BAY-9835: A dual Chemical Probe for ADAMTS7, ADAMTS12

Version 1.0 (17th June 2024)

Web link for more details: https://www.sgc-ffm.uni-frankfurt.de/#!specificprobeoverview/BAY-9835

Overview

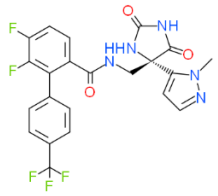
ADAMTS7 and ADAMTS12 are secreted zinc metalloprotease. ADAMTS7 shows proteolytic activity against extracellular matrix proteins (e.g. COMP, TSP1, TIMP1, LTBP4, EFEMP1). The catalytic function of ADAMTS7 is mediating plaque formation in coronary artery disease (CAD). An ADAMTS7 inhibitor might lead to reduced plaque formation in coronary artery disease and might reduce restenosis after stent placement in CAD or PAD. ADAMTS-12 performs essential roles in modulation and recovery from inflammatory processes such as colitis, endotoxic sepsis and pancreatitis.

Summary

Chemical Probe Name	BAY-9835
Negative control compound	BAY-1880
Target(s) (synonyms)	ADAMTS7 (COMPase), ADAMTS12
Recommended *in vitro* assay concentration	Use at concentration of 100 nM for BAY-9835 and BAY-1880; use with negative control for best interpretation of data
Suitability for *in* vivo use and recommended dose	Tested in vivo with mice and rats (30 mg/kg p.o. once daily)
Publications	PMID: 38348661(Compound 32)
In vitro assay(s) used to characterise	Biochemical enzymatic assay
Cellular assay(s) for target-engagement	Fibulin-3 cellular cleavage assay

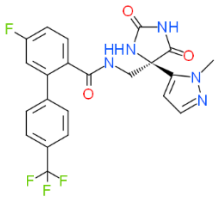
Chemical Probe & Negative Control Structures and Use

BAY-9835 Chemical Probe



SMILES:Cn1c(ccn1)[C@@]1(CNC(c2ccc(c(c2c2ccc(cc2)C(F)(F)F)F)F)=O)C(NC(N1)=O)=O
InChiKey: LPQXZOJIUVOCAL-NRFANRHFSA-N
Molecular weight: 493.12 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-1880 Negative Control



SMILES:Cn1c(ccn1)[C@]1(CNC(c2ccc(cc2c2ccc(cc2)C(F)(F)F)F)=O)C(NC(N1)=O)=O
InChiKey: QUNSQTFKUUXCCS-OAQYLSRUSA-N
Molecular weight: 475.13 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-9835 is a potent inhibitor of ADAMTS7 and ADAMTS12 in a biochemical enzymatic assay with IC_{50}= 6nM for hADAMTS7 and 30 nM for ADAMTS12. The protease panel is clean with the closest off-targets hADAM8 (IC_{50} = 2.25 µM) and hADAMTS4 (IC_{50} = 6.726 µM). The Eurofins Panlabs panel with 77 targets at 10 µM is clean. All 12 targets of the in-house kinase panel have an IC_{50} > 20 µM.

Potency in Cells and Cellular Target Engagement:

In the Fibulin-3 cellular cleavage assay a close analogue of BAY-9835, Cpd 29, significantly inhibits mADAMTS7 at 100 nM.