

Pharmacophore modeling and its applications

Rashmi Tyagi¹, Amisha Singh², Kamal Kumar Chaudhary³ and Manoj Kumar Yadav^{1,4}

¹Centre for Drug Design Discovery and Development (C4D), SRM University, India, ²Department of Biotechnology, JAIN University, India, ³School of Biosciences, IMS Ghaziabad University Courses Campus, India, ⁴Department of Bioinformatics, SRM University, India

17.1 Introduction

A pharmacophore describes the molecular characteristics of a small molecule engaged for its proper functioning (biological or pharmacological) inside the cell atmosphere (Langer & Hoffmann, 2006; Mason, Good, & Martin, 2005). Molecular features may be related to its geometry, spatiality, physiology, and several other characteristics that must have a role in its action (Guner, 2005; Kaalia, Kumar, Srinivasan, & Ghosh, 2015). A pharmacophore is an excellent example of exhibiting a relation between the 3D structure and activity of a molecule (McGregor & Muskal, 1999; Taha, Bustanji, & Al-Ghoussein, 2008). The study of pharmacokinetics/pharmacodynamics and ADME-Tox properties of a compound is an essential step to establish them as a potential drug-like compound. ADMET screen is an essential and decisive factor for synthetic as well as native molecules (Hughes, Rees, Kalindjian, & Philpott, 2011; Lundblad, 2016; Terstappen & Reggiani, 2001). An obligatory requirement of favorable, adverse and inhibitory reactions of ligand (small molecules) is a potential target to carry out a specific ligand–target interaction (Tripathi & Misra, 2017). The in-depth study of protein–ligand interactions is an essential starting point in the drug development process. The use of pharmacophore modeling will make it more precise (Khedkar, Malde, Coutinho, & Srivastava, 2007). The pharmacophore concept first introduced in 1970 is to understand and study the small molecular interactions (receptor–ligand) without their detailed structural knowledge (Guner, 2005; van Drie, 2012). Pharmacophore modeling has a role in computer-aided drug design (CADD) combined with similarity analysis and quantitative structure-activity relationship (QSAR) studies (Ansari, Ghasemi, & Niazi, 2019; Taha et al., 2008). Generally, the definition of pharmacophore aims to study the arrangement of the fragments or functional groups of an active compound, essential for their biological action. The pharmacophore features extracted from the ligand–receptor interactions present at the binding site are further utilized to screen compound libraries having billions of novel compounds (Yadav, Kumar, Teli, & Kim, 2020). The accurate determination of biologically active compounds is a vital requirement for a good pharmacophore model.

A vital quality of the pharmacophore conception is the amalgamation of atom-centric representations and their pharmacophore functions where different features are designed using important atoms or groups involved in the biological interactions (Yang, 2010). The pharmacophore characteristics include hydrogen bond acceptor (HBA), hydrogen bond donor (HBD), positively charged or negatively charged groups, hydrophobic groups, or aromatic moieties (Muegge, 2002; Sakkiah, Thangapandian, & John, 2010). For a general understanding, the pharmacophore features are treated as points; for example, the centroid position of five- or six-membered rings. Interfeature distances are used to separate the feature points, which is another vital component of pharmacophore models. The geometrical arrangements of features and chemical attributes of a pharmacophore are expressed by the combination of features and their interfeature distances (Schwab, 2010).

Pharmacophore modeling is an important step in drug design, and it helps in screening potential inhibitors using the information of their pharmacophore features. Drug design is multistep that requires millions of dollars for developing a magic bullet to cure a particular disease. Researchers working in the biopharmaceutical industry want to harness the power of the pharmacophore modeling concept to select the bioactive substance using the underneath background biological information. This will not only enhance the accuracy of the process but also minimize the time of the drug

design process. The pharmacophore concept of drug design can be divided into structure-based pharmacophore modeling (Tripathi & Misra, 2017) and ligand-based pharmacophore modeling (Bembenek, Tounge, & Reynolds, 2009). Structure-based pharmacophore modeling relies on the already available knowledge of ligand or reported inhibitor-receptor complex. Ligand-based pharmacophore modeling takes advantage of pharmacophore features (hydrogen bonding, hydrophobic, and aromatic contacts using metal interactions and charged interactions) for designing novel drugs (Yadav et al., 2020). There are online available bioinformatics tools for pharmacophore modeling.

Currently, a general pharmacophore-based computational strategy comprises multiple steps. The initial step involves searching for a 3D structure of a biological target responsible for some disease. Then pharmacophore modeling is accompanied with virtual screening against databases of small compounds so that one may find an encouraging molecule having the properties to be a new potential medicine. After procuring the hits, evaluating its physio-chemical features as these properties play a crucial role to establish them as a potent inhibitor. Furthermore, the selected molecules' biological activities are also studied using enzyme-catalyzed metabolic pathway predictor servers by identifying metabolic pathways and biotransformation of high scored hits. Then, their bioavailability with ADME-Tox properties is evaluated by using ADME-Tox predictor servers in the light of the Lipinski rule of five. The compounds with desired bioavailability, bioactivity, and ADMET properties are the best candidates for in vitro validation. Thus the pharmacophore concept speeds up the drug designing process. Nowadays, the pharmacophore approach is being used for developing personalized medicines according to the genetic profile of patients (Acharya, Coop, Polli, & MacKerell, 2010; Wolber, Seidel, Bendix, & Langer, 2008). Virtual screening (Tyagi, Srivastava, & Jain, 2020) is one of the popularly used pharmacophore approach applications. Apart from that, the pharmacophore concept is popularly applicable in ADME-Tox modeling, off-target prediction, side effects prediction, and target identification. The molecular docking simulation process is becoming more advanced due to the integration of the pharmacophore concept. Thus improves the accuracy of binding pose prediction (Qing, Lee, & De Raeymaeker, 2014). The pharmacophore modeling is a subset that comes under CADD. The different steps are involved in a CADD process by using which one can able to design a drug from scratch (Fig. 17.1).

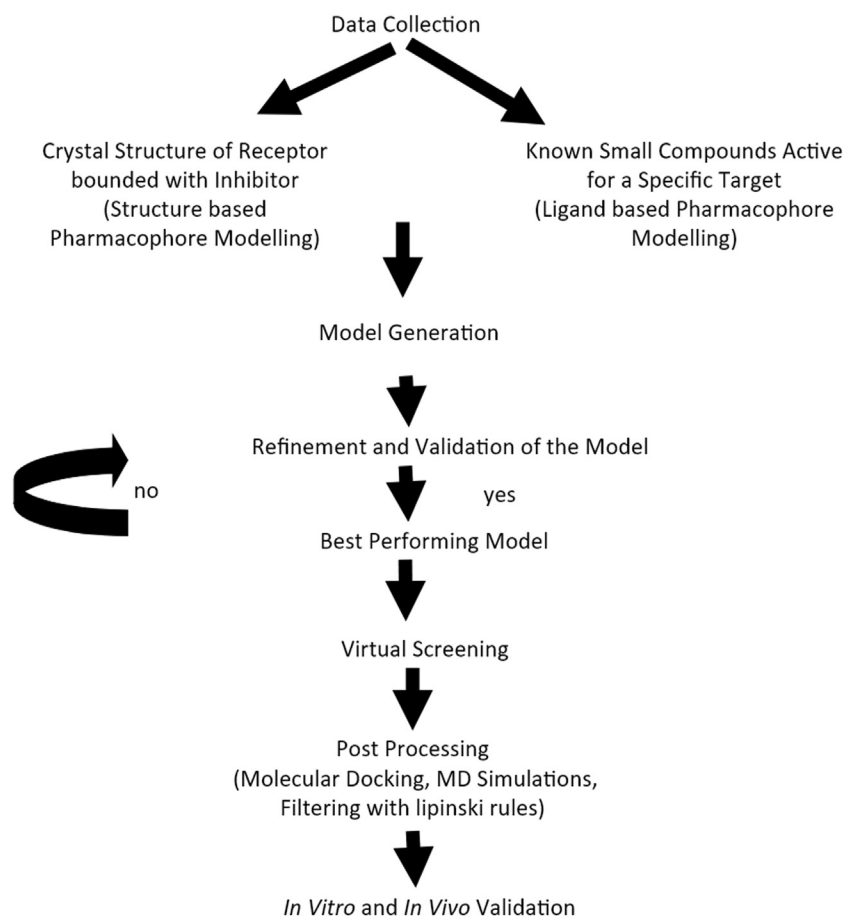


FIGURE 17.1 Flowchart depicting the process of computational drug design.

The pharmacophore concept says that the common chemical functionality between the molecules having similar three-dimensional structures is the basis of their similar type of biological functionality. The physicochemical features, namely, HBA, HBD, positive and negative ionizable chemical groups, hydrophobic groups, and metal-binding groups, are responsible for searching the similarity in their 3D structures. Apart from that, some space restrictions (XVOL), called forbidden spaces; are also introduced to exhibit the binding pocket's shape and size (Lu, Yang, & Chen, 2018; Politis, Colombo, Colombo, & Rekkas, 2017). A database can be searched using a 3D pharmacophore model designed with chemical features (McGregor & Muskal, 1999, 2000). In general, spheres are used to represent various features using the radius of tolerance to calculate the deviation from the mean position. All the features are processed electronically using logical gates, AND, OR, NOT, or their combinations. The accuracy of a pharmacophore model is directly proportional to the reliability of the dataset. In vitro, experiments result in data generation. This dataset is supposed to be the most authentic; hence, the compounds used for developing the pharmacophore model must be structurally correct and curated (Cherkasov, Muratov, & Fourches, 2014; Fourches, Muratov, & Tropsha, 2010).

17.2 Basics of pharmacophore modeling

Ideally, IC^{50} values are used as the measure of reliability obtained from in vitro data as well as, target-based and cell-free methods with the removal of some effects, such as cell efflux cell uptake and metabolism. Cell-based data depends upon target interaction with the ligand with modification in protein expression or degradation, trafficking of protein, and effect on the stability of cell membrane. For inactive molecules, it is a must to gain knowledge about the basis of their inactivity, whether it is due to the absence of interactions with the target or due to metabolic processes or efflux pump activity. There are chances of error in in vitro data (fluorometry based, spectrophotometry based, and because of the presence of chromophoric group) so it needs to be examined carefully. Presently a large amount of data (in silico/in vitro) is increasing exponentially and being deposited in various databases so all types of data can be retrieved from numerous databases like, for the activity data various sources are available publically, such as open PHACT (Williams, Harland, & Groth, 2012), chEMBL (Gaulton, Bellis, & Bento, 2012), and PubChem (Nakata, 2015), while retrieving the activity data from data sources careful attention is required because a single compound may be active against multiple targets and can be results of different bioassays. Minor errors are present in every database (a release of chEMBL usually has 5% wrong structure and 3% wrong targets information with 1% error in entry deposition) so a user must pay proper attention while data selection.

17.2.1 Division of initial data into diverse datasets

The raw (initial) data are divided into three different datasets: a training set, a test set, and a decoy set, to generate a successful pharmacophore model (Zhou, Xu, & Liu, 2015). This data splitting can be better understood with the help of a flowchart, as shown in Fig. 17.2

17.2.1.1 Training set

For the ligand-based pharmacophore modeling, a group of compounds with known activity is considered as a training dataset which provides the base for modeling. Typically, there must be two active molecules in a set of a training group. In a particular training set, compounds are separated based on their activity: very potent, moderately potent, and inactive (in semiquantitative pharmacophore model). The pharmacophore models are generated based upon common chemical features of highly active molecules with diverse 3D structures (Leach, Gillet, Lewis, & Taylor, 2010; Seidel, Ibis, Bendix, & Wolber, 2010).

17.2.1.2 Test set

Once the construction of a certain pharmacophore model is completed using a training set of potent molecules; it needs to be evaluated to know the model's performance (often smaller than the training set of compounds). Known compounds (active/inactive) are used to assess the output of the model and are represented as a test set. The intention of using the test set is to remove the inactive compounds from active data before employing the model for the unknown dataset. Furthermore, some refinement can be required to make the potential model by introducing some hindrance factors and features (Leach et al., 2010; Seidel et al., 2010).

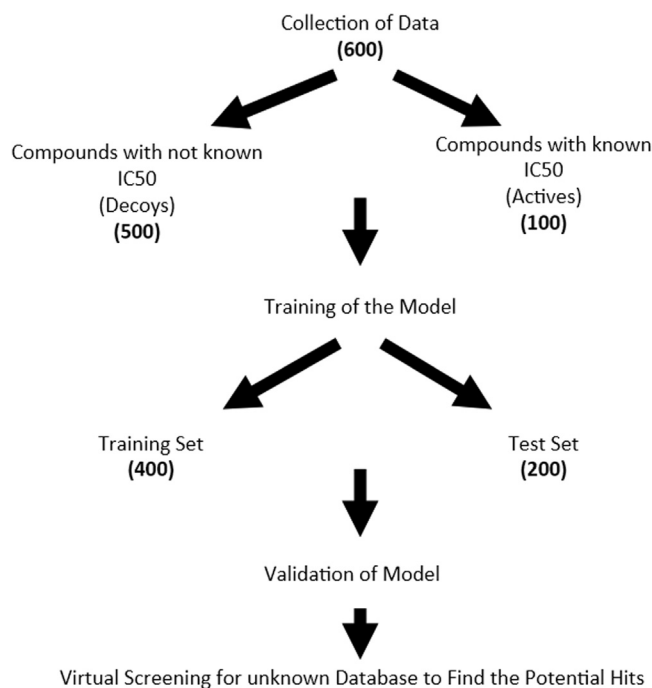


FIGURE 17.2 A general protocol for dividing the data into various datasets.

17.2.1.3 Decoy set

A decoy set is a group of compounds considered to be inactive because precise information about their biological activity is missing. These are a category of compounds having only structural differences, but their physicochemical properties are similar (Huang, Shoichet, & Irwin, 2006). The decoy set is used to know the quality of the pharmacophore model by evaluating the specificity with which a model can able to find the active compounds from a database. Ideally, 40 inactive compounds (decoy) are taken with one active compound present in a test set. Decoy compounds can be downloaded using the directory of useful decoys (DUD) (Huang et al., 2006) for certain targets. If decoys are not available in the directory for some targets, they can be retrieved from databases, such as chEMBL (Gaulton et al., 2012) or PubChem (Nakata, 2015). DUE-E is the improved version of DUD developed by Shoichet Lab, San Francisco University.

17.2.2 Conformational analysis with three-dimensional structures

The 2D and 3D structural information of a molecule is essential for a successful pharmacophore generation. 2D structures have information about chemical bonds, stereochemistry while 3D representation has all the details about geometry with bond angle, bond length, and shape of compounds. For pharmacophore modeling, 3-dimensional structure generation is required with X, Y, and Z coordinates and the length and angles with standard values. Because bioactivity of the molecules is dependent mainly on the three-dimensional structure so the user must have an accurate 3D configuration (Sadowski, Gasteiger, & Klebe, 1994). Experimentally derived 3D structure could be downloaded from the Cambridge Crystallographic Data Center. Molecules with 3D configuration can be manually generated from 2D using online tools or 3D structure generator CONCORD and CORINA (Sadowski & Gasteiger, 1993). These are reliable tools generating structures with high accuracy and structures are aligned well with X-ray crystal structures. A widely used program for generating 3D structures is OMEGA (<http://www.eyesopen.com>). The OMEGA algorithm consists of five phases. The initial two phases generate the 3D configuration of molecules having stable confirmations of commercially available compounds using the dictionary of torsions, having torsion rule of energetically favorable rotatable bonds. Then, in the third or actual confirmation elucidation process, the 2D structure of a molecule is fragmented. Later on, the 3D structure of the molecule is constructed using the information of 2D fragments available in databases (Hawkins, Skillman, & Warren, 2010). The fourth step completed with the comparison of rotatable bonds of the 3D conformations with the torsion angles in the dictionary and favorable torsions are selected to remove the internal clashes. In the last or fifth phase, for the final structure of a molecule, all conformations are sampled by the ordering of conformers using the

scoring function, MMFF94. The lowest-scoring conformers are selected with discarding high scoring conformations (with a score over than maximum allowed threshold RMSD). Algorithms are permitted to continue from the lowest-scoring conformer to 10 units higher than it, and this number of units can be user-defined. OMEGA provides very accurate 3D conformations, but it is not a fast and exhaustive method as it is using only a single algorithm compared to Discovery Studio.

Discovery Studio implements a more advanced algorithm and works with six different algorithms to make it fast and explore all the conformation space: (1) FAST, (2) BEST, (3) CAESAR, (4) systematic search, (5) random search, and (6) Boltzmann jump. As their names are indicating FAST and BEST provides quick and accurate results assigning random torsion angles and Cartesian coordinates with the minimization of native structures [using CHARMM (Brooks, Bruccoleri, & Olafson, 1983; Schleif, 2006), MMFF (Halgren & Nachbar, 1996; Halgren, 1996)/CFF (Lifson & Waeshel, 1968)]. Poling algorithm searches all the stable conformations. CAESAR divides the compounds into nodes, which are designated as rings and rigid structures, where the edges of rings are represented as rotatable bonds. The process of division of compounds into nodes is continued till all smaller units are found out. Further confirmation search of all small units is completed with the energy pruning and local rotational symmetry to remove nonunique torsions.

17.3 Different methods of pharmacophore generation

There are two methods of a pharmacophore generation: (1) ligand-based method (Caporuscio & Tafi, 2011; Sliwoski, Kothiwale, Meiler, & Lowe, 2014; Yang, 2010) and (2) structure-based method (Caporuscio & Tafi, 2011; Griffith, Luu, Garner, & Keller, 2005; Sliwoski et al., 2014). The ligand-based is an indirect one compared to structure-based methods. Ligand-based models are used in the situation when we do not have a three-dimensional structure of the target protein. Some active molecules or ligand (inhibitors) for that target, which are already known, are used to search the new inhibitors on the basis of their functional properties called features employed to generate a model (Patel, Modi, & Chhabria, 2018). Initially, the model is trained with common features of multiple known compounds called shared pharmacophore proceeding with evaluation along with validation of the model. A structure-based pharmacophore model is constructed when the crystal structure of the receptor is accessible (Griffith et al., 2005). The three-dimensional structure of protein bounded with potential inhibitor is supposed to be ideal because it provides information about residues and structure of the active site pocket. So the interaction between ligand–receptor provides the ground for the structure-based model. Sometimes we can use a homology model of target protein in the absence of its crystal structure.

There are various ways to generate pharmacophore models: using machine learning algorithms, for example, SVM, random forest (Lin, Li, & Lin, 2020; Vamathevan, Clark, & Czodrowski, 2019; Wang, Han, & Yan, 2020), and automated modeling using pharmacophore generation tools, for example, Discovery Studio (Accelrys Software Inc, 2012; Biovia, 2016), LigandScout (Wolber & Langer, 2005), MOE (Molecular Operating Environment (MOE), 2015), PHASE (Schrödinger, 2020), Pharmer (Koes & Camacho, 2011), and PharmaGist (Schneidman-Duhovny, Dror, & Inbar, 2008).

Pharmacophore models consist of various features (HB donor, HB acceptor, etc.) of ligand–receptor complexes. Center and the tolerance sphere are very crucial in determining the efficiency of a model. In general, a pharmacophore model contains three types of information: type, location, and weight. The “type” means the feature; “location” means the coordinates of the feature while weight determines the extent of the importance. The weight is taken into account during the determination of a geometric fit value of compounds (Khedkar et al., 2007). A general protocol explaining different steps to generate a pharmacophore model is shown in Fig. 17.3.

17.3.1 Ligand-based pharmacophore modeling

Numerous algorithms are available for the construction of a ligand-based pharmacophore model (Langer & Hoffmann, 2006). However, two types of methods are commonly used for the generation of ligand-based pharmacophore models: one is the RMSD-based model and the other one is an overlay-based model (Sanders, Barbosa, & Zarzycka, 2012). For the RMSD-based methods, pharmacophore fitness is calculated based upon the distance enclosed by groups of features of compounds to be matched and feature midpoint in the model (algorithms: PHASE, MOE, and Pharmer). In the overlay method, radii of features are taken into account to know the fitness between compound and pharmacophore model (algorithms based on overlay method; HipHop and HypoGen in Discovery Studio, the ligand-based modeling algorithm, espresso, in LigandScout, PharmaGist).

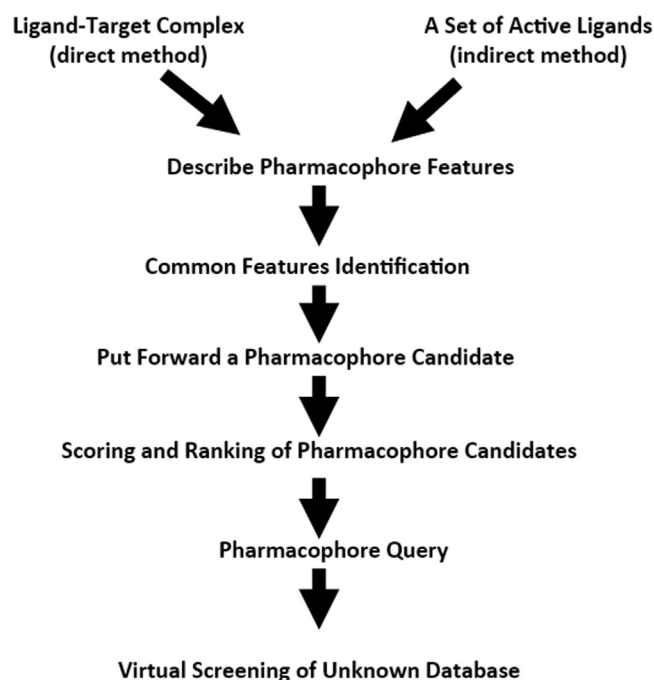


FIGURE 17.3 A general protocol for pharmacophore modeling.

17.3.1.1 Ligand-based pharmacophore modeling using Accelrys' HipHop algorithm in Discovery Studio

The algorithm is mainly used to identify the typical 3D configuration of the training molecules (molecules with known activity against the target) (Barnum, Greene, Smellie, & Sprague, 1996). This needs a requirement of the 3D structure of a compound and its functional features. The pharmacophore model construction starts with the identification of a common spatial arrangement of features of training molecules. The number of groups of features is increased until it stops finding more shared features configuration. The 3D similarity with the model, the type of chemical features with pharmacophore fitness, and the extent of their superimposition under the certain tolerance value provide the basis for evaluating a pharmacophore model.

The algorithm uses a fitness function to create many models. The HipHop refinement algorithm (Sutter, Li, & Maynard, 2011) refines the molecule as it is trained with some inactive molecules. Refinement is accomplished by integrating the steric hindrance using XVOL as space restriction to the molecule.

This process of refinement completed in four main steps:

1. First of all, active molecules are aligned to the model to estimated allowed volume.
2. Alignment of inactive molecules is carried out.
3. The remaining volume between an inactive molecule and the allowed volume of the active molecule is calculated called candidate space.
4. XVOL space is introduced at the candidate space to remove the inactive compound mapping.

An advanced algorithm called Hypogen algorithm (Langer & Hoffmann, 2006; Lin, 2000) is available in Discovery Studio, which is used to generate a 3D QSAR model. The current algorithm requires the active molecule with in vitro data (IC^{50} values are considered ideal), provide a more efficient ligand-based pharmacophore model.

17.3.1.2 Ligand-based pharmacophore modeling using LigandScout's espresso algorithm

The espresso algorithm of LigandScout (Seidel et al., 2010; Wolber, Dornhofer, & Langer, 2006) is comprised of various algorithms employed for different purposes. Ligand-based pharmacophore modeling using LigandScout is achieved in six distinct phases.

1. Omega algorithm (Hawkins & Nicholls, 2012; Hawkins et al., 2010) is utilized for the development of different configurations of compounds adopting as input.

2. Molecules are ranked in accordance with their flexibility, and all conformations of molecules are analyzed by granting the pharmacophore features to each conformation of molecules.
3. Hungarian algorithm (Wolber et al., 2006) is applied for the alignment of at least two flexible molecules with all the conformations all pharmacophore features.
4. Furthermore, retrieving the perfect alignment (high score) conformations, commonplace pharmacophore features are analyzed as well as created, which is designated as intermediate pharmacophore feature for the next phase.
5. In the fifth step, suitable ranks are provided to the intermediate pharmacophore making the use of various scoring functions (chemical feature overlap, atoms overlap, or their combination).
6. The steps of the espresso algorithm are repeated from first to fifth until all the conformation of two molecules is completely processed. If any of the conformations are found to be unmatched to intermediate pharmacophore, it is abolished, and that model is not preceded further.

There are two types of alignment methods to create a pharmacophore model: a combination of shared pharmacophore features based and merged pharmacophore features based. The intersecting part between overall pharmacophore features of the molecules used as input makes the shared feature model. The common features existing in all training molecules are included in the final common feature models. All features of the aligned molecules are summated in a merged feature pharmacophore. Sometimes the number of features becomes very large, so there must be a defined boundary where we omit unnecessary features. XVOL boundary may be introduced for steric restrictions, placing it surrounding the model pass over the information regarding inactive compounds fitting.

17.3.2 Structure-based pharmacophore modeling

The orientations and interactions between a ligand and receptor are a piece of the necessary information for structure-based pharmacophore modeling. The molecular docking approach is the source of complexes made with protein–ligand. The protein data bank contains plenty of crystal structures of target proteins bounded with their inhibitors (Protein Data Bank, 2019). Automated modeling algorithm analyses the interacting residues surrounded the ligand inside the active site pocket; these residues provide the ground for the model. Refinement is the crucial part of structure-based pharmacophore modeling to give optimal performance because it is based on single receptor-ligand complex interaction. There are different ways to generate a structure-based pharmacophore model.

17.3.2.1 Structure-based drug discovery with Discovery Studio's interaction generation protocol

An interaction map is constructed by the in-depth study of the active site of a protein. LUDI, interaction map (Böhm, 1992) is used to create a basic pharmacophore model. Space where the functional group of the ligands has interaction with protein needs to be analyzed carefully to build a model. Four types (aliphatic, aromatic, lipophilic, HB acceptor, HB donor; Böhm, 1992) of interactions are taken into account by two programs. NH/OH group are supposed to be the sites of HB donor of enzymes while keto group with unprotonated nitrogen atoms on the sites of HB acceptors. HB donors and HB acceptors are positioned according to their definite length with a specific bond angle. Each HB donor atoms require four acceptor interaction sites, while the HB acceptor requires two interaction sites (Böhm, 1992). Aliphatic carbons, carbon rings, and amide with sulfur are positioned within a certain radius and treated as aliphatic lipophilic and aromatic lipophilic atoms. In Discovery Studio, there is a user-defined function called density of polar and nonpolar interactions, and this is directly proportional to the complexity of interaction maps.

17.3.2.2 Structure-based pharmacophore modeling with LigandScout

All the chemical features involved in protein–ligand interaction are taken into account in LigandScout's structure-based pharmacophore model generation (Wolber & Langer, 2005). LigandScout program considers the majority of non-acidic hydroxyl, thiols, and amides as HBDs. A hydrogen bond is designated if the HB acceptor heavy atom is situated within the range defined by the program (the hydrogen bond is permissible within the range of 109.5 degrees \pm the angle between the heavy atom and the HBA position). The tolerance sphere can be increased, and the angle of restriction may be set by the user to allow more conformational flexibility for the model. Some by default designations of LigandScout are hydrophobic areas indicated by spheres with hydrophobic group branches with chains all around (Wolber & Langer, 2005). The hydrophobicity scoring function of the program is utilized to analyze the hydrophobic group if the program ensures the group as hydrophobic, then the adjacent volume of the macromolecule is analyzed. In case a hydrophobic area is positioned within a range of 1–5 Å in the protein direction, a spherical hydrophobic shape of 1.5 Å is set over the hydrophobic ligand portion. These are user-defined features that can be changed in the settings:

PI groups: the atoms/groups, which are found to be protonated at physiological PH range and NI groups: the atoms or groups, which are deprotonated at physiological pH range (Wolber & Langer, 2005). If PI–NI groups with their interaction partner are detected under the range of 1.5–5.6 Å by the program, a chemical feature and sphere are introduced having 1.5 Å of tolerance radius to that atom (user can alter the distance).

Important parameters defined by LigandScout are: the distance between H bond must be between 2.5 and 3.8 Å, the angle between donor and acceptor is set to be 180 degrees (Wolber & Langer, 2005), and angle difference from the breakage of bonds in both directions must be 34 degrees. The hydrogen bonds are specified in a different way in the case of SP² and SP³ hybridization because of the difference in their flexibility. Around the hydrogen bond, a cone of 146 degrees is introduced to define the acceptor atom space for the sp² donor atom. Likewise, for the sp³ donor atom, there is a freedom of rotation between the donor atom and hydrogen atom. The hydrogen bond is permissible within the specific range of 109.5 degrees ± the angle between the heavy atom and the position of the HB acceptor. The basic protocol for pharmacophore modeling is shown in Fig. 17.3.

17.4 Validation of pharmacophore models

The validation of a pharmacophore model is an essential and multistep process preceding the screening of compounds. The process can be repeated and revalidated if the results of experimental validation after virtual screening are not consistent with the pharmacophore model-based screening score (Akram, Waratchareeyakul, & Haupenthal, 2017).

On the basis of validation results, a pharmacophore model can be upgraded by using validation data as an input. More refinement methods must be employed if the model does not provide concordant output with in vitro results. For theoretical validation, a group of compounds called a test set is utilized (known compound) with determined activity to test the performance of a model. If initial data from the various experimental outputs do not have inactive compounds, it is necessary to have a decoy set (John, Thangapandian, & Arooj, 2011).

Generally, hits are categorized as:

- True positive hits: all the active candidates detected by the model.
- False positive hits: all the inactive candidates detected by the model.
- True negative hits: inactive candidates that are not detected by the model.
- False negative hits: active candidates that are not detected by the model.

Some important parameters can be determined by screening the test compounds to know the number of active or inactive (decoy) compounds.

Sensitivity and specificity are two specific parameters that are crucial for the performance of a model. Sensitivity is the capacity of searching active compounds or how well a model can find them. Specificity is the capacity of a model to differentiate active compounds from inactive compounds (John et al., 2011; Mishra & Singh, 2010). Furthermore, there are parameters: yield of actives (YA) and enrichment factor (EF). These two parameters, together, are used to search the active compounds from the database with optimal performance of a model.

Equations for sensitivity, specificity, YA, and EF factors are displayed below:

$$\text{Sensitivity} = \frac{\text{number of true positives detected}}{\text{total true positives in the database}} \quad (17.1)$$

$$\text{Specificity} = \frac{\text{number of true positives detected}}{\text{total true positives in the database}} \quad (17.2)$$

$$\text{YA} = \frac{\text{number of true positives}}{\text{total number of hits}} \quad (17.3)$$

$$\text{EF} = \frac{\text{YA}}{\text{true positive hits present in the database/size of database}} \quad (17.4)$$

17.4.1 Receiver operating characteristic curve

ROC analysis is used to measure the performance of a pharmacophore model (Bradley, 1997; Chow, Lehr, & Pong, 2010; Metz, 1978). The curve is used to plot the rate of true positives and false positives of the hits table with ranks. If there is a need to compare two or more models, the ROC curve is a vital requirement. It notifies about how efficiently a model ranks the active compounds. A plateau after the steep rise of the curve is the indication of a high number of

active compounds than inactive compounds. After the steep rise, if the curve gets a level, a user can set a threshold value for the hits. For comparing two models, if curves do not cross each other than the curve with an initial higher steeply rise is supposed to perform better. In case, two curves cross each other, another parameter area under the curve (AUC) is introduced for comparing the model equation (Narkhede, 2018). AUC is a valuable measure because it provides the scores on the basis of the efficiency of the model except for visual inspection. Numerical integration of all the rectangles is utilized to get the AUC obtained by sensitivity and specificity of each active compound. The AUC score ranges between 0 and 1, where 0 tells that all of the inactive molecules will rank first, and 1 means all of the active molecules rank first whereas the 0.5 value of AUC depicted random selection of compounds with AUC of high value signify the better performance of a model (Akram et al., 2017).

For obtaining a model of optimal quality, the ROC curve should have a steep slope with a high AUC value, which will provide all the active hits without the inactive with specificity and sensitivity value of 1 along with high EF, which is termed as an ideal curve. An ideal ROC curve is shown below in Fig. 17.4, having the specificity and sensitivity value of 1 and AUC is displayed in Fig. 17.5. There are four points to be considered in a ROC curve, explained with the help of Fig. 17.4. First, the red dotted line going vertically upward and horizontally toward the right corner is exhibiting an ideal model or curve with a specificity and sensitivity score of 1 with a high EF value. The ideal model is practically rare. Second, a green model has better performance than a random model, and third is a black diagonal which signifies the random model having fit values of an equal number of actives and inactive with sensitivity and specificity value of 0.5. A random model is not considered good for virtual screening. At last fourth curve, below the random model's horizontal black line also not used for further analysis.

Ideal model performance is not possible because if a model detects more active compounds, inactive also come in the same frequency. Hence, an increase in sensitivity is always compensated with the loss of specificity. So to get rid of this shortcoming of the curve, multiple restrictive models are employed covering various chemical groups of compounds. The combinational model implying all parameters is theoretically validated. Now the resultant final pharmacophore model is ready to implement in virtual screening (Gomes, Muratov, & Pereira, 2017).

17.4.2 Structure-based pharmacophore modeling approach for the design of azaindole derivatives as DprE1 inhibitors for tuberculosis: a case study

Decaprenyl-phosphoryl-D-ribose 2-epimerase (DprE) is a crucial drug target for *Mycobacterium tuberculosis*. DprE is a donor of arabinose sugars, which is utilized in the formation of cell wall components, lipoarabinomannan and arabinogalactan, using the decaprenyl-phosphoryl-D-arabinose pathway. So, it is essential for the growth and survival of *M. tuberculosis*. Blocking this enzyme can able to inhibit the synthesis of the bacterial cell wall and will lead to inhibit the pathogen. A structure-based pharmacophore model is developed using the PHASE module of Schrodinger suite with default parameters on the basis of structural information of DprE-TCA1 complex with PDB ID: 4 KW5 (Kb, Kumari, &

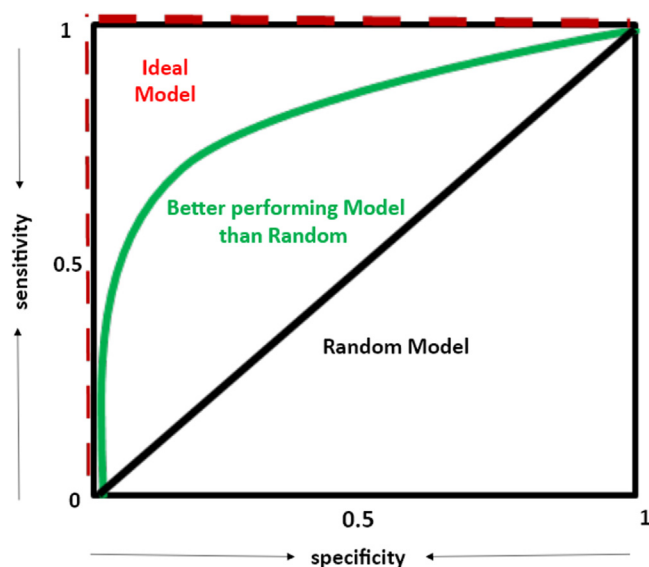


FIGURE 17.4 Ideal receiver operating characteristic curve with a straight line up and continuously toward the upper right corner horizontally exhibited in red dotted line. Receiver operating characteristic curve with good performance in the green color and random curve in the black color diagonal with specificity and sensitivity score 0.5. From Murgueitio, M. S., Rakers, C., Frank, A., & Wolber, G. (2017). Balancing inflammation: Computational design of small-molecule toll-like receptor modulators. Trends in Pharmacological Sciences, 38, 155–168. <https://doi.org/10.1016/j.tips.2016.10.007>.

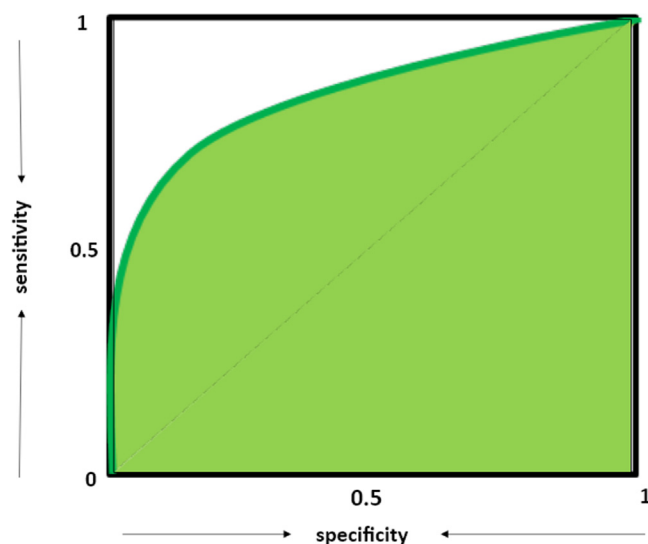


FIGURE 17.5 Area under the curve values designate the green area under the receiver operating characteristic curve. From Murgueitio, M. S., Rakers, C., Frank, A., & Wolber, G. (2017). Balancing inflammation: Computational design of small-molecule toll-like receptor modulators. *Trends in Pharmacological Sciences*, 38, 155–168. <https://doi.org/10.1016/j.tips.2016.10.007>.

Shetty, 2020). The pharmacophore model was used to screen a library of 156 azinadole derivatives retrieved from the ZINC15 database using TBA7371 as a reference compound (an azaindole derivative having a noncovalent property, and it is in the first phase of clinical trials as DprE1 inhibitor). Azaindoles are found to be very potent compounds against drug-sensitive and isoniazid/rifampin-resistant strains. A four featured model was developed comprising of two hydrogen bond acceptors and two aromatic rings (4-AARR) at specific distances. The library was screened against this model, based on similar ligand sites as well as fitness score (Schrödinger, 2020). Glide docking and prime rescoring were accomplished with top-scored 25 molecules from filtering using structure-based pharmacophore model, and two potential hit compounds (ZINC000170251946 and ZINC000170252277) were identified, which were further used for the investigation of DprE1 inhibition experimentally. Using the Qikprop of Schrodinger Suite, both of these molecules were found to exhibit drug-likeness features. Furthermore, Induced-fit docking and Molecular Dynamics simulation studies were employed to identify the final one hit compound. So it was conferred that ZINC000170252277 compound can be used for the next level in vitro and in vivo validations for DprE1 inhibition.

17.5 Recent trends in pharmacophore generation

Pharmacophore modeling is a computational technique applied in various computer-based biological applications using structural based and ligand-based approaches. Pharmacophore modeling has wide applications in different CADD projects. Besides, 3D pharmacophore models are applied in virtual screening and protein functionality studies. Studies have reported that 3D pharmacophore models combined with molecular dynamics (MD) simulations can dynamically reveal the macromolecular-ligand interactions by mimicking the physiological environment of cells. In a recent development, 3D pharmacophore is used in conjunction with the machine learning algorithm for screening an array of new molecules (Sato, Honma, & Yokoyama, 2010).

17.5.1 Machine-learning models incorporated with pharmacophore descriptors

In the current era, machine-learning methods are the most discussed and worked area in data science. Several pharmacophore approaches, such as HS-pharm and Pharm-IF, have trained machine-learning models to work more efficiently. In the HS-pharm approach, more than 3000 protein–ligand complexes were selected and analyzed to classify their atoms into interacting and noninteracting residues. Furthermore, the interacting atoms were used to generate fingerprints.

Through machine-learning approach (decision tree and Bayesian classifiers), fingerprints were trained to extract the most important interacting residues from the protein–ligand complex (Barillari, Marcou, & Rognan, 2008). Similarly, interaction fingerprints *Pharm-IF* of several pharmacophore models were trained with machine-learning algorithms to filter the most relevant docking poses in the protein–ligand interactions. Furthermore, after generating the atomistic models of pharmacophore models, the most prominent drug targets were selected (Sato et al., 2010).

In a recent development, DeepSite and other software were successfully implemented with neural networks for better prediction of druggability in drugs. Here, grid points and their atomic pharmacophore descriptors for approximately 7000 protein complexes were assigned. Furthermore, subgrids were selected in the assigned grids, which contain the protein-binding pocket. These subgrids were used to train with a neural network, a machine-learning algorithm. The approach has further led to a clear and precise description of the binding pocket and its affinity (Jiménez, Doerr, & Martínez-Rosell, 2017).

17.5.2 Prediction of pharmacokinetic properties

The most important parameter to predict the druggability of drugs is ADMET (pharmacokinetic) properties. Prediction of correct ADMET properties is a prime requirement for the designing of suitable and desired drug molecules. The pharmacophore modeling approach can be used in the prediction of ADMET properties. Prediction of correct ADMET properties and binding affinity in a list of pharmacophore models of drugs can create an idea of common binding and affinity values with similar ADMET properties in the drugs having similar properties with previously taken drugs (Choudhury, Deva Priyakumar, & Narahari Sastry, 2016).

A recent study on hexadecahydro-1*H*-cyclopenta[*a*]phenanthrene framework (HHCPF) has reported the integration of pharmacophore modeling with the QSAR method. This combination has provided an insight into the relationship between pharmacophore features at a particular position and target binding site properties in a group of drug molecules. Here, the docked complexes of HHCPF drug molecules with their targets were taken into consideration, and different ADMET properties of drugs were compared with different target structures extracted from databases, such as DrugBank, PDB, and UniProt (Macalino, Gosu, Hong, & Choi, 2015).

17.5.3 Target identification and de novo ligand design using pharmacophore approaches

Target identification for active drug molecules is possible through pharmacophore models. The target identification helps in the study of the mechanism of action of selected drugs. In addition, pharmacophore modeling helps in exploring the existing knowledge on drug repositioning and polypharmacology of drugs (Keiser, Roth, & Armbruster, 2007; Koutsoukas, Simms, & Kirchmair, 2011). On the basis of pharmacophore fingerprints of known drug molecules and their mechanism of action; potential drug candidates are listed. Now, pharmacophore models can be generated by predicting the active sites on the target proteins involved in diseases. The target protein structure can be obtained from the PDB database. The active site mapped with the highest score can be predicted as the potential drug target (Xu, Liu, & Wang, 2015). De novo ligand designing of a compound or ligand having desired pharmacophore properties is possible after analyzing the designed pharmacophore models. For instance, a computer program, NEWLEAD can able to develop novel and desired ligand molecules by analyzing their pharmacophore features and connecting the missing links using linkers, that is, atoms, chain, or ring structures (Tschinke & Cohen, 1993).

17.5.4 Protein functionality studies

Pharmacophore modeling is a widely used approach to understand protein functionality at the mechanistic level. Furthermore, the ligand-dependent function of a receptor can be analyzed using a pharmacophore modeling approach. For instance, G-protein-coupled receptors (GPCRs) are one of the most important and widely studied drug targets in various diseases. GPCR drug target has complex pharmacophore features and flexibility in the receptor's functioning in a ligand-dependent manner. A study has effectively analyzed the receptor-specific binding pattern in closely related receptors from the same protein family by analyzing the binding patterns and key residues present in the loop regions (Bermudez, Rakers, & Wolber, 2015). Some studies have taken the concept of biased nature of ligand toward the specific pathways in which their specific GPCRs targets were involved as an analyzing pattern. Some ligands have shown conformational restrictions toward the extracellular region (Bermudez & Bock, 2019; Bermudez et al., 2015).

17.5.5 3D pharmacophore modeling using a web platform

With recent advancements in the development of a pharmacophore modeling approach, a lot of web-based applications and portals are available. These web-based applications are freely accessible and provide ease to work without any requirement of local installation. At a time, they can easily access the databases for millions of targets and ligand molecules for multiple users. For instance, the PharmaGist web portal provides a facility for ligand-based 3D pharmacophore

generation. Here, each submitted ligand is aligned on reference ligand by their rotatable bonds required for flexible alignment on respective target molecule for 3D pharmacophore generation (Schneidman-Duhovny, Rossi, & Avila-Sakar, 2012). Similarly, the Pharmervirtual screening software is used for the virtual screening of several databases containing small molecules (Koes & Camacho, 2011). ZINCPharmer is specifically used for the virtual screening of small molecules from the ZINC database (Chatzieftheriou, Anogiannakis, Theodorou, & Lagaros, 2019; Koes & Camacho, 2011).

17.5.6 Pharmacophore methods in light of molecular dynamics simulations

The active sites present on the target molecule are highly flexible, so the structure-based pharmacophore having a single conformation of the drug–target interaction will not reveal all the features involved in the interaction. Dynamic pharmacophore models will solve the problem related to flexibility in the active site region.

MD simulation works on the principle of the dynamic nature of protein–ligand complexes present in the cellular environment. MD simulation approaches may create an adynamic pharmacophore model that is complementary to the flexible active sites (binding pockets) of the target. The integration of all the conformations of a pharmacophore model using MD simulation is one of the most advanced approaches of 3D pharmacophore modeling. Since both the target and ligands are dynamic entities, target–ligand complex and their interaction patterns are also the same. The dynamics of the complex is easily mapped through the MD simulation approach.

In one of the studies, information from MD simulation is integrated with 3D pharmacophore models to perform virtual screening for HIV protease and HIV1 integrase inhibitors (Carlson, Masukawa, & Rubins, 2000). In a recent study a single pharmacophore generated from the PDB structure of a protein is merged with approximately 2000 MD simulations (20 ns) generated pharmacophore structures derived from the protein–ligand complex. From this approach, two different features for pharmacophore structures were derived: one from the PDB-generated structures and another from the MD simulation-generated structures. The differences between the two features help in distinguishing between active and inactive molecules during virtual screening (Sun, Gao, & Dong, 2018).

With the development of different approaches for integrated MD simulation and 3D pharmacophore model generation, a lot of software are developed based on these approaches. Hydration site-restricted pharmacophore works on the principle of the hydration site restriction where the pharmacophore is generated on the basis of hydration sites present on the protein molecules and having unfavorable thermodynamic properties reported by MD simulation. This approach filters more relevant and entropically favorable ligands for the target protein (Hu & Lill, 2012).

The site identification by ligand competitive saturation approach and the surface of proteins having probe molecules containing different pharmacophore features are analyzed using MD simulation. The resulting probability maps of probe molecules (having pharmacophore features) are prioritized according to their free energy to design the most effective and relevant pharmacophore model for the target protein (Yu, Lakkaraju, & Raman, 2015; Yu, Lakkaraju, Raman, & MacKerell, 2014).

The Dynophore approach involves a combination of MD simulation and 3D pharmacophore models whose spatio-temporal feature is analyzed via statistical approach. Dynophore application analyzes the chemical interaction features of the protein–ligand complex in combination with MD simulation conformers. Dynophore analyses feature (hydrogen bonds, lipophilic contact, and charges) and extract their interaction points from MD trajectory. The extracted features are statistically ranked based on the interaction pattern of the protein. Furthermore, the best statistically fit model is used to design a 3D pharmacophore model (Sydow, 2015).

Common hits approach and MYSHAPE, both works on structure optimization of 3D pharmacophores based on MD simulation. The common hits approach grouped the MD simulation-generated 3D pharmacophore models according to their interaction patterns. These pharmacophore models are further used for virtual screening for creating a virtual library of ligands (Wieder, Garon, & Perricone, 2017). In contrast, the MYSPACE approach optimizes the shape-dependent pharmacophore features obtained from MD-simulated protein–ligand complexes (Perricone, Wieder, & Seidel, 2017).

GRids of phArmacophore Interaction fieLds (*GRAIL*) approach represents the molecular interaction fields of pharmacophore models generated in MD simulation. This approach also generates atom densities of a protein, ligand, and water present in the interaction complex (Schuetz, Seidel, & Garon, 2018). The PyRodalgorithm generates a 3D pharmacophore model based on heuristic scoring functions for water molecules that are present at or near the protein-binding site. Furthermore, the pharmacophore-binding pocket is analyzed for hydration site-specific features in the pharmacophore models. The model is further used for virtual screening (Schaller, Pach, & Wolber, 2019). AutoDock Bias with Solvent Sites approach involves cosolvent-based MD simulation of protein, which occurs in the presence of

ethanol and water molecules. Furthermore, binding sites (hotspots) of the ethanol hydroxyl and methyl groups are analyzed from MD trajectories. Finally, the calculated free energies of ethanol are introduced in AutoDock. This docking approach is investigated and compared with previous features (Arcon, Modenutti, & Avendaño, 2019).

Pharmmaker is a recent approach that uses the cosolvent simulation for the generation of 3D pharmacophore models. The pharmacophore model is further used for the virtual screening of ligand molecules. In a case study, after cosolvent simulation, different probe molecules and their druggability are accessed using DruGUI (Bakan, Nevins, Lakdawala, & Bahar, 2012). Furthermore, Pharmmaker processed the most druggable binding site by analyzing the binding sites in protein–ligand interactions. The snapshots of the interactions are used to design a 3D pharmacophore model and virtual screening (Lee, Krieger, Li, & Bahar, 2020).

17.6 Applications of pharmacophore modeling

3D pharmacophore is developed from either a group of active ligands or protein (target)–ligand complexes of apo targets. The developed 3D pharmacophores are used to screen the library of compounds (ligands) by the process of virtual screening (Fig. 17.6). The compounds that satisfy the required parameters of the query pharmacophore are further validated through experimental procedures (Schaller, Šribar, & Noonan, 2020).

17.6.1 Generation of e-pharmacophore for virtual screening of drug molecules

In a case study, a virtual library of ligand molecules was constructed against mycobacterial target cyclopropane synthase (CmaA1). Mycobacterial cell wall contains mycolic acid, which provides drug resistance and pathogenicity to bacteria. Enzyme CmaA1 is involved in mycolic acid's biosynthesis, and hence, CmaA1 can act as an efficient drug target. The five different stages of cis-cyclopropanation of unsaturated mycolic acid were studied using MD simulation to map the peculiar features responsible for mycolic acid biosynthesis. The MD simulation trajectories were used to model and validate pharmacophores and have further revealed the conformational diversity at the binding sites of the CmaA1 when they bind to different ligands corresponding to different functions. Forty different structural snapshots were obtained from MD trajectories for two binding sites of CmaA1. The structural poses were used to generate e-pharmacophore models, which have further revealed the properties of active sites with interacting residues. After the model validation, e-pharmacophores (query pharmacophores) were used to screen ligands from databases to construct a virtual library of ligands using a virtual screening approach. Docking studies were performed for the two different sets of ligands (active and inactive), and ADMET properties were studied. Ligand molecules with good ADMET values were used for hit prioritization (Choudhry, Priyakumar, & Sastry, 2016; Choudhury, Deva Priyakumar, & Sastry, 2014; Choudhury, Priyakumar, & Sastry, 2015).

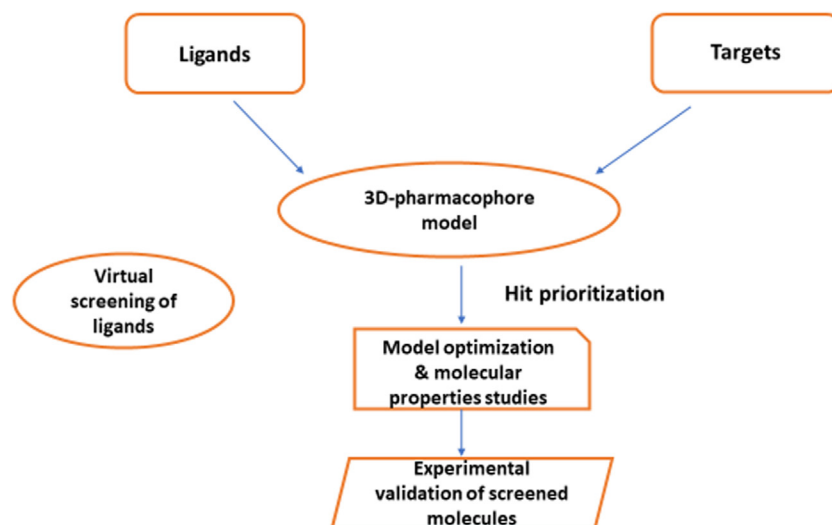


FIGURE 17.6 The procedure of virtual screening using 3D pharmacophore models.

17.6.2 ADME-Tox analysis

The majority of compounds fail in the clinical trials despite all the desired properties due to their unsatisfactory ADMET, which is a chief contributing aspect (Alavijeh & Palmer, 2004; Lin & Lu, 1997; Zhang & Tang, 2018). Accordingly, extensively acknowledged ADMET attributes urgency to generalized initial for the duration of the drug discovery progress along with pharmacophore modeling processes were regularly used as aforesaid ADMET prediction (Guner & Bowen, 2013). Pharmacophore models were used to pick out possible synergy of drugs with drug-metabolizing enzymes by means of identical chemical groups of investigation of molecules against famous ADMET profile drug molecules (Yamashita & Hashida, 2004). Enzymes of important significance were found that ADMET profile is the cytochrome P450 (CYP) that begins drug breakdown. Antiquated envisioned such simplest six isozymes of CYP (1A2, 2C9, 2C19, 2D6, 2E1, and 3A4) culpable in as much as up to 90% of drug metabolism (Lynch & Price, 2007). On the basis of purposeful interactions about familiar drugs along with CYP enzymes, pharmacophore models based on receptor were bring about which might be capably directed toward expect druggable compound binding with positive CYP as well as determine the opportunity in regard to deterioration along the way of a particular enzyme (De Groot & Ekins, 2002; Ekins, De Groot, & Jones, 2001; Masimirembwa, Ridderström, Zamora, & Andersson, 2002). For uridine 5'-diphosphate-glucuronosyltransferases, models, such as ADMET pharmacophore, were generated; these models are enzymes and related to drug clearance and transporters in combination with P-glycoprotein and natural cation (Sorich, Miners, McKinnon, & Smith, 2004; Sorich, Smith, McKinnon, & Miners, 2002).

17.6.3 Generation of a multitarget ligand

A multitarget ligand approach is highly effective in targeting more than one target. This approach can reduce experimental cost and time for the designing of a novel drug. For instance, the biochemical pathway of the arachidonic acid cascade is responsible for an effective inflammatory response. The response produces several proinflammatory mediators, such as leukotrienes, via 5-lipoxygenase-activating (FLA) protein. The pathway also produces antiinflammatory molecules, such as epoxyeicosatrienoic acids, which later on hydrolyzed to soluble epoxide hydrolase (sEH). Targeting FLA protein and sEH molecules is an effective approach to design drugs for inflammation. Drug molecules that target both the aforesaid molecules are screened and filtered using a pharmacophore-based virtual screening approach (Temml, Garscha, & Romp, 2017). First, virtual inhibitors were screened for FLA protein using ligand-based pharmacophore models. Hit molecules selected for sEH inhibitor were further prioritized to select one novel dual inhibitor for FLA and sEH targets (Waltenberger, Garscha, & Temml, 2016).

17.6.4 Modulation of the immune system

Modulators are small molecules that can able to change or modulate the immune responses. For instance, toll-like receptors (TLRs) recognize the molecular patterns responsible for infection and, in turn, activate innate immune responses (Yuk & Jo, 2011). Designing TLRs' modulator molecules is a highly effective strategy to target several diseases, such as cancer, autoimmune diseases, neurological disorders, and allergies (Murgueitio, Rakers, Frank, & Wolber, 2017). A recent study conducted by Sribar et al. in 2019 has reported a novel TLR8 modulator after structure-based virtual screening and experimental validation. Here, through the molecular docking approach, different binding modes of the screened molecule were analyzed. Furthermore, the molecules were filtered based on the best binding poses. The best pose is used to design a 3D pharmacophore model, which was further used for virtual screening purposes.

17.6.5 Pharmacophore-guided drug target identification

Although usually breath-taking intention in reference to CADD is about to analyze furthermore enhance drug alike molecules as a particular target, effective adverse scenario additionally occurs. Generally, drug alike molecules were recognized; however, the mechanism of action is uncertain. The compounds mentioned above were regularly originating from natural medicinal or advanced phenotypic drug. Instances, as discussed earlier, CADD may additionally help regarding target pick out. Chemoinformatic tools based on similarity along with a recognized mechanism of action were engaged toward finding near analog compounds (Keiser et al., 2007; Koutsoukas et al., 2011). Still, pharmacophore modeling is comparatively preferred with a pharmacophore query for the screening of compounds. The purpose is to find out maximum alike pharmacophore features that grip into the molecule. These types of pharmacophore compilation may be built by extracting protein structural information from the PDB database (Wolber et al., 2008).

Furthermore, this approach is applied against a target regarding accustomed compound along with an unidentified mechanism of action. Applying LigandScouttool, numerous metabolites from plants along with a couple of potential druggable targets (proteins) can be analyzed. Preliminary verification against these compounds versus particular drug targets corroborates the appropriateness of the approach. Reasonably predicted pharmacophore models play an essential aspect within the destiny and at the time that drug repositioning and polypharmacology emerges as extra all over the place (Hu & Lill, 2012; Koutsoukas et al., 2011; Lu et al., 2018). Willingly, the aforementioned method can additionally boost expecting viable aspect outcomes or off goals that may be taken under consideration to layout greater specific compounds (Wieder, Perricone, Seidel, & Langer, 2016).

17.7 Future perspectives of pharmacophore models

Pharmacophore modeling antiquated about ago that affecting inception based on CADD and has derived from a primary idea right into a properly installed CADD method with programs, such as target identification, scaffold hopping, ligand optimization, virtual screening, and similarity metrics, along with others. Integrity and adaptability of pharmacophore idea perhaps predicted yet trends might be built inside the destiny as a unique function.

17.7.1 Fragment-based drug design

After a long time, fragment-based drug design plays a more effective role in the analytical improvement of new drugs (Kumar, Voet, & Zhang, 2012). In the screening of receptors with closeness, smaller molecules having a molecular weight, 350 Da are used to compare larger molecules with a molecular weight of 500 Da is a precise biophysical approach. Fragments having few resemblances with the targets are further developed into larger and more potential compounds, and fragments that are binding to adjoining regions may also be related so well. A few hundred compounds are sampled with the help of a single small molecule fragment effortlessly, which makes fragment-based drug design a relevant approach for in silico screening. Previously in vitro is trying for docking and pharmacophore modeling in CADD but now fragment-like compounds recognize in this approach. After this for the de novo design of inhibitors, the next fragment recombination may be used (Böhm, 1992, 1993). In earlier techniques, the beginning place is a single pharmacophore query, which has two subpockets inside the binding site of the receptor. Despite this, an additional new pharmacophore characteristic is introduced, which does not constitute a molecular perception characteristic but shows an atom in the fragments where there is an overlapping of two fragments from the different pockets and can be linked with each other.

17.7.2 Protein–protein interaction inhibition

Earlier, the protein–protein interactions (PPIs) are supposed to be a very tough or undruggable target. Later on, high-throughput screening results in identifying a small molecule that can disrupt the PPIs (Wells & McClendon, 2007). These molecules are termed as small molecules PPI inhibitors (SMPPPIs). The structural study of ligands and proteins of PPI complexes shows that the inhibitors mimicked these proteins present at PPI interfaces (Fry, 2008). In terms of shape, chemistry, and electrostatic capacity level, the SMPPPIs, which are placed to replicate the herbal interaction, are no longer accessible (Voet, Berenger, & Zhang, 2013). The pharmacophore queries constructed due to this mimicry from PPI complex systems express that it may be used to identify through digital screening (Voet & Zhang, 2012). By hiring various strategies, the pharmacophore efficiency of the amino acids present at the PPI interface can be mapped (Voet et al., 2013). For the discoveries of many SMPPPI, we are thankful to pharmacophore search functions (Reddy, Li, Fischer, & Dekker, 2012; Voet, Callewaert, & Ulens, 2011), consent of PPI interface (Mustata, Li, & Zevola, 2010; Voet et al., 2013) interactions both manually and automatic methods or by identifying important interactions by using molecular field analysis (Tintori, Corradi, & Magnani, 2008). PPIs act as auspicious achievements for regulating beside the point signaling, as located in illnesses consisting of most cancers. The pharmacophore modeling encourages the discovery of novel SMPPPI by creating the queries, which encode the crucial interactions at the PPI interface, both as a single screening tool and also with the involvement of other techniques.

17.7.3 A potential role in protein design

As determined previously, the drug design approach originated from pharmacophore modeling is currently an essential part of CADD, which displays commitment about the presently sprouted area of protein designing through

computational approaches (Tintori et al., 2008). Preferably drug design against a particular protein target, computational protein designing (homology modelling), intent to derive a series of amino acids, which may pleat into the desired configuration as well as function for the further research and analysis. In various instances that can contain protein with native ligand (Tinberg, Khare, & Dou, 2013) and sometimes not, where the imaginary such pharmacophore approach can be utilized without a doubt through the way of overturning the procedure design of small molecule drug for a regarded shape of the protein. Mainly, appropriate templates of proteins (in case of enzymes or any other case) must be diagnosed regarding the remodeling process of designing protein. Interested ligand will work as a query to attempt to become aware of feasible binding proteins that could thereafter be improved to provide the choicest integral to the ligand (Nivón, Moretti, & Baker, 2013). Identical to the fitting of a ligand along with a pharmacophore query compound, the side chains of proteins may be suited to appearance depict integral synergy needed on the interface to treat as the perfect protein-ligand complex.

17.8 Conclusion

Almost a century ago, the pharmacophore modeling idea was used as a future image for valuable drug interaction, and in few decades, with the help of various applications of drug discovery packages, CADD techniques have become more-established. Pharmacophore models, with various information of modeling, may be utilized to search new compounds and their derivatives, convert the scaffold to new compounds with the same goal, virtual screening against novel inhibitors, ADME-Tox profile of compounds, and inspect potential off-targets or equitable supplement using different molecular strategies. Due to limitations in pharmacophore idea, various treatments are performed to counter them. This versatility makes pharmacophore modeling a blessing for medicinal chemists in CADD to achieve the destiny.

Conflict of interest

The authors declare that they have no conflict of interest.

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