

Electronic-structural study of the interaction of inhibitors of the protein Abl-Bcr tyrosine kinase in mutated form against the wild-type

Washington A. Pereira (PG), João B. L. Martins (PQ)

Address: Universidade de Brasília (UnB)

Abstract

The proteins kinase are a larger family of proteins in eukaryotes, they are the key central communication for intracellular control, regulation and signal transduction[1]. The regulatory mechanism includes various phenomena ranging from chemical and Structural properties of the protein until transcriptional control[2]. Therefore, the understanding from the mechanism of control of the kinase proteins and focus of many researches. In Chronic Myeloid Leukemia, a tyrosine kinase (TK) is improperly activated by the accidental fusion of the Bcr gene with Intracellular gene encoding tyrosine kinase, that specific protein, using it as a therapeutic target, making a Bcr-Abl tyrosine kinase hitherto the main target for the design of new drugs, not only for the control of the disease, but also for Mechanism of cure. They will be used for molecular calculation, among them, molecular mechanics. Ab initio methods and hybrid methods. It was used to measure a protein antenna with drug programs such as Auto-Docking Vina. The study may shed light on an electronic activity of the protein and which residues play crucial roles in interacting with the primers. To better understand the structural and electronic functioning of the protein Tyrosine (DM / MM) and guantum models (ab initio, Semi-Empirical among others). With these tools it will be possible to compare the different mutations and different inhibitors and may point out the best possible inhibitor characteristic to achieve complete inhibition. The procedure using is to choose the best protein in the database of Protein Data Bank (PDB) structures, select the molecules of the main drugs, which are deposited in the database Zinc fingerings using the docking program Auto Docking Vina, map the amino acids that are participating Directly or indirectly from the inhibition and type of interaction that each residue makes with the protein, applying methods like ONIOM, determining the energy that these amino acids have with inhibitor. The study of molecular dynamics to understand the structural behavior and conformations that protein assumes the different stimuli, finally the electronic study comprising importance of each amino acid of the active site in inhibition. Finally, a fragment docking was performed, directing the main residues and choosing new molecules. From the mid-1970s, methods known as hybrids appeared. These methods consist of the combination of different types of approximations, ab initio, semiempirical and molecular mechanics, thus trying



to take advantage of each one And circumventing some of its limitations. The ONIOM method then appeared [3]. Simulation of Molecular Dynamics (DM) is one of the most versatile computational techniques for the study of biological macromolecules. In rational structure-based drug planning, DM simulations have contributed extensively at various stages of the process [4].

Keywords: tyrosine kinase, Ab initio methods, molecular modeling



Figure 1. Interacion wich TKIs and TK



Figure 2. Selected wastes Applying ONIOM method

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