Toward Second Generation Hepatitis C Virus NS3 Serine Protease Inhibitors: Discovery of Novel P4 Modified Analogues with Improved Potency and Pharmacokinetic Profile

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Received December 22, 2008

Hepatitis C virus (HCV) infection is a global health crisis leading to liver cirrhosis, hepatocellular carcinoma, and liver failure in humans. Recently, we disclosed the discovery of Boceprevir, SCH 503034 (**1**), a novel, potent, selective, orally bioavailable NS3 protease inhibitor that is currently undergoing phase III clinical trials. Our efforts toward a second generation HCV NS3 serine protease inhibitor were directed at improving the overall profile of the inhibitor. This article will elaborate on our studies leading to the discovery of new P4 modified inhibitors with enhanced potency and improved oral bioavailability. Thus, introduction of ether and carbamate-derived P4 moieties resulted in improving the replicon potency significantly. Incorporation of the P′ secondary amide residue afforded significant improvement in pharmacokinetic properties. Combining the preferred moieties, identified from comprehensive SAR studies, resulted in inhibitors that displayed superior potency and very good oral as well as target organ exposure in rats.

Introduction

Hepatitis C virus (HCV[a]) infection is a global health crisis leading to liver cirrhosis, hepatocellular carcinoma, and liver failure in humans.[1] It has been estimated that 3% of the human population worldwide is chronically infected with HCV.[2] α-Interferon monotherapy and α-interferon−ribavirin combination therapy are the standard treatment for this infection.[3] While therapeutic effectiveness has been improved with the introduction of pegylated version of α-interferon, it is still far from ideal for the hard to treat genotype-1 patients.[4] Hence, there is an unmet medical need to discover and develop new and more effective protocols for the treatment of HCV infection.

HCV is a positive stranded RNA virus belonging to the Flaviviridae family. Upon entering a suitable host cell, the HCV genome encodes a polyprotein of approximately 3000 amino acid residues. Post-translational modification of the polyprotein is mediated by host and viral proteases, ultimately resulting in viral replication. Intense efforts were focused in the past decade to discover novel small molecule agents that directly inhibit viral replication. Since the identification of this virus, the NS3 serine protease contained within the N-terminal region of the NS3 protein has been studied extensively.[5] This chymotrypsin-like serine protease is implicated in viral replication and therefore is an attractive target for HCV antiviral therapeutics.[6] Proof of concept studies in humans have validated this hypothesis.[7] We recently disclosed the synthesis and development of Boceprevir, (1*R*,5*S*)-*N*-[3-amino-1-(cyclobutylmethyl)-2-3-dioxopropyl]-3-[2(*S*)-[[[(1,1-dimethylethyl)-amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (SCH 503034), **1**,[8] a selective, potent, orally bioavailable HCV NS3 protease inhibitor that is efficacious in humans and currently undergoing phase III clinical trials. Other molecules, including (1*S*,3a*R*,6a*S*)-2-((*S*)-2-((*S*)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethylbutanoyl)-*N*-((*S*)-1-(cyclopropylamino)-1,2-dioxohexan-3-yl)octahydrocyclopenta[*c*]pyrrole-1-carboxamide, (VX950) currently in phase III studies, have also been advanced to clinical trials and found to be effective.[9]

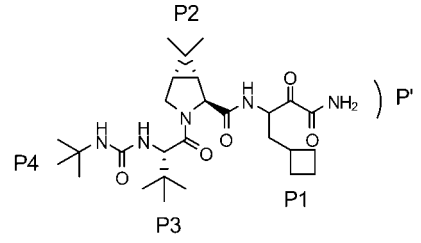

Figure 1. Profile of **1** (SCH 503034).

As shown in Figure 1, inhibitor **1** exhibited $K_i^* = 14$ nM in the enzyme binding assay,[10] $EC_{90} = 350$ nM in the cell-based replicon assay,[11] and acceptable pharmacokinetic profile in rats. In our efforts to identify a second generation HCV NS3 serine protease inhibitor, we focused on improving the potency and pharmacokinetic profile of the inhibitor. On the basis of the X-ray crystal structure of **1** bound to the NS3 protease, exploration of the P4 area seemed attractive since additional interaction with the enzyme may improve the potency. Herein, we will detail our studies in the P4 area, specifically the introduction of ether and carbamate capped P4 moieties, which resulted in inhibitors with very good potency. Comprehensive SAR studies, along with the introduction of a P′ secondary amide residue to increase metabolic stability, provided inhibitors with appreciable enhancement in the rat pharmacokinetic profile.

Synthesis of Inhibitors. Synthesis of ether cap derived target compounds are shown in Scheme 1. Etherification of (*S*) *N*-Boc-*tert*-leucinol under neutral conditions followed by deprotection resulted in **2**. Treatment with phosgene provided the isocyanate **3**. Reaction of previously described[8] intermediate **4** with isocyanate **3** followed by ester hydrolysis afforded the ether

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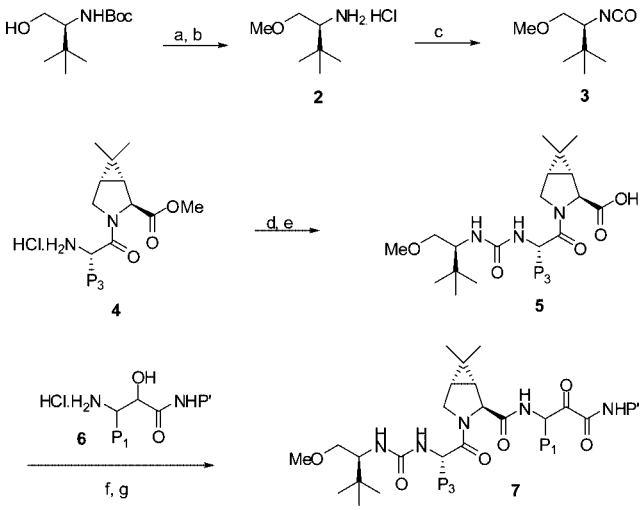
[a] Abbreviations: HCV, hepatitis C virus; DM periodinane, Dess-Martin's periodinane; Cys159, cysteine159; β-MeChg, β-methylcyclohexyl glycine; norval, norvaline; norleu, norleucine; $C_{6\ h}$, liver concentration at 6 h.

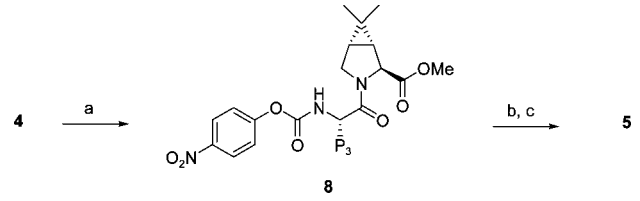
10.1021/jm801616e CCC: $40.75
Published on Web 04/16/2009

Scheme 1[a]



[a] a. MeI, CuO, MeCN; b. 4M HCl/dioxane; c. Phosgene (20% in toluene), CH_2Cl_2, aq. $NaHCO_3$; d. **3**, DIPEA, CH_2Cl_2; e. Aq LiOH, THF; f. **6**, EDCI, HOOBt, NMM, CH_2Cl_2, DMF; g. DM periodinane, CH_2Cl_2.

Scheme 2[a]



[a] a. 4-Nitrophenylchloroformate, DIPEA, CH_2Cl_2; b. **2**, DIPEA, CH_2Cl_2; c. Aq LiOH, THF.

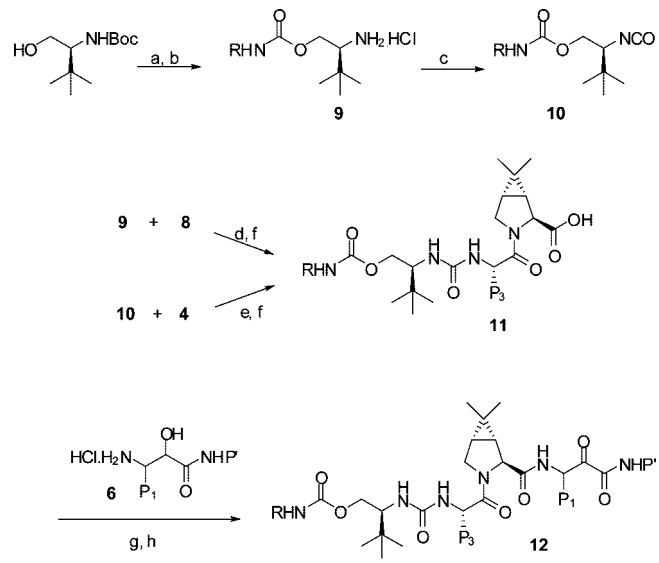
capped intermediate **5**. Coupling of the P4−P2 acid **5** with P1−P′ intermediate **6** followed by oxidation (Dess-Martin or modified Moffatt protocol) provided the required P4 ether capped inhibitors **7** in 60−75% yield. A variation of the isocyanate methodology to obtain intermediate **5** is shown in Scheme 2. Thus, amine hydrochloride **4** was treated with 4-nitrophenyl chloroformate to provide the activated carbamate **8**, which was subsequently converted to the required acid **5** via treatment with **2** followed by basic hydrolysis.

Synthesis of P4 carbamate capped inhibitors is described in Scheme 3. Treatment of (*S*)*N*-Boc-*tert*-leucinol with isocyanates (commercial or prepared via reaction of known amines with phosgene solution) using copper chloride and subsequent removal of the *t*-Boc protecting group delivered compound **9**. Conversion to isocyanate **10** essentially followed the previously described procedures. P4−P2 acid **11** was obtained using two routes: treatment of amine hydrochloride **9** with activated carbamate **8**, followed by hydrolysis or reaction of isocyanate **10** with known P3−P2 intermediate **4**, followed by LiOH hydrolysis. Final assembly of P4 capped inhibitors **12** was carried out as described above in a two step protocol. Scheme 4 depicts the synthesis of *N*,*N*-dimethyl carbamate capped inhibitor **15**. Thus, (*S*)*N*-Boc-*tert*-leucinol was converted to the activated carbonate **13** via treatment with 4-nitrophenyl chloroformate. Reaction of **13** with *N*,*N*-dimethylamine hydrochloride followed by deprotection afforded the required intermediate **14**, which was further processed to inhibitor **15** using procedures described earlier.

Results and Discussion

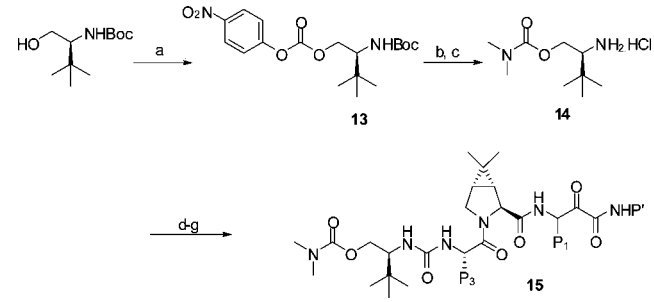
The X-ray crystal structure of **1** bound to the NS3 protease indicated that exploration of the P4 area may result in additional

Scheme 3[a]



[a] a. RNCO, CuCl, DMF; b. 4M HCl/dioxane; c. phosgene (20% in toluene), CH_2Cl_2, aq. $NaHCO_3$; d. DIPEA, CH_2Cl_2; e. DIPEA, CH_2Cl_2; f. aq. LiOH, THF; g. **6**, EDCI, HOOBt, NMM, CH_2Cl_2, DMF; h. DM periodinane, CH_2Cl_2.

Scheme 4[a]

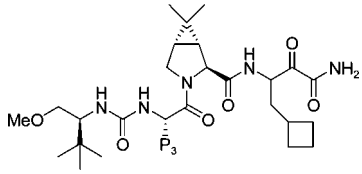


[a] a. 4-Nitrophenylchloroformate, DIPEA, CH_2Cl_2; b. dimethylamine hydrochloride, DIPEA, CH_2Cl_2; c. 4M HCl in dioxane; d. **8**, DIPEA, CH_2Cl_2; e. aq LiOH, THF; f. **6**, EDCI, HOOBt, NMM, CH_2Cl_2, DMF; h. DM periodinane, CH_2Cl_2.

interactions. It also revealed the presence of the cysteine159 (Cys159) residue on the protease surface in close proximity to the S4 pocket. On the basis of these observations, we decided to incorporate groups off the urea P3 cap of **1** that could interact with Cys159. Our investigation resulted in the identification of (*S*)-*tert*-leucinol derived ethers and carbamates as suitable P4 moieties, with the carbamate cap providing superior potency. During our studies that led to the discovery of **1**, we also observed that inhibitors containing the P′ secondary amide residue exhibited good rat pharmacokinetic profile, presumably due to greater metabolic stability of the secondary amide compared to that of the primary amide moiety present in **1**. Hence, in order to improve the pharmacokinetic profile of P4 capped inhibitors, we set out to incorporate the P′ secondary amide residue. Introduction of the allyl amide P′ residue provided significant enhancement in rat pharmacokinetic properties. Results of our studies are described below.

Our investigation toward the identification of a suitable second generation HCV NS3 serine protease inhibitor started with the introduction of *tert*-leucinol derived ethers and carbamates as P4 moieties. Incorporation of methyl ether capped *tert*-leucinol derived urea cap onto the core of **1** gave compound **16**, which resulted in a loss of enzyme potency (K_i* = 120 nm). Interestingly, variation of the P3 moiety resulted in restoring

Table 1



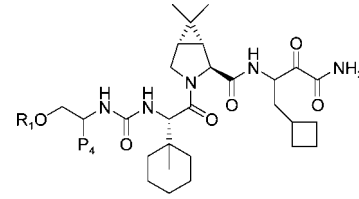
Compd	P_3	Ki* (nM)	EC_{90} (nM)
16		120	na
17		30	300
18		24	150
19		22	400
20		15	200

the potency. Thus, P3 cyclohexylglycine derived inhibitor **17** was essentially equipotent to **1** (K_i* = 30 nm, EC_{90} = 300 nM). Similar results were obtained with P3 β-methylcyclopentyl glycine derived inhibitor **19** (K_i* = 22 nm, EC_{90} = 400 nM). However, introduction of P3 β-methylcyclohexyl glycine or 2-indanylglycine (**18** or **20**, respectively) improved replicon potency further, with EC_{90} of 150 nM and 200 nM, respectively. Both inhibitors showed good enzyme potency as well (see Table 1).

Having improved the replicon potency in the P4 ether capped series (via modification of P3), we then decided to study the effect of P4 substitutions. The results are shown in Table 2. Replacement of the *t*-butyl group at P4 with i-propyl moiety was tolerated (**21**, K_i* = 12 nM, EC_{90} = 200 nM). Disubstitution at the P4 α-center resulted in a loss of potency (compounds **22** and **23**). Further ether modifications (**24** and **25**) also resulted in diminished potency. Additionally, inhibitor **20** with good replicon potency displayed poor exposure (AUC = 0.1 μM·h) when dosed orally in rats. Hence, in an effort to further improve the replicon potency and address pharmacokinetic issues, we then turned our attention toward incorporating the carbamate moiety at the P4 position.

Targets derived from the P4 carbamate moiety were synthesized as described in Schemes 3 and 4. Since 2-indanyl glycine and β-methylcyclohexyl glycine at P3 exhibited a similar profile and, moreover, due to ease of availability of the former, our studies in the carbamate series were initiated with 2-indanyl glycine residue at P3 (Table 3). Introduction of the methyl carbamate cap resulted in encouraging results, with **27** showing good potency (K_i* = 9 nM, EC_{90} = 200 nM). Extending the cap by an additional carbon atom provided ethyl carbamate capped inhibitor **28**, which improved the potency further (K_i* = 7 nM, EC_{90} = 100 nM). Incorporation of other alkyl groups were also well tolerated (compounds **29** and **30**, with EC_{90} = 200 nM). *N*,*N*-Disubstitution resulted in a loss of potency (**31**, K_i* = 23 nM, EC_{90} = 300 nM). Thus, the ethyl carbamate cap afforded the best potency. We then varied the P3 residue to find out its effect on potency of the inhibitor. Both *tert*-leucine and cyclohexylglcine at P3, while retaining the binding potency,

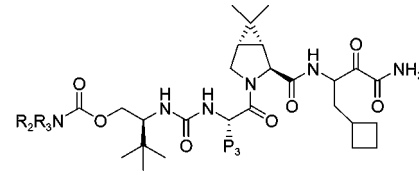
Table 2

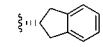
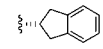
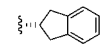
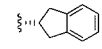


Compd	R_1	P_4	Ki* (nM)	EC_{90} (nM)
18	Me		24	150
21	Me		12	200
22	Me		170	na
23	Me		50	na
24	tBu		100	na
25	tBu		120	na
26[a]	Bn		130	na

[a] P3 tLeu.

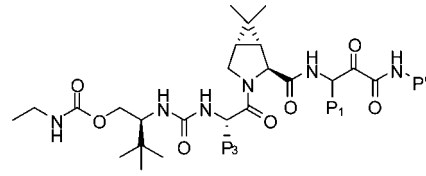
Table 3



Compd	R_2R_3N	P_3	Ki* (nM)	EC_{90} (nM)
27			9	200
28			7	100
29			9	200
30			12	200
31			23	300
32			9	250
33			10	600
34			8	150

exhibited diminished replicon potency (**32** and **33**). Once again, P3 β-methylcyclohexyl glycine containing inhibitor **34** displayed a profile similar to that of compound **28** with the 2-indanyl glycine P3 residue. Inhibitor **28**, with a very good potency

Table 4



Compd	P_3	P_1	P'	Ki* (nM)	EC_{90} (nM)
35			H	7	200
36				50	400
37				33	400
38				23	400
39				10	550
40				28	150
41				28	400
42				9	150
43				16	200
44				21	200

profile, was evaluated for oral exposure in rats. Unfortunately, **28** displayed low oral exposure (AUC = 0.3 μM, 10 mpk) when dosed in rats. Furthermore, rat liver concentration was also not optimal (244 ng/g after 1 h). We observed a similar PK profile for a few other inhibitors (unpublished results) containing the P′ primary amide moiety.

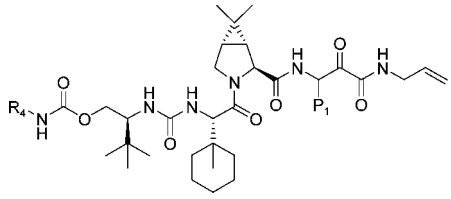
During our exploratory studies that led to the discovery of **1**, we observed that P′ secondary amides, specifically allyl amides, provided inhibitors with very good rat PK profile. In an attempt to improve the PK profile of P4 carbamate derived inhibitors, we then set out to introduce an allyl residue at the P′ position. We also knew from our previous studies that the P1 cyclobutyl alanine moiety was not well tolerated with the incorporation of an allyl (or similar small alkyl) residue at P′. Because of these considerations, our P′ SAR studies were carried out with various P1 surrogates to identify the appropriate P1−P′ combination.

Results obtained with P′ secondary amides are shown in Table 4. Compound **35** demonstrated that the P1 cyclopropylalanine containing inhibitor displayed a similar potency profile compared to that of P1 cyclobutylalanine derived inhibitor **28** (Table 3). Introduction of the allyl residue at the P′ position resulted in **36** with a loss of potency. Further variation of the P1 moiety (norval **37**, norleu **38**, and butynylglycine **39**) resulted in a loss in replicon potency. Interestingly, **39** with butynylglycine P1 displayed very good enzyme potency (K_i* = 10 nM).

When a similar study was carried out with the P3 β-methylcyclohexyl glycine residue, improvement in replicon potency was observed (Table 4). Thus, **40** with norval P1 and allyl amide at P′ exhibited K_i* of 28 nM and replicon EC_{90} of 150 nM. While **41**, with P1 norleu was less potent (EC_{90} = 400 nM), butynyl glycine P1 inhibitor **42** displayed very good potency profile (K_i* = 9 nM, EC_{90} = 150 nM). Introduction of propyl amide (**43**, K_i* = 16 nM, EC_{90} = 200 nM) or ethyl amide (**44**, K_i* = 21 nM, EC_{90} = 200 nM) were also well tolerated at P′. Thus, for the P4 ethylcarbamate capped inhibitors, the optimal P3/P1/P′ combination turned out to be β-methylcyclohexyl glycine/butynyl glycine/allyl amide, respectively.

Having established the appropriate substitution pattern for the inhibitor core, we then decided to study the effect of cap variation once again in an attempt to improve the overall profile of the inhibitor. Since propyl (**40**) and butynyl (**42**) residues at P1 displayed similar replicon potency, we decided to use both moieties for further SAR studies. We varied alkyl substitution on the carbamate cap, and the results are shown in Table 5. Replacement of ethyl carbamate with i-propyl carbamate afforded equipotent inhibitors (**45**, EC_{90} = 150 nM; **46**, EC_{90} = 150 nM). Incorporation of the i-butyl carbamate cap improved the replicon potency of P1 butynylglycine inhibitor (**48**, EC_{90} = 70 nM). Cyclizing the terminal carbon atoms of i-butyl carbamate to cyclopropylmethyl carbamate resulted in inhibitors (**49** and **50**) with improved replicon potency (EC_{90} = 100 nM and 70 nM, respectively). Increasing the ring size to cyclohexyl resulted in a loss of potency (**51** and **52**), clearly indicating the appropriate size requirement for the P4 carbamate cap. Modifications were carried out at the P4 position as well. However,

Table 5



Compd	R_4	P_1	Ki* (nM)	EC_{90} (nM)
40			28	150
42			9	150
45			24	150
46			8	150
47			58	na
48			9	70
49			32	100
50			7	70
51			130	na
52			20	250
53[a]			84	na
54[a]			13	200
55[b]			210	700
56[b]			9	600

[a] P_4 = Chg; [b] P_4 = spiroChg.

both moieties, cyclohexyl (**53** and **54**) and spirocyclohexyl (**55** and **56**) at P4, resulted in diminished enzyme and replicon potency.

Selected compounds with good potency were evaluated in rat PK study and the results are listed in Table 6. The compounds were dosed orally (10 mpk) as a suspension in 0.4% HPMC. Compound **37**, with 2-indanylglycine residue at P3, did not show appreciable AUC (0.7 μM.h) when dosed orally at 10 mpk. Interestingly, compounds with P3 β-methylcyclohexyl glycine residue displayed very good exposure. Thus, inhibitor **45** containing the P1-norval moiety exhibited an oral AUC of 6.6 μM·h with good concentration in the liver (808 ng/g at 6 h). The corresponding P1-butynyl analogue, **46**, showed slightly better AUC (7.9 μM·h) and even higher liver concentration (1111 ng/g). The isobutyl and cyclopropylmethyl-capped carbamate analogues, **48** and **50**, displayed very good PK profile as well. Finally, the ethyl carbamate-capped inhibitor **42** exhibited the best PK profile with an AUC of 26 μM·h and an oral bioavailability of 43%. This compound also demonstrated good liver concentration when measured at the 6 h time point (1106 ng/g). Clearly, inhibitors with the β-methylcyclohexyl glycine residue showed excellent oral exposure and good target organ concentration in rats.

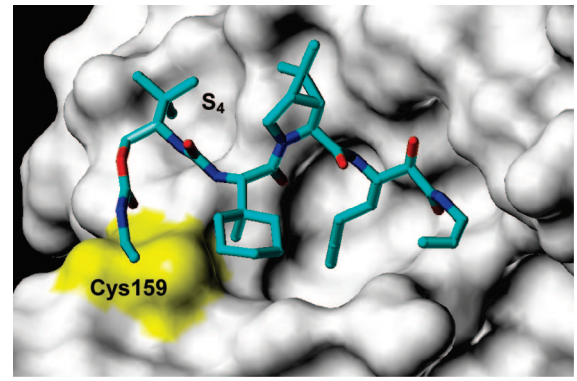


Figure 2. Model of inhibitor **42** docked to the surface of NS3 protease.

Table 6. Rat PK Data (po, 10 mpk) for Selected Compounds

compd	AUC (μM·h)$_{0-6\ h}$	liver conc. $C_{6\ h}$ (ng/g)
37	0.7	na
45	6.6	808
46	7.9	1111
48	4.9	750
50	5.0	581
42	26 (F=43%)[a]	1106

[a] AUC (μM·h)$_{0-24\ h}$.

Figure 2 depicts a model of inhibitor **42** docked onto the NS3 protease surface. The core (P3−P′) displayed interactions similar to those observed previously[8] for other inhibitors. Significantly, the P4 moiety was buried well into the S4 pocket, thus gaining additional hydrophobic interactions. The carbonyl oxygen of the carbamate moiety seemed to be in close proximity for the hydrogen bonding interaction with Cys159. These two additional interactions resulted in improved potency for this class of inhibitors.

Conclusions

Our exploration toward a suitable second generation HCV NS3 serine protease inhibitor resulted in the discovery of P4 ether and carbamate-derived compounds that provided fruitful results. Key hydrogen bond with Cys-159 and additional hydrophobic interactions with the enzyme S4 pocket may have resulted in enhanced potency. The ether-capped inhibitors improved replicon potency, but exhibited poor oral PK (in rats). While carbamate-capped inhibitors containing the P′ primary amide moiety improved the replicon potency, oral exposure in rats were poor as well. Incorporation of the P′ secondary amide, especially the allyl moiety, retained the potency and improved rat oral exposure significantly. Moreover, selected compounds displayed good distribution in the target organ, with liver exposure of 7−15 × EC_{90} at the 6 h time point. From our SAR studies, β-methylcyclohexylglycine was the preferred moiety at the P3 position, with the t-leucinol derived carbamate cap being the preferred P4 moiety. Compound **42**, incorporating the preferred moieties displayed replicon EC_{90} = 150 nM, with very good oral exposure in rats (AUC = 26 μM·h, F = 46%) and high liver concentration (1106 ng/g at 6 h). Additionally, inhibitors **48** and **50** exhibited superior binding (K_i* = 9 and 7 nM, respectively) and replicon potency (EC_{90} = 70 nM). Thus, we achieved potency (EC_{90}) improvement 5× over that of **1**, with significant enhancement in rat PK properties. In summary, thorough SAR studies with the introduction of ether and

carbamate-derived P4 caps resulted in novel HCV NS3 serine protease inhibitors with improved potency and pharmacokinetic profile.

Experimental Section

General Methods. Reagents and solvents, including anhydrous THF, dichloromethane, and DMF, were purchased from Aldrich, Acros, or other commercial sources and were used without further purification. Reactions that were moisture sensitive or using anhydrous solvents were performed under either nitrogen or argon atmosphere. Analytical thin layer chromatography (TLC) was performed on precoated silica gel plates obtained from Analtech. Visualization was accomplished with UV light or by staining with basic $KMnO_4$ solution or ethanolic H_2SO_4 solution. Compounds were purified by flash chromatography either on a glass column using Merck silica gel 60 (230−400 mesh) or on an ISCO RediSep disposable silica gel prepacked cartridges. NMR spectra were recorded at 300, 400, or 500 MHz for ^{1}H and at 75, 100, or 125 MHz for ^{13}C on a Bruker or Varian spectrometer with $CDCl_3$ or DMSO-d_6 as solvent. The chemical shifts are given in ppm, referenced to the deuterated solvent signal. Purity of target compounds were determined using LC-MS analysis. LC/MS analyses were performed using an Applied Biosystems API-150 mass spectrometer and a Shimadzu SCL-10A LC system. Column: Phenomenex Gemini C18, 5 μm, 50 mm × 4.6 mm ID. Gradient: from 90% water, 10% CH_3CN, 0.05%TFA, 5 min to 5% water, 95% CH_3CN, 0.05% TFA in 5 min. UV detection: 254 nm. Purity of targets compounds was ≥95%.

(1*R*,2*S*,5*S*)-Methyl-6,6-dimethyl-3-((*S*)-2-(1-methylcyclohexyl)-2-((4-nitrophenoxy)carbonylamino)acetyl)-3-azabicyclo[3.1.0]hexane-2-carboxylate (8, P3 = β-MeChg). To a cold (10 °C) solution of previously described intermediate **4**[12] (3.1 g, 8.66 mmol) in dichloromethane (50 mL) was added pyridine (1.76 mL, 21.7 mmol) followed by 4-nitrophenyl chloroformate (5.24 g, 26 mmol). Reaction temperature was maintained for 16 h. The reaction mixture was then quenched with saturated ammonium chloride solution (50 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 40 mL). The combined organic layer was washed with saturated sodium bicarbonate solution (100 mL), brine (100 mL), dried (Na_2SO_4), filtered, and concentrated. The crude residue was purified in a prepacked silica cartridge using 0−20% EtOAc in CH_2Cl_2 to give 3.74 g of **8**. ^{1}H NMR ($CDCl_3$) δ 8.24−8.21 (m, 2H), 7.28−2.26 (m, 2H), 5.79 (d, J = 9.75 Hz, 1H), 4.51 (app. s, 1H), 4.30 (d, J = 9.41 Hz, 1H), 3.97−3.88 (m, 2H), 3.77 (s, 3H), 1.63−1.42 (m, 11H), 1.12−1.05 (m, 7H), 0.92 (s, 3H).

(*S*)-2-Amino-3,3-dimethylbutyl ethylcarbamate hydrochloride (9, R = Et). To a solution of (*S*)-*N*-*t*-boc-leucinol (4 g, 18.43 mmol) in DMF (180 mL) was added copper (I) chloride (1.86 g, 18.8 mmol) followed by ethyl isocyanate (1.88 mL, 23.96 mmol). The reaction mixture was stirred at room temperature for 4 h when TLC (20/80 EtOAc/CH_2Cl_2) indicated reaction completion. The reaction mixture was diluted with diethyl ether (350 mL) and filtered through a pad of Celite. The filtrate was washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4), filtered, and concentrated to give 5.24 g of the *N*-*t*-boc protected intermediate (LC-MS = 289.1, M + H^+). This material (4.73 g) was treated with 4 M HCl in dioxane (70 mL) at room temperature for 4.5 h. The reaction mixture was then concentrated to provide 3.8 g of **9**. LC-MS (M + H^+) = 189.1.

(1*R*,2*S*,5*S*)-3-((2*S*,6*S*)-6-*tert*-Butyl-2-(1-methylcyclohexyl)-4,9-dioxo-8-oxa-3,5,10-triazadodecane)-6,6-dimethyl-3-azabicyclo[3.1.0]-hexane-2-carboxylic acid (11, P3 = β-MeChg, R = Et). To a cold (0 °C) solution of the above-described intermediates, **8** (0.5 g, 1.03 mmol) and **9** (0.3 g, 1.33 mmol) in dichloromethane (40 mL) was added DIPEA (0.57 mL, 3.075 mmol). The reaction mixture was maintained at that temperature for 12 h. At this time, another portion of **9** was added (0.12 g), and the temperature was maintained for an additional 5 h when TLC (20/80 EtOAc/CH_2Cl_2) indicated reaction completion. The reaction mixture was then quenched with saturated ammonium chloride solution (50 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 30 mL). The combined organic layer was washed with saturated sodium bicarbonate solution (100 mL) and brine (100 mL), dried (Na_2SO_4), filtered, and concentrated. The crude residue was purified in a prepacked silica cartridge using 0−20% EtOAc in CH_2Cl_2 to give 0.46 g of the methyl ester intermediate. This material was taken in THF/MeOH (10 mL each) and treated with aq. 1 M LiOH (2.6 mL) at room temperature for 4 h. The reaction mixture was concentrated, and the residue was acidified with aq. 1 N HCl (25 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layer was washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), filtered, and concentrated to give 0.44 g of **11**, LC-MS (M + H^+) = 523.1.

2(*S*)-[[[[2-[(1*R*,5*S*)-2(*S*)-[[[1-[1,2-Dioxo-2-(2-propenylamino)-ethyl]-4-pentynyl]amino]carbonyl]-6,6-dimethyl-3-azabicyclo-[3.1.0]hex-3-yl]-1(*S*)-(1-methylcyclohexyl)-2-oxoethyl]amino]carbonyl]amino]-3,3-dimethylbutyl ethylcarbamate (42). To a cold (0 °C) solution of the above-described intermediate **11** (0.25 g, 0.478 mmol) and intermediate **6** (P1 = butynyl, R′ = allyl, 0.12 M in CH_2Cl_2, 5.14 mL, 0.622 mmol) in CH_2Cl_2/DMF (9 mL/6 mL) were added HATU (0.24 g, 0.621 mmol) and DIPEA (0.264 mL, 1.434 mmol). The reaction mixture was maintained between 0−10 °C, over 16 h. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and washed with saturated ammonium chloride solution (30 mL), saturated sodium bicarbonate solution (30 mL), water (30 mL), and brine (30 mL), dried (Na_2SO_4), filtered, and concentrated. The crude residue was then taken in CH_2Cl_2 (12 mL) and treated with Dess-Martin's periodinane (0.405 g, 0.956 mmol) at room temperature for 4 h. The reaction mixture was diluted with CH_2Cl_2 (40 mL), washed with 10% aq sodium thiosulfate solution (50 mL), saturated sodium bicarbonate solution (2 × 50 mL), and brine (50 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified in a prepacked silica cartridge using 20−50% acetone in hexanes to give 0.243 g of **42** as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88 and 8.77 (app.t, J = 5.99 and 6.30 Hz, 1H), 8.52 and 8.44 (d, J = 6.93 and 7.56 Hz, 1H), 6.78 (br. s, 1H), 6.09 (d, J = 9.45 Hz, 1H), 6.02 (d J = 9.77 Hz, 1H), 5.83−5.74 (m, 1H), 5.13−5.04 (m, 2H), 5.03−4.97 (m, 1H), 4.24 (s, 1H), 4.20 (d, J = 7.88 Hz, 1H), 4.01 (d, J = 11.03 Hz, 1H), 3.90 (d, J = 10.40 Hz, 1H), 3.84−3.72 (m, 4H), 3.59−3.55 (m, 1H), 2.99−2.95 (m, 2H), 2.79 (app. t, J = 2.52 Hz, 1H), 2.36−2.31 (m, 2H), 2.01−1.94 (m, 1H), 1.73−1.65 (m, 1H), 1.56−1.07 (m, 12H), 0.99−0.78 (complex, 21H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.53, 197.06, 172.10, 171.42, 161.68, 158.89, 156.98, 135.34, 135.06, 134.98, 116.47, 116.33, 84.33, 84.13, 72.65, 72.54, 64.59, 60.08, 58.70, 56.98, 54.19, 48.27, 41.70, 37.82, 35.89, 34.89, 34.39, 34.10, 31.38, 30.46, 29.93, 29.18, 27.88, 27.33, 26.93, 26.88, 26.78, 22.19, 22.01, 19.93, 19.35, 15.91, 15.56, 15.20, 13.50. LCMS (M + H)$^+$: 699.2.

(1*R*,5*S*)-*N*-[3-Amino-1-(cyclobutylmethyl)-2,3-diooxopropyl]-3-[2(*S*)-cyclohexyl-2-[[[[1(*S*)-(methoxymethyl)-2,2-dimethylpropyl]amino]carbonyl]amino]-1-oxoethyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (17). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.29 and 8.09 (d, J = 7.25 and 7.56 Hz, 1H), 8.01 (d, J = 12.92 Hz, 1H), 7.78 (d, J = 8.51 Hz, 1H), 6.01 (app. d, J = 9.45 Hz, 1H), 5.87 (app. t, J = 7.88 Hz, 1H), 4.95−4.89 (m, 1H), 4.26 and 4.22 (s, 1H), 4.13−4.06 (m, 1H), 3.88 (d, J = 12.92 Hz, 1H), 3.80−3.70 (m, 1H), 3.51−3.47 (m, 1H), 3.25−3.19 (m, 5H), 2.46−2.30 (m, 1H), 2.00−1.92 (m, 2H), 1.80−1.40 (m, 16H), 1.30−1.25 (m, 1H), 1.14−1.08 (m, 2H), 1.00−0.80 (m, 15H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.58, 198.06, 171.96, 171.84, 171.81, 171.64, 163.80, 163.67, 158.82, 73.43, 60.62, 60.07, 58.89, 56.83, 56.34, 56.14, 52.81, 47.75, 47.64, 37.70, 37.59, 34.78, 34.75, 33.03, 31.58, 29.89, 29.72, 29.36, 29.28, 28.74, 28.67, 28.46, 28.27, 28.20, 27.58, 26.97, 26.90, 26.41, 19.45, 18.68, 18.63, 13.53, 13.44. LCMS (M + H)$^+$: 604.1.

**(1*R*,5*S*)-*N*-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(*S*)-[[[[1(*S*)-(methoxymethyl)-2,2-dimethylpropyl]amino]carbonyl]amino]-2-(1-methylcyclohexyl)-1-oxoethyl]-6,6-dimethyl-

3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (18). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27 and 8.10 (d, J = 7.56 and 7.56 Hz, 1H), 8.03 and 7.98 (s, 1H), 7.77 (s, 1H), 6.17−6.09 (m, 1H), 6.01−5.98 (m, 1H), 4.99−4.95 and 4.87−4.83 (m, 1H), 4.26−4.19 (m, 2H), 3.94−3.89 (m, 1H), 3.82−3.75 (m, 1H), 3.53−3.49 (m, 1H), 3.23−3.05 (m, 5H), 2.49−2.35 (m, 1H), 2.00−1.88 (m, 2H), 1.80−1.70 (m, 3H), 1.66−1.08 (m, 15H), 0.99−0.94 (m, 6H), 0.80−0.72 (m, 12H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.65, 198.02, 171.80, 171.69, 171.63, 171.41, 163.92, 163.71, 158.95, 158.88, 73.52, 60.42, 60.04, 58.89, 56.86, 52.96, 52.69, 48.33, 48.28, 37.86, 37.65, 37.56, 34.86, 34.80, 33.00, 32.96, 31.41, 30.46, 28.77, 28.64, 28.58, 28.28, 28.25, 27.58, 26.94, 26.91, 26.77, 22.19, 22.01, 19.99, 19.91, 19.34, 19.30, 18.72, 18.55, 13.53, 13.46. HRMS calcd for $C_{33}H_{56}N_5O_6$ (M + H)$^+$: 618.4230. Found: 618.4237.

(1*R*,5*S*)-*N*-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(*S*)-[[[[1(*S*)-(methoxymethyl)-2,2-dimethylpropyl]amino]carbonyl]amino]-2-(1-methylcyclopentyl)-1-oxoethyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (19). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.28 and 8.15 (d, J = 7.25 and 7.25 Hz, 1H), 8.02 and 7.97 (bs, 1H), 7.76 (d, J = 4.09 Hz, 1H), 6.13 (app. t, J = 10.40 Hz, 1H), 6.01−5.98 (m, 1H), 4.97−4.93 and 4.86−4.82 (m, 1H), 4.35−4.31 (m, 1H), 4.28 and 4.24 (s, 1H), 3.92−3.89 (m, 1H), 3.79−3.72 (m, 1H), 3.53−3.49 (m, 1H), 3.23−3.18 (m, 5H), 2.49−2.30 (m, 1H), 2.01−1.93 (m, 2H), 1.79−1.42 (m, 14H), 1.28−1.16 (m, 2H), 0.99−0.96 (m, 6H), 0.90−0.70 (m, 12H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.64, 198.01, 171.93, 171.80, 171.72, 171..64, 163.93, 163.69, 158.96, 158.88, 73.49, 60.33, 59.97, 58.88, 56.87, 56.61, 56.47, 52.91, 52.69, 48.20, 48.12, 46.28, 37.63, 37.52, 36.56, 36.46, 36.20, 36.06, 34.84, 34.79, 33.02, 33.96, 31.53, 31.46, 28.77, 28.64, 28.25, 27.58, 26.95, 25.13, 25.10, 24.85, 19.34, 18.72, 18.58, 13.54, 13.48. HRMS calcd for $C_{32}H_{54}N_5O_6$ (M + H)$^+$: 604.4074. Found: 604.4101.

(1*R*,5*S*)-*N*-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]3-[2(*S*)-(2,3-dihydro-1*H*-inden-2-yl)-2-[[[[1(*S*)-(methoxymethyl)2,2-dimethylpropyl]amino]carbonyl]amino]-1-oxoethyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (20). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.34 and 8.17 (d, J = 7.56 and 7.25 Hz, 1H), 8.04 (d, J = 13.24 Hz, 1H), 7.79 (bs, 1H), 7.20−7.14 (m, 2H), 7.11−7.09 (m, 2H), 6.25 (d, J = 9.14 Hz, 1H),5.92 (d, J = 9.77 Hz, 1H), 5.00−4.94 (m, 1H), 4.32−4.24 (m, 2H), 3.82 (d, J = 13.55 Hz, 1H), 3.77−3.63 (m, 1H), 3.52−3.47 (m, 1H), 3.25−3.22 (m, 2H), 3.20 (s, 3H), 2.90−2.60 (m, 5H), 2.49−2.35 (m, 1H), 2.04−1.95 (m, 2H), 1.83−1.73 (m, 3H), 1.68−1.59 (m, 3H), 1.43−1.26 (m, 2H), 1.00 and 0.98 (s, 3H), 0.83−0.80 (m, 12H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.60, 198.95, 171.88, 171.71, 171.65, 163.79, 163.70, 158.77, 143.44, 143.43, 143.20, 143.19, 127.03, 126.97, 125.28, 125.06, 73.40, 60.74, 58.91, 56.87, 54.50, 54.18, 52.89, 52.83, 47.68, 47.51, 42.77, 42.52, 37.58, 37.54, 36.03, 35.84, 35.80, 34.78, 33.08, 31.64, 31.61, 28.69, 28.27, 28.19, 27.59, 26.95, 26.88, 19.48, 18.68, 13.57, 13.50. HRMS calcd for $C_{35}H_{52}N_5O_6$ (M + H)$^+$: 638.3918. Found: 638.3944.

(1*R*,5*S*)-*N*-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2-[[[[1(*S*)-(methoxymethyl)-2-methylpropyl]amino]carbonyl]-amino]-2(*S*)-(1-methylcyclohexyl)-1-oxoethyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (21). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.26 and 8.07 (d, J = 7.25 and 7.25 Hz, 1H), 8.01 and 7.97 (s, 1H), 7.76 (s, 1H), 6.13 (app. t, J = 9.45 Hz, 1H), 5.97 (d, J = 9.45 Hz, 1H), 4.99−4.94 and 4.88−4.84 (m, 1H), 4.27−4.21 (m, 2H), 3.94−3.89 (m, 1H), 3.83−3.75 (m, 1H), 3.54−3.50 (m, 1H), 3.28−3.18 (m, 5H), 2.49−2.30 (m, 1H), 1.98−1.92 (m, 2H), 1.81−1.71(m, 3H), 1.65−1.09 (m, 16H), 1.00−0.94 (m, 6H), 0.79−0.74 (m, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.64, 198.00, 171.79, 171.62, 171.33, 163.90, 163.71, 158.85, 158.76, 73.96, 60.42, 60.03, 59.07, 58.58, 54.14, 52.97, 52.71, 48.31, 48.27, 37.83, 37.66, 37.58, 34.55, 34.41, 34.19, 33.00, 32.97, 31.40, 31.42, 29.83, 29.77, 28.77, 28.64, 28.29, 28.25, 27.83, 27.67, 26.96, 26.92, 26.76, 22.18, 22.00, 20.35, 20.01, 19.94, 19.33, 19.30, 18.71, 18.55, 18.35, 13.45, 13.37. HRMS calcd for $C_{32}H_{54}N_5O_6$(M + H)$^+$: 604.4074. Found: 604.4087.

(1*R*,5*S*)-*N*-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(*S*)-[[[[1(*S*)-(methoxymethyl)-1-methylbutyl]amino]carbonyl]amino]-2-(1-methylcyclohexyl)acetyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (22). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.26 and 807 (d, J = 8.19 and 8.51 Hz, 1H), 8.02 and 7.98 (s, 1H), 7.76 (s, 1H), 6.11 (app. t, J = 9.77 Hz, 1H), 5.82 (s, 1H), 4.98−4.93 and 4.87−4.82 (m, 1H), 4.29 and 4.25 (s, 1H), 4.21−4.14 (m, 1H), 3.98−3.93 (m, 1H), 3.81−3.72 (m, 1H), 3.34−3.31 (m, 2H), 3.22 (s, 3H), 2.49−2.36 (m, 1H), 1.99−1.14 (m, 24H), 1.09 (s, 3H), 1.00−0.92 (m, 6H), 0.90−0.80 (m, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.64, 198.01, 171.82, 171.64, 171.66, 171.43, 163.85, 163.70, 158.10, 158.00, 78.21, 60.45, 60.03, 59.41, 58.20, 55.29, 52.98, 52.71, 48.30, 39.38, 37.75, 37.66, 37.57, 34.52, 34.36, 34.09, 33.00, 32.96, 31.42, 28.77, 28.64, 28.29, 28.25, 27.89, 27.73, 27.00, 26.96, 26.74, 23.27, 22.18, 21.99, 20.03, 19.95, 19.35, 18.71, 18.55, 17.10, 15.41, 13.46, 13.38. HRMS calcd for $C_{33}H_{56}N_5O_6$ (M + H)$^+$: 650.4493. Found: 650.4512.

(1*R*,5*S*)-*N*-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(*S*)-[[[[1(*R*)-(methoxymethyl)-1,3-dimethylbutyl]amino]carbonyl]amino]-2-(1-methylcyclohexyl)acetyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (23). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27 and 8.07 (d, J = 7.56 and 7.25 Hz, 1H), 8.02 and 7.98 (s, 1H), 7.77 (s, 1H), 6.12 (app. t, J = 9.45 Hz, 1H), 5.80 (bs, 1H), 4.98−4.94 and 4.88−4.84 (m, 1H), 4.29 and 4.25 (d, J = 14.81 Hz, 1H), 4.19 (app. t, J = 10.08 Hz, 1H), 3.95 (dd, J = 10.40, 18.60 Hz, 1H), 3.82−3.75 (m, 1H), 3.27−3.25 (m, 2H), 3.22 (s, 3H), 2.49−2.35 (m, 1H), 2.00−1.92 (m, 2H), 1.81−1.14 (m, 21 H), 1.12−0.81 (m, 18H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.64, 198.02, 171.81, 171.70, 171.66, 171.38, 163.89, 163.71, 157.93, 157.86, 78.69, 69.37, 60.46, 60.04, 59.34, 58.09, 56.68, 55.65, 52.98, 52.71, 48.32, 44.60, 44.54, 37.89, 37.87, 37.67, 37.58, 34.53, 34.37, 34.14, 33.00, 32.97, 31.44, 30.45, 28.77, 28.64, 28.30, 28.25, 27.88, 27.75, 26.98, 26.94, 26.77, 25.58, 25.21, 24.10, 23.82, 22.20, 22.01, 20.05, 19.96, 19.39, 19.35, 18.71, 18.55, 13.62, 13.53. HRMS calcd for $C_{34}H_{58}N_5O_6$ (M + H)$^+$: 632.4387. Found: 632.4405.

(1*R*,5*S*)-*N*-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(*S*)-[[[[1(*S*)-[(1,1-dimethylethoxy)methyl]-2,2-dimethylpropyl]amino]carbonyl]amino]-2-(1-methylcyclohexyl)acetyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (24). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.25 and 8.04 (d, J = 8.19 and 8.51 Hz, 1H), 8.02 and 7.98 (s, 1H), 7.77 (s, 1H), 6.23 (d, J = 9.77 Hz, 1H), 5.91−5.87 (m, 1H), 4.98−4.94 and 4.88−4.84 (m, 1H), 4.29−4.23 (m, 2H), 3.95−3.90 (m, 1H), 3.82−3.75 (m, 2H), 3.33−3.20 (m, 2H), 2.49−2.35 (m, 1H), 1.99−1.91 (m, 2H), 1.85−1.71 (m, 3H), 1.65−1.14 (m, 15H), 1.09 (s, 9H), 0.99−0.94 (m, 6H), 0.82 (s, 9H), 0.80 and 0.76 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.63, 198.01, 171.81, 171.68, 171.65, 171.41, 163.90, 163.71, 158.91, 158.85, 110.47, 72.95, 62.68, 60.42, 59.96, 58.38, 58.27, 57.62, 52.98, 52.71, 48.28, 48.23, 37.67, 37.57, 34.91, 34.83, 34.42, 34.31, 34.20, 34.15, 32.99, 32.97, 31.41, 30.44, 28.77, 28.65, 28.30, 28.24, 28.08, 27.89, 27.62, 26.95, 26.91, 26.87, 26.78, 22.22, 22.02, 20.15, 20.08, 19.29, 18.71, 18.55, 13.44, 13.35. LCMS (M + H)$^+$: 660.2.

(1*R*,5*S*)-*N*-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(*S*)-[[[[1-[(1,1-dimethylethoxy)methyl]cyclohexyl]amino]carbonyl]-amino]-2-(1-methylcyclohexyl)acetyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (25). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.26 and 8.06 (d, J = 7.25 and 8.19 Hz, 1H), 8.02 and 7.98 (s, 1H), 7.76 (s, 1H), 6.12 (app. t, J = 8.82 Hz, 1H), 5.66 (s, 1H), 4.99−4.93 and 4.88−4.82 (m, 1H), 4.29 and 4.25 (s, 1H), 4.20 (app. t, J = 11.66 Hz, 1H), 3.99−3.93 (m, 1H), 3.81−3.72 (m, 1H), 3.24−3.20 (m, 2H), 2.49−2.36 (m, 1H), 2.01−1.90 (m, 2H), 1.85−1.14 (m, 28H), 1.07 (s, 9H), 0.99−0.92 (m, 6H), 0.82 and 0.80 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.64, 198.00,

171.83, 171.80,k 171.67, 171.48, 163.89, 163.71, 157.90, 157.82, 72.60, 69.38, 67.15, 60.45, 60.03, 58.02, 56.66, 54.89, 52.98, 52.70, 48.29, 37.80, 37.66, 37.58, 34.54, 34.44, 34.17, 32.99, 32.96, 32.66, 31.89, 31.39, 30.43, 28.77, 28.64, 28.27, 27.86, 27.71, 26.99, 26.95, 26.77, 26.31, 22.19, 22.01, 21.63, 20.09, 19.35, 19.32, 18.71, 18.55, 13.49, 13.42. HRMS calcd for $C_{37}H_{62}N_5O_6$ $(M + H)^+$: 672.4700. Found: 672.4731.

(1*R*,5*S*)-*N*-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(*S*)-[[[[2,2-dimethyl-1(*S*)-[(phenylmethoxy)methyl]propyl]-amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (26). HRMS calcd for $C_{36}H_{56}N_5O_6$ $(M + H)^+$: 654.4230. Found: 654.4246.

2(*S*)-[[[[2-[(1*R*,5*S*)-2(*S*)-[[[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]amino]carbonyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-yl]-1(*S*)-(2,3-dihydro-1*H*-inden-2-yl)-2-oxoethyl]amino]carbonyl]amino]-3,3-dimethylbutyl Methylcarbamate (27). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.34 and 8.16 (d, J = 6.93, 7.56 Hz, 1H), 8.04 (d, J = 12.92 Hz, 1H), 7.79 (d, J = 4.09 Hz, 1H), 7.21−7.10 (m, 4H), 6.91 (d, J = 4.41 Hz, 1H), 6.26 (d, J = 8.82 Hz, 1H), 5.92 (d, J = 9.77 Hz, 1H), 4.99−4.94 (m, 1H), 4.33−4.24 (m, 2H), 4.06 (d, J = 13.82 Hz, 1H), 3.88−3.80 (m, 2H), 3.77−3.64 (m, 1H), 3.61−3.55 (m, 1H), 2.90−2.79 (m, 2H), 2.75−2.61 (m, 3H), 2.56 (d, J = 4.72 Hz, 3H), 2.49−2.36 (m, 1H), 2.02−1.95 (m, 2H), 1.84−1.73 (m, 3H), 1.68−1.58 (m, 3H), 1.45−1.37 (m, 1H), 1.34−1.24 (m, 1H), 1.02−0.98 (m, 3H), 0.84−0.81 (m, 12H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.61, 198.16, 171.83, 171.61, 163.79, 163.69, 158.68, 157.68, 143.45, 143.23, 127.02, 126.95, 125.32, 125.07, 64.72, 60.73, 60.16, 57.05, 52.91, 52.82, 47.68, 47.51, 42.78, 42.56, 37.61, 37.55, 36.04, 35.86, 35.81, 35.75, 34.78, 34.75, 33.08, 31.65, 31.63, 28.70, 28.29, 28.19, 27.88, 27.35, 26.97, 26.88, 19.49, 18.69, 18.67, 13.57, 13.51. HRMS calcd for $C_{36}H_{53}N_6O_7$ $(M + H)^+$: 681.3976. Found: 681.3991.

2(*S*)-[[[[2-[(1*R*,5*S*)-2(*S*)-[[[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]amino]carbonyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-yl]-1(*S*)-(2,3-dihydro-1*H*-inden-2-yl)-2-oxoethyl]amino]carbonyl]amino]-3,3-dimethylbutyl Ethylcarbamate (28). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.34 and 8.16 (d, J = 7.88 and 7.25 Hz, 1H), 8.04 (d, J = 12.93 Hz, 1H), 7.80 (d, J = 4.10 Hz, 1H), 7.18−7.04 (m, 5H), 6.26−6.6.25 (m, 1H), 5.93−5.91 (m, 1H), 4.99−4.94 (m, 1H), 4.30−4.23 (m, 2H), 4.05−4.03 (m, 1H), 3.88−3.54 (m, 4H), 3.02−2.97 (m, 2H), 2.91−2.59 (m, 5H), 2.49−2.35 (m, 1H), 2.03−1.95 (m, 2H), 1.85−1.71 (m, 3H), 1.68−1.58 (m, 3H), 1.43−1.39 (m, 1H), 1.33−1.24 (m, 1H), 1.02−0.98 (m, 6H), 0.89−0.76 (m, 12H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 198.62, 198.16, 171.84, 171.67, 164.09, 163.80, 158.89, 157.01, 143.46, 143.27, 127.03, 127.01, 125.30, 125.07, 110.23, 64.54, 60.72, 60.16, 57.01, 54.48, 53.06, 52.91, 52.82, 47.69, 47.52, 42.82, 42.57, 37.60, 37.54, 36.03, 36.85, 35.93, 35.82, 34.78, 33.09, 33.07, 31.66, 30.48, 28.70, 28.28, 28.20, 27.68, 27.55, 27.34, 26.96, 26.88, 19.48, 18.68, 15.96, 13.58, 13.51. LCMS $(M + H)^+$: 695.4.

2(*S*)-[[[[2-[(1*R*,5*S*)-2(*S*)-[[[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]amino]carbonyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-yl]-1(*S*)-(2,3-dihydro-1*H*-inden-2-yl)-2-oxoethyl]amino]carbonyl]amino]3,3-dimethylbutyl (1-methylethyl)carbamate (29). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.37 and 8.17 (d, J = 7.25 and 7.56 Hz, 1H), 8.05 (d, J = 13.24 Hz, 1H), 7.80 (bs, 1H), 7.22−7.09 (m, 4H), 6.96 (bs, 1H), 6.25 (d, J = 10.40 Hz, 1H), 5.92 (d, J = 8.82 Hz, 1H), 5.00−4.94 (m, 1H), 4.28−4.24 (m, 2H), 4.04 (d, J = 11.66 Hz, 1H), 3.85−3.55 (m, 5H), 2.90−2.78 (m, 2H), 2.76−2.59 (m, 3H), 2.49−2.35 (m, 1H), 2.02−1.95 (m, 2H), 1.83−1.73 (m, 3H), 1.68−1.57 (m, 3H), 1.43−1.23 (m, 2H), 1.06−0.98 (m, 9H), 0.84−0.80 (m, 12H). LCMS $(M + H)^+$: 709.2.

2(*S*)-[[[[2-[(1*R*,5*S*)-2(*S*)-[[[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]amino]carbonyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-yl]-1(*S*)-(2,3-dihydro-1*H*-inden-2-yl)-2-oxoethyl]amino]carbonyl]amino]-3,3-dimethylbutyl (1,1-dimethylethyl)carbamate (30). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.34 and 8.17 (d, J = 6.93 and 7.56 Hz, 1H), 8.04 (d, J = 12.92 Hz, 1H), 7.79 (bs, 1H), 7.21−7.14 (m, 2H), 7.11−7.09 (m, 2H), 6.75 (bs, 1H), 6.24 (d, J = 9.14 Hz, 1H), 5.91 (bs, 1H), 4.99−4.94 (m, 1H), 4.31−4.24 (m, 2H), 4.02−3.98 (m, 1H), 3.82−3.79 (m, 2H), 3.66−3.54 (m, 2H), 2.92−2.58 (m, 5H), 2.49−2.35 (m, 1H), 2.03−1.93 (m, 2H), 1.83−1.73 (m, 3H), 1.68−1.57 (m, 3H), 1.46−1.38 (m, 2H), 1.21 (s, 9H), 1.00−0.97 (m, 3H), 0.82−0.81 (m, 12H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.61, 198.15, 171.82, 171.66, 163.79, 163.69, 158.70, 155.62, 143.48, 143.45, 143.24, 143.21, 127.03, 126.95, 125.23, 125.08, 110.22, 60.78, 60.19, 57.01, 52.92, 52.79, 50.20, 47.70, 47.56, 42.78, 42.56, 37.63, 37.56, 36.04, 35.90, 35.86, 34.85, 33.08, 31.65, 29.53, 28.69, 28.28, 28.19, 27.68, 27.56, 27.31, 26.96, 26.88, 19.52, 18.68, 13.59, 13.53. LCMS $(M + H)^+$: 723.2.

2(*S*)-[[[[2-[(1*R*,5*S*)-2(*S*)-[[[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropylamino]amino]carbonyl]-6,6-dimethyl-3-azabicyclo[3.1.0]-hex-3-yl]-1(*S*)-(2,3-dihydro-1*H*-inden-2-yl)-2-oxoethyl]amino]carbonyl]amino]-3,3-dimethylbutyl Dimethylcarbamate (31). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.33 and 8.15 (d, J = 6.30 and 7.56 Hz, 1H), 8.03 (d, J = 11.66 Hz, 1H), 7.78 (bs, 1H), 7.17−7.10 (m, 4H), 6.30 (d, J = 8.51 Hz, 1H), 5.97 (d, J = 10.08 Hz, 1H), 4.99−4.92 (m, 1H), 4.31−4.24 (m, 2H), 4.11 (d, J = 11.03 Hz, 1H), 3.85−3.76 (m, 2H), 3.66−3.60 (m, 2H), 2.90−2.62 (m, 11H), 2.49−2.36 (m, 1H), 2.02−1.95 (m, 2H), 1.84−1.75 (m, 3H), 1.70−1.58 (m, 3H), 1.45−1.39 (m, 1H), 1.33−1.27 (m, 1H), 1.00−0.97 (m, 3H), 0.90−0.80 (m, 12H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.61, 198.16, 171.63, 171.58, 171.50, 163.78, 163.68, 158.64, 156.63, 143.41, 143.38, 143.11, 127.00, 125.20, 125.11, 65.58, 60.78, 60.16, 56.84, 54.29, 53.98, 52.93, 52.83, 47.71, 47.53, 42.61, 42.42, 37.58, 37.54, 36.85, 36.29, 36.03, 35.87, 35.61, 34.46, 33.10, 31.61, 28.69, 28.29, 28.19, 27.61, 27.39, 26.94, 26.86, 19.46, 18.68, 13.55, 13.48. HRMS calcd for $C_{37}H_{55}N_6O_7$ $(M + H)^+$: 695.4132. Found: 695.4149.

(1*R*,5*S*)-*N*-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(*S*)-[[[[1(*S*)-[[[(ethylamino)carbonyl]oxy]methyl]-2,2-dimethylpropyl]amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (32). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.29 and 8.20 (d, J = 7.3 and 7.0 Hz, 1H), 8.02 and 7.97 (app. s, 1H), 7.76−7.74 (m, 1H), 7.01−6.96 (m, 1H), 6.08−6.02 (m, 2H), 4.99−4.95 and 4.88−4.83 (m, 1H), 4.27 (app. s, 1H), 4.21−4.16 (m, 1H), 4.04−4.02 (m, 1H), 3.92−3.74 (m, 3H), 3.60−3.56 (m, 1H), 2.99−2.96 (m, 2H), 1.99−1.94 (m, 2H), 1.81−1.72 (m, 2H), 1.66−1.54 (m, 2H), 1.45−1.41 (m, 1H), 1.28−1.25 (m, 2H), 1.00−0.77 (complex, 29H).

2(*S*)-[[[[2-[(1*R*,5*S*)-2(*S*)-[[[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]amino]carbonyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-yl]-1(*S*)-cyclohexyl-2-oxoethyl]amino]carbonyl]amino]-3,3-dimethylbutyl Ethylcarbamate (33). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.29 and 8.09 (d, J = 7.2 and 7.9 Hz, 1H), 7.99 and 8.01 (app. s, 1H), 7.77 and 7.78 (app. s, 1H), 6.98−6.96 (m, 1H), 6.03−6.00 (m, 1H), 5.90−5.86 (m, 1H), 4.95−4.90 (m, 1H), 4.25 and 4.22 (app. s, 1H), 4.12−4.00 (m, 2H), 3.93−3.73 (m, 3H), 3.70−3.58 (m, 1H), 2.99−2.97 (m, 2H), 2.49−2.46 and 2.37−2.31 (m, 1H), 2.01−1.96 (m, 2H), 1.81−1.40 (m, 10H), 1.31−1.24 (m, 2H), 1.12−0.88 (complex, 16H), 0.82 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 198.60, 198.07, 175.20, 171.95, 171.81, 171.59, 163.70, 158.71, 156.98, 64.62, 60.61, 56.98, 52.84, 47.75, 37.76, 37.63, 35.89, 34.85, 33.06, 31.62, 28.75, 28.68, 28.29, 28.23, 27.37, 26.98, 26.93, 26.44, 19.43, 18.69, 15.91, 13.54, 13.44. LCMS $(M + H)^+$: 661.2.

2(*S*)-[[[[2-[(1*R*,5*S*)-2(*S*)-[[[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]amino]carbonyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-yl]-1(*S*)-(1-methylcyclohexyl)-2-oxoethyl]amino]carbonyl]amino]-3,3-dimethylbutyl Ethylcarbamate (34). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.26 and 8.09 (d, J = 6.30 and 9.14 Hz, 1H), 8.02 and 7.98 (s, 1H), 7.77 (s, 1H), 6.98 (t, J = 7.25 Hz, 1H), 6.11 (app. d, J = 11.35 Hz, 1H), 6.02 (app. d, J = 9.45 Hz, 1H), 4.99−4.95 and 4.87−4.83 (m, 1H), 4.26−4.21 (m, 2H), 4.01−3.98 (m, 1H), 3.90

(app. t, J = 11.03 Hz, 1H), 3.84−3.75 (m, 2H), 3.60−3.55 (m, 1H), 3.00−2.95 (m, 2H), 1.98−1.93 (m, 2H), 1.80−1.72 (m, 3H), 1.66−1.07 (m, 15H), 0.99−0.94 (m, 9H), 0.84−0.77 (m, 12H). (Note: 1 proton is apparently hidden under the solvent peak). LCMS $(M + H)^+$: 675.4.

2(*S*)-[[[[2-[(1*R*,5*S*)-2(*S*)-[[[3-Amino-1-(cyclopropylmethyl)-2,3-dioxopropyl]amino]carbonyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-yl]-1(*S*)-(2,3-dihydro-1*H*-inden-2-yl)-2-oxoethyl]amino]carbonyl]amino]-3,3-dimethylbutyl Ethylcarbamate (35). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.45 and 8.32 (d, J = 7.56 and 6.94 Hz, 1H), 8.04 (d, J = 7.25 Hz, 1H), 7.78 (d, J = 7.88 Hz, 1H), 7.22−7.04 (m, 5H), 6.28−6.6.22 (m, 1H), 5.96−5.90 (m, 1H), 5.17−5.10 (m, 1H), 4.32−4.20 (m, 2H), 4.05−4.02 (m, 1H), 3.83 (app. d, J = 10.1 Hz, 2H), 3.75−3.58 (m, 2H), 3.02−2.97 (m, 2H), 2.89−2.58 (m, 5H), 1.73−1.63 (m, 1H), 1.56−1.26 (m, 3H), 1.02−0.98 (m, 6H), 0.89−0.75 (m, 13H), 0.47−0.35 (m, 2H), 0.15−0.02 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 198.49, 198.07, 171.90, 171.78, 171.67, 171.62, 163.71, 163.53, 158.69, 157.01, 143.44, 143.40, 143.12, 126.96, 125.32, 125.09, 109.93, 64.58, 64.53, 60.59, 60.14, 57.02, 55.13, 54.95, 47.71, 47.60, 42.71, 42.61, 36.00, 35.93, 35.88, 35.82, 34.79, 31.70, 30.46, 27.63, 27.57, 27.34, 26.98, 26.89, 26.80, 19.50, 15.96, 13.59, 13.53, 8.83, 8.71, 5.92, 5.23, 5.04, 4.90. LCMS $(M + H)^+$: 681.2.

2(*S*)-[[[[2-[(1*R*,5*S*)-2(*S*)-[[[1-(Cyclopropylmethyl)-2,3-dioxo-3-(2-propenylamino)propyl]amino]carbonyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-yl]-1(*S*)-(2,3-dihydro-1*H*-inden-2-yl)-2-oxoethyl]amino]carbonyl]amino]-3,3-dimethylbutyl Ethylcarbamate (36). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.91−8.85(m, 1H), 8.50 and 8.39 (d, J = 6.62 and 7.25 Hz, 1H), 7.22−7.09 (m, 4H), 7.03 (bs, 1H), 6.26 (d, J = 7.56 Hz, 1H), 5.92 (d, J = 8.51 Hz, 1H), 5.84−5.76 (m, 1H), 5.14−5.05 (m, 3H), 4.32−4.21 (m, 2H), 4.05 (app. d, J = 11.03 Hz, 1H), 3.84 (app. d, J = 9.77 Hz, 2H), 3.75−3.55 (m, 4H), 3.01−2.97 (m, 2H), 2.91−2.59 (m, 5H), 1.76−1.67 (m, 1H), 1.55−1.28 (m, 3H), 1.01−0.98 (m, 6H), 0.92−0.80 (m, 13H), 0.47−0.36 (m, 2H), 0.14−0.03 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.01, 197.59, 171.94, 171.77, 171.67, 161.64, 161.43, 158.69, 157.00, 143.52, 135.11, 127.04, 125.35, 125.10, 116.48, 116.42, 64.54, 60.52, 60.11, 57.01, 55.46, 55.27, 47.70, 47.57, 42.67, 41.73, 35.93, 35.80, 31.70, 31.62, 27.64, 27.59, 27.34, 26.98, 26.90, 19.50, 15.96, 13.57, 13.52, 8.83, 8.72, 5.99, 5.92, 5.26, 5.04. HRMS calcd for $C_{39}H_{57}N_6O_7$ $(M + H)^+$: 721.4289. Found: 721.4301.

2(*S*)-[[[[1(*S*)-(2,3-Dihydro-1*H*-inden-2-yl)-2-[(1*R*,5*S*)-2(*S*)-[[[1-[1,2-dioxo-2-(2-propenylamino)ethyl]butyl]amino]carbonyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-yl]-2-oxoethyl]amino]carbonyl]amino]-3,3-dimethylbutyl Ethylcarbamate (37). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.91 and 8.87(t, J = 5.99 and 5.67 Hz, 1H), 8.44 and 8.31 (d, J = 6.93 and 7.56 Hz, 1H), 7.20−7.09 (m, 4H), 7.04 (app. t, J = 5.04 Hz, 1H), 6.24(app. t, J = 8.51 Hz, 1H), 5.92 (d, J = 9.45 Hz, 1H), 5.84−5.77 (m, 1H), 5.13−5.05 (m, 2H), 5.02−4.96 (m, 1H), 4.29−4.21 (m, 2H), 4.05 (app. d, J = 12.92 Hz, 1H), 3.82−3.56 (m, 6H), 3.01−2.96 (m, 2H), 2.89−2.59 (m, 5H), 1.74−1.66 (m, 1H), 1.55−1.46 (m,1H), 1.44−1.24(m, 4H), 1.01−0.98 (m, 6H), 0.90−0.87 (m, 3H), 0.82 (m, 12H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.22, 197.80, 172.05, 171.82, 171.66, 161.87, 158.67, 157.06, 143.29, 135.05, 135.02, 127.01, 126.98, 126.91, 125.09, 116.47, 116.38, 110.00, 64.53, 60.64, 57.09, 54.58, 54.28, 41.71, 36.00, 35.92, 35.84, 34.79, 32.58, 32.43, 27.62, 27.56, 27.34, 26.99, 26.88, 19.71, 19.60, 19.50, 15.99, 14.46, 14.41, 13.59, 13.52. HRMS calcd for $C_{38}H_{57}N_6O_7$ $(M + H)^+$: 709.4289. Found: 709.4284.

2(*S*)-[[[[1(*S*)-(2,3-Dihydro-1*H*-inden-2-yl)-2-[(1*R*,5*S*)-2(*S*)-[[[1-[1,2-dioxo-2-(2-propenylamino)ethyl]pentyl]amino]carbonyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-yl]-2-oxoethyl]amino]carbonyl]amino]-3,3-dimethylbutyl Ethylcarbamate (38). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.92−8.85 (m, 1H), 8.43 and 8.30 (app. d, J = 6.4 and 7.3 Hz, 1H), 7.18−7.10 (m, 1H), 7.04−7.00 (m, 1H), 6.26−6.22 (m, 1H), 5.92 (br. d, J = 9.16 Hz, 1H), 5.84−5.77 (m, 1H), 5.11−5.05 (m, 2H), 4.99−4.95 (m, 1H), 4.31−4.27 (m, 2H), 4.07−4.03 (m, 1H), 3.85−3.56 (m, 6H), 3.01−2.99 (m, 2H), 2.91−2.60 (m, 5H), 1.80−1.73 (m, 1H), 1.56−1.25 (m, 7H), 1.02−0.82 (complex, 21H). LCMS $(M + H)^+$: 723.2.

2(*S*)-[[[[1(*S*)-(2,3-Dihydro-1*H*-inden-2-yl)-2-[(1*R*,5*S*)-2(*S*)-[[[1-[1,2-dioxo-2-(2-propenylamino)ethyl]-4-pentynyl]amino]carbonyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-yl]-2-oxoethyl]amino]carbonyl]amino]-3,3-dimethylbutyl Ethylcarbamate (39). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.89 (app. t, J = 5.99 Hz, 1H), 8.51 (d, J = 6.93 Hz, 1H), 7.21−7.09 (m, 4H), 7.03 (bs, 1H), 6.25 (bs, 1H), 5.92 (d, J = 10.71 Hz, 1H), 5.83−5.75 (m, 1H), 5.15−5.05 (m, 2H), 5.03−4.97 (m, 1H), 4.28−4.21 (m, 2H), 4.05 (app. d, J = 8.51 Hz, 1H), 3.85−3.55 (m, 6H), 3.02−2.96 (m, 2H), 2.90−2.81 (m, 3H), 2.75−2.62 (m, 3H), 2.33−2.22 (m, 2H), 2.05−1.96 (m, 1H), 1.78−1.71 (m, 1H), 1.42−1.25 (m, 2H), 1.02−0.97 (m, 6H), 0.83−0.82 (m, 12H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 197.55, 172.10, 171.92, 171.71, 161.91, 158.75, 157.01, 143.45, 143.23, 135.99, 135.01, 126.96, 125.39, 125.16, 116.47, 84.22, 72.79, 64.50, 60.27, 56.99, 54.25, 47.62, 41.70, 35.92, 34.80, 31.53, 30.46, 29.78, 27.75, 27.34, 26.92, 19.52, 15.96, 15.56, 13.60, 13.55. HRMS calcd for $C_{39}H_{55}N_6O_7$ $(M + H)^+$: 719.4132. Found: 719.4119.

2(*S*)-[[[[2-[(1*R*,5*S*)-2(*S*)-[[[1-[1,2-Dioxo-2-(2-propenylamino)-ethyl]butyl]amino]carbonyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-yl]-1(*S*)-(1-methylcyclohexyl)-2-oxoethyl]amino]carbonyl]amino]-3,3-dimethylbutyl Ethylcarbamate (40). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.87 and 8.81 (app. t, J = 5.99 Hz, 1H), 8.35 and 8.23 (d, J = 6.93 and 7.56 Hz, 1H), 6.97 (d, J = 5.04 Hz, 1H), 6.09 (app. t, J = 10.40 Hz, 1H), 6.01 (d, J = 8.19 Hz, 1H), 5.84−5.75 (m, 1H), 5.13−5.04 (m, 2H), 5.00−4.95 and 4.93−4.87 (m, 1H), 4.28−4.22 (m, 2H), 4.01 (app. d, J = 10.08 Hz, 1H), 3.91 (app. t, J = 10.08 Hz, 1H), 3.86−3.64 (m, 4H), 3.62−3.56 (m, 1H), 2.98−2.94 (m, 2H), 1.74−1.65 (m, 1H), 1.55−1.06 (m, 15H), 1.00−0.78 (complex, 24H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 198.21, 197.65, 171.98, 171.80, 171.60, 171.31, 163.71, 163.36, 162.03, 161.69, 158.82, 156.96, 156.92, 135.33, 135.01, 116.46, 116.37, 64.60, 60.34, 59.95, 58.68, 57.01, 54.37, 48.31, 41.70, 37.86, 35.89, 34.84, 34.52, 34.40, 34.13, 32.56, 31.55, 31.47, 27.35, 26.98, 26.92, 26.88, 26.77, 22.20, 22.02, 19.99, 19.58, 19.44, 19.30, 15.91, 14.44, 14.24, 13.51, 13.45. LCMS $(M + H)^+$: 689.2.

2(*S*)-[[[[2-[(1*R*,5*S*)-2(*S*)-[[[1-[1,2-Dioxo-2-(2-propenylamino)-ethyl]pentyl]amino]carbonyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-yl]-1(*S*)-(1-methylcyclohexyl)-2-oxoethyl]amino]carbonyl]amino]-3,3-dimethylbutyl Ethylcarbamate (41). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.89 and 8.83 (app.t, J = 5.99 and 6.30 Hz, 1H), 8.36 and 8.25 (d, J = 6.62 and 7.56 Hz, 1H), 6.99 (d, J = 5.04 Hz, 1H), 6.18−6.07 (m, 1H), 6.02−5.99 (m, 1H), 5.84−5.75 (m, 1H), 5.17−5.02 (m, 2H), 4.98−4.94 and 4.87−4.83 (m, 1H), 4.28−4.20 (m, 2H), 4.00 (d, J = 9.14 Hz, 1H), 3.91 (app. t, J = 9.14 Hz, 1H), 3.84−3.71 (m, 4H), 3.64−3.56 (m, 1H), 2.99−2.94 (m, 2H), 1.77−1.68 (m, 1H), 1.56−1.06 (m, 17H), 0.99−0.78 (complex, 24H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 198.19, 197.62, 173.71, 171.99, 171.80, 171.37, 162.02, 161.66, 158.88, 158.82, 156.98, 141.38, 135.04, 135.00, 133.30, 130.89, 128.99, 125.03, 116.43, 116.33, 95.34, 69.37, 64.59, 60.31, 59.94, 58.95, 56.95, 56.69, 54.50, 48.31, 41.69, 37.52, 35.89, 34.84, 34.33, 34.10, 31.64, 31.53, 31.50, 30.46, 30.19, 30.04, 28.39, 28.18, 27.33, 26.97, 26.92, 26.86, 26.75, 22.63, 22.58, 22.54, 22.19, 22.00, 19.96, 19.31, 15.91, 14.55, 13.52, 13.44. LCMS $(M + H)^+$: 703.2.

2(*S*)-[[[[2-[(1*R*,5*S*)-2(*S*)-[[[1-[2-(Ethylamino)-1,2-dioxoethyl]-4-pentynyl]amino]carbonyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-yl]-1(*S*)-(1-methylcyclohexyl)-2-oxoethyl]amino]carbonyl]amino]-3,3-dimethylbutyl ethylcarbamate (44). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.71 and 8.61 (app. t, J = 6.0 and 6.1 Hz, 1H), 8.47−8.45 and 8.42 (m and d, J = 7.0 Hz, 1H), 7.01−6.91 (m, 1H), 6.20−6.08 (m, 2H), 5.03−4.99 and 4.79−4.73 (m, 1H), 4.25−4.22 (m, 2H), 4.02−3.73 (m, 4H), 3.60−3.56 (m, 1H), 3.17−3.06 (m, 2H),

3.00−2.93 (m, 2H), 2.80 (s, 1H), 2.38−2.20 (m, 2H), 1.90−1.82 (m, 1H), 1.72−1.65 (m, 1H), 1.55−0.76 (complex, 36H). LCMS $(M + H)^+$: 687.2.

2(*S*)-[[[[2-[(1*R*,5*S*)-2(*S*)-[[[1-[1,2-Dioxo-2-(2-propenylamino)-ethyl]butyl]amino]carbonyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-yl]-1(*S*)-(1-methylcyclohexyl)-2-oxoethyl]amino]carbonyl]amino]-3,3-dimethylbutyl (1-methylethyl)carbamate (45). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88 and 8.82 (app. t, J = 5.99 and 6.30 Hz, 1H), 8.36 and 8.25 (d, J = 6.93 and 7.56 Hz, 1H), 6.90 (br. s, 1H), 6.09 (app. t, J = 10.08 Hz, 1H), 6.02 (d, J = 8.82 Hz, 1H), 5.83−5.75 (m, 1H), 5.12−5.04 (m, 2H), 4.99−4.95 and 4.90−4.86 (m, 1H), 4.28−4.20 (m, 2H), 4.00 (d, J = 9.14 Hz, 1H), 3.90 (app. t, J = 9.77 Hz, 1H), 3.84−3.68 (m, 4H), 3.62−3.53 (m, 2H), 1.73−1.64 (m, 1H), 1.54−1.07 (m, 15H), 1.03−0.78 (complex, 27H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 198.22, 197.65, 171.99, 171.81, 171.58, 171.40, 162.02, 161.65, 158.90, 158.84, 156.32, 141.33, 135.34, 135.05, 135.01, 131.96, 131.24, 130.87, 129.00, 127.17, 121.29, 116.45, 116.36, 64.68, 60.32, 59.95, 58.69, 56.93, 54.38, 48.29, 43.12, 41.70, 37.84, 34.11, 32.53, 31.54, 31.47, 30.46, 27.80, 27.73, 27.31, 26.97, 26.91, 26.77, 23.41, 23.33, 22.18, 22.00, 19.93, 19.87, 19.60, 19.44, 19.35, 19.31, 14.46, 14.35, 13.52, 13.46. LCMS $(M + H)^+$: 703.2.

2(*S*)-[[[[2-[(1*R*,5*S*)-2(*S*)-[[[1-[1,2-Dioxo-2-(2-propenylamino)ethyl]-4-pentynyl]amino]carbonyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-yl]-1(*S*)-(1-methylcyclohexyl)-2-oxoethyl]amino]carbonyl]amino]-3,3-dimethylbutyl (1-methylethyl)carbamate (46). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88 and 8.77 (app. t, J = 5.90 and 6.30 Hz, 1H), 8.54 and 8.44 (d, J = 6.93 and 8.19 Hz, 1H), 6.90 (br. s, 1H), 6.08 (app. t, J = 8.51 Hz, 1H), 6.02 (d, J = 10.08 Hz, 1H), 5.83−5.73 (m, 1H), 5.13−5.05 (m, 2H), 5.03−4.97 (m, 1H), 4.24 (s, 1H), 4.21 (d, J = 7.88 Hz, 1H), 4.00 (d, J = 10.4 Hz, 1H), 3.90 (d, J = 10.08 Hz, 1H), 3.85−3.73 (m, 4H), 3.71−3.55 (m, 2H), 2.79 (app. t, J = 2.52 Hz, 1H), 2.36−2.18 (m, 2H), 2.01−1.89 (m, 1H), 1.79−1.66 (m, 1H), 1.53−1.20 (m, 12H), 1.04−0.78 (complex, 24H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.54, 197.07, 172.10, 171.44, 161.68, 158.90, 135.98, 135.06, 134.98, 116.47, 116.33, 84.13, 72.66, 72.54, 64.40, 60.08, 58.75, 56.97, 54.19, 48.29, 43.12, 41.70, 37.81, 34.91, 34.39, 34.09, 31.39, 29.93, 27.88, 27.31, 26.93, 26.88, 26.77, 23.41, 23.33, 22.19, 22.02, 19.91, 19.35, 15.57, 15.20, 13.51, 13.46. LCMS $(M + H)^+$: 713.2.

2(*S*)-[[[[2-[(1*R*,5*S*)-2(*S*)-[[[1-[1,2-Dioxo-2-(2-propenylamino)ethyl]butyl]amino]carbonyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-yl]-1(*S*)-(1-methylcyclohexyl)-2-oxoethyl]amino]carbonyl]amino]-3,3-dimethylbutyl (2-methylpropyl)carbamate (47). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.85 and 8.79 (app. t, J = 5.99 Hz, 1H), 8.33 and 8.21 (d, J = 6.93 and 7.25 Hz, 1H), 6.99 (d, J = 4.41 Hz, 1H), 6.10−6.00 (m, 2H), 5.83−5.76 (m, 1H), 5.12−5.05 (m, 2H), 5.00−4.96 and 4.91−4.87 (m, 1H), 4.28−4.20 (m, 2H), 4.02 (d, J = 11.03 Hz, 1H), 3.91 (app. t, J = 9.77 Hz, 1H), 3.86−3.68 (m, 4H), 3.64−3.57 (m, 1H), 2.77 (app. t, J = 5.99 Hz, 2H), 1.74−1.60 (m, 1H), 1.54−1.07 (m, 16H), 1.00−0.76 (m, 27 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 198.20, 197.64, 171.97, 171.80, 171.61, 171.41, 162.04, 161.71, 158.83, 157.31, 135.05, 135.01, 116.47, 116.38, 64.65, 60.35, 59.97, 58.70, 56.97, 56.70, 54.39, 48.75, 48.28, 41.70, 37.86, 34.86, 34.53, 34.41, 34.14, 32.58, 32.55, 31.54, 31.47, 30.46, 29.11, 27.81, 27.75, 27.34, 26.98, 26.93, 26.77, 22.19, 22.02, 20.82, 19.94, 19.90, 19.58, 19.43, 19.35, 13.51, 13.45. LCMS $(M + H)^+$: 717.2.

2(*S*)-[[[[2-[(1*R*,5*S*)-2(*S*)-[[[1-[1,2-Dioxo-2-(2-propenylamino)ethyl]-4-pentynyl]amino]carbonyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-yl]-1(*S*)-(1-methylcyclohexyl)-2-oxoethyl]amino]carbonyl]amino]-3,3-dimethylbutyl (2-methylpropyl)carbamate (48). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88 and 8.78 (app. t, J = 5.99 Hz, 1H), 8.54 and 8.44 (d, J = 6.62 Hz, 1H), 7.04 (br. s, 1H), 6.08 (d, J = 11.66 Hz, 1H), 6.02 (d, J = 9.46 Hz, 1H), 5.87−5.73 (m, 1H), 5.14−5.05 (m, 2H), 5.03−4.98 (m, 1H), 4.24 (s, 1H), 4.20 (d, J = 7.88 Hz, 1H), 4.01 (d, J = 11.03 Hz, 1H), 3.90 (d, J = 10.40 Hz, 1H), 3.86−3.68 (m, 4H), 3.60−3.56 (m, 1H), 2.80 (s, 1H), 2.78−2.75 (m, 2H), 2.37−2.19 (m, 2H), 2.00−1.89 (m, 1H),1.84−1.01 (m, 14H), 0.99−0.69 (m, 24H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.54, 172.13, 172.10, 161.69, 158.91, 157.32, 135.07, 134.99, 116.48, 84.15, 72.67, 64.61, 60.08, 58.73, 56.97, 54.20, 48.74, 48.27, 41.71, 37.82, 34.89, 34.39, 34.12, 34.09, 31.38, 30.47, 29.93, 29.18, 29.12, 27.87, 27.32, 26.94, 26.88, 26.79, 22.20, 22.01, 20.84, 19.90, 19.36, 15.57, 13.51, 13.46. LCMS $(M + H)^+$: 727.2.

2(*S*)-[[[[2-[(1*R*,5*S*)-2(*S*)-[[[1-[1,2-Dioxo-2-(2-propenylamino)ethyl]butyl]amino]carbonyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-yl]-1(*S*)-(1-methylcyclohexyl)-2-oxoethyl]amino]carbonyl]amino]-3,3-dimethylbutyl (cyclopropylmethyl)carbamate (49). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.90 and 8.84 (d, J = 5.99 Hz, 1H), 8.38 and 8.29 (d, J = 6.62 and 7.25 Hz, 1H), 7.13−7.09 (m, 1H), 6.11−6.01 (m, 2H), 5.83−5.75 (m, 1H), 5.11−5.04 (m, 2H), 4.99−4.95 and 4.90−4.86 (m, 1H), 4.26 and 4.24 (s, 1H), 4.20 (app. t, J = 9.45 Hz, 1H), 4.02 (d, J = 9.77 Hz, 1H), 3.90 (app. t, J = 9.77 Hz, 1H), 3.84−3.67 (m, 4H), 3.61−3.55 (m, 1H), 2.85−2.82 (m, 2H), 1.74−1.64 (m, 1H), 1.54−1.06 (m, 16H), 0.99−0.78 (complex, 21H), 0.38−0.34 (m, 2H), 0.15−0.10 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.21, 197.65, 171.99, 171.80, 171.59, 171.38, 162.02, 161.68, 158.90, 158.84, 157.21, 135.05, 135.01, 116.45, 116.36, 64.79, 60.31, 59.96, 58.73, 56.99, 54.36, 48.28, 45.42, 41.70, 37.83, 34.91, 34.87, 34.49, 34.39, 34.36, 34.11, 32.54, 31.54, 31.47, 30.46, 27.80, 27.75, 27.35, 26.97, 27.92, 26.76, 22.19, 22.01, 19.95, 19.89, 19.59, 19.49, 19.44, 19.32, 14.45, 14.34, 13.52, 13.46, 12.00, 3.90. LCMS $(M + H)^+$: 715.2.

2(*S*)-[[[[2-[(1*R*,5*S*)-2(*S*)-[[[1-[1,2-Dioxo-2-(2-propenylamino)ethyl]-4-pentynyl]amino]carbonyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-yl]-1(*S*)-(1-methylcyclohexyl)-2-oxoethyl]amino]carbonyl]amino]-3,3-dimethylbutyl (cyclopropylmethyl)carbamate (50). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88 and 8.77 (t, J = 5.99 Hz, 1H), 8.54 and 8.44 (d, J = 6.94 Hz, 1H), 7.09 (bs, 1H), 6.11−6.01 (m, 2H), 5.83−5.74 (m, 1H), 5.15−5.05 (m, 2H), 5.03−4.98 (m, 1H), 4.24 (s, 1H), 4.20 (d, J = 7.57 Hz, 1H), 4.03−4.00 (m, 1H), 3.90 (d, J = 10.40 Hz, 1H), 3.85−3.66 (m, 4H), 3.61−3.55 (m, 1H), 2.84 (app. t, J = 6.30 Hz, 2H), 2.80 (app. t, J = 2.52 Hz, 1H), 2.37−2.19 (m, 2H), 2.01−1.91 (m, 1H), 1.73−1.03 (m, 14H), 1.02−0.74 (complex, 21H), 0.37−0.34 (m, 2H), 0.14−0.07 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.54, 172.10, 171.43, 161.69, 135.99, 134.98, 116.48, 116.40, 96.84, 96.74, 84.17, 84.09, 72.76, 72.61, 71.67, 64.83, 64.72, 58.82, 58.12, 56.89, 54.07, 48.25, 45.30, 41.70, 37.88, 35.05, 34.32, 34.01, 31.40, 30.35, 30.04, 29.21, 27.34, 27.01, 26.91, 26.70, 22.24, 22.02, 19.90, 19.40, 15.55, 13.47, 13.00, 12.05, 3.90. LCMS $(M + H)^+$: 725.2.

2(*S*)-[[[[2-[(1*R*,5*S*)-2(*S*)-[[[1-[1,2-Dioxo-2-(2-propenylamino)ethyl]butyl]amino]carbonyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-yl]-1(*S*)-(1-methylcyclohexyl)-2-oxoethyl]amino]carbonyl]amino]-3,3-dimethylbutyl (cyclohexylmethyl)carbamate (51). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88 and 8.82 (t, J = 5.99 Hz, 1H), 8.36 and 8.24 (d, J = 6.62 and 7.56 Hz, 1H), 7.00−6.96 (m, 1H), 6.07 (app. t, J = 10.71 Hz, 1H), 6.02 (d, J = 10.71 Hz, 1H), 5.83−5.76 (m, 1H), 5.12−5.04 (m, 2H), 4.99−4.95 and 4.90−4.86 (m, 1H), 4.30 and 4.26 (s, 1H), 4.22 (app. t, J = 8.82 Hz, 1H), 4.02 (d, J = 11.35 Hz, 1H), 3.91 (app. t, J = 10.08 Hz, 1H), 3.82−3.69 (m, 4H), 3.60−3.55 (m, 1H), 2.80−2.75 (m, 2H), 1.74−1.59 (m, 6H), 1.54−1.07 (m, 21H), 0.99−0.78 (complex, 21H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 198.22, 197.66, 171.99, 171.81, 171.58, 171.40, 162.02, 161.65, 158.89, 158.83, 157.29, 135.05, 135.01, 116.44, 116.36, 64.68, 60.31, 59.95, 58.68, 56.92, 54.34, 48.27, 47.46, 41.70, 38.50, 37.83, 37.81, 34.83, 34.55, 34.41, 34.10, 32.52, 31.55, 31.47, 31.14, 30.47, 27.33, 26.97, 26.94, 26.77, 26.27, 22.18, 22.02, 19.91, 19.85, 19.60, 19.44, 19.35, 19.32, 14.46, 14.35, 13.52, 13.46. LCMS $(M + H)^+$: 757.2.

2(*S*)-[[[[2-[(1*R*,5*S*)-2(*S*)-[[[1-[1,2-Dioxo-2-(2-propenylamino)ethyl]-4-pentynyl]amino]carbonyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-yl]-1(*S*)-(1-methylcyclohexyl)-2-oxoethyl]amino]carbonyl]amino]-

3,3-dimethylbutyl (cyclohexylmethyl)carbamate (52). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.85 and 8.75 (t, J = 5.99 Hz, 1H), 8.50 and 8.42 (d, J = 6.93 Hz, 1H), 6.95 (br. s, 1H), 6.07 (d, J = 11.03 Hz, 1H), 6.02 (d, J = 9.45 Hz, 1H), 5.83−5.74 (m, 1H), 5.13−5.05 (m, 2H), 5.03−4.97 (m, 1H), 4.24 (s, 1H), 4.21 (d, J = 6.62 Hz, 1H), 4.02 (d, J = 10.71 Hz, 1H), 3.91 (d, J = 10.40 Hz, 1H), 3.83−3.68 (m, 4H), 3.60−3.57 (m, 1H), 2.80−2.77 (m, 3H), 2.34−2.20 (m, 2H), 2.00−1.91 (m, 1H), 1.74−1.08 (m, 24H), 0.99−0.76 (m, 18 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.52, 197.06, 172.51, 172.44, 172.09, 171.45, 162.35, 161.73, 158.90, 157.29, 135.98, 134.98, 116.49, 116.36, 84.32, 84.15, 72.59, 72.50, 64.70, 60.09, 58.72, 56.95, 56.70, 54.21, 48.26, 47.47, 41.71, 38.50, 37.83, 34.87, 34.46, 34.11, 31.39, 31.13, 30.47, 29.97, 27.90, 27.33, 26.94, 26.80, 26.27, 22.21, 22.04, 19.93, 19.35, 15.56, 13.49, 13.44. LCMS (M + H)$^+$: 767.2.

2(*S*)-Cyclohexyl-2-[[[[2-[(1*R*,5*S*)-2(*S*)-[[[1-[1,2-dioxo-2-(2-propenylamino)ethyl]butyl]amino]carbonyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-yl]-1(*S*)-(1-methylcyclohexyl)-2-oxoethyl]-amino]carbonyl]amino]ethyl Ethylcarbamate (53). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.85 and 8.79 (t, J = 5.99 Hz, 1H), 8.33 and 8.19 (d, J = 6.93 and 7.25 Hz, 1H), 7.02 (br. s, 1H), 6.11 (app. t, J = 10.08 Hz, 1H), 5.99 (d, J = 10.08 Hz, 1H), 5.84−5.76 (m, 1H), 5.12−5.05 (m, 2H), 5.00−4.96 and 4.92−4.87 (m, 1H), 4.32−4.22 (m, 2H), 3.92 (app. t, J = 9.45 Hz, 1H), 3.87−3.71 (m, 5H), 3.62−3.57 (m, 1H), 3.03−2.96 (m, 2H), 1.72−1.06 (m, 27H), 1.01−0.80 (complex, 15H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 198.21, 197.65, 171.95, 171.77, 171.53, 171.34, 162.02, 161.71, 158.70, 158.65, 156.86, 135.31, 135.05, 135.01, 131.96, 131.23, 127.15, 116.47, 116.39, 64.80, 60.36, 59.96, 58.52, 54.39, 53.43, 48.26, 41.70, 37.85, 37.83, 35.90, 34.54, 34.41, 34.16, 32.59, 31.54, 31.47, 30.47, 30.20, 28.30, 27.80, 27.72, 27.02, 26.96, 26.90, 26.74, 26.66, 22.19, 21.99, 20.04, 19.99, 19.57, 19.44, 19.33, 19.28, 15.88, 14.44, 14.33, 13.35, 13.27. LCMS (M + H)$^+$: 715.2.

2(*S*)-Cyclohexyl-2-[[[[2-[(1*R*,5*S*)-2(*S*)-[[[1-[1,2-dioxo-2-(2-propenylamino)ethyl]-4-pentynyl]amino]carbonyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-yl]-1(*S*)-(1-methylcyclohexyl)-2-oxoethyl]-amino]carbonyl]amino]ethyl Ethylcarbamate (54). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88 and 8.78 (app. t, J = 6.0 and 5.9 Hz, 1H), 8.52 and 8.44 (d, J = 7.2 and 6.9 Hz, 1H), 7.07−7.05 (m, 1H), 6.14−6.09 (m, 1H), 5.99 (br. d, 1H), 5.82−5.73 (m, 1H), 5.13−5.02 (m, 2H), 5.00−4.96 and 4.74−4.70 (m, 1H), 4.25 (s, 1H), 4.21 (app. d, J = 6.6 Hz, 1H), 3.91−3.72 (m, 6H), 3.69−3.57 (m, 1H), 3.00−2.95 (m, 2H), 2.79 (app. s, 1H), 2.33−2.21 (m, 2H), 2.00−1.88 (m, 1H), 1.69−0.78 (complex, 36H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.59, 171.13, 170.40, 160.73, 157.76, 155.92, 134.03, 115.53, 115.39, 83.37, 83.18, 71.74, 71.62, 59.11, 55.75, 53.27, 52.45, 40.75, 36.86, 34.94, 33.45, 33.19, 30.43, 29.52, 29.25, 28.99, 27.32, 26.91, 26.02, 25.82, 25.72, 21.24, 21.05, 19.04, 18.40, 14.96, 14.62, 12.40. LCMS (M + H)$^+$: 725.2.

[1-[[[[2-[(1*R*,5*S*)-2(*S*)-[[[1-[1,2-Dioxo-2-(2-propenylamino)ethyl]-butyl]amino]carbonyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-yl]-1(*S*)-(1-methylcyclohexyl)-2-oxoethyl]amino]carbonyl]amino]cyclohexyl]methyl Ethylcarbamate (55). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.89 and 8.84 (app. t, J = 6.1 and 6.0 Hz, 1H), 8.36 and 8.22 (d, J = 7.0 and 7.3 Hz, 1H), 7.01−6.98 (m, 1H), 6.22−6.17 (m, 1H), 5.82−5.75 (m, 2H), 5.12−5.04 (m, 2H), 4.98−4.94 and 4.90−4.86 (m, 1H), 4.28 and 4.25 (s, 1H), 4.18 (br. t, 1H), 4.03−3.94 (m, 3H), 3.80−3.68 (m, 3H), 3.00−2.94 (m, 2H), 1.96−1.93 (br. d, 1H), 1.81−1.79 (br. d, 1H), 1.72−1.64 (m, 1H), 1.53−0.75 (complex, 38H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.28, 196.72, 171.06, 170.88, 161.05, 160.70, 156.11, 134.41, 134.10, 131.03, 130.31, 126.22, 115.51, 115.41, 68.05, 59.41, 58.98, 55.75, 53.48, 47.37, 40.75, 36.77, 34.91, 33.16, 31.58, 31.46, 30.58, 30.51, 29.52, 26.76, 26.08, 26.01, 25.81, 25.16, 21.21, 21.04, 20.46, 19.07, 19.02, 18.67, 18.52, 18.44, 18.39, 15.01, 13.52, 13.42, 12.38, 12.30. LCMS (M + H)$^+$: 701.2.

[1-[[[[2-[(1*R*,5*S*)-2(*S*)-[[[1-[1,2-Dioxo-2-(2-propenylamino)ethyl]-4-pentynyl]amino]carbonyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-yl]-1(*S*)-(1-methylcyclohexyl)-2-oxoethyl]amino]carbonyl]amino]cyclohexyl]methyl Ethylcarbamate (56). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88 and 8.78 (t, J = 5.99 Hz, 1H), 8.50 and 8.44 (d, J = 6.93 and 7.25 Hz, 1H), 6.99 (app. t, J = 5.04 Hz, 1H), 6.19 (app. t, J = 10.08 Hz, 1H), 5.83−5.74 (m, 2H), 5.14−5.05 (m, 2H), 5.03−4.96 and 4.77−4.70 (m, 1H), 4.26 (s, 1H), 4.22−4.15 (m, 1H), 4.04−3.94 (m, 3H), 3.80−3.68 (m, 3H), 3.00−2.95 (m, 2H), 2.79 (app. t, J = 2.52 Hz, 1H), 2.34−2.20 (m, 2H), 2.01−1.92 (m, 2H), 1.87−1.66 (m, 2H), 1.57−0.81 (complex, 32H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.54, 197.08, 172.13, 172.11, 171.88, 171.45, 161.68, 158.85, 157.06, 135.98, 135.06, 134.98, 116.47, 116.34, 116.00, 84.31, 84.14, 72.68, 72.56, 69.01, 60.26, 60.06, 58.18, 54.44, 54.23, 48.27, 41.70, 37.67, 35.85, 34.41, 34.11, 32.41, 31.37, 30.46, 29.93, 27.85, 26.98, 26.91, 26.77, 26.11, 22.17, 21.99, 21.41, 20.01, 19.38, 15.94, 15.57, 15.22, 13.31, 13.24. LCMS (M + H)$^+$: 711.2.

Acknowledgment. We thank the Structural Chemistry Department at Schering-Plough Research Institute for NMR and MS analysis for all new compounds. We thank Dr. Z. Guo for modeling studies. We thank Dr. L. Nair for assistance in the preparation of the experimental section of this manuscript.

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JM801616E