Second-Generation Highly Potent and Selective Inhibitors of the Hepatitis C Virus NS3 Serine Protease

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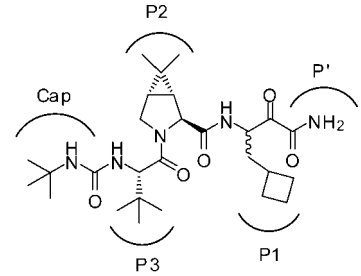
Received September 30, 2008

The hepatitis C virus (HCV) infection is a leading cause of chronic liver disease. The moderate efficacy along with side effects of the current pegylated interferon and ribavirin combination therapy underscores the need for more effective and safer new treatment. In an effort to improve upon our current clinical candidate, Boceprevir (SCH 503034), extensive SAR studies were performed on the P3 capping moieties. This led to the discovery of *tert*-leucinol derived cyclic imides as a potent series of novel P3 capping groups. Thus, the introduction of these imide caps improved the cell-based replicon EC_{90} by more than 10-fold. A number of imides with various substitutions, ring sizes, bicyclic systems, and heterocyclic rings were explored. The 4,4-dimethyl substituted glutarimide emerged as the best cap as exemplified in compound **21** (K_i* = 4 nM, EC_{90} = 40 nM). Systematic optimization of different positions (P′, P3, and P1) of the inhibitor resulted in the identification of the lead compound **46**, which had an excellent potency (K_i* = 4 nM, EC_{90} = 30 nM) and good pharmacokinetic profile (22% and 35% bioavailability in rats and dogs, respectively). X-ray structure of inhibitor **46** bound to the enzyme revealed that there was an additional hydrogen bonding interaction between one of the imide carbonyls and Cys159.

Introduction

Hepatitis C virus (HCV) has infected an estimated 3% of the world's population, over 170 million people.[1] The slow progression and mild symptoms of the HCV infection make it easily undetected. Most infections progress to a chronic state that persists for decades and eventually lead to cirrhosis, liver failure, or liver cancer.[2] Currently, the most effective therapies involve the treatment with pegylated α-interferon in combination with antiviral agent ribavirin.[3] The infection is considered cured when there is a sustained virologic response (SVR) defined as the absence of HCV RNA in serum at the end of treatment and six-months post treatment. The SVR rate for patients with genotype-1 HCV is about 40% with the current therapy.[3] Lack of efficacy along and the side effects with these therapies necessitates the need for new and more effective HCV treatments.

Hepatitis C virus (HCV) is a positive strand RNA virus with a single open frame of ∼9600 nucleosides. Located at N-terminal portion of nonstructural (NS) protein NS3 is a serine protease. The NS3 protease has demonstrated a vital role in the replication of the HCV virus.[4] There is compelling evidence to suggest that the inhibition of NS3 protease is a viable strategy for the development of small molecule antiviral agents. It has been determined that the HCV NS3 protease belongs to the trypsin or chymotrypsin super family of serine proteases.[5] A small polypeptide cofactor, NS4A, is essential for the protease's activity.[6] The X-ray structure of the protease has revealed a shallow and solvent exposed substrate binding region, and the inhibitor binding energy is mainly derived from weak lipophilic and electrostatic interactions.[7] Despite tremendous difficulty encountered in the process, intensive efforts have been focused on NS3 serine protease and a number of novel inhibitors have been reported.[8] Several drug candidates have or are being progressed into clinical trials in human beings. The earliest entry, BILN-2061,[9] an NS3 protease inhibitor from Boehringer-Ingelheim, failed in phase I clinical trials due to cardiac toxicity. Currently, the most advanced candidates are Telapravir (VX-950)[10] from Vertex and **1** (Boceprevir, SCH 503034, Figure 1)[11] from Schering-Plough. Both of these drugs are in phase III clinical trials.



1

Ki* = 14 nM
EC_{90} = 350 nM
Rat bioavail. 26 %
Monkey bioavail. 4-11 %
Dog bioavail. 30 %

Figure 1. Compound **1**: the HCV protease inhibitor that is currently in phase III clinical trials.

The first-generation HCV NS3 protease inhibitor (**1**) was shown to be a potent inhibitor of the NS3 protease with a enzymatic continuous assay K_i* of 14 nM and a cell-based replicon assay EC_{90} of 350 nM.[11] It had a favorable pharmacokinetic (PK) profile in rats and dogs (26% and 34% bioavailability, respectively) but low bioavailability in monkeys (4−11%). The goal for a second-generation inhibitor was to improve the potency by at least 10-fold while maintaining or improving upon PK profile. Modeling studies based on X-ray crystal structure of compound **1** revealed that there was ample room for the P3

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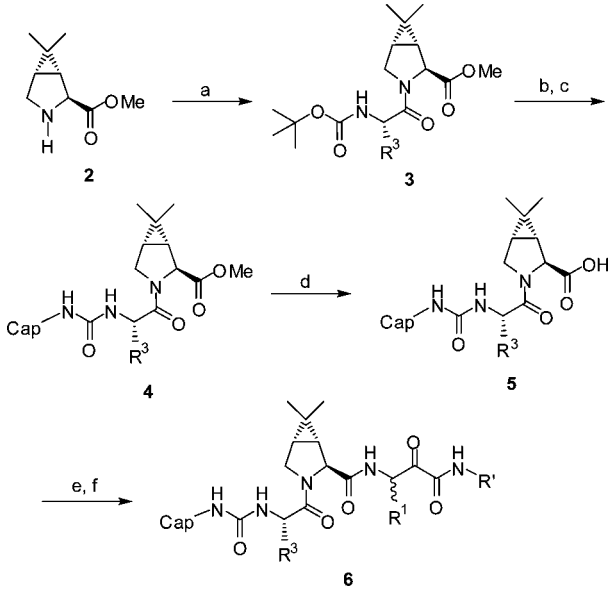
10.1021/jm801238q CCC: $40.75
Published on Web 02/05/2009

Scheme 1[a]



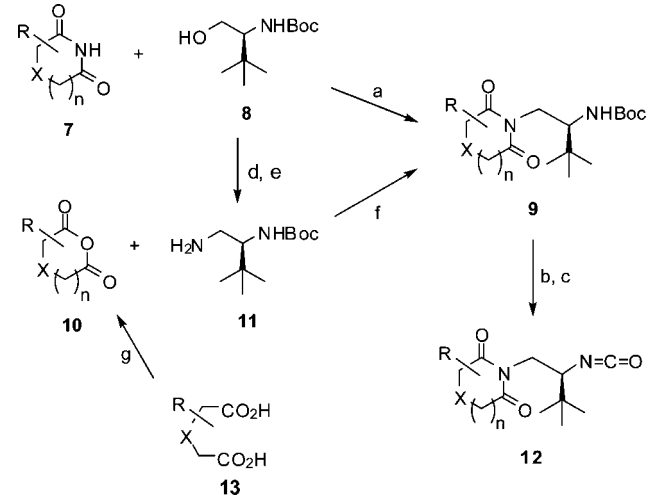
[a] Reaction conditions: (a) Boc-P3-OH, EDC, HOOBt; DMF/CH_2Cl_2; (b) 4 M HCl; *p*-dioxane; (c) appropriate isocyanate, *i*-Pr_2NEt, CH_2Cl_2; (d) LiOH, THF/MeOH/H_2O; (e) P1-α-hydroxyamide, EDC, HOOBt, DMF/CH_2Cl_2; (f) Dess−Martin periodinane.

cap to be extended beyond the *tert*-butyl group. The Cys159 amino acid residue of the protein backbone in the S4 region provided an opportunity for additional hydrogen bonding interaction. It was envisioned that an extended P3 cap having carbonyl or sulfonyl groups at appropriate distance could engage in a hydrogen bonding with Cys159. In the course of an extensive search for the optimal functionality to establish the hydrogen bond, it was discovered that cyclic imides derived from *tert*-leucinol provided the most potent P3 cappings. With optimized imide capping in hand, systematic investigation of structure−activity relationship (SAR) was also conducted at other sites of the inhibitor such as P3, P1, and P′. The combination of the optimal moiety in each position gave rise to a potent inhibitor with favorable PK profile. Herein, we report the SAR development and the discovery of the second-generation HCV NS3 protease inhibitor.

Synthesis of HCV Protease Inhibitors. The general synthesis of the inhibitors is outlined in Scheme 1 and has been described previously.[11,12] Starting from the unique *gem*-dimethylcyclopropylproline P2 core (**2**), coupling with a Boc[a]-protected P3 amino acid gave a dipeptide (**3**). Removal of the Boc group and reaction with an isocyanate of the capping moiety afforded compound **4**. Hydrolysis of methyl ester to carboxylic acid **5** and its subsequent coupling with a P1 α-hydroxyamide amine provided a tripeptide. Dess−Martin periodinane oxidation[13] of this α-hydroxyamide furnished the desired α-ketoamide **6**. Earlier experience indicated the difficulty in obtaining acceptable PK from primary α-ketoamides (R′ = H), it was thus decided to perform all subsequent SAR studies on secondary ketoamides. Among various R′ groups investigated, allyl group was one of the best moieties for providing good potency and PK. It was used as the R′ group for initial explorations.

The capping moiety, focus of the current SAR development, was synthesized according to one of the general procedures depicted in Scheme 2. A Mitsunobu reaction[14] of a commercially available cyclic imide **7** and Boc-*t*-leucinol **8** gave the key intermediate **9**. Removal of the Boc-protecting group and subsequent reaction with phosgene would provide the desired isocyanate intermediate (**12**) for further capping. If cyclic imide was not available, then **9** could be obtained through a two-step procedure from cyclic anhydride **10**. Thus, Boc-*t*-leucine amine **11** was prepared from alcohol **8** through a Mitsunobu reaction with phthalimide followed by removal of the phthalyl group using hydrazine. After opening of the cyclic anhydride **10** with **11**, the cyclic imide of type **9** could be obtained by the treatment with acetic anhydride. Finally, if neither **7** nor **10** were available, then the cyclic anhydride could be accessed via cyclization of a diacid of type **13**.

Scheme 2[a]



[a] Reaction conditions: (a) DIAD, PPh_3, THF; (b) 4 M HCl, *p*-dioxane; (c) phosgene, $NaHCO_3$, H_2O /CH_2Cl_2; (d) phthalimide, DIAD, PPh_3, THF; (e) NH_2NH_2, EtOH; (f) reflux, toluene, then Ac_2O, Et_3N, 90 °C; (g) Ac_2O, 100 °C.

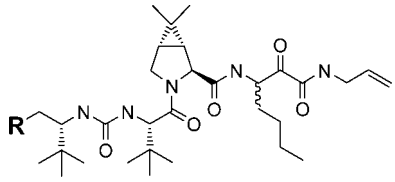
Results and Discussions

P3 Capping SAR: Discovery of Cyclic Imides as Potent Capping Moiety. All inhibitors synthesized were tested in HCV continuous enzymatic assay[15] using the NS4A-tethered single chain NS3 serine protease.[16] The K_i* values in the assay reflected the equilibrium constant determined by the reversible covalent bond formed between the ketone and serine and other interactions between the inhibitors and the enzyme.[17] Compounds with good potency were then evaluated in a replicon-based cellular assay.[18] EC_{90}, the concentration required for inhibition of 90% of replicon replication, was obtained as a measure of replicon cellular potency. Both enzyme and replicon assays were performed in the absence of human serum. To address the issue of selectivity among serine proteases, all inhibitors were assayed against human neutrophil elastase (HNE), which is a serine protease structurally most closely related to HCV NS3 serine protease. All compounds were assayed as a mixture of two diastereomers at P1 α-center. The ratio of two isomers varied between 2:1 and 1:2. Rapid equilibrium was observed under enzyme and cellular assay conditions, which deemed the separation of the two isomers less meaningful.

Guided by X-ray structures of inhibitors bound to the protein, an extensive search for the P3 capping moieties that could form strong hydrogen bonding with Cys159 was conducted. Among the structures that were capable of hydrogen bonding, cyclic

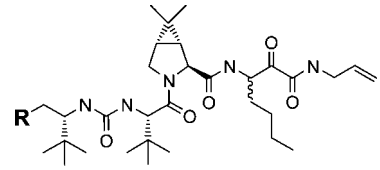
[a] Abbreviations: Boc, *tert*-butoxy carbonyl; EDC, *N*-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride; HOOBt, 3-hydroxy-1,2,3-benzotriazin-4(3*H*)-one; DIAD, diisopropyl azodicarboxylate; HPBCD, hydroxypropyl β cyclodextrin.

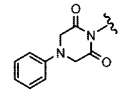
Table 1. Cyclic Imides as P3 Capping



Compound	R	Ki* (nM)	EC_{90} (nM)	HNE/HCV (n = 4)
14		30	750	500
15		13	230	2000
16		8	150	69000
17		5	70	9500
18		6	200	3800
19		6	60	7000
20		7	35	3100
21		**4**	**40**	**9300**
22		8	40	2500

Table 2. Heterocyclic Imides as P3 Cappings

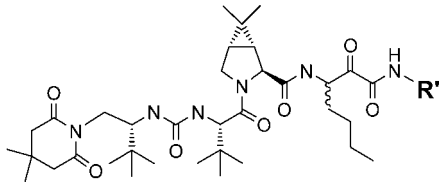


Compound	R	Ki* (nM)	EC_{90} (nM)	HNE/HCV (n = 4)
23		8	500	7200
24		**6**	**40**	**9500**
25		12	100	90
26		4	150	4300
27		7	60	1400
28		8	1000	1200
29		19	250	1200
30		11	250	2500
31		8	60	1600

imides were identified as a promising moiety (Table 1). The most potent cyclic imides were those derived from *tert*-leucine amine. The first compound in this series, phthalimide derivative **14** (Table 1), had a enzyme assay potency (K_i*) of 30 nM and cell-based replicon assay potency (EC_{90}) of 750 nM. Its selectivity against elastase (HNE/HCV) was 500. On the basis of the size of the S4 pocket, it was speculated that a smaller group might have a better fit. Encouragingly, changing the capping from phthalimide to succinimide analogue (**15**) improved potency and selectivity 2−4 fold. To make the ring more flexible, six-membered glutarimide was introduced. To our delight, compound (**16**) further improved potency about 2-fold to K_i* of 8 nM and EC_{90} of 150 nM. The selectivity (HNE/HCV = 69000) was more than 30-fold higher than that of **15**. Encouraged by these results, we prepared a number of derivatives (**17**−**22**) based on the six-membered imide ring system. Three bicyclic imides (**17**−**19**) and three substituted glutarimides (**20**−**22**) are shown in Table 1. Compound **17** had a fused 5,3-bicyclic imide capping. It was significantly more potent than **16** in both enzyme and replicon assays (5 and 70 nM, respectively). Although its selectivity was lower than **16**, at 9500-fold, it was still extremely high. The spiro-5,6-bicyclic imide cap in compound **18** maintained excellent binding (K_i* = 6 nM) but lost some cellular potency (200 nM) and selectivity (3800). The profile of [3,2,1]-bicyclic imide capped compound **19** was similar to that of **17**, with excellent potency and very high selectivity. Substitutions on the glutarimide improved replicon potency even further. Thus, the 3,3-dimethylglutarimide cap lowered EC_{90} of compound **20** by another 2-fold to 35 nM while maintaining good enzyme activity and selectivity. On the other hand, the 4,4-dimethyl analogue **21** achieved best potency in both enzyme and replicon assays (4 and 40 nM, respectively). It also had outstanding selectivity of 9300-fold against HNE. The ethyl analogue of **21** did not provide any further enhancement in potency in **22** (K_i* = 8 nM, EC_{90} = 40 nM), but decreased the selectivity by almost 4-fold to 2500.

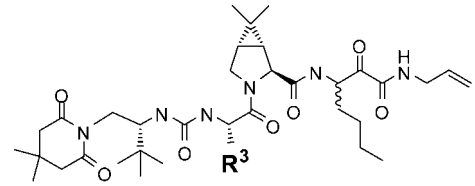
Besides the carbocyclic imides P3 cappings shown in Table 1, a parallel SAR study of heterocyclic imides with variations in ring size and substitutions was also conducted (Table 2). Replacing C-4 of the glutarimide with an oxygen gave rise to the morpholine-dione analogue **23**, which upheld enzyme activity (K_i* = 8 nM) but lost considerable cellular potency (500 nM) and selectivity. The corresponding methylated 1,4-dinitrogen analogue (piperazine-dione) **24** demonstrated excellent potency and selectivity with a profile that was similar to compound **21**. The *N*-phenyl analogue (**25**), however, was much less potent and selective. The 1,3-biazo cyclic imides (**26**, **27**) were also prepared. Although they had good K_i*s, with or without *N*-methyl substitution, the cellular potency and selectiv-

Table 3. SAR of P′ Moieties



Compound	R′	Ki* (nM)	EC_{90} (nM)	HNE/HCV (n = 4)
33		13	70	8200
21		**4**	**40**	**9300**
34		21	80	910
35		5	30	6100
36		14	40	1100
37		12	100	900
38		22	80	2500

Table 4. P3 Residue Investigation



Compound	R^3	Ki* (nM)	EC_{90} (nM)	HNE/HCV (n = 4)
39		2	45	2400
40		4	45	1000
41		4	100	1800
42		32	80	220
21		**4**	**40**	**9300**

ity were not as good as their carbocyclic and 1,4-dinitrogen analogues. Because of their cyclic imide-type structures, several hydantoin derivatives (**28**−**31**) were also investigated. The unsubstituted hydantoin **28** was essentially inactive in the cellular assay. Although *N*-methyl and 4,4-dimethyl analogues had improved replicon activity (both with EC_{90} = 250 nM), they were still far less potent than glutarimide capped inhibitors. Finally, the trimethyl substituted hydantoin analogue **31** achieved a respectable EC_{90} of 60 nM but much less selective.

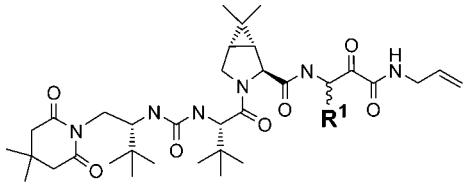
In summary, we have achieved great success in the cyclic imide SAR studies (Tables 1−2): a 10-fold improvement in potency and extremely high selectivity had been accomplished. The 4,4-dimethyl glutarimide (**21**) and 4-*N*-methyl piperazinedione (**24**) analogues were the most potent in both enzyme and replicon assays and were also among the most selective against elastase. Because of the more favorable PK property (discussed in a later section) of compound **21**, glutarimide capping was used in further SAR investigations below.

Modifications of P′ Moiety. Earlier SAR's were performed with allyl amide at prime side. Although it was one of the best group discovered as P′ moiety, further evaluation was still needed to determine whether there was a better alternative. Several potential alkyl and aromatic groups were examined, and the results are given in Table 3. The shorter ethyl group in compound **33** decreased both enzyme and cellular potency by about 2-fold compared to **21**. In compound **34**, the allyl group was replaced by saturated *n*-propyl chain, when the potency and selectivity deteriorated even further, demonstrating that saturated alkyl moieties were not as good as allyl group at P′ position. Next, a cyclopropyl group was introduced. It had some sp^2 characteristics in the ring system and conceivably could mimic the allyl moiety. Indeed, compound **35** had an excellent EC_{90} of 30 nM, the best replicon potency achieved so far. Its selectivity against elastase (HNE/HCV = 6100) was somewhat lower that of **21**. Then, three aromatic moieties were tested (**36**−**38**). The benzyl analogue was equally potent in cellular assay (40 nM), but the enzyme activity and selectivity were significantly lower. Both thiophene and pyridine derivatives (**37** and **38**) showed 2−5 fold loss in K_i* or EC_{90} and much lower selectivity. In summary, this P′ residue investigation confirmed that allyl group was still one of the best moiety at that position. Although cyclopropyl analogue **35** was slightly more potent, it was less selective. As a result, further SAR studies were performed with allyl amide.

P3 Residue Optimization. It is evident from previous SAR studies and X-ray structure that the S3 region of HCV NS3 protease is highly lipophilic and the P3 moiety binds to the enzyme mainly through hydrophobic interactions.[7] On the basis of earlier experience, modifications of the P3 side chain were limited to branched alkyl groups or 5−6-membered aliphatic rings. In this study, five different P3 moieties were incorporated and the test results are summarized in Table 4. In contrast to the *tert*-leucine P3 residue used in **21**, all four other inhibitors had cyclic ring structures at P3 position. Cyclohexylglycine in **39** provided better enzyme activity of 2 nM, but its replicon potency and selectivity were worse. Considered a hybrid of cyclohexylglycine and *tert*-leucine, the β-methyl cyclohexylglycine derivative **40** did not improve either potency or selectivity. The P3 2-indanylglycine analogue **41** maintained enzyme activity but lost significant cellular potency and selectivity. Finally, the β-methyl indanylglycine P3 derived **42** was also quite disappointing in both potency and selectivity. This limited evaluation of these P3 residues proved the superiority of the *tert*-butyl group as P3 side chain.

SAR Study of P1 Residue. From our previous studies and the X-ray structure of the NS3 protease,[7] it was also apparent

Table 5. P1 Residue Optimization



Compound	R^1	Ki* (nM)	EC_{90} (nM)	HNE/HCV (n = 4)
43		4	40	1600
21		4	40	9300
44		2	40	230
45		7	40	6400
46		**4**	**30**	**7100**
47		**7**	**30**	**11000**

that the S1 pocket was small and narrow. The preferred P1 side chain was either a short linear alkyl chain or a small ring attached to a short alkyl chain. Compound **1** had a cyclobutyl methyl P1 side chain, which was one of the largest group the S1 pocket could accommodate. Several aliphatic side chains with different lengths and ring sizes were investigated, and the results are listed in Table 5. The norvaline derivative **43**, which had a short *n*-propyl side chain, was found to be equally potent to compound **21** but much less selective against elastase (HNE/HCV = 1600). On the other hand, P1 side chain of compound **44** had the same number of carbons but a smaller terminal alkyne. It also showed excellent potency in enzyme and replicon assays. However, its selectivity was on the lower side at 230-fold. Compound **1**, the clinical candidate, had cyclobutylalanine at P1 position. When this same residue was put into current combination, the resulting inhibitor (**45**) demonstrated an excellent but similar profile compared with **21**. When the smaller cyclopropylalanine was used at P1 position, improvement was observed in all properties. Thus, compound **46** had an excellent K_i* of 4 nM, the best replicon EC_{90} of 30 nM, and very high selectivity of 7100-fold. With the success of the cyclopropyl ring system, the one-carbon longer homocyclopropylalanine P1 analogue (**47**) was prepared. It was also an excellent inhibitor of HCV protease with the best cellular activity and selectivity. After these extensive SAR developments, two compounds (**46**, **47**) emerged as the leads with excellent overall profile. The goal of improving replicon activity by more than 10-fold over the compound **1** has been achieved.

Pharmacokinetic Property of Selected Compounds. The promising compounds from above SAR studies were evaluated in rats for their PK properties. The oral area under the curve (PO AUC) results for selected compounds are listed in Table 6. Compounds **16**, **24**, **39**, and **47** have lower PO AUC's that were below 1.0 μM·h. Two compounds (**21** and **46**) stood out with better rat PK (AUC of 1.58 and 1.2 μM·h, respectively), but compound **46** had better activity in replicon. Although compounds **46** and **47** were equally potent, the former had better PK in rats. On the basis of its overall superior profile, inhibitor **46** was selected for further PK studies.

Table 6. Rat PO AUC of Selected Compounds

compd	K_i*	EC_{90}	rat PO AUC[a] (μM·h)
16	8	150	0.44
21	4	40	1.58
24	6	40	0.36
39	2	45	0.45
46	**4**	**30**	**1.2**
47	7	30	0.50

[a] 10 mg/kg administered with 20% HPBCD.

Table 7. PK Parameters of Compound **46**

compd **46**	rat	monkey	dog
AUC(PO) (μM·h)	0.9[a]	0.1[b]	1.2[b]
AUC(IV) (μM·h)	1.6[b]	0.7[d]	2.2[c]
$t_{1/2}$ (IV) (h)	7.4	2.3	2.7
bioavailability (%)	22	4	35
rat liver conc (ng/g)	1796	NA	NA

[a] 10 mg/kg. [b] 3 mg/kg. [c] 2 mg/kg. [d] 1 mg/kg. All administered with 0.4% MC.

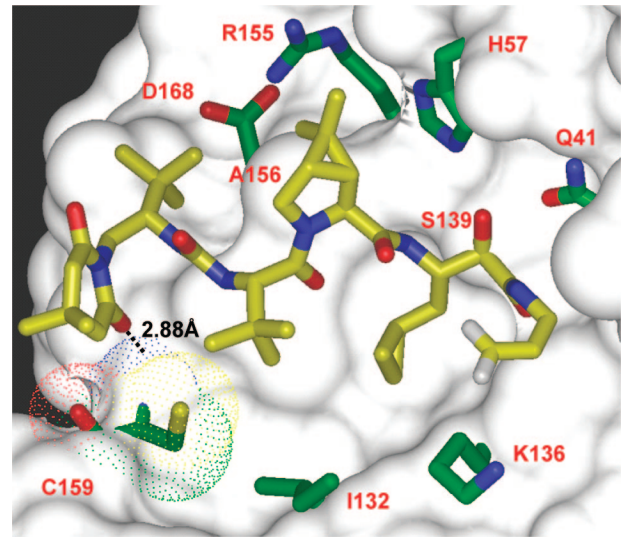


Figure 2. X-ray structure of compound **46** bound to HCV NS3 protease surface.

The results of full PK studies of compound **46** in rats, monkeys, and dogs are shown in Table 7. All samples were administered with 0.4% hydroxypropyl methylcellulose (MC). Compound **46** had a respectable 0.9 μM·h PO AUC and 22% bioavailability in rats. The PK data in monkeys were less impressive with 0.1 μM·h AUC and 4% bioavailability. The results were, however, very good in dogs with 1.2 μM·h AUC and 35% bioavailability. It was also highly concentrated in rat liver after 6 h (1796 ng/g), which is our target organ. It was quite encouraging that the overall PK profile was very similar to that of compound **1**, our clinical candidate, which had demonstrated good pharmacokinetic properties in human. Compound **46** was 12 times more potent than **1**.

X- Ray Structure of Compound 46. The X-ray crystal structure of inhibitor **46** bound to the enzyme surface was determined (Figure 2). The bindings of the P1, P2, and P3 residues with their respective pockets/surface were similar to

that reported for compound **1**.[11] The α-ketoamide formed a reversible covalent bond with Ser139 hydroxyl group. The prime side allyl group wrapped around the surface and had some interaction with the alkyl portion of the side chain of the backbone residue Lys136. The newly discovered cyclic imide capping group occupied the S4 pocket with its *tert*-butyl group. The glutarimide moiety formed a strong hydrogen bonding with residue Cys159, between one of the two imide carbonyls and amide N−H. This critical interaction provided the observed enhancement in potency.

Conclusion

Starting from current clinical candidate, compound **1**, extensive SAR studies were performed on the P3 capping moieties. This effort led to the discovery of *tert*-leucine amine derived cyclic imides as a potent series of novel P3 capping groups. A number of cyclic imides were explored with variations in substitutions, ring sizes, ring numbers, ring types (spiro and fused), and various heteroatom incorporations. The introduction of these imide cappings improved the cell-based replicon EC_{90} by more than 10-fold in many compounds. The 4,4-dimethyl substituted glutarimide cap emerged as the best as exemplified in compound **21** (K_i* = 4 nM, EC_{90} = 40 nM). Systematic optimization of P′, P3, and P1 residues resulted in the identification of the best moiety for each position. The combination of these optimal moieties led to compound **46**, which had an excellent potency (K_i* = 4 nM, EC_{90} = 30 nM) and good pharmacokinetic profiles (22% and 35% bioavailabilities in rats and dogs, respectively). X-ray structure of the inhibitor **46** bound to the enzyme revealed that there was a strong hydrogen bonding interaction between one of the imide carbonyls and Cys159. Compared with compound **1**, compound **46** provided a 12-fold improvement in cellular potency and maintained a good PK profile.

Experimental Section

General Methods. Reagents and solvents, including anhydrous THF, dichloromethane and DMF, were purchased from Aldrich or other commercial sources and were used without further purification. Reactions that were moisture sensitive or using anhydrous solvents were performed under either a nitrogen or an 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, ethanolic H_2SO_4, or Vaughn's reagent. 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 column. 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 internal TMS or deuterated solvent signal.

General experimental procedures were described in earlier publications[11,12] for the synthesis of P2 core, peptide coupling, Boc group deprotection, hydrolysis of ester to carboxylic acid, and Dess−Martin periodinane oxidation. The syntheses of cyclic imide from various starting material were performed according to literature procedures with some minor modifications.

(1*R*,5*S*)-3-[2(*S*)-[[[[1(*S*)-[(1,3-Dihydro-1,3-dioxo-2*H*-iso-indol-2-yl)-methyl]-2,2-dimethylpropyl]amino]carbonyl]-amino-3,3-dimethyl-1-oxobutyl]-*N*-[1-[1,2-dioxo-2-(2-propenylamino)ethyl]pentyl]-6,6-dimethyl-3-azabicyclo-[3.1.0]hexane-2(*S*)-carboxamide (14). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.86 and 8.81 (t, J = 5.99 Hz, 1 H), 8.33 and 8.20 (d, J = 6.62 and 7.25 Hz, 1H), 7.77 (bs, 3 H), 6.10−5.92 (m, 2 H), 5.80−5.73 (m, 1H), 5.19−5.02 (m, 2 H), 4.93−4.88 (m, 2 H), 4.85−4.80 (m, 1H), 4.29−4.26 and 4.21−4.18 (m, 1 H), 3.90−3.53 (m, 6 H), 3.47 (t, J = 12.6 Hz, 1 H), 1.74−1.62 (m, 1 H), 1.55−1.37 (m, 2 H), 1.35−1.10 (m, 6 H), 1.01−0.58 (m, 26 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.35, 171.76, 171.30, 171.17, 168.66, 161.70, 158.67, 158.49, 135.02, 135.00, 134.88, 132.51, 123.71, 116.45, 116.34, 109.99, 60.09, 57.29, 57.22, 55.34, 54.49, 41.67, 39.46, 34.96, 34.38, 31.45, 30.20, 30.01, 28.37, 28.19, 27.45, 27.19, 27.04, 26.95, 26.90, 26.73, 22.58, 22.55, 19.20, 14.55, 13.19, 13.14.

(1*R*,5*S*)-*N*-[1-[1,2-dioxo-2-(2-propenylamino)ethyl]-pentyl]-3-[2(*S*)-[[[[1(*S*)-[(2,5-dioxo-1-pyrrolidinyl)methyl]-2,2-dimethylpropyl]-amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (15). The compound was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.32 and 8.18 (d, J = 6.93, 7.25 Hz, 1H), 8.02 (d, J = 13.9 Hz, 1 H), 7.76 (s, 1 H), 7.35−7.22 (m, 1 H), 6.16−6.06 (m, 2 H), 5.87 (d, J = 9.46 Hz, 2 H), 5.00−4.92 (m, 1 H), 4.32−4.09 (m, 3 H), 4.03−3.80 (m, 2 H), 3.77−3.69 (m, 1 H), 3.63 (t, J = 9.62 Hz, 2 H), 2.47−2.41 (m, 4 H), 1.74−1.62 (m, 2 H), 1.62−1.02 (m, 11 H), 0.99−0.70 (m, 22 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 197.73, 197.11, 177.23, 170.96, 170.74, 170.52, 170.30, 163.06, 162.77, 157.91, 157.87, 59.53, 59.23, 58.87, 56.67, 56.58, 54.84, 54.82, 53.70, 53.66, 53.07, 53.04, 47.27, 47.22,, 34.17, 34.15, 33.31, 31.70, 31.56, 30.54, 30.48, 29.51, 27.77, 26.69, 26.55, 26.06, 26.01, 25.97, 20.83, 18.63, 18.54, 18.29, 18.07, 13.88, 13.81, 13.49, 13.42, 13.33, 12.31, 12.25. HRMS calcd for $C_{35}H_{56}N_6O_7$, 673.4289 $(M + H)^+$; found, 673.4286.

(1*R*,2*S*,5*S*)-*N*-(1-(allylamino)-1,2-dioxoheptan-3-yl)-3-((2*S*)-2-(3-((2*R*)-1-(2,4-dioxo-3-azabicyclo[3.1.0]hexan-3-yl)-3,3-dimethylbutan-2-yl)ureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (17). 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 and 6.93 Hz, 1 H), 8.37 and 8.30 (d, J = 6.62 and 7.25 Hz, 1 H), 6.15−6.11 (m, 1 H), 5.89−5.86 (m, 1 H), 5.82−5.75 (m, 1 H), 5.12−5.03 (m, 2 H), 4.97−4.93 and 4.86−4.16 (m, 1 H), 4.26 (d, J = 8.19 Hz, 1 H), 4.19−4.16 (m, 1 H), 3.92 (t, J = 10.1 Hz, 1 H), 3.78−3.67 (m, 4 H), 3.45 (t, J = 10.1 Hz, 1 H), 3.12 (t, J = 12.92 Hz, 1 H), 2.48−2.41 (m, 2 H), 1.76−1.21 (m, 10 H), 0.99−0.73 (m, 27 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.17, 197.56, 175.89, 175.81, 171.95, 171.75, 171.51, 171.30, 161.98, 161.61, 159.00, 158.96, 135.03, 134.99, 116.43, 116.33, 60.09, 59.81, 57.73, 57.65, 55.92, 55.87, 54.50, 48.24, 41.69, 38.86, 38.79, 35.01, 34.99, 34.51, 31.47, 30.19, 30.01, 28.37, 28.19, 27.69, 27.61, 27.09, 27.02, 26.97, 26.93, 26.82, 22.61, 22.56, 20.45, 20.27, 19.26, 14.55, 13.33, 13.28. HRMS calcd for $C_{36}H_{56}N_6O_7$, 685.4289 $(M + H)^+$; found, 685.4296.

(1*R*,5*S*)-3-[2(*S*)-[[[[1(*S*)-[(7,9-Dioxo-8-Azaspiro[4.5]dec-8-yl)methyl]-2,2-dimethylpropyl]amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-*N*-[1-[1,2-dioxo-2-(2-propenylamino)ethyl]pentyl]-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 8.88 and 8.82 (t, J = 6.30 and 5.99 Hz, 1 H), 8.37 and 8.32 (d, J = 6.62 and 7.25 Hz, 1 H), 6.12 (t, J = 11.1 Hz, 1 H), 5.82−5.74 (m, 2 H), 5.11−5.03 (m, 2 H), 4.97−4.82 (m, 1 H), 4.25−4.07 (m, 3 H), 3.90−3.54 (m, 6 H), 2.54 (bs, 4 H), 1.74−1.09 (m, 16 H), 0.98−0.95 (m, 3 H), 0.91−0.78 (m, 21 H), 0.75−0.72 (m, 3 H).

(1*R*,5*S*)-3-[2(*S*)-[[[[1(*S*)-[(2,4-dioxo-3-azabicyclo[3.2.1]oct-3-yl)-methyl]-2,2-dimethylpropyl]amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-*N*-[1-[1,2-dioxo-2-(2-propenyl-amino)ethyl]pentyl]-6,6-dimethyl-3-azabicyclo-[3.1.0]hexane-2(*S*)-carboxamide (19). The compound is isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.87 and 8.80 (t, J = 5.99 Hz, 1 H), 8.36 and 8.30 (d, J = 6.94 and 7.25 Hz, 1 H), 6.12 (q, J = 10.4 and 2.52 Hz, 1 H), 5.82−5.74 (m, 2 H), 5.11−5.03 (m, 2 H), 4.96−4.92 and 4.85−4.81 (m, 1 H), 4.25 (d, J = 7.88 Hz, 1 H), 4.16−4.07 (m, 1 H), 3.92 (t, J = 9.46 Hz, 1 H), 3.78−3.58 (m, 5 H), 2.96 and 2.89 (s, 2 H), 2.04 (d, J = 11.35 Hz, 1 H), 1.94 (s, 2 H), 1.77−1.67 (m, 3 H), 1.54−1.19 (m, 8 H), 0.98−0.74 (m, 28 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 197.28, 196.66, 176.15, 176.07, 171.13, 170.94, 170.81, 170.61, 161.12, 160.74, 134.12, 134.08, 115.56, 115.47, 59.23, 58.94, 53.59, 53.57, 47.34, 47.24, 44.33, 40.79,

34.00, 33.98, 30.59, 30.58, 29.26, 29.09, 27.47, 27.27, 26.90, 26.83, 26.55, 26.30, 26.08, 26.02, 21.70, 21.65, 18.40, 13.67, 13.65, 12.57, 12.53. HRMS calcd for $C_{38}H_{60}N_6O_7$, 713.4602 $(M + H)^+$; found, 713.4612.

(1*R*,5*S*)-3-[2(*S*)-[[[[1(*S*)-[(4,4-dimethyl-2,6-dioxo-1-piperidinyl)-methyl]-2,2-dimethylpropyl]amino]-carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-*N*-[1-[1,2-dioxo-2-(2-propenylamino)ethyl]pentyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide. (21). The compound is 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, 1 H), 8.35 and 8.28 (d, $J = 6.94$ and 7.25 Hz, 1 H), 6.12 (t, $J = 11.35$ Hz, 2 H), 5.81−5.73 (m, 2 H), 5.12−5.02 (m, 2 H), 4.96−4.92 and 4.85−4.80 (m, 1 H), 4.24 (d, $J = 9.46$ Hz, 1 H), 4.10 and 4.08 (dd, $J = 4.41$ and 10.09 Hz, 1 H), 3.88 (t, $J = 8.99$ Hz, 1 H), 3.81−3.55 (m, 6 H), 2.44−2.35 (m, 4 H), 1.75−1.66 (m, 1 H), 1.53−1.19 (m, 6 H), 0.97−0.73 (m, 33 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.31, 196.70, 171.87, 171.19, 171.00, 170.82, 170.62, 161.16, 160.77, 158.18, 158.13, 134.15, 134.10, 115.61, 115.52, 115.03, 59.30, 59.01, 57.08, 56.98, 56.93, 54.95, 54.90, 53.65, 53.62, 47.38, 47.37, 45.50, 40.84, 35.34, 34.26, 34.24, 34.14, 34.11, 30.62, 29.30, 29.14, 28.38, 27.52, 27.33, 27.23, 26.93, 26.85, 26.79, 26.33, 26.12, 26.08, 21.74, 21.69, 18.45, 13.71, 13.69, 12.61, 12.56. HRMS calcd for $C_{38}H_{62}N_6O_7$, 715.4758 $(M + H)^+$; found, 715.4763.

(1*R*,5*S*)-*N*-[1-[1,2-Dioxo-2-(2-propenylamino)ethyl]pentyl]-3-[2(*S*)-[[[[1(*S*)-[(4-ethyl-4-methyl-2,6-dioxo-1-piperidinyl)methyl]-2,2-dimethylpropyl]amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-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 8.88 and 8.82 (t, $J = 5.99$ and 6.62 Hz, 1 H), 8.37 and 8.31 (d, $J = 6.93$ and 6.30 Hz, 1 H), 6.15−6.10 (m, 1 H), 5.82−5.75 (m, 2 H), 5.15−5.04 (m, 2 H), 4.97−4.81 (m, 1 H),4.25−3.56 (m, 9 H), 2.47−2.29 (m, 4 H), 1.72−1.20 (m,10 H), 0.98−0.72 (m, 33 H). HRMS calcd for $C_{39}H_{64}N_6O_7$, 751.4734 $(M + Na)^+$; found, 751.4768.

(1*R*,5*S*)-3-[2(*S*)-[[[[1(*S*)-[(3,5-Dioxo-4-morpholinyl)methyl]-2,2-dimethylpropyl]amino]-carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-*N*-[1-[1,2-dioxo-2-(2-propenylamino)ethyl]pentyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (23). The compound is isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.87 and 8.82 (d, $J = 5.99$ Hz, 1 H), 8.36 and 8.26 (d, $J = 6.93$ and 7.25 Hz, 1H), 6.13−6.08 (m, 1 H), 5.85−5.75 (m, 2 H), 5.12−5.03 (m, 2 H), 4.97−4.93, 4.87−4.83 (m, 1 H), 4.31−4.14 (m, 6 H), 3.91 (t, $J = 10.08$ Hz, 1 H), 3.80−3.62 (m, 6 H), 1.75−1.46 (m, 1 H), 1.40−1.22 (m, 7 H), 0.99−0.75 (m, 27 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 198.19, 197.58, 171.99, 171.79, 171.55, 171.34, 170.42, 161.97, 161.63, 158.92, 158.88, 135.04, 135.00, 116.44, 116.35, 67.74, 60.12, 59.80, 57.69, 57.62, 55.64, 54.51, 41.68, 35.07, 35.04, 34.53, 31.47, 30.19, 30.01, 28.37, 28.19, 27.69, 27.60, 27.05, 26.99, 26.94, 22.60, 22.56, 19.27, 14.55, 13.30, 13.24. HRMS calcd for $C_{35}H_{56}N_6O_8$, 689.4238 $(M + H)^+$; found, 689.4213.

(1*R*,5*S*)-3-[2(*S*)-[[[[2,2-Dimethyl-1(*S*)-[(4-methyl-2,6-dioxo-1-piperazinyl)methyl]propyl]amino]carbonyl]-amino]-3,3-dimethyl-1-oxobutyl]-*N*-[1-[1,2-dioxo-2-(2-propenylamino)ethyl]pentyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (24). The compound was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88 and 8.82 (d, $J = 5.99$ and 5.67 Hz, 1H), 8.36 and 8.28 (d, $J = 6.62$ and 7.25 Hz, 1 H), 6.14−6.09 (m, 1 H), 5.82−5.76 (m, 2 H), 5.12−5.04 (m, 3 H), 4.97−4.93 and 4.86−4.82 (m, 1 H), 4.26−3.58 (m, 12 H), 2.22 (s, 3 H), 1.76−1.14 (m, 8 H), 0.99−0.74 (m, 27 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 198.19, 197.25, 171.99, 171.38, 170.85, 170.88, 158.90, 158.85, 135.04, 135.00, 116.44, 116.36, 89.96, 59.90, 59.70, 58.34, 57.63, 55.58, 54.51, 48.23, 43.84, 41.69, 35.08, 34.80, 31.49, 30.11, 28.45, 28.21, 27.14, 26.96, 26.89, 22.58, 19.24, 14.61, 13.40, 13.27. HRMS calcd for $C_{36}H_{59}N_7O_7$, 702.4554 $(M + H)^+$; found, 702.4531.

(1*R*,5*S*)-3-[2(*S*)-[[[[1(*S*)-[(2,6-Dioxo-4-phenyl-1-piperazinyl)methyl]-2,2-dimethylpropyl]amino]-carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-*N*-[1-[1,2-dioxo-2-(2-propenylamino)ethyl]-pentyl]-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 8.87 and 8.81 (t, $J = 5.99$ and 6.30 Hz, 1 H), 8.37−8.34 and 8.28−8.28 (m, 1 H), 7.59−7.23 (m, 3 H), 7.10−6.87 (m, 2 H), 6.13−6.07 (m, 1 H), 5.85−5.74 (m, 2 H), 5.13−5.03 (m, 2 H), 4.28−4.01 (m,5 H), 3.93−3.60 (m, 8 H), 1.78−1.14 (m, 8 H), 0.98−0.71 (m, 27 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.17, 197.56, 175.36, 171.98, 171.78, 171.52, 171.30, 170.13, 163.89, 161.98, 161.62, 158.97, 148.47, 135.03, 134.99, 130.06, 125.72, 123.25, 121.23, 116.59, 116.43, 116.34, 60.12, 59.81, 57.98, 57.66, 55.45, 54.50, 52.98, 48.19, 41.68, 34.97, 34.54, 34.28, 34.00, 32.12, 31.47, 30.18, 30.00, 29.23, 28.36, 28.19, 27.71, 27.02, 25.45, 22.97, 22.59, 19.27, 14.87, 14.56, 14.55, 13.33, 13.27. HRMS calcd for $C_{41}H_{61}N_7O_7$, 764.4711 $(M + H)^+$; found, 764.4723.

(1*R*,5*S*)-3-[2(*S*)-[[[[2,2-Dimethyl-1(*S*)-[(tetrahydro-2,6-dioxo-1(2*H*)-pyrimidinyl)methyl]propyl]amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-*N*-[1-[1,2-dioxo-2-(2-propenylamino)ethyl]pentyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (26). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88 and 8.83 (t, $J = 8.19$ and 6.30 Hz, 1H), 8.36 and 8.27 (d, $J = 7.88$ and 7.25 Hz, 1 H), 7.64 (bs, 1 H), 6.15−6.09 (m, 1 H), 5.82−5.74 (m, 2 H), 5.11−4.83 (m, 3 H), 4.26−4.15 (m, 2 H), 3.98−3.56 (m, 7 H), 3.06 (m, 2 H), 2.48−2.40 (m, 2 H), 1.74−1.07 (m, 8 H), 0.98−0.74 (m, 27 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.18, 197.58, 152.01, 171.80, 171.66, 171.45, 170.55, 161.98, 161.62, 159.14, 154.90, 135.04, 135.00, 116.44, 116.35, 60.09, 59.78, 57.76, 57.67, 56.23, 54.52, 48.23, 41.69, 35.14, 35.04, 34.44, 32.51, 31.44, 30.13, 30.05, 28.43, 28.14, 27.74, 27.62, 27.09, 26.96, 22.60, 19.24, 14.57, 13.37, 13.33. HRMS calcd for $C_{35}H_{57}N_7O_7$, 688.4398 $(M + H)^+$; found, 688.4418.

(1*R*,5*S*)-3-[2(*S*)-[[[[2,2-Dimethyl-1(*S*)-[(tetrahydro-3-methyl-2,6-dioxo-1(2*H*)-pyrimidinyl)methyl]propyl]amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-*N*-[1-[1,2-dioxo-2-(2-propenylamino)-ethyl]pentyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (27). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88 and 8.83 (t, $J = 6.30$ and 5.67 Hz, 1 H), 8.37 and 8.29 (d, $J = 6.62$ and 7.56 Hz, 1 H), 6.13−6.08 (m, 1 H), 5.82−5.75 (m, 2 H), 5.11−5.02 (m, 2 H), 4.97−4.93 and 4.87−4.83 (m, 1 H), 4.26 (d, $J = 9.14$ Hz, 1 H), 4.19−4.14 (m, 2 H), 3.94−3.89 (m, 2 H), 3.78−3.58 (m, 4 H), 3.21 (t, $J = 6.62$ Hz, 2 H), 2.86 (s, 3 H), 2.57−2.46 (m, 2 H), 1.76−1.07 (m, 8 H), 0.98−0.74 (m, 27 H). HRMS calcd for $C_{36}H_{59}N_7O_7$, 702.4554 $(M + H)^+$; found, 702.4531.

(1*R*,5*S*)-3-[2(*S*)-[[[[1(*S*)-[(2,5-Dioxo-imidazolidinyl)-methyl]-2,2-dimethylpropyl]amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-*N*-[1-[1,2-dioxo-2-(2-propenyl-amino)ethyl]pentyl]-6,6-dimethyl-3-azabicyclo[3.1.0]-hexane-2(*S*)-carboxamide (28). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88 and 8.83 (t, $J = 5.99$ and 5.99 Hz, 1H), 8.37 and 8.27 (d, $J = 6.62$ and 7.25 Hz, 1 H), 7.88 (s, 1 H), 6.10−6.04(m, 1 H), 5.89−5.72 (m, 2 H), 5.11−5.00 (m, 2 H), 4.97−4.92 and 4.87−4.82 (m, 1 H), 4.26 (d, $J = 11.66$ Hz, 1 H), 4.18−4.14 (m, 1 H), 3.91−3.60 (m, 8 H), 3.23 (t, $J = 13.24$ Hz, 1 H), 1.74−1.21 (m, 8 H), 0.98−0.74 (m, 27 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.18, 197.58, 172.64, 171.91, 171.80, 171.53, 171.35, 161.96, 161.60, 158.75, 158.71, 158.43, 135.03, 134.99, 130.88, 129.02, 116.44, 116.36, 60.12, 59.78, 59.79, 57.52, 56.00, 54.50, 48.19, 46.54, 41.69, 35.15, 35.13, 34.41, 31.50, 31.47, 30.45, 30.17, 30.02, 28.38, 28.20, 27.65, 27.56, 27.01, 26.93, 22.60, 22.56, 19.27, 14.57, 13.29, 13.22. HRMS calcd for $C_{34}H_{55}N_7O_7$, 674.4241 $(M + H)^+$; found, 674.4246.

(1*R*,5*S*)-3-[2(*S*)-[[[[2,2-Dimethyl-1(*S*)-[(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)methyl]propyl]amino]-carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-*N*-[1-[1,2-dioxo-2-(2-propenylamino)ethyl]pentyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (31). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88 and 8.83 (t, $J = 5.99$ and 6.30 Hz, 1 H), 8.37 and 8.29 (d, $J = 6.93$ and 7.25 Hz, 1 H), 6.11−6.05 (m, 1 H), 5.93−5.89 (m, 1 H), 5.82−5.74 (m, 1 H), 5.11−5.03 (m, 2 H), 4.96−4.92 and 4.86−4.82 (m, 1 H), 4.25 (d, $J = 8.82$ Hz, 1 H), 4.17−4.08 (m, 2 H), 3.91−3.63 (m, 4 H), 3.47−3.42 (m, 1 H),

3.23−3.18 (m, 1 H), 2.71 (s, 3 H), 1.75−1.19 (m, 14 H), 0.98−0.74 (m, 27 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.17, 197.56, 177.10, 171.99, 171.78, 171.55, 171.35, 161.97, 161.61, 158.79, 158.74, 155.46, 135.02, 134.98, 116.44, 116.35, 61.20, 60.12, 59.79, 57.72. 57.62, 56.07, 55.72, 54.48, 48.14, 41.68, 35.05, 35.01, 34.50, 31.45, 30.19, 29.97, 28.35, 28.19, 27.67, 27.56, 27.09, 26.92, 24.94, 24.85, 22.59, 22.55, 22.36, 21.74, 19.26, 14.55, 13.36, 13.28. HRMS calcd for $C_{37}H_{61}N_7O_7$, 716.4711 $(M + H)^+$; found, 716.4718.

(1*R*,5*S*)-3-[2(*S*)-[[[[1(*S*)-[(4,4-Dimethyl-2,6-dioxo-1-piperidinyl)-methyl]-2,2-dimethylpropyl]amino]-carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-*N*-[1-[2-(ethylamino)-1,2-dioxoethyl]pentyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (33). This compound was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.71 and 8.67 (t, J = 5.67 and 5.99 Hz, 1 H), 8.36 and 8.27 (d, J = 6.93 and 7.56 Hz, 1 H), 6.13 (t, J = 10.08 Hz, 1 H), 5.79 (d, J = 10.4 Hz, 1 H), 4.98−4.94 and 4.89−4.85 (m, 1 H), 4.25 (d, J = 5.99 Hz, 1 H), 4.11 (m, 1 H), 3.89 (t, J = 10.08 Hz, 1 H), 3.80 (t, J = 11.66 Hz, 1 H), 3.74−3.63(m, 2 H), 3.58 (d, J = 11.66 Hz, 1H), 2.44−2.36 (m, 4 H), 1.76−1.20 (m, 8 H), 1.03 (t, J = 7.25 Hz, 3 H), 0.99 (d, J = 9.14 Hz, 3 H), 0.94 (s, 6 H), 0.86−0.75 (m, 21 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.39, 197.81, 172.67, 172.02, 171.80, 171.65, 171.44, 161.74, 161.29, 159.0, 158.95, 130.24, 116.08, 60.15, 59.83, 57.91, 57.81, 55.75, 54.44, 48.09, 46.36, 35.10, 34.97, 34.29, 31.57, 31.52, 30.16, 30.06, 29.24, 28.43, 28.24, 28.03, 27.75, 27.66, 27.21, 26.95, 22.56, 19.30, 15.11, 14.57, 13.48, 13.43. HRMS calcd for $C_{37}H_{62}N_6O_7$, 703.4758 $(M + H)^+$; found, 703.4726.

(1*R*,5*S*)-3-[2(*S*)-[[[[1(*S*)-[(4,4-Dimethyl-2,6-dioxo-1-piperidinyl)-methyl]-2,2-dimethylpropyl]amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-*N*-[1-[1,2-dioxo-2-(propylamino)ethyl]-pentyl]-6,6-dimethyl-3-azabicyclo-[3.1.0]hexane-2(*S*)-carboxamide (34). The compound is isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.68 and 8.63 (t, J = 5.99 Hz, 1 H), 8.32 and 8.24 (d, J = 6.93 and 7.25 Hz, 1H), 6.15−6.10 (m, 1 H), 5.79 and 5.77 (dd, J = 3.15 and 10.72 Hz, 1 H), 4.97−4.93 and 4.88−4.84 (m, 1 H), 4.25 (d, J = 7.25 Hz, 1 H), 4.12−4.07 (m, 1 H), 3.88, 3.79 (t, J = 9.62 and 11.82 Hz, 2 H), 3.73−3.55 (m, 4 H), 3.08−3.01 (m, 2 H), 2.46−2.34 (m, 5 H), 1.75−1.66 (m, 1 H), 1.51−1.13 (m, 8 H), 0.97−0.85 (m, 32 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.50, 196.89, 171.81, 171.80, 171.12, 170.89, 170.77, 170.55, 161.15, 160.76, 158.11, 158.09, 158.06, 59.26, 58.95, 57.01, 56.92, 54.87, 54.82, 53.56, 53.52, 47.31, 45.46, 34.21, 34.19, 34.07, 34.05, 30.64, 30.61, 29.26, 29.16, 28.33, 27.48, 27.28, 27.18, 26.86, 26.77, 26.29, 26.28, 26.07, 26.04, 21.91, 21.88, 21.67, 21.63, 18.40, 13.66, 13.64, 12.57, 12.51, 11.22. HRMS calcd for $C_{38}H_{64}N_6O_7$, 717.4915 $(M + H)^+$; found, 717.4914.

(1*R*,5*S*)-3-[2(*S*)-[[[[1(*S*)-[(4,4-Dimethyl-2,6-dioxo-1-piperidinyl)-methyl]-2,2-dimethylpropyl]amino]-carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-*N*-[1-[1,2-dioxo-2-[(2-thienylmethyl)amino]ethyl]pentyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (37). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.33 and 9.28 (d, J = 7.56 Hz, 1 H), 8.37and 8.29 (d, J = 7.25 Hz, 1 H), 7.39 (d, J = 5.04 Hz, 1 H), 6.97−6.94 (m, 2 H), 6.14 (t, J = 12.61 Hz, 1 H), 5.79 (d, J = 10.71 Hz, 1 H), 5.01−4.97 and 4.89−4.84 (m, 1 H), 4.47−4.08 (m, 4 H), 3.91−3.56 (m, 5 H), 2.45−2.36 (m, 4 H), 1.74−1.15 (m, 8 H), 0.98−0.93 (m, 9 H), 0.86 (s, 9 H), 0.82−0.74 (m, 15 H). HRMS calcd for $C_{40}H_{62}N_6O_7S$, 771.4479 $(M + H)^+$; found, 771.4478.

(1*R*,5*S*)-3-[2(*S*)-Cyclohexyl-2-[[[[1(*S*)-[(4,4-dimethyl-2,6-dioxo-1-piperidinyl)methyl]-2,2-dimethylpropyl]amino]-carbonyl]amino]acetyl]-*N*-[1-[1,2-dioxo-2-(2-propenyl-amino)ethyl]pentyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (39). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.88 and 8.84 (d, J = 5.99 and 6.30 Hz, 1 H), 8.38 and 8.24 (d, J = 7.56 and 6.62 Hz, 1 H), 6.05 (t, J = 7.56 Hz, 1H), 5.83−5.75 (m, 1H), 5.64−5.61 (m, 1 H), 5.10−5.04 (m, 2 H), 4.93−4.89 (m, 1 H), 4.23 (d, J = 12.92 Hz, 1 H), 4.00−3.57 (m, 8 H), 2.45−2.36 (m, 4 H), 1.72−1.07 (m, 19 H), 0.98−0.76 (m, 22 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.18, 197.67, 172.72, 172.01, 171.77, 171.65, 161.87, 161.63, 158.58, 141.30, 134.97, 116.45, 116.36, 60.42, 59.90, 55.91, 55.78, 54.65, 54.27, 47.77, 47.56, 46.36, 41.68, 35.07, 31.58, 30.17, 29.82, 29.61, 29.25, 28.44, 28.20, 28.05, 27.61, 27.53, 26.96, 26.20, 22.58, 22.53, 19.38, 14.55, 13.52, 13.43. HRMS calcd for $C_{40}H_{64}N_6O_7$, 741.4915 $(M + H)^+$; found, 741.4890.

(1*R*,5*S*)-3-[2(*S*)-[[[[1(*S*)-[(4,4-Dimethyl-2,6-dioxo-1-piperidinyl)-methyl]-2,2-dimethylpropyl]amino]-carbonyl] amino]-2-(1-methyl-cyclohexyl)acetyl]-*N*-[1-[1,2-dioxo-2-(2-propenylamino)-ethyl]pentyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (40). 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, 1 H), 8.34 and 8.21 (d, J = 6.94 and 7.25 Hz, 1 H), 6.15 (q, J = 10.09 and 4.10 Hz, 1 H), 5.82−5.74 (m, 2 H), 5.11−5.03 (m, 2 H), 4.96−4.92 and 4.86−4.82 (m, 1 H), 4.24 (d, J = 15.13 Hz, 1 H), 4.17 (q, J = 7.25 and 2.52 Hz, 1 H), 3.89 (t, J = 10.09 Hz, 1 H), 3.81−3.56 (m, 7 H), 2.48−2.34 (m, 4 H), 1.76−1.67 (m, 1 H), 1.51−1.06 (m, 8 H), 0.97−0.93 (m, 11 H), 0.89 (s, 4 H), 0.86−0.72 (m, 20 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 197.29, 196.70, 171.76, 171.74, 171.11, 170.90, 170.60, 170.35, 161.11, 160.75, 158.08, 158.03, 134.12, 134.08, 115.55, 115.45, 59.36, 58.98, 54.89, 54.84, 53.61, 47.35, 47.33, 45.49, 40.79, 40.77, 36.83, 36.79, 34.14, 33.55, 33.47, 33.38, 33.33, 30.55, 30.52, 29.30, 29.16, 28.35, 27.49, 27.27, 27.16, 26.83, 26.74, 26.05, 26.00, 25.87, 25.86, 21.73, 21.68, 21.30, 21.16, 19.18, 18.39, 18.36, 13.66, 12.58, 12.51. HRMS calcd for $C_{41}H_{66}N_6O_7$, 755.5071 $(M + H)^+$; found, 755.5086.

(1*R*,5*S*)-3-[2(*S*)-(2,3-Dihydro-1*H*-inden-2-yl)-2-[[[[1(*S*)-[(4,4-dimethyl-2,6-dioxo-1-piperidinyl)methyl]-2,2-dimethylpropyl]amino]carbonyl]amino]acetyl]-*N*-[1-[1,2-dioxo-2-(2-propenylamino)-ethyl]pentyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (41). The product was isolated as mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.91 and 8.81 (t, J = 6.36 and 11.98 Hz, 1 H), 8.43 and 8.29 (d, J = 6.93 and 9.14 Hz, 1 H), 7.16−7.10 (m, 4 H), 6.31 (t, J = 8.19 Hz, 1 H), 5.83−5.76 (m, 1 H), 5.67(d, J = 6.62 Hz, 1H), 5.13−4.95 (m, 3 H), 4.25 (d, J = 15.44 Hz, 1 H), 4.16−4.08 (m, 1 H), 3.82−3.76 (m, 4 H), 3.67−3.54 (m, 3 H), 2.86−2.56 (m, 5 H), 2.44 (bs, 4 H), 1.78−1.48 (m, 2 H), 1.38−1.21 (m, 6 H), 0.97 (bs, 9 H), 0.88−0.77 (m, 15 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.19, 197.75, 172.77, 172.05, 171.85, 171.59, 171.55, 161.85, 161.67, 158.73, 143.40, 143.01, 134.98, 130.87, 129.02, 127.09, 127.00, 125.16, 116.46, 116.38, 60.60, 60.12, 55.90, 54.70, 54.43, 53.88, 47.65, 47.08, 46.50, 41.70, 36.89, 35.05, 30.05, 29.30, 28.47, 28.29, 28.02, 27.58, 26.97, 26.95, 22.55, 19.44, 14.57, 13.48, 13.55. HRMS calcd for $C_{43}H_{62}N_6O_7$, 775.4758 $(M + H)^+$; found, 775.4777.

(1*R*,5*S*)-3-[2(*S*)-(2,3-Dihydro-2-methyl-1*H*-inden-2-yl)-2-[[[[1(*S*)-[(4,4-dimethyl-2,6-dioxo-1-piperidinyl)methyl]-2,2-dimethylpropyl]-amino]carbonyl]amino]acetyl]-*N*-[1-[1,2-dioxo-2-(2-propenylamino)ethyl]pentyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (42). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.89 and 8.83 (t, J = 5.99 and 5.99 Hz, 1 H), 8.40 and 8.35 (d, J = 6.93 and 7.56 Hz, 1 H), 7.15−7.09 (m, 4 H), 6.32 (t, J = 11.66 Hz, 1 H), 5.82−5.74 (m, 2 H), 5.12−5.03 (m, 2 H), 4.97−4.93 and 4.89−4.84 (m, 1 H), 4.36 (t, J = 10.40 Hz, 1 H), 4.27 (d, J = 9.77 Hz, 1 H), 3.86−3.56 (m, 7 H), 3.12−3.08 (m, 2 H), 2.46−2.35 (m, 6 H), 1.75−1.22 (m, 8 H), 1.02−0.97 (m, 3 H), 0.87−0.77 (m, 24 H).

(1*R*,5*S*)-3-[2(*S*)-[[[[1(*S*)-[(4,4-Dimethyl-2,6-dioxo-1-piperidinyl)-methyl]-2,2-dimethylpropyl]amino]carbonyl]-amino]-3,3-dimethyl-1-oxobutyl]-*N*-[1-[1,2-dioxo-2-(2-propenylamino)ethyl]butyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (43). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.86 and 8.81 (t, J = 6.15 and 5.99 Hz, 1 H), 8.36 and 8.31 (d, J = 6.93 and 7.25 Hz, 1 H), 6.12 (t, J = 9.93 Hz, 1 H), 5.82−5.74 (m, 2 H), 5.11−5.03 (m, 2 H), 4.98−4.93 and 4.87−4.83 (m, 1 H), 4.25 (d, J = 5.36 Hz, 1 H), 4.09 (q, J = 4.10 and 5.68 Hz, 1 H), 3.88 (q, J = 7.88 and 2.52 Hz, 1 H), 3.82−3.64 (m, 5 H), 3.58 (d, J = 12.61 Hz, 1 H), 2.41 (q, J = 15.76 Hz and 7.88 Hz, 4 H), 1.72−1.62 (m, 1 H), 1.53−1.14 (m, 6 H), 0.98−0.93 (m, 8 H), 0.85−0.74 (m, 24 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 197.23, 196.61, 171.68, 171.67, 171.02, 170.81, 170.65, 170.49, 161.05, 160.67, 158.04, 157.99, 134.08, 134.03,

115.48, 115.39, 114.97, 68.39, 59.14, 58.88, 56.98, 56.89, 55.72, 54.78, 54.73, 53.37, 53.33, 47.23, 45.41, 40.71, 38.66, 38.59, 34.14, 34.11, 34.00, 33.97, 31.52, 30.52, 30.50, 29.48, 28.25, 27.11, 26.82, 26.74, 26.24, 26.22, 26.00, 25.97, 18.59, 18.44, 18.33, 18.32, 13.46, 13.35, 12.50, 12.46. HRMS calcd for $C_{37}H_{60}N_6O_7$, 701.4602 $(M + H)^+$; found, 701.4617.

(1*R*,5*S*)-3-[2(*S*)-[[[[1(*S*)-[(4,4-Dimethyl-2,6-dioxo-1-piperidinyl)-methyl]-2,2-dimethylpropyl]amino]-carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-*N*-[1-[1,2-dioxo-2-(2-propenylamino)ethyl]-4-pentynyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (44). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.87 and 8.76 (t, $J = 6.30$ and 5.99 Hz, 1H), 8.60 and 8.45 (d, $J = 7.25$ and 6.93 Hz, 1 H), 6.15−6.12 (m, 1 H), 5.82−5.73 (m, 2 H), 5.12−4.96 (m, 3 H), 4.22−4.07 (m, 2 H), 3.89−3.55 (m, 7 H), 2.80−2.79 (m, 1 H), 2.46−2.35 (m, 4 H), 2.33−1.14 (m, 6 H), 0.98−0.93 (m, 9 H), 0.89−0.75 (m, 21 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 197.53, 196.99, 172.67, 172.10, 171.49, 162.35, 161.64, 159.01, 135.06, 134.98, 116.47, 116.33, 84.02, 72.62, 72.55, 59.99, 57.78, 55.67, 54.17, 48.22, 46.47, 46.25, 41.58, 35.07, 34.96, 31.36, 29.89, 29.33, 28.81, 29.23, 28.11, 28.06, 27.89, 27.22, 26.94, 19.27, 15.60, 15.13, 13.45, 13.44.

(1*R*,5*S*)-*N*-[1-(Cyclobutylmethyl)-2,3-ioxo-3-(2-propenylamino)-propyl]-3-[2(*S*)-[[[[1(*S*)-[(4,4-dimethyl-2,6-dioxo-1-piperidinyl)-methyl]-2,2-dimethylpropyl]amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (45). The product was obtained as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.86 and 8.83 (t, $J = 13.24$ and 5.99 Hz, 1 H), 8.33 and 8.29 (d, $J = 8.82$ and 7.25 Hz, 1 H), 6.14 (d, $J = 12.61$ Hz, 1 H), 5.78−5.75 (m, 2 H), 5.11−5.03((m, 2 H), 4.94−4.90 and 4.78−4.75 (m, 1 H), 4.24−4.23 (m, 1 H), 4.11−4.08 (m, 2 H), 3.90−3.56 (m, 6 H), 2.48−2.34 (m, 4 H), 1.97−1.91 (m, 2 H), 1.79−1.72 (m, 3 H), 1.65−1.57 (m, 3 H), 1.39−1.37(m, 1 H), 1.24−1.14 (m, 2 H), 0.98−0.75 (m, 31 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.14, 197.50, 172.67, 172.66, 171.85, 171.67, 171.65, 171.46, 161.84, 161.54, 159.03, 158.96, 135.06, 135.01, 116.47, 116.39, 60.07, 59.89, 57.95, 57.85, 55.74, 55.69, 53.25, 53.03, 48.19, 46.36, 41.70, 37.59, 37.38, 35.12, 35.10, 34.97, 34.94, 33.03, 32.96, 31.46, 31.38, 29.24, 28.80, 28.62, 28.24, 28.22, 28.08, 27.83, 27.71, 27.20, 26.95, 19.30, 18.73, 18.56, 13.47, 13.44. HRMS calcd for $C_{39}H_{62}N_6O_7$, 727.4758 $(M + H)^+$; found, 727.4772.

(1*R*,5*S*)-*N*-[1-(Cyclopropylmethyl)-2,3-dioxo-3-(2-propenylamino)-propyl]-3-[2(*S*)-[[[[1(*S*)-[(4,4-dimethyl-2,6-dioxo-1-piperidinyl)-methyl]-2,2-dimethylpropyl]amino]-carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (46). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.84 and 8.80 (t, $J = 6.15$ Hz, 1 H), 8.41 and 8.38 (d, $J = 6.62$ and 6.94 Hz, 1 H), 6.12 (t, $J = 11.19$ Hz, 1 H), 5.81−5.73 (m, 2 H), 5.10−4.94 (m, 3 H), 4.26 (s, 1 H), 4.12−4.08 (m, 1 H), 3.88 (t, $J = 9.14$ Hz, 1 H), 3.81−3.55 (m, 7 H), 2.41 (q, $J = 16.39$ and 11.35 Hz, 4 H), 1.72−1.67 and 1.63−1.57 (m, 1 H), 1.55−1.36 (m, 2 H), 1.29 and 1.25 (d, $J = 7.57$ and 7.88 Hz, 1 H), 0.97−073 (m, 30 H), 045−0.33 (m, 2 H), 0.12−0.0 (m, 2 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 197.08, 196.53, 171.04, 170.77, 170.76, 170.60, 160.85, 160.46, 158.12, 158.08, 134.13, 134.09, 115.59, 115.53, 59.15, 58.95, 57.06, 56.93, 54.87, 54.84, 54.42, 54.38, 47.33, 45.47, 40.80, 34.98, 34.83, 34.21, 34.19, 34.08, 34.05, 30.62, 30.50, 28.33, 27.19, 26.83, 26.77, 26.31, 26.67, 26.09, 26.05, 18.41, 18.39, 12.58, 12.55, 7.86, 7.63, 4.99, 4.33, 3.99. HRMS calcd for $C_{38}H_{60}N_6O_7$, 713.4602 $(M + H)^+$; found, 713.4612.

(1*R*,5*S*)-*N*-[1-(2-Cyclopropylethyl)-2,3-dioxo-3-(2-propenylamino)-propyl]-3-[2(*S*)-[[[[1(*S*)-[(4,4-dimethyl-2,6-dioxo-1-piperidinyl)-methyl]-2,2-dimethylpropyl]amino]-carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (47). The product was isolated as a mixture of two diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99−7.64 (m, 2 H), 5.88−5.77 (m, 1 H), 5.72−5.66 (m, 1 H), 5.63−5.56 (m, 1 H), 5.24−5.13 (m, 2 H), 5.05−4.99 (m, 1 H), 4.54−4.40 (m, 2 H), 4.04−3.81 (m, 7 H), 2.53−2.41 (m, 4 H), 2.12−2.04 (m, 1 H), 1.72−1.23 (m, 6 H), 1.03(s, 3 H), 0.97−0.86 (m, 24 H), 0.76 (bs, 3 H), 0.41 (d, $J = 8.05$ Hz, 2 H), 0.06−0.0 (m, 2 H).

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JM801238Q