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MOLECULAR FIELD TOPOLOGY ANALYSIS AS AN ADVANCED TOOL FOR QSAR/QSPR STUDIES

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There exist numerous techniques for the evaluation of quantitative structure-activity/property relationships (QSAR/QSPR) based on various descriptors of a chemical structure. Most of the approaches employ so called global descriptors characterizing the molecule as a whole. However the application of local (atomic) descriptors allows one to consider the detailed ways of structure optimization to increase both activity and selectivity of the potential drug candidate or improve any other useful properties depending on the local features of the chemical structure.

Molecular Field Topology Analysis (MFTA) [1-3] is a QSAR approach based on the local descriptors. First, a so-called molecular supergraph is constructed which is a simple graph such that the molecular graphs of all training set structures can be represented as its subgraphs. A uniform descriptor set for the statistical analysis is obtained by superimposing each training set structure onto the molecular supergraph. Each supergraph vertex is assigned the values of effective atomic charge, van der Waals radius, H-bond donor and H-bond acceptor ability, local lipophilicity and other parameters for the corresponding atom of the training set structure. For unoccupied vertices the neutral descriptor values are used. The predictive QSAR/QSPR models are derived using the Partial Least Squares Regression or Artificial Neural Networks machine learning methods. The analysis of the impact of local descriptors on the activity/property for different supergraph positions is highly helpful in search for new promising structures as well as in understanding their action. In addition, the MFTA models can be used for the virtual screening of promising structures in chemical databases or compound libraries built by means of specially designed structural generators.

Recent advances of MFTA allow one to apply this tool to the design of new catalysts, antioxidants, dyes, enzyme inhibitors, receptor agonists, antagonists and modulators, virus entry inhibitors, etc. Special approaches were proposed for the molecular design of drugs having optimal activity and selectivity profile, including multi-target drugs.

The joint application of the MFTA in conjunction with other QSAR/QSPR approaches (e.g. ADMET models based on fragmental descriptors) and molecular modeling techniques is especially fruitful.

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