Design and Synthesis of Pyrrolidine-5,5′-*trans*-Lactams (5-Oxo-hexahydropyrrolo[3,2-*b*]pyrroles) as Novel Mechanism-Based Inhibitors of Human Cytomegalovirus Protease. 4. Antiviral Activity and Plasma Stability

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A series of chiral, (*S*)-proline-α-methylpyrrolidine-5,5-*trans*-lactam serine protease inhibitors has been developed as antivirals of human cytomegalovirus (HCMV). The SAR of the functionality on the proline nitrogen has shown that derivatives of para-substituted phenyl ureas > para-substituted phenyl sulfonamides > para-substituted phenyl carboxamide for activity against HCMV δAla protease, producing para-substituted phenyl ureas with single figure nM potency (K_i) against the viral enzyme. The SAR of the functionality on the lactam nitrogen has defined the steric and electronic requirements for high human plasma stability while retaining good activity against HCMV protease. The combination of high potency against HCMV δAla protease and high human plasma stability has produced compounds with significant in vitro antiviral activity against human cytomegalovirus with the 6-hydroxymethyl benzothiazole derivative **72** being equivalent in potency to ganciclovir. The parent benzothiazole **56** had good pharmacokinetics in dogs with 29% bioavailability and good brain and ocular penetration in guinea pigs.

Introduction

Human herpes viruses cause a range of diseases: HSV-1 (cold sores), HSV-2 (genital herpes), VZV (chicken pox, shingles), and HCMV (retinitis, pneumonitis). The current treatment of these diseases uses nucleoside (acyclovir, ganciclovir) and phosphate (PFA) substrate analogues. Because of the toxicity associated with PFA and ganciclovir, together with the emergence of mutants resistant to acyclovir, there is a need for a new class of antiherpes compounds based on a novel mechanism.

Human herpes viruses encode a serine protease, which is essential for viral replication.[1] Recent X-ray structures of the serine proteases of HCMV, HSV-1, HSV-2, and VZV revealed that these enzymes belong to a novel class of serine proteases where the active site is composed of the His, His, Ser triad.[3−6] Substrate cleavage sites across all the herpes virus family are unique and highly conserved, and these enzymes have become attractive molecular targets for the design of novel antiviral drugs.[1,2] We recently reported on the design and synthesis of a novel class of mechanism based inhibitors of human cytomegalovirus protease,[7−9,14] based on the α-methylpyrrolidine-5,5′-*trans*-lactam template incorporating the natural substrate requirements of the consensus sequence of HCMV protease (Scheme 1). Mechanism of action studies using ESI-MS together with enzymatic degradation of the acylated HCMV protease showed that these inhibitors acylate HCMV protease at the active site serine (Ser 132) in a time-dependent and reversible manner.[9] SAR in this series of α-methylpyrrolidine-5,5′-*trans*-lactam has defined the size, the relative stereochemisty of the substituent adjacent to the lactam carbonyl, and its chirality. Optimization of the acyl function on the lactam nitrogen has extended the substitution pattern on the lactam nitrogen for activity against HCMV δAla protease to CO-cyclopropyl > COMe > CO2Me > SO2Me > CONHMe. Optimization of the functionality on the pyrrolidine nitrogen gave the highly potent dansyl-*S*-proline derivatives **1** and **2**, with K_i's in the low nanomolar range against HCMV δAla protease, which are highly selective over the mammalian enzymes elastase, thrombin and acetylcholine esterase.[9] However, they were not stable to human plasma.[14] We now report on work to define further the requirements of the substituent on the pyrrolidine nitrogen that accesses the S4 pocket, and on work to exploit the functionality on the lactam nitrogen of this template to give stability in human plasma and whole cell antiviral activity. This has given plasma stable inhibitors with low nanomolar potency against the HCMV δAla protease and antiviral activity equivalent to ganciclovir in whole cells.

Chemistry

We reported previously[9] that a dansyl-*S*-proline group on the pyrrolidine nitrogen and a cyclopropyl- or methylcarbonyl function on the lactam nitrogen was optimal for maximum potency in the novel chiral pyrrolidine-5,5′-*trans*-lactam inhibitors (**1** and **2**) of HCMV protease (Scheme 1). To investigate further the potency require-

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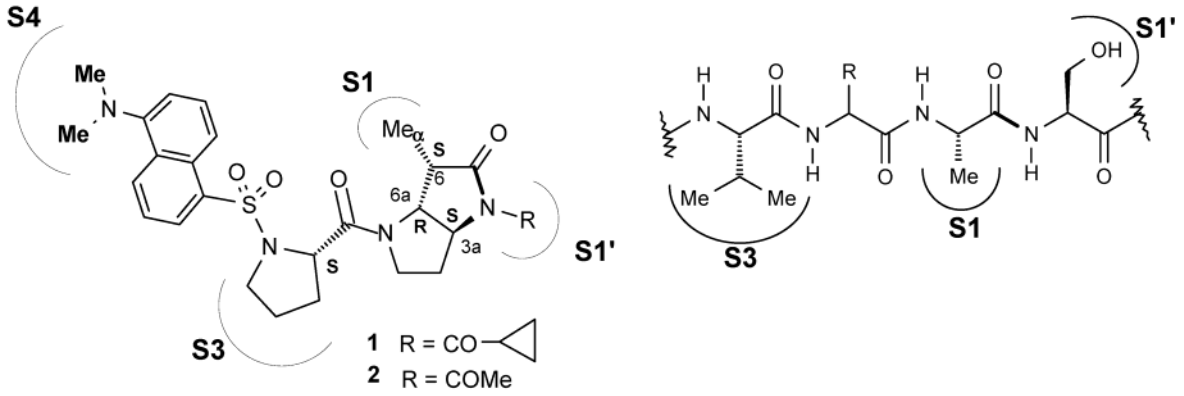
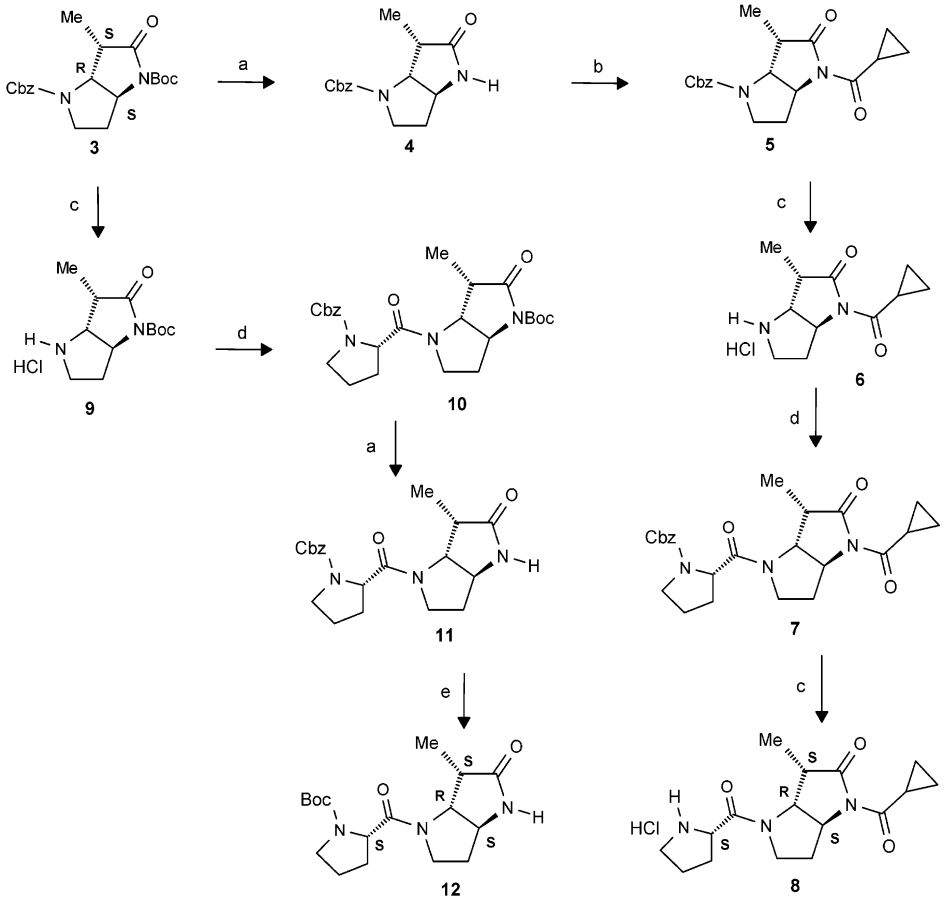
Scheme 1



Scheme 2[a]



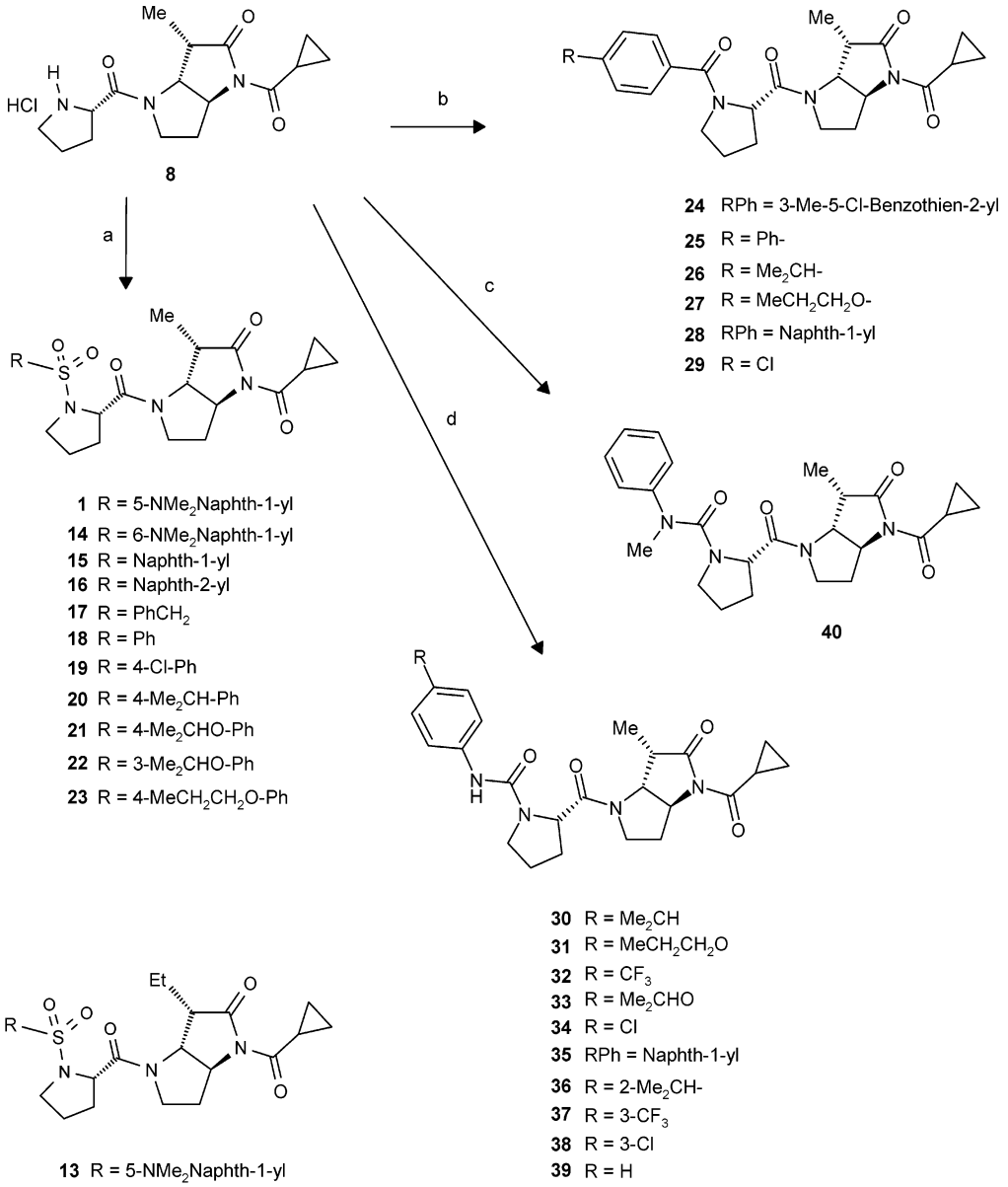
[a] Reagents and conditions: TFA, 1 h, RT; (b) LHMDS (1.4eq)/THF, −78 °C then cyclopropylCOCl; (c) 10% Pd/C (Degussa, 50% H_2O), isoPrOH, 2 h, RT, then HCl (1.1eq) Et_2O; (d) Cbz-(S)-proline, TBTU, HOBT, $^{i}Pr_2EtN$, DMF, RT; (e) Boc anhydride (1.3eq)/ 10% Pd/C (Degussa, 50% H_2O), isoPrOH, 2 h, RT.

ments of substituents on the pyrrolidine nitrogen and the carbonyl function on the lactam nitrogen, the chiral intermediates **8** and **12** were prepared as outlined in Scheme 2.

Deprotection of **3** with TFA followed by acylation of **4** with cyclopropyl carbonyl chloride gave the chiral (cyclopropyl) *trans*-lactam **5** in 65% overall yield. Hydrogenolysis of **5** with hydrogen in the presence of palladium gave the amine **6** in 74% yield, which was coupled with Cbz-(*S*)-proline using *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′,-tetramethyluronium tetrafluoroborate/1-hydroxybenzotriazole (TBTU/HOBT) in DMF at room temperature to give the protected prolyl *trans*-lactam **7.** This, on further hydrogenolysis, gave the amine **8** in 87% overall yield. Similarly hydrogenolysis of **3** with hydrogen in the presence of palladium gave **9** in 93% yield, which was coupled with Cbz-(*S*)-proline using TBTU/HOBT at room temperature to give protected prolyl *trans*-lactam **10** in 88% yield. Deprotection of **10** with trifluoroacetic acid gave the lactam **11** in 98% yield, which on hydrogenolysis in the presence of di-*tert*-butyl dicarbonate gave the Boc-protected prolyl *trans*-lactam **12** in 90% yield.

Exploration of the substituents on the proline nitrogen has been done with a variety of linkers, namely, sulfonamide, amide, and urea (Scheme 3). The sulfona-

Scheme 3[a]

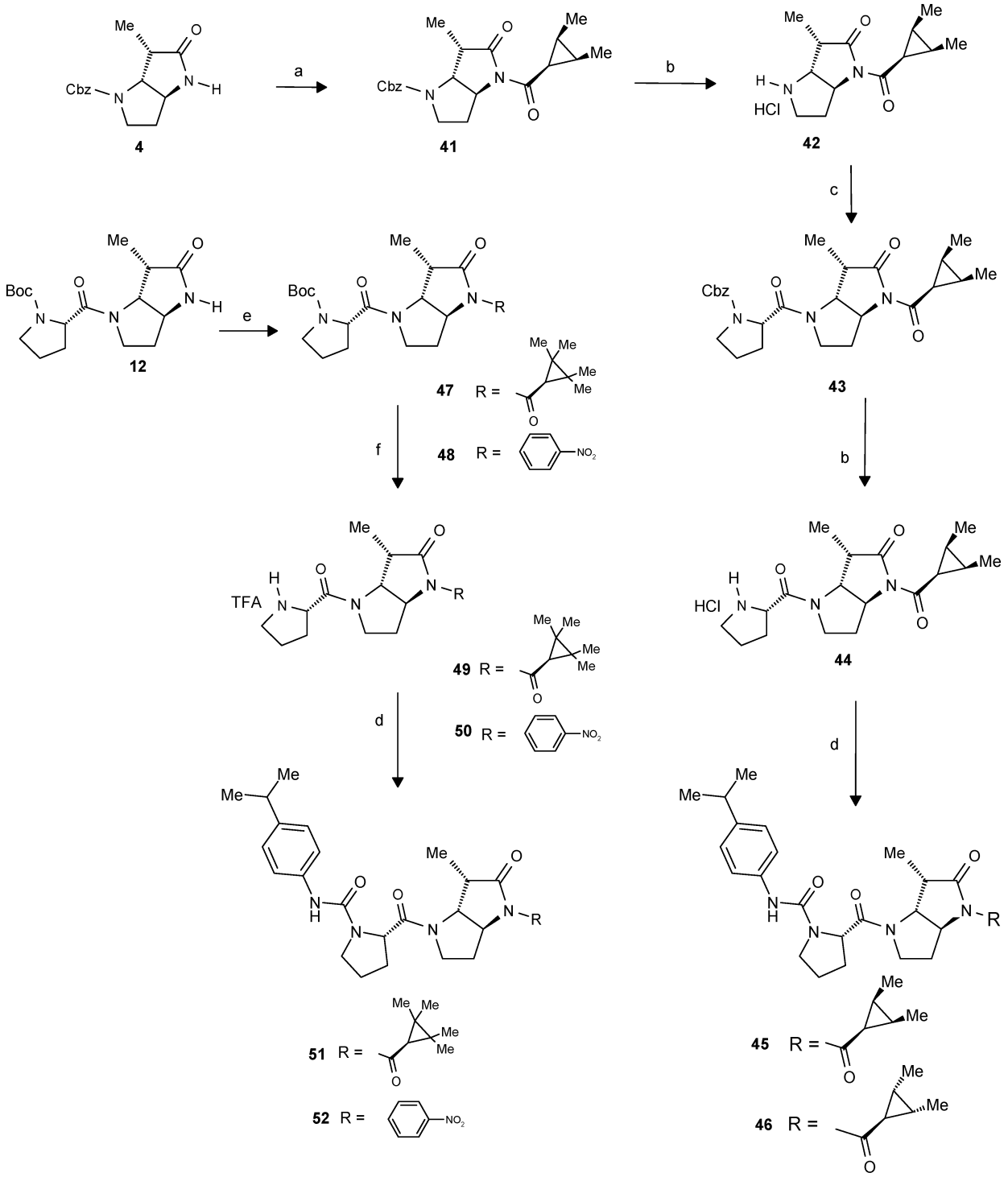


[a] Reagents and conditions: (a) RSO_2Cl, (1.1−1.5eq), Et_3N, MeCN, RT; (b) RCO_2H, TBTU, HOBT, $^iPr_2EtN$, DMF, RT; (c) PhNMeCOCl, Et_3N, MeCN, RT; (d) RN=C=O, Et_3N, MeCN, RT.

mides **1** and **14**−**23** were prepared by reacting the proline **8** with the corresponding sulfonyl chloride at RT in the presence of triethylamine. Similarly **13** was prepared from the ethyl analogue of **8**.[13] Sulfonyl chlorides that were not commercially available were prepared by diazotisation of the corresponding aniline in the presence of SO_2 and CuCl,[10] or by reaction of the sulfonic acid with triphosgene.[11] The reaction of proline **8** with the corresponding aromatic acids in the presence of TBTU/HOBT at room temperature gave the amides **24**−**29**. The ureas **30**−**39** were prepared by reacting **8** with the corresponding isocyanides, while the *N*-methylated urea **40** was prepared in 79% yield by reacting **8** with *N*-methyl-*N*-phenylcarbamoyl chloride in the presence of triethylamine.

The cyclopropyl derivatives (Scheme 4) were prepared by acylating the anions of the lactam **4** and lactam **12** with cyclopropyl carbonyl chloride or the corresponding mixed anhydride. Acylation of the anion of the chiral lactam **4** with (c-2, c-3-dimethylcyclopropyl-r-1-carboxylic) anhydride gave the dimethylcyclopropanyl derivative **41** in 96% yield. Deprotection of **41** with hydrogen in the presence of 10% of palladium on carbon gave the amine **42** in 92% yield, which was then coupled with Cbz-(*S*)-proline to give the protected proline **43** in 70% yield. Deprotection of **43** with hydrogen in the presence of 10% of palladium on carbon gave the amine **44** in 96% yield, which was reacted with 4-(isopropyl)phenyl isocyanate in the presence of triethylamine to give the urea **45** in 47% yield. A similar sequence of reactions starting from **4** and (t-2, t-3-dimethylcyclopropyl-r-1-carboxylic) anhydride gave the t-2, t-3-dimethylcyclopropyl-r-1-carbonyl derivative urea **46**.[15] Similarly reaction of the Boc protected lactam **12** with tetramethylcyclopropanecarboxylic anhydride gave **47** in 68% yield, which was carried through to the urea **51** via the proline **49** in a manner similar to **45** (Scheme 4). Reaction of the lactam **12** with 4-nitrobromobenzene under Cu

Scheme 4[a]

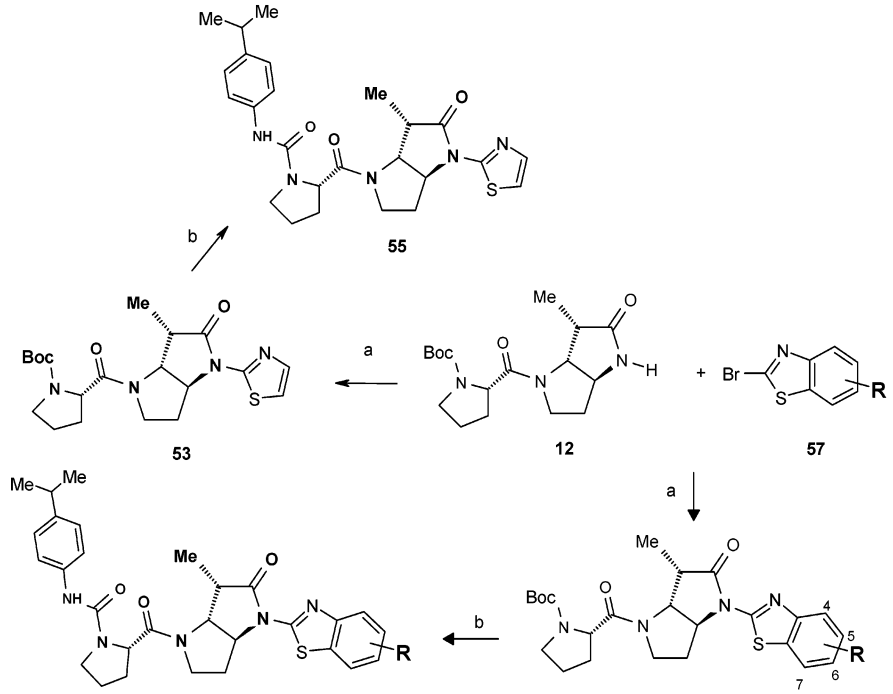


[a] Reagents and conditions: (a) LHMDS (1.4eq)/THF, −78 °C then (diMecyclopropylCO)(Me_3CO)O; (b) 10% Pd/C (Degussa, 50% H_2O), isoPrOH, 2 h, RT, then HCl (1.1eq) Et_2O; (c) Cbz-(*S*)-proline, TBTU, HOBT, $^iPr_2EtN$, DMF, RT; (d) 4-$Me_2CHC_6H_4N{=}C{=}O$, Et_3N, MeCN, RT; (e) LHMDS (1.4eq)/THF, −78 °C then (tetraMecyclopropylCO)(Me_3CO)O or CuCl, K_2CO_3, TDA-1, *p*NO_2PhBr, *p*Xylene; (f) TFA, 1 h, RT;

catalysis using modified Goldberg conditions[16] (CuCl/TDA-1/K_2CO_3/xylene/Δ) gave the N-aryl lactam **48** in 65% yield. Similarly **53** and **54** were prepared (Scheme 5) in 37% and 47% yield, respectively, by reacting **12** with 2-bromothiazole and 2-bromobenzothiazole. Deprotection of **48** with trifluoroacetic acid gave the amine **50** in quantitative yield, which reacted with 4-(isopropyl)phenyl isocyanate to give the urea **52** in 49% yield. Similarly deprotection of **53** and **54** with trifluoroacetic acid gave **55** and **56** in 87% and 85% yield, respectively.

The substituted benzothiazole derivatives **58**−**71** were prepared by reacting lactam **12** with the corresponding substituted bromobenzothiazole **57** under Cu catalysis using modified Goldberg conditions.[16] Deprotection of **58**−**71** with trifluoroacetic acid and reaction of the resulting prolines with 4 -(isopropyl)phenyl isocyanate

Scheme 5[a]



R =

56 H
72 6-CH_2OH
73 4-MeO
74 5-Cl
75 6-MeO-7-aza
76 4-MeO-7-Me
77 6-MeO
78 4-Cl
79 5-MeO
80 5-SO_2CHF_2
81 6-NO_2
82 6-OCF_3
83 6-F
84 6-CO_2Et
85 7-aza

R =

54 H
58 6-$CH_2OTBDPS$
59 4-MeO
60 5-Cl
61 6-MeO-7-aza
62 4-MeO-7-Me
63 6-MeO
64 4-Cl
65 5-MeO
66 5-SO_2CHF_2
67 6-NO_2
68 6-OCF_3
69 6-F
70 6-CO_2Et
71 7-aza

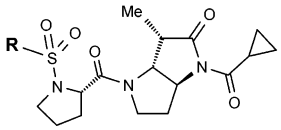
[a] Reagents and conditions: (a) CuCl, 2-bromoheterocycle, TDA-1, K_2CO_3, xylene, Δ; (b) TFA, then 4-Me_2CH-C_6H_4NCO, Et_3N, MeCN, RT.

in the presence of triethylamine gave the corresponding ureas **72**−**85** (Scheme 5).

Results and Discussions

Functionalization at the Pyrrolidine Nitrogen. Previously we had shown that the conformationally restricted, chiral, dansyl-*S*-proline α-methyl-5, 5′-*trans*-lactam **1** (K_i = 20nM) (Table 1) had high potency against human cytomegalovirus (HCMV) protease.[9] To reduce the overall molecular weight, the first part of our lead exploration focused on whether the bicyclic ring and the dimethylamino functionality of the dansyl group are essential for activity. Removal of the 5-NMe_2 group to give the unsubstituted 1-naphthyl derivative **15** (K_i = 60nM) caused a loss in potency, and no improvement was obtained with the unsubstituted 2-naphthyl derivative **16** (K_i = 40nM). Moving the NMe_2 group to the 6-position **14** caused a larger loss in potency, indicating that this group is not tolerated an this position. Removal of either ring from the unsubstituted 1-naphthyl derivative **15** (K_i = 60nM) to give the phenyl derivative **18** or the benzyl analogue **17** caused a large loss of potency. However, modeling indicated that the space occupied by the 5-NMe_2 on the naphthalene ring could be occupied by 4-substitution of a monocyclic phenyl ring. It was found that additional binding could be gained by having a medium-sized, hydrophobic group at this position, illustrated by the greater potency of the 4-isopropyl **20** over the unsubstituted phenyl derivative **18** (Table 1). Also the 4-isopropoxy **21** (K_i = 39nM) was equivalent in terms of potency to the 2-naphthalene derivative **16** (K_i = 40nM). However, moving the isopropoxy group to the 3-position **22** caused a large loss in activity, while the 4-propoxy **23** (K_i = 33nM) illustrates that for high potency, it is not essential to have the fused bicyclic ring that is present in the lead dansylproline derivative **1**. Hence, increasing the size of the 4-substitutent increased potency in the order H < Me_2CH < $Me_2CHO \equiv MeCH_2CH_2O$.

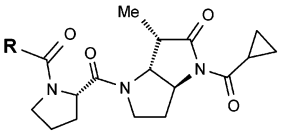
Table 1. Pyrrolidine-5, 5′-*trans*-Lactam Sulfonamide Inhibitors of HCMV Protease



		HCMV protease[a]	
compd	R	IC_{50} (μM)[17]	K_i (nM)[17]
1	5-NMe_2-naphth-1-yl	0.34	20
14	6-NMe_2-naphth-1-yl	1.1	
15	naphth-1-yl	0.37	60
16	naphth-2-yl	<0.19	40
17	$PhCH_2$−	2.1	
18	Ph−	1.8	
19	4-Cl-Ph−	0.84	
20	4-Me_2CH-Ph−	0.46	99
21	4-Me_2CHO-Ph−	0.40	39
22	3-Me_2CHO-Ph−	65	
23	4-$MeCH_2CH_2O$-Ph−	0.23	33

[a] HCMV *p*NA assay.[9]

Table 2. Pyrrolidine-5,5′-*trans*-Lactam Carboxamide Inhibitors of HCMV Protease



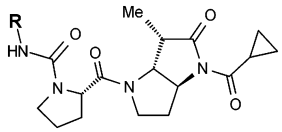
		HCMV protease[a]	
compd	R	IC_{50} (μM)[17]	K_i (nM)[17]
24	5-Cl-3-Me−benzothien-2-yl	0.19	2
25	4-Ph-Ph−	0.30	21
26	4-Me_2CH-Ph−	0.39	
27	4-$MeCH_2CH_2O$-Ph−	0.54	79
28	naphth-1-yl	0.89	
29	4-Cl-Ph−	1.4	

[a] HCMV *p*NA assay.[9]

Having achieved potency with monocyclic sulfonamides, we investigated changing the linker to carboxamide. In general the monocyclic carboxamide (Table 2) were less active than the monocyclic sulfonamides. This is possibly due to a shorter linker between the proline and aromatic rings preventing access of the latter into the hydrophobic binding pocket thought to be necessary for activity. This can be seen by comparing the 4-chlorophenyl, the naphth-1-yl, and 4-propoxyphenyl derivatives **29**, **28**, and **27** of the carboxamide (Table 2) with the corresponding derivatives in the sulfonamide series **19**, **15**, and **23** (Table 1), the exception being the isopropyl derivatives **20** and **26**, which have similar potency. The lower activity of the carboxamide could be overcome by increasing the lipophilic bulk around the aromatic group, as illustrated to the larger 5-chloro-3-methyl-benzothienyl-2-carboxamide derivative **24**.

We further investigated extending the length of the linker by changing from carboxamide and sulfonamide to urea in the monocyclic series in an effort to increase potency. In general the monocyclic ureas (Table 3) were more active than the carboxamide and sulfonamides, possibly due to the longer linker between the proline and aromatic rings allowing further access of the latter into the hydrophobic binding pocket.

Table 3. Pyrrolidine-5,5′-*trans*-Lactam Urea Inhibitors of HCMV Protease



		HCMV protease[a]	
compd	R	IC_{50} (μM)[17]	K_i (nM)[17]
30	4-Me_2CH-Ph−	0.20	2
31	4-$MeCH_2CH_2O$-Ph−	0.21	9
32	4-CF_3-Ph−	0.23	15
33	4-Me_2CHO-Ph−	0.18	18
34	4-Cl-Ph−	0.26	38
35	naphth-1-yl	0.65	
36	2-Me_2CH-Ph−	0.47	
37	3-CF_3-Ph−	0.59	
38	3-Cl-Ph−	0.65	
39	Ph−	1.4	

[a] HCMV *p*NA assay.[9]

Removing the second ring in the 1-naphthyl derivative **35** to give the phenyl derivative **39** resulted in a loss in potency; however, compounds with increased potency relative to the 1-naphthyl derivative **35** could be obtained by increasing the size of the 4-substituent in the phenyl series as shown by moving from the chloro derivative **34** (K_i = 38nM) to the trifluoromethyl derivative **32** (K_i = 15nM) to the *n*-propoxy derivative **31** (K_i = 9nM) to the isopropyl derivative **30** (K_i = 2nM). Moving the chloro substituent in **34** and trifluoromethyl substituent in **32** to the 3 positions in **38** and **37**, respectively, caused a loss of activity, as did moving the isopropyl substituent in **30** to the 2 position in **36**.

Compared to the dansylproline series, the 4-substituted phenyl ureas have two advantages, reduced molecular weight and increased solubility. The SAR established for inhibition of HCMV protease have shown that in the substituted proline *trans*-lactams, the 4-substituted phenyl ureas > 4-substituted phenyl sulfonamides > 4-substituted phenyl carboxamides in terms of potency (Table 4).

Generally, the urea series looked the most promising, with **30** showing the highest potency against the enzyme (IC_{50} = 0.2μM, K_i = 2nM) (Table 3). It is noteworthy that when **30** was assayed with 0 min as well as the normal 15 min preincubation time the IC_{50} values in the *p*NA assay were closely similar (0.24μM and 0.20μM respectively), indicating rapid binding and inhibition of the enzyme. This has been confirmed by ESI-MS studies showing that the compound rapidly acylates HCMV protease, giving 90% of the acyl−enzyme complex after 5 min, and remaining 58% acylated after 24 h (Figure 1). This stability of the acyl−enzyme complex is higher than that of other cyclopropylcarbonyl *trans*-lactams.[14] Interestingly, methyl substitution on the urea nitrogen in **39** (IC_{50} = 1.4μM) to give derivative **40** (Scheme 3) leads to a complete loss of activity (IC_{50} = >20μM). This could be due to an altered conformation of the rigid urea linker, or the methyl group could make an unfavorable contact with the enzyme.

Plasma Stability. The most potent monocyclic urea is the 4-isopropyl-phenyl urea **30**, however it is unstable in human plasma ($t_{1/2}$ < 1 h). Recently we have achieved

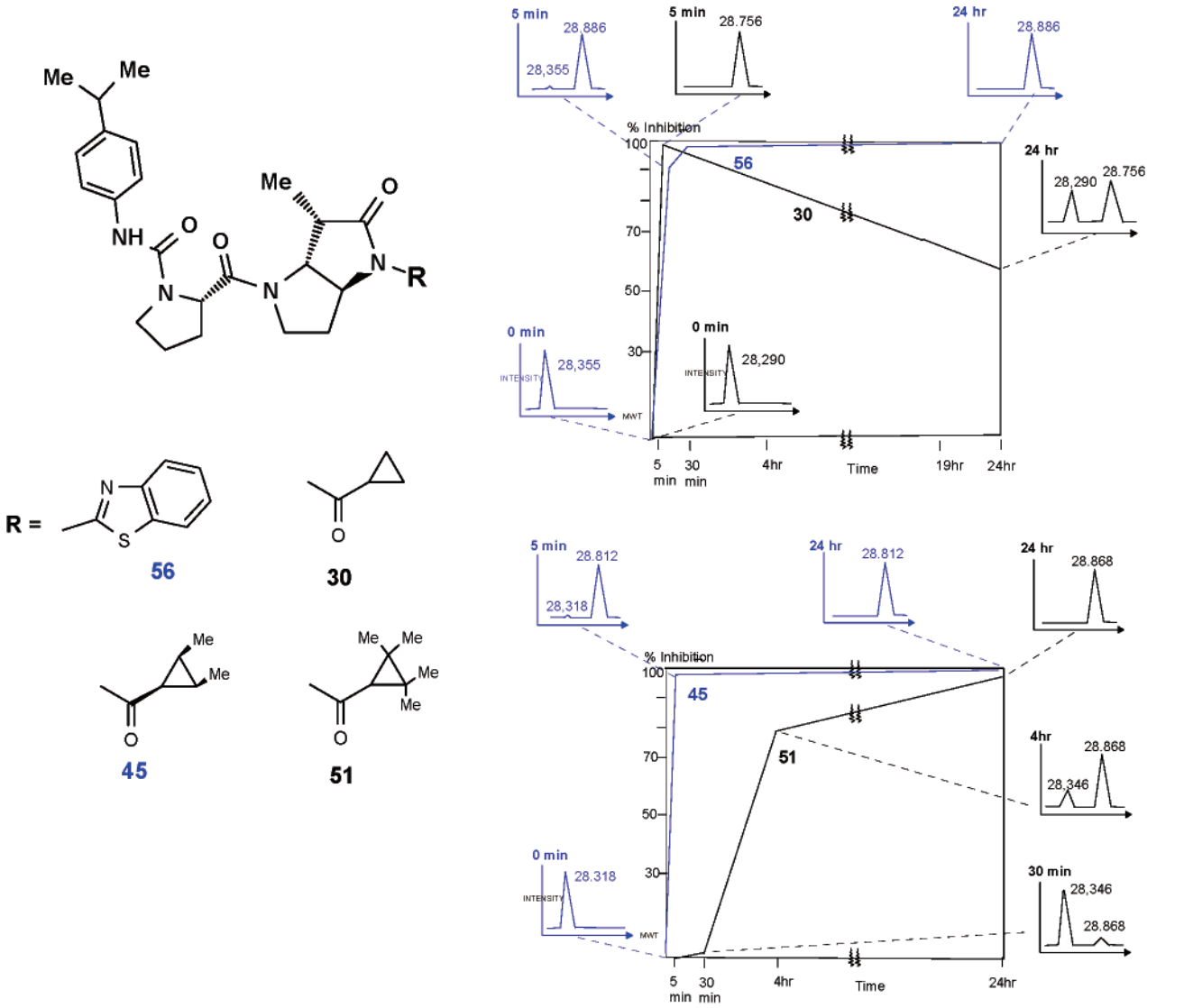
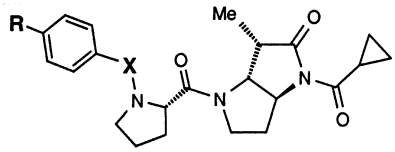
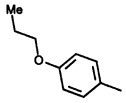


Figure 1. MS characterization of the acylation of HCMV δAla protease by α-methyl-pyrrolidine-5,5′-*trans*-lactams.

Table 4. Variation in Potency of Pyrrolidine-5,5′-*trans*-Lactam Inhibitors of HCMV Protease with Aryl to Proline Ring Linkage

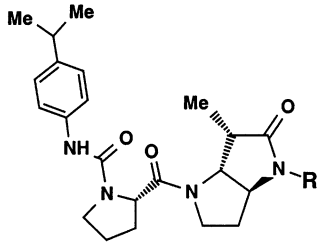


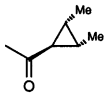
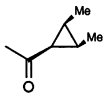
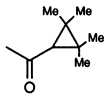
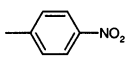
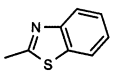
R	HCMV Protease [a]	X		
		NHCO	SO_2	CO
	IC_{50} (μM)[17]	0.26	0.84	1.4
	K_i (nM)[17]	9	33	79

[a] HCMV *p*NA assay.[9]

success[14] in increasing stability to human plasma, while retaining potency against HCMV protease, in the dansylproline series of α-methyl pyrrolidine-5,5′-*trans*-lactams. This strategy has been applied to the 4-subtituted phenyl urea series (Table 5). Two approaches were pursued, one was to sterically hinder the approach of the hydrolytic plasma enzymes to the lactam carbonyl, and the other was to make the lactam carbonyl less reactive by making the lactam nitrogen substituent less electron withdrawing. Substitution of the cyclopropyl ring with methyl groups increased the plasma stability of these acyl derivatives in the order cyclopropyl carbonyl < t-2, t-3-dimethylcyclopropyl-r-1-carbonyl < c-2, c-3-dimethylcyclopropyl-r-1-carbonyl < 2,2,3,3-tetramethylcyclopropyl carbonyl. However, although the t-2, t-3-dimethylcyclopropyl-r-1-carbonyl derivative **46** is slightly more stable ($t_{1/2}$ = 1.5 h) than **30**, it is significantly less active, whereas the tetramethylcyclopropyl derivative **51**, which is >16 times more stable, is considerably less active (>100 fold). A better balance is achieved with the c-2, c-3-dimethylcyclopropyl-r-1-carbonyl derivative **45** that is > 6 times more stable than the cyclopropyl derivative **30** while retaining good potency. Replacing the cyclopropyl carbonyl substituent with an electron withdrawing aryl or heterocyclic ring dramatically increased stability to human plasma ($t_{1/2}$ >24 h) in this series (Table 5). However, even though the 2-thiazole **55** is more potent than the 4-nitrophenyl derivative **52**, both are significantly less active than **30**. In contrast, the benzothiazole **56** had comparable potency to **30** with a K_i = 10 nM. Although the thiazole

Table 5. Human Plasma Stability, Inhibition of HCMV Protease and HCMV Antiviral Activity of Chiral Pyrrolidine-5, 5′-*trans*-Lactam Analogues



compd	R	human Plasma Stability,[a] $t_{1/2}$ (*hr*)	HCMV protease[b] IC_{50} (μM)[17]	HCMV protease[b] K_i (nM)[17]	HCMV[c] strain AD169 IC_{50} μM	cytotoxicity[d] $CCID_{50}$ μM
30		0.5	0.2	2.4	31	274
46		1.5	1.8		>30	375
45		6	0.3	16	10	219
51		16	>20		>35	38
52		> 24	8.7		>70	69
55		> 24	1.5	446	>30	280
56		> 24	0.18	10	5	>500

[a] Tested in fresh human plasma 100 μM[14]. [b] HCMV *p*NA assay.[9] [c] HCMV Elisa assay (see experimental). [d] Vero cell cytotoxicity assay.[12]

Table 6. Selectivity of Pyrrolidine-5,5′-*trans*-Lactam Inhibitors for HCMV Protease Compared to Mammalian Serine Proteases

	thrombin	acetylcholine esterase	elastase	HCMV protease[a]	
	IC_{50} μM	IC_{50} μM	IC_{50} (μM)	IC50 (μM)[17]	K_i (nM)[17]
56	>200	>100	>10	0.18	10
45	>200	>100	>10	0.30	16

[a] HCMV *p*NA assay.[9]

and the benzothiazole groups have similar electron withdrawing properties, the greater potency of benzothiazole **56** compared to thiazole **55** is probably due to the greater hydrophobic contact of the former making a better fit in the S1′pocket (see Modeling section).

Selectivity and Mechanism of Action. The 4-isopropylphenylurea-(*S*)-proline-*trans*-lactams **56** and **45** show selectivity for the viral HCMV protease (Table 6) over acetylcholine esterase and the mammalian proteases elastase and thrombin by at least 2 orders of magnitude, showing no significant activity against these enzymes at the concentrations tested.

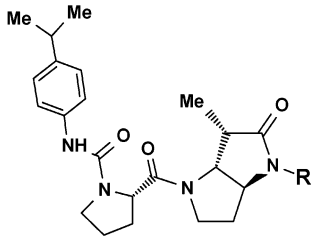
MS Analysis of the Acylation of HCMV protease. Comparison of the plasma stability's of the compounds (Table 5) with the rates at which the compounds acylate the enzyme and the rates at which the acyl−enzyme complexes are deacylated (Figure 1) enables the following general conclusions to be drawn.

Compounds that have poor plasma stability (e.g., **30**) produce an acyl−enzyme that shows significant turnover during a 24h incubation period. By contrast, compounds with greater plasma stability (e.g., **45**, **51**, and **56**) generate acyl−enzymes that show no turnover in 24h.

Most compounds studied acylated the enzyme rapidly under the conditions used; acylation of the enzyme was normally complete within 5 min. However, the tetramethylated cyclopropylcarbonyl **51** acylated the enzyme much more slowly. Less than 5% of the enzyme was acylated within 30 min, and even after 4h 25% was still unacylated, although by 24 h the enzyme was fully acylated. The reason for the slow acylation of HCMV protease by **51** has not been investigated further, but it may well be due to the presence of the four methyl groups sterically hindering the approach of the compound to the active site serine residue.

Antiviral Activity. Because HCMV cellular assays require 7 days to complete, plasma unstable compounds did not initially show antiviral activity. Studies have since shown that a modified ELISA technique(see experimental), delaying the single addition of compounds to 48 h post infection (hpi), is suitable for the titration of both stable and unstable *trans*-lactams for activity against HCMV. Parallel comparisons with plaque reduction assays[12] yield similar IC_{50} values for stable *trans*-lactams, but not for the plasma labile analogue **1**. The technique has the additional advantage of providing an exposure time of the cells to the drug equal to the Vero cytotoxicity assay.[12] Of the five plasma

Table 7. Human Plasma Stability, Inhibition of HCMV Protease and HCMV Antiviral Activity of Chiral Pyrrolidine-5,5′-*trans*-Lactam Benzothiazole Analogues



			HCMV protease[b]			
compd	R	human plasma stability,[a] $t_{1/2}$ (hr)	IC_{50} (μM)[17]	K_i (nM)[17]	HCMV[c] strain AD169 IC_{50} (μM)	cytotoxicity[d] $CCID_{50}$ (μM)
56	H	>24	0.18	10	5	>500
76	4-MeO-7-Me	>24	1.1		17.4 pl	126
78	4-Cl		0.29	41	17.1	>500
73	4-MeO		0.24	38	5.2	89
74	5-Cl		0.46	27	49	266
80	5-SO_2CHF_2		0.21	10	2.2 pl	>500
79	5-MeO		0.23	22	2.4 pl	>500
83	6-F	>24	0.36	17	12.3	298
81	6-NO_2	24	0.39	25	8.7	128
84	6-CO_2Et	9	0.35	7.4	5.1	>500
82	6-OCF_3	11	0.46	20	5.3	>500
77	6-MeO	>24	0.22	43	3.2	>500
72	6-CH_2OH	>20	0.31	40	0.52	125
85	7-aza	8	0.29	21	3.6	<31
75	6- MeO-7-aza	9	0.87	117	31 pl	>500
	ganciclovir	–	–		0.72 pl	>500

[a] Tested in fresh human plasma 100 μM.[14] [b] HCMV *p*NA assay.[9] [c] HCMV Elisa assay (see experimental). pl = IC_{50} in antiviral plaque reduction assay.[12] [d] Vero cell cytotoxicity assay.[12]

stable compounds **45**, **51**, **52**, **55**, and **56**, (Table 5) only **45** and **56** had antiviral activity, showing that low nM potency against HCMV protease and sufficient plasma stability are required to obtain low μM activity against the virus in whole cells (Table 7). A variety of substituted benzothiazoles was prepared in an attempt to increase potency against the protease and antiviral activity. In general, potency against the HCMV protease is greater with electron-withdrawing groups and less with electron-donating groups; however, most derivatives were less active than the unsubstituted parent **56**. Also replacing the benzothiazole in **56** by 7-pyridothiazole to give **85** had no significant effect on protease activity. The best HCMV protease inhibitors were the 6-CO_2Et derivative **84** (K_i = 7.4nM) and 5-SO_2CHF_2 derivative **80**(K_i = 10 nM), which were similar to **56**. Modeling suggests that this is because these benzothiazoles make no extra interactions in the "canyon" at S1′ (see Modeling section). The disubstituted 4-OMe-7-Me benzothiazole **76** was 5-fold less active than the 4-OMe analogue **73**, indicating that the 7-Me substitution prevents the efficient binding of the benzothiazole ring in the canyon at S1′. Also, the 6-OMe analogue **75** of the 7-*aza* derivative **85** was 5-fold less active than the parent. In general potency against the protease does not translate to the in vitro HCMV antiviral assay, possibly because the extent of penetration of both the cellular and nuclear membranes to reach the target protease varies for each compound. Substitution on the benzothiazole ring at the 4, 5, 6, or 7 positions with electron-donating or -withdrawing groups had only a small effect on anti-viral potency (IC_{50} = 2.2−19 μM) compared to the unsubstituted parent. Only four analogues, 5-OMe **79**, 5-SO_2CHF_2 **80**, 6-OMe **77**, and 6-CH_2OH **72**, were more potent as antivirals than the parent **56**. Also the analogues 4-OMe **73** and 7-pyridyl **85** were toxic to Vero cells. The 6-CH_2OH analogue **72** designed to interact with Asn 62 at S1′ has no increase in potency against the protease but possess submicromolar activity (IC_{50} = 0.5μM) against the virus and is equivalent in potency to ganciclovir.

Modeling. The crystal structure of HCMV protease was obtained recently and used to model the conformationally restricted, chiral, dansyl-(*S*)-proline-α-methyl-5,5-*trans*-lactam **1** into the active site groove of the enzyme.[9] Similarly we have modeled our antiviral, plasma stable, 4-isopropylphenylurea-(*S*)-proline benzothiazole analogue **56** into the active site groove of HCMV protease, in what could be considered as an initial binding complex (Figure 2).

Both **1** and **56** can make a lot of similar interactions with HCMV protease when modeled into the active site. In both, the C-1 *trans*-lactam carbonyl is situated in the oxyanion pocket formed by the backbone amide NH of arginine 165 and arginine 166, and it is in position for attack by the hydroxyl of serine 132, which is part of the active-site catalytic triad formed by serine 132, histidine 63, and histidine 157. The lactam substituent extends into the prime sites of the enzyme. The model shows that α-Me in the (*S*)-configuration is easily accommodated in the S1 pocket, as expected from the substrate requirements of a conserved alanine at this position for this enzyme. However, different length, rigidity, hybridization, and directional aspects of substituents on the proline and lactam nitrogens of **1** and **56** account for the greater potency of the latter and are seen in their different interactions with HCMV protease. The urea carbonyl oxygen in **56** is capable of forming a

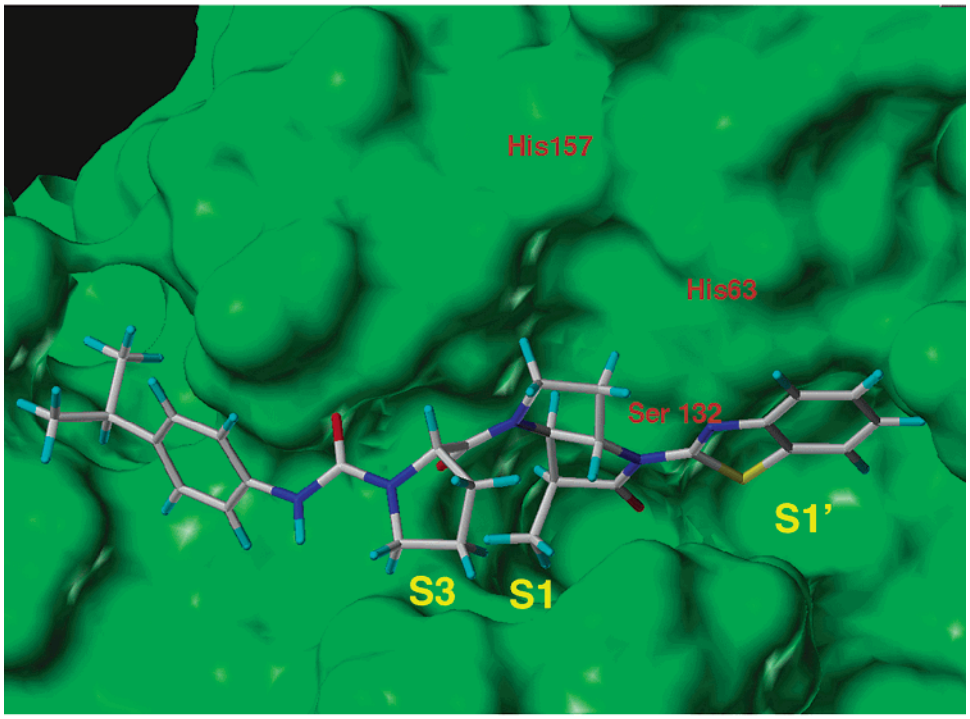


Figure 2. HCMV protease active site and inhibitor **56**.

Table 8. Pharmacokinetics of **56** in Dog and Guinea Pig

56	C_{max} (ng/mL)	T_{max} (h)	AUC0-t (ng mL^{-1} h^{-1})	AUC0-inf (ng mL^{-1} h^{-1})	$t_{1/2}$ (h)	CL (mL min^{-1} kg^{-1})	V_{dss} (L/kg)	F (%)
dog	5480	0.08	9660	9750	1.5	8	0.8	29
guinea pig	32000	0.08	2210	2230	1	60	1.6	-

hydrogen bond to the backbone NH of Ser135, which is performed by one of the sulfonamide oxygen's present in **1**. The *trans*-lactam of **56** fits better into the very shallow S2 pocket compared with the same region of the *trans*-lactam moiety in **1**. The (*S*)-proline carbonyl oxygen in **56** is almost within hydrogen bonding distance of Arg166 (2.95Angstrom), whereas the same carbonyl oxygen in **1** is almost 3.8 Å away. The 4-isopropylphenyl ring of **56** fits further into the P4 pocket than the 5-dimethylaminoaryl ring of the dansyl group in **1**. Similarly the benzothiazole of **56** fits further into the P1′ pocket than the cyclopropylcarbonyl of **1**.

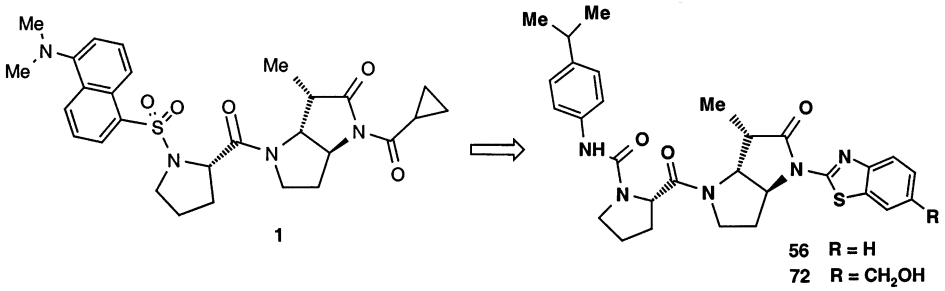
Inspection of our inhibitor **56** at S1 indicated that a group larger than methyl at this position may be tolerated. However preparation of the dansylproline *trans*-lactam **13**[13] ($IC_{50} \geq 100$ μM) with ethyl at this position resulted in >300-fold loss of potency compared to the corresponding methyl analogue **1** ($IC_{50} = 0.35$ μM). Longer preincubation times, up to 24 h, did not result in significant improvement on the inhibition of HCMV protease by **13** (3% at 30 min to 42% at 24 h at 100 μM concentration). Substitution of the ureas NH in the phenylurea **39** ($IC_{50} = 1.4$ μM) with NMe **40** ($IC_{50} \geq 20$ μM) leads to a complete loss of activity. This could be due to an altered conformation of the rigid urea linker, or the methyl group could make an unfavorable contact with the enzyme. Modeling suggests that although no untoward interaction is seen with the protein in noncovalent docking, as **40** approaches closer to the covalent mode the urea N-Me substituent would be likely to cause a severe steric clash in the region of Glu31.

The energy minimized semi-rigid *trans*-lactam proline urea **56** docked into the active site of the enzyme fits round the "nose" of the enzyme. This enables the proline ring, via its rigid urea linker, to position the *para*-substituted aromatic ring into the S4 pocket, which is occupied by tyrosine at P4 in the natural substrate. Part of the proline ring occupies the S3 pocket.

The benzothiazole function extends into the S′ prime sites of the enzyme. The benzothiazole makes a better hydrophobic interaction in the S1 pocket than the smaller thiazole, which accounts for its greater potency (Table 5). However, the disubstituted 4-OMe-7-Me benzothiazole **76** was 5-fold less active than the 4-OMe analogue **73**. Modeling suggests that although no untoward interaction is seen between **76** and the protease in the noncovalent docking, as **76** approaches closer to the covalent mode the substitution at the 7-position would cause sterically undesirable clashes with the protease, since the molecule lies much deeper in the P1′ pocket. A variety of substitutions on the benzothiazole ring at the 4, 5, 6, or 7 positions had little positive effect on protease activity. Even the 6-CH_2OH analogue **72** designed to interact with Asn 62 at S1′ had no increase in potency against the protease. Modeling suggests that this is because these benzothiazoles make no effective extra interactions in the active site at S1′.

Pharmacokinetics. The pharmacokinetics of the benzothiazole **56** was determined in the dog after intravenous administration. It had a low plasma clearance (8 mL min^{-1} kg^{-1}), a moderate volume of distribution (0.8 L/kg), a half-life of 1.5 h, and a reasonable bioavailability after oral dosing (29%) (Table 8). The

Table 9. Plasmas Stability, HCMV Protease and Antiviral Activity of **56** and **72**, and Pharmacokinetics of **56** in Dog



					dog			
compd	human plasma stability,[a] $t_{1/2}$ (hr)	HCMV protease[b] K_i (nM)[17]	HCMV[c] strain AD169 IC_{50} (μM)	cytotoxicity[d] $CCID_{50}$ (μM)	$t_{1/2}$ (hrs)	V_{dss} (L/kg)	CL (mL min^{-1} kg^{-1})	F (%)
56	>24	10	5	490	1.5	0.8	8	29
72	>24	16	0.5	125				

[a] Tested in fresh human plasma 100 μM[14]. [b] HCMV *p*NA assay.[9] [c] HCMV Elisa assay (see experimental). [d] Vero cell cytotoxicity assay.[12]

pharmacokinetics was also determined in the guinea pig after intravenous administration (Table 8). Furthermore, since the compound is a potential treatment for infection of the CNS and the retinitis caused by HCMV, the ability of **56** to access the brain and the eye was also investigated in this study. Although **56** had a reasonable half-life in the guinea-pig (1 h) and a moderate volume of distribution (1.6 L/kg), it had a high plasma clearance (60 mL/min/kg). Despite this high clearance, drug levels were measurable in both the brain and the vitreous humor. These declined in a biexponential manner with a half-life of approximately 0.5 h in both tissues. The plasma:brain ratio was 1:5, while the plasma:vitreous humor ratio was 1:2, indicating that the drug gains access to both tissues.

Conclusions

The chiral, dansyl-(*S*)-proline-(*SRS*)-α-methyl-5,5′-*trans*-lactam **1** was defined [9] previously as the required template for nanomolar potency against HCMV δAla protease. We have now developed the SAR for the substituent on the (*S*)-proline and have shown that a single 4-substituted phenyl ring is sufficient for good potency against HCMV δAla protease, and the potency increases in the order CO < SO_2 < NHCO for the linker from this 4-substituted phenyl ring to the (*S*)-proline. The optimal (*S*)-proline substituent was found to be the 4-isopropylphenylurea. Plasma stability has been optimized in the 4-isopropylphenylurea-(*S*)-proline series, while retaining low nanomolar potency against HCMV δAla protease, by modifying the substituents on the lactam nitrogen to give the c-2, c-3-dimethylcyclopropyl-r-1-carbonyl derivative **45** and the benzothiazole derivative **56**. ESI/MS studies have revealed that the plasma stable *trans*-lactams **45** and **56** rapidly acylate HCMV protease and the enzyme remained fully acylated after 24 h. SAR studies have shown that plasma stability and low nM potency against HCMV δAla protease are required to give antiviral activity in whole cells. Both **45** and **56** have low nM potency against the viral protease and micromolar antiviral activity against HCMV. The crystal structure of HCMV protease was obtained and used to model the conformationally restricted, chiral, 4-isopropylphenylurea-(*S*)-proline-(*SRS*)-α-methyl-5,5′-*trans*-lactam benzothiazole **56** into the active site groove of the enzyme enabling us to direct and rationalize the SAR in this series. Developing the SAR in the substituted benzothiazoles produced the 6-hydroxymethyl benzothiazole **72**, which has an in vitro antiviral potency equivalent to ganciclovir. Both plasma stable, benzothiazole *trans*-lactams **56** and **72** are potent inhibitors of HCMV protease in the low nM range and have low micromolar potency against the HCMV virus and a good therapeutic index (≥100) (Table 9), and are (>100) selective for the viral protease (HCMV) over the mammalian proteases elastase and thrombin and also acetylcholine esterase. Also **56** has a good PK profile in the dog with an oral bioavailability of 29% and good CNS and ocular penetration in the guinea pig.

General Procedures

Melting points were obtained using an Electrothermal digital melting point apparatus and are uncorrected. All purifications by flash chromatography were performed using Kieselgel 60, Merck 9385 silica gel. Preparative plate chromatography was performed using Whatman PK6F silica gel 60A plates eluting with ethyl acetate−cyclohexane mixtures. Monitoring of reactions by TLC used Merck 60 F254 silica gel glass backed plates (5 × 10 cm), eluted with mixtures of ethyl acetate and cyclohexane, and visualized by UV light, followed by heating with aqueous phosphomolybdic acid. Analytical HPLC were run on a Hewlett-Packard 1090 HPLC instrument, equipped with an Intersil M column ODS2. Standard conditions were eluent system A (H_2O, 0.1% H_3PO_4), B (95% MeCN/H_2O, 0.1% H_3PO_4): gradient 0% B 2 min, 0−100% B 40 min, 100% B 10 min; flow rate = 1 mL/min, λ = 215 nm). Retention times (t_r) are given in minutes. LCMS were run on a Hewlett-Packard 1050 coupled with a Micromass Platform II equipped with a Supelco ABZplus column. Standard conditions were eluent system A (H_2O, 0.1% formic acid, 10 mmol ammonium acetate) B (MeCN, 0.05% formic acid): gradient **1** 100% A 0.7 min, 100% A−100% B 3.5 min, 100% B 3.5 min, 100% to 0% B 0.3 min; flow rate = 1 mL/min). Gradient **2** 100%A 0.7 min, 100% A−100% B 4.2 min, 100% B 1.1 min, 100% to 0% B 0.2 min; flow rate = 1 mL/min). Gradient **3** 100% A 3 min, 100% A−100% B 20 min, 100% B 5 min, 100% to 0% B 2 min; flow rate = 1 mL/min). All NMR spectra were run on a Bruker 250 MHz instrument generally as solutions in $CDCl_3$ unless otherwise stated. IR spectra were recorded on a Bio-rad FTS7 spectrometer from thin films on NaCl plates, a KBr mix or solutions in the solvent specified. Mass spectra were run by an electrospray Hewlett-Packard 5989B instrument. CD spectra were recorded in acetonitrile on a Jasco J-720A spectropolarimeter. Final organic solutions were dried over $MgSO_4$

before filtration and evaporation using a Buchi Rotavapor. Ambient temperature was 20 °C. All solvents used were Fisons analytical reagents except for pentane (Aldrich Chemical Co.) and anhydrous THF (Fluka sureseal). All other reagents were usually obtained from Aldrich, Fluka or Lancaster. Elemental microanalyses were determined by the Microanalytical Laboratory, GlaxoSmithKline Stevenage.

Benzyl (3a*S*,6*S*,6a*R*)-4-(Cyclopropylcarbonyl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrole-1(2*H*)-carboxylate (5). To a solution of **4**[9] (922 mg, 1 equiv, 2.75 mmol) in dry tetrahydrofuran (7 mL) at −78 °C under nitrogen was added 1M LHMDS solution in tetrahydrofuran (3.3 mL, 1.2 equiv, 3.3 mmol), keeping the temperature below −70 °C. The solution was kept at −78 °C for 10 min, then at 0 °C for 10 min, and recooled to −78 °C; cyclopropanecarbonyl chloride (0.75 mL, 3 equiv, 8.25 mmol) was added, and the reaction mixture was then stirred at −78 °C for 1 h. The reaction mixture was quenched with saturated aqueous ammonium chloride (25 mL) and then allowed to warm to room temperature. Water was added (20 mL), and then the aqueous phase was extracted with ethyl acetate (100 mL), and the combined organic phase was washed with water (30 mL) and brine (30 mL), dried, and evaporated to give a yellow oil. This oil was purified by flash column chromatography eluting with cyclohexanes−ethyl acetate (4:1) to yield **5** (334 mg, 35%) as a pale yellow gum: IR (KBr) ν_{max} 1747, 1713, 1704, 1693, 1681 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36 (s, 5H, C_6H_5), 5.13 (ABq, J = 12.5 Hz, 2H, PhCH_2), 3.93−3.60 (m, 3H, NCH_2CH$_2$, NCHCH$_2$), 3.55−3.44 (m, 1H, NCHCHMe), 3.30−2.80 (m, 2H, CHMe, COCH(CH$_2$)$_2$), 2.75−2.62 (m, 1H, NCH$_2$CHH), 2.05−1.85 (m, 1H, NCH$_2$CHH), 1.30−0.85 (m, 7H, COCH(CH_2)$_2$), and CHMe); MS (thermospray) m/z 343 (MH)$^+$. Anal. ($C_{19}H_{22}N_2O_4$) C, H, N.

(3*S*,3a*R*,6a*S*)-1-(Cyclopropylcarbonyl)-3-methylhexahydropyrrolo[3,2-*b*]pyrrol-2(1*H*)-one hydrochloride (6). A solution of **5** (330 mg, 0.96 mmol) in 2-propanol (30 mL) was added to the palladium catalyst (119 mg, 10% Pd/C, Degussa type, E101, NE/W, 50% H_2O) under nitrogen and the resulting mixture stirred vigorously under an atmosphere of hydrogen for 2.75 h. The catalyst was filtered off under an atmosphere of nitrogen, and a 1 M solution of hydrogen chloride in diethyl ether (1 mL, 1 equiv, 1 mmol) was added to the filtrate. Evaporation of the solvent gave **6** (175 mg, 74%) as a colorless gum: ^{1}H NMR ($CDCl_3$) δ 4.10−3.79 (m, 2H, NCHHCH$_2$ + NCHCH$_2$), 3.37 (dd, J = 11.6 Hz, 6.7 Hz, 1H, NCHHCH$_2$), 3.22−3.05 (m, 1H, NCHCHMe), 2.95−2.75 (m, 2H, CHMe, COCH(CH$_2$)$_2$), 2.07−1.87 (m, 1H, NCHCHH), 1.67−1.56 (m, 1H, NCHCHH), 1.27−0.88 (m, 7H, CHMe, COCH(CH_2)$_2$); MS (thermospray) m/z 209 (MH$^+$), 417 (2MH$^+$). Anal. ($C_{11}H_{16}N_2O_2$) C, H, N.

The following compounds were similarly prepared.

***tert*-Butyl (3*S*,3a*R*,6a*S*)-3-Methyl-2-oxohexahydropyrrolo[3,2-*b*]pyrrole-1(2*H*)-carboxylate hydrochloride (9).** Compound **3**[9] was deprotected with hydrogen in the presence of Pd /C as described for **6** to yield **9** (93%) as a white solid: ^{1}H NMR (d^6-DMSO) δ 9.44 (br s, 1H, NH), 3.93−3.29 (m, 4H, NCH_2CH$_2$, NCHCH$_2$, NCHCHMe), 2.91−2.75 (m, 1H, CHMe), 2.46−2.30 (m, 1H, NCH$_2$CHH), 2.12−1.92 (m, 1H, NCH$_2$CHH), 1.46 (s, 9H, t-Bu), 1.20 (d, J = 7.3 Hz) and 1.04 (d, J = 6.1 Hz) (3H, CHCH_3); LCMS m/z 241 (MH$^+$) single component 100%, gradient 1 (t_R 1.66 min); MS (Thermospray) m/z 481 (2MH$^+$), 241 (MH$^+$), 141 (M-Boc$^+$). HPLC: 95% (t_R 8.5 min). Anal. ($C_{12}H_{20}N_2O_3$.HCl·0.25C_3H_8O) C, H, N.

((3*S*,3a*R*,6a*S*)-1-(Cyclopropylcarbonyl)-3-methyl-4-[(2*S*)-pyrrolidin-2-ylcarbonyl]hexahydropyrrolo[3,2-*b*]pyrrol-2(1*H*)-one hydrochloride (8). Compound **7** was deprotected with hydrogen in the presence of Pd/C as described for **6** to give **8** (94%) as a white foam, identical to that prepared previously.[9]

(3*S*,3a*R*,6a*S*)-1-[(*cis*-2,3-Dimethylcyclopropyl)-*cis*-carbonyl]-3-methylhexahydropyrrolo[3,2-*b*]pyrrol-2(1*H*)-one hydrochloride (42). Compound **41** was deprotected with hydrogen in the presence of Pd /C as described for **6** to give **42** (98%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 10.28−9.80 (broad s, 2H, NH_2^+), 4.08−3.80 (m, 3H, NCH_2CH$_2$, NCHCH$_2$), 3.38−3.29 (m, 1H, NCHCHMe), 3.14−3.04 (m, 1H, CHMe), 2.88−2.77 (m, 2H, NCH$_2$CHH, COCHCHMeCHMe), 2.01−1.88 (m, 1H, NCH$_2$CHH), 1.73−1.56 (m, 2H, COCHCHMeCHMe), 1.46 (d, J = 7.5 Hz, 3H, CHMe), 1.23−1.13 (m, 6H, COCHCHMeCHMe). HPLC: 99.7% (t_R 11.78 min); LCMS m/z 237 (MH$^+$) single component 100%, gradient 2 (t_R 1.93 min) gradient 3 (t_R 8.44min); HRMS calcd for $C_{13}H_{21}N_2O_2$ (MH$^+$) 237.1603, found 237.1609.

((3*S*,3a*R*,6a*S*)-1-[(*cis*-2,3-Dimethylcyclopropyl)-*cis*-carbonyl]-3-methyl-4-[(2*S*)-pyrrolidin-2-ylcarbonyl]hexahydropyrrolo[3,2-*b*]pyrrol-2(1*H*)-one hydrochloride (44). Compound **43** was deprotected with hydrogen in the presence of Pd /C as described for **6** to give **44** (96%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 11.20 and 8.00 (2 broad s, 2H, NH_2^+), 4.80−4.68 (m, 1H, NCHCO), 4.21 (t, J = 9.5 Hz, 1H, NCHHCH$_2$-CH$_2$), 3.85−3.40 (m, 5H, NCHHCH$_2$CH$_2$, NCH_2CH$_2$, NCHCH$_2$, NCHCHMe), 3.28−3.13 (m, 1H, CHMe), 2.88−2.69 (m, 2H, NCH$_2$CHH, COCHCHMeCHMe), 2.25−1.53 (m, 7H, NCH$_2$-CHH, NCH$_2$CH_2CH_2, COCHCHMeCHMe); 1.25−1.09 (m, 9H, CHMe, COCHCHMeCHMe); MS (thermospray) m/z 334 (MH$^+$). Anal. ($C_{18}H_{27}N_3O_3$·HCl) C, H, N.

***tert*-Butyl (3*S*,3a*R*,6a*S*)-4-({(2*S*)-1-[(Benzyloxy)carbonyl]pyrrolidin-2-yl}carbonyl)-3-methyl-2-oxohexahydropyrrolo[3,2-*b*]pyrrole-1(2*H*)-carboxylate (10).** To a stirred suspension of Cbz-(*S*)-proline (8 g, 32.1 mmol), TBTU (10.3 g, 32.1 mmol), and HOBT·H_2O (4.5 g, 32.1 mmol) in anhydrous acetonitrile (65 mL) was added diisopropylethylamine (10.6 mL, 61 mmol), and the resulting solution was stirred for 20 min. The hydrochloride salt **9** (7.45 g, 27 mmol) was added, followed by acetonitrile (35 mL) and anhydrous dimethylformamide (30 mL) to give a clear solution which was stirred at 20 °C for 24 h. The solution was poured into ethyl acetate (500 mL), and the solution was washed with water (500 mL). The aqueous phase was back-extracted with ethyl acetate (300 mL), and the combined organic phases were washed sequentially with 2M HCl (3 × 200 mL), water (2 × 200 mL), and saturated brine (200 mL), then dried and evaporated to give a gum (18.5 g). This gum was purified by flash column chromatography eluting with cyclohexanes−ethyl acetate (2:1 to 3:1) to yield **10** (11.26 g, 88.5%) as a white foam: ^{1}H NMR (CDCl3 shows rotameric forms) δ 7.40−7.28 (m, 5H, C_6H_5), 5.22−4.93 (m, 2H, PhCH_2), 4.49−4.20 and 3.83−3.45 and 3.32−2.97 and 2.64−2.51 (4m, 9H, NCHCO, NCH_2CH$_2$CH$_2$, NCH_2CH$_2$, NCHCHMe, NCHCH$_2$, NCHCHH, CHMe), 2.32−1.76 (m, 5H, NCHCHH + NCH$_2$CH_2CH_2), 1.54 (s, 9H, Bu^t), 1.13 and 1.06 and 1.86 (d, 3H, J = 7 Hz, CHMe); HPLC 100% (t_R 26.4 min); LCMS m/z 472 (MH$^+$) gradient 1 (t_R 3.01 min); TLC R_f 0.31 (cyclohexanes−ethyl acetate, 4:1); HRMS calcd for $C_{25}H_{34}N_3O_6$ (MH$^+$) 472.2448, found 472.2446.

The following compounds were similarly prepared.

Benzyl (2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(Cyclopropylcarbonyl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]-carbonyl}pyrrolidine-1-carboxylate. (7). Compound **6** was reacted with Cbz-(*S*)-proline as described for **10** to give **7** (87%) as a white amorphous solid, identical to that prepared previously.[9]

Benzyl (2*S*)-2-{[(3a*R*,6*R*,6a*S*)-4-{[*cis*-2,3-Dimethylcyclopropyl]-*cis*- carbonyl}-6-methyl-5-oxohexahydropyrrolo-[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}pyrrolidine-1-carboxylate (43). Compound **42** was reacted with Cbz- (*S*)-proline as described for **10** to give **43** (77%) as a white foam: ^{1}H NMR (DMSO heated at 120° to get the rotomers to coalesce) δ 7.40−7.23 (m, 5H, C_6H_5), 5.08 (d, J = 13 Hz, 1H) and 5.02 (d, J = 13 Hz, 1H, PhCH_2), 3.95−3.30 (m, 6H, NCH_2CH$_2$, NCH_2CH$_2$CH$_2$, NCHCHMe and NCHCH$_2$), 3.38 (m, 1H, NCH-CO), 3.03 (m, 1H, CHMe), 2.70 (t, J = 9 Hz, 1H, COCHCHMe), 2.28−2.15 and 2.00−1.75 (2m, 1H and 5H, NCH$_2$CH_2 and NCH$_2$CH_2CH_2), 1.58−1.47 (m, 2H, CHCHMeCHMe), 1.15 and 1.12 (2d, J = 7.5 Hz, 2 × 3H, CHCHMeCHMe), 1.06 (br m, 3H, Me); MS (thermospray) m/z 468 (MH$^+$); Circular dichroism (CH$_3$CN) λ_{max}199.8 nm, dE 3.89, E22341, λ_{max}221.6 nm, dE −17.90, E11748, λ_{max}242.6 nm, dE 16.00, E1661; LCMS m/z 468 (MH$^+$) single component 95%, gradient 2 (t_R 3.30 min)

gradient 3 (t_R 15.08min); HRMS calcd for $C_{26}H_{34}N_3O_5$ (MH^+) 468.2498, found 468.2489.

Benzyl (2*S*)-2-{[(3a*S*,6*S*,6a*R*)-6-Methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}pyrrolidine-1-carboxylate (11). To a solution of **10** (11.2 g, 23.8 mmol) in dichloromethane (60 mL) was added trifluoroacetic acid (20 mL). The solution was stirred in a cold water bath for 45 min and then concentrated in vacuo. Toluene (100 mL) was added and evaporated off and the resulting gum dissolved in ethyl acetate (250 mL). The solution was washed sequentially with saturated aqueous sodium bicarbonate solution (2 × 100 mL), water (2 × 100 mL), and saturated brine (100 mL), then dried and evaporated to a foam. The aqueous washes were combined and extracted with ethyl acetate (3 × 300 mL), and the organic extracts were combined, washed with saturated brine (50 mL), then dried and evaporated to give a crisp foam. The batches of foam were combined, dissolved in ethyl acetate (50 mL), and evaporated to give **11** (8.68 g, 98%) as a white solid: ^{1}H NMR (CDCl3 shows rotameric forms) δ 7.39−7.28 (m, 5H, C_6H_5), 6.14−5.92 (2m, 1H, N*H*), 5.22−4.92 (m, 2H, PhCH_2), 4.48−3.98 (2m, 2H, NC*H*CO, NC*H*HCH$_2$), 3.82−2.84 (2m, 6H, NCH_2-CH$_2$CH$_2$, NCH*H*CH$_2$, NC*H*CHMe, NC*H*CH$_2$, C*H*Me), 2.34−1.77 (m, 6H, NCH$_2$CH_2CH_2, NCHCH_2), 1.48−0.78 (4m, 3H, CH*Me*); HPLC 100% (t_R 18.2 min); TLC R_f 0.12 (ethyl acetate-toluene- acetic acid, 25:5:1); LCMS *m*/*z* 372 (MH^+) single component 99%, gradient 2 (t_R 2.46 min), gradient 3 (t_R 10.92min); HRMS calcd for $C_{20}H_{26}N_3O_4$ (MH^+) 372.1923, found 372.1928.

***tert*-Butyl (2*S*)-2-{[(3a*S*,6*S*,6a*R*)-6-Methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}pyrrolidine-1-carboxylate (12).** A solution of **11** (8.0 g, 21.5 mmol) and di-*tert*-butyl dicarbonate (6.0 g, 27.5 g) in 2-propanol (350 mL) was hydrogenated in the presence of the palladium catalyst (2 g, 10% Pd/C, Degussa type, E101, NE/W, 50% H_2O) for 5 h. The catalyst was filtered off and the filtrate evaporated to a white foam (6.5 g). Crystallization from toluene (35 mL) and cyclohexane (40 mL) gave **12** (5.6 g, 77%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 6.09−5.90 (2m, 1H, CON*H*), 4.45−3.97 (2m, 2H, NC*H*CO, NC*H*HCH$_2$), 3.81−3.36 (m, 5H, NCH_2CH$_2$CH$_2$, NCH*H*CH$_2$, NC*H*CHMe, NC*H*CH$_2$), 3.20−2.78 (2m, 1H, C*H*Me), 2.37−1.75 (m, 6H, NCH$_2$CH_2CH_2, NCHCH_2), 1.50−1.05 (3m, 12H, *Bu*^{t}, CH*Me*); LCMS *m*/*z* 338 (MH^+) single component 99.8%, gradient 1 (t_R 2.25min); HPLC 100% (t_R 16.77 min); TLC R_f 0.12 (ethyl acetate- toluene- acetic acid, 25:5:1). Anal. ($C_{17}H_{27}N_3O_4$) C, H, N.

(3*S*,3a*R*,6a*S*)-1-(Cyclopropylcarbonyl)-3-methyl-4-{[(2*S*)-1-(1-naphthylsulfonyl)pyrrolidin-2-yl]carbonyl}-hexahydropyrrolo[3,2-*b*]pyrrol-2(1*H*)-one (15). To a solution of **8** (30.7 mg, 89.8 μmol, 1 equiv) in dry MeCN (2 mL) was added triethylamine (29 μL, 207 μmol, 2.3 equiv). To this solution was added a solution of 1-naphthylsulfonyl chloride (28.2 mg, 105 μmol, 1.2 equiv) in dry MeCN (1 mL). The reaction mixture was stirred at room temperature for 3 h before 2-propanol (10 μL) was added to quench unreacted sulfonyl chloride. The mixture was evaporated to dryness, redissolved in dichloromethane (15 mL), and washed with water (15 mL), sat. $NaHCO_3$ solution (15 mL) and water (15 mL) and then dried, and the solvent was evaporated to give a white solid. This solid was purified by flash column chromatography eluting with cyclohexanes−ethyl acetate to give **15** (29 mg, 65%) as a white solid: IR (KBr) ν_{max} 1747.8, 1682.4, 1668.2 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.77 (d, J = 8.8 Hz, 1H, aryl*H*), 8.30 (d, J = 7 Hz, 1H, aryl*H*), 8.05 (d, J = 7 Hz, 1H, aryl*H*), 7.92 (d, J = 7.9 Hz, 1H, aryl*H*), 7.72−7.50 (m, 3H, aryl*H*), 4.74 (dd, J = 7.9 Hz, J = 5.1 Hz, 1H, NC*H*CO), 4.254 (t, J = 10.2 Hz, 1H, NC*H*HCH$_2$CH$_2$),3.88−3.36 (m, 5H, NCH*H*CH$_2$CH$_2$, NCH_2CH$_2$, NC*H*CHMe, NC*H*CH$_2$), 3.34−3.22 (quintet, J = 7.4 Hz, 1H, C*H*Me), 3.00−2.87 (m, 1H, COC*H*CH$_2$CH$_2$), 2.83−2.69 (m, 1H, NCH$_2$C*H*H), 2.30−1.83 (m, 5H, NCH2*CH2*CH2, NCH2CH2*CH2* and NCH$_2$CH*H*), 1.30−0.92 (m, 7H, CH*Me*, COCHCH_2CH_2); MS (thermospray) *m*/*z* 496 (MH^+); HPLC 100% (t_R 27.79 min). Anal. ($C_{26}H_{29}N_3O_5S$) C, H, N, S.

Preparation of 1, 14, and 16−23. Using essentially the same procedure as for the preparation of **15**, the following compounds listed in Scheme 3 were prepared from **8**.

(3*S*,3a*R*,6a*S*)-1-(Cyclopropylcarbonyl)-4-[((2*S*)-1-{[6-(dimethylamino)-1-naphthyl]sulfonyl}pyrrolidin-2-yl)-carbonyl]-3-methylhexahydropyrrolo[3,2-*b*]pyrrol-2(1*H*)-one (14). Compound **8** was reacted with [6-(dimethylamino)-naphth-1-yl]sulfonyl chloride as described for **15** to give **14** (64%) as a green/yellow solid: IR (KBr) ν_{max} 1747.6, 1684.9, 1665.5, 1618.9 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.64 (d, J = 9.3 Hz, 1H, aryl*H*), 7.94 (d, J = 7 Hz, 1H, aryl*H*), 7.85 (d, J = 9.3 Hz, 1H, aryl*H*), 7.44−7.27 (m, 2H, aryl*H*), 6.96−6.89 (m, 1H, aryl*H*), 4.67 (dd, J = 4.8 Hz, J = 7.8 Hz, 1H, NC*H*CO), 4.31−4.10 (m, 1H, NC*H*HCH$_2$CH$_2$), 3.88−3.25 (m, 6H, NCH*H*CH$_2$CH$_2$, NCH_2CH$_2$, NC*H*CHMe, NC*H*CH$_2$, C*H*Me), 3.14−3.06 (m, 6H, NMe_2), 3.02−2.88 (m, 1H, COC*H*CH$_2$CH$_2$), 2.83−2.68 (m, 1H, NCH$_2$C*H*H), 2.22−1.77 (m, 5H, NCH2*CH2*CH2, NCH2CH2*CH2* and NCH$_2$CH*H*), 1.31−0.94 (m, 7H, CH*Me*, COCHCH_2CH_2); MS (thermospray) *m*/*z* 539 (MH^+); HPLC 99% (t_R 27.20 min). Anal. ($C_{28}H_{34}N_4O_5S$) C, H, N.

(3*S*,3a*R*,6a*S*)-1-(Cyclopropylcarbonyl)-4-[((2*S*)-1-{[5-(dimethylamino)-1-naphthyl]sulfonyl}pyrrolidin-2-yl)-carbonyl]-3-methylhexahydropyrrolo[3,2-*b*]pyrrol-2(1*H*)-one (1). Compound **8** was reacted with 5-(dimethylamino)-naphth-1-yl]sulfonyl chloride as described for **15** to give **1** as a green/yellow foam (80%), identical with that prepared previously.[9]

(3*S*,3a*R*,6a*S*)-1-(Cyclopropylcarbonyl)-3-methyl-4-{[(2*S*)-1-(2-naphthylsulfonyl)pyrrolidin-2-yl]carbonyl}-hexahydropyrrolo[3,2-*b*]pyrrol-2(1*H*)-one (16). Compound **8** was reacted with 2-naphthylsulfonyl chloride as described for **15** to give **16** (59%) as a white solid: IR (KBr) ν_{max} 1753.8, 1673.9, 1658.1 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.46 (s, 1H, aryl*H*), 8.01−7.87 (m, 4H, aryl*H*), 7.69−7.59 (m, 2H, aryl*H*), 4.65−4.60 (dd, J = 4.9 Hz, J = 7.9 Hz, 1H, NC*H*CO), 4.32 (t, J = 9.5 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.94−3.38 (m, 5H, NCH*H*CH$_2$CH$_2$, NCH_2CH$_2$, NC*H*CHMe and NC*H*CH$_2$), 3.30 (m, 1H, C*H*Me), 2.95 (m, 1H, COC*H*CH$_2$CH$_2$), 2.81 (m, 1H, NCH$_2$C*H*H), 2.20−1.72 (m, 5H, NCH2*CH2*CH2, NCH2CH2*CH2* and NCH2CH*H*), 1.28−0.95 (m, 7H, CH*Me* and COCHCH_2CH_2); MS (thermospray) *m*/*z* 496 (MH^+). HPLC: 98% (t_R 27.18 min). Anal. ($C_{26}H_{29}N_3O_5S$) C, H, N, S.

(3*S*,3a*R*,6a*S*)-4-{[(2*S*)-1-(Benzylsulfonyl)pyrrolidin-2-yl]carbonyl}-1-(cyclopropylcarbonyl)-3-methylhexahydropyrrolo[3,2-*b*]pyrrol-2(1*H*)-one (17). Compound **8** was reacted with benzylsulfonyl chloride as described for **15** to give **17** (58%) as a white solid: IR (KBr) ν_{max} 1747.46 (m), 1667.65 (m), 1650.87 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.68−7.49 and 7.44−7.32 (2m, 5H, aryl*H*), 4.51−4.25 (m, 3H, NC*H*CO, PhCH_2SO$_2$), 4.12−4.01 (t, J = 9.5 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.77−3.28 (m, 5H, NCH*H*CH$_2$CH$_2$, NCH_2CH$_2$, NC*H*CHMe and NC*H*CH$_2$), 3.15−3.04 (m, 1H, C*H*Me), 3.00−2.88 (m, 1H, COC*H*CH$_2$CH$_2$), 2.80−2.67 (m, 1H, NCH$_2$C*H*H), 2.29−1.80 (m, 5H, NCH$_2$CH_2CH_2, NCH$_2$CH*H*), 1.20−0.95 (m, 7H, CH*Me* and COCHCH_2CH_2); MS (thermospray) *m*/*z* 460 (MH^+). HPLC: 96% (t_R 25.05 min). Anal. ($C_{23}H_{29}N_3O_5S$) C, H, N, S.

(3*S*,3a*R*,6a*S*)-1-(Cyclopropylcarbonyl)-3-methyl-4-{[(2*S*)1-(phenylsulfonyl)pyrrolidin-2-yl]carbonyl}-hexahydropyrrolo[3,2-*b*]pyrrol-2(1*H*)-one (18). Compound **8** was reacted with phenylsulfonyl chloride as described for **15** to give **18** (80%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.93−7.85 (m, 2H, aryl*H*), 7.60−7.49 (m, 3H, aryl*H*), 4.57−4.52 (dd, J = 4.5 Hz, J = 7.6 Hz, 1H, NC*H*CO), 4.28 (t, J = 9.5 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.90−3.64, 3.57−3.38 (m, 5H, NCH*H*CH$_2$CH$_2$, NCH_2CH$_2$, NC*H*CHMe and NC*H*CH$_2$), 3.32 (m, 1H, C*H*Me), 2.94 (m, 1H, COC*H*CH$_2$CH$_2$), 2.79 (m, 1H, NCH$_2$C*H*H), 2.20−1.75 (m, 5H, NCH2*CH2*CH2, NCH2CH2*CH2* and NCH2CH*H*), 1.25−0.95 (m, 7H, CH*Me* and COCHCH_2CH_2); LCMS *m*/*z* 446 (MH^+) single component 99%, gradient 1 (t_R 4.12 min). HPLC: 100% (t_R 24.31 min). Anal. ($C_{22}H_{27}N_3O_5S$) C, H, N, S.

(3*S*,3a*R*,6a*S*)-4-({(2*S*)-1-[(4-Chlorophenyl)sulfonyl]pyrrolidin-2-yl}carbonyl)-1-(cyclopropylcarbonyl)-3-methylhexahydropyrrolo[3,2-*b*]pyrrol-2(1*H*)-one (19). Com-

pound **8** was reacted with 4-chlorophenylsulfonyl chloride as described for **15** to give **19** (49%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.94−7.81 (m, 2H, aryl*H*), 7.54−7.45 (m, 2H, aryl*H*), 4.61−4.56 (dd, J = 4.7 Hz, J = 7.0 Hz, 1H, NC*H*CO), 4.26 (t, J = 9.8 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.91−3.64 and 3.64−3.26 (2m, 6H, NCH*H*CH$_2$CH$_2$, NC*H*$_2$CH$_2$, NC*H*CHMe, NC*H*CH$_2$ and C*H*Me), 2.94 (m, 1H, COC*H*CH$_2$CH$_2$), 2.79 (m, 1H, NCH$_2$C*H*H), 2.26−1.80 (m, 5H, NCH2*CH2*CH2, NCH2CH2*CH2* and NCH2CH*H*), 1.28−0.95 (m, 7H, CH*Me* and COCH*CH$_2$CH$_2$*); LCMS m/z 480 (MH$^+$) single component 99% gradient 3 (t_R 14.44 min). HPLC: 100% (t_R 28.26 min); HRMS calcd for $C_{22}H_{27}ClN_3O_5S$ (MH$^+$) 480.1360, found 480.1353.

(3*S*,3a*R*,6a*S*)-1-(Cyclopropylcarbonyl)-4-({(2*S*)-1-[(4-isopropylphenyl)sulfonyl]pyrrolidin-2-yl}carbonyl)-3-methylhexahydropyrrolo[3,2-*b*]pyrrol-2(1*H*)-one (20). Compound **8** was reacted with 4- isopropyphenylsulfonyl chloride as described for **15** to give **20** (44%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.84−7.77 (m, 2H, aryl*H*), 7.40−7.32 (m, 2H, aryl*H*), 4.56−4.51 (dd, J = 4.9 Hz, J = 7.9 Hz, 1H, NC*H*CO), 4.28 (t, J = 9.5 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.91−3.64 and 3.57−3.26 (2m, 6H, NCH*H*CH$_2$CH$_2$, NC*H*$_2$CH$_2$, NC*H*CHMe, NC*H*CH$_2$ and C*H*Me), 3.05−2.88 (m, 2H, COC*H*CH$_2$-CH$_2$ and arylC*H*Me$_2$), 2.78 (m, 1H, NCH$_2$C*H*H), 2.17−1.72 (m, 5H, NCH2*CH2*CH2, NCH2CH2*CH2* and NCH2CH*H*), 1.27 (d, J = 7.3 Hz, 6H, arylCH*Me$_2$*), 1.20−0.94 (m, 7H, CH*Me* and COCH*CH$_2$CH$_2$*); LCMS m/z 488 (MH$^+$) single component 99.3% gradient 1 (t_R 4.57 min), gradient 3 (t_R 15.22 min). HPLC: 100% (t_R 29.52 min). HRMS calcd for $C_{25}H_{34}N_3O_5S$ (MH$^+$) 488.2219, found 488.2202.

(3*S*,3a*R*,6a*S*)-1-(Cyclopropylcarbonyl)-4-({(2*S*)-1-[(4-isopropoxyphenyl) sulfonyl]pyrrolidin-2-yl}carbonyl)-3-methylhexahydropyrrolo[3,2-*b*]pyrrol-2(1*H*)-one (21). Compound **8** was reacted with 4- isopropoxyphenylsulfonyl chloride as described for **15** to give **21** (43%) as a beige solid: ^{1}H NMR ($CDCl_3$) δ 7.83−7.77 (m, 2H, aryl*H*), 6.97−6.91 (m, 2H, aryl*H*), 4.67−4.58 (m, 1H, arylOC*H*Me$_2$), 4.55−4.48 (dd, J = 4.9 Hz, J = 7.9 Hz, 1H, NC*H*CO), 4.28 (t, J = 9.5 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.91−3.65, 3.59−3.27 (m, 6H, NCH*H*CH$_2$CH$_2$, NC*H*$_2$CH$_2$, NC*H*CHMe, NC*H*CH$_2$ and C*H*Me), 2.99−2.89 (m, H, COC*H*CH$_2$CH$_2$), 2.78 (m, 1H, NCH$_2$C*H*H), 2.20−1.74 (m, 5H, NCH2*CH2*CH2, NCH2CH2*CH2* and NCH2CH*H*), 1.37 (d, J = 6.1 Hz, 6H, arylOCH*Me$_2$*), 1.20−0.94 (m, 7H, CH*Me* and COCH*CH$_2$CH$_2$*); MS (thermospray) m/z 504 (MH$^+$). HPLC: 94% (t_R 28.36 min). Anal. ($C_{25}H_{33}N_3O_6S$) C, H, N, S.

(3*S*,3a*R*,6a*S*)-1-(Cyclopropylcarbonyl)-4-({(2*S*)-1-[(3-isopropoxyphenyl) sulfonyl]pyrrolidin-2-yl}carbonyl)-3-methylhexahydropyrrolo[3,2-*b*]pyrrol-2(1*H*)- (22). Compound **8** was reacted with 3-isopropoxyphenylsulfonyl chloride as described for **15** to give **22** (43%) as a white solid: IR (KBr) ν_{max} 1753.9 (m), 1673.9 (m), 1660.9 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.44−7.36 and 7.11−7.03 (2m, 4H, aryl*H*), 4.67−4.50 (m, 2H, arylOC*H*Me$_2$, NC*H*CO), 4.34−4.23 (t, J = 9.2 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.91−3.23 (m, 6H, NCH*H*CH$_2$CH$_2$, NC*H*$_2$CH$_2$, NC*H*CHMe, NC*H*CH$_2$, C*H*Me), 3.00−2.83 (m, 1H, COC*H*CH$_2$-CH$_2$), 2.84−2.72 (m, 1H, NCH$_2$C*H*H), 2.20−1.73 (m, 5H, NCH$_2$*CH$_2$*CH$_2$, NCH$_2$CH*H*), 1.86 and 1.85 (2d, J = 6.1 Hz, 6H, arylOCH*Me$_2$*), 1.20−0.95 (m, 7H, CH*Me* and COCH*CH$_2$CH$_2$*); MS (thermospray) m/z 504 (MH$^+$), 436 (MH−COcyclopropyl$^+$). HPLC: 100% (t_R 28.32 min). Anal. ($C_{25}H_{33}N_3O_6S$) C, H, N, S.

(3S,3aR,6aS)-1-(Cyclopropylcarbonyl)-3-methyl-4-({(2*S*)-1-[(4-propoxyphenyl)sulfonyl]pyrrolidin-2-yl}carbonyl)hexahydropyrrolo[3,2-*b*]pyrrol-2(1*H*)-one (23). Compound **8** was reacted with 4-propoxyphenylsulfonyl chloride as described for **15** to give **23** (85%) as a beige solid: ^{1}H NMR ($CDCl_3$) δ 7.85−7.78 (m, 2H, aryl*H*), 7.02−6.94 (m, 2H, aryl*H*), 4.56−4.44 (dd, J = 4.9 Hz, J = 7.3 Hz, 1H, NC*H*CO), 4.56−4.44 (dd, J = 4.9 Hz, J = 7.3 Hz, 1H, NC*H*CO), 4.28 (t, J = 9.8 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.97 (m, 2H, 4-MeCH$_2$C*H*$_2$-OPh), 3.92−3.62, 3.62−3.4, 3.47−3.26 (3m, 6H, NCH*H*CH$_2$-CH$_2$, NC*H*$_2$CH$_2$, NC*H*CHMe, NC*H*CH$_2$ and C*H*Me), 2.94 (m, H, COC*H*CH$_2$CH$_2$), 2.78 (m, 1H, NCH$_2$C*H*H), 2.21−1.68 (m, 7H, NCH2*CH2*CH2, NCH2CH2*CH2*, NCH2CH*H* and 4-MeC*H*$_2$-CH$_2$OPh), 1.30−0.93 (m, 9H, CH*Me*, COCH*CH$_2$CH$_2$* and 4-MeC*H*$_2$CH$_2$OPh); MS (thermospray) m/z 504 (MH$^+$). HPLC: 100% (t_R 28.86 min). Anal. ($C_{25}H_{33}N_3O_6S$) C, H, N, S.

(3*S*,3a*R*,6a*S*)-1-(Cyclopropylcarbonyl)-4-[((2*S*)-1-{[5-(dimethylamino)-1-naphthyl]sulfonyl}pyrrolidin-2-yl)-carbonyl]-3-ethylhexahydropyrrolo[3,2-b]pyrrol-2(1H)-one (13). Compound **13** was prepared from ethyl analogue of **3** as described for the methyl isomer **1** (Schemes 2 and 3) [13] as a white solid: ^{1}H NMR ($CDCl_3$) δ 8.54 (d, J = 8.0 Hz, 1H, dansyl-2*H*), 8.42 (d, J = 8.5 Hz, 1H, dansyl-4*H*), 8.28 (dd, J = 7.3 Hz, 1.2 Hz, 1H, dansyl-8*H*), 7.60−7.48 (m, 2H, dansyl-3*H*, dansyl-7*H*), 7.18 (d, J = 7.3 Hz, 1H, dansyl-6*H*), 4.75 (dd, J = 7.9 Hz, 4.9 Hz, 1H, NC*H*CO), 4.27 (t, J = 9.5 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.84−3.36 (m, 5H, NCH*H*CH$_2$CH$_2$, NC*H*$_2$CH$_2$, NC*H*CHEt, NC*H*CH$_2$), 3.10−2.85 (m, 8H, C*H*Et, N*Me$_2$*, COC*H*CH$_2$CH$_2$), 2.78−2.67 (m, 1H, NCH$_2$C*H*H), 2.29−1.82 (m, 5H, NCH$_2$*CH$_2$*CH$_2$, NCH$_2$CH*H*), 1.31−1.22 (m, 2H, CHC*H*$_2$-Me), 1.28−0.87 (7H, m, CHCH$_2$*Me*, COCH*CH$_2$CH$_2$*); MS (thermospray) m/z 553 (MH$^+$); LCMS m/z 553 (MH$^+$) single component 99% gradient 1 (t_R 4.72 min). Anal. ($C_{29}H_{36}N_4O_5S$) C, H, N, S.

(3*S*,3a*R*,6a*S*)-1-(Cyclopropylcarbonyl)-3-methyl-4-{[(2*S*)-1-(1-naphthoyl)pyrrolidin-2-yl]carbonyl}-hexahydropyrrolo[3,2-*b*]pyrrol-2(1*H*)-one (28). To a stirred solution of 1-naphthoic acid (22 mg, 0.125 mmol) in dry dimethylformamide (2 mL) at room temperature were added solutions of HOBT (16 mg, 0.115 mmol) in DMF (0.5 mL) and TBTU (39 mg, 0.122 mmol) in acetonitrile (0.5 mL). After stirring at room temperature for 20 min, a solution of **8** (0.036 mg, 0.105 mmol) in dry DMF (0.5 mL) was added followed by diisopropylethylamine (0.037 mL, 0.21 mmol). After stirring at room temperature for 18 h, the mixture was diluted with dichloromethane (15 mL) and water (15 mL), the organic and aqueous layers were separated, and the latter was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were washed with 2N HCl (15 mL), water (15 mL), saturated $NaHCO_3$ solution (15 mL), and again with water (15 mL), dried over $MgSO_4$, filtered, and evaporated to leave an orange oil, which was purified by preparative plate chromatography eluting with ethyl acetate-cyclohexane(1:1) to give **28** (25 mg, 51%) as an off-white, glassy solid: IR (KBr) ν_{max} 1746.5, 1687.8, 1660.1, 1650.5, 1631.2 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.11−8.04 (d, J = 7.9 Hz, 1H, aryl*H*), 7.92−7.83 (m, 2H, aryl*H*), 7.63−7.45 (m, 4H, aryl*H*), 4.87−4.78 (dd, J = 5.5 Hz, J = 8.0 Hz, 1H, NC*H*CO), 4.67 (t, J = 9.5 Hz, 1H, NC*H*HCH$_2$-CH$_2$), 3.94−3.66, 3.52−3.36 and 3.27−3.17 (3m, 6H, NCH*H*CH$_2$-CH$_2$, NC*H*$_2$CH$_2$, NC*H*CHMe, NC*H*CH$_2$ and C*H*Me), 2.96 (m, 1H, COC*H*CH$_2$CH$_2$), 2.80 (m, 1H, NCH$_2$C*H*H), 2.39−1.78 (m, 5H, NCH2*CH2*CH2, NCH2CH2*CH2* and NCH2CH*H*), 1.28−0.93 (m, 7H, CH*Me* and COCH*CH$_2$CH$_2$*); MS (thermospray) m/z 460 (MH$^+$); 478 (MNH$_4^+$); HPLC 98% (t_R 25.45 min). Anal. ($C_{27}H_{29}N_3O_4$) C, H, N.

The following compounds were similarly prepared.

(3*S*,3a*R*,6a*S*)-4-({(2*S*)-1-[(5-Chloro-3-methyl-1-benzothien-2-yl)carbonyl]pyrrolidin-2-yl}carbonyl)-1-(cyclopropylcarbonyl)-3-methylhexahydropyrrolo[3,2-*b*]pyrrol-2(1*H*)-one (24). Compound **8** was reacted with (5-chloro-3-methyl-1-benzothien-2-yl)carbonyl chloride as described for **28** to give **24** (78%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.76−7.70 and 7.39−7.34 (2m, 3H, aryl), 4.78−4.70 (m, 1H, NC*H*CO), 4.56 (t, J = 9.5 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.90−3.30 (m, 6H, NCH*H*CH$_2$CH$_2$, NC*H*$_2$CH$_2$, NC*H*CHMe, NC*H*CH$_2$, C*H*Me), 3.00−2.89 (m, 1H, COC*H*CH$_2$CH$_2$); 2.85−2.73 (m, 1H, NCH$_2$C*H*H), 2.49 (s, 3H, aryl*Me*), 2.41−1.86 (m, 5H, NCH$_2$*CH$_2$*CH$_2$, NCH$_2$CH*H*), 1.22−0.93 (m, 7H, CH*Me*, COCH*CH$_2$CH$_2$*); MS (thermospray) m/z 514 (MH$^+$); HPLC 98.51% (t_R = 29.54 min). LCMS m/z 514 (MH$^+$) single component 99.5% gradient 3 (t_R 15.40 min). Anal. ($C_{26}H_{28}$-ClN_3O_4S) C, H, N.

(3*S*,3a*R*,6a*S*)-4-{[(2*S*)-1-(1,1′-Biphenyl-4-ylcarbonyl)-pyrrolidin-2-yl]carbonyl}-1-(cyclopropylcarbonyl)-3-methylhexahydropyrrolo[3,2-*b*]pyrrol-2(1*H*)-one (25). Compound **8** was reacted with 4-phenylbenzoyl chloride as described for **28** to give **25** (54%) as a white solid: ^{1}H NMR ($CDCl_3$) δ

7.69−7.58 and 7.50−7.33 (2m, 9H, arylH), 4.78−4.70 (m, 1H, NC*H*CO), 4.61 (t, J = 9.5 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.91−3.58 (m, 5H, NCH*H*CH$_2$CH$_2$, NC*H*$_2$CH$_2$, NC*H*CHMe, NC*H*CH$_2$), 3.41−3.28 (m, 1H, C*H*Me), 3.00−2.89 (m, 1H, COC*H*CH$_2$CH$_2$), 2.84−2.71 (m, 1H, NCH$_2$C*H*H), 2.35−1.81 (m, 5H, NCH$_2$*CH*$_2$CH$_2$, NCH$_2$CH*H*), 1.22−0.93 (m, 7H, CH*Me*, COCH*CH*$_2$*CH*$_2$); MS (thermospray) *m*/*z* 486 (MH$^+$); LCMS *m*/*z* 508 (MNa$^+$) single component 99.8% gradient 2 (t_R 3.10 min), gradient 3 (t_R 14.52 min); HRMS calcd for $C_{29}H_{32}N_3O_4$ (MH$^+$) 486.2393, found 486.2397.

(3*S*,3a*R*,6a*S*)-1-(Cyclopropylcarbonyl)-4-{[(2*S*)-1-(4-isopropylbenzoyl)pyrrolidin-2-yl]carbonyl}-3-methylhexahydropyrrolo[3,2-*b*]pyrrol-2(1*H*)- (26). Compound **8** was reacted with 4-isopropylbenzoyl chloride as described for **28** to give **26** (18%) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.53−7.48 and 7.26−7.21 (2m, 4H, arylH), 4.75−4.68 (m, 1H, NC*H*CO), 4.60 (t, J = 9.5 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.88−3.55 (m, 5H, NCH*H*CH$_2$CH$_2$, NC*H*$_2$CH$_2$, NC*H*CHMe, NC*H*CH$_2$), 3.40−3.27 (m, 1H, C*H*Me), 3.02−2.70 (m, 3H, COC*H*CH$_2$CH$_2$, NCH$_2$C*H*H, arylC*H*Me$_2$), 2.35−1.81 (m, 5H, NCH$_2$*CH*$_2$CH$_2$, NCH$_2$CH*H*), 1.28−0.95 (m, 13H, arylCH*Me*$_2$, CH*Me*, COCH*CH*$_2$*CH*$_2$); MS (thermospray) *m*/*z* 452 (MH$^+$); LCMS *m*/*z* 474 (MNa$^+$) single component 99.4% gradient 3 (t_R 14.18 min); HPLC 100% (t_R = 26.50 min). HRMS calcd for $C_{26}H_{34}N_3O_4$ (MH$^+$) 452.2549, found 452.2548.

(3*S*,3a*R*,6a*S*)-1-(Cyclopropylcarbonyl)-3-methyl-4-{[(2*S*)-1-(4-propoxybenzoyl)pyrrolidin-2-yl]carbonyl}-hexahydropyrrolo[3,2-*b*]pyrrol-2(1*H*)-one (27). Compound **8** was reacted with 4-propoxybenzoyl chloride as described for **28** to give **27** (59%) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.58−7.53 and 6.91−6.86 (2m, 4H, arylH), 4.71 (t, J = 7.0 Hz, 1H, NC*H*CO), 4.60 (t, J = 9.2 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.94 (t, J = 6.4 Hz, 2H, arylOC*H*$_2$CH$_2$Me), 3.89−3.55 (m, 5H, NCH*H*CH$_2$CH$_2$, NC*H*$_2$CH$_2$, NC*H*CHMe, NC*H*CH$_2$), 3.39−3.26 (m, 1H, C*H*Me), 3.00−2.89 (m, 1H, COC*H*CH$_2$CH$_2$), 2.82−2.71 (m, 1H, NCH$_2$C*H*H), 2.35−1.74 (m, 7H, arylOCH$_2$C*H*$_2$Me, NCH$_2$*CH*$_2$C*H*$_2$, NCH$_2$CH*H*), 1.26−0.95 (m, 10H, arylOCH$_2$-CH$_2$*Me*, CH*Me*, COCH*CH*$_2$*CH*$_2$); MS (thermospray) *m*/*z* 468 (MH$^+$); HPLC 100% (t_R = 26.02 min); LCMS *m*/*z* 468 (MH$^+$) single component 99.6% gradient 3 (t_R 13.92 min); HRMS calcd for $C_{26}H_{34}N_3O_5$ (MH$^+$) 468.2498, found 468.2482.

(3*S*,3a*R*,6a*S*)-4-{[(2*S*)-1-(4-Chlorobenzoyl)pyrrolidin-2-yl]carbonyl}-1-(cyclopropylcarbonyl)-3-methylhexahydropyrrolo[3,2-*b*]pyrrol-2(1*H*)-one (29). Compound **8** was reacted with 4-chlorobenzoyl chloride as described for **28** to give **29** (87%) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.56−7.50 (m, 2H, aryl*H*), 7.41−7.30 (m, 2H, aryl*H*), 4.70 (t, J = 7.0 Hz, 1H, NC*H*CO), 4.55 (t, J = 9.8 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.90−3.46, 3.39−3.27 (2m, 6H, NCH*H*CH$_2$CH$_2$, NC*H*$_2$CH$_2$, NC*H*-CHMe, NC*H*CH$_2$ and C*H*Me), 2.94 (m, 1H, COC*H*CH$_2$CH$_2$), 2.78 (m, 1H, NCH$_2$C*H*H), 2.37−1.78 (m, 5H, NCH$_2$*CH*$_2$CH$_2$ and NCH$_2$CH$_2$*CH*$_2$ and NCH$_2$CH*H*), 1.31−0.95 (m, 7H, CH*Me* and COCH*CH*$_2$*CH*$_2$); MS (thermospray) *m*/*z* 444 (MH$^+$); LCMS *m*/*z* 444 (MH$^+$) single component 99.7% gradient 3 (t_R 13.23 min); HPLC 100% (t_R = 24.01min); HRMS calcd for $C_{23}H_{27}ClN_3O_4$ (MH$^+$) 444.1690, found 444.1689.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(Cyclopropylcarbonyl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-*N*-methyl-N-phenylpyrrolidine-1-carboxamide (40). To a solution of **8** (20 mg, 0.06 mmol) in acetonitrile (2 mL) was added triethylamine (0.02 mL, 0.15 mmol, 2.5 equiv) followed by *N*-methyl-N-phenylcarbamoyl chloride (15 mg, 0.15 mmol, 1.5 equiv). The resulting solution was left at room temperature for 16 h, quenched with 2-propanol (0.1 mL) and then evaporated to dryness. The resulting residue was purified by preparative TLC eluting with ethyl acetate/cyclohexane (2:1) to give **40** (22 mg, 79%) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.41−7.08 (m, 5H, aryl*H*), 4.60−4.40 (m, 2H, NC*H*CO, NC*H*HCH$_2$CH$_2$), 3.84−3.60 (m, 5H, NCH*H*CH$_2$CH$_2$, NC*H*$_2$CH$_2$, NC*H*CHMe, NC*H*CH$_2$), 3.42−3.30 (m, 1H, C*H*Me), 3.24 (s, 3H, arylN*Me*CO), 3.00−2.66 (2m, 2H, COC*H*CH$_2$CH$_2$, NCH$_2$C*H*H), 2.17−1.55 (m, 5H, NCH$_2$*CH*$_2$C*H*$_2$, NCH$_2$CH*H*), 1.30−0.95 (m, 7H, CH*Me*, COCH*CH*$_2$*CH*$_2$); MS (thermospray) *m*/*z* 439 (MH$^+$). Anal. ($C_{24}H_{30}N_4O_4$) C, H, N.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(Cyclopropylcarbonyl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-N-(4-isopropylphenyl)pyrrolidine-1-carboxamide (30). To a solution of proline **8** (0.03 g, 0.09 mmol) in dry acetonitrile (2 mL) was added dry triethylamine (0.03 mL, 0.22 mmol) followed by 4-(isopropyl)phenyl isocyanate (0.022 g, 0.135 mmol). The reaction mixture was left standing at room-temperature overnight, then quenched with 2-propanol (0.1 mL). It was then evaporated to dryness and purified using preparative plate chromatography eluting with ethyl acetate-cyclohexane (2:1) to give **30** (77%) as an amorphous solid: ^{1}H NMR (CDCl$_3$) δ 7.26−7.21 and 7.16−7.11 (2m, 4H, aryl*H*), 6.19 (s, 1H, CON*H*), 4.65 (dd, J = 7.6 Hz, 3.7 Hz, 1H, NC*H*CO), 4.47 (t, J = 9.5 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.88−3.44 (m, 5H, NCH*H*CH$_2$CH$_2$, NC*H*$_2$CH$_2$, NC*H*CHMe, NC*H*CH$_2$), 3.37−3.24 (m, 1H, C*H*Me), 2.99−2.66 (m, 3H, COC*H*CH$_2$CH$_2$, NCH$_2$C*H*H, arylC*H*Me$_2$), 2.45−1.85 (m, 5H, NCH$_2$*CH*$_2$C*H*$_2$, NCH$_2$CH*H*), 1.28−0.95 (m, 13H, arylCH*Me*$_2$, CH*Me*, COCH*CH*$_2$*CH*$_2$); MS (thermospray) *m*/*z* 467 (MH$^+$); HPLC 100% (t_R 27.843min); LCMS *m*/*z* 467 (MH$^+$) single component 99.6% gradient 1 (t_R 4.28min); HRMS calcd for $C_{26}H_{34}N_4O_4$ (MH$^+$) 467.265831, found 467.264975.

The following compounds were similarly prepared.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(Cyclopropylcarbonyl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-N-(4-propoxyphenyl)pyrrolidine-1-carboxamide (31). Compound **8** was reacted with 4-propoxyphenyl isocyanate as described for **30** to give **31** (53%) as a white solid: ^{1}H NMR (CDCl$_3$): δ 7.24−7.18 and 6.85−6.79 (2m, 4H, aryl*H*), 6.11 (s, 1H, CON*H*), 4.63 (dd, J = 8.0 Hz, 4.0 Hz, 1H, NC*H*CO), 4.45 (t, J = 9.5 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.91−3.45 (m, 7H, arylOC*H*$_2$CH$_2$Me, NCH*H*CH$_2$CH$_2$, NC*H*$_2$CH$_2$, NC*H*CHMe, NC*H*CH$_2$), 3.36−3.23 (m, 1H, C*H*Me), 2.98−2.88 (m, 1H, COC*H*CH$_2$CH$_2$), 2.78−2.66 (m, 1H, NCH$_2$C*H*H), 2.40−1.70 (m, 7H, arylOCH$_2$C*H*$_2$Me, NCH$_2$*CH*$_2$C*H*$_2$, NCH$_2$CH*H*), 1.19−0.95 (m, 10H, arylOCH$_2$CH$_2$*Me*, CH*Me*, COCH*CH*$_2$*CH*$_2$); MS (thermospray) *m*/*z* 483 (MH$^+$). Anal. ($C_{26}H_{34}N_4O_5$) C, H, N.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(Cyclopropylcarbonyl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-N-[4-(trifluoromethyl)phenyl]pyrrolidine-1-carboxamide (32). Compound **8** was reacted with 4-(trifluoromethyl)phenyl isocyanate as described for **30** to give **32** (90%) as a white powder: ^{1}H NMR (CDCl$_3$): δ 7.55−7.43 (m, 4H, aryl*H*), 6.42 (s, 1H, CON*H*), 4.65 (dd, J = 8.0 Hz, 4.0 Hz, 1H, NC*H*CO), 4.41 (t, J = 9.5 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.86−3.47 (m, 5H, NCH*H*CH$_2$CH$_2$, NC*H*$_2$CH$_2$, NC*H*CHMe, NC*H*CH$_2$), 3.36−3.23 (m, 1H, C*H*Me), 2.99−2.89 (m, 1H, COC*H*CH$_2$CH$_2$), 2.82−2.70 (m, 1H, NCH$_2$C*H*H), 2.42−1.86 (m, 5H, NCH$_2$*CH*$_2$C*H*$_2$, NCH$_2$-CH*H*), 1.19−0.95 (m, 7H, CH*Me*, COCH*CH*$_2$*CH*$_2$); MS (thermospray) *m*/*z* 493 (MH$^+$); LCMS *m*/*z* 493 (MH$^+$) single component 99.7% gradient 1 (t_R 4.65min), gradient 3 (t_R 14.39min); HRMS calcd for $C_{24}H_{28}F_3N_4O_4$ (MH$^+$) 493.2063, found 493.2047.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(Cyclopropylcarbonyl)-6-meth-yl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-N-(4-isopropoxyphenyl)pyrrolidine-1-carboxamide (33). Compound **8** was reacted with 4-(isopropoxy)-phenyl isocyanate as described for **30** to give **33** (12%) as a white powder: ^{1}H NMR (CDCl$_3$): δ 7.24−7.17 and 6.85−6.78 (2m, 4H, aryl*H*), 6.11 (s, 1H, CON*H*), 4.63 (dd, J = 7.3 Hz, 4.3 Hz, 1H, NC*H*CO), 4.51−4.40 (m, 2H, arylOC*H*Me$_2$, NC*H*HCH$_2$-CH$_2$), 3.84−3.44 (m, 5H, NCH*H*CH$_2$CH$_2$, NC*H*$_2$CH$_2$, NC*H*-CHMe, NC*H*CH$_2$), 3.36−3.23 (m, 1H, C*H*Me), 2.98−2.88 (m, 1H, COC*H*CH$_2$CH$_2$), 2.77−2.66 (m, 1H, NCH$_2$C*H*H), 2.40−1.87 (m, 5H, NCH$_2$*CH*$_2$C*H*$_2$, NCH$_2$CH*H*), 1.19−0.95 (m, 13H, aryl-OCH*Me*$_2$, CH*Me*, COCH*CH*$_2$*CH*$_2$); MS (thermospray) *m*/*z* 483 (MH$^+$); HPLC 100%, (t_R 25.36min). Anal. ($C_{26}H_{34}N_4O_5$) C, H, N.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(Cyclopropylcarbonyl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-N-(4-chlorophenyl)pyrrolidine-1-carboxamide (34). Compound **8** was reacted with 4-chlorophenyl isocyanate as described for **30** to give **34** (66%) as a white powder: ^{1}H NMR (CDCl$_3$): δ 7.32−7.20 (m, 4H, aryl*H*), 6.24 (s, 1H, CON*H*), 4.63 (dd, J = 8.0 Hz, 4.3 Hz, 1H, NC*H*CO), 4.41 (t, J = 9.5 Hz, 1H,

NC*H*HCH$_2$CH$_2$), 3.85−3.43 (m, 5H, NCH*H*CH$_2$CH$_2$, NC*H*$_2$CH$_2$, NC*H*CHMe, NC*H*CH$_2$), 3.36−3.23 (m, 1H, C*H*Me), 2.99−2.89 (m, 1H, COC*H*CH$_2$CH$_2$), 2.80−2.69 (m, 1H, NCH$_2$C*H*H), 2.40−1.88 (m, 5H, NCH$_2$*CH*$_2$C*H*$_2$, NCH$_2$CH*H*), 1.19−0.95 (m, 7H, CH*Me*, COCH*CH*$_2$*CH*$_2$); MS (thermospray) *m/z* 459 (MH$^+$); LCMS *m/z* 459 (MH$^+$) single component 99.7% gradient 3 (t_R 13.64 min); HPLC 99.65% (t_R 24.99min). HRMS calcd for $C_{23}H_{28}ClN_4O_4$ (MH$^+$) 459.1799, found 459.1787

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(Cyclopropylcarbonyl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-N-(1-naphthyl)pyrrolidine-1-carboxamide (35). Compound **8** was reacted with 1-naphthyl isocyanate as described for **30** to give **35** (74%) as a white solid: ^{1}H NMR (CDCl$_3$): δ 7.91−7.41 (m, 7H, aryl*H*), 6.57 (s, 1H, CON*H*), 4.70 (dd, J = 8.0 Hz, 4.3 Hz, 1H, NC*H*CO), 4.42 (t, J = 9.5 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.89−3.50 (m, 5H, NCH*H*CH$_2$CH$_2$, NC*H*$_2$CH$_2$, NC*H*CHMe, NC*H*CH$_2$), 3.36−3.25 (m, 1H, C*H*Me), 2.98−2.87 (m, 1H, COC*H*CH$_2$CH$_2$), 2.76−2.65 (m, 1H, NCH$_2$C*H*H), 2.48−1.94 (m, 5H, NCH$_2$*CH*$_2$C*H*$_2$, NCH$_2$CH*H*), 1.29−0.95 (m, 7H, CH*Me*, COCH*CH*$_2$*CH*$_2$); MS (thermospray) *m/z* 475 (MH$^+$); LCMS *m/z* 475 (MH$^+$) single component 99.5% gradient 3 (t_R 13.31 min); HPLC 99% (t_R 24.7 min). HRMS calcd for $C_{27}H_{31}N_4O_4$ (MH$^+$) 475.2345, found 475.2331.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(Cyclopropylcarbonyl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-N-(2-isopropylphenyl)pyrrolidine-1-carboxamide (36). Compound **8** was reacted with 2-(isopropyl)phenyl isocyanate as described for **30** to give **36** (73%) as a white solid: ^{1}H NMR (CDCl$_3$): δ 7.61 (dd, J = 7.9 Hz, 1.8 Hz, 1H, aryl-*6H*), 7.25−7.06 (m, 3H, aryl-*3,4,5H*), 6.13 (s, 1H, CON*H*), 4.65 (dd, J = 7.9 Hz, 4.3 Hz, 1H, NC*H*CO), 4.46 (t, J = 9.5 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.84−3.48 (m, 5H, NCH*H*CH$_2$CH$_2$, NC*H*$_2$CH$_2$, NC*H*CHMe, NC*H*CH$_2$), 3.37−3.23 (m, 1H, C*H*Me), 3.11−2.86 (m, 2H, arylC*H*Me$_2$, COC*H*CH$_2$CH$_2$), 2.75−2.64 (m, 1H, NCH$_2$C*H*H), 2.45−1.89 (m, 5H, NCH$_2$*CH*$_2$C*H*$_2$, NCH$_2$CH*H*), 1.28−0.95 (m, 13H, arylCH*Me*$_2$, CH*Me*, COCH*CH*$_2$*CH*$_2$); MS (thermospray) *m/z* 467 (MH$^+$); HPLC 97.69% (t_R 26.13min). Anal. ($C_{25}H_{34}N_4O_4$) C, H, N.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(Cyclopropylcarbonyl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-N-[3-(trifluoromethyl)phenyl]pyrrolidine-1-carboxamide (37). Compound **8** was reacted with 3-(trifluoro)phenyl isocyanate as described for **30** to give **37** as a white solid (95%): ^{1}H NMR (CDCl$_3$): δ 7.72−7.21 (m, 4H, aryl*H*), 6.41 (s, 1H, CON*H*), 4.64 (dd, J = 7.9 Hz, 4.3 Hz, 1H, NC*H*CO), 4.41 (t, J = 9.5 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.85−3.49 (m, 5H, NCH*H*CH$_2$CH$_2$, NC*H*$_2$CH$_2$, NC*H*CHMe, NC*H*CH$_2$), 3.36−3.24 (m, 1H, C*H*Me), 2.99−2.87 (m, 1H, COC*H*CH$_2$CH$_2$), 2.82−2.70 (m, 1H, NCH$_2$C*H*H), 2.40−1.90 (m, 5H, NCH$_2$*CH*$_2$C*H*$_2$, NCH$_2$-CH*H*), 1.27−0.95 (m, 7H, CH*Me*, COCH*CH*$_2$*CH*$_2$); MS (thermospray) *m/z* 493 (MH$^+$); HPLC 83.35% (t_R 27.19min). Anal. ($C_{24}H_{27}F_3N_4O_4$) C, H, N.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(Cyclopropylcarbonyl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-N-(3-chlorophenyl)pyrrolidine-1-carboxamide (38). Compound **8** was reacted with 3-chlorophenyl isocyanate as described for **30** to give **38** (62%) as a white solid: ^{1}H NMR (CDCl$_3$): δ 7.51−7.49 (m, 1H, aryl-*2H*), 7.20−7.16 (m, 2H, aryl-*4H*, −*6H*), 7.02−6.97 (m, 1H, aryl-*5H*), 6.27 (s, 1H, CON*H*), 4.63 (dd, J = 7.9 Hz, 4.3 Hz, 1H, NC*H*CO), 4.41 (t, J = 9.5 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.85−3.43 (m, 5H, NCH*H*CH$_2$CH$_2$, NC*H*$_2$CH$_2$, NC*H*CHMe, NC*H*CH$_2$), 3.36−3.24 (m, 1H, C*H*Me), 2.99−2.86 (m, 1H, COC*H*CH$_2$CH$_2$), 2.81−2.70 (m, 1H, NCH$_2$C*H*H), 2.40−1.90 (m, 5H, NCH$_2$*CH*$_2$C*H*$_2$, NCH$_2$CH*H*), 1.24−0.95 (m, 7H, CH*Me*, COCH*CH*$_2$*CH*$_2$); MS (thermospray) *m/z* 459 (MH$^+$); HPLC 98.97% (t_R 25.52min). Anal. ($C_{23}H_{27}$-ClN_4O_4) C, H, N.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(Cyclopropylcarbonyl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-N-phenylpyrrolidine-1-carboxamide (39). Compound **8** was reacted with phenyl isocyanate as described for **30** to give **39** (80%) as a white solid: ^{1}H NMR (CDCl$_3$): δ 7.37−6.99 (m, 5H, aryl*H*), 6.24 (s, 1H, CON*H*), 4.65 (dd, J = 7.9 Hz, 4.3 Hz, 1H, NC*H*CO), 4.45 (t, J = 9.5 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.85−3.45 (m, 5H, NCH*H*CH$_2$CH$_2$, NC*H*$_2$CH$_2$, NC*H*CHMe, NC*H*CH$_2$), 3.36−3.24 (m, 1H, C*H*Me), 2.99−2.87 (m, 1H, COC*H*CH$_2$CH$_2$), 2.79−2.68 (m, 1H, NCH$_2$C*H*H), 2.40−1.90 (m, 5H, NCH$_2$*CH*$_2$C*H*$_2$, NCH$_2$CH*H*), 1.27−0.95 (m, 7H, CH*Me*, COCH*CH*$_2$*CH*$_2$); MS (thermospray) *m/z* 425 (MH$^+$); HPLC 98.62% (t_R 22.08min). Anal. ($C_{23}H_{28}N_4O_4$) C, H, N.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-{[-*cis*-2,3-Dimethylcyclopropyl] -*cis*-carbonyl}-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-N-(4-isopropylphenyl)pyrrolidine-1-carboxamide (45). Compound **44** was reacted with 4-(isopropyl)phenyl isocyanate as described for **30** to give **45** (47%) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.29−7.19 and 7.18−7.08 (pseudo-ABq, J = 8.5 Hz, 4H, aryl*H*), 6.20 (bs,1H, NH), 4.68−4.60 (m, 1H, NC*H*CO), 4.55−4.38 (m, 1H, NC*H*HCH$_2$CH$_2$), 3.84−3.34 (m, 5H, NCH*H*CH$_2$CH$_2$, NC*H*$_2$CH$_2$, NC*H*CH$_2$, NC*H*CHMe), 3.32−3.18 (m, 1H, C*H*Me), 2.94−2.69 (m, 3H, NCH$_2$C*H*H, arylC*H*Me$_2$, NCOC*H*CHMeCHMe), 2.40−1.87 (m, 5H, NCH$_2$C*H*$_2$C*H*$_2$, NCH$_2$CH*H*), 1.60 (m, 2H, NCO-CHC*H*MeC*H*Me), 1.20 (m, 15H, 5× CH$_3$); MS (thermospray) *m/z* 495 (MH$^+$), 334 (M-4-(isopropyl)phenyl isocyanate group$^+$); LCMS *m/z* 495 (MH$^+$) single component 99.5% gradient 1 (t_R 4.50 min); HRMS calcd for $C_{28}H_{38}N_4O_4$ (MH$^+$) 495.297131, found 495.297733; HPLC 100% (t_R 28.71min).

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-6-Methyl-5-oxo-4-[(2,2,3,3-tetramethylcyclopropyl)carbonyl]hexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-N-(4-isopropylphenyl)pyrrolidine-1-carboxamide (51). Compound **49** was reacted with 4-(isopropyl)phenyl isocyanate as described for **30** to give **51** (37%) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.26−7.21 and 7.15−7.10-(2m, 4H, aryl*H*), 6.19 (s, 1H, CON*H*), 4.97−4.61 (m, 1H, NC*H*CO), 4.44 (t, J = 9.4 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.83−3.45 (m, 5H, NCH*H*CH$_2$CH$_2$, NC*H*$_2$CH$_2$, NC*H*CH$_2$, NC*H*CHMe), 3.29−3.16 (m, 1H, C*H*Me), 2.91−2.67 (m, 2H, NCH$_2$C*H*H, arylC*H*Me$_2$), 2.40−1.87 (m, 6H, COC*H*CMe$_2$CMe$_2$, NCH$_2$C*H*$_2$C*H*$_2$, NCH$_2$CH*H*), 1.30−1.10 (m, 21H, arylCH*Me*$_2$, CH*Me*, COCHC*Me*$_2$C*Me*$_2$); LCMS *m/z* 523 (MH$^+$) single component 98% gradient 1 (t_R 5.48min). Anal. ($C_{30}H_{42}N_4O_4$) C, H, N.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-6-Methyl-4-(4-nitrophenyl)-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-N-(4-isopropylphenyl)pyrrolidine-1-carboxamide (52). Compound **50** was reacted with 4-(isopropyl)phenyl isocyanate as described for **30** to give **52** (49%) as a pale yellow foam: ^{1}H NMR (CDCl$_3$) δ 8.30−8.23 and 7.62−7.55 (2m, 4H, 4-O$_2$N-aryl*H*), 7.26−7.21 and 7.16−7.11 (2m, 4H, 4-^{i}Pr-aryl*H*), 4.71−4.60 (m, 2H, NC*H*CO, NC*H*HCH$_2$CH$_2$), 4.07−3.29 (m, 6H, NCH*H*CH$_2$CH$_2$, NC*H*$_2$CH$_2$, NC*H*CH$_2$, NC*H*CHMe, C*H*Me), 2.91−2.77 (m, 1H, NCH$_2$C*H*H), 2.67−2.54 (m, 1H, arylC*H*Me$_2$), 2.45−1.90 (m, 5H, NCH$_2$C*H*$_2$C*H*$_2$, NCH$_2$CH*H*), 1.24−1.13 (m, 9H, arylCH*Me*$_2$, CH*Me*); MS (thermospray) *m/z* 520 (MH$^+$); HPLC 100% (t_R 29.4 min). Anal. ($C_{28}H_{33}N_5O_5$) C, H, N.

Benzyl (3a*S*,6*S*,6a*R*)-4-{[-*cis*-2,3-Dimethylcyclopropyl] -*cis*-carbonyl}-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]-pyrrole-1(2*H*)-carboxylate (41). To a solution of (c-2, c-3-dimethylcyclopropyl-r-1-carboxylic) acid (678 mg, 5.95 mmol) in anhydrous tetrahydrofuran (20 mL), stirred under nitrogen at −13 °C, was added methanesulfonyl chloride (250 μL, 3.23 mmol) followed by a solution of triethylamine (1.5 mL, 10.8 mmol) in anhydrous tetrahydrofuran (10 mL) dropwise over 15 min at −12 to −14 °C. The resulting suspension was stirred below −11 °C for 1h and then allowed to warm to 20 °C over 2.5 h. Solid was filtered off and washed with ether, and the combined filtrates were evaporated. The residue was partitioned between ether (2 × 50 mL) and ice-cold saturated aqueous sodium bicarbonate solution (25 mL). The combined organic phases were washed with water (20 mL) and saturated brine (20 mL), dried, and evaporated to give (c-2, c-3-dimethylcyclopropyl-r-1-carboxylic) anhydride (543 mg, 87%) as an oil which crystallized: IR (KBr) ν_{max} 1788, 1732, 1024 cm^{-1}; ^{1}H NMR (CHCl$_3$) δ 1.68 (dd, J = 9.0 Hz, 7.5 Hz, 2H, COC*H*CHMeCHMe x 2), 1.61−1.54 (m, 4H, COCHC*H*MeC*H*Me x 2), 1.24−1.21 (m, 12H, COCHCH*Me*CH*Me* x 2); MS (thermospray) *m/z* 228 (MNH4$^+$). To a solution of the *trans*-lactam **4** (600 mg, 2.19 mmol) in anhydrous tetrahydrofuran (8 mL)

stirred under nitrogen at −78 °C was slowly added 1M LHMDS solution in tetrahydrofuran (2.4 mL, 2.4 mmol). The yellow solution was stirred for a further 20 min at −78 °C, and then a solution of (c-2, c-3-dimethylcyclopropyl-r-1-carboxylic) anhydride (510 mg, 2.42 mmol) in anhydrous tetrahydrofuran (7 mL) was slowly added. The resulting solution was stirred for 1 h under nitrogen at −78 °C and then poured into saturated aqueous ammonium chloride solution (50 mL). The solution was extracted with ethyl acetate (2 × 50 mL), and the combined organic phases were washed sequentially with saturated aqueous sodium bicarbonate solution (20 mL), water (20 mL) and saturated brine (20 mL), dried, and evaporated to give an oil which crystallized (1.09 g). The crude product was purified by column chromatography eluting with cyclohexane−dichloromethane to give **41** (785 mg, 96%) as a white foam: IR (KBr) ν_{max} 1746, 1713, 1682 cm^{-1}; ^{1}H NMR ($CHCl_3$) δ 7.40−7.31 (m, 5H, aryl*H*), 5.16 and 5.09 (Abq, J = 12.5 Hz, 2H, PhCH_2O), 3.92−3.63 (m, 3H, NCH_2CH$_2$, NC*H*CH$_2$), 3.46 (dd, J = 11.0 Hz, 7.0 Hz, 1H, NC*H*CHMe), 3.25−3.11 and 3.04−2.90 (2 broad s, 1H, C*H*Me), 2.87−2.78 (m, 1H, COC*H*-CHMeCHMe), 2.75−2.67 (m, 1H, NCH$_2$C*H*H), 1.98−1.85 (m, 1H, NCH$_2$CH*H*), 1.69−1.53 (m, 2H, COCHC*H*MeC*H*Me), 1.30−1.06 (m, 9H, CH*Me*, COCHCH*Me*CH*Me*); LCMS *m*/*z* 371 (MH$^+$) single component 100% gradient 2 (t_R 3.53 min) gradient 3 (t_R 16.38); HRMS calcd for $C_{21}H_{27}N_2O_4$ (MH$^+$) 371.1971, found 371.1962.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-{[-*cis*-2,3-Dimethylcyclopropyl] -*trans*-carbonyl}-6-methyl-5-oxohexahydropyrrolo-[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-N-(4-isopropylphenyl)-pyrrolidine-1-carboxamide (46). Compound **4** was reacted with the anhydride prepared from (t-2, t-3-dimethylcyclopropyl-r-1-carboxylic) acid[15] and the intermediate converted through as described for the cis, cis-dimethyl isomer **45** to give **46** (67%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.24 and 7.11 (pseudo-Abq, J = 8.5 Hz, 4H, aryl*H*), 6.21 (s, 1H, CON*H*), 4.64 (dd, J = 8.0 Hz, 4.3 Hz, 1H, NC*H*CO), 4.45 (t, J = 8.0 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.83−3.45(m, 5H, NCH*H*CH$_2$CH$_2$, NCH_2CH$_2$, NC*H*CH$_2$, NC*H*CHMe), 3.32−3.20 (m, 1H, C*H*Me), 2.92−2.65 (m, 2H, NCH$_2$C*H*H, arylC*H*Me$_2$), 2.42−1.89 (m, 6H, COC*H*-CHMeCHMe, NCH$_2$CH_2CH_2, NCH$_2$CH*H*), 1.74−1.53 (m, 2H, COCHC*H*MeC*H*Me), 1.25−1.10 (m, 15H, arylCH*Me*$_2$, CH*Me*, COCHCH*Me*CH*Me*). Anal. ($C_{28}H_{38}N_4O_4$) C, H, N.

***tert*-Butyl (2*S*)-2-{[(3a*S*,6*S*,6a*R*)-6-methyl-5-oxo-4-[(2,2,3,3-tetramethylcyclopropyl)carbonyl]hexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}pyrrolidine-1-carboxylate (47)**. Derived from **12** and the mixed anhydride prepared from 2,2,3,3-tetramethylcyclopropanecarboxylic acid and trimethylacetyl chloride as described for **41** to give **47** (68%) as a white solid. ^{1}H NMR ($CDCl_3$) shows complex overlapping signals due to rotameric forms: δ 4.47−3.20 (m, 8H, NC*H*CO, NCH_2CH$_2$CH$_2$, NCH_2CH$_2$, NC*H*CH$_2$, NC*H*CHMe, C*H*Me), 3.08−2.63 (m, 1H, NCH$_2$C*H*H), 2.38−1.75 (m, 6H, COC*H*CMe$_2$-CMe$_2$, NCH$_2$CH*H*, NCH$_2$CH_2CH_2), 1.49−1.09 (m, 24H, *Bu*^{t}, CH*Me*, COCHC*Me*$_2$C*Me*$_2$); MS (thermospray) *m*/*z* 462 (MH$^+$), 362 (M-Boc$^+$); TLC R*f* 0.36 (cyclohexane−ethyl acetate, 1:1); LCMS *m*/*z* 462 (MH$^+$) single component 99% gradient 1 (t_R 4.88 min), gradient 2 (t_R 3.46 min), gradient 3 (t_R 16.17 min); HRMS calcd for $C_{25}H_{40}N_3O_5$ (MH$^+$) 462.2968, found 462.2974.

(3*S*,3a*R*,6a*S*)-3-Methyl-4-[(2*S*)-pyrrolidin-2-ylcarbonyl]-1-[(2,2,3,3-tetramethylcyclopropyl)carbonyl]hexahydropyrrolo[3,2-*b*]pyrrol-2(1*H*)-one trifluoroacetate (49). To a solution of **47** (75 mgs, 0.16 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (1 mL), and the mixture was left at 21° C for 1.5 h. The mixture was evaporated to dryness, toluene (2 × 5 mL) was added, and the mixture evaporated and then left under high vacuum for 24 h at room temperature to give **49** (76 mg, 99%) as a pale yellow foam: ^{1}H NMR ($CDCl_3$) δ 6.20−5.70 (broad s, 2H, NH_2^+), 4.60−4.40 (m, 2H, NC*H*CO, NC*H*HCH$_2$CH$_2$), 4.35−3.20 (m, 6H, NCH*H*CH$_2$CH$_2$, NCH_2CH$_2$, NC*H*CH$_2$, NC*H*CHMe, C*H*Me), 2.50−2.00 (m, 7H, NCH$_2$CH_2, NCH$_2$CH_2CH_2, COC*H*CMe$_2$CMe$_2$), 1.30−1.05 (m, 15H, CH*Me*, COCHC*Me*$_2$C*Me*$_2$); MS (thermospray) *m*/*z* 362 (MH$^+$), 380 (MNH$_4^+$). Anal. ($C_{20}H_{31}N_3O_3$·$C_2HF_3O_2$) C, H, N.

(3*S*,3a*R*,6a*S*)-3-Methyl-1-(4-nitrophenyl)-4-[(2*S*)-pyrrolidin-2-ylcarbonyl]hexahydropyrrolo[3,2-*b*]pyrrol-2(1*H*)-one trifluoroacetate (50). Compound **48** was deprotected with trifluoroacetic acid as described for **49** to give **50** (99%) as a yellow glass: ^{1}H NMR ($CDCl_3$) δ 12.40−12.05 (broad s, exch., 0.5H, N*H*), 8.33−8.24 and 7.62−7.53 (2m, 4H, aryl*H*), 4.94−4.84 (m, 1H, NC*H*CO), 4.28−3.30 (m, 7H, NCH_2CH$_2$CH$_2$, NCH_2CH$_2$, NC*H*CH$_2$, NC*H*CHMe, C*H*Me), 2.80−2.60 (m, 1H, NCH$_2$C*H*H), 2.37−1.90 (m, 5H, NCH$_2$CH_2CH_2, NCH$_2$CH*H*), 1.34−1.13 (m, 3H, CH*Me*); MS (thermospray) *m*/*z* 359 (MH$^+$). Anal. ($C_{18}H_{22}N_4O_4$·$C_2HF_3O_2$) C, H, N.

***tert*-Butyl (2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(1,3-Benzothiazol-2-yl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}pyrrolidine-1-carboxylate (54).** A mixture of Boc-proline translactam **12** (40.4 mg, 0.12 mmol, 1 equiv), copper (1) chloride (12 mg, 0.12 mmol, 1 equiv), potassium carbonate (27.5 mg, 0.2 mmol, 1.66 equiv), TDA-1 (11.1μL, 0.03 mmol, 0.29 equiv), and 2-bromobenzothiazole (45 mg, 0.21 mmol, 1.75 equiv) in *p*-xylene (25 mL) was stirred and refluxed under nitrogen. After 4.5 h the mixture was left to stand at room temperature overnight before it was reheated and stirred at reflux for a further 5.25 h and then allowed to cool to room temperature overnight. Then the mixture was filtered and the residue washed with ethyl acetate (10 mL). The filtrate and washings were combined and washed with 1M hydrochloric acid (10 mL), water (7.5 mL), and brine (7.5 mL), dried, and evaporated to leave a yellow solid. The crude material was purified by preparative plate chromatography eluting with ethyl acetate-cyclohexane (1:1) to give **54** (26.2 mg, 46%) as a white solid: NMR ($CDCl_3$) δ 7.80 (t, J = 6.7 Hz, 2H, benzothiazolyl-*4H* and -*7H*) 7.44 and 7.31 (2t, J = 7.5 Hz, 2H, benzothiazolyl-*5H* and -*6H*), 4.44 (m, 1H, NC*H*CO), 4.15, 3.85 and 3.53 (3m, 6H, NC*H*CHMe, NCH_2CH$_2$CH$_2$, NCH_2CH$_2$ and NC*H*CH$_2$),3.45 (m, 1H, C*H*Me), 3.17 and 2.37 (2m, 2H, NCH$_2$CH_2), 2.16 and 1.91 (2m, 4H, NCH$_2$CH_2CH$_2$, NCH$_2$-CH$_2$CH_2), 1.44 (d, J = 6.1 Hz, (rotamers) 9H, Bu^t), 1.20 (m, 3H, CH*Me*); MS (thermospray) *m*/*z* 471 (MH$^+$), 371 (M-Boc$^+$); HPLC 100% (t_R 31.44min); HRMS calcd for $C_{24}H_{30}N_4O_4S$ (MH$^+$) 471.206603, found 471.206283.

The following compounds were similarly prepared.

***tert*-Butyl (2*S*)-2-{[(3a*S*,6*S*,6a*R*)-6-Methyl-4-(4-nitrophenyl)-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]-carbonyl}pyrrolidine-1-carboxylate (48).** Compound **12** was reacted with 4-nitrobromobenzene as described for **54** to give **48** (65%) as a yellow foam: ^{1}H NMR ($CDCl_3$) δ 8.30−8.22 and 7.64−7.56 (2m, 4H, aryl*H*), 4.53−3.10 (m, 8H, NC*H*CO, NCH_2CH$_2$CH$_2$, NCH_2CH$_2$, NC*H*CH$_2$, NC*H*CHMe, C*H*Me), 2.75−2.55 (m, 1H, NCH$_2$C*H*H), 2.30−1.81 (m, 5H, NCH$_2$CH*H*, NCH$_2$CH_2CH_2), 1.49−1.40 (m, 9H, *Bu*^{t}), 1.20−1.13 (m, 3H, CH*Me*); MS (thermospray) *m*/*z* 459 (MH$^+$), 359 (M-Boc$^+$); LCMS *m*/*z* 459 (MH$^+$) single component 100% gradient 2 (t_R 3.12 min) gradient 3 (t_R 14.04min); HPLC 100% (t_R 26.7min); HRMS calcd for $C_{23}H_{30}N_4O_6$ (MNa$^+$) 481.2063, found 481.2071.

***tert*-Butyl (2*S*)-2-{[(3a*S*,6*S*,6a*R*)-6-Methyl-5-oxo-4-(1,3-thiazol-2-yl)hexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]-carbonyl}pyrrolidine-1-carboxylate (53)**. Compound **12** was reacted with 2-bromothiazole as described for **54** to give **53** (37%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.44 (d, J = 3.7 Hz, 1H, SCHC*H*N), 7.02 (m, 1H, SC*H*), 4.42 (m, 1H, NC*H*CO), 4.22−3.38 (m, 7H, NC*H*CHMe, C*H*Me, NCH_2CH$_2$CH$_2$, NCH_2-CH$_2$ and NC*H*CH$_2$), 3.01 (m, 1H, NCH$_2$C*H*H), 2.43−1.82 (m, 5H, NCH$_2$CH_2CH$_2$, NCH$_2$CH$_2$CH_2, NCH$_2$CH*H*), 1.46 (d, J = 6.7 Hz, 9H, Bu^t), 1.17 (dd, J = 7.3 Hz, 3.7 Hz, 3H, CH*Me*); MS (thermospray) *m*/*z* 421 (MH$^+$); LCMS *m*/*z* 421 (MH$^+$) single component 98% gradient 2 (t_R 2.91 min), gradient 3 (t_R 13.13 min); HRMS calcd for $C_{20}H_{29}N_4O_4S$ (MH$^+$) 421.1910, found 421.1905; HPLC 100% (t_R 24.06 min).

***tert*-Butyl (2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-[6-({[*tert*-Butyl(diphenyl)silyl]oxy} methyl)-1,3-benzothiazol-2-yl]-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-pyrrolidine-1-carboxylate (58).** Prepared in a manner similar to **54** by reacting **12** with 2-bromo-6-(*tert*-butyldiphenylsilanyloxymethyl)-benzothiazole[12] to give **58** (57% yield) as a pale yellow foam:^{1}H NMR ($CDCl_3$) δ 7.81−7.63 (m,

4H, arylH), 7.49−7.31 (m, 9H, arylH), 4.85 (s, 2H, arylCH_2), 4.52−4.04 (m, 3H, NC*H*CO, NC*H*HCH_2CH_2, NC*H*CHMe), 3.98−3.07 (m, 6H, NCH*H*CH_2CH_2, NCH_2CH_2, NC*H*CH_2, C*H*Me, NCH_2C*H*H), 2.49−1.80 (m, 5H, NCH_2CH*H*, NCH_2CH_2CH_2), 1.44 (2s, 9H, t-BuO_2C), 1.29−1.16 (m, 3H, *Me*), 1.10 (s, 9H, t-BuSiO); MS (thermospray) *m*/*z* 739 (MH^+), 639 ((MH−Boc$^+$); LCMS *m*/*z* 739 (MH^+) single component 99.5% gradient 1 (t_R 4.51 min); HPLC 100% (t_R 43.6min). Anal. ($C_{41}H_{50}N_4O_5SSi$) C, H, N, S.

***tert*-Butyl (2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(4-Methoxy-1,3-benzothiazol-2-yl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}pyrrolidine-1-carboxylate (59)**. Prepared in a manner similar to **54** by reacting **12** with 2-bromo-4-methoxy-benzothiazole[12] to give **59 (**61% yield) as a white solid:^{1}H NMR ($CDCl_3$) δ 7.41 (d, J = 7.9 Hz, 1H, benzothiazolyl-*7H*), 7.27 (m, 1H, benzothiazolyl-*6H*), 6.90 (d, J = 7.9 Hz, 1H, benzothiazolyl-*5H*), 4.43 (m, 1H, NC*H*CO), 4.02 (s, 3H, OCH_3), 4.29−4.07, 3.95−3.69 and 3.68−3.36 (3m, 7H, NC*H*CHMe, NCH_2CH_2CH_2, C*H*Me, NCH_2CH_2 and NC*H*CH_2), 3.19 and 2.39 (2m, 2H, NCH_2CH_2), 2.20 and 1.90 (2m, 4H, NCH_2CH_2CH_2, NCH_2CH_2CH_2), 1.45 (d, J = 7.3 Hz, (rotamers) 9H, Bu^t), 1.18 (m, 3H, CH*Me*); MS (thermospray) *m*/*z* 501 (MH^+), 401 (MH−Boc$^+$); HPLC 98.5% (t_R 29.5min). Anal. ($C_{25}H_{32}N_4O_5S$·0.15 $CHCl_3$) C, H, N.

***tert*-Butyl (2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(5-Chloro-1,3-benzothiazol-2-yl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}pyrrolidine-1-carboxylate (60)**. Prepared in a manner similar to **54** by reacting **12** with 2-bromo-5-chloro-benzothiazole[12] to give **60 (**16% yield) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 1.2 Hz, 1H, benzothiazolyl-*4H*), 7.72 (d, J = 8.5 Hz, 1H, benzothiazolyl-*7H*), 7.28 (m, 1H, benzothiazolyl-*6H*), 4.44 (m, 2H, NC*H*CO, NCH*H*CH_2), 4.13 (m, 1H, NC*H*CH_2), 3.99−3.70 and 3.68−3.36 (2m, 5H, NC*H*CHMe, NCH_2CH_2CH_2, C*H*Me, NC*H*HCH_2) 3.12 and 2.37 (2m, 2H, NCH_2CH_2), 2.30−2.00 and 2.00−1.81 (2m, 4H, NCH_2CH_2CH_2), 1.45 (d, J = 5.5 Hz, (rotamers) 9H, Bu^t), 1.20 (m, 3H, CH*Me*); MS (thermospray) *m*/*z* 505 (MH^+), 405 (MH−Boc$^+$). Anal. ($C_{24}H_{29}ClN_4O_4S$) C, H, N, S.

***tert*-Butyl (2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(5-Methoxy[1,3]-thiazolo[5,4-*b*]pyridin-2-yl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}pyrrolidine-1-carboxylate (61).** Prepared in a manner similar to **54** by reacting **12** with 2-bromo-6- methoxy-7aza-benzothiazole[12] to give **61** (80% yield) as a glassy solid:^{1}H NMR ($CDCl_3$) (rotamers) δ 7.78 (d, J = 8.5 Hz, 1H, azabenzothiazolyl-*4H*); 6.80 (d, J = 8.5 Hz, 1H, azabenzothiazolyl-5*H*); 4.50−4.33 (m, 2H, NC*H*CO, NC*H*HCH_2); 4.20−4.01 (m, 1H, NC*H*CH_2); 4.00 (s, 3H, ArO*Me*); 3.97−3.02 (m, 6H, NCH*H*CH_2, NC*H*CHMe, NCH_2CH_2CH_2, C*H*Me, NCH_2C*H*H), 2.42−1.81 (m, 5H, NCH_2CH*H*, NCH_2CH_2CH_2), 1.47−1.41 and 1.24−1.16 (2m, 12H, *Bu^t*, CH*Me*). MS (thermospray) *m*/*z* 502 (MH^+). Anal. ($C_{24}H_{31}N_5O_5S$) C, H, N, S.

***tert*-Butyl (2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(4-Methoxy-7-methyl-1,3-benzothiazol-2-yl)-6-methyl-5-oxohexahydropyrrolo-[3,2-*b*]pyrrol-1(*2H*)-yl]carbonyl}pyrrolidine-1-carboxylate (62).** Prepared in a manner similar to **54** by reacting **12** with 2-bromo-4-methoxy-7-methyl-benzothiazole[12] to give **62** (53% yield) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 7.05 (d, J = 7 Hz, 1H) and 6.83 (d, J = 8 Hz, 1H benzothiazolyl-*5H* and −*6H*), 4.47 (m, 1H, NC*H*CO), 4.39 (m, 1H, NC*H*HCH_2), 4.18 (m, 1H, NC*H*CH_2), 4.00 (s, 3H, OCH_3), 3.94−3.71 and 3.67−3.36 (2m, 5H, NC*H*CHMe, NCH_2CH_2CH_2, C*H*Me, NCH*H*CH_2), 3.20 (m, 1H, NCH_2C*H*H), 2.48 (s, 3H, arylCH_3), 2.50−2.02 and 1.97−1.80 (2m, 5H, NCH_2CH*H*, NCH_2CH_2CH_2, NCH_2CH_2CH_2), 1.45 (d, J = 7.3 Hz, (rotamers) 9H, Bu^t), 1.19 (m, 3H, CH*Me*); MS (thermospray) *m*/*z* 515 (MH^+), 415 (MH−Boc$^+$); LCMS *m*/*z* 515 (MH^+) single component 100% gradient 2 (t_R 3.42 min), gradient 3 (t_R 15.83 min); HRMS calcd for $C_{26}H_{35}N_4O_5S$ (MH^+) 515.2328, found 515.2345.

***tert*-Butyl (2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(6-Methoxy-1,3-benzothiazol-2-yl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}pyrrolidine-1-carboxylate (63).** Prepared in a manner similar to **54** by reacting **12** with 2-bromo-6-methoxy-benzothiazole[12] to give **63** (58% yield) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.68 (d, J = 8.6 Hz, 1H, benzothiazolyl-*4H*), 7.28 (d, J = 2.5 Hz, 1H, benzothiazolyl-*7H*), 7.03 (dd, J = 8.7 Hz, 2.5 Hz, 1H, benzothiazolyl-*5H*), 4.44 (m, 1H, NC*H*CO), 3.87 (s, 3H, OCH_3), 4.24−4.01, 3.98−3.69 and 3.67−3.36 (3m, 7H, NC*H*CHMe, NCH_2CH_2CH_2, C*H*Me, NCH_2CH_2 and NC*H*CH_2), 3.13 and 2.35 (2m, 2H, NCH_2CH_2), 2.27−2.00 and 2.00−1.80 (2m, 4H, NCH_2CH_2CH_2, NCH_2-CH_2CH_2), 1.44 (d, J = 6.1 Hz, (rotamers) 9H, Bu^t), 1.19 (m, 3H, CH*Me*); MS (thermospray) *m*/*z* 501 (MH^+), 401 (MH−Boc$^+$); LCMS *m*/*z* 501 (MH^+) single component 100% gradient 2 (t_R 3.38 min), gradient 3 (t_R 15.44 min); HRMS calcd for $C_{25}H_{33}N_4O_5S$ (MH^+) 501.2172, found 501.2165.

***tert*-Butyl (2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(4-Chloro-1,3-benzothiazol-2-yl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}pyrrolidine-1-carboxylate (64).** Prepared in a manner similar to **54** by reacting **12** with 2-bromo-4-chloro-benzothiazole[12] to give **64 (**55% yield) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.71 and 7.46 (2d, J = 8 Hz, 2H, benzothiazolyl-*5H* and −*7H*), 7.23 (m, 1H, benzothiazolyl-*6H*), 4.54−4.07 (m, 3H, NC*H*CO, NCH_2CH_2), 4.01−3.70 and 3.69−3.36 (2m, 5H, NC*H*CHMe, NCH_2CH_2CH_2, C*H*Me, NC*H*CH_2), 3.21 and 2.40 (2m, 2H, NCH_2CH_2), 2.32−2.01 and 1.98−1.78 (2m, 4H, NCH_2CH_2CH_2, NCH_2CH_2CH_2), 1.46 (d, J = 6.1 Hz, (rotamers) 9H, Bu^t), 1.20 (m, 3H, CH*Me*); MS (thermospray) *m*/*z* 505 (MH^+), 405 (MH−Boc$^+$). Anal. ($C_{24}H_{29}ClN_4O_4S$) C, H, N, S.

***tert*-Butyl (2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(5-Methoxy-1,3-benzothiazol-2-yl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}pyrrolidine-1-carboxylate (65).** Prepared in a manner similar to **54** by reacting **12** with 2-bromo-5- methoxy-benzothiazole[12] to give **65 (**37% yield) as an off-white foam: ^{1}H NMR ($CDCl_3$) δ 7.66 (d, J = 8 Hz, 1H, benzothiazolyl-*7H*), 7.30 (d, J = 2 Hz, 1H, benzothiazolyl-*4H*), 6.95 (dd, J = 8.5 Hz, 2.5 Hz, 1H, benzothiazolyl-*6H*), 4.48 (m, 1H, NC*H*CO), 4.42 (m, 1H, NC*H*HCH_2), 4.13 (m, 1H, NC*H*CH_2), 3.88 (s, 3H, OCH_3), 3.96−3.69 and 3.65−3.36 (2m, 5H, NC*H*-CHMe, NCH_2CH_2CH_2, C*H*Me and NCH*H*CH_2), 3.14 and 2.38 (2m, 2H, NCH_2CH_2), 2.30−2.01 and 1.98−1.80 (2m, 4H, NCH_2CH_2CH_2, NCH_2CH_2CH_2), 1.45 (d, J = 6 Hz, (rotamers) 9H, Bu^t), 1.20 (m, 3H, CH*Me*); MS (thermospray) *m*/*z* 501 (MH^+), 401 (MH−Boc$^+$); LCMS *m*/*z* 501 (MH^+) single component 98% gradient 2 (t_R 3.39 min) gradient 3 (t_R 15.44 min); HRMS calcd for $C_{25}H_{33}N_4O_5S$ (MH^+) 501.2172, found 501.2162.

***tert*-Butyl (2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-{5-[(Difluoromethyl)-sulfonyl]-1,3-benzothiazol-2-yl}-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}pyrrolidine-1-carboxylate (66).** Prepared in a manner similar to **54** by reacting **12** with 2-bromo-5-(difluoromethyl)sulfonyl-benzothiazole[12] to give **66 (**27.5% yield) as a cream solid: ^{1}H NMR ($CDCl_3$) δ 8.40 (d, J = 1.2 Hz, 1H, benzothiazolyl-*4H*), 8.07 (d, J = 8 Hz, 1H, benzothiazolyl-*7H*), 7.87 (m, 1H, benzothiazolyl-*6H*), 6.24 (t, J = 54 Hz, 1H, CF_2H), 4.45 (m, 2H, NC*H*CO and NC*H*HCH_2), 4.31−4.05, 4.01−3.73 and 3.67−3.34 (3m, 6H, NC*H*CHMe, NCH_2CH_2CH_2, C*H*Me, NCH*H*CH_2 and NC*H*CH_2), 3.14 (m, 1H, NCH$_2$CH*H*), 2.51−2.02 and 1.97−1.78 (2m, 5H, NCH$_2$C*H*H, NCH2C*H2*CH2, NCH$_2$CH$_2$CH_2), 1.45 (d, J = 5 Hz, (rotamers) 9H, Bu^t), 1.20 (m, 3H, CH*Me*); MS (thermospray) *m*/*z* 585 (MH^+), 485 (MH−Boc$^+$). Anal. ($C_{25}H_{30}F_2N_4O_6S_2$) C, H, N.

***tert*-Butyl (2*S*)-2-{[(3a*S*,6*S*,6a*R*)-6-Methyl-4-(6-nitro-1,3-benzothiazol-2-yl)-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}pyrrolidine-1-carboxylate (67).** Prepared in a manner similar to **54** by reacting **12** with 2-bromo-6-nitro-benzothiazole[12] to give **67 (**13% yield) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 8.72 (d, J = 2.5 Hz, 1H, benzothiazolyl-*7H*), 8.30 (dd, J = 9 Hz, 2 Hz, 1H, benzothiazolyl-*5H*), 7.82 (d, J = 8.5 Hz, 1H, benzothiazolyl-*4H*), 4.53−4.37 and 4.29−4.06 (2m, 3H, NC*H*CO, NC*H*HCH_2 and NC*H*CH_2), 4.04−3.73 and 3.69−3.36 (2m, 5H, NC*H*CHMe, NCH_2CH_2CH_2, C*H*Me, NCH*H*CH_2), 3.14 and 2.42 (2m, 2H, NCH_2CH_2), 2.32−2.02 and 1.99−1.83 (2m, 4H, NCH_2CH_2CH_2, NCH_2CH_2CH_2), 1.45 (d, J = 5 Hz, (rotamers) 9H, Bu^t), 1.24 (m, 3H, CH*Me*); MS (thermospray) *m*/*z* 516 (MH^+), 416 (MH−Boc$^+$). Anal. ($C_{24}H_{29}N_5O_6S$) C, H, N, S.

***tert*-Butyl (2*S*)-2-{[(3a*S*,6*S*,6a*R*)-6-Methyl-5-oxo-4-[6-(trifluoromethoxy)-1,3-benzothiazol-2-yl]hexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}pyrrolidine-1-carboxylate (68).** Prepared in a manner similar to **54** by reacting **12** with 2-bromo-6-trifluoromethoxy-benzothiazole[12] to give **68 (**53% yield) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.77 (d, J = 8.5 Hz, 1H, benzothiazolyl-*4H*), 7.67 (m, 1H benzothiazolyl-*7H*), 7.30 (m, 1H, benzothiazolyl-*5H*), 4.54−4.01 (m, 3H, NC*H*CO, NCH_2CH$_2$), 3.98−3.70 and 3.69−3.35 (2m, 5H, NC*H*CHMe, NCH_2CH$_2$CH$_2$, C*H*Me, and NC*H*CH$_2$), 3.13 (m, 1H, NCH$_2$C*H*H), 2.48−1.79 (m, 5H, NCH$_2$NH*H*, NCH2C*H2*CH2, NCH$_2$CH$_2$CH_2), 1.46 (d, J = 6.1 Hz, (rotamers) 9H, Bu^t), 1.20 (m, 3H, CH*Me*); MS (thermospray) *m*/*z* 555 (MH$^+$), 455 (MH−Boc$^+$); LCMS *m*/*z* 555 (MH$^+$) single component 100% gradient 2 (t_R 3.70 min), gradient 3 (t_R 17.11 min); HRMS calcd for $C_{25}H_{30}F_3N_4O_5S$ (MH$^+$) 555.1889, found 555.1902.

***tert*-Butyl (2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(6-Fluoro-1,3-benzothiazol-2-yl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]-pyrrol-1(2*H*)-yl]carbonyl}pyrrolidine-1-carboxylate (69).** Prepared in a manner similar to **54** by reacting **12** with 2-bromo-6-fluoro-benzothiazole[12] to give **69 (**45% yield) as an off-white foam: ^{1}H NMR ($CDCl_3$) δ 7.71 (dd, J = 8.5 Hz, 4.5 Hz, 1H, benzothiazolyl-*4H*), 7.46 (dd, J = 8 Hz, 2.5 Hz, 1H, benzothiazolyl-*7H*), 7.16 (m, 1H, benzothiazolyl-*5H*), 4.52−4.36 (m, 2H, NC*H*CO, NCH*H*CH$_2$), 4.14 (m, 1H, NC*H*CH$_2$), 3.97−3.70, 3.66−3.36 (2m, 5H, NC*H*CHMe, NCH_2CH$_2$CH$_2$, C*H*Me, NC*H*HCH$_2$), 3.12 and 2.38 (2m, 2H, NCH$_2$CH_2), 2.34−2.04 and 1.98−1.80 (2m, 4H, NCH$_2$CH_2CH$_2$, NCH$_2$CH$_2$CH_2), 1.45 (d, J = 6 Hz, (rotamers) 9H, *Bu*^{t}), 1.20 (m, 3H, CH*Me*); MS (thermospray) *m*/*z* 489 (MH$^+$), 389 (MH−Boc$^+$). Anal. ($C_{24}H_{29}$-FN_4O_4S) C, H, N, S.

Ethyl 2-[(3*S*,3a*R*,6a*S*)-4-{[(2*S*)-1-(*tert*-Butoxycarbonyl)-pyrrolidin-2-yl]carbonyl}-3-methyl-2-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]-1,3-benzothiazole-6-carboxylate (70). Prepared in a manner similar to **54** by reacting **12** with 2-bromo-6-ethoxycarbonylbenzothiazole[12] to give **70** (38% yield) as a white solid: ^{1}H NMR ($CDCl_3$) δ 8.53 (d, J = 1.8 Hz, 1H, benzothiazolyl-7*H*); 8.12 (dd, J = 8.6 Hz, 1.8 Hz, 1H, benzothiazolyl-5*H*); 7.80 (d, J = 8.6 Hz, 1H, benzothiazolyl-4*H*); 4.50−4.36 (m, 3H, NC*H*CO, $CO_2C_H_2$Me); 4.30−3.07 (m, 8H, NCH_2CH$_2$CH$_2$, NCH_2CH$_2$, NC*H*CH$_2$, NC*H*CHMe, C*H*Me, NCH$_2$C*H*H); 2.49−1.84 (m, 5H, NCH$_2$CH*H*, NCH$_2$CH_2CH$_2$); 1.50−1.38 and 1.27−1.17 (2m, 15H, *Bu*^{t}, CO_2CH_2*Me*, CH*Me*); MS (thermospray) *m*/*z* 543 (MH$^+$); LCMS *m*/*z* 543 (MH$^+$) single component 100% gradient 1 (t_R 4.78 min), gradient 2 (t_R 3.58 min), gradient 3 (t_R 14.63 min); HRMS calcd for $C_{27}H_{35}N_4O_6S$ (MH$^+$) 543.2277, found 543.2283.

***tert*-Butyl (2*S*)-2-{[(3a*S*,6*S*,6a*R*)-6-Methyl-5-oxo-4-[1,3]-thiazolo[5,4-*b*]pyridin-2-ylhexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}pyrrolidine-1-carboxylate (71).** Prepared in a manner similar to **54** by reacting **12** with 2-bromo-7-aza-benzothiazole[12] to give **71** (28% yield) as a white solid: ^{1}H NMR ($CDCl_3$) shows rotameric forms: δ 8.50−8.45 (m, 1H, pyridyl-*2H*), 7.98 (dd, J = 8.3 Hz, 1.5 Hz, 1H, pyridyl-*4H*), 7.36 (dd, J = 8.3 Hz, 4.9 Hz, 1H, pyridyl-*3H*), 4.49−4.00 (2m, 3H, NC*H*CO, NC*H*HCH$_2$, NC*H*CH$_2$), 4.99−3.70 (m, 2H, NCH-*H*CH$_2$, NC*H*CHMe), 3.61−3.05 (2m, 4H, NCH_2CH$_2$CH$_2$, C*H*Me, NCH$_2$C*H*H), 2.47−1.80 (3m, 5H, NCH$_2$CH*H*, NCH$_2$CH_2CH$_2$), 1.48−1.40 (m, 9H, *Bu*^{t}) 1.26−1.16 (m, 3H, CH*Me*); MS (thermospray) *m*/*z* 472 (MH$^+$), 372 (MH−Boc$^+$). Anal. ($C_{23}H_{29}N_5O_4S$) C, H, N, S.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(1,3-Benzothiazol-2-yl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-N-(4-isopropylphenyl)pyrrolidine-1-carboxamide (56). To **54** (64 mg, 136 μmol) was added trifluoroacetic acid (315 μL, 4.09 mmol) at room temperature. After 10 min the solution was azeotroped with toluene (1 mL × 2) to leave a yellow gum (78 mg), which was dissolved in acetonitrile (2 mL) and 4-(isopropyl)phenyl isocyanate (30 μL, 188 μmol, 1.37 equiv) added followed by triethylamine (47.5 μL, 341 μmol, 2.5 equiv). The mixture was left to stand at room temperature for 4 h before it was directly purified using preparative plate chromatography eluting with ethyl acetate to give **56** (62 mg, 85%) as an off-white solid: ^{1}H NMR ($CDCl_3$) δ 7.80 (dd, J = 8 Hz, 4 Hz, 2H, benzothiazolyl-*4H* and −7H); 7.44 (m, 1H, benzothiazolyl-*5H*); 7.36−7.22 (m, 3H, benzothiazolyl-*6H*, aryl); 7.14 (d, J = 8 Hz, 2H, aryl); 6.23 (s, 1H, N*H*); 4.70 (dd, J = 8 Hz, 4 Hz, 1H, NC*H*CO); 4.62 (t, J = 10 Hz, 1H, NCH*H*CH$_2$); 4.13 (m, 1H, NC*H*CH$_2$); 3.99−3.64 (m, 3H, NC*H*CHMe, NCH*H*CH$_2$CH$_2$, NC*H*HCH$_2$); 3.54 (m, 1H, NC*H*HCH$_2$CH$_2$); 3.45 (m, 1H, C*H*Me); 3.14 (m, 1H, NCH$_2$CH*H*); 2.86 (m, 1H, C*H*Me$_2$); 2.48−1.92 (m, 5H, NCH$_2$C*H*H, NCH$_2$C*H*$_2$CH$_2$), 1.21 (d, J = 7 Hz, 9H, 3 x Me); MS (thermospray) *m*/*z* 532 (MH$^+$), 371 (M-[4-(isopropyl)phenyl isocyanate group]$^+$); Circular dichroism (CH_3CN) λ_{max}198.0 nm, dE −11.0, E42843, λ_{max}212.4 nm, dE 8.47, E34234, λ_{max}228.0 nm, dE −4.01, E25880, λ_{max}239.0 nm, dE 2.94, E25077, λ_{max}248.2 nm, dE 0.47, E23038, λ_{max}-257.2 nm, dE 4.78, E11031; LCMS *m*/*z* 532 (MH$^+$) single component 99% gradient 2 (t_R 3.61 min), gradient 3 (t_R 16.55 min); HRMS calcd for $C_{29}H_{34}N_5O_3S$ (MH$^+$) 532.2382, found 532.2393.

The following compounds were similarly prepared.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-6-Methyl-5-oxo-4-(1,3-thiazol-2-yl) hexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-N-(4-isopropylphenyl) pyrrolidine-1-carboxamide (55). Prepared in a manner similar to **56** from **53** to give **55** (96% yield) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.45 (d, 1H, J = 3.5 Hz, thiazolyl-*4H*), 7.25−7.22 (m, 2H, aryl -*2H*, -*6H*), 7.17−7.12 (m, 2H, aryl -*3H*, -*5H*), 7.01 (d, J = 3.5 Hz, 1H, thiazolyl-*5H*), 6.19 (s, exch., 1H, CON*H*), 4.67 (dd, J = 8.0 Hz, 4.5 Hz, 1H, NC*H*CO), 4.58 (t, J = 9.5 Hz, 1H, NC*H*HCH$_2$), 4.09−4.00 (m, 1H, NC*H*CH$_2$), 3.93−3.85 (m, 1H, NCH*H*CH$_2$), 3.78−3.73 (m, 1H, NC*H*HCH$_2$CH$_2$), 3.72−3.65 (m, 1H, NCH*H*CH$_2$CH$_2$), 3.52 (dd, J = 14.5 Hz, 7.5 Hz, 1H, NC*H*CHMe), 3.40 (quintet, J = 7.5 Hz, 1H, C*H*Me), 3.02−2.95 (m, 1H, NCH$_2$C*H*H), 2.84 (septet, J = 7.0 Hz, 1H, arylC*H*Me$_2$), 2.41−2.17 (m, 3H, NCH$_2$C*H*H, NCH$_2$C*H*HCH$_2$, NCH$_2$CH$_2$C*H*H), 2.13−2.03 (m, 1H, NCH$_2$CH*H*CH$_2$), 2.03−1.94 (m, 1H, NCH$_2$CH$_2$CH*H*), 1.20 (d, J = 7.0 Hz, 6H, arylCH*Me$_2$*), 1.17 (d, J = 7.5 Hz, 3H, CH*Me*); MS (thermospray) *m*/*z* 482 (MH$^+$). Anal. ($C_{25}H_{31}N_5O_3S$) C, H, N.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(4-Methoxy-1,3-benzothiazol-2-yl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-N-(4-isopropylphenyl)pyrrolidine-1-carboxamide (73). Prepared in a manner similar to **56** from **59** to give **73** (90% yield) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.40 (d, J = 7 Hz, 1H, benzothiazolyl-*7H*); 7.25 (m, 3H, benzothiazolyl-*6H*, aryl); 7.13 (d, J = 8.5 Hz, 2H, aryl); 6.89 (d, J = 8 Hz, 1H, benzothiazolyl-*5H*); 6.20 (s, 1H, N*H*); 4.68 (m, 1H, NC*H*CO); 4.58 (m, 1H, NCH*H*CH$_2$); 4.19 (m, 1H, NC*H*CH$_2$); 4.02 (s, 3H, O*Me*), 3.98−3.62 (m, 3H, NC*H*CHMe, NCH*H*CH$_2$-CH$_2$, NC*H*HCH$_2$); 3.58−3.34 (m, 2H, NC*H*HCH$_2$CH$_2$, C*H*Me); 3.16 (m, 1H, NCH$_2$CH*H*); 2.85 (m, 1H, C*H*Me$_2$); 2.53−1.91 (m, 5H, NCH$_2$C*H*H, NCH$_2$CH_2CH_2), 1.20 (m, 9H, CH*Me$_2$*, *Me*); MS (thermospray) *m*/*z* 562 (MH$^+$), 401 (M-[4-(isopropyl)phenyl isocyanate group]$^+$). Anal. ($C_{30}H_{35}N_5O_4S$·0.05 EtOAc) C, H, N.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(5-Chloro-1,3-benzothiazol-2-yl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-N-(4-isopropylphenyl)pyrrolidine-1-carboxamide (74). Prepared in a manner similar to **56** from **60** to give **74** (74% yield) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 2.5 Hz, 1H, benzothiazoyl-*4H*), 7.71 (d, J = 8.5 Hz, 1H, benzothiazolyl-*7H*), 7.27 (m, 3H, benzothiazolyl-*6H*, aryl), 7.12 (d, J = 8.5 Hz, 2H, aryl), 6.33 (s, 1H, N*H*), 4.67 (dd, J = 8 Hz, 4 Hz, 1H, NC*H*CO), 4.59 (t, J = 10 Hz, 1H, NCH*H*CH$_2$), 4.10 (m, 1H, NC*H*CH$_2$), 3.91 (m, 1H, NC*H*HCH$_2$), 3.74 (dd, J = 11 Hz, 8 Hz, 1H, NC*H*CHMe), 3.67 (m, 1H, NC*H*HCH$_2$CH$_2$), 3.58−3.36 (m, 2H, C*H*Me, NCH*H*CH$_2$CH$_2$), 3.07 (m,1H, NCH$_2$-CH*H*), 2.84 (m, 1H, C*H*Me$_2$), 2.44−1.70 (m, 5H, NCH$_2$C*H*H, NCH$_2$CH_2CH_2), 1.19 (d, J = 7 Hz, 9H, CH*Me$_2$*, *Me*): MS (thermospray) *m*/*z* 566 (MH$^+$), 405 (M-[4-(isopropyl)phenyl isocyanate group] $^+$); LCMS *m*/*z* 566 (MH$^+$) single component 98.0% gradient 1 (t_R 4.92 min); HPLC 100% (t_R 35.58 min). Anal. ($C_{29}H_{32}ClN_5O_3S$·0.15$CHCl_3$) C, H, N.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(5-Methoxy[1,3]thiazolo[5,4-*b*]-pyridin-2-yl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-N-(4-isopropylphenyl)pyrrolidine-1-carboxamide (75). Prepared in a manner similar to **56** from

61 to give **75** (95% yield) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 8.5 Hz, 1H, pyridothiazolyl-*4H*), 7.28−7.21 and 7.17−7.10 (2m, 4H, aryl*H*), 6.80 (d, J = 8.5 Hz, 1H, pyridothiazolyl-*5H*), 6.19 (s, 1H, CON*H*), 4.72−4.51 (m, 2H, NC*H*CO, NC*H*HCH$_2$CH$_2$), 4.15−3.35 (m, 9H, NCH*H*CH$_2$CH$_2$, heteroarylO*Me*, NC*H*$_2$CH$_2$, NC*H*CH$_2$, NC*H*CHMe, arylC*H*Me$_2$), 3.14−3.00 (m, 1H, C*H*Me), 2.91−2.78 (m, 1H, NCH$_2$C*H*H), 2.45−1.90 (m, 5H, NCH$_2$CH*H*, NCH$_2$C*H*$_2$CH$_2$), 1.25−1.15 (m, 9H, arylCH*Me*$_2$, CH*Me*); MS (thermospray) *m*/*z* 563 (MH$^+$); LCMS *m*/*z* 563 (MH$^+$) single component 100% gradient 2 (t_R 3.49 min), gradient 3 (t_R 16.30min); HRMS calcd for $C_{29}H_{35}N_6O_4S$ (MH$^+$) 563.2441, found 563.2425.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(4-Methoxy-7-methyl-1,3-benzothiazol-2-yl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-N-(4-isopropylphenyl)pyrrolidine-1-carboxamide (76). Prepared in a manner similar to **56** from **62** to give **76** (91% yield) as a cream solid: ^{1}H NMR ($CDCl_3$) δ 7.25 (d, J = 9 Hz, 2H, aryl), 7.13 (d, J = 8.5 Hz, 2H, aryl), 7.04 (d, J = 8 Hz, 1H, benzothiazolyl-*5H*), 6.82 (d, J = 8 Hz, 1H, benzothiazolyl-*6H*), 6.22 (s, 1H, N*H*), 4.68 (dd, J = 7 Hz, 4 Hz, 1H, NC*H*CO), 4.58 (t, J = 9.5 Hz, 1H, NCH*H*CH$_2$), 4.19 (m, 1H, NC*H*CH$_2$), 4.00 (s, 3H, OC*H*$_3$), 3.89 (m, 1H, NC*H*HCH$_2$), 3.78 (dd, J = 11 Hz, 7 Hz, 1H, NC*H*CHMe), 3.68 (m, 1H, NC*H*HCH$_2$CH$_2$), 3.52 (m, 1H, NCH*H*CH$_2$CH$_2$), 3.44 (m, 1H, C*H*Me,), 3.15 (m,1H, NCH$_2$CH*H*), 2.84 (m, 1H, C*H*Me$_2$), 2.47 (s, 3H, arylC*H*$_3$), 2.46−1.91 (m, 5H, NCH$_2$C*H*H, NCH$_2$C*H*$_2$CH$_2$), 1.20 (m, 9H, CH*Me*$_2$, *Me*); MS (thermospray) *m*/*z* 576 (MH$^+$), 415 (M-[4-(isopropyl)phenyl isocyanate group] $^+$); LCMS *m*/*z* 576 (MH$^+$) single component 99.7% gradient 2 (t_R 3.55 min), gradient 3 (t_R 16.59 min); HRMS calcd for $C_{31}H_{38}N_5O_4S$ (MH$^+$) 576.2645, found 576.2626.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(6-Methoxy-1,3-benzothiazol-2-yl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-N-(4-isopropylphenyl)pyrrolidine-1-carboxamide (77). Prepared in a manner similar to **56** from **63** to give **77** (85% yield) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.67 (d, J = 8.5 Hz, 1H, benzothiazolyl-*4H*); 7.25 (m, 3H, benzothiazole-*7H*, aryl); 7.13 (d, J = 8.5 Hz, 2H, aryl); 7.02 (dd, J = 9 Hz, 3 Hz, 1H, benzothiazolyl-*5H*); 6.21 (s, 1H, N*H*); 4.68 (m, 1H, NC*H*CO); 4.59 (t, J = 9.5 Hz, 1H, NCH*H*CH$_2$); 4.10 (m, 1H, NC*H*CH$_2$); 3.87 (s, 3H, O*Me*), 3.88−3.64 (m, 3H, NC*H*CHMe, NCH*H*CH$_2$CH$_2$, NC*H*HCH$_2$); 3.58−3.36 (m, 2H, NC*H*HCH$_2$CH$_2$, C*H*Me); 3.09 (m, 1H, NCH$_2$CH*H*); 2.84 (m, 1H, C*H*Me$_2$); 2.45−1.83 (m, 5H, NCH$_2$C*H*H, NCH$_2$C*H*$_2$CH$_2$), 1.20 (m, 9H, CH*Me*$_2$, *Me*); MS (thermospray) *m*/*z* 562 (MH$^+$), 401 (M-[4-(isopropyl)phenyl isocyanate group] $^+$); LCMS *m*/*z* 562 (MH$^+$) single component 99.5% gradient 2 (t_R 3.52 min), gradient 3 (t_R 16.52 min); HRMS calcd for $C_{30}H_{36}N_5O_4S$ (MH$^+$) 562.2488, found 562.2477.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(4-Chloro-1,3-benzothiazol-2-yl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-N-(4-isopropylphenyl)pyrrolidine-1-carboxamide (78). Prepared in a manner similar to **56** from **64** to give **78** (93% yield) as a pale yellow solid: ^{1}H NMR ($CDCl_3$) δ 7.70 and 7.45 (2dd, J = 1.2 Hz, 8 Hz, 2H, benzothiazolyl-*5H* and −*7H*), 7.25 (m, 3H, benzothiazolyl-*6H*, aryl), 7.13 (d, J = 8.5 Hz, 2H, aryl), 6.21 (s, 1H, N*H*), 4.69 (dd, J = 7 Hz, 4 Hz, 1H, NC*H*CO), 4.59 (t, J = 9.5 Hz, 1H, NCH*H*CH$_2$), 4.16 (m, 1H, NC*H*CH$_2$), 3.94 (m, 1H, NC*H*HCH$_2$), 3.80 (dd, J = 11 Hz, 7 Hz, 1H, NC*H*CHMe), 3.69 (m, 1H, NC*H*HCH$_2$CH$_2$), 3.59−3.39 (m, 2H, C*H*Me, NCH*H*CH$_2$CH$_2$), 3.19 (m, 1H, NCH$_2$CH*H*), 2.85(m,1H,C*H*Me$_2$),2.51−1.86(m,5H,NCH$_2$C*H*H,NCH$_2$C*H*$_2$CH$_2$), 1.22 (m, 9H, CH*Me*$_2$, *Me*); MS (thermospray) *m*/*z* 566 (MH$^+$), 405 (M-[4-(isopropyl)phenyl isocyanate group]$^+$); LCMS *m*/*z* 566 (MH$^+$) single component 99.8% gradient 2 (t_R 3.69 min), gradient 3 (t_R 17.36 min); HRMS calcd for $C_{29}H_{33}ClN_5O_3S$ (MH$^+$) 566.1993, found 566.1979.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(5-Methoxy-1,3-benzothiazol-2-yl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-N-(4-isopropylphenyl)pyrrolidine-1-carboxamide (79). Prepared in a manner similar to **56** from **65** to give **79** (65% yield) as a cream solid: ^{1}H NMR ($CDCl_3$) δ 7.66 (d, J = 8.5 Hz, 1H, benzothiazolyl-*7H*), 7.31 (d, J = 2.5 Hz, 1H, benzothiazolyl-*4H*), 7.25 (d, J = 8.5 Hz, 2H, aryl), 7.13 (d, J = 8.5 Hz, 2H, aryl), 6.95 (dd, J = 9 Hz, 2.5 Hz, benzothiazolyl-*6H*), 6.27 (s, 1H, N*H*), 4.68 (dd, J = 7.5 Hz, 4 Hz, 1H, NC*H*CO), 4.60 (t, J = 9.5 Hz, 1H, NCH*H*CH$_2$), 4.09 (m, 1H, NC*H*CH$_2$), 3.92 (m, 1H, NC*H*HCH$_2$), 3.88 (s, 3H, OC*H*$_3$), 3.76 (dd, J = 11 Hz, 7 Hz, 1H, NC*H*CHMe), 3.68 (m, 1H, NC*H*HCH$_2$-CH$_2$), 3.52 (m, 1H, NCH*H*CH$_2$CH$_2$), 3.43 (m, 1H, C*H*Me), 3.11 (m, 1H, NCH$_2$CH*H*), 2.84 (m, 1H, C*H*Me$_2$), 2.46−1.92 (m, 5H, NCH$_2$C*H*H, NCH$_2$C*H*$_2$CH$_2$), 1.20 (m, 9H, CH*Me*$_2$, *Me*); MS (thermospray) *m*/*z* 562 (MH$^+$), 401 (M-[4-(isopropyl)phenyl isocyanate group] $^+$); LCMS *m*/*z* 562 (MH$^+$) single component 99.7% gradient 2 (t_R 3.52 min), gradient 3 (t_R 16.47 min); HRMS calcd for $C_{30}H_{36}N_5O_4S$ (MH$^+$) 562.2488, found 562.2162.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-{5-[(Difluoromethyl)sulfonyl]-1,3-benzothiazol-2-yl}-6-methyl-5-oxohexahydropyrrolo-[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-N-(4-isopropylphenyl)-pyrrolidine-1-carboxamide (80). Prepared in a manner similar to **56** from **66** to give **80** (55% yield) as a cream solid: ^{1}H NMR ($CDCl_3$) δ 8.40 (d, J = 1 Hz, 1H, benzothiazolyl-*4H*), 8.06 (d, J = 8 Hz, 1H, benzothiazolyl-*7H*), 7.86 (dd, J = 8 Hz, 1.5 Hz, 1H, benzothiazoyl-*6H*), 7.24 (d, J = 9 Hz, 2H, aryl), 7.13 (d, J = 8.5 Hz, 2H, aryl), 6.27 (s, 1H, N*H*), 6.23 (t, J = 53 Hz, 1H, C*H*F$_2$), 4.66 (m, 2H, NC*H*CO, NCH*H*CH$_2$), 4.12 (m, 1H, NC*H*CH$_2$), 3.95 (m, 1H, NC*H*HCH$_2$), 3.80 (dd, J = 11 Hz, 7 Hz, 1H, NC*H*CHMe), 3.68 (m, 1H, NC*H*HCH$_2$CH$_2$), 3.50 (m, 2H, NCH*H*CH$_2$CH$_2$, C*H*Me), 3.01 (m, 1H, NCH$_2$CH*H*), 2.84 (m, 1H, C*H*Me$_2$), 2.49−1.92 (m, 5H, NCH$_2$C*H*H, NCH$_2$C*H*$_2$CH$_2$), 1.20 (m, 9H, CH*Me*$_2$, *Me*); MS (thermospray) *m*/*z* 646 (MH$^+$), 485 (M-[4-(isopropyl)phenyl isocyanate group] $^+$); LCMS *m*/*z* 646 (MH$^+$) single component 99.5% gradient 2 (t_R 3.53 min), gradient 3 (t_R 16.32 min); HRMS calcd for $C_{30}H_{34}F_2N_5O_5S_2$ (MH$^+$) 646.1969, found 646.1976.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-6-Methyl-4-(6-nitro-1,3-benzothiazol-2-yl)-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]-carbonyl}-N-(4-isopropylphenyl)pyrrolidine-1-carboxamide (81). Prepared in a manner similar to **56** from **67** to give **81** (76% yield) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 8.74 (d, J = 2.5 Hz, 1H, benzothiazolyl-*7H*), 8.31 (dd, J = 9 Hz, 2 Hz, 1H, benzothiazolyl-*5H*), 7.83 (d, J = 9 Hz, 1H, benzothiazolyl-*4H*), 7.24 (d, J = 8.5 Hz, 2H, aryl), 7.13 (d, J = 8.5 Hz, 2H, aryl), 6.28 (s, 1H, N*H*), 4.65 (m, 2H, NC*H*CO, NCH*H*CH$_2$), 4.13 (m, 1H, NC*H*CH$_2$), 3.94 (m, 1H, NC*H*HCH$_2$), 3.79 (dd, J = 11 Hz, 7 Hz, 1H, NC*H*CHMe), 3.69 (m, 1H, NC*H*HCH$_2$CH$_2$), 3.59−3.41 (m, 2H, C*H*Me, NCH*H*CH$_2$CH$_2$), 3.11 (m, 1H, NCH$_2$-CH*H*), 2.84 (m, 1H, C*H*Me$_2$), 2.49−1.92 (m, 5H, NCH$_2$C*H*H, NCH$_2$C*H*$_2$CH$_2$), 1.20 (m, 9H, CH*Me*$_2$, *Me*); MS (thermospray) *m*/*z* 577 (MH$^+$), 416 (M-[4-(isopropyl)phenyl isocyanate group] $^+$); LCMS *m*/*z* 577 (MH$^+$) single component 99.8% gradient 2 (t_R 3.60 min), gradient 3 (t_R 16.74 min); HRMS calcd for $C_{29}H_{33}N_6O_5S$ (MH$^+$) 577.2233, found 577.2222.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-6-Methyl-5-oxo-4-[6-(trifluoromethoxy)-1,3-benzothiazol-2-yl]hexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-N-(4-isopropylphenyl)pyrrolidine-1-carboxamide (82). Prepared in a manner similar to **56** from **68** to give **82** (81% yield) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 8.5 Hz, 1H, benzothiazolyl-*4H*), 7.67 (br, 1H, benzothiazolyl-*7H*), 7.27 (m, 3H, benzothiazolyl-*5H*, aryl), 7.13 (d, J = 8.5 Hz, 2H, aryl), 6.20 (s, 1H, N*H*), 4.74−4.58 (m, 2H, NC*H*CO, NCH*H*CH$_2$), 4.12 (m, 1H, NC*H*HCH$_2$), 3.93, 3.78 and 3.69 (3m, 3H, NC*H*$_2$CH$_2$CH$_2$, NC*H*CH$_2$), 3.53 (m, 1H, NC*H*CHMe), 3.45 (m, 1H, C*H*Me), 3.10 (m, 1H, NCH$_2$-CH*H*), 2.85 (m, 1H, C*H*Me$_2$), 2.47−1.91 (m, 5H, NCH$_2$C*H*H, NCH$_2$C*H*$_2$CH$_2$), 1.22 (m, 9H, CH*Me*$_2$, *Me*); MS (thermospray) *m*/*z* 616 (MH$^+$), 455 (M-[4-(isopropyl)phenyl isocyanate group] $^+$); LCMS *m*/*z* 616 (MH$^+$) single component 99.7% gradient 2 (t_R 3.74 min), gradient 3 (t_R 17.74 min); HRMS calcd for $C_{30}H_{33}F_3N_5O_4S_2$ (MH$^+$) 616.2205, found 616.2194.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(6-Fluoro-1,3-benzothiazol-2-yl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-N-(4-isopropylphenyl)pyrrolidine-1-carboxamide (83). Prepared in a manner similar to **56** from **69** to give **83** (89% yield) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.72 (dd, J = 9 Hz, 4.5 Hz, 1H, benzothiazolyl-*4H*), 7.49 (dd, J = 8.5 Hz, 2.5 Hz, 1H, benzothiazolyl-*7H*), 7.24 (d, J = 9.5 Hz, 2H, aryl), 7.15 (m, 3H, aryl, benzothiazolyl-*5H*), 6.23 (s, 1H,

N*H*), 4.68 (dd, J = 8 Hz, 4 Hz, 1H, NC*H*CO), 4.61 (t, J = 10 Hz, 1H, NCH*H*CH_2), 4.10 (m, 1H, NC*H*CH_2), 3.91 (m, 1H, NC*H*HCH_2), 3.77(dd, J = 11 Hz, 7 Hz, 1H, NC*H*CHMe), 3.69 (m, 1H, NC*H*HCH_2CH_2), 3.52 (m, 1H, NCH*H*CH_2CH_2), 3.43 (m, 1H, C*H*Me), 3.09 (m, 1H, NCH_2CH*H*), 2.84 (m, 1H, C*H*Me_2), 2.47−1.92 (m, 5H, NCH_2C*H*H, NCH_2C*H*$_2C$*H*$_2$), 1.20 (m, 9H, CH*Me*$_2$, *Me*); MS (thermospray) m/z 550 (MH^+), 389 (M-[4-(isopropyl)phenyl isocyanate group] $^+$); LCMS m/z 550 (MH^+) single component 99.4% gradient 2 (t_R 3.54 min), gradient 3 (t_R 16.71 min); HRMS calcd for $C_{29}H_{33}FN_5O_3S$ (MH^+) 550.2288, found 550.2278.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-(6-Ethylcarboxylate-1,3-benzothiazol-2-yl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]-pyrrol-1(2*H*)-yl]carbonyl}-N-(4-isopropylphenyl)pyrrolidine-1-carboxamide (84). Prepared in a manner similar to **56** from **70** to give **84** (62% yield) as a cream solid: ^{1}H NMR ($CDCl_3$) δ 8.53 (d, J = 1.8 Hz, 1H, benzothiazolyl-7*H*); 8.12 (dd, J = 1.8 Hz, J = 8.6 Hz, 1H, benzothiazolyl-5*H*); 7.81 (d, J = 8.6 Hz, 1H, benzothiazolyl-4*H*); 7.24−7.13 (ABq, J = 8.5 Hz, 4H, aryl*H*); 6.20 (s, 1H, CON*H*); 4.72−4.57 (m, 2H, NC*H*CO, NC*H*CH_2); 4.41 (q, J = 7.1 Hz, 2H, CO_2CH_2Me); 4.20−4.05 (m, 1H, NC*H*CH_2); 4.00−3.39 (m, 5H, NC*HH*CH_2-CH_2, NC*H*HCH_2, NC*H*CHMe and C*H*Me); 3.19−3.06 (m, 1H, NCH_2C*H*H); 2.91−2.78 (m, 1H, C*H*Me_2); 2.45−1.94 (m, 5H, NCH_2CH*H*, $NCH_2CH_2CH_2$); 1.43 (t, J = 7.0 Hz, 3H, CO_2-CH_2*Me*); 1.21−1.17 (m, 9H, CH*Me*, CH*Me*$_2$); LCMS m/z 604.5 (MH^+) single component 98.% gradient 1 (t_R 4.96 min). Anal. ($C_{32}H_{37}N_5O_5S$) C, H, N, S.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-6-Methyl-5-oxo-4-[1,3]thiazolo-[5,4-*b*]pyridin-2-ylhexahydropyrrolo[3,2-*b*]pyrrol-1(2*H*)-yl]carbonyl}-N-(4-isopropylphenyl)pyrrolidine-1-carboxamide (85). Prepared in a manner similar to **56** from **71** to give **85** (75% yield) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (dd, J = 4.8 Hz, 1.5 Hz, 1H, pyridyl-*2H*), 8.01 (dd, J = 8.3 Hz, 1.5 Hz, 1H, pyridyl-*4H*), 7.37 (dd, J = 8.3 Hz, 4.8 Hz, 1H, pyridyl-*3H*), 7.26−7.22 (m, 2H, aryl-*2H, 6H*), 7.16−7.12 (m, 2H, aryl-*3H, 5H*), 6.19 (s, exch., 1H, CON*H*), 4.67 (dd, J = 8 Hz, 4 Hz, 1H, NC*H*CO), 4.63 (t, J = 9.5 Hz, 1H, NC*H*HCH_2), 4.15−4.07 (m, 1H, NC*H*CH_2), 3.97−3.89 (m, 1H, NCH*H*CH_2), 3.83−3.77 (m, 1H, NC*H*CHMe), 3.72−3.66 (m, 1H, NC*H*HCH_2CH_2), 3.56−3.50 (m, 1H, NCH*H*CH_2CH_2), 3.46 (quintet, J = 7.3 Hz, 1H, C*H*Me), 3.14−3.07 (m, 1H, NCH_2C*H*H), 2.85 (septet, J = 7 Hz, 1H, arylC*H*Me_2), 2.45−2.32 (m, 2H, NCH_2CH*H*, NCH_2C*H*HCH_2), 2.29−2.19 (m, 1H, NCH_2CH_2C*H*H), 2.15−2.05 (m, 1H, NCH_2CH*H*CH_2), 2.03−1.95 (m, 1H, NCH_2CH_2CH*H*), 1.21 (d, J = 7 Hz, 3H, CH*Me*), 1.20 (d, J = 7 Hz, 6H, arylCH*Me*$_2$); LCMS m/z 533 (MH^+) single component 99.7% gradient 2 (t_R 3.23 min), gradient 3 (t_R 15.03 min); HRMS calcd for $C_{28}H_{33}N_6O_3S$ (MH^+) 533.2335, found 533.2325.

(2*S*)-2-{[(3a*S*,6*S*,6a*R*)-4-[6-(Hydroxymethyl)-1,3-benzothiazol-2-yl]-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]-pyrrol-1(2*H*)-yl]carbonyl}-N-(4-isopropylphenyl)pyrrolidine-1-carboxamide (72). To a solution of **58** (0.125 g, 0.169 mmol) in dry 1,4-dioxane (1 mL) was added a 4.0M solution of HCl in 1,4-dioxane (0.5 mL). The reaction mixture was allowed to stir at room temperature under an atmosphere of nitrogen for 68 h. The reaction mixture was then evaporated to dryness and azeotroped with toluene (×3) to give a cream residue, which was used in the next step without further purification. The crude mixture was treated in a manner similar to that used to prepare **56** to give **72** (25% yield) as an off-white solid: IR (KBr) ν_{max} 1729.8, 1684.8, 1669.6, 1654.3, 1518.3 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.82 (d, J = 1.8 Hz, 1H, benzothiazolyl-7*H*);); 7.6 (d, J = 8.6 Hz, 1H, benzothiazolyl-4*H*); 7.43 (dd, J = 1.8 Hz, J = 8.6 Hz, 1H, benzothiazolyl-5*H*); 7.26−7.14 (ABq, J = 8.8 Hz, 4H, aryl*H*); 6.23 (s, 1H, N*H*), 4.79 (s, 2H, CH_2OH), 4.68 (dd, J = 3.8 Hz, J = 7.5 Hz, 1H, NC*H*CO); 4.59 (t, J = 9.4 Hz, 1H, NC*HH*CH_2); 4.12−4.00 (m, 1H, NC*H*CH_2); 3.96−3.82 (m, 1H, NCH*H*CH_2); 3.75−3.63 (m, 1H, NC*H*CHMe); 3.59−3.30 (m, 3H, N$CH_2CH_2CH_2$, C*H*Me); 3.13−3.01 (m, 1H, NCH_2C*H*H); 2.91−2.78 (m, 1H,C*H*Me_2); 2.43−1.90 (m, 5H, $NCH_2CH_2CH_2$, NCH_2CH*H*); 1.20 (d, J = 7 Hz, 6H, CH*Me*$_2$); 1.16 (d, J = 7.5 Hz, 3H, CH*Me*); LCMS m/z 562 (MH^+) single component 98.8% gradient 1 (t_R 3.16 min); HPLC 94% (t_R 27.4 min). Anal. ($C_{30}H_{35}N_5O_4S$) C, H, N, S.

Antiviral Assay. (Enzyme Linked ImmunoSorbant Assay (ELISA) for HCMV protease inhibitors). Trypsin stripped MRC5 cells were suspended to a concentration of 10^5 cells per ml in assay medium (Gibco DMEM supplemented with 5% fetal calf serum and antibiotics). This cell suspension was dispensed into 96-well microplates at 100 μL per well. Three columns of wells were allocated for each compound to be tested. Two of these columns received 50 μL per well of human cytomegalovirus (HCMV strain AD169), diluted to give an infectivity ratio of 0.01 plaque-forming unit per cell, and the third column received 50 μL of medium. Then the plates were incubated at 37°C in a 5% CO_2 atmosphere for 48 h. Test compounds were formulated to a concentration of 40mM in DMSO to provide a stock solution. Twofold dilution series in medium were prepared from this stock at 4 times the required final concentrations. The compound dilutions were added to the assay plates at 50 μL per well using three wells (two infected and one uninfected) per dilution. Virus and cell controls received 50 μL of medium. The plates were then re-incubated for a further 5 days.

Growth medium was tipped from the plates and the cell sheets were washed once by gentle immersion in phosphate buffered saline (PBS). The wash was removed and the cells fixed by the addition of 100 μL per well of 1:1 mix of acetone and methanol for 3 min. Following a further wash in PBS, the plates were blocked with 100 μL per well ELISA diluent (PBS + 0.05% v/v Tween 20 + 2% w/v skimmed milk powder) at 37 °C for 30 min. The plates were then washed once with PBS + 0.05% Tween 20, and 50 μL of murine monoclonal antibody (HCMV MAb 34 binding to the viral gB protein, Biogenesis Ltd.), diluted 1:760, was added to each well. After incubation at 37°C for 2 h, the plates were washed three times in PBS/Tween, blotted dry and 50 μL of rabbit, anti-mouse IgG antibody conjugated to horseradish peroxidase (DAKO), preadsorbed with uninfected MRC5 cells and diluted 1:1500, was added to each well. The plates were incubated for another hour and then washed thoroughly five times and dried. Substrate solution, orthophenylene diamine (OPD)/peroxide in urea buffer (Sigmafast kit), was added at 50 μL per well, and color allowed to develop at room temperature. The reaction was stopped by the addition of 25 μL of 12.5% sulfuric acid to each well, and the plates were read spectrophotometrically at a wavelength of 490 nm.

The mean color development of duplicate infected wells at each compound concentration was calculated as a percentage of the mean adsorption of untreated, infected controls after both values had been adjusted for nonspecific background. These percentage inhibition values were plotted against compound concentration and the 50% inhibitory concentration (IC_{50}) derived by regression analysis.

On completion of the ELISA stage, plates were washed with water and stained with 20% v/v carbol fuchsin for 30 min, then washed again and dried. The uninfected columns of cells for each compound were examined microscopically. In-assay cytotoxicity was recorded as the lowest concentration of compound that produced any visible effect on the cell monolayers.

References

(1) Gibson, W.; Welch, A. R.; Hall, M. R. T. Assemblin, a herpesvirus serine maturational proteinase and a new molecular target for antivirals. *Perspect. Drug Discovery Des.* **1994**, *2*, 413−426.

(2) (a) Holwerda, B. C. Herpesvirus proteases: targets for novel antiviral drugs. *Antiviral Res.* **1997**, *35*, 1−21. (b) Qiu, X. Y.; Abdelmeguid, S. S. Human Herpes Proteases. In *Proteases of Infectious Agents*; Dunn, B. M., Ed.; Academic Press.; San Diego, 1999; Chapter 3, pp 93−115. (c) Waxman, L.; Darke, P. L. The herpes proteases as targets for antiviral chemotherapy. *Antiviral Chem. Chemother.* **2000**, *11*, 1−22.

(3) Chen, P.; Tsuge, H.; Almassy, R. J.; Gribskov, C. L.; Katoh, S.; Vanderpool, D. L.; Marbosiak, S. A.; Pinko, C.; Matthews, D. A.; Kan, C. C. Structure of the Human Cytomegalovirus Protease Catalytic Domain Reveals a Novel Serine Protease Fold and Catalytic Triad. *Cell* **1996**, *86*, 835−843.

(4) Tong, L.; Qian, C. G.; Massariol, M. J.; Bonneau, P. R.; Cordingley, M. G.; LaGace, L. A. A New Serine-Protease Fold Revealed by the Crystal Structure of Human Cytomegalovirus Protease. *Nature* **1996**, *383*(N6597), 272−275.
(5) Qiu, X. Y.; Culp, J. S.; Dilella, A. G.; Hellmig, B.; Hoog, S. S.; Janson, C. A.; Smith, W. W.; Abdelmeguid, S. S. Unique Fold and Active Site in Cytomegalovirus Protease. *Nature* **1996**, *383*(N6597), 275−279.
(6) Shieh, H. S.; Kurumbail, R. G.; Stevens, A. M.; Stegeman, R. A.; Sturman, E. J.; Pak, J. Y.; Wittwer, A. J.; Palmier, M. O.; Wiegand, R. C.; Holwerda, B. C.; Stallings, W. C. Three-Dimensional Structure of Human Cytomegalovirus Protease. *Nature* **1996**, *383*(N6597), 279−282.
(7) Borthwick, A. D.; Angier, S. J.; Crame, A. J.; Exall, A. M.; Haley, T. M.; Hart, G. J.; Mason, A. M.; Pennell, A. M. K.; Weingarten, G. W. Design and Synthesis of Pyrrolidine-5,5-*trans*-lactams (5-Oxo-hexahydro-pyrrolo[3,2-b]pyrroles) as Novel Mechanism-Based Inhibitors of Human Cytomegalovirus Protease. 1. The α-Methyl-*trans*-lactam Template. *J. Med. Chem.* **2000**, *43*, 4452−4464.
(8) Borthwick, A. D.; Crame, A. J.; Davies, D. E.; Exall, A. M.; Jackson, D. L.; Mason, A. M.; Pennell, A. M. K.; Weingarten, G. W. Stereoselective Synthesis of α-Methyl and *β*-Methyl-5,5-Pyrrolidine-*trans*-lactams (5-Oxo-hexahydro-pyrrolo[3,2-b]pyrroles) and Stereoselective Alkylation of the Strained Pyrrolidine-5,5-*trans*-lactam Ring System *Synth. Lett.* **2000**, 504−508.
(9) Borthwick, A. D.; Crame, A. J.; Ertl, P. F.; Exall, A. M.; Haley, T. M.; Hart, G. J.; Mason, A. M.; Pennell, A. M. K.; Singh, O. M. P.; Weingarten, G. W.; Woolven, J. M. Design and Synthesis of Pyrrolidine 5,5-*trans*-lactams (5-Oxo-hexahydro-pyrrolo[3,2-b]-pyrroles) as Novel Mechanism-Based inhibitors of Human Cytomegalovirus Protease. 2. Potency and Chirality. *J. Med. Chem.* **2002**, *45*, 1−18.
(10) Hoffman, V. R. *m*-Trifluoromethylbenzenesulphonyl Chloride. *Org. Synth.* **1982**, *60*, 121−126.
(11) Reynolds, R. C.; Crooks, P. A.; Maddry, J. A.; Shamin Akhtar, M.; Montgomery, J. A.; Secrist III, J. A. Synthesis of Thymidine Dimers Containing Internucleoside Sulfonate and Sulfonamide Linkages. *J. Org. Chem.* **1992**, *57*, 2983−2985.
(12) Borthwick, Alan David; Davies, David Evan; Exall, Anne Marjorie; Jackson, Deborah Lynette; Mason, Andrew McMurtrie; Pennell, Andrew Michael Kenneth; Rahim, Saad George; Trivedi, Naimisha; Weingarten, Gordon Gad. Preparation of pyrrolo-pyrrolidinones as antiviral agents**.** World patent WO 9843975 A1 1998.
(13) Borthwick, A. D.; Fogden, Y. C. unpublished work based on the synthesis of the α-methyl derivative **1** from the ethyl analogue of **3**, 1997.
(14) Borthwick, A. D.; Exall, A. M.; Haley, T. M.; Jackson, D. L.; Mason, A. M.; Weingarten, G. W. Design and Synthesis of Pyrrolidine-5,5-*trans*-lactams (5-Oxo-hexahydro-pyrrolo[3,2-b]-pyrroles) as Novel Mechanism-Based inhibitors of Human Cytomegalovirus Protease. 3. Potency and Plasma Stability. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1719−1722.
(15) Borthwick, A. D.; Exall, A. M. Unpublished work based on the synthesis of the c-2, c-3-dimethylcyclopropyl-r-1-carbonyl isomer **45** (Scheme 4) from **4** and t-2, t-3-dimethylcyclopropyl-r-1-carboxylic acid, 1996.
(16) Greiner, A. An Improvement of the N-Arylation of Amides − Application to the Synthesis of Substituted 3-(Acetyl-N-Phenylamino)-Pyridines. *Synthesis* **1989**, 312−313.
(17) IC_{50} values were determined as described previously (ref 18). The enzyme concentration used in these assays is, nominally, 0.5 μM. Thus, the lowest theoretical IC_{50} value that can be determined is 0.25 μM. However, in practice, experimental error means that if values lower than 1−1.5 μM are obtained, the limit of the assay must be considered to have been reached. To allow some discrimination between compounds, whose IC_{50} values are at or around the limit of the assay, an alternative approach was needed. This was achieved by fitting the rate against inhibitor concentration data to an equation describing tight-binding behavior (ref 19). Using this approach, potencies as low as 5 nM could be determined with confidence, and structure−activity relationships could be deduced that was not apparent when using IC_{50} measurements.
(18) Borthwick, A. D.; Weingarten, G.; Haley, T. M.; Tomaszewski, M.; Wang, W.; Hu, Z.; Bedard, J.; Jin, H.; Yuen, L.; Mansour, T. S. Design and Synthesis of Monocyclic *β*-Lactams as Mechanism-Based Inhibitors of Human Cytomegalovirus Protease. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 365−370.
(19) Cha, S. Tight-binding Inhibitors-I Kinetic Behaviour. *Biochem. Pharmacol.* **1975**, *24*, 2177−2185.

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