opnMe by Boehringer Ingelheim

DPAP1 Inhibitor

BI-2051

Boehringer Ingelheim

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Summary

BI-2051 is a very potent and highly selective dipeptidyl aminopeptidase 1 (DPAP1) inhibitor. BI-2051 inhibits recombinant *P. falciparum* DPAP1 with an IC_{50} of 0.3 nM. BI-2051 is highly soluble at pH 2.2, 4.5, 7 and displays good *in vitro* PK properties in rats.

Chemical Structure

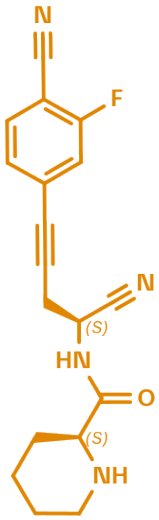

Figure 1: 2D structure of BI-2051

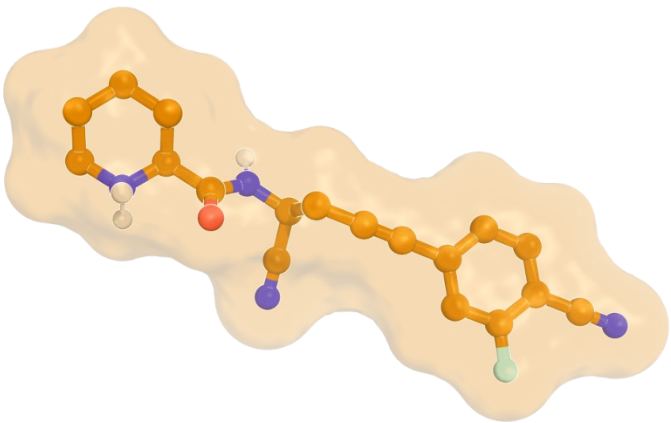

Figure 2: BI-2051, 3D conformation

Highlights

BI-2051 is a very potent inhibitor of the *Plasmodium falciparum* protease, DPAP1 (IC_{50} = 0.3 nM). It is highly selective versus the homologous human proteases CatC, CatK and CatL, and shows a good *in vitro* PK profile with high solubility and good cellular permeability. This compound is suitable for *in vitro* experiments.

Target information

Dipeptidyl aminopeptidase 1 (DPAP1) is a cysteine exopeptidase expressed in the food vacuoles of the parasite *Plasmodium falciparum*[1].
P. falciparum uses the hemoglobin in the host erythrocytes as a source of amino acids and this catabolism is essential for the intraerythrocytic growth of the parasite. Hemoglobin is taken up by the cytostome and delivered into the food vacuole. In the food vacuole, hemoglobin is degraded by aspartic, cysteine and metalloproteases. DPAP1 catalyzes the final step, the release of small peptides or amino acids from globin-derived oligopeptides[1]. DPAP1 is therefore a potential target to interfere with the growth of *P. falciparum* during the erythrocytic phase of its life cycle[2].
DPAP1 shows significant sequence homology to the human protease Cathepsin C (CatC).

In vitro activity

BI-2051 displays an IC_{50} = 0.3 nM in a DPAP1 assay using recombinant protein.

PROBE NAME	BI-2051	BI-2054
MW [Da, free base][a]	324.4	324.4
DPAP1 (IC_{50}) [nM][b]	0.3	204.5
Human CatC (IC_{50}) [nM]	2.7	>30,000
Human CatK (IC_{50}) [nM]	4.3	n.a.
Human CatL (IC_{50}) [nM]	>100,000	n.a

[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] Assay conditions for the CatC assay are available in the patent WO2014140075. For DPAP1, CatK, and CatL the assay conditions are identical except for the enzyme nature, concentration, buffer and substrates. More detailed experimental conditions can always be obtained via the "Contact us" form.
For DPAP1, the substrate is H-Pro-Arg-AMC
For CatC, the substrate is Gly-Arg-AMC
For CatL, the substrate is Z-Phe-Arg-AMC
For CatK, the substrate is Z-Gly-Pro-Arg-AMC

In vitro DMPK and CMC parameters

BI-2051 is a highly soluble and permeable compound. It has good *in vitro* PK properties in rats, but displays a weaker microsomal stability in mice.

PROBE NAME	BI-2051	BI-2054
logP @ pH 11	2.6	2.6
Solubility @ pH 6.8 [µg/mL]	>70	>103
Caco-2 permeability AB @ pH 7.4 [*10^{-6} cm/s]	53.7	27
Caco-2 efflux ratio	0.45	1.3
Microsomal stability (human/mouse/rat) [% Q_H]	<23 / 40 / 29	n.a.
Hepatocyte stability (human/mouse/rat) [% Q_H]	25 / n.d. / n.d.	n.a.
hERG [inh. % @ 10 µM, IC_{50} (µM)]	59, 7.7	n.a.
CYP 3A4 (IC_{50}) [µM]	>50	>50
CYP 2C8 (IC_{50}) [µM]	>50	>50
CYP 2C9 (IC_{50}) [µM]	>50	>50
CYP 2C19 (IC_{50}) [µM]	>50	>50
CYP 2D6 (IC_{50}) [µM]	44.4	24.5

In vivo pharmacology

No *in vivo* data available.

Negative control

BI-2054 can be used as a negative control. It is the distomer of active probe BI-2051.

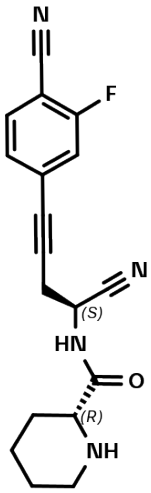

Figure 3: BI-2054 serves as a negative control

Selectivity

BI-2051 is > 8000x selective for P. falciparum DPAP1 versus the homologous human enzymes CatC, CatK and CatL.
BI-2051 and its negative control BI-2054 were tested on 44 targets in a selectivity panel and showed ≥1,000-fold selectivity for all targets (≤ 50% inhibition @ 10 µM).

SELECTIVITY DATA AVAILABLE	BI-2051	BI-2054
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.

No co-crystal structure available.

Reference molecule(s)

No reference molecules available

Supplementary data

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

References

1. Klemba M., Gluzman I., Goldberg D. E. A Plasmodium falciparum dipeptidyl aminopeptidase I participates in vacuolar hemoglobin degradation *J Biol Chem* **2004**, 279(41), 43000–43007. DOI: 10.1074/jbc.M408123200, PubMed: 15304495.

2. Deu E., Leyva M. J., Albrow V. E., Rice M. J., Ellman J. A., Bogyo M. Functional studies of Plasmodium falciparum dipeptidyl aminopeptidase I using small molecule inhibitors and active site probes *Chem Biol* **2010**, 17(8), 808–819. DOI: 10.1016/j.chembiol.2010.06.007, PubMed: 20797610.