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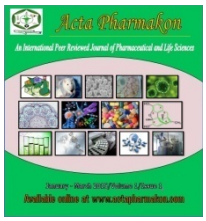

Review Article

Applications of QSAR to Microtubule-stabilizing Anti Cancer Agents of Natural Origin

Pt. Kartikay Pandey[*1,2] (K. Pandey)[a]

[1]Hygia Institute of Pharmaceutical Education and Research (affiliated to Gautam Buddh Technical University, Lucknow), (www.hygia.in), opposite Sahara City Homes, Prabandh Nagar, Lucknow-226020, India.

[2]Dr. Pandey's Laboratories and Research Foundation, (an R & D organization under the auspices of Pt. Muneeshwar Dutt Pandey Samajik Utthan Avam Shodh Samiti (Arpan), 537Gha/84, Behind Madiyaon Police Station, Sitapur Road, Lucknow-226021.

[a] Abbreviated name, as appears in several previous publications.

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Corresponding Author:
Dr. Kartikay Pandey
Email Id:
drkartikaypandey@gmail.com

ABSTRACT

QSAR/QSPR have now become indispensable for modern day Drug research. Their path-breaking concepts are bringing about a sea change in the modern drug research. Chemical entities involving MSSAs, are exclusively known for their clinical utility, in anticancer chemotherapy. Their utility can be enhanced, and explored by applying QSAR studies. Several marine natural products have been shown be active as cytotoxic agents. QSAR studies also need to be done on such potent chemical compounds. An overview of the vital QSAR concepts involved in such extremely useful studies is attempted here.

1. INTRODUCTION

QSARs (Quantitative Structure–Activity relationships) are based on the postulation that the structure of a molecule (i.e. its geometric, steric and electronic properties) must contain the features responsible for its physical, chemical, and biological properties, and on the ability to represent the chemical by one, or more, numerical descriptor(s). By QSAR models, the biological activity (or property, reactivity, etc.) of a new or untested

chemical can be inferred from the molecular structure of similar compounds whose activities (properties, reactivities, etc.) have already been assessed. The QSPR (Quantitative Structure–Property relationship) acronym is used when a property is modeled.

The Quantitative structure-activity and structure property relationship (QSAR & QSPR) studies are incontestably of colossal importance in modern chemistry and biochemistry. The idea of QSAR is to revolutionize searches for compounds with preferred properties using chemical insight and experience into a mathematically quantified and computerized form. Once a correlation between structure and activity/property is found, whichever number of compounds, including those not yet known/synthesized, can be willingly screened on the computer in order to choose structures with the properties desired. It is then possible to select the most capable compounds to synthesize and test in the laboratory. Thus, the QSAR technique conserves resources and expedite the procedure of development of new molecules for use as drugs, materials, additives, or for any other purpose. To obtain a significant correlation, it is vital that suitable descriptors be employed, whether they are theoretical, empirical, or derived from readily available experimental characteristics of the structures. Numerous descriptors reflect simple molecular properties and thus can provide an insight into the physicochemical nature of the activity/property under consideration. Current developments in computational hardware and the coming up of efficient algorithms have assisted the routine development of molecular quantum mechanical calculations. Novel semiempirical methods supply realistic quantum-chemical molecular quantities in a relatively short computational time frame. Quantum chemical calculations are therefore an attractive source of new molecular descriptors, which can, in principle, express all of the electronic and geometric properties of molecules and their interactions.

It has been almost 40 years from the time when the QSAR modeling was first used into the practice of agro-chemistry, drug design, toxicology, industrial and environmental chemistry. Its rising power in the following years may be attributed also to the rapid and extensive development in methodologies and computational techniques that have allowed delineating and refining the scores of variables and approaches used in this modeling approach.[1]

2. CoMFA

It was first introduced in 1988, and since then, comparative molecular field analysis (CoMFA) has become rapidly one of the most powerful tools for three-dimensional quantitative structure-activity relationship (3D QSAR) studies.[2] The CoMFA approach is based on the assumption that since most drug-receptor interactions are noncovalent, changes in the biological activity of compounds should correlate with the steric and electrostatic fields of these molecules. In order to develop the numerical representation of those fields, all molecules under investigation are first structurally aligned and the steric electrostatic fields around them sampled with probe atoms. Usually a sp3 carbon atom with a positive unit charge (+1) is moved on a rectangular grid that encompasses the aligned molecules, which is analysed using a combination of various complicated methodologies. CoMFA has been used for the quantitative description of enzyme

inhibition activities of compounds, receptor antagonist and agonist activities, antiviral activities, and carcinogenic and toxicological properties of compounds. The CoMFA approach has been mostly used in biomedical QSAR studies; however, it has also been applied for the description of the chemical reactivity of compounds[3].

3. APPLICATION OF QSAR TO ANTICANCER COMPOUNDS

A rational approach to cancer therapy involves the design of small molecule ligands that interfere with microtubule dynamics through their specific binding to the β-subunit of tubulin, leading to mitotic arrest and cell death. Taxol is a highly functionalized diterpenoid isolated from *Taxus brevifolia* (Pacific Yew tree), was the first compound recognized to interact specifically and reversibly with the β-subunit of the tubulin heterodimer, promoting microtubule stabilization and consequently, blocking cells in the mitotic phase of the cell cycle.

The unique mechanism of action as a microtubule-stabilizing antimitotic agent (MSAA) is responsible by the extraordinary clinical success achieved by Taxol and related taxanes in the treatment of a variety of cancers. Although taxanes are the most prominent among the known MSAAs, their scarceness, poor pharmacokinetic properties, high systemic toxicity and resistance have led to the identification of novel compounds having similar mechanisms of action. These include non-taxane microtubule-stabilizing natural products, such as discodermolide, epothilone and dictyostatin. These promising anticancer agents competitively inhibit the binding of paclitaxel to tubulin polymers, indicating an overlapping binding site in the β-tubulin cavity, which can accommodate a variety of structurally diverse MSAAs in unique and independent ways.

The marine polyketide discodermolide is one of the most potent MSAAs known. In addition to its potent antiproliferative and apoptosis-inducing activities, discodermolide is more water soluble than paclitaxel and retains substantial activity against taxane-resistant cell lines. These physicochemical and biological characteristics have qualified discodermolide as a lead compound for the development of new, more effective and safer anticancer drugs.

An important strategy in the design of new β-specific tubulin modulators is to identify key properties of the chemical structure related to their ability to induce a cytotoxic response as a consequence of modulation of microtubule functions through tubulin-binding. Structure and ligand-based drug design approaches have become fundamental components of modern drug discovery. Quantitative structure-activity relationship methods have been successfully employed to assist the design of new small molecule drug candidates, ranging from enzyme inhibitors to receptor ligands. However, there is only a small number of QSAR studies found in the literature for taxoid-site tubulin modulators. This proves the importance of QSAR studies involving this class of tubulin modulators.[4]

In the CoMFA method, it is possible to represent the relationships between molecular properties (steric and electrostatic) and biological activity in the 3D protein environment of the β-tubulin binding site, indicating potential regions for obtaining specificity. The final 3D QSAR models along with the information gathered from 3D contour maps provide important insights into the structural and chemical basis for potent microtubule stabilization and antitumoral properties of discodermolide. The identification

of key intermolecular features associated with affinity and specificity should be a valuable tool for the design of promising candidates for clinical development.

4. MOLECULAR ALIGNMENT STRATEGIES

The determination of the spatial structural alignments of the discodermolide analogs in the binding pocket of β-tubulin can critically affect the outcome of the CoMFA studies, since the analyses are highly dependent on the quality of the alignments. 3D structural information on the interaction of small molecule modulators with the β-tubulin cavity is limited to crystal structures of the complexes of αβ-tubulin dimers with paclitaxel, docetaxel and epothilone A (PBD IDs JFF, 1TUB and 1TVK, respectively). Although tubulin-discodermolide complexes are not available to date, the crystal structures of the known receptor-ligand complexes have provided an important basis for the understanding of the fundamental chemical and structural requirements for β-tubulin binding by the discodermolide analogs. However, it should be noted that the scenario is more complex due to the high flexibility of the discodermolide system, creating new challenges in the drug design arena. For this reason, two molecular alignment approaches need to be considered. In the first, a receptor-independent strategy is applied, derived from a rigid superimposition of the minimum energy conformations of the discodermolide analogs, while in the second, a receptor-based approach, can be used.[5]

Importantly, the 3D molecular differences in the two distinct alignment approaches were quantitatively investigated using the CoMFA method, through its steric and electrostatic fields (Figure1).

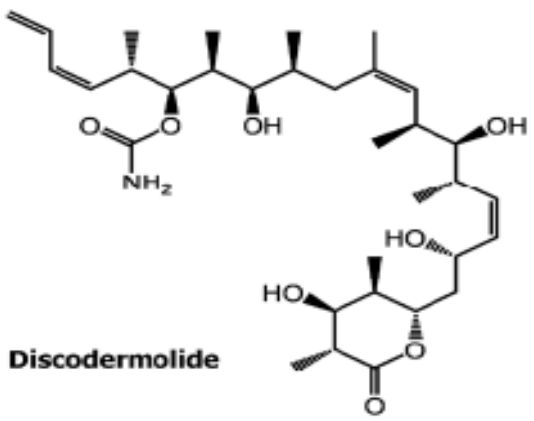

Figure 1

5. CONCLUSIONS

The applications of QSAR/QSPR and related technologies, in drug research, forensic, agriculture, medical science, etc., is bound to undergo a revolutionary change in the near future, for the betterment of science, and mankind. Most work employing quantum chemical descriptors has been carried out in the field of QSAR rather than QSPR, i.e. the descriptors have been correlated with biological activities such as enzyme inhibition activity, hallucinogenic activity, etc. In part this has been because, traditionally, the search for quantitative relationships with chemical structure started with the development of theoretical drug design methods. Quantum-chemical descriptors have also been reported to correlate the reactivity of organic compounds, octanol/water partition coefficients, chromatographic retention indices, and various physical properties of molecules. The remarkable capability of QSAR/QSPR to predict the activity/property/toxicity, of chemical compounds, can be variously used in the interest of development of modern technologies. Efforts can also be made and explored, whether novel, innovative, and powerful technologies, and

concepts, such as Nanotechnology, can be amalgamated with QSAR, enhancing its powers, and reach to unimaginable limits. Strong inter-disciplinary efforts are required to achieve such challenging, but highly rewarding tasks. The marine natural products, including those from the Indian Ocean, have the potential of providing effective anticancer agents (similar to Taxol), and even Vascular Disruptive agents, like Combretastatins, and Sorafenib.[6,7,8,9] Some other useful applications of marine natural products, such as diagnostic aids, etc., are also being explored, so as to fully exploit their utility in medicine, and research.[10,11] The success of the research in marine natural products depends much on active international cooperation, and on adopting a coherent approach by the scientific community. The fruits of such endeavors will be really sweet and relishing for us for a long time to come.

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