A REVIEW ON DRUG DESIGN

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Abstract **- A sophisticated pharmaceutical science with a lengthy history is drug design. Since the end of the 19th century, when Emil Fisher proposed that the drug-receptor interaction is similar to the interaction between a key and a lock, many advances have been achieved in the field of drug design. Drug design has gradually evolved into a disciplined science with a strong theoretical foundation and real-world applications. The most cutting-edge method for finding new drugs right now is drug design. In order to accomplish its primary objective—the creation of efficient, specialised, non-toxic, safe, and well-tolerated drugs—it makes use of scientific and technological advancements and incorporates them into a diverse array of methodologies and instruments. One of the fields of science that is now undergoing the most intense development is drug design, and the impact of artificial intelligence. The goal of the current overview is to summarise some of the most significant turning points in the history of drug design, to describe some of the most popular techniques now in use, and to sketch the author's vision for the future. The review informs the reader on the material in Molecules' Special Issue "Drug Design—Science and Practice," without claiming to completely cover the vast spectrum of drug design subjects.**

Keywords **– Drug design, drug discovery and development, QSAR, molecular docking, molecular dynamics, virtual screening, artificial intelligence.**

➢ DRUG DESIGN

➢ Introduction :

Medicine design is the process of creating a new drug by molecularly altering an existing chemical to maximise desired benefits and minimise unwanted side effects.

Two ways of drug design:

1. Creation of ligands with desired characteristics for targets with known structural and functional characteristics.
2. Creating ligands for targets whose structural details may or may not be known that have predetermined attributes.

Basic concept of the drug management cycle:

Drug designing:

- Organic or chemical compounds.
- Individual chemicals or a combination of several substances.
- Traditional treatments were used in the past for therapy. In the modern day, sickness is treated at the molecular level.

History:

1. Plants or natural goods: Medical substances were derived from plants and natural items.
Example: Congestive heart failure treatment with fox gloves.
2. Unintentional observation: In 1928, Alexander Fleming saw how mould affected things.

• Pencillin is a material produced by mould (penicillium).

Types:

These several approaches are frequently utilised in the creation of pharmaceuticals.

A. Mechanism-based drug design;
B. drug design based on structure
C. Ligand-based drug design
D. Receptor Based drug design
E. Computer based drug design

A. Drug design based on mechanisms : When the disease process is comprehended at the molecular level and the target molecule (s) are determined, drugs may be carefully developed to interact with target molecules in a way that disrupts the disease.

B. Structure-based Drug Design: This is one of the first methods in drug development.

• Contributed to the development of a new medicine.

Calculations are used to learn more about the structural dynamics and electronic characteristics of ligands.

• Drug design based on structure may be loosely classified into two types.

1) Ligand-based .

2) Based on receptor.

1. Drug design based on ligands:

• In the first category, ligands for a specific receptor are sought after.

> Several hundred ligand candidates are examined.

• This process is typically known as ligand-based drug design.

• The process of synthesising novel lead compounds is more efficient.

2. Based on receptor :

Ligand molecules are built up within the confines of the binding pocket by assembling small pieces in a stepwise manner. These pieces can either be individual atoms or molecular fragments. The key benefit of such a method is that novel structures not contained in a nay database, can be suggested.

C. Ligand-based drug design

D. Receptor Based drug design

E. Computer based drug design

- **Techniques of drug design:**

1) X – ray crystallography: • Starting place for getting knowledge from mechanism drug design.

• Discover the structural details of molecules.

• Offers the vitally necessary coordinates required for the data processing by computer modelling systems.

2) Comparative protein modelling, sometimes referred to as homology modelling.

• Building atomic-resolution models of the target and a similar homologous protein's experimental three-dimensional structure..

- **Docking:**

• Docking seeks to match two molecules as closely as possible.

• It entails locating the proper key for the lock.

Determine, given two biological compounds.

- The two molecules' ability to decide.

If true, what is the complex's optimal orientation for maximising interaction while decreasing overall energy?

- **Goal:**

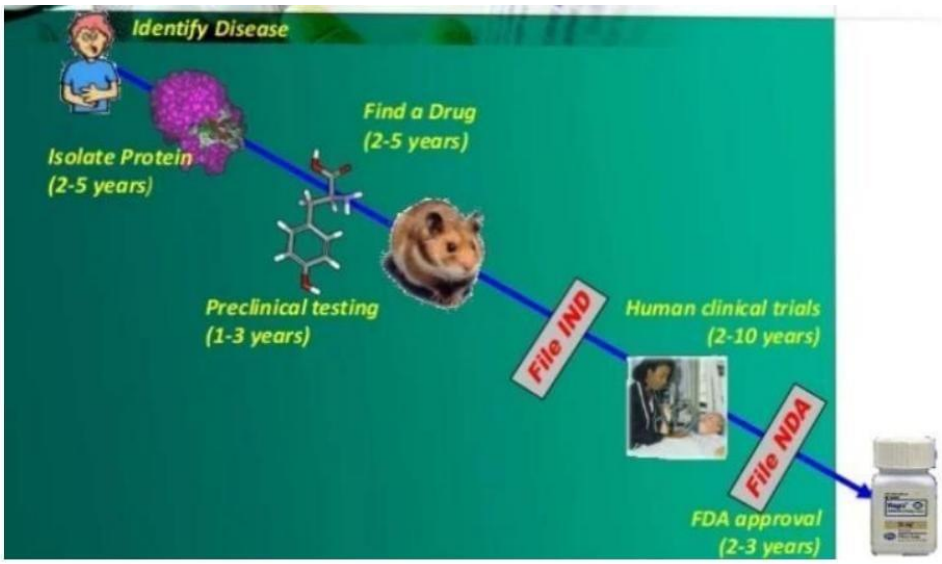
being able to do a search on a database of molecular structures and get a list of all the molecules that can talk to the structure in the search.

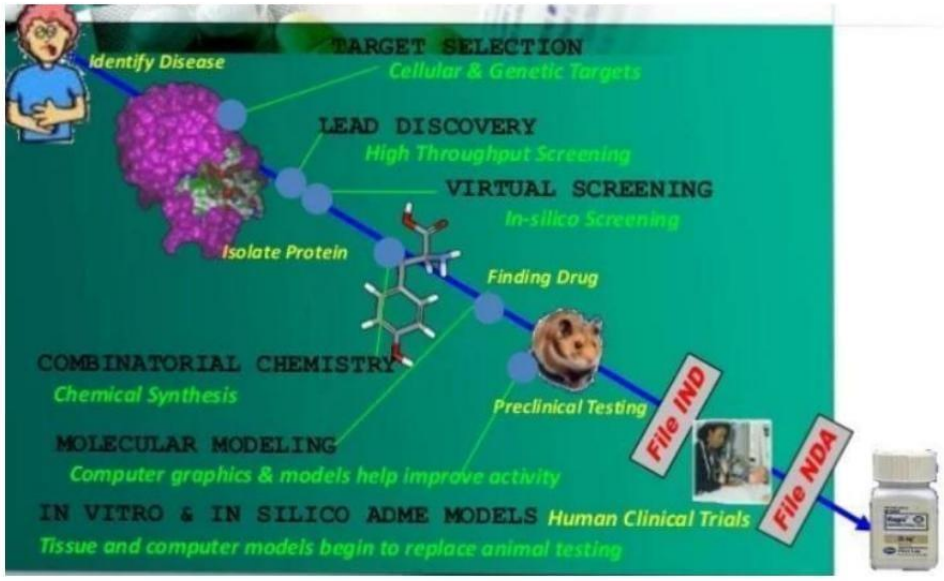
How is a drug developed:

• A novel therapeutic drug's development is a:

1. Complex
2. Lengthy
3. Expensive

The development of a medication from a basic idea can take ten to fifteen years and more than $500 million.





Advantage:

- Cost-effectiveness improvements;
- Techniques for avoiding harmful side effects.
- Drugs that are well tolerated,
- safe, and
- less expensively designed.
- Expensive\s.

Disadvantage:

- Modern drug design strategies can make drug discovery more successful and logical.
- Time-consuming
- Challenging

➢ **QSAR**

(Quantitative structure- activity relationship)

• A correlation between quantitative structure and activity Is a mathematical connection that uses an equation to relate measurable or calculable chemical attributes to a certain biological activity

In order to apply these rules to assess the biological activity of novel compounds, QSAR seeks to establish a reliable link between molecular characteristics and biological activity.

• Acquiring knowledge of electronic effect, steric effect, and lipophilicity in QSAR.

• By changing the lead compound's chemical structure, it may be possible to create a more effective therapeutic agent by retaining or enhancing the desired pharmacologic impact while reducing undesirable pharmacological, physical, and chemical features.

• To employ target analogues as pharmacological probes to learn more about the lead molecule's pharmacology and potentially to uncover new information about basic biology

• Improved knowledge of action modes and improved activity prediction of novel or analogue compounds are among the objectives of QSAR investigations.

❖ **Steps:**

1. Selection of Data set and extraction of structural/empirical descriptors
2. Variable selection,
3. Model construction and
4. Validation evaluation.

❖ **Parameter:**

Various parameter uses in QSAR parameter

1. Lipophilic parameter – Partition coefficient molar refractivity.
2. Electronic parameter- Hammet constant
3. Steric parameter – Taft's constant verloop steric parameter

1. LIPOPHILIC PARAMETERS:

Partitioning of the substance between an aqueous and non-aqueous phase is known as lipophilicity.

➢ • P = [drug] in octanol / [drug] in water is the partition coefficient.

➢ Typically, a straight line is achieved for a short range of log P, such as 1-4. For instance, log 1/C = 0.75 log P + 2.30

➢ Get a parabolic curve if the graph is stretched to very high log P values. log 1/C = (log P)2 + K2 log P + k3

➢ When P is low, the log P word predominates.

➢ The activity of hydrophobic substituent constants, also known as -substituent constants, decreases when P is big because log P squared dominates. Hansch and colleagues established this constant using the equation below. PX equals Log PX - Log PH

➢ A positive value means that the drug prefers the organic phase and that the substitute has a higher lipophilicity than hydrogen.

➢ If the value is negative, the substituent has The medication prefers the aqueous phase and has a lower lipophilicity than hydrogen.

2. ELECTRONIC PARAMETERS:

Electron Withdrawing Groups; The Hammett constant(); sx = log (Kx/Kbenzoic)

Equilibrium swings to the right and Kx exceeds Kbenzoic.

S will be positive as sx = log Kx - log Kbenzoic.

The value of the Hammett constant relies on whether the substituent is para- or meta-substituted -ortho not measured owing to steric effects. It also takes into consideration resonance and inductive effects.

3. STERIC SUBSTITUTION CONSTANT:

It serves as a gauge of the size of the group it represents and how that affects how closely the medicine interacts with the receptor site. considerably more difficult to quantify

Examples include Taft's steric factor (Es) (1956), a value determined by experimentation using rate constants.

The MW, density, and index of refraction are all included in the equation for molar refractivity (MR), which measures the volume filled by an atom or group. Verloop steric parameter is calculated using bond angles, van der Waals radii, and bond lengths using a computer programme.

QSAR HAS THE FOLLOWING ADVANTAGES:

• It offers a method to quantify the relationship between structure and activity utilising the physiochemical characteristics of the system.

• Theoretically, intended compounds may be predicted before their chemical synthesis into new analogues.

• Understanding the interactions between the functional groups of newly synthesised compounds and the activity of the target protein or enzyme might be valuable.

DISADVANTAGES OF QSAR:
• Correlations in biological data may be incorrect due to experimental error.
• If the training set of molecules is smaller, it is conceivable that some of the attributes may not be adequately reflected in the data, making it hard to predict which molecules would be the most active.
• Ligands binding proteins or receptors may not be accessible in some 3D QSAR experiments.

- **Application**:
- QSARs are employed in many different disciplines, including risk assessment, toxicity prediction, and regulatory choices, in addition to drug development and lead optimization..

- **Experimental**

1. CADD Overview:
The main categories of CADD techniques are:
CAD Computer-aided design is the process of creating and documenting a product utilising software.
Engineering drawings need the use of visual symbols such point lines, curves, planes, and shapes. In essence, it gives a detailed graphical depiction of each component's explanation.
The following are the two basic methodologies for drug design with CADD:
1. Direct or structure-based medication design
2. Ligand based drug design / indirect approach
1. Structure-based drug design:

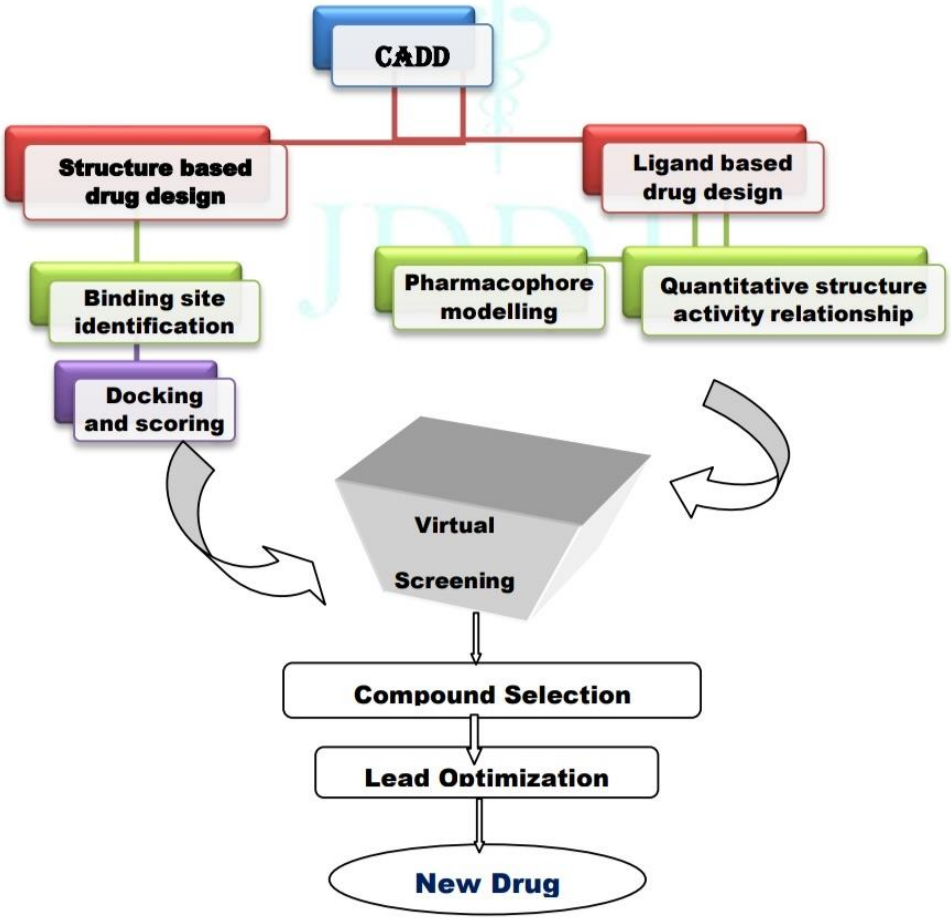


Figure 3: General Representation of workflow for CADD.

Structure-based drug design (SBDD) is a technique that makes use of computational chemistry techniques to find or create novel chemical compounds that potentially bind to a target and inhibit that target protein.

1. Ligand-Based drug design:

When 3D receptor information is lacking or unavailable, ligand-based drug design, which uses the understanding of compounds that bind to the biological target of interest, is a valuable technique for finding new medications.

Application of Ligand-based Drug Design:

- New compound structure evaluation,
- chemical structure improvement,
- and new compound bioactivity and ADMET characteristics prediction

2. Chemical structure drawing:

Best Online Tools for Drawing Chemical Structures

1. ChemDraw:

- The most complete and potent drawing tool for communicating chemistry research is called "ChemDraw," which enables users to depict biological as well as chemical structures and interactions.
- Users may also use it to explore 3D structures, forecast characteristics and spectra, and convert chemical structures to IUPAC names.
- It generates accurate structures from chemical names and gives structures precise IUPAC designations.
- It also uses the direct atom to spectral correlation to estimate NMR spectra from a ChemDraw structure.

2. Chemdoodle:

- Chemdoodle is a sophisticated function that allows you to totally recreate chemical diagrams from photos of molecules without any chemical information being given.
- This programme produces intricate illustrations of mechanisms.
- Both arrows and arrowheads may be fully customised.
- Only ChemDoodle's text fields support superscript and subscript merge formatting, making it the easiest tool for creating chemical writing such as atomic notations.
- ChemDoodle has hundreds of chemical characteristics that contribute to the creation of visuals of the highest calibre.
- ChemDoodle is a sophisticated capability that allows you to totally recreate chemical diagrams from photographs of molecules without any chemical information being given. It is possible to utilise the retrieved chemical drawings for additional editing or analysis.

3. Chemsketch:

- The sketching programme ChemSketch enables you to depict chemical structures such as organics, organometallics, and polymers.

- Additionally, it has capabilities for identifying structures, calculating molecular parameters (such as molecular weight, density, and molar refractivity), cleaning and visualising 2D and 3D structures, and predicting logP.

- Molecular modelling software called ChemSketch is used to draw and edit pictures of chemical structures.

- This tool enables the understanding of the structure of chemical bonds and the characteristics of functional groups in molecules and molecular models shown in two and three dimensions.
- •With more than 2 million users worldwide, ChemSketch is a simple-to-use, chemically intelligent molecular structure sketching programme..

4. Marvin:

You can create, modify, publish, render, import, and export chemical structures with the Marvin suite, a chemically intelligent desktop toolkit.

• It also enables file conversions between several graphical and chemical file formats.
• For making science available across all platforms, Marvin is a fully functional chemical editor.
• In addition, it features integrated property calculators that can produce real-time answers, built-in structure and valence checks that can offer help.
• Marvin converts chemistry into a digital environment and supports the most chemical file formats that are accepted by industry.

5. BKChem:

• BKChem is a free Python programming tool for creating chemical diagrams.
• BKChem can quickly generate the fundamental structure and its connections to the symbols of each element by using symbols and the necessary components of any chemical formula.
• It is a cross-platform programme that enables sketching of molecular structures and basic chemical compounds.
• BKChem defines bond length and angles with structure by sketching each bond individually.
• For those who lack the confidence to create their own molecular charts, it also includes a variety of ready-to-use templates.

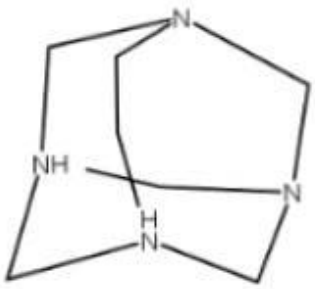
• Any aspiring scientist or science publisher who frequently has to draw intricate chemical compound diagrams would find BKChem handy.

3. Chemical Structure Presentation:

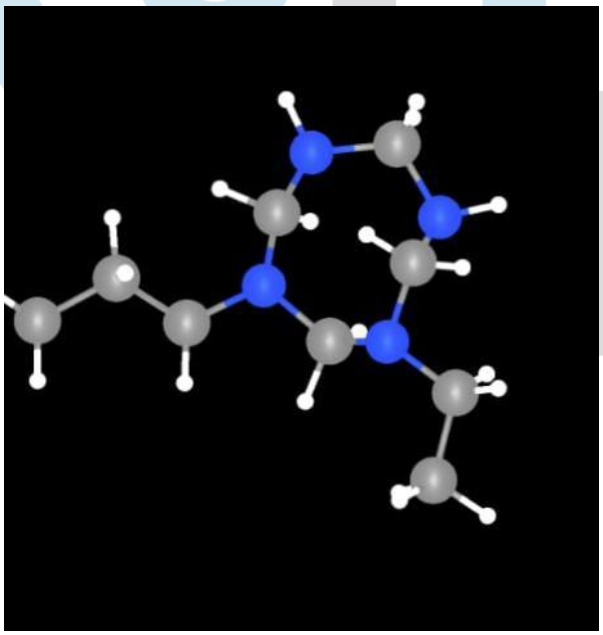
1. Hexamine:

3D Structure of Hexamine:

Hexamine

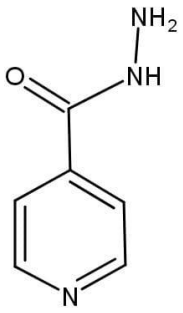


IUPAC NAME - 1,3,5,7-tetraazatricyclo[3.3.1.13,7]decane
Molecular formula- C6H12N4
Molecular weight -140.19



2. Isoniazid:

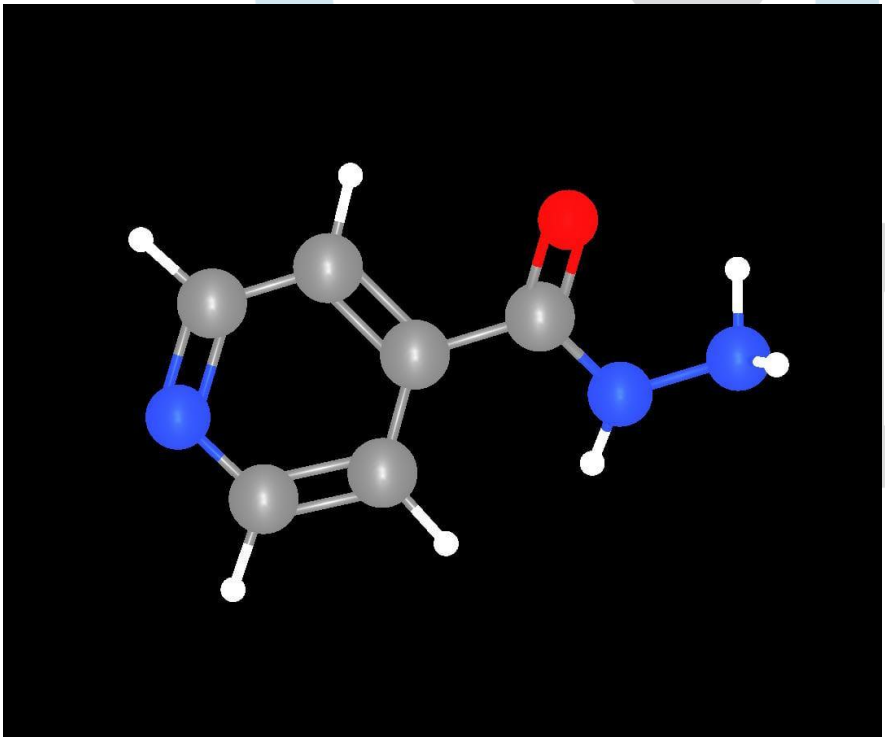
Isoniazid



pyridine-4-carbohydrazide

Formula: $C_6H_7ON_3$
Exact Mass: 137.06
Mol.Wt.: 137.14
Elem.Anal.: C,52.55; H,5.15; O,11.67; N,30.64
m/z: 137.06 (100.0%); 138.09 (7.9%)

3D Structure of Isoniazid:



Chemical databases search:

Chemical databases are crucial throughout the entire medicinal chemistry process.

Databases might include

• Details on the composition of chemicals, for instance. Merck index, Beilstein chemical abstracts

Information about compound structure and production, for instance. a compound register kept internally

• Biology activity data, such as results from internal research or the MDL Drug Data Report (MDDR)

Types of chemical databases:

1. Bioactivity databases:

Structures or other chemical details are correlated with bioactivity results obtained through bioassay in publications, patents, and screening programmes by bioactivity databases.

2. Crystallographic database:

Data on X-ray crystal structure is kept in crystallographic databases. Protein Data Bank and Cambridge Structural Database are common examples.

3. NMR spectra database:

Chemical structure and NMR data are correlated in a database of NMR spectra. These databases frequently provide additional characterisation information, such mass spectrometry and FTIR data.

4. Reaction database:

The majority of chemical databases provide data on stable compounds, however reaction databases also contain information on intermediates and briefly generated unstable molecules. Information regarding products, educts, and reaction processes may be found in reaction data banks.

5. Thermophysical database:

• Phase equilibria, such as vapor-liquid equilibrium, solubility of gases in liquids, liquids in solids (SLE), temperatures of mixing, vaporisation, and fusion are all covered by thermophysical data.

• Caloric information such as heat capacity, formation heat, and combustion.

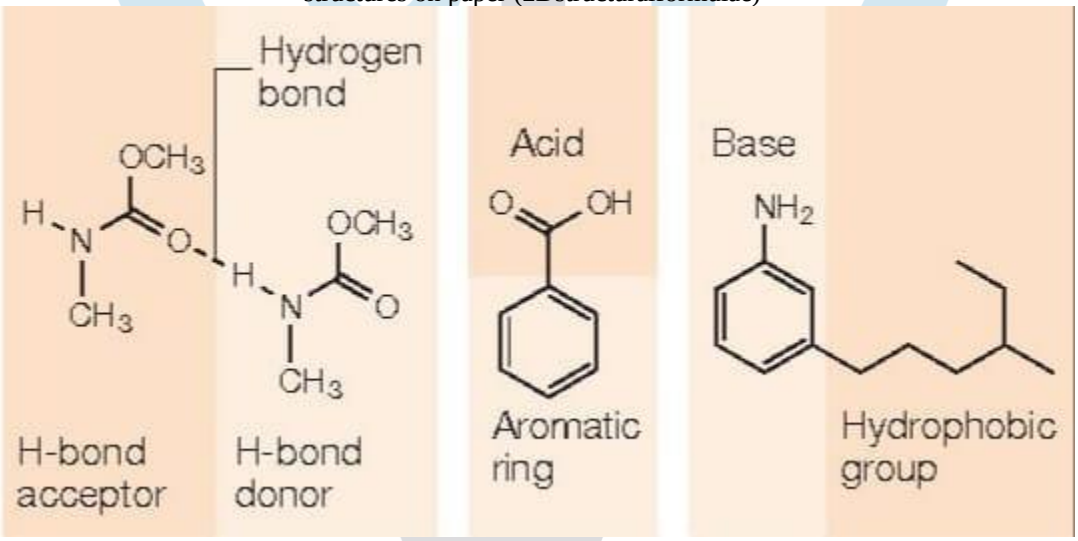
• Transport characteristics like heat conductivity and viscosity.

What is a chemical database used for?

Accessible Chemical Databases These databases are essentially data aggregators that and combine data from numerous sources. Other gather databases often provide specialised data for a limited number of substances pertinent to certain emphasis areas.

How does a chemical database work?

A chemical database is a type of database created particularly to hold data about chemicals. Stable molecules make up the majority of chemical databases. Lines denoting chemical bonds between atoms are historically used to illustrate chemical structures on paper (2Dstructuralformulae)



Chemical structure representation:

For showing chemical structure in digital databases, there are two main methods.

• As adjacency matrices/connection tables containing extra bond (edges) and atom attribute (node) information, such as: MDL Molfile, PDB, CML

• As a depth-first, breadth-first linear string notation, such as SMILES/SMARTS, SLN, WLN, or InChl

These methods have been improved to reflect stereochemical variations, charges, and unique bonding types like those seen in organic-metallic complexes. The primary benefit of a computer is its potential for rapid and increasing storage.

Pharmacophore modeling:

- Ehrlich initially used the term "pharmacophore" in 1909, defining it as "A molecular framework that transmits (phoros) the main features important for a drug's (pharmacon) biological effect." Pharmacophore modelling:
- The Pharmacophore technique hasn't altered in decades, but computer technologies have enabled it to develop concurrently.
- The medicinal chemist can better understand the chemical properties of the active site with the help of the pharmacophore model. In order to secure the best supramolecular interactions with a particular biological target and to activate (or inhibit) its biological response, it is "an ensemble of steric and electronic properties that are required."
- The protocol based on structures The initial step in pharmacophore modelling is to examine the complementary chemical characteristics of the active site and their relationships to spatial interactions. A pharmacophore model is created by assembling chosen chemical characteristics.
- This study lightens the strain on medicinal chemists by aiding in the selection and improvement of the lead molecule. There are further programmes, such as DS visualizer® and ligand scoutR. A vital computational technique that supports drug development in the absence of a macromolecular target structure is ligand-based pharmacophore modelling.
- It often entails extracting the chemical characteristics of ligands into three-dimensional structures to show interactions with macromolecular targets.
- The pharmacophore concept was soon used for rational drug design procedures and has since been regularly applied to virtual screening.
- Even in the lack of a 3D molecular structure for a particular receptor of therapeutic relevance, the concept is quite powerful.
- Scopes of Pharmacophore Modeling Making ligands and finding novel medications are basic jobs for a medicinal chemist.

Ligand:

• The idea of similarity, which states that if ligand structures are similar, they may display comparable physical, chemical, and biological properties, is the foundation for drug design. This strategy is based on the idea that molecules with comparable structural characteristics are more likely to have similar properties. Thus, ligand-based drug design, based on which multiple compounds may be designed, seems to be the best option.

• It can make it easier to recognise typical chemical and biological traits.

Styles for Pharmacophore Generation :

There are two ways to conclude a pharmacophore

1. Direct styles

2. circular styles.

While the circular fashion simply uses a group of ligands, the direct system makes use of both the ligand and the receptor information. Because there are so many receptor demitasse structures available, medicinal druggists generally employ circular approaches. The direct approaches, still, are helpful for experimenters to readdress the known protein structures. A pharmacophore model is a flexible tool for the generation of lead motes.

Steps in Identifying a Pharmacophore:

1. In general, all the algorithms for pharmacophore identification use the following six steps for pharmacophore modeling:
2. Input
3. Conformational search
4. Feature extraction
5. Structure representation
6. Pattern identification
7. Scoring

1. **Inputs:** Pharmacophore identification requires a variety of inputs, including ligands, which should be gathered and utilised as inputs. This information will enable the chemist to create an appropriate lead using a wide range of ligands.
2. **Conformational Search**: Numerous conformational configurations are produced by rotation along the carbon-carbon single bond. These conformations cause the development of a number of scaffolds with various energy densities. The conformation with the lowest energy level is regarded as the best, and the other conformations are synchronised similarly.
3. **Feature Extraction:** Before beginning the pharmacophore modelling, all the atomic, electronic, and function-based characteristics of the molecule should be carefully examined.
4. **Structure Representation**: The foundation attributes should always be set aside when the entire structure is meticulously examined for all the qualities.
5. **Pattern Identification:**

There are various stages involved in identification of common features of pharmacophore as:

- The constructive stage:

This reveals pharmacophore possibilities that are shared by the group of ligands that are the most active. This is accomplished by contrasting the shared traits of the group of ligands.

- In the subtractive step, pharmacophore candidates that were developed in the prior stage and that are also found in more than half of the least active ligands are eliminated.

- After the subtractive steps, the pharmacophore molecules move on to the optimization stage, which entails repeated efforts to enhance their score pattern.

6. **Scoring:** This phase involved scoring depending on the results that were collected. The medicinal chemist was able to better comprehend the structure of practical and significant ligands and Pharmacophore thanks to this.

DOCKING :

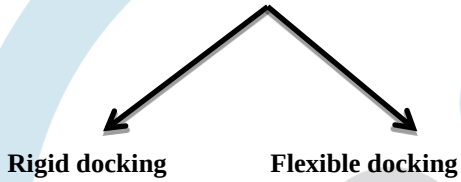
Instruction of docking:

Molecular docking is a technique for computationally determining the architecture of compounds made up of two or more different molecules. Predicting intended three-dimensional structures is the goal of docking investigations. Only appropriate incentive structures are generated by docking in and of themselves. The structures that are most likely to exist in nature are sorted using scoring systems from among these possibilities. The current paper describes the state of the art in numerous computational aspects of virtual screening of a library of small molecules using molecular docking.

Definition of Docking:

Reconstruction of the ligand structure, as well as its placement and orientation inside these sites (often referred to as pose), and evaluation of the binding affinity

Types of docking :



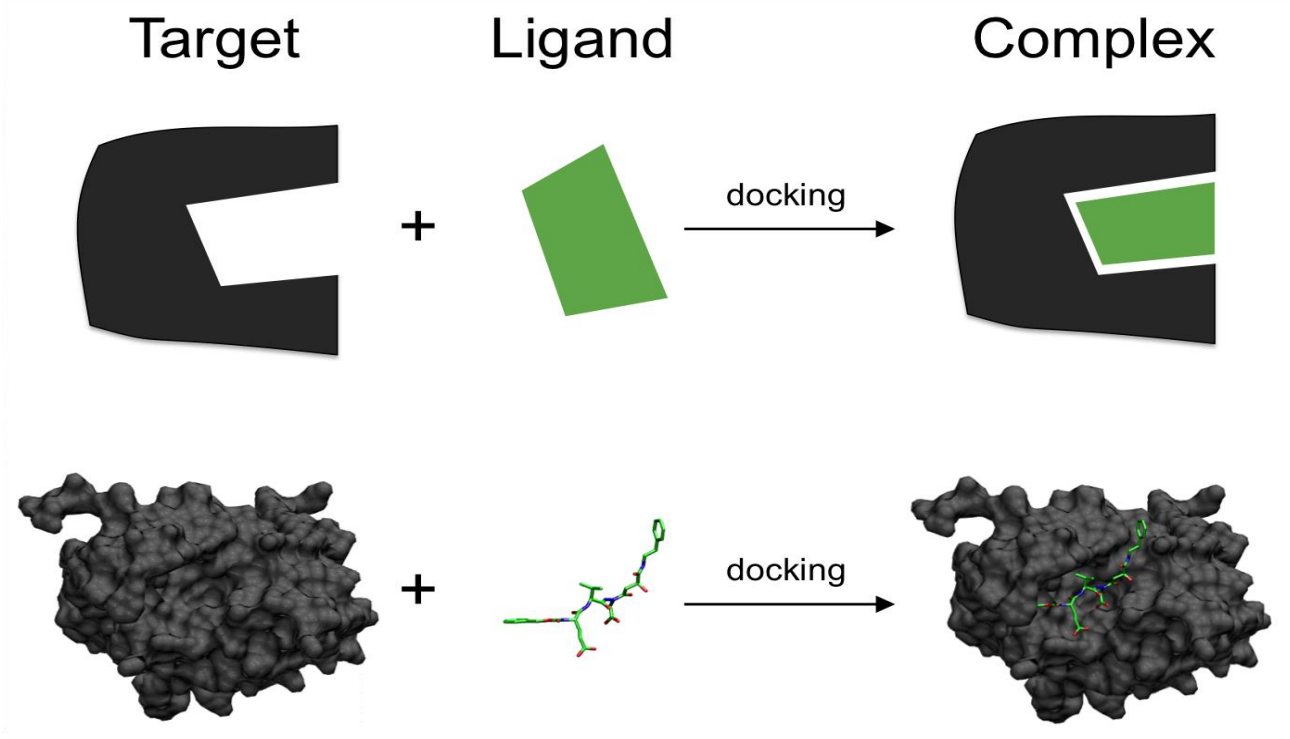
1. Rigid docking:

We are looking for a three-dimensional rearrangement of one of the compounds that produces the best match to the other compounds in terms of a scoring system, assuming that the compounds are rigid. It is possible for the ligand to form its shape with or without receptor binding activity.

2. Flexible docking : Further advances in computing power made it feasible to simulate potential changes in the interior geometry of the interacting partners that may take place during the formation of a complex.

3.

Structure of Docking:



Problem of Docking:

- Absence of a computational model with synergy.
- A lack of good datasets.
- A lack of uniformity.

- Absence of precise coring functions.
- Multidomain protein problems
- Examining the impact of many drugs.

Application of Docking:

- De-orphaning of a receptor;
- Virtual screening (Hit identification);
- Drug discovery (lead optimization);
- Prediction of KA (biological activity);
- Binding-site identification (blind docking);
- Protein-protein interactions (of protein-nucleic acid)
- Protein engineering;
- Structure-function research;
- Enzymatic reaction processes

Factors of affecting docking:

A. Intramolecular Forces

- Bond Length
- Bond Angle
- and Dihedral Angle

B..Intermolecular Forces

- Hydrophobicity,
- electrostatic forces,
- dipole forces,
- H-bonding, and
- Van der Waal forces

Importance of docking:

A) Millions of compounds can be screened for one target protein in drug development, especially with virtual screening.
B) Few molecules can be evaluated in trials.
C) Time and money efficient.

Analysis of docking:

We can define how tiny molecules behave at the binding site of target proteins and shed light on basic biological processes by using the molecular docking technique.

One of the most fundamental and significant methods for drug discovery has been molecular docking studies. It enables the prediction of the molecular interactions that bind a protein to a ligand and keep them together.

The body's defensive mechanism against germs and injuries is inflammation. Numerous inflammatory mediators are produced and released by cells throughout the inflammation process, and they have a variety of biological effects. Numerous chronic illnesses, including cancer, type 2 diabetes mellitus, arthritis, cardiovascular disease, and asthma, are caused by unchecked inflammation.

Nonsteroidal anti-inflammatory medications (NSAIDs) and steroids are frequently used to reduce inflammatory reactions. NSAIDs have an anti-inflammatory action by inhibiting the COX enzyme, or cyclooxygenase. However, due to nonselective COX-1 and COX-2 inhibition, its prolonged usage results in gastrointestinal damage. Strong anti-inflammatory action is produced by glucocorticoids, which decrease the transcription of pro-inflammatory cytokines and chemokines and increase the transcription of anti-inflammatory cytokines.

ADMET:

The primary goal of drug development is to transform a molecule with a therapeutic effect into a medication that can be administered to patients. A medicine must act at the target location, produce its pharmacological effects, and be removed after a sufficient amount of time, ideally long enough to support once-daily dosage. The exploration and explanation of pharmacokinetic processes are aided by the characterization of absorption, distribution, metabolism, and excretion (ADME) features, which then give safety considerations for a novel medication on which risk-based evaluations may be made.

Chemical absorption:

A chemical response between the compounds being absorbed and those being absorbed is known as chemical absorption or reactive absorption. It can occasionally be combined with physical absorption. This kind of absorption is influenced by the reaction's stoichiometry and the concentration of its reactants. They can be performed in a variety of units with a wide range of phase flow interactions.

Chemical distribution:

A method of presenting the results of a common-cause system of variation in which individual values are unpredictable but the outcomes as a whole form a pattern characterised in terms of location, spread, and shape. A representation of the frequency of recurrence of a feature.

Metabolism:
The process of metabolism involves turning xenobiotic substances, which are typically more lipophilic, into hydrophilic metabolites that may be excreted from the body. Enzymes are involved in the metabolism of drugs, and it may take a number of research investigations to pinpoint the main metabolites and pertinent metabolic pathways.
To confirm key participants in a drug's metabolism and satisfy regulatory submission requirements, a few primary in vitro drug metabolism studies are carried out. Among these studies are metabolic stability to forecast a drug's half-life in vivo, metabolite characterization and identification across species to clarify the metabolites formed and ascertain whether any are particular to humans or disproportionately higher in humans than in preclinical species, and reaction phenotyping studies to shed light on the enzymes involved in metabolism.

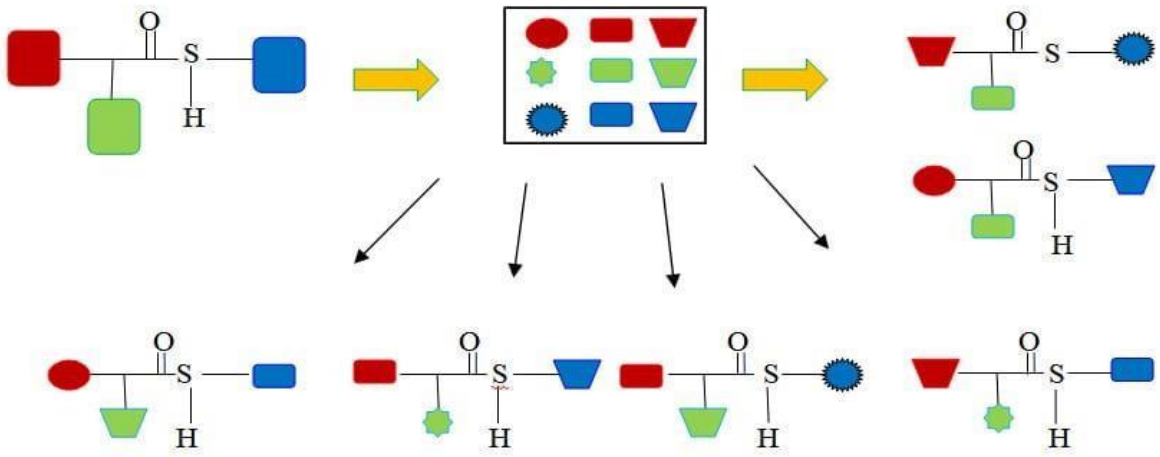
Excretion:
The removal material From body is known as excretion. Most of the time, the parent medication and all of its metabolites are finally eliminated from the body.
Which excretion pathways are the most significant must be distinguished. Drugs are often eliminated by the kidney's or liver's production of urine or bile and faeces, although they can also be expelled through perspiration, tears, or breathing.

Toxicity of Docking:

Although research on the enantioselectivities of imidazolinone (IMI) herbicide interactions are scarce, all imidazolinone (IMI) herbicides are chiral and comprise two enantiomers. This research is a thorough evaluation of the stereoselective bioactivity toward target organisms (Echinochloa crus-galli and Microcystis aeruginosa) and toxicity toward Michigan Cancer Foundation-7 (MCF-7) cells of the enantiomers and racemates of IMI herbicides. In the inhibition of target species, R-imidazolinones were shown to be more effective than S-IMIs, and neither enantiomer exhibited estrogenic action.

Additionally, it was looked at how well the IMI herbicides were able to limit target growth due to their molecular architectures. The enantioselectivity of the acetohydroxyacid synthase (AHAS) activity of the IMIs was rationally explained structurally thanks to molecular modelling. These results support the use of enantiopure R-IMI herbicides to benefit from their superiority versus racemates.

➢ **Combinatorial chemistry:**
Combinatorial chemistry, often known as Combichem, is a branch of chemical synthesis that enables the creation of several molecules (tens of thousands or millions) in a single step.
This procedure creates a combination from many components/sets of unique compounds and structures that were created using software.
The synthesis of tiny molecules and peptides is done using this area of chemistry.
Principal:
Combinatorial chemistry is based on the possibility of producing a large number of structurally unique molecules simultaneously in a process and submitting them for pharmacological testing. With these strategies, it takes less time and money to produce new treatments that are competitive, marketable, and effective.



The synthesis of complicated natural product-like libraries, such as those based on carbohydrates, is becoming more popular. "Phase trafficking" techniques are being employed more frequently to combine synthesis with purification. Combinatorial chemistry was originally used in the synthesis of peptides with the primary objective of being able to synthesise, purify, chemically analyse, and physiologically test all of the structures in the library with the least amount of synthetic trials.

Types:
1. solid phase combinatorial chemistry
2. solution phase combinatorial chemistry

1) Solid phase combinatorial chemistry:
Reagents or products in this kind of combinatorial chemistry are adhered to a solid substrate, such a polystyrene bead. These beds are readily available, and filtering is a fairly simple method of product purification.
Chemistry on the solid surface is superior to that in solution. Similar to how huge reagent excesses can be utilised to force a reaction to completion in solid-phase synthesis.

2) Solution phase combinatorial chemistry:
The majority of synthetic chemistry occurs in the solution phase. Because of the limitations of solid phase chemistry and the ease of purification, solution phase approaches have been investigated as an alternative to solid phase chemistry.
PEG is a typical solvent used in solution phase synthesis; at ambient temperature, it can be either liquid or solid, and it has different degrees of solubility in both aqueous and organic solvents.

Uses:
Some important use of combinational chemistry is:
- A "combination library" is created by the synthesis of several distinct compounds and the screening of those compounds for biological activity.
- In combinational chemistry, several distinct yet structurally related compounds are quickly synthesised.

HTS (High Throughput Screening):
In the last two decades, the drug discovery process known as high-throughput screening (HTS) has grown highly well-liked and has even become a common practise in the pharmaceutical sector.
Additionally, it is utilised to describe the toxicological, pharmacokinetic, and metabolic information regarding novel medications. It utilises completely automated robotic technologies and allows for the daily testing of many chemicals for various biological and chemical processes. In the process of finding new drugs, HTS is crucial.
More than 100,000 samples are reviewed using the HTS every day since it is superior to other scanners due to its simplicity, speed, cheap cost, and great efficiency. Utilizing HTS to find promising results helps speed up the drug discovery process.
Types of high throughput assays: There are two primary categories for HTS:
1. A biochemical test
a.Heterogeneous assay
b.homogenous test
2. Cell-Based Analysis
a.First Messenger Assay
b.Reporter Gene Assay.
C. Test for Cell Proliferation

1.Biochemical Assay:
The specific target is used in a pure form in biochemical tests, which include receptor, protein, or enzyme-based assays. Scintillation proximity assay (SPA), radiometric, and colorimetric fluorescence detection methods are most often used in biochemical assays.
The biological response examined in the HTS essay includes both complex networks operating in cellular settings and isolated biochemical systems with purified receptors or enzymes for signal transmission.
Biochemical assays They are divided into two parts:
A. **Homogeneous assay:**
• The measurements of a homogeneous assay are based on the unique physical/chemical characteristics of the analyte or on interactions between the analyte and the environment.
• There is just one phase in the procedure; the addition of the reagent can be done all at once or in stages.
• It may be linked with several HTS detection techniques, such as radiometric, fluorescence, etc.
• Because there are just a few stages in an experiment, a homogenous essay is simple.
B. **Heterogeneous assay:**
• The heterogeneous assay includes extra procedures, such as filtration and centrifugation, that separate the components that need to be analysed from the remainder of the components that might interfere with the assay. Higher stairs make it more difficult.
• Heterogeneous assays are typically conducted when homogeneous assays are unsuccessful or when a high signal-to-background ratio is necessary.
1. Cell Based Assay:
The term "cell-based assay" refers to any assay that is conducted within of cells. The following classes can be applied to cell-based HTS assays:
A. Second Messenger Assay:
• It keeps track of each transaction that the active cell-surface receptor makes. Second messenger assays frequently measure quick, fleeting fluorescence signals that appear within milliseconds or seconds.
• Many fluorescent compounds are employed in the construction of second messenger assays for receptor stimulation and ion-channel activation since they are known to respond to changes in intracellular calcium iron content, membrane potential, and numerous other factors.

B. Reporter Gene Assay:

- It keeps track of cellular responses at the translational level. It shows changes to a signal transduction pathway by indicating the presence or absence of a gene product.

- In plasmids, reporter genes are frequently utilised. It is used for development and screening of combinatorial protein libraries in in vitro studies.

C. cell proliferation assay:

• It keeps track of the cell's overall development or lack thereof in response to outside stimuli. These may be used for automation quickly and easily.

Applications:

• Measuring molecular interaction
• Examine morphological alterations.
• Measurements of concentration and aggregation, as well as diffusion analysis
• May be used in enzymatic and binding experiments.
• Fluorescent protein structural and molecular dynamics in vivo and in vitro.
• This has been used to measure biological characteristics such protein denaturation and protein-nucleic acid interactions, among others. vii) Employed in research on Tyrosine Kinase Assays, receptor/ligand studies, etc.

➢ **Sources of Drugs :**

(Drugs from natural sources)

Sources of drugs:

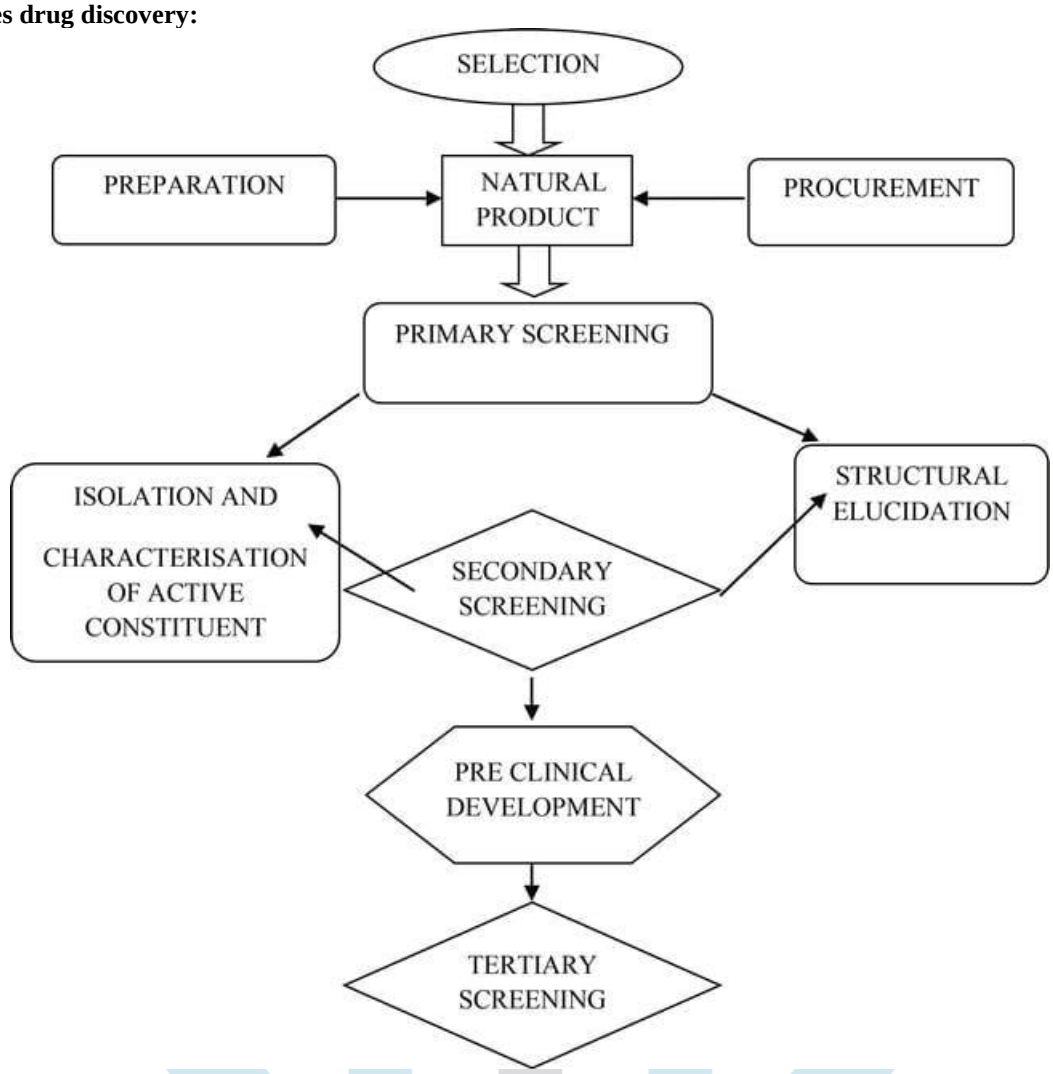
Natural therapeutic agents are made from naturally occurring molecules that have active ingredients extracted from sources including microorganisms, minerals, and animals.

Drugs may come from natural, synthetic, or biosynthetic sources. Natural sources include medicines with a plant, animal, microbiological, marine, mineral, or geographical origin. Plant medications are derived from the complete plant, plant parts, secretions, and exudates.

Drugs from natural sources:

1. Acacia
2. Indian Liquorice
3. Neem
4. Methi
5. Ginger
6. Cinchona
7. Rauwolfia
8. Khair
9. Adulsa
10. Lasun

Natural sources drug discovery:



Drugs are obtained from six major sources:

1. Plant sources
2. Animal sources
3. Mineral/ Earth sources
4. Microbiological sources
5. Semi synthetic sources/ Synthetic sources
6. Recombinant DNA technology

1. Plant sources:

The majority of medications in ancient times were obtained from plants, making plant sources the earliest source of pharmaceuticals.
• Almost all plant components, including the leaves, stem, bark, fruits, and roots, are used.

- **Leaves:**

Digitalis purpurea leaves are the source of the cardiac glycosides digitoxin and digoxin.

- **Roots:**

Emetine, a substance found in ipecacuanha root, is used to cause vomiting in cases of unintentional poisoning. Additionally, it possesses antiarrhythmic qualities.

- **Bark:**

Antimalarial medications quinine and quinidine are found in cinnamon bark. Additionally, quinidine possesses antiarrhythmic qualities.

2. Animal sources:

- Thyroxin, which is used to treat hypertension, is derived from sheep thyroid.
- A and D are found in cod liver, which is utilised as a food source.
- Pituitary gonadotropins, which are used to treat infertility, are produced by the anterior pituitary.
- Animal blood is utilised in the creation of vaccinations.

3. Mineral sources:

- Sources that are metallic and nonmetallic
- Iron helps treat iron deficiency anaemia,
- while mercurial salts help treat syphilis.

4. Synthetic/ semi synthetic sources:

- **Synthetic Sources:**

• A medicine is said to as synthetic when both its chemical structure and its nucleus are changed from a natural source.
Emetine Bismuth Iodide is one example.

- **Semi Synthetic Source:**

• We refer to a medicine as semi-synthetic when the chemical structure is changed but the drug's natural source's nucleus is preserved.
Examples include apomorphine, dialcetyl morphine, ethinyl estradiol, homatropine, amoxicillin, and methyl testosterone. The majority of medications used today, such as anti-anxiety medications and anti-convulsants, are semi-synthetic.

5. Microbiological sources:

- Streptomycin is provided by actinobacteria.

6. Recombinant DNA technology:

Recombinant DNA technique uses restriction endonucleases to cleave DNA, and the desired gene is linked to DNA that replicates quickly. (Viral. Bacteria or plasmid)

Advantages:

- Non-toxic; • Easily accessible
- Inertness.
- Less negative consequences.
- Cheaper.
- Quick to degrade.
- Improved chemical and mechanical stability.
- Clinically relevant.

Disadvantages:

- Variation from batch to batch.
- Low manufacturing volume.
- Absence of inherent biocompatibility
- Expensive and challenging synthesis.
- A solubility issue with water.

Conclusion:

Drug design is the process of coming up with novel treatments based on an understanding of a biological target. This review talks about several forms of drug discovery, lead discovery, lead modification, and drug design principles. An essential method of lead modification known as bioisosterism has been found to be effective in reducing toxicity or altering the activity of a lead. It may also play a key part in changing the pharmakinetics of a lead. When compared to computational approaches, the process of discovering new drugs through laboratory experimentation takes a long time and costs a lot of money.

References:

1) Dr CHANDAN R. S. and Dr. Mrs. ALPANA J ASNANI textbook of Medicinal chemistry – III (Introduction to drug design and development) page No. 12.1 and 12.37.

2) Drug designing (https:// www.slideshare, net/zainab Saif / drug –designing – 70366013.

3) A short introduction to drug design and discovery (https: / www.slideshare , net/ NEETHUSASOKAN / drug – design – and discovery.

4) Dr CHANDAN R. S. and Dr. Mrs. ALPANA J ASNANI textbook of Medicinal chemistry – III (Introduction to drug design and development) page No. 14.1 to 14.5.

5) Hanson CLA substituent constant for comelation analysis in chemistry and biology, new York, John wiley and sens. 1979.

6) Cros A action des/alcool amylique sur / organism 1863.

7) Grumatian T. Cronin the impact of variable selection on the modeling of oestrogenicty. SAR QSAR environment Res 2005, 16(1-2) 17 1-190.

8) Dr. SANJAY G. WALODE and Dr(Mrs.) ALPANJ ASNANI textbook of Medicinal Chemistry (Computer Aided Drug Design) Page No. – 12.22 to 12.23.

9) RJPPD Research Journal of pharmacology and pharmacodynamics (A bimonthly peer reviewed international Journal of Pharmacology) volume 13/ Issue 2/ April – June/ 2021.

Review article Drug discovery (combinatorial chemistry and high throughput screening) page no. 47 to 50.

10) Dr. SANJAY G. WALODE, Dr.CHANDAN R.S. and Dr(Mrs.) ALPANA J. ASNANI textbook of Medicinal Chemistry III (Combinatorial chemistry) Page No. – 12.22 to 12.23.

11) www.tou.ac.il> Knowing .org > wiki > Ab…

12) Azob A. Nassar A. Azob AN. Anti- inflammatory activity of natural products. Molecules 2016 : (21) : 1321. Dol : 10. 3390 / molecule 21101321.

13) Orlando BJ Molkowski MG. crystal structure of rofecoxib bound to human cyclooxygenose –2 Acto cryst.2016 : (F72) : 772 – 776. Dol : 10. 1107 / 52053230X16014230.

14) Http: // www.Scrubchem.org.

15) Https: // pubchem.ncbi.nlm.nib.gov/

16) CHEMBL Database

17) Journal of the ACM, Cite See X 10.1.1361.

18) Https: //www.Slideshare.net > sources

19) Https: // slideshare.com > slide

20) 7th edition Foye's Principles of Medicinal Chemistry (Book)

Thomosl Lemke / David A. Williams Victoria F. Roche / S. William Zito.