Chemical Structure Indices in **In Silico Molecular Design**

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Abstract

The chemical structure indices have a significant role in providing direction to the design of chemotherapeutic agents. These indices come from the experimental domain as well as through the computations. While the experimental properties of compounds have practical value, the indices from computational domain offer fast and economic inputs to simulations. This review article discusses various methods and issues involved in the generation of physicochemical, quantum chemical, graph theoretical, chirality indices, flexible descriptors, molecular fingerprints and 3D chemical space descriptors etc for *in silico* molecular design approaches. A futuristic perspective of structural indices in drug design is outlined.

Keywords

Chemical structure indices • *In silico* drug design • QSAR • Molecular modeling

1. Introduction

Information encompasses all types of data – qualitative as well as quantitative – which may be processed or unprocessed. It may have been designed to address a simple event or a more complex situation emerged from a statistically defined quantity with a probability of occurrence, etc. In the hierarchy of information flow, notion qualifies as the first qualitative, irregular and vague estimation of information. In this flow, parameters and measurements take the center stage with premonitions (the amorphous state of information) at the origin of the flow line and

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the inferences and decisions at its crystalline end. In it, a parameter is a composition of set of rules designed to define a concept, property or any other relevant information. In the hierarchy of information, a parameter takes precedence over measurement. In this scenario, the origin of the concept of parameterization is time immemorial and it goes along with the consciousness. Figure 1 shows a schematic illustration of hierarchy of information flow which is equally relevant and valid for *in silico* molecular design approaches.

Figure 1. A schematic illustration showing hierarchy of information flow from premonitions to decisions. The irregular enclosure of notion symbolizes its vague nature; the circular enclosures symbolize the ubiquitous as well as universal nature of parameters and measurements; the rectangular enclosures symbolize the well-defined confines of inferences and decisions. In this evolution of 'Notions' to 'Decisions', the chemical structure parameters and their measurements are vital components of *in silico* molecular design approaches.

A wide spectrum of properties originated from different concepts represents the sequence of chemical information. In this, the compound's nature / atom type etc correspond to one end of the property spectrum and quantum chemical states

represent the other end of the same. The empirical formulas, molecular formulas, structural formulas etc are spread in between these two extremes. Any physicochemical property or biological activity of a compound is a net result of different forces operating in that compound's environment. This realization has made the whole environment of the compound as a potential source of information to investigate its interplay with the properties and activities. They address different aspects of *in silico* molecular design and lend credence to the design of additional or new compounds for the chosen goal. The increasing cost of chemical and biochemical studies together with stringent biological and environmental regulations have given impetus to these approaches [1]. Moreover, due to the cost effectiveness, they are in high demand in drug research. The classical and higher-dimension graphical quantitative structure activity relationship (QSAR) (also, quantitative structure property relationships i.e. QSPRs) [2, 3] procedures and different virtual modeling approaches such as docking [4], virtual screening [5], homology modeling [6] are integral parts of *in silico* molecular design approaches for drug research. An assumption fundamental and common to all these modeling approaches is that the variation in the biological response can be expressed as a function of the variations in the chemical structure space. These theoretical studies are iterative processes with scope for prediction and feedback tuning for rectification/ improvement, if any. During the last 5 years different reviews have appeared in literature covering the role of topological parameters [7, 8], *in silico* prediction of pharmacokinetic [9] and toxicological profiles [10], drug-drug interactions [11], discrimination of drug like from non-drug like molecules [12], virtual screening methods [5], data-mining techniques [13], feature selection methods [14] etc in drug research. The parameterization chemical structure is an open end challenge. The algorithms and software available today effortlessly compute a few thousand structural indices of compounds for different end uses. In spite of the large number of descriptors, new molecular features are needed to address different aspects so far not tamed, for example, various aspects of molecular recognition [15] challenges of supramolecular chemistry [16] etc. In this

backdrop, this review article discusses the various methods and issues involved in the generation of different chemical structural indices. A futuristic perspective of structural indices in drug design is outlined.

2. Chemical Structural Indices

In isolation, a data point is only a qualified number. A collection of such qualified numbers makes a variable or descriptor. Appropriate parameterization of chemical compounds is essential to comprehend the wealth of information embedded in them. Reliable physicochemical and other property data are also essential to many areas of chemical and biochemical studies which include drugs and pharmaceuticals. Ever since Hansch's [17] and Free and Wilson's [18] observations on the relationship between the chemical structure and its biological response, the progress of classical or 2D-QSAR is largely associated and synonymous with the developments in the numerical characterization of chemical structure and integration of diverse statistical approaches to handle the constantly increasing structural parameters in deriving meaningful inferences. The fundamental QSAR equation of Hansch has been proposed using partition coefficient ($\log P$ or its derivative π), Hammett σ constant as physicochemical descriptors [17]. The Free-Wilson method with indicator variables as descriptors is purely a non-parametric approach [18]. Apart from these physicochemical and indicator variables, several experimental, empirical and non-empirical chemical structural descriptors have been tried in QSAR studies and added to the list of variables as potential descriptors of drug-receptor interactions.

The most common and characteristic numerical descriptors of chemicals are elemental composition, molecular weight, melting point, boiling point, solubility, etc. These parameters represent only a tiny fraction of all possible experimental molecular measurements. The impracticality of experimentally determining physicochemical properties of all existing chemicals can be easily understood. This awareness has generated momentum to find alternative ways of numerical characterization of chemicals. In this context theoretical parameters of chemicals

which provide reliable estimates of the properties of non-tested as well as not easily amenable compounds are of significant interest.

The descriptors of chemical structures can be broadly categorized as 0D (e.g. molecular weight), 1D (e.g., bond/ functional group counts), 2D (structural formula related or 2D positional descriptors) and 3D (descriptors from 3D-molecular conformation) parameters. For a classical QSAR study, 0D to 2D-structure related parameters or substituent position indices of the compounds form the descriptor database. In these studies, if the compounds of interest belong to a homologous series, then varying structural parts alone are considered for parameterization after excluding the common core structure. The tacit assumption of this practice is that each one of the selected fragments of the whole structure occupies approximately the same position in space with respect to all other analogues. This assumption is true to a very large extent for compounds with rigid structural frames. However, the substituents' relative orientations and location in space are left to the intuitive interpretation of the researchers. In the succeeding parts the molecular descriptors have been addressed according to their origin i.e. physicochemical, quantum chemical, graph theoretical, etc.

2.1 Physicochemical Indices

Physicochemical properties are the earliest and most fundamental molecular indices used in drug design approaches. Among them, logP (logarithm of octanol-water partition coefficient) [19, 20], MR (molar refractivity) [19, 20], E_s (Taft's steric constant) [21] and σ (Hammett sigma constant) [19, 20, 22] are the most common and widely used descriptors in correlation studies. In drug-receptor interactions these descriptors infer the possibilities of hydrophobic/ hydrophilic, polarisability/ dispersive, steric and electronic forces between the ligand and the receptor site. In drug design studies, logP or partition coefficient is one of the most fundamental properties of the compounds responsible not only for interaction at the receptor site but also for its transportation from the site of administration to the site of action.

Different experimental procedures such as shake-flask method [19], HPLC method [23] etc., are available to determine the logP values of organic compounds. In view of its importance, various computational approaches namely, fragmental constants [19, 20, 24, 25], additive atomic contributions [26, 27], charge densities [28] and conformationally dependent hydrophobic indices [29, 30] are developed to theoretically calculate the logP of a non-ionizable organic compound between two mutually immiscible solvents, 1-octanol and water. Among these computational approaches, fragmental constant methods [19, 20, 24, 25] are the most popular ones. Similar to Hammett σ constant, Hansch π - constant has been defined to account for the hydrophobic contribution of aromatic substituent groups ($\pi_x = \log P_x - \log P_H$, where P_x and P_H are the partition coefficients of substituted and parent compounds respectively). The subject has been reviewed [19, 31, 32]. Giving due recognition to the pH of biological system, a pH based logP value (logD) has been proposed for use in place of logP [33]. Different physicochemical descriptors introduced to model drug-receptor interactions have been shown in Table 1 along with their physical meanings [19–22, 24–26, 33–39].

2.2 Quantum chemical indices

Indices from quantum chemical methods provide a precise and complete account of electronic effects of compounds. They offer atom-by-atom as well as cumulative electronic profile of the chemical structure. For a very long time, application of quantum chemical procedures and the indices have been restricted to Huckel Molecular Orbital (HMO) and Extended HMO (EHMO) methods due to the limitations on the part of computational hardware. With the advent of high performance computers, different *ab initio* and semiempirical quantum-chemical methods have been implemented in theoretical drug design [40, 41]. However, many *ab initio* quantum chemical calculations are still not practicable in QSAR and modeling studies in view of the large computational requirements of these

Tab. 1. Some physicochemical parameters used in QSAR and modeling studies

Parameters	Symbol	Inference	Ref.
Hydrophobic			
Solubility	S	solubility	19
Partition coefficient	$K_{o/w}$	hydrophilicity / hydrophobicity of molecules	19
Overall lipophilicity	logP	do	19, 20
Calculated logP	ClogP	do	19, 20
Retardation factor	R_f	do	19, 20
Chromatographic R_m value	R_m	do	19, 20
Distribution coefficient	logD	pH dependant measure of hydrophobicity	33
Hydrophobic constant	π	hydrophobicity of chemical atoms or groups	19, 20
Hydrophobic fragmental constant	f	hydrophobicity of chemical atoms or groups	20, 24, 25
Electronic			
Hammett's sigma constants	σ	inductive and mesomeric effect	19, 20, 22
Taft's inductive constants	σ^*	polar / inductive / resonance effect	34
Mesomeric effect	M	mesomeric and resonance effect	19, 20
Dipole moment	μ	polarity	19
Dielectric constant	D	charge	19
Ionization constants	pKa	degree of ionization	19
Electronic field effect	F	electronic field effect	35
Resonance effect	R	electronic resonance effect	35
NMR chemical shifts	δ	electron environment of nucleus	36
Polarizability			
Molar refractivity	MR	Polarizability parameter	19, 20, 26
Molar volume	MV	Polarizability parameter	19, 20
Parachor	PA	Polarizability parameter	19, 20
Steric			
Molecular weight	MW	bulkiness / steric hindrance	19, 20
Bulk steric parameter	r_v	do	19, 20
Taft's steric constant	Es	do	21
Molecular surface area	MSA	do	19
Sterimol parameters	L; B ₁ -B ₅	do	37
Charton steric parameter	u	do	38
van der Waals volume	V_{vdw}	do	39

calculations. Instead of *ab initio* methods, semiempirical quantum-chemical methods are often used for the calculation of many electronic descriptors of molecules and their constituent atoms. The most commonly used descriptor are different kinds of charge densities, atomic and molecular orbital (HOMO, LUMO) energies, σ and π orbital electron densities, σ - and π -bond orders, free-valences, electrophilic-, nucleophilic- and radical-superdelocalizabilities, atom-atom and molecular polarizabilities, dipole moments and a variety of energy indices. The computation of atom-by-atom property profiles of compounds gives scope to analyze them at angstrom level. The increased number of descriptors (due to atom-by-atom property profiles) rapidly escalates the time required for their analysis. MOPAC (Molecular Orbital PACKage) is a general-purpose semiempirical molecular orbital package commonly used in QSAR and modeling studies. Gaussian [42] and GAMESS (General Atomic and Molecular Electronic Structure System) [43] are some other quantum chemistry packages of interest to QSAR and modeling studies. Apart from these, different molecular mechanic approaches are also used in molecular modeling for simulations and conformational analysis [44–46]. Some of these aspects have been reviewed [19, 47].

2.3 Graph Theoretical Indices

Graph Theoretical Indices are non-empirical descriptors. They account for a very large number of descriptors out of the total used in modeling studies. A graph is an expression of relationship between a set of points (vertices) interconnected through lines (edges). In this perspective all chemical structures are graphical objects with constituent atoms serving as vertices and the chemical bonds between them as edges. They are also addressed as topological graphs of chemical structures. While the topological indices are derived from simple atomic connectivity table of the molecule (2D-structure), Cartesian coordinates of the same are used for deriving the topographical indices. The concepts surrounding this representation of chemical structure in association with the fundamental properties of elements (vertices) have opened avenues for the generation of a very large number of

characteristic numerical descriptors to quantify the embedded features of chemical structures and parts thereof from different perspectives. Physicochemical properties such as mass, volume, electronegativity or polarizability of vertices are commonly used as weighting factors in the descriptor computation. Almost all topological descriptors are calculated from the H-suppressed molecular graphs. Some of the early and most fundamental graph theoretical descriptors are Wiener index (W), Altenburg polynomial, Gordon and Scantlebury index, Hosoya's Z-index, Randic's connectivity index, Keir and Hall's molecular connectivity indices [48–50].

Several computer programs based on graph theory have been developed to calculate characteristic descriptors of the molecules and their structural fragments. POLLY [51] Molconn-Z [52], TOPS-MODE (TOPological Substructural MOlecular DEsign) [53, 54], CODESSA (COMprehensive DEScriptors for Structural and Statistical Analysis) [55, 56], DRAGON [57] and MODEL [58] are some of the well known or recent programs embedded with graph theoretical concepts for characterizing the chemical structure and compute large number of descriptors for modeling and other studies. POLLY uses vertex information content, in terms of properties, in graph theory to compute several topological indices for QSAR-QSPR analysis [51, 59]. The Molconn-Z software computes a wide variety of topological indices addressing molecular connectivities of different orders, shapes, electrotopological states, topological equivalences etc [52]. Estrada proposed TOPS-MODE descriptors based on the spectral moments of the bonds [53, 54]. In the computation of these descriptors, the main diagonal entries of the topological matrix are considered in terms of bond weights representing hydrophobic, polarity, electronic and steric features of molecules. They deal with the physicochemical and electronic properties of different regions of the molecule. CODESSA provides an environment to compute different classes of descriptors i.e. topological, geometrical, electronic, quantum chemical as well as multivariate analysis methods [55]. DRAGON provides a platform for the computation of a variety of 2D- and 3D-graph theoretical descriptors. They include 2DAUTO (2D-autocorrelation), WHIM (Weighted Holistic Invariant Molecular), BCUT (molecular descriptors for the

chemical similarity/diversity), RDF (Radial Distribution Function), 3D-MoRSE (3D-Molecule Representation of Structures based on Electron diffraction), GETAWAY (GEometry, Topology, and Atom-Weights Assembly) and several other descriptors including 0D and 1D categories [57]. Different computational strategies are involved in different groups of descriptors. These strategies include transformations involving autocorrelation functions (2DAUTO) [60–62], eigenvalues, eigenvectors [63], radial distribution function (RDF) [64], electron diffraction data (3D-MoRSE) [65], concepts of leverage (similar to regression diagnostics) (GETAWAY) [66]. Eigenvalues represent the characteristic roots of polynomials. If the origin of the polynomial is adjacency (or distance) matrix of a graph, the resultant eigenvalues are characteristic to that adjacency (or distance) matrix of the graph and represent intramolecular ordering of vertices. Using these concepts several eigenvalue based topological indices have been developed and tested for their ability in correlating physicochemical properties of compounds [63].

Some geometrical descriptors useful in QSAR studies are 3D-Balaban index (J3D) [67], 3D Petitjean shape index (PJI3) [68] and Gravitational indices [69]. Among these, J3D [67] characterizes geometric distance degrees, PJI3 [68] is the fraction of the difference of geometric diameter and radius to the geometric radius, and Gravitational indices [69] reflect the mass distribution in molecules. The information content of these and many other graph theoretical descriptors have been validated through correlation studies involving different additive-constitutive properties of hydrocarbons [70–72] and biological properties of several classes of compounds [73–76]. An interesting application of graph theory is the explanation and prediction of ^{13}C -NMR profile of organic compounds [77].

In addition to small molecules, the graph theoretical concepts have been extended to address and advance the understanding of characteristics of nucleic acids and proteins. For example, in nucleic acids graph theory has been used for analyzing the features of RNA and DNA and for calculating the sequence-dependent melting stability of duplex DNA oligomers [78]. In proteins, the graph theoretical principles have been used to understand their sequence, structure [79],

domains [80] and internal flexibilities [81]. Its utility has been demonstrated in the characterization of large proteomic maps as well [82].

2.4 Graph Reconstruction (Inverse QSAR)

Concepts of molecule rebuilding from QSAR equations or 'inverse QSAR' have developed in tune with QSAR's main objective of identifying structures with desired activity prior to their synthesis. Most of the developments in inverse QSAR revolve around the graph theoretical concepts. It is associated with the reconstruction of structural fragments from the vertex and edge information of descriptors present in identified QSAR equations [83]. It is a mathematical strategy to predict structures of interest from the descriptors of **QSAR** equations. It is based on the presumption that if nonempirical structure indices $V_1, V_2, V_3 \dots$ truly encode the basic elements of molecular structure and are related to the property or activity (**P**) of the molecule, then for a desired (target) property value P_T , a target molecule can be reconstructed using the structural fragments generated from the appropriate $V_{1T}, V_{2T}, V_{3T} \dots$ values [84]. This process of molecule rebuilding from QSAR equations is also addressed by other names such as graph reconstruction, inverse structure generation, inverse imaging etc [84]. Different algorithms have come up in inverse QSAR to tackle the reconstruction of molecules from their identified characteristics [85–88]. The utility of these inverse QSAR approaches have been validated by reconstruction of structures of interest in various studies involving biological [84, 88], physicochemical [89] and spectral activities and properties [87]. Vertex prioritization schemes have also been used to develop characteristic molecular indices for QSAR/QSPR studies [84].

2.5 Chirality Indices

These indices are relatively new to QSAR and modeling studies. The loss of plane of symmetry in molecules results in optical isomerism or chirality. In organic compounds, for all practical purposes, asymmetric substitution of tetrahedral carbon results in optical isomerism. Except for their response to plane polarized light, optical isomers exhibit the same or even identical physicochemical properties,

viz., hydrophobicity, solubility, steric, electronic, etc. However, biological macromolecules, for example enzymes, generally exhibit high order of selectivity in their affinity for optical isomers. In view of this, different descriptors have been developed to address the chirality of compounds in QSAR models. Schultz *et al.* have introduced a chiral factor equal to +1 or -1 for asymmetric center with R- or S-configuration, respectively, in the computation of topological indices of optical isomers [90]. Julian-Ortiz introduced different chirality-sensitive molecular and charge topological indices to predict the properties of chiral compounds [91]. In another approach, attempts have been made to address the chiral atom in terms of groups and atoms attached to it. For this, computation of a few conceptual parameters, namely, flexibility of rotation, probability of availability, and net detachability, have been defined for the atoms/groups attached to the tetrahedral carbon. They have been investigated in a QSAR study of some 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors [92]. Golbraikh *et al.* have introduced several new chirality descriptors starting from the modified Zagreb group index, connectivity indices and topological charge indices with the use of an additional term called chirality correction to vertex degrees of asymmetric atoms in a molecular graph [93]. They extended this approach to compute topological indices to distinguish between *Z* and *E* isomers [94]. Randic has introduced graph theory based two-dimensional chirality descriptors with possible extension to three-dimensional chirality [95]. Rassat *et al.* have proposed topological rotational strengths as chirality descriptors for polyhedral graphs [96]. QSAR models of enantioselective compounds have been developed with chirality sensitive molecular descriptors [97].

2.6 Flexible Descriptors

The concept of flexible descriptors is a new development in QSAR/ QSPR studies. The molecular descriptors so far discussed are rigid in nature and remain with a fixed value for a specific property of the compound or part of it. Randic's variable vertex-connectivity index is an example of flexible descriptor [98]. The main

difference between Kier and Hall's valence vertex connectivity index [99] (rigid descriptor) and Randic's variable vertex-connectivity index [98] (flexible descriptor) is that while the former uses fixed vertex weights, the optimized vertex weights are used by the latter. Flexible descriptors are also generated from optimization of correlation weights of local graphs invariants [100], linear combinations of connectivity indices [101] and higher level connectivity terms [102]. SMILES (Simplified Molecular Input Line Entry System) notation has also been used in the generation of these descriptors [103]. Most of these flexible descriptors are size dependent. Different biological activities (DHFR inhibitors [104]; anti-HIV-1 agents [105]) and physicochemical properties (partial molar volumes of amino acids [106]; aqueous solubility of purine/ pyrimidines [101]) have been modeled with flexible descriptors.

2.7 Molecular Fingerprints

These concepts are relatively new to chemoinformatics and modeling studies. Molecular fingerprints are binary representations of chemical structures. Different methods are introduced by different chemical information system companies in a quest to improve the efficiency of operations in chemical database query system. The Daylight Chemical Information Systems fingerprint is normally referred to as a path-based approach or hash-key fingerprints and "learns" from the structures [107]. Unique subgraphs up to a maximum size eight are identified from chemical structure to represent as fixed length bit string. Typical sizes for Daylight fingerprints are 512 or 1024 bits in length. These fingerprints can be folded to decrease the length and increase the bit density. The fingerprints from Molecular Design Limited (MDL) are referred to as "key" based fingerprints [108]. A "key" is a pre-defined pattern matching of the structure and does not "learn" it from the chemical dataset. The number of keys in MDL is 966. So a fingerprint of maximum 966-bit length is possible from MDL. No folding of fingerprint occurs with this type. Fingerprints of Barnard Chemical Information Systems (BCI) use both of the Daylight and MDL approaches [109]. In this, similar to a dictionary, the keys for the

fingerprints are first generated from the set and then implemented in the description. Typically in BCI, the fingerprint bit lengths are of the order of 5,000 bits. More methods have come up to encapsulate the geometric [110] and shape [111] information into the fingerprints. All these approaches have variety of applications in drug research concerning to the characterization of chemical structures, diversity/similarity analysis, selection and acquisition of compound from libraries and databases [110–114]. Hologram QSAR (HQSAR), a QSAR technique devoid of molecular descriptors, also uses characteristic fragment fingerprints (molecular holograms) as predictive variables of biological activity [115]. Recently, Schwaha and Ecker reviewed similarity principles in ligand-based drug discovery and ADMET profiling [116]. The molecular spectra – ^1H NMR, MASS, and IR as well as simulated IR and ^{13}C NMR spectra – of compounds have been used as the 3D-descriptors for the prediction of biological activities [117]. Shell Research Limited has developed EVA (Eigen VALues) descriptors as molecular field parameters for the 3D-QSAR/ QSPR modeling studies [58, 118]. They are computed from the normal modes of molecular moments fundamental to IR and Raman spectra in the vibration frequency range of $1\text{--}4000\text{ cm}^{-1}$. Apart from these, QSAR and modeling studies absorb lots of user defined indicator or dummy variables to account for special or distinct characteristics of molecules. All these indicator variables are specific to a molecular site and confine themselves to a limited domain of the particular study.

2.8 Chemical Space Indices of 3D QSAR

These indices provide a more realistic account of the nature of the chemical space surrounding the molecule and surmount the limitations of descriptors from 2D-structure. A reliable conformation of chemical structures is a prerequisite for all 3D-approaches. Depending on way of parameterization of conformational space these procedures are categorized as conformational-alignment dependent and alignment free approaches. Pharmacophore and grid based approaches use the alignment dependent descriptors for the development of models. In pharmacophore

based approaches, the selected pharmacophore pattern and the spatial locations of the remaining structural fragments serve for the generation of the property database of the compounds under investigation [119]. From these indices, atoms and functional groups relevant to the biological activity are identified to model the activity. In grid-based approaches (eg. Comparative molecular field analysis, CoMFA) the descriptors are referred to as 'fields' [120]. In these approaches, first a rectangular (cuboid) grid is generated from the superimposition pattern of appropriate structural conformations of the compounds in the analysis. The chosen fields around each conformation are determined by placing them successively in the grid and by moving a unit function of the selected property (probe atoms/groups) around their conformational space [120]. Steric, electrostatic, hydrophobic, hydrogen-bond (H-bond) donor and acceptor properties are the most commonly used fields in grid based approaches. The descriptors of the alignment free approaches (e.g., Comparative molecular moment analysis CoMMA), are computed from the Cartesian and/ or internal coordinates in association with physicochemical/ electronic properties of the atoms of the molecules [121]. Recently Cramer and Wendt reviewed several issues of 3D-QSAR [122].

3. Conclusion

Any robust decision support system draws inferences from respective core disciplines in combination with quantification approaches and mathematical formalisms. The type of quantification protocol to be adopted for a given challenge largely depends on the environment of the experiment. The understanding of the challenge helps in translating it into mathematical terms and putting it for tests, which in turn provide inference for decisions. Chemical structures being a component of drug-receptor system, their indices have a significant role in comprehending and rationalising the information content embedded in the drug-receptor interactions. Fujita has reviewed some success stories of conventional QSAR approaches resulting in commercializable bioactive compounds [123].

Fig. 2. A potential Neuropeptide Y5 receptor (NPY5R) antagonist (compound **d**) developed from a virtual screening of hydrophobic and topological similarity features of three seed structures (compounds **a–c**).

A virtual screening of a large database with a pharmacophore model developed from the hydrophobic and topological similarity of three seed structures (compounds **a–c**, Figure 2) has paved the way for the discovery of a thiazole derivative (compound **d**; Figure 2) as potential Neuropeptide Y5 receptor (NPY5R) antagonist [124, 125].

More reports are available in literature highlighting the role of structural indices in the predictive and diagnostic aspects of drug-receptor interactions. The main challenge of *in silico* molecular design approaches is generation of structural fragments from *de facto* modeling descriptors. Inverse-QSAR is an attempt in this direction [83–89]. Developments in new metrics are required to address different features of drug-receptor interactions so far not tamed. For example, various aspects of molecular recognition [15], supramolecular chemistry [16], co-factor cooperation in drug identification at the receptor etc need more realistic indices. It is of common knowledge that a small variation in the molecule leads to far reaching changes in its activity, for example uracil is a nucleic acid base whereas 5-fluorouracil is anticancer drug [126]. The changes in the biological profiles of these

compounds are far beyond the incremental changes in the physicochemical features of the respective analogues. This type of ‘biological-tunnelling-effects’ of the compounds needs investigation to identify and quantify the operating forces. In the current state of knowledge ‘tailoring’ molecules according to the ‘needs’ of biological activity is still a dream to come true. The developments in the area of artificial intelligence coupled with the chemical indices of features thus far not tamed will come to aid in this direction. Due to space constraints, only selected articles are cited in the review. Even though the economic and environmental constraints have given initial momentum to *in silico* molecular design approaches, at present it is required due to its ability to provide intuitive reflections of the complex drug-receptor interactions.

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