Journal of Medicinal Chemistry Article

*J. Med. Chem.* **2010,** *53,* 3075–3085 **3075**
DOI: 10.1021/jm9016027

# Cyclic Sulfones as Novel P3-Caps for Hepatitis C Virus NS3/4A (HCV NS3/4A) Protease Inhibitors: Synthesis and Evaluation of Inhibitors with Improved Potency and Pharmacokinetic Profiles

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*Received October 29, 2009*

HCV infection affects more than 170 million people worldwide and many of those patients will reach the end stage complications of the disease which include hepatocarcinoma and liver failure. The success rate for treatment of patients infected with genotype-1 is about 40%. Therefore, novel treatments are needed to combat the infection. The HCV NS3 protease inhibitor Boceprevir (**1**) was reported by our research group and efforts continue for the discovery of more potent compounds with improved pharmacokinetic profiles. A new series of HCV NS3 protease inhibitors having a cyclic sulfone P3-cap have been discovered. Compounds **43** and **44** showed $K_i$* values in the single-digit nM range and their cellular potency was improved by 10-fold compared to **1**. The pharmacokinetic profiles of **43** and **44** in rats and monkeys were also improved to achieve higher plasma levels after oral administration.

## Introduction

Hepatitis C virus (HCV[a]) infection remains a public health burden by afflicting more than 170 million people worldwide.[1] Chronic HCV infection is the leading cause for liver failure and liver cancer. The health care costs associated with HCV are expected to increase substantially as the majority of patients reach the end stage complications of the disease. The current standard of care for HCV infection is a combination of peginterferon and ribavirin.[2] This treatment is effective and can successfully deliver sustained virologic response (SVR) in $>75\%$ of patients infected with genotype-2 and -3. However, patients infected with genotype-1, which include most of the patients in U.S., Europe, and Japan, achieve only 40% SVR. Therefore, tremendous efforts have been directed to develop new and more effective therapeutic agents for the treatment of HCV infection.

The HCV genome is a (+)-RNA strand that encodes a polyprotein that contains both structural and nonstructural proteins.[3] The C-terminus of the HCV NS3 enzyme is a serine protease that plays an important role in viral replication because it is responsible for the cis-cleavage of the NS3-NS4 junction and the trans-cleavage of the NS4B, NS5A, and NS5B junctions to deliver proteins essential for replication.[4] Because of the pivotal role that HCV NS3/4A plays in viral replication, numerous groups have engaged in research activities directed toward finding potent and selective inhibitors that could provide patients with alternative treatments. To date, several compounds have undergone clinical trials including our first generation HCV NS3 protease inhibitor boceprevir (**1**),[5] which is currently in phase III. Other HCV NS3/4A inhibitors include telaprevir (VX-950),[6] also in phase III, ciluprevir (BILN 2061),[7] and more recently danoprevir (ITMN-191) and vaniprevir (MK-7009).[8]

Our research group has actively pursued the identification of a second generation HCV NS3 protease inhibitor. On the basis of our experience in the development of **1**, the following criteria were established for the new compound: (a) improved cellular potency compared to that of **1** ($EC_{90}$ = 350 nM) to potentially reduce the dose needed for effectively reducing viral load in humans; therefore, a 5-fold or higher increase in the cellular potency was set as a requirement for the second generation compound; (b) improved pharmacokinetic profile to attain higher exposure in primates and target once a day dosing for humans.

Herein, we report the results obtained for a new class of HCV NS3/4A inhibitors containing a cyclic sulfone moiety at the P4-site while maintaining the ketoamide moiety that had proven to be an effective serine trap for the enzyme. We describe the rationale that led us to design inhibitors that extend beyond the *tert*-butylurea P3-cap and a diastereoselective method for the synthesis of the chiral cyclic sulfones that were evaluated in this study.

## Design of P4 Cyclic Sulfone Cap

The structure and partial profile of **1** are shown in Figure 1. Structural features of **1** include the ketoamide moiety, which

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[a] Abbreviations: HCV, hepatitis C virus; PK, pharmacokinetic; AUC, area under the curve; SAR, structure−activity relationship; THF, tetrahydrofuran; PhMe, toluene; DCM, dichloromethane; HATU, 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; DIPEA, diisopropylethylamine; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; TFA, trifluoroacetic acid; TLC, thin layer chromatography; NMR, nuclear magnetic resonance; LC−MS, liquid chromatography−mass spectrometry; LRMS, low resolution mass spectrometry; HRMS, high resolution mass spectrometry.

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Published on Web 03/19/2010

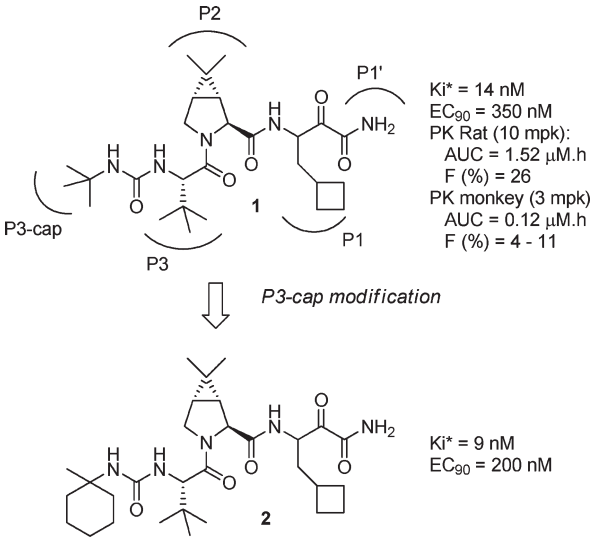



**Figure 1.** Modification of P3-cap. From *tert*-butylurea (compound **1**) to cyclohexylmethylurea (compound **2**).

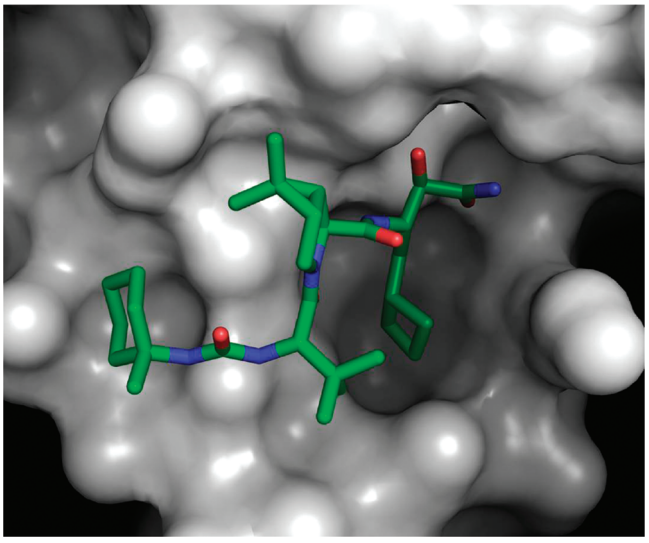


**Figure 2.** Molecular modeling of compound **2** bound to HCV NS3/4A active site.

serves as trap for Ser-139, and the *tert*-butylurea which serves as P3-capping. Also, a unique characteristic of compound **1** is the fused *gem*-dimethylcyclopropane proline group at the P2-site. We previously established that this proline derived amino acid provided inhibitors with better potency and PK profiles.[9]

To continue the structure−activity relationship (SAR) studies in **1**, we synthesized the cyclohexylmethylurea analogue **2** and had its potency measured. The binding affinity and cellular potency of **2** and all other inhibitors synthesized for this study were determined following previously reported procedures.[10] Compound **2** had improved binding and cellular potencies, $K_i$* = 9 nM and $EC_{90}$ = 200 nM. Molecular modeling of compound **2** bound to HCV NS3 protease active site showed that **2** had a hydrophobic interaction between its cyclohexyl ring and the S4-pocket (Figure 2). Furthermore, it was determined that the methyl group in the cyclohexylmethyl urea P3-cap could be used as a point of attachment for other groups to extend into the S4-pocket. Toward this end, we used the aforementioned methyl group to append different structural moieties such as sulfonamides and carbonyl groups,

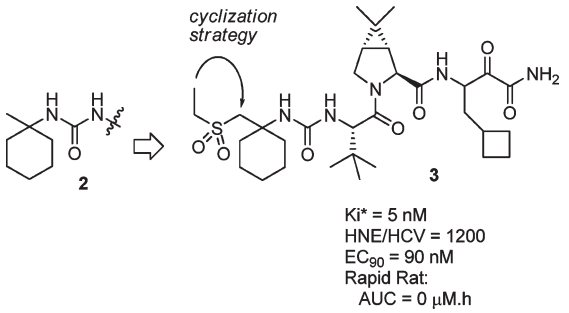



**Figure 3.** Modification of P3-cap. From cyclohexylmethylurea to ethylsulfone and cyclization strategy.

among others.[11] More recently, several inhibitors containing alkyl- and arylsulfones were also investigated.[12] Thus, the ethylsulfone analogue **3** is a representative example from the sulfone series (Figure 3). Compound **3** showed improved cellular potency ($K_i$* = 5 nM and $EC_{90}$ = 90 nM). This cellular potency represented a 2-fold improvement compared to **2** and almost 4-fold compared to **1**. Unfortunately, plasma levels of **3** after oral administration in rats could not be attained ($AUC_{(0-6h)} = 0\ \mu M \cdot h$ at 10 mpk).[13] It is important to mention the synergy existing between the sulfone moiety and the spirocyclohexyl group; sulfone analogues having a *gem*-dimethyl moiety instead of the spirocyclohexyl group showed poor cellular potency with $EC_{90}$ values in the micromolar range. Therefore, the spirocyclohexyl group was maintained in our targets to further expand the SAR studies in the sulfone series.

Modifications of compound **3** to further improve its potency and PK profiles were based on SAR developed in our group. As indicated above, compound **3** did not attain detectable levels in plasma after oral administration in rats, and similar PK profiles were observed for other sulfone analogues with primary ketoamides. Therefore, we anticipated improvement of oral exposure in rats and other species by capping the P1′ moiety.[5] Also, we envisioned a novel class of cyclic sulfone inhibitors based on the ethylsulfone moiety in **3**. The tethering of the ethyl group onto the methylene spacer between the sulfone and the spirocyclohexyl groups was deemed appropriate (as indicated by the arrow in Figure 3). This modification would lead to a more rigid structure that could potentially have improved potency and PK profiles. Molecular modeling suggested that inhibitors having either *R*- or *S*-stereochemistry in the cyclic sulfone moiety would have appropriate binding. Thus, we initiated the diastereoselective synthesis of compounds having four-, five-, and six-membered cyclic sulfone P3-caps to evaluate their potency and PK profiles. Details for the diastereoselective synthesis of the proposed targets are described below.

## Chemistry

The retrosynthetic analysis for synthesis of targets of type **4** is shown in Figure 4. The key disconnections include the urea linkage between the P3−P4 groups and the amide bond between P1−P2 groups. These disconnections gave the cyclic sulfone P3-cap **5**, P2−P3 dipeptide **6**, and hydroxyamide **7** as synthons for preparation of target compounds. Syntheses of fragments **6** and **7** have been described in previous communications from our research group.[5] Synthesis of the P4-cyclic sulfone **5** required an approach that allowed the stereocontrolled installation of the chiral center at the α-position to the

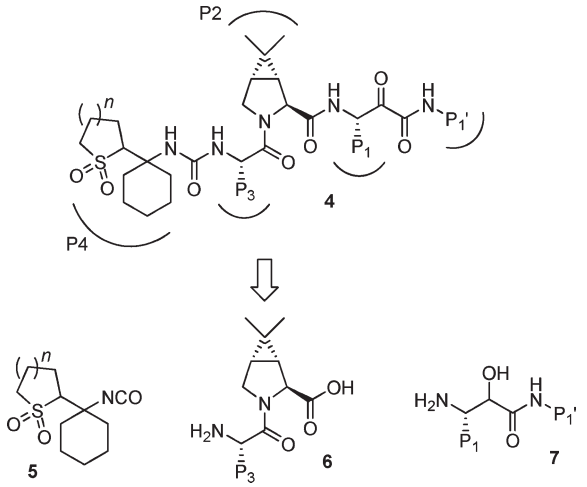



**Figure 4.** Retrosynthetic analysis of proposed targets.

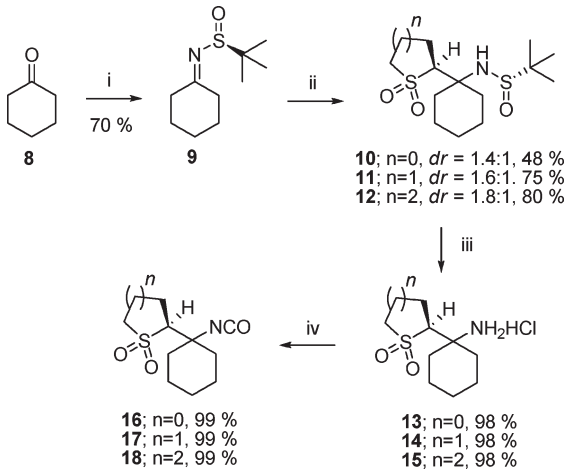
sulfone moiety. We have previously reported the synthesis of $\beta$-substituted $\beta$-aminosulfones via addition of sulfonyl anions to chiral sulfinylimines derived from aldehydes.[14] We considered using a similar approach to investigate the addition of sulfonyl anions to sulfinylimines derived from cyclohexanone (Scheme 1). Two important issues were expected to be addressed following this approach: (a) efficiency of the addition (competition between addition and deprotonation of the imine could lead to undesired side reactions); (b) level of stereocontrol in the addition reaction (effectiveness of the chiral sulfoxide to control the stereochemical outcome of the reaction).

Synthesis of chiral sulfinylimine **9** from cyclohexanone and (*S*)-*tert*-butanesulfinamide was accomplished in 70% yield following standard procedures (Scheme 1).[15] The next crucial step was to install the required stereogenic center in the α-position relative to the sulfone. This reaction was carried out by deprotonation of four-, five-, and six-membered cyclic sulfones followed by reaction with the sulfinylimine **9**. The reactions proceeded in good yields albeit the level of stereocontrol was modest. Nevertheless, the diastereomeric products **10**−**12** in all cases were easily separated by silica gel chromatography.

After separation of the diastereomeric products *S*,*S*-**10** to *S*,*S*-**12** from the *S*,*R*-**10** to *S*,*R*-**12**, the amines were unmasked by cleavage of the sulfinamide group under acidic conditions to deliver the corresponding optically pure amines **13**−**15** in quantitative yields with *S*-stereochemistry in addition to their corresponding enantiomers *R*-**13** to *R*-**15** (not shown). The stereochemical assignment was secured by single-crystal X-ray analysis of the urea **19** derived from amine hydrochloride *R*-**14** (Scheme 2).[16] The stereochemical assignment for the rest of the amines was established by NMR analysis using **11** as reference compound. The amines were converted to the corresponding isocyanates **16**−**18** using standard procedures.

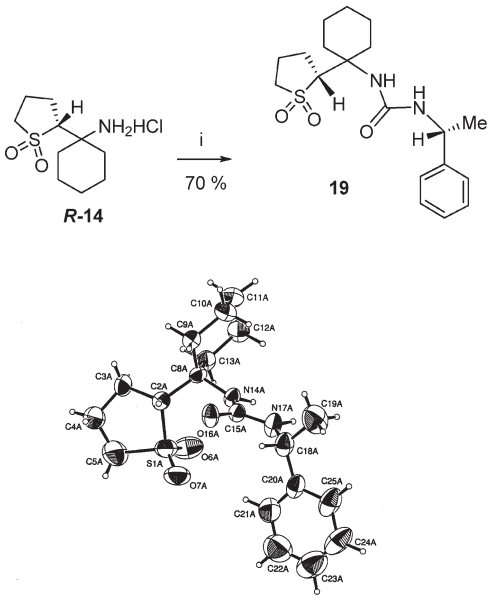
Synthesis of target **25** is shown in Scheme 3. Isocyanate *R*-**17** was coupled to the P2−P3 dipeptide **20** following previously described procedures to give **21**. Then the methyl ester in **21** was hydrolyzed with lithium hydroxide and the resulting acid **22** was coupled with the P1−P1′ amine **23** using HATU to deliver hydroxyamide **24**. Oxidation of **24** to yield ketoamide **25** was accomplished using Dess−Martin reagent. All target compounds presented in this study were synthesized using this general protocol.

**Scheme 1.** Stereoselective Synthesis of Cyclic Sulfones via Addition of Sulfonyl Anions to Chiral Sulfinylimines[a]




[a] Reagents and conditions: (i) (*S*)-*t*-butanesulfinamide, $Ti(OEt)_4$, THF, 65 °C; (ii) sulfone, *n*-BuLi, THF, −78 °C; (iii) 4 M HCl, MeOH, 0−25 °C; (iv) $C(O)Cl_2$, PhMe/DCM, aq $NaHCO_3$, 0 °C.

**Scheme 2.** Synthesis of Urea **19** for Assignment of Stereochemistry via Single Crystal X-ray Analysis[a]

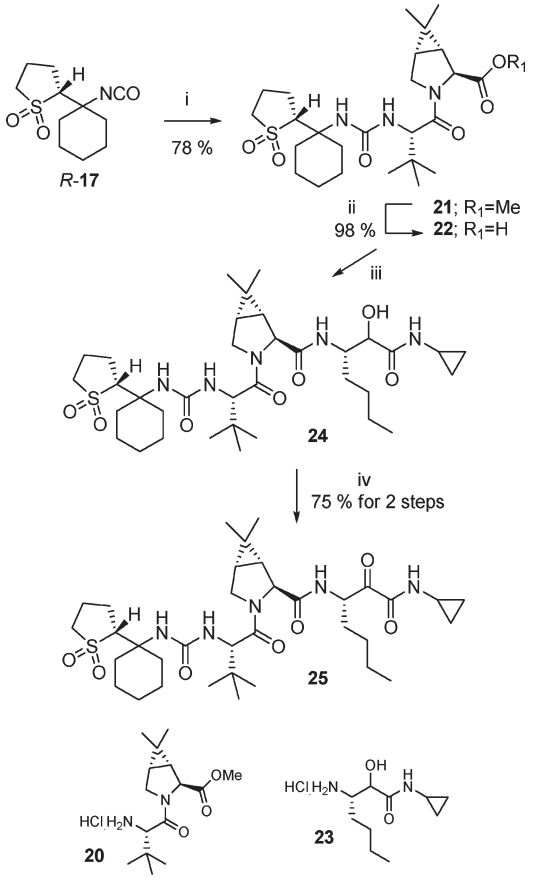



[a] ORTEP diagram for urea **19** is shown at the bottom. Reagents and conditions: (i) (*R*)-(1-isocyanatoethyl)benzene, aq $NaHCO_3$, 25 °C.

## Results and Discussion

The first set of target compounds synthesized were expected to provide information about the optimum ring size for binding and the required configuration at the chiral center in the α-position relative to the sulfone moiety. As mentioned above, an improvement in PK profile of target compounds was expected by capping the primary ketoamide with small alkyl groups. Therefore, target compounds were synthesized containing allyl and cyclopropyl groups to evaluate their potency and PK profiles. In addition, SAR studies had demonstrated that branched P1 groups were less tolerated when the primary ketoamides were capped.[5] Consequently, we decided to start our studies with analogues having the nonbranched amino acid norleucine at the P1 site and cyclopropyl at the P1′.[17] Table 1 shows binding and cellular

**Scheme 3.** Synthesis of Targets Containing Cyclic Sulfones as P3-Caps[a]

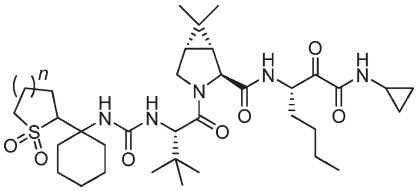



[a] Reagents and conditions: (i) **20**, DIPEA, DMF; (ii) LiOH, THF/$H_2O$; (iii) **23**, HATU, *N*-methylmorpholine, DMF/DCM; (iv) Dess−Martin periodinane, DCM.

potencies for compounds **25**−**30**. This set of compounds included targets with the proposed four-, five-, and six-membered cyclic sulfone P3-caps and had either *S*- or *R*-configuration in the chiral center present in the cyclic sulfone moiety. Remarkably, all the compounds had excellent binding potency with $K_i$* values in the low nanomolar range. Moreover, the results indicated that there was not an apparent preference for absolute configuration of the chiral center in the cyclic sulfone moiety which suggested that both *R*- and *S*-isomers were appropriately predisposed to bind tightly to the HCV NS3/4A active site. This result could be explained based on the fact that the sulfone moiety could adopt different conformations when the inhibitors are bound to the enzyme. However, we observed a slight preference for the *R*-isomer when measuring cellular potency. This effect was more evident for the four-membered sulfone analogues. The *R*-isomer **27** had $EC_{90}$ = 60 nM, whereas the *S*-isomers **28** had $EC_{90}$ = 120 nM. In contrast, the difference in $EC_{90}$ values between *R*- and *S*-isomers in both five- and six-membered analogues was negligible. For example, in the five-membered series the $EC_{90}$ values for the *R*- and *S*-isomers were 20 and 30 nM, respectively.

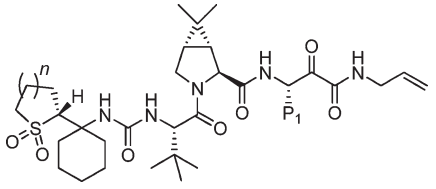
From this study, it was determined that five- and six-membered sulfone analogues were slightly more potent than the corresponding four-membered counterparts, and further investigations were continued preferentially on the *R*-isomers of five- and six-membered sulfone analogues.[18] It is important to mention that to pursue a thorough SAR investigation, a small number of compounds having the five-membered cyclic sulfone moiety and primary ketoamides were prepared (compounds not shown). However, the cellular potency for all those compounds were significantly higher ($EC_{90}$ ≥ 400 nM) compared to the compounds presented in Table 1.

**Table 1.** Cyclic Sulfone Derived P3-Caps: SAR for Ring Size and Absolute Configuration



| compd | *n* | absolute config | $K_i$* (nM) | $EC_{90}$ (nM) |
|---|---|---|---|---|
| **25** | 1 | *R* | 4 | 20 |
| **26** | 1 | *S* | 4 | 30 |
| **27** | 0 | *R* | 10 | 60 |
| **28** | 0 | *S* | 5 | 120 |
| **29** | 2 | *R* | 10 | 50 |
| **30** | 2 | *S* | 11 | 60 |

**Table 2.** Five- and Six-Membered Cyclic Sulfone Inhibitors: Evaluation of P1′-Allyl Group[a]



| cmpd | *n* | P1 | $K_i$* (nM) | $EC_{90}$ (nM) |
|---|---|---|---|---|
| **31** | 2 |  | 12 | 60 |
| **32** | 2 |  | 3 | 30 |
| **33** | 2 |  | 4 | 40 |
| **34** | 1 |  | 3 | 30 |
| **35**§ | 1 |  | 6 | 35 |
| **36** | 1 |  | 4 | 35 |

[a] (§) Epimeric mixture at P1 site.

The evaluation of compounds with P1′ allyl group and *tert*-butylglycine at P3 was carried out. Norleucine, norvaline, and homocyclopropylalanine amino acids were chosen for the P1 site SAR investigations. These three amino acids have been extensively used in SAR development for HCV NS3 protease inhibitors.[5,9] The potency data for allyl containing analogues are shown in Table 2. The data clearly showed that both five- and six-membered series were potent with $K_i$* values in the single-digit nanomolar range and no significant difference was observed between the two series. Also, cellular potency was very similar for compounds in both series with $EC_{90}$ values

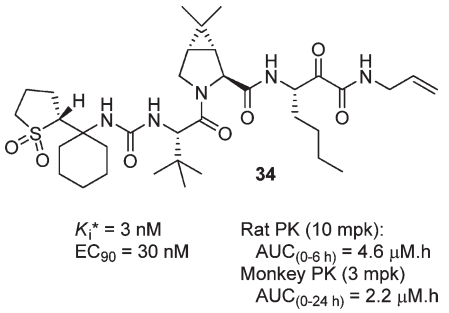



**Figure 5.** Potency and pharmacokinetic profile for compound **34**.

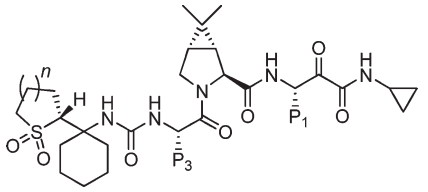
that ranged from 30 to 60 nM for the six-membered compounds **31**−**33** and from 30 to 35 nM for the five-membered analogues **34**−**36**. A trend showing slightly better cellular potency for five-membered analogues as a group could be observed, and further investigation of pharmacokinetic profile was started for compounds in the five-membered series.

The norleucine compound **34** in the five-membered series was further examined in the rapid rat experiment to determine its plasma levels after oral administration[19] (Figure 5). Compound **34** achieved high plasma levels with $AUC_{(0-6h)}$ = 4.6 $\mu M \cdot h$ at 10 mpk. Encouraged by the positive results obtained in the PK experiments, compound **34** was orally dosed in monkeys at 3 mpk. Once again, compound **34** achieved good plasma levels with an $AUC_{(0-24h)}$ = 2.2 $\mu M \cdot h$. Comparison between plasma levels in monkeys of compound **34** and that of **1** (AUC = 0.12 $\mu M \cdot h$) showed a > 18-fold improvement in AUC. It is important to mention that analogues of **1** having a P1′-allyl group showed poor binding and cellular potencies ($K_i$* ≥ 100 nM). Therefore, the potency and PK data of **34** and the other five- and six-membered cyclic sulfone analogues demonstrated that a new P3-cap that delivered inhibitors with improved potency and pharmacokinetic profiles had been discovered.

In spite of the positive results obtained for compound **34** in potency and pharmacokinetic experiments, the allyl group at the P1′ site remained a concern because of its potential to undergo metabolic activation to form a reactive species via epoxidation. To assess this potential liability, compound **34** was subjected to incubation with microsomes in the presence of glutathione. Unfortunately, under this conditions the oxidation of the allyl group was observed and the corresponding glutathione adducts arising from the reactive intermediate were detected. This unfavorable result prompted us to abandon the P1′ allyl series and focus instead on profiling the P1′ cyclopropyl analogues.

The cyclopropyl group had been employed in the P1′ site in our earlier SAR studies to determine optimum ring size and stereochemistry of the newly synthesized cyclic sulfone P3 caps. To further evaluate the five- and six-membered cyclic sulfone series with P1′ cyclopropyl, we prepared targets having similar amino acids in the P1 (norleucine, norvaline, homocyclopropylalanine) and P3 (*tert*-butylglycine) sites. The data for these targets are shown in Table 3. The $K_i$* and $EC_{90}$ values for the P1′ cyclopropyl analogues **25**, **29**, **37**−**40** were similar to their P1′ allyl counterparts, and only slight improvements were observed in a few cases. Once again, most of the compounds in both five- and six-membered series had $K_i$* values in the single-digit nanomolar range. However, in the P1′ cyclopropyl series, the five-membered compounds showed a trend for slightly better cellular potency with $EC_{90}$ values between 20 and 40 nM (compounds **25**, **39**, **40**), whereas

**Table 3.** Five- and Six-Membered Cyclic Sulfone Inhibitors: P1′-Cyclopropyl Analogues[a]



| cmpd | *n* | P1 | P3 | $K_i$* (nM) | $EC_{90}$ (nM) | AUC§ (μM.h) |
|---|---|---|---|---|---|---|
| **29** | 2 |  |  | 10 | 50 | na† |
| **37** | 2 |  |  | 12 | 40 | 0.2 |
| **38** | 2 |  |  | 6 | 40 | 0.8 |
| **25** | 1 |  |  | 4 | 20 | 0.9 |
| **39** | 1 |  |  | 4 | 20 | 0.3 |
| **40** | 1 |  |  | 4 | 40 | 0.5 |
| **41** | 2 |  |  | 8 | 100 | na† |
| **42** | 2 |  |  | 7 | 50 | 0.8 |
| **43** | 1 |  |  | 3 | 40 | 2.7 |
| **44** | 1 |  |  | 2 | 20 | 1.2 |
| **45** | 1 |  |  | 3 | 40 | 1.5 |

[a] (§) Determined in rats at 10 mpk in 0.4% MC. (†) Not available.

the six-membered analogues had $EC_{90}$ values between 40 and 50 nM (compounds **29**, **37**, **38**). The pharmacokinetic profiles for P1′ cyclopropyl analogues were also investigated in rats (determined at 10 mpk in 0.4% MC).[13,19] Unfortunately, all compounds showed suboptimal AUC values in the range of 0.2−0.9 $\mu M \cdot h$. Norleucine compound **25** in the five-membered series gave the highest exposure after oral administration ($AUC_{(0-6h)}$ = 0.9 $\mu M \cdot h$). A comparison of the plasma levels achieved by compound **34** (P1′ allyl) with its direct analogue **25** (P1′ cyclopropyl) revealed a significant drop for the latter. Furthermore, all other compounds in the P1′ cyclopropyl series, including five- and six-membered analogues, showed lower plasma levels than **25**. The data clearly showed that replacement of the P1′ allyl group with a cyclopropyl group was effective to retain binding and cellular potencies but resulted in lower plasma levels after oral administration in rats. In order to correct this issue, we decided to introduce the β-methylcyclohexylglycine amino acid at the P3 site. This unnatural amino acid was previously reported by our group, and it has proved to be a useful P3 replacement for a number of inhibitors.[20] Moreover, the use of β-methylcyclohexylglycine amino acid has resulted in inhibitors with improved pharmacokinetic profiles. The binding potency for

**Table 4.** Plasma Levels for Selected Compounds after Oral Administration in Monkeys

| compd | $AUC_{(0-24h)}$ ($\mu M \cdot h$)[a] | $[ccmpd]_{8h}$ (nM) | [8 h]/$EC_{90}$ |
|---|---|---|---|
| **25** | 0.4 | 10 | 0.5 |
| **43** | 9.0 | 742 | 37 |
| **44** | 20.8 | 934 | 47 |
| **45** | 3.5 | 303 | 8 |

[a] Determined at 3 mpk dose in 0.4% MC.

compounds having $\beta$-methylcyclohexylglycine at P3 was again in the single-digit nanomolar range for compounds in both five- and six-membered series (**41**−**45**). The previous observation regarding better cellular potencies for five-membered sulfone analogues was again confirmed from these targets. Thus, five-membered compounds **43**−**45** had $EC_{90}$ values between 20 and 40 nM and were slightly more potent than their six-membered counterparts **41** and **42** ($EC_{90}$ values between 50 and 100 nM). The pharmacokinetic profile of $\beta$-methylcyclohexylglycine analogues was subsequently evaluated in rats.[13,19] In the five-membered series, the $\beta$-methylcyclohexylglycine compounds **43**−**45** showed higher plasma levels compared to their *tert*-butylglycine counterparts **25**, **39**, **40**. Thus, the norleucine analogue **43** attained the highest plasma levels ($AUC_{(0-6h)}$ = 2.7 $\mu M \cdot h$) whereas the norvaline and homocyclopropylalanine compounds **50** and **51** showed AUC values of 1.2 and 1.5 $\mu M \cdot h$, respectively. These results clearly demonstrated that introduction of the unnatural amino acid $\beta$-methylcyclohexylglycine at the P3-site had a positive effect in the pharmacokinetic profile of our compounds without being detrimental to their cellular potency.

On the basis of potency and exposure in rats, key compounds were selected for PK studies in monkeys (at 3 mpk dose in 0.4% MC). The data shown in Table 4 include the exposure after oral administration, concentration of the compounds in plasma after 8 h, and the ratio between their concentrations at 8 h over $EC_{90}$.

The PK data in Table 4 clearly demonstrated that compounds with $\beta$-methylcyclohexylglycine P3 in the five-membered series could achieve high plasma levels after oral administration. A direct comparison between the *tert*-butylglycine analogue **25** ($AUC_{(0-24h)}$ = 0.4 $\mu M \cdot h$) and the $\beta$-methylcyclohexylglycine analogue **43** ($AUC_{(0-24h)}$ = 9.0 $\mu M \cdot h$) demonstrated an improvement in exposure of more than 20 times. Furthermore, the plasma concentration of **25** at 8 h was only 10 nM which was lower than the compound's $EC_{90}$. In contrast, **43** had a high plasma concentration at 8 h (742 nM) which was equivalent to 37 times its $EC_{90}$. The norvaline analogue **44** had the highest AUC value (20.8 $\mu M \cdot h$) in the $\beta$-methylcyclohexylglycine series. Moreover, the compound's concentration in plasma at 8 h and the ratio between concentration over $EC_{90}$ were also the highest for these two analogues, 934 nM and 47, respectively. The homocyclopropylalanine analogue **45** had moderate exposure ($AUC_{(0-24h)}$ = 3.5 $\mu M \cdot h$) and plasma concentration at 8 h (303 nM). In summary, compounds **43** and **44** achieved high plasma levels after oral administration and their concentration in plasma after 8 h was still a lot higher than their $EC_{90}$ values. All the cyclic sulfone analogues tested in the monkey PK assay in this study demonstrated higher exposures than our clinical candidate **1**. Compounds **43** and **44** (in the five-membered series with $\beta$-methylcyclohexylglycine P3 and cyclopropyl P1′) stood out in terms of potency and plasma levels achieved. We are currently profiling compounds **43** and **44** to determine their viability as potential second generation HCV NS3 inhibitors.

## Conclusions

A novel class of HCV NS3 protease inhibitors has been discovered and provide potential second generation compounds for development. An approach based on SAR development in the S4 region of the HCV NS3/4A enzyme was employed for the identification of a cyclic sulfone P3-cap for compounds with improved potency and PK profiles compared to **1**. The cyclic sulfone moiety fitted well in the S4 pocket, and systematic modifications allowed determination of the appropriate ring size and absolute configuration for optimum potency. Initial experiments showed that five- and six-membered sulfones were the most active and that having the *R*-configuration at the chiral center α to the sulfone moiety was preferred. Further evaluation of target compounds determined that inhibitors in the five-membered series had better PK profiles. Finally, introduction of the $\beta$-methylcyclohexylglycine at the P3 site provided compounds with high plasma levels in rats and monkeys. The five-membered sulfone analogues **43** and **44** stood out for their potency and PK profiles. Binding and cellular potencies for these two compounds were improved by more than 10-fold compared to **1**. Moreover, modifications using unnatural amino acids developed in our group resulted in significant improvements for **43** and **44** in terms of plasma levels attained after oral administration in monkeys. The substantial improvement in PK profile for **43** and **44** compared to **1** was an important step toward identification of a viable second generation candidate for clinical development.

## Experimental Section

Dry solvents were purchased from Aldrich or Acros and used without further purification. Other solvents or reagents were used as obtained except when otherwise noted. Analytical thin layer chromatography (TLC) was performed on precoated silica gel plates available from Analtech. Visualization was accomplished with UV light or by staining with basic $KMnO_4$ solution, methanolic $H_2SO_4$, or Vaughn's reagent. 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. NMR spectra were recorded in $CDCl_3$ or DMSO-$d_6$ in 400 or 500 MHz ($^1$H NMR) and in 100 or 125 MHz ($^{13}$C NMR). Low and high resolution mass spectra were obtained using electron spray or FAB ionization methods. Purity of compounds was determined by LC−MS analysis using Agilent chromatographic systems under the following conditions: sample concentration, 1 mg/mL in methanol; column, Agilent SBC (3.0 mm × 50 mm, 1.8 $\mu$m); flow rate, 1.0 mL/min; solvent A, $H_2O$−0.1% TFA; solvent B, acetonitrile−0.1% TFA; gradient table, 0 min at 10% B, 0.3 min at 10% B, 1.5 min at 95% B, 2.7 min at 95% B; UV detector, 254 nM. Compounds presented in this manuscript showed ≥95% purity.

**(*S*)-*N*-Cyclohexylidene-2-methylpropane-2-sulfinamide (9). 9** was prepared in 70% yield according to the procedure described in ref 15. $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ 2.86 (1H, ddd, $J$ = 5.12, 8.05, 13.18 Hz), 2.70 (1H, ddd, 5.12, 8.05, 13.91 Hz), 2.41 (2H, t, $J$ = 6.59 Hz), 1.70−1.86 (4H, m), 1.66 (2H, dd, $J$ = 5.12, 10.98 Hz), 1.21 (9H, s).

**General Procedure for Addition of Sulfonyl Anions to *N*-Sulfinylimine 9.** *n*-Butyllithium (1.3 equiv, 8.1 mL of a 1.6 M solution in hexanes) was added over 10 min to a cooled (−78 °C) solution of sulfone (1.35 equiv, 1.8 g, 13.41 mmol) in 50 mL of dry THF under anhydrous atmosphere. The mixture was stirred for 30 min at that temperature and then transferred via cannula

to a solution of sulfinylimine **9** (2.0 g, 9.93 mmol) in 50 mL of dry THF at −78 °C. After addition was completed, the reaction mixture was stirred for 3 h. The reaction was quenched at −78 °C by addition of 5 mL of aqueous saturated ammonium chloride solution. The mixture was allowed to reach room temperature and then partitioned between dichloromethane (100 mL) and aqueous saturated sodium bicarbonate solution (50 mL). The aqueous layer was back-extracted with dichloromethane (2 × 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel to afford the corresponding diastereomeric *S*,*S*- and *S*,*R*-products.

***N*-[1-(1,1-Dioxido-2(*S*)-thietanyl)cyclohexyl]-2-methyl-2-propane-(*S*)-sulfinamide (*S*,*S*-10).** *S*,*S*-**10** was obtained in 48% yield according to the general procedure. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 4.82 (1H, dd, $J$ = 8.78, 9.52 Hz), 4.33 (1H, s), 3.95 (1H, dt, $J$ = 9.52, 13.18 Hz), 3.82 (1H, dt, $J$ = 7.32, 13.18 Hz), 2.18 (1H, d, $J$ = 8.78 Hz), 2.15 (1H, m), 2.01 (3H, m), 1.34−1.74 (7H, m), 1.22 (9H, s). LRMS (ESI) calcd for $C_{13}H_{26}NO_3S_2$ [M + H]$^+$, 308.14; found, 308.03

***N*-[1-(1,1-Dioxido-2(*R*)-thietanyl)cyclohexyl]-2-methyl-2-propane-(*S*)-sulfinamide (*S*,*R*-10).** *S*,*R*-**10** was obtained in 48% yield according to the general procedure. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 4.97 (1H, s), 4.44 (1H, t, $J$=9.52 Hz), 4.02 (1H, ddt, $J$ = 1.46, 5.12, 13.18 Hz), 3.93 (1H, ddd, $J$ = 8.05, 10.25, 13.18 Hz), 2.85 (1H, ddt, $J$ = 8.05, 8.78, 10.98 Hz), 2.06 (2H, m), 1.83 (1H, m), 1.76 (1H, ddd, $J$=3.66, 9.52, 13.18 Hz), 1.29−1.66 (7H, m), 1.26 (9H, s). LRMS (ESI) calcd for $C_{13}H_{25}NO_3S_2Na$ [M + Na]$^+$, 330.12; found, 330.02.

***N*-[1-(Tetrahydro-1,1-dioxido-2(*S*)-thienyl)cyclohexyl]-2-methyl-2-propane-(*S*)-sulfinamide (*S*,*S*-11).** *S*,*S*-**11** was obtained in 75% yield according to the general procedure. $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ 5.16 (1H, s), 3.10 (1H, dd, $J$=7.88, 11.35 Hz), 3.08 (1H, m), 3.06 (1H, d, $J$ = 5.04 Hz), 2.78 (1H, ddt, $J$ = 5.99, 7.25, 11.98 Hz), 2.21 (2H, m), 2.07 (2H, m), 1.97 (1H, m), 1.88 (1H, m), 1.49−1.66 (5H, m), 1.46 (1H, m), 1.37 (1H, m), 1.26 (9H, s). $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ 69.0, 58.7, 56.6, 52.8, 38.0, 33.1, 25.1, 24.5, 23.0, 21.3, 21.1, 20.0 ppm. LRMS (ESI) calcd for $C_{14}H_{28}NO_3S_2$ [M + H]$^+$, 322.15; found, 322.05. LRMS (ESI) calcd for $C_{14}H_{27}NO_3S_2Na$ [M + Na]$^+$, 344.13; found, 344.00.

***N*-[1-(Tetrahydro-1,1-dioxido-2(*R*)-thienyl)cyclohexyl]-2-methyl-2-propane-(*S*)-sulfinamide (*S*,*R*-11).** *S*,*R*-**11** was obtained in 75% yield according to the general procedure. $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ 4.85 (1H, s), 3.59 (1H, dd, $J$=7.88, 10.40 Hz), 3.16 (1H, m), 2.90 (1H, ddd, $J$ = 7.25, 10.71, 13.24 Hz), 2.35 (1H, 13.87 Hz), 1.97−2.23 (6H, m), 1.64−1.80 (3H, m), 1.57 (2H, m), 1.37 (2H, m), 1.24 (9H, s). $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ 65.0, 58.9, 56.2, 52.9, 36.7, 33.5, 24.8, 24.2, 23.0, 22.2, 21.6, 19.4 ppm. LRMS (ESI) calcd for $C_{14}H_{28}NO_3S_2$ [M + H]$^+$: 322.15; found, 322.02. LRMS (ESI) calcd for $C_{14}H_{27}NO_3S_2Na$ [M + Na]$^+$: 344.13; found, 344.00.

***N*-[1-(Tetrahydro-1,1-dioxido-2*H*-thiopyran-2(*S*)-yl)cyclohexyl]-2-methyl-2-propane-(*S*)-sulfinamide (*S*,*S*-12).** *S*,*S*-**12** was obtained in 80% yield according to the general procedure. $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ 5.15 (1H, s), 3.76 (1H, dd, $J$ = 2.52, 12.92 Hz), 3.00 (1H, dt, $J$ = 4.72, 13.87 Hz), 2.98 (1H, m), 2.91 (1H, ddd, $J$ = 2.52, 3.46, 13.87 Hz), 2.19 (2H, m), 2.01−2.15 (4H, m), 1.93 (2H, m), 1.83 (1H, m), 1.72 (1H, dt, $J$ = 3.78, 11.35 Hz), 1.39−1.68 (5H, m), 1.27 (9H, s). $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ 69.8, 61.1, 56.3, 54.5, 52.1, 34.1, 31.9, 26.1, 25.2, 24.2, 22.9, 21.1, 21.0 ppm.

***N*-[1-(Tetrahydro-1,1-dioxido-2*H*-thiopyran-2(*R*)-yl)cyclohexyl]-2-methyl-2-propane-(*S*)-sulfinamide (*S*,*R*-12).** *S*,*R*-**12** was obtained in 80% yield according to the general procedure. $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ 4.18 (1H, s), 3.25 (1H, dd, $J$ = 2.83, 12.61 Hz), 2.98 (2H, m), 2.26 (3H, m), 2.18 (1H, m), 1.94−2.13 (4H, m), 1.73 (1H, d, $J$ = 13.87 Hz), 1.56 (4H, m), 1.45 (3H, m), 1.27 (9H, s). $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ 69.0, 60.9, 56.5, 55.3, 36.3, 33.5, 25.2, 25.1, 24.7, 24.0, 22.9, 21.6, 21.3 ppm.

**1-(Tetrahydro-1,1-dioxido-2(*R*)-thienyl)cyclohexanamine, Hydrochloride (*R*-14).** The sulfinamide *S*,*R*-**11** (1.55 g, 4.82 mmol) was dissolved in 50 mL of methanol and treated with 20 mL of 4 M HCl solution in dioxane. The mixture was stirred for about 1 h at which point all the starting material had been consumed as determined by TLC (acetone/hexanes, 35:65). The solvents were evaporated to dryness. Dichloromethane was added (10 mL) to make a cloudy solution. Upon addition of 100 mL of ether, a white precipitated formed. The precipitate was recovered by filtration (Whatman no. 1) to yield the amine hydrochloride *R*-**14** (1.22 g, 98%) as a white powder. $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ 8.61 (3H, broad s), 3.47 (1H, dd, $J$ = 7.32, 12.44 Hz), 3.24 (1H, m), 3.18 (1H, ddt, $J$ = 4.39, 7.32, 13.18 Hz), 2.75 (1H, ddt, $J$ = 5.12, 8.05, 13.18 Hz), 2.35 (3H, m), 2.17 (2H, m), 2.04 (2H, m), 1.92 (1H, dd, $J$ = 5.12, 9.52 Hz), 1.84 (1H, m), 1.61 (2H, m), 1.51 (1H, m), 1.39 (1H, m). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 62.4, 57.7, 52.9, 34.1, 32.2, 24.1, 24.0, 21.1, 20.7, 19.7 ppm. LRMS (ESI) calcd for $C_{10}H_{20}NO_2S$ [M + H]$^+$, 218.12; found, 218.32.

***N*-(1(*R*)-Phenylethyl)-*N*′-[1-(tetrahydro-1,1-dioxido-2(*R*)-thienyl)cyclohexyl]urea (19).** A solution of amine hydrochloride *R*-**14** (100 mg, 0.394 mmol) in 10 mL of dichloromethane was treated with aqueous saturated sodium bicarbonate solution (0.5 mL) at 0 °C. (*R*)-(1-Isocyanatoethyl)benzene (1.2 equiv, 69 mg) was added, and the resulting mixture was allowed to reach room temperature and stirred for 2 h. Some amine starting material was still unreacted, and more isocyanate was added (69 mg). After 2 h the mixture was diluted with dichloromethane (50 mL) and dried over magnesium sulfate. The mixture was filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient, acetone/hexanes, 1:9 to 1:1) to afford the product **19** (100 mg, 70%) as a white solid. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.36 (4H, m), 7.24 (1H, t, $J$=7.32 Hz), 4.93 (1H, broad s), 4.70 (2H, m), 3.73 (1H, dd, $J$=7.32, 11.71 Hz), 3.08 (1H, m), 2.82 (1H, ddd, $J$ = 7.32, 10.25, 12.44 Hz), 2.51 (1H, d, $J$ = 11.71 Hz), 2.40 (1H, m), 1.87−2.20 (4H, m), 1.24−1.53 (6H, m), 1.43 (3H, d, $J$ = 6.59 Hz), 1.11 (1H, m), 1.00 (1H, m). LRMS (ESI) calcd for $C_{19}H_{29}N_2O_3S$ [M + H]$^+$, 365.19; found, 365.29. Calcd for $C_{19}H_{28}N_2O_3SNa$ [M + Na]$^+$, 387.17; found, 387.20.

**Methyl (1*R*,5*S*)-3-[3,3-Dimethyl-1-oxo-2(*S*)-[[[[1-(tetrahydro-1,1-dioxido-2(*R*)-thienyl)cyclohexyl]amino]carbonyl]amino]butyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxylate (21).** A solution of amine hydrochloride *R*-**14** (2.0 g, 7.88 mmol) in 40 mL of dichloromethane was treated with 20 mL of aqueous saturated sodium bicarbonate solution and stirred vigorously for 10 min at 0 °C. Stirring was stopped, and layers were allowed to separate. Phosgene (10 mL of 20% solution in toluene) was added through a needle to the organic layer in one portion. The mixture was vigorously stirred immediately after addition for 10 min at 0 °C and further stirred at room temp for 3 h. The mixture was diluted with 150 mL of dichloromethane, and layers were separated. The organic layer was washed with 50 mL of cold aqueous saturated sodium bicarbonate solution and dried over magnesium sulfate. The organic layer was filtered and diluted with 15 mL of toluene. The resulting solution was concentrated to almost dryness and adjusted with toluene to give a 0.525 M solution of *R*-**17** in toluene.

In a separate flask, a solution of amine hydrochloride **20** (1.25 equiv, 1.99 g) in 50 mL of dichloromethane was treated with *N*-methylmorpholine (4.0 equiv, 2.2 mL, d 0.920) at 0 °C. After 5 min, 9.5 mL of the isocyanate *R*-**17** solution (0.525 M solution in toluene) was added. The mixture was stirred overnight (temperature from 0 to 25 °C). The reaction was quenched by addition of aqueous 1 M HCl (80 mL). The mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient, acetone/hexanes, 1:9 to 1:1) to afford the product **21** (2.06 g, 78%) as a white solid. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 5.08 (1H, broad s), 4.79 (1H, s), 4.45 (1H, s), 4.33 (1H, broad s), 4.05 (1H, d, $J$ = 10.25 Hz), 3.85 (1H, dd, $J$ = 3.66, 10.25 Hz), 3.73 (3H, s), 3.68 (1H, dd, $J$ = 7.32, 11.71 Hz), 3.09 (1H, m), 2.92 (1H, ddd, $J$ = 7.32, 10.98,

13.18 Hz), 2.58 (1H, d, $J$ = 10.25 Hz), 2.38 (1H, m), 1.87−2.19 (4H, m), 1.34−1.67 (9H, m), 1.18 (1H, m), 1.01 (12H, s), 0.89 (3H, s). LRMS (ESI) calcd for $C_{26}H_{44}N_3O_6S$ [M + H]$^+$, 526.30; found, 526.35.

**(1*R*,5*S*)-*N*-[1(*S*)-[2-(Cyclopropylamino)-1,2-dioxoethyl]pentyl]-3-[3,3-dimethyl-1-oxo-2(*S*)-[[[[1-(tetrahydro-1,1-dioxido-2(*R*)-thienyl)cyclohexyl]amino]carbonyl]amino]butyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (25).** A solution of methyl ester **21** (2.03 g, 3.86 mmol) in 120 mL of a 2:1 mixture of THF/water was cooled to 0 °C and treated with lithium hydroxide monohydrate (2.5 equiv, 404 mg). The mixture was stirred for 10 min, and the cooling bath was removed. The mixture was stirred at room temperature until all starting material had been consumed as determined by TLC (acetone/hexanes, 3:7). After 3 h, the mixture was treated with aqueous 1 M HCl (∼100 mL) to make the mixture acidic (pH 2). The mixture was extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford the carboxylic acid **22** (1.93 g, 98%) as a white solid. LRMS (ESI) calcd for $C_{25}H_{42}N_3O_6S$ [M + H]$^+$, 512.28; found, 512.28.

A solution of carboxylic acid **22** (130 mg, 0.254 mmol) in 3 mL of dry dichloromethane and 3 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 equiv, 135 mg). The amine hydrochloride **23** (1.2 equiv, 72 mg) was added followed by *N*-methylmorpholine (4.0 equiv, 0.11 mL, d 0.920). The reaction mixture was stirred overnight (temperature from 0 to 25 °C). All the volatiles were removed under vacuum, and the residue was dissolved in 60 mL of ethyl acetate. The organic layer was washed with water (10 mL), aqueous 1 M HCl (10 mL), aqueous saturated sodium bicarbonate solution (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford the crude product **24** (∼99%, 175 mg) which was used without further purification. The hydroxyamide **24** (175 mg, 0.251 mmol) was dissolved in 10 mL of dry dichloromethane and treated with Dess−Martin periodinane (2.0 equiv, 215 mg). The reaction mixture was stirred at room temperature for 30 min. The mixture was treated with aqueous 1 M sodium thiosulfate solution (10 mL) and stirred for 5 min. Aqueous saturated sodium bicarbonate solution (10 mL) was also added, and stirring was continued for a further 10 min. The mixture was extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient, acetone/hexanes, 1:9 to 4:6) to afford the product **25** (130 mg, 75%) as a white powder. $^1$H NMR (DMSO-$d_6$, 500 MHz): $\delta$ 8.74 (1H, d, $J$ = 5.04 Hz), 8.36 (1H, d, $J$ = 6.62 Hz), 6.21 (1H, d, $J$ = 9.77 Hz), 6.08 (1H, s), 4.94 (1H, ddd, $J$ = 3.78, 6.62, 9.45 Hz), 4.30 (1H, s), 4.13 (1H, d, $J$ = 10.08 Hz), 3.93 (1H, d, $J$ = 10.40 Hz), 3.83 (1H, dd, $J$ = 7.88, 11.35 Hz), 3.72 (1H, dd, $J$ = 5.35, 10.08 Hz), 3.12 (1H, m), 2.88 (1H, ddd, $J$ = 7.56, 10.40, 12.92 Hz), 2.74 (1H, m), 2.46 (1H, d, $J$=11.66 Hz), 1.86−2.05 (4H, m), 1.75 (2H, m), 1.64 (1H, dt, $J$ = 4.41, 12.92 Hz), 1.21−1.58 (13H, m), 1.08 (1H, m), 1.00 (3H, s), 0.90 (9H, s), 0.86 (3H, t, $J$ = 7.25 Hz), 0.83 (3H, s), 0.65 (2H, m), 0.57 (2H, m). $^{13}$C NMR (DMSO-$d_6$, 125 MHz): $\delta$ 197.0, 171.0, 170.5, 161.9, 156.8, 66.3, 58.9, 56.6, 55.0, 53.5, 52.4, 47.3, 34.0, 30.6, 30.2, 29.2, 27.4, 26.8, 26.2, 26.0, 25.0, 23.9, 22.4, 21.6, 20.6, 20.3, 18.5, 18.3, 13.6, 12.2, 5.4, 5.3 ppm. HRMS (FAB) calcd for $C_{35}H_{58}N_5O_7S$ [M + H]$^+$, 692.4057; found, 692.4043.

**(1*R*,5*S*)-*N*-[1(*S*)-[2-(Cyclopropylamino)-1,2-dioxoethyl]pentyl]-3-[3,3-dimethyl-1-oxo-2(*S*)-[[[[1-(tetrahydro-1,1-dioxido-2(*S*)-thienyl)cyclohexyl]amino]carbonyl]amino]butyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (26).** $^1$H NMR (DMSO-$d_6$, 500 MHz): $\delta$ 8.74 (1H, d, $J$ = 5.35 Hz), 8.37 (1H, d, $J$ = 6.93 Hz), 6.26 (1H, d, $J$ = 10.08 Hz), 6.01 (1H, s), 4.94 (1H, ddd, $J$ = 3.78, 6.93, 9.45 Hz), 4.30 (1H, s), 4.17 (1H, d, $J$ = 10.08 Hz), 3.90 (1H, d, $J$ = 10.40 Hz), 3.83 (1H, dd, $J$ = 9.14, 9.77 Hz), 3.72 (1H, dd, $J$ = 5.35, 10.08 Hz), 3.12 (1H, m), 2.89 (1H, ddd, $J$ = 7.56, 10.08, 12.92 Hz), 2.74 (1H, m), 1.99 (3H, m), 1.70−1.85 (4H, m), 1.21−1.57 (14H, m), 1.09 (1H, m), 1.00 (3H, s), 0.89 (9H, s), 0.86 (3H, t = 7.25 Hz), 0.82 (3H, s), 0.65 (2H, m), 0.57 (2H, m). $^{13}$C NMR (DMSO-$d_6$, 125 MHz): $\delta$ 197.0, 171.0, 170.2, 161.9, 156.6, 66.3, 58.9, 56.3, 55.1, 53.5, 52.3, 47.3, 34.2, 30.6, 29.9, 29.2, 27.4, 26.7, 26.3, 26.2, 26.0, 25.0, 23.8, 22.4, 21.6, 20.5, 20.3, 18.5, 18.4, 13.6, 12.4, 5.4, 5.3 ppm. HRMS (FAB) calcd for $C_{35}H_{58}N_5O_7S$ [M + H]$^+$, 692.4057; found, 692.4037.

**(1*R*,5*S*)-*N*-[1(*S*)-[2-(Cyclopropylamino)-1,2-dioxoethyl]pentyl]-3-[2(*S*)-[[[[1-(1,1-dioxido-2(*R*)-thietanyl)cyclohexyl]amino]carbonyl]-amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]-hexane-2(*S*)-carboxamide (27).** $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.71 (1H, d, $J$ = 7.81 Hz), 7.32 (1H, d, $J$ = 3.90 Hz), 5.78 (1H, d, $J$ = 10.16 Hz), 5.49 (1H, dt, $J$ = 3.12, 8.59 Hz), 5.15 (1H, s), 4.60 (1H, s), 4.57 (1H, t, $J$ = 9.37 Hz), 4.50 (1H, d, $J$ = 10.16 Hz), 4.00 (1H, d, $J$ = 10.16 Hz), 3.77−3.96 (4H, m), 2.81 (2H, m), 2.53 (1H, ddd, $J$ = 8.59, 10.94, 19.53 Hz), 2.17 (1H, ddt, $J$=4.68, 7.03, 10.16 Hz), 1.95 (2H, m), 1.46−1.59 (7H, m), 1.16−1.45 (9H, m), 1.00 (3H, s), 0.95 (9H, s), 0.87 (3H, m), 0.86 (3H, s), 0.64 (2H, m). $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ 197.9, 172.2, 170.6, 160.3, 157.2, 87.8, 62.6, 59.6, 57.6, 56.4, 53.7, 48.5, 35.3, 32.2, 30.9, 29.6, 27.8, 27.3, 26.4, 25.3, 22.6, 21.8, 21.0, 18.6, 13.7, 12.6, 10.1, 6.3, 6.2, 1.0 ppm. LRMS (ESI) calcd for $C_{34}H_{56}N_5O_7S$ [M + H]$^+$, 678.39; found, 678.52.

**(1*R*,5*S*)-*N*-[1(*S*)-[2-(Cyclopropylamino)-1,2-dioxoethyl]pentyl]-3-[2(*S*)-[[[[1-(1,1-dioxido-2(*S*)-thietanyl)cyclohexyl]amino]carbonyl]-amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]-hexane-2(*S*)-carboxamide (28).** $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ 7.55 (1H, d, $J$ = 6.93 Hz), 7.09 (1H, s), 5.51 (1H, s), 5.36 (1H, ddd, $J$ = 4.41, 7.88, 8.82 Hz), 5.09 (1H, dd, $J$ = 9.45, 9.77 Hz), 4.93 (1H, s), 4.51 (1H, s), 4.48 (1H, d, $J$ = 9.77 Hz), 4.01 (1H, d, $J$ = 10.40 Hz), 3.75−3.92 (3H, m), 2.80 (1H, m), 2.51 (1H, d, $J$ = 9.45 Hz), 2.31 (1H, d, $J$ = 10.71 Hz), 2.19 (1H, m), 2.06 (1H, ddt, $J$ = 4.41, 10.08, 11.03 Hz), 1.95 (1H, ddd, $J$ = 4.41, 8.82, 12.92 Hz), 1.17−1.63 (14H, m), 1.00 (3H, s), 0.96 (9H, s), 0.84−0.89 (6H, m), 0.83 (3H, s), 0.62 (2H, m). $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ 196.9, 172.6, 170.6, 160.4, 156.8, 85.5, 62.0, 59.8, 57.7, 55.9, 53.8, 48.6, 35.0, 32.3, 31.7, 31.5, 31.1, 29.6, 27.5, 27.4, 26.5, 26.3, 25.3, 22.6, 22.4, 21.8, 21.0, 20.8, 18.8, 14.0, 13.6, 12.7, 10.3, 6.4, 6.3 ppm. HRMS (FAB) calcd for $C_{34}H_{56}N_5O_7S$ [M + H]$^+$, 678.3900; found, 678.3883.

**(1*R*,5*S*)-*N*-[1(*S*)-[2-(Cyclopropylamino)-1,2-dioxoethyl]pentyl]-3-[3,3-dimethyl-1-oxo-2(*S*)-[[[[1-(tetrahydro-1,1-dioxido-2(*H*)-thiopyran-2(*R*)-yl)cyclohexyl]amino]carbonyl]amino]butyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (29).** $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ 7.51 (1H, d, $J$ = 7.2 Hz), 7.06 (1H, d, $J$ = 3.4 Hz), 5.51 (1H, d, $J$ = 10.0 Hz), 5.30−5.36 (1H, m), 4.79 (1H, s), 4.50 (1H, s), 4.47 (1H, d, $J$ = 10.0 Hz), 4.02 (1H, d, $J$=10.7), 3.87 (1H, d, $J$ = 12.5 Hz), 3.83 (1H, dd, $J$ = 10.7 and 5.3 Hz), 2.86−2.92 (2H, m), 2.76−2.83 (1H, m), 2.32−2.38 (1H, m), 2.24−2.30 (1H, m), 2.10−2.16 (1H, m), 1.08−2.06 (22H, m), 1.00 (3H, s), 0.98 (9H, s), 0.84−0.90 (5H, m), 0.83 (3H, s), 0.59−0.64 (2H, m). $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ 196.7, 172.8, 170.1, 160.5, 156.7, 67.0, 60.0, 58.0, 57.5, 54.8, 53.9, 48.5, 35.1, 32.7, 31.8, 31.1, 29.5, 27.7, 27.4, 26.4 (3C), 26.3, 26.2, 25.4, 25.3, 24.4, 22.5, 22.0, 21.2, 20.8, 18.8, 13.7, 12.6, 6.5, 6.4 ppm. HRMS (FAB) calcd for $C_{36}H_{60}N_5O_7S$ [M + H]$^+$, 706.421 34; found, 706.420 70.

**(1*R*,5*S*)-*N*-[1(*S*)-[2-(Cyclopropylamino)-1,2-dioxoethyl]pentyl]-3-[3,3-dimethyl-1-oxo-2(*S*)-[[[[1-(tetrahydro-1,1-dioxido-2*H*-thiopyran-2(*S*)-yl)cyclohexyl]amino]carbonyl]amino]butyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (30).** $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ 7.37 (1H, d, $J$=6.9 Hz), 7.01 (1H, d, $J$ = 3.0 Hz), 5.35 (1H, d, $J$ = 10.0 Hz), 5.28−5.35 (1H, m), 4.58 (1H, s), 4.49 (1H, s), 4.42 (1H, d, $J$ = 9.9 Hz), 4.04 (1H, d, $J$ = 10.4 Hz), 3.80 (1H, dd, $J$=10.4, 5.2 Hz), 3.69 (1H, d, $J$ = 12.5 Hz), 2.82−2.93 (2H, m), 2.75−2.81 (1H, m), 2.56 (1H, d, $J$ = 13.3 Hz), 2.21 (1H, d, $J$=13.6 Hz), 1.16−2.08 (21H, m),

1.01 (3H, s), 0.97 (9H, s), 0.87 (3H, t, $J$ = 6.3 Hz), 0.86 (3H, s), 0.83 (2H, m), 0.55−0.64 (2H, m). $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ 196.6, 172.6, 170.6, 160.5, 156.7, 68.0, 59.9, 58.2, 57.7, 55.0, 54.1, 48.5, 35.1, 33.2, 33.0, 31.1, 29.2, 27.8, 27.4, 26.4 (4C), 26.1, 25.3, 25.2, 24.4, 22.4, 22.1, 21.5, 21.2, 18.8, 13.7, 12.8, 6.5, 6.4 ppm. HRMS (ESI) calcd for $C_{36}H_{60}N_5O_7S$ $[M + H]^+$: 706.421 34; found, 706.418 81.

**(1*R*,5*S*)-3-[3,3-Dimethyl-1-oxo-2(*S*)-[[[[1-(tetrahydro-1,1-dioxido-2*H*-thiopyran-2(*R*)-yl)cyclohexyl]amino]carbonyl]amino]butyl]-*N*-[1(*S*)-[1,2-dioxo-2-(2-propenylamino)ethyl]butyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (32).** $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ 7.72 (1H, d, $J$ = 8.0 Hz), 7.27 (1H, t, $J$ = 5.9 Hz), 5.90 (1H, d, $J$ = 9.9 Hz), 5.77−5.86 (1H, m), 5.38−5.46 (1H, m), 5.20 (1H, dq, $J$ = 17.1, 1.3 Hz), 5.16 (1H, dq, $J$ = 17.1, 1.3 Hz), 5.04 (1H, s), 4.54 (1H, d, $J$ = 10.0 Hz), 4.52 (1H, s), 3.97 (1H, d, $J$ = 9.9 Hz), 3.84−3.94 (5H, m), 2.83−2.92 (2H, m), 2.25−2.37 (2H, m), 2.08−2.16 (1H, m) 1.96−2.16 (2H, m), 1.81−1.92 (3H, m), 1.64−1.77 (1H, m), 1.33−1.52 (12H, m), 0.99 (3H, s), 0.97 (9H, s), 0.90 (3H, t, $J$ = 7.3 Hz), 0.82 (3H, s). $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ 196.3, 172.5, 171.0, 159.1, 156.8, 132.8, 117.3, 67.1, 60.0, 57.9, 57.3, 54.7, 53.5, 48.7, 41.7 35.3, 33.4, 32.7, 31.8, 30.2, 27.4, 26.6 (3C), 26.3, 26.2, 25.4, 25.3, 24.4, 21.2, 20.8, 18.9, 18.7, 13.3, 12.9 ppm. HRMS (FAB) calcd for $C_{35}H_{58}N_5O_7S$ $[M + H]^+$: 692.405 69; found, 692.405 55.

**(1*R*,5*S*)-3-[3,3-Dimethyl-1-oxo-2(*S*)-[[[[1-(tetrahydro-1,1-dioxido-2(*R*)-thienyl)cyclohexyl]amino]carbonyl]amino]butyl]-*N*-[1(*S*)-[1,2-dioxo-2-(2-propenylamino)ethyl]pentyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (34).** $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 8.84 (1H, t, $J$ = 5.47 Hz), 8.33 (1H, d, $J$ = 7.03 Hz), 6.21 (1H, d, $J$ = 10.16 Hz), 6.07 (1H, s), 5.79 (1H, m), 5.09 (1H, d, $J$ = 17.19 Hz), 5.06 (1H, d, $J$ = 10.16 Hz), 4.96 (1H, m), 4.31 (1H, s), 4.14 (1H, d, $J$ = 10.16 Hz), 3.93 (1H, d, $J$ = 10.16 Hz), 3.82 (1H, dd, $J$ = 8.59, 10.94 Hz), 3.74 (3H, m), 3.11 (1H, m), 2.87 (1H, m), 2.45 (1H, m), 1.86−2.07 (4H, m), 1.75 (2H, m), 1.65 (1H, dt, $J$ = 4.68, 12.50 Hz), 1.19−1.59 (13H, m), 1.10 (1H, m), 1.01 (3H, s), 0.90 (9H, s), 0.86 (3H, t, $J$ = 7.03 Hz), 0.84 (3H, s). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 197.1, 170.9, 170.5, 160.6, 156.8, 133.9, 115.4, 66.3, 58.8, 56.6, 55.0, 53.5, 52.3, 47.2, 40.7, 33.9, 30.6, 30.5, 30.2, 29.2, 27.3, 26.8, 26.2, 26.0, 24.9, 23.8, 21.5, 20.6, 20.3, 18.5, 18.3, 13.5, 12.2 ppm. LRMS (ESI) calcd for $C_{35}H_{58}N_5O_7S$ $[M + H]^+$, 692.41; found, 692.24.

**(1*R*,5*S*)-*N*-[1-(2-Cyclopropylethyl)-2,3-dioxo-3-(2-propenylamino)propyl]-3-[3,3-dimethyl-1-oxo-2(*S*)-[[[[1-(tetrahydro-1,1-dioxido-2(*R*)-thienyl)cyclohexyl]amino]carbonyl]amino]butyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (36).** $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.36 (1H, d, $J$ = 6.25 Hz), 7.04 (1H, t, $J$ = 5.47 Hz), 5.84 (1H, ddt, $J$ = 5.47, 10.94, 17.19 Hz), 5.36 (1H, m), 5.22 (1H, d, $J$ = 17.19 Hz), 5.19 (1H, d, $J$ = 10.94 Hz), 4.81 (1H, broad s), 4.47 (1H, s), 4.44 (1H, s), 4.09 (1H, d, $J$ = 10.16 Hz), 3.94 (2H, m), 3.79 (2H, m), 3.10 (1H, m), 2.91 (1H, ddd, $J$ = 7.03, 10.16, 12.50 Hz), 2.54 (1H, d, $J$ = 8.59 Hz), 2.47 (1H, d, $J$ = 8.59 Hz), 1.89−2.22 (6H, m), 1.13−1.80 (13H, m), 1.02 (3H, s), 1.00 (9H, s), 0.85 (3H, s), 0.66 (1H, m), 0.42 (2H, dd, $J$ = 1.56, 7.81 Hz), 0.04 (1H, m), 0.01 (1H, dd, $J$ = 1.56, 4.68 Hz). $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ 196.4, 172.9, 170.5, 159.0, 156.8, 132.7, 117.4, 67.8, 59.9, 57.9, 56.6, 54.2, 52.7, 48.5, 41.6, 34.9, 33.6, 31.5, 31.4, 30.7, 29.2, 27.5, 26.4, 26.3, 25.4, 24.9, 21.1, 21.0, 19.4, 18.7, 12.6, 10.3, 4.6, 4.3 ppm. LRMS (ESI) calcd for $C_{36}H_{58}N_5O_7S$ $[M + H]^+$, 704.41; found, 704.32.

**(1*R*,5*S*)-*N*-[3-(Cyclopropylamino)-1(*S*)-(2-cyclopropylethyl)-2,3-dioxopropyl]-3-[3,3-dimethyl-1-oxo-2(*S*)-[[[[1-(tetrahydro-1,1-dioxido-2*H*-thiopyran-2(*R*)-yl)cyclohexyl]amino]carbonyl]amino]butyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (38).** $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ 7.62 (1H, d, $J$ = 7.7 Hz), 7.17 (1H, d, $J$ = 3.7 Hz), 5.75 (1H, d, $J$ = 9.8 Hz), 5.41−5.48 (1H, m), 4.98 (1H, s), 4.52 (1H, d, $J$ = 9.8 Hz), 4.51 (1H, s), 3.99 (1H, d, $J$ = 10.4 Hz), 3.82−3.91 (2H, m), 2.84−2.92 (2H, m), 2.76−2.82 (1H, m), 2.25−2.38 (2H, m), 1.08−2.16 (20H, m), 0.97 (12H, s), 0.80−0.88 (2H, m), 0.82 (3H, s), 0.60−0.70 (3H, m), 0.36−0.44 (2H, m), −0.08−−0.06 (2H, m). $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ 197.2, 172.6, 170.9, 160.5, 156.7, 67.1, 59.9, 57.9, 57.3, 54.7, 53.7, 48.6, 35.2, 32.7, 31.7, 31.6, 30.5, 30.0, 27.4, 26.5 (3C), 26.3, 26.2, 25.4, 25.3, 24.4, 22.5, 21.3, 20.8, 18.9, 12.8, 10.1, 6.4, 6.4, 4.7, 4.2 ppm. HRMS (FAB) calcd for $C_{37}H_{60}N_5O_7S$ $[M + H]^+$, 718.421 34; found, 718.421 84.

**(1*R*,5*S*)-*N*-[1(*S*)-[2-(Cyclopropylamino)-1,2-dioxoethyl]butyl]-3-[3,3-dimethyl-1-oxo-2(*S*)-[[[[1-(tetrahydro-1,1-dioxido-2(*R*)-thienyl)cyclohexyl]amino]carbonyl]amino]butyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (39).** $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.75 (1H, d, $J$ = 8.59 Hz), 7.20 (1H, d, $J$ = 3.12 Hz), 5.74 (1H, d, $J$ = 9.37 Hz), 5.44 (1H, dt, $J$ = 3.12, 8.59 Hz), 5.11 (1H, s), 4.55 (1H, m), 4.54 (1H, s), 4.03 (1H, d, $J$ = 10.94 Hz), 3.95 (1H, dd, $J$ = 7.81, 11.72 Hz), 3.87 (1H, dd, $J$ = 4.68, 10.16 Hz), 3.11 (1H, m), 2.91 (1H, ddd, $J$ = 7.81, 10.94, 13.28 Hz), 2.81 (1H, ddt, $J$ = 3.90, 7.03, 10.94 Hz), 2.54 (1H, d, $J$ = 7.03 Hz), 2.46 (1H, d, $J$ = 7.03 Hz), 1.31−2.19 (17H, m), 1.15 (1H, m), 0.99 (3H, s), 0.97 (9H, s), 0.91 (3H, t, $J$ = 7.03 Hz), 0.85 (2H, m), 0.83 (3H, s), 0.63 (2H, m). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 197.4, 172.6, 170.8, 160.3, 156.7, 67.4, 59.7, 57.3, 56.3, 53.4, 52.8, 48.6, 35.1, 33.3, 33.0, 30.9, 29.9, 27.3, 26.5, 26.3, 25.5, 25.0, 22.5, 21.0, 20.9, 19.4, 18.8, 18.7, 13.2, 12.8, 6.4, 6.3 ppm. LRMS (ESI) calcd for $C_{34}H_{56}N_5O_7S$ $[M + H]^+$: 678.39; found, 678.25.

**(1*R*,5*S*)-*N*-[1(*S*)-[2-(Cyclopropylamino)-1,2-dioxoethyl]pentyl]-6,6-dimethyl-3-[2(*S*)-(1-methylcyclohexyl)-2-[[[[1-(tetrahydro-1,1-dioxido-2(*R*)-thienyl)cyclohexyl]amino]carbonyl]amino]acetyl]-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (43).** $^1$H NMR (DMSO-$d_6$, 500 MHz): $\delta$ 8.74 (1H, d, $J$ = 5.04 Hz), 8.34 (1H, d, $J$ = 6.93 Hz), 6.24 (1H, d, $J$ = 10.08 Hz), 6.06 (1H, s), 4.94 (1H, ddd, $J$ = 4.09, 6.93, 9.45 Hz), 4.29 (1H, s), 4.17 (1H, d, $J$ = 10.08 Hz), 3.95 (1H, d, $J$ = 10.40 Hz), 3.83 (1H, dd, $J$ = 7.88, 11.35 Hz), 3.74 (1H, dd, $J$ = 5.35, 10.08 Hz), 3.13 (1H, m), 2.87 (1H, ddd, $J$ = 7.88, 10.40, 12.92 Hz), 2.74 (1H, m), 2.46 (1H, d, $J$=11.35 Hz), 1.86−2.05 (4H, m), 1.75 (2H, m), 1.64 (1H, dt, $J$ = 4.41, 12.61 Hz), 1.18−1.58 (22H, m), 1.09 (2H, m), 1.00 (3H, s), 0.92 (3H, s), 0.86 (3H, t, $J$ = 6.93 Hz), 0.82 (3H, s), 0.65 (2H, m), 0.57 (2H, m). $^{13}$C NMR (DMSO-$d_6$, 125 MHz): $\delta$ 197.0, 171.0, 170.4, 161.9, 156.8, 66.3, 58.9, 57.2, 55.0, 53.5, 52.4, 47.3, 36.7, 33.4, 33.0, 30.6, 30.5, 30.2, 29.2, 27.4, 26.8, 26.0, 25.8, 25.0, 23.9, 22.3, 21.6, 21.2, 21.0, 20.6, 20.3, 19.0, 18.5, 18.3, 13.6, 12.2, 5.3, 5.2 ppm. HRMS (ESI) calcd for $C_{38}H_{62}N_5O_7S$ $[M + H]^+$, 732.437 00; found, 732.440 36.

**(1*R*,5*S*)-*N*-[1(*S*)-[2-(Cyclopropylamino)-1,2-dioxoethyl]butyl]-6,6-dimethyl-3-[2(*S*)-(1-methylcyclohexyl)-2-[[[[1-(tetrahydro-1,1-dioxido-2(*R*)-thienyl)cyclohexyl]amino]carbonyl]amino]acetyl]-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (44).** $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.65 (1H, d, $J$ = 7.81 Hz), 7.16 (1H, d, $J$ = 3.90 Hz), 5.54 (1H, d, $J$ = 9.37 Hz), 5.41 (1H, dt, $J$ = 4.68, 9.37 Hz), 5.06 (1H, s), 4.54 (1H, s), 4.51 (1H, d, $J$ = 10.16 Hz), 4.06 (1H, d, $J$ = 10.16 Hz), 3.87 (1H, d, $J$ = 10.16 Hz), 3.86 (1H, m), 3.11 (1H, m), 2.90 (1H, ddd, $J$ = 7.81, 10.16, 13.28 Hz), 2.80 (1H, ddt, $J$ = 3.90, 7.81, 10.94 Hz), 2.55 (1H, d, $J$ = 9.37 Hz), 2.46 (1H, d, $J$ = 9.37 Hz), 1.67−2.20 (8H, m), 1.08−1.62 (19H, m), 1.00 (3H, s), 0.97 (3H, s), 0.91 (3H, t, $J$ = 7.03 Hz), 0.83 (6H, s), 0.62 (2H, m). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 197.3, 172.6, 170.6, 160.3, 156.8, 67.6, 59.6, 58.6, 56.4, 53.6, 52.7, 48.6, 38.0, 34.2, 33.6, 33.3, 33.2, 31.1, 29.6, 29.3, 27.3, 26.3, 26.1, 25.5, 25.0, 22.5, 21.6, 21.5, 20.9, 19.4, 19.0, 18.6, 13.4, 12.7, 6.4, 6.3 ppm. LRMS (ESI) calcd for $C_{37}H_{60}N_5O_7S$ $[M + H]^+$, 718.42; found, 718.28

**(1*R*,5*S*)-*N*-[3-(Cyclopropylamino)-1(*S*)-(2-cyclopropylethyl)-2,3-dioxopropyl]-6,6-dimethyl-3-[2(*S*)-(1-methylcyclohexyl)-2-[[[[1-(tetrahydro-1,1-dioxido-2(*R*)-thienyl)cyclohexyl]amino]carbonyl]amino]-acetyl]-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxamide (45).** $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.58 (1H, d, $J$ = 7.03 Hz), 7.15 (1H, d, $J$ = 3.90 Hz), 5.44 (2H, m), 5.01 (1H, s), 4.53 (1H, s), 4.49 (1H, d, $J$ = 9.37 Hz), 4.08 (1H, d, $J$ = 10.94 Hz), 3.86 (1H, d, $J$ = 10.94 Hz), 3.85 (1H, m), 3.11 (1H, m), 2.89 (1H, ddd, $J$ = 7.81, 10.94, 13.28 Hz), 2.80 (1H, ddt, $J$ = 3.90, 7.03, 10.94 Hz), 2.54 (1H, d, $J$ = 8.59 Hz), 2.47 (1H, d, $J$ = 9.37 Hz), 1.90−2.21 (5H, m), 1.06−1.76 (22H, m), 1.00 (3H, s), 0.98 (3H, s), 0.84 (6H, s), 0.67 (1H, m), 0.62 (2H, m), 0.41 (2H, dd, $J$ = 1.56, 7.89 Hz), 0.01 (1H, dd, $J$ = 4.68, 18.75

Hz), 0.00 (1H, m). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 197.3, 172.6, 170.6, 160.3, 156.8, 67.6, 59.6, 58.6, 56.4, 53.8, 52.7, 48.5, 37.9, 34.2, 33.7, 33.4, 31.3, 31.2, 30.7, 29.2, 27.3, 26.4, 26.1, 25.4, 25.0, 22.5, 21.6, 21.5, 21.0, 20.9, 19.4, 19.0, 18.5, 12.6, 10.2, 6.3, 6.3, 4.7, 4.2 ppm. LRMS (ESI) calcd for $C_{39}H_{62}N_5O_7S$ $[M + H]^+$, 744.44; found, 744.33.

**Acknowledgment.** We thank John Pichardo, Sony Agrawal, Andrea Hart, and Robert Budich, Schering-Plough Research Institute, for their support in this project.

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(16) Crystal structure of compound **19** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 763018.

(17) On the basis of our previous experience in the development of **1**, we decided to use enantiomerically pure P1-groups in all target compounds presented herein to avoid problems associated with handling diastereomeric mixtures.

(18) To perform a thorough SAR investigation, selected five- and six-membered analogues having the *S*-configuration in the cyclic

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