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Chapter 1

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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References

[1] Hansch C, Maloney PP, Fujita T, Muir RM. Correlation of biological activity of phenoxyacetic acids with Hammett substituent constants and partition coefficients. Nature. 1962;**194**:178-180

[2] Hansch C, Muir RM, Fujita T, Maloney PP, Geiger CF, Streich M. The correlation of biological activity of plant growth-regulators and chloromycetin derivatives with Hammett constants and partition coefficients. Journal of the American Chemical Society. 1963;**85**:2817-2824

[3] Todeschini R, Consonni V. Handbook of Molecular Descriptors. Wiley-VCH; Weinheim, 2000

[4] Gozalbes R, Doucet JP, Derouin F. Application of topological descriptors in QSAR and drug design: History and new trends. Current Drug Targets—Infectious Disorders. 2002;**2**:93-102

[5] Ivanciuc O, Balaban AT. In: Devillers J, Balaban AT, editors. Topological Indices and Related Descriptors in QSAR and QSPR. The Netherlands: Gordon and Breach Science Publishers; 1999. pp. 59-167

[6] Gutman I. A formula for the Wiener number of trees and its extension to graphs containing cycles, Graph Theory Notes, New York. 1994;**27**:9-15

[7] Randié M, Guo X, Oxley T, Krishnapriyan H. Wiener matrix: Source of novel graph invariants. Journal of Chemical Information and Computer Sciences. 1993;**33**:709-716

[8] Ivanciuc O, Balaban AT. Design of topological indices. Part 3. New identification numbers for chemical structures: MINID and MINSID. Croatica Chemica Acta. 1996;**69**:9-16

[9] Balaban AT, Balaban TS. New vertex invariants and topological indices of chemical graphs based on information on distances. The Journal of Mathematical Chemistry. 1991;**8**:383-397

[10] Carter S, Trinajstić N, Nikolić S. A note on the use of ID numbers in QSAR studies. Acta Pharmaceutica Jugoslavica. 1967;**37**:37-42

[11] Carter S, Trinajstić N, Nikolić S. On the use of ID numbers in drug research: A QSAR of neuroleptic pharmacophores. Medical Science Research. 1988;**16**:185-186

[12] Kier LB, Hall LH. An electrotopological-state index for atoms in molecules. Pharmaceutical Research. 1990;**7**:801-807

[13] Hall LH, Kier LB. Electrotopological state indices for atom types: A novel combination of electronic, topological, and valence state information. Journal of Chemical Information and Computer Sciences. 1995;**35**:1039-1045

[14] Tomasz P, Jerzy L, Mark TC. Recent Advances in QSAR Studies: Methods and Applications. Dordrecht, Heidelberg, London, New York: Springer 2010

[15] Cartier A, Rivail JL. Electronic descriptors in quantitative structure activity relationships. Chemometrics and Intelligent Laboratory Systems. 1937;**1**(4):335-347

[16] Karelson M, Lobanov VS, Katritzky AR. Quantum-chemical descriptors in QSAR/QSPR studies. Chemical Reviews. 1996;**96**(3):1027-1044

[17] Prabhakar YS. Quantum QSAR of the antirhinoviral activity of 9-benzylpurines. Drug Design and Delivery. 1991;**7**:227-239

[18] Cardozo MG, Iimura Y, Sugimoto H, Yamanishi Y, Hopfinger AJ. QSAR analyses of the substituted indanone and benzylpiperidine rings of a series of indanone-benzylpiperidine inhibitors of acetylcholinesterase. Journal of Medicinal Chemistry. 1992;**35**:584-589

[19] Sklenar H, Jager J. Molecular structure–biological activity relationships on the basis of quantum-chemical calculations. International Journal of Quantum Chemistry. 1979;**16**:467-484

[20] Alves CN, Pinheiro JC, Camargo AJ, Ferreira MMC, da Silva ABF. A structure–activity relationship study of HEPT-analog compounds with anti-HIV activity. Journal of Molecular Structure (THEOCHEM). 2000;**530**:39-47

[21] Ghose AK, Pritchett A, Crippen GM. Atomic physicochemical parameters for three dimensional structure directed quantitative structure-activity relationships III: Modeling hydrophobic interactions. Journal of Computational Chemistry. 1988;**9**:80-90

[22] Bhat S, Sulea T, Purisima EO. Coupled atomic charge selectivity for optimal ligand charge distributions at protein binding sites. Journal of Computational Chemistry. 2006;**27**:1899-1907

[23] Nguyên TA. Frontier Orbitals: A Practical Manual. John Wiley & Sons Ltd.; Southport, Merseyside, United Kingdom 2007

[24] Rosenkranz HS, Klopman G. Decreased electrophilicity of chemical carcinogenic only at the maximum tolerated dose. Mutation Research. 1992;**282**(4):241-246

[25] Rosenkranz HS, Klopman G. Relationships between electronegativity and genotoxicity. Mutation Research. 1995;**328**:215-227

[26] Patricia R, Gino B, Terry T, John W, Moiz M. Prediction of acute mammalian toxicity using QSAR methods: A case study of sulfur mustard and its breakdown products molecules. 2012;**17**:8982-9001

[27] Demchuk E, Ruiz P, Chou S, Fowler BA. SAR/QSAR methods in public health practice. Toxicology and Applied Pharmacology. 2011;**254**:192-197

[28] Ruiz P, Mumtaz M, Gombar V. Assessing the toxic effects of ethylene glycol ethers using quantitative structure toxicity relationship models. Toxicology and Applied Pharmacology. 2011;**254**:198-205

[29] Enslein K. The future of toxicity prediction with QSAR. In Vitro Toxicology. 1993;**6**: 163-169

[30] Tong JB, Chang J, Liu SL, Bai M. A quantitative structure–activity relationship (QSAR) study of peptide drugs based on a new descriptor of amino acids. Journal of the Serbian Chemical Society. 2015;**80**(3):343-353

[31] Mariya AT, Aleksandar MV, Jovana BV, Dušica BS, Andrey AT. QSAR modeling of the antimicrobial activity of peptides as a mathematical function of a sequence of amino acids. Computational Biology and Chemistry. 2015;**59**:126-130

[32] Mikut R, Hilpert K. Interpretable features for the activity prediction of short antimicrobial peptides using fuzzy logic. International Journal of Peptide Research and Therapeutics. 2009;**15**(2):129-137

[33] Reyhaneh J, Somaieh S, Abolfazl B. A review of QSAR studies to predict activity of ACE peptide inhibitors. Pharmaceutical Sciences. 2014;**20**:122-129

[34] Wenlock MC, Carlsson LA. How experimental errors influence drug metabolism and pharmacokinetic QSAR/QSPR models. Journal of Chemical Information and Modeling. 2015;**55**:125-134

[35] Klopman G, Dimayuga M, Talafous J. META. 1. A program for the evaluation of metabolic transformation of chemicals. Journal of Chemical Information and Modeling. 1994;**34**:1320-1325

[36] Braga RC, Andrade CH. QSAR and QM/MM approaches applied to drug metabolism prediction. Mini-Reviews in Medicinal Chemistry. 2012;**12**:573-582

[37] Yuan HZ, Michael HA, Joelle L, Anne H, Chris NL, Gordon B, Brad S, Ian C. Rate-limited steps of human oral absorption and QSAR studies. Pharmaceutical Research. 2002;**19**(10):1446-1457

[38] Zhao YH, Le J, Abraham MH, Hersey A, Eddershaw PJ, Luscombe CN, Butina D, Beck G, Sherborne B, Cooper I, Platts JA. Evaluation of human intestinal absorption data for use in QSAR studies and a quantitative relationship obtained with the Abraham descriptors. Journal of Pharmaceutical Sciences. 2001;**90**:749-784

[39] Gabriele C, Emanuele C, De Benoit B, Kantharaj E, Claire M, Trevor H, Riccardo V. MetaSite: Understanding metabolism in human cytochromes from the perspective of the chemist. Journal of Medicinal Chemistry. 2005;**48**:6970-6979

[40] Majid Z, Mohammad S, Farzin H, Mohammad AD, Kaveh T. Prediction of pharmacokinetic parameters using a genetic algorithm combined with an artificial neural network for a series of alkaloid drugs. Scientia Pharmaceutica. 2014;**82**:53-70

[41] Norris DA, Leesman GD, Sinko PJ, Grass GM. Development of predictive pharmacokinetic simulation models for drug discovery. Journal of Controlled Release. 2000;**65**:55-62

[42] Pires DEV, Blundell TL, Ascher DB. pkCSM: Predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures Journal of Medicinal Chemistry. 2015;**58**:4066-4072

[43] Cao D, Wang J, Zhou R, Li Y, Yu H, Hou T. ADMET evaluation in drug discovery. 11. PharmacoKinetics Knowledge Base (PKKB): A comprehensive database of pharmacokinetic and toxic properties for drugs. Journal of Chemical Information and Modeling. 2012;**52**:1132-1137

[44] Obach RS, Lombardo F, Waters NJ. Trend analysis of a database of intravenous pharmacokinetic parameters in humans for 670 drug compounds. Drug Metabolism and Disposition. 2008;**36**:1385-1405

[45] Narender S, Sidhartha C, Ruifeng L, Mohamed Diwan MA, Gregory T, Anders W. QSAR classification model for antibacterial compounds and its use in virtual screening. Journal of Chemical Information and Modeling. 2012;**52**:2559-2569

[46] Hu Y, Unwalla R, Denny RA, Bikker J, Di L, Humblet C. Development of QSAR models for microsomal stability: Identification of good and bad structural features for rat, human and mouse microsomal stability. Journal of Computer-Aided Molecular Design. 2010;**24**:23-35

[47] Bray PG, Hawley SR, Mungthin M, Ward SA. Physicochemical properties correlated with drug resistance and the reversal of drug resistance in *Plasmodium falciparum*. Molecular Pharmacology. 1996;**50**(6):1559-1566