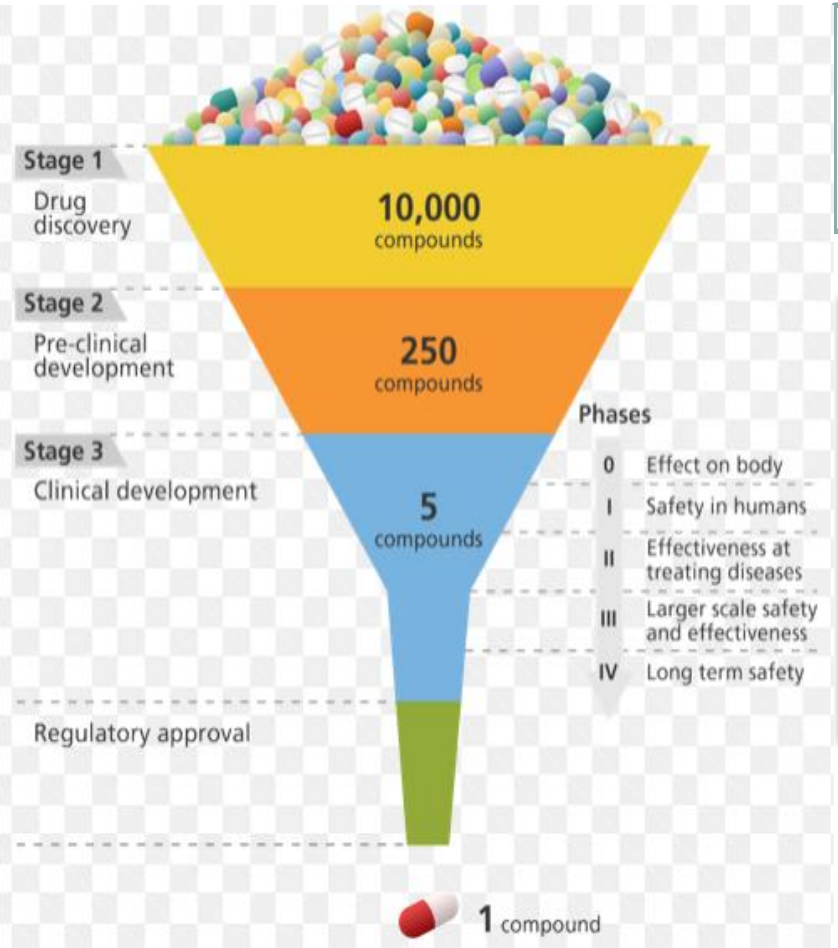
Introduction to Drug Design and Discovery



Course: Drug Design
Course code: 0510518

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Learning Outcomes

At the end of this lesson students will be able to

- Outline the entire process involved in the drug discovery and computer-aided drug design (DD) methodologies.
- Outline the entire process involved to Explain structure-based DD Including the molecular docking technique.
- Describe about QSAR and pharmacophore modeling in ligand-based DD.
- Explain the steric-electronic modifications in de novo drug design method.
- Define the interdisciplinary contribution as well as the key role of medicinal chemists in drug discovery and DD.
- Explain the clinical trials in drug discovery process.

Introduction to Drug Design and Discovery

Medicinal Chemistry is the science that deals with the discovery and design of new therapeutic chemicals or biochemicals and their development into useful medicines.

Medicines: substances used to treat diseases.
Drugs: molecules used as medicines or as components in medicines to diagnose, cure, mitigate, treat, or prevent disease.

Drug acting on different targets

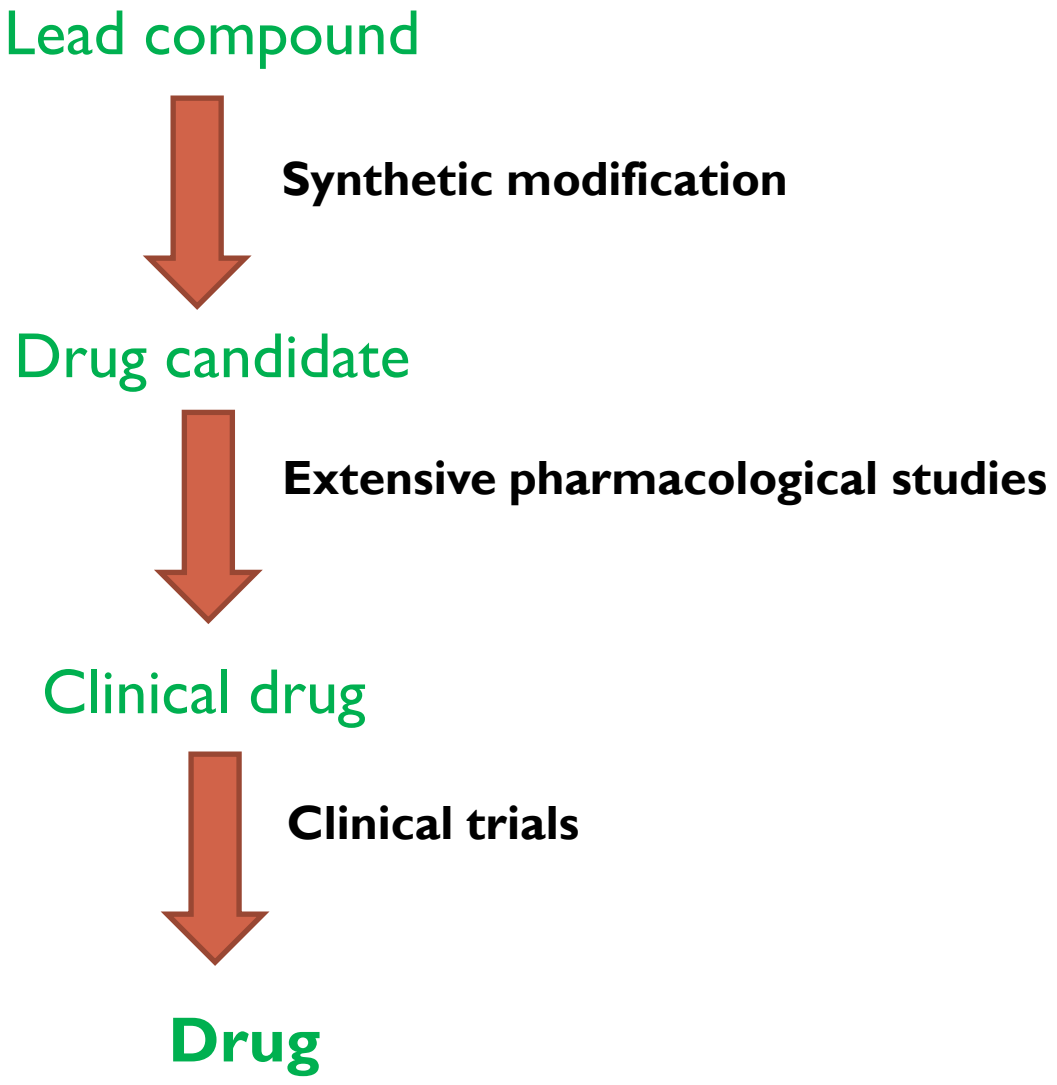
- Enzyme, transporter: inhibitor,
- Receptor - agonists or antagonists.
- DNA, Ion channel : blockers

Role of Medicinal Chemists

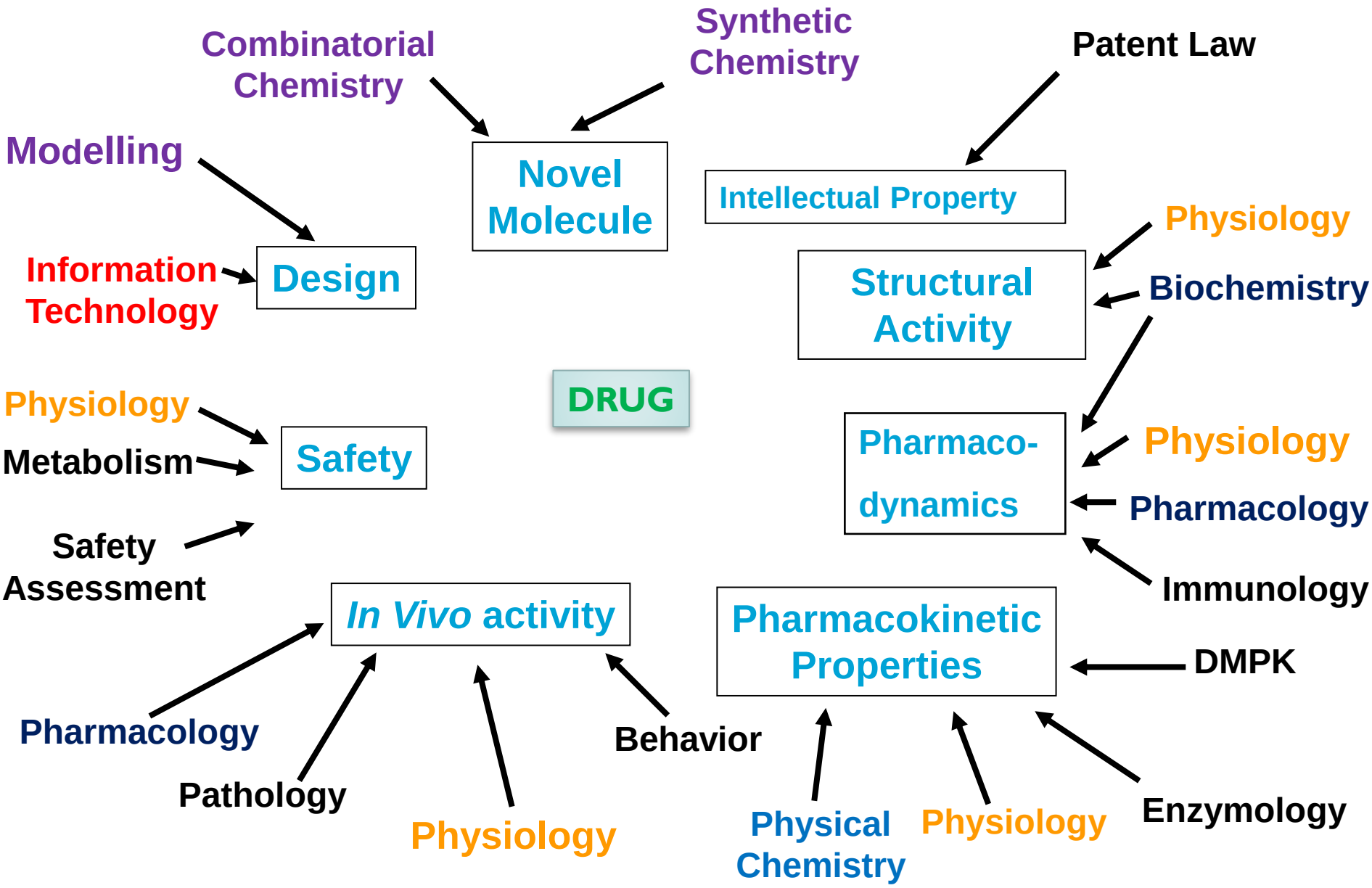
- Isolation of compounds from nature.
- Synthesis of new molecules.
- Investigations of the relationships between the structure of compounds (natural and/or synthetic) and their biological activities (SAR).
- Elucidation of the drug-protein interactions.
- Determination of pharmacokinetic (PK) properties of drugs.

  - ✓ Absorption (A)
  - ✓ Distribution (D)
  - ✓ Metabolism (M)
  - ✓ Elimination (E)
  - ✓ Toxicity (T)

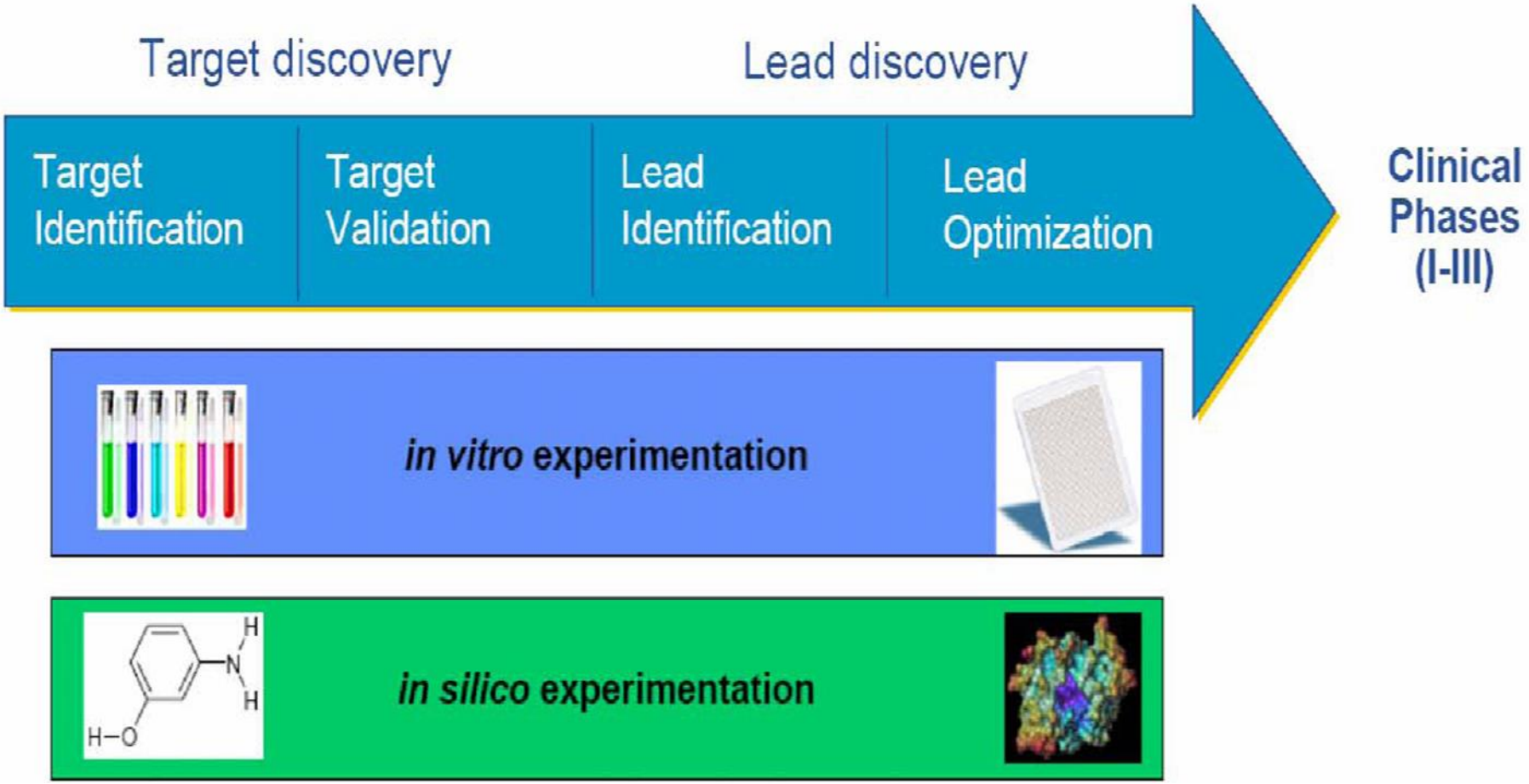
Lead to Drug Development



Drug Discovery—Merging of Disciplines



- **Problem: development of a drug takes 12 to 15 years and costs approximately 800 million dollars**

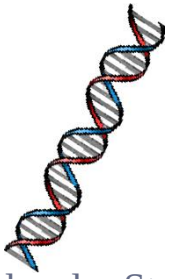


Target selection & validation

Discovery

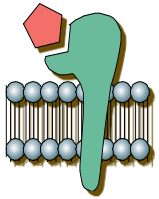
Development

Studies of
Disease Mechanisms



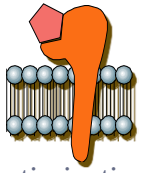
Molecular Studies

Animal Studies
- relevant species
- transgenic KO/KI mice
- conditional KOs
- agonists/antagonists
- antibodies
- antisense
- RNAi



Target
-receptor; -ion channel; -transporter;
-enzyme; - signalling molecule

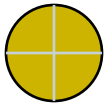
Lead Search
-Develop assays (use of automation)
-Chemical diversity
-Highly iterative process



Lead optimization
-selectivity
-efficacy in animal models
-tolerability: AEs mechanism-
based or structure-based?
-pharmacokinetics
-highly iterative process

Drug Candidate
safety testing

Human Studies
Phases I,II, III



Drug Approval
and Registration

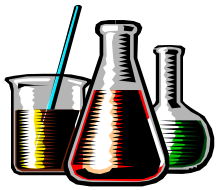
Development

Pre-Clinical

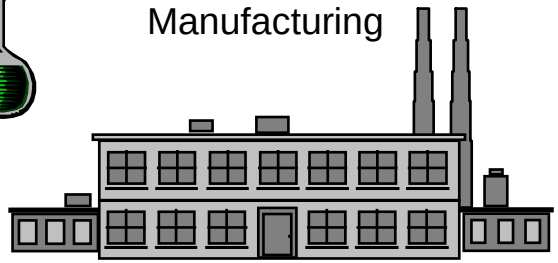
Safety Assessment
Toxicology

Drug Metabolism
(ADME)

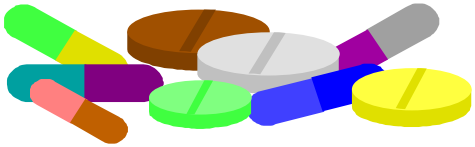
Pharmacology



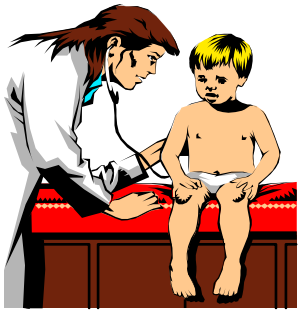
Process R&D
Chem Eng. R&D
Manufacturing



Pharmaceutical R&D
Formulation



Bio Process R&D



Clinical Investigator
& patient

Clinical Pharmacology
Clinical Research

Regulatory Affairs
Project Planning & Management
Marketing

Statistics & Epidemiology
Data Coordination
Research Information Systems
Information Services

Clinical

Investigational New Drug

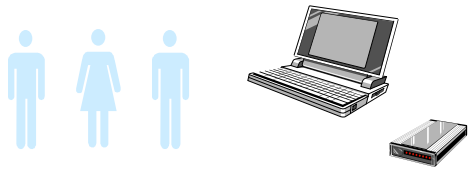
IND

application

Clinical Trials

Phase I

20 - 100 healthy volunteers take drug for about one month



Remote data entry

Outcome
1. Absorption and metabolism
2. Effects on organs and tissue
3. Side effects as dosage is increased

Phase II

Several hundred health-impaired patients

Treatment Group Control Group

Outcome
1. Effectiveness in treating disease
2. Short-term side effects in health -impaired patients
3. Dose range

Phase III

Hundreds or thousands of health-impaired patients

Outcome
1. Benefit/risk relationship of drug
2. Less common and longer term side effects
3. Labeling information

Compassionate Use

Clinical Trials Continued

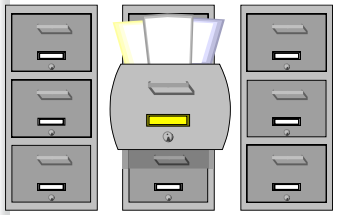
Advisory Committee

Regulatory Review Team

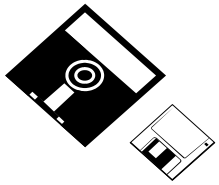
APPROVAL PROCESS
(Ex. FDA)

Reviews, comments, and discussions

Submit to Regulatory Agencies



New Drug Application (NDA)



Drug Co./Regulatory liaison activities

Worldwide Marketing Authorization (WMA) in other countries

Clinical trials-Different Phases

- Phase-I (lasts for 1 month -1 year): Evaluation of the safety, tolerability, pharmacokinetic and pharmacological activity of drugs on 20-100 volunteers.

- Phase-II (lasts for 1-3 years): further assess the efficacy , safety of drugs in addition to dosing regimen in 300-600 patients.

- Phase-III (last for 2-6 years): covers several thousands of patients in clinics or hospitals; study the activity and possible side effects on the long term.

- Phase-IV: Post marketing feedback, after prescribing drugs to the out patients.

Major steps involved in any drug discovery process

Target identification (to identify the potential biological target of the disease)

↓

Target validation (to make sure that the selected biological target is suitable and valid)

↓

Lead Identification (to identify suitable molecules bind to the validated target)

↓

Lead Modificiation (based on the properties, the identified lead can be modified to reduce toxicity, side effects, etc)

↓

Synthesis of compounds

↓

In-vitro evaluation by different biological assays (lab testing)

↓

In-vivo evaluation (testing new compounds using animal models for activity and toxicity)

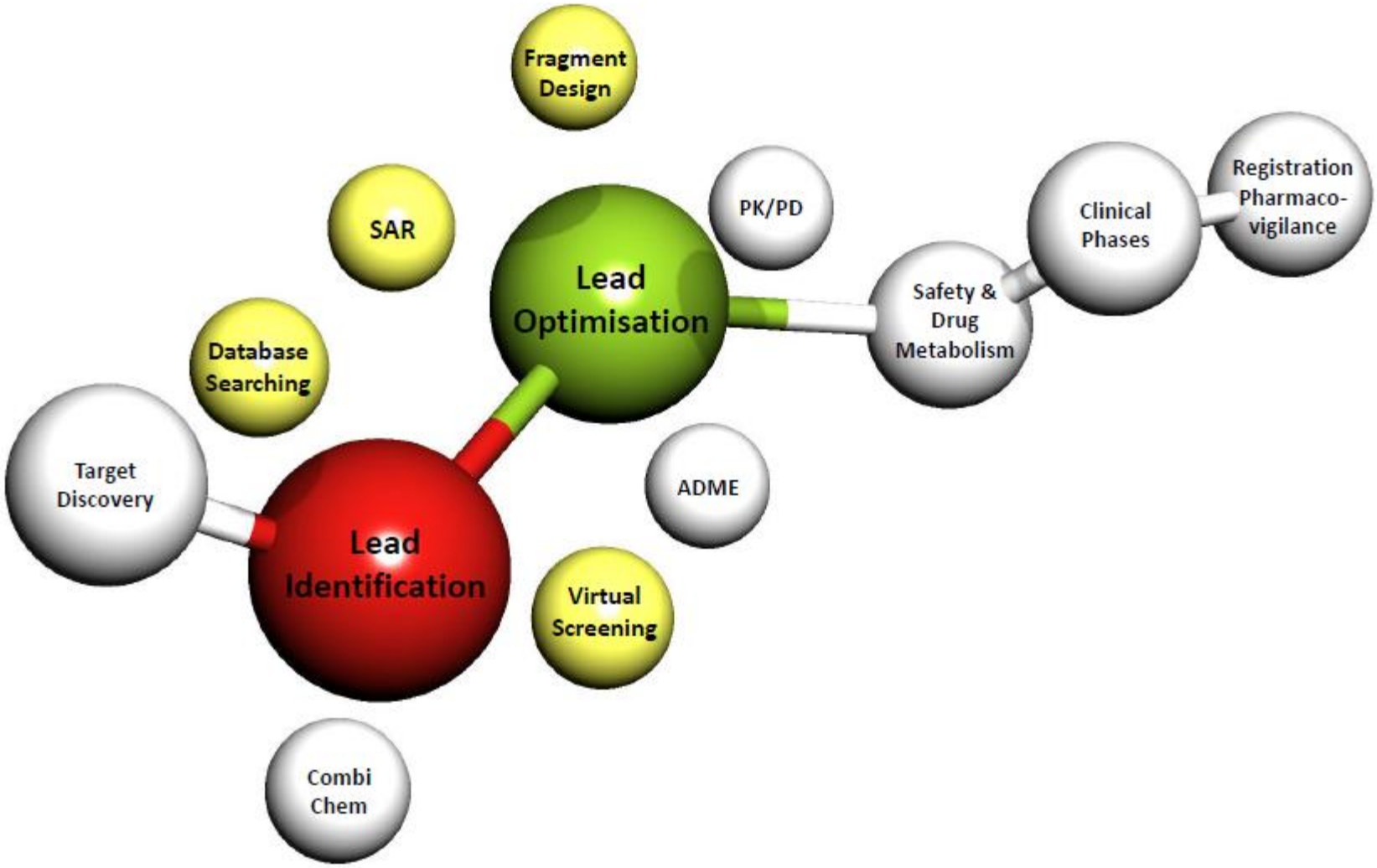
↓

Clinical Trials (Phase-I: Drug evaluation involving human healthy volunteers
Phase-II: Drug evaluation involving small number of patients for testing activity, dosing and side effects)
Phase-III: Drug evaluation involving large number of on patients to test activity and toxicity at the long term side effects)
Phase-IV: Post marketing survey: Drug follow up after market release to report any new side effects and complications)

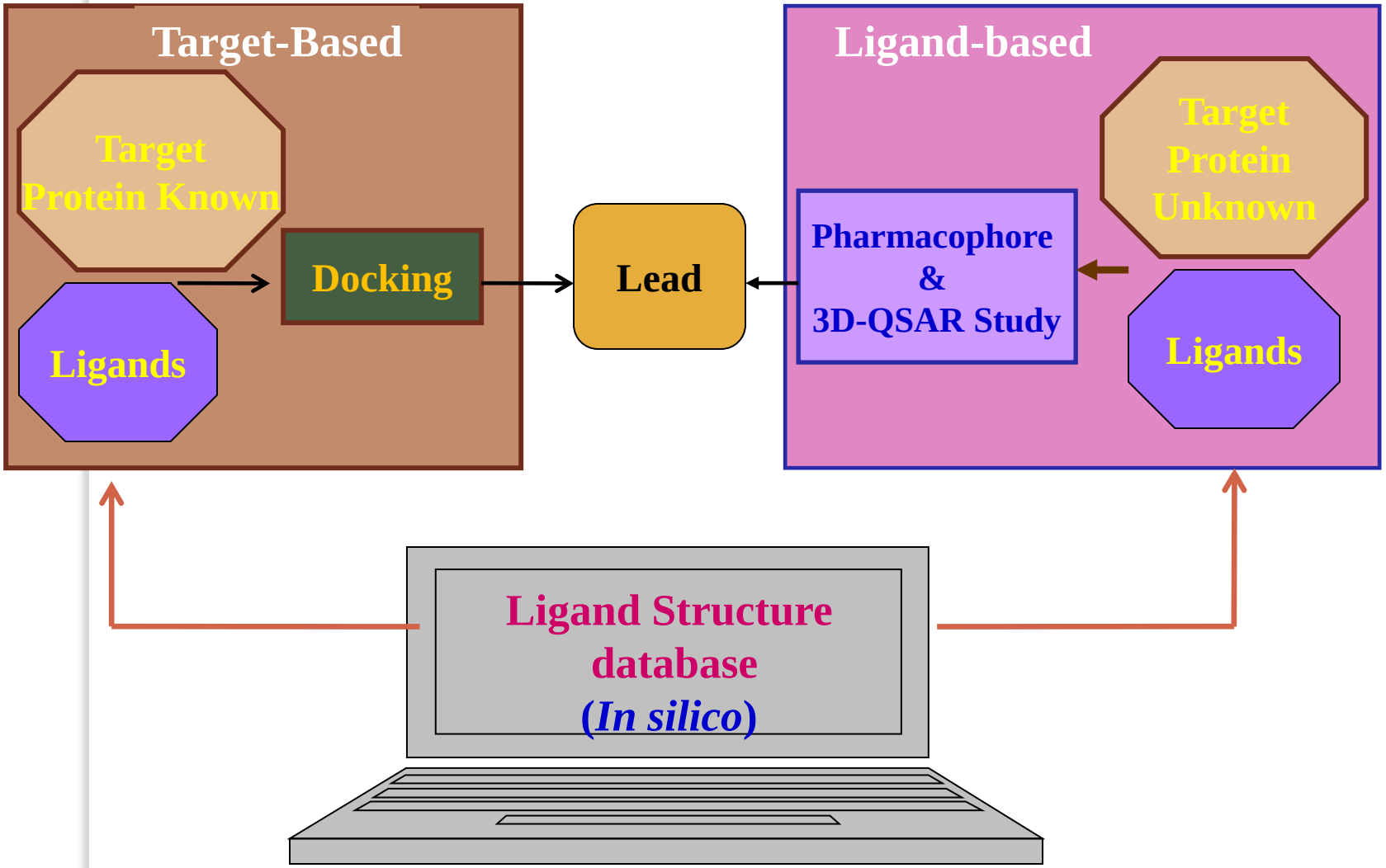
↓

In-vitro evaluation by different biological assays (lab testing)

Drug Design


Fragment Design
SAR
PK/PD
Lead Optimisation
Clinical Phases
Registration Pharmaco-vigilance
Safety & Drug Metabolism
Database Searching
Target Discovery
ADME
Lead Identification
Virtual Screening
Combi Chem

Drug Design Strategies Based on Molecular Mechanics



Molecular Modeling: Computer Aided Drug Design

Molecular Mechanics

Quantum Mechanics

Structure-based Drug Design
or
Target-based Drug Design
(Docking Studies)

Ligand-based Drug Design

- QSAR Studies (2D, 3D etc.)
- Pharmacophore Mapping

Three-dimensional (3D) Structure of Target Known (Receptor/enzyme)

Specify the binding site surrounding the bound co-crystal ligand

Three-dimensional (3D) Structure of Target NOT Known/available

Homology Modeling of Target protein / receptor

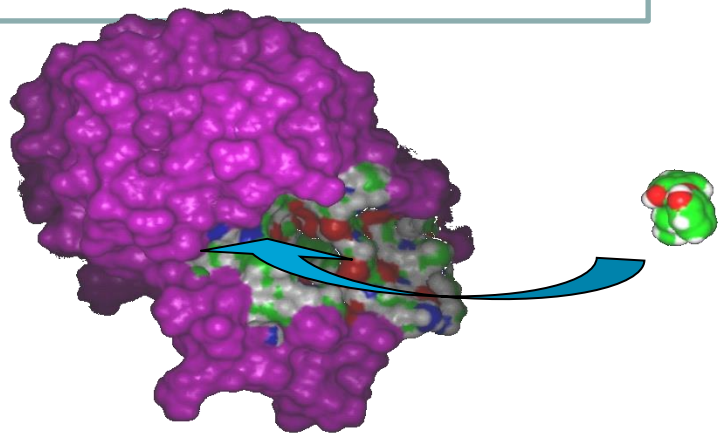
Search / Identify binding site in Homology Model

Specify the binding-site

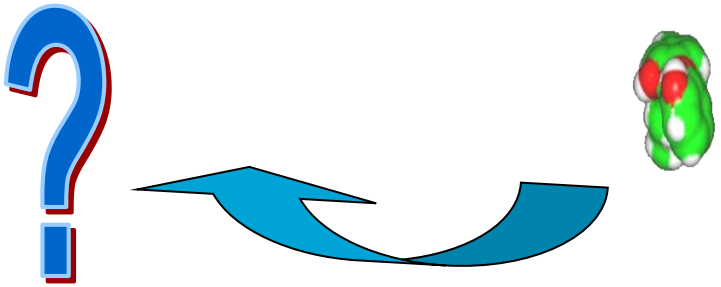
Docking studies

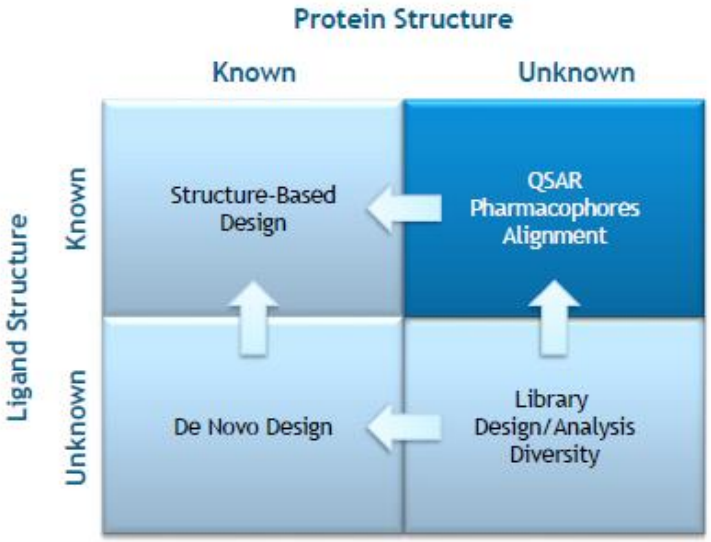
Drug Design

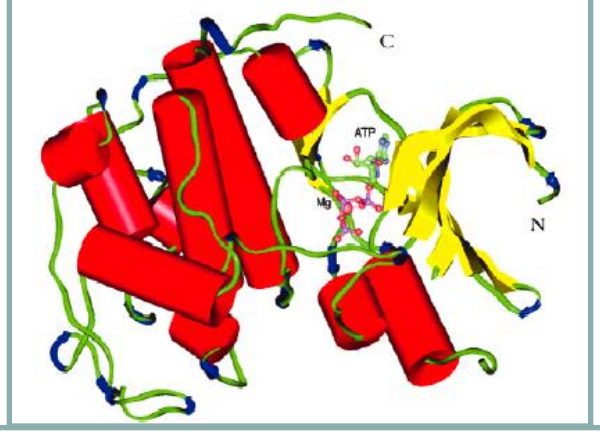
Structure based

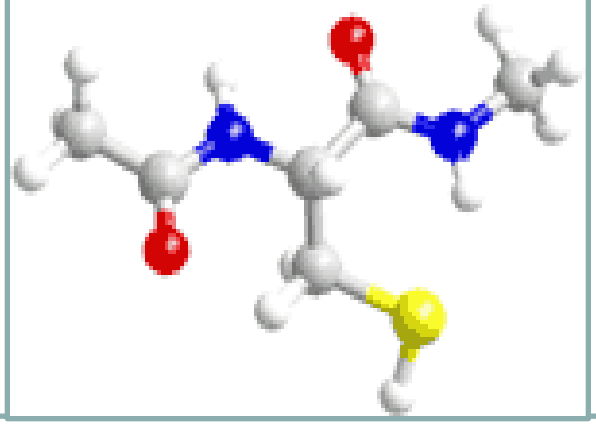


Ligand based









Target (structure) based drug design

- Receptor structure is known
- Mechanism is known
- Ligands and their biological activities are known/ unknown

Ligand (analog) based drug design

- Receptor structure is not known
- Mechanism is known/ unknown
- Ligands and their biological activities are known

Ligand-based Approach:

- Statistical analysis of the relationships between molecular structures and their descriptors to provide correlations for predicting biological activities (QSAR)
- Exploring common pharmacophore features amongst a set of active compounds (Pharmacophore modeling)
- Deriving predictive models if SAR data is available (QSAR and Pharmacophore modeling)
- Searching for compounds with similar properties (Library analysis & Pharmacophore modeling)

Structure-based Drug Design

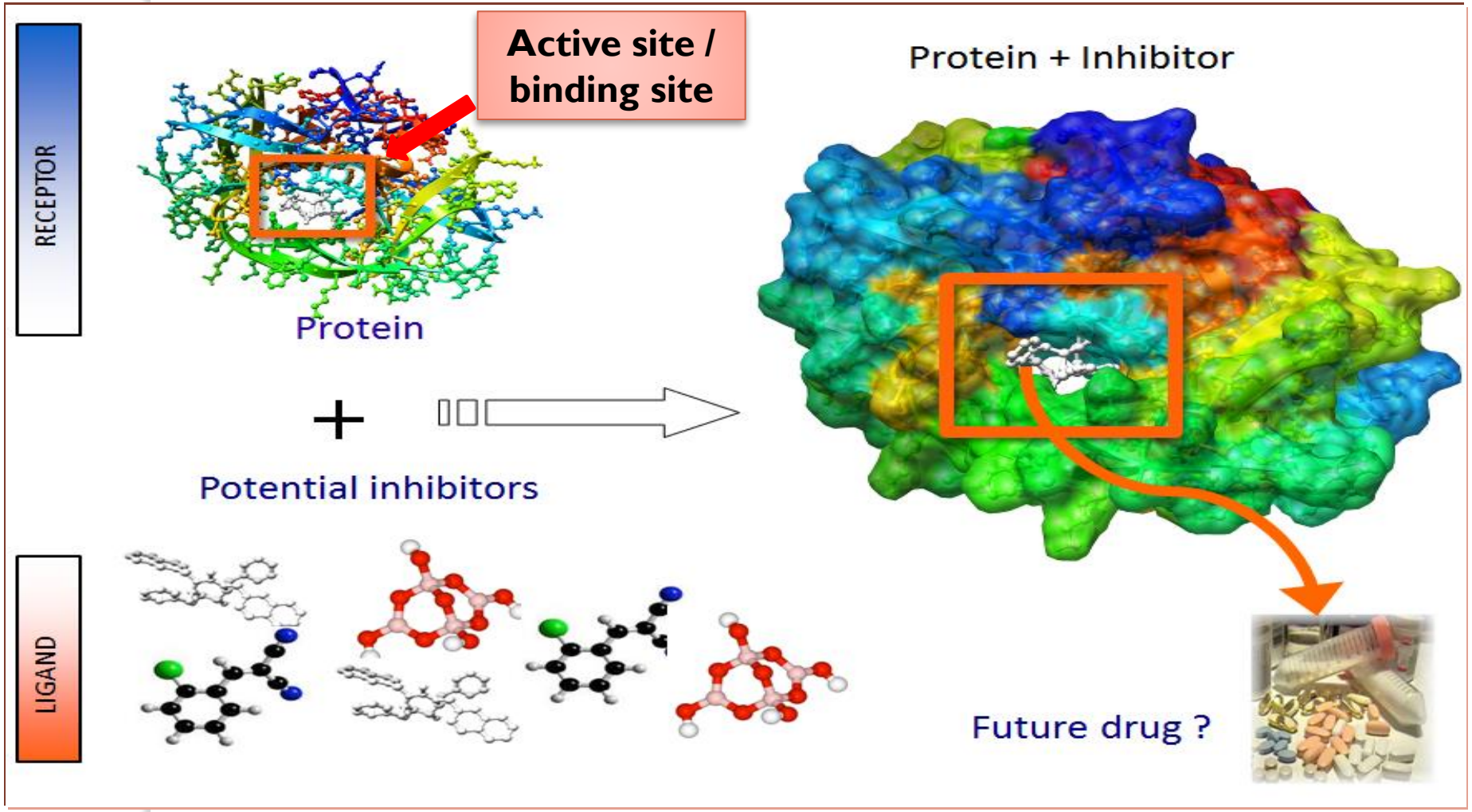
- Structure-based drug design:
  - The macromolecular target can be isolated and crystallized…then the structure will be determined using X-ray crystallography.
  - This structure will not give information about the binding site.
  - The co-crystal structure (structure of protein with the inhibitor inside) is better (WHY?):
    - Where is the active site?
    - The distance between inhibitor and binding site boundaries.
    - The possible bonds between inhibitor and binding site.

How to use co-crystal structure in drug design

- First the inhibitor will be removed from the active site (*in silico*).
- The enzyme structure will be minimized to get the lowest energy state.
- Then lead compounds will be inserted (docked) into the active site to see how they fit.
- Best fit compounds will be synthesized and tested for activity.

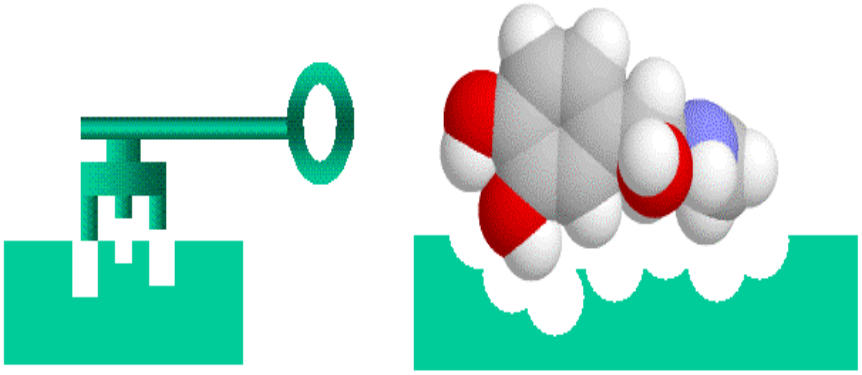
Structure-based (target-based) Drug Design

- It is used to **design a new drug molecule** **based on the knowledge of the three-dimensional (3D) structure of the biological target**.



MOLECULAR DOCKING

- **Docking is the identification of low energy conformation after binding of ligand molecule with biological target (receptor or enzyme).**
- **The compound that binds perfectly to the active site of target and having minimum energy may considered as drug molecule.**
- **The process of "docking" a ligand to a binding site of a target mimics the natural course of interaction of the ligand and its target (receptor or enzyme) via the lowest energy pathway.**



WHY DOCKING?

- Drug work by interacting with biological target (receptor/enzyme)
- Docking helps to decide a candidate drug will interact appropriately with a target protein?
- Examine binding model of known ligands to suggest modification.
- Screen databases of 3D structure to find novel ligands.
- Drug interaction with receptor can be as an agonist or an antagonist.

Types to Docking

- Ligand-protein docking
- Protein-protein interaction
- Protein–DNA interaction

Approaches to Docking	Ligand	Target receptor/ enzyme
Rigid body docking	Rigid	Rigid
Semi-flexible docking	Flexible	Rigid
Flexible docking	Flexible	Flexible

Approaches to Docking

A. **Rigid body docking:** Both **target (protein)** and **ligand** are treated as **rigid bodies**.

B. **Semi-flexible docking:** Only the **ligand is** considered as **flexible target (protein) is** considered as **rigid body**

C. **Flexible docking: Both ligand and protein** are treated as **flexible** molecules.

Scoring Functions

During the docking process, they serve as **fitness functions** in the optimization of the **placement of the ligand.**

When the docking is completed, the scoring function is used to **rank each ligand in the database.**

Some common scoring functions are:

1. **Force-field methods**
2. **Empirical free energy scoring functions**
3. **Knowledge-based potential of mean force**

Docking Softwares

Free for Academics:

- DOCK
- AutoDOCK
- Surflex
- FRED
- eHits

Commercial:

- GOLD/Glide/FlexX/Discovery studio-CDOCKER.

If you do not have the crystal structure of your target enzyme

- **Three options:**

  - Use recombinant DNA technology to produce the enzyme using bacterial cell.

  - Use the homologue of this enzyme from other organism such as bacteria or parasite (homology modeling/comparative modeling).

  - Use Ligand Based Drug Design.

Ligand-based Drug Design

- Here the crystal structure of the target enzyme or receptor is not available.
- But their ligands are well defined and characterized.
- This method not involves molecular docking or homology modeling methods.
- This method works based on the concept of 'similar chemical structures have similar chemical activity'.

Ligand-based Drug Design

This method will

- Begin with biologically active compounds.
- Describe what chemistry those compounds have in common.
- Few new compounds that match this description.
- Compounds that match the description will also be active.

Initial two steps involving the process called 'model building' while the final two steps are known as 'database screening'.

Methods in Ligand-based Drug Design

Methods	Description type
Molecular Properties, ADME	Discrete properties
Model building/QSAR	Statistics used in discrete properties
Substructure matching	Discrete 2D substructures
2D fingerprints	'Bitstring model' of 2D structure
Shape-based screening	Overall molecular shape
Field-based QSAR	Molecular field (steric/electrostatic)
3D pharmacophores	Specific arrangement of chemical features (H-bond donors, acceptors, ring aromatic, hydrophobic)

QSAR (Quantitative Structure-Activity Relationship)

- QSAR is a mathematical relationship between a **biological activity** of a molecular system and its **geometric and chemical characteristics**.

A general formula for a quantitative structure-activity relationship (QSAR) can be given by the following:

Activity = f (molecular or fragmental properties)

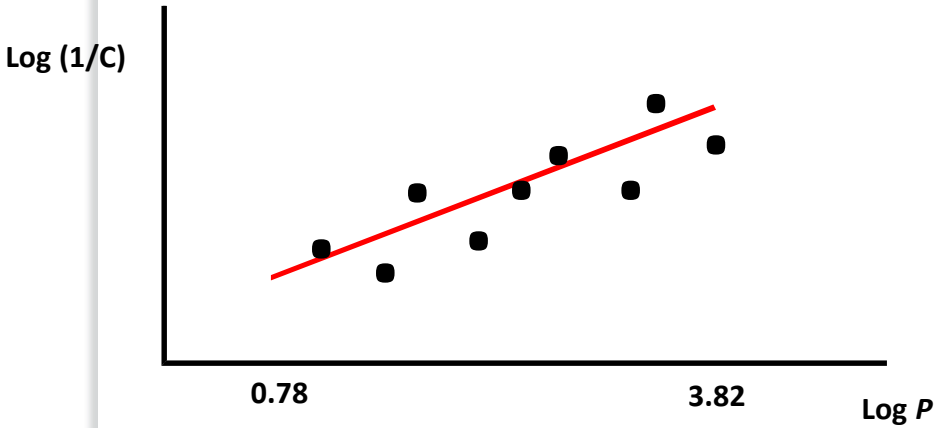
- QSAR attempts to find consistent relationship between biological activity and molecular properties, so that these "rules" can be used to evaluate the activity of new compounds.

QSAR (Quantitative Structure-Activity Relationship)

- ✓ QSAR is a statistical approach that attempts to relate physico-chemical properties of molecules to their biological activities.
- ✓ Various descriptors like molecular weight, number of rotatable bonds, LogP etc. are commonly used in QSAR.

Example: Hydrophobicity Vs Biological Activity

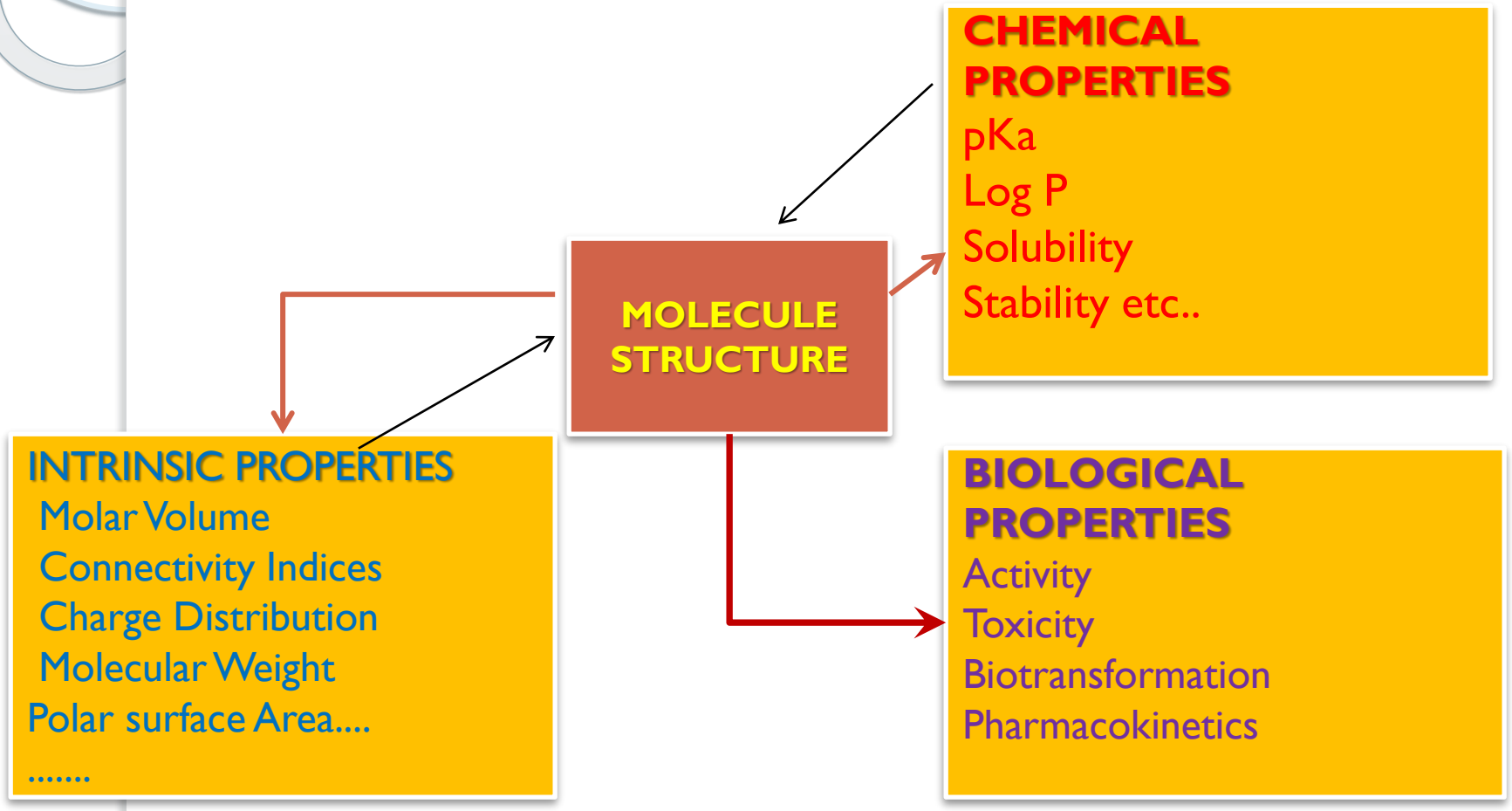
- **Activity of drugs is often related to *P*** **e.g. binding of drugs to serum albumin**
  (straight line - limited range of log *P*)



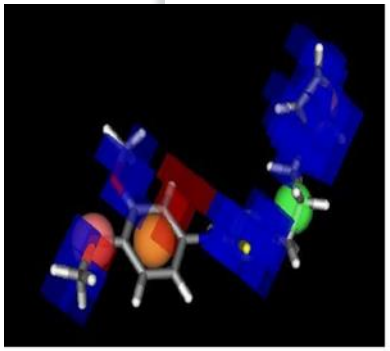
$$\text{Log}\left(\frac{1}{C}\right) = m\log P + C$$

Molecular Properties

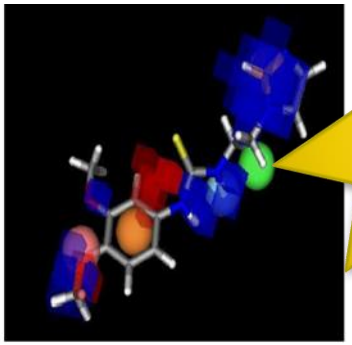
1000's of Structure Properties for Correlation



Types of QSAR Results



Active compound – more blue regions



Less Active compound – less blue

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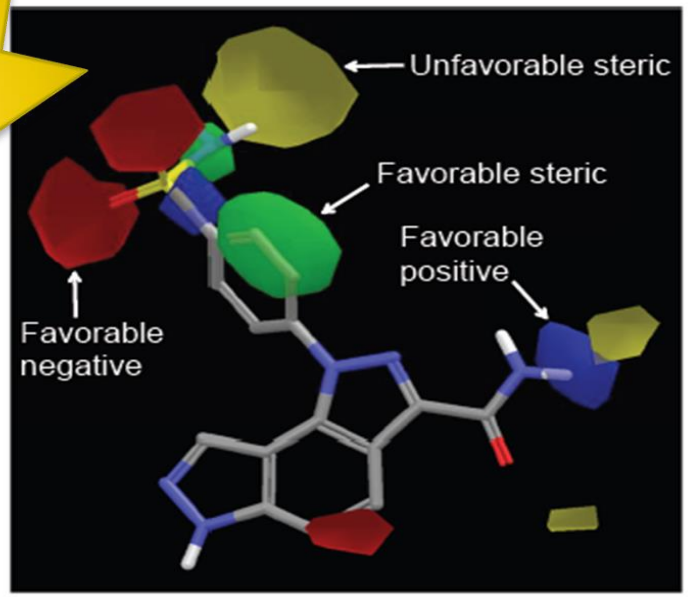
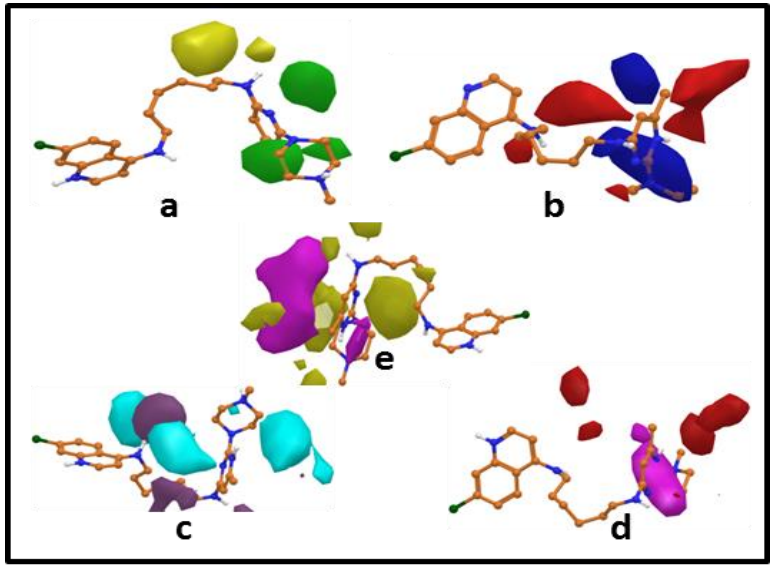


Atom based - QSAR

Good (blue contour) and Bad (red contour) regions for – Hydrogen bond donors and Acceptors, Hydropobic, Negative groups, Positive groups, electron with drawing and donating groups

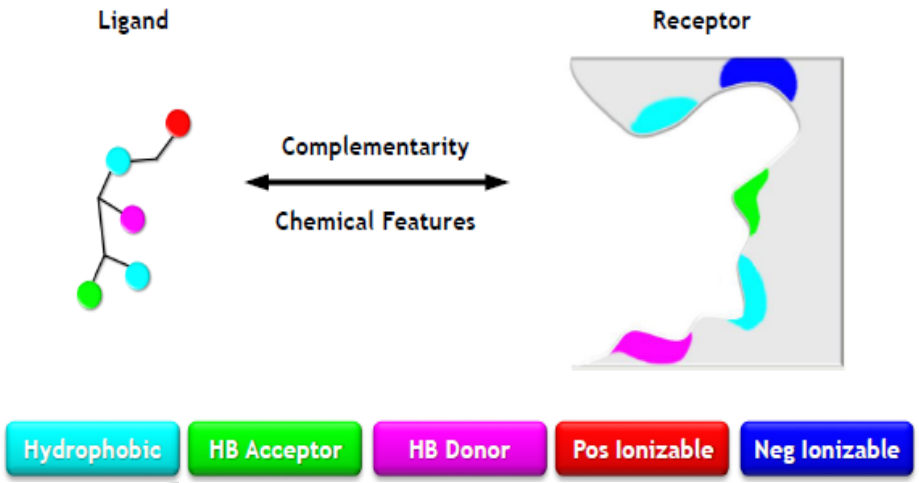


G-QSAR

Field-QSAR

(green) and unfavourable (yellow) **steric contours**; favourable (blue) and unfavourable (red) **electrostatic contours**;favourable (plum) and unfavourable (cyan) **hydrogen bond donor contours;**favourable (red) and unfavourable (magenta**) hydrogen bond acceptor contours**;favourable (yellow) and unfavourable (magenta) **hydrophobic contours**

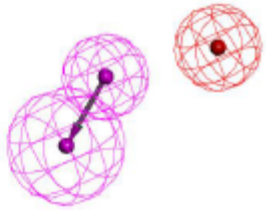
Pharmacophore Modeling



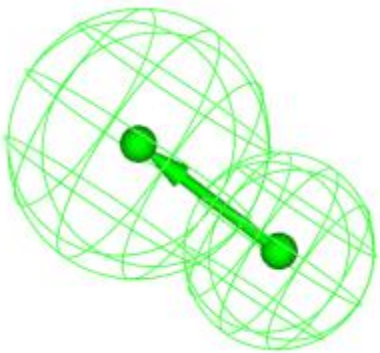
A pharmacophore is the ensemble of steric and electronic features that is necessary to ensure the optimal molecular interactions with a specific biological target and to trigger (or block) its biological response

A pharmacophore feature without a location constraint only indicates the absence or presence of a chemical function

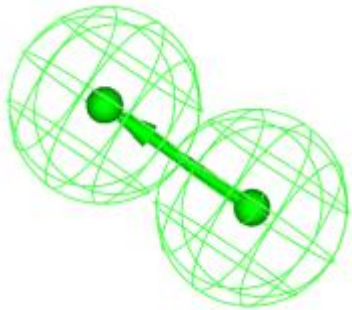
The location constraint specifies the 3D coordinates of the features and defines the spatial relationship of the features to each other



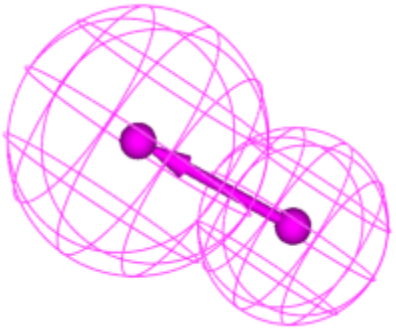
Pharmacophoric Features



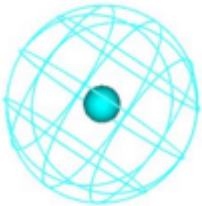
H bond Acceptor



H bond Acceptor-Lipophilic



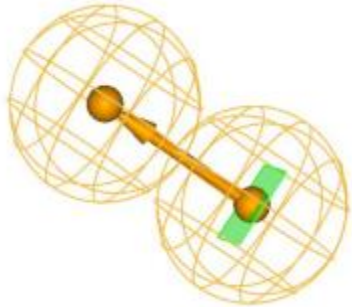
H bond Donor



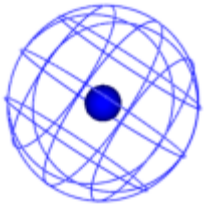
Hydrophobic

Hydrophobic-Aliphatic

Hydrophobic-Aromatic



Ring aromatic

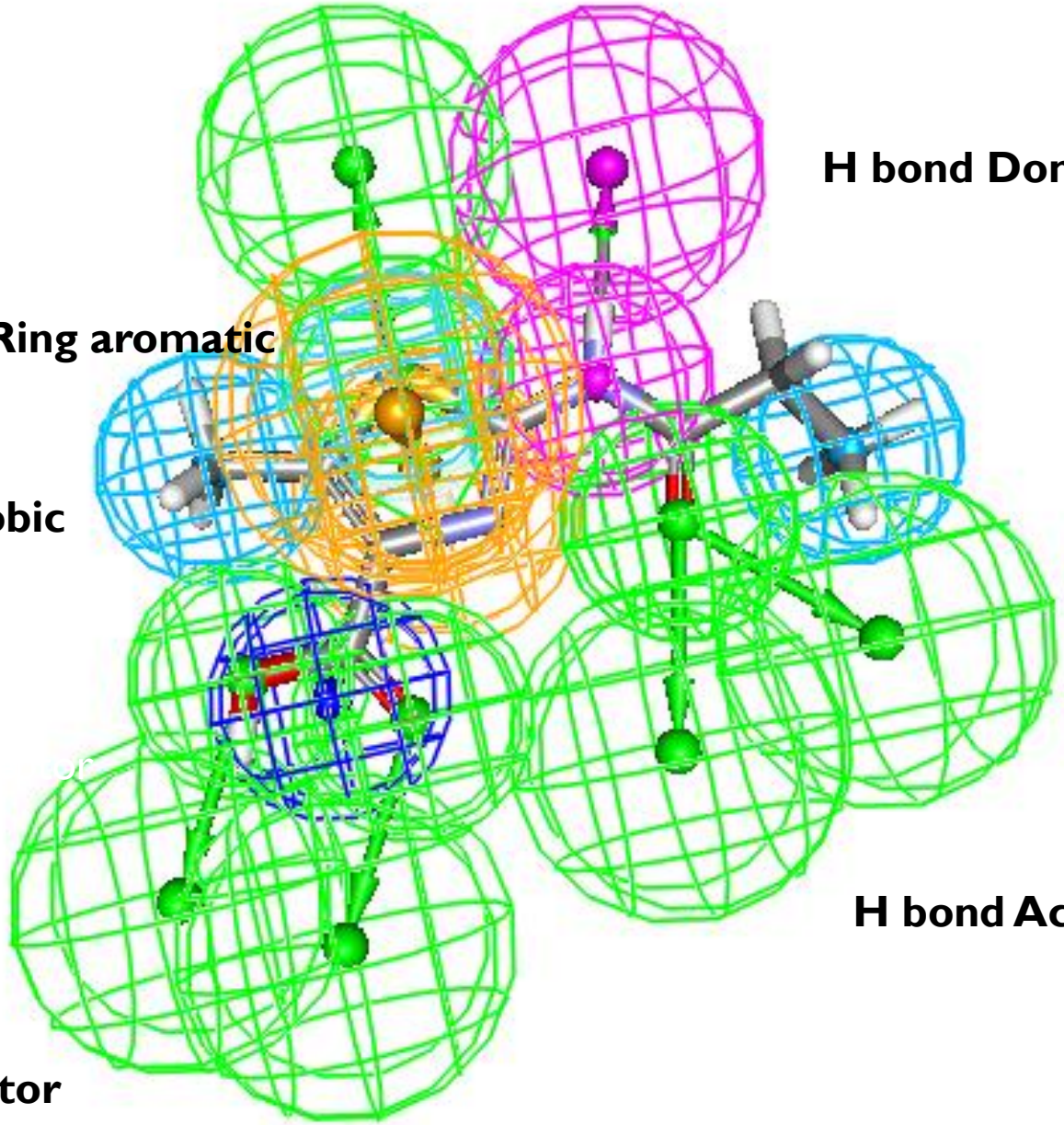


Negatively Ionizable

Positively Ionizable

Negative Charge

Positive Charge


H bond Donor
Ring aromatic
Hydrophobic
H bond Acceptor
H bond Acceptor

Virtual Screening (VS)

The process of screening large databases on the computer for molecules having desired properties and biological activity and also to predict their binding to a target receptor.

OR

Use of high-performance computing to analyze large database of chemical compounds in order to identify possible drug candidates.

It has evolved over the past decade as a well accepted strategy in the discovery of new lead compounds

Significance of Virtual Screening ?

- VS is a computational filter:
  - Reduces the size of a chemical library to be screened experimentally– Saves time & money

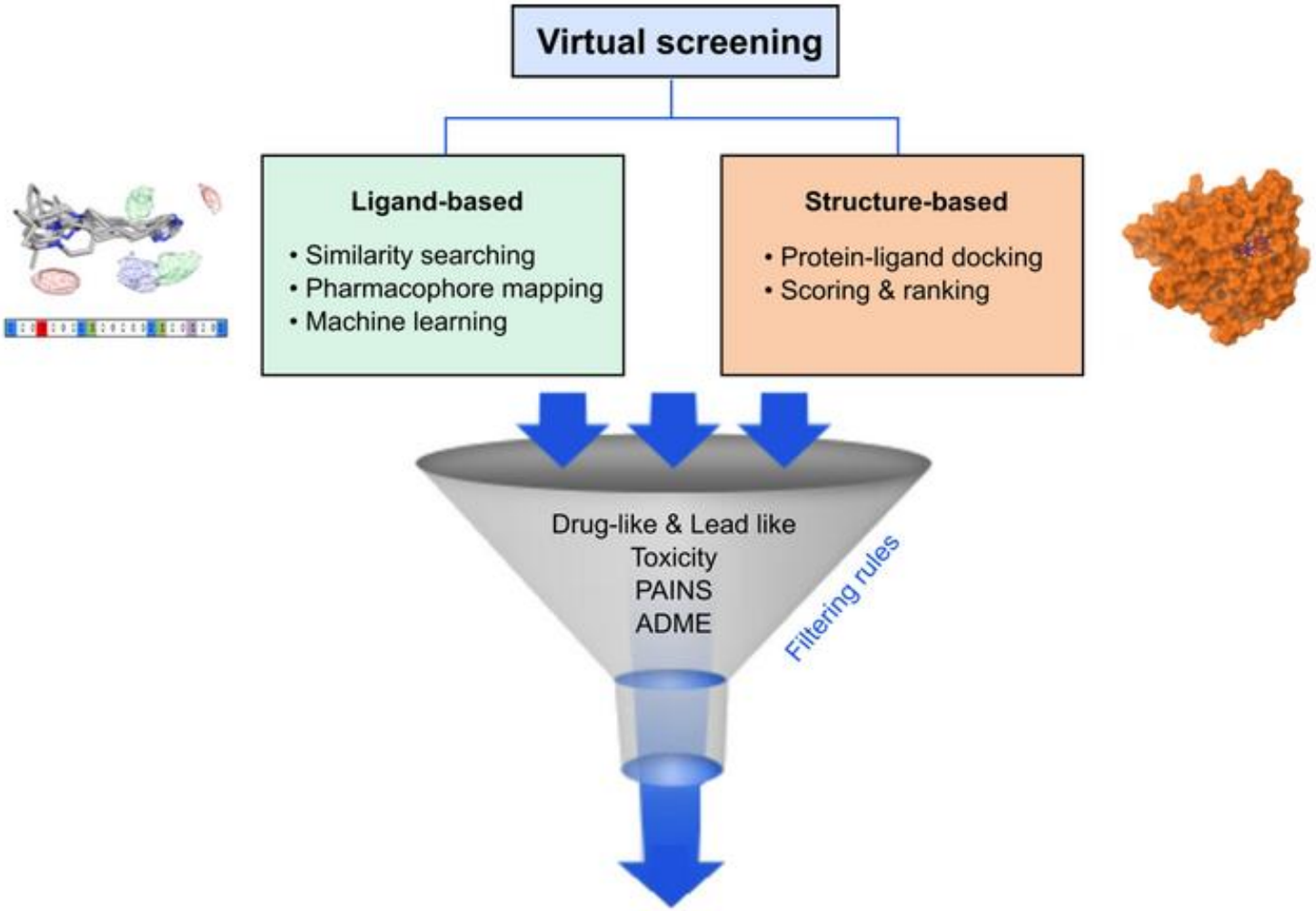
- May improve likelihood of finding interesting compounds
  - As opposed to random screening
  - Enhance "hit rates"

HTS versus VS:

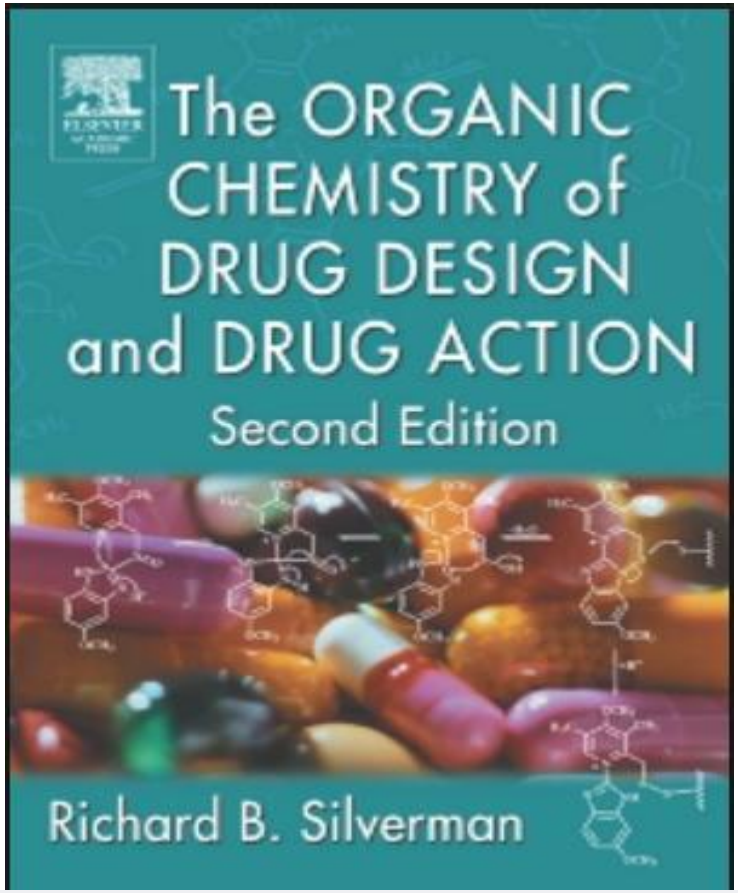
Use VS to exclude compounds which are predicted not to bind, helping to "enrich" the library

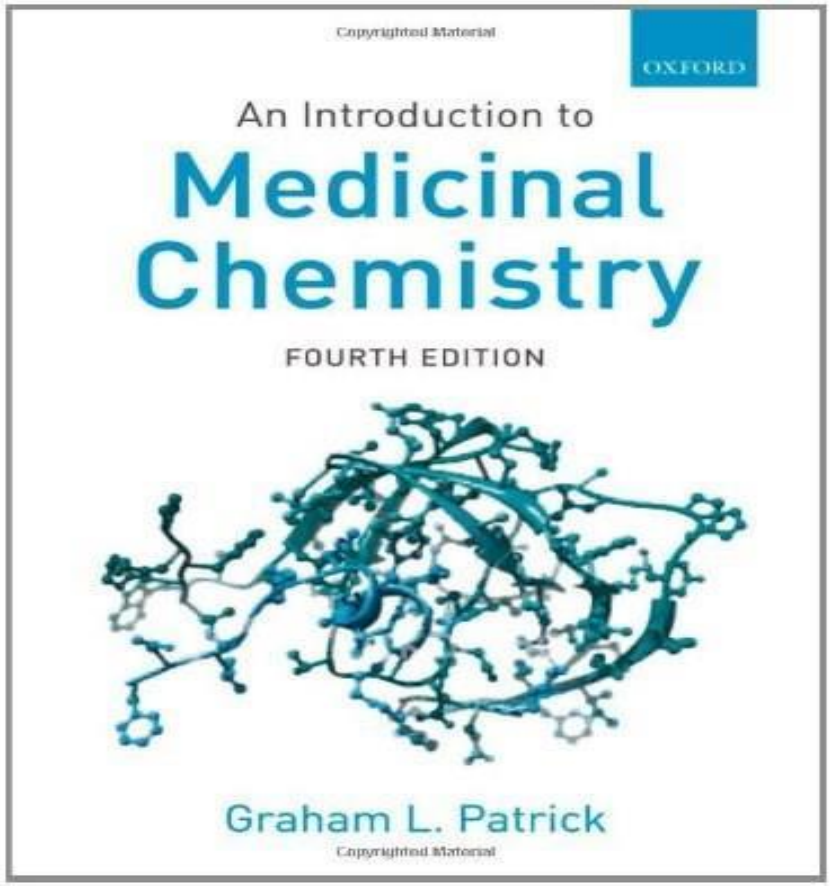
VS can also help to identify false-negatives in HTS

VIRTUAL SCREENING



Recommended Books





1. The organic chemistry of drug design by Richard B. Silverman. Second edition, Elsevier, 2004.

2. An introduction to Medicinal Chemistry by Graham L. Patrick. Fourth edition, Oxford, 2009.


Thank
You