Investigating the binding affinity between the A2AR receptor and its ligand to produce potential treatment for Parkinson's disease through computational molecular docking

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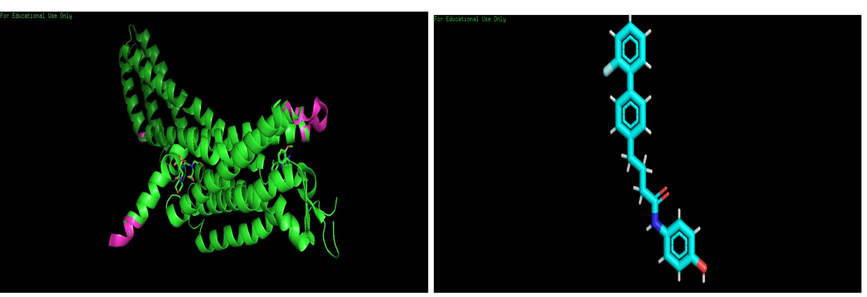
Introduction

Molecular docking is an advanced technique allowing researchers and scientists to get a better understanding of molecular dynamics among drug molecules to support drug design. In this experiment, it studies how adenosine A2AR receptor, which is linked to Parkinson and Alzheimer's diseases, and its antagonist- Compound 1 can bind to one another at a preferred orientation using CB-Dock, showing potential improvements for neurodegenerative diseases.

FIGURE 1 and 2: Computerized structures of 5UIG and Cmpd-1 respectively using PyMol



Methods

AutoDock and CB-Dock are user-friendly software that help identify binding sites, calculate the center and the associated sites, and perform docking. Scoring function will be used to support the calculation.

$$V = W_{vdw}\sum_{i,j}\left(\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}}\right) + W_{hbond}\sum_{i,j}E(t)\left(\frac{C_{ij}}{r_{ij}^{12}} - \frac{D_{ij}}{r_{ij}^{10}}\right) + W_{elec}$$

$$\sum_{i,j}\frac{q_i q_j}{\epsilon(r_{ij})r_{ij}} + W_{sol}\sum_{i,j}\left(S_i V_j + S_j V_i\right)e^{\left(-r_{ij}^2/2\sigma^2\right)}$$

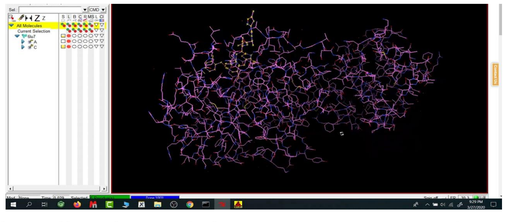


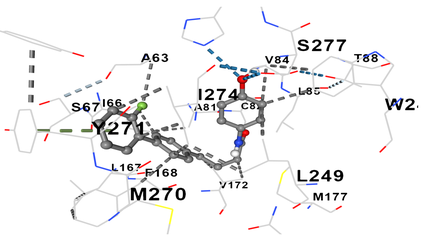
Figure 3 : Visualization of the 3D structure of A2AR receptor protein 5UIG and ligand Cmpd-1 docked together.

Data and files extracted and supported by PubChem and Protein Data Bank

Results

- Compound 1 has the best binding affinity to the protein 5UIG at the cavity pocket with the Vina Score of -10.2 out of 5 dockings. It has the lowest and most negative value.
- The result applies to the idea that the lower the binding energy values are, the more stable the complex is.

Vina score	Cavity size	Center			Size		
		x	y	z	x	y	z
-10.2	1100	147	37	17	25	25	25
-8.5	382	170	19	16	25	25	25
-8.2	247	162	14	6	25	25	25
-7.4	571	178	7	34	25	25	25
-7.3	448	159	10	18	25	25	25



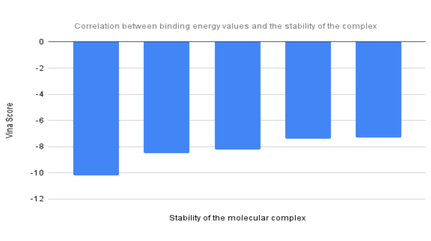


FIGURE 4 and 5: CAD images of protein-ligand binding and specific residues

FIGURE 6 and 7: Chart and Table with Vina Score data and relationship between one binding affinity value and its stability

Discussion

- In this experiment, they are knowledge-based and dictated by the statistical observations of intermolecular contacts and rooted in assumptions.
- This method is unable to validate the diverse and complex docking orientations between two molecules. There are a lot of simplifications.

Discussion continued

- In actuality, these macromolecules are moving around in a dynamic, highly electrostatic environment
- The protein also fluctuates and the ligand is meant to interact with some conformations but not others leading to misrepresentation of the accurate conformation.

Conclusion

- Advanced simulations like CB-Dock, Auto dock make it possible for pharmacists and manufacturers to conduct experimentations to determine a potential drug candidate can dock and activate a target protein. There are still some computational limitations and drawbacks.

- The major obstacle: lack of reproducibility. Regardless, Cmpd-1 is valuable in facilitating a novel protein-antagonist compound that is valuable to anti-Parkinson disease medications.

References

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