BI-5524: A Chemical Probe for ELANE

Version 1.0 (29th January 2024)

Web link for more details: https://www.sgc-ffm.uni-frankfurt.de/#!specificprobeoverview/BI-5524

Overview

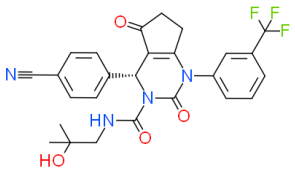
ELANE is a serine protease, which is expressed in bone marrow precursor cells and stored in the granules of peripheral blood neutrophils at high concentrations. Upon neutrophil activation, neutrophil elastase is secreted causing degradation of the extracellular matrix components, like elastin, fibronectin, laminin, collagen and proteoglycans. It also plays a role in the activation of proinflammatory pathways. ELANE function is required for microbial clearance and an appropriate innate immune response. ELANE dysregulation is implicated to play a role in chronic inflammatory and fibrotic diseases in different organs.

Summary

Chemical Probe Name	BI-5524
Negative control compound	BI-5525
Target(s) (synonyms)	ELANE (Elastase)
Recommended concentration for cellular use	Use at concentration 100 nM for BI-5524 and BI-5525; use with control and orthogonal probe for best interpretation of data
Suitability for *in* vivo use and recommended dose	Tested in mouse and rat with with 1-10 µM/kg
Publications	None at time of publication
Orthogonal chemical probes	BAY-678
In vitro assay(s) used to characterise	Human ELANE inhibitor assay
Cellular assay(s) for target-engagement	Inhibition of zymosan-stimulated ELANE activity in human plasma

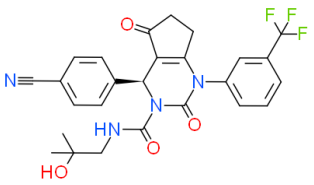
Chemical Probe & Negative Control Structures and Use

BI-5524 Chemical Probe



SMILES: CC(C)(CNC(N1C(N(C2CCC(C=2[C@H]1c1ccc(C#N)cc1)=O)c1cccc(c1)C(F)(F)F)=O)=O)O
InChiKey: DOVSNSDMRJVTMR-JOCHJYFZSA-N
Molecular weight: 512.17 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

BI-5525 Negative Control



SMILES: CC(C)(CNC(N1C(N(C2CCC(C=2[C@@H]1c1ccc(C#N)cc1)=O)c1cccc(c1)C(F)(F)F)=O)=O)O
InChiKey: DOVSNSDMRJVTMR-QFIPXVFZSA-N
Molecular weight: 512.17 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
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Chemical Probe Profile

In vitro Potency & Selectivity:

BI-3812 shows potent activity on human ELANE with IC_{50} = 0.5 nM in an inhibitor assay. Highly selective against closely related proteases: PRTN3 (IC_{50} = 367 nM) and CTSG (IC_{50} >10 µM). The Reaction Biology protease panel with 43 targets at 1 µM is clean. The Eurofins Cerep screen with 81 targets at 10 µM is clean.

Potency in Cells and Cellular Target Engagement:

The zymosan-stimulated ELANE activity in human plasma is inhibited with an IC_{50} =1.2 nM.