Computer Aided Drug Design Methods

Tugba ERTAN-BOLELLİ, Ph.D.

Associate Professor

Ankara University, Faculty of Pharmacy,

Pharmaceutical Chemistry Department

DRUG DEVELOPMENT PROCESS

Out of every 10,000-15,000 new compounds identified during discovery, **five are considered safe for testing** in human volunteers. **Only one of these compounds** is typically approved **as a marketed drug.**

3-6 YEARS	6-7 YEARS	0.5-2 YEARS
Drug Discovery	Clinical Trials	FDA Review
Pre-clinical	Phase I: 20-100 Volunteers	Manufacturing
	Phase II: 100-500 Volunteers	Phase IV Post-Approval
	Phase III: 1,000-5,000 Volunteers	
Pre-discovery	IND Submitted	NDA Submitted

AVERAGE COST: $1 billion+ **DURATION:** 10-15 years*

PPD

Because of,

- ✓ the cost and the time
- ✓ the reasons for many diseases are not fully explained,

it has become necessary to design drugs in a rational way.

Computer-Aided Drug Design (CADD)

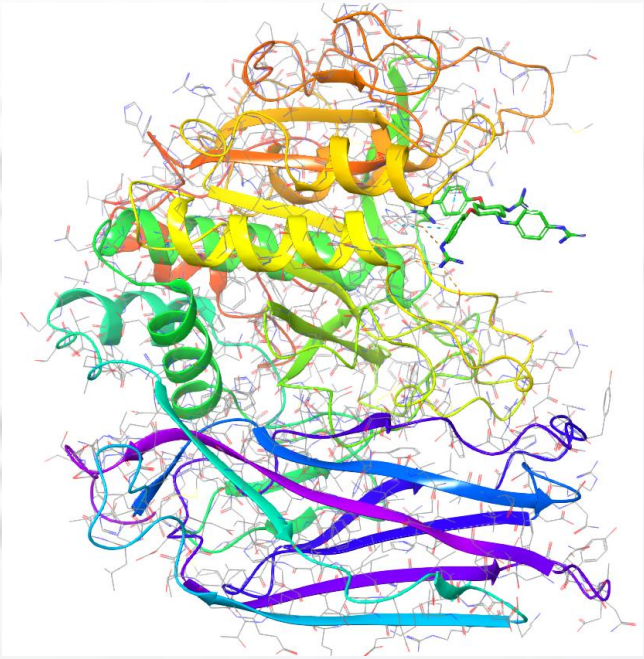
is a new technology and accelerates the process of drug development using the accumulated knowledge of existing drugs and diseases in combination with other interdisciplinary inputs.

In these way it is possible to

- ✓ design of new drug candidates,
- ✓ estimate the activity of new molecules before synthesis.

Computer aided drug design techniques play an important role in;

1. Design of new chemical compounds which may be the drug active substances,
2. Reach more effective compounds
3. Define mechanism of action of the drugs



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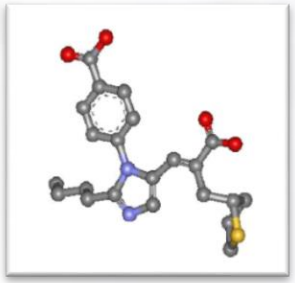
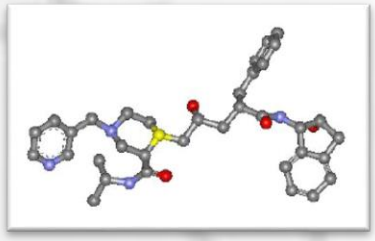
DRUGS DISCOVERED BY COMPUTER AIDED DRUG DESIGN METHODS

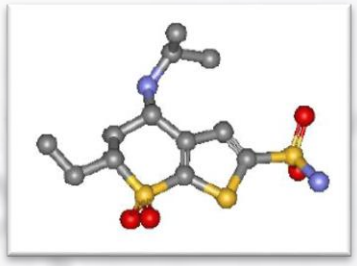
TEVETEN® for hypertension treatment-Abbott
Eprosartan: Angiotensin II receptor antagonist, Molecular Modelling

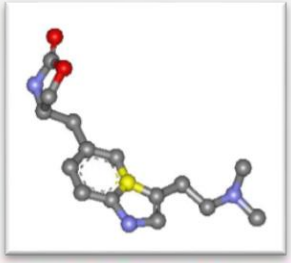




CRIXIVAN® for AIDS –Merck
Indinavir: HIV-1 Protease Inhibitor, X-ray crystallography, Moleculer Mechanics Calculations and Receptor Based Design

TRUSOPT® for Glaucoma treatment-Merck
Dorzolamide: Carbonic anhydrase inhibitor *ab inito* Calculations and Receptor Based Design

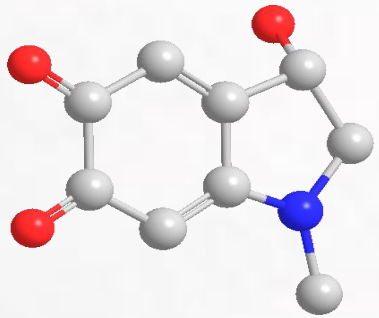




ZOMIG® for Migrain treatment-Wellcome, Zeneca
Zolmitriptan: 5HT1-agonist, Pharmacophore Analysis and Ligand Based Design

COMPUTER-AIDED DRUG DESIGN

- Molecular modeling studies



- Quantitative structure activity relationship (QSAR)

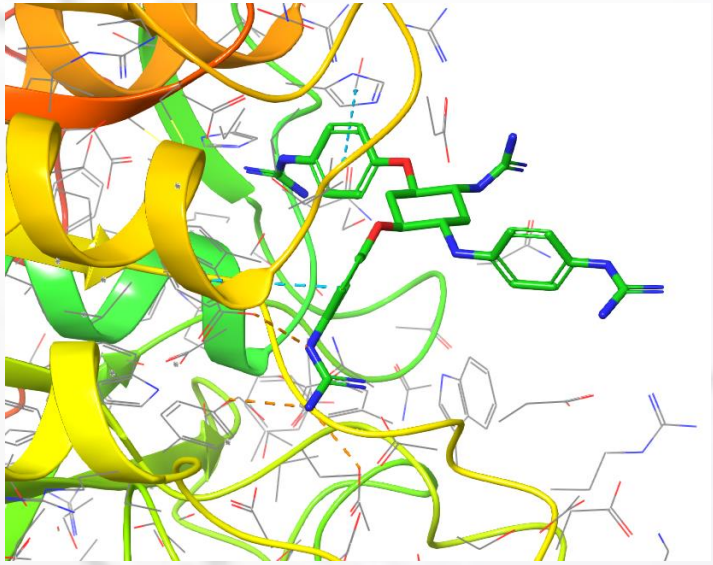
Molecular modeling

The aim of molecular modeling is to understand

a. the basic relationship between chemical and physical properties,

b. chemical structure and

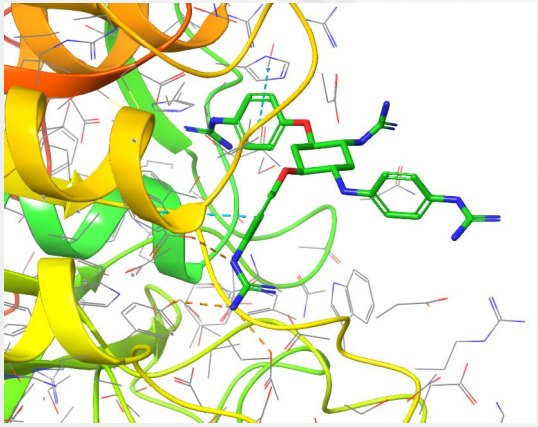
c. 3D structure of a molecule.



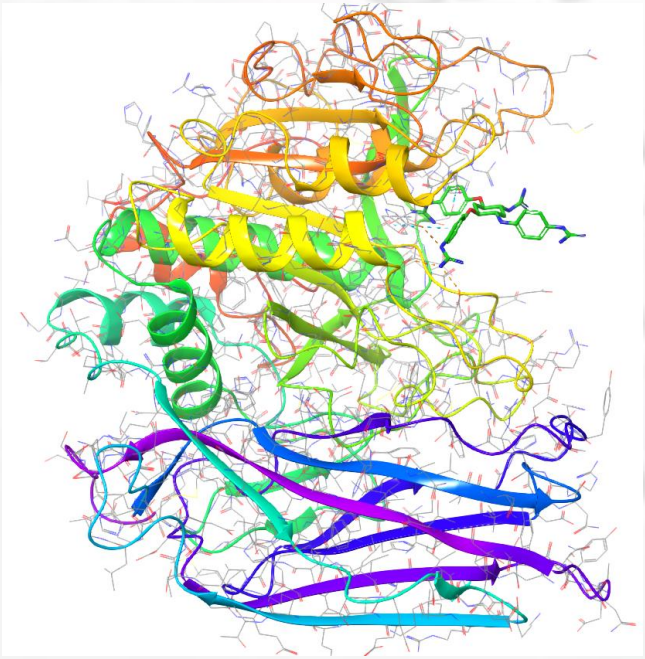
3-dimensional study is the definition of all properties of a compound in space.

Using molecular modeling techniques gathering information about;

1. 3D structure of the molecule
2. Physicochemical properties of the molecule
3. Comparison of a molecule with other molecules
4. Investigate the receptor-drug interactions



Close view



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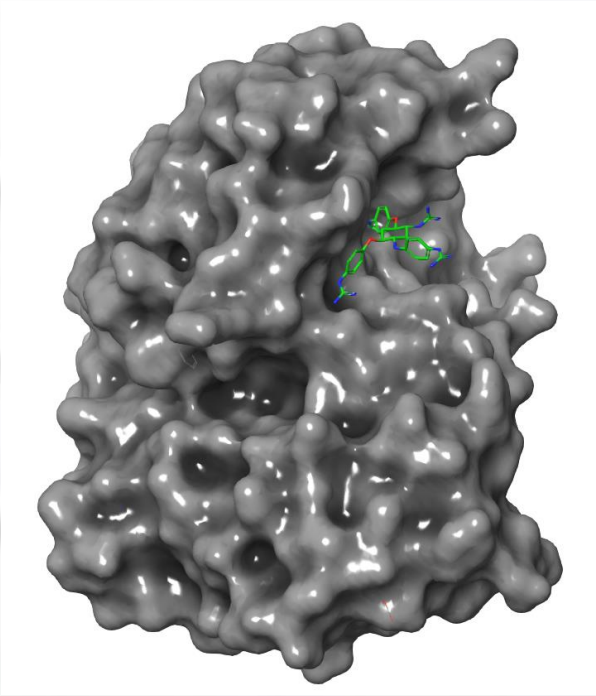
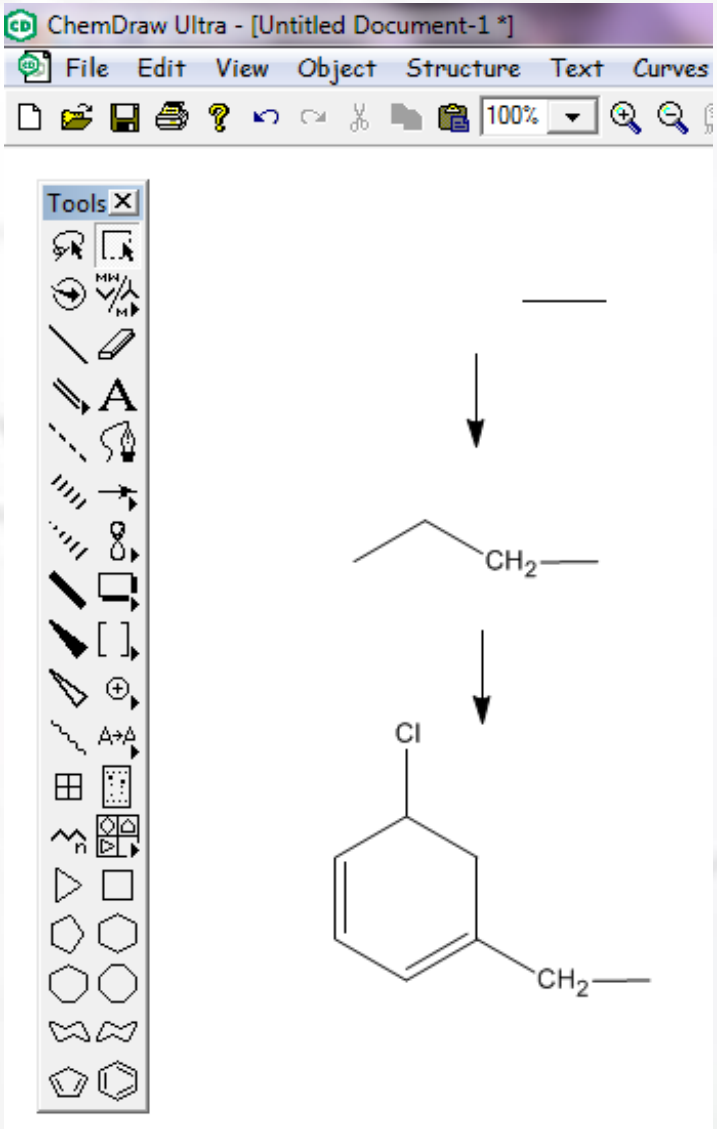
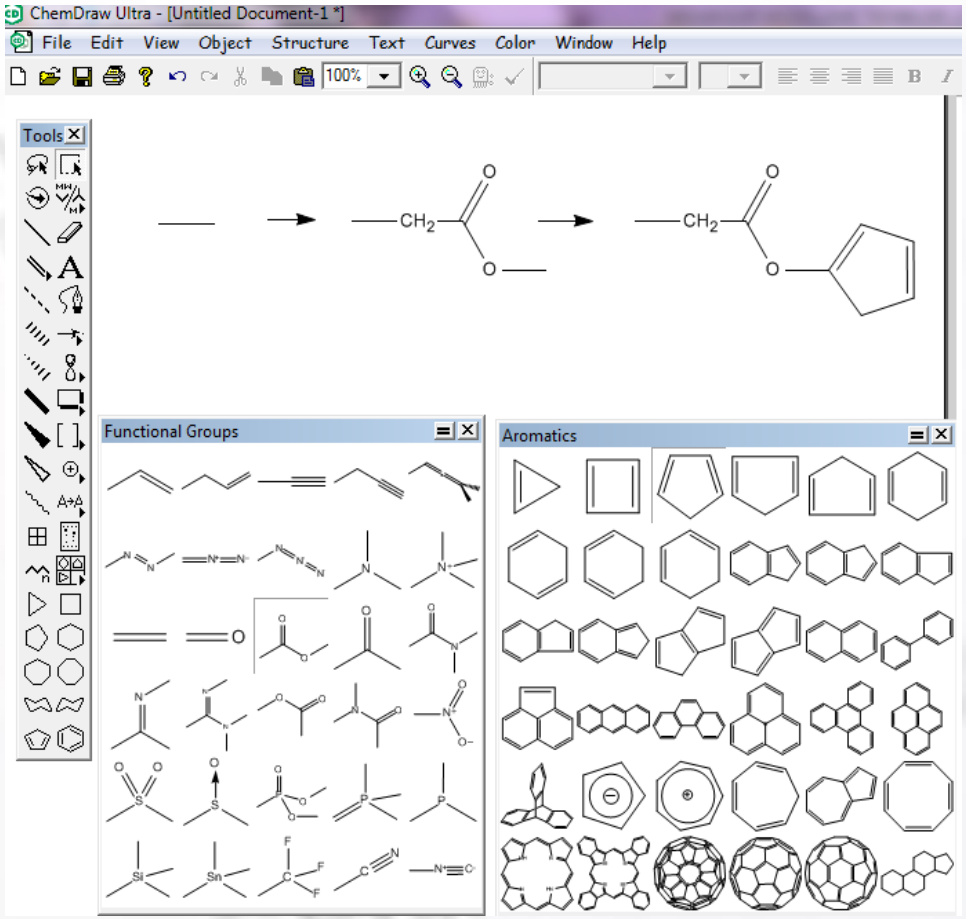


surface

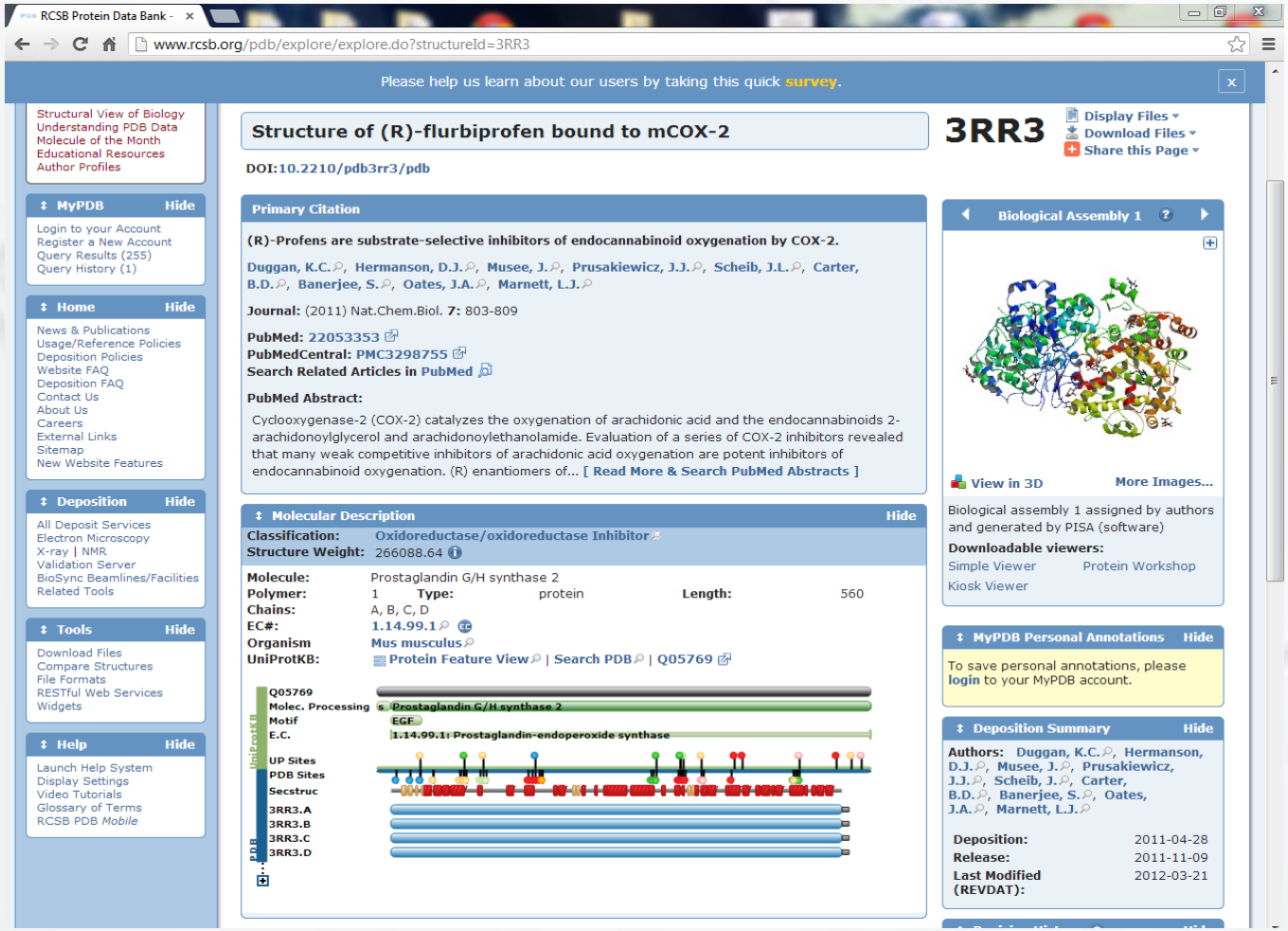
3D structure can be created by using the drawing features in the software

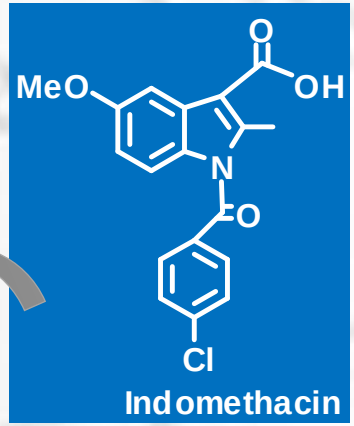


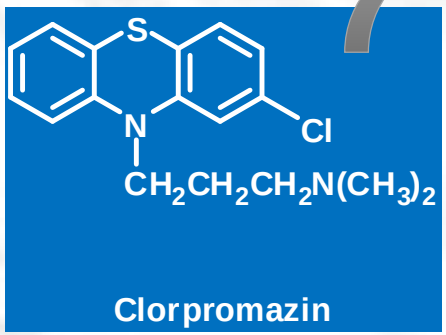
3D structures can be created by using the fragment data in a program (software).

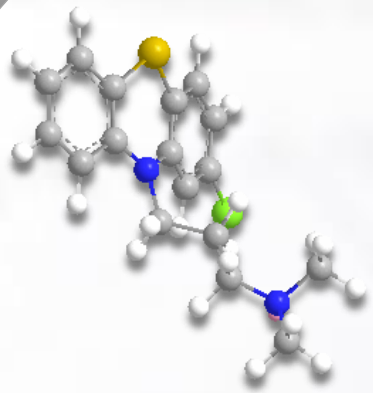


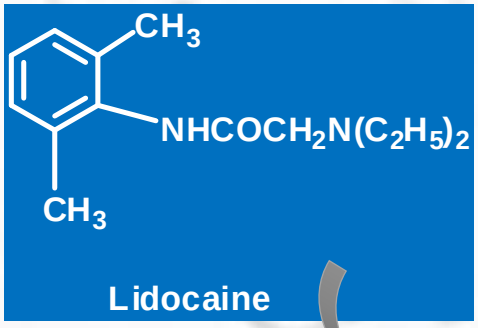
The three-dimensional structure of the molecule can be taken directly from the data banks created by X-ray crystallography.

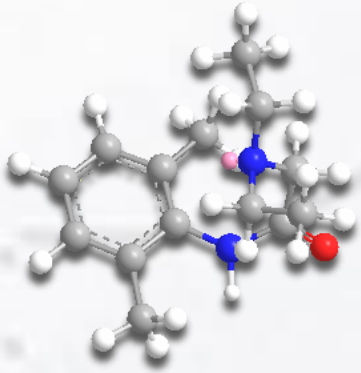












Atoms in Molecule

Carbon → GREY

Hydrogen → WHITE

Nitrogen → BLUE

Oxygen → RED

Let's watch a video

This video is about SARS-CoV-2 Structure (COVID-19 Coronavirus)

You can find the link below:

https://www.youtube.com/watch?v=IuJqbV4D8Cc&list=FLD5BNZVjYcwC62PKTJs47Gg

There are two basic starting points for computer aided drug design:

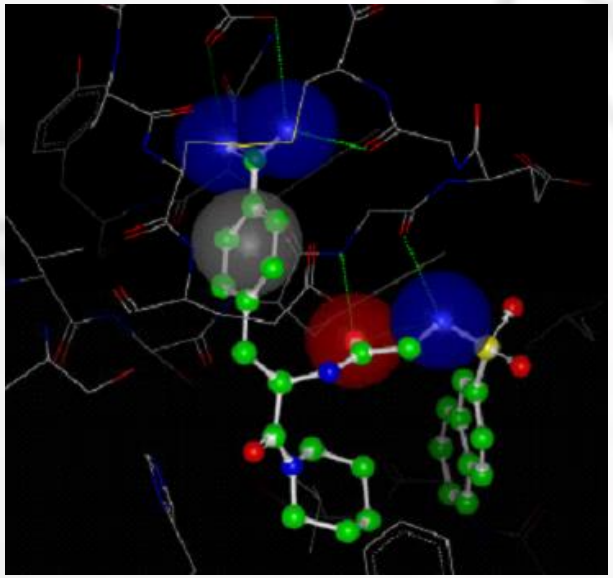
1- Target = Receptors, enzymes or nucleic acids

2- Effector(ligand) = There may be natural endogenous substances or drugs which occupy the active site of the target and affect the target positively or negatively.

STRUCTURE-BASED DESIGN

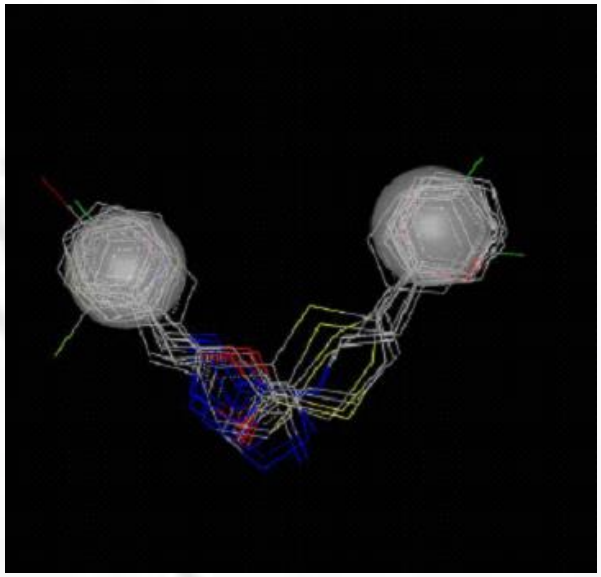
LIGAND BASED DESIGN

STRUCTURE-BASED DESIGN



It is aimed to design molecules with the knowledge of receptor structure

LIGAND BASED DESIGN



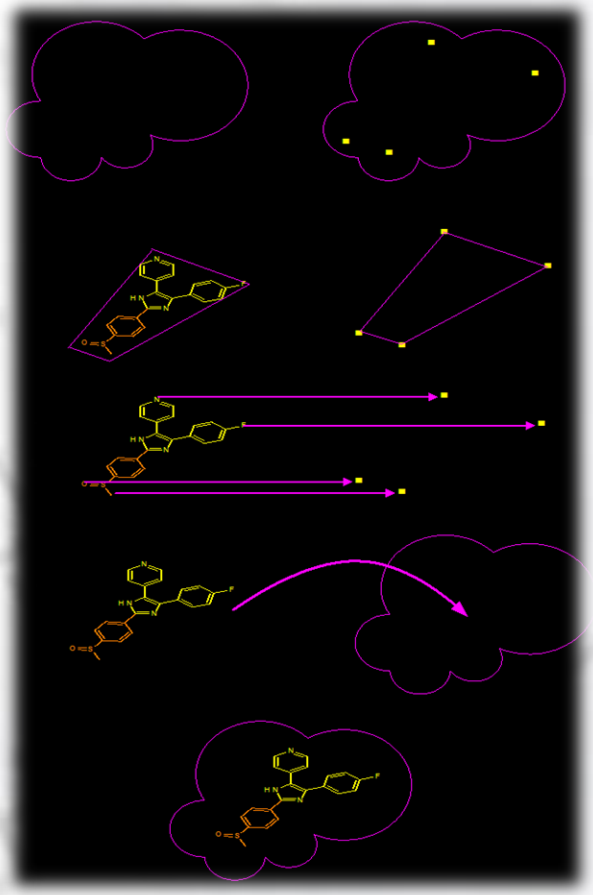
It is aimed to predict the structure of the receptor by using the structures of the active compunds.

STRUCTURE-BASED DESIGN

Design of compounds from known receptor structure

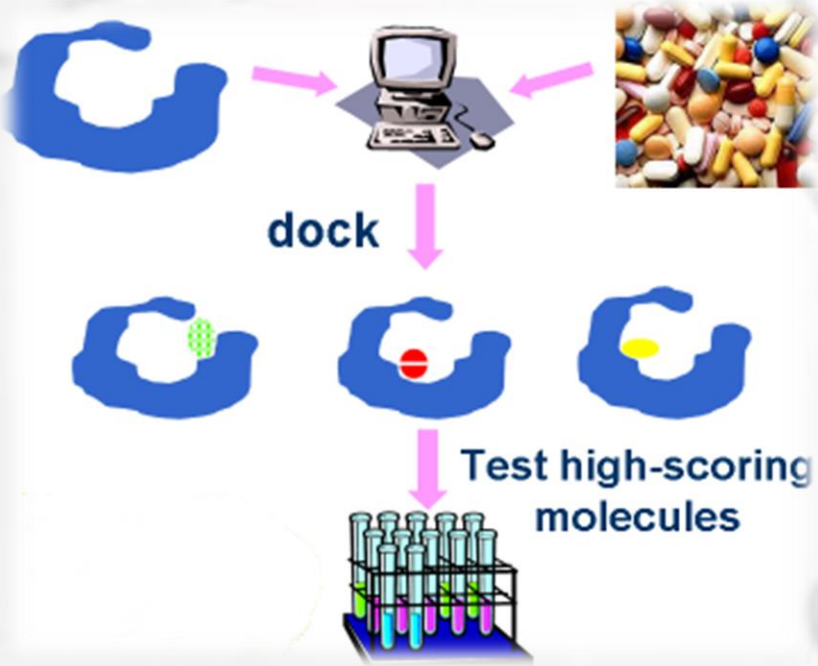
- Receptor structure is known
- Mechanism of action is known
- Ligands and their biological activities are known or unknown

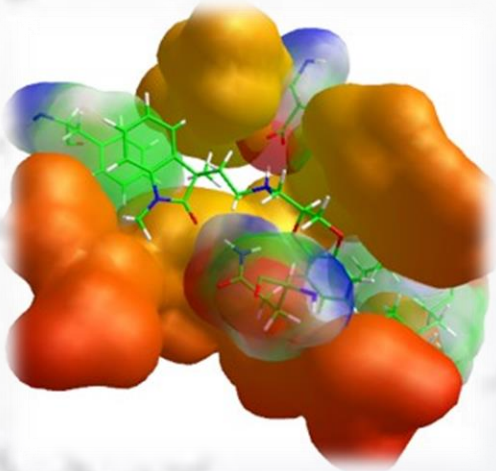
DOCKING



DOCKING

The compound, which may be effective, is designed by evaluating the suitability of sterically or electrostatically to the pockets in the receptor.





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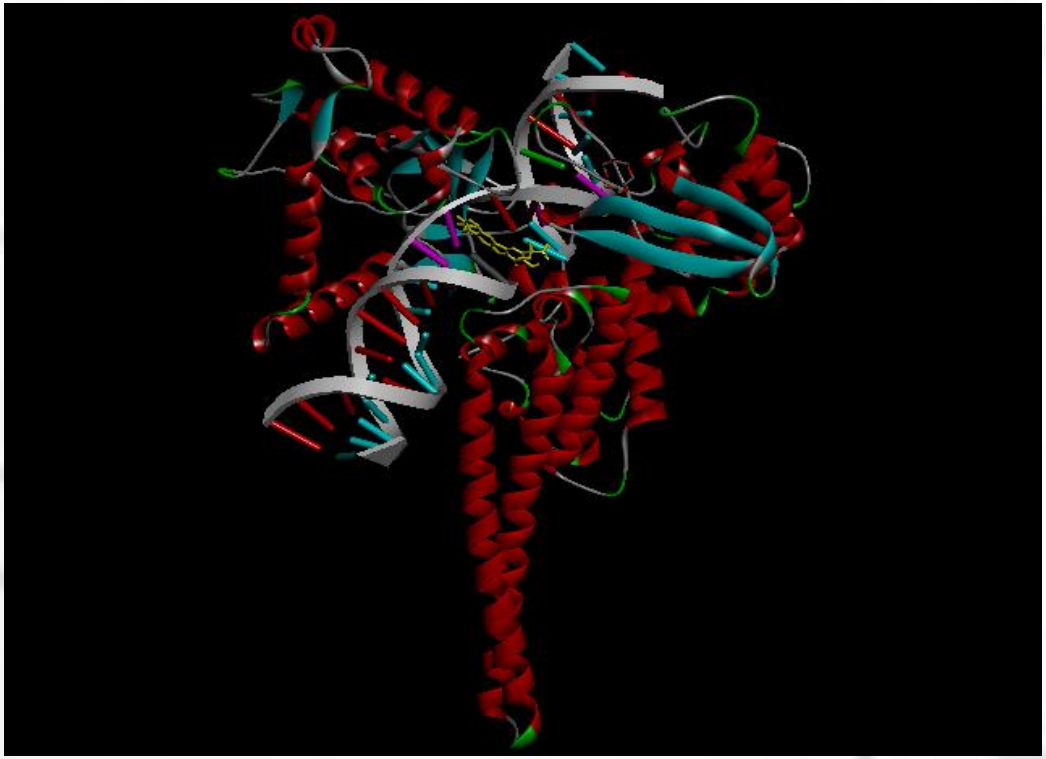
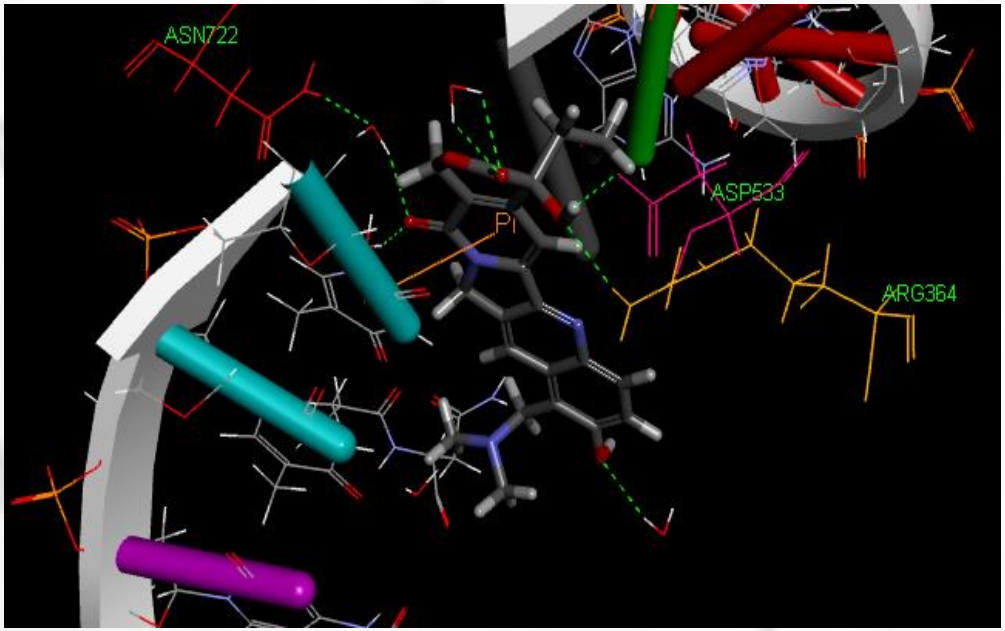


- Interaction of Topotecan (yellow) with Topoisomerase I enzyme and DNA (Pdb: 1K4T)

DOCKING

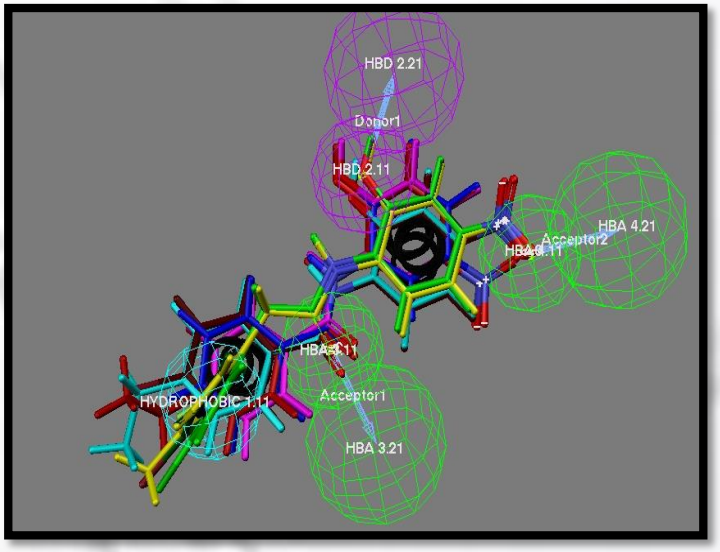


- Docking pose of Topotecan (Hydrogen bonds and pi interactions)

LIGAND-BASED DESIGN

Prediction of receptor structure from the structure of active molecules

- The structure of the receptor is unknown
- The mechanism of action might be known or unknown
- Ligand and biological activities of ligands are known



PHARMACOPHORE ANALYSIS

Pharmacophore

Is a part of a molecule that is responsible for a particular biological or pharmacological interaction.

Pharmacophore features

- **Hydrogen bond donor or acceptor**
- **Electrostatic,**
- **Hydrophobic,**
- **Aromatic,**
- **Steric... .**