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Computational Medicinal Chemistry: A Useful Tool for Pharmaceutical Sciences and Drug Development

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Abbreviations : HTS: High Throughput Screening; MM: Molecular Mechanics; QM: Quantum Mechanics

Opinion

Historically, the use of modern medicines for the treatment of health problems represented a major change in the paradigms of medical science. Serious problems such as the establishment of infections, pain as well as disorders of the central nervous system have come to find effective relief from the use of small organic molecules, incorporated into pharmaceutical forms, with curative or palliative purpose [1]. Since the establishment of modern medical chemistry [2], in the XIX century, the efforts of emerging pharmaceutical companies and government laboratories having focused on the isolation of compounds from natural sources and the synthesis or semi-synthesis of bioactive. However, this development has been accompanied by some drawbacks, such as the Thalidomide tragedy in the 1960s and the acquired resistance phenomenon to antibiotics [3], generating the imperative need to generate New Chemical Entities and better understand their mechanism of action at the molecular level.

Corroborating this scenario, the capitalist pressure for the development of innovative molecules allied to the development of modern computing, robotics and automation, led to the development of strategies that allowed to obtain diverse libraries of compounds in a shorter time (combinatorial chemistry) [4], automated tests of high performance, as High Throughput Screening (HTS) [5] as well as application of Theoretical and Computational Chemistry approaches for the development and optimization of lead compounds [6]. Basically, computational chemistry approaches consists in the implementation of different levels of theory for the construction and visualization of molecular structures, obtaining optimized geometries, physicochemical properties, reactivity studies, among others, using computer programs [7]. Two levels of theory are the basis of methods in Computational Chemistry, where the energy evaluation of collections of atoms or molecules can be accomplished through classical force field equations (Molecular Mechanics, MM) or from the consideration and unfolding of equation of Schrodinger (Quantum Mechanics, QM).

Thus, by understanding the forces acting on a collection of atoms and their geometries of greater stability, various physico-chemical properties related to the electronic structure (energy of orbital's, dipole moment, molecular polarizability), parameters related to geometry constitutional, correlations between atoms), estimation of empirical descriptors (LogP, pKa) among other approaches. In this sense, we observe that these descriptions at the molecular level can be applied in the understanding of the properties of bioactive molecules. The scientific literature points to several successful examples in the use of computational chemistry on the design and optimization of lead compounds, with application in pharmaceutical sciences [8-11].

In the field of Computational Medicinal Chemistry, two strategies are widely used: Molecular docking algorithms and QSAR modeling studies. Molecular docking consists in the search for the best orientation and conformation of a ligand (small organic molecule) in the binding site of a macromolecule (for example a protein) [12]. Considering that most drugs act by binding to specific biological targets, these can be exploited in understanding the mechanism of action of molecules. Several routines can be used [12], such as virtual screening, which tests in a virtual library of compounds which molecule has a better chance of interacting with an elected target; pharmacophoric mapping, which consists in identifying functional regions or groups of a series of ligands, responsible for recognition and pharmacological effect; confirmation and understanding of the mechanism of action of molecules submitted to bench tests, among others.

On the other hand, the strategy known as Studies of the Structure-Activity Quantitative Relationship, QSAR, aims to obtain a mathematical model relating a dependent variable (in the case of biological activity) with independent variables (molecular properties), with the purpose of assisting in the design and prediction of new compounds or analogues not yet tested [13]. These methods involve the generation of molecular descriptors generated by several methods in computational chemistry, biological activities obtained experimentally, chemo metric methods to select which molecular properties have the best relation with the activity, mathematical techniques of multivariate regression [13]. As we can see, these strategies are complementary to the synthetic and pharmacological efforts of the bench, providing cost savings and time in the development of research.

Another great contribution of the computational chemistry methods applied to the pharmaceutical sciences is the better understanding of the relationships between small organic molecules and their biological properties. These approaches are also considered regarding aspects of environmental regulation and public health in models that predict the potential toxicity of chemicals. Given these observations, as well as the advances that the science of Computational Medicinal Chemistry has acquired over the years, we consider that it is still insufficient the dissemination of these strategies on undergraduate and postgraduate courses related to chemistry and pharmaceutical sciences. Academic research and the emergence of new drugs are expensive and time-consuming processes, so the more they are disseminated and used, these strategies will be able to gain more space and can be more and more improved, assisting in chemistry teaching, as well research and development of new medicines.

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