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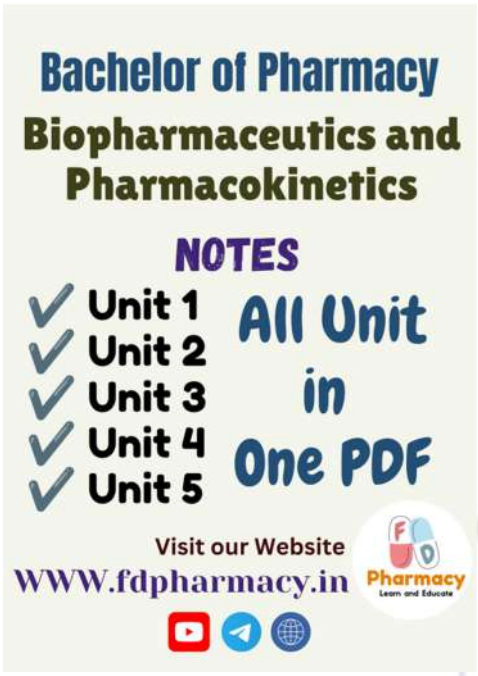
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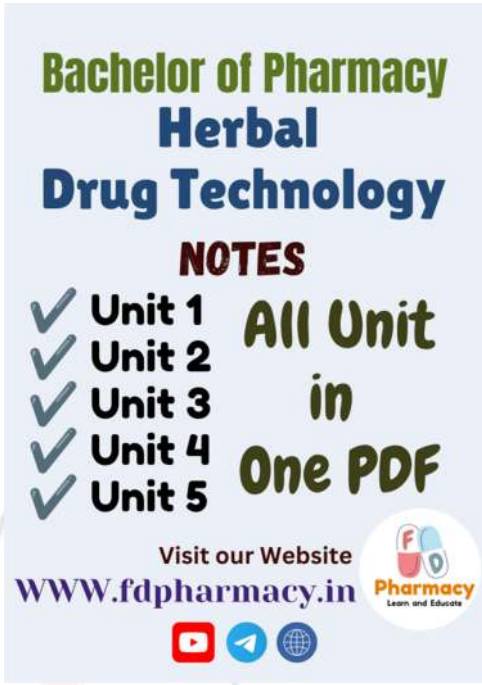
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MEDICINAL CHEMISTRY - III

UNIT 5

TOPIC :

- **Introduction to Drug Design**

  Various approaches used in drug design.

  Physicochemical parameters used in quantitative structure activity relationship (QSAR) such as partition coefficient, Hammet's electronic parameter, Tafts steric parameter and Hansch analysis. Pharmacophore modeling and docking techniques.

Introduction to Drug Design

- Drug design is a systematic and rational process of discovering or developing new drugs by understanding the biological target, disease mechanism, and interaction between drug molecules and biological systems.
- The main aim of drug design is to create safe, effective, selective, and stable drugs with minimum side effects.

Meaning of Drug

- A drug is a chemical substance which, when administered to a living organism, produces a biological response and is used for the prevention, diagnosis, or treatment of diseases.

Objectives of Drug Design

- To increase therapeutic efficacy
- To improve selectivity toward biological targets
- To reduce toxicity and side effects
- To optimize pharmacokinetic properties (ADME)
- To enhance patient compliance

Stages of Drug Design

1. Target Identification and Validation

- Target identification is the process of selecting a biological molecule involved in a disease, while target validation confirms that modifying this target produces a therapeutic effect. It ensures the target is disease-specific and druggable. This step reduces failure in later stages of drug development.

2. Lead Compound Identification

- Lead compound identification involves finding chemical compounds that show desired biological activity against the selected target. These compounds are obtained from natural sources, synthetic libraries, or screening methods. Lead compounds possess moderate potency and acceptable safety.

3. Lead Optimization

- Lead optimization is the chemical modification of lead compounds to improve potency, selectivity, bioavailability, and safety. SAR and QSAR studies are commonly used. The optimized lead becomes a potential drug candidate.

4. Preclinical Studies

- Preclinical studies are conducted using in vitro systems and animals to evaluate pharmacological activity and toxicity. These studies assess ADME properties and safe dose levels. They ensure the drug is safe before human testing.

5. Clinical Trials

- Clinical trials are systematic studies conducted in humans to evaluate safety, efficacy, and dosage. They are divided into Phase I, II, III, and IV. This stage confirms the therapeutic value of the drug in patients.

VARIOUS APPROACHES USED IN DRUG DESIGN

1. Lead-Based Drug Design

➢ A lead compound is a chemical compound showing desired biological activity, which is optimized to develop a drug.

Process

- Identification of lead compound
- Structural modification
- Optimization of activity
- Reduction of toxicity

Sources of Lead Compounds

- Natural products
- Existing drugs
- Synthetic chemicals
- Computer-aided screening

Example

- Modification of morphine → codeine, naloxone.

Advantages

❖ Rational and systematic.
❖ Higher success rate.

2. Structure–Activity Relationship (SAR) Approach

➢ SAR studies the relationship between chemical structure and biological activity.

Explanation

- Small changes in structure cause changes in activity.
- Helps identify pharmacophore.

Applications

- Optimization of potency.
- Reduction of side effects.

Example

- Barbiturates: Alkyl chain length affects sedative activity.

3. Quantitative Structure–Activity Relationship (QSAR)

➢ QSAR uses mathematical and statistical models to relate physicochemical properties with biological activity.

Parameters Used

- Lipophilicity (log P)

Electronic effects (Hammett constant)

- Steric effects (Taft constant)

Advantages

➢ Reduces animal testing, Predicts activity of new compounds.

Limitations

❖ Requires large data sets.

4. Target-Based Drug Design (Rational Drug Design)

→ This approach designs drugs based on specific biological targets such as enzymes, receptors, or DNA.

Steps

- Identification of target
- Target validation
- Lead identification
- Optimization

Example

▪ ACE inhibitors (Captopril) designed for ACE enzyme.

Advantages

❖ Highly specific, Fewer side effects.

5. Structure-Based Drug Design (SBDD)

→ Drug design based on the three-dimensional structure of the biological target.

Techniques Used

- X-ray crystallography, NMR spectroscopy, Molecular docking

Example

❖ HIV protease inhibitors.

Physicochemical Parameters Used In QSAR

1. Partition Coefficient (π or log P)

→ The partition coefficient is the ratio of concentration of a compound in oil phase to that in aqueous phase at equilibrium.

$$P - \frac{[Drug]_{oil}}{[Drug]_{water}}$$

$$\log P - \log\left(\frac{[Drug]_{oil}}{[Drug]_{water}}\right)$$

Explanation

- Usually measured using n-octanol/water system.
- Indicates lipophilicity of a drug.
- Higher log P → more lipid soluble.

Importance in Drug Design

- Affects absorption, distribution, membrane permeability, and bioavailability.
- Very high log P → poor solubility & toxicity.
- Very low log P → poor membrane penetration.

Example

- CNS drugs require moderate log P to cross the blood–brain barrier.

Limitations

- Not suitable for ionizable drugs without correction.
- Does not account for metabolism.

2. Hammett's Electronic Parameter (σ)

- Hammett constant (σ) measures the electron-withdrawing or electron-donating nature of substituents on an aromatic ring.

Hammett Equation

$$\log\left(\frac{k}{k_0}\right) = \sigma\rho$$

Where:

- **k** = rate constant of substituted compound
- **k_0** = rate constant of unsubstituted compound
- **σ** = Hammett constant
- **ρ** = reaction constant

Interpretation

- σ > 0 → Electron-withdrawing group (–NO_2, –Cl)
- σ < 0 → Electron-donating group (–OH, –CH_3)
- σ = 0 → Hydrogen

Role in QSAR

- Influences drug–receptor binding
- Affects ionization, metabolism, and stability

Example

- Electron-withdrawing groups increase activity in sulfonamides.

Limitations

- Applicable mainly to aromatic systems
- Less useful for aliphatic compounds

3. Taft's Steric Parameter (Es)

→ Taft steric parameter (Es) measures the steric bulk (size) of substituents and their effect on biological activity.

Taft Equation

$$\log\left(\frac{k}{k_0}\right) = \rho^*\sigma^* + \delta E_s$$

Where:

Es = steric parameter

δ = steric sensitivity constant

Explanation

- Larger substituents hinder receptor binding.
- Steric effects affect enzyme interaction and receptor fit.

Interpretation

- More negative Es → bulky substituent
- Less steric hindrance → better activity

Example

- Bulky groups near active site reduce activity of esterases.

Importance

- Helps in selecting optimum substituent size.
- Useful in enzyme-targeted drugs.

4. Hansch Analysis

→ Hansch analysis is a statistical QSAR method that correlates biological activity with lipophilic, electronic, and steric parameters.

Hansch Equation

$$\log(1/C) = a(\log P) + b(\log P)^2 + c\sigma + dE_s + k$$

Where:

- C = concentration producing biological effect
- log P = lipophilicity
- σ = electronic parameter
- Es = steric parameter
- a, b, c, d, k = constants

Significance

- Predicts optimum lipophilicity
- Identifies most important parameter affecting activity
- Helps design more potent analogs

Applications

- Optimization of lead compounds
- Reduction of toxicity
- Prediction of biological activity

Advantages

- Quantitative and scientific
- Reduces experimental cost

Limitations

- Requires large data set
- Not applicable for complex biological systems

Pharmacophore Modeling and Docking Techniques

1. Pharmacophore Modeling

- A pharmacophore is the three-dimensional arrangement of essential chemical features required for a drug to interact with a specific biological target and produce a biological response.

Pharmacophoric Features

- Hydrogen bond donor (HBD)
- Hydrogen bond acceptor (HBA)
- Aromatic ring
- Hydrophobic group
- Positive ionizable group
- Negative ionizable group

Types of Pharmacophore Modeling

A. Ligand-Based Pharmacophore Modeling

→ Used when the 3D structure of the target is unknown, but several active ligands are known.

Steps:

- Selection of active compounds
- Alignment of ligands
- Identification of common features
- Generation of pharmacophore model
- Validation

Example: Design of β-blockers.

B. Structure-Based Pharmacophore Modeling

→ Used when the 3D structure of the receptor or enzyme is known.

Steps:

- Target structure determination
- Binding site identification
- Mapping interactions
- Pharmacophore generation

Example: HIV protease inhibitors.

Applications of Pharmacophore Modeling

- Virtual screening of drug libraries
- Lead optimization
- Identification of new drug candidates
- Understanding mechanism of action

Advantages

- Reduces cost and time
- Requires fewer experimental studies
- Useful in early drug discovery

Limitations

- Depends on quality of input data
- Cannot predict ADME properties

2. Molecular Docking Techniques

→ Molecular docking is a computational technique used to predict the preferred orientation and binding affinity of a drug molecule (ligand) when it binds to a biological target (receptor).

Objectives of Docking

- Predict binding mode
- Calculate binding energy
- Understand drug–receptor interactions

Docking Process (Steps)

Target Preparation

- Removal of water molecules
- Addition of hydrogen atoms

Ligand Preparation

- Geometry optimization
- Charge assignment

Binding Site Identification

Docking Simulation

- Placement of ligand in binding site

Scoring and Ranking

- Evaluation of binding affinity

Types of Docking

A. Rigid Docking

- Both ligand and receptor are rigid
- Fast but less accurate

B. Flexible Docking

- Ligand is flexible
- More accurate and realistic

C. Induced Fit Docking

- Both ligand and receptor adapt
- Highly accurate but computationally expensive

Scoring Functions

- Force-field based
- Empirical scoring
- Knowledge-based scoring

Examples

- Docking of ACE inhibitors
- Docking of anticancer drugs with kinases

Applications of Docking

- Lead identification
- Optimization of binding affinity
- Prediction of drug resistance
- Structure-based drug design

Advantages

- Visualizes drug–receptor interaction
- Saves experimental cost
- High throughput screening

Limitations

- Accuracy depends on scoring function
- Cannot fully simulate biological environment