Bioorganic & Medicinal Chemistry Letters 21 (2011) 2048–2054

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Synthesis and SAR of acyclic HCV NS3 protease inhibitors with novel P4-benzoxaborole moieties

Xianfeng Li [a,*], Suoming Zhang [a], Yong-Kang Zhang [a], Yang Liu [a], Charles Z. Ding [a], Yasheen Zhou [a], Jacob J. Plattner [a], Stephen J. Baker [a], Wei Bu [a], Liang Liu [a], Wieslaw M. Kazmierski [b,*], Maosheng Duan [b], Richard M. Grimes [b], Lois L. Wright [b], Gary K. Smith [b], Richard L. Jarvest [c], 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 12 January 2011
Revised 1 February 2011
Accepted 2 February 2011
Available online 23 February 2011

Keywords:
Synthesis and SAR
Structure–activity relationships
Benzoxaborole
HCV NS3 protease
Acyclic inhibitors

ABSTRACT

We have synthesized and evaluated a new series of acyclic P4-benzoxaborole-based HCV NS3 protease inhibitors. Structure–activity relationships were investigated, leading to the identification of compounds **5g** and **17** with low nanomolar potency in the enzymatic and cell-based replicon assay. The linker-truncated compound **5j** was found to exhibit improved absorption and oral bioavailability in rats, suggesting that further reduction of molecular weight and polar surface area could result in improved drug-like properties of this novel series.

Hepatitis C virus (HCV) infection is the principal cause of chronic liver disease that can lead to cirrhosis, carcinoma and liver failure.[1] More than 200 million people worldwide are chronically infected by this virus. Currently, the most effective 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, this treatment regimen cures only less than 50% of patients infected with genotype-1 which is the predominant genotype (while genotype 1a is most abundant in the US, the majority of sequences in Europe and Japan are from genotype 1b).[3] Limited efficacy and adverse side effects of current treatment, and high prevalence of infection worldwide highlight an urgent need for more effective, convenient, and well-tolerated treatments.[4]

HCV NS3 serine protease plays a critical role in the HCV replication by cleaving downstream sites (with the assistance of the cofactor NS4A) along the HCV viral polyprotein to produce functional proteins. Recently, NS3/4A protease inhibitors have emerged as a promising treatment for HCV infection.[5] There are two distinct classes of NS3 protease inhibitors in clinical development. The first class is comprised of serine-trap inhibitors, exemplified by VX-950 (telaprevir)[6] and SCH-503034 (boceprevir).[7] The second class is represented by reversible noncovalent inhibitors such as macrocyclic inhibitors BILN-2061 (ciluprevir),[8] ITMN-191 (danoprevir),[9] TMC-435350[10] and MK-7009 (vaniprevir).[11] Due to concern over cardiac issues in animals treated with macrocyclic BILN-2061,[12] newer acyclic inhibitors have recently been developed exemplified by BI-201335[13] and BMS-650032.[14] However, a rapid development of viral resistance has been observed for patients treated with HCV NS3 protease inhibitors.[15] Therefore, the discovery of new NS3 protease inhibitors with novel binding paradigm and thus potentially differentiated resistance profile is highly desirable.

As part of our ongoing efforts to discover new HCV NS3 protease inhibitors,[16–19] we have recently identified a novel series of P4-benzoxaborole based macrocyclic NS3 protease inhibitors as exemplified by compound **1** (Fig. 1).[19] These macrocyclic inhibitors are

* 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 © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2011.02.006

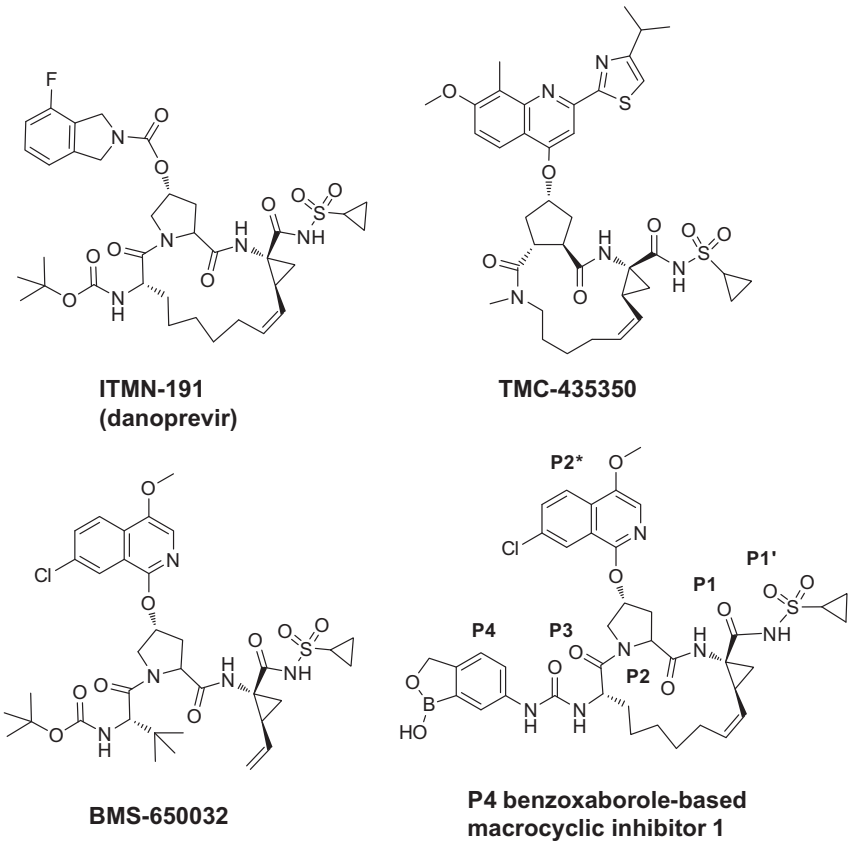


Figure 1. Selected known NS3 serine protease inhibitors.

very potent in the HCV NS3 protease and cell-based replicon assays. However, these macrocyclic compounds had high molecular weight (MW) and polar surface area (PSA), which may limit their oral absorption and bioavailability. In parallel, we also pursued an acyclic series with the plan to potentially, if needed, rebalance their physicochemical properties (MW and PSA) in order to improve their in vivo absorption and bioavailability. In this Letter, we detail the SAR in this acyclic series by exploring various linkers and substitutions around the benzoxaborole moiety as well as the P2* groups.

Figure 2 lists functionalized benzoxaboroles **2a**–**i** that were used to make P4-benzoxaborole acyclic inhibitors **5a**–**i**, Table 1.

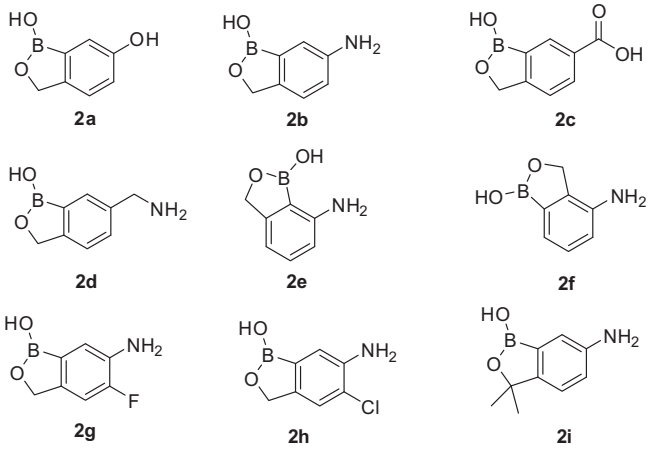


Figure 2. Functionalized benzoxaboroles prepared.

Benzoxaboroles **2a**–**d** and **2g** were prepared as described in our previous publication.[19] Benzoxaboroles **2e**–**f** and **2h**–**i** were prepared according to procedures described in Supplementary data.

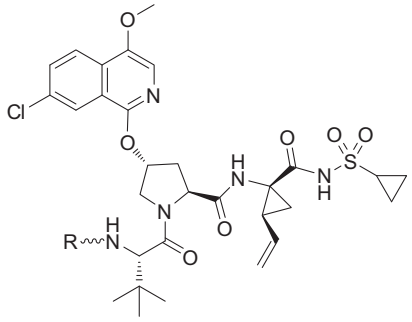
Our initial medicinal chemistry efforts examined the acyclic series with P2* isoquinoline group, which was successfully demonstrated by Bristol-Myers Squibb[14] and our group[19] to support high potency of NS3/4A inhibitors in two different series. Introduction of P4-benzoxaborole groups in this P2* isoquinoline based acyclic series to explore SAR was carried out according to Scheme 1. Coupling of amine **3**[20] with Boc-protected L-*tert*-leucine and subsequent Boc removal afforded amine **4**. The carbamate-linked compound (**5a**) was prepared by reaction of **4** with benzoxaborole **2a** in the presence of CDI. The urea-linked compounds (**5b**, **5d**–**i**) were prepared via the isocyanide reaction with amino benzoxaboroles (**2b**, **2d**–**i**), as described previously.[19] Amide **5c** was prepared by HATU/DIEA—mediated coupling of **4** with benzoxaborole carboxylic acid **2c**.

A shorter amine-based linker-truncated compound **5j** was synthesized according to Scheme 2. Reductive amination of 3,3-dimethyl-2-oxobutanoic acid **6** with **2b** gave the benzoxaborole-substituted amino acid **7**. Coupling of **7** with amine **3** in presence of HATU and DIEA afforded diastereomers, subsequently separated by the prep-HPLC. The active diastereomer in the enzyme assay was assumed to be **5j**, although the absolute stereochemistry has not been determined.

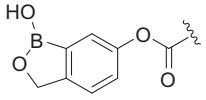
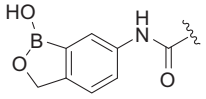
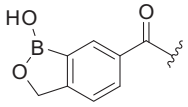
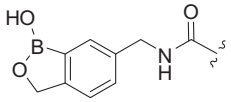
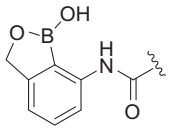
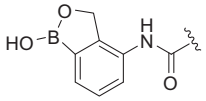
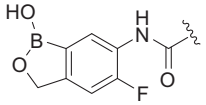
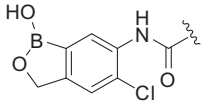
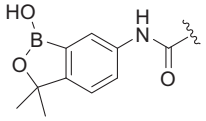
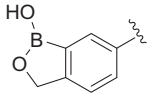
The inhibitory activity of the P4-benzoxaborole based inhibitors were evaluated by FRET NS3/4A 1a protease domain assays.[21a,b] Cellular activity was determined using 1a and 1b HCV replicon assay.[22] Results are reported in Table 1.

Compound **5a** with a carbamate linker exhibited nanomolar potency against NS3 1a enzyme with IC_{50} value of 1.3 nM. It displayed cellular activity in the replicon 1a and 1b assay with EC_{50}

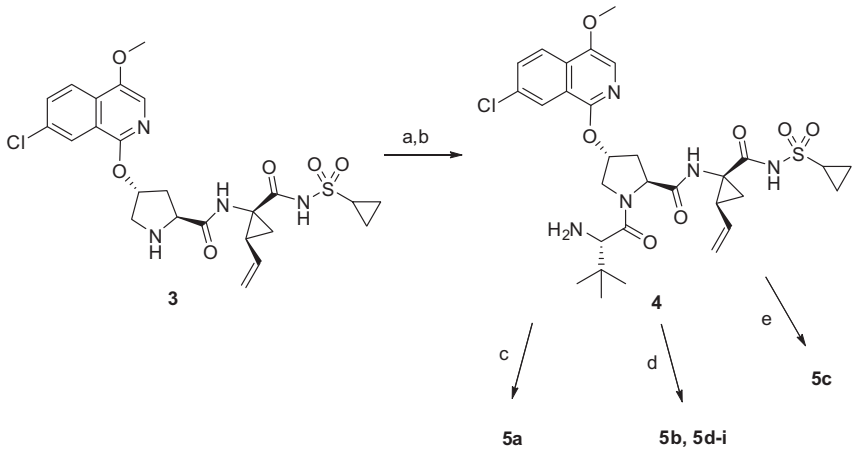
Table 1
In vitro activity of acyclic inhibitors **5a–j** with various linkers and substitutions



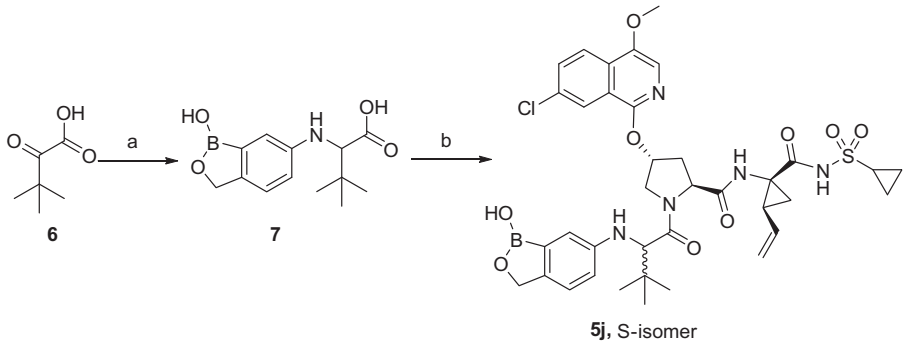
5a-j

Compd	R group	NS3/4A 1a IC_{50}[a,b] (nM)	Replicon EC_{50}[c] (nM)	
			1a	1b
1		0.6[a]	60	3.9
5a		1.3[a]	170	23
5b		2.2[a]	160	24
5c		4.6[b]	290	91
5d		2.0[b]	130	25
5e		16[b]	65	38
5f		4.0[b]	500	81
5g		1.7[a]	31	4.3
5h		1.3[b]	47	34
5i		26[b]	280	130
5j[d]		4.5[b]	110	34

[a] FRET assay as described in Ref. 21a.
[b] FRET assay as described in Ref. 21b.
[c] Replicon assay as described in Ref. 22.
[d] The active diastereomer, and the absolute stereochemistry not determined. The other diastereomer showed IC_{50} of 350 nM in the same enzyme assay.



Scheme 1. Reagents and conditions: (a) Boc-L-*tert*-leucine, HATU, DIEA, DCM, overnight, 70%; (b) 4 N HCl, dioxane, 100%; (c) **2a**, CDI, DCM, DMF, rt, 48 h, 19%; (d) triphosgene, TEA, THF, rt, 4 h; then **2b**, **2d–i**, rt, overnight, 10–50%; (e) **2c**, HATU, DIEA, anhydrous DMF, rt, overnight, 41%.



Scheme 2. Reagents and conditions: (a) **2b**, acetic acid, 4 h, then $NaBH(OAc)_3$, overnight, 13%; (b) **3**, HATU, DIEA, DCM, overnight, 19%.

values of 170 and 23 nM, respectively. Replacement of the carbamate linker in **5a** with urea in **5b** resulted in similar enzyme (IC_{50} = 2.2 nM) and replicon potency (replicon 1a, EC_{50} = 160 nM; replicon 1b, EC_{50} = 24 nM). Extending the urea linker in **5d** retained potency. On the other hand, replacing the urea linker with an amide in **5c** was detrimental to potency in both enzymatic and replicon assay. Compounds **5e** and **5f** are regioisomers of **5b**. Isomer **5f** was found to be less active than **5b** in the enzyme and replicon assay. Interestingly, while **5e** was 8-fold less potent than **5b** in the enzyme assay, it was about equipotent to **5b** in the replicon assay. We hypothesized that the ability of the benzoxaborole BOH group to form an intramolecular H-bonding with the amide hydrogen may have resulted in improved cell permeability[23] and thus replicon potency. The differential activity of various P4-benzoxaborole regioisomers contrasts the results observed in our P1′-benzoxaborole series,[18] where very little difference in potency is observed within acylsulfamoyl benzoxaborole regioisomers. This result underlines special structural role played by the P4-benzoxaborole moiety. A limited exploration of substitution around the benzoxaborole ring was also conducted. The most effective substitution was *para*-F atom in the phenyl ring, which improved replicon potency fivefold in compound **5g** (1a, EC_{50} = 31 nM; 1b, EC_{50} = 4.3 nM). These results were very encouraging considering that the fluoro-containing inhibitor **5g** was equipotent to the macrocyclic compound **1** in the replicon assay. Gem-dimethyl benzoxaborole ring substitution in **5i** was detrimental to potency, potentially due to disfavorable interactions with the enzyme. Finally, compound **5j**, which connects P3 moiety directly to the benzoxaborole ring was found about equipotent to other linker-containing unsubstituted benzoxaborole compounds, such as **5a**, **5b** and **5d**.

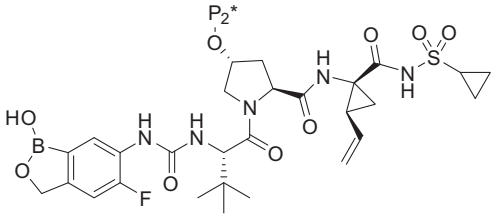
Encouraged by benefits of the fluoro substituent in **5g**, we decided to explore the impact of other P2* groups on the activity of the fluoro-containing acyclic series (Table 2). Compound **12** with P2*-isoindoline group and **17** with P2*-quinoline group were prepared according to Schemes 3 and 4, respectively.

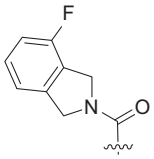
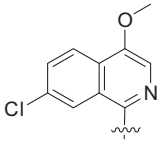
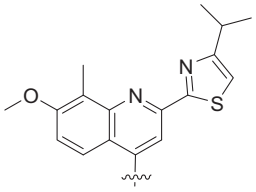
As shown in Scheme 3, acid **8** with P2*-isoindoline group was prepared using our previously published procedure.[24] Subsequent reaction of acid **8** with (1*R*,2*S*)-ethyl-1-amino-2-vinylcyclopropanecarboxylate **9**, followed by hydrolysis afforded acid **10**. Reaction of **10** with cyclopropanesulfonamide, followed by Boc removal gave amine **11**. The urea-linked P4-benzoxaborole compound **12** was prepared via the isocyanide reaction with amino benzoxaborole **2g**, as described.[19]

P2*-quinoline-based compound **17** was synthesized as described in Scheme 4. To that end, acid **13** was prepared according to a literature procedure.[25] Reaction of **13** with (1*R*,2*S*)-1-amino-*N*-(cyclopropylsulfonyl)-2-vinylcyclopropane carboxamide **14** followed by Boc removal afforded amine **15**. Coupling of amine **15** with Boc-protected L-*tert*-leucine and subsequent Boc removal gave amine **16**. Subsequently, urea-linked compound **17** was prepared via the isocyanide reaction with amino benzoxaborole **2g**, as described.[19]

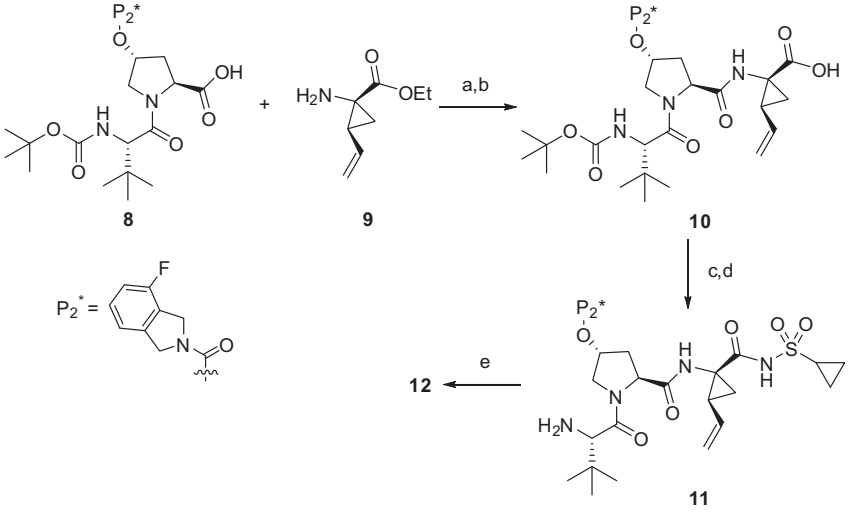
The P2*-isoindoline-based compound **12** was equipotent to **5b** in the enzyme assay, but was 10-fold less potent in the replicon assay. This observation is consistent with the result obtained from our previous macrocyclic series.[19] Compound **17**, on the other hand, exhibited 3–4-fold improvement in replicon 1a assay.

Table 2
In vitro activity of acyclic inhibitors with different P2* groups



Compd	P2* group	*c* Log *P*	NS3/4A 1a IC_{50}[a,b] (nM)	Replicon EC_{50}[c] (nM)	
				1a	1b
12		3.88	1.1[a]	360	56
5g		5.22	1.7[a]	31	4.3
17		6.85	3.1[b]	8.1	8.6

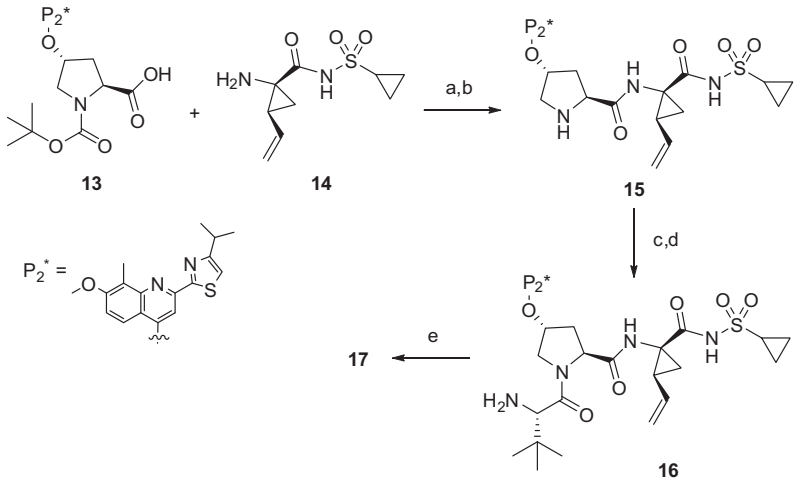
[a] FRET assay as described in Ref. 21a.
[b] FRET assay as described in Ref. 21b.
[c] Replicon assay as described in Ref. 22.



Scheme 3. Reagents and conditions: (a) EDC, HOBt, NMM, rt, overnight, 84%; (b) LiOH, THF, water, rt, 48 h, 90%; (c) cyclopropanesulfonamide, HATU, DIEA, DMAP, DBU, DMF, rt, overnight, 85%; (d) TFA, DCM, rt, 2 h, 85%; (e) triphosgene, TEA, THF, −40 °C, 1 h; then **2g**, rt, 24 h, 30%.

Despite a limited set of compounds, we note an apparent correlation between the cell-based potency (especially replicon 1a) and *c* Log *P* values of these compounds, suggesting that increased lipophilicity might improve compound's cell permeability.

We previously reported that the benzoxaborole-bearing macrocyclic HCV protease inhibitors showed very low oral exposure in rats.[18,19] Subsequent portal vein sampling and analysis suggested that poor oral bioavailability was primarily caused by low com-

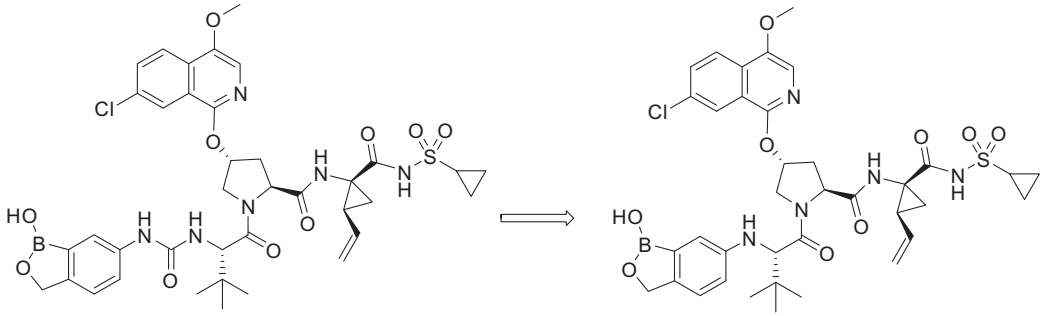


Scheme 4. Reagents and conditions: (a) EDC, HOBt, NMM, rt, overnight, 74%; (b) 4 N HCl, dioxane, overnight, quant.; (c) Boc-L-*tert*-leucine, HATU, DIEA, DCM, overnight, 70%; (d) 4 N HCl, dioxane, overnight, quant.; (e) triphosgene, TEA, THF, 4 h; then **2g**, rt, 24 h, 44%.

pound absorption, possibly reflecting compounds' unfavorable physicochemical properties, such as high MW and PSA. The acyclic inhibitors described herein have somewhat reduced molecular weight, but have PSA values similar to their corresponding macrocyclic counterparts. Consequently, many inhibitors in this acyclic benzoxaborole series still exhibited low oral exposure in rats, as exemplified by **5b**, Table 3. However, compared to **5b**, the linker truncated compound **5j** exhibited improved absorption (4.9%) and oral bioavailability (4.3%) in rats, potentially due to its more drug-like properties, such as reduced MW (by 43) and PSA (by 29). This result was further corroborated by finding out that the permeability of **5j** in the parallel artificial membrane permeability assay (PAMPA) was 10-fold greater than **5b**. Therefore, these results suggest that further reduction of MW and PSA in benzoxaborole-based compounds may be an effective strategy towards drug-like boron-containing HCV protease inhibitors.

In conclusion, we synthesized and evaluated a new series of acyclic P4-benzoxaboroles-based NS3 protease inhibitors. Compounds in this series exhibited nanomolar potencies in enzymatic and cell-based replicon assays. The fluoro-containing acyclic inhibitor **5g** is characterized by cell-based potency comparable to the macrocyclic compound **1**. Furthermore, compared to **5g**, compound **17** exhibited further 3–4-fold improved potency in replicon 1a assay. While most compounds in this class had low oral avail-

Table 3
Physicochemical properties and PK parameters of selected inhibitors in male Sprague–Dawley rats[a]



Parameter	Compd	
	5b	**5j**
MW	823	780
c log *P*	5.2	5.6
m log *D*	4.5	4.0
PSA	214	185
PAMPA	7.2	73
CL (mL/h/kg), iv	476	2927
$AUC_{0\text{-inf}}$ (h μg/mL), po	0.041	0.075
% Absorption[b]	0.92	4.9
%*F*[c]	0.42	4.3

[a] Compounds were dosed orally at a dose of 5 mg/kg ($n = 3$) and intravenously at a dose of 1 mg/kg ($n = 3$).
[b] Calculated from portal vein drug concentrations after oral administration as compared to that after IV administration.
[c] Calculated from jugular vein drug concentrations after oral administration as compared to that after IV administration.

ability in rat PK model, the linker-truncated compound **5j** was better absorbed in vitro and in vivo and had comparatively better oral bioavailability, thus suggesting that further reduction of MW and PSA could result in improved drug-like properties of this novel series. Further efforts directed towards both improving the PK and characterizing the influence of benzoxaborole moiety on HCV resistance profile of new benzoxaborole-containing inhibitors will be reported in due course.

Acknowledgments

The authors acknowledge Dazhong Fan, Xuelei Qian, Liang Liao, Dianjun Chen, Xiantao Dong, Peng Liang, Jianbin Xiao, Guanghui Li, Shuanghui Wang, Chong Li, Gang Lü, Baojuan Zhao and Xinming Zhou for technical assistance and timely supply of key intermediates.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.02.006.

References and notes

1. Zoulim, F.; Chevallier, M.; Maynard, M.; Trepo, C. *Rev. Med. Virol.* **2003**, *13*, 57.
2. Fried, M. W. *Hepatology* **2002**, *36*, S237.
3. Pearlman, B. L. *Am. J. Med.* **2004**, *117*, 344.
4. For a recent review on HCV anti-viral agents, see: (a) Flisiak, R.; Parfieniuk, A. *Expert Opin. Invest. Drugs* **2010**, *19*, 63; (b) Kwong, A. D.; McNair, L.; Jacobson, I.; George, S. *Curr. Opin. Pharmacol.* **2008**, *8*, 522.
5. For a recent review on HCV NS3/4A protease inhibitors, see: (a) Chen, K. X.; Njoroge, F. G. *Curr. Opin. Invest. Drugs* **2009**, *10*, 821; (b) Reiser, M.; Timm, J. *Expert Rev. Anti. Infect. Ther.* **2009**, *7*, 537.
6. Lin, C.; Kwong, A. D.; Perni, R. B. *Infect. Disord. Drug Targets* **2006**, *6*, 3.
7. Njoroge, F. G.; Chen, K. X.; Shih, N. Y.; Piwinski, J. J. *Acc. Chem. Res.* **2008**, *41*, 50.
8. Llinàs-Brunet, M.; Bailey, M. D.; Bolger, G.; Brochu, C.; Faucher, A. M.; Ferland, J. M.; Garneau, M.; Ghiro, E.; Gorys, V.; Grand-Maître, C.; Halmos, T.; Lapeyre-Paquette, N.; Liard, F.; Poirier, M.; Rhéaume, M.; Tsantrizos, Y. S.; Lamarre, D. *J. Med. Chem.* **2004**, *47*, 1605.
9. Seiwert, S. D.; Andrews, S. W.; Jiang, Y.; Serebryany, V.; Tan, H.; Kossen, K.; Rajagopalan, P. T.; Misialek, S.; Stevens, S. K.; Stoycheva, A.; Hong, J.; Lim, S. R.; Qin, X.; Rieger, R.; Condroski, K. R.; Zhang, H.; Do, M. G.; Lemieux, C.; Hingorani, G. P.; Hartley, D. P.; Josey, J. A.; Pan, L.; Beigelman, L.; Blatt, L. M. *Antimicrob. Agents Chemother.* **2008**, *52*, 4432.
10. Raboisson, P.; de Kock, H.; Rosenquist, A.; Nilsson, M.; Salvador-Oden, L.; Lin, T. I.; Roue, N.; Ivanov, V.; Wähling, H.; Wickström, K.; Hamelink, E.; Edlund, M.; Vrang, L.; Vendeville, S.; Van de Vreken, W.; McGowan, D.; Tahri, A.; Hu, L.; Boutton, C.; Lenz, O.; Delouvroy, F.; Pille, G.; Surleraux, D.; Wigerinck, P.; Samuelsson, B.; Simmen, K. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4853.
11. McCauley, J. A.; McIntyre, C. J.; Rudd, M. T.; Nguyen, K. T.; Romano, J. J.; Butcher, J. W.; Gilbert, K. F.; Bush, K. J.; Holloway, M. K.; Swestock, J.; Wan, B. L.; Carroll, S. S.; Dimuzio, J. M.; Graham, D. J.; Ludmerer, S. W.; Mao, S. S.; Stahlhut, M. W.; Fandozzi, C. M.; Trainor, N.; Olsen, D. B.; Vacca, J. P.; Liverton, N. J. *J. Med. Chem.* **2010**, *53*, 2443.
12. Hinrichsen, H.; Benhamou, Y.; Wedemeyer, H.; Reiser, M.; Sentjens, R. E.; Calleja, J. L.; Forns, X.; Erhardt, A.; Crönlein, J.; Chaves, R. L.; Yong, C. L.; Nehmiz, G.; Steinmann, G. G. *Gastroenterology* **2004**, *127*, 1347.
13. Llinàs-Brunet, M.; Bailey, M. D.; Goudreau, N.; Bhardwaj, P. K.; Bordeleau, J.; Bös, M.; Bousquet, Y.; Cordingley, M. G.; Duan, J.; Forgione, P.; Garneau, M.; Ghiro, E.; Gorys, V.; Goulet, S.; Halmos, T.; Kawai, S. H.; Naud, J.; Poupart, M. A.; White, P. W. *J. Med. Chem.* **2010**, *53*, 6466.
14. (a) Chemical and Engineering News (April 12, 2010 issue), 88, pp 30–33.; (b) Perrone, R.K.; Wang, C.; Ying, W.; Song, A.I. WO 2009085659.
15. Rong, L.; Dahari, H.; Ribeiro, R. M.; Perelson, A. S. *Sci. Transl. Med.* **2010**, *2*, 30ra32.
16. Li, X.; Zhang, Y.-K.; Liu, Y.; Ding, C. Z.; Li, Q.; Zhou, Y.; Plattner, J. J.; Baker, S. J.; Qian, X.; Fan, D.; Liao, L.; Ni, Z.-J.; White, G. V.; Mordaunt, J. E.; Lazarides, L. X.; Slater, M. J.; Jarvest, R. L.; Thommes, P.; Ellis, M.; Edge, C. M.; Hubbard, J. A.; Somers, D.; Rowland, P.; Nassau, P.; McDowell, B.; Skarzynski, T. J.; Kazmierski, W. M.; Grimes, R. M.; Wright, L. L.; Smith, G. K.; Zou, W.; Wright, J.; Pennicott, L. E. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3550.
17. Li, X.; Zhang, Y.-K.; Liu, Y.; Ding, C. Z.; Zhou, Y.; Li, Q.; Plattner, J. J.; Baker, S. J.; Zhang, S.; Kazmierski, W. M.; Wright, L. L.; Smith, G. K.; Grimes, R. M.; Crosby, R. M.; Creech, K. L.; Carballo, L. H.; Slater, M. J.; Jarvest, R. L.; Thommes, P.; Hubbard, J. A.; Convery, M. A.; Nassau, P. M.; McDowell, W.; Skarzynski, T. J.; Qian, X.; Fan, D.; Liao, L.; Ni, Z.-J.; Pennicott, L. E.; Zou, W.; Wright, J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5695.
18. Li, X.; Zhang, Y.-K.; Liu, Y.; Zhang, S.; Ding, C. Z.; Zhou, Y.; Plattner, J. J.; Baker, S. J.; Liu, L.; Bu, W.; Kazmierski, W. M.; Wright, L. L.; Smith, G. K.; Jarvest, R. L.; Duan, M.; Ji, J.-J.; Cooper, J. P.; Tallant, M. D.; Crosby, R. M.; Creech, K.; Ni, Z.-J.; Zou, W.; Wright, J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7493.
19. Ding, C. Z.; Zhang, Y.-K.; Li, X.; Liu, Y.; Zhang, S.; Zhou, Y.; Plattner, J. J.; Baker, S. J.; Liu, L.; Duan, M.; Jarvest, R. L.; Ji, J.; Kazmierski, W. M.; Tallant, M. D.; Wright, L. L.; Smith, G. K.; Crosby, R. M.; Wang, A. A.; Ni, Z.-J.; Zou, W.; Wright, J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7317.
20. Sin, N.; Venables, B. L.; Sun, L.-Q.; Sit, S.-Y.; Chen, Y.; Scola, P. M. WO 2008060927.
21. (a) Compounds were assayed in the fluorescence enzymatic assay using HCV NS3/4A 1a protease domain. Conditions: 0.75 nM enzyme (1a domain), 2 μM NS4A, 0.5 μM peptide substrate (Ac-DE-Dap(QXL520)-EE-Abu-ψ-[COO]-AS-C(5-FAMsp)-NH_2 is the FRET substrate purchased from Anaspec Inc. San Jose, CA) in 50 mM HEPES, 20% sucrose, 5 mM DTT, and 0.05% NP-40. Wavelengths of 490 ex and 520 em were used on a Molecular Devices plate reader to measure initial rates; (b) Compounds were assayed in the fluorescence enzymatic assay using HCV NS3/4A 1a protease domain. Conditions: 1 nM enzyme (1a domain), 2 μM NS4A, 5 μM peptide substrate (Ac-DE-D(EDANS)-EE-Abu-ψ-[COO]-AS-K(DABCYL)-NH_2 is the FRET substrate purchased from Anaspec Inc. San Jose, CA) in 50 mM HEPES, 20% sucrose, 5 mM DTT, and 0.05% NP-40. Wavelengths of 355 ex and 495 em were used on a Molecular Devices plate reader to measure initial rates.
22. Lohmann, V.; Korner, F.; Koch, J.-O.; Herian, U.; Theilman, L.; Batenschlager, R. *Science* **1999**, *285*, 110.
23. Kuhn, B.; Mohr, P.; Stahl, M. *J. Med. Chem.* **2010**, *53*, 2601.
24. Fan, D.; Jarvest, R. L.; Lazarides, L.; Li, Q.; Li, X.; Liu, Y.; Liao, L.; Mordaunt, J. E.; Ni, Z.-J.; Plattner, J. J.; Qian, X.; Slater, M. J.; White, G. V.; Zhang, Y.-K. WO 2009046098.
25. Vendeville, S.; Nilsson, M.; de Kock, H.; Lin, T.-I.; Antonov, D.; Classon, B.; Ayesa, S.; Ivanov, V.; Johansson, P. O.; Kahnberg, P.; Eneroth, A.; Wikstrom, K.; Vrang, L.; Edlund, M.; Lindström, S.; Van de Vreken, W.; McGowan, D.; Tahri, A.; Hu, L.; Lenz, O.; Delouvroy, F.; Van Dooren, M.; Kindermans, N.; Surleraux, D.; Wigerinck, P.; Rosenquist, A.; Samuelsson, B.; Simmen, K.; Raboisson, P. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6189.