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Research Article

Computational Characterization of the Binding Energy and Interactions between Trimethoprim and Dihydrofolate Reductases of *Candida albicans*, *Staphylococcus aureus* and *Thermotoga Maritima*

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Abstract

Trimethoprim (TMP) is an antibiotic primarily used for the treatment of bladder infections. Computational characterization of the binding energy and interactions between trimethoprim and dihydrofolate reductases of *Candida albicans, Staphylococcus aureus* and *Thermotoga maritima* were carried out using Patch dock and Fire dock online software packages. The interactions are hydrogen bonding and steric interactions. The best binding energy between trimethoprim and dihydrofolate reductases of *Candida albicans, Staphylococcus aureus* and *Thermotoga maritima* were -38.79, -22.50 and -26.23 Kcal/mol. The negative values of the binding energies showed that the interactions were quite favourable.

Keywords: Trimethoprim; Binding Energy; Molecular Docking; Hydrogen Bonding; Interactions

Introduction

Trimethoprim (TMP) is an antibiotic primarily used for the treatment of bladder infections [1]. Alternatively, it is used for the treatment of cavity infections and travellers' looseness of the bowels. With sulpha or antibacterial drug it can be used for *pneumocystis carinii pneumonia* in folks with HIV/AIDS [1,2]. It is administered orally [1]. Nausea, changes in style, and rash are some of the common side effects.

Seldomly, blood issues like not enough platelets or white blood cells may also arise [1]. There is proof of potential damage throughout physiological state in some animals however not humans [3]. It works by blocking folic acid metabolism via dihydrofolate enzyme in some bacterium which ends up in their death [1].

Trimethoprim was initial employed in 1962 [4]. It is on the globe Health Organization's List of Essential Medicines, the foremost necessary medications required during a basic health system [5]. It is accessible as a generic medication and is not terribly pricy [6]. In the United States ten days of treatment is about twenty-one USD [1].

It is primarily employed in the treatment of tract infections, though it can also be used against any vulnerable aerobic microorganism species [7]. It cannot be used for the management of Pneumocystis jiroveci respiratory disorder [7]. It is usually not suggested for the treatment of anaerobic infections like eubacteria difficile rubor (the leading reason behind antibiotic-induced diarrhoea) [7]. Trimethoprim has been employed in trials to treat rubor [8]. Resistance to trimethoprim is increasing, however it is still a primary line antibiotic in several countries [9].

Metabolism of 10 - 20% of trimethoprim occurs in the liver and the rest is eliminated as urine. Therefore, trimethoprim ought to be used with caution in people with excretory organ and liver impairments.

Indefinite quantity adjustment is not required for liver impairment however, dosage adjusted is necessary for individuals with excretory organ impairment [10].

Based on report that trimethoprim crosses the placenta and may have an effect on folic acid metabolism, there has been growing proof of the danger of structural birth defects related to trimethoprim, particularly throughout the primary trimester of physiological state [11]. The trophoblasts within the early vertebrate are sensitive to changes within the folic acid cycle. Recent report showed a doubling in the risk of miscarriage in pregnant ladies exposed to trimethoprim within the early physiological state [12].

Trimethoprim binds to dihydrofolate enzyme and inhibits the reduction of dihydrofolic acid (DHF) to tetrahydrofolic acid (THF) [13]. THF is a necessary precursor within the nucleoside synthesis

pathway and interference with this pathway inhibits microorganism DNA synthesis [13]. Trimethoprim's affinity for microorganism dihydrofolate enzyme is a thousand-fold bigger than its affinity for human dihydrofolate enzyme [13]. Sulfamethoxazole inhibits dihydropteroate synthase [13]. Trimethoprim and sulpha drug can be used as combination therapy because of potential synergistic effects, and reduced development of resistance [13].

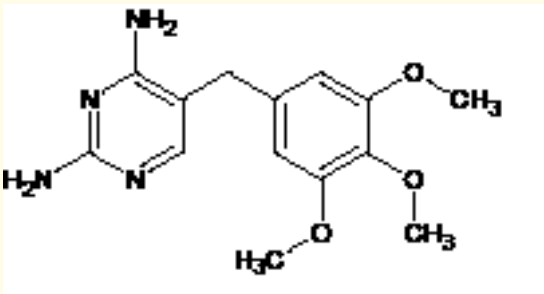

Figure 1: Structure of Trimethoprim.

This work is aimed at studying the computational characterization of the binding energy and interactions between trimethoprim and bacterial dihydrofolate reductases.

Materials and Methods

Molecular Docking

Docking studies were performed using the Patch dock and firedock online server software packages. The protein data bank (PDB) files of the crystal structures of *Candida albicans* dihydrofolate reductase having PDB entry number 1AI9, *Thermotoga maritima* dihydrofolate reductase with PDB ID 1D1G and *S. aureus* dihydrofolate reductase receptor having PDB ID 4FGH were downloaded from the protein data bank website. Regularization and optimization for protein and ligand were performed. Determination of the essential amino acids in binding site were carried out and compared with the present literature. The interactive docking method was carried out for all the conformers of each compound in the selected active site. Each docked compound was assigned a score according to its fit in the ligand binding pocket (LBP) and its binding mode.

Results and Discussion

The solution Tables of the docking scores for Trimethoprim - *Candida albicans* dihydrofolate reductase, *Thermotoga maritima* dihydrofolate reductase and *S. aureus* dihydrofolate reductase are presented in Tables 1-3 respectively. Trimethoprim docked with *Candida albicans* dihydrofolate reductase and molecular interaction of *Candida albicans* dihydrofolate reductase with trimethoprim are shown in Figures 2a and 2b respectively. Trimethoprim docked with *Thermotoga maritima* dihydrofolate reductase and molecular interaction of *Thermotoga maritima* dihydrofolate reductase complexed with trimethoprim are presented in Figures 3a and 3b respectively. Trimethoprim docked with *S. aureus* dihydrofolate reductase and molecular interaction of *S. aureus* dihydrofolate reductase complexed with trimethoprim are shown in Figures 4a and 4b respectively.

Figure 2a: Trimethoprim Docked with *Candida Albicans* Dihydrofolate Reductase.

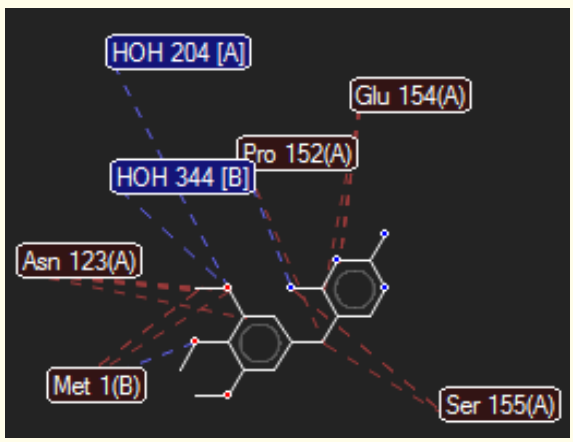

Figure 2b: Molecular Interaction of *Candida Albicans* Dihydrofolate Reductase with Trimethoprim.

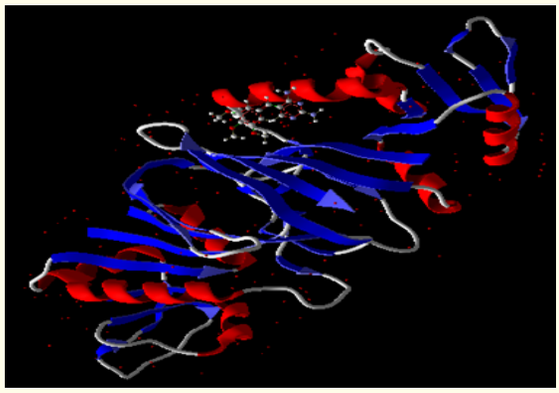

Figure 3a: Trimethoprim Docked with *Thermotoga Maritima* Dihydrofolate Reductase.

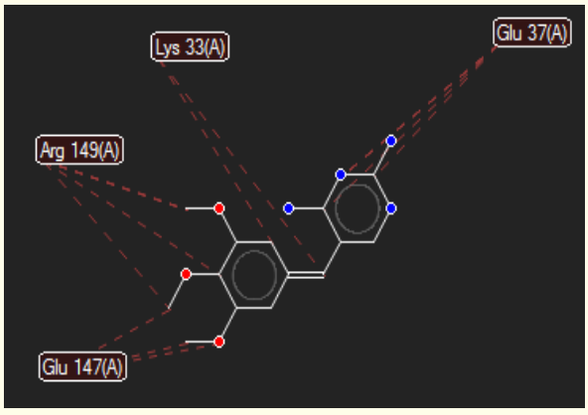

Figure 3b: Molecular Interaction of *Thermotoga Maritima* Dihydrofolate Reductase Complexed with Trimethoprim.

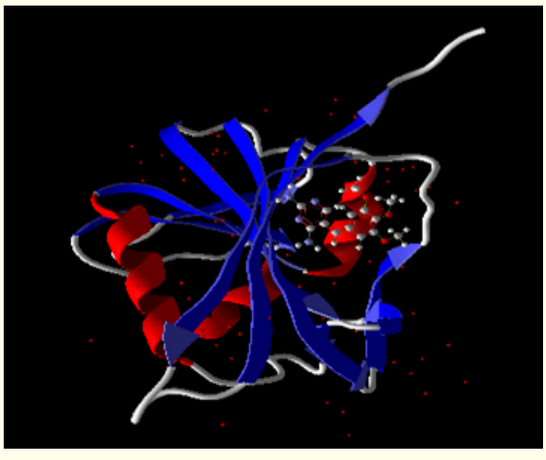

Figure 4a: Trimethoprim Docked with *S. aureus* Dihydrofolate Reductase.

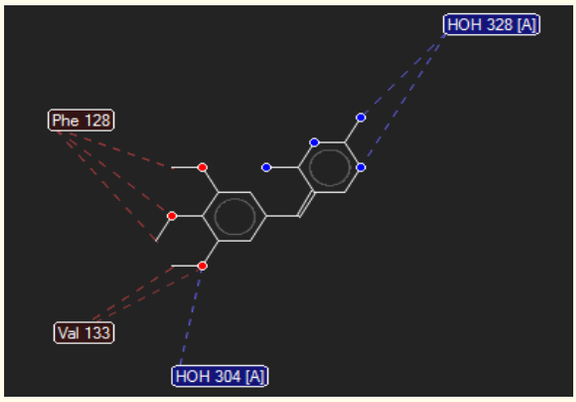

Figure 4b: Molecular Interaction of *S. aureus* Dihydrofolate Reductase Complexed with Trimethoprim.

Table 1: Solution Table for Trimethoprim - *Candida Albicans* Dihydrofolate Reductase.

Rank	Solution Number	Global Energy (Kcal/mol)	Attractive VdW (Kcal/mol)	Repulsive VdW (Kcal/mol)	ACE (Kcal/mol)
		↓			
1	10	-38.79	-17.09	9.99	-14.17
2	4	-31.70	-14.14	3.22	-8.54
3	7	-28.07	-12.70	3.48	-7.70
4	6	-22.07	-10.34	2.72	-6.77
5	8	-19.95	-12.22	7.87	-5.75
6	9	-17.62	-10.51	4.14	-3.82
7	5	327.16	-19.28	462.11	-8.72
8	3	425.09	-20.18	585.72	-8.31
9	2	495.87	-19.76	675.17	-9.25
10	1	1159.88	-18.52	1504.78	-10.27

Table 2: Solution Table for Trimethoprim - *Thermotoga Maritima* Dihydrofolate Reductase.

Rank	Solution Number	Global Energy (Kcal/mol)	Attractive VdW (Kcal/mol)	Repulsive VdW (Kcal/mol)	ACE (Kcal/mol)
		↓			
1	10	-22.50	-12.22	3.64	-6.52
2	8	-20.11	-13.30	6.64	-5.64
3	6	-18.37	-10.79	3.01	-5.28
4	7	-16.99	-13.44	10.43	-5.15
5	4	-15.28	-9.44	2.90	-4.00
6	3	-13.47	-9.19	2.50	-3.98
7	2	-11.14	-13.35	3.82	1.60
8	5	-10.57	-11.13	14.95	-5.52
9	9	1.66	-4.11	1.23	2.15
10	1	3.14	-7.60	2.33	5.08

Table 3: Solution Table for Trimethoprim - *S. aureus* dihydrofo late reductase.

Rank	Solution Number	Global Energy (Kcal/mol)	Attractive VdW (Kcal/mol)	Repulsive VdW (Kcal/mol)	ACE (Kcal/mol)
		↓			
1	10	-26.23	-10.97	2.88	-9.53
2	6	-25.40	-11.02	3.18	-9.89
3	5	-21.80	-15.30	3.54	-3.24
4	3	-20.33	-10.91	6.35	-8.67
5	4	-17.09	-9.98	2.67	-5.63
6	9	-15.76	-9.01	1.69	-5.32
7	8	-14.62	-8.35	1.27	-5.50
8	2	-10.79	-9.32	4.27	-3.92
9	1	-3.59	-6.90	1.32	-0.21
10	7	-2.92	-3.08	1.03	-2.43

The docking of trimethoprim into the active site of dihydrofolate reductase were conducted to get information about the interaction of these compounds inside the receptor. The docking results of trimethoprim into the active site of *Candida albicans* dihydrofolate reductase receptor showed hydrogen bonding interaction between HOH 204(A) and methoxyl oxygen with bond length of 0.00 Å and binding energy of -0.22 (kcal/mol). Hydrogen bonding occurred between HOH 344(B) of the receptor and methoxyl group of the ligand with bond length of 0.00 Å and binding energy of -2.50 (kcal/mol).

Hydrogen bonding between Met 1(B) and oxygen of methoxyl group in the ligand. Hydrogen bonding between Pro 152(A) and NH_2 of trimethoprim with bond length of 2.95 Å and binding energy of -0.95 (kcal/mol) (Figure 2b). Steric interactions were observed between trimethoprim and Asn 123(A), Met 1(B), Glu 154 (A), Ser 155(A). The global energy of -38.79 kcal/mol (Table 1) showed that these interactions were quite favourable due to negative free energy and suitable bond lengths.

The molecular docking study of trimethoprim into the binding pocket of *Thermotoga maritima* dihydrofolate reductase revealed steric interactions with Glu 147 (A), Arg 149 (A), Lys 33(A), Glu 37(A) (Figure 3b). The global energy of -22.50 kcal/mol (Table 2) showed that these interactions were quite favourable due to negative free energy and suitable bond lengths.

The docking results of trimethoprim into the active site of *S. aureus* dihydrofolate reductase receptor showed hydrogen bonding with HOH 304 (A) with bond length 0.00 Å and binding energy -0.01 kcal/mol.

Hydrogen bonding with HOH 328 (A), bond length 0.00 Å and binding energy -2.29 kcal/mol. Steric interactions were observed between trimethoprim and Phe 128, Val 133. The global energy of -26.23 kcal/mol (Table 3) showed that these interactions were quite favourable due to negative free energy and suitable bond lengths.

Conclusion

The negative values of the global energy and atomic contact energy (ACE) showed that the interactions were quite favourable. The interactions are hydrogen bonding and steric interactions.

Acknowledgements

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Conflict of Interest

No conflict of interest.

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