

Introduction to Drug Design

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- Drug design involves discovering or creating therapeutic agents based on a biological target.
- It combines chemistry, biology, pharmacology, and computational science to develop safe and effective drugs.

Key Aspects

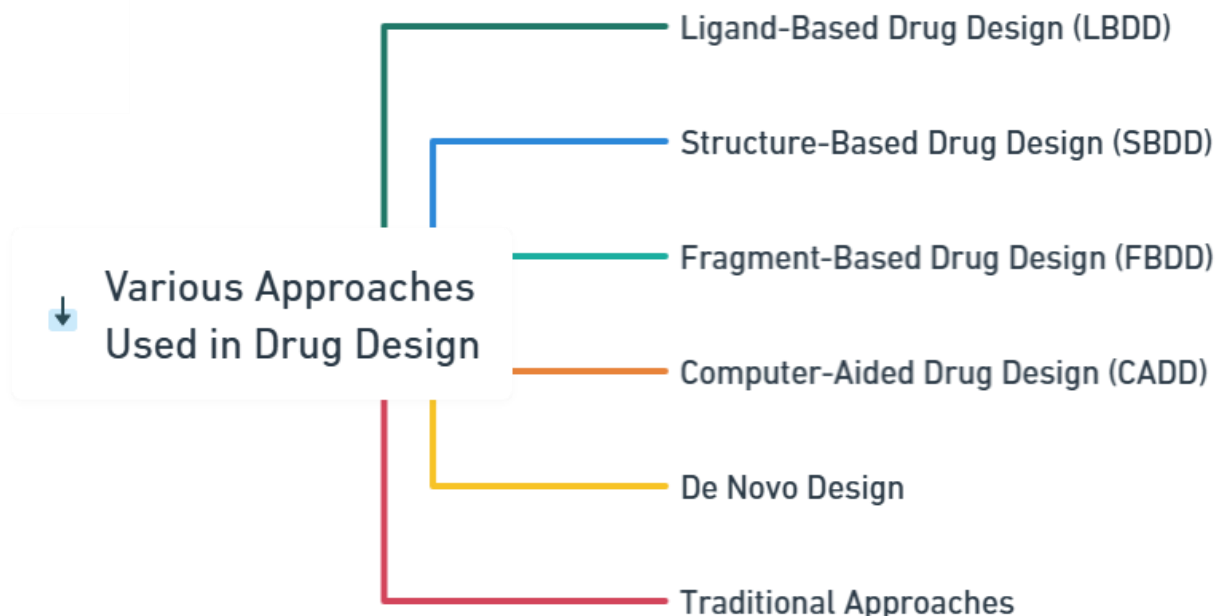
- **Target Identification:** Selecting a biological molecule for therapeutic modulation.
- **Lead Discovery:** Identifying active compounds from natural sources, screening, or rational design.
- **Lead Optimization:** Enhancing potency, selectivity, and pharmacokinetics (ADME).
- **Preclinical & Clinical Testing:** Assessing efficacy and safety in biological systems and humans.

Rational Drug Design

- Traditional drug discovery relied on trial-and-error screening of large chemical libraries.
- Modern **rational drug design** leverages:
 - Molecular target structures (e.g., proteins),
 - Structure–activity relationships (SAR) of known ligands,
 - Computational modeling (e.g., docking, virtual screening),
 - Physicochemical properties affecting bioavailability and safety.
- By integrating these approaches, researchers can design and optimize drug candidates more efficiently, accelerating development.

Various Approaches Used in Drug Design

- Drug design can follow several broad strategies.
- While different pharmaceutical projects may use more than one approach, the main methods often fall into these categories:



1. Ligand-Based Drug Design (LBDD)

- Uses knowledge of known ligands binding to a target.
- Employs Quantitative Structure–Activity Relationships (QSAR) to link chemical structures with biological activity.
- **Pharmacophore modeling** identifies essential molecular features for binding.

2. Structure-Based Drug Design (SBDD)

- Uses 3D structural data (e.g., X-ray crystallography, NMR) to design or optimize ligands.
- **Molecular docking** predicts how compounds bind to a target.

3. Fragment-Based Drug Design (FBDD)

- Screens small molecular fragments that weakly bind to the target.
- Fragments are modified or linked to enhance affinity and specificity.

4. Computer-Aided Drug Design (CADD)

- Uses computational techniques, including LBDD and SBDD.
- Employs molecular modeling, simulations, virtual screening, and QSAR.

5. De Novo Design

- Designs novel compounds from scratch using computational algorithms.
- Iteratively refines structures for optimal target interaction.

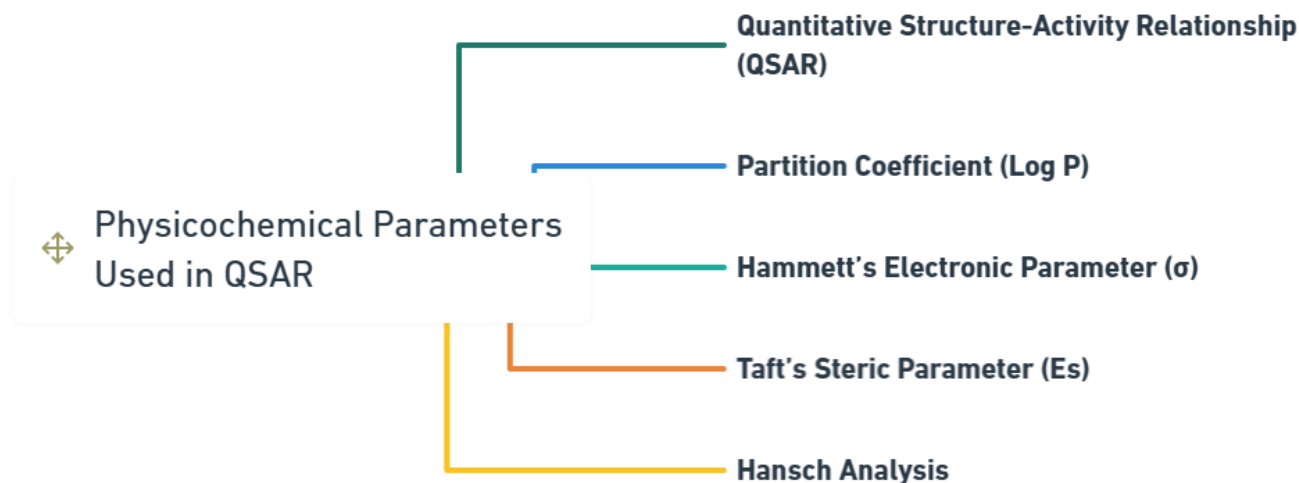
6. Traditional Approaches

- Relies on natural product isolation, serendipitous discoveries, and high-throughput screening.
- Has historically yielded key drugs (e.g., penicillin, taxol).

Physicochemical Parameters Used in QSAR

- Quantitative Structure-Activity Relationship (QSAR) is a mathematical modeling technique used to predict the biological activity of molecules based on their physicochemical properties.

Several key parameters are used in QSAR studies:



1. Partition Coefficient (Log P)

- **Definition:** The ratio of a compound's concentration in a lipid (octanol) phase to its concentration in a water phase.
- **Importance:** Measures the **lipophilicity** of a compound, which affects its ability to cross cell membranes and its distribution in the body.

Formula:

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

Impact on Drug Design:

- **High Log P** → Increased membrane permeability but poor water solubility (risk of bioavailability issues).
- **Low Log P** → Better solubility in water but poor cell membrane penetration.

2. Hammett's Electronic Parameter (σ)

- **Definition:** A measure of the **electronic effects** of substituents on a benzene ring.
- **Usage:** Helps predict how electron-withdrawing or electron-donating groups influence drug activity.

Formula:

$$\sigma = \frac{\log K_X}{K_H}$$

- where K_X are the equilibrium constants for substituted and unsubstituted compounds, respectively.



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