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Exploring the flap dynamics of the South African subtype C HIV protease in presence of FDA-approved inhibitors: MD study

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The aspartyl protease human immunodeficiency virus type 1 (HIV-1) is a 99-amino acid-long homodimer responsible for processing the Gag and Gag-Pol polyproteins into functional constituent proteins necessary for development of infectious HIV particles. Of global infections recorded, sub-Saharan African region is represented by 56 % where nearly 25 million people are living with HIV. South Africa has been shown to carry the heaviest HIV burden in sub-Saharan Africa where the HIV-1 subtype C (C-SA) is the prominent strain. Most of the HIV-1 scientific research has been done specifically for subtype B and this has been highlighted by the weaker binding affinity displayed by the South African HIV-1 subtype C for most of the clinically approved protease inhibitors when compared to the HIV-1 subtype B protease.

The two flaps of the HIV-1 PR are very essential in functioning of the enzyme as their conformations control entry of the substrate into the catalytic site of the enzyme and also to release product. It is very important to explore and understand the dynamics of these flaps in binding of different inhibitors with different binding affinities. In addition, studies have highlighted the focus on inhibiting the cleaving function of HIV-1 PR with protease inhibitors (PIs) by competing with the natural substrate for the enzyme's active or catalytic site and thus rendering its ineffective. It has been shown that in addition to the active site, more regions of the enzyme can be possible targets for inhibition process by developing drugs that can hinder the opening of the flaps or disrupt the stability of the dimer interface.

This study involved the use of computational techniques to explore the major contributing factors other than interactions with the binding site, in binding affinity of FDA approved second generation PIs complexed to HIV-1 C-SA PR. In pursuance of this objective, molecular dynamics simulations were performed using Amber 14 with the ff99SB force field, binding-free energy calculations and dynamic analyses were also utilized. Several distances, different angles between certain residues were all taken into consideration.

Our findings do show that apart from binding free-energy calculations, not one single factor but several factors contribute to the binding affinity of protease inhibitors. It is clear from these results that in the development of new HIV-1 drugs, more emphasis should be made in the design of drugs with, not only better binding in the active site but also with better interaction with other regions of the enzyme. Another interesting emphasis

drawn from this study is that there is still need for drug development targeting HIV-1 PR C-SA as the currently available drugs were modelled around the inhibition of HIV-1 subtype B.

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