Lecture

Tuesday, October 8th 2019 at 2:00 PM

Chemistry building, 5th floor, academic room

Application of Molecular Modeling Techniques in Drug Discovery

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The drug discovery cycle is a long, time consuming and a costly process. Computer aided drug design (CADD) has occupied an important position in the drug discovery pipeline due to its successful application in the identification of several drugs (e.g. captopril, dorzolamide, aliskiren) [1,2]. In this lecture, we will take you through the journey to the general introduction and importance of various basic techniques of CADD. In the end we will discuss two exciting case studies which encapsulate the application of these techniques.

(i) The first case study is based on the enzyme phospholipase C gamma 1 (PLCγ1), which is a potential drug target for various pathological conditions such as immune disorders, systemic lupus erythematosus, and cancers. In this work, a systematic virtual screening protocol is adopted to identify novel inhibitors against the PLCγ1. An in-depth biophysical analysis provides an opportunity to identify new inhibitors through pharmacophore mapping, molecular docking, and MD simulations. From such a systematic procedure, a total of seven compounds emerged as promising inhibitors, all characterized by a stable binding with PLCγ1 and a comparable or higher binding affinity to ritonavir ($\Delta G_{bind} \leq$ -25 kcal/mol), one of the most potent inhibitor reported till now [3].

(ii) The second case study is about the structural exploration of human granzyme B (hGzmB), an executive component of perforin/granzyme mediated apoptotic pathway. In this work, long classical molecular dynamics (MD) simulations are employed to systematically analyze the structural dynamics of hGzmB in the interconversion of active and inactive conformation. Based on these observations a chain of intramolecular interactions was proposed to be responsible for the conformational dynamics in hGzmB. The proposed mechanism was also supported from in silico mutational studies, where Arg216Ala mutation resulted into the failure of substrate binding. This critical understanding of hGzmB activation at the atomic level is of prime importance for the identification of hGzmB modulating agents, by guided tailoring of structural features in therapeutic agents [4,5].

[1]. Expert Opin. Drug Discov. 2006, 1, 103 [2]. Annu Rev. Biophys Biomol. Struct. 1998, 27, 249 [3]. Int. J. Mol. Sci. 2019, 20, 4721 [4]. Front. Immunol. 2013, 4, 497 [5]. Allergy 2014, 69, 1454.

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