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Review Article

The Basic Journey of A Molecule From Pharmacophore To Successful Drug Candidate By Computer Aided Drug Design – A Detailed Review

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ABSTRACT

Computer Aided Drug Design aims at developing *in – silico* or computer software-based techniques and methods to design and develop a drug molecule which have Pharmacological activity when binds to the desired target and have minimum side effect. For a drug to show desired biological effect, the drug target should be chosen with special emphasis such that normal body functioning does not get hampered. The bioactive conformer of the ligand molecule is chosen which have highest docking score and shows three point attachment to the receptor's active site. Drug designing can be broadly classified as Structure based and Ligand Based process. The Structure based process is more systematic based on drug – receptor binding. This involves docking of the different ligand poses to the receptor's active site. Higher the docking score, or lesser the free energy, more stable is the drug-receptor binding complex. The Ligand Based process is less systematic process which depends Pharmacophore generation from known ligands followed by screening in Chemical Library. The Pharmacophore modelling and QSAR process is common to both types of drug discovery. The QSAR modification of the ligand followed by docking is done to obtain the ligand possibly to be a drug. This follows the ADMET testing of the ligand. If the ligand passes the ADMET testing with less toxicity and desirable ADME property, it can be called a drug. This review encompass all the processes a molecule undergo to be a drug.

INTRODUCTION

Computer Aided Drug Design is *in silico* method of drug designing for a particular disease [1]. *In silico* can be defined as a computer software mediated approach where studies are done through software [2]. After proper evidence of action from *in silico* studies, studies are conducted on animal model *in vivo* or on animal organ in similar environment outside human body, called *in vitro* approach [3]. Previously drug was designed

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manually and physically. The ligand were screened manually through High Throughput Screening [4] where multiple well – highly automated apparatus were used to determine the binding efficiency of a molecule to a given drug target. This increased the time consumption of the studies and moreover increased the cost and labor [5]. Physical High throughput screening since is a manual process, utilized a huge amount of chemicals and labor [5]. These limitation of HTS led to development of computerized method which would in turn save time, cost, labour and increased efficiency. Moreover, Physical HTS had chances of false positive and false negative result [4,5]. Ghost sample often occur in physical HTS, where it showed biological activity during screening, which later showed no affinity due to degradation. These all limitations were encompassed by development of computerized method [6, 7].

Basic Terminologies of Drug Development

For a drug designing, there are few basic terminologies that are often used [8]. A **target** is a biological macromolecule to which a ligand binds to stop the increase or decrease the progression of a disease [8]. Based on the pathophysiology of the disease the target which could be feasible is identified. There are some conditions of development of a drug target [9, 10]

1. The target should be involved in disease pathophysiology
2. The target should be specific to the causative organism in case of pathogen caused disease
3. The target should be effective (γ-secretase is involved in progression of Alzheimer's disease but is not a successful target for drug) [11]
4. The target selected in case of pathogenic disease should not hamper normal functioning of our body (RNA polymerase is not inhibited in DNA virus infection) [12]
5. The drug target should be selective and specific to the disease.

Ligand are molecules which are obtained from natural sources, or from synthetic routes, that have affinity to the drug target and when bind to specific drug target shows Pharmacological activity. For a drug development, the first step is the target identification [13, 14].

Pharmacological activity is the activity elicited when the ligand binds to the desired drug target and shows desired effect either by agonistic or antagonistic activity [15, 16]

Side effects are undesirable effects of the ligand. This is caused either due to different possible conformation of ligand which binds to different active site of different receptor [16]. Else, side effect might also be caused because of similarity of the amino acid sequence of the targeted active site with any other protein folding. This leads to the drug moiety bind to both the active sites, leading to undesirable side effects [15, 17].

A drug is a ligand which shows desired Pharmacological effect [15, 16]. Due to the chiral carbon centers, there are possibility of number of stereo isomers or conformers. It has been seen that one enantiomer has more potency and selectivity to receptor binding. This is called **three-point attachment**. For a drug candidate or ligand to successfully bind to receptor, it should get attached to the receptor at three points of interaction at least. The confirmation that shows interactions at three point are more active. This is the reason of one conformer to be more potent than other which fails to show three-point attachment. This is called **Eason Stedman Hypothesis** [17-22]**.** The concept of three-point attachment is illustrated in Figure 1.

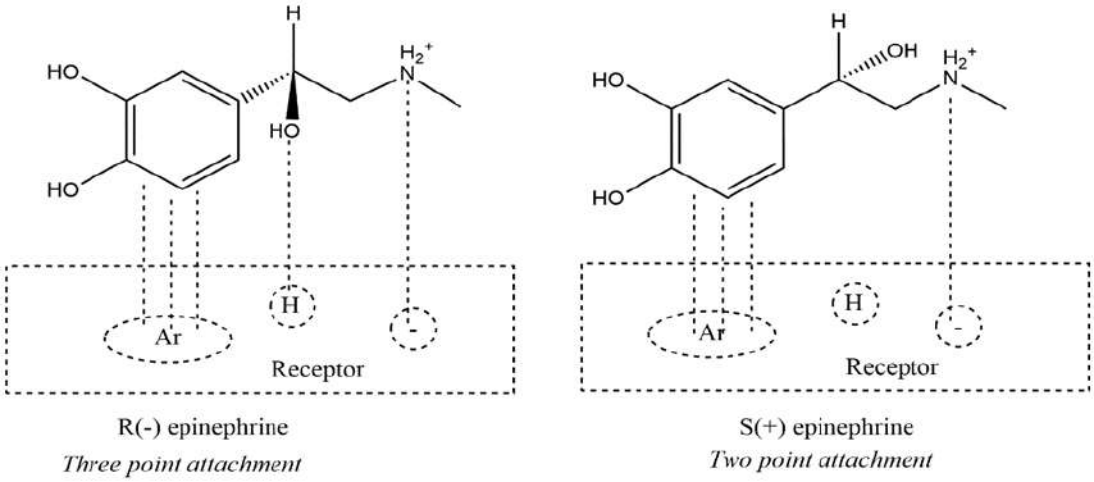

Figure 1: S-epinephrine shows two point attachment with the receptor, whereas R-epinephrine shows three point attachment. Hence, R-epinephrine shows higher potency than S-epinephrine

Sources of Lead Compound

Lead compound can be obtained from different sources [23, 24, 25, 26]:

(a) Natural Sources: Obtained from the nature

(i) Plant sources – Placlitaxel (Pacific Yew), Vincristine (*Catharantin roseus*); Sanguinarine

(ii) Animal sources – Captopril (*B. jararca* – snake); Heparin (porcine intestine)

(iii) Marine source – Ziconotide (venum of snail, *Conus mangus*), Cytarabine (Ara-C) from Marine sponge

(iv) Microbial source – Penicllin (*Penicillium notatum*); Chlortetracycline (*Streptomyces aurifaciens*)

(v) Natural ligand – Salbutamol (Adrenaline)

(b) Chemical Database – Atorvastatin, Lovastatin

(c) Library screening – Isoniazid

Drug design is defined as the entire process of identifying a disease to development of a new drug to inhibit the progression of the disease [27, 28]. Two major types of drug design are Traditional based and Rational based drug design [29, 30].

Traditional drug design is defined as discovery of lead or drug from indigenous natural sources without the knowledge of structure of receptor or ligand. It solely depend on natural sources without knowledge of protein or receptor. It is a non systematic approach. Example of drugs discovered are Random Screening (paclitaxel); Serendipity (Penicillin); Ethnopharmacological (Quinine) [28].

Rational Drug Design is defined as the discovery of drug or lead compound using the knowledge of target and the drug-receptor interaction. Unlike traditional based drug design, here knowledge of receptor and ligand is required. Based on chemical moieties from database and natural sources, this method provides more systematic approach. Some drug discovered in this way are Ritonavir (HIV polymerase); Linsopril (ACE inhibitor); Imatinib [30, 31].

Approaches Of Drug Design By Virtual Screening

Virtual Screening (VS) is a Computer Aided method that involves in silico screening of a library of chemical compounds, to identify those that are most likely to bind to a specific target [32]. According to Lipinski Rule of 5, which describes the properties required by a molecule to have drug likeliness are described in Table 01.

Parameter	Requirement
Molecular weight	< 500Da
Partition Coefficient	<5
Number of Hydrogen bond acceptor	<10
Number of Hydrogen bond donor	<5
Number of rotatable bonds	<10

Table 01: Properties a molecule should have to be a drug molecule as per to Lipinski Rule of five [33, 34]

There are two different major approaches of virtual screening and drug design. Namely Structure based or Target Based drug design and Ligand based Drug design. The comparison between the two are demonstrated in Table 02.

Parameter	Target Based Drug Design	Ligand Based Drug Design
Type	It is the direct approach to drug design	It is the indirect approach to design
Knowledge of receptor	3D structure of the receptor is known	3D structure of the receptor is unknown
Definition	lead molecule is designed using the knowledge of 3D structure of target molecule	lead is designed using knowledge of pre-existing molecule that bind to the target
Pre-existing ligand	No pre-existing ligand to the receptor is required	There should be pre-existing ligands of the receptor
Method involved	Docking of ligand to receptor	Pharmacophore screening or Scaffold hopping
Approach	More scientific and logical	Less scientific
Accuracy	Higher	Lower
Properties	Dissimilar compounds having affinity to the receptor can be predicted	Confines to only similar compounds

Table 02: Comparison between Target Based and Ligand Based Drug Design [35, 36, 45, 46]

Structure Based Drug Discovery

It is the approach of drug design based on the knowledge of the receptor. Here the structure of the receptor is known. The binding sites of the receptor is known [35-41]

1. **Generation of Active Site** [35, 36, 37]

a) If the active sites are known from the structure of PDB, direct docking is done

b) If the proteins structure is known but the active site is not known, ligands are docked at various sites of the protein. The site where the docking score of the ligands is more, it is the active site

c) If the protein structure is unknown, homology modelling is used to generate the structure of the protein. This is discussed later in the review

2. Docking

Docking is defined as a computerized process which evaluates the binding affinity of different conformers of a ligand to the given active site of the receptor [36].

The different ligands are docked with the receptor at various poses to obtain the docking score. Scoring is an energy function, where the total energy is the energy of the complex subtracted from energy of receptor and energy of ligand. More negative the free energy, more stable the complex [42, 43].

Ligand showing lower energy is more suitable to be a lead compound. However, ligand that shows high docking score is more suitable to be a lead [43]. From these lead molecules, pharmacophore is generated. According to Ehrlich, it is “a molecular framework that carries the essential features responsible for a drug’s biological activity” [44].

Ligand Based Drug Discovery

In Ligand Based Drug Design, the structure of the receptor is unknown. The lead compound is detected by Pharmacophoric search or by topological similarity. It is indirect method. Based on the knowledge of known ligand that bind to the target. The 3D structure of the receptor is unknown [45, 46]

1. **Pharmacophore Screening:**

Different ligands bind to the target. From chemical library, the ligands that has binding affinity to the receptor are found. The ligands are aligned and the structural and electronic features required for binding are ensembled. This is called Pharmacophore [44, 47]. This pharmacophore is used to screen ligands in Chemical library. Ligands with similarity are chosen [46].

2. **Quantitative Structure Activity Relationship:**

QSAR called Quantitative Structure Activity Relationship. QSAR relates the structural properties of a molecule to its biological activity quantitatively [48]. QSAR is a computational approach that develops mathematical relationship between biological activity of a molecule and its geometric and chemical properties. Descriptors are defined as numerical representation of molecular features. These numerical features are generated by algorithm to encode about shape, size, electronic, steric features of molecule.

From the pharmacophore that has been built previously, scaffold is generated. It is followed by change in bonds or the core of scaffold (scaffold hopping). The molecule is modified structurally by QSAR. This obtains the hit molecule [49, 50].

Pharmacophore Modelling

Pharmacophore can be defined as the 3D arrangement of structural (steric and electronic) features required by a molecule to bind to a receptor [51]. These are ensemble of structural and electronic features The Pharmacophore is obtained from two or more ligands which has capability of binding to a receptor [51, 52].

The total technique of development of pharmacophore from the ligands and map the spatial arrangement for further drug design is called Pharmacophore modelling [53].

Components of a Pharmacophore [51-55]:

1. **Functional groups or chemical moieties:** Moieties (groups of atoms within the molecule) present that contribute to its pharmacological activity by forming interactions with the target
   a) **Hydrogen bond features:** H-bond donor and acceptor that can form linkage with the target
   b) **Aromatic ring:** With $\pi = \pi$ bond that can provide steric features and cause hydrophobic interactions
   c) **Hydrophobic interactions:** Non-polar residue that can interact with non-polar site of target
2. **Geometry:** The spatial arrangements, distance between group, angles formed by different groups in the ligand are taken by pharmacophore mapping [56]

Process of Pharmacophore generation

Different ligands that bind to the receptor are taken. Structural alignment of the molecules are done to take the common features taken. Then the pharmacophore is generated [56, 57].

1. **In Structure based drug design:** Different ligand docked with target and scores are taken. Based on the score, the ligands are grouped. Ligands for each group taken. Structural alignment is done. Structural alignment can be defined as superimposing or aligning molecular structures based on common features. The common feature of a base molecule serves as point of super-imposition of other molecules on it. The features which are present in most of the ligands that are marked. The common features are used to build a Pharmacophore. Features of different Pharmacophore are taken to make a final Pharmacophore [57, 58, 59].
2. **In Ligand Based Drug Design:** Different ligands are taken and structural alignment is done based on the similar properties of them. This is called Pharmacophore [59, 60].

Pharmacophore Mapping

Placement or spatial arrangement of Pharmacophoric features in 3D structure is called pharmacophore mapping. It comprises of the sub-structure of molecule responsible for Pharmacological action [56, 57]. Steric and electronic features between group required for binding. Potential conformations are generated. 3D relationship between pharmacophore element in each conformer is generated. The distance of separation or the geometry required in the structure to bind to the receptor is determined by Pharmacophore mapping. This helps to create bioactive conformation [59-61]. Example of Pharmacophore Mapping is demonstrated in Figure 02.

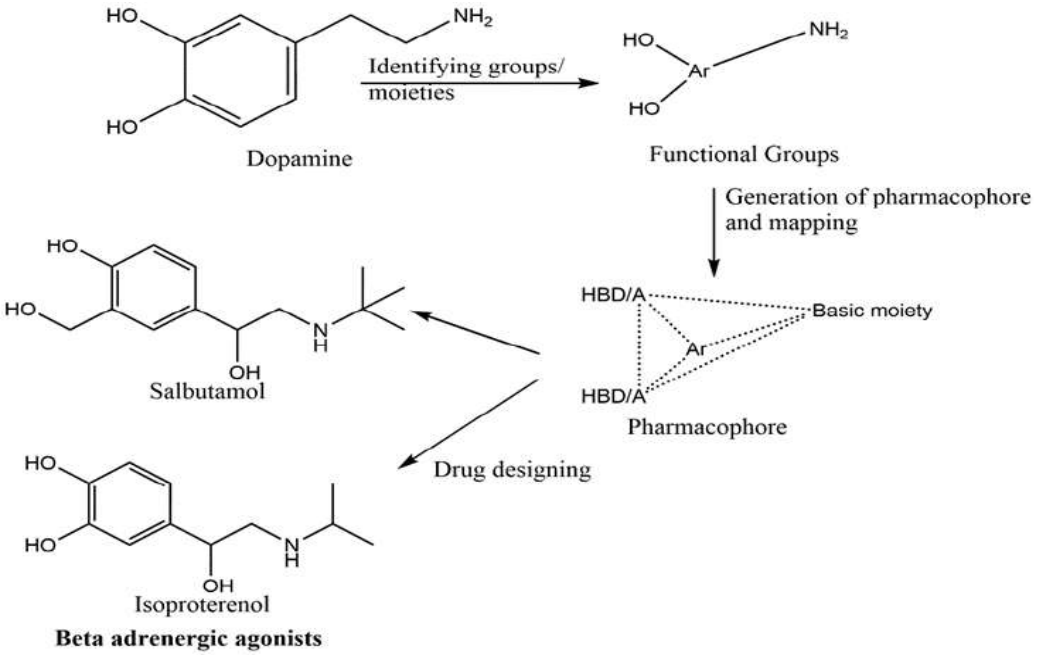

Figure 02: An example of development of drug from a pharmacophore. Ligand like dopamine is used to generate a pharmacophore, from which beta adrenergic agonist like Salbutamol and isoproterenol are developed.

Drug Design after Pharmacophore Generation

Pharmacophore is generated and mapped to develop the spatial arrangement of the features. In LBVS, from the pharmacophore, similar ligand are screened out from chemical library. In SBVS, the molecule developed from the pharmacophore is called scaffold. The change in structure of scaffold is called scaffold hopping followed by QSAR analysis [58, 61, 62]

Homology Modeling Of Protein Structure Determination

Homology modeling is defined as insilico or computational method of determining 3D structure of a protein with known amino acid sequence, by comparing it with template protein with similar sequence and known 3D structure [63, 64]. Homology comes from homologous, meaning same. Modelling means to create 3D structure [65]. It is done when protein structure is not present in database or have not been found out. In Homology Modeling, the protein whose structure is to be determined is called the target protein. The protein with 40% similar sequence of target protein and known structure is called the template protein. Template protein serves as the starting point of homology modelling [66, 67]. Structure of protein is conserved more than AA sequence during evolution. Proteins with similar sequences are likely to have similar structures [68]. The steps

involved in Homology Modeling are illustrated in a flowchart as Figure 03.:

1. **Identification of template strand.**

The first step of Homology modeling is selection of the template strand. Done by BLAST and FASTA. BLAST or Basic Local Alignment Search Tool is a bioinformatics tool, that uses comparison algorithm to find sequence in database similar to search query. It uses comparison algorithm and uses the template as search query [69, 70]. The target sequence (Query) is broken to words (3 amino acid sequence). This process is called seeding. The words are searched for similar sequence in database. These search are scored by substitution matrix. If the score is greater than the threshold, then it is a match. The search is extended to both direction [70, 71]. The complete sequence finding and scoring in entire query without gap is done by High scoring segment pair (HSP). Substitution methods used PAM (Protein Accepted Mutation); BLOSM (Block substituted Mutation)

2. Sequence alignment of query with template

This process involves alignment of the similar portion of sequence of query and template protein to get better accurate structure. It aligns two or more amino acid sequence to find similarity between them to produce phylogenic tree. There are two methods of sequence alignment: (a) Global alignment: Align entire length of sequence to maximize similarity; (b) Local alignment: Aligns only the portion of sequence with high density similarity. The similarity of the sequence is scored. Better the alignment of similarity of sequence, more accurate is the structure [65, 68, 72, 73].

Types of Sequence alignment

a) Pair wise sequence: Aligns two sequence to find optimal pairing sequence – Dot matrix method, Dynamic programming, Word method
b) Multiple sequence alignment: Multiple biological sequence are aligned to obtain maximum pairing; More common – Exhaustive algorithm, Heuristic algorithm (Progressive, iterative, block based methods) [72, 73]

It uses software like Proline and T-Coffee

3. Backbone building of 3D structure

Based on the similarity of aligned amino acid sequence, the backbone of the query sequence is generated [63]. If the alignment of the sequence matches, the entire coordinate of the similar structure is copied. If it does not match, the backbone of amino acid (H_2N-C and C=O) is copied. The processes are (a) Rigid body assembly: The protein structure broken down core, region, similar portion brought together and joined. (b) Segment matching: Atomic positions from template are taken as lead and segment from database are selected. They are aligned and joined to create backbone. This create the basic backbone core of amino acids joined by peptide bond [65]

4. **Loop modelling**

During backbone generation, some portion of the structure contains gap or irregularities. These are called loops. These are structurally less conserved and hence are modified. These loops when filled gives functionality of protein [74]. The methods are (a) Database search method: Searches through the database to fill the gaps and loops by segments of similar structures and (b) Conformational search method: Produces random loop and random segment filling. These are scored. The best score is given. It is ab-initio method because it does not depend on pre-existing information [75, 76].

5. Side chain modelling

This predict conformation of the side chain that are attached to the backbone of amino acid. These side chains are positions of ligand – protein binding [65, 66]. Side chain gives specific properties of protein. Uses preferred side chain conformation called rotamers from rotamers library. Rotamers are scored in library based on frequency of their occurrence [77].

6. Model Optimization

Initial model revised to improve accuracy and stability. Adjusting position of groups/ atoms causing steric hindrance. Energy minimization of the model is done to find most stable confirmation. Excessive energy minimization removes residue – loss of protein conformation: (a) Monte-Carlo [different conformation of molecule are made and most stable one is selected]; (b) Molecular dynamics [Movement of position of atom and interaction between atoms of model is identified to find the most stable conformer] [74, 75]

7. Model Validation

It evaluate the biological relevance of the protein so formed and compares generated 3D structure to experimentally determined structure at PDB. It access model's stereochemistry, physical parameters, knowledge-based parameters, statistical mechanics [66, 67, 78].

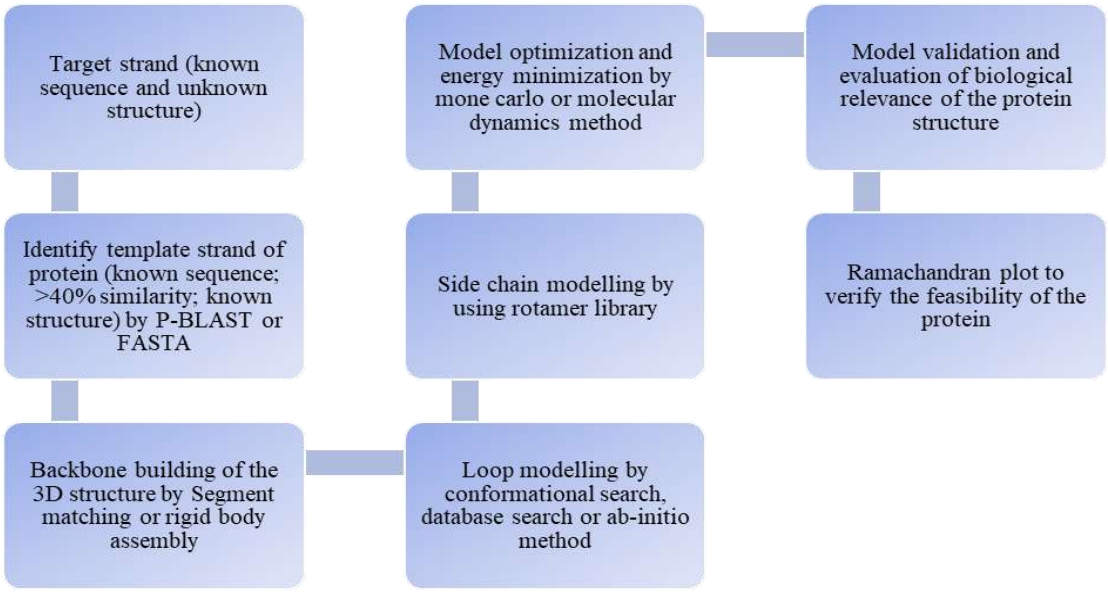

Figure 03: Flowchart of basic steps of Homology Modeling to determine 3D structure of a protein with known sequence but unknown structure

Ramachandran Plot in Homology Modeling

Amino acid contains two bonds that can rotate: ψ angle between alpha Carbon and Carbon of carbonyl group and ϕ angle between alpha Carbon and the Nitrogen atom. These two dihedral angles are called torsion angle and are responsible for 3D structure of protein. A partial double bond between two Carbon induce planar 180^o structure ω angle [79]. The Ramachandran plot is a graph of four quadrants with phi at x-axis and psi angle at y-axis. CN Ramachandran assumed atoms to be rigid sphere. So, on rotating the ψ and ϕ angles, the atoms collided in sterically unfavourable conformations. Graphical plot is represented in Figure 04.

The four quadrants represented [79, 80]:

1. All conformation allowed. Left handed alpha helix is possible
2. Largest quadrant where beta sheet is possible
3. Quadrant where right handed alpha helix structure of protein is possible
4. Disfavoured conformation due to steric hindrance

Exception:

Glycine is only amino acid with R=H. So, no steric clashes possible. All conformation even in blank portion of graph is possible.

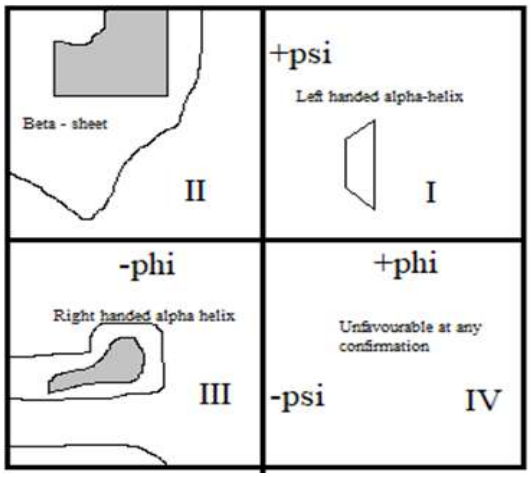

Figure 04. Different coordinates of Ramachandran Plot represented simply

After prediction of protein structure, Ramachandran plot is used. It has several utility. It checks whether the predicted protein structure is energetically favourable. It shows the allowed and disallowed portions of torsion angle of the amino acids, check biological feasibility of proteins. The folding in protein present in secondary structure can also be determined by the Ramachandran Plot. Finally, it predicts the secondary structures present in the protein – α-helix and β-sheet [79, 81].

Docking In Structure Based Drug Design

Protein – ligand docking is defined as a computational in-silico approach used to determine the binding affinity of ligand to the receptor [82]. For a ligand to show Pharmacological activity, it must bind to the receptor and for that it should have sufficient binding affinity. It is measured in terms of binding energy (kcal/mol). More negative the binding energy, better stable is the ligand-protein binding complex [83].

Pose Generation in Docking

Pose is defined as the conformation or orientation of the ligand molecule within the target receptor binding site [83]. A molecule due to rotational and translational change at a single bond can have multiple conformers. These different conformers can bind to the receptor. These orientations of the ligand is called pose [84].

Rotation around C – C single bond can produce multiple conformations. A molecule might have different conformations. These conformations when analyzed gives details of the binding energy, affinity of different conformers of the ligand possible. Pose generation explores all degree of freedom in molecule and finds the conformation which have highest binding affinity [84]. It identifies the conformation at which a ligand bind to receptors.

There are different search algorithm which generates pose of a ligand [85]. These algorithms are useful in generating different poses a ligand can have while binding to the receptor.

1. **Systematic Search:** Explore all degree of freedom in molecule. There is a limitation of lack of combinatorial search. It divide the ligand to rigid and flexible part and then dock them to active site individually. Gradual guided progression of the ligand through the space. A pruning algorithm is applied to remove unfavourable conformations early on, thereby reducing the complexity of the problem [85, 86].

(a) Stepwise/ Incremental method [LUDI, FlexX, Glide, Hammerhead]

Generally two approaches: (i) Followed in De-novo drug design: Ligand is divided into fragments, the core fragment, side chain fragments are docked in the active site of receptor and fragments linked. (ii) Rigid and flexible fragments found and flexible conformation change by increasing the rotation [87]

$N = \sum_{i=1}^{N} \frac{360}{\theta_{i,j}}$ where N is Number of rotatable bond; $\theta_{i,j}$ = Size of incremental rotational angle

(b) Conformational method

Analyze different torsional angle in the molecule. Torsional angle changed with some degree increment and then docked. The change in torsional angle produce different conformers of the ligand [86, 87]

(c) Database search [FLOG]

Generate multiple conformation of the ligand. Uses the different conformation and data stored in database. These library based conformations are calculated once – Rigid body docking [88]

2. **Random Search/ Stochastic Method:** Random changes to the ligand which does not depend on rotational or torsional angle. These random changes produces multiple conformation. These conformations are evaluated by pre-defined probability function. This method is random, unbiased, more accuracy

(a) Monte Carlo Method [AutoDock, MOE-Dock]

Random conformational changes are generated. Random changes without pre-defined criteria in the degree of freedom produces different conformations. The pose are selected comparing the score with the previous one [89].

(b) Genetic Method [GOLD]

Probability based conformational changes are made. The changes are made based on concept of natural selection. Permutations based on crossing over and mutation made. These creates random different conformation [90].

(c) Tabu search Method [MOE-Dock]

Different random conformation of the ligand is formed. The conformation is changed by rotational or translational change. This forms multiple different ligands

3. **Simulation Method**

It is a complex and more accurate method. In this method protein and ligand are separated by physical distance. Different conformational change of ligand is generated to find complementary binding position to the receptor's active site. Due to complementary interaction site of protein and receptor, binding occurs [89, 90]

(a) Geometry Based simulation [PatchDock, FlexX, MOE-Dock]

Focus on geometric complementarity between protein and ligand. Does not consider energy of the ligand molecule. Done mainly in case of rigid docking. It explores translational and rotational changes of ligand to find steric hindrance or steric clashes. It is based on shape matching, surface complementarity, and geometric hashing [89, 91]

(b) Energy based simulation [AutoDock, Glide]

Focus on minimization of energy of the ligand as well as its geometric complementarity. The energy minimization of the molecule is done by local and global minima. It considers flexible docking as geometric complementarity is considered for binding and energy minimization for most stable ligand. It explore H-bonding, van der waal interaction, hydrophobic interaction [92, 93]

Pose Selection/ Scoring

It is a part of protein – ligand docking, where the different conformations of ligands (pose) are scored, evaluated and ranked based on the protein-ligand interaction stability [94 – 96]

1. **Force field [DOCK, GOLD, AutoDock]:** The potential energy of a molecule based on its orientation of position of atoms and how it influences other molecules. $Force\ field\ S = E_{ligand} + E_{complex}$ [94]

It quantify some of protein ligand interaction energy and internal ligand interaction energy, solvation energy.

a) Ligand protein interaction – bonded interaction – Van der waal interaction, Columbic Electrostatic energy
b) Internal ligand interaction – non-bonded interaction – steric strain, repulsion

Based on these interactions, G-Score or Global Energy Score is assigned.

2. **Emperical based [LUDI, AutoDock]:** Based on various types of interaction protein – ligand. It compare solvent accessible surface area of the bonded structure to the unbound receptor. Done by multiple regression

analysis. Takes in consideration N-O hydrogen bond, O-O hydrogen bond, salt bridge, aromatic ring stacking. The different interactions considered are: [97]

a) Unfavorable (No. of rotatable bonds – increase entropy; hydrophobic – hydrophilic interaction)
b) Favorable (Hydrophobic – hydrophobic interaction, no. of H-bond of the ligand)

3. **Knowledge based:** Based on statistical data present in Database. Modeling based on atomic interaction pair data. PMF score (potential of Mean Force) is assigned. It is based on distance between ligand receptor pairs of atoms [98].

Admet Studies

ADMET profiling of drug refers to demonstration of its Pharmacokinetic parameters and its toxicity. A ligand with good docking score may have toxicity. ADMET refers to Absorption, Distribution, Metabolism, Elimination and Toxicity. During docking studies and QSAR analysis, the molecules are preferably made such that they have rigidity in their structure [99, 100].

A ligand with good docking score and less toxicity may have inferior pharmacokinetic parameters [100]

For a drug to be absorbed, and distributed in body, there should be multiple properties of the drug [101].

1. **Absorption:** The rate at which drug is absorbed from Gastrointestinal tract is called absorption. For oral route, absorption plays vital role. Intravenous route has no role of absorption. It is measured by log P (partition coefficient), Solubility, pKa of the drug. Log P is measured using n-octanol which resembles the cell membrane because of long non polar chain and small polar hydroxyl group. The drug should have solubility in the body fluid [99,100].
2. **Distribution:** It is the process by which absorbed drug molecule move from cell and body fluid. The drug should reach the target site. This is determined by distribution. Permeability of drug plays important role in distribution. Higher the drug – protein binding, lesser is the unbound drug for Pharmacological activity. Less drug protein binding is desirable for Pharmacological activity.
3. **Metabolism:** Metabolism is also called biotransformation of drug. It is the process how the drug gets chemically modified in-vivo to make a more water soluble derivative by body enzymes, specially liver micorosmal enzyme to facilitate drug elimination. Higher metabolism of drug indicates rapid biotransformation. The drug rapidly is converted to its metabolite. Hence duration of action and potency decreases. It should be ensured that the drug has no effect on liver microsomal CYP enzymes [101, 102].
4. **Elimination:** The metabolites of the drug should be water soluble to facilitate elimination. Before administration of next dose, clearance of the drug from body should be ensured. Or else would lead to accumulation of drug in fat depot and continuous bioaccumulation would lead to negative effects [102].
5. **Toxicity:** Rigid molecules have less number of confirmation. So, less binding to other receptors causes less toxicity. But different proteins are their whose active site has similar sequence of AA. This induces binding of ligand to other receptor and leads to toxicity. Toxicity types: Hepatotoxicity, Renal toxicity, Carcinogenicity, Mutagenicity [102].

The complete process of drug discovery is schematically represented in Figure 05.

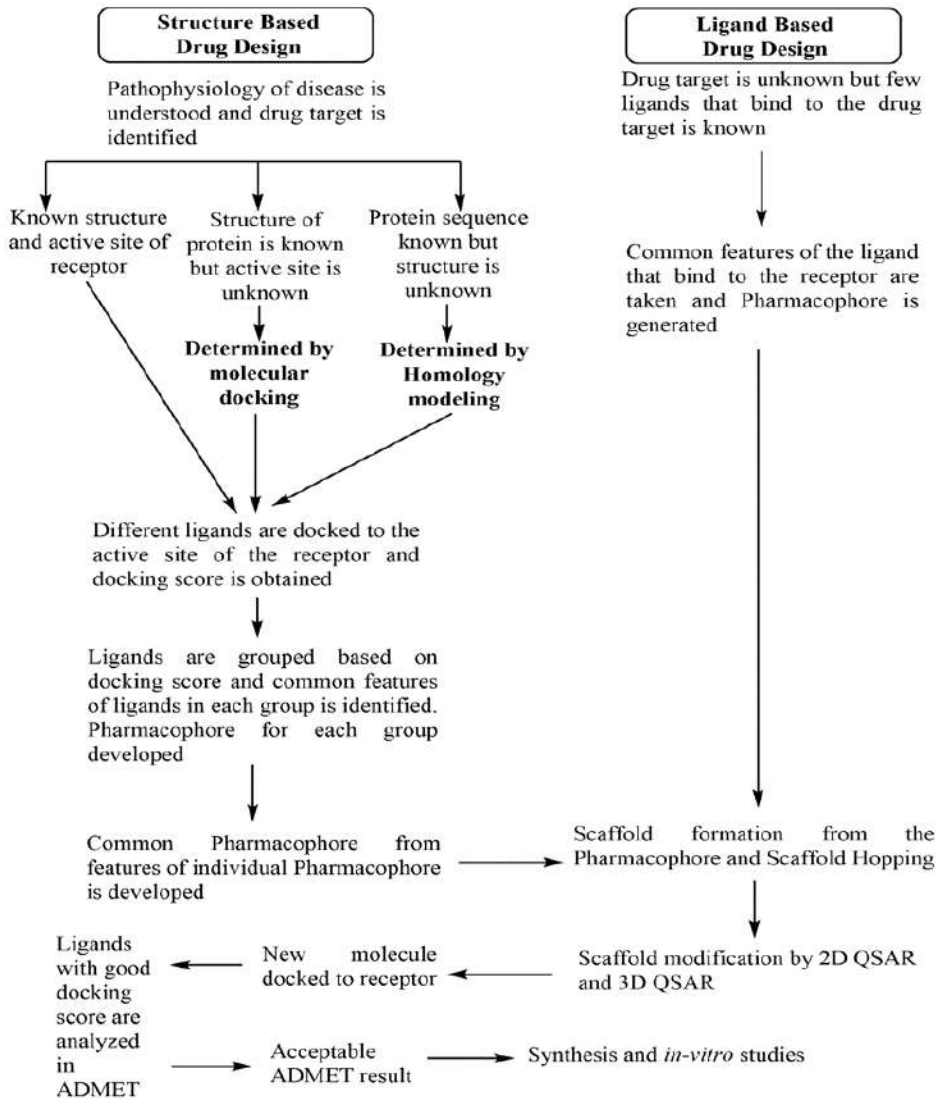

Figure 05: Flowchart for drug development by Structure Based and Ligand Based Drug Designing

CONCLUSION:

Structure based Drug Discovery is more sophisticated technique. Ligand is taken is docked to the receptor and a pharmacophore is generated. This pharmacophore is modeled to develop its 3D spatial conformation. The pharmacophore is ensemble of electronic and steric features. This pharmacophore is used to develop a scaffold molecule with all properties of the pharmacophore. QSAR studies modifies the Pharmacophore using Craig Plot and physicochemical properties. The molecules are docked to the receptor. The ligands which shows appreciable docking score are send for ADMET studies. If the ADMET score is remarkable with less toxicity and good Pharmacokinetics properties, the drug is developed in the laboratory and later tested *in-vivo* in clinical trials.

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