

Prodrugs of Nicotinamide N-Methyltransferase (NNMT) Inhibitors as Novel Therapeutic Agents

Synchronizes peptide and enhancer release to significantly boost oral peptide absorption.

Researchers at Purdue have developed a series of potent and selective prodrug inhibitors for Nicotinamide N-methyltransferase (NNMT), an enzyme that is implicated in cancer and metabolic diseases such as obesity and diabetes. Thus far, there has been a lack of research on specific and potent inhibitors for NNMT in vivo for cancer cell lines and animal models. As such, the potential for new inhibitor drugs for NNMT has not been fully realized.

Researchers at Purdue have developed a series of NNMT-specific inhibitors with prodrug groups that induce a stronger endocytic response, only activating the drug in the reducing environment within hypoxic cancer cells. Upon testing, the researchers found that several of the drug candidates within the series had significant inhibition of the NNMT enzyme in vitro (low nanomolar level) as well as significant inhibition of total cancer cell growth in vivo (low micromolar level). Additionally, when tested on a mouse model, it was found that mice treated with the NNMT prodrug inhibitor also had reduced weight gain when compared to the control, indicating it could be used to treat obesity.

Technology Validation:

-Degree of inhibition determined by utilizing S-adenosylhomocysteine hydrolase to process the NNMT product to homocysteine, to which its concentration can be quantified with a thiol-sensitive fluorescent molecule and a spectrophotometer.

-Ability to inhibit cancer growth and obesity tested with mouse model. MDA-MB231 breast cancer cells were administered to four experimental groups of mice, 1) mice fed control diet; 2) mice fed control diet and NNMT prodrug inhibitor; 3) mice fed high fat diet (HFD); and 4) mice fed HFD diet and NNMT

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prodrug inhibitor. The researchers measured body weight and tumor size for each mouse over three days and found that treatment with the NNMT prodrug inhibitor prevented weight gain and tumor growth in both experimental groups.

Advantages:

- Highly specific to NNMT and cancer cells
- Significant enzyme and cancer growth inhibitor
- Reduced weight gain

Applications:

- Cancer treatment
- Obesity treatment

TRL: Biotechnology

Intellectual Property:

Provisional-Patent, 2023-08-29, United States

PCT-Patent, 2024-08-28, WO

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