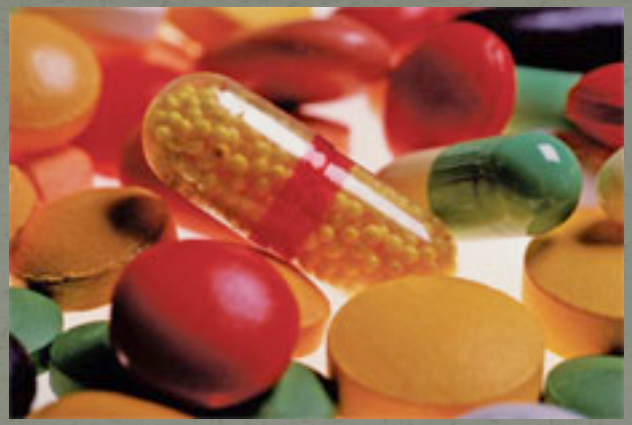
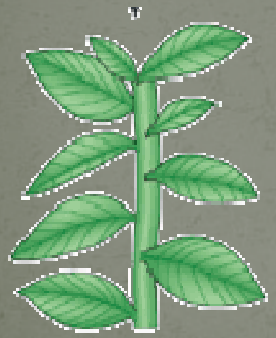
RATIONAL DRUG DESIGN

Drug Design & Discovery: Introduction

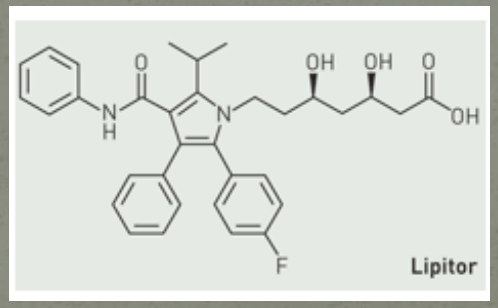


Drugs:

Natural sources



Synthetic sources



Targets:

Ideal Drug

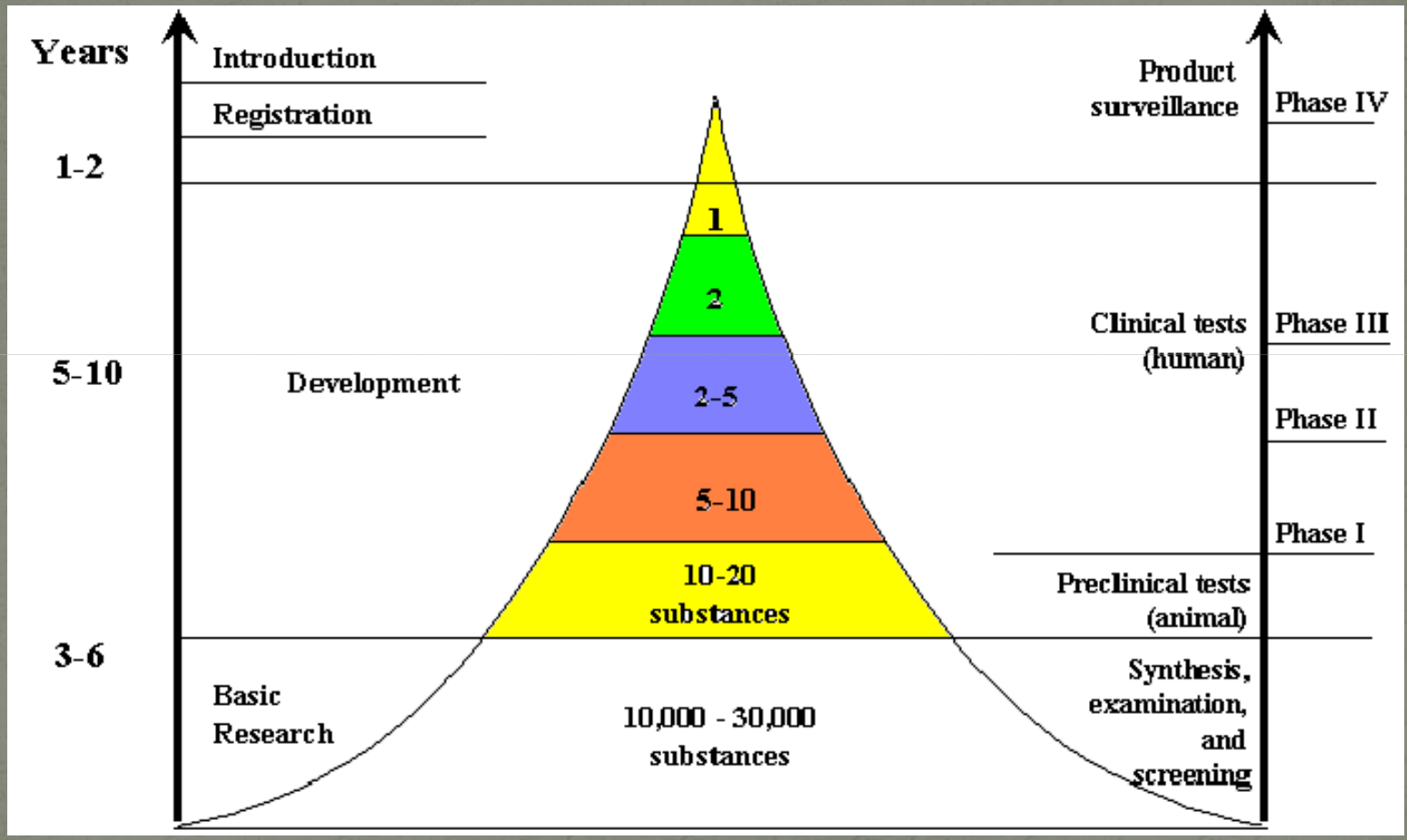
1) target: bio-molecule ,involved in signaling or metabolic pathways, that are specific to disease process by either protein-protein or protein-nucleic acid interactions.

2)antagonist action-inhibiting functions of the disease causing proteins.

3) Inhibiting interactions of the proteins.

4)Activates other proteins, that are deregulated in such disease like cancer.

Discovering and Developing the 'One Drug'



Pharmaceutical R&D
A Multi-Disciplinary Team

Administrative Support Analytical Chemistry Animal Health Anti-infective Disease Bacteriology

Behavioral Sciences Biochemistry Biology Biometrics Cardiology Cardiovascular Science Clinical Research

Communication Computer Science Cytogenetics Developmental Physiology DNA Sequencing Diabetology

Document Preparation Dosage Form Development Drug Absorption Drug Degradation Drug Delivery

Electrical Engineering Electron Microscopy Electrophysiology Environmental Health & Safety Employee Resources

Endocrinology Enzymology Facilities Maintenance Fermentation Finance Formulation

Gastroenterology Graphic Design Histomorphology Intestinal Permeability Law Library Science Medical Services

Mechanical Engineering Medicinal Chemistry Molecular Biology Molecular Genetics Molecular Models

Natural Products Neurobiology Neurochemistry Neurology Neurophysiology Obesity

Oncology Organic Chemistry Pathology Peptide Chemistry Pharmacokinetics Pharmacology Photochemistry

Physical Chemistry Physiology Phytochemistry Planning Powder Flow Process Development

Project Management Protein Chemistry Psychiatry Public Relations Pulmonary Physiology

Radiochemistry Radiology Robotics Spectroscopy Statistics Sterile Manufacturing Tabletting Taxonomy

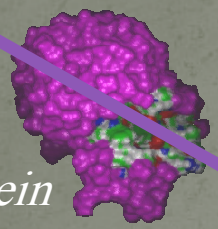
Technical Information Toxicology Transdermal Drug Delivery Veterinary Science Virology X-ray Spectroscopy

Over 100 Different Disciplines Working Together

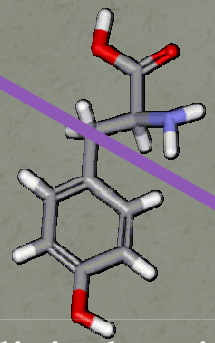
Drug Discovery & Development

Identify disease

Drug Design
- Molecular Modeling
- Virtual Screening



Isolate protein involved in disease (2-5 years)

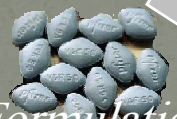


Find a drug effective against disease protein (2-5 years)

Preclinical testing (1-3 years)

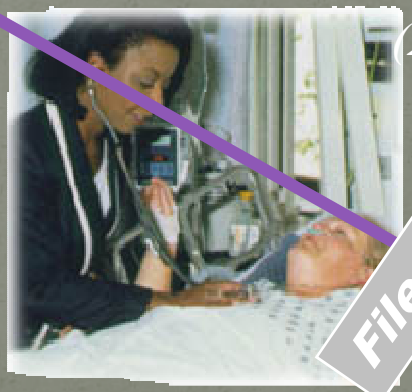
Scale-up

File IND

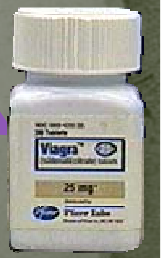


Formulation

Human clinical trials (2-10 years)



File NDA



FDA approval (2-3 years)

Drug designing is:

1)challenging

2)Expensive

3)Time consuming

So, Multidisciplinary approach:

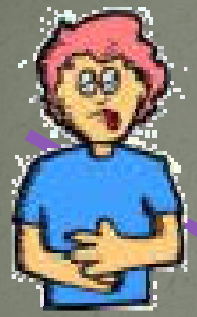
Computational tools, methodologies for structure guided approach + Global gen expression data analysis by softwares.

Hence,

1) Efficiency increased
2) Cost effectiveness
3) Time saved
4) Strategies to overcome toxic side effects

- Medicinal chemists 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 fierce competition amongst different drug companies .

Technology is impacting this process



Identify disease

GENOMICS, PROTEOMICS & BIOPHARM.

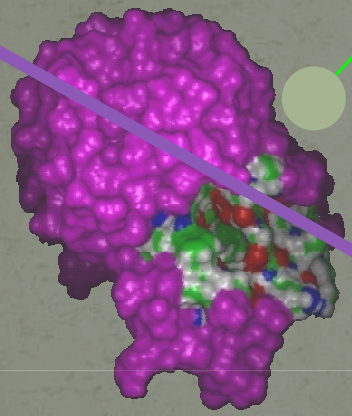
Potentially producing many more targets and "personalized" targets

HIGH THROUGHPUT SCREENING

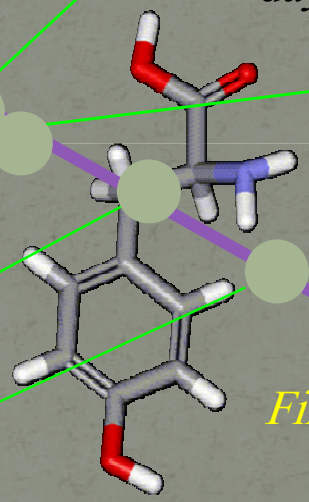
Screening up to 100,000 compounds a day for activity against a target protein

VIRTUAL SCREENING

Using a computer to predict activity



Isolate protein



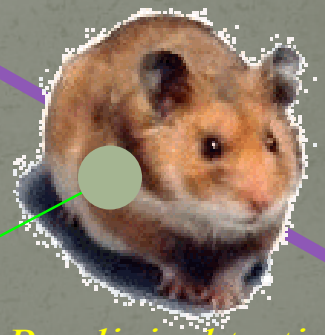
Find drug

COMBINATORIAL CHEMISTRY

Rapidly producing vast numbers of compounds

MOLECULAR MODELING

Computer graphics & models help improve activity



Preclinical testing

IN VITRO & IN SILICO ADME MODELS

Tissue and computer models begin to replace animal testing

Drug Discovery overview

Approaches to drug discovery:

- Serendipity (luck)
- Chemical Modification
- Screening
- Rational

Drug Design

2 ways:

A) Development of ligands with desired properties for targets having known structure and functions.

B) Development of ligands with predefined properties for targets whose structural information may be or may not be known.

This, unknown target information can be found by global gene expression data.

First generation Rational approach in Drug design

- In 1970s the medicinal chemists considered molecules as topological entities in 2 dimension (2D) with associated chemical properties.
- QSAR concept became quite popular. It was implemented in computers and constituted first generation rational approach to drug design

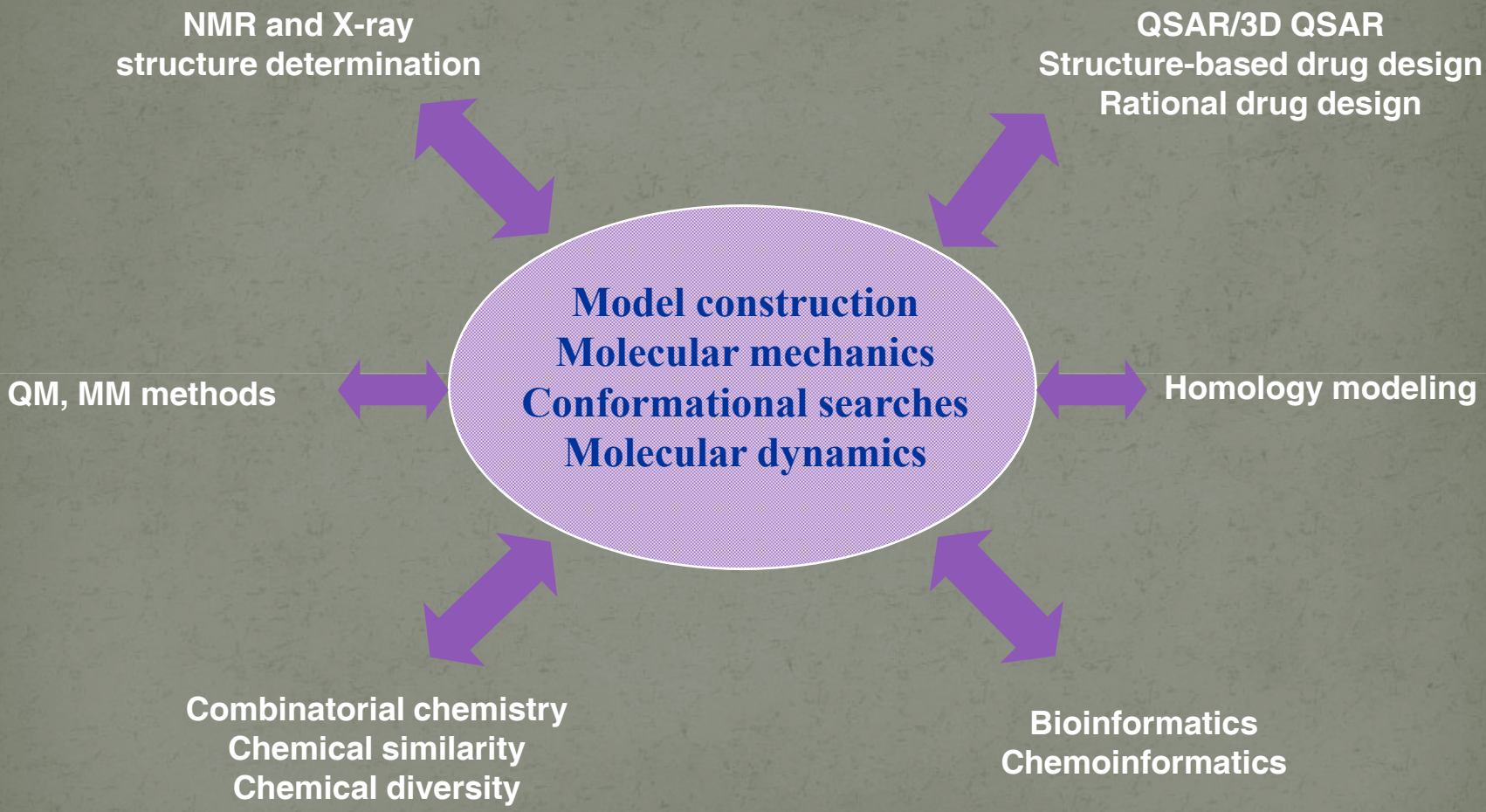
2nd generation rational drug design

- **The acceptance by medicinal chemists of molecular modeling was favored by the fact that the QSAR was now supplemented by 3D visualization.**
- **The "lock and key" complementarily is actually supported by 3D model. Computer aided molecular design (CAMD) is expected to contribute to intelligent lead .**

Evolutionary drug designing

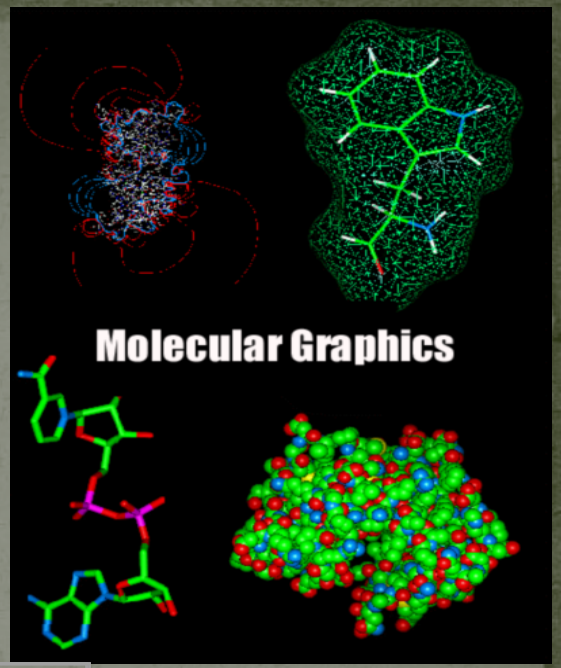
- Ancient times: Natural products with biological activities used as drugs.
- Chemical Era: Synthetic organic compounds
- Rationalizing design process: SAR & Computational Chemistry based Drugs
- Biochemical era: To elucidate biochemical pathways and macromolecular structures as target as well as drug.

Molecular Modeling



What is Molecular Modeling?

- **Molecular Graphics**: Visual representation of molecules & their properties.



- **Computational Chemistry**: Simulation of atomic/molecular properties of compound through computer solvable equations.

$$\Sigma\Sigma\ (b'-b'_0)[V_1\cos\phi]\ b'\phi\ \Sigma\Sigma\ (\theta-\theta_0)\ [V_1\cos\phi]$$

- **Statistical Modeling**: D-R, QSAR/3-D QSAR Molecular data
- **Information Management**: Organizational databases retrieval /search & processing of properties of 1000… of compounds.

MM = Computation + Visualization + Statistical modeling + Molecular Data Management

COMPUTATIONAL TOOLS: QM/MM

(A) MOLECULAR MECHANICS (MM)

(B) QUANTUM MECHANICS (QM)

COMPUTATIONAL TOOLS

Quantum Mechanics (QM)

- ***Ab-initio*** **and semi-empirical methods**
- **Considers electronic effect & electronic structure of the molecule**
- **Calculates charge distribution and orbital energies**
- **Can simulate bond breaking and formation**
- **Upper atom limit of about 100-120 atoms**

COMPUTATIONAL TOOLS

Molecular Mechanics (MM)

- Totally empirical technique applicable to both small and macromolecular systems
- a molecule is described as a series of charged points (atoms) linked by springs (bonds)
- The potential energy of molecule is described by a mathematical function called a FORCE FIELD

When Newton meets Schrödinger...

Sir Isaac Newton (1642 - 1727)

$$F = ma$$

Erwin Schrödinger (1887 - 1961)

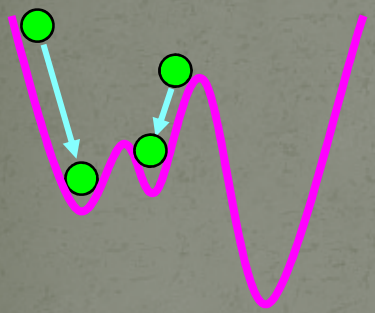
$$\hat{H}\Psi = \varepsilon\Psi$$

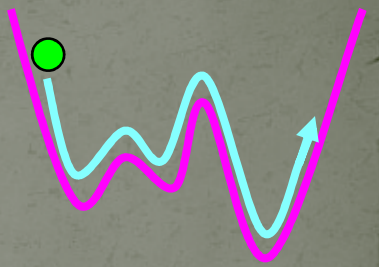
When Quantum Chemistry Starts to Move...

Traditional QC Methods

Mixed Quantum-Classical

Classical MD Simulations





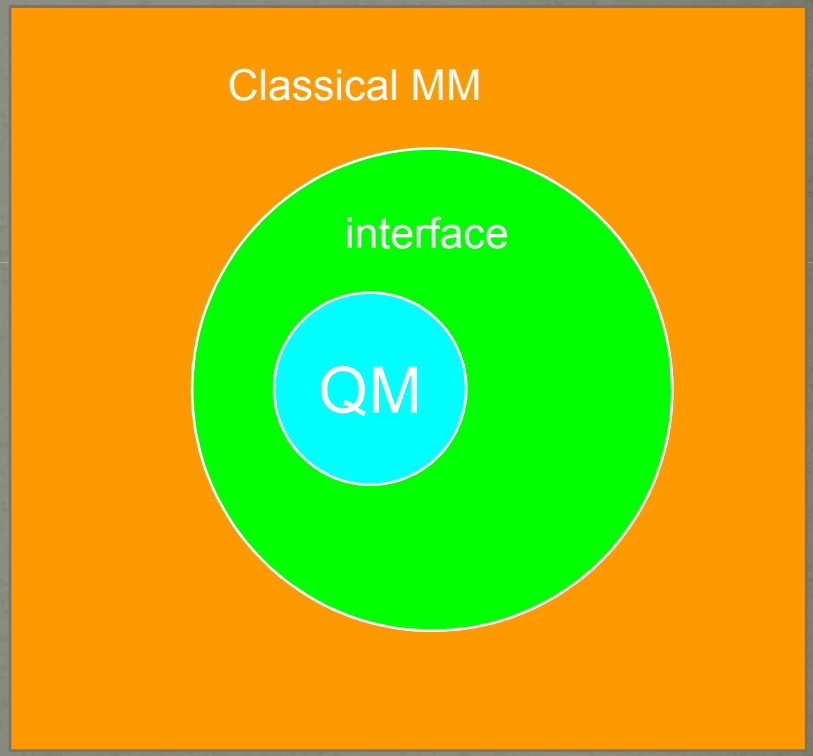
First-Principles Car-Parrinello MD

Mixed Quantum-Classical in a complex environment - QM/MM

Main idea

Partitioning the system into

1. **chemical active** part treated by QM methods
2. Interface region
3. large **environment** that is modeled by a classical force field



Mixed Quantum-Classical in a complex environment - QM/MM

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Basic modeling Strategies

		Receptor Structure	
		Unknown	**Known**
Ligand Structure	**Unknown**	Generate 3D structures, Similarity/dissimilarity Homology modelling HTS, Comb. Chemistry (Build the lock, then find the key)	Active Site Search Receptor Based DD de NOVO design, 3D searching (Build or find the key that fits the lock)
	Known	Indirect DD Ligand-Based DD Analogs Design 2D/3D QSAR & Pharmacophore	Rational Drug Design (Structure-based DD) Molecular Docking (Drug-Receptor interaction)

Computer Aided Drug Design Techniques

- Physicochemical Properties Calculations
    - Partition Coefficient (LogP), Dissociation Constant (pKa) etc.
- Drug Design
    - Ligand Based Drug Design
        - QSARs
        - Pharmacophore Perception
    - Structure Based Drug Design
        - Docking & Scoring
        - de-novo drug design
- Pharmacokinetic Modeling (QSPRs)
    - Absorption, Metabolism, Distribution and Toxicity etc.
- Cheminformatics
    - Database Management
    - Similarity / Diversity Searches

-All techniques joins together to form VIRTUAL SCREENING protocols

Quantitative Structure Activity Relationships (QSAR)

- QSARs are the mathematical relationships linking chemical structures with biological activity using physicochemical or any other derived property as an interface.

Biological Activity = f(Physico-chemical properties)

- Mathematical Methods used in QSAR includes various regression and pattern recognition techniques.
- Physicochemical or any other property used for generating QSARs is termed as Descriptors and treated as independent variable.
- Biological property is treated as dependent variable.

QSAR and Drug Design

Compounds + biological activity

New compounds with improved biological activity

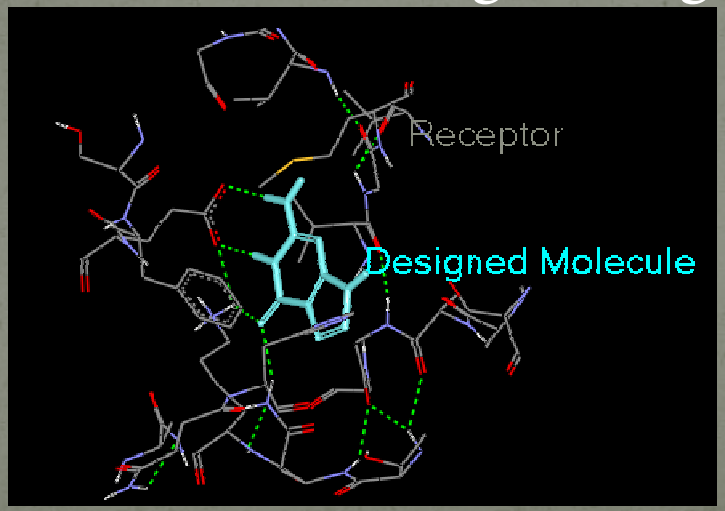
Receptor-based Drug Design

•Examine the 3D structure of the biological target (an X-ray/ NMR structure.

•Hopefully one where the target is complexed with a small molecule ligand (Co-crystallized)

•Look for specific chemical groups that could be part of an attractive interaction between the target protein and the ligand.

•Design a new ligands that will have sites of complementary interactions with the biological target.

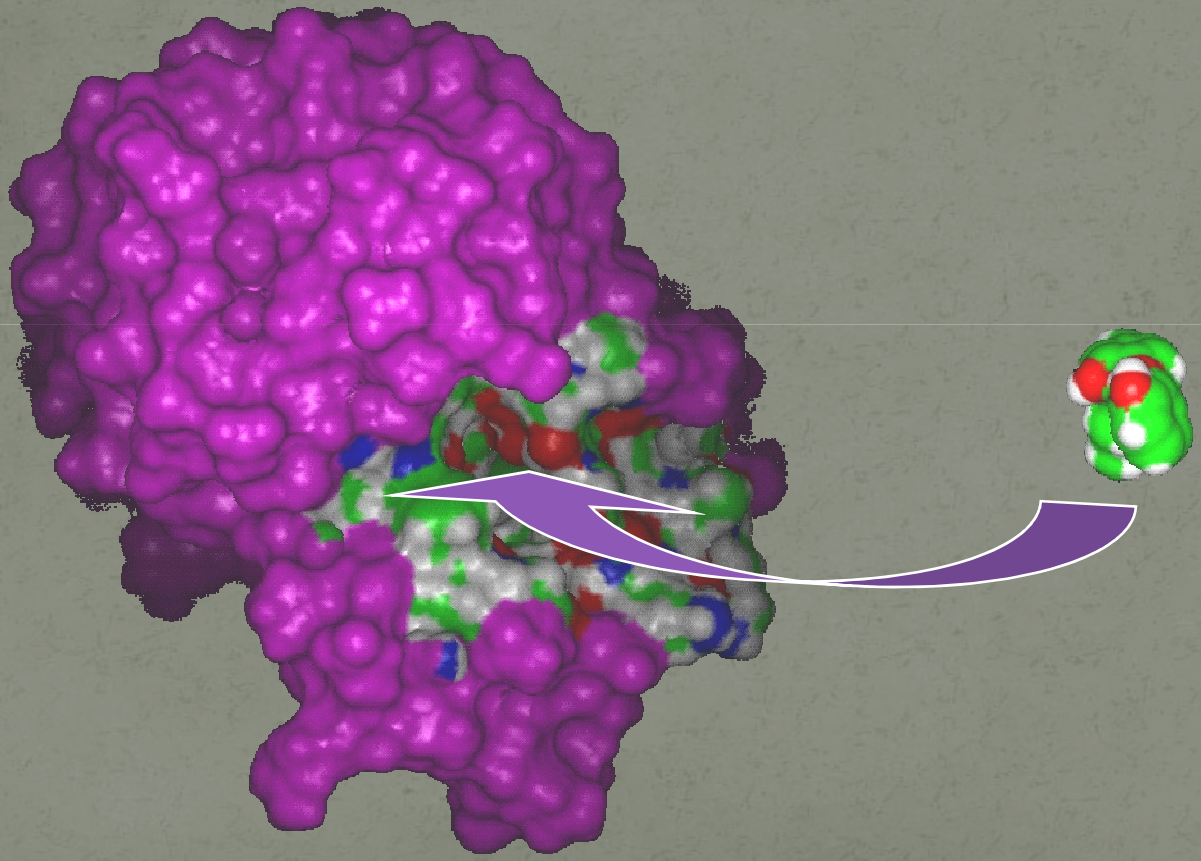


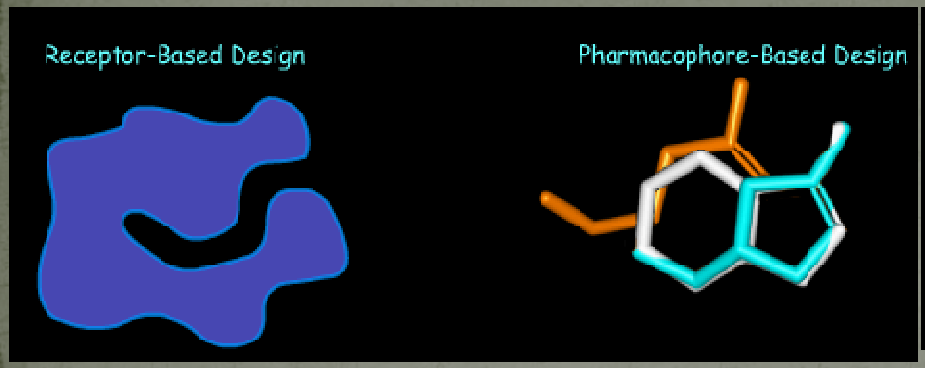
Advantage: Visualization allows direct design of molecules

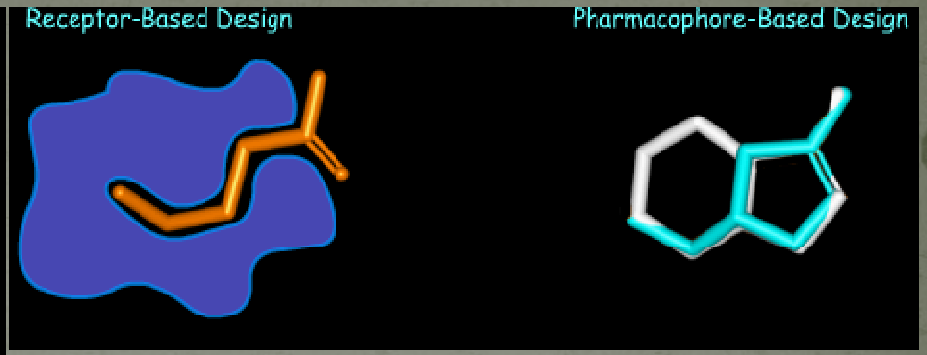
Docking Process

- Put a compound in the approximate area where binding occurs
- Docking algorithm encodes orientation of compound and conformations.
- Optimize binding to protein
  - Minimize energy
  - Hydrogen bonding
  - Hydrophobic interactions
- Scoring

“Docking” compounds into proteins computationally

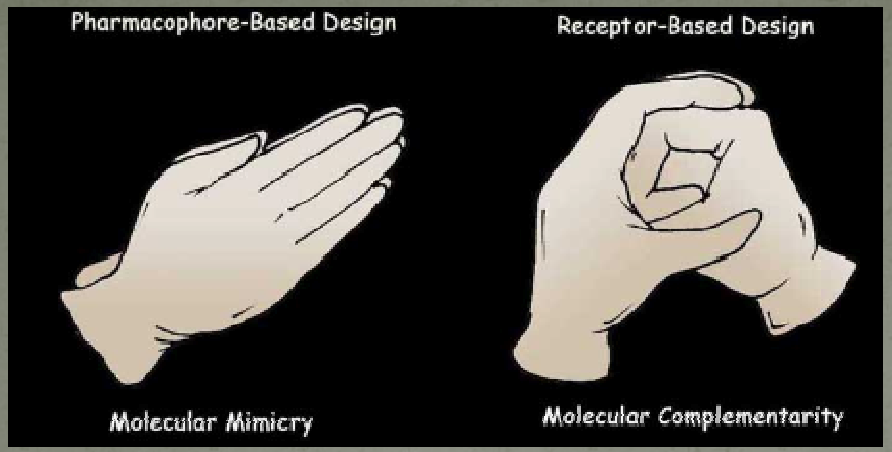




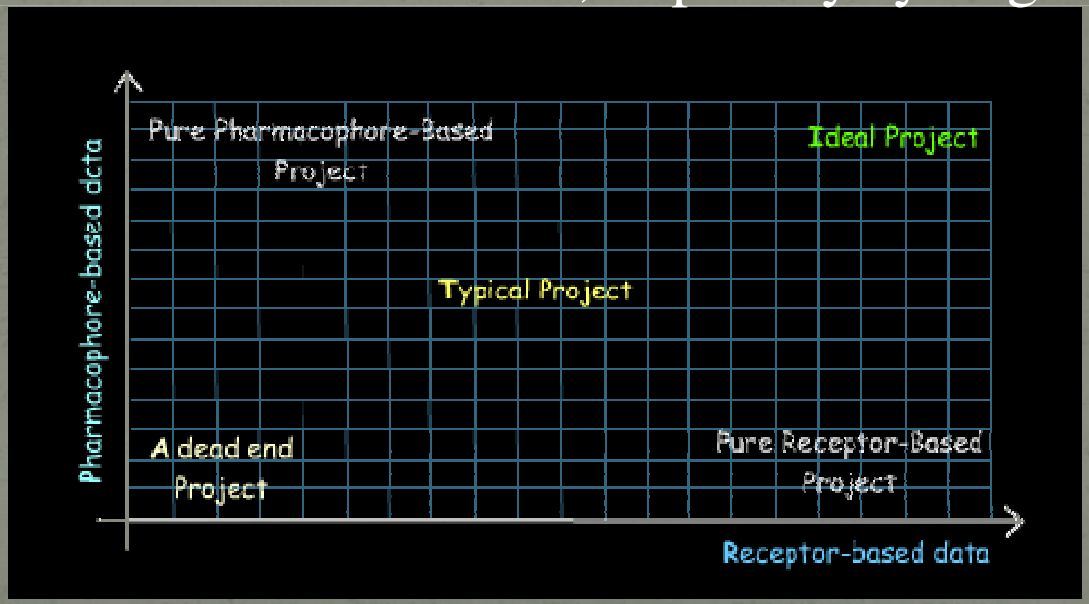


- Can pursue both receptor and pharmacophore-based approaches independently
- If the binding mode of the ligand and target is known, information from each approach can be used to help the other

Ideally, identify a structural model that explains the biological activities of the known small molecules on the basis of their interactions with the 3D structure of the target protein.



Typical projects are not purely receptor or pharmacophore-based; they use combination of information, hopefully synergistically

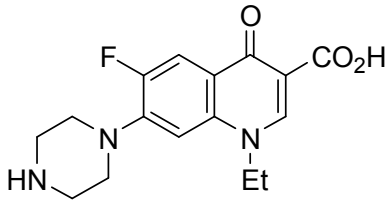


Drug Design Successes (Fruits of QSAR)

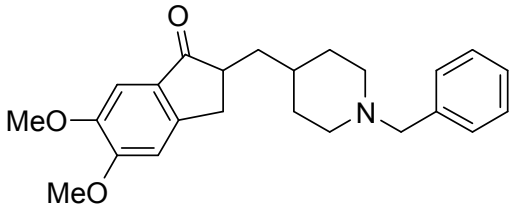
Name of the drug discovered	Biol. Activity
1. Erythromycin analogs	Antibacterial
2. New Sulfonamide dervs.	Antibacterial
3. Rifampicin dervs.	Anti-T.B.
4. Napthoquinones	Antimalerials
5. Mitomycins	Antileukemia
6. Pyridine –2-methanol's	Spasmolytics
7. Cyclopropalamines	MAO inhibitors
8. β-Carbolines	MAO Inhibitors
9. Phenyl oxazolidines	Radioprotectives
10.Hydantoin dervs.	Anti CNS-tumors
11.Quinolones	Antibacterial

Drug Design Successes

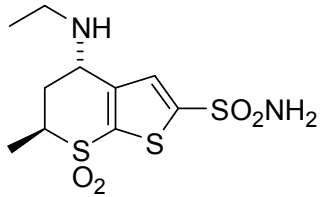
While we are still waiting for a drug *totally* designed from scratch, many drugs have been developed with major contributions from computational methods



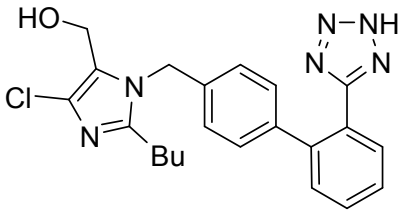
norfloxacin (1983)
antibiotic
first of the 6-fluoroquinolones
QSAR studies



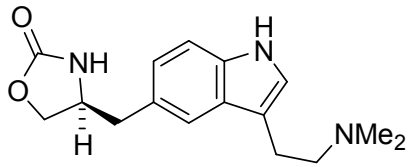
donepezil (1996)
Alzheimer's treatment
acetylcholinesterase inhibitor
shape analysis and docking studies



dorzolamide [Trusopt] (1994)
glaucoma treatment
carbonic anhydrase inhibitor
SBLD and *ab initio* calcs



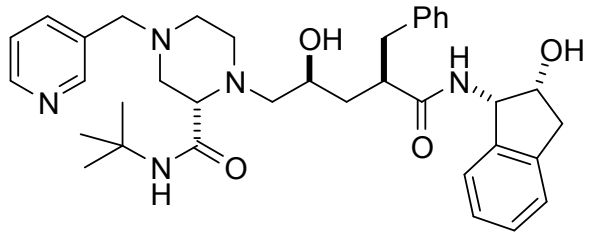
losartan [Cozaar] (1995)
angiotensin II antagonist
anti-hypertensive
Modeling Angiotensin II octapeptide



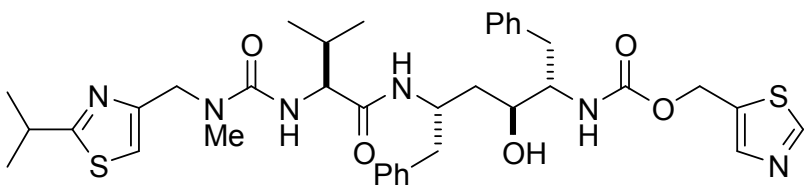
zolmatriptan [Zomig] 1995
5-HT_{1D} agonist
migraine treatment
Molecular modeling

Drug Design Successes-2

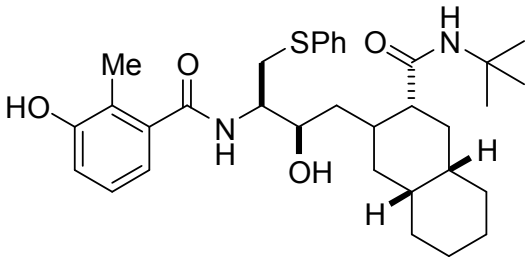
HIV-1 protease inhibitors



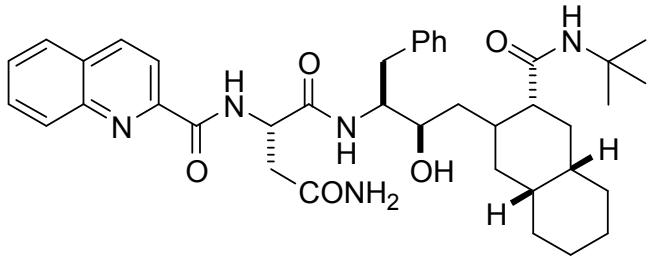
indinavir [Crixivan] (Merck, 1996)
X-ray data from enzyme and molecular mechanics



ritonavir [Norvir] (Abbott, 1995)
peptidomimetic strategy



nelfinivir [Viracept] (Agouron, 1996)



saquinavir [Invirase, Fortovase] (Roche, 1990)
transition state mimic of enzyme substrate

SUMMARY

Drug Discovery is a multidisciplinary, complex, costly and intellect intensive process.

Modern drug design techniques can make drug discovery process more fruitful & rational.

Knowledge management and technique specific expertise can save time & cost, which is a paramount need of the hour.

Thank you very much