Abstract

Fibroblast activation protein (FAP) is a serine protease which is expressed predominantly in epithelial tumor stroma and can thus be potentially used in tumor imaging and diagnosis[1,2]. To this date, several selective and highly potent low-molecular inhibitors of FAP were developed[3]. However, all structure-activity relationship (SAR) studies have disregarded the region following the position of the scissile bond in the substrate. In this thesis, a total of six novel α-ketoamide FAP inhibitors were synthesized and fully characterized, in order to explore the abovementioned region. Two of the prepared inhibitors exhibit higher inhibitory potencies than the best state-of-the-art FAP inhibitors. Additionally, the effect of fluorine atoms in the C3-position of pyrrolidine on the FAP inhibitory potency and selectivity towards FAP over its homologs was examined. For this purpose, a lead-hit α-ketoamide inhibitor from a broader SAR study conducted in the Konvalinka lab at IOCB Prague was used.

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3) K. Jansen, L. Heirbaut, R. Verkerk, J. D. Cheng, J. Joossens, P. Cos, L. Maes, A.-M. Lambeir, I. De Meester, K. Augustyns and P. Van der Veken, *J. Med. Chem.*, **2014**, 57, 3053–3074.