

Cyclic Peptide Stimulators of the Proteasome

Low-cost, scalable route to optically pure bis-THF ligands for HIV protease inhibitors.

Cyclic Peptide Proteasome Stimulators (CyPPS) have gained prominence for their ability to selectively catalyze the degradation of disordered proteins, leaving structured proteins untouched. CyPPS address proteinopathies—conditions arising from structurally misfolded proteins that impact cellular, tissue, and organ functions. Some of these diseases include neurodegenerative disorders like Alzheimer's and Parkinson's. Various small molecules and peptides have been found to stimulate the proteasome; however, these proteasome stimulators are disadvantageous due to lack of potency, selectivity, and inactivity in cell-based assays. There is a clear need for proteasome stimulators with low toxicity that show selectivity of cyclic, misfolded peptides.

Researchers at Purdue have developed various cyclic proteasome stimulator based upon previously developed predicted natural products (pNPs) that show high selectivity and potency. These developed CyPPS demonstrate incredible efficacy in accelerating the proteasomal degradation of specific malfunctioning proteins while leaving other functioning proteins intact. The CyPPS can be synthesized utilizing well-established techniques, such as solid-phase peptide synthesis. Furthermore, the developed peptides exhibit no toxicity to human cells and hemolysis.

Technology Validation:

- Efficacy of the cyclic peptides was demonstrated through verification of misfolded protein degradation, cell permeability and uptake
- Structure and activity of various proteasomes were confirmed via TAS-1 biochemical assay
- Two-way analysis of variance (ANOVA) analysis was performed comparing the efficacy of various active CyPPS

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Category

Biotechnology & Life
Sciences/Biomarker Discovery &
Diagnostics
Pharmaceuticals/Drug Discovery
& Development
Biotechnology & Life
Sciences/Analytical & Diagnostic
Instrumentation

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Advantages:

- Non-hemolytic
- Non-toxic to humans
- High selectivity

Applications:

- Creutzfeldtâ€ˆ Jakob disease
- Alzheimer's disease
- Parkinson's disease
- Amyloidosis
- Huntington's disease

Related Publication:

Discovery and Development of Cyclic Peptide Proteasome Stimulators

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TRL: Pharmaceuticals

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