DCAF16-BASED COVALENT HANDLE FOR THE RATIONAL DESIGN OF MONOVALENT DEGRADERS

Tech ID: 33464 / UC Case 2024-080-0

PATENT STATUS

Patent Pending

BRIEF DESCRIPTION

Targeted protein degradation represents a transformative approach in drug discovery by using small molecules to hijack the cell's natural disposal machinery. In this advancement, UC Berkeley researchers have engineered a vinylsulfonyl covalent handle designed for the rational construction of monovalent degraders. Unlike traditional bivalent degraders (PROTACs), which can be large and difficult to deliver into cells, these monovalent molecules are more compact and specifically target a cysteine residue within DCAF16, a substrate receptor of the CUL4-DDB1 E3 ubiquitin ligase. By covalently "gluing" the target protein to DCAF16, the system triggers the ubiquitination and subsequent proteasomal destruction of disease-causing proteins.

SUGGESTED USES

- Cancer Therapeutics: Developing potent degraders for oncogenic transcription factors or scaffolding proteins that are typically considered "undruggable" by traditional inhibitors.
- Neurodegenerative Disease Research: Targeting the removal of misfolded or aggregated proteins associated with conditions like Alzheimer's or Parkinson's disease.
- Chemical Biology Tools: Utilizing the DCAF16 handle to create probes that help validate new protein targets by observing the phenotypic effects of their rapid depletion.
- Overcoming Drug Resistance: Degrading mutated versions of proteins that have developed resistance to occupancy-based inhibitors.
- Expansion of the Degradable Proteome: Providing a new "handle" for E3 ligase recruitment, allowing researchers to target proteins that may not be effectively recruited by common ligases like CRBN or VHL.

ADVANTAGES

- Improved Drug-Like Properties: Monovalent degraders are significantly smaller than bivalent PROTACs, leading to better cellular permeability and potential oral bioavailability.
- Enhanced Precision: The vinylsulfonyl handle forms a stable covalent bond with a specific cysteine on DCAF16, ensuring high-affinity recruitment and consistent degradation kinetics.
- Nuclear Localization: DCAF16 is predominantly located in the nucleus, making this technology particularly effective for degrading nuclear-resident proteins like transcription factors.
- Rational Design Platform: The modular nature of the covalent handle allows for the rapid "plug-and-play" synthesis of degraders for a wide variety of target proteins.
- Reduced Off-Target Risks: The specific covalent interaction limits non-specific recruitment of other E3 ligases, potentially minimizing systemic toxicity.

RELATED MATERIALS

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- 14-3-3 Covalent Molecular Glue Stabilizers
- Covalent Degrader of the Oncogenic Transcription Factor CTNNB1
- Stereoselective Covalent Destabilizing Degradation of the Oncogenic Transcription Factor MYC

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OTHER INFORMATION

CATEGORIZED AS

- **Biotechnology**
  - Proteomics
- **Medical**
  - New Chemical Entities
  - Drug Leads
- **Research Tools**
  - Reagents

RELATED CASES

2024-080-0

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