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"A REVIEW ON PHARMACOPHORE MODELLING IN DRUG DESIGN"

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ABSTRACT

Pharmacophore modelling is a successful subfield of computer-aided drug design that is quite diversified. The pharmacophore concept has been frequently used in the rational design of new medications. We examine the computational implementation of this concept and its implications in this study. In the drug development process, this term is frequently used. Pharmacophores are a type of symbol that can be used to represent and communicate information. By schematically portraying the main parts of molecular structure on a 2D or 3D level, you can identify molecules on a 2D or 3D level recognition. Virtual screening is the most popular use of pharmacophores, and there are several types of virtual screening. Depending on the pre-existing knowledge, different solutions are feasible. The pharmacophore concept, on the other hand, is also beneficial for ADME-tax modelling, side effect and off-target prediction, and target prediction identification. In addition, pharmacophores are frequently used in conjunction with molecular docking. To improve virtual screening, use simulations. Pharma We wrap up this overview by highlighting some of the new areas where pharmacophore modelling can help us make considerable progress. Protein–protein interaction inhibitors and protein design are two examples.

Keywords *- ADME-tox, pharmacophore fingerprint, computer-aided drug design, protein design, virtual screening design.*

1. INTRODUCTION

What exactly is computer-assisted drug design (CADD)?

- Drug design is a time-consuming and costly procedure in the development of novel medicines. This method has been used in herbal treatments for millennia. Drugs have only had a (semi)synthetic origin since the last century. Because first-generation chemicals frequently lack both efficacy and safety, they must be improved. While previously, this was a trial-and-error procedure, reasonable ways for increasing potency were quickly devised. Since the 1980s, computers have become a more prominent and pervasive instrument in drug development, as they have in any data management procedure. Computer-aided drug design is the term used to describe the intersection of computational and pharmaceutical research (CADD).1

- Although these are highly concentrated in the early stages, CADD covers a broad spectrum of applications spanning the drug discovery pipeline. CADD's major goal is to streamline and rationalize the drug design process while lowering expenses. The initial step in drug development is to find the first hit compounds, which can take a long time. High-throughput screening (HTS), which involves testing tens of thousands of people, has been undertaken chemicals that have a good activity assay In silico, in vitro HTS has a counterpart. It's also known as virtual screening, and it's used to filter chemical libraries. computational strategies for identifying those who are most likely to be active for a particular period of time target. The potency of hit and lead compounds needs to be increased later in the drug discovery pipeline. New derivatives are created with or without a new scaffold at the molecule's core. The ultimate goal is to create compounds that are highly effective and specific while still having a strong intellectual property position. This can be accomplished via traditional medicinal chemistry methods, in which the design is based on observable structure–activity relationships (SAR) or structural data. Computational approaches, on the other hand, can be used to develop a variety of derivatives based on various scaffolds and then score them for potency. This method selects the most promising derivatives from a large chemical space in a a short period of time the potency of the chemicals, however, is not the only factor to consider. Toxicity and pharmacokinetic features (absorption, distribution, metabolism, and excretion). If a chemical is to be clinically helpful, it must also pass the ADME-toxification test. Virtual approaches have been created to predict the ADME-tox profile of drug-like molecules early in the research phase, in addition to a battery of in vitro and in vivo trials.

- Chemo-informatics, the application of data storage, handling, and retrieval methods to chemical structures, their properties, and biological activity, is the foundation of all CADD technologies. Chemo-informatics also includes the calculation of molecular descriptors, which are used to filter compounds and characterize a chemical or physical attribute based on the structure of the molecules. Molecular fingerprints are frequently used to compare and measure (dis)similarity between molecules.

- Another important CADD subfield is quantitative structure activity/property relationship (QSAR/QSPR), in which the physicochemical properties (as determined by molecular descriptors) of a group of inhibitors are linked to inhibitory activity or toxicity in order to develop a predictive model for new inhibitors.

- The CADD approaches mentioned earlier are among the most well-known, although there are many others, including artificial intelligence-based systems. However, pharmacophore modelling, a very successful CADD approach, is the subject of this paper. The history, progress, and present constraints of pharmacophore modelling are covered in this paper, which is geared at medicinal chemists and anyone new to CADD. The numerous pharmacophore modelling programmes and algorithms are not listed or compared.2

What is a pharmacophore, and how does it work?

- A pharmacophore is a molecular framework with a precise 3D arrangement of functional groups that are required to bind a macromolecule and/or an enzyme active site.

- Various steric-electro steric and hydrophobic interactions, depending on the size of the active.

- A pharmacophore model is created by combining a set of known ligands for a specific target.

- The multiple confirmations of the set of compounds create pharmacophore hypotheses.

- The conformational search might be extremely vast, and the following strategies can be used to approach it.

    i) The Systemic Approach
    ii) Clique Detection Algorithm
    iii) Distance Geometry Method

2. INTRODUCTION TO HISTORY

Paul Ehrlich invented the pharmacophore concept in the late 1800s. At the time, it was thought that a biological effect was caused by particular "chemical groups" or functions in a molecule, and that compounds with similar effects shared similar functions. In his 1960 book Chemo biodynamics and Drug Design, Schueler developed the term pharmacophore, which he defined as "a molecular framework that conveys (phoros) the key elements responsible for a drug's (pharmakon) biological activity."[5] As a result, pharmacophores were no longer defined as "chemical groups," but rather as "patterns of abstract properties." The International Union of Pure and Applied Chemistry has defined a pharmacophore as follows since 1997: A pharmacophore is an ensemble of steric and electronic features that is required to ensure optimal supramolecular interactions with a specific biological target and to trigger (or block) its biological response. The pharmacophore should be regarded as the largest common denominator among a set of active compounds' molecular interaction characteristics. As a result, a pharmacophore is an abstract term that does not reflect an actual molecule or a set of chemical groups. Despite this precise definition, many in medicinal chemistry use the term pharmacophore to refer to simple but important chemical functions of a molecule (such as guanidine or sulphonamides) or common chemical scaffolds (such as flavones or prostaglandins). The long definition is frequently shortened to "A pharmacophore is a pattern of features of a molecule that is responsible for a biological effect," which emphasises the key idea that a pharmacophore is made up of features rather than chemical groups.[6]

- **Concepts of pharmacophore in CADD:**

Despite the fact that the pharmacophore notion predates any electronic computer, it has become a significant tool in CADD. A pharmacophore feature can be simplified to any atom or group in a molecule that exhibits particular behaviours linked to molecular recognition. These molecular patterns can be classified as hydrogen bond donors or acceptors, cationic, anionic, aromatic, or hydrophobic, as well as any combination of these characteristics. At the pharmacophore level, different compounds can be compared; this is referred to as "pharmacophore fingerprinting." A pharmacophore is frequently referred to as a "query" when only a few pharmacophore properties are taken into account in a 3D model.[7]

- **Fingerprint of the pharmacophore:**

While molecules are three-dimensional objects, the pharmacophore representation reduces them to a collection of two-dimensional or three-dimensional properties. A pharmacophore fingerprint is a variation on this idea that annotates a molecule with a unique data string. For each ligand, all possible three- or four-point sets of pharmacophore characteristics (points) are listed. 49 When employing 3D fingerprints, the distance between the feature points is measured in bonds (for topological fingerprints) or by distance-binning (Figure 1). The fingerprint that results is a string that describes the frequency of every conceivable combination at present points within the text. Several pharmacophore fingerprint variants have been developed and are widely used.

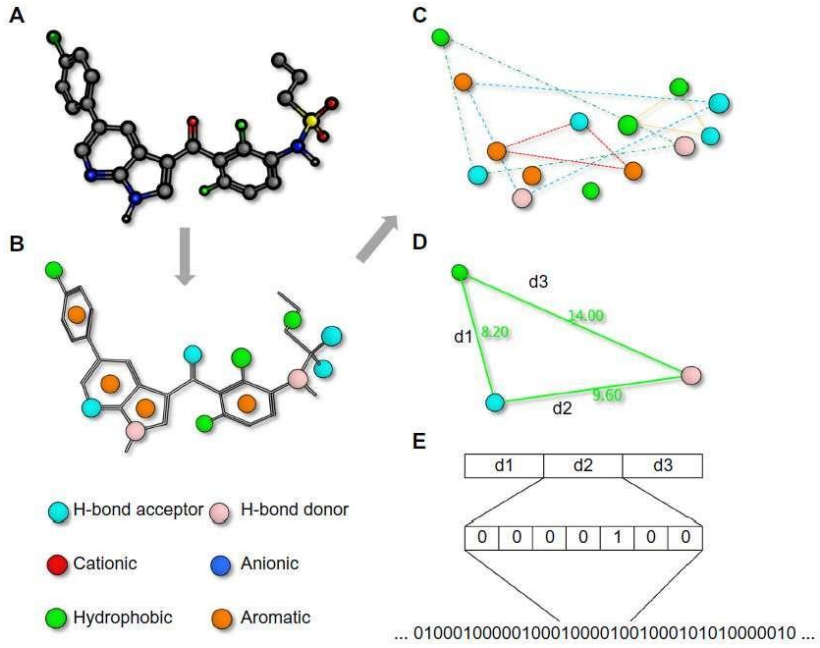

fig.1 pharmacophorefingerprints.

A pharmacophore fingerprint is a string that represents a small molecule ligand (A) that has been annotated with molecular interaction properties (B). Typically, every three-(or four-) point combination of molecular interaction features (C) is calculated, with varied distances between the features estimated either through space or by the number of bond lengths (D), and the frequency of occurrence is kept in a string (E). Such strings are handy for comparing the similarity of numerous molecules quickly. A fingerprint like this can be used to compare the similarity of molecules or a library of compounds. Alternatively, a fingerprint model can be utilised to discover the essential contributing factors to biological function by analysing the common elements of active ligands.[8]

- **Pharmacophore Model or Query:**

Model of a pharmacophore or a question A pharmacophore model is made up of a few features that are arranged in a 3D layout. Each feature is usually depicted as a sphere (though there are variations), with a radius indicating the tolerance for deviation from the exact place (Figure 2). To mix diverse interaction patterns inside one label, the features can be labelled as a single feature or any logic combination consisting of "AND," "OR," and "NOT." Additional characteristics can be used to describe prohibited volume interactions (typically to represent the receptor boundary).[9]

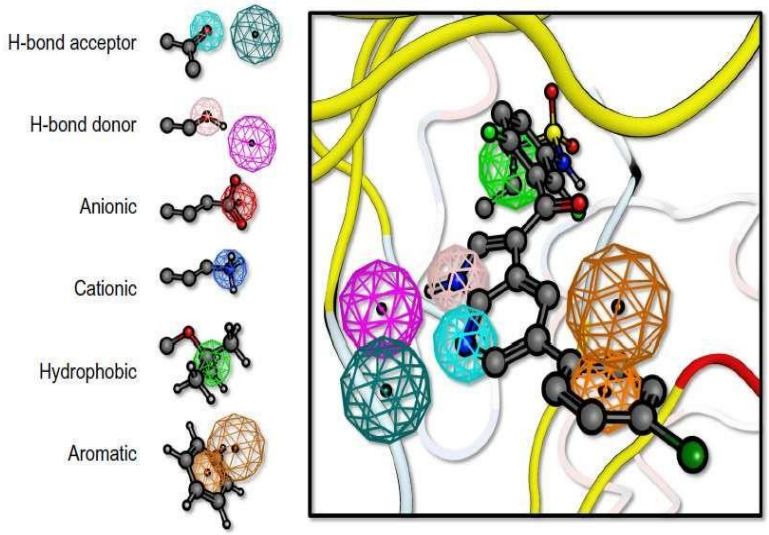

fig. 2 pharmacophore query

Notes:

A pharmacophore query is made up of various elements. Hydrogen bond acceptors or donors, anionic, cationic, hydrophobic, and aromatic groups are examples of molecular recognition motifs. The geometric constraint's strictness is determined by the sphere's radius. A second feature can be used to indicate the vector of the contact for features where the correct direction of the interaction is critical, such as hydrogen bonds and the aromatic plane (or the normal of the plane). Any of these properties can be included in a pharmacophore query, along with varying radii and logic operations like "AND," "OR," and "NOT." A hypothetical pharmacophore query for BRAF kinase is shown on the left.

Typical queries for screening small molecule libraries of compounds include pharmacophore characteristics. 1 of 5 All of the compounds are found in their low-energy biorelevant conformations in these libraries. By aligning the pharmacophore properties of the molecule with the query, each of these conformations is suited to the pharmacophore query. A molecule is called a hit molecule if it can fit inside the spheres representing the query features. Partially matching may be allowed if the pharmacophore query is too complex to discover hit compounds from a particular library. Only specific qualities that are regarded important for activity are matched in such circumstances. Models like these can also be used to align molecules or make molecular docking simulations easier. Multiple ways for building pharmacophore models, either manually or with automated algorithms, are possible depending on the situation and the type of experiment, and this is described in the next chapter.

- **Only the structure of the protein is known.**

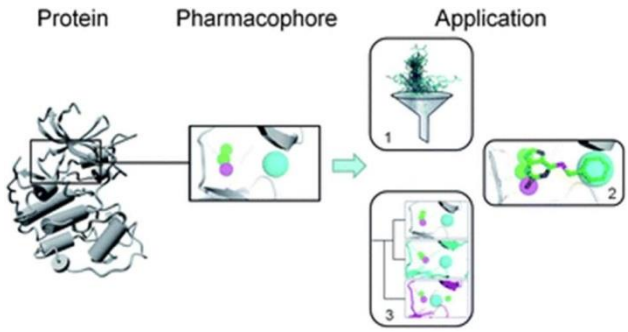

fig. 3 structure of protein

In the last scenario, the protein receptor's structure is known, but no active ligands are. In this situation, the chemical properties of the binding site of interest can be used to create a probable pharmacophore model. There are a variety of computational methods for converting 3D atomic structures of protein binding sites into queries. A pharmacophore query can be created using the interaction maps of the de novo drug design tool LUDI.HS-Pharm is a knowledge-based strategy that prioritises the most interesting interacting atoms and generates an interaction map within the binding site using machine-learning algorithms. The interaction map is then transformed into pharmacophore characteristics.[10]

Another method for analysing the pocket and identifying significant interactions is to use the GRID package. The most favourable sites of atomic probes in the binding site can be determined and transformed into pharmacophore characteristics using molecular interaction fields.[6] Although many successes have been reported, the lack of any ligand structural information is a significant disadvantage to drug design, as it is difficult to map the features in 3D space that can still be covered by atoms that are restrained by bond lengths and angles in the ligands in the absence of a molecular scaffold.

Pharmacophore searches are used in all of these cases to find active chemicals that meet particular geometric and chemical constraints. A pharmacophore query, due to its simple yet versatile nature, can be used not only to identify active molecules, as suggested by the IUPAC (International Union of Pure and Applied Chemistry) definition of a pharmacophore, but also as a negative query to identify molecules with undesirable properties.

A double pharmacophore query was used to discover stringent human androgen receptor (hAR) antagonists in recent work by Voet et al.[11] Anti-androgens that block the hAR function are frequently used in prostate cancer treatment. Resistant mutations in the hAR, on the other hand, tend to turn antagonists into agonists. The structural information of the hAR with drugs in the agonist and antagonist conformations was employed in their research. The known antagonists in agonistic conformation were used to construct a pharmacophore query, which was then remapped in 3D onto a second query in antagonistic conformation. Compounds that only fulfilled the antagonist query but not the agonistic query were found using a combined pharmacophore screening technique.[10]

- **Pharmacophore methods in docking simulations**

The compounds' purely antagonistic effect toward both wild-type hAR and drug-resistant mutants was validated by experimental evaluation. As mentioned in the preceding section, pharmacophore models make excellent searches for virtual database screening. Nonetheless, a so-called hierarchical strategy in virtual screening, in which several technologies are merged sequentially, is one of the most prevalent options. This is also known as the funnel concept, in which the compounds most likely to be active are removed at each successive step, leaving just the most promising compounds for virtual screening. Every level in the hierarchical technique typically includes a more sophisticated, computationally demanding step than the one before it.

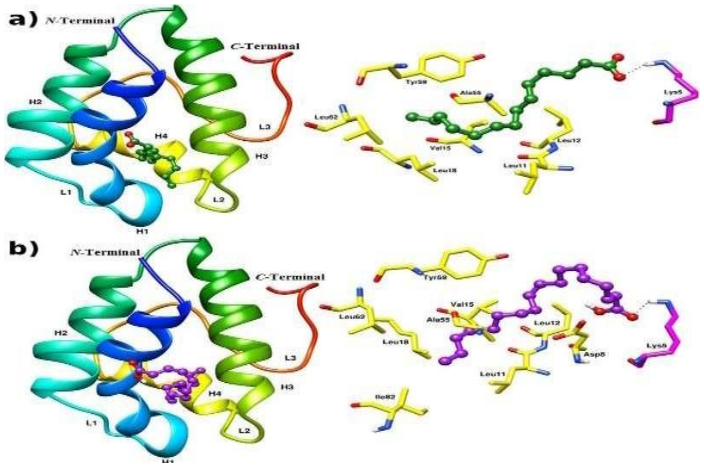

fig. 4 molecular docking simulation

As a result, pharmacophore models are frequently used as a filter to find compounds that meet the query's simple geometric and chemical functionality requirements before moving on to more difficult and computationally intensive procedures like molecular docking.[12]

Molecular docking simulations are computational methods that seek to predict the affinity (free energy of binding) of a chemical for a certain receptor as well as the quality of the interaction, frequently by employing a scoring function. Large databases of compounds are frequently screened for a given target using molecular docking simulations, and compounds are rated according to their expected affinity.

The highest scoring compounds are most certainly inert, and better compounds are ranked below them due to the large number and diversity of the screening compounds, as well as the awareness that the majority of the screened compounds are in reality probably inactive. Although this rating is still better than chance, only a few compounds are normally chosen from the top scorers, and many of these turn out to be inactive.

Combining docking-based virtual screening with pharmacophore-based virtual screening has several options:

- Prior to docking simulations, the library of ligands can be pre-filtered using a pharmacophore query.
- Any compounds that fail to bond according to the pharmacophore query can be removed from the docking simulations using a pharmacophore query. Compounds that would have scored highly in a pure pharmacophore search but fail to bind due to some hypothesis based on further information, such as incompatibility of the overall ligand structure with the receptor site, can also be discarded using this strategy. The ligands are evaluated in absolute conformation in this situation, and they should not be allowed to align with the pharmacophore characteristics.
- Another option is to use the pharmacophore alignment to guide the docking simulation location. In this situation, the pharmacophore model can be utilized to direct the placement of the ligand by using a constraint while scoring the different docking postures, similar to how it can be used to fit a molecule into a pharmacophore query. A user-defined query or an autonomously generated receptor-based pharmacophore query could be the source of the pharmacophore query.
- Pharmacophore models are highly beneficial for adding active drugs to the top-scoring docking results. This was proved in the recent SAMPL4 virtual screening competition, in which contestants were asked to rank a series of compounds for a specified target, HIV-1 Integrase, without having any prior knowledge of the compounds' activity. The best results for the group were obtained utilizing a hierarchical strategy that included pharmacophore pre-filtering and pharmacophore post-filtering of docking findings.

3. ANALYSIS OF CONFORMATION

Molecular modelling studies were conducted on a series of 1-phenyl-3-amino-1,2,3,4-tetrahydronaphthalenes (phenylaminotetralins, PATs), several PAT structural analogues, and various non-PAT ligands that show a wide range of affinities for a novel sigma 3 receptor linked to stimulation

of tyrosine hydroxylase and dopamine synthesis in the rodent brain. A pharmacophore mapping programme (DISCO) was used to discover structural elements that are common to ligands with moderate to high binding affinity for sigma 3 sites in order to construct a ligand-binding model for the sigma 3 receptor. After that, DISCO was used to suggest a pharmacophoric region that comprised one low-energy conformation of each molecule in the training set.

The obtained alignment was used in a comparative molecular field analysis (CoMFA) investigation to try to link the steric and electrostatic fields of the compounds to their sigma 3 receptor binding affinities. From the CoMFA study, a suitable prediction model was created, which will be used in the development of further PAT analogues with high affinity and selectivity for the sigma 3 receptor. The excluded volumes that resulted from comparing the molecular volumes of active and inactive substances were visualized to investigate the sigma 3 receptor's steric tolerance limitations.

Validation of Pharmacophores:

A logical approach for the generation of novel active hits is outlined here, combining validated pharmacophore modelling with molecular docking studies. Various active inhibitors in the IC50 range of 0.02–72 nM were used to construct a pharmacophore model, which was then refined using the DISCOtech module and the genetic algorithm similarity programme. Receiver operating curve and Güner–Henry score methods were used to validate the best pharmacophore model, which was then followed by 3D virtual screening. As hits, several compounds with various structures (scaffolds) were found. Following the application of drug likeliness filtering, molecules with the greatest Q fit values and a known inhibitor were docked in the catalytic domain site of HDAC class-1 for further investigation of their binding manner. Finally, in silico pharmacokinetics and toxicities for active hit compounds, also known as possible HDAC class-1 inhibitors, were anticipated. Finally, four ligands are created that meet the pharmacophoric criteria and can be further developed into strong hits.

Drug target discovery using pharmacophores:

While the goal of CADD is usually to find and optimize drug-like compounds for a specific target, the situation can also be reversed. Drug compounds are frequently identified, but the mechanism of action is unknown. These chemicals are frequently produced from herbal medicine or medications that have been phenotypically created. In such circumstances, CADD might be able to assist in locating the target. To find close analogue molecules with a known mode of action, chemoinformatic fingerprint-based similarity methods are used. However, rather than screening drugs with a pharmacophore query, pharmacophore modelling may be an option. The query might be the molecule itself, and the goal is to find the most likely pharmacophore model that fits the molecule. These pharmacophore model collections can be created manually or automatically using the PDB database.[13] Similarly, this method can be used to find a target for a chemical with a previously unknown action.

Rollinger et al. provided an example of such a method. Several plant metabolites were studied using Ligand Scout, and multiple potential therapeutic targets for these molecules were discovered. The applicability of this procedure was confirmed through experimental testing of the compounds for the indicated targets. As polypharmacology and drug repositioning grow more common, pharmacophore models are likely to play a larger role in the future. Alternatively, this method may aid in the prediction of potential side effects or off-target effects that can be factored into the development of more targeted molecules.[14]

Pharmacophore techniques have limitations.

Despite the numerous successful cases of drug design using pharmacophore modelling, as with any technology, it is not without flaws, and users should be aware of the technique's limits.

The lack of adequate scoring metrics is a fundamental constraint of virtual screening by pharmacophore. Unlike docking simulations, which use scoring functions to estimate affinity, and similarity searches, which use similarity metrics like the Tanimoto score, pharmacophore queries lack a solid, generic scoring metric. The root mean square deviation between the characteristics of the query and atoms of the molecule is widely used to express the quality of fitting the ligand into a pharmacophore query. This metric, on the other hand, is unable to account for any similarities with known inhibitors, as well as predict overall compatibility with the receptor protein. As a result, molecules that match a pharmacophore query may be very different from other inhibitors, with functional groups that are incompatible with the receptor binding site, rendering them inactive despite being a perfect match.

A pharmacophore-based virtual screen is further limited by its reliance on a pre-computed conformation database. There are only a few low-energy conformations per molecule in these databases.[9] Because the conformation is lacking, it's possible that an active molecule cannot be found. This is especially true for rotatable bonds with tiny molecular functions like hydroxyl groups, which can take on a variety of shapes. Different rotations would be difficult to discern in terms of root mean square deviation changes during conformation creation, and hence may not be properly sampled. During the fitting process, pharmacophore search algorithms can frequently spin such bonds to obtain conformations with correct orientations on the tiny flexible polar groups.

Finally, there is no one-size-fits-all approach to constructing a pharmacophore query. Pharmacophore models can extract molecules in many circumstances, although alternative models may have worked in other cases. For example, in the case of Christ et al against De Luca et al, a similar but slightly different pharmacophore was designed for a similar target.[14] Despite the fact that the screens were conducted on a comparable dataset, totally distinct compounds were discovered. Although this is just one example, there are undoubtedly many more. This is also evident in the examination of a large range of kinase inhibitors. Kinase inhibitors are often quite similar to one another but have vastly diverse kinase activity patterns.

Although pharmacophore techniques to identify kinase inhibitors would almost certainly identify kinase-inhibitor-like compounds, there is no guarantee that these molecules will be active for the targeted kinase. Finally, good outcomes may necessitate a great deal of experience as well as a dash of

serendipity. During the virtual screening SAMPL4 challenge, the impact of expert knowledge on in silico screening, also known as the in cerebra step, was demonstrated. While target identification, side effect prediction, and ADME-tox profiling appear to be potential applications for pharmacophore modelling, success is limited for new chemical classes due to a lack of information.

Perspectives for the future:

Pharmacophore modelling has been there since the beginning of CADD and has progressed from a simple concept to a well-established CADD technology with applications such as similarity metrics, virtual screening, ligand optimization, scaffold hopping, and target identification. Given the pharmacophore concept's simplicity and versatility, it's likely that more developments may be developed in the future for other uses.

Drug development based on fragments:

Fragment-based drug design has become a well-established strategy for the rational generation of new medications over the last two decades. 101 Rather than screening drug-like compounds (with molecular weights about 500 Da), very sensitive biophysical approaches are being used to screen smaller molecules with molecular weights up to 350 Da (referred to as fragments) for affinity with a receptor. Fragments that demonstrate some affinity for the target can be developed into larger, more effective molecules, and fragments that attach to nearby locations can also be connected.

In silico screening approaches are ideal for fragment-based design since the diversity of tiny molecule fragments may be quickly examined with a few hundred molecules. CADD approaches such as docking and pharmacophore modelling have thus been utilised in silico to find fragment-like drugs prior to in vitro testing; subsequent fragment recombination can be used for de novo inhibitor design.

A single pharmacophore query that spans two (or more) sub-pockets in the receptor binding site is the starting point in a first approach. An extra pharmacophore characteristic is introduced that does not reflect a molecular recognition feature, but rather an atom in the fragments, where the two fragments of the various pockets may overlap and become linked.

The fragments that satisfy the qualities included in a sub-pocket of the pharmacophore query, as well as the linking feature, are then identified. The suitability of the fragment hits for the different sub-pockets is next assessed in terms of the potential of maintaining the correct conformation once the two fragments are linked. The newly proposed molecules can then be produced and analyzed.

Cavalluzzo et al created a novel small molecule inhibitor binding to the LEDGF/p75 protein, based on an inhibitory peptide, employing a different but similar method.[15] They employed predetermined amino acid side chain fragments from the inhibitory peptide and built a pharmacophore query to connect the two predefined pieces with a third scaffold fragment that replicated the peptide's interactions. All potential compounds were virtually enumerated, and the chemical synthesizability of those that were able to assume a conformation similar to the pharmacophore query after joining all segments was evaluated. The compound's inhibitory potency was found to be 30 M IC50 after synthesis, compared to 7.4 M IC50 for the most potent inhibitory peptide. Computational pharmacophore approaches can be used to identify novel derivatives even after active fragments have been found using traditional in vitro methods. For instance, pharmacophore fingerprint-based similarity searches and the creation of 3D pharmacophore queries are effective methods for identifying larger and more potent compounds from small molecule libraries[19]

- **A potential role in protein design?**

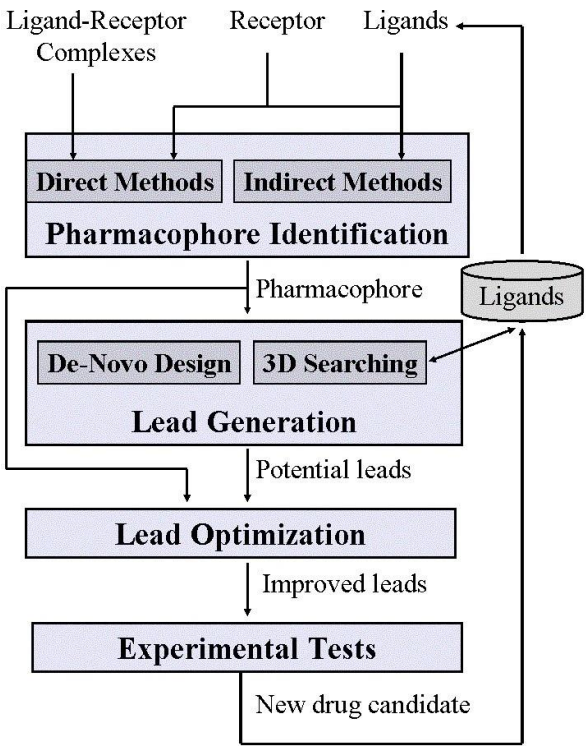

fig. 5 protein design

Despite the fact that pharmacophore modelling began as a drug design concept and is now a significant component of CADD, pharmacophore modelling shows promise in the rapidly growing field of computational protein design.[15] The goal of computational protein design is to develop an amino acid sequence that will fold into a given structure with a specified function, rather than creating pharmaceuticals for a specific protein target. Many of these interactions may entail protein–small molecule ligand interactions, and it's easy to see how pharmacophores may be used simply by reversing the small molecule drug discovery procedure for a known protein structure.

First and foremost, suitable protein templates (enzymes or otherwise) for the protein redesign process should be discovered. The ligand of interest might be used as a query to find potential binding proteins, which could then be modified to offer the ligand the best complementarity. Second, various rotamers of different amino acids are frequently tested during the virtual protein design process to discover the most desirable ones. Protein side chains can be fitted to features characterizing the complementary interactions necessary at the protein–ligand interface, similar to ligand fitting with a pharmacophore query.[16]

- **APPLICATIONS**

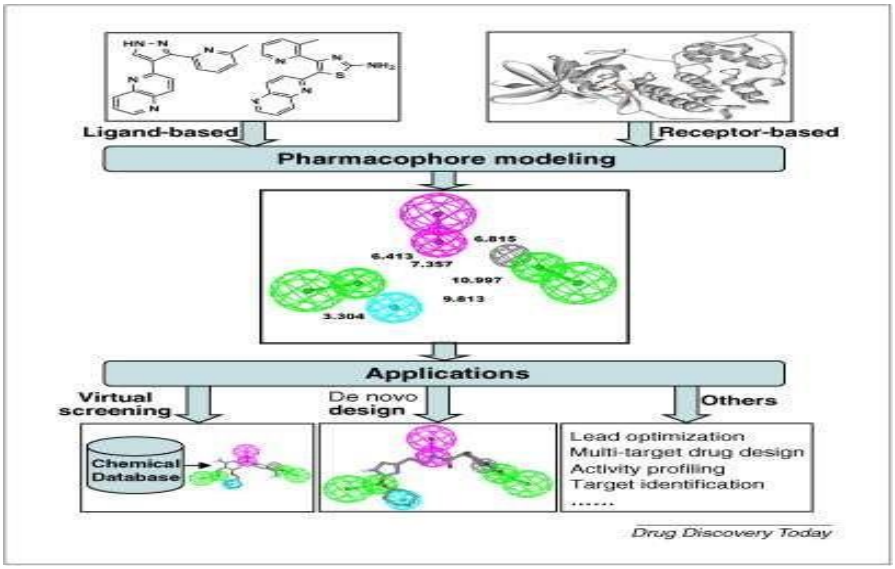

fig. 6 application of pharmacophore modeling

In computer-aided drug design, pharmacophore modelling is commonly used in three areas. The first is the identification of pharmacophoric characteristics in a drug molecule that are required to have a certain biological effect and create clear structure–activity connections. A well-developed pharmacophore model, which includes information about the receptor binding cavity's dimension, can be used to create new and more active compounds that fit the model. Such pharmacophore models are frequently used as the starting point for 3 D-QSAR analysis (e.g., C oMFA [33]), which allows for quantitative predictions. The second is scaffold hopping, which is the method of virtually screening vast chemical libraries to find compounds with diverse scaffolds (new chemotypes).

The use of parallel pharmacophore-based screening to estimate pharmacological profiles for lead structures in silico is the third domain. The use of 3D pharmacophore models may be able to predict unfavorable side effects in the early phases of drug development, reducing the likelihood of late failure of therapeutic candidates.

4. CONCLUSION

The pharmacophore notion was first proposed about a century ago as a useful image of drug interactions, and with the development in computational power over the last few decades, it has evolved into a well-established CADD approach with a variety of uses in drug discovery. Pharmacophores can be used to identify derivatives of compounds, change the scaffold to new compounds with a similar target, virtual screen for novel inhibitors, profile compounds for ADME-tox, investigate possible off-targets, or simply complement other molecular methods, depending on the prior knowledge of the system. While the pharmacophore approach has limitations, there are various therapies accessible at any time to counteract them.

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