

## AN OVERVIEW ON MOLECULAR DOCKING

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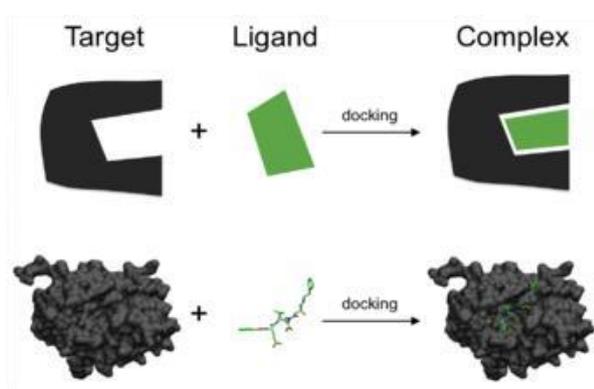
### ABSTRACT

Molecular docking has become an increasingly important tool for drug discovery. It has been widely employed as a rapid and inexpensive technology in both academic and industrial settings over the past decades. The molecular docking method explores the behavior of small molecules in the binding sites of target proteins. The goal of molecular docking is to predict three – dimensional structures of interest. With docking strategies, the druggability of compounds and their specificity against a particular target can be calculated for further lead optimization processes. Several important aspects of molecular docking in terms of its model, applications, different types of softwares used and some examples are briefly discussed in this article.

**KEYWORDS:** Molecular docking, computer-aided drug design, structure based drug design, conformations, optimization, virtual screening.

### INTRODUCTION

Docking plays a significant role in the rational drug design, which facilitates the prediction of preferred binding orientation of one molecule to another, for example ligand and receptor, when both interacted to form a stable complex. The information gathered from the preferred orientation may aids to predict binding free energy, binding affinity and binding constant of complexes. In this day and age, molecular docking is also used to estimate the binding orientation of small molecules to their target, aiming to determine their tentative binding parameter. Thus molecular docking act as a valuable tool in drug design and analysis.<sup>[1]</sup>



Docking is a method which forecast the preferred orientation of one molecule to another molecule when

bound to each other to form a stable complex. The main objective of molecular docking is to achieve an optimized confirmation for both the protein and ligand and relative orientation between protein and ligand so as the free energy of the overall system is minimized.<sup>[2]</sup>

The docking approaches are normally initiated by procuring 3D structures of target and ligand. Followed by assigning protonation states and partial charges. The next step is to detect target binding site, if it is not previously known or a blind docking simulation may be performed. Then the molecular docking calculations are carried out by two major steps: posing and scoring, thus a ranked list of possible target-ligand complexes are generated. The various softwares which were developed during the last ten years are AutoDock, AutoDock Vina, DockThor, GOLD, FlexX and Molegro Virtual Docker.

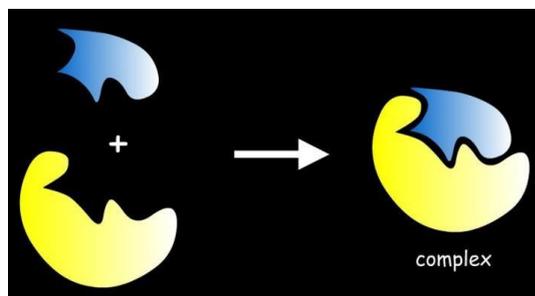
*In silico* method (computational approaches) should be robust and vigorous, so that it can produce a premier impact on target recognition.<sup>[3]</sup>

### DOCKING MODELS

YEAR	MODEL	AUTHORS
1890	Lock and Key	Emil Fischer
1958	Induced Fit	Daniel Koshland
2003	Conformation Ensemble	Buyong Ma <i>et. al</i>

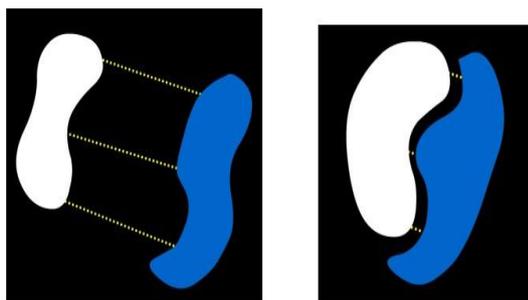
### The Lock and Key Theory

As early as 1890, Emil Fischer proposed a model called the lock-and-key model. Explains how biological systems work. The substrate fits into the active site of the large molecule, just like a key fits into a lock. Biological locks have unique stereochemical features essential to their function.



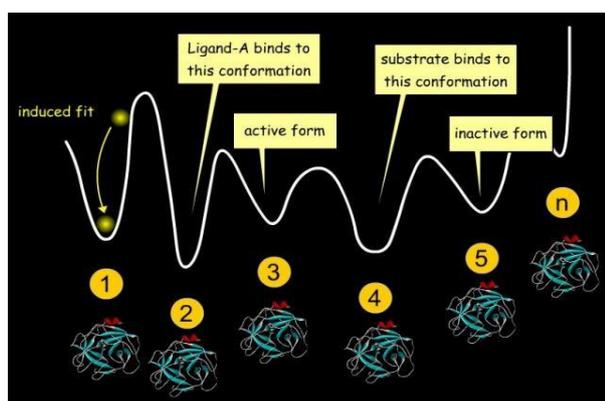
### The Induced Fit Theory

In 1958 Daniel Koshland proposed the induced fit theory. The basic idea is that in the recognition process, the ligand and the target mutually adapt to each other through small conformational changes, until optimal alignment is achieved.



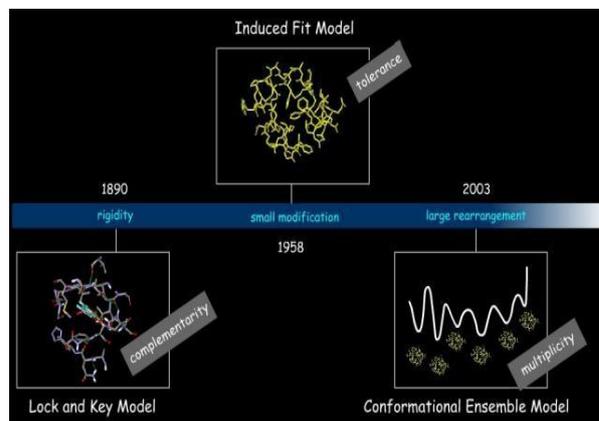
### The Conformation Ensemble Model

In 2003 Buyong Ma *et. al* proposed Conformation Ensemble Model. In addition to the small induced fit adaptation, it has been noticed that proteins can undergo much larger conformational changes. The model describes proteins as a pre-existing set of conformational states. The ductility of a protein allows it to move from one state to another.



### From the Lock and Key to the Ensemble Model

The lock-and-key, induced-fit and conformation ensemble models are not contradictory. Each one focuses on a particular aspect of the recognition process. The lock-and-key model introduces the principle of 3D complementarity, the induced-fit model explains how complementarity is achieved, and the ensemble model shows the structural complexity of proteins.<sup>[4]</sup>



### APPLICATIONS OF MOLECULAR DOCKING

A conventional drug discovery may take years to decades for the discovery of novel drugs and it is extravagant, so to evade this, docking is used to cut down research timeframe and cost by reducing wet lab experiments. Docking strives to bring the best matching between two molecules. It foretells the inhibition constant and binding affinity between molecules. If we exactly know how and where the known ligand binds then ;

- We are able to see important parts for binding.
- We can put forward changes to improve affinity.
- We can evade changes that will clash with the protein.

Thus, before carrying out experimental part of any investigations, it can signify the practicability of any task.

There are certain areas, where molecular docking has transformed the findings. Particularly, the interaction between small molecule (Example ligand) and protein target (Example enzyme) may forecast the induction or inhibition of enzymes. Such type of information may act as a raw material for the rational drug design and discovery, as well as in the mechanistic study. Molecular docking is widely used in the drug development and modern drug development. Some of the major applications are;

- Hit Identification (Virtual Screening)
- Hit Identification is the primary step in successful drug discovery. In this process Hits (small molecules), which is binding to the target and modifying it's function are identified. Hits with high quality make faster progress in drug discovery with lower attrition rates.

Molecular docking along with scoring functions can be used to evaluate immense database for finding potential drug candidates *in silico*, which can target the molecule of interest.

- **Lead Optimization (Drug Discovery)**

Lead optimization is the process in which a drug candidate is designed after a lead compound is identified. It aims to improve the most promising compounds to enhance efficacy, reduce toxicity or increase absorption. Molecular docking can be used to predict the binding mode or pose, that is, in where and in which relative orientation a ligand interacts with a protein. These types of information may be used to design potent and selective analogues.

- **Bioremediation**

Molecular docking of protein and ligand can be used to predict pollutants that can be degraded by enzymes.

- It is used to evaluate the side effects that may be caused by interaction with other proteins such as Cytochrome P450, Proteases and so on.
- It is used to determine the specificity of the potential drugs to homologous proteins.
- It is an essential tool for predicting protein – protein interactions.<sup>[2]</sup>
- Drug – DNA Interaction Studies

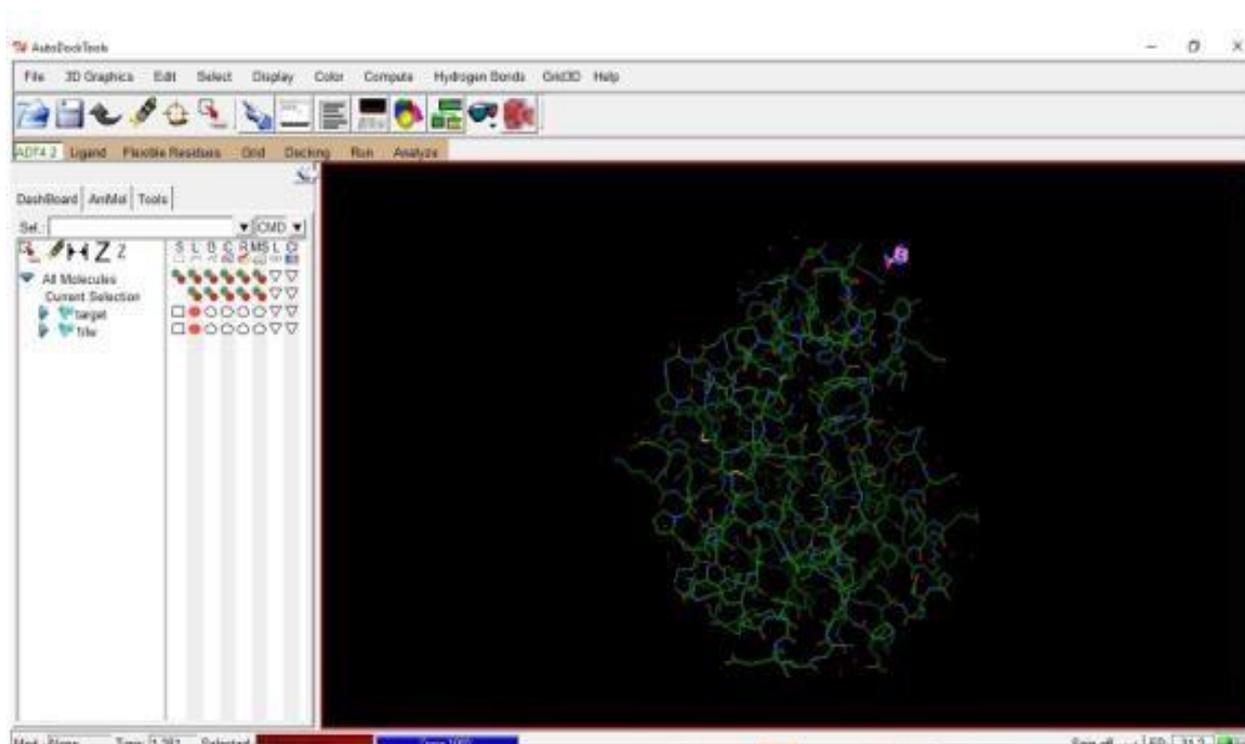
Cancer treatment involves the utilization of chemotherapy. Cytotoxic effects of several chemotherapeutic agents are not well characterized. Many of the chemotherapeutic agents possess nucleic acid and auxiliary processes as their main cellular target. Considering this, researchers struggled to elucidate the underlying anticancer mechanism of drugs at molecular level by investigating the interactions between nucleic acid and drugs. Here, molecular docking plays a vital role in the prediction of drug's binding properties to nucleic acid. These types of information are helpful in the establishment of a correlation between drug's molecular structure and its cytotoxicity.<sup>[5]</sup>

### SOFTWARES USED FOR MOLECULAR DOCKING

The number of notable docking softwares currently available is high and has steadily increased over the past decades. The following list presents an overview of the most common notable programs.<sup>[6]</sup>

#### AutoDock

AutoDock is an offline software used for docking. It is a suite of automated docking tools. It is molecular simulation software. This protein is particularly effective for ligand docking. It is designed to predict how small molecules such as substrates or drug candidates bind to a receptor of a known 3D structure.



#### AutoDock contains two main programs

- AutoDock for the docking of the ligand to a set of grids describing the target protein
- Auto Grid for pre-calculating these grids.

#### Current distribution of AutoDock consists of two generations of softwares

##### 1) AutoDock 4

It is a free software. The introduction of AutoDock 4 includes three major improvements.

- The docking results are more accurate and reliable.
- It can optionally model flexibility in the target macromolecules.
- It enables AutoDock's use in evaluating protein-protein interactions.

## 2) AutoDock Vina

AutoDock Vina is the successor of AutoDock, vastly improved in terms of accuracy and performance. It is available under the Apache license.<sup>[7]</sup>

## SwissDock

It is a web server used to perform protein-ligand docking simulations intuitively and elegantly. Swiss Dock is based on the EA Dock DSS program and has a simple and unified interface.<sup>[8]</sup>

## PatchDock

PatchDock is an algorithm for molecular docking. The aim is to find docking changes that give good molecular shape. Inputs are two molecules of any type: proteins,

DNA, peptides, drugs. The output shape is a list of possible complexes ordered by complementarity criterion.<sup>[9]</sup>

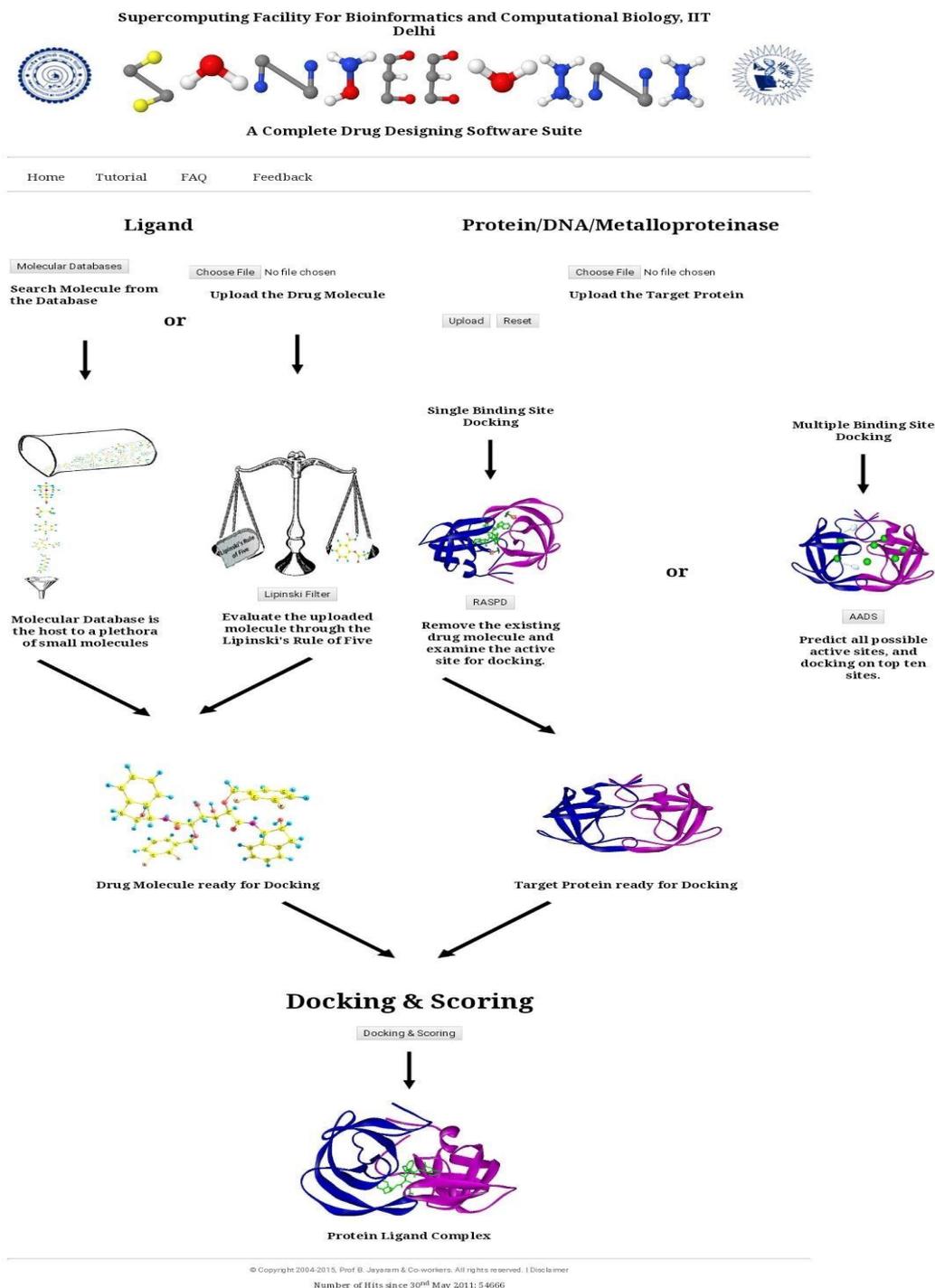
## LeDock

LeDock is a simple proprietary molecular docking software that can be used for docking of ligands with protein target. LeDock is based on simulated annealing and evolutionary optimization of the ligand pose and its rotatable bonds, using a physics/knowledge-based scoring scheme derived from years of prospective virtual screening campaigns.<sup>[10]</sup>

## Sanjeevini

Sanjeevini software has been developed as a computational route that clearly paves the way towards

automating lead design, combining any number of known or new candidate molecules from a small but a versatile set of building blocks called templates, investigations for drug affinities, optimizing their geometry, determination of partial atomic charges and specifying other force field parameters, docking the candidates in to the active site of a given biological target, estimating the interaction/binding energy, performing molecular dynamics simulations with explicit solvent and salt on the biomolecular target, the candidate and the complex followed by a rigorous analysis of the binding free energy for further optimization.<sup>[11]</sup>



**FlexAID**

FlexAID is a molecular docking software that can use small molecules and peptides as ligands and proteins and nucleic acids as docking targets. As the name suggests, FlexAID supports full ligand flexibility as well side-chain flexibility of the target. It uses a soft scoring function based on complementarity of the two surfaces ligand and target.<sup>[12]</sup>

**GOLD**

GOLD has proven success in virtual screening, lead optimization and identification of the correct binding

modes of active molecules. Gold docking software is reliable, flexible, configurable.<sup>[13]</sup>

**Hex Protein Docking**

Hex is an interactive protein docking and molecular superposition program, written by Dave Ritchie. Hex understands protein and DNA structures in PDB format, and it can read small molecule SDF files as well.<sup>[14]</sup>

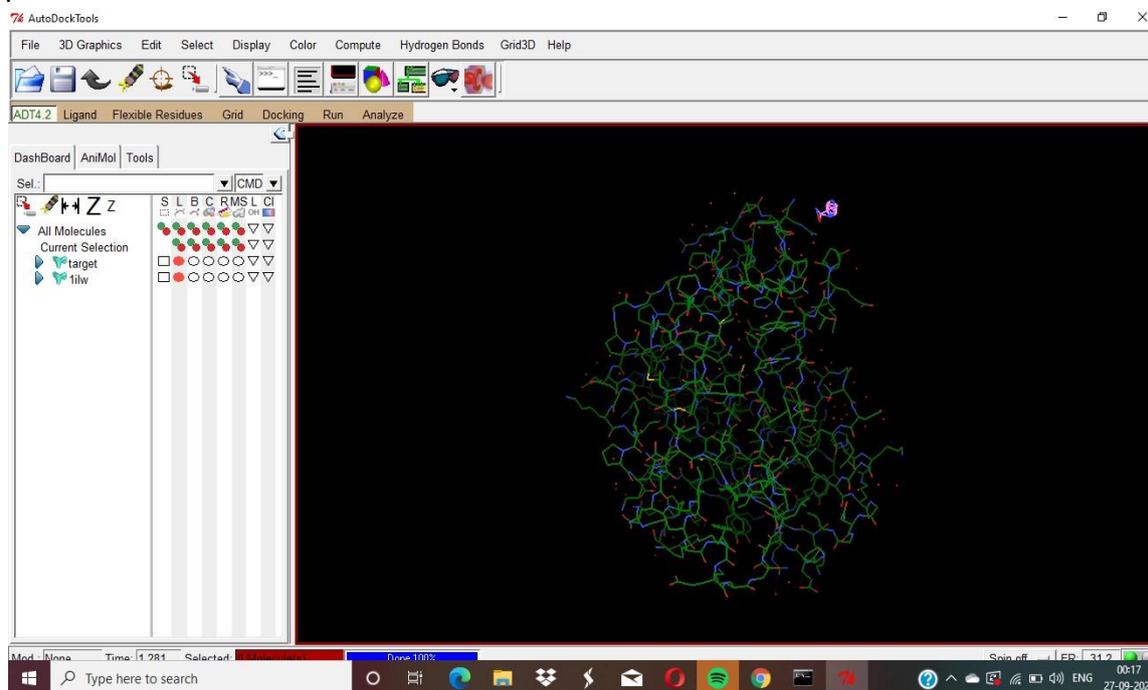
Program	Year Published	Organization	Description
AutoDock	1990	The Scripps Research Institute	Automated docking of the linker to a macromolecule by Lamarckian genetic algorithm and experimental free energy scoring function
DockVision	1992	DockVision	Based on Monte Carlo algorithms, genetic algorithm and database inspection
ADAM	1994	IMMD Inc	Predicting the stable binding mode of a flexible ligand for macromolecule targeting
DIVALI	1995	University of California-San Francisco	Based on AMBER-type potential function and genetic algorithm
GOLD	1995	Collaboration between the University of Sheffield, GlaxoSmithKline plc and CCDC	Genetic algorithm based, flexible ligand, partial flexibility for protein
Hammerhead	1996	Arris Pharmaceutical Corporation	Fast, fully automated docking of flexible ligands to protein binding sites
ICM-Dock	1997	Molsoft	Docking program based on pseudo-Brownian sampling and local minimization
SANDOCK	1998	University of Edinburgh	Guided matching algorithm
SEED	1999	University of Zurich	Automated docking of fragments with evaluation of free energy of binding including electrostatic solvation effects in the continuum dielectric approximation
DARWIN	2000	The Wistar Institute	Prediction of the interaction between a protein and another biological molecule by genetic algorithm
FlexX	2001	BioSolveIT	Incremental build based docking program
PatchDock	2002	Tel Aviv University	The algorithm carries out rigid docking, with surface variability/flexibility implicitly addressed through liberal intermolecular penetration
HADDOCK	2003	Centre Bijvoet Center for Biomolecular Research	Makes use of biochemical and/or biophysical interaction data such as chemical shift perturbation data resulting from NMR titration experiments, mutagenesis data or bioinformatic predictions. Developed for protein-protein docking, but can also be applied to protein-ligand docking.
GEMDOCK	2004	National Chiao Tung University	Generic Evolutionary Method for molecular docking
Glide	2004	Schrödinger	Exhaustive search based docking program
YUCCA	2005	Virginia Tech	Rigid protein-small-molecule docking
Molegro Virtual Docker	2006	Molexus	Based on a new heuristic search algorithm that combines differential evolution with a cavity prediction algorithm
EADock	2007	Swiss Institute of Bioinformatics	Based on evolutionary algorithms
HEX	2008	Dave Ritchie	An interactive protein docking and molecular superposition program
DockingServer	2009	Virtua Drug Ltd	Integrates a number of computational chemistry software

AutoDock Vina	2010	The Scripps Research Institute	New generation of <u>AutoDock</u>
SwissDock	2011	Swiss Institute of Bioinformatics	Webservice to predict interaction between a protein and a small molecule ligand
smina	2012	University of Pittsburgh	A customized fork of <u>AutoDock Vina</u> with a better support scoring function and a high-performance energy minimization
FlexAID	2015	University of Sherbrooke	Target side-chain flexibility and soft scoring function, based on surface complementarity
LeDock	2016	Lephar	Program for fast and accurate flexible docking of small molecules into a protein
AutoDock Vina Extended	2018	OneAngstrom	Extension of <u>AutoDock Vina</u> for easy setup and analysis
MedusaDock 2.0	2019	Dokholyan Laboratory	Rapid flexible docking using a stochastic rotamer library of ligands.

## RESULT

### DOCKING STUDY OF PYRAZINAMIDE AS ANTITUBERCULAR AGENT

The compound Pyrazinamide was subjected to in-silico screening by auto dock software. The receptor selected was 1ILW.



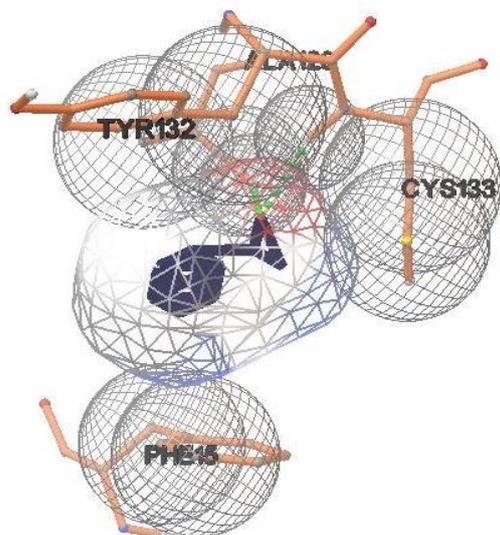
Both the ligand and protein were then subjected to docking by Auto dock 1.5.6 software. About 10 confirmations were analyzed and among them those with highest negative binding energy and least inhibition

constant was chosen as the best confirmation. The data of binding energy and inhibition constant of selected 10 confirmations were given in the table below.

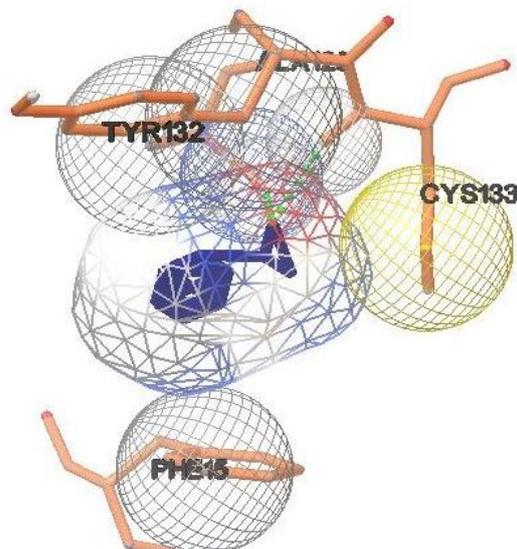
SL. NO	CONFIRMATIONS	BINDING ENERGY	INHIBITION CONSTANT
1	1	-5.06	196.66nM
2	2	-5.06	194.87nM
3	3	-5.06	196.27nM
4	4	-5.06	194.36nM
5	5	-5.06	195.3nM
6	6	-5.06	194.99nM
7	7	-5.05	197.26nM
8	8	-5.01	214.27nM
9	9	-5.06	195.12nM
10	10	-5.06	195.12nM

The docking poses of the best confirmation were given in diagram a, b, c, and d.

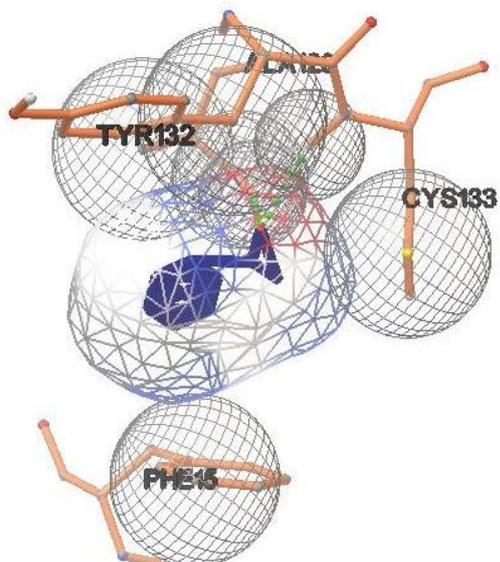
**Diagram (a)** Confirmation number 2  
Amino acid involved in interaction –  
TYR132,ALA129,CYS133,PHE15



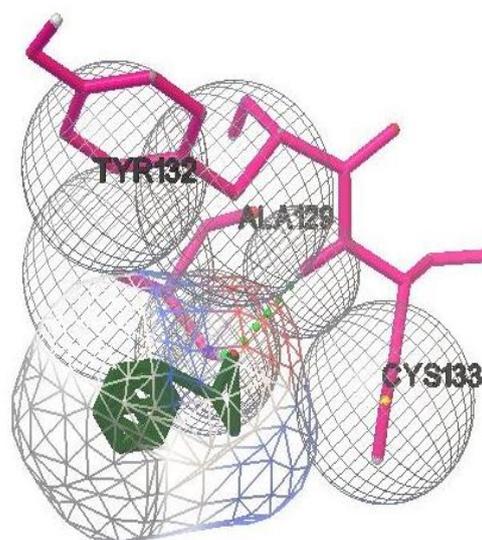
**Diagram (b)** Confirmation number 4  
Amino acids involved in interaction –  
TYR132,CYS133,ALA129,PHE15



**Diagram (c)** Confirmation number 6  
Amino acids involved in interaction –  
ALA29,TYR132,CYS133,PHE15



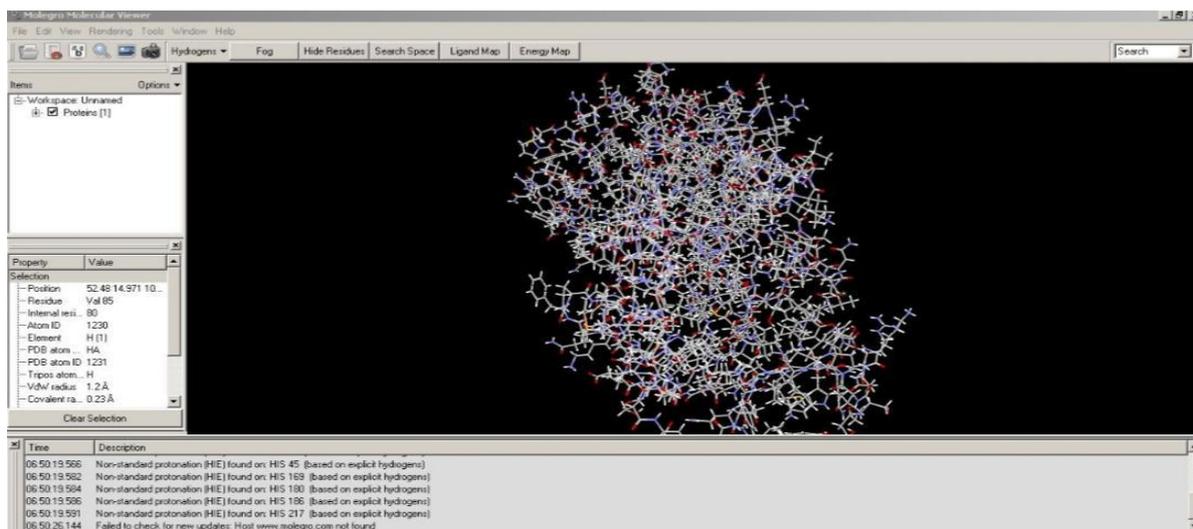
**Diagram (d)** Confirmation number 10  
Amino acids involved in interaction -  
TYR132,ALA129,CYS133



### DOCKING STUDY OF AMANTADINE AS A POTENTIAL TREATMENT FOR COVID-19

The compound Amantadine was subjected to in-silico screening by auto dock software. The receptor selected

was 7bro (crystal structure of the 2019-nCoV main protease).

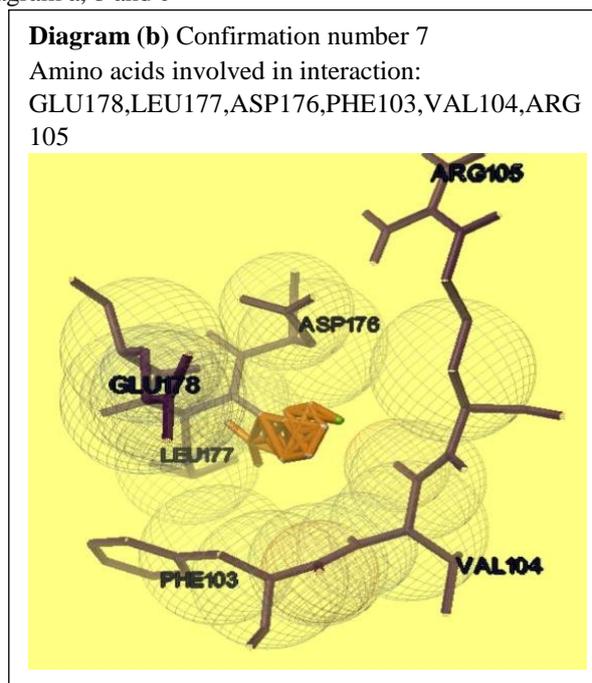
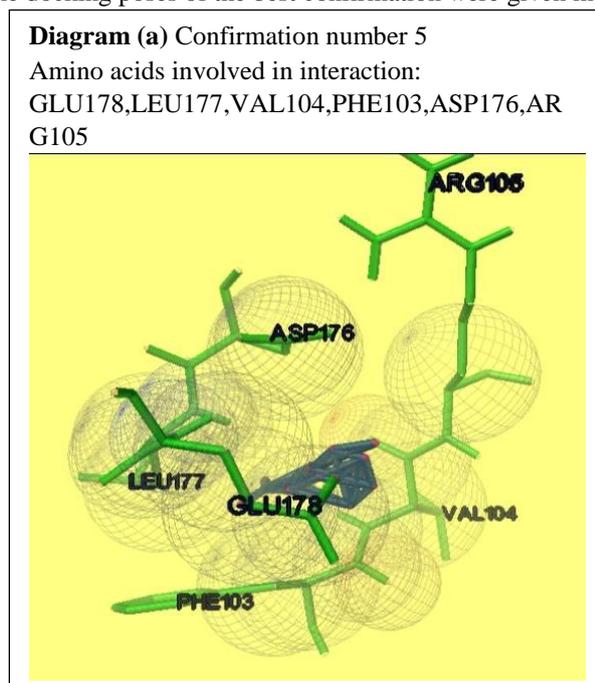


Both the ligand and protein were then subjected to docking by Auto dock 1.5.6 software. About 10 confirmations was analyzed and among them those with highest negative binding energy and least inhibition

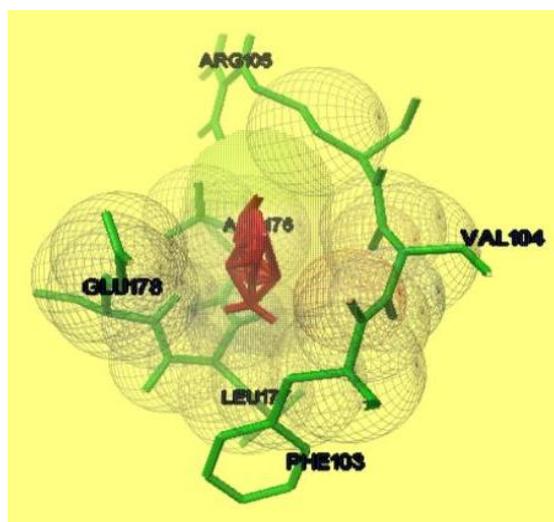
constant was chosen as confirmation. The data of binding energy and inhibition constant of selected 10 confirmation were given in the table below.

Sl. No	Confirmations	Binding Energy	Inhibition Constant
1	1	-6.59	14.79nM
2	2	-6.7	12.19nM
3	3	-6.41	20.05nM
4	4	-6.47	18.15nM
5	5	-6.67	12.99nM
6	6	-6.6	14.41nM
7	7	-5.53	8.7nM
8	8	-5.51	91.51nM
9	9	-6.57	15.36nM
10	10	-5.29	131.69nM

The docking poses of the best confirmation were given in diagram a, b and c

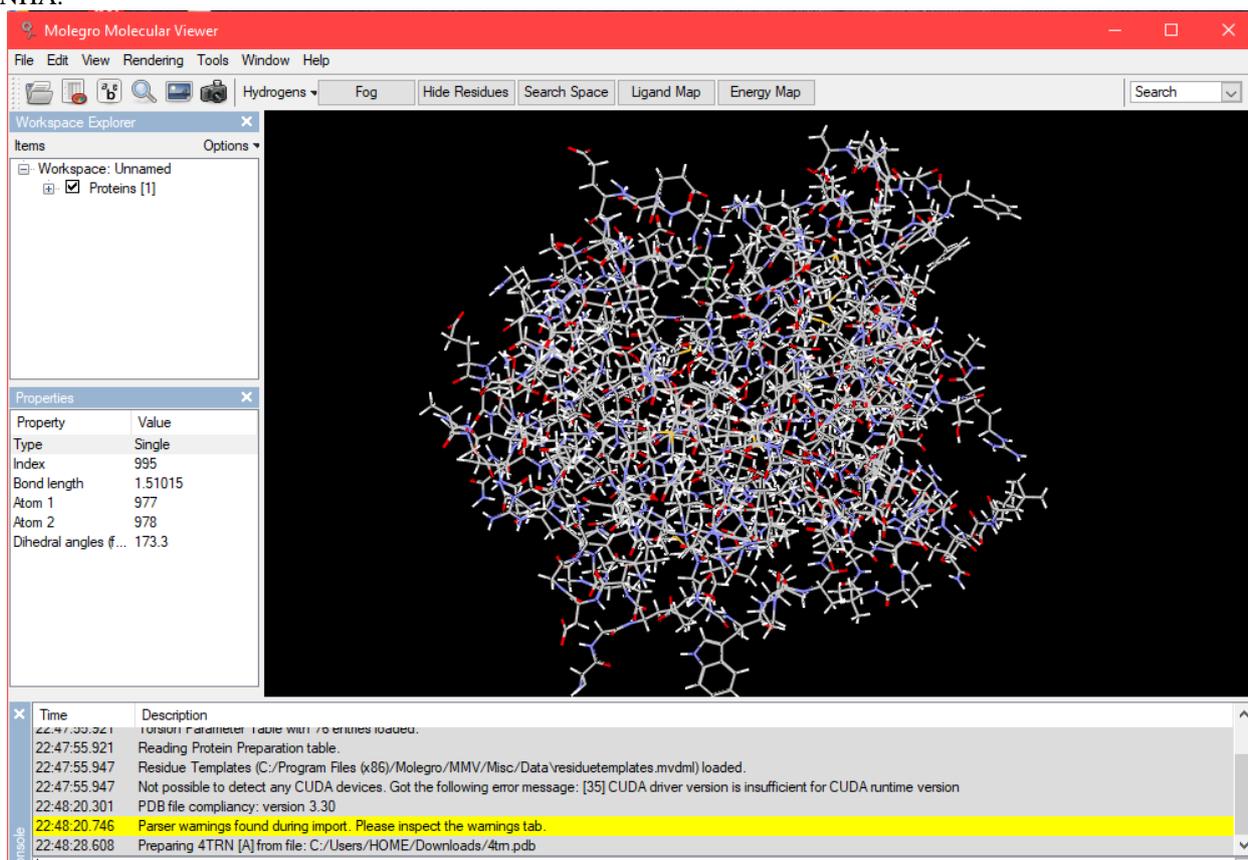


**Diagram (c)** Confirmation number 2  
Amino acids involved in  
interaction: ASP176, GLU178, LEU177, PHE103, VAL104, ARG105



### DOCKING STUDY OF ETHIONAMIDE AS ANTITUBERCULAR AGENT

The compound Ethionamide was subjected to in-silico screening by auto dock software. The receptor selected was INHA.



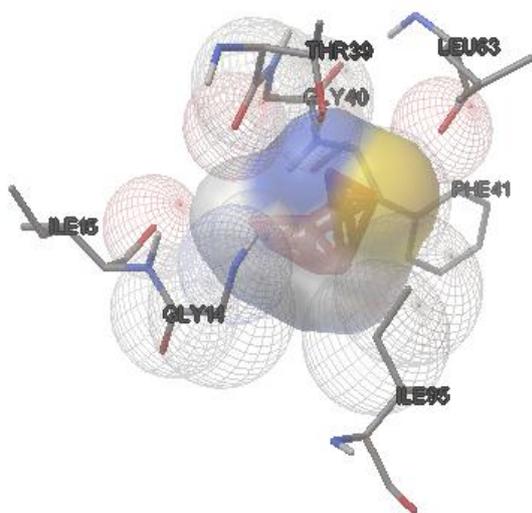
Both the ligand and protein were then subjected to docking by Auto dock 1.5.6 software. About 10 confirmations was analyzed and among them those with highest negative binding energy and least inhibition

constant was chosen as the best confirmation. The data of binding energy and inhibition constant of selected 10 confirmation were given in the table below.

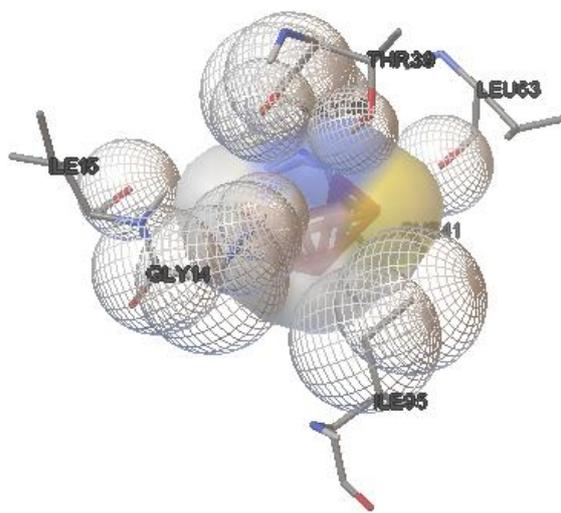
Sl. No	Confirmations	Binding Energy	Inhibition Constant
1	1	-5.5	93.02nM
2	2	-5.75	64.61nM
3	3	-5.82	54.19nM
4	4	-5.82	54.23nM
5	5	-5.81	54.67nM
6	6	-5.5	93.67nM
7	7	-5.5	92.5nM
8	8	-4.98	222.55nM
9	9	-5.82	54.29nM
10	10	-5.82	54.39nM

The docking poses of the best confirmation were given in diagram a, b, c, and d.

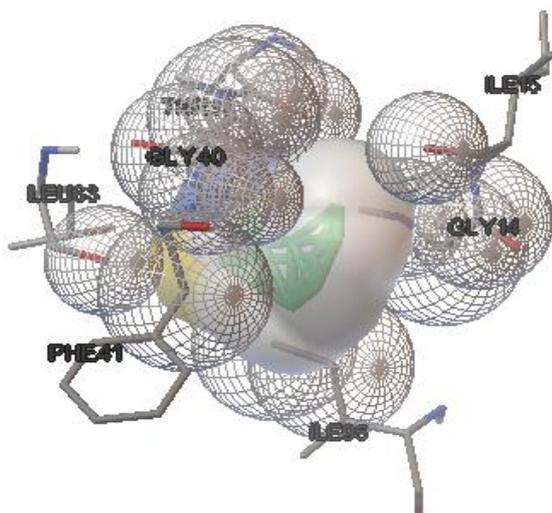
**Diagram (a)** Confirmation number 3  
Amino acids involved in interaction – THR39, LEU63, GLY40, ILE15, GLY14, ILE95, PHE41



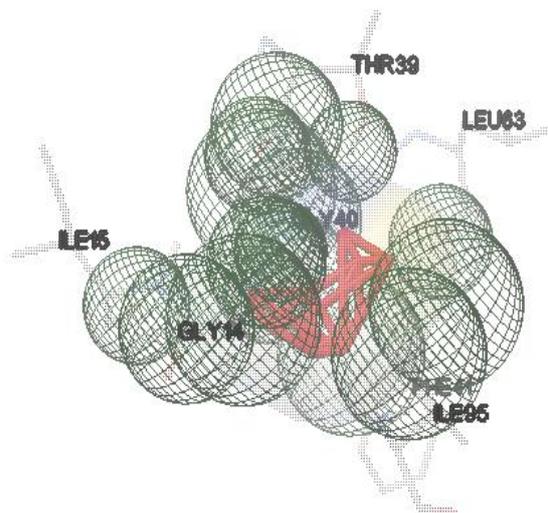
**Diagram (b)** Confirmation number 4  
Amino acid involved in interaction- THR39, LEU63, GLY40, ILE15, GLY14, ILE95, PHE41



**Diagram (c)** Confirmation number 9  
Amino acid involved in interaction- THR39, LEU63, GLY40, ILE15, GLY14, ILE95, PHE41



**Diagram (d)** Confirmation number 10  
Amino acid involved in interaction- THR39, LEU63, GLY40, ILE15, GLY14, ILE95, PHE41.



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