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Discovery of a Potent and Selective Noncovalent Linear Inhibitor of the Hepatitis C Virus NS3 Protease (BI 201335)

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C-Terminal carboxylic acid containing inhibitors of the NS3 protease are reported. A novel series of linear tripeptide inhibitors that are very potent and selective against the NS3 protease are described. A substantial contribution to the potency of these linear inhibitors arises from the introduction of a C8 substituent on the B-ring of the quinoline moiety found on the P2 of these inhibitors. The introduction of a C8 methyl group results not only in a modest increase in the cell-based potency of these inhibitors but more importantly in a much better pharmacokinetic profile in rats as well. Exploration of C8-substitutions led to the identification of the bromo derivative as the best group at this position, resulting in a significant increase in the cell-based potency of this class of inhibitors. Structure−activity studies on the C8-bromo derivatives ultimately led to the discovery of clinical candidate **29** (BI 201335), a very potent and selective inhibitor of genotype1 NS3 protease with a promising PK profile in rats.

Hepatitis C virus (HCV) infects an estimated 130−170 million people worldwide[1] and is one of the major reasons for liver transplantation.[2] Although the virus was discovered over 20 years ago,[3] no direct-acting antiviral has yet reached the market. Current therapy consists of treatment with pegylated interferon in combination with ribavirin.[4] This treatment is usually accompanied by side effects and, most importantly, is only effective in ∼40−50% of the patients infected with HCV genotype 1. The quest for virus-specific therapies to treat HCV infections began shortly after discovery of the virus and continues to be major focus of pharmaceutical research.

HCV is a positive strand RNA virus belonging to the Flaviviridae family. The HCV genome consists of a 9.6 kb RNA which encodes a polyprotein of ∼3000 amino acids. This polyprotein is cleaved co- and post-translationally by both host and viral proteases. The structural proteins are processed by host peptidases, whereas the nonstructural (NS) proteins are processed by two virally encoded proteases, the NS2/3 and the NS3 proteases. The NS2/3 protease is responsible for a single cleavage between NS2 and NS3, while the NS3 protease is responsible for the release of the remaining downstream nonstructural proteins.[5] Several viral proteins have been shown to be essential for viral replication in chimpanzees and are thus considered validated targets for antivirals.[6]

The NS3 protease, located at the N-terminal third of the NS3 protein, is a 180-amino acid chymotrypsin-like serine protease, and it was one of the first viral proteins investigated as a target for antiviral development.[7] In 2002, the first proof-of-concept in man for a direct acting anti-HCV drug was achieved with the Boehringer Ingelheim NS3 protease inhibitor BILN 2061 (ciluprevir, **1**)[8,9] To date, no HCV inhibitor has reached the market, although several compounds are currently in clinical trials, with the NS3 protease inhibitors telaprevir[10] and boceprevir,[11] in phase III, being the most advanced.

Inhibitors of serine proteases are typically peptidic compounds containing an electrophilic moiety that reacts with the active site serine to form a reversible or irreversible covalent bond.[12] For example, telaprevir and boceprevir both feature α-ketoamides that form a covalent reversible bond with the active site residue serine 139.[13] A distinctive feature of the NS3 protease is that it is also susceptible to product inhibition by the N-terminal cleavage product of peptide substrates.[14,15] The carboxylic acid terminus of cleavage products can establish crucial interactions with the enzyme active site, which are unusual among serine proteases and thus also impart selectivity with respect to other serine proteases.[16,17] These are noncovalent inhibitors that have only ionic interactions with the catalytic site on the NS3 protease

We have reported several series of C-terminus carboxylic acid containing HCV NS3 protease inhibitors, initially leading to the discovery of **1**,[18] a compound belonging to noncovalent series of inhibitors (Table 1) and containing (1*R*,2*S*)-1-amino-2-vinylcyclopropylcarboxylic acid (vinyl-ACCA)[19] as the P1[20] residue. However, the development of this compound was discontinued because of the observation of cardiotoxicity in high-dose monkey toxicology studies.[21] These discoveries fueled an intensive effort to discover novel, noncovalent NS3 protease inhibitors.[22] Several compounds from these studies have entered clinical development. Clinical candidates RG-7227/ITMN-191,[23] TMC43530,[24] MK-7009,[25] and BMS-650032 all belong to this class of noncovalent inhibitors containing a derivative of vinyl- or ethyl-ACCA at P1 and a cyclopropylacylsulfonamide at P1′.

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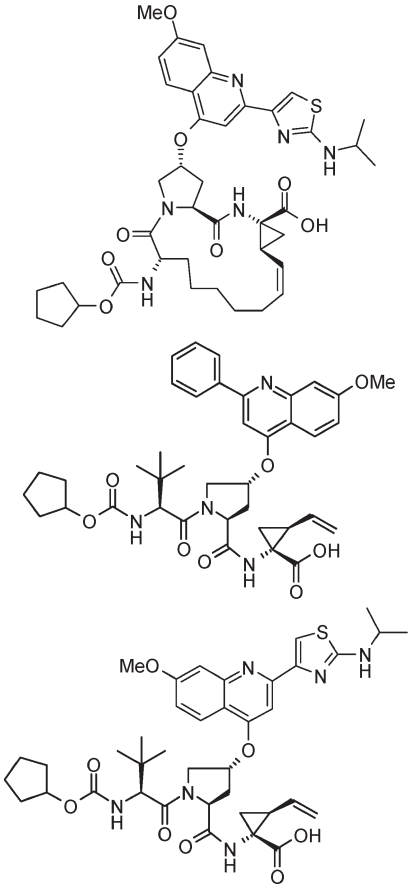
Table 1. Early Inhibitors of the HCV NS3 Protease



1 (BILN 2061)
IC_{50} = 0.003 μM
EC_{50} = 0.002 μM

Compound 2
IC_{50} = 0.014 μM
EC_{50} = 0.55 μM

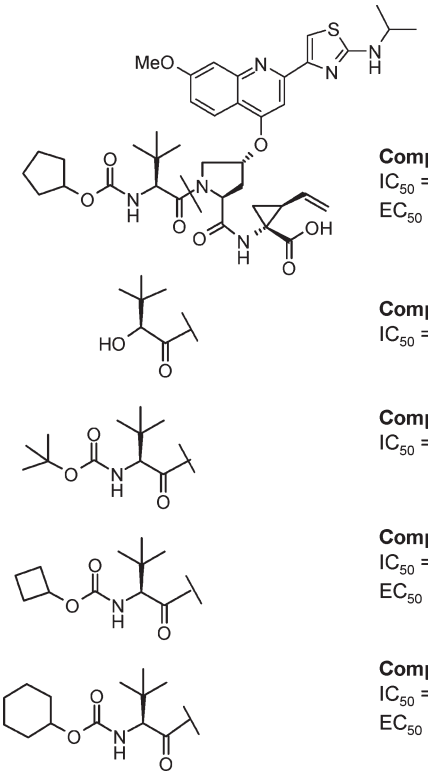
Compound 3
IC_{50} = 0.014 μM
EC_{50} = 0.045 μM

We decided to continue our work on the C-terminal carboxylic acid, vinyl-ACCA containing inhibitors, since in addition to providing very good potency, it also provides excellent selectivity and better solubility than observed for other classes of inhibitors. In addition to the macrocyclic inhibitor **1**, we have also published our work on a related series of linear inhibitors, with compound **2** (Table 1) being representative of this class.[26] One advantage of the linear series of inhibitors lies in the fact that the synthetic challenges and costs associated with the production of the drug substance are significantly reduced.

In an attempt to merge both series, we introduced the quinoline moiety found in **1** into the linear derivative **2**. This resulted in compound **3** (Table 1) which displayed more than a 10-fold improvement in potency in the replicon assay, providing the first noncovalent linear tripeptide inhibitor with cellular activity below 100 nM. With this encouraging result, our goal was to further increase the cell-based potency of this linear series while evaluating and improving its ADME/PK[a] profile. In this paper, we report our optimization studies that have focused on the N-terminal end of the molecule (capping group) and the P2 aminothiazolquinoline moiety that have culminated in the discovery of compound **29** (BI 201335), a potent and selective noncovalent linear tripeptide inhibitor currently being investigated in phase IIb clinical trials.

[a] Abbreviations: ADME, administration, distribution, metabolism, and excretion; $AUC_{0-\infty}$, area under the curve; DCM, dichloromethane; DIPEA. diisopropylethylamine; DMAP, dimethylaminopyridine ; DMSO, dimethyl sulfoxide; EtOAc, ethyl acetate; HPLC, high pressure liquid chromatography; PK, pharmacokinetic; MES, 2-(*N*-morpholino)ethanesulfonic acid; TBTU, *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate; TCEP, tris(2-carboxyethyl)phosphine; TFA, trifluoroacetic acid; THF, tetrahydrofuran; Tris, tris(hydroxymethyl)aminomethane.

Table 2. Capping Group Optimization



Compound 3
IC_{50} = 0.014 ± 0.002 μM
EC_{50} = 0.045 ± 0.019 μM

Compound 15
IC_{50} = 0.320 ± 0,063 μM

Compound 16
IC_{50} = 0.043 ± 0.008 μM

Compound 17
IC_{50} = 0.012 ± 0.002 μM
EC_{50} = 0.110 ± 0.030 μM

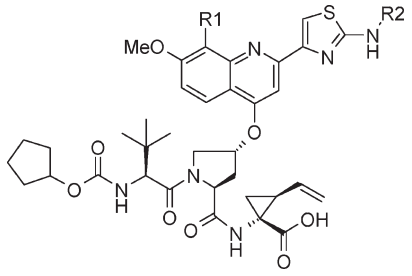
Compound 18
IC_{50} = 0.018 ± 0.004 μM
EC_{50} = 0.090 ± 0.018 μM

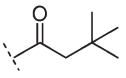
Synthesis of Inhibitors

The synthesis of the compounds shown in Table 2 was performed in solution by sequential coupling of each amino acid derivative using a previously described procedure.[18,27] Since most of our SAR efforts focused on variations of the 4*R*-hydroxyproline substituents, represented by the compounds shown in Tables 3 and 5, we wanted to develop the synthesis of an advanced intermediate that would allow us to introduce variations of this group as late as possible in the synthetic sequence. Tripeptide **7** (Scheme 1) containing a good leaving group at the 4-oxoproline was chosen as such an intermediate. The desired compounds shown in Tables 3 and 5 were then synthesized by introducing, via an S_N2 reaction, the required 2-carbomethoxy-4-hydroxyquinoline derivative resulting in an inversion of configuration at the 4-hydroxyproline. The synthesis of tripeptide **6** was performed in solution by sequential coupling of each amino acid derivative, as described previously.[26] The synthesis of (1*R*,2*S*)-1-amino-2-vinylcyclopropylcarboxylic acid methyl ester used in the preparation of these compounds and the synthesis of dipeptide **5** have also both been reported.[28]

Coupling of dipeptide derivative **5** to the *tert*-leucine cyclopentyl carbamate **4** yielded tripeptide **6**. Next, the *p*-nitrobenzoate group in **6** was hydrolyzed and the resulting free hydroxyl group was converted to the brosylate **7** by treatment with *p*-bromobenzensulfonyl chloride. The brosylate group was displaced with the appropriately 8-substituted 2-carbomethoxy 4-hydroxy-7-methoxyquinoline derivatives **11a**−**e** to afford tripeptides **12a**−**e**. Next, conversion of the quinoline 2-carbomethoxy moiety of tripeptides **12a**−**e** into the final aminothiazole derivatives was carried out by a selective hydrolysis of the methyl ester, followed by conversion of the resulting carboxylic acid to the various diazoketones and then to the corresponding bromoketones **13a**−**e**. Conversion to diazoketones is carried out using diazomethane, and extreme

Table 3. Impact of Substitution on the A-Ring



Compound	R1	R2	IC_{50}(nM)	EC_{50}(nM)
3	H		14 ± 2	45 ± 19
19	H		5 ± 1	34 ± 20
20	H		17± 8	68 ± 26
21	Me		15 ± 3	40 ± 6
22	Me		8 ± 2	19 ± 7
23	Me		10 ± 2	17 ± 8

caution should be used since diazomehane gas may explode violently. The bromoketones **13a**−**e** were then treated with the properly substituted thioureas **14a**−**g** to produce the required aminothiazole derivatives. Finally the C-terminal esters were hydrolyzed under basic conditions to produce the compounds shown in Tables 3 and 5.

The synthesis of different 8-substituted 2-carbomethoxy 4-hydroxy-7-methoxyquinoline derivatives was carried out from the corresponding anilines according to a reported procedure[29] shown in Scheme 2.

Commercially or readily available anisidines (**8a**−**e**) were treated with dimethylacetylene dicarboxylate **9** to form aducts **10a**−**e** which, upon heating at ~250 °C, underwent cyclization to produce the different 8-substituted 2-carbomethoxy 4-hydroxy-7-methoxyquinoline derivatives **11a**−**e**.

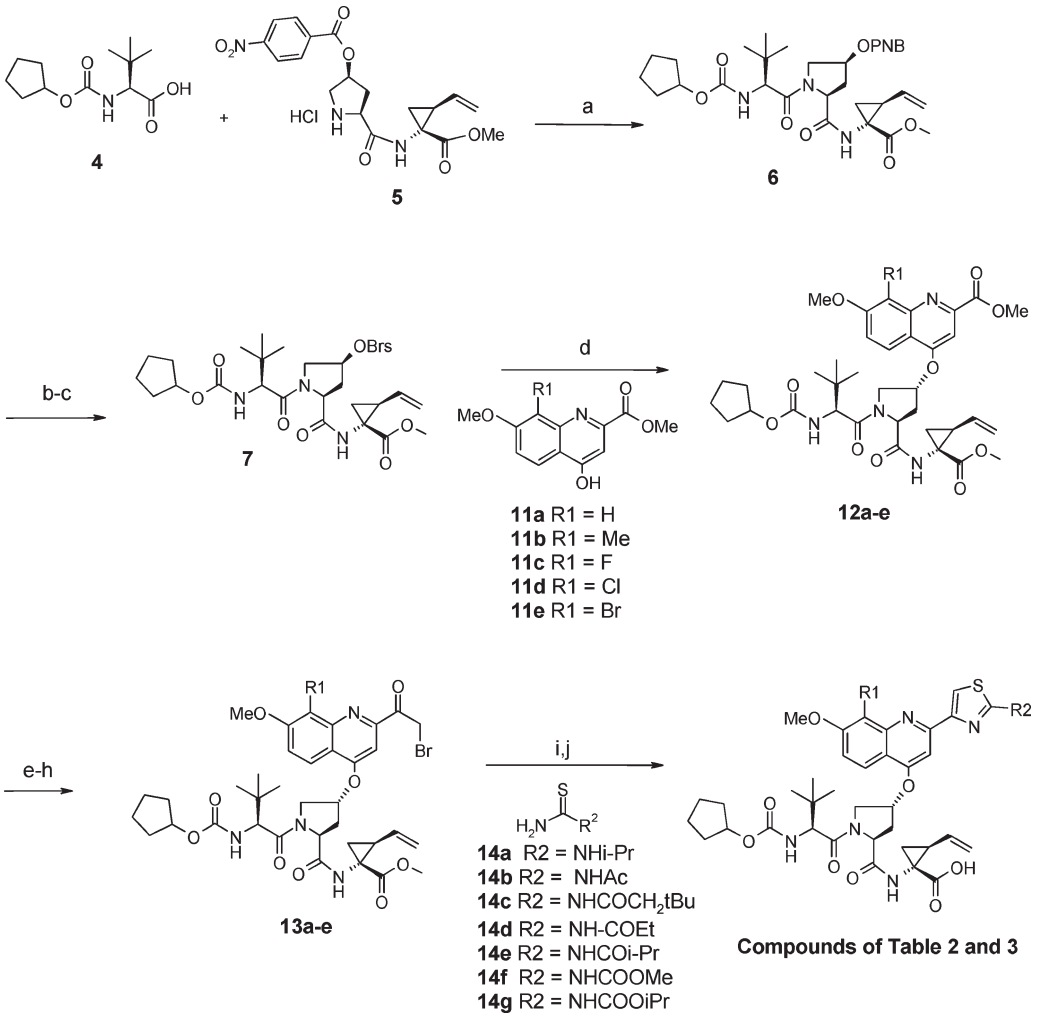
Results and Discussion

Compound **3** (Table 2), which resulted from the introduction of the compound **1** quinoline moiety into our linear, tripeptidyl series of inhibitors, was selected as the starting point for further optimization. From the outset, the peptide backbone was retained, as we had already shown that it makes optimal interactions with the enzyme which mimic the canonical substrate binding mode, with both the NH and CO groups of the P3 residue and the NH group of the P1 moiety being involved in key hydrogen bonds with the protein.[26] In addition, both the vinyl-ACCA derivative at P1 and the *tert*-butylglycine moiety at P3 were kept constant, as they already had been subjected to extensive optimization in the past and found to be optimal. The C-terminal carboxylic acid makes key interactions with the catalytic triad and the oxyanion hole,[17] providing not only good potency but also specificity toward NS3 versus human and other serine proteases.[16] In addition, another advantage over the other classes of reported NS3 protease inhibitors is the increase in solubility at high pH for this series. The *tert*-leucine found at P3 was also maintained. One of the main roles of the P3 *tert*-butyl side chain is to rigidify the peptidic backbone and to favor the overall extended conformation, found in the bound state, for the inhibitor in solution.[26] Therefore, the current study focused essentially on optimizing both the capping group and the P2 aminothiazolquinoline moiety. First, truncating the compound to the hydroxyl dipeptide **15** (Table 2) resulted in a substantial loss in potency. Urea derivatives were also evaluated but, as observed in previous series, did not provide any significant advantage.[18,26] Carbamate substituents, other than the cyclopentyl, were next investigated. The derivative **16** containing a *tert*-butyl carbamate was found to be less potent, while the corresponding four-membered ring (**17**) and six-membered ring (**18**) carbamates displayed similar potency to the cyclopentyl analogue (Table 2). However, in the cellular assay the cyclopentyl derivative **3** was found to be the best, displaying a 2-fold improved activity compared to the other cyclic carbamates. Ultimately, this group was maintained throughout our subsequent SAR efforts, since we had shown previously that it fits well in the S4 binding pocket and also imparts good properties to the inhibitor including chemical stability.[26]

We evaluated the pharmacokinetic properties of reference compound **3** in rats in order to see if the linear tripeptide series had the potential to provide good oral bioavailability. Compound **3** which was quite stable ($T_{1/2}$ > 100 min) upon incubation in both human and rat liver microsomes was found to have a good pharmacokinetic profile in rats, with an oral bioavailability of 54% (Table 4). Specifically, compound **3** displayed a maximum plasma concentration (C_{max}) of 0.79 μM and an $AUC_{0-\infty}$ of 2.4 μM·h after an oral dose of 5 mg/kg in rats, as well as a half-life ($T_{1/2}$) of 2.6 h and a moderate clearance (Cl) of 24 (mL/min)/kg following an intravenous (iv) dose of 2 mg/kg. Encouraged by this very promising profile, we focused on improving the cell-based potency of this linear tripeptide series, setting a target of EC_{50} < 10 nM while maintaining/improving ADME/PK properties. On the basis of past success with the macrocyclic series,[18] we felt that modifying the P2 aminothiazol-quinoline moiety might also represent the most attractive way of achieving this goal.

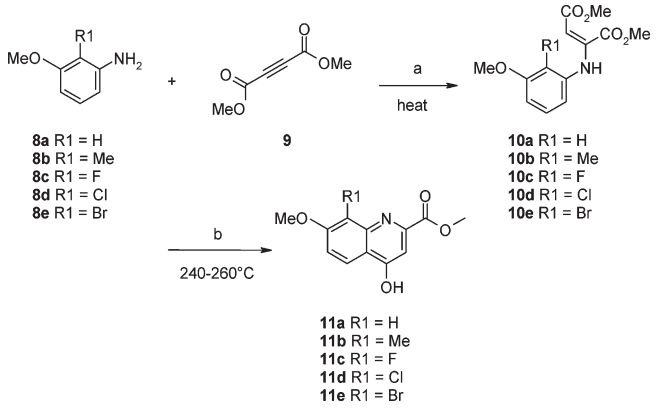
A quick evaluation of the SAR at the aminothiazol moiety revealed that an acetyl group as in compound **19** was well tolerated providing a compound with slightly improved potency over the reference compound **3** bearing an isopropyl, as shown in Table 3. Increasing the size of the acyl group to a *tert*-butylacetyl moiety as in **20** led to a partial loss in both the enzymatic and cellular potencies. At this point, the potency of these inhibitors still had to be improved by at least 10-fold, and we reasoned that this gain would likely not come solely through modification of the aminothiazol substituent. We had previously shown in a tetrapeptide series that substitutions around the B-ring of the quinoline were only tolerated at the C7 and C8 positions, with the introduction of either a C7- or a C8-methoxy producing a significant increase in potency and giving rise to inhibitors with almost equipotent activities.[26] Unfortunately, combining both the C7- and C8-methoxy substituents into the same analogue was found to be detrimental

Scheme 1. General Synthetic Route for Inhibitors of Tables 3 and 5[a]



[a] Reagents and conditions: (a) TBTU, DIPEA, DCM, room temp, 14 h; (b) 1 equiv of LiOH, H_2O/THF, 0 °C, 3 h; (c) brosyl chloride, DMAP, DCM, 0 °C to room temp; (d) **11a**−**11c**, Cs_2CO_3, NMP, 70 °C, 7 h; (e) 1.1 equiv of 1 N NaOH, H_2O−THF, 0 °C to room temp; (f) IBCF, TEA, THF, 0 °C to room temp; (g) CH_2N_2, Et_2O, 0 °C to room temp; (h) HBr (48% aq), THF; (i) **14a**−**g**, *i*-PrOH, 50 °C, 1 h; (j) LiOH, H_2O−MeOH−THF.

Scheme 2. Synthesis of the Different 8-Substituted 2-Carbomethoxy-4-hydroxy-7-methoxyquinoline Derivatives[a]



[a] Reagents and conditions: (a) **8a**−**e**, MeOH, 70 °C, 5 h; (b) Ph_2O, 240 °C, 6−8 min.

to activity, not providing the desired additive effect. Nevertheless, we felt that it might be worth revisiting disubstitution of the quinoline ring at C7 and C8, with the introduction this time of smaller substituents at C8 while maintaining the methoxy moiety at C7. Specifically, the introduction of a methyl group at C8 was found to be well tolerated in both the alkyl and acyl aminothiazol series (Table 3). Indeed, the introduction of a C8-methyl to the reference analogue **3** resulted in **21**, an equipotent inhibitor. Interestingly, the introduction of the C8-methyl on the aminothiazole acyl derivative **19** resulted in an increase in the cell-based potency of the corresponding inhibitor (**22**, $EC_{50} = 19$ nM). Extending the acetyl chain by one carbon to the propionyl (compound **23**) was also well tolerated, giving rise to an equipotent analogue. Compounds **22** and **23** represented our first examples of acyclic tripeptide inhibitors displaying $EC_{50} < 20$ nM in the replicon assay.

Encouraged by these results, we then evaluated the pharmacokinetic parameters of these new analogues in order to see if we had been able to maintain or improve their overall PK profile through the simple chemical modifications we had introduced. Surprisingly, compound **19**, which was found to be stable ($T_{1/2} > 100$ min) upon incubation in both human and rat liver microsomes, did not achieve significant plasma levels when dosed orally in rats at 5 mg/kg, in contrast to the reference derivative **3**. We generally found throughout our optimization efforts that the rat oral absorption of these linear compounds was greatly influenced by the nature of the substitution on the amino

Table 4. Pharmacokinetic Parameters in Rats after Oral and Intravenous Administration

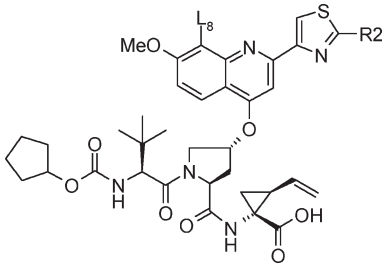
	oral, 5 mg/kg		iv, 2 mg/kg			
compd	C_{max} (μM)	$AUC_{0-\infty}$ (μM·h)	$T_{1/2}$ (h)	V_{ss} (L/kg)	Cl ((mL/min)/kg)	F (%)
3	0.79	2.4	2.6	3.7	24	54
20	1.1	2.8	1.2	0.83	14	39
23	0.82	3.5	1.7	1.8	15	56

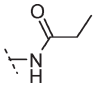
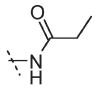
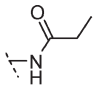
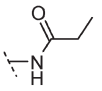
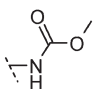
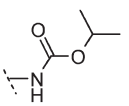
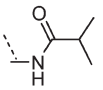
group of the aminothiazole moiety. Small alkyl (e.g., methyl) or acyl groups (such as in **19**) produced quite potent compounds that unfortunately displayed very low oral absorption in rats or higher species (data not shown). Increasing the size of the alkyl or acyl group led, in most cases, to an increase in rat oral absorption. For instance, compounds containing either an isopropyl such as reference compound **3** or a *tert*-butylacetyl moiety as **20** showed good oral PK profile when dosed in rats as highlighted in Table 4. Interestingly, while an oral dose of 5 mg/kg showed a similar profile for both compounds, an intravenous dose of 2 mg/kg led to somewhat different parameters, with **20** showing a slower clearance (14 (mL/min)/kg) and a smaller volume of distribution (V_{ss} = 0.83 vs 3.7 L/kg).

As mentioned earlier, the introduction of a C8-methyl on the quinoline ring of the aminothiazol acyl series resulted in an improvement in the cell-based potency of these inhibitors, with **22** and **23** both displaying EC_{50} < 20 nM. However, the full benefit of introducing the C8-Me became more evident when we profiled the ADME properties of these inhibitors. For instance, compound **22**, when dosed orally in rats at 4 mg/kg, achieved plasma concentrations of 0.3 and 0.4 μM at 1 h and 2 h postdosing. This represented a clear advantage over compound **19** which did not show significant plasma levels (< 0.02 μM) at a similar dose. Similarly, when compound **21** was dosed orally in rats (4 mg/kg), respective plasma concentrations of 0.9 and 1.2 μM were detected at 1 and 2 h time points postdosing. Compound **23**, containing a propionyl group instead of the acetyl group, showed the best overall profile, and its full rat PK evaluation is shown in Table 4. Very good oral absorption was observed for this compound with a C_{max} of 0.82 μM and an $AUC_{0-\infty}$ of 3.5 μM·h achieved after administration of dose of 5 mg/kg. Its iv profile was also quite interesting with a half-life ($T_{1/2}$) of 1.7 h and a clearance (Cl) of 15 (mL/min)/kg following a 2 mg/kg dose. In addition to displaying a good overall PK profile in rat, with a bioavailability of 56%, another advantage of compound **23** over the other analogues was its potency of < 20 nM in the replicon assay. Analogue **23** therefore became our new reference compound.

Having observed an increase in potency and rat bioavailability by introducing the C8-Me, we wanted to investigate the effect of other substituents such as halogen at this position. As shown in Table 5, replacement of the C8-methyl moiety of **23** by a fluoro, chloro, or bromo substituent was well tolerated, providing inhibitors with equipotent activities in the enzymatic assay (IC_{50} = 7 nM). The effect of these substituents on the cellular potency was slightly different, with the C8-fluoro analogue **24** being 2-fold less potent while both the C8-chloro and C8-bromo analogues (**25** and **26**) showed improved activities. Ultimately, the introduction of the C8-bromo substituent was found to be optimal, with analogue **26** exhibiting an EC_{50} of 5 nM which represented our first observation of single-digit nanomolar activity in the replicon assay for a linear tripeptide inhibitor. The effect of the C8-bromo substituent on the overall ADME properties was subsequently evaluated and is shown in Table 6.

Table 5. Effect of C8-Substitution on the Potency of the Inhibitors



Compound	L8	R2	IC_{50} (nM)	EC_{50} (nM)
23	Me		10 ± 2	17 ± 8
24	F		7 ± 2	36 ± 10
25	Cl		7 ± 2	11± 2
26	Br		7 ± 2	5 ± 1
27	Br		6 ± 1	3 ± 1
28	Br		6 ± 2	6 ± 2
29 (BI 201335)	Br		3 ± 1	3 ± 1

Compound **26** was found to have human and rat liver microsome stablilities ($T_{1/2}$ > 300 min) comparable to that of reference compound **23**. However, when the bromo derivative **26** was dosed orally in rats, a significantly lower overall plasma exposure was observed. Indeed, after oral dosing at 5 mg/kg, the C_{max} (0.13 μM) and $AUC_{0-\infty}$ (0.34 μM·h) achieved for **26** (Table 6) were found to be considerably lower (7- to 10-fold) than those observed for the C8-methyl analogue **23** (Table 4). Following an iv dose of 2 mg/kg, a similar half-life and volume of distribution were observed for both compounds, although **26** showed a much faster clearance (28 (mL/min)/kg), which may have contributed to the substantial decrease in overall bioavailability (F = 11%). Having nevertheless achieved the desired level of potency with derivative **26**, we decided to keep the C8-bromo substituent and revisit the SAR at the amonothiazole moiety with the goal of finding a substituent that might display a better balance

Table 6. Pharmacokinetic Parameters in Rats after Oral and Intravenous Administration

	oral, 5 mg/kg		iv, 2 mg/kg			
compd	C_{max} (μM)	$AUC_{0-\infty}$ (μM·h)	$T_{1/2}$ (h)	V_{ss} (L/kg)	Cl ((mL/min)/kg)	F (%)
26	0.13	0.34	1.7	1.8	28	11
28	0.13	0.9	2.9	1.2	6	29
29	0.6	1.7	1.2	1.9	20	40

between potency and ADME profile. A wide variety of substituents were tolerated on the aminothiazole moiety in the C8-bromo series, which ultimately enabled us to identify several derivatives that fulfilled the desired potency criteria (EC_{50} < 10 nM). Table 5 highlights three of these inhibitors, such as the methyl and isopropyl carbamate derivatives **27** and **28**, respectively, and the acyl analogue **29**. This last compound displayed the best overall potency with IC_{50} and EC_{50} values of 3 nM. Moreover, the in vitro ADME profile of these three compounds revealed that they were all quite stable in human ($T_{1/2}$ > 100 min) and rat liver microsomes ($T_{1/2}$ > 300 min). Unfortunately, the two aminothiazole carbamate derivatives did not achieve good plasma exposure when dosed orally in rats, as was earlier observed for compound **26**. For instance, analogue **27** showed a plasma level of only 0.1 μM at 1 h postdosing (4 mg/kg oral dose). Only a marginal improvement was observed for compound **28** over **26** when its full PK profile was evaluated in rat following an oral dose of 5 mg/kg (C_{max} = 0.13 μM, $AUC_{0-\infty}$ = 0.90 μM·h) and a 2 mg/kg iv dose ($T_{1/2}$ = 2.9 h, Cl = 6 (mL/min)/kg), resulting in an oral bioavailability of 29% (Table 6). However, the aminothiazole acyl derivative **29** was demonstrated to possess an improved PK profile when evaluated at these oral and intravenous doses (Table 6). Indeed, the oral exposure was significantly improved with respect to the other C8-bromo containing derivatives with a C_{max} of 0.60 μM, $AUC_{0-\infty}$ = 1.7 μM·h. The $T_{1/2}$ was found to be 1.2 h with moderate clearance. The overall oral bioavailability in rats for compound **29** was 40%. Although the PK profile of **29** was not as good as that of **23** (F = 56%), its superior potency in both the enzymatic and replicon assays made it a more interesting candidate for further development. A further beneficial feature of compound **29** lies in the fact that the compound partitions favorably into the liver in rats with a 40-fold increase in liver versus plasma concentration after oral dosing. Moreover, differences in the cross-species PK profile of these compounds further supported the selection of **29** (manuscript in preparation). For all these reasons **29** was selected for further advancement in development, and the complete preclinical profile of this compound will be published elsewhere. Compound **29** is currently being evaluated in phase IIb clinical trials.

Conclusion

Very potent and specific linear tripeptide inhibitors of the NS3 serine protease have been identified. Our initial goal of obtaining linear inhibitors with cell-based potencies less than 10 nM and with good overall ADME profiles was achieved. Crucial to these achievements was the discovery of the impact of the C8-substituent of the P2 quinoline moiety of these inhibitors on the properties of the present inhibitors. The introduction of a C8-Me group was beneficial to increasing the plasma exposure in rats after oral dosing and, in some cases, also improved the potency of the inhibitors. Scanning different substituents at the C8-position of the quinoline revealed that the bromo group was optimal for increasing the cell-based potency of this series. Several derivatives with different substitutions at the aminothiazole moiety met our potency criteria. Differentiation of these inhibitors was possible based on their rat PK profiles, and compound **29** was ultimately selected for development. Initial four-week antiviral results for this promising drug candidate have been reported in both treatment-naive patients and in patients who failed previous treatment with current gold-standard therapy.[30] Compound **29** is now being evaluated in phase IIb clinical trials, and this compound could become the first noncovalent linear NS3 protease inhibitor available for treatment of HCV patients

Experimental Section

General. All commercially obtained solvents and reagents were used as received without further purification. All reactions were carried out under an atmosphere of argon. Temperatures are given in degrees Celsius. Solution percentages express a weight to volume relationship, and solution ratios express a volume to volume relationship, unless stated otherwise. NMR spectra were recorded on a Bruker AVANCEII (400 MHz for ^{1}H NMR) spectrometer and were referenced to either DMSO-d_6 (2.50 ppm) or $CDCl_3$ (7.27 ppm). Data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, br = broad, m = multiplet), coupling constant (J, reported to the nearest 0.5 Hz), and integration. Mass spectra were obtained from a Micromass AutoSpec instrument using FAB as ionization mode with NBA as a matrix support. Purification of crude material was performed either by flash column chromatography or by using a CombiFlash Companion using RediSep Silica or SilicaSep columns according to preprogrammed gradient and flow rate separation conditions in hexane/EtOAc or DCM/MeOH. The final compounds were purified either by column chromatography to yield the neutral compound or by preparative HPLC in a Waters 2767 sample manager with pumps 2525, column fluidics organizer (CFO), PDA detector 2996, and MassLynx 4.1 using either a Whatman Partisil 10-ODS-3 column, 2.2 cm × 50 cm, or a YMC Combi-Prep ODS-AQ column, 50 mm × 20 mm i.d., S, 5 μm, 120 Å, and a linear gradient program from 2% to 100% AcCN/water (0.06% TFA). Fractions were analyzed by analytical HPLC, and the pure fractions were combined, concentrated, frozen, and lyophilized to yield the desired compound as the trifluoroacetate salt. The lyophilized TFA salt was dissolved in water, and either 2 N or 10 N NaOH was added dropwise until a pH of 14 was maintained. The pH was readjusted to 7 with 2 N HCl and the neutral product extracted into EtOAc (3×). The combined extracts were washed with water (2×) and brine (1×), dried over $MgSO_4$, filtered, and evaporated to dryness. The obtained solid was dissolved in acetonitrile/water, frozen, and relyophilized to provide the neutral product. The neutral inhibitor HPLC purity was measured by using an Waters Alliance 2695 separation module with a Waters 2487 dual λ absorbance detector. A YMC Combiscreen ODS-AQ HPLC column was used: 50 × 4.6 mm i.d.; S-5 μm, 12 nm (catalog no. CCAQS05-0546WT, AQ-300-CC). Linear gradient at 220 nm was as follows: 5−100% B; solvent A, 0.06% TFA/H_2O; sovlent B, 0.06% TFA/CH_3CN. Parameters of the analytical C_{18} reversed phase column and the eluting system were as follows: 0.06% TFA in water−0.06% TFA in acetonitrile gradient (20−100% acetonitrile over 30 min). All compounds tested in vitro were determined to be of >95% purity by HPLC.

Enzymatic Assays. Biochemical assays were carried out as described previously.[31] In brief, reactions comprised 0.5 nM genotype 1b NS3-NS4A enzyme,[32] 5 μM fluorogenic depsipeptide substrate anthranilyl-DDIVPAbu[C(O)-O]AMY(3-NO_2)-TW-OH, and inhibitor in a reaction buffer composed of 50 mM Tris-HCl, pH 8.0, 0.25 M sodium citrate, 0.01% *n*-dodecyl-β-D-maltoside, 1 mM TCEP, and 5% DMSO. Mixtures were incubated at 23 °C for 60−70 min and terminated by the addition of 1 M MES (pH 5.8). Fluorescence of the N-terminal product anthranilyl-DDIVP-Abu was measured using a PolarStar Galaxy plate reader (BMG). Calculated percent inhibition at each inhibitor concentration was then used to determine the median effective concentration (IC_{50}) by the NLIN procedure of SAS (Statistical Software System; SAS Institute Inc., Cary, NC).

Cell-Based Replicon Assay. The bicistronic luciferase reporter replicon, encoding the Con1 genotype 1b NS2-NS5B coding region, and the experimental procedures for measuring EC_{50} values in the experiments reported above have been described elsewhere.[33] Compounds were incubated with cells for 72 h, and the relative levels of luciferase present were determined using the Bright-Glo luciferase substrate (Promega) on a Packard Topcount instrument EC_{50} values were determined by the nonlinear regression routine NLIN procedure of SAS (EC_{50}).

Pharmacokinetics. All protocols involving animal experimentation were reviewed and approved by the local Animal Care and Use Committee. In-life procedures were in compliance with the Guide for the Care and Use of Laboratory Animals from the Canadian Council of Animal Care. All rat PK and distribution studies were performed at Boehringer Ingelheim (Canada) Ltd. Rat pharmacokinetic studies were performed using male Sprague−Dawley rats (275−300 g, Charles River, St-Constant, Quebec, Canada). Animals were fasted overnight with access to 10% dextrose in water. Standard oral PK with individual compounds were performed at an oral dose of 5 mg/kg in a dosing volume of 10 mL/kg of a vehicle consisting of 0.5% Methocel and 0.3% Tween-80. Blood samples were collected from the canulated right carotid at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, and 8 h postdosing, and plasma samples from three rats were pooled at each time point. Intravenous PK experiments were performed at a dose of 2 mg/kg, with an additional sample collection time at 5 min. For rapid oral PK screening studies, a cassette of four compounds (4 mg/compound) were dosed in two rats and plasma samples collected only at 1 and 2 h postdosing. Extracts for LC−MS analysis were obtained from plasma samples by solid-phase extraction. The temporal profiles of drug concentrations in plasma were analyzed by noncompartmental methods using WinNonlin (version 3.1; Scientific Consulting, Inc., Cary, NC).

2-Carbomethoxy-4-hydroxy-7-methoxy-8-methylquinoline (11b). Dimethyl acetylenedicarboxylate **9** (3.6 mL, 29.3 mmol) was added dropwise to a solution of 2-methyl-3-methoxyaniline **8b** (3.95 g, 28.8 mmol) in MeOH (100 mL) (reaction is exothermic). The mixture was heated at a gentle reflux for 5 h, cooled, and concentrated under vacuum. The crude material was purified by column chromatography (SiO_2) to provide diester **10b** (6.5 g, 80.8%). Diester **10b** (6.5 g, 23.3 mmol) was then dissolved in diphenyl ether (12 mL) and the reaction mixture placed into a preheated sand bath at a bath temperature of 350−400 °C. Once the reaction mixture attained an internal temperature of 240 °C (MeOH evolution observed at 230−240 °C), a count of 6 min was begun before the bath was removed and the reaction mixture allowed to cool to room temperature. When the mixture cooled, the product precipitated. The mixture was diluted with diethyl ether, filtered, and dried to give a tan colored solid (3.48 g crude). The crude material was purified by silica gel chromatography to provide **11b** (2.1 g, 37%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81 (s, 1H), 8.25 (d, J = 9.0 Hz, 1H), 7.05 (d, J = 9.0 Hz, 1H), 6.92 (s, 1H), 4.06 (s, 3H), 3.99 (s, 3H), 2.38 (s, 3H). MS (ESI): 246.0 $(M - H)^-$, 248.1 $(M + H)^+$. HPLC homogeneity: 95%.

2-Carbomethoxy-8-fluoro-4-hydroxy-7-methoxyquinoline (11c). Starting with 2-fluoro-3-methoxyaniline **8c** and using the procedure described above gave **11c**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.96 (s, 1H), 8.10 (dd, J = 9.0, 1.5 Hz, 1H), 7.09 (dd, J = 9.0, 8.4 Hz, 1H), 6.92 (s, 1H), 4.06 (s, 3H), 4.05 (s, 3H). MS (ESI): 249.9 $(M - H)^-$, 252.0 $(M + H)^+$. HPLC homogeneity: 97%.

2-Carbomethoxy-8-chloro-4-hydroxy-7-methoxyquinoline (11d). Starting with 2-chloro-3-methoxyaniline **8d** and using the procedure described above gave **11d**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.47 (s, 1H), 8.32 (d, J = 8.8 Hz, 1H), 7.18 (s, 1H), 7.12 (d, J = 8.7 Hz, 1H), 4.06 (s, 3H), 4.05 (s, 3H). MS (ESI): 265.9 $(M - H)^-$, 267.8 $(M + H)^+$. HPLC homogeneity: >99%.

2-Carbomethoxy-8-bromo-4-hydroxy-7-methoxyquinoline (11e). Starting with 2-bromo-3-methoxyaniline **8e** and using the procedure described above gave **11e**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.37 (s, 1H), 8.33 (d, J = 8.9 Hz, 1H), 7.06 (d, J = 8.9 Hz, 1H), 6.95 (s, 1H), 4.07 (s, 6H). MS (ESI): 310.0, 312.0 $(M - H)^-$, 312.0, 314.0 $(M + H)^+$. HPLC homogeneity: 98%.

Synthesis of Inhibitors (Compounds from Tables 3 and 5). The inhibitors from these tables were synthesized as outlined in the chemistry section of the manuscript. The synthetic sequence leading to the preparation of compound **29** serves as a representative example for the series.

***N*-[(Cyclopentyloxy)carbonyl]-L-*tert*-leucine (4).** To a suspension of carbonic acid cyclopentyl ester 2,5-dioxopyrrolidin-1-yl ester (9.00 g; 39.6 mmol) and *tert*-leucine (6.24 g; 47.5 mmol) in THF (350 mL) were added distilled water (100 mL) and triethylamine (16.6 mL, 119 mmol). The homogeneous solution was allowed to stir at room temperature for 2.5 h. The THF was evaporated and the aqueous residue further diluted with water (100 mL). The mixture was rendered basic by the addition of 1 N NaOH (25 mL, final pH >10) and then extracted with EtOAc (2 × 200 mL). The aqueous phase was then acidified with 1 N HCl (~70 mL, final pH <2) and the turbid solution extracted with EtOAc (2 × 200 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated to afford carbamate **3** (8.69 g) as a white solid. ^{1}H NMR (400 MHz DMSO-d_6): δ 12.46 (s, 1H), 7.11 (d, J = 8.9 Hz, 1H), 4.94 (bs, 1H), 3.78 (d, J = 8.9 Hz, 1H), 1.85−1.72 (m, 2H), 1.70−1.48 (m, 6H), 0.94 (s, 9H). MS (ESI): 241.8 $(M - H)^-$, 243.9 $(M + H)^+$, 265.9 $(M + Na)^+$. HPLC homogeneity: 95%.

***N*-[(Cyclopentyloxy)carbonyl]-3-methyl-L-valyl-(4*S*)-*N*-[(1*R*,2*S*)-2-ethenyl-1-(methoxycarbonyl)cyclopropyl]-4-hydroxy-L-prolinamide (6).** Carbamate **4** (6.15 g, 22.5 mmol) and TBTU (7.72 g, 24.7 mmol) were suspended in dichloromethane (100 mL) and rapidly stirred before the addition of DIPEA (3.92 mL, 22.5 mmol) at room temperature. After 10 min, a solution of (3*S*,5*S*)-5-{[(1*R*,2*S*)-2-ethenyl-1-(methoxycarbonyl)cyclopropyl]carbamoyl}-pyrrolidin-3-yl 4-nitrobenzoate (**5**) (10.39 g, 23.6 mmol) in anhydrous dichloromethane (100 mL) containing DIPEA (4.11 mL, 23.62 mmol) was poured into the reaction mixture. The resulting yellow solution was stirred for 14 h before being concentrated in vacuo. The resulting residue was diluted with EtOAc (450 mL) and washed with 0.05 N HCl (2 × 200 mL), saturated Na_2CO_3 (300 mL), and finally saturated brine (150 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated to afford tripeptide **6** as a pale yellow foam (15.68 g, quantitative). ^{1}H NMR (400 MHz, $CDCl_3$): about 90:10 mixture of cis−trans proline rotamers, major rotamer description; δ 8.27 (d, J = 8.4 Hz, 2H), 8.19 (d, J = 8.4 Hz, 2H), 7.96 (s, 1H), 5.77−5.66 (m, 1H), 5.62−5.56 (m, 1H), 5.29−5.15 (m, 2H), 5.15−5.04 (m, 2H), 4.82 (d, J = 9.0 Hz, 1H), 4.32−4.25 (m, 2H), 3.93 (d, J = 11.8 Hz, 1H), 3.58 (s, 3H), 3.04 (br d, J = 14.4 Hz, 1H), 2.34−2.25 (m, 1H), 2.10−2.01 (m, 1H), 1.96−1.54 (m, 9H), 1.41 (dd, J = 9.4, 5.5 Hz, 1H), 1.07 (s, 9H). MS (ESI): 627.4 $(M - H)^-$, 629.4 $(M + H)^+$, 652.4 $(M + Na)^+$. HPLC homogeneity: 96%.

***N*-[(Cyclopentyloxy)carbonyl]-3-methyl-L-valyl-(4*S*)-*N*-[(1*R*,2*S*)-2-ethenyl-1-(methoxycarbonyl)cyclopropyl]-4-hydroxy-L-prolinamide (7).** Tripeptide **6** (15.68 g, 24,97 mmol) was dissolved in THF (200 mL) and water (30 mL), and the resulting solution was cooled to 0 °C. A solution of lithium hydroxide monohydrate (1.18 g, 28.12 mmol) was

added over 3 min during vigorous stirring. After 3 h at 0 °C, the excess base was neutralized with 1 N HCl (final pH ~6) before the THF was evaporated. The resulting aqueous suspension (yellow gum) was extracted with EtOAc (2 × 200 mL) and washed with saturated $NaHCO_3$ (2 × 300 mL). The combined extracts were dried over $MgSO_4$ and concentrated to give a yellow foam. Silica gel chromatography using EtOAc as an eluent afforded the free alcohol as a white amorphous solid (9.77 g, 91%). The alcohol (9.77 g, 20.85 mmol) was combined with brosyl chloride (11.19 g, 43.79 mmol) and DMAP (254 mg, 2.09 mmol) in dichloromethane (75 mL) at 0 °C before being treated dropwise with triethylamine (10.2 mL, 72.98 mmol). The yellow solution was stirred 1 h at 0 °C and then slowly warmed to room temperature and stirred for 60 h. The reaction mixture was concentrated to dryness, diluted with EtOAc, and washed with saturated $NaHCO_3$, water, and saturated brine before being dried ($MgSO_4$), filtered, and concentrated to dryness. The crude material was purified by silica gel chromatography with a gradient of EtOAc in hexanes to provide the tripeptide **6** as a white foam (11.66 g, 74% over three steps). ^{1}H NMR (400 MHz, DMSO-d_6): about 84:16 mixture of cis−trans proline rotamers, major rotamer description; δ 8.58 (s, 1H), 7.92 (d, J = 8.6 Hz, 2H), 7.85 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 8.7 Hz, 1H), 5.68−5.56 (m, 1H), 5.23 (dd, J = 17.3, 1.6 Hz, 1H), 5.20−5.12 (m, 1H), 5.09 (dd, J = 10.3, 1.8 Hz, 1H), 4.94−4.89 (m, 1H), 4.36 (dd, J = 9.0, 4.7 Hz, 1H), 4.07−3.95 (m, 2H), 3.59 (dd, J = 11.7, 4.1 Hz, 1H), 3.56 (s, 3H), 2.43−2.27 (m, 1H), 2.09−1.99 (m, 2H), 1.84−1.70 (m, 2H), 1.69−1.46 (m, 7H), 1.25 (dd, J = 9.3, 5.3 Hz, 1H), 0.92 (s, 9H). MS (ESI): 698.1, 699.1 $(M - H)^-$, 698.2, 700.2 $(M + H)^+$. HPLC homogeneity: 99%.

***N*-[(Cyclopentyloxy)carbonyl]-3-methyl-L-valyl-(4*R*)-4-{[8-bromo-7-methoxy-2-(methoxycarbonyl)quinolin-4-yl]oxy}-*N*-[(1*R*,2*S*)-2-ethenyl-1-(methoxycarbonyl)cyclopropyl]-L-prolinamide (12e).** Tripeptide **7** (0.5 g, 0.71 mmol), bromoquinoline **11e** (234 mg, 0.75 mmol), and ground cesium carbonate (56 mg; 0.78 mmol) were dissolved in 1-methyl-2-pyrrolidinone (7.6 mL) before being heated to 70 °C (7 h). The solution was cooled to room temperature and poured into EtOAc before being washed with H_2O, saturated $NaHCO_3$, and brine. The organic phase was dried ($MgSO_4$), filtered, and concentrated to dryness before being purification by silica gel chromatography (7:3 EtOAc in hexanes) to afford tripeptide **12e** (0.429 g, 77%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): about 89:11 mixture of cis−trans proline rotamers, major rotamer description; δ 8.21 (d, J = 9.3 Hz, 1H), 7.58 (s, 1H), 7.51 (s, 1H), 7.30 (d, J = 9.3 Hz, 1H), 5.81−5.70 (m, 1H), 5.42−5.36 (m, 1H), 5.31 (dd, J = 17.3, 1.2 Hz, 1H), 5.25 (d, J = 9.2 Hz, 1H), 5.15 (dd, J = 10.2, 1.2 Hz, 1H), 4.90−4.84 (m, 1H), 4.81 (t, J = 7.6 Hz, 1H), 4.48 (d, J = 12.1 Hz, 1H), 4.36 (d, J = 9.6 Hz, 1H), 4.08 (s, 3H), 4.07 (s, 3H), 3.96 (dd, J = 12.0, 4.4 Hz, 1H), 3.69 (s, 3H), 3.06−2.98 (m, 1H), 2.44 (dd, J = 14.2, 8.2 Hz, 1H), 2.14 (dd, J = 17.2, 8.8 Hz, 1H), 1.88 (dd, J = 8.1, 5.7 Hz, 1H), 1.84−1.49 (m, 8H), 1.44 (dd, J = 9.6, 5.6 Hz, 1H), 1.07 (s, 9H). MS (electrospray): 775.2 $(M + 2H)^+$. HPLC homogeneity: 96%.

***N*-[(Cyclopentyloxy)carbonyl]-3-methyl-L-valyl-(4*R*)-4-{[8-bromo-2-(bromoacetyl)-7-methoxyquinolin-4-yl]oxy}-*N*-[(1*R*,2*S*)-2-ethenyl-1-(methoxycarbonyl)cyclopropyl]-L-prolinamide (13e).** Tripeptide **12e** (4.00 g, 5.17 mmol) in 75 mL of a 4:1 mixture of THF and H_2O was cooled to 0 °C before the addition of an aqueous solution of 1 N NaOH (5.7 mL). The resulting solution was stirred for 15 min at 0 °C, followed by 1.5 h at room temperature. The mixture was quenched with 1 M HCl, evaporated to near dryness, diluted with water, then frozen and lyophilized to provide the corresponding acid as the sodium salt (3.93 g). The sodium salt was dissolved in THF (65 mL) followed by triethylamine (0.981 mL, 7.04 mmol) before being cooled to 0 °C. Isobutyl chloroformate (0.913 mL, 7.04 mmol) was added dropwise, and the resulting white suspension was stirred at 0 °C for 1 h. This mixture was then treated with a solution of diazomethane (0.67 M in diethyl ether, 45 mL, 30.19 mmol). The reaction mixture was stirred for 15 min at 0 °C and then 1 h at room temperature before being concentrated to a thick suspension. This suspension was dissolved in EtOAc, washed with saturated $NaHCO_3$ (2×), brine (1×), and then dried ($MgSO_4$), filtered, and concentrated to give the corresponding diazoketone (2.91 g). The diazoketone (2.91 g, 3.7 mmol) was dissolved in THF (80 mL) and cooled to 0 °C before the dropwise addition of an HBr solution (48% aq, 2.7 mL) followed by stirring for 1.25 h. The mixture was quenched with a saturated $NaHCO_3$ solution and the THF evaporated in vacuo. The residue was diluted with EtOAc, washed with a saturated $NaHCO_3$ and saturated brine before being dried ($MgSO_4$), filtered, and concentrated to provide the crude bromoketone **13e** (2.99 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): about 90:10 mixture of cis−trans proline rotamers, major rotamer description; δ 8.19 (d, J = 9.2 Hz, 1H), 7.58 (s, 1H), 7.41 (s, 1H), 7.31 (d, J = 9.3 Hz, 1H), 5.81−5.70 (m, 1H), 5.43−5.35 (m, 1H), 5.31 (d, J = 17.2 Hz, 1H), 5.25−5.10 (m, 4H), 4.86−4.74 (m, 2H), 4.45 (d, J = 12.0 Hz, 1H), 4.32 (d, J = 9.5 Hz, 1H), 4.08 (s, 3H), 3.94 (dd, J = 12.1, 4.1 Hz, 1H), 3.69 (s, 3H), 3.06−2.98 (m, 1H), 2.43 (dd, J = 13.5, 8.4 Hz, 1H), 2.14 (dd, J = 17.2, 8.8 Hz, 1H), 1.91−1.85 (m, 1H), 1.84−1.37 (m, 9H), 1.05 (s, 9H). MS (electrospray): 773.3 $(MH + 2)^+$ 771.3 $(M + H)^+$ 769 $(M - H)^-$. HPLC homogeneity: 95%.

***N*-[(Cyclopentyloxy)carbonyl]-3-methyl-L-valyl-(4*R*)-4-[(8-bromo-7-methoxy-2-{2-[(2-methylpropanoyl)amino]-1,3-thiazol-4-yl}quinolin-4-yl)oxy]-*N*-[(1*R*,2*S*)-1-carboxy-2-ethenylcyclopropyl]-L-prolinamide (29).** A yellow solution of α-bromoketone **13e** (0.80 g, 0.956 mmol) and isobutyrylthiourea **14e** (0.159 g, 1.05 mmol) in isopropanol (30 mL) was heated at 75 °C for 1 h. The solution was cooled to room temperature and evaporated to dryness. The crude material was purified by silica gel chromatography to provide the methyl ester of compound **29** (0.59 g, 70% yield). To a solution of the methyl ester (0.59 g, 0.67 mmol) in a 12 mL mixture of THF/MeOH/H_2O (2:1:1) was added solid LiOH monohydrate (0.28 g, 6.66 mmol). The resulting mixture was stirred at room temperature overnight and then concentrated. The residue was partitioned between EtOAc (30 mL) and saturated brine (30 mL) before the pH was adjusted to 6.0 with 1 N HCl. The aqueous phase was re-extracted several times with EtOAc. The combined organic extract were washed with water and saturated brine, dried ($MgSO_4$), and concentrated to yield compound **29** as a pale yellow solid (0.57 g, 92% yield). ^{1}H NMR (400 MHz, DMSO-d_6): about 86:14 mixture of rotamers, major rotamer description; δ 12.48 (br s, 1H) 12.34 (s, 1H), 8.56 (s, 1H), 8.17 (d, J = 9.2 Hz, 1H), 8.03 (s, 1H), 7.46 (s, 1H), 7.34 (d, J = 9.4 Hz, 1H), 7.02 (d, J = 8.6 Hz, 1H), 5.80−5.65 (m, 1H), 5.48−5.37 (m, 1H), 5.18 (dd, J = 17.0, 1.4 Hz, 1H), 5.05 (dd, J = 10.1, 1.6 Hz, 1H), 4.63−4.55 (m, 1H), 4.43 (t, J = 8.6 Hz, 1H), 4.37 (d, J = 11.7 Hz, 1H), 4.07 (d, J = 8.6 Hz, 1H), 4.01 (s, 3H), 3.94 (br d, J = 9.4 Hz, 1H), 2.85−2.77 (m, 1H), 2.58−2.49 (m, 1H), 2.30−2.20 (m, 1H), 2.06−1.97 (m, 1H), 1.78−1.20 (m, 10H), 1.14 (d, J = 6.7 Hz, 6H), 0.96 (s, 9H). MS (ESI): 869.1, 871.1 $(M - H)^-$, 867.1, 869.1 $(M + H)^+$. HPLC homogeneity: >99%.

Synthesis of Compounds from Tables 3 and 5. The synthesis was performed using the same procedure as outlined above for compound **29** but using the appropriate quinoline and thiourea derivatives. The overall reaction sequence was performed on a similar scale and gave comparable yields. The characterization of these compounds is as follows.

***N*-[(Cyclopentyloxy)carbonyl]-3-methyl-L-valyl-(4*R*)-*N*-[(1*R*,2*S*)-1-carboxy-2-ethenylcyclopropyl]-4-({7-methoxy-2-[2-(propan-2-ylamino)-1,3-thiazol-4-yl]quinolin-4-yl}oxy)-L-prolinamide (3).** ^{1}H NMR (400 MHz, DMSO-d_6): about 82:18 mixture of rotamers, major rotamer description; δ 12.50 (br s, 1H), 8.54 (s, 1H), 8.02 (d, J = 9.0 Hz, 1H), 7.70 (d, J = 7.2 Hz, 1H), 7.44 (s, 1H), 7.18 (s, 1H), 7.28 (s, 1H), 7.01 (d, J = 8.6 Hz, 1H), 6.98 (d, J = 9.0 Hz, 1H), 5.43−5.35 (m, 1H), 5.19 (d, J = 16.6 Hz, 1H), 5.06 (d, J = 11.1 Hz, 1H), 4.77−4.70 (m, 1H), 4.43 (t, J = 8.3 Hz, 1H), 4.32 (d, J = 11.3 Hz, 1H), 4.12 (d, J = 8.6 Hz, 1H), 4.00−3.93 (m, 1H), 3.90 (s, 3H), 3.86−3.76 (m, 1H), 2.53−2.45 (m, 1H), 2.08−1.98 (m, 1H), 1.81−1.36 (m, 9H), 1.31−1.25 (m, 1H), 1.25 (d, J = 5.7 Hz, 6H), 0.97 (s, 9H). MS (ESI): 761.4 $(M - H)^-$, 763.5 $(M + H)^+$. HPLC homogeneity: 99%.

(1*R*,2*S*)-2-Ethenyl-1-{[(4*R*)-1-[(2*S*)-2-hydroxy-3,3-dimethylbutanoyl]-4-({7-methoxy-2-[2-(propan-2-ylamino)-1,3-thiazol-4-yl]quinolin-4-yl}oxy)-L-prolyl]amino}cyclopropanecarboxylic Acid (15). ^{1}H NMR (400 MHz, DMSO-d_6): about 82:18 mixture of rotamers, major rotamer description; δ 10.40 (br s, 1H), 8.60 (s, 1H), 8.18 (br s, 1H), 8.06 (d, J = 9.2 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.81 (br s, 1H), 7.71 (s, 1H), 7.39 (br d, J = 8.3 Hz, 1H), 5.79−5.65 (m, 2H), 5.20 (d, J = 16.9 Hz, 1H), 5.07 (d, J = 10.2 Hz, 1H), 4.53 (t, J = 8.6 Hz, 1H), 4.33 (d, J = 12.7 Hz, 1H), 4.21−4.08 (m, 1H), 3.98 (s, 3H), 3.99−3.93 (m, 1H), 3.90 (br s, 1H), 2.57 (dd, J = 12.8, 7.2 Hz, 1H), 2.35−2.27 (m, 1H), 2.08−2.00 (m, 1H), 1.92−1.82 (m, 1H), 1.56 (dd, J = 7.8, 4.9 Hz, 1H), 1.25 (d, J = 6.7 Hz, 6H), 0.90 (s, 9H). MS (ESI): 650.3 (M − H)$^-$, 652.3 (M + H)$^+$. HPLC homogeneity: 95%.

***N*-(*tert*-Butoxycarbonyl)-3-methyl-L-valyl-(4*R*)-*N*-[(1*R*,2*S*)-1-carboxy-2-ethenylcyclopropyl]-4-({7-methoxy-2-[2-(propan-2-ylamino)-1,3-thiazol-4-yl]quinolin-4-yl}oxy)-L-prolinamide (16).** ^{1}H NMR (400 MHz, DMSO-d_6): about 90:10 mixture of rotamers, major rotamer description; δ 12.52 (br s, 1H), 8.60 (s, 1H), 8.27, (br s, 1H), 8.22 (d, J = 9.2 Hz, 1H), 8.06 (d, J = 7.3 Hz, 1H), 7.86 (s, 1H), 7.75 (s, 1H), 7.26 (d, J = 8.6 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 5.81−5.68 (m, 2H), 5.19 (d, J = 17.2 Hz, 1H), 5.06 (d, J = 10.2 Hz, 1H), 4.54−4.43 (m, 2H), 4.22−4.09 (m, 1H), 4.01 (d, J = 8.3 Hz, 1H), 4.00−3.90 (m, 1H), 3.97 (s, 3H), 2.59 (dd, J = 13.9, 7.8 Hz, 1H), 2.38−2.29 (m, 1H), 2.01 (dd, J = 17.2, 8.9 Hz, 1H), 1.56 (dd, J = 7.7, 5.0 Hz, 1H), 1.31−1.25 (m, 1H), 1.26 (d, J = 6.7 Hz, 6H), 1.19 (s, 9H), 0.97 (s, 9H). MS (ESI): 751.2 (M − H)$^-$, 749.2 (M + H)$^+$. HPLC homogeneity: H_2O): 97%.

***N*-[(Cyclobutyloxy)carbonyl]-3-methyl-L-valyl-(4*R*)-*N*-[(1*R*,2*S*)-1-carboxy-2-ethenylcyclopropyl]-4-({7-methoxy-2-[2-(propan-2-ylamino)-1,3-thiazol-4-yl]quinolin-4-yl}oxy)-L-prolinamide (17).** ^{1}H NMR (400 MHz, DMSO-d_6): about 87:13 mixture of rotamers, major rotamer description; δ 12.47 (br s, 1H), 8.59 (s, 1H), 8.29−8.20 (br s, 1H), 8.19 (d, J = 9.2 Hz, 1H), 8.04 (br s, 1H), 7.85 (br s, 1H), 7.73 (br s, 1H), 7.32 (br d, J = 8.6 Hz, 1H), 7.17 (d, J = 8.2 Hz, 1H), 5.79−5.67 (m, 2H), 5.20 (dd, J = 17.1, 1.4 Hz, 1H), 5.07 (dd, J = 10.2, 1.8 Hz, 1H), 4.53−4.42 (m, 2H), 4.36−3.96 (m, 3H), 3.98 (s, 3H), 3.93 (dd, J = 12.5, 3.1 Hz, 1H), 2.64−2.54 (m, 1H), 2.38−2.28 (m, 1H), 2.06−1.91 (m, 3H), 1.89−1.74 (m, 2H), 1.70−1.52 (m, 2H), 1.47−1.37 (m, 1H), 1.29−1.26 (m, 1H), 1.26 (d, J = 6.7 Hz, 6H), 0.96 (s, 9H). MS (ESI): 747.4 (M − H)$^-$, 749.3 (M + H)$^+$. HPLC homogeneity: 97%.

***N*-[(Cyclohexyloxy)carbonyl]-3-methyl-L-valyl-(4*R*)-*N*-[(1*R*,2*S*)-1-carboxy-2-ethenylcyclopropyl]-4-({7-methoxy-2-[2-(propan-2-ylamino)-1,3-thiazol-4-yl]quinolin-4-yl}oxy)-L-prolinamide (18).** ^{1}H NMR (400 MHz, DMSO-d_6): about 88:12 mixture of rotamers, major rotamer description; δ 12.51 (br s, 1H), 8.62 (s, 1H), 8.26 (br s, 1H), 8.22 (d, J = 8.2 Hz, 1H), 8.05 (br s, 1H), 7.86 (br s, 1H), 7.72 (br s, 1H), 7.24 (br d, J = 7.9 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 5.82−5.61 (m, 2H), 5.21 (d, J = 17.2 Hz, 1H), 5.08 (d, J = 10.2 Hz, 1H), 4.61−4.37 (m, 2H), 4.25−3.86 (m, 4H), 3.98 (s, 3H), 2.64−2.48 (m, 1H), 2.38−2.28 (m, 1H), 2.01 (dd, J = 17.1, 8.8 Hz, 1H), 1.72−1.41 (m, 5H), 1.32−1.05 (m, 7H), 1.28 (d, J = 6.8 Hz, 6H), 0.98 (s, 9H). MS (ESI): 775.4 (M − H)$^-$, 777.3 (M + H)$^+$. HPLC homogeneity: 98%.

***N*-[(Cyclopentyloxy)carbonyl]-3-methyl-L-valyl-(4*R*)-4-({2-[2-(acetylamino)-1,3-thiazol-4-yl]-7-methoxyquinolin-4-yl}oxy)-*N*-[(1*R*,2*S*)-1-carboxy-2-ethenylcyclopropyl]-L-prolinamide (19).** ^{1}H NMR (400 MHz, DMSO-d_6): about 86:14 mixture of rotamers, major rotamer description; δ 12.38 (br s, 2H), 8.57 (s, 1H), 8.37 (br s, 1H), 8.18 (d, J = 9.2 Hz, 1H), 7.63 (s, 1H), 7.56 (s, 1H), 7.21 (d, J = 9.0 Hz, 1H), 7.02 (d, J = 7.9 Hz, 1H), 5.77−5.67 (m, 1H), 5.59 (br m, 1H), 5.19 (d, J = 17.2 Hz, 1H), 5.06 (d, J = 10.2 Hz, 1H), 4.61−4.54 (m, 1H), 4.51−4.41 (m, 2H), 4.07 (d, J = 8.6 Hz, 1H), 4.01−3.95 (m, 1H), 3.95 (s, 3H), 2.59 (dd, J = 12.9, 7.2 Hz, 1H), 2.35−2.26 (m, 1H), 2.23 (s, 3H), 2.07−1.97 (m, 1H), 1.71−1.31 (m, 9H), 1.27 (dd, J = 9.4, 4.9 Hz, 1H), 0.97 (s, 9H). MS (ESI): 761.1 (M − H)$^-$, 763.1 (M + H)$^+$. HPLC homogeneity: > 99%.

***N*-[(Cyclopentyloxy)carbonyl]-3-methyl-L-valyl-(4*R*)-*N*-[(1*R*,2*S*)-1-carboxy-2-ethenylcyclopropyl]-4-[(2-{2-[(3,3-dimethylbutanoyl)-amino]-1,3-thiazol-4-yl}-7-methoxyquinolin-4-yl)oxy]-L-prolinamide (20).** ^{1}H NMR (400 MHz, DMSO-d_6): about 85:15 mixture of rotamers, major rotamer description; δ 12.42 (br s, 1H), 12.29 (s, 1H), 8.54 (s, 1H), 8.07 (d, J = 9.2 Hz, 1H), 8.02 (br s, 1H), 7.46 (s, 1H), 7.35 (s, 1H), 7.06 (d, J = 9.2 Hz, 1H), 7.00 (d, J = 8.6 Hz, 1H), 5.79−5.66 (m, 1H), 5.47−5.38 (m, 1H), 5.19 (d, J = 17.2 Hz, 1H), 5.06 (d, J = 10.3 Hz, 1H), 4.78−4.67 (m, 1H), 4.48−4.33 (m, 2H), 4.12 (d, J = 8.4 Hz, 1H), 4.03−3.93 (m, 1H), 3.92 (s, 3H), 2.58−2.49 (m, 1H), 2.43 (s, 2H), 2.31−2.19 (m, 1H), 2.08−1.98 (m, 1H), 1.83−1.15 (m, 10H),), 1.04 (s, 9H),), 0.97 (s, 9H). MS (ESI): 817.4 (M − H)$^-$, 819.4 (M + H)$^+$. HPLC homogeneity: > 99%.

***N*-[(Cyclopentyloxy)carbonyl]-3-methyl-L-valyl-(4*R*)-*N*-[(1*R*,2*S*)-1-carboxy-2-ethenylcyclopropyl]-4-({7-methoxy-8-methyl-2-[2-(propan-2-ylamino)-1,3-thiazol-4-yl]quinolin-4-yl}oxy)-L-prolinamide (21).** ^{1}H NMR (400 MHz, DMSO-d_6): about 88:12 mixture of rotamers, major rotamer description; δ 12.55 (br s, 1H), 8.58 (s, 1H), 8.07 (d, J = 7.1 Hz, 1H), 8.06 (br s, 1H), 7.89 (d, J = 9 Hz, 1H), 7.57 (br d, J = 6.9 Hz, 1H), 7.34 (br s, 1H), 7.02 (d, J = 8.6 Hz, 1H), 5.78−5.66 (m, 1H), 5.61−5.49 (br s, 1H), 5.23 (d, J = 17.0 Hz, 1H), 5.07 (d, J = 11.9 Hz, 1H), 4.55 (br s, 1H), 4.46 (t, J = 8.4 Hz, 1H), 4.38 (d, J = 11.2 Hz, 1H), 4.08 (d, J = 8.6 Hz, 1H), 4.03−3.97 (m, 1H), 3.96 (s, 3H), 3.92−3.83 (m, 1H), 2.56 (s, 3H), 2.53−2.47 (m, 1H), 2.38−2.25 (m, 1H), 2.08−1.98 (m, 1H), 1.71−1.35 (m, 9H), 1.35−1.27 (m, 1H), 1.27 (d, J = 6.3 Hz, 6H), 0.96 (s, 9H). MS (ESI): 775.4 (M − H)$^-$, 777.5 (M + H)$^+$. HPLC homogeneity: 95%.

***N*-[(Cyclopentyloxy)carbonyl]-3-methyl-L-valyl-(4*R*)-4-({2-[2-(acetylamino)-1,3-thiazol-4-yl]-7-methoxy-8-methylquinolin-4-yl}oxy)-*N*-[(1*R*,2*S*)-1-carboxy-2-ethenylcyclopropyl]-L-prolinamide (22).** ^{1}H NMR (400 MHz, DMSO-d_6): about 85:15 mixture of rotamers, major rotamer description; δ 12.32 (br s, 2H), 8.57 (s, 1H), 8.15−8.03 (m, 1H), 8.04 (d, J = 9.2 Hz, 1H), 7.47−7.37 (m, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.03 (d, J = 8.6 Hz, 1H), 5.78−5.65 (m, 1H), 5.45−5.38 (m, 1H), 5.19 (d, J = 17.0 Hz, 1H), 5.05 (d, J = 10.7 Hz, 1H), 4.72−4.62 (m, 1H), 4.46−4.32 (m, 2H), 4.16−4.08 (m, 1H), 4.03−3.90 (m, 1H), 3.94 (s, 3H), 2.60 (s, 3H), 2.30−2.19 (m, 1H), 2.20 (s, 3H), 2.06−1.97 (m, 1H), 1.81−1.21 (m, 11H), 0.97 (s, 9H). MS (ESI): 775.4 (M − H)$^-$, 777.5 (M + H)$^+$. HPLC homogeneity: 99%.

***N*-[(Cyclopentyloxy)carbonyl]-3-methyl-L-valyl-(4*R*)-*N*-[(1*R*,2*S*)-1-carboxy-2-ethenylcyclopropyl]-4-({7-methoxy-8-methyl-2-[2-(propanoylamino)-1,3-thiazol-4-yl]quinolin-4-yl}oxy)-L-prolinamide (23).** ^{1}H NMR (400 MHz, DMSO-d_6): about 85:15 mixture of rotamers, major rotamer description; δ 12.37 (br s, 1H), 12.33 (br s, 1H), 8.55 (s, 1H), 8.15−8.02 (m, 1H), 8.04 (d, J = 9.0 Hz, 1H), 7.49−7.38 (m, 1H), 7.29 (d, J = 9.2 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 5.78−5.66 (m, 1H), 5.46−5.39 (m, 1H), 5.18 (d, J = 17.0 Hz, 1H), 5.05 (d, J = 10.0 Hz, 1H), 4.71−4.62 (m, 1H), 4.47−4.32 (m, 2H), 4.15−4.09 (m, 1H), 4.03−3.92 (m, 1H), 3.94 (s, 3H), 2.60 (s, 3H), 2.58−2.40 (m, 2H), 2.30−2.20 (m, 1H), 2.07−1.97 (m, 1H), 1.80−1.21 (m, 11H), 1.13 (t, J = 7.5 Hz, 3H), 0.97 (s, 9H). MS (ESI): 789.4 (M − H)$^-$, 791.4 (M + H)$^+$. HPLC homogeneity: 98%.

***N*-[(Cyclopentyloxy)carbonyl]-3-methyl-L-valyl-(4*R*)-*N*-[(1*R*,2*S*)-1-carboxy-2-ethenylcyclopropyl]-4-({8-fluoro-7-methoxy-2-[2-(propanoylamino)-1,3-thiazol-4-yl]quinolin-4-yl}oxy)-L-prolinamide (24).** ^{1}H NMR (400 MHz, DMSO-d_6): about 85:15 mixture of rotamers, major rotamer description; δ 12.39 (br s, 1H) 12.35 (s, 1H), 8.54 (s, 1H), 8.03 (s, 1H), 7.92 (d, J = 9.2 Hz, 1H), 7.47 (s, 1H), 7.38 (t, J = 8.3 Hz, 1H), 6.98 (d, J = 8.7 Hz, 1H), 5.78−5.65 (m, 1H), 5.47−5.38 (m, 1H), 5.18 (dd, J = 17.2, 1.4 Hz 1H), 5.05 (dd, J = 10.3, 1.6 Hz, 1H), 4.69−4.60 (m, 1H), 4.48−4.30 (m, 2H), 4.14−3.90 (m, 2H), 3.98 (s, 3H), 2.60−2.39 (m, 3H), 2.30−2.20 (m, 1H), 2.06−1.97 (m, 1H), 1.80−1.37 (m, 8H), 1.37−1.20 (m, 2H), 1.12 (t, J = 7.5 Hz, 3H), 0.96 (s, 9H). MS (ESI): 793.3 (M − H)$^-$, 795.3 (M + H)$^+$. HPLC homogeneity: 98%.

***N*-[(Cyclopentyloxy)carbonyl]-3-methyl-L-valyl-(4*R*)-*N*-[(1*R*,2*S*)-1-carboxy-2-ethenylcyclopropyl]-4-({8-chloro-7-methoxy-2-[2-(propanoylamino)-1,3-thiazol-4-yl]quinolin-4-yl}oxy)-L-prolinamide (25).**

^{1}H NMR (400 MHz, DMSO-d_6): about 88:12 mixture of rotamers, major rotamer description; δ 12.49 (br s, 1H) 12.34 (s, 1H), 8.55 (s, 1H), 8.12 (d, J = 9.2 Hz, 1H), 8.05 (s, 1H), 7.48 (s, 1H), 7.39 (d, J = 9.2 Hz, 1H), 6.98 (d, J = 8.6 Hz, 1H), 5.80−5.66 (m, 1H), 5.49−5.37 (m, 1H), 5.19 (d, J = 17.0 Hz, 1H), 5.07 (d, J = 10.4 Hz, 1H), 4.70−4.54 (m, 1H), 4.45 (t, J = 8.6 Hz, 1H), 4.38 (d, J = 11.5 Hz, 1H), 4.09 (d, J = 8.8 Hz, 1H), 4.01 (s, 3H), 3.96 (br d, J = 10.6 Hz, 1H), 2.60−2.43 (m, 3H), 2.32−2.22 (m, 1H), 2.06−1.98 (m, 1H), 1.80−1.41 (m, 8H), 1.39−1.21 (m, 2H), 1.13 (t, J = 7.5 Hz, 3H), 0.96 (s, 9H). MS (ESI): 809.3 (M − H)$^-$, 811.3 (M + H)$^+$. HPLC homogeneity: 96%.

***N*-[(Cyclopentyloxy)carbonyl]-3-methyl-L-valyl-(4*R*)-4-({8-bromo-7-methoxy-2-[2-(propanoylamino)-1,3-thiazol-4-yl]quinolin-4-yl}-oxy)-*N*-[(1*R*,2*S*)-1-carboxy-2-ethenylcyclopropyl]-L-prolinamide (26).** ^{1}H NMR (400 MHz, DMSO-d_6): about 85:15 mixture of rotamers, major rotamer description; δ 12.50 (br s, 1H) 12.33 (s, 1H), 8.55 (s, 1H), 8.17 (d, J = 9.2 Hz, 1H), 8.04 (s, 1H), 7.47 (s, 1H), 7.35 (d, J = 9.2 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 5.80−5.66 (m, 1H), 5.47−5.37 (m, 1H), 5.19 (d, J = 17.1 Hz, 1H), 5.07 (d, J = 10.4 Hz, 1H), 4.67−4.55 (m, 1H), 4.45 (t, J = 8.4 Hz, 1H), 4.38 (d, J = 11.7 Hz, 1H), 4.08 (d, J = 8.8 Hz, 1H), 4.01 (s, 3H), 3.95 (br d, J = 8.6 Hz, 1H), 2.60−2.47 (m, 3H), 2.32−2.21 (m, 1H), 2.06−1.98 (m, 1H), 1.77−1.37 (m, 8H), 1.36−1.23 (m, 2H), 1.13 (t, J = 7.6 Hz, 3H), 0.96 (s, 9H). MS (ESI): 855.2, 857.2 (M − H)$^-$, 853.1, 855.1 (M + H)$^+$. HPLC homogeneity: 97%.

***N*-[(Cyclopentyloxy)carbonyl]-3-methyl-L-valyl-(4*R*)-4-[(8-bromo-7-methoxy-2-{2-[(methoxycarbonyl)amino]-1,3-thiazol-4-yl}-quinolin-4-yl)oxy]-*N*-[(1*R*,2*S*)-1-carboxy-2-ethenylcyclopropyl]-L-prolinamide (27).** ^{1}H NMR (400 MHz, DMSO-d_6): about 88:12 mixture of rotamers, major rotamer description; δ 12.49 (br s, 1H) 12.06 (s, 1H), 8.55 (s, 1H), 8.16 (d, J = 9.2 Hz, 1H), 8.04 (s, 1H), 7.45 (s, 1H), 7.35 (d, J = 9.4 Hz, 1H), 6.98 (d, J = 8.6 Hz, 1H), 5.80−5.66 (m, 1H), 5.48−5.37 (m, 1H), 5.19 (d, J = 17.1 Hz, 1H), 5.06 (d, J = 10.2 Hz, 1H), 4.65−4.55 (m, 1H), 4.45 (t, J = 8.5 Hz, 1H), 4.37 (d, J = 11.9 Hz, 1H), 4.08 (d, J = 8.8 Hz, 1H), 4.01 (s, 3H), 3.96 (br d, J = 9.4 Hz, 1H), 3.78 (s, 3H), 2.58−2.48 (m, 1H), 2.32−2.21 (m, 1H), 2.06−1.98 (m, 1H), 1.71−1.37 (m, 8H), 1.36−1.26 (m, 2H), 0.96 (s, 9H). MS (ESI): 855.1, 857.1 (M − H)$^-$, 857.2, 859.2 (M + H)$^+$. HPLC homogeneity: >99%.

***N*-[(Cyclopentyloxy)carbonyl]-3-methyl-L-valyl-(4*R*)-4-{[8-bromo-7-methoxy-2-({[(propan-2-yloxy)carbonyl]amino}-1,3-thiazol-4-yl)quinolin-4-yl]oxy}-*N*-[(1*R*,2*S*)-1-carboxy-2-ethenylcyclopropyl]-L-prolinamide (28).** ^{1}H NMR (400 MHz, DMSO-d_6): about 85:15 mixture of rotamers, major rotamer description; δ 12.45 (br s, 1H) 11.90 (s, 1H), 8.55 (s, 1H), 8.16 (d, J = 9.2 Hz, 1H), 8.03 (s, 1H), 7.45 (s, 1H), 7.35 (d, J = 9.4 Hz, 1H), 6.98 (d, J = 8.6 Hz, 1H), 5.81−5.66 (m, 1H), 5.48−5.37 (m, 1H), 5.19 (d, J = 17.0 Hz, 1H), 5.07 (d, J = 10.4 Hz, 1H), 4.99 (m, 1H), 4.67−4.55 (m, 1H), 4.45 (t, J = 8.4 Hz, 1H), 4.38 (d, J = 11.9 Hz, 1H), 4.08 (d, J = 8.8 Hz, 1H), 4.01 (s, 3H), 3.96 (br d, J = 9.4 Hz, 1H), 2.58−2.48 (m, 1H), 2.32−2.21 (m, 1H), 2.06−1.98 (m, 1H), 1.71−1.37 (m, 8H), 1.36−1.26 (m, 2H), 1.29 (d, J = 6.3 Hz, 6H), 0.96 (s, 9H). MS (ESI): 883.2, 885.2 (M − H)$^-$, 885.3, 887.3 (M + H)$^+$. HPLC homogeneity: >99%.

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Supporting Information Available: Full ^{1}H and ^{13}C NMR characterization and assignments provided for **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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