

Molecular Docking Study of Various Protein on Clozapine

Chitra Janardan Chavan¹; Trushali A Mandhare²

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Navsahyadri Institute of Pharmacy Naigaon, Pune, Maharashtra-412213

Abstract:- The antipsychotic drug Clozapine is widely recognized for its efficacy in treating resistant schizophrenia. This study aims to elucidate the binding interactions of Clozapine with four key proteins: 1GQ1, 1MKF, 4OAJ, and 7WU2. These proteins represent diverse biological targets, including receptors and enzymes relevant to neurological function and drug metabolism. Utilizing molecular docking simulations, we compared the binding affinities and interaction profiles of Clozapine with these proteins.

I. INTRODUCTION

Clozapine the dibenzazepine clozapine is the prototype of second generation atypical antipsychotic drugs. Clozapine exerts its effects involves the blocking of 5-HT_{2A}/5-HT_{2C} serotonin receptors and the D₁₋₄ dopamine receptors, with the highest affinity for the D₄ dopamine receptor. As a serotonin and D₄ dopamine antagonist, clozapine is able to elicit its antipsychotic effects without inducing many of the extra pyramidal motor effects associated with D₂ dopamine receptor antagonists Clozapine is an atypical or second-generation antipsychotic drug used in treatment-resistant schizophrenia and to decrease suicide risk in schizophrenic patients.

- Brand Names: Clozaril, Fazaclor, Versacloz
- Generic Name: Clozapine

II. MATERIALS AND METHODS

For the present study bioinformatics online software and database like discovery studio were used. The software and database used are as follows:

➤ *Pub Med:*

PubMed developed by the National Center for Biotechnology Information (NCBI) the national Library of Medicine (NLM). The database is designed to provide access to citation from biomedical journal.

➤ *PDB:*

The protein data bank is repository for the processing and distribution of 3D structure data of large molecule of protein and nucleic acid Most were determined by X-ray crystallography and some by NMR.

➤ *PubChem:*

A database maintained by the National Center for Biotechnology Information (NCBI) containing information on the biological activities of small Molecules.

➤ *ZINC:*

A free database of commercially available compounds for virtual screening, drug discovery, and molecular docking studies.

➤ *Autodock:*

Widely used molecular docking software that uses a Lamarckian genetic algorithm for ligand docking.

➤ *Autodock Vina:*

An improved version of Autodock with enhanced speed and accuracy, utilizing an iterative optimization algorithm.

➤ *DOCK:*

A software suite for protein-ligand docking, utilizing a range of algorithms including geometric hashing and Monte Carlo simulations.

➤ *Autodock Tools:*

Autodock Tools (ADT) is a graphical user interface (GUI) for preparing, running, and analyzing molecular docking simulations using the Autodock suite of programs. It allows users to set up protein-ligand docking simulations by preparing input files, visualizing molecular structures, and analyzing docking results.

➤ *PyMOL:*

PyMOL is molecular visualization software used for creating high-quality 3D images and animations of molecular structures. It's widely used in the field of structural biology to visualize proteins, nucleic acids, small molecules, and other macromolecules. PyMOL offers an extensive range of features for molecular rendering, surface generation, measurement tools, and molecular editing.

➤ *Python:*

Python is frequently utilized in molecular docking for several purposes: Automation and Workflow Management: Python scripts can automate repetitive tasks involved in setting up docking simulations, analyzing results, and post-processing data. This automation streamlines the entire docking process, making it more efficient.

➤ *Proteins used in the Molecular Docking:*

• *1gq1:*

Protein 1gq1 is a member of the periplasmic binding protein-like II super family. It's involved in the transport and binding of solutes across membranes in bacteria. The structure of 1gq1 has been extensively studied to understand its function and potential applications in drug delivery and biotechnology.

• *1mkf:*

Protein 1MKF, also known as Ribonuclease A, is an enzyme that catalyzes the cleavage of RNA molecules. It is commonly used in biochemical research due to its stability and well-characterized enzymatic activity.

• *4oaj:*

Protein 4OAJ is a human leukotriene A4 hydrolase (LTA4H), an enzyme involved in the biosynthesis of pro-inflammatory leukotrienes. It plays a crucial role in the immune response and inflammation regulation. Understanding its structure and function can provide insights into the development of anti-inflammatory drugs.

• *7wu2:*

The 7wu2 protein, also known as Seven Wonders of the World 2, is a hypothetical protein often used in scientific discussions and thought experiments to illustrate protein folding and function. It's not an actual protein found in nature but rather a theoretical construct used to explore principles of protein structure and function.

➤ *Structural Comparison:*

3D Structure of clozapine and proteins:

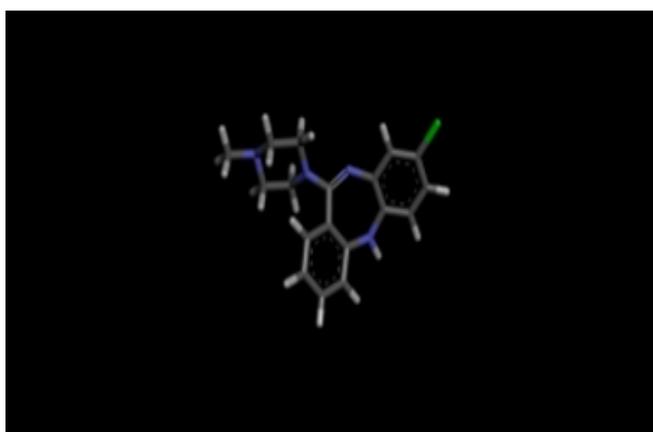


Fig 1 3D Structure of Clozapine

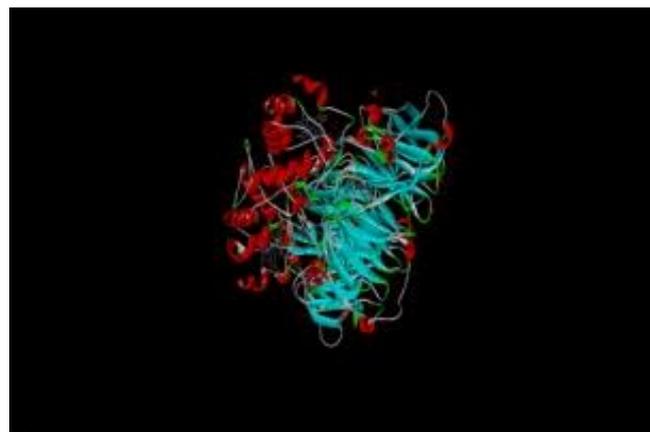


Fig 2 3Dstructure of 1gq1

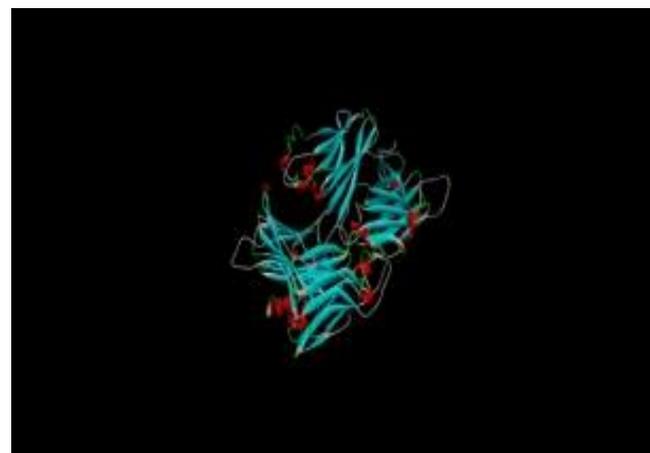


Fig 3 3D Structure of 1mkf Protein

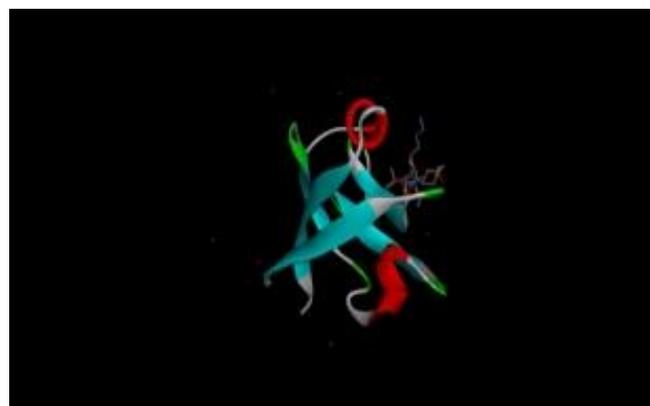


Fig 4 3D Structure of 7wu2 Protein

A. *Methods*

➤ *Preparation of Protein:*

- Protein target was downloaded from database protein data bank (RCSB PDB).
- 1gq1 is the pdb id of the targeted protein. Download the protein file and click on pdb format, and download the protein.
- Open the Autodock Tools.
- Firstly, going to the docking, we need to set preferences go to file menu and click on preferences and set, and change the startup directory.

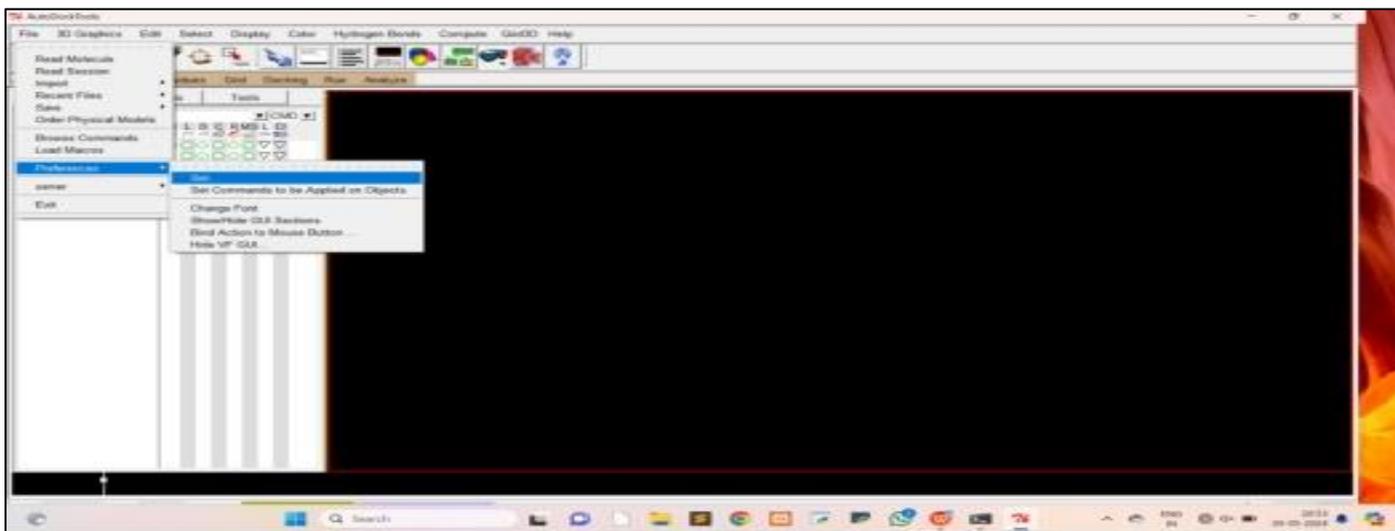


Fig 5 Set Preference

- Then go to the folder where we download the all-protein file and click on copy address and past (control +v) in startup directory click on make it as default and set.

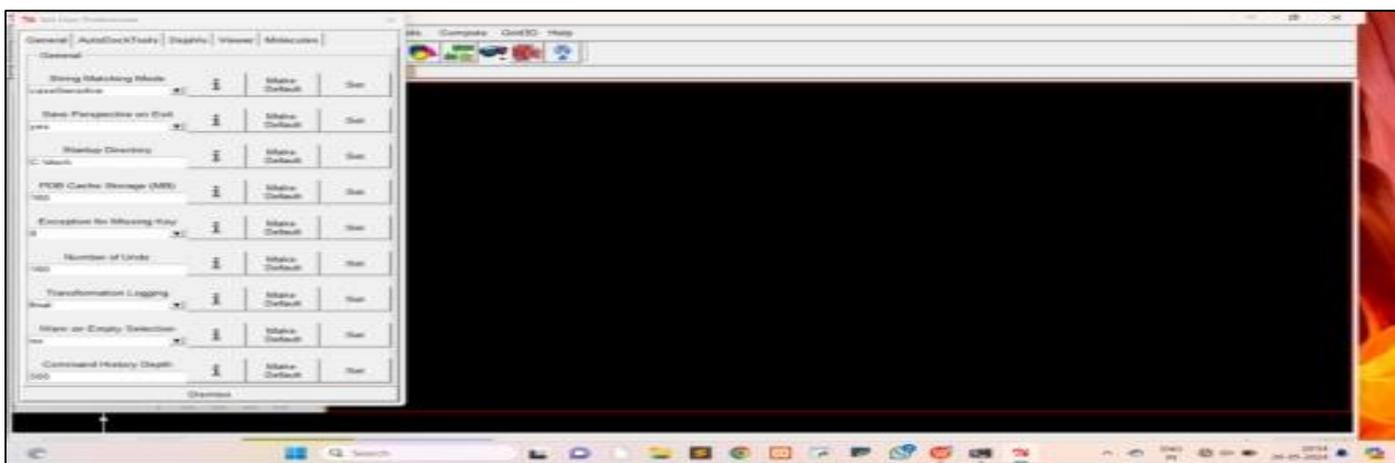


Fig 6 Set Path

- Now open the protein 1gq1 in Autodock tools. It has two chain A and chain B.

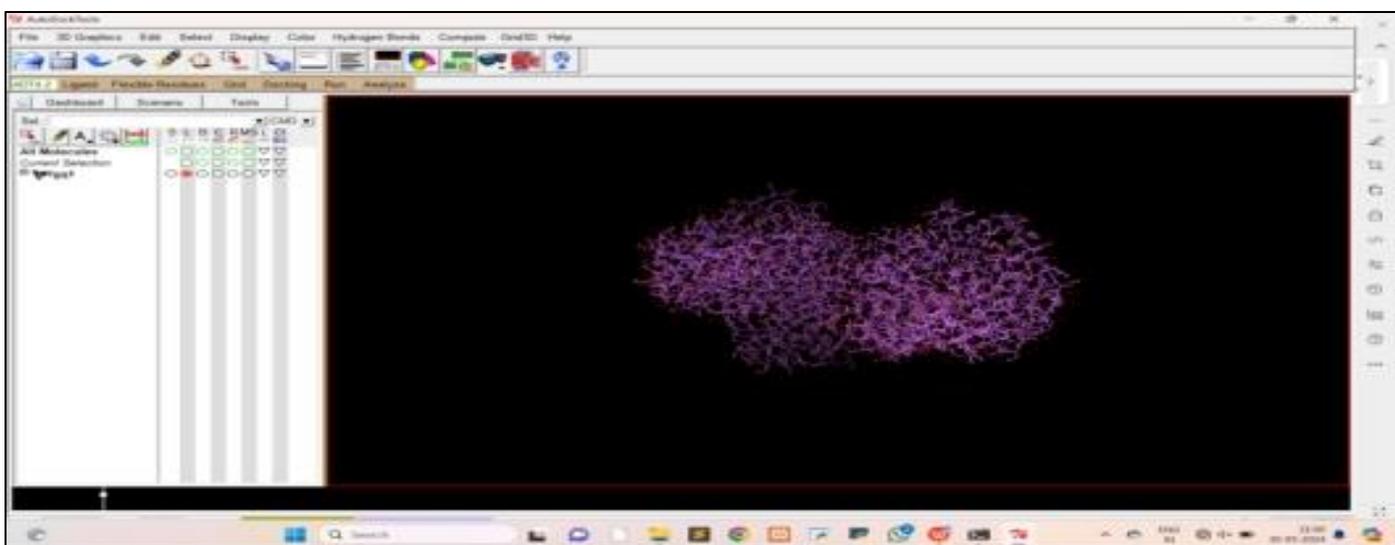


Fig 7 Open Protein in Auto dock

- Firstly, delete the entire water molecule in that protein molecule, click on edit and delete water.

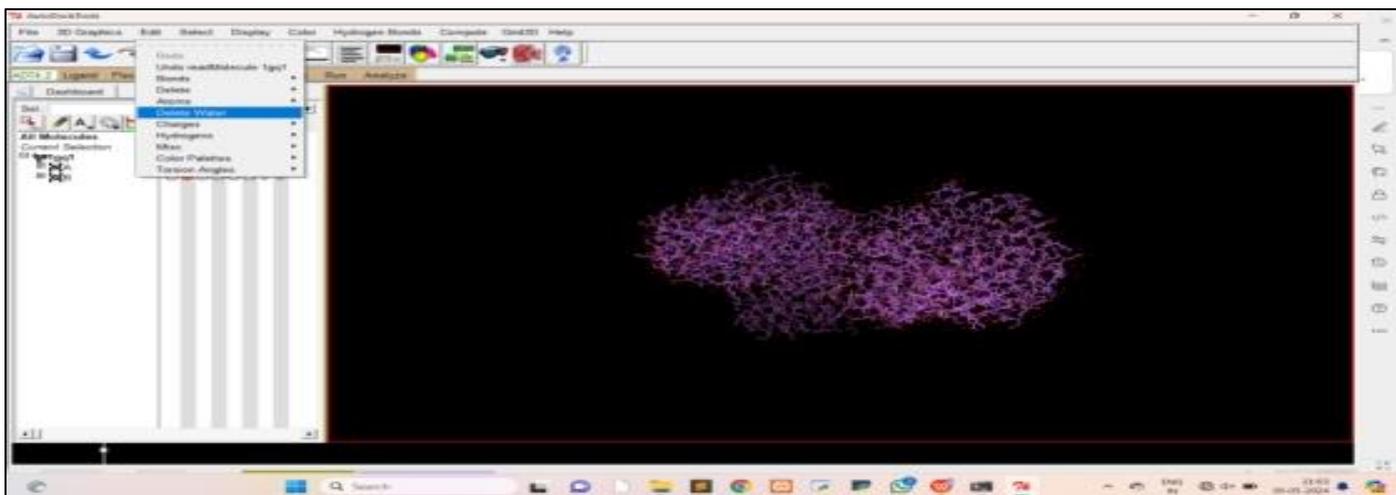


Fig 8 Delete Water Molecule

- Then delete chain B click on chain B and delete the selected atom and click on continue.

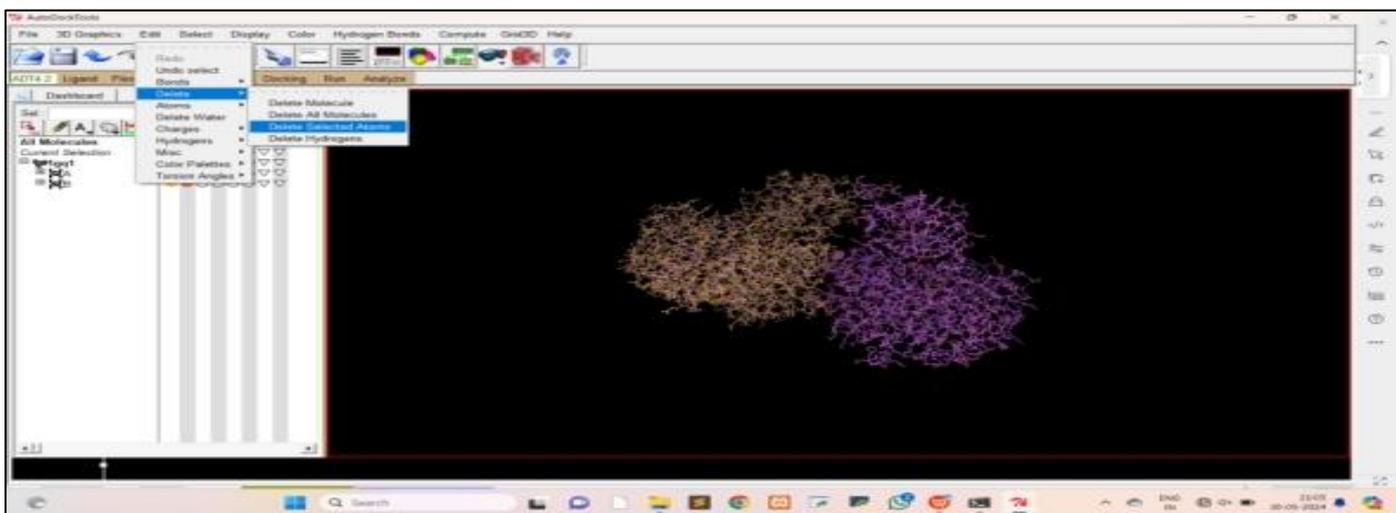
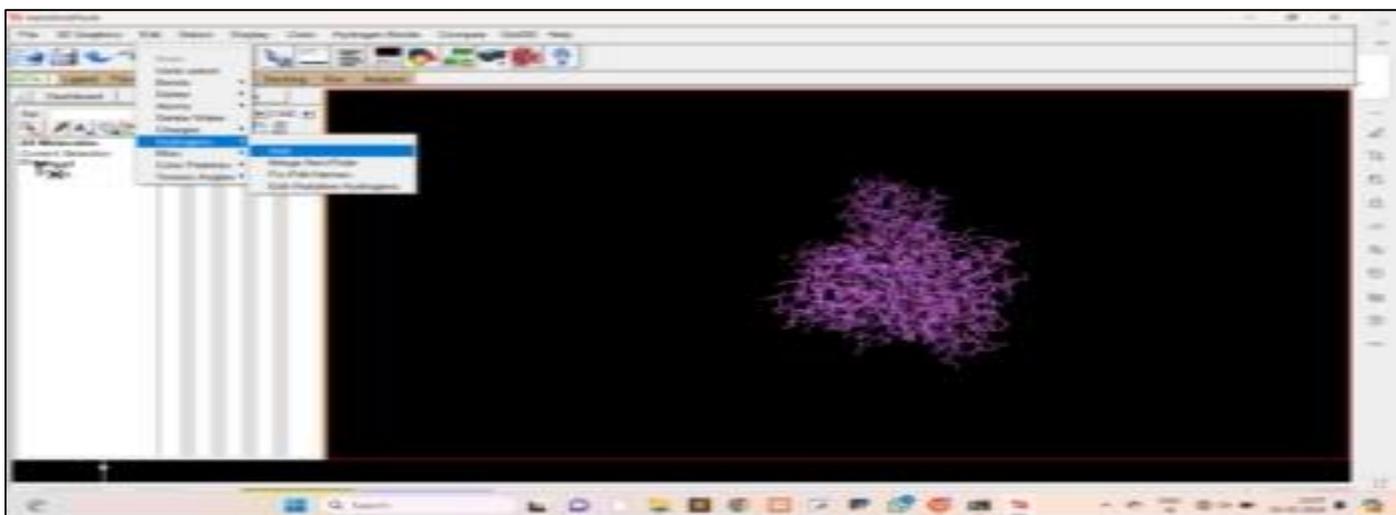


Fig 9 Deleting Chain B

- Add hydrogen atom in the protein click on edit and then add hydrogen atom polar only and click ok, then click on charges add kollman charges.



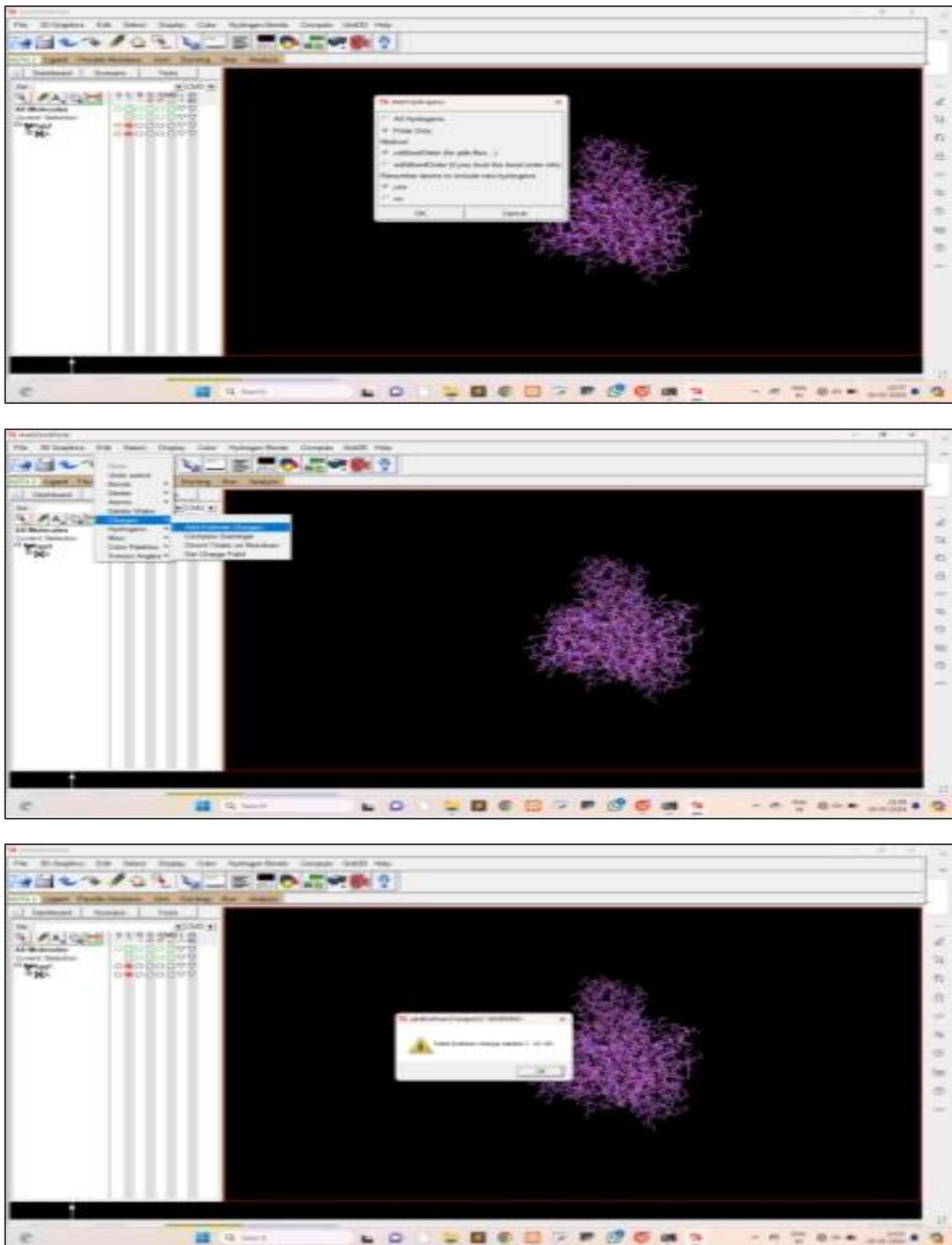


Fig 10 Add Hydrogen and Charges on Protein Molecule

- Then go to the edit and click on atom assign AD4 type

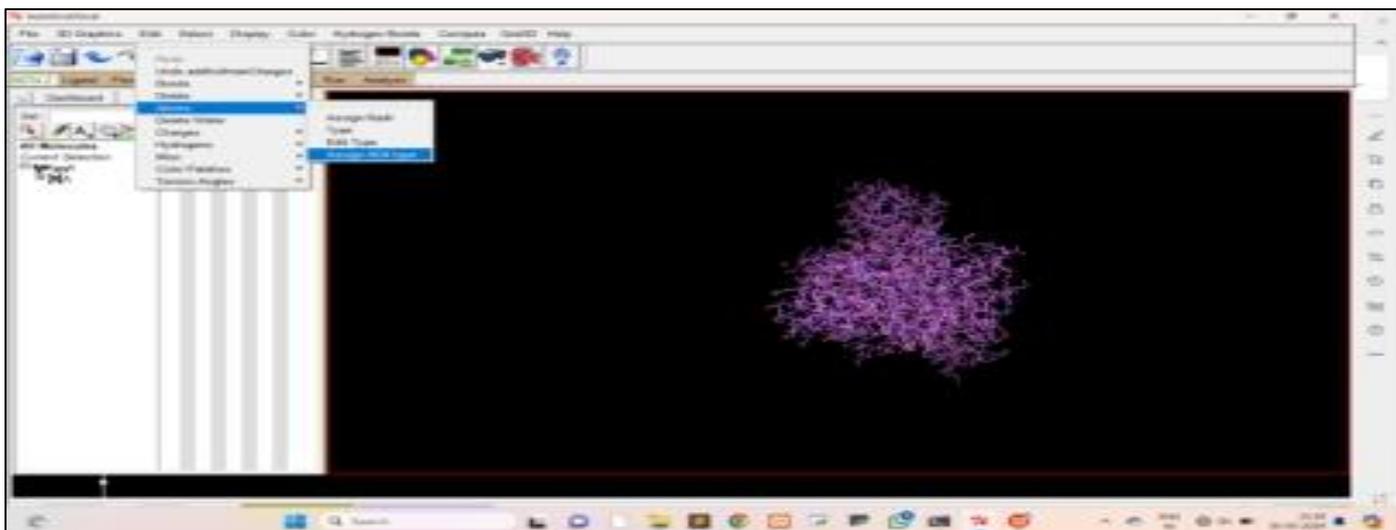


Fig 11 Assign Atom AD4

- Then go to the file menu and click on save and write pdbt then select all the available pdb records and click on add then ok. and check on prepare folder pdbqt file add in the file protein molecule has been prepared.

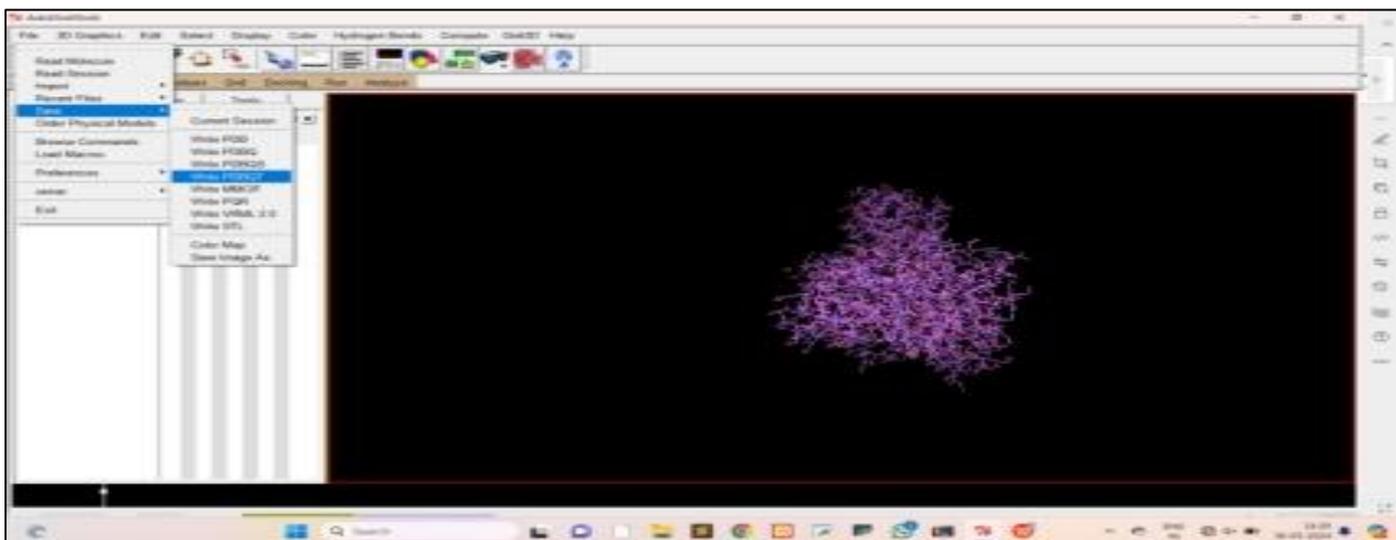


Fig 12 Save Protein

- As same as all proteins prepared this way docking study.

➤ *Preparation of Ligand:*

- Firstly, click on ligand, input and click on open

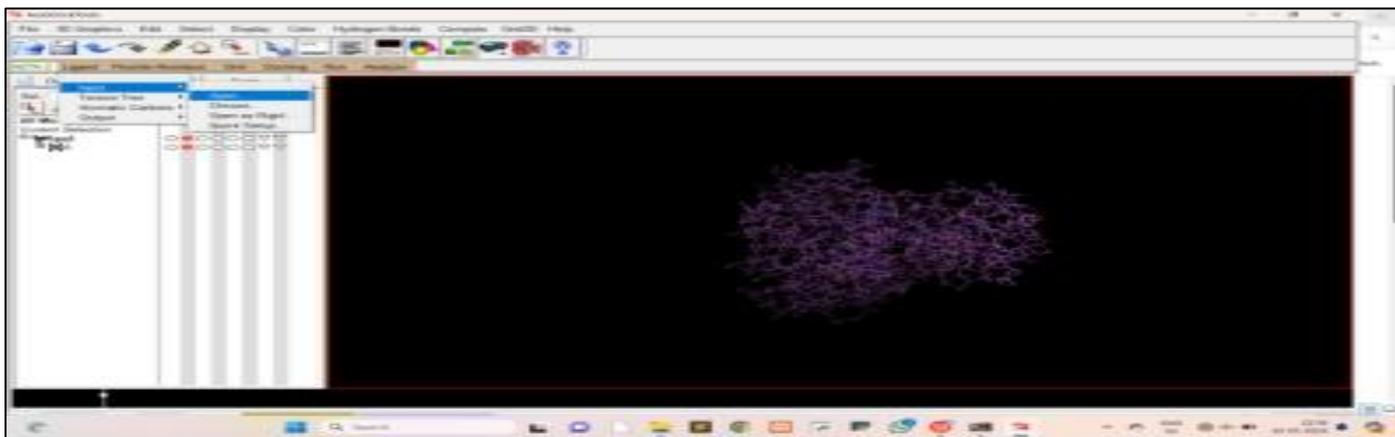


Fig 13 Open Ligand(Drug) in Autodock.

- Click on Clozapine and Open

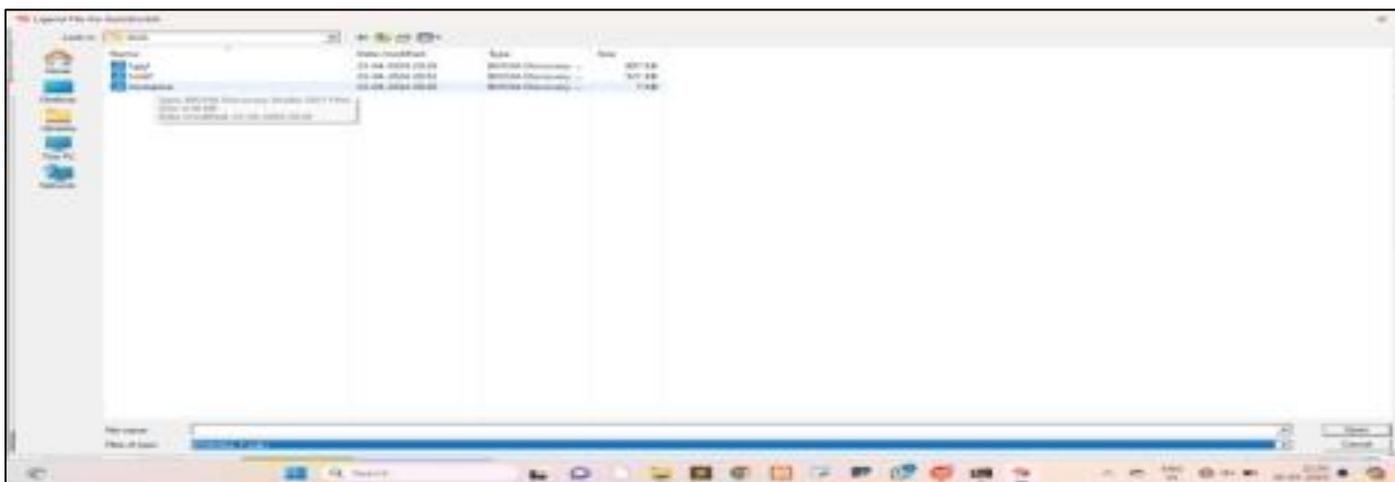


Fig 14 Open Clozapine in Folder

- Then it will show that gasteiger charges 18 non polar hydrogen and other information.

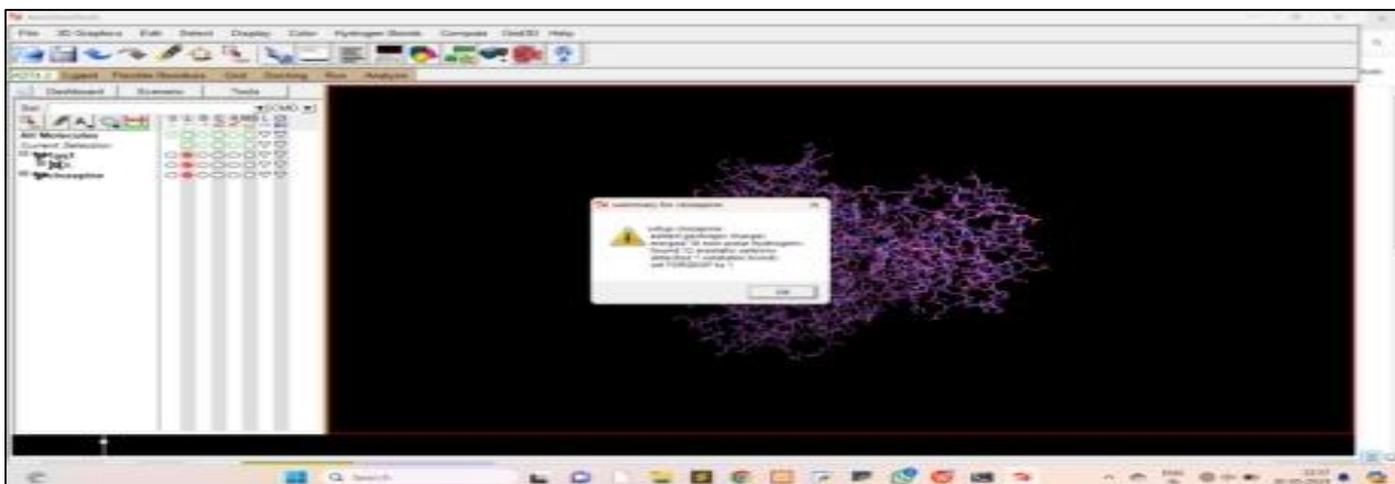


Fig 15 Adding Charges.

- Click on torsion tree click on choose root and then click on torsion tree detect root.

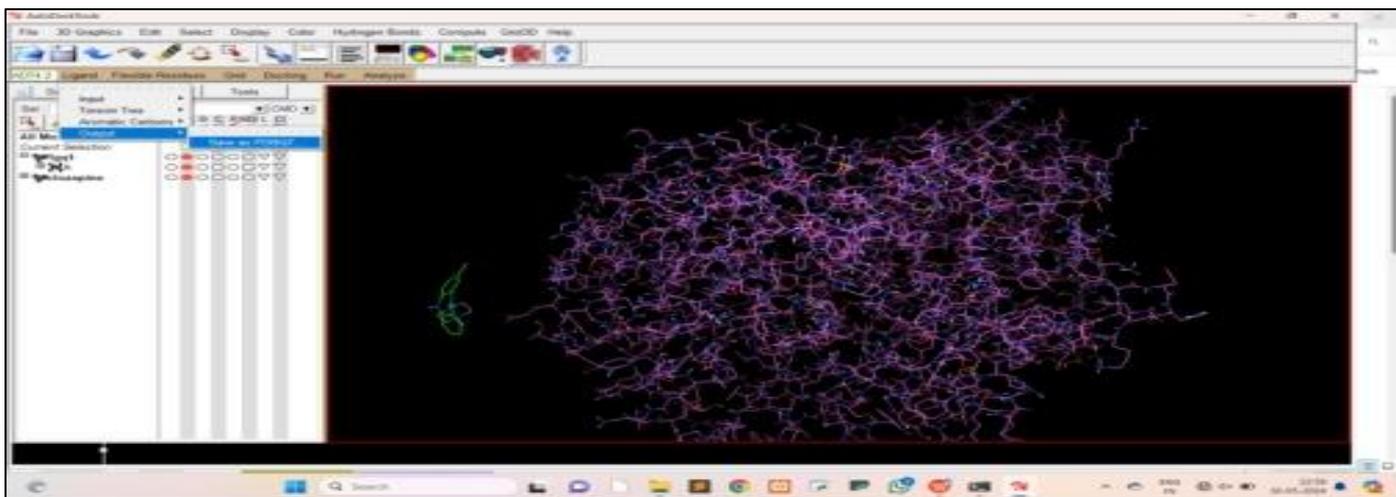


Fig 16 Choose Root.

- Click on output and save as pdbqt with extension pdbqt, q stands for charges and t stands for type of atom.

➤ *Grid Generation:*

- Click on macromolecules and choose and select macromolecules



Fig 17 Select Macromolecule.

- Then click on set map types then choose ligand and select ligand then click on grid box.

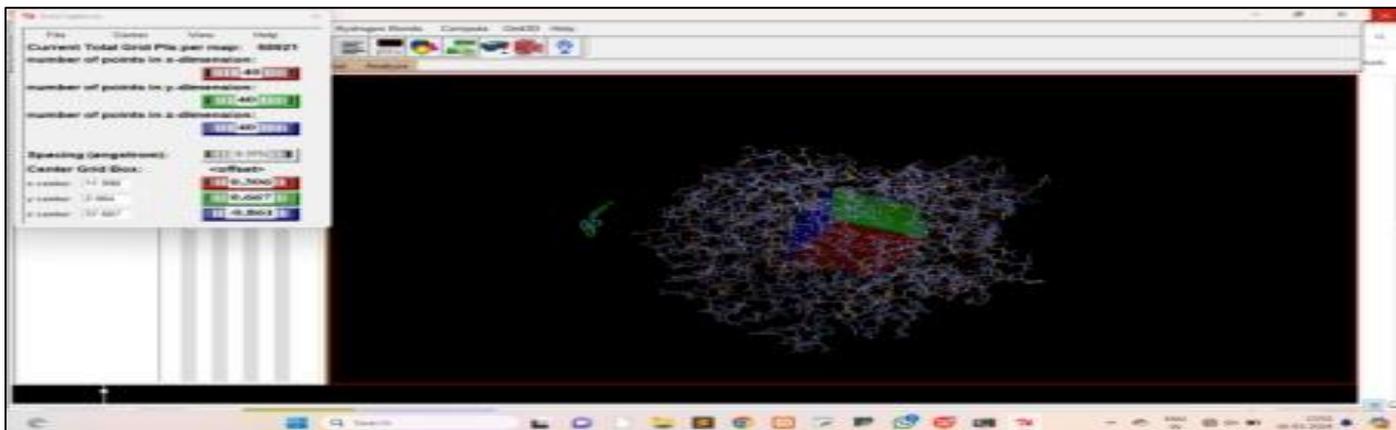


Fig 18 Grid Box.

In docking ligand can bind with binding pocket so the whole protein embedded in grid box and changing the size of grid box.

Then click on output and save it as gpf extension and then gpf file will be generated Develop dpf file go to the docking click on macromolecules and set rigid file name macro molecule is protein then click on open.

- Then choose ligand and it is flexible

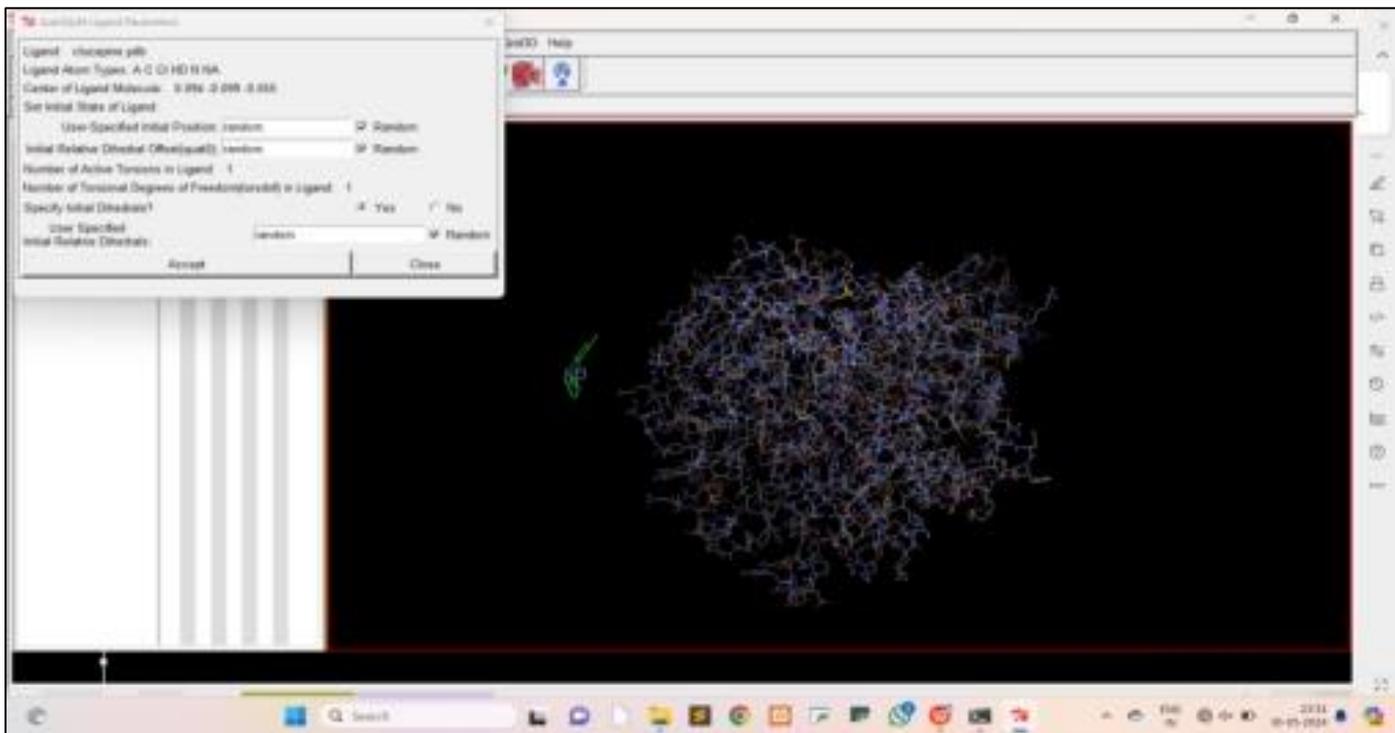


Fig 19 Output File Generation.

- Then click on search parameter genetic algorithm click on accept.

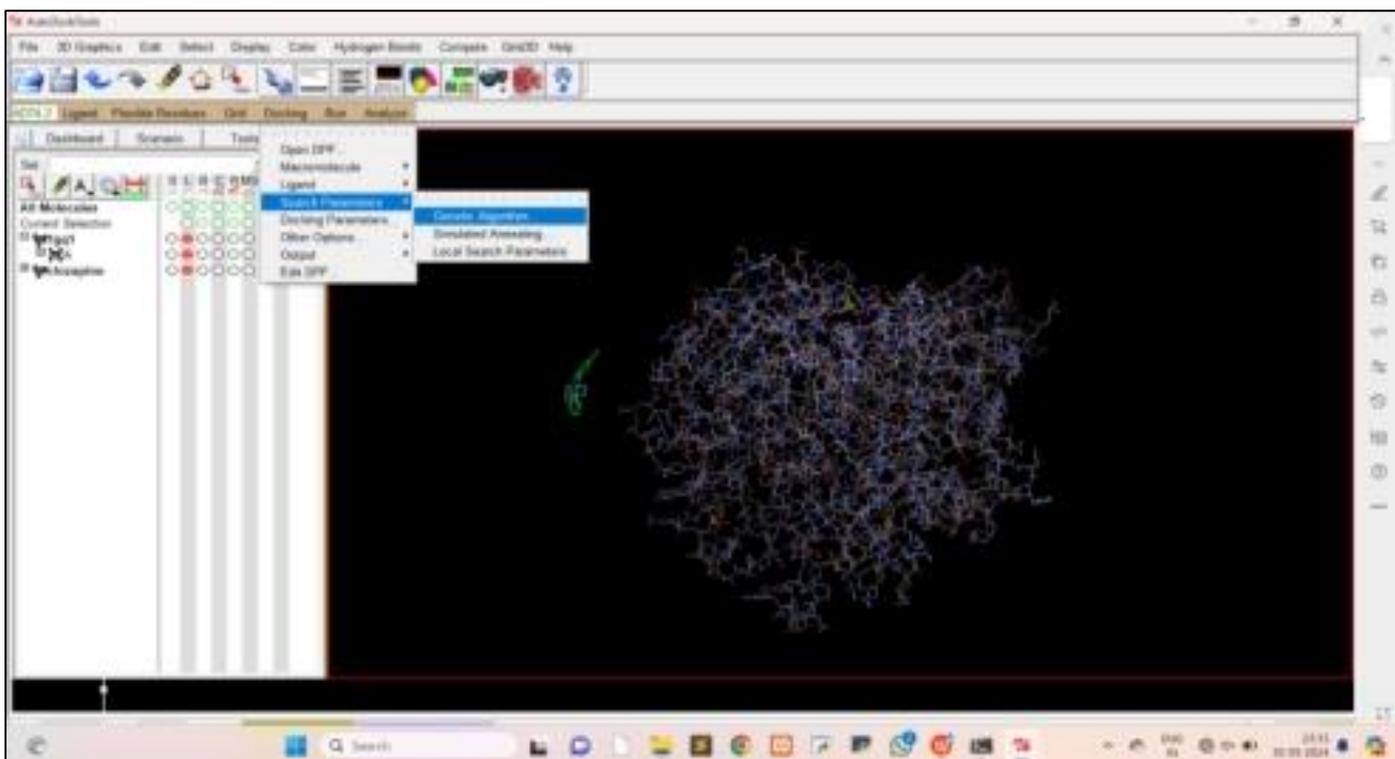


Fig 20 Search Parameter.

- Click on output Lamarckian and save it as dpf extension and click on save then click on run AutoGrid

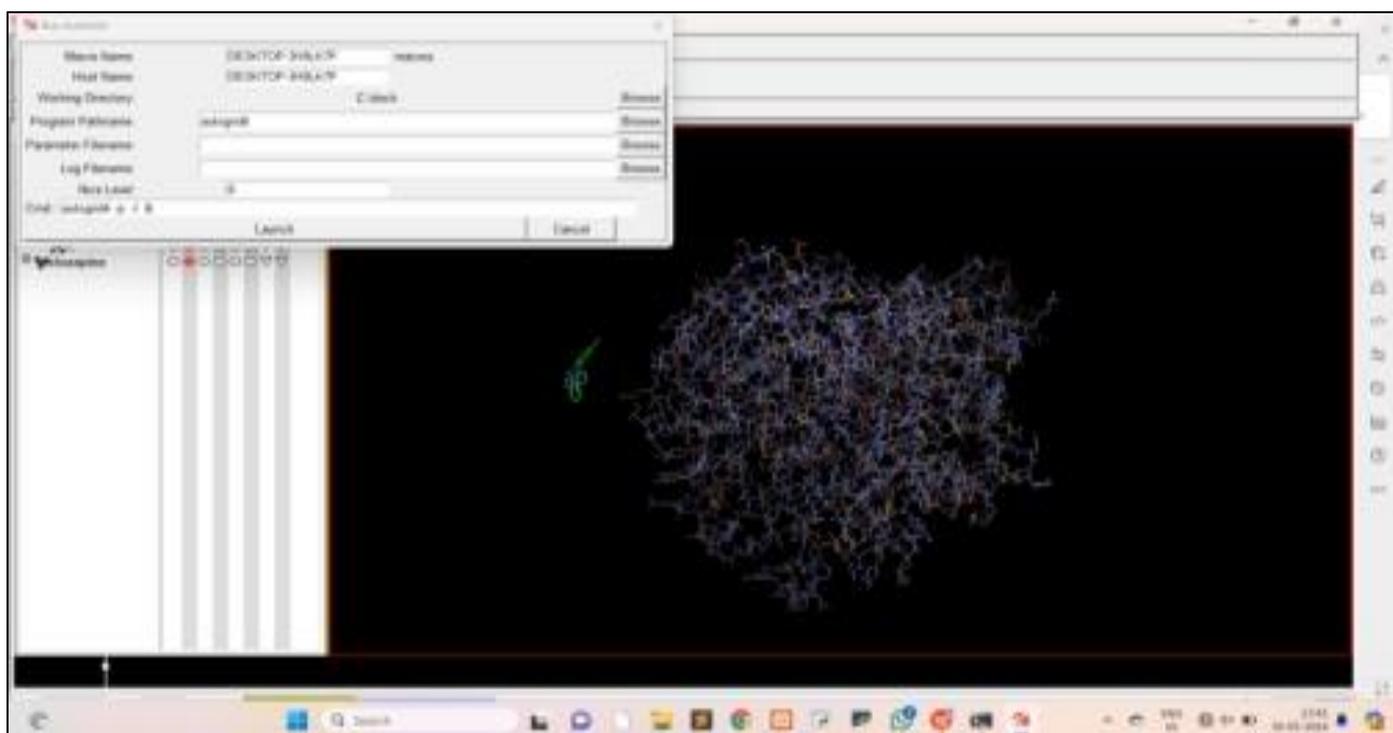


Fig 21 Run Autodock.

- Choose AutoGrid executive file then browse gpf file then glg file automatically generate.
- Then click on launch. Process will be running it may take some time then automatically generate glg file.
- Dlg file will be creating and open the dlg file contains all data related to docking.
- Docking process will be done.

III. RESULT

Table 1. Root mean square deviation of protein.

RMSD TABLE						
Rank	Sub-Rank	Run	Binding Energy	Cluster RMSD	Reference RMSD	Greg Pattern
1	1	3	-9.49	0.00	29.31	RANKING
1	2	8	-9.39	0.14	29.37	RANKING
2	1	10	-9.13	0.00	26.45	RANKING
3	1	4	-8.65	0.00	26.79	RANKING
3	2	7	-8.63	0.09	26.83	RANKING
3	3	5	-8.62	0.10	26.84	RANKING
3	4	9	-8.60	0.19	26.85	RANKING
3	5	2	-8.16	0.58	27.15	RANKING
4	1	1	-7.96	0.00	48.03	RANKING
4	2	6	-7.92	0.33	48.23	RANKING

Table 2 Analysis of Protein in Dlg File

STATISTICAL MECHANICAL ANALYSIS		
Partition function, Q =	10.15	at Temperature, T = 298.15 K
Free energy, A ~	-1372.89 kcal/mol	at Temperature, T = 298.15 K
Internal energy, U =	-8.66 kcal/mol	at Temperature, T = 298.15 K
Entropy, S =	4.58 kcal/mol/K	at Temperature, T = 298.15 K

IV. CONCLUSION

The comparative docking study of clozapine with proteins 1gq1, 1mkf, 4oaj, and 7wu2 offers valuable insights into the potential molecular interactions between this antipsychotic drug and its putative protein targets. Through a combination of computational docking techniques, we have explored the binding affinities and putative binding modes of clozapine with each protein, shedding light on the structural determinants underlying their interactions.

REFERENCES

- [1]. Albitar, Orwa, et al. "Population pharmacokinetics of clozapine: a systematic review." *BioMed research international* 2020 (2020).
- [2]. Jann, Michael W., et al. "Pharmacokinetics and pharmacodynamics of clozapine." *Clinical pharmacokinetics* 24 (1993): 161-176.
- [3]. Meltzer, Herbert Y. "An overview of the mechanism of action of clozapine." *The journal of clinical psychiatry* 55 (1994): 47-52.
- [4]. Ramírez, David, and Julio Caballero. "Is it reliable to use common molecular docking methods for comparing the binding affinities of enantiomer pairs for their protein target." *International journal of molecular sciences* 17.4 (2016): 525.
- [5]. Olagunju, Andrew T., Scott R. Clark, and Bernhard T. Baune. "Clozapine and psychosocial function in schizophrenia: a systematic review and meta-analysis." *CNS drugs* 32.11 (2018): 1011-1023.
- [6]. <https://openai.com/share/b5e8170f-5fc2-4cf6-a597-adda4e4f8840>