

BAY-277: A Chemical Probe for METAP2

Version 1.0 (10th January 2024)

Web link for more details: <https://www.sgc-ffm.uni-frankfurt.de/#!/specificprobeoverview/BAY-277>

Overview

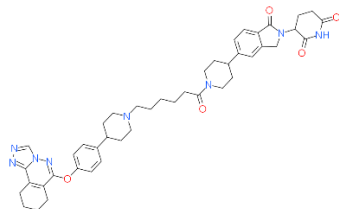
METAP2 catalyzes the hydrolytic cleavage of initiator methionine from newly synthesized peptides and protects the alpha subunit of eukaryotic initiation factor 2 from inhibitory phosphorylation. METAP2 is overexpressed across various types of cancer and KO/KD results in anti-angiogenesis and direct tumor growth inhibition.

Summary

Chemical Probe Name	BAY-277 (degrader)
Negative control compound	BAY-8805 (BAY-896 additional control inhibitor)
Target(s) (synonyms)	METAP2 (Methionyl Aminopeptidase 2)
Recommended <i>in vitro</i> assay concentration	Use at concentration of 100 nM for BAY-277 and BAY-8805; use with negative control and the additional control inhibitor BAY-896 for best interpretation of data
Suitability for <i>in vivo</i> use and recommended dose	Tested in mice with 5- 25 mg/kg IP for 14 days q2d with good tolerability
Publications	None at time of writing
<i>In vitro</i> assay(s) used to characterise	METAP2 biochemical assay
Cellular assay(s) for target-engagement	Degradation in HT1080 cells (Capillary electrophoresis (CE)) and in HUVEC cells (Western Blot (WB)), 2D HUVEC cells proliferation

Chemical Probe & Negative Control Structures and Use

BAY-277 Chemical Probe



SMILES:

C(CCC(N1CCC(CC1)c1ccc2C(N(Cc2c1)C1CCC(NC1=O)=O)=O)CCN1CCC(CC1)c1ccc(cc1)OC1C2CCCC=2c2nncn2N=1

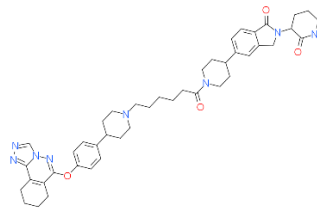
InChiKey: HLNCBKSDCCIOPT-UHFFFAOYSA-N

Molecular weight: 772.41 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

BAY-8805 Negative Control



SMILES:

C(CCC(N1CCC(CC1)c1ccc2C(N(Cc2c1)C1CCCN1=O)=O)CCN1CCC(CC1)c1ccc(cc1)OC1C2CCCC=2c2nncn2N=1

InChiKey: LMHDKCMDVMZRMU-UHFFFAOYSA-N

Molecular weight: 758.43 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:

BAY-277 is a potent degrader for METAP2 with a IC₅₀ = 5.8 nM in a hMETAP2 biochemical assay. Proteomics: MetAP2 is the only protein among ~5000 detected proteins in HUVEC cells which is highly reduced in a proteomics analysis. Closest off-targets in a Panlabs panel (76 targets) at 10 μM are [% inh.] DRD3 (90), HRH3 (81), ADRA2C (79). The Eurofins kinase panel at 1 μM is clean (25 kinases > 10 % inh., max 29% inh.).

Potency in Cells and Cellular Target Engagement:

DC₅₀ = 8.93 nM for the degradation in HT1080 cells (CE), DC₅₀ = 0.2 nM for the degradation in HUVEC cells (WB) and IC₅₀ = 12 nM in the 2D HUVEC cells proliferation assay.