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

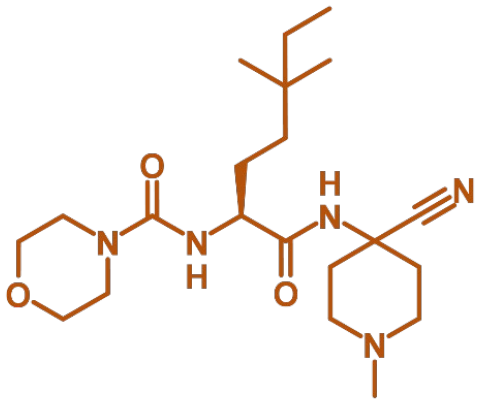

Figure 1: 2-D structures of BI-1915

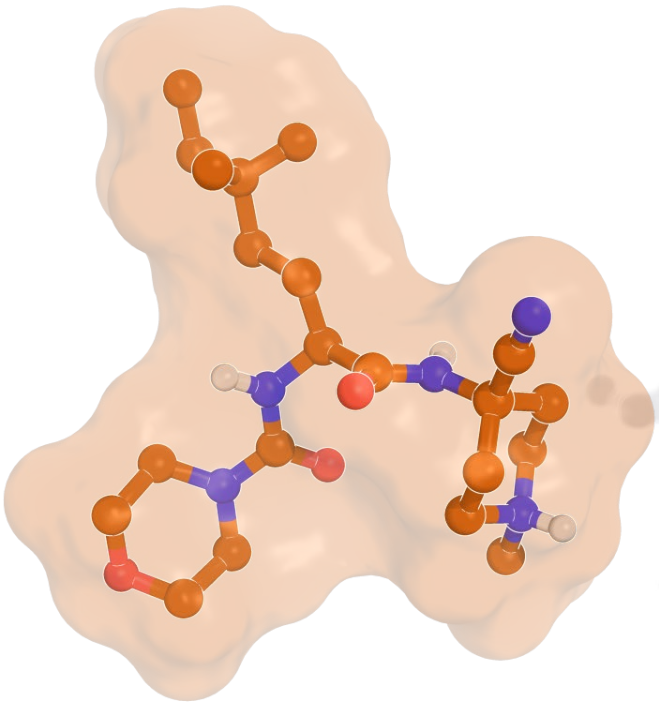

Figure 2: 3-D structures of BI-1915

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.

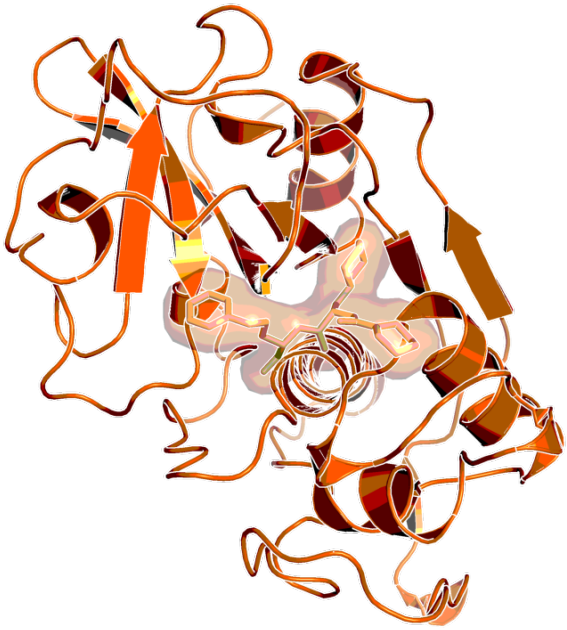

Figure 3: Human Cathepsin S in complex with an analog of BI-1915 (PDB Code 2R9M)[1]

In vitro activity

The *in vitro* 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 Cathespin S (IC_{50} > 20µM) 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 EC_{50} 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 IC_{50} of 0.3 mg/kg.

In vitro compound 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), and also the *in vivo* tool BI-1124 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 (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][b]	0.017	0.007	>20
Antigen challenge cell assay (IC_{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 @ pH 7.4 [*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.

Negative control

BI-1920 offered as 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.

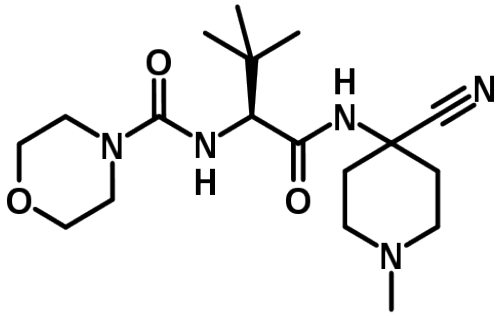

Figure 4: BI-1920 which serves as a negative control

Selectivity

SELECTIVITY DATA AVAILABLE	BI-1915	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.

References

1. Ward Y. D., David S. Thomson D. S., Frye L. L., Cywin C. H.,Morwick T., Emmanuel M. J., Zindell R., McNeil D., Bekkali Y., Hrapchak M., DeTuri M., Crane K., White D., Pav S., Wang Y., Hao M.-H., Grygon C. A., Labadia M. E., Freeman D.M., Davidson W., Hopkins J. L., Brown M. L. and Spero D. M. Design and Synthesis of Dipeptide Nitriles as Reversible and Potent Cathepsin S Inhibitors, *J. Med. Chem.* **2002**, *45*, 5471-5482. DOI: 10.1021/jm020209i, PubMed.

2. Liu W., Spero D. M. Cysteine protease cathepsin S as a key step in antigen presentation, *Drug News Perspect.* **2004**, *17*, 357-363, PubMed.

3. Desai S. N., White D. M., O'shea K. M., Brown M. L., Cywin C. L., Spero D. M., Panzenbeck M. J. An orally active reversible inhibitor of cathepsin S inhibits human trans vivo delayed-type hypersensitivity, *Eur. J. Pharmacol.* **2006**, *24*, 168-174, DOI: 10.1016/j.ejphar.2006.03.051, PubMed.

4. Bekkali Y., Thomson D. S., Betageri R., Emmanuel M. J., Hao M. H., Hickey E., Liu W., Patel U., Ward Y. D., Young E. R., Nelson R, Kukulka A., Brown M. L., Crane K., White D., Freeman D. M., Labadia M. E., Wildeson J., Spero D. M. Identification of a novel class of succinyl-nitrile-

based Cathepsin S inhibitors, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2465-2469. DOI: 10.1016/j.bmcl.2007.02.046. PubMed.

5. Gupta S., Singh R. K., Dastidar S., Ray A. Cystein cathepsin S as an immunomodulatory target: present and future trends. *Expert Opin. Ther. Targets* **2008**, *12*, 291-299. DOI: 10.1517/14728222.12.3.291. PubMed.

6. Lee-Dutra A., Wiener D. K., Sun S. Cathepsin S inhibitors: 2004 – 2010 Expert Opin Ther Pat. **2011**, *21*, 311-337. DOI: 10.1517/13543776.2011.553800, PubMed.

7. Moss N., Xiong Z., Burke M., Cogan D., Gao D.A., Haverty K., Heim-Riether A., Hickey E. R., Nagaraja R., Netherton M., O'Shea K., Ramsden P., Schwartz R., Shih D.T., Ward Y., Young E., Zhang Q. Exploration of cathepsin S inhibitors characterized by a triazole P1-P2 amide replacement. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7189-7193. DOI: 10.1021/jm060701s. PubMed.