Cathepsin S inhibitor | BI-1124

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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

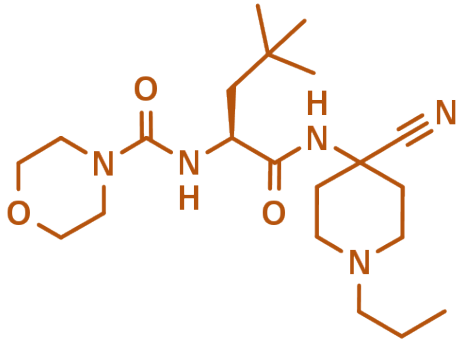

Figure 1: 2-D structures of BI-1915

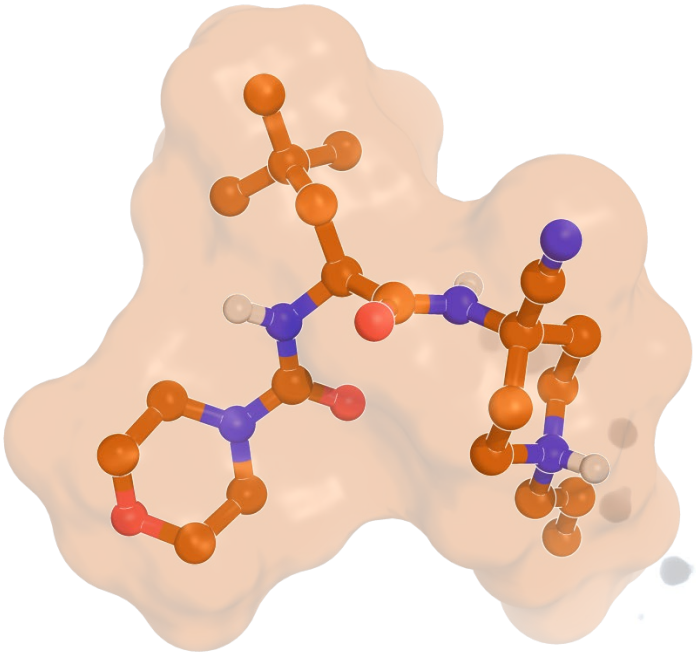

Figure 2: 3-D structures of BI-1915

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.

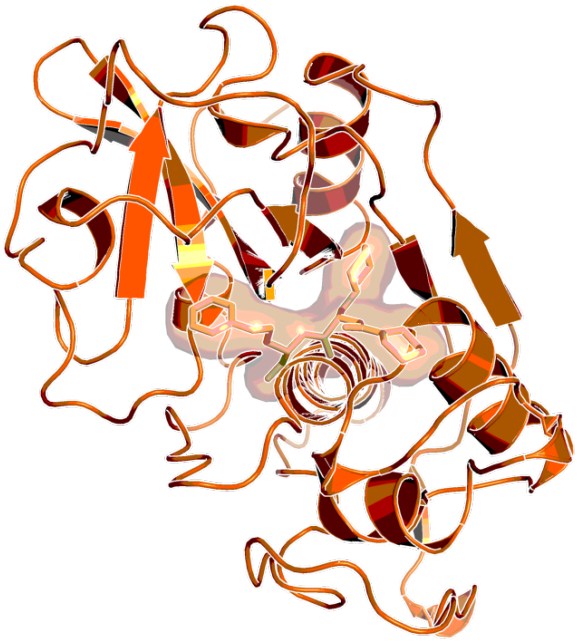

Figure 3: Human Cathepsin S in complex with an analog of BI-1124 (PDB Code 2R9M)[1]

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 NAMES / NEGATIVE CONTROL	BI-1915 (*in vitro* molecule)	BI-1124 (*in vivo* molecule)	BI-1920 (*negative control*)
MW (free base) [Da]	407.6	407.6	365.5
MW (brosylate salt) [Da][a]	644.6	644.6	602.5
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]	>30	0.29	n.d.
Cathepsin K IC_{50} [µM]	>10	0.35	n.d.
Cathepsin B IC_{50} [µM]	>10	6.8	n.d.

[a] The compounds will be delivered as the brosylate salts.

[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*)
logP	1.8	n.d.	n.d.

Solubility @ pH 7.4 [µg/ml]	1.7 mg/mL	>0.3 mg/mL	n.d.
CACO permeability @ pH7.4 [*10^{-6} cm/s]	1.7	0.7	n.d.
CACO efflux ratio	4.1	16.2	n.d.
MDCK permeability P_{app}a-b/b-a @ 1µM [10^{-6} cm/s]	n.d.	n.d.	n.d.
MDCK efflux ratio	n.d.	n.d.	n.d.
Microsomal stability (human/mouse/rat) [% Q_H]	60 / 72 / 31	<24 / n.d. / n.d.	<11/ n.d. / n.d.
Hepatocyte stability (human/mouse/rat) [% Q_H]	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]	n.d.	>50	n.d.
CYP 2C8 (IC_{50}) [µM]	n.d.	n.d.	n.d.
CYP 2C9 (IC_{50}) [µM]	n.d.	>50	n.d.
CYP 2C19 (IC_{50}) [µM]	n.d.	n.d.	n.d.
CYP 2D6 (IC_{50}) [µM]	n.d.	>50	n.d.

In vivo DMPK parameters

BI-1124	MOUSE
Clearance [%Q_H][a]	55
Mean residence time after iv dose [h][a]	1.3
Mean residence time after po dose [h][b]	3.8
V_{ss} [l/kg][a]	3.8
t_{max} [h][b]	0.7
C_{max} [nM][b]	370
F [%]	29

[a] i.v. dose 0.4 [mg/kg]

[b] p.o. dose 4.0 [mg/kg]

In vivo pharmacology

BI-1915 and BI-1124 were investigated in a T cell receptor transgenic DO11 mouse model in which the compounds were 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-1915 and 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.

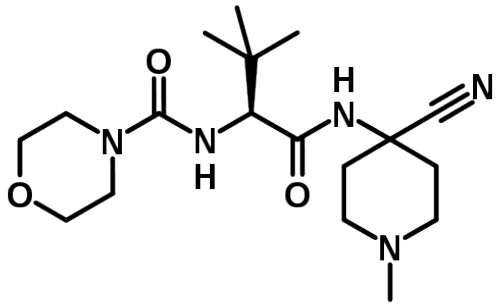

Figure 4: BI-1920 which serves as a negative control

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 Xray 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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