

Cathepsin S inhibitor

BI-1124

Table of contents

Summary.....	2
Chemical Structure.....	2
Highlights	3
Target information.....	3
<i>In vitro</i> activity.....	4
<i>In vitro</i> DMPK and CMC parameters	4
<i>In vivo</i> DMPK parameters	5
<i>In vivo</i> pharmacology.....	5
Negative control.....	6
Selectivity	6
Co-crystal structure of the Boehringer Ingelheim probe compound and the target protein.....	6
Reference molecule(s).....	6
Supplementary data.....	7
References.....	7

Summary

BI-1124 is a highly potent inhibitor of the lysosomal cysteine protease Cathepsin S (IC_{50} 7 nM) with a superior pharmacokinetic profile and good selectivity against Cat K, B, and L. It is suitable for *in vivo* use.

Chemical Structure

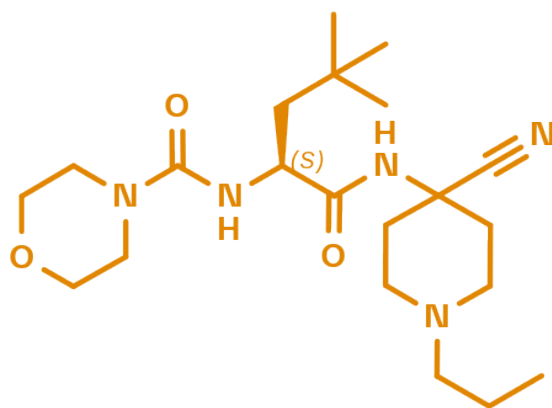


Figure 1: 2D structures of BI-1124

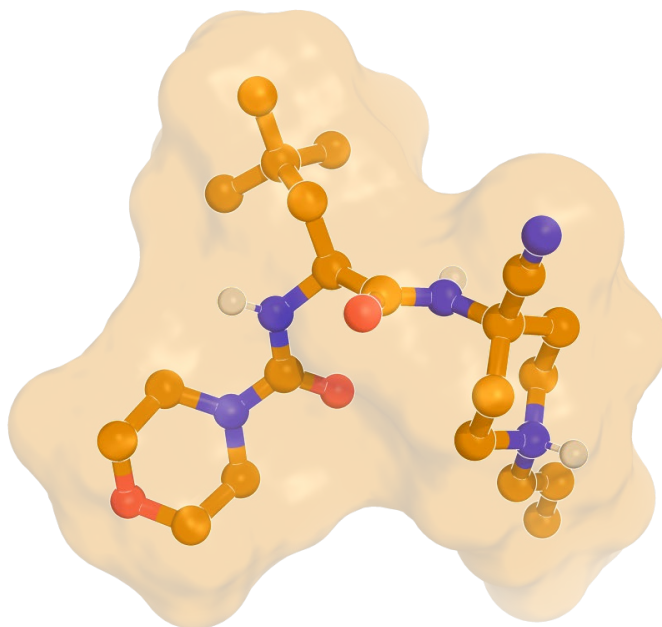


Figure 2: 3D structures of BI-1124

Highlights

BI-1124 is a highly potent inhibitor of the lysosomal cysteine protease Cathepsin S ($IC_{50} = 7$ nM). It shows good selectivity against the related cathepsins K, B and L (> 40-fold). BI-1124 has a PK profile superior to BI-1915 and shows effective dose-dependent inhibition of the specific secretion of ovalbumin-induced IL-2 in T-cells. This compound is suitable for *in vivo* studies.

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.

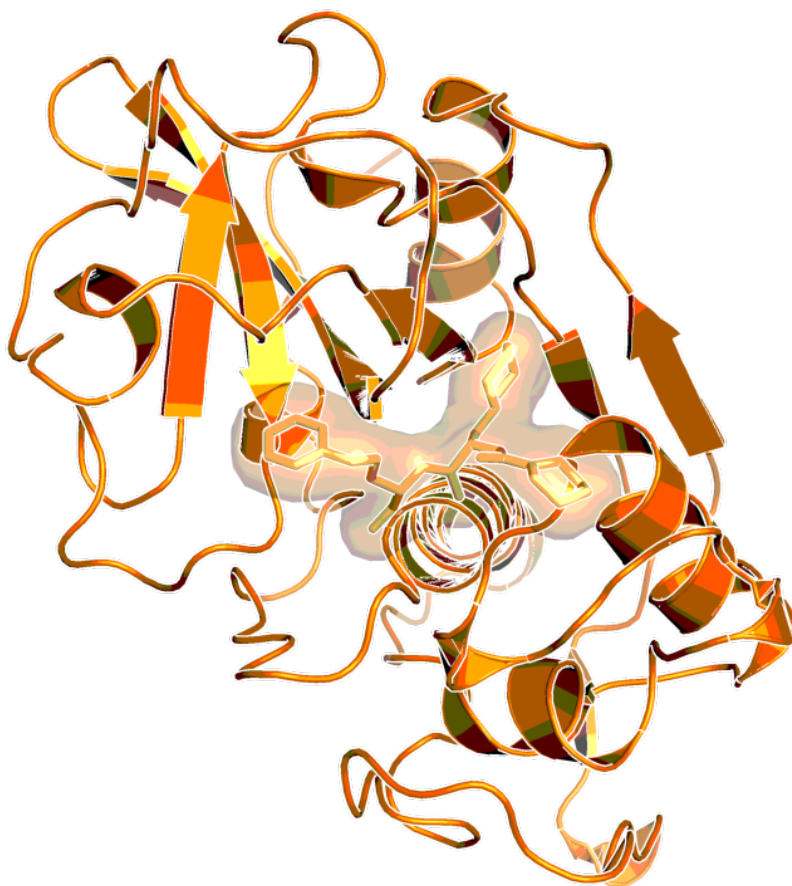


Figure 3: Human Cathepsin S in complex with an analog of BI-1124 (PDB Code: 2R9M)¹

In vitro activity

The *in vitro* molecule BI-1915 and the *in vivo* 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 molecules effectively block the specific ovalbumin induced IL-2 secretion in T-cells with EC₅₀ values of 2.8 nM and 0.5 nM, respectively.

PROBE NAME / 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] ^b	0.031	0.009	272
Inhibition of Cathepsin S (IC ₅₀) [μM] ^c	0.017	0.007	>20
Antigen challenge cell assay (EC ₅₀) [nM] ^c	2.8	0.5	n.a.
Cathepsin L IC ₅₀ [μM] ^c	>30	0.29	n.a.
Cathepsin K IC ₅₀ [μM] ^c	>10	0.35	n.a.
Cathepsin B IC ₅₀ [μM] ^c	>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	2.5	1.0
Solubility @ pH 7.4 [μg/mL]	1.7	77.6	n.a.
Caco-2 permeability AB @ pH 7.4 [$\times 10^{-6}$ 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 / 83 / 43	<24 / 52 / <22	n.a. / 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]	>50	>50	n.a.
CYP 2C8 (IC ₅₀) [μM]	>50	>50	n.a.
CYP 2C9 (IC ₅₀) [μM]	>50	>50	n.a.
CYP 2C19 (IC ₅₀) [μM]	>50	>50	n.a.
CYP 2D6 (IC ₅₀) [μM]	>50	>50	n.a.

In vivo DMPK parameters

BI-1124	Mouse
Clearance [%Q _H] ^a	55
Mean residence time after <i>i.v.</i> dose [h] ^a	1.3
V _{ss} [L/kg] ^a	3.8
C _{max} [nM] ^b	370
F [%]	79

^a *i.v.* dose: 0.4 mg/kg

^b *p.o.* dose: 1.0 mg/kg

In vivo pharmacology

BI-1124 was investigated in a T-cell receptor transgenic DO11 mouse model in which the compound was dosed orally followed by an *i.v.* antigen (ovalbumin) at 0.5 hour with a readout of plasma IL-2 at 3.5 hours.

BI-1124 showed dose-dependent inhibition of the ovalbumin induced IL-2 secretion with an EC₅₀ of 3 mg/kg and 0.3 mg/kg, respectively.

Negative control

BI-1920 is offered as a negative control with low binding affinity to Cathepsin S (K_D 270 μ M) and an IC_{50} for the inhibition of Cathepsin S of >20 μ M.

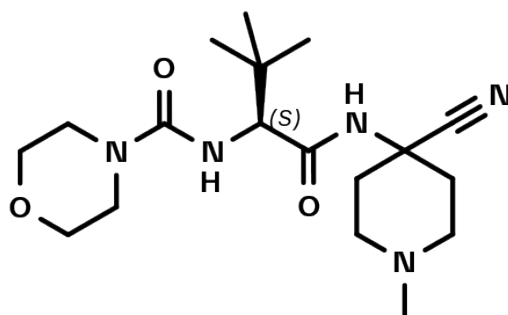


Figure 4: BI-1920 which serves as a negative control

Selectivity

The *in vivo* tool BI-1124 shows good selectivity (>40 fold) against Cat K, B and L. The *in vitro* tool BI-1915 shows excellent selectivity (>500 fold) against related cathepsins with IC_{50} values of >10 μ M (Cat K and Cat B) and >30 μ M (Cat L).

SELECTIVITY DATA AVAILABLE	BI-1124	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 [opnMe](#).

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