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# Structure–activity relationship study on a novel series of cyclopentane-containing macrocyclic inhibitors of the hepatitis C virus NS3/4A protease leading to the discovery of TMC435350

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ABSTRACT

SAR analysis performed with a limited set of cyclopentane-containing macrocycles led to the identification of *N*-[17-[2-(4-isopropylthiazole-2-yl)-7-methoxy-8-methylquinolin-4-yloxy]-13-methyl-2,14-dioxo-3,13-diazatricyclo [13.3.0.0$^{4,6}$]octadec-7-ene-4-carbonyl](cyclopropyl)sulfonamide (TMC435350, **32c**) as a potent inhibitor of HCV NS3/4A protease ($K_i$ = 0.36 nM) and viral replication (replicon $EC_{50}$ = 7.8 nM). TMC435350 also displayed low in vitro clearance and high permeability, which were confirmed by in vivo pharmacokinetic studies. TMC435350 is currently being evaluated in the clinics.



The virally encoded serine protease NS3/4A is essential to the life cycle of the hepatitis C virus (HCV), an important human pathogen causing chronic hepatitis, liver cirrhosis, and ultimately hepatocellular carcinoma.[1] The search for potent and selective HCV NS3/4A protease inhibitors is a major focus in the pharmaceutical industry of ultimately delivering more efficacious and better-tolerated drugs to treat HCV-infected patients. Indeed, the current therapies based upon the combination of pegylated interferon-α with ribavirin provide a sustained virological response (SVR) in around 50% of patients infected with genotype 1, and are often associated with tolerability issues, highlighting an urgent therapeutic need.[2] To date, the most advanced NS3/4A protease inhibitors VX-950 (**1**, Chart 1)[3] and SCH 503034 (**4**)[4] belong to the covalent reversible serine-trap inhibitors incorporating a reactive electrophilic α-ketoamide center at the cleavage site that targets the catalytic Ser139 of the active site of the enzyme via a fully reversible mechanism. However, the first clinical proof-of-concept for HCV NS3/4A protease inhibitors as therapeutic agents was established with the non-covalent macrocyclic β-strand mimic BILN 2061 (**2**, Chart 1).[5] Subsequently, the clinical development of BILN 2061 was discontinued due to cardiotoxicity issues in primates given supratherapeutic doses for several weeks.[6] Although the mechanism by which BILN 2061 (**2**)[5] elicits cardiovascular damage was not reported, the toxicity observed with this pioneer drug is believed to be compound specific. As a result, we and others have recently presented data on macrocyclic HCV NS3/4A protease inhibitors entering into clinical development.[7] We now report on our efforts to optimize a novel series of cyclopentane-containing macrocyclic inhibitors of the HCV NS3/4A protease, which has led to the identification of the clinical candidate *N*-[17-[2-(4-isopropylthiazole-2-yl)-7-methoxy-8-methylquinolin-4-yloxy]-13-methyl-2,14-dioxo-3,13-diazatricyclo[13.3.0.0$^{4,6}$]octadec-7-ene-4-carbonyl](cyclopropyl)sulfonamide (TMC435350, **32c**, Table 1), which is currently being evaluated in clinical trials (Table 2).

The structure of BILN 2061 (**2**)[5] is characterized by a 15-membered macrocycle incorporating three unnatural amino acid residues (P1, P2, P3), as shown in Chart 1. BILN 2061[5] was obtained following successive truncations of the N-terminal cleavage products of the NS5A/5B substrate peptide, leading to a tetrapeptide inhibitor **3a**,[8] which was further optimized to improve its pharmaceutical properties resulting in **2**.[5] Recently, the replacement of the P2 *N*-acyl-(4*R*)-hydroxyproline of **3a**[8] with a trisubstituted cyclopentane dicarbonyl moiety has been reported, leading to the

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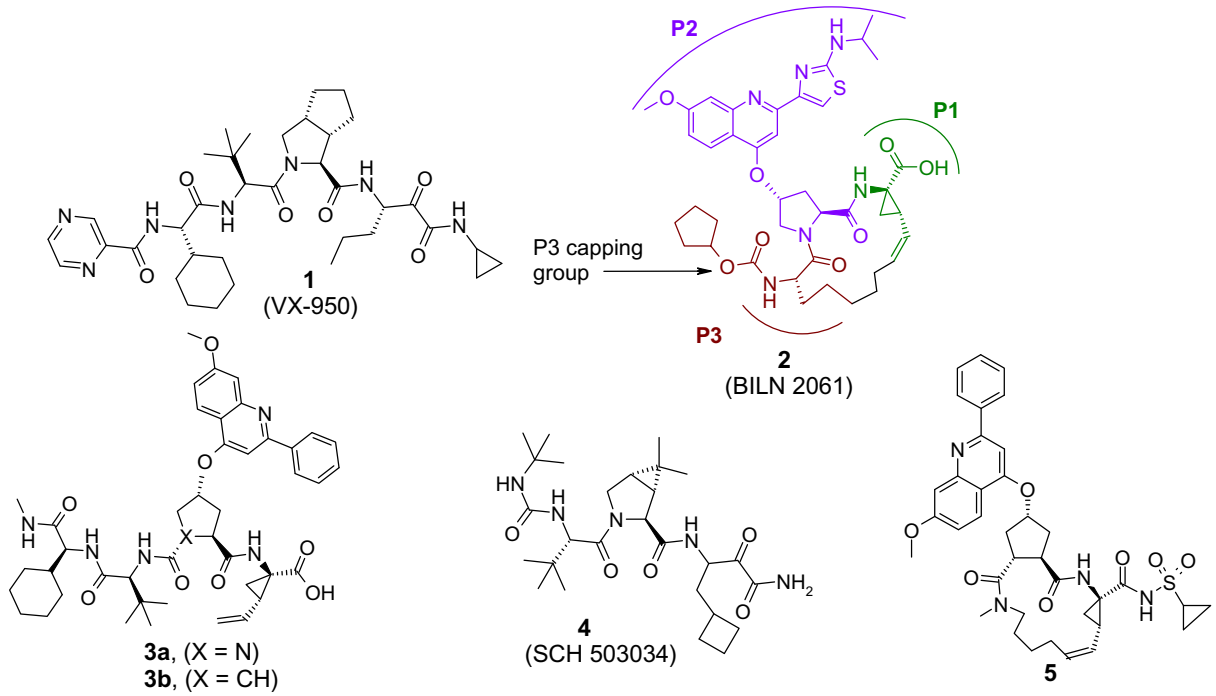


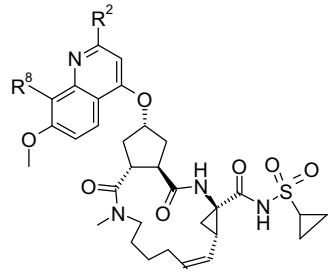

**Chart 1.** NS3/4A protease inhibitors reported in the literature: **1** (VX-950);[3] **2** (BILN 2061)[5] with the P1 (in green), P2 (in blue), and P3 (in brown) moieties; **3a**[8], **3b**;[9] **4** (SCH 503034)[4] and **5**.[10]

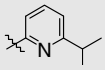
discovery of a novel series of potent HCV NS3/4A protease inhibitors exemplified by **3b**[8] (Chart 1). Encouraged by the enzymatic potency of **3b** ($K_i$ = 22 nM), we decided to explore whether the cyclopentane moiety could also be used in the rigidified macrocyclic series as a surrogate for the P2 pyrrolidine of **2**.[5] Initial structure–activity relationships (SAR) led to the macrocyclic inhibitor **5**[10] (Chart 1), a potent and specific HCV NS3/4A protease inhibitor ($K_i$ = 0.41 nM) exhibiting promising cell-based HCV replicon activity ($EC_{50}$ = 9 nM).[10] Although **5**[10] showed promising in vitro Caco-2 permeability data (A–B apparent permeability coefficient $P_{app} = 3.8 \times 10^{-6}$ cm/s) and medium intrinsic clearance in both human and rat liver microsomes ($Cl_{int}$ = 46 μL/min/mg), the inhibitor was found to be poorly absorbed in rat after oral administration of 15 mg/kg ($F$ = 2.5%), and was rapidly eliminated (clearance = 2.79 L/h/kg). Further studies revealed that the observed poor PK profile was attributed to a very high excretion of the parent drug **5**[10] in the bile. Indeed, 95% of the product was found unchanged in the bile 1 h after iv administration of 1 mg/kg of **5**.[10] Since the P2 quinoline has been reported in the literature to be a key moiety regulating the overall PK profile of macrocyclic HCV protease inhibitors,[5] we decided to expand the SAR analysis to this P2 heterocyclic moiety by (i) replacing the 2-phenyl group with different 5- and 6-member heterocycles and (ii) adding a small sized substituent at the 8-position. In the present work we report on the SAR analysis of this novel cyclopentane series, leading to the drug candidate TMC435350 (**32c**).

The synthesis of the target products **32a–h** and **37** (Table 1) is outlined in Schemes 1–4. Preparation of 2-substituted quinolines **11a–g** was carried out either from commercially available *m*-anisidine **8d** to generate the 8-non-substituted quinolines **11a**, **11b**, and **11g**, or from the 2-substituted 3-methoxyanilines **8a–c** obtained via a Curtius rearrangement[11] from the corresponding 3-methoxybenzoic acids **6a–c**, as depicted in Scheme 1. The 2-ethyl-3-methoxy aniline **8e** was synthesized following a literature procedure.[12] Electrophilic aromatic substitution of 3-methoxyanilines **8a–e** with boron trichloride followed by the addition of acetonitrile and aluminum chloride afforded the corresponding ketones **9a–e** in 40–73% yield.[13] Finally, acylation of the anilines **9a–e** followed by a subsequent treatment of intermediates **10a–g** with potassium *tert*-butoxide led to the desired quinolin-4-ols **11a–g** in 58–88% yield via a tandem of ring closure and aromatization reactions.[13]

The isopropylaminothiazolequinoline **11h**[14] (Chart 2) was synthesized according to a literature procedure, and the isopropylpyrazolylquinoline **19** was synthesized following an adaptation of the literature procedure[13] as depicted in Scheme 2. Diethyl ethoxymethylenemalonate (**12**) was condensed with the methoxyaniline **8a**, then cyclized at elevated temperature (230 °C) to provide the ester **13** in 58% yield. Saponification of **13**, followed by the subsequent decarboxylation led to the quinolin-4-ol **14** (96% yield), which was converted to the corresponding 4-chloroderivative **15** by treatment with phosphorus oxychloride. Oxidation with metachloroperbenzoic acid provided the N-oxide derivative **16** in a non-optimized yield of only 18%. Subsequent displacement of the 4-chloro group with sodium benzylalcoholate followed by the treatment of intermediate **17** with phosphorus oxychloride led to the key 2-chloro intermediate in 90% yield, which was ultimately displaced with the commercially available 3-isopropylpyrazole at elevated temperature (155 °C) leading to the desired quinoline **19** in 95% yield. The target macrocyclic products **31a–h** (Table 1) were efficiently prepared in a 7-step procedure either from the lactone acid **25**[9,15] or from its *tert*-butyl ester **20**[9] as depicted in Scheme 3.[10] These two synthetic pathways differ in the order of introduction of the P1 and P3 moieties on the P2 cyclopentane central scaffold. In the first case, the *tert*-butyl protected lactone **20** is opened by treatment with lithium hydroxide, followed by the peptidic coupling of the in situ generated acid with the P1 vinylcyclopropyl aminoacid ester **21**, leading to **22** in 89% isolated yield. Introduction of the P2 quinoline moieties **11a** and **11g** onto the cyclopentylalcohol **22** was achieved by a Mitsunobu reaction,[16] which provided the proper configuration of the chiral center at position 3 of the cyclopentane, leading to intermediates **23a** and **23b** in 63% and 68% yield, respectively. Subsequent deprotection of the

**Table 1**
Optimization of the positions 2 and 8 of the quinoline



| Compound | $R^2$ | $R^8$ | NS3/4A $K_i$[a] (nM) | HUH7-Rep $EC_{50}$[b] (nM) | $Cl_{int}$[c] (μL/min/mg) | $P_{app}$ A–B[d] (cm/s) |
|---|---|---|---|---|---|---|
| **5** |  | H | 0.41 | 9 | 46 | 3.8 |
| **37** |  | H | 1.4 | 17 | 15 | 1.4 |
| **32a** |  | H | 0.20 | 11 | 38 | 1.6 |
| **32b** |  | H | 0.84 | 17 | 16 | 13 |
| **32c** |  | Me | 0.36 | 7.8 | <6 | 8.4 |
| **32d** |  | Et | 3.1 | 66 | — | — |
| **32e** |  | F | 0.55 | 57 | — | — |
| **32f** |  | Cl | 0.10 | 2.9 | 9.0 | 5.8 |
| **32g** |  | Me | 0.16 | 9.7 | <6 | 15 |
| **32h** |  | Me | 0.30 | 6.8 | <6 | 12 |

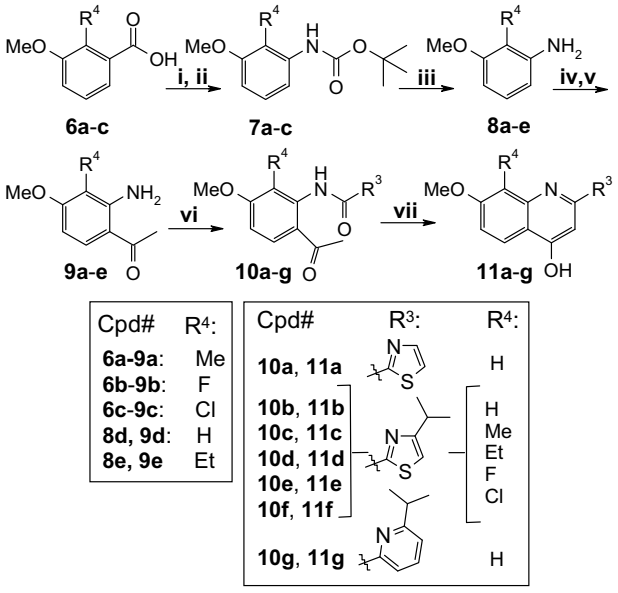
[a] Inhibition of the full-length HCV NS3/4A protease[20] measured by the inhibition constants ($K_i$ values).[21]
[b] Inhibition of HCV replication in Huh-7-Rep cells (luciferase assay) for macrocyclic inhibitors **32a–h** and **37** measured by 50% effective concentration ($EC_{50}$).[22]
[c] Intrinsic clearance in human liver microsomes (HLM).
[d] A–B apparent permeability coefficient ($P_{app}$) measured in Caco-2 cells.

*tert*-butyl acid group followed by the introduction of the P3 alkenylamine **26**[17] led to the non-cyclic intermediates **24a** and **24h**. Alternatively, the other open derivatives **24b–g** were prepared from the lactone acid **25**, which was submitted to a tandem of coupling reactions first with the *N*-methylhex-5-enamine (**26**)[17] (68% yield), then with the P1 aminoacid **21**[8,14] to provide **28** in 60% yield. This approach was better suited to explore the SAR on the P2 quinoline moiety because the final products could be obtained in only

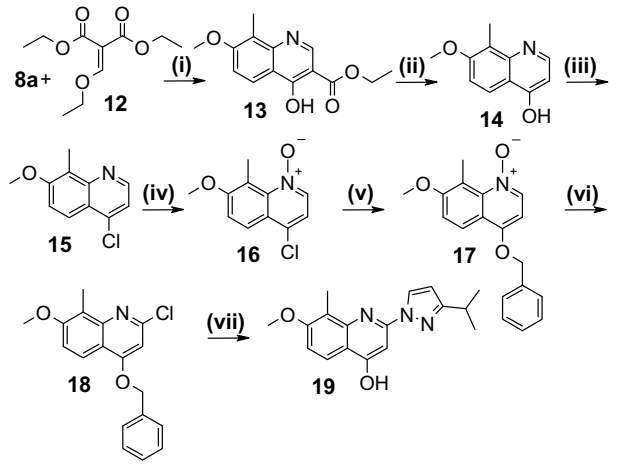
**Table 2**
Mean plasma levels ($n = 2$) together with some basic pharmacokinetic parameters of macrocycles **32c**, **32g** and **32h** after a single intravenous (2 mg base-eq./kg) and oral administration (20 mg base-eq./kg) in the male Sprague–Dawley rats

| | | Compound | | |
|---|---|---|---|---|
| | | **32c** | **32g** | **32h** |
| Iv (2 mg/kg, $n = 2$) | Cl (L/h/kg) | 0.505 | 2.5 | 1.4 |
| | $Vd_{ss}$ (L/kg) | 0.49 | 4.6 | 0.70 |
| | AUC (μM h) | 5.21 | 1.05 | 1.36 |
| | Liver/plasma ratio | 63.5[1] | 23.5[2] | ND[3] |
| Oral (10 mg/kg, $n = 2$) | AUC (μM h) | 2.79 | 1.30 | 1.4 |
| | $C_{max}$ (μM) | 0.73 | 0.31 | 0.30 |
| | $T_{max}$ (h) | 3.0 | 1.5 | 2.0 |
| | $T_{1/2}$ | 2.8 | 2.2 | 5.8 |
| | $F$ (%) | 11 | 25 | 31 |
| | Liver/plasma ratio | 32[1] | 44[2] | ND[3] |

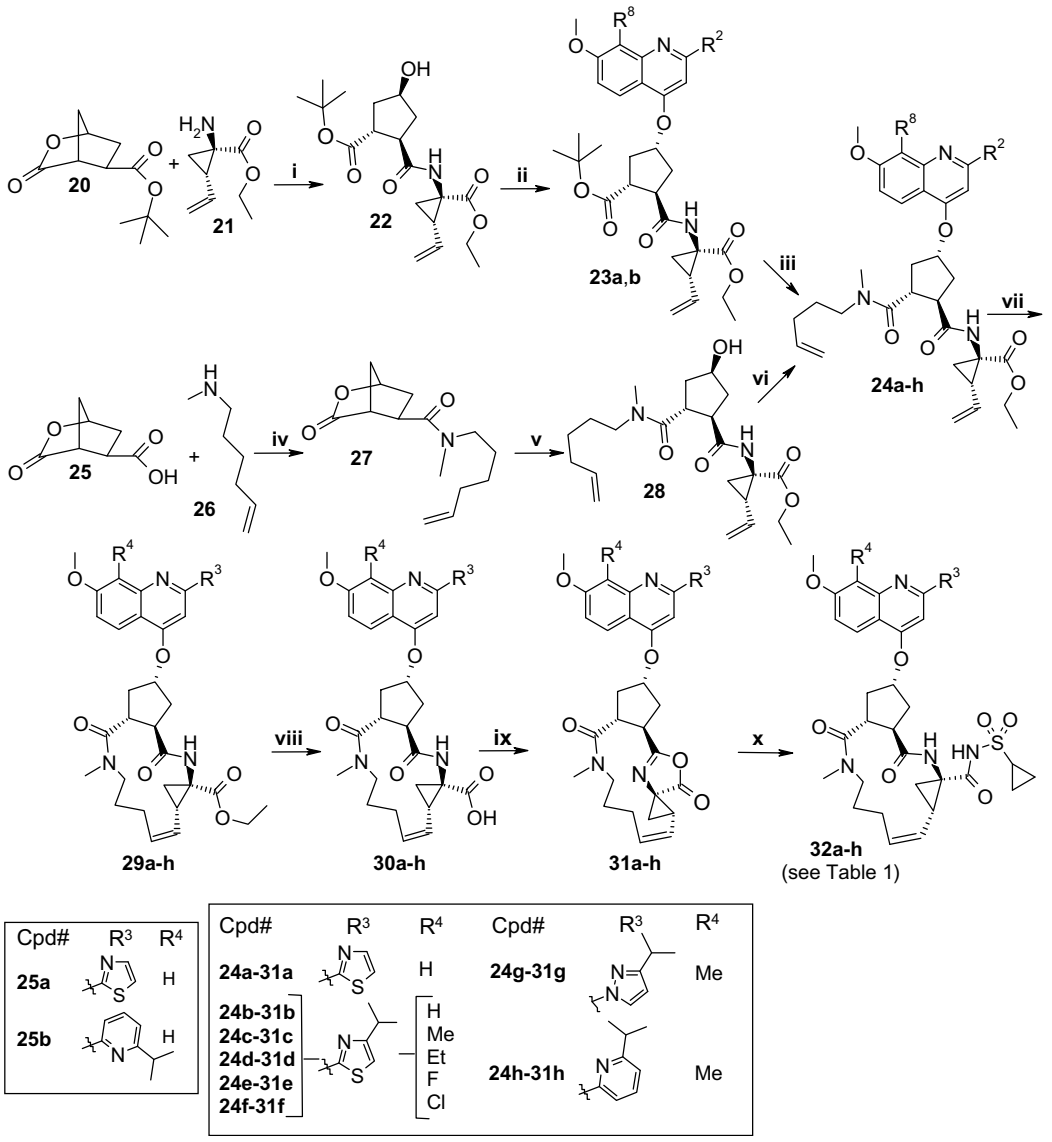
Liver/plasma ratios were determined [1]at 6 h, [2]at 8 h, [3]at 24 h (at this timepoint the compound was no longer quantifiable in the blood or in the liver).




**Scheme 1.** Reactions and conditions: (i) TEA, diphenylphosphorylazide (dppa), toluene, 100 °C; (ii) *tert*-BuOH, toluene, 100 °C; (iii) TFA, $CH_2Cl_2$, 20 °C; (iv) $BCl_3$, xylene, 0 °C; (v) $CH_3CN$, $AlCl_3$, $CH_2Cl_2$, 0–70 °C; (vi) $R^3COCl$, dioxane, rt; (vii) *tert*-BuOK, *tert*-BuOH, 100 °C.




**Scheme 2.** Reactions and conditions: (i) a—$Et_2O$, rt; b—diphenyl ether, 230 °C; (ii) a—NaOH, $H_2O$, reflux; b—diphenylether 250 °C; (iii) $POCl_3$, reflux; (iv) metachloroperbenzoic acid, $CHCl_3$, rt; (v) NaH, benzylalcohol, 0 °C to rt; (vi) $POCl_3$, −78 °C to reflux; (vii) 3-isopropylpyrazole, 155 °C.

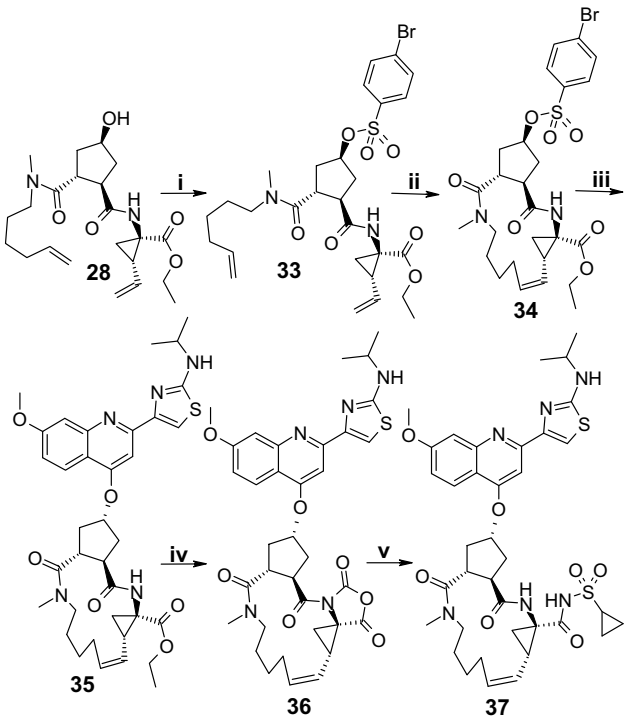



**Scheme 3.** Reactions and conditions: (i) a—LiOH, dioxane/water, 0 °C; b—(1*R*,2*S*)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester hydrochloride, diisopropylethylamine, HATU, DMF, 0 °C; (ii) **11a** or **11g**, $PPh_3$, DIAD, THF, 0 °C; (iii) a—triethylsilane, TFA, $CH_2Cl_2$, rt; b—**25**, diisopropylethylamine, HATU, DMF, 0 °C to rt; (iv) HATU, diisopropylethylamine, DMF, 0 °C to rt; (v) a—LiOH, THF/MeOH/water, 0 °C; b—**21**, HATU, diisopropylethylamine, DMF, 0 °C to rt; (vi) **11b–f** or **19**, $PPh_3$, DIAD, THF, −15 °C to rt; (vii) Hoveyda-Grubbs 1st generation catalyst,[19] dichloroethane, 70 °C; (viii) LiOH, THF/MeOH/water, rt; (ix) CDI, THF, reflux; (x) cyclopropylsulfonamide, DBU, THF, 50 °C.

four steps from a common intermediate **28**, considering that the intermediates **31a–h** were not isolated.

Mitsunobu coupling reaction[16] between **28** and quinolines **11b–g** provided the open derivatives **24b–g** in 56–72% yield. The macrocyclic ring esters **29a–h** were obtained in satisfactory yields (60–83%) by ring-closing olefin metathesis[10,18] of the open precursors **24a–h**, using the Hoveyda-Grubbs 1st generation catalyst.[19] In this reaction, the cis derivatives **29a–h** were obtained as the major products together with traces of the trans isomer. Hydrolysis of the ethyl esters **29a–h**, followed by the activation of the so-formed acids **30a–h** with carbonyldiimidazole afforded the corresponding oxazolidinediones **31a–h**, which were readily opened with cyclopropylsulfonamide in the presence of DBU to afford the final target products **32a–h** in 40–78% yield. NMR analysis confirmed that the stereochemistry of the different chiral centers was perfectly retained throughout the synthesis. Attempt to use the procedures reported in Scheme 3 for the preparation of the isopropylaminothiazolequinoline derivative **37** led to very low overall yield, probably due to the presence of the unprotected amidine function on the P2 quinoline, which can hamper the Mitsunobu coupling reaction. As an alternative synthesis, the cyclopentanol **28** was converted to a brosylate intermediate **33** in 80% yield, which was directly cyclized to the corresponding macrocycle **34** via a ring-closing olefin metathesis[18] (Scheme 4). The subsequent displacement of the brosylate activating group of **34** with the quinoline **11h** in the presence of a base, led to the ester **35**, which was then converted to the final product **37**, following a procedure similar to the one reported in Scheme 3 for the synthesis of **32a–h**.

The new macrocyclic derivatives **32a–h** and **37** (Table 1) prepared in the present study were first tested 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.[20] The inhibition constants ($K_i$ values)[21] were determined, and are listed in Table 1. The cell-based activities ($EC_{50}$) were measured in the Huh7-Rep cell line containing the subgenomic bicistronic replicon clone ET with a luciferase readout.[22] $EC_{50}$'s were calculated as the concentration of compound that caused a 50%




**Scheme 4.** Reactions and conditions: (i) 2,2,2-diazobicyclooctane, 4-$BrPhSO_2Cl$, toluene, $CH_2Cl_2$, rt; (ii) Hoveyda-Grubbs 1st generation catalyst,[19] dichloromethane, rt; (iii) **10h**, *N*-methylpyrrolidinone, $Cs_2CO_3$, 60 °C; (iv) a—LiOH, THF/MeOH/water, rt; b—CDI, THF, reflux; (v) cyclopropylsulfonamide, DBU, THF, 50 °C.

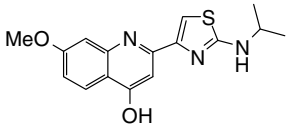



**Chart 2.** Quinoline **11h**.

reduction in luciferase signals compared to that of the untreated control. Since the main drawback for the initial lead **5**[10] was the poor PK profile, the apparent permeability coefficient in Caco-2 cells ($P_{app}$ A–B) and the stability in human liver microsomes, measured by the intrinsic clearance (HLM $Cl_{int}$), were evaluated for the most active derivatives listed in Table 1. The introduction of the BILN 2061 (**2**)[5] 2-isopropylaminothiazol-4-yl moiety in the position 2 of the quinoline led to **37**, a potent ($EC_{50}$ = 17 nM) derivative with relative low permeability (A–B $P_{app} = 1.4 \times 10^{-6}$ cm/s) derivative. Although similar low permeability was also observed with the thiazol-2-yl derivative **32a** (A–B $P_{app} = 1.6 \times 10^{-6}$ cms/s) a high $P_{app}$ value was observed for the 4-isopropyl analog **32b** (A–B $P_{app} = 13 \times 10^{-6}$ cm/s). Further optimization of the potency and pharmaceutical properties of **32b** was achieved by the introduction of either a methyl or a chloro substituent in position 8 of the quinoline leading to compounds **32c** and **32f**, respectively, as shown in Table 1.

These two compounds exhibit an improved potency ($EC_{50}$ = 7.8 nM and 2.9 nM, respectively, for **32c** and **32f**) compared to **32b** ($EC_{50}$ = 17 nM) and an improved stability in HLM ($Cl_{int}$ < 6 μL/min/mg for **32c** and 9.0 μL/min/mg for **32f** vs 16 μL/min/mg for **32b**). However, although the methyl derivative **32c** exhibits a similar permeability compared to the parent molecule **32b** (Caco-2 $P_{app\ A-B} = 8.4 \times 10^{-6}$ cm/s and $13 \times 10^{-6}$ cm/s, respectively), the 8-chloro derivative **32f** was found significantly less permeable (Caco-2 $P_{app\ A-B} = 5.8 \times 10^{-6}$ cm/s). Finally, the bioisosteric replacement of the isopropylthiazole with an isopropylpyrazole and an isopropylpyridyl led to two compounds, **32g** and **32h**, respectively, with similar potency and stability/permeability profile.

Based on these promising in vitro data, the three lead compounds **32c**, **32g**, and **32h** were selected for rat PK analysis.

The plasma kinetics, oral bioavailability together with liver tissue distribution in male Sprague–Dawley rats were determined after a single oral administration of 20 mg/kg of macrocycles **32c**, **32g**, and **32h** using 50% PEG-400 in water as vehicle. These data were analyzed and compared to those obtained after a single intravenous (iv) administration of 2 mg/kg in 20% hydroxypropyl-β-cyclodextrine. The compound levels were quantifiable up to 8 h post-administration. The mean maximum concentrations ($C_{max}$) in the plasma were all achieved between 1.5 and 3.0 h post-dose ($T_{max}$), indicating a rapid (for **32g**) to medium–slow (for **32c** and **32h**) rate of absorption. Given that viral replication of HCV is reported 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, **32c** and **32g** were found to be well distributed with the high concentration observed in the liver (liver/plasma ratio after oral administration is 32 and 44, respectively). Since the residual concentration of **32h** in the blood and in the liver was below the detection limit after 24 h the liver/plasma ratio could not be estimated. The mean half-life ($T_{1/2}$) was found similar for **32c** and **32g** (2.8 and 2.2 h, respectively), but was significantly higher for **32h** (5.8 h). More differences were observed for the clearance (Cl), volume of distribution ($Vd_{ss}$), and area under the curve (AUC) parameters. While **32c** exhibits a low clearance (Cl = 0.505 L/h/kg) associated with a low $Vd_{ss}$ (0.490 L/kg) and high $C_{max}$ (0.73 μM) and high AUC (2.79 μM h), **32g** and **32h**, respectively, exhibit a 3 and 5 times higher clearance, associated with a significantly lower $C_{max}$ and AUC (Table 1). An excellent PK profile for **32c** was also observed in Beagle dog. The oral bioavailability ($F$) after single oral administration of 6.5 mg/kg of **32c** was found as high as 100%, with a high $C_{max}$ (4.72 μM) and AUC (14,986 ng h/mL) combined with a medium-long half-life ($T_{1/2}$ = 5.1 h). Moreover, a negligible attenuation (~2-fold) of potency for **32c** was observed in the presence of human serum albumin (40 μg/mL). A detailed biological profile of **32c** will be published in due course.

In summary, we report here on the successful replacement of the pyrrolidine ring from the proline-containing macrocycle (e.g., **2**)[5] with a cyclopentane surrogate leading to a novel series of HCV NS3/4A protease inhibitors combining high potency in the HCV replicon with good rat and dog pharmacokinetic profiles. Altogether, these results prompted the selection of **32c** (TMC435350) for further preclinical and clinical development as an HCV drug candidate.

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