



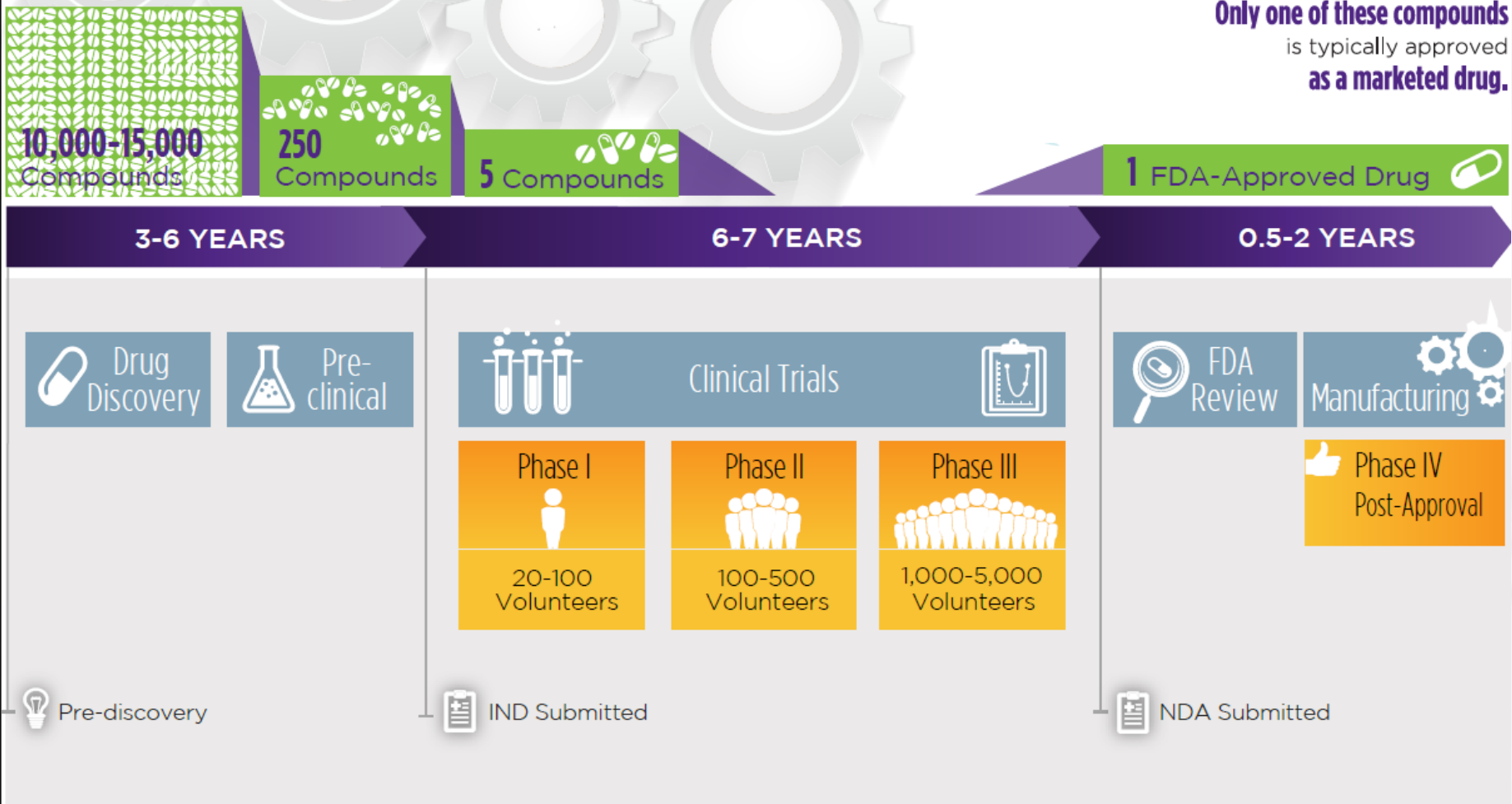
Computer Aided Drug Design Methods

Tugba ERTAN-BOLELLI, 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.



AVERAGE COST: \$1 billion+

DURATION: 10-15 years*





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



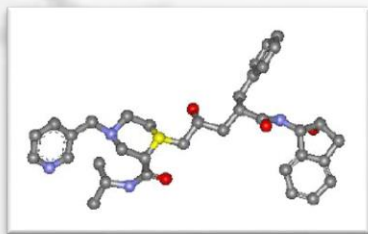
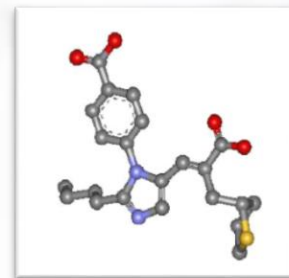
PDB ID: 5MIM



DRUGS DISCOVERED BY COMPUTER AIDED DRUG DESIGN METHODS

TEVETEN® for hypertension treatment-Abbott

Eprosartan: Angiotensin II receptor antagonist,
Molecular Modelling

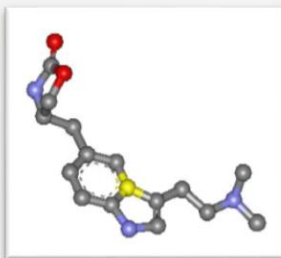
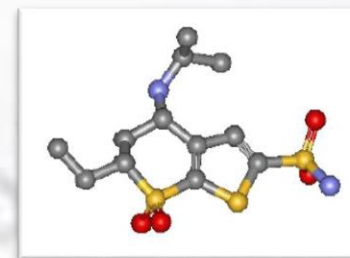


CRIVAN® for AIDS –Merck

Indinavir: HIV-1 Protease Inhibitor, X-ray crystallography,
Molecular Mechanics Calculations and Receptor Based
Design

TRUSOPT® for Glaucoma treatment-Merck

Dorzolamide: Carbonic anhydrase inhibitor *ab initio*
Calculations and Receptor Based Design



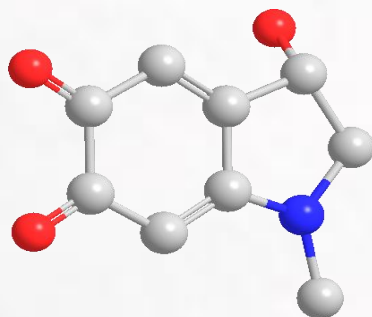
ZOMIG® for Migrain treatment-Wellcome, Zeneca

Zolmitriptan: 5HT1-agonist, Pharmacophore Analysis and
Ligand Based Design



COMPUTER-AIDED DRUG DESIGN

- Molecular modeling studies



- Quantitative structure activity relationship (QSAR)

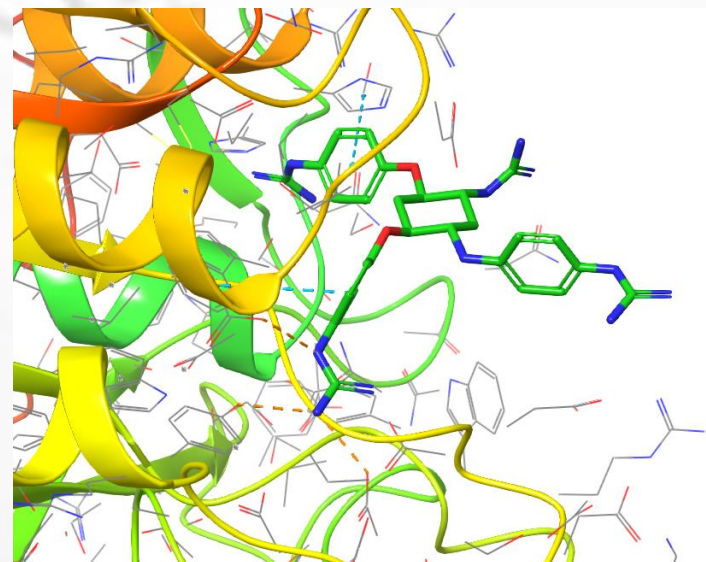


Molecular modeling

The aim of molecular modeling is to understand

- the basic relationship between chemical and physical properties,
- chemical structure and
- 3D structure of a molecule.

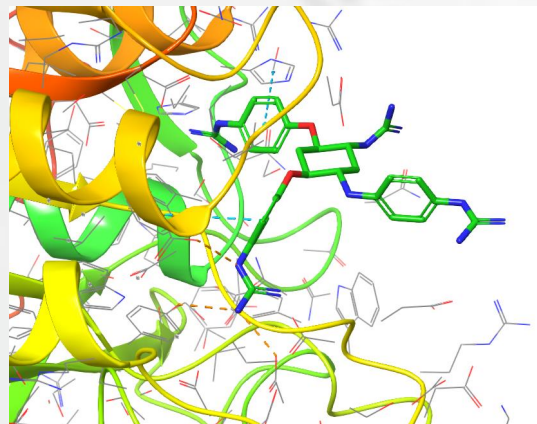
3-dimensional study is the definition of all properties of a compound in space.



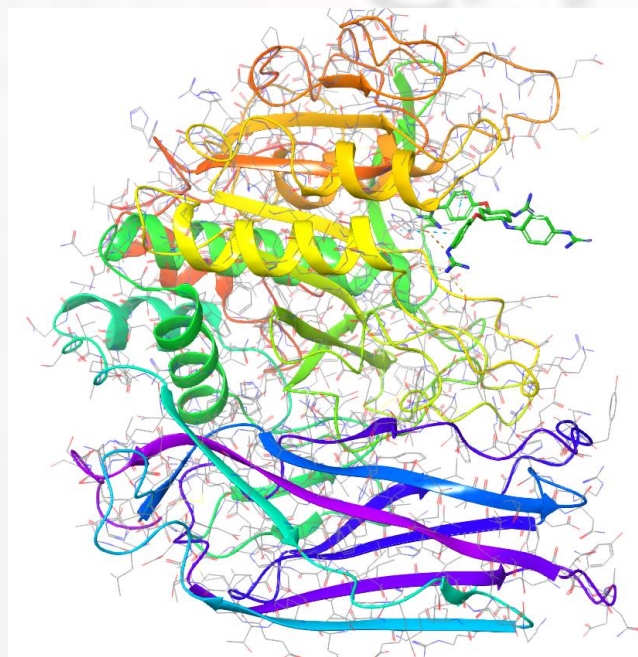


Using molecular modeling techniques gathering information about;

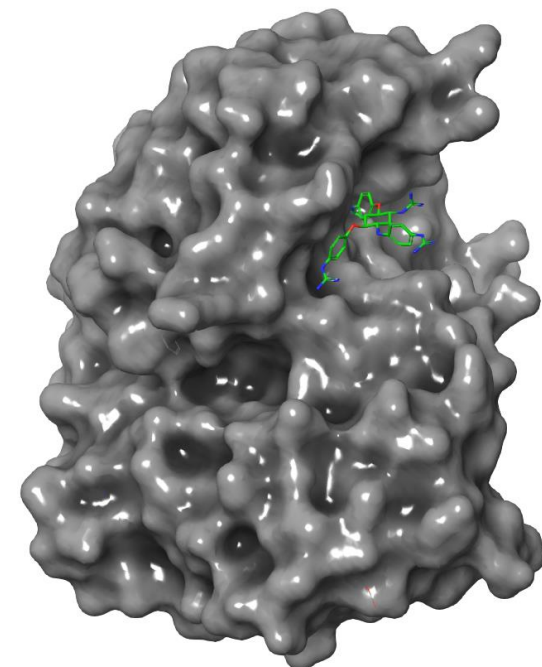
1. 3D structure of the molecule
2. Physicochemical properties of the molecule
3. Comparison of a molecule with other molecules
4. Investigate the receptor-drug interactions



Close view



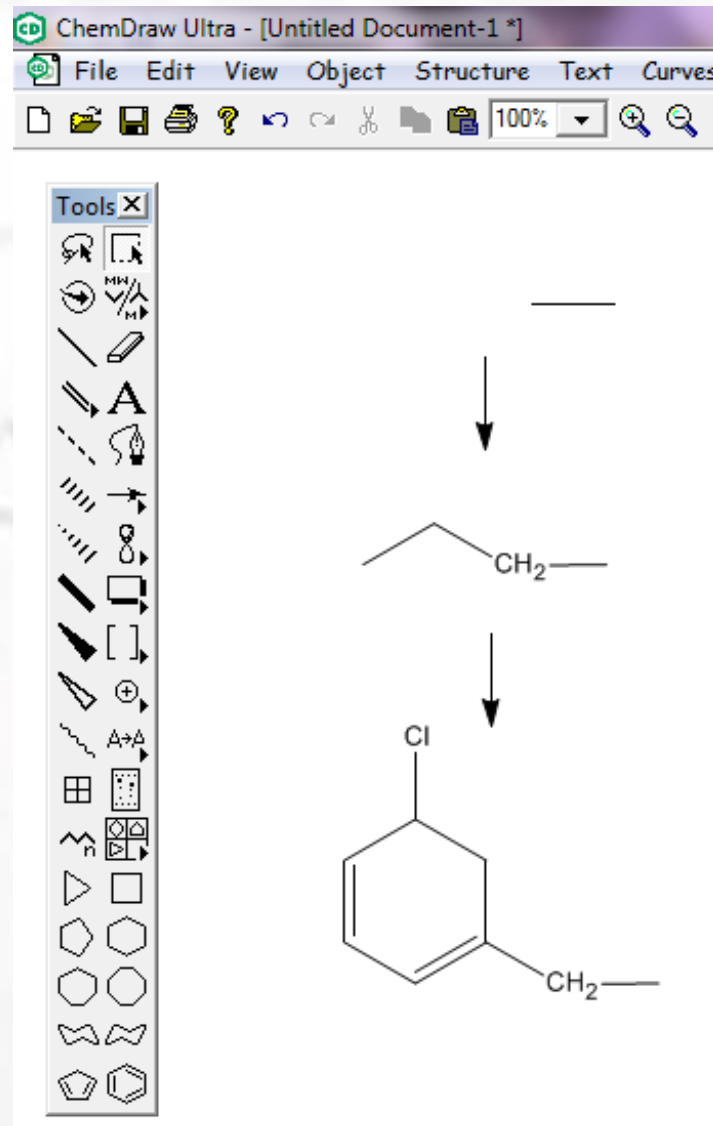
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surface

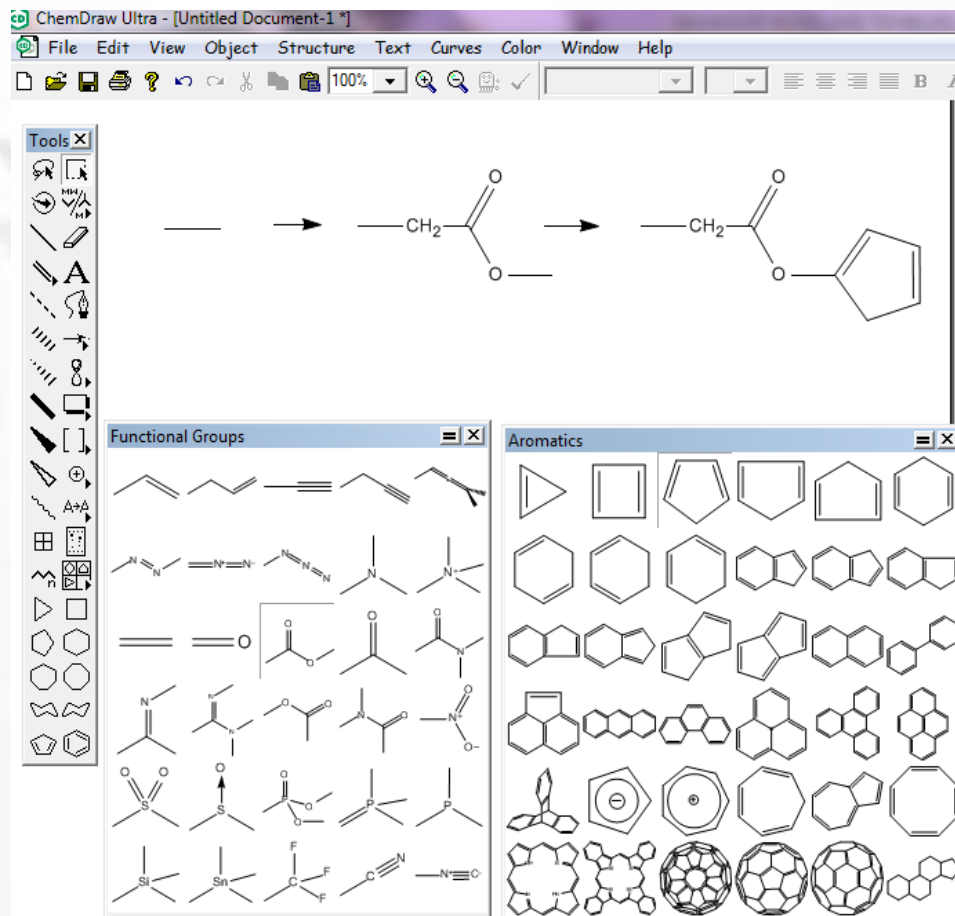


3D structure can be created by using the drawing features in the software





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.

RCSB Protein Data Bank - x
www.rcsb.org/pdb/explore/explore.do?structureid=3RR3

Please help us learn about our users by taking this quick [survey](#).

Structure of (R)-flurbiprofen bound to mCOX-2

3RR3 [Display Files](#) [Download Files](#) [Share This Page](#)

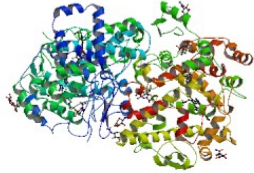
DOI:10.2210/pdb3rr3/pdb

Primary Citation

(R)-Profens are substrate-selective inhibitors of endocannabinoid oxygenation by COX-2.
Duggan, K.C.¹, Hermanson, D.J.¹, Musee, J.¹, Prusakiewicz, J.J.¹, Scheib, J.L.¹, Carter, B.D.¹, Banerjee, S.¹, Oates, J.A.¹, Marnett, L.J.¹
Journal: (2011) Nat.Chem.Biol. 7: 803-809
PubMed: 22053353 [PubMedCentral: PMC3298755](#)
[Search Related Articles in PubMed](#)

PubMed Abstract:
Cyclooxygenase-2 (COX-2) catalyzes the oxygenation of arachidonic acid and the endocannabinoids 2-arachidonoylglycerol and arachidonylethanolamide. Evaluation of a series of COX-2 inhibitors revealed that many weak competitive inhibitors of arachidonic acid oxygenation are potent inhibitors of endocannabinoid oxygenation. (R) enantiomers of... [[Read More & Search PubMed Abstracts](#)]

Biological Assembly 1



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Biological assembly 1 assigned by authors and generated by PISA (software)

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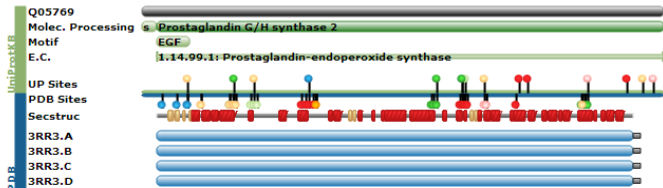
Deposition Summary

Authors: Duggan, K.C.¹, Hermanson, D.J.¹, Musee, J.¹, Prusakiewicz, J.J.¹, Scheib, J.L.¹, Carter, B.D.¹, Banerjee, S.¹, Oates, J.A.¹, Marnett, L.J.¹
Deposition: 2011-04-28
Release: 2011-11-09
Last Modified (REVDAT): 2012-03-21

Molecular Description

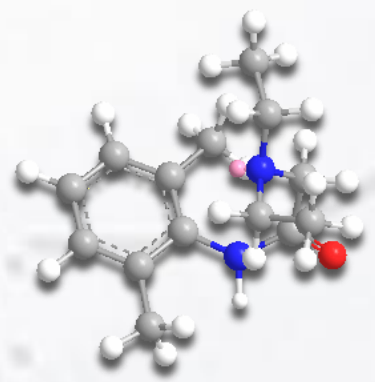
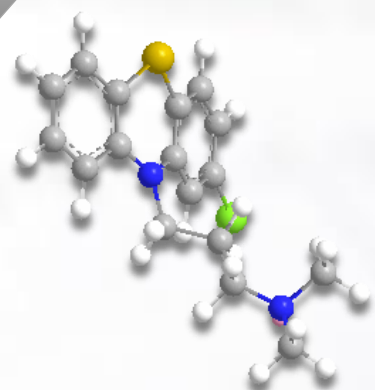
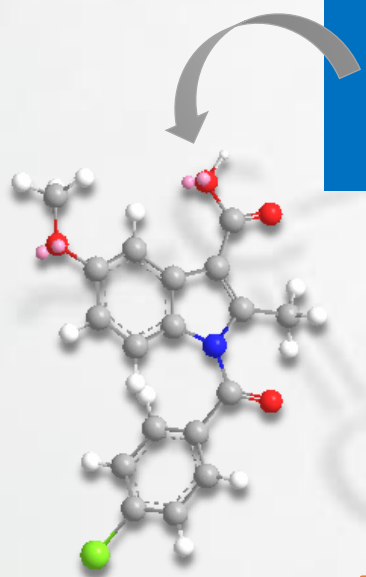
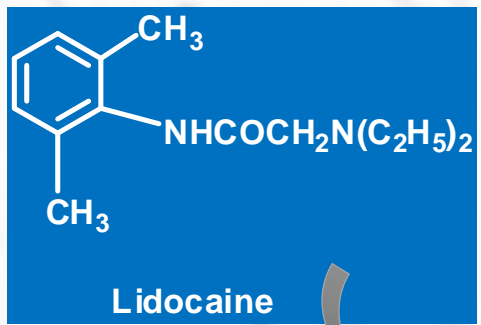
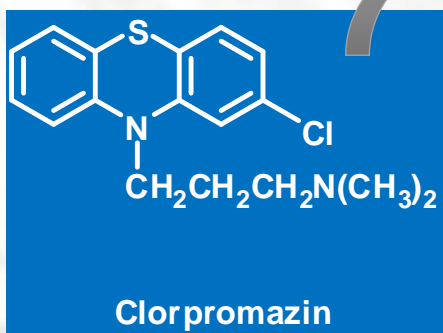
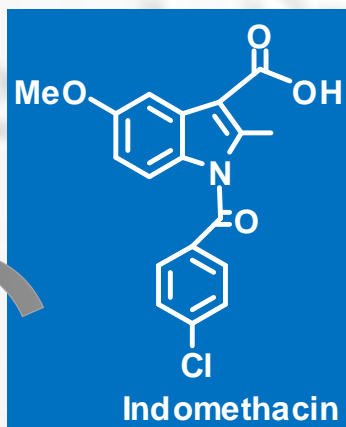
Classification: Oxidoreductase/oxidoreductase Inhibitor
Structure Weight: 266088.64

Molecule:	Prostaglandin G/H synthase 2
Polymer:	1 Type: protein Length: 560
Chains:	A, B, C, D
EC#:	1.14.99.1 EC
Organism:	Mus musculus
UniProtKB:	Protein Feature View Search PDB Q05769



UniProtKB: Q05769 Molec. Processing Motif EGF E.C. 1.14.99.1: Prostaglandin-endoperoxide synthase

PDB: 3RR3.A, 3RR3.B, 3RR3.C, 3RR3.D



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=luJqbV4D8Cc&list=FLD5BNZVjYcwC62PKTJs47Gg>



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

1- Target = Receptors, enzymes or nucleic acids

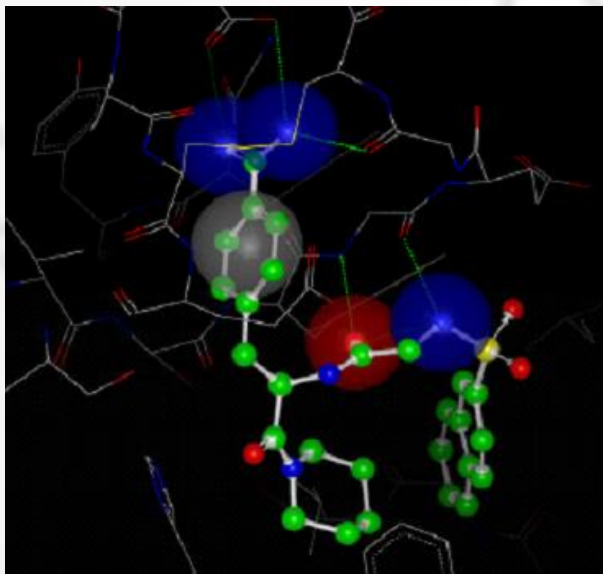
2- Effector(ligand) = There may be natural endogenous substances or drugs which occupy the active site of the target and affect the target positively or negatively.

STRUCTURE-BASED DESIGN

LIGAND BASED DESIGN

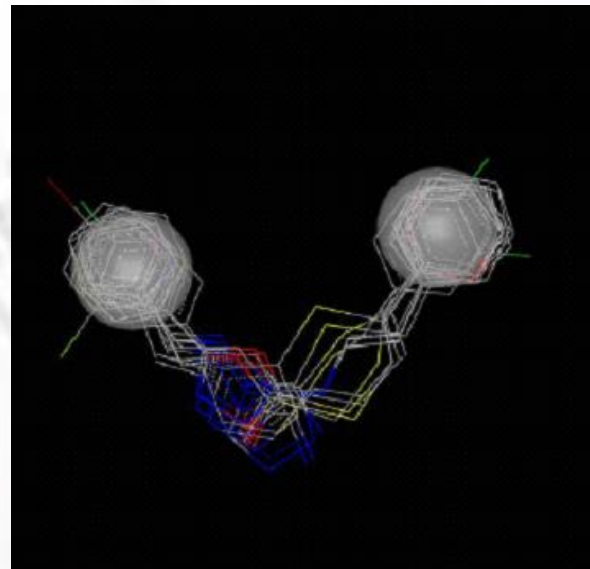


STRUCTURE-BASED DESIGN



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 compounds.

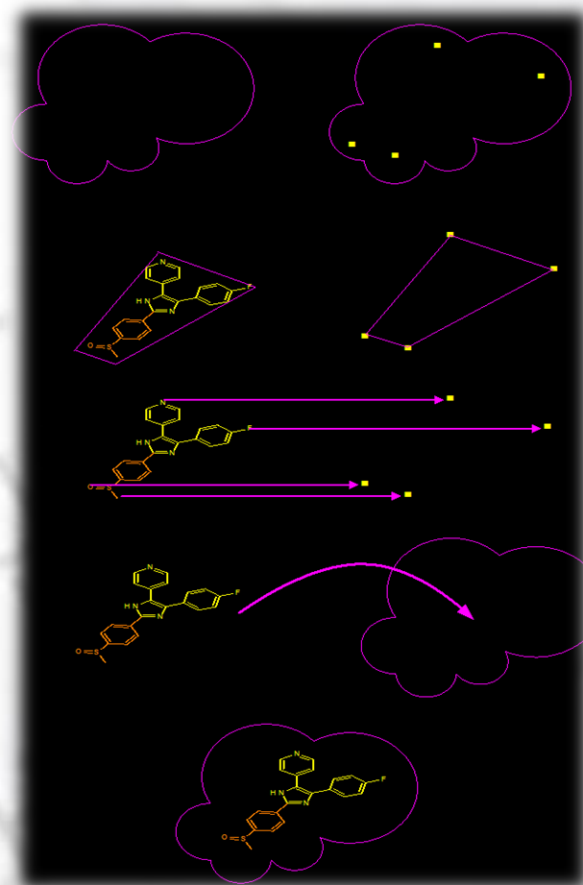


STRUCTURE-BASED DESIGN

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

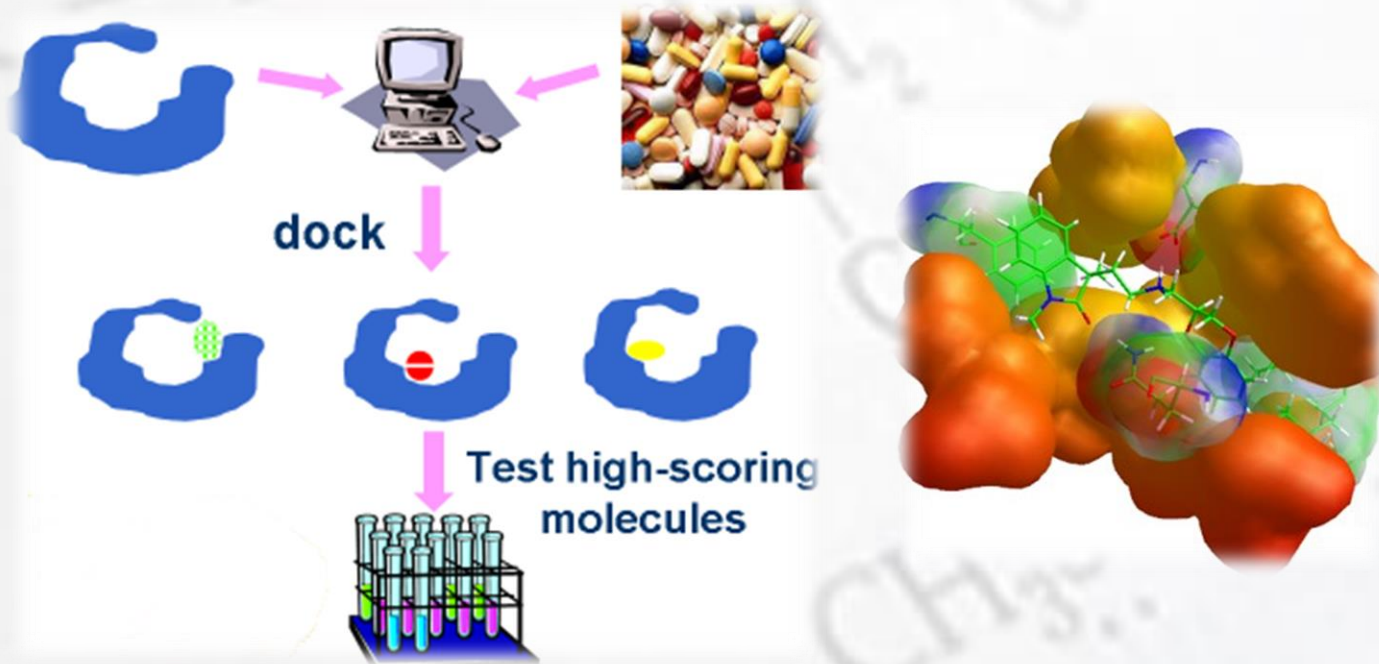
DOCKING





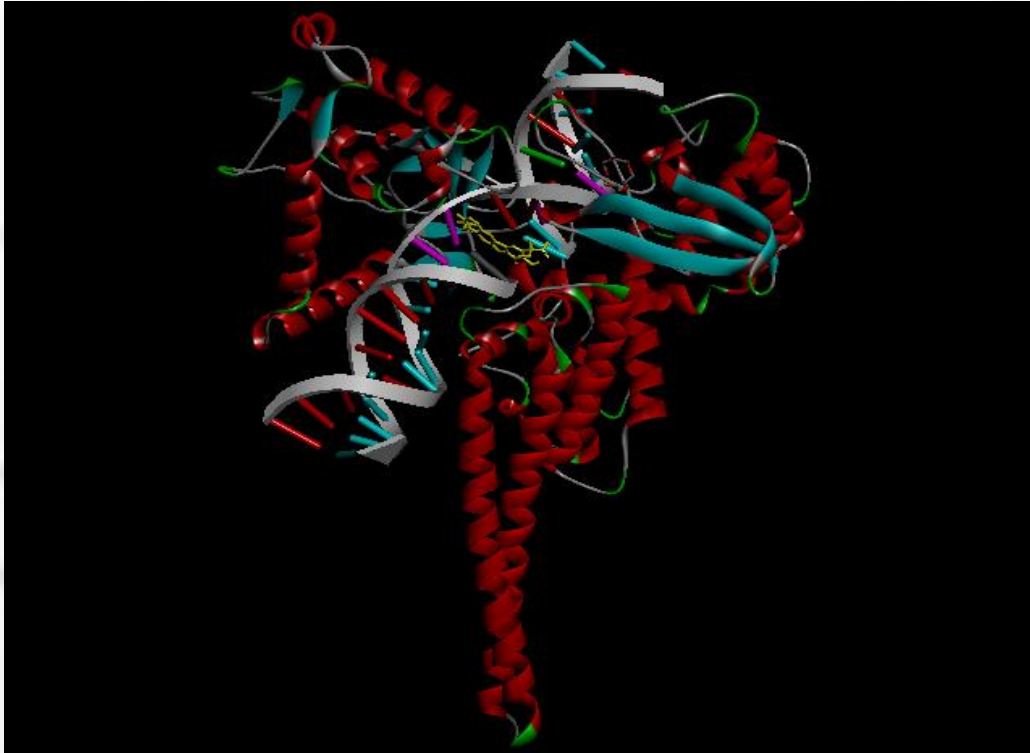
DOCKING

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





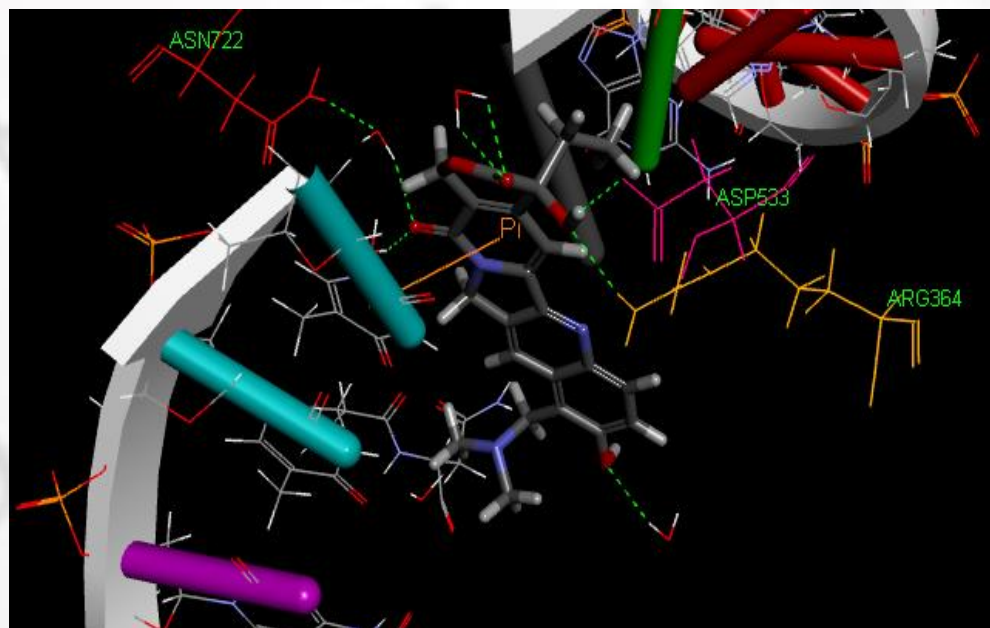
DOCKING



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



DOCKING



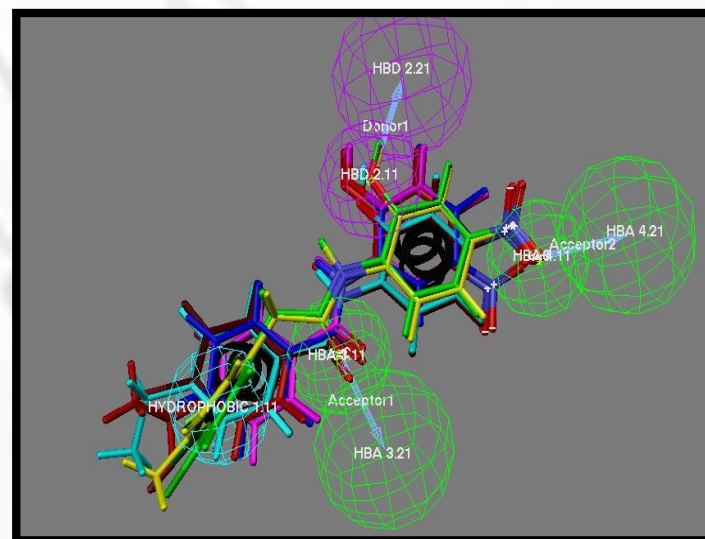
- Docking pose of Topotecan (Hydrogen bonds and pi interactions)



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... .

