opnMe by Boehringer Ingelheim

HCV protease inhibitor

BI-1388

Boehringer Ingelheim

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Summary

BI-1388 is a highly selective inhibitor of NS3 protease with nanomolar potency across various HCV genotypes and against resistant mutants D168V and R155K.

Chemical Structure

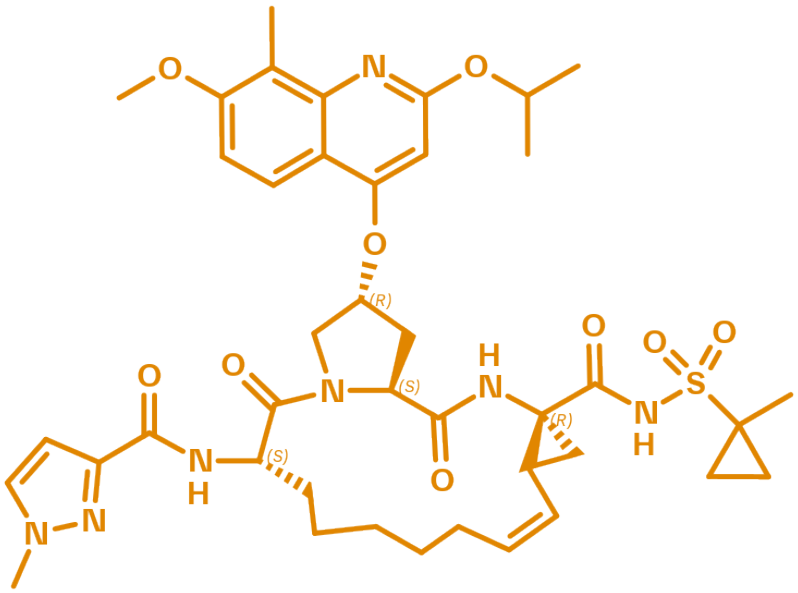

Figure 1: 2D structure of BI-1388, an inhibitor of HCV NS3 protease

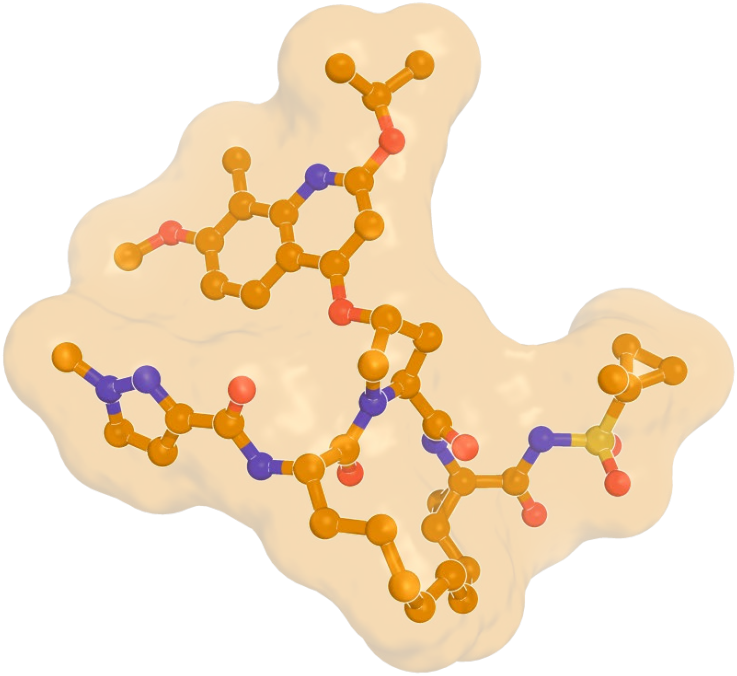

Figure 2: 3D structure of BI-1388, an inhibitor of HCV NS3 protease

Highlights

BI-1388 is a highly selective inhibitor of HCV NS3 protease. It binds to the active site of NS3 and inhibits protease activity and viral replication with nanomolar to picomolar potency across various HCV genotypes and resistant mutants D168V and R155K. BI-1388 demonstrated high selectivity against other serine/cysteine proteases and it is characterized by exceptional liver partitioning.

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].

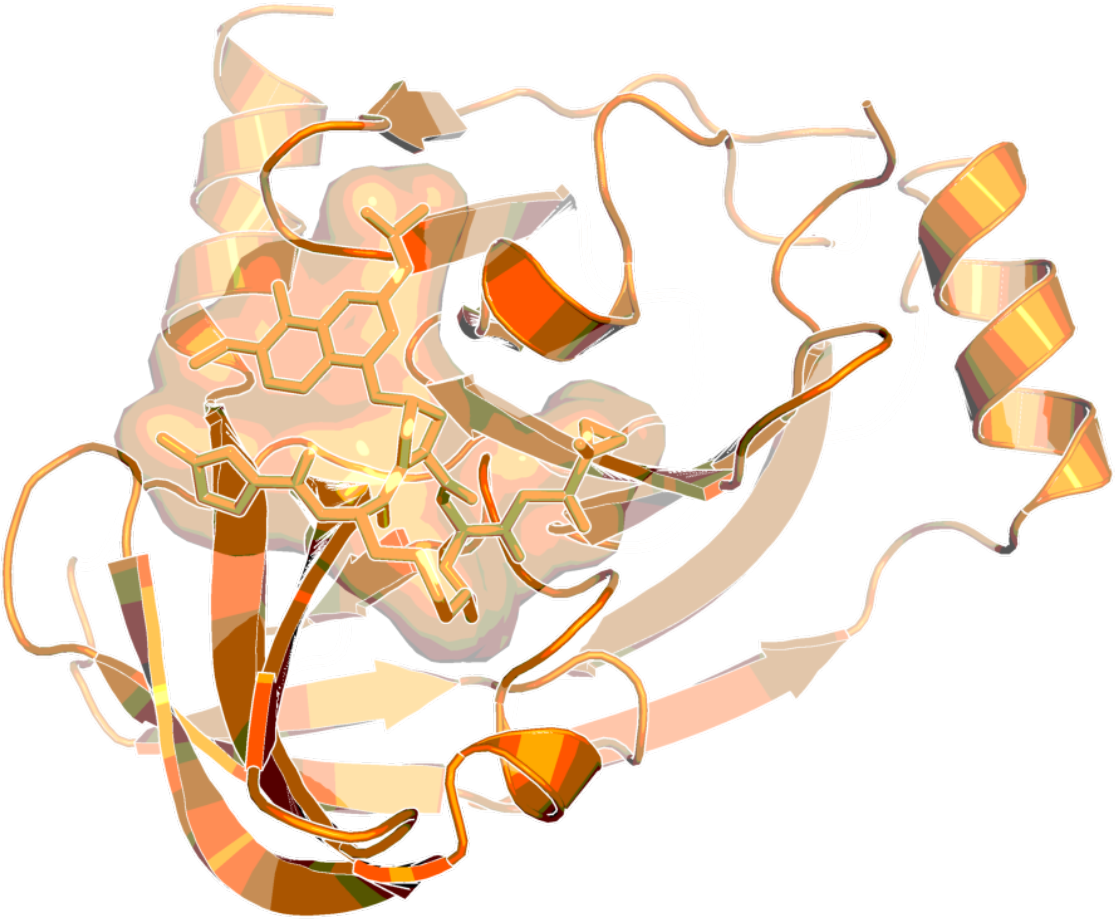

Figure 3: BI-1388 bound to the active site of NS3 (PDB code: 4i31)[3]

In vitro activity

PROBE NAME	BI-1388
MW [Da, free base][a]	820.0
IC_{50} [nM], WT enzyme, genotype 1a[b]	0.48

IC_{50} [nM], WT enzyme, genotype 1b[b]	1.1
IC_{50} [nM], WT enzyme, genotype 2a[b]	0.14
IC_{50} [nM], WT enzyme, genotype 3a[b]	12
IC_{50} [nM], WT enzyme, genotype 4a[b]	0.23
IC_{50} [nM], WT enzyme, genotype 5a[b]	0.24
IC_{50} [nM], WT enzyme, genotype 6a[b]	0.16
IC_{50} [nM], R155K, genotype 1a[b]	4.7
IC_{50} [nM], D168V, genotype 1a[b]	58
IC_{50} [nM], A156T, genotype 1b[b]	2.7
IC_{50} [nM], D156V, genotype 1b[b]	4.3
IC_{50} [nM], D168A, genotype 1b[b]	16
IC_{50} [nM], D168V, genotype 1b[b]	15
EC_{50} [nM], WT, replicon assay, genotype 1a[c]	0.11
EC_{50} [nM], R155K, replicon assay, genotype 1a[c]	1.0
EC_{50} [nM], WT, replicon assay, genotype 1b[c]	0.11
EC_{50} [nM], D168V, replicon assay, genotype 1b[c]	0.14

[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, see ref. 3 for assay details
[c] Cell-based HCV RNA replication Luciferase reporter assay, see ref. 3 for assay details

In vitro DMPK and CMC parameters

PROBE NAME / NEGATIVE CONTROL	BI-1388
logD @ pH 11	2.3
Solubility @ pH 7 [µg/mL]	3.4

Caco-2 permeability AB @ pH 7.4 [*10^{-6} cm/s]	10
Caco-2 efflux ratio	1.2
Hepatocyte stability (human) [% Q_H]	20
Plasma Protein Binding (human,mouse) [%]	99.8 / 99.8
CYP 1A2 (IC_{50}) [µM]	>30
CYP 2C9 (IC_{50}) [µM]	6.4
CYP 2C19 (IC_{50}) [µM]	>30
CYP 2D6 (IC_{50}) [µM]	>30

In vivo DMPK parameters

Pharmacokinetic profile of BI-1388 in rat.

ROUTE	BI-1388	RAT
i.v.[a]	Clearance [mL/min/kg]	19
	$t_{1/2}$ [h]	2.6
	V_{ss} [L/kg]	0.97
p.o.[b]	F [%]	14
	C_{max} [nM]	1.3
	$AUC_{0\text{-}inf}$ [nM*h]	1.4

[a] *i.v.* dose: 3.3 mg/kg (70% PEG-400 and 30% water)
[b] *p.o.* dose: 4.1 mg/kg (1% MP, 0.3% Tween-80, and Methocel 0.5%)

Selectivity

SELECTIVITY DATA AVAILABLE	BI-1388
SafetyScreen44™ with kind support of eurofins	Yes
Invitrogen®	No
DiscoverX®	No
Dundee	No

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

The X-ray structure of BI-1388 in complex with NS3 is available (PDB code: 4i31, 4i32, 4i33 – complexes with WT and resistant mutants D168V and R155K)

Reference molecule(s)

For a recent review of HCV NS3 protease inhibitors see reference 6.

Supplementary data

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

References

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