MOLECULAR DOOCKING AND ITS APPLICATION TOWARD MODERN DRUG DISCOVERY

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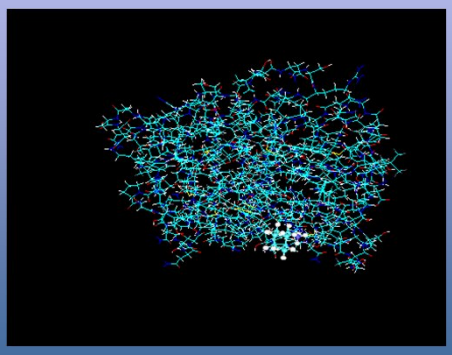

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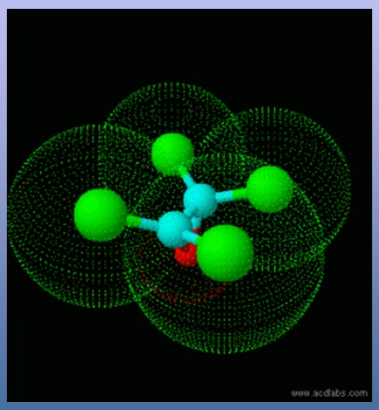
Outline of the Seminar

- Drug Discovery and Development
- What is CADD
- Computer-Aided Drug Design Approaches
- What is Molecular Docking
- Applications of Molecular Docking in Drug designing
- Case Study
- Success stories in Molecular Docking
- Conclusion
- Acknowledgement



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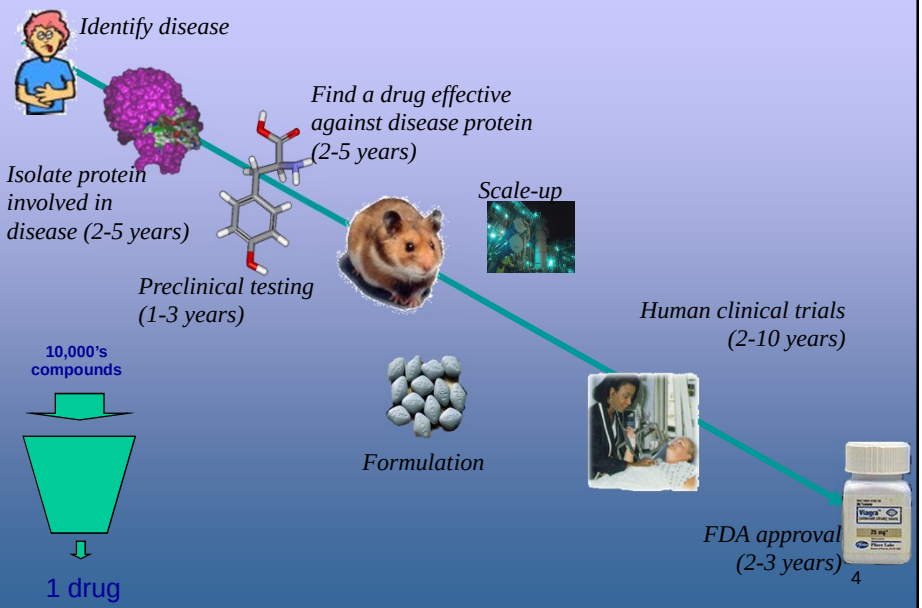
Drug Discovery & Development



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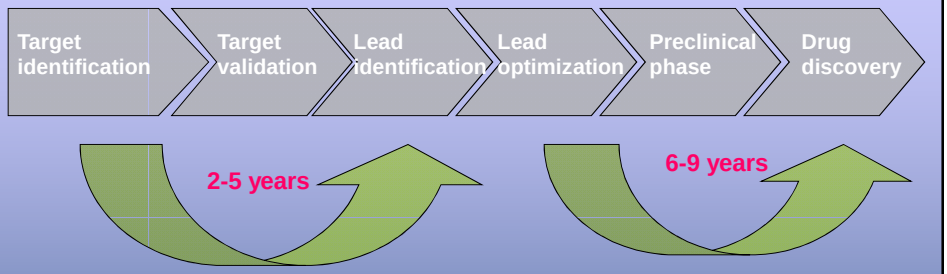
Modern Drug Discovery Process



- Drug discovery is an expensive process involving high R & D cost and extensive clinical testing
- A typical development time is estimated to be 10-15 years.
- Costs an average of 500 to 800 million U.S. dollars per drug.

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Drug Discovery Technologies

- Target identification
  - Genomics, gene expression profiling and proteomics
- Target Validation
  - Gene knock-out, inhibition assay
- Lead Identification
  - High throughput screening, fragment based screening, combinatorial libraries
- Lead Optimization
  - Medicinal chemistry driven optimization, X-ray crystallography, QSAR, ADME profiling (bioavailability)
- Pre Clinical Phase
  - Pharmacodynamics (PD), Pharmacokinetics (PK), ADME, and toxicity testing through animals
- Clinical Phase
  - Human trials

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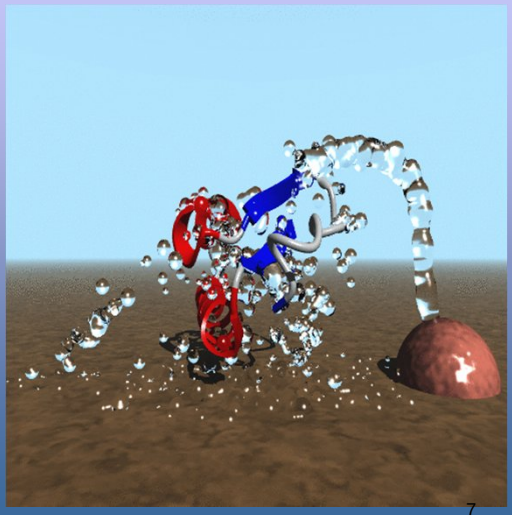
Drug Targets

- Enzyme – inhibitors
- Receptors - agonists or antagonists
- Ion channel – blockers
- Transporter –inhibitors
- DNA - blockers



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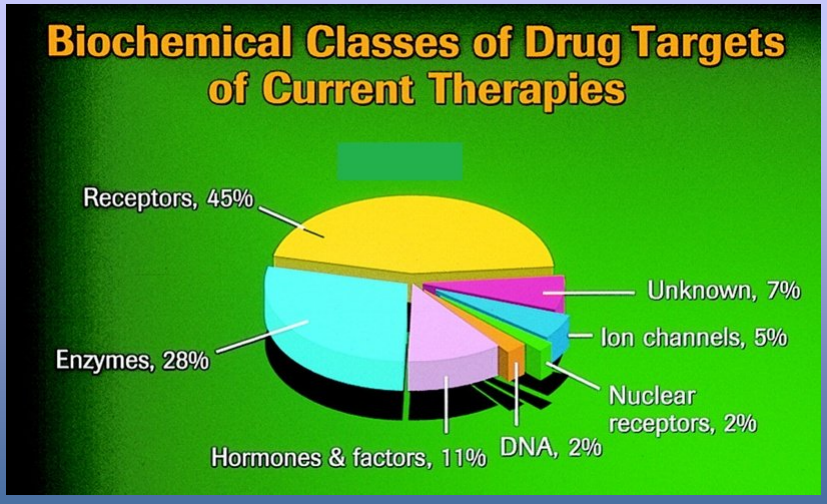
Currently Used Drug Targets



J. Drews Science 287, 1960 -1964 (2000)

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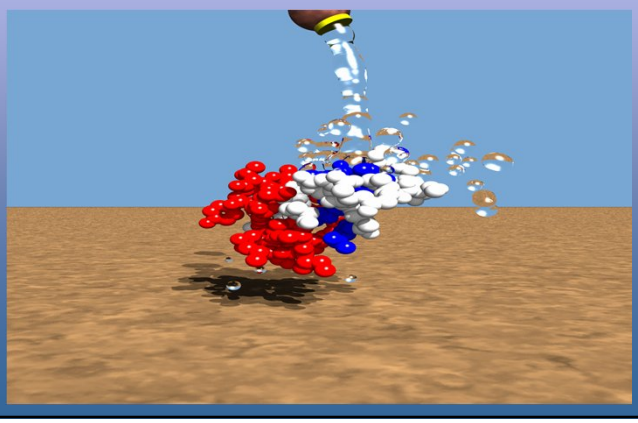
What is CADD????

Computational Chemistry/CADD is the chemistry whose major goals are to create efficient mathematical approximations and computer programs that calculate the properties of future drug molecules and thus helping in the process of drug design and discovery.



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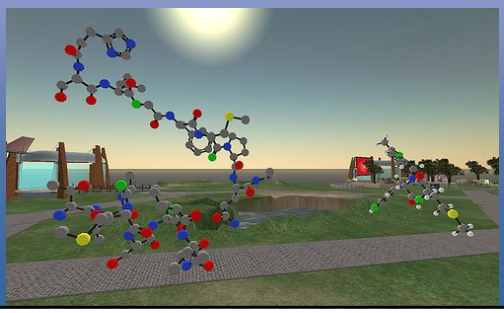
Why CADD…?

- Drug Discovery today are facing a serious challenge because of the increased cost and enormous amount of time taken to discover a new drug, and also because of rigorous competition amongst different pharmaceutical companies.



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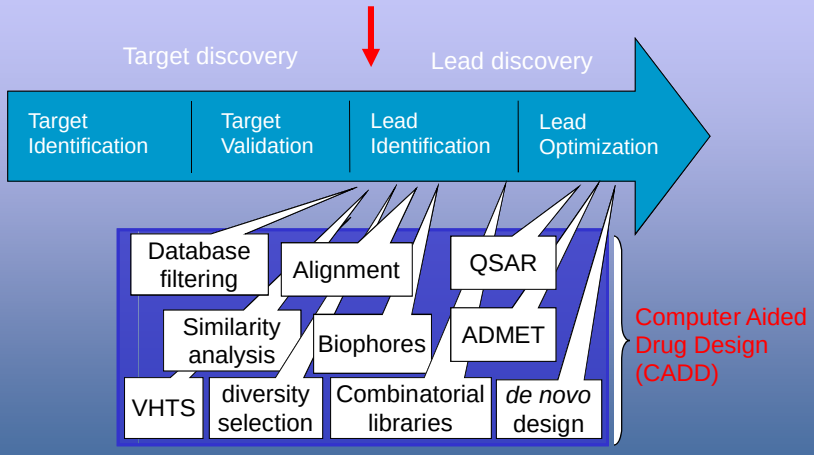
Phases of CADD



SAVING 12 – 15 years, Costs: 500 - 800 million US $

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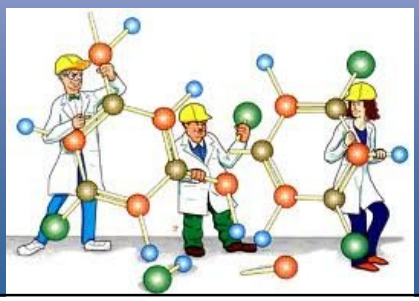
Goals of CADD

- Define a target structure,
- and/ or its binding site,
- and/ or its active ligand (possibly bound to protein),
- find a new molecule that changes the target's activity



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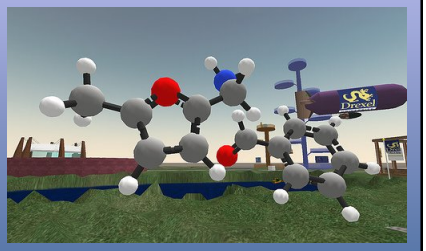
Computer Aided Drug Design

A. Structure-based drug design

- **.Moleckular docking**
- •Structure-based pharmacophore modeling
- •Hmology modeling
- •MD simulation

B. Ligand-based drug design

- •3-QSAR
- •Similarity search
- •Ligand-based pharmacophore modeling
- •ADME prediction



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What is docking?

Docking is the identification of the low-energy binding modes of a small molecule, or ligand, within the active site of a macromolecule, or receptor, whose structure is known.

Two main Tasks of Molecular Docking

- Sampling of conformational (Ligand) space
- Scoring protein-ligand complexes

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Types of Docking

There are 2 types of docking

1. Rigid docking
2. Flexible docking

1. Rigid Docking

If we assume that the molecules are rigid, then we are looking for a transformation in 3D space of one of the molecules which brings it to an optimal fit with the other molecules in terms of a scoring function. In this case the search space is restricted to three rotational and translational degree of freedom.

2. Flexible Docking

If we consider molecule flexibility then in addition to transformation, our aim to find the confirmations of the receptor and the ligand molecules, as they appear in complex.

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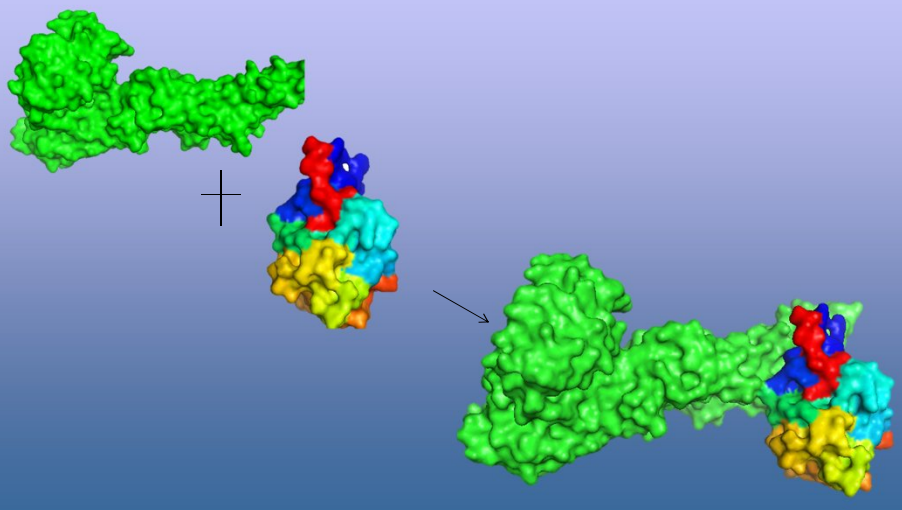
Categories of docking

1. Protein-Protein Docking:
   - Both molecules are rigid
   - Interaction produces no change in conformation
   - Similar to lock-and key model
2. Protein-Ligand Docking:
   - Ligand is flexible but the receptor protein is rigid
   - Interaction produces conformational changes in ligand

Protein-Protein Docking



Protein-Protein Docking procedure

1. Preparing receptor and ligand Protein.
   a. Remove all unwanted chains and ligands.
   b. Add hydrogen and charges.
   c. Minimize energy by selective force field (AMBER99).

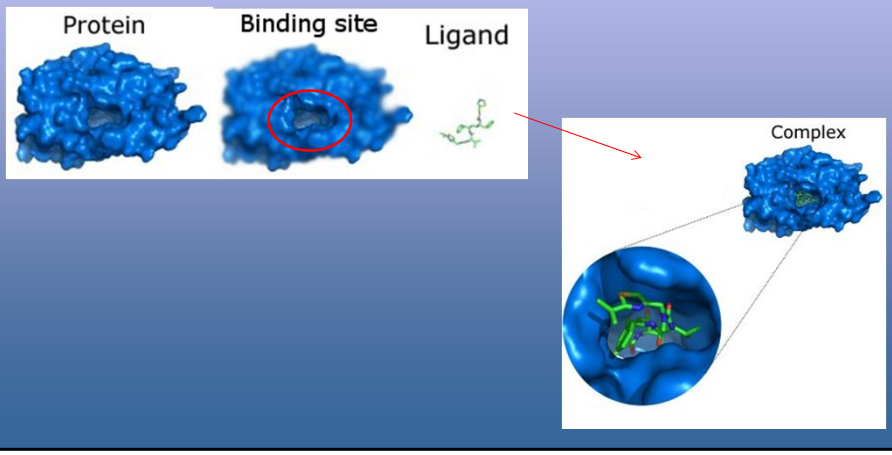
2. Select Docking server.
   GRAMM-X, Pydock, Patch-Dock, Z-Dock, etc

3. Get created complexes and subject to re-ranking

4. Find interfacing residues and polar interaction

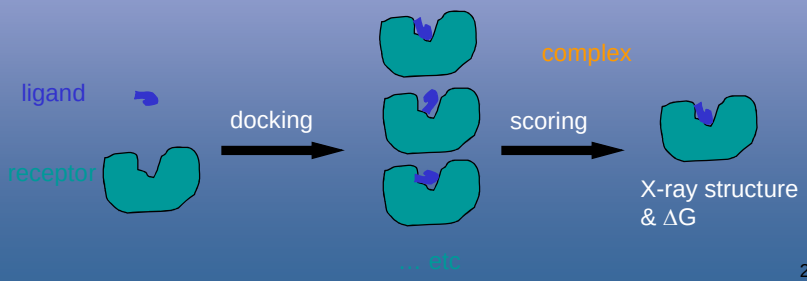
Protein-ligand docking

- Computational method that mimics the binding of a ligand to a protein



What are Docking & Scoring?

- To place a ligand (small molecule) into the binding site of a receptor in the manners appropriate for optimal interactions with a receptor.
- To evaluate the ligand-receptor interactions in a way that may discriminate the experimentally observed mode from others and estimate the binding affinity.



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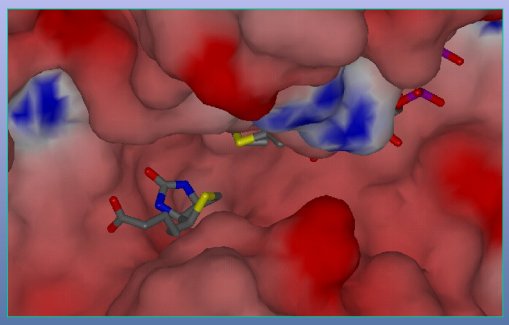
Available Docking Programs

- DOCK
- MOE-Dock
- FlexX
- GOLD
- AutoDOCK
- FRED
- Hammerhead
- FLOG



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FLEXX

- Receptor is treated as rigid
- Incremental construction algorithm:
  - Break Ligand up into rigid fragments
  - Dock fragments into pocket of receptor
  - Reassemble ligand from fragments in low energy conformations

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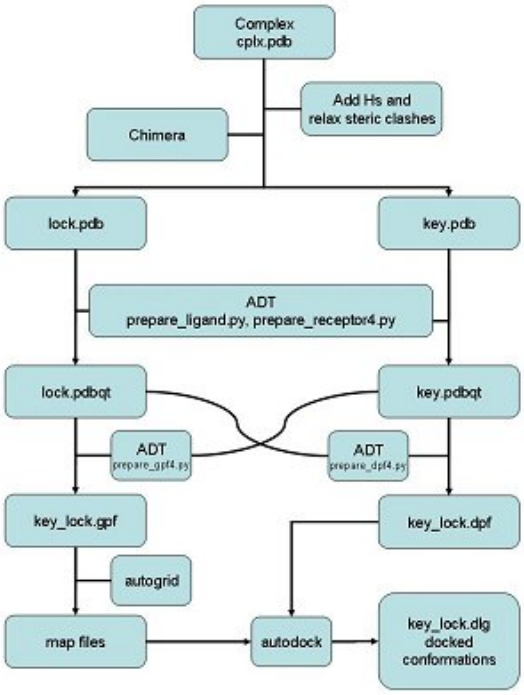
Components of docking software

- Typically, protein-ligand docking software consist of two main components which work together:
- **1. Search algorithm**
  - Generates a large number of poses of a molecule in the binding site
- **2. Scoring function**
  - Calculates a score or binding affinity for a particular pose

- The binding affinity or a **score** representing the strength of binding

$$\Delta G_{bind} = \Delta G_{solvent} + \Delta G_{conf} + \Delta G_{\text{int}} + \Delta G_{rot} + \Delta G_{t/r} + \Delta G_{vib}$$

Docking Flow Chart Using Chimera and Autodock



Ligand Preparation for Docking using Autodock

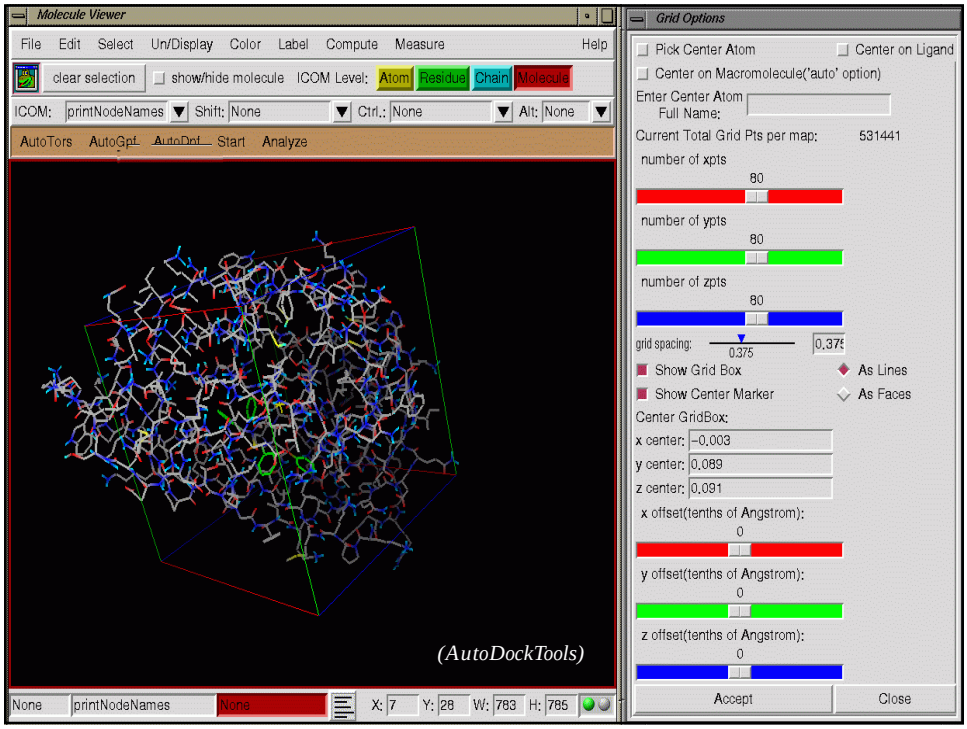
- Assign charges
- Define rotatable bonds
- Rename aromatic carbons
- Write .pdbq ligand file

Preparation of Protein using Autodock

- Add essential hydrogens
- Load charges
- Remove Water Molecules
- Write .pdbqs protein file

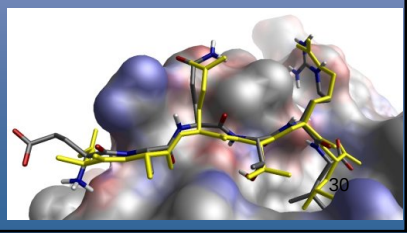
Grid Preparation

- AutoDock uses grid-based docking
- Ligand-protein interaction energies are pre-calculated and then used as a look-up table during simulation



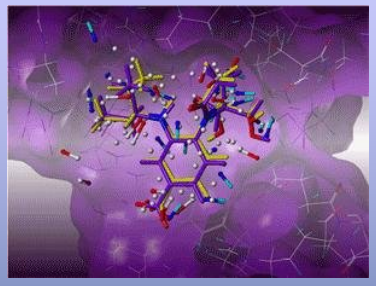
Application of Molecular Docking in Modern Drug Discovery

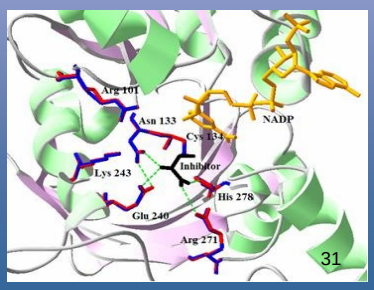
- Determine the lowest free energy structures for the receptor-ligand complex
- Search database and rank hits for lead generation
- Calculate the differential binding of a ligand to two different macromolecular receptors
- Study the geometry of a particular complex
- Propose modification of a lead molecules to optimize potency or other properties
- de novo design for lead generation
- Library design



Application of Molecular Docking in Modern Drug Discovery

- Screening for the side effects that can be caused by the interactions with other proteins, like proteases, Cytochrome P450 and others can be done.
- It is also possible to check the specificity of the potential drug against homologous proteins through docking.
- Docking is also a widely used tool in predicting protein-protein interactions.
- Knowledge of the molecular associations aids in understanding a variety of pathways taking place in the living and in revealing of the possible pharmacological targets.





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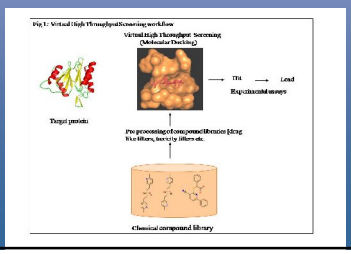
Application of Molecular Docking in Modern Drug Discovery

Docking-Based Virtual High Throughput Screening

- Less expensive than High Throughput Screening
- Faster than conventional screening
- Scanning a large number of potential drug like molecules in very less time.
- HTS itself is a trial and error approach but can be better complemented by virtual screening.



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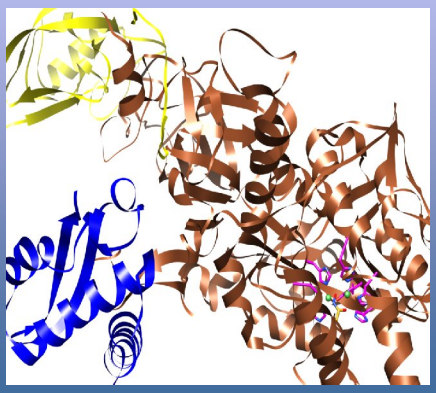
Application of Molecular Docking in Modern Drug Discovery

Introduction to Urease Enzyme

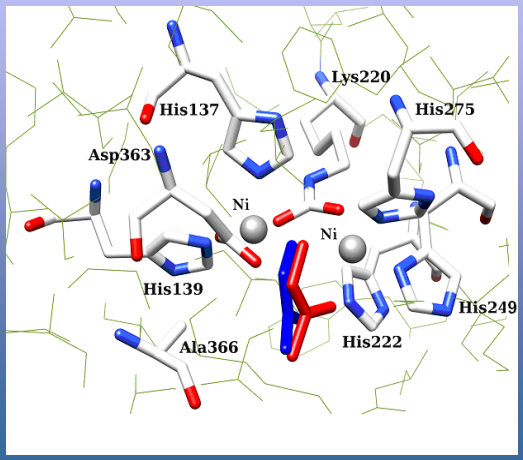
- Urease is a nickel containing hydrolase enzyme.
- It hydrolyze urea into ammonia and carbon dioxide.
- Urease found in a variety of bacteria, fungi, algae and plants.
- The primary role of urease is to enable organism to use urea as a nitrogen source.
- Bacterial ureases are involved in the pathogenesis of many disease in animal and human.
- Urease allows HP to survives at low pH of stomach, and play important role in the pathogenesis of stomach and peptic ulcers.
- In agriculture, high urease activity cause significant environmental and economical problems.



Application of Molecular Docking in Modern Drug Discovery

Validation of Docking Protocols

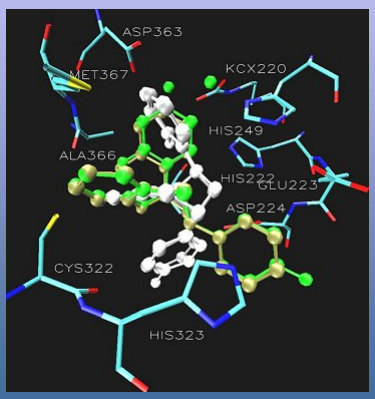
Conformational comparison of acetohydroxamic acid, from the crystal structure (red) and that from FlexX docking result (blue) in the active site of BP urease.



Application of Molecular Docking in Modern Drug Discovery

Case Study: Molecular docking of urease inhibitors

Superimposition of the docking pose of 6a (tan), 6b (gray), 7a (green) 7b (white) showing the difference in the orientation of ring B in the catalytic core of urease. Additionally the active site of urease clearly demonstrating the role of Asp224 and Cys322. The ligands are represented as a ball and stick model.



Journal of Enzyme Inhibition and Medicinal Chemistry, February 2009; 24(1): 151–156

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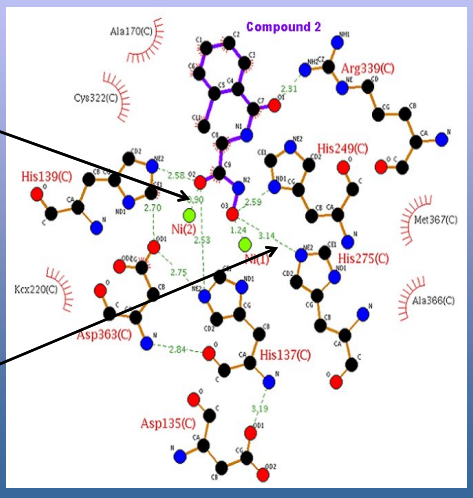
Application of Molecular Docking in Modern Drug Discovery

Binding mode of compound 2 in the active site of BP urease

Ligand and nickel Coordination

Hydrogen bonding between ligand and protein residue



09/01/2010

Application of Molecular Docking in Modern Drug Discovery

Case Study: Identification of Novel Urease Inhibitors by High-Throughput Virtual and in Vitro Screening

3000 compunds

↓ Scoring

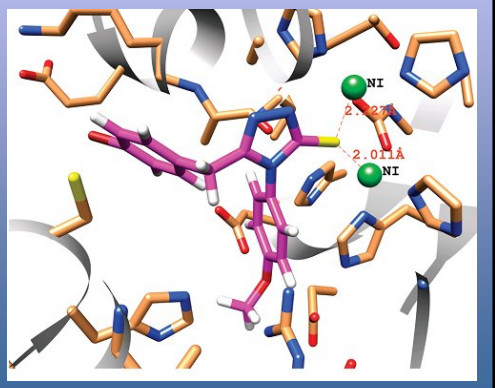
200 compunds

↓ Binding mode

34 compunds

↓ Biological testing

14 active compunds



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ACS Med. Chem. Lett. 2010, 1, 145–149

Application of Molecular Docking in Modern Drug Discovery

Identification of Inhibitors for Simultaneous Inhibition of Anti-Coagulation and Anti-Infamatory Activities of Snake vemon Phospholipase A_2

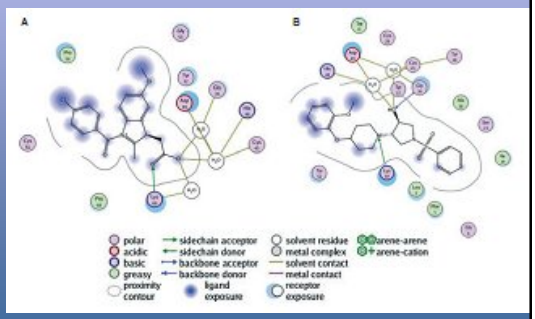
169000 compunds

↓ Pharmacophore Based-screening

300 compunds

↓ Molecular docking

32 promising compunds



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Chem Biol Drug Des 2012; 79: 431–441

Growing Evidence of Success…. !!

Molecular Docking has resulted in several breakthrough classes of new drug.

Drug	Target	Company
Dorzolamid	Carbonic anhydrase (Hypercapnic Vantilatory failure)	Merck Sharp and Dohme (Harlow, UK)
Saquinavir	HIV protease	Roche (Welwyn, UK)
Relenza	Neuraminidase	Biota (Melbourne, Australia)
AG85, ag337, ag331	Thymidylate synthase	Agouron (La Jolla, CA, USA)

Bailey, D. *et al.*, *Drug Discovery Today*, **6**(2) 57-59 (**2001**)

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Growing Evidence of Success…. !!

1. Discovery of Indinavir, the HIV protease inhibitor.
2. Identification of Haloperidol as a lead compound in a structure-based design for non-peptide inhibitor of HIV.
3. Carbonic Anhydrase (treatment of glaucoma)
4. Renin (treatment of hypertension)
5. Dyhrofolate reductase (antibacterial)
6. Neuraminidase (antiviral)
7. HIV-1 aspartic proteinase (anti-acquired immunodeficiency syndrome)

1. Wlodawer, A. Rational approaches to AIDS drug design through structural biology. *Annu. Rev. Med.* 53, **2002**,595-614.
2. DesJarlais, R.L. *etal* Structure-based design of nonpeptide inhibitors specific for the human immunodeficiency virus 1 protease. *Proc. Natl.Acad. Sci. U.S.A.* 87, **1990**, 6644-48.

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Growing Evidence of Success…. !!

1. Trypanosomal glyceraldehyde-3-phosphate dehydrogenase (anti parasitic)
2. Thymidylate synthase and purine nucleoside phosphorylase (anticancer)
3. Elastase (treatment of emphysema)
4. Collagenase (Rheumatoid and Osteoarthritis)
5. Phispholipase A_2 (anti inflammatory)
6. Glycogen phosphorylase (treatment of diabetes mellitus)

Amedo C., Rudolf W., Claus E. Computer-Aided Design of Thrombin inhibitors. *News Physiol. Sci.*, 13, **1998**,182-89.

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Conclusion

Molecular docking give the promising effect on identification and optimization in modern drug discovery

The combination of the chemical information of natural products with docking-based virtual screening will play an important role in drug discovery in the post-genomic era as more and more new potential targets are emerging from the functional genomic studies.

Docking-based virtual screening lead to much higher hit rate than traditional screening methods (e.g., HTS)

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Conclusion

Docking method provides an opportunity for the designing of active compounds.

However, it has to be emphasized that docking-based virtual screening is not the replacement of the actual experimental screening. As a matter of fact, these two methods are highly complementary.

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Future Directions

Pharmaceutical history indicated that natural products provided a large number of drugs to the market. But, even for the currently used drug targets, available natural products have not been tested completely

Computational medicinal methods, can contribute its unique role in achieving the task of examining the interaction of all existing natural products with all possible targets.

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Acknowledgement

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Dr. Asifullah
Asst. Professor Khyber Medical University Peshawar
Mr. Masaud Shah
Dr. Suleman
Dr. Asnad
Dr. Zahida

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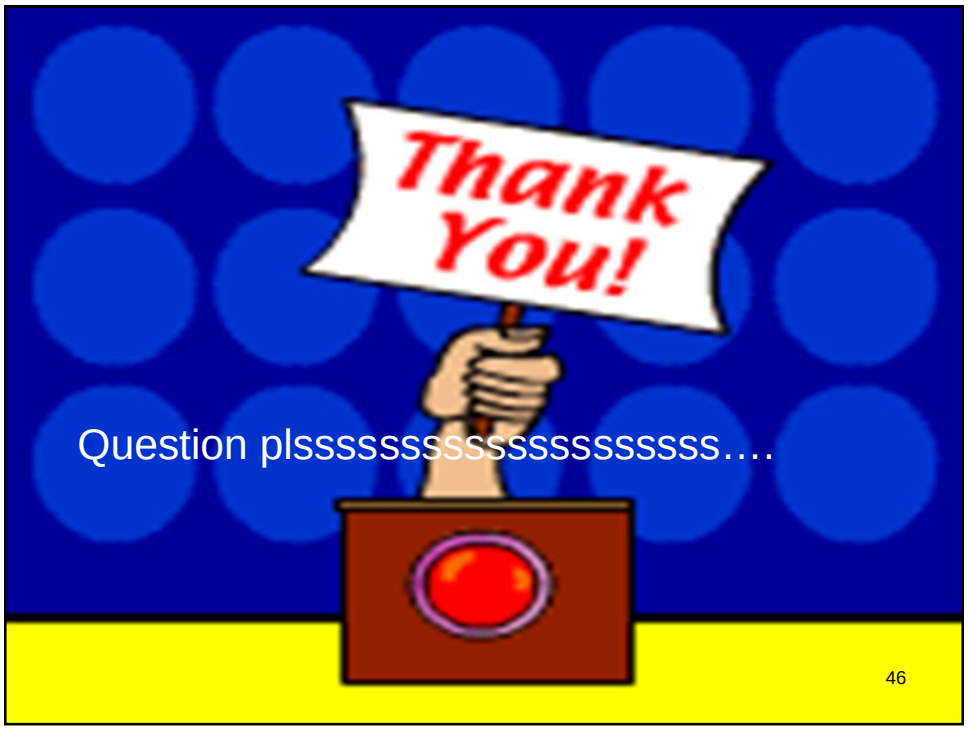

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Scale up: the ability to function with different amounts of required work.

Pharmacodynamics is the study of the biochemical and physiological effects of drugs on the body

Pharmacokinetics includes the study of the mechanisms of absorption and distribution of an administered drug, the rate at which a drug action begins and the duration of the effect, the chemical changes

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