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Discovery of novel potent and selective dipeptide hepatitis C virus NS3/4A serine protease inhibitors

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ABSTRACT

Starting from the previously reported HCV NS3/4A protease inhibitor BILN 2061 (**1**), we have used a fast-follower approach to identify a novel series of HCV NS3/4A protease inhibitors in which (i) the P3 amino moiety and its capping group have been truncated, (ii) a sulfonamide is introduced in the P1 cyclopropyl amino acid, (iii) the position 8 of the quinoline is substituted with a methyl or halo group, and (iv) the ring size of the macrocycle has been reduced to 14 atoms. SAR analysis performed with a limited set of compounds led to the identification of *N*-{17-[8-chloro-2-(4-isopropylthiazol-2-yl)-7-methoxyquinolin-4-yloxy]-2,14-dioxo-3,15-diazatricyclo [13.3.0.0 [Bartenschlager, R.; Lohmann, V. *J. Gen. Virol.* 2000, *81*, 1631; Vincent Soriano, Antonio Madejon, Eugenia Vispo, Pablo Labarga, Javier Garcia-Samaniego, Luz Martin-Carbonero, Julie Sheldon, Marcelle Bottecchia, Paula Tuma, Pablo Barreiro Expert Opin. Emerg. Drugs, 2008, *13*, 1–19]]octadec-7-ene-4-carbonyl}(1-methylcyclopropyl)(1-methylcyclopropyl)sulfonamide **19l** an extremely potent (K_i = 0.20 nM, EC_{50} = 3.7 nM), selective, and orally bioavailable dipeptide NS3/4A protease inhibitor, which has features attractive for further preclinical development.

An estimated 3% of the global human population is infected by hepatitis C virus (HCV),[1] an infection that often leads to cirrhosis, hepatocellular carcinoma, and liver failure in later life. The current standard of care therapy is based upon the use of pegylated interferon-α in combination with ribavirin, leading to a sustained virological response (SVR) in approximately 50% of patients infected with genotype 1 virus.[2] Moreover, this limited efficacy is often associated with side effects leading to discontinuation of treatment.[3] In this context, there is an urgent need for more effective, convenient, and well-tolerated therapies. The HCV non-structural protein 3 (NS3) serine protease has been shown to be essential for viral replication.[4] Together with RNA-dependent RNA polymerase (RdRp) NS5B, NS3/4A protease are the most promising targets in the search for next generation anti-HCV drugs.[5] As such, multiple antiviral agents targeting NS3/4A protease activity are currently under clinical development.[6]

On the basis of the initial finding that N-terminal cleavage products of NS3/4A protease peptide substrates are competitive inhibitors of this enzyme,[7,8] preliminary SAR studies allowed the identification of nanomolar substrate-based hexapeptide inhibitors.[7,9] Since it is well documented that polypeptides are unlikely to permeate cells resulting in limited oral bioavailability,[10] the peptidic character of this first series of NS3/4A inhibitors was decreased by successive *N*-terminal truncations leading to the discovery of potent and selective tripeptide inhibitors.[9] Further, improvement of pharmaceutical properties was achieved by the design of macrocyclic β-strand mimic scaffolds that culminated with the discovery of the potent, highly selective, and orally bioavailable drug BILN 2061 (**1**).[11] This inhibitor is characterized by three unnatural amino acid residues (P1, P2, and P3), oriented in a macrocycle as shown in Chart 1. Oral administration of BILN

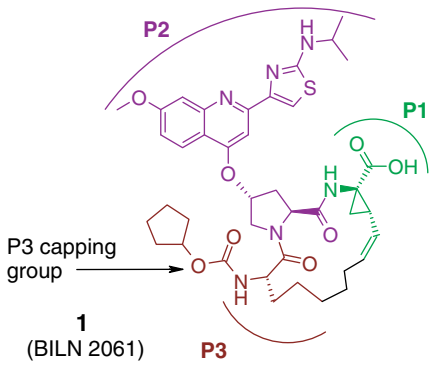

Chart 1. NS3/4A protease inhibitor **1** (BILN 2061) with the P1, P2 and P3 moieties.[11]

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2061 to patients infected with the hepatitis C genotype 1 virus resulted in an impressive reduction of viral RNA levels, establishing the first proof-of-concept for HCV NS3/4A protease inhibitors as therapeutic agents.[12] Further development of this compound was discontinued due to cardiotoxicity findings in primates given supratherapeutic doses for several weeks.[13] Although the mechanism by which BILN 2061 exerts cardiotoxic effects has not been published, a number of companies have initiated fast-follower programs with the rationale that the toxicity observed with the pioneer drug should be compound specific. As a result, several groups have recently reported on macrocyclic HCV NS3/4A protease inhibitors entering phase 1 clinical trials.[6,14] In this letter, we report on our efforts to design a novel series of NS3/4A protease inhibitors obtained by further truncation of the *N*-terminal part of previously reported macrocyclic series (e.g., BILN 2061, **1**).[11]

Although the optimization of the *N*-terminal cleavage products of NS3/4A protease peptide substrates into tripeptide macrocyclic β-strand mimics (e.g., BILN 2061) is well documented,[9,11] the importance of the P3 amino moiety and its capping group in the overall potency and pharmaceutical properties of this series of inhibitors have never been reported. Previously, however, the successful truncation of P3 capping groups has been reported for another series of macrocyclic HCV NS3/4A inhibitors incorporating a cyclopentane dicarboxylic acid as a mimic of proline in the P2 position.[15] Previous structural studies have indicated that the rigid carbamate functionality of the capping group is responsible of the proper positioning of the *N*-terminal alkyl group into the shallow S4 binding pocket of the enzyme,[16] and that both the amino and carbonyl groups of the P3 residue are involved in hydrogen bonding to the protein backbone.[16–18] Given the remarkable potency of BILN-2061, we predicted that the truncation of the P3 amino moiety and its capping group should lead to a compound which retains enough intrinsic potency to be further optimized into a novel series of drug-like NS3/4A protease inhibitors.

The synthesis of the target products **19a**–**l** (Table 1) is outlined in Schemes 1 and 2. Preparation of 2-substituted quinolines **7a**–**f** was carried out either from commercially available *m*-anisidine **4d** to generate the 8 non-substituted quinolines **7a** and **7d**, or from the 2-substituted 3-methoxyanilines **4a**–**c** obtained via a Curtius rearrangement[19] from the corresponding 3-methoxybenzoic acids **2a**–**c**, as depicted in Scheme 1. Treatment of 3-methoxyanilines **4a**–**d** with boron trichloride followed by the addition of acetonitrile and aluminum chloride afforded the corresponding ketones **5a**–**d** via an aromatic electrophilic substitution in 40–73% yield.[20] Finally, acylation of the anilines **5a**–**d** followed by the subsequent ring closure and aromatization of intermediates **6a**–**f** led to the desired quinolin-4-ol derivatives **7a**–**f** (58-88%).[20]

The other 4-hydroxyquinolines **7g** and **7h** were prepared following the procedures reported in the literature.[11,21]

The target macrocyclic products **19a**–**l** were efficiently prepared in a 10-step procedure from the *N*-Boc-*trans*-4-hydroxy-L-proline **8**, 7-octenoic acid, or 8-nonenoic acid, (2*R*,3*S*)-3-vinyl-2-amino-2-cyclopropylcarboxylic acid ethyl ester **9**, and the 4-hydroxyquinolines **7a**–**h** as depicted in Scheme 2. This synthesis represents an adaptation of the literature procedure reported for the synthesis of BILN 2061.[11,21,22] Given the high cost of *cis*-hydroxyproline, we have utilized a tandem of epimerization sequence involving two successive Mitsunobu reactions,[23] which allowed the use of the readily available *N*-Boc-*trans*-4-hydroxy-L-proline as a starting material for the P2 core.

The P1 cyclopropyl amino acid **9**[24] was coupled to the P2 proline core **8** using a standard HATU-mediated peptide coupling procedure in 97% yield. Inversion of the configuration at the position 4 of intermediate **10** via a Mitsunobu reaction[23] was achieved using *p*-nitrobenzoic acid to give ester **11** in 78% yield. Subsequent unmasking of the BOC protecting group followed by the introduction of the alkenylcarbonyl moiety using a standard peptide coupling procedure with HATU led to the esters **13a** and **13b** in 97% and 93% isolated yields, respectively. The regioselective hydrolysis of the *p*-nitrophenyl moiety of **13a** and **13b** was performed with lithium hydroxide at low temperature to afford alcohols **14a** and **14b,** respectively (91% and 87% yield, respectively). Introduction of the P2 quinoline moieties **7a**–**h** onto the proline central scaffold of **14a** and **14b** was achieved by a Mitsunobu reaction,[23] which provided the definitive configuration of the chiral center at position 4 of the proline via a second epimerization leading to non-cyclic intermediates **15a**–**k**. Subsequently, the 14- and 15-membered macrocyclic ring esters **16a**–**k** were obtained in good yields (68–87%) by ring-closing olefin metathesis of the open precursors **15a**–**k** using Hoveyda–Grubbs 1st generation catalyst. Interestingly, previous cyclization studies performed with intermediate **15a** in refluxing dichloromethane did not produce the desired product **16a** with satisfactory yields.[25] Instead, a complex mixture of *cis* and *trans* olefins was observed in these reaction conditions with low overall yields (<15%).

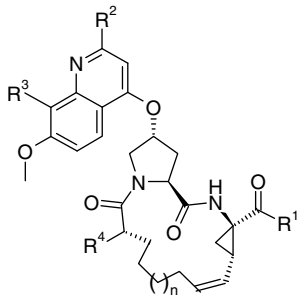
In the present study, the fact that **16a** was obtained as the major product in good yield (71%) with only traces of the *trans* derivative is most likely due to the elevated temperature used, which may allow the open structures **15** to adopt the preorganized conformation needed for the cyclization to the thermodynamically more stable ruthenium complex, thereby giving access to the *cis* olefin macrocycle. Thus, we suggest that the temperature used in the present study is high enough to overcome the rotational barrier of the proline amide in position 1 leading to a rapid equilibrium between the *cis* and *trans* rotamers. This hypothesis is in accordance with previous studies performed with similar diolefin substrates, showing the coalescence of resonances obtained at elevated temperature (67 and 77 °C) in ^{1}H NMR spectroscopy experiments.[25] Hydrolysis of the ethyl esters **16a**–**j** provided the corresponding acids **17a**–**j** in quantitative yields.

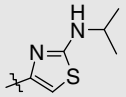
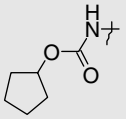
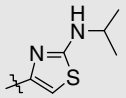
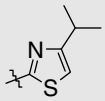
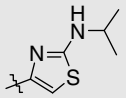
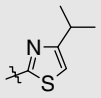
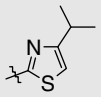
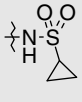
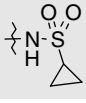
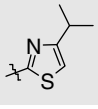
Finally, treatment of acids **17a**–**j** with carbonyldiimidazole led to the oxazolidinediones **18a**–**j**, that were subsequently opened with sulfonamides to complete the synthesis of the target products **19a**–**l**. Reduction of the double bond in the macrocycle of **19c** was performed with 2,4,6-triisopropylbenzenesulfonohydrazide and triethylamine at 80 °C in methanol to give **19m** (Chart 2) in only 6% yield after purification (reaction conditions non-optimized).

The new macrocyclic derivatives **19a–m** prepared in the present study were first tested for their inhibition of the full-length NS3 protease activity in a biochemical assay in presence of a truncated NS4A cofactor, as described earlier.[26] The inhibition constants (K_i values)[27] were determined and are listed in Table 1. The cell-based activities were measured in the Huh7-Rep cell line containing the subgenomic bicistronic replicon clone ET with a luciferase reporter read out.[28] Inhibitory activities (EC_{50}'s) were calculated as the concentration of compound that caused a 50% reduction in luciferase signals compared to that of the untreated control (Chart 3).

The truncation of the terminal P3 amino moiety and its capping group of BILN 2061 provided the dipeptide proline amide **17a**, in which the P3 amino acid has been replaced by an acyl group linking the P2 proline with the P1 cyclopropyl amino acid. Although, this modification led to a dramatic decrease in intrinsic potency, **17a** still retained significant potency on the enzyme with a K_i of 46 nM. This observation prompted us to further investigate structure–activity relationships (SAR) of this shorter and less peptidic series of NS3/4A protease inhibitors. Indeed, we predicted that the decrease in intrinsic potency due to the cleavage of the P2 NH-capping group moiety could be compensated by further optimizations. Since recent studies on NS3/4A protease inhibitors have demonstrated the utility of acylsulfonamides as valuable bioisosteres of the carboxylic acid,[29] we explored whether the introduc-

Table 1
HCV inhibition and metabolic stability



Compound	R^1	R^2	R^3	R^4	*n*	Ns3-K_i (nm)[a]	HUH7-Rep EC50 (μM)[b]	HLM stability (% metb.)[c]
1	–OH		H		2	0.3	0.00163	28.5
17a	–OH		H	H	2	46	1.98	–
17g	–OH		H	H	2	18	5.04	–
19a			H	H	2	0.9	0.204	91.5
19b			H	H	2	0.5	0.00397	–
19c			H	H	2	0.65	0.0180	98
19d			H	H	2	1.0	0.0168	100
19e			CH_3	H	2	0.50	0.00437	98.4
19f			CH_3	H	2	2.8	0.00584	–
19g			Br	H	2	0.10	0.00190	100
19h			H	H	1	0.40	0.0239	82.4

(*continued on next page*)

Table 1 (*continued*)

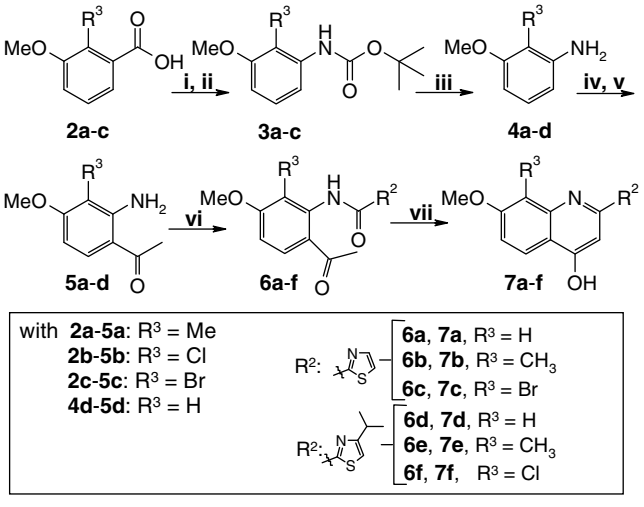
Compound	R^1	R^2	R^3	R^4	*n*	Ns3-K_i (nm)[a]	HUH7-Rep EC50 (μM)[b]	HLM stability (% metb.)[c]
19i			CH_3	H	1	0.20	0.00355	50.2
19j			CH_3	H	1	0.40	0.0141	28.8
19k			Cl	H	1	0.40	0.0117	—
19l			Cl	H	1	0.20	0.00376	42.6

[a] Inhibition of the full-length HCV NS3/4A protease[26] measured by the inhibition constants (K_i values).[27]

[b] Inhibition of HCV replication in Huh-7-Rep cells containing the subgenomic bicistronic replicon clone ET with a luciferase reporter read out for macrocyclic HCV NS3/4A protease inhibitors **1, 17a, 17g, 19a–l** measured by 50% effective concentration (EC_{50}).[28]

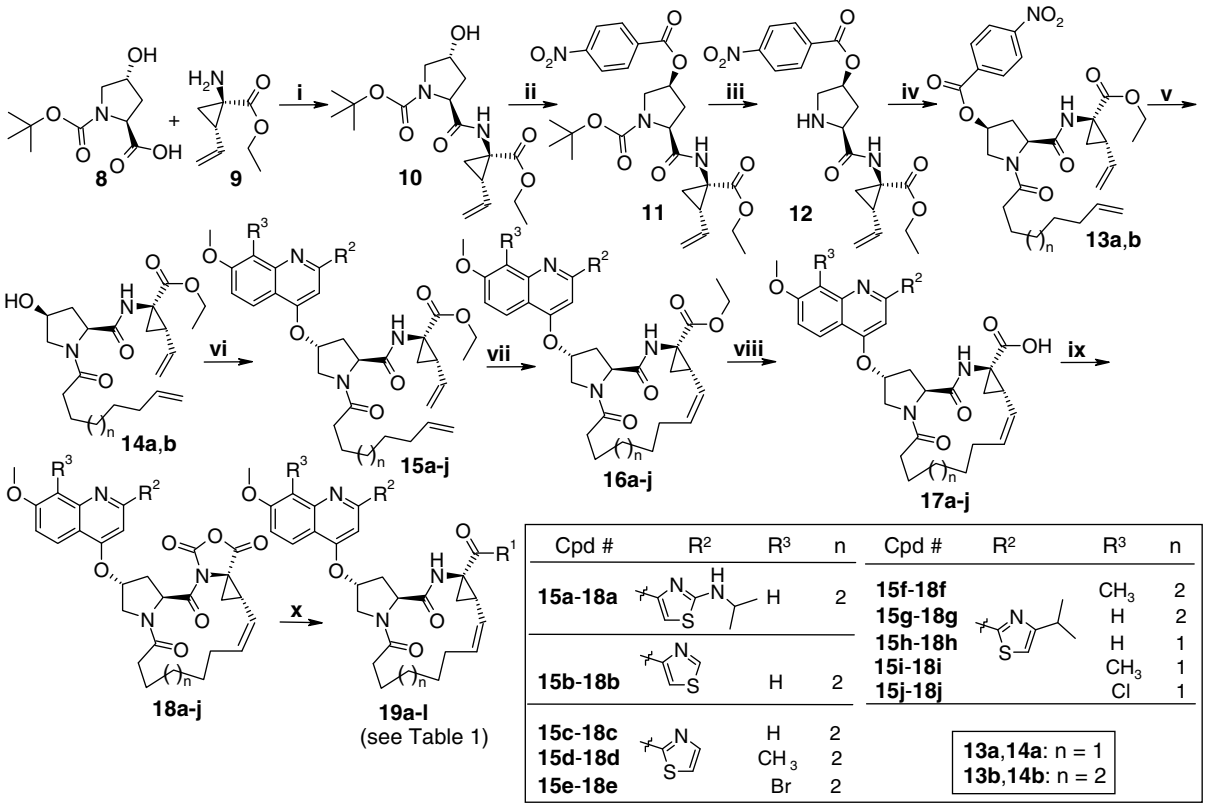
[c] Human liver microsomes (HLMs) stability measured by the percentage of metabolized product after 15 min at 37 °C in the presence of 5 μM of tested compound.

tion of this moiety into the acid P1 residue could also positively impact the potency of the resulting compound **19a**. To our satisfaction, a substantial increase in intrinsic potency was observed for the cyclopropylsulfonamide analogue **19a** (K_i = 0.9 nM) compared to the original acid derivative **17a** (K_i = 46 nM). A similar beneficial effect on the replicon cell-based assay was observed (EC_{50} = 1.98 μM and 20.4 nM, respectively, for **17a** and **19a**), making this series of P3-truncated macrocyclic inhibitors interesting candidates for further optimization. However, despite the dramatically improved potency in both enzymatic and cell-based assays, the very low metabolic stability of **19a**, measured in vitro using human liver microsome (HLM) preparations, rapidly emerged as a major drawback for this novel series. In fact, **19a** was found to be 91.5% metabolized after 15 min, whereas BILN 2061 was only 28.5% metabolized under the same conditions. Therefore, we decided to explore the effect on both the potency and HLM stability



Scheme 1. Reactions and conditions: (i) TEA, diphenylphosphorylazide (dppa), toluene, 100 °C; (ii) *t*-BuOH, toluene, 100 °C; (iii) TFA, CH_2Cl_2, 20 °C; (iv) BCl_3, xylene, 0 °C; (v) CH_3CN, $AlCl_3$, CH_2Cl_2, 0 °C to 70 °C; (vi) R^2COOH, $POCl_3$, pyridine, −20 to 0 °C; (vii) *t*BuOK, *t*BuOH, 80 °C.

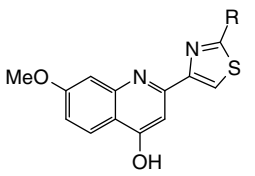
of subtle changes in three different parts of the macrocyclic inhibitor: (i) P1 cyclopropylsulfonamide, (ii) P2 quinoline moiety, and (iii) the macrocycle (ring size and saturation of the double bond). Since we have found with a similar macrocyclic series (data published elsewhere) that the incorporation of a 2-thiazole in position 2 of the quinoline provided a compound which exhibits better Caco permeability (P*app* values) compared to the 2-isopropylaminothiazol-4-yl present in compounds BILN 2061, **17a**, and **19a**, we decided to perform this study on the 2-thiazolylquinoline series. Although the first compounds synthesized **17g** and **19c** were found equipotent compared to the corresponding isopropylaminothiazole analogues **17a** and **19a**, the metabolic stability was still very poor (98% metabolized). The saturation of the double bond in the macrocycle of **19c** was found to be highly detrimental for the potency of the resulting compound **19m** (**19c** and **19m**, EC_{50} = 18 and 65.9 nM, respectively). This significant loss in potency might be due to the unfavorable increased flexibility of **19m** leading to an entropy penalty to adopt the proper bioactive conformation.[30] Interestingly, the introduction of either a methyl (**19e** and **19f**, EC_{50} = 4.3 and 5.8 nM, respectively) or a bromo substituent (**19g**, EC_{50} = 1.9 nM) in the position 8 of the quinoline led to derivatives that were approximately fourfold more potent in the replicon assay, providing single digit nanomolar NS3/4A inhibitors. This improvement in replicon activity of the 8-substituted derivatives **19e–g** is not fully understood at this point and might be explained by more favorable overall physicochemical properties leading to improved cell permeability. However, the metabolic stability of **19e–g** remained very poor. Since the parent drug candidate BILN 2061 (**1**) was found metabolically stable, we hypothesized that the low stability observed in the present series might be attributed to the more flexible scaffold generated by the cleavage of the P3-NH-capping group moiety, known to constrain the inhibitor in a β-strand mimic conformation.[9,11] To verify this hypothesis, we synthesized a series of more rigid 14-membered macrocycles listed in Table 1 (**19h–l**). Following this approach, we were gratified to see that metabolic stability of **19h** was significantly better (82.4% metabolized) than the corresponding 15-membered analogue **19c** (98% metabolized). In addition, the replicon activity was not affected throughout this ring constriction



Scheme 2. Reactions and conditions: (i) HATU, diisopropylethylamine, DMF, 0–20 °C; (ii) *p*-nitrobenzoic acid, PPh_3, DIAD, THF, −20 to 20 °C; (iii) TFA, CH_2Cl_2, 20 °C; (iv) 7-octenoic acid (for $n = 1$) or 8-nonenoic acid (for $n = 2$) HATU, diisopropylethylamine, DMF, 0– 20 °C; (v) LiOH, H_2O/THF, 0 °C; (vi) **7a**-**h**, PPh_3, DIAD, THF, -20 °C to room temperature; (vii) Hoveyda-Grubbs 1st generation catalyst, dichloroethane, 70 °C; (viii) LiOH, H_2O/MeOH/THF, 20 °C; (ix) CDI, THF, reflux; (x) cyclopropylsulfonamide or methylcyclopropylsulfonamide, DBU, THF, 50 °C.

(EC_{50} = 23.4 and 18 nM, respectively). This beneficial effect was even more pronounced for the 8-methyl quinoline derivative **19i** (50.2% metabolized). Eventually, introduction of a methyl group in the P1 cyclopropyl sulfonamide moiety led to a compound that was only 28.8% metabolized in the HLM assay. Similarly, the 8-chloroquinoline derivative **19l** turned out to be stable (42.6% metabolized) and very potent (EC_{50} = 3.76 nM) inhibitor of the HCV NS3/4A protease. Together with the good permeability data observed with **19l** in Caco-2 cells (P*app* apical to basolateral =11.1 × 10^{-6} cm/s), we selected this compound as the lead for this novel series of P3 truncated derivatives. It is noteworthy that all the compounds tested in this study, including **19l**, did not exhibit any significant cytotoxicity toward both MT4-LTR-Luc and Huh7-CMV-Luc cell lines (CC_{50} > 20 μM). To verify if the promising in vitro parameters (Caco-2 permeability and improved HLM stability) reflected the in vivo situation, the pharmacokinetic (PK) properties of **19l** were investigated and the data are summarized in Table 2 and Fig. 1.

The plasma kinetics, oral bioavailability together with heart and liver-plasma tissue distribution in male SD rats were determined after a single intravenous (IV) administration of 2 mg/kg of **19l** using 20% hydroxypropyl β-cyclodextrine as vehicle. These data were compared to an oral administration of 10 mg/kg of **19l** in a 50% PEG400 solution in which 2.5% vitamin E-TPGS was added. The compound levels were quantifiable up to 8 h post administration. As shown in Figure 1 and Table 2, the mean maximum concentration (C_{max} = 715 ng/mL) in the plasma was achieved at 0.75 h post-dose (T_{max}), indicating a rapid absorption of **19l**. Given that viral replication of HCV is known to occur primarily in hepatocytes, achieving high drug concentrations in the liver is believed to be critical for the clinical success of HCV inhibitors. In this respect, **19l** was found to be well distributed in the liver with a very high concentration observed after 8 h (3655 ng/g and 7665 ng/mg after IV and oral administration, respectively). In contrast, the heart exposure was found to be very low (15.1 ng/g and 35.8 ng/mg after IV and oral administration, respectively), revealing a 200-fold higher concentration in the liver relative to the heart tissue. Furthermore, the mean half-life of **19l** in the plasma ($t_{1/2\,(2-8h)}$) was found to be 2.73 h after oral administration. The oral bioavail-



7g: R = H
7h: R = *i*-PrNH

Chart 2. Quinoline reported in the literature.[11,21]

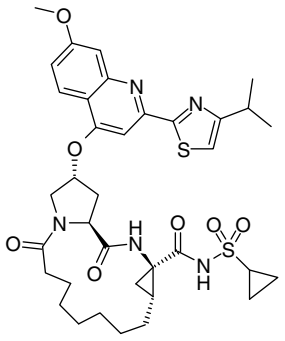


Chart 3. 19m (K_i = 1.9 nM, EC_{50} = 65.9 nM).

Table 2
Mean plasma and tissue levels ($n = 2$) together with some basic pharmacokinetic parameters of macrocycle **19l** after a single intravenous administration of 2 mg/kg in hydroxypropyl-β-cyclodextrine and oral administration of 10 mg/kg in vitamin E-TPGS in the male SD rat

		Intravenous ($n = 2$)	Oral ($n = 2$)
Concentrations (ng/mL)	0.12 h	1500	—
	0.33 h	708	—
	0.5 h	—	698
	1 h	449	693
	2 h	290	632
	4 h	139	363
	8 h	53	133
C_{max} (ng/ml)		—	715
T_{max} (h)		—	0.75
$T_{1/2}$ (2–8 h) (h)		2.49	2.73
$AUC_{(0-8h)}$ (ng h/mL)		1961	3067
AUC_{0-inf} (ng h/mL)		2154	3607
Vd_{ss} (l/kg)		2.75	—
Cl (l/h/kg)		3.94	—
F (%)			31
Heart (8 h) (ng/g)		15.1	72.7
Liver (8 h) (ng/g)		3655	7665

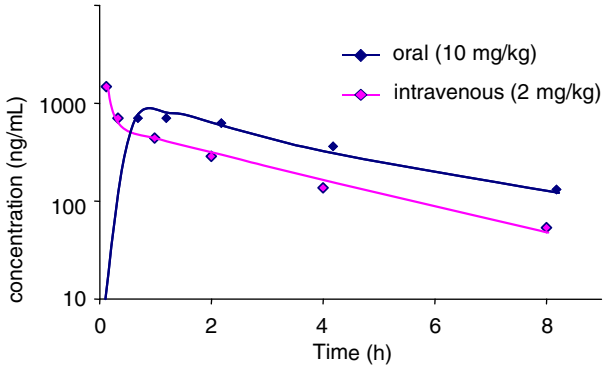


Figure 1. Mean plasma concentrations ($n = 3$) of **19l** after a single intravenous administration of 2 mg/kg in hydroxypropyl-β-cyclodextrine and oral administration of 10 mg/kg in vitamin E-TPGS in the male SD rat.

ability (F) and oral AUC are, respectively, 31% and 3607 ng.h/mL. A promising PK profile was also observed in Beagle dog ($n = 3$) after a single intravenous (IV) administration of 1 mg/kg of **19l** characterized by a high AUC (1322 ng h/mL) and low clearance (0.73 l/h/kg). The observed oral bioavailability (F) after single oral administration of 4 mg/kg was 21%, with a C_{max} at 498 ng/mL, a half-life ($T_{1/2}$) of 4.0 h, and an AUC of 928 ng h/mL.

In conclusion, we have reported here a novel series of potent and non-cytotoxic P3-truncated macrocyclic HCV NS3/4A protease inhibitors. Structure–activity relationships studies performed with a very limited set of compounds (<20) in parallel on the potency and HLM stability led to the identification of *N*-{17-[8-chloro-2-(4-isopropylthiazol-2-yl)-7-methoxy-quinolin-4-yloxy]-2,14-dioxo-3,15-diazatricyclo [13.3.0.0^{4,6}]octadec-7-ene-4-carbonyl}-(1-methylcyclo propyl)-(1-methylcyclopropyl)sulfonamide **19l**, a potent ($K_i = 0.2$ nM, $EC_{50} = 3.76$ nM), non-cytotoxic ($CC_{50} > 20$ μM), and metabolically stable HCV inhibitor. Moreover, **19l** exhibits advantageous drug metabolism and pharmacokinetic properties in rat and dog, with a high liver exposure after oral administration, but limited heart exposure observed in rat. Further preclinical exploration of this novel inhibitor series is warranted.

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