

Cathepsin S inhibitor

BI-1915

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Summary

BI-1915 is a highly potent inhibitor of Cathepsin S (IC_{50} 17 nM) with excellent selectivity against related cathepsins and is therefore a valuable tool for *in vitro* experiments.

Chemical Structure

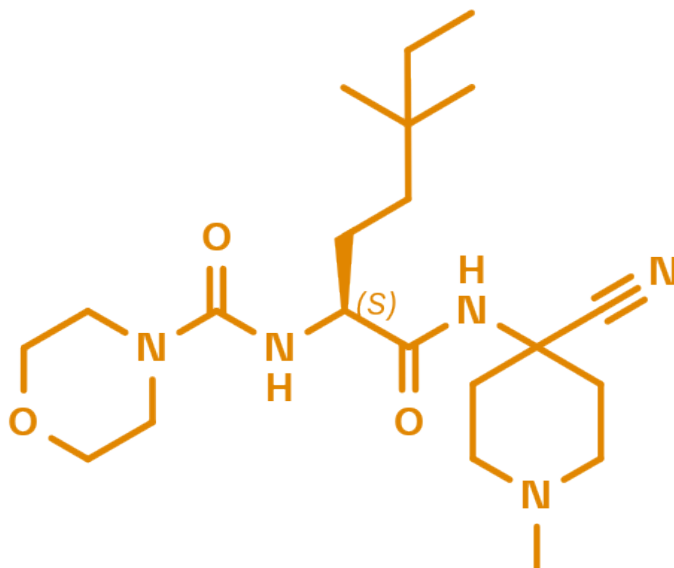


Figure 1: 2D structures of BI-1915

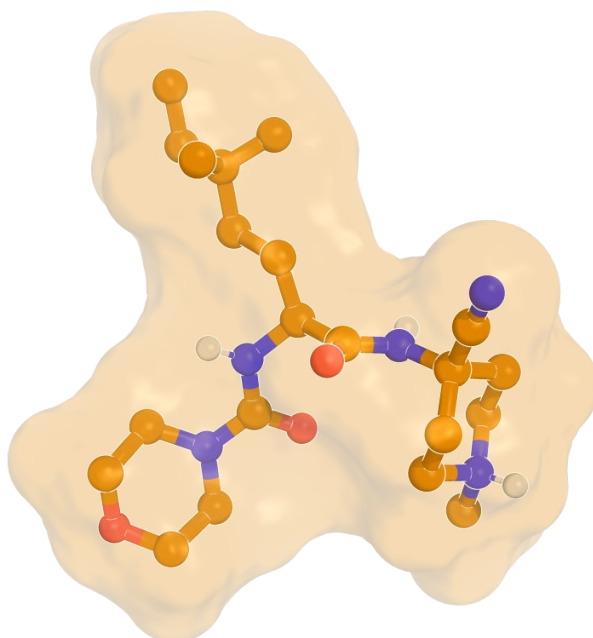


Figure 2: 3D structures of BI-1915

Highlights

BI-1915 is a highly potent inhibitor of Cathepsin S (CatS) ($IC_{50} = 17$ nM). It shows excellent selectivity against related cathepsins (> 500-fold). BI-1915 was shown to effectively block the specific secretion of ovalbumin-induced IL-2 in T-cells. This compound is suitable for in vitro experiments.

Target information

Cathepsin S is a 24 kD lysosomal cysteine protease that plays a pivotal role in antigen processing and presentation, which are important processes in normal immune responses and autoimmunity.

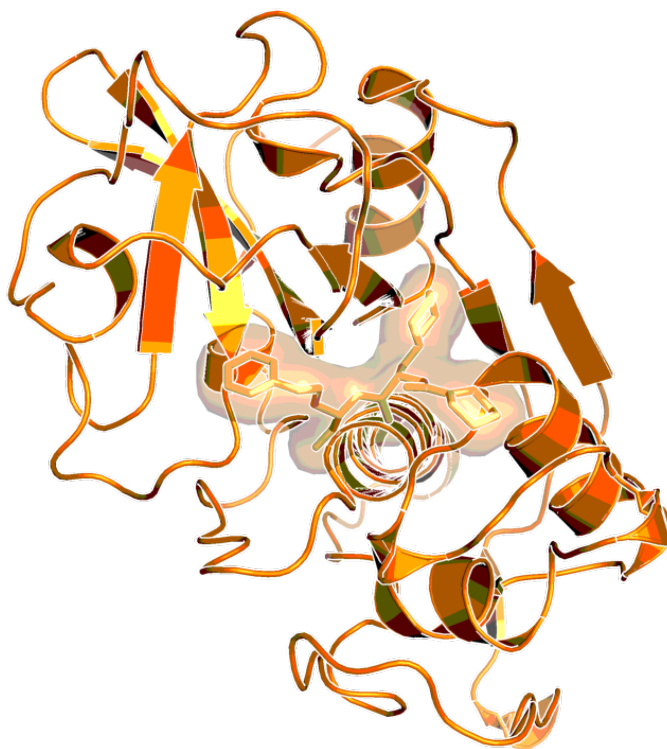


Figure 3: Human Cathepsin S in complex with an analog of BI-1915 (PDB Code: 2R9M)¹

In vitro activity

The *in vitro* suitable molecule BI-1915 and the *in vivo* ready compound BI-1124 are both highly potent inhibitors of Cathepsin S with IC₅₀ values of 17 nM and 7 nM, respectively. BI-1920 does not inhibit Cathepsin S (IC₅₀ > 20 μM) and can serve as a structurally related negative control for *in vitro* experiments.

Both tools effectively block the specific ovalbumin induced IL-2 secretion in T-cells with EC₅₀ values of 2.8 nM and 0.5 nM, respectively. Furthermore, BI-1124 has a superior PK profile and showed dose-dependent inhibition of the ovalbumin induced IL-2 secretion in a T cell receptor transgenic DO11 mouse model with and IC₅₀ of 0.3 mg/kg.

In vitro compound BI-1915 shows excellent selectivity (>500 fold) against related cathepsins with IC₅₀ values of >10 μM (Cat K and Cat B) and >30 μM (Cat L), and BI-1124 also shows good selectivity (>40 fold) against Cat K, B, and L.

PROBE NAMES / NEGATIVE CONTROL	BI-1915 (IN VITRO MOLECULE)	BI-1124 (IN VIVO MOLECULE)	BI-1920 (NEGATIVE CONTROL)
MW [Da, free base] ^a	407.6	407.6	365.5
Binding to Cathepsin S (K _D) [μM] ^c	0.031	0.009	272
Inhibition of Cathepsin S (IC ₅₀) [μM] ^c	0.017	0.007	>20
Antigen challenge cell assay (IC ₅₀) [nM] ^d	2.8	0.5	n.a.
Cathepsin L IC ₅₀ [μM]	>30	0.29	n.a.
Cathepsin K IC ₅₀ [μM]	>10	0.35	n.a.
Cathepsin B IC ₅₀ [μM]	>10	6.8	n.a.

^a For the salt form you will get, please refer to the label on the vial and for the molecular weight of the salt, please refer to the FAQs

^b Determined by SPR.

^c For assay conditions see reference 7, supplementary data.

In vitro DMPK and CMC parameters

PROBE NAME / NEGATIVE CONTROL	BI-1915 (IN VITRO MOLECULE)	BI-1124 (IN VIVO MOLECULE)	BI-1920 (NEGATIVE CONTROL)
logD @ pH 11	1.8	n.a.	n.a.
Solubility @ pH 7.4 [$\mu\text{g/mL}$]	1.7	>0.3	n.a.
Caco-2 permeability AB @ pH 7.4 [$\cdot 10^{-6} \text{ cm/s}$]	1.7	0.7	n.a.
Caco-2 efflux ratio	4.1	16.2	n.a.
Microsomal stability (human/mouse/rat) [% Q _H]	60 / 72 / 31	<24 / n.a. / n.a.	<11 / n.a. / n.a.
Plasma Protein Binding (human) [%]	26	n.a.	n.a.
hERG IC ₅₀ [μM]	>300	n.a.	n.a.
CYP 3A4 (IC ₅₀) [μM]	n.a.	>50	n.a.
CYP 2C9 (IC ₅₀) [μM]	n.a.	>50	n.a.
CYP 2D6 (IC ₅₀) [μM]	n.a.	>50	n.a.

Negative control

BI-1920 offered as negative control with low binding affinity to Cathepsin S (K_D 270 μM) and an IC₅₀ for the inhibition of Cathepsin S of >20 μM .

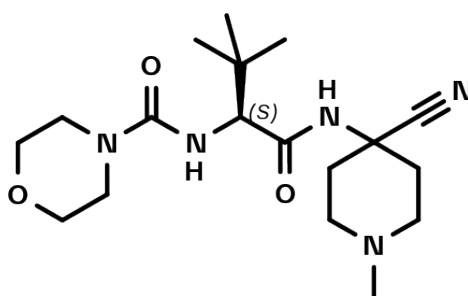


Figure 4: BI-1920 which serves as a negative control

Selectivity

The *in vitro* tool BI-1915 shows excellent selectivity (>500 fold) against related cathepsins with IC₅₀ values of >10 µM (Cat K and Cat B) and >30 µM (Cat L).

SELECTIVITY DATA AVAILABLE	BI-1915	BI-1920
SafetyScreen44™ with kind support of 	Yes	Yes
Invitrogen®	No	No
DiscoverX®	No	No
Dundee	No	No

Co-crystal structure of the Boehringer Ingelheim probe compound and the target protein.

The X-ray crystal structure of Cathepsin S in complex with an analog of BI-1915 is available (PDB code: 2R9O, Reference 1).

Reference molecule(s)

See reference 6.

Supplementary data

Selectivity data can be downloaded free of charge from [openMe](#).

References

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