



Small Molecule Allosteric Regulation of the Human DNA Cytosine Methyltransferase (DNMT3A) Enzyme

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OTHER INFORMATION

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Small molecule allosteric regulation, DNA cytosine methyltransferase (DNMT3A), Enzyme inhibition, Cancer treatment, Acute myeloid leukemia (AML), Altered DNA methylation patterns, Gene expression changes, Chemotherapy alternatives, Allosteric inhibitor drugs

CATEGORIZED AS

- **Medical**
 - Disease: Cancer
 - New Chemical Entities, Drug Leads
 - Therapeutics

RELATED CASES

2023-895-0

BACKGROUND

Many cancers, including difficult-to-treat acute myeloid leukemia (AML), are made of up cells that have mutations in the human DNA cytosine methyltransferase (DNMT3A) gene. These genetic alterations in DNMT3A can lead to altered patterns of DNA methylation and resultant changes in gene expression, fueling the uncontrolled replication of these aberrant cells. Treatment of cancers including but not limited to blood-based cancers like AML remains a challenge, particularly due to the dose-limiting toxicity that undermines the effectiveness of current chemotherapy-based approaches. This toxicity most likely derives from the diverse cofactor S-adenosyl-L-methionine (AdoMet)-dependent methyltransferase enzymes that are also inhibited with current small molecule drug approaches. Allosteric inhibitor drugs that leverage a completely different pathway and are not involved in binding to the active site of this class of enzymes (AdoMet) could provide a lower-toxicity alternative chemotherapy treatment that could benefit a broad group of cancer patients, including those with AML.

DESCRIPTION

Researchers at the University of California, Santa Barbara have employed pyrazolone and pyridazine, two known allosteric inhibitors of DNMT3A, to interfere with the interaction between DNMT3A and partner proteins which dysregulate the activity of DNMT3A. This dysregulation contributes to altered methylation patterns in AML patients and changes in the regulation of critical genes. Rather than targeting DNA methylation with commonly used chemotherapy drugs, including highly toxic inhibitors such as azacytidine and decitabine, pyrazolone and pyridazine can be used to treat patients effectively without the toxicity. These drugs inhibit enzymatic activity by disrupting protein-protein interactions (PPIs) at the tetramer interface of DNMT3A in the DNMT3A homo- or heterotetramer. Using these small molecules could circumvent the toxicity of conventional treatments and provide an alternative that is as effective or more effective at inhibiting methylation by DNMT3A.

ADVANTAGES

- ▶ Effectively inhibits methylation by DNMT3A with a lower toxicity profile compared to conventional chemotherapy drugs
- ▶ Provides an alternative treatment option for a broader group of cancer patients (notably AML patients)
- ▶ Blazes a trail for future novel derivatives of pyrazolone and pyridazine

APPLICATIONS

- ▶ Therapeutics
- ▶ Cancer treatment

PATENT STATUS

Patent Pending

RELATED MATERIALS

- ▶ [First-in-Class Allosteric Inhibitors of DNMT3A Disrupt Protein-Protein Interactions and Induce Acute Myeloid Leukemia Cell Differentiation](#)

