

Chymase inhibitor

BI-1942

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Summary

BI-1942 is a highly potent inhibitor of Chymase ($IC_{50} = 0.4$ nM) that can be used as tool compound to test biological hypotheses *in vitro*.

Chemical Structure

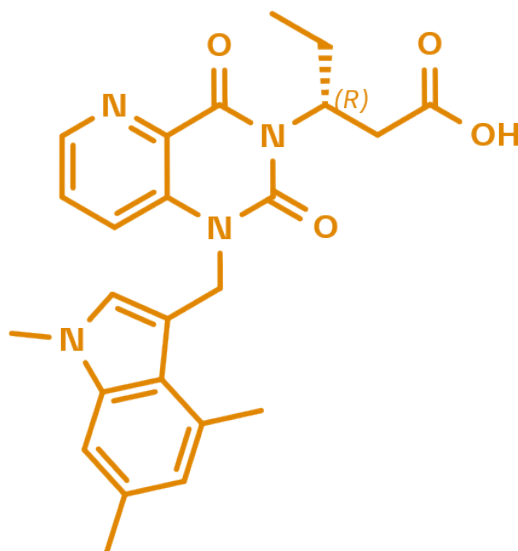


Figure 1: 2D structure of BI-1942, a Chymase inhibitor

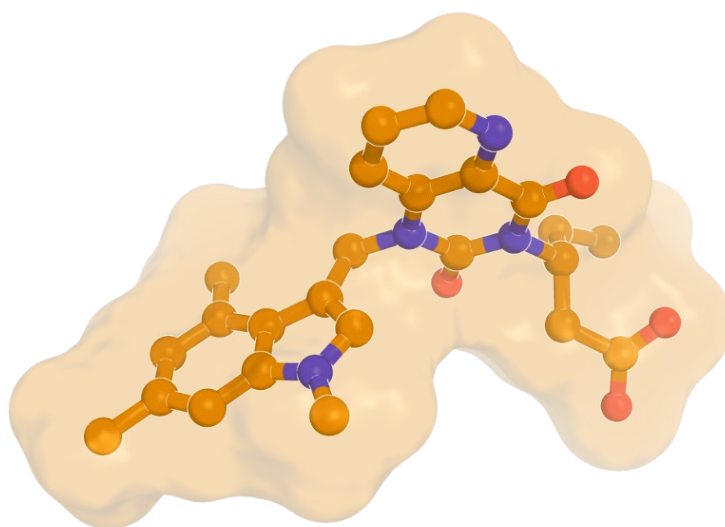


Figure 2: BI-1942, 3D conformation

Highlights

BI-1942 is a highly potent inhibitor of human chymase ($IC_{50} = 0.4 \text{ nM}$). It was tested in a panel of 37 proteases and showed more than 100-fold selectivity against Cathepsin G. This compound is a suitable tool to study the role of chymase *in vitro*. There is no available data regarding *in vivo* experiments.

Target information

Chymase plays an important and diverse role in the homeostasis for a number of cardiovascular processes and has been linked to heart failure. Chymase is a chymotrypsin-like serine protease that is stored in a latent form in the secretory granules of mast cells. Upon stimulation, it is released in its active form into the local tissue, contributing to the activation of TGF- β , matrix metalloproteases and cytokines. Cardiac chymase has been shown to be involved in the formation of angiotensin II and to play an important role in activating TGF- β 1 and IL-1 β , generating endothelin, altering apolipoprotein metabolism and degrading the extracellular matrix.

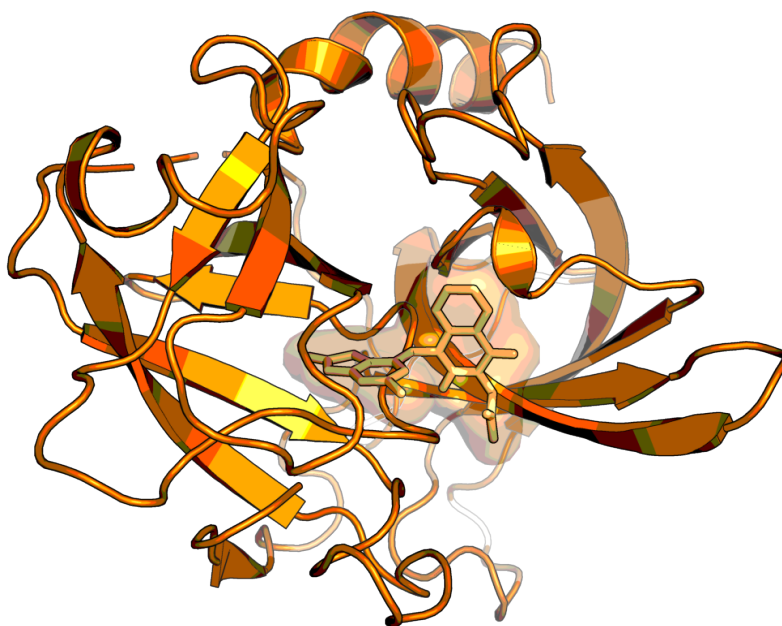


Figure 3: Chymase in complex with a close analog of BI-1942 (Boehringer Ingelheim internal structure).

In vitro activity

PROBE NAME / NEGATIVE CONTROL	BI-1942	BI-1829
MW [Da, free base] ^a	434.5	419.5
Inhibition of human chymase IC ₅₀ [nM] ^b	0.4	850

^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 For a detailed assay conditions see reference 1

In vitro DMPK and CMC parameters

PROBE NAME / NEGATIVE CONTROL	BI-1942	BI-1829
logD @ pH 11	1.4	1.4
Solubility @ pH 7.4 [µg/mL]	> 93	n.d.
Solubility @ pH 4.5 [µg/mL]	50	n.d.
Microsomal stability (human/mouse/rat) [% Q _H]	< 30	n.d.
Plasma Protein Binding (human) [%]	97.3	n.d.

Negative Control

Structurally related BI-1829 shows much weaker inhibition of human Chymase (IC₅₀ = 850 nM) and therefore is a suitable negative control for *in vitro* experiments.

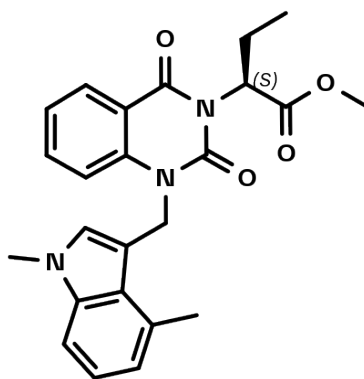



Figure 4: BI-1829 which serves as a negative control

Selectivity

BI-1942 was tested in a protease panel (37 proteases) at 10 μ M and only hit chymase and cathepsin G (inhibition or stimulation higher than 50%). BI-1942 is more than 100-fold selective against cathepsin G (IC_{50} = 110 nM)^a.

The selectivity of the compound against a selection of 315 GPCR targets was also tested simultaneously and in parallel using the PRESTO-TANGO selectivity screen provided by the Psychoactive Drug Screening Program (PDSP)⁵. Significant inhibition (modulation) observed for 2 of the 315 GPCRs tested @ 10 μ M (KOR 96%Inh, 5-HT1D 53%Inh).

Selectivity data available	BI-1942	BI-1829
SafetyScreen44™ with kind support of  eurofins	Yes	Yes
PRESTO-TANGO (PDSP)	Yes	No
Invitrogen®	No	No
DiscoverX®	No	No
Dundee	No	No

^a For detailed assay conditions please refer to Reference 1

Co-crystal structure of the Boehringer Ingelheim probe compound and the target protein.

No X-ray co-crystal structure with BI-1942 is available. For a structurally related compound a X-ray structure was solved at BI (see Figure 3).

Reference molecule(s) – Inhibitors

For reference molecules see Reference 4.

Supplementary data

2D structure files can be downloaded free of charge from [openMe](https://openme.org).

References

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