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Targeting BRAT1 with Curcusone Diterpenoids and Analogs for Cancer Treatment

A total synthesis route for the natural product curcusone and its derivatives yields the first small molecule inhibitors targeting the oncogenic BRAT1 protein for use in cancer therapeutics.

Purdue University researchers have identified the natural product curcusone and its derivatives as the first small molecule inhibitors for the oncogenic protein BRAT1 for use in cancer therapeutics. Nature provides a plethora of natural molecules which often leads to identification of novel targets in human diseases such as cancer. However, accessing sufficient quantities of natural products for in depth biological investigation and therapeutic development remains a significant challenge. To alleviate this dilemma, researchers at Purdue completed a total synthesis of the natural product curcusone and its derivatives to investigate their anticancer properties. Target engagement assays including competitive chemoproteomics, thermal shift, and pulldown assays provided evidence that curcusone D targeted the oncogenic protein BRAT1. Comparative global proteomics analysis of curcosone D-treated or BRAT1 knockdown HeLa cells revealed the downregulation of several proteins implicated in cancer-related pathways. Curcusone D displaced a probe bound to BRAT1 in HeLa cells with a half maximal effective concentration of 1.5 micromolar. These experiments confirm curcusone D as the first small molecule inhibitor of BRAT1 and pave an initial path for the use of curcusone D and its derivatives as anticancer therapeutics.

Advantages:

-First BRAT1 Small Molecule Inhibitor

-Total Synthesis of Curcusone Derivatives

Potential Applications:

-Cancer Treatment

Technology ID

2021-DAI-69235

Category

Biotechnology & Life Sciences/Synthetic Biology & Genetic Engineering

Pharmaceuticals/Drug Discovery & Development

Pharmaceuticals/Small Molecule Therapeutics

Pharmaceuticals/Research Tools & Assays

Authors

Alexander Adibekian

Zhongjian Cai

Chengsen Cui

Mingji Dai

Brendan Dwyer

Further information

Joe Kasper

JRKasper@prf.org

Nathan Smith

nesmith@prf.org

View online

-Natural Product Synthesis

Technology Validation:

Competitive proteomics, thermal shift assays, and pulldowns in cell lysates confirm curcusone D targeting of BRAT1. Global proteomics analysis in curcusone D and BRAT1 knockout HeLa and MDA-MB-231 cell lines reveal several downregulated proteins implicated in cancer. Curcusone D displayed the strongest cytotoxic effect of all the synthesized curcusone derivatives with an EC50 value of 13.8 uM against proliferation of the MCF-7 cell line The half maximal effective concentration of curcusone D in endogenous HeLa cells was experimentally determined to be 1.5 micromolar through a competitive enrichment assay.

TRL: 3

Intellectual Property:

Provisional-Gov. Funding, 2020-09-29, United States | NATL-Patent, 2021-09-27, Japan | NATL-Patent, 2021-09-27, Canada | NATL-Patent, 2021-09-27, Europe | NATL-Patent, 2021-09-27, China | PCT-Gov. Funding, 2021-09-27, WO | NATL-Patent, 2023-03-29, United States

Keywords: Curcusone D, BRAT1 inhibitor, small molecule inhibitor, cancer therapeutics, oncogenic protein, natural product synthesis, competitive chemoproteomics, thermal shift assays, cancer treatment, cell line analysis