**PhD Thesis: Design and synthesis of new integrase inhibitors**

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## Abstract

The viral enzyme integrase (IN) is essential for the replication of human immunodeficiency virus type 1 (HIV-1) and represents an important target for the development of new antiretroviral drugs. In this PhD project, we focused on the N-terminal domain of integrase (NTD) for the development and synthesis of a library of overlapping peptide sequences, with specific length and specific offset covering the entire native protein sequence NTD IN 1-50. The most potent fragment, VVAKEIVAH (peptide **18**), inhibits the HIV-1 IN activity with an $IC_{50}$ value of 4.5 μM. Amino acid substitution analysis on this peptide revealed essential residues for activity and allowed us to identify two nonapeptides (peptides **24** and **25**), that show a potency of inhibition similar to peptide **18**. Interestingly, peptide **18** does not interfere with the dynamic interplay between IN subunits, while peptides **24** and **25** modulate these interactions in different manners. In fact, peptide **24** inhibits the IN-IN dimerization, while peptide **25** promotes IN multimerization, with $IC_{50}$ values of 32 and 4.8 μM, respectively. In addition, peptide **25** has shown to have selective anti-infective cell activity for HIV-1. Moreover, the NMR analysis showed an alpha helix conformation of peptide **25**, which could be essential for the interaction with IN. These results indicated peptide **25** as a hit for further development of new chemotherapeutic agents against HIV-1. In addition, we observed that the peptide **5**, EKYHSNWRAM, conveniently conjugated with the cell-penetrating fragment TAT, inhibits replication of HIV-1 and HIV-2 in infected MT-4 cells.

**Keywords:** HIV-1, integrase, N-terminal domain, peptides, inhibitors.