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Drug Designing, Discovery and Development Techniques

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1. Introduction

Human body is a complex chemical machinery, with as many as thousands of chemicals, namely proteins, carbohydrates, fats, etc. which exist all together. Every process in the body is some sort of chemical conversion that leads to movements, thought processes, feelings, pain and many more such complex as well as simple processes. The human body has also been provided with all the necessary chemical components or precursors, various enzymes and neurotransmitters for the balanced and proper functioning of all the life sustaining processes. Yet it so happens that some machineries or bioprocesses fail to function due to several exogenous or endogenous factors. Hence providing external aids, which we call "Drugs" or "Medicines", becomes essential to restore the normal functioning. Drugs are nothing but chemical entities of synthetic or natural origin, which only modulate the body functions and have no new action on the body. This explanation however does not fit the chemotherapeutic agents used to treat parasitic infections, as they have no action on the human body, but, are targeted to the invading organism (Richard et al., 2009). The exogenous factors are varied right from parasitic invasion to some chemical entities which tend to disrupt the normal bodily functions. Hence repairing becomes mandatory, if bodily repair mechanism cannot match the rate of damage. The endogenous factor maybe faulty, functioning of organs, any genetic or congenital factor, over or under-production of some precursors which may lead to disorders. The classical examples of disorders due to endogenous factors are the neurodegenerative disorders like Parkinsonism and Alzheimer's disease which arise due to the imbalance of acetylcholine and dopamine in the central nervous systems. Though there is no cure for these disorders but drugs and therapies have been developed to prolong and improve the quality of life. (Moore et al., 2005; Cummings et al., 1998). Hence, drug discovery can also called as patient-oriented science meant for improving the quality of life by developing newer and safer agents.

Drug discovery plays an important role for the growth of any pharmaceutical industry and also to the society, as newer and safe drugs are launched in the market with the view to

improve the therapeutic value and safety of the agents. The pharmaceutical industry has consistently shown that it can discover and develop innovative medicines for a wide range of diseases (Ratti & Trist, 2011). The revenue that flows in with the invention of newer agents has always been the motivation for the industry to keep up the pace and keep abreast with the ever increasing demand for medicines.

The advent of molecular biology, along with numerous developments in the screening and synthetic chemistry technologies, has allowed learning both, the knowledge about the receptor and random screening to be used for drug discovery. Today, more or less all pharmaceutical industries follow common techniques for discovering drugs. These include cloning and expressing human receptors and enzymes in formats that allow high-throughput screening and the application of combinatorial chemistry. Thus, random screening can now be done with libraries sufficiently large and diverse to have a relatively high probability to find a novel molecule. These libraries are possible because they can be generated by the techniques of combinatorial chemistry (Black, 2000).

Drug research, as we know it today, began its career when chemistry had reached a degree of maturity that allowed its principles and methods to be applied to the problems outside of chemistry itself and when pharmacology had become a well-defined scientific discipline in its own right. By 1870, some of the essential foundations of chemical theory had been laid. Avogadro's atomic hypothesis had been confirmed and a periodic table of elements established. Chemistry had developed a theory that allowed it to organize the elements according to their atomic weights and valencies. There were set of theories of acids and bases. In 1865, August Kekulé formulated his pioneering theory on the structure of aromatic organic molecules (Drews, 2000a and 1999b). During the first half of the 20th century drug research began shaping up and was developed by several new technologies, which carried the drug discovery process to its best. Biochemistry also had tremendous influence on drug research in many ways. The concept of targeting enzymes as drug targets came in to existence, that led to the designing of enzyme substrates which acted either as inhibitors or showed their action by modifying various feedback mechanisms. (Meidrum & Roughton, 1933).

Table 1 shows some important discoveries in the field of medicine, right from 19th century to 21st century

Sr. no	Year of Discovery	Drug Name	Category
1.	1806	Morphine	Hypnotic agent
2.	1899	Aspirin	Analgesic and Anti-pyretic agent
3.	1922	Insulin	Anti-Diabetic agent
4.	1928	Penicillin	Antibiotic
5.	1960	Chlordiazepoxide	Tranquillizer
6.	1971	L-dopa	Anti-Parkinson agent
7.	1987	Artemisinin	Anti-malarial agent
8.	1998	Sildenafil	Erectile Dysfunctioning treatment
9.	1999	Celecoxib, Rofecoxib	Selective COX-2 inhibitors
10.	1999	Zanamavir, Oseltamivir	Anti-influenza agents
11.	2001	Imatinib	Leukemia treatment

Table 1. Important discoveries in medicine

The present day drug discovery process is a very time consuming process as it takes at least 14-16 years of research for a molecule to completely transform into a drug. There are several 100 basic research projects, before desired molecule is discovered. But, this molecule is not yet ready to be called as a drug. After the pre-clinical establishment and confirmation of its action and toxicity data, the FDA approves the candidate for clinical studies. The Clinical phase of the study takes at least 6-8 years, before the candidate can be launched in to the market. After this stage, the molecule is said to have transformed from a molecule to drug. Even after the launch of the drug in the market, the post-marketing surveillance and pharmacovigilance program is being carried out to find out whether any new adverse reaction or incompatibilities towards other agents, when given as combination therapies. (Congreve, et al., 2005). Figure 1 depicts the entire drug discovery process with the tentative timeline.

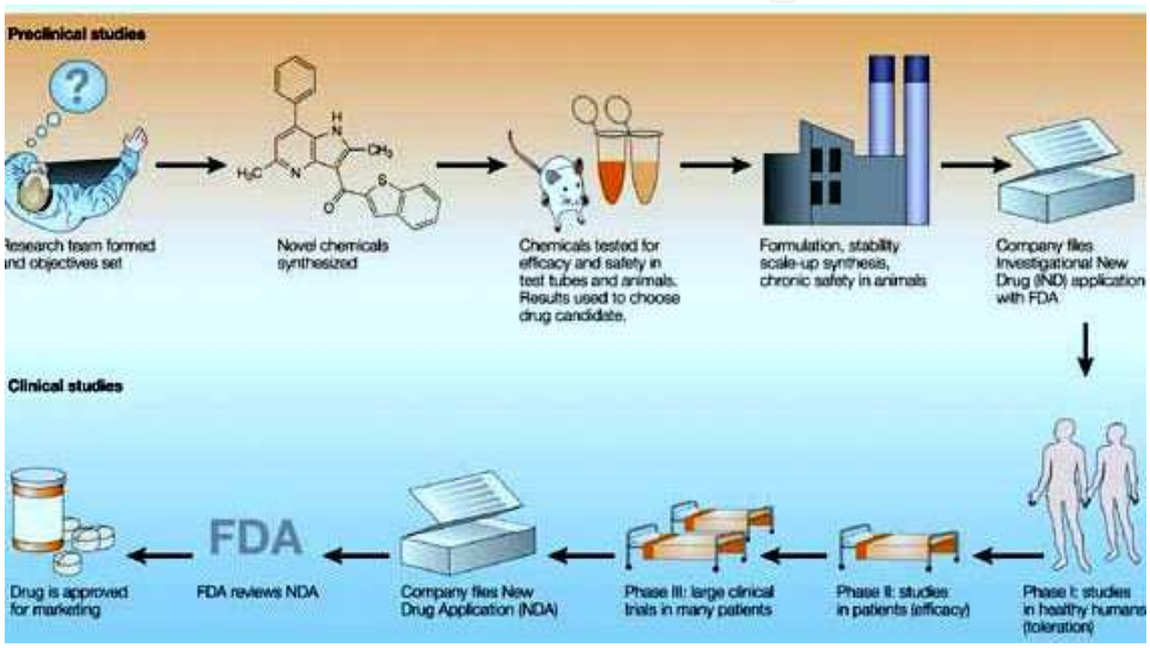

Fig. 1. Drug discovery and development process (Lombardino and Lowe, 2004).

2. Drug discovery process

Drug discovery process basically is a patient oriented science, where researchers strive to improve the existing drugs or invent a totally new chemical entity, which should be ideally more potent than any existing drug of a similar category. If not, then at least it should be safer than those existing. This process is a very time consuming and expensive activity, calling for the expertise of many eminent researchers. It takes nearly 12-14 years of exhaustive research and a huge amount of financial investment for the discovery of a single drug. Right from the chemical synthesis to its clinical development and finally formulating it to a suitable form. Failure at any stage would mean a huge loss for the company. Hence, a lot of planning is required even before the project is underway. Recently, with the use of technology the process is becoming a less risky business, because of the ability of the computers to predict the possible outcomes. This will surely reduce the efforts in fruitless directions (Augen, 2002).

The following paragraphs shall discuss the various stages of drug discovery process.

2.1 Identification of biological targets

The human body functions normally by the virtue of the biochemical process which go on, producing all the necessary chemicals required for numerous functions to undergo smoothly within the body. Many of these processes are regulated by the enzymes and the endogenous effector molecules via their respective receptors. A diseased state, may hence, be identified by, either the abnormal biochemical functioning or, over or underproduction of some of the intermediates. Hence , the most important and most common biological targets for drug discovery are either enzymes regulating the biochemistry or the receptors through which many hormones and endogenous effectors show their response. For example, inhibition of human dihydrofolate reductase, by methotrexate, brought under control the growth of tumour in humans (Borsa and Whitemore, 1969). Similarly, blocking of the beta-adrenoceptors in the cardiac muscles was found to reduce the hypertensive state (Pearson, et al., 1989). Another type of biological targets are nucleic acids. Though they are rarely targeted as compared to those mentioned above, yet they are important targets. (Overington, et al., 2006).

2.2 Validation of biological targets

Once the target is identified, it becomes absolutely necessary to confirm, that the correct target has been identified. The use of reliable and suitable animal models and the latest techniques in gene targeting and expression are all essential to the validation process. (Abuin, et al., 2002). Validation also helps researchers to identify any secondary target that the drug may bind to, which may lead to any sort of unwanted or adverse reaction. Ideally the drug candidate should be such that it binds to a single target only, but this seldom happens. Thus, binding to other targets, apart from the correct target leads to unwanted pharmacological actions. These cannot be completely avoided. It can be minimized to negligible extent. (Marton, et al., 1998). G-protein coupled receptors (GCPRs) are the most common and the major targets where a drug binds. Hence, over 30% of drugs in market are modulators of GPCR. The quantitative polymerase chain reaction (qPCR) analysis is one of the techniques used to measure the mRNA expression on the receptor. (Wise, et al., 2002).

2.3 Lead structure search

A lead compound is the one that has basic structural requirements for exhibiting the desired action. This means that, a lead compound has many structural spaces for further development of the structure, to give a compound with further enhanced action. High-throughput screening is a technique, which helps to identify the lead compound out of the many synthesized compounds or those compounds which are collected from the natural source. Hence, it becomes utmost important to identify the lead compound, as this forms the basis for further development of the molecule(s). (Bleicher, et al., 2003). Figure 2 illustrates the design cycle for lead search. The various other techniques involved in lead identification are virtual screening, informatics, pharmacaphore mapping, High throughput docking, NMR-based screening and chemical genetics. (Xue and Bajorath, 2000).

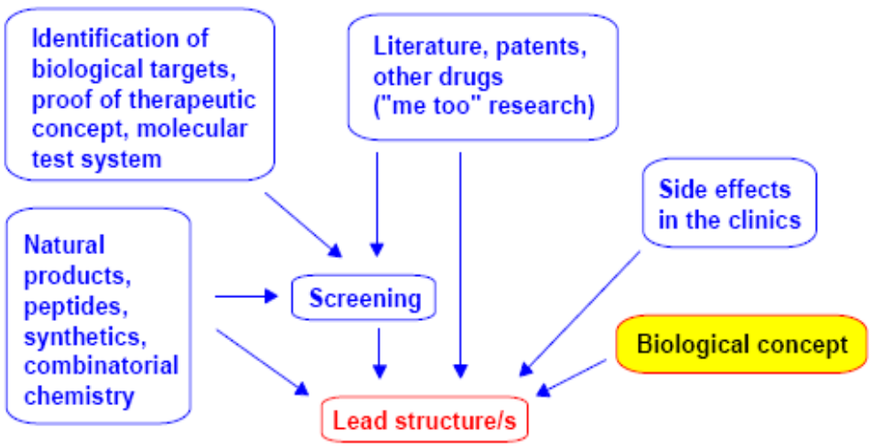

Fig. 2. The Design cycle describes the optimization of a lead structure to one or several development candidates.

2.4 Lead optimization

As soon as the lead structure is identified, the next step is to optimize the same. Here, the chemists in close collaboration with the pharmacologists will carefully study the structure-activity relationship and will synthesize such other derivatives, so as to get a compound with the best possible desired activity. The various other approaches for lead optimization are Structure-Based Drug Design (SBDD), Quantitative Structure-Activity Relationship (QSAR) and Computer-Assisted Drug Design (CADD). All such approaches generate a huge amount of data, so as to assist the chemist in optimizing the lead to the best possible structure, with best possible desired action. These aforementioned approaches shall be dealt in detail in the later part of the chapter. (Joseph-McCarthy, 1999 & Ooms, 2000). Figure 3 represents the design cycle for lead optimization and drug development.

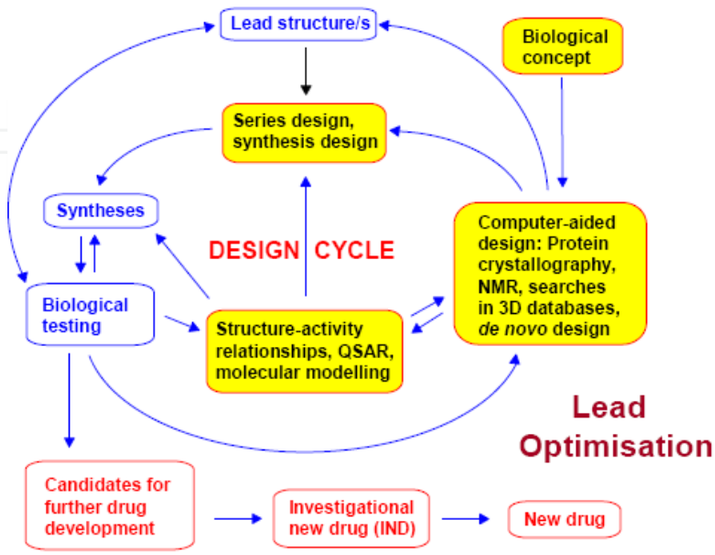

Fig. 3. Design cycle for lead optimization

2.5 Preclinical studies

The main objective of preclinical studies is to ascertain the safety of the newly developed molecule. A newly developed molecule is never permitted to be tested on the human body, unless supported by a confirmed data about the pharmacology and toxicology of the molecule which is, based on animal studies is obtained. This phase, generally deals with elucidating the mode of action the molecule and getting an idea about the pharmacokinetics (PK) and pharmacodynamics (PD) of the molecule. However, the most important is the toxicological data obtained from the animal study, which gives the rough estimate about the possible adverse reactions that may be likely to be seen during the course of the therapy. These are carried out in two stages, in-vitro studies and in-vivo studies. The in-vitro studies make use of different cell-lines and tissue preparations. The in-vivo studies are performed on the live animals and are observed the changes in the animal's behavior. (Caldwell, et al., 2001 & Smith, and van de Waterbeemd, 1999).

2.6 Clinical trials

The next stage after preclinical studies is the clinical studies, actual testing of the molecule in the human volunteers. This phase allows to assess the safety and efficacy of the new molecule. This phase also allows to gather information about the toxicological effects in the human body, as seldom the toxicity shown by animals, cannot be always directly correlated to the humans. Before the start of this stage, the innovator should file an application, namely, "Investigational New Drug (IND)", as the FDA approves based on the preclinical data, the innovator can proceed for clinical studies. This stage consists of three phases, phase 1, phase 2, phase 3 and the phase 4 studies are carried out after the drug has been launched in to the market.

Phase 1 studies are usually carried out on healthy human volunteers and on a small group of people. This phase evaluates the safety, tolerability and PK and PD of the new molecule.

Phase 2 studies are generally carried out on a small population with the target disease. In this phase, the drug's efficacy and safety, metabolism and PK are evaluated in a diseased human body.

Phase 3 studies are extensive and multiple site studies. This phase, covers a large group of individuals with target disease. This phase basically is a therapeutic confirmatory phase, as all the parameters studied in the phase 2 of the study are confirmed in this phase. This phase may take somewhere about 3-6 years to complete. After this phase is successfully completed, the company files the "NEW DRUG APPLICATION (NDA)"to the FDA. Once the FDA issues an approval to the company, based on their data compiled from the clinical trials, the drug can be launched in the market.

Phase 4 (Post-Marketing survilience) studies are carried out, after the drug has been launched into the market. The company continues its monitoring of the drug. The rationale behind this phase is to check for any new adverse or serious reaction which was not detected in the earlier phases and may be observed in this phase. If so happens that some serious adverse reaction is observed, the company may withdraw the drug from the market. (Singh, et al., 2011).

2.7 Formulations for clinical studies

The formulations for clinical studies are usually prepared as capsule dosage form, as it is easy for formulation and also easy for administration. Apart from this advantage, there is another key factor to be considered while formulating a trial batch, as the drug itself has not been tested in humans, any untoward action can be directly ascertained to the drug in the absence of any excipients. Capsules, unlike the tablets can be formulated without any or minimal excipients. Liquid dosage forms may also be formulated, provided the drug is water-soluble, for the ease of preparation and water being the safest medium. Formulations should be properly tested for its stability and must be stable at least for the period the trials are underway. The other reason for choosing simple formulations is to avoid any time lag, as the process of trials itself is lengthy. Any more delay, may further lead to the delay in marketing the drug.

3. Computer-aided drug design

Computers, have found their way in every field of science and technology today. The boon of computers is that a large number of calculations and observations can be done in no time. Drug discovery and designing is no exception to this generalization. Drug designing has received a many fold face-lift by the virtue of computer software dedicated to the designing of ligands and identifying the biological targets. Computer generated structures serve to be good predictive models for the evaluation of biological activity.

A drug exhibits its action when it binds to its biological target, usually receptors. Receptors are nothing but proteins with active sites for the binding of ligands. Hence, in order to design a good ligand, it becomes necessary to know the structure of such receptors and to identify their active sites accurately. The two important aspects involved in predicting molecular-interactions in computer-aided drug design (CADD) are development of pharmacophore-based and molecular docking and scoring techniques. Computerized structure of the known proteins is based on the experimental data present in various literatures and protein data banks. With this, it is possible to deduce the 3D structure of the all the known proteins with the help of sequence homology approach. Hence, these hypothetical proteins behave more or less like the real proteins in their native biological environment (Taft, et al., 2008). Recently, many computer-assisted models are being developed and several thousand candidates are being screened for various activities using these models. The methods of choice for this purpose are computer programs that superimpose molecules by a flexible alignment to derive pharmacophoric patterns and/or quantitative structure-activity relationships, dock molecules to the surface of a protein 3D structure or to a hypothetical pseudoreceptor, or construct new ligands within a predefined binding site (Klebe, 1995 & Kubinyi, 1998a).

Different molecular property fields, such as electrostatic, steric, hydrophobic, hydrogen bond acceptor and donor fields, as well as their weighed combinations, have been used to achieve a fully automated alignment of the molecules. (Mestres, et al., 1997). The process of docking process involves the prediction of ligand conformation and orientation within a targeted binding site. Docking is basically performed for accurate structural modelling and correct prediction of the biological activity. Figure 5 depicts an image witch is generated by docking studies (representational purpose only)

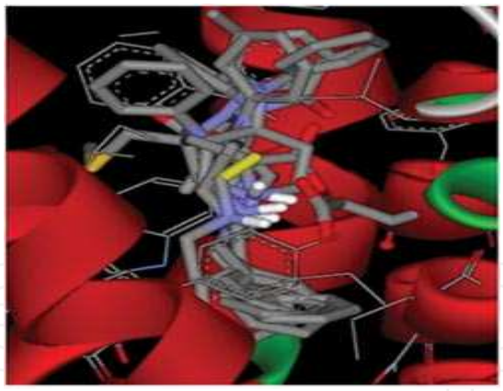

Fig. 5. Representation of molecular docking (Bo, et al., 2010).

Type of study	Software programme	Innovator
Protein-Ligand docking	AUTODOCK	The Scripps Research Institute
	COMBIBUILD	Sandia National Labs
	DOCKVISION	University of Alberta
	FRED	OpenEye
	FLEXIDOCK	Tripos
	FLEXX	BioSolveIT GmbH
	GLIDE	Schrödinger GmbH
	GOLD	CDCC
	HINT!	Virginia Commonwealth University
Protein-Ligand & Protein-Protein docking	DOCK	UCSF Molecular Design Institute
	GRAMM	University of Kansas
	ICM-DOCk	MolSoft LLC

Table 2. lists the various computer programmes used for docking studies. (Structure based drug design and molecular modelling, http://www.imb-jena.de/~rake/Bioinformatics_WEB/dd_tools.html)

4. Molecular modelling and drug design

Theoretical studies of biological molecules permit the study of the relationships between structure, function and dynamics at the atomic level. The entire process is about simulation of the biological processes and quantum mechanical calculation based on the principles of chemistry and physics.

4.1 Molecular mechanics- force field (Potential energy function)

Current generation force fields (or potential energy functions) provide a reasonably good compromise between accuracy and computational efficiency. They are often calibrated to experimental results and quantum mechanical calculations of small model compounds. Their ability to reproduce physical properties measurable by experiment is tested; these

properties include structural data obtained from x-ray crystallography and NMR, dynamic data obtained from spectroscopy and inelastic neutron scattering and thermodynamic data. (MacKerell, et al., 1995).

The molecular structures, properties and energies of a molecule are better understood through the use of the mechanical molecular model. This model involves the development of a simple molecular mechanics energy equation representing the sum of various energy interaction terms comprised of bonds, angles, torsions of both bonded and non-bonded atoms. Force fields the model serves as a simple descriptor for vibrations in molecules. The concept of force fields is now widely employed as one of the simplest tools in molecular modeling.

Force fields are fundamentally important in de novo drug design programs, in pharmacophore mapping, and represent the "scoring functions" in many docking programs. As scoring functions, force fields are used to rank "ligand poses" obtained by a docking algorithm, or in de novo ligand design programs to suggest placement of fragments in the sites in the enzyme with the highest binding affinity. In all these applications, force fields are mainly used to compute the interaction energy between the protein and the ligand as pair-wise interaction potentials consisting of van der Waals and electrostatic interactions, in addition to H-bond energy between the ligand and the enzyme. (Pissurlenkar, et al., 2009).

4.2 Energy minimization methods

The goal of energy minimization is to find a route from an initial conformation to the nearest minimum energy conformation using the smallest number of calculations possible. NMR and X-ray crystal structures tend to have high energy interactions like Pauli repulsions. That is because the methods to retrieve molecular structures are not perfect and especially in x-ray-structures there are crystal contacts, which lead to a compaction of the molecules. Moreover, hydrogen atoms are added to relatively arbitrary positions near their neighbors. Thus, there are atoms lying too close together so that the Pauli repulsion outweighs the dispersion attraction and the energy is raised high above natural energy levels. These high energy interactions lead to local distortions which result in an unstable simulation. They can be released by minimizing the energy of the structure before starting a run. The minimization results in a structure with energy near the lowest possible energy the system can have. (Leach, 2001 & Höltje, et al., 2003)

4.3 Conformational analysis

Conformational analysis deals with the computation of minimal energy configurations of deformable molecules and docking involves matching one molecular structure to the receptor site of another molecule and computing the most energetically favorable 3-D conformation. (Go and Scherga, 1970).

4.3.1 Systematic search (Scheraga, et al., 1992)

Due to the convoluted nature of the potential energy surface of molecules, minimization usually leads to the nearest local minimum, and not the global minimum. To scan the

potential surface with some surety of completeness, systematic, or grid, search procedures have been developed. The following protocol is used for the same,

1. Rigid geometry approximation
2. Combinatorial nature of the problem
3. Pruning the combinatorial tree
4. Rigid body rotations
5. Exploitation of rings
6. Conformational clustering and families
7. Conformational analysis

4.3.2 Monte Carlo simulation

The Monte Carlo simulation is based on statistical mechanics and generates sufficient different configurations of a system by computer simulation to allow the desired structural, statistical, and thermodynamic properties to be calculated as a weighted average of these properties over these configurations. A useful application has combined Monte Carlo sampling with variable temperatures (simulated annealing) to optimize the docking of ligands into active sites. (Allen, & Tildesley, 1989)

4.3.4 Molecular dynamic simulation

Molecular dynamics is a deterministic process based on the simulation of molecular motion by solving Newton's equations of motion for each atom and incrementing the position and velocity of each atom by use of a small time increment. Molecular dynamics simulations represent another technique to sample configuration space, based on the aforementioned principle. Combined with the use of "reasonable" temperatures (a few hundreds or thousands of degrees), this means that only the local area around the starting point is sampled, and that only relatively small barriers (a few tens of a kJ/mol) can be overcome. Different (local) minima may be generated by selecting configurations at suitable intervals during the simulation and subsequently minimizing these structures. MD methods use the inherent dynamics of the system to search out the low-energy deformation modes and they can be used for sampling the conformational space for large confined systems (Tuckerman, & Martyna, 2000).

4.4 Structure-based and Ligand-based drug design approaches

Structure-based drug design by the use of structural biology remains one of the most logical approaches in drug discovery. It combines information from several fields: X- ray crystallography and/or NMR, molecular modeling, synthetic organic chemistry, QSAR, and biological evaluation (Marrone, et al., 1997). Figure 6 shows the schematic process.

Many of the naturally occurring molecules are found to be very potent, and also the endogenous chemicals give a lot of information for drug designing. The use of such ligands to generate and design newer ligands is called ligand-based drug design. Many a times straightforward design process starts from conformationally restricted natural receptor ligands, such as from polypeptides or proteins. Some of the applications of structure and ligand based drug design are Renin and protease inhibitors, β-lactamase inhibitors, reverse

transcriptase inhibitors, angiotensin converting enzyme inhibitors, HIV-1 integrase inhibitors and many more. (Kubinyi, 1998b).

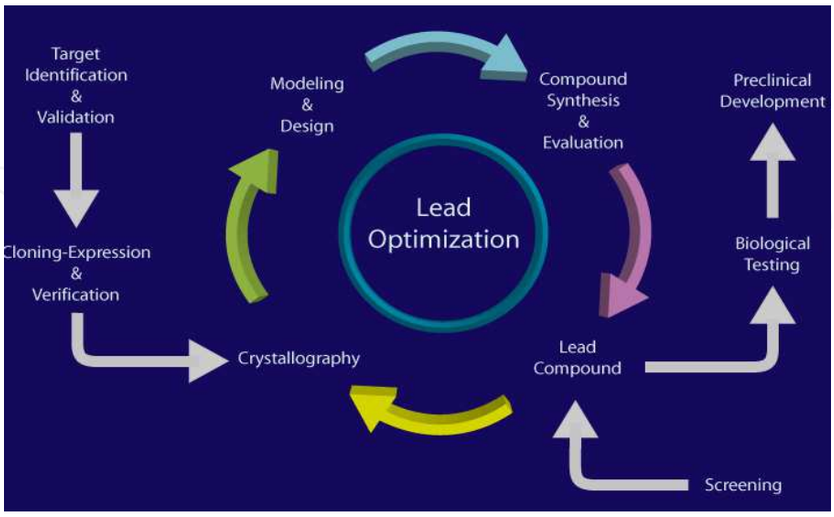

Fig. 6. Representation of structure based drug design.

4.5 3D pharmacophore modeling

Various conformations of a range of ligands that all act at the same receptor site can provide significantly more information than just a single ligand structure. With a sufficiently broad range of ligands, it is often possible to generate a pharmacophore model of the receptor site. The advantage of such a pharmacophore model is that smaller, non-peptide molecules that might have improved stability and bioavailability over their peptide counterparts can be designed, relative easy and certain amount of confidence towards getting successful outcome. (Nielsen, et al., 1999).

4.6 Rational drug design

The Concept of rational drug design simply lies in logical reasoning before designing any therapeutic agents. For example, to prepare any competitive inhibitor of a particular target, the logic of predicting the structure is to simply design an molecule with similar structural features exhibited by the endogenous agent or by closely examining the active binding site. Close examination of the active site gives many hints about the interacting amino acid residues, so it becomes simple to predict the nature and type of substituents and the favorable position in the molecule, which will favor better binding.

4.6.1 Design of enzyme inhibitors

Almost every biochemical process in the human or parasite is catalyzed by various enzymes of diverse function. As a result enzymes have always been the hot target for designing new drugs for various clinical conditions. The most popular example is the inhibition of acetylcholinesterase enzyme in the human brain is one of the most successful targets to treat the symptoms of Alzheimer's disease. The first step in designing an agent to inhibit an enzyme is to study thoroughly the structure and the binding site/pocket of the endogenous

substrate. It is always favorable to design the new agent based on the structural requirements into the pocket of the catalytic site of the enzyme based on endogenous substrate or agents already designed for the purpose. The binding of the inhibitor should be more preferred or favourable than the endogenous substrate, in order to develop a successful inhibitor and at the same time care should also be taken so as to not develop an irreversible inhibitor, this may permanently destroy the enzyme. Popular drugs designed in this fashion are the HIV-1 protease inhibitors, thrombin inhibitors, neuraminidase inhibitors and many more. (Prasad, et al., 1996, Kimball, 1995 & Wade, 1997).

4.6.2 De Novo Ligand design

Designing of novel chemical structures that are capable of interacting with a receptor of known structure using methodology that is much more reliable, is what we call De Novo Ligand design. Techniques for the design of novel structures to interact with a known receptor site are becoming more and more available and have shown a lot of promise for the future. The thorough understanding of the various classes of chemicals interacting with the particular receptor, can give a lot of information to design novel agents by replacing the scaffold with another one to have similar sort of interaction and at the same binding site. (Klebe, 2000 & Bohm, and Stahl, 2000).

5. Quantitative Structure Activity Relationship (QSAR)

QSAR correlate, within congeneric series of compounds, affinities of ligands to their binding sites, inhibition constants, rate constants, and other biological activities, either with certain structural features (Free Wilson analysis) or with atomic, group or molecular properties, such as lipophilicity, polarizability, electronic and steric properties. (Kubinyi, 1995).

5.1 Parameters

5.1.2 Hydrophobicity

Molecular recognition depends strongly on hydrophobic interactions between ligands and receptors. Hydrophobicities of solutes can readily be determined by measuring partition coefficients designated as P. Partition coefficients are additive-constitutive, free energy-related properties. Log P represents the overall hydrophobicity of a molecule, which includes the sum of the hydrophobic contributions of the "parent" molecule and its substituent. Whole-molecule approaches use molecular properties or spatial properties to predict log P values. (Taylor, 1990 & Kellogg, et al., 1992).

5.1.3 Electronic

Electronic attributes of molecules are intimately related to their chemical reactivities and biological activities. The extent to which a given reaction responds to electronic perturbation constitutes a measure of the electronic demands of that reaction, which is determined by its mechanism. Hammett employed, as a model reaction, and determined their equilibrium constants K_a, which led to the definition of an operational constant, called the Hammett's constant σ, It is a measure of the size of the electronic effect for a given substituent and represents a measure of electronic charge distribution in the parent nucleus. (Hammett, 1966).

5.1.4 Steric effects

The quantitation of steric effects is complex and challenging in all other situations, particularly at the molecular level. Sterics are of utmost importance in ligand-receptor interactions as well as in transport phenomena in biological systems. The first steric parameter to be quantified was Taft's E_s constant. One of the most widely used steric parameters is molar refraction (MR). MR is generally scaled by 0.1 and used in biological QSAR, where intermolecular effects are of primary importance. The failure of the MR descriptor to adequately address three-dimensional shape issues led to Verloop's development of STERIMOL parameters, which define the steric constraints of a given substituent along several fixed axes. (Taft, 1956, Tute, 1990 & Verloop, 1987).

5.2 Quantitative models

All QSAR analyses are based on the assumption of linear additive contributions of the different structural properties or features of a compound to its biological activity, provided that there are no nonlinear dependences of transport or binding on certain physicochemical properties. (Kubinyi, 1997).

5.2.1 Hansch analysis

The linear free-energy-related Hansch model, also sometimes referred to as the 'extrathermodynamic approach. The model makes use of log P and Hammett constant. The equation of this model is as follows

$$\log 1/C = a(\log P)^2 + b\log P + c\sigma + \ldots + k$$

where P is the partition coefficient, σ is the Hammett electronic parameter, k is a constant term, and a, b, c are the regression coefficient. This equation is built on the concept that the permeation of drug in the cell, and the binding of the drug are function of its lipophilicity, electronic properties and other linear free-energy related properties. (Hansch, and Leo, 1995).

5.2.2 Free Wilson analysis

Free-Wilson approach is truly a structure-activity-based methodology because it incorporates the contributions made by various structural fragments to the overall biological activity. The equation of this model is as follows

$$BA_i = \sum_j a_j X_{ij} + \mu$$

Where BA stands for biological activity, X_j is the j^{th} substituent, which carries a value 1 if present and 0 if absent, a_j represents the contribution of the jth substituent to biological activity. (Franke, 1984 & Free, and Wilson, 1964).

5.3 Other QSAR approaches

In this section, we discuss some of the most widely used 3D-QSAR techniques. The review by Evans et al on 3D-QSAR is worth reading for further understanding (Verma, et al., 2010).

5.3.1 Hologram Quantitative Structure Activity relationship (HQSAR)

Hologram QSAR is a unique QSAR method. This method does not require the exact 3D information for the ligands. In this technique, the molecule is hashed to a molecular fingerprint that encodes the frequency of the occurrence of various molecular fragment types. In simpler words, the fragment size controls both the minimum and maximum length of the fragments to be included in the hologram fingerprint. Molecular holograms are produced by generating all the linear and branched fragments, which range in size from 4 to 7 atoms. (Suh, et al., 2002).

5.3.2 Comparative Molecular Field Analysis (CoMFA)

Comparative molecular field analysis (CoMFA) is a promising new approach to structure-activity correlation. Work on CoMFA began in at 70's and is one of the more famous 3D QSAR methods. It provides steric and electrostatic values in addition to ClogP values. ClogP means the hydrophobic parameters of the ligands. (Cramer, et al., 1988 &Wold, et al., 1984).

5.3.3 Comparative Molecular Similarity Indices Analysis (CoMSIA)

Comparative Molecular Similarity Indices Analysis (CoMSIA) is known as one of the newer 3D QSAR methodology. This technique is most commonly used in drug discovery to find the common features that are important in binding to the relevant biological receptor. In this technique, both steric and electrostatic features, hydrogen bond donor, hydrogen bond acceptor and hydrophobic fields are considered. (Malinowski, and Howery, 1980).

6. Combinatorial chemistry and High-Throughput Screening (HTS)

Combinatorial Chemistry is a technology for synthesizing and characterizing collections of compounds and screening them against various diseases. It was primarily used for the synthesis of peptide and oligonucleotide libraries. Many compounds discovered combinatorially have at least entered preclinical or clinical trials. That's some proof of the value of combinatorial chemistry. But the bottom line is that many researchers in academia, industry, and government already recognize it as an integral component of the drug discovery repertoire. (Borman, 2002).

High-Throughput Screening (HTS) a high-tech approach for drug discovery, is more and more gaining popularity among industrial researchers as well as students doing their post-graduate and/or doctorate research projects. It is basically a process of screening and assaying huge number of biological modulators and effectors against selected and specific targets. The principles and methods of HTS find their application for screening of combinatorial chemistry, genomics, protein, and peptide libraries. The main purpose or goal of this technique is to hasten the drug discovery process by screening the large compound libraries with a speed which may exceed a few thousand compounds per day or per week. For any assay or screening by HTS to be successful several steps like target identification, reagent preparation, compound management, assay development and high-throughput library screening should be carried out with utmost care and precision. (Martis, et al., 2011a).

7. Conclusions

Many more approaches like metabolomics, genomics, proteomics also compliment well with the other techniques so that more target specific agents can be discovered with more accuracy. The review on metabolomics shall explain more in detail (Martis, et al., 2011b). Drug discovery is yet more to be explored, even more than that explored till date. The findings of the human genome project has added more understanding to the target identification. Nature has made all the provisions for curing a disease or disorder, human efforts of finding is what is required. Exploring natural sources which is ill-explored should be effective done as nature is source of countless chemicals which could lead to a successful drug candidates.

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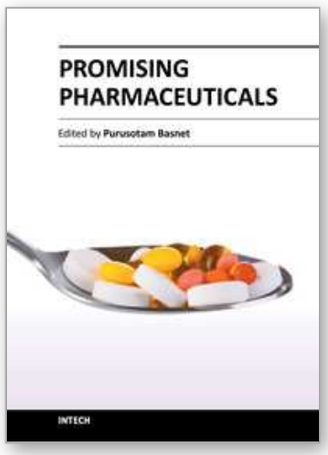

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From the dawn of civilization, humans have been dreaming of happy, healthy and long-life. Our life expectancy is twice longer than 100 years ago. We know more about the diseases. Therefore we have developed new drugs to fight against them. The demand for drugs was so high that we developed Pharma industries. Although Pharma industries took responsibility of producing the needed drugs and gave us a quality of life, misuse of drugs brought further complication. Therefore, discovery, production, distribution, and the phase of administration of patients' quality assurance has to be controlled with a technological procedure and tight regulations to make the system as effective as possible for the benefit of human health. Our book provides selected but vital information on the sources, tools, technologies and regulations regarding the current status of medicine development.

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