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Potent inhibitors of the hepatitis C virus NS3 protease: Use of a novel P2 cyclopentane-derived template

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Abstract—The HCV NS3 protease is essential for replication of the hepatitis C virus (HCV) and therefore constitutes a promising new drug target for anti-HCV therapy. Several potent and promising HCV NS3 protease inhibitors, some of which display low nanomolar activities, were identified from a series of novel inhibitors incorporating a trisubstituted cyclopentane dicarboxylic acid moiety as a surrogate for the widely used *N*-acyl-(4*R*)-hydroxyproline in the P2 position.

1. Introduction

Hepatitis C virus (HCV) infection is a serious and predominantly chronic disease which over time leads to cirrhosis and hepatocellular carcinoma and which today is the leading cause of liver transplantation in the developed world.[1] An estimated 170 million people, 3% of the world population, are infected with the virus[2] and the existing therapy consisting of PEGylated α-interferon in combination with the nucleoside analog ribavirin is only effective in ~50% of genotype 1 infected patients.[3] In addition this therapy is associated with severe adverse effects leading to discontinuation of treatment in some patient populations indicating the paramount need for the development of new, effective, and well-tolerated treatment paradigms.[2b] In recent years a vast number of reports have appeared describing different classes of compounds targeting key viral enzymes.[4,5] One of the most promising and well-characterized targets to emerge is the NS3 protease,[6,7] a 180 amino acid long chymotrypsin-like serine protease,[2b] responsible for the cleavage at four out of five sites of the non-structural portion of the polyprotein.[8] The NS3 protease has been shown to be essential for viral replication[9] and validation of this drug target was first demonstrated in a two-day proof-of-concept study in man with the very potent and highly specific product-based macrocyclic NS3 protease inhibitor BILN 2061 (Fig. 1).[10] BILN 2061 contains a trisubstituted *N*-acyl-(4*R*)-hydroxyproline moiety in the P2 position, a theme that can be seen in many potent inhibitors reported in the last years,[2b,10,11] for example, the linear compound **A**[2b] (Fig. 1).

A number of product-based NS3 protease inhibitors based on other motifs and strategies have also been described such as those incorporating the cysteine mimic (*S*)-2-amino-4,4-difluorobutyric acid in the P1 position.[12] VX-950 (Fig. 1) is the most advanced NS3 protease inhibitor belonging to another class of NS3 inhibitors, namely the electrophilic or serine-trap inhibitors. The most prominent feature of this class of inhibitors is that they contain a reactive electrophilic center at the cleavage site. Whilst this results in covalent interaction with the catalytic Ser139 of the active site of the NS3 enzyme, the kinetics observed is generally fully reversible. VX-950, an α-ketoamide inhibitor of this

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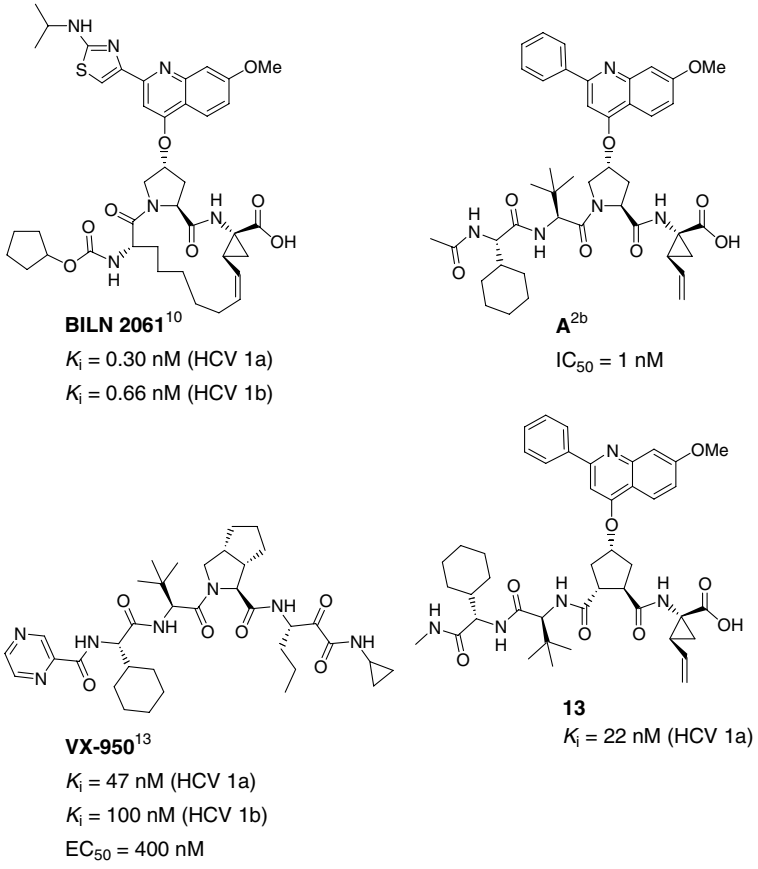


Figure 1. Two potent HCV NS3 protease inhibitors incorporating a 4-hydroxyproline moiety (**BILN 2061** and **A**), the electrophilic inhibitor VX-950, and compound **13**, one of the most potent inhibitors in our novel series containing a trisubstituted cyclopentane moiety as a hydroxyproline mimic.

class displaying K_i values of 47 and 100 nM for HCV NS3 1a and 1b, respectively, was recently reported to have completed phase Ib clinical trials with promising results.[13]

The amino acid L-proline has frequently been used as a building block in peptidomimetic inhibitors targeting a number of proteases. L-Proline has been incorporated in inhibitors targeting, for example, HIV,[14] angiotensin converting enzyme (ACE),[15] thrombin,[16] and also HCV.[17] Previous work on thrombin inhibitors from our laboratory has shown that the *N*-acylproline moiety **I** (Fig. 2) can be replaced with isosteric five-membered ring templates, exemplified by structures **II** and **III**[18] (Fig. 2), delivering inhibitors with low to modest inhibitory activities toward thrombin.

We now report on the synthesis of HCV NS3 protease inhibitors incorporating a novel trisubstituted cyclopentane moiety (**V**, Fig. 2) in the P2 position, exemplified by inhibitor **13** (Fig. 1, Scheme 3, Table 1), displaying a highly promising K_i value of 22 nM. The synthesis of these novel inhibitors starting from the pivotal intermediate *trans*-(3*R*,4*R*)-bis(methoxycarbonyl)cyclopentanone ((−)-**1**)[19] delivering several target compounds with nanomolar activity is discussed. In addition, an extensive SAR analysis of these new inhibitors has been performed.

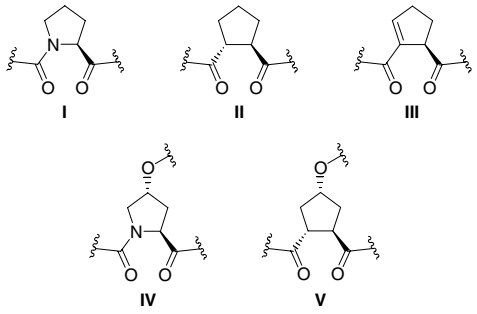


Figure 2. *N*-Acylproline (**I**), previously reported *N*-acylproline isosteres (**II** and **III**), *N*-acyl-(4*R*)-hydroxyproline (**IV**), and our cyclopentane-based *N*-acyl-(4*R*)-hydroxyproline isostere (**V**) used in the synthesis of novel HCV NS3 protease inhibitors.

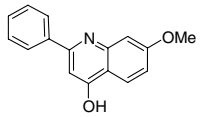
2. Results and discussion

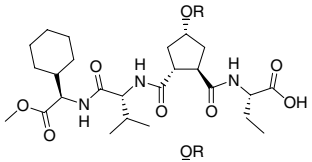
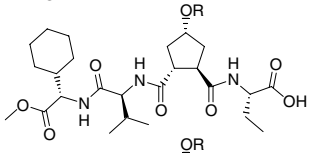
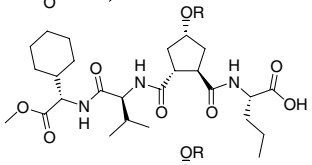
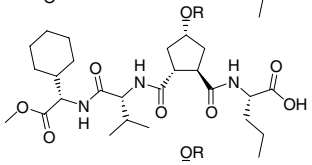
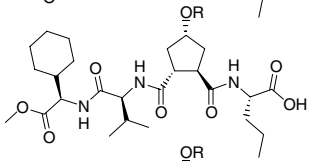
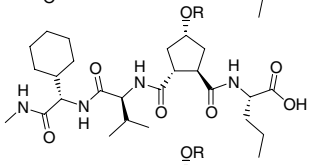
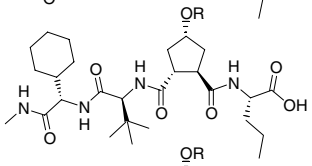
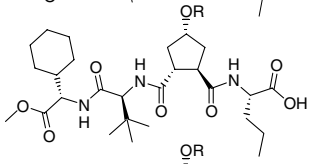
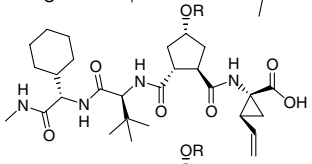
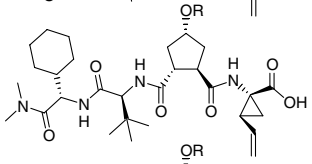
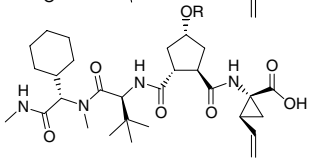
2.1. Chemistry

Figure 3 depicts the structures of the target molecules synthesized all encompassing the trisubstituted cyclopentane scaffold **V**.

The R_1 amino acid derivatives **B**, **C**, and **E** were all commercially available or readily synthesized from suitably protected and commercially available precursors. The vinylcyclopropane amino acid **D** was synthesized according to literature procedure[20] (Fig. 3). The R_2

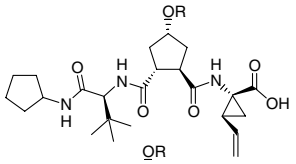
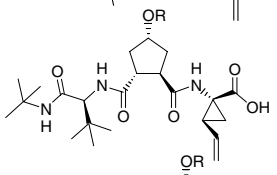
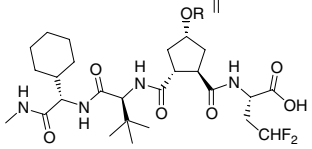
Table 1. Target molecules, synthesis methods, total yields, and inhibition constants

R-OH : 

Compound	Structure	Method	Yield[a] (%) (5 or 6 steps)	K_i[b] (μM) HCV NS3 1a	% Inh[c] at 10 μM
14		**I**	30	ND	21
15		**I**	21	ND	65
16		**I**	66	2.3	100
17		**I**	42	ND	35
18		**I**	32	ND	37
19		**I**	40	6.6	
9		**I**	61	1.7	
20		**I**	61	1.2	
13		**II**	30	0.022	
21		**II**	37	0.016	
22		**II**	23	>10	

(*continued on next page*)

Table 1 (*continued*)

Compound	Structure	Method	Yield[a] (%) (5 or 6 steps)	K_i[b] (μM) HCV NS3 1a	% Inh[c] at 10 μM
23		**II**	23	2.7	
24		**II**	40	6.9	
25		**II**	16	0.56	

[a] Total yield over five steps for Method I and over six steps for Method II.
[b] ND, not determined.
[c] % Inh at 10 μM for compounds where the K_i values have not been measured or where it is important for the SAR discussion.

2-phenyl-7-methoxy-4-quinolinol moiety (**F**) was also synthesized according to a published procedure.[2b,21] The R_3 dipeptides or capped amino acids, **G**–**Q**, were all synthesized employing standard peptide coupling conditions and standard amino acid protection/deprotection protocols using commercially available and suitably protected amino acids with the exception of the N-methylated compound **O**, where Fmoc-Chg-OH initially was N-methylated using paraformaldehyde and *p*-toluenesulfonic acid in refluxing toluene followed by the treatment with triethylsilane (Et_3SiH) and trifluoroacetic acid (TFA) in chloroform,[22] before using the standard peptide synthesis protocol. The corresponding dipeptide where the nitrogen on *tert*-butyl glycine had been methylated was also prepared using the same procedure as in the synthesis of **O**. However, the properties of an inhibitor incorporating this R_3-group could not be evaluated, since coupling of the corresponding dipeptide to the template was unsuccessful in spite of evaluating a large number of coupling reagents and conditions. The low coupling reactivity is likely to be due to steric hindrance.

The synthesis of the two bicyclic lactone scaffolds employed in the synthesis of the target molecules is outlined in Scheme 1.

trans-(3*R*,4*R*)-bis(Methoxycarbonyl)cyclopentanone ((−)-**1**), used as starting material, was prepared according to literature procedure.[19a] Treatment of (−)-**1** with sodium borohydride in methanol furnished the alcohol **2**[23] in 76% yield. Compound **2** was then allowed to react with sodium hydroxide in methanol to hydrolyze the methyl esters, followed by reaction with acetic anhydride in pyridine[24] to provide the bicyclic lactone **3**[23] in 88% total yield. The methyl ester protected scaffold (**4**) was afforded in 81% yield by reacting **3** with methyl iodide and silver (I) oxide in acetone. Treatment of **3** with di-*tert*-butyl dicarbonate (Boc_2O) and 4-dimethylaminopyridine (DMAP) in dichloromethane (DCM) yielded the *tert*-butyl ester protected scaffold (**5**) in 52% (Scheme 1).

Scheme 2 depicts the synthesis of target molecule **9** according to Method I, also employed in the synthesis of target compounds **14**–**20** (Table 1). The lactone (**4**) was opened by allowing it to react with H-Nva-O*t*Bu, diisopropylethylamine (DIEA), and 2-hydroxypyridine[25] in refluxing THF to give amide **6** in 96% yield. Mitsunobu-like conditions using 2-phenyl-7-methoxy-4-quinolinol, triphenylphosphine, and diisopropyl azodicarboxylate (DIAD) in THF then provided compound **7** in 78% yield.[11c]

The methyl ester in compound **7** was then hydrolyzed using lithium hydroxide in dioxane/water 1:1, and the corresponding acid was then coupled with amine **L** (Fig. 3) using *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) and DIEA in DMF to give compound **8** in 81% yield. Finally, the *tert*-butyl ester in **8** was hydrolyzed by reaction with TFA and Et_3SiH in DCM[26] yielding **9** in quantitative yield (Scheme 2).

Method II, used for the synthesis of target molecules **13** and **21**–**25** (Table 1), is described in Scheme 3. Initial attempts to open the *tert*-butyl scaffold (**5**) directly with the vinylcyclopropyl amino acid **D** using the same conditions as in Method I (DIEA, 2-hydroxypyridine in refluxing THF) were not successful. Instead, scaffold **5** was opened by careful treatment with lithium hydroxide in dioxane/water 1:1 at 0 °C to afford the corresponding carboxylic acid, which was then coupled with **D** using HATU and DIEA in DMF to give the amide **10** in 89% total yield (Scheme 3).

Applying similar Mitsunobu conditions with 2-phenyl-7-methoxy-4-quinolinol as used in the synthesis of compound **7** furnished compound **11** in 68% yield.[11c] Hydrolysis of the *tert*-butyl ester in **11** was then performed with TFA and Et_3SiH in DCM,[26] yielding the corresponding acid, which was coupled to dipeptide **L** (Fig. 3) using HATU and DIEA in DMF to afford

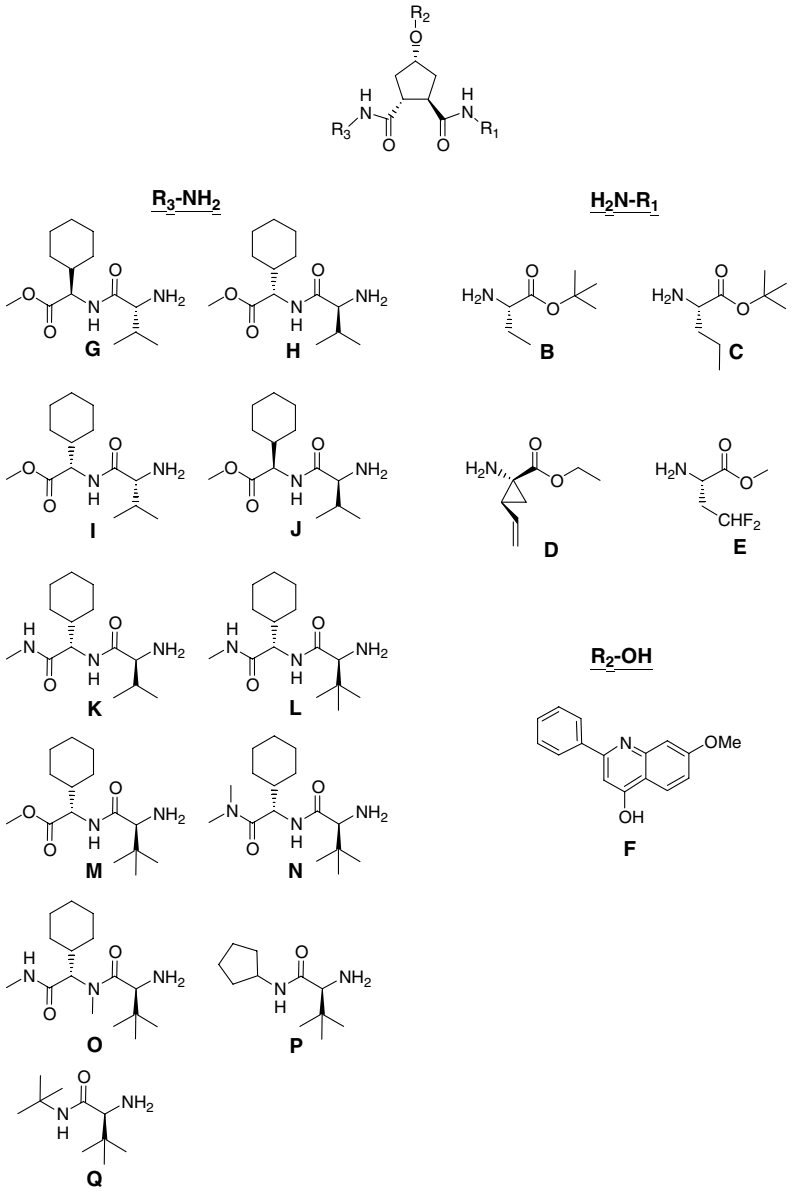
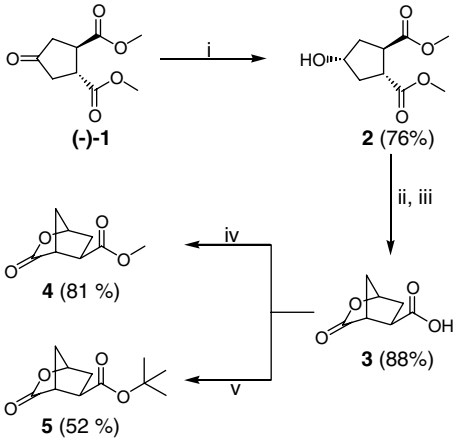


Figure 3. A general picture of the central cyclopentane scaffold and the different R_1, R_2, and R_3 substituents that were used in this report.

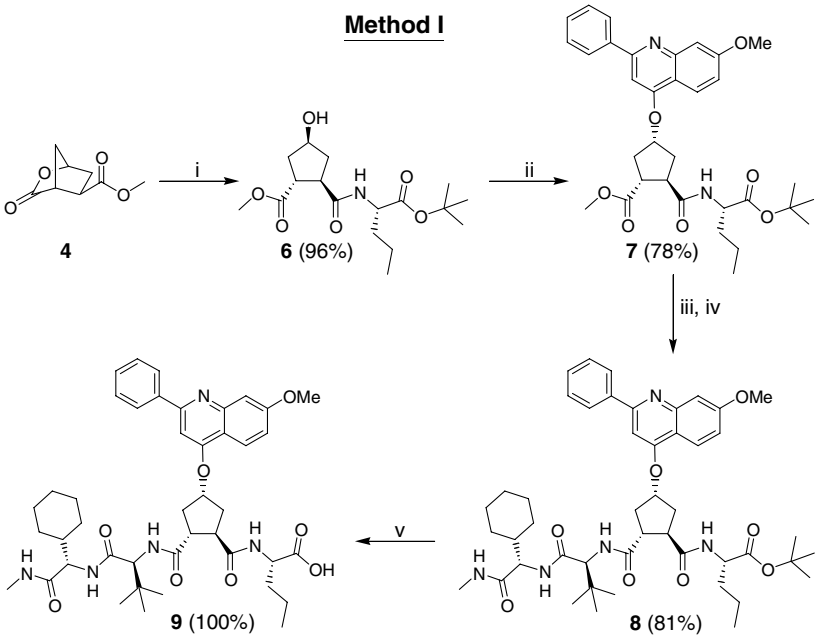


Scheme 1. Reagents and conditions: (i) $NaBH_4$, MeOH, 0 °C; (ii) NaOH (1 M), MeOH; (iii) Ac_2O, pyridine; (iv) MeI, Ag_2O, acetone; (v) Boc_2O, DMAP, CH_2Cl_2.

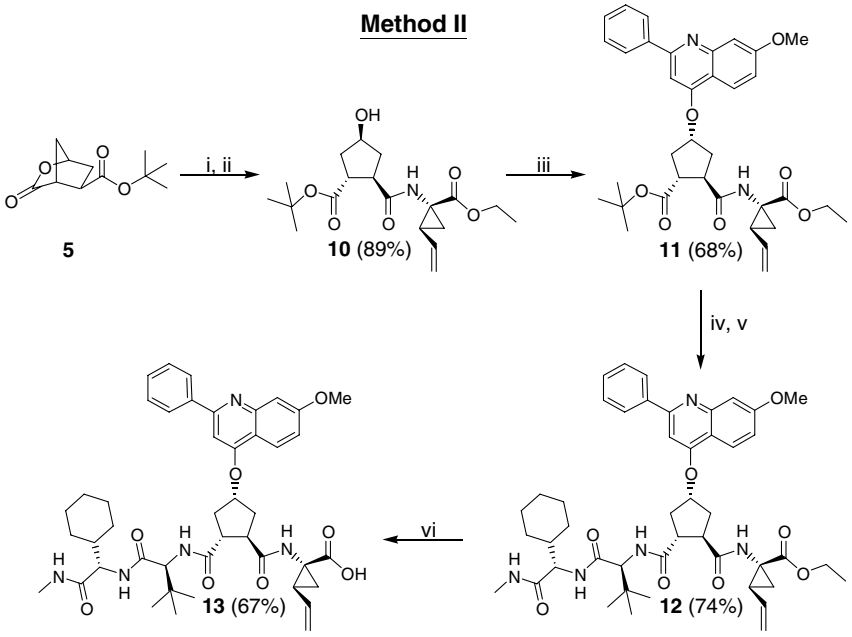
compound **12** in 74% total yield. Finally, the ethyl ester was hydrolyzed using lithium hydroxide in THF/MeOH/water 2:1:1 to yield target compound **13** in 67% (Scheme 3).

3. Biological data and structure–activity relationships

All products were screened against the HCV NS3 1a protease and the percent inhibition was determined at three concentrations: 10, 1, and 0.1 μM. The K_i values were determined for the most potent inhibitors after the initial screenings. Table 1 summarizes all inhibitors synthesized and the methods used for the synthesis of each individual inhibitor along with the total yields. The K_i values, if measured, and the percent inhibition at a concentration of 10 μM for selected compounds are also included in Table 1.



Scheme 2. Reagents and conditions: (i) H-Nva-O*t*Bu, DIEA, 2-hydroxypyridine, THF, reflux; (ii) 2-phenyl-7-methoxy-4-quinolinol, PPh_3, DIAD, THF; (iii) LiOH, dioxane/H_2O 1:1; (iv) **L**, HATU, DIEA, DMF; (v) TFA, Et_3SiH, CH_2Cl_2.



Scheme 3. Reagents and conditions: (i) LiOH, dioxane/H_2O 1:1, 0 °C; (ii) **D**, HATU, DIEA, DMF; (iii) 2-phenyl-7-methoxy-4-quinolinol, PPh_3, DIAD, THF; (iv) TFA, Et_3SiH, CH_2Cl_2; (v) **L**, HATU, DIEA, DMF; (vi) LiOH, THF/MeOH/H_2O 2:1:1.

All the inhibitors discussed below contain a P2 2-phenyl-7-methoxy-4-quinoline substituent, which has been reported to play an important role in stabilizing the catalytic machinery in the correct geometry by shielding that part of the protease from exposure to solvent,[27] and is a substituent found to furnish potent inhibitors,[2b,10b,11b,11c] for example, compound **A**[2b] (Fig. 1). In addition, the P2 aryl substituent likely interacts favorably with the helicase domain of the NS3 protein.[28]

First, it was important to establish the preferred stereochemistry at the P3–P4 positions of these inhibitors. The P3–P4 substituents of the compounds incorporating this new template have a reversed direction, compared with the general *N-C* direction seen in, for example, inhibitor **A**. Another feature to be considered is that this P2 cyclopentane template is not planar at the 1-position of the ring, since it is sp^3 hybridized, whereas proline has a nitrogen atom in the corresponding ring position and is planar.

The X-ray crystal structure, PDB entry 1CU1, of a bound product of the NS3-mediated cleavage[28a] (the C-terminal of the full length single strand NS3 con-

struct) was used as starting point for the modeling to predict the stereochemical requirements of the substituents at the P3–P4 positions (Fig. 4).

Compound **14** (Table 1), having the D-configurations at the P3 and P4 positions, was thus aligned with the NS3 product using GASP (Genetic Algorithm Similarity Program) included in Sybyl 7.1 (Tripos Inc.).[29] As depicted in Figure 5, the side chains having D-configurations in the P3–P4 positions do not overlay at all well with the side chains of the product and no good alignment could be obtained.

In contrast, alignment of compound **15** (Table 1), having the L-amino acids at P3 and P4, gives a very good overlay with the side chains of the bound cleavage product (Fig. 6). The carbonyl of the acyl cyclopentyl moiety adopts the same position as the P3-carbonyl of the product and the P3-NH of compound **15** shows the same interaction as the P2-NH of the product (PDB entry 1CU1) and the P3-side chain is positioned as the P3 side chain of the product. The same pattern of binding is valid for the side chain and the amide of the P4 substituent (Fig. 6). In view of the molecular modeling performed it was thus anticipated that the L-configuration would be generally preferred for both the P3 and P4 amino acids.

To verify the modeling results experimentally, inhibitor **14**, with D stereochemistry on both the valine and the cyclohexyl glycine moieties, and inhibitor **15** with the L-configuration on the corresponding residues were synthesized. Compounds **14** and **15** are both weakly active compounds but **15** is clearly the most active of the two displaying 65% inhibition at a concentration of 10 μM compared to 21% inhibition exhibited by **14**, which is in agreement with the modeling predictions. The relatively low potency of these two compounds, and compound **15** in particular, can obviously be attributed to the use of the non-optimized Abu P1 substituent as a cysteine mimic. Compound **16** encompasses the reportedly better norvaline as the P1 substituent, which yielded improved activity properties, with a measurable K_i value

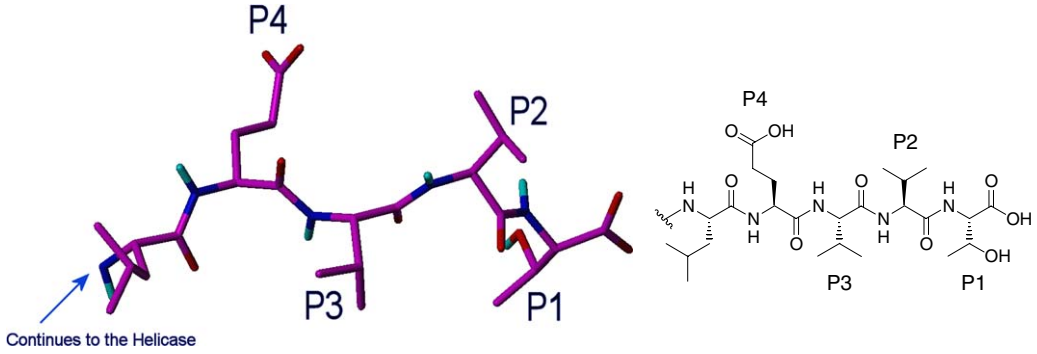


Figure 4. The C-terminus of the helicase domain (a product of the NS3-mediated cleavage of the NS3–NS4A junction of the HCV polyprotein) in its bound conformation to the NS3 active site obtained from the published X-ray crystal structure (PDB entry 1CU1), and a simple chemical structure showing the amino acid sequence in question.

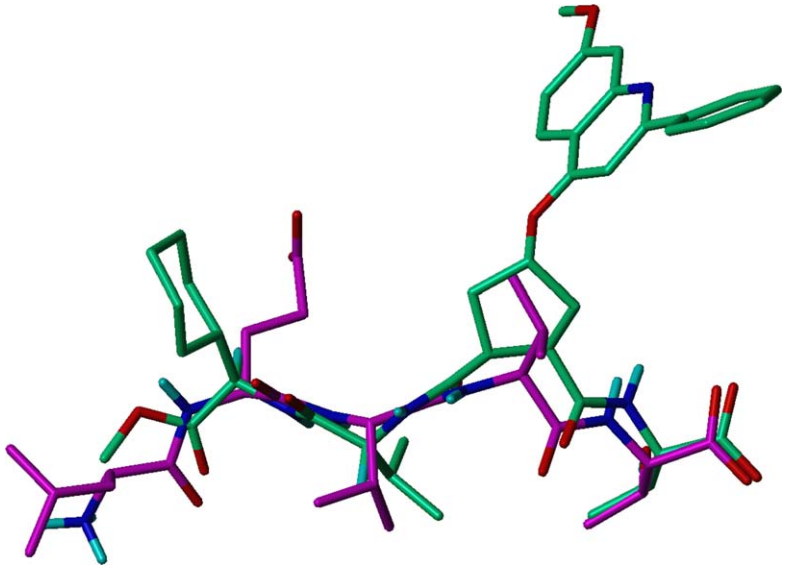


Figure 5. A modeled structure of compound **14** containing D-amino acids at the P3 and P4 positions (green) superimposed on the bound C-terminus helicase residue (magenta). The P3 and P4 side chains do not overlay with the side chains of the product and will not fit in the S3 and S4 pockets of the NS3 protease.

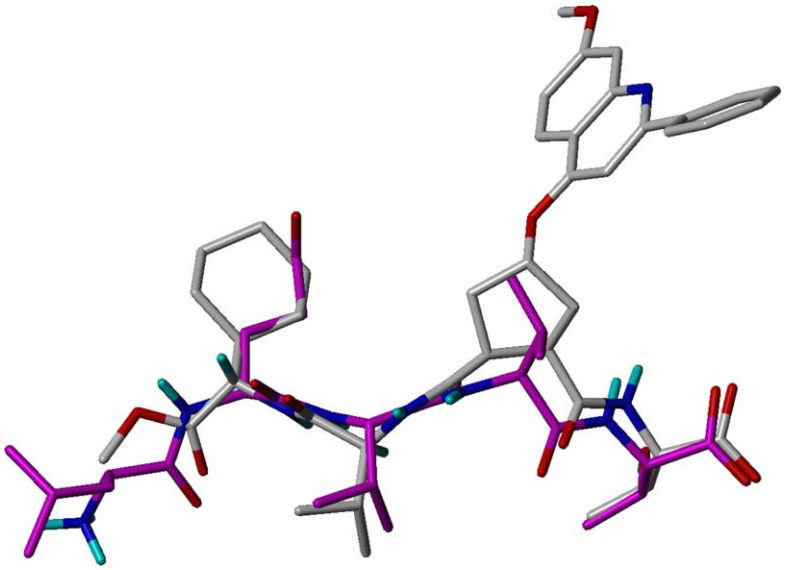


Figure 6. Compound **15** (gray) containing the natural L-amino acids in P3 and P4 superimposed on the bound C-terminus helicase residue (magenta). The picture clearly shows that L-configurations of P3 and P4 are required to get an overlay that fits well with the conformation of the bound product.

of 2.3 μM and 100% inhibition at a concentration of 10 μM. In order to rule out the possibility that combinations of D-L or L-D configurations of the P3–P4 substituents could provide more potent inhibitors, compounds **17** and **18** were prepared with **17** having D-valine and L-cyclohexyl glycine and **18** having the opposite (L-D) configurations on the two moieties. The two compounds, **17** and **18**, were both found to display low activity, 35% and 37% inhibition, respectively, at 10 μM concentrations, which further confirms the importance of L-configurations of the P3–P4 residues. All compounds discussed up to this point incorporate a metabolically labile methyl ester capping group on the P4 amino acid. Replacing the methyl ester with a methyl amide delivered inhibitors with slightly lower potency as can be seen by comparing the methyl amide compound **19** with the corresponding methyl ester compound **16** having K_i values of 6.6 and 2.3 μM, respectively. It has previously been shown that substitution of valine for *tert*-butyl glycine can yield more potent NS3 inhibitors.[2b] This modification furnished compound **9**, which is almost four times more potent than the corresponding valine-containing compound **19**, exhibiting a promising K_i value of 1.7 μM. The corresponding methyl ester capped compound **20** is in this case essentially equipotent with a K_i value of 1.2 μM. This indicates that the metabolically more stable methyl amide functions well as a methyl ester isostere in more optimized compounds.

Llinàs-Brunet et al. have shown that (1*R*,2*S*)-1-amino-2-vinylcyclopropane carboxylic acid is an outstanding P1 substituent and a cysteine replacement with an optimal fit in the hydrophobic S1 pocket of the NS3 protease,[11c,d] and it has been incorporated in an array of very potent inhibitors, for example, BILN 2061 and compound **A** (Fig. 1).

This P1 substituent in the current series rendered the very potent inhibitor **13**, which is almost 80 times more potent than the corresponding norvaline substituted compound **9**, exhibiting the impressive K_i value of 22 nM. To further investigate the binding modes of these inhibitors an *N*-methylation study of the amide nitrogens in the P3–P4 portion was conducted for inhibitors **21** and **22**, to examine the impact of hydrogen bond interactions with the NS3 protein. The methylation product of the amide nitrogen closest to the cyclopentane ring could however not be obtained, probably due to steric hindrance impeding the subsequent coupling reaction.

Compound **21**, with an added methyl substituent on the nitrogen of the capping group, is an almost equipotent inhibitor compared with compound **9** displaying a K_i value of 16 nM versus 22 nM, suggesting that the hydrogen on the capping methyl amide is not contributing in hydrogen bond interactions. Whilst this is true for the terminal amide nitrogen, it is noteworthy that an almost total loss of activity is encountered when the amide nitrogen of the cyclohexyl glycine moiety is methylated, that is, in compound **22**, displaying a K_i of >10 μM, highlighting the importance of this position for hydrogen bond interaction.

Compounds **23** and **24** are inhibitors of lower molecular weights where the P3 residue has been capped with cyclopentylamine or *tert*-butylamine. Neither is very potent with **23** displaying a K_i of 2.7 μM and **24** a K_i of 6.9 μM.

Compound **25** has the (*S*)-2-amino-4,4-difluorobutyric acid cysteine mimic reported by Narjes et al.[12a] in the P1 position. This P1 substituent provides an increase in potency compared to the molecules containing Abu or norvaline, with a K_i of 0.56 μM, but it is still substantially less potent, about 25 times, than the corresponding inhibitor (**13**) containing the (1*R*,2*S*)-1-amino-2-vinylcyclopropane carboxylic acid residue.

A general observation regarding this series of inhibitors is that the P1 substituent is crucial to provide potent compounds. Furthermore, we can conclude that these inhibitors, even though incorporating an optimized P1 residue, still are extremely sensitive to modifications in the P3–P4 region, for example, methylation at certain positions (compound **22**), and truncations as in compounds **23** and **24**, leading to serious losses in activity.

4. Conclusion

We have developed efficient synthetic routes to an interesting and novel series of HCV NS3 protease inhibitors comprising a trisubstituted cyclopentane *N*-acyl-(4*R*)-hydroxyproline mimic in the P2 position. Different P1 and P3–P4 substituents were evaluated in order to determine preferred substituent patterns for these new cyclopentane-based inhibitors. With proper choice of substituents, very potent and promising inhibitors in the low nanomolar range could be obtained from this cyclopentane-derived scaffold, that is, compounds **13**, **21**, and **25**, which exhibit K_i values of 22, 16, and 560 nM, respectively. These results suggest that the frequently used P2 hydroxyproline scaffold (**IV**, Fig. 2) can successfully be displaced by a properly substituted cyclopentane scaffold (**V**, Fig. 2), and that further refinements of the compounds presented herein could provide even more effective HCV NS3 protease inhibitors.

5. Experimental section

5.1. HCV NS3 protease enzyme assay[30]

The inhibition assay with HCV protease was performed using recombinant full length NS3 enzyme (Poliakov et al.)[31] and NS4A (KKGSVVIVGRIVLSGK, Gunnar Lindeberg, Department of Medicinal Chemistry, Uppsala University, Sweden) in final concentrations of 3.5 nM and 14 μM, respectively. The test compounds were dissolved and diluted in DMSO and were added to the assay buffer containing 50 mM HEPES, pH 7.5, 40% glycerol, 0.1% CHAPS, and 10 mM DTT. The maximum final DMSO concentration in the assay was 1%. After a pre-incubation for 30 min at room temperature, the enzyme reaction was started by adding the FRET substrate Ac-Asp-Glu-Asp(EDANS)-Glu-Glu-Abu-ψ-(COO)Ala-Ser-Lys(DABCYL)-NH2 (RET S1, AnaSpec, San Jose, CA, USA) to a final concentration of 2 μM. The enzyme activity was continously measured over time (20 min) in a fluorescence reader (Fluorocan Ascent, ThermoLab systems, Stockholm, Sweden) with 355 nm as excitation and 500 nm as emission wavelengths, respectively.

IC_{50} values were calculated by non-linear fitting into the equation $(1 - v_i/v_o) = (I)/((I) + IC_{50})$ and the K_i value was calculated from the IC_{50} value using the equation $K_i = IC_{50}/(1 + S/K_m)$ assuming a competitive enzyme inhibition.

6. General methods

NMR-spectra were recorded on a Varian 300 MHz instrument using $CDCl_3$ and CD_3OD as solvents. TMS was used as reference. Optical rotations were measured using a Perkin-Elmer 141 polarimeter. TLC was carried out on Merck precoated 60 F_{254} plates using UV-light and charring with ethanol/sulfuric acid/*p*-anisaldehyde/acetic acid 90:3:2:1, and a solution of 0.5% ninhydrin in ethanol for visualization. Flash column chromatography was performed using silica gel 60 (0.040–0.063 mm, Merck). Organic phases were dried over anhydrous magnesium sulfate. Concentrations were performed under diminished pressure (1–2 kPa) at a bath temperature of 40 °C. MALDI-TOF-spectra were recorded on a Voyager-DE STR Biospectrometry Workstation using α-cyano-4-hydroxycinnamic acid as a matrix and reference. HPLC was performed on a preparative C-18 column.

7. LC–MS purity measurements

7.1. Chromatography system A

Column: Phenomenex C18 150 × 4.6 mm; Pump: Gilson gradient pump 322; UV/vis-detector: Gilson 155; MS detector: Thermo Finnigan Surveyor MSQ; Software: Gilson UniPoint 4.0 and Xcalibur 1.3. Gradient: methanol 40–100% over 10 min at 1 mL/min followed by 100% for 5 min at 1 mL/min. To all solvents formic acid (0.1% v/v) was added. Peaks were detected at 254 nm.

7.2. Chromatography system B

As system A except: Gradient: acetonitrile 0–100% over 10 min at 1 mL/min followed by 100% for 5 min at 1 mL/min.

8. General synthetic procedures (used in the synthesis, protections, and deprotections of compounds *B*, *C*, *E*, and *G–Q*)

8.1. Peptide coupling

To the acid (0.264 mmol) dissolved in DMF (5 mL) were added the amine (0.313 mmol) and diisopropylethylamine (DIEA) (0.792 mmol). The solution was cooled to 0 °C. HATU (0.316 mmol) was added and the mixture was stirred for 0.5 h at 0 °C and for an additional 2 h at room temperature. The solvent was then evaporated and the residue extracted with EtOAc, washed with brine, dried, filtered, and concentrated. The product was purified by flash column chromatography or HPLC.

8.2. Boc protection of amino acids

Triethylamine (6.40 mmol) was added dropwise to a stirred solution of the amino acid (2.29 mmol) and di-*tert*-butyl dicarbonate (2.74 mmol) in dioxane/water 1:1 (8 mL) and the solution was stirred overnight. The mix-

ture was extracted with petroleum ether (2×) and the aqueous phase was cooled to 0 °C and carefully acidified to pH 3 by slow addition of 4 M $NaHSO_4 \cdot H_2O$ solution. The acidified water phase was extracted with EtOAc (3×) and the combined organic phases were washed with brine (2×) and was then dried, filtered, and concentrated. No further purification was needed.

8.3. Boc/*tert*-butyl ester deprotection

To a solution of the protected compound (0.362 mmol) in methylene chloride (3 mL) were added triethylsilane (0.742 mmol) and TFA (3 mL). The mixture was stirred for 2 h at room temperature and was then evaporated and coevaporated with toluene.

8.4. *tert*-Butyl ester protection

The acid (9.16 mmol), *tert*-butanol (9.16 mmol), and DMAP (4.76 mmol) were dissolved in DCM (40 mL) at 0 °C. EDC (10.7 mmol) was added and the mixture was stirred at 0 °C for 2 h, thereafter at room temperature overnight. The mixture was evaporated, extracted with EtOAc, and washed with saturated $NaHCO_3$ solution. After drying, filtration, and evaporation the crude product was purified by flash column chromatography.

8.5. Methyl ester protection

The acid (5.19 mmol) was dissolved in acetone (28 mL) and MeI (78.7 mmol) and Ag_2O (5.9 mmol) were added. The mixture was allowed to stir overnight and was thereafter filtered through Celite, evaporated, and purified by flash column chromatography.

8.6. Methyl ester deprotection

The methyl ester (0.597 mmol) was dissolved in dioxane/water (1:1) (11 mL) and the mixture was cooled to 0 °C. LiOH (1.0 M, 0.815 mmol) was added dropwise to the solution and the mixture was stirred at 0 °C for 1 h. After neutralization using 1 M HCl, the solvents were evaporated and coevaporated with toluene.

8.7. Z-group deprotection

The protected compound (0.299 mmol) was dissolved in ethanol (95%) (8 mL). 10% palladium on active carbon (40 mg) and hydrogen (atmospheric pressure, with flushing) were added and the mixture was stirred for 90 min. The suspension was filtered through Celite followed by evaporation of the ethanol.

8.8. N-methylation of Fmoc protected amino acids

The Fmoc protected amino acid (5.271 mmol) was suspended in 80 mL toluene, and paraformaldehyde (840 mg) followed by *p*-TsOH (0.242 mmol) were added. The reaction mixture was refluxed for 1 h with azeotropic removal of water before it was cooled to room temperature, washed with aqueous 1 M $NaHCO_3$, dried, filtered, and concentrated. To the residue in 30 mL $CHCl_3$ and 30 mL TFA was added Et_3SiH (15.81 mmol). After stirring for 22 h, the solvents were removed in vacuo. Purification was performed by crystallization from EtOAc/hexane.

8.9. Fmoc deprotection

The Fmoc protected amino acid (3.235 mmol) was dissolved in 25 mL DMF containing 20% piperidine, and the mixture was stirred for 2 h. The solvents were evaporated and the remainder was extracted with EtOAc and washed with brine. The organic phase was dried, filtered, and concentrated. Purification was performed by flash column chromatography.

9. Synthetic procedures

9.1. (1*R*,2*S*)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester hydrochloride (D)

Synthesized according to Ref. 20.

9.2. 2-Phenyl-7-methoxy-4-quinolinol (F)

Synthesized according to Refs. 2b and 21.

9.3. *trans*-(3*R*,4*R*)-bis(Methoxycarbonyl)cyclopentanone ((−)-1)

Synthesized according to Ref. 19 $[\alpha]_D^{22}$ −132 (*c* 1.6, $CHCl_3$) (lit. $[\alpha]_D^{22}$ −133).

9.4. *trans*-(3*R*,4*R*)-bis(Methoxycarbonyl)cyclopentanol (2)

Sodium borohydride (1.11 g, 0.029 mol) was added to a stirred solution of (−)-**1** (4.88 g, 0.0244 mol) in methanol (300 mL) at 0 °C. After 1 h, the reaction was quenched with 90 mL brine, concentrated, and extracted with ethyl acetate. The organic phases were pooled, dried, filtered, and concentrated. The crude product was purified by flash column chromatography (toluene/ethyl acetate 1:1) to give **2** (3.73 g, 76%) as a yellow oil. Compound **2**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.90–2.30 (m, 4H), 3.20–3.30 (m, 1H), 3.38–3.50 (m, 1H), 3.72 (s, 6H), 4.37–4.45 (m, 1H).

9.5. 3-Oxo-2-oxa-bicyclo[2.2.1]heptane-5-carboxylic acid (3)

Sodium hydroxide (1 M, 74 mL, 0.074 mol) was added to a stirred solution of **2** (3.73 g, 0.018 mol) in methanol (105 mL) at room temperature. After 4 h, the reaction mixture was neutralized with 3 M HCl, evaporated and co-evaporated with toluene several times. Pyridine (75 mL) and Ac_2O (53 mL) were added and the reaction mixture was allowed to shake overnight at room temperature. The mixture was then co-evaporated with toluene and purified by flash column chromatography (ethyl acetate + 1% acetic acid) to give **3** (2.51 g, 88%) as a slightly yellow oil. All analytical data are in accordance with Ref. 23.

9.6. 3-Oxo-2-oxa-bicyclo[2.2.1]heptane-5-carboxylic acid methyl ester (4)

To a solution of **3** (44 mg, 0.282 mmol) in acetone (1.5 mL) were added methyl iodide (593 mg, 4.17 mmol) and silver (I) oxide (68 mg, 0.293 mmol). The suspension was stirred at room temperature overnight. The mixture was filtered through Celite and the solvent was evaporated. Flash column chromatography (toluene/ethyl acetate 4:1) provided **4** (39 mg, 81%) as colorless crystals. Compound **4**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.96 (d, J = 10.7 Hz, 1H), 2.21–2.25 (m, 3H), 2.91–2.95 (m, 1H), 3.16 (s, 1H), 3.75 (s, 3H), 4.98 (app. s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 33.3, 38.0, 39.6, 45.8, 52.6, 80.4, 173.1, 176.3.

9.7. 3-Oxo-2-oxa-bicyclo[2.2.1]heptane-5-carboxylic acid *tert*-butyl ester (5)

DMAP (14 mg, 0.115 mmol) and di-*tert*-butyl dicarbonate (Boc_2O) (252 mg, 1.44 mmol) were added to a stirred solution of **3** (180 mg, 1.15 mmol) in 2 mL CH_2Cl_2 under argon atmosphere at 0 °C. The reaction mixture was allowed to attain room temperature and was stirred overnight. The reaction mixture was concentrated and the crude product was purified by flash column chromatography (toluene/ethyl acetate gradient 15:1, 9:1, 6:1, 4:1, 2:1) to give **5** (126 mg, 52%) as colorless crystals. Compound **5**: ^{1}H NMR (CD_3OD, 300 MHz) δ 1.45 (s, 9H), 1.90 (d, J = 11.0 Hz, 1H), 2.10–2.19 (m, 3H), 2.76–2.83 (m, 1H), 3.10 (s, 1H), 4.99 (s, 1H); ^{13}C NMR (CD_3OD, 75.5 MHz) δ 27.1, 33.0, 37.7, 40.8, 46.1, 81.1, 81.6, 172.0, 177.7.

10. Method I

10.1. (1*R*,2*R*,4*S*)-2-((*S*)-1-*tert*-Butoxycarbonyl-butylcarbamoyl)-4-hydroxy-cyclopentanecarboxylic acid methyl ester (6)

Compound **4** (263 mg, 1.55 mmol) and H-Nva-O*t*Bu (420 mg, 2.42 mmol) were dissolved in dry THF (20 mL). DIEA (530 μL, 3.04 mmol) and 2-hydroxypyridine (260 mg, 2.73 mmol) were added and the mixture was refluxed for five days. The solvent was evaporated and the crude product was purified by flash column chromatography (toluene/EtOAc 1:2) to give **6** (510 mg, 96%). Compound **6**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.93 (t, J = 7.3 Hz, 3H), 1.29–1.40 (m, 2H), 1.47 (s, 9H), 1.57–1.70 (m, 1H), 1.70–1.83 (m, 1H), 1.83–2.05 (m, 2H), 2.05–2.24 (m, 2H), 3.08–3.18 (m, 1H), 3.23–3.33 (m, 1H), 3.71 (s, 3H), 4.34 (br s, 1H), 4.38–4.49 (m, 2H), 7.03 (b, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.4, 18.1, 27.6, 34.0, 37.9, 40.0, 46.3, 46.5, 51.7, 52.6, 72.7, 81.5, 171.2, 175.1, 175.5.

10.2. (1*R*,2*R*,4*R*)-2-((*S*)-1-*tert*-Butoxycarbonyl-butylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarboxylic acid methyl ester (7)

Compound **6** (249 mg, 0.725 mmol), 2-phenyl-7-methoxy-4-quinolinol (310 mg, 1.23 mmol), and PPh_3 (580 mg, 2.21 mmol) were dissolved in dry THF, and the temperature was lowered to 0 °C. DIAD (435 μL, 2.21 mmol) dissolved in 2 mL dry THF, was added to the mixture during 5 min. After 2 h, the temperature was raised to room temperature and the solution was stirred overnight. Evaporation and purification by flash column chromatography (toluene/EtOAc gradient 6:1 to 4:1) gave **7** (324 mg, 78%). Compound **7**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (t, J = 7.1 Hz, 3H), 1.26–1.40 (m, 2H), 1.46 (s, 9H), 1.57–1.71(m, 1H), 1.76–1.88 (m, 1H), 2.34–2.70 (m, 4H), 3.22–3.32 (m, 1H), 3.45 (q, J = 8.2 Hz, 1H), 3.63 (s, 3H), 3.94 (s, 3H), 4.44–4.56 (m, 1H), 5.16–5.24 (m, 1H), 6.53 (b, 1H), 6.92–7.02 (m, 2H) 7.11 (dd, J = 2.5, 9.1 Hz, 1H), 7.40–7.56 (m, 3H), 7.96 (d, J = 9.1 Hz, 1H), 8.03 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.6, 18.3, 27.9, 34.5, 35.6, 46.2, 46.4, 52.1, 52.6, 55.3, 78.2, 81.8, 98.1, 107.4, 115.2, 118.0, 122.8, 127.3, 127.4, 128.5, 128.6, 128.9, 129.0, 140.2, 151.2, 159.0, 160.3, 161.1, 171.5, 172.6, 174.4.

10.3. (*S*)-2-{[(1*R*,2*R*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methylcarbamoyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-pentanoic acid *tert*-butyl ester (8)

Compound **7** (38 mg, 0.066 mmol) was dissolved in dioxane/water 1:1 (4 mL) and the solution was cooled to 0 °C and 1 M LiOH (132 μL, 0.132 mmol) was added. The temperature was raised to room temperature and the solution was stirred for 2 h after which it was neutralized by addition of 1 M HCl and evaporated and coevaporated with toluene. The residue and amine **L** were dissolved in DMF and coupled using General Synthetic Procedure A (Peptide coupling). Purification with HPLC (MeOH/water 9:1 + 0.2% TEA) provided compound **8** (44 mg, 81%) as a colorless solid. Compound **8**: ^{1}H NMR ($CDCl_3$, 300 MHz) rotamers (5:1) δ 0.79 (t, J = 7.3 Hz, 3H), 0.85–1.19 (m, 3H), 0.93 (s, overlapped, 9H), 1.20–1.35 (m, 2H), 1.39 (s, 1.5 H), 1.43 (s, 7.5 H), 1.54–1.79 (m, 6H), 2.06–2.28 (m, 3H), 2.39–2.51 (m, 2H), 2.66–2.78 (m, 1H), 2.74 (d, overlapped, J = 4.7 Hz, 3H), 3.42–3.68 (m, 2H), 3.84 (s, 2.5 H), 3.88 (s, 0.5 H), 4.19 (t, J = 8.9 Hz, 1H), 4.39–4.59 (m, 1H), 4.68 (d, J = 9.6 Hz, 1H), 5.04–5.14 (m, 1H), 6.77 (s, 1H), 6.88–7.06 (m, 2H), 7.26–7.47 (m, 6H), 7.53 (b, 1H), 7.85–7.97 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.7, 18.7, 25.6, 25.7, 26.0, 26.7, 28.0, 28.9, 29,7, 34.5, 34.7, 37.7, 38.0, 39.2, 46.6, 47.7, 52.7, 55.3, 58.5, 60.3, 77.9, 81.7, 98.0, 107.4, 115.0, 117.9, 122.8, 127.4, 128.6, 129.0, 140.2, 151.2, 158.9, 160.6, 161.1, 170.9, 171.6, 171.8, 172.7, 173.3. MALDI-TOF: $(M+H)^+$ calcd: 828.5, found: 828.6; $(M+Na)^+$ calcd: 850.5, found: 850.6; $(M+K)^+$ calcd: 866.6, found: 866.6.

10.4. (*S*)-2-{[(1*R*,2*R*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methylcarbamoyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-pentanoic acid (9)

Compound **8** (21 mg, 0.025 mmol) was dissolved in CH_2Cl_2 (1.5 mL) and triethylsilane (10 μL, 0.063 mmol)

and TFA (1.5 mL) were added. The solution was stirred for 2 h at room temperature after which the solvents were evaporated and coevaporated with toluene to provide compound **9** (20 mg, 100%) as a colorless solid. Compound **9**: ^{1}H NMR (CD_3OD, 300 MHz) δ 0.93 (t, overlapped, 3H), 0.98 (s, 9H), 0.99–1.25 (m, 4H), 1.30–1.49 (m, 3H), 1.50–1.90 (m, 8H), 2.25–2.39 (m, 2H), 2.54–2.62 (m, 1H), 2.64 (s, 3H), 2.72–2.87 (m, 1H), 3.34–3.57 (m, 3H), 4.02–4.13 (m, 1H), 4.06 (s, overlapped, 3H), 4.27–4.36 (m, 1H), 4.37–4.47 (m, 1H), 5.57–5.66 (m, 1H), 7.45 (dd, J = 2.3, 9.2 Hz, 1H), 7.48 (s, 1H), 7.54 (d, J = 2.2 Hz, 1H), 7.69–7.79 (m, 3H), 8.01–8.07 (m, 2H), 8.42 (d, J = 9.3 Hz, 1H); ^{13}C NMR (CD_3OD, 75.5 MHz) δ 14.0, 20.2, 26.0, 26.9, 27.2, 30.1, 30.7, 34.6, 35.3, 37.2, 39.1, 41.2, 47.7, 53.7, 56.9, 59.4, 59.5, 62.5, 83.7, 100.4, 101.3, 102.2, 116.2, 121.7, 126.7, 129.8, 130.8, 133.3, 133.9, 143.5, 157.9, 166.6, 168.5, 172.5, 173.6, 175.3, 175.4, 175.5. HRMS calcd $(M+H)^+$: 772.4285; found: 772.4311. LC–MS Purity System A: t_R = 7.25 min, 95%; System B: t_R = 7.43 min, 95%.

11. Method II

11.1. (1*R*,2*R*,4*S*)-2-((1*R*,2*S*)-1-Ethoxycarbonyl-2-vinyl-cyclopropylcarbamoyl)-4-hydroxy-cyclopentanecarboxylic acid *tert*-butyl ester (10)

Compound **5** (56 mg, 0.264 mmol) was dissolved in dioxane/water 1:1 (5 mL) and the mixture was cooled to 0 °C. 1M lithium hydroxide (520 μL, 0.520 mmol) was added and the mixture was stirred at 0 °C for 45 min, after which the mixture was neutralized with 1 M hydrochloric acid and evaporated and coevaporated with toluene. The residue was dissolved in DMF (5 mL) and coupled to (1*R*,2*S*)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester hydrochloride using General Synthetic Procedure A (Peptide coupling). Purification by flash column chromatography (toluene/EtOAc 1:1) provided compound **10** (86 mg, 89%) as a colorless oil. Compound **10**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.16 (t, J = 7.3 Hz, 3H), 1.40 (s, 9H), 1.70–1.83 (m, 2H), 1.92–2.00 (m, 2H), 2.03–2.14 (m, 2H), 2.93–3.04 (m, 1H), 3.09–3.19 (m, 1H), 3.93–4.17 (m, 1H), 4.26 (br s, 1H), 5.06 (dd, J = 1.7, 10.2 Hz, 1H), 5.23 (dd, J = 1.7, 17.0 Hz, 1H), 5.66 (ddd, J = 8.8, 10.2, 17.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.0, 22.8, 27.9, 33.1, 37.1, 40.1, 40.2, 45.6, 47.8, 61.3, 73.0, 81.2, 117.8, 133.2, 169.8, 174.2, 177.7.

11.2. (1*R*,2*R*,4*R*)-2-((1*R*,2*S*)-1-Ethoxycarbonyl-2-vinyl-cyclopropylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarboxylic acid *tert*-butyl ester (11)

Compound **10** (73 mg, 0.199 mmol) was dissolved in dry THF (4 mL) and 2-phenyl-7-methoxy-4-quinolinol (86 mg, 0.342 mmol) and triphenylphosphine (141 mg, 0.538 mmol) were added. The mixture was cooled to 0 °C and DIAD (111 μL, 0.567 mmol) dissolved in 1 mL THF was added dropwise and the mixture was stirred for 48 h at room temperature. The solvent was evaporated and the crude product was purified by flash column chromatography gradient elution (toluene/EtOAc 9:1, 6:1, 4:1) to give compound **11** (81 mg, 68%). Compound **11**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, J = 7.1 Hz, 3H), 1.37 (s, 9H), 1.50 (dd, J = 5.5, 9.6 Hz, 1H), 1.89 (dd, J = 5.5, 8.0 Hz, 1H), 2.12 (app q, J = 8.7 Hz, 1H), 2.24–2.34 (m, 1H), 2.41–2.54 (m, 3H), 3.09–3.19 (m, 1H), 3.30–3.42 (m, 1H), 3.94 (s, 3H), 4.09–4.21 (m, 2H), 5.12 (dd, J = 1.8, 10.3 Hz, 1H), 5.15–5.21 (m, 1H), 5.28 (dd, J = 1.8, 17.2 Hz, 1H), 5.76 (ddd, J = 8.5, 10.3, 17.2 Hz), 7.02 (s, 2H), 7.08 (dd, J = 2.6, 9.2 Hz, 1H), 7.41–7.55 (m, 4H), 7.96 (d, J = 9.1 Hz, 1H), 8.05 (d, J = 6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.3, 23.1, 27.9, 33.5, 35.1, 35.6, 40.2, 45.4, 45.7, 47.2, 55.5, 61.3, 78.6, 81.9, 98.3, 107.5, 115.4, 117.8, 118.0, 123.0, 127.5, 128.8, 129.2, 133.6, 140.4, 151.3, 159.2, 160.5, 161.3, 170.0, 173.9, 174.4.

11.3. (1*R*,2*S*)-1-{[(1*R*,2*R*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methylcarbamoyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid ethyl ester (12)

To a solution of compound **11** (30 mg, 0.050 mmol) in methylene chloride (1.5 mL) were added triethylsilane (21 μL, 0.132 mmol) and TFA (1.5 mL). The mixture was stirred for 2 h at room temperature and was then evaporated and coevaporated with toluene. The residue and amine **L** were dissolved in DMF and coupled using General Synthetic Procedure A (Peptide coupling). Purification using HPLC (MeOH/water 9:1 + 0.2% triethylamine) provided compound **12** (30 mg, 74%) as a colorless solid. Compound **12**: ^{1}H NMR (CD_3OD, 300 MHz) δ 0.81–1.14 (m, 4H), 0.99 (s, overlapped, 9H), 1.21 (t, J = 7.1 Hz, 3H), 1.35–1.51 (m, 4H), 1.52–1.65 (m, 3H), 1.66–1.72 (m, 2H), 2.03–2.20 (m, 2H), 2.24–2.39 (m, 1H), 2.46–2.56 (m, 1H), 2.66 (s, 3H), 2.72–2.85 (m, 1H), 3.39–3.48 (m, 2H), 3.90 (s, 3H), 4.03–4.15 (m, 3H), 4.44 (s, 1H), 5.09 (dd, J = 1.9, 10.3 Hz, 1H), 5.19–5.27 (m, 1H), 5.25 (dd, overlapped, 1H), 5.79 (ddd, J = 8.8, 10.3, 17.2 Hz, 1H), 6.99 (s, 1H), 7.07 (dd, J = 2.5, 9.1 Hz, 1H), 7.29 (d, J = 2.5 Hz, 1H), 7.43–7.52 (m, 3H), 7.86–7.98 (m, 2H), 8.05 (d, J = 9.3 Hz, 1H); ^{13}C NMR (CD_3OD, 75.5 MHz) δ 14.7, 23.4, 26.0, 26.9, 27.1, 27.3, 30.1, 30.7, 35.0, 35.4, 38.3, 38.8, 40.9, 41.0, 47.9, 55.9, 59.6, 62.0, 62.4, 79.8, 99.9, 107.3, 116.4, 118.0, 119.1, 124.4, 128.9, 129.8, 130.5, 135.3, 141.3, 152.1, 161.1, 162.4, 163.0, 171.6, 172.5, 173.7, 175.2, 176.8. MALDI-TOF: $(M+H)^+$ calcd: 810.4, found: 810.5; $(M+Na)^+$ calcd: 832.4, found: 832.4; $(M+K)^+$ calcd: 848.5, found: 848.4.

11.4. (1*R*,2*S*)-1-{[(1*R*,2*R*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methylcarbamoyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (13)

To a solution of compound **12** (20 mg, 0.025 mmol) in THF/MeOH/water 2:1:1 (2 mL) at 0 °C was added 1 M LiOH (175 μL, 0.175 mmol) and the solution was allowed to attain room temperature and was stirred for 48 h. The solution was acidified to pH 3 with 1 M HCl and was then evaporated and coevaporated with

toluene. The crude product was purified by HPLC (MeOH/water 3:2 + 0.2% TFA followed by MeOH/water 4:1 + 0.2% TFA) to give compound **13** (13 mg, 67%) as a colorless solid. Compound **13**: ^{1}H NMR (CD_3OD, 300 MHz) δ 0.82–0.98 (m, 1H), 1.01 (s, 9H), 1.05–1.26 (m, 3H), 1.34–1.43 (m, 1H), 1.49–1.77 (m, 8H), 2.10–2.21 (m, 1H), 2.28–2.42 (m, 2H), 2.50–2.61 (m, 1H), 2.64 (s, 3H), 2.68–2.81 (m, 1H), 3.36–3.45 (m, 2H), 4.04–4.11 (m, 1H), 4.06 (s, overlapped, 3H), 4.27 (d, J = 8.8 Hz, 1H), 5.10 (dd, J = 1.8, 10.3 Hz, 1H), 5.28 (dd, J = 1.8, 17.2 Hz, 1H), 5.59–5.68 (m, 1H), 5.82 (ddd, J = 9.1, 10.3, 17.2 Hz, 1H), 7.44 (dd, J = 2.5, 11.8 Hz, 1H), 7.50 (s, 1H), 7.53 (d, J = 2.5 Hz, 1H), 7.69–7.78 (m, 3H), 8.02–8.07 (m, 2H), 8.39 (d, J = 9.3 Hz, 1H); ^{13}C NMR (CD_3OD, 75.5 MHz) δ 23.5, 26.0, 26.9, 27.2, 27.3, 30.0, 30.7, 34.7, 35.3, 37.0, 38.7, 41.0, 41.3, 47.4, 56.9, 59.4, 62.7, 83.9, 100.4, 102.2, 116.2, 117.7, 121.7, 126.7, 129.8, 130.8, 133.4, 133.9, 135.6, 143.5, 158.0, 166.6, 168.6, 172.5, 173.4, 173.6, 175.4, 176.4. HRMS calcd $(M+H)^+$: 782.4129; found: 782.4158. LC–MS Purity System A: t_R = 7.09 min, 98%; System B: t_R = 7.45 min, 98%.

12. Target compounds

12.1. (*S*)-2-{[(1*R*,2*R*,4*S*)-2-{(*R*)-1-[((*R*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propyl-carbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-butyric acid (14)

Compound **14** was obtained in 30% total yield as a colorless solid using Method I. Compound **14**: ^{1}H NMR (CD_3OD, 300 MHz) δ 0.82–1.02 (m, 9H), 1.04–1.42 (m, 6H), 1.52–1.80 (m, 6H), 1.80–1.96 (m, overlapped, 1H), 2.00–2.14 (m, 1H), 2.29–2.46 (m, 2H), 2.51–2.65 (m, 1H), 2.68–2.84 (m, 1H), 3.24–3.39 (m, overlapped, 1H), 3.47–3.60 (m, 1H), 3.67 (s, 3H), 4.07 (s, 3H), 4.18–4.27 (m, 2H), 4.28–4.38 (m, 1H), 5.64 (app. br s, 1H), 7.44 (dd, J = 2.3, 6.9 Hz, 1H), 7.42 (s, 2H), 7.67–7.81 (m, 3H), 8.04 (d, J = 7.8 Hz, 2H), 8.41 (d, J = 9.1 Hz, 1H); ^{13}C NMR (CD_3OD, 75.5 MHz) δ 10.8, 18.5, 19.6, 25.7, 27.1, 27.1, 30.1, 30.6, 31.9, 37.3, 38.2, 41.1, 47.8, 52.3, 55.4, 56.9, 59.0, 59.1, 60.2, 83.8, 100.5, 102.2, 116.3, 121.6, 126.8, 129.8, 130.8, 133.6, 133.8, 143.7, 158.1, 166.5, 168.5, 173.4, 173.8, 175.4, 175.7, 175.7. HRMS calcd $(M+H)^+$: 745.3813; found: 745.3849. LC–MS Purity System A: t_R = 7.58 min, 100%; System B: t_R = 7.78 min, 100%.

12.2. (*S*)-2-{[(1*R*,2*R*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-butyric acid (15)

Compound **15** was obtained in 21% total yield as a colorless solid using Method I. Compound **15**: ^{1}H NMR (CD_3OD, 300 MHz) δ 0.82–0.99 (m, 9H), 0.82–1.40 (m, overlapped, 6H), 1.48–1.78 (m, 6H), 1.80–1.95 (m, 1H), 1.97–2.12 (m, 1H), 2.22–2.40 (m, overlapped, 2H), 2.51–2.64 (m, 1H), 2.71–2.90 (m, 1H), 3.16–3.39 (m, overlapped, 1H), 3.49–3.59 (m, 1H), 3.63 (s, 3H), 3.95 (s, 3H), 4.12–4.23 (m, 2H), 4.28–4.38 (m, 1H), 5.31 (b, 1H), 7.43 (dd, J = 2.2, 9.3 Hz, 1H), 7.47 (s, 1H), 7.51 (s, 1H), 7.66–7.89 (m, 3H), 7.99–8.07 (m, 2H), 8.42 (d, J = 9.1 Hz, 1H); ^{13}C NMR (CD_3OD, 75.5 MHz) δ 10.7, 18.8, 19.7, 25.8, 27.0, 27.0, 29.7, 30.5, 31.8, 37.7, 38.9, 41.2, 47.9, 52.3, 55.3, 56.9, 58.8, 60.6, 83.6, 100.7, 102.2, 116.3, 121.5, 126.7, 129.8, 130.8, 133.7, 133.8, 143.9, 158.2, 166.4, 168.3, 173.3, 173.8, 175.2, 175.5, 175.6. HRMS calcd $(M+H)^+$: 745.3813; found: 745.3787. LC–MS Purity System A: t_R = 7.86 min, 99%; System B: t_R = 7.66 min, 98%.

12.3. (*S*)-2-{[(1*R*,2*R*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-pentanoic acid (16)

Compound **16** was obtained in 66% total yield as a colorless solid using Method I. Compound **16**: ^{1}H NMR (CD_3OD, 300 MHz) δ 0.86–1.00 (m, 9H), 1.01–1.24 (m, 4H), 1.36–1.46 (m, 2H), 1.48–1.75 (m, 8H), 1.70–1.89 (m, overlapped, 1H), 1.96–2.12 (m, 1H), 2.22–2.40 (m, overlapped, 2H), 2.49–2.64 (m, 1H), 2.72–2.91 (m, 1H), 3.26–3.40 (m, overlapped, 1H), 3.50–3.68 (m, overlapped, 1H), 3.62 (s, 3H), 4.05 (s, 3H), 4.09–4.17 (m, 1H), 4.17–4.25 (m, 1H), 4.35–4.45 (m, 1H), 5.62 (b, 1H), 7.44 (dd, J = 2.2, 9.3 Hz, 1H), 7.49 (s, 1H), 7.53 (d, J = 2.2 Hz, 1H), 7.65–7.78 (m, 3H), 7.98–8.06 (m, 2H), 8.41 (dd, J = 2.8, 9.3 Hz, 1H); ^{13}C NMR (CD_3OD, 75.5 MHz) δ 13.9, 18.8, 19.7, 20.2, 27.0, 29.7, 30.5, 31.8, 34.6, 37.7, 38.9, 41.1, 47.8, 52.3, 53.6, 56.9, 58.8, 58.9, 60.3, 83.8, 100.4, 102.2, 116.2, 121.6, 126.7, 129.8, 130.8, 133.3, 133.8, 143.5, 157.9, 166.5, 168.5, 173.3, 173.9, 175.5, 175.5, 175.6. HRMS calcd $(M+H)^+$: 759.3969; found: 759.4001. LC–MS Purity System A: t_R = 8.05 min, 98%; System B: t_R = 7.86 min, 100%.

12.4. (*S*)-2-{[(1*R*,2*R*,4*S*)-2-{(*R*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-pentanoic acid (17)

Compound **17** was obtained in 42% total yield as a colorless solid using Method I. Compound **17**: ^{1}H NMR (CD_3OD, 300 MHz) δ 0.86–0.97 (m, 9H), 1.04–1.19 (m, 2H), 1.20–1.33 (m, 3H), 1.34–1.49 (m, 2H), 1.58–1.69 (m, 3H), 1.70–1.89 (m, 4H), 2.04–2.16 (m, 1H), 2.32–2.45 (m, 2H), 2.46–2.67 (m, 2H), 2.70–2.84 (m, 1H), 3.36–3.46 (m, 1H), 3.47–3.60 (m, 1H), 3.69 (s, 3H), 4.06 (s, 3H), 4.26–4.43 (m, 3H), 5.61–5.70 (m, 1H), 7.45 (dd, J = 1.8, 9.2 Hz, 1H), 7.53 (s, 1H), 7.54 (d, overlapped, 1H), 7.68–7.78 (m, 3H), 8.02–8.09 (m, 2H), 8.40 (d, J = 9.3 Hz, 1H); ^{13}C NMR ($CDCl_3$,75.5 MHz) δ 13.8, 18.1, 19.3, 19.7, 26.1, 28.7, 29.7, 30.3, 33.4, 36.0, 36.7, 40.7, 41.2, 43.8, 47.0, 47.5, 52.4, 52.7, 53.5, 56.4, 57.4, 59.4, 82.1, 100.1, 100.2, 114.8, 119.9, 121.1, 124.9, 128.6, 129.4, 131.0, 132.4, 142.7, 155.8, 164.8, 166.6, 171.9, 172.7, 173.4, 173.9, 174.8. HRMS calcd $(M+H)^+$: 759.3969; found: 759.3998. LC–MS Purity System A: t_R = 8.92 min, 97%; System B: t_R = 8.12 min, 100%.

12.5. (*S*)-2-{[(1*R*,2*R*,4*S*)-2-{(*S*)-1-[((*R*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-pentanoic acid (18)

Compound **18** was obtained in 32% total yield as a colorless solid using Method I. Compound **18**: ^{1}H NMR (CD_3OD, 300 MHz, rotamers) δ 0.90–1.04 (m, 9H), 1.13–1.21 (m, 2H), 1.22–1.32 (m, 3H), 1.33–1.49 (m, 2H), 1.52–1.64 (m, 3H), 1.65–1.89 (m, 5H), 2.01–2.14 (m, 1H), 2.26–2.42 (m, 2H), 2.52–2.67 (m, 1H), 2.74–2.88 (m, 1H), 3.32–3.41 (m, overlapped, 1H), 3.47–3.58 (m, 1H), 3.59 (s, 3H), 4.06 (s, 3H), 4.20–4.34 (m, 2H), 4.36–4.45 (m, 1H), 5.59–5.69 (m, 1H), 7.45 (dd, J = 2.3, 9.2 Hz, 1H), 7.49 (s, 1H), 7.52 (d, J = 2.3 Hz, 1H), 7.68–7.80 (m, 3H), 8.01–8.08 (m, 2H), 8.44 (d, J = 9.1 Hz, 1H); ^{13}C NMR (CD_3OD, 75.5 MHz) δ 12.8, 17.2, 18.8, 19.0, 21.1, 25.8, 28.6, 29.5, 30.8, 33.5, 36.4, 37.8, 40.0, 46.6, 51.1, 52.5, 55.7, 57.5, 58.9, 82.5, 99.3, 101.0, 115.1, 120.4, 125.5, 128.6, 129.6, 132.5, 132.6, 142.6, 156.9, 165.3, 167.2, 172.1, 172.5, 174.3. HRMS calcd $(M+H)^+$: 759.3969; found: 759.3976. LC–MS Purity System A: t_R = 8.39 min, 98%; System B: t_R = 7.93 min, 96%.

12.6. (*S*)-2-{[(1*R*,2*R*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methylcarbamoyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-pentanoic acid (19)

Compound **19** was obtained in 40% total yield as a colorless solid using Method I. Compound **19**: ^{1}H NMR (CD_3OD, 300 MHz) δ 0.84–0.99 (m, 9H), 1.00–1.24 (m, 4H), 1.27–1.46 (m, 3H), 1.50–1.74 (m, 7H), 1.75–1.86 (m, 1H), 1.99–2.14 (m, 1H), 2.23–2.40 (m, 2H), 2.52–2.59 (m, 1H), 2.63 (s, 3H), 2.75–2.90 (m, 1H), 3.16–3.26 (m, 1H), 3.46–3.59 (m, 1H), 4.01–4.11 (m, 1H), 4.06 (s, overlapped, 3H), 4.13–4.21 (m, 1H), 4.35–4.43 (m, 1H), 5.59–5.67 (m, 1H), 7.41–7.54 (m, 3H), 7.68–7.79 (m, 3H), 8.04 (d, J = 6.6 Hz, 2H), 8.44 (d, J = 9.1 Hz, 1H). HRMS calcd $(M+H)^+$: 758.4129; found: 758.4145. LC–MS Purity System A: t_R = 6.61 min, 98%; System B: t_R = 7.41 min, 100%.

12.7. (*S*)-2-{[(1*R*,2*R*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-pentanoic acid (20)

Compound **20** was obtained in 61% total yield as a colorless solid using Method I. Compound **20** ^{1}H NMR (CD_3OD, 300 MHz) δ 0.94 (t, J = 7.4 Hz, 3H), 0.98–1.09 (m, 2H), 1.00 (s, 9H), 1.10–1.28 (m, 4H), 1.35–1.48 (m, 2H), 1.52–1.74 (m, 7H), 1.75–1.89 (m, 1H), 2.26–2.39 (m, 2H), 2.54–2.64 (m, 1H), 2.73–2.87 (m, 1H), 3.34–3.43 (m, 1H), 3.44–3.59 (m, 1H), 3.66 (s, 3H), 4.07 (s, 3H), 4.14–4.22 (m, 1H), 4.34 (d, J = 9.1 Hz, 1H), 4.36–4.46 (m, 1H), 5.57–5.66 (m, 1H), 7.41–7.58 (m, 3H), 7.66–7.78 (m, 4H), 8.01–8.08 (m, 1H), 8.43 (d, J = 9.1 Hz, 1H); ^{13}C NMR (CD_3OD, 75.5 MHz) δ 14.0, 20.2, 24.9, 27.0, 27.1, 29.8, 30.5, 34.6, 35.3, 37.2, 39.1, 41.2, 46.9, 47.7, 52.2, 53.7, 56.9, 59.0, 62.2, 83.8, 100.4, 102.2, 116.2, 121.7, 126.7, 129.2, 129.8, 130.8, 133.4, 133.8, 143.5, 158.0, 166.5, 168.5, 172.9, 173.2, 175.3, 175.5, 179.8. HRMS calcd $(M+H)^+$: 773.4126; found: 773.4119. LC–MS Purity System A: t_R = 8.56 min, 100%; System B: t_R = 8.07 min, 100%.

12.8. (1*R*,2*S*)-1-{[(1*R*,2*R*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-dimethylcarbamoyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)- cyclopentanecarbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (21)

Compound **21** was obtained in 37% total yield as a colorless solid using Method II. Compound **21**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.75–0.87 (m, 2H), 0.90 (s, 9H), 0.98–1.17 (m, 3H), 1.32–1.63 (m, 8H), 1.81–1.98 (m, 2H), 2.10–2.21 (m, 1H), 2.28–2.40 (m, 1H), 2.74–2.89 (m, 1H), 2.90–3.03 (m, 1H), 2.95 (s, overlapped, 3H), 3.05–3.19 (m, 1H), 3.10 (s, 3H), 3.63–3.78 (m, 1H), 3.99 (s, 3H), 4.47 (d, J = 9.9 Hz, 1H), 4.70–4.80 (m, 1H), 5.11 (d, J = 11.3 Hz, 1H), 5.27 (d, J = 16.7 Hz, 1H), 5.67–5.87 (m, 2H), 6.70 (br s, 1H), 7.21 (b, 1H), 7.29 (dd, J = 1.9, 9.3 Hz, 1H), 7.39 (s, 1H), 7.48–7.60 (m, 3H), 7.74 (s, 1H), 7.92 (d, J = 6.6 Hz, 2H), 8.16 (d, J = 9.3 Hz, 1H), 8.86 (b, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 25.9, 26.1, 27.0, 28.2, 30.0, 32.8, 33.9, 34.8, 36.5, 38.2, 38.8, 40.7, 41.3, 43.7, 44.7, 49.4, 54.1, 56.8, 62.6, 81.7, 100.2, 100.3, 114.9, 118.8, 121.9, 124.7, 128.9, 130.0, 132.0, 133.1, 133.5, 143.1, 156.9, 165.5, 167.1, 171.7, 172.3, 174.1, 174.6, 175.0. HRMS calcd $(M+H)^+$: 796.4285; found: 796.4312. LC–MS Purity System A: t_R = 7.62 min, 100%; System B: t_R = 7.64 min, 99%.

12.9. (1*R*,2*S*)-1-{[(1*R*,2*R*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methylcarbamoyl-methyl)-methyl-carbamoyl]-2,2-dimethyl- propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)- cyclopentanecarbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (22)

Compound **22** was obtained in 23% total yield as a colorless solid using Method II. Compound **22**: ^{1}H NMR (CD_3OD, 300 MHz) δ 0.84–1.06 (m, 2H), 1.00 (s, overlapped, 9H), 1.12–1.26 (m, 2H), 1.30–1.41 (m, 4H), 1.42–1.68 (m, 3H), 1.70–1.78 (m, 2H), 1.80–1.92 (m, 1H), 2.11–2.27 (m, 2H), 2.28–2.40 (m, 1H), 2.50–2.63 (m, 1H), 2.67 (s, 3H), 2.70–2.80 (m, 1H), 3.12 (s, 3H), 3.34–3.46 (m, 1H), 3.99 (s, 1H), 4.08 (s, 3H), 4.73 (d, J = 11.3 Hz, 1H), 5.10 (dd, J = 1.9, 10.2 Hz, 1H), 5.28 (dd, J = 1.4, 17.3 Hz, 1H), 5.59–5.67 (m, 1H), 5.83 (ddd, J = 8.8, 10.2, 17.3 Hz, 1H), 7.45 (dd, J = 2.2, 9.2 Hz, 1H), 7.50 (s, 1H), 7.54 (d, J = 2.2 Hz, 1H), 7.70–7.80 (m, 3H), 8.00–8.07 (m, 2H), 8.42 (d, J = 9.3 Hz, 1H); ^{13}C NMR (CD_3OD, 75.5 MHz) δ 23.5, 26.0, 26.5, 26.9, 27.3, 29.5, 30.7, 32.1, 34.7, 36.1, 36.5, 37.1, 38.6, 41.0, 47.3, 56.9, 57.0, 61.7, 83.9, 100.4, 102.2, 116.2, 117.7, 121.7, 126.7, 129.8, 130.8, 133.3, 133.9, 135.5, 143.5, 158.0, 166.6, 168.5, 172.3, 173.2, 174.2, 175.3, 176.3. HRMS calcd $(M+H)^+$: 796.4285; found: 796.4307. LC–MS Purity System A: t_R = 7.46 min, 99%; System B: t_R = 7.58 min, 100%.

12.10. (1*R*,2*S*)-1-{[(1*R*,2*R*,4*S*)-2-((*S*)-1-Cyclopentylcarbamoyl-2,2-dimethyl-propylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (23)

Compound **23** was obtained in 23% total yield as a colorless solid using Method II. Compound **23**: ^{1}H NMR (CD_3OD, 300 MHz) δ 0.98 (s, 9H), 1.28–1.48 (m, 3H), 1.49–1.76 (m, 5H), 1.78–1.94 (m, 2H), 2.10–2.24 (m, 1H), 2.26–2.45 (m, 2H), 2.50–2.62 (m, 1H), 2.66–2.79 (m, 1H), 3.35–3.48 (m, 2H), 3.94–4.03 (m, 1H), 4.06 (s, 3H), 4.16–4.24 (m, 1H), 5.10 (dd, J = 1.8, 10.3 Hz, 1H), 5.29 (dd, J = 1.8, 17.2 Hz, 1H), 5.62 (b, 1H), 5.82 (ddd, J = 9.1, 10.3, 17.2 Hz, 1H), 7.43 (dd, J = 2.5, 9.3 Hz, 1H), 7.50 (s, 1H), 7.50–7.69 (dd, overlapped, 1H), 7.67–7.80 (m, 3H), 8.01–8.11 (m, 2H), 8.39 (d, J = 9.3 Hz, 1H); ^{13}C NMR (CD_3OD, 75.5 MHz) δ 24.7, 24.7, 27.3, 33.1, 33.6, 34.7, 35.4, 36.9, 38.7, 41.0, 47.4, 52.3, 56.9, 62.3, 83.9, 100.4, 102.3, 116.2, 117.7, 121.6, 126.7, 129.8, 130.8, 133.4, 133.8, 135.6, 143.5, 158.0, 166.5, 168.6, 171.9, 173.4, 175.2, 176.4. HRMS calcd $(M+H)^+$: 697.3601; found: 697.3589. LC–MS Purity System A: t_R = 7.34 min, 98%; System B: t_R = 7.63 min, 100%.

12.11. (1*R*,2*S*)-1-{[(1*R*,2*R*,4*S*)-2-((*S*)-1-*tert*-Butylcarbamoyl-2,2-dimethyl-propylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (24)

Compound **24** was obtained in 40% total yield as a colorless solid using Method II. Compound **24**: ^{1}H NMR (CD_3OD, 300 MHz) δ 0.99 (s, 9H), 1.26 (s, 9H), 1.34–1.42 (m, 1H), 1.69–1.76 (m, 1H), 2.12–2.23 (m, 1H), 2.28–2.44 (m, 2H), 2.51–2.62 (m, 1H), 2.65–2.79 (m, 1H), 3.35–3.43 (m, 2H), 4.06 (s, 3H), 4.12–4.19 (m, 1H), 5.10 (dd, J = 1.7, 10.4 Hz, 1H), 5.29 (dd, J = 1.7, 17.3 Hz, 1H), 5.59–5.67 (m, 1H), 5.83 (ddd, J = 9.1, 10.4, 17.3 Hz, 1H), 7.44 (dd, J = 2.3, 9.2 Hz, 1H), 7.47–7.55 (m, 2H), 7.68–7.78 (m, 3H), 8.01–8.07 (m, 2H), 8.40 (d, J = 9.3 Hz, 1H); ^{13}C NMR (CD_3OD, 75.5 MHz) δ 23.4, 27.3, 28.8, 34.8, 35.5, 36.8, 38.8, 40.9, 46.7, 47.3, 52.2, 56.9, 62.5, 77.3, 83.9, 100.4, 102.3, 113.2, 117.7, 121.6, 126.7, 129.8, 130.8, 133.4, 133.8, 135.6, 143.5, 158.0, 161.1, 166.6, 168.6, 171.7, 173.4, 175.1, 176.4. HRMS calcd $(M+H)^+$: 685.3601; found: 685.3616. LC–MS Purity System A: t_R = 7.42 min, 99%; System B: t_R = 7.68 min, 100%.

12.12. (*S*)-2-{[(1*R*,2*R*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexylmethylcarbamoyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-4,4-difluoro-butyric acid (25)

Compound **25** was obtained in 16% total yield as a colorless solid using Method II. Compound **25**: ^{1}H NMR (CD_3OD, 300 MHz) δ 0.97 (s, 9H), 0.88–1.23 (m, 4H), 1.24–1.43 (m, 2H), 1.50–1.75 (m, 5H), 2.16–2.46 (m, 4H), 2.54–2.65 (m, 1H), 2.63 (s, 3H), 2.74–2.88 (m, 1H), 3.33–3.56 (m, 3H), 4.04–4.11 (m, 1H), 4.06 (s, 3H), 4.25–4.31 (m, 1H), 4.58–4.68 (m, 1H), 5.59–5.66 (m, 1H), 5.96 (tt, J = 5.0, 56.3 Hz, 1H), 7.45 (dd, J = 2.5, 9.3 Hz, 1H), 7.49 (s, 1H), 7.53 (d, J = 2.2 Hz, 1H), 7.69–7.78 (m, 3H), 7.98–8.06 (m, 2H), 8.41 (d, J = 9.3 Hz, 1H); ^{13}C NMR (CD_3OD, 75.5 MHz) δ 26.0, 26.9, 27.2, 30.0, 30.7, 35.2, 36.9, 37.2, 38.9, 41.3, 47.6, 56.9, 59.4, 62.6, 83.7, 100.5, 102.2, 116.2, 116.9, 121.7, 126.7, 129.8, 129.9, 130.8, 133.4, 133.9, 143.6, 158.0, 166.6, 168.5, 172.5, 173.5, 175.3, 175.4. HRMS calcd $(M+H)^+$: 794.3940; found: 794.3926. LC–MS Purity System A: t_R = 7.05 min, 97%; System B: t_R = 7.48 min, 97%.

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