opnMe by Boehringer Ingelheim

Cathepsin S inhibitor

BI-1124

Boehringer Ingelheim

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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

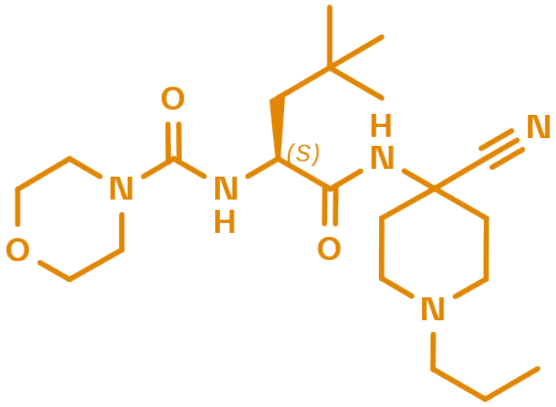

Figure 1: 2D structures of BI-1124

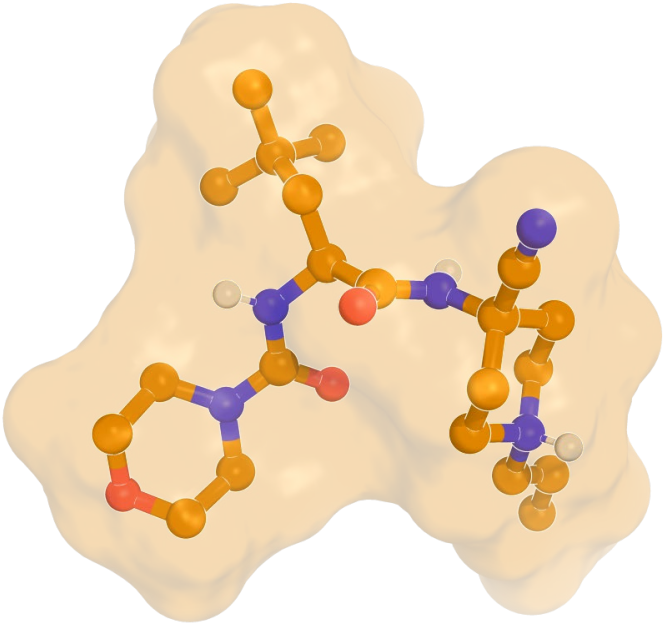

Figure 2: 3D structures of BI-1124

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.

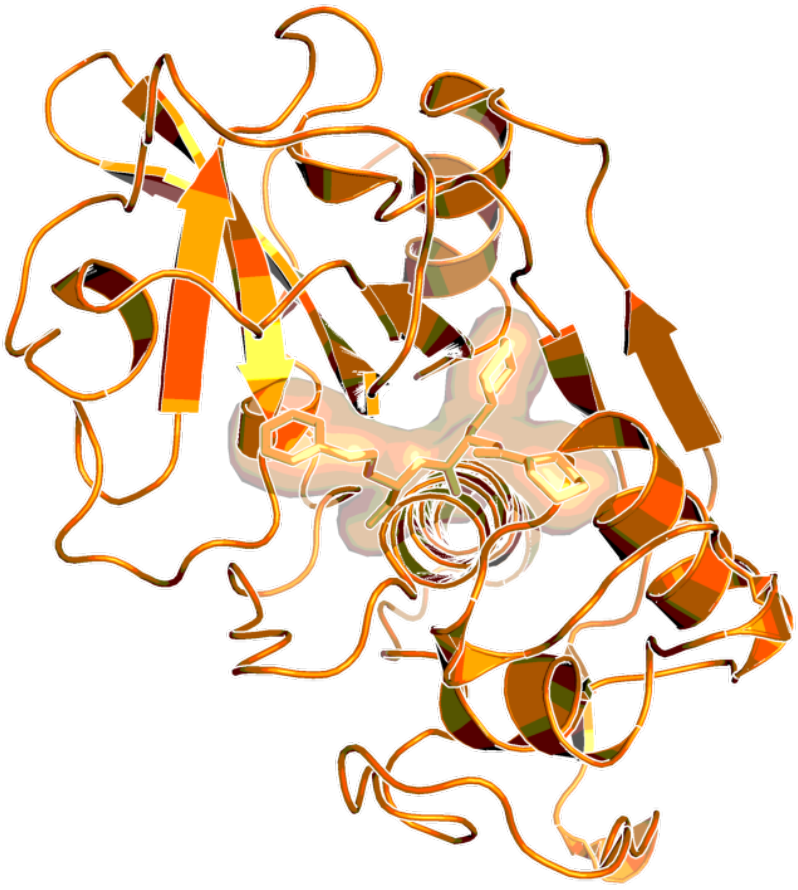

Figure 3: Human Cathepsin S in complex with an analog of BI-1124 (PDB Code: 2R9M)[1]

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 IC_{50} values of 17 nM and 7 nM, respectively. BI-1920 does not inhibit Cathepsin S (IC_{50} > 20µM) 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 EC_{50} 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.d.
Cathepsin L IC_{50} [µM][c]	>30	0.29	n.d.
Cathepsin K IC_{50} [µM][c]	>10	0.35	n.d.
Cathepsin B IC_{50} [µM][c]	>10	6.8	n.d.

[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 mg/mL	77.6	n.d.
Caco-2 permeability AB @ pH 7.4 [$*10^{-6}$ cm/s]	1.7	0.7	n.d.
Caco-2 efflux ratio	4.1	16.2	n.d.

Microsomal stability (human/mouse/rat) [% Q_H]	60 / 83 / 43	<24 / 52 / <22	n.d. / n.d. / n.d.
Plasma Protein Binding (human) [%]	26	n.d.	n.d.
hERG (IC_{50}) [µM]	>300	n.d.	n.d.
CYP 3A4 (IC_{50}) [µM]	>50	>50	n.d.
CYP 2C8 (IC_{50}) [µM]	>50	>50	n.d.
CYP 2C9 (IC_{50}) [µM]	>50	>50	n.d.
CYP 2C19 (IC_{50}) [µM]	>50	>50	n.d.
CYP 2D6 (IC_{50}) [µM]	>50	>50	n.d.

In vivo DMPK parameters

BI-1124	Mouse
Clearance [%Q_H][a]	55
Mean residence time after *i.v.* 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 EC_{50} 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 µM) and an IC_{50} for the inhibition of Cathepsin S of >20µM.

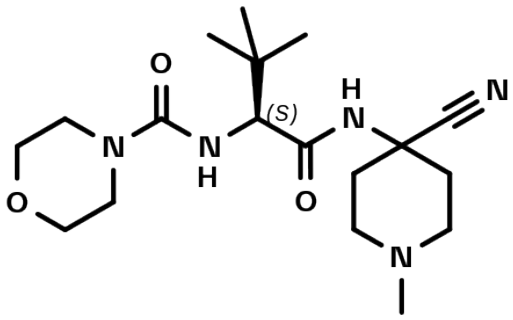

Figure 4: BI-1920 which serves as a negative control

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 µM (Cat K and Cat B) and >30 µM (Cat L).

SELECTIVITY DATA AVAILABLE	BI-1124	BI-1920
SafetyScreen44™ with kind support of eurofins	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.

References

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