IN SILICO DOCKING AND ADMET PREDICTION OF A NOVEL ANTIBACTERIAL DERIVATIVES (SCHIFF BASE) TARGETING DIHYDROPTEROATE SYNTHASE (1AJ2)

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Abstract: Schiff base-containing (imine or azomethine–C=N–) derivatives have been investigated in relation to a broad range of activity, including antibacterial activity, antiviral activity, anticancer activity, polymer technology and in many other areas due to the presence of moiety in their structures. Antibacterial activity of Schiff bases can achieve by various enzyme inhibitory mechanism. Primary target for the antibacterial drugs is inhibiting dihydropteroate synthase (DHPS) enzyme which result in inhibition of bacterial folate synthesis and act as bactericidal. In this research article pharmacokinetic properties, bioactivity score, in silico docking studies and toxicity prediction of 10 Schiff base compounds i.e. SB1, SB2, SB3, SB4, SB5, SB6, SB7, SB8, SB9, and SB10 were carried out against dihydropteroate synthase enzyme (1AJ2) was examined and possible probability were recorded.

Keywords: Schiff base, Dihydropteroate Synthase Inhibition, Molecular Docking, ADME Prediction, Antibacterial activity.

1. INTRODUCTION-

In 1864 the term Schiff base was introduced by germen chemist Hugo Schiff. [1] SBs are easy to synthesized and inexpensive compounds as compared to another chemical compound. [2] In recent years, SBs gained a lot of attention due to their broad activity including antibacterial activity, antiviral activity, antimicrobial activity, and antifungal activity. [3] Researchers synthesize various new SBs derivatives and explore their potent antibacterial action. [4,5] SBs act as antibacterial agent by showing various mechanism of action they are as follows-

- By inhibiting cell wall synthesis
- By inhibition of ribosome function
- By nucleic acid synthesis inhibition
- By inhibition of foliate metabolism
- By change in cell membrane function [6]

In this research article author select a target i.e. dihydropteroate synthase enzyme (1AJ2). This enzyme is necessary for the bacterial folate biosynthesis, which catalyzes the addition of p-aminobenzoic acid (pABA) to dihydropterin pyrophosphate (DHPP) to form pteroic acid as a key step in bacterial folate biosynthesis. This pathway plays crucial role in the synthesis of nucleic acid. [7]

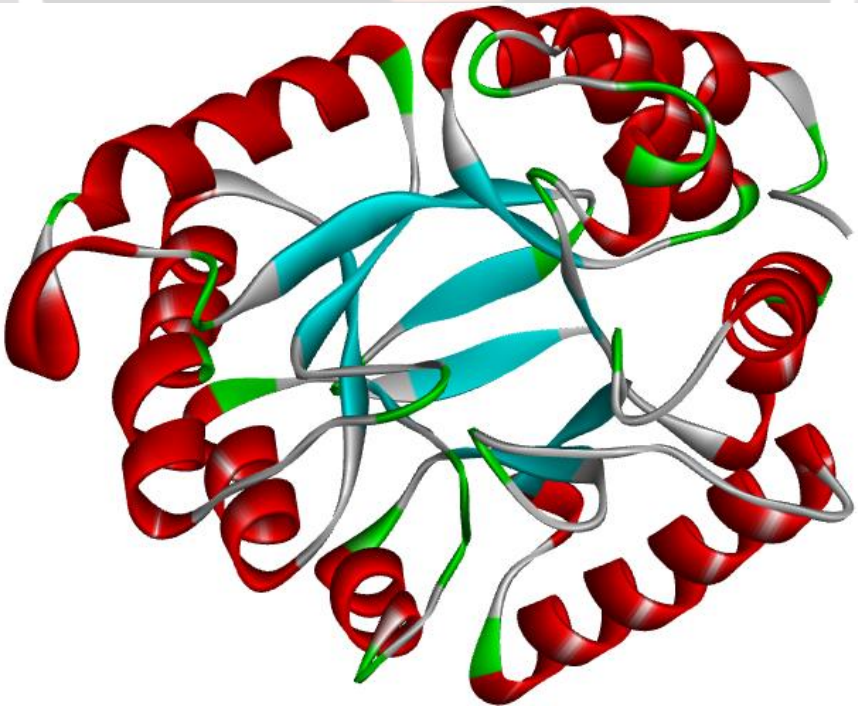
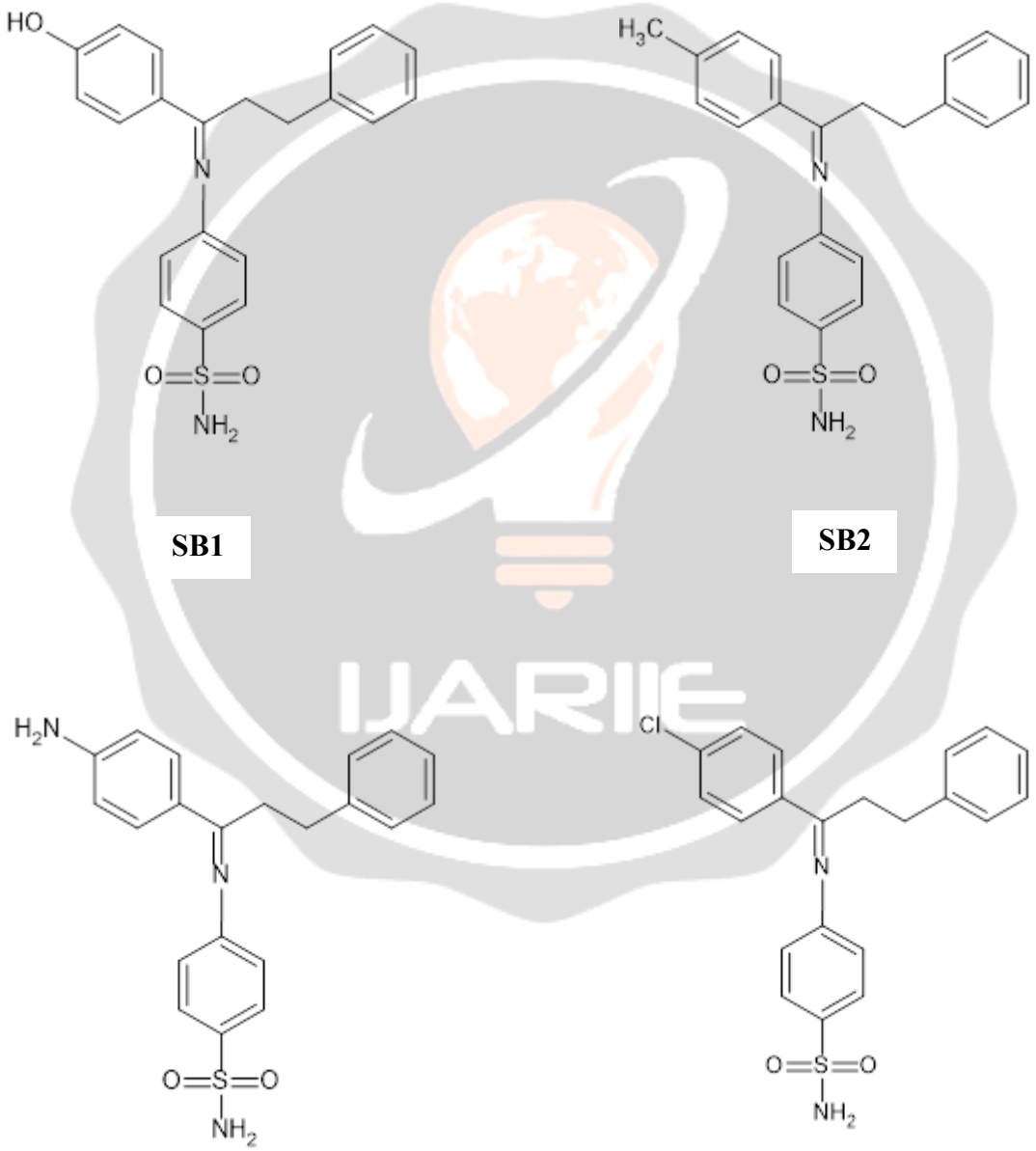


Fig. 1 3D structure of Dihydropteroate Synthase enzyme (1AJ2). [8]

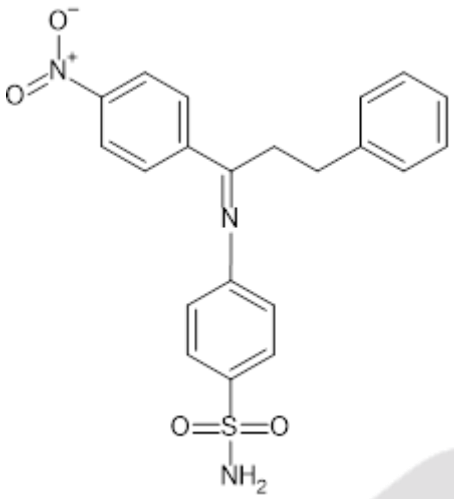
In bacteria, antibacterial SBs derivatives act as a competitive inhibitor of the dihydropteroate synthase enzyme (1AJ2). Hence SBs derivatives exhibit bactericidal effect in bacteria. [9]

In this study we aim to investigate the antibacterial effect of novel SBs derivatives against dihydropteroate synthase enzyme (1AJ2). This carryout by various computational techniques like ADME prediction, toxicity prediction, molecular docking etc. [10] Followings are the SBs derivatives which are prepare by substituting various groups on novel Schiff base moiety. [11]

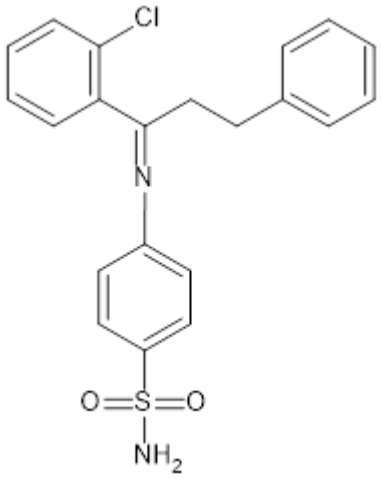


SB1 **SB2**

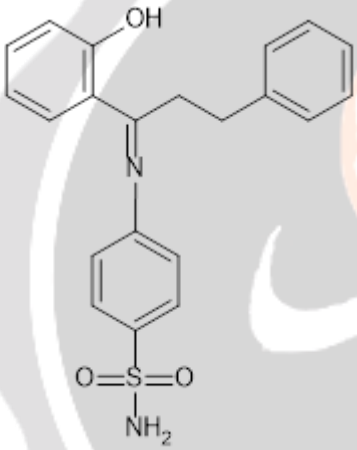
SB3 **SB4**



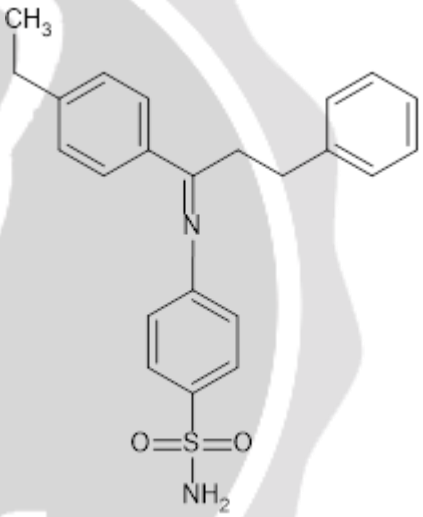
SB5



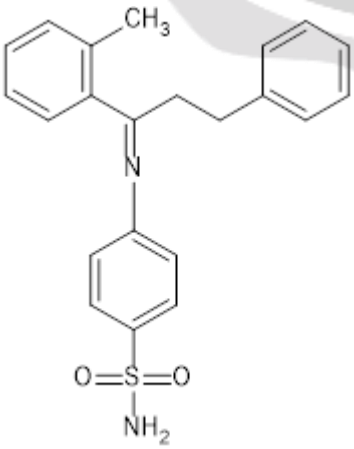
SB6



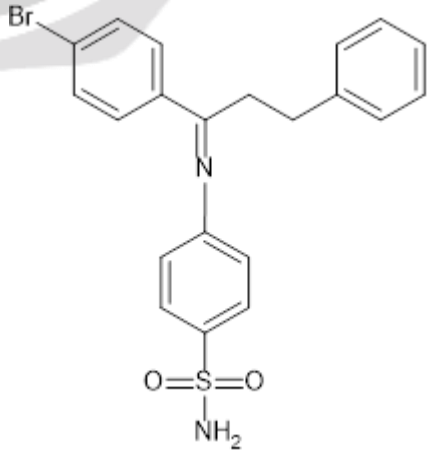
SB7



SB8



SB9



SB10

2. MATERIALS AND METHOD-

2.1. Ligand preparation- With the help of ChemSketch tool [12] A set of 10 compounds were prepared by substituting various electron donating group and electron withdrawing group (-Cl, -CH_3, -NH_2, -Br, -C_2H_5) on basic moiety prepare by the Schiff base method. [13] Then SBs derivatives converted into the SDF format. [14]

2.2. Protein preparation- 3D crystal structure of dihydropteroate synthase (1AJ2) protein was download from RCSB, Protein Data Bank as PDB format [8] and open in Biovia Discovery studio Visualizer36 V16.1.0.15350. [15] During the protein preparation process the hetro atom, water molecules, excessive chain and the pre- exist ligand on that protein were removed and file save in the form of MDL MOL/ SD file. [16]

2.3. ADMET and drug-likeness prediction- The SwissADME [17] tool were used to screening of various pharmacokinetic properties of SBs derivatives like Gastrointestinal absorption, Blood Brain Barries permeation, P-gp subs, CYP1A2 inhibitor, CYP2C19 inhibitor, CYP2C9 inhibitor, CYP2D6 inhibitor, CYP3A4 inhibitor, Log Kp, Bioavailability were predicted and present in tabular format. [18]

2.4. Prediction of Toxicity- The Protox 3.0 tool [19] were used to predict the toxicity of SBs derivatives which including organ toxicities like hepatotoxicity, carcinogenicity, mutagenicity, cytotoxicity, immunogenicity etc. [20]

2.5. Molecular Properties and Bioactivity Scores of the ligands- The SwissADME [17] tool were used to predict the molecular properties like MlogP (partition coefficient between n-octanol and water), TPSA, number of hydrogen bond donors and number of hydrogen bond acceptors, molecular weight, and the number of rotatable bonds, molecular volume was calculated and present in tabular format. [21] Another one software i.e. Molinspiration was used to predict ligands modulating GPCR, Ion channels, Nuclear receptors, and also predict the ligands as Kinase inhibitors, Protease inhibitors and Enzyme inhibitors. [22]

2.6. Molecular Docking Studies- Docking studies were carried out by using One click Docking tool. [23] Targeted protein DHPS enzyme (1AJ2) was download from Protein Data Bank then prepare a protein by removing the hetro atom, water molecules, excessive chain and the pre- exist ligand. Now all prepared protein upload on M-cule Docking and dock with new derivatives. Binding affinity and types of interaction present in the ligand and target were examined by using Discovery studio Visualizer36 V16.1.0.15350. [(15,24)]

3. RESULTS AND DISCUSSION-

3.1 Screening of designed derivatives through ADMET analysis- Table no.1 evaluation of SBs derivatives on the basis of based on Lipinski's rule of five [25], also known as Pfizer's rule of five or the rule of five (RO5) which specifies that an orally active medication should obey the following rules: less than 5 hydrogen-bond donors, less than 10 hydrogen-bond acceptors, a molecular mass less than 500, and log P less than 5. Other important properties, such as total polar surface area (TPSA), the amount of rotatable bonds, and molar refractivity, were measured as well. A compound's TPSA should be less than 140 Å2, and the number of rotatable bonds should be less than 10. In table no.2 bioactivity scores were calculated for SBs derivative as GPCR ligands, ion channel modulators (ICM), kinase inhibitors (KI), nuclear receptor ligands (NRL), protease inhibitors (PI), and enzyme inhibitors (EI). Values more than 0.00 indicate considerable activity, scores between 0.00 and -0.5 indicate mild activity, and scores less than -0.5 indicate inactivity. [26] In table no.3 all SBs derivative had high human intestinal absorption (HIA) except SB5. While all of the derivatives do not cross the blood-brain barrier (BBB).

Table 1. Calculations of Lipinski rule of five for the designed derivatives SB1-SB10)

Ligand	Molecular weight	TPSA	Molar refractivity	MlogP	Rotatable bonds	H-bond donors	H-bond acceptors
SB1	380.46	101.13	107.26	2.69	6	2	5
SB2	378.49	80.90	110.20	3.47	6	1	4
SB3	379.48	106.92	109.64	2.69	6	2	4
SB4	398.91	80.90	110.24	3.74	6	1	4
SB5	409.46	126.72	114.06	2.29	7	1	6
SB6	398.91	110.24	110.24	3.74	6	1	4
SB7	380.4	101.13	107.26	2.69	6	2	5
SB8	392.51	80.90	115.01	3.68	7	1	4
SB9	378.49	80.90	110.20	3.47	6	1	4
SB10	443.36	80.90	112.93	3.84	6	1	4

Table 2: Bioactivity Scores of designed derivatives (SB1-SB10)

Ligands	GPCR	ICM	KI	NRL	PI	EI

SB1	0.05	-0.23	-0.05	-0.14	0.02	0.11
SB2	-0.03	-0.33	-0.13	-0.30	-0.04	0.01
SB3	0.04	-0.21	-0.02	-0.30	0.07	0.14
SB4	0.01	-0.27	-0.11	-0.29	-0.03	0.03
SB5	-0.12	-0.28	-0.21	-0.33	-0.11	-0.03
SB6	-0.01	-0.32	-0.15	-0.36	-0.05	-0.05
SB7	0.01	-0.23	-0.15	-0.21	-0.03	0.08
SB8	-0.02	-0.27	-0.14	-0.26	-0.02	0.05
SB9	-0.04	-0.33	-0.11	-0.26	-0.03	0.02
SB10	-0.08	-0.33	-0.13	-0.38	-0.10	-0.01

Table 3. The pharmacokinetic properties of the designed derivatives (SB1-SB10)

Codes	GI abs.	BBB perm.	CYP 1A2	CYP2 C19	CYP2 C9	CYP2 D6	CYP3A4	Log Kp (cm/s)	Bioavailability
			inhibitor						
SB1	High	No	No	Yes	Yes	Yes	Yes	-6.11	0.55
SB2	High	No	Yes	Yes	Yes	No	Yes	-5.58	0.55
SB3	High	No	Yes	Yes	Yes	Yes	Yes	-6.33	0.55
SB4	High	No	Yes	Yes	Yes	No	Yes	-5.52	0.55
SB5	Low	No	No	Yes	Yes	No	Yes	-6.15	0.55
SB6	High	No	Yes	Yes	Yes	No	Yes	-5.52	0.55
SB7	High	No	No	Yes	Yes	Yes	Yes	-6.11	0.55
SB8	High	No	Yes	Yes	Yes	Yes	Yes	-5.36	0.55
SB9	High	No	Yes	Yes	Yes	No	Yes	-5.58	0.55
SB10	High	No	Yes	Yes	Yes	No	Yes	-5.75	0.55

3.2 Molecular docking- From the initial screening through Lipinski rule, ADME calculations, and bioactivity score, molecules SB1-SB10 successfully passed all the filters and displayed most drug-likeness nature. In table no.4 SBs derivatives selected for docking against dihydropteroate synthase enzyme (1AJ2) had exhibited more potent interactions and binding affinity with the target. Binding affinities (kcal/mol), and the types of interaction of the docked molecules are examined and the molecules' 2D and 3D docking postures are represented. More

the negative docking score show the higher affinity of ligand towards the target. SB3 derivative shows highest negative docking score (-8.9 Kcal/mol) and SB10 shows lowest negative docking score (-8.1 Kcal/mol).

Table 4. The binding interactions of all the designed derivatives (SB1-SB10) with DHPS enzyme (1AJ2)

Comp Code	Binding affinity (Kcal/mol)	Type of interaction
SB1	-8.2	Van der Waals, Conventional Hydrogen bond, Pi-Cation, Pi-Alkyl, Alkyl, Carbon Hydrogen Bond
SB2	-8.2	Van der Waals, Conventional Hydrogen bond, Pi-Cation, Pi-Alkyl, Alkyl, Carbon Hydrogen Bond
SB3	-8.9	Van der Waals, Conventional Hydrogen bond, Alkyl, Pi-Alkyl
SB4	-8.7	Van der Waals, Conventional Hydrogen bond, Alkyl, Pi-Alkyl
SB5	-8.8	Van der Waals, Conventional Hydrogen bond, Pi-Cation, Pi-Alkyl, Alkyl, Carbon Hydrogen Bond
SB6	-8.6	Van der Waals, Conventional Hydrogen bond, Carbon Hydrogen Bond, Pi-Alkyl
SB7	-8.4	Van der Waals, Conventional Hydrogen bond, Alkyl, Pi-Alkyl
SB8	-8.3	Van der Waals, Conventional Hydrogen bond, Pi-Cation, Pi-Alkyl, Alkyl
SB9	-8.5	Van der Waals, Conventional Hydrogen bond, Alkyl, Pi-Alkyl, Carbon Hydrogen Bond
SB10	-8.1	Van der Waals, Conventional Hydrogen bond, Pi-Cation, Pi-Alkyl, Carbon Hydrogen Bond, Alkyl

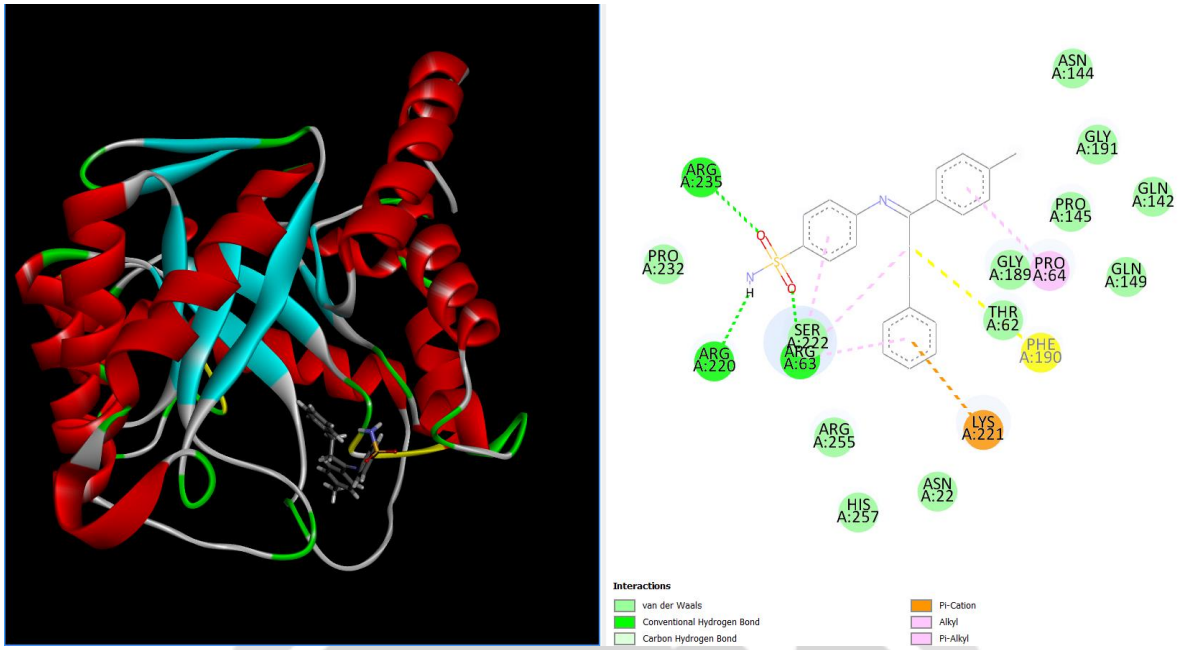


Figure 2. 3D and 2D docking poses of ligand SB1 with dihydropteroate synthase enzyme (1AJ2).

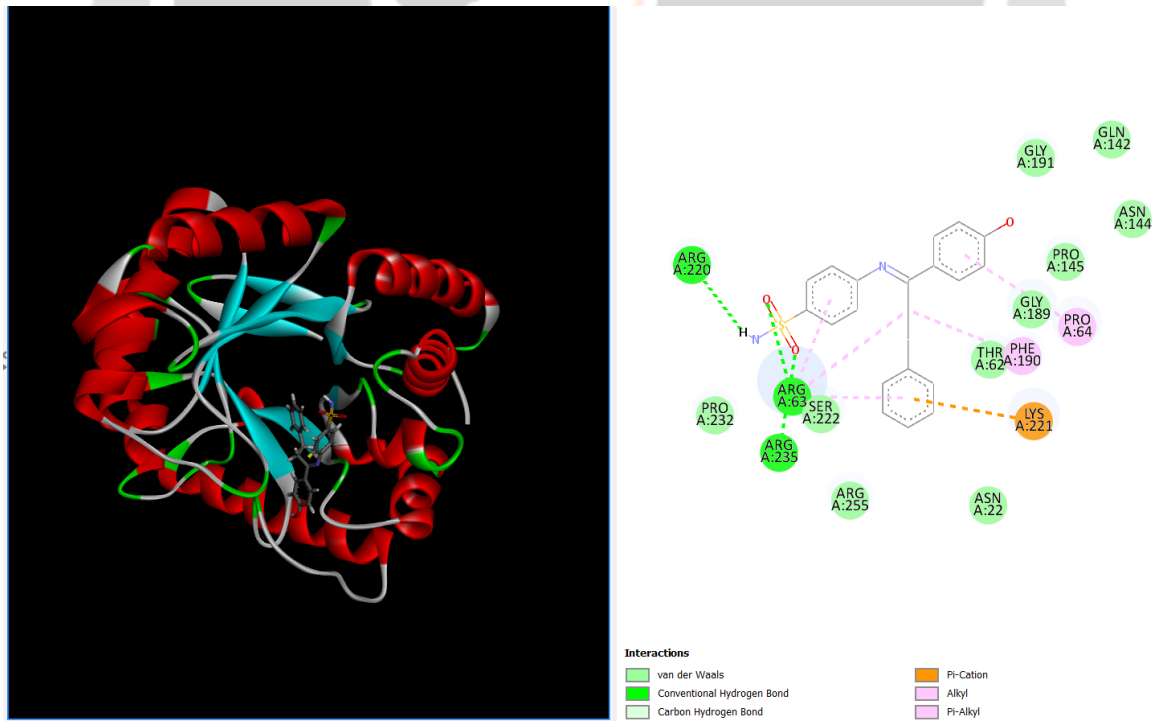


Figure 3. 3D and 2D docking poses of ligand SB2 with dihydropteroate synthase enzyme (1AJ2).

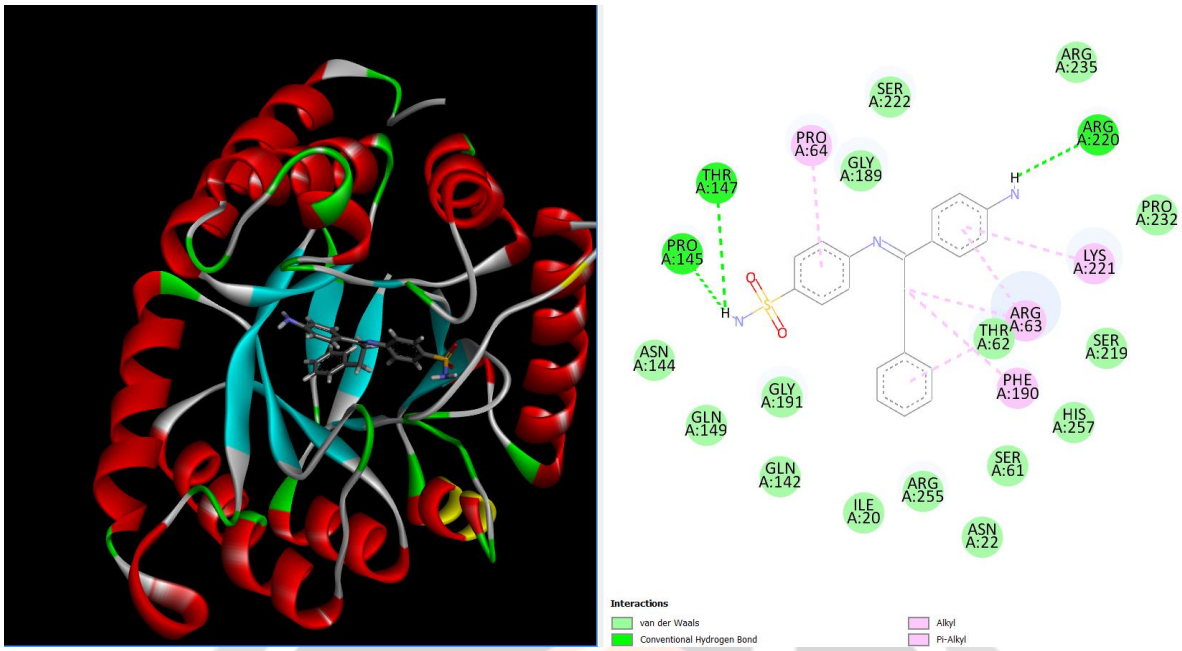


Figure 4. 3D and 2D docking poses of ligand SB3 with dihydropteroate synthase enzyme (1AJ2).

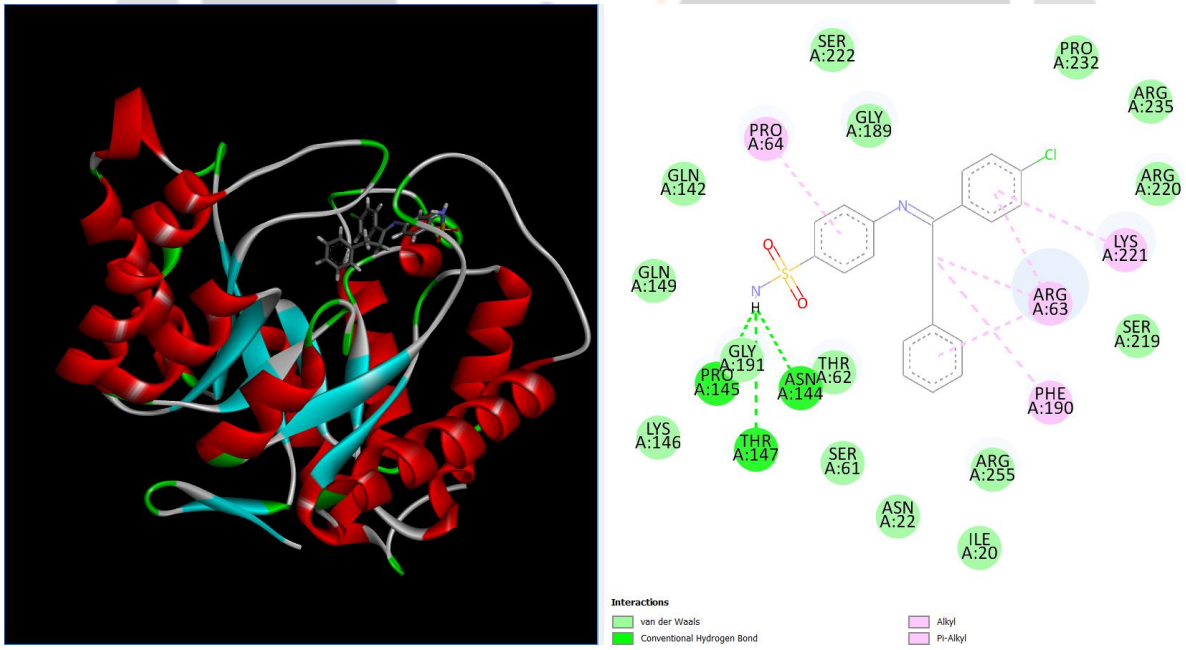


Figure 5. 3D and 2D docking poses of ligand SB4 with dihydropteroate synthase enzyme (1AJ2).

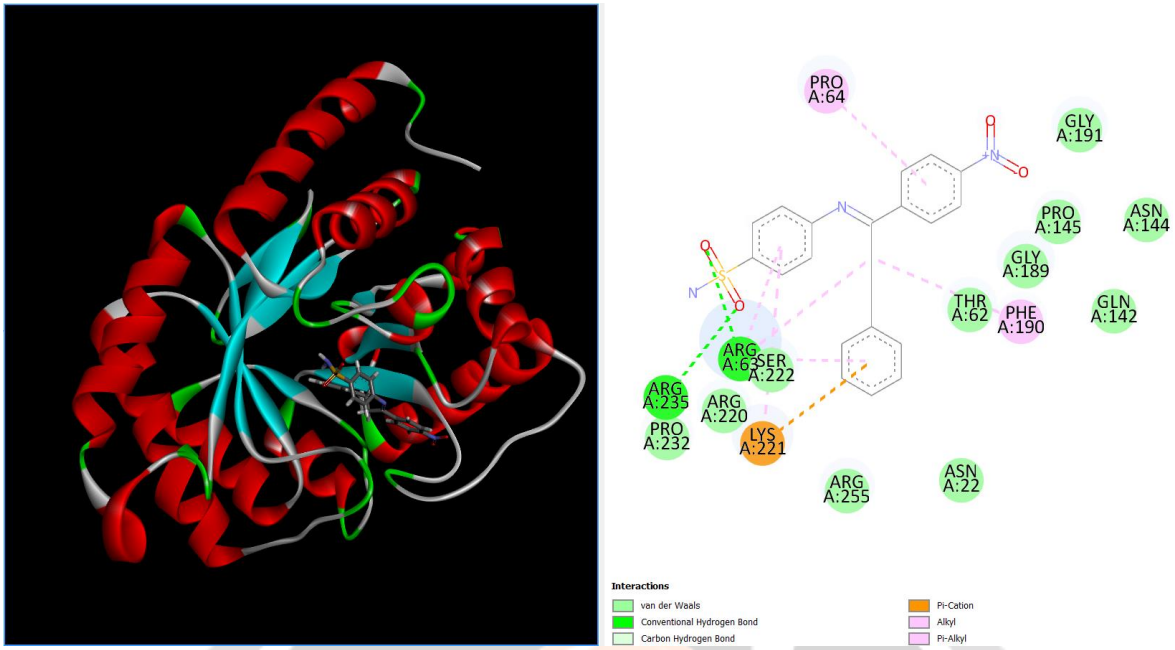


Figure 6. 3D and 2D docking poses of ligand SB5 with dihydropteroate synthase enzyme (1AJ2).

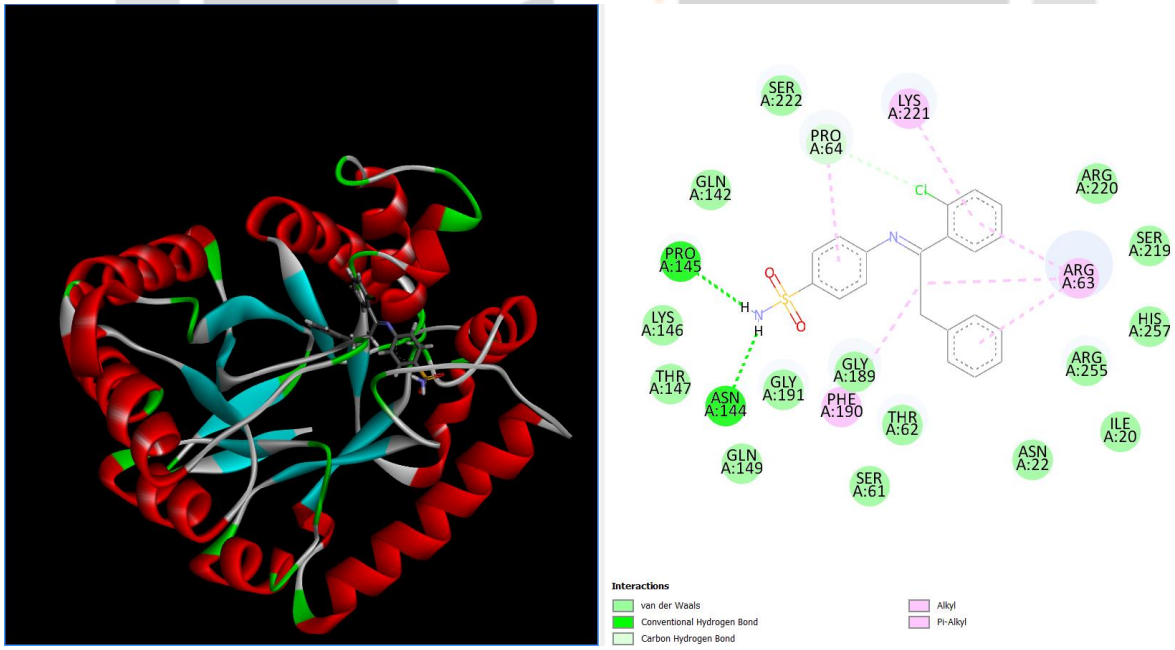


Figure 7. 3D and 2D docking poses of ligand SB6 with dihydropteroate synthase enzyme (1AJ2).

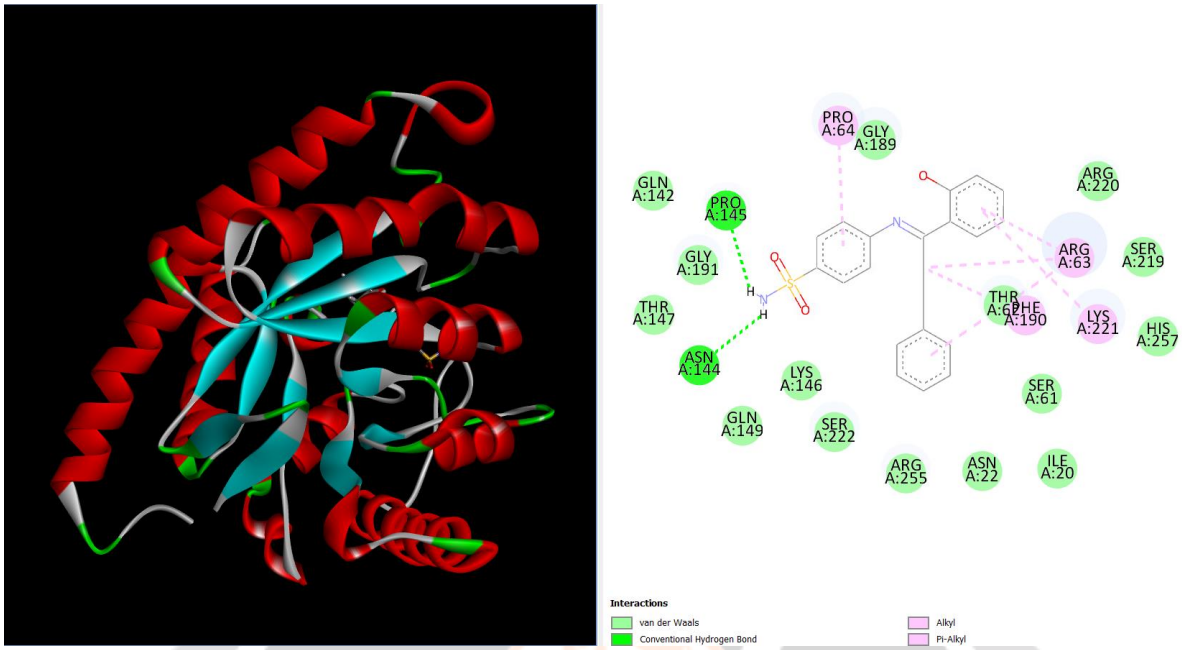


Figure 8. 3D and 2D docking poses of ligand SB7 with dihydropteroate synthase enzyme (1AJ2).

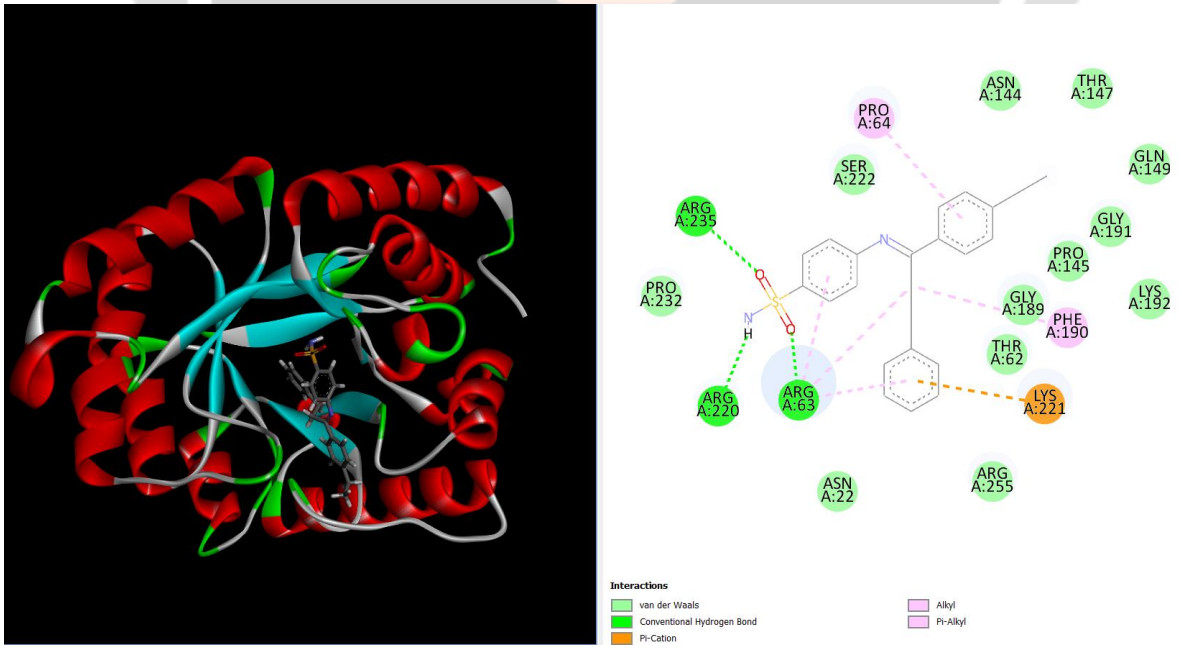


Figure 9. 3D and 2D docking poses of ligand SB8 with dihydropteroate synthase enzyme (1AJ2).

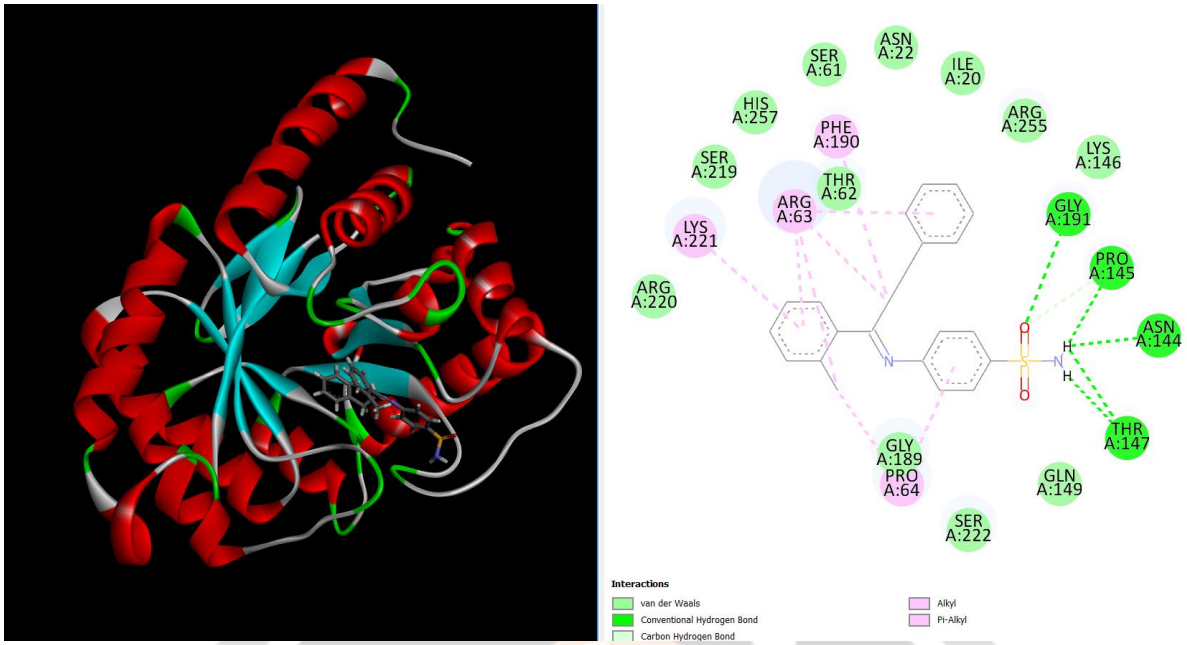


Figure 10. 3D and 2D docking poses of ligand SB9 with dihydropteroate synthase enzyme (1AJ2).

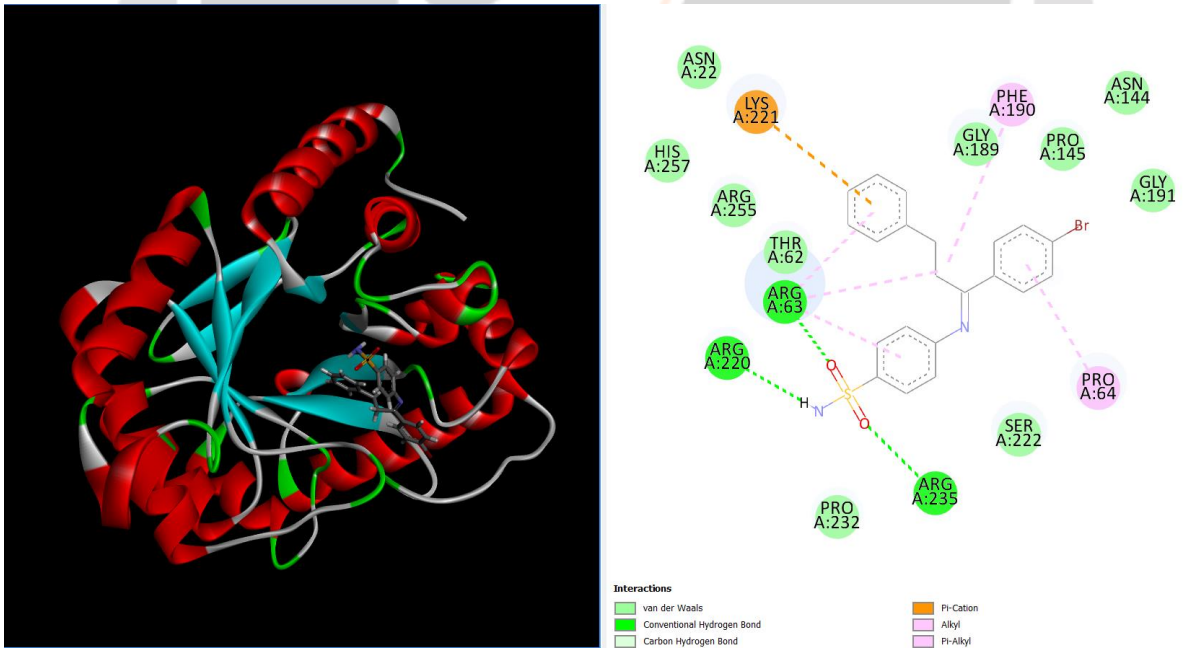


Figure 11. 3D and 2D docking poses of ligand SB10 with dihydropteroate synthase enzyme (1AJ2).

3.3 Prediction of Toxicity- In this study toxicity of SBs derivatives was assessed by using various toxicological endpoints such as hepatotoxicity, carcinogenicity, mutagenicity, cytotoxicity, immunogenicity. The results of toxicity prediction were quantified in binary form i.e. active/ inactive. [27] Most of the SB's derivatives shows the possibility of carcinogenicity could have the ability to cause or increase the prevalence of tumors except SB4, SB6, SB7.

Table 3.1. The toxicity profiles of the designed derivatives (SB1-SB10)

Ligand	Hepato-toxicity	Carcino-genicity	Immuno-toxicity	Muta-genicity	Cyto-toxicity
SB1	Inactive	Active	Inactive	Inactive	Inactive
SB2	Inactive	Active	Inactive	Inactive	Inactive
SB3	Inactive	Active	Inactive	Inactive	Inactive
SB4	Inactive	Inactive	Inactive	Inactive	Inactive
SB5	Inactive	Active	Inactive	Inactive	Inactive
SB6	Inactive	Inactive	Inactive	Inactive	Inactive
SB7	Inactive	Inactive	Inactive	Inactive	Inactive
SB8	Inactive	Active	Inactive	Inactive	Inactive
SB9	Inactive	Active	Inactive	Inactive	Inactive
SB10	Inactive	Active	Inactive	Inactive	Inactive

3. CONCLUSION-

According to the results of docking analysis Schiff base compound SB3, SB4, SB5 and SB6 had highest binding affinity score i.e. -8.9 Kcal/mol, -8.7 Kcal/mol, -8.8 Kcal/mol and -8.6 Kcal/mol respectively. In silico toxicity prediction study suggest that compound SB4, SB6, SB7 exabits low or negligible toxicity in hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity, cytotoxicity. Based on above conclusion compound SB4 and SB6 can be a promising ligand for antibacterial activity. This in silico results suggest to researcher for further investigation through in vitro and in vivo studies to confirm the predicted properties and explore the therapeutic action of compound SB3 and SB5. The computational data from this study will guide further development and optimization of the Schiff base (bearing- imine) derivatives for a dihydropteroate synthase (1AJ2) Inhibition.

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