INNOVATION PARTNERSHIPS
UNIVERSITY OF MICHIGAN

2-Hydroxybenzoic Acid Derivatives as Inhibitors and Degraders of Sirtuins

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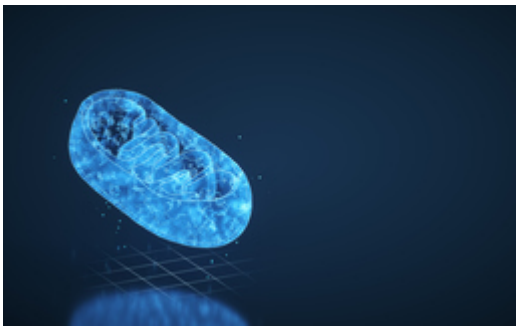

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Category
Therapeutics and Vaccines
Life Sciences

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OVERVIEW

A novel class of 2-hydroxybenzoic acid derivatives that modulate sirtuin5 (SIRT5)

- Permits selective degradation of SIRT5 proteins in the mitochondrial matrix
- Provides a means to inhibit SIRT5 with the goal of causing tumor cell death

BACKGROUND

Sirtuins are a family of signaling proteins involved in metabolic regulation whose physical structure is consistent across many life forms. These proteins influence cellular processes such as transcription, apoptosis, inflammation, stress resistance, and aging. There are seven sirtuin members encoded in mammalian genomes, designated SIRT1 through SIRT 7. SIRT 5 resides predominately in the mitochondrial matrix and is specifically known to influence pathways related to ammonia detoxification, fatty acid oxidation, cellular respiration, ketone body formation, tricarboxylic acid cycle (TCA), glycolysis, and reactive oxygen species (ROS) metabolism. Dysregulated or uncontrolled SIRT 5 activity is associated with diseases including cancer, Alzheimer,Äôs dementia, and Parkinson,Äôs disease. So, a need exists to better understand the biology of SIRT5 and to modulate its behavior to treat diseases associated with its dysfunction.

INNOVATION

Researchers at the University of Michigan have discovered a series of 2-hydroxybenzoic acid derivatives as inhibitors and degraders of SIRT5. The scientists have found that SIRT5 depletion induces rapid cell death in specific cancer types such as melanoma, Ewing sarcoma, malignant peripheral nerve sheath tumor, and neuroblastoma. The researchers screened an in-house

library of compounds using a thermal shift assay to identify this novel class of 2-hydroxybenzoic acid derivatives, and they developed proteolysis targeting chimeric (PROTAC) molecules that selectively induce the degradation of SIRT5 proteins in the mitochondrial matrix. The wide range of substrates for SIRT5 suggest that successful modulation of its function may influence various disease types. These inhibitors and degraders may be useful in the treatment of all the disorders associated with SIRT5 dysfunction.