MOLECULAR MODELING IN DRUG DISCOVERY

The discovery and development process for a compound, which is suitable to market with the right combination of activity, specificity, stability, and safety is an intricate, arduous and expensive task. Drug design is an iterative process, which begins with a compound that shows interesting biological profile activity, and culminates after optimizing the activity, chemical synthesis, approval from the Food and Drug Administration (FDA) and finally marketing. Naturally, this process involves teams of varied experience. In recent years, the pharmaceutical industry recognized the requirement and crucial role played by the molecular modeling and computational approaches to problem solving besides the expertise of physicians, synthetic organic chemists, biochemists, biotechnologists, etc.

Computational chemistry views the three-dimensional molecular structures as numerical models and all the properties of such molecular systems are evaluated by solving the equations of motion using either quantum or classical mechanical principles. Although molecular quantum mechanical calculations are computationally expensive, they have seen rapid growth and found applications in various fields due to the enormous growth witnessed in the development of efficient algorithms and hardware. These calculations have better predicting abilities as compared to classical mechanical methods. Predicting the molecule's affinity for its target paves a way for the synthesis and development of potential new drugs.

Determining structural requirements for drugs to bind to proteins which function within the cell membrane is a formidable challenge, primarily due to the difficulty in obtaining crystals suitable for X-ray diffraction. In such cases comparative protein modeling studies become an essential alternative.

How to build a new designer drug?

In the beginning, it is a basic requirement to know what features an "ideal" drug should fulfil the following criteria's:

- must be safe,
- should be well absorbed orally and bioavailable,
- metabolically stable and with a long half-life,

• nontoxic with minimal or no side pharmaceutical effects,
• should have selective distribution to target tissues.

Drug designing methods

Most important/critical step involved during drug designing is computation part i.e., a computational tool which increases the effectiveness of drug molecule inside the body by making it more precise, and pharmaceutically active. Salient features of such drug design software include:

Affinity Automated, flexible docking:

• Applies the free energy of the ligand/receptor complex to spontaneously discover the optimal binding modes of the ligand to the receptor (energy-driven method) through AutoDock (Automated Docking of Flexible Ligands to Receptors),
• It comprises of three distinct computer programs, including

(i) AutoDock - performing ligand docking to a set of grids with the targeted protein,
(ii) Auto Grid for pre-calculating the atomic affinities, and
(iii) Auto Tors set up will be treated as movable in the ligand,

• Deliver a programmed process for forecasting the interactions of ligand - biomolecular target and helps to narrow the conformational opportunities and identify the suitable structures,
• Applies a Monte Carlo (MC) simulated annealing (SA) technique for the exploration with an extraordinary energy estimation using grid-based molecular affinity potentials,
• Reported as a potential approach for docking a flexible ligand into the binding site of a static protein. Application of flexible docking includes virtual screening, protein-protein docking, combinatorial library design, X-ray crystallography, SBDD, and biochemical mechanism studies.

• SBDD (Structure-based drug design) program build to aid the design of combinatorial libraries,
• Prediction of the software is applied to find out nanomolar inhibitor Cathepsin Ds.

RATIONAL DRUG DESIGN APPROACHES

Three-dimensional (3D) Structure of Biological Targets

A systemic pharmacological approach facilitates the in-depth understanding of how cells work on a large scale resolution and detailed examination in order to fabricate the therapeutic chemical compounds. Accordingly, the field of system biology helps in understanding the unprecedented molecular instruments to model and tinker with biological phenomena. Similarly, systems pharmacology provides an alternative to overcome most issues in critical steps of the drug discovery pipeline, from the inception of the target idea through clinical evaluation. In this scenario, the role of high-resolution three-dimensional (3D) structures of proteins and complexes has been recognized by the researchers as fundamental for both systems biology and the rational design of drug molecules. The ligand/enzyme binding modes are very specific to the enzyme conformations, and approach is capable of finding the best ligand/enzyme complexes. This leads to the computational analog of the experimental "SAR by NMR" and "tether" pathway, which allows building block approach for developing potent therapeutic molecules. In recent time, there are few ongoing areas where these drugs are prepared which are listed below:

Targeting the dopamine D 3 receptor (D3 R)

Dopamine is a neurotransmitter hormone which is distributed in both the periphery and the central nervous system (CNS). Dopamine (IUPAC name: 4-(2-amino ethyl) benzene-1,2-diol) is a biomolecules compound that acts as a catecholamine neurotransmitter and a hormone. Dopamine is also available in most, if not all, immune cells and accumulating pharmacological and genetic evidence has indicated a vital role of dopamine in the regulation of inflammatory responses involved in the autoimmune disorder. So the goal of a research is to provide a way to get access to

this target site and provide the effective drugs. There are many receptors but the physiological effects of dopamine are affected by five closely related yet functionally distinct G protein-coupled receptors (GPCRs) that are further categorized as into five subtypes: D1, D2, D3, D4 and D5 receptors, encoded in humans by genes DRD1, DRD2, DRD3, DRD4 and DRD5, respectively. Many studies have revealed that D Rs can exert some of their biological effects through alternative cAMP-independent signaling pathways involving ion channels, receptor tyrosine kinases, protein kinase B, nitrogen-activated protein 5kinase (MAPK) or proteins such as 2-arrestins.
The main focus is on the central nervous system which is linked with the functional and biological properties of D3R. Since, the D3R is a target of pharmacotherapeutic interest in the ability of neurological and neuropsychiatric disorders, including Parkinson's disease (PD), depression, restless leg syndrome (RLS), schizophrenia and drug addiction. The discovery of the D1R-D3R heteromer in 28 native tissues provides a novel insight and explains how these receptors may function in an integrated way.

Progress in structure-based drug design against influenza A virus

Influenza is caused by acute influenza virus infection and resulted in significant morbidity and mortality in humans. When researchers are preparing to combat the anticipated global outbreak of the deadly H5N1 avian influenza, another pandemic of influenza subtype, the H1N1 swine influenza, had existents the world over four continents and almost all countries from April of 2009 to May of 2010. Extrapolating the statistical results in Pittsburgh to the entire US population, Zimmer and Burke estimated that 62.9 million peoples became infected in the 2009- H1N1 influenza pandemic. In the same era, Centers for Disease Control and Prevention (CDC) reported that approximately 60.8 million cases were infected with pandemic influenza A (H1N1) virus (pH1N1) with 274,304 hospitalizations and 12,469 deaths due to pH1N1.Until today only three anti-influenza drugs have been approved by FDA:

• Rapivab (peramivir),
• Relenza (zanamivir),

• Tamiflu (oseltamivir phosphate)

The commercial drugs oseltamivir and zanamivir were designed based on the structure of target protein neuraminidase (NA) of the influenza virus. Zanamivir has a hydrophilic glycerol side chain, which can significantly reduce its octanol--water partition coefficient (logPo/w). Therefore, zanamivir is formulated as a micronized dry powder for inhalation to inhibit the neuraminidase molecule active site on the surface of the influenza virus. In contrast to zanamivir, oseltamivir has the chemical substitutions of the hydrophobic L-ethylpropoxy group and the guanidine group with an amine, which reduces the polarity and increases the hydrophobicity of the compound. Oseltamivir can, therefore, be formulated as an oral drug that is very convenient for patients. In the clinical treatments, oseltamivir was used as a powerful weapon, however, both H1N1 and H5N1 viruses have acquired drug resistance to oseltamivir, and to a less degree to zanamivir as reported in the clinical cases in North America and Europe.

Drug Design for HER2 Receptor

Human Epidermal Growth Factor Receptor 2 (HER2) also referred as ErbB2, c-erbB2 or HER2/neu, is a 185 kDa protein (p185) with an intracellular tyrosine kinase domain and an extracellular ligand binding domain. HER2 plays an important role in cell growth, survival, and differentiation in a complex manner and mediates major signalling pathways. Several HER2 inhibitors passed the clinical trials including Iressa (Gefitinib), Tarceva (Erlotinib), and Tykerb (Lapatinib). These drugs are all ATP competitive inhibitors. However, these drugs were known to have side effects on the majority of patients within a year of treatment. Side effects include skin rashes, scalp lesions, and swelling on fingers and toes. Huang, Lee developed a molecular simulation of HER2 model using Accelrys Discovery Studio 2.5 (DS 2.5). Authors observed hydrogen bond interactions, salt-bridge formations and pi-stacking between the ligands and Phe731, Lys753, Asp863 and Asp808 of HER2 protein. Notably, all the top candidates had H-bond donor substructures that interact with Asp863 and Asp808. From the ligand-based approach, four important pharmacophore features were reported including two hydrogen bond acceptor; one hydrogen bond donor and one hydrophobic component and considered as the potential HER2 inhibitors.

Quantitative Structure-Activity Relationships (QSAR)

Structure-Activity Relationship (SAR) is a predominant technique to relate the structure-related properties (biochemical structure of the interested therapeutic compound) and target properties (biological activity of the interested therapeutic compound). Theoretically, QSAR is relating the chemical structure to a chemical property (e.g., water solubility) or biological activity. Both the qualitative SARs and quantitative SARs are referred to QSARs. There is a scarcity of knowledge between identified hits and necessary steps should be taken to convert the identified hits in preclinical trials. Historically, endogenous ligands were marked long before their cognate bimolecular target site was isolated and their chemical and stereo structure was established. Earlier published data on ligands/biomolecules with chemical structure was basic and scarce compared with the latest experimental chemistry details. However, that previous information repeatedly demonstrated that there is a lack of understanding, knowledge and hypotheses on the physiological and pharmaceutical parameter of these ligands. Structure-based approaches have the following advantages:

• A reasonable number of initial chemical lead may be envisaged (it is often the case that a broad screening approach would give so may rising to many initial 'hits' which may be difficult to prioritize);

• The structural knowledge within the endogenous peptide may be used in optimizing the initial chemical lead(s) and to build in receptor selectivity;

• Since the beginning part of the drug design is endogenous peptide against, therefore, conceivable that non-peptide antagonists or agonists may be generated (broad screening very rarely provides non-peptide agonists);

• If successful, such an approach should result in the rapid existence of novel non-peptide receptor ligands.

Purpose of QSAR

Following are the purpose of QSAR:

(i) To calculate biological activity and physicochemical quality by rational means,

(ii) To comprehend and rationalize the activity of action within a group of chemicals,

(iii) Economic product amplification,
(iv) Predictions could lower the need for lengthy & expensive animal tests. Reduction of animals tests and discomfort to animals,
(v) Other areas for growth are green and greener chemistry to increase efficiency and eliminate waste QSARs are also models or mathematical relationship (often a statistical correlation), which relates a structure-related property to the presence or absence, or potency of another property or activity of interest. Brown and Fraser first developed the relationship between chemical composition and physiological relations in the mid of 18th century. QSARs most basic mathematical form is:

$$Activity = f\left(physiochemical\ and/or\ structural\ properties\right) + error \tag{1}$$

The error includes a model error (bias) and observational variability, that is, the variability in observations even on a correct model. Organisation for Economic Cooperation and Development (OECD) reported the framework for the development of (Q)SAR model:
(i) A data set that provides activity (usually measured experimentally) for a group of chemicals (i.e., the dependent variable). This group of chemicals is typically defined by some selection criteria,
(ii) Structural criteria or structure-related property data set for the same group of chemicals (i.e., the independent variables),
(iii) A means of relating (usually a statistical analysis method) these two data arrays. Methods for relating structure to activity range from the simple, linear regression, through more complex approaches such as partial least squares analysis to the most complex, machine learning techniques such as neural networks.

Uses of (Q)SAR to fill data gaps

(Q)SAR may be used to predict properties and activities for untested compounds, which are in the same group of chemicals.

Table 1: (Q)SAR approaches[21]

	Compound A	Compound B	Compound C	Compound D	Compound E
Structure X	+	+	-	+	+
Property Y	1	2	3	4	5
Activity Z	+	+	-	+	?
Activity T	10	15	5	?	30

Table 1 described the approaches of (Q)SAR. An examination of the data in table 1, in particular for Structure X reveals chemicals A, B, D, and E form a group of the similar chemical as Structure X is common to all four compounds (but not to chemical C). For this group of chemicals, a qualitative relationship is observed between Structure X and Activity Z. Using this relationship, measured values of Activity Z for compounds A, B and D can be used to fill the data gap of Activity Z for the untested compound E. This is done by reading-across from compound A, B, and D to compound E (predicting Activity Z to be positive for Compound E). For this same group of similar chemicals, the relationship between Property Y and Activity T is quantitative and modeled as [Activity T = 5.0 (Property Y) + 5.0]. Using this (Q)SAR model the potency of Activity T for compound D is predicted to be.

Applications of QSAR

QSAR is approved by many authorities including the European Union, REACH (Registration, Evaluation, Authorization, and Restriction of Chemicals) regulation. The chemical descriptor space whose convex hull is obtained or get by a specific training group of chemicals is known as training set's applicability domain. Prediction properties of biochemical’s are located outside the applicability domain with lower reliability (on average) when compared to prediction within the applicability domain. The assessment of the reliability of QSAR outcome remains a research topic. The QSAR mathematical equations utilized to predict the biological mechanism of discovered molecules before their synthesis.

FACTORS TO BE CONSIDER DURING DRUG DESIGN

Especially in the part of older drug discovery where high sensitivity and rapid sample throughput is momentary and where samples are pooled or "cocktailed" ranked as dosing or analysis. Several factors are considered while making any chemical compound as a drug. When an entry of drug molecule is observed in the micro level of inner part of the body, it can able to alternate the biological pathway which affected human health also. So while making a new drug researcher should consider many case and effect which are mentioned below:

Safety and Efficacy

Human life is very costly as it never gets by any form and newly coming unwanted particles in the human body totally change their lifestyle. When an unwanted particle enters through the Gastrointestinal System or any mode, it may affect their immune system. Hence, it's very important to design and formulate a new drug molecule which should not intercept the functioning of the body. Drug companies seeking to sell a drug in the world must first test it. This test is obtained by various ways like a LIMIT TEST or ASSAY TEST. After successful completion of all these analysis drug manufacture may approach CDER (Centre for Drug Evaluation and Research) to certify safe and granted for human consumption. A team of CDER statisticians, chemists, pharmacologists, and other scientists gives their own thoughts in the company's work and proposed labelling.

Drugs should be well absorbed orally and bioavailable

Drugs that we take inside human body have the capacity to degrade it. So the ultimate goal is to prepare drugs in such a way that after all degradation the quantity, or % which required in body got that. Bioavailability is the part of the administered drug that encounters the systemic circulation in a chemically unchanged form. For instance, if 500 mg of a drug is administered orally and 50 mg of this drug is absorbed unchanged, then the bioavailability is 0.1. When the drug is given orally, only part of

the administered dose appears in the plasma. By plotting plasma concentrations of the drug versus time, one can measure the area under the curve (AUC). This curve reflects the extent of absorption of the drug. Bioavailability of a drug administered orally is the ratio of the area calculated for oral administration compared with the area calculated for IV injection.

Metabolic stability and half-life

Metabolic stability refers to the exhibition of compounds to bioactive in the reference of selecting and/or designing drugs with favorable pharmacokinetic properties. As we know that every drug has their own life in term of pharmaceutical effect inside the body and the main role of a pharmacist is to discover a new drug which has a long stability. But due to environmental conditions, these drugs may degrade easily. Since these factors plays a vital role in defining the pharmacological and toxicological profile of drugs. Optimization of metabolic stability is a crucial part of the drug discovery process because the ADME profile of the drug will be evaluated based on the scope and depth of the metabolic stability issues.

Non-toxicity and minimal side effects

Targeted drug delivery, is also known as SDD (smart drug delivery), is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others. So the priority is to design drugs in such a manner that it only effects on the active site and not affect the rest parts of the body. For instance, Paracetamol (acetaminophen) is a pain reliever and a fever reducer and work on the active site where the actual pain occurs, but beside it, it also blocks the COX 2 hormones which are produced by the pancreas to rebuild or reproduces the inner layer of the stomach. As a result, when we access paracetamol, it produces side effect as ulcer, so the goal should produce the drugs that have minimum side effect

CONCLUSION

In the early 60’s, drug discovery was based on screening thousands of natural and synthetic compounds for their biological activity. Since the early 1980’s, the contribution of molecular biology, protein crystallography, and computational chemistry brought the Rational Drug Design - novel approach for predicting binding affinity. Increase in computation speed and novel simulation tools over the decade make computer simulation as an extremely attractive approach in the development of new drugs. Still, the success of the computer simulations can significantly be increased by enabling a greater number of researchers and validation of the simulations with experimental work.

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