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Structure-activity relationships of 4-hydroxy-4-biaryl-proline acylsulfonamide tripeptides: A series of potent NS3 protease inhibitors for the treatment of hepatitis C virus

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ABSTRACT

The design and synthesis of a series of tripeptide acylsulfonamides as potent inhibitors of the HCV NS3/4A serine protease is described. These analogues house a C4 aryl, C4 hydroxy-proline at the S2 position of the tripeptide scaffold. Information relating to structure-activity relationships as well as the pharmacokinetic and cardiovascular profiles of these analogues is provided.

Hepatitis C virus (HCV) has emerged as a pathogen posing a serious threat to public health.[1] It is estimated that up to 200 million people worldwide are chronically infected with HCV, a five-fold higher prevalence than HIV-1 infection. A significant fraction of those infected with HCV develop progressive liver disease which can lead to cirrhosis and hepatocellular carcinoma. To address this medical need, we embarked on an extensive research effort that culminated in the discovery of three direct-acting antiviral drugs, two of which, the NS5A replication complex inhibitor daclatasvir and the NS3 protease inhibitor asunaprevir, have been approved for use in combination for the treatment of HCV, while the third, the NS5B RNA-dependent, RNA polymerase inhibitor beclabuvir, is in late-stage clinical trials. These agents each inhibit the function of an essential viral protein and thereby provide an alternative option for the treatment of this disease.[2]

In our pursuit of HCV NS3 protease inhibitors, compound **2** (Fig. 1) was an early program lead that illustrated the importance of the cyclopropyl acylsulfonamide moiety in exacting potency towards the NS3/4A protease complex. This tripeptide acylsulfonamide was over 100-fold more active in a cell-based HCV genotype 1b (GT-1b) replicon assay than the corresponding carboxylic acid **1**.[3,4] Hence, the cyclopropyl acylsulfonamide group provided access to potent inhibitors of the NS3 protease in a linear, tripeptide series that obviated the need to employ either *P*1-*P*3 macrocyclization or mechanism-based inhibition to derive potency.[3–7] While the potency of **2** was promising, the pharmacokinetic (PK) profile of this compound was poor and efforts were directed at optimizing the ADME and antiviral properties in this chemical series. This optimization effort has been described in detail and led to the discovery of BMS-605339 (**3**) as the first compound from this series that was advanced into clinical studies for the treatment of HCV. Treatment of HCV GT-1-infected subjects with a single 120 mg oral dose of BMS-605339 (**3**) resulted in a ~1.8 $\log_{10}$ reduction in viral load.[7] While there were no overt clinical findings observed in subjects receiving drug, there were sub-clinical observations of significance. Specifically, mild bradycardia, PR interval prolongation and junctional escape rhythms were recorded in one healthy volunteer

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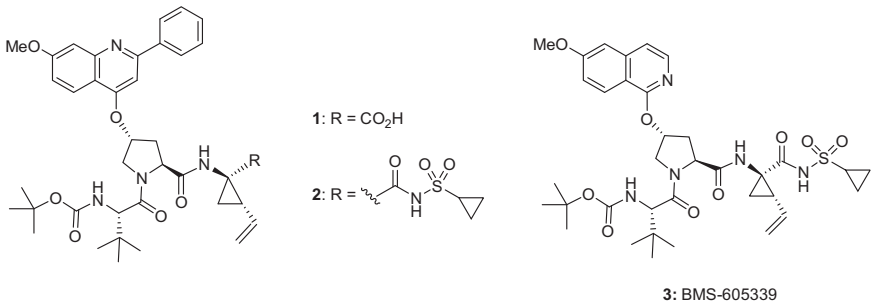

Fig. 1. Key structures in the discovery of BMS-605339 (**3**).

and one HCV-infected subject. Similar cardiovascular effects had been observed pre-clinically in dogs, but only at drug plasma concentrations over 100-fold higher than the clinical exposure. These data suggested that humans were more sensitive to the cardiovascular (CV) effects of BMS-605339 (**3**) than preclinical species, and thereby the clinical development of **3** was halted.[7]

The clinical findings with BMS-605339 (**3**) focused our effort on the discovery of a compound that was free of the CV liabilities associated with this compound. As previously described, an isolated rabbit Langendorff heart model had been employed to assess the CV effects of BMS-605339 and analogues thereof. From that effort, compounds were identified that were free of CV effects by virtue of relatively small structural modifications in the *P2** region of the molecule and this approach ultimately led to the discovery of BMS-650032 (**4**, asunaprevir).[8] However, the CV signal in this chemical series was nonetheless problematic as testing for this liability was both resource-intensive and low throughput in nature. Moreover, while singletons could be identified that were free of a CV signal, clear SARs were not realized in compounds bearing the parent, *P2*-proline-C4 aryloxy motif. Herein, we describe an SAR track that ran parallel to the discovery of asunaprevir wherein a deep seated structural change at the *P2* subsite was explored.[5,9] We reasoned that a significant structural modification in this region of the molecule might provide a chemical series free of the cardiovascular signal associated with the parent C4-aryloxy-proline series. The objective of this work, beyond minimizing CV risk, was to identify a lead with activity in the replicon assay with an EC_{50} value less than 10 nM, as well as pharmacokinetic parameters comparable to the clinical lead BMS-605339 (**3**). It should be noted, that Boehringer-Ingelheim has recently described their efforts on a structurally similar chemical series.[10] However, the rationale and outcome described herein are distinct since our effort was driven by a need to find chemical space free of the cardiovascular liability associated with BMS-605339 (**3**).

As illustrated in the co-crystal structure of asunaprevir (**4**) with the HCV NS3/4A protease complex (Fig. 2), the S2 subsite of the enzyme is expansive and solvent-exposed. We focused attention on the design of a *P2** moiety that connected the aromatic substructure directly to the C4-carbon of the proline, as depicted in **5a**. A model of **5a** in the binding pocket suggested that the interactions of the C4-phenyl group with the *P2** subsite of the enzyme were favorable, while the requisite interactions between the tripeptide backbone and the enzyme were maintained. The functionalized proline group of **5a** was readily assessable as there was literature precedent for the face-selective addition of Grignard reagents to the α-face of C4-ketoprolines to yield the desired stereochemistry inherent to **5a**.[11,12] In this synthetic approach, the initial target molecules would incorporate a hydroxyl group in the form of a proline C4 tertiary alcohol as captured in the structure of **5**a. Since this hydroxyl group was not predicted to have direct contact with the enzyme, it was viewed as a potential handle with which to modulate physicochemical properties in this series.

The C4-hydroxy-proline-tripeptide backbone scaffold of the targeted molecules **5a-y** was assembled by the pathways outlined

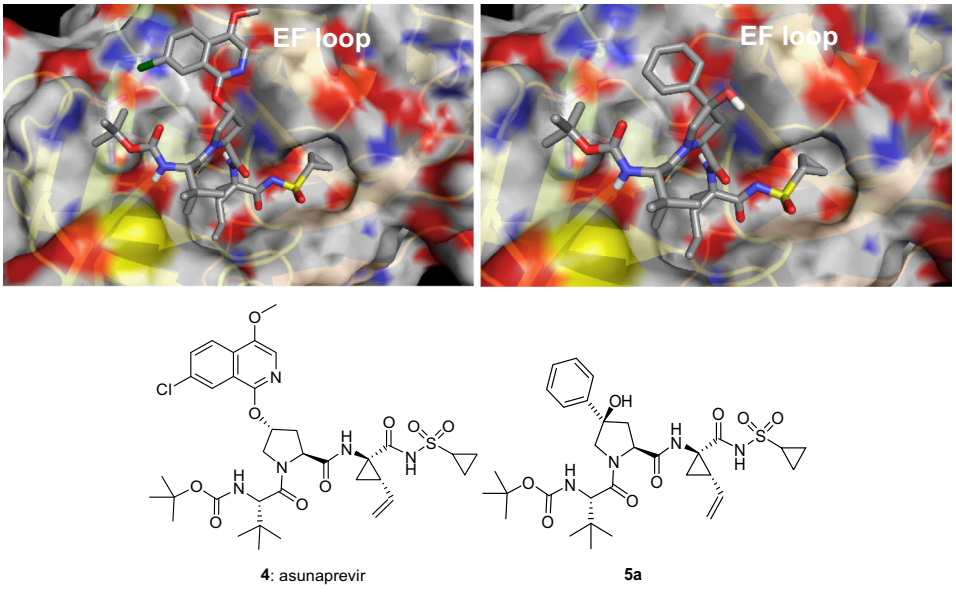

Fig. 2. (a) X-ray co-crystallographic structure of asunaprevir (**4**) and HCV NS3/4A protease.[13] (b) Model of **5a** of the proposed C4-aryl proline series bound to HCV NS3/4A protease.

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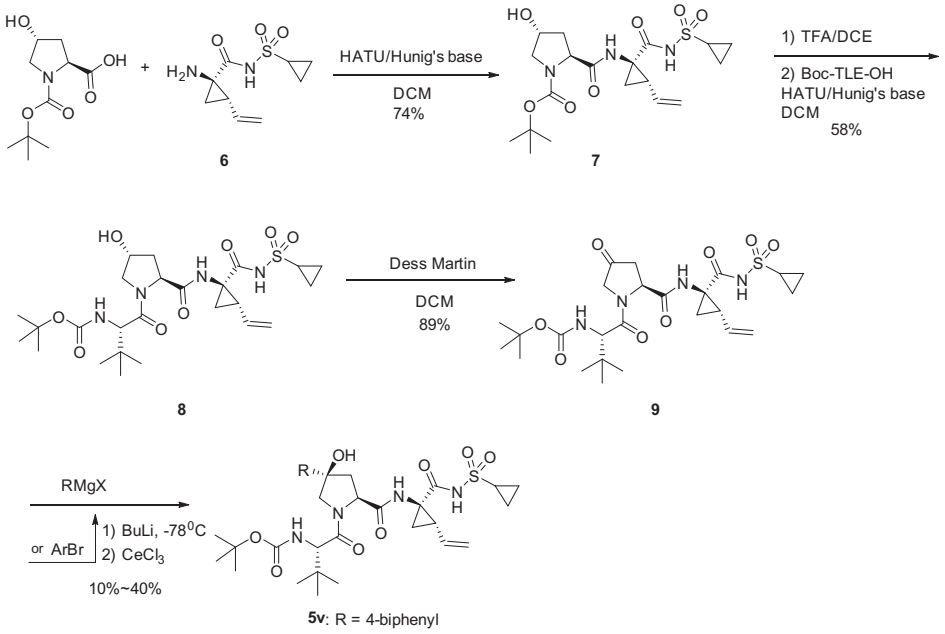
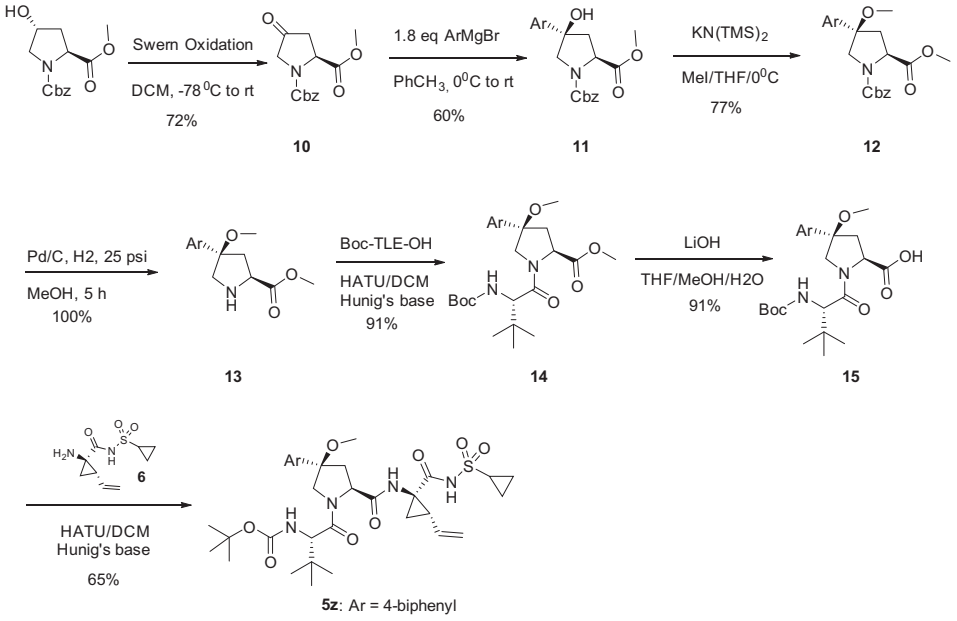


Scheme 1. Synthetic route to prepare 4-OH-4-aryl proline acylsulfonamide tripeptide **5**.

in Scheme 1. Standard amide coupling of commercially-available (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid with the *P*1-P1′ element **6** afforded amide **7** in 74% yield. Deprotection of the Boc moiety using TFA followed by amide coupling, provided the tripeptidic alcohol **8** in 58% yield over the 2 steps. Oxidation using the Dess-Martin periodinane reagent furnished ketone **9** in good yield. Addition of either commercially-available Grignard reagents, or organocerium reagents made *in situ* by treating aryl bromides with *n*-butyllithium followed by trans-metalation with cerium (III) chloride, afforded the desired tertiary alcohols **5a–y** in yields ranging from 10% ∼ 40%.

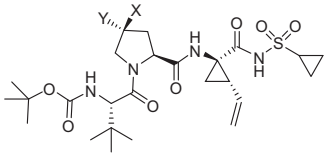
The C4-methoxy proline analogue **5z** was prepared through an alternative route (Scheme 2) that relied upon Swern oxidation of *N*-Cbz-4-hydroxy proline methyl ester to provide the ketone intermediate **10** in 72% yield. Addition of commercially-available 4-biphenylmagnesium bromide furnished the alcohol **11** in reasonable yield. Methylation of **11** with methyl iodide provided the 4-methoxy proline derivative **12** in 77% yield, which was followed by catalytic hydrogenation to quantitatively remove the Cbz protecting group. Amide coupling of **13** led to **14** in 91% yield and subsequent saponification using aqueous LiOH afforded acid **15** in excellent yield. Finally, coupling with the *P*1-P1′ amine **6** furnished the desired product **5z** in 65% yield.

The SAR exploration began with a simple, unsubstituted phenyl ring at the C4 position of proline, represented by **5a**, which demonstrated an IC_{50} of 140 nM in a GT-1a NS3/4A protease inhibition assay (Table 1). This activity was encouraging since **5a** was 27-fold more potent than the corresponding C-4 keto-proline **9**



Scheme 2. Synthetic route to prepare 4-MeO-4-aryl proline acylsulfonamide tripeptide **5z**.

Table 1
Structure, HCV inhibitory activity and cytotoxicity of 4-hydroxy proline acylsulfonamide tripeptides.



5

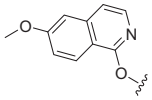
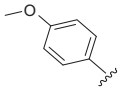
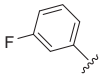
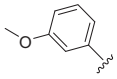
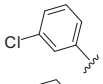
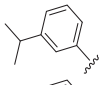
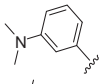
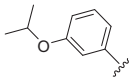
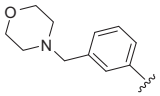
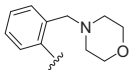
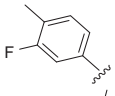
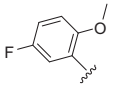
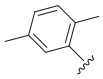
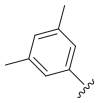
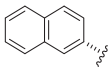
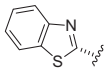
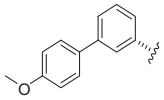
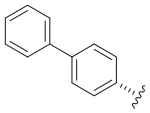
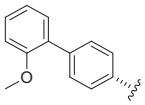
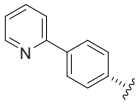
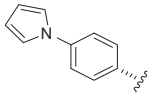
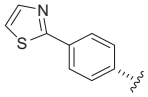
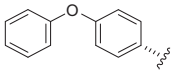
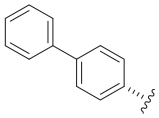
Compd	X	Y	GT1a enzyme inhibition IC_{50} (μM)	GT1b replicon EC_{50} (μM)	CC_{50} (μM)
3	H		0.001	0.012	67.3
5a	OH		0.140	2.36	>100
5b	OH		0.190	2.47	>100
5c	OH		0.105	1.47	>100
5d	OH		0.057	4.06	>100
5e	OH		0.052	3.70	>100
5f	OH		0.080	3.66	>100
5g	OH		0.076	3.27	>100
5h	OH		0.703	8.37	>100
5i	OH		0.960	3.40	>100
5j	OH		0.101	6.25	>100
5k	OH		0.162	3.46	>100
5l	OH		0.291	4.95	>100
5m	OH		0.134	7.70	>100
5n	OH		0.568	4.24	>100
5o	OH		0.728	3.94	>100
5p	OH		0.136	2.31	>100

Table 1 (*continued*)

Compd	X	Y	GT1a enzyme inhibition IC_{50} (μM)	GT1b replicon EC_{50} (μM)	CC_{50} (μM)
5q	OH		0.080	6.45	>100
9	N/A		3.90	70.7	N/A
5r	OH		1.50	30.5	>100
5s	OH		0.026	0.412	88.4
5t	OH		0.127	1.12	>100
5u	OH		0.620	3.21	46.9
5v	OH		0.004	0.026	43.5
5w	OH		0.005	0.024	37.2
5xa	OH		0.002	0.039	>100
5xb	OH		0.007	0.097	>100
5xc	OH		0.002	0.041	>100
5y	OH		0.050	0.265	55.1
5z	OMe		0.002	0.009	36.4

IC_{50} values represent the means of at least two independent inhibition measurements derived from the HCV NS3/4A GT-1a protease, while EC_{50} values represent the means of at least two independent inhibition measurements derived from the HCV GT-1b replicon assay.

(IC_{50} = 3.9 μM). Hence, the presence of the phenyl substituent in **5a** and the concurrent change in hybridization at C-4 compared to **9**, resulted in a substantial potency gain. Consistent with this observation, the C4-allyl analogue, **5r** was ~10-fold less active (IC_{50} = 1.5 μM) than **5a**, suggesting the significance of the rigid aromatic ring in **5a** for enhancing potency. A model of the binding mode of **5a** with the enzyme suggested that the C4-phenyl group packed against the side chain of Arg155, while the hydrogen-bond donors and acceptors along the backbone as well as the acylsulfonamide functionality made contact with the enzyme in the fashion previously described. The model also indicated the potential for further contact points through the addition of substituents to the phenyl ring of **5a**, providing an immediate direction for the next phase of the study.

The addition of a single substituent to the phenyl ring of **5a** was considered first. Substitution at the *para* position with methoxy (**5b**) and fluoro (**5c**) did not exert a significant impact on inhibitory potency, while *meta* substitution seemed to be only marginally more favorable in the biochemical assay (compare the IC_{50} values of **5d**-**g** with those of **5b**-**c**). Bulkiness at this position was detrimental to potency (**5h**, **5i**), while insertion of more flexible linkers such as oxygen and methylene between the phenyl ring and the bulky alkyl moiety retrieved activity (**5j, 5k** vs. **5h**, **5i**). The addition of a second substituent to the aryl ring was not productive as these analogues failed to significantly enhance potency (**5m–p**). However, incorporating two substituents by fusing a second phenyl ring to the aryl moiety in **5a** provided the naphthyl analogue **5s** which resulted in a 5-fold boost in inhibitory potency. An assessment of the potential binding mode of **5s** suggested that the expanded planarity of the *P*2* substituent functioned to enhance hydrophobic and electrostatic interactions with Arg155 while also facilitating desolvation of the binding pocket (Fig. 3). In contrast to the naphthyl moiety in **5s**, a 2-benzothiazole heterocycle (**5t**) at this site did not lead to a gain in potency.[14] The reduced potency of **5t** compared to **5s**, can be explained by the preferred conformation for the benzothiazole moiety in **5t** in which the carbamate moiety of

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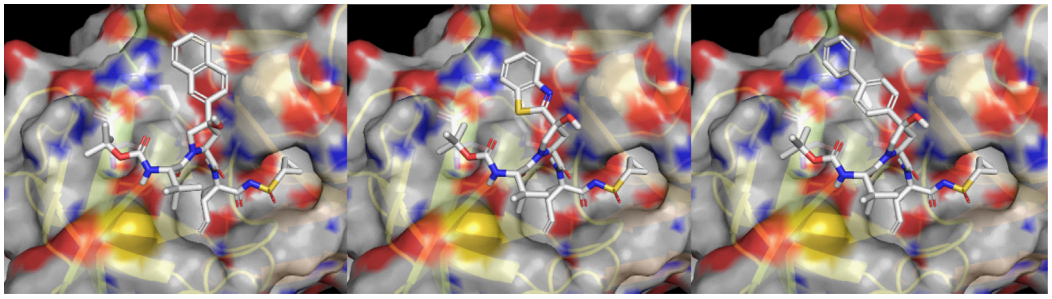
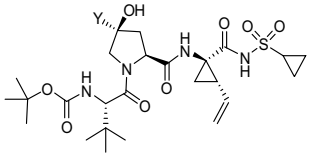


5s 5t 5v



5s: 2-nathphyl
5t: 2-benzothiazole
5v: 4-biphenyl

Fig. 3. Models of **5s**, **5t** and **5v** bound to HCV NS3 protease.

Table 2
Comparative HCV inhibitory activity and rat pharmacokinetic screening results.

Entry	GT1a enzyme screen IC_{50} (μM)	GT1b cell-based replicon screen EC_{50} (μM)	PAMPA nm/s @pH 5.5/7.4	4 h screen, ID, PO Plasma AUC (μM-h)/Liver level (μg/g)	Full Rat PK
5v	0.004	0.022	79/211	0.90/0.128	N/A
5z	0.002	0.009	381/438	2.45/195.3	F = 58%, AUC = 14.1 μM-h, Cl = 17.8 mL/min/kg, $T_{1/2}$ = 4.6 h, PO 24 h Liver = 1.1 μM 795.1 μg/g
3	0.002	0.012	574/178	10.4/64.7	F = 18%, AUC = 14.1 μM-h, Cl = 4.4 mL/min/kg, $T_{1/2}$ = 4.4 h, PO 24 h Liver = 0.74 μM 528.2 μg/g

Table 3
Cardiac electrophysiology parameters in isolated rabbit hearts (compounds perfused at 10 μM).

Compound	Experimental parameters	HR (%)	SNRT (%)	CF (%)
3	10 min	−13 ± 6	69 ± 33	12 ± 13
	n = 6, 20 min	−32 ± 13	360 ± 229	10 ± 4
4	10 min	1 ± 1	−1 ± 5	−3 ± 7
	n = 4, 20 min	−1 ± 2	4 ± 6	−1 ± 6
5v	10 min	−2 ± 1	2 ± 4	2 ± 2
	n = 2, 20 min	−4 ± 1	7 ± 3	−2 ± 1
5z	10 min	−6 ± 1	8 ± 4	27 ± 8
	n = 2, 20 min	−3 ± 7	7 ± 2	20 ± 6
Vehicle	Vehicle, 10 min	−1 ± 1	3 ± 1	−4 ± 6
	n = 3, 20 min	−3 ± 3	4 ± 5	−6 ± 8

the *P*3 cap interfaces with the sulfur atom of the heterocycle ring, thus destabilizing the preferred binding mode (Fig. 3).

The activity of **5s** encouraged further consideration of structural alternatives at *P*2* and to this end the biphenyl moiety, an important and useful building block in several drugs and natural products, was considered.[15] The additional flexibility inherent to the biphenyl motif compared to a naphthyl ring held potential as a means of further improving affinity for the NS3 protease by virtue of the expanded conformational binding modes offered by this linear array. Modeling suggested that positioning a second phenyl group in the *para*- position was optimal and the experimental data were consistent with this hypothesis. For example, the *meta*-biphenyl analogue **5u** was similar in potency to the parent **5a**, while the corresponding *para*- isomer **5v** provided a 35-fold increase in potency in the biochemical enzyme assay, and a 90-fold improved effect in the cell-based HCV GT-1b replicon assay when compared to the unsubstituted parent. An assessment of the plausible binding modes suggested that the *para*-biphenyl orients into

the hydrophobic pocket beyond the S2 region, while the distal phenyl ring packs optimally against the side chain of Arg155, establishing both hydrophobic and electrostatic contacts. It is interesting to note that replacement of the distal phenyl ring with 5- or 6-membered heterocycles (**5xa**, **5xb**, **5xc**) maintained the inhibitory potency toward NS3 protease in the biochemical enzyme assay, although this effect deteriorated somewhat in the cell-based replicon assay, perhaps due to permeability issues associated with these more polar elements.

The activity of **5v** warranted an exploration of its pharmacokinetic profile with compound **3** used as a point of reference. Upon intraduodenal (ID) dosing to rats, **5v** showed a 10-fold lower plasma exposure and 5-fold lower liver levels when compared to **3** (Table 2). With a need to enhance the absorption properties of this biphenyl series, we considered structural modifications to reduce polarity and thereby potentially increase permeability. As noted above, in its bound conformation, the tertiary hydroxyl moiety in **5v** is predicted to be devoid of any direct or water-bridged indirect interactions with the protein but instead projects into solvent. Hence, capping this hydrogen bond donor with a hydrophobic moiety, specifically a methyl group, was considered as a means of reducing the polarity of this chemical series and potentially improving permeability.[16]

To this end, the C4-biphenyl-C4-methoxy analogue **5z** was synthesized with characterization revealing it to be a key compound in the series. The C4-methoxy group of **5z** improved activity over its hydroxyl counterpart **5v** in both the biochemical and replicon assays (Table 1). The activity gains in the biochemical assay observed with **5z** might be explained by a lowering of the desolvation penalty associated with ligand binding to the enzyme, while the increase in cell-based replicon activity may be a consequence of the enhanced permeability of this compound, a notion supported by the enhanced permeability of **5z** compared to **5v** in the parallel artificial membrane permeability assay (PAMPA) assay (Table 2).

The simplicity of the optimized *P2** functionality in **5z** was attractive and the PK properties of this biphenyl analogue were assessed. Upon intra-duodenal (ID) dosing of **5z** to rats the observed plasma and liver levels were respectively 3- and 15-fold higher than that found with **5v** (Table 2). The enhanced systemic exposure of **5z** compared to **5v** can be attributed to the methoxy group in the former which distinguishes this matched pair of structures and is consistent with the *in vitro* PAMPA permeability profiles of these compounds. In a 24 h PK study, administration of **5z** to rats at a dose of 15 mg/kg resulted in good oral bioavailability at 58%, with plasma exposure of 14.1 μM-h and liver levels of 795 μg/g at the 24 h time point. Intravenous dosing of **5z** at 5 mg/kg resulted in modest clearance of 17.8 mL/min/kg and a half-life of 4.6 h. The pharmacokinetic profile of **5z** is similar to that observed for BMS-605339 (**3**) with respect to $t_{1/2}$ in plasma and concentration of drug in the liver at 24 h (Table 2), while the oral bioavailability of **5z** was greater than that observed for BMS-605339 (**3**).

Compound **5z** was next evaluated in the isolated rabbit heart model where it was perfused at a fixed and protein-free concentration of 10 μM with key cardiovascular parameters monitored as a function of time. Of importance were effects on heart rate (HR) and sinoatrial node recovery time (SNRT) since these findings had been significant for **3** and *ex post facto* were found to correlate with clinical findings. Infusion of **5z** to isolated hearts produced changes in HR and SNRT that were comparable to vehicle over the 20 min perfusion period (Table 3). A similarly favorable CV profile with respect to HR and SNRT was also observed with the C4-hydroxy analogue **5v**. These data suggested that the CV signal observed with BMS-605339 (**3**), was mitigated by the structural changes incorporated into the *P2* motif found in **5v** and **5z**. However, **5z** produced changes to coronary flow that while modest, were not observed with BMS-605339 (**3**) or asunaprevir (**4**). Moreover, given the observation that humans appeared to be more sensitive to the CV effects of **3** than were preclinical species, the cardiovascular effects of **5z**, although mild in the Langendorff rabbit preparation, were a cause for some concern. Hence, while **5z** provided to be a compelling compound with respect to its potency and PK properties, further study of this compound was halted due to the potential concern around the preclinical CV profile. As a consequence, more detailed preclinical profiling of asunaprevir (**4**) became the focus of the program.

In summary, a series of potent, tripeptidic NS3 protease inhibitors incorporating an aryl moiety at C-4 of the *P2* proline residue is described. Structure-activity relationships established in the *P2** region of the molecules defined a linear biaryl system as optimal for potency. Modeling studies assessing plausible binding modes suggested that the *para*-biphenyl orients into the hydrophobic pocket beyond the S2 region, while the distal phenyl ring packs optimally against the side chain of Arg155, establishing both hydrophobic and electrostatic contacts. The pharmacokinetic profile of the C4-biaryl, C4 hydroxy lead, **5v**, was relatively poor, however methylation of this hydroxy moiety provided **5z**, which had an enhanced PK profile and likewise improved antiviral activity. This lead was tested in the isolated heart model, where a slight increase in coronary flow was observed. Although this finding was modest, it nonetheless provided a point of differentiation from the program lead, asunaprevir (**4**), which was proven free of a CF effect in this *ex vivo* assay. While the biaryl series described herein did not progress to the clinical stage, these findings provide further insight into potential applications of the C4 proline biaryl series as a *P2* functionality when targeting proteases and as a general motif in considering drug-like functionality.

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