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

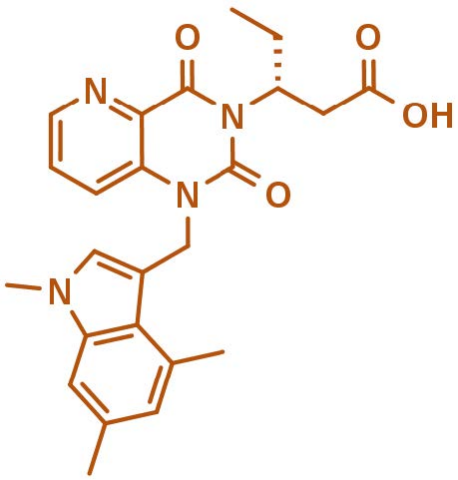

Figure 1: 2-D structure of BI-1942, a Chymase inhibitor

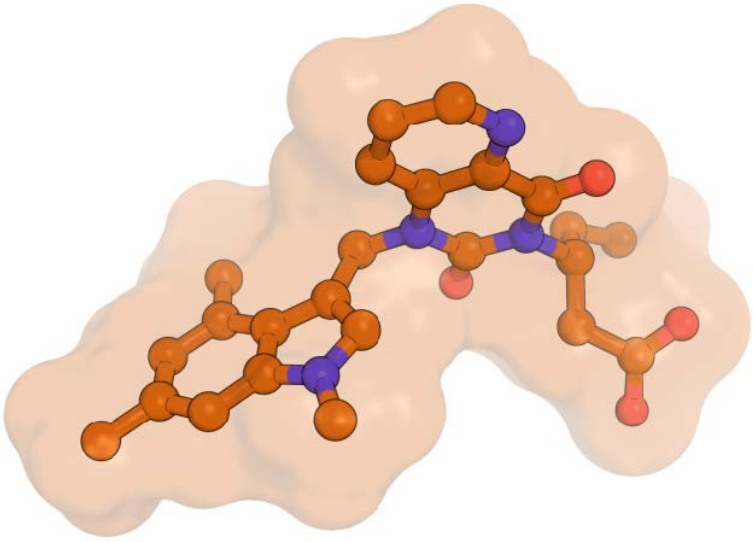

Figure 2: BI-1942, 3D conformation

Highlights

BI-1942 is a highly potent inhibitor of human chymase (IC_{50} = 0.4 nM) that can be used to test biological hypotheses involving this target *in vitro*. With BI-1829 we also offer a structurally close analog that is more than 1000 fold less active (IC_{50} = 850 nM) and can thus be used as negative control for *in vitro* studies.

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-ß, 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-ß1 and IL-1ß, generating endothelin, altering apolipoprotein metabolism and degrading the extracellular matrix.

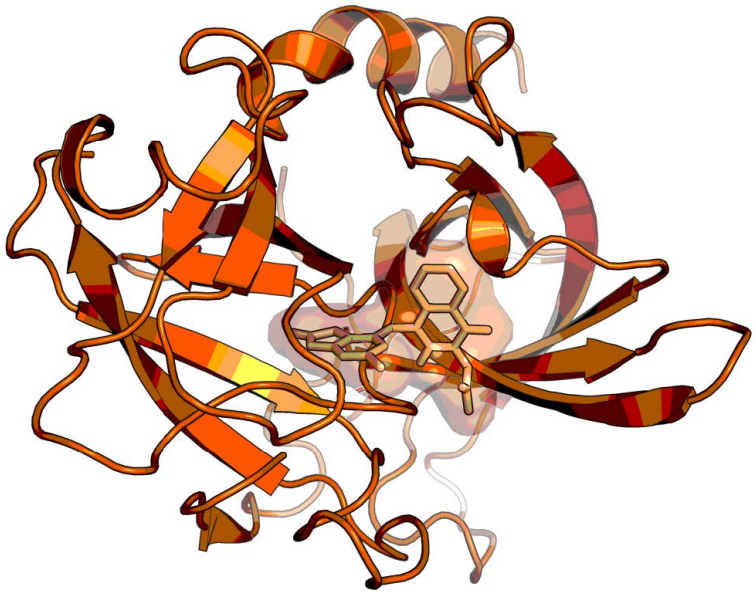

Figure 3: Chymase in complex with a close analog of BI-1942 (Boehringer Ingelheim internal structure).

In vitro activity

PROBE NAME / NEGATIVE CONTROL	BI-1942	BI-1829
MW [Da]	434.5	419.5
Inhibition of human chymase IC_{50} [nM]*	0.4	850

[a] for a detailed assay conditions see reference 1

In vitro DMPK and CMC parameters

PROBE NAME / NEGATIVE CONTROL	BI-1942	BI1829
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.

In vivo DMPK parameters

No data available.

Negative Control

Structurally related BI-1829 shows much weaker inhibition of human Chymase (IC_{50} = 850 nM) and therefore is a suitable negative control for *in vitro* experiments.

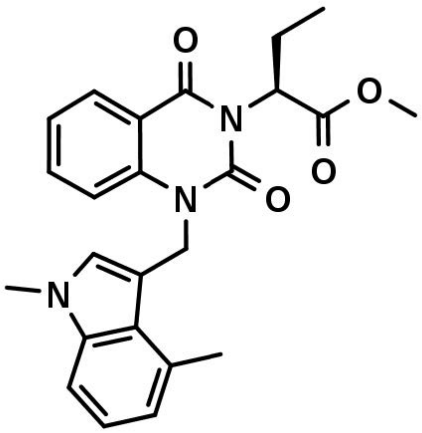

Figure 4: BI-1829 which serves as a negative control

Selectivity

BI-1942 is more than 100-fold selective against cathepsin G (IC_{50} = 110 nM)*.

Selectivity data from external assay panels is not available.

*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 an Xray structure was solved at BI (see Figure 3).

Reference molecule(s) - Inhibitors

For reference molecules see Reference 4.

Supplementary data

2-D structure files can be downloaded free of charge from opnMe.

Summary

Chymase plays an important and diverse role in the homeostasis for a number of cardiovascular processes and has been linked to heart failure. BI-1942 is a potent inhibitor of human chymase with an IC_{50} value of 0.4 nM and >100 fold selectivity against Cathepsin G and is thus a suitable tool for testing biological hypotheses involving human Chymase *in vitro*.

References

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