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Molecular Docking Studies Of Benzothiazole Based Schiff Base Derivatives Against Adenosine A_{2a} Receptor As Potential Anti Parkinsonian Agents

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Abstract:

In recent years, Parkinson's disease (PD) has become a major health concern, especially for adults. Parkinson disease is the most prevalent neurological movement disorder. It was shown that all adenosine A_{2A} receptor antagonists have antiparkinsonian effects. Several Schiff-based compounds based on benzothiazoles were created in the current work and their anti-parkinsonian activity was assessed by docking them against the adenosine A_{2A} receptor (pdb id:5UIG). All adenosine A_{2A} receptor antagonists, including Theophylline and Istradefylline, have been demonstrated to have antiparkinsonian properties.

Keywords: Benzimidazole based Schiff base, Parkinson's Disease, Adenosine A_{2A} Receptor Antagonists Chemsketch software, iGEMDOCK Software, Molecular Docking and Discovery Studio Visualizer.

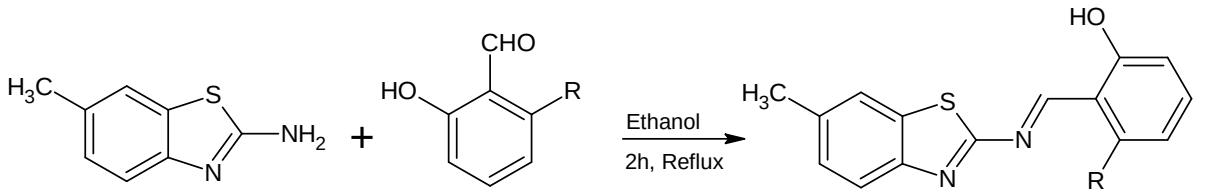
Introduction:

In its ring, a heterocyclic molecule must have at least two different element atoms. "Benzothiazole-based Schiff bases are a class of organic compounds derived from the condensation reaction of benzothiazole with various aldehydes or ketones." Benzothiazole is composed of a thiazole ring

fused with a benzene ring. These substances are interesting for medicinal chemistry and catalysis because of their varied chemical and pharmacological characteristics. Potential uses for their distinct molecular structure and functional groups include corrosion inhibition, fluorescence probes, and medication development. Promising biological activities are displayed by benzothiazole-based Schiff bases [Suyambulingam, et al., 2020, Gawad, et al., 2019, Sheldrick, et al., 2008, Gill, et al., 2015, Mene, et al., 2016] which include, among other things, anti-tubercular[Reshma, et al., 2017, Venugopala, et al., 2019, Keri, et al., 2015,Telvekar, et al., 2012] anti-Parkinson [vijaya kishore kanakaraju1, et al., 2023, zheng, et al., 2018, pourcher, et al., 2005, zúñiga-ramírez, et al ., 2013] analgesic [Oketani, et al., 2001], antifungal [joseyphus, et al., 2008, jarrahpour, et al., 2004], antibacterial [Bhat, et al., 2016, Basser, et al., 2001, da silva cm, et al., 2001, ceramella, et al., 2022, Jorge, et al., 2024, al zoubi, et al., 2013] and anticancer [Mohamed, et al., 2017, Marwein, et al., 2019, Congreve, et al., 2018, Gessi, et al., 2017] properties.

Material and method:

Scheme:



Amino benzothiazole Derivatives

Substituted aldehyde derivatives

Benzothiazole based schiff bases

The synthesis techniques for Schiff bases based on benzothiazoles in the above scheme were taken from the body of existing literature. Several amino benzothiazole derivatives and aldehyde derivatives were chosen using the synthesis method described above, and the resultant product, Schiff bases based on benzothiazoles, was created. After screening the number of compounds with Top Kat program [vijaya kishore kanakaraju, et al.,2023, daina, et al., 2019] Swiss ADME software [vijaya kishore kanakaraju, et al.,2023] was used to forecast the attributes of ADMET. about the toxicity of *Insilco* Molecular docking assays were performed on designed compounds that exhibited good ADME qualities and were anticipated to be non-toxic and non-carcinogenic.

Molecular Docking:

Swiss target prediction: The protein target was chosen from the generated compound library using information from the Swiss Target Prediction algorithm, following the previously established plan. Swiss Target Prediction software was used to forecast the whole pool of safe, non-toxic, and non-carcinogenic chemicals associated with the target protein.

The Adenosine A_{2A} receptor [Azam, et al., 2009, Morelli, et al., 2001, vijaya kishore kanakaraju, et al.,2023] has been shown to be a potential target for most drugs.

Swiss ADME: Swiss ADME software is mainly used for the design ligands are shows pharmacokinetics properties are not. Pharmacokinetic properties are absorption, distribution, metabolism, and excretion. In the swiss ADME software mainly observe Lipinski's rules.

Rule-1: molecular weight of the compound less than 500 Daltons.

Rule-2: Hydrogen bond acceptor less than 10.

Rule-3: Hydrogen bond donor less than 5.

Rule-4: Partition coefficient or lipophilicity (log P) less than 5.
Rule-5: compound must be shows "0" violation.
The top two ligands (A27& A3) and Adenosine A_{2A} receptor antagonist like Istradefylline and Theophylline are exhibiting Lipinski's rule as shown in below table.

Table-1:

Lipinski's rules	A27	A3	Istradefylline	Theophylline
Molecular weight in Daltons	300.33	299.30	384.43	183.19
Hydrogen bond acceptor	5	5	5	4
Hydrogen bond donor	2	1	0	2
Lipophilicity (log P)	3.03	2.70	2.51	-1.50
Violation	0	0	0	0

Using the Chemsketch program, the ligand's 2D structure was drawn and saved in the .mol format. Avogadro tool was used to convert ligand structures into pdb format. Drug docking, screening, and analysis are aided by an automated drug design tool known as iGEMDOCK, or the Genetic Evolutionary Method for Molecular Docking. The orientation and structure of the ligands with respect to the protein's active site are calculated by this program. *In silico* docking simulations were utilized to assess the molecular interactions of a few safe medications with the Adenosine A_{2A} receptor and pdb id is 5uig and cocrystal complex with 8D1, with the help of a cocrystallized ligand inhibitor from the PDB. To visualize and analyse ligand interactions are identify by using Biovia. A traditional docking procedure and scoring function were used to identify the ideal postures. Post-docking interaction profile analysis was also performed to determine the interactions between the ligand and the target protein.

Utilizing Insilco toxicity prediction, safe and non-carcinogenic compounds were found. These molecules, apart from standard Adenosine A_{2A} receptor antagonists as Istradefylline [Jenner, et al., 2021, Park, et al., 2012] and Theophylline [Kulisevsky, et al., 2002, Bishnoi, et al.,2007] were chosen for molecular docking. Molecular interactions and binding affinities were assessed using docking simulations.

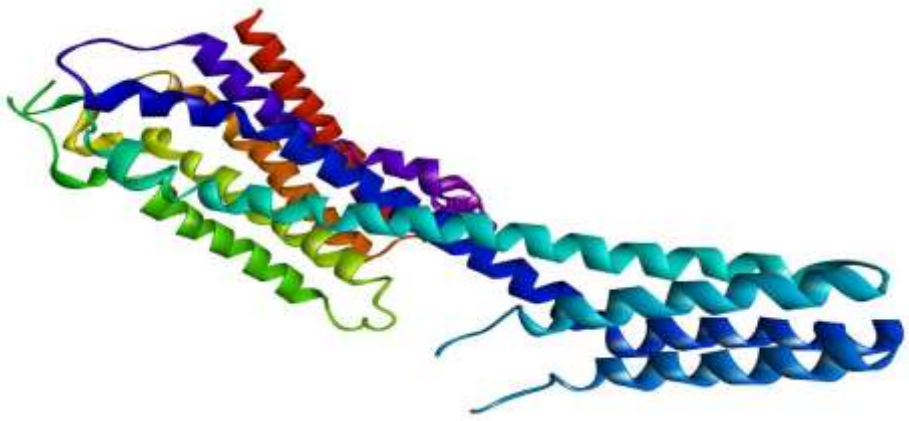
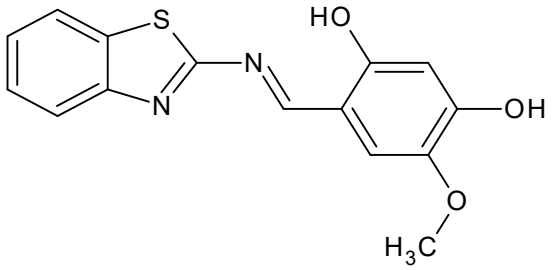


Figure 1: The Adenosine A_{2A} receptor has been cleaned; its PDB ID is 5UIG.

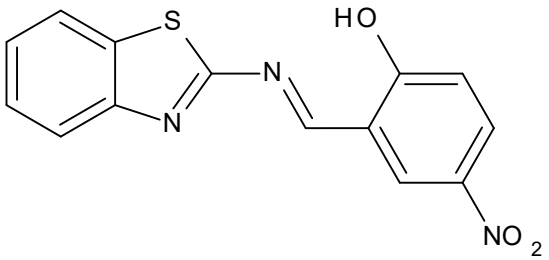
Better binding energies are shown by the two ligand structures that were chosen for visualization the top 2 structures are

1.A27



4-{(*E*)-[(1,3-benzothiazol-2-yl) imino] methyl}-6-methoxybenzene-1,3-diol

2. A3



2-{(*E*)-[(1,3-benzothiazol-2-yl) imino] methyl}-4-nitrophenol

Results and Discussion:

The design compounds are more binding affinity to adenosine A_{2A} receptor when compare to adenosine A_{2A} receptor antagonist like Istradefylline and Theophylline. Top 10 compounds are more binding energies than Istradefylline and Theophylline are shown in Table-2. The top two compounds and adenosine A_{2A} receptor antagonists like Istradefylline and Theophylline are visualized shown in Table-3, Table-4, Table-5 and Table-6.

Table-2: The top ten molecules that include the adenosine A_{2A} receptor interact and have binding energies that are

COMPOUND CODE	BINDING ENERGY (K.CAL/MOL)	Interacting active site amino acid residues
A27	-87.0089	ASN:42, VAL:31, ILE:238, LEU:235, ARG:102, THR:41, VAL:45, ILE:292, PHE:295: LEU:37
A3	-84.1544	VAL:31, ASN:42, ILE:238, LEU:235, TYR:288, ILE:292, VAL:45, ILE:98, ARG:102, LEU:37, PHE:295
A4	-84.114	VAL:31, ASN:42, ILE:238, LEU:235, TYR:288, ILE:292, VAL:45, ILE:98, ARG:102, THR:41, LEU:37, PHE:295

A1	-84.079	ARG:102, ASN:42, ASN:39, LEU:235, TYR:288, VAL:45, LEU:37, GLU:194, ILE:98, ILE:238, THR:41, ILE:292
A14	-83.4871	ASN:42, LEU:235, ILE:238, TYR:288, VAL:45, ILE:292, ARG:102, ILE:98, THR:41, LEU:37, VAL:31, PHE:295
A31	-83.2063	ASN:42, ARG:102, THR:41, LEU:235, ILE:238, VAL:45, ILE:292, ASN:39, ILE:98, TYR:288, LEU:37, GLU:294, ASN:36
A6	-81.2877	ASN:42, LEU:37, ASN:39, ILE:292, THR:41, ILE:98, TYR:288, ILE:238, VAL:45, ASN:36, GLU:294, ARG:102, ALA:231, LEU:235, SER:234
A5	-81.0339	VAL:31, ASN:42, ILE:238, LEU:235, TYR:288, ILE:98, ARG:102, THR:41, ILE:292, PHE:295, LEU:37
A36	-80.3505	ALA:99, TYR:288, ALA:231, SER:234 ILE:292, LEU:235, ARG:102, HIS:230, VAL:45, ILE:238, ILE:98
A2	-80.2285	ASN:42, ILE:238, LEU:235, TYR:288, ILE:292, VAL:45, PHE:295, LE:98, ARG:102, THR:41, LEU:37, VAL:31,
COCRYSTALIZED LIGAND	-79.3683	ASN:42, ILE:98, VAL:45, LEU:37, GLU:294, ASN:36, LEU:235, ILE:292, THR:41, ILE:238, TYR:288, ARG:102, ASN:39
ISTRADEFYLLINE	-75.9925	HIS:230, ARG:291, ALA:231, ARG:293, ALA:231, ILE:98, LEU:235, ILE:292, TYR:288, ILE:238, ARG:102
THEOPHYLLINE	-60.7097	ALA:231, LEU:235, ARG:102

In the above table green colour indicates number of hydrogen bonds present in the compound

Table-3: Adenosine A_{2A} receptor docking and data visualization of A27

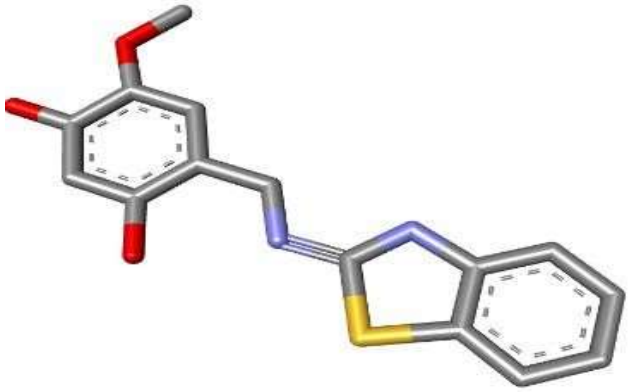
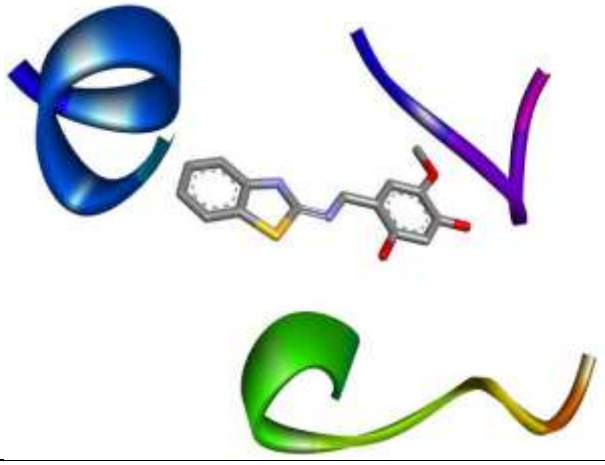
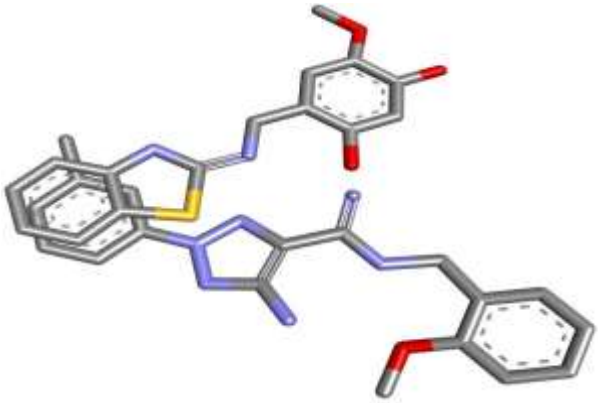
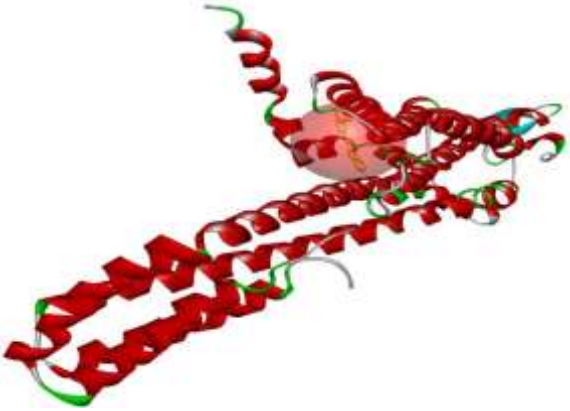
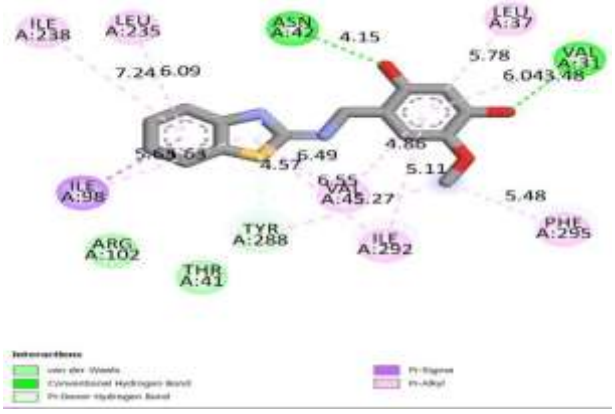
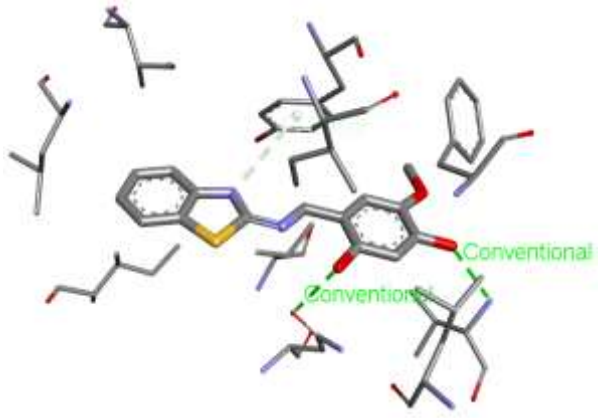
	
1. A27 only ligand	2. A27 ligand with adenosine A_{2A} receptor complex
	
3. A27 ligand with cocrystallized ligand complex	4. A27 ligand with adenosine A_{2A} whole receptor complex
	
5. A27 2D interaction with adenosine A_{2A} receptor	6. A27 3D interaction with adenosine A_{2A} receptor

Table-4: Adenosine A_{2A} receptor docking and data visualization of A3

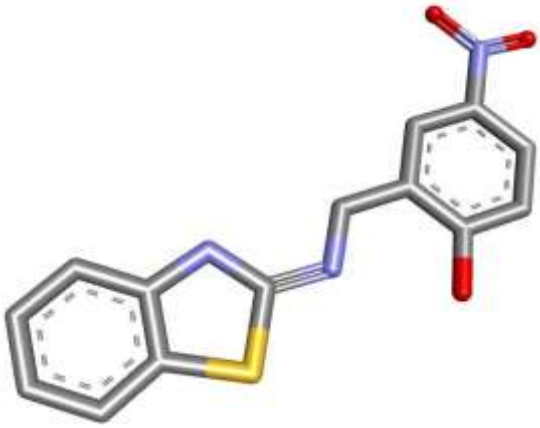
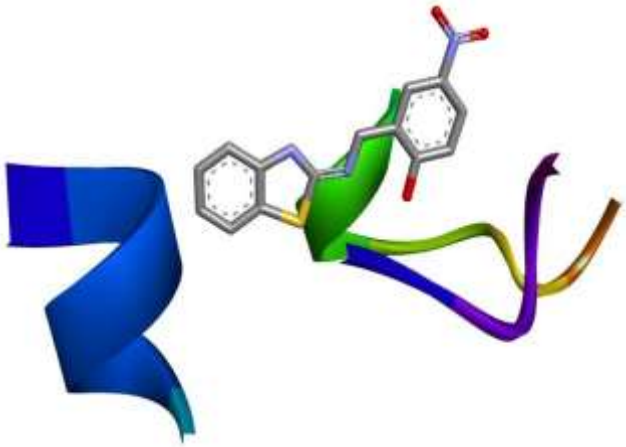
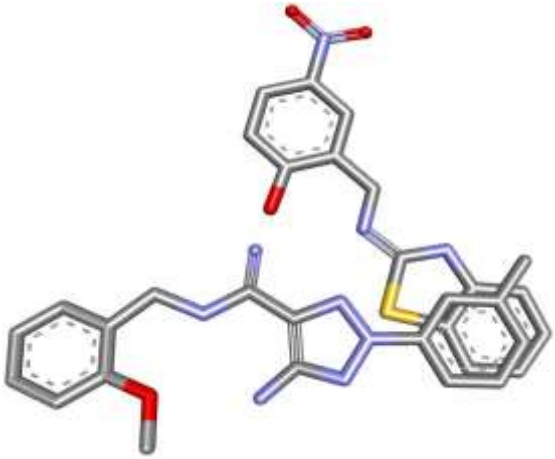
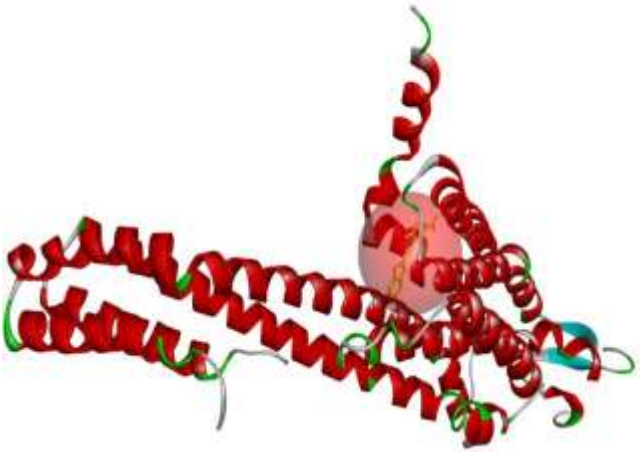
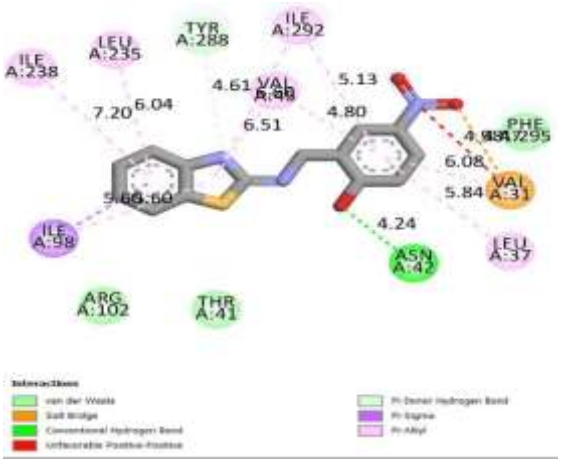
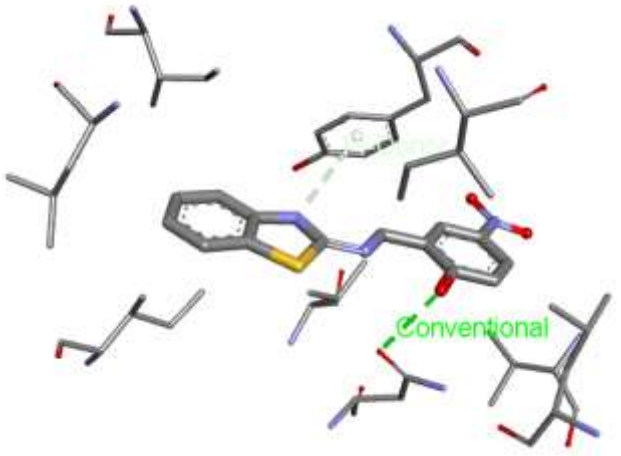
	
1. A3 only ligand	2. A3 ligand with adenosine A_{2A} receptor complex
	
3. A3 ligand with cocrystallized ligand complex	4. A3 ligand with adenosine A_{2A} whole receptor complex
	
5. A3 2D interaction with adenosine A_{2A} receptor	6. A3 3D interaction with adenosine A_{2A} receptor

Table 5: Adenosine A_{2A} receptor docking and data visualization of Istrdefylline

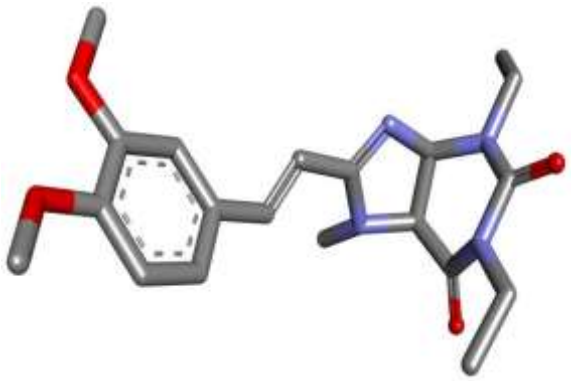
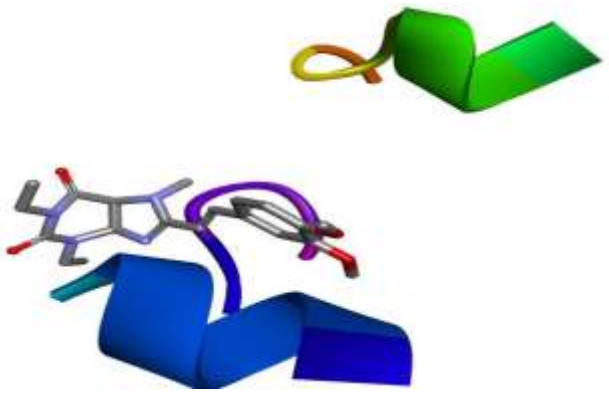
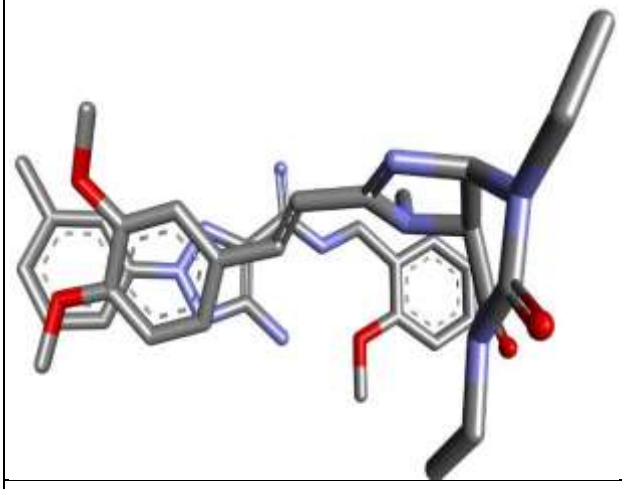
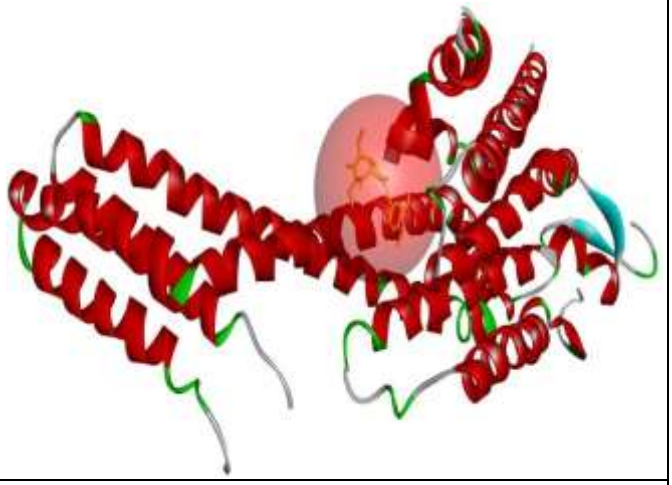
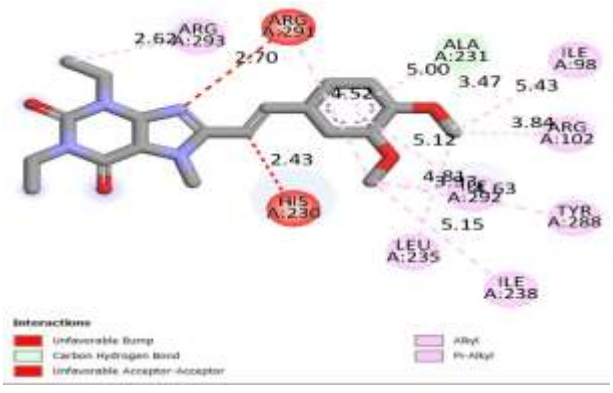
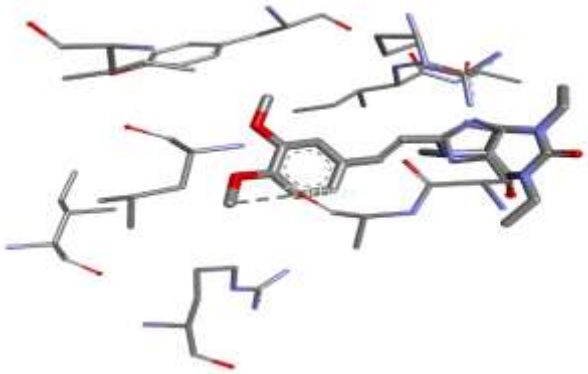
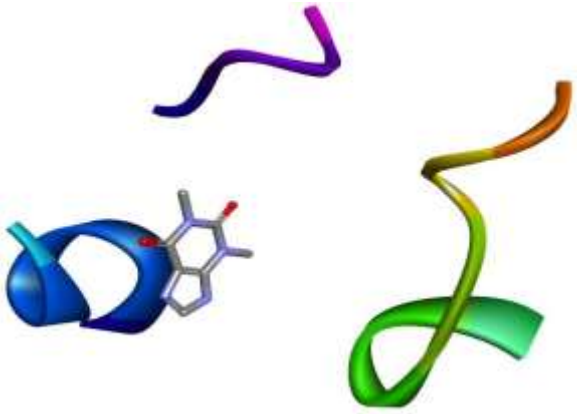
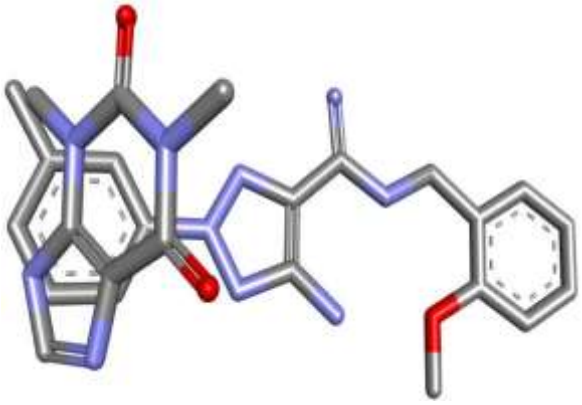
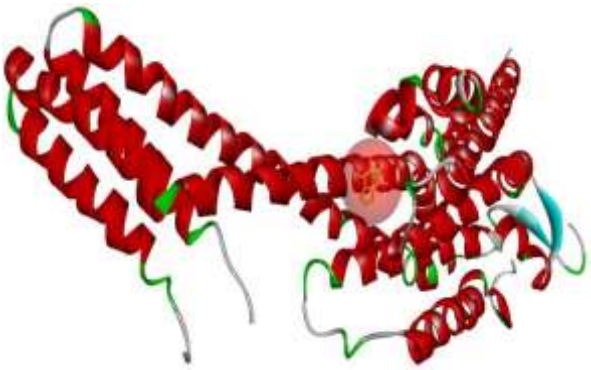
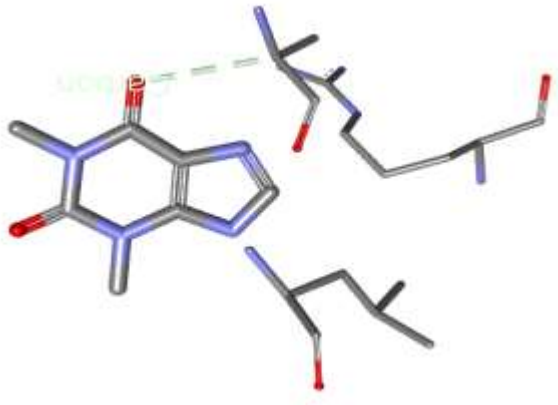
	
1. Istradefylline only ligand	2. Istradefylline ligand with adenosine A_{2A} receptor complex
	
3. Istradefylline ligand with cocrystallized ligand complex	4. Istradefylline ligand with adenosine A_{2A} whole receptor complex
	
5. Istradefylline 2D interaction with adenosine A_{2A} receptor	6. Istradefylline 3d interaction with adenosine A_{2A} receptor

Table-6: Adenosine A_{2A} receptor docking and data visualization of Theophylline

	
1. Theophylline only ligand	2. Theophylline ligand with adenosineA_{2A} receptor complex
	
3.Theophylline ligand with cocrystallized ligand complex	4.Theophylline ligand with adenosine A_{2A} whole receptor complex
	
5. Theophylline 2D interaction with adenosine A_{2A} receptor	6. Theophylline 3D interaction with adenosine A_{2A} receptor

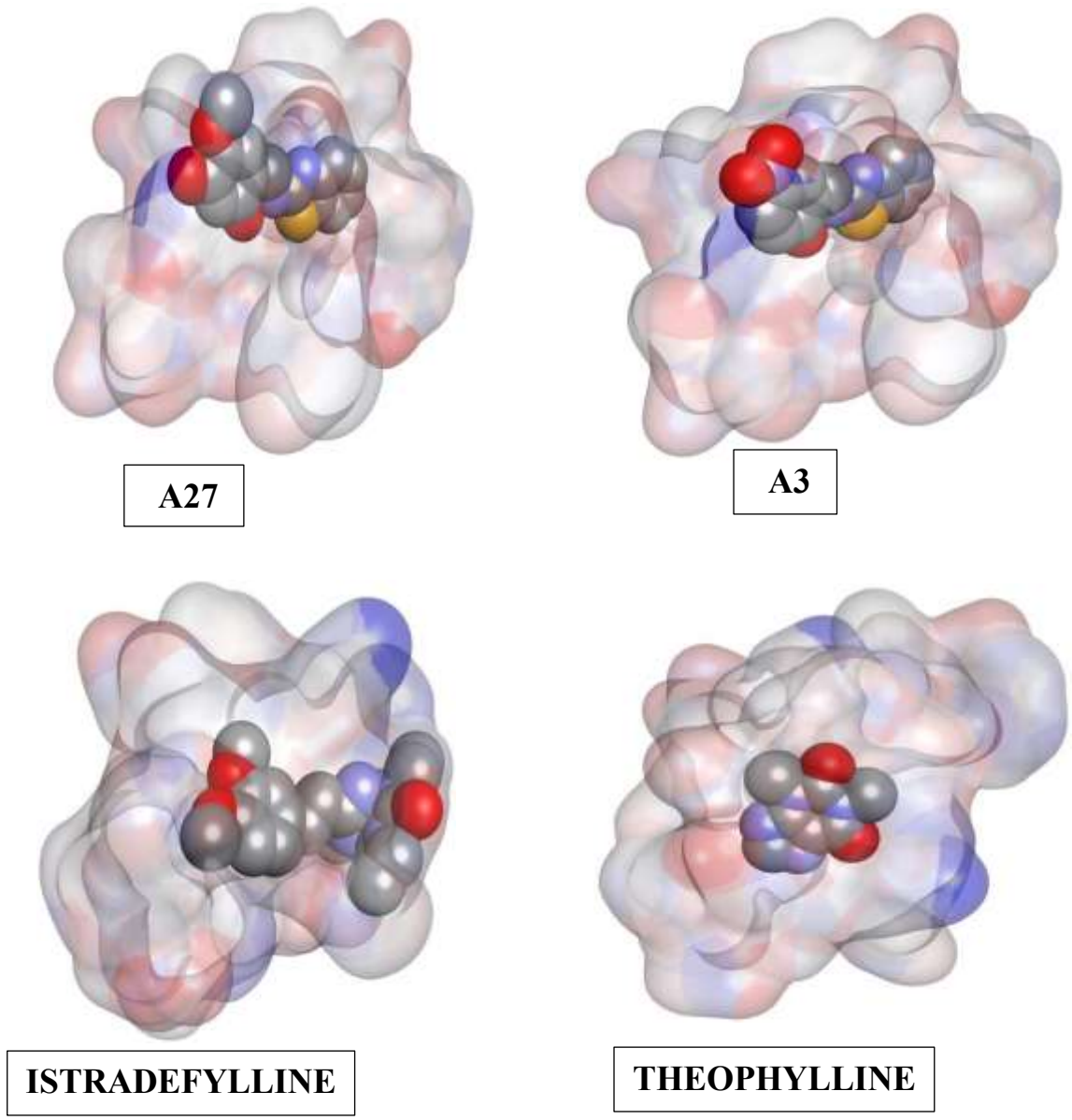


Figure 2: shows the binding mechanisms of A27, A3, Istradefylline, and Theophylline with A_{2A} protein as well as the active site pocket surface.

Conclusion:

In summary, A27 and A3B rank first and tenth, respectively, with binding energies greater than those of traditional adenosine A_{2A} receptor antagonists. The binding energies of A27 (-87.0089 kcal/mol) and A3 (87.1544 kcal/mol) are superior to those of typical antagonists such as Istradefylline (-75.9925 kcal/mol) and Theophylline (-60.7097).

1.Five amino acid residues are shared by Istradefylline and A27, which are ILE:238, LEU:235, ARG:102, TYR:288, and ILE:292.

2. Six amino acid residues are shared by Istradefylline and A3: ILE:238, LEU:235, TYR:288, ILE:292, ILE:98, and ARG:102.

3. Two amino acid residues are shared by Theophylline and A27, specifically: ARG:102, LEU:235

4. Theophylline and A3 have two amino acid residues in common: LEU:235 and ARG:102.

Binding pocket analysis: the top ligands and standard ligands are Istradefylline and Theophylline was docked in the centre of the binding pocket. The improved binding energy has been ascribed to

this. which is shown in fig-2 The existence of electron-donating groups like two OH groups and electron withdrawing groups like one OCH3 group may be the cause of A27 higher binding affinity. One electron-donating OH group and one electron-withdrawing N_{O2} group may be the cause of A3 superior binding affinity. Since compounds A27 and A3 have higher binding affinities and energies than common Adenosine A2A receptor antagonists like Istradefylline and Theophylline. A27 ligand contain two hydrogen bonds and A3 ligand contain one hydrogen bonds, standard ligand Istradefylline and theophylline has no hydrogen bond finally A27 and A3 ligand are shown better Parkinson's activity top compound are further prepared and check *In vivo* activities.

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