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Computational docking assisted designing of novel phosphate ester carrier for sulphamethoxazole drug as promising anti-bacterial compounds

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ABSTRACT

Aiming to obtain new anti-bacterial agents, nine novel compounds (8-16) having the same essential moieties (phosphate ester, Schiff base and sulfonamide) were subjected to virtual molecular docking screening to investigate the interaction between these compounds and amino acids existing in the active site of dihydropteroate synthase. compounds (5-7) were synthesized, and on the basis of that, proposals for subsequent compounds were built. Virtual compounds were built based on previously prepared compounds (1-6). Docking score, root mean square deviation (RMSD), hydrogen bond type, Pi-Pi bond, salt bridge, and Pi-Cation, and their distance, bonding site of the target and ligand are calculated. The docking score of all compounds was more than standard drug (sulfamethoxazole), and according to these results, our designing compounds may thus serve as potential anti-bacterial drugs.

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Introduction

The enzyme known as dihydropteroate synthase (DHPS) is designated as EC:2.5.1.15. It serves as a useful target for sulfonamide antibiotics that compete with the para-amino benzoic acid (PABA) precursor because it creates dihydropteroate in bacteria but not in the majority of eukaryotes, including humans. It is important in the synthesis of para-aminobenzoic acid, which then leads to the formation of 7,8-dihydropyrotaroate, which ultimately leads to the final compound (7,8-dihydrofolate). Targeting DHPS are sulfonamides, analogs of substrates that compete with para-aminobenzoic acid.[1] PABA is condensed with 7,8-dihydropterin-6-hydroxymethyl-PP in the dihydropteroate synthase process. In dihydropteroate, the release of the good leaving group PPi happens simultaneously with the creation of amide bonds. Following glutamylation, the folate coenzyme scaffold is formed. Sulfonamide antibiotics function as PABA analogs on this enzymatic step in the synthesis of folate,[1] as shown in Figure 1.

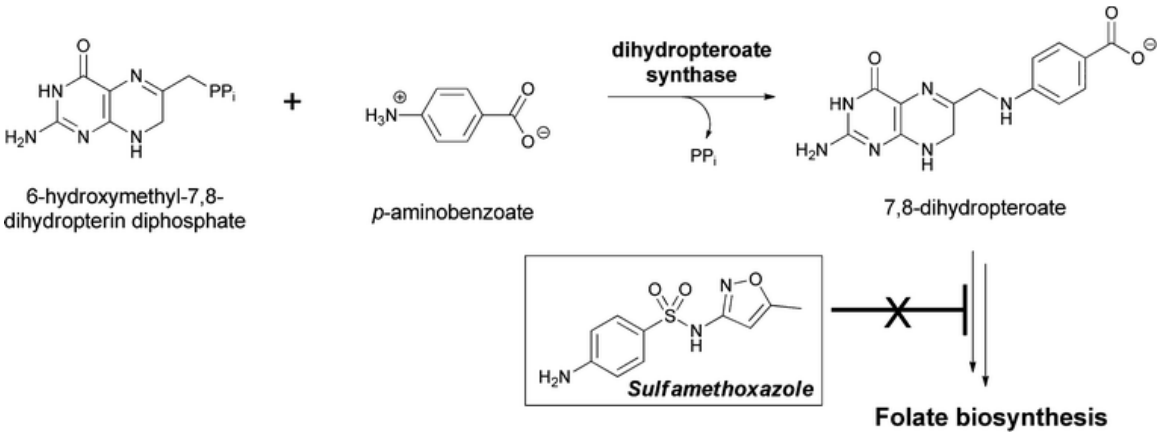

Figure 1: Folate biosynthesis [1]

Bacterial DHPS (gene sul or folP) is a 275–315 amino acid protein that can either be found on plasmids that are resistant to antibiotics or is encoded on the chromosome. The fungus Pneumocystis jirovecii (formerly P. carinii) contains a multifunctional folate synthesis enzyme (gene fas) that has a C-terminal domain called DHPS.

The highly successful sulfa medications have been used for over 70 years to treat DHPS [2]. However, the advent of sulfa drug resistance has severely limited their utility [3, 4], prompting a number of novel DHPS inhibitors to be developed [5].

Sulfa treatments were the first antimicrobial drugs to be successfully tested against pyogenic bacterial infections. Gram-positive and gram-negative bacteria strains that are common and resistant are effective sulfonamide agents, researchers have found. Sulfonamides' antibacterial effect is based on the competitive suppression of DHPS, which is required for the production of folate, and hence inhibits DNA replication. [6]. Bacteria have evolved resistance to well-known sulfonamide

medications as a result of their long-term use, and their ability to inhibit microbial pathways has gradually deteriorated [7]. To find active sulfonamide derivatives, ligand-based techniques have been widely used.

To achieve optimum biological activity, a variety of research projects have been conducted to design innovative sulfonamide scaffolds. [8-14]. Schiff bases are considered bioactive materials because the azomethine group contributes to bioactivity by engaging with and creating hydrogen bonds with specific sites in cell structures. [15].

Since most medications have undesirable side effects, many scientists and researchers are working to improve and increase the effectiveness of medications by making various alterations [16].

Because of their high intrinsic hydrophilicity and a variety of biological roles inside the cell, phosphate esters are a very strong instrument for increasing bioavailability or helping to deliver medications to cells in general. [17].

To our knowledge, no attempt has been made to develop a phosphate ester with sulfonamide and azomethine moieties, or to investigate computational docking. As a result, we conducted virtual screening using docking studies for nine sulfonamide compounds against DHPS, with the hope that this new phosphate ester-containing sulfonamide and azomethine groups will enhance inhibitory activity of the target enzyme while also acting as a decoy for the bacterial resistance mechanism.

Experimental part

1: Chemistry

Designing Tris formyl phenyl phosphate ester (1-3)

Our group previously produced three tri phosphate ester(1-3) by reacting three equivalents of (o-, m-, p-) hydroxy benzaldehyde with one equivalent of $POCl_3$ [18].

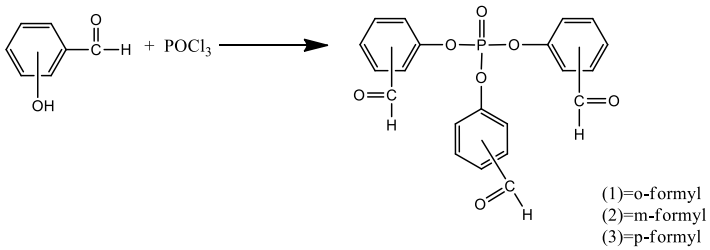

Figure 2: Synthesis of tris formyl phenyl phosphate ester

Designing of tris(((4-(N-(5-methylisoxazol-3-yl) sulfamoyl)phenyl) imino) methyl)phenyl)phosphate (5-7) [18]

Three of the nine compounds (5-7) were also synthesized through reactions of compounds (1-3) with three equivalents of sulfamethoxazole drug in the presence of acetic acid as catalyst, figure 3.

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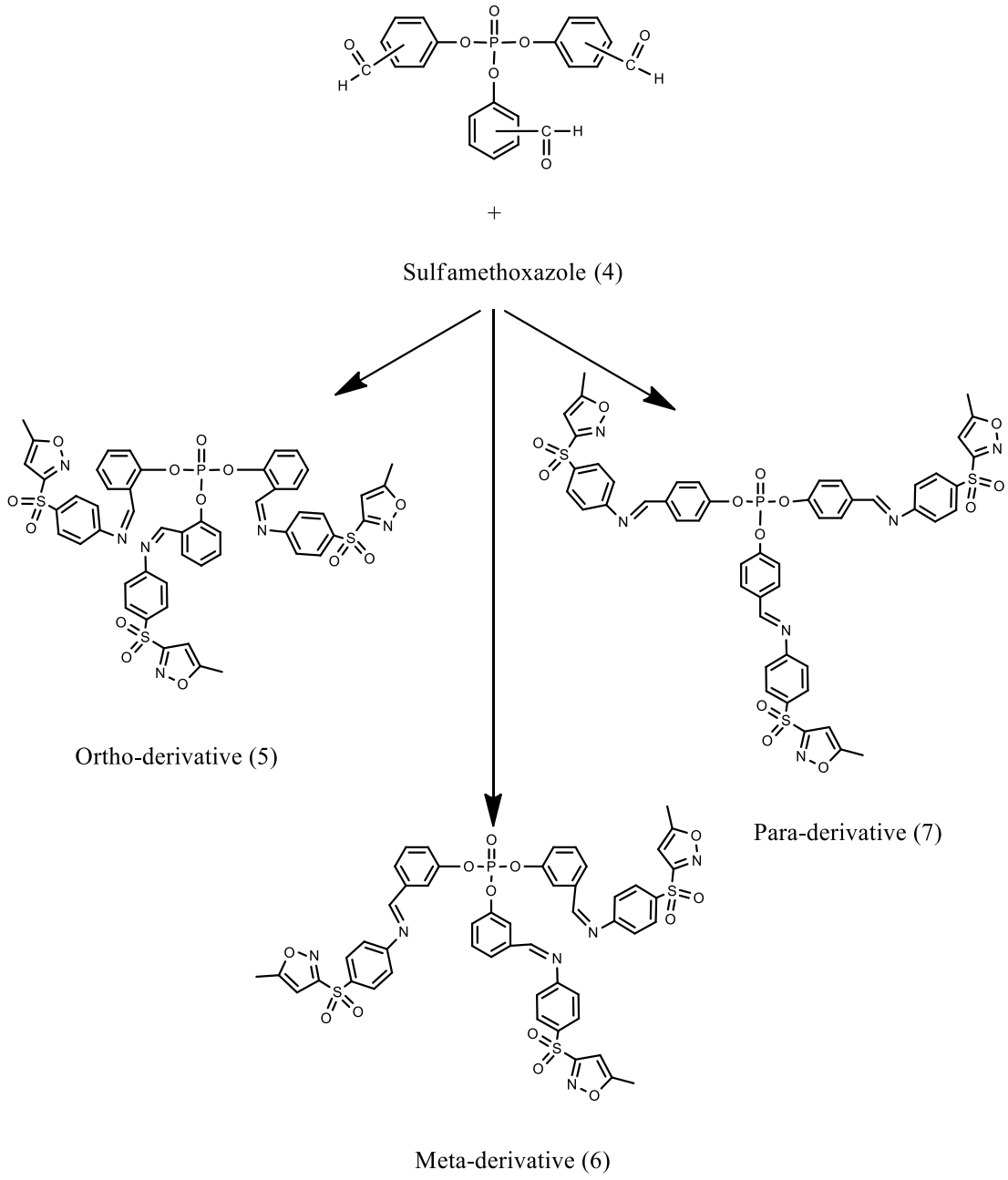
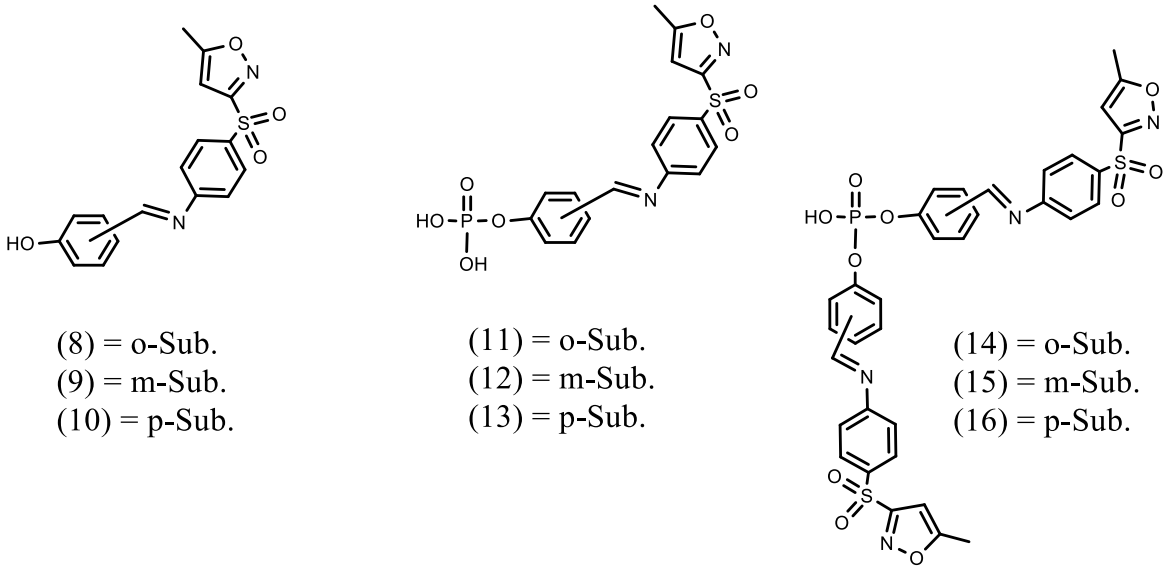


Figure 3: Sulfamethoxazole derivatives

The physical and spectral data of these compounds (5-7) were previously addressed, and the results revealed that the structures given to these compounds were correct. The other six designing compounds (8-12) which have the following structural formula will be synthesized in near future.



(8) = o-Sub.
(9) = m-Sub.
(10) = p-Sub.

(11) = o-Sub.
(12) = m-Sub.
(13) = p-Sub.

(14) = o-Sub.
(15) = m-Sub.
(16) = p-Sub.

Figure 4: The proposed designing compounds

2: Molecular modeling

The proposed compounds were installed at binding sites for dihydropteroate synthase using Schrödinger Maestro version 12.5.139, MMshare 5.1.139 for all docking simulations, and the structures of dihydropteroate synthase were retrieved from (RCSB protein Data Bank (PDB)) under the symbol (5U10). Insights into the interactions between the prepared compounds and the enzyme were gained from the findings of the examination of the fusion between the proposed compounds and the enzyme active site, as well as the use of the sulfamethoxazole medication as a reference for the prepared compounds, Before docking with Maestro tools, water molecules from the enzyme were removed and hydrogen atoms were inserted in the standard geometry. Chem 3D ultra visualizing program was used to reduce the energy of the designed compounds to the lowest possible level and produce the best standard 3D structure format.

Results and discussion

The docking investigations were performed on all of the compounds (8-16) from the schemes, and the molecular docking was done against dihydropteroate synthase (DHPS). Table 1 shows the Root Mean Square Deviation (RMSD), and docking score, for all suggested compounds (8-16) and the reference (4).

Table 1: molecular docking data for Sulphamethoxazole (4) and the proposed compounds (5-16) with dihydropteroate synthase

Compounds	RMSD (°A)	Docking Score (Kcal/mole)
4	0.049	-3.706
5	0.268	-5.036
6	0.283	-3.229
7	0.041	-5.718
8	0.047	-4.967
9	0.041	-4.902
10	0.161	-5.253
11	0.080	-5.151
12	0.057	-4.363
13	0.062	-4.009
14	0.049	-6.834
15	0.294	-4.225
16	0.067	-4.205

Table 2 shows the positions and types of interactions, the distances between the proposed compounds (4-12)-DHPS complexes and the reference (sulfamethoxazole) binding values.

Table 2: Interactions types and distances of sulfamethoxazole, the proposed compounds (4-12)–DHPS complexes

Compounds	Interactions	Distance Å	Bonding	Bonding Types	Binding site of target	Binding site of ligand
4	A:ARG235:HH12-:1:O322	2.36	Hydrogen Bond	Conventional Hydrogen Bond	A:ARG235:HH12	:1:O322
	A:SER222:H-:1:N318	2.52	Hydrogen Bond	Conventional Hydrogen Bond	A:SER222:H	:1:N318
	A:SER222:H-:1:O326	1.89	Hydrogen Bond	Conventional Hydrogen Bond	A:SER222:H	:1:O326
	A:SER222:HG-:1:O326	2.14	Hydrogen Bond	Conventional Hydrogen Bond	A:SER222:HG	:1:O326

	A:GLY189:O-:1:H342	2.73	Aromatic-H bond	Oxygen-hydrogen bond	A:GLY189	:1:H342
	A:PHE190-:1	5.43	Pi-Pi bond	Pi-Pi-Stacking	A:PHE190	:1
5	A:SER61:HG-:5O:N59	2.08	Hydrogen bond	Conventional Hydrogen Bond	A:SER61:HG	:5O:N59
	A:SER222:H-:5O:O36	2.58	Hydrogen bond	Conventional Hydrogen Bond	A:SER222:H	:5O:O36
	A:PRO64:O-5O:H78	2.60	Aromatic-H bond	Oxygen-hydrogen bond	A:PRO64:O	:5O:H78
	A:PRO64:O-:5O:H109	2.63	Aromatic-H bond	Oxygen-hydrogen bond	A:PRO64:O	:5O:H109
6	A:ALA67:H-:5M:O441	2.68	Hydrogen bond	Conventional Hydrogen Bond	A:ALA67:H	:5M:O441
	A:SER61:HG-:5M:O442	1.62	Hydrogen bond	Conventional Hydrogen Bond	A:SER61:HG	:5M:O442
	A:ARG63:NH2-:5M	5.00	Pi-Cation	Metal coordinate	A:ARG63:NH2	:5M
7	A:ARG77:HH12-:5P:O492	1.77	Hydrogen bond	Conventional Hydrogen Bond	A:ARG77:HH12	5P:O492
	A:ARG77:HH22:5P:N484	2.26	Hydrogen bond	Conventional Hydrogen Bond	A:ARG77:HH22	:5P:N484
	A:ARG77:HH22-:5P:N490	4.53	Salt bridg	Salt Bridge, Attractive Charge	A:ARG77:HH22	:5P:N490
	A:ARG63:NH2-:5P	4.05	Pi-Cation	Metal coordinate	A:ARG63:NH2	:5P

	A:PRO64:O70 -:5P:H546	2.64	Aromatic -H bond	Oxygen-hydrogen bond	A:PRO64:O 70	:5P:H56 4
	A:PRO64:O70 -:5P:H545	2.41	Aromatic -H bond	Oxygen-hydrogen bond	A:PRO64:O 70	:5P:H54 5
8	A:ARG220:HH 11-:2O:O364	1.79	Hydroge n bond	Conventional Hydrogen Bond	A:ARG220: HH11	:2O:O3 64
	A:SER222:H- :2O:O379	2.65	Hydroge n bond	Conventional Hydrogen Bond	A:SER222: H	:2O:O3 79
	A:ARG63:NH2 -:2O	3.42	Pi-Cation	Metal coordinate	A:ARG63:N H2	:2O
	A:ARG63:NH2 -:2O:N361	3.09	Salt bridg	Salt Bridge, Attractive Charge	A:ARG63:N H2	:2O:N36 1
	A:PHE190:- :2O	5.40	Pi-Pi bond	Pi-Pi stacking	A:PHE190	:2O
	A:GLY189:O9 1:-:2O:H390	2.58	Aromatic -H bond	Oxygen-hydrogen bond	A:GLY189: O91	:2O:H39 0
9	A:ARG63:HH1 1-:2M:N300	2.32	Hydroge n bond	Conventional Hydrogen Bond	A:ARG63:H H11	:2M:N3 00
	A:ARG63:NH2 -:2M:N361	3.86	Pi-Cation	Metal coordinate	A:ARG63:N H2	:2M:N3 61
	A:GLY189:O6 1-:2M:H338	1.87	Hydroge n bond	Conventional Hydrogen Bond	A:GLY189: O61	:2M:H3 38
	A:PHE190- :2M	5.17	Pi-Pi bond	Pi-Pi-Stacking	A:PHE190	:2M
	A:ARG220:HH 11-:2P:O365	1.78	Hydroge n bond	Conventional Hydrogen Bond	A:ARG220: HH11	:2P:O36 5

10	A:GLY189:O91-:2P:H394	1.94	Hydrogen bond	Conventional Hydrogen Bond	A:GLY189:O91	2P:H394
	A:ARG63:NH2-:2P	3.53	Pi-Cation	Metal coordinate	A:ARG63:NH2	:2P
	A:ARG63:NH2-:2P:N362	3.24	Salt bridg	Salt Bridge, Attractive Charge	A:ARG63:NH2	:2P:N362
	A:PHE190-:2P	5.41	Pi-Pi bond	Pi-Pi-Stacking	A:PHE190	:2P
11	A:ARG220:HH11-:3O:O394	2.04	Hydrogen bond	Conventional Hydrogen Bond	A:ARG220:HH11	:3O:O394
	A:SER222:HG-:3O:O411	1.67	Hydrogen bond	Conventional Hydrogen Bond	A:SER222:HG	:3O:O411
	A:ARG63:NH2-:3O	3.26	Pi-Cation	Metal coordinate	A:ARG63:NH2	:3O
	A:ARG63:NH2-:3O:N391	3.40	Salt bridg	Salt Bridge, Attractive Charge	A:ARG63:NH2	:3O:N391
12	A:ARG220:HH11-:3O:O27	1.85	Hydrogen bond	Conventional Hydrogen Bond	A:ARG220:HH11	:3O:O27
	A:SER222:HG-:3M:O9	1.98	Hydrogen bond	Conventional Hydrogen Bond	A:SER222:HG	:3M:O9
	A:SER222:H-:3M:O9	2.05	Hydrogen bond	Conventional Hydrogen Bond	A:SER222:H	:3M:O9
	A:ARG63:HH22-:3M:O28	1.76	Hydrogen bond	Conventional Hydrogen Bond	A:ARG63:HH22	:3M:O28
	A:ARG63:NH2-:3M:O28	2.74	Salt bridg	Salt Bridge, Attractive Charge	A:ARG63:NH2	:3M:O28

13	A:GLY226:HE21-:3P:O221	1.94	Hydrogen bond	Conventional Hydrogen Bond	A:GLY226:HE21	:3P:O221
	A:ARG220:HH11-:3P:O239	1.70	Hydrogen bond	Conventional Hydrogen Bond	ARG220:HH11	:3P:O239
	A:ARG220:NH2-:3P:O239	4.89	Salt bridg	Salt Bridge, Attractive Charge	ARG220:NH2	:3P:O239
	A:ARG63:HH22-:3O:O238	1.79	Hydrogen bond	Conventional Hydrogen Bond	A:ARG63:HH22	:3O:O238
	A:ARG63:NH2-:3O:O240	4.40	Salt bridg	Salt Bridge, Attractive Charge	A:ARG63:NH2	:3O:O240
	A:ARG63:NH2-:3O:O239	4.61	Salt bridg	Salt Bridge, Attractive Charge	A:ARG63:NH2	:3O:O239
14	A:SER222:H-:4O:O484	1.65	Hydrogen bond	Conventional Hydrogen Bond	A:SER222:H	:4O:O484
	ARG220:HH11-:4O:O494	2.28	Hydrogen bond	Conventional Hydrogen Bond	ARG220:HH11	:4O:O494
	A:ARG63:HH11-:4O:N463	2.33	Hydrogen bond	Conventional Hydrogen Bond	A:ARG63:HH11	:4O:N463
	A:ARG63:NH2-:4O	3.68	Pi-Cation	Metal coordinate	A:ARG63:NH2	:4O
	A:ARG63:NH2-:4O:N491	3.21	Salt bridg	Salt Bridge, Attractive Charge	A:ARG63:NH2	:4O:N491
	A:PHE190-:4O	5.04	Pi-Pi bond	Pi-Pi-Stacking	A:PHE190	:4O
	A:GLN226:HE21-:4M:O9	2.09	Hydrogen bond	Conventional Hydrogen Bond	A:GLN226:HE21	:4M:O9

15	A:ARG63:HH12-:4M:N463	2.58	Hydrogen bond	Conventional Hydrogen Bond	A:ARG63:HH12	:4M:N463
	A:ARG63:HH22-:4M:N463	1.91	Hydrogen bond	Conventional Hydrogen Bond	A:ARG63:HH22	:4M:N463
	ARG220:HH11-:4M:O28	2.00	Hydrogen bond	Conventional Hydrogen Bond	ARG220:HH11	:4M:O28
	A:ARG63:NH2-:4M:O28	4.35	Salt bridg	Salt Bridge, Attractive Charge	A:ARG63:NH2	:4M:O28
16	ARG220:HH11-:4P:O39	2.07	Hydrogen bond	Conventional Hydrogen Bond	ARG220:HH11	:4P:O39
	A:GLN149:HE21-:4P:O27	2.01	Hydrogen bond	Conventional Hydrogen Bond	A:GLN149:HE21	:4P:O27
	A:ARG235:HH12-:4P:O10	2.35	Hydrogen bond	Conventional Hydrogen Bond	A:ARG235:HH12	:4P:O10
	A:ARG235:HH22-:4P:O10	2.07	Hydrogen bond	Conventional Hydrogen Bond	A:ARG235:HH22	:4P:O10
	A:ARG63:HH12-:4P:N463	2.58	Hydrogen bond	Conventional Hydrogen Bond	A:ARG63:HH12	:4P:N463
	A:ARG63:HH22-:4P:N36	2.12	Hydrogen bond	Conventional Hydrogen Bond	A:ARG63:HH22	:4P:N36
	A:ARG63:NH2-:4P:N36	3.06	Salt bridg	Salt Bridge, Attractive Charge	A:ARG63:NH2	:4P:N36

The reference (sulfamethoxazole) and all of the proposed compounds (4-16) were docked into the active site of DHPS (figure 5 to 30).

Compound (4) as shown in Figure 5, exhibited four hydrogen bonding interactions at the DHPS active site: first, binding pocket Arg235 residues with the oxygen lone pair of

the heterocyclic part; second, binding pocket Ser222 residues with the oxygen lone pair of a sulphonyl group, third, binding pocket Ser222(SH residue) with the lone pair of oxygen atoms of a sulphonyl group, and the fourth one, binding pocket Ser222 with the nitrogen lone pair of the heterocyclic part, addition to that, Pi-Pi stacking between Phe190 and the aromatic ring of compound 4, and binding pocket Gly189 with the oxygen lone pair of a sulphonyl group. Compound (4)'s binding score with binding pocket was found to be -3.706 Kcal /mole.

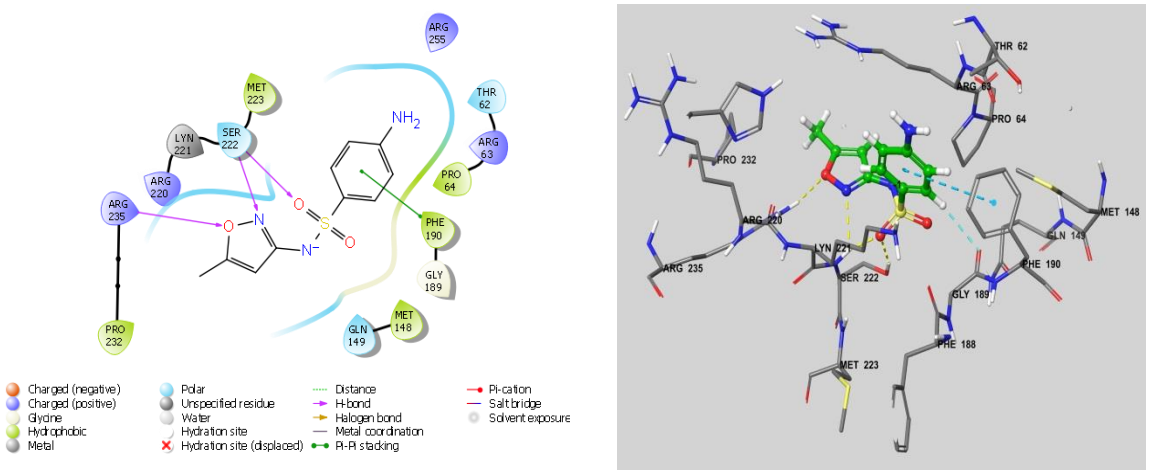


Figure 5: Interaction between sulfamethoxazole (4) and DHPS

Compound (5), as shown in Figure 6, exhibited two hydrogen bonding interactions at the DHPS active site: first, binding pocket Ser222 residues with the oxygen lone pair of the sulfonyl group; second, binding pocket Ser61 residues with a nitrogen atom (negative charge) of the sulfonamide group. Compound (5)'s binding score was found to be -5.036 Kcal /mole.

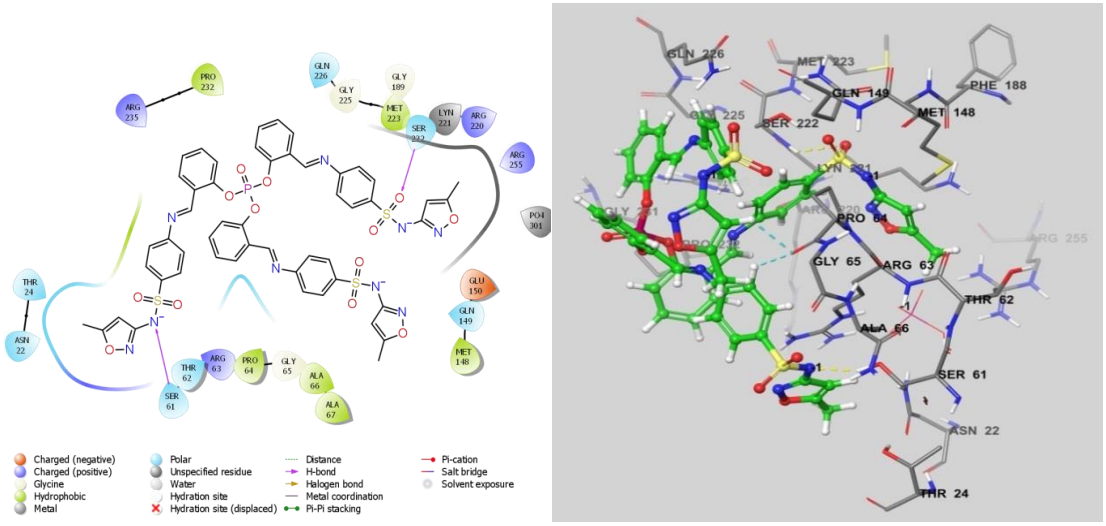


Figure 6: Interaction between compound (5) and DHPS

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As shown in Figure 7, the compound (6) interacts with the DHPS binding pocket in two ways: first, a strong hydrogen bond between Ala67 residue and the oxygen lone pair of the sulfonyl group; second, a strong hydrogen bond between the second lone pair oxygen atom of the sulfonyl group of Ser-61 group. Furthermore, the arene cation interaction of Arg63 with the benzene ring of the sulfamethoxazole ring was observed. The binding score of compounds (6) with the DHPS binding pocket was found to be -3.22 Kcal/mole.

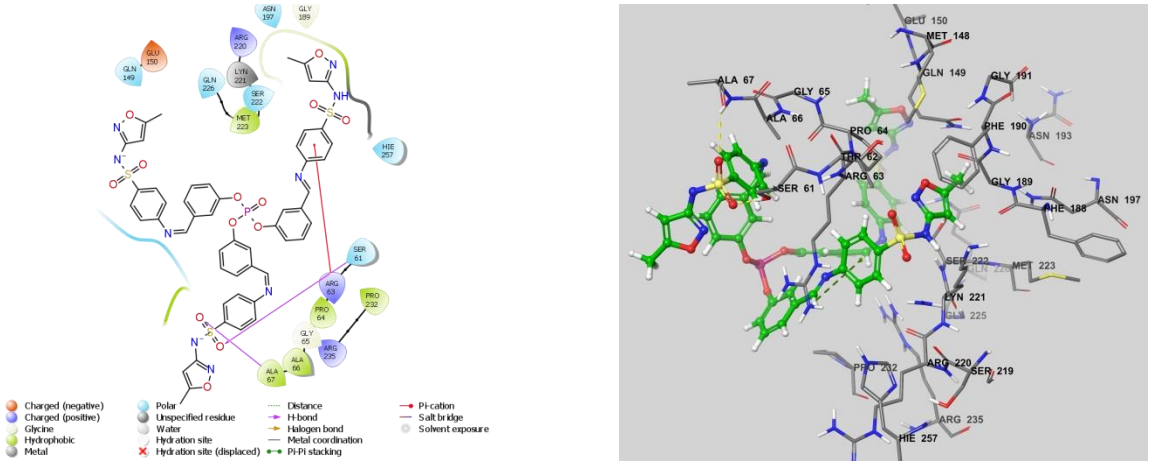

Figure 7: Interaction between compound (6) and DHPS

Figure 8 show how compound (7) interacts with the DHPS binding pocket: first, a strong hydrogen bond between the Arg77 residue and the nitrogen atom of the oxazole ring; second, the Arg77 residue and the negative charge nitrogen of the sulfonamide group; third, the Arg77 residue and the lone pair of oxygen atoms of the sulfonyl group, also Arg63 residue exhibited π cation interaction with π electrons of sulfa oxazole ring. Binding score of compounds (7) with DHPS binding pocket was observed to be -5.718 Kcal/ mole.

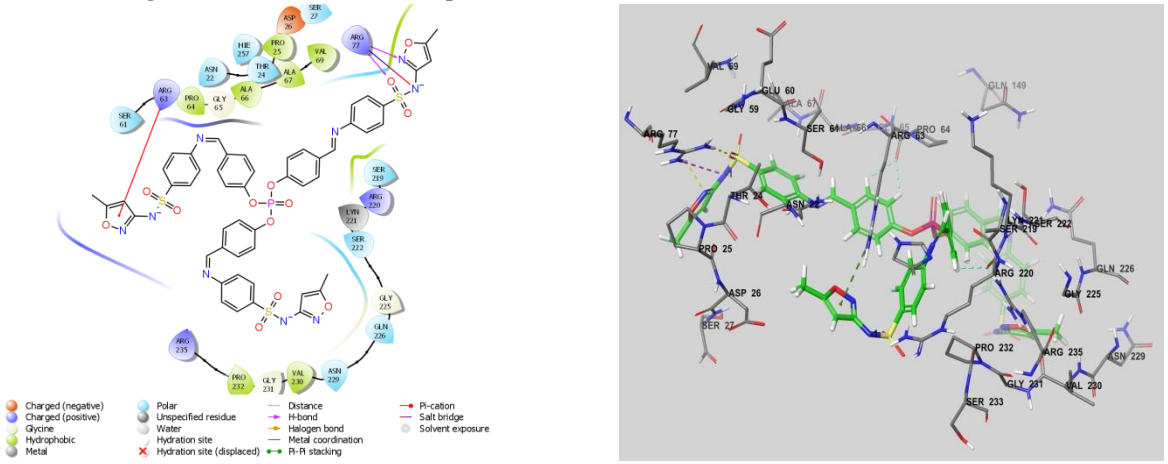

Figure 8: Interaction between compound (7) and DHPS

As depicted in figure 9, compound (8), form three hydrogen bonding interactions at the active site of the DHPS; first, binding pocket Arg220 residue with involving lone pair electron on the oxygen atom of the sulfonamide group; second, binding pocket Ser222 residue with lone pair electron on oxygen atom of the hydroxyl group; third, binding pocket Arg63 residue with nitrogen atom (negative charge) on the of the sulfonamide group. Also, Arg63 residue exhibited π cation interaction with π electron of benzene ring system, Arg63 residue form salt bridge interaction with the nitrogen atom (negative charge) of the sulfonamide group. Binding score of compounds (8) with binding pocket of DHPS was observed to be -4.967 Kcal/ mole.

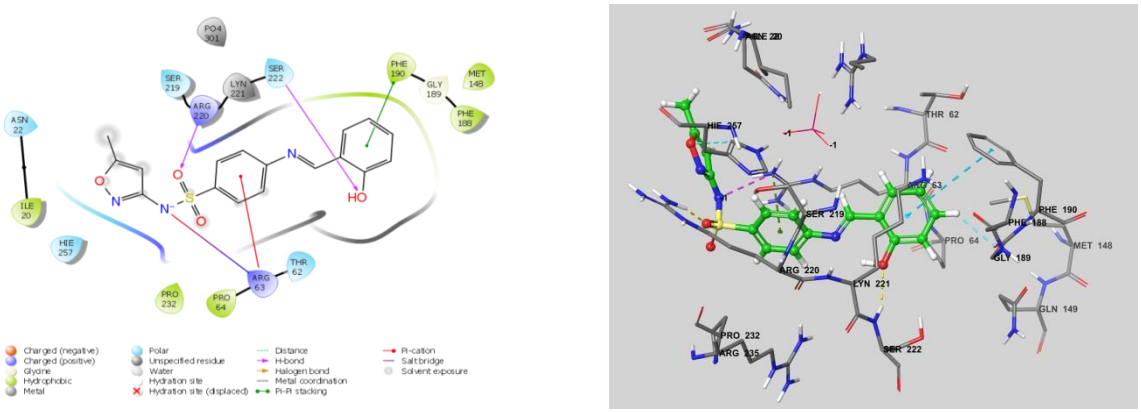

Figure 9: Interaction between compound (8) and DHPS

Compound 9 forms three hydrogen bonding interactions at the DHPS active site, as shown in figure 10. The first involves binding pocket Arg63 residue with the lone pair electron on the nitrogen atom of the oxazole ring, and the second involves binding pocket Gly189 residue with the lone pair electron on the oxygen atom of the hydroxyl group. In addition, residue Phe190 form π-π bond interaction with π electron system of the benzene ring, also, Arg63 residue exhibited π cation interaction with π electron system of the benzene sulfonamide group. Binding score of compounds (9) with binding site of DHPS was observed to be -4.902 Kcal/ mole.

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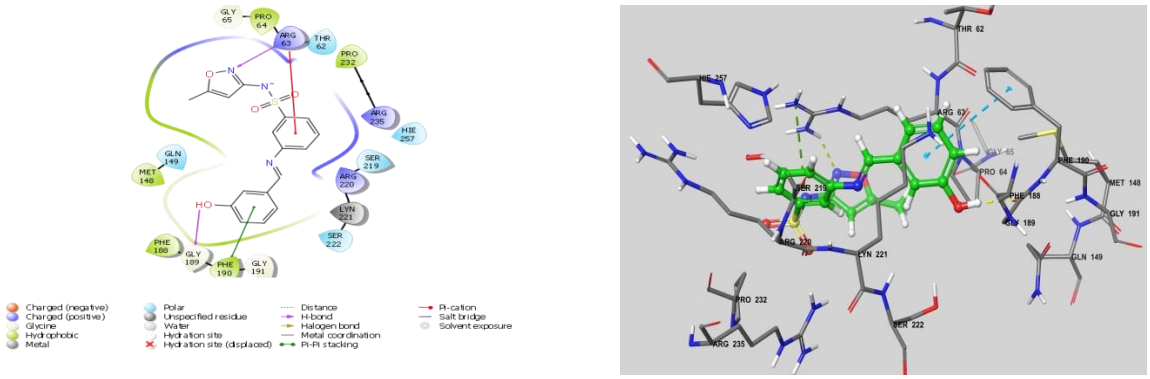

Figure 10: Interaction between compound (9) and DHPS

At the active site of the DHPS, compound (10) exhibited two hydrogen bonding interactions: first, binding pocket Arg220 residue with the lone pair electron on the oxygen atom of the sulfonamide group; second, binding pocket Gly189 residue with the electron lone pair on the oxygen atom of the hydroxyl group. In addition, Arg63 residue form strong π cation interaction with π electron system of the benzene ring, also residue Arg63 exhibited salt bridge interaction with the nitrogen atom (negative charge) of the sulfonamide group, as shown in figure 11. Binding score of compounds (10) with binding site of DHPS was observed to be -5.253 Kcal/ mole.

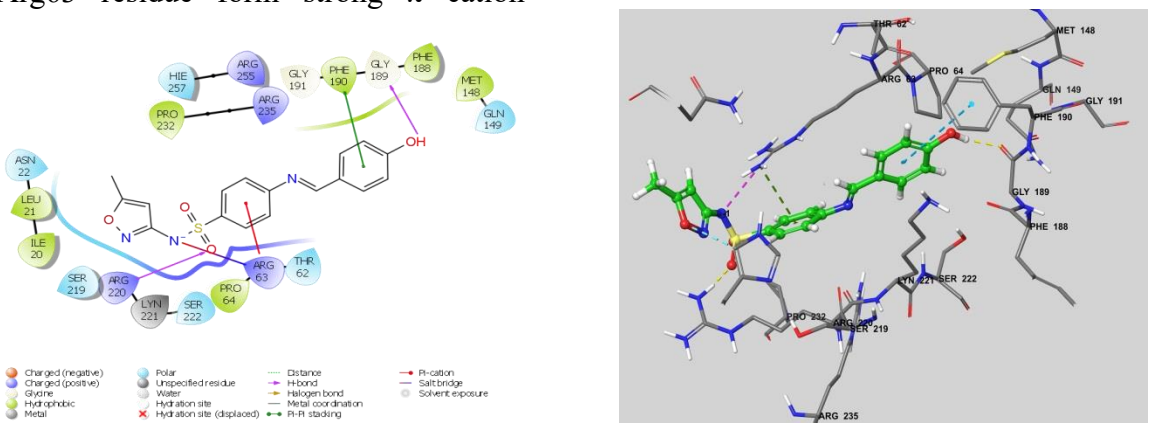

Figure 11: Interaction between compound (10) and DHPS

Compound (11) forms three hydrogen bonding interactions at the DHPS active site, as shown in Figure 12: first, binding pocket Arg220 residue with involving the oxygen lone pair of the sulfonyl group; second, binding pocket Arg63 residue with involving on nitrogen (negative charge) of sulfonamide group; third, binding pocket Arg63 residue with involving on negative charge on nitrogen atom of sulfonamide group; third, binding pocket Ser222 residue with the oxygen lone pair of the phosphate ester group. Furthermore, in addition to strong hydrogen bonding, the Arg63 residue demonstrated significant cation contact with the benzene ring of the sulfamethoxazole medication and formed

a salt bridge. Compound (11) with binding pocket has a binding score of -5.151 Kcal/mole.

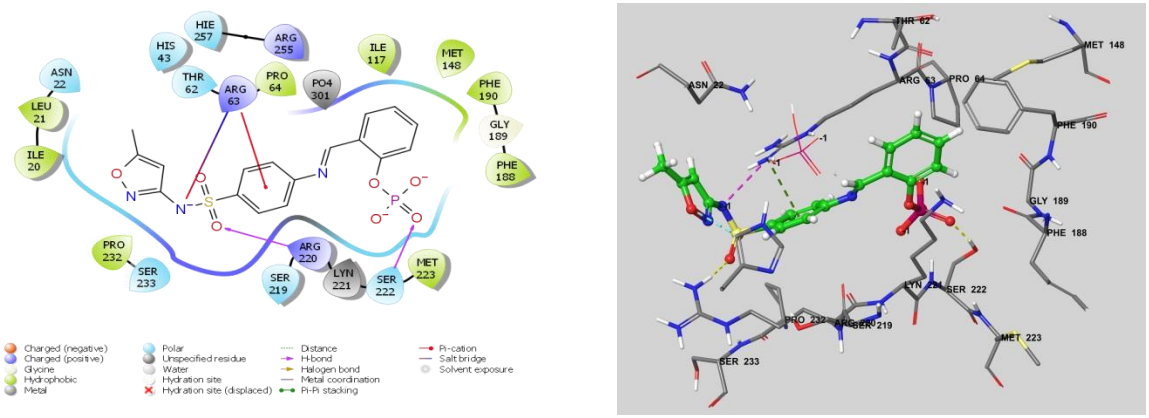

Figure 12: Interaction between compound (11) and DHPS

Compound (12) displayed three hydrogen bonding interactions at the DHPS active site, as shown in Figures 21 and 22; first, strong hydrogen bond interaction between Ser222 residue and the lone pair of electrons on oxygen atom of sulfonyl group; second, strong hydrogen bond between the Arg220 residue and the oxygen atom of the phosphate ester group's lone pair of electrons; third, strong hydrogen bond between Arg63 and the negative charge on oxygen atom of the phosphate ester group. Furthermore, hydrogen bond interactions between the Arg63 residue and the oxygen atom (negative charge) of the phosphate ester generate a strong bridge contact, as shown in figure 13. Compound (12) had a binding score of -4.363 Kcal/mole with the binding pocket of DHPS.

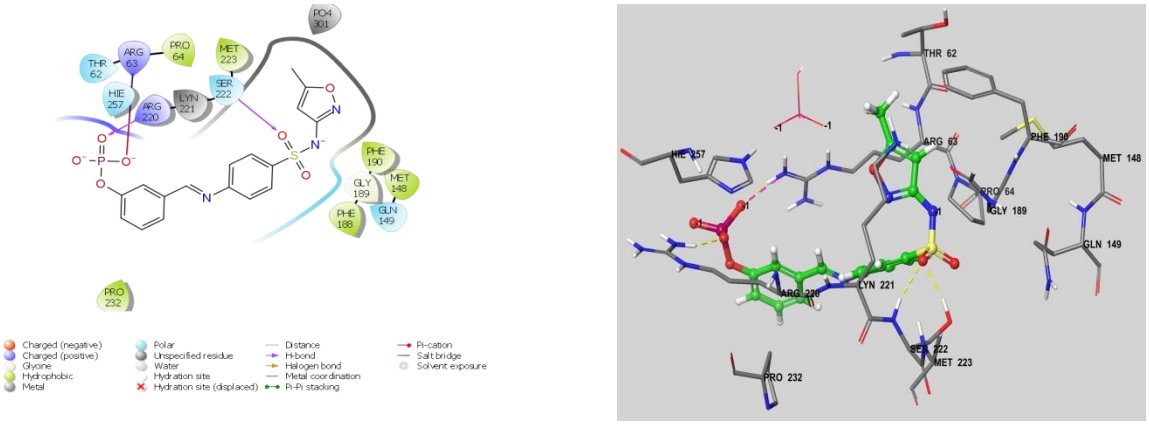

Figure 13: Interaction between compound (12) and DHPS

As depicted in figure 14, compound (13) makes three hydrogen bonding interaction at the DHPS active site; first, strong hydrogen bond between Gly226 residue and the oxygen lone pair of the sulfonamide group; second, strong hydrogen bond between Arg63 and the oxygen atom (negative charge) of the phosphate ester; third, Arg220 residue and the oxygen atom (negative charge) of the phosphate ester group. In addition of that, three attractive charge forces of the salt bridge which formed between Arg63 and Arg220 residues with the oxygen lone pair of the phosphate ester group. Binding score of compound (13) with binding sitr of DHPS was observed to be -4.009 Kcal/ mole.

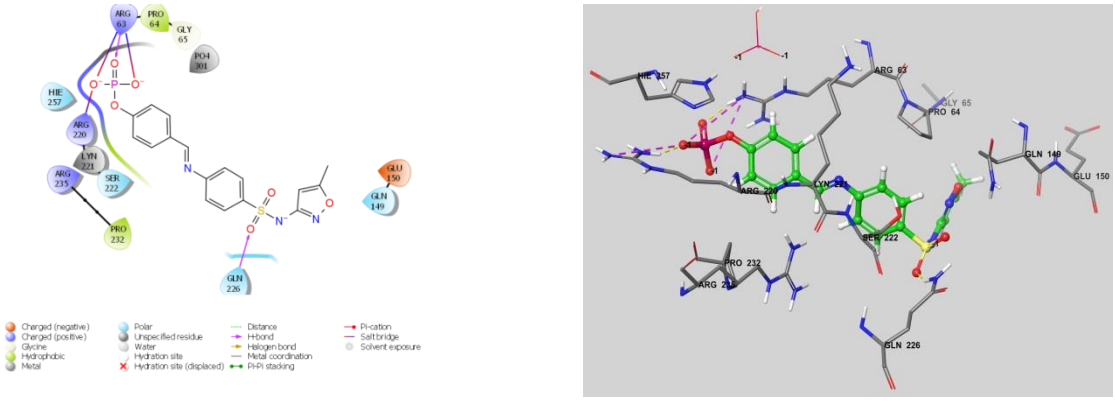

Figure 14: Interaction between compound (13) and DHPS

Compound (14) displayed three hydrogen bonding interactions at the DHPS active site, as shown in figure 15, strong hydrogen bond between binding pocket Ser222 residue involving negative charge on oxygen atom of the phosphate ester; second, binding pocket Arg220 residue with the lone pair electron on the oxygen atom of the sulfonamide group; third, binding pocket Arg63 residue with the negative charge on the nitrogen atom of the sulfonamide group; also, residue Arg63 exhibited π cation interaction with π-electron system of the benzene sulfonamide, this residue also form attractive charge salt bridge forces type with negative charge nitrogen atom of the sulfonamide group. Finally, Phe190 residue exhibited π-π bond interaction with the π-electron system of the benzene ring. Binding score of compound (14) with binding pocket of DHPS was observed to be -6.834 Kcal/ mole.

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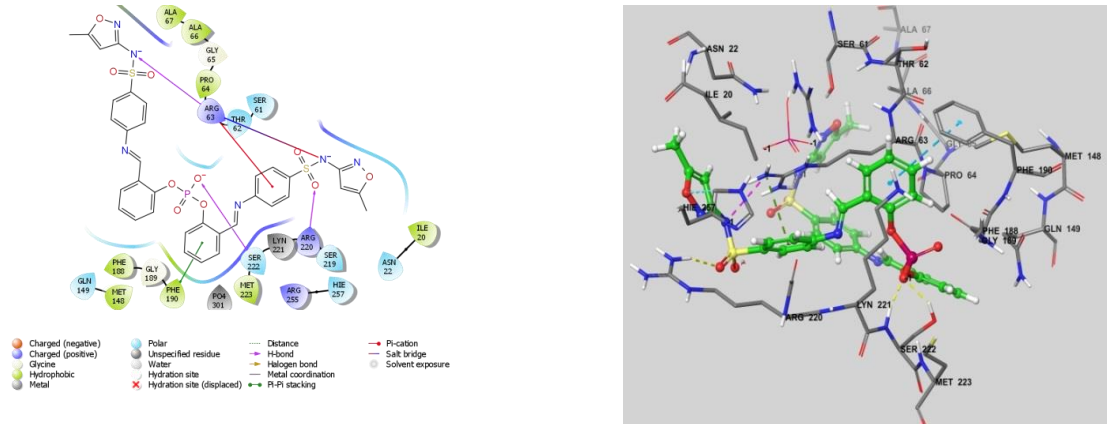

Figure 15: Interaction between compound (14) and DHPS

As depicted in figure 16, compound (15) make four hydrogen bonding interaction at the active site of the DHPS; first, strong hydrogen bond interaction between Gln226 residue and the lone pair of electron on the oxygen atom of sulfonamide group; second, strong hydrogen bond between Arg220 residue and the negative charge on the oxygen atom of the phosphate ester group; third, strong hydrogen bond interaction between Arg63 residue and the lone pair electron on the oxygen atom of the phosphate ester group; fourth, strong hydrogen bond between Arg63 residue and the negative charge on the oxygen atom of the phosphate ester group. In addition, Arg220 residue form salt bridge interaction the lone pair electron on the oxygen atom of the phosphate ester group of compound (15). Binding score of compound (15) with binding site of DHPS was observed to be -4.225 Kcal/ mole.

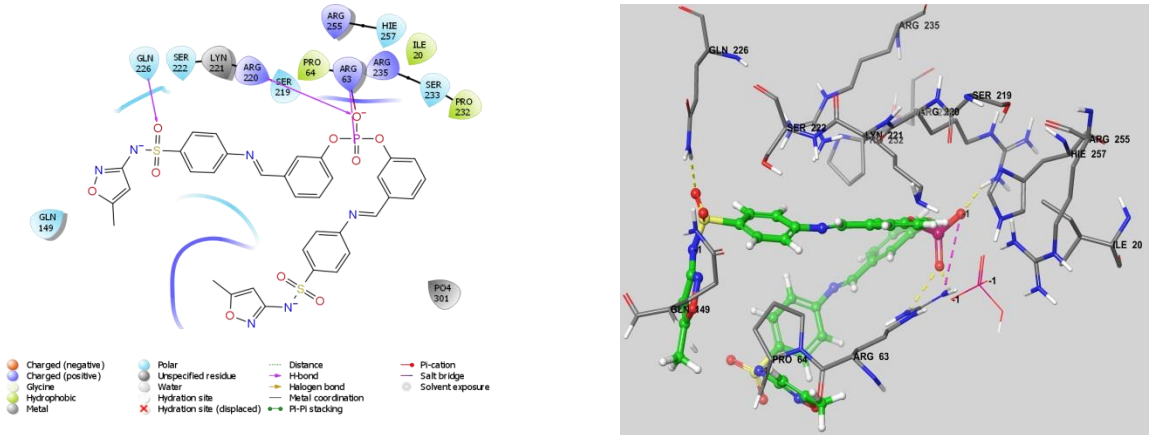

Figure 16: Interaction between compound (15) and DHPS

Compound (16) forms four hydrogen bonding interactions at the active site of the DHPS, as shown in Figures 17, first, strong hydrogen bond between Gln149 residue and the lone pair of oxygen atom on the phosphate ester group; second, strong hydrogen bond interaction between Arg235 residue and the oxygen lone pair on the sulfonamide group; third, Arg235 residue and the nitrogen atom (negative charge) of the sulfonamide group; fourth, Arg220 residue and the lone pair of oxygen atom on the sulfonamide group. Arg63 residue forms strong attractive charge forces, salt bridge type, in addition to these four hydrogen bond interactions. Compound (16) had a binding score with the DHPS binding site -4.205 Kcal/mole.

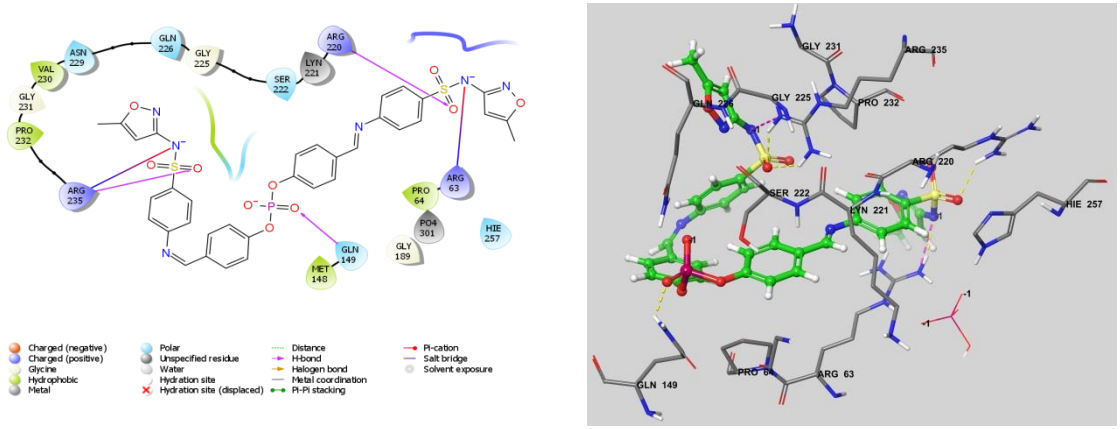

Figure 17: Interaction between compound (16) and DHPS

According to the results that emerged from the molecular docking, compound 14 is the highest compound proposed to bind to the DHPS enzyme, and the reason is due to the steric structure and distribution of the active groups that are compatible with the shape of the active site of the enzyme, which gave the possibility of the compound to bind more strongly than other compounds, and on the contrary Compound 2 is the least bound compound to the enzyme due to the inappropriateness of its groups with the form of the active site of the enzyme.

Conclusions

From the above data, the following observations can be drawn: -

1-The docking score of all compounds (5-16) was more than standard drug (sulfamethoxazole) (4), and the docking score of compounds (5, 7, 10, 11) was found to be the higher than the other compounds, and compound (14) was found to have the highest docking score value (-6.834 Kcal/mole).

2-Arg222, Arg220, Arg63, and Ser222, were found to be the common amino acid fragment of DHPS interaction with our compounds

3- Results also indicated that the hydrogen bond distance between our compounds and DHPS was found at (less the 2.6 ◦A) which indicated the presence of a strong bonding mode (polar-polar interaction) mode with the enzyme.

4-The higher value of docking score for our compounds comparing with the standard drug probably due to the elongation of sulfamethoxazole drug by replacing the

terminal amino group with (N=CH-Ar) moieties which offers an upgraded π-electron, delocalization across-(enzyme-drug) system which lead to enhancement the mode type of interaction (hydrogen bond, π-cation interaction, π-π interaction, and salt bridge interaction). The groups (P=O, O=P-O, oxazole ring, O=S=O and $(O=)_2$S-N) act as acceptor, while N-H for DHPS, act as donor. These groups played an important position in ligand-receptor interaction for the formation of hydrogen bonds.

5- Because of the presence of the imine group, Schiff base, the intermolecular interactions (H-bonds, π-π, π-cation, and salt bridge), added more stability to the target DHPS protein by giving designing compounds with the best orientation.

6-The presence of phosphate ester group lead to enhance the lipophilicity which could facilitate the penetration of these compounds across the biological membrane easily, also the presence of this group resulted in increase the number of hydrogen bonding leading to enhance biological activity.

7-According to these results, these derivatives may thus serve as potential anti-bacterial, and also these results encouraged us to synthesize the others, and development of a good promising drugs through docking simulation.

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