E while Figure 6 showed the 2D representation of the binding interactions between 1906 and the amino residues of 3P3E. There are different amino acid residues involved: LEU 18, MET 62, THR 190, PHE 191 and ILE 197. Interaction with pi electrons involved LEU 18 and ILE 197, while other important interactions include H-bonding interactions with PHE 190 (3.3Å); and THR 190 (3.11, 3.64 and 3.11Å) , MET 62 and PHE 191; respectively (Table 7).

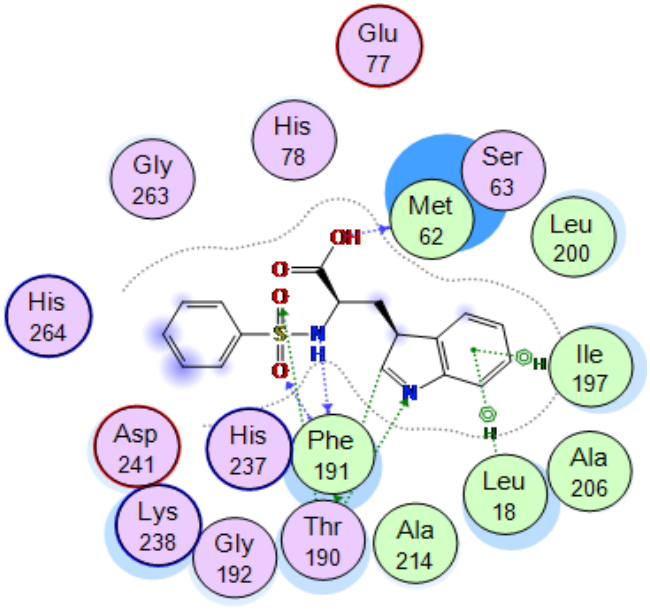


Figure 5. 2D representation of the binding interactions between 1906 and the amino residues of 3P3E

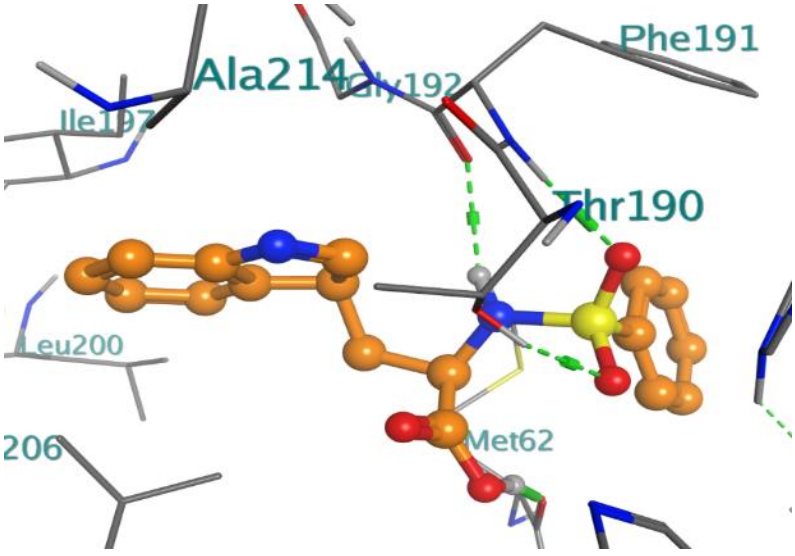


Figure 6. Binding pose of compound 1906 in the binding cavity of 3P3E (the green dotted lines signify H-bond)

Table 7. Chemical interactions of compound 1906 with amino residues of 3P3E

Receptor	Interaction	Distance (Å)	E (kcal/mol)
MET 62	H-donor	2.81	-4.3
PHE 191	H-donor	3.24	-1.1
THR 190	H-donor	3.03	-0.2
THR 190	H-acceptor	3.11	-1.0
PHE 191	H-acceptor	3.33	-1.9
THR 190	H-acceptor	3.64	-0.2
LEU 18	pi-H	4.46	-0.4
ILE 197	pi-H	3.74	-0.2

4. CONCLUSIONS

The 10 synthesized compounds docked into the active binding sites of bacteria protein ID; 5MMN, 3P3E, 3FCE and 3G75 showed appreciable binding affinity with all the drug targets when compared to the binding affinity with the standard drug Ciprofloxacin. The result showed that Ciprofloxacin will give better result for the treatment of diseases caused by *E-coli*, while compounds 1906, 1909 and 1902 will give better result than Ciprofloxacin when used in the treatment of diseases caused by *Pseudomonas*. Diseases caused by *Bacillus aureus* will be better treated with 1901, 1902 and 1904 while Ciprofloxacin will better use for the treatment of ill health caused by *Staphylococcus aureus* when compared to the analysed sulfonamide drugs.

The analysed 10 sulfonamide compounds showed potential drug candidates by obeying all the physicochemical parameters that qualifies a compound to be used as drug and therefore, can be clinically use for the treatment of diseases caused by the named organisms.

References

[1] LiverTox. Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012–. Sulfonamides. PMID: 2017 31643703

[2] Henry, R.I. The mode of action of sulphonamide. *Bacteriological Reviews* 1943, 7(4): 175-262

[3] Ugwu, D. I, Okoro, U.C, and Chukwurah, T.D. Nickel catalyzed synthesis of *N*-aryl and *N*-heteroaryl substituted benzene sulphonamides and their biological activities evaluation. *Journal of Medicinal Chemistry* 2014, 4(3): 357-360

[4] Konda, S., Raparthi, S., Bhaskar, K., Munaganti, R.K., Guguloth, V., Nagarapu, L., and Akkewar D.M. Synthesis and antimicrobial activity of novel benzoxazine sulfonamide derivatives. *Bioorg. Med. Chem. Lett;* 2015, 25: 1643–1646

[5] Owa, T., and Nagasu, T. Novel sulphonamide derivatives for the treatment of cancer. *Expert Opin. Ther. Pat;* 2000, 10: 1725–1740

[6] Liu, Zl., Tian, W., Wang, Y. *et al.* A novel sulfonamide agent, MPSP-001, exhibits potent activity against human cancer cells *in vitro* through disruption of microtubule. *Acta Pharmacol Sin.* 2012, 33, 261–270

[7] Chandna, N., Kumar, S., Kaushik, P., Kaushik, D., Roy, S.K., Gupta, G.K., Jachak, S.M., Kapoor, J.K., and Sharma, P.KSynthesis of novel celecoxib analogues by bioisosteric replacement of sulfonamide as potent anti-inflammatory agents and cyclooxygenase inhibitors. *Bioorg. Med. Chem* 2013, 21: 4581–4590

[8] Sameena, B., Kalim, J., Shamim, A., Rathish, I.G., Surender, S., and Alam, M.S. Synthesis and biological evaluation of some new 2-pyrazolines bearing benzene sulfonamide moiety as potential anti-inflammatory and anti-cancer agents. *Eur. J. Med. Che* 2011, 46: 5763–5768

[9] Hamaguchi, T., Hirose, T., Asakawa, H., Itoh, Y., Kamado, K., Tokunaga, K., Tomita, K., Masuda, H., Watanabe, N., and Namba, M. Efficacy of glimepiride in type 2 diabetic patients treated with glibenclamide. *Diabetes Res Clin Pract.* 66 Suppl; 2004, 1: S129-32. doi: 10.1016/j.diabres.2003

[10] Allen, H.B., and Lee, D.A. A general practice assessment of mefruside ('Baycaron') in the treatment of oedema and hypertension. *Curr. Med. Res. Opin* 1973, 1: 547–553

[11] Chandna N., Kumar S., Kaushik P., Kaushik D., Roy S.K., Gupta G.K., Jachak S.M., Kapoor J.K., Sharma P.K. Synthesis of novel celecoxib analogues by bioisosteric replacement of sulfonamide as potent anti-inflammatory agents and cyclooxygenase inhibitors. *Bioorg. Med. Che* 2013, 21: 4581–4590

[12] Sameena, B., Kalim, J., Shamim, A., Rathish, I.G., Surender, S., and Alam M.S. Synthesis and biological evaluation of some new 2-pyrazolines bearing benzene sulfonamide moiety as potential anti-inflammatory and anti-cancer agents. *Eur. J. Med. Che;* 2011, 46:5 763–5768

[13] Thakur, A., Manohar, S., Velez Gerena, C.E., Zayas, B., Kumar, V., Malhotra, S.V., and Rawat D.S. Novel 3,5-bis(arylidiene)-4-piperidone based monocarbonyl analogs of curcumin: anticancer activity evaluation and mode of action study. *Med. Chem. Commun;* 2014, 5(5): 576–586

[14] Ghorab, M.M., Alsaid, M.S., El-Gaby, M.S., Safwat, N.A., Elaasser, M.M., and Soliman, A.M. Biological evaluation of some new *N*-(2,6-dimethoxypyrimidinyl)thioureido benzenesulfonamide derivatives as potential antimicrobial and anticancer agents. *Eur. J. Med. Chem;* 2016, 124: 299–310

[15] Shen, C.H., Wang, Y.F., Kovalevsky, A.Y., Harrison, R.W., and Weber, I.T. Amprenavir complexes with HIV-1 protease and its drug-resistant mutants altering hydrophobic clusters. *FEBS J* 2010, 277: 3699–3714

[16] Aadil, A., Shahzad, M., Muhammad, N.T., Saima S., Muhammad, S., Usman, A.R., Khadija N., and Hummera, R. Synthesis, antioxidant, enzyme inhibition and DNA binding studies of novel *N*-benzylated derivatives of sulphonamide. *J. Mol. Struc;* 2016, 1117: 269–275

[17] Boechat, N., Pinheiro, L.C., Santos-Filho, O.A., and Silva, I.C. Design and synthesis of new *N*-(5-Trifluoromethyl)-1*H*-1,2,4-triazol-3-yl benzenesulfonamides as possible antimalarial prototypes. *Molecules;* 2011. 16:8083–8097.

[18] Quintana C., Silva G., Klahn A.H., Artigas V., Fuentealba M., Biot C., Halloum I., Kremer L., Novoa N., and Arancibia R. New cyrhetrenyl and ferrocenyl sulfonamides: synthesis, characterization, X-ray crystallography, theoretical study and anti-Mycobacterium tuberculosis activity. *Polyhedron* 2017, 134: 166–172

[19] Gawin, R., De Clercq, E., Naesens, L., and Koszytkowska-Stawin´ska, M. Synthesis and antiviral evaluation of acyclic azanucleosides developed from sulfanilamide as a lead structure. *Bioorg. Med. Che;* 2008.16:8379–8389.

[20] Subhakara, N.R., Sarinivas R.A., Adharvana, M.C., Ravi, K.V., Jyothy, V and Himabindu, V. Synthesis and antimicrobial activity of sulfonamide derivatives at c-8 alkyl chain of anacardic acid mixture isolated from a natural product cashew nut shell liquid (CNSL). *Journal of Chemical Science;* 2012, 124: 723-730

[21] Blonde, I. Sildenafil citrate for eractile dysfunction in man with diabetes and cardiovascular risk factor: A retrospective analysis of pooled data from placebo-controlled trials. *Current Medicinal Research Opinio;* 2006, 22(II). 2111-2120

[22] Gonzalez M. A., Gorman D. B., Hamilton C. T., and Roth G. A. Process development for the sulfonamide herbicide pyroxsulam. *Organic Process Research & Developmen;*. 2008, 12(2): 301–303

[23] Eno, E.E., Taer,A., Fatma, K., Ian, L.,Cemil, O., Murat, S and Saviour, A.U. Theoretical studies of some sulphonamides as common inhibitors for mild steel in acidic medium. *Intanational Journal of Quantum Chemistry*; 2010, 110, 2614-2636

[24] Adindu, Chinonso, B., Dike Kelechi, S., Chidiebere, Maduabuchi, A., Ikpa Chinyere, B. C. and Okafor, Kevin, U. Investigating The Corrosion And Microbial Inhibiting Properties Of Some Sulphonamide Compounds. *Gsj:* 2021, 9 (7).

[25] Brackett, C.C., Singh, H., and Block, J.H. Likelihood and mechanisms of cross-allergenicity between sulfonamide antibiotics and other drugs containing a sulphonamide functional group. *Pharmacolotherapy* 2004, 24(7):856-70

[26] Byarugaba, D.K. A view on antimicrobial resistance in developing countries and responsible risk factors. *Int J Antimicrob Agents;* 2004, 24: 105–10

[27] Laxminarayan R, Duse A, Wattal C, Zaidi AKM, Wertheim HFL, Sumpradit N, Antibiotic resistance-the need for global solutions. *Lancet Infect Dis*; 2013. 13: 1057–98

[28] Mancuso, G. Midiri, A., Gerace, E.and Biondo, C. Bacterial Antibiotic Resistance: The Most Critical Pathogens. *Pathogens;* 2021, 10, 1310

[29] Cornaglia, G. Fighting infections due to multidrug-resistant Gram-positive pathogens. *Clinical Microbiology and Infection;* 2009, 15(3): 209–211

[30] Sliwoski, G., Kothiwale, S., Meiler, J., and Lowe, E.W. Computational methods in drug discovery. *Pharmacol Rev*; 2013, 66(1): 334-95

[31] Steven, M. Ronkin, Michael, Badia, Steve, Bellon, Anne-Laure, Grillot, Christian, H. Gross, Trudy, H., Grossman, Nagraj Mani, Jonathan, D. Parsons., Dean, Stamos, Martin, Trudeau, Yunyi, Wei, and Paul, S. Charifson. Discovery of pyrazolthiazoles as novel and potent inhibitors of bacterial gyrase. *Bioorganic & Medicinal Chemistry Letters;* 2010, 20: 2828–2831

[32] Osman, K.T., Du, L., He, Y., and Luo, Y. Crystal structure of *Bacillus aureus* D-alanyl carrier protein ligase (DltA) in complex with ATP. *J. Mol. Biol*; 2009, 388: 345-355

[33] Liang, X., Lee, C.J., Chen, X., Chung, H.S., Zeng, D., Raetz, C.R., Li, Y., Zhou, P., and Toone, E.J. Syntheses, structures and antibiotic activities of LpxC inhibitors based on the diacetylene scaffold. *Bioorg Med Chem*; 2011, 15; 19(2): 852-60

[34] Ikpa, Chinyere B.C And Okoro, Uchechukwu C. Synthesis of New Para-toluene Sulphonamide Derivatives of Amino Acids and Their Anti Bacterial Activities. *IOSR Journal of Applied Chemistry* (2016, 9 (6)

[35] Olayinka, O. Ajani, Oluwole, B. Familoni, Johnbull, O. Echeme, Feipeng, Wu, and Zheng, Sujiang. Synthesis and Antibacterial Activity of N,N-Diethylamide Bearing Benzenesulfonamide Derivatives. *American Chemical Science Journal* 2013, 3(1): 34-49

[36] Ikpa, Chinyere B.C., Okoro Uchechukwu C., Ubochi Collins I and Nwanorh Kieran O. Synthesis, Characterization and Antibacterial Activity of 2-Phenylsulphonamide Derivatives of Some Amino Acids. *International Letters of Chemistry, Physics and Astronomy* 2016, 3, (70): 42-47

[37] Ratchanok, P., Prasit, M., Veda, P., Anusit, T., Supaluk, P., Somsak, R., and Virapong, P. Investigations on Anticancer and Antimalarial Activities of Indole-Sulfonamide Derivatives and In Silico Studies. *ACS Omega* 2021, 6, 47, 31854–31868

[38] Ugwu, D.I., Okoro, U.C., Ukoha, P.O., Gupta, A. and Okafor.S.N. Novel anti-inflammatory and analgesic agents: synthesis, molecular docking and in vivo studies, *Journal of Enzyme Inhibition and Medicinal Chemistry*; 2018, 33: 1, 405-415

[39] McNally, V.A., Rajabi. M., Gbaj, A. Design, synthesis and enzymatic evaluation of 6-bridged imidazolyluracil derivatives as inhibitors of human thymidine phosphorylase. *J Pharm Pharmacol* 2007, 59: 537-542

[40] Alumi, Z., Belaidi, S., Lanez, T., and Tchouar, N. Structure activity relationship, QSAR modeling and drug-like calculations of TP inhibition of 1,3,4-oxadiazoline-2-thione derivatives. *Int Lett Chem Phys Astron* 2014, 37: 113–24

[41] Veber, D.F., Johnson, S.R., Cheng, H.Y., Smith, B.R., Ward, K.W., and Kopple, K.D Molecular Properties That Influence the Oral Bioavailability of Drug Candidates. *J. Med. Chem* 2002, 45, 2615–2623