Synthesis of HIV-1 Reverse Transcriptase Inhibitors

Gistrova, Tereza (School: Gymnazium Zlin - Lesni Ctvrt)

Nowadays, the Human Immunodeficiency Virus type 1 (HIV-1) is treated by inhibitors of various types, especially substances able to block key stages of HIV life cycle. Within the last years, the most attention has been devoted to non-nucleoside reverse transcriptase inhibitors (NNRTIs), diarylpyrimidine (DAPY) derivatives in particular. Recently, it has been shown that carbonyl to hydrazone functionality replacement in DAPY derivatives led to significant increase in activity. With this objective in mind, a series of novel DAPY derivatives were proposed and synthesized by reacting the carbonyl compounds with hydrazine sulfate/amines. The reaction afforded the desired Schiff bases as well as unexpected byproducts. Hence, an efficient synthetic methodology towards novel DAPY derivatives has been developed. The series of synthesized anti-HIV inhibitors was tested against wild type and clinically relevant mutant HIV strains. All compounds were tested for their ability to inhibit replication of HIV-1 in infected MT-4 cells. Whereas starting carbonyl compound showed IC50 = 5.3 nM, the corresponding Schiff base possesses high nanomolar activity with IC50 = 2.2 nM. Methylene-linked byproduct, formed by reduction, displayed even higher inhibition activity with IC50 = 1.5 nM and diminished toxicity (CC50 = 42,167 nM). Based on this unexpected observation, the prochiral ketone was further reduced with hydride producing racemic alcohol, which showed comparable low nanomolar inhibition (IC50 = 5.0 nM). Pure enantiomers were subsequently separated using chromatography with chiral stationary phase; the (S)-enantiomer showed the lowest inhibition constant IC50 = 2.1 nM.

Awards Won:

Third Award of $1,000