ACCEPTED ABSTRACTS JOURNAL OF NANOMEDICINE & NANOTECHNOLOGY 2019, VOLUME 10 | DOI: 10.4172/2157-7439-C1-101

An insight to the molecular interactions of the FDA approved PR drugs against L38L↑N↑L PR mutant

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The aspartate protease of the human immune deficiency type-1 virus (HIV-1) has become a crucial antiviral target in which many useful antiretroviral inhibitors have been developed. However, it seems that the emergence of new HIV-1 PR mutations enhances drug resistance, hence, the available FDA approved drugs show less activity towards the protease. A mutation and insertion designated L38L↑N↑L PR was recently reported from a subtype of C-SA HIV-1. An integrated two-layered ONIOM (QM:MM) method was employed in this study to examine the binding affinities of the nine HIV PR inhibitors against this mutant. The computed binding free energies, as well as experimental data, revealed a reduced inhibitory activity towards the L38L↑N↑L PR in comparison with subtype C-SA HIV-1 PR. This observation suggests that the insertion and mutations significantly affect the binding affinities or characteristics of the HIV PIs and/or parent PR. The same trend for the computational binding free energies was observed for eight of the nine inhibitors with respect to the experimental binding free energies. The outcome of this study shows that the ONIOM method can be used as a reliable computational approach to rationalize lead compounds against specific targets. The nature of the intermolecular interactions in terms of the host-guest hydrogen bond is discussed using the atoms in molecules analysis. The natural bond orbital analysis was also used to determine the extent of charge transfer between the QM region of the L38L↑N↑L PR enzyme and FDA approved drugs. AIM analysis showed that the interaction between the QM region of the L38L↑N↑L PR and FDA approved drugs are electrostatic dominant, the bond stability computed from the NBO analysis supports the results from the AIM application. Future studies will focus on the improvement of the computational model by considering explicit water molecules in the active pocket. We believe that this approach has the potential to provide information that will aid in the design of much improved HIV-1 PR antiviral drugs.

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