



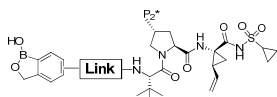
Acyclic HCV NS3/4A Serine Protease Inhibitors with Benzoxaborole at P4 Position: Design, Synthesis and SAR

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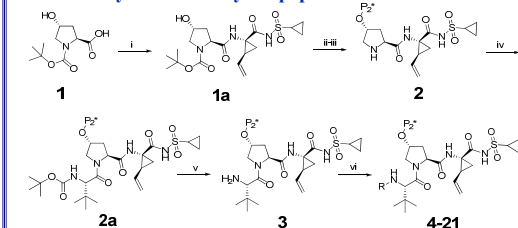
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Abstract

The NS3/4A serine protease of HCV has emerged as a drugable target for management of HCV infection because it is essential for viral replication. Herein, we report the synthesis and SAR of a new series of acyclic tripeptide-containing P4 benzoxaborole inhibitors that exhibit good biochemical potency and cellular activity. Compound **25** in this disclosure showed single digit nanomolar activity in both NS3/4A protease enzyme and cellular replicon assay, especially active against replicon genotype 1a (EC₅₀=8 nM).



Scheme 1. Synthesis of acyclic peptides with P4 benzoxaborole



Conditions and reagents: i) (1R, 2S)-1-amino-N-(cyclopropylsulfonyl)-2-vinylcyclopropane carboxamide, HATU, DIEA, DMF, rt. ii) CDI, DCM, 5h, then 4-fluoroisindoline, overnight, or chloro-quinoline/isoquinoline, *t*-BuOK, DMSO, rt, 2h. iii) TFA/DCM. iv) Boc-amino acid, HATU, DIEA, DMF. v) TFA/DCM, rt or HCl/dioxane, rt. vi) CDI or phosgene or 4-nitrophenyl carbonochloridate, benzoxaboroles in DCM.

SAR of Linker Variations

Inhibitors target preferentially genotype 1b
 Ureas provide better replicon potency
 Polar amine, such as in compd 8, diminishes cellular potency

| Compd | R- | NS3/4A Enzyme 1a IC ₅₀ (uM)* | HCV replicon EC ₅₀ (uM) | |
|-------|----|---|------------------------------------|-------|
| | | | 1a | 1b |
| 4 | | 0.0022 | >0.50 | 0.123 |
| 5 | | 0.0023 | >0.50 | 0.050 |
| 6 | | 0.0064 | >0.50 | 0.327 |
| 7 | | 0.0209 | >0.50 | 0.17 |
| 8 | | 0.0741 | >0.50 | >0.5 |
| 9 | | 0.0021 | >0.50 | 0.021 |
| 10 | | 0.0043 | 0.169 | 0.060 |
| 11 | | 0.0013 | >0.50 | 0.050 |
| 12 | | 0.0042 | >0.50 | 0.206 |
| 13 | | 0.0037 | >0.50 | 0.485 |

SAR of Benzoxaborole Core Substitutions and Linking Site

C-6-Linked benzoxaboroles are more potent than other positional linked ones (**5** vs **14**, **15**)
 Halo substitutions enhance cellular potency
 C-3 methyl substitutions are indifferent or unfavorable

| Compd | R- | NS3/4A Enzyme 1a IC ₅₀ (uM)* | HCV replicon EC ₅₀ (uM) | |
|-------|----|---|------------------------------------|-------|
| | | | 1a | 1b |
| 5 | | 0.0023 | >0.50 | 0.050 |
| 14 | | 0.0046 | >0.50 | 0.117 |
| 15 | | 0.0050 | >0.50 | 0.174 |
| 16 | | 0.0016 | 0.555 | 0.037 |
| 17 | | 0.0018 | 0.624 | 0.014 |
| 18 | | 0.0011 | 0.610 | 0.021 |
| 19 | | 0.0014 | 0.484 | 0.025 |
| 20 | | 0.0059 | >0.50 | 0.214 |
| 21 | | 0.0023 | >0.50 | 0.037 |

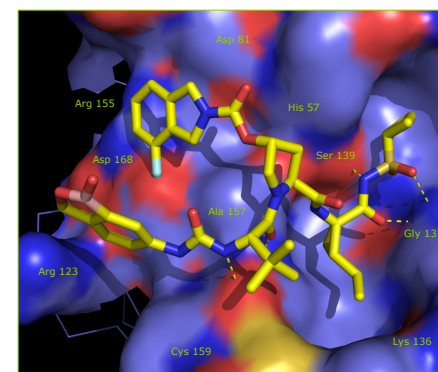


Figure 1. Inhibitor **5** docked into the active site of HCV NS3/4A protease. Potential hydrogen bonds are shown by dotted lines

SAR of P2* Variations

Both quinoline P2* enhance both replicon 1a and 1b activity, 2'-heteroarylquinolines are better than isoquinoline.
 Cellular potency appears to positively correlate with ClogP, the higher the ClogP, the better potency

| compd | R- | P ₂ * | ClogP | NS3/4A Enzyme 1a IC ₅₀ (uM)* | HCV replicon EC ₅₀ (uM) | |
|-------|----|------------------|-------|---|------------------------------------|--------|
| | | | | | 1a | 1b |
| 5 | | | 1.61 | 0.0023 | >0.50 | 0.050 |
| 22 | | | 3.43 | 0.0031 | 0.180 | 0.025 |
| 23 | | | 3.88 | 0.0017 | 0.050 | 0.002 |
| 18 | | | 1.67 | 0.0011 | 0.610 | 0.021 |
| 24 | | | 3.49 | 0.0016 | 0.0716 | 0.0039 |
| 25 | | | 5.27 | 0.0031 | 0.0081 | 0.0086 |
| 4 | | | 1.93 | 0.0022 | >0.50 | 0.123 |
| 26 | | | 3.75 | 0.0015 | 0.242 | 0.018 |
| 27 | | | 4.20 | 0.0012 | 0.071 | 0.013 |

*FRET assay (QXL520) with HCV NS3/4A 1a protease domain in the buffer containing 20% sucrose

Conclusions

- Acyclic peptido HCV inhibitors with P4 benzoxaboroles were designed and prepared. These inhibitors exhibit potent enzymatic potency.
- Clear SAR is evident in modifying the benzoxaborole core structure and the linking groups in between benzoxaborole and tripeptide fragmentation.
- Quinolines or isoquinolines P2* provide more potent cell-active inhibitors than isoindoline P2*.
- Compound **25** showed single digit nanomolar activity in both genotype 1a and 1b replicon assay. Further evaluation of the series is clearly warranted.

References

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