opnMe by Boehringer Ingelheim

# Chymase inhibitor

## BI-1942

Boehringer Ingelheim

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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

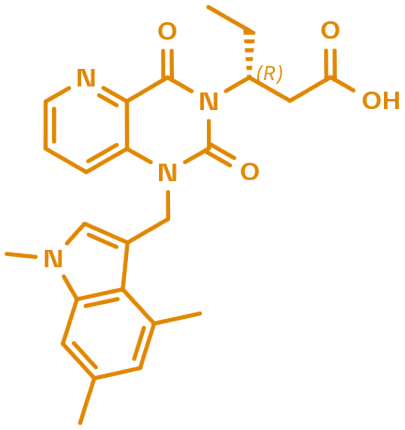


**Figure 1: 2D structure of BI-1942, a Chymase inhibitor**

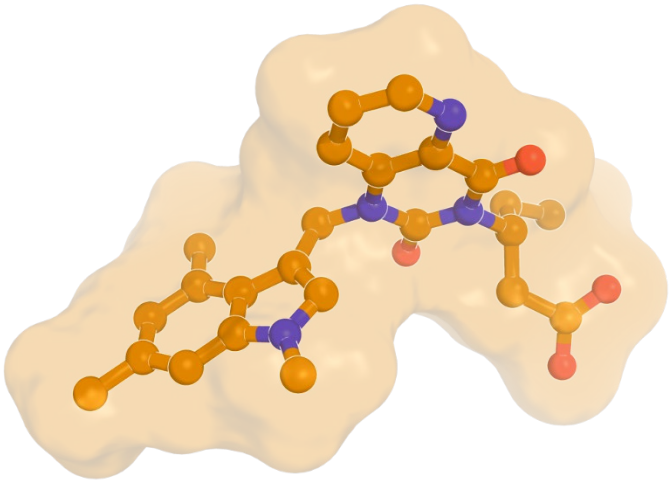

**Figure 2: BI-1942, 3D conformation**

## Highlights

BI-1942 is a highly potent inhibitor of human chymase ($IC_{50}$ = 0.4 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-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.

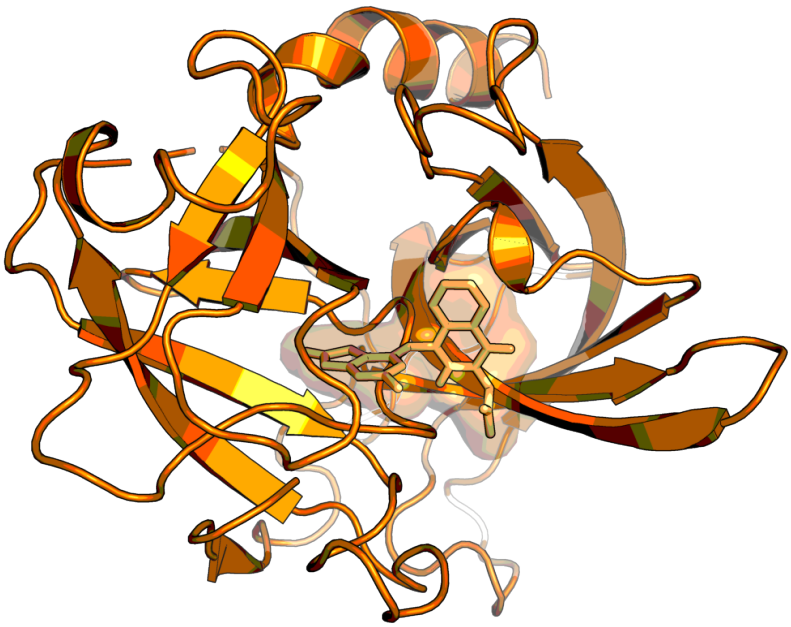

**Figure 3: Chymase in complex with a close analog of BI-1942 (Boehringer Ingelheim internal structure).**

## *In vitro* activity

| PROBE NAME / NEGATIVE CONTROL | BI-1942 | BI-1829 |
|---|---|---|
| MW [Da, 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 ($IC_{50}$ = 850 nM) and therefore is a suitable negative control for *in vitro* experiments.

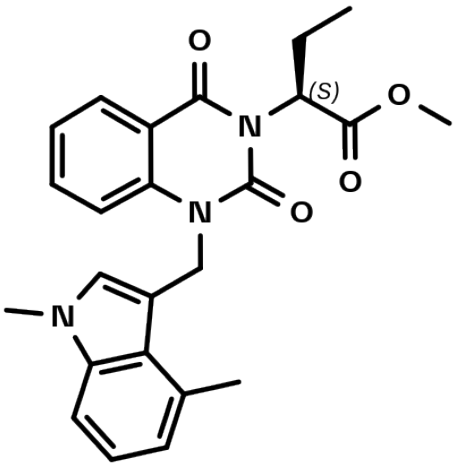


**Figure 4: BI-1829 which serves as a negative control**

## Selectivity

BI-1942 was tested in a protease panel (37 proteases) at 10 µM 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].

| Selectivity data available | BI-1942 | BI-1829 |
|---|---|---|
| SafetyScreen44™ with kind support of eurofins | Yes | Yes |
| PDSP[5] | 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 opnMe.

## References


1. Taylor S. J., Padyana A. K., Abeywardane A., Liang S., Hao M.-H., Lombaert S. de, Proudfoot J., Farmer B. S., Li X., Collins B., Martin L., Albaugh D. R., Hill-Drzewi M., Pullen S. S., Takahashi H. Discovery of potent, selective chymase inhibitors via fragment linking strategies *J Med Chem* **2013**, 56(11), 4465–4481. DOI: 10.1021/jm400138z, PubMed: 23659209.
2. Lo H. Y., Nemoto P. A., Kim J. M., Hao M.-H., Qian K. C., Farrow N. A., Albaugh D. R., Fowler D. M., Schneiderman R. D., Michael August E., Martin L., Hill-Drzewi M., Pullen S. S., Takahashi H., Lombaert S. de Benzimidazolone as potent chymase inhibitor: Modulation of reactive metabolite formation in the hydrophobic (P1) region *Bioorg Med Chem Lett* **2011**, 21(15), 4533–4539. DOI: 10.1016/j.bmcl.2011.05.126, PubMed: 21733690.
3. Tojo H., Urata H. Chymase inhibition and cardiovascular protection *Cardiovasc Drugs Ther* **2013**, 27(2), 139–143. DOI: 10.1007/s10557-013-6450-4, PubMed: 23468322.
4. Yahiro E., Miura S., Imaizumi S., Uehara Y., Saku K. Chymase Inhibitors *CPD* **2013**, 19(17), 3065–3071. DOI: 10.2174/1381612811319170014, PubMed:23176221.
5. Kroeze W. K., Sassano M. F., Huang XP., Lansu K., McCorvy J. D., Giguère P. M., Sciaky N., Roth B. L. PRESTO-Tango as an open-source resource for interrogation of the druggable human GPCRome *Nat Struct Mol Biol*. **2015**, 22(5):362-9. DOI: 10.1038/nsmb.3014, PubMed.