Design and Synthesis of P2–P4 Macrocycles Containing a Unique Spirocyclic Proline: A New Class of HCV NS3/4A Inhibitors

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S Supporting Information

ABSTRACT: A new class of hepatitis C NS3/4A inhibitors was identified by introducing a novel spirocyclic proline–P2 surrogate onto the P2–P4 macrocyclic core of MK-5172 (grazoprevir). The potency profile of new analogues showed excellent pan-genotypic activity for most compounds. The potency evaluation included the most difficult genotype 3a (EC_{50} values ≤ 10 nM) and other key genotype 1b mutants. Molecular modeling was used to design new target compounds and rationalize our results. A synthetic approach based on the Julia–Kocienski olefination and macrolactamization to assemble the P2–P4 macrocyclic core containing the novel spirocyclic proline–P2 moiety is presented as well.

KEYWORDS: Hepatitis C, HCV, HCV NS3/4A, antivirals, MK-5172, MK-8831

Hepatitis C is a liver infection caused by the hepatitis C virus (HCV). There is an estimated 130–150 million people infected around the world.¹ In the United States alone 3.2 million people are infected with the virus and the disease will progress to a chronic stage in approximately 75–85% of patients.² Since chronic HCV infection is the leading cause of cirrhosis, hepatocellular carcinoma, and liver transplantation, the disease represents a major burden for patients and health care systems worldwide.^{3,4} The HCV virus was identified more than two decades ago, and its discovery triggered an enormous research effort to identify direct acting antiviral agents capable of curing the disease. The HCV virus is a (+)-strand RNA that encodes a polyprotein of approximately 3000 amino acids, which contains the necessary enzymes for viral replication. The HCV NS3/4A protease is one of those enzymes that plays an essential role in viral replication.^{5,6} HCV protease inhibitors were the first direct acting antivirals approved for treatment of the disease and remain an integral component of new combination therapies aiming for all-oral regimens.⁷

Our research group reported the discovery of the HCV protease inhibitor MK-5172 (grazoprevir) (1),⁸ Figure 1, which has been approved by the United States Food and Drug Administration for the treatment of HCV infection in combination with the HCV 5a inhibitor MK-8742 (elbasvir). MK-5172 (grazoprevir) has proven effective in treating the HCV infection with greater than 95% sustained virologic response (SVR) in patients infected with genotype-1.⁹ Due to its impressive clinical results MK-5172 received “breakthrough therapy” designation by the FDA prior to its approval. More recently, we disclosed the identification of MK-8831 (2),¹⁰ Figure 1, which represents a new class of HCV NS3/4A

Figure 1. HCV NS3/4A inhibitors MK5172 (1) and MK8831 (2).

inhibitors containing a unique “spirocyclic” proline as P2-surrogate. MK-8831 was advanced to clinical trials to assess its efficacy.

The unique “spirocyclic” proline present in MK-8831 was designed to reduce the entropic cost of binding of inhibitors having an ether-linked biaryl group attached to the P2-proline such as grazoprevir, paritaprevir, simeprevir (a cyclopentane ring replaces the P2-proline in simeprevir), and others. An improvement in potency was expected by rigidifying the ether-linkage into the required bioactive conformation. The successful investigation of this hypothesis was extensively described in our previous communication.¹⁰

While the clinical evaluation of MK-5172 (grazoprevir) and MK-8831 was ongoing, we envisioned a new class of HCV protease inhibitors resulting from the hybridization of the

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structural motifs present in each of the clinical candidates. Thus, combination of the P2–P4 macrocyclic ring of MK-5172 (grazoprevir) with the spirocyclic proline of MK-8831 led to an unprecedented class of molecules such as **4** as depicted in Figure 2. To enable the proposed spirocyclization of the P2–

Figure 2. Proposed modifications in MK-5172 (grazoprevir). Quinoxaline replacement with quinoline and spirocyclization (blue arrow) in the P2-proline led to “spirocyclic” proline motif of MK-8831, which is embedded in the P2–P4 macrocyclic ring. Also, an alternative P1–P3 macrocyclization is shown (green arrow).

proline, the quinoxaline ring was replaced with a quinoline ring, which forms part of the 18-membered P2–P4 macrocyclic structure. Other proposed modifications were based on our previous knowledge of the structure–activity relationships (SAR) developed for this series. Those modifications included different ring sizes of the cycloalkyl ring attached to the carbamate moiety, different substituents in the P3- and P1'-positions, and ultimately the P1–P3 macrocyclization to form a P1–P3/P2–P4 bis-macrocyclic structure. Herein, we report the identification of a new class of HCV NS3/4A protease inhibitors inspired from the combination of the distinctive

characteristics of the clinical candidates MK-5172 (grazoprevir) and MK-8831, the successful development of a suitable synthetic route for preparation of the proposed target molecules, and the subsequent determination of their potency profiles. Molecular modeling analysis is also presented to support our results.

MK-5172 (grazoprevir) (**1**) and MK-8831 (**2**) have excellent potency profiles across different genotypes (gt). Their enzyme inhibition values (IC_{50}) are ≤ 1 nM across different genotypes including the more difficult to treat genotype-3, see Table 1. Therefore, our research group was eager to determine whether the new “hybridized” target molecules would retain the same potency profile in both enzyme inhibition (IC_{50}) and cellular assays (replicon EC_{50}). Based on our molecular modeling analysis, the introduction of the spirocyclic proline into the P2–P4 macrocyclic ring should not disrupt any of the interactions required for binding onto the active site (Figure 3). On the contrary, our expectation was that the spirocyclic proline should reduce the entropic cost of binding by presenting a more rigid P2 moiety to the active site. Thus, compound **5**, a direct analogue of MK-5172 (grazoprevir), was synthesized, and it showed an excellent potency profile across genotypes (Table 1). The potency of compound **5** against gt1a (0.02 nM) and gt1b (0.01 nM) was similar to that of MK-5172 (grazoprevir). Compound **5** performed very well against gt2a (0.05 nM), gt3a (0.64 nM), and gt1b mutants. Compound **5** was also tested in a cell-based replicon assay including gt1a–b, gt2a, and the difficult to treat gt3a. The newly designed compound **5** had excellent potency with EC_{50} values in the single-digit nanomolar range against all of them. Overall, the potency profile of compound **5** validated the novel structural

Table 1. Potency Profiles for MK-5172 (Grazoprevir) (**1**), MK-8831 (**2**), and Novel Spirocyclic Proline Containing P2–P4 Macrocyclic Analogues^a

<div> <div>5; P₃=<i>t</i>-Bu; R₁=H</div> <div>6; P₃=<i>t</i>-Bu; R₁=Me</div> <div>7; P₃=<i>t</i>-Bu; R₁=H, P₁-single bond</div> <div>8; P₃=MeCHG; R₁=H</div> <div>9; P₃=MeCHG; R₁=Me</div> <div>10; R₁=H</div> <div>11; R₁=Me</div> <div>13</div> <div>MeCHG=</div> </div>												
compd	enzyme inhibition IC_{50} (nM)								replicon EC_{50} (nM)			
	1a	1b	2a	3a	1b R155K	1b A156T	1b A156V	1b D168Y	1a	1b	2a	3a
1	0.02	0.01	0.14	0.75	0.06	3.82	6.09	0.22	0.6	0.6	5.4	7.2
2	0.01	0.01	0.02	0.53	0.01	0.59	3.67	0.03	3.7	1.2	2.0	2.0
5	0.02	0.01	0.05	0.64	0.02	3.83	3.91	0.03	2.8	1.6	3.9	8.0
6	0.04	0.03	0.05	0.68	0.05	3.90	3.79	0.01	4.7	1.0	1.8	3.3
7	0.06	0.03	0.16	1.18	0.08	25.21	18.89	0.15	10.3	2.8	8.4	17.3
8	0.05	0.03	0.08	1.00	0.05	4.86	5.77	0.05	8.1	1.0	2.7	5.7
9	0.05	0.04	0.05	0.47	0.07	4.86	3.76	0.03	8.5	1.5	1.2	4.5
10	0.02	0.01	0.05	0.51	0.03	3.09	3.41	0.04	4.8	0.9	4.5	6.8
11	0.04	0.02	0.05	0.70	0.04	2.80	3.96	0.05	12.5	1.8	3.6	5.7
13	0.05	0.02	0.06	0.26	0.05	0.34	0.27	0.04	4.7	0.8	1.7	2.3

^aTwo internal standard compounds were included in all the assay runs to track the robustness of the assays ($n = 3$), and data were within 3-fold of the reported values. Standard deviation was within 10%.

Figure 3. Comparison of the energy-minimized conformations of MK-5172 (grazoprevir) (yellow) and the proposed P2–P4 macrocycles containing the unique spirocyclic proline–P2 surrogate of MK-8831 (cyan). The active site of NS3/4A protease is shown as surface.

class and warranted the design and synthesis of new target molecules.

The extensive efforts toward the identification of HCV NS3 protease inhibitors by our research group and others have resulted in a deep understanding of the structural modifications that could positively affect the potency profile of target molecules. It has previously been determined that in some cases the introduction of a methyl group into the cyclopropyl acylsulfonamide–P1' improved potency and plasma exposure.^{11,12} Thus, compound **6** was synthesized and had its activity measured. Its enzyme inhibition profile across genotypes and mutants was similar to that of compound **5**. Our expectation for potency improvement was observed in the replicon assay. Compound **6** showed 2-fold improvement against gt2a (EC_{50} = 1.8 nM) compared to compound **5**. Moreover, its potency against gt3a was also improved (EC_{50} = 3.3 nM). Compound **6** showed excellent activity against gt3a, which was close to that of MK-8831 (**2**) (EC_{50} = 2 nM). In order to investigate the effect of saturation of the vinyl group at the P1 group, compound **7** was synthesized. The potency profile for **7** showed mixed results having similar potency against some genotypes and mutants such as gt1a, gt1b, and gt1b R155K (IC_{50} = 0.06, 0.03, and 0.08 nM, respectively) but less active against gt2a and gt3a (IC_{50} = 0.16 and 1.18 nM, respectively). Furthermore, a significant loss in potency against mutants gt1b A156T and gt1b A156V was observed (IC_{50} > 18 nM). The potency loss was also seen in the replicon assay, the loss in activity against gt3a (EC_{50} = 17.3 nM) was 2-fold compared to **5**.

During the course of our investigations on the P2–P4 macrocyclic analogues we identified the unnatural amino acid 1-methyl-cyclohexylglycine as an excellent surrogate for the P3-site. Introducing this amino acid into some of our target molecules improved their potency, and in some cases, an improvement in plasma concentration after oral administration was also observed. Therefore, we decided to investigate the effect of the 1-methyl-cyclohexylglycine amino acid in our new scaffold. Compound **8** was synthesized and profiled. A direct comparison of its activity profile with its close analogue **5** showed similar potency for most of the genotypes. However, compound **8** had a 2-fold loss in activity (IC_{50} = 1.0 nM)

against gt3a. Loss in potency was also seen for the gt1b mutants A156T and A156V. In the cell based assay compound **8** fared better than its analogue **5**. With the exception of gt1a (for which there was a 3-fold loss in activity, EC_{50} = 8.1 nM) replicon potency of **8** improved in all other genotypes. In the difficult to treat gt3a, compound **8** had excellent potency (EC_{50} = 5.7 nM). As we had anticipated, introduction of the 1-methyl-cyclohexylglycine proved beneficial and an improved potency profile was obtained for **8**. We demonstrated that the introduction of a methyl group in the acylsulfonamide P1' group gave a boost in potency in this series (see compound **5**). Thus, compound **9**, which contains the 1-methyl-cyclohexylglycine and an additional methyl group in the acylsulfonamide at the P1' group, was synthesized. Enzyme inhibition activity for **9** against gt3a (IC_{50} = 0.47 nM) was indeed improved when compared with compound **8** and MK-8831 (**2**). We quickly moved to obtain replicon activity for compound **9** and compare it with that of the clinical candidates and the new analogues. Thus, the gt1a replicon potency of **9** (EC_{50} = 8.5 nM) still remained high compared to **5** and MK-8831 (**2**). In the gt2a replicon, compound **9** (EC_{50} = 1.2 nM) had the best potency among compounds in this series. The gt3a replicon potency of **9** (EC_{50} = 4.5 nM) was in the low single digit nanomolar range. Compound **9** was more active than compounds **5** and **8**, which do not possess the methyl group in the acylsulfonamide–P1'. It became clear that the methyl group in the acylsulfonamide–P1' rendered the compounds in this new “hybrid” series more active in the replicon assay across genotypes. The *t*-butylglycine–P3 analogue **6** is slightly more active than **9** across genotypes and mutants. However, compound **9** was in some instances more potent than the clinical candidate MK-8831 (**2**).

As mentioned before, our team was also interested in investigating the effect of different ring size in the carbamate moiety at the P4-site. One change that led to improvements in potency and pharmacokinetic profiles in some P2–P4 macrocyclic subclasses was the utilization of a cyclopentane ring instead of the more constrained cyclopropane ring. To investigate the effect of the ring size at the P4-site in both enzyme inhibition and cellular potency, we moved to synthesize cyclopentane containing analogues. Compound **10** showed similar potency against gt1a and gt1b compared to MK-8831 (**2**). Excellent potency was observed against gt2a (IC_{50} = 0.05 nM) and gt3a (IC_{50} = 0.51 nM). Moreover, compound **10** also showed improvements against some of the gt1b mutant strains such as gt1b A156V (IC_{50} = 3.41 nM) and gt1b D168Y (IC_{50} = 0.04 nM). However, the gains observed in the enzyme inhibition assays did not translate into better cellular potency. Based on the knowledge gained from compounds **6** and **9** regarding the methyl substitution in the acylsulfonamide P1' and its observed advantage for potency, compound **11** was prepared. Contrary to our expectations, the potency profile of compound **11** showed no apparent gain in potency across genotypes compared to its parent compound **10**. Furthermore, compound **11** showed a significant loss in cellular potency against gt1a (EC_{50} = 12.5 nM) and gt1b (EC_{50} = 1.8 nM). Although slight gains were made for gt2a (EC_{50} = 3.6 nM) and gt3a (EC_{50} = 5.7 nM) compared to compound **5**. The results obtained in the enzyme inhibition and cellular assays for compounds **10** and **11**, which contain a cyclopentane ring in the carbamate P4-site, led to the conclusion that a more constrained cyclopropane ring is preferred at the P4-site to

obtain analogues with better potency profiles in this class of compounds.

Our research group has also reported the identification of P1–P3/P2–P4 bis-macrocycles as viable HCV NS3/4A protease inhibitors.^{13,14} MK-6325 (**12**) represents compounds in this class with an excellent potency profile across genotypes and mutant strains (Figure 4).

Figure 4. Structure of MK-6325 (**12**) and proposed cyclization at the P2–proline to generate novel spirocyclic proline P2 containing bis-macrocycle **13**. Model of compound **13** (green) bound to the active site of NS3/4A protease (surface).

MK-6325 (**12**) shares many of the structural features of MK-5172 (grazoprevir) (**1**) such as the quinoxaline–P2 and the P2–P4 macrocyclic core but it has an additional macrocyclic ring formed by the tethering the P1 and P3 groups. We decided to introduce the spirocyclic proline into the structure of MK-6325 (**12**) and evaluate the potency profile of the resulting hybrid analogue. Thus, bis-macrocycle **13** was synthesized and had its activity measured. We were delighted to see further improvement in enzyme inhibition potency across genotypes. Compound **13** possessed the best potency against gt3a (IC_{50} = 0.26 nM). This gain in potency represented an improvement compared to MK-8831 (**2**). Moreover, we had determined that many analogues in the spirocyclic proline P2 series had poor performance against the gt1b mutant strains A156T and A156V; compound **13**, however, showed the best potency against these two mutant strains (IC_{50} = 0.34 and 0.27 nM, respectively). Since A156 is enclosed in the P2–P4 macrocycle, mutation of A156 to a bulkier residue such as threonine or valine, as seen in clinically relevant variations, would cause steric conflict in this region. Those steric interactions explain the loss of potency compared to binding to the wild-type protein. With the bis-macrocycle **13**, the unfavorable interactions at P2–P4 region due to the A156T and A156V mutations are partially compensated by optimizing the interactions of the P1–P3 macrocycle with the protein and therefore results in improved potency profiles. Compound **13** showed remarkable potency in the cellular assays as well. For example, **13** showed excellent potency in the replicon assay against gt3a (EC_{50} = 2.3 nM). When compared to the other

spirocyclic–P2 macrocycles, **13** possessed the best cellular potency in the series against gt3a.

Synthesis of P2–P4 Macrocyclic Inhibitors Containing a Novel Spirocyclic–Proline Motif. The synthesis of the target molecules presented in this letter required the development of a new strategy to assemble the P2–P4 macrocycle ring containing the spirocyclic proline–P2 motif. The previously described methods utilizing palladium catalyzed (Sonogashira, Suzuki) or ring-closing metathesis reactions were not suitable for building the required intermediates to access the final products.^{15,16} An alternative method to append the five carbon alkyl chain to the biaryl–P2 was devised. This method utilizes the Julia–Kocienski olefination reaction in an advanced intermediate that already contains the spirocyclic proline motif. The assembly of the P2–P4 macrocyclic scaffold was achieved via lactamization to connect the P2 and P3 residues.^{17,18}

Pharmacokinetic Profile for Spirocyclic–Proline Containing P2–P4 Macrocyclic Inhibitor **10 and Bis-macrocycle **13**.** The pharmacokinetic (PK) profile for the new analogues was investigated in rats utilizing their potassium salt forms. The data for the potassium salt of compounds **10** and **13** is shown in Table 2 along with MK-8831. The total CL for

Table 2. Pharmacokinetic Profile of the Potassium Salt of Compound **10**, **13**, and MK-8831 in Rats

compd	CL (mL/min/kg)	V_d (L/kg)	$T_{1/2}$ (h)	PO dosing	
				AUC (μ M h)	[liver] _{24h} (μ M)
MK8831 ^a	4.7	0.3	2.8	9.2	28.0
10 ^a	5.7	5.0	15.6	3.2	1.5
13 ^b	12.4	8.6	NA	0.8	0.003

^aIV (2 mg/kg, PEG200), PO (5 mg/kg, MC). ^bIV (2 mg/kg), PO (10 mg/kg).

compound **10** was somewhat similar to that of MK-8831, but its volume of distribution (V_d = 5.0 L/kg) showed improvement compared to MK-8831 (V_d = 0.3 L/kg). A substantial improvement was observed in the half-life ($T_{1/2}$) of compound **10** compared to the clinical candidate MK-8831. Compound **10** had $T_{1/2}$ = 15.6 h, whereas $T_{1/2}$ value for MK-8831 was 2.8 h. Compound **10** also demonstrated effective partitioning into liver tissue. After a 5 mg/kg oral administration the total liver concentration of **10** was remarkably high after 24 h of dosing (1.47 μ M). The sustained liver concentration of **10** ensures a concentration >200 times that of its gt3a EC_{50} value at the 24 h point. In contrast, the PK profile of bis-macrocycle **13** did not meet our expectations. Compound **13** showed high total CL (12.4 mL/min/kg), very low exposure after oral administration (AUC = 0.8 μ M h), and negligible concentration in the liver after 24 h. The exposure and liver concentration were low compared to compound **10**, even though PO dose for compound **13** was 2-fold higher compared to compound **10**.

In summary, combination of the structural motifs of the clinical candidates MK-5172 (grazoprevir) and MK-8831 led to the discovery of an unprecedented class of HCV NS3/4A protease inhibitors with broad genotype activity. The unique spirocyclic proline–P2 of MK-8831 was introduced onto the P2–P4 macrocyclic scaffold of MK-5172 (grazoprevir). Previously reported synthetic strategies to assemble P2–P4 macrocyclic compounds were not suitable to introduce the unique spirocyclic proline–P2 and a new synthetic approach

was developed to synthesize the required analogues. The alkyl chain of the macrocycle was introduced via Julia–Kocienski olefination, and the cyclization was attained via macro-lactamization. Compounds **6** and **9** showed excellent potency profiles across different genotypes and mutant strains in both enzyme and cellular assays. Their potency gains represent an improvement over the potency profiles of clinical candidates such as MK-8831. The P1–P3/P2–P4 bis-macrocycle **13** showed excellent binding and cellular potency as well. The additional P1–P3 macrocycle played a significant role in the observed potency improvement. Additional molecular modeling studies to explain these gains are ongoing and will be reported elsewhere. Initial pharmacokinetic screening of compound **10** in rats showed improvements in total CL, $T_{1/2}$, and total liver concentration. The potency and pharmacokinetic profiles of the analogues presented here demonstrate the potential for compounds in this class to become follow ups for our clinical candidates.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.6b00321.

Synthetic scheme for compound **11** and detailed description of the synthetic route. Experimental procedures for the synthesis of intermediates, target molecules **5–11**, and bis-macrocycle **13**. Spectroscopical data and copies of ^1H NMR spectra for selected intermediates and target compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS

HCV, hepatitis C virus; RNA, ribonucleic acid; SVR, sustained virologic response; FDA, Food and Drug Administration; SAR, structure–activity relationship; gt, genotype; PK, pharmacokinetic; IV, intravenous; PO, per os

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(18) See [Supporting Information](#) for a synthetic scheme and detailed description of the synthetic route. Synthesis of intermediates, target molecules **5–11**, and *bis*-macrocycle **13** is also described in the [Supporting Information](#).