HCV polymerase inhibitor | BI 207127

Table of contents

Summary

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

Chemical Structure

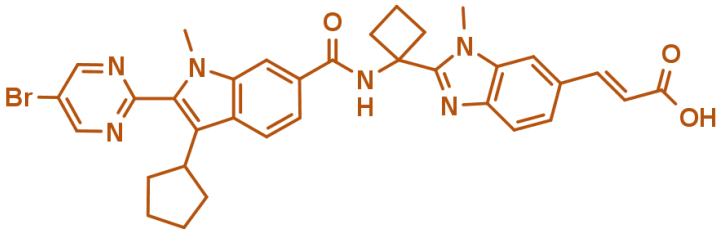

Figure 1: 2-D structure of BI 207127, an inhibitor of HCV polymerase

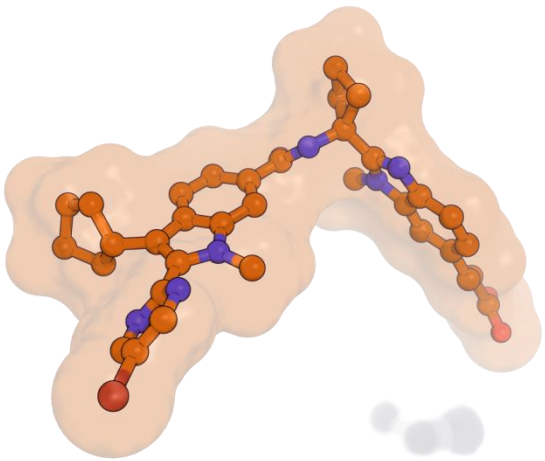

Figure 2: 3-D structure of BI 207127, an inhibitor of HCV polymerase

Highlights

BI 207127 is a highly potent and specific inhibitor of genotype(GT)-1 HCV polymerase activity (IC_{50} = 50 nM) and of antiviral activity (EC_{50} values of 11 and 23 nM in cell-based replicon GT1b and GT1a assays, respectively). It shows weak or no inhibition in specificity assays that include poliovirus RdRp, mammalian DdRp II, and DNA polymerase α, β, and γ. Furthermore, its in vitro ADME and in vivo cross-species PK profiles are consistent with further progression into drug development. BI 207127 displayed good antiviral potency and tolerability in clinical trials of short-term treatment either as a single agent or in combination with pegylated interferon-α2a/ribavirin (RBV) in HCV GT1 patients. 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.

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.

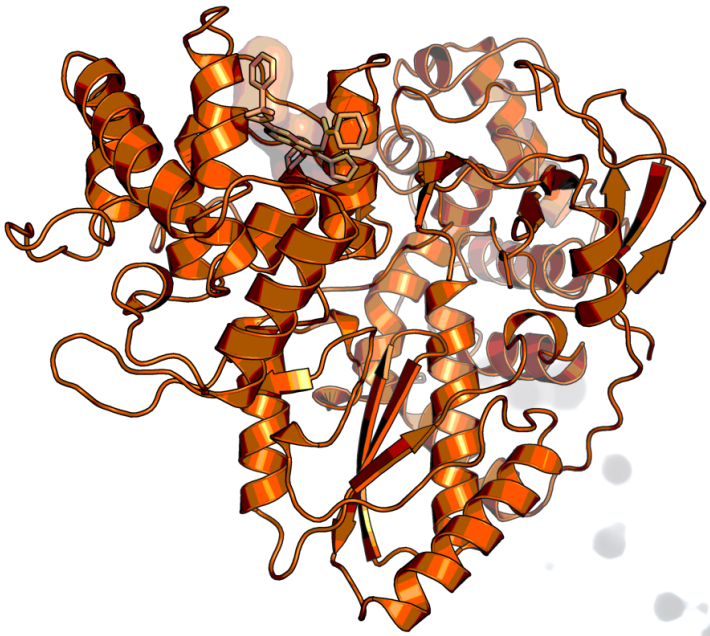

Figure 3: Hepatitis C virus polymerase in complex with an inhibitor bound to thumb-domain pocket 1 (PDB code: 4gmc)

In vivo DMPK parameters

Summary of pharmacokinetic parameters for deleobuvir in plasma[a]

PROBE NAME /NEGATIVE CONTROL	BI 207127	BI-7656
$t_{½}$ [h]	2.84	n.d.
t_{max} [h]	3.5	n.d.
C_{max} [nM]	3620	n.d.
AUC_{0-inf} [nMh]	19300	n.d.
CL [ml/min/kg]	14.3	n.d.

[a]Quantification by a validated LC-MS/MS method using synthetic standards

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

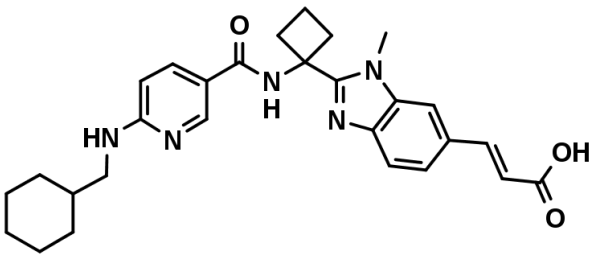

Figure 4: BI-7656

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).

Summary

BI 207127 (deleobuvir) is a highly potent inhibitor of the enzymatic function of NS5B, the RNA polymerase of HCV, and of viral replication (~20 nM). It inhibits NS5B by binding to allosteric pocket 1 of the thumb domain of the enzyme. BI 207127 was an investigational oral drug against HCV infection, successfully tested in clinical trials, where it showed good tolerability.

References

1. C. Sarrazin , M. Manns, J. L. Calleja, J. Garcia-Samaniego, X. Forns, R. Kaste, X. Bai, J. Wu, J. O. Stern, HCVerso: An Open-Label, Phase IIb Study of Faldaprevir and Deleobuvir with Ribavirin in Hepatitis C Virus Genotype-1b-Infected Patients with Cirrhosis and Moderate Hepatic Impairment", *PLoS One* **2016**, *11*, e0168544. doi: 10.1371/journal.pone.0168544; PubMed

2. S. Zeuzem, P. Mantry, V. Soriano, R. J. Buynak, J. F. Dufour, P. J. Pockros, D. Wright, P. Angus, M. Buti, J. O. Stern, W. Kadus, R. Vinisko, W. Böcher, F. J. Mensa, Faldaprevir, deleobuvir and ribavirin in IL28B non-CC patients with HCV genotype-1a infection included in the SOUND-C3 phase 2b study, *Eur J Gastroenterol Hepatol*. **2016**, *28*, 923-926, DOI: 10.1097/MEG.0000000000000649; PubMed

3. D. Larrey, A. W. Lohse, C. Trepo, J. P. Bronowicki, K. Arasteh, M. Bourlière, J. L. Calleja, J. O. Stern, G. Nehmiz, N. Abdallah, K. L. Berger, M. Marquis, J. Steffgen, G. Kukolj, Antiviral Effect, Safety, and Pharmacokinetics of Five-Day Oral Administration of Deleobuvir (BI 207127), an Investigational Hepatitis C Virus RNA Polymerase Inhibitor, in Patients with Chronic Hepatitis C, *Antimicrob. Agents Chemother*. **2013**, *57*, 4727-4735, DOI: 10.1128/AAC.00565-13, PubMed

4. S. R. LaPlante, M. Bös, C. Brochu, C. Chabot, R. Coulombe, J. R. Gillard, A. Jakalian, M. Poirier, J. Rancourt, T. Stammers, B. Thavonekham, P. L. Beaulieu, G. Kukolj G, Y. S. Tsantrizos, Conformation-based restrictions and scaffold replacement in the design of hepatitis C virus polymerase inhibitors: discovery of deleobuvir (BI 207127), *J. Med. Chem*. **2014**, *57*, 1845-1854, DOI: 10.1021/jm4011862, PubMed

5. J. Duan, G. Bolger, M. Garneau, M. Amad, J. Batonga, H. Montpetit, F. Otis, M. Jutras, N. Lapeyre, M. Rhéaume, G. Kukolj, P. W. White, R. C. Bethell, Michael G. Cordingley, The liver partition coefficient corrected inhibitory quotient and the pharmacokinetic-pharmacodynamic relationship of directly acting anti-hepatitis C virus agents in humans. *Antimicrob. Agents Chemother*. **2012**, *56*, 5381–5386, DOI: 10.1128/AAC.01028-12, PubMed

6. Y. Tsantrizos, C. Chabot, P. Beaulieu, C. Brochu, M. Poirier, T. Stammers, T. Bounkham, J. Rancourt, Viral Polymerase Inhibitors, WO2005080388 A1, 2005

7. L.-Z. Chen, J. P. Sabo, E. Philip, L. Rowland, Y. Mao, B. Latli, D. Ramsden, D. A. Mandarino, R. S. Sanea, Mass Balance, Metabolite Profile, and In Vitro-In Vivo Comparison of Clearance Pathways of Deleobuvir, a Hepatitis C Virus Polymerase Inhibitor; Antimicrob. Agents Chemother. 2015, 59, 25-37 DOI: 10.1128/AAC.03861-14; PubMed