Molecular Docking, Pharmacophore Modeling, and Quantum Mechanical Analysis of Methylxanthines Binding to the Adenosine Receptor

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Introduction

Adenosine receptors are G protein-coupled receptors that play a key role in regulating physiological processes such as neurotransmission, inflammation, and cellular signaling. Methylxanthines, including caffeine, theobromine, and theophylline, are known antagonists of these receptors and are widely studied for their stimulatory and therapeutic effects. Differences in molecular structure among these compounds influence their binding behavior and receptor affinity, which can impact their biological activity.

While the general binding behavior of methylxanthines is well established, the electronic factors that contribute to these interactions are not fully understood. In particular, the role of electron distribution and its influence on ligand–receptor interactions requires further investigation. This study combines molecular docking and *ab initio* quantum mechanical analysis to better understand how these compounds interact with the adenosine receptor. Using MOE 2024, each ligand was docked to generate four low-energy conformations ranked by binding Gibbs free energy. Quantum mechanical calculations were performed using Gaussian 16 at the B3LYP/6-31G level of theory, with LUMO maps used to identify regions of electron acceptance. The goal of this research is to establish a relationship between electronic structure and binding behavior, providing insight into how differences among methylxanthines influence receptor affinity and interaction stability.

Binding Affinity & Analysis

Molecule	ΔG_{bind} (kcal/mol)
Adenosine	-6.7395
Caffeine	-5.9157
Theobromine	-5.8767
Theophylline	-4.5275

Table 5: The ΔG_{bind} *(approximate: $S \approx G_{bind}$)* values of the docked molecules to the adenosine receptor using MOE 2024.

Adenosine > Caffeine > Theobromine > Theophylline

Molecule	ΔG (kcal/mol)
Adenosine	-604,508
Caffeine	-426,859
Theobromine	-402,198
Theophylline	-402,195

Table 6: The ΔG *(Standard Gibbs Free Energy)* of adenosine and methylxanthines computed using Gaussian 16. These values describe intrinsic molecular stability and complement docking-derived binding energies (ΔG_{bind}) used to evaluate receptor affinity.

Adenosine > Caffeine > Theobromine > Theophylline

HOMO & LUMO

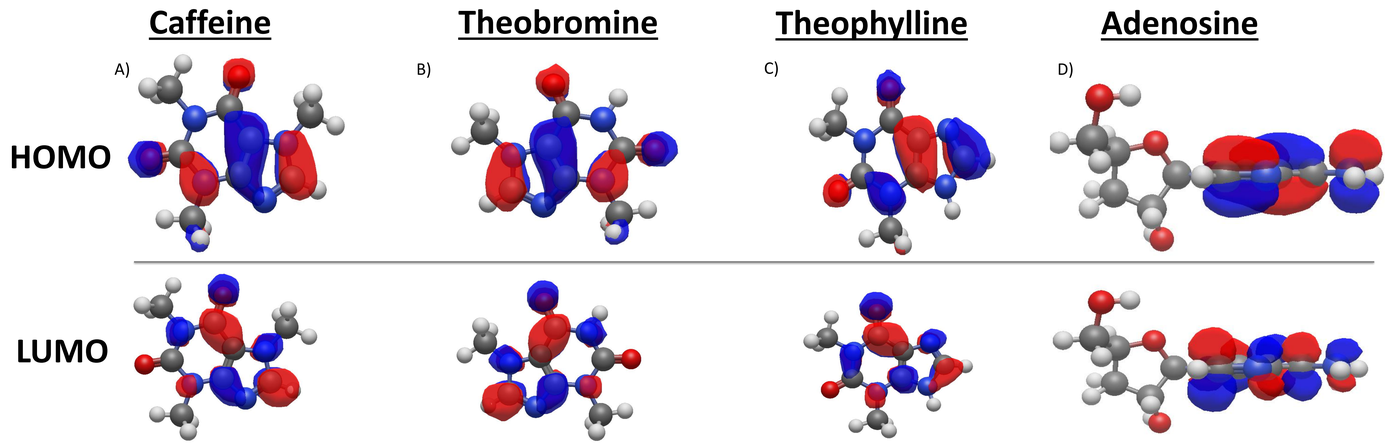

Figure 2: Comparison of HOMO and LUMO orbitals for caffeine (a), theobromine (b), theophylline (c), and adenosine (d). The spatial distribution of frontier orbitals is correlated with binding interactions observed in Figure 1, suggesting that HOMO orbitals are more involved in binding for methylxanthines, while LUMO contributions are more significant for adenosine.

Methods

The starting point for this study was to obtain the molecular structures of caffeine, adenosine, theobromine, and theophylline, which were prepared and optimized for computational analysis. Initial geometries were constructed and visualized using MOE 2024, followed by geometry optimization and quantum mechanical calculations performed using Gaussian 16. Density functional theory calculations were carried out at the B3LYP/6-31G** level of theory, and semi-empirical calculations were also performed using the PM3 method for comparison. All calculations were conducted in the gas phase unless otherwise specified, and each job was executed using 6 processor cores. Formatted checkpoint (fchk) files generated from Gaussian were analyzed in Avogadro 2 to visualize LUMO orbital maps and assess regions of electron acceptance relevant to ligand–receptor interactions.

For molecular docking studies, the adenosine receptor structure (PDB: 3EML & 2YDO) were obtained and prepared using MOE 2024. The receptor was energy minimized using the AmberEHT force field and protonated using the Protonate3D module at a physiological pH of 7.4 with a salt concentration of 0.1 M. Ligand structures were similarly minimized and protonated prior to docking. Each ligand was docked into the receptor active site using MOE 2024, generating four low-energy conformations ranked by binding Gibbs free energy (ΔG, kcal/mol). Docking parameters: Triangle Matcher -> London dG with 30 poses. Induced Fit -> GBVI/wSA dG with 5 poses. The top-ranked poses were selected for further analysis.

Post-docking analysis was performed using MOE 2024 to generate ligand–receptor interaction maps, identifying key interactions such as hydrogen bonding, electrostatic effects, and hydrophobic contacts within the active site. Binding residues were analyzed to assess their role in ligand stabilization. Gaussian 16 outputs were processed in Avogadro 2 to visualize LUMO orbital maps and identify regions of electron acceptance. These results were compared to evaluate how electronic structure relates to binding interactions and receptor affinity.

Map Results

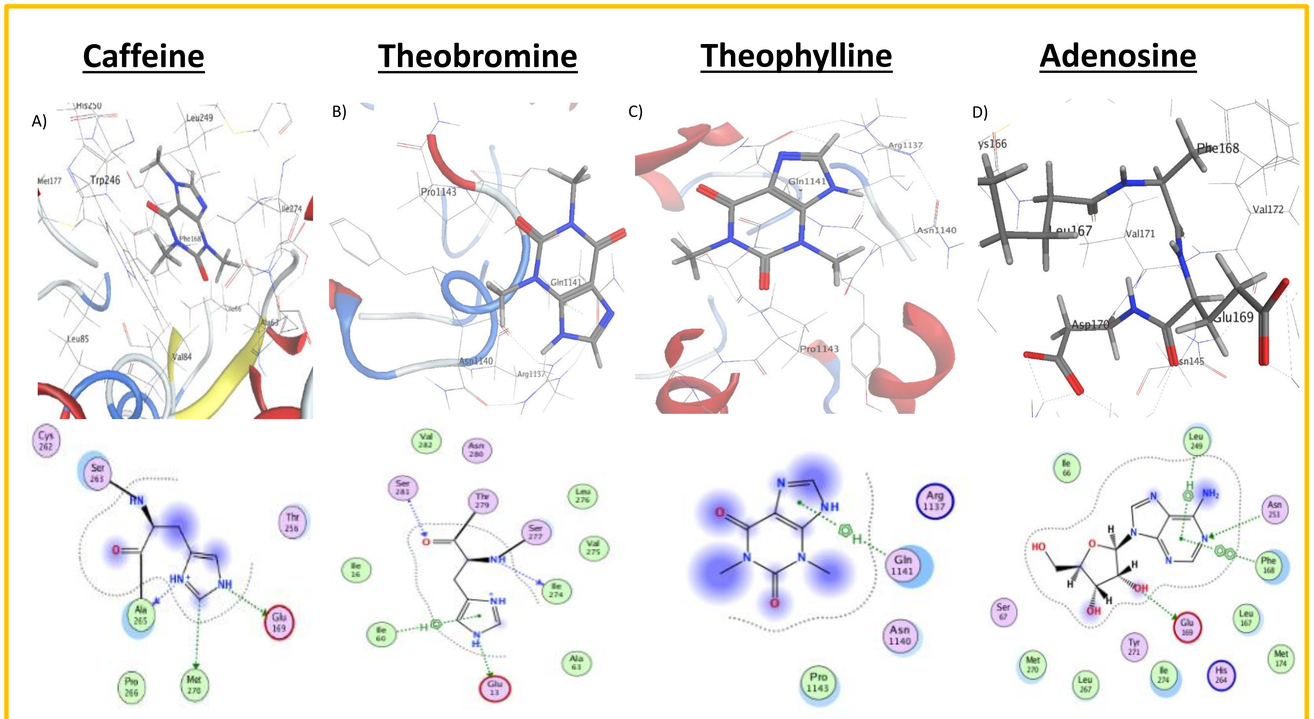

Figure 1: Docking and electronic structure analysis of adenosine (D) and methylxanthines (caffeine (A), theobromine (B), and theophylline (C)) in the adenosine receptor. For each ligand, the top panel shows the docked pose within the receptor binding site, the middle panel displays ligand–receptor interaction maps. Adenosine exhibits the strongest binding interactions, while methylxanthines show reduced affinity consistent with competitive antagonist behavior.

References

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Conclusion

- Adenosine exhibited the strongest binding affinity ($\Delta G_{bind} \approx -6.74$ kcal/mol), confirming its role as the natural ligand with optimal receptor complementarity.
- Methylxanthines (theobromine, caffeine, theophylline) showed weaker binding, consistent with their function as competitive antagonists at the adenosine receptor.
- Binding affinity trends correlate with structural features, where increased methyl substitution alters hydrogen bonding capacity and steric interactions within the binding pocket.
- Combined docking and quantum mechanical analysis supports that electronic structure (HOMO–LUMO distribution) influences receptor interaction stability, providing insight into ligand–receptor specificity.

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