ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

pubs.acs.org/acsmedchemlett

Treatment of Cancer with NAMPT Inhibitors

Ahmed F. Abdel-Magid*

Therachem Research Medilab (India) Pvt. Ltd., Jaipur, India

Title:	Novel Pyridyloxy Acetyl Tetrahydroisoquinoline Compounds Useful as NAMPT Inhibitors		
Patent Application Number:	WO 2015/054060 Al	**Publication date:**	16 April 2015
Priority Application:	EP 13382399.7	**Priority date:**	9 October 2013
Inventors:	Burkholder, T. P.; Del Prado, M. F.; Fernandez, M. C.; Heinz, L. J., II; Prieto, L.; Zhao, G.		
Assignee Company:	Eli Lilly and Company; Lilly Corporate Center, Indianapolis, Indiana 46285, USA		
Disease Area:	Cancer	**Biological Target:**	Nicotinamide phosphoribosyl transferase (NAMPT)

Summary:

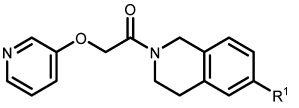
The invention in this patent application relates to pyridyloxyacetyl tetrahydroisoquinoline derivatives represented generally by formula (I). These compounds inhibit the activity of nicotinamide phosphoribosyl transferase (NAMPT) and may potentially provide a useful treatment for several forms of cancer.

Nicotinamide adenine dinucleotide (NAD) is a coenzyme that is involved in cellular redox reactions. It exists in two forms, the oxidized (NAD^+) and reduced (NADH) forms. NAD^+ is essential for metabolism, energy production, DNA repair, and signaling in many types of cancer cells. The biosynthesis of NAD is achieved from nicotinamide, nicotinic acid, or tryptophan. The biosynthesis of NAD from nicotinamide is a major route that is referred to as the NAD salvage pathway. Nicotinamide phosphoribosyl transferase (NAMPT) catalyzes the conversion of nictotinamide to nicotinamide mononucleotide (NMN), which is the rate-limiting step in the NAD biosynthetic salvage pathway. NAMPT is essential for the biosynthesis of NAD and found to be upregulated in many cancer cells. Studies have shown that NAMPT is overexpressed in several types of tumor cells including breast cancer, gastric cancer, colorectal cancer, liver cancer, renal cancer, brain cancer, melanoma, prostate cancer, NSCLC, and others. This overexpression in cancer cells is linked to tumor progression. Thus, the inhibition of NAMPT can lead to depletion of NAD^+, which in turn inhibits the synthesis of adenosine-5′-triphosphate (ATP). This effect eventually causes the attenuation of cancer cell proliferation.

In addition to the depletion of NAD^+ in cancer cells, NAMPT inhibitors may also deplete the NAD^+ in normal cells to such low levels that can be harmful to these cells. This potential harmful side effect may be managed by implementing a corrective measure using an alternative NAD biosynthetic pathway. Nicotinic acid phosphoribosyl transferase (NAPRT) is an enzyme that is essential for the conversion of nicotinic acid to NAD. This enzyme is expressed in normal human tissues and in only some tumors. Studies have shown that the coadministration of nicotinic acid with certain NAMPT inhibitors enhances the therapeutic index of these inhibitors. The coadministration of nicotinic acid allows the continued biosynthesis of NAD^+ in normal cells through the NAPRT-mediated nicotinic acid pathway. This does not appear to affect the antitumor activity of NAMPT inhibitors on NAPRT-deficient tumor cells.

While there are several known NAMPT inhibitors, there remains a need for alternative NAMPT inhibitors such as the disclosed compounds in this patent application, which may be useful for the treatment of cancer.

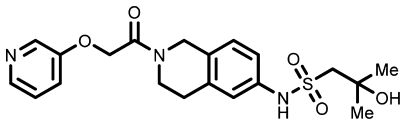
Important Compound Classes:



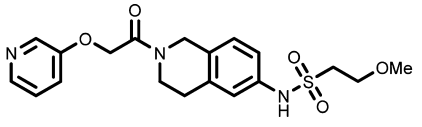
Formula (I)

Received: May 6, 2015
Published: May 13, 2015

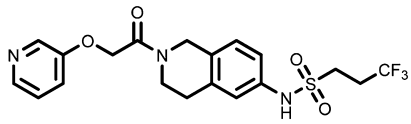
Key Structures: The inventors disclosed 20 compounds of formula (I) including the following four representative examples:



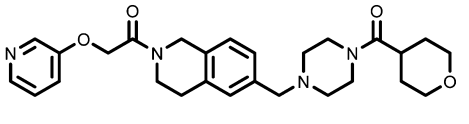
1



2



5



16

Biological Assay: The following assays were used to test the invention compounds as inhibitors of NAMPT.

- NAMPT Biochemical Assay
- Assay for NAD^+/NMN Levels in A2780 Cells
- Cell Proliferation Assay ± NA (Nicotinic Acid)
- A2780 Proliferation Assay ± NAM (Nicotinamide)
- Cell Viability Assay
- LC−MS Analysis of NAD^+ and Carbohydrate Metabolites in A2780 Cancer Cells
- IVTI Assay
- LC−MS Analysis of NAD^+ in A2780 and NCI-H1155 Tumor Xenografts
- Efficacy in Xenograft Tumor Models

Biological Data: Representative disclosed biological data for compounds **1** and **2** from two assays:

	Inhibition of NAD^+ Formation in A2780 Tumor Xenografts		Inhibition of NAD^+ Formation in NCI-H1155 Tumor Xenografts	
Treatment group	NAD levels (*pmol*/mg tissue)	Standard Error of Means (*pmol*/mg tissue)	NAD levels (*pmol*/mg tissue)	Standard Error of Means (*pmol*/mg tissue)
Vehicle	56.30	9.48	20.08	2.39
Example 1: 5 mg/kg (BID)	5.04	1.21	7.48	1.50
Example 1: 10 mg/kg (BID)	2.55	0.63	3.63	1.31
Example 1: 20 mg/kg (BID)	3.29	1.85	1.82	0.35
Vehicle	55.03	18.11	57.97	10.65
Example 2: 8 mg/kg (BID)	3.97	1.09	5.19	1.26
Example 2: 16 mg/kg (BID)	6.52	1.56	1.98	0.63
Example 2: 32 mg/kg (BID)	6.38	0.91	0.84	0.39

Recent Review Articles:

1. Montecucco, F.; Cea, M.; Bauer, I.; Soncini, D.; Caffa, I.; Lasiglie, D.; Nahimana, A.; Uccelli, A.; Bruzzone, S.; Nencioni, A. *Curr. Drug Targets* **2013**, *14* (6), 637−643.
2. Galli, U.; Travelli, C.; Massarotti, A.; Fakhfouri, G.; Rahimian, R.; Tron, G. C.; Genazzani, A. A. *J. Med. Chem.* **2013**, *56* (16), 6279−6296.
3. Galli, M.; Van Gool, F.; Rongvaux, A.; Andris, F.; Leo, O. *Cancer Res.* **2010**, *70* (1), 8−11.

AUTHOR INFORMATION

Corresponding Author

*Address: 1383 Jasper Drive, Ambler, Pennsylvania 19002, United States. Tel: 215-913-7202. E-mail: afmagid@comcast.net.

Notes

The authors declare no competing financial interest.