Bioorganic & Medicinal Chemistry Letters 20 (2010) 7493–7497

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis of new acylsulfamoyl benzoxaboroles as potent inhibitors of HCV NS3 protease

Xianfeng Li [a,*], Yong-Kang Zhang [a], Yang Liu [a], Suoming Zhang [a], Charles Z. Ding [a], Yasheen Zhou [a], Jacob J. Plattner [a], Stephen J. Baker [a], Liang Liu [a], Wei Bu [a], Wieslaw M. Kazmierski [b,*], Lois L. Wright [b], Gary K. Smith [b], Richard L. Jarvest [c], Maosheng Duan [b], Jing-Jing Ji [b], Joel P. Cooper [b], Matthew D. Tallant [b], Renae M. Crosby [b], Katrina Creech [b], Zhi-Jie Ni [d], Wuxin Zou [e], Jon Wright [e]

[a] Anacor Pharmaceuticals, Inc., 1020 E. Meadow Circle, Palo Alto, CA 94303, USA
[b] GlaxoSmithKline, Five Moore Drive, Research Triangle Park, NC 27709, USA
[c] GlaxoSmithKline, Gunnels Wood Road, Stevenage, Herts SG1 2NY, UK
[d] Acme Bioscience, Inc., 3941 E. Bayshore Road, Palo Alto, CA 94303, USA
[e] BioDuro LLC, Building E, No. 29, Life Science Park Road, Beijing 102206, PR China

ARTICLE INFO

Article history:
Received 9 September 2010
Revised 28 September 2010
Accepted 1 October 2010
Available online 30 October 2010

Keywords:
Hepatitis C virus
HCV NS3
Protease inhibitor
Macrocyclic inhibitor
Benzoxaborole

ABSTRACT

HCV NS3/4A serine protease is essential for the replication of the HCV virus and has been a clinically validated target. A series of HCV NS3/4A protease inhibitors containing a novel acylsulfamoyl benzoxaborole moiety at the P1′ region was synthesized and evaluated. The resulting P1–P3 and P2–P4 macrocyclic inhibitors exhibited sub-nanomolar potency in the enzymatic assay and low nanomolar activity in the cell-based replicon assay. The in vivo PK evaluations of selected compounds are also described.

Hepatitis C virus (HCV) is a major cause of chronic liver disease that can lead to cirrhosis, carcinoma and liver failure. It is estimated that over 200 million people are chronically infected with this virus and it is the leading cause of liver transplants.[1] The current standard treatment for HCV infection is based on a combination therapy of injectable pegylated interferon-α (PEG IFN-α) and antiviral drug ribavirin. This treatment, indirectly targeting the virus, is associated with significant side effects often leading to treatment discontinuation in certain patient populations.[2] In addition, approximately 50% of genotype-1 (the predominant genotype in the US) patients do not respond to this treatment regimen. Giving the high prevalence of the disease infection worldwide, there is an enormous unmet medical need for new therapies against HCV infection.[3]

HCV NS3/4A protease inhibitors have emerged as a promising potential treatment for HCV infection.[4] Two major classes of NS3 protease inhibitors have been developed. The first class is comprised of serine-trap inhibitors. The most advanced drugs are VX-950 (telaprevir)[5] and SCH-503034 (boceprevir),[6] currently in Phase III clinical trials. The second class is represented by reversible noncovalent inhibitors such as BILN-2061 (ciluprevir, Fig. 1), the first compound in its class to achieve clinical proof of concept.[7] Although its development was halted due to cardiac issues in animals, BILN-2061 prompted extensive investigation on further optimization of the peptide framework and P1 carboxylic acid region. To replace the P1 carboxylic acid, many different groups (e.g., tetrazole, acylcyanamide, acysulfonamide, phosphonate) have been studied.[8] Among them, cyclopropyl acylsulfonamide appears to be the preferred replacement for the P1 carboxylic acid.[9] Further application of this strategy led to the discovery of a number of clinical candidates including ITMN-191 (danoprevir),[10] TMC-435350 (medivir)[11] and MK-7009 (vaniprevir),[12] currently in advanced clinical trials. However, rapid emergence of drug-resistance has recently been observed for HCV NS3 protease inhibitors.[13] Therefore, there remains a need for the discovery of new HCV NS3 protease inhibitors with novel binding properties.

As part of our continued efforts to discover novel HCV NS3 protease inhibitors,[14] we envisioned that acylsulfamoyl benzoxaborole could be used to replace the cyclopropyl acylsulfonamide moiety (Fig. 2). Benzoxaboroles[15,16] are organoboron compounds that have emerged as a new class of potential therapeutic agents.

* Corresponding authors. Tel.: +1 650 543 7587; fax: +1 650 543 7660 (X.L.); tel.: +1 919 483 9462; fax: +1 919 315 6923 (W.M.K.).
E-mail addresses: xli@anacor.com (X. Li), wieslaw.m.kazmierski@gsk.com (W.M. Kazmierski).

0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.10.007

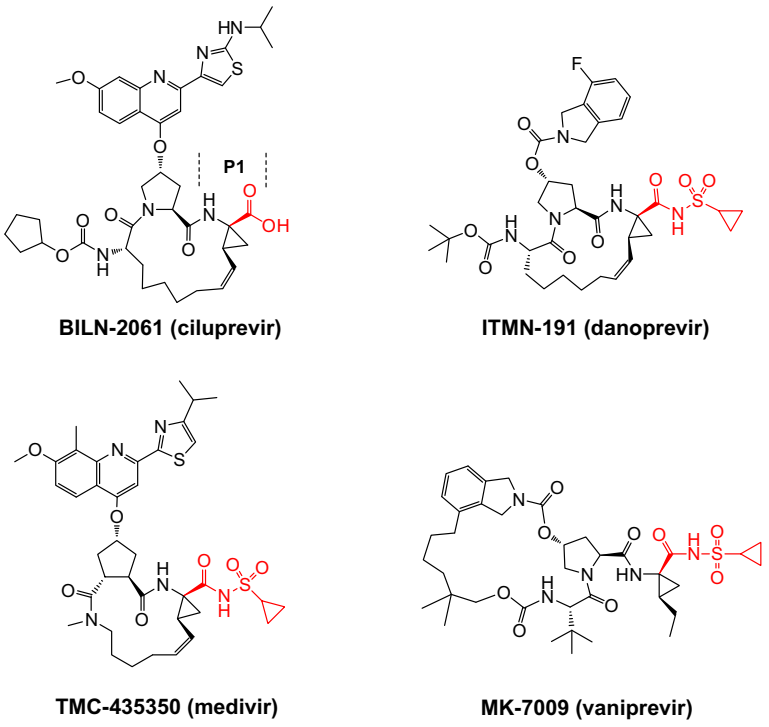

Figure 1. Selected reversible noncovalent inhibitors of HCV NS3 protease in advanced clinical trials.

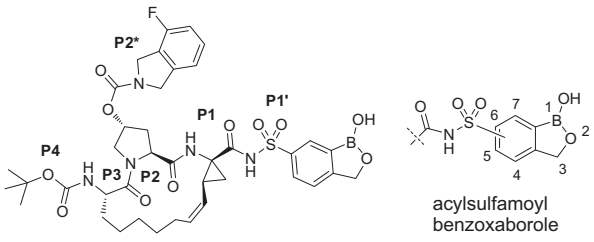

Figure 2. Hypothetical P1–P3 macrocyclic inhibitor in which an acylsulfamoyl benzoxaborole is used to replace the cyclopropyl acylsulfonamide in danoprevir.

Compounds containing a benzoxaborole moiety have been shown to interact with a variety of biological targets and also exhibit good drug properties.[15] Studies of a hypothetical benzoxaborole inhibitor derived from danoprevir (ITMN-191) docked into HCV NS3 protease suggest the benzoxaborole moiety can potentially form polar interactions with Thr 42, and positively charged Lys 136 (Fig. 3).[17] Our strategy was to scan for new potential benzoxaborole interactions with the protease by exploring the impact of two distinct macrocyclic series and different regioisomers of acylsulfamoyl benzoxaboroles on the inhibitory potency.

Boronate **4** or **5**, an important intermediate towards the 6-acylsulfamoyl benzoxaboroles, was prepared according to Scheme 1. Reaction of bromide **1** with pinacol diborane in the presence of palladium catalyst afforded boronate **2**. Bromination of **2** with NBS and AIBN gave benzyl bromide **3**. Subsequently, treatment of **3** with sodium acetate in glacial acetic acid gave the corresponding benzyl acetate **4**. Reaction of **4** with sodium hydroxide followed by acid treatment resulted in 6-sulfamoyl benzoxaborole **5**. We found that either boronate **4** or **5** could be coupled to HCV NS3 inhibitor scaffolds to form the targeted acylsulfamoyl benzoxaborole inhibitors.[18]

Similarly, towards the 5-acylsulfamoyl benzoxaboroles, the boronate intermediate **10** was prepared according to Scheme 2, while

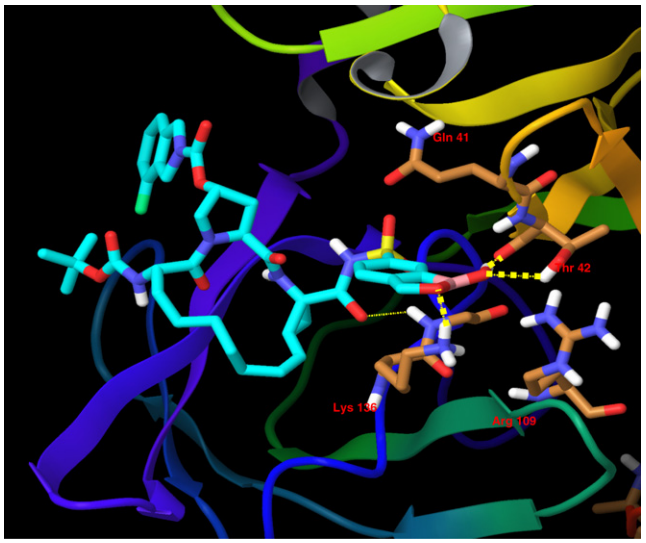

Figure 3. Modeling of a hypothetical benzoxaborole inhibitor derived from danoprevir with HCV NS3 protease. Potential polar interactions for P1′-benzoxaborole include main chain and side chain of Thr 42, and positively charged Lys 136. The Boc group in danoprevir was replaced with a chemically more-stable cyclopentyl carbamate in compound **17**.

the boronate **15**, an intermediate towards 4-acylsulfamoyl benzoxaboroles, was prepared according to Scheme 3. The sulfonamides **7** and **12** used in the synthesis were made from the starting sulfonyl chlorides **6** and **11**, respectively.

With these key intermediates in hand, we set out to investigate the P1–P3/P2–P4 macrocyclic series and also explore the impact of regioisomers of acylsulfamoyl benzoxaboroles. The P1–P3 macrocyclic inhibitors **17**–**18** were synthesized according to Scheme 4. Initially one of our targeted compounds was the hypothetical P1–P3 macrocyclic inhibitor in which 6-acylsulfamoyl benzoxaborole is