opnMe by Boehringer Ingelheim

HCV protease inhibitor

BI-1230

Boehringer Ingelheim

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Summary

BI-1230 is a nanomolar inhibitor of HCV protease and of viral replication with good *in vivo* PK characteristics.

Chemical Structure

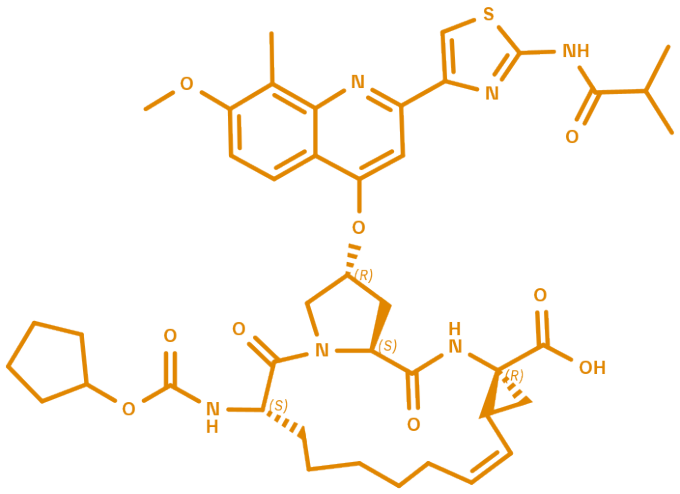

Figure 1: 2D structure of BI-1230, an inhibitor of HCV NS3 protease

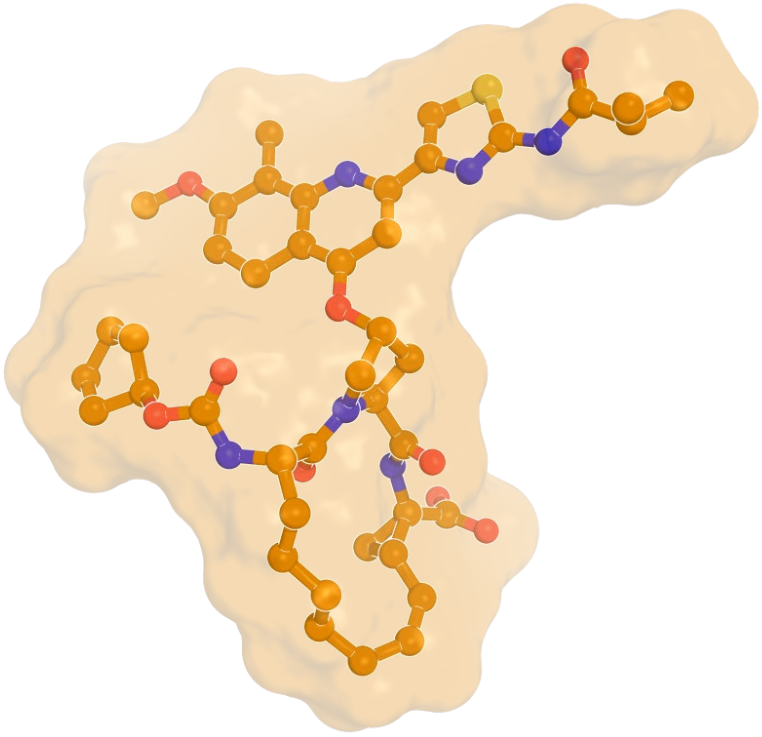

Figure 2: 3D structure of BI-1230, an inhibitor of HCV NS3 protease

Highlights

BI-1230 is a single-digit nanomolar inhibitor of HCV NS3 protease activity and of viral replication. It binds to the active site of NS3 and was shown to be highly selective against other serine/cysteine proteases. BI-1230 shows good *in vivo* PK properties, including half-life and bioavailability. As such, this compound is a valuable tool for both *in vitro* and *in vivo* studies. We also offer faldaprevir from our infectious diseases pipeline for pre-clinical research purposes.

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 aa) into individual, non-structural (NS) proteins with various functions. 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. BI-1230 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].

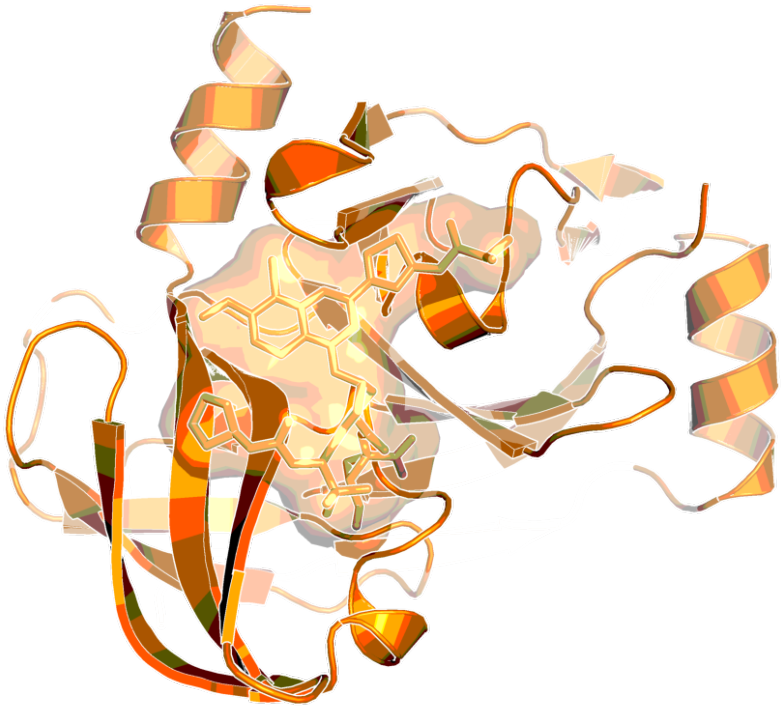

Figure 3: 3: X-ray structure of HCV NS3 protease with faldaprevir, a close analog of BI-1230 (PDB code: 3p8n)

In vitro activity

PROBE NAME / NEGATIVE CONTROL	BI-1230	BI-1675
MW [Da, free base][a]	817.0	554.6
IC_{50} [nM][b]	6.7	4870
EC_{50} [nM], replicon assay, genotype 1a[c]	4.6	n.d.
EC_{50} [nM], replicon assay, genotype 1b[c]	<1.8	n.d.

[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

PROBE NAME / NEGATIVE CONTROL	BI-1230	BI-1675
logD @ pH 11	2.7	0.4
Solubility @ pH 7 [µg/mL]	<39	n.d.
Caco-2 permeability AB @ pH 7.4 [$*10^{-6}$ cm/s]	8.7	0.1
Caco-2 efflux ratio	0.3	2.5
Microsomal stability [% Q_H]	<24	n.d.
Plasma Protein Binding human [%]	99.9	n.d
CYP 1A2 (IC_{50}) [µM]	13.9	n.d
CYP 2C9 (IC_{50}) [µM]	4	n.d
CYP 2C19 (IC_{50}) [µM]	2	n.d
CYP 2D6 (IC_{50}) [µM]	>30	n.d

In vivo DMPK parameters

In vivo DMPK parameters of BI-1230 in rat and dog.[a,b]

ROUTE		RAT[A]	DOG[B]
i.v.	Clearance [mL/min/kg]	15	1.9
	Mean residence time after *i.v.* dose [h]	2.3	3.4
	V_{ss} [L/kg]	2.1	0.4
p.o.	$T_{1/2}$ [h]	2.1	5.1
	t_{max} [h]	1.8	1.7
	C_{max} [nM]	405	7370
	$AUC_{0\text{-}inf}$ [nM*h]	2550	49700
	F [%]	42	92

[a] *i.v.* dose: 1.6 mg/kg, *p.o.* dose: 4 mg/kg
[b] *i.v.* dose: 1.1 mg/kg, *p.o.* dose: 2.2 mg/kg

Negative control

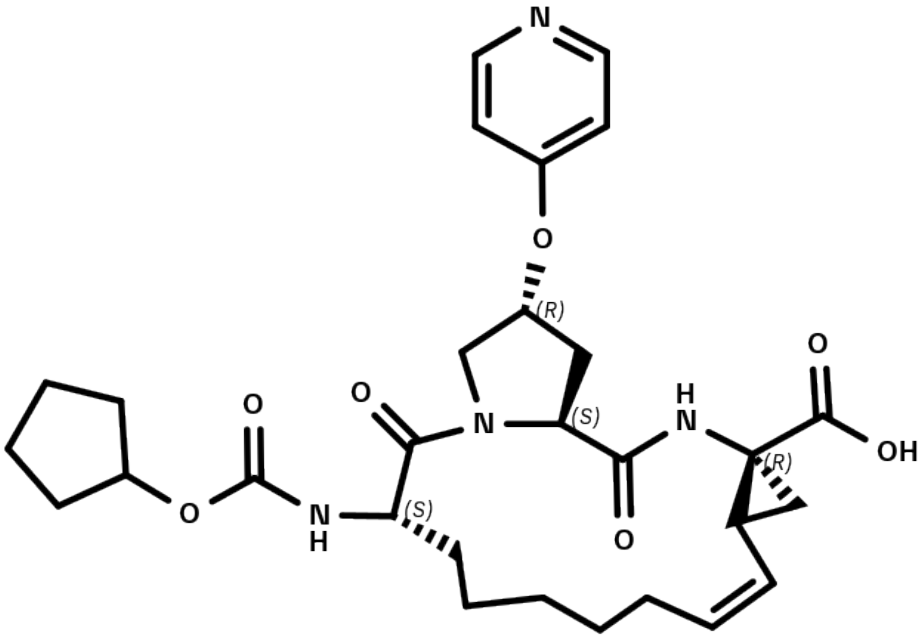

Figure 4: Structure of BI-1675 offered as negative control

Selectivity

BI-1230 is highly selective against other serine/cysteine proteases.

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)[6]. Significant inhibition (modulation) observed for 3 of the 315 GPCRs tested @ 10 µM (Alpha2B 60%Inh, Alpha2C 57%Inh, Beta3 57%Inh).

SELECTIVITY DATA AVAILABLE	BI-1230	BI-1675
SafetyScreen44™ with kind support of eurofins	Yes	Yes
PRESTO-TANGO (PDSP)	Yes	Yes
Invitrogen®	No	No
DiscoverX®	No	No
Dundee	No	No

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

An X-ray structure of BI-1230 in complex with NS3 is not available. However, the structure with the highly related faldaprevir (BI 201335) was solved.

Reference molecule(s)

For a recent review of HCV NS3 protease inhibitors see reference 5.

Supplementary data

2D structures can be downloaded free of charge from opnMe.

References

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