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Discovery of the First Selective Nanomolar Inhibitors of ERAP2 by Kinetic Target-Guided Synthesis
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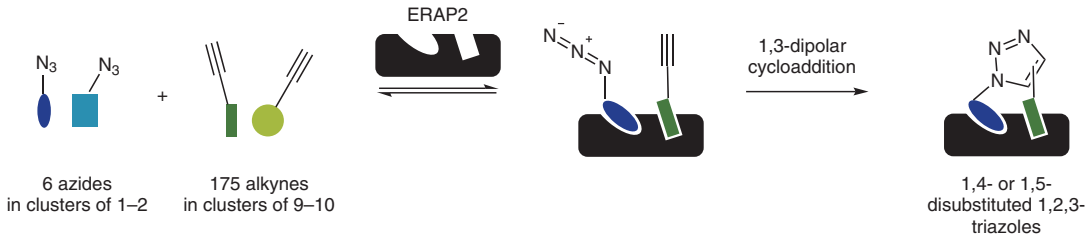
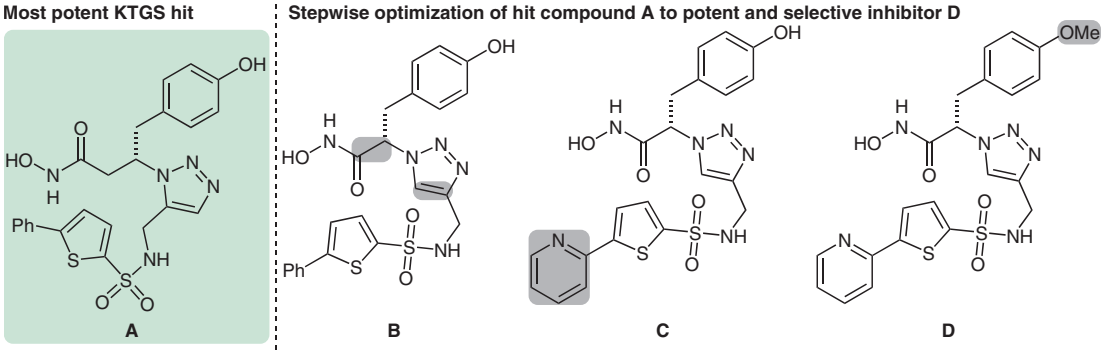
Kinetic Target-Guided Synthesis of ERAP2 Inhibitors

Kinetic target-guided synthesis (KTGS) of ERAP2 ligands:



Most potent KTGS hit

Stepwise optimization of hit compound A to potent and selective inhibitor D



ERAP2 IC_{50} (nM): 850
IRAP IC_{50} (nM): 84

ERAP2 IC_{50} (nM): 760
IRAP IC_{50} (nM): 620

ERAP2 IC_{50} (nM): 470
IRAP IC_{50} (nM): 610

ERAP2 IC_{50} (nM): 3.9
IRAP IC_{50} (nM): 186

Significance: Endoplasmic reticulum aminopeptidase 2 (ERAP2) is involved in the trimming of antigenic peptides and modulates the immunopeptidome presented at the cell surface by major histocompatibility complex class I. It is a target for the treatment of autoimmune disease and in cancer immunotherapy. Previously developed ERAP 2 inhibitors lacked selectivity over related enzymes such as insulin-regulated aminopeptidase (IRAP) or displayed low potency. In the highlighted article, the authors used kinetic target-guided synthesis (KTGS) to develop the first nanomolar and selective ERAP2 inhibitors. In KTGS, the protein serves as a template for an equilibrium-controlled selection of alkynes and azides. The fragments that fit best to the binding site are linked by a (3+2)-cycloaddition to form triazole ligands. This method can be used to identify inhibitors that bind to previously unknown protein conformations by utilizing the flexibility of the target.

Comment: Six azides were incubated with mixtures of alkynes in the presence and absence of ERAP2. Mass spectrometry was used to assess the selectivity of the protein-templated triazole formation. This resulted in the identification of 19 hit compounds out of 1050 possible combinations. The selection was further narrowed to 6 compounds, of which compound **A** was the most potent. The structure was then optimized for potency and selectivity over IRAP. Switching from a 1,5- to a 1,4-triazole core and shortening the hydroxamic acid tail (**B**) changed the binding mode and improved selectivity towards ERAP2. Exchanging the phenyl group for a 2-pyridyl group (**C**) and introduction of a methyl group on the phenolic hydroxy group resulted in a potent and selective inhibitor (**D**) of ERAP2 by improving interactions with non-conserved residues.

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Category
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Key words
ERAP2 inhibitors
kinetic target-guided synthesis
triazoles