

Covalent Small-Molecule Inhibitors of DCN1 Protein

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Category

Therapeutics and Vaccines

Life Sciences



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OVERVIEW

Small molecule inhibitors that influence dysregulation of intracellular proteins

- Strong, covalent bonding of the inhibitor to the UBC12-DCN1 binding site
- Useful for oxidative stress diseases as well as nerve and muscle degeneration

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MODALITY

Oral or injectable small-molecule drug

INDICATION

Treatment of diseases involving protein homeostasis failure, including neurodegenerative disorders, muscular and nerve degeneration, cardiovascular complications, renal disease, and fibrotic conditions

PUBLICATIONS

- ["Targeting DCN1-UBC12 Protein-Protein Interaction for Regulation of Neddylation Pathway"](#)
- ["High-Affinity Peptidomimetic Inhibitors of the DCN1-UBC12 Protein-Protein Interaction"](#)
- ["A potent small-molecule inhibitor of the DCN1-UBC12 interaction that selectively blocks cullin 3 neddylation"](#)



INTELLECTUAL PROPERTY

- [US10500194](#) "Covalent small molecule DCN1 inhibitors and therapeutic methods using the same"
- [EP3609876](#) "Covalent small molecule dcn1 inhibitors and therapeutic methods using the same"
- [AU2018251687](#) "Covalent small molecule DCN1 inhibitors and therapeutic methods using the same"
- [CA3059256](#) "Covalent small molecule dcn1 inhibitors and therapeutic methods using the same"
- [CN201880038225.2](#) "Covalent small molecule DCN1 inhibitors and therapeutic methods using the same"

BACKGROUND

Cellular protein homeostasis involves the regulated destruction of intracellular proteins by the ubiquitin-proteasome system (UPS). Cullin-Ring ligases (CRL) are a central component of the UPS, and their dysregulation can cause illnesses including cancer, cardiovascular disease, neurodegenerative disorders, and viral infections. A ligase named DCN1 acts as a scaffolding to facilitate other enzymes including UBC12 in their efforts to identify and destroy cellular proteins. DCN1 maintains a shape that provides a well-defined pocket for use as a binding surface for interactions between protein-regulating enzymes. A need exists to find small molecule inhibitors of the UBC12-DCN1 protein interaction in an effort to treat diseases associated with dysregulation of the UPS.

INNOVATION

University of Michigan researchers have discovered a method for producing small molecule inhibitors that can bind with the site in DCN1 bonds with UBC12, thereby causing inhibition of the UBC12-DCN1 protein to protein interactions and providing a method for treating diseases caused by UPS dysregulation. The inhibitors form a strong, or covalent, bond with the DCN1 binding site to modulate the effects of Cullin-Ring ligases and cause preservation of certain proteins which may otherwise inappropriately be destroyed in certain diseases. The ability of compounds of this invention to covalently bind to DCN1 for inhibition of the interaction between DCN1 and UBC12 leads to a highly consequential boost in potency as compared to their non-covalent inhibitor counterparts. The benefits of this type of interaction can extend to patients with oxidative stress-related diseases and conditions, neurodegenerative diseases and conditions, metabolic disorders, and muscular nerve degeneration.