METHODS FOR THE SYNTHESIS OF PEPTIDE MACROCYCLES WITH EMBEDDED HETEROCYCLES

Tech ID: 33491 / UC Case 2024-090-0

PATENT STATUS

Patent Pending

BRIEF DESCRIPTION

Developing structurally complex peptide macrocycles is a critical strategy for addressing "undruggable" protein-protein interactions. To expand the chemical space available for drug discovery, UC Berkeley researchers have developed a versatile synthesis method that embeds quinoline and other heterocycles directly into the macrocyclic backbone. The approach utilizes substituted 2-aminocarbonyl co-substrates to produce peptide hybrids featuring biaryl atropisomeric axes. These axes provide a unique form of axial chirality that can be engineered to be either conformationally mobile or stable, allowing for the precise three-dimensional "locking" of the peptide into a target-optimal shape. By integrating these rigid pharmacophores, the resulting macrocycles achieve enhanced topological diversity and superior binding affinity compared to traditional cyclic peptides.

SUGGESTED USES

- Inhibition of Protein-Protein Interactions (PPIs): Utilizing the large surface area and rigid architecture of these macrocycles to block flat, shallow binding sites on disease-relevant proteins.
- Next-Generation Peptide Therapeutics: Developing orally bioavailable or cell-permeable drug leads that mimic natural binding motifs while offering greater structural complexity.
- Protease-Resistant Biologics: Engineering stable macrocyclic frameworks that resist enzymatic degradation in the bloodstream, extending the half-life of therapeutic peptides.
- High-Throughput Screening Libraries: Creating diverse libraries of atropisomeric peptide hybrids for the identification of selective binders to challenging intracellular targets.
- Biochemical Probes: Designing highly specific chemical tools to study protein function and localization in complex biological systems.

ADVANTAGES

- Tunable Conformational Rigidity: The atropisomeric axis allows for "programming" the molecule's shape, ensuring a high-affinity fit with its biological target.
- Enhanced Metabolic Stability: Heterocycle embedding and macrocyclization significantly improve resistance to proteolysis compared to linear or simple cyclic peptides.
- Increased Pharmacological Potency: Pre-organizing the binding conformation reduces the entropic penalty of binding, leading to higher potency and selectivity.
- Modular Synthetic Route: The use of accessible 2-aminocarbonyl co-substrates facilitates the streamlined production of a wide variety of heterocycle-peptide hybrids.
- Expanded Chemical Space: Introduces topological and stereochemical complexity (axial chirality) that is not available in canonical genetically encoded peptides.

RELATED MATERIALS

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

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OTHER INFORMATION

CATEGORIZED AS

- **Biotechnology**
  - Proteomics
- **Materials & Chemicals**
  - Chemicals
- **Medical**
  - New Chemical Entities, Drug Leads
- **Research Tools**
  - Protein Synthesis

RELATED CASES

2024-090-0

- Improved Vehicles For Endosomal Escape
- Design Rules For Endosomal Escape
- Ribosomal Synthesis Of Ketone-Containing Peptide Backbone Via O To C Acyl Shift

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