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FROM MOLECULES TO MEDICINES: ADVANCE IN DRUG DESIGN AND DISCOVERY AND AN OVERVIEW ON KEY PROCESSES IN DEVELOPING SAFE AND EFFECTIVE DRUGS

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ABSTRACT

The aim of present work is to study different stages of drug discovery and its significance to understand the different parameters, stages in drug development also to develop safe and effective drugs for unmet medical needs. The process of finding new drugs is still difficult and expensive, and it usually takes more than ten years from target identification to regulatory approval. Recent developments in experimental and computational techniques have improved efficiency and success rates by streamlining several phases of the drug discovery process. Target identification and lead optimization have been transformed by computational methods like molecular docking, virtual screening, and artificial intelligence, which enable more accurate predictions of drug-target interactions. By confirming biological activity and enhancing pharmacokinetics, experimental approaches like next-generation sequencing and high-throughput screening (HTS) enhance these computational approaches. The integration of computational and experimental methods in drug development is reviewed in this article, with a focus on how they might work together to save costs, increase accuracy, and shorten turnaround times. Successful application case studies highlight the advantages and difficulties of this multidisciplinary approach.[1]

KEYWORDS: Drug discovery, Lead optimization, High throughput Screening (HTS), Virtual Screening, Pharmacokinetics, Computational techniques, Molecular docking, Drug-target interactions.

INTRODUCTION

The process by which medications are found and created is known as drug discovery. This procedure seeks to find a substance that can be used therapeutically to cure illness. An essential component of drug discovery is drug design. It is an organized process for finding, selecting, and modifying drug molecules based on the physico-chemical characteristics of the drug or the molecular interactions between the drug and target proteins. Finding and developing a medicine from an initial concept to its release onto the market is a very complicated process that is part of the drug discovery approach .Finding novel, safe, and effective therapeutic agents is the goal of the complicated multistage process of drug design and development. Bringing a single medicine to market has historically been a costly and time-consuming procedure that frequently takes ten years and billions of dollars. Drug design's primary goal is to identify and enhance compounds that interact with particular biological targets such as proteins or nucleic acids involved in disease processes. After a possible "hit" molecule is identified, additional refinement yields "lead" compounds, which undergo strict security, efficacy, and selectivity testing prior to entering clinical trials.[2] The discovery and optimization stages of drug development have been greatly sped up by developments in computational methods including molecular modeling, virtual screening, and structure-based drug design. These methods reduce the need for laboratory trial-and-error and make it easier to identify potential candidates by enabling researchers to forecast molecular interactions with greater accuracy.[3] Despite these developments, problems including drug resistance, minimizing side effects, and improving pharmacokinetic characteristics still exist. Medicinal chemistry and biotechnology advancements keep pushing the creation of new treatments, and current studies aim to increase the efficacy and predictability of the drug discovery procedure in order to satisfy the rising need for individualized and efficient drugs. The main aim of drug design is to develop a drug with high degree of therapeutic index.[4]

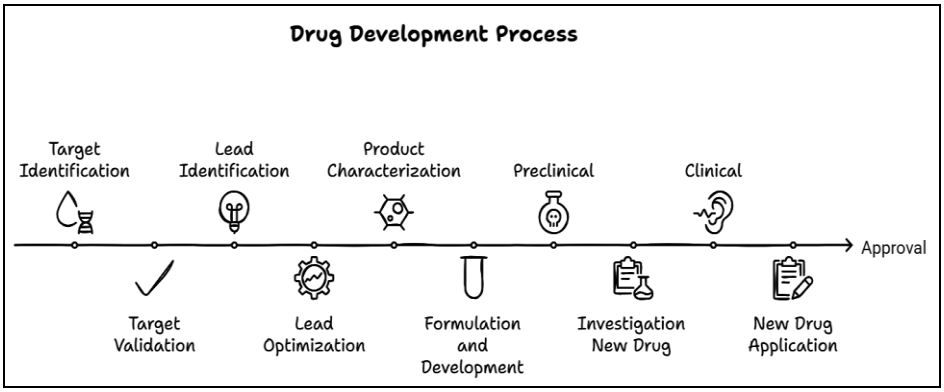

Fig no 1: Process of drug design.

1. Target identification
2. Target validation
3. Lead identification
4. Lead optimization
5. Product characterization
6. Formulation and development
7. Preclinical
8. Investigation new drug
9. Clinical
10. New drug application
11. Approval

Target identification

There are two primary reasons why drugs fail in the clinic they are unsafe, and they don't accomplish their intended results. Therefore, target identification and validation are among the most crucial stages in the development of a novel medication. The term "target" is broad and can refer to a variety of biological things, such as proteins, genes, and DNA. Finding a disease's biological cause and possible intervention targets is the first stage in the drug discovery process. The first step in identifying a target is to isolate the role of a potential treatment target (gene or nucleic acid/protein) and how it contributes to the illness. Determination of The molecular characterization comes after the target. mechanisms that the target is addressing. A perfect target ought to be safe, effective, and compliant with clinical and commercial specifications and be "druggable." The methods employed for Molecular principles may serve as the foundation for target identification. genetics, biophysics, biochemistry, biology, or other disciplines.[5][6]

Target validation

The drug target has to be validated experimentally according to the proposed mode of action. Here data link directly to the probability of clinical efficacy (i.e. experiments in human cells/tissues of eminent importance). Functional studies can apply genetic knockdown, knockout or, using target specific tools, if SMOL compounds or tool antibodies are available. In vitro cell-based mechanistic studies can be used to reveal regulative characteristics of targets and the pathways in which they are involved. Finally, depending on the disease, it can be necessary to evaluate the relevance of a particular target for the disease in appropriate animal models. Target validation can be carried out using knockout or transgenic animals, provided that functional orthology between mice and humans is provided and that appropriate disease models are available. However, there are generally risks associated with translating in vivo validation into humans. In contrast, some models claim to be While some are highly predictive of the human situation, others exhibit significant differences.[7][8]

Lead Identification

A chemical lead is a molecule that is drug-like, synthetically stable, and active in primary and secondary tests with acceptable specificity, affinity, and selectivity for the target receptor. This calls for defining the structure-activity link, assessing the feasibility of synthetic materials, obtaining early proof of in vivo efficacy, and target interaction. Characteristics of chemical lead are.

SAR defined

- Drug ability (preliminary toxicity, hERG)
- Synthetic feasibility
- Select mechanistic assays
- In vitro assessment of drug resistance and efflux potential
- Evidence of in vivo efficacy of chemical class
- PK/Toxicity of chemical class known based on preliminary toxicity or in silico studies

A drug ability assessment is frequently carried out to reduce the number of compounds that fail during the medication development process. This evaluation is crucial for changing a transformation of a lead molecule into a drug. Regarding a compound for something to be deemed druggable, it must have the capacity to bond to a particular target, but it's also crucial that pharmacokinetic characteristics of the chemical with respect to absorption, distribution,

excretion, and metabolism. Additional tests will assess the compound's possible toxicity in screens. such as the cytotoxicity assay and the Ames test.[9][6][7]

Lead Optimization

The molecules that were designated as "Leads" in the previous step undergo optimization. It is thought that this step is crucial to the process of finding new drugs. Currently, leads are altered to offer the "best" analogs with increased potency, pharmacodynamics, pharmacokinetic, and efficacious characteristics. The Changes are achieved through chemical alterations selected by analysis of structure and activity. If you are aware of the target structure, based design could also be used to implement the modifications. Because this procedure involves simultaneous optimization of several parameters, it is an expensive and time-consuming step. In the The lead optimization phase of the overall drug discovery process is believed to be a step that limits the rate.[10]

Product characterization

Product characterization in drug design involves assessing various attributes of a drug candidate, such as its molecular structure, physical properties, pharmacokinetics, toxicity, and pharmacodynamics. This process ensures that the molecule is suitable for further development and is critical for identifying its mechanism of action, potential therapeutic uses, and safety profile.[11]

Formulation and Development

A phase of medication development known as pharmaceutical formulation involves characterizing the physicochemical characteristics of active pharmaceutical ingredients (APIs) in order to create a dosage form that is stable, bioavailable, and ideal for a particular mode of administration.

The parameters which are evaluated during formulation and development.

- Solubility in different media and solvents
- Dissolution of the active pharmaceutical ingredient (API)
- Accelerated Stability Services under various conditions
- Solid state properties (polymorphs, particle size, particle shape etc.)
- Formulation services and capabilities
- Formulation development of new chemical entities (NCE)
- Optimization of existing formulations

• Process development for selected dosage forms
• Novel formulations for improved delivery of existing dosage forms
• Controlled release and sustained release formulations
• Self-emulsifying drug delivery systems
• Colloidal drug delivery systems
• Sub-micron and Nano-emulsions.[6]

Preclinical

The investigation is guided by preclinical testing, which eliminates compounds with minimal or no pharmacological promise once a set of lead compounds is available. This stage consists basic measurements of cell and tissue cultures, in vitro assays, engagement with biological targets, including proteins, which can be carried out using isothermal titration micro calorimetry. An animal in vivo experiments, selecting them based on their physiological and biological traits can appear to be human. Preclinical research enables the advancement of make compounds a candidate, which will then be forwarded to the next stages involved in finding new medications.[12]

Investigation new drug

It is an application submitted to the FDA to begin human clinical trials in the event that preclinical trial results indicate the medicine is safe.

High-quality preclinical data should be included in the IND application to support the drug's human testing. Nearly 85% of medications undergo clinical trials, for which applications are submitted to the IND. An organization, referred to as a Sponsor, is in charge of submitting the IND application.

The FDA can arrange a pre-IND assessment to discuss a number of topics.

❖ The way in which animal research is designed in order to support clinical investigations.
❖ The planned procedure for carrying out the clinical trial.
❖ The production, chemistry, and management of the experimental medication.[13][6][7]

Clinical Trials

Clinical trials are prospective biological or behavioural research projects that use human volunteers (participants) and/or human-derived materials, which includes observed behaviour, responses to questions, and/or the collection of tissue or specimen samples. The

purpose of clinical trials is to provide an answer to a particular research topic. They are employed to assess the safety, effectiveness, and efficiency of novel behaviour or biological interventions.[14]

Phase 0

According to the U.S. Food and Drug Administration's (FDA) 2006 Guidance on Exploratory Investigational New Drug (IND) Studies, exploratory, first-in-human studies are now referred to as phase 0. Phase 0 trials are intended to expedite the development of promising medications or imaging agents by determining early on whether the medication or agent behaves in humans in a manner consistent with preclinical research. One of the unique characteristics of Phase 0 trials is that a small number of subjects (10 to 15) are given single sub therapeutic doses of the study drug in order to collect initial data on the agent's pharmacokinetics (how the body processes the drug) and pharmacodynamics (how the drug works in the body).[15]

Phase 1

The main goal of phase I trials is to determine the safety and dosage range of a new medication in 20–100 healthy participants. Pharmacokinetics is the study of how a medication is absorbed, distributed, metabolized, and eliminated by the body. Frequent blood draws are used to measure the amount of medication in the blood plasma, frequently in an inpatient setting.

Regardless of when pharmacokinetic trials are carried out throughout a drug's development, they are typically regarded as Phase I trials. A novel drug's dosage range is established by giving progressively higher dosages to one or more subject groups while keeping a careful eye out for any negative side effects. Finding the highest tolerated dosage that doesn't result in intolerable side effects is the aim.

Even if an experimental medication has survived the preclinical stage of testing, phase I studies may still have dangers. Volunteer subjects in phase I research usually receive compensation for their time and effort because they usually receive little to no benefit from the study. Phase I trials are often carried out with healthy volunteers, although they can sometimes occasionally involve patients who are very sick or near death, such as those with cancer or AIDS.

It takes several months to finish a Phase I experiment. Approximately 70% of investigational medications pass this preliminary testing stage.[16]

Phase 2

The medication will go through a phase II trial after its initial safety has been determined. A phase II trial's objective is to examine the medication's short-term safety and therapeutic effectiveness in individuals suffering from the ailment or disease it is meant to treat. In order to examine the drug's effectiveness and side effects across dosages, patients are administered the various dosages that were determined to be safe in the phase I trial. The medication will move on to a phase III trial once its safety and effectiveness in treating the ailment or condition it is meant to treat have been established in patients.[17]

Phase II trials use between 100 and 300 participants to assess how well an investigational medication works for a specific illness or condition. This stage could span anywhere from a few months to two years.

An answer to the question "Does Drug X improve Disease Y?" comes from a Phase II experiment.

A phase II trial's secondary goal is to determine the therapeutic dose level and frequency of administration. This addresses the inquiries, "What quantity of Drug X works better on Disease Y, (1 mg, 2 mg or 3 mg)?" along with "Does Drug X work better on Disease Y taken once or twice a day?

The majority of Phase II studies are randomized, meaning that participants are chosen at random (by chance, not by choice) to receive a placebo (an inert, harmless substance), the experimental medicine, or a regular treatment. A control group is made up of people who receive either a placebo or the usual course of treatment.[17][16]

Phase III

The gold standard for comparing the effects of an experimental therapy versus conventional therapy for a disease of interest is phase III clinical trials. Planning a phase III study begins with defining the statistical hypothesis that the trial is intended to test. Typically, this hypothesis is that the experimental therapy offers some efficacy benefits above standard therapy without causing appreciable damage. In a phase III trial, a predetermined number of patients from the target population are randomly assigned to either standard or experimental

treatment. A protocol defining the endpoints of interest, particularly the primary endpoint that is selected to demonstrate a clinical benefit of experimental therapy over conventional therapy, governs the patients' treatment and follow-up.[18]

Phase III studies involve hundreds to thousands of individuals for whom the medicine is intended and are carried out at several facilities. Data on a drug's safety and effectiveness are continuously generated through extensive testing. The majority of Phase III studies are blinded and randomized, just like Phase II.

Following FDA approval, phase III trials supply the majority of the data required for a medicine's labeling and package insert**.**

A medication in this stage may be one of the 25–30% that make it through Phases I, II, and III and may be studied for a number of years. A pharmaceutical company can apply for FDA approval to market a medicine.[18][16]

Phase IV

Following FDA approval of the medication or device, phase 4 studies are carried out. Also known as post-marketing surveillance, these studies include pharmacovigilance and after approval, ongoing technical support. In addition to several methods of observation and evaluation utilized to assess the effectiveness, cost efficiency and security of participation in real-world parameters. Regulations may necessitate phase IV studies. authority (e.g., risk assessment, labeling modification management or reduction action plan) or could be implemented through the sponsoring business to compete or for other causes. Thus, the real example of a medication's safety basically needs during the months and even years that indicate extending the shelf life of a medication. After reviewing complaints about side effects from both prescription and over-the-counter medications, the FDA may decide to increase dose or take safeguards.[19]

New drug application

Only after the medication has passed all three stages of clinical trials and includes all relevant data from both humans and animals can a New Drug Application (NDA) be submitted. data evaluations, medication pharmacokinetics, and its production and expected labeling.

The preclinical, Risk-benefit analysis and clinical reports are examined at the Drug Evaluation Center. When clinical research demonstrates that a novel medication is reasonably

safe and effective and won't put patients at unreasonable danger, the maker files a New NDAs, or drug applications, are the formal request to produce and distribute the medication in the US.

Although an NDA is typically approved in two years, this procedure can take anywhere from two months to several years to complete. The company that is innovating is allowed to sell the medication following an NDA's approval and is thought to be undergoing Phase IV studies. During this stage, new regions, applications or populations, long-term impacts, and It is investigated how participants react to various dosages.[20] [13]

Approval

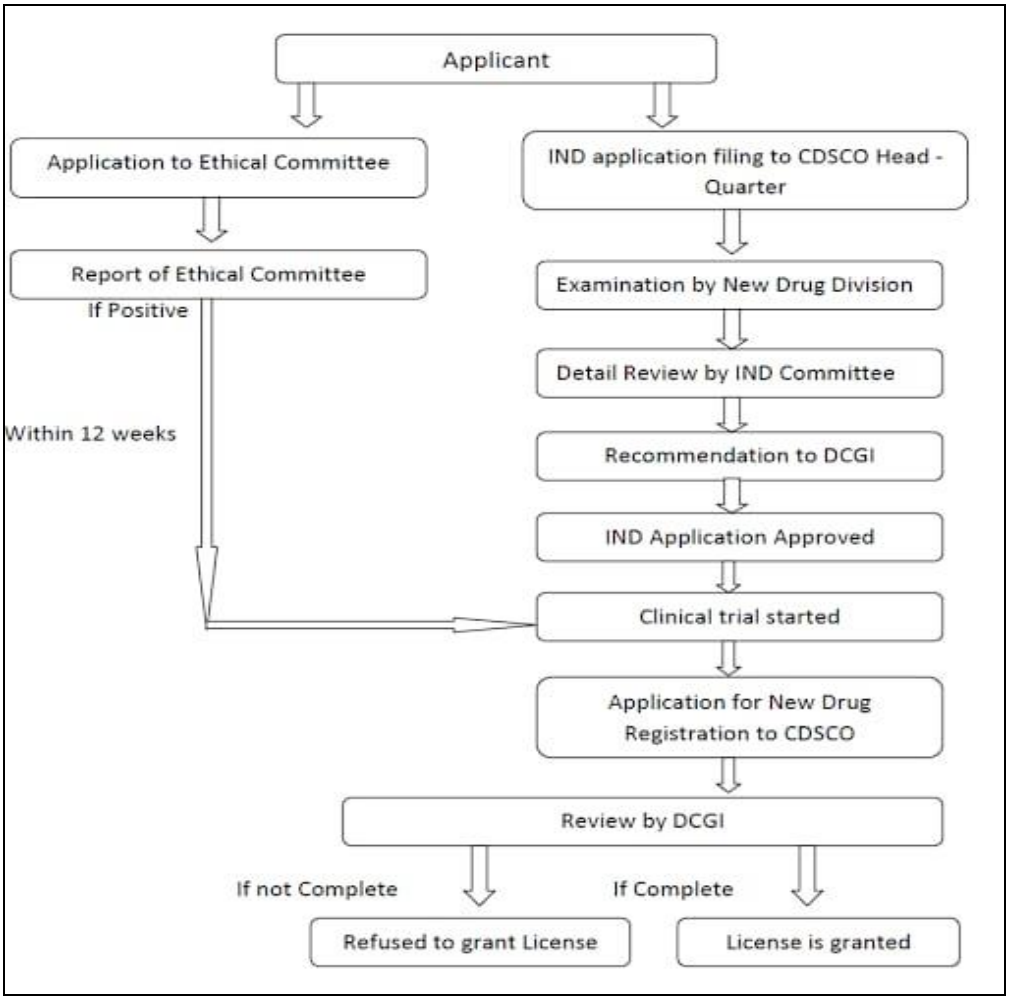

Fig no 2: Flow chart of Drug Approval Process in India.[21]

❖ **Quantitative structural activity relationship (QSAR)**

QSAR (Quantitative Structure-Activity Relationship) is a widely used method in computational chemistry and drug discovery. It aims to establish mathematical relationships

between the structural properties of molecules and their biological activities or other properties.[22]

The foundation of quantitative drug design is the understanding that physicochemical parameters that is, physical characteristics like solubility, lipophilicity, electronic effects, ionization, stereochemistry, and so on have a significant impact on the chemistry of the compounds and in turn affect their biological properties. Richet published the first attempt in 1893 to link a physicochemical property to a pharmacological action.[22]

A computerized statistical method called a quantitative structural activity relationship (QSAR) can be used to explain the observed variation in structure changes brought about by replacement. These models show quantitatively how a ligand's structural characteristics impact a target's activity response when it binds to it. Electronic, hydrophobic, steric, and substructure effects are some examples of molecular factors that can be utilized to create QSAR models.[23]

Steps involved in QSAR

I) Preparing molecules for QSAR experiment: Acquire a congeneric set of ligands that have demonstrated a broad range of action in a comparable biological assay.

II) Selection for Descriptors in Training set: Find and identify the molecular descriptors associated with the physiochemical characteristics of the substances.

III) Calculate Values for Descriptors in Training Set: Divide the molecules into training and test sets at random. Determine and compute the correlation coefficient that best explains the connection between biological activity and descriptor values using the training set.

IV) Evaluation of Internal and External Validation: Evaluate the stability of the statistical equation using the molecules from the test set. Use a statistical model to predict a novel chemical's biological activity.[23]

Advantages of QSAR

1 Cost-Effective: QSAR models can predict the biological activity or toxicity of compounds without the need for expensive and time-consuming laboratory experiments.

2 Time-Saving: QSAR models can quickly evaluate large libraries of compounds, accelerating the drug discovery process by identifying promising candidates early on.

Disadvantages of QSAR

1 Due to the biological data experimental error it may have false correlation.

2 It's not necessary that qsar study will gave successful results on each application.

❖ Parameters of QSAR

➢ *Physicochemical parameters in QSAR*

1. Partition Coefficient

The partition coefficient indicates a drug's lipophilicity and its capacity to pass across cell membranes. It is defined as the proportion of unionized medication that is evenly distributed between the aqueous and organic layers. The aqueous drug solution and the organic layer, which is saturated with water, are two immiscible solvents that can be shaken with equal quantities of a drug until equilibrium is reached in order to calculate the partition coefficient. A calculation is made to determine the drug's content in one of the layers. For the study, the octanol–water partitioning system is frequently utilized. The lipophilic–hydrophilic balance of a medicine is described by the partition coefficient, which encourages absorption even when it does not by itself. The partition coefficient describes a drug's lipophilic–hydrophilic balance and aids in screening compounds for biological characteristics, even though it by itself cannot reveal information about absorption.

Octanol–water partition coefficients may be obtained by distributing a drug between n-octanol and water in a separatory funnel and, after equilibration, determining the concentration of drug in each layer.

P=[Drug]octanol/[Drug]water

The relative distribution is known as the partition coefficient (P) and is. obtained from the following equation: log(p)= concentration of drug in octanol/concentration of drug in aqueous solution.

The values that are obtained are usually exponential numbers and it is therefore common to express partition coefficients as the logarithm of the partition coefficient, logP.[24]

2. Electronic parameter

How well a particular reaction reacts to electronic perception is a measure of its electronic demands, which are dictated by its mechanism. By adding substituent groups to the framework and subsequently changing the reaction rates, the whole process is explained. It is

obvious that different substituents' electronic effects will affect the polarity and ionization of the medication.

It affects the drug's ability to engage with the binding site or how quickly it can cross the cell membrane. When discussing substituents on an aromatic ring, the Hammett substituent constant (σ) is utilized. It is a measurement of the electronic charge distribution in the benzene nucleus and indicates the magnitude of the electronic effect, i.e., whether an electron is withdrawing or donating for a certain substituent.

$\sigma x = \log K_X - \log K_H$ or $\log (K_X/K_H) = - Pk_x + pK_H$

The aromatic ring has a reduced ability to stabilize the carboxylate ion if the substituent X is an electron-donating group (I+). A smaller kx value indicates a weaker acid as the equilibrium moves to the left. The value of σx for an electron withdrawing substituent will be positive if the substituent X is an electron withdrawing group (I-), which has a smaller Kx value than the benzoic acid itself.

The value of the Hammett constant relies on the substituent, whether it is para or meta substituted, and accounts for both resonance and inductive effects. Because of steric effects, ortho is not measured.[25]

3. Steric parameters

The way a medicine interacts with the receptor binding site depends on its bulk, size, and shape. Compared to hydrophobic and electrical factors, steric qualities are more challenging to measure. The steric characteristics of substituents have been measured using Taft's steric factor. This is limited to substituents that interact sterically with the reaction's tetrahedral transition state rather than through internal hydrogen binding or resonance.

Steric factor can also be measured using molecular refractivity. By computing Verloop steric parameters from standard bond angles, Vander Waals radii, bond lengths, and substituent conformation, the computer software Sterimol is used to measure steric factor.[25]

4. Theoretical approach

I. Hansch analysis

Hammett's relationship-based QSAR uses electronic properties as structure descriptors. When researchers tried to apply Hammett-type correlations to biological systems, they ran into problems, which meant that other structural descriptors were required. The numerical data on

lipophilicity, electronic, and steric effect on the model development was introduced by Hansch et al. in 1962.

The most widely utilized physicochemical parameters that are related to biological activity by the Hansch equation are log P or π, σ, and steric factor.

Log BA = a log p + b σ + c Es + constant (linear)

Log BA = a log p + b (log p)2 + c σ + d Es + constant (nonlinear)

- Partition coefficient; log P
- Hammett constant; σ
- Taft's steric parameter; Es

The Hansch model links physicochemical characteristics and biological activity. The multiple regression analysis determines the coefficients (a, b, c, d, and constant).[26]

II. Free Wilson Analysis

It is also known as the additivity model or de novo approach. This method is based on the assumption that the introduction of a particular substituent at a particular molecular position always contributes in the same way to the biological potency of the whole molecule, as expressed by the equation:

Log BA = contribution of unsubstituted parent compound + contribution of corresponding Substituents.

Log BA = μ + Σ ai aj

- where ai = number of positions at which substitution occurs
- aj = number of substituents at that position
- μ = overall average.[26]

❖ **Role of topological descriptors in drug design**

1. Wiener index (W) and Platt index

The C-C bonds that exist between every pair of C-atoms in an alkane are referred to as the Wiener index. The boiling points of a few straight-chain and branched-chain alkanes have been ascertained using this index. Furthermore, the toxicity of certain nitrobenzene's to T. pyriformis has been predicted using the Wiener index. The entire sum of the neighbouring bonds for every atom in an alkane is known as the Platt index. Several QSAR models have

employed this index to investigate the anti-leishmanial properties of phloroglucinol–terpene adducts.[27]

2. Hosoya index (Z)

This index relates to the total amount of non-adjacent bonds in a compound. The utility of the Hosoya index in combination with other descriptors was reported in a QSAR study to predict the anti-Alzheimer activity of a group of N-aryl derivatives.[27]

3. Zagreb indices

The Zagreb index is determined by summing the squares of the number of non-H-bonds that heavy atoms in a compound form. The Zagreb It was discovered that group parameters M1 and M2 were helpful in forecasting cephalosporin pharmacokinetic characteristics in people.[28]

4. Balaban index (J)

The Balaban index is a connectivity measure that considers the total of the average distances between atoms in a molecule. The QSAR was significantly modeled by the index. investigation of benzenesulfonamide as an inhibitor of carbonic anhydrase.[28]

5. E-state index

Kier and Hall (1999) created this index by combining the topological and electrical characteristics that define the atomic level of interaction inside the molecule. Using a combination of physicochemical descriptors and the E-state index, successful QSAR modelling of hydroxyphenylureas (antioxidants) and benzo furan derivatives (melatonin receptor) has been documented.[29] [27] [28]

❖ **introduction to CADD**

Computer-aided drug design (CADD) is a modern approach in pharmaceutical research that uses computational methods to accelerate and optimize the drug discovery process. Screening, optimizing, and assessing the compound's activity in relation to the target is the main goal of CADD. Both academic institutions and large pharmaceutical firms use it as part of their multidisciplinary strategy to improve efficacy and reduce or eliminate negative effects. The Progress in CADD is predicated on structural prediction, target identification, similarity, validation, knowledge of the protein-ligand interaction, binding site/cavity, and studying the molecular dynamics simulations based on a large collection of chemicals,

physiological circumstances, calculating biological activity using ADMET characteristics, and tallying The lead needs to have a qualitative structure-based assessment relationship, or QSAR.[30]

A new area of study called computer-aided drug design (CADD) has attracted a lot of attention due to its potential to speed up and reduce the cost of the drug development process. A medicine's commercial availability sometimes takes 10 to 15 years, and drug discovery research is costly and time-consuming. CADD has greatly affected this field of study.

Depending on whether 3D protein structures or ligands are available, CADD employs two distinct approaches. They are referred to as.

1. Structure-based drug design (SBDD)
2. Ligand-based drug design (LBDD)
3. In certain instances, combining the two methods has demonstrated high precision in identifying the lead compounds.[31]

1. structure-based drug design (SBDD)

SBDD is the process of developing an inhibitor for a medicine by using its structural information. This approach requires a receptor structure or structures. In majority The structure of the receptor is typically established by NMR and X-ray crystallography are examples of experimental methods. if The protein medication target's structure is not accessible. It is possible to predict structure using computational techniques such as threading and modelling homology. Threading, sometimes referred to as fold, is a modelling technique for proteins without similar proteins having a recognized structure. As threading is underway, a compatibility with the specified amino acid sequence, the frameworks inside a database of recognized folds. The way the query is organized folds are used to build proteins.[32]

Table no 01: Software for structure-based drug design(SBDD).[30]

Stages	Tool used	Brief description	Links
1Target modelling	SWISS-MODEL	Homology modelling	http://expasy.org
	MODELER	Homology Modelling	MODELLER (salilab.org)
2 Binding site	CASTp	Binding site prediction	CASTp 3.0: Computed Atlas of Surface Topography of proteins (uic.edu)
	Active site Prediction tool	Active site prediction	ACTIVE SITE PREDICTION SERVER (scfbio-iitd.res.in)

2. ligand-based drug design (LBDD)

Ligand-based drug design is a method that uses knowledge of compounds that bind to the biological target of interest when receptor 3D information is unavailable. 3D connections between quantitative structure and activity (3D QSAR) and Among the most significant and frequently utilized are pharmacophore modelling tools for designing drugs based on ligands. They are able to offer forecast models appropriate for optimizing and identifying leads. Additional details about these techniques and how they are used to The design and development of LOX inhibitors are described elsewhere in the evaluation.[32]

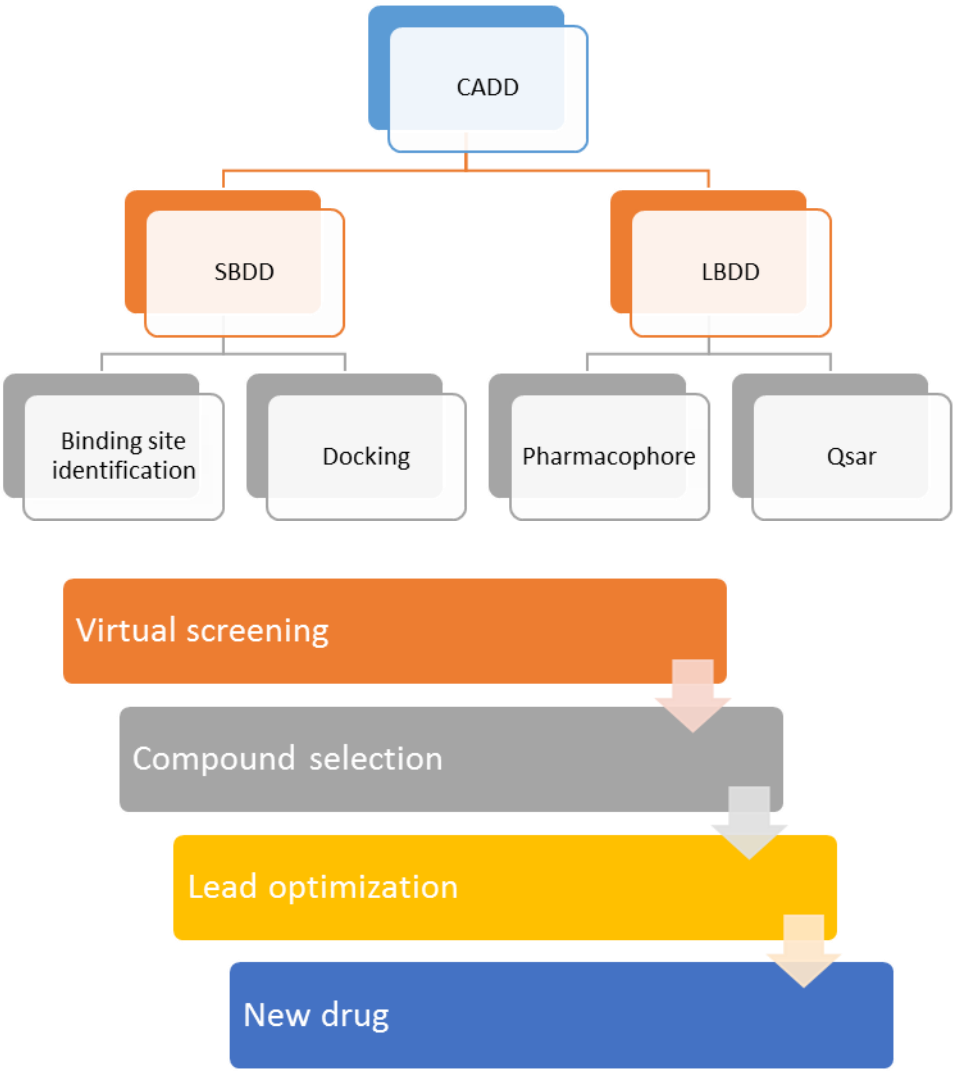

Fig no3: Representative Workflow of computer aided drug design.

❖ **Chemical structure drawing**

Drawing chemical structures is a basic chemistry ability that helps professionals, students, and researchers properly and artistically convey complicated molecular structures. In disciplines like drug development, medicinal chemistry, and material science, an

understanding of molecular structures, bonding, reactivity, and biological interactions is essential.[33]

1. Chemdraw

Chemdraw," the most comprehensive and powerful drawing tool for conveying chemistry research, allows users to illustrate both chemical and biological structures and interactions.

• It can also be used to forecast properties and spectra, investigate three-dimensional structures, and transform chemical compounds into names from IUPAC.

• It provides correct IUPAC designations for structures and creates accurate structures from chemical names.

• It also estimates NMR spectra from a ChemDraw structure using the direct atom to spectral correlation.

2. Chemdoodle

• Chemdoodle is an advanced feature that lets you completely generate chemical diagrams from molecular images without providing any chemical details.

• This program creates detailed mechanism illustrations.

• Arrowheads and arrows can both be completely customized.

• ChemDoodle is the simplest tool for constructing text fields because it is the only one that supports superscript and subscript merge formatting. Atomic notations are examples of chemical writing.

• ChemDoodle features hundreds of chemical properties that help create the best possible graphics.

• ChemDoodle's advanced feature lets you completely generate chemical diagrams from pictures of molecules without providing any chemical details. The chemical drawings that were recovered can be used for further editing or evaluating.

3. Chemsketch

• You may illustrate chemical structures like organics, organometallics, and polymers with the sketching tool ChemSketch. It also contains features for recognizing structures, determining molecular characteristics (such molecular weight, density, and molar refractivity), as well as forecasting logP and cleaning and visualizing 2D and 3D structures.

• ChemSketch is a molecular modelling program used to create and modify images of chemical structures.

• This tool makes it possible to comprehend the properties of functional groups and the structure of chemical bonds in Two- and three-dimensional representations of molecules and molecular models. ChemSketch is an easy-to-use, chemically intelligent molecular structure tool with over 2 million users globally. sketching software.

4. Marvin

The Marvin suite is a chemically intelligent desktop toolkit that allows you to design, edit, publish, render, import, and export chemical structures. Additionally, it makes file conversions between a variety of chemical and graphical file types possible.

• Marvin is a fully functional chemical editor that helps make science accessible on all platforms.

• It also has built-in structural and valence checks, as well as integrated property calculators that can generate responses in real time. It may be of assistance.

• Marvin supports the majority of industry-accepted chemical file formats and transforms chemistry into a digital environment.

5. Bkchem

Using symbols and the essential elements of any chemical formula, BKChem, a free Python programming tool for making chemical diagrams, can rapidly produce the basic structure and its relationships to the symbols of each element.

• It is a cross-platform application that makes it possible to sketch fundamental chemical compounds and molecular structures.

• By drawing each bond separately, BKChem establishes bond length and angles with structure.

• It also offers a range of pre-made templates for people who are hesitant to make their own molecular charts.[34]

❖ **Chemical structure presentation**

Because it can be challenging to visualize the shape and structure of atoms and molecules, chemistry can be a challenging subject to comprehend. The modelling of molecules has evolved over the years. Although each molecular representation has pros and cons, they all help scientists better comprehend chemistry. Below the given data show the different presentations methods of butane (C_4H_{10}).[35]

Lewis dot structure are two-dimensional depictions of molecules that show the chemical symbol for each atom. Non-bonding electrons are shown as tiny dots adjacent to the chemical symbols, whereas lines show bonds to neighbouring atoms.

Bond line notation displays specific atoms as their chemical symbols, leaving out hydrogen atoms that are thought to be part of the structure and showing certain carbon atoms as corners between lines. The chemistry of living things, or organic chemistry, is the main field that uses bond-line notation.

Ball and stick models are three-dimensional models in which links between atoms are represented by sticks and atoms themselves are represented by spheres of various colours. Different colours correspond to different atoms; for instance, carbon is typically represented by black, and hydrogen by white.

Space fill models are three-dimensional representations that depict atoms as coloured spheres, much to ball and stick models. They vary in that the spheres that represent atoms are fused together, and the size of the sphere corresponds to the size of the actual atom, rather than sticks, which stand in for bonds as in the ball and stick model.[35]

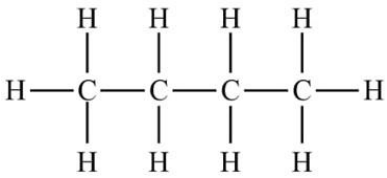

Fig no.4 Lewis Dot Image courtesy of Benjah-bmm27 from Wikipedia.

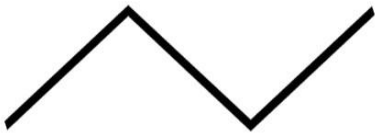

Fig no.5 Bond line notation Image created by Jmol.

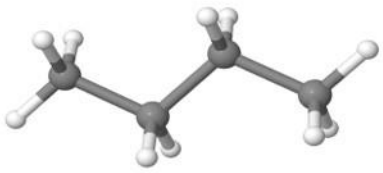

Fig no.6: Ball and stick Image created by Jmol.

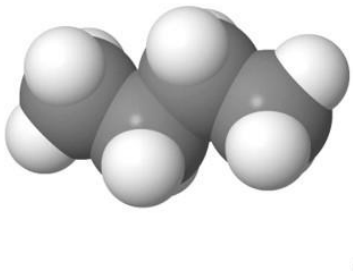

Fig no.7: Space fill image created by Jmol[35]

❖ Chemical Database search

The quantity of chemical data in the public domain has been steadily growing over the last ten years. As a result, numerous databases were created to gather, organize, and share publicly accessible chemical data in an effort to improve its usability and accessibility. Crucially, these databases and information from various scientific fields (including genetics, genomics, pharmacology, toxicology, medicine, bioinformatics, and systems biology) to chemical data, helping biomedical researchers use these publicly available data to find new drugs. Scientists should know which databases have the information they require and how to fully utilize them in order to optimize the value. PubChem, Chemspider, ChEMBL, Binding db., PDBbind, Drug Bank, Unichem, these are few chemical database search libraries.[36]

➢ PubChem

Without a doubt, PubChem is the most well-known internet database. established in 2004 by NIH to assist with the roadmap initiative's New Pathways to Discovery component. PubChem compiles and arranges data regarding the biological functions of chemical compounds into an extensive biological database and serves as the initiative's informatics foundation, enabling the scientific community to employ small molecule chemical compounds in their studies. PubChem is made up of three interconnected databases: PubChem Compound, PubChem Substance, and PubChem Bio-Assay. PubChem Compound offers biological property information for 18 million distinct structures. every chemical. Records of chemicals from depositors are available in PubChem Substance. into the system. These include commercial databases, chemical suppliers, publishers, and other sources. Records of specific compounds are available in the PubChem Compound database. Substances. Information regarding bioassays can be found on PubChem Bioassay. utilizing precise words related to the bioassay. Chemical names, property ranges, structures, substructures, and structural similarity are examples of alphanumeric text variables that can be used to search PubChem. It contains around 38.7 million chemicals as of December 2007 and million distinct building types.[37] [38]

➢ eMolecules

A free online database of about 8 million distinct chemical structures is available from eMolecules.[39] The database offers a way to find a vendor for a specific chemical and is put together using information provided by more than 150 providers. mixture. They are offering a free service by making compounds available for purchase. access online resources that are comparable to those found in for-profit databases like Symyx Cambridgesoft's Chemical

Directory[40], CAS' ChemCats[41], and several more suppliers, including ChemACX.[42] The system provides access to around 4 million screening chemicals that are sold commercially and numerous tens of thousands of intermediates and construction blocks.[37] [42]

➢ **ChemSpider**

ChemSpider was released to the public in March 2007 with the intention of "building a structure centric community for chemists". ChemSpider has grown into a resource containing almost 18 million unique chemical structures and recently shared its data with PubChem providing about 7 million unique compounds. The data sources have been gathered from chemical vendors as well as commercial database vendors and publishers and members of the Open Notebook Science community.

The developers of ChemSpider have made available a number of web services to allow integration to the system for the purpose of searching the system as well as generation of InChI identifiers and conversion routines. These features set ChemSpider apart from the main public chemistry databases and include real-time curation of the data, association of analytical data with chemical structures, real-time deposition of single or batch chemical structures (including with activity data), and transaction-based predictions of physicochemical data. Additionally, in order to promote linkages between the systems, ChemSpider has integrated the SureChem patent database[43] collection of structures.[44] [37]

❖ **Pharmacophore**

Paul Ehrlich created the first pharmacophore concept in the late 19th century. The idea at the time was that compounds with similar effects shared similar functions, and that specific "chemical groups" or activities of a molecule were what caused a biological effect. In his work from 1960 Chemo biodynamics and Drug Design, Schueler introduced the term "pharmacophore," which he defined as "a molecular framework that carries (phoros) the essential features responsible for a drug's (pharmacon) biological activity.[45] As a result, "patterns of abstract features" rather than "chemical groups" were now considered when defining a pharmacophore**.** Since 1997, the International Union of Pure and Applied Chemistry has defined a pharmacophore as follows.

A pharmacophore is the ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target and to trigger (or block) its biological response.[46]

A pharmacophore model can be created either structure-based, by probing potential interaction points between the macromolecular target and ligands, or ligand-based, by superposing a group of active molecules and extracting common chemical features that are crucial for their bioactivity. Virtual screening, de novo design, and other applications including lead optimization and multi target drug design have made significant use of pharmacophore techniques.[47]

Ligand based: The first active ligands in ligand-based pharmacophore modelling are found through database searches or the available literature. A training set and a test set are created from the data set. The training set ligands are then subjected to feature analysis. The alignment of the active ligands allows for the detection of shared characteristics. The creation of pharmacophore models and their ranking are the following stages. Lastly, pharmacophore model validation is carried out, and based on the outcomes, the optimal pharmacophore model is chosen.[48]

Structure based: The initial stage in structure-based pharmacophore modelling is to choose and prepare the target protein structure. The binding site is the second step. Forecast. Next, complementary chemical characteristics of The amino acids in the binding site and their configurations include determined by closely examining it. Following this, the Features of pharmacophores that ought to be improved by the modified instruments in the programs used, are produced. Lastly, important pharmacophore characteristics chosen to be in charge of the activity. Ligand Scout[49], MOE[50], is one of the often utilized Structure-based pharmacophore software modelling. Likewise, there are numerous software programs and servers for modelling pharmacophores. The Programs and servers that are often used are summarized using the alphabet.

A variety of pharmacophore modelling tools are available. Software for creating pharmacophore models includes Hip-hop, HypoGen, Pharmer, PHASE, GASP, Pharma Gist, Pharm Mapper, MOE, Ligand Scout, and GALAHAD.[51]

Table no 02: Program and server used in Pharmacophore modelling.

Program/server	Brief Description
CATALYST-Hip Hop[51][52]	Now included in the BIOVIA Discovery Studio is CATALYST. It includes the Hip Hop and HypoGen algorithms, which are used to generate pharmacophores. Hip Hop provides active ligand alignment versus a particular target and determines the three-dimensional configurations of shared characteristics through the overlap of different structures.
CATALYST-HypoGen[53][51]	Using data from biological analysis, it produces hypotheses that can quantitatively evaluate a molecule's activity. Consequently, it makes it possible to correlate the activity and structural data for modelling of pharmacophores.
GALAHAD[54]	By using a modified genetic algorithm, the program improves the GASP program's performance by addressing some of its flaws. It speeds up processing by utilizing prefabricated buildings as a foundation.
GASP[55]	The SYBYL package includes GASP. It detects pharmacophores using a genetic approach. In contrast to the other pharmacophore tests, conformational search is used to out immediately in the GASP procedure and is a crucial component of the program. Random spinings with a single low energy structure are used to assess conformational changes prior to superimposition on every molecule that is input.
PharmaGist[56]	This openly available server is utilized for the creation of ligand-based pharmacophores. This web service uses several adaptable alignments of the input molecules to find pharmacophores.
Pharmer[57]	This pharmacophore approach bases the search on the breadth and intricacy of the query rather than the screened molecular library. The source code is accessible, and the method is incredibly quick. with an open-source license attached.
PharmMapper[58]	It is a publicly available web service that is used to find possible input ligand targets. It uses semi-rigid pharmacophore mapping to calculate pharmacophores.

Application

- Pharmacophore modelling is used in ADMET prediction, ligand profiling, virtual screening, docking, and fishing drug targets.
- Because of the concept's simplicity and adaptability, new viewpoints are also anticipated for pharmacophore medalling's numerous future uses. Thus, in addition to the uses described above, it might find use in polypharmacology, drug Repurposing and anticipating adverse effects.[58] [51]

❖ Docking

The process of positioning molecules in the best possible configurations to engage with a receptor is known as docking. Docking is a phenomenon that can be seen in a cell when molecules join forces to create a sustainable complex.[59]

Fundamentals of molecular docking. Using computer-based techniques, molecular docking seeks to anticipate the ligand-receptor complex. The two primary processes in the docking procedure are ligand sampling and the application of a scoring function. Sampling algorithms assist in determining the most energetically advantageous ligand conformations in the protein's active site, considering their binding. setting. Following that, a scoring system is used to rate these confirmations.[60]

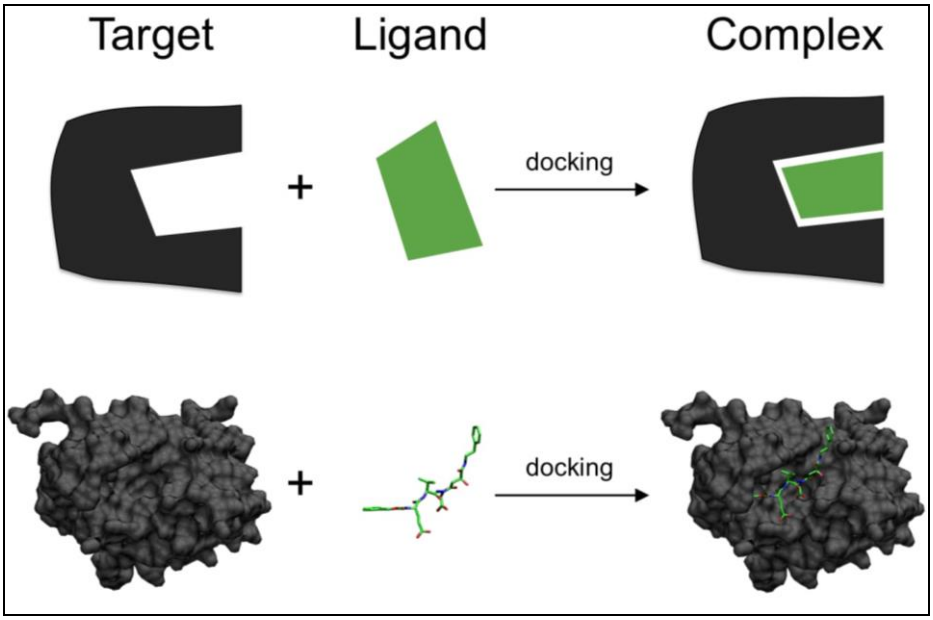

Fig no:08 Schematic diagram of docking a undersized molecule ligand (green) to a protein target (black) produce a steady compound.[61]

❖ **Types of docking**

1. Rigid docking
2. Flexible docking

1. Rigid docking

If we believe that the molecules are inflexible, we are searching for a transformation of one of them in three dimensions that would result in the greatest advantageous match with the additional molecules in features of a scoring system. Verification of The ligand might be generated without receptor or when receptor binding occurs action.[61] [59]

2. Flexible docking

In addition to change, we consider molecular flexibility and seek to identify the receptor and ligand confirmations. As molecules appear in complex.[62]

❖ **Models of molecular docking**

1. The lock and key theory

In 1890, Emil Fischer developed a theory known as the "lock-and-key model" to explain how biological processes work, as seen in figure 09. The substrate is placed inside similar to a key; the active location of a macromolecule is placed inside a lock. Figure 09 shows the unique stereo chemical characteristics of biological locks that are necessary for them to function.[63]

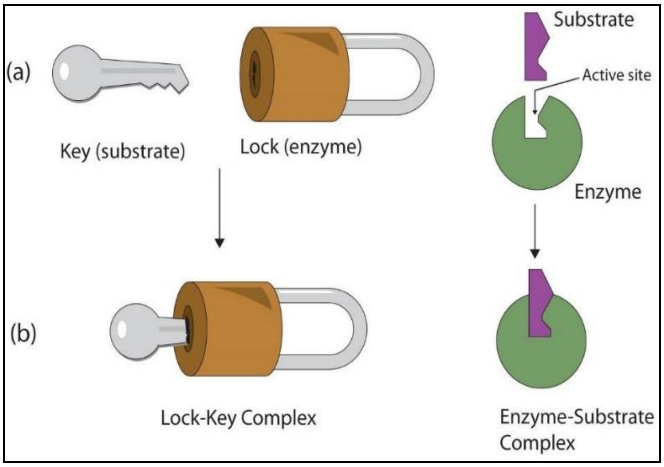

Fig no 09: The lock and key theory.[63] [59]

2. Induced fit theory

The "induced fit theory" was put forth by Daniel Koshland in 1958.

The basic idea is that both the ligand and the target, as shown in figure 10, are involved in character recognition. And to adjust to each other through slight conformational shifts until the perfect fit is achieved.[63] [59]

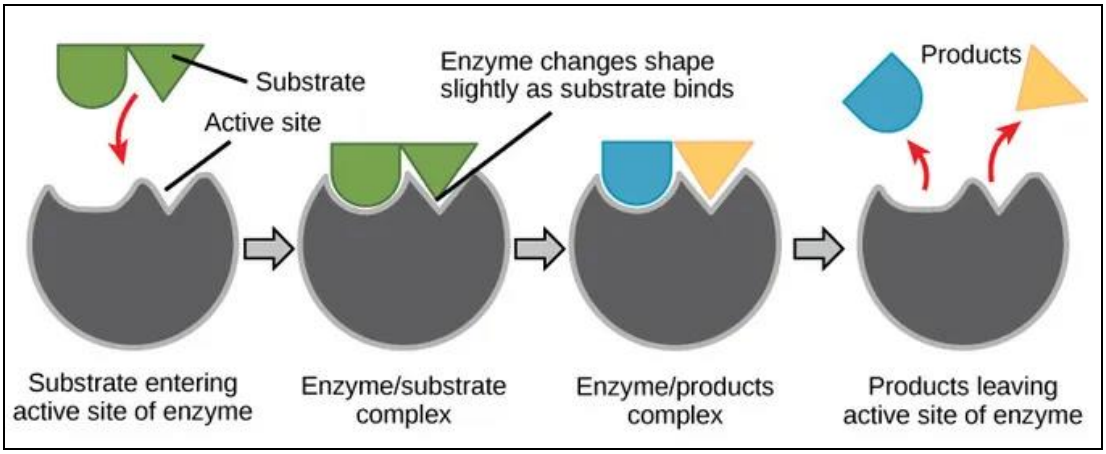

Fig no 10: Induced fit model.[63] [59]

❖ Major Steps Involved in Mechanics of Molecular Docking

The docking process involves the following steps

Step I – preparation of protein: The Protein Data Bank (PDB) must be consulted in order to obtain the protein's three-dimensional structure, which should then be pre-processed. This needs to acknowledge the water's amputation. molecules out of the cavity, keep the charges stable, significant the absent residue, manufacturing the Depending on the parameter, side chains, etc. accessible.[64]

Step II – active site prediction

Following protein production, the protein's active site needs to be predicted. There are numerous active sites in the receptor strength, but only the one of The issue needs to be selected. In general, the Heteroatoms and water molecules are indifferent if there.[64] [65]

Step III – preparation of ligand

Ligands can be drawn using the Chem. sketch tool or retrieved from a variety of databases, including ZINC and Pub Chem. While selecting the Hence, the appropriate LIPINSKY'S RULE OF 5 is employing. The five Lipinski rules help with discrimination. between drug-like and non-drug-like. The computer CADDD, or assisted drug design and detection approach. It guarantees a high likelihood of success or failure as a result of medication resemblance for molecules left behind with two or more of the rules that must be followed. To select a ligand, permit to the.

Lipinski’s rule

1) A lesser amount of five hydrogen bond donors.
2) A lesser amount of ten hydrogen bond acceptors.
3) Molecular mass less than 500 Da.
4) High lipophilicity (expressed as Log not over 5.
5) Molar refractivity should be between 40-130.[66]

Step IV

Docking: The protein and ligand are positioned next to each other, and the interactions are examined.[67]

Table no 03: Listing of molecular docking tools with brief description.

Name	Brief description
Dock[68] [69]	Anchor-and-Grow based docking program, for flexible ligand and flexible protein. (http://dock.compbio.ucsf.edu/).
Auto dock[70]	For Flexible ligand, Flexible protein side chains. Compatible for Linux, Window and Mac OS. (http://autodock.scripps.edu/).
Hex[71]	Mainly for protein-protein and protein-DNA docking. (http://hex.loria.fr/)
FTDock[72]	For rigid-body docking, based on based on Fourier correlation algorithm. (http://www.sbg.bio.ic.ac.uk/docking/ftdock.html)
Auto Dock Vina[73]	Improved version of AutoDock4, fast, betters binding energy.(http://vina.scripps.edu/)
HADDock[74]	It is use for protein-protein/protein-ligand docking. (http://www.nmr.chem.uu.nl/haddock/)

Applications

1. Hit Identification: Large databases of possible medications can be quickly screened in silico to identify compounds using docking collectives with scoring functions. That are probably going to attach to proteins are a group of focus.[75]
2. Lead optimization: Docking can be used to determine the location and direction of a ligand's binding to a protein (also known as the binding mode or pose). This can then be utilized to design stronger and more specific analogs.[76]
3. Bioremediation: Additionally, contaminants that can be broken down by enzymes can be predicted via protein ligand docking.[77]

❖ **Combinatorial chemistry**

Combinatorial chemistry is a potent technique used in drug design and discovery that finds compounds with desired biological properties by synthesizing a large number of molecules at once or in a quick sequence.[78]

The systemic and repeating covalent bonding of various building blocks of a wide range of distinct chemical entities is known as combinatorial chemistry. Combinatorial chemistry is a revolutionary technique that allows us to create multiple potential molecules at once that could generate a huge number of compounds, or libraries, all at once. Chemical combinatorial processes entail the quick synthesis or computer modelling of several distinct yet frequently fundamentally associated compounds or substances. In CADD (Computer Assisted Design), combinatorial chemistry is particularly prevalent. medication design) and can be completed online using web-based tools like Molinspiration. Formerly, Traditionally, chemists have

created a single compound at a time. For instance, chemical A and compound B would have reacted to produce product AB, which would have been separated following reaction work-up and purification using chromatography, distillation, or crystallization. Unlike this method, is possible to create every possible combination of compounds A1 to Am using combinatorial chemistry. B1 to Bn compound. Despite the fact that industry has only just begun to use combinatorial chemistry, its origins date back to the 1960s, when Bruce, a researcher at Rockefeller University, Merrifield began researching peptide solid-state synthesis.[79]

A vast number of chemical entities are created by condensing a limited number of chemical entities using the scientific process known as combinatorial chemistry. substances in every combination specified by a little series of chemical reactions.[79] [78]

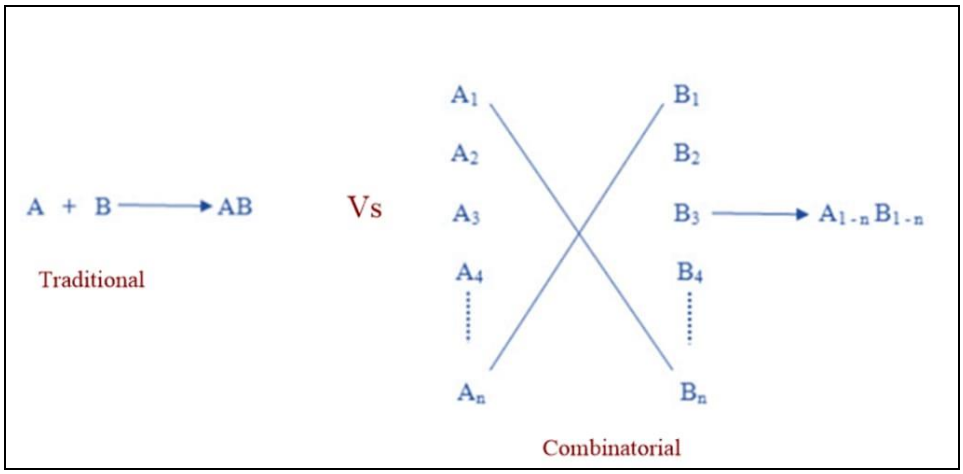

Fig no 11: Combinatorial chemistry.[80]

❖ **Principle of Combinatorial Chemistry**

The fundamental idea behind these investigations is to first prepare a huge number of compounds, from which additional components are subsequently extracted. It's a method. by which a unique, structurally big molecule can be quickly synthesized and submitted for investigation of pharmacology. Researchers are able to combine a variety of quantities of chemicals quickly utilizing basic approach. Fundamental Combinatorial Concept the Chemical Combinatorial chemistry's idea is crucial to medication development and material research.[81] [79]

Basic idea of this study includes:

1.Numerous compounds can form at once,

2.high throughput screening yields effective material.

Types of combinatorial synthesis

1. Solid phase synthesis: In the pharmaceutical industry as well as other areas of discovery, combinatorial chemistry is crucial to lead discovery and hit optimization processes. Originally developed for peptide synthesis and later oligonucleotide synthesis, solid phase techniques have only recently been applied more broadly to organic synthesis. Merrifield coined the term "solid phase peptide synthesis" in 1963 to refer to the process of creating a peptide on a polymer that remained insoluble during the synthesis.[82]

In solid phase combinatorial chemistry, the starting compound is attached to an insoluble resin bead, reagents are added to the solution in excess, and the resulting products can be isolated by simple filtration, which traps the beads while the excess reagent is washed away.[83]

2. Solution phase synthesis: This technique builds a library of compounds by conducting the synthesis in a solution and adding different reagents. After that, the compound mixture is examined for biological activity.

3. Parallel synthesis: This process creates a variety of compounds by conducting a sequence of reactions in parallel. Numerous chemicals can be synthesized quickly using this method.

A range of tests are usually used to screen a library of compounds for biological activity after they have been produced. This may involve checking for interference with enzyme function, binding to a specific target, or impacts on cell survival or growth.[84]

Applications of Combinatorial Chemistry

1. Drug discovery
2. Drug Optimization.
3. Preparation of New Catalyst[84]

❖ **High throughput screening (HTS)**

It is a crucial method for rapidly and effectively screening a large number of compounds for biological activity in drug discovery.

The pharmaceutical industry has adopted High-Throughput Screening (HTS) as a common drug discovery tool when it became widely popular twenty years ago. It is essentially a procedure for screening and testing a lot of effectors and biological modulators directed

against particular and targeted targets. The usage of it is not limited to industrial scientists as well as among scholars. Assays for HTS are used to screen for Protein, peptide, genomic, and combinatorial chemical libraries are among the several kinds of libraries. The primary objective of the HTS approach is to screen big compounds in order to expedite drug discovery. Thousands of chemicals every day or week may be added to libraries at this rate.[85]

Definition

In high throughput screening (HTS), thousands to millions of samples are quickly tested for biological activity at the model organism, cellular, route, or molecular level. HTS in its most prevalent form is a method of experimentation where 10^3-10^6 tiny molecules Parallel screening is performed on substances with known structures. Another material, including chemical blends and natural products Antibodies, oligonucleotides, and extracts can also be screened. Due to HTS's usual goal of screening 100,000 or additional samples daily, comparatively easy, and automated Suitable assay designs, sample handling with robotic assistance, Additionally, automated data processing is essential. Pharmaceutical and biotechnology firms frequently employ HTS to find chemicals (referred to as hits) with pharmacological or biological activity. These serve as the foundation for optimization of pharmaceutical chemicals during pharmacological investigation or the creation of drugs.[86]

There are multiple steps that make up the process

1. Choosing a target: Choosing a target for screening is the first stage in HTS. Finding a protein or other molecular structure may be necessary for this. that contributes to a specific biological process or disease.
2. Compound libraries: Following the selection of a target, a screening library of compounds is put together. This could entail creating new compounds or choose from pre-existing compound libraries.
3. Assay development: To gauge the chemicals' impact on the target, an assay is subsequently created. This could entail creating an easily automated biochemical or cell-based test.
4. Screening: Following the development of the assay, the compounds undergo high-throughput screening against the target. This could entail dispensing and testing a lot of substances utilizing robotic equipment.

5. Data analysis: In order to find compounds that exhibit action against the target, the screening data is finally examined. These substances may then be improved and further described for the creation of new drugs.[87]

❖ Type of high throughput assay (HTS)

HTS are mainly categorised into two types

- Biochemical assay
- Cell based assay

➢ Biochemical assay

Biochemical assays use the specific target in a pure form and are based on receptors, proteins, or enzymes. The most common methods used in biochemical assays include colorimetric fluorescence detection, radiometric, and scintillation proximity assay (SPA). The biological reactions assessed by the HTS assay range from a complex network operating in the cellular milieu to an isolated biochemical system with purified receptors or enzymes to a signal transduction pathway. Additionally, biochemical assays are separated into two categories.[88][34]

1. Heterogeneous assay

Additional procedures like filtration and centrifugation are used in heterogeneous assays to separate the component to be evaluated from the other components that could interfere with the experiment. Higher stairs make it more difficult. When a high signal to background ratio is needed or a homogeneous assay fails, heterogeneous assays are typically conducted.[89]

2. Homogeneous assay

The unique physical and chemical characteristics of the analyte or the interaction between the analyte and its surroundings serve as the basis for measurements in homogenous assays. Reagents can be introduced in one step or in several steps; the method is one-step. It only entails routine procedures like reading, incubation, and fluid addition. For HTS, it can be combined with other detection methods, such as radiometric and fluorescence. The primary benefit of a homogeneous test is its ease of use due to its minimal assay step.[89]

➢ Cell based assay

The term "cell-based assay" refers to any assay that is conducted inside living cells. The following classifications apply to cell-based assays for HTS.

3. Second messenger assay

It keeps an eye on the signal transduction from cell-surface receptors that are active. Usually, second messenger assays measure brief, rapid fluorescent signals that happen in a matter of milliseconds or seconds. Since many fluorescent compounds are known to react to variations in membrane potential, intracellular calcium ion concentration, and other factors, they are employed in the creation of second messenger assays for ion-channel activation and receptor stimulation.[90][89]

➢ Reporter gene assay

It tracks transcriptional and translational reactions in cells. It shows whether a gene product is present or absent, which in turn represents modifications to a signal transduction pathway. The most common reporter genes used are plasmids. Combinatorial protein libraries in array format are generated and screened in vitro. The benefits of in vitro coupled reporter gene assay and polymerase chain reaction (PCR) were utilized in this investigation.[91][89]

❖ ADMET

The process of creating safe and efficient medications is difficult and resource-intensive, requiring a thorough comprehension of how a drug affects the body. From preclinical testing and medication discovery to clinical trials and regulatory approval, this process consists of multiple steps. At every step, assessing a drug's ADME-Tox characteristics which stand for Absorption, Distribution, Metabolism, Excretion, and Toxicity is essential.

Absorption, distribution, metabolism, and excretion, or ADMET, is a critical process in drug research that evaluates the physiological behaviour of therapeutic molecules. Knowing these procedures helps guarantee that a drug reaches its intended location, has the expected effects, and can be safely removed in order to maximize pharmacokinetics and safety and to guide risk evaluations. profile of new medications.

In order to evaluate a drug candidate's pharmacokinetics (PK) and pharmacodynamics (PD), ADME-Tox characteristics are crucial. In the end, they improve decision-making and lower failure risks by assisting researchers and pharmaceutical corporations in identifying possible problems early in the drug development process.[92][93]

➢ **Absorption**

The process by which a medication leaves the site of administration and enters the bloodstream is called absorption. It is a crucial component since it has a direct impact on a drug's bioavailability, or the percentage of the dose that enters the bloodstream.

Factors affecting absorption

1. route of administration: There are several ways to give drugs, including intramuscular, intravenous, and oral. The chosen path has a big influence on absorption.
2. Chemical properties: The chemical characteristics of a medicine, such as its solubility and lipophilicity, affect its capacity to pass across biological membranes.
3. Formulation: A drug product's absorption rate may be impacted by its formulation, including whether it is in the form of tablets, capsules, or injections.

➢ **Distribution**

The term "distribution" describes how a medicine spreads throughout the body after entering the bloodstream. Because it influences the medication's concentration at the target location and possible interactions with other tissues, it is essential to comprehend how a drug is distributed.

Factors Affecting Distribution

1. Plasma Protein Binding: Drugs' distribution to tissues can be decreased by their ability to bind to plasma proteins. Drugs that are highly bound could have a lower distribution volume.
2. Blood-Brain Barrier (BBB): Many medications' ability to enter the brain is restricted by the blood-brain barrier (BBB), which affects how they are distributed throughout the central nervous system.
3. Tissue Perfusion: Drug distribution is more significant in highly vascularized tissues.

➢ **Metabolism**

The process by which the body chemically changes medications to make them easier to eliminate is called metabolism, and it frequently takes place in the liver. Pharmacologically inactive substances can change into active forms through drug metabolism, and vice versa.

Significance of Metabolism

1. Activation: Metabolic activation is necessary for the effectiveness of certain medications.

2. Detoxification: Toxic substances can be changed by metabolism into less dangerous forms for removal.
3. Elimination: Because they are frequently more soluble in water, metabolites are easier for the body to eliminate.
4. Cytochrome P450 Enzymes: Enzymes known as cytochrome P450 (CYP) are important for drug metabolism. Predicting a drug's metabolism requires an understanding of how it interacts with particular CYP enzymes.

➢ **Excretion**

The body gets rid of medicines and their metabolites through a process called excretion. Although the kidneys are the main source, other pathways including breath and feces may also be involved.

1. Renal Excretion: The kidneys use glomerular filtration, tubular secretion, and reabsorption to filter medications from the bloodstream into urine.
2. Biliary Excretion: Bile, which is then expelled through faeces, is produced by the excretion of certain medications and their metabolites
3. Pulmonary Excretion: The lungs can be used to expel volatile chemicals and gaseous anaesthetics.

➢ **Toxicity**

In ADME-Tox evaluation, toxicity assessment is a crucial component. It entails assessing a drug's possible negative impacts on living things.

- **Types of Toxicity**

1. Acute Toxicity: unfavourable effects that start right away after being exposed to a substance.
2. Chronic Toxicity: long-term negative consequences that accumulate over time.
3. Organ Toxicity: adverse effects that are specific to a given organ or system.[94]

❖ **Source of drugs**

Drug sources: Drugs can come from natural, synthetic, or biosynthetic sources. Natural sources include medications with plant, animal, mineral, marine, and microbiological origins. Plant medications come from the whole plant, plant parts, plant secretions, and plant exudate.

1. Plants Examples: Taxol (from Pacific yew tree), Quinine (from cinchona tree), and Artemisinin (from sweet wormwood)

2. Microbes: Examples: Penicillin (from Penicillium Mold), Streptomycin (from Streptomyces bacteria), and Erythromycin (from Saccharopolyspora erythroid).
3. Marine Organisms: -Examples: Ziconotide (from cone snails), Ara-C (from sea squirts), and Eribulin (from sea sponge).
4. Animals Examples: Hirudin (from medicinal leeches), Conotoxins (from cone snails), and Venoms used in certain medicines.[95]
5. Fungi: Examples: Statins (from Aspergillus terreus), Cyclosporine (from Tolypocladiuminflatum), and Griseofulvin (from Penicillium Griseofulvin).
6. Venoms and Toxins Examples: Captopril (from snake venom), Prialt (from cone snail venom), and Botulinum toxin (used in Botox).
7. Algae: Examples: Carrageenan (from red algae), Fucoidan (from brown algae), and Spirulina-derived compounds.
8. Insects: Examples: Cantharidin (from blister beetles), Melittin (from bee venom), and Anticoagulants found in leech saliva
9. Endophytic Microorganisms: with me compounds with medicinal properties. Microorganisms Living within plants can produce
10. Terrestrial and Aquatic Ecosystems: Various ecosystems harbour unique organisms that may contain compounds with therapeutic potential.[96][97]

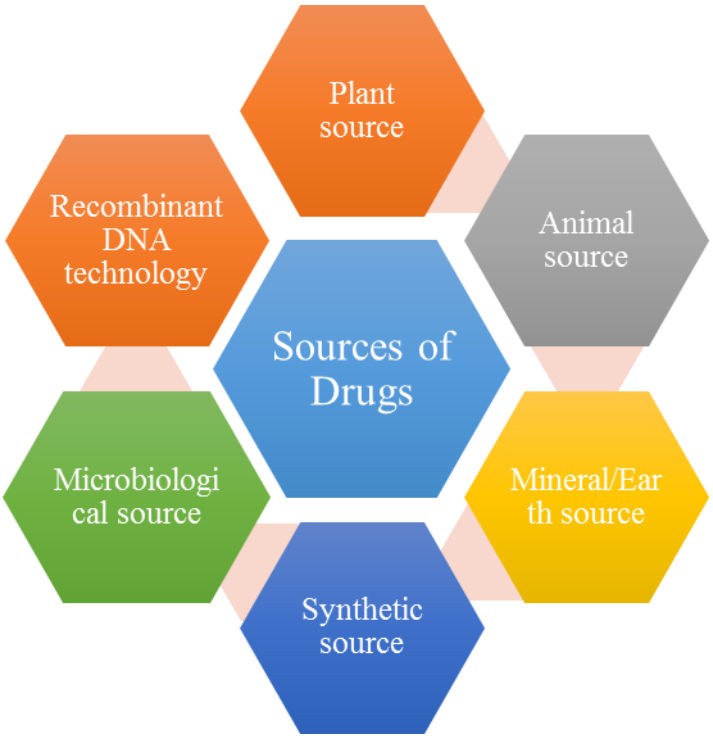

Fig no 12: Source of drugs.

❖ CONCLUSION

Drug design is the process of coming up with novel treatments based on an understanding of a biological target. This report talks about several forms of drug discovery, lead discovery, lead modification and drug design principles. As compared to computational approaches, the process of discovering new drugs through laboratory experimentation takes a long time and costs a lot of money.

Drug design explain its pivotal role in modern healthcare, where the demand for more targeted, efficient, and safer therapies is continually increasing. Advances in computational methods, molecular biology, and medicinal chemistry have propelled drug design to the forefront of pharmaceutical innovation, enabling the development of drugs that are not only more effective but also tailored to specific patient needs. By focusing on drug design, this report aims to provide insights into the methodologies that are shaping the future of pharmacology, highlighting both the challenges and opportunities for creating next-generation therapeutics.

REFERENCE

1. Hughes, J. P., et al. "Principles of Early Drug Discovery." British Journal of Pharmacology, 2011; 162(6): 1239–1249.
2. Schneider, G. "Automating Drug Discovery." Nature Reviews Drug Discovery, 2018; 17(2): 97–113.
3. Lovering, F., Bikker, J., and C. Humblet. "Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success." Journal of Medicinal Chemistry, 2009; 52(21): 6752–6756.
4. DiMasi, J. A., Grabowski, H. G., and R. W. Hansen. "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs." Journal of Health Economics, 2016; 47: 20–33.
5. Terstappen, G., Schlüpen, C., Raggiaschi, R., and G. Gaviraghi. "Target Deconvolution Strategies in Drug Discovery." Nature Reviews Drug Discovery, 2007; 6(11): 891–903.
6. Deore, Amol, Jayprabha Dhumane, Rushikesh Wagh, and Rushikesh Sonawane. "The Stages of Drug Discovery and Development Process." Asian Journal of Pharmaceutical Research and Development, 2019; 7: 62-67. doi:10.22270/ajprd.v7i6.616.
7. Shultana, Shamima, et al. "Drug design, discovery and development and their safety or efficacy on human body.", 2021.

8. Gashaw, Isabella, Peter Ellinghaus, Anette Sommer, and Khusru Asadullah. "What Makes a Good Drug Target?" Drug Discovery Today, 2011; 175: S24-S30.
9. Patidar, A. K., G. Selvam, M. Jeyakandan, A. K. Mobiya, A. Bagherwal, G. Sanadya, and R. Mehta. "Lead Discovery and Lead Optimization: A Useful Strategy in Molecular Modification of Lead Compound in Analog Design." International Journal of Drug Design and Discovery, 2011; 2: 458-463.
10. Umashankar, V., and S. Gurunathan. "Drug discovery: An appraisal." Int J Pharm Pharmaceutical Sci, 2015; 7: 59-66.
11. Smith, C. G., and J. T. O'Donnell. The Process of New Drug Discovery and Development. 2nd ed., CRC Press, 2006.
12. de Oliveiraa, André M., and Mithun Rudrapalb. "Introduction to drug design and discovery." Computer Aided Drug Design (CADD): From Ligand-Based Methods to Structure-Based Approaches, 2022; 1.
13. Chakraborty, Krishnasis, and Kavita Yadav. "Drug approval process in US, Europe and India and its regulatory requirements: A Review." International Journal of Drug Regulatory Affairs (IJDRA), 2018; 6.3: 31-39.
14. Wright, Brenda. "Introduction to clinical trials." A Comprehensive and Practical Guide to Clinical Trials. Academic Press, 2017; 1-9.
15. Thorat, S. B., et al. "Clinical trial: a review." International Journal of pharmaceutical sciences Review and Research, 2010; 1.2: 101-106.
16. https://med.uc.edu/depart/psychiatry/research/clinical-research/crm/trial-phases-1-2-3-defined
17. Sedgwick, Philip. "The Four Phases of Clinical Research Trials." BMJ, 2014; 348: 1-2.
18. Buyse, Marc. "Phase III Design: Principles." Chinese Clinical Oncology, 2016; 5: 1-13.
19. Adams, Christopher P., and Vanessa V. Brantner. New Drug Development: Estimating Entry from Human Clinical Trials. Bureau of Economics, Federal Trade Commission, 2003.
20. https://www.access.gpo.gov/nara/cfr/waisidx_03/21cf
21. Vishal, Prajapati. "A REVIEW ON DRUG APPROVAL PROCESS FOR US, EUROPE AND INDIA." (2014).
22. https://www.academia.edu/114997578/The_Organic_Chemistry_of_Drug_Design_and_Drug_Action
23. Vemula, Divya, "CADD, AI and ML in drug discovery: A comprehensive review." European Journal of Pharmaceutical Sciences, 2023; 181: 106324.

24. Rice, Joseph E., editor. "Chapter 5 - Partition Coefficients." Organic Chemistry Concepts and Applications for Medicinal Chemistry, Academic Press, 2014; 85-92. ISBN 9780128007396.
25. Prema, V., Meera Sivaramakrishnan, and M. Rabiya. "A Concise Review on role of QSAR in Drug Design." Asian Journal of Research in Chemistry, 2023; 16.6: 459-466.
26. Hansch, Corwin, and Toshio Fujita. "Analysis of the Structure-Activity Relationship of Drugs." Journal of Medicinal Chemistry, 1964; 7(1): 1-11.
27. Ivanciuc, Ovidiu. "QSAR Comparative Study of Wiener Descriptors for Weighted Molecular Graphs." Journal of Chemical Information and Computer Sciences, 2000; 40(6): 1412-1422.
28. Dearden, J. C. "The Use of Topological Indices in QSAR and QSPR Modeling." Advances in QSAR Modeling: Applications in Pharmaceutical, Chemical, Food, Agricultural and Enviro
29. Darlami, Janki, and Shweta Sharma. "The role of physicochemical and topological parameters in drug design." Frontiers in Drug Discovery, 2024; 4: 1424402.
30. https://microbenotes.com/computer-aided-drug-design-cadd/
31. Vemula, Divya, et al. "CADD, AI and ML in drug discovery: A comprehensive review." European journal of pharmaceutical sciences: official journal of the European Federation for Pharmaceutical Sciences, 2023; 181: 106324.
32. Aparoy, Polamarasetty, Kakularam Kumar Reddy, and Pallu Reddanna. "Structure and ligand based drug design strategies in the development of novel 5-LOX inhibitors." Current medicinal chemistry, 2012; 19.22: 3763-3778.
33. Smith, Michael B., and Jerry March. March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure. 6th ed., Wiley, 2007.
34. "A Review on Drug Design." International Journal of Science & Engineering Development Research, Feb. 2023; 8(1): 336-353. www.ijrti.org/papers/IJRTI2301053.pdf. Accessed [date of access].
35. https://manoa.hawaii.edu/exploringourfluidearth/chemical/chemistry-and-seawater/covalent-compounds/compare-contrast-connect-chemical-structures-visualizing-invisible
36. Kim, Sunghwan. "Public chemical databases." 2019; 628-639.
37. Williams, Antony J. "Public chemical compound databases." Current Opinion in Drug Discovery and Development, 2008; 11.3: 393.
38. https://pubchem.ncbi.nlm.nih.gov/

39. https://www.emolecules.com
40. https://www.mdli.com/products/experiment/available_chem_dir/index.jsp
41. https://www.cas.org/expertise/cascontent/chemcats.html
42. https://www.cambridgesoft.com/databases/details/?db=12
43. https://www.surechem.org/
44. https://www.chemspider.com/docs/Structure_Searching_of_Patents_Using_ChemSpid
45. Schueler, F.W. Chemobiodynamics and Drug Design. McGraw-Hill, 1960.
46. Qing, Xiaoyu, et al. "Pharmacophore modeling: advances, limitations, and current utility in drug discovery." Journal of Receptor, Ligand and Channel Research, 2014; 81-92.
47. Yang, Sheng-Yong. "Pharmacophore modeling and applications in drug discovery: challenges and recent advances." Drug discovery today, 2010; 15.11-12: 444-450.
48. Noha, S. M., and D. Schuster. "Pharmacophore Modeling." In Silico Drug Discovery and Design, edited by M. A. Lill, 2013; 80–93.
49. Wolber, Gerhard, and Thierry Langer. "LigandScout: 3-D Pharmacophores Derived from Protein-Bound Ligands and Their Use as Virtual Screening Filters." Journal of Chemical Information and Modeling, 2005; 45(1): 160–169.
50. Vilar, Santiago, Giulia Cozza, and Stefano Moro. "Medicinal Chemistry and the Molecular Operating Environment (MOE): Application of QSAR and Molecular Docking to Drug Discovery." Current Topics in Medicinal Chemistry, 2008; 8(18): 1555–1572.
51. Muhammed, Muhammed Tilahun, and Esin Akı-yalcın. "Pharmacophore modeling in drug discovery: methodology and current status." Journal of the Turkish Chemical Society Section A: Chemistry, 2021; 8.3: 749-762.
52. Barnum, D., J. Greene, A. Smellie, and P. Sprague. "Identification of Common Functional Configurations among Molecules." Journal of Chemical Information and Computer Sciences, 1996; 36: 563–571.
53. Lin, Shu-Kun, J. M. Sutter, and R. Hoffman. "HypoGen: An Automated System for Generating Predictive 3D Pharmacophore Models." Pharmacophore Perception, Development and Use in Drug Design, edited by Osman Güner, International University Line, 2000; 171–189.
54. Richmond, N. J., C. A. Abrams, P. R. N. Wolohan, E. Abrahamian, P. Willett, and R. D. Clark. "GALAHAD: 1. Pharmacophore Identification by Hypermolecular Alignment of Ligands in 3D." Journal of Computer-Aided Molecular Design, 2006; 20(9): 567–587.

55. Patel, Y., V. J. Gillet, G. Bravi, and A. R. Leach. "A Comparison of the Pharmacophore Identification Programs: Catalyst, DISCO, and GASP." Journal of Computer-Aided Molecular Design, 2002; 16(8–9): 653–681.
56. Schneidman-Duhovny, Dina, Oren Dror, Yuval Inbar, Ruth Nussinov, and Haim J. Wolfson. "PharmaGist: A Webserver for Ligand-Based Pharmacophore Detection." Nucleic Acids Research, vol. 36, Web Server issue, 2008; 223–228.
57. Koes, David R., and Carlos J. Camacho. "Pharmer: Efficient and Exact Pharmacophore Search." Journal of Chemical Information and Modeling, 2011; 51(6): 1307–1314.
58. Liu, X., et al. "PharmMapper Server: A Web Server for Potential Drug Target Identification Using Pharmacophore Mapping Approach." Nucleic Acids Research, 2010; 38(2): 5-7.
59. Raval, Keval, and Tejas Ganatra. "Basics, types and applications of molecular docking: A review." IP International Journal of Comprehensive and Advanced Pharmacology, 2022; 7.1: 12-16.
60. Agu, P. C., et al. "Molecular docking as a tool for the discovery of molecular targets of nutraceuticals in diseases management." Scientific Reports 13.1 (2023): 13398-13398.
61. Vasant, Otari Kishor,. "A review on molecular docking." International Research Journal of Pure and Applied Chemistry, 2021; 22.3: 60-68.
62. Dar, Ayaz Mahmood, Shafia Mir "Molecular Docking: Approaches, Types, Applications and Basic Challenges." Journal of Analytical & Bioanalytical Techniques, 2017; 8(2).
63. Dias, R., and W. D. Azevedo. "Molecular Docking Algorithms." Current Drug Targets, 2008; 9(12): 1040-47.
64. McMartin, C., R. S. Bohacek, "QXP: Powerful, Rapid Computer Algorithms for Structure-based Drug Design." Journal of Computational Aided Molecular Design, 1997; 11: 333-44.
65. Schnecke, V., L. A. Kuhn, "Virtual Screening with Solvation and Ligand-Induced Complementarity." Perspectives in Drug Discovery, 2000; 20: 171-90.
66. Jain, A. N., "Surflex: Fully Automatic Flexible Molecular Docking Using a Molecular Similarity-Based Search Engine." Journal of Medicinal Chemistry, 2003; 46: 499-511.
67. Avinash, R., A. Veerabhadra Rao, "A Review on Molecular Docking: Novel Tool in Drug Design and Analysis." Journal of Harmonized Research in Pharmacy, 2013; 2(4): 215-18.
68. Singla, Deepak, "Open source software and web services for designing therapeutic molecules." Current topics in medicinal chemistry, 2013; 13(10): 1172-1191.

69. Lang, P. T., "DOCK 6: Combining Techniques to Model RNA-Small Molecule Complexes." RNA, 2009; 15(6): 1219-30.
70. Morris, G. M., R. Huey, and A. J. Olson. "Using AutoDock for Ligand-Receptor Docking." Current Protocols in Bioinformatics, 2008; chapter 8, unit 8.14.
71. Macindoe, G.,"HexServer: An FFT-Based Protein Docking Server Powered by Graphics Processors." Nucleic Acids Research, vol. 38, Web Server issue, 2010; W445–W449.
72. Jackson, R. M., H. A. Gabb, and M. J. Sternberg. "Rapid Refinement of Protein Interfaces Incorporating Solvation: Application to the Docking Problem." Journal of Molecular Biology, 1998; 276(1): 265–285.
73. Trott, O., and A. J. Olson. "AutoDock Vina: Improving the Speed and Accuracy of Docking with a New Scoring Function, Efficient Optimization, and Multithreading." Journal of Computational Chemistry, 2010; 31(2): 455–461.
74. Dominguez, C., R. Boelens, and A. M. J. J. Bonvin. "HADDOCK: A Protein-Protein Docking Approach Based on Biochemical or Biophysical Information." Journal of the American Chemical Society, 2003; 125(7): 1731–1737.
75. https://biolabs.com/drug-
76. https://images.app.goo.gl/MaR4g
77. Suresh, P. S., A. Kumar, R. Kumar, V. P. Singh, et al. "An In Silico Approach to Bioremediation: Laccase as a Case Study." Journal of Molecular Graphics and Modelling, 2008; 26(5): 8459.
78. Pandeya, S. N. "Combinatorial chemistry: A novel method in drug discovery and its application." 2005.
79. Kumar, Dr. Konda, and B. Keerthana. "Combinatorial Chemistry and Its Application: A Modern Synthetic Approach." 2020.
80. https://scienceinfo.com/combinatorial-synthesis-types-advantages/
81. QSAR and Combinatorial Science." February 2005; 24: p. 1.
82. Gordon, Kirsteen, and Shankar Balasubramanian. "Solid Phase Synthesis – Designer Linkers for Combinatorial Chemistry: A Review." Journal of Chemical Technology and Biotechnology, 1999; 74: 835-851.
83. Borman, S. "Combinatorial Chemistry." Chemical & Engineering News, American Chemical Society, 6 Apr. 1998; 47-67.
84. Boger, Dale L., and M. Patel. "Solution-Phase Synthesis of Libraries." Current Opinion in Chemical Biology, 2001; 5(3): 343-347.

85. Szymański, Paweł, Magdalena Markowicz, and Elżbieta Mikiciuk-Olasik. "Adaptation of high-throughput screening in drug discovery—toxicological screening tests." International journal of molecular sciences, 2011; 13.1: 427-452.
86. Attene-Ramos, Matias S., "Systematic study of mitochondrial toxicity of environmental chemicals using quantitative high throughput screening." Chemical research in toxicology 26.9 (2013): 1323-1332.
87. Hughes, James P., Sally Rees, Steven B. Kalindjian, and Kevin L. Philpott. "Principles of Early Drug Discovery." British Journal of Pharmacology, 2011; 162(6): 1239-1249.
88. Kellenberger, E., et al. "Identification of Nonpeptide CCR5 Receptor Agonists by Structure-Based Virtual Screening." Journal of Medicinal Chemistry, 2007; 50(6): 1294-1303.
89. Kumar, Ravi. "Drug discovery (Lead identification and high throughput screening)." Research Journal of Pharmacology and Pharmacodynamics, 2021; 13.2: 46-50.
90. Li, A. P. "Preclinical in Vitro Screening Assays for Drug-Like Properties." Drug Discovery Today, 2005; 2: 179–185.
91. Lipinski, C. A., et al. "Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings." Advanced Drug Delivery Reviews, 1997; 23: 3–25.
92. van de Waterbeemd, Han, Ed Gifford, and Dennis A. Smith. "ADMET in Drug Discovery: Integration and Optimization of Pharmacokinetic and Toxicity Properties." Drug Discovery Today, 2001; 6(16): 838-845.
93. https://pmc.ncbi.nlm.nih.gov/articles/PMC6350845/
94. https://medium.com/@santuchal/admet-an-essential-component-in-drug-discovery-and-development-f503a5aae5dd
95. https://www.slideshare.net/slideshow/sources-of-drug-easy-notes-of-pharmacology/237039820
96. https://www.slideshare.net/slideshow/sources-of-drugs/58809660