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Matched and mixed cap derivatives in the tetracyclic indole class of HCV NS5A inhibitors

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ABSTRACT

A matched and mixed capping SAR study was conducted on the tetracyclic indole class of HCV NS5A inhibitors to examine the influence of modifications of this region on the overall HCV virologic resistance profiles.

1. Introduction

According to the World Health Organization, over 130-150 million individuals have been infected worldwide with hepatitis C virus (HCV) with about three million new patients contracting HCV each year.[1] While HCV is often asymptomatic, it can progress to chronic hepatitis leading to liver cirrhosis and in many cases hepatocellular carcinoma. Previously, the standard of care for the treatment of HCV was a combination of interferon-α (PEG-IFN-α) and ribavirin (RBV) which demonstrated poor tolerability as well as only moderate efficacy towards the most predominant genotype (GT), GT1, in the world.[2] More recently, two HCV protease inhibitors, boceprevir and telaprevir, have been added to the above-mentioned standard of care to provide a sustained virologic response (SVR) of 70–80% in genotype 1 HCV-infected subjects.[3] The current focus towards improving response rates and curing HCV has centered around the identification of superior direct-acting antiviral agents (DAAs) which might confer more effective, tolerable, interferon-sparing treatment regimens. Towards this end, drug discovery efforts have centered upon the discovery of new therapeutic agents interfering with HCV replication which include non-structural (NS) viral proteins such as NS2, NS3 (protease), NS4A, NS4B, NS5B (polymerase), and NS5A. NS5A is a large phosphoprotein (49 kDa) which has no known enzymatic activity but has been shown to be essential for viral RNA replication.[4] Although the exact role of this protein in the HCV replication cycle remains uncertain, the value of NS5A inhibition as a therapeutic target[5,6] has been demonstrated in the clinic and this area of study remains active in both academia and the pharmaceutical industry.[7] To date, four NS5A inhibitors have gained regulatory approval and are shown in Figure 1.[8-11]

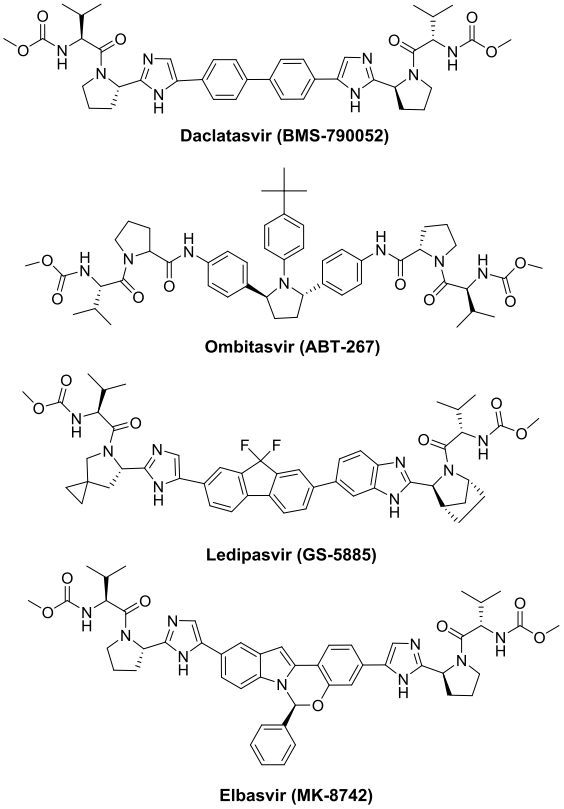


Figure 1. Approved HCV NS5A inhibitors.[8-11]

In a continued effort to explore the tetracyclic indole class of NS5A inhibitors, efforts were undertaken to examine the impact of structural modifications of the two imidazole L-Pro-L-Val methyl carbamate (Moc) regions (Figure 1). While a brief SAR exploration had been previously conducted in an earlier series (MK-4882) to replace the two terminal L-valine methyl carbamate moieties (Val Moc),[11] we sought to explore the impact on the virologic profile of broader changes to the amino acid end caps in the current series.

In order to access the "capped" tetracyclic indole derivatives, a flexible, convergent synthetic route to assemble these derivatives was developed, which is shown in Figure 2. The parent molecule, **1**, was disconnected into a chiral tetracyclic indole core (**2**), a common bromo imidazole Boc-L-proline fragment **3**, and different carboxylic acid fragments **4** which would provide the diversity for this study. At the outset, the tetracyclic indole core bearing the (*S*)-phenyl configuration at the aminal position was selected as a point for comparison to the impact that the structural changes might have on the overall virologic profile. In addition, we wanted to access the tetracyclic indole cores which allowed for variation of the substitution at X and Y.

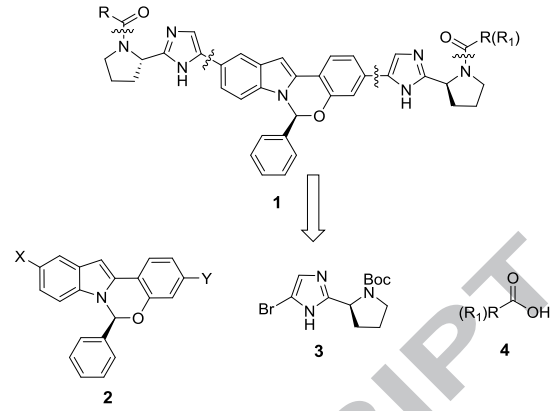
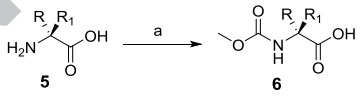


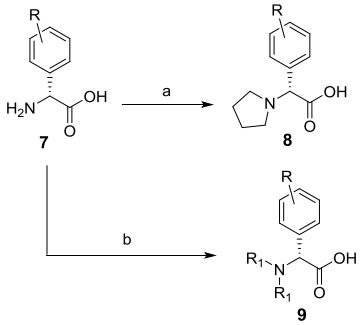
Figure 2. Retrosynthetic analysis of tetracyclic indole capped derivatives.

Initial chemistry efforts focused upon preparation of the required methyl carbamate (Moc) caps from α-amino acids which are shown in Scheme 1. Treatment of **5** with methyl chloroformate under Schotten-Baumann conditions afforded the Moc-protected amino acids **6** which could be used directly without purification.



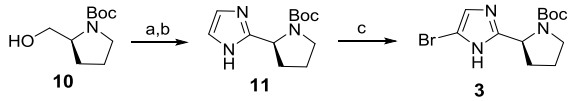
Scheme 1. a) $ClCO_2Me$, NaOH, $NaHCO_3$, H_2O.

In addition to the Moc amino acid caps from Scheme 1, several (*R*)-phenyl glycine-derived caps were prepared directly from the commercially available substituted (*R*)-phenyl glycine starting materials shown in Scheme 2.[12] Treatment of **7** with 1,4-dibromobutane under basic conditions afforded acid **8** while the corresponding dialkylated acids **9** were prepared by reductive amination in the presence of excess aldehyde (Scheme 2).



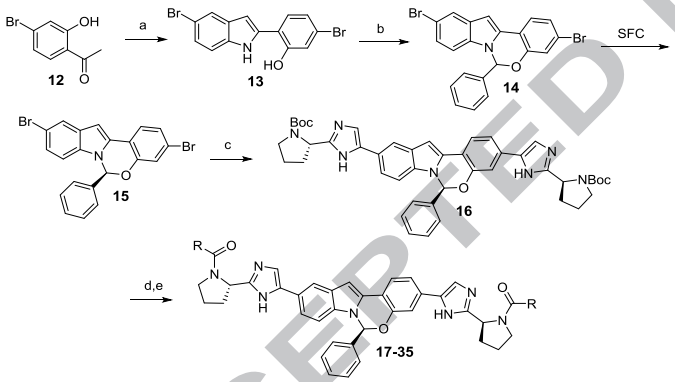
Scheme 2. a) 1,4-dibromobutane, Na_2CO_3; b) R_1CHO, $NaCNBH_3$.

The preparation of the required bromoimidazole Boc-L-proline fragment **3** is illustrated in Scheme 3.[11] Oxidation of the Boc-L-prolinol **10** with Dess-Martin periodinane followed by condensation with glyoxal in the presence of 7M ammonia in MeOH afforded the imidazole **11**. Bromination with NBS afforded the intermediate dibromo adduct which was treated under reductive conditions employing Na_2SO_3 to afford bromide **3** which was ready for coupling.



Scheme 3. a) Dess-Martin periodinane, CH_2Cl_2, 0 °C; b) glyoxal, 7N NH_3 in MeOH, rt; c) NBS, THF then Na_2SO_3, EtOH/H_2O, reflux.

Having prepared the key caps and bromoimidazole fragments, attention initially focused on preparation of tetracyclic indole derivatives bearing identical caps on both flanking pyrrolidines. The synthetic preparation of symmetric capped derivatives is shown in Scheme 4.[11] Utilizing a Fischer indole synthesis protocol, 5-bromoacetophenone **12** was condensed with *p*-bromophenylhydrazine under acidic conditions to form the intermediate hydrazone which was treated at high temperature with PPA to afford the intermediate indole **13**. Treatment of **13** with α,α-dibromotoluene and K_2CO_3 afforded the tetracyclic indole derivative **14**. With this key intermediate in hand, attention turned toward accessing the enantiomerically pure aminal intermediate with the (*S*)-stereochemistry.[13] Compound **14** was subjected to chiral SFC separation to yield the enantiomerically pure aminal **15**.[12] Treatment of dibromide intermediate **15** with two equivalents of bis(pinacolato)diboron in the presence of KOAc and $PdCl_2$(dppf) afforded the intermediate bis-pinacol boronate ester which was then treated with two equivalents of bromoimidazole intermediate **3** to afford the bis Boc adduct **16**. Global deprotection was achieved with HCl followed by treatment with various carboxylic acid caps afforded the final compounds **17-35** (Scheme 4).



Scheme 4. a) 1. *p*-bromophenylhydrazine, AcOH, EtOH, reflux; then 2. PPA, 110 °C; b) α,α-dibromotoluene, K_2CO_3, DMF, 100 °C; c) bis(pinacolato)diboron, KOAc, $PdCl_2$(dppf), dioxane, 110 °C then bromoimidazole **3**, 1M Na_2CO_3, $PdCl_2$(dppf), THF, 90 °C; d) 4N HCl, MeOH; e) RCO_2H, HATU, DIPEA, DMF.

The virologic profile of the matched Moc cap tetracyclic indole analogs, against several HCV wild-type (WT) genotypes (1a and 2b) and resistant mutants (Y93H and L31V), are summarized in Table 1. Simple alkyl, branched alkyl, as well as cycloalkyl side chains (**17-22**) demonstrated weaker activity across GT2b, GT1a Y93H, and GT1a L31V replicon assays. Introduction of a difluoro moiety into the cyclohexyl group (**23**) showed improved activity versus both GT1a Y93H and GT1a L31V when compared to compounds **17-22**. Since these modifications did not improve the overall virologic profiles, efforts focused upon the introduction of additional functionality such oxygen into the sidechain region. Introduction of a 4-tetrahydropyran group led to compound **24** which showed an improved virologic profile against both GT2b and GT1a L31V genotypes albeit at the expense of GT1a shown in Table 1. Incorporation of either an *S*-threonine (**25**) or methoxy-capped *S*-threonine side chain (**26**) led to dramatic losses in GT1a Y93H activity. However, introduction of the methoxy homoserine and the homo 4-tetrahydropyran moieties (**27** and **28**) led to compounds that possessed reasonable profiles against both wild-type (1a and 2b) as well as mutant genotypes (1a Y93H and 1a L31V). With the emerging SAR in Table 1 suggesting the value of having an oxygen in the side chain, additional compounds were prepared to explore this trend which are summarized in Table 2. The (*R*)-tetrahydrofuran amide (**29**) as well as the spirocyclic tetrahydropyran Moc derivative (**30**) demonstrated at least a 1000-fold loss in replicon activity across genotypes. Not surprisingly, compound **31** confirmed the preferred (*S*)-stereochemistry of the side chain in the Moc derivatives as found in compound **24**. Interestingly, several (*R*)-phenyl glycine derivatives (**32** and **34**) possessed improved GT2b activity at the expense of GT1a Y93H as shown in Table 1.[14] Also of note, the substitution on both the phenyl ring and amine for these analogs proved to be very influential in the potencies against both wild-type and mutant genotypes as illustrated by compounds **33** and **35**. In light of the emergence of several interesting non-valine derived caps from Tables 1 and 2, efforts were initiated to prepare mixed cap tetracyclic indole derivatives bearing a single L-Val Moc cap along with an optimized cap from the initial SAR screening. It was unclear what the impact of this mixed capping on both the overall virologic profile as well as pharmacokinetic profile in rat.

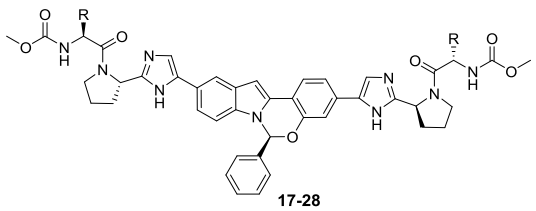
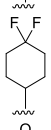


Table 1. *In vitro* virologic profiles of symmetrical Moc capped tetracyclic indole derivatives **17-28**.

		Genotype, EC_{90} (nM)[a]			
Compd	R	1a	2b	1a Y93H	1a L31V
MK-8742		0.006	11	28	1
17		0.042	>100	>100	6.4
18		0.016	65	>100	1.6
19		0.011	>100	>100	1.8
20		0.028	>100	>100	>100
21		0.014	52	>100	4.1
22		0.10	>100	>100	11
23		0.030	77	39	0.65
24		0.060	1.2	23	<0.2
25		0.019	17	>100	nt[b]
26		>1	>100	>100	>100

27		0.061	91	46	2.1
28		0.10	18	40	0.77

[a]Values are the mean of two (n =2) runs. See ref 15 for assay details.
[b]nt = not tested

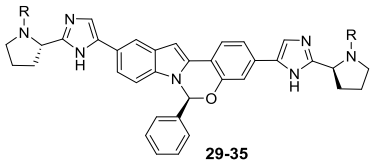
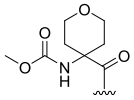
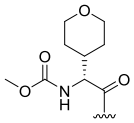
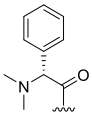
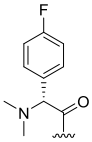
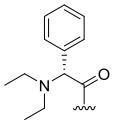
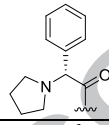
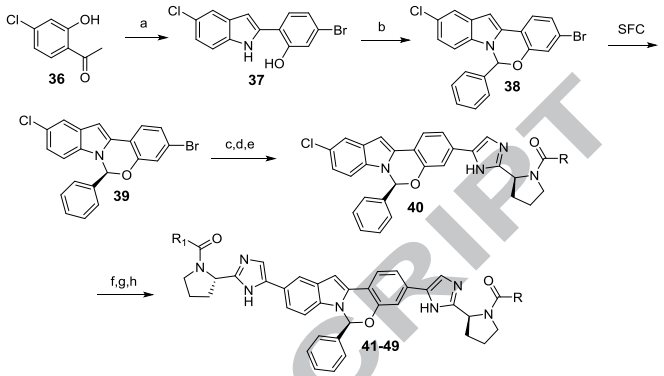


Table 2. *In vitro* virologic profiles of additional symmetrical capped tetracyclic indole derivatives **29-35**.

		Genotype, EC_{90} (nM)[a]			
Compd	R	1a	2b	1a Y93H	1a L31V
29		1	>100	>100	>100
30		1.4	>100	>100	>100
31		8.6	>100	>100	>100
32		0.30	0.87	>100	2.1
33		0.98	>100	>100	>100
34		0.27	3.1	>100	0.6
35		3.9	13	>100	3.9

[a]Values are the mean of two (n =2) runs. See ref 15 for assay details.

In order to access the mixed capped tetracyclic indole derivatives, a modified synthetic route, based upon Scheme 4, was adopted which relied upon the preparation of a differentially substituted tetracyclic indole fragment **39** shown in Scheme 5. The preparation begins with a two-step Fisher indole synthesis using 5-chloroacetophenone **36** followed by a SFC separation provided the enantiomerically pure indole **39**.[16] Functionalization of the bromide of **39** was achieved by treatment under the previously described borylation/Suzuki coupling employing $PdCl_2$(dppf) and bromoimidazole **3** to afford the intermediate Boc adduct which was deprotected and subjected to HATU coupling with the requisite carboxylic acid fragment to afford **40** (Scheme 5). With compound **40** in hand, treatment with $Pd_2(dba)_3$ in the presence of bis(pinacolato)diboron and KOAc afforded the intermediate boronate which was treated directly with bromoimidazole **3** to afford the Boc-protected intermediate. Treatment with HCl followed by HATU-mediated coupling with a different carboxylic acid afforded the final compounds **41-49** shown in Tables 3 and 4.



Scheme 5. a) 1. *p*-bromophenylhydrazine, AcOH, EtOH, reflux; then 2. PPA, 110 °C; b) α,α-dibromotoluene, K_2CO_3, DMF, 100 °C; (c) bis(pinacolato)diboron, KOAc, $PdCl_2$(dppf), dioxane, 110 °C then bromoimidazole **3**, 1M Na_2CO_3, $PdCl_2$(dppf), THF, 90 °C; d) 4N HCl, MeOH; e) RCO_2H, HATU, DIPEA, DMF; f) bis(pinacolato)diboron, KOAc, $Pd_2(dba)_3$, dioxane, 120 °C then **3**, 1M Na_2CO_3, THF, 90 °C; g) 4N HCl, MeOH; h) R_1CO_2H, HATU, DIPEA, DMF.

The *in vitro* virologic profiles of the mixed cap derivatives are summarized in Table 3. While these analogs generally showed a slight loss in GT1a activity, both of the differentially substituted isopropyl/4-tetrahydropyran derivatives (**41** and **46**) demonstrated comparable activity versus GT2b, GT1a Y93H, and GT1a L31V to the base compound (Table 3). In addition, the methylene extended 4-tetrahydropyran derivative **44** demonstrated a similar virologic profile to these analogs (Table 3). It should be pointed out the combination of a "non-optimal" spirocyclic 4-tetrahydropyran Moc cap with a valine Moc in compound **45** did improve the both the GT1a and GT1a L31V activities compared to the bis adduct (**30**) but GT2b or GT1a Y93H remained unchanged. The other combinations (**42-43**, **47-48**) in Table 3 demonstrated reasonable activity across both wild-type and mutant genotypes. In addition to the methyl carbamate caps, combination of a (*R*)-phenyl glycine derived cap with the L-Val Moc cap in compound **49** (Table 4) was intriguing as it demonstrated the ability to improve the GT1a and GT1a Y93H activity compared to the bis phenyl glycine derivative **34** found in Table 2.

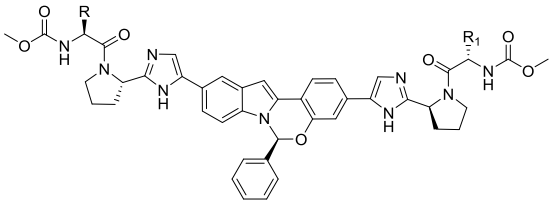
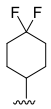


Table 3. *In vitro* virologic profiles of mixed Moc capped tetracyclic indole derivatives **41-48**.

			Genotype, EC_{90} (nM)[a]			
Compd	R	R_1	1a	2b	1a Y93H	1a L31V
MK-8742			0.006	11	28	1
41			0.060	9	11	0.6
42			0.039	35	54	nt[b]
43			0.018	23	34	0.89
44			0.014	8.9	24	0.33
45			0.035	>100	>100	14.7
46			0.061	4	11	0.4
47			0.062	5	50	1.1
48			0.060	50	77	4.3

[a]Values are the mean of two (n =2) runs. See ref 15 for assay details.
[b]nt = not tested.

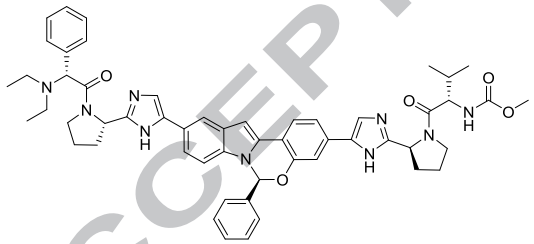


Table 4. *In vitro* virologic profile of *R*-phenylglycineEt_2/L-Val Moc capped tetracyclic indole derivative **49**.

	Genotype, EC_{90} (nM)[a]			
Compd	1a	2b	1a Y93H	1a L31V
49	0.045	4	44	nt[b]

[a]Values are the mean of two (n =2) runs. See ref 15 for assay details.
[b]nt = not tested

Having identified a number of different cap modifications that possessed intriguing virologic profiles, it remained to look at the pharmacokinetic profiles of representative examples of both matched and mixed capping series. Towards this end, the pharmacokinetic profiles of compounds **24** and **46** in rat are summarized in Table 5. The bis-THP Moc derivative **24** demonstrated very poor oral exposure and very high clearance. Likewise, the differentially capped analog, **46**, also demonstrated inferior pharmacokinetic properties.

Table 5. Rat pharmacokinetic profiles of **24** and **46**.

Compd	Dose (mpk)	AUC (μM.h)	Cmax (μM)	T ½ (h)	Cl (ml/min/kg)	F%
24	5	0.004	0.02	2.4	82	0
46[a]	10	nd[b]	0.031	--	--	--

[a]T_{max} = 0.75 h, 1h conc = 0.030 μM; [b]nd = not determined

In conclusion, a systematic capping effort was carried out on the tetracyclic indole scaffold, which identified several non-Val Moc caps which appear to show modest improvements in the overall in vitro virologic profile. More specifically, the incorporation of either (*S*)-4-tetrahydropyran methyl carbamate (**24**) or (*R*)-phenyl glycine diethylamino (**34**) caps into this series in a matched sense produced analogs with improved activity versus both GT1b and GT1a L31V. In addition, these caps could also be partnered with a L-Val Moc cap to produce mixed capped compounds with intriguing mutant profiles against both GT1a Y93H and GT1a L31V. While the capped derivatives described in this work demonstrated poor rat pharmacokinetic profiles, the combination of these caps with additional structural modifications to the scaffold may hold promise in producing analogs with even better resistance profiles.[17] These analogs provide a platform onto which new derivatives with improved pharmacokinetic profiles and stability may emerge. These efforts will be the topic of future disclosures.

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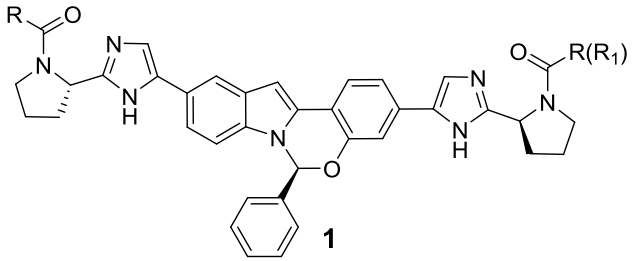

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