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IN SILICO METHODS FOR DRUG DESIGNING AND DRUG DISCOVERY

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ABSTRACT

Today is the world of the computer technology and it is widely used in the pharmaceutical industry also. The drug development and discovery of the new drug is the very time taking process.[1,2] For the development of the new drug it takes a time up to 12-15 years. For the development of the new drug the investors invest the money in large amount but he cannot confident about the success of the development of new drug for to avoid the wastage of the money the predevelopment techniques are used to study the properties of the drug. At the beginning of the industrial development the predevelopment property of the drug are studied by using the laboratories methods but in the modern word the computerized technology are used in the study of the new drug molecule.[3,4] For the prediction of the new drug hypothesis the in vivo and in vitro methods are used at the beginning but at this new generation of the modern drug designing and development of the new drug the computerized methods are used.[6,7] Recently, a trend towards the use of in-silico method is used for the modeling for the computer aided drug designing. There are different techniques used in in-silico drug designing visualization, homology, molecular dynamic, molecular docking, energy minimization and QSAR etc. in in silico drug design can take part considerable in all stages of drug development from the preclinical discovery stage to late stage clinical development. This review gives an idea about the predevelopment test in new drug designing, its potential and future prospect.[3,5,9]

KEYWORDS: Predevelopment test, In-silico, Molecular docking, QSAR, Ligand based method, In vivo and in vitro, De novo drug design, MD simulation.

INTRODUCTION

The most fundamental goal in drug design is to predict how the given molecule is bind to the target and how much strong bond is form. The molecular mechanismBHHH or dynamics is used for the estimation of the strength of small molecule. The computerized method is able to predict. The affinity before the compound is synthesized. The drug delivery and drug development is very time taking process. The pharmaceutical industry integrated with information technology for the development of new drug.[8,9] The computer aided drug design is being utilized for the prediction of the ADME properties and also the toxicity of the new drug. The predevelopment techniques for the new drug improve the effectiveness and efficiency of the drug discovery. It decreases the animal, cost and time for the development of the new drug and also increasing the predictability.[10,11]

The drug discovery and the development of new drug are very costly up to multi-million dollars for the drug reach into the market. It required the huge investment and time for the development of new drug, but the success rates a very less i.e. only five out of 10,000 new compound make their way or reach at the human testing after preliminary evaluation on animals. The majority drug are failed at the later stages due to lack of the pharmacokinetic properties like, absorption, distribution, metabolism, excretion and toxicity. The drug designing and drug development process are speed up after the advanced computerized techniques. Due to this technique the pharmaceutical companies and research group done incredible work. The various methods are used for the development of the new drug are as follows:

The computerized techniques are very useful for the development of the mew drug. It is generally classified in to two parts one is the structure based drug design [SBDD] and another is the ligand based drug design [LBDD]. SBDD methods are used for the analysis of the macromolecular target present in the 3-dimensional structural information, typically of proteins or RNA, for the biological function it is used to identify the key sites and interaction. Such information can then be utilized to design new drugs that can compete with essential

interactions involving the target and thus interrupt the biological pathways essential for survival of the microorganism(s). LBDD methods are used for the detection of the relationship between the physicochemical properties and antibiotic activities for antibiotic ligands, referred to as a structure-activity relationship (SAR).[12,13]

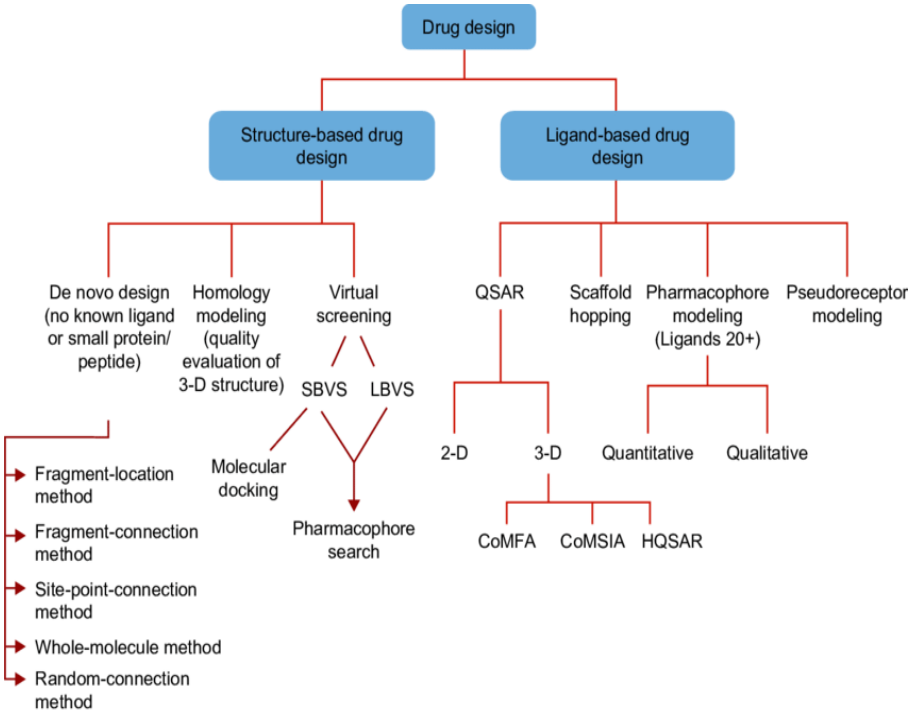

Fig. 1: The drug designing techniques used for development of new drug.

Pre-development test are used for the study of pharmacokinetic properties of the drug and the development of the new drug. The predevelopment prediction of ADME of a new drug reduces the chances of its failure at the drug development stage. It is not used only for the ADME prediction but also molecular descriptors calculation, drug likeness prediction, drug toxicity prediction.

Need of computer aided drug designing in the development of the new drug:

- The computerized pre-development test are used for the prediction of the
  Pharmacokinetic properties of the drug before its development.
- The computerized pre-development test is giving the idea about the toxicity of the drug before its development.
- The lot of money will be required for the development of new drug due to CADD [computer aided drug design] give the clearity about the potency of the drug.
- The other method are used for the pre-development study of the new drug are the in-vivo and in-vitro analysis, which is very lengthy and laboratories process.
- The lot of money is required for the development of the new drug to avoid the wastes of the money the CADD is required.
- The CADD is the software based process required a less time as compare to the laboratories method.
- The CADD is less time taking process which gives the speed for the development of the new drug.
- The CADD is having the significant role in the development of the new drug and it is very easy process.
- The CADD plays an important role in the discovery of the effective, specific, non-toxic, safe and well-tolerated drug.
- Overall the CADD is the economical method as well as the simple and less time consuming.

Therefore, the CADD is the very useful and economical process for the development of the new drug. Which avoid the wastes of the money and time required for the development of the new drug. The laboratories method are the time taking and having difficult to the handling also. Today, a large number of computerized methods are used to identify potential lead molecules from huge compound libraries.

The methods used for the computer aided drug design:

There are many methods are used for the computer aided drug design which is categorized in to two categories are as follows:

1. **Structure based drug design.[SBDD]**
2. **Ligand based drug design.[LBDD]**

1. Structure Based Drug Design [SBDD]:

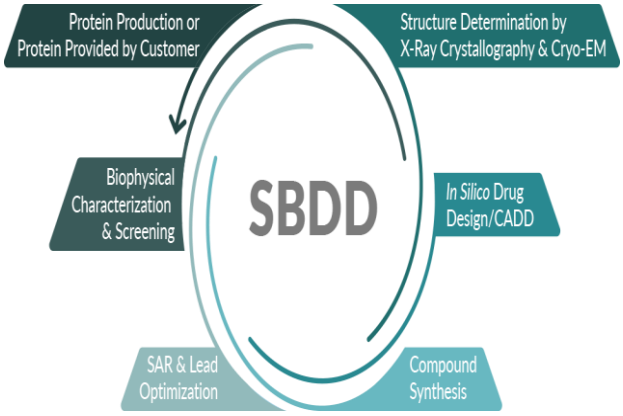

Fig. 2: Structure based drug design.

It is the very important technique used in the development of new drug. It is help in the discovery of the new drug. It is depends on the knowledge of the three dimensional structure of the biological target. Which obtain form the X- ray crystallography or NMR spectroscopy method. When the experimental structure of the target is not available, then the homology model of the target based on the experimental structure of related protein is create by using this model the new drug is predicted to bind with high affinity, alternatively many computerized procedure are suggest for new drug.[15,16]

The structure based drug design is divided into the following categories:

- **Molecular Docking**
- **In-silico ADME**
- **De novo drug design**
- **Molecular dynamics, etc.**

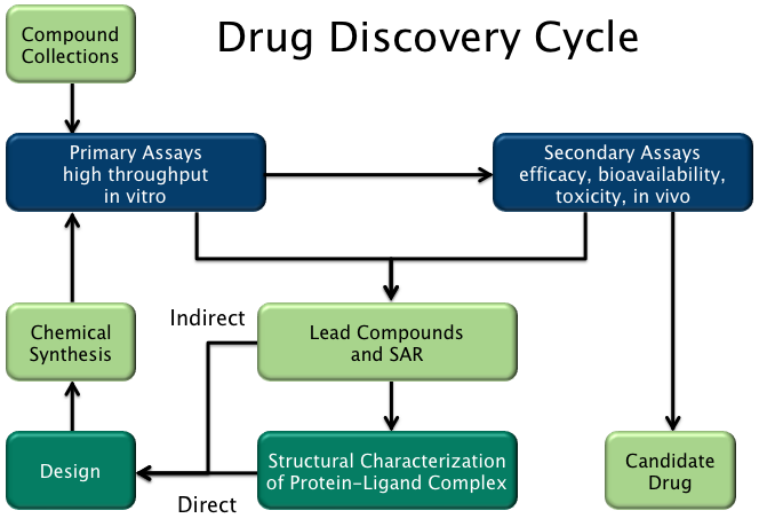

Fig. 3: Drug discovery cycle highlighting both ligand-based (Indirect) and Structure-based (direct) drug design strategies.

2. LIGAND BASED DRUG DESIGN [LBDD]

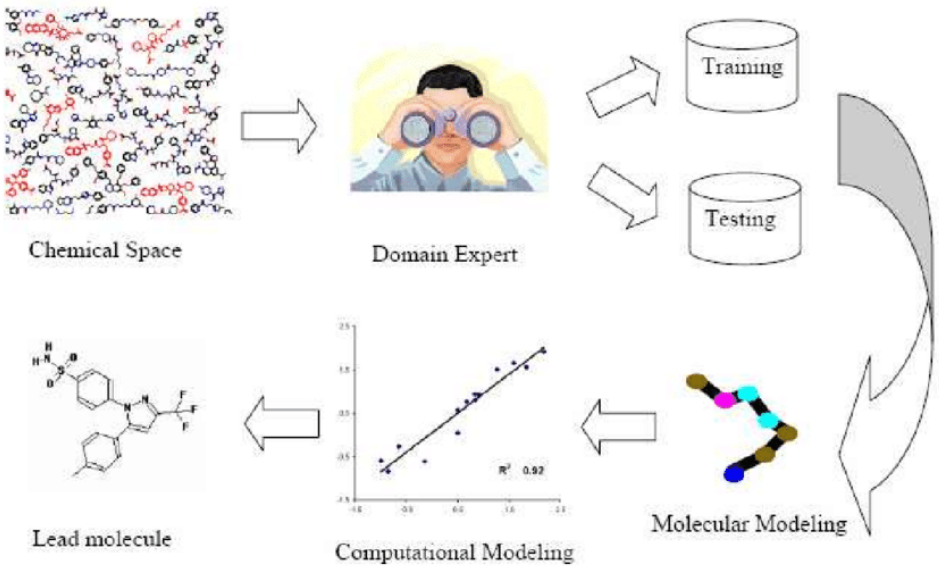

Fig. 4: General steps involved in ligand based drug design.

The LBDD [ligand based drug design] is also called as the indirect drug design. It depends on the knowledge of the other molecules that binds to the biological target of interest. These molecules are used to derive a pharmacophore model that defines the minimum necessary structural characteristics for the molecule for possessing in order to bind the target. The molded of the biological target may construct on the base of knowledge of what binds to it and this model in used to develop or design new molecular entities that interact with the target. The other method is the QSAR [qualitative structure activity relationship] in this method the correlation between calculated properties of molecules and their experimentally determined biological activity may be derived. These relationships used to predict the activity of new drug.[16,17,18]

When the three dimensional structure of the target receptor are not available at that time the ligand based drug design is significantly used. In the LBDD the structural and physicochemical properties are derived by using the information about the set of active compounds against a particular target receptor. This is based on the fact that structural resemblances correspond to similar biological functions.

Generated pharmacophore model elucidates the spacing of chemical features in ligands that are essential for interaction with the target receptor. H-bond donors/acceptors, hydrophobic areas, aromatic ring systems, and +ve /−ve charged ionizable groups are a number of the chemical features used in pharmacophore modeling. Ligands with different scaffolds but the similar spacing of the above-mentioned key interacting functional moieties can be identified using pharmacophore based virtual screening.[18]

The conformations of the active molecules within the target binding site are often integrated into the pharmacophore model for further application in QSAR studies in the molecular alignment stage.

The ligand based drug design [LBDD] is divided in the following categories

- QSAR [Qualitative structure activity relationship] method.
- Pharmacophore modeling.
- Virtual screening.

The computer aided drug design [CADD] is broadly classified as follows

- Combinatorial chemistry.
- High through put screening.
- Virtual screening.
- Pharmacophore modeling.
- Structure-based drug design (Molecular docking).
- Ligand-based drug design (pharmacophore).
- Quantitative structure-activity and structure-property relationships.
- MD stimulation.
- Database preparation.
- SILCS- Pharm.
- Similarity search.
- Single step free energy perturbation [SSFEP].
- In silico ADME
- Docking

Some of the above computer aided drug design methods are explain as follows

1. **QSAR [Qualitative structure activity relationship]**

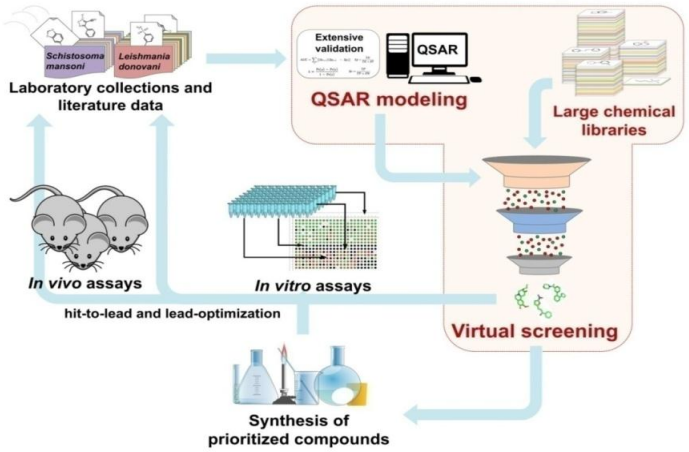

Fig. 5: QSAR based virtual screening.

The QSAR analysis is most commonly used LBDD method; it correlates the variations in the bioactivity of the compounds. Which the change in molecular structure by using this correlation the statistically significant model are constructed and final model is used for to predict the biological activity of new molecule. It is widely used in the drug discovery for the lead identification or lead optimization.[16,18]

The technique of QSAR was developed by the scientist "*Hansch and Fujita"* in 1964 i.e. 58 years ago. Where in it the affinity of ligand to their binding sites, rates and inhibition constant are correlated with other biological end point i.e. atomic group or molecular Properties such as lipophilicity, polarizability, electronic parameters and steric properties (Hanch analysis) or with some structural features (free-Wilson analysis) , but for the designing of new molecule there are some limitation of the classical approach i.e. the lack of understanding of the 3D structure of the molecules force to think the scientist for the look for another alternative so, the scientist combine the existing classical Hansch and Free-Wilson approaches to form a 3D QSAR, which are useful for the three- dimensional properties of ligand to predict their biological activity.[18,19,20]

Applications of QSAR

Chemical

1. **Detection of boiling points.**
2. **Detection of relationship between carbons in alkenes.**
3. **Hammett equation.**
4. **Taft equation.**
5. **pKa prediction.**

Biological

1. **Detection of metabolic pathway.**
2. **Drug discovery.**
3. **Prediction of partition coefficient.**
4. **Prediction of toxicity.**

Other applications

1. **Risk management.**
2. **Detection of genotoxicity impurities.**

The QSAR equations are used to predict biological activities of newer drug before their synthesis.

2. Virtual ligand screening

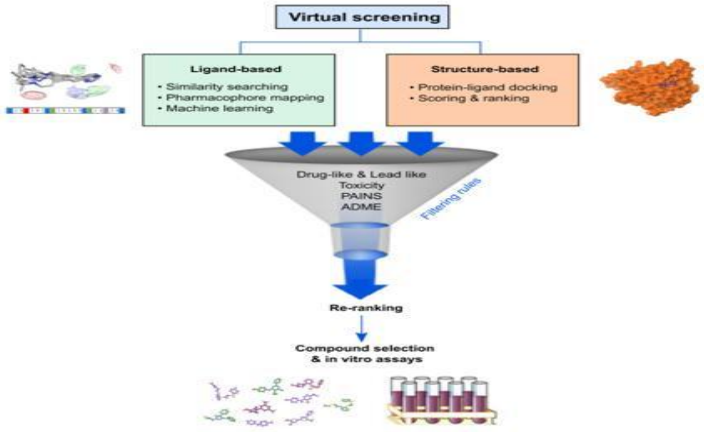

Fig. 6: Virtual ligand screening.

The virtual screening is the computerized method used for drug discovery. It is very useful for a small molecule to identify the structure which binds to a drug target, typically a protein receptor or enzyme[21,22].

It is defined as "automatically evaluating very large libraries of compounds" by using computer program. It is used for the designing and optimization of new drug. The virtual screening method is the most accurate for the drug discovery.

Virtual screening can also be defined as a set of computational methods that analyzes large databases or collections of compounds in order to identify potential hit candidates.[24,25]

Methods of virtual screening

- Ligand –Based virtual screening.
- Structure –Based virtual screening.
- Hybrid method for virtual screening.

Advantages of VS compare to laboratory experiments

- Low cost.
- Investigation of new compound which not synthesized before.
- The number of possible virtual molecule available for virtual screening is much higher than there available for HTS.
- The Virtual screening is the low cost than the expensive HTS method because the number of compounds used in Virtual screening is less than HTS method.

3. De-novo drug design

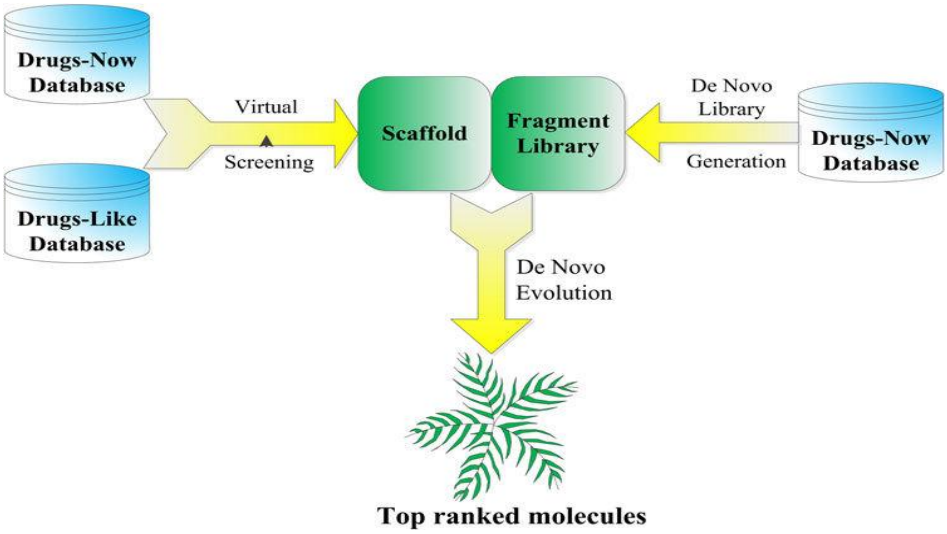

Fig. 7: The flow chart of De-novo drug design.

De-novo drug design is the computerized method for to generate novel molecular structure from atomic building blocks with no a priori relationships.

It refers to the design of novel chemical entities that fit a set of constraints using computational growth algorithm. The world "de novo" means "from the beginning" indicates that this method, one can generate novel molecular entities without a starting template.

The major components of the de novo drug design contain a description of the receptor active site or ligand pharmacophore modeling, construction of the molecule and evaluation of the general molecules.

The de novo drug design is an interactive process in which the three-dimensional structure of the receptor is used to design newer molecules of the drug. The de novo contains the lead target complexes and the design of lead modifications using molecular modelling tools.

This method is successfully used for to design new chemical classes of compounds that present similar substituent's to the target using a template or scaffold, which is chemically distinct from previously characterized lead.[17,18]

The classification of the de- novo drug design:

- **Structure based De-novo drug design**
- **Ligand based De- novo drug design**

Tools

- **Topas**
- **Synopsis**
- **DOGS**

Advantages of De novo drug design:

- Exploration of a broader chemical space.
- Potential for novel and improved therapies.
- Development of drug candidates.
- Economical method.
- Time efficient.

4. Molecular docking

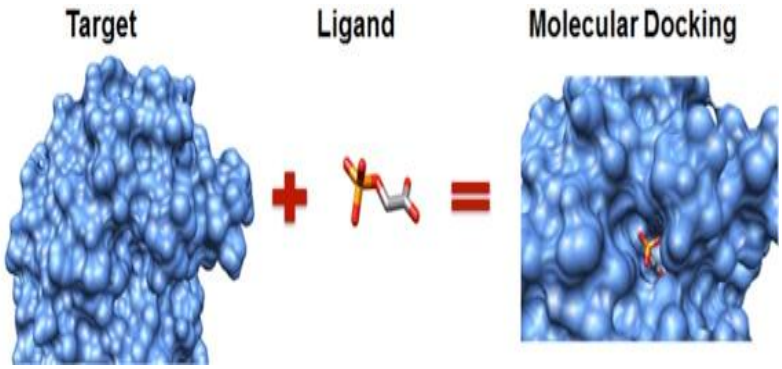

Fig. 8: Molecular docking.

The principle by which small molecules [ligands] recognize and interact with a receptor [macromolecules targets] having the most importance in the Research and Development [R and D] process. The molecular docking is one of the most commonly used techniques. Docking is a method which predicts the preferred orientation of one ligand which form a stable complex when bound in an active site.[23]

The main aim of the molecular docking is to study an optimized ligand and the relative direction between proteins and ligands such that the free energy of the overall system is minimized. The molecular docking is one of the most frequently used methods in structure based drug design [SBDD]. The docking plays an important role in the rational drug design. Molecular docking is the process involves playing molecules appropriate orientation to interact with a receptor. It is the natural process which occurs with second in a cell, when attached into each other to form a stable complex.[21,22]

The molecular docking is mostly used method because of its ability to predict with a significant degree of accuracy the conformation of small-molecule ligands with in the applicable binding site.

Types of molecular docking

- **Rigid docking.**
- **Flexible docking.**
- **Manual docking.**

Application of molecular docking

- It is used for the prediction of binding mode of already known ligands.
- Identify novel and potent ligands.
- As a binding affinity predictive tool.
- The flurbiprofen, a nonsteroidal anti-inflammatory (NSAID) drug used against rheumatoid and osteoarthritis targeting Cyclooxygenase-2 (COX-2) discovered through molecular docking approach.

Limitations

- A restricted sampling of ligand as well as receptor conformations in pose prediction.
- The use of approximated scoring functions.

5. Scaffold hopping

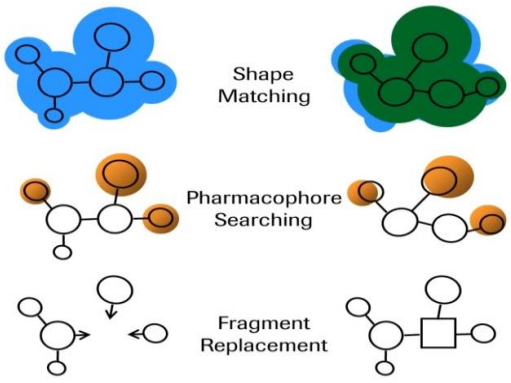

Fig. 13: Scaffold hopping.

Scaffold hopping is the technique to discover structurally new compound starting from known active compound by modifying the central core structure of the molecule. Scaffold hopping has been widely used by medicinal chemist to discover equal potency compound with new backbone that have improved properties of the new compound[26,27,28].

The Scaffold hopping was introduced in 1999 by scientist Schneider et al.

Classification

- Heterocyclic Replacement.
- Ring Opening or Closer.
- Peptidomimetics.
- Topology based hopping.

Applications

- It is used for to improve the physicochemical property of the drug.
- It also improve ADME property of drug.
- It used to synthesis of new drug having the same potency and more effective as compare to parent drug.

CONCLUSIONS

The computer aided drug designing is the simplest method for the development of the new drug as compared to the in-vivo and in-vitro methods. The in silico methods are predict the properties of the drug before its development due to which the lose of money in the development of un-effective product will be reduced.

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Abbreviations

QSAR	Qualitative Structure Activity Relationship.
SBDD	Structure Based Drug Design.
LBDD	Ligand Based Drug Design.
SBVS	Structure Based Virtual Screening.
LBVS	Ligand Based Virtual Screening.
CADD	Computer Aided Drug Design.
VS	Virtual Screening.
MD Simulation	Molecular Dynamics Simulations.
SILCS	Site Identification by Ligand Competitive Saturation.
SSFEP	Single Step free Energy Perturbation.
NSAID	Non-Steroidal Anti-inflamatory Drug.
COX-2	Cyclo-oxygenase-2

REFERENCE

1. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific reports, 2017; 3, 7(1): 1-3.
2. Daina A, Zoete V. Application of the SwissDrugDesign online resources in virtual screening. International journal of molecular sciences, 2019; 18, 20(18): 4612.
3. Boobis A, Gundert-Remy U, Kremers P, Macheras P, Pelkonen O. In silico prediction of ADME and pharmacokinetics: Report of an expert meeting organised by COST B15. European Journal of Pharmaceutical Sciences, 2002; 1, 17(4-5): 183-93.
4. Rognan D. The impact of in silico screening in the discovery of novel and safer drug candidates. Pharmacology & therapeutics, 2017; 1, 175: 47-66.
5. Ekins S, Mestres J, Testa B. In silico pharmacology for drug discovery: methods for virtual ligand screening and profiling. British journal of pharmacology, 2007; 152(1): 9-20.
6. Noori HR, Spanagel R. In silico pharmacology: drug design and discovery's gate to the future. In Silico Pharmacology, 2013; 1(1): 1-2.
7. Andrade EL, Bento AF, Cavalli J, Oliveira SK, Freitas CS, Marcon R, Schwanke RC, Siqueira JM, Calixto JB. Non-clinical studies required for new drug development-Part I: early in silico and in vitro studies, new target discovery and validation, proof of principles and robustness of animal studies. Brazilian Journal of Medical and Biological Research, 2016; 24: 49.
8. Nantsupawat T, Soontrapa S, Klomjit S, Jenkins LA. Rivaroxaban monograph. The Southwest Respiratory and Critical Care Chronicles, 2015; 15, 3(10): 27-33.
9. Butina D, Segall MD, Frankcombe K. Predicting ADME properties in silico: methods and models. Drug discovery today, 2002; 6, 7(11): S83-8.
10. Tao L, Zhang P, Qin C, Chen SY, Zhang C, Chen Z, Zhu F, Yang SY, Wei YQ, Chen YZ. Recent progresses in the exploration of machine learning methods as in-silico ADME prediction tools. Advanced Drug Delivery Reviews, 2015; 23, 86: 83-100.
11. Alqahtani S. In silico ADME-Tox modeling: progress and prospects. Expert opinion on drug metabolism & toxicology, 2017; 2, 13(11): 1147-58.

12. M Honorio K, L Moda T, D Andricopulo A. Pharmacokinetic properties and in silico ADME modeling in drug discovery. Medicinal Chemistry, 2013; 1, 9(2): 163-76.
13. Fatouros DG, Douroumis D, Nikolakis V, Ntais S, Moschovi AM, Trivedi V, Khima B, Roldo M, Nazar H, Cox PA. In vitro and in silico investigations of drug delivery via zeolite BEA. Journal of Materials Chemistry, 2011; 21(21): 7789-94.
14. Chaturvedi PR, Decker CJ, Odinecs A. Prediction of pharmacokinetic properties using experimental approaches during early drug discovery. Current Opinion in Chemical Biology, 2001; 1, 5(4): 452-63.
15. Byeon JJ, Park MH, Shin SH, Park Y, Lee BI, Choi JM, Kim N, Park SJ, Park MJ, Lim JH, Na YG. In vitro, in silico, and in vivo assessments of pharmacokinetic properties of ZM241385. Molecules, 2020; 2, 25(5): 1106.
16. Balani SK, Miwa GT, Gan LS, Wu JT, Lee FW (2005). "Strategy of utilizing in vitro and in vivo ADME tools for lead optimization and drug candidate selection". Current Topics in Medicinal chemistry.
17. Mouchlis VD, Afantitis A, Serra A, Fratello M, Papadiamantis AG, Aidinis V, Lynch I, Greco D, Melagraki G. Advances in de novo drug design: From conventional to machine learning methods. International journal of molecular sciences, 2021; 7, 22(4): 1676.
18. Dhingra N. Computer-Aided Drug Design and Development: An Integrated Approach.
19. Yu W, MacKerell AD. Computer-aided drug design methods. InAntibiotics. Humana Press, New York, NY, 2017; 85-106.
20. Chow SC. Statistical design and analysis of stability studies. Chapman and Hall/CRC, 2007; 30.
21. Morris GM, Lim-Wilby M. Molecular docking. InMolecular modeling of proteins Humana Press, 2008; 365-382.
22. Fan J, Fu A, Zhang L. Progress in molecular docking. Quantitative Biology, 2019; 7(2): 83-9.
23. Pagadala NS, Syed K, Tuszynski J. Software for molecular docking: a review. Biophysical reviews, 2017; 9(2): 91-102.
24. Klebe G. Virtual ligand screening: strategies, perspectives and limitations. Drug discovery today, 2006; 1, 11(13-14): 580-94.
25. Villoutreix BO, Eudes R, Miteva MA. Structure-based virtual ligand screening: recent success stories. Combinatorial chemistry & high throughput screening, 2009; 1, 12(10): 1000-16.
26. Böhm HJ, Flohr A, Stahl M. Scaffold hopping. Drug discovery today: Technologies, 2004; 1, 1(3): 217-24.
27. Sun H, Tawa G, Wallqvist A. Classification of scaffold-hopping approaches. Drug discovery today, 2012; 1, 17(7-8): 310-24.
28. Schneider G, Schneider P, Renner S. Scaffold-hopping: how far can you jump?. QSAR & Combinatorial Science, 2006; 25(12): 1162-71