Inhibiting cysteine cathepsins by targeting sites outside of the active site

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M. Novinec[I]

[I]Faculty of Chemistry and Chemical Technology, University of Ljubljana, Ljubljana, Slovenia

Human cysteine cathepsins are appealing drug targets in numerous diseases, including autoimmune, inflammatory and metabolic diseases. Unfortunately, no cathepsin inhibitor has been successfully launched on the market so far. Traditional cathepsin inhibitors target the active site and are often plagued by low selectivity and off-target effects. Therefore, alternative stategies of these peptidases are emerging that target sites outside of the active site.

We are investigating mechanisms of allosteric inhibition of selected cysteine cathepsins, focusing on synthetic and natural small molecules (effectors). Using a combination of in silico screening and experimental methods, we discovered and characterized the first allosteric effectors of cathepsin K, a target in osteoporosis and osteoarthritis. Two compounds from the US NCI/DTP Open Chemical Repository (NSC13345 and NSC94914) were shown to bind to a novel allosteric site on cathepsin K and acted as partial inhibitors of its activity. Based on the structure of compound NSC13345, we synthesized novel effectors with improved activity and affinity in the low micromolar range. Recently, a succinimide-amino acid scaffold initially designed to target cathepsin K was also diversified to target cathepsin S, which is associated with cardiovascular and pulmonary diseases, resulting in the first partial inhibitors of this peptidase. The identified effectors showed good selectivity over other closely related peptidases and our current efforts are aimed at improving their affinity.

Moreover, we recently discovered that selected natural derivatives of cinnamic acid are reversible, full inhibitors of all cysteine cathepsins that act via kinetic mechanisms other than specific (competitive) inhibition, indicating that they bind outside of the active site. We are currently investigating their structure-activity relationships and the potential of this scaffold for development of specific inhibitors of individual cathepsins.