Recent Developments in 3D QSAR and Molecular Docking Studies of Organic and Nanostructures

51

Bakhtiyor Rasulev

Contents

Abstract

The development of quantitative structure–activity relationship (QSAR) methods is going very fast for the last decades. OSAR approach already plays an important role in lead structure optimization, and nowadays, with development of big data approaches and computer power, it can even handle a huge amount of data associated with combinatorial chemistry. One of the recent developments is a three-dimensional QSAR, i.e., 3D QSAR. For the last two decades, 3D-OSAR has already been successfully applied to many datasets, especially of enzyme and receptor ligands. Moreover, quite often 3D QSAR investigations are going together with protein–ligand docking studies and this combination works synergistically. In this review, we outline recent advances in development and applications of 3D QSAR and protein–ligand docking approaches, as well as combined approaches for conventional organic compounds and for nanostructured materials, such as fullerenes and carbon nanotubes.

B. Rasulev (✉)
Center for Computationally Assisted Science and Technology, North Dakota State University, Fargo, ND, USA
e-mail: rasulev@icnanotox.org; bakhtiyor.rasulev@ndsu.edu

J. Leszczynski et al. (eds.), *Handbook of Computational Chemistry*,
DOI 10.1007/978-3-319-27282-5_54

Introduction

The methodology of quantitative structure–activity relationship (QSAR) is very well described in various publications (Hansch et al. 1995; Kubinyi 1997a, b; Eriksson et al. 2003). In short, QSAR is a method to find correlations and mathematical models for congeneric series of compounds, affinities of ligands to their binding sites, rate constants, inhibition constants, toxicological effect, and many other biological activities, based on structural features, as well as group and molecular properties, such as electronic properties, polarizability, or steric properties (Klebe et al. 1994; Hansch et al. 1995; Karelson et al. 1996; Kubinyi 1997a, b; Perkins et al. 2003; Isayev et al. 2006; Martin 2009; Rasulev et al. 2010; Puzyn et al. 2011).

Thus, QSAR approaches have been used for many types of biological activities to describe correlations for series of drugs and drug candidates (Kubinyi 1997a, b; Veber et al. 2002). In addition, in case of available crystallographic data on the proteins, the QSAR models can be developed with the additional information from the three-dimensional (3D) structures of these proteins, interacting with drug candidates, by applying protein–ligand docking data for further QSAR analysis, or, if there is no data on 3D structure of protein, then developing QSAR based on three-dimensional features of investigated molecules (Moro et al. 2005; Ragno et al. 2005; Gupta et al. 2009; Hu et al. 2009; Sun et al. 2010; Araújo et al. 2011; Ahmed et al. 2013). The second approach was named as 3D3D QSAR QSAR approach (Wise et al. 1983; Cramer and Bunce 1987; Cramer et al. 1988; Clark et al. 1990). There are also many other multidimensional approaches, including 4D QSAR and 5D QSAR, but all of them are just extension of QSAR analysis to a number of conformations (orientations, tautomers, stereoisomers, or protonation states) per molecule, number of concentrations (dosages) per compound, etc (Lill 2007). In overall, when talking about 3D QSAR, computational chemists usually assume that the QSAR analysis takes into account a three-dimensional structure of the compound in minimal energy conformation and builds QSAR model based on various 3D fields generated (Kubinyi 1997a, b).

A first similar to 3D QSAR approach was developed by Cramer in 1983, which was the predecessor of 3D approaches called dynamic lattice-oriented molecular modeling system (DYLOMMS) that involves the use of PCA to extract vectors from the molecular interaction fields, which are then correlated with biological activities (Wise et al. 1983). Later authors improved this approach and by combining the two existing techniques, GRID and PLS, has developed a powerful 3D QSAR methodology, so-called comparative molecular field analysis (CoMFA) (Cramer et al. 1988; Clark et al. 1990). Soon after, CoMFA has become a prototype of 3D QSAR methods (Kim et al. 1998; Todeschini and Gramatica 1998; Podlogar and Ferguson 2000). CoMFA approach was then implemented in the Sybyl software (Tripos 2006) from Tripos Inc.

As it was mentioned before, a good and fruitful approach is a combination of molecular docking and 3D QSAR pharmacophore methods (Patel et al. 2008; Gupta et al. 2009; Araújo et al. 2011; Ahmed et al. 2013). Molecular docking and 3D QSAR model are the two potent methods in drug discovery process. Thus,

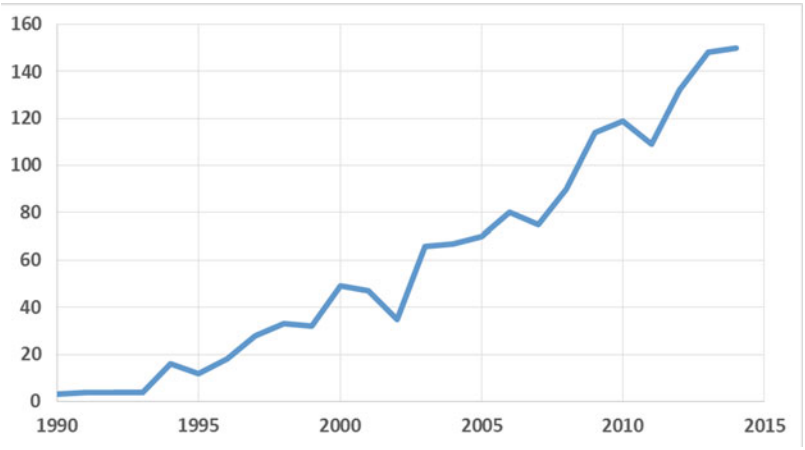

Fig. 1 A number of 3D QSAR-related papers for a period of 1990–2014 (Source – Web of Science)

virtual screening using 3D QSAR approaches followed by docking has become one of the reputable methods for drug discovery and enhancing the efficiency in lead optimization (Oprea and Matter 2004). The main advantage of this combined approach of 3D QSAR and pharmacophore-based docking is to focus on specific key interaction for protein–ligand binding to improve drug candidates. Ameliorate the selection of active compounds; it is optimal to use both methods like molecular docking and 3D QSAR modeling (Gopalakrishnan et al. 2005; Klebe 2006; Perola 2006; Pajeva et al. 2009; Yang 2010).

Since the time of development of 3D QSAR approach, a number of papers and methods' developments were published within 3D QSAR methodology. Let's briefly list and explain these methods here and then discuss recent developments and applications of these 3D QSARs in the assessment of the properties of biologically active compounds and development of drugs and drug candidates. As can be seen from Fig. 1, the number of publications related to 3D QSAR approach is increasing every year, from 3 to 5 publications in the beginning of 1990s to about 150 publications per year in 2014. It confirms the increasing importance of the method and successful application in many drug design projects.

Ligand-Based 3D QSAR Methods

To give some view on a number of 3D QSAR methods developed for the last three decades, we listed below the ligand-based 3D QSAR methods and very short description per each of them.

CoMFA – Comparative molecular field analysis is the method which correlates the field values of the structure with biological activities. CoMFA generates an

equation correlating the biological activity with the contribution of interaction energy fields at every grid point (Cramer et al. 1988). The method was developed in the 1988 and still one of the most popular ones for 3D QSAR modeling.

CoMSIA – Comparative molecular similarity indices analysis (CoMSIA) method, where the molecular similarity indices calculated from steric and electrostatic alignment (SEAL) similarity fields and applied as descriptors to encode steric, electrostatic, hydrophobic, and hydrogen bonding properties (Klebe et al. 1994). This is a development of CoMFA method and also gets very popular in drug design.

GRID – This method and program was designed as an alternative to the original CoMFA approach. It is actually a force field which calculates the interaction energy fields in molecular-field analysis and determines the energetically favorable binding sites on molecules of known structure. The method to some extent is similar to CoMFA, and it computes explicit nonbonded (or non-covalent) interactions between a molecule of known 3D structure and a probe (i.e., a chemical group with certain user-defined properties). The probe is located at the sample positions on a lattice throughout and around the macromolecule. The method offers two distinct advantages, one of them is the use of a 6–4 potential function for calculating the interaction energies, which is smoother than the 6–12 form of the Lennard-Jones type in CoMFA, and another advantage is the availability of different types of probes (Goodford 1985). Moreover, the program in addition of computing the regular steric and electrostatic potentials also calculates the hydrogen bonding potential using a hydrogen bond donor and acceptor, as well as the hydrophobic potential using a "DRY probe." Later on, a water probe was included to calculate hydrophobic interactions (Kim et al. 1998; Kim 2001).

MSA – Molecular shape analysis (MSA) is a ligand-based 3D QSAR method which attempts to merge conformational analysis with the classical Hansch approach. The method deals with the quantitative characterization, representation, and manipulation of molecular shape in the construction of a QSAR model (Hopfinger 1980).

HASL – Inverse grid-based approach represents the shapes of the molecules inside an active site as a collection of grid points (Doweyko 1988). The methodology of this approach begins with the intermediate conversion of the Cartesian coordinates (x, y, z) for superposed set of molecules to a 3D grid consisting of the regularly spaced points that are (1) arranged orthogonally to each other, (2) separated by a particular distance termed as the resolution (which determines the number of grid points representing a molecule), and (3) all sprawl within the van der Waals radii of the atoms in the molecule.

Thus, the resulting set of points is referred to as the molecular lattice and represents the receptor active site map (like in CoMFA). Quite important that the overall lattice dimensions are dependent on the size of the molecules and the resolution chosen.

GRIND – This is the method that uses *gr*id-*in*dependent *d*escriptors (GRIND) which encode the spatial distribution of the molecular interaction fields (MIF) of the studied compounds (Pastor et al. 2000). In the anchor-GRIND method (Fontaine

et al. 2005), to compare the MIF distribution of different compounds, the user defines a single common position in the structure of all the compounds in the series, so-called anchor point. This anchor point does not provide enough geometrical constrains to align the compounds studied; however, it is used by the method as a common reference point, making it possible to describe the geometry of the MIF regions in a more precise way than GRIND does. The anchor point is particularly easy to assign in datasets having some chemical substituents well known as being crucial for the activity. In the anchor-GRIND approach, the R groups are described with two blocks of variables: the anchor-MIF and the MIFMIF blocks (Fig. 2). The first one describes the geometrical distribution of the R MIF relative to the anchor point, while the second one describes the geometrical distribution of the MIF within each R group. These blocks are obtained after the following steps: (i) every R group is considered as attached to the scaffold, (ii) the anchor point is set automatically on an atom of the scaffold, (iii) a set of MIF are calculated with the program GRID (Goodford 1985) as well as the shape field implemented in the program Almond (Cruciani et al. 2004), and (iv), as the last step, the blocks of descriptors

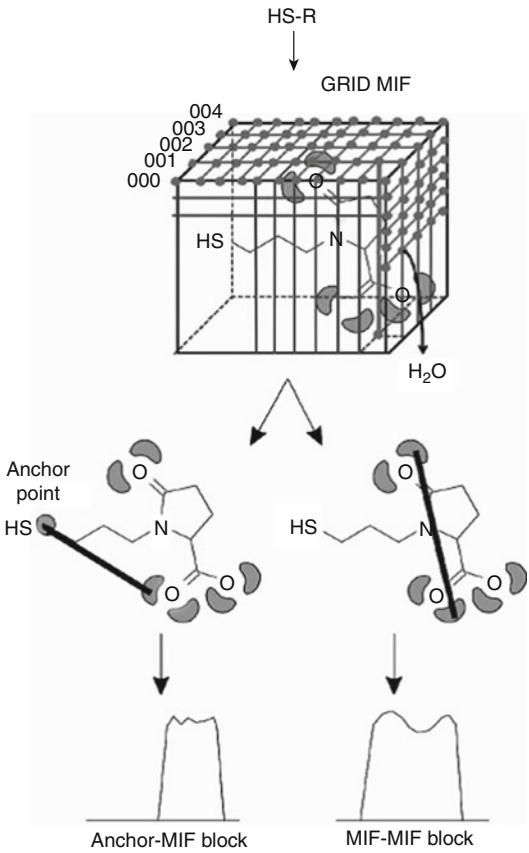

Fig. 2 Calculation of the anchor-GRIND descriptors for an ACE inhibitor with the anchor point set on the zinc binder sulfur atom (Reproduced with permission from reference (Fontaine et al. 2005) Copyright, American Chemical Society, 2005)

are computed from the anchor point and the filtered MIF. Authors also were able to incorporate a molecular shape into the GRIND descriptors (Fontaine et al. 2004).

GERM – Genetically evolved receptor model (GERM) is a method for 3D QSAR and also for constructing 3D models of protein-binding sites in the absence of a crystallographically established or homology-modeled structure of the receptor (Walters and Hinds 1994). As for many 3D QSAR datasets, the primary requirement for GERM is a structure–activity set for which a sensible alignment of realistic conformers has been determined. The methodology is the following: it encloses the superimposed set of molecules in a shell of atoms (analogous to the first layer of atoms in the active site) and allocates these atoms with explicit atom types (aliphatic H, polar H, etc., to match the types of atoms found in the investigated proteins).

CoMMA – Comparative molecular moment analysis (CoMMA) is one of the unique alignment-independent 3D QSAR methods, which involves the computation of molecular similarity descriptors (similar to CoMSIA) based on the spatial moments of molecular mass (i.e. shape) and charge distributions up to second-order as well as related quantities (Silverman and Platt 1996).

COMBINE – Comparative binding energy analysis (COMBINE) method was developed to make use of the structural data from ligand–protein complexes, within a 3D QSAR methodology. The method is based on the hypothesis where free energy of binding can be correlated with a subset of energy components calculated from the structures of receptors and ligands in bound and unbound forms (Ortiz et al. 1995; Lushington et al. 2007).

CoMSA – Comparative molecular surface analysis (CoMSA) is a non-grid 3D QSAR method that utilizes the molecular surface to define the regions of the compounds which are required to be compared using the mean electrostatic potentials (MEPs) (Polanski et al. 2002, 2006). In overall, the methodology proceeds by subjecting the molecules in the dataset to geometry optimization and assigning them with partial atomic charges.

AFMoC – Adaptation of fields for molecular comparison (AFMoC) is a close to 3D QSAR method that involves fields derived from the protein environments (i.e. not from the superimposed ligands as in CoMFA); therefore, it is also known as a "reverse" CoMFA (=AFMoC) approach or protein-dependent 3D QSAR (Gohlke and Klebe 2002). The methodology is the following: a regularly spaced grid is placed into the receptor binding site, followed by mapping of the knowledge-based pair potentials between protein atoms and ligand atom probes onto the grid intersections resulting in the potential fields. Thus, based on these potential fields, specific interaction fields are generated by multiplying distance-dependent atom-type properties of actual ligands docked into the active site with the neighboring grid values. In result, these atom-type-specific interaction fields are then correlated with the binding affinities using PLS technique, which assigns individual weighting factors to each field value.

CoRIA – Comparative residue interaction analysis (CoRIA) is a 3D QSAR approach which utilizes the descriptors that describe the thermodynamic events involved in ligand binding, to explore both the qualitative and the quantitative features of the ligand–receptor recognition process. The CoRIA methodology is

the following: initially it simply consisted of calculating the nonbonded (van der Waals and coulombic) interaction energies between the ligand and the individual active site residues of the receptor that are involved in interaction with the ligand (Datar et al. 2006; Dhaked et al. 2009). By employing the genetic algorithm-supported PLS technique (G-PLS), these energies then correlated with the biological activities of molecules, along with the other physiochemical variables describing the thermodynamics of binding, such as surface area, lipophilicity, molar refractivity, molecular volume, strain energy, etc.

SOMFA – Self-organizing molecular-field analysis, where firstly the mean activity of training set is subtracted from the activity of each molecule to get their mean-centered activity values. The methodology is the following:

- A 3D grid around the molecules with values at the grid points signifying the shape or electrostatic potential is generated.
- The shape or electrostatic potential value at every grid point for each molecule is multiplied by its mean-centered activity.
- The grid values for each molecule are summed up to give the master grids for each property.
- Then the so-called $\text{SOMFA}_{\text{property,i}}$ descriptors from the master grid values are calculated and correlated with the log-transformed molecular activities (Robinson et al. 1999).

kNN-MFA – This relatively new method was developed and reported in 2006 by Ajmani et al. (2006). kNN-MFA is a k-nearest neighbor molecular-field analysis. kNN-MFA adopts a k-nearest neighbor principle for generating relationships of molecular fields with the experimentally reported activity. This method utilizes the active analogue principle that lies at the foundation of medicinal chemistry. Like many 3D QSAR methods, kNN-MFA requires suitable alignment of a given set of molecules. This is followed by generation of a common rectangular grid around the molecules. The steric and electrostatic interaction energies are computed at the lattice points of the grid using a methyl probe of charge $+1$. These interaction energy values are considered for relationship generation and utilized as descriptors to decide nearness between molecules.

3D-HoVAIFA – This method based on three-dimensional holographic vector of atomic interaction field analysis (Zhou et al. 2007). Initially the holographic vector for 3D QSAR methods was developed by Zhou et al. in 2007 (Zhou et al. 2007). Proceeding from two spatial invariants, namely, atom relative distance and atomic properties on the bases of three common nonbonded (electrostatic, van der Waals, and hydrophobic) interactions which are directly associated with bioactivities, 3D-HoVAIF method derives multidimensional vectors to represent molecular steric structural characteristics.

CMF – This is a recently introduced continuous molecular-field approach (Baskin and Zhokhova 2013). This is a novel approach that consists in encapsulating continuous molecular fields into specially constructed kernels. It is based on the application of continuous functions for the description of molecular fields instead

of finite sets of molecular descriptors (such as interaction energies computed at grid nodes) commonly used for this purpose. The feasibility of using molecular-field kernels in combination with the support vector regression (SVR) machine learning method to build 3D QSAR models has been demonstrated by the same authors earlier (Zhokhova et al. 2009). Authors claim that by combining different types of molecular fields and methods of their approximation, different types of kernels with different types of kernel-based machine learning methods, it is possible not only to present lots of existing methods in chemoinformatics and medicinal chemistry as particular cases within a single methodology but also to develop new approaches aimed at solving new problems (Baskin and Zhokhova 2013). The example of application of this approach is described later in this chapter.

PHASE – This is a flexible system (engine) (Dixon et al. 2006) for common pharmacophore identification and assessment, 3D QSAR model development, and 3D database creation and searching (within Schrodinger Suite, Schrodinger, LLC). It includes some subprograms, for example, LigPrep, which attaches hydrogens, converts 2D structures to 3D, generates stereoisomers, and, optionally, neutralizes charged structures or determines the most probable ionization state at a user-defined pH. It also includes MacroModel conformational search engine to generate a series of 3D structures that sample the thermally accessible conformational states. For purposes of 3D modeling and pharmacophore model development, each ligand structure is represented by a set of points in 3D space, which coincide with various chemical features that may facilitate non-covalent binding between the ligand and its target receptor. PHASE provides six built-in types of pharmacophore features: hydrogen bond acceptor (A), hydrogen bond donor (D), hydrophobic (H), negative ionizable (N), positive ionizable (P), and aromatic ring (R). In addition, users may define up to three custom feature types (x, y, z) to account for characteristics that don't fit clearly into any of the six built-in categories. To construct a 3D QSAR model, a rectangular grid is defined to encompass the space occupied by the aligned training set molecules. This grid divides space into uniformly sized cubes, typically 1 Å on each side, which are occupied by the atoms or pharmacophore sites that define each molecule.

APF – In 2008, Totrov M (Totrov 2008) introduced atomic property fields (APF) for 3D QSAR analysis. APF concept is introduced as a continuous, multicomponent 3D potential that reflects preferences for various atomic properties at each point in space (Fig. 3). The approach is extended to multiple flexible ligand alignments using an iterative procedure, Self-Consistent atomic Property Fields by Optimization (SCAPFOld). The application of atomic property fields and SCAPFOld for virtual ligand screening and 3D QSAR is tested on published benchmarks. The new method is shown to perform competitively in comparison to current state-of-the-art methods (CoMFA and CoMSIA).

Thus, there are studies with comparative analysis of these two methods, PHASE and Catalyst (HypoGen). In 2007, Evans et al. (2007) provided a comparative study of PHASE and Catalyst methods for their performance in determining 3D QSARs and concluded that the performance of PHASE is better than or equal to that of Catalyst HypoGen, with the datasets and parameters used. Authors found that within

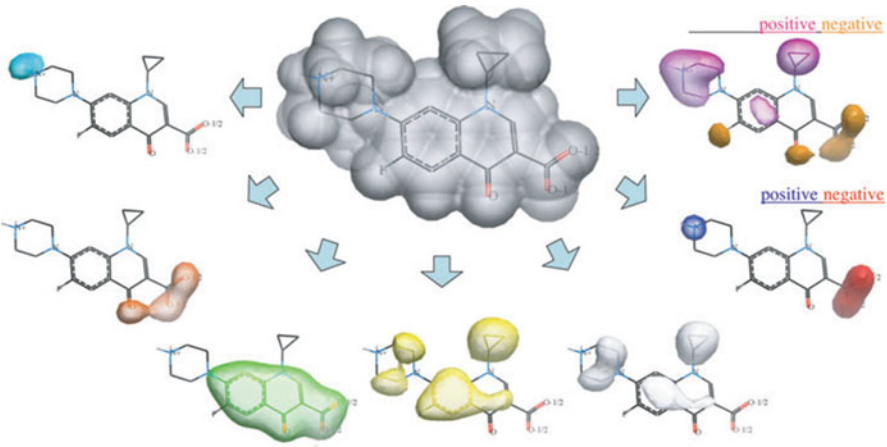

Fig. 3 An overall scheme of APF potentials visualized for an example of a drug molecule. Transparent blobs are the equipotential contours of various APF components (Reproduced with Permission from reference (Totrov 2008). Copyright John Wiley and Sons, 2008)

PHASE, the atom-based grid QSAR model generally performed better than the pharmacophore-based grid, and by using overlays from Catalyst to build PHASE grid QSAR models, they found evidence that better performance of PHASE on these datasets was due to the use of the grid technique.

Recent Advances in 3D QSAR Studies of Organic Compounds

In this part of the review, we discuss the new developments in the methods and in applications of 3D QSARs for various chemicals, including nanostructured materials.

For the last 10 years, there was mainly improvement of the 3D QSAR approaches which were developed before 2005. As it was discussed above, all these methods as CoMFA, CoMSIA, GRID, SOMFA, etc., were developed in late 1990s and early 2000s. Some of the recently introduced methods are just improvements of old approaches. However, if we take a look at applications, we can see many interesting publications and novel ligand developments which were designed by 3D QSAR and docking methods.

Recently, a quite interesting study was performed by Virsodia et al. (2008) on antitubercular activity of 23 substituted *N*-phenyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamides by application of 3D QSAR using CoMFA and CoMSIA methods. Authors synthesized and assessed the antitubercular activity of all investigated compounds followed by comprehensive 3D QSAR modeling. Authors were able to get good models with $r^2 = 0.98$ and 0.95, with cross-validated $q^2 = 0.68$ and 0.58, respectively. Authors stated that CoMFA and

CoMSIA contours helped them to design some new molecules with improved activity (Virsodia et al. 2008).

Another CoMFA and CoMSIA study was performed by Ravichandran et al. (2009) by analysis of anti-HIV activity of 96 1,3,4-thiazolidine derivatives. Authors were able to get good models by CoMFA and CoMSIA with r^2 values 0.931 and 0.972, respectively. The predictive model was evaluated using a test set comprising of 17 molecules, and the predicted r^2 values of CoMFA and CoMSIA models were 0.861 and 0.958, respectively.

With the use of CoMSIA method, Kumar et al. (2009) were able to investigate novel Bignelli dihydropyrimidines with potential anticancer activity. The developed model based on 32 compounds showed a good statistical data – for training set $q^2 = 0.51$, while for the test set $r^2 = 0.93$.

Raparti et al. in 2009 (Raparti et al. 2009) reported a study based on a novel kNN-MFA 3D QSAR which was discussed above, where authors synthesized, assessed for antimycobacterial activity, and investigated by 2D and 3D QSAR approaches a series of ten compounds (4-(morpholin-4-yl)-N0-(arylidene)benzohydrazides). Authors were able to get satisfactory for this size of dataset statistical results for 3D QSAR model against *M. tuberculosis* (Raparti et al. 2009), with $r^2 = 0.910$ and $q^2 = 0.507$, respectively.

Another kNN-MFA 3D QSAR study was conducted and published by Kishore Jha et al. in 2010 (Jha et al. 2010). Authors evaluated the antimicrobial activity of 21 compounds by kNN-MFA combined with various selection procedures. As selection methods, authors were using simulated annealing (SA), genetic algorithms (GA), and stepwise (SW) forward–backward methods. The developed model showed satisfactory results for this kind of studies, with $q^2 = 0.696$ and $r^2_{pred} = 0.615$. Authors concluded that the 3D QSAR study has shown that less electronegative substituent would be favorable for the activity, and therefore the future molecules should be designed with less electronegative group to result in potentially active molecules.

Thus, recently, Araújo et al. (2011) studied acetylcholine inhibitors (AChEIs) by application of combined approach, so-called receptor-dependent 3D QSAR (RD 3D QSAR) where they investigated a series of 60 benzylpiperidine inhibitors of human acetylcholinesterase. They received two models with $r^2 = 0.86$, $q^2 = 0.74$ and $r^2 = 0.90$, $q^2 = 0.75$, which were validated by a combined GA-PLS approach. Based on those models, authors have proposed four new benzylpiperidine derivatives and predicted the pIC_{50} for each molecule. The good predicted potency of one of the benzylpiperidine derivatives indicated a promising potency for this candidate as a new HuAChE inhibitor (Araújo et al. 2011).

In another similar study, in 2009 Gupta et al. (2009) conducted an interesting combined study with protein–ligand docking-based 3D QSAR study of HIV-1 integrase inhibitors. They were using protein–ligand docking to identify a potential binding mode for 43 inhibitors at HIV-1 IN active site, and best docked conformation of certain molecule was used as a template for alignment. The docking was followed by CoMFA and CoMSIA modeling, and authors developed very good models with r^2_{cv} values of 0.728 and 0.794, respectively, and non-cross-

validated ones $r^2_{ncv} = 0.934$ and 0.928. This combined docking-based 3D QSAR methodology showed really good predictive abilities and can be employed further in the development of better inhibitors for various proteins.

One more study is worth to discuss where authors applied a combination of docking and 3D QSAR to reveal the most important structural factors for the activity. Here, Hu et al. (2009) applied a receptor- and ligand-based 3D QSAR study for a series of 68 non-nucleoside HIV-1 reverse transcriptase inhibitors (2-amino-6-arylsulfonylbenzonitriles and their thio and sulfinyl congeners). Authors were applying docking simulations to position the inhibitors into RT active site to determine the most probable binding mode and most reliable conformations. This complex receptor-based and ligand-based alignment procedure and different alignment modes allowed authors to obtain reliable and predictive CoMFA and CoMSIA models with cross-validated q^2 value of 0.723 and 0.760, respectively. Authors concluded that the CoMFA steric and CoMSIA hydrophobic fields support the idea that bulkier and hydrophobic groups are favorable to bioactivity in the 3- and 5-positions of the B (benzene)-ring. At the same time, these groups are unfavorable in the 4-position. Also, the CoMSIA H-bond donor and acceptor fields suggest that the sulfide and sulfone inhibitors are more active than the sulfoxide ones due to H-bonding with protein residues.

It is good to mention here another interesting study where combination of methods is used, including molecular docking and 3D QSAR to develop a predictive QSAR model. Moro et al. (2006) suggested the use a combination of molecular electrostatic potential (MEP) surface properties (autocorrelation vectors) with the conventional partial least-square (PLS) analysis to produce a robust ligand-based 3D structure–activity relationship (autoMEP/PLS). They applied this approach to predict human A3 receptor antagonist activities. First of all, the approach was suggested as an efficient and alternative pharmacodynamic-driven filtering method for small-size virtual libraries. For this, authors generated a small-sized combinatorial library (841 compounds) that was derived from the scaffold of the known human A3 antagonist pyrazolo-triazolo-pyrimidines (Moro et al. 2005). This is another successful example of combined approach of docking and 3D QSAR to investigate and design active analogue compounds. Authors were using MULTIDOCK code that is part of MOE suite (Molecular Operating Environment (MOE) 2016) to get a conformational sampling and then calculate interaction energies using MMFF94 (Halgren 1996) and use it for further steps. The MEPs were derived from a classical point charge model: the electrostatic potential for each molecule is obtained by moving a unit positive point charge across the van der Waals surface, and it is calculated at various points j on this surface (Moro et al. 2006). Authors were able to test the approach by synthesizing several predicted potent compounds, and they found that all the newly synthesized compounds are correctly predicted as potent human A3 antagonists (Moro et al. 2006).

As a continuation of development of pharmacophore- and docking-based methods for QSAR, the novel PHASE code was developed. This updated code then was used by Amnerkar and Bhusari (2010) to investigate by 3D QSAR approach the anticonvulsant activity of some prop-2-eneamido and 1-acetyl-pyrazolin derivatives

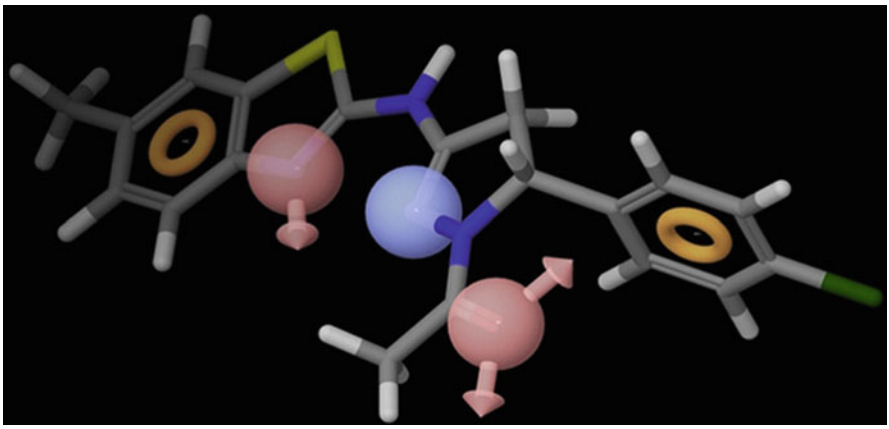

Fig. 4 Common pharmacophore generated from the best PHASE hypothesis. Pharmacophore features are *red sphere* for hydrogen bond acceptors (A) with the *arrows* pointing in the direction of lone pair, *blue sphere* for positively charged group (P), and *orange* torus for aromatic rings (R). Compound 52 aligned to the pharmacophore for which *blue* indicates nitrogen, *yellow* refers to sulfur, *green* indicates chlorine, *gray* indicates carbon, and *white* refers to hydrogen (Reproduced with Permission from reference (Amnerkar and Bhusari 2010). Copyright Elsevier, 2010)

of aminobenzothiazole. They received a statistically significant 3D QSAR model with r^2 of 0.922 and q^2 of 0.814. The model was analyzed in order to understand the trends of investigated molecules for their anticonvulsant properties. Authors found the influence of electron withdrawing, hydrogen bond donor, and negative/positive ionic and hydrophobic groups to anticonvulsant activity. Authors believe that the derived 3D QSAR as well as clues for possible structural modifications will be of interest and significance for the strategic design of more potent molecules in the benzothiazoles as anticonvulsant agents. The pharmacophore hypothesis generated from PHASE-based 3D QSAR analysis can be seen in Fig. 4.

Another PHASE application for 3D QSAR study is published by Pulla et al. (2016). Authors applied a 3D QSAR approach to investigate silent mating-type information regulation 2 homologue 1 (SIRT1) which is the homologous enzyme of silent information regulator-2 gene in yeast. SIRT1 was believed to be overexpressed in many cancers (prostate, colon) and inflammatory disorders (rheumatoid arthritis); that is why it has good therapeutic importance. Authors conducted both structure-based and ligand-based drug design strategies with utilizing high-throughput virtual screening of chemical databases. Then an energy-based pharmacophore was generated using the crystal structure of SIRT1 bound with a small molecule inhibitor and compared with a ligand-based pharmacophore model that showed four similar features. A 3D QSAR model was developed and applied to generated structures. Among the designed compounds, Lead 17 emerged as a promising SIRT1 inhibitor with IC_{50} of 4.34 μM and, at nanomolar concentration (360 nM), attenuated the proliferation of prostate cancer cells (LnCAP) (Pulla et al. 2016). The 3D QSAR model was developed using PHASE 3.4 module in Maestro 9.3 software

package developed by Schrodinger, LLC (Dixon et al. 2006). Docking studies were executed using Glide 5.8 module (Halgren et al. 2004). Authors were validating the pharmacophore model by set composed of 1055 compounds, consisting of 1000 decoys and 55 known inhibitors. The drug-like decoy set of 1000 compounds was obtained from the Glide module (Halgren et al. 2004). A final 3D QSAR model was developed based on dataset of 79 molecules reported as SIRT1 inhibitors in various literatures. To develop QSAR model, PHASE module relied on PLS regression applied to a large set of binary-valued variables. Each independent variable in the model originated from the grid of cubic volume elements spanning the space occupied by the training set ligands. Each training ligand in the training set was represented by binary code consisting of set of bit values (0 or 1) indicating the volume of elements occupied by van der Waals model of the ligand. Authors were able to get a very good 3D QSAR model with $r^2 = 0.953$, $q^2 = 0.908$, and $r^2_{ext} = 0.941$. A validated 3D QSAR model (for ADHRR 802) authors used to generate contour maps could help in understanding the importance of functional groups at specific positions toward biological activity. These insights could be known by comparing the contour maps of the most and least active compounds, as shown in Fig. 5 represented in Pulla et al. (2016). The blue and red cubes indicated the favorable and unfavorable regions, respectively, of the hydrogen bond donor effect, while light-red and yellow cubes indicated favorable and unfavorable regions, respectively, of the hydrophobic effect, and the cyan and orange cubes indicated favorable and unfavorable regions, respectively, of the electron-withdrawing effect. From Fig. 5a, it can be seen that the blue favorable regions of the hydrogen bond donor effect were nearer to the donor feature (D5) of the active molecule; however, it could also be observed that blue boxes were also concentrated at the amide group beside thiophen, thus illustrating that additional donor groups at these regions (blue cubes) could increase biological activity. At the same time, in the inactive molecule, red unfavorable boxes were observed around the donor feature (D5), inferring the biological inactiveness of the molecule. In the case of the hydrophobic effect, the light-red color cubes were seen surrounding the hydrophobic feature (H8, piperidine) of the active molecule, whereas the presence of few yellow unfavorable cubes indicated that these hydrophobic groups were not in the right position in the inactive molecule, illustrating the weak biological activity. Next, in the case of the electron-withdrawing effect of the active molecule, the favorable cyan cubes were seen around the acceptor feature (A3), and cyan cubes were also seen near the pyrimidine ring. It inferred that the acceptor features near the pyrimidine ring could further increase the bioactivity of the molecule. However, in the case of the inactive molecule, mostly unfavorable orange cubes were observed around the acceptor feature (A3), illustrating the importance of the electron-withdrawing group in the activity of lead molecules.

Thus, another new combined docking-based 3D QSAR study (Sun et al. 2010) was published with the analysis of influenza neuraminidase inhibitors. The study was based on novel 3D-HoVAIFA method which is based on three-dimensional holographic vector of atomic interaction field analysis (Zhou et al. 2007). As it was mentioned above, initially the holographic vector for 3D QSAR was developed by

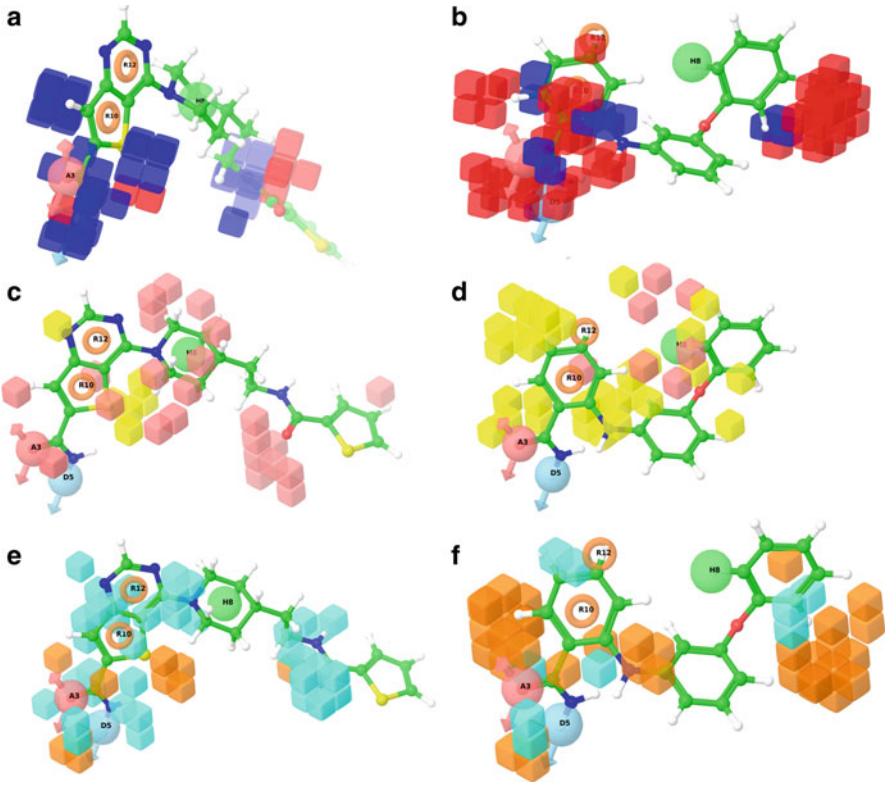

Fig. 5 Contour maps of the most active and inactive molecules: (**a**) the hydrogen bond donor effect (most active), (**b**) the least active (*blue* denotes favorable, *red* denotes unfavorable), (**c**) the hydrophobic effect (most active), (**d**) the least active (*light red* denotes favorable, *yellow* denotes unfavorable), (**e**) electron-withdrawing effect (most active), and (**f**) the least active (*cyan* denotes favorable, *orange* denotes unfavorable) (Reproduced with Permission from ref (Pulla et al. 2016). Copyright, American Chemical Society, 2016)

Zhou et al. in 2007 (Zhou et al. 2007). The method uses atomic relative distance and atomic properties on the bases of three common nonbonded (electrostatic, van der Waals, and hydrophobic) interactions which are directly associated with bioactivities, and then 3D-HoVAIF method derives multidimensional vectors to represent molecular steric structural characteristics for further 3D QSAR analysis. Similarly to previous study, authors conducted a docking study to find the best docking pose and template for alignment. Then authors were able to get good models for a large dataset of 124 compounds and received the following correlation coefficients, $r^2 = 0.789$ and $r^2_{cv} = 0.732$. Authors claim that 3D-HoVAIFA can be applicable to molecular structural characterization and bioactivity prediction. In addition, it was showed that HoVAIFA and docking results are corresponding (Sun et al. 2010), which illustrates that HoVAIFA is an effective methodology for characterization of complex interactions of drug molecules.

One more docking-based 3D QSAR study was published in 2010 by Sakkiah et al. (2010), where authors conducted 3D QSAR pharmacophore-based virtual screening and molecular docking for the identification of potential HSP90 inhibitors. Authors were using HYPO and HYPOGEN (Li et al. 2000) 3D-based pharmacophore models. Based on the training set of 16 compounds, they were able to develop a good model using pharmacophore generation module in Discovery Studio (Accelrys) and then apply it for test set of 30 compounds. For predicting activity, the correlation coefficients of the model for training and test sets were 0.93 and 0.91, respectively. Authors then applied the model to virtual screening of about 160,000 compounds (Maybridge and Scaffold databases) and finally selected 1150 compounds for docking studies. Finally, 36 selected compounds were reported that were showing high activity based on 3D QSAR model and docking analysis. The developed HYPOGEN pharmacophore model that was used for virtual screening of 160,000 compounds from the databases is represented in Fig. 6.

Recently introduced and discussed previously the CMF approach for 3D QSAR analysis was successfully applied for several datasets (Baskin and Zhokhova 2013). Authors applied CMF approach to build 3D QSAR models for eight datasets through the use of five types of molecular fields (the electrostatic, steric, hydrophobic, hydrogen bond acceptor and donor ones). The 3D QSAR models were developed for the following datasets: 114 angiotensin converting enzyme (ACE) inhibitors, 111

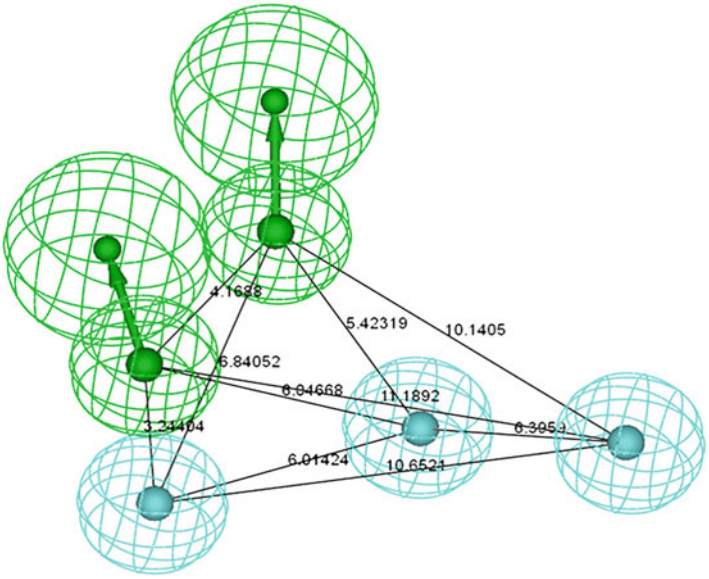

Fig. 6 Catalyst HypoGen pharmacophore model, where H and HBA are illustrated in *cyan* and *green*, respectively (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article) (Reproduced with Permission from reference Sakkiah et al. 2010) Copyright Elsevier, 2010)

acetylcholinesterase (AChE) inhibitors, 163 ligands for benzodiazepine receptors (BZR), 322 cyclooxygenase-2 (COX-2) inhibitors, 397 dihydrofolatereductase (DHFR) inhibitors, 66 glycogen phosphorylase b (GPB) inhibitors, 76 thermolysin (THER) inhibitors, and 88 thrombine (THR) inhibitors. Authors were able to get good models and then compare statistical characteristics of the developed models with the same characteristics built earlier for the same datasets using the most popular 3D QSAR methods, CoMFA and CoMSIA, based on the use of molecular fields. Almost for all cases authors received better statistics than in original works. For example, for ACE inhibitors, CMF approach showed $q^2 = 0.72$, while CoMFA and CoMSIA showed 0.68 and 0.65, respectively. 3D QSAR for AChE inhibitors showed for CMF $q^2 = 0.58$, while for CoMFA and CoMSIA, it was 0.52 and 0.48, respectively. 3D QSAR for DHFR inhibitors showed for CMF $q^2 = 0.67$, while for CoMFA and CoMSIA, it was only 0.49 and 0.53, respectively. Other datasets also showed better results. The only one dataset, for BZR receptors, showed not so high values ($q^2 = 0.40$) but comparable with previous data received by CoMFA and CoMSIA – 0.32 and 0.41, respectively. As follows from the results presented in this paper, this particular implementation of the CMF approach provides an appealing alternative to the traditional lattice-based methodology. This method provides either comparable or enhanced predictive performance in comparison with state-of-the-art 3D QSAR methods, such as CoMFA and CoMSIA. Authors also discussed advantages and disadvantages of this approach. The potential advantages of this approach result from the ability to approximate electronic molecular structures with any desirable accuracy level, the ability to leverage the valuable information contained in partial derivatives of molecular fields (otherwise lost upon discretization) to analyze models and enhance their predictive performance, the ability to apply integral transforms to molecular fields and models, etc. The most attractive features of the CMF approach are its versatility and universality. At the same time, of the most serious limitations of the CMF approach, at least in its present form, comes from the mere nature of kernel-based machine learning methods. The amount of computational resources needed to calculate a kernel matrix scales as a square of the number of compounds in the training set. The mean amount of computational resources needed to calculate each element of a kernel matrix also scales as a square of the average number of atoms in molecules. As a result, it becomes impractical to build 3D QSAR models using a training set with more than 300 medium-sized compounds (Baskin and Zhokhova 2013).

Another interesting combination approach, Shih et al. (2011) in 2011 proposed a combination of 3D QSAR methods in order to get better predictivity for the dataset. Authors proposed for the first time a combination approach to integrate the pharmacophore (PhModel) (Taha et al. 2008), CoMFA, and CoMSIA models for B-RAF (RAF family of serine/threonine kinases). The PhModel was implemented by the program Accelrys Discovery Studio 2.1. First, authors established ten PhModels and used them to align diverse inhibitor structures for generating the CoMFA and CoMSIA models. Then the partial least-square (PLS) method was used and known B-RAF inhibitors to validate the prediction ability of CoMFA and CoMSIA models. Finally, the goodness of hit (GH) test score was used as a

benchmark for appraising the prediction ability of CoMFA and CoMSIA models to screen a compound database. Thus, ten PhModels were generated based on the 27 training set inhibitors. Each PhModel included four features: hydrogen bond acceptor (A), hydrogen bond donor (D), hydrophobic (HY), and ring aromatic (RA). The correlation coefficients for ten PhModels were very good and ranged from 0.964 to 0.902. Authors claim that this approach could be applied to screen inhibitor databases, optimize inhibitor structures, and identify novelty potent or specific inhibitors (Shih et al. 2011).

One more combination study for RAF inhibitors is worth to mention, was performed by Yang et al. (2011) which was applied as a combination of docking, molecular dynamics (MD), molecular mechanics Poisson–Boltzmann surface area (MM/PBSA) calculations, and 3D QSAR analysis to investigate the detailed binding mode between B-RAF kinases with the series of inhibitors and also to find the key structural features affecting the inhibiting activities. Considering the difficulty in the accurate estimation of electrostatic interaction, the QM-polarized ligand docking and GBSA rescoring were applied to predict probable poses of these inhibitors bound into the active site of B-RAF kinase. To obtain the rational conformation for developing 3D QSAR models, authors applied the docking-based conformation selection strategy. Moreover, the detailed interactions were analyzed on the basis of the results from MD simulation and the free energy calculation for two inhibitors with much difference in their activity. Authors investigated 61 B-RAF inhibitors and developed CoMFA and CoMSIA models with $r^2 = 0.917$ and 0.940, respectively. In result, the structure-based 3D QSAR models provided a further structural analysis and modifiable information for understanding the SARs of these inhibitors. The important hydrophobic property of the 3-substitution of B-ring was required to be type 2 inhibitors. The five substitutable positions of the C-ring could be further modified. Authors concluded that the results obtained from the combined computational approach will be helpful for the rational design of novel type 2 RAF kinase inhibitors.

Recently, a group of computational scientists is proposed to apply a protein–protein interaction (PPI) analysis to target small molecules. Since currently in worlds life science, research is going on the booming of interactome studies, a lot of interactions can be measured in a high-throughput way, taking into account that large-scale datasets are already available. Studies show that many different types of interactions can be potential drug targets. This boom of HTS studies greatly broadens the drug target search space, which makes the drug target discovery difficult. In this case, computational methods are highly desired to efficiently provide candidates for further experiments and hold the promise to greatly accelerate the discovery of novel drug targets. Thus, Wang et al. (2016) published a study where they suggested a new method, where inhibition of protein–protein interaction (PPI) analysis offered as a promising source to improve the specificity of drugs with fewer adverse side effects. They proposed a machine learning method to predict PPI targets in a genomic-wide scale. Authors developed a computational method, named as PrePPItar (Wang et al. 2016), to predict PPIs as drug targets by uncovering the potential associations between drugs and PPIs (Fig. 7). Authors investigated the

databases and manually constructed a gold-standard positive dataset for drug and PPI interactions. Their effort leads to a dataset with 227 associations among 63 PPIs and 113 FDA-approved drugs and allowed them to build models and learn the association rules from the data. Also, authors were able to characterize drugs by profiling in chemical structure, drug ATC-code annotation, and side-effect space and represent PPI similarity by a symmetrical S-kernel based on protein amino acid sequence. At the end, a support vector machine (SVM) is used to predict novel associations between drugs and PPIs. The PrePPItar method was validated on the well-established gold-standard dataset. Authors found that all chemical structures, drug ATC code, and side-effect information are predictive for PPI target. Authors claim that PrePPItar can serve as a useful tool for PPI target discovery and provide a general heterogeneous data-integrative framework.

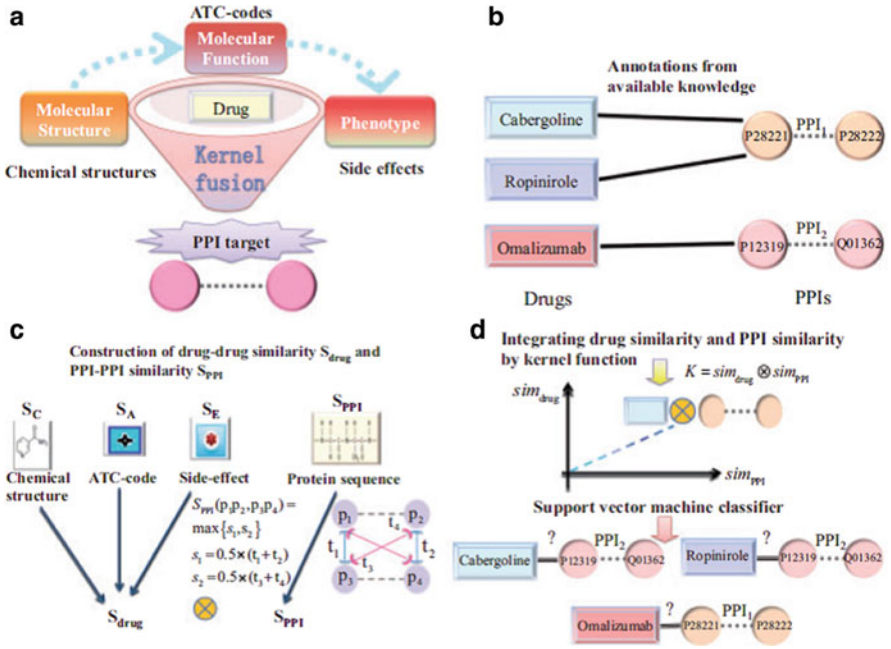

Fig. 7 The proposed flowchart for the PrePPITar. (**a**) The schematic plot for our PrePPItar method. PrePPItar applies the kernel fusion method to integrate multiple information about drug, including chemical structure, ATC code, and drug side effect to detect the interactions between drugs and PPIs. (**b**) Collecting known associations between drugs and PPIs as gold-standard positives in a bipartite graph. (**c**) Calculating drug–drug and PPI–PPI similarity metrics, where t_i; $i = 1$; 2; 3; 4 are the sequence similarity among proteins. (**d**) Relating the similarity among drugs and similarity among PPIs by Kronecker product kernel and applying SVM-based algorithm to predict the unknown associations between drugs and PPIs (Reproduced with Permission from reference (Wang et al. 2016). Copyright Oxford University Press, 2016)

3D QSARs and Combined Docking Studies of Nanostructured Materials

Nanomaterials are becoming an important component of the modern life and have been the subject of increasing number of investigations involving various areas of natural sciences and technology. However, theoretical modeling of physicochemical and biological activity of these species is still very scarce. The prediction of properties and activities of "classical" substances via correlating with molecular descriptors is a well-known procedure, by application QSAR and 3D QSAR methods. In spite of this, the application of QSAR for the nanomaterials is a very complicated task, because of "nonclassical" structure of these materials. Here, we would like to show first applications of the 3D QSAR and docking methods for nanostructured materials, which are nevertheless possible and can be useful in predicting their various properties and activities (toxicity).

Thus, one of the first 3D QSAR studies for nanostructured materials was provided in 2008. Durdagi et al. 2008a have investigated novel fullerene analogues as potential HIV PR inhibitors. It was the first work where authors analyzed nanostructured compounds for anti-HIV activity using protein–ligand docking and 3D QSAR approaches. Moreover, authors conducted MD simulations of ligand-free and the inhibitor bound HIV-1 PR systems to complement some previous studies and to provide proper input structure of HIV-1 PR in further docking simulations. Then, five different combinations of stereoelectronic fields of 3D QSAR/CoMSIA models were obtained from the set of biologically evaluated and computationally designed fullerene derivatives (where training set = 43 and test set = 6) in order to predict novel compounds with improved inhibition effect. The best 3D QSAR/CoMSIA model yielded a cross-validated r^2 value of 0.739 and a non-cross-validated r^2 value of 0.993. Authors stated that the derived model indicated the importance of steric (42.6 %), electrostatic (12.7 %), H-bond donor (16.7 %), and H-bond acceptor (28.0 %) contributions (Fig. 8). In addition, the derived contour plots together with applied de novo drug design were then used as pilot models for proposing the novel analogues with enhanced binding affinities. Interestingly, the investigated by authors the nanostructured compounds have triggered the interest of medicinal chemists to look for novel fullerene-type HIV-1 PR inhibitors possessing higher bioactivity. Later this year, authors published a second study for the same type of fullerene-based nanomaterials (Durdagi et al. 2008b).

The same group published in 2009 another study for fullerene derivatives but functionalized by amino acids (Durdagi et al. 2009). Authors used in silico screening approach in order to propose potent fullerene analogues as anti-HIV drugs. Two of the most promising derivatives showing significant binding scores were subjected to biological studies that confirmed the efficacy of the new compounds. The results showed that new leads can be discovered possessing higher bioactivity. Authors used docking approach together with MD simulations to get the best hits during the virtual screening.

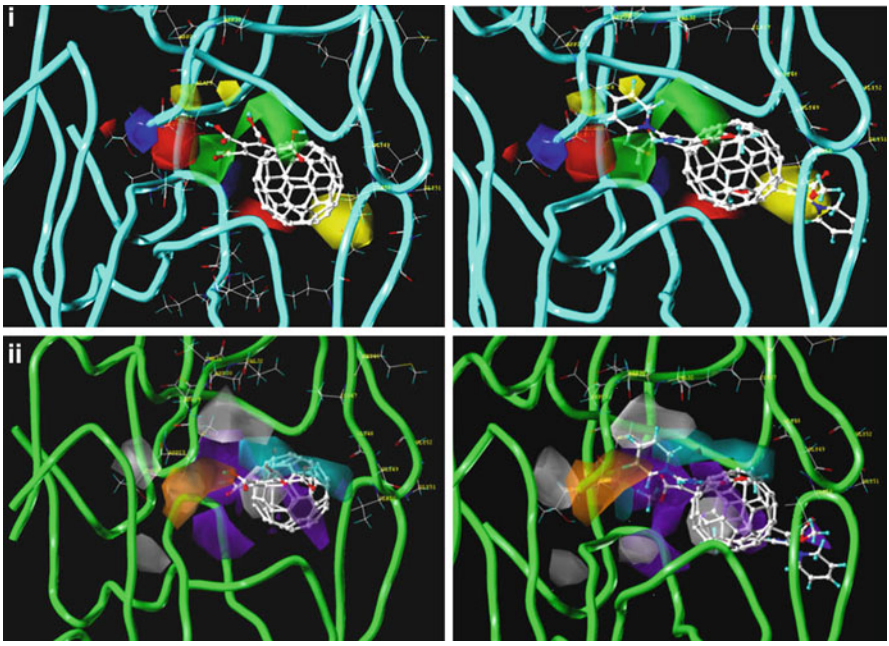

Fig. 8 (**i**) CoMSIA steric/electrostatic contour maps of template compound 23 (template compound; has best binding affinity in training set, *left* on the figure) and compound 36 (has worst binding affinity in training set, *right* on the figure). Sterically favored areas are shown in *green* color (contribution level of 80 %). Sterically unfavored areas are shown in *yellow* color (contribution level of 20 %). Positive potential favored areas are shown in *blue* color (contribution level of 80 %). Positive potential unfavored areas are shown in *red* color (contribution level of 20 %). (**ii**) CoMSIA H-bond donor/H-bond acceptor contour maps of compounds 23 and 36 (on the *left* and *right* of the figure, correspondingly). The individual contributions from the H-bond donor and H-bond acceptor favored and disfavored levels are fixed at 80 % and 20 %, respectively. The contours for H-bond donor favored fields have been shown in *cyan* color, while its disfavored fields have been shown in *purple* color. H-bond acceptor favored fields have been shown in *orange* color, while its disfavored fields have been shown in *white* color (Reproduced with Permission from ref (Durdagi et al. 2008a). Copyright Elsevier, 2008)

In 2011, the same group provided further analysis to design better anti-HIV fullerene-based inhibitors (Tzoupis et al. 2011). In this study authors employed a docking technique, two 3D QSAR models, MD simulations and the MM–PBSA method. In particular, authors investigated (1) hydrogen bonding (H-bond) interactions between specific fullerene derivatives and the protease, (2) the regions of HIV-1 PR that play a significant role in binding, (3) protease changes upon binding, and (4) various contributions to the binding free energy, in order to identify the most significant of them. The CoMFA and CoMSIA methods were applied too, to build 3D QSAR models, where good correlation coefficients were received, for both methods, $r^2 = 0.842$ and 0.928, respectively. Authors claim that the computed binding free energies are in satisfactory agreement with the experimental results.

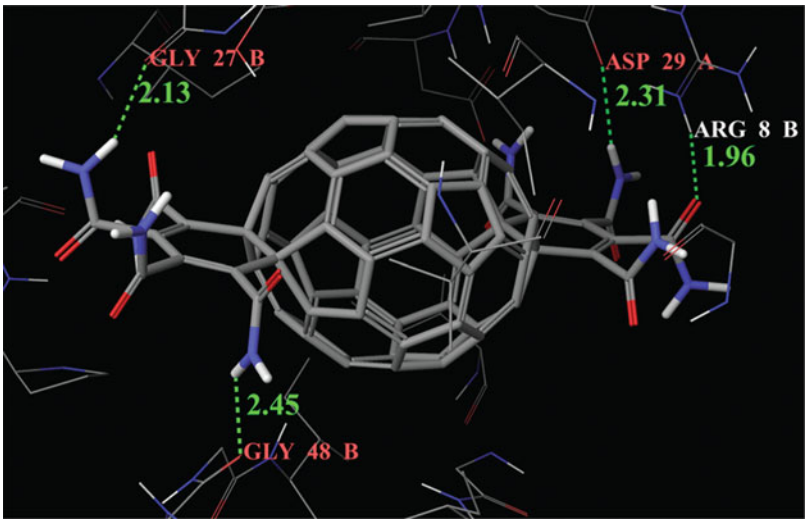

Fig. 9 The binding site interactions. H-bonds formed by the ligand 42 in the binding site (Glide) (Reproduced with Permission from reference (Ahmed et al. 2013). Copyright, Royal Society of Chemistry, 2013)

Another group published in 2013 a study that conducted a comprehensive investigation of fullerene analogues by combined computational approach including quantum chemical, molecular docking, and 3D descriptors-based QSAR (Ahmed et al. 2013). Authors stated that the protein–ligand docking studies and improved structure–activity models have been able both to predict binding affinities for the set of fullerene-C_{60} derivatives and to help in finding mechanisms of fullerene derivative interactions with human immunodeficiency virus type 1 aspartic protease, HIV-1 PR. Protein–ligand docking revealed several important molecular fragments that are responsible for the interaction with HIV-1 PR (Fig. 9). In addition, a density functional theory method has been utilized to identify the optimal geometries and predict physicochemical parameters of 49 studied compounds. The five-variable GA-MLRA-based model showed the best predictive ability ($r^2_{train} = 0.882$ and $r^2_{test} = 0.738$), with high internal and external correlation coefficients.

Calvaresi and Zerbetto (2010) published a study where they investigated a fullerene binding with a set of proteins. Authors investigated about 20 proteins that are known to modify their activity upon interaction with C60. The set was examined using PatchDock (Schneidman-Duhovny et al. 2005) software with an algorithm that appraises quantitatively the interaction of C60 and the surface of each protein. The redundancy of the set allowed them to establish the predictive power of the approach that finds explicitly the most probable site where C60 docks on each protein. About 80 % of the known fullerene-binding proteins fall in the top 10 % of scorers. The close match between the model and experiments vouches for the accuracy of the model and validates its predictions. Authors identified the sites

of docking and discussed them in view of the existing experimental data available for protein – C60 interaction. In addition, authors identified new proteins that can interact with C60 and discussed for possible future applications as drug targets and fullerene derivative bioconjugate materials.

Later, Calvaresi and Zerbetto (2011) published another study, where they investigated the binding of fullerene C60 with 1099 proteins. They one more time confirmed that hydrophobic pockets of certain proteins can accomodate a carbon cage either in full or in part. Since the identification of proteins that are able to discriminate between different cages is an open issue, they were interested in investigating much larger library than in Calvaresi and Zerbetto (2010). Prediction of candidates is achieved with an inverse docking procedure that accurately accounts for (i) van der Waals interactions between the cage and the protein surface, (ii) desolvation free energy, (iii) shape complementarity, and (iv) minimization of the number of steric clashes through conformational variations. A set of 1099 protein structures is divided into four categories that either select C60 or C70 (p-C60 or p-C70) and either accommodate the cages in the same pocket or in different pockets. Thus, authors also confirmed the agreement with the experiments, where the KcsA potassium channel is predicted to have one of the best performances for both cages.

Recently, in 2015 Xavier et al. (Esposito et al. 2015) published a QSAR study of decorated carbon nanotube investigation for toxicity using 4D fingerprints. In this study, authors proposed detailed mechanisms of action, relating to nanotoxicity, for a series of decorated (functionalized) carbon nanotube complexes based on previously reported QSAR models. Possible mechanisms of nanotoxicity for six endpoints (bovine serum albumin, carbonic anhydrase, chymotrypsin, hemoglobin along with cell viability, and nitrogen oxide production) have been extracted from the corresponding optimized QSAR models. The molecular features relevant to each of the endpoint respective mechanism of action for the decorated nanotubes are also discussed in the study. Based on the molecular information contained within the optimal QSAR models for each nanotoxicity endpoint, either the decorator attached to the nanotube is directly responsible for the expression of a particular activity, irrespective of the decorator's 3D geometry and independent of the nanotube, or those decorators having structures that place the functional groups of the decorators as far as possible from the nanotube surface most strongly influence the biological activity.

A docking study, together with comprehensive DFT analysis was conducted by Saikia et al. (2013). Authors made a simulation to analyze the interaction of nanomaterials with biomolecular systems, where they performed density functional calculations on the interaction of pyrazinamide (PZA) drug with functionalized single-wall CNT (fSWCNT) as a function of nanotube chirality and length, followed by docking simulation of fSWCNT with pncA protein. The functionalization of pristine SWCNT that facilitates in enhancing the reactivity of the nanotubes and formation of such type of nanotube-drug conjugate is thermodynamically feasible. Docking studies predicted the plausible binding mechanism and suggested that PZA loaded fSWCNT facilitates in the target-specific binding of PZA within the protein

following a lock and key mechanism. Authors noticed that no major structural deformation in the protein was observed after binding with CNT, and the interaction between ligand and receptor is mainly hydrophobic in nature. Authors anticipate that these findings may provide new routes toward the drug delivery mechanism by CNTs with long-term practical implications in tuberculosischemotherapy.

In another study, Turabekova et al. (2014) published a comprehensive study of carbon nanotube and pristine fullerene interactions with Toll-like receptors (TLRs), which are responsible for immune response. Having experimental data on hands and conducting comprehensive protein–ligand investigation, authors were able to show that CNT and fullerenes can bind to certain TLRs. Authors suggested a hypothetical model providing the potential mechanistic explanation for immune and inflammatory responses observed upon exposure to carbon nanoparticles. Specifically, authors performed a theoretical study to analyze CNT and C60 fullerene interactions with the available X-ray structures of TLR homo- and heterodimer extracellular domains. This assumption was based on the fact that similar to the known TLR ligands, both CNTs and fullerenes induce, in cells, the secretion of certain inflammatory protein mediators, such as interleukins and chemokines. These proteins are observed within inflammation downstream processes resulting from the ligand molecule-dependent inhibition or activation of TLR-induced signal transduction. The computational studies have shown that the internal hydrophobic pockets of some TLRs might be capable of binding small-sized carbon nanostructures (5,5 armchair SWCNTs containing 11 carbon atom layers and C60 fullerene). High binding scores and minor structural alterations induced in TLR ectodomains upon binding C60 and CNTs further supported the proposed hypothesis (Fig. 10). Additionally, the proposed hypothesis is strengthened by the indirect experimental

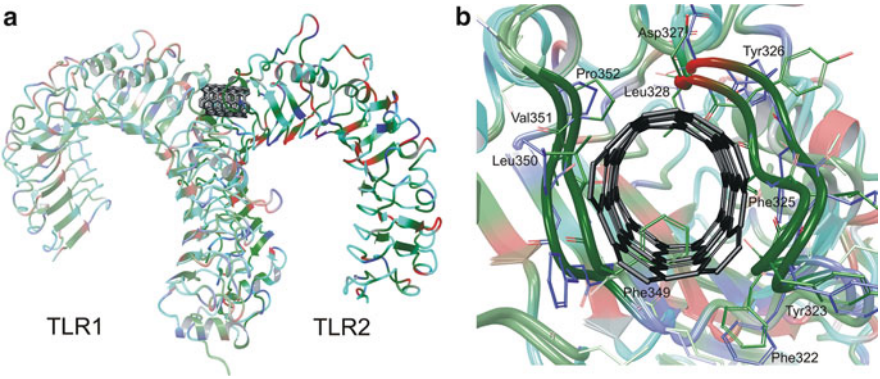

Fig. 10 5,5 CNT-bound TLR1/TLR2 ECDs: (**a**) 5,5 CNT is bound to the TLR1 and TLR2 ECD interface dimerization area, (**b**) aligned structures of TLR2 ECDs before (*green* carbon atoms) and after (*blue* carbon atoms) the impact OPLS2005 refinement upon binding 5,5 CNTs. The orientation of two parallel entrance loops and the side chains of hydrophobic Phe349, Phe325, and Leu328 preventing the nanotube from intrusion are shown to be optimized (Reproduced with Permission from reference (Turabekova et al. 2014). Copyright, Royal Society of Chemistry, 2014)

findings indicating that CNTs and fullerenes induce an excessive expression of specific cytokines and chemokines (i.e., IL-8 and MCP1).

Later, this kind of interaction was confirmed by MD simulation provided by Mozolewska et al. (2014). In this study, authors made an attempt to determine if the nanotubes could interfere with the innate immune system by interacting with TLRs. For this purpose, authors used the following TLR structures downloaded from the RCSB Protein Data Bank: TLR2 (3A7C), TLR4/MD (3FXI), TLR5 (3V47), TLR3 (2A0Z), and the complexes of TLR1/TLR2 (2Z7X) and TLR2/TLR6 (3A79). The results of steered molecular dynamics (SMD) simulations have shown that nanotubes interact very strongly with the binding pockets of some receptors (e.g., TLR2), which results in their binding to these sites without substantial use of the external force.

Concluding Remarks

In this chapter, we discussed 3D QSAR and protein-ligand docking methods, recent applications of them for conventional organic compounds design and for nanostructured materials. Despite of all pitfalls, the 3D QSAR approach confirmed the importance and value in drug design and medicinal chemistry. Moreover, the combination of 3D QSAR approach with other techniques, including protein–ligand docking study gives much better improvement in predictions of biologically active compounds and drug candidates. The development of methods for 3D QSAR still continues, giving improved predictions for conventional organic compounds. Thus, we believe that 3D QSAR methods in the near future will be able to encode and model various organic and nanomaterials for important biological and physicochemical property improvement.

Bibliography

Ahmed, L., Rasulev, B., Turabekova, M., Leszczynska, D., & Leszczynski, J. (2013). Receptor-and ligand-based study of fullerene analogues: comprehensive computational approach including quantum-chemical, QSAR and molecular docking simulations. *Organic and Biomolecular Chemistry, 11*(35), 5798–5808.

Ajmani, S., Jadhav, K., & Kulkarni, S. A. (2006). Three-dimensional QSAR using the k-nearest neighbor method and its interpretation. *Journal of Chemical Information and Modeling, 46*(1), 24–31.

Amnerkar, N. D., & Bhusari, K. P. (2010). Synthesis, anticonvulsant activity and 3D-QSAR study of some prop-2-eneamido and 1-acetyl-pyrazolin derivatives of aminobenzothiazole. *European Journal of Medicinal Chemistry, 45*(1), 149–159.

Araújo, J. Q., de Brito, M. A., Hoelz, L. V. B., de Alencastro, R. B., Castro, H. C., Rodrigues, C. R., & Albuquerque, M. G. (2011). Receptor-dependent (RD) 3D-QSAR approach of a series of benzylpiperidine inhibitors of human acetylcholinesterase (HuAChE). *European Journal of Medicinal Chemistry, 46*(1), 39–51.

Baskin, I. I., & Zhokhova, N. I. (2013). The continuous molecular fields approach to building 3D-QSAR models. *Journal of Computer-Aided Molecular Design, 27*(5), 427–442.

Calvaresi, M., & Zerbetto, F. (2010). Baiting proteins with C60. *ACS Nano, 4*(4), 2283–2299.

Calvaresi, M., & Zerbetto, F. (2011). Fullerene sorting proteins. *Nanoscale, 3*(7), 2873–2881.
Clark, M., Cramer, R. D., Jones, D. M., Patterson, D. E., & Simeroth, P. E. (1990). Comparative molecular field analysis (CoMFA). 2. Toward its use with 3D-structural databases. *Tetrahedron Computer Methodology, 3*(1), 47–59.
Cramer, R., & Bunce, J. D. (1987). The Dylomms method: Initial results from a comparative study of approaches to 3d QSAR. In Hadzi D., Jerman-Blazic B. (eds) QSAR in drug design and toxicology (pp. 3–12).
Cramer, R. D., Patterson, D. E., & Bunce, J. D. (1988). Comparative molecular field analysis (CoMFA). 1. Effect of shape on binding of steroids to carrier proteins. *Journal of the American Chemical Society, 110*(18), 5959–5967.
Cruciani, G., Fontaine, F., & Pastor, M. (2004). *Almond; 3.3.0*. Perugia: Molecular Discovery Ltd.
Datar, P. A., Khedkar, S. A., Malde, A. K., & Coutinho, E. C. (2006). Comparative residue interaction analysis (CoRIA): A 3D-QSAR approach to explore the binding contributions of active site residues with ligands. *Journal of Computer-Aided Molecular Design, 20*(6), 343–360.
Dhaked, D. K., Verma, J., Saran, A., & Coutinho, E. C. (2009). Exploring the binding of HIV-1 integrase inhibitors by comparative residue interaction analysis (CoRIA). *Journal of Molecular Modeling, 15*(3), 233–245.
Dixon, S. L., Smondyrev, A. M., Knoll, E. H., Rao, S. N., Shaw, D. E., & Friesner, R. A. (2006). PHASE: A new engine for pharmacophore perception, 3D QSAR model development, and 3D database screening. 1. Methodology and preliminary results. *Journal of Computer-Aided Molecular Design, 20*, 647–671.
Doweyko, A. M. (1988). The hypothetical active site lattice. An approach to modelling active sites from data on inhibitor molecules. *Journal of Medicinal Chemistry, 31*(7), 1396–1406.
Durdagi, S., Mavromoustakos, T., Chronakis, N., & Papadopoulos, M. G. (2008a). Computational design of novel fullerene analogues as potential HIV-1 PR inhibitors: Analysis of the binding interactions between fullerene inhibitors and HIV-1 PR residues using 3D QSAR, molecular docking and molecular dynamics simulations. *Bioorganic and Medicinal Chemistry, 16*(23), 9957–9974.
Durdagi, S., Mavromoustakos, T., & Papadopoulos, M. G. (2008b). 3D QSAR CoMFA/CoMSIA, molecular docking and molecular dynamics studies of fullerene-based HIV-1 PR inhibitors. *Bioorganic and Medicinal Chemistry Letters, 18*(23), 6283–6289.
Durdagi, S., Supuran, C. T., Strom, T. A., Doostdar, N., Kumar, M. K., Barron, A. R., Mavromoustakos, T., & Papadopoulos, M. G. (2009). In silico drug screening approach for the design of magic bullets: A successful example with anti-HIV fullerene derivatized amino acids. *Journal of Chemical Information and Modeling, 49*(5), 1139–1143.
Eriksson, L., Jaworska, J., Worth, A. P., Cronin, M. T., McDowell, R. M., & Gramatica, P. (2003). Methods for reliability and uncertainty assessment and for applicability evaluations of classification-and regression-based QSARs. *Environmental Health Perspectives, 111*(10), 1361.
Esposito, E. X., Hopfinger, A. J., Shao, C.-Y., Su, B.-H., Chen, S.-Z., & Tseng, Y. J. (2015). Exploring possible mechanisms of action for the nanotoxicity and protein binding of decorated nanotubes: Interpretation of physicochemical properties from optimal QSAR models. *Toxicology and Applied Pharmacology, 288*(1), 52–62.
Evans, D. A., Doman, T. N., Thorner, D. A., & Bodkin, M. J. (2007). 3D QSAR methods: Phase and catalyst compared. *Journal of Chemical Information and Modeling, 47*(3), 1248–1257.
Fontaine, F., Pastor, M., & Sanz, F. (2004). Incorporating molecular shape into the alignment-free GRid-IN dependent descriptors. *Journal of Medicinal Chemistry, 47*(11), 2805–2815.
Fontaine, F., Pastor, M., Zamora, I., & Sanz, F. (2005). Anchor-GRIND: Filling the gap between standard 3D QSAR and the GRid-IN dependent descriptors. *Journal of Medicinal Chemistry, 48*(7), 2687–2694.
Gohlke, H., & Klebe, G. (2002). DrugScore meets CoMFA: Adaptation of fields for molecular comparison (AFMoC) or how to tailor knowledge-based pair-potentials to a particular protein. *Journal of Medicinal Chemistry, 45*(19), 4153–4170.

Goodford, P. J. (1985). A computational procedure for determining energetically favorable binding sites on biologically important macromolecules. *Journal of Medicinal Chemistry, 28*(7), 849–857.

Gopalakrishnan, B., Aparna, V., Jeevan, J., Ravi, M., & Desiraju, G. (2005). A virtual screening approach for thymidine monophosphate kinase inhibitors as antitubercular agents based on docking and pharmacophore models. *Journal of Chemical Information and Modeling, 45*(4), 1101–1108.

Gupta, P., Roy, N., & Garg, P. (2009). Docking-based 3D-QSAR study of HIV-1 integrase inhibitors. *European Journal of Medicinal Chemistry, 44*(11), 4276–4287.

Halgren, T. A. (1996). Merck molecular force field. I. Basis, form, scope, parameterization, and performance of MMFF94. *Journal of Computational Chemistry, 17*(5-6), 490–519.

Halgren, T. A., Murphy, R. B., Friesner, R. A., Beard, H. S., Frye, L. L., Pollard, W. T., & Banks, J. L. (2004). Glide: A new approach for rapid, accurate docking and scoring. 2. Enrichment factors in database screening. *Journal of Medicinal Chemistry, 47*, 1750–1759.

Hansch, C., Leo, A., Hoekman, D., & Leo, A. (1995). *Exploring QSAR*. Washington, DC: American Chemical Society.

Hopfinger, A. J. (1980). A QSAR investigation of dihydrofolate reductase inhibition by Baker triazines based upon molecular shape analysis. *Journal of the American Chemical Society, 102*(24), 7196–7206.

Hu, R., Barbault, F., Delamar, M., & Zhang, R. (2009). Receptor-and ligand-based 3D-QSAR study for a series of non-nucleoside HIV-1 reverse transcriptase inhibitors. *Bioorganic and Medicinal Chemistry, 17*(6), 2400–2409.

Isayev, O., Rasulev, B., Gorb, L., & Leszczynski, J. (2006). Structure-toxicity relationships of nitroaromatic compounds. *Molecular Diversity, 10*(2), 233–245.

Jha, K. K., Samad, A., Kumar, Y., Shaharyar, M., Khosa, R. L., Jain, J., Kumar, V., & Singh, P. (2010). Design, synthesis and biological evaluation of 1, 3, 4-oxadiazole derivatives. *European Journal of Medicinal Chemistry, 45*(11), 4963–4967.

Karelson, M., Lobanov, V. S., & Katritzky, A. R. (1996). Quantum-chemical descriptors in QSAR/QSPR studies. *Chemical Reviews, 96*(3), 1027–1044.

Kim, K. H. (2001). Thermodynamic aspects of hydrophobicity and biological QSAR. *Journal of Computer-Aided Molecular Design, 15*(4), 367–380.

Kim, K. H., Greco, G., & Novellino, E. (1998). A critical review of recent CoMFA applications. In Kubinyi H., Folkers G., Martin Y.C. (eds) In *3D QSAR in drug design* (pp. 257–315). Springer.

Klebe, G. (2006). Virtual ligand screening: Strategies, perspectives and limitations. *Drug Discovery Today, 11*(13), 580–594.

Klebe, G., Abraham, U., & Mietzner, T. (1994). Molecular similarity indices in a comparative analysis (CoMSIA) of drug molecules to correlate and predict their biological activity. *Journal of Medicinal Chemistry, 37*(24), 4130–4146.

Kubinyi, H. (1997a). QSAR and 3D QSAR in drug design Part 1: Methodology. *Drug Discovery Today, 2*(11), 457–467.

Kubinyi, H. (1997b). QSAR and 3D QSAR in drug design part 2: Applications and problems. *Drug Discovery Today, 2*(12), 538–546.

Kumar, B. P., Sankar, G., Baig, R. N., & Chandrashekaran, S. (2009). Novel Biginelli dihydropyrimidines with potential anticancer activity: A parallel synthesis and CoMSIA study. *European Journal of Medicinal Chemistry, 44*(10), 4192–4198.

Li, H., Sutter, J., & Hoffmann, R. (2000). HypoGen: An automated system for generating 3D predictive pharmacophore models. In *Pharmacophore perception, development, and use in drug design* (Vol. 2, p. 171).

Lill, M. A. (2007). Multi-dimensional QSAR in drug discovery. *Drug Discovery Today, 12*(23), 1013–1017.

Lushington, G. H., Guo, J.-X., & Wang, J. L. (2007). Whither combine? New opportunities for receptor-based QSAR. *Current Medicinal Chemistry, 14*(17), 1863–1877.

Martin, Y. C. (2009). Let's not forget tautomers. *Journal of Computer-Aided Molecular Design, 23*(10), 693–704.

Molecular Operating Environment (MOE). (2016). Chemical Computing Group Inc. 1010 Sherbooke St. West, Suite #910, Montreal, QC, Canada, H3A 2R7.

Moro, S., Braiuca, P., Deflorian, F., Ferrari, C., Pastorin, G., Cacciari, B., Baraldi, P. G., Varani, K., Borea, P. A., & Spalluto, G. (2005). Combined target-based and ligand-based drug design approach as a tool to define a novel 3D-pharmacophore model of human A3 adenosine receptor antagonists: Pyrazolo [4, 3-e] 1, 2, 4-triazolo [1, 5-c] pyrimidine derivatives as a key study. *Journal of Medicinal Chemistry, 48*(1), 152–162.

Moro, S., Bacilieri, M., Cacciari, B., Bolcato, C., Cusan, C., Pastorin, G., Klotz, K.-N., & Spalluto, G. (2006). The application of a 3D-QSAR (autoMEP/PLS) approach as an efficient pharmacodynamic-driven filtering method for small-sized virtual library: Application to a lead optimization of a human A 3 adenosine receptor antagonist. *Bioorganic and Medicinal Chemistry, 14*(14), 4923–4932.

Mozolewska, M. A., Krupa, P., Rasulev, B., Liwo, A., & Leszczynski, J. (2014). Preliminary studies of interaction between nanotubes and toll-like receptors. *Task Quarterly, 18*(4), 351–355.

Oprea, T. I., & Matter, H. (2004). Integrating virtual screening in lead discovery. *Current Opinion in Chemical Biology, 8*(4), 349–358.

Ortiz, A. R., Pisabarro, M. T., Gago, F., & Wade, R. C. (1995). Prediction of drug binding affinities by comparative binding energy analysis. *Journal of Medicinal Chemistry, 38*(14), 2681–2691.

Pajeva, I. K., Globisch, C., & Wiese, M. (2009). Combined pharmacophore modeling, docking, and 3D QSAR studies of ABCB1 and ABCC1 transporter inhibitors. *ChemMedChem, 4*(11), 1883–1896.

Pastor, M., Cruciani, G., McLay, I., Pickett, S., & Clementi, S. (2000). GRid-INdependent descriptors (GRIND): A novel class of alignment-independent three-dimensional molecular descriptors. *Journal of Medicinal Chemistry, 43*, 3233–3243.

Patel, P. D., Patel, M. R., Kaushik-Basu, N., & Talele, T. T. (2008). 3D QSAR and molecular docking studies of benzimidazole derivatives as hepatitis C virus NS5B polymerase inhibitors. *Journal of Chemical Information and Modeling, 48*(1), 42–55.

Perkins, R., Fang, H., Tong, W., & Welsh, W. J. (2003). Quantitative structure-activity relationship methods: Perspectives on drug discovery and toxicology. *Environmental Toxicology and Chemistry, 22*(8), 1666–1679.

Perola, E. (2006). Minimizing false positives in kinase virtual screens. *Proteins: Structure, Function, and Bioinformatics, 64*(2), 422–435.

Podlogar, B. L., & Ferguson, D. M. (2000). QSAR and CoMFA: A perspective on the practical application to drug discovery. *Drug Design and Discovery, 17*(1), 4.

Polanski, J., Gieleciak, R., & Bak, A. (2002). The comparative molecular surface analysis (CoMSA)-a nongrid 3D QSAR method by a coupled neural network and PLS system: Predicting p K a values of benzoic and alkanoic acids. *Journal of Chemical Information and Computer Science, 42*(2), 184–191.

Polanski, J., Bak, A., Gieleciak, R., & Magdziarz, T. (2006). Modeling robust QSAR. *Journal of Chemical Information and Modeling, 46*(6), 2310–2318.

Pulla, V. K., Sriram, D. S., Viswanadha, S., Sriram, D., & Yogeeswari, P. (2016). Energy-based pharmacophore and three-dimensional quantitative structure–activity relationship (3D-QSAR) modeling combined with virtual screening to identify novel small-molecule inhibitors of silent mating-type information regulation 2 homologue 1 (SIRT1). *Journal of Chemical Information and Modeling, 56*(1), 173–187.

Puzyn, T., Rasulev, B., Gajewicz, A., Hu, X., Dasari, T. P., Michalkova, A., Hwang, H.-M., Toropov, A., Leszczynska, D., & Leszczynski, J. (2011). Using nano-QSAR to predict the cytotoxicity of metal oxide nanoparticles. *Nature Nanotechnology, 6*(3), 175–178.

Ragno, R., Artico, M., De Martino, G., La Regina, G., Coluccia, A., Di Pasquali, A., & Silvestri, R. (2005). Docking and 3-D QSAR studies on indolyl aryl sulfones. Binding mode exploration at the HIV-1 reverse transcriptase non-nucleoside binding site and design of highly active N-(2-hydroxyethyl) carboxamide and N-(2-hydroxyethyl) carbohydrazide derivatives. *Journal of Medicinal Chemistry, 48*(1), 213–223.

Raparti, V., Chitre, T., Bothara, K., Kumar, V., Dangre, S., Khachane, C., Gore, S., & Deshmane, B. (2009). Novel 4-(morpholin-4-yl)-N′-(arylidene) benzohydrazides: Synthesis, antimycobacterial activity and QSAR investigations. *European Journal of Medicinal Chemistry, 44*(10), 3954–3960.

Rasulev, B., Kušić, H., Leszczynska, D., Leszczynski, J., & Koprivanac, N. (2010). QSAR modeling of acute toxicity on mammals caused by aromatic compounds: The case study using oral LD 50 for rats. *Journal of Environmental Monitoring, 12*(5), 1037–1044.

Ravichandran, V., Kumar, B. P., Sankar, S., & Agrawal, R. (2009). Predicting anti-HIV activity of 1, 3, 4-thiazolidinone derivatives: 3D-QSAR approach. *European Journal of Medicinal Chemistry, 44*(3), 1180–1187.

Robinson, D. D., Winn, P. J., Lyne, P. D., & Richards, W. G. (1999). Self-organizing molecular field analysis: A tool for structure-activity studies. *Journal of Medicinal Chemistry, 42*(4), 573–583.

Saikia, N., Rajkhowa, S., & Deka, R. C. (2013). Density functional and molecular docking studies towards investigating the role of single-wall carbon nanotubes as nanocarrier for loading and delivery of pyrazinamide antitubercular drug onto pncA protein. *Journal of Computer-Aided Molecular Design, 27*(3), 257–276.

Sakkiah, S., Thangapandian, S., John, S., Kwon, Y. J., & Lee, K. W. (2010). 3D QSAR pharmacophore based virtual screening and molecular docking for identification of potential HSP90 inhibitors. *European Journal of Medicinal Chemistry, 45*(6), 2132–2140.

Schneidman-Duhovny, D., Inbar, Y., Nussinov, R., & Wolfson, H. J. (2005). PatchDock and SymmDock: Servers for rigid and symmetric docking. *Nucleic Acids Research, 33*(Suppl 2), W363–W367.

Shih, K.-C., Lin, C.-Y., Zhou, J., Chi, H.-C., Chen, T.-S., Wang, C.-C., Tseng, H.-W., & Tang, C.-Y. (2011). Development of novel 3D-QSAR combination approach for screening and optimizing B-Raf inhibitors in silico. *Journal of Chemical Information and Modeling, 51*(2), 398–407.

Silverman, B., & Platt, D. E. (1996). Comparative molecular moment analysis (CoMMA): 3D-QSAR without molecular superposition. *Journal of Medicinal Chemistry, 39*(11), 2129–2140.

Sun, J., Cai, S., Yan, N., & Mei, H. (2010). Docking and 3D-QSAR studies of influenza neuraminidase inhibitors using three-dimensional holographic vector of atomic interaction field analysis. *European Journal of Medicinal Chemistry, 45*(3), 1008–1014.

Taha, M. O., Dahabiyeh, L. A., Bustanji, Y., Zalloum, H., & Saleh, S. (2008). Combining ligand-based pharmacophore modeling, quantitative structure-activity relationship analysis and in silico screening for the discovery of new potent hormone sensitive lipase inhibitors. *Journal of Medicinal Chemistry, 51*, 6478–6494.

Todeschini, R., & Gramatica, P. (1998). *3D QSAR in drug design* (Vol. 2, pp. 355–360). Dordrecht: Kluwer/ESCOM.

Totrov, M. (2008). Atomic property fields: Generalized 3D pharmacophoric potential for automated ligand superposition, pharmacophore elucidation and 3D QSAR. *Chemical Biology and Drug Design, 71*(1), 15–27.

Tripos. (2006). SYBYL, version 7.3, 2006, St, Louis.

Turabekova, M., Rasulev, B., Theodore, M., Jackman, J., Leszczynska, D., & Leszczynski, J. (2014). Immunotoxicity of nanoparticles: A computational study suggests that CNTs and C 60 fullerenes might be recognized as pathogens by Toll-like receptors. *Nanoscale, 6*(7), 3488–3495.

Tzoupis, H., Leonis, G., Durdagi, S., Mouchlis, V., Mavromoustakos, T., & Papadopoulos, M. G. (2011). Binding of novel fullerene inhibitors to HIV-1 protease: Insight through molecular dynamics and molecular mechanics Poisson–Boltzmann surface area calculations. *Journal of Computer-Aided Molecular Design, 25*(10), 959–976.

Veber, D. F., Johnson, S. R., Cheng, H.-Y., Smith, B. R., Ward, K. W., & Kopple, K. D. (2002). Molecular properties that influence the oral bioavailability of drug candidates. *Journal of Medicinal Chemistry, 45*(12), 2615–2623.

Virsodia, V., Pissurlenkar, R. R., Manvar, D., Dholakia, C., Adlakha, P., Shah, A., & Coutinho, E. C. (2008). Synthesis, screening for antitubercular activity and 3D-QSAR studies of substituted

N-phenyl-6-methyl-2-oxo-4-phenyl-1, 2, 3, 4-tetrahydro-pyrimidine-5-carboxamides. *European Journal of Medicinal Chemistry, 43*(10), 2103–2115.

Walters, D. E., & Hinds, R. M. (1994). Genetically evolved receptor models: A computational approach to construction of receptor models. *Journal of Medicinal Chemistry, 37*(16), 2527–2536.

Wang, Y.-C., Chen, S.-L., Deng, N.-Y., & Wang, Y. (2016). Computational probing protein–protein interactions targeting small molecules. *Bioinformatics, 32*(2), 226–234.

Wise, M., Cramer, R. D., Smith, D., & Exman, I. (1983). *Progress in three-dimensional drug design: The use of real-time colour graphics and computer postulation of bioactive molecules in DYLOMMS*. Amsterdam: Elsevier.

Yang, S.-Y. (2010). Pharmacophore modeling and applications in drug discovery: Challenges and recent advances. *Drug Discovery Today, 15*(11), 444–450.

Yang, Y., Qin, J., Liu, H., & Yao, X. (2011). Molecular dynamics simulation, free energy calculation and structure-based 3D-QSAR studies of B-RAF kinase inhibitors. *Journal of Chemical Information and Modeling, 51*(3), 680–692.

Zhokhova, N. I., Baskin, I. I., Bakhronov, D. K., Palyulin, V. A., & Zefirov, N. S. (2009). Method of continuous molecular fields in the search for quantitative structure-activity relationships. *Doklady Chemistry, 429*(1), 273–276.

Zhou, P., Tian, F., & Li, Z. (2007). Three dimensional holographic vector of atomic interaction field (3D-HoVAIF). *Chemometrics and Intelligent Laboratory Systems, 87*(1), 88–94.