Chapter 7
Dissection of HIV-1 Protease Subtype B Inhibitors Resistance Through Molecular Modeling Approaches:
Resistance to Protease Inhibitors

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ABSTRACT

Protease (PR) is an important enzyme required for the posttranslational processing of the viral gene products of type-1 human immunodeficiency virus (HIV-1). Protease inhibitors (PI) act as competitive inhibitors that bind to the active site of PR. The I84V mutation contributes resistance to multiple PIs, and structurally, this mutation affects both sides of the enzyme active site. In order to get insights about this major resistance site to PR inhibitors using in silico approaches, in this chapter, the wild-type (WT) and mutant (MT) I84V of PR were modeled and docked with all PR inhibitors: Atazanavir, Darunavir, Indinavir, Lopinavir, Nelfinavir, Saquinavir, and Tipranavir. Docking results revealed that in comparison to the WT, the binding score was higher for the MT-I84V. Thus, it can be suggested that the high affinity towards inhibitors in the MT could be due to the presence of energetically favorable interactions, which may lead to tight binding of inhibitors with the MT protein, leading to the development of PR resistance against PIs in HIV-1 eventually.

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INTRODUCTION

Protease (PR) is an essential enzyme that is required for the posttranslational processing of the viral gag and gag-pol polyprotein gene products, which yields the structural proteins and enzymes of the type-1 human immunodeficiency virus (HIV-1) particle. HIV-PR is a dimeric aspartic protease that consists of two identical, non-covalently associated subunits of 99-amino acid residues (Wlodawer & Erickson, 1993). The active site is covered over by two P-hairpin structures, or "flaps," that are highly flexible and undergo large localized conformational changes during the binding and release of inhibitors and substrates (Collins, Burt, & Erickson, 1995). To date several crystal structures of HIV-PR inhibitor complexes have been solved to aid the process of inhibitor design, these complexes enables to understand the mechanisms of resistance at an atomic level (Appelt, 1993; Fitzgerald & Springer, 1991). Mutations of specificity-determining residues that would directly interfere with inhibitor binding constitute an obvious mechanism for resistance to PR inhibitors which are otherwise known as PI. On the other hand, mutations at the non-active site of the enzyme that indirectly interfere with inhibitor binding via long-range structural perturbations represent other resistance pathways. Such mutations that eventually result in an enzyme with enhanced catalysis and cleavage site mutations that lead to enhanced processing by mutant enzymes, and "regulatory'' mutations elsewhere in the genome that lead to improved viral growth in the presence of PR inhibitors (Erickson, Gulnik, & Markowitz, 1999).

Clinically resistance to PIs such as Atazanavir ATV, Darunavir (DRV), Indinavir (IDV), Lopinavir (LPV), Nelfinavir (NFV), Saquinavir (SQV) and Tipranavir (TPV) has been well documented. More mutations are selected by the PI than by any other class of anti-retro virals. The effect of PI resistance mutations on individual PI may be difficult to quantify when many mutations are present in the same virus isolate or when mutations occur in unusual patterns. The effect of PI resistance mutations on drug susceptibility can also be modulated by gag cleavage site mutations and possibly other parts of gag that influence Gag-Pol processing (Guha & Haldar, 2012).

Twenty-three mutations in 16 codons of the PR gene related to major drug-resistance to PIs were identified by phenotypic resistance assays according to the estimates of International AIDS Society (Rhee et al., 2003). Differences in polymorphisms in the protease gene have been reported among different subtypes. For examples, the D30N mutation is associated with subtype B viruses and the L90M mutation is favored in the subtypes G, CRF02_AG, and CRF02_AE isolates with treatment failure (Santos & Soares, 2011).