DEPTH OF BIOLOGY

Unit- 3

Rational Drug Design-

Traditional vs rational drug design, Methods followed in traditional drug design, High throughput screening, Concepts of Rational Drug Design, Rational Drug Design Methods: Structure and Pharmacophore based approaches

Virtual Screening techniques: Drug likeness screening, Concept of pharmacophore mapping and pharmacophore based

Screening,

Made with Goodnotes

Rational Drug Design- Traditional vs rational drug design

Rational Drug Design-

Definition

Rational drug design means designing drugs based on the knowledge of biological targets (like enzymes, receptors, DNA).

Instead of trial and error, scientists use structural information and computational tools to design drugs that fit and act on the target.

Made with Goodnotes

DEPTH OF BIOLOGY

Traditional Drug Design (Old Method)-

Based on trial and error → Drugs discovered randomly from natural sources (plants, microbes, animals).

Example: Penicillin was discovered accidentally from Penicillium fungus.

Screening of thousands of compounds was needed to find an active drug.

Little or no knowledge of the exact molecular target.

Very time-consuming and expensive.

Often leads to drugs with more side effects because of poor selectivity.

Made with Goodnotes

DEPTH OF BIOLOGY

Rational Drug Design (Modern Method)-
Based on understanding of the disease mechanism and target structure.
Requires knowledge of 3D structure of the target (from X-ray, NMR, or computational prediction).

Uses computational tools (in silico methods) like docking, molecular modeling.
Drugs are designed to fit exactly into the active site (like lock and key).
More specific and selective, hence fewer side effects.
Saves time and cost compared to random screening.

Examples:
HIV protease inhibitors (designed for the enzyme HIV protease).
Imatinib (Gleevec) designed for BCR-ABL tyrosine kinase in cancer.

Made with Goodnotes

Comparison: Traditional vs Rational Drug Design

Feature	Traditional Drug Design	Rational Drug Design
Approach	Trial and error, random	Scientific, target-based
Target knowledge	Unknown	Known (3D structure available)
Process	Screening many compounds	Designing specific compounds
Time & Cost	Very high	Relatively lower
Selectivity	Low (more side effects)	High (fewer side effects)
Examples	Penicillin, Morphine	HIV protease inhibitors

Made with Goodnotes

DEPTH OF BIOLOGY

DEPTH OF BIOLOGY

Methods followed in traditional drug design

Traditional drug design is also called the conventional or empirical approach. It mainly depends on trial and error, random discoveries, and screening of natural compounds.

Made with Goodnotes

DEPTH OF BIOLOGY

1. Natural Product Screening-

Drugs were obtained directly from plants, animals, or microbes.

Example:

Morphine from opium poppy.

Penicillin from Penicillium fungus.

Limitation: Required testing of thousands of extracts to find activity.

2. Serendipitous Discovery (Accidental Findings)-

Drugs were discovered by chance, without prior planning.

Example:

Penicillin (discovered accidentally by Alexander Fleming).

Chlorpromazine (found to have antipsychotic activity while testing for other uses).

Made with Goodnotes

3. Chemical Modification of Natural Compounds

Once a natural compound showed activity, scientists modified its structure to improve efficacy, safety, or solubility.

Example:

Modification of morphine → codeine, heroin derivatives.

Modification of salicylic acid → aspirin.

4. Random Screening of Synthetic Compounds

Large libraries of synthetic molecules were prepared and tested randomly on animals or cells.

Example: Sulfonamides were discovered during screening of synthetic dyes.

Limitation: Time-consuming, expensive, low success rate.

Made with Goodnotes

DEPTH OF BIOLOGY

5. Observation of Traditional Medicine (Ethnopharmacology)
Knowledge from folk medicine and Ayurveda/Chinese medicine guided drug discovery.

Example:
Quinine (antimalarial) from cinchona bark.
Reserpine (antihypertensive) from Rauwolfia serpentina.

Made with Goodnotes

DEPTH OF BIOLOGY

High Throughput Screening (HTS)

Introduction

High Throughput Screening (HTS) is a modern technique used in drug discovery.
It allows researchers to quickly test thousands to millions of compounds against a biological target (enzyme, receptor, or cell).

HTS is a robotics- and computer-based method, making the process fast, automated, and efficient.

Principle-

A large number of compounds are tested in parallel using small sample volumes in multi-well plates (96, 384, or 1536 wells).
Robotics perform liquid handling.
Detection systems (fluorescence, luminescence, absorbance) measure biological activity.
Data analysis software identifies "hits" (active compounds).

Made with Goodnotes

DEPTH OF BIOLOGY

Steps in High Throughput Screening-

-Target Identification & Assay Development

Define a biological target (e.g., enzyme, receptor).

Develop a reliable assay to measure activity.

-Compound Library Preparation

Create or collect thousands of natural, synthetic, or combinatorial compounds.

-Robotic Screening

Robotic systems automatically add compounds to assay plates.

Each well contains the target + one compound.

Made with Goodnotes

DEPTH OF BIOLOGY

Detection / Readout

Measure effect of each compound using techniques like fluorescence, radioactivity, or luminescence.

Data Analysis

Software analyzes results to find compounds that show desired activity.

Hit Identification

Active compounds (“hits”) are selected for further testing and optimization.

Made with Goodnotes

DEPTH OF BIOLOGY

Applications of HTS-

Drug Discovery → Identifies potential lead compounds.

Enzyme Inhibition Studies → Finds inhibitors or activators.

Receptor Binding Studies → Identifies ligands.

Toxicity Testing → Screens compounds for safety.

Functional Genomics & Proteomics → Studies biological pathways.

Advantages-

Rapid screening of thousands to millions of compounds.

Highly automated and reproducible.

Reduces time and cost of early drug discovery.

Provides a large number of hit compounds for optimization

Made with Goodnotes

DEPTH OF BIOLOGY

Limitations-

Requires expensive equipment and robotics.
May give false positives or false negatives.
Needs validated assays (good assay design is crucial).
Hits often require further optimization (not always ready-to-use drugs).

Made with Goodnotes

Concept of Rational Drug Design (RDD)

Definition

Rational Drug Design is the scientific process of designing new drugs based on knowledge of the biological target (enzyme, receptor, nucleic acid).
Instead of random screening, it uses structural and mechanistic information to design specific molecules.

Concept / Principle

Disease occurs due to malfunction of a specific biological target.
If the 3D structure of the target is known (through X-ray, NMR, or computational modeling), scientists can design a drug that fits into the active/binding site.
This follows the lock-and-key model → the drug (key) is designed to fit exactly into the target (lock).

Made with Goodnotes

DEPTH OF BIOLOGY

Approaches in Rational Drug Design-

Structure-Based Drug Design (SBDD): Uses 3D structure of the target to design drugs (e.g., HIV protease inhibitors).

Ligand-Based Drug Design (LBDD): Uses knowledge of ligands (drugs) that bind to the target, even if structure of the target is not fully known.

Steps in Rational Drug Design-

-Identification of disease target (enzyme, receptor).
-Determination of target structure (3D structure).
-Computer-aided design of molecules to interact with the target.
-Synthesis and testing of these molecules.
-Optimization of lead compounds for better activity and fewer side effects.

Made with Goodnotes

DEPTH OF BIOLOGY

Advantages

More selective and specific drugs.

Fewer side effects.

Saves time and cost compared to traditional drug discovery.

Examples

Imatinib (Gleevec): designed to inhibit BCR-ABL tyrosine kinase in leukemia.

HIV protease inhibitors: designed for HIV treatment.

Made with Goodnotes

Methods of Rational Drug Design (RDD)

Rational drug design uses scientific knowledge of the biological target or ligands to create effective and selective drugs. The main methods are:

1. Structure-Based Drug Design (SBDD)-

Concept: Uses the 3D structure of the target protein/receptor to design drugs that fit into the active site.

Structure obtained from X-ray crystallography, NMR, or computational prediction.
Works on the lock-and-key principle.

Made with Goodnotes

DEPTH OF BIOLOGY

Steps-

Identify and validate the biological target.

Obtain the 3D structure of the target.

Identify active/binding sites (pockets, grooves).

Design molecules (in silico) that can bind specifically.

Test binding using molecular docking and scoring functions.

Synthesize and evaluate promising candidates.

Applications

Enzyme inhibitors.

Kinase inhibitors in cancer.

Antiviral drugs.

Examples-

HIV protease inhibitors (ritonavir, saquinavir).

Imatinib (Gleevec) for BCR-ABL kinase in leukemia.

Made with Goodnotes

2. Ligand-Based Drug Design (LBDD)-

Concept: Used when the 3D structure of the target is not available.
Relies on the study of known ligands (compounds that already bind to the target).
Similar ligands are assumed to produce similar activity.

Techniques

1. QSAR (Quantitative Structure-Activity Relationship):
Relates chemical structure to biological activity using mathematical models.
Example: SAR studies of sulfonamides.

2. Pharmacophore Modeling:
Identifies essential features (e.g., hydrogen bond donor/acceptor, hydrophobic groups) required for activity.

Made with Goodnotes

DEPTH OF BIOLOGY

3. Similarity Searching-

Finds new ligands with structural similarity to active compounds.

Applications

Useful in early drug discovery when target structure is unknown.

Drug repurposing and analog development.

Examples-

Development of β-blockers based on known adrenergic ligands.

SAR studies leading to improved sulfonamide antibiotics.

Made with Goodnotes

DEPTH OF BIOLOGY

3. Computer-Aided Drug Design (CADD)-

Concept: Uses computational tools and bioinformatics to support both SBDD and LBDD.

Helps in virtual screening of millions of compounds before laboratory testing.
Techniques

Molecular docking – simulates binding of drug to target.
Molecular dynamics – studies stability and movement of drug-target complex.
Virtual screening – screens large chemical libraries in silico.
ADMET prediction – predicts absorption, distribution, metabolism, excretion, and toxicity of compounds.

Made with Goodnotes

4. De Novo Drug Design-

Concept: Designing completely new molecules from scratch without relying on existing ligands.

Molecules are built inside the binding site by computational programs.
Optimized for shape, size, and interactions.

Steps
Identify binding pocket in the target.
Computationally generate new molecules that fit.
Optimize binding affinity and drug-like properties.
Synthesize and test selected molecules.

Made with Goodnotes

Summary Table: Methods of Rational Drug Design

Method	Basis of Design	Techniques Used	Example
Structure-Based Drug Design (SBDD)	3D structure of protein target	Molecular docking, site mapping	HIV protease inhibitors, Imatinib
Ligand-Based Drug Design (LBDD)	Known active ligands	QSAR, pharmacophore modeling, similarity searching	β-blockers, sulfonamides
Computer-Aided Drug Design (CADD)	Computational modeling	Docking, molecular dynamics, ADMET prediction	COVID-19 antiviral screening
De Novo Drug Design	New molecules from scratch	Fragment-based design, in silico synthesis	Novel kinase inhibitors

Made with Goodnotes

DEPTH OF BIOLOGY

Structure and Pharmacophore based approaches

1. Structure-Based Drug Design (SBDD)-

Concept: Uses the 3D structure of the biological target (enzyme, receptor, protein) to design or optimize small molecules (drugs).

Basis: Requires detailed structural information of the target, usually obtained from X-ray crystallography, NMR, or cryo-EM.

Process:

Identify the binding site of the target (active site or allosteric site).

Design or optimize molecules that fit into this pocket.

Use computational tools (like molecular docking, molecular dynamics).

Made with Goodnotes

DEPTH OF BIOLOGY

Applications:

Designing HIV protease inhibitors, kinase inhibitors, etc.

Advantages:

Precise design with atomic-level detail.
Can predict binding interactions and optimize potency.

Limitations:

Needs accurate 3D structure of target.
Computationally demanding.

Made with Goodnotes

DEPTH OF BIOLOGY

2. Pharmacophore-Based Drug Design (PhBDD) -

Concept: Focuses on the arrangement of chemical features necessary for a drug to interact with its target, even when the 3D structure of the protein is not fully known.

Pharmacophore = An abstract description of molecular features essential for activity (like hydrogen bond donors, acceptors, aromatic rings, hydrophobic centers, positive/negative ionizable groups).

Process:
Analyze known active molecules (ligand-based approach).
Identify common features required for activity.
Develop a pharmacophore model.
Screen chemical databases for molecules matching this model.

Made with Goodnotes

DEPTH OF BIOLOGY

Applications:

When protein structure is unavailable.

Used in virtual screening and hit identification.

Advantages:

Can be applied without target structure.

Helps identify novel scaffolds.

Limitations:

Less precise than SBDD.

Depends on the quality of known active ligands.

Made with Goodnotes

DEPTH OF BIOLOGY

Virtual Screening techniques

Virtual screening = computer-aided method to search large chemical libraries and identify molecules (hits) likely to bind with a biological target.

It is widely used in drug discovery to save time and cost compared to experimental (wet lab) screening.

Two main categories:
Structure-Based Virtual Screening (SBVS)
Ligand-Based Virtual Screening (LBVS)

Made with Goodnotes

DEPTH OF BIOLOGY

Structure-Based Virtual Screening (SBVS)-

Concept: Uses the 3D structure of the biological target (enzyme, receptor, protein).

Steps:

Identify the target protein structure (from X-ray crystallography, NMR, cryo-EM, or homology modeling).

Locate the binding site (active site or pocket).

Perform molecular docking of chemical compounds.

Score and rank molecules based on binding affinity.

Techniques used:

Molecular Docking (predicts binding orientation and affinity).

Molecular Dynamics simulations (check stability of protein-ligand complex).

Pharmacophore modeling (target-based).

Advantages: Accurate when protein structure is available.

Limitations: Requires good-quality target structure.

DEPTH OF BIOLOGY

Ligand-Based Virtual Screening (LBVS)

Concept: Used when protein 3D structure is unknown, but active ligands are available.

Steps:

Collect known active molecules (ligands).
Identify common features responsible for activity.
Screen chemical databases for molecules with similar features.

Techniques used:

Pharmacophore Modeling (ligand-based).
Quantitative Structure–Activity Relationship (QSAR) models.
Similarity Search (2D fingerprints, Tanimoto coefficient).
Shape-based Screening (compares molecular shape/volume).

Advantages: Useful when protein structure is unavailable.

Made with Goodnotes

DEPTH OF BIOLOGY

-Hybrid Virtual Screening Approaches
Combine SBVS + LBVS for more reliable results.

Example: Use ligand pharmacophore models to filter compounds before docking into the protein target.

Applications of Virtual Screening-

Identification of new drug leads from large compound libraries.
Repurposing of existing drugs.
Screening of natural products or combinatorial libraries.
Reducing experimental cost and time in early drug discovery.

Made with Goodnotes

DEPTH OF BIOLOGY

Drug-Likeness Screening

Not all molecules that show activity in a lab can become good drugs.

Drug-likeness screening is the process of checking whether a compound has the right physicochemical and pharmacokinetic properties (ADMET: Absorption, Distribution, Metabolism, Excretion, Toxicity) to be developed into a drug.

This screening is usually done before synthesis or early in discovery using computational (in silico) tools.

Objective / Purpose-

To filter out unsuitable molecules at an early stage.
To check oral bioavailability and safety.
To save time, cost, and effort in drug discovery.

Made with Goodnotes

DEPTH OF BIOLOGY

Parameters Used in Drug-Likeness Screening

(a) Physicochemical Properties-

Molecular weight

Lipophilicity (LogP)

Hydrogen bonding ability

Polarity (PSA)

Flexibility (rotatable bonds)

(b) Pharmacokinetic Properties (ADMET)

Absorption (can it be absorbed orally?)

Distribution (can it reach the target site?)

Metabolism (is it stable or broken down too fast?)

Excretion (does it leave the body safely?)

Toxicity (is it harmful?)

Made with Goodnotes

DEPTH OF BIOLOGY

Rules and Guidelines

(i) Lipinski's Rule of Five

A good oral drug usually has:

Molecular weight < 500 Da

LogP < 5

H-bond donors ≤ 5

H-bond acceptors ≤ 10

(ii) Veber's Rules

Rotatable bonds ≤ 10

PSA ≤ 140 $Å^2$

(iii) Other Rules

Good water solubility

No toxic or reactive groups

Methods of Screening-

In silico (Computer-aided)-

Predict drug-likeness using software (e.g., SwissADME).

In vitro assays-

Cell-based studies (e.g., Caco-2 permeability test).

ADMET models-

Simulations to check metabolism, toxicity, clearance.

Made with Goodnotes

DEPTH OF BIOLOGY

Applications

Used in lead identification and optimization.

Helps in high-throughput screening.

Reduces late-stage clinical trial failures.

Advantages

Saves time and money.

Improves success rate of drug candidates.

Provides early prediction of oral drug potential.

Limitations

Rules are not absolute (some drugs break them).

Cannot predict rare or long-term side effects.

Does not guarantee success, only increases probability.

Made with Goodnotes

Concept of Pharmacophore Mapping-

Definition of Pharmacophore-

A pharmacophore is defined as the 3D arrangement of essential chemical features required for a molecule to interact with a specific biological target and produce a desired biological effect.

These features include:
Hydrogen bond donors
Hydrogen bond acceptors
Hydrophobic centers
Aromatic rings
Positively or negatively ionizable groups

Made with Goodnotes

DEPTH OF BIOLOGY

Concept of Pharmacophore Mapping-

Pharmacophore mapping is the process of identifying, aligning, and visualizing the essential chemical features of active compounds.

It helps in understanding the structural requirements for biological activity.
It is ligand-based, meaning it is developed from molecules (ligands) known to bind to a target, even when the 3D structure of the protein is unknown.

Made with Goodnotes

DEPTH OF BIOLOGY

Steps in Pharmacophore Mapping-

Selection of Active Compounds
Collect a set of molecules that are active against the same target (e.g., enzyme inhibitors).

Identification of Common Features
Analyze molecules to find recurring pharmacophoric features (H-bond donors/ acceptors, hydrophobic groups, etc.).

3D Alignment of Molecules
Superimpose compounds in 3D space so that common features overlap.

Pharmacophore Model Generation
Develop a 3D model that shows the spatial arrangement of the essential features.

Made with Goodnotes

DEPTH OF BIOLOGY

Validation of the Model-

Check whether the pharmacophore can correctly distinguish active molecules from inactive ones.

Importance of Pharmacophore Mapping-

Drug Design: Provides a template to design new drug-like molecules.
Lead Optimization: Helps in modifying existing compounds to improve activity.
Virtual Screening: Used to search large chemical databases for compounds that match the pharmacophore.
Understanding Mechanism: Explains why structurally different molecules may produce the same biological activity.

Made with Goodnotes

DEPTH OF BIOLOGY

Example-

Suppose we study 4 inhibitors of an enzyme:

After mapping, all inhibitors show:

1 hydrogen bond donor at a fixed position,

1 hydrophobic group near the donor,

1 aromatic ring at a specific distance.

This arrangement forms the pharmacophore map.

Any new compound matching this arrangement is likely to show inhibitory activity.

Limitations-

Accuracy depends on quality of input molecules.

Cannot always predict exact binding affinity.

May not explain activity for very diverse compounds.

Made with Goodnotes

DEPTH OF BIOLOGY

Pharmacophore-Based Screening

Pharmacophore-based screening is a virtual screening technique where a pharmacophore model is used as a 3D queryto search large chemical libraries.

The goal is to identify compounds that fit the pharmacophore features and may act as potential drug candidates.

Once a pharmacophore model is built (from known active ligands or protein-ligand complexes), it can be applied to scan databases.

Only molecules that match the spatial arrangement of essential features (H-bond donor/acceptor, hydrophobic centers, aromatic ring, ionizable groups) are selected. These are considered as "hits" for further testing.

Made with Goodnotes

Steps in Pharmacophore-Based Screening

1. Pharmacophore Model Development

Generate a pharmacophore model using:

Known active compounds (ligand-based approach), or

Protein-ligand complex structures (structure-based approach).

2. Preparation of Compound Database

Collect chemical libraries (millions of molecules).

Convert 2D structures into 3D conformations.

3. Screening Process

The pharmacophore model is used as a search query.

Database molecules are compared to check if they fit the pharmacophoric features.

Made with Goodnotes

DEPTH OF BIOLOGY

4. Scoring and Ranking

Compounds are scored based on how well they match the pharmacophore.

5. Top-ranked compounds are shortlisted as potential hits.

Filtering for Drug-Likeness

Apply filters (Lipinski's rule of 5, ADMET properties) to remove unsuitable compounds.

6. Experimental Validation

Selected hits are synthesized or obtained and tested in biological assays.

Made with Goodnotes

DEPTH OF BIOLOGY

4. Applications

Hit Identification: Finding new active compounds from large databases.
Lead Discovery: Identifying novel scaffolds that interact with the same target.
Drug Repurposing: Discovering new uses for existing drugs by matching pharmacophores.
Optimization: Helps in refining leads by comparing how modifications affect pharmacophore matching.

5. Advantages

Can screen millions of compounds quickly and cheaply.
Works even when the protein structure is unknown.
Identifies chemically diverse compounds with the same activity.
Reduces the number of compounds needed for experimental screening.

Made with Goodnotes

DEPTH OF BIOLOGY

Limitations

Success depends on the quality of the pharmacophore model.

May produce false positives (compounds that fit the model but are inactive).

Cannot predict exact binding affinity or full pharmacokinetics.

Example

A pharmacophore model for an HIV protease inhibitor includes:

2 hydrogen bond acceptors

1 hydrophobic group

1 aromatic ring

Screening a chemical database using this model identifies novel compounds that were not structurally similar to known inhibitors but showed anti-HIV activity in experiments.

Made with Goodnotes