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P4 capped amides and lactams as HCV NS3 protease inhibitors with improved potency and DMPK profile

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ABSTRACT

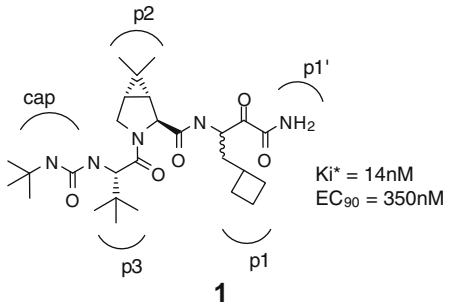
SAR studies on the extension of P3 unit of Boceprevir (**1**, SCH 503034) with amides and lactams and their synthesis is described. Extensive SAR studies resulted in the identification of **36** bearing 4, 4-dimethyl lactam as the new P4 cap unit with improved potency ($K_i^* = 15$ nM, EC 90 = 70 nM) and pharmacokinetic properties (Rat AUC (PO) = 3.52 μM h) compared to **1**.

The hepatitis C virus is a major health hazard affecting over 170 million individuals worldwide[1a] and its infection is a leading cause of chronic liver disease and death from liver disease in the United states.[1b–d] The current standard of care treatment is a combination of subcutaneous pegylated interferon-α with oral nucleoside drug ribavirin.[2] Response rates for HCV patients having genotypes 2 or 3 on a 24 week treatment of this is 80% whereas those with genotype 1 are treated for 48 weeks with response rates of less than 50%. With the opportunity to improve response rates, especially for genotype 1 patients, and given the side effects associated with the current therapy, it is necessary to search for novel potent and drug like inhibitors of NS3 enzyme of HCV with the intent of improving treatment outcomes and potentially shorten treatment duration.

The NS3 protease which is located at N-terminal portion of NS3 protein has a demonstrated vital role in the replication of the HCV virus.[3] Hence there is compelling evidences[4] to suggest that the inhibition of NS3 protease would be a viable strategy for the development of small molecules as antiviral agents. It has been determined that the HCV NS3 protease belongs to the trypsin or chymotrypsin super family of serine protease.[5] For efficient processing, the protease forms a complex with a small polypeptide co-factor NS4A.[6] The structure data of the protease have revealed a shallow and solvent exposed substrate binding region, where the binding energy is mainly derived from weak lipophilic and electrostatic interactions.[7] Despite tremendous difficulty encountered in the process, intensive efforts have been focused on NS3 serine protease and a number of novel inhibitors have been reported.[8] More recently, peptidomimetics like BILN 2061[9], VX-950[10] and MK-7009[11] are reported to show the antiviral activity by inhibiting the replication of the virus along with our clinical candidate SCH 503034 (Fig. 1).[12] Currently, the most advanced candidates are telapravir (VX-950) from Vertex and Boceprevir (SCH 503034) from Schering–Plough which are in phase III clinical trials.

All the inhibitors were synthesized according to the general Scheme 1. The gem dimethyl proline derivative **2** was prepared by a modified published procedure.[13] **2** was coupled to the P3 *N*-Boc *tert*-leucine[14,12] followed by acidic deprotection of the Boc and subsequent coupling with the P4 isocyanate to afford the P4 methyl ester **4**.

Hydrolysis of the methyl ester **4** with LiOH to acid **5** and by subsequent coupling with the P1 unit under EDCI, HOOBt conditions



1

Figure 1. Boceprevir (SCH 503034).

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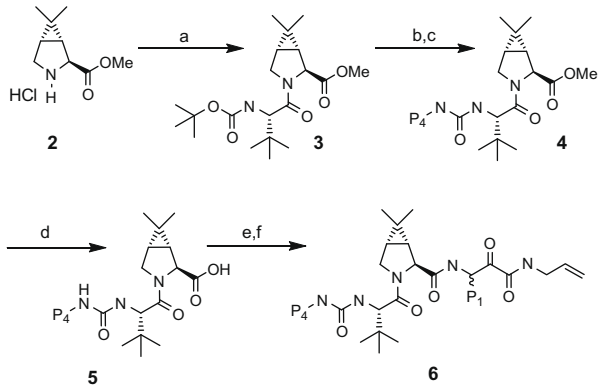
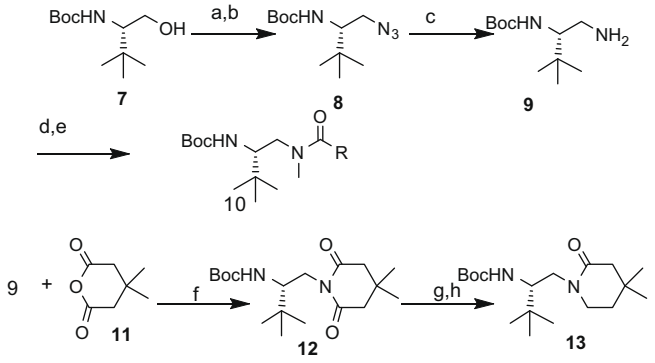


Scheme 1. Synthesis of the P3 capped amide and lactam analog of **1**. Reagents and conditions: (a) *tert*-leucine, EDCI, HOOBt, DMF/CH_2Cl_2; (b) 4 M HCl/dioxane, rt; (c) P4NCO, DIPEA, CH_2Cl_2; (d) LiOH, THF/MeOH/H_2O; (e) P1 hydroxy allyl amide, EDCI, HOOBt, DMF/CH_2Cl_2; (f) Dess–Martin periodinane.

followed by the oxidation of the resulting hydroxyl amide with Dess–Martin Periodonane afforded the keto amide of type **6**. The P4 amide capings were synthesized using the general procedure outlined in Scheme 2. The amine, **9** was synthesized from the corresponding alcohol via mesylation, displacement of the mesylate with the azide followed by reduction of the azide **8**. Condensation of amine **9** with the anhydride **11** resulted in the imide **12**. Selective reduction of the imide to the lactam was achieved via a two step reduction sequence with lithium triethyl borohydride followed by sodium cyano borohydride.[15]

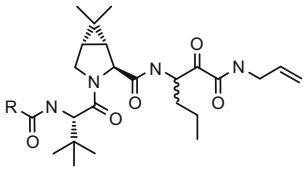
All inhibitors were tested in the HCV continuous enzymatic assay[16] using the NS4A-tethered single chain NS3 serine protease.[17] The K_i^* values reflected the equilibrium constant determined by the reversible covalent bond formed between the ketone and serine and other interactions between the inhibitors and the enzyme.[18] The concentration required for inhibition of 90% of virus replication, EC_{90}, was obtained as a measure of replicon cellular potency.[19] Inhibitors were tested for the activity against one of the most structurally close related serine protease, human neutrophil elastase (HNE) to determine the selectivity between HCV and HNE.

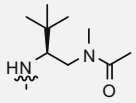
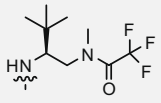
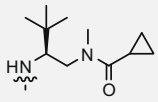
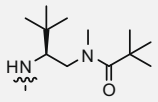
Based on X-ray structure of inhibitor **1** we envisioned that the extension of P3 unit with a group having carbonyl at the appropriate position would possibly engage in hydrogen bonding with Cys 159.[20] Amides and their bioisosteres were one of the initial choices and were evaluated first as the potential P4 capped inhibitors. Amide **15** ($K_i^* = 37$ nM) showed 40-fold improvement in potency compared to **14** bearing tertiary butyl carbamate P4. It is observed



Scheme 2. Reagents and conditions: (a) Mesylchloride, pyridine, rt, 4 h; (b) NaN_3, DMF, 60 °C, 18 h; (c) Pd/C, H_2 (1 atm), 3 h; (d) acetyl chloride, Pyr, CH_2Cl_2, 18 h; (e) Cs_2CO_3, MeI, DMF, 4 h; (f) toluene, reflux, then Ac_2O, Et_3N, 90 °C; (g) $LiEt_3BH$, CH_2Cl_2, −78 °C, 15 min; (f) $NaCNBH_3$, CH_3CN, AcOH.

Table 1
SAR of amides



Entry	R	K_i^* (nM)	EC_{90} (μM)	HNE/HCV
14		1500	—	—
15		37	0.55	150
16		42	—	75
17		91	—	280
18		23,000	—	—

with inhibitors **16**–**18** that bulky groups are not tolerated next to the carbonyl of the amide (Table 1).

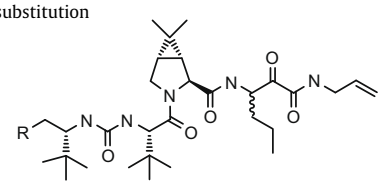
Tethering of the *N*-alkyl to the methyl group of amide **15** was adopted as a method to rigidify the molecule. We discovered that the constrained five membered lactam **19** was equipotent to the acyclic amide **15**. The six membered lactam, **20** showed twofold improvements in potency and HNE selectivity compared to the acyclic amide **15**.

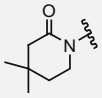
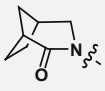
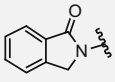
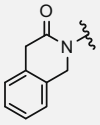
Encouraged by these preliminary results, we decided to probe further the P4 area using substituted and bicyclic lactams (**21**–**23**) and aromatic lactams (**24**, **25**) and the results are shown in Table 2. As observed with acyclic amides, substitution next to the carbonyl (**21**, $K_i^* = 89$ nM) resulted in sixfold loss in potency. However gem dimethyl substitution at the 4 position was well tolerated and seemed to have a profound effect in cellular activity (**22**, $EC_{90} = 80$ nM) with a fourfold improvement compared to **20**. The bicyclic lactam **23** ($K_i^* = 8$ nM, $EC_{90} = 60$ nM) also showed improvement in potency and selectivity. However the rat exposure for **23** was not good enough to pursue this series further. The aromatic lactam **24** ($K_i^* = 40$ nM) was less active in the enzymatic assay compared to **22**. Although aromatic fused six membered lactam **25** ($K_i^* = 19$ nM, $EC_{90} = 250$ nM) exhibited similar enzymatic activity, both the replicon activity and HNE selectivity were poor compared to **22**.

The importance of carbonyl group for potency by engaging in hydrogen bonding with Cys 159 was revealed with cyclic amine **26** which resulted in complete loss in potency. Heteroatoms were incorporated in the lactam ring to modify the electronic property of the carbonyl group (**27** and **28**). Both the carbamate **27** ($K_i^* = 10$ nM, $EC_{90} = 350$ nM) and urea **28** ($K_i^* = 4.9$ nM, $EC_{90} = 175$ nM) were well tolerated and showed a similar or slightly improved activity compared to the corresponding lactam **20**. Unfortunately urea **28** ($K_i^* = 4.9$ nM, $EC_{90} = 175$ nM) exhibited a poor DMPK profile (Table 4) and this series was discontinued.

Our earlier SAR studies and X-ray structure of inhibitors showed that the P3 moiety binds to the S3 pocket mainly through lipophilic interactions.[7] With the discovery of six membered lactams **20** and

Table 2
SAR of cyclic P4 substitution



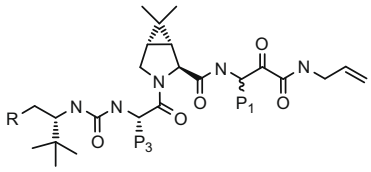
Entry	R	K_i^* (nM)	EC_{90} (μM)	HNE/HCV
19		37	0.70	60
20		14	0.35	320
21		89	—	90
22		17	0.08	310
23		8	0.06	613
24		40	—	1500
25		19	0.20	250
26		2300	—	—
27		10	0.35	100
28		4.9	0.18	360

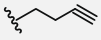
22 we turned our efforts towards the optimization of the P3 and P1 residues and the results are outlined in Table 3. Since it is known from our previous SAR studies which led to the discovery of **1** that norvaline P1 in combination with the allyl amide P1′ provided inhibitors with very good rat PK profile[12], we kept norvaline at the P1 for our P4 and P3 optimization studies.

Our initial P3 optimization started with the unsubstituted lactam **20**. Tertiary butyl glycine P3 replacements with cyclohexyl, **29** ($K_i^* = 1.8$ nM, $EC_{90} = 110$ nM) provided improvement in both enzyme and cellular potency but poor HNE selectivity. Indanyl glycine at P3, **30** ($K_i^* = 9$ nM, $EC_{90} = 80$ nM) further improved the cell potency but lacked selectivity. In addition both **29** and **30** had poor oral exposure in rat (Table 4) compared to **22**. Analogs of **29** and **30** with 4,4-dimethyl lactam at P4 were prepared (**31**, $K_i^* = 1.9$ nM, $EC_{90} = 45$ nM and **32**, $K_i^* = 7$ nM, $EC_{90} = 80$ nM) but did not provide inhibitors with desired selectivity.

We clearly established with the SAR above the superiority of 4,4-dimethyl lactam at P4 and the *tert*-butyl glycine at P3. Our next focus was to optimize the P1 unit keeping tertiary butyl P3 and 4,4-dimethyl lactam P4. From our previous structure activity studies[12] it was demonstrated that norleucine at P1 improves the HNE selectivity. Thus changing the P1 from norvaline (**22**) to norleucine afforded **33** ($K_i^* = 19$ nM, $EC_{90} = 80$ nM) with similar potency both in enzymatic and cellular assays with threefold improvement in

Table 3
SAR of P3 and P1 substitutions



Entry	P4	P3	P1	K_i^* (nM)	EC_{90} (μM)	HNE/HCV
29				1.8	0.110	7
30				9	0.080	18
31				1.9	0.045	60
32				7	0.080	110
33				19	0.080	850
34				28	0.070	1900
35				5	0.060	210
36				15	0.070	870

HNE selectivity. Compound **34** with the cyclobutyl P1 which constitutes Boceprevir **1** was less active in the enzymatic assay compared to their norvaline (**22**) and norleucine (**33**) analogs but showed a sixfold improvement in selectivity. Although the butynyl P1 **35** showed the best activity in this class, HNE selectivity and rat exposure were poor. Cyclopropyl analog **36** ($K_i^* = 15$ nM, $EC_{90} = 70$ nM) emerged as the best compound in this series with improved potency and replicon activity as well as exposure and HNE selectivity.

Selected analogs were profiled in the pharmacokinetic studies and they showed moderate to good exposure in rapid rat models (Table 4). All the lactams showed a better profile in the rapid rat exposure compared to our clinical candidate **1**. Inhibitor **34** with

Table 4
Rapid Rat PO AUC of selected analogs

Compound	K_i^* (nM)	EC_{90} (μM)	PO AUC μM h (10 mpk)
22	17	0.080	2.30
23	8	0.060	0.53
28	4.9	0.175	0.07
29	1.8	0.110	0.70
30	9	0.080	0.68
33	19	0.080	2.09
34	28	0.070	1.00
35	5	0.060	0.49
36	**15**	**0.070**	**3.52**
SCH503034 (**1**)	14	0.350	0.14

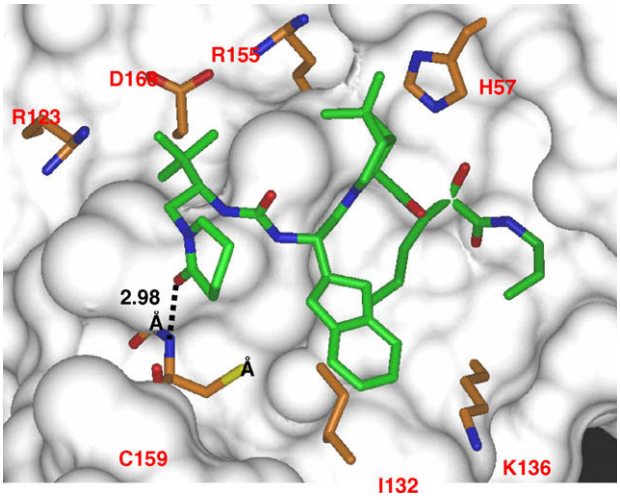


Figure 2. X-ray structure **30** bound to NS3 protease.

cyclobutyl P1 exhibited sevenfold improvement in the rat exposure and fivefold improvement in the cell potency compared to the clinical candidate **1**. Both compounds, **22** ($K_i^* = 17$ nM, $EC_{90} = 80$ nM) and **33** ($K_i^* = 19$ nM, $EC_{90} = 80$ nM) with norvaline and norleucine respectively at P1 position, showed a 15-fold improvement in exposure compared to **1**. Inhibitor **36** ($K_i^* = 15$ nM, $EC_{90} = 70$ nM) stood out as the best in this class by exhibiting excellent potency profiles with very good rat exposure (3.52 M h) and good selectivity against elastase.

The single X-ray crystal structure of a representative compound **30** is shown in Figure 2.[21] The bindings of the P1, P2 and P3 residues with their respective pockets were similar to those reported for Bocepevir.[12] The additional interaction observed is with the carbonyl carbon of the lactam which occupies the S4 pocket. There is strong hydrogen bonding interaction with Cys 159 nitrogen and the lactam carbonyl. This accounts for the enhancement in potency.

In conclusion, we identified highly potent new inhibitors as HCV NS3 serine protease inhibitors. Systematic SAR studies of the different regions of our clinical candidate, Boceprevir, resulted in an improvement in potency and replicon activity by 6–9-folds (**23**, $K_i^* = 8$ nM, $EC_{90} = 60$ nM and **31,** $K_i^* = 1.9$ nM, $EC_{90} = 45$ nM) by incorporating the 4,4-dimethyl lactam as the P4 cap. Most of these inhibitors showed improved pharmacokinetic properties compared to **1** in rapid rat model. Our SAR studies with amides and lactams as the P4 cap resulted in the identification of potent inhibitor **36** with excellent potency ($K_i^* = 15$ nM, $EC_{90} = 70$ nM) and selectivity against HNE (870) and good rat exposure (3.52 μM h).

Acknowledgements

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