

BI-1915: A Chemical Probe for CTSS

Version 1.0 (17th June 2024)

Web link for more details: <https://www.sgc-ffm.uni-frankfurt.de/#!specificprobeoverview/BI-1915>

Overview

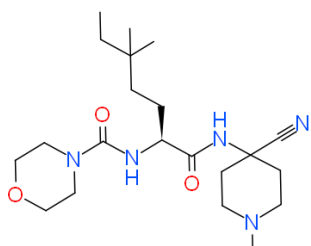
CTSS is a member of the peptidase C1 family of cysteine cathepsins. It plays a pivotal role in antigen processing and presentation, which are important processes in normal immune responses and autoimmunity. Its inhibition is expected to result in immunosuppression, making this enzyme an attractive target to potentially treat autoimmune and inflammatory diseases.

Summary

Chemical Probe Name	BI-1915
Negative control compound	BI-1920
Target(s) (synonyms)	CTSS (Cathepsin S)
Recommended <i>in vitro</i> assay concentration	Use at concentration of 1 μ M for BI-1915 and BI-1920; use with control for best interpretation of data
Suitability for <i>in vivo</i> use and recommended dose	Not for <i>in vivo</i> use.
Publications	PMID: 23084902 (Compound 2)
<i>In vitro</i> assay(s) used to characterise	SPR, luminescent based enzymatic assay
Cellular assay(s) for target-engagement	Antigen challenge cell assay

Chemical Probe & Negative Control Structures and Use

BI-1915 Chemical Probe



SMILES: CCC(C)(C)CC[C@@H](C(NC1(CCN(C)CC1)C#N)=O)NC(N1CCOCC1)=O

InChiKey: SYRVEVZSXHRXIX-KRWDZBQOSA-N

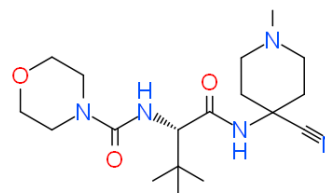
Molecular weight: 407.29 g/mol

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-1920 Negative Control



SMILES: CC(C)(C)[C@H](C(NC1(CCN(C)CC1)C#N)=O)NC(N1CCOCC1)=O

InChiKey: ZJHRAJHJNQDON-CQSZACIVSA-N

Molecular weight: 365.24 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:

BI-1915 shows potent activity on human CTSS with $K_d = 31$ nM (SPR) and inhibits CTSS in a luminescent based enzymatic assay with $IC_{50} = 17$ nM. Highly selective against closely related proteases (IC_{50} [μ M]): CTSK (> 10), CTSL (> 30), CTSB (> 10). The Reaction Biology protease panel with 43 targets at 10 μ M is clean, except for papain (87% inhibition). The Eurofins Cerep SafetyScreen44 at 10 μ M is clean.

Potency in Cells and Cellular Target Engagement:

In an Antigen challenge cell assay which is based on the use of B cells to 'present' exogenous antigen, i.e. added ovalbumin, via a cathepsin S dependent process to T cells, $IC_{50} = 2.8$ nM. BI-1915 effectively blocks the specific secretion of ovalbumin-induced IL-2 in T-cells.