opnMe by Boehringer Ingelheim

HCV polymerase inhibitor

BI 207127

Boehringer Ingelheim

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Summary

BI 207127 (Deleobuvir) was an investigational drug against HCV infection, successfully tested in clinical trials, with good tolerability.

Chemical Structure

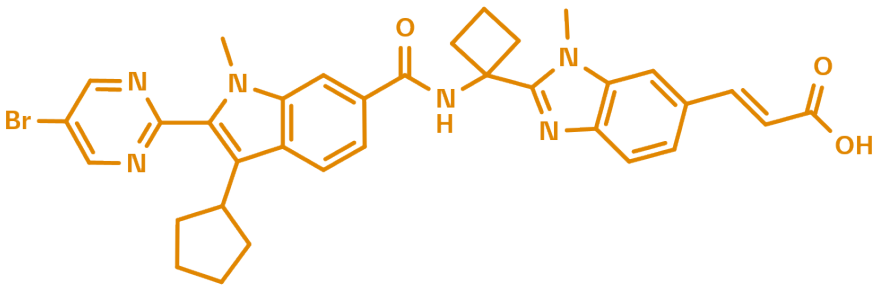

Figure 1: 2D structure of BI 207127, an inhibitor of HCV polymerase

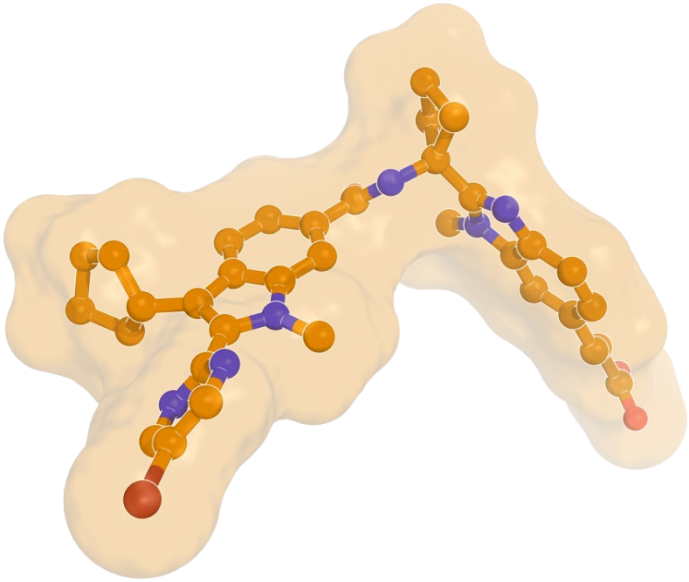

Figure 2: 3D structure of BI 207127, an inhibitor of HCV polymerase

Highlights

BI 207127, also known as Deleobuvir, is a highly potent and specific inhibitor of GT-1 HCV NS5B polymerase. It inhibits the enzymatic function of NS5B by binding to pocket 1 of its thumb domain and, in turn, inhibits viral replication of HCV. With its good ADME-PK profile, this compound is suitable for both *in vitro* and *in vivo* experiments. BI-207127 has been successfully tested in clinical trials, where it showed good tolerability and high antiviral potency against HCV infection.

Target information

HCV NS5B is an RNA-dependent RNA polymerase that is essential for the replication of the genome of the hepatitis c virus. BI 207127 inhibits the polymerase activity by binding to pocket 1 of the thumb domain of NS5B - the exact molecular mechanism of this allosteric inhibition is unknown.

It shows weak or no inhibition in specificity assays that include poliovirus RdRp, mammalian DdRp II, and DNA polymerase α, β, and γ. Moreover, the interferon-free combination of our NS3 protease inhibitor faldaprevir with BI 207127 and ribavirin has demonstrated high efficacy and good tolerability in GT1b treatment-naive patients in phase II clinical trials. However, efficacy against GT1a has proven suboptimal in more recent trials, leading to the discontinuation of the development of BI 207127 as an anti-HCV drug.

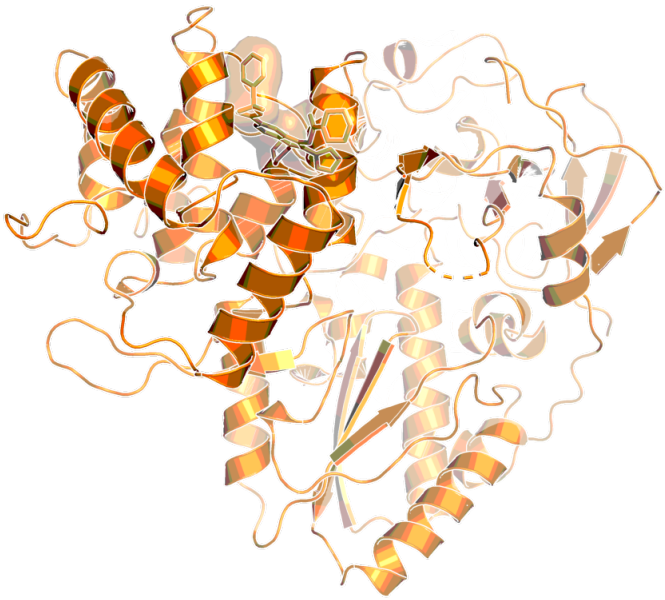

Figure 3: Hepatitis C virus polymerase in complex with an inhibitor bound to thumb-domain pocket 1 (PDB code: 4gmc)

In vitro activity

BI 207127 is a highly potent and specific inhibitor of genotype(GT)-1 HCV polymerase activity (IC_{50} = 19 nM) and of antiviral activity (EC_{50} values of 11 and 23 nM in cell-based replicon GT1b and GT1a assays, respectively).

PROBE NAME / NEGATIVE CONTROL	BI 207127	BI-7656
MW [Da, free base][a]	653.6	487.6
IC_{50} [nM][b]	50	>5000
HepG2 (IC_{50}) [µM][c]	0.024	>100
EC_{50} [nM], replicon assay, genotype 1a[c]	23	n.d.
EC_{50} [nM], replicon assay, genotype 1b[c]	11	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, HCV NS5B polymerase D21, SPA measuring 3H-UTP incorporation
[c] Cell-based replicon assay using RT-PCR for RNA quantification, genotype background 1a and 1b, Huh7 cells, 72 h incubation

In vitro DMPK and CMC parameters

BI 207127 is a permeable but poorly soluble tool compound with moderate microsomal stability. Efforts to improve the solubility led to the discovery of BI-7656, the negative control.

PROBE NAME / NEGATIVE CONTROL	BI 207127	BI-7656
logD @ pH11	1.9	0.8
Solubility @ pH 7 [µg/mL]	10.9	n.a.
Caco-2 permeability AB @ pH 7.4 [*10^{-6} cm/s]	15	n.a.
Caco-2 efflux ratio	0.5	n.a.
Hepatocyte clearance $t_{1/2}$ (human) [min]	256	n.a.
Plasma Protein Binding human [%]	99.6	n.a.

In vivo DMPK parameters

Summary of pharmacokinetic parameters for Deleobuvir in plasma.

BI 207127	RAT
Clearance [mL/min/kg][a]	1.2
$t_{1/2}$ [h][b]	4.4
t_{max} [h]	3.5
C_{max} [nM]	18000
AUC_{0-inf} [nMh]	60000
F [%]	31

[a] *i.v.* dose: 0.5 mg/kg
[b] *p.o.* dose: 1mg/kg

Two major metabolites of deleobuvir were identified in plasma: an acyl glucuronide and an alkene reduction metabolite formed in the gastrointestinal (GI) tract by gut bacteria (CD 6168), representing 20% and 15% of the total drug-related material, respectively. For additional details please see Chen *et al*[6].

Negative control

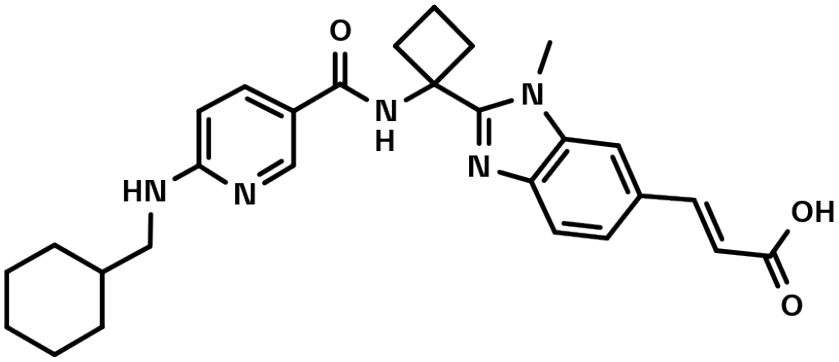

Figure 4: negative control BI-7656

Selectivity

SELECTIVITY DATA AVAILABLE	BI 207127	BI-7656
SafetyScreen44™ with kind support of eurofins	Yes	Yes
Invitrogen®	No	No
DiscoverX®	No	No
Dundee	No	No

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

While the X-ray structure of NS5B in complex with BI 207127 was not solved, structures with other pocket 1-binding allosteric inhibitors are available (example: 4gmc.pdb; see section "Target Information"). A model of the NS5B:BI 207127 complex was built based on such structures (see reference 4 for details).

Supplementary data

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

References

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