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Molecular Docking Studies of Schiff Based Derivatives Against Adenosine A2a Receptor as Potential Anti Parkinsonian Agents

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Abstract: In the recent years, Parkinson's disease has grown to be a serious health issue. It was demonstrated that the antiparkinsonian effects of all adenosine A2A receptor antagonists. For anti-parkinsonian efficacy, a large number of Schiff-based derivatives were created and docked against the Adenosine A2a receptor (pdb id:3EML) in the current work. We examined the ligands with common Adenosine A2a receptor antagonists like caffeine and Istradefylline.

Keywords: Schiff base, Adenosine A2A Receptor Antagonists, Parkinson's Disease, Molecular Docking, iGEMDOCK Software, and Discovery Studio Visualizer, Analysis of Variance (ANOVA), Hypothesis Testing, Significance Level, P-Value

1. Introduction:

Schiff bases are significant class of drugs for the therapy of numerous diseases. They have been in the research area of interest; since long ago. Hugo Schiff originally characterized Schiff Bases about 160 years ago. An aldehyde or ketone that contains carbonyl group and has a nitrogen-based equivalent is called a Schiff base. It is created by condensing a primary amine with the carbonyl group and substituting the carbonyl group with an imine group known as azomethine [Hameed et al., 2017, Raczuk, et al., 2022 & Kajal et al., 2013]. Particularly adaptable compounds with C = N (imine) groups are aniline-Schiff bases, which have been shown to exhibit a wide range of biological functions [Dasilva, et al., 2011, Ceramella, et al., 2022, Jorge, et al., 2024, Alzoubi, et al., 2013 & Bhattacharya, et al., 2021]. Antibacterial, antifungal, [Joseyphus, et al., 2008, Jarrahpour, et al., 2004] anticancer [Matela, et al., 2020], and Anti-inflammatory [Sandhu, et al., 2023]. Adenosine A2a antagonist have potent anti Parkinson's activity [Subramanian, et al., 2023, Chand, et al., 2023, Avram, et al., 2022, Cristalli, et al., 2008, Zuniga, et al., 2020, Chen, et al., 2020, Pourcher, et al., 2015, Franco, et al., 2021, Wang, et al., 2021, Jacobson, et al., 2022, Kanda, et al., 2020. Elmer, et al., 2020, Zheng, et al., 2018, Aryati, et al., 2019 and Shang, et al., 2021].

2. Materials And Methods:

ChemSketch software was used to sketch the ligands in mol format, and Avogadro software was used for converting them to pdb format. Molecular docking studies were carried out by using the iGEMDOCK software, and the outcomes were finally visualized by using Discovery Studio Visualizer.

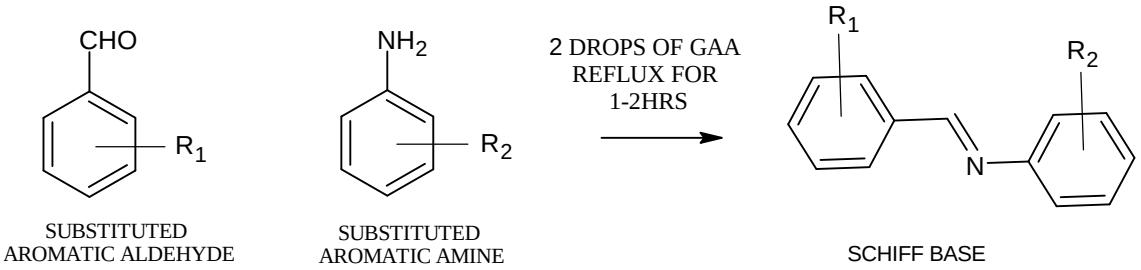


Figure 1: Scheme for designing the final compounds

The synthetic procedures for Schiff bases were taken from the existing literature. Different aromatic aldehydes and aromatic amines were chosen from the above-mentioned synthetic scheme (Figure 1), and the final products were designed in accordance with the scheme [Shukla, et al., 2017, Adesina, et al., 2022 and Yerma, et al., 2022]. Using SwissADME software [Daina, et al., 2017, Vijay Kishore, et al., 2023] the ADME properties of a vast library of designed molecules were predicted. Priorly they were screened Insilco using TopKat software [Prival, et al., 2001, Vijay Kishore, et al., 2023 & Daina, et al., 2019] for toxicity. Designed compounds with good ADME properties and anticipated non-carcinogenic and non-toxic compounds were chosen for molecular docking experiments.

2.1. Molecular Docking: The Swiss Target Prediction software [Hanwell, et al., 2012, Hsu, et al., 2011, Jacobson, et al., 2022] was used to choose the protein target for the library of compounds that were designed in accordance with the previously outlined scheme. Swiss Target Prediction software predicted every possible combination for the target protein, including safe, non-toxic, and non-carcinogenic ligands. Adenosine A2a receptor has been identified as a potential target to the majority of ligands. ChemSketch software was used to sketch the ligands 2D structures, which were then saved in. mol format. By using the Avogadro tool [Jenner, et al., 2021, Pinna, et al., 2014, Mizuno, et al., 2013] the ligand structures in. mol format were converted into the pdb format. Docking studies were conducted for the safe, non-carcinogenic developed compounds with good ADME features to evaluate binding

poses and interactions. IGEMDOCK software was utilized for docking, screening, and analysis. Together with common Adenosine A2a receptor antagonists like caffeine Istradefylline were selected for molecular docking. This software calculates the ligand's orientation and structure with respect to the protein's active site. Adenosine A2a receptor was obtained from Protein data bank in order to assess the molecular interactions between the adenosine A2a receptor (PDB ID: 3EML A2a receptor co crystallized with ZM241385) (Figure 2) and the designed ligands along with standard antagonists [Mori, et al., 2015, Berger, et al., 2020 & Uchida, et al., 2014].

An accurate docking strategy was chosen, and the standard docking procedure was observed too. The best ligands were determined using the scoring mechanism. The software computed the score function by combining electrostatic energy, hydrogen bonding and Vander Waals energy. Insilco toxicity prediction was utilized to identify safe and non-carcinogenic chemicals. Docking simulations were used to evaluate molecular interactions and binding affinities. Among all the compounds, the top two compounds with the best binding energies and molecular interaction profiles were selected for visualization.

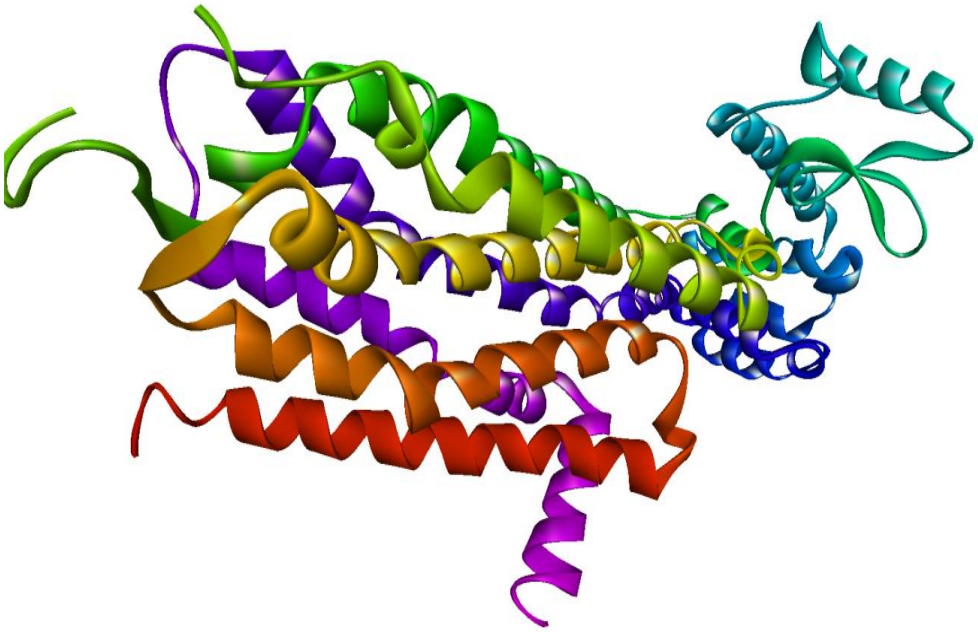
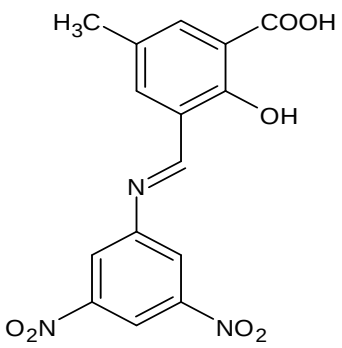


Figure 2: Adenosine A2a receptor cleaned (PDB ID: 3EML)

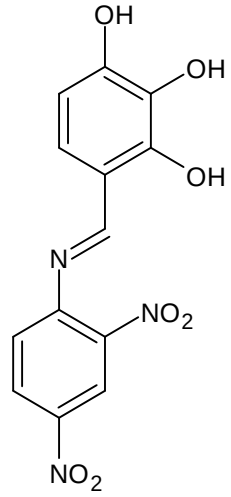
3. Results and Discussion

The majority of the designed ligands binds to the adenosine A2a receptor with greater affinity. Compared to the conventional Adenosine A2a receptor antagonists like Istradefylline (-92 kcal/mol) and caffeine (-57.70 kcal/mol), all of the ligands have higher binding energies. Compounds 20A9B (-101. K.cal/mol) and 2A3B (-99.03 kcal/mol) which are ranked highest, were selected for visualization Figure 1, Table 1-5).



3,5-dinitrophenyl)imino]methyl}-2-hydroxy-5-methylbenzoic acid

2A3B



4-[(2,4-dinitrophenyl)imino]methyl}benzene-1,2,3-triol

20A9B

Table 1: Interaction and binding energy summary of the top 10 compounds against adenosine A2a receptor

Ligand Code	**Binding Energy (K. Cal/mol)**	**Interacting active site amino acid residues**
20A9B	**-101.44**	**HIS:264, ALA:265, PHE:168, PRO:266, LEU:267, MET:270, LEU:167, GLU:169, ASP:170**
2A3B	**-99.04**	**ASN:253, TYR:271,** VAL**:84, MET:270, HIS:250 TRP:246 MET:177, LEU:249, ASN:181, LEU:85, GLU:169, ALA:63, ILE:66, ILE:274,**
20A17B	-96.88	**PHE:168, GLU:169,** HIS:264, SER:67, CYS:166, TYR;271, LEU:267, ASP:170, ALA:63, LEU:167, ILE:274, ILE:66
20A7B	-96.26	**PHE:168,** PRO:266, LEU:267, ALA:265, MET:270, GLU:169, ASP:170, HIS:264
20A5B	-95.78	**HIS:264, PHE;168,** PRO:266, ALA:265, MET:270, LEU:167, LEU:267, GLU:169, ASP:170
20A4B	-95.16	**PHE:168,** LEU:167, MET:270, LEU:267, ALA:265, PRO:266, ASP:170, GLU:169, HIS:264
20A15B	-94.41	**PHE:168, SER:277**, LEU:167, ASN:253, MET:177, LEU:85, TRP:246, HIS:278, MET:270, LEU:249, VAL:84, ILE:274
20A3B	-93.76	**PHE:168, HIS;264, PRO**:266, ALA:265, MET:270, LEU:167, LEU:267, ASP:170, GLU:169
20A20B	-97.49	**PHE:168,** LEU:167, MET:270, ALA:265, PRO:266, LEU:267, HIS:264,
Co-Crystallized ligand	**-96.57**	**GLU:169, ASN:253, ASN:181,** VAL:186, THR:88, HIS:250, TRP:246, HIS:264, LEU:267, TYR:271, MET:177, VAL:84,

Istradefylline	**-92.10**	PHE:168, SER:277, ILE:66, LEU:167, MET:270, HIS:264, GLU:169, ALA:63, VAL:84, HIS:278, TRP:246, ILE:274, LEU:249
Caffeine	**-57.70**	GLU:169, LEU:167, PHE:168, MET:270, ILE:274, SER:67, ILE:66, TYR:271

Table 2: Adenosine A2a receptor docking and visualization data of 20A9B

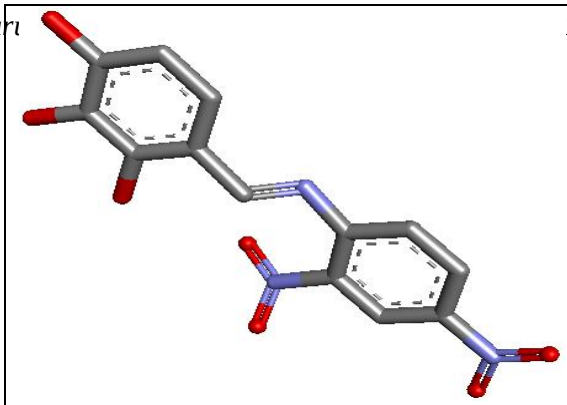
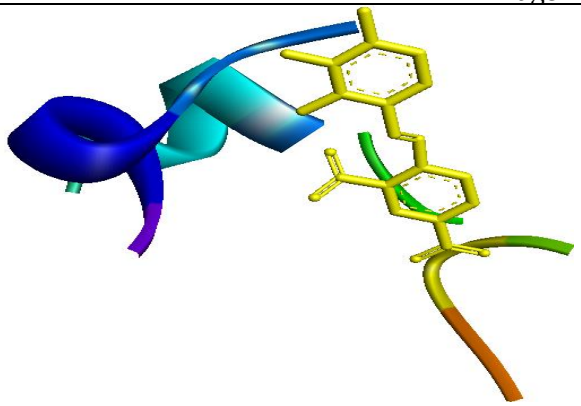
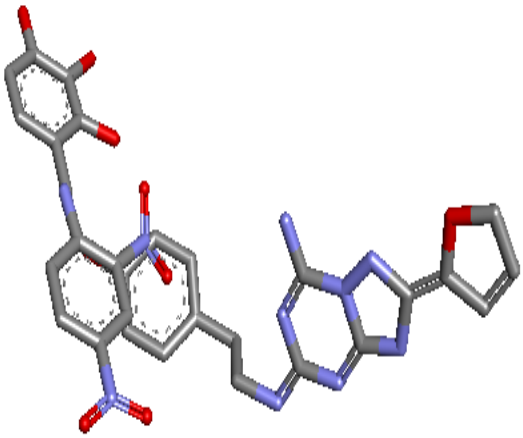
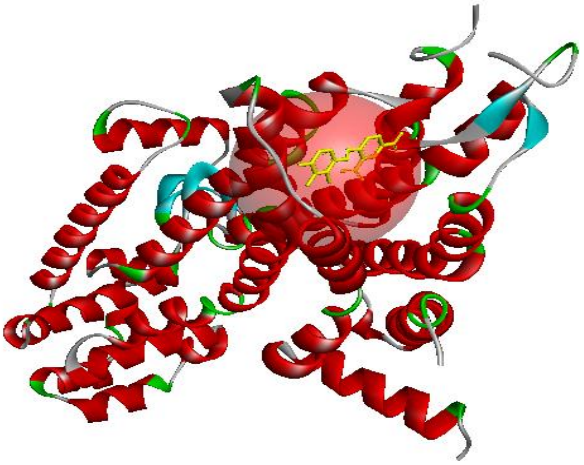
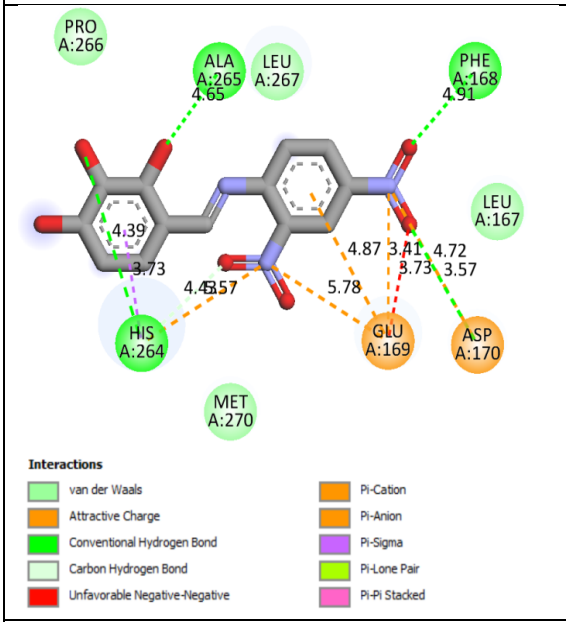
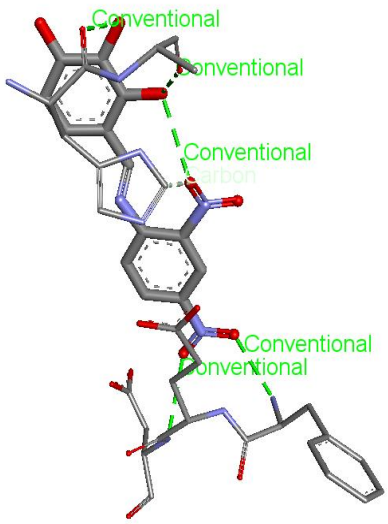
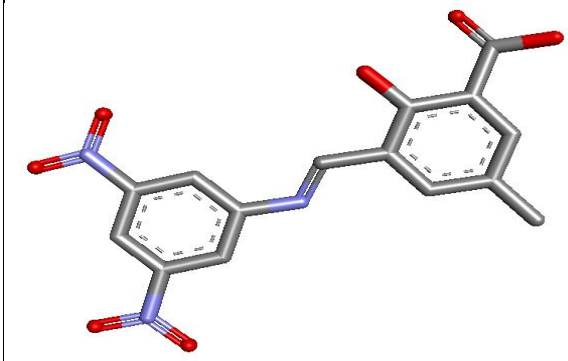
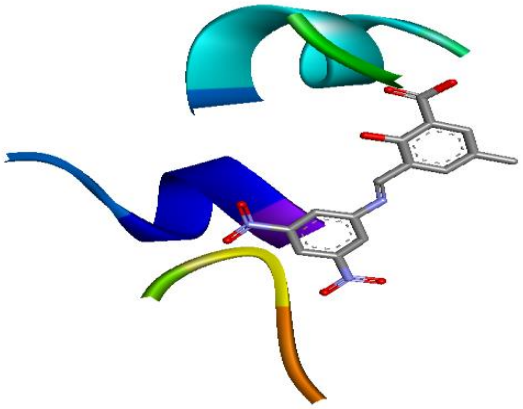
	
1. 20A9B Ligand	2. 20A9B Ligand with AdenosineA2a Receptor complex
	
3. 20A9B Ligand + cocrystalized ligand overlap	4. 20A9B Ligand with Adenosine A2a whole Receptor
	
5. 20A9B Ligand 2-Dimension interaction with Adenosine A2a receptor	6. 20A 9B Ligand 3-Dimension interaction with Adenosine A2a receptor

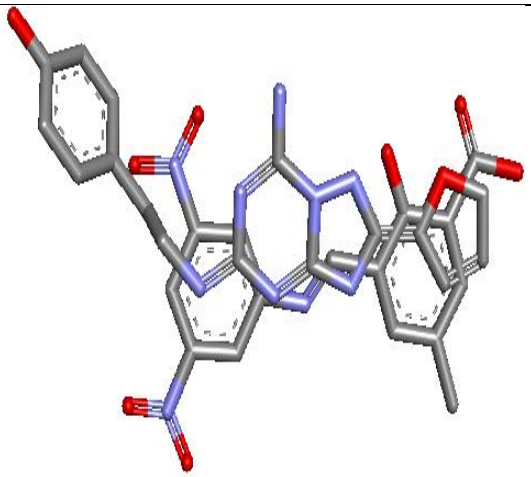
Table 3: Adenosine A2a receptor docking and visualization data of 2A3B



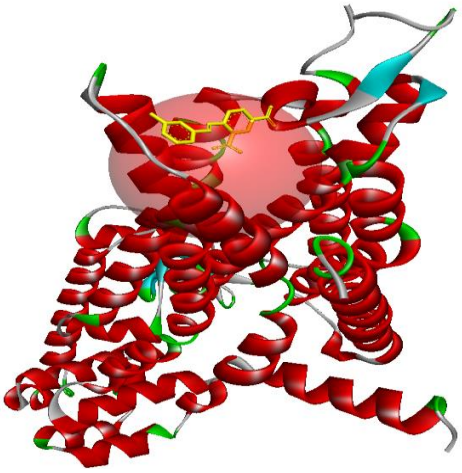
1. 2A3B Ligand



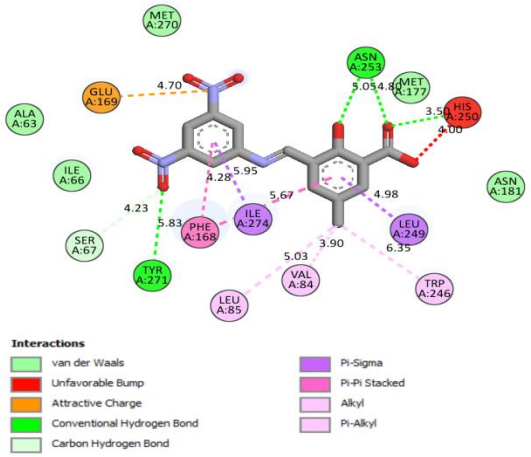
2. 2A3B Ligand with AdenosineA2a Receptor complex



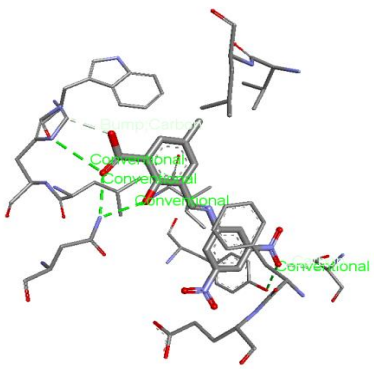
3. 2A3B Ligand + cocrystalized ligand overlap



4. 2A3B Ligand with Adenosine A2a whole Receptor



5. 2A3B Ligand 2-Dimension interaction with Adenosine A2a receptor



6.2A3B 3-Dimension interaction with Adenosine A2a receptor

Table 4: Adenosine A2a receptor docking and visualization data of Caffeine

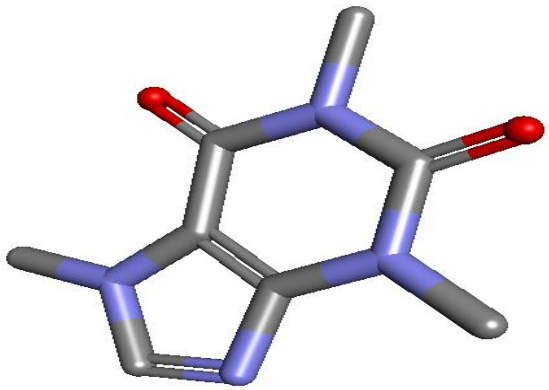
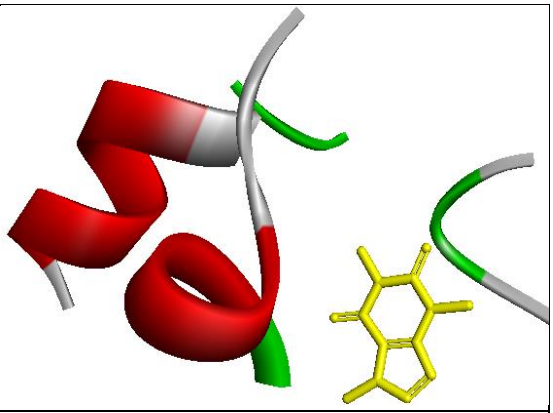
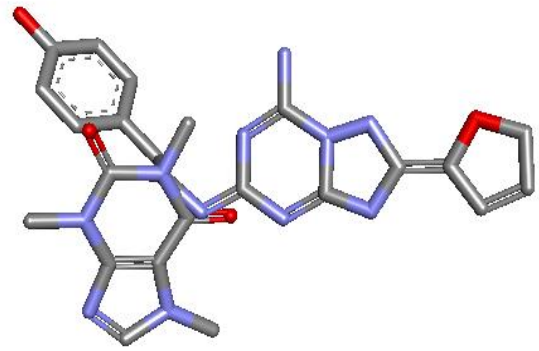
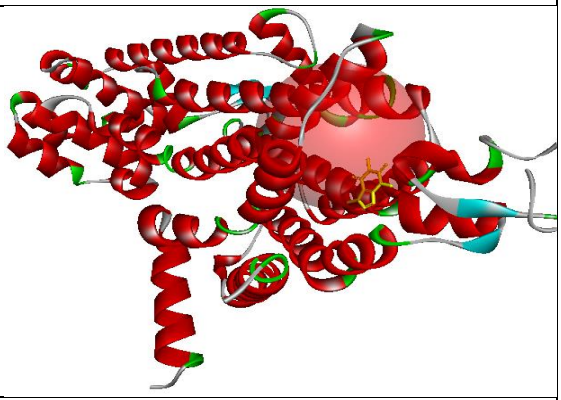
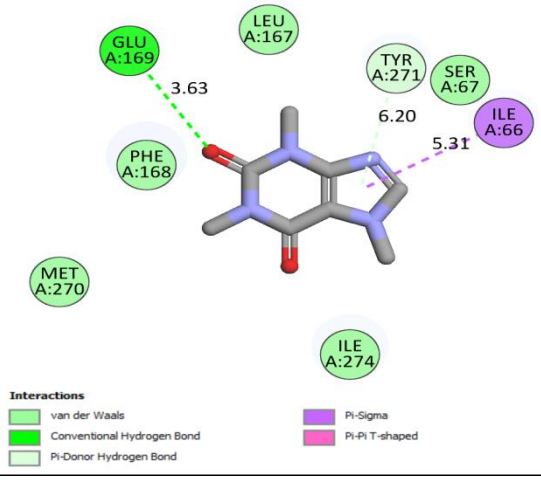
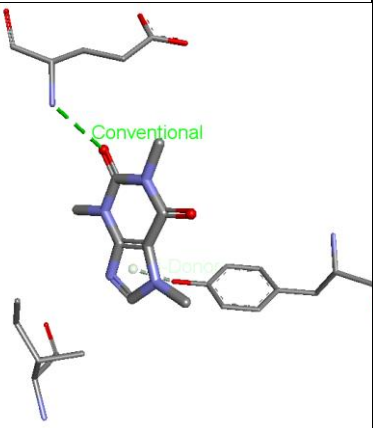
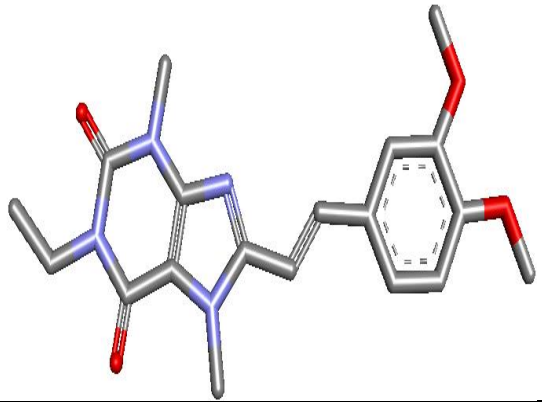
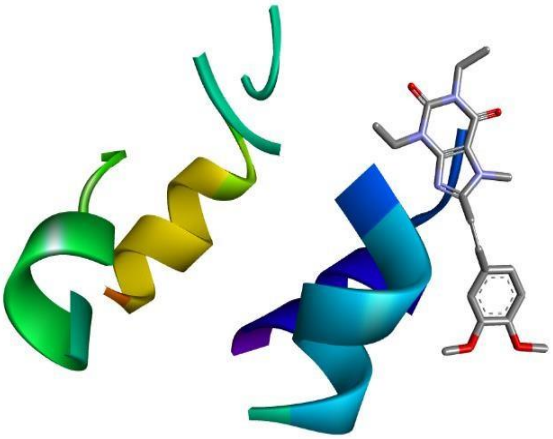
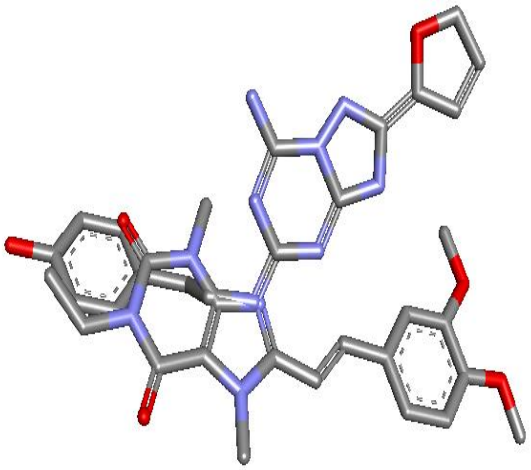
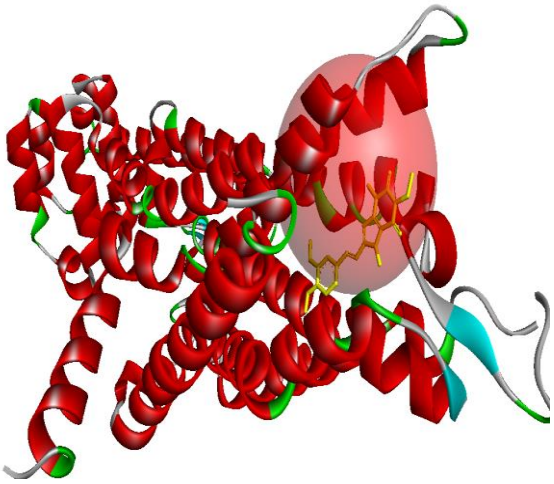
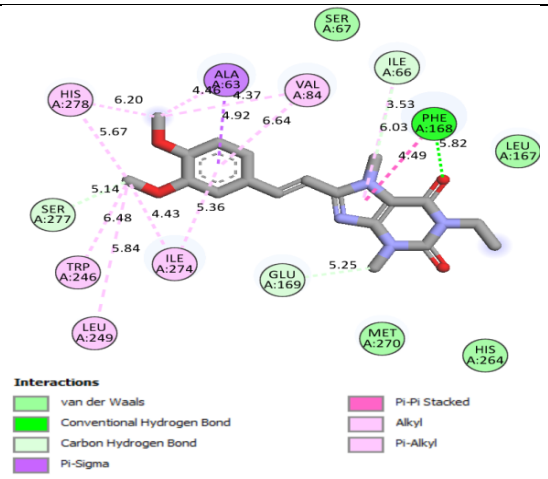
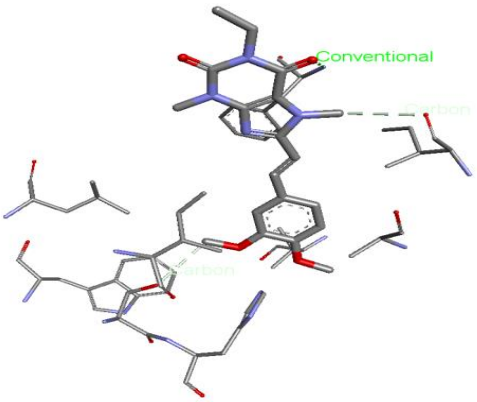
	
1. Caffeine Ligand	2. Caffeine Ligand with AdenosineA2a Receptor complex
	
3. Caffeine Ligand + cocrystalized ligand overlap	4. Caffeine Ligand with Adenosine A2a whole Receptor
	
5. caffeine 2-Dimension interaction with Adenosine A2a receptor	6. caffeine 3-Dimension interaction with Adenosine A2a receptor

Table 5- Adenosine A2a receptor docking and visualization data of Istradefylline

	
1. Istradefylline Ligand	2. Istradefylline Ligand with AdenosineA2a Receptor complex
	
3. Istradefylline Ligand + cocrystalized ligand overlap	4. Istradefylline Ligand with Adenosine A2a whole Receptor
	
5. Istradefylline 2-Dimension interaction with Adenosine A2a receptor	6. Istradefylline 3-Dimension interaction with Adenosine A2a receptor

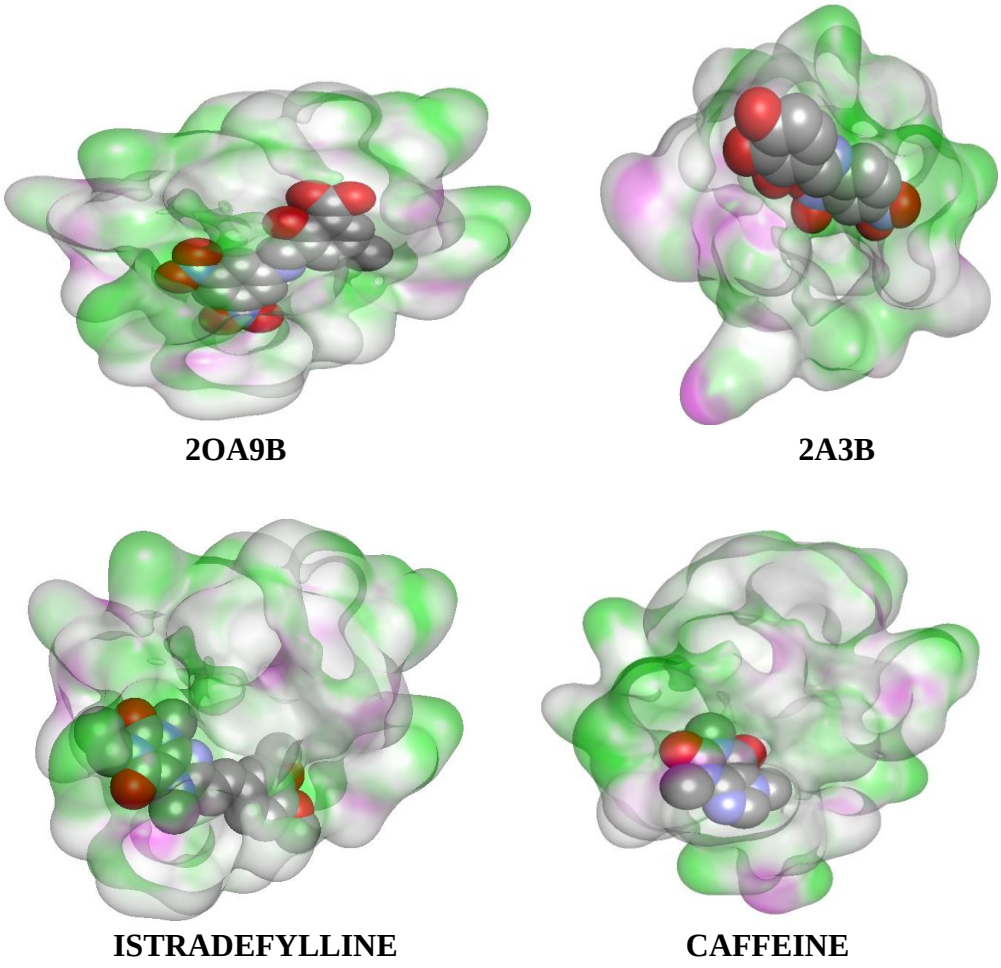


Figure 3: Binding pocket Analysis of 20A9B,2A3B, Caffeine and Istradefylline with A2a Receptor.

Statistical Applications & example:

Let's say we have conducted molecular docking studies of five Schiff based derivatives against the adenosine A2A receptor to evaluate their potential as anti-Parkinsonian agents. After performing the docking simulations, we obtain binding affinity scores for each ligand-receptor complex. These binding affinity scores represent the strength of interaction between the ligand and the receptor, with lower scores indicating stronger binding.

Here are the binding affinity scores obtained for the five derivatives:

- Derivative 1: -8.5 kcal/mol
- Derivative 2: -7.2 kcal/mol
- Derivative 3: -9.1 kcal/mol
- Derivative 4: -6.8 kcal/mol
- Derivative 5: -8.9 kcal/mol

To analyze these data statistically, we can perform a one-way analysis of variance (ANOVA) to determine if there are statistically significant differences in the binding affinities among the five

derivatives.

The null hypothesis (H_0) for the ANOVA test is that there are no significant differences in the binding affinities of the derivatives, while the alternative hypothesis (H_1) is that there are differences.

Using a significance level (α) of 0.05, if the p-value obtained from the ANOVA test is less than 0.05, we reject the null hypothesis and conclude that there are significant differences in the binding affinities among the derivatives.

Let's assume the ANOVA test yields the following results:

- F-statistic: 4.68
- p-value: 0.015

Since the p-value (0.015) is less than the significance level (0.05), we reject the null hypothesis and conclude that there are significant differences in the binding affinities among the derivatives.

To further investigate which derivatives, differ significantly from each other, we can perform post-hoc tests such as Tukey's Honestly Significant Difference (HSD) test or Bonferroni correction. This statistical analysis helps in identifying the most promising Schiff based derivatives with the highest binding affinities for further investigation as potential anti-Parkinsonian agents.

4.Conclusion:

In conclusion, the binding energies of nearly all of the top 10 molecules are greater than the common adenosine A2a receptor antagonists. Since the binding energies of the top two compounds 20A9B and 2A3B, are higher than those of common Adenosine A2a receptor antagonists, they were selected for visualization. With binding energies of -101.44 kcal/mol and -99.04 kcal/mol, respectively, the designed compounds 20A9B and 2A3B have very good binding energies than common antagonists like Istradefylline (-92.10 kcal/mol) and caffeine (-57.70 kcal/mol). The top 2 ligands were compared with the co-crystallized ligand [ZMA241385] for structural similarity. In 3d interactions the number of conventional hydrogen bonds were visualized. Ligands 2d interactions gave a clear-cut idea of the interacting amino acid residues and their distance from that of the active pocket site. Compound 2A3B has two hydrogen bond connections through the amino acid residue ASN:253, TYR:271 whereas Compound 20A9B interacts with the receptor through three hydrogen bonds with the amino acid residues HIS:264, ALA:265 and PHE:168. Istradefylline (PHE:168) and caffeine (GLU:169) are examples of typical antagonists that have only one hydrogen bond interaction (Figure 2, Table 1).

Istradefylline and 20A9B contain four amino acid residues in common, namely PHE:168[4.91], MET:270, LEU:167, and GLU:169[3.41]. Istradefylline and2A3B has six residues of common amino acids in common namely MET:270, TRP:246[6.35], LEU:249[4.98], ILE:274[5.95], ILE:66 GLU:169[4.70]. Caffeine and 20A9B contain four amino acid residues in common, namely PHE:168 [4.91], MET:270, LEU:167, GLU:169 [5.78]. Caffeine and 2A3B contains three amino acid residues in common TYR:271 [5.83] ILE:66, MET:270.

When the binding pocket analysis was compared, the standard ligands Istradefylline, caffeine and the top ligands were docked in the center of the binding pocket. This has attributed for the better binding energy. The higher binding affinity of 20A9B may be due to the presence of electron-

donating groups, such as three OH groups are present on the aromatic aldehyde ring. electron-withdrawing groups, such as two NO_2 groups are present on the aromatic amine ring. The higher binding affinity of 2A3B may be due to the presence of electron-withdrawing groups, such as two NO_2 groups, and electron-donating groups such as OH, CH_3 and COOH. Since compounds 20A9B and 2A3B have higher binding affinities and energies than typical Adenosine A2a receptor antagonists such Istradefylline and caffeine, they can be further synthesized and used for in vivo activities.

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