Aza-Peptide Carbonyls: A New Class of Immunoproteasome Inhibitors

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The proteasome is a large protein complex that plays a critical part in the ubiquitin-proteasome pathway (UPP): a process responsible for the degradation of ubiquitin marked regulatory proteins, immune responses, and apoptosis. Increased activity of proteasome activity in cancer cells combined with the proapoptotic effects of proteasome inhibition make the proteasome a promising target in cancer treatment, particularly multiple myeloma. The aim of this specific project is to make inhibitors targeting the immunoproteasome for the treatment of autoimmune diseases and inflammatory disorders.

Current Proteasome Inhibitors

Current proteasome inhibitors are established treatments for multiple myeloma patients; however, both drugs have been linked to side effects, specifically Bortezomib has been linked to peripheral neuropathy¹.

Key features of our new proteasome inhibitors:

• An α-carbonylhydrazide as the electrophilic warhead.
• An achiral P1 aza-amino acid residue, to limit off-target activity.
• An optimized peptide portion corresponding to the preferred proteasome substrates to ensure selectivity.

Our Inhibitor Design

Chemical Warhead: The electrophilic site for attack by the protease active site nucleophilic residue

Our Inhibitor Design

synthesize the first aza-peptide carbonyl inhibitor targeting the immunoproteasome with a Nle at the P1 position: Cbz-Leu-Leu-ANie-OMe
• We are in the process of optimizing the peptidyl portion to obtain more immunoproteasome specific inhibitors (Cbz-Ala-Tyr(OMe)-ALeu).

Synthesis

References