WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Review Article on Drug Design and Discovery

[1]Miss. Bamane Kiran Chandrashekhar, [2]Miss. Vilaskar Harshada, [3]Mr. Shipate Swapnil M.

[1,2,3]MSS's College of Pharmacy, Medha, Satara.

ABSTRACT

Drug discovery is the process by which drugs are discovered and designed. It is a process that aims at identifying a compound therapeutically useful in treating disease. The method of drug discovery involves the identification of the development of a drug from an initial idea to its entry into the market is a very complex process that can take around 5-10 years and cost $1.7 billion. The idea for new development can come from various sources, including the current necessities of the market, new emerging diseases, academic and clinical research, the commercial sector, etc. Once a target for discovery has been chosen, the pharmaceutical industries or the associated academic centers work on the early processes to identify the chemical molecules with suitable characteristics to make the targeted drugs.

Introduction

Drug discovery can be described as the process of identifying chemical entities that have the potential to become therapeutic agents. A key goal of drug discovery campaigns is the recognition of new molecular entities that may be of value in the treatment of diseases that qualify as presenting unmet medical needs. These diseases do not have definitively useful therapies and are actually or potentially life-threatening. Marketed drugs at this point represent a relatively small number of drug target types. Drugs targeted against G-protein coupled receptors, nuclear (hormone) receptors, and ion channels represent slightly less than 50% of the marketed drugs. By far, drugs directed against enzymes represent the largest portion of marketed drugs. Expansion into new types of drug targets may be necessary to fill certain therapeutic voids, but a matter of great intellectual challenge is how to choose a target likely to be of value, especially when venturing into less well-explored types of drug targets[1].

Drug Design and Discovery

Drug design and discovery is the process of developing new medications to treat diseases or improve the effectiveness of existing treatments. It involves identifying potential drug targets, designing and synthesizing molecules that interact with those targets, and testing their safety and efficacy in preclinical and clinical trials.

Process-

I. The process typically begins with target identification, which involves identifying the molecular structures or biological pathways involved in a disease. This information can be obtained through a variety of approaches, including genetic studies, bioinformatics, and high-throughput screening [2].

II. Once a target has been identified, the next step is to design and synthesize molecules that can interact with it in a specific way. This can involve a range of techniques, including computer modeling, medicinal chemistry, and combinatorial chemistry.

III. The synthesized molecules are tested in vitro and in vivo to assess their efficacy and safety. In vitro tests typically involve testing the compounds on cells or tissues in a lab setting, while in vivo tests involve testing them in animal models[3].

IV. If the compounds show promise in preclinical testing, they may then move on to clinical trials in humans. These trials involve testing the drugs on increasingly large groups of patients to assess their safety, efficacy, and optimal dosages[4].

V. If a drug completes clinical trials, it can then be approved for use by regulatory agencies such as the FDA or EMA, and marketed to healthcare providers and patients[5]. The entire drug design and discovery process can take many years and involve significant investment, but it can ultimately lead to new treatments that improve health and save lives.

Target Identification

Target identification is a critical step in the drug design process. It involves identifying the molecular structures or biological pathways that are involved in a disease, and that can be targeted by drugs to several approaches can several approaches that can be used for target identification, including:

a) Genetics: The identification of genes that are associated with a disease can provide clues to potential drug targets[6]. This can involve sequencing the genomes of affected individuals or studying genetic mutations that are linked to the disease.

b) Bioinformatics: This involves using computational methods to analyze large datasets of genetic and biological information to identify potential drug targets [7].

c) High-throughput screening [8]: This involves testing large numbers of molecules or compounds to identify those that have a specific effect on the disease target.

d) Reverse pharmacology: This approach involves identifying drugs that are effective in treating a particular backward and then working backward to identify the molecular targets that they interact with[9].

e) Knowledge-based approaches: These rely on existing knowledge of the disease and its underlying mechanisms to identify potential drug targets.

Once a potential target has been identified, researchers can use a variety of techniques to validate it and determine whether it is a viable drug target. This can include in vitro and in vivo experiments to study the target's role in the disease, as well as tests to determine the target's druggability (i.e., whether it is amenable to drug binding and inhibition). Overall, target identification is a crucial step in the drug design process, as it lays the foundation for the subsequent steps of drug discovery and development.

Combinatorial chemistry

Combinatorial chemistry is a powerful approach used in drug design and discovery, in which large numbers of molecules are synthesized simultaneously or in a rapid sequence to identify compounds with desirable biological properties.

Methods for conducting combinatorial chemistry, including:

a. Solid-phase synthesis: In this method, the starting material is attached to a solid support, and various reagents are added to create a library of molecules. After synthesis, the compounds are cleaved from the support and screened for their biological activity.

b. Solution-phase synthesis: In this method, the synthesis is carried out in a solution, and various reagents are added to create a library of molecules. The resulting mixture of compounds is then screened for biological activity[10].

c. Parallel synthesis: In this method, a series of reactions are conducted in parallel, each producing a different compound. This approach allows for the rapid synthesis of a large number of compounds.

d. Once a library of compounds has been synthesized, they are typically screened for their biological activity using a variety of assays. This can include screening for binding to a particular target, inhibition of enzymatic activity, or effects on cell growth or viability.

Overall, combinatorial chemistry is a valuable tool in drug discovery, as it allows for the rapid creation and screening of large libraries of molecules, which can help to identify new drug candidates or optimize existing ones.

High-throughput screening (HTS)

It is a key approach used in drug discovery to quickly and efficiently screen large numbers of compounds for their biological activity.

HTS typically involves using robotic systems to rapidly test thousands or even millions of compounds in a short period[11]. The compounds are typically tested for their ability to interact with a particular target or to modulate a specific biological pathway.HTS can be used to identify lead compounds for drug development, to optimize the properties of existing drugs, or to identify new targets for drug discovery. The process can be broken down into several steps:

1. Selection of a target: The first step in HTS is to select a target for screening. This may involve identifying a protein or other molecular structure that is involved in a particular disease or biological process.

2. Compound libraries: Once a target has been selected, a library of compounds is assembled for screening. This may involve synthesizing new compounds or selecting from existing libraries of compounds.

3. Assay development: Next, an assay is developed to measure the activity of the compounds on the target. This may involve designing a biochemical or cell-based assay that can be easily automated.

4. Screening: Once the assay has been developed, the compounds are screened against the target in a high-throughput manner[12]. This may involve using robotic systems to dispense and test large numbers of compounds.

5. Data analysis: Finally, the data from the screening is analyzed to identify compounds that show activity against the target. These compounds may then be further characterized and optimized for drug development.

Overall, HTS is a powerful tool in drug discovery that allows researchers to quickly and efficiently screen large numbers of compounds for their biological activity.

3-D QSAR in drug design

Quantitative structure-activity relationships (QSAR) have been applied for decades in the development of relationships between the physicochemical properties of chemical substances and their biological activities to obtain a reliable statistical model for the prediction of the activities of new chemical entities. The fundamental principle underlying formalism is that the difference in structural properties is responsible for the variations in the biological activities of the compounds. In the classical QSAR studies, affinities of ligands to their binding sites, inhibition constants, rate constants, and other biological endpoints, with atomic, group, or molecular properties such as lipophilicity, polarizability, electronic and steric properties (Hansch analysis) or with certain structural features (Free-Wilson analysis) have been correlated[13].

Hansch Analysis

Hansch analysis is the investigation of the quantitative relationship between the biological activity of a series of compounds and their physicochemical substituent or global parameters representing hydrophobic, electronic, steric, and other effects using multiple regression correlation methodology. Hansch equation for dealing with extended hydrophobicity ranges[14].

$\text{Log } 1/C = - a (\log P)^2 + b. \log P + c \sigma + k$

❖ **Application**

1. Hansch analysis can be used to describe complex biological data, where several different transport processes and equilibria contribute to the overall structural activity relationships.

2. Instead of wasting thousands of animals nowadays enzyme inhibition, receptor binding, and cell culture data are used to derive the activity profiles [15].

Free Wilson Analysis

The free Wilson Model is easy to apply .especially in the early phase of structure-activity analyses it is a simple method to derive substituent contributions and to have a first look at their possible dependence on different physiochemical properties[16].

$BA = ai\ xi + u$

❖ **Limitation**

1. Only a small number of new analogs can be predicted from a free Wilson analysis.
2. It is limited to linear add structure-activity relationships.

Structure-Based drug design

SBDD is a more specific, efficient, and rapid process for lead discovery and optimization because it deals with the 3D structure of a target protein and knowledge about the disease at the molecular level. Among the relevant computational techniques, structure-based virtual screening (SBVS), molecular docking, and molecular dynamics (MD) simulations are the most common methods used in SBDD. These methods have numerous applications in the ligand–protein ligand–protein and–protein interactions, and evaluation of the conformational changes occurring during the docking process. In recent years, developments in the software industry have been driven by a massive surge in software packages for efficient drug discovery processes. Nonetheless, it is important to choose outstanding packages for an efficient SBDD process. [17].

CADD

Drug discovery utilizes chemical biology and computational drug design approaches for the efficient identification and optimization of lead compounds. Chemical biology is mostly involved in the elucidation of the biological function of a target and the mechanism of action of a chemical modulator. On the other hand, computer-aided drug design makes use of the structural knowledge of either the target (structure-based) or known ligands with bioactivity (ligand-based) to facilitate the determination of promising candidate drugs[18]. The term "design" is to be understood broadly to encompass conceptualization, synthesis, realization, and evolution of artifacts, processes, and systems (both natural and artificial).

Pharmacophore

A pharmacophore is a molecular frame that describes the vital features responsible for the biological activity of a molecule[19]. Pharmacophore models are generated to increase the understanding–of protein-ligand–protein interactions. They can be employed in identifying new molecules that satisfy the pharmacophore requirements and are thus expected to be active.

Docking

Essentially, molecular docking aims to give a prediction of the ligand-receptor complex structure using computation methods [20]. Docking can be achieved through two interrelated steps: first by sampling conformations of the ligand in the active site of the protein; then ranking these conformations via a scoring function. Ideally, sampling algorithms should be able to reproduce the experimental binding mode and the scoring function should also rank it highest among all generated conformations. From these two perspectives, we give a brief overview of basic docking theory[21].

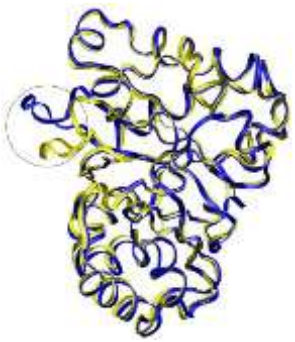

Figure 1 Fig. Superimposed apo- (in yellow) and holo- (in blue) crystal structures of triosephosphate isomerase. PDB code 1YPI and 2YPI, respectively. The 11 residue-loop composed of the landing site is the only region that has large motion upon ligand binding (in a circle).

Conclusion

Drug design and discovery is a complex and multifaceted process that involves identifying potential drug targets, designing and synthesizing molecules that interact with those targets, and testing their safety and efficacy in preclinical and clinical trials.

The process typically begins with target identification, which involves identifying the molecular structures or biological pathways involved in a disease. This information can be obtained through a variety of approaches, including genetic studies, bioinformatics, and high-throughput screening.

Once a potential drug target has been identified, researchers can use a variety of techniques to design and synthesize molecules that can interact with the target in a specific way. This can involve a range of techniques, including computer modeling, medicinal chemistry, and combinatorial chemistry.

The synthesized molecules are tested in vitro and in vivo to assess their efficacy and safety. In vitro tests typically involve testing the compounds on cells or tissues in a lab setting, while in vivo tests involve testing them in animal models. If the compounds show promise in preclinical testing, they may then move on to clinical trials in humans. These trials involve testing the drugs on increasingly large groups of patients to assess their safety, efficacy, and optimal dosages. If a drug completes clinical trials, it can then be approved for use by regulatory agencies such as the FDA or EMA, and marketed to healthcare providers and patients.

Overall, drug design and discovery is a time-consuming and resource-intensive process, but it has the potential to yield new treatments that improve health and save lives. The development of new drugs is essential to address unmet medical needs to improve the health outcomes of patients suffering from diseases.

Reference

1. Maria Batool, Sangdun Choi, National library of medicine - A structure-based drug discovery paradigm 2019 Jun; 20(11): 2783.
2. Monica scene, Vlado dancik, Bridget K Wagner, Target identification and mechanism of action in chemical biology 2017, 2013 Apr; 9(4): 232–240.
3. William Y. Kim and Norman E. Sharpless; Drug efficacy testing in mice .2013 2012; 355: 19–38.
4. JP Hughes, S Rees, SB Kalindjian, and KL Philpott, Br J Pharmacol. 2011 Mar; 162(6): 1239–1249.
5. Shahin Akhondzadeh, Ph.D., FBPharmacolS, Editor in Chief, Avicenna J Med Biotechnol. 2016 Oct-Dec; 8(4): 151.
6. Matteo Floris,Stefania Olla, David Schlessinger,and Francesco Cucca, 2018 May 23. doi: 10.1016/j.tig.2018.04.004 34(7): 558–570.
7. Ardeshir Bayat, MRC fellow, BMJ. 2002 Apr 27; 324(7344): 1018–1022.

8. M.S. Attene-Ramos, Encyclopedia of Toxicology (Third Edition), 2014, Pages 916-917.
9. Ashwinikumar A. Raut, Mukund S. Chorghade Ashok D.B. Vaidya, Reverse Pharmacology 2017, Pages 89-126.
10. Jianbin Wu,a,b Guanghui An,b Siqi Lin,b Jianbo Xie,b Wei Zhou,a,b Hao Sun,a Yi Pan,a and Guigen Licorresponding authora,b, Chem Commun (Camb). 2014 Feb 7; 50(10): 1259–1261.
11. M.S. Attene-Ramos, C.P. Austin, M. Xia, High Throughput Screening, Encyclopedia of Toxicology (Third Edition) 2014, Pages 916-917.
12. . M.S. Attene-Ramos, C.P. Austin, M. Xia, High Throughput Screening, Encyclopedia of Toxicology (Third Edition) 2014, Pages 916-917.
13. Jitender Verma 1, Vijay M Khedkar, Evans C Coutinho, 3D-QSAR in drug design-a review, 2010;10(1):95-115.
14. Bharat Jhanwarb, Vandana Sharmaa, Rajeev K Singlaa, Birendra Shrivastava, QSAR - Hansch Analysis and Related Approaches in Drug Design, Pharmacologyonline 1: 306-344 (2011).
15. Anju Verma, Megha Verma, and Anchal Singh, Animal tissue culture principles and applications, Animal Biotechnology. 2020: 269–293.
16. Hongming Chen, Beyond the Scope of Free-Wilson Analysis: Building Interpretable QSAR Models with Machine Learning Algorithms June 2013 Journal of Chemical Information and Modeling 53(6):1324-36.
17. JP Hughes, S Rees, SB Kalindjian, and KL Philpott, Principles of early drug discovery, Br J Pharmacol. 2011 Mar; 162(6): 1239–1249.
18. Stephani Joy Y. Macalino, Vijayakumar Gosu, Sunhye Hong & Sun Choi, Role of computer-aided drug design in modern drug discovery 1686–1701 (2015).
19. Muhammed Tilahun Muhammed, Esin Aki-Yalcin Pharmacophore Modeling in Drug Discovery: Methodology and Current Status; 2021;8(3):749–62.
20. Francesca Stanzione, Ilenia Giangreco, Jason C. Cole, Use of molecular docking computational tools in drug discovery, Progress in Medicinal Chemistry Volume 60, 2021, Pages 273-343.
21. Xuan-Yu Meng, Hong-Xing Zang,& Meng Cui - Molecular Docking: A powerful approach for structure-based drug discovery 2011 Jun 1; 7(2): 146–157.
22. Tejaswi Santosh Ubhe, A Brief Overview on Tablet and Its Types October 2020.