"STRUCTURE BASE DRUG DESIGN"

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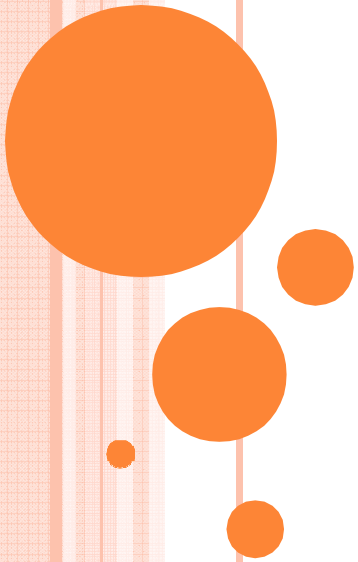
Content

❖ Abstract:-

- As the world's population increases and health problems expand accordingly, the need to discover new therapeutics will become even more pressing.
- Drug discovery is important to the medical health of humankind; it is also an important component of our economic health.
- New chemical entities (NCEs) as therapeutics for human disease
- Access to the complete human genome sequence as well as to the complete sequences of pathogenic organisms provides information that can result in a large quantity of therapeutic targets.
- Structure-based design is one of the first techniques to be used in drug design.
- Structure based design refers specifically to finding and complementing the 3D structure (binding and/or active site) of a target molecule such as a receptor protein.
- The aim of this review is to give an outline of studies in the field of structure based drug design that has helped in the discovery process of new drugs.

DRUG-

- Drug are small molecules design to bind, interact,and modulate the activity of specific biological receptors.
- Receptors are proteins that bind and interact with other molecules to perform the numerous functions required for the maintenance of life.
- The role of drugs is to correct the functioning of these receptors to remedy the resulting medical condition.



STRUCTURAL FRAGMENTS OF A DRUG MOLECULE: Pharmacophore

- The three-dimensional arrangement of atoms within a drug molecule that permits a specific binding interaction with a desired receptor is called Pharmacophore.
- The pharmacophore is the bioactive face of the molecule and is that portion of the molecule that establishes intermolecular interactions with the receptor site .

- we see our native ligand bound within the active site.
- Assume that through biochemical investigation, we determine that the phenyl ring (blue) and the carboxylic acid group (green) are vital to receptor interaction.
- Thus, we deduce that these two groups must be the pharmacophore that a ligand must present to the receptor for binding.
- This is shown in the upper right derivative compound where a bicyclic group has been substituted. Because it maintains the pharmacophore and retains its complementary size and shape, it has a reasonable chance of successfully binding.
- However, any drug that we develop which lacks a complete pharmacophore may not interact with the receptor target.

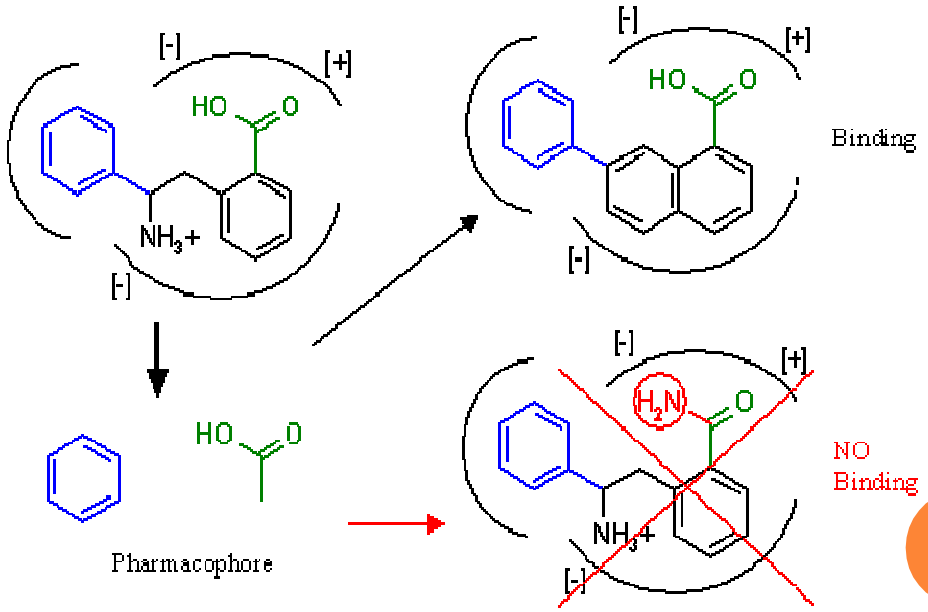


Figure 3. Pharmacophore and receptor binding.

Aims & Objectives:-

- The central aim of the course is to impart an understanding of what medicinal chemists have to think about when attempting to design new drugs.
- To understand how to relate chemical structure to biological activity.
- To understand how to conduct a structure-activity analysis.
- Identify at least one small molecule with improved activity over existing drugs with the same target.
- Submit some of the molecules produced for pharmaceutical testing

Drug design

Drug design, sometimes referred to as rational drug design or more simply rational design, is the inventive process of finding new medications based on the knowledge of a biological target..

DRUG DESIGN APPROACHS
A CONCEPTUAL APPROACH

- Drug design may be divided into two phases.

1) Basic concepts about drug,receptors,and drug- receptor interaction.
2) Basic concepts about drug-receptor interactions applied to human disease.

- First phase
  - comprises the essential building blocks of drug design and may be divided into three logical steps:

Step1-

- Involves knowing what property turn a molecule into a drug.
- All drugs may be molecules, but all molecules are certainly not drugs.
- Drug molecules are “small”organic molecules (molecular weight usually below 800g/mol. Often below 500).eg ;Penicillin, acetylsalicyclic acid,and morphine are all small orrganic molecules.

Step II-

- Involves knowing what propertes turn a macromolecule into a receptor.
- All receptors may be macromolecules, but all macromolecules are certainly not receptors.
- Receptor macromolecules are frequently proteins or glycoprotein's.

Step III-

- Involves knowing how to design and synthesize a drug to fit into a receptor
- This prototype compound is referred to as the lead compound.

Second phase-

- Once the basics of drug design are in place,the drug designer next focuses upon the task of connecting a drug-receptor interaction to a human disease- this is the goal of the second phase.
- This phase of drug design requires an understanding of biochemistry and of the molecular pathology of the disease being treated.

DRUG DESIGN :A PRACTICAL APPROACH

- This strategy uses a molecular-level understanding of human biochemistry and pathology to drive the design of drug .
- Drug like molecules engineered to fit precisely into targets of drug action (druggable targets)

DRUG DESIGN :THE HUMANITARIAN APPROCH

In traditional medicine there are two major therapeutic approaches to the treatment of human disease:

a) Surgical procedures are labour intensive and time demanding; they help a limit number of individuals,one at a time, mostly in rich or developed nations.

b) Medical therapeutics offer hope in both developed and developing parts of the world-hopefully to rich and poor alike

Basic Principles of Drug Design

- Medicinal chemistry is the applied science that is focused on the design of new chemical entities (NCEs) and their optimization and development as useful drug molecule for the treatment of disease processes.
- In achieving this mandate, the medicinal chemist must design and synthesize new molecules,ascertain how they interact with biological macromolecules (such as proteins or nucleic acids),elucidate the relationship between their structure and biological activities,determine their absorption and distribution throughout the body ,and evaluate their metabolic transformations.

The challenges of drug design

- We can begin to appreciate the difficulties in designing drugs towards specific target receptors.
- Major tasks and concerns in drug development
- Achieve active site complementary:
- Consider biochemical mechanism of receptor
- Adhere to laws of chemistry.
- Synthetic feasibility
- Biological considerations
- Patent considerations
- Characterize medical condition and determine receptor targets .
- The pharmacophore must be presented to the receptor in order for recognition and binding to occur. Otherwise, the designed ligand will have **no chance of interacting with the receptor.**

TYPES OF DRUG DESIGN

Ligand based drug design:

- Ligand-based drug design (or indirect drug design) relies on knowledge of other molecules that bind to the biological target of interest.
- These other molecules may be used to derive a pharmacophore model that defines the minimum necessary structural characteristics a molecule must possess in order to bind to the target.
- Alternatively, a quantitative structure-activity relationship (QSAR), in which a correlation between calculated properties of molecules and their experimentally determined biological activity, may be derived.
- These QSAR relationships in turn may be used to predict the activity of new analogs.

Rational drug discovery

- Rational drug design begins with a hypothesis that modulation of a specific biological target may have therapeutic value.
- In order for a biomolecule to be selected as a drug target, two essential pieces of information are required.
- **The first** is evidence that modulation of the target will have therapeutic value.
- This knowledge may come from, for example, disease linkage studies that show an association between mutations in the biological target and certain disease states.
- **The second** is that the target is "drugable". This means that it is capable of binding to a small molecule and that its activity can be modulated by the small molecule.

Computer-aided drug design

- Computer-aided drug design uses computational chemistry to discover, enhance, or study drugs and related biologically active molecules.
- The most fundamental goal is to predict whether a given molecule will bind to a target and if so how strongly
- Ideally the computational method should be able to predict affinity before a compound is synthesized and hence in theory only one compound needs to be synthesized.

Structure Base Drug Design

- Structure-based drug design (or direct drug design) relies on knowledge of the three dimensional structure of the biological target obtained through methods such as x-ray crystallography or NMR spectroscopy.
- If an experimental structure of a target is not available, it may be possible to create a homology model of the target based on the experimental structure of a related protein.
- Using the structure of the biological target,In parallel, information about the structural dynamics and electronic properties about ligands has also increased. This has encouraged the rapid development of the structure-based drug design.

- Current methods for structure-based drug design can be divided roughly into two categories.

a) The first category is about "finding" ligands for a given receptor, which is usually referred as database searching.The key advantage of database searching is that it saves synthetic effort to obtain new lead compounds.

b) Another category of structure-based drug design methods is about "building"ligands, which is usually referred as receptor-based drug design. The key advantage of such a method is that novel structures, not contained in any database, can be suggested.

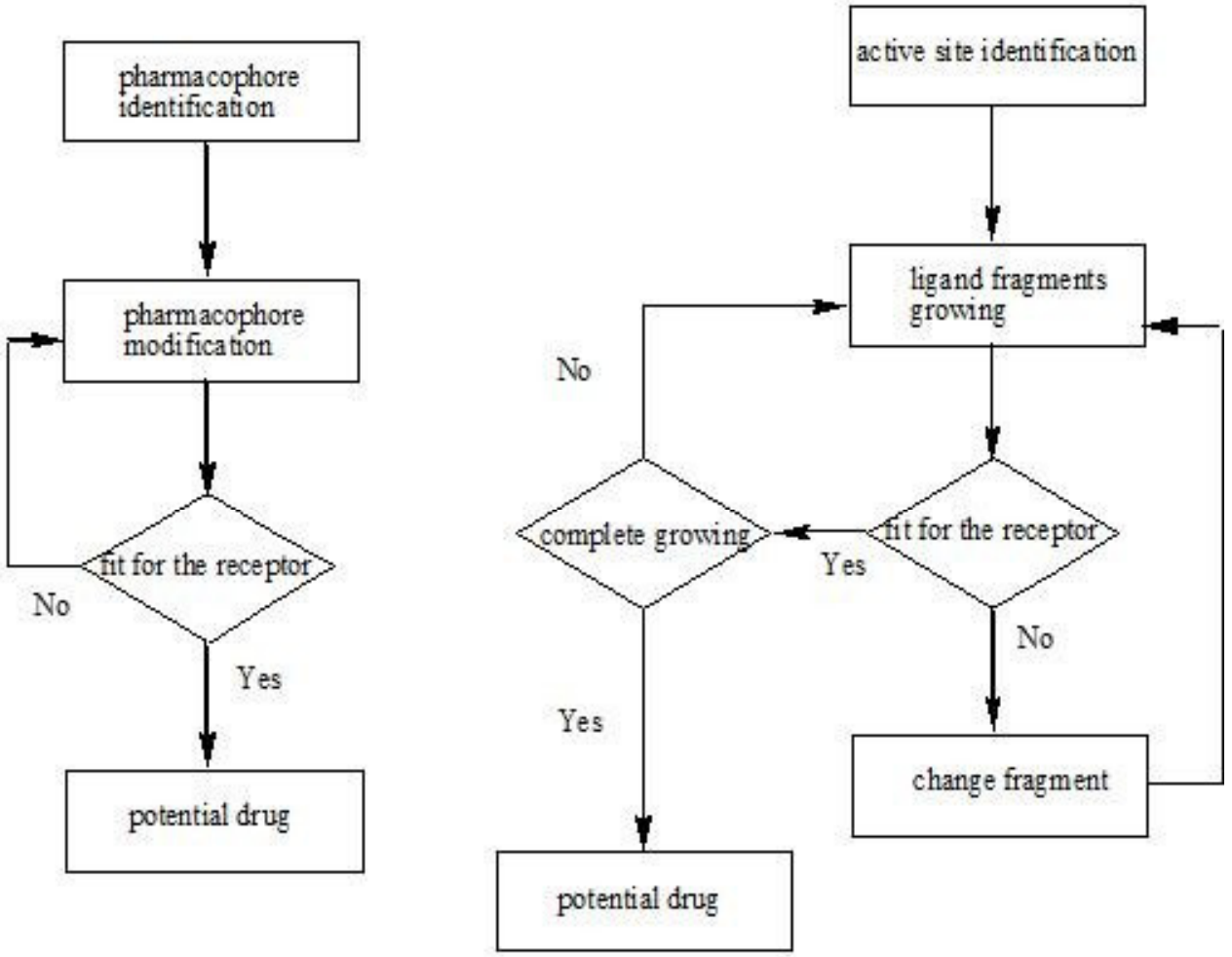


Fig.5: Flow charts of two strategies of structure-based drug design

Structure Base Drug design process

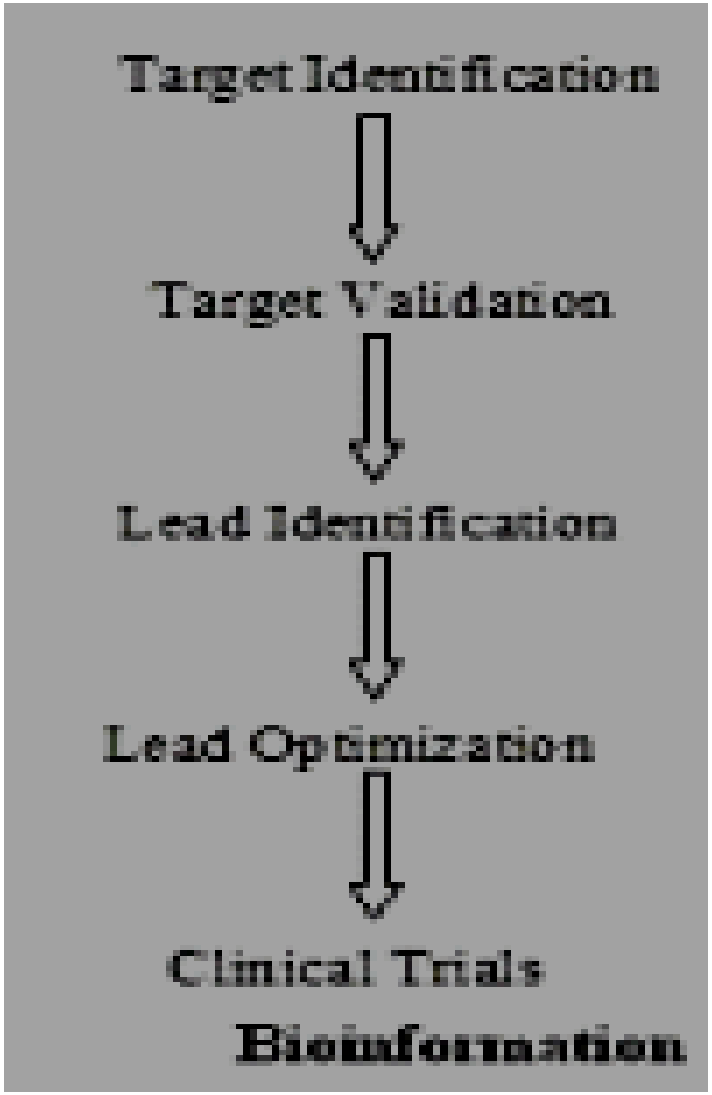


Fig:6 structure base drug design process

Target identification

- The choice of a drug target is primarily made on a biological and biochemical basis.
- The ideal target macromolecule for structure-based drug design is one that is closely linked to human disease and binds a small molecule in order to carry out a function.
- The target should be unique
- Practices such as systems biology, clustering, and drug affinity response have matured to help with the identification of biological targets
- Homology modeling or comparative modeling is the most reliable method for target structure prediction that builds 3D structures for unknown proteins based on the known homologous protein structures (i.e. >40% similarity)

Evaluating of identified target

- Once a target has been identified, it is necessary to obtain accurate structural information.
- There are three primary methods for structure determination that are useful for drug design:X-ray crystallography, NMR, and homology modeling.
- Crystal structures are the most common source of structural information for drug design, since structures determined to high resolution may be available, and the method is useful for proteins that range in size from a few amino acid.

Target validation

- The binding site is a small region, a pocket or bumps, where ligand molecules can best fit or bind to activate the receptor and/or target and produce the desirable effect.
- Thus, recognizing the binding site or the active site residues in the target structure is of high importance in SBDD. Because the proteins are capable of undergoing conformational changes, recognizing the accurate binding site residues is difficult
- It is an accepted fact that proper selection of chemical compounds, with minimal potency and specificity, during the early phases of drug discovery plays a vital part in the success
- Structure-based design begins with the identification of a potential ligand binding site on the target molecule.

Lead Drug Evaluation

- Once a small molecule has been identified as potentially binding to the target molecule, it must be evaluated before proceeding to further stages.
- It is important to consider that the ranking assigned by the scoring function is not always indicative of a true binding constant, since the model of the target:ligand interaction is inherently an approximation.
- Usually, several molecules which scored well during the docking run are evaluated in further tests since even the top scoring molecule could fail in vitro assays.
- Leads are first evaluated visually with computer graphics and can often be optimized at this step for increased affinity.
- Leads are also evaluated for their likelihood to be orally bioavailable which states that good leads generally have less than five hydrogen bond donors and less than ten hydrogen bond acceptors, a molecular weight less than 500, and a calculated log of the partition coefficien less than 5

- **Lead Optimization:-**Various approaches are employed in order to improve the desired pharmacological properties of the lead nucleus.
- **Identification of active part(the pharmaco-phore)**
  - Any drug molecule consists of both, essential and nonessential parts.
  - Essential part is important in governing pharmacodynamic (drug-receptor interaction) property
  - while Non-essential part influences pharmacokinetic features.Once such pharmacophore is identified,structural modification can be done to improve pharmacokinetic properties of the drug
- **Functional group optimization**
  - The activity of a drug can be correlated to its structure in terms of the contribution of its functional groups to the lipophilicity, electronic and steric features of the drug skeleton..
- **Structure activity relationship studies:-**
  - SAR studies usually involve the interpretation of activity in terms of the structural features of a drug molecule.
  - Generalized conclusions then can be made after examining a sufficient number of drug analogs for example, sulphonamides are found to be associated with diuretic and antidiabetic activities in addition to their antibacterial activity.

Homologation:

- A homologous series is a group of compounds that differ by a constant unit, generally a CH_2 group.
- Usually increasing the length of a saturated carbon side-chain from one (CH_3) to 5 to 9 atoms produces an increase in pharmacological effects.
- Further increase results in a decrease in the activity.
- This is probably either due to increase in lipophilicity beyond optimum value (hence decreased absorption and distribution) or decrease in concentration of free drug (i.e., micelle formation).
- For example, maximum hypnotic activity is seen from 1-hexanol to 1-octanol.

Cyclization of the side –Chain :

- Change in the potency or change in the activity spectra can be brought about by transformation of alkyl side chain into cyclic analogs.

DOCKING-

- The aim of molecular docking is to find the “best” match between a putative ligand and a target with known structure by placing a molecule into the binding site of the target in a non-covalent fashion.
- There are three baasic tsks:

1) Characterization of the binding site;
2) Positioning of the ligand into the binding site
3) Evaluating the strength of interaction for a specific receptor-ligand complex (scoring).

- Docking a process of predicting the ligand conformation and its orientation inside the target structure, plays a vital part in SBDD

Structural based design: Docking

Induced fit docking

Substrate (ligand) + *Enzyme (receptor)*

Substrate (ligand) + *Enzyme (receptor)*

Lock and Key

Induced Fit

Conclusion

- Thus, it can be said that pharmaceutical and biotechnology research has undergone great change.
- Traditionally, the crucial impasse in the industry's search for new drug targets was the availability of biological data.
- Now with the advent of human genomic sequence, bioinformatics offers several approaches for the prediction of structure and function of proteins on the basis of sequence and structural similarities.
- The protein sequence→structure→function relationship is well established and reveals that the structural details at atomic level help understand molecular function of proteins.
- Impressive technological advances in areas such as structural characterization of biomacromolecules, computer sciences and molecular biology have made rational drug design feasible and present a holistic approach
- The approaches and methodologies used in drug design have changed over time, In addition to the experimental techniques, a variety of computational approaches have been applied at the various stages of the drug-design process: in the early stages these approaches focused on reducing the number of possible ligands, whereas in the later stages, during lead-optimization, the emphasis is on decreasing experimental costs and reducing the period of discovery.

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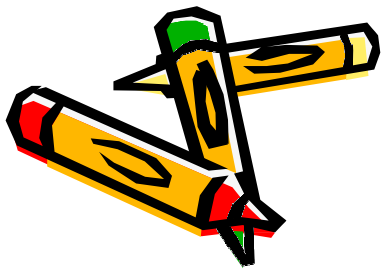

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