MEDICINAL CHEMISTRY - III

UNIT 5 NOTES

DRUG DESIGN

- APPROACHES TO DRUG DESIGN
- QSAR
- PARTITION COEFFICIENT
- HAMMET'S PARAMETERS
- HANSCH ANALYSIS
- PHARMACOPHORE MODELING
- COMBINATORIAL CHEMISTRY

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Introduction To Drug Design

Drug design is a systemic & knowledge-based process of discovering & developing new chemical compounds that can scientifically interact with biological targets (such as enzymes, receptors or nucliec acids) to produce a desired therapeutic effect.

Key Features

① **Scientific & Rational Approach**

Drug design uses scientific methods & tools to identify & create drugs, unlike traditional trial and error drug discovery.

② **Target-Based Process**

The process begins with identifying a biological target that plays a key role in the disease (an enzyme or receptors) and then designing a drug that can bind to it & modify its action.

③ **Bioactive Molecule Development**

The goal is to create a bioactive compound that can interact effectively & selectively with the target to treat or manage the disease.

④ **Use of Computational Tools**

Mordern drug design involves the use of computer based methods, such as :

- Moleculer Docking
- Pharmacophore Modelling
- QSAR

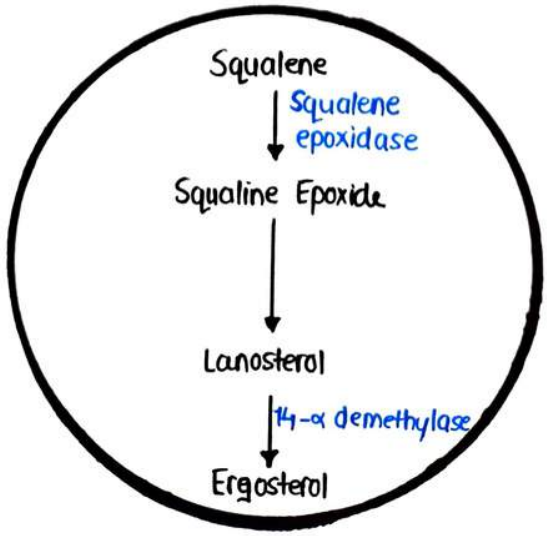
ANTIFUNGAL AGENTS

- Antifungal agents un drugs or substances used to prevent or treat fungal infections by inhibiting the growth or killing fungal cells.
- A fungal infections also known as a mycosis, is a disease caused by fungi invading & growing on or inside the human body.
- There are mainly two types of fungal infections :

① Superficial : Ringworm, Candiasis
② Systemic : Candida albicans

FUNGI

- Fungi are eukaryotic micro-organisms.
- They posses mitochondria, nucliei, cell membrane & cell wall.
- Their cell wall contains chitin (Polymer of N-acetylglucosamine) as well as polysaccharides.
- Ergosterol is the major component of fungal cell membrane.



⑤ Optimization of Drug Properties

After designing a prototype compound, its chemical structure is modified to improves

- Potency
- Selectivity
- ADME
- Toxicity (safety)

VARIOUS APPROACHES USED IN DRUG DESIGNING

- Drug design can be carried out using several scientific approches, depending on the available information about the disease & target.
- The major approaches are :

① Structure - Based Drug design
② Ligand Based Drug Design
③ Rational Drug Design
④ Prodrug Design

STRUCTURE BASED DRUG DESIGN

- SBDD is a method in which the 3D structure of a biological target (usually a protein or enzyme) is used to design drug molecules that can fit & bind precisely in the active site of the target, leading to desired therapeutic effect.
- It is based on principle : "If we know the shape of the lock (protein), we can design the perfect key (drug) to fit into it.

STEPS IN SBDD

- Identify the protein/ enzyme responsible for the disease, i.e. HIV protease in AIDS.
- Find the active site of the protein where drug can bind.
- Design or select small molecules that can fit into the active site.
- Study key interactions :
  - Hydrogen Bonds
  - Hydrophobic forces
  - Electrostatic Intereactions etc.
- Calculate binding energy — Lower energy = Better fit
- Improve molecule binding, selectivity, solubility & safety.

ADVANTAGES

- Time saving & cost - effective.
- High specificity (less side effects).
- Helpful in designing novel (new drugs).

LIMITATIONS

- Requires accurate 3D structure.
- Protein flexibility can make predictions difficult.

EXAMPLE

- HIV Protease Inhibitors.
- Scientist used SBDD to design drugs like :
  - Saquinavir
  - Ritonavir

- These drugs binds to HIV protease & inhibit viral replication.

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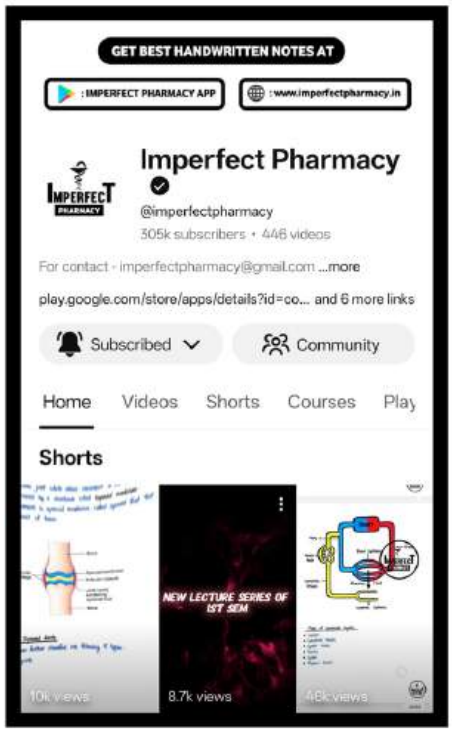

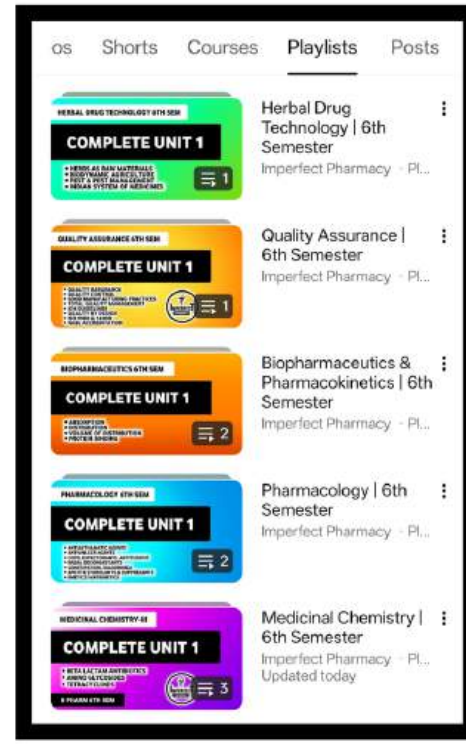

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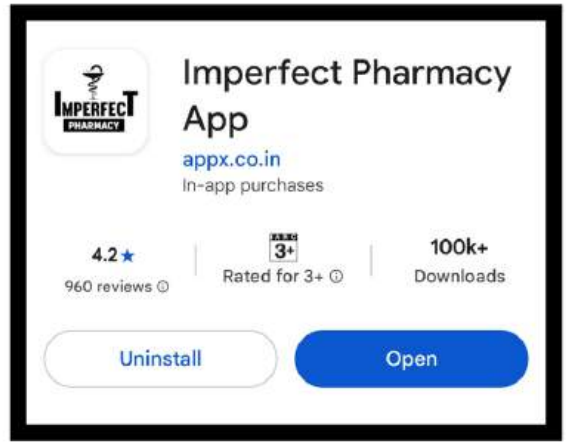


VIDEOS : ▶ IMPERFECT PHARMACY

LIGAND BASED DRUG DESIGN

- It is a method used to design new drugs based on knowledge of existing molecules (ligands) that are already known to bind to the biological target.
- This approach is used mainly when we don't have the idea about shape of protein / enzyme involved in disease.

STEPS IN LBDD

- Gather molecules (ligands) know to bind the target.
- Analyze their structure & common features.
- Use pharmacophore or QSAR Model.
- For example :- A pharmacophore model is a 3D arrangement of features in a molecule (like hydrogen bond) that is essential for biological activity.
  - In pharmacophore modelling, we identify these important features from known ligands & design new molecules that have the same features.

- Design new compounds based on those models.
- Optimize it to improve potency, selectivity, solubility etc.

ADVANTAGES

- Work even without protein structure.
- Fast & Cost-effective.
- Useful in early stages of drug discovery.

PRODRUGS

A prodrug is an inactive or less active precursor of a drug that requires biotransformation / metabolism (usually by enzymatic action in the body) to convert into its active pharmacological form.

IDEAL PROPERTIES

- Drug and the carrier linkage must be cleared in vivo.
- It should have not intrinsic pharmacological activity.
- It should rapidly transform, chemically or enzymatically, into the active form where desired.
- The metabolic fragments, apart from the active drug, should be nontoxic.

OBJECTIVES

They are designed with following objectives:

① Pharmaceutical Objectives:

- To improve water/lipid solubility.
- To improve chemical stability.
- To alter organoleptic properties.
- To decrease irritation and paint at injection site.

② Pharmacokinetic Objectives

- To improve absorption.
- To reduce presystemic metabolism.
- To increase organ/tissue - selectivity.

③ Pharmacodynamic Objectives

- To decrease toxicity.
- To improve therapeutic index.

Designing Of Prodrug

- Prodrugs are chemically modifies drug molecule that are inactive or less active in their administered form & require biotransformation in the body to release the active drug.
- Following factors needed to be considered while designing of prodrug structure :

① Parent drug:

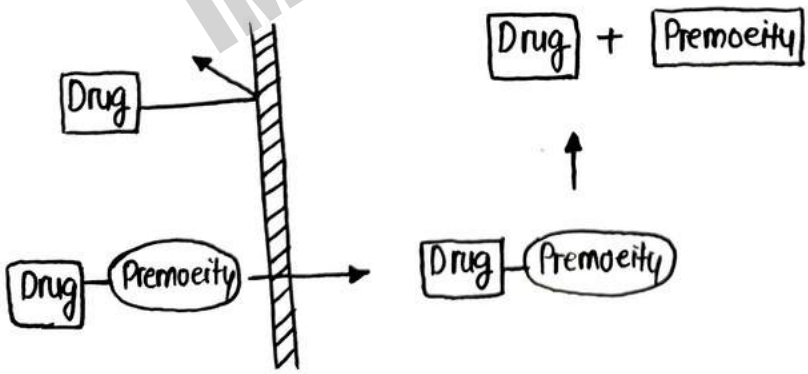
- In this functional groups are important as it helps in modifying drugs to make effective prodrugs.

② Premoeity

- This should ideally be safe & rapidly excreted from the body.
- The choice of premoeity should be considered with respect to the disease state, dose & duration of therapy.

③ Parent & Prodrugs

The absorption, distribution, metabolism & excretion need to be comprehensively understood.



Physiological barrier

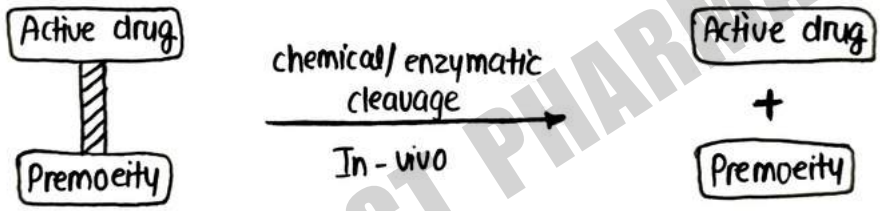
Classification Of Prodrug

Prodrugs are mainly classified into two types:

① Carrier - Linked prodrug
② Bioprecursors

① Carrier Linked Prodrugs

- These prodrugs are formed by attaching an active drugs to a non-toxic carrier (premoeity) via a chemical linkage.
- After administration, the linkage is enzymatically or chemically broken down, releasing the active drug.



- It is further divided into following subtypes:

① Double prodrugs
② Macromolecular Prodrugs
③ Site- specific Prodrugs
④ Mutual prodrugs

① Double Prodrugs

- A prodrug that turns into another prodrug before becoming the active drug.
- This two-step activation can improve targeting and control over drug release.

② Macromolecular Prodrugs

- In this drug attached to a big molecule (like a protein or polymer).
- This makes the drug stay longer in the body or go to a specific place (like a tumor).
- Example: Cancer drugs linked to antibodies to target tumors specifically.

③ Site-specific Prodrugs

- Designed to became active only in certain parts of the body (like liver or tumor cells) to avoid harming healthy tissues & reduce side effects.

④ Mutual Prodrugs

- In this two active drugs are combined into one.
- Each drug helps the other gets into the body better.
- Example: Ben Oxylate (Aspirin + Paracetamol) - combines pain relief & anti-inflammatory action.

② Bioprecursors

- They do not contain a carrier group. Instead the molecular structure itself is modified so that the drug becomes active undergoing metabolic transformation such as oxidation or reduction.
- Example: Prontosil ⟶ Sulfanilamide

Application Of Prodrug Design

① Improve Oral Bioavailability

- Better absorption.
- Example = Valacyclovir ⟶ Acyclovir

② Enhance Solubility

- Useful for IV use.
- Example = Fosphenytoin ⟶ Phenytoin

③ Prolong Drug Action

- Sustained / Controlled release.
- Example: Lisdexamfetamine ⟶ Dextroamphetamine

④ Reduce Toxicity / Side effects

- Safer delivery
- Example = Aspirin ⟶ Salicyclic Acid

⑤ Targeted Drug delivery

- Activated in specific tissues.
- Example: Capecitabine → 5- Fluorouracil (activated in tumors).

⑥ Mask taste / Odor

- Better patient compliance
- Example: Chloramphenicol palmitate → Chloramphenicol

⑦ Improve stability

- Protect drug from degradation
- Example: Enalapril → Enalaprilat

⑧ Enhance CNS Delivery

- Crosses blood-brain barrier
- Example: Levodopa → Dopamine

QSAR

- QSAR stands for Quantitative Structural Activity Relationship.
- It is a method where we create a mathematical relationship b/w the chemical structure of a compound and its biological activity.
- In simple terms we study the chemical structure of drugs & use math to predict how well they work in the body without actually testing them in the laboratory.

Parameters Used In QSAR

Some important parameters used in QSAR are:

- Partition Coefficient
- Hammet's Electronic Parameter
- Tafts Steric Parameter
- Hansch Analysis

① PARTITION COEFFICIENT

- Partition coefficient is a measure of how a compound distributes itself between two immiscible solvents - usually octanol (oil phase & water) aqueous phase.
- It is denoted by P.

$$P = \frac{\text{Concentration of drug in octanol (oil)}}{\text{Concentration of drug in water}}$$

- In QSAR studies, log P is used instead of P because :
  - It converts large numerical ranges into managable values.
    i.e $P=1 \longrightarrow \log P = 0$, $P = 10 \longrightarrow \log P = 1$
  - It helps in forming linear or parabolic relationships with biological activity.
  - It simplifies data analysis & interpretation.

IMPORTANCE OF LOG P

- Measures Hydrophobicity.

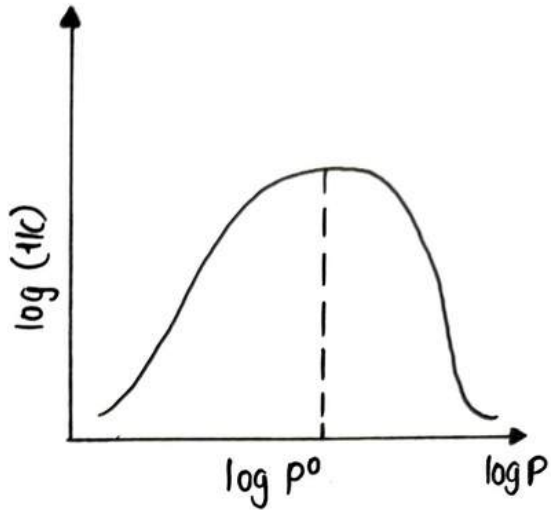
① High log P ⟶ More hydrophobic / lipophillic.

② Low log P ⟶ More hydrophillic.

- The value of, log P should niether be too high nor too low, it should be moderate to produce required biological response.
- The relationship b/w log P & biological response is defined as:

$$\log\left[\frac{1}{C}\right] = -k_1 \log P + k_2$$

- Here 1/C = Biological activity



- The graph shows how biological activity (log 1/C) changes with lipophillicity (log P) of a drug.
- Here :

① **At low log P:** Drug is not lipophillic enough, so it cannot pass through cell membrane easily → low activity.

② **log P°:** This point biological activity is maximum as value of log P is moderate → Max activity.

③ **At very high log P:** Drug becomes too lipophillic, get stuck in membrane → Activity decreases.

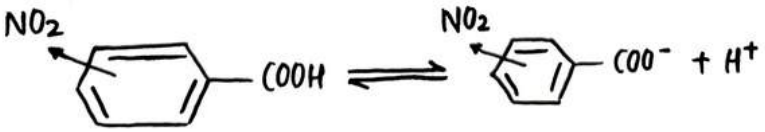
HAMMET'S ELECTRONIC PARAMETER

- The Hammet's electronic parameter denoted by sigma, is a quantitative measure of the electronic effect of a substituent on the reactivity of a benzene ring.
- It essentially - quantifies whether a substituent is electron - donating or electron - withdrawing through inductive and resonance effects.
- If the group is electron - withdrawing (like NO_2), it stabilizes the negative charge and increase acidity ⟶ Gives positive σ value.
- If the group is electron - donating (like CH_3), it reduces acidity ⟶ Gives negative σ value.

EXAMPLE

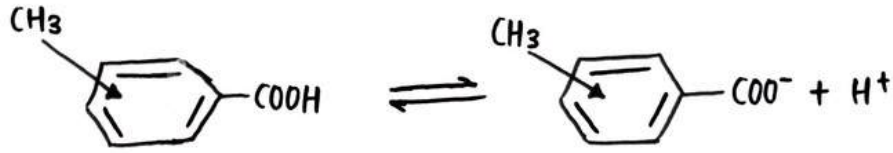
- Let's take Benzoic Acid (C_6H_5COOH) as the base compound.
- Now suppose we attach different groups to the Para position (i.e. 4- position) on the benzene ring:

① Para - Nitrobenzoic Acid (NO_2 group added), NO_2 is electron - withdrawing group.
It pulls electrons from the ring, stabilizing the carboxylate ion (COO^-)
So it increases the acidity
$\sigma = +0.78$ (Positive Value)



[Electron - withdrawing Group]

② Para- Methyl benzoic Acid (CH_3 group added). CH_3 is electron-donating group.
It pushes electron into the ring, destabilizing the carboxylate ion, so it decreases acidity.
σ = -0.17 (Negative Value)



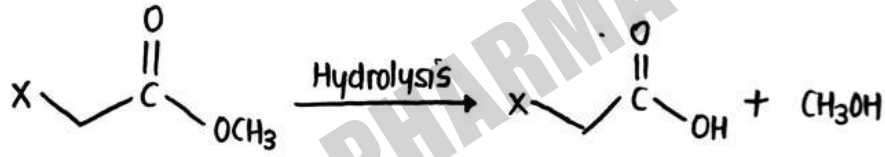
[Electron Donating Group]

③ TAFT'S STERIC PARAMETER

- Taft's Steric Parameter is a quantitative measure of steric effect of a substituent.
- It reflects how the size & bulkiness of a group affect the rate of a chemical reaction or biological activity of a molecule.
- It is denoted by Es
- It was introduced by R.W. Taft in 1956.

Measurement of Es

- Originally it was calculated by comparing the rate of hydrolysis of esters.



- The more bulky the substituent, the more it shows down the reaction because of steric hindrana present.
- If Es = 0, No steric effect.
- If Es < 0, steric hindrana present.
- More negative Es ⟶ More bulky the group.

Importance

- Drugs with bulky groups may not fit well into receptor binding site.
- It helps to relate biological response with size of substituents.
- Helps medicinal chemist modify drug structures to reduces steric hindrance & improve biological response.

④ HANSCH ANALYSIS

Hansh Analysis is a QSAR method developed by Corwin Hansch that establishes a mathematical relationship between a drug's physiochemical properties and its biological activity.

Hansch Equation

$$\log 1/C = k_1 \log P + k_2 \sigma, k_3 E_s + k_4$$

Here,
- $1/C$ = Biological activity
- $\log P$ = Lipophillicity
- σ = Hammett's Electronic Parameter
- E_s = Taft's Steric Parameter
- K_1, k_2, k_3, k_4 = Constants

ADVANTAGES

- Combine multiple parameters ($\log P, \sigma, E_s$)
- Produces quantitative models.

APPLICATION

- Predicts activity of new drug.
- Helps optimize chemical structure.
- Used in drug design, lead optimization.

PHARMACOPHORE MODELLING

- A pharmacophore is the essential set of structural features in a drug molecule that is neccessary to ensure optimal intereactions with specific biological target and trigger to biological response.
- Pharmacophore modelling is the process of identifying & mapping these key features responsible for the biological activity of molecules.
- The concept of pharmacophore was first introduced in 1909 by Paul Ehrlich.

KEY FEATURES IN PHARMACOPHORE

These are the common chemical groups involved :

- Hydrogen Bond Donor : Donets a hydrogen for bonding.
- Hydrogen Bond Acceptor: Accepts a hydrogen bond.
- Hydrophobic Groups : Intreacts with hydrophobic parts of receptor.
- Aromatic rings : Intereact with proteins.
- Positive/Negative Ionizable Groups : Charged groups involved in electrostatic interactions.

TYPES OF PHARMACOPHORE MODELLING

① Ligand Based Model
② Structure Based Model

Note : Above topics are already explained in Drug Designing.

Applications Of Pharmacophore Modelling

- Designing new drugs
- Load optimization
- Predicting activity of unknown compounds
- Understanding SAR

Molecular Docking

- Molecular docking is a computational technique used to predict the preffered orientation (binding pose) of a ligand (drug molecule) when it binds to a target receptor (usually a protein / enzyme).
- The goal is to find how well the ligand fits into the active site of the receptor and to estimate the binding affinity or interaction strength.

Purpose Of Docking

- To study ligand - receptor interactions.
- To predict biological activity
- To design new drugs with better binding affinity

Steps In Molecular Docking

1. Prepare Ligand & Protein : Both are converted into 3D structures.
2. Define Binding site : Active site where ligand will bind.
3. Docking Simulation : The computer tries various orientation of ligand inside binding site.
4. Scoring function : Each pose is given a score based on binding energy or fit.

Basic Principle

- Docking simulates the binding process between ligand and receptor using alogorithims and ranks the poses based on how stable & strong the interaction is.

Types

① Rigid Docking: Both ligand & receptor are treated as rigid.
② Flexible Docking: Ligand is flexible, receptor may be partially flexible.

Docking Score

- It represents the binding energy.
- Lower score = stronger binding = Potentially better drugs.

Applications

- Drug discovery & design.
- Lead optimization.
- Structure-based virtual screening.
- Understanding drug-receptor mechanisms.
- Prediction of binding modes.

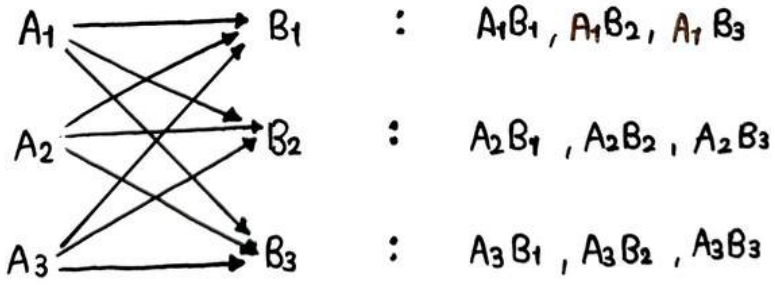
COMBINATORIAL CHEMISTRY

INTRODUCTION

- Combinatorial chemistry is a technique based to create a large number of different chemical compounds (compound library) quickly and efficiently.
- These compounds are then screened to find potential drugs or biologically active molecules.
- Instedd of making one compound at a time, hundreds or thousands of compounds are prepared simultaneously by combining different sets of chemical building blocks.

EXAMPLE :

- Let's suppose, we have 3 different acids → A_1, A_2, A_3 & 3 different Amines → B_1, B_2, B_3
- Now if we combined them, we get 9 different possible combinations



- Means we get 9 different compounds from one ~~sig~~ single type of reactions, thats combinatorial chemistry.

Purpose Of Combinatorial Chemistry

- To speed up the drug discovery process.
- To generate diverse molecules in less time.
- To increase the chance of finding a lead compound.
- Used in drug discovery, material science and agrochemicals.

Basic Steps:

① Selection of building blocks : Choose starting chemicals like amines, acids, aldehydes etc.

② Reaction Scheme Selection : A general chemical reactions is selected (e.g. amine bond formation)

③ Synthesis (solid- phase / Solution -phase) : The combination are made using solid or liquid media.

④ Library Generation : Many compounds are created by combining different building blocks.

⑤ Screening : The compounds are tested for biological activity using high throughput screening.

⑥ Hit Identification & Optimization : The most active compounds (hits) are modified and improved to make better drugs (leads).

Types Of Combinatorial Chemistry

It is of two types :

- Solid Phase Synthesis
- Liquid Phase Synthesis

① Solid Phase Synthesis

A method where the starting molecule is attached to a solid support (like resin beads), and all reactions happen on that bead.

Process :

- A resin bead is taken.
- First building block is attached to the bead.
- Reactions are done step-by-step.
- After each step, the bead is washed to improve impurities.
- At the end, the final compound is cut off (cleaved) from the bead.

Uses :

- Peptide synthesis
- Small molecule libraries
- Drug discovery programs

② Solution - Phase Synthesis

A method where all reactants and reactions take place in a liquid solvent (like ethanol, water, etc)

Process:

- Reactants are dissolved in a liquid.
- Reactions take place freely in solution.
- The product is then purified using filtration, extraction etc.

Uses:

- Synthesis of small organic molecules.
- Natural product analogues.
- Larger scale chemistry.

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