Lead Compound: Approaches of CADD

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ABSTRACT:-

The process of designing new drugs with the aim of enhancing existing ones is referred to as "drug design." The synthesis of biologically active compounds based on naturally occurring drugs, and the synthesis of structural analogues of naturally occurring lead molecules are all examples of random screening of synthetic compounds and the application of the bioisosteric principle are only a few of the techniques that have been used. As a result, the most recent trend in drug development is to either completely reinvent a lead or optimise an established lead. Lead chemical structure can be used to make chemical alterations to improve potency, selectivity, or pharmacokinetic properties. Furthermore, freshly developed pharmacologically active moieties may lack drug-like properties, necessitating chemical modification before being studied physiologically or therapeutically. While computer-aided drug design is still in its infancy, it is projected to play a considerably larger role in the near future, given the many astonishing breakthroughs made in recent years.

KEYWORDS:-

Lead compound, CADD, Optimization, Pharmacophore, Active moieties, Software

INTRODUCTION:-

Computer aided drug design refers to all computer-assisted techniques used to discover, design, and optimise biologically active compounds with the potential to be used as drugs. The drug development process includes three pre-clinical stages before clinical trials: 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 is being used to find active drug candidates, pick leads, and optimise leads, that is, to transform biologically active compounds into appropriate drugs by enhancing their physicochemical, pharmaceutical, and 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.[2]

CADD capabilities include:[3]

- Virtual screening using 2D similarity searches, 3D pharmacophore searches and high-throughput docking of databases composed of more than 6 million distinct compounds
- Designing target-focused compound libraries
- Lead optimization using structure- or ligand-based design
- Profiling and filtering of chemical libraries for molecules with desired drug-like and DMPK properties
- Establishing quantitative structure activity relationships (QSARs)
- Computer modeling of DMPK properties including CYP inhibition and metabolism

There are mainly two types of approaches for drug design through CADD is the following:

1. Structure based drug design / direct approach

2. Ligand based drug design / indirect approach

LEAD COMPOUNDS:-

Lead compound is a chemical compound that has pharmacological or biological activity likely to be therapeutically useful, but may nevertheless have suboptimal structure that requires modification to fit better to the target. Lead drugs offer the prospect of being followed by back-up compounds called analogs.[4]

ROLE OF LEAD IN DRUG DESIGN:-

Its chemical structure serves as a starting point for chemical modifications in order to improve potency, selectivity, or pharmacokinetic parameters. Further more, newly invented pharmacologically active moieties may have poor drug-likeness and may require chemical modification to become drug-like enough to be tested biologically or clinically.

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.[5]

SOURCES OF LEAD MOLECULES:-[6]

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

1.NATURAL SUBSTANCES:-

Animal products, derivatives, and analogues of natural substances make up the majority of medicines in clinical use. As a lead molecule, a variety of natural products were used. A large number of natural substances have structural characteristics that are difficult to replicate using synthetic organic chemistry. The structural complexity of many natural substances motivates the development of simpler analogues.

EXAMPLES:-

a) Plants

b) Animals

2.CHEMICAL LIBRARIES:-

Chemical libraries can contain a lead molecule. High-throughput screening approaches may be used to scan libraries for potential leads. 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:-

Novel medicines have also been created using computers. For example, if the 3D structure of a protein has been determined using X-ray crystallography, molecular modelling software packages may be used to investigate the macromolecule's binding site. Molecules that suit and attach to the binding site can be built in silico. Crystallographic studies and computational methods were used in the development of the anti-influenza drug oseltamivir, as well as the anti-hypertensive drug, aliskiren.

GENERATION OF LEAD COMPOUNDS:-

Lead generaton is also known as Hit to lead is a stage in early drug discovery where small molecule hits from a high throughput screen (HTS) are evaluated and undergo limited optimization to identify promising lead compounds. These lead compounds undergo more extensive optimization in a subsequent step of drug discovery called lead optimization. [7]

The drug discovery process generally follows the following path that includes a lead generation stage:

Target validation
⇩
Assay development
⇩
High-throughput screening
⇩
Lead generation
⇩
Lead optimization
⇩
Preclinical development
⇩
Clinical development

The lead generation stage starts with confirmation and evaluation of the initial screening of generation and is followed by synthesis of analogs. Typically the initial screening generation display binding affinities for

their biological target in the 10^{-6} M concentration range. Through limited lead generation optimization, the affinities of the geneartion are often improved by several orders of magnitude to the 10^{-9} M range. The generation also undergo limited optimization to improve metabolic half life so that the compounds can be tested in animal models of disease and also to improve selectivity against other biological targets binding that may result in undesirable side effects. On average, only one in every 5,000 compounds that enters drug discovery to the stage of preclinical development becomes an approved drug.[8]

CONCLUSION:-

In practically every aspect of the drug development process, computer-aided drug design (CADD) has been used. There has been a lot of progress in the invention and implementation of unique ideas over the previous few years. As a result, both lead identification and lead optimization, which are key tasks in the drug development process, are made easier. Structure-based de novo drug design has tremendously aided the ongoing improvement in protein structure predictions. 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 tremendous success in terms of enhancing lead compound bioactivity quickly and dramatically. A combination quantum mechanics/molecular mechanics technique to evaluate the consistency of lead compounds has discovered a balance point between accuracy and performance. While computer-aided drug design is still in its infancy, it is projected to play a considerably larger role in the near future, given the many astonishing breakthroughs made in recent years.

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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. Shekhar, C. In Silico Pharmacology: Computer-aided methods could transform drug development. Chem. Biol., **2008**, 15, 413- 414.
3. https://www.amriglobal.com/solutions/discovery/computer-aided-drug-discovery-cadd.
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. Keseru GM, Makara GM (Aug 2006). "Hit discovery and hit-to-lead approaches". Drug Discovery Today. **11** (15–16): 741–8.doi:10.1016/j.drudis.2006.06.016. PMID 16846802.
8. https://drugdevelopment.fi/drug-development/hit-to-lead