Abstract

Targeted protein degradation is a novel concept of chemical biology that has been formulated about 20 years ago. Its central postulate is based on the fact that instead of suppressing protein activity with low-molecular inhibitors, we can instead use molecular tools to hijack the host organism's own degradation pathways and force it to degrade chosen proteins by itself. This diploma thesis revolves around the preparation of biocompatible polymeric conjugates called "iBodies" that will be used to induce targeted lysosomal degradation of two model enzymes – Fibroblast activation protein α, and Glutamate carboxypeptidase II.

First, a total of four low-molecular ligands were prepared and fully characterized by standard methods of organic synthesis. The first two are mannose-6-phosphonate derivatives that serve as the inducers of protein degradation *via* the cellular endosomal-lysosomal degradation pathway. The remaining two are known potent inhibitors of the chosen model enzymes that will serve as their targeting-ligands. The prepared compounds were then used to prepare a total of eight poly-*N*-(2-hydroxypropyl)methacrylamide conjugates called iBodies, after which the polymeric conjugates were fully characterized by standard means of macromolecular chemistry. Afterwards, the obtained conjugates will be used in biological experiments at the Department of Human Pathogens, IOCB Prague, to investigate their ability to induce lysosomal protein degradation of the model enzymes.

Keywords: protease inhibitors; molecular recognition; polymer conjugates; LYTAC; iBodies