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Synthesis and SAR of potent inhibitors of the Hepatitis C virus NS3/4A protease: Exploration of P2 quinazoline substituents

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ABSTRACT

Novel NS3/4A protease inhibitors comprising quinazoline derivatives as P2 substituent were synthesized. High potency inhibitors displaying advantageous PK properties have been obtained through the optimization of quinazoline P2 substituents in three series exhibiting macrocyclic P2 cyclopentane dicarboxylic acid and P2 proline urea motifs. For the quinazoline moiety it was found that 8-methyl substitution in the P2 cyclopentane dicarboxylic acid series improved on the metabolic stability in human liver microsomes. By comparison, the proline urea series displayed advantageous Caco-2 permeability over the cyclopentane series. Pharmacokinetic properties in vivo were assessed in rat on selected compounds, where excellent exposure and liver-to-plasma ratios were demonstrated for a member of the 14-membered quinazoline substituted P2 proline urea series.

According to The World Health Organization about 170 million people, 3% of the global population, are infected by Hepatitis C virus (HCV), with 3–4 million new infections occurring each year.[1] Individuals who become chronically infected usually progress to end-stage liver diseases and approximately 2–4% develop hepatocellular carcinomas. Untreated HCV infection is the leading cause of liver transplantation due to liver cirrhosis, hepatocellular carcinoma, and ultimately liver failure.

The current standard of care treatment for chronic HCV is a combination of pegylated interferon-α and ribavirin. Approximately 42–46% of genotype 1 infected patients respond fully to PEG-IFN/ribavirin combination therapy. Patients infected with HCV genotype 2 and 3 show substantially higher response rates, with sustained virological response (SVR) of around 90% and 80%, respectively, after 24 weeks of therapy.[2] The sustained virological response in patients co-infected with HIV is notably poor, that is, 30–40%, in genotype 1 patients.[3]

The limitations of today's treatments are substantial,[4] including inconvenient dosing regimes and severe side effects such as hemolytic anemia, flu-like symptoms, and neuropsychiatric events. The severe side effects result in 10–20% of premature withdrawals from therapy. The need for new efficacious drugs for HCV genotype 1 infected patients and for patients not responding to standard of care is urgent. High SVR rates, shortened duration of treatment and improved safety profiles together with more convenient once daily dosing regimens are some of the goals for future treatments.

The virally encoded NS3/4A serine protease, a hetero dimeric serine protease essential for viral replication, is an intensively studied HCV drug target. Highly promising NS3/4A inhibitors have been developed, and there are today several drug candidates in the clinical pipeline. The most advanced candidates are VX-950 (telaprevir)[5] and SCH-503034 (boceprevir)[6] which currently are in phase III clinical trials. Both telaprevir (I) and boceprevir (II) are linear peptidomimetic inhibitors incorporating an α-ketoamide

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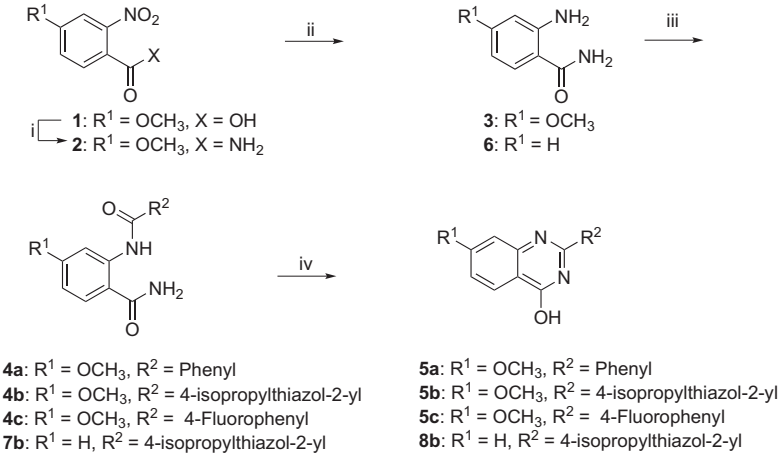
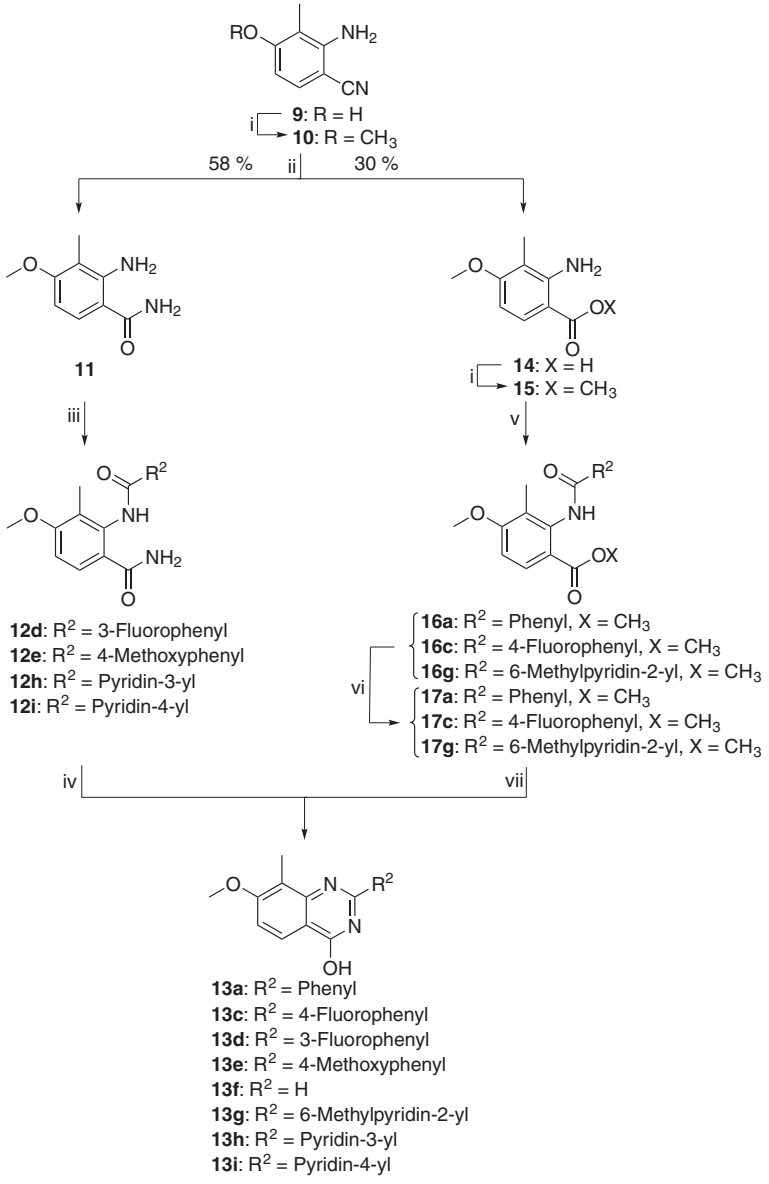


Scheme 1. Reagents and condition: (i) oxalyl chloride, DMF, DCM, then NH_3 71%; (ii) Raney-Ni, EtOH, H_2, 3.5 bar, 95%; (iii) R_2-COOH, HOBt, EDAC, TEA, DMF, 55–90%; (iv) Na_2CO_3, EtOH/H_2O 1:1, reflux, 77–90%.



Scheme 2. Reagents and conditions: (i) MeI, K_2CO_3, DMF; (ii) 2 M NaOH, EtOH; (iii) R_2-COCl, pyridine, THF; (iv) Na_2CO_3, EtOH/H_2O 1:1, reflux, 60–95% over two steps, note: **13f** was formed as a biproduct when the procedure was performed in DMF rather than in EtOH; (v) R_2-COOH, pyridine, DCM, 50–56%; (vi) 1 M LiOH, EtOH, 60 °C; (g) formamide, 150 °C, 71–89% over two steps.

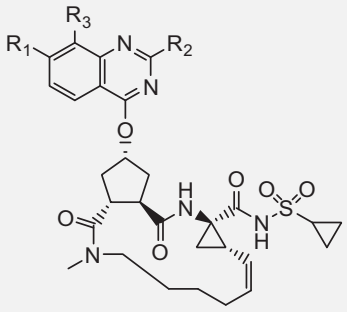
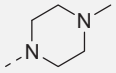
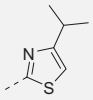
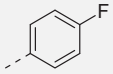
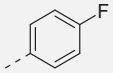
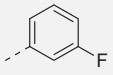
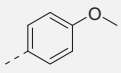
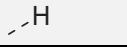
that reacts covalently with the catalytic Ser139 in the active site via a reversible mechanism. Another class of NS3/4A inhibitors is the non-covalent binding macrocyclic inhibitors chemically characterized by a hydrocarbon linkage from the P1-side chain to the P3-side chain, as in TMC435[7] and ITMN-191/R-7227[8] or by a linkage from the P2 substituent to the P4-side chain as in MK-7009.[9] Key features of these three compounds are the P1 sulfone amides interacting with the oxyanion pocket of the active site as well as relatively large quinoline and indoline P2 substituents.

We now report on quinazolines as novel P2 substituents in the previously described cyclopentane[7,10] and proline urea[11] based macrocyclic NS3/4A inhibitors.

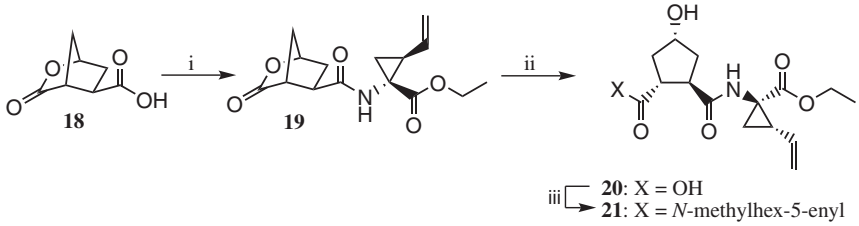
The syntheses of the corresponding 4-quinazolinols are outlined in Schemes 1 and 2. The carboxylic acid **1**[12] was treated with oxalyl chloride in dichloromethane/dimethylformamide followed by the displacement of the so-formed acyl chloride with ammonia leading to amide **2**. Subsequent reduction of the nitro group furnished amine **3**. Amines **3** and **6** were coupled with carboxylic acids (Table 1 for R^2 groups) under standard conditions which gave intermediates **4a–c** and **7b**. Subsequent condensation in refluxing ethanol–water in the presence of sodium carbonate provided the quinazolinols **5a–c** and **8b**.

The preparation of 8-methyl substituted quinazolinols is outlined in Scheme 2. Alkylation of **9**[13] furnished the methyl ether

Table 1
SAR for the P2 cyclopentane series

Structure	Compound	R^1	R^2	R^3	K_i (nM) HCV NS3 1a	EC_{50} (nM) HCV NS3 1b	Cl_{int} (μL/min/mg)	P_{app} ($cm/s \times 10^{-6}$)
	**25**	H		H	0.4	52	58	21
	31	H		H	6.2	390	Nd	Nd
	32	H		H	1.2	830	Nd	Nd
	39b	H		H	0.8	120	Nd	Nd
	45a	MeO		H	0.4	14	88	13
	45b	MeO		H	1.2	58	76	6
	45c	MeO		H	0.2	11	32	20
	51a	MeO		Me	0.1	5	<6	13
	51c	MeO		Me	0.4	10	<6	3
	51d	MeO		Me	0.4	20	10	5
	51e	MeO		Me	0.6	8	11	9
	51f	MeO		Me	>1000	>1000	Nd	Nd

Nd, not determined.



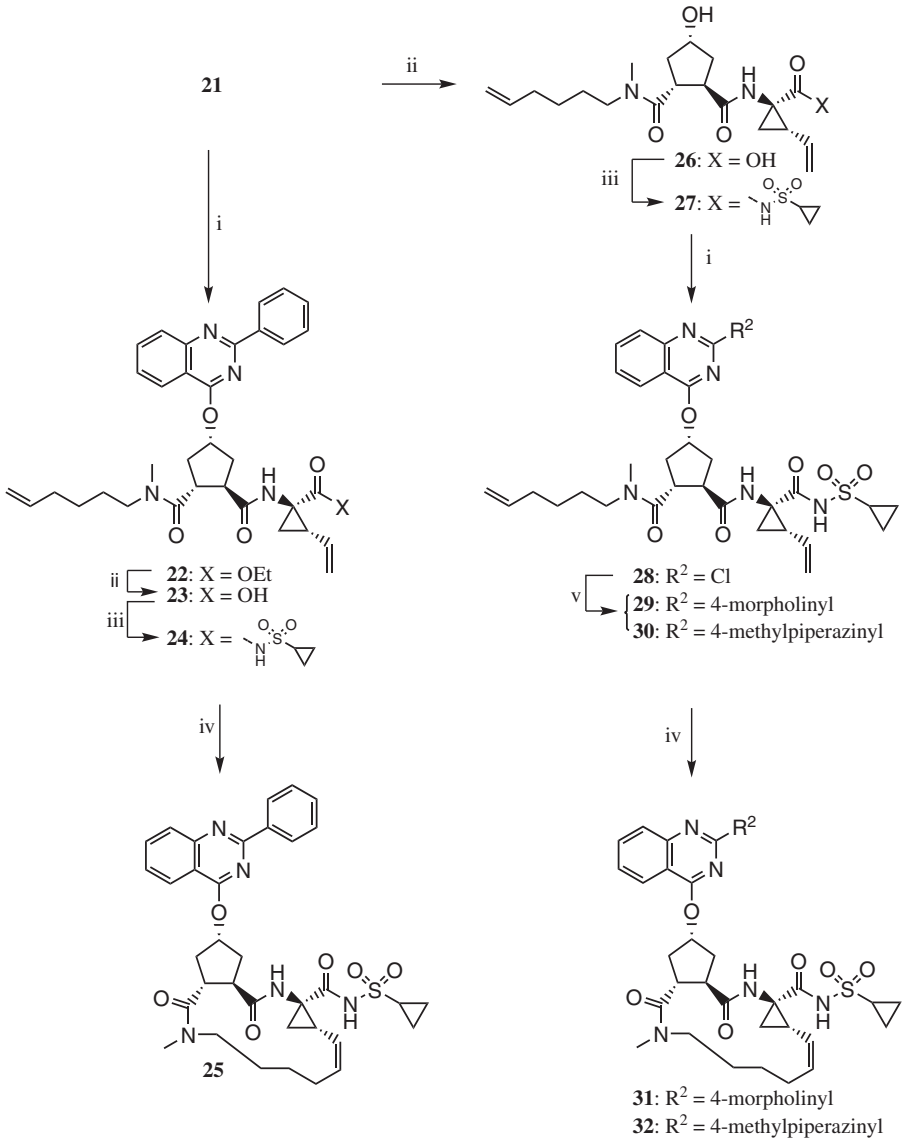
Scheme 3. Reagents and conditions: (i) (1*R*,2*S*)-ethyl 1-amino-2-vinylcyclopropanecarboxylate, HATU, DIPEA, 2:1 DCM/DMF, rt, 1 h; (ii) H_2O, DIPEA, microwaves 100 °C, 40 min; (iii) *N*-methylhex-5-en-1-amine, HATU, DIPEA, DCM/DMF (4:1), 0 °C to rt, 73% over three steps.

10. Hydrolysis of the nitrile **10** under basic conditions delivered a mixture of **11** and **14** (58% and 30% yield, respectively, over the two steps) which was separated. Compound **11** was reacted with the corresponding acid chlorides to obtain amides **12d**, **12e**, **12h**, and **12i**, which were cyclized providing the corresponding quinazolinols **13d–f** and **13h–i** in 60–95% yields, respectively. Starting from **14**, the carboxylic acid was esterified into **15** and subsequently coupled with the corresponding carboxylic acids under standard conditions rendering the amides **16a**, **16c**, and **16g** which after ester hydrolysis and reaction with formamide at elevated temperatures gave the corresponding quinazolinols **13a**, **13c**, and **13g** in 71–89% yield.

The synthetic routes to the target products are outlined in Schemes 3–6. Initially, the route outlined in Schemes 3 and 4 was used for synthesis of the targets products in the cyclopentane series.

Carboxylic acid **18**[10a] (Scheme 3) was coupled with (1*R*,2*S*)-ethyl-1-amino-2-vinylcyclopropanecarboxylate[14] providing intermediate **19**. Subsequent lactone hydrolysis to acid **20** and coupling with *N*-methylhex-5-en-1-amine gave the common intermediate **21** in 73% overall yield over three steps.

Two routes using the intermediate **21** were employed. Reacting **21** with 4-chloro-2-phenylquinazoline[15] in the presence of sodium hydride in DMF gave a mixture of ester **22** and acid **23**, where **22** was hydrolyzed to **23** in 49% yield and coupled with cyclopropanesulfonamide under microwave irradiation[16] giving **24** in 90% crude yield. Finally ring-closing olefin metathesis using Hoveyda–Grubbs 2nd generation catalyst under microwave irradiation furnished the target product **25** in 29% yield over the two steps. Alternatively, ester hydrolysis of **21** afforded the carboxylic acid **26** which was coupled with cyclopropanesulfonamide providing **27** in 77% yield over the two steps. Reaction of **27** as described, vide supra, rendered the chloro derivative **28** in 79% yield. Nucleophilic aromatic substitution of **28** using neat amines under microwave irradiation gave derivatives **29** and **30** (52% and 82% yield, respectively), which were subsequently subjected to ring-closing olefin metathesis, providing target products **31** and **32** (56% and 22% yield, respectively).



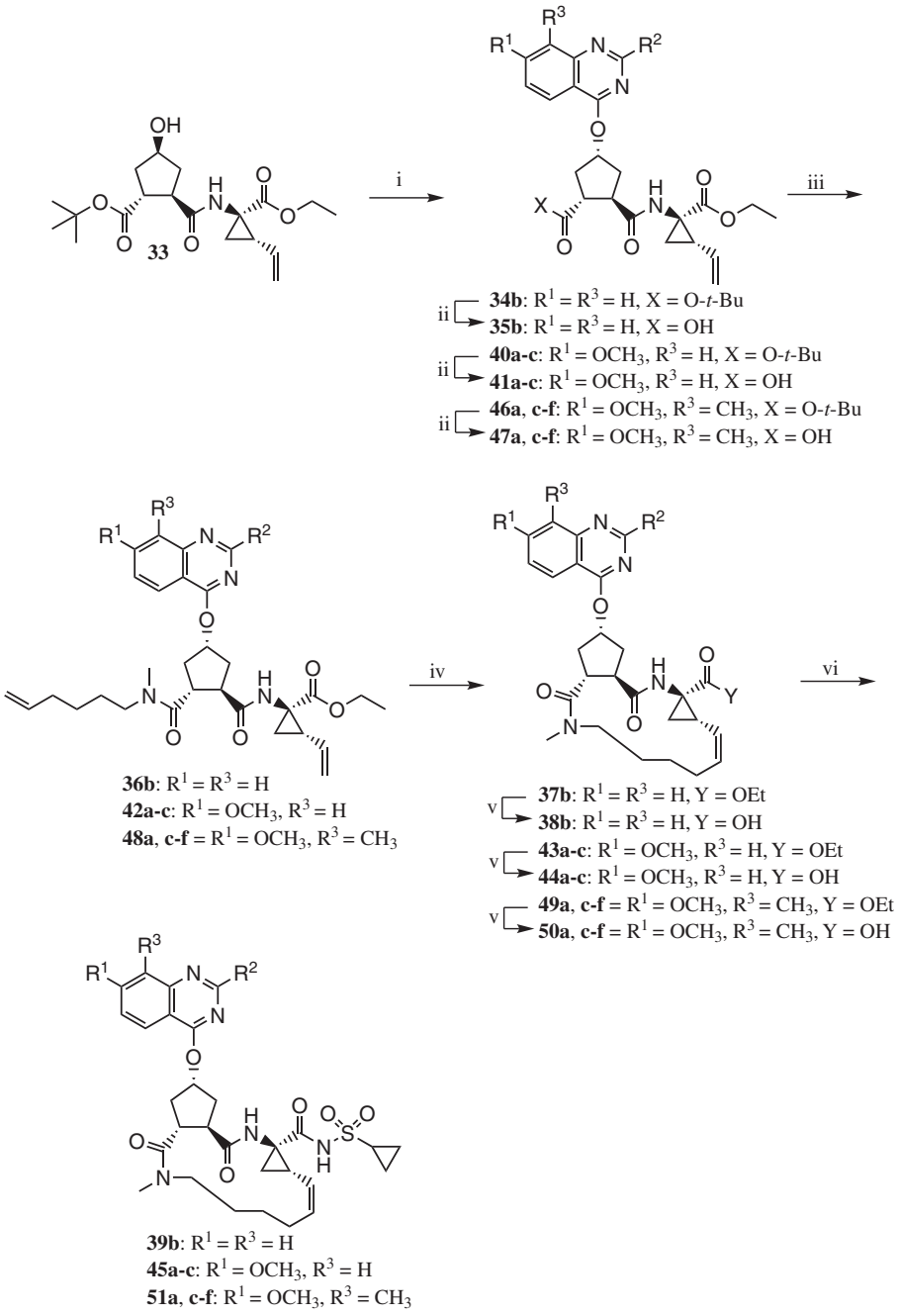
Scheme 4. Reagents and conditions: (i) 2,4-dichloroquinazoline or 4-chloro-2-phenylquinazoline, NaH, DMF, 0 °C to rt; (ii) aq 2 M LiOH DMF, microwaves 130 °C, 30 min; (iii) cyclopropanesulfonamide, EDAC, DMAP, DBU, 1:1 DCM/DMF, microwaves 100 °C, 30 min; (iv) Hoveyda–Grubbs catalyst 2nd generation, DCE, microwaves 150 °C, 15 min; (v) neat 4-morpholine or 4-methylpiperazine or 2-pyrazoline, microwaves 120 °C, 10 min.

The target products in the cyclopentane series were also prepared from the earlier described building block **33**[7,10] as outlined in Scheme 5.

Reacting **33** with quinazolinols **5a–c**, **8b**, **13a**, and **13c–f** under Mitsunobu conditions gave **34b**, **40a–c**, **46a**, and **46c–f** in 68–99% yield. Acidic hydrolysis of the *tert*-butyl esters of **34b**, **40a–c**, **46a**, and **46c–f** followed by HATU promoted coupling with *N*-methylhex-5-enamine delivered **36b**, **42a–c**, **48a**, and **48c–f** in good yields (60–85%). Ring-closing olefin metathesis of **36b**, **42a–c**, **48a**, and **48c–f** using Hoveyda–Grubbs catalyst (1st or 2nd) provided **37b**, **43a–c**, **49a**, and **49c–f** in moderate to good yields (30–80%). Ester hydrolysis of **37b**, **43a–c**, **49a**, and **49c–f** under basic conditions followed by EDAC promoted coupling to cyclopropylsulfonamide gave target products **39b**, **45a–c**, **51a**, and **51c–f** in moderate yields (10–40%) after preparative-HPLC purification.

The synthesis of the P2 proline urea target products from the key intermediate **52**[11] is outlined in Scheme 6.

N-deprotection[11] of **52** resulted in **53** (95% crude yield), followed by treatment with phosgene yielding **54** and subsequent coupling with *N*-methylhex-5-enamine delivering the proline urea **55** (90% yield over the two steps). Ring-closing olefin metathesis of **55** using Hoveyda–Grubbs 2nd generation catalyst provided **56** in 74% yield. Selective hydrolysis of the 4-nitrobenzyl ester of **56** afforded the alcohol **57** in 80% yield. Reacting **57** with quinazolinols **13a**, **13c**, **13e**, and **13g–i** under Mitsunobu conditions

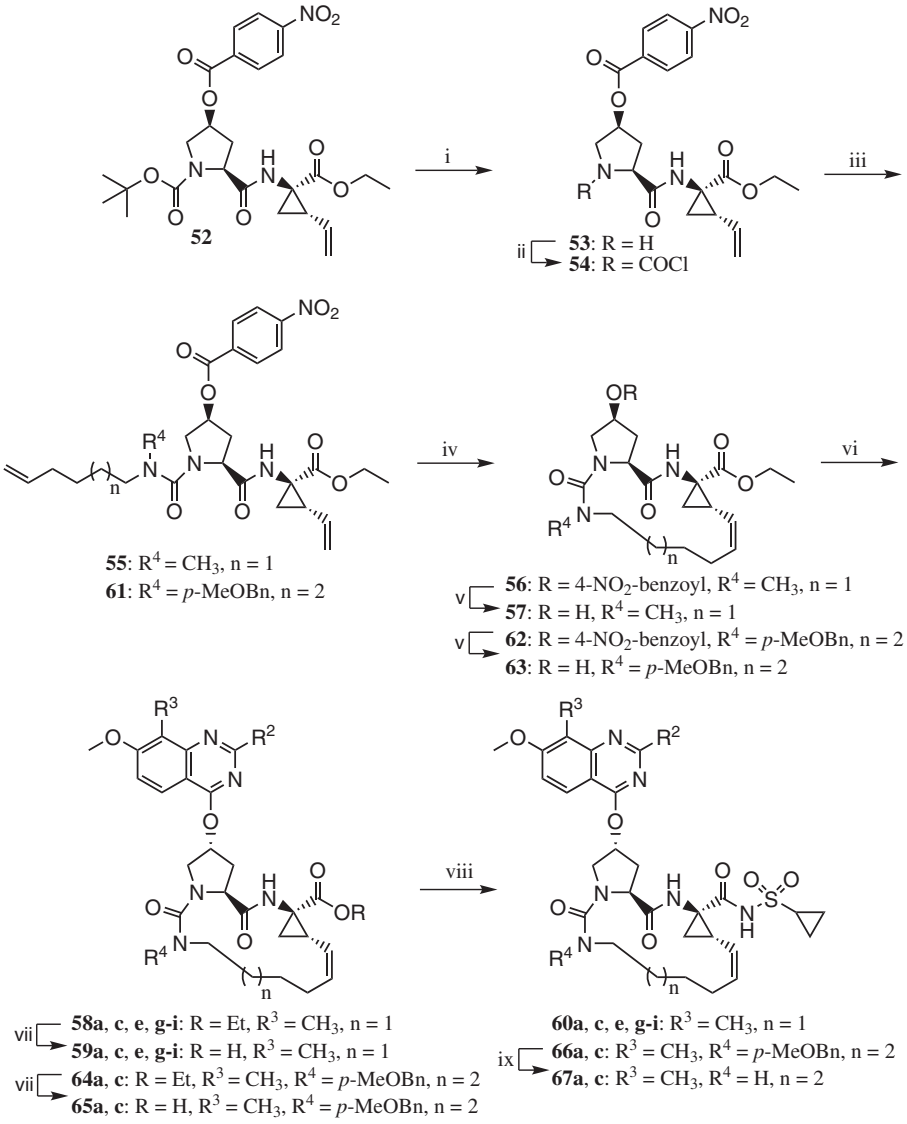


Scheme 5. Reagents and conditions: (i) quinazolinol, PPh_3, DIAD, THF, 0 °C to rt overnight; (ii) 2:1 DCM/TFA, Et_3SiH, 0 °C to rt, 1 h; (iii) *N*-methylhex-5-enamine, HATU, DIPEA, DMF, 0 °C to rt, 1–3 h; (iv) Hoveyda–Grubbs catalyst (1st or 2nd), 1,2-dichloroethane, reflux, 4–12 h; (v) 2:1:1 THF/MeOH/H_2O, aq 1 M LiOH; (vi) EDAC, DCM, rt, 3–12 h, then cyclopropylsulfonamide, DBU 6–12 h. R^2 substituents are defined in Schemes 1 and 2 (**a–f**).

delivered **58a**, **58c**, **58e**, and **58g–i** in moderate to good yields (30–85%). Ester hydrolysis of **58a**, **58c**, **58e**, and **58g–i** followed by coupling to cyclopropylsulfonamide gave target products **60a**, **60c**, **60e**, and **60g–i** in 40–85% yields over the two steps. Similarly the target compounds **66a** and **66c** were obtained from quinazolinols **13a** and **13c** in 20% and 12% yield, respectively, over the six steps. N-deprotection of **66a** and **66c** under acidic conditions gave target compounds **67a** and **67c** (62% and 38% yield, respectively).

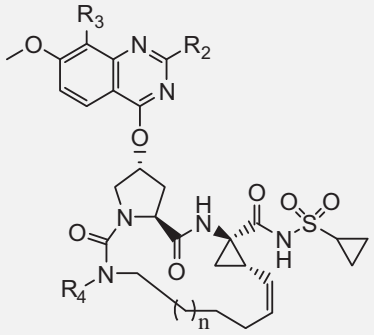
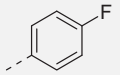
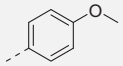
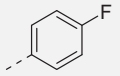
The novel quinazoline containing macrocyclic inhibitors were evaluated in a biochemical assay for their inhibitory capacities on the full-length HCV NS3/4A protease incorporating the central part of the cofactor NS4A as described earlier.[17] The inhibition constants (K_i values)[18,19] were determined, and are listed in Tables 1 and 2. The cell-based activities (EC_{50}) were measured in the Huh7-replicon cell line containing subgenomic bicistronic replicon clone ET with a luciferase readout.[20] For initial in vitro PK profiling, the stability in human liver microsomes (HLM), measured as the intrinsic clearance (Cl_{int}), and the A–B apparent permeability coefficient in Caco-2 cells (P_{app}), were evaluated for most of the final compounds in Tables 1 and 2.

The initial lead **25** in this series, having a 7-phenylquinazoline substituent, displayed high potency on enzyme (K_i = 0.4 nM), moderate potency in the cell-based HCV replicon assay (EC_{50} = 52 nM), moderate stability in human liver microsomes (Cl_{int} = 58 μL/min/mg), and excellent permeability in the Caco-2 cell-based assay (P_{app} = 21 × 10^{-6} cm/s). These data encouraged us to continue exploration of the quinazoline P2 substituent in both the cyclopentane series as well as the earlier described macrocyclic proline urea series. Quinazoline modifications were evaluated by introducing substituents in positions 2, 7, and 8. While introduction of a methoxy substituent in position 7 of the quinazoline (**45a**) resulted in improved cell-based potency (EC_{50} = 14 nM) other key in vitro DMPK properties (Cl_{int} = 88 μL/min/mg) were not improved upon. The introduction of a 4-isopropylthiazolyl moiety as in derivatives **39b** (K_i = 0.8 nM, EC_{50} = 120 nM) and **45b** (K_i = 1.2 nM, EC_{50} = 58 nM) resulted in loss of potency at both the enzyme level and in the replicon cell-based assay. This is in contrast to our earlier findings of quinazoline substitutions and could possibly be explained by repulsion between the nitrogen's in the quinazoline and the hetero atoms in the thiazolyl substituent, inducing the



Scheme 6. Reagents and conditions; (i) 2:1 DCM/TFA, 0 °C to rt, 1.5 h; (ii) phosgene in toluene, THF, $NaHCO_3$, rt, 1 h; (iii) DCM, $NaHCO_3$, *N*-methylhex-5-enamine or hept-6-enyl-(*p*-methoxybenzyl)-amine, rt overnight, 85–90% over three steps; (iv) Hoveyda–Grubbs catalyst 2nd generation, 1,2-dichloroethane, reflux, 4–12 h; (v) aq 1 M LiOH, H_2O, THF, MeOH, 0 °C, 4 h, 55–65% over two steps; (vi) quinazolinol, PPh_3, DIAD, THF, 0 °C to rt overnight, 30–85%; (vii) 2:1:1 THF/MeOH/H_2O, aq 1 M LiOH; (viii) EDAC, DCM, rt 5 h, then cyclopropylsulfonamide, DBU, rt overnight, 45–80%; (ix) 2:1 DCM/TFA, rt 30 min, 38–62%.

Table 2
SAR for the P2 proline urea series

Structure	Compound	R^2	R^3	R^4	n	K_i (nM) HCV NS3 1a	EC_{50} (nM) HCV NS3 1b	Cl_{int} (μL/min/mg)	P_{app} ($cm/s \times 10^{-6}$)
	**60a**		Me	Me	1	0.2	11	17	26
	60c		Me	Me	1	0.3	16	<6	32
	60e		Me	Me	1	0.6	3	8	33
	60g		Me	Me	1	0.9	130	Nd	Nd
	60h		Me	Me	1	2.8	13	Nd	Nd
	60i		Me	Me	1	0.2	7	14	0.4
	67a		Me	H	2	0.3	23	26	38
	67c		Me	H	2	0.2	16	20	32

Nd, not determined.

Table 3
Mean plasma levels ($n = 2$) together with pharmacokinetic parameters of the four macrocyclic compounds **51a**, **60a**, **60c**, and **67c** after a single intravenous (2 mg base-equiv/kg) and oral administration (20 mg base-equiv/kg) in the male Sprague–Dawley rats

		Compound			
		51a	**60a**	**60c**	**67c**
Iv (2 mg/kg, $n = 2$)	Cl (L/h/kg)	1	0.69	0.56	1.6
	V_{dss}	0.56	1.1	2	1.2
	AUC (μM h)	Nd	8.4	Nd	Nd
	Liver/plasma ratio (6 h)	Nd	38	Nd	2.5
Oral (10 mg/kg, $n = 2$)	AUC (μM h)	3.3	15	11	1.7
	C_{max} (μM)	0.66	3.4	2.6	0.39
	T_{max} (h)	2	5	5	2
	$T_{1/2}$ (h)	3.8	Nd	Nd	Nd
	F (%)	40	73	Nd	38
	Liver/plasma ratio (6 h)	Nd	32	42	100

Nd, not determined.

thiazolyl substituent to adopt a non-coplanar and for interacting with the NS3 enzyme less optimal conformation. The metabolic stability was improved by modifications of the phenyl substituent in position 2 of the quinazoline as well as the introduction of a methyl group in position 8 of the quinazoline. This is exemplified by compounds **51a** ($Cl_{int} < 6$ μL/min/mg), **51c** ($Cl_{int} < 6$ μL/min/mg), **51d** ($Cl_{int} = 10$ μL/min/mg), and **51e** ($Cl_{int} = 11$ μL/min/mg) demonstrating excellent stability in human liver microsomes with retained potency. Surprisingly, for compound **51c** the introduction of the 8-methyl substituent led to an unexpected reduction of Caco-2 permeability ($P_{app} = 3 \times 10^{-6}$ cm/s), possibly due to lower solubility resulting from increased lipophilicity.

Complete removal of the substituent in the position 2, as for compound **51f**, resulted in almost complete loss in activity indicating that an aromatic- or a heteroaromatic substituent in this position plays a critical role for the binding interactions of these inhibitors. Interestingly, compounds **31** ($K_i = 6.2$ nM, $EC_{50} = 390$ nM) and **32** ($K_i = 12$ nM, $EC_{50} = 830$ nM) having non-aromatic substituents in position 2 of the quinazoline gave approximately a 10-fold potency drop in both the enzymatic- and in the cell-based assays. Possibly this could be due to the stringent criteria for the conformation of the P2 substituent.

The quinazoline P2 substituents were also explored in the proline urea series. In the 14-membered *N*-methyl proline urea series, the enzymatic and cellular potency as well as stability in human liver microsomes were comparable to the data seen for the cyclopentane series. For this series further improved Caco-2 permeability was obtained with P_{app} values of 26×10^{-6} and 32×10^{-6} cm/s for **60a** and **60c**, respectively. The two compounds prepared in the 15-membered NH proline urea series **67a** ($EC_{50} = 23$ nM, $P_{app} = 38 \times 10^{-6}$ cm/s) and **67c** ($EC_{50} = 16$ nM, $P_{app} = 32 \times 10^{-6}$ cm/s) had similar properties compared with the 14-membered analogs (**60a** and **60c**), but displaying decreased metabolic stability ($Cl_{int} = 26$ and 20 μL/min/mg). Further improved potency in the cell-based replicon assay was obtained with the introduction of a 4-methoxyphenyl substituent, that is, **60e**, where the overall favorable in vitro DMPK properties were retained ($Cl_{int} = 8$ μL/min/mg, $P_{app} = 33 \times 10^{-6}$ cm/s). Similarly 4-pyridyl

substitution (**60i**) resulted in improved potency (EC_{50} = 7 nM), however with loss of permeability in the Caco-2 assay ($P_{app} = 0.4 \times 10^{-6}$ cm/s). The corresponding pyridyl substitutions of **60h**, and in particular of **60g** however resulted in decreased potency (EC_{50} = 13 and 130 nM, respectively).

Based on the excellent potency and in vitro DMPK properties for these quinazoline containing inhibitors four compounds were selected for evaluation of their in vivo pharmacokinetic properties in rats. This comprised examples from all three series, that is, the cyclopentane series (**51a**), the 14-membered *N*-methyl proline urea series (**60a** and **60c**), as well as the 15-membered NH proline urea series (**67c**) and the results are shown in Table 3.

The mean plasma levels, liver-to-plasma ratios together with pharmacokinetic parameters were determined after a single intravenous and oral administration in male Sprague–Dawley rats. The proline urea derivatives **60a**, **60c**, and **67c** were all found to have favorable liver-to-plasma ratios (32–100) after 6 h and were hence well distributed to the liver. The cyclopentane derivative **51a** did however not reach detectable concentrations and the liver-to-plasma ratio could thus not be determined. When comparing the two compounds **51a** (C_{max} = 0.66 μM) and **60a** (C_{max} = 3.4 μM), the mean maximum plasma concentrations (C_{max}) were achieved after 2 h for the cyclopentane derivative and after 5 h for the proline compound indicating a slower absorption for **60a** but also a higher C_{max} and hence a larger area under the curve (AUC).

The 15-membered NH proline urea derivative **67c** exhibited three times higher clearance (1.6 L/h/kg), associated with a significantly lower C_{max} (0.39 μM) and AUC (1.7 μM h) compared with the two 14-membered *N*-methyl proline urea derivatives **60a** and **60c**.

Taken together, these in vivo PK results support further SAR studies on quinazoline substituted P2 proline ureas of the 14-membered macrocyclic ring series to access potent HCV protease inhibitors displaying high oral bioavailability in combination with high liver-to-plasma ratios.

References and notes

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