HCV protease inhibitor | BI-1230

Table of contents

Summary

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

Chemical Structure

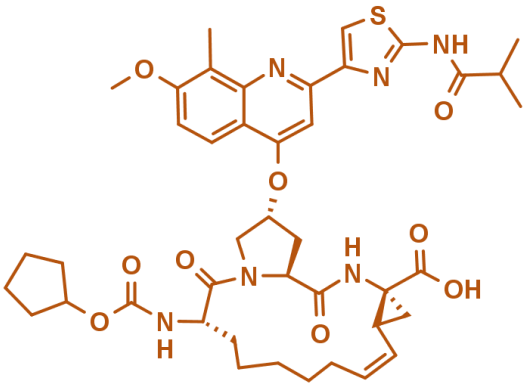

Figure 1: 2-D structure of BI-1230, an inhibitor of HCV NS3 protease

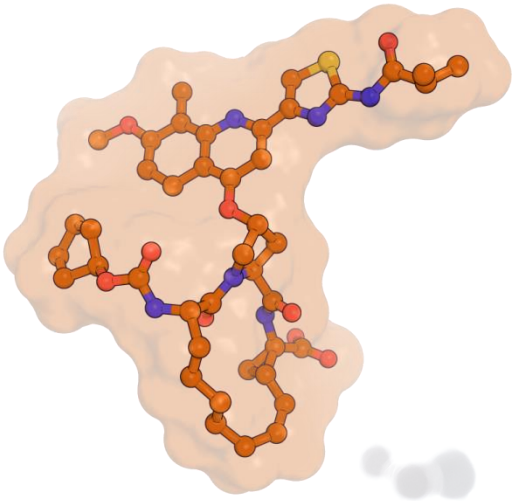

Figure 2: 3-D structure of BI-1230, an inhibitor of HCV NS3 protease

Highlights

BI-1230 binds to the active site of NS3 that is located in the shallow and broad protein-protein interaction surface of the protease and the helicase domain of the enzyme. It is a single digit nanomolar inhibitor of protease activity and of viral replication that was shown to be highly selective against other serine/cysteine proteases. Pharmacokinetic evaluation shows good half-life and bioavailability, making BI-1230 a valuable *in vitro* and *in vivo* tool compound.

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].

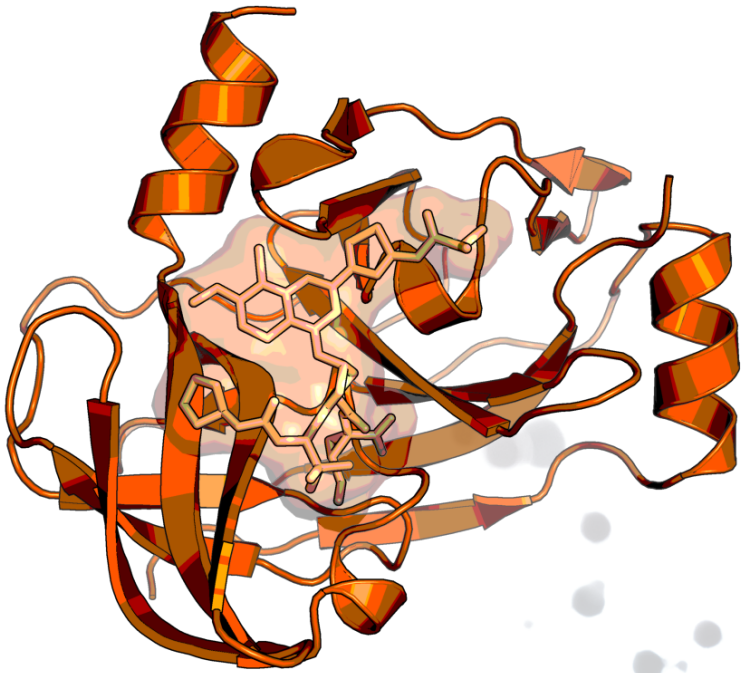

Figure 3: X-ray structure of HCV NS3 protease with BI 201335, a close analog of BI-1230 (PDB code: 3p8n)

In vitro activity

PROBE NAME / NEGATIVE CONTROL	BI-1230	BI-1675
MW [Da]	817	669
IC_{50} [nM][a]	6.7	4870
EC_{50} [nM], replicon assay, genotype 1a[b]	4.6	n.d.
EC_{50} [nM], replicon assay, genotype 1b[b]	<1.8	n.d.

[a] Enzymatic assay, NS3-NS4A heterodimer, fluorogenic substrate, 60 min incubation
[b] 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
Aqueous solubility @ pH 7 [µg/ml]	20	n.d.|
CACO permeability @ pH 7.4 [$*10^{-6}$ cm/s]	8.7	n.d.
CACO efflux ratio	0.3	n.d.
Microsomal stability [% Q_H]	<24	n.d.
Plasma protein binding human [%]	99.9	n.d.

In vivo DMPK parameters

In vivo DMPK parameters of BI-1230 in the rat, dog,and cynomolgus monkey[a]

ROUTE		RAT	DOG	MONKEY
i.v.	CL [ml/min/kg]	15	1.9	1.2
	Mean residence time after iv dose (h)	2.3	3.4	6.6
	V_{ss} [l/kg]	2.05	0.39	0.49
p.o.	$t_{1/2(}$h)	2.1	5.1	8.9
	t_{max}(h)	1.8	1.7	4.0
	Cmax(nM)	405	7370	3930
	$AUC_{0\text{-}inf}$(nM*h)	2550	49700	38330
	F [%]	42	92	45

[a]Dose = i.v., 2 mg/kg; p.o., 5 mg/kg

Negative control

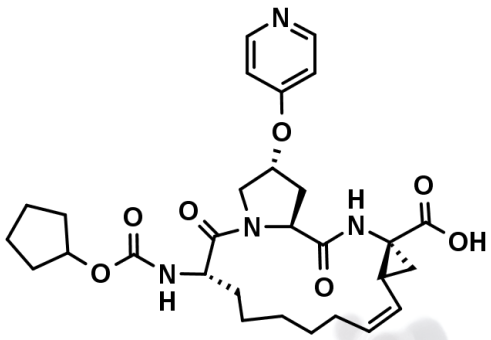

Figure 4: BI-1675, negative control

Selectivity

BI-1230 is highly selective against other serine/cysteine proteases.
Data from selectivity assay panels are not available.

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 BI 201335 was solved (see Figure 3.)

Reference molecule(s)

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

Summary

BI-1230 is a single digit nanomolar inhibitor of HCV NS3 protease activity and of viral replication. BI-1230 was shown to be highly selective against other serine/cysteine proteases and to be suitable for *in vivo* studies.

References

1. Youla S. Tsantrizos, Gordon Bolger, Pierre Bonneau, Dale R. Cameron, Nathalie Goudreau, George Kukolj, Steven R. LaPlante, Montse Llinàs-Brunet, Herbert Nar, Daniel Lamarre Macrocyclic Inhibitors of the NS3 Protease as Potential Therapeutic Agents of Hepatitis C Virus Infection, *Angw. Chem. Int. Ed.* **2003**, *42*, 1355-1360, DOI: 10.1002/anie.200390347, PubMed.
2. Xudong Wei, Chutian Shu, Nizar Haddad, Xingzhong Zeng, Nitinchandra D. Patel, Zhulin Tan, Jianxiu Liu, Heewon Lee, Sherry Shen, Scot Campbell, Richard J. Varsolona, Carl A. Busacca, Azad Hossain, Nathan K. Yee, and Chris H. Senanayake A Highly Convergent and Efficient Synthesis of a Macrocyclic Hepatitis C Virus Protease Inhibitor BI 201302, *Org. Lett.* **2013**, *15*, 1016-1019. DOI: 10.1021/ol303498m, PubMed.
3. WO 2005/028501A1, US 8552205
4. Daniel Lamarre, Paul C. Anderson, Murray Bailey, Pierre Beaulieu, Gordon Bolger, Pierre Bonneau, Michael Bös, Dale R. Cameron, Mireille Cartier, Michael G. Cordingley, Anne-Marie Faucher, Nathalie Goudreau, Stephen H. Kawai, George Kukolj, Lisette Lagacé, Steven R. LaPlante, Hans Narjes, Marc-André Poupart, Jean Rancourt, Roel E. Sentjens, Roger St George, Bruno Simoneau, Gerhard Steinmann, Diane Thibeault, Youla S. Tsantrizos, Steven M. Weldon, Chan-Loi Yong, Montse Llinàs-Brunet, An NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus *Nature* **2003**, *426*, 186-189, DOI: 10.1038/nature02099, PubMed.
5. J. A. McCauley, T. M. Rudd, Hepatitis C virus NS3/4a protease inhibitors, Curr. Opin. Pharmacol. **2016**, *30*, 84-92, DOI: 10.1016/j.coph.2016.07.015, PubMed