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IN SILICO STUDY OF COMPUTER ADDED DRUG DESIGN FOR CHLOROQUINE AS ANTI-VIRAL AGENT

Sanket Anil Ingle[1*], Seema Pralhad Rathod[2], Shailesh Subhash Bansode[3], Rushikesh Dhanraj Salunke[4]

[1]*Student of Bachelor in pharmacy, Dr.Babsaheb Ambedkar Technological University, Raigad,Lonere.*
[2]*Department of Pharmaceutical chemistry, Faculty of Medicinal chemistry, Dr.Babsaheb Ambedkar Technological University , Raigad, Lonere*
[3]*Student of Bachelor in pharmacy, Dr.Babsaheb Ambedkar Technological University, Raigad,Lonere.*
[4]*Student of Bachelor in pharmacy, Dr.Babsaheb Ambedkar Technological University, Raigad,Lonere.*

*****Corresponding Author*

ABSTRACT

A significant amount of research has been done recently to find medications that can effectively treat the coronavirus illness 2019 (COVID-19). New approaches to enhancing the sufficiency of these medications were sparked by the uncertainty around the use of chloroquine to treat this sickness. Significant attention has been paid to the efficient use of zinc complexes as an adjuvant to chloroquine in the treatment of COVID-19. Density functional theory (DFT) was used to examine molecule electrostatic potential, electrical characteristics, and geometries at the 6LU7. This work studied the interaction of quinoline-based antimalarial drugs with the peptidase domain of ACE2 receptor. The X-ray crystal structure of human ACE2 receptor was downloaded from Protein Data Bank.

KEYWORDS: *COVID-19, Chloroquine, molecular docking, Molecular dynamics, Remdesivir.*

1) INTRODUCTION

The pandemic's rapid global spread was caused by human-to-human transmission. The World Health Organization (WHO) states that as of April 2020, there were more than two million documented instances of infection and suspicion across several nations. Researchers from a variety of scientific domains have been spurred by the crisis to develop a vaccine against this unusual illness. Chloroquine (CQ) has long been mentioned as a possible treatment for pneumonia exacerbations(1). This paper's primary contribution is the molecular docking study's determination of the chloroquine derivatives potency of inhibition against the COVID-19 virus(2).

German company Bayer developed the antimalarial medication chloroquine in 1934 to take the role of natural antimalarial medications. Patients with SARS-CoV-2 infection have shown good response to this medication. The broad range of antiviral activity of this medication may be explained by the potential disruption of sialic acid production caused by chloroquine(3).

Nevertheless, it is unclear how chloroquine works as an antiviral against 2019-CoV. Angiotensin-converting enzyme 2 (ACE2) serves as 2019-nCoV's entrance receptor into host cells, according to a recent research. The host cell is bound by the S protein's receptor binding domain (RBD)(3).

1.1 PubChem

A public chemical database hosted by the National Institutes of Health (NIH) is called PubChem. "Open" indicates that you are able to upload your scientific data to PubChem and allow other users to utilize it. PubChem is now a vital source of chemical knowledge for scientists, students, and the general public, having launched in 2004. The programmatic services on our website and for several million consumers globally supply data each month(4).

Larger molecules including nucleotides, carbohydrates, lipids, peptides, and chemically altered macromolecules are also present in PubChem, although they are predominantly tiny molecules. We gather data on a wide range of topics, including identifiers, chemical and physical characteristics, biological activity, patents, health, safety, and toxicity(4).

1.2 RCSB PDB

The global Protein Data Bank (PDB) repository of 3D structural data for big biological molecules (proteins, DNA, and RNA) is housed at RCSB PDB (RCSB.org), the US data center for the archive. This data is crucial for basic biology research as well as health, energy, and biotechnology education(5).

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The first digital data repository in biology and medicine to be made available to the public was the Protein Data Bank (PDB). Currently, it is a preeminent worldwide repository for experimental data essential to scientific advancement[5].

1.3 Molinspiration

A wide range of cheminformatics software tools are available from Molinspiration to support the manipulation and processing of molecules. These tools include the conversion of SMILES and SDfiles, normalization of molecules, tautomer generation, molecule fragmentation, calculation of various molecular properties required for QSAR, drug design and molecular modeling, high-quality molecule depiction, and molecular database tools that support substructure and similarity searches. Additionally supported by our solutions are data visualization, bioactivity prediction, and fragment-based virtual screening. Since the Molinspiration tools are designed in Java, they are essentially compatible with all computer platforms[6].

1.4 Molecular Docking Vina

In the modern era of pharmaceutical research, many methods of molecular modeling have been employed to study complex chemical and biological systems in a variety of programs of drug discovery. It is very important to integrate experimental strategies into computational approaches in the identification, characterization, and development of novel and propitious compounds. Small molecular compounds (ligands) are docked into the binding site of the receptor, following which the binding affinity of the complex is estimated. This constitutes a significant part of the structure-based drug design process[7].

1.5 Molecular Docking

Every docking experiment used the optimized model as the docking target and the AutoDock Vina program. Molecular docking is the only screening approach used molecular dynamics simulation has not been performed. RdRp antagonists include ribavirin and Remdesivir. Ribavirin is ineffective against the novel coronavirus, however Remdesivir could be. To investigate the binding differences between the two compounds, molecular docking was utilized.

Before the ligands were examined in relation to the SARS-CoV-2 target proteins, the structures of the small molecules were optimized using the classical MM2 force field; the active site aspartates of targets were treated as rigid. By removing all water molecules, allocating Gasteiger partial charges, and adding polar hydrogen, the 6lu7 protein structure was created. The grid coordinates for the ligand position in the Mpro protein were X = -41.1626, Y = 1.88447, and Z = 36.7796. The parameters of the Genetic Algorithm (GA) were assigned at the 100 GA run and 150 population size. Autodock 4.2 was utilized to perform docking calculations for molecules, with the assistance of Auto Dock Tools 1.5.7.

1.6 Ligand and Target Preparation

All compounds' ideal structures are depicted. Both CQ and HCQ are widely used as antimalarial medications and have a broad range of in-vitro action against viruses. Numerous investigations revealed that the primary COVID-19 protease, Mpro (PDB ID 6LU7), is essential to the virus's ability to replicate. This makes it a strong candidate for medications that act as inhibitors [1].

1.7 Ligand and Protein Preparation

The RCSB PDB database provided the 3D structures of the COVID-19 protein. There are thousands of protein structures in the Protein Data Bank (PDB) collection that were discovered using NMR or crystallographic X-ray analysis. In terms of ligands, the online PubChem database provided the 2D structures of chloroquine. The MDL Mol file format was used to store the ligands. Then, they were transformed with Accelrys Discovery Studio Visualizer into a PDB file format[2].

1.8 BIOVIA Drug Discovery Studio

Many molecular modeling techniques have been used in the current era of pharmaceutical research to explore intricate chemical and biological systems in a range of drug discovery projects. In order to identify, characterize, and develop new and promising molecules, it is critical to include experimental procedures with computational approaches. Molecular docking is a widely utilized method in contemporary drug design and research that investigates ligand conformations within the macromolecular target binding site and yields an estimate of the free energy of receptor-ligand binding for each conformation.

- **Software**

Table no: 1 Used tools in molecular docking

Sr.no	Software
1	RCSB database
2	Pubchem
3	Pymol
4	Autodock tool
5	Autodock vina
6	Uniport

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7	Protein plus server
8	Biovia drug discovery studio

2) AIMS AND OBJECTIVE

2.1 Aims In Silico Study Of Computer Added Drug Design For Chloroquine As Anti-Viral Agent.

2.2 Objectives

1. To carry out a comprehensive literature survey and selective drug.
2. To make the drug discovery process cost effective.
3. To reduced time required for drug development.
4. Summarize the mechanism of action of chloroquine.
5. To obtained the PDB files of targets from RCSB PDB website.
6. To carry out molecular docking study for the prediction of activity to compare with standard drug molecule.
7. Target identification and understanding of mechanism.
8. Identify the most common adverse effects of chloroquine.
9. Review the appropriate monitoring of patients treated with chloroquine.
10. Outline the importance of collaboration and coordination among the interprofessional team that can enhance patient care when prescribing and monitoring chloroquine to improve patient outcomes for patients receiving prophylaxis and treatment with chloroquine.

3) RECEPTOR AND LIGAND PROFILE

3.1 Receptor profile: (RCSB PDB Database)

1. Receptor name: The crystal structure of COVID-19 main protease in complex with an inhibitor N3.

- **PDB DOL:** https://doi.org/10.2210/pdb6LU7/pdb
- **Classification:** viral protein
- **Organism(s):** Severe acute respiratory syndrome coronavirus 2, synthetic construct
- **Expression system:** Escherichia coli BL21(DE3)
- **Mutation(s):** No

Experimental data

- **Method:** X-RAY DIFFRACTION.
- **Resolution:** 2.16 Å.
- **R-Value Free:** 0.235.
- **R-Value Work:** 0.202.
- **R-Value Observed:** 0.204.

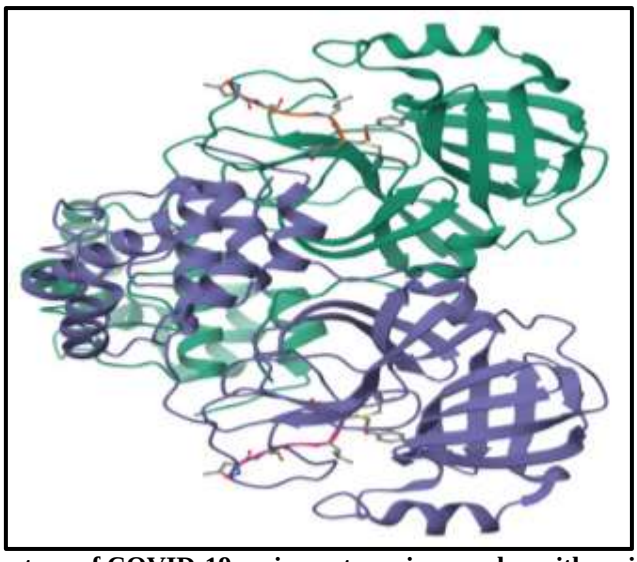

Figure No 1: The crystal structure of COVID-19 main protease in complex with an inhibitor N3(PDB ID:6LU7).

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2. **Receptor name:** Structure of SARS-CoV-2 chimeric receptor-binding domain complexed with its receptor human ACE2.

- **PDB DOI:** https://doi.org/10.2210/pdb6VW1/pdb
- **Classification: CELL INVASION**
- **Organism(s):** Homo sapiens, Severe acute respiratory syndrome-related coronavirus, Severe acute respiratory syndrome coronavirus 2
- **Expression System:** Spodoptera frugiperda
- **Mutation(s):** No
- **Membrane Protein:** Yes.

Experimental data

- **Method:** X-RAY DIFFRACTION
- **Resolution:** 2.68 Å
- **R-Value Free:** 0.229
- **R-Value Work:** 0.197
- **R-Value Observed:** 0.199

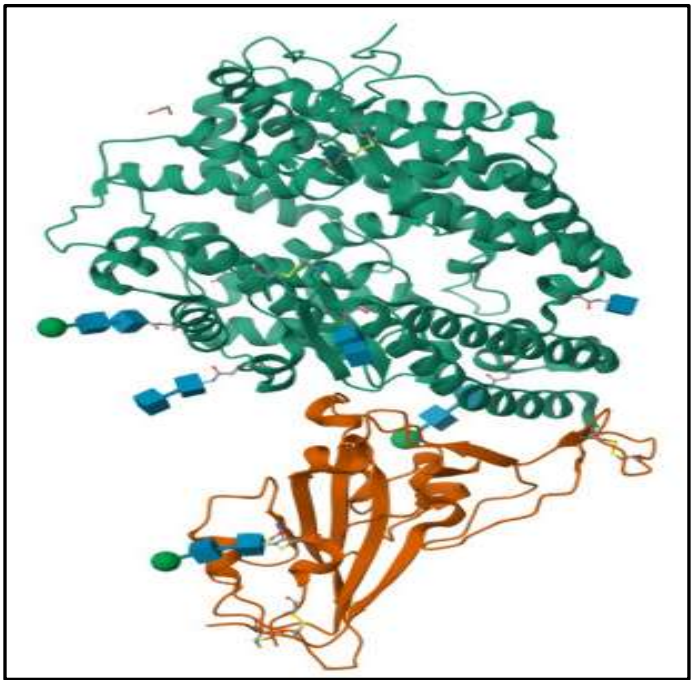

Figure No: 2 Structure of SARS-CoV-2 chimeric receptor-binding domain complexed with its receptor human ACE2 (PDB ID:6VW1).

3.2 Ligand profile

PubChem: 2719
Drug name: Chloroquine
Classification: Anti-malaria, Anti-viral.
Molecular formula: $C_{18}H_{16}CIN_3$
Structure:

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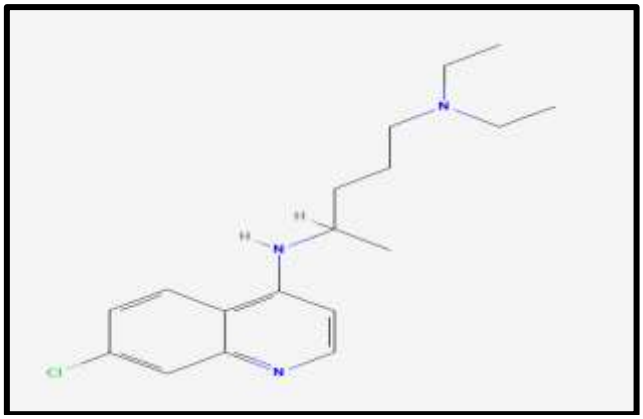


Figure no: 3 Structure Of Chloroquine

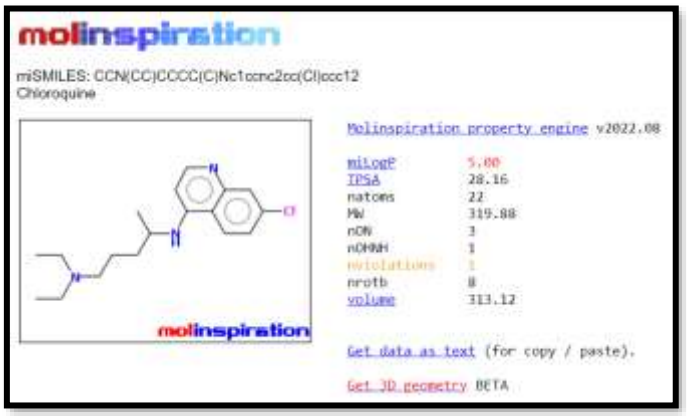
IUPAC Name: 4-*N*-(7-chloroquinolin-4-yl)-1-*N*,1-*N*-diethylpentane-1,4-diamine
Molecular weight: 319.9 g/mol
Canonical smile format: CCN(CC)CCCC(C)NC1=C2C=CC(=CC2=NC=C1)Cl
Melting point: 87-89.5 ºC
Mechanism of action: Chloroquine inhibits the action of heme polymerase in malarial trophozoites, preventing the conversion of heme to hemazoin. _Plasmodium_ species continue to accumulate toxic heme, killing the parasite. Chloroquine passively diffuses through cell membranes and into endosomes, lysosomes, and Golgi vesicles where it becomes protonated, trapping the chloroquine in the organelle and raising the surrounding pH. The raised pH in endosomes, prevent virus particles from utilizing their activity for fusion and entry into the cell. Chloroquine does not affect the level of ACE2 expression on cell surfaces, but inhibits terminal glycosylation of ACE2, the receptor that SARS-CoV and SARS-CoV-2 target for cell entry.

4) EXPERIMENTAL WORK

4.1 Molinspiration

Material and method

It well be use for the determination or observation of bioactivity and property of drug compounds. It also shows there molecular weight and many properties.



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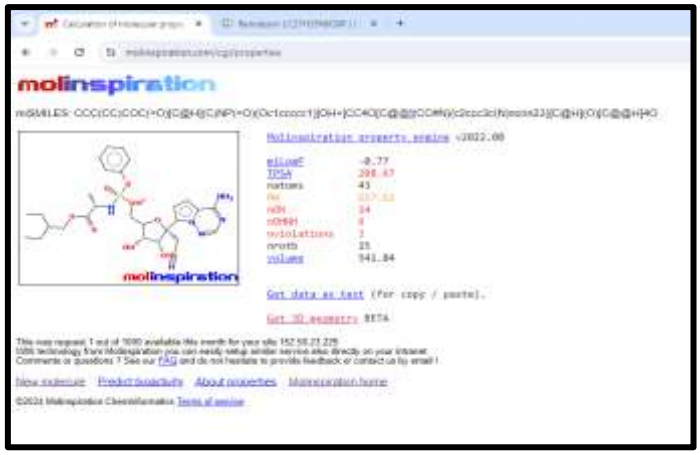

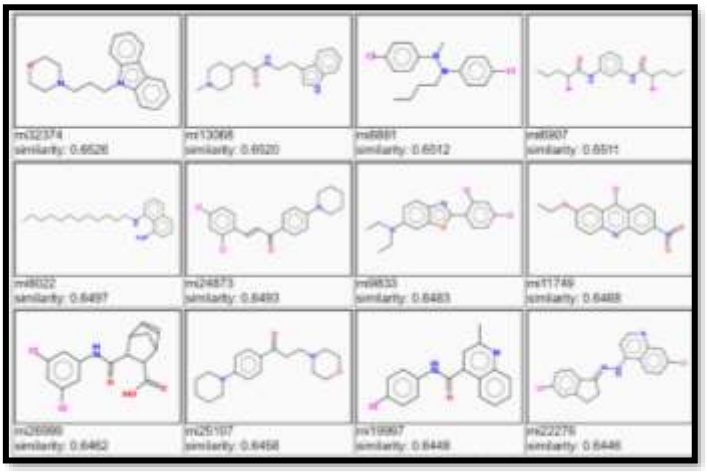

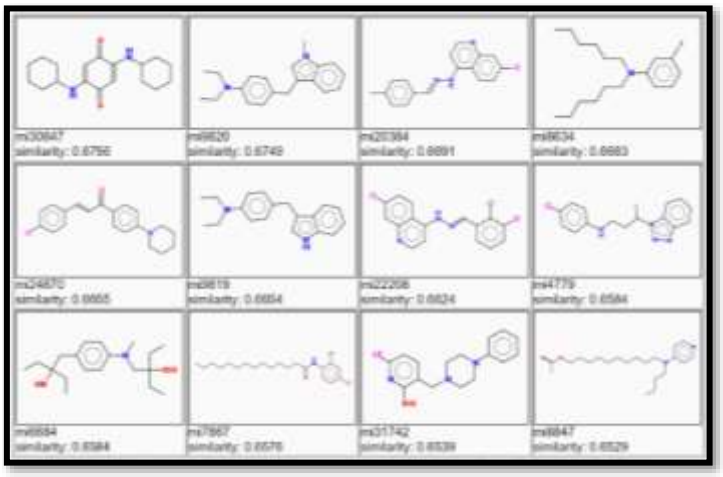

Results: Molinspiration

Table no 2: Properties of chloroquine

Sr no	Drug name	miLogP	TPSA	natoms	Molecular weight	nON	nOHNH	nviolations	nrotb	Volume
1	Chloroquine	5.00	28.16	22	319.88	3	1	1	8	313.12
2	Remdesivir	-0.77	208.67	43	617.62	14	6	3	15	541.84

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Table no 3: Predict Bioactivity of Chloroquine

Sr no	Drug name	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	Chloroquine	0.32	0.32	0.38	-0.19	0.05	0.11
2	Remdesivir	0.18	-0.40	0.21	-0.34	0.31	0.17

- **Discussion**

A) Molecular Property

In this study, drug activity predictions had shown for test and standard drugs using the Molinspiration platform results had shown in Table no 2. The observed Lipinski's nú of five scores indicated good drug-likeness. The MiLogP values of these pounds were below 5, ranging from 5.00 to -0.77 suggesting their good permeability cell membranes. the Topological Polar Surface Area (TPSA) of the compounds, which provides information about their polarity. All the selected drugs had TPSA values below 160 except for Chloroquine, which had lower values is 28.16 and higher TPSA values ranging from 208.67 for standard drug. The TPSA value is an important parameter for analyzing ang transport properties and their ability to cross cell membranes.

The molecular weight (MW) of the selected drugs was within an acceptable range 319.88), except for Remdesivir, which had a higher MW (617.62). Lower molecular weight compounds are typically more easily absorbed, diffused, and transported compared high molecular weight compounds. Beyond a certain limit, an increase in molecular wright can lead to increased bulkiness of the molecules. The number of atoms and non- hydrogen atoms (nON) for all the selected drugs were less than 10 respectively. Molinspiration results indicated that the number of rotatable bonds and violations (nOHNH and n-violations) were less than 5 respectively, within acceptable ranges, implying appropriate molecular flexibility and compliance with chemical rules. The molecular volume (MV) was also calculated to assess the transport properties of the molecules, including blood-brain barrier penetration. Most compounds had an MV value within the acceptable range (≤500), except for Remdesivir, which had a higher MV (541.84)

B) Bioactivity Scores

Bioactivity scores of the compounds based on their interactions with GPCR ligands, ion channel modulators, kinase inhibitors, nuclear receptor ligands, protease inhibitors, and enzyme inhibitors results has shown in Table 3. Among the selected compounds, Chloroquine, and Remdesivir demonstrated lower bioactivity scores (<<5-0) toward GPCR ligands. For ion channel modulators, Chloroquine, and Remdesivir exhibited higher properties (0) than other compounds (<0).

In the case of kinase inhibitors and nuclear receptor ligands (score <0) Chloroquine, and Remdesivir showed higher activity.

Overall, the predictions based on Molinspiration provide valuable insights into the drug-likeness and potential bioactivity of the selected compounds. However, it is important to remember that these are computational predictions and munt be validated through studies before drawing definitive conclusions about their pharmacological properties.

- **Conclusion**

In conclusion, the drug activity predictions using the Molinspiration platform for a set of test and standard drugs provided valuable insights into their molecular properties and potential bioactivity. The observed Lipinski's rule of five scores indicated that all the selected compounds demonstrated good drug-likeness, as they complied with the acceptable ranges for various properties.

The MiLogP values, which represent the lipophilicity of the compounds, were below for all the drugs, suggesting good permeability across cell membranes. The Topological Polar Surface Area (TPSA) values indicated the polarity of the compounds, with most of them having TPSA values below 160 A, except for a few compounds with higher values. TPSA is an important parameter for understanding drug transport properties and cell membrane penetration. The molecular weight (MW) of the selected drugs was generally within the acceptable range (≤500), except for moenomycin, which had a higher MW. Lower molecular weight compounds are typically more favorable for absorption, diffusion, and transport.

4.2 Molecular Docking

4.2.1 Material

In the present work following tools have been used to carry out the molecular docking of proposed compound.

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Table no 4: Tools for molecular docking.

Sr.No	Tool Name	About Tool
1	Autodock Vina (Molecular Docking Sofware)	Version: 1.1.2 Developed By: The Scripps Research Institute
2	Glide (Schrodinger Inc., USA)	Version: 2.2 Developed By: Schrodinger LLC
3	Mgl Tool (Required For File PDBQT File Generation)	Version: 1.5.7 Developed By: The Scripps Research Institute
4	The Pymol Molecule Graphics System	Version: 2.3.4 Developed By: Schrodinger LLC
5	Discovery Studio Visualizer (BIOVIA)	Version: 21.1.0.20298 Developed By: Dassault System Biovia Corp.

- **Auto Dock Vina**

Molecular docking is a computational procedure that attempts to predict noncovalent binding of macromolecules or, more frequently, of a macromolecule (receptor) and a small molecule (ligand) efficiently, starting with their unbound structures, structures obtained from MD simulations, or homology modeling, etc. The goal is to predict the bound conformations and the binding affinity[8]. AutoDock Vina, a new program for molecular docking and virtual screening, is presented.

AutoDock Vina achieves an approximately two orders of magnitude speed-up compared to the molecular docking software previously developed in our lab (AutoDock 4), while also significantly improving the accuracy of the binding mode predictions, judging by our tests on the training set used in AutoDock 4 development.

- **Producer**

4.2.2 Steps of protein preparation

i. Open the PDB format of receptor 6lu7 in auto dock vina by clicking vina by clicking “file in subsection read molecule”.

ii. Go to edit and delete water molecule, select from string as shown in Fig no: 4.

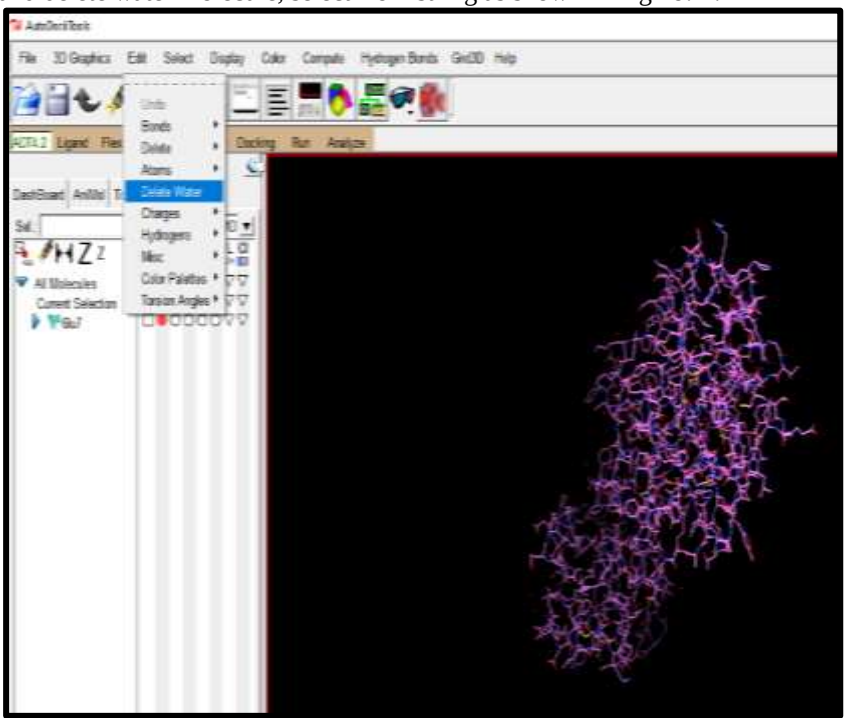

Figure no 4: Protein preparation.

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iii. Then go to select and click on select from string and add hetatm atom as shown in Fig no: 5.

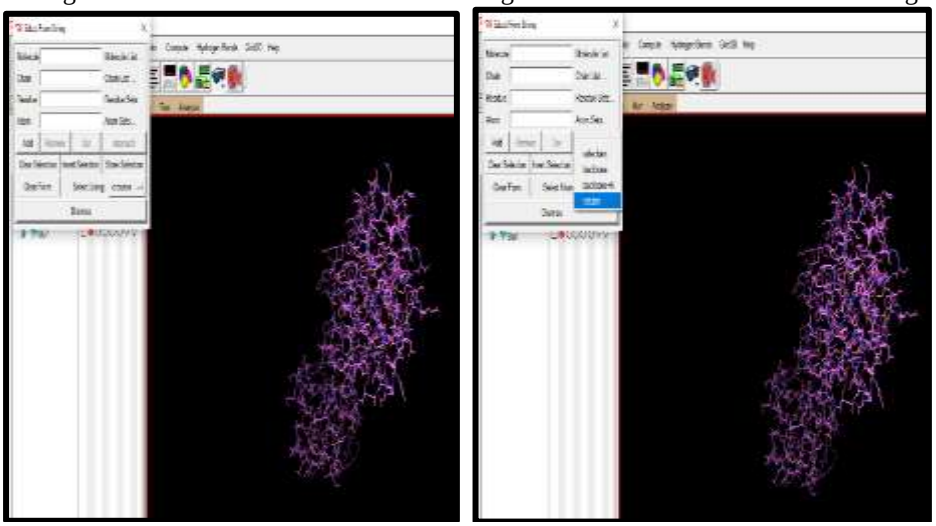

Figure no 5: Select & click select from string and add hetatm.

iv. Then go to edit and click on Delete Selected Atoms as shown in Fig no: 6.

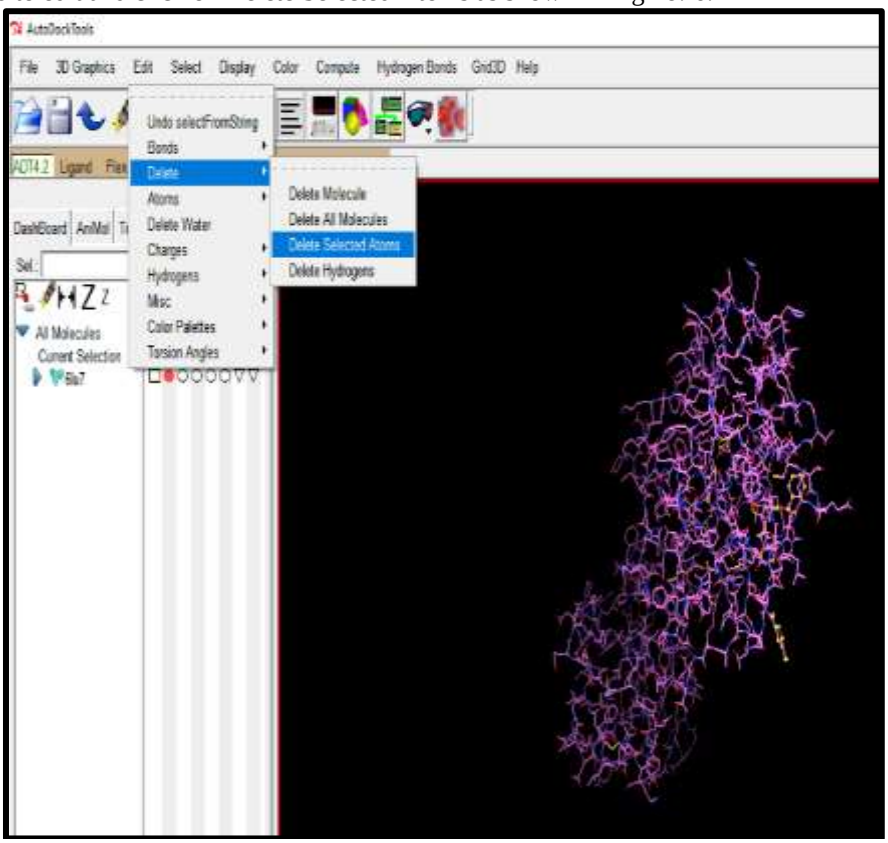

Figure no 6: Delete selected Atom.

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v. Then go to edit and click on "add hydrogen (polar only) as show in Fig no: 7.

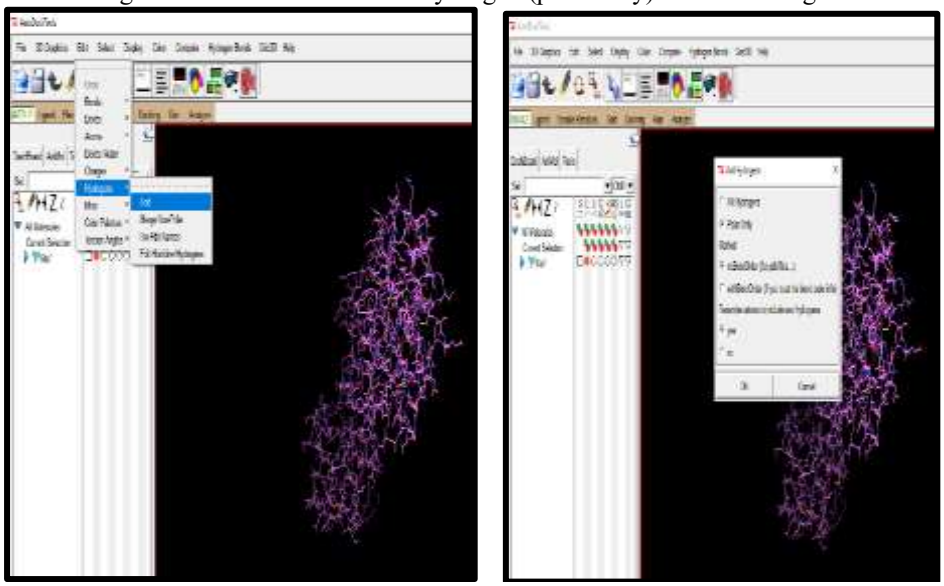

Figure no 7: Add hydrogen (polar only)

vi. Then go to edit and "add kollman charges" as shown in Fig no: 8.

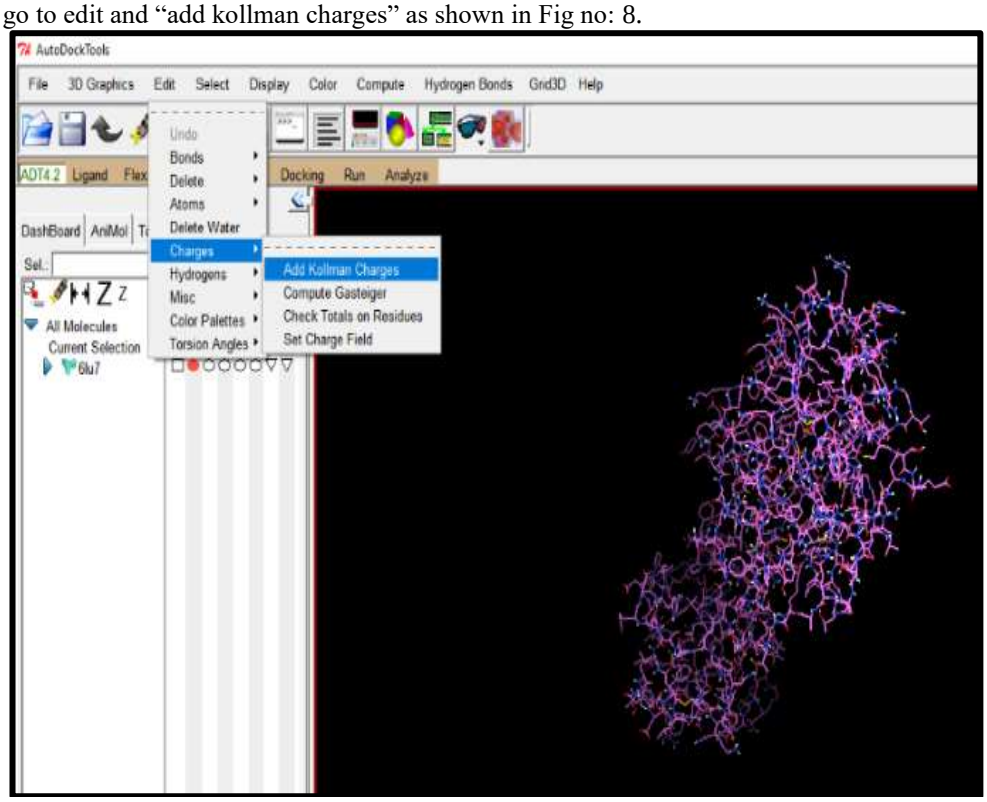

Figure no 8: Add Kollman Charges.

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vii. Then go to edit and click on atoms chose "Assign AD4 type".as shown in the Fig no: 9.

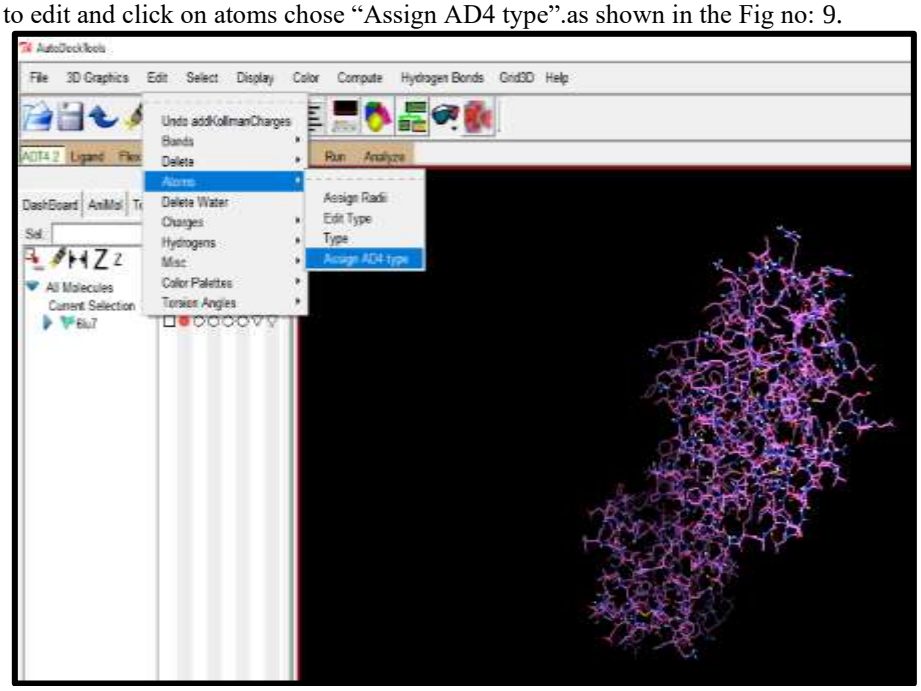

Figure no 9: Assign AD4 type.

viii. Then go to the file section and save bottom then select PDBQT format to save & select the END and add molecule, as shown in Fig no: 10.

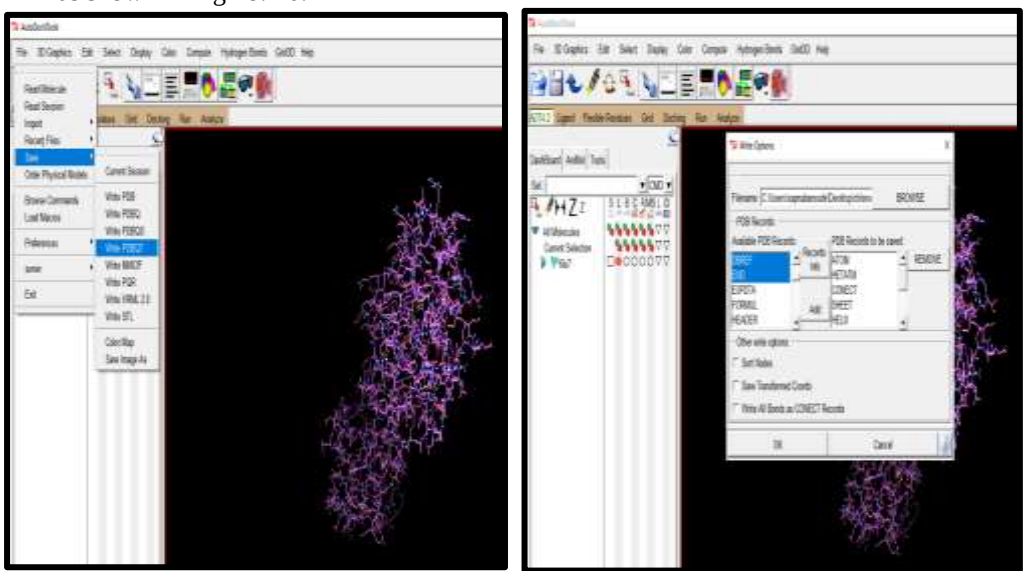

Figure no 10: Save as PDBQT.

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4.2.3 Ligand Preparation

i. the ligand section then choose input add click on the open option. As shown in fig no: 11.

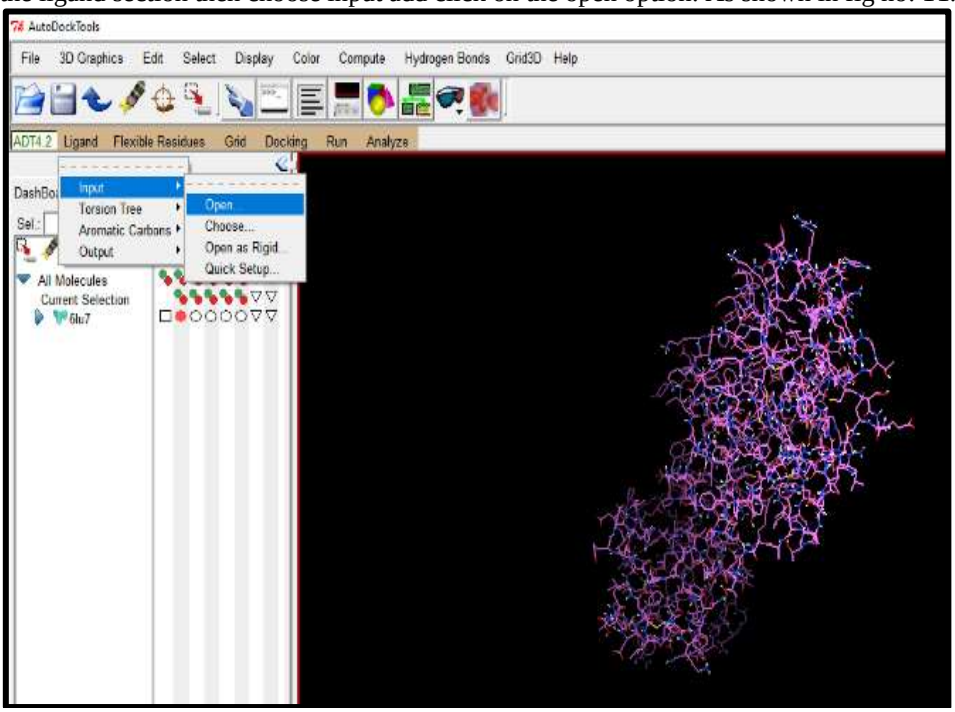

Figure no 11: Click the ligand section then choose input add click.

ii. After loading the molecule click the on-torsion tree under the same ligand section and click on choose root then detect root. as shown in Fig no: 12.

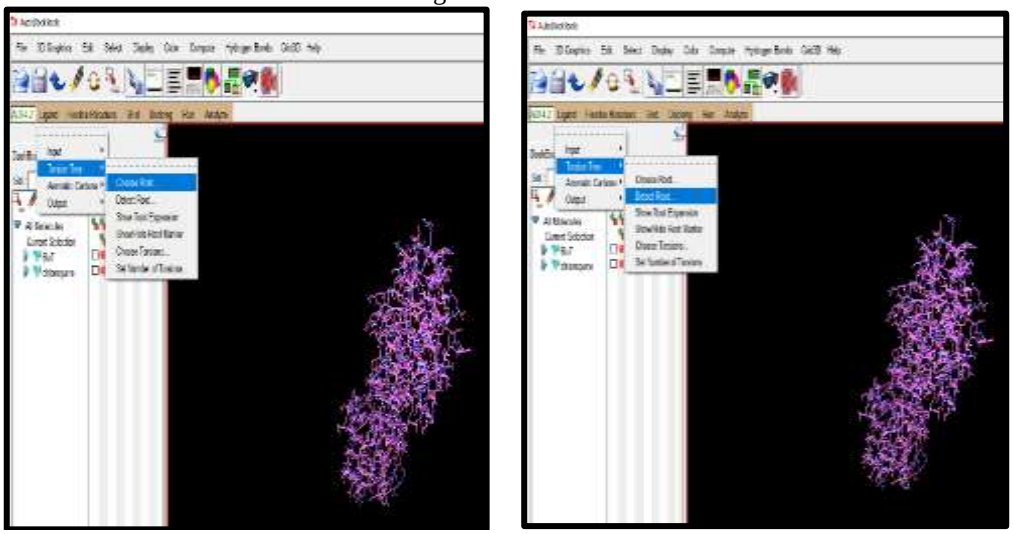

Figure no 12: Choose root then detect root.

iii. Then go to the output option and save it in PDBQT format. As shown in fig no: 13.

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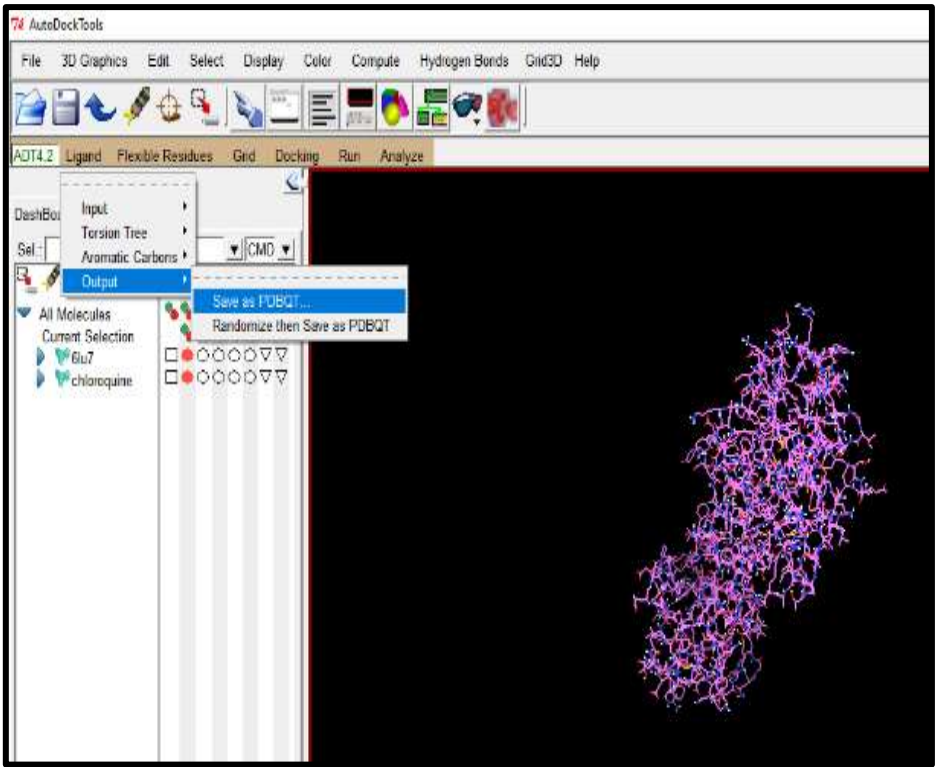

Figure no 13: Save as PDBQT.

4.2.4 Grid generation:

i. Open PDBQT of 6lu7 receptor which is saved in an earlier step. then the grid and choose and choose a receptor as a macromolecule. Then select the 6lu7 receptor molecule and click No for reserve change as shown in Fig no: 14.

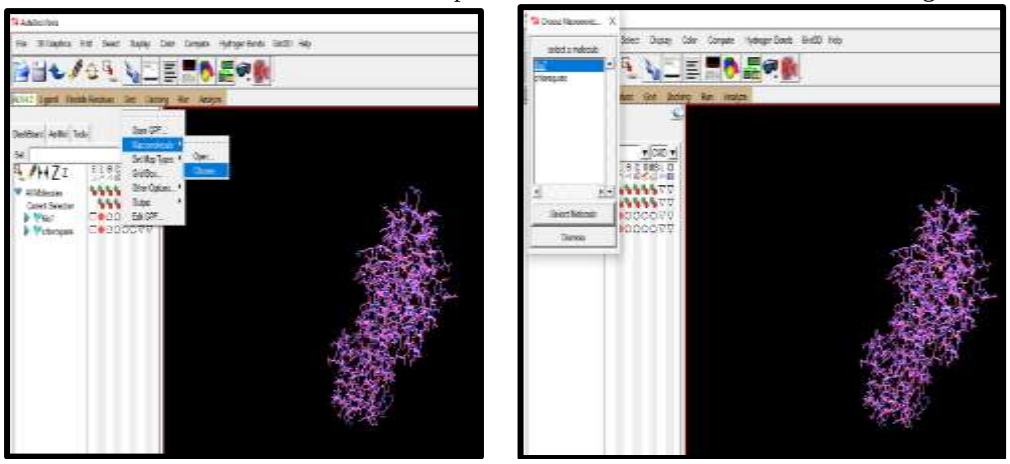

Figure no 14: Choose ligand.

ii. Then click on the grid box Adjust the grid box using the grid box coordinates so that the receptor molecule is enclosed within the box then click the button in the grid option and select "output grid dimension file" as shown in Fig no: 15.

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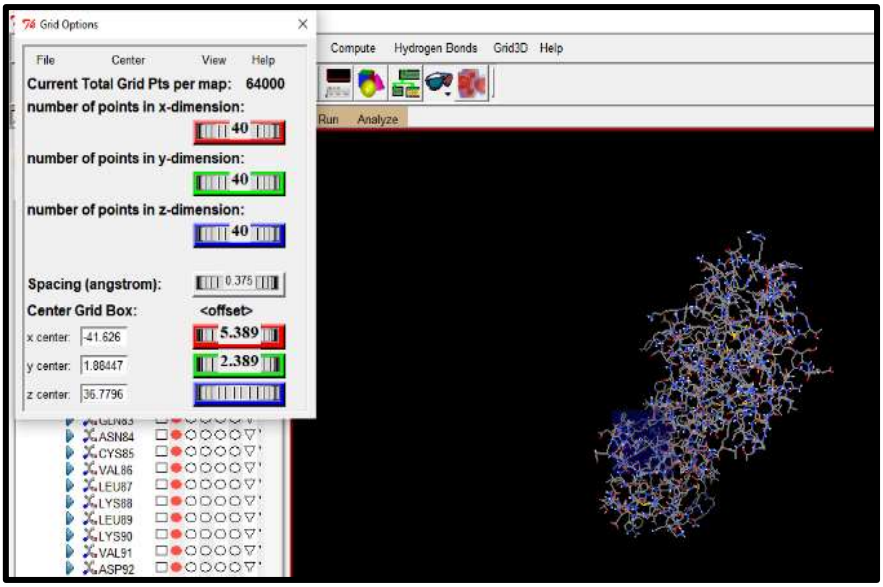

Figure no 15: Output Grid Dimension File.

4.2.5 Config file:

Open a new document file and enter the configuration details of the grid box, receptor name, ligand name, energy range and exhaustiveness as given in picture not as shown in Fig no: 16.

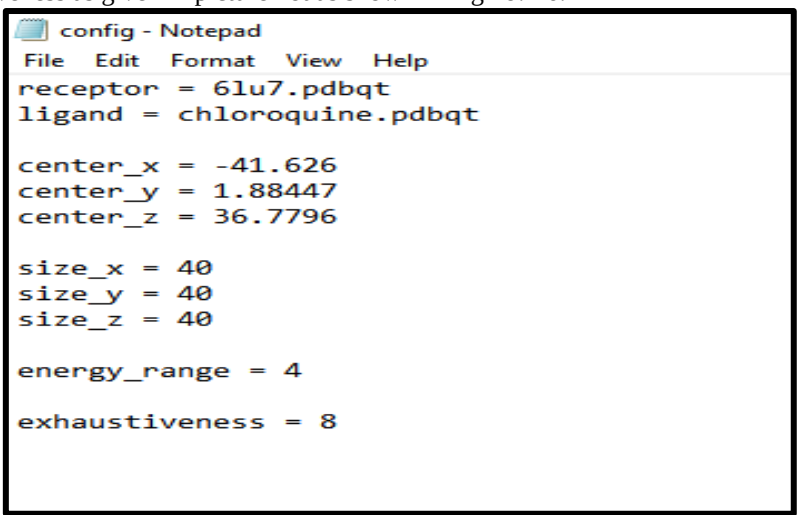

Figure no 16: Config file.

4.2.6 Command Prompt

1) Search for command prompt in your laptop or computer.
2) Then enter, followed by 'cd' Paste the folder location in which all require are present them press enter.
3) Then run docking vina copy address "vina search --receptor 6lu7.pdbqt --ligand chloroquine.pdbqt --config config.txt --log log.txt --out output.pdbqt as shown in Fig no:17.

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Figure no 17: Command prompt.

4) Then run docking vina copy address "vina search --receptor 6lu7.pdbqt --ligand chloroquine.pdbqt --config config.txt --log log.txt --out output.pdbqt as shown in Fig no:18.

Figure no 18: Run Docking Vina Copy Address "Vina Search-Receptor"

5) After that it will take some time and give us the result of docking as shown in Fig no: 19.

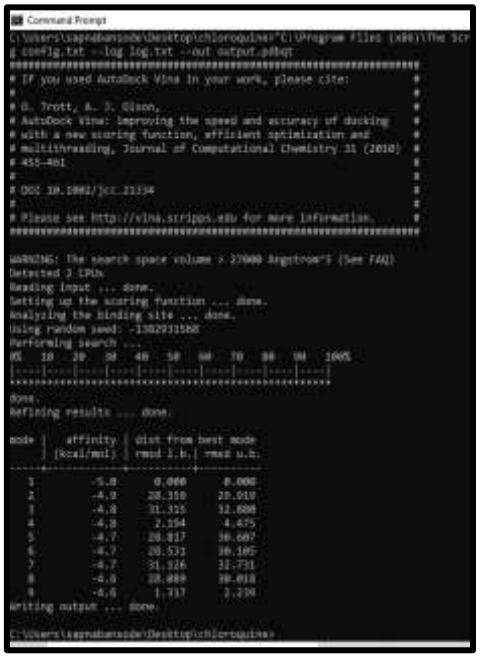

Figure no 19: Final result

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6) Then Output file of the result will automatically save in the command folder, which can be read by using notepad as shown in Fig no: 20.

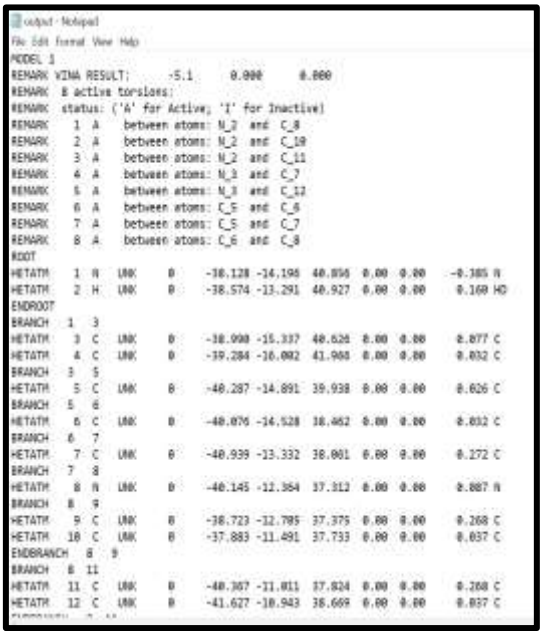

Figure no 20: Out file from command folder.

4.2.7 Visualization Of Docking Result (Docking Complex):

1. For the visualization of result we use "discovery studio 2021 BIOVIA" terminal look like as shown in the Fig no: 21

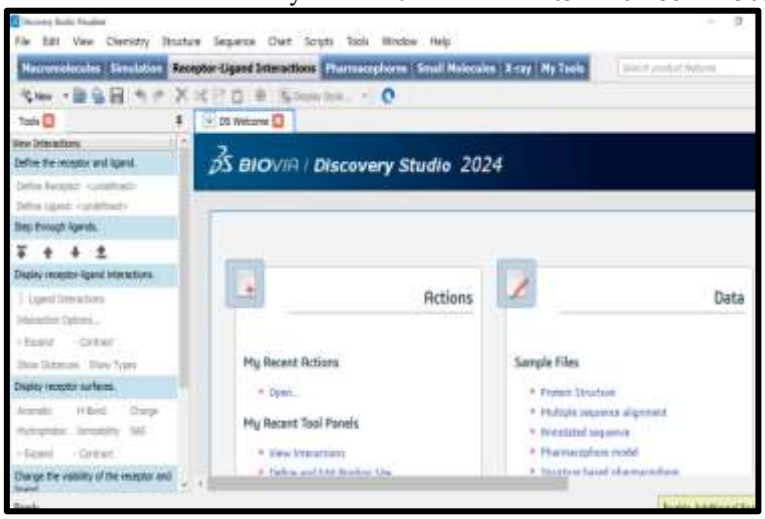

Figure no 21: Terminal of discovery studio 2021 BIOVIA

2. Open out file obtained from docking by click on file section. Then delete all poses by clicking on it except best pose which will be 1 in all case, as shown in Fig no: 22.

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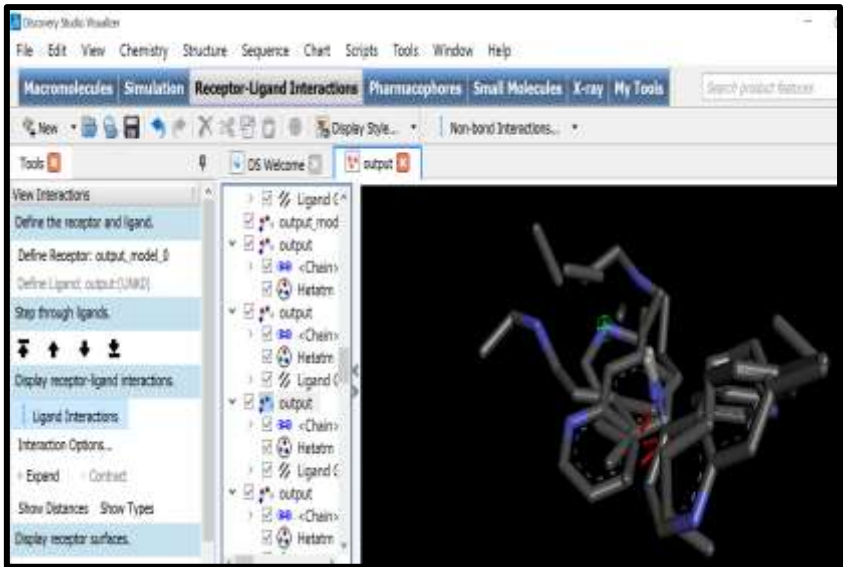

Figure 22: Terminal after load out result file

3. Now go to file section and open 6lu7 receptor PDBQT file in new terminal of Biova software. From this terminal copy receptor and paste it in ligand terminal. As shown in the Fig no: 23

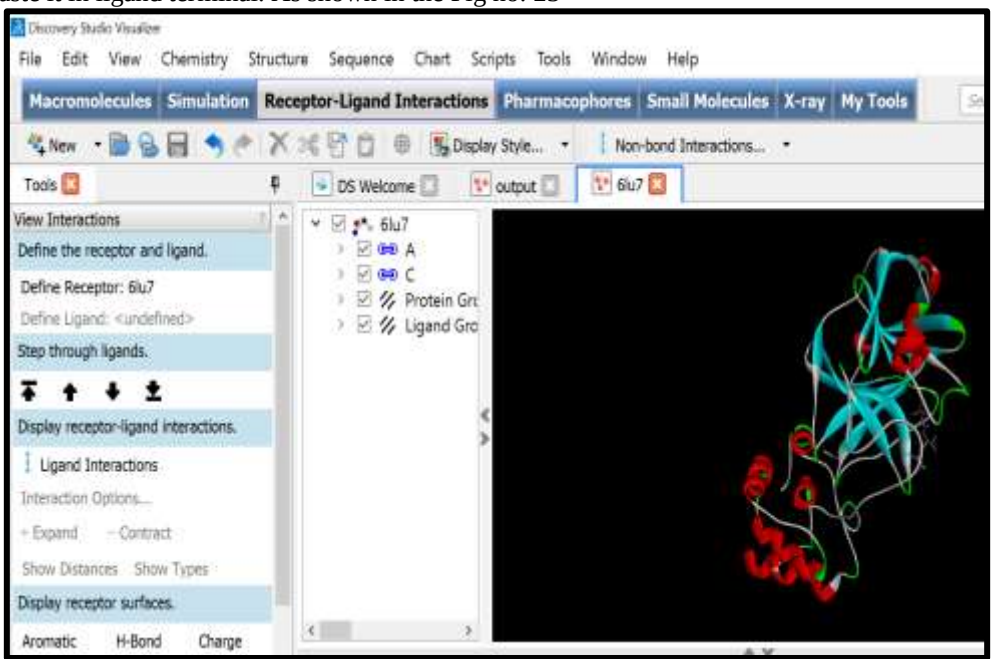

Figure no 23: Complex of ligand with receptor with suitable pose

4. After define receptor and ligand from the complex, then click on "ligand -receptor complex" as shown in the Fig no: 24

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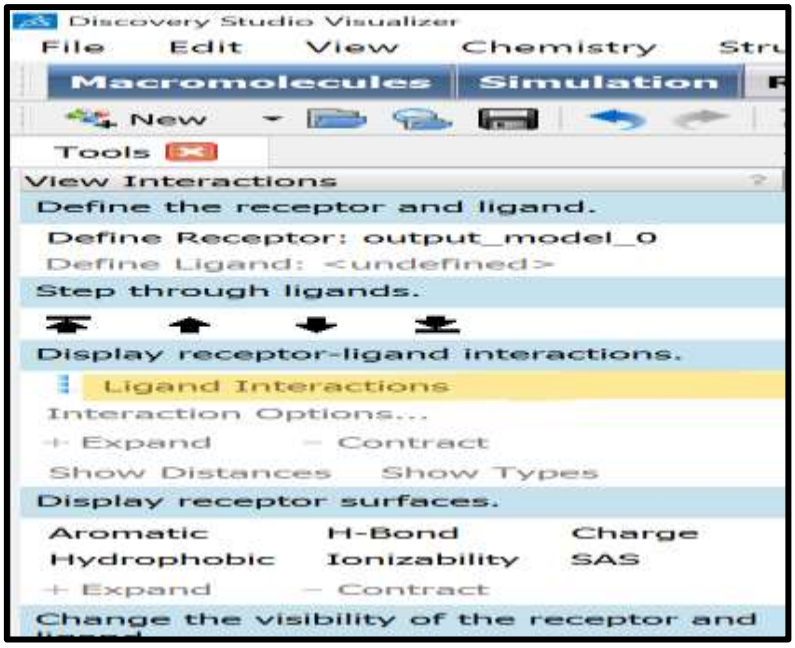

Figure no 24: Ligand interaction option

5. In 'Show' receptor-ligand interaction in 3D diagram, click on 'show 3D diagram, where you will get image of amino acid attached to ligand in 3D format Fig no: 25

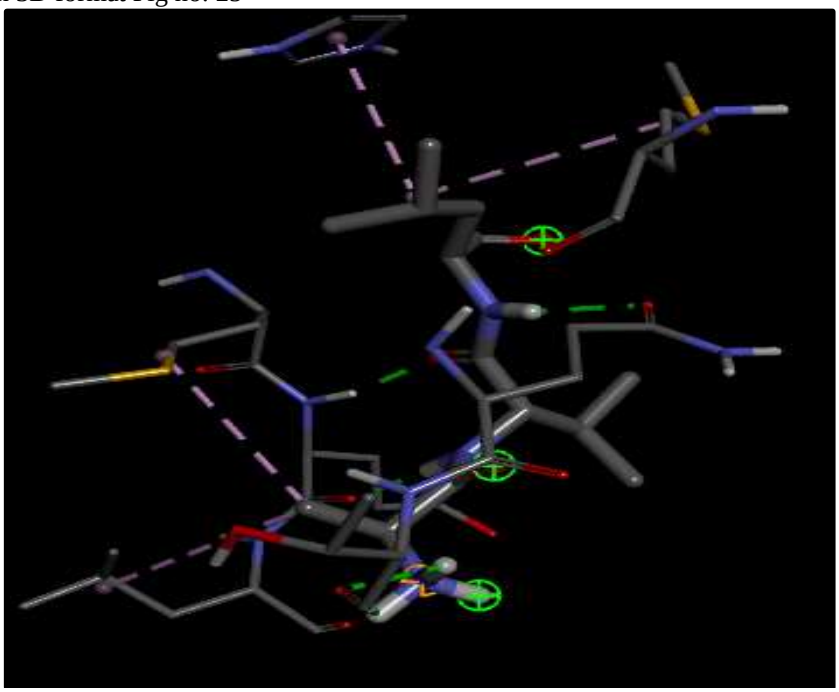

Figure no 25: 3D structure of ligand.

6. In Show receptor-ligand interaction in 2D diagram, click on 'show 2D diagram", where you will get image of amino acid attached to ligand in 2D format Fig no: 26

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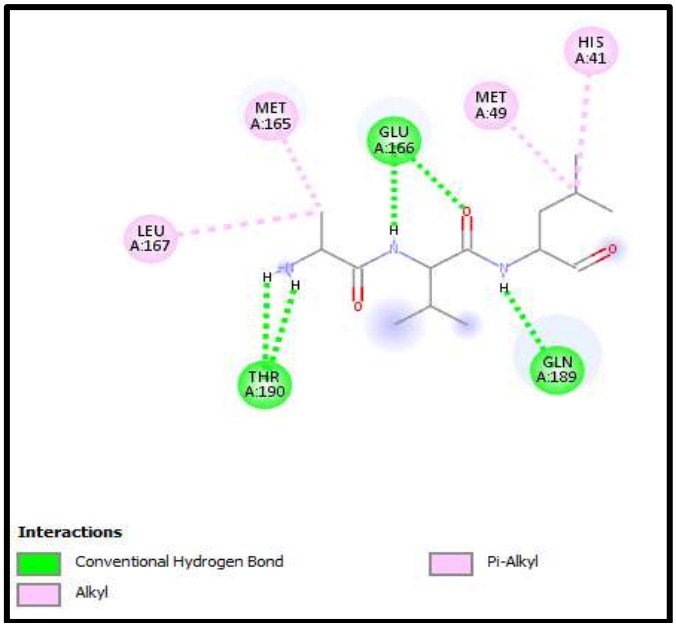
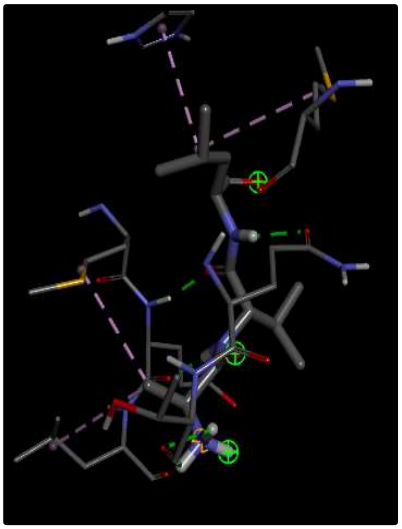
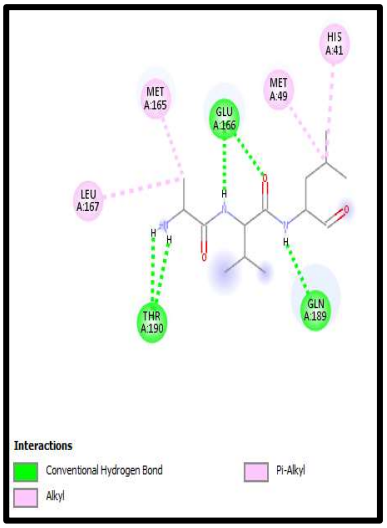


Figure no 26: 3D structure of ligand.

Sr no	Ligand name	3D Orientation	2D Orentation
1	**Chloroquine**		

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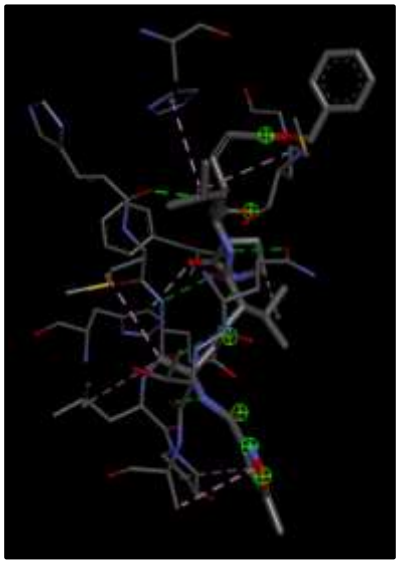
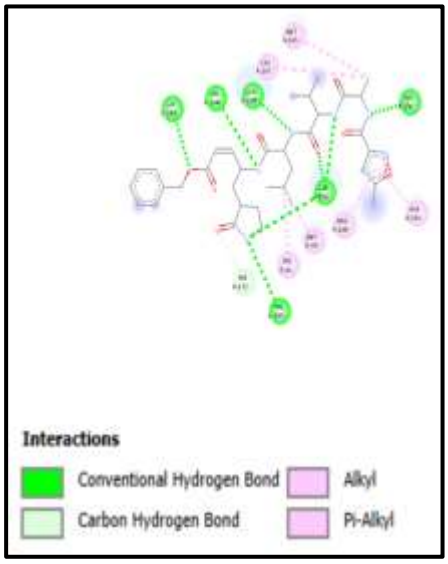
2	Remdesivir		

Table No 5: 2D And 3D Oreantation Of Standard And Test Drug

Table 5 Result of molecular docking

Sr no	Ligand name	Binding energy	Amino acid attached
1	Chloroquine	-5.5	LEU A:165, JLU A:166, LEU A:167, JEN A:189, GLN A:189, MET A:49, THR A:90
2	Remdesivir	-5.8	TRP A:218, ARG A:217, LEU A:220, ARG A:222, ASN A:221, PHE A:223

4) RESULT DOCKING

4.1 Docking Result of chloroquine

The result of test drug chloroquine and their target viral protein, PDB ID binding energy and standard drug like a Remdesivir for comparative study have been summarised as below table by autodock vina tool.

Sr.no	Target name	Viral name	PDB ID	Binding energy of test drug	Binding energy of standard
1	Acute respiratory syndrome	Escherichia coli	6lu7	-5.5	-7.4
2	Homo sapiens	Spodoptera frugiperda	6vw1	-5.8	-7.2

5) DISCUSSION

Molecular docking studies have been performed on chloroquine (test drug) and Remdesivir (standard drug) to understand their binding mechanisms and potential interactions with target proteins. chloroquine is a anti-viral drug used for the treatment of various viral infections caused by viruses (Escherichia coli, Spodoptera frugiperda). Remdesivir, on the other hand, is an vaccine use in covid-19 for the treatment of corona virus. It's known for its effectiveness, but it can also have side effects including fever, nausea, vomiting, sweating, and shivering symptoms.

6) CONCLUSION

Combining the DFT approach with molecular docking simulations, chloroquine derivatives have been explored due of their remarkable efficacy in treating the COVID-19 pandemic. It will also you as anti-malarial agent. Remdesivir is use as standard drug in COVID-19 pandemic and shows more effectiveness than chloroquine. But it also have major side effects. Chloroquine shows minor effects on peoples.

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