Cathepsin C Substrate | BI-1750

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Summary

BI-1750 is a stable and highly selective intracellular substrate for the human protease Cathepsin C (CatC).

Chemical Structure

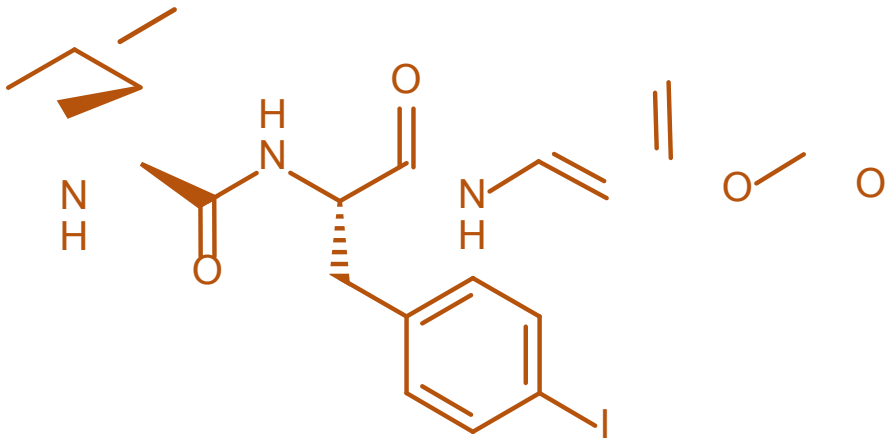

Figure 1: 2-D structure of BI-1750

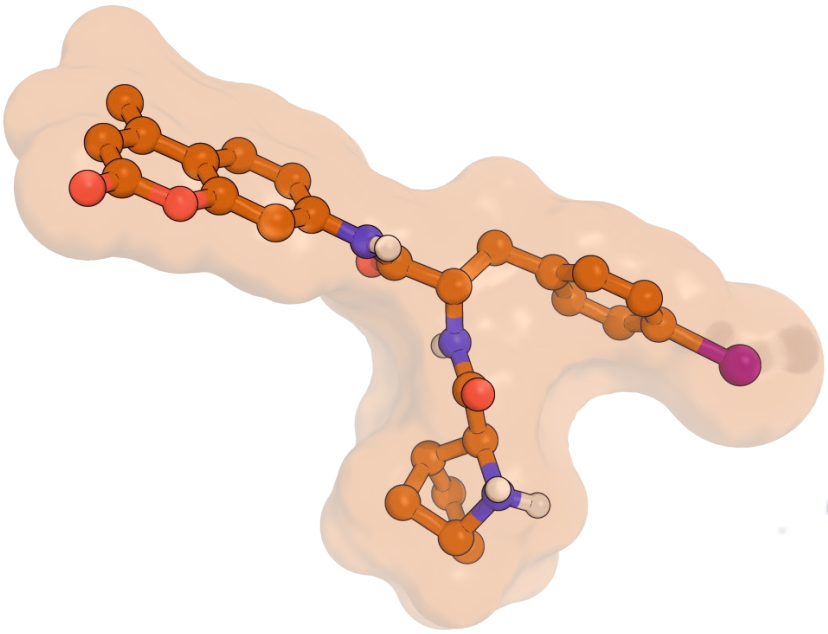

Figure 2: BI-1750, 3D conformation

Highlights

BI-1750 is a novel fluorophore substrate of the protease Cathepsin C (CatC). At 50 µM, BI-1750 is converted by CatC with a Michaelis-Menten kinetic and its highly selective versus the related proteases CatB, CatF, CatH, CatK, CatL and CatS. BI-1750 is well permeable and can be used to monitor intracellular CatC activity in human whole blood assays and other cellular systems. It can also be used to monitor intracellular CatC activity in cells from rats and minipigs.

Target information

Cathepsin C (CatC) is a lysosomal cysteine protease. It is expressed at high levels in lung, kidney, and placenta and at moderate to low levels in many other organs. Among immune/inflammatory cells, the mRNA is expressed at high levels in polymorphonuclear leukocytes and alveolar macrophages and their precursor cells[1].
In the bone marrow, CatC activates neutrophil serine proteases (NSPs) during myelopoiesis of neutrophils. Inhibition of CatC leads to a decrease in neutrophil elastase (NE), cathepsin G (CG), proteinase 3 (PR3) and NSP4 activities in circulating neutrophils[2].

In vitro activity

BI-1750 behaves like a substrate for Cathepsin C and all assays proving this behaviour are given below with different assay conditions.

PROBE NAME	BI-1750
MW [Da]	685.43
CatC (IC_{50}) [nM][a]	120,000

[a] assay conditions for CatC assay are available in the patent WO2014140075. More detailed experimental conditions can always be obtained via the "Contact us" formular.

At 50 µM, BI-1750 is enzymatically cleaved by CatC similar to the standard substrate Gly-Arg-AMC:

SUBSTRATE	VMAX [RFU/SEC]
50 µM Gly-Arg-AMC	29
50 µM BI-1750	22

BI-1750 is converted by isolated primary human neutrophils (PMN) depending on cell-number:

PMN (*1E5)	SUBSTRATE TURNOVER [RFU/30 MIN]
19.4	5,045
9.7	2,763
4.85	1,526
2.43	769
1.21	408
0.61	179
0.3	69

Turnover of BI-1750 in human whole blood: (40 µM BI-1750, 30 min incubation at 37°C)

PLASMA CONTROL [RFU, N=10]	WHOLE BLOOD [RFU, N=10]
750 +/- 32	6,449 +/- 171

In vitro DMPK and CMC parameters

No data available, this tool can be used to monitor intracellular CatC activity in human whole blood assays and other cellular systems but in *in vivo* assays.

In vivo DMPK parameters

No data available, this tool can be used to monitor intracellular CatC activity in human whole blood assays and other cellular systems but in *in vivo* assays.

Selectivity

BI-1750 is not converted by the related enzymes CatB, CatF, CatH, CatK, CatL and CatS.

ENZYME	ENZYME SPECIFIC SUBSTRATE		BI-1750
	SUBSTRATE	TURNOVER [RFU/MIN]	TURNOVER [RFU/MIN]
CatB	Z-Arg-Arg-AMC	80	0
CatF	Z-Leu-Arg-AMC	26	0
CatH	H-Arg-AMC	86	0
CatL	Z-Phe-Arg-AMC	114	0

CatK	Z-GPR-AMC	36	0
CatS	Z-Val-Val-Arg-AMC	69	0.1

BI-1750	SELECTIVITY DATA AVAILABLE
Cerep®	No
Panlabs®	No
Invitrogen®	No
DiscoverX®	No
Dundee	No

Reference molecule(s) - Inhibitors

Daniel Guay, Christian Beaulieu and David M. Percival Therapeutic Utility and Medicinal Chemistry of Cathepsin C Inhibitors *Current Topics in Medicinal Chemistry* 2010, *10*, 2010, 708-716 DOI: 10.2174/156802610791113469, PubMed

Summary

BI-1750 is a stable and highly selective intracellular substrate for the human protease Cathepsin C (CatC).[1] It can be used to monitor intracellular CatC activity in ex vivo whole blood assays or other cellular systems. This substrate works in whole blood assays from rats and minipigs as well.

References

1. Narayanam V. Rao, Gopna V. Rao and John R. Hoidal Human Dipeptidylpeptidase I Gene characterization, localization and expression *Journal of Biological Chemistry* 1997, *272*, 10260-10265 DOI: 10.1074/jbc.272.15.10260, PubMed.

2. Brice Korkmaz, Marshall S. Horwitz, Dieter E. Jenne and Francis Gauthier Neutrophil Elastase, Proteinase 3, and Cathepsin G as Therapeutic Targets in Human Diseases *Pharmcological Review* 2010, *62*, 726-759 DOI: 10.1124/pr.110.002733, PubMed