ROLE OF LEAD MOLECULES IN CADD

Ravikant Vishwakarma, Manoj Kumar Yadav, Piyush Yadav, Shashikant Maury, Vishal Prajapati

Prasad Institute of Technology, Jaunpur, UP, India

(Department of Pharmacy)

ABSTRACT:-

The word "drug design" refers to the objective creation of new drugs. Random screening of synthetic compounds, synthetic of biologically active compounds based on naturally occurring drugs, synthesis of structural analogues of naturally occurring lead molecules, and implementation of the bioisosteric theory are some of the methods that have been used. As a result, the latest trend in drug design is to either fully innovate a lead or optimise an existing lead. A leading molecule is another name for a lead. The lead is a prototype molecule with the desired biological or pharmacological activity, but it may also have a number of undesirable properties, such as high toxicity, other biological activities (side effects), insolubility, or metabolism issues, which are simple to manipulate once established. This is a fairly straightforward procedure. The real challenge is identifying such a lead molecule and determining the best bioactive positions on its simple skeleton.

KEYWORDS:-

CAAD, Lead molecule, Prototype, Analogues, Combinatorial Chemistry, Docking

INTRODUCTION:-

All computer-assisted techniques used to discover, design, and optimise biologically active compounds with the potential to be used as drugs are referred to as computer aided drug design. Prior to clinical trials, the drug development phase entails three pre-clinical stages: target selection, lead identification, and clinical candidate selection. Structure-based computer-aided drug design (CADD) using docking techniques, virtual screening and library design, as well as target/structure focusing combinatorial chemistry, has become a powerful tool in the multi-step phase of drug development, thanks to rapid developments in structural biology and computer technology.[1]

CADD speeds up drug discovery by combining current drug and disease knowledge with inter-disciplinary contributions from other fields. This procedure makes extensive use of mathematical models and modelling methods focused on the assessment of possible drug safety risks and the design of new trials. Fast expansion in this area has been made possible by advances in software and hardware computational power and sophistication, identification of molecular targets, and an increasing database of publicly available target protein structures.[2]

CADD is being utilized to identify active drug candidates, select leads and optimize leads i.e. transform biologically active compounds into suitable drugs by improving their physicochemical, pharmaceutical, ADMET/PK properties. The term biological target is frequently used in pharmaceutical research to describe the native protein in the body whose activity is modified by a drug resulting in a desirable therapeutic effect, in this context, the biological target is often referred to as a drug target.[3]

The most common drug targets of currently marketed drugs include as below-

• Enzymes
• Ligand-gated ion channels
• Voltage-gated ion channels
• G protein-coupled receptors
• Nuclear hormone receptors
• Transporters
• DNA, Integrins, Miscellaneous

LEAD MOLECULE:-

Lead molecule is prototype molecule that has a number of attractive characteristics including the desirable biological & pharmacological activity but may have undesirable characteristics such a high toxicity, other biological activity (absorption difficulty, insolubility or metabolism problem). Lead compounds are sometimes called developmental candidates. This is because the discovery and selection of lead compounds occurs prior to preclinical and clinical development of the candidate.[4]

Lead compounds are typically used as starting points in drug design to give new drug entities. Drug design strategies can be used to improve the compound's pharmacodynamic and pharmacokinetic properties.[5]

The resulting compounds from drug design go through a series of preclinical studies and become clinical candidates if the compounds don't exhibit adverse effects or toxicity during in vitro and in vivo studies. After going through marketing obstacles and clinical trials, compounds that pass are released on the market as new drug entities. New drug entities are generally monitored for safety after their release on the market. This is known as postmarketing surveillance or Phase IV clinical trial.[6]

DISCOVERY OF LEAD MOLECULE:-

Before lead molecules can be discovered, a suitable target for rational drug design must be selected on the basis of biological plausibility or identified through screening potential lead molecules against multiple targets. Drug libraries are often tested by high throughput screening (active compounds are designated as "hits") which can screen molecules for their ability to inhibit (antagonist) or stimulate (agonist) a receptor of interest as well as determine their selectivity for them.[7]

A lead molecule may arise from a variety of different sources. Lead molecules are found by characterizing natural product, employing combinatorial chemistry, or by molecular modeling as in rational drug design. Chemicals identified as hits through high-throughput screening may also become lead molecules.Once a

lead molecule is selected it must undergo lead optimization, which involves making the compound more "drug-like". This is where Lipinski's rule of five comes into play, sometimes also referred to as the "Pfizer rule" or simply as the "rule of five". Other factors, such as the ease of scaling up the manufacturing of the chemical, must be taken into consideration.[7]

SOURCES OF LEAD MOLECULES:-[6]

1. Natural substances
2. Chemical libraries
3. Computational medicinal chemistry

1.NATURAL SUBSTANCES:-

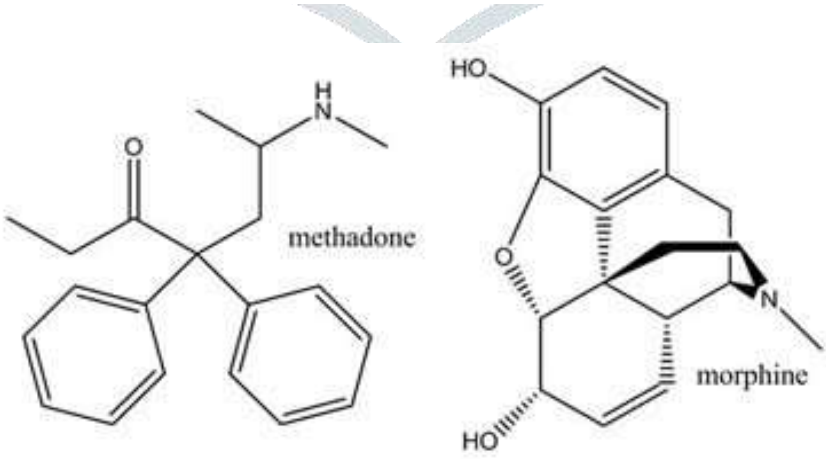
Most drugs in clinical use are natural products or derivatives and analogues of natural substances. Many natural products were used as lead molecule. A vast amount of natural substances contain structural features that are difficult to achieve through synthetic organic chemistry. The structural complexity of many natural substances motivates the development of simpler analogues.

EXAMPLES:-

a) PLANTS:-

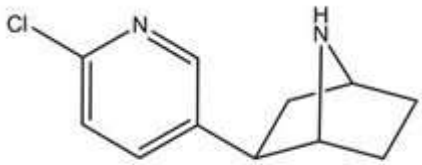
Small molecule pharmaceuticals and lead molecule are abundant in plants.

Methadone is a structurally simpler acyclic analogue of the opioid analgesic morphine that is used to treat opioid addiction. Morphine is the most common opiate extracted from opium, which is the dried latex obtained from the opium poppy Papaver somniferum:



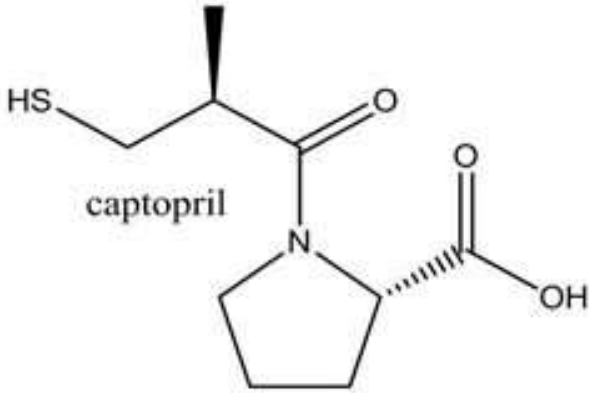
b) ANIMALS:-

Epibatidine is a powerful analgesic derived from the epipedobates tricolour tissue (phantasmal poison frog). Epibatidine is hundreds of times more powerful than morphine. However, since the compound's therapeutic dose is similar to its toxic dose, synthetic analogues are being developed. Epibatidine is a possible lead molecule for new analgesics.



epibatidine

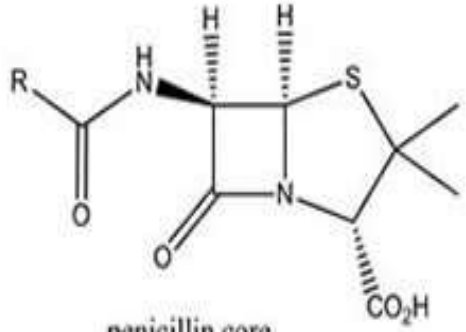
Failed Phase II clinical trials



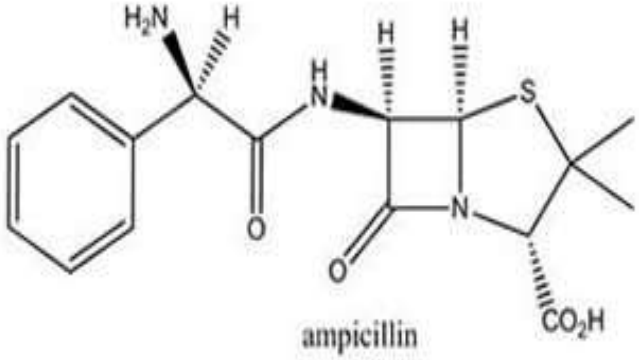
Teprotide is a nonapeptide isolated from the venom of *bothrops jararaca* (Brazilian pit viper). It is a known inhibitor of the Angiotensin Converting Enzyme (ACE). Teprotide was used as a lead compound for the development of the ACE inhibitor, captopril.

c) MICROORGANISM:-

Serendipity led to the discovery of penicillins in penicillium fungi. Natural penicillin derivatives with improved efficacy, such as ampicillin, a broad-spectrum antibiotic, have been developed.

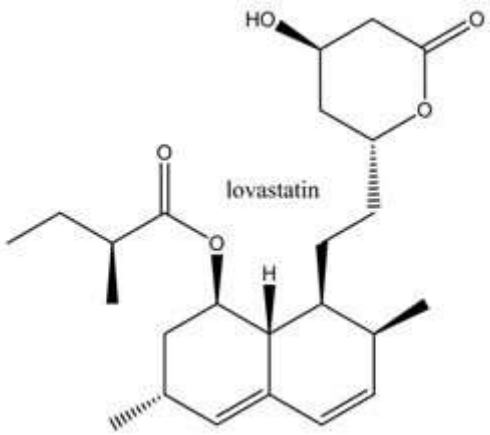


penicillin core
R = variable group



ampicillin

The fungal molecule, lovastatin was one of the molecules that served as the lead for the development of other statins (HMG-CoA reductase inhibitors). Lovastatin is produced by several species of fungi such as the common edible mushroom, *pleurotus ostreatus* (oyster mushroom).



2.CHEMICAL LIBRARIES:-

A lead molecule may be found in chemical libraries. Libraries can be searched for possible leads through high throughput screening methods. The associated database that stores the library's information can also provide useful information. Through computerised searching methods, lead molecules may be found.

3.COMPUTATIONAL MEDICINAL CHEMISTRY:-

Computers have also been used to design novel drugs. For instance, if the 3D structure of a protein has been resolved though X-ray crystallography, it is possible use molecular modelling software packages to study the binding site of the macromolecule.In silico, molecules can be designed that is able to fit and bind to the binding site. Crystallographic studies and computational methods were used in the development of the anti-influenza drug oseltamivir, as well as the anti-hypertensive drug, aliskiren.

METHOD OF LEAD DISCOVERY

There are various method of lead discovery are-

I. RANDOM SCREENING:-

A provided series' molecules (both synthetic and naturally occurring) are all checked. Despite the fact that it requires more budget and manpower, this approach can be used to find leads with unusual activities. This technique was used to discover antibiotics including streptomycin and tetracycline.[8]

II. NONRANDOM SREENING:-

It's a tweaked version of random screening that was created to reduce random screening's excessive budgetary and manpower requirements. Only molecules with similar structure skeletons that are called lead are screened using this process.[8]

III. DRUG METABOLISM STUDIES:-

To shorten the time a drug stays in the body, metabolic biotransformation occurs with the aid of enzymes. The drug's structure has been altered to increase its polarity, allowing it to be excreted more quickly from the body. It is carried out regardless of whether the resulting drug metabolites have higher activity or toxicity. Sulphanilamide was discovered thanks to the metabolic structure.[9]

IV. CLINICAL OBSERVATION:-

The majority of medications have several pharmacological activities. The key operation is known as the therapeutic effect, while the other activities are known as the drug's side effects. Such drugs could be used as lead molecules for structural modifications to improve secondary effect potency.[10]

CONCLUSION:-

Computer-aided drug design (CADD) has been used in almost every phase of the drug development process. Over the last few years, there has been a lot of progress in the creation and implementation of novel approaches. As a result, both lead identification and lead optimization, which are key tasks in the drug development process, are made easier. The constant improvement in protein structure predictions has benefited greatly from structure-based de novo drug design. The dawn of widespread awareness of the synthetic accessibility of lead compounds, as well as concerted efforts to overcome it, has ushered in a bright future for de novo design. Furthermore, free energy perturbation guided lead optimization has been a huge success in terms of rapidly and significantly improving lead compound bioactivity. In assessing the consistency of lead compounds, a hybrid quantum mechanics/molecular mechanics approach has revealed a balance point between accuracy and performance. While computer-aided drug design is still in its infancy, given the many remarkable advances made in recent years, it is expected to play a much larger role in the near future.

ACKNOWLEDGEMENT:-

We would like to express our heartfelt gratitude to my esteemed professors, who provided me with a golden opportunity at each and every stage. We would like to express our gratitude to everyone who was directly or indirectly involved in the completion of this study. We are very grateful to my parents, who have always been supportive of us.

REFERENCES:-

1. Lewis RA (2011). "Chapter 4: The Development of Molecular Modelling Programs: The Use and Limitations of Physical Models". In Gramatica P, Livingstone DJ, Davis AM (eds.). Drug Design Strategies: Quantitative Approaches. RSC Drug Discovery. Royal Society of Chemistry. pp. 88–107. doi:10.1039/9781849733410-00088. ISBN 978-1849731669.
2. Azevedo WF, Dias R (Dec 2008). "Computational methods for calculation of ligand-binding affinity". Current Drug Targets. 9 (12): 1031–9. doi:10.2174/138945008786949405. PMID 19128212.
3. Becker OM, Dhanoa DS, Marantz Y, Chen D, Shacham S, Cheruku S, Heifetz A, Mohanty P, Fichman M, Sharadendu A, Nudelman R, Kauffman M, Noiman S (Jun 2006). "An integrated in silico 3D model-driven discovery of a novel, potent, and selective amidosulfonamide 5-HT1A agonist (PRX-00023) for the treatment of anxiety and depression". Journal of Medicinal Chemistry. **49** (11): 3116–35. doi:10.1021/jm0508641. PMID 16722631.
4. Siddiqui Anees Ahmad, Kumar Harish, Khisal Subuhi, "Computer-Aided Drug Design" CBS Publisher & Distributors. pp 12-14.
5. Hughes JP., Rees S., Kalindjian SB., Philpott KL., (March 2011). "Principles of early drug discovery". British Journal of Pharmacology. 162 (6):1239-1249. doi:10.1111/j.1476-5381.2010.01127.x. PMC 3058157. PMID 21091654
6. https://pharmafactz.com/modern-drug-discovery-lead-identification.
7. Schneider, Gisbert (2013). "Prediction of Drug-Like Properties". Landes Bioscience. Retrieved 20 November 2017.
8. Larson RS (2006) Methods in Molecular Biology: Bioinformatics and Drug Discovery. Department of Pathology, University of New Mexico School of Medicine, Albuquerque, NM 1: 227-228.
9. M. Trunzer, B. Faller, A. Zimmerlin Metabolic soft spot identification and compound optimization in early discovery phases using MetaSite and LC–MS/MS validation J Med Chem, 52 (2009), pp. 329-335
10. Wermuth, C. Selective Optimization of Side Activities: Another Way for Drug Discovery. J. Med. Chem. 2004, 47, 1303–1314.