opnMe by Boehringer Ingelheim

HCV protease inhibitor faldaprevir

BI 201335

Boehringer Ingelheim

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Summary

Faldaprevir (BI 201335) is a highly potent and selective HCV NS3/4A protease inhibitor especially efficacious against HCV genotype 1a/1b provided for pre-clinical research use only.

Chemical Structure

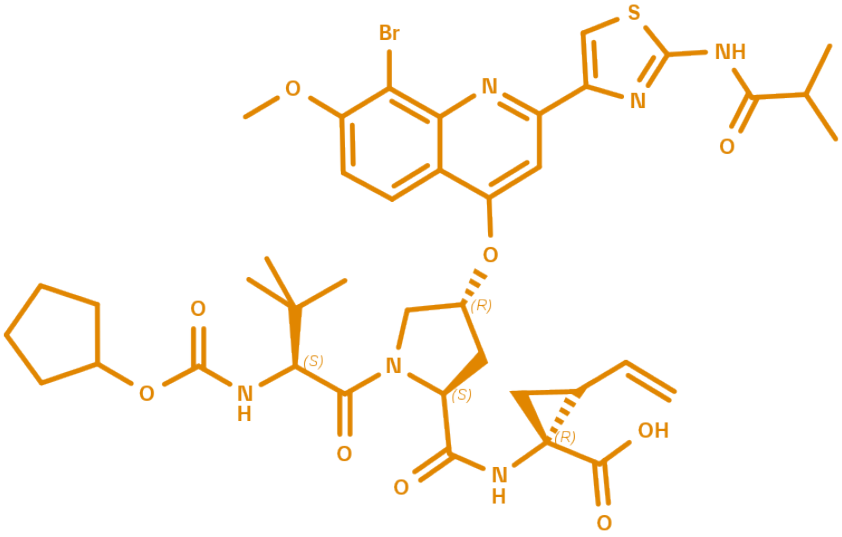

Figure 1: 2D structure of faldaprevir

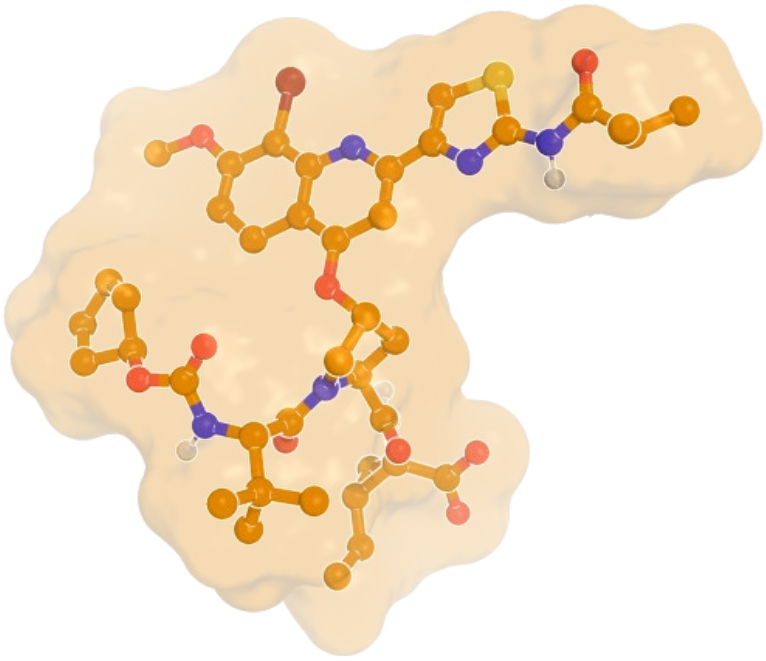

Figure 2: Faldaprevir, 3D conformation

Highlights

Faldaprevir (BI-201335) is a highly potent and selective Hepatitis C Virus (HCV) NS3-NS4 protease inhibitor. It has shown a good ADME profile both *in vitro* and *in vivo*, so its predicted PK profile in humans is also good. This compound is available for pre-clinical research purposes only and can be used together with the BI-1230 inhibitor, which is also available on our website. We recommend ordering both compounds for your experiments.

Target information

HCV NS3 protease is a 180-amino acid chymotrypsin-like serine protease. Its function is the auto-proteolytic cleavage of HCV viral polyprotein (~3000 a.a.) into individual, non-structural (NS) proteins with different purposes[1-3]. Thus, it is an essential component of HCV replication and infectivity. The NS3 protein contains two functional domains: a serine protease- and a helicase domain. The active site of NS3 is located in the shallow and wide protein-protein interaction surface of these domains. Faldaprevir and other known NS3 inhibitors cover significant parts of this interaction surface in addition to the active site. Boehringer Ingelheim was the first company to establish proof-of-concept in humans for an HCV NS3 protease inhibitor as a treatment of HCV infection[4]. Faldaprevir is a highly optimized noncovalent competitive inhibitor of NS3-NS4A proteases (HCV genotypes 1a and 1b) with Ki values in the low nanomolar range. Values of 2 to 230 nM were measured against the NS3-NS4A proteases of HCV genotypes 2 to 6. It is a very weak inhibitor of cathepsin B and showed no inhibition of human leukocyte elastase.

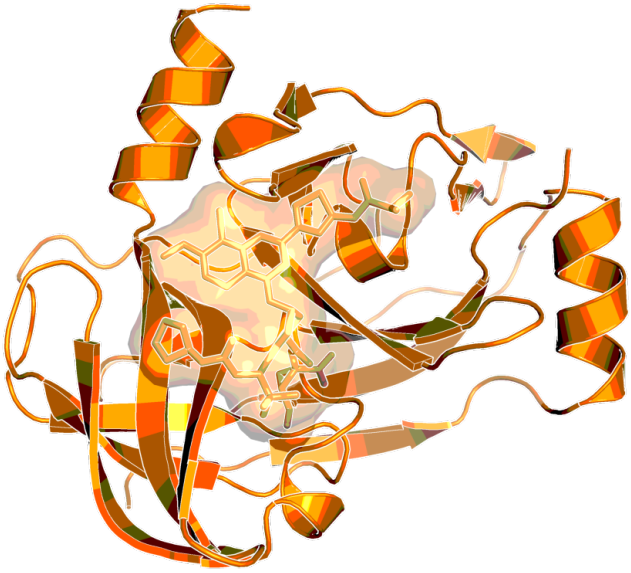

Figure 3: X-ray structure of HCV NS3 protease with faldaprevir (BI 201335) (PDB code: 3p8n)[1]

In vitro activity

PROBE NAME / NEGATIVE CONTROL	FALDAPREVIR	BI-1675
MW [Da, free base][a]	869.8	554.6
IC_{50} [nM][b]	5.2	4870
EC_{50} [nM], replicon assay, genotype 1a[c]	13	n.a.
EC_{50} [nM], replicon assay, genotype 1b[c]	7.1	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] Enzymatic assay, NS3-NS4A heterodimer, fluorogenic substrate, 60 min incubation
[c] Cell-based HCVPV RNA replication Luciferase reporter assay, genotype background 1a and 1b, Huh7 cells, 72 h incubation

In vitro DMPK and CMC parameters

Faldaprevir displays good permeability in Caco-2 cells assays and a high microsomal stability.

PROBE NAME / NEGATIVE CONTROL	FALDAPREVIR	BI-1675
logD @ pH 11	2.1	0.4
Solubility @ pH 7 [µg/mL]	8.1	n.a.
Caco-2 permeability AB @ pH 7.4 [$*10^{-6}$ cm/s]	2.1	0.1
Caco-2 efflux ratio	4.8	2.5
MDCK permeability P_{appAB} @ 1µM [10^{-6} cm/s]	1 / 20	n.a.
MDCK efflux ratio	20	n.a.
Microsomal stability (human/rat/dog) [% Q_H]	17 / <5.6 / <10.9	n.a.
Plasma Protein Binding (human/mouse/rat) [%]	99.8 / 99.2 / 100	n.a.
CYP 1A2 (IC_{50}) [µM]	>30	n.a.
CYP 2C9 (IC_{50}) [µM]	2.8	n.a.
CYP 2C19 (IC_{50}) [µM]	5.8	n.a.
CYP 2D6 (IC_{50}) [µM]	>30	n.a.

In vivo DMPK parameters

Faldaprevir was investigated as part of more than 50 clinical trials and can be regarded as a well-characterized molecule for *in vivo* usage. Note: As part of the opnMe, the compound is shared only for pre-clinical research purposes.

FALDAPREVIR	RAT[A]	DOG[B]
Clearance [mL/(min*kg)][a]	20	2.1
Mean residence time after *i.v.* dose [h][a]	1.6	2.6
t_{max} [h][b]	1.5	1
V_{ss} [L/kg][a]	1.9	0.3

[a] *i.v.* dose: 1.7 mg/kg; [b] *p.o.* dose: 4.3 mg/kg.
[b] *i.v.* dose: 1.7 mg/kg; [b] *p.o.* dose: 3.4 mg/kg. For more details on PK data please see reference 3

Negative control

BI-1675 can be used as negative control although it is structurally more related to BI-1230. It is recommended to order and test all three compounds in parallel.

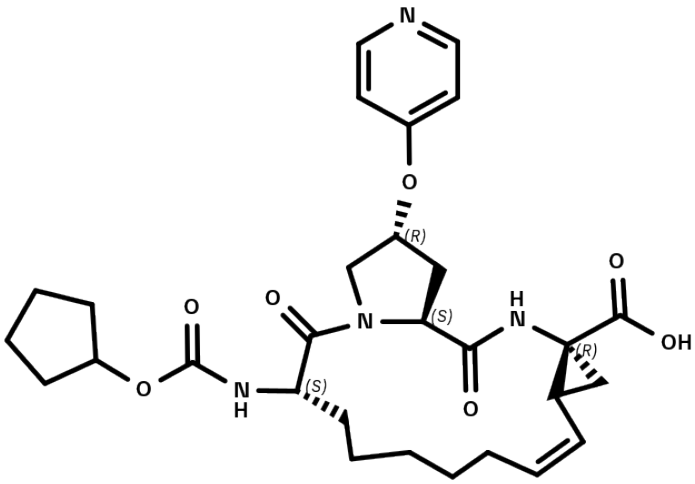

Figure 4: BI-1675 which serves as a negative control for BI-1230 and Faldaprevir

Selectivity

Faldaprevir is highly selective against other serine/cysteine proteases[1-3].
Data from selectivity assay panels currently not available.

SELECTIVITY DATA AVAILABLE	FALDAPREVIR	BI-1675
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.

X-ray structure of HCV NS3 protease with faldaprevir (BI 201335) is available (Figure 3, PDB code: 3p8n)[1]

Reference molecule(s)

BI-1230, which is also available on opnMe.com. For a review of HCV NS3 protease inhibitors please see reference 5.

Supplementary data

Selectivity data can be downloaded free of charge from opnMe.

References

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