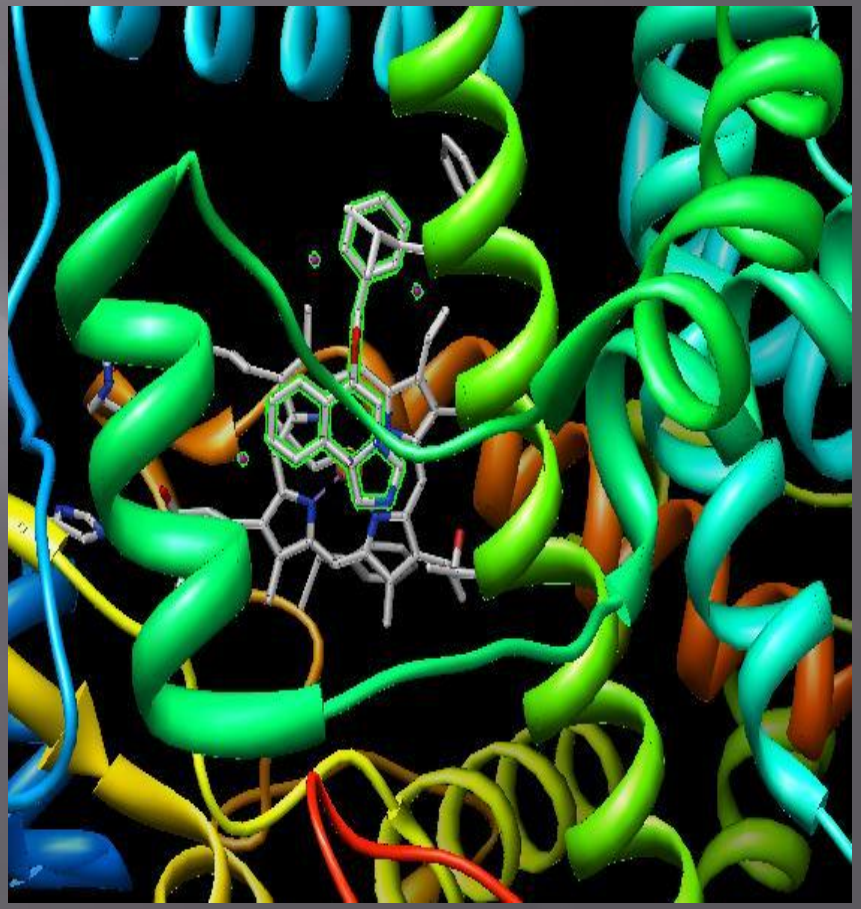
MOLECULAR DOCKING: Its Application & Significance

What is Docking?

- Docking attempts to find the "best" matching between two molecules.
- Docking procedures aim to identify correct poses of ligands in the binding pocket of the protein.
- It combines energy evaluation through grids of affinity potential employing various search algorithms to find the suitable binding position for a ligand on a given protein.

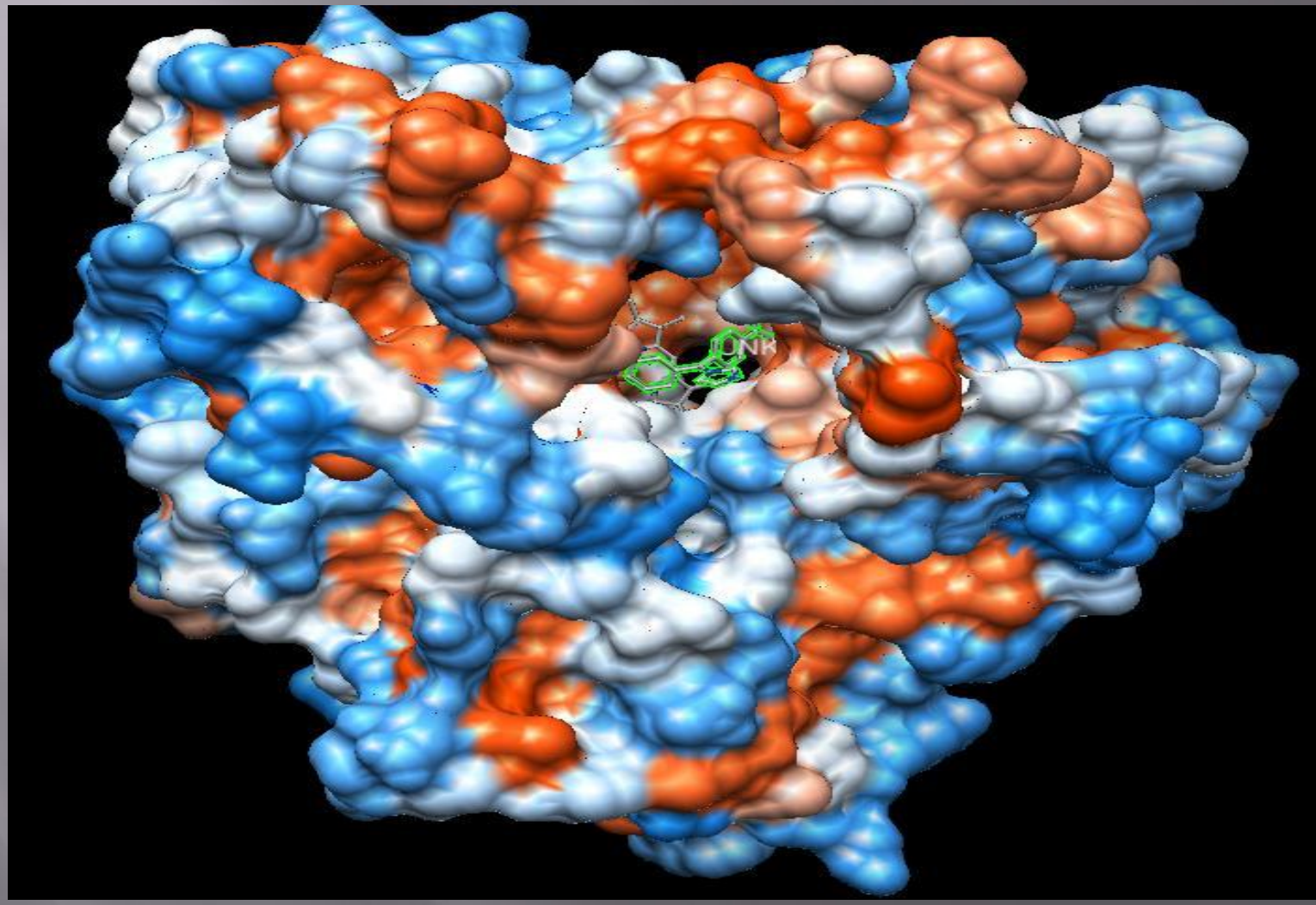


Why is docking important?

- It is of extreme relevance in **cellular biology**, where function is accomplished by proteins interacting with themselves and with other molecular components.

- It is the key to rational **drug design**: The results of docking can be used to find inhibitors for specific target proteins and thus to design new drugs. It is gaining importance as the number of proteins whose structure is known increases.

Example - Bifonazole



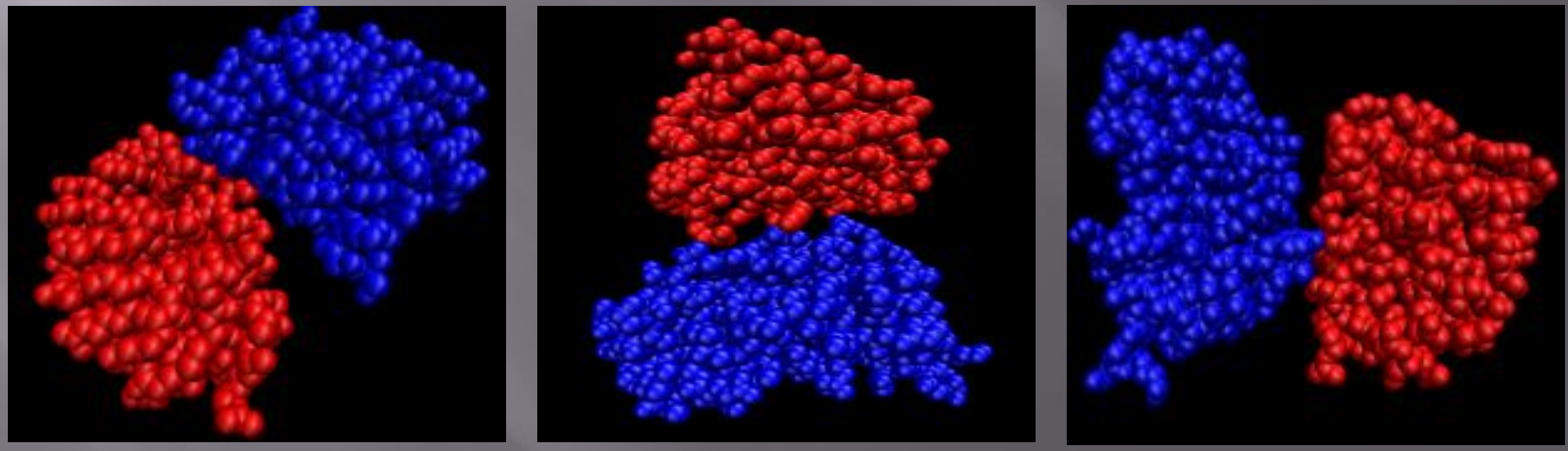
Types of Docking Studies

- **Protein-Protein Docking:**
  - **Both molecules usually considered rigid.**
  - **6 degrees of freedom.**
  - **First apply steric constraints to limit search space and the examine energetics of possible binding conformations.**

- **Protein-Ligand Docking:**
  - **Flexible ligand, rigid-receptor.**
  - **Search space much larger.**
  - **Either reduce flexible ligand to rigid fragments connected by one or several hinges, or search the conformational space using monte-carlo methods or molecular dynamics.**

Difficulty in Docking

- Both molecules are flexible and may alter each other's structure as they interact:
  - Hundreds to thousands of degrees of freedom (DOF)
  - Total possible conformations are astronomical



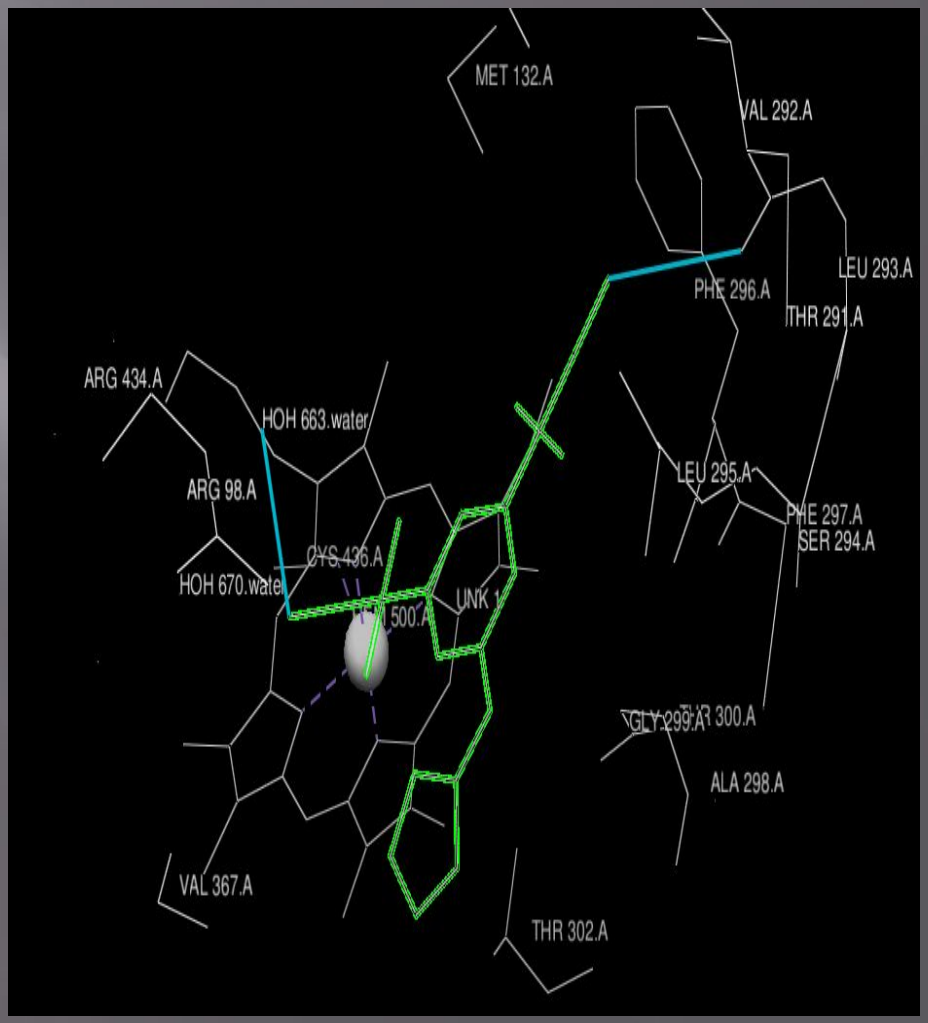
AUTODOCK

AUTODOCK works in 5 steps:

- **Step 1** Start with crystal coordinates of target receptor.
- **Step 2** Generate molecular topology (AD4) for receptor.
- **Step** 3 Ligands are bounded to the active site of the receptor.
- **Step 4** Matching: Grid centers are then matched to the ligand atoms, to determine possible orientations for the ligand.
- **Step 5** Scoring: Find the top scoring orientation.

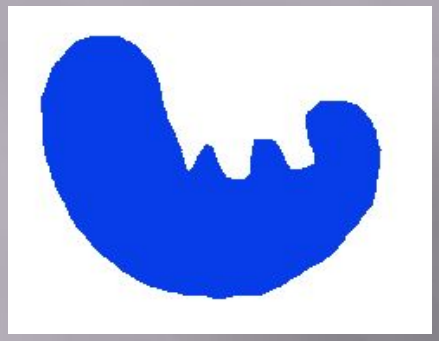
Binding Modes of Bifonazole with Cytochrome P450

Confirmation of Bifonazole bounded to CYP 2B4



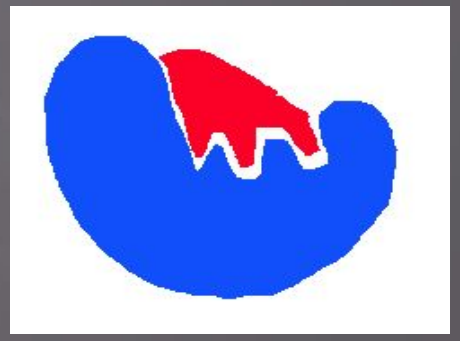
Docked confirmation of Bifonazole showing hydrogen bonding with VAL 292

How Drugs Work



Enzyme

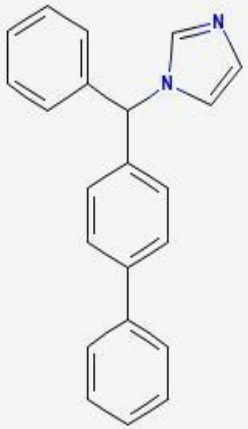
Substrate



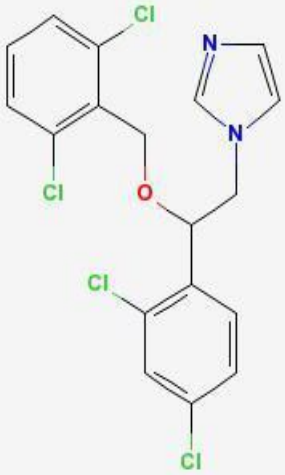
Enzyme-substrate complex

Lock-and-key model

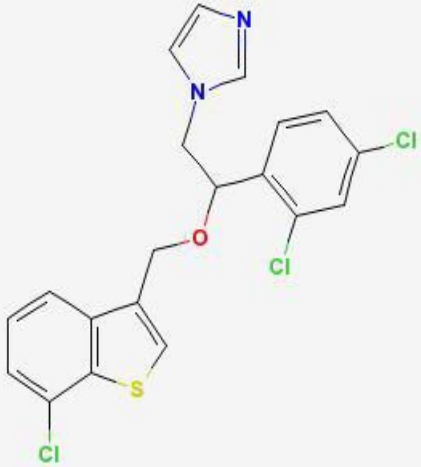
Ligand Selection



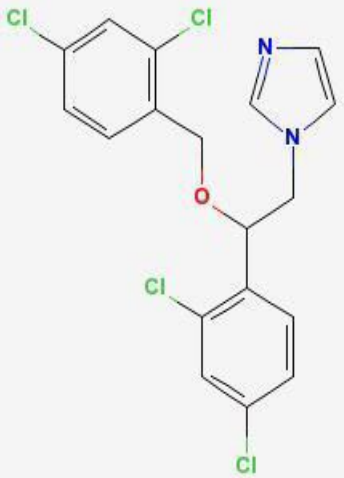
1. Bifonazole



2. Isoconazole



3. Sertaconazole



4. Miconazole

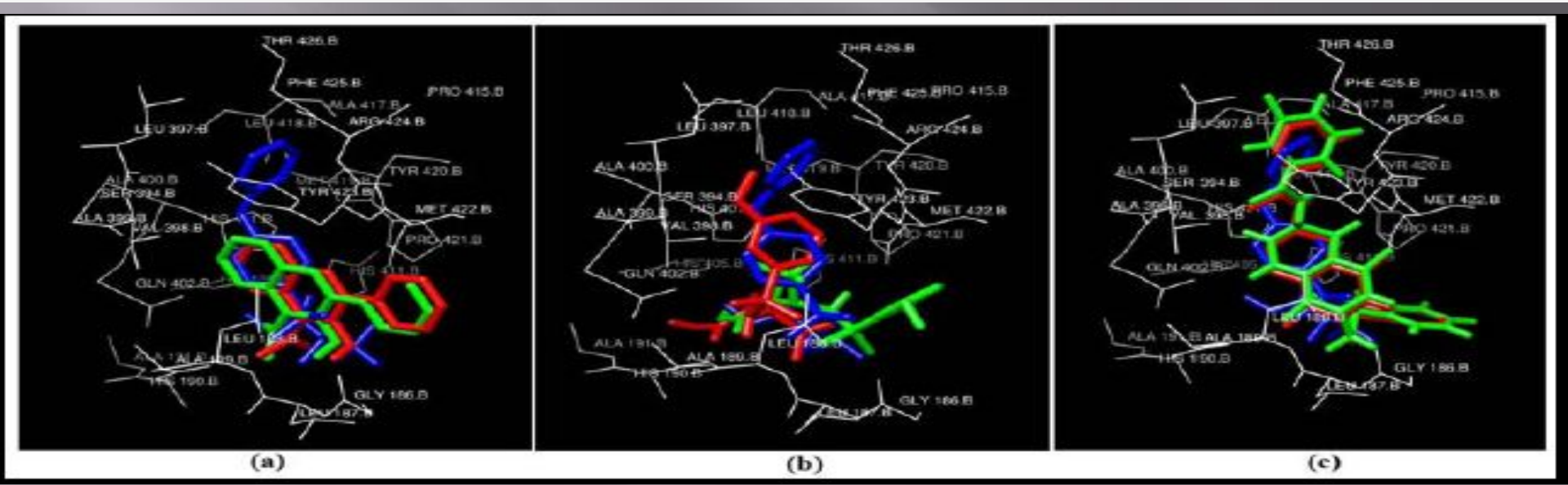


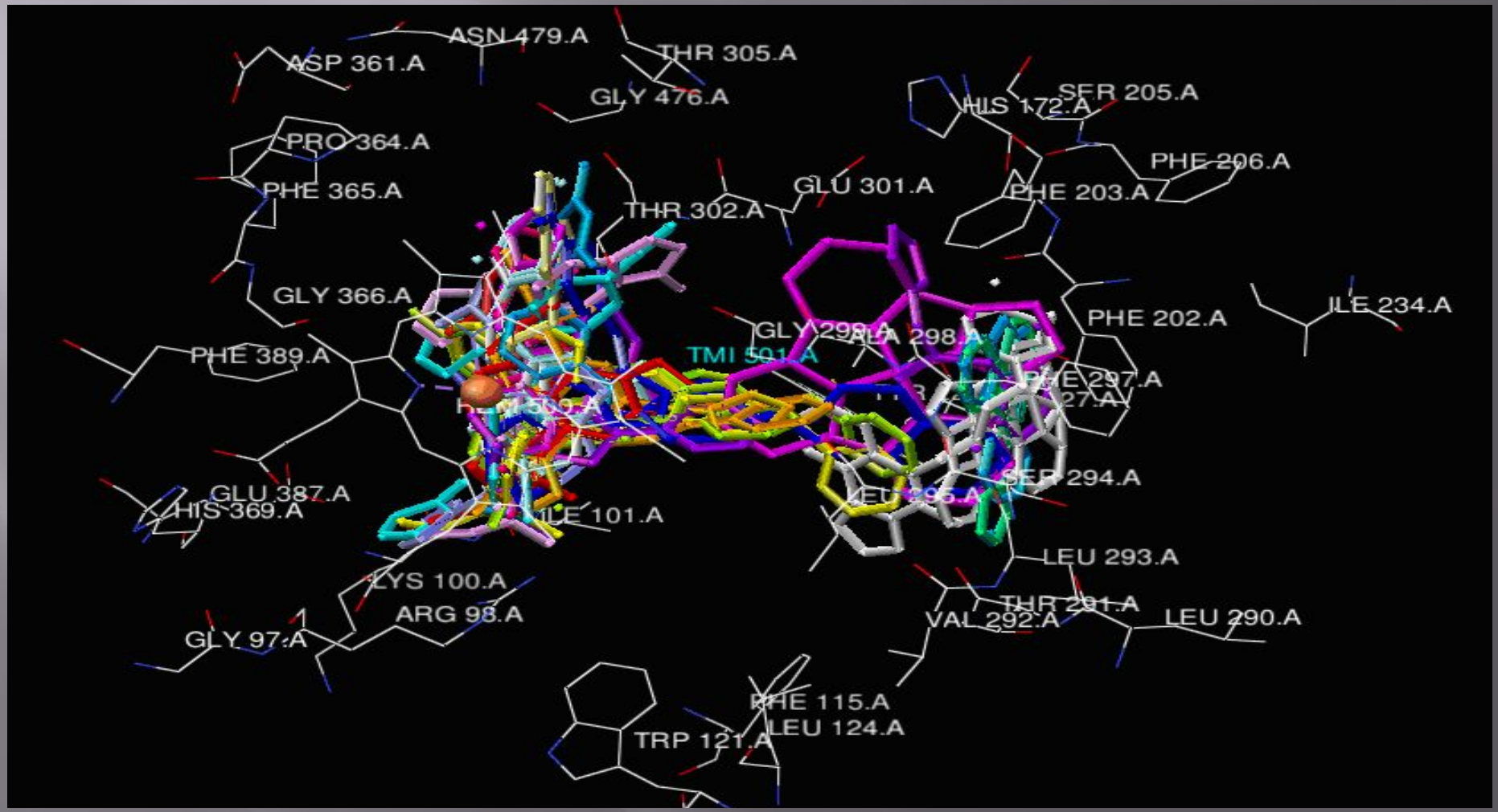
Figure 1: Docked conformations of Inhibitors in Red (Autodock) and Green (Flexidock) with respect to crystal structure ligand in blue. (a) Carboxylic acid ZBG (b) Sulfonamide Hydroxamate ZBG (c) Thio ester based ZBG

Ligand Interaction

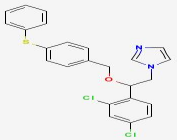
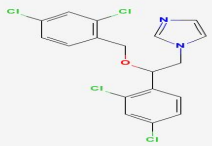
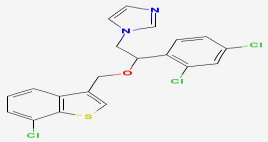
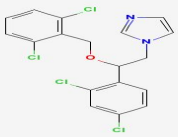
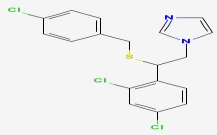
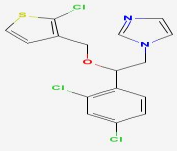
Table 2: Ligands with hydrogen bond with structures of protein used in group 2 of docking studies (NA : not available)

	Structure without water and ligand co-ordinates (group 2)		Structure without HETATMS (group 2)	
Ligands	No of H bonds	Residues	No of H bonds	Residues
Anastrozole	1	val-292	NA	NA
Ditazole	NA	NA	4	arg-98,arg- 434, heme
Eprosartan	2	arg-98, arg-125	3	arg-98
Etomidate	NA	NA	1	leu-295
Fenticonazole	NA	NA	1	phe-202
Flutrimazole	NA	NA	1	thr-302
Isoconazole	NA	NA	1	thr-302
Letrozole	2	ala-298, val-292	2	heme
Pilocarpin	1	thr-302	NA	NA
Sertaconazole	1	thr-302	NA	NA

Virtual Screening

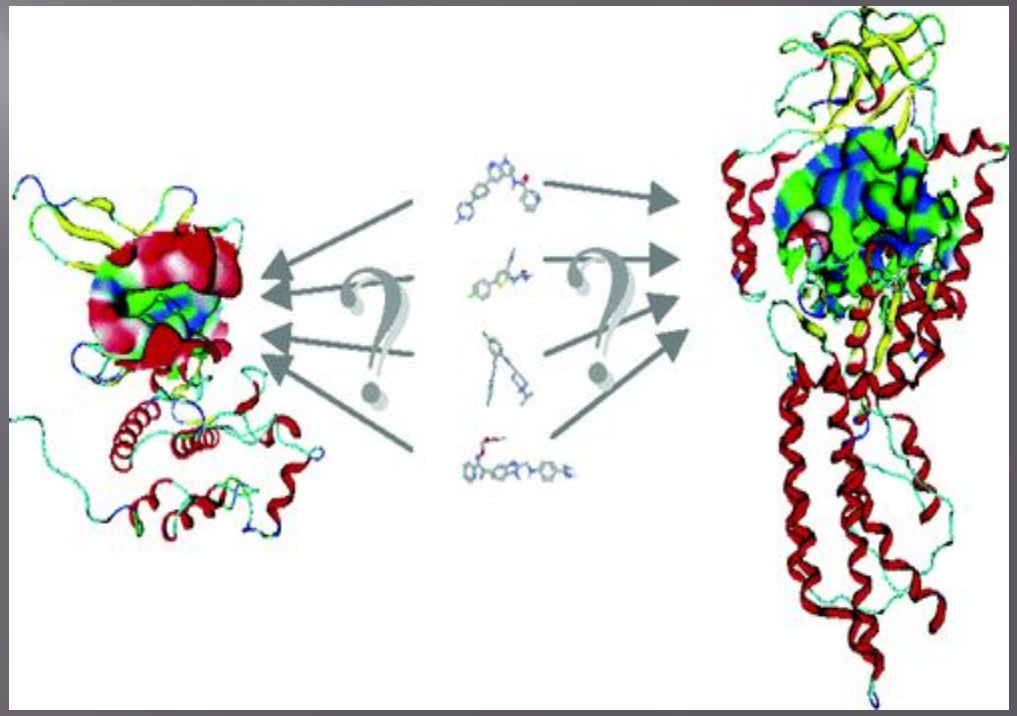


Virtual Screening on the basis of Binding Energy

Ligands	Structure	Binding Energy (Kcal/mol)	Rule of Five	Elimination t1/2 values	Cluster RMSD
Fenticonazole		-9.26	Yes	10-20 hrs	0.35
Miconazole		-8.69	Yes	20-30 hrs	0.80
Sertaconazole		-8.67	Yes	20-30 hrs	0.68
Isoconazole		-8.25	Yes	20-40 hrs	0.80
Sulconazole		-7.97	Yes	20-30 hrs	0.58
Tioconazole		-8.05	Yes	10-20 hrs	0.41

Docking programs are combination of two strategies

1. Search Algorithm
2. Scoring Function



Search Algorithm

1. Search Algorithm is used to generate multiple protein ligand confirmations.

2. Most of the programs perform flexible ligand-rigid receptor docking, and some of them are highly capable of predicting poses that resemble the experimental structure for many target proteins.

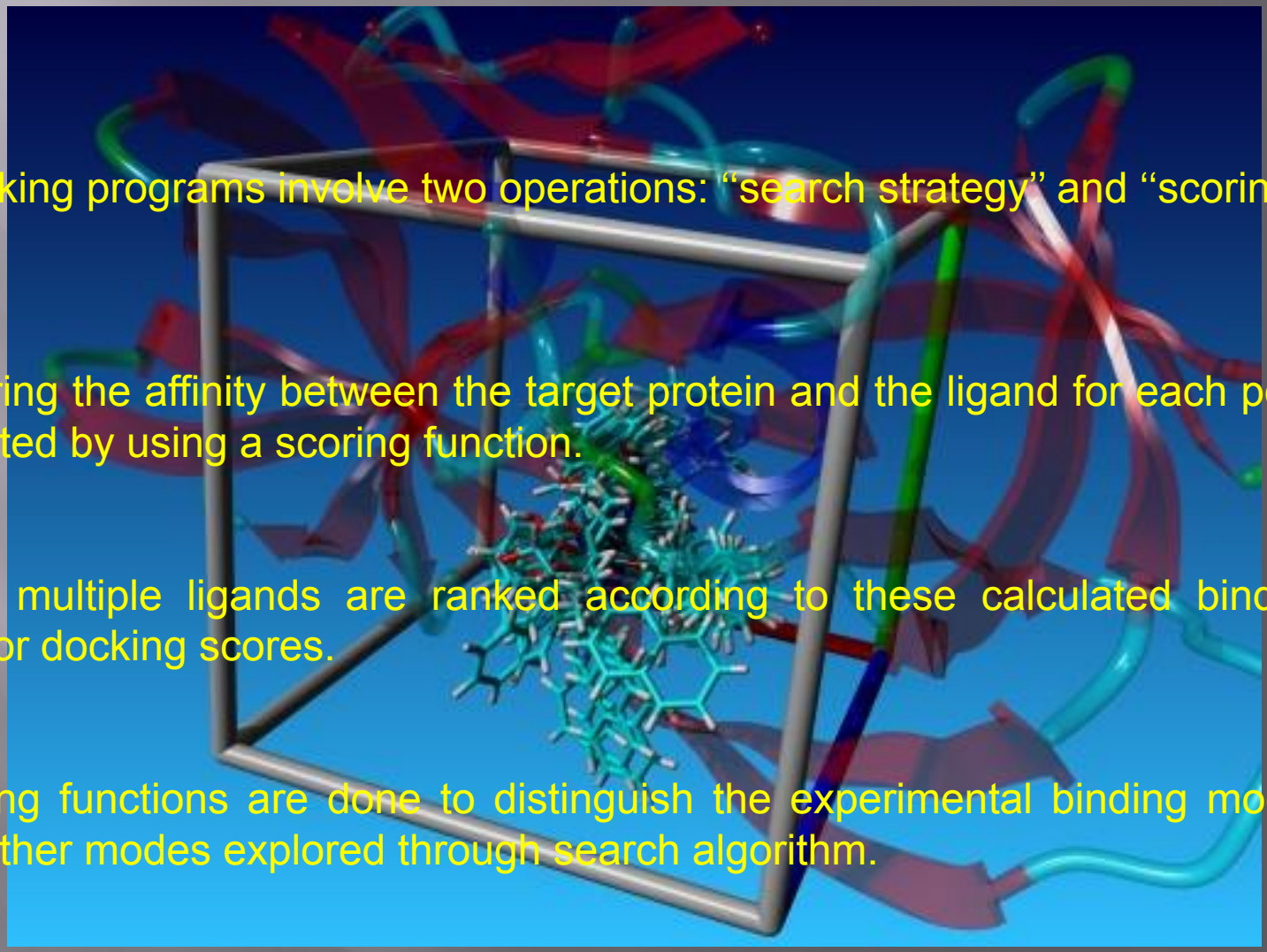
3. Search algorithms generates an optimum number of configurations that include the experimentally determined binding mode.

Algorithms

Common search Algorithms used are:

1. Genetic Algorithms: Autodock, GOLD.
2. Monte Carlo Methods: Prodock, Glide.
3. Incremental reconstruction Algorithm: Dock and Flex X.

Scoring Functions



Most docking programs involve two operations: “search strategy” and “scoring”.

1. In scoring the affinity between the target protein and the ligand for each pose is calculated by using a scoring function.

2. Then, multiple ligands are ranked according to these calculated binding affinities or docking scores.

3. Scoring functions are done to distinguish the experimental binding modes from all other modes explored through search algorithm.

There are only three classes of scoring functions:

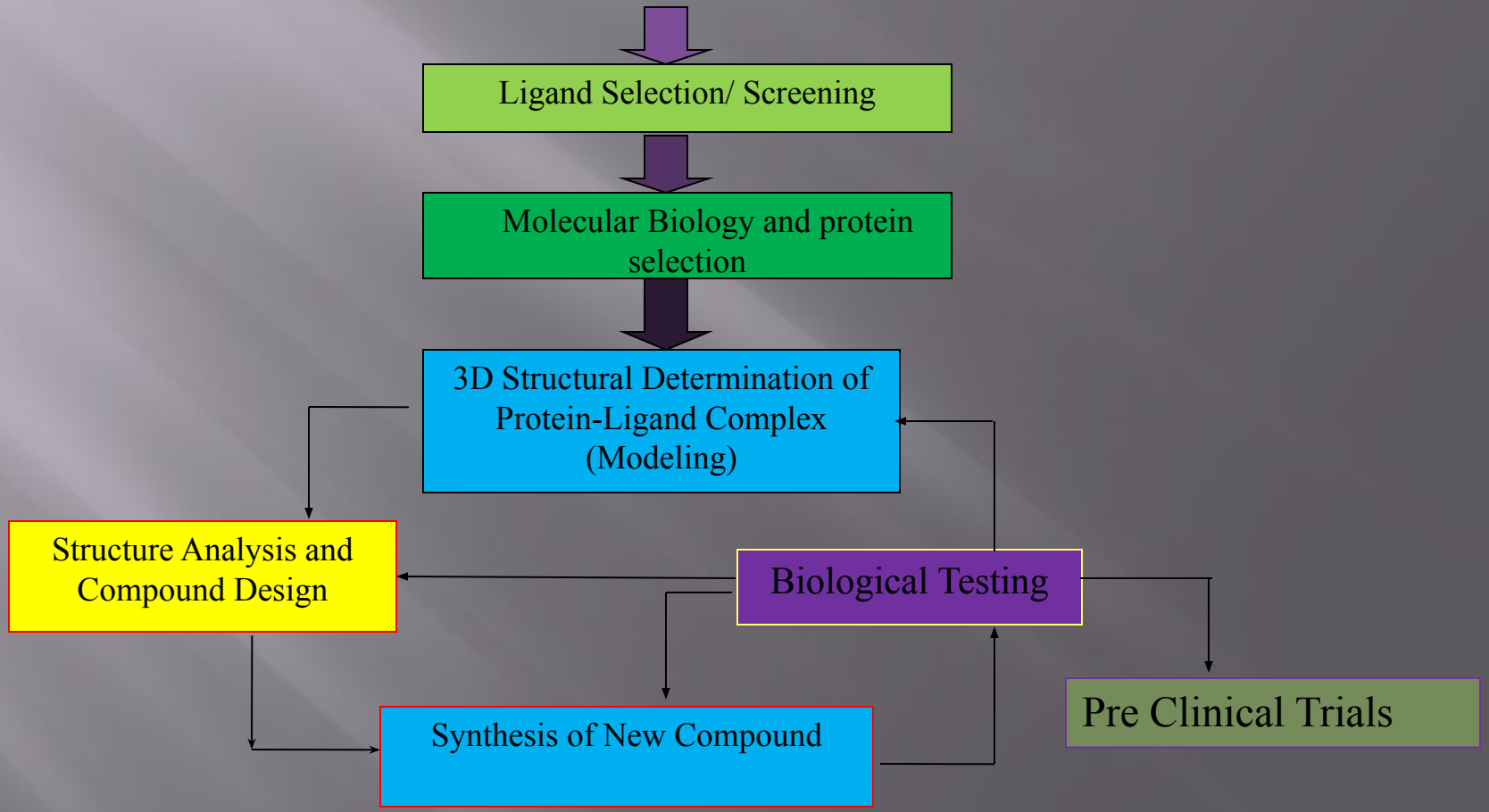
1. Force field based scoring Function.
2. Empirical free energy scoring functions.
3. Knowledge based function.

- Most docking programs utilize the scoring function in one or more than one ways: e.g. In Autodock
- The solutions are scored using an energy-based scoring function, which includes terms accounting for:

1. Short-ranged van der Waals and electrostatic interactions,
2. Loss of entropy upon ligand binding,
3. Hydrogen bonding
4. Solvation.

Applications of Docking:

Structure based Drug Design (SBDD)

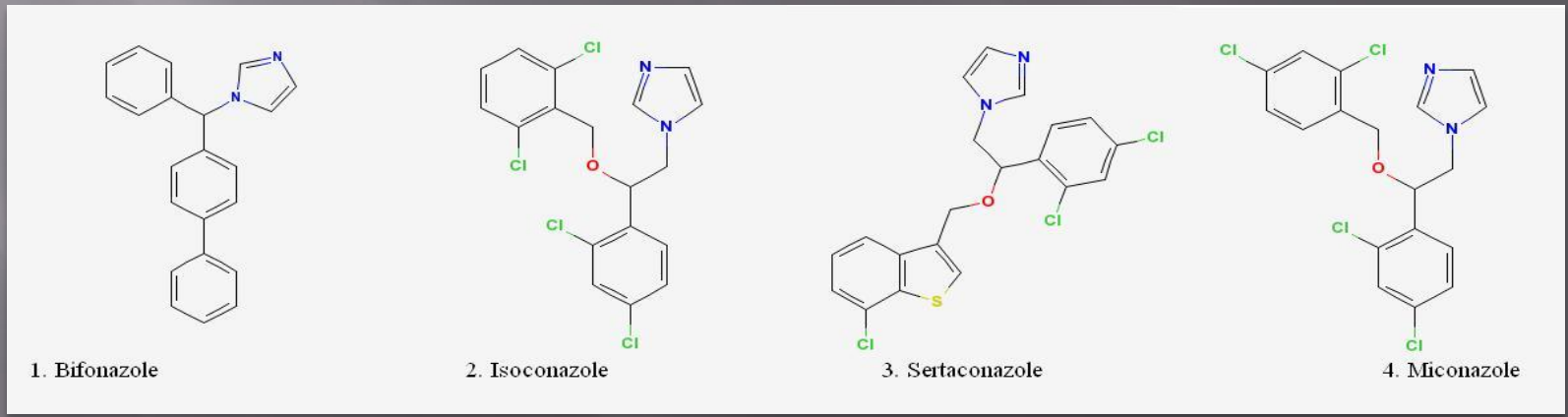


Ligand Selection/ Screening

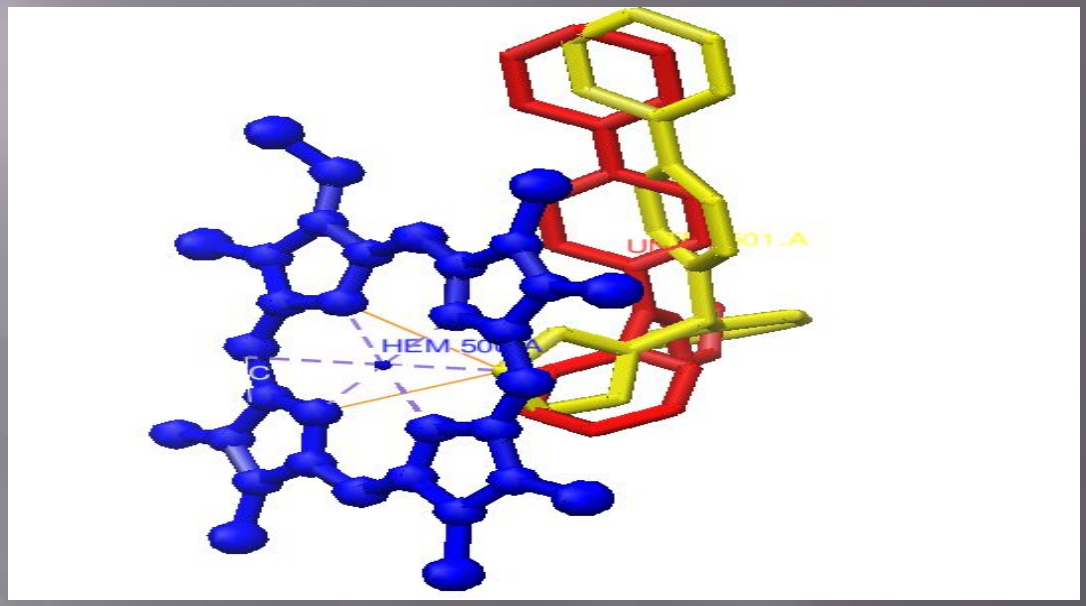
Molecular Docking is one of the principal tools for Ligand selection and screening.

1. The screening of large databases for possible lead compounds is becoming a routine procedure.

2. Large virtual libraries of compounds are reduced in size to a manageable subset, which, if successful, includes molecules with high binding affinities to a target receptor.



Structure Analysis and Compound Design



1. Docking can be used to predict in where and in which relative orientation a ligand binds to a protein (also referred to as the binding mode or pose).

2. It can be used to predict changes in flexible receptor with respect to ligand.

Uses:

1. Protein Ligand docking can also be used in predicting pollutants that can be degraded by using enzymes.

2. Protein-ligand docking can be used to study substrate specificity for screening pollutants in order to predict potential targets for degradation.