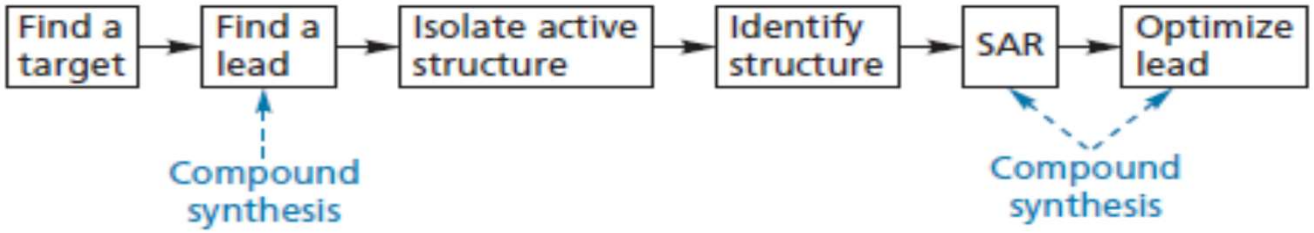
Combinatorial and parallel synthesis

The full set of compounds produced by Combinatorial and parallel synthesis is called a ***compound library***

Lec. 7

Combinatorial and parallel synthesis in medicinal chemistry projects



- The procedures used in combinatorial synthesis are designed to produce mixtures of different compounds within each reaction vessel, whereas those used in parallel synthesis produce a single product in each vessel.

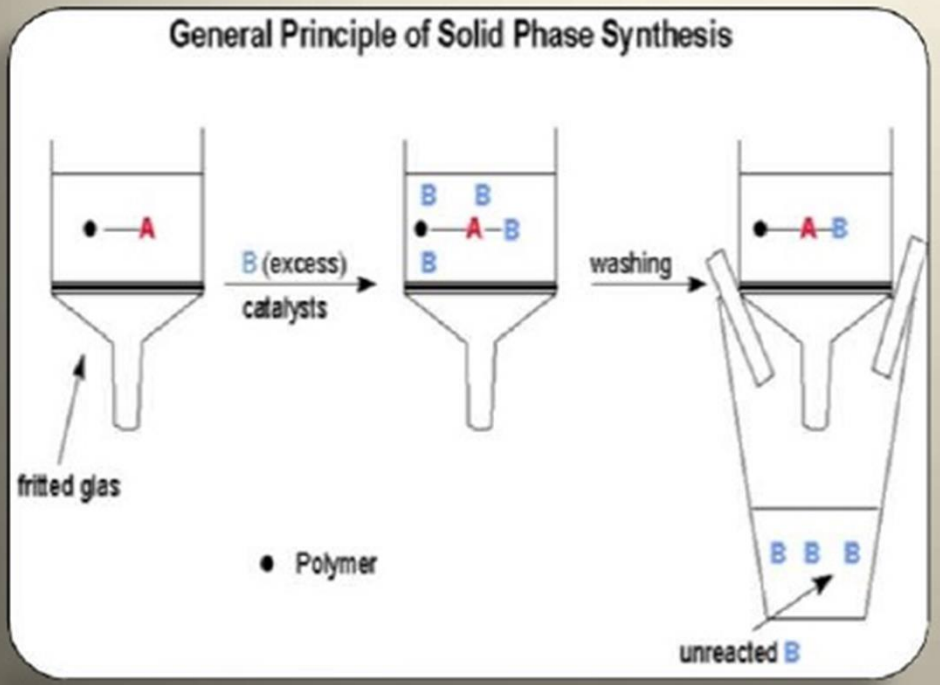
Solid phase techniques

- Solid phase techniques can be used to carry out reactions where the starting material is linked to a solid support, such as a resin bead.

Advantages:

- excess reagents or unbound by-products from each reaction can be easily removed by washing the resin.
- large excesses of reagents can be used to drive the reactions to completion (greater than 99%).
- intermediates in a reaction sequence are bound to the bead and do not need to be purified.

SOLID PHASE TECHNIQUE :



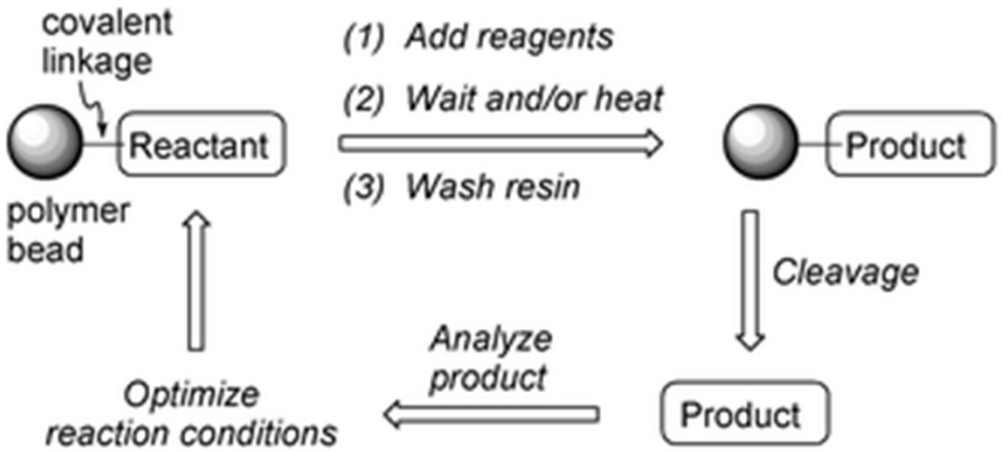
- **The solid support**

  e.g. Cross-linked polystyrene Bead

- **The anchor / linker**

  e.g. Polystyrene resin , Tentagel resin , Polyacrylamide resin, Glass & ceramic beads .

Solid phase techniques



Solid phase techniques

Advantages:

- the polymeric support can be regenerated and reused.
- automation is possible.
- if a combinatorial synthesis is being carried out, a range of different starting materials can be bound to separate beads. The individual beads can be separated at the end of the experiment to give individual products.

Parallel synthesis

- a reaction is carried out in a series of wells such that each well contains a single product. This method is a 'quality rather than quantity'
- often used for focused lead optimization studies.
- typical medicinal chemist may synthesize one or two new entities a week.
- With parallel synthesis, that **same researcher** can synthesize a dozen or more pure molecules.
- can be carried out on **solid phase** and also be carried out **in solution**

  "solution phase organic synthesis (SPOS)"

Combinatorial synthesis

- In combinatorial synthesis, mixtures of compounds are deliberately produced in each reaction vessel,
- The structures in each reaction vessel of a combinatorial synthesis are not separated and purified, but are tested for biological activity as a whole.
- Active mix .....one or more cpd active or false positive.
- Inactive mix .... then there is no need to continue studies on that mixture and it is stored.
- Overall, there is an economy of effort, as a negative result for a mixture of 100 compounds saves the effort of synthesizing, purifying, and identifying each component of that mixture.

The mix and split method in combinatorial synthesis

- Mix and split strategy used to minimize the effort involved and to maximize the number of different structures obtained.
- NO. of possible dipeptides.

By using mix and split method:

Each individual bead may contain a large number of molecules, but all the molecules on that bead are identical

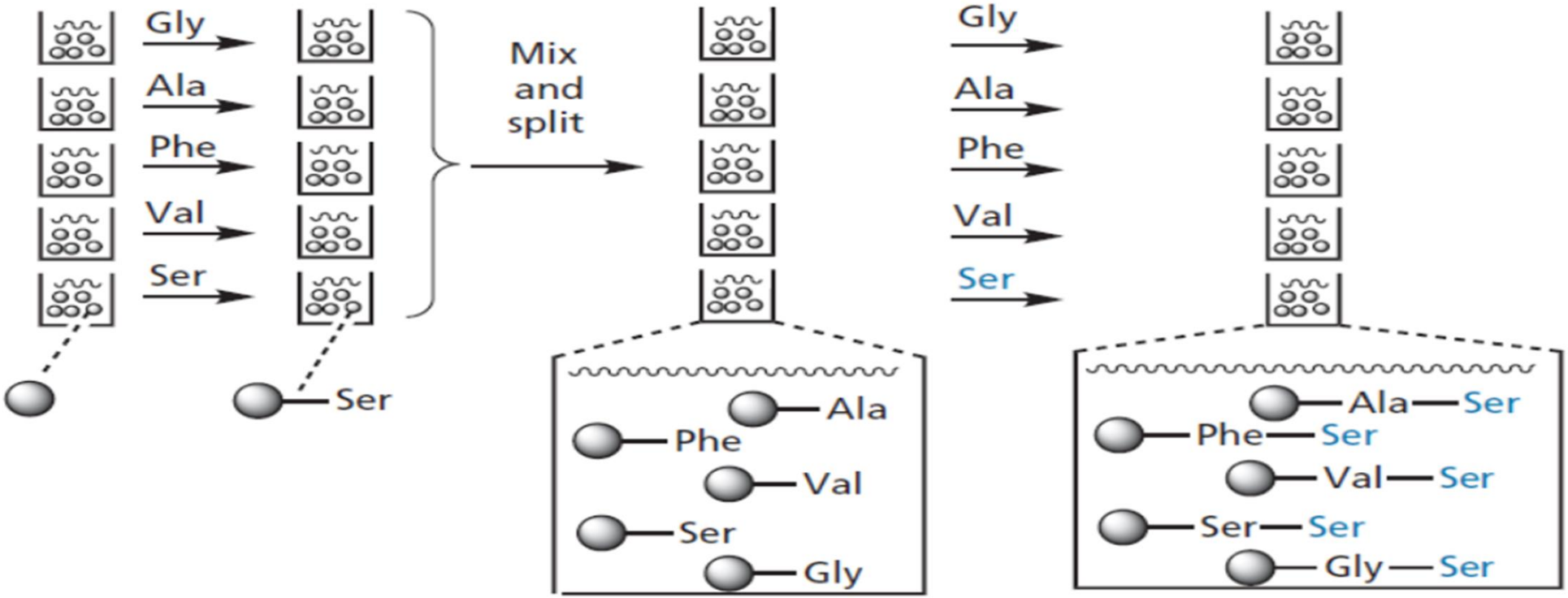
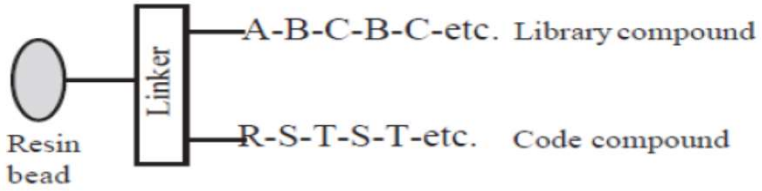


FIGURE 16.29 Synthesis of five different dipeptides using the mix and split strategy.

Structure determination of the active compound(s)

Tagging:

two molecules are built up on the same bead. One of these is the intended structure, the other is a molecular tag (usually a peptide or oligonucleotide) which will act as a code for each step of the synthesis.



Key:

Building block	Code compound
A	R
B	S
C	T

Compounds used for tagging must satisfy a number of criteria:

(1) The concentration of the tag should be just sufficient for its analysis, that is, the majority of the linkers should be occupied by the combinatorial synthesis.

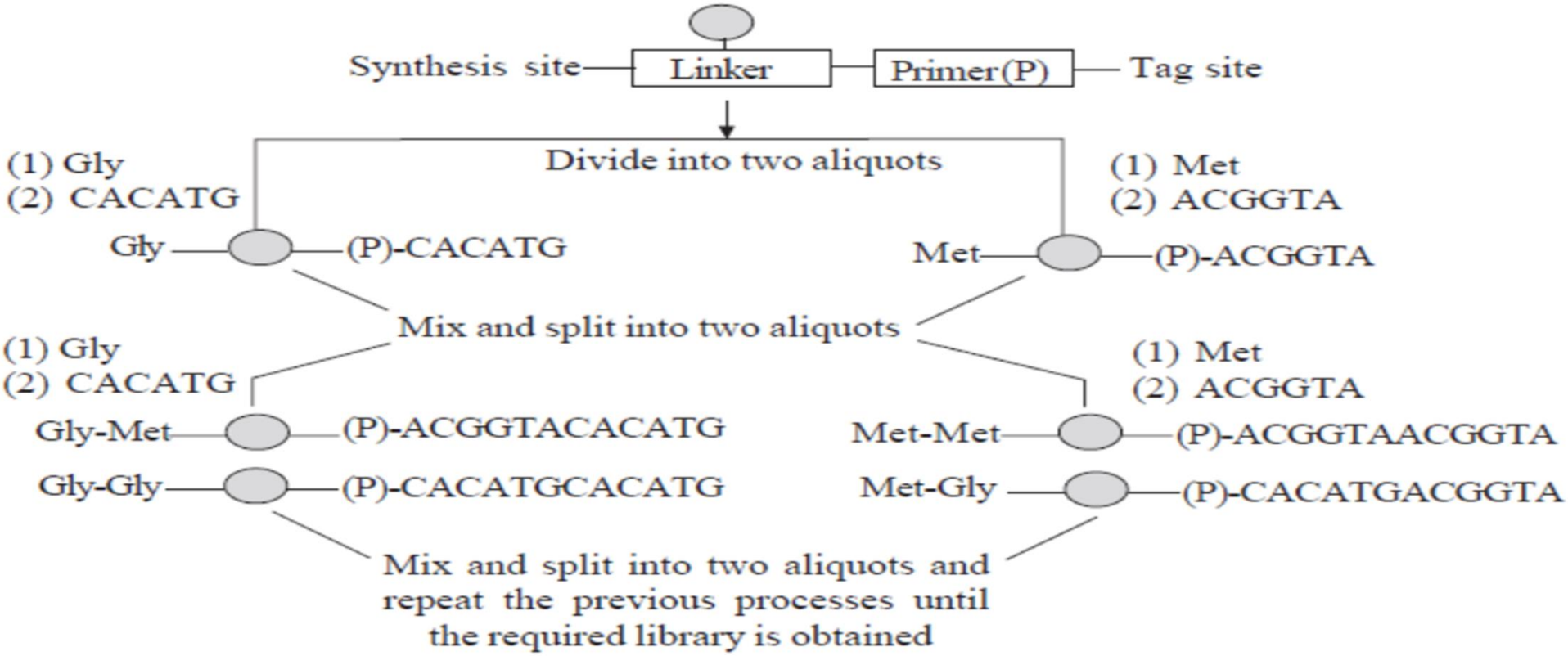
(2) The tagging reaction must take place under conditions that are compatible with those used for the synthesis of the library compound.

(3) It must be possible to separate the tag from the library compound.

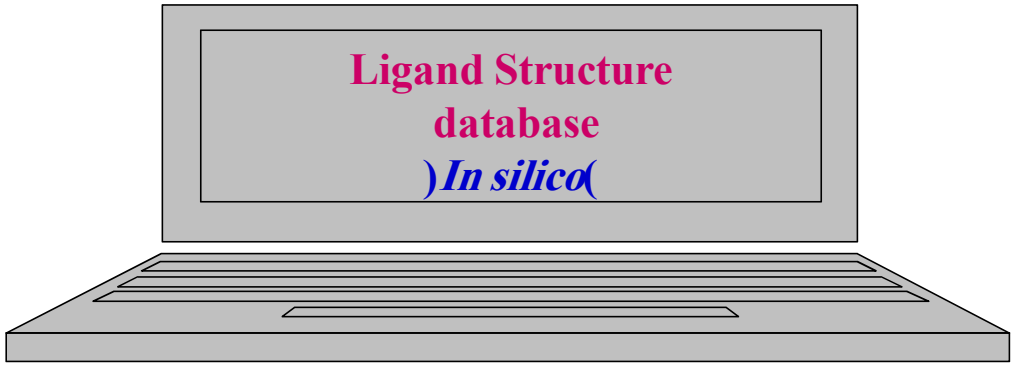
(4) Analysis of the tag should be rapid and accurate using methods that could be automated.

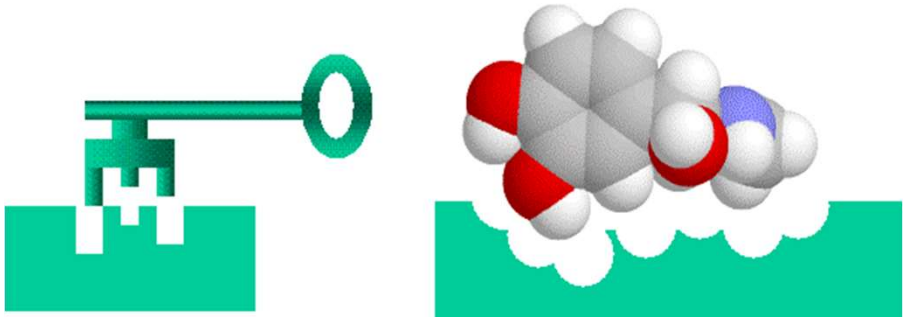
Table 5.2 The use of oligonucleotides to encode amino acids in peptide synthesis

Amino acid	Structure	Oligonucleotide code
Glycine (Gly)	NH_2 CH_2COOH	CACATG
Methionine (Met)	$CH_3SCH_2CH_2CHCOOH$ NH_2	ACGGTA



Computer-aided Drug Design





Lec. 8

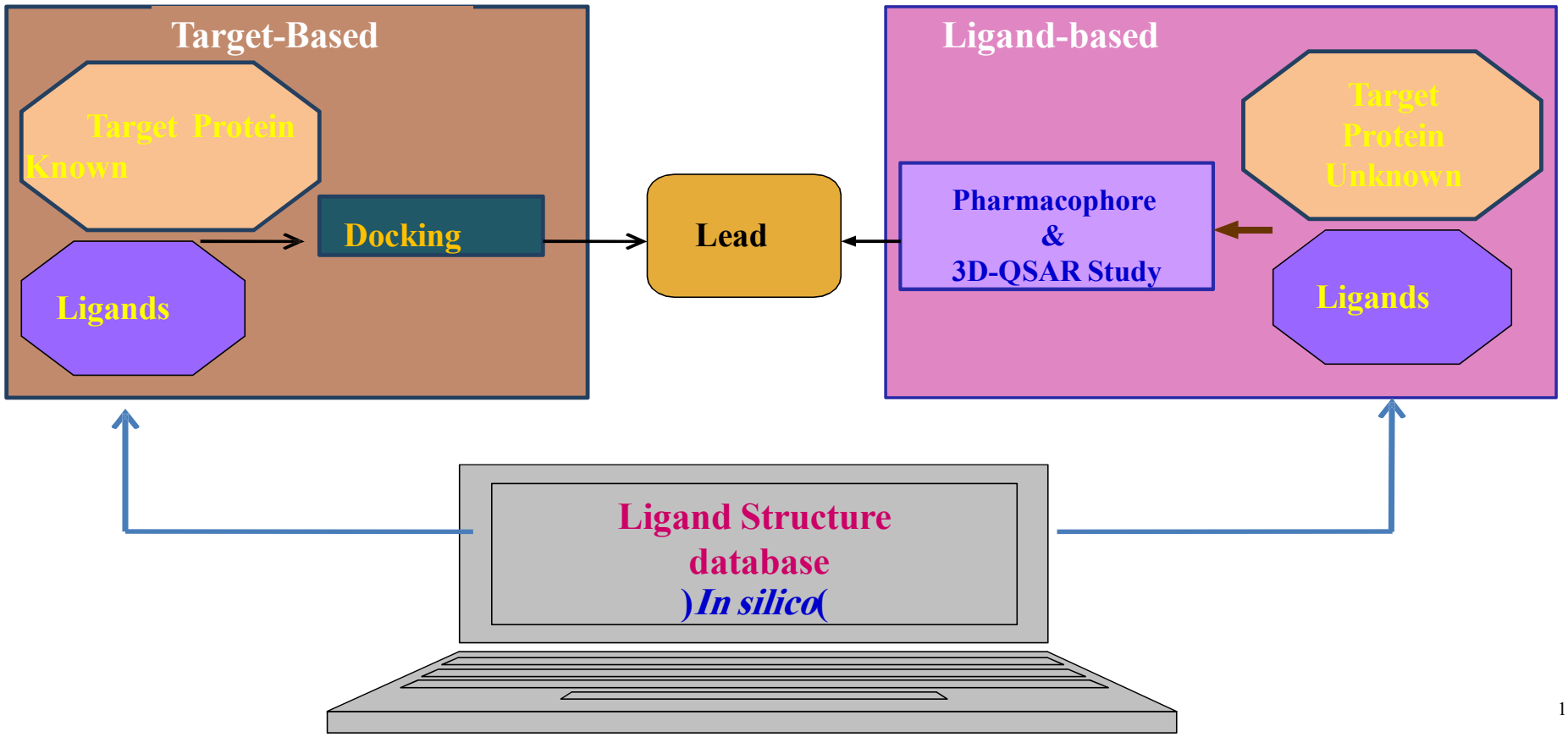
- Drug: Medicine or substance which has a physiological effect when administered into the body.

- Drug acting on different targets

  - Enzyme - inhibitors
  - Receptor - agonists or antagonists
  - Ion channels - blockers
  - Transporter - update inhibitors
  - DNA – blockers.

- Computer-aided drug design uses computational approaches to discover, develop, and analyze drugs and similar biologically active molecules.

Drug Design Strategies Based on Molecular Mechanics



Structure-based Drug Design

Structure-based drug design (SBDD)

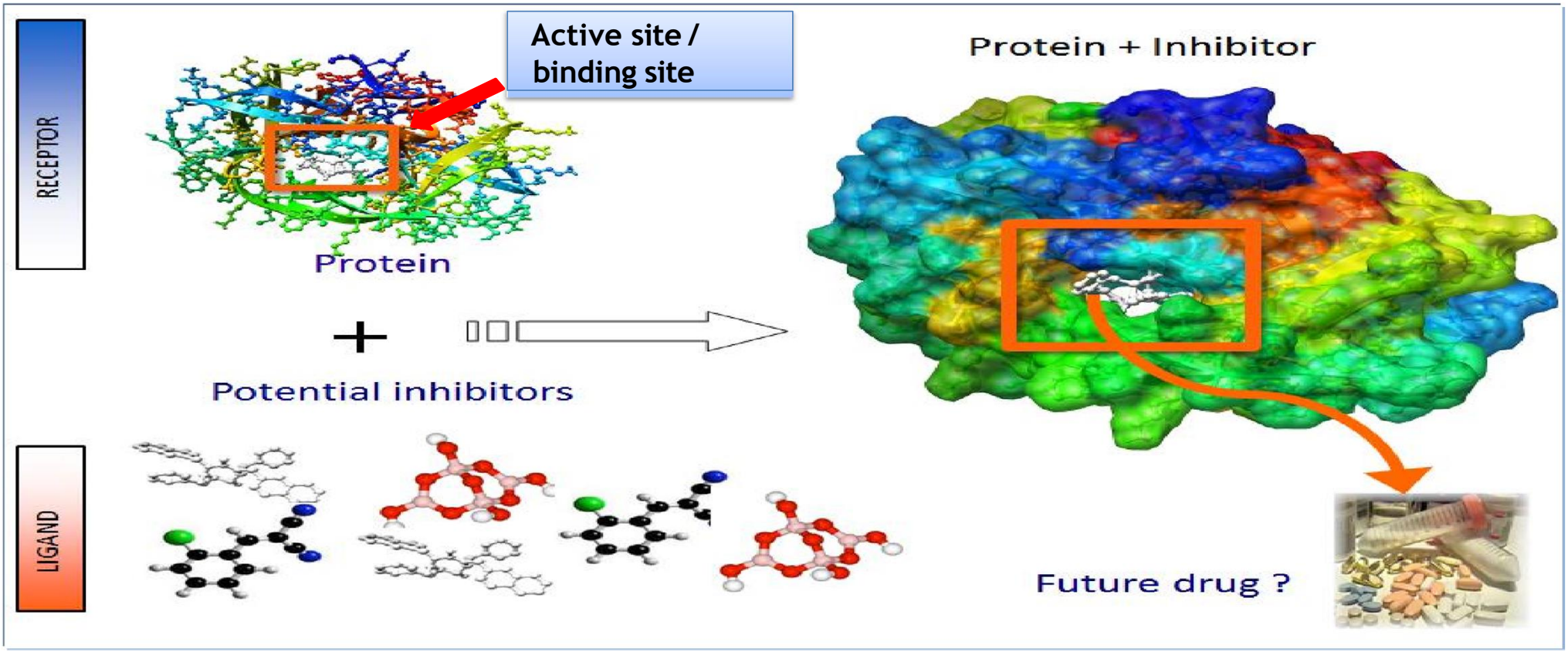
- The macromolecular target can be isolated and crystallized…then the structure will be determined using X-ray crystallography.
- This structure will not give information about the binding site.
- The co-crystal structure (structure of protein with the inhibitor inside) is better (WHY)
  - Where is the 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.

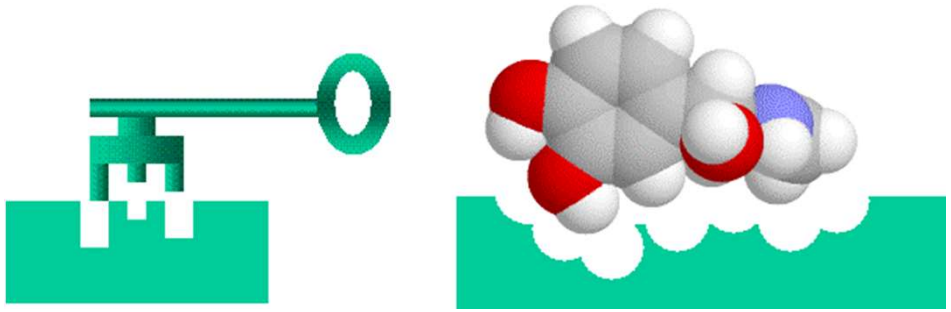
Structure-based (target-based) Drug Design

- 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.

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.

Docking Softwares: (for your information/ Not for exam)

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, then we have 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 (LBDD(

- 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 (LBDD)

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.’

QSAR (Quantitative Structure-Activity Relationship)

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

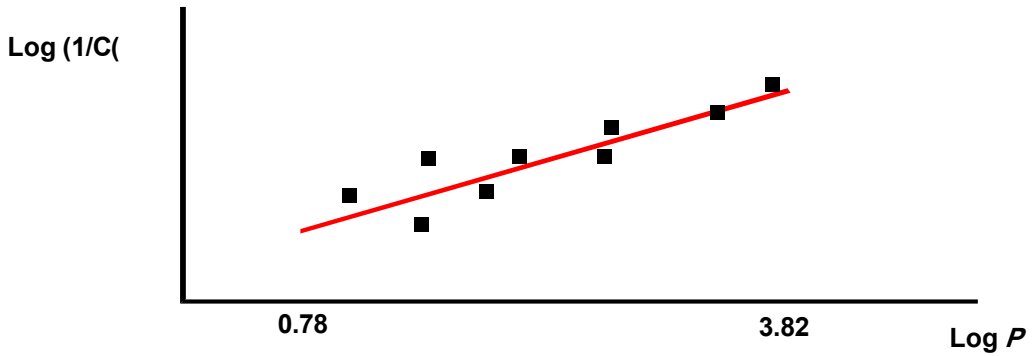
- QSAR attempts to find consistent relationship between biological activity and molecular properties, so that these "rules" can be used to evaluate the activity of new compounds.
- QSAR is considered as a kind of statistical approach that attempts to correlate physico-chemical properties of molecules to their biological activities.
- Various descriptors like molecular weight, number of rotatable bonds, LogP, ... are commonly used in QSAR.

QSAR (Quantitative Structure-Activity Relationship)

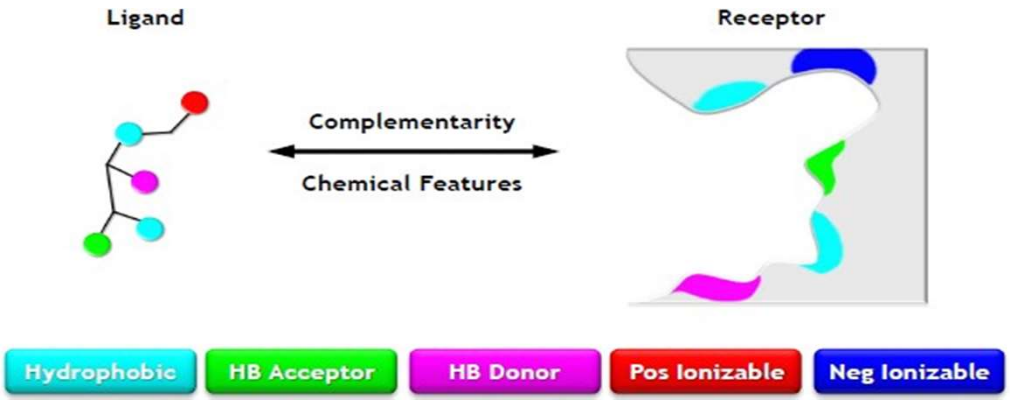
Example: Hydrophobicity Vs Biological Activity

- Activity of drugs is often related to P e.g. binding of drugs to serum albumin

)straight line - limited range of log P(



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