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Rational Drug Design and Optimization of New Leads using Modern Quantitative structure-activity relationship (QSAR) Techniques.

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Abstract

Drug discovery and designis avery challenging, expensive and time taking process. I*n silico* approaches involving computational tools and methodologies hasbecome a part of the drug designing anddiscoveryprocess from drug target search, selection to its lead optimization.Over several last few years.Quantitative structure-activity relationship (QSAR) has become a very essential tool for new lead identification, its design and optimization to discover reliable predictive models.This review article will focus on the summarised overview of ligandbaseddrug design approaches using advancecomputational techniques likepharmacophore modelling, andmodern QSAR techniques etc., along with the recent developments in this field and their application in new drug discovery for therapeutic purposes.The review concludes with an outlook on the scope and challenges of the rational drug design using QSAR studies.

Keywords: Drug design, quantitative structure-activity relationship, pharmacophore modelling, lead identification

INTRODUCTION

A. DRUG DISCOVERY AND DEVELOPMENT PROCESS

Drug design and development and its marketingis a tedious, time taking and cost effectiveprocess. The cost of this process has been increasing significantly since the last thirty four years [1].Computer-aided drug design (CADD) has been generally accepted and widely used in the area of modern drug discovery and development for its high efficiency in the design ofnew pharmacophores and their optimization into lead compounds, thus helps in saving both time andmoney in the large scale synthesis and biological analysis.
The important steps of the process of drug discovery are:

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1. **Lead Identification:** A critical step is the identification of lead compounds. Leads can be obtained from natural products, molecular design, modification of natural and synthetic products, biochemical aspect of the disease process and broad screening of synthetic compounds etc.
2. **Lead Optimization:**The identification of lead molecules through the synthesis and analysis lead compounds to develop structure activity relationships, calculation of physicochemical properties and using them for lead identification from techniques like quantitative structure activity relationships (QSARs). Modern techniques such as combinatorial chemistry with high throughput screening (HTS) provide us an enormous number of new chemical entities but these techniques have not been proved cost effective because of high costs of reagents and modern equipments, there has been a strong demand for the computer aided techniques which are quick, reliable and cost effective to rationalize these early steps in drug development.
3. **Pre-Clinical Lead Development:***In-vivo* studies in animals, animal safety studies, drug metabolism studies and large scale synthesis come under pre-clinical lead development.
4. **Clinical Lead Development:** It involves the small scale safety and dose identification tests in human volunteers as per guidelines (clinical trials phase I-IV), toxicity studies and followed by development of clinical study protocols employing clinical investigations on patients (phase II) and comparative double blind studies on patients' studies (phase III). [2]
5. **Computer Assisted Drug Design (CADD**)

All the world's major pharmaceutical companies are now using Computational tools. Computer assisted molecular design is an emerging technology that makes use of knowledge of the structural and physicochemical aspects of the receptor/ligand interaction to identify pharmacophore or aid in the design of molecules.[3] [4]

Computers have become an important part of the drug design process and have a large number ofapplications, which include structure analysis, superimposition (alignment), and lead compound design,identification of active conformations and pharmacophores, combinatorial design, protein and binding site structure, ligand binding, quantitative structure activity relationship (QSAR)studies etc.

B. RATIONAL DRUG DESIGN

Rational design of novel drugs is getting more and more popular and tends to substitute the classical approach. The most important characteristic of the rational drug design is to utilize the system under study for developing a strategy for potential leads in drug discovery. [5]

Rational drug design is divided into two main categories:

a. Development of small molecules withtargets, biomolecules, whose functionality is in cellular processes and 3D structural information is also available. This approach of drug design is well established and is being applied extensively by the pharmaceutical industries.

b. Development of small molecules with known properties for targets, whose cellular functions and their structural information may be known or unknown. [6]

Objectives of Structure Guided–Computer Aided Drug Design [7]

• To quantitatively correlate the relationships between chemical structures change and its respective effectin biological activity.

• To optimize the existing leads.

• To predict the biological effect of unknown compounds.

1. Structure Guided–Computer Aided Drug Design

Structure guided drug design approach is an important part of drug development for known 3D structures of potential drug binding sites, which are the active sites. In structure based drug design, a known 3D structure of a target bound to its natural ligand or a drug is determined either by X-ray crystallography or by NMR to identify its binding site. Lead discovery requires,the starting point of structure based drug design for a known target. Once

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the ligand bound 3D structure is known, a virtual screening of chemical compounds can be possible**.**As a typical discipline in the area of CADD, the quantitative structure-activity relationships (QSAR) have been evolved a lot and became more systematic from its original basic idea [8]. The conventional QSAR technique, which was developed by *Hansch and Fujita*, assumed that there was a relationship between the properties and structure of a molecule, and it was possible to establish simple mathematical equations for the description of a given properties shared by a set of active compounds which had a definite chemical diversity but some extent of structural similarity [8].

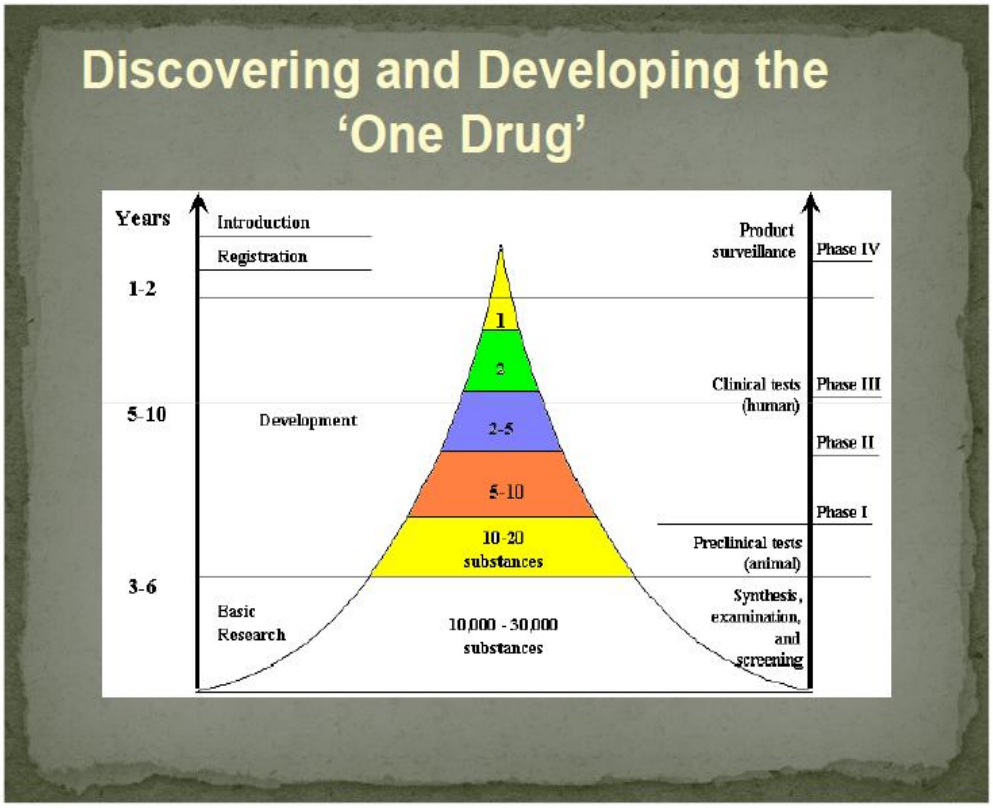

Figure 1: Drug discovery and development timeline

Different types of modern QSAR methods arebased on the classic QSAR. These methods have become powerful tools to predict the physicochemical and biological properties of unknown compounds, thushelps to accelerate the process of designing novel compounds and their optimization [8]. These computational techniqueshelps in the design of novel, and potent inhibitors because they can predict the mechanism of ligand-receptor interactions. In this article, our main focus is on the combination of classical QSAR, 3D-QSAR and application of these recent computational techniques in drug design.

2. 2D-QSAR

Today, the biological activity of a compound is considered to be dependent on its physicochemical properties. Based on this, researchers have tried to predict and changephysicochemical properties and structure into molecular descriptors. As a result, QSAR has rapidly become an important tool in drug discovery & development. A good QSAR model is mainly dependent on the best choice of descriptors, so chemical structure, molecular shape, and electrostatic properties all of them play a significant role in the binding of ligands to its targets and form complexes and should therefore correlate with the activity of the compounds. Hence, robust and efficient descriptors for molecular shape, electrostatic, and

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2D structural description could be sufficient to be used to construct structure-activity relationships.Most molecular descriptors developed for QSAR models could be classified as:

a. Steric Parameters

These include Taft's steric substituent constants (Es); calculated molecular refractivity-CMR; molecular volume and molecular surface area; molecular van der Waals volume and radius constants; Charton's steric constants; Sterimol parameters; and molecular shape parameters.

b. Electronic Parameters

These are mainly Hammett substituent constants; Taft's substituents constants; constants for inductive effects; *p*Ka value; and quantum chemical parameters related to electronic structure, such as the energy of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), net atomic charges, molecular polarizability.

c. **Hydrophobicity Parameters**

Includes the logarithm of the octanol-water partition coefficient (logP); calculated logP(ClogP); the p fragmental constant; the logarithm of the molar aqueous solubility (logw);the logarithm of the retention factor of high performance liquid chromatography (log*K*); chromatographic Rf values.

d. Other Parameters

Including topological descriptors (such as molecular connectivity indices); indicator parameters; hydrogen bonding descriptors that estimate the basicity or acidity factors; counts of hydrogen bond acceptors or donors; and the molecular similarity index.

These descriptors listed above have been used to derive successful QSAR models [9]. Nowa days, the importance of chiral drugs has become well known. In 2000, for example, the wordwide annual sale of chiral drugs was $133 billion, which represented almost 40% of all drug sales [9]. If a drug candidate is a racemate, the US Food & Drug Administration (FDA) requires a detailed study of both enantiomers [09-12]. Because of the stereo-specificity of biological effects, QSAR techniques must take into account atomic chirality.

3. 3D-QSAR

3D-QSAR methods are very useful in drug design and have advantages such as feasible computational time and fast generation of models that may be helpful to predict the biological properties of new compounds and guide modifications on the structure of known ligands to enhance affinity and activity. [13]There are two different approaches to develop QSAR models from 3D structures of compounds:***The ligand-based approach***, also called ***receptor-independent (RI***), and the ***structure-based or receptor dependent (RD***) methods. The most used ligand-based methods to modelling 3D-QSAR are based on pharmacophore, shape or molecular fields [15]. Methods based on molecular fields have been widely used in the last decades to describe important properties related to ligand-receptor complex such ashydrophobic, electrostatic, and hydrogen-bonding and van der Waals interactions [15].

4. 3D-QSAR Methods

a. Comparative Molecular Field Analysis (CoMFA)

The CoMFA method, introduced by Cramer *et al.* in 1988, is based on the principle that molecular non-covalent interactions are important to explain an observed biological effect. The first step in a CoMFA study is the selection of chemically related compounds, i.e., molecules that have a common pharmacophore (not necessarily the same molecular skeleton, in contrast to classical QSAR methods) and should act *via* the same mechanism of action. As pharmacophore refers to 3D structures, structures of all molecules are converted to 3D.Then,

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atomic partial charges are calculated and low energy molecular structures (conformations) are generated. In the next step, the superimposition of 3D structures has beendone. The aligned structures are placed on a 3D lattice box with defined grid spacing. The steric and electrostaticfields, Lennard-Jones and Coulomb potentials, respectively, are calculated between a probe atom and molecules at each lattice intersection. The calculated MIFs are used as descriptors and stored in a matrix in which each row represents a compound of the training set and each column the value of the interaction energy, in kcal/mol, at a given grid point. The biological data is stored in a column and have to be correlated with the descriptors matrix. Since the number of columns in descriptors matrix exceed the number of rows, it is difficult to correlate the biological activity with field values by regression analysis [16].

b. Comparative Molecular Similarity Indices (CoMSIA)

Comparative Molecular Similarity Indices (CoMSIA) is a technique similar toCoMFA. However, the molecular field expression of CoMSIA includeshydrophobic, hydrogen-bond donor and acceptor terminology in addition to steric and coulombiccontributions. CoMSIA also calculates the similarity indices bycomparing each ligand with a common probe with a radius of 1Å, and charge,hydrophobicity and hydrogen bond properties equal to 1. CoMSIA usesGaussian function to describe steric, electrostatic and hydrophobic components of the energyfunction. CoMSIA avoids the use of an arbitrary cutoff value forthe energy calculations. Similarity indices corresponding to CoMSIA molecular fields definethe ligand-protein binding interaction [17].

Classification	Examples
Basis of Intermolecular modelling, or information used to developed QSAR	
Ligand-based 3D-QSAR	CoMFA, CoMSIA, COMPASS, GERM, CoMMA, SoMFA
Receptor-based 3D-QSAR	COMBINE, AFMoC, HIFA, CoRIA
Bases of alignment criterion	
Alignment-dependent 3D-QSAR	CoMFA, CoMSIA, GERM, COMBINE, AFMoC, HIFA, CoRIA
Alignment-independent 3D-QSAR	COMPASS, CoMMA, HQSAR, WHIM, EVA/CoSA, GRIND
Basis of the chemo metric technique used for correlating structural properties and activities	
Liner 3D-QSAR	CoMFA, CoMSIA, AFMoC, GERM, CoMMA, SoMFA
Non-Liner 3D-QSAR	COMPASS, QPLS

Table 1: Classification of 3D-QSAR approaches [7]

5. 3D QSAR Model DevelopmentPARAMETERS:

a. Data Collection and Structure Preparation

The training data set of compounds was collected from the literature. The 2D structures were transformed into 3D structures using a computer programme such as ChemBio3D Ultra (PerkinElmer/Cambridge Soft, UK).

b. Conformation Search and Pharmacophore Generation.

Another computer programme used to determine a hypothesis for the 3D conformation (such as FieldTemplater module of Forge v10 (Cresset Inc., UK) software). The Field Templater generated hypothesis for the bioactive conformation will then represented with its calculated field points, resulting in a 3D field point pattern. The field points will then be generated by

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using XED (eXtended Electron Distribution) force field. Four different molecular fields such as positive and negative electrostatic, 'shape' (van der Waals), and 'hydrophobic' fields (a density function correlated with steric bulk and hydrophobicity) have to be calculated.

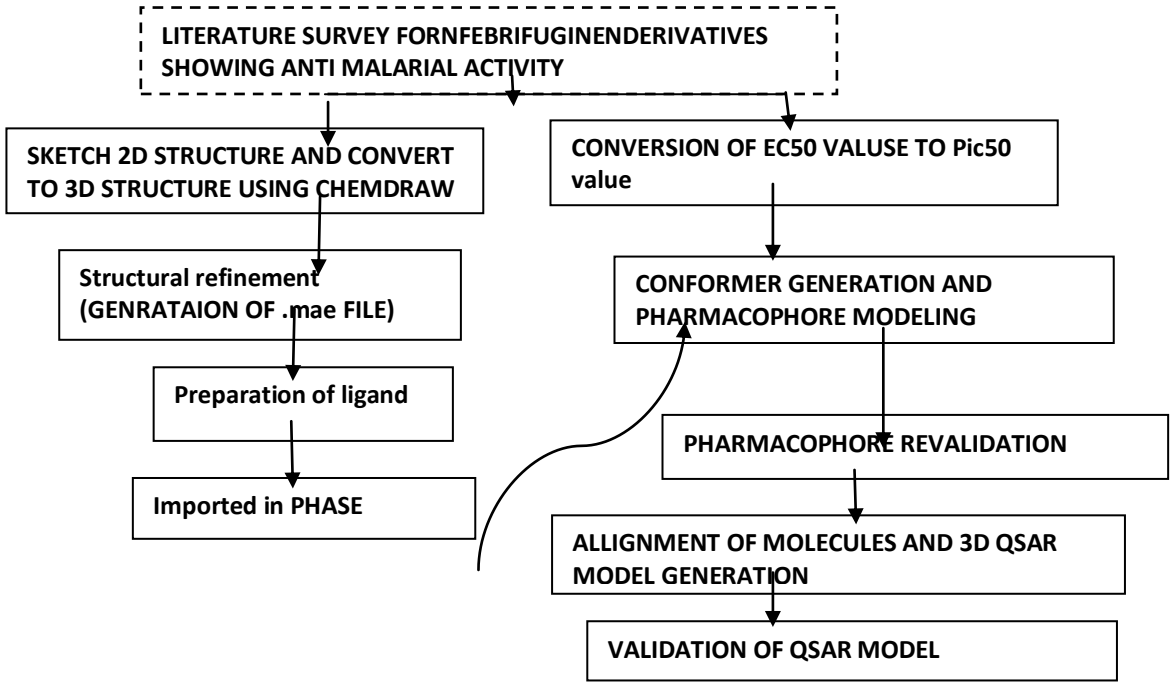

Figure 2: Graphical representation of Pharmacophore model generation and QSAR analysis

The field point pattern provides a compressed representation of the compound's shape, electrostatics, and hydrophobicity. The XED method used for the conformational analysis and design of a pharmacophore which resembles the bioactive conformation.

c. Compound Alignment and 3D QSAR Model Development

The 3D-QSAR method explains descriptors by calculating the different molecular properties at the intersection point of a 3D frame. This method includes the whole volume of the aligned training set compounds. The pharmacophore template, obtained from the Field Template module directly transferred into the Forge v10 (Cresset Inc., UK) software, then compounds are aligned with the identified template. Field point based descriptors will then use for building 3D-QSAR model. After the alignment of all the training set compounds with known IC50 value onto the identified pharmacophore template, Forge software uses 50% field similarity and 50% dice volume similarity. The superimposed compounds with the best matching low energy conformations with the template molecule, taken into consideration for building the 3D-QSAR model. The experimental activity (IC50) of the data set compounds were converted to its positive-logarithmic scale by using the formula: **[pIC50 = −log (IC50)]** and defined as the dependent variable.

d. Validation of The QSAR Model

The best model is validated by regression analysis to get regression coefficient (r2), cross-regression coefficient (q2) and similarity score (Sim) of conformers for each ligand with respect to the pivot. The derived QSAR model has to be assessed using leave-one-out (LOO) technique to optimize the activity-prediction model. The LOO cross-validation (LOOCV) is considered one of the most effective methods of regression model validation with small training dataset. [23]

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6. PHARMACOPHORE MODELLING

The term pharmacophore was introduced by Paul Ehrlich in the early 1900s, which referred as "molecular framework that carries (phoros) the essential features responsible for a drug's (pharmacon) biological activity". Later, it became clear that the presence of pharmacophoric features was insufficient for activity and their 3D disposition in three-dimensional space was also

Very important. Therefore, the term was expanded to refer to the 3D arrangement of featuresthat enables a molecule to exhibit a specific biological activity. Practically a pharmacophore model consists of a three dimensional configuration of chemical functions surrounded by tolerance spheres. A tolerance sphere defines area in space which should be occupied by a specific type of feature. Hydrogen bond donors and acceptors, positively and negatively charged groups, and hydrophobic regions are typical features (of pharmacophoric groups). Often, a pharmacophore will contain one or more "dummy" atoms, which are used to define a geometric entity (centroid of a ring, a lone pair direction, excluded volume etc.). These pharmacophoric groupings can be considered an illustration of the important concept of bioisosteres, which may be atoms, functional groups or molecules with similar physical and chemical properties such that they produce generally similar biological properties .[2]

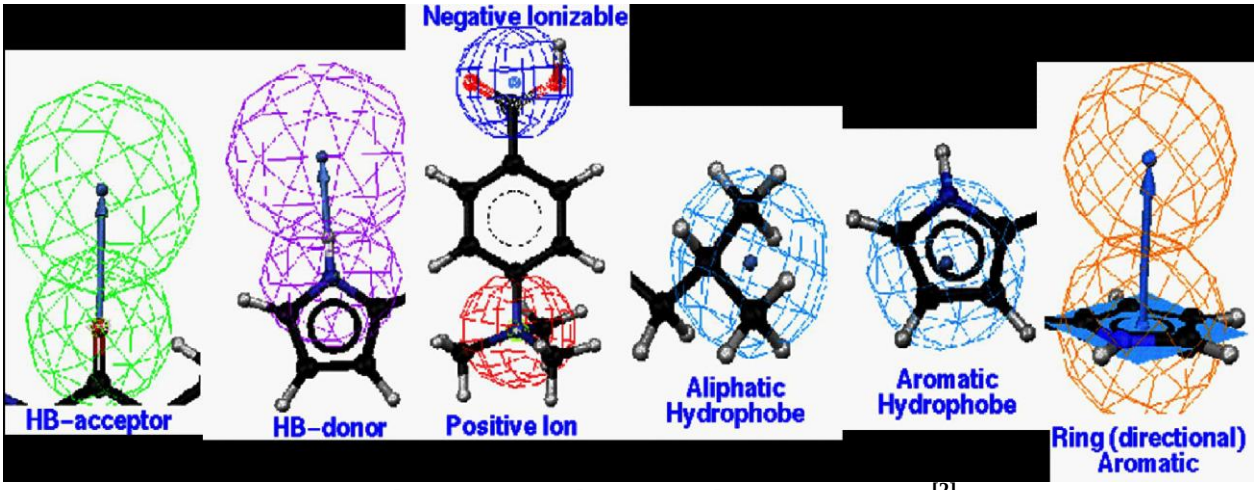

Figure 3. The common pharmacophoric structures[2]

7. CURRENT TRENDS IN QSAR MODELLING

Chemical similarity may help with qualitative evaluation of compound's bioactivity but its quantitative estimation requires the use of statistical tools that can help design the relationship between chemical structure and bioactivity. Currently, there is much talk about the use of artificial intelligence (AI) in chemistry. The difference between AI and MLis in the following way.

AI is the combination of tasks that demonstrate characteristics of human intelligence, while ML is a subset of AI which accesses data, analyses trends and generates intelligent, actionable understandings. Many people use AI in the same context as ML in many data-rich field, starting from health care to astronomy. In this regard one can say that AI has been used in chemistry since the 1960 as QSAR. Generally ML explains a set of techniques for predicting a property Y based on known examples, where each examplei has property Y (i) and a set of k features X(i,j), j = 1 to k. but both of these have their philosophical limitations.

This section concentrates on trends in QSAR in the pharmaceutical industry because, arguably, that is where the opportunities and challenges for innovation and potential impact

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on society are greatest. Most pharmaceutical companies are likely to focus on developing QSAR models for ***on-target (e.g., binding of ligands to targets) and off-target (secondary pharmacology)*** activities, as well as ***ADMET (absorption, distribution, metabolism, excretion, and toxicity)***properties. Besides that, most popular application of QSAR is the prediction of trends, which are accurate enough to prioritize sets of compounds for synthesis and experimental evaluation.

Here we will describe some modern trends in the field of QSAR.

1. ***Data. Data driven modelling methods*** are clearly highly dependent on the size of data set, quality, and diversity. The size and dissimilarity of datasets have enormously increased since past few years due to technological advances in robotics and miniaturization (similar trends of course are observed in nearly any area of research and technology development). We analyse huge volumes of data for a specific project, typically for 104–106 different molecules. Data generation is resource intensive, and data always contain experimental error. Other than pharmaceutical industries, the availability of large volumes of published, or otherwise public domain data in databases like ChEMBL, PubChem, or ZINC has transformed the field.

2. Validation methods.An external test set is used asa common method of validating a QSAR model and a Part of the data is kept aside then the remainder is used to train the model. This model is used to find out the test set endpoints and a measurement for the accuracy of prediction is calculated.

Validation of QSAR generated models for properties of chemical mixtures is more complicated. Regarding that, the points out approach is not different from conventional QSAR methods, but should be used only for predicting the same mixtures with new composition. The compounds out approach is suitable for predicting new mixtures of compounds from the modelling set; the mixtures out approach is for mixtures of one compound from the modelling set and one new compound; and the everything out approach (the most rigorous) is for mixtures of completely new compounds.

3. Multitask modelling. In conventional method of drug design using QSAR, only one predicted activity is modeled at a time. However, drug development, needs multiple activities, both on- and off-target for prioritizing compounds. Ranking compounds based on more than one predicted activity simultaneously is called multi-parameter optimization or multi-task modeling.

These multiple activities may also includethe related targets in one species, the same target in different species, the same target under different experimental conditions etc. . . .

Multitask modeling is expected to be helpful when data are significantly less, i.e. not every molecule is tested on all target sites, and the hope is that information will ‘‘leak’’ or ‘‘read across’’ different targets and reinforce structure–activity trends. Several methods have been proposed for multitask QSAR modeling including perturbation theory + machine learning (PTML), inductive learning and multi-objective optimization as applied in proteochemometricsmodeling. The most common way of handling multitaskmodeling currently is with deep neural nets, especially convolutional neural nets.

4. Applicability domain (AD).An applicability domain defines the space of molecular features on which the model has been trained and to which it should be applied; the AD provides a means for estimating the reliability of property predictions for new molecules from a QSAR model. It permits finding out less reliable predictions and helps identify additional molecules that might be needed to expand the model AD into more productive chemical spaces. Interestingly, AD is one area where QSAR is ahead of ML, although there a difference of opinion on the best approach to this issue.

5. Modelability.A statistically significant model can be generated from a given dataset depends on a number of conditions. If the size of the experimental error in the measured

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dependent variable approaches the magnitude of the variation across multiple molecules in the dataset, it becomes increasingly hard to generate meaningful models. The signal to noise ratio in the data set is very less.Considering activity and descriptors together, the relatively new concept of Modelability proposes that predictivity of QSAR models is then limited by activity cliffs. As explained above, activity cliffs exist when very similar compounds have different biological properties, making the target property of compounds hard to predict. This problem is not easily resolve by changing either the QSAR method or the descriptors used. An exception is that using stereochemicallydependent descriptors can reduce activity cliffs where different stereoisomers exhibit very different activities. Metrics that estimates the prevalence of activity cliffs in a dataset are good predictors of themodelability of that dataset. Clearly, these metrics cannot distinguish activity cliffs that are intrinsic to the SAR response surface from those that are artifacts due to large experimental uncertainties in the measured activities.

6. Interpretability. An important process in QSAR modeling is selecting the most suitable subset of descriptors. This enhances the ability of models to generalize well and can make analysis easier because some descriptors are used in the model. Thus models are usually interpreted in two ways. The first is to find out which descriptors are the most important for driving improved properties of molecules. This is called ‘‘descriptor importance’’ for QSAR or ‘‘feature importance’’ for ML in general. The second, applicable to models trained on substructure-type descriptors, is to project the most important features from the model onto exemplar molecules to highlight structural features associated with more favourable activity. A molecule with atoms coloured according to their contribution represents a molecular ‘‘heat map.’’ Another important, descriptor- and model-independent method for interpreting features is to apply small perturbations to the input descriptors one at a time, while keeping the other constant, and observing the effect on the modelled property (sensitivity analysis, effectively generating partial derivatives of the response with respect to the descriptors). These techniques of interpretation have limitations as well. It is important to recall that no statistical method can distinguish correlation from causation, and interpretations cannot always be related to a mechanism. A practical approach towards mechanistic interpretability, lateral validation, is to observe trends across related phenomena: When the choice of variables, the sign and size of their coefficients are similar across multiple

7. ML methods. There are many standard methods of ML in QSAR.In AI applications, such as image Classification or speech recognition, DNNs have been shown to be superior to any techniques that came before. DNNs began to be applied to QSAR66 after the Merck Molecular Activity Challenge in 2012. In less than a decade we have seen an enormous growth in publications using diverse DNN architectures for modelling chemically-related properties. To put DNNs into context for QSAR, there are many other ML methods used in QSAR modeling including k-nearest neighbours (kNN) partial least squares (PLS), support vector machines (SVM),70 relevance vector machines, (RVM), random forest (RF), Gaussian processes (GP),73 and boosting. In the pharmaceutical industry (in fact, in any discipline), ML and DNN methods can be compared to older methods by the following:

a. Prediction accuracy
b. Number of sensitive and tunable hyper-parameters
c. Need for descriptor selection
d. Length of training time
e. Length of prediction time (including uploading the model into memory)
f. Domain of applicability (determined mainly by descriptors and training set characteristics)
g. Interpretability of models[37]

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8. FUTURE PERSPECTIVES ON PHARMACOPHORE MODELLING[25]

For the pharmacophore concept, it can be anticipated that there is a possibility for further developments.

a. Fragment-Based Drug Design

since last two decades, fragment-based drug design has become a successful and widely sued method for the rational design of novel drugs.[25] Rather than screening drugs like molecules (with molecular weights of around 500 Da), smaller molecules having molecular weight up to 350 Da (referred to as fragments) are being screened for affinity with a receptor using highly sensitive biophysical methods. Fragments showing some affinity for the target are grown into bigger and more potent compounds, and fragments binding to adjacent areas can be linked as well.Since the diversity of small molecular fragments can easily be sampled with a few hundred compounds, in silico screening methods are highly suitable for fragment-based design. CADD methods such as docking and pharmacophore modeling have therefore also been used to identify fragments *InSilico*prior to testing *In Vitro*; subsequent fragment recombination can be used for the de novo design of inhibitors.[26, 27]

b. Protein–Protein Interaction (PPI) Inhibition

Structural analysis of proteins in PPI complexes and inhibitor complexes show that the interactions at the PPI interface are being copied by the ligand [28]. SMPPII are found to copy the natural interactions not only in terms of shape and chemistry, but even at the electrostatic potential level.[29] This mimicry suggests that the pharmacophore searches created from PPI complex structures can be used to identify SMPPII via virtual screening.[30] . Different methods can be employed to design the pharmacophore features onto the amino acids present at the PPI interface.[31] Several SMPPII discoveries have been achieved, thanks to pharmacophore searches [32-36]. PPIs are promising targets for controlling inappropriate signalling, as found in diseases such as cancer. The usefulness of pharmacophore modelling to create queries encoding the key interactions at the PPI interface will probably strongly stimulate the discovery of novel SMPPII using pharmacophores.

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 foradme-tox, investigate possible off-targets
- Complement other molecular methods.

While there are some possible boundaries to the pharmacophore concept, multiple remedies are available at any time to counter them. it is expected that pharmacophore modelingwill play an important role in CADD for the foreseeable future, and any medicinal chemist should be aware of its benefits and possibilities.

7. CONCLUSION

This paper summarizes various rational drug design and current drug design techniques with special focus on lead optimisation and pharmacophore modelling using 3D QSAR techniques. Apart from an overview of classical QSAR tools, modern structural analysis techniques also discussed in this review. Various receptor dependent ligand binding approaches pharmacophore modelling techniques with the future perspectives also summarized here.

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