TP-040: A Chemical Probe for OGA

Version 1.0 (19th October 2021)

Web link for more details: https://www.sgc-ffm.uni-frankfurt.de/#!specificprobeoverview/TP-040

Overview

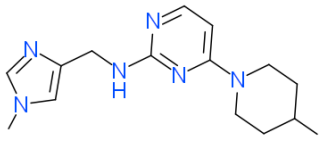
OGA, a member of the family of hexosaminidases, catalyzes the removal of the O-GlcNAc post-translational modification from serine and threonine. OGA activity is the highest at neutral pH and it localizes mainly to the cytosol. OGlcNAc plays an important role in the aggregation of the tau protein as found in neurodegenerative disorders, such as Alzheimer's disease, Pick's disease, and Parkinson's disease. O-GlcNAcylated tau protein displays improved stability and solubility compared with its unmodified state, which in turn leads to a suppression of the aggregation of the tau protein. Therefore, inhibition of OGA may prevent the formation of aggregations.

Summary

Chemical Probe Name	TP-040
Negative control compound	TP-040n
Target(s) (synonyms)	OGA (O-GlcNAcase, Nuclear cytoplasmic O-GlcNAcase and acetyltransferase, NCOAT, HEXC, MGEA5, MEA5)
Recommended *in vitro* assay concentration	Use at concentration up to 10 µM for TP-040 and TP-040n; use with control and orthogonal probe for best interpretation of data
Suitability for *in* vivo use and recommended dose	Tested in mice with 30 mg/kg (oral dose); shows a good pharmacokinetic profile with brain penetration. The *in vivo* efficacy was not tested.
Publications	PMID: 33404239
Orthogonal chemical probes	JNJ-65355394
In vitro assay(s) used to characterise	Human OGA enzymatic assay
Cellular assay(s) for target-engagement	Glycosylation in-cell western assay

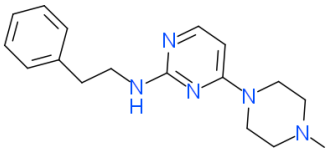
Chemical Probe & Negative Control Structures and Use

TP-040 Chemical Probe



SMILES: CC1CCN(CC1)c1ccnc(NCc2cn(C)cn2)n1
InChiKey: PWKAYICUBVNJAZ-UHFFFAOYSA-N
Molecular weight: 286.19 g/mol
Storage: As a dry powder or as DMSO stock solutions (10 mM) at -20 °C. DMSO stocks beyond 3-6 months or 2 freeze/thaw cycles should be tested for activity before use
Dissolution: Soluble in DMSO up to 10 mM; use only 1 freeze/thaw cycle per aliquot

TP-040n Negative Control



SMILES: CN1CCN(CC1)c1ccnc(NCCc2ccccc2)n1
InChiKey: BNXNWRSVYQHTOH-UHFFFAOYSA-N
Molecular weight: 297.2 g/mol
Storage: As a dry powder or as DMSO stock solutions (10 mM) at -20 °C. DMSO stocks beyond 3-6 months or 2 freeze/thaw cycles should be tested for activity before use
Dissolution: Soluble in DMSO up to 10 mM; use only 1 freeze/thaw cycle per aliquot

Chemical Probe Profile

In vitro Potency & Selectivity:

TP-040 shows potent activity on OGA (IC_{50} = 46 nM) and no activity on HEXB (IC_{50} > 10 µM; > 210-fold). All 277 kinases tested at 1 µM show < 50 % inhibition.

Potency in Cells and Cellular Target Engagement:

The EC_{50} was 450 nM for the increase in the level of O-GlcNAcylated protein in human neuroblastoma SH-SY5Y cells.