



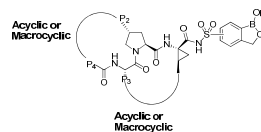
## Synthesis and Evaluation of Novel Inhibitors Containing P1' Benzoxaborole for HCV NS3/4A Serine Protease

Yang Liu<sup>1</sup>, Y.-K. Zhang<sup>1</sup>, X. Li<sup>1</sup>, S. Zhang<sup>1</sup>, C. Z. Ding<sup>1</sup>, Q. Li<sup>1</sup>, Y. Zhou<sup>1</sup>, J. J. Plattner<sup>1</sup>, S. J. Baker<sup>1</sup>, L. Feng<sup>1</sup>, L. Liu<sup>1</sup>, W. M. Kazmierski<sup>2</sup>, M. Duan<sup>2</sup>, J. Li<sup>2</sup>, J. Cooper<sup>2</sup>, R. M. Grimes<sup>2</sup>, M. D. Tallant<sup>2</sup>, L. L. Wright<sup>2</sup>, G. K. Smith<sup>2</sup>, R. M. Crosby<sup>2</sup>, A. A. Wang<sup>2</sup>, R. L. Jarvest<sup>3</sup>, M. J. Slater<sup>3</sup>, C. M. Edge<sup>3</sup>, J. A. Hubbard<sup>3</sup>, P. Nassau<sup>3</sup>, B. McDowell<sup>3</sup>, T. J. Skarzynski<sup>3</sup>, Z.-J. Ni<sup>4</sup>, X. Qian<sup>4</sup>, D. Fan<sup>4</sup>, L. Liao<sup>4</sup>, D. Chen<sup>4</sup>, X. Dong<sup>5</sup>, P. Liang<sup>5</sup>, J. Xiao<sup>5</sup>, G. Li<sup>5</sup>, S. Wang<sup>5</sup>, C. Li<sup>5</sup>, G. Lü<sup>5</sup>, B. Zhao<sup>5</sup>, X. Zhou<sup>5</sup>, W. Zou<sup>5</sup>, J. Wright<sup>5</sup>

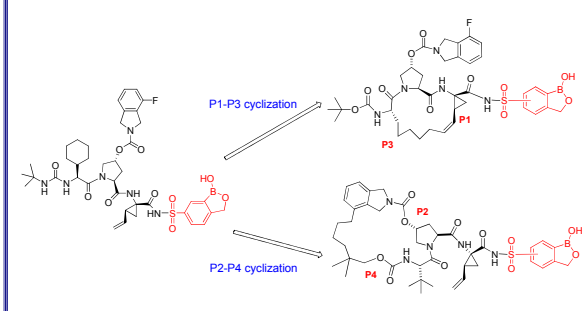
<sup>1</sup>Anacor Pharmaceuticals, Inc., 1020 E. Meadow Circle, Palo Alto, CA; <sup>2</sup>GlaxoSmithKline, Five Moore Drive, Research Triangle Park, NC; <sup>3</sup>GlaxoSmithKline, Gunnels Wood Road, Stevenage, Herts, UK; <sup>4</sup>Acme Bioscience, Inc., 3941 E. Bayshore Road, Palo Alto, CA; <sup>5</sup>BioDuro LLC, Life Science Park Road, Changping District, Beijing, China.

### Abstract

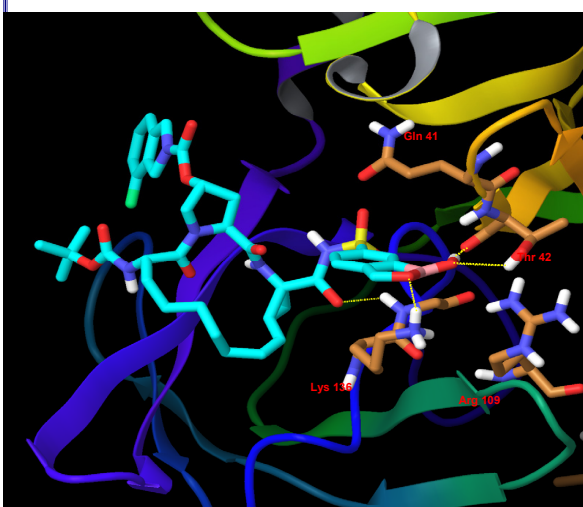
HCV virus chronically infects more than 200 million people worldwide and current treatment option has been very limited. There is urgent demand for research and development aiming for discovery of new efficacious therapeutics. The HCV NS3/4A serine protease is considered to be essential for the replication of the virus and has been a clinically validated target. We have designed new series of acyclic, P1-P3 and P2-P4 macrocyclic compounds that contain benzoxaborole (CBO) at the P1' position. The resulting inhibitors show good enzymatic and replicon activities.



### Progressive Chemistry Strategy to P1'-CBO Based Inhibitors



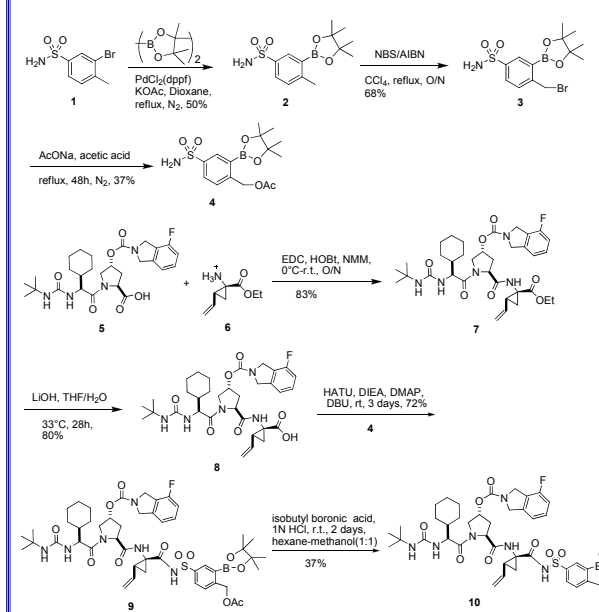
### Modeling of P1'-CBO with HCV NS3 Protease



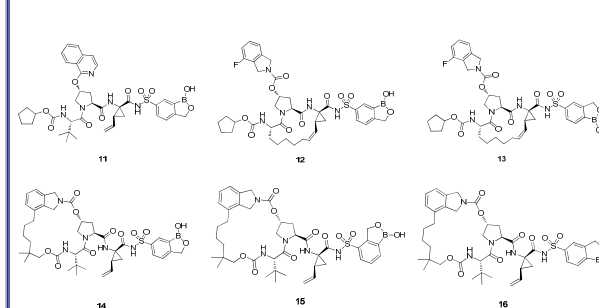
Potential polar interactions for P1'-CBO: 1) Mainchain & sidechain of Thr 42; 2) Positively charged Lys 136 & Arg 109

\*Docked compound is a P1-P3 macrocyclic **12** analog with Boc at the P4 position. During its synthesis, Boc group was replaced with a chemically stable cyclopentyl carbamate to give **12**.

### Representative Synthesis of Inhibitor 10 with P1'-CBO



### P1-P3 and P2-P4 Macrocyclic P1'-CBO Inhibitors



Compounds	NS3/4A Enzyme 1a IC <sub>50</sub> (nM) <sup>a</sup>	HCV replicon EC <sub>50</sub> (nM)	
		1a	1b
<b>10</b>	2.85	8,811	209
<b>11</b>	12.7	>10,000	1,150
<b>12</b>	0.81	213.8	6.3
<b>13</b>	0.81	87.1	7.94
<b>14</b>	0.43	96.6	16.4
<b>15</b>	0.32	64.6	8.7
<b>16</b>	0.81	80.4	10.5

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

### Conclusion

- Chemistry developed for the synthesis of acyclic, P1-P3 and P2-P4 macrocyclic inhibitors (**10-16**) of HCV NS3 serine protease with different P1'-CBO regioisomers
- Both P1-P3 and P2-P4 macrocyclic inhibitors significantly improve enzymatic and especially replicon potencies, when compared to the linear analogs
- P1-P3 macrocyclic inhibitors are as active as P2-P4 macrocyclic inhibitors, suggesting that two cyclization strategies can be equally effective in enhancing inhibitory potencies
- P1'-CBO regioisomers show similar enzymatic and replicon potencies, indicating multiple interactions between P1'-CBO and HCV NS3 serine protease

### References

- SJ Baker, CZ Ding, et al., *Future Med. Chem.* **2009**, *1*, 1275.
- YK Zhang, X Li, et al., *BIT's 7th Annual Congress of International Drug Discovery Science and Technology*, Shanghai, China, October 25, 2009.