Drug Design

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Introduction of drug design

- Drug design is the process of discovering and developing new medications based on the understanding of biological targets.
- It involves creating molecules that interact with specific proteins, enzymes, or receptors in the body to treat diseases.

Various Approaches Used In Drug Design

1. Ligand-Based Drug Design (LBDD)

Aim:-This approach uses knowledge of existing molecules (ligands) that bind to the target protein to design new compounds.

Methods:

- **Quantitative Structure-Activity Relationship (QSAR):** This method correlates the structure of a molecule with its biological activity, allowing for prediction of activity for new compounds.
- **Pharmacophore Modeling:** Identifies the key features of a molecule that are responsible for its interaction with the target.
- **Analog Drug Design:** Modifies known active molecules to improve their properties.
- **Combinatorial Chemistry:** Synthesizes a large library of compounds to screen for activity.
- **Natural Products as Leads:** Uses naturally occurring compounds as starting points for drug design.

Various Approaches Used In Drug Design

2. Structure-Based Drug Design (SBDD)

Aim:-This approach uses the three-dimensional structure of the target protein to guide the design of new compounds.

Methods:

- **Molecular Docking:** Predicts how drug molecules bind to protein targets by finding low-energy conformations.
- **X-ray Crystallography, Cryo-EM, NMR Spectroscopy:** These techniques are used to determine the three-dimensional structure of proteins.
- **Computational Structure Modeling:** Uses computer simulations to predict protein structures and interactions.

Various Approaches Used In Drug Design

3. Other Approaches:

1. **Random Screening:** Involves screening a large number of compounds, including synthetic chemicals and natural products, for activity against a target.

2. **Natural Product Screening:** Focuses on identifying bioactive compounds from natural sources, such as plants and animals.

3. **Bioisosteric Principle:** Replaces one part of a molecule with another that has similar properties.

4. **Metabolic Studies:** Studies the metabolic pathways of a drug to optimize its effectiveness and safety.

5. **Target-based drug design:** Uses information about the biological target to design new compounds.

6. **In silico drug designing:** Drug design within computers.

Various Approaches Used In Drug Design

4. Modern Approaches

1. **AI & Machine Learning** – Speeds up drug discovery by predicting molecular interactions.
2. **Virtual Screening** – Simulates drug interactions before physical testing.
3. **CRISPR & Gene Editing** – Helps in designing precision medicines.

Physicochemical Parameters used in QSAR

1. Partition Coefficient (log P)

The **partition coefficient (P)** measures the distribution of a compound between two immiscible phases, usually **octanol and water**:

$$P = \frac{[\text{compound}]_{octanol}}{[\text{compound}]_{water}}$$

$$\log P = \log_{10}\left(\frac{[\text{compound}]_{octanol}}{[\text{compound}]_{water}}\right)$$

- A **high log P** indicates the compound is **lipophilic** (fat-loving, more soluble in octanol).
- A **low log P** indicates the compound is **hydrophilic** (water-loving, more soluble in water).

Physicochemical Parameters used in QSAR

In QSAR, log P is often used to model:-

Absorption, distribution, permeability (ADMET properties), Bioavailability, Toxicity, Membrane transport

Examples of Use

QSAR models may include log P as a feature like:

$$\text{Activity} = a \cdot \log P + b \cdot (\text{MW}) + c \cdot (\text{HBD}) + \cdots + z$$

Where:

- MW = molecular weight
- HBD = hydrogen bond donors

Tools to Calculate log P :-ChemAxon, ACD/Labs, Molinspiration, RDKit (open source), SwissADME (web-based)

Physicochemical Parameters used in QSAR

2. Hammett Electronic Parameters

Hammett's σ constants are **numerical values** that represent how a substituent affects the **electron density** of an aromatic ring (especially benzene), relative to hydrogen.

$$\sigma = \log\left(\frac{K_X}{K_H}\right)$$

Where:

- **K_X** - is the equilibrium constant with substituent X
- **K_H -** is the equilibrium constant with a hydrogen substituent

Physicochemical Parameters used in QSAR

When building a QSAR model, you can use σ values as electronic descriptors to correlate with:-

Binding affinity, Enzyme inhibition, Toxicity, Reaction rates

Example QSAR Equation:-

$$\log(\text{Activity}) = a \cdot \sigma + b \cdot \log P + c$$

Where:-

- **σ :-** Hammett electronic parameter
- **log P :-** lipophilicity
- **a,b,c :-** regression coefficients

Physicochemical Parameters used in QSAR

3. Taft's Steric Parameter (Es)

Taft's steric parameter (denoted as E_s) quantifies the steric bulk or hindrance of a substituent, helping to predict how a compound's structure influences its biological activity.

The **Taft steric constant Es** is derived from reaction rates of esters in hydrolysis reactions:-

$$E_s = \log\left(\frac{k_{\mathrm{CH_3}}}{k_X}\right)$$

Where:

- **kCH3 :-** is the rate of hydrolysis of **methyl ester** (minimal steric hindrance),
- **kX :-**is the rate of ester with substituent X.

Physicochemical Parameters used in QSAR

In **QSAR, Es is used**

as a **steric descriptor** to represent how bulky groups near a pharmacophore or active site might **hinder binding**, **affect orientation**, or **alter biological activity**.

QSAR equation example:

$$\log(\text{Activity}) = a \cdot \sigma + b \cdot E_s + c \cdot \log P + d$$

Where:

- **σ :-** is Hammett's electronic parameter,
- **Es :-** is Taft's steric parameter,
- **Log P :-** is lipophilicity.

Physicochemical Parameters used in QSAR

4. Hansch analysis

Hansch analysis is a classic QSAR method developed by Corwin Hansch in the 1960s. It uses linear regression to relate biological activity of compounds to their physicochemical properties, such as:-

- **log P** (lipophilicity)
- **σ** (Hammett electronic parameters)
- **Es** (Taft steric parameters)
- Other descriptors (MW, pKa, PSA, etc.)

Physicochemical Parameters used in QSAR

Purpose of Hansch Analysis

To **quantify** how structural changes in a molecule affect biological activity through:- Hydrophobic interactions (log P), Electronic interactions (σ), Steric effects (Es)

Hansch Equation:

$$\log(\text{Activity}) = a \cdot \log P + b \cdot \log^2 P + c \cdot \sigma + d \cdot E_s + e$$

Where:-

- **log P**: lipophilicity (often nonlinear, hence squared term)
- **σ**: electronic effect (Hammett parameter)
- **Es**: steric effect (Taft parameter)
- **a, b, c, d, e**: regression coefficients from training data

Pharmacophore Modeling

Pharmacophore modeling is a technique in computer-aided drug design (CADD) that identifies and extracts the essential steric and electronic features of a ligand that are necessary for it to interact with a specific biological target and trigger a biological response.

Pharmacophore Modeling

1. Ligand-Based Pharmacophore Modeling

- This approach focuses on identifying common features or "pharmacophoric elements" (like hydrogen bond donors/acceptors, hydrophobic regions, etc.) that are present in a set of known ligands that bind to a specific target.
- It analyzes the structural and chemical properties of these ligands to determine which features are essential for binding and biological activity.
- Ligand-based pharmacophores are useful for identifying novel ligands that might interact with the same target, even without knowing the target's 3D structure.

Example: If you have a set of known inhibitors for a certain enzyme, you can use ligand-based pharmacophore modeling to identify the key features that these inhibitors share, which can then be used to design new, potentially more effective inhibitors.

Pharmacophore Modeling

2. Structure-Based Pharmacophore Modeling

- This approach uses the known 3D structure of the target protein (obtained through X-ray crystallography, NMR, or other methods) to identify potential binding sites and favorable interactions.
- It analyzes the protein's active site and surrounding regions to determine the types of chemical and spatial features that are likely to be important for ligand binding.
- Structure-based pharmacophores can be used to guide the design of new ligands that are likely to bind to the target protein in a specific way.

Example: If you have the 3D structure of a protein and you want to design a new inhibitor, you can use structure-based pharmacophore modeling to identify the key features of the binding site that are important for binding, and then design a ligand that will fit those features.

Pharmacophore Modeling

Applications:

1. Virtual Screening:

Pharmacophore models can be used to screen large databases of molecules to identify potential drug candidates that are likely to bind to the target and elicit the desired biological effect.

2. Lead Optimization:

Once a lead compound is identified, pharmacophore modeling can help to optimize its structure by identifying features that can be modified to improve its activity or other desirable properties.

3. Target Identification:

Pharmacophore models can be used to identify the target of a drug or to predict the potential targets of a new drug candidate.

4. ADME-Tox Prediction:

Pharmacophore models can be used to predict the absorption, distribution, metabolism, and excretion (ADME) and toxicity (Tox) of a drug candidate.

5. Side Effects Modeling:

Pharmacophore models can be used to predict the potential side effects of a drug candidate by identifying off-target interactions.

Pharmacophore Modeling

Software:

Many software programs are available for pharmacophore modeling, including:-

1) HipHop,
2) HypoGen,
3) DISCO,
4) GASP,
5) GALAHAD,
6) PHASE,
7) MOE, and others.

Docking Techniques

Docking is a method which involves orientation and a best attempt to find a matching between two molecules it involves binding of one ligand to the active site of protein receptor to form a complex. The best way involved in explaining molecular docking is “Lock and Key system “the steps involve in this system is:-

- Finding the better orientation for the key which will go best in opening up the lock.
- On the surface the key lock is present.
- On which the direction to turn the lock is given.

Hence, the protein can be taken as the lock the ligand can be thought as a key.

Docking Techniques

Types of Docking:-

1. **Rigid Docking:** Both the protein and ligand are treated as rigid structures, simplifying the calculations.

2. **Flexible Docking:** The protein and/or ligand are allowed to change their conformations during the docking process, allowing for more accurate predictions of binding interactions.

3. **Semi-flexible Docking:** Only the ligand is allowed to change conformation, while the protein is kept rigid.

Docking Techniques

Applications in Medicinal Chemistry:

1) **Drug Discovery:** Molecular docking helps identify potential drug candidates and predict their binding affinity and efficacy.

2) **Lead Optimization:** It can be used to optimize the binding properties of lead compounds by suggesting modifications that enhance their interaction with the target.

3) **Virtual Screening:** Docking can be used to screen large databases of molecules to identify those that are likely to bind to a specific target.

4) **Understanding Drug-Target Interactions:** Docking provides insights into the molecular mechanisms of drug action and can help predict the potential for adverse drug reactions.

Docking Techniques

Software:-

Several software packages are available for molecular docking, including :-

1. AutoDock
2. GOLD
3. Schrodinger.

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