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REVIEW ARTICLE

APPLICATION OF PHARMACOPHORE IN COMPUTER AIDED DRUG DESIGN

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ABSTRACT: When there is a paucity of structural data for the target receptor, pharmacophore mapping becomes one of the most important aspects of the drug design process. This is particularly true. After having its beginnings in the process of discovering lead molecules, the approach is now being used in the process of lead optimization. As a query, pharmacophores can be used to obtain potential leads from structural databases (lead discovery). They can also be used to create molecules with distinct desirable features (lead optimization), and they can be used to employ pharmacophore fingerprints in order to evaluate the similarity and variety of compounds. Additional applications include the alignment of molecules based on the 3D chemical feature configurations of the molecules and the building of prediction 3D QSAR models. After a brief introduction to the progression of pharmacophores over the course of time, this investigation will focus on the history of pharmacophore detection methods, beginning with their inception and progressing all the way up to the development of cutting-edge tools such as Catalyst, GASP, and DISCO. In addition, we highlight some recent accomplishments in the field of drug development by making use of conventional approaches to pharmacophore generation.

Key Words: Pharmacophore Modeling, Fingerprinting, Virtual Screening, Database Search.

INTRODUCTION:

The process of detecting lead compounds via the use of trustworthy and cost-effective virtual screening (VS) of databases is gaining popularity in the business that deals with the creation of new drugs. There is a growing amount of pressure being put on the pharmaceutical sector to quicken the rate at which new treatments are introduced to the market. The use of VS is seen as a complementary method to high-throughput screening experiments. Utilizing VS in combination with structural biology is likely to result in an increase in the percentage of successful lead identification attempts. In addition, as the number of potential targets has expanded, there has been a corresponding rise in the need for accurate target validation as well as technologies that can swiftly discover a large number of high-quality candidate leads. Because of recent developments in computer methods, VS has the potential to make a substantial influence on the process of developing new drugs [1-5].

History of Pharmacophore:

It is generally agreed that Paul Ehrlich was the first person to apply the pharmacophore idea to the process of deriving colours from chromophores (the part of a molecule responsible for imparting color). In 1890, he came up with the term "molecular structure" to describe anything that "bears" (phoros) the important features that are responsible for a drug's (pharmacon) biological activity. According to Peter Günd's definition, a pharmacophore is "a collection of structural features of a molecule that are detected at a receptor site and are responsible for that molecule's biological activity." This definition can be found in his book "Molecular Pharmacology [6].

Pharmacophore Method:

With the assistance of pharmacophore modelling, which is a useful tool for comprehending the available data, it is possible to develop new medications with enhanced activity, selectivity, and/or pharmacokinetics properties. In order to build pharmacophore models, it is important to first conduct an analysis of the structure-activity connections between active analogues and then uncover the common structural features shared by these analogues. It is possible to identify the pharmacophore in one of two ways: either directly, by analysing complexes of receptors and ligands, or indirectly, by comparing the structures of related compounds (using just a list of ligands known to interact with a certain receptor). However, direct approaches are becoming more important as the pace at which new protein structures are found rises. Depending on the level of mechanisation that is included into these tactics, one may classify them as either manual or automated (algorithm-based).

The hands-on technique involves painstakingly analysing molecules to determine the structural and chemical similarities as well as differences that exist between the active and inactive groups. Calculations of the spatial linkages among the three-dimensional characteristics of the common features are performed at the first phase of pharmacophore development. After that, it is put through a battery of statistical and/or logical tests to ensure that it is accurate. The last step is to make any necessary adjustments to the model's parameters in order to

bring the values that are predicted closer in line with those that actually occur [7].

Pharmacophore modeling And Virtual Screening:

In pharmacophore modelling, digital screening is often used to classify substances that have the desired biological effect. This is done for the goal of pharmacophore modelling. The researchers do this by creating a pharmacophore model (query) that contains the appropriate three-dimensional organisation of the appropriate interaction pattern. Constructing a query of this kind may take many different forms, depending on how much information is currently known about the protein target in question.

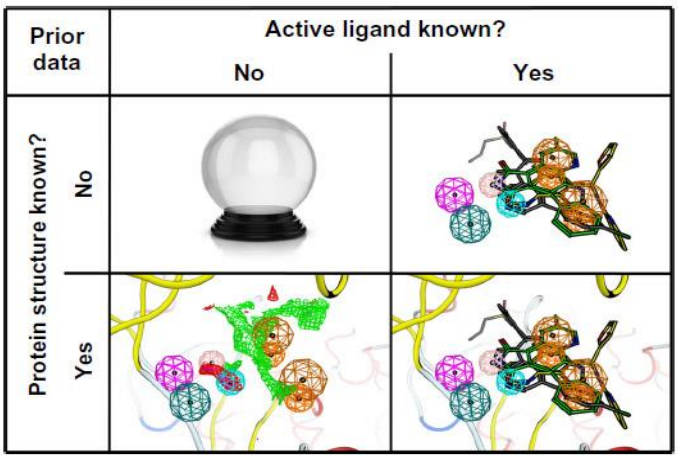

Fig. 1: Pharmacophore modeling

After the discovery of several active ligands as well as variations that are inactive, the data on the ligands should be separated into a training set and an assessment set in order to evaluate the pharmacophore query that was produced as a consequence.

Pharmacophore Fingerprinting:

Through the use of the Chem-X programme, one is able to generate a pharmacophore fingerprint or key, wherein the fingerprint is determined by a restricted number of pharmacophores (also known as the pharmacophore space). Pharmacophore fingerprints have a broad range of potential applications, some of which include, but are not limited to, the determination of chemical similarities, the establishment of libraries, the evaluation of diversity, and the discovery of new active compounds. In most cases, Chem-X will use either a three-point or a four-point pharmacophore model. In this context, n refers to the total number of pharmacophore properties (centres). In the vast majority of instances, interactions between ligands and receptors are unable to take place without the participation of these seven key locations. There is a wide range of H-bond donors and acceptors available, some examples of which include positively charged centres, aromatic ring centroids, hydrophobic centres, acidic centres, and simple centres. Within the centre of a lipophilic molecule is where you will find the nucleus of a hydrophobic molecule [8].

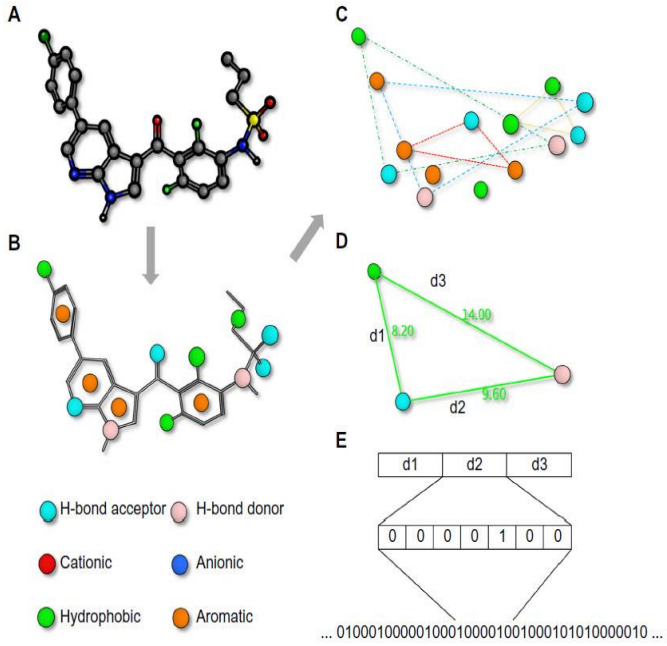

Fig. 2: Pharmacophore Fingerprinting

Four centres and six inter-center distances are what make up the definition of a 4-point pharmacophore. In addition to this, a continuous range of inter-center distances is segmented into distinct groups of a certain size. Consider a pharmacophore that has fifteen distance intervals on each hand, as well as four points, six sides, and six sides total. There are a total of 156 four-point pharmacophores, however there are a potential 156 different combinations of those four points (where 210 is the number of ways to choose four centres from the seven centre groups) [9,10].

Database Search and Preparation:

The availability of a ligand database is one of the most important conditions for performing VS utilising the docking or pharmacophore-based search approaches (DB). This can be accomplished by using a public database, such as MayBridge, the database maintained by the National Cancer Institute (NCI), Cambridge Structure Database (CSD), World Drug Index (WDI), or a proprietary database, such as the Available Chemicals Directory (ACD), Cambridge Structure Database (CSD), or World Drug Index (WDI). Another option is to obtain a database from a chemical supplier. After a primary filtering of "drug-like" features such as variants of Lipinski's rule of 5, the polar surface area, and so on, a library of reagents and compounds with known chemistries that are easily synthesizable could be used for VS. This would come after a primary filtering of "drug-like" features [11-19].

Application of Pharmacophore:
De Novo Design of Ligands:

With the use of the pharmacophore, one is able to create new ligands that are compatible with the parameters of the pharmacophore model. As input, New Lead 20 makes use of the

disconnected components that make up the pharmacophore model. After that, we employ very small chemical groups to bind these components together. It is possible to employ LUDI in conjunction with de novo design to create a pharmacophore that is based on the structure of the receptor if the structure of the receptor is known. Therefore, the pharmacophore strategy offers a quick and simple method of searching for already discovered compounds as well as developing novel molecules in situations when there are no active ligands available (as is frequently the case at the outset of a new project).

Database Searches Based on Pharmacophore:

A list of compounds that "hit" the pharmacophore query may be obtained by searching across 3D chemical databases using a pharmacophore query. This process provides the list. It's likely that some of these discoveries represent unique chemical families, while others are tried-and-true active molecules. Both of these possibilities are feasible. Researchers have a better chance of finding new lead compounds with pharmacological activity that has not been found yet if they use pharmacophore searching. The possibility that certain compounds will be effective in the process of medicine development is increased when there is a greater number of choices available [20].

Lead Optimization:

The process of boosting the binding affinity of a compound while concurrently improving its ADME qualities is known as "lead optimization." Either pharmacophore searching or pharmacophore-based de novo design may be used to develop new drugs that contain the pharmacophore. This indicates that there is a strong chance that they will become bioactive, but that they will have their own distinctive pharmacokinetic and pharmacological profile. The usage of 3D-QSAR models in conjunction with methods such as the co-molar force assay may be used in order to make predictions about the biological behaviour of candidate molecules (lead optimization) [21].

CONCLUSION:

There is a good chance that the number of possible targets for protein engineering will substantially increase as more and more genome projects are completed. This results in an increased reliance on pharmacophores in three-dimensional searches for the discovery of new, more powerful lead drugs. Finding (receptor-based) pharmacophores now relies more heavily on indirect methods, however this is expected to change as more protein structures are deciphered and direct methods become more viable alternatives.

Due to the absence of a receptor structure, pharmacophores are an extremely important component in computer-assisted drug design (CADD). The use of pharmacophores in drug design and development is a strong strategy because they may give a broad range of compounds that may have the required biological activity but make use of wholly different chemical scaffolds. This makes the pharmacophore method very useful. It is essential to recognise a pharmacophore, even if it is possible that this feature is absent from certain SAR datasets. A single pharmacophore may not be able to precisely identify all potential ligands since it is possible for many pharmacophores to coexist inside the same binding site. Keep in mind that a pharmacophore is required, but not sufficient, for the ligand to bind at the receptor site. Other criteria, including as the features of the transport mechanism and the quantity of the ligand, must also be taken into consideration.

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CONFLICT OF INTEREST: Nil

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