

Molecular Docking Studies of Paracetamol with SARS-CoV-2 RBD Spike Protein

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Abstract:

SARS-CoV-2 causes Covid-19 disease. Very few medications are available to overcome these symptoms. Here in silico studies have been done using FDA-approved anti inflammatory drugs like paracetamol against SARS-CoV-2. Here protein-ligand complexes are formed and docking analysis is used to calculate their binding attractions. Docking paracetamol with protein target 8bg2 yielded binding energy of -5.31. In silico molecular docking studies show that paracetamol can act as a hindrance against SARS-CoV-2 targets. Yet in vitro and in vivo studies are required.

Keywords: 8BG2, Paracetamol, Molecular Docking

1. Introduction:

Paracetamol is a potential therapeutic agent for Covid-19 due to its anti pyretic, anti inflammatory and analgesic drug. It has extensive clinical uses due to its multiple molecular and cellular targets. Cyclooxygenase enzyme (COX) exists in two forms COX-1 and COX-2 . Paracetamol inhibits this enzyme thus hindering the biosynthesis of prostanoids and its inflammatory nature. The activity of serine 530 residue of COX-1 is inhibited irreversibly by the acetyl group of Paracetamol even in very low doses.

Paracetamol has the capacity to bring few conformational changes in protein molecule by blocking its active site or combining with other drugs.

Molecular docking is a computational tool to predict interactions of a small ligand molecule with a large receptor protein molecule. Here computer software programs are used to predict the possible interactions between three dimensional structures of two molecules. This is very important in drug discovery process to save time [1-4]. A computer generated representation of small molecules is placed in the active site of the target in various positions, conformations and orientations. This process is called molecular docking. Here molecular docking studies were conducted to study the interactions of paracetamol with 8bg2 protein receptor individually [5-7].

2. Materials and Methods:

2.1 Preparation of Ligand:

The drug molecule paracetamol was retrieved from PubChem Database (<https://pubchem.ncbi.nlm.nih.gov>) and loaded in Chem Draw Ultra Version 12.0 in three-dimensional SDF structure (CID:1983) (Fig 1). Open Babel-2.3.2 is used to convert ligand file format from MDL MOL (SDF) to PDB. Auto Dock 4.2.6 application was launched. Ligands are then made torsion free and saved in PDBQT format. Hydrogen atoms mainly polar ones are added followed by addition of Kollmann charges. Atoms were assigned to AD4 type. Then Gasteiger charges were computed and then PDB format is saved as PDBQT format.

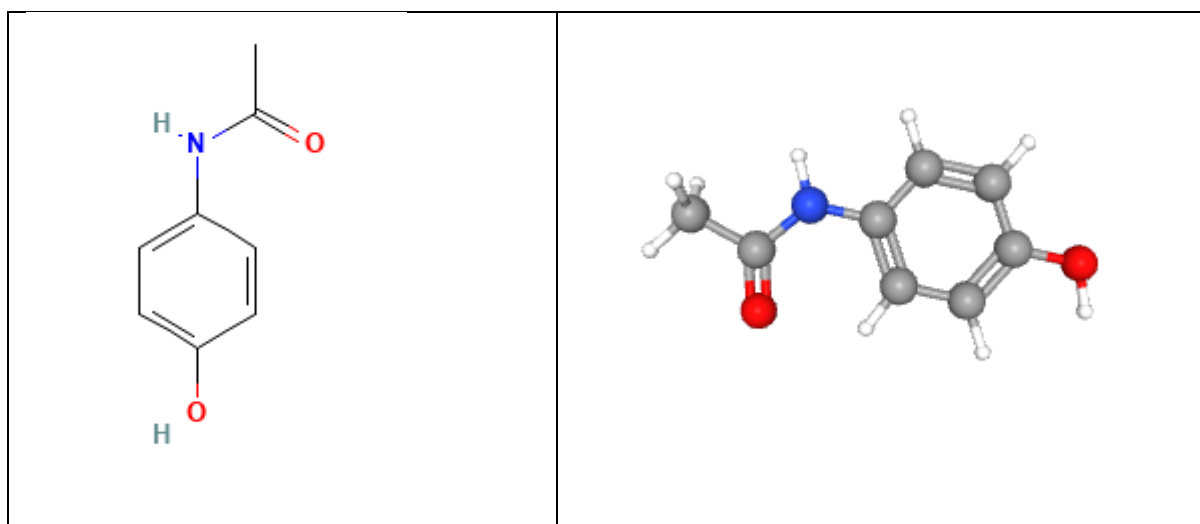


Fig. 1: 2D and 3D structure of Paracetamol (CID:1983)

2.2 Retrieval of Target Proteins:

RCSB Protein Data Bank (<https://www.rcsb.org/>) was used to obtain high resolution 3D structures of the newly described SARS-CoV-2 enzyme (PDB ID: 8BG2) (Fig 2).



Fig. 2: 3D structure of SARS-CoV-2 therapeutic target protein (PDB ID 8BG2)

2.3 Preparation of target proteins:

The experimentally determined 3D structures of target protein molecule 8BG2 was retrieved from RCSB Protein Data Bank. The legacy pdb format files are then downloaded. The raw protein is then opened in Discovery Studio Visualizer software. Water molecule HETATM and other unwanted chains are removed. Protein is then saved in pdb format. Hydrogen atoms mainly polar ones are added followed by addition of Kollmann charges. Atoms are assigned to AD4 type. Then Gasteiger charges are computed. The topology of the structure including bond angles and bond order were assigned and energy minimization was done. The PDB format is now changed to PDBQT format [8-9].

2.4 Generation of Grid:

A Grid box was set around the protein molecule in the XYZ angle of $60 \text{ \AA} \times 60 \text{ \AA} \times 60 \text{ \AA}$ centred at $-48.292, 34.23, 1.272$ XYZ coordinates for ligand paracetamol.

2.5 Molecular Docking:

After preparing both protein and ligand in PDBQT format, the target protein 8bg2 which is considered as a rigid molecule and the ligand paracetamol is docked in it as it is considered flexible. Search parameters like Genetic Algorithm and other docking parameters are fixed. Finally Lamarckian Genetic Algorithm is run resulting in complexion of docking. Each

docking phase is done for nearly ten runs. 100 Kcal/mol threshold energy is used with maximum interaction of 2000. Out of the ten runs the one having lowest binding energy is the best conformer for docking operation. This PDB format of the docked conformer is used for further analysis. Binding site analysis of nearly 100 docked structures of 8bg2 with paracetamol is done. The one having lowest binding energy and maximum number of conformations is the best docked conformer. Ligand binds to amino acids of protein target by hydrogen bonds and other hydrophobic interactive amino acids including vanderwaals and electrostatic interactions. There are other π -interactions such as π -alkyl, π - π , π - σ , π -S interactions, π - π stacking are also seen in charge transfer. Docking results of paracetamol with protein target 8bg2 is done [11-13] (Table 1).

Table 1: Protein Ligand docking results

Name of the ligand	Protein PDB ID	Binding Energy (KCal/mol)	Ligand Efficiency	Number of Hydrogen Bonds	Hydrogen Bond interactive Amino acids	Hydrophobic interactive amino acids
Paracetamol	8BG2	-5.31	0.48	1	Ser35, Asp98	Phe106, Gly50, Tyr52, Ser233, Leu235, His104, Trp47, Phe58, Ser103

Discovery Studio Visualiser software was used to obtain 2 and 3 Dimensional structures of the docked protein ligand complex. Paracetamol showed hydrophobic interactions with Phe106, Gly50, Tyr52, Ser233, Leu235, His104, Trp47, Phe58, Ser103 (Fig 4). These results clearly demonstrate their ability to bind with active site residues thus blocking their interactions.

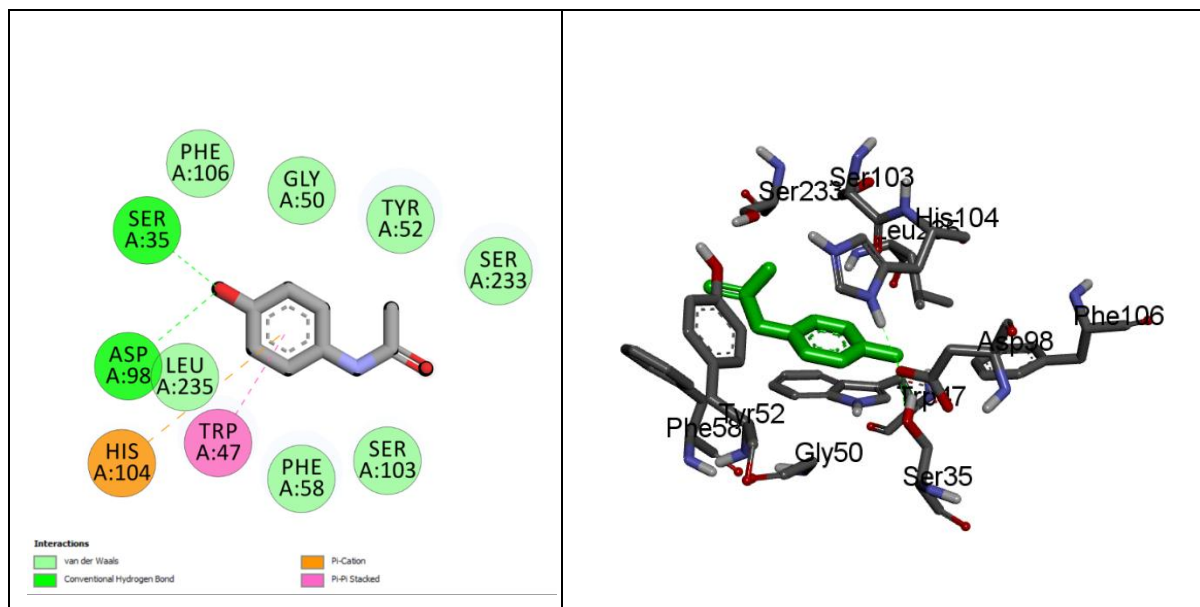


Fig.4 2D and 3D structures obtained by molecular docking of paracetamol with 8bg2

Chimera software is used to find the surface representation of paracetamol with the protein 8bg2 (Fig 5).

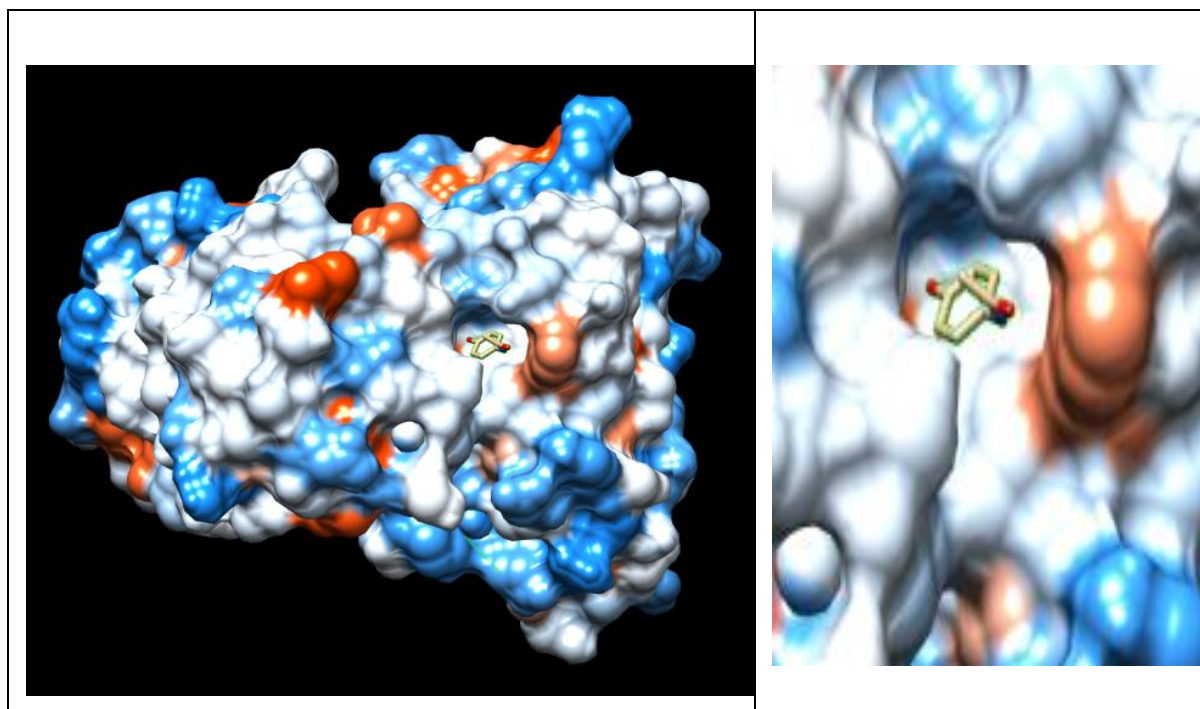


Fig 5. Molecular docking surface representation of paracetamol with 8bg2.

3. Conclusion:

In silico molecular docking studies suggest that paracetamol acts as a powerful inhibitors towards targets of SARS-CoV-2. However in vitro and in vivo experiments are needed to verify our predictions further.

4. Acknowledgement:

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5. References:

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