Binding of clinically approved protease inhibitors to South African HIV-1 subtype C protease: kinetics and thermodynamics

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HIV-1/AIDS is a major health problem world-wide. Over 70% of infected individuals are in Africa with South Africa displaying one of the fastest rates of HIV-1 infection. Subtypes A and C predominate on the African continent while subtype B is prevalent in Western Europe and North America. Our study reports on the enzyme kinetics and binding specificity of clinically approved antiretroviral protease inhibitors of the South African HIV-1 subtype C protease (SAPRC). Isothermal titration calorimetry (ITC) measurements were performed to dissect the binding energetics of four protease inhibitors in clinical use (saquinavir, indinavir, nelfinavir and ritonavir) and a second-generation inhibitor (KNI-764) to SAPRC. Thermodynamic parameters indicated that binding of antiretroviral drugs to SAPRC is entropically driven. SAPRC binding to indinavir, saquinavir and nelfinavir are enthalpically unfavourable with ritonavir and KNI-764 being enthalpically favourable. The kinetic properties (K_m, k_{cat} and k_{cat}/K_m values) of the SAPRC are lower than the subtype B protease values. The K_d values suggest that the amino acid changes in SAPRC lower the binding affinities toward the clinical inhibitors but not necessarily to the extent where they induce the appearance of mutations. Crystal structure studies of the apo- and drug-complexed (ritonavir) structures of SAPRC are in progress and this should enhance our understanding of the nature of the interactions involved. Naturally occurring polymorphisms may enhance the effects of mutations thus causing drug resistance and therefore reduce the prolonged use of antiretroviral inhibitors.

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