Lesya Ukrainka Volyn National University

IV International Scientific Conference

CURRENT PROBLEMS OF CHEMISTRY, MATERIALS SCIENCE AND ECOLOGY

Proceedings

ISBN 978-966-940-518-0

2023 December 7-9, Lutsk, Ukraine

IV International Scientific Conference
CURRENT PROBLEMS OF CHEMISTRY, MATERIALS SCIENCE AND ECOLOGY

Lutsk, Ukraine, 7-9 December 2023

Proceedings

Актуальні проблеми хімії, матеріалознавства та екології

Луцьк, Україна, 7-9 грудня 2023 р.

Матеріали
IV Міжнародної наукової конференції
присвяченої світлій пам'яті Олега Васильовича Парасюка

в рамках відзначення 150 річчя
Наукового товариства імені Тараса Шевченка

Луцьк
Вежа-Друк
2023

BIOACTIVE CONFORMATIONAL ENSEMBLES IN COMPUTER-AIDED DRUG DISCOVERY

Klenina Olena[1,2], Chaban Taras[2]

[1] - University San Pablo-CEU, Urbanización Montepríncipe, 28668 Boadilla del Monte, Spain

[2] -Danylo Halytsky Lviv National Medical University, Lviv, Ukraine

olena_klenina@yahoo.com

Computer-aided rational drug design encompasses the identification of potential biological targets for drug candidates followed by an intensive search ensues to find a drug-like small molecules that can modulate the function of the identified macromolecule resulting in a therapeutic effect. This approach becomes possible due to the availability of information about the three-dimensional chemical structures of ligands and biomolecules. Thus, to be efficient, computer-aided drug design (CADD) techniques including both ligand- and structure-based, must be accurate with the structural data manipulation as the knowledge of macromolecules and ligands structures as well as unbound and receptor-bound conformations is the precondition of the vital importance for the application of 3*D* computational molecular modeling approaches.

The aim of the current work was to analyze, systematize and summarize the recent literature data discussing conformational ensembles of small organic molecules, the main approaches and techniques applied for their generation and the conformational sampling of drug-like molecules significance in modern computer-aided drug design.

Three-dimensional spatial arrangements of atoms that organic molecules can adopt are known as conformations, their diversity is ensured by rotational bonds, changes in bond lengths, bond angles and torsions, interconversion between different conformations can be achieved by rotations about formally single bonds. Thus, a set of stable spatial geometric structures of a molecule with the constant connectivity matrix constitutes the set of its conformations. In their turn, conformational ensembles are represented by the sets of equilibrium conformations existing under certain thermodynamic conditions in defined environmental medium. Consequently, thorough conformational analysis is critically important in many areas of research, such as drug discovery, protein engineering, and the design of catalysts.

Conformer generation leading to exploring and sampling the low energy conformational space of drug-like molecules continues to be a relevant task focusing on ligands structure pre-organization with the aim to minimize energetic penalties associated with undesired flexibility, sub-optimal arrangement of functional groups interacting with the protein binding site or unwanted internal stabilization.

Drug-like molecules can adopt a great number of conformations depending on the amount of rotatable bonds, angels and torsions flexibility and the rigidity properties of their rings and cycles. It was shown that even the solid-state ligands bounded to corresponding biotargets can possess conformational diversity. Structural data drawn from the Protein Data Bank (PDB) revealed that the same ligand precented in at least two different protein−ligand structures may be found in multiple conformations which differed significantly (RMSD > 2 Å) [1]. This means that a small molecule must adopt the bioactive conformation that is the conformation which can be recognized by the receptor and produce the biological response. Bioactive conformations construction for flexible small organic molecules is challenging and complex problem in modern drug design reasoned by the large number of degrees of freedom even for relatively small ligands.

The common practice of ligands conformational ensembles generation is based on computational molecular modeling techniques. The accuracy of such predictions is warranted by more quantitative assessment of potential sources of errors. The additional source of error termed “conformer focusing” is connected to quantitative estimation of free-energy change associated with the conformer focusing for the ligand [2]. Upon forming the ligand-receptor complex, many conformers of the unbound ligand become sterically inaccessible which is resulted in some of its degrees of freedom loss. It was shown that the preferred bound conformer of the ligand is likely not the lowest-energy or most-populated one in the unbound state, which yields a reorganization energy penalty [3].

Currently available methods for bioactive conformational ensembles generation may be classified as theoretical or knowledge-based [4]. The first group of methods comprises force-field and quantum-mechanical calculations, while the second one usually relies on experimental crystal-structure data contained in public structural databases. In the knowledge-based approach the specific force field is applied for the structure refinement of the obtained conformers. The quality of the generated ensembles and their distinct

conformers depends on the size of the ensemble and on the accuracy of the force-field [5].

The group of theoretical methods implements systematic or stochastic searching algorithms involving the use of force-fields, while the knowledge-based methods are mainly exploring systematic search only. Systematic search ensures the whole conformational space analysis by systematic verification of all possible structural combinations while stochastic approach suppose the random variations in all flexible torsions. Systematic sampling is commonly deriving from experimental crystal data for a small molecule, followed by coordinate refinement for the elimination of conformations with steric clash.

Stochastic methods used to generate a reliable ensemble of conformations are the most complex and time-consuming methods for conformational sampling and they are based on Monte Carlo (MC) and Molecular dynamics (MD) simulations and different kinds of their combinations. These methods rely on a suitably well-parametrized force field that describes the forces to which the atoms in the system are subject. A trajectory is generated, typically at constant temperature, and the resulting conformations can be subjected to clustering and further analysis. Stochastic methods are general and can work with large, complex, multicomponent systems.

The quality of the conformational ensembles generated with different computational approaches are commonly assessed by their accuracy, generally measured as the root-mean-square deviation (RMSD) in Å between the experimentally determined bioactive conformation and any computed conformers of an ensemble, ensemble size, and computing time [6].

As the post-procedure of the conformational sampling generated ensembles are collected and subjected to a clustering procedure to derive representative conformers.

Thus, it may be concluded that the conformational sampling of drug-like molecules is an important step in computational drug discovery process which utilizes several freely and commercially available algorithms which allow the conformational ensembles generation and the representation of unbound and receptor-bound ligand conformations with adequate accuracy.

References:

1. Hawkins, P. C. Conformation generation: the state of the art // Journal of chemical information and modeling. – 2017. – Vol. 57, № 8. – P. 1747-1756.

2. Tirado-Rives, J., Jorgensen, W. L. Contribution of conformer focusing to the uncertainty in predicting free energies for protein− ligand binding // Journal of medicinal chemistry. – 2006. – Vol. 49, № 20. – P. 5880-5884.

3. Perola, E., Charifson, P. S. Conformational analysis of drug-like molecules bound to proteins: an extensive study of ligand reorganization upon binding // Journal of medicinal chemistry. – 2004. – Vol. 47, № 10. – P. 2499-2510.

4. Taylor, R., Cole, J., et al. Knowledge-based libraries for predicting the geometric preferences of druglike molecules // Journal of Chemical Information and Modeling. – 2014. – Vol. 54, № 9. – P. 2500-2514.

5. Zivanovic, S., Bayarri, G., et al. Bioactive conformational ensemble server and database. A public framework to speed up in Silico drug discovery // Journal of Chemical Theory and Computation. – 2020. – Vol. 16, № 10. – P. 6586-6597.

6. Friedrich, N. O., de Bruyn Kops, et al. Benchmarking commercial conformer ensemble generators // Journal of chemical information and modeling. – 2017. – Vol. 57, № 11. – P. 2719-2728.