Novel Inorganic Metallacarborane Inhibitors of HIV-1 Protease

Krystufek, Robin

Protease inhibitors used in clinical practice can be denoted as highly potent weapons against HIV. Unfortunately, the virus easily mutates and becomes more and more resistant. This is the main reason for further development of new antivirals overcoming the raising viral resistance. Recently, a new class of potential protease inhibitors (metallacarborane derivatives) was discovered.

In this project, a series of new cobalt bis(dicarbollide) (COSAN) derivatives were designed and synthetized considering the current knowledge about impacts of structural changes on the inhibition properties. Selected inhibitors were subjected to further biochemical assay to determine their capability to cope with mutated strains of HIV-1 protease. I identified three from totally eight inhibitors as mixed inhibitors; the others were competitive, with IC50 values ranging from 40 to 320 nM. Several inhibitors exhibited very low Ki while the best inhibitor and the lead drug of the series (GB273 and uracil-bis-COSAN-dioxanate) showed Ki = 5,92 ± 0,82 nM. The mode of inhibition was verified using X-ray diffraction spectroscopy. Some of the synthetized inhibitors exhibited a correlation of the inhibition constants, e.g. derivatives of L and D enantiomers of tyrosine and phenylalanine. In contrast to protease inhibitors currently used in clinical practice, the main advantage of newly prepared inhibitors can be seen in their stable Ki values and vitality upon treatment with mutated strains of the HIV protease.

Awards Won:

Second Award of $2,000