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Discovery of novel P_3 sulfonamide-capped inhibitors of HCV NS3 protease. Inhibitors with improved cellular potencies

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ABSTRACT

Hepatitis C Virus (HCV) infection is the major cause of chronic liver disease, leading to cirrhosis and hepatocellular carcinoma, which affects more than 200 million people worldwide. Currently the only therapeutic regimens are subcutaneous interferon-α or PEG-interferon alone or in combination with oral ribavirin. Although combination therapy is reasonably successful with the majority of genotypes, its efficacy against the predominant genotype (genotype 1) is moderate at best, with only ~50% of the patients showing sustained virological response. We recently disclosed the discovery of Boceprevir, SCH 503034 (**1**), which is a novel, potent, selective, orally bioavailable NS3 protease inhibitor that has been shown to be efficacious in humans and is currently undergoing clinical trials. As second generation compounds, we have further explored various novel structures with the aim of improving enzyme and cellular binding activities of **1**. Herein, we disclose our efforts toward the identification of a novel P_3 sulfonamide-capped inhibitor that demonstrated improved binding and cellular activity compared to **1**. X-ray structure of one of these inhibitors bound to the enzyme revealed a hydrogen bond of the P_3 sulfonamide group to Cys-159 which resulted in improved binding and cellular potency.

1. Introduction

Hepatitis C virus is the primary etiological agent responsible for non-A, non-B hepatitis, transmitted by unscreened blood transfusions. Majority of these infections turn chronic with slow progression to liver cirrhosis and hepatocellular carcinoma.[1] Pegylated α-interferon alone or in combination with ribavirin is the preferred treatment for HCV infections.[2] Interferon therapy is effective only in ~50% of patients infected with genotype-1. Lack of effective methods to treat genotype-1 HCV infections, and interferon non-responders necessitates discovery of new drugs. Investigational new therapies are primarily focused toward the inhibition of key viral enzymes in virus life cycle vital for HCV replication and maturation.[3]

Hepatitis C virus is a positive strand RNA virus of ~9600 kB. It encodes a polyprotein of ~3000 amino acids that are post-translationally modified to produce mature virions.[4] The encoded polyprotein contains all the structural and nonstructural proteins C-E1-E2-P7-NS2-NS3-NS4A-NS4B-NS5A-NS5B. It undergoes an autocatalytic cleavage of NS2-NS3 junction followed by cleavage of the NS4A-NS4B, NS4B-NS5A, and NS5A-NS5B catalyzed by NS3 protease.[5] This central role played by NS3 protease in the development of mature hepatitis C virus makes it an excellent target for drug discovery. Development of small molecule inhibitors of this enzyme would potentially arrest the processing of the aforementioned polyprotein required for viral replication. This has been a field of intense investigation by various groups worldwide.[6] We recently disclosed the synthesis and development of Boceprevir, SCH 503034 (**1**),[7] which is a selective, potent, orally bioavailable HCV NS3 protease inhibitor that is efficacious in humans and currently undergoing Phase III clinical trials. Several other molecules including VX950, ITMN-191, MK-7009, TMC435350, and BILN 2061 have also been advanced to clinical trials and found to be effective.[6]

As shown in Figure 1, **1** demonstrated a $K_i^* = 14$ nM in the continuous enzyme binding assay[8] and an $EC_{90} = 0.35$ μM in the replicon-based cellular assay.[9] It also demonstrated excellent selectivity against human neutrophil elastase (HNE). Compound **1** was readily absorbed in rats and dogs demonstrating acceptable PK. In an effort to develop a potential back-up to **1**, we decided to identify an inhibitor that was fivefold more potent than **1** in the replicon cellular assay while maintaining similar enzyme binding and HNE selectivity. Herein, we describe our efforts in the identification of P_3-capped sulfonamide series of inhibitors that were significantly more potent than **1** in the enzyme and cellular assays and demonstrated good PK in rats.

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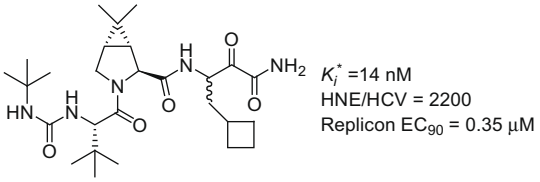


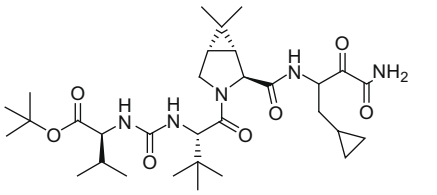
***Boceprevir*, 1 (Sch 503034)**

Figure 1.

While investigating the SAR in the P_3 capping of **1,** it was observed that replacement of *tert*-butyl urea group with valine-derived P_3 capping group yielded **2**, a compound that showed some improvement in cellular activity. Further SAR in this region demonstrated that replacement of the P_3 valine cap with appropriately modified sulfonamide moiety resulted in compound **3** (see Figure 2) which exhibited an EC_{90} = 0.13 μM. In the current work, we describe our efforts in modifying **3** and report identification of a sulfonamide and sulfonyl urea series of inhibitors that have improved cellular potency compared to **1**.

2. Chemistry

Reduction of amino acids of type **4** with $LiAlH_4$, followed by protection of the resultant amino alcohol with Boc_2O yielded compounds of type **5** (Scheme 1). Protected amino alcohol of type **5** was converted to diamine of type **6** by reaction with PPh_3, phthalimide and DEAD followed by deprotection of phthalimido group with hydrazine. Amines of type **6** were converted to sulfonamides **7** by treatment with suitable sulfonyl chloride followed by deprotection of the Boc group with 4 M HCl. Amine salts of type **7**, were directly used to synthesize inhibitors or converted to isocyanates of type **8** by treatment with phosgene.



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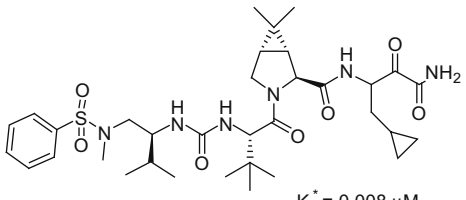
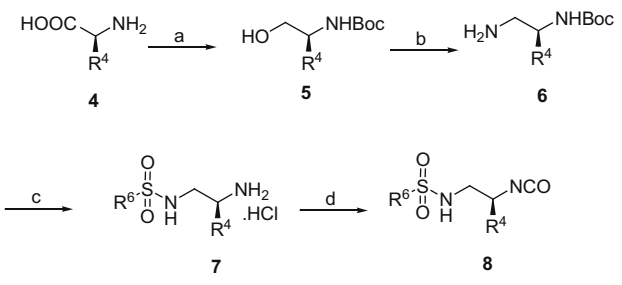
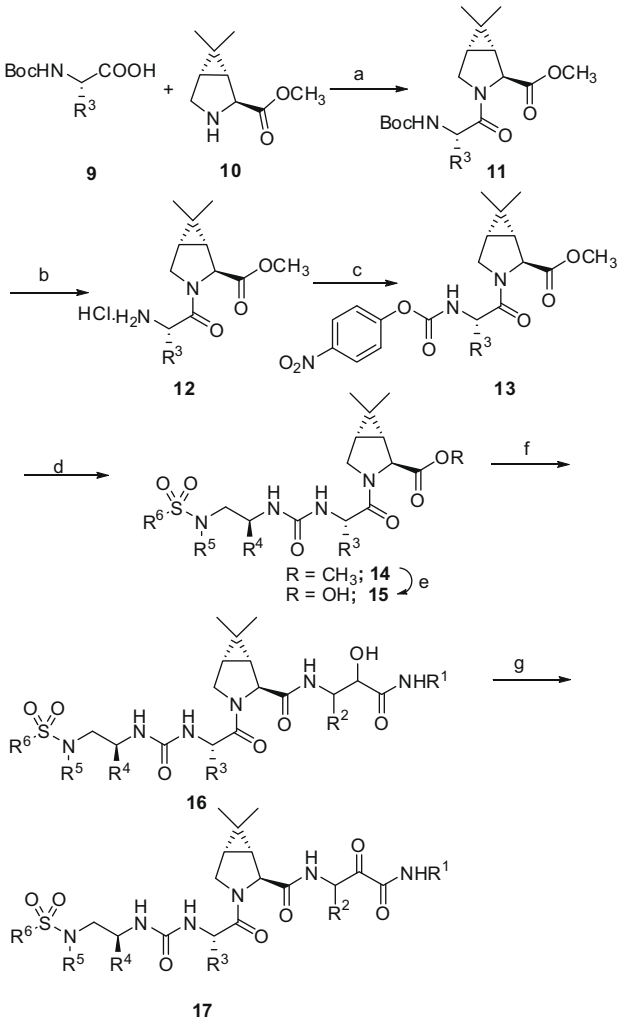


3

Figure 2.



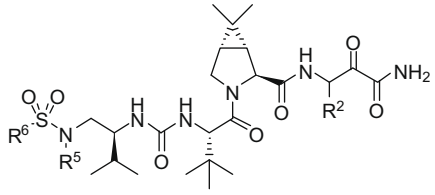
Scheme 1. Reagents and conditions: (a) (i) $LiAlH_4$, THF, reflux; (ii) Boc_2O; (b) (i) PPh_3, phtalimide, DEAD, THF; (ii) NH_2NH_2, ethanol; (c), (i) R^6SO_2Cl, Et_3N, CH_2Cl_2; (ii) 4 M HCl in dioxane; (d) $COCl_2$, satd aq $NaHCO_3$, CH_2Cl_2.



Scheme 2. Reagents and conditions: (a) HATU, NMM, DMF/CH_2Cl_2, rt; (b) 4 M HCl in dioxane; (c) 4-nitrophenylchloroformate, NMM, CH_2Cl_2; (d) (i) **7**, NMM, CH_3CN; (ii) Cs_2CO_3, R^5I, DMF; (e) aq LiOH, THF, rt; (f) $HCl{\cdot}H_2NCH(R^2)CH(OH)CONHR^1$, HATU, NMM, CH_2Cl_2/DMF, 0 °C; (g) Dess–Martin reagent (R^1 *not H*) or EDCI·HCl, DMSO, $CHCl_2COOH$ ($R^1 = H$).

Syntheses of inhibitors derived from amines of type **7** and isocyanates of type **8** were accomplished using procedures shown in Scheme 2. Thus, coupling of P_3 amino acid **9** with proline derivative **10**[10] using HATU protocol resulted in dipeptides of type **11** which were converted to amine salts of type **12** by treatment with 4 M HCl in dioxane. Reaction of amine salts of type **12** with isocyanates of type **8** resulted in compounds of type **14** (R^5 = H). Alternatively, amine salts **12** were treated with 4-nitrophenyl chloroformate to yield 4-nitrophenyl carbamate **13** which on treatment with **7** yielded ureas of type **14** (R^5 = H). Further alkylation of sulfonamide nitrogen with methyl iodide in the presence of Cs_2CO_3 introduced the N-alkyl that resulted in compound of type **14** (R^5 = methyl). Hydrolysis of methyl ester yielded acid **15** which was coupled with P_1 hydroxy amide segment to yield hydroxy amides of type **16**. These hydroxy amide derivatives were oxidized to targets of type **17** using methods previously described.[7]

Table 1



Compd	R^6	R^5	R^2	K_i^* (μM)[a]	EC_{90} (μM)
18		H		0.010	0.55
19		Me		0.006	0.13
20	Me—	H		0.031	2.00
21	Me—	Me		0.004	0.35
22		H		0.023	0.60
23		Me		0.012	0.10

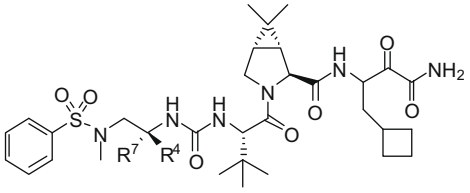
[a] K_i^* value represents for a mixture of diastereomers at P_1 and within twofold for 95% confidence.

3. Discussion

Effect of P_4-sulfonamide methyl group on cellular activity: Initially, we explored the effect of N substitution on the cellular activity of inhibitors of type **3** (Table 1). The phenylsulfonamide analog compound **18** that lacked the *N*-methyl substitution had a K_i^* = 0.01 μM and a replicon cellular activity EC_{90} = 0.55 μM, whereas the corresponding N-methylated derivative **19** had a K_i^* = 0.006 μM and EC_{90} = 0.13 μM, a fourfold improvement in cellular potency compared to **18**. Similarly, the methyl sulfonamide-derived compound **20** lacking the *N*-methyl substituent had a K_i^* = 0.031 μM and EC_{90} = 2.0 μM, whereas the N-methylated analog **21** demonstrated a K_i^* = 0.004 μM and EC_{90} = 0.35 μM; a sixfold improvement in cellular activity. A similar improvement was also observed in the thiophene-capped compound where the N-methylated compound **23** (K_i^* = 0.012 μM and EC_{90} = 0.1 μM) was sixfold more potent than the corresponding non-methylated compound **22** (K_i^* = 0.023 μM and EC_{90} = 0.6 μM). It was worth noting that the thiophene sulfonamide derivative **23** also had improved cellular potency compared to the first generation compound **1**.

Having demonstrated that the N-methylation had profound effect on the cellular activity we next decided to evaluate the effect of P_4 substitutions on cellular activity (see Table 2). The cyclobutyl alanine P_1 analog of **19**, inhibitor **24** demonstrated similar binding and cellular activities (K_i^* = 0.008 μM, EC_{90} = 0.14 μM) to **19**. However, **24** demonstrated improved HNE/HCV selectivity compared to **19** (3100 vs 680). Substituting valine with isoleucine resulted in compound **25** (K_i^* = 0.013 μM and EC_{90} = 0.25 μM) with a slight loss in both enzyme potency and cellular activity. Incorporation of α-branched amino acid *tert*-butylglycine resulted in inhibitor **26** (K_i^* = 0.005 μM and EC_{90} = 0.075 μM) with a twofold improved activity over **24** and fourfold improvement in comparison to first generation compound **1**. We further probed the P_4 region by introducing quaternary amino acids. Thus, incorporation of α-methyl leucine resulted in compound **27** (K_i^* = 0.080 μM) with a 20-fold loss in activity compared to **25**.

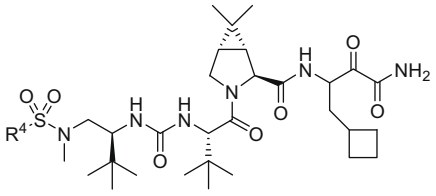
Table 2



Compd	R^4	R^7	K_i^* (μM)[a]	EC_{90} (μM)
24		H	0.008	0.14
25		H	0.013	0.25
26		H	0.005	0.075
27		Me	0.080	—
28			0.012	0.40

[a] K_i^* value represents for a mixture of diastereomers at P_1 and within twofold for 95% confidence.

Table 3



Compd	R^4	K_i^* (μM)[b]	EC_{90} (μM)	Rat AUC (μM h)[11]
29	Me	0.005	0.15	0.06
30	Me	0.004	0.15	0.00
31		0.005	0.09	0.09
32		0.004	0.06	0.11
33[a]		0.004	0.08	NA

[a] β-methylcyclohexylglycine P_3 was used.
[b] K_i^* value represents for a mixture of diastereomers at P_1 and within twofold for 95% confidence.

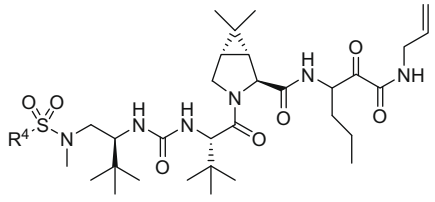
Constriction of R^4 and R^7 into a ring, resulted in spirocyclohexyl derivative **28** (K_i^* = 0.012 μM and EC_{90} = 0.4 μM). In summary, SAR studies of P_4 capping groups identified *tert*-butyl glycine as an optimal substituent that facilitated the achievement of improved enzyme binding as well as cellular activity. It was therefore decided to further investigate SAR of subsequent inhibitors using this substituent as the P_4 residue.

We next explored the effect of various substituents of the sulfonamide moiety. As outlined in Table 3 introduction of methyl sulfonamide group resulted in compound **29** with K_i^* = 0.005 μM and EC_{90} = 0.15 μM, a twofold improvement in cellular activity compared to **1**. The replacement of methyl sulfonamide with ethyl sulfonamide resulted in an equipotent compound **30** (K_i^* = 0.004 μM and EC_{90} = 0.15 μM). The effect of branching was evaluated by incorporating cyclopropyl sulfonamide resulting in compound **31** (K_i^* = 0.005 μM and EC_{90} = 0.09 μM) with improved cellular activity compared to **1**. Incorporating thiophene and pyridyl sulfonamides resulted in inhibitors **32** (K_i^* = 0.004 μM and EC_{90} = 0.06 μM) and **33** (K_i^* = 0.004 μM and EC_{90} = 0.08 μM) with further improved cellular activity. We were very encouraged by this result and decided to evaluate some of the very active compounds in rapid rat assay to evaluate their pharmacokinetic properties.[11] As shown in Table 3, the oral PK of these inhibitors in rats was poor. Compound **32** had an AUC = 0.11 μM h and **30** demonstrated no oral PK at all.

Having established that introduction of sulfonamide yielded compounds with improved cellular potencies we next decided to explore ways to improve their pharmacokinetics. Previously, in the discovery of **1** we had demonstrated that the replacement of a primary ketoamide with an allyl amide group at P_1' in combination with P_1 norleucine, or norvaline resulted in compounds with improved PK.[7] We therefore decided to investigate allyl amide analogs of these more potent sulfonamide derivatives.

As shown in Table 4 the ethyl sulfonamide derivative **34** had a K_i^* = 0.010 μM and EC_{90} = 0.15 μM. Introduction of allyl moiety at P_1' resulted in a compound with similar cellular activity compared to primary amide derivative **30**, however it exhibited some rat PK ($AUC_{0-6\ h}$ = 0.34 μM h). The introduction of an allyl amide in compound derived from thiophene sulfonamide **32** resulted in compound **35** which had an EC_{90} = 0.26 μM and had a much improved PK ($AUC_{0-6\ h}$ = 1.38 μM h). Similarly allylamide derivative of 2-pyridine sulfonamide resulted in compound **36** with good cellular activity (EC_{90} = 0.18 μM) and similar PK ($AUC_{0-6\ h}$ = 1.02 μM h) as **35**. From these studies it was clear that one could improve oral exposure of these classes of compounds by synthesizing the corresponding allyl amide derivatives. However, these allyl amide compounds needed further improvement in replicon cellular potency.

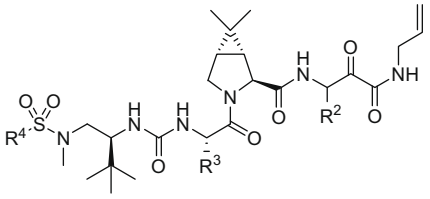
Table 4

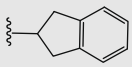
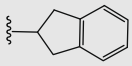
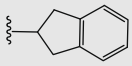


Cpd.	R^4	K_i^* (μM)[a]	EC_{90} (μM)	Rat AUC (μM h)
34		0.010	0.15	0.34
35		0.010	0.26	1.38
36		0.014	0.18	1.02

[a] K_i^* value represents for a mixture of diastereomers at P_1 and within twofold for 95% confidence.

Table 5



Cpd.	R^2	R^3	R^4	K_i^* (μM)[a]	EC_{90} (μM)
37				0.006	0.10
38				0.006	0.06
39				0.006	0.08
40				0.011	0.10

[a] K_i^* value represents for a mixture of diastereomers at P_1 and within twofold for 95% confidence.

To improve the cellular potency of these allyl amide inhibitors we decided to explore the effect of varying of P_1 and P_3 residues. Once again our previous experience with the discovery of **1** had demonstrated that the P_1 and P_3 had a synergistic effect on enzyme binding and replicon cellular potency. We therefore explored the effect of substitution of P_3 from *tert*-butyl glycine with cyclohexylglycine, and indanylglycine. Table 5 summarizes the effect of these modifications on potency.

It was clear that introduction of indanylglycine had a profound effect on the cellular potency of these compounds. In the series of compounds containing ethyl sulfonamide-derived P_3 cap, introduction of P_3 indanylglycine with P_1 norvaline resulted in compound **37** with K_i^* = 0.006 μM and EC_{90} = 0.1 μM. The incorporation of norleucine at P_1 resulted in compound **38** with K_i^* = 0.006 μM and EC_{90} = 0.06 μM, a fivefold improvement in cellular activity relative to **1**. The analog containing dimethylsulfonyl urea cap along with P_3 indanyl glycine and P_1 norvaline (**40**) demonstrated enzyme binding K_i^* = 0.011 μM and EC_{90} = 0.10 μM, whereas the corresponding analog containing P_1 norleucine and P_3 cyclohexylglycine, compound **39,** had an enzyme activity of K_i^* = 0.006 μM and EC_{90} = 0.08 μM (see Table 5).

Compounds **38** and **39** were further evaluated for their rat PK in the rapid rat assay. Compound **38** demonstrated an AUC_{0-6h} = 1.2 μM h and compound **39** had an AUC_{0-6h} = 1.74 μM h when dosed at 10 mpk. Evaluation of **38** in monkeys achieved an AUC = 0.69 μM h when dosed at 3 mpk in monkeys.

The X-ray structure of a phenyl sulfonamide-capped inhibitor **41** bound to HCV NS3 protease was solved and is shown in Figure 3. From the structure, it was clear that P_1 cyclobutyl moiety occupied S_1 pocket. As previously described P_2 dimethylcyclopropylproline residue adopted a bent conformation that allowed maximum overlap of the methylenes of proline and cyclopropyl ring to Ala-156. The conformation adopted by cyclopropanated proline

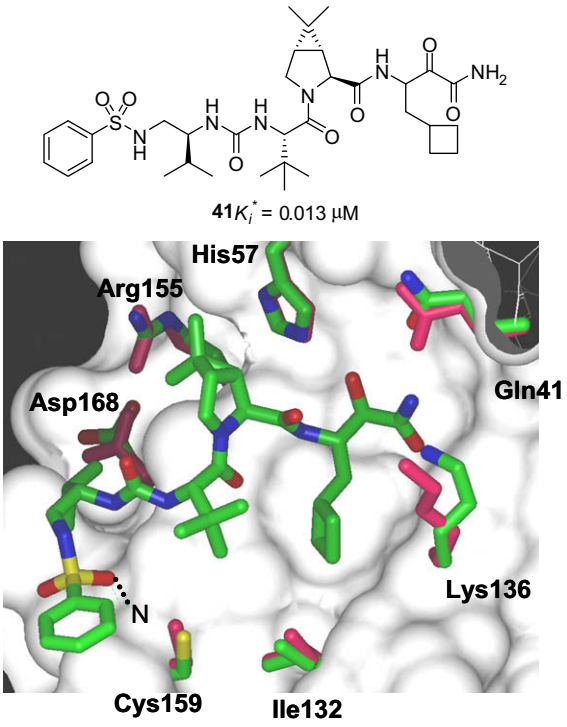


Figure 3. X-ray structure of inhibitor **41** bound to NS3 protease.

allowed the methyl group proximal to the carbonyl to interact with His-57 and the methyl group distal to carbonyl to interact with Ala-156 and Arg-155. P_3 *tert*-butyl glycine occupied the S_3 pocket while P_4 valine group at S_4 pocket interacted with the protease effectively. The electrophilic ketoamide reversibly trapped Ser-139 to form a covalent bond with the enzyme and the hydrogen of the P_1 amide donated a hydrogen bond to the peptidic back bone of the protein, locking the inhibitor to the surface.

In addition to van der Walls contacts, inhibitor **41** formed a series of specific hydrogen bonds with the protein surface. Mapping out these various hydrogen bonding interactions that existed between inhibitor and NS3 protease, it was evident that the urea nitrogens donated two hydrogen bonds to Ala-157. Additionally, the nitrogen of the P_1 norvaline donated a hydrogen bond to Arg-155 and oxygen of P_3 carbonyl group accepted a hydrogen bond from the Ala-157. In addition to these hydrogen bonds that existed in interaction of **1**, the P_4 sulfonamide group made important interaction to the peptidic backbone; Oxygens of the sulfonamide group accepted a hydrogen bond to Cys-159 enhancing binding and specificity. The combination of hydrophobic interactions and the array of hydrogen bonds contributed for improved binding (K_i^*) and cellular potency of these inhibitors.

4. Conclusions

In search of a second generation compound to **Sch 503034 (1)** we have identified a novel series of P_4 sulfonamide-derived inhibitors that have improved enzyme binding (K_i^*) and cellular potency (EC_{90}) by 8–10-fold with respect to **1**. Initially, novel valine-derived diamine residues capped with sulfonamide groups were identified as excellent P_3 capping group that enhanced enzyme binding of inhibitors of type **1**. The replicon cellular potencies of these inhibitors were optimized by introduction of a methyl group at the sulfonamide nitrogen, and by identification of *tert*-butyl glycine as an optimal P_4 group. Primary ketoamide inhibitors of type **32** were achieved and shown to have $EC_{90} < 0.1$ μM.

To improve the oral availability of these compounds, a P_1' allyl amide series were chosen for further investigation. Although these series of compounds displayed poor enzyme binding and replicon cellular potency, by systematic optimization of P_3, P_1, and the P_4 sulfonamide groups, two series of compounds derived from ethylsulfonamide capping with P_3 indanyl glycine and P_4 dimethylsulfonyl urea derived cap with P_3 cyclohexyl glycine were identified. These groups provided compounds with excellent binding and improved cellular potencies. Evaluation of these potent compounds in rapid rat and rapid monkey assays also identified compound **38** (K_i^* = 0.006 μM and EC_{90} = 0.060 μM) with a good rat (AUC = 1.2 μM h) and monkey (AUC = 0.69 μM h). The X-ray structure of a phenyl sulfonamide-capped derivative bound to the NS3 protease was solved. It revealed novel interaction of the oxygens of P_4 sulfonamide moiety to Cys-159, in addition to interactions observed in **1** that contributed to enhancement in enzyme binding and replicon cellular potency.

5. Experimental

5.1. General

Dry solvents were purchased from Aldrich or Acros and were used without further purification. Other solvents or reagents were used as obtained except when otherwise noted. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel plates available from Analtech. Column chromatography was performed using Merck Silica Gel 60 (particle size 0.040–0.055 mm, 230–400 mesh), or using Biotage or Isco chromatographic systems. Many compounds were further purified using Varian normal phase HPLC with YMC-diol column with a solvent system solvent A (hexanes) and solvent B (a mixture of isopropanol, CH_2Cl_2, and acetonitrile). Visualization was accomplished with UV light or by staining with basic $KMnO_4$ solution, methanolic H_2SO_4, or Vaughn's reagent. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 unless otherwise noted in either 300, 400 or 500 MHz (^{1}H NMR), or 75, 100 or 125 MHz (^{13}C NMR). Mass spectra were obtained using electron spray or FAB ionization methods. ^{1}H NMR and ^{13}C NMR described for the final products comprise two sets of signals (representing two molecules) accounting for two diastereomers at P_1.

5.1.1. (*S*)-*tert*-Butyl-1-hydroxy-3,3-dimethylbutan-2-ylcarbamate (5)

(L)-*tert*-Leucine (10.0 g, 96 mmol) was slowly added under reflux to a solution of $LiAlH_4$ (152 mL, 1 M soln in THF). The reaction mixture was refluxed for 6 h and cooled to 0 °C and carefully quenched by addition of aq NaOH (10%, 10 mL) and water (10 mL). It was stirred at rt for 10 min and treated with di-*tert*-butyldicarbonate (18.22 g, 84 mmol) and stirred overnight at 60 °C. The reaction mixture was filtered, the filtrate was concentrated in vacuo, and the residue was purified by chromatography (SiO_2, EtOAc/hexnaes) to yield Boc-protected *tert*-leucinol **5** (10.2 g, 62%).

5.1.2. (*R*)-*tert*-Butyl-1-amino-3,3-dimethylbutan-2-ylcarbamate (6, R^4 = *tert*-butyl)

A flame dried flask was charged with phthalimide (5.5 g, 37.5 mmol), dry THF (30 mL), PPh_3 (19.6 g, 75.0 mmol), and **5** (5.5 g, 25 mmol).The reaction mixture was cooled to 0 °C and treated with DEAD (10.8 g, 62.5 mmol) dropwise. The reaction mixture was stirred at rt. for 2 h and concentrated in vacuo. The residue was purified by chromatography (SiO_2 EtOAc/hexanes 2:3) to yield pthalimide displaced product (3.94 g, 67%). MS (ESI, *m/z* relative intensity) 715 [(2 M+Na)$^+$, 15], 369 [(M+Na)$^+$, 30], 347 (M$^+$, 10), 264 (100), 247 (80).

The isolated phthalimide derivative (4.00 g, 11.5 mmol) was treated with hydrazine (2 M soln in ethanol, 25 mL) and stirred

at rt. overnight. The reaction mixture was filtered and the filtrate was concentrated in vacuo to yield **7** (2.5 g ~100%) which was used in the next reaction without purification. ^{1}H NMR (400 MHz, DMSO-d_6), δ, 6.47 (d, 1H, J = 9.5 Hz), 3.11 (dt, 1H, J = 2.9 & 10.3 Hz), 2.66 (dd, 1H, J = 2.9 & 12.4 Hz), 2.33 (dd, 1H, J = 2.2 & 12.4 Hz), 1.37 (s, 3H), 0.79 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6), δ, 157.2, 77.8, 62.6, 41.6, 39.6, 29.0, 27.3 MS (ESI, *m/z* relative intensity) 239 [(M+Na)$^+$, 10], 217[(M+1)$^+$, 20], 161 (100), 117 (40).

5.1.3. (*S*)-*N*-(2-Amino-3,3-dimethylbutyl)methanesulfonamide (7, R^6 = Me, R^5 = H, R^4 = *tert*-butyl)

A solution of **6** (2.12 g, 9.8 mmol) in CH_2Cl_2 was cooled to 0 °C and treated with Et_3N (3.3 mL, 24.5 mmol) and methanesulfonyl chloride (1.68 g, 17.7 mmol) and stirred at rt for 3 h. The reaction mixture was diluted with CH_2Cl_2 and the residue was washed with aq HCl (1 M), brine, dried ($MgSO_4$), filtered, concentrated in vacuo, and purified by chromatography (SiO_2, acetone/hexanes) to yield mesylated product which was deprotected in the next step. 1.62 g (5.5 mmol) of this mesylated product was dissolved in 4 M HCl in dioxane and was stirred at rt for 1 h. The reaction mixture was concentrated in vacuo to yield **7** which was used in the next step without further purification.

5.1.4. (1*R*,2*S*,5*S*)-Methyl-3-((*S*)-3,3-dimethyl-2-((4-nitrophenoxy)carbonylamino)butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate (13, R^3 = ^{t}Bu)

A solution of amine **12**[7] (R^3 = ^{t}Bu, 19.5 g, 61.16 mmol) in CH_2Cl_2 (200 mL) at −78 °C was treated with NMM (18.56 g, 183.47 mmol), 4-nitrophenyl chloroformate (14.80 g, 73.39 mmol) and stirred at rt for 24 h. The reaction mixture was concentrated in vacuo, diluted with EtOAc (1 L) and washed with excess aq $NaHCO_3$ (1 L), brine (1 L), dried ($MgSO_4$), filtered, concentrated in vacuo and purified by chromatography (SiO_2, EtOAc/Hexanes) to yield **13** (19.4 g, 71%) as a colorless foam. ^{1}H NMR (300 MHz, $CDCl_3$), δ, 8.24 (d, 2H, J = 9.4 Hz), 7.28 (d, 2H, J = 9.4 Hz), 5.79 (d, 1H, J = 9.9 Hz), 4.51 (s, 1H), 4.30 (d, 1H, J = 9.4 Hz), 3.96–3.85 (m, 2H), 3.78 (s, 3H), 1.49 (d, 2H, J = 2.2 Hz), 1.11 (s, 9H), 1.05 (s, 3H), 0.92 (s, 3H).

5.1.5. (1*R*,5*S*)-Methyl-3-((*S*)-2-(3-((*S*)-3,3-dimethyl-1-(methylsulfonamido)butan-2-yl)ureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate (14; R^3 = R^4 = ^{t}Bu; R^6 = Me; R^5 = H)

A solution of **7** (1.48 g, 6.44) in dry dichloromethane was cooled to 0 °C and was treated with Et_3N (2.14 mL, 16.1 mmol) and **13** (2.88 g, 6.44 mmol) in CH_2Cl_2. The mixture was stirred at −20 °C overnight. It was diluted with CH_2Cl_2 and washed with brine, then it was dried and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc/Hexanes 0→50%) to yield **14** as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$), δ, 5.79 (d, 1H, J = 9.5 Hz), 5.64 (bt, 1H, J = 5.13 Hz), 5.11 (br s, 1H), 4.41 (d, 1H, J = 9.5 Hz), 4.39 (s, 1H), 3.96 (d, 1H, J = 10.3 Hz), 3.86 (dd, 1H, J = 5.1 & 5.3 Hz), 3.71 (s, 3H), 3.60 (bt, 1H, J = 8.8 Hz), 3.42–3.37 (m, 1H), 1.48–1.39 (m, 2H), 1.00 (s, 3H), 0.98 (s, 9H), 0.84 (s, 9H), 0.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ, 172.6, 172.3, 159.4, 60.1, 58.5, 52.6, 48.1, 44.6, 41.4, 35.5, 34.5, 30.6, 26.8, 26.8, 26.5, 19.8, 12.8, 28.0; MS (ESI, *m/z* relative intensity) 1028 [(2 M+Na), 20], 525 [(M+Na), 50], 503 [(M+1)+, 90], 344 (100).

5.1.6. (1*R*,5*S*)-3-((*S*)-2-(3-((*S*)-3,3-Dimethyl-1-(*N*-methylmethylsulfonamido)butan-2-yl)ureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (14; R^3 = R^4 = ^{t}Bu; R^6 = R^5 = Me)

A solution of **14** (R^5 = H, 200 mg, 0.39 mmol) in dry DMF (5.00 mL) was treated with Cs_2CO_3 (194.5 mg, 0.59 mmol) and methyl iodide (123.8 μL, 1.98 mmol) and was stirred at rt for 4 h. The reaction mixture was diluted with EtOAc and the organic layer was separated and washed with water. The organic layer was dried (MgSO4), filtered, concentrated in vacuo and the residue was purified by chromatography (SiO_2, EtOAc/Hexanes) to yield **14** (R^5 = CH_3, 93 mg, 50%) as a colorless solid; ^{1}H NMR (400 MHz, DMSO-d_6), δ, 6.15 (d, 1H, J = 10.3 Hz), 6.01 (d, 1H, J = 10.3 Hz), 4.23 (d, 1H, J = 10.3 Hz), 4.16 (s, 1H), 3.94 (d, 1H, J = 11.0 Hz), 3.77 (dd, 1H, J = 5.1 & 10.3 Hz), 3.62 (s, 3H), 3.62–3.57 (m, 1H), 3.20 (dd, 1H, J = 3.7 &, 10.3 Hz), 2.95 (dd, 1H, J = 11.0 & 3.0 Hz), 2.82 (s, 3H), 2.73 (s, 3H), 1.48 (dd, 1H, J = 5.9 & 7.3 Hz), 1.38 (d, 1H, J = 7.3 Hz), 0.97 (s, 3H), 0.91 (s, 9H), 0.78 (s, 9H), 0.75 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6), δ 172.4, 171.9, 158.8, 59.4, 57.7, 55.8, 52.7, 51.1, 47.8, 36.9, 35.2, 35.1, 34.9, 30.4, 27.7, 27.0, 26.9, 26.6, 19.6, 13.0; MS (ESI, *m/z* relative intensity) 539 [(M+Na)$^+$, 50], 517 [(M+1)$^+$, 100], 348 (100).

A solution of ester **14** (90.2 mg, 0.17 mmol) was dissolved in THF and H_2O (approximately 3:1 ratio) and treated with $LiOH{\cdot}H_2O$ (18 mg, 0.44 mmol). The reaction mixture was treated with MeOH until homogeneous. The reaction mixture was stirred at rt for approximately 3 h. The reaction mixture was treated with 1 M aq HCl and concentrated in vacuo. The organic layer was extracted with CH_2Cl_2, dried ($MgSO_4$), filtered, and concentrated in vacuo to yield carboxylic acid **15** that was used in the next step without purification.

5.1.7. (1*R*,5*S*)-*N*-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(*S*)-[[[[2,2-dimethyl-1(*S*)-[[methyl-(methylsulfonyl)amino]methyl]propyl]amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (29)

A solution of **15** (220 mg, 0.438 mmol) was dissolved in 1:1 DCM/DMF. It was cooled to −20 °C and was treated with amine salt[7] (110 mg, 0.525 mmol), HATU (250 mg, 0.657 mmol), and NMM (111 mg, 1.1 mmol). The mixture was stirred at −20 °C overnight and concentrated in vacuo. The residue was diluted with EtOAc (200 ml) and washed with aqueous HCl (1 M soln.), satd aq $NaHCO_3$ and brine. The reaction mixture was dried ($MgSO_4$), filtered, concentrated in vacuo to yield **16** that was used as it is in the next step.

The crude hydroxy amide **16** (288 mg, 0.44 mmol) was dissolved in 1:1 DMSO/DCM (5 ml). It was cooled to 0 °C and treated with EDCI (843 mg, 4.4 mmol) and dichloroacetic acid (284 mg, 2.2 mmol). The mixture was stirred at room temperature for 3 h. It was diluted with EtOAc and was washed with 1 M $NaHSO_3$, satd aq $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, acetone/hexanes 3:7) to yield **29** as a colorless solid ^{1}H NMR (500 MHz, DMSO-d_6), δ, 8.29 (d, 1H, J = 7.3 Hz), 8.19 (d, 1H, J = 7.3 Hz), 8.02 (s, 1H), 7.98 (s, 1H), 7.76 (s, 1H), 7.75 (s, 1H), 6.15 (d, 1H, J = 11.0 Hz), 6.14 (d, 1H, J = 11.0 Hz), 6.06–6.04 (m, 2H), 4.99–4.95 (m, 1H), 4.87–4.84 (m, 1H), 4.28 (s, 1H), 4.27 (s, 1H), 4.22 (dd, 2H, J = 6.0 & 3.7 Hz), 3.91 (t, 2H, J = 10.7 Hz), 3.80–3.74 (m, 2H), 3.64 (dt, 2H, J = 2.8 & 10.4 Hz), 3.22 (dd, 2H, J = 3.2 & 11.0 Hz), 3.01–2.95 (m, 2H), 2.85 (s, 6H), 2.76 (s, 6H), 2.00–0.77 (m, 22H), 1.00 (s, 3H), 0.99 (s, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.81 (s, 9H), 0.81 (s, 9H), 0.80 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6), δ, 198.6, 197.9, 171.7, 171.7, 171.5, 171.4, 163.9, 163.7, 158.9, 158.8, 60.2, 59.9, 57.9, 57.8, 55.8, 52.9, 52.7, 51.1, 48.3, 48.2, 37.6, 37.5, 37.0, 36.9, 35.2, 35.1, 35.0, 34.9, 33.0, 31.5, 31.4, 28.8, 28.6, 28.2, 27.8, 27.6, 27.1, 26.9, 19.3, 18.7, 18.5, 13.4; MS (ESI, *m/z* relative intensity) 655 [(M+1)$^+$, 30], 348 (100).

5.1.8. (*1R,5S*)-*N*-[3-Amino-1-(cyclopropylmethyl)-2,3-dioxopropyl]-3-[3,3-dimethyl-2(*S*)-[[[[2-methyl-1(*R*)-[[methyl(phenylsulfonyl)amino]methyl]propyl]amino]-carbonyl]amino]-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2(*S*)-carboxamide (19)

^{1}H NMR (500 MHz, DMSO-d_6), δ, 8.38 (d, 1H, J = 6.5 Hz), 8.32 (d, 1H, J = 7.5 Hz), 8.01 (s, 1H), 7.99 (s, 1H), 7.77–7.69 (m, 12H), 6.16

(d, 1H, J = 10.0 Hz), 6.13 (d, 1H, J = 10.0 Hz), 5.98 (d, 2H, J = 9.5 Hz), 5.12–5.08 (m, 1H), 5.07–5.03 (m,1H), 4.33–4.26 (m, 2H), 4.22–4.15 (m, 4 H), 3.92–3.88 (m, 2H), 3.79–3.73 (m, 2H), 2.98–2.94 (m, 2H), 2.75–2.71 (m, 2H), 2.64 (s, 6H), 1.78–1.31 (m, 10 H), 1.01 (s, 3H), 0.99 (s, 3H), 0.91–0.86 (m, 20 H), 0.81–0.77 (m, 18H), 0.43–0.37 (m, 4 H), 0.31–0.04 (m, 4 H); ^{13}C NMR (125 MHz, DMSO-d_6), δ, 198.4, 197.9, 171.8, 171.6, 171.5, 171.4, 163.8, 163.5, 158.8, 158.7, 137.6, 133.7, 130.2, 127.9, 60.3, 60.2, 59.9, 58.0, 57.9, 55.0, 52.8, 52.4, 48.3, 35.9, 35.9, 35.2, 31.5, 31.4, 29.8, 27.7, 27.6, 27.2, 27.0, 26.9, 20.5, 19.3, 16.9, 13.4, 13.3, 8.7, 8.5, 5.9, 5.2, 4.9; MS (ESI, m/z relative intensity) MS (ESI, m/z relative intensity) 743 [(M+CH_3OH+Na)$^+$, 20], 711 [(M+Na)$^+$, 10], 689 [(M+1)$^+$, 50], 396 (100), 129 (70).

5.1.9. (1*R*,5*S*)-*N*-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[3,3-dimethyl-2(*S*)-[[[[2-methyl-1(*S*)-[[(methylsulfonyl)amino]methyl]propyl]amino]-carbonyl]amino]butyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2(*S*)-carboxamide (20)

^{1}H NMR (500 MHz, DMSO-d_6), δ, 8.29 (d, 1H, J = 7.5 Hz), 8.19 (d, 1H, J = 7.5 Hz), 8.01 (s, 1H), 7.97 (s, 1H), 7.76 (s, 1H), 7.75 (s, 1H), 6.95 (d, 1H, J = 6.0 Hz), 6.93 (d, 1H, J = 5.5 Hz), 6.17–6.13 (m, 2H), 5.97 (d, 1H, J = 9.5 Hz), 5.96 (d, 1H, J = 9.0 Hz), 4.96–4.95 (m, 1H), 4.92 (d, 1H, J = 11.0 Hz), 4.88–4.84 (m, 1H), 4.74 (d, 1H, J = 11.0 Hz), 4.29 (s, 1H), 4.28 (s, 1H), 4.24–4.18 (m, 2H), 3.94–3.74 (m, 4 H), 3.58–3.51 (m, 2H), 2.95–2.83 (m, 2H), 2.88 (s, 3H), 2.70 (s, 3H), 1.99–1.27 (m, 24 H), 1.01 (s, 3H), 1.00 (s, 3H), 0.92 (s, 9H), 0.91 (s, 9H), 0.79–0.76 (m, 18H); ^{13}C NMR (125 MHz, DMSO-d_6), δ, 198.6, 197.9, 171.7, 171.6, 171.5, 171.4, 163.9, 163.7, 159.0, 158.9, 60.3, 60.2, 60.0, 58.1, 58.0, 58.0, 54.4, 53.0, 52.7, 48.3, 48.2, 45.9, 39.1, 37.6, 37.5, 36.6, 35.2, 33.1, 33.0, 31.5, 31.4, 29.6, 29.6, 28.8, 28.7, 28.6, 28.5, 28.3, 27.7, 27.0, 20.3, 19.3, 18.7, 18.6, 17.4, 13.4, 13.3; MS (ESI, m/z relative intensity) 649 [(M+Na)$^+$, 10], 627 [(M+1)$^+$, 40], 117 (100).

5.1.10. (1*R*,5*S*)-*N*-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[3,3-dimethyl-2(*S*)-[[[[2-methyl-1(*S*)-[[methyl(2-thienylsulfonyl)amino]methyl]propyl]amino]-carbonyl]amino]-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (23)

^{1}H NMR (500 MHz, DMSO-d_6), δ, 8.29 (d, 1H, J = 7.3 Hz), 8.18 (d, 1H, J = 7.6 Hz), 8.01 (d, 2H, J = 4.7 Hz), 8.02–8.00 (br s, 1H), 7.98 (s, 1H), 7.77 (s, 1H), 7.76 (s, 1H), 7.66 (d, 2H, J = 4.2 Hz), 7.26 (t, 2H, J = 4.7 Hz), 6.17 (d, 1H, J = 6.6 Hz), 6.15 (d, 1H, J = 6.9 Hz), 6.00 (d, 2H, J = 9.1 Hz), 4.29 (s, 1H), 4.28 (s, 1H), 4.22–4.19 (m, 2H), 3.91–3.70 (m, 8 H), 2.96 (dd, 2H, J = 6.6 & 13.2Hz), 2.73 (dd, 2H, J = 7.8 & 12.6 Hz), 2.68 (s, 6H), 1.98–1.95 (m, 4 H), 1.81–1.58 (m, 16H), 1.44–1.41 (m, 2H), 1.28 (t, 2H, J = 7.3 Hz), 1.01 (s, 3H), 1.00 (s, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.81 (s, 3H), 0.80 (d, 6H, J = 6.9 Hz), 0.79 (s, 3H), 0.79 (d, 6H, J = 6.9 Hz). ^{13}C NMR (125 MHz, DMSO-d_6), δ, 198.6, 197.9, 171.7, 171.6, 158.8, 158.7, 134.0, 133.2, 129.0, 137.4, 60.2, 60.0, 58.0, 53.0, 52.7, 52.4, 52.9, 48.3, 36.1, 37.6, 37.5, 35.2, 33.0, 31.5, 31.4, 29.8, 28.7, 28.6, 28.2, 27.8, 27.6, 27.1, 26.9, 20.4, 19.3, 18.7, 18.5, 16.9, 13.3. MS (ESI, m/z relative intensity) 709 [(M+1)$^+$, 15], 402 (100), 374 (30), 308 (45).

5.1.11. (1*R*,5*S*)-*N*-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[3,3-dimethyl-2(*S*)-[[[[2-methyl-1(*R*)-[[methyl(phenylsulfonyl)amino]methyl]propyl]amino]-carbonyl]amino]-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2(*S*)-carboxamide (24)

^{1}H NMR (500 MHz, DMSO-d_6), δ, 8.29 (d, 1H, J = 7.3 Hz), 8.18 (d, 1H, J = 6.9 Hz), 8.02 (s, 1H), 7.98 (s, 1H), 7.78–7.62 (m, 12H), 6.17 (d, 1H, J = 8.0 Hz), 6.15 (d, 1H, J = 10.5 Hz), 5.98 (d, 2H, J = 7.9 Hz), 5.00–4.95 (m, 1H), 4.92 (d, 1H, J = 10.7 Hz), 4.89–4.83 (m, 1H), 4.74 (d, 1H, J = 11.3 Hz), 4.28 (s, 2H), 4.22–4.18 (m, 2H), 3.95–3.66 (m, 4 H), 3.00 (s, 1H), 2.97–2.94 (m, 1H), 2.75–2.70 (m, 1H), 2.69 (s, 1H), 2.64 (s, 3H), 2.61 (s, 3H), 1.86–1.28 (m, 24 H), 1.00 (s, 3H), 0.99 (s, 3H), 0.91 (m, 18H), 0.81–0.78 (m, 18H). ^{13}C NMR (125 MHz, DMSO-d_6), δ, 198.6, 197.9, 171.7, 171.6, 171.5, 171.3, 163.9, 163.7, 158.8, 158.7, 137.6, 133.7, 130.2, 127.9, 60.2, 60.0, 58.0, 57.9, 52.9, 52.8, 52.7, 52.3, 48.2, 37.6, 36.5, 35.9, 35.2, 33.0, 31.5, 29.8, 28.7, 28.6, 28.2, 27.1, 26.9, 27.8, 27.6, 20.4, 18.7, 19.3, 18.5, 16.9, 13.3; MS (ESI, m/z relative intensity) 757 [(M+CH_3OH+-Na)$^+$, 20], 725 [(M+Na)$^+$, 10], 703 [(M+1)$^+$, 50], 396 (100), 129 (40).

5.1.12. (1*R*,5*S*)-*N*-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-6,6-dimethyl-3-[2(*S*)-[[[[2(*S*)-methyl-1(*S*)-[[methyl(phenylsulfonyl)amino]methyl]butyl]amino]-carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (25)

^{1}H NMR (500 MHz, DMSO-d_6), δ, 8.29 (d, 1H, J = 7.3 Hz), 8.18 (d, 1H, J = 7.6 Hz), 8.02 (s, 1H), 7.98 (s, 1H), 7.77–7.62 (m, 12H), 6.16 (d, 1H, J = 9.7 Hz), 6.14 (d, 1H, J = 9.4 Hz), 6.01 (d, 2H, 9.5 Hz), 4.99–4.95 (m, 1H), 4.88–4.84 (m, 1H), 4.29 (s, 1H), 4.28 (s, 1H), 4.19 (dd, 2H, J = 7.3 & 10.1 Hz), 3.89 (t, 2H, J = 11.1 Hz), 3.79–3.70 (m, 4 H), 3.00 (d, 1H, J = 6.3 Hz), 2.97 (d, 1H, J = 5.7 Hz), 2.80–2.75 (m, 2H), 2.64 (s, 6H), 2.01–1.93 (m, 4 H), 1.84–1.64 (m, 4 H), 1.65–1.56 (m, 4 H), 1.49–1.40 (m, 6H), 1.30–0.79 (m, 28 H), 1.01 (s, 3H), 1.00 (s, 3H), 0.91 (s, 9H), 0.90 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6), δ, 198.6, 197.9, 171.7, 171.5, 171.3, 163.9, 163.7, 158.7, 158.6, 137.8, 133.7, 130.2, 127.9, 60.2, 60.0, 58.0, 57.9, 52.9, 52.7, 52.3, 48.2, 37.6, 37.5, 37.1, 36.0, 35.2, 33.0, 32.1, 31.5, 31.4, 29.2, 28.7, 28.6, 28.2, 27.8, 27.6, 27.1, 26.9, 24.3, 22.9, 19.3, 18.7, 18.5, 16.4, 16.4, 16.3, 14.7, 13.3, 12.4; MS (ESI, m/z relative intensity) 717 [(M+1)$^+$, 100], 410(88).

5.1.13. (1*R*,5*S*)-*N*-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(S)-[[[[2,2-dimethyl-1(*S*)-[[methyl(phenylsulfonyl)amino]methyl]propyl]amino]-carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide [26]

^{1}H NMR (500 MHz, DMSO-d_6), δ 8.28 (d, 1H, J = 7.5 Hz), 8.17 (d, 1H, J = 7.5 Hz), 8.02 (s, 1H), 7.98 (s, 1H), 7.77 (bd, 6H), 7.69 (bt, 2H), 7.62 (bt, 4 H), 6.15 (d, 1H, J =7.5 Hz), 6.13 (d, 1H, J = 7.5 Hz), 6.04 (d, 2H, J = 10 Hz), 4.99- 4.95 (m, 1H), 4.89–4.85 (m, 1H), 4.28 (s, 1H), 4.27 (s, 1H), 4.24 (dd, 2H, J = 7.0 & 4.8 Hz), 3.92 (t, 2H, J = 8.8 Hz), 3.81–3.74 (m, 2H), 3.64 (dt, 2H, J =10 & 2.5 Hz), 3.03 (bt, 1H, J = 3.0 Hz), 3.00 (bt, 1H, J =3.0 Hz), 2.91–2.86 (m, 2H), 2.63 (s, 6H), 2.52–2.45 (m, 1H), 2.41–2.33 (m, 1H), 2.01–1.89 (m, 4 H), 1.82–1.55 (m, 12H), 1.45–1.42 (m, 2H), 1.28 (dd, 2H, J = 6.0 & 4.0 Hz), 1.00 (s, 3H), 0.99 (s, 3H), 0.93 (s, 9H), 0.92 (s, 9H), 0.82 (s, 9H), 0.81 (s, 9H), 0.78 (s, 3H), 0.77 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6), δ, 198.6; 197.9; 171.7; 171.7; 171.6; 171.4; 163.9; 163.7; 158.8; 158.8; 138.1; 133.6; 130.2; 127.9; 60.2; 60.0; 57.9; 57.8; 56.1; 52.9; 52.7; 51.3; 51.3; 48.3; 48.2; 37.6; 37.5; 35.8; 35.2; 35.2; 35.1; 35.0; 33.0; 33.0; 31.5; 31.4; 28.8; 28.6; 28.2; 27.8; 27.6; 27.1; 27.0; 26.9; 19.3; 18.7; 18.6; 13.4; 13.3; MS (ESI, m/z relative intensity) 717 [(M+1)$^+$, 100], 410 (60), 126 (30).

5.1.14. (1*R*,5*S*)-*N*-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(*S*)-[[[[1,3-dimethyl-1-[[methyl(phenylsulfonyl)amino]methyl]butyl]amino]-carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2(*S*)-carboxamide (27)

^{1}H NMR (500 MHz, DMSO-d_6), δ, 8.29, 8.27 (2d, 1H, J = 7.6 Hz), 8.23, 8.20 (2 d, 1H, J = 7.3 Hz), 8.01 (s, 1H), 7.97 (s, 1H), 7.76–7.62 (m, 12H), 6.12–6.09 (m, 2H), 5.97 (d, 2H), 4.97–4.91 (m, 1H), 4.86–4.83 (m, 1H), 4.24 (s, 1H), 4.19 (s, 1H), 4.13–4.07 (m, 2H), 3.81–3.70 (m, 4 H), 2.64, 2.61 (s, 3H), 2.61 (s, 3H), 1.99–1.13 (m, 28 H), 1.16 (s, 3H), 1.13 (s, 3H), 0.98–0.54 (m, 46H); ^{13}C NMR (125 MHz, DMSO-d_6), δ, 198.6, 197.9, 171.7, 171.5, 171.3, 163.9,

163.7, 157.7, 137.9, 137.8, 133.7, 130.2, 127.9, 60.2, 59.9, 57.5, 57.3, 56.9, 56.8, 56.1, 52.9, 52.7, 48.3, 45.0, 43.0, 37.8, 37.6, 37.5, 36.5, 35.2, 35.1, 33.0, 32.9, 31.4, 28.7, 28.6, 28.2, 27.8, 27.7, 27.1, 26.8, 26.0, 25.9, 24.7, 24.6, 26.8, 24.2, 24.1, 24.1, 19.3, 18.7, 18.5, 19.2, 13.5, 13.2; MS (ESI, *m/z* relative intensity) 731 [$(M+1)^+$, 40], 424 (100).

5.1.15. (1*R*,5*S*)-*N*-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[3,3-dimethyl-2(*S*)-[[[[1-[[methyl(phenylsulfonyl)amino]methyl]cyclohexyl]amino]carbonyl]amino]-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2(*S*)-carboxamide (28)

^{1}H NMR (500 MHz, DMSO-d_6), δ, 8.27 (d, 1H, J = 7.3 Hz), 8.18 (d, 1H, J = 7.3 Hz), 8.01 (s, 1H), 7.97 (s, 1H), 7.77–7.64 (m, 12H), 6.27–6.21 (m, 2H), 5.93 (s, 2H), 4.99–4.94 (m, 1H), 4.87–4.83 (m, 1H), 4.22 (s, 2H), 4.16–4.05 (m, 2H), 3.86–3.81 (m, 2H), 3.74–3.69 (m, 2H), 3.22–3.14 (m, 4 H), 2.60 (2s, 6H), 1.98–0.87 (m, 42H), 0.96 (s, 3H), 0.95 (s, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.63 (s, 3H), 0.61 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6), δ, 198.6, 197.9, 171.7, 171.4, 163.9, 163.7, 157.8, 157.7, 137.9, 133.7, 130.2, 127.9, 60.2, 59.9, 57.5, 57.4, 56.9, 55.1, 52.9, 52.7, 48.2, 43.0, 38.0, 37.6, 37.5, 35.0, 33.7, 33.5, 33.0, 32.9, 31.4, 31.3, 28.7, 28.6, 28.2, 27.8, 27.6, 26.9, 26.2, 21.4, 21.3, 19.2, 18.7, 18.5, 13.2, 13.1; MS (ESI, *m/z* relative intensity) 751 [$(M+Na)^+$, 25], 729 [$(M+1)^+$, 85], 422 (20), 117 (100).

5.1.16. (1*R*,5*S*)-*N*-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(*S*)-[[[[1(*S*)-[[(ethylsulfonyl)methylamino]methyl]-2,2-dimethylpropyl]amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide [30]

^{1}H NMR (500 MHz, DMSO-d_6), δ, 8.29 (d, 1H, J = 7.3 Hz), 8.19 (d, 1H, J = 7.6 Hz), 8.02 (s, 1H), 7.98 (s, 1H), 7.76 (s, 1H), 7.75 (s, 1H), 6.14–6.11 (m, 2H), 6.06–6.03 (m, 2H), 4.99–4.95 (m, 1H), 4.88–4.84 (m, 1H), 4.28 (s, 1H), 4.27 (s, 1H), 4.24–4.20 (m, 2H), 3.90 (s, 1H), 3.89 (s, 1H), 3.82–3.74 (m, 2H), 3.63 (dt, 2H, J = 2.8 & 10.7 Hz), 3.26 (b, 1H), 3.23 (b, 1H), 3.06–3.00 (m, 6H), 2.79 (s, 3H), 2.78 (s, 3H), 2.00–1.93 (m, 4 H), 1.81–1.54 (m, 12H), 1.44–1.41 (m, 2H), 1.28 (dd, 2H, J = 5.3 & 7.5 Hz), 1.18 (t, 6H, J = 7.2 Hz), 1.19–1.15 (m, 2H), 1.01 (s, 3H), 0.99 (s, 3H), 0.92 (s, 9H), 0.91 (s, 9H), 0.81 (s, 18H), 0.79 (s, 3H), 0.77 (s, 3H);^{13}C NMR (125 MHz, DMSO-d_6), δ, 198.6, 197.9, 171.7, 171.5, 171.4, 163.9, 163.7, 158.9, 158.8, 60.2, 59.9, 58.0, 57.9, 55.9, 55.8, 52.9, 52.7, 50.9, 48.3, 45.3, 45.2, 37.6, 37.5, 35.3, 35.1, 35.0, 33.0, 31.5, 31.4, 30.4, 28.8, 28.6, 28.2, 27.8, 27.6, 27.1, 26.9, 19.3, 18.7, 18.5, 13.4, 13.4, 8.6. MS (ESI, *m/z* relative intensity) 669 [$(M+1)^+$, 50], 362 (100).

5.1.17. (1*R*,5*S*)-*N*-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(*S*)-[[[[1(*S*)-[[(cyclopropylsulfonyl)methylamino]methyl]-2,2-dimethylpropyl]amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (31)

^{1}H NMR (500 MHz, DMSO-d_6), δ, 8.29 (d, 1H, J = 7.3 Hz), 8.18 (d, 1H, J = 7.6 Hz), 8.01(s, 1H), 7.97 (s, 1H), 7.76 (s, 1H), 7.75 (s, 1H), 6.15–6.13 (m, 2H), 6.06–6.04 (m, 2H), 4.99–4.95 (m, 1H), 4.88–4.84 (m, 1H), 4.27 (2 s, 2H), 4.22 (d, 1H, J = 6.6 Hz), 4.20 (d, 1H, J = 6.6 Hz), 3.90 (t, 2H, J = 10.1 Hz), 3.79–3.73 (m, 2H), 3.69–3.65 (m, 2H), 3.03–2.97 (m, 2H), 2.79 (s, 6H), 2.58–2.54 (m, 4 H), 2.03–1.94 (m, 4 H), 1.81–1.73 (m, 6H), 1.66–155 (m, 6H), 1.49–1.26 (m, 4 H), 1.00 (s, 3H), 0.99 (s, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.81 (s, 18H), 0.79 (s, 3H), 0.77 (s, 3H), 2.02–0.76 (m, 10 H); ^{13}C NMR (125 MHz, DMSO-d_6), δ, 198.6, 197.9, 171.7, 171.5, 171.4, 163.7, 158.9, 158.8, 60.2, 59.9, 58.0, 57.9, 56.0, 52.9, 52.7, 51.3, 48.3, 37.6, 35.7, 35.1, 35.0, 33.0, 33.0, 31.5, 31.4, 31.3, 28.7, 28.6, 28.3, 28.2, 27.6, 27.5, 27.1, 26.9, 19.3, 18.7, 18.5, 13.4, 13.4, 4.9, 4.8. MS (ESI, *m/z* relative intensity) 681 [$(M+1)^+$, 20], 374 (100).

5.1.18. (1*R*,5*S*)-*N*-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(s)-[[[[2,2-dimethyl-1(*S*)-[[methyl(2-pyridinylsulfonyl)amino]methyl]propyl]amino]carbonyl]amino]-2-(1-methylcyclohexyl)acetyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (33)

^{1}H NMR (500 MHz, DMSO-d_6), δ 8.75 (d, 2H, J = 4.0 Hz), 8.26 (s, 1H), 8.25 (s, 1H), 8.09 (dt, 2H, J =2.0 & 7.5 Hz), 8.05–7.98 (m, 3H), 7.91 (d, 1H, J = 8.0 Hz), 7.77 (s, 2H), 7.70–7.67 (m, 2H), 6.17 (d, 1H, J = 9.5 Hz), 6.15 (d, 1H, J = 10.0 Hz), 6.00–5.99 (dd, 2H, J = 8.0 & 10.0 Hz), 5.02–4.93 (m, 1H), 4.88–4.81 (m, 1H), 4.32–4.22 (m, 4 H), 3.98 (d, 1H, J =10.5 Hz), 3.94 (d, 1H, J =10.0 Hz), 3.84–3.81 (m, 1H), 3.79–3.76 (m, 1H), 3.67 (t, 2H, J = 10.5 Hz), 3.30–3.27 (b, 2H), 3.02 (t, 2H, J =10.5 Hz), 2.78 (s, 6H), 2.03–1.93 (m, 4 H), 1.87–0.75 (m, 44 H), 1.00 (s, 3H), 0.99 (s, 3H), 0.96 (s, 9H), 0.81 (s, 9H), 0.79 (s, 3H), 0.78 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6), δ, 198.6, 198.2, 198.0, 171.7, 171.6, 171.6, 171.3, 163.9, 163.7, 158.8, 158.7, 157.2, 151.0, 139.5, 127.9, 123.3, 60.4, 60.0, 58.3, 58.3, 56.2, 53.0, 52.7, 52.3, 48.3, 48.2, 37.9, 37.7, 37.6, 36.4, 35.0, 34.9, 34.5, 34.3, 34.1, 34.1, 33.0, 33.0, 31.4, 28.8, 28.6, 28.3, 28.2, 27.8, 27.6, 27.0, 26.9, 26.9, 26.7, 22.2, 22.0, 20.1, 20.0, 19.3, 19.3, 18.7, 18.5, 13.4, 13.3. MS (ESI, *m/z* relative intensity) 780 [$(M+Na)^+$, 10], 758 [$(M+1)^+$, 60], 451 (100).

5.1.19. (1*R*,5*S*)-*N*-[1-(Propyl)-2,3-dioxo-2-(2-propenylamino)propyl]-3-[2(*S*)-[[[[1(*S*)-[[(ethylsulfonyl)methylamino]methyl]-2,2-dimethylpropyl]amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (34)

^{1}H NMR (500 MHz, DMSO-d_6), δ 8.87 (t, 1H, J = 6.0 Hz), 8.81 (t, 1H, J = 6.0 Hz), 8.38 (d, 1H, J = 6.5 Hz), 8.33 (d, 1H, J = 7.0 Hz), 6.12 (d, 1H, J = 10.5 Hz), 6.10 (d, 1H, J = 11.0 Hz), 6.06 (d, 1H, J = 4.0 Hz), 6.04 (d, 1H, J = 4.5 Hz), 5.84–5.76 (m, 2H), 5.13–5.05 (m, 4 H), 5.00–4.96 (m, 1H), 4.95–4.85 (m, 1H), 4.29 (s, 1H), 4.28 (s, 1H), 4.22 (d, 1H, J = 4.5 Hz), 4.20 (d, 1H, J = 4.5 Hz), 3.93–3.89 (m, 2H), 3.80–3.71 (m, 6H), 3.63 (dt, 2H, J = 10 & 2.5 Hz), 3.26 (b, 1H), 3.23 (b, 1H), 3.06–3.00 (m, 6H), 2.78 (s, 6H), 1.74–1.65 (m, 2H), 1.55–1.23 (m, 10 H), 1.18 (t, 6H), 1.07 (s, 3H), 0.99 (s, 3H), 0.90 (s, 18H), 0.90–0.85 (m, 6H), 0.80 (s, 21H), 0.77 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6), δ, 224.4, 198.2, 197.6, 171.9, 171.7, 171.6, 171.5, 162.0, 161.6, 158.9, 158.9, 135.0, 135.0, 116.4, 116.4, 60.2, 59.9, 58.0, 57.9, 55.9, 54.4, 54.3, 50.9, 48.3, 45.3, 45.2, 41.7, 35.4, 35.1, 35.1, 35.0, 35.0, 32.5, 31.5, 31.5, 27.8, 27.7, 27.1, 27.0, 19.5, 19.4, 19.3, 19.3, 14.4, 14.3, 13.4, 13.4, 8.7. MS (ESI, *m/z* relative intensity) 683 [$(M+1)^+$, 100], 362 (30).

5.1.20. (1*R*,5*S*)-*N*-[1-(Propyl)-2,3-dioxo-3-(2-propenylamino)propyl]-3-[2(*S*)-[[[[2,2-dimethyl-1(S)-[[methyl(2-thienylsulfonyl)amino]methyl]propyl]amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (35)

^{1}H NMR (500 MHz, DMSO-d_6), δ, 8.85 (t, 1H, J = 6.0 Hz), 8.82 (t, 1H, J = 6.0 Hz), 8.38 (d, 1H, J = 6.5 Hz), 8.31 (d, 1H, J = 7.5 Hz), 7.99 (dd, 2H, J = 5.0 & 1.0 Hz), 7.65 (dd, 2H, J = 1.0 & 4.0 Hz), 7.25 (dd, 2H, J = 3.5 & 1.0 Hz), 6.14–5.30 (m, 4 H), 5.84–5.76 (m, 2H), 5.13–5.05 (m, 4 H), 5.00–4.96 (m, 1H), 4.91–4.86 (m, 1H), 4.30 (s, 1H), 4.28 (s, 1H), 4.24 (d, 1H, J = 9.5 Hz), 4.23 (d, 1H, J = 10.0 Hz), 3.93 (d, 1H, J = 9.5 Hz), 3.92 (d, 1H, J = 9.5 Hz), 3.81 – 3.64 (m, 8 H), 3.02 (bd, 2H, J = 12.5 Hz), 2.86 (bt, 2H, J = 12.5 Hz), 2.68 (s, 6H), 1.79–1.62 (m, 2H), 1.55 – 1.24 (m, 10 H), 1.07 (s, 3H), 0.99 (s, 3H), 0.72 (s, 18H), 0.82 (s, 18H), 0.80 (s, 3H), 0.77 (s, 3H), 0.93–0.86 (m, 6H).^{13}C NMR (125 MHz, DMSO-d_6), δ, 198.2, 197.6, 171.9, 171.8, 171.6, 171.4, 162.0, 161.6, 158.9, 158.8, 137.9, 135.1, 135.0, 133.8, 132.9, 128.9, 116.5, 116.4, 60.2, 59.9, 57.9, 57.8, 56.1, 54.4, 54.3, 51.6, 48.2, 48.2, 41.7, 36.0, 35.2, 35.0, 35.0, 32.5, 31.5, 27.8, 27.7, 27.1, 27.0, 19.5, 19.4, 19.3, 14.4, 14.3, 13.4, 13.3. MS (ESI, *m/z* relative intensity) 737 [$(M+1)^+$, 100], 416 (30).

5.1.21. (1*R*,5*S*)-*N*-[1-(Propyl)-2,3-dioxo-3-(2-propenylamino) propyl]-3-[2(*S*)-[[[[2,2-dimethyl-1(*S*)-[[methyl(2-thienylsulfonyl)amino]methyl]propyl]amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]-hexane-2(*S*)-carboxamide (36)

^{1}H NMR (500 MHz, DMSO-d_6), δ, 8.88 (t, 1H, J = 6.0 Hz), 8.82 (t, 1H, J = 6.0 Hz), 8.75 (d, 2H, J = 4.5 Hz), 8.38 (d, 1H, J = 6.5 Hz), 8.30 (d, 1H, J = 7.5 Hz), 8.10 (dt, 2H, J = 1.5 & 7.5 Hz), 7.91 (d, 2H, J = 8.0 Hz), 7.68 (dd, 2H, J = 5.0 & 3.0 Hz), 6.14 (d, 1H, J = 10.5 Hz), 6.11 (d, 1H, J = 9.5 Hz), 6.04 (d, 2H, J = 10.0 Hz), 5.84–5.76 (m, 2H), 5.13–5.05 (m, 4 H), 5.00–4.96 (m, 1H), 4.92–4.85 (m, 1H), 4.30 (s, 1H), 4.28 (s, 1H), 4.24 (d, 1H, J = 10 Hz), 4.23 (d, 1H, J = 10 Hz), 4.00–3.91 (m, 2H), 3.80–3.64 (m, 8 H), 3.31–2.92 (m, 2H), 3.03 (bt, 2H, J = 13.0 Hz) 2.78 (s, 6H), 1.75–1.66 (m, 2H), 1.57–1.24 (m, 10 H), 1.09 (s, 3H), 0.99 (s, 3H), 0.92 (s, 18H), 0.92–0.85 (m, 6H), 0.81 (s, 21H), 0.78 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6), δ 198.2, 197.6, 171.9, 171.8, 171.6, 171.4, 162.0, 161.6, 158.8, 158.7, 157.2, 151.0, 139.5, 135.0, 135.0, 127.9, 123.3, 116.4, 116.4, 60.2, 59.9, 57.9, 57.8, 56.3, 54.4, 54.3, 52.3, 48.2, 41.7, 36.4, 35.2, 35.2, 35.0, 35.0, 32.5, 31.5, 31.5, 27.8, 27.7, 27.2, 27.0, 27.0, 26.9, 19.5, 19.4, 19.3, 19.3, 14.4, 14.3, 13.4, 13.3. MS (ESI, *m/z* relative intensity) 754 [(M+Na)$^+$, 20], 732 [(M+1)$^+$, 100], 411 (30).

5.1.22. (1R,5S)-3-[2(S)-(2,3-Dihydro-1h-inden-2-yl)-2-[[[[1(S)-[[(ethylsulfonyl)methylamino]methyl]-2,2-dimethylpropyl] amino]carbonyl]amino]acetyl]-*N*-[1-[1,2-dioxo-2-(2-propenylamino)ethyl]butyl]-6,6-dimethyl-3-azabicyclo[3.1.0]-hexane-2(S)-carboxamide (37)

^{1}H NMR (DMSO-d_6, 500 MHz), δ, 8.90 (t, 1H, J = 6.0 Hz), 8.87 (t, 1H, J = 6.3 Hz), 8.43 (d, 1H, J = 6.6 Hz), 8.29 (d, 1H, J = 7.6 Hz), 7.18–7.10 (m, 8 H), 6.31–3.24 (m, 2H), 5.92 (d, 2H, J = 10.4 Hz), 5.85–5.78 (m, 2H), 5.15–4.96 (m, 4 H), 5.03–4.97 (m, 2H), 4.30–4.27 (m, 4 H), 3.86–3.61 (m, 10 H), 3.23 (m, 1H), 3.20 (m, 1H), 3.09–2.99 (m, 6H), 2.90–2.64 (m, 8 H), 2.80 (s, 3H), 2.79 (s, 3H), 1.75–1.69 (m, 2H), 1.58–1.48 (m, 3H), 1.43–1.24 (m, 9H), 1.18 (t, 6H, J = 7.6 Hz), 1.00 (s, 3H), 0.99 (s, 3H), 0.90 (t, 3H, J = 7.3 Hz), 0.89 (t, 3H, J = 7.3 Hz), 0.84–0.82 (m, 24 H). ^{13}C NMR (DMSO-d_6, 125 MHz), δ, 198.2, 197.7, 172.0, 171.8, 171.5, 161.8, 161.7, 158.7, 143.3, 143.2, 135.0, 127.0, 126.9, 125.2, 125.1, 125.0, 116.4, 60.6, 60.1, 55.6, 54.6, 54.4, 54.1, 50.9, 50.9, 47.6, 47.5, 44.9, 42.6, 42.5, 41.7, 36.0, 35.9, 35.7, 35.4, 34.9, 31.7, 31.6, 30.1, 28.4, 28.3, 27.6, 27.5, 27.0, 26.9, 22.6, 22.5, 19.4, 14.5, 13.5, 13.4, 8.6.

5.1.23. (1*R*,5*S*)-3-[2(*S*)-Cyclohexyl-2-[[[[1(S)-[[[(dimethylamino) sulfonyl]methylamino]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 (39)

^{1}H NMR (DMSO-d_6, 500 MHz), δ, 8.88 (t, 1H, J = 5.7 Hz), 8.84 (t, 1H, J = 5.7 Hz), 8.38 (d, 1H, J =6.3 Hz), 8.24 (d, 1H, J = 7.3 Hz), 6.04 (d, 2H, J = 8.2 Hz), 6.02 (d, 2H, J = 8.8 Hz), 5.86–5.77 (m, 4 H), 5.13–5.06 (m, 3H), 4.95–4.91 (m, 1H), 4.27 (s, 1H), 4.24 (s, 1H), 4.15–4.09 (m, 2H), 3.92–3.90 (m, 2H), 3.80–3.71 (m, 6H), 3.61 (t, 2H, J = 9.5 Hz), 3.19 (bd, 2H), 2.92 (t, 2H, J = 11.4 Hz), 2.71 (s, 6H), 2.69 (s, 12H), 1.75–1.65 (m, 2H), 1.65–1.59 (m, 8 H), 1.49–1.25 (m, 14 H), 1.12 (br s, 6H), 1.07 (s, 3H), 0.99 (s, 3H), 0.87–0.80 (m, 20 H), 0.80 (s, 18H); ^{13}C NMR (DMSO-d_6, 125 MHz), δ, 198.1, 197.7, 171.9, 171.9, 171.7, 161.9, 161.6, 158.6, 135.0, 135.0, 116.4, 116.3, 60.5, 60.0, 58.7, 56.1, 55.9, 55.9, 54.6, 54.4, 51.6, 49.0, 47.7, 47.6, 41.7, 38.5, 36.0, 34.9, 34.9, 31.0, 30.1, 29.8, 29.6, 29.1, 29.1, 28.4, 28.2, 27.6, 27.6, 27.0, 26.9, 26.3, 26.3, 26.3, 25.8, 22.5, 22.5, 19.4, 19.4, 14.5, 13.5, 13.4; MS (ES) *m/z* relative intensity 739[(M+1)$^+$, 100], 475(40), 403(80).

5.1.24. (1*R*,5*S*)-3-[2(*S*)-(2,3-Dihydro-1H-inden-2-yl)-2-[[[[1(*S*)-[[[(dimethylamino)sulfonyl]methylamino]methyl]-2,2-dimethylpropyl]amino]carbonyl]amino]acetyl]-*N*-[1-[1,2-dioxo-2-(2-propenylamino)ethyl]butyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (40)

^{1}H NMR (500 MHz, DMSO-d_6), δ, 8.90 (t, 1H, J = 6.0 Hz), 8.87 (t, 1H, J = 6.0 Hz), 8.43 (d, 1H, J = 6.6 Hz), 8.29 (d, 1H, J = 7.5 Hz), 7.20–7.10 (m, 8 H), 6.28 (d, 1H, J = 9.1 Hz), 6.26 (d, 1H, J = 9.1 Hz), 5.89 (d, 2H, J = 10.0 Hz), 5.85–5.78 (m, 2H), 5.15–5.06 (m, 4 H), 5.03–4.96 (m, 2H), 4.33–4.27 (m, 4 H), 3.85–3.71 (m, 8 H), 3.65–3.60 (m, 4 H), 3.22–3.18 (m, 2H), 3.00–2.63 (m, 8 H), 3.73 (s, 3H), 2.72 (s, 3H), 2.70 (s, 12H), 1.77–1.26 (m, 10 H), 1.00 (s, 3H), 0.99 (s, 3H), 0.82 (s, 9H), 0.81 (s, 9H), 0.93–0.80 (m, 16H); ^{13}C NMR (125 MHz, DMSO-d_6), δ, 198.2, 197.8, 171.9, 171.8, 171.6, 171.5, 161.8, 161.7, 158.7, 143.3, 143.3, 143.2, 143.2, 135.0, 135.0, 127.0, 126.9, 125.2, 125.2, 125.0, 116.4, 116.4, 60.6, 60.1, 58.7, 55.9, 54.5, 54.3, 51.6, 49.0, 42.5, 42.4, 41.7, 38.5, 36.0, 35.9, 35.6, 34.8, 33.7, 32.6, 32.4, 31.7, 31.6, 31.0, 27.6, 27.4, 27.0, 26.9, 26.8, 25.8, 19.6, 19.6, 19.4, 19.4, 14.4, 14.4, 13.5, 13.4; MS (ES) *m/z* relative intensity 758 [(M+1)$^+$, 100], 495 (34), 437 (43).

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