# Enhanced Cell-potent Inhibitors for NTMT1/2 for Treating Cancers

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**Categories:**
- Biotechnology

**Keywords:**
- Biotechnology
- Cell-potent Inhibitor
- NTMT1/2
- Peptidomimetic inhibitor
- Selective

NCS: Researchers at Purdue University have designed a series of new peptidomimetic inhibitors for protein alpha-N-terminal methyltransferases (NTMTs). NTMTs recognize a unique N-terminal of a protein and catalyze the addition of 1-3 methyl group(s) to it. The exact role and function of NTMTs is unknown, but NTMT1 plays an important role in mitosis, DNA damage repair, stem cell maintenance, glioblastoma, and cervical cell proliferation and migration. NTMT1 is a potential anti-cancer target as it is overexpressed in several cancers such as gastrointestinal, colorectal and melanoma. To improve the cellular inhibition activity of previously invented peptidomimetic inhibitors, the Purdue researchers designed several cell-potent peptidomimetic inhibitors of N-terminal methylation. These inhibitors displayed not only increased cellular inhibition, but they were also optimized for increased hydrophobicity which co-relates with increased cell permeability. The most potent inhibitor (IC50 = 0.9 uM) exhibited over 2-fold increased inhibition on cellular N-terminal methylation levels with a cellular IC50 value of ~50 µM compared to previously reported peptidomimetic inhibitors of NTMT1. It also exhibited over 300-fold selectivity to several other methyltransferases. These cell-potent inhibitors serve as valuable tools to study the function and role of NTMTs and the alpha-N-terminal methylation pathway in cancer and stem cell maintenance.

Technology Validation: In vitro cytotoxicity studies were conducted in normal and NTMT1 knock-out HCT116 cells.

Related Publications:

G Dong, ID Iyamu, JZ Vilseck, D Chen, R Huang. (2022) Improved Cell-Potent and Selective Peptidomimetic Inhibitors of Protein N-Terminal Methyltransferase 1. Molecules, 27, 1381.

https://www.mdpi.com/1420-3049/27/4/1381

Chen D, Dong G, Deng Y, Noinaj N, Huang R. (2021) Structure-based Discovery of Cell-potent Peptidomimetic Inhibitors for Protein N-terminal Methyltransferase 1. ACS Medicinal Chemistry Letters. 12, 485-493. https://pubs.acs.org/doi/full/10.1021/acsmedchemlett.1c00012

Mackie BD, Chen D, Dong G, Dong C, Parker H, Schaner Tooley C, Noinaj N, Min J, Huang R. (2020) Selective Peptidomimetic Inhibitors of NTMT1/2: Rational design, synthesis, characterization, and crystallographic studies. Journal of Medicinal Chemistry. 63, 9512-9522. PMID: 32689795. PMCID: PMC74286280. https://pubs.acs.org/doi/10.1021/acs.jmedchem.0c00689

Advantages

- Fully characterized in biochemical and biophysical methods
- highly effective inhibition of N-terminal methylation
- high selectivity to a panel of methyltransferases

Applications

- novel cancer treatment for cervical cancer and glioblastoma
- stem cell therapy
- studying NTMTs and the alpha-N-terminal methylation pathway

**People:**

- Huang, Rong (Project leader)
- Chen, Dongxing
- Dong, Guangping

**Intellectual Property:**

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