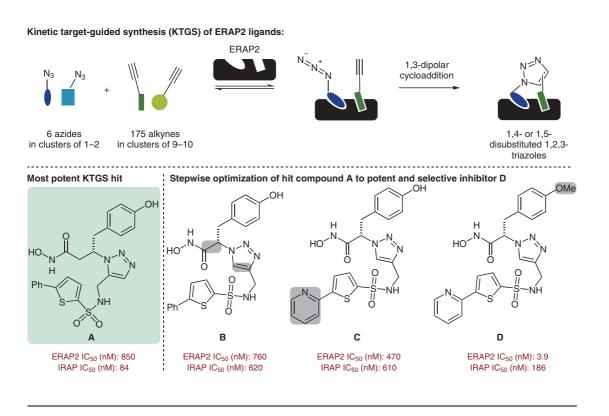
M. BOUVIER*, R. DEPREZ-POULAIN* ET AL. (UNIVERSITY OF ILLINOIS AT CHICAGO, USA; PÔLE RECHERCHE AND UNIVERSITY LILLE, FRANCE) Discovery of the First Selective Nanomolar Inhibitors of ERAP2 by Kinetic Target-Guided Synthesis Angew. Chem. Int. Ed. **2022**, 61, e202203560 DOI: 10.1002/anie.202203560.

Kinetic Target-Guided Synthesis of ERAP2 Inhibitors



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-quided 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 nonconserved residues.

Category

Innovative Drug Discovery and Development

Key words

ERAP2 inhibitors

kinetic targetguided synthesis

triazoles

Synfact