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Introductory Chapter: Some Quantitative Structure Activity Relationship Descriptor

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http://dx.doi.org/10.5772/intechopen.69642

1. Quantitative structure activity relationship

The Quantitative structure–activity relationship (QSAR) specifies the function between any property of the system under examination and the molecular system and its any geometric and chemical characteristics. QSAR tries to find a relationship between activity and molecular characterization so that these functions can be used to calculate the property of the new compounds.

QSAR models are available at the intersection of chemistry, statistics and property of the system. This property can be activity inhibition and so on. These requirements for the creation of the QSAR model are a data set, providing experimental measurements for the system. These datasets typically consist of hundred or fewer compounds associated with a specific parameter such as inhibition efficiency, intestinal absorption, volume of distribution, blood-brain barrier penetration or activity of biological targets. Corwin Hansch initiated the field of quantitative structure-activity relationships in the years 1962 and 1963, and they reported a study on the structure-activity relationships of plant growth regulators and their dependency on Hammett constants and hydrophobicity with the publications [1, 2].

The concept of QSAR is used for drug discovery and development and has gained wide applicability for correlating molecular information with biological activities, and the quantitative structure-property relationship (QSPR) is an alternative to experimental processing that envisages various physical and chemical properties. QSPR is related to the structure and any physical-chemical properties of the compounds taken into account. QSAR/QSPR associates biological activities or physical-chemical properties with certain structural features or atomic, group or molecular descriptors in the series of compounds. The QSAR/QSPR model includes structure representation, descriptive analysis and modeling. Todeschini and Consonni [3] defined the molecular descriptor as the following "The molecular descriptor is the final result

of a logic and mathematical procedure which transforms chemical information encoded within a symbolic representation of a molecule into a useful number or the result of some standardized experiment." Chemical structural features are called molecular descriptor, and they are closely related to target property of the compounds. There are many molecular descriptors. Some of them are conformational, fragment constants, electronic, receptor, quantum mechanical, graph-theoretic, topological, information-content, molecular shape analysis, spatial, structural, thermodynamic, pKa, Absorption, distribution, metabolism, and excretion (ADME), molecular field analysis and receptor surface analysis descriptors. The descriptors may be classified as topological, geometrical, electronic and hybrid or 3D descriptors.

Topological indices are two-dimensional descriptors which take into account the internal atomic arrangement of compounds, and which encode in numerical form information about molecular size, shape, branching, presence of heteroatoms and multiple bonds and are a very useful tool for drug design specialists, with advantages such as offering a simple way of measuring molecular branching, shape and size [4, 5]. Third generation of topological indices is the hyper-Wiener index [6, 7] or the molecular identification (ID) numbers [8], the information indices [9–11], and the electrotopological state (E-state) indices [12, 13].

Geometrical descriptors or 3D descriptors in general provide much more information and discrimination power than topological descriptors for similar molecular structures and molecule conformations due to involving knowledge of the relative positions of the atoms in 3D space [14].

A number of geometric descriptors have been proposed by several scientific communities in the last decade to get molecular information for development of QSAR/QSPR models [3].

Electronic descriptors can be used in the design of a training set in QSAR studies, and the electronic identifiers obtained by quantum mechanical calculations are more precisely than those obtained by semiempirical calculations [15].

Quantum chemically derived descriptors can be subdivided as atomic charges, molecular orbital energies, frontier orbital densities, atom-atom polarizabilities, molecular polarizability, dipole moment and polarity indices, and energy [16], free valence of atoms [17], atomic orbital electron populations [18], overlap populations [19], partitioning of energy data into one-center and two-center terms [19], and vectors of lone pair densities [19] are the other quantum chemical descriptors successfully used in QSAR/QSPR studies.

Since electrostatic interactions play important role in a chemical reaction, one of the most fundamental descriptors to be used in QSAR are quantum chemically computed atomic charges. The atomic charges have been used for the prediction of anti-HIV-1 activities of 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT)-analog compounds [20]. They explained octanol-water partition coefficients of organic compounds with the atomic charges [16, 21]. Bhat et al. [22] reported optimal ligand-charge distribution at protein-binding sites with the help of atomic charge

Highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) are very popular quantum chemical descriptors. The strongest Frontier orbitals (FO)

interaction involves the HOMO of the nucleophile and the LUMO of the substrate [23]. They reported that mutagens have lower LUMO energies than nonmutagens [24] and also reported that carcinogens, as a group, have lower LUMO energies than noncarcinogens [25].

As a conclusion, a QSAR/QSPR tries to find a consistent relationship between molecular properties and variability in biological activity for a number of compounds so that these equations can be used to evaluate new chemical entities.

QSAR has been applied successfully and extensively to find predictive models for activity of bioactive agents for the toxicity prediction [26–29], activity of peptides [30–33], drug metabolism [34–36], gastrointestinal absorption [37–39], prediction of pharmacokinetic and ADME properties [40–44], drug resistance and physicochemical properties [45–47].

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