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REVIEW ARTICLE ON DRUG DESIGN

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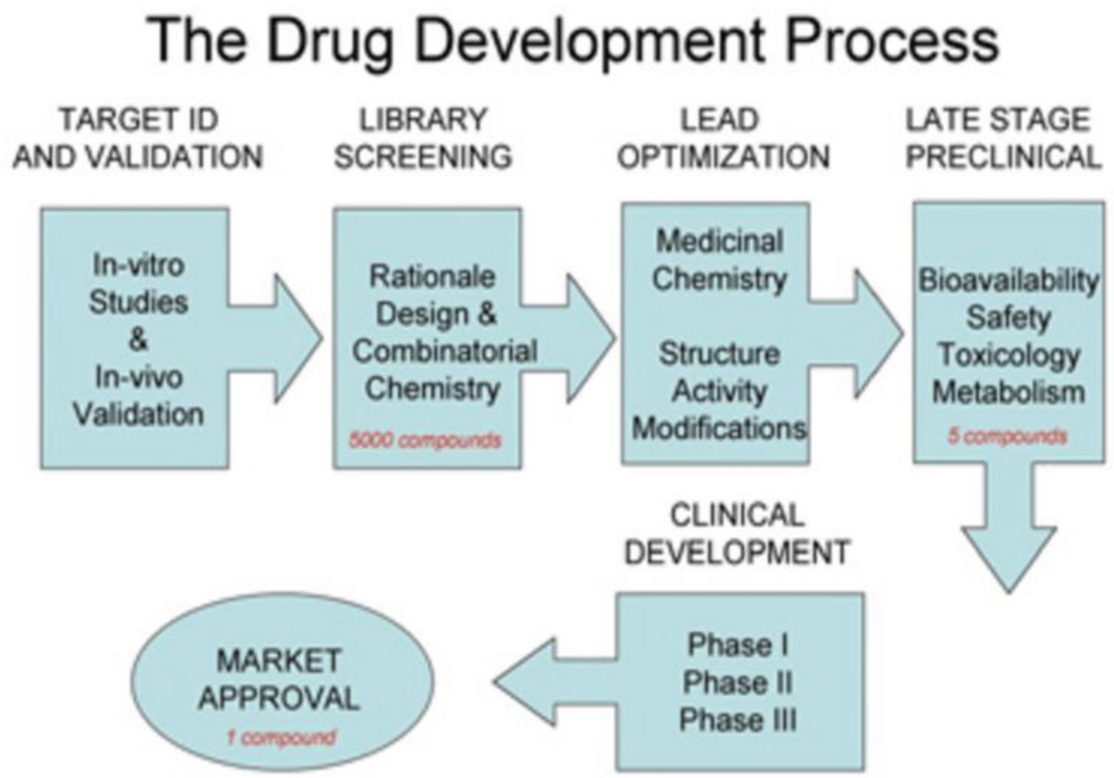
Abstract:

Pharmaceutical drug discovery is an expensive and time consuming process.The development of a drug from an initial idea to its entry into the market is a very complex process which can take around 5-10 yrs. and cost is very high upto billion. It is an development process involves use of variety of computational techniques ,such as structure activity relationship ,quantitative structure activity relationship ,molecular mechanics ,quantam mechanics,molecular dynamics and drug protein docking. The idea for a new development can come from a variety of sources which include the current necessities of the market, new emerging diseases , academic and clinical research , commercial sector. The pharmaceutical industry is under pressure in developing cost effectiveness drug molecule from the previous knowledge and established Quantitative Structure Activity Relationships.The structure based design is one of reliable and promising techniques used in drug designing. In drug design , the main aim is to find out the three dimensional structure of pharmacologically significant receptor ligand complexes. The aim of this review is to give an overview on the rational drug design approaches with a case study on drug discovery for influenza A virus , HER2 Receptor , targeting dopamine D3 receptor , purpose , and applications of QSAR. This article highlight the benefits and promises of developing tools for drug discovery.

Key Words : CADD , Pharmacophore , Docking , QSAR , ADMET

The lack of approved drugs or vaccines continues to be a challenge and further necessitates the discovery of new therapeutic molecules. Various molecular modelling techniques involved in structure based drug design anr molecular docking and molecular dynamic simulation , whereas ligand based drug design includes pharmacophore modelling , quantitative structure activity relationships(QSARs), and artificial intelligence (AI).The structural elucidation of pharmacological drug targets and the discovery of preclinical drug candidates molecules have accelerated both structure based as well as ligand based drug design. This revies article will help the clinicians and researchers to exploit the immense potential of computer aided drug design in designing and identification of drug molecules and thereby helping in the management of fatal diseases .The field of structure based drug design is a rapidly growing area in which many successes have occurred in recent years. The explosion of genomic, proteomic, and structural information has provided hundreds of new targets and oppurtunities for future drug lead discovery. The evaluation of a structure of that target, the pivotal questions to consider in choosing method for drug lead discovery, and evaluation of the drug leads. Key principles in the field of structure based drug design will be illustrated through a case study by that explores drug design for Amp C B-lactamase.

Computer aided drug design(CADD) is an evolving cascade of research area encompassing many facts .The theoretical basis of CADD involves quantam mechanics and molecular modelling studies like structure based drug design; ligand based drug design; database searching and binding affinity based on the knowledge of a biological target.In this review we present the areas where CADD tools support drug discovery process.In order to have one effective and safe drug, millions of molecules are screened. Animal studies often fail to predict clinical results due to inter species differences in enzyme, transporters and biological pathways.Although many in vitro assays use human cells, they lack the interplay of body systems and biochemical pathways. Due to this shortcomings both in vitro and in vivo studies often to fail predict clinical outcomes.Nearly 30% of molecules entering clinical trials fail baecause of insufficient safety.



Pharmacophore based techniques are nowadays an important part of many computer aided drug design workflows and have been successfully applied for tasks such as virtual screening, lead optimization and de novo design. Natural products, on the other hand , can serve as a valuable source for unconventional molecular scaffolds that stimulate ideas for novel lead compounds in a more diverse chemical space that does not follow the rules of traditional medicinal chemistry. In this review provides a brief introduction to the pharmacophore concept, the methods for pharmacophore model generation, and their applications. This show the pharmacophore based methods which get mainly applied on synthetic drug like molecules work equally well in the realm of natural products and thus can serve as a valuable tool for researchers in the field of natural product inspired drug design.

Introduction:

Drug design is an integrated developing discipline which portends an era of “Tailored drug”.It is an development process involves use of variety of computational techniques ,such as structure activity relationship ,quantitative structure activity relationship(QSAR),molecular mechanics ,quantam mechanics,molecular dynamics and drug protein docking. The QSAR establish a statistical relationship between biological activity or environmental behaviour of the chemicals of interest and their structural properties. QSAR predict chemical behaviour of directly from chemical structure and stimulate adverse effect in cells ,tissues and lab animals minimizing the need to use animals test to comply with regulatory requirements for human health and ecotoxicology.

Disposition of drugs in individual region of biosynthesis is one of the main factors determining the place, mode and intensity of their action .The biological activity may be “Positive” as in drug design or “Negative” as in toxicology .Drug design frequently but not necessarily relies on computer modelling is often referred to as “Computer aided drug design”. Drug design that relies on the knowledge of three dimensional structure of the biomolecular target is known as “structure based drug design”. Drug design is the inventive process of finding new medications based on the knowledge of a biological target. despite advances in biotechnology and understanding of biological systems ,drug discovery is still lengthy ,costly ,difficult ,and inefficient process with a high attrition rate of new therapeutic discovery. In the most basic sense ,drug design involves the design of molecules that are complementary in shape and charge to molecular target with which they interact and bind .Drug development and discovery includes preclinical research on cell based and animals models and clinical trials on humans ,and finally move forward to the step of obtaining regulatory approval in order to market the drug.The drug is most commonly an organic small molecules that activates or inhibits the function of a biomolecules such as a protein (receptor and enzymes),which in turn results in a therapeutic benefit to the patient .In the most basic sense ,drug design involves the design of small molecules that are complementary in shape and change to the biomolecular target with which the interact and therefore will bind to it.

Principles of Drug design:

Lipinski's Rule of Fives:

Lipinski's rule also known as the Pfizer rule of five or simply the rule of five is a rule of thumb to evaluate drug likeness or determine chemical compound with a certain pharmacological or biological activity has properties that would make it alikely orally active drug in humans .The rule was formulated by Christoper in 1997 ,based on the observation that most medication drugs are relatively small and lipophilic molecules.

The rule describes molecular properties for drugs pharmacokinetics in the human body including their ADME .Hence ,the rule does not predict if a compound is a pharmacologically active.

The rule is important to keep in mind during drug discovery when a pharmacologically active lead structure is optimized stepwise to increase the activity and selectivity of the compound as well as to ensure drug like physicochemical properties are maintained as describes by Lipinski's rule .

Components of the Rule:

1)Not more than 5 hydrogen bond donors.

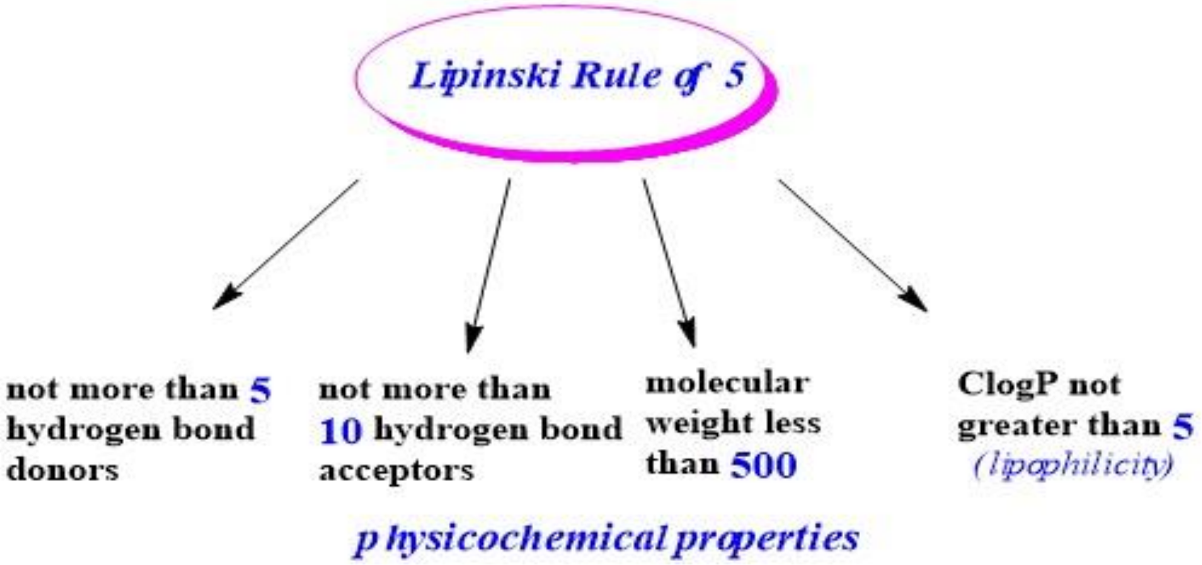
2)Not more than 10 hydrogen bond acceptors.

3)A molecular mass less than 500 daltons.

4)An alcohol water partition coefficient (log p)not more than 5.

Note that all numbers are multiplies of five which is the origin of the rules name.

The Lipinski's Rule of Five states that an orally bioavailable drug must neither possess more than five hydrogen bond donors nor more than 10 hydrogen bond acceptors ;its molecular weight must not be grater than 500 g/mol and its log p value not greater than 5 .



Docking:

Docking is a small molecules to protein binding sites was pioneered during early 1980 and remains a highly active area of drug research .When only the structure of a target and its active site is available high throughout docking is primarily used as a hit identification tool.

Molecular Docking:

The computational schemes that attempt to find the best matching between two molecules such as “a receptor and a ligand”.The subject of docking is the formation of non covalent complexex.

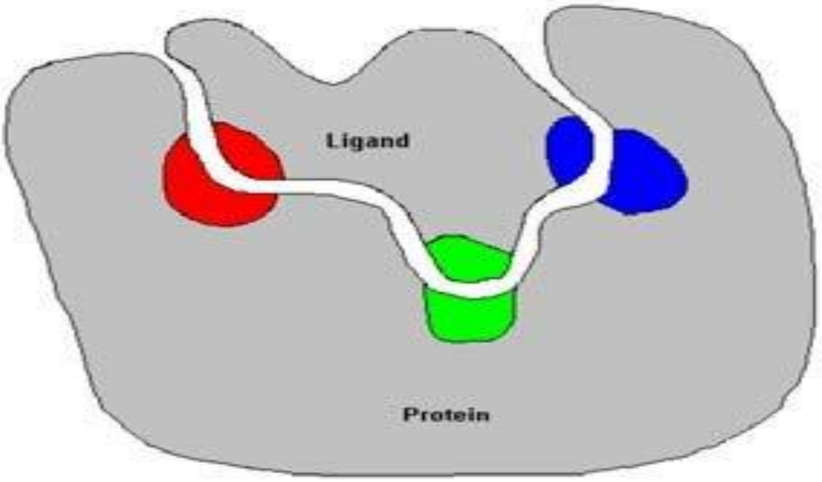


Fig. A best match between a protein and a ligand molecule.

Types of Docking:

1) Blind docking:

Blind docking is the docking to homology models of a target ,where the position of active site is assumed to be similar to one in a template protein .Docking to models of transmembranes proteins ,such as G-proteins coupled receptors.

Blind Docking refers to docking a ligand to the whole surface of a protein without any prior knowledge of the target pocket. Blind docking involves several trials/runs and several energy calculations before a favourable protein-ligand complex pose is found. However, the number of trials and energy evaluations necessary for a blind docking job is unknown.

In this type active site of the protein is not known and search for the binding site and subsequently the binding mode ligand is required. It is important for investigating protein protein interactions .

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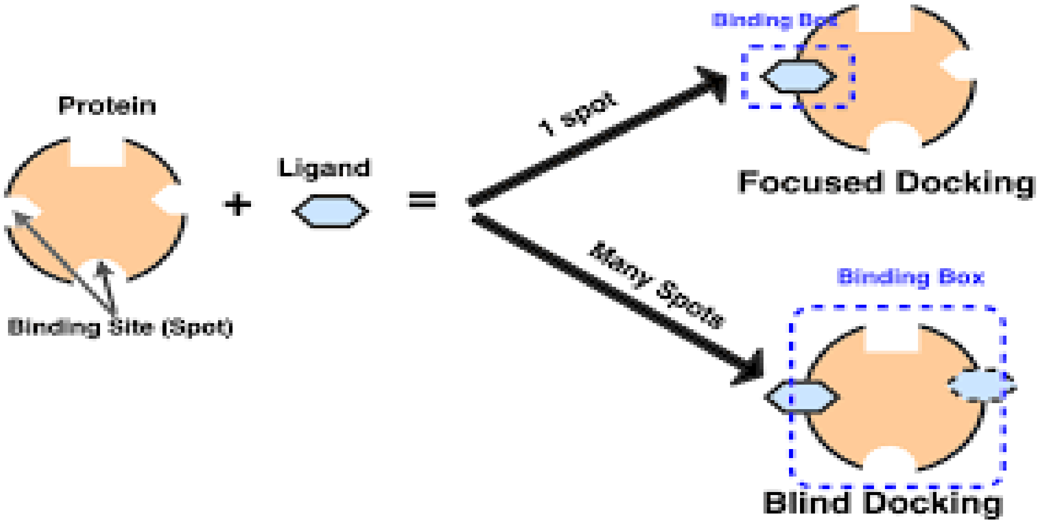


Fig: Simple and Blind docking

2)Direct docking:

If the active site of the binding is known from X-ray diffraction or from NMR studies ,docking into the known active is called a ‘direct docking’.

During direct docking .certain factors such as presence of cofactors ,discrete crystal molecules of water, and catalytic metal ions in the active site of protein or ionized states of the compounds aswell as the effects of the pH ,induced fit and conformational changes of protein must be taken into account if they are participating in protein-ligand interaction.

Key features of direct docking:

1) compatible with various types of probers.
2) retrofit of existing prober possible.
3) for top-load applications only.
4) facilitated installation due to simple prober head plate exchange.
5) onsite installation possible.
6) ease of use + handling.
7) smart + cost-effective solution.

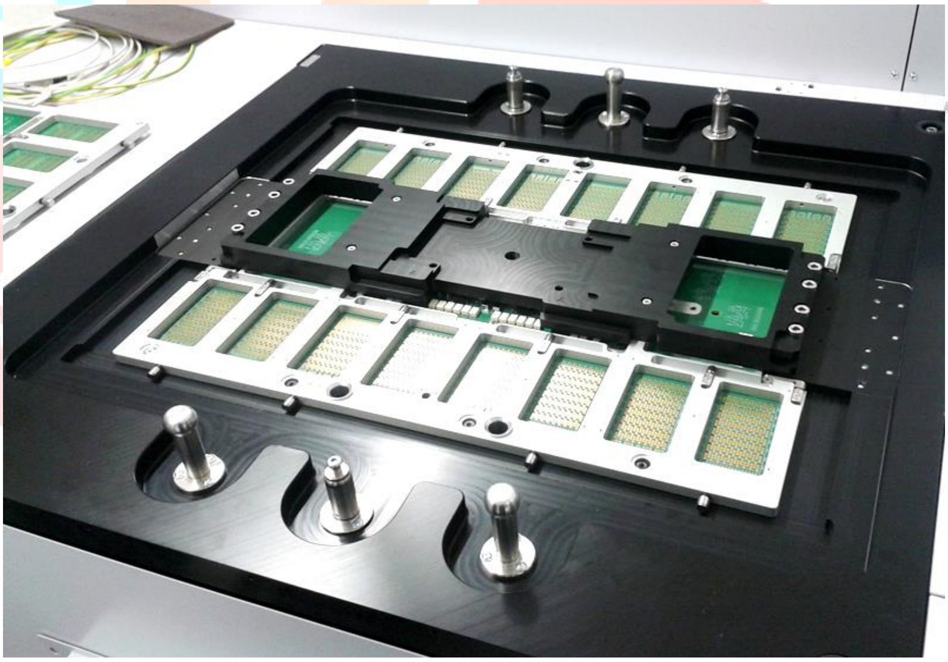


Fig : Direct docking wafer probing w/o pogo tower.

QSAR (Quantitative Structure Activity Relationship):

Quantitative structure activity relationship (QSAR)studies represent a non experimental part of drug design encompassing the study of both structure activity and structure property relations in broad sense. The most commonly used mathematical techniques in classical quantitative structure activity relationships (QSAR) work is multiple regression analysis. QSAR is an intellectual exercise of assembling , manipulating , and examining data obtained from physical , chemical, and biological experiments, and correlating them to biological activity . Biological activity of a drug depends on the types and magnitude of interactions between the receptor and the drug molecule .

Various structural attributes of a drug molecule, such as electronic distribution , steric features etc. ,are the determining factors regulating the interactions . Parameters must be properties that are capable of being represented by a numerical value. These values square measure wont to manufacture a general equation relating drug activity with the parameters. The goals QSAR studies include a better understanding of the modes of actions, prediction of newer analogs with better activity , classification of active /inactive compounds and optimization of the lead compound to reduce toxicity and increase selectivity.

The main properties of a drug that seem to influence its activity measure its lipophilicity, the electronic effects within the molecule and the size and shape of the molecule. Lipophilicity is a measure of a drug’s solubility in lipid membranes. This is usually an important factor in determining how easily a drug passes through lipid membranes. It is used as a live of the convenience of distribution of a drug to its target website. The parameters commonly used to represent these properties are partition coefficients and lipophilic substitution constants for lipophilicity, Hammetts constants for electronic effects and tafts Es steric constants for steric effects .

QSAR derived equations take the general form

Biological activity = Function (parameter)

In which the activity is normally expressed as log [1/(concentration term)]where the concentration term is usually C the minimum concentration required to cause a defined biological response .QSAR studies square measures ordinarily applied on teams of connected compounds. However, QSAR studies on structurally diverse sets of compounds are becoming more common. In both instances it is important to consider as wide range of parameters as possible. The different parameters are:

1)The lipophilic parameters

- A. Partition coefficient(P)
- B. Lipophilic substituent constants (p)
- C. Distribution coefficients

2)Electronic parameters

- A. The Hammett constant(s)

3)Steric parameters

4)The Taft steric parameter(ES)

HANSH ANALYSIS :

Hansh and co workers in the early 1960s proposed a multiparameter approach to the problem based on the lipophilicity of the drug and the electronic and steric influences of groups found in its structure. They realised that the biological activity of a compound is a function of its ability to reach and bind to its target site.Hansh planned that drug action may well be divided into 2 stages:

1.The transport of the drug to its site of action.

2.The binding of the drug to the target site.

Hansh postulated that the biological activity of a drug may well be associated with all or a number of these factors by straight forward mathematical relationships supported the final format :

Log 1/C1/4 k1[partition parameter]+k2[electronic parameter]+k3[steric parameter]+k4

Where,

C is the minimum concentration required to cause a specific biological response and k1, k2, k3, k4 are numerical constants obtained by feeding the data into a suitable computer statistical package.

Achievements of QSAR:

1)Forecasting of biological activity.

2)selection of proper substituent's.

3)Bioisosterism.

4)Drug receptor interaction.

5)Pharmacokinetics information's.

6)Time saving in synthesis process.

7)NO need to synthesis of derivatives liabrary.

Limitation of QSAR:

1)Regression analysis

2)Improper conditions of biological testing

3)Multiple mode of actions

QSAR methodology:

QSAR methodologies have the potential of decreasing substantially the time and effort required for the discovery of new medicines A major step in constructing the QSAR models is to find a set of molecular descriptors that represents variations of the structural properties of the molecule. The QSAR analysis employs statistical methods to derive quantitative mathematical relationship between chemical structure and biological activity. The process of QSAR modelling can be divided into three stages: development, model validation and application.

Development:

For the development of the model the compounds gathered from literature source could be divided into training and test set. The training sets are used in model construction while the test set for external validation.

The structures of the complexes under study could be drawn in 2D Chem Draw. These could be converted into 3D objects using the default conversion procedure implemented in the CS Chem 3D ultra. The generated 3D structures of the complex were then subjected to energy minimization and geometry optimization using Spartan. Molecular descriptors could be calculated using chemical software's such as Dragon, Gaussian, PADEL, etc. Molecular descriptors can be defined as the essential information of a molecule in terms of its physicochemical properties such as constitutional, electronic, geometrical, hydrophobic, lipophilicity, solubility, steric, quantum chemical and topological descriptors. Multivariate analysis such as multi linear regression, Partial least Square etc could be carried out for correlating molecular descriptors with observed activity.

Internal model validation:

The developed models were validated internally by leave- one- out (LOO) cross- validation technique. In this technique, one compound is eliminated from the data set at random in each cycle and the model is built using the rest of the compounds. The model thus formed is used for predicting the activity of the eliminated compound.

Randomization test:

The Robustness of the developed QSAR model was checked using Y-randomization technique in which model randomization was employed. In Y-randomization, validation was performed by permutating the response values, Activity (Y) with respect to the descriptor (X) matrix which was unaltered. The deviation in the values of the squared mean correlation coefficient of the randomized model (Rr^2) from the squared correlation coefficient of the non-random model (R^2) is reflected in the value of R^2_p parameter computed from the expression.

Application:

1) The application of QSAR models depends on statistical significance and predictive ability of the models.
2) The prediction of a model response using QSAR is valid only if the compound being predicted is within the applicability domain of the model.
3) The applicability domain is a theoretical region of the chemical space, defined by the model descriptors and model response and thus by the nature of the training set molecules.
4) It is possible to check whether a new chemical lies within applicability domain using the leverage approach.
5) A compound will be considered outside the applicability domain when the leverage values is higher than the critical value of 3p/n, where p is the number of model variables plus 1 and n is the number of objects used to develop the model.

CADD (Computer Aided Drug Design):

Computer-aided drug design (CADD) provides a variety of tools and techniques that assist in the various stages of drug design, thereby reducing the cost of drug research and development time. Drug discovery and the development of a new drug is a long, complex, costly and highly risky process that has no equal in the commercial world. Therefore, computer-aided drug design (CADD) approaches are widely used in the pharmaceutical industry to speed up the process. The cost advantage of using computational tools in the lead optimization phase of drug development is significant. The cost and time invested by pharmacological research laboratories are heavy at various stages of drug discovery, starting from therapeutic target setting candidate drug discovery to evaluating the efficacy and safety of newly developed drugs, drug optimization through preclinical and extensive clinical trials. Major pharmaceutical companies have invested heavily in routine ultra High Throughput Screening (uHTS) of large numbers of drug-like molecules. In parallel, drug design and optimization are increasingly using computers for virtual screening. Recent advances in DNA microarray experiments are discovering that thousands of genes involved in a disease can be used to gain in-depth information about disease targets, metabolic pathways, and toxicity of drugs. Theoretical tools include empirical molecular mechanics, quantum mechanics, and more recently statistical mechanics. This latest advance allowed the inclusion of overt solvent effects.

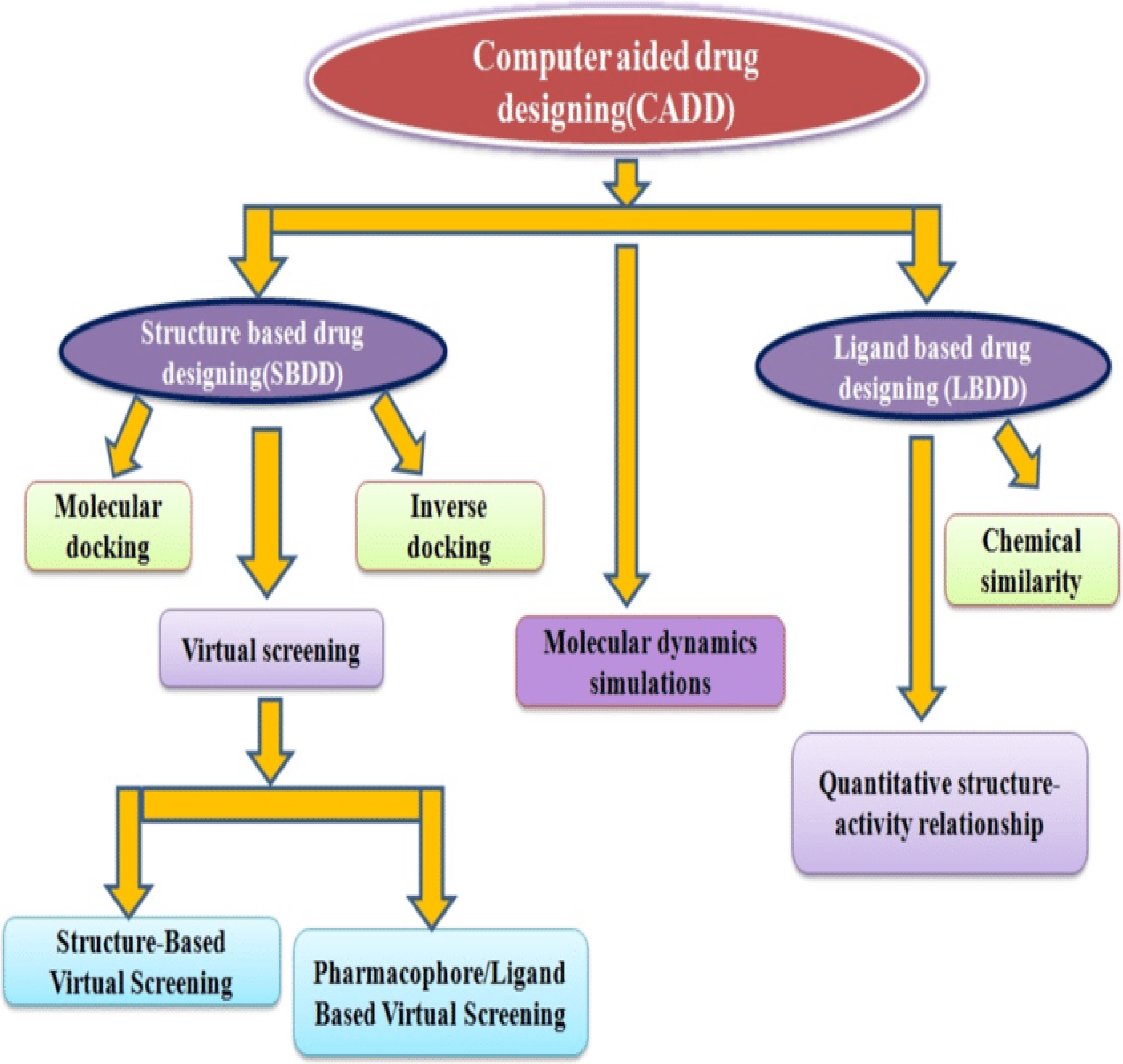


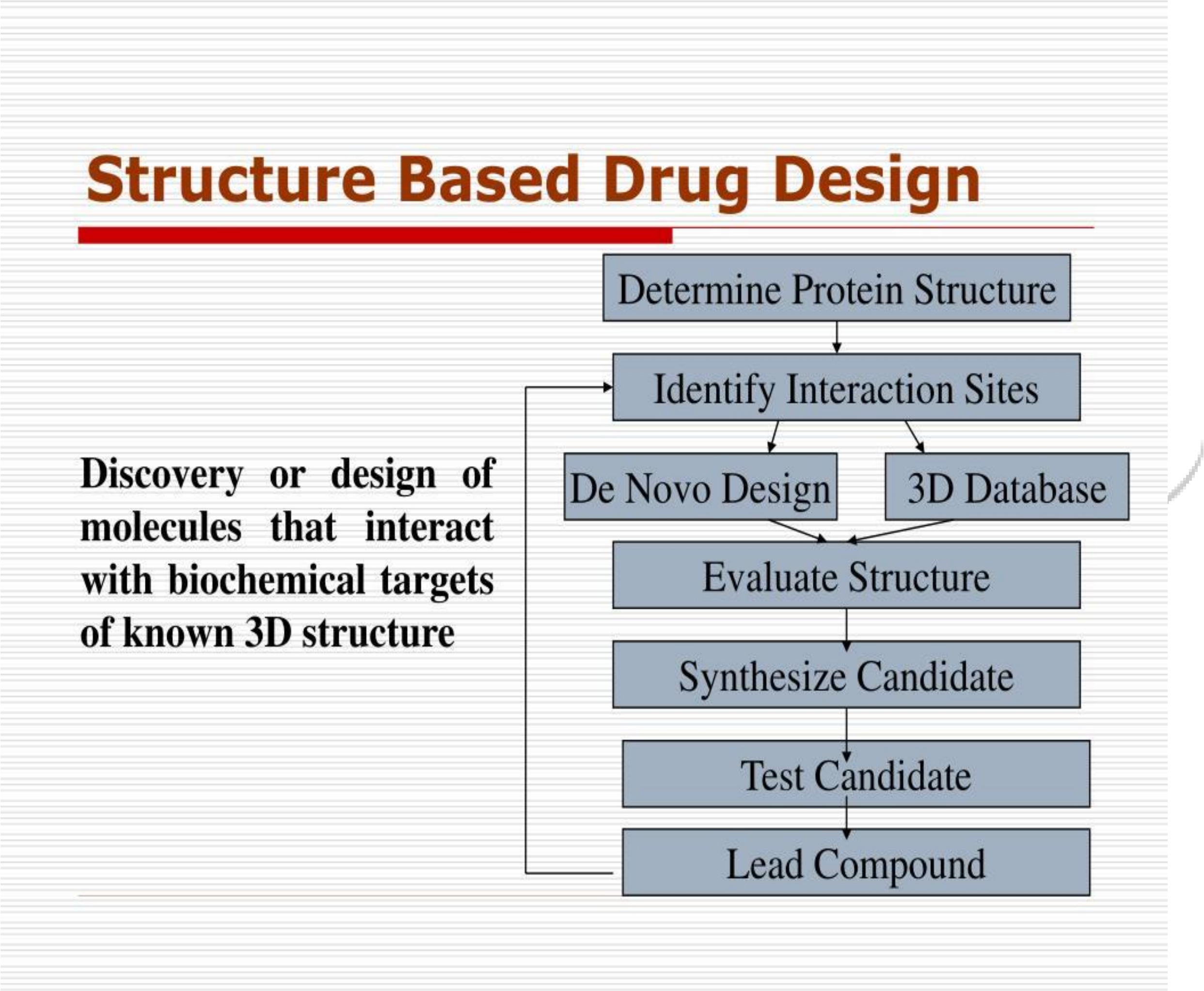
Fig: Computer Aided Drug Design Pharmaceutical Drug Sources .

There are two major types of CADD:

1)Structure Based Drug Design:

The structure of the target protein is known in structure based drug design (SBDD).These methods are very efficient and alternative approach to the discovery and development of drug design course .The three dimensional (3D)structure of proteins are provided in SBDD. The availability of 3D structures of therapeutically important proteins favours identification of binding cavities and has laid the foundation for structure-based drug design (SBDD). This is becoming a fundamental part of industrial drug discovery projects and of academic researches .

SBDD is a more specific, efficient, and rapid process for lead discovery and optimization because it deals with the 3D structure of a target protein and knowledge about the disease at the molecular level . Among the relevant computational techniques, structure-based virtual screening (SBVS), molecular docking, and molecular dynamics (MD) simulations are the most common methods used in SBDD. These methods have numerous applications in the analysis of binding energetics, ligand–protein interactions, and evaluation of the conformational changes occurring during the docking process.



Structure Based Drug Design

Discovery or design of molecules that interact with biochemical targets of known 3D structure

2)Ligand Based Drug Design:

Ligand based drug design is an indirect approach to facilitate the development of pharmacologically active compounds by studying molecules that interact with the biological target of interest. Ligand based drug design methods are useful in absence of an experimental 3D structure. Due to the lack of an experimental structure, the known ligand molecules that bind to the target are studied to understand the structural and physicochemical properties of the ligands that correlate with the desired pharmacological activity of those ligands.

Ligand based method may include natural products or substrate analogues that interact with the target molecule yielding the desired pharmacological effect. In some cases, usually in which data pertaining to the 3-D structure of a target protein are not available, drug design can instead be based on processes using the known ligands of a target protein as the starting point. This approach is known as “ligand-based drug design”.

Pharmacophore:

The original concept of the pharmacophore was developed by Paul Ehrlich during the late 1800s. At that time, the understanding was that certain “chemical groups” or functions in a molecule were responsible for a biological effect, and molecules with similar effect had similar functions in common. The word pharmacophore was coined much later, by Schueler in his 1960 book ***Chemobiodynamics** and Drug Design*, and was defined as “a molecular framework that carries (phoros) the essential features responsible for a drug’s (pharmacon) biological activity.” The definition of a pharmacophore was therefore no longer concerned with “chemical groups” but “patterns of abstract features.”

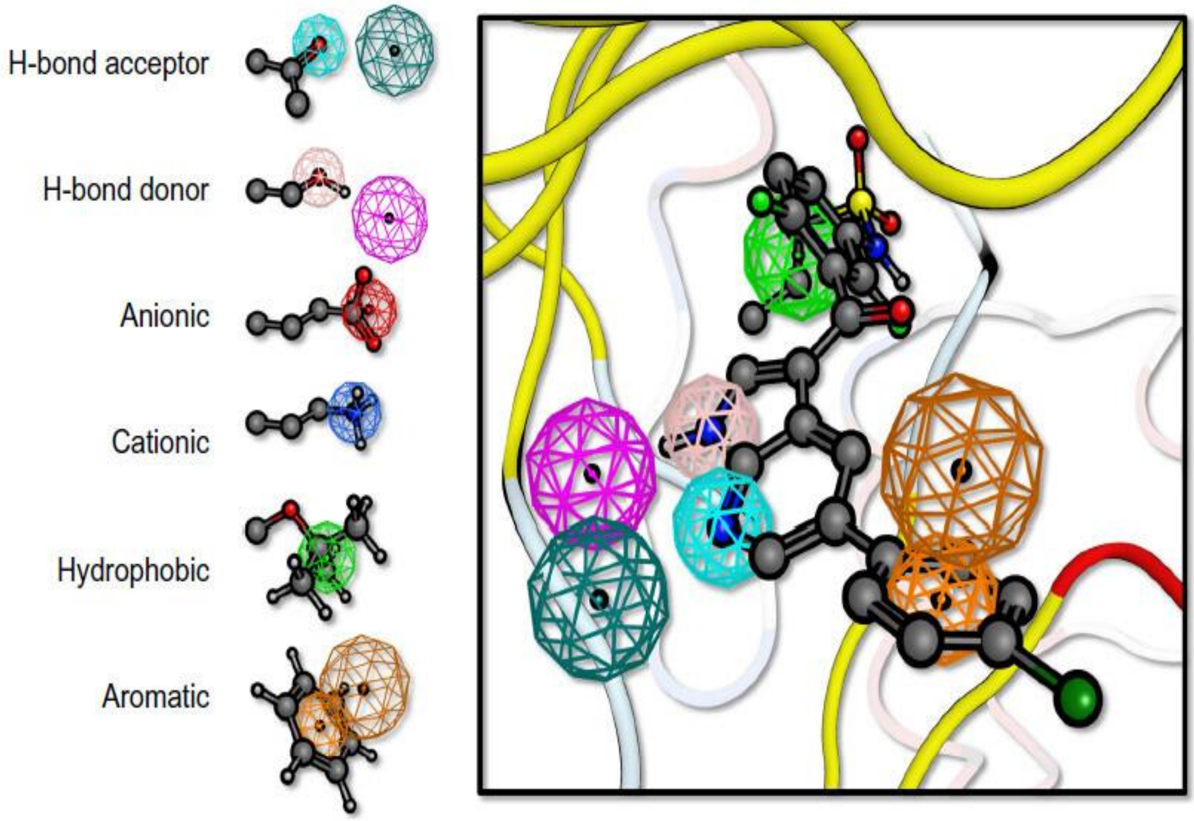
Since 1997, a pharmacophore has been defined by the International Union of Pure and Applied Chemistry as:

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.

The pharmacophore should be considered as the largest common denominator of the molecular interaction features shared by a set of active molecules. Thus a pharmacophore does not represent a real molecule or a set of chemical groups, but is an abstract concept. Despite this clear definition, the term pharmacophore is often misused by many in medicinal chemistry to describe simple yet essential chemical functionalities in a molecule (such as guanidine or sulfonamides), or common chemical scaffolds (such as flavones or prostaglandins). Often the long definition is simplified to “A pharmacophore is the pattern of features of a molecule that is responsible for a biological effect,” which captures the essential notion that a pharmacophore is built from features rather than defined chemical groups.

Pharmacophore concepts in CADD:

The pharmacophore concept predates any form of electronic computer, it has nevertheless become an important tool in CADD. Every type of atom or group in a molecule that exhibits certain properties related to molecular recognition can be reduced to a pharmacophore feature. These molecular patterns can be labeled as hydrogen bond donors or acceptors, cationic, anionic, aromatic, or hydrophobic, and any possible combinations. Different molecules can be compared at the pharmacophore level; this usage is often described as “pharmacophore fingerprints.” When only a few pharmacophore features are considered in a 3D model the pharmacophore is sometimes described as a “query.”



Pharmacophore fingerprint:

The molecules are 3D entities, the pharmacophore representation reduces a molecule to a collection of features at the 2D or 3D level. A pharmacophore fingerprint is an extension of this concept, and typically annotates a molecule as a unique data string. All possible three-point or four-point sets of pharmacophore features are enumerated for each ligand. The distance between the feature points is counted in bonds (for topological fingerprints), or by distance-binning when using 3D fingerprints .The resulting fingerprint is a string describing the frequency of every possible combination at predefined positions within the string. Several variants of pharmacophore fingerprints have been designed and are frequently used.

Pharmacophore modeling in virtual screening:

Pharmacophore modeling is most often applied to virtual screening in order to identify molecules triggering the desired biological effect. For this purpose, researchers create a pharmacophore model (query) that most likely encodes the correct 3D organization of the required interaction pattern. Depending on how much is known about the particular protein target, different options are available to construct such a query.

Pharmacophore methods in docking simulations:

As indicated in the previous section, pharmacophore models are very suitable as queries for virtual screening of databases. Nevertheless, one of the more common approaches in virtual screening is a so-called hierarchical approach in which different methods are combined consecutively. This is also known as the funnel principle, where at each consecutive step the compounds most unlikely to be active are removed, leaving the most promising compounds for virtual screening. Typically, every step of the hierarchical approach consists of a more complex, computationally demanding step than the previous one. As such, pharmacophore models are often utilized as a filter to identify compounds that fulfill simple geometric and chemical functionality requirements of the query, prior to more complicated and computationally demanding approaches such as molecular docking.

Molecular docking simulations are computational methods that aim to predict the binding mode of a compound for a given receptor as well as the quality of the interaction, often by attempting to predict the affinity (free energy of binding) using a scoring function. Often molecular docking simulations are used to screen large datasets of compounds for a given target, and compounds are ranked according to their predicted affinity. Due to the high number and diversity of the screening compounds, as well as the knowledge that most of the screened compounds are in fact probably inactive, the top scoring compounds are most likely inactive and better compounds are ranked below them. Although this ranking can still be better than random, typically only a few compounds are selected from those scoring best, and many of them often turn out to be inactive.

Several options are available for combining docking-based virtual screening with pharmacophore-based virtual screening:

- The database of ligands can be pre-filtered using a pharmacophore query, prior to evaluation using docking simulations.
- The docking simulations can be post-filtered using a pharmacophore query to remove any compounds that fail to bind according to the pharmacophore query.
- The method can also discard compounds that would have scored well in a pure pharmacophore search, but that fail to bind according to some hypothesis taking more information into account, such as incompatibility of the overall ligand structure with the receptor site. In such a case, the ligands are evaluated in absolute conformation and should not be allowed to align with the pharmacophore features.
- Another alternative is to use the pharmacophore alignment to guide the placement during the docking simulations.
- The pharmacophore model can in this case be used for the placement of the ligand, similarly to the fitting of a molecule into the pharmacophore query; or to guide the placement by using a constraint while scoring the different docking poses.
- The pharmacophore query could originate from a user-defined query or an automatically generated receptor-based pharmacophore query.

Pharmacophore models are very useful for enriching the top scoring docking results with active compounds. This was demonstrated in the recent SAMPL4 virtual screening challenge where competitors were asked to rank a set of compounds for a given target, HIV-1 Integrase, without any knowledge of activity of the compounds in the library. The top results were obtained for the group using a hierarchical method consisting of pharmacophore pre-filtering as well as pharmacophore post-filtering of the docking results.

ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity.):

ADMET Evaluation function module is composed of a series of high-quality prediction models trained by multi-task graph attention framework. It enables the users to conveniently and efficiently implement the calculation and prediction of 17 physicochemical properties, 13 medicinal chemistry measures, 23 ADME endpoints, and 27 toxicity endpoints and 8 toxicophore rules (751 substructures), thereby selecting promising lead compounds for further exploration.

Acyclic diene metathesis polymerization (ADMET) is a step growth polycondensation reaction which releases ethylene as a by product. Elimination of ethylene by applying vacuum to the reaction vessel is the driving force of the reaction. Polymerization occurs either in bulk at high temperature up to 190 °C or with the use of solvents at considerably lower temperatures *via* metathesis using an appropriate catalyst.

The first well-defined metathesis catalyst was created by Schrock in 1986 based on tungsten after which molybdenum-containing Schrock catalysts became prevalent. Both are most effective for producing high molecular weight polymers with degrees of polymerization higher than 150 for hydrocarbon polymers, while being less useful for polymers containing functional groups. Catalysts containing late transition metals, primarily ruthenium, developed by Grubbs and coworkers are best used when functional groups are present; their use has expanded metathesis chemistry considerably. The first-generation ruthenium catalyst, known as Grubbs' first-generation, led to a variety of new ruthenium structures featuring diverse reactivity and functional group tolerance, while maintaining low rates of olefin isomerization and consequently, chain walking. shows the structures of Schrock's molybdenum and Grubbs' first-generation catalyst.

ADMET monomers normally are α,ω-dienes that produce unsaturated ADMET polymers. The major advantage of ADMET chemistry is the formation of repeat units with symmetrically disposed functionalities (both hydrocarbon and otherwise) along the polymer backbone, a key feature that is a direct consequence of the monomer symmetry. The unsaturated polymer can be further saturated by exhaustive hydrogenation of the polymer chain. shows a symmetric α,ω-diene that yields an unsaturated ADMET polymer with a generic functionality. Functionality is precisely placed along the polymer backbone by controlling symmetrically the length between terminal olefins. Depending upon the nature of the introduced functionality and the design of the α,ω-diene monomer, a diverse library of saturated and unsaturated ADMET polymers can be obtained with the functionality either incorporated in the polymer chain or pendant along the chain.

The first significant ADMET polymerization work appeared in 1991[4] followed by the creation of diverse polymers containing precisely placed in-chain or pendant functional groups. For example, when the R group is an alkyl chain, the resultant polymer can be seen as a model polyolefin; many other polymers containing sulphur, boron, silicon, and amino acids have been synthesized. The following sections review the synthetic methods used for the preparation of those monomers and polymers, along with discussion of secondary structure elucidation and applications of ADMET polymers as functional materials.

Synthesis:

As is true for any step polymerization, performing an ADMET reaction is straightforward requiring highly pure monomer and quantitative conversion.[5] Monomer synthesis can be accomplished in a number of ways. The following sections show different approaches for obtaining α,ω-diene monomers containing alkyl chains, halogens, carboxylic and phosphonic acids, sulfur, boron, amino acid and amphiphile branches and their use in ADMET polymerization.

Polyethylene with precisely placed alkyl branches:

Polyethylene (PE) is the highest volume polymer produced worldwide; its industrial production is currently an indicator of a country's development. While polyethylene's repeat unit usually is shown in its most simple form, in fact the primary, secondary, tertiary structures are complex. Consequently, careful studies of structure–property relationships, thermal behaviour, and morphology of this polymer remain useful. Various forms of polyethylene are synthesized commercially *via* chain propagation chemistry using free-radical initiation, heterogeneous Ziegler–Natta catalysis, metallocene-based catalysis and most recently, late transition metal catalytic systems. Linear low density polyethylenes, copolymers of ethylene and α-olefins are of interest since their thermal and mechanical properties can be tuned for specific applications. The type, concentration, and distribution of the α-olefin monomer along the polymer chain determines the physical properties of the material. For example, propene, 1-butene and 1-octene result in methyl, ethyl and hexyl branches, respectively. Although polymer behaviour also can be manipulated by controlling the polymerization process, LLDPE structures nicely tune material properties created by statistical incorporation of the desired comonomer.

ADMET avoids the random nature of branching in polyethylene by generating precision repeat units, again, a consequence of step rather than chain polymerization methodology. The most significant early ADMET reference was reported in 1991 creating perfectly linear, nonbranched ADMET polyethylene (PE) the polymerization of 1,9-decadiene, followed by exhaustive saturation with hydrogen. Since then ADMET has been used to produce functionalized unsaturated polyolefins as well as saturated PE models with perfect primary structures. The first ADMET synthetic and thermal studies yielded precision PEs with methyl, ethyl and hexyl branches; these ADMET polymers modeled commercial versions made *via* Ziegler–Natta or metallocene chemistry. Specifically they were precision examples duly named ethylene/1-propene (EP), ethylene/1-butane (EB), and ethylene/1-octene (EO).

ADMET monomer synthesis initially comprised reaction schemes requiring several steps. Since then, monomer synthesis for such alkyl branched precision polymers has been reduced to just two steps. The following sections describe the history of monomer synthesis including the preferred two step approach. The result has been the preparation of a family of alkyl α,ω-diene monomers for short chain branching (methyl, ethyl, *etc.*) to long chain branching (up to 21 carbons).

Chemical Structure Drawing :

Objectives:

After completing this section, you should be able to,

1)Propose one or more acceptable Kekule structures for any given molecular formula.

2)write the molecular formula of a compound , given its Kekule structure.

3)Draw the short hand structure of a compound , given its Kekule structure.

4)Interpret short hand structures and convert them Kekule structures.

5)Write the molecular formula of a compound , given its short hand structure.

Through general chemistry, you may have already experienced looking at molecular structures using Lewis structures. Because organic chemistry can involve large molecules it would be beneficial if Lewis structures could be abbreviated. The three different ways to draw organic molecules include Kekulé Formulas, Condensed Formulas, and Skeletal structures (also called line-bond structures or line formulas).

During this course, you will view molecules written in all three forms. It will be more helpful if you become comfortable going from one style of drawing to another, and look at drawings and understanding what they represent. Developing the ability to convert between different types of formulas requires practice, and in most cases the aid of molecular models. Many kinds of model kits are available to students and professional chemists, and the beginning student is encouraged to obtain one.

Simplification of structural formulas may be achieved without any loss of the information they convey. Kekule formulas is just organic chemistry's term for Lewis structures you have previously encountered. In **condensed structural formulas**, the bonds to each carbon are omitted, but each distinct structural unit (group) is written with subscript numbers designating multiple substituents, including the hydrogens. **Line formulas** omit the symbols for carbon and hydrogen entirely (unless the hydrogen is bonded to an atom other than carbon). Each straight line segment represents a bond, the ends and intersections of the lines are carbon atoms, and the correct number of hydrogens is calculated from the tetravalency of carbon. Non-bonding valence shell electrons are omitted in these formulas.

1)Kekule (Lewis Structures):

A Kekulé Formula or structural formula displays the atoms of the molecule in the order they are bonded. It also depicts how the atoms are bonded to one another, for example single, double, and triple covalent bond. Covalent bonds are shown using lines. The number of dashes indicate whether the bond is a single, double, or triple covalent bond. All atom labels are shown and all lone pairs are shown.

2)Condensed Formula:

A condensed formula is made up of the elemental symbols. Condensed structural formulas show the order of atoms like a structural formula but are written in a single line to save space and make it more convenient and faster to write out. The order of the atoms suggests the connectivity in the molecule. Condensed structural formulas are also helpful when showing that a group of atoms is connected to a single atom in a compound. When this happens, parenthesis are used around the group of atoms to show they are together. Also, if more than one of the same substituent is attached to a given atom, it is show with a subscript number. An example is CH_4, which represents four hydrogens attached to the same carbon. Condensed formulas can be read from either direction and H_3C is the same as CH_3, although the latter is more common.

Eg.1) CH3CH2OH ,

2)ClCH2CH2CH(OCH3)CH3

3)Line Formula:

Line angle formulas imply a carbon atom at corners and ends of lines. Each carbon atom is understood to be attached to enough hydrogen atoms to give each carbon atom four bonds. Because organic compounds can be complex at times , line angle formulas are used to write carbon and hydrogen atoms more efficiently by replacing the letter “C” with lines.A carbon atom is present wherever a line intersects another line. Hydrogen atoms are omitted but are assumed to be present to complete each of carbon’s four bonds Hydrogens that are attached to elements other than carbon are shown.Atoms labels for all other elements are shown . lone pair electrons are usually omitted. They are assumed to be present to complete the octet of non carbon atoms. Line formulas help show the structure and order of the atoms in a compound.

Combinatorial Chemistry and HTS:

Combinatorial chemistry involves the rapid synthesis or the computer simulation of a large number of different but often structurally related molecules or materials. In a combinatorial synthesis, the number of compounds made increases exponentially with the number of chemical steps. In a binary light-directed synthesis, 2n compounds can be made in n chemical steps. Combinatorial chemistry is especially common in CADD (Computer aided drug design) and can be done online with web based software, such as molinspiration.

History of Combinatorial Chemistry:

Combinatorial chemistry was first conceived about 15 years ago - although it wasn't called that until the early 1990s. Initially, the field focused primarily on the synthesis of peptide and oligonucleotide libraries. H. Mario Geysen, distinguished research scientist at Glaxo Welcome Inc., Research Triangle Park, N.C., helped jump-start the field in 1984 when his group developed a technique for synthesizing peptides on pin-shaped solid supports.

At the Coronado conference, Geysen reported on his group's recent development of an encoding strategy in which molecular tags are attached to beads or linker groups used in solid-phase synthesis. After the products have been assayed, the tags are cleaved and determined by mass spectrometry (MS) to identify potential lead compounds. Although combinatorial chemistry has only really been taken up by industry since the 1990s, its roots can be seen as far back as the 1960s when a researcher at Rockefeller University, Bruce Merrifield, started investigating the solid-state synthesis of peptides 19 .

In the past decade there has been a lot of research and development in combinatorial chemistry applied to the discovery of new compounds and materials. This work was pioneered by P.G. Schultz et al. in the mid-nineties (Science, 1995, 268: 1738-1740) in the context of luminescent materials obtained by code position of elements on a silicon substrate. Since then the work has been pioneered by several academic groups as well as industries with large R&D programs.

Principle of Combinatorial Chemistry:

Combinatorial chemistry is a technique by which large numbers of structurally distinct molecules may be synthesized in a time and submitted for pharmacological assay. The key of combinatorial chemistry is that a large range of analogues is synthesized using the same reaction conditions, the same reaction vessels. In this way, the chemist can synthesize many hundreds or thousands of compounds in one time instead of preparing only a few by simple methodology 4 . In the past, chemists have traditionally made one compound at a time.

For example compound A would have been reacted with compound B to give product AB, which would have been isolated after reaction work up and purification through crystallization, distillation or chromatography.

Concepts of Combinatorial Chemistry and Combinatorial Technologies:

Combinatorial Technology and Combinatorial Chemistry is a new field joining computer assisted combinatorial chemistry with synthesis of chemical libraries followed by automated screening. The main purpose is to generate thousands structurally diverse compounds as maximizing their diversity, libraries, which are then considered in an experimental screening and synthesis on the basis of their properties.

Combinatorial synthesis on Solid-phase :

Since Merrifield pioneered solid phase synthesis back in 1963, work, which earns him a Nobel Prize, the subject, has changed radically. Merrifield's Solid Phase synthesis concept, first developed for biopolymer, has spread in every field where organic synthesis is involved. Many laboratories and companies focused on the development of technologies and chemistry suitable to SPS. This resulted in the spectacular outburst of combinatorial chemistry, which profoundly changed the approach for new drugs, new catalyst or new natural discovery.

1) A cross linked, insoluble polymeric material that is inert to the condition of synthesis.

2) Some means of linking the substrate to this solid phase that permits selective cleavage of some or all of the product from the solid support during synthesis for analysis of the extent of reaction(s), and ultimately to give the final product of interest .

3) A chemical protection strategy to allow selective protection and deprotection of reactive groups.

Synthesis of Combinatorial Library:

Combinatorial synthesis on solid phase can generate very large numbers of products, using a method described as mix and split synthesis. This technique was pioneered by Furka and has been enthusiastically exploited by many others since its first disclosure. For example, Houghten has used mix and split on a macro scale in a "tea bag" approach for the generation of large libraries of peptides.

The method works as follows: a sample of resin support material is divided into a number of equal portions (x) and each of these is individually reacted with a single different reagent. After completion of the reactions, and subsequent washing to remove excess reagents, the individual portions are recombined; the whole is thoroughly mixed, and may then be divided again into portions. Reaction with a further set of activated reagents gives the complete set of possible dimeric: units as mixtures and this whole process may then be repeated as necessary (for a total of n times). The number of compounds obtained arises from the geometric increase in potential products; in this case x to the power of n.

Combinatorial synthesis in Solution:

Despite the focus on the use of solid-phase techniques for the synthesis of combinatorial libraries, there have been few examples where libraries have successfully been made and screened in solution. The benefit of preparing libraries on resin beads has been explained as offering advantages in handling, especially where a need to separate excess reagents from the reaction products is attached to the resin. In most of case a simple filtration effects a rapid purification and the product are ready to further synthetic transformation. But it should be remember that using solid phase chemistry brings several disadvantages as well.

Clearly the range of chemistry available on solid phase is limited and it is difficult to monitor the progress of reaction when the substrate and product are attached to the solid phase 26 . Indeed some groups have expressed a preference for solution libraries because there is no prior requirement to develop workable solid phase coupling and linking techniques.

The difficulty is purifying large number of compounds without sophisticated automated processes.

Parallel Solution Phase synthesis:

Manual or automated approaches can be used for the parallel preparation of tens to hundreds of analogues of a biologically active substrate. The products are synthesised using reliable coupling and functional group interconversion chemistry and are progressed to screening after removal of solvent and volatile by products.

Resins for Solid Phase synthesis:

In solid phase support synthesis, the solid support is generally based on a polystyrene resin. The most commonly used resin supports for SPS include spherical beads of lightly cross linked gel type polystyrene (1–2% divinylbenzene) and poly(styrene-oxyethylene) graft copolymers which are functionalised to allow attachment of linkers and substrate molecules.

Advantages:

1)Rapid synthesis

2)Large number

3)Richer data from screening

4)Increased likelihood of success

5)Broader patent protection

Disadvantages:

1)It is difficult to characterise the identification of unexpected product combination.

2)Difficulty of conforming the degree to expected chemistry and substrate molecule is major problem in the combinatorial organic synthesis.

High-throughput screening:

High-throughput screening (**HTS**) is a method for scientific experimentation especially used in drug discovery and relevant to the fields of biology materials , science and chemistry. Using robotics, data processing/control software, liquid handling devices, and sensitive detectors, high-throughput screening allows a researcher to quickly conduct millions of chemical, genetic, or pharmacological tests. Through this process one can quickly recognize active compounds, antibodies, or genes that modulate a particular biomolecular pathway. The results of these experiments provide starting points for drug design and for understanding the noninteraction or role of a particular location.

Types of High Throughput Screening Assays :

1)Homogeneous assay

2)Heterogeneous assay

-Biochemical assays

Assay plate preparation:

The key labware or testing vessel of HTS is the microtiter plate, which is a small container, usually disposable and made of plastic, that features a grid of small, open divots called *wells*. In general, microplates for HTS have either 96, 192, 384, 1536, 3456 or 6144 wells. These are all multiples of 96, reflecting the original 96-well microplate with spaced wells of 8 x 12 with 9 mm spacing. Most of the wells contain test items, depending on the nature of the experiment. These could be different chemical compounds dissolved e.g. in an aqueous solution of dimethyl sulfoxide (DMSO). The wells could also contain cells or enzymes of some type of proteins.

. Reaction observation:

To prepare for an assay, the researcher fills each well of the plate with some biological entity that they wish to conduct the experiment upon, such as a protein, cells, or an animal embryo. After some incubation time has passed to allow the biological matter to absorb, bind to, or otherwise react (or fail to react) with the compounds in the wells, measurements are taken across all the plate's wells, either manually or by a machine. Manual measurements are often necessary when the researcher is using microscopy to (for example) seek changes or defects in embryonic development caused by the wells' compounds, looking for effects that a computer could not easily determine by itself. Otherwise, a specialized automated analysis machine can run a number of experiments on the wells (such as shining polarized light on them and measuring reflectivity, which can be an indication of protein binding). In this case, the machine outputs the result of each experiment as a grid of numeric values, with each number mapping to the value obtained from a single well. A high-capacity analysis machine can measure dozens of plates in the space of a few minutes like this, generating thousands of experimental datapoints very quickly.

Automation systems:

Automation is an essential element in HTS's usefulness. Typically, an integrated robot system consisting of one or more robots transports assay-microplates from station to station for sample and reagent addition, mixing, incubation, and finally readout or detection. An HTS system can usually prepare, incubate, and analyse many plates simultaneously, further speeding the data-collection process. HTS robots that can test up to 100,000 compounds per day currently exist. Automatic colony pickers pick thousands of microbial colonies for high throughput genetic screening. The term u HTS or *ultra-high-throughput screening* refers (circa 2008) to screening in excess of 100,000 compounds per day.

Quality control:

High-quality HTS assays are critical in HTS experiments. The development of high-quality HTS assays requires the integration of both experimental and computational approaches for quality control (QC). Three important means of QC are, (i) good plate design, (ii) the selection of effective positive and negative chemical/biological controls, and (iii) the development of effective QC metrics to measure the degree of differentiation so that assays with inferior data quality can be identified. A good plate design helps to identify systematic errors and determine what normalization should be used to remove reduce the impact of systematic errors on both QC and hit selection.

DRUGS FROM NATURAL SOURCES:

A natural product is a chemical compound or substance produced by a living organism – found in nature. Natural sources of drug are –plant, animal, mineral, microorganisms. Plant sources are leaf, bark, fruit, seeds. Drugs obtained from animal sources are heparin, insulin, thyroxin, cod liver oil, antitoxic cera. Microorganism sources are bacterial, fungi, molds etc. mineral sources are ferrous sulphate, magnesium sulphate, sodium bi carbonate, aluminium hydroxide. Animal sources are In the broadest sense, natural products include any substance produced by life. the field of organic chemistry, the definition of natural products is usually restricted to mean purified organic compounds isolated from natural sources that are produced by the pathways of primary or secondary metabolism. Many secondary metabolites are cytotoxic and have been selected and optimized through evolution for use as "chemical warfare" agents against prey, predators, and competing organisms. synthetic analogs of natural products with improved potency and safety can be prepared and therefore natural products are often used as starting points for drug discovery.

Natural products have served as a major source of drugs for centuries, and about half of the pharmaceuticals in use today are derived from natural products. Interest in natural products research is strong and can be attributed to several factors, including unmet therapeutic needs, the remarkable diversity of both chemical structures and biological activities of naturally occurring secondary metabolites. About 40% of the drugs used are derived from natural sources. Plants provide a fertile source of natural products many of which are clinically important medicinal agents. Different strategies will result in a herbal medicine or in an isolated active compound. Drug discovery scientists often refer to these ideas as "leads," and chemicals that have desirable properties in lab tests are called lead compounds. Pharmaceutical chemists seek ideas for new drugs not only in plants, but in any part of nature where they may find valuable clues.

India is the biggest supplier of licit demand for opium required primarily for medicinal purposes. Besides this, India is located close to the major poppy growing areas of the world, with "Golden Crescent" on the Northwest and "Golden Triangle" on the North-East. The processes of industrialization, urbanization and migration have led to loosening of the traditional methods of social control rendering an individual vulnerable to the stresses and strains of modern life. The introduction of synthetic drugs and intravenous drug use leading to HIV/AIDS has added a new dimension to the problem, especially in the Northeast states of the country Ayurveda and charka shamhita, have contributed towards this boom in Drug discovery.

Conclusion :

Drug design is the creative process of finding new remedies based on the knowledge of biological target This review discusses principle of drug design, various approaches of drug design , lead discovery , lead modification and various types of drug discovery . Bio-isosterism is an important lead modification approach that has been shown to be useful to attenuate toxicity or to modify the activity of a lead , and may have a significant role in the alteration of pharmacokinetics of a lead .

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