Abstract

Human cathepsin K (KatK) is a lysosomal cysteine protease expressed predominantly in osteoclasts. It is the most effective enzyme for collagen breakdown and its physiological function lies in the degradation of the extracellular bone matrix. Increased enzymatic activity of KatK is associated with osteoporosis, rheumatoid arthritis, and osteoarthritis. This makes KatK a target for the treatment of pathologies, and chemotherapeutics based on protease inhibitors are being developed for its regulation. This work deals with reactive peptidomimetic and low molecular weight inhibitors of KatK namely thiadiazoles, vinyl ketones, and cyanohydrazides. It focuses mainly on the determination of the binding mode of selective inhibitors and characterization of their key interactions with the active site of KatK. Crystallographic structural analysis was combined with approaches of computational chemistry, enzymological analysis, and cell-based assays to elucidate the relationship between structure and biochemical activity of the investigated inhibitors. The obtained results provide important information for the design and optimization of new highly effective and selective KatK inhibitors as potential drugs and diagnostic probes.

Keywords: cathepsin K, protease, inhibitor, 3D structure, osteoporosis