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PHARMACOPHORE MODELLING: AN OVERVIEW

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ABSTRACT

A pharmacophore is a tool used to determine the specific component of a molecule that is responsible for its activity. The time and expense required to create new medications is decreased by this aspect of computer-aided Drug Discovery. A variety of computer tools are employed in the drug Discovery process for pharmacophore modeling in virtual screening and for structural studies. This article describes the fundamentals of pharmacophore modeling, the creation of Pharmacophores, their uses and other relevant subjects.

KEYWORDS: Pharmacophore, Ligands, Biological activity, Drug discovery.

INTRODUCTION

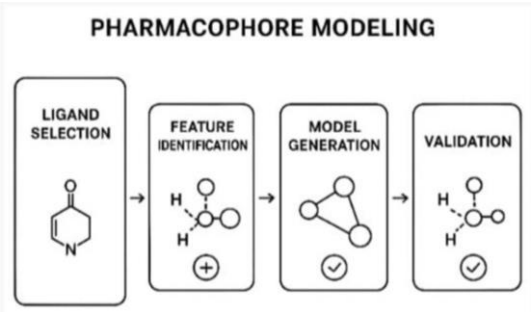

Fig. 1: Pharmacophore modelling.

A Pharmacophore is a technique that explains a molecule's structural characteristics that give it it's activity.[1] Paul Ehrlich first proposed the pharmacophore theory in the early 1900s, describing the molecular characteristics responsible for biological activity.[2] Understanding how a ligand interacts with a protein through pharmacophore models facilitates the discovery of novel compounds with the desired activity.[3] When the target structure is un available , the structural details of an active ligand that binds to the target are used to model the pharmacophore. This type of modeling is known as ligand- based modeling.[4] It is possible to construct the pharmacophore model using the target's structural characteristics if the target structure is available This technique is called structure-based pharmacophore modeling.[3]

Several tools are used for pharmacophore modeling, such as MOE, Pharma Gist, Hypogen, Hip Hop and others.[5]

These tools help in the drug discovery process A Pharmacophore has the following features:

a) hydrogen bond acceptor.
b) hydrogen bond donor.
c) negative ionizable.
d) positive ionizable.
e) hydrophobic volume.[6]

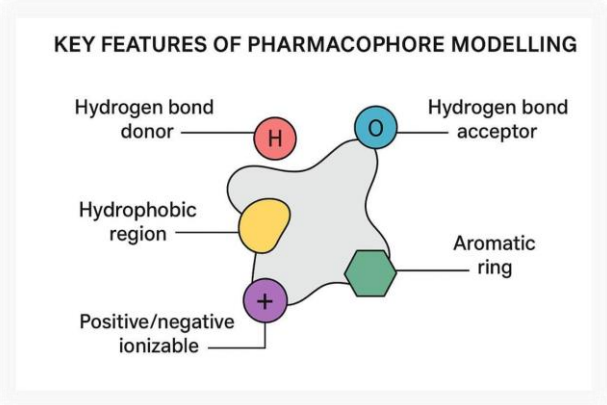

Fig. 2: features of Pharmacophore modelling Key.

The workflow of Pharmacophore modelling is as follow

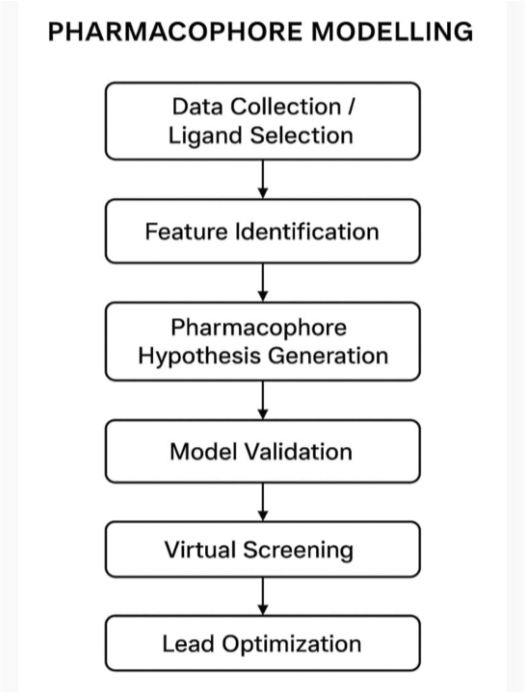

Fig. 3: Workflow of pharmacophore modelling.

PRINCIPLE

Structure-based pharmacophore modeling and ligand-based pharmacophore modeling are the two main approaches for pharmacophore modeling that are used in drug discovery process.[3&4]

Ligand based pharmacophore modeling

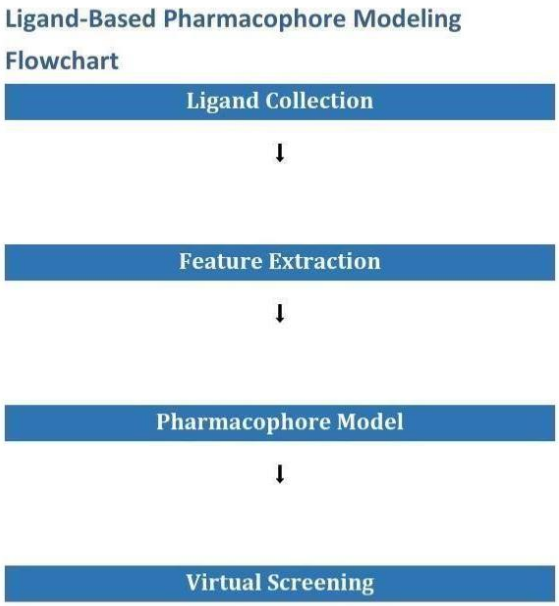

Fig. 4: Flowchart of Ligand – Based Pharmacophore Modelling.

Finding active ligands in a database is the first stage in ligand-based pharmacophore modeling.

A training set and a test set are then created from data set. By aligning the active ligands is analyzed to find common features, leading to the creation of a pharmacophore model. The most successful pharmacophore model is then chosen through a ranking process and validation using the outcomes.[7&8]

Structure based pharmacophore modeling

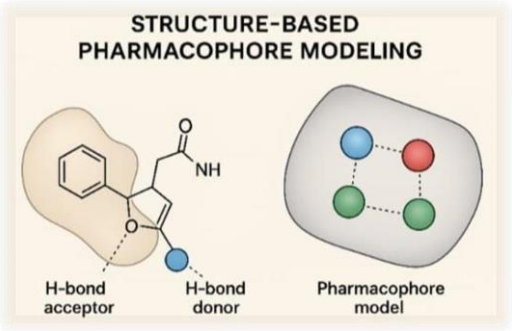

Fig. 5: Structure -Based pharmacophore Modelling.

Choosing and preparing the target protein structure is the first step in the structure-based pharmacophore modeling. Following the prediction of the binding site, different chemical properties of the amino acids at the binding site are identified, and their arrangement is observed[9] Lastly, a variety of software tools, including MOE[10] and HypoGen,[5&2] are used to generate pharmacophore features.

When structural information about the targeted receptors is not available, pharmacophore generation is essential for drug design. It helps to find molecules that interact with particular biological target and evaluate their activity (lead discovery), while also improving the desired effects and reducing drug deficiencies through chemical modification (lead optimization). Virtual screening also uses the pharmacophore approach, while enables the identification of particular ligand that bind to specific drugs targets and show activity, like proteins Pharmacopore based virtual screening.

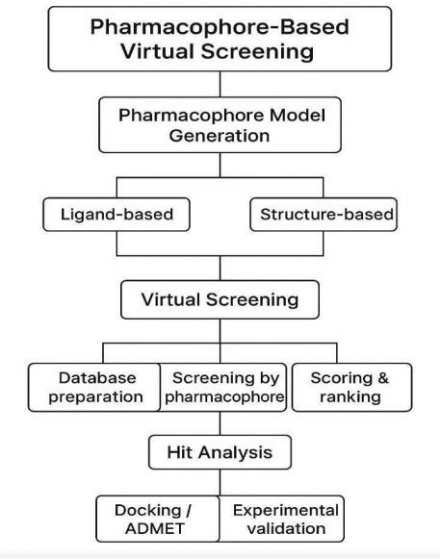

Fig. 6: Pharmacophore Based Virtual Screening.

Finding new active chemicals is best done by using a method called pharmacophore-based virtual screening.[11] This is because virtual screening tools help a lot in finding active molecules faster when developing new drugs. They do this by using computer tests. These tests help pick out chemicals from large collections that are most likely to work with a specific target. Also, virtual screening helps find chemicals that might be harmful or have bad effects on the body.

In this way, pharmacophore models can be used to find new molecules. These molecules have the right features to work against a certain target. A pharmacophore shows how chemical parts are arranged in space, not exact chemical groups. So, the chemicals found often look very different from each other.[12]

Pharmacophore-based screening can be done directly with special software. This software helps screen a list of chemicals that you prepare yourself. Other useful free tools for virtual screening are Pharmit and ZINC Pharmer. Pharmit lets you either bring in a ready-made pharmacophore search or create one from target and/or chemical structures. You can then use these searches to check a desired list of chemicals from available collections or your own. The results are quickly calculated and sorted by things like how much energy they have.[13] ZINC Pharmer is an easytouse online tool. It uses special technology called Pharmer to find molecules from the ZINC database that are available to buy. You can use a special model called a pharmacophore model for this search. You can bring this model in from other tools or create it from existing molecules or structures.[14]

Usually, after you have a pharmacophore model, the first step is to look through a database of many compounds. These compounds often have details about their 3D shape, what they target, and if they are available for sale. Some free databases you can use are Protein Data Bank (PDB).[15]

Pub Chem,[16] ChEMBL,[17] Zinc,[18] and Drugbank.[19] There are also paid databases like MDL Drug Data Report.

To make the search faster and use less computer power, you can set some rules. For example, you can remove compounds that are too big to fit, or use rules like Lipinski's Rule of Five.[20] You can also get rid of compounds that are known to cause problems in many tests. This helps to improve things like how well a drug dissolves, how it's absorbed, and how it spreads in the body.[21]

It's important to know that some studies check for harmful effects and how a drug moves through the body only after a process called molecular docking. So, researchers have to decide.

They can either filter out many molecules first, which means fewer molecules need more testing. Or, they can test a larger group of molecules to find possible drug candidates. Even if these candidates are harmful, they can still be used as a starting point to make new compounds.

Docking is a computer process. It moves molecules around in 3D space to find the best fit between a drug and its target.[22] This fit helps to get the best score. Docking creates drugtarget pairs. These pairs can then be checked more closely to see if they are good enough for lab experiments.

One way to check them is called molecular dynamics (MD).[22] This is a key computer method. It helps us understand how stable the drug is when It's attached to its target. This gives a more accurate idea of how strongly they bind together.[23&24]

After these computer searches, the best compounds that show the right properties need to be tested in the lab. This is called in vitro validation. It confirms if the computer results are correct.

The steps mentioned above are a common way to do virtual screening. This process is shown in a picture called 'Virtual screening workflow.' It includes basic filters and methods for virtual screening. It's like a multi-step process. Virtual screening uses a series of filters to find a small group of compounds that might have biological effects. Recently, MD simulations have been used to search for different shapes of molecules without needing the usual docking steps. They use very accurate computer models and advanced search methods.[17]

This process's steps are depicted in the flowchart

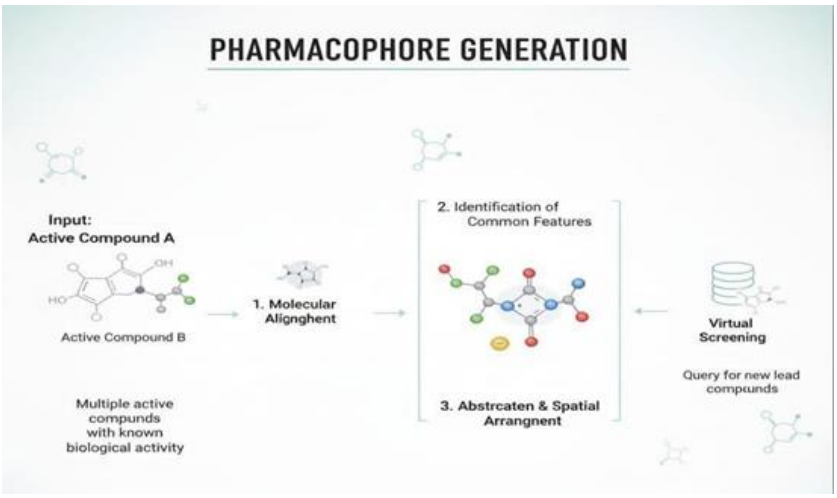

Fig. 7: Pharmacophore generation.

APPLICATIONS

1. In Drug Discovery

Due to it's adaptability and user-friendliness, pharmacophore modeling is used in drug discovery. It assists in evaluating the possible the adverse effects of current medications and finding alternate uses for them.[25]

2. In Virtual Screening

Pharmacophore modeling is used in virtual screening to determine which compounds contribute to biological activity. To generate pharmacophore model for use, the ligand data is separated into training and test sets when both active and inactive ligands are present. Validation is then carried out.[26]

3. Use in docking

By combining docking- based molecular modeling and pharmacophore approaches, the drawbacks of each approach are reduced to produce better outcomes. The Pharmacophore model aids in ligand selection and ranking and acts as an initial filter to reduce the number of

molecules that need docking. Additionally, after docking, pharmacophore models are used to identify the proper mode of binding for a compound.[27]

4. ADMET Applications

To reduce the likelihood of failure, the Pharmacophore modeling technique is used to evaluate ADMET properties before drug development.[28]

CONCLUSION

Pharmacophore modeling is a useful method for determining the molecular characteristics that are essential to its action. It has multiple applications at different stages often drug discovery process, including virtual screening, docking, and ADMET analysis. As the quality of Pharmacophore models are developed, their significance in drug discovery increases.

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