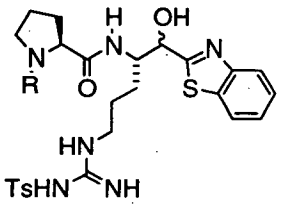
Table 7. The pH Stability Profile of **59** under Enzymatic Assay Conditions

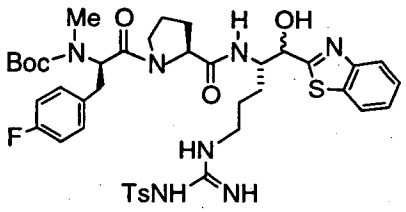
pH (buffer)[a]	T (°C)	time	%L[b]	%D[b]
ca. 6.5 (H_2O)	23	3.0 h	98	2
ca. 6.5 (H_2O)	23	16 days	73	23
7.40 (thr)	23	5.0 h	91	9
7.40 (thr)[c]	37	35 min	93	6
7.40 (tryp)[c]	37	35 min	87	9
7.85 (thr)	23	4.75 h	81	18
7.85 (thr)	37	35 min	92	8
8.40 (tryp)	23	3.75 h	53	25
8.40 (tryp)	37	35 min	73	14

[a] thr = thrombin buffer: 0.01 M TRIS, 0.01 M HEPES , 0.5 M NaCl, 0.1% PEG. tryp = trypsin buffer: 0.03 M TRIS, 0.03 M imidazole, 0.2 M NaCl. Each buffer was adjusted to the pH shown with either HCl or NaOH. [b] %L-Arg and %D-Arg epimers as determined by the following analytical HPLC conditions: 70% H_2O (0.2% TFA)/30% MeCN (0.16% TFA) eluting on three 25 x 100 mm Waters Bondapak® PrepPak® cartridges (15-20 mm) C-18 columns (pore size = 125 Å); flow rate = 15 mL/min; UV detection at 254 nM; inject 100 µL of 2 mg/mL solution. Results are given for the average of two experiments.

4-Fluoro-*N*-methyl-D-phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-(2-benzothiazolylcarbonyl)butyl]-L-prolinamide (6). Sodium hydride (1.59 g, 52.5 mmol; 80% in mineral oil) was added in portions to a solution of *N*-(*tert*-butoxycarbonyl)-4-fluoro-D-phenylalanine (5.00 g, 17.6 mmol) and methyl iodide (20.0 g, 141 mmol) in THF (250 mL) while vigorously stirring at 0 °C. The reaction mixture was slowly warmed to room temperature over 18 h. Ethyl acetate (100 mL) and water (1 mL; CAUTION) were added, the reaction mixture was stirred for 1 h, and the solvents were removed in vacuo. The residue was partitioned between water (120 mL) and Et_2O (50 mL) and the organic layer was extracted with 5% aq $NaHCO_3$. The combined aqueous extracts were acidified to pH 3-4 with 10% aq citric acid and extracted with EtOAc (2 x 100 mL). The combined EtOAc extracts were washed with water (2 x 50 mL), 5% aq sodium thiosulfate (2 x 50 mL), water (2 x 50 mL), dried ($MgSO_4$) and concentrated in vacuo to give *N*-methyl-*N*-(*tert*-butoxycarbonyl)-4-fluoro-D-phenylalanine (5.48 g, 100%) as a clear oil. A solution of **5c** (17.5 g, 31 mmol), *N*-(*tert*-butoxycarbonyl)-L-proline (6.70 g, 31 mmol), and HOBT (4.60 g, 34 mmol) in acetonitrile (1000 mL) was adjusted to pH 7-8 with triethylamine (ca. 10-11 mL), treated with DCC (7.40 g, 36 mmol), and stirred over 18 h. The reaction mixture was filtered through filter agent and the filtrate was concentrated in vacuo. The residue was dissolved in EtOAc (600 mL) and washed with water (50 mL), 1 N HCl (50 mL), water (50 mL), saturated aq $NaHCO_3$ (50 mL), brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo to give **6a** (21.0 g, 105%). A solution of **6a** (20.0 g, 31 mmol) in CH_2Cl_2 (300 mL) was cooled to 5 °C, treated with TFA (80 mL), and stirred for 2 h. The reaction mixture was concentrated in vacuo and the residue was triturated with Et_2O (2 x 1 L) to afford **6b** (18.7 g, 92%) as a cream-colored solid.



6a R = Boc
6b R = H • TFA



6c

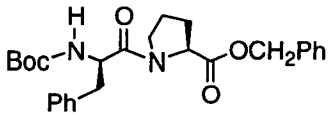
A solution containing **6b** (1.00 g, 1.52 mmol), *N*-methyl-*N*-(*tert*-butoxycarbonyl)-4-fluoro-D-phenylalanine (1.13 g, 3.79 mmol) and HOBT (0.230 g, 1.67 mmol) in MeCN (75 mL) was adjusted to pH 7-8 by the addition of triethylamine under argon. DCC (0.430 g, 2.08 mmol) was added and the reaction mixture was stirred over 4 h. The reaction mixture was filtered through filter agent and the filtrate was concentrated in vacuo and dissolved in EtOAc (150 mL). The EtOAc solution was extracted with water (25 mL), 10% aq citric acid (2 x 25 mL), saturated aq $NaHCO_3$ (2 x 25 mL), brine (2 x 25 mL), dried (Na_2SO_4) and concentrated in vacuo to give **6c** (1.30 g, 100%) as an amber glass. This material (1.30 g) was oxidized with the Dess-Martin periodinane and deprotected with anhydrous HF as described for compound **4**. The resulting solid was purified by reverse-phase HPLC eluting with water/MeCN/TFA (70:30:0.2) to give **6** (0.34 g) as a white solid: mp 70-125 °C; $[\alpha]_D^{25}$ –79.7°; IR ν_{max} 3364, 1672, 1203 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50-1.60 (m, 1H), 1.75-1.95 (ov m, 5H), 1.95-2.05 (m, 1H), 2.15-2.25 (m, 1H), 2.60-2.70 (m, 2H), 2.70 (s, 3H), 3.00-3.10 (m, 1H), 3.20-3.30 (m, 2H), 3.50-3.60 (m, 1H), 4.35-4.45 (m, 2H), 5.60-5.63 (m, 0.97H), 5.66-5.70 (m, 0.03H), 7.05-5.15 (m, 2H), 7.25-7.35 (m, 2H), 7.60-7.70 (m, 2H), 8.12 (d, 1H, *J* = 6.9 Hz), 8.2 (d, 1H, *J* = 6.9 Hz); MS (FAB) *m/z* 568.2 $(MH)^+$. Anal. ($C_{28}H_{34}F_1N_7O_3S$•2.1 CF_3CO_2H•1.1 H_2O) C, H, N, F, H_2O.

2,3,4,5,6-Pentafluoro-*N*-methyl-D-phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-(2-benzothiazolylcarbonyl)butyl]-L-prolinamide (7). *N*-(tert-Butoxycarbonyl)-2,3,4,5,6-pentafluoro-D-phenylalanine (5.0 g, 13.4 mmol; CAS# 136207-26-6) was converted to **7** by the methods described for **6**. The resulting tan solid was purified by reverse-phase HPLC eluting with water/MeCN/TFA (65:35:0.2) to give **7** (0.23 g) as a white solid: mp 98-125 °C; $[\alpha]_D^{25}$ -56.2°; IR ν_{max} 3374, 1668, 1203 cm^{-1}; ^1H NMR δ 1.78-2.3 (ov m, 10H), 2.6 (s, 3H), 3.3-3.5 (ov m, 3H), 3.79-3.85 (m, 1H), 4.5-4.6 (m, 2H), 5.6-5.65 (m, 1H), 7.58-7.67 (m, 2H), 8.1 (d, 1H, *J* = 6.9 Hz), 8.2 (d, 1H, *J* = 6.9 Hz); MS (FAB) *m/z* 640.2 $(MH)^+$. Anal. ($C_{28}H_{30}F_5N_7O_3S$•2.25 CF_3CO_2H•1.25 H_2O) C, H, N, F, H_2O.

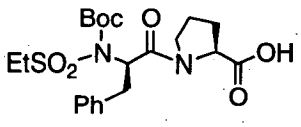
3-Cyclohexyl-*N*-methyl-D-alanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-(2-benzothiazolylcarbonyl)butyl]-L-prolinamide (8). *N*-(*tert*-Butoxycarbonyl)-D-cyclohexylalanine (4.45 g, 17.4 mmol) was converted to **8** by the methods described for **6**. The resulting tan solid was purified by reverse-phase HPLC eluting with water/MeCN/TFA (65:35:0.2) to give **8** (0.51 g) as a white solid: mp 80-100 °C; $[\alpha]_D^{25}$ –41.0° (*c* 0.71, MeOH); IR ν_{max} 3358, 2932, 1670, 1203, 1139 cm^{-1}; ^1H NMR δ 0.95-1.05 (m, 3H), 1.13-1.49 (ov m, 4H), 1.60-1.90 (ov m, 10H), 2.00-2.10 (m, 3H), 2.15-2.35 (ov m, 3H), 2.65 (s, 3H), 3.50-3.60 (m, 1H), 3.80-3.90 (m, 1H), 4.20-4.30 (m, 1H), 4.50-4.60 (m, 1H), 5.60-5.70 (m, 1H), 7.60-7.70(m, 2H), 8.11 (d, 1H, *J* = 6.9 Hz), 8.19 (d, 1H, *J* = 6.9 Hz); MS (FAB) *m/z* 556.2 $(MH)^+$. Anal. ($C_{28}H_{41}N_7O_3S$•3.0 CF_3CO_2H•0.75 H_2O) C, H, N, F, H_2O.

***N*-Acetyl-D-phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-(2-benzothiazolylcarbonyl)-butyl]-L-prolinamide (9).** *N*-Acetyl-D-phenylalanyl-L-proline (0.78 g, 3.79 mmol) was converted to **9** by the methods described for **5**. The resulting tan solid was purified by reverse-phase HPLC eluting with water/MeCN/TFA (65:35:0.2) to give **9** (0.52 g) as a white solid: mp 65-120 °C; $[\alpha]_D^{25}$ –81.7°; IR ν_{max} 3293, 1659, 1202, 1135 cm^{-1}; ^1H NMR δ 1.30-1.60 (ov m, 2H), 1.70-1.90 (ov m, 6H), 2.00 (s, 3H), 2.15-2.25 (m, 1H), 2.75-2.85 (m, 1H), 2.95-3.05 (m, 1H), 3.15-3.25 (m, 1H), 3.50-3.80 (m, 2H), 4.30-4.30 (m, 1H), 4.70-4.80 (m, 1H), 5.55-5.57 (m, 0.74H), 5.62-5.65 (m, 0.26H), 7.20-7.30 (m, 5H), 7.60-7.70 (m, 2H), 8.11 (d, 1H, *J* = 6.9 Hz), 8.19 (d, 1H, *J* = 6.9 Hz); MS (FAB) m/z 578.8 $(MH)^+$. Anal. ($C_{29}H_{35}N_7O_4S$•1.4 CF_3CO_2H•1.0H_2O) C, H, N, F, H_2O.

***N*-(Ethylsulfonyl)-D-phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-(2-benzothiazolyl-carbonyl)butyl]-L-prolinamide (10).** A solution of *N*-(*tert*-butoxycarbonyl)-D-phenylalanine (5.60 g, 21.1 mmol), L-proline benzyl ester hydrochloride (5.11 g, 21.1 mmol), HOBT (2.85 g, 21.1 mmol), and triethylamine (8.8 mL, 63.3 mmol) in acetonitrile (50 mL) was cooled to 5 °C and treated with DCC (6.5 g, 31.7 mmol). The reaction mixture was warmed to room temperature, stirred for 18 h, quenched with water (10 mL), stirred for 15 min, filtered through filter agent, and the filtrate was concentrated in vacuo. The residue was dissolved in EtOAc and extracted with 10% aq citric acid (2x), saturated aq $NaHCO_3$ (2x), brine (2x), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by normal-phase chromatography hexane/EtOAc (3:1) to give **10a** as an oil (7.27 g, 76%; CAS# 64471-88-1).



10a



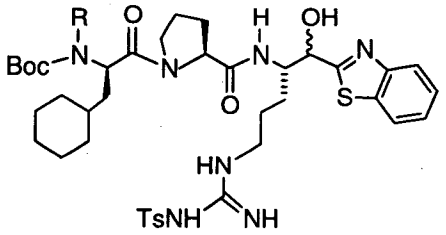
10b

Benzyl ester **10a** was dissolved in CH_2Cl_2 (50 mL), treated with TFA (25 mL) and stirred for 2 h. The reaction mixture was concentrated in vacuo, dissolved in CH_2Cl_2 (100 mL), cooled to 5 °C, and treated with triethylamine (8.6 mL, 62 mmol) followed by ethanesulfonyl chloride (2.2 mL, 23 mmol). After

stirring for 1 h at 0-5 °C, the reaction mixture was quenched by the addition of saturated aq $NaHCO_3$ (25 mL) and the layers were separated. The organic layer was extracted with 1 N HCl (2x), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was dissolved in MeOH (140 mL), treated with 2 N KOH (35 mL), and stirred for 2 h. The reaction mixture was concentrate in vacuo and the residue was partitioned between 1 N HCl and EtOAc. The acidic aqueous layer was extracted with EtOAc (2x) and the combined organic extracts were washed with brine (2x), dried ($MgSO_4$), filtered and concentrated in vacuo to afford **10b** (4.94 g, 90%; CAS# 172348-40-2); which (0.989 g, 2.79 mmol) was converted to **10** by the methods described for **5**. The resulting tan solid was purified by reverse-phase HPLC eluting with water/MeCN/TFA (70:30:0.2) to give **10** (0.067 g) as a white solid: ^{1}H NMR δ 0.85 (m, 1H), 1.15-1.25 (m, 3H), 1.60-1.95 (ov m, 8H), 2.15-2.25 (m, 1H), 2.75-3.15 (ov m, 5H), 3.70-3.80 (m, 1H), 3.15-3.25 (m, 1H), 4.35-4.45 (m, 2H), 5.55-5.65 (m, 1H), 7.25-7.35 (m, 5H), 7.60-7.70 (m, 2H), 8.11 (d, 1H, J = 6.9 Hz), 8.19 (d, 1H, J = 6.9 Hz); MS (FAB) *m/z* 628.5 $(MH)^+$. Anal. ($C_{29}H_{37}N_7O_5S_2$•1.5 CF_3CO_2H•1.6H_2O) C, H, N, F, H_2O.

***N*-Methyl-α-methyl-D-phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-(2-benzothiazolylcarbonyl)butyl]-L-prolinamide (11).** A solution of D-α-methylphenylalanine[57] (0.49 g, 2.73 mmol) in 22 mL of 1,4-dioxane/water (1:1) and triethylamine (1.5 mL, 11 mmol) was treated with di-*tert*-butyl dicarbonate (1.20 g, 5.57 mmol) while stirring. After 18 h, the reaction mixture was partitioned between 1 N HCl and EtOAc (100 mL). The organic layer was extracted with water (3x), brine (3x), dried (Na_2SO_4), filtered through filter agent and concentrated in vacuo to give *N*-(*tert*-butoxycarbonyl)-D-α-methylphenylalanine[57] (0.76 g, 100%) as an oil. This oil was combined with L-proline benzyl ester hydrochloride (0.89 g, 3.68 mmol) in CH_2Cl_2 (26 mL) and the resulting solution was adjusted to pH 7-8 with triethylamine (ca. 3 mL) and treated with BOP-Cl (0.94 g, 3.69 mmol) while stirring. After 18 h, the reaction mixture was extracted with 1 N HCl (2x), saturated aq $NaHCO_3$ (2x), brine (2x), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by normal-phase chromatography eluting with hexane/EtOAc (7:3) to furnish *N*-(*tert*-butoxycarbonyl)-D-α-methylphenylalanyl-L-proline benzyl ester (0.23 g, 18%). This ester (0.20 g, 0.43 mmol) was dissolved in EtOH (20 mL) and combined with 10% Pd on activated carbon (0.040 g) and place under hydrogen pressure (50 psig) on a Parr hydrogenator for 18 h. The reaction mixture was filtered through filter agent and concentrated in vacuo. The green residue was partially dissolved in CH_2Cl_2, filtered through filter agent, and concentrated in vacuo to provide *N*-(*tert*-butoxycarbonyl)-D-α-methylphenylalanyl-L-proline (0.16 g, 100%). This material ((0.16 g, 0.43 mmol) was converted to **11** by the methods described for **5**. The resulting tan solid was purified by reverse-phase HPLC eluting with water/MeCN/TFA (65:35:0.2) to give **11** (0.040 g) as a white solid: ^{1}H NMR δ 1.75 (s, 3H), 1.80-2.10 (ov m, 6H), 2.15-2.25 (m, 2H), 3.10-3.30 (ov m, 4H), 3.40-3.50 (m, 1H), 3.60-3.70 (m, 1H), 4.50-4.60 (m, 1H), 5.60-5.70 (m, 1H), 7.15-7.25 (m, 2H), 7.35-7.45 (m, 3H), 7.60-7.70 (m, 2H), 8.11 (d, 1H, J = 6.9 Hz), 8.19 (d, 1H, J = 6.9 Hz); MS (FAB) *m/z* 550.6 $(MH)^+$. Anal. ($C_{28}H_{35}N_7O_3S$•2.6 CF_3CO_2H•1.5 H_2O) C, H, N, F.

***N*-(Carboxymethyl)-3-cyclohexyl-D-alanyl-N-[(1*S*)-4-[(aminoiminomethyl)amino]-1-(2-benzothiazolylcarbonyl)butyl]-L-prolinamide (12).** Compound **12a** (1.25 g, 1.57 mmol), prepared by the methods used to prepare **5d**, was dissolved in 20 mL of TFA/CH_2Cl_2 (1:1) and stirred for 18 h. The reaction mixture was concentrated in vacuo. The residue was combined with *tert*-butyl bromoacetate (0.31 mL, 2.10 mmol), dissolved in acetonitrile (17 mL), and treated with potassium carbonate (0.94 g, 6.80 mmol). The reaction mixture was heated at 50-60 °C over 18 h, cooled to room temperature, filtered through filter agent, and concentrated in vacuo. The residue was purified by normal-phase chromatography eluting with EtOAc/hexane (7:3) to provide **12b** (0.84 g, 69%).



12a R = H
12b R = CH_2CO_2t-Bu

Compound **12b** (0.84 g, 1.03 mmol) was converted to **12** by the methods described for **5**. The resulting tan solid was purified by reverse-phase HPLC eluting with water/MeCN/TFA (70:30:0.2) to give **12** (0.081 g) as a white solid: ^{1}H NMR δ 0.9-1.5 (ov m, 7H), 1.60-2.35 (ov m, 17H), 3.25 (m, 1H), 3.50-3.60 (m, 1H), 3.70-3.80 (m, 1H), 4.15-4.25 (m, 1H), 4.50-4.60 (m, 1H), 5.65-5.75 (m, 1H), 7.60-7.70 (m, 2H), 8.13 (d, 1H, *J* = 6.9 Hz), 8.20 (d, 1H, *J* = 6.9 Hz); MS (FAB) *m/z* 600.4 (MH)+. Anal. ($C_{29}H_{41}N_7O_5S$•2.5 CF_3CO_2H•2.0 H_2O) C, H, N, F, H_2O.

***N*-Methyl-β-phenyl-D-phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-(2-benzothiazolylcarbonyl)butyl]-L-prolinamide (13).** *N-tert*-Butoxycarbonyl-3,3-diphenyl-D-alanine (5.00 g, 14.6 mmol) was converted to **13** by the methods described for **6**. The resulting tan solid was purified by reverse-phase HPLC with water/MeCN/TFA (65:35:0.2) to give **13** (0.46 g) as a white solid: mp 80-135 °C; $[\alpha]_D^{20}$ –134.7°; IR ν_{max} 3352, 1674, 1203, 1136 cm^{-1}; ^{1}H NMR δ 1.25-1.35 (m, 1H), 1.70-1.90 (ov m, 8H), 2.55-2.65 (s, 3H), 2.90-3.00 (m, 2H), 3.50-3.80 (m, 1H), 4.45-4.55 (m, 1H), 4.95-5.05 (m, 1H), 5.15-5.25 (m, 1H), 5.65-5.75 (m, 1H), 7.05-7.3 (ov m, 10H) 7.55-7.65 (ov m, 2H), 8.11 (d, 1H, *J* = 6.9 Hz), 8.19 (d, 1H, *J* = 6.9 Hz); MS (FAB) *m/z* 626.4 (MH)+. Anal. ($C_{34}H_{39}N_7O_3S$•2.25 CF_3CO_2H•1.9 H_2O) C, H, N, F, H_2O.

(2*S*)-*N*-[(1*S*)-4-[(Aminoiminomethyl)amino]-1-(2-benzothiazolylcarbonyl)butyl]-1-(1-oxo-3,3-diphenylpropyl)-2-pyrrolidinecarboxamide (14). A solution of DCC (18.2 g, 88.4 mmol) in THF (35 mL) was added dropwise to a stirred solution of 3,3-diphenylpropionic acid (20.0 g, 88.4 mmol), 2,4,5-trichlorophenol (17.45 g, 88.4 mmol) and THF (50 mL) under argon at -20 °C. The reaction mixture was stirred at -20 °C for 2.5 h, placed in a refrigerator at 0°C for 16 h, and filtered through filter agent. The mother liquor was concentrated in vacuo and recrystallized from EtOH to give the activated ester, 2,4,5-trichlorophenyl 3,3-diphenylpropanoate (CAS# 179746-20-4), as a solid. This reagent (15.0 g, 37.0 mmol) was added to a mixture of L-proline (4.26 g, 37.0 mmol), triethylamine (5.15 mL) and pyridine (45 mL) at 5 °C under argon. The reaction mixture was warmed to room temperature, stirred for 76 h, and concentrated in vacuo. An aqueous solution of $NaHCO_3$ (3.42 g/130 mL) and Et_2O (100 mL) were added to the residue and the resulting mixture was stirred for 45 min. The organic layer was extracted several times with water. The combined aqueous layer was extracted with two portions of Et_2O, acidified with 1 N HCl and extracted with EtOAc (3x). The combined EtOAc extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give the proline intermediate 1-(1-oxo-3,3-diphenylpropyl)-L-proline (CAS# 179746-21-5), as a solid. This compound (0.16 g, 0.49 mmol) was converted to **14** by the methods described for **5**. The resulting tan solid was purified by reverse-phase HPLC eluting with water/MeCN/TFA (70:30:0.2) to give **14** (0.056 g) as a white solid: mp 106-120 °C; $[\alpha]_D^{19}$ –74.0° (*c* 0.60); IR ν_{max} 1674, 1450, 1204, 1135 cm^{-1}; ^{1}H NMR δ 1.50-2.30 (ov m, 8H), 2.90-3.20 (ov m, 4H), 3.50-3.70 (m, 1H), 4.30-4.35 (m, 1H), 4.45-4.60 (m, 2H), 5.50-5.70 (m, 1H), 7.05-7.30 (ov m, 10H), 7.55-7.65 (ov m,

2H), 8.11 (d, 1H, *J* = 6.9 Hz), 8.19 (d, 1H, *J* = 6.9 Hz); MS (FAB) *m/z* 597.3 $(MH)^+$. Anal. ($C_{33}H_{36}N_6O_3S$•1.75 CF_3CO_2H•1.75 H_2O) C, H, N, H_2O.

***N*-Methyl-*D*-2-phenylglycyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-(2-benzothiazolylcarbonyl)butyl]-L-prolinamide (15).** *N*-Carbobenzyloxy-D-phenylglycine (5.00 g, 17.5 mmol) was converted to **15** by the methods described for **6**. The resulting tan solid was purified by reverse-phase HPLC eluting with water/MeCN/TFA (70:30:0.2) to give **15** (0.16 g) as a white solid: mp 60-125 °C; $[\alpha]_D^{22}$ –43.0°; IR ν_{max} 3368, 1672, 1203, 1135 cm^{-1}; ^1H NMR δ 1.00-1.45 (m, 1H), 1.55-2.30 (ov m, 8H), 2.15-2.25 (m, 1H), 2.60 (s, 3H), 2.80-2.90 (m, 1H), 3.55-3.65 (m, 1H), 4.15-4.25 (m, 1H), 4.35-4.45 (m, 1H), 4.95-5.05 (m, 1H), 5.60-5.63 (m, 0.85H), 5.68-5.70 (m, 0.15H), 7.25-7.35 (m, 5H), 7.45-7.55 (m, 3H), 7.60-7.70 (m, 4H), 8.11 (d, 1H, *J* = 6.9 Hz), 8.19 (d, 1H, *J* = 6.9 Hz); MS (FAB) *m/z* 536.3 $(MH)^+$. Anal. ($C_{27}H_{33}N_7O_3S$•2.1 CF_3CO_2H•1.9 H_2O) C, H, N, H_2O.

D-2-Cyclohexyl-*N*-methylglycyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-(2-benzothiazolylcarbonyl)butyl]-L-prolinamide (16). *N*-Carbobenzyloxy-D-cyclohexylglycine (5.00 g, 17.5 mmol; CAS# 69901-85-5) was converted to **16** by the methods described for **6**. The resulting tan solid was purified by reverse-phase HPLC eluting with water/MeCN/TFA (65:35:0.2) to give **16** (0.16 g) as a white solid: mp 65-125 °C; $[\alpha]_D^{25}$ –64.8°; IR ν_{max} 3352, 1675, 1204, 1136 cm^{-1}; ^1H NMR δ 1.08-1.19 (ov m, 3H), 1.70-1.90 (ov m, 12H), 2.00-2.10(m, 3H), 2.10-2.35 (m, 3H), 2.65 (s, 3H), 3.55-3.65 (m, 1H), 3.80-3.90 (m, 1H), 3.95-4.05 (m, 1H), 4.55-4.65 (m, 1H), 5.60-5.70 (m, 1H), 7.60-7.70 (m, 2H), 8.11 (d, 1H, *J* = 6.9 Hz), 8.19 (d, 1H, *J* = 6.9 Hz); MS (FAB) *m/z* 542.2 $(MH)^+$. Anal. ($C_{27}H_{39}N_7O_3S$•2.0 CF_3CO_2H•2.0 H_2O) C, H, N, F, H_2O.

(2*S*)-*N*-[(1*S*)-4-[(Aminoiminomethyl)amino]-1-(2-benzothiazolylcarbonyl)butyl]-1-[[1-(methylamino)cyclohexyl]carbonyl]-2-pyrrolidinecarboxamide (17). A stirring solution of 1-aminocyclohexanecarboxylic acid hydrochloride (2.94 g, 20.5 mmol) in 1,4-dioxane (90 mL) was diluted with a solution of NaOH (3.90 g, 97.6 mmol) in water (90 mL) as treated with a solution of di-*tert*-butyl dicarbonate (23.4 g, 107 mmol) in 1,4-dioxane (40 mL). After 18 h, the reaction mixture was cooled to 5 °C, acidified to pH 3-4 with concd aq HCl, and extracted with EtOAc (2x). The combined organic extracts were washed with water (4x), brine (2x), dried (Na_2SO_4), filtered, and concentrated in vacuo to afford of 1-(*N*-*tert*-butoxycarbonylamino)cyclohexanecarboxylic acid (4.27 g, 86%) as a white solid. This material (1.50 g, 6.17 mmol) was combined with L-proline benzyl ester hydrochloride (1.50 g, 6.21 mmol) in CH_2Cl_2 (60 mL) and the resulting solution was adjusted to pH 7-8 with triethylamine (ca. 3 mL) and treated with BOP-Cl (1.60 g, 6.29 mmol) while stirring. After 1.5 h, the reaction mixture was extracted with 1 N HCl (2x), saturated aq $NaHCO_3$ (2x), brine (2x), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by normal-phase chromatography eluting with hexane/EtOAc (7:3) to furnish 1-[[(N-tert-butoxycarbonylamino)cyclohexyl]carbonyl]-L-proline benzyl ester (1.53 g, 57%). This ester was dissolved in EtOH (50 mL) and combined with 10% Pd on activated carbon (0.27 g) and place under hydrogen pressure (50 psig) on a Parr hydrogenator for 18 h. The reaction mixture was filtered through filter agent and concentrated in vacuo to provide 1-[[(N-tert-butoxycarbonylamino)cyclohexyl]-carbonyl]-L-proline (1.20 g, 100%). A stirring solution of this material (1.14 g, 3.35 mmol) and methyl iodide (3.80 g, 26.8 mmol) in THF (23 mL) was cooled to 5 °C and treated with sodium hydride (0.300 g, 10 mmol; 80% in mineral oil). After 2 h, EtOAc was added (50 mL) followed by water (1 mL) and the reaction mixture was concentrated in vacuo. The residue was partitioned between water and Et_2O and the organic layer was extracted with saturated aq $NaHCO_3$. The combined aqueous extracts were acidified to pH 3-4 with 10% aq citric acid and extracted with EtOAc (3x). The combined EtOAc extracts were washed with 5% aq sodium thiosulfate (2x), brine (2x), dried (Na_2SO_4), filtered, and concentrated in vacuo to furnish 1-[[1-[[(1,1-dimethylethoxy)carbonyl]methylamino]cyclohexyl]carbonyl]-L-proline (0.95 g, 80%; CAS# 179747-16-1). This material (0.95 g, 2.68 mmol) was converted to **17** by the methods

described for **5**. The resulting tan solid was purified by reverse-phase HPLC eluting with water/MeCN/TFA (65:35:0.2) to give **17** (0.13 g) as a white solid: $[\alpha]_D^{25}$ –44.8°; ^{1}H NMR δ 1.40-1.60 (m, 4H), 1.70-2.10 (ov m, 12H), 2.15-2.45 (m, 4H), 2.65 (s, 3H), 3.80-3.90 (m, 2H), 4.55-4.65 (m, 1H), 5.60-5.70 (m, 1H), 7.60-7.70 (m, 2H), 8.11 (d, 1H, J = 6.9 Hz), 8.19 (d, 1H, J = 6.9 Hz); MS (FAB) *m*/z 528.4 $(MH)^+$. Anal. ($C_{26}H_{37}N_7O_3S$•2.3 CF_3CO_2H•1.8 H_2O) C, H, N, F; H_2O: calcd 3.94; found 3.11.

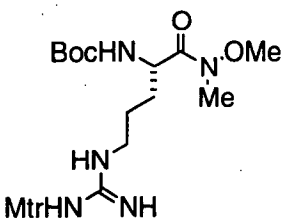
2,2-Diphenylglycyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-(2-benzothiazolyl-carbonyl)-butyl]-L-prolinamide (18). N-Carbobenzoxyl-2,2-diphenylglycine[58] (1.01 g, 2.80 mmol) was converted to **18** by the methods described for **6**. The resulting tan solid was purified by reverse-phase HPLC eluting with water/MeCN/TFA (60:40:0.2) to give **18** (0.034 g) as a white solid: $[\alpha]_D^{25}$ –16.0°; ^{1}H NMR δ 1.55-1.65 (m, 1H), 1.70-1.95 (ov m, 7H), 2.00-2.10 (m, 1H), 2.20-2.30 (m, 1H), 2.35-2.45 (m, 1H), 2.80-2.90 (m, 1H), 4.65-4.75 (m, 1H), 5.65 (m, 1H), 7.50-7.70 (ov m, 10H), 7.80-7.90 (m, 2H), 8.11 (d, 1H, *J* = 6.9 Hz), 8.19 (d, 1H, *J* = 6.9 Hz); MS (FAB) *m*/z 589.4 $(MH)^+$. Anal. ($C_{32}H_{35}N_7O_3S$•2.58 CF_3CO_2H•0.95 H_2O) C, H, N, F; H_2O: calcd 1.88; found 1.37.

(2*S*)-*N*-[(1*S*)-4-[(Aminoiminomethyl)amino]-1-(2-benzothiazolylcarbonyl)butyl]-1-[(9-hydroxy-9H-fluoren-9-yl)carbonyl]-2-pyrrolidinecarboxamide (19). A solution of 9-hydroxy-9H-fluorene-9-carboxylic acid (1.32 g, 5.82 mmol), triethylamine (2.40 mL, 17.5 mmol), and L-proline *tert*-butyl ester (0.500 g, 2.92 mmol) in CH_2Cl_2 (25 mL) was cooled to 5 °C and treated with PyBrOP (2.71 g, 5.82 mmol). After 5 h, water (15 mL) was added and the layers were separated. The organic layer was extracted with 1 M $KHSO_4$ (2x), saturated aq $NaHCO_3$, brine (2x), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by normal-phase chromatography eluting with hexane/EtOAc (4:1) to afford 1-[(9-hydroxy-9H-fluoren-9-yl)carbonyl]-L-proline *tert*-butyl ester (1.98 g, 90%). This ester (1.62 g, 4.28 mmol) was dissolved in CH_2Cl_2 (50 mL), treated with TFA (50 mL) and stirred for 2 h. The reaction mixture was concentrated in vacuo to 1-[(9-hydroxy-9H-fluoren-9-yl)carbonyl]-L-proline as the trifluoroacetate salt, which was converted to **19** by the methods described for **5**. The resulting tan solid was purified by reverse-phase HPLC eluting with water/MeCN/TFA (90:10:0.2 to 50:50:0.2) to give **19** (0.248 g) as a white solid: ^{1}H NMR δ 1.35-2.0 (ov m, 8H), 2.13-2.49 (ov m, 2H), 3.25-3.40 (m, 1H), 4.50-4.60 (m, 1H), 4.45-4.60 (m, 2H), 5.05-5.60 (m, 0.3H), 5.80-5.85 (m, 0.6H) 7.30-7.80 (ov m, 10H), 7.55-7.65 (ov m, 2H), 8.10-8.25 (ov m, 2H); MS (ES) *m*/z 597.3 $(MH)^+$. Anal. ($C_{32}H_{32}N_6O_4S$•1.5 CF_3CO_2H•0.60 H_2O) C, H, N, F, H_2O.

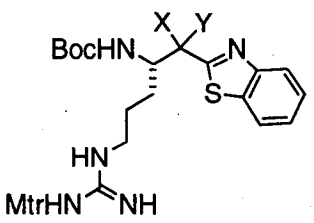
(2*S*)-1-Acetyl-*N*-[4-[(aminoiminomethyl)amino]-1-(2-benzothiazolylcarbonyl)butyl]-2-pyrrolidinecarboxamide (20). The BOP reagent (25.0 g, 56 mmol) was added in one portion to a stirring solution of *N*-α-(*tert*-butoxycarbonyl)-N^G-(4-methoxy-2,3,6-trimethylbenzenesulfonyl)-L-arginine (25.0 g, 51.3 mmol; CAS# 102185-38-6), *N,O*-dimethylhydroxylamine HCl (7.6 g, 56 mmol), triethylamine (22 mL, 154 mmol) in dry DMF (100 mL) under argon at 0 °C. The reaction mixture was slowly warmed to room temperature over 2 h, filtered through filter agent and concentrated in vacuo. The residue was dissolved in EtOAc, washed sequentially with H_2O (3x), 1 M $KHSO_4$, saturated aq $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by normal-phase chromatography eluting with EtOAc/CH_2Cl_2 (3:1) to give **20a**[59] (27.1 g, 100%; CAS# 142801-55-6) as a white solid.

2.5 M Butyllithium in hexane (164 mL, 410 mmol) was added dropwise at -78 °C under argon to a stirred solution of benzothiazole (69.2 g, 512 mmol) in dry THF (1 L) at a rate that kept the reaction temperature below -64 °C. On completion of addition, the reaction mixture was stirred for 30 min at -70 °C and a solution of **20a** (27.1 g, 51.2 mmol) in dry THF (200 mL) was added at a rate that maintained the temperature below -70 °C. The reaction was stirred for 15 min, quenched with saturated aq NH_4Cl (500 mL), and stirred for 16 h at 23 °C. The resulting organic layer was separated, diluted with EtOAc, washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The thick syrupy residue was triturated

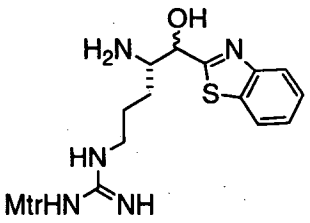
with hexane (3x) and purified by normal-phase chromatography with CH_2Cl_2/EtOAc (7:3) to afford **20b** (15.0 g, 54%) as a light yellow solid.



20a



20b X/Y = O
20c X/Y = H, OH



20d

Sodium borohydride (4.9 g, 129 mmol) was added portionwise to a stirring solution of **20b** (15.0 g, 25 mmol) in MeOH (200 mL) under argon at 0 °C. The reaction mixture was slowly warmed to 23 °C over 1 h, quenched with acetone (30 mL), and concentrated in vacuo. The residue was dissolved in EtOAc, washed with water (2x), brine, dried (Na_2SO_4) and concentrated in vacuo to give **20c** (15.0 g, 100%) as a yellow solid. *p*-Toluenesulfonic acid monohydrate was added at 23 °C to solution of **20c** (1.00 g, 1.65 mmol) in CH_2Cl_2 (20 mL) until the solution was saturated. The reaction was stirred at 23 °C for 6 h, diluted with EtOAc, extracted twice with a 1:1 mixture of brine and 10% aq Na_2CO_3, dried (Na_2SO_4), and concentrated in vacuo to give **20d** (0.75 g, 90%) as a yellow solid. Compound **20d** and *N*-acetyl-L-proline were coupled with DCC and oxidized with the Dess-Martin periodinane according to the methods described for **5**. The resulting ketone (0.040 g, 0.062 mmol) was dissolved in TFA (6 mL), stirred at 23 °C for 6 h, and concentrated in vacuo to give crude **20**, which was purified by reverse-phase HPLC eluting with water/MeCN/TFA (90:10:0.2 to 60:40:0.2) to yield **20** (0.010 g) as a white solid: ^{1}H NMR δ 1.80-1.90 (m, 3H), 1.91-2.00 (m, 3H), 2.08 (s, 1.5H), 2.07 (s, 1.5H), 2.15-2.25 (m, 2H), 3.55-3.65 (m, 4H), 4.40-4.50 (m, 1H), 5.60-5.70 (m, 0.5H), 5.71-5.75 (m, 0.5H), 7.60-7.70 (m, 2H), 8.15 (dd, 1H, *J* = 1.5, 7.5 Hz), 8.21 (dd, 1H, *J* = 1.5, 7.5 Hz); MS (ES) *m*/z 431.0 $(MH)^+$. Anal. ($C_{20}H_{26}N_6O_3S$•1.3 CF_3CO_2H•1.4 H_2O) C, H, N, F, H_2O.

[5-(2-Benzothiazolyl)-4-(formylamino)-5-oxopentyl]guanidine (22). Compound **5c** (0.500 g, 0.89 mmol) was combined with ethyl formate (15 mL, 186 mmol) and the pH of the resulting solution was adjusted to pH 9 with triethylamine (20 drops). The stirring reaction mixture was heated at reflux for 3.5 h, concentrated in vacuo and partitioned between $CHCl_3$ and 0.1 N HCl. The organic layer was extracted with 0.1 N HCl, saturated aq $NaHCO_3$ (2x), brine (2x), dried (Na_2SO_4), filtered and concentrated in vacuo to afford the corresponding formylated product as a white solid (0.275 g, 65%). This material was oxidized with Dess Martin periodinane and deprotected according to the methods described for **5** to afford crude **22** as a tan solid. The crude material was purified by reverse-phase HPLC eluting with water/MeCN/TFA (70:30:0.2) to give **22** (0.140 g) as a white solid: mp 40-100 °C; $[\alpha]_D^{24}$ +1.8°; ^{1}H NMR δ 1.50-2.25 (ov m, 4H), 1.75-1.85 (m, 1H), 3.10-3.20 (m, 1H), 5.80-5.90 (m, 1H), 7.60-7.70 (m, 2H), 8.10-8.20 (m, 1H), 8.21-8.30 (m, 1H); MS (FAB) *m*/z 320.2 $(MH)^+$. Anal. ($C_{14}H_{17}N_5O_2S$•1.32 CF_3CO_2H•0.71 H_2O) C, H, N, F, H_2O.

(2*S*)-*N*-[(1*S*)-4-[(Aminoiminomethyl)amino]-1-(2-benzothiazolylcarbonyl)butyl]-2-pyrrolidinecarboxamide (24). *N*-(*tert*-Butoxycarbonyl)-L-proline (0.484 g, 2.25 mmol) and **5c** (0.830 g, 1.50 mmol) were coupled, oxidized, and deprotected to give **24** according to the methods described for **5**. The resulting crude material was purified by reverse-phase HPLC eluting with water/MeCN/TFA (30:20:0.1) to afford **24** as a white solid (0.052 g): $[\alpha]_D^{25}$ –17.4°; IR ν_{max} 3195, 1676, 1204 cm^{-1}; ^{1}H NMR δ 1.78-2.3

(ov m, 8H), 2.45-2.55 (m, 2H), 3.30-3.40 (m, 2H), 4.35-4.45 (m, 1H), 5.60-5.70 (m, 1H), 7.60-7.70 (m, 2H), 8.12 (d, 1H, J = 6.9 Hz), 8.21 (d, 1H, J = 6.9 Hz). Anal. ($C_{18}H_{24}N_6O_2S$•1.9 CF_3CO_2H•0.9 H_2O) C, H, N, F, H_2O.

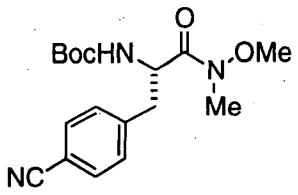
***N*-Methyl-D-phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-(2-benzothiazolylcarbonyl)-butyl]-L-valinamide (25).** *N*-(*tert*-Butoxycarbonyl)-*N*-methyl-D-phenylalanine hydrochloride (1.76 g, 7.22 mmol) and L-valine benzyl ester hydrochloride (2.00 g, 7.16 mmol) were converted to **25** according to the methods described for **11**. The resulting crude material was purified by reverse-phase HPLC eluting with water/MeCN/TFA (30:20:0.1) to afford **25** as a white solid (0.136 g): $[\alpha]_D^{25}$ –31.2°; IR ν_{max} 3345, 3199, 1671, 1204, 1136 cm^{-1}; ^1H NMR δ 0.60-0.70 (m, 3H), 0.71-0.80 (m, 3H), 0.95-1.05 (m, 1H), 1.7-2.2 (ov m, 6H), 2.62 (s, 0.9H), 2.71 (s, 2.1H), 3.05-3.25 (ov m, 2H), 4.00-4.40 (ov m, 2H), 5.65-5.75 (m, 1H), 7.10-7.40 (ov m, 5H), 7.60-7.70 (m, 2H), 8.10-8.14 (m, 1H), 8.15-8.20 (m, 1H); MS (FAB) *m*/z 552.3 $(MH)^+$. Anal. ($C_{28}H_{37}N_7O_3S$•2.3 CF_3CO_2H•0.8 H_2O) C, H, N, F; H_2O: calcd 1.74; found 2.76.

[2*S*-[1(*S),2*R**(*R**)]]-N-[4-[(Aminoiminomethyl)amino]-1-(2-benzothiazolylcarbonyl)-butyl]-1-[2-(methylamino)-1-oxo-3-phenylpropyl]-2-piperidinecarboxamide (26).** *N*-(*tert*-Butoxycarbonyl)-L-homoproline benzyl ester hydrochloride (1.03 g, 4.49 mmol) and **5c** (2.40 g, 4.38 mmol) were converted to **26** according to the methods described for **6**. The resulting crude material was purified by reverse-phase HPLC eluting with water/MeCN/TFA (65:35:0.2) to afford **26** as a white solid (0.569 g): $[\alpha]_D^{25}$ -60.5°; IR ν_{max} 3370, 1672, 1203 cm^{-1}; ^1H NMR δ 1.10-1.50 (ov m, 4H), 1.70-1.95 (ov m, 4H), 2.10-2.20 (ov m, 4H), 2.65 (s, 0.52H), 2.70 (s, 2.48H), 2.95-3.05 (m, 2H), 3.20-3.30 (m, 2H), 4.65-4.75 (m, 1H), 5.00-5.10 (m, 1H), 5.55-5.656 (m, 1H), 7.20-7.30 (ov m, 5H), 7.60-7.70 (m, 2H), 8.12 (d, 1H, J = 6.9 Hz), 8.21 (d, 1H, J = 6.9 Hz); MS (FAB) *m*/z 564.3 $(MH)^+$. Anal. ($C_{29}H_{37}N_7O_3S$•2.42 CF_3CO_2H•1.28 H_2O) C, H, N, F, H_2O.

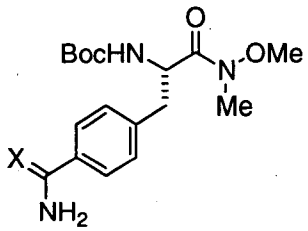
***N*-Methyl-D-phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-(2-benzothiazolylcarbonyl)butyl]-*N*-methyl-L-prolinamide (29).** Boc-N-Me-Arg(Tos)OH (5.00 g, 12.4 mmol; CAS# 179746-65-7) was converted to **29** by the methods described for **5**. The resulting crude material was purified by reverse-phase HPLC with water/MeCN/TFA (65:35:0.2) to afford **29** as a white solid (0.340 g): $[\alpha]_D^{25}$ –91.3°; IR ν_{max} 3149, 1694, 1203 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.50-0.95 (m, 3H), 1.20-1.30 (m, 4H), 1.50-2.25 (ov m, 8H), 2.6-2.75 (b ov m, 3H), 2.90-3.50 (b ov m, 6H), 4.00-4.30 (b ov m, 1H), 4.60-4.70 (b ov m, 1H), 5.3 (b, 1H), 6.35-6.45 (m, 1H), 7.20-7.30 (m, 5H), 7.45-7.55 (m, 2H), 7.85-7.95 (ov m, 2H); MS (FAB) *m*/z 564.3 $(MH)^+$. Anal. ($C_{29}H_{37}N_7O_3S$•2.42 CF_3CO_2H•1.28 H_2O) C, H, N, F, H_2O.

***N*-Methyl-D-phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-(2-benzothiazolylcarbonyl)pentyl]-L-prolinamide (30).** Boc-HomoArg(NO_2)-OH (2.00g, 6.00 mmol; CAS# 28968-64-1) was converted to **30** by the methods described for **5**. The resulting crude material was purified by reverse-phase HPLC eluting with water/MeCN/TFA (90:10:0.2 to 65:35:0.2 over 75 min) to afford **30** as a white solid (0.238 g): ^1H NMR (CD_3OD) δ 1.40-1.50 (m, 1H), 1.60-2.10 (ov m, 9H), 2.15-2.25 (m, 1H), 2.45-2.55 (m, 1H), 2.70 (s, 3H), 3.00-3.10 (m, 1H), 3.15-3.25 (m, 2H), 3.45-3.55 (m, 1H), 4.35-4.45 (m, 2H), 5.60-5.70 (m, 1H), 7.25-7.34 (m, 2H), 7.35-7.40 (m, 3H), 7.55-7.65 (m, 2H) 8.05-8.15 (m, 1H), 8.18-8.23 (m, 1H); MS (FAB) *m*/z 564.3 $(MH)^+$. Anal. ($C_{29}H_{37}N_7O_3S$•2.3 CF_3CO_2H•1.0 H_2O) C, H, N, F, H_2O.

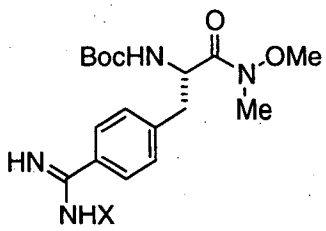
***N*-Methyl-D-phenylalanyl-*N*-[(1*S*)-1-[[4-(aminoiminomethyl)phenyl]methyl]-2-(2-benzothiazolyl)-2-oxoethyl]-L-prolinamide (31).** Hydrogen sulfide gas was bubbled at room temperature into a stirring solution of **31a**[60] (28.7 g, 86.1 mmol; CAS# 179746-96-4) and triethylamine (100 mL) in pyridine (400 mL) over a 3 h period. After 3 days, the dark amber-green reaction mixture was concentrated in vacuo to about 300 mL, diluted with water (500 mL), cooled to 5 °C, acidified to pH 4-5 with concd aq HCl and extracted with EtOAc (500 mL). The organic layer was extracted with 1 N HCl (2 x 250 mL), brine (2 x 250 mL), dried ($MgSO_4$) and concentrated in vacuo to furnish **31b** (27.8 g, 88%) as a yellow glass.



31a



31b X = S
31c X = $S^+Me\ I^-$



31d X = H • HI
31e X = Tos

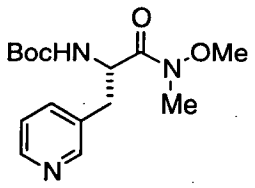
A solution of **31b** (27.0g, 73.6 mmol) in acetone (750 mL) was treated with methyl iodide (75 mL) and heated at reflux for 1 h. The reaction mixture was cooled to room temperature, concentrated in vacuo to a volume of 150 mL, and cooled with a –78 °C bath. The resulting precipitate was removed by filtration the filtrate was concentrated in vacuo to give of crude **31c** (39.6 g, >100%) as an amber glass. This material combined with ammonium acetate (8.70 g, 112 mmol), dissolved in MeOH (200 mL), heated at reflux for 3.5 h and concentrated in vacuo. The residue was partially dissolved in $CHCl_3$ (500 mL) and filtered through filter agent. The filtrate was extracted with saturated aq $NaHCO_3$ (200 mL), brine (250 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to afford **31d** (24.3 g, 65%) as a light yellow glass. A solution of this material (24.3 g, 69.0 mmol) and tosyl chloride (14.6 g, 76.0 mmol) in acetone (500 mL) was cooled to -15 °C. DBU (21.4 g, 139 mmol) was added dropwise while stirring at -15 °C over 45 min and the reaction mixture was slowly warmed to room temperature over 3 h. The reaction mixture was diluted with 100 mL of MeOH and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with EtOAc/hexane (3:1) to give **31e** (14.4 g, 41%) as a white solid.

Compound **31e** (5.04 g, 10.0 mmol) was converted to **31** by the methods described for **5** with the exception that the HF deprotection required 6 h at room temperature. The resulting crude material was purified by reverse-phase HPLC eluting with water/MeCN/TFA (65:35:0.2) to afford **31** as a white solid (0.150 g): $[\alpha]_D^{25}$ –18.0°; IR ν_{max} 3068, 1678, 1203 cm^{-1}; ^1H NMR δ 1.35-1.45 (m, 1H), 1.60-2.00 (ov m, 3H), 2.40-2.50 (m, 1H), 2.55-2.60 (m, 1H), 2.70 (s, 3H), 3.00-3.10 (m, 1H), 3.20-3.30 (m, 1H), 3.38-3.48 (m, 1H), 3.50-3.60 (m, 1H), 4.35-4.45 (m, 2H), 5.90-5.98 (m, 0.75H), 6.00-6.10 (m, .25H), 7.30 (d, 2H, J = 6.5 Hz), 7.20-7.40 (m, 5H), 7.60 (d, 2H, J = 7.1 Hz), 7.70 (d, 2H, J = 6.5 Hz), 8.10 (d, 1H, J = 7.1 Hz), 8.20 (d, 1H, J = 7.1 Hz); MS (FAB) *m/z* 583.2 $(MH)^+$. Anal. ($C_{32}H_{34}N_6O_3S$•2.25 CF_3CO_2H•1.0 H_2O) C, H, N, F, H_2O.

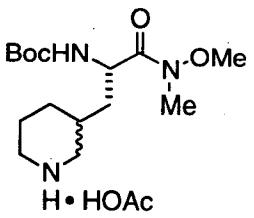
(1*S*)- and (1*R*)- N-Methyl-D-phenylalanyl-N-[1-[[3-(aminoiminomethyl)phenyl]methyl]-2-(2-benzo-thiazolyl)-2-oxoethyl]-L-prolinamide (32 and 33). Sodium bicarbonate (7.81 g, 93.0 mmol) was cautiously added to a stirring solution of (3-amidinophenyl)-D,L-alanine[61] dihydrochloride (8.48 g, 30.2 mmol; CAS# 52117-05-2) in 40 mL of 1,4-dioxane/water (1:1). The reaction mixture was treated with a solution of di-tert-butyl dicarbonate (6.61 g, 30.3 mmol) in 1,4-dioxane (9 mL). After 18 h, the reaction mixture was cooled to 5 °C and the pH was adjusted to pH 12 with 4 N NaOH. A solution of 4-methoxy-2,3,6-trimethylbenzenesulfonyl chloride (18.55 g, 74.6 mmol) in 1,4-dioxane (23 mL) was added to the reaction mixture dropwise at 5 °C. After the addition, the reaction mixture was warmed to room temperature and the pH was adjusted to pH 12 with 4 N NaOH. After 3 h, the pH was adjusted to pH 2-3 with 1 N HCl and the reaction mixture was extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with water (1x), brine (2x), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by normal-phase chromatography eluting with CH_2Cl_2/*i*-PrOH/HOAc (94:5:1) to afford *N*-[(1,1-dimethylethoxy)carbonyl]-3-[imino[[(4-methoxy-2,3,6-trimethylphenyl)sulfonyl]-amino]methyl]-D,L-phenylalanine (3.35 g, 21%); CAS# 174894-05-4), which was converted to a mixture of

32 and **33** by the methods described for **5**. These compounds were separated and purified by reverse-phase HPLC eluting with water/MeCN/TFA (90:10:0.2 to 70:30:0.2) to afford **32** (0.079 g; slow eluter) and **33** (0.069 g; fast eluter) as white solids. Compound **32**: ^{1}H NMR δ 1.35-1.45 (m, 1H), 1.70-2.00 (ov m, 3H), 2.40-2.50 (m, 1H), 2.70 (s, 3H), 3.00-3.10 (m, 1H), 3.25-3.35 (m, 2H), 3.40-3.60 (ov m, 2H), 4.35-4.45 (m, 2H), 5.95-6.05 (m, 1H), 7.25-7.35 (m, 2H), 7.36-7.40 (m, 3H), 7.50-7.60 (m, 1H), 7.60-7.70 (m, 4H), 7.83 (s, 1H), 8.10 (d, 1H, J = 7.1 Hz), 8.20 (d, 1H, J = 7.1 Hz); MS (ES) *m/z* 583.3 $(MH)^+$. Anal. ($C_{32}H_{34}N_6O_3S$•2.4 CF_3CO_2H•1.4 H_2O) C, H, N, F, H_2O. Compound **33**: ^{1}H NMR δ 1.15-1.25 (m, 1H), 1.30-1.50 (ov m, 2H), 1.70-1.80 (m, 1H), 2.30-2.50 (ov m, 2H), 2.60 (s, 3H), 2.95-3.25 (ov m, 2H), 3.55-3.65 (m, 2H), 4.25-4.35 (m, 2H), 5.85-5.95 (m, 1H), 7.15-7.25 (m, 2H), 7.26-7.35 (m, 3H), 7.50-7.60 (m, 1H), 7.61-7.70 (m, 4H), 7.83 (s, 1H), 8.10 (d, 1H, J = 7.1 Hz), 8.20 (d, 1H, J = 7.1 Hz); MS (ES) *m/z* 583.3 $(MH)^+$. Anal. ($C_{32}H_{34}N_6O_3S$•2.3 CF_3CO_2H•1.6 H_2O) C, H, N, F, H_2O.

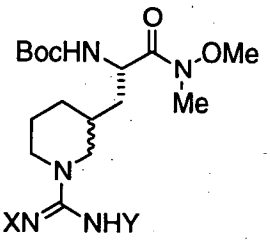
***N*-Methyl-D-phenylalanyl-*N*-[(1*S*)-1-[[(3*R*)-1-(aminoiminomethyl)-3-piperidinyl]methyl]-2-(2-benzothiazolyl)-2-oxoethyl]-L-prolinamide (34).** *N*-(*tert*-Butoxycarbonyl)-3-(3-pyridyl)-L-alanine (5.00 g, 18.8 mmol; CAS# 117142-26-4) was combined with *N,O*-dimethylhydroxylamine hydrochloride (2.75 g, 28.2 mmol) and triethylamine (8.0 mL, 56.4 mmol) in DMF (200 mL) and the resulting solution was treated with BOP-Cl (7.20 g, 28.2 mmol) while stirring. After 18 h, the reaction mixture filtered through filter agent and concentrated in vacuo at 60 °C. The residue was dissolved in CH_2Cl_2 (100 mL) and extracted with water (3x), saturated aq $NaHCO_3$ (3x), brine (3x), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by normal-phase chromatography eluting with CH_2Cl_2/MeOH/concd aq NH_4OH (97:2.7:0.3) to furnish **34a** (3.74 g, 56%). Compound **34a** (3.74 g, 12.1 mmol) was dissolved in EtOH (16 mL), glacial acetic acid (5 mL) and water (5 mL). Platinum oxide (0.374 g) was added and the reaction mixture was placed on a Parr hydrogenator under hydrogen pressure (50 psig). After 18 h, the reaction mixture was filtered through filter agent and concentrated in vacuo to afford **34b** (4.54 g, 100%).



34a



34b



34c X = Y = Cbz
34d X = Y = H
34e X = H, Y = Ts

Compound **34b** (4.54 g, 12.1 mmol) and 1,3-bis(benzyloxycarbonyl)-2-methylthiopseudourea (4.34 g, 12.1 mmol; CAS# 25508-20-7) were dissolved in THF (50 mL) and treated with *N*-methylmorpholine (3.0 mL, 29.7 mmol). After stirring for 4 days, the reaction mixture was concentrated in vacuo, dissolved in EtOAc. The EtOAc solution was extracted with 1 M $KHSO_4$ (3x), brine (2x), dried ($NaSO_4$), filtered and concentrated in vacuo. The residue was purified by normal-phase chromatography eluting with EtOAc/hexane (1:1) to provide **34c** (5.34 g, 70%). This material (5.30 g, 8.47 mmol) was dissolved in MeOH (50 mL) and 10% Pd on activated carbon (0.530 g) was added and the reaction mixture was placed on a Parr hydrogenator under hydrogen pressure (50 psig). After 18 h, the reaction mixture was filtered through filter agent and concentrated in vacuo to afford **34d** (3.03 g, 100%).

Compound **34d** (3.00 g, 8.39 mmol) was dissolved in CH_2Cl_2 (100 mL), combined with 4 N NaOH (100 mL), cooled to 0 °C, and treated with *p*-toluenesulfonyl chloride (1.78 g, 9.35 mmol). After 2 h, the

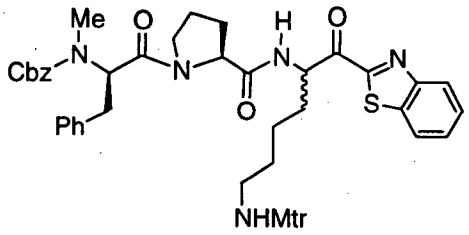
organic layer was isolated and extracted with 1 M $KHSO_4$ (2x), brine, dried ($MgSO_4$), filtered and concentrated in vacuo to afford **34e** as a mixture of diastereomers. These diastereomers were separated by normal-phase chromatography eluting with EtOAc/hexane (7:3) to provide the 2.44 g and 1.27 g of the faster and slower eluting diastereomers, respectively. The relative stereochemistry of each diastereomer was established by NOE studies. The slower eluting diastereomer of **34e** (1.23 g, 2.40 mmol) was converted to **34** by the methods described for **5**. The resulting crude material was purified by reverse-phase HPLC eluting with water/MeCN/TFA (90:10:0.2 to 70:30:0.2) to afford **34** (0.240 g) as a white solid: ^{1}H NMR (DMSO-d_6) δ 1.20-1.50 (ov m, 3H), 1.60-1.70 (m, 3H), 1.80-1.90 (m, 4H), 1.95-2.05 (m, 1H), 2.53 (s, 3H), 2.85-2.95 (m, 2H), 3.00-3.20 (ov m, 2H), 3.40-3.50 (m, 1H), 3.65-3.75 (m, 1H), 4.25-4.35 (m, 1H), 4.40 (s, 1H), 5.45-5.55 (m, 1H), 7.15-7.25 (m, 2H), 7.26-7.33 (m, 3H), 7.40-7.50 (m, 4H), 7.60-7.70 (m, 2H), 8.18 (d, 1H, J = 7.1 Hz), 8.21 (d, 1H, J = 7.1 Hz), 8.65 (d, 1H, J = 7.0 Hz), 8.82 (br s, 1H), 9.30 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 23.921, 24.103, 28.150, 29.533, 31.513, 32.410, 33.350, 36.415, 46.193, 47.219, 51.051, 52.566, 59.521, 60.024, 123.643, 125.503, 127.902, 127.988, 128.659, 128.962, 129.800, 134.464, 136.677, 153.190, 156.093, 158.459, 158.775, 164.601, 165.756, 171.305, 193.672; MS (ES) m/z 590 $(MH)^+$. Anal. ($C_{31}H_{39}N_7O_3S$•2.3 CF_3CO_2H•1.5 H_2O) C, H, N, F, H_2O.

(1*S*)- and (1*R*)-*N*-Methyl-D-phenylalanyl-*N*-[1-[[(3*S*)-1-(aminoiminomethyl)-3-piperidinyl]-methyl]-2-(2-benzothiazolyl)-2-oxoethyl]-L-prolinamide (35 and 36). The faster eluting diastereomer of **34e** (1.63 g, 2.86 mmol) was converted to a crude mixture of **35** and **36** by the methods described for **34**. This mixture was purified by reverse-phase HPLC eluting with water/MeCN/TFA (90:10:0.2 to 65:36:0.2) to afford **35** (0.176 g; slower eluter) and **36** (0.068 g, faster eluter) as white solids. Compound **35**: ^{1}H NMR δ 1.40-1.50 (m, 2H), 1.55-2.15 (ov m, 9H), 2.45-2.55 (m, 1H), 2.60 (s, 3H), 2.90-3.10 (ov m, 4H), 3.45-3.55 (m, 1H), 3.75-3.85 (m, 1H), 4.10-4.20 (m, 1H), 4.35-4.45 (m, 1H), 4.46-5.00 (m, 1H), 5.80-5.90 (m, 1H), 7.20-7.30 (m, 2H), 7.35-7.40 (m, 3H), 7.60-7.70 (m, 2H), 8.10 (d, 1H, J = 7.1 Hz), 8.20 (d, 1H, J = 7.1 Hz); MS (ES) m/z 590.3 $(MH)^+$. Anal. ($C_{31}H_{39}N_7O_3S$•2.5 CF_3CO_2H•0.8 H_2O) C, H, N, F, H_2O. Compound **36**: ^{1}H NMR δ 1.25-2.15 (ov m, 8H), 2.45-2.55 (m, 1H), 2.67 (s, 3H), 2.90-3.30 (ov m, 7H), 3.40-3.50 (m, 1H), 3.75-3.85 (m, 2H), 4.15-4.25 (m, 1H), 4.35-4.45 (m, 1H), 5.85-5.95 (m, 1H), 7.20-7.40 (ov m, 5H), 7.55-7.65 (m, 2H), 8.18 (d, 1H, J = 7.1 Hz), 8.21 (d, 1H, J = 7.1 Hz); MS (ES) m/z 590.3 $(MH)^+$. Anal. ($C_{31}H_{39}N_7O_3S$•2.3 CF_3CO_2H•0.9 H_2O) C, H, N, F, H_2O.

(1*S*)- and (1*R*)- *N*-Methyl-D-phenylalanyl-*N*-[1-(2-benzothiazolylcarbonyl)-5-(amino)pentyl]-L-prolinamide (37 and 38). A stirring solution of Boc-Lys-OMe•HCl (5.00 g, 16.8 mmol; CAS# 99532-86-2) and triethylamine (4.70 mL, 33.6 mmol) in CH_2Cl_2 (80 mL) was cooled to 0 °C and treated with 4-methoxy-2,3,6-trimethylbenzenesulfonyl chloride (4.19 g, 16.8 mmol). The reaction mixture was slowly warmed to room temperature over 18 h and extracted with 1 M $KHSO_4$ (2x), saturated $NaHCO_3$ (2x), brine, dried ($MgSO_4$), filtered and concentrated in vacuo to give of crude Boc-Lys(Mtr)-OMe. This material was dissolved in MeOH (150 mL) and treated with 2 N KOH (50 mL). After 30 min, the reaction mixture was concentrated in vacuo to a volume of 50 mL, acidified to pH 3 with concd aq HCl and extracted with EtOAc (3x). The combined organic extracts were washed with brine (2x), dried (Na_2SO_4), filtered and concentrated in vacuo to give Boc-Lys(Mtr)-OH (11.2 g, > 100%; CAS# 83031-09-8) as a pale yellow solid. This material was converted to **37a** according to the methods described for **5**.

Compound **37a** (3.08 g, 3.55 mmol) was combined with pentamethylbenzene (22 g, 148 mmol), dimethylsulfide (87 mL, 1200 mmol), dissolved in TFA (261 mL) and cooled to 0 °C. Anhydrous hydrogen bromide (39 g, 482 mmol) was bubbled into the reaction mixture. After the HBr addition, the reaction mixture was warmed to room temperature and stirred for 2.5 h. The reaction mixture was concentrated in vacuo and the residue was triturated with Et_2O (4x). The resulting crude solid was purified by reverse-phase HPLC eluting with water/MeCN/TFA (90:10:0.2 to 50:50:0.2) to afford **37** (0.272 g; slower eluter) and **38** (0.265 g; faster eluter) as white solids. Compound **37**: ^{1}H NMR δ 1.35-1.45 (m, 1H), 1.60-2.00 (ov

m, 8H), 2.15-2.25 (m, 1H), 2.40-2.50 (m, 1H), 2.70 (s, 3H), 2.90-3.10 (m, 3H), 3.40-3.50 (m, 2H), 4.40-4.50 (m, 2H), 5.60-5.70 (m, 1H), 7.20-7.30 (m, 2H), 7.31-7.40 (m, 3H), 7.60-7.70 (m, 2H), 8.10 (d, 1H, J = 7.1 Hz), 8.20 (d, 1H, J = 7.1 Hz); MS (ES) *m/z* 522.2 $(MH)^+$. Anal. ($C_{28}H_{35}N_5O_3S$•2.2 CF_3CO_2H•1.0 H_2O) C, H, N, F, H_2O. Compound **38**: ^1H NMR δ 1.35-1.45 (m, 1H), 1.60-2.00 (ov m, 8H), 2.15-2.25 (m, 1H), 2.40-2.50 (m, 1H), 2.70 (s, 3H), 2.90-3.10 (m, 3H), 3.40-3.50 (m, 2H), 4.40-4.50 (m, 2H), 5.70-5.75 (m, 1H), 7.20-7.30 (m, 2H), 7.31-7.40 (m, 3H), 7.6-7.7 (m, 2H), 8.10 (d, 1H, J = 7.1 Hz), 8.20 (d, 1H, J = 7.1 Hz); MS (ES) *m/z* 522.2 $(MH)^+$. Anal. ($C_{28}H_{35}N_5O_3S$•2.2 CF_3CO_2H•1.0 H_2O) C, H, N, F, H_2O.



37a

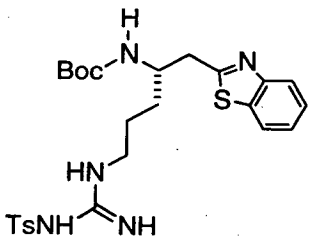
(1*S*)- and (1*R*)- *N*-Methyl-D-phenylalanyl-*N*-[1-(2-benzothiazolylcarbonyl)-5-(methylamino)-pentyl]-L-prolinamide (39 and 40). *N*6-Methyl-L-lysine monohydrochloride (4.33 g, 22.0 mmol; CAS# 7622-29-9) was combined with $CuCO_3$•$Cu(OH)_2$ (8.00 g, 36.1 mmol) and water (74 mL), and heated at reflux with mechanical stirring over 19 h. The resulting black suspension was cooled to room temperature, filtered through filter agent, and the dark blue filtrate was concentrated in vacuo. The solid residue was dissolved in water (37 mL), treated with $NaHCO_3$ (7.32 g, 87.0 mmol), and diluted with acetone (23 mL). A solution of 4-methoxy-2,3,6-trimethylbenzenesulfonyl chloride (6.10 g, 24.5 mmol) in acetone (23 mL) was added dropwise to the reaction mixture over 30 min. After stirring for 18 h, the reaction mixture was concentrated in vacuo. The resulting blue residue was triturated with water (3x) and dissolved in 50 mL of glacial acetic acid/water (1:1). Hydrogen sulfide was bubbled into the solution over 15 min and a brownish-black precipitate formed. The reaction mixture was filtered through filter agent and the filtrate was concentrated in vacuo to give *N*6-[(4-methoxy-2,3,6-trimethylphenyl)sulfonyl]-*N*6-methyl-L-lysine (9.52 g, >100%; CAS# 179747-19-4) as a tan solid, which (5.00 g, 13.4 mmol) was dissolved in 1,4-dioxane (52 mL), diluted with H_2O (52 mL), cooled to 0 °C, and adjusted to pH 11 with aqueous 3 N NaOH. Di-*tert*-butyl dicarbonate (8.79 g, 40.2 mmol) was added and the reaction mixture was stirred at 0 °C while maintaining the pH at pH 10-11 over 18 h. The solvents were removed in vacuo and the residue was partitioned between H_2O (100 mL) and Et_2O. The basic aqueous layer (pH 11) was extracted again with Et_2O (2x), cooled to 0 °C, adjusted to pH 3 with 3 N HCl, and extracted with EtOAc (3x). The combined EtOAc extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give *N*2-[(1,1-dimethylethoxy)carbonyl]-*N*6-[(4-methoxy-2,3,6-trimethylphenyl)-sulfonyl]-*N*6-methyl-L-lysine, (3.34 g, 53%; CAS# 179747-01-4) as a white foam; FAB-MS *m/z* 473 $(MH)^+$, which (3.14 g, 6.64 mmol) was converted to a 2.8:1 mixture of **39** and **40** according to methods described for **37** and **38**. The resulting crude solid was purified by reverse-phase HPLC (water/MeCN/TFA, 75:25:0.2) to afford **39** (0.163 g; slow eluter) and **40** (0.058 g; fast eluter) as white solids. Compound **39**: ^1H NMR δ 1.35-1.45 (m, 1H), 1.60-2.00 (ov m, 8H), 2.15-2.25 (m, 1H), 2.40-2.50 (m, 1H), 2.70 (s, 6H), 3.00-3.10 (m, 4H), 3.40-3.50 (m, 1H), 4.35-4.45 (m, 2H), 5.55-5.65 (m, 0.1H), 5.65-5.70 (m, 0.9H), 7.20-7.30 (m, 2H), 7.31-7.40 (m, 3H), 7.60-7.70 (m, 2H), 8.1 (d, 1H, *J* = 7.1 Hz), 8.2 (d, 1H, *J* = 7.1 Hz); MS (ES) *m/z* 536.2 $(MH)^+$. Anal. ($C_{29}H_{37}N_5O_3S$•2.1 CF_3CO_2H•0.27 HBr•1.0 H_2O) C, H, N, Br, F, H_2O.

Compound **40**: ^{1}H NMR δ 1.35-1.45 (m, 1H), 1.55-1.65 (m, 2H), 1.7-1.9 (ov m, 5H), 1.95-2.05 (m, 1H), 2.06-2.1 (m, 1H), 2.45-2.55 (m, 1H), 2.65 (s, 3H), 2.7 (s, 3H), 2.95-3.05 (m, 3H), 3.2-3.3 (m, 1H), 3.35-3.45 (m, 1H), 4.3-4.45 (m, 2H), 5.55-5.65 (m, 0.92H), 5.65-5.70 (m, 0.08H), 7.25-7.4 (ov m, 5H), 7.6-7.7 (m, 2H), 8.1 (d, 1H, *J* = 7.1 Hz), 8.2 (d, 1H, *J* = 7.1 Hz); MS (ES) *m/z* 536.1 (MH)+. Anal. ($C_{29}H_{37}N_5O_3S$•2.15 CF_3CO_2H•0.27 HBr•0.8 H_2O) C, H, N, Br, F, H_2O.

***N*-Methyl-D-phenylalanyl-*N*-[(1*S*)-1-(2-benzothiazolylcarbonyl)pentyl]-L-prolinamide (44).** [(1*S*)-1-[(Methoxymethylamino)carbonyl]pentyl]carbamic acid, 1,1-dimethylethyl ester (3.00 g, 10.9 mmol; CAS# 104062-69-3) was converted to **44** according to the methods described for **5**. The resulting tan solid was purified by reverse-phase HPLC eluting with water/MeCN/TFA (45:55:0.2) to give **44** (0.550 g) as a white solid: $[\alpha]_D^{25}$ –80.7°; IR ν_{max} 2960, 1671, 1204 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.50-1.05 (m, 3H), 1.35-1.45 (m, 6H), 1.70-2.30 (ov m, 6H), 2.83 (s, 3H), 3.05-3.15 (m, 1H), 3.30-3.60 (ov m, 2H), 4.25-4.35 (m, 1H), 4.50-4.55 (m, 0.5H), 4.60-4.65 (m, 0.5H), 5.65-5.70 (m, 1H), 7.10-7.35 (ov m, 5H), 7.50-7.60 (m, 2H), 7.85-7.95 (m, 1H), 8.10-8.20 (m, 2H); MS (FAB) *m/z* 507.3 (MH)+. Anal. ($C_{28}H_{34}N_4O_3S$•1.5 CF_3CO_2H•0.3 H_2O) C, H, N, F, H_2O.

***N*-Methyl-D-phenylalanyl-*N*-[(1*S*)-2-(2-benzothiazolyl)-2-oxo-1-(phenylmethyl)ethyl]-L-prolinamide (45).** [(1*S*)-2-(Methoxymethylamino)-2-oxo-1-(phenylmethyl)ethyl]carbamic acid, 1,1-dimethylethyl ester (2.80 g, 9.1 mmol; CAS# 87694-53-9) was converted to **45** by the methods described for **5**. The resulting tan solid was purified by reverse-phase HPLC eluting with water/MeCN/TFA (45:55:0.2) to give **45** (0.310 g) as a white solid: mp 74-95 °C; $[\alpha]_D^{25}$ –45.3°; IR ν_{max} 3031, 1671, 1202 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30-1.40 (m, 1H), 1.65-1.70 (m, 1H), 2.00-2.50 (m, 6H), 2.60 (s, 3H), 3.05-3.10 (m, 1H), 3.25-3.60 (ov m, 4H), 4.25-4.30 (m, 0.5H), 4.35-4.40 (m, 0.5H), 6.05-6.10 (m, 1H), 7.08-7.34 (ov, m, 10H), 7.55-7.65 (m, 2H), 7.85-7.90 (m, 1H), 8.15-8.20 (m, 1H); MS (FAB) *m/z* 541.3 (MH)+. Anal. ($C_{31}H_{32}N_4O_3S$•1.5 CF_3CO_2H•0.7 H_2O) C, H, N, F, H_2O.

(1*S*)- and (1*R*)- *N*-Methyl-D-phenylalanyl-*N*-[4-[(aminoiminomethyl)amino]-1-(2-benzothiazolylmethyl)butyl]-L-prolinamide (46 and 47). A solution of **5b** (0.548 g, 1.00 mmol) in 1,2-dichlorethane (19 mL) was treated with 1,1'-thiocarbonyldiimidazole (0.214 g, 1.10 mmol), stirred for 3.5 h, and concentrated in vacuo. The residue was dissolved in THF (10 mL), diluted with toluene (22 mL), and added dropwise to a refluxing solution of tributyltin hydride (353 µL, 1.30 mmol) in toluene (50 mL). After 3.5 h, the reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was dissolved in acetonitrile (50 mL) and extracted with hexane (2x). The acetonitrile layer was concentrated in vacuo and the residue was purified by normal phase chromatography eluting with CH_2Cl_2/MeOH (19:1) to afford **46a** (0.192 g, 36%).



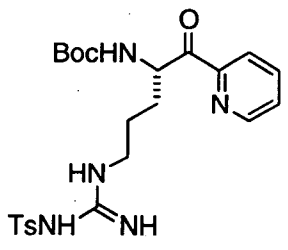
46a

Compound **46a** was converted to a mixture of **46** and **47** according to the methods described for **5**. The resulting crude solid was purified by reverse-phase HPLC eluting with water/MeCN/TFA (80:20:0.2 to 60:40:0.2) to afford **41** (0.037 g; slower eluter) and **42** (0.048 g; faster eluter) as white solids. Compound

46: ^{1}H NMR δ 1.20-1.25 (m, 1H), 1.45-1.55 (m, 2H), 1.75-1.85 (m, 5H), 2.35-2.40 (m, 1H), 2.70 (s, 3H), 3.00-3.05 (m, 1H), 3.15-3.25 (m, 4H), 3.30-3.40 (m, 2H), 4.10-4.15 (m, 1H), 4.30-4.40 (m, 2H), 7.20-7.25 (m, 2H), 7.30-7.40 (m, 3H) 7.40 (dd, 1H, *J* = 7.1, 7.1 Hz), 7.50 (dd, 1H, *J* = 7.1, 7.1 Hz), 7.85-7.95 (m, 2H); MS (ES) *m*/z 536 (MH)$^+$. Anal. ($C_{28}H_{37}N_7O_2S$•2.3 CF_3CO_2H•2.0 H_2O) C, H, N, F, H_2O. Compound **47**: ^{1}H NMR δ 1.35-1.40 (m, 1H), 1.55-1.80 (ov m, 6H), 1.85-1.90 (m, 1H), 2.45-2.50 (m, 1H), 2.65 (s, 3H), 3.00-3.50 (ov m, 5H), 4.20-4.40 (ov m, 3H), 7.20-7.25 (m, 2H), 7.30-7.35 (m, 3H) 7.40 (dd, 1H, *J* = 7.1, 7.1 Hz), 7.50 (dd, 1H, *J* = 7.1, 7.1 Hz), 7.95 (m, 2H); MS (ES) *m*/z 536 (MH)$^+$. Anal. ($C_{28}H_{37}N_7O_2S$•2.3 CF_3CO_2H•2.0 H_2O) C, H, N, F, H_2O.

N-Methyl-D-phenylalanyl-N-[(1*S*)-4-[(aminoiminomethyl)amino]-1-(2-benzothiazolylhydroxymethyl)butyl]-L-prolinamide (48 and 49). Compound **3c** (1.00 g, 1.19 mmol) was deprotected with anhydrous HF as described for **5** to give a crude mixture of **48** and **49**. This mixture was purified by reverse-phase HPLC eluting with water/MeCN/TFA (70:30:0.2) to afford **48** (0.409 g; faster eluter) and **49** (0.186 g; slower eluter) as white solids. The absolute stereochemistry of the alcohol is unknown for both compounds. Compound **48**: mp 77-180 °C (dec); $[\alpha]_D^{20}$ –61.8 ° (*c* 1.21, MeOH); IR ν_{max} 3354, 1669, 1203 cm^{-1}; ^{1}H NMR δ 1.20-1.30 (m, 1H), 1.40-1.50 (m, 2H), 1.60-1.70 (m. 3H), 1.75-1.85 (m, 3H), 2.35-2.45 (m, 1H), 2.67 (s, 3H), 3.00-3.10 (m, 1H), 3.15-3.24 (m, 3H), 4.20-4.28 (m, 1H), 4.30-4.40 (m, 2H), 4.90 (d, 1H, *J* = 6.0 Hz), 7.15-7.20 (m, 2H), 7.25-7.30 (m, 3H) 7.39 (dd, 1H, *J* = 7.1, 7.1 Hz), 7.49 (dd, 1H, *J* = 7.1, 7.1 Hz), 7.87 (d, 1H, *J* = 7.1 Hz), 7.94 (d, 1H, *J* = 7.1 Hz); MS (FAB) *m*/z 552.5 (MH)$^+$. Anal. ($C_{28}H_{37}N_7O_3S$•4.0 CF_3CO_2H•1.5 H_2O) C, H, N, F; H_2O: calcd 2.61; found 0.92. Compound **49**: mp 65-175 °C (dec); $[\alpha]_D^{25}$ –69.7°; IR ν_{max} 3363, 1665, 1202, 1173 cm^{-1}; ^{1}H NMR δ 1.10-1.20 (m, 1H), 1.25-1.35 (m, 2H), 1.61-1.86 (ov m, 6H), 2.30-2.40 (m, 1H), 2.63 (s, 3H), 2.95-3.05 (m, 1H), 3.15-3.28 (m, 3H), 4.20-4.30 (m, 2H), 4.40-4.50 (m, 1H), 4.95-5.05 (m, 1H), 7.15-7.20 (m, 2H), 7.25-7.30 (m, 3H), 7.39 (dd, 1H, *J* = 7.1, 7.1 Hz), 7.49 (dd, 1H, *J* = 7.1, 7.1 Hz), 7.87 (d, 1H, *J* = 7.1 Hz), 7.94 (d, 1H, *J* = 7.1 Hz); MS (FAB) *m*/z 552.5 (MH)$^+$. Anal. ($C_{28}H_{37}N_7O_3S$•4.25 CF_3CO_2H•1.75 H_2O) C, H, N, F, H_2O.

***N*-Methyl-D-phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-(2-pyridinyl-carbonyl)-butyl]-L-prolinamide (50).** 1.6 M Butyllithium in hexane (32 mL, 51.2 mmol) was added dropwise to a stirring solution of 2-bromopyridine (5.70 mL, 59.4 mmol) in THF (110 mL) at over 15 min at –78 °C to -74 °C. After 3 min, a 78 °C solution of Weinreb amide **4a** (0.800 g, 1.70 mmol) in THF (30 mL) was added to the reaction mixture over 6 min at –78 °C to –70 °C. After 2 h, the reaction mixture was poured into saturated aq NH_4Cl (600 mL), stirred for 10 min and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with water (3x), brine, dried (Na_2SO_4) and concentrated in vacuo to give a green oil. This oil was purified via normal-phase chromatography eluting with EtOAc/hexane (4:1) to give **50a** (0.530 g, 64%)as a pale yellow foam.

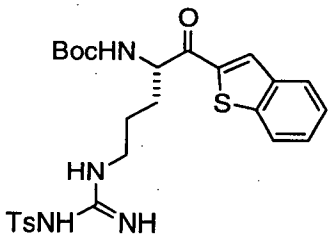


50a

Compound **50a** was converted to crude **50** according to the methods described for **5**. This resulting tan sold was purified by reverse-phase HPLC eluting with water/MeCN/TFA (80:20:0.2) to afford **50**

(0.057 g) as a white solid: mp 40-68 °C; IR ν_{max} 1674, 1433, 1204, 1134 cm^{-1}; ^1H NMR δ 1.35-1.50 (m, 1H), 1.60-2.30 (ov m, 7H), 2.47-2.63 (ov m, 4H), 2.90-3.50 (m, 5H), 4.15-4.25 (m, 1H), 4.35-4.40 (m, 1H), 5.85-5.90 (m, 1H), 7.27-7.40 (ov m, 6H), 7.60-7.70 (m, 1H), 7.95-8.05 (m, 1H), 8.65-8.75 (m, 1H); MS (FAB) *m/z* 494.3 $(MH)^+$. Anal. ($C_{26}H_{35}N_7O_3$•2.75 CF_3CO_2H•2.75 H_2O) C, H, N, H_2O.

***N*-Methyl-D-phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-(benzo[b]thien-2-yl-carbonyl)butyl]-L-prolinamide (51).** 1.6 M Butyllithium in hexane (21 mL, 34 mmol) was added dropwise to a stirring solution of benzo[b]thiophene (5.69 g, 42.4 mmol; CAS# 95-15-8) in THF (154 mL) at over 30 min at –70 °C to -65 °C. After the addition, the reaction mixture was warmed to room temperature for 2 h and then cooled to –78 °C. A solution of Weinreb amide **4a** (2.00 g, 4.24 mmol) in THF (110 mL) was added dropwise over 1.25 h to the reaction mixture at –78 °C to -70 °C. After 1 h, the reaction mixture was poured into saturated aq NH_4Cl (150 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (2x), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was triturated with hexane (3x) and purified by normal-phase chromatography eluting with EtOAc/hexane (1.9:1) to afford **51a** (1.81 g, 78%). Compound **51a** was converted to crude **51** according to the methods described for **5**. This resulting tan sold was purified by reverse-phase HPLC eluting with water/MeCN/TFA (62:38:0.2) to afford **51** (0.401 g) as a white solid: $[\alpha]_D^{25}$ –78.3°; ^1H NMR δ 1.35-1.45 (m, 1H), 1.75-2.10 (ov m, 7H), 2.45-2.55 (m, 1H), 2.70 (s, 3H), 3.00-3.10 (m, 1H), 3.20-3.30 (ov m, 3H), 3.40-3.50 (m, 1H), 4.35-4.45 (m, 2H), 5.35-5.45 (m, 1H), 7.25-7.34 (m, 2H), 7.35-7.40 (m, 3H), 7.45-7.55 (m, 2H), 7.90-8.00 (m, 2H), 8.28 (s, 1H); MS (FAB) *m/z* 549.3 $(MH)^+$. Anal. ($C_{29}H_{36}N_6O_3S$•2.4 CF_3CO_2H•1.5 H_2O) C, H, N, F, H_2O.

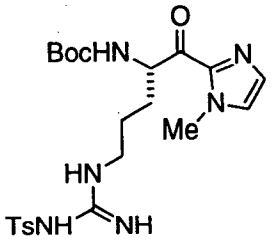


51a

***N*-Methyl-D-phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-[(1-methyl-1H-imidazol-2-yl)carbonyl]butyl]-L-prolinamide (52).** 1.6 M *n*-Butyllithium in hexane (28 mL, 44.9 mmol) was added dropwise to a stirring solution of 1-methylimidazole (4.20 mL, 52.4 mmol) in THF (106 mL) at over 20 min at –78 °C to -72 °C. After the addition, the reaction mixture was warmed to 0 °C for 22 min and then cooled to –78 °C. A solution of Weinreb amide **4a** (0.706 g, 1.49 mmol) in THF (20 mL) was added dropwise over 5 min to the reaction mixture at –78 °C to -70 °C. After 1 h, the reaction mixture was poured into saturated aq NH_4Cl (350 mL) and stirred for 1 h. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water (2 x 500 mL), brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and concentrated in vacuo to give afford **52a** (0.61 g, 83%) as a white foam.

Compound **52a** was converted to crude **52** according tothe methods described for **5**. This resulting tan sold was purified by reverse-phase HPLC eluting with water/MeCN/TFA (62:38:0.2) to afford **52** (0.401 g) as a white solid: mp 70-83 °C; $[\alpha]_D^{25}$ –63.7°; IR ν_{max} 3172, 1672, 1203, 1138 cm^{-1}; ^1H NMR (D_2O) δ 1.15-1.25 (m, 1H), 1.20-1.30 (m, 1H), 1.40-1.50 (m, 1H), 1.55-2.00 (ov m, 6H), 2.45-2.55 (m, 2H),

2.56 (s, 0.23H), 2.60 (s, 2.76H), 2.95-3.05 (m, 1H), 3.10-3.28 (m, 3H), 3.95 (s, 3H), 4.05-4.15 (m, 0.5H), 4.16-4.20 (m, 0.5H), 4.40-4.50 (m, 1H), 7.15-7.25 (m, 2H), 7.26-7.35 (m, 5H). Anal. ($C_{25}H_{36}N_8O_3$•3.9 CF_3CO_2H•1.1 H_2O) C, H, H_2O; N: calcd 11.66; found 12.09.



52a

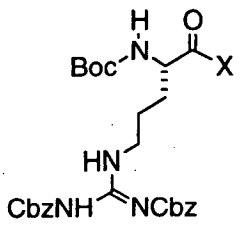
***N*-Methyl-D-phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-[(1H-benzimidazol-2-yl-carbonyl)butyl]-L-prolinamide (53).** 1,2-Phenylenediamine (0.183 g, 1.69 mmol; CAS# 95-54-5) was reacted with imidate **3b** and converted to **53** according to the methods described for **3**. The crude product was purified by reverse-phase HPLC eluting with water/MeCN/TFA (70:30:0.2) to afford **53** (0.151 g) as a white solid: mp 65-80 °C; $[\alpha]_D^{25}$ –63.1° (*c* 1.00, H_2O); IR ν_{max} 3391, 1672, 1203, 1138 cm^{-1}; Appears to be primarily the hydrate by ^1H NMR in D_2O: ^1H NMR (D_2O) δ 0.80-1.20 (ov m, 2H), 1.50-1.80 (ov m, 6H), 1.90-2.10 (ov m, 2H), 2.30-2.40 (m, 2H), 2.55 (s, 2.66H), 2.60 (s, 0.34H), 2.90-3.30 (ov m, 5H), 7.10-7.15 (m, 2H), 7.25-7.35 (m, 3H), 7.50-7.60 (m, 2H), 7.65-7.75 (m, 2H); MS (FAB) *m*/z 533.5 $(MH)^+$. Anal. ($C_{28}H_{36}N_8O_3$•3.75 CF_3CO_2H•1.0 H_2O) C, H, N, H_2O.

***N*-Methyl-D-phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-[(1-methyl-1H-benzimid-azol-2-yl)carbonyl]butyl]-L-prolinamide (54).** A mechanically stirred solution of 2-bromobenz-imidazole[64] (12.5 g, 0.063 mmol; CAS# 54624-57-6) in 1 N NaOH (146 mL) was treated with dimethyl sulfate (10.8 mL, 114 mmol) at room temperature. After the addition, the reaction mixture was warmed to 40 °C, stirred for 2 h, and cooled to 5 °C. The resulting precipitate was isolated by filtration to afford 2-bromo-1-methylbenzimidazole (10.5 g, 79%; CAS# 49572-60-3) as a white solid. This material was converted to **54** according to the methods described for **50**. The resulting crude product was purified by reverse-phase HPLC eluting with water/MeCN/TFA (75:25:0.2) to afford **54** (0.385 g) as a white solid: mp 70-90 °C; $[\alpha]_D^{25}$ -57.8°; IR ν_{max} 3355, 3199, 1670, 1202, 1137 cm^{-1}; ^1H NMR (D_2O) δ 0.50-0.90 (m, 1.5H), 1.00-1.05 (m, 0.5H), 1.50-2.15 (ov m, 7H), 2.40-2.45 (m, 1H), 2.53 (s, 0.55H), 2.55 (s, 2.44H), 2.90-3.30 (ov m, 5H), 4.05 (ov m, 5H), 7.15-7.20 (m, 2H), 7.25-7.30 (m, 3H), 7.55-7.85 (ov m, 4H); MS (FAB) *m*/z 547.8 $(MH)^+$. Anal. ($C_{29}H_{38}N_8O_3$•4.0 CF_3CO_2H•1.0 H_2O) C, H, N, F, H_2O.

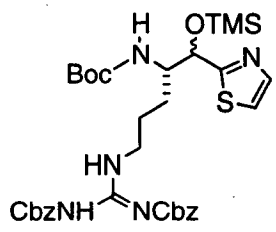
***N*-Methyl-D-phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-[(1,4-dihydro-4-oxo-2-quin-azolinyl)carbonyl]butyl]-L-prolinamide (56).** Anthranilic acid (0.784 g, 5.71 mmol; CAS# 118-92-3) was reacted with imidate **55b** and converted to **56** according to the methods described for **55**. The resulting crude product was purified by reverse-phase HPLC eluting with water/MeCN/TFA (75:25:0.2) to afford **56** (0.024 g) as a white solid: mp 122-138 °C; IR ν_{max} 3391, 1677, 1469, 1205, 1134 cm^{-1}; ^1H NMR δ 0.85-2.30 (ov m, 8H), 2.40-2.50 (m, 1H), 2.55 (s, 0.39H), 2.60 (s, 2.6H), 2.80-3.45 (ov m, 5H), 3.95-4.50 (ov m, 2H), 5.65-5.75 (ov m, 1H), 7.05-7.35 (ov m, 5H), 7.50-7.90 (ov m, 3H), 8.10-8.30 (ov m, 1H); MS (FAB) *m*/z 561.3 $(MH)^+$. Anal. ($C_{29}H_{36}N_8O_4$•2.6 CF_3CO_2H•3.0 H_2O) C, H, N, H_2O.

***N*-Methyl-D-phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-(2-thiazolylcarbonyl)butyl]-L-prolinamide (57).** 1,1'-Carbonyldiimidazole (0.657 g, 4.05 mmol) was added to a solution of **57a** (2.00 g, 3.69 mmol; CAS# 120267-95-0) and THF (11 mL) at 0 °C under argon and the resulting mixture

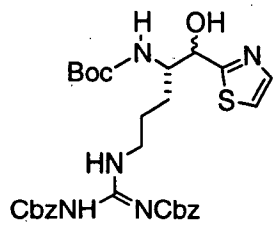
was stirred for 1 h at 0 °C. The mixture was cooled to -48 °C and a solution of 1 M DIBAL in hexane (10.3 mL, 10.3 mmol) was added at a rate that kept the reaction temperature between -48 and -42 °C. The reaction mixture was stirred for 30 min at -48 °C and solution of aq $KHSO_4$ (1.40 g in 5.5 mL) was added dropwise over 10 min at a temperature of between -40 and -28 °C. The mixture was warmed to room temperature, CH_2Cl_2 was added, and the resulting solid was filtered and washed with CH_2Cl_2 (3x). The combined filtrates were washed with water (2x), dried ($MgSO_4$) and concentrated in vacuo to give **57b**[65] (1.39 g, 72%; CAS# 151145-22-1) as a colorless oil. This oil was recrystallized from in 2-propanol/hexane to give aldehyde **57b** was a white solid (0.71 g, 36%): mp 105-107 °C.



57a X = OH
57b X = H



57c



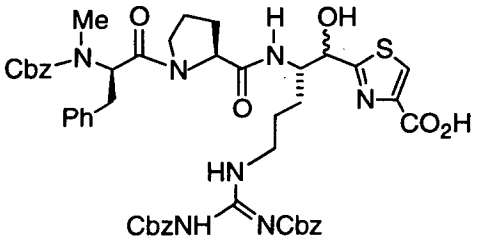
57d

A mixture of aldehyde **57b** (0.765 g, 1.36 mmol), CH_2Cl_2 (5 mL) and 2-(trimethylsilyl)thiazole (1.07 g, 6.8 mmol) was stirred for 18 h. The reaction mixture was concentrated in vacuo to give **57c** as an oil. A solution of **57c** (0.914 g, 1.36 mmol) in CH_2Cl_2 was treated with TFA (6 mL). The reaction mixture was stirred for 6 h, concentrated in vacuo and purified by normal-phase chromatography eluting with CH_2Cl_2/MeOH/concd aq NH_4OH (95:4.5:0.5) to give a single diastereomer. The isolated product was dissolved in CH_2Cl_2, dried (K_2CO_3), filtered and concentrated in vacuo to give the alcohol **57d** (0.300 g, 43%) as a glass. Compound **57d** was converted to **57** according to the methods described for **5**. The resulting crude product was purified by reverse-phase HPLC eluting with water/MeCN/TFA (50:50:0.2) to afford **57** (0.034 g) as a white solid: IR ν_{max} 3370, 1674, 1203, 1134 cm^{-1}; ^1H NMR δ 1.35-1.45 (m, 1H), 1.60-1.86 (ov m, 5H), 1.97-2.11 (ov m, 2H), 2.55-2.65 (m, 1H), 2.80 (s, 3H), 2.90-3.00 (m, 1H), 3.15-3.25 (m, 3H), 3.35-3.45 (m, 1H), 3.46-3.54 (m, 0.5H), 3.55-3.65 (m, 0.5H), 4.15-4.25 (m, 1H), 4.35-4.45 (m, 1H), 5.35-5.40 (m, 0.03H), 5.40-5.50 (m, 0.97H), 7.15-7.25 (m, 2H), 7.30-7.40 (m, 3H), 7.95-8.05 (m, 1H), 8.06-8.10 (m, 1H); MS (FAB) *m/z* 500.2 $(MH)^+$. Anal. ($C_{24}H_{33}N_7O_3S$•1.0 CF_3CO_2H•1.2 H_2O) C, H, N, H_2O.

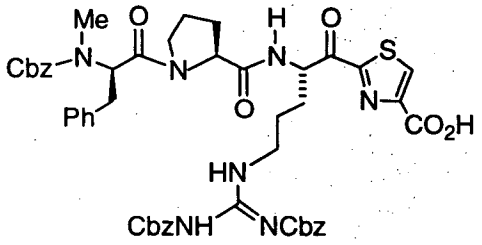
***N*-Methyl-D-phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-[(4-carboxy-2-thiazolyl)-carbonyl]butyl]-L-prolinamide (58).** Compound **59a** (0.560 g, 0.665 mmol) was combined with LiOH (0.065 g, 2.64 mmol) and H_2O (0.1 mL) in 1,4-dioxane (0.9 mL) and stirred for 3 h. The resulting mixture was diluted with H_2O and extracted with Et_2O (3x). The aqueous layer was separated and acidified to pH 4 with 1 N HCl and extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo to give the acid **58a** (0.540 g, 100%) as a solid.

A mixture of **58a** (0.25 g, 0.31 mmol) and the Dess-Martin periodinane (0.20 g, 0.464 mmol) in CH_2Cl_2 (10 mL) was stirred for 1 h. An additional portion of periodinane was added (0.13 g, 0.31 mmol) . After 2 h, the reaction mixture was quenched with 0.1 M $Na_2S_2O_3$ (15 mL) and stirred for 15 min. The layers were separated and the aqueous layer was acidified to pH 3.0 with acetic acid and extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with brine, filtered through filter agent, and concentrated in vacuo. The residue was purified by reverse-phase HPLC eluting with water/MeCN/TFA (50:50:0.2) to give the **58b** as a solid. Ketone **58b** (0.14 g, 0.17 mmol) was deprotected with HF to afford

58 according to the method described for **5**. The resulting crude solid was purified by reverse-phase HPLC eluting with water/MeCN/TFA (70:30:0.2) to give **58** (0.068 g) as a white solid: mp 93-170 °C (dec); $[\alpha]_D^{25}$ –86.5° (*c* 0.65, H_2O); IR ν_{max} 3346, 1670, 1202 cm^{-1}; ^1H NMR δ 1.4-2.2 (ov m, 8H), 2.50-2.65 (m, 1H), 2.63 (s, 0.35 H), 2.67 (s, 2.64H), 3.05-3.45 (ov m, 5H), 4.35-4.40 (m, 1H), 4.45-4.55 (m, 1H), 5.35-5.45 (m, 1H), 7.20-7.30 (m, 2H), 7.35-7.45 (m, 3H), 8.55 (s, 1H); MS (FAB) *m/z* 544.4 $(MH)^+$. Anal. ($C_{25}H_{33}N_7O_5S$•2.5 CF_3CO_2H•1.7 H_2O) C, H, N, H_2O.

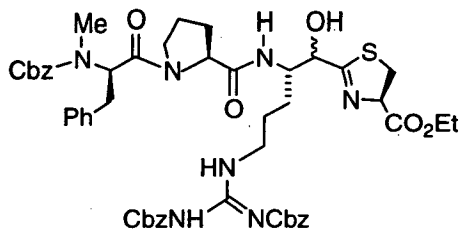


58a

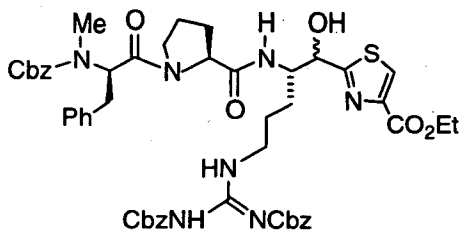


58b

***N*-Methyl-D-phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-[[4-(ethoxycarbonyl)-2-thiazolyl]carbonyl]butyl]-L-prolinamide (59).** A mixture of **3b** (5.09 g, 6.52 mmol) and L-cysteine ethyl ester hydrochloride (2.42 g, 13.05 mmol) in CH_2Cl_2 (127 mL) was stirred over 16 h. The resulting mixture was filtered through filter agent, concentrated in vacuo, and partitioned between brine and EtOAc. The aqueous layer was extracted with EtOAc (3x) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by normal-phase chromatography eluting with CH_2Cl_2/MeOH/concd aq NH_4OH (90:9:1) to give **59a** as a white foam. A mixture of **59a** (1.43 g, 1.69 mmol) and MnO_2 (1.47 g, 14.38 mmol) in CH_2Cl_2 (40 mL) was stirred for 18 h. The resulting mixture was filtered through filter agent and concentrated in vacuo. The residue was purified by normal-phase chromatography with CH_2Cl_2 (9:1) to give thiazole **59b** (1.00 g, 70%) as a white solid. Compound **59b** (0.880 g, 1.05 mmol) was converted to **59** according to the methods described for **5**. The resulting crude product was purified by reverse-phase HPLC eluting with water/MeCN/TFA (60:40:0.2) to afford **59** (0.120 g) as a white solid: mp 100-119 °C; $[\alpha]_D^{25}$ –48.0° (*c* 0.75, H_2O); IR ν_{max} 3371, 1674, 1204, 1134 cm^{-1}; ^1H NMR (D_2O) δ 1.10-1.32 (ov m, 3H), 1.51-2.00 (ov m, 8H), 2.23-2.50 (ov m, 4H), 2.82-2.93 (m, 1H), 3.06-3.19 (m, 3H), 3.27-3.40 (m, 1H), 4.12-4.33 (m, 4H), 5.72-5.80 (m, 1H), 7.10-7.27 (ov m, 5H), 8.66 (s, 1H); MS (FAB) *m/z* 572.3 $(MH)^+$. Anal. ($C_{27}H_{37}N_7O_5S$•1.6 CF_3CO_2H•2.0 H_2O) C, H, N, H_2O.



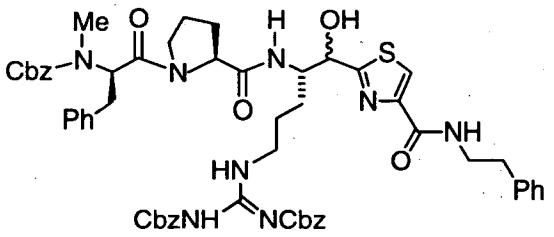
59a



59b

***N*-Methyl-D-phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-[[4-[[(2-phenylethyl)-amino]carbonyl]-2-thiazolyl]carbonyl]butyl]-L-prolinamide (60).** BOP-Cl (0.169 g, 0.399 mmol) was

added to a stirred mixture of **58a** (0.250 g, 0.307 mmol), triethylamine (86 μL, 0.614 mmol) DMF (9 mL) and phenethylamine (58 μL, 0.461 mmol) at 5 °C. The reaction mixture was slowly warmed to room temperature over 18 h, concentrated in vacuo, and partitioned between EtOAc and saturated aq $NaHCO_3$. The aqueous layer was extracted with EtOAc (3x) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified via normal-phase chromatography eluting with CH_2Cl_2/MeOH/concentrated NH_4OH (95:4.5:0.5) to furnish **60a** (0.120 g, 43%) as a white foam. Compound **60a** (0.120 g, 0.131 mmol) was converted to **60** according to the methods described for **5**. The resulting crude product was purified by reverse-phase HPLC eluting with water/MeCN/TFA (70:30:0.2) to afford **60** (0.043 g) as a white solid: mp 120-140 °C; $[\alpha]_D^{25}$ –67.5° (*c* 0.74); IR ν_{max} 3385, 1670, 1203 cm^{-1}; ^1H NMR (D_2O) δ 1.10-1.15 (m, 1H), 1.40-1.50 (m, 4H), 1.80-1.85 (m, 1H), 2.00-2.10 (m, 2H), 2.55-2.60 (m, 1H), 2.65 (s, 0.39H), 2.69 (s, 2.61H), 2.90-3.00 (m, 2H), 3.10-3.20 (m, 3H), 3.25-3.30 (m, 1H), 3.35-3.40 (m, 1H), 3.60-3.70 (m, 2H), 4.30-4.35 (m, 1H), 4.40-4.45 (m, 1H), 5.30-5.35(m, 1H), 7.20-7.40 (ov m, 10H), 8.50 (s, 1H); MS (FAB) *m/z* 647.5 $(MH)^+$. Anal. ($C_{33}H_{42}N_8O_4S$•2.6 CF_3CO_2H•1.2 H_2O) C, H, N, H_2O.



60a

***N*-Methyl-D-phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-[(4,5,6,7-tetrahydro-2-benzothiazolyl)carbonyl]butyl]-L-prolinamide (61).** 2-Amino-4,5,6,7-tetrahydrobenzothiazole (9.00 g, 58.4 mmol) was dissolved in 430 mL of warm phosphoric acid (85% in water) in a mechanically stirred beaker and cooled to –10 °C. A solution of $NaNO_2$ (24.2 g, 350 mmol) in water (75 mL) was added dropwise over 20 min to the reaction mixture while maintaining the temperature at –10 to –4 °C. After the addition, the reaction mixture was stirred at –8 °C for 1 h and added slowly to a mechanically stirred beaker containing 50% aq hypophosphorous acid (140 mL) at 0 °C. After 3 h, the reaction mixture was diluted to 3 L with water, the pH was adjusted to pH 7.1 with Na_2CO_3 (ca. 780 g), combined with 2 L of EtOAc/$CHCl_3$ (1:1) and stirred for 30 min. The layers were separated and the aqueous layer was extracted with twice with EtOAc/$CHCl_3$ (1:1). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was distilled on a Kugelrohr apparatus at 100-120 °C (0.5-1.0 mm Hg) to give 4,5,6,7-tetrahydrobenzothiazole (4.72 g, 58%; CAS# 4433-49-2) as a colorless viscous oil. This material (4.00 g, 28.8 mmol) was reacted with Weinreb amide **4a** (1.70 g, 3.60 mmol) and converted to **61** according to the methods described for **5**. The resulting crude product was purified by reverse-phase HPLC eluting with water/MeCN/TFA (60:40:0.2) to afford **61** (0.358 g) as a white solid: mp 50-60 °C; $[\alpha]_D^{25}$ –71.7° (*c* 0.69); IR ν_{max} 3373, 1670, 1203 cm^{-1}; ^1H NMR δ 1.40-1.45 (m, 1H), 1.70-2.15 (ov m, 8H), 2.45-2.50 (m, 1H), 2.70 (s, 3H), 2.85-2.95 (m, 4H), 3.00-3.05(m, 1H), 3.20-3.30 (m, 3H), 3.40-3.45 (m, 1H), 3.60-3.65 (m, 2H), 4.35-4.40 (m, 2H), 4.45-4.50 (m, 1H), 5.50-5.60 (m, 0.9H), 5.60-5.70 (m, 0.1H), 7.26-7.37 (ov m, 5H); MS (FAB) *m/z* 554.3 $(MH)^+$. Anal. ($C_{28}H_{39}N_7O_3S$•2.6 CF_3CO_2H•1.4 H_2O) C, H, N, F, H_2O.

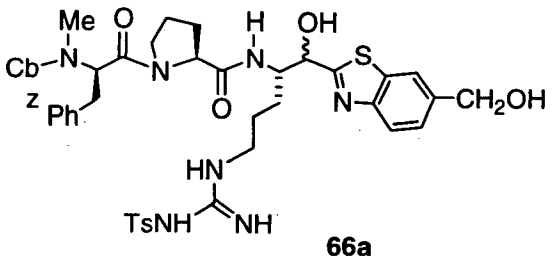
***N*-Methyl-D-phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-(naphtho[2,1-d]-thiazol-2-ylcarbonyl)butyl]-L-prolinamide (62).** A slurry of 2-amino-1-thiocyanatonaphthalene[66] (9.40 g, 47.0 mmol; CAS# 2476-69-9) in EtOH (24 mL) was added in portions to a solution of sodium sulfide nonahydrate (28.2 g, 118 mmol) in water 75 mL at 60 °C. After the addition, the reaction mixture was warmed to 85 °C, stirred for 40 min, and cooled to room temperature. The reaction mixture was filtered and the pH of the filtrate was adjusted to pH 6.5 with 5 N acetic acid and extracted with $CHCl_3$ (3x). The combined organic extracts were washed with water, dried (Na_2SO_4), filtered and concentrated in vacuo to afford 2-amino-1-naphthalenethiol (CAS# 53338-20-8) as a yellow oil. This material was combined with ethyl orthoformate (16 mL, 96.0 mmol) and concd H_2SO_4 (0.3 mL, 0.56 mmol) in a round-bottomed flask fitted with a distillation apparatus. The reaction mixture was heated with a silicone oil bath from 100-170 °C and the distilled EtOH was collected. After 20 min at 170 °C, the reaction mixture was cooled to room temperature and dissolved in $CHCl_3$ (300 mL). This solution was washed with water, saturated aq $NaHCO_3$, water, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by normal-phase chromatography with CH_2Cl_2/MeOH (97:3) to furnish naphtho[2,1-d]thiazole (5.4 g, 62%; CAS# 234-47-9) as a light yellow solid. This material (4.90 g, 26.8 mmol) was reacted with Weinreb amide **4a** (1.30 g, 2.94 mmol) and converted to **62** according to the methods described for **5**. The resulting crude product was purified by reverse-phase HPLC eluting with water/MeCN/TFA (63:37:0.2) to afford **62** (0.523 g) as a white solid: mp 50-80 °C; $[\alpha]_D^{25}$ –103.0°; IR ν_{max} 3366, 1669, 1204, 1175 cm^{-1}; ^1H NMR δ 1.40-1.45 (m, 1H), 1.60-2.00 (ov m, 6H), 2.20-2.25 (m, 1H), 2.45-2.50 (m, 1H), 2.60 (s, 3H), 3.00-3.05 (m, 1H), 3.25-3.30 (m, 1H), 3.40-3.45 (m, 1H), 3.60-3.70 (m, 2H), 4.35-4.45 (m, 2H), 5.65-5.74 (m, 0.9H), 5.75-5.80 (m, 0.1H), 7.20-7.40 (ov m, 5H), 7.65-7.70 (m, 1H), 8.05-8.25 (ov m, 5H); MS (FAB) *m/z* 600.5 $(MH)^+$. Anal. ($C_{32}H_{37}N_7O_3S$•3.46 CF_3CO_2H•1.3 H_2O) C, H, N, F, H_2O.

***N*-Methyl-D-phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-[(6-methoxy-2-benzo-thiazolyl)carbonyl]butyl]-L-prolinamide (63).** 6-Methoxybenzothiazole[67] (3.91 g, 23.7 mmol; CAS# 2942-13-4) was reacted with **4a** (0.744 g, 1.58 mmol) and converted to **63** according to the methods described for **5**. The crude product was purified by reverse-phase HPLC eluting with water/MeCN/TFA (70:30:0.2) to afford **63** (0.143 g) as a white solid: mp 113-122 °C; $[\alpha]_D^{25}$ -76.6° (*c* 0.73); IR ν_{max} 1676, 1551, 1489, 1205, 1135 cm^{-1}; ^1H NMR δ 1.35-1.50 (m, 1H), 1.70-2.0 (ov m, 6H), 2.10-2.25 (m, 1H), 2.50-2.59 (m, 2H), 2.60 (s, 3H), 2.95-3.05 (m, 2H), 3.25-3.35 (m, 1H), 3.4-3.45 (m, 1H), 3.90 (s, 3H), 4.20-4.30 (m, 1H), 4.35-4.40 (m, 1H), 5.60-5.75 (m, 1H), 7.20-7.40 (ov m, 6H), 7.60 (s, 1H), 8.10-8.15 (m, 1H); MS (FAB) *m/z* 580.3 $(MH)^+$. Anal. ($C_{29}H_{37}N_7O_4S$•2.3 CF_3CO_2H•1.75 H_2O) C, H, N, H_2O.

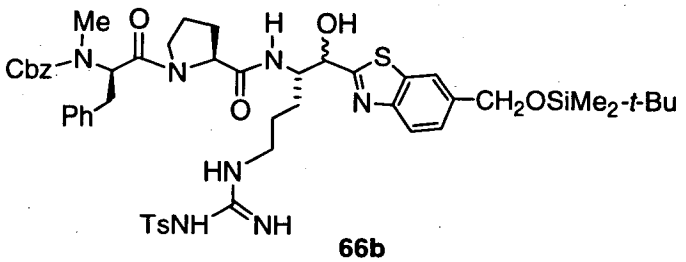
***N*-Methyl-D-phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-[(6-hydroxy-2-benzo-thiazolyl)carbonyl]butyl]-L-prolinamide (64).** A solution of 6-hydroxybenzothiazole (4.85 g, 32.1 mmol; CAS# 13599-84-3), imidazole (5.46 g, 80.2 mmol) in THF (120 mL) was treated with *tert*-butylchlorodiphenylsilane (9.20 mL, 35.3 mmol). After 5 h, the reaction mixture was cooled to 5 °C and filtered and the filtrate was concentrated in vacuo. The residue was purified via normal-phase chromatography eluting with hexane/EtOAc (4:1) to afford 6-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-benzothiazole (10.1 g, 81%; CAS# 186182-22-9) as a colorless oil. This material (9.38 g, 24.1 mmol) was reacted with Weinreb amide **4a** (0.757 g, 1.60 mmol) and converted to **64** according to the methods describe for **5**. The resulting crude product was purified by reverse-phase HPLC eluting with water/MeCN/TFA (73:27:0.2) to afford **64** (0.101 g) as a white solid: mp 118-128 °C; $[\alpha]_D^{25}$ –80.3° (*c* 0.80); IR ν_{max} 1676, 1552, 1480, 1203, 1135 cm^{-1}; ^1H NMR δ 1.32-1.47 (m, 1H), 1.70-2.00 (ov m, 6H), 2.12-2.28 (m, 1H), 2.32-2.61 (ov m, 4H), 2.82-3.00 (m, 1H), 3.05-3.15 (m, 1H), 3.40-3.50 (m, 1H), 4.00-4.10 (m, 1H), 4.20-4.30 (m, 1H), 4.30-4.40 (m, 1H), 5.60-5.70 (m, 1H), 7.10-7.35 (ov m, 8H), 7.95-8.00 (m, 1H); MS (FAB) *m/z* 566.3 $(MH)^+$. Anal. ($C_{28}H_{35}N_7O_4S$•2.0 CF_3CO_2H•1.5 H_2O) C, H, N, H_2O.

***N*-Methyl-D-phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-[(6-fluoro-2-benzothiazolyl)carbonyl]butyl]-L-prolinamide (65).** A solution of sodium nitrite (24.6 g, 35.7 mmol) in water (80 mL) was added dropwise to a stirred solution of 2-amino-6-fluorobenzothiazole (10.0 g, 59.5 mmol) in 85% aq phosphoric acid at -10 °C at a rate such that the reaction temperature did not exceed -4°C. This mixture was maintained at -8 °C for 1 h, poured into 50% aq hypophosphorous acid at 0 °C and warmed to room temperature over 2 h. Water was added to give a total volume of 3 L and the resulting mixture was adjusted to pH 7.0 with Na_2CO_3. The aqueous layer and the solid precipitate were extracted with several portions of $CHCl_3$/EtOAc (1:1) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was distilled on a Kugelrohr apparatus at 100-120 °C (0.5 mm Hg) to provide 6-fluorobenzothiazole (7.15 g 83%; CAS# 118220-71-6) as a white solid. This material (9.38 g, 24.1 mmol) was reacted with Weinreb amide **4a** (0.757 g, 1.60 mmol) and converted to **65** according to the methods describe for **5**. The resulting crude product was purified by reverse-phase HPLC eluting with water/MeCN/TFA (70:30:0.2) to afford **65** (0.397 g) as a white solid: mp 65-80 °C; $[\alpha]_D^{25}$ –72.9° (*c* 0.63); IR ν_{max} 3350, 1669, 1199, 1136 cm^{-1}; ^1H NMR δ 1.40-1.50 (m, 1H), 1.76-2.00 (ov m, 6H), 2.15-2.20 (m, 1H), 2.45-2.50 (m, 1H), 2.60-2.65 (m, 1H), 2.70 (s, 3H), 3.00-3.05 (m, 1H), 3.25-3.35 (m, 1H), 3.40-3.45 (m, 1H), 3.50-3.55 (m, 1H), 4.35-4.45 (m, 2H), 5.55-5.64 (m, 0.97H), 5.65-5.70 (m, 0.03H), 7.20-7.50 (ov m, 6H), 7.80-7.85 (m, 1H), 8.15-8.20 (m, 1H); MS (FAB) *m/z* 568.5 $(MH)^+$. Anal. ($C_{28}H_{34}FN_7O_3S$•3.0 CF_3CO_2H•1.1 H_2O) C, H, N, F, H_2O.

***N*-Methyl-D-phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-[[6-(hydroxymethyl)-2-benzothiazolyl]carbonyl]butyl]-L-prolinamide (66).** A solution of 1.0 M DIBAL in hexane (10 mL, 10 mmol) was added dropwise to a stirred solution of **4d** (1.50 g, 1.67 mmol) in CH_2Cl_2 (160 mL) at –78 °C to –74 °C. The reaction mixture was stirred for 45 min and quenched with saturated aq NH_4Cl (50 mL) and warmed to room temperature. The pH of the reaction mixture was adjusted to pH 3.0 with 1 N HCl and the layers were separated. The aqueous was extracted with CH_2Cl_2 (2x) and the combined organic extracts were washed with successive portions of saturated aq $NaHCO_3$, water, brine, dried (Na_2SO_4) and concentrated to give crude **66a** (0.650 g, 45%), which was used without purification. A solution of **66a** (0.145 g, 0.167 mmol), triethylamine (140 µL, 1.00 mmol), and DMAP (0.0612g, 0.50 mmol) in CH_2Cl_2 (15 mL) was cooled to 5 °C, treated with *tert*-butyldimethylsilyl chloride (0.0453g, 0.30 mmol), and slowly warmed to room temperature over 8 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL), washed with 10% aq citric acid, saturated aq $NaHCO_3$, water, brine, dried (Na_2SO_4), and concentrated in vacuo to provide **66b** (0.160 g, 98%). Compound **66b** was converted to **66** according to the methods describe for **5**. The resulting crude product was purified by reverse-phase HPLC eluting with water/MeCN/TFA (70:30:0.2) to afford **66** (0.397 g) as a white solid: mp 95-110 °C; IR ν_{max} 3348, 1674, 1203, 1136 cm^{-1}; ^1H NMR δ 0.95-1.00 (m, 1H), 1.25-2.05 (ov m, 11H), 2.45-2.50 (m, 1H), 2.70 (s, 2.7H), 2.60 (s, 0.3H), 3.00-3.05 (m, 1H), 3.40-3.60 (ov m, 2H), 4.25-4.30 (m, 1H), 4.35-4.40 (m, 1H), 5.60-5.70 (m, 9H), 5.70-5.75 (m, 0.1H), 7.20-7.40 (ov m, 5H), 7.55-7.60 (m, 1H), 7.65-7.70 (m, 1H), 8.10-8.15 (ov s, 1H). HRMS *m/z* 580.2716 (580.2706 calcd for $C_{13}H_{16}N_4OS + H^+$).



66a



66b

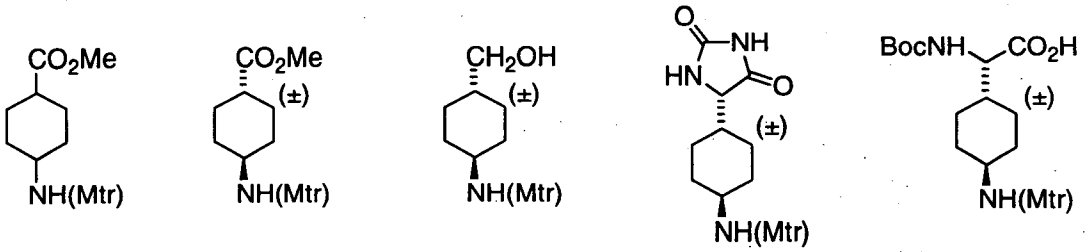
***N*-Methyl-D-phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-[[6-(aminocarbonyl)-2-benzothiazolyl]carbonyl]butyl]-L-prolinamide (67).** Compound **4d** was saponified as described for **4** and the resulting acid (800g, 0.90 mmol) was combined with HOBT (0.37 g, 2.70 mmol), dissolved in 20 mL of CH_2Cl_2/DMF (4:1) and treated with DCC (0.37 g, 1.80 mmol) while stirring. After 10 min, aq 29% NH_4OH (586 μL, 4.5 mmol) was added. The mixture was stirred for 5 h and another portion of HOBT (0.007 g), DCC (0.007 g), and concentrated aq NH_4OH (20 μL) was added. After 2 h of stirring, the mixture was diluted with EtOAc (ca. 60 mL) and the resulting organic layer was washed with successive portions of saturated aq $NaHCO_3$ (2x) and brine (2x), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by normal-phase chromatography eluting with CH_2Cl_2/MeOH (12:1 to 10:1) to give the corresponding 6-carboxamidobenzothiazole derivative (0.23 g; 29%) as a white solid. This derivative was converted to **67** by the methods described for **5**. The resulting tan solid was purified by reverse-phase HPLC eluting with water/MeCN/TFA (80:20:0.2) to give **67** (0.147 g) as a pale yellow solid: mp 130-143 °C; $[\alpha]_D^{25}$ -76.0° (*c* 0.30); IR ν_{max} 3186, 1665, 1203, 1133 cm^{-1}; ^1H NMR δ 1.40-1.45 (m, 1H) 1.77-2.00 (m, 8H), 2.15-2.20 (m, 1H), 2.50-2.55 (m, 1H), 2.68 (s, 3H), 3.00-3.08 (m, 1H), 3.25-3.30 (m, 1H), 3.40-3.50 (m, 1H), 4.35-4.45 (m, 2H), 5.60-5.70 (m, 0.8H), 5.70-5.75 (m, 0.2H), 7.20-7.45 (ov m, 5H), 8.10-8.15 (m, 1H), 8.21-8.25 (m, 1H), 8.65 (s, 1H); MS (FAB) *m/z* 593.4 $(MH)^+$. Anal. ($C_{29}H_{36}N_8O_4S$•2.9 CF_3CO_2H•3.2 H_2O) C, H, N, F, H_2O.

Methyl-D-phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-[[6-(methoxycarbonyl)-2-benzothiazolyl]carbonyl]butyl]-L-prolinamide (68). Compound **68** was prepared in the same manner as **4** starting from Weinreb amide **4a** (1.42 g, 3.0 mmol) with the exception that the esterification and saponification steps were removed. The resulting solid was purified by reverse-phase HPLC using water/MeCN/TFA (70:30:0.2) to give **68** (0.50 g) as a white solid: mp 70-90 °C; $[\alpha]_D^{25}$ –82.6° (*c* 0.50); IR ν_{max} 3381, 1673, 1202, 1134 cm^{-1}; ^1H NMR δ 1.35-1.45 (m, 1H) 1.77-1.97 (m, 8H), 2.15-2.25 (m 1H), 2.50-2.55 (m, 1H), 2.60 (s, 0.56H), 2.70 (s, 2.43H), 3.00-3.10 (m, 1H), 3.20-3.30 (m, 1H), 3.40-3.50 (m, 1H), 3.97 (s, 3H), 4.30-4.40 (m, 2H), 5.60-5.70 (m, 1H), 7.26-7.37 (ov m, 5H), 8.25 (ov s, 2H), 8.83 (s, 1H); MS (FAB) *m/z* 608.3 $(MH)^+$. Anal. ($C_{30}H_{37}N_7O_5S$•2.5 CF_3CO_2H•1.7 H_2O) C, H, N, F, H_2O.

***N*-Methyl-D-phenylalanyl-*N*-[1-[*trans*-4-aminocyclohexyl]-2-(2-benzothiazolyl)-2-oxoethyl]-L-prolinamide (69).** A slurry of a mixture of *cis* and *trans* (±)-4-aminocyclohexanecarboxylic acid (5.00 g, 34.9 mmol; CAS# 1776-53-0) in MeOH (170 mL) and 2,2-diemthoxypropane (34 mL) was treated with 4 M HCl in 1,4-dioxane (17.4 mL; 69.8 mmol). The resulting solution was stirred for 18h, concentrated in vacuo. The residue was triturated with Et_2O (3x), dissolved in CH_2Cl_2 (170 mL) and treated with triethylamine (19 mL, 136 mmol). The reaction mixture was cooled to 0 °C and treated with 4-methoxy-2,3,6-trimethylbenzenesulfonyl chloride (8.70 g, 34.9 mmol). The reaction mixture was slowly warmed to room temperature over 4 h and filtered through filter agent. The filtrate was washed with 10% aq citric acid (2x), saturated aq $NaHCO_3$ (2x), dried ($MgSO_4$), filtered and concentrated in vacuo to afford **69a** (12.0 g, 93%). A slurry of **69a** (11.26 g, 30.5 mmol) in MeOH (270 mL) was treated with sodium methoxide (1.35 g, 24.9 mmol) and heated at reflux for 18 h. The reaction mixture was concentrated in vacuo and partitioned between EtOAc and ice cold 1 N HCl. The organic layer was washed with 1 N HCl, saturated aq $NaHCO_3$ (2x), brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue, a 1.7:1 mixture of *trans* and *cis* isomers, was purified by normal-phase chromatography with hexane/EtOAc (4:1) to provide (6.21 g, 58%; slower eluting) and (3.67 g, 34%; faster eluting) of *trans*- (**69b**) and *cis*- (**69a**) methyl 4-[[(4-methoxy-2,3,6-trimethylphenyl)sulfonyl]amino]cyclohexanecarboxylate.

A solution of **69b** (15.38 g, 41.6 mmol) in THF (100 mL) was cooled to 0 °C and 1 M $LiAlH_4$ in THF (64 mL, 64 mmol) was added dropwise while maintaining the reaction temperature at 0-5 °C. The reaction mixture was slowly warmed to room temperature over 18 h and quenched with 1 N NaOH (CAUTION). The reaction mixture was filtered through filter agent and the filtrate was concentrated in

vacuo. The residue was dissolved in EtOAc and washed with 1 N HCl, brine (2x), dried (Na_2SO_4), filtered and concentrated in vacuo to furnish **69c** (9.57 g, 67%). A solution of **69c** (9.56 g, 28.0 mmol) in CH_2Cl_2 (250 mL) was treated with the Dess-Martin periodinane (14.25 g, 34 mmol). After 18 h, the reaction was quenched by the addition of 150 mL of quench solution (75 g of $Na_2S_2O_3$ in 300 mL of saturated aq $NaHCO_3$), vigorously stirred for 15 min and the layers were separated. The aqueous layer was isolated and extracted with CH_2Cl_2 (2x) and the combined organic extracts were washed with saturated $NaHCO_3$ (2x), brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by normal-phase chromatography eluting with hexane/EtOAc (7:3) to afford aldehyde **69d** (2.52 g, 51%). A slurry of **69d** (5.50 g, 16.2 mmol), ammonium carbonate (6.06 g, 63.1 mmol) and potassium cyanide (1.58 g, 24.3 mmol) in 30 mL of EtOH/water (1:1) was heated at reflux for 5 h. The reaction mixture was cooled to room temperature and acidified to pH 3 with 1 N HCl. A white precipitate formed which was isolated by filtration and recrystallized from MeOH to give **69e** (2.22 g, 34%) as a white solid. A slurry of **69e** (2.53 g, 6.18 mmol) in 4 M NaOH (50 mL) was heated at reflux for 18 h, cooled to 0 °C, and treated with di-*tert*-butyl dicarbonate (1.46 g, 6.80 mmol). The reaction mixture was slowly warmed to room temperature over 18 h, cooled to 5 °C, acidified to pH 3 with citric acid, and extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo to furnish **69f** (2.54 g, 81%). Compound **69f** (2.49 g, 4.02 mmol) was converted to **69** according to the methods described for **41**. The crude solid was purified by reverse-phase HPLC eluting with water/MeCN/TFA (90:10:0.2 to 60:40:0.2) to afford **69** (0.273) as a white solid: ^{1}H NMR δ 1.19-1.38 (ov m, 6H) 1.25-2.30 (ov m, 13H), 2.40-2.50 (m, 1H), 2.60-2.70 (ov s, 3H), 3.00-3.15 (m, 2H), 3.18-3.25 (m, 1H), 3.40-3.50 (m, 1H), 4.30-4.45 (m, 2H), 5.65-5.80 (ov m, 1H), 7.20-7.40 (ov m, 5H), 8.11-8.25 (ov m, 2H); MS (ES) *m/z* 548.5 $(MH)^+$. Anal. ($C_{30}H_{37}N_5O_3S$•2.2 CF_3CO_2H•1.8 H_2O) C, H, N, F, H_2O.

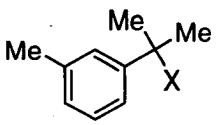


69a **69b** **69c** X = CH_2OH **69d** X = C(O)H **69e** **69f**

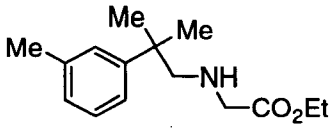
***N*-(Ethylsulfonyl)-D-phenylalanyl-*N*-[1-[*trans*-4-aminocyclohexyl]-2-(2-benzothiazolyl)-2-oxo-ethyl]-L-prolinamide (70).** Compound **70** was prepared from **69f** (0.680 g, 1.40 mmol) and **10b** according to the methods described for **41**. The resulting crude solid was purified by reverse-phase HPLC eluting with water/MeCN/TFA (70:30:0.2) to afford **70** (0.054) as a white solid: ^{1}H NMR δ 1.19-1.38 (ov m, 6H) 1.25-2.30 (ov m, 13H), 2.40-2.50 (m, 1H), 2.60-2.70 (ov s, 3H), 3.00-3.15 (m, 2H), 3.18-3.25 (m, 1H), 3.40-3.50 (m, 1H), 4.30-4.45 (m, 2H), 5.65-5.80 (ov m, 1H), 7.20-7.40 (ov m, 5H), 8.11-8.25 (ov m, 2H). MS (ES) *m/z* 626.4 $(MH)^+$. Anal. ($C_{31}H_{39}N_5O_5S_2$•1.4 CF_3CO_2H•1.5 H_2O) C, H, N, F, H_2O.

***N*-[[(1*S*)-4-[(Aminoiminomethyl)amino]-1-(2-benzothiazolylcarbonyl)butyl]carbamoyl-methyl]-*N*-[2-methyl-2-(3-methylphenyl)propyl]-3-benzenepropanamide (73).** A solution of ethyl 3-methylbenzeneacetate (17.8 g, 100 mmol; CAS# 40061-55-0) in DMF (300 mL) was treated with sodium hydride (16.0 g of 60% w/w, 400 mmol) at 0 °C. After the addition, methyl iodide (56.8 g, 400 mmol) was added dropwise at 0-5 °C and slowly warmed to room temperature over 18 h. The reaction

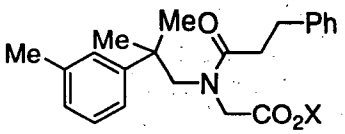
mixture was cooled to 5 °C, neutralized with 1 N HCl, and concentrated in vacuo. The residue was partitioned between water (300 mL) and Et_2O. The aqueous layer was extracted with Et_2O (2x) and the combined organic extracts were washed with brine (2x), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified via normal-phase chromatography eluting with hexane/CH_2Cl_2 (4:1) to afford **73a** (17.7 g, 86%; CAS# 363186-16-7).



73a X = CO_2Et
73b X = CH_2OH
73c X = C(O)H



73d



73e X = Et
73f X = H

A solution of **73a** in Et_2O (500 mL) was treated dropwise with 1 M $LiAlH_4$ in Et_2O (94 mL, 94 mmol). After the addition, the reaction mixture was heated at reflux for 30 min, cooled to room temperature, and quenched (CAUTION) with saturated aq potassium sodium tartrate (Rochelle salt). The reaction mixture was filtered through filter agent and the layers were separated. The organic layer was washed with brine (2x), dried Na_2SO_4), filtered and concentrated in vacuo to give **73b** (12.0 g, 78%).

A solution of **73b** (11.45 g, 69.7 mmol) and triethylamine (100 mL, 718 mmol) in DMSO (225 mL) was treated dropwise with a solution of sulfur trioxide pyridine complex in DMSO (225 mL). After 2 h, the reaction mixture was cooled to 5 °C, acidified to pH 2 with 3 N HCl, and extracted with EtOAc (3x). The combined EtOAc extracts were washed with 1 N HCl (2x), brine (2x), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was partially dissolved in CH_2Cl_2 (200 mL), filtered through filter agent and concentrated in vacuo to give aldehyde **73c** (10.2 g, 90%). A solution of **73c** (9.52 g, 58.7 mmol) in MeOH (150 mL) was treated with ethyl glycinate hydrochloride (45.4 g, 325 mmol). Triethylamine (ca. 15 mL) was added until the pH of the reaction mixture was pH 6. Molecular sieves (10 g of 3 Å) were added followed by $NaBH_3CN$ (2.21 g, 35.2 mmol). The reaction mixture was vigorously stirred for 1 h, concentrated in vacuo, and partitioned between water and Et_2O. The organic extract was washed with brine (2x), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by normal-phase chromatography eluting with hexane/EtOAc (4:1) to provide **73d** (10.3 g, 70%). A solution of **73d** (10.0, 40.3 mmol), *N*-methylmorpholine (13.3 mL, 121 mmol), in THF (200 mL) was cooled to 5 °C and treated dropwise over 20 min with a solution of 3-phenylpropionyl chloride (6.80 g, 40.3 mmol). After the addition, the reaction mixture was slowly warmed to room temperature over 18 h. The reaction mixture was filtered through filter agent and concentrated in vacuo. The residue was dissolved in EtOAc (150 mL) and washed with 3 N HCl (3x), saturated aq $NaHCO_3$ (3x), brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified via normal-phase chromatography eluting with hexane/EtOAc (5.7:1) to afford **73e** (13.7 g, 89%). A soution of **73e** (13.6 g, 35.6 mmol) and 4 M KOH (100 mL, 400 mmol) in absolute EtOH (100 mL) was stirred for 18 h. The reaction mixture was concentrated in vacuo, acidified to pH 2-3 with 1 N HCl, and extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo to provide **73f** (11.6 g, 92%). Compound **73f** (2.00 g, 5.60 mmol) was coupled with **4b** and converted to **73** according to the methods described for **5**. The resulting crude solid was purified by reverse-phase HPLC eluting with water/MeCN/TFA (60:40:0.2 to 50:50:0.2) to afford **73** (0.240 g) as a white solid: ^1H NMR δ 1.25 (s, 3H) 1.35 (br s, 4H), 1.65-1.81 (ov m 3H), 2.00-2.20 (ov m, 6H), 2.45-2.50 (m, 1H), 2.60-2.67 (m,

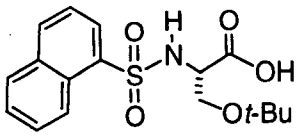
1H), 2.80-2.88 (m, 1H), 3.40-3.65 (ov m, 3.5H), 3.95-4.02 (m, 0.5H), 5.50-5.52 (m, 0.5H), 5.55-5.63 (m, 0.5H), 6.98-7.25 (ov m, 9H), 7.55-7.65 (m, 2H), 8.08-8.20 (ov m, 2H); MS (ES) *m*/z 628.5 (MH)+. Anal. ($C_{35}H_{42}N_6O_3S$•1.5 CF_3CO_2H•0.67 H_2O) C, H, N, F, H_2O.

(3*S*)-*N*-[(1S)-4-[(Aminoiminomethyl)amino]-1-(2-benzothiazolylcarbonyl)butyl]-hexahydro-2-oxo-3-[[(phenylmethyl)sulfonyl]amino]-1H-azepine-1-acetamide (74). (3*S*)-Hexahydro-2-oxo-3-[[(phenylmethyl)sulfonyl]amino]-1*H*-azepine-1-acetic acid[68] (0.665 g, 1.95 mmol; CAS# 174960-90-8) was converted to **74** according to the methods described for **5**. The resulting crude solid was purified by reverse-phase HPLC eluting with water/MeCN/TFA (60:40:0.2) to afford **74** (0.381 g) as a white solid: ^{1}H NMR δ 1.50-1.60 (ov m, 5H), 1.75-1.85 (m, 5H), 2.15-2.20 (m, 1H), 3.35-3.40 (m, 3H), 3.85 (d, 0.5H, *J* = 9 Hz), 3.96 (d, 0.5H, *J* = 9 Hz), 4.00 (d, 0.5H, *J* = 15 Hz), 4.14 (d, 1H, *J* = 1.5), 4.32 (d, 0.5H, *J* = 15 Hz), 4.36 (s, 2H), 5.70-5.78 (m, 1H), 7.30-7.40 (ov m, 3H), 7.41-7.44 (ov m, 2H), 7.60-7.70 (ov m, 2H), 8.12 (d, 1H, *J* = 7.3 Hz), 8.21 (d, 1H, *J* = 7.3 Hz); MS (ES) *m*/z 614.6 (MH)+. Anal. ($C_{28}H_{35}N_7O_5S_2$•1.17 CF_3CO_2H•1.0 H_2O) C, H, N, F, H_2O.

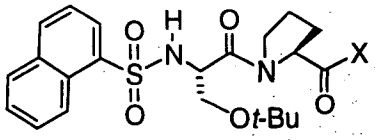
***N*-(1-Oxo-2-propylpentyl)-L-α-aspartyl-N-[(1*S*)-4-[(aminoiminomethyl)amino]-1-(2-benzothiazolylcarbonyl)butyl]-L-prolinamide, Methyl Ester (75).** Compound **6b** (1.69 g, 2.56 mmol) was coupled with Boc-Asp(OMe)-OH (0.633 g, 2.56 mmol) according to the methods described for **6** to afford **75a** (1.51 g, 76%). This material (1.25 g, 1.57 mmol) was dissolved in CH_2Cl_2 (10 mL), treated with TFA (10 mL), and stirred for 18 h. The reaction mixture was concentrated in vacuo, dissolved in acetonitrile (17 mL) and treated with *tert*-butyl 2-bromoacetate (305 µL, 2.07 mmol) and potassium carbonate (0.940 g, 6.8 mmol). The reaction mixture was vigorously stirred at 50-60 °C for 20 h, cooled to room temperature and filtered through filter agent. The filtrate was concentrated in vacuo and the residue was purified via normal phase chromatography eluting with EtOAc/hexane (2.3:1) to provide **75b** (0.870 g, 42%). Compound **75b** was converted to **75** according to the methods described for **5**. The resulting crude solid was purified by reverse-phase HPLC eluting with water/MeCN/TFA (60:40:0.2 to 40:60:0.2) to afford **75** (0.441 g) as a white solid: $[\alpha]_D^{18}$ –55.0°; ^{1}H NMR δ 0.85-0.95 (ov m, 6H) 1.20-1.40 (ov m, 6H), 1.50-1.55 (m 3H), 1.80-1.85 (m, 3H), 2.00-2.05 (m, 3H), 2.20-2.25 (m, 3H), 2.68-2.73 (m, 1H), 2.92-2.98 (m, 1H), 3.48-3.55 (m, 1H), 3.70 (s, 3H), 3.78-3.82 (m, 1H), 3.91-3.97 (m, 1H), 4.48-4.55 (m, 1H), 4.95-5.05 (m, 1H), 5.65-5.75 (m, 1H), 7.60-7.68 (m, 2H), 8.10 (d, 1H, *J* = 7.1 Hz), 8.20 (d, 1H, *J* = 7.1 Hz); MS (ES) *m*/z 644.5 (MH)+. Anal. ($C_{31}H_{45}N_7O_6S$•1.6 CF_3CO_2H•0.9 H_2O) C, H, N, F, H_2O.

(*S*)-4-(Methylsulfonyl)-*N*-[(phenylmethyl)sulfonyl]-L-2-aminobutanoyl-*N*-[4-[(aminoiminomethyl)amino]-1-(2-benzothiazolylcarbonyl)butyl]-L-prolinamide (76). 4-(Methylsulfonyl)-*N*-[(phenylmethyl)sulfonyl]-L-2-aminobutanoyl-L-proline[69] (1.83 g, 4.23 mmol; CAS# 159945-86-5) was converted to **76** according to the methods described for **5**. The resulting crude solid was purified by reverse-phase HPLC eluting with water/MeCN/TFA (75:25:0.2 to 50:50:0.2) to afford **74** (0.303 g) as a white solid: ^{1}H NMR δ 1.50-2.55 (ov m, 10H), 2.90-3.58 (ov m, 9H), 4.05-4.50 (ov m, 4H), 5.60-5.85 (ov m, 1H), 7.15-7.75 (ov m, 7H), 8.00-8.30 (ov m, 2H); MS (ES) *m*/z 706.2 (MH)+. Anal. ($C_{30}H_{39}N_7O_7S_3$•1.3 CF_3CO_2H•1.0 H_2O) C, H, N, F, H_2O.

***N*-(1-Naphthalenylsulfonyl)-L-seryl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-(2-benzothiazolylcarbonyl)butyl]-L-prolinamide (77).** A solution of *O*-*tert*-butyl-L-serine (2.0 g, 11.7 mmol), triethylamine (5.2 mL, 37.3 mmol) in CH_2Cl_2 (100 mL) was cooled to 0 °C and while stirring under argon. 1-Naphthalenensulfonyl chloride (4.0 g, 17.6 mmol) was added and the reaction was slowly warmed to room temperature over 18 h, extracted with 1 N HCl (3x), brine, dried $MgSO_4$, and concentrated in vacuo. The residue was purified via normal-phase chromatography eluting with EtOAc/hexane/acetic acid (60:40:1) to afford **77a**.



77a

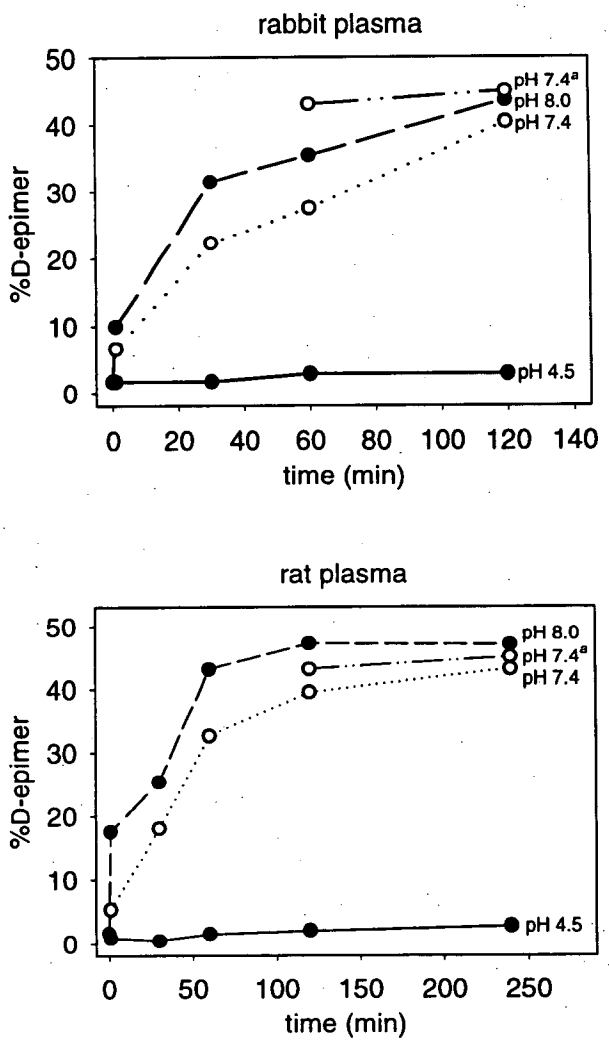


77b X = OCH_2Ph
77c X = OH

A mixture of **77a** (3.93 g, 11.1 mmol), L-proline benzyl ester hydrochloride (4.02 g, 16.6 mmol), 1-hydroxybenzotriazole (HOBT; 2.24 g, 16.6 mmol) and triethylamine (5.0 mL, 35.9 mmol) in acetonitrile (50 mL) was treated with DCC (4.60 g, 22.2 mmol) while stirring at room temperature under argon. After 18 h, the reaction mixture was filtered through diatomaceous earth and concentrated in vacuo. The residue was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc (3x). The combined organic extracts were extracted with saturated aq $NaHCO_3$ (3x), brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by normal-phase chromatography eluting with hexanes/EtOAc (7:3) to furnish **77b** (2.54 g, 42%) as a white foam. A solution of **77b** (2.42 g, 4.50 mmol) and 2 M KOH (10 mL, 20 mmol) in MeOH (30 mL) was stirred for 18 h. The reaction mixture was concentrated in vacuo, acidified to pH 2-3 with 1 N HCl, and extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo to provide **77c** (2.02 g, 100%; CAS# 287182-97-2). Compound **77c** (2.02 g, 4.50 mmol) was converted to **77** according to the methods described for **5**. The resulting crude solid was purified by reverse-phase HPLC eluting with water/MeCN/TFA (70:30:0.2) to afford **77** (0.840) as a white solid: ^{1}H NMR δ 1.86 (ov m, 7H), 2.05-2.15 (m, 1H), 3.10-3.25 (ov m, 3H), 3.50-3.90 (ov m, 4H), 4.20-4.25 (m, 1H), 5.50-5.60 (m, 1H), 7.57-7.70 (ov m, 5H), 8.00-8.32 (ov m, 5H), 8.65-8.75 (m, 1H); MS (ES) *m/z* 666.2 $(MH)^+$. Anal. ($C_{31}H_{35}N_7O_6S_2$•1.5 CF_3CO_2H•0.7 H_2O) C, H, N, F, H_2O.

L-Phenylalanyl-*N*-[(1*S*)-4-[(aminoiminomethyl)amino]-1-(2-benzothiazolylcarbonyl)-butyl]-L-prolinamide (78). Compound **78** was prepared from Boc-L-Phe-L-Pro-OH (0.322 g, 0.89 mmol) and **20d** (0.374 g, 0.74 mmol) according to the methods decribed for **20**. The resulting crude solid was purified by reverse-phase HPLC eluting with water/MeCN/TFA (90:10:0.2 to 10:90:0.2) to afford **78** (0.0342 g) as a white solid: $[\alpha]_D^{25}$ -33.0°; ^{1}H NMR δ 1.05-2.40 (ov m, 8H), 2.85-3.00 (m, 1H), 3.00-3.40 (m, 2H), 3.40-3.75 (m, 1.3H), 3.90-3.95 (m, 0.2 H), 4.20-4.60 (ov m, 1.6H), 5.20-5.25 (m, 0.2 H), 5.45-5.50 (m, 0.2H), 5.70-5.80 (m, 0.6H), 7.20-7.70 (ov m, 7H), 7.55-7.65 (m, 2H), 7.90-8.00 (m, 0.6H), 8.14 (d, 0.7H, J = 6.9 Hz), 8.23 (d, 0.7H, J = 6.9 Hz); MS (ES) *m/z* 536 $(MH)^+$. Anal. ($C_{27}H_{33}N_7O_3S$•2.3 CF_3CO_2H•0.17 H_2O) C, H, N, F, H_2O; H: calcd 4.07; found 4.48.

Stereochemical Stability Profile of 3 in Rabbit and Rat Plasma



The stereochemcal stability profile of **3** in rabbit and rat plasma shown above was determined at pH 4.5, pH 7.4 and pH 8.0 at 23 °C, except where noted. The percentages of the D-arginine epimer (**27**) were determined using the following analytical HPLC conditions: 65:35 MeCN/AQ (AQ = 0.05 M $NH_4{\bullet}H_2PO_4$ + 0.005M octanesulfonic acid in H_2O adjusted to pH 7.5) eluting at 1 mL/min on a Zorbax SB-C8 column (4.6 x 75 mm); flow rate = 1 mL/min; UV detection at 310 nM. Retention times were 3.4 and 4.2 min for **27** and **3**, respectively. [a] Conducted at 37 °C.

Enzyme Inhibition Assays

The ability of thrombin inhibitors to inhibit the enzymatic action of thrombin and other biologically important serine proteases is measured in terms of their K_i and IC_{50} values. For determination of K_i values the rate of increase in absorbance at 405 nM due to hydrolysis of synthetic chromogenic peptide substrates is measured in the presence and absence of inhibitors (I) with a microplate reader at 37°C. The synthetic chromogenic peptide substances used are: 5-100 μM H-D-HHT-L-Ala-L-Arg-pNA for thrombin, 0.1-3 mM Cbo-Gly-D-Ala-Arg-pNA for trypsin, 20-500 μM H-D-Nle-HHT-Lys-pNA for plasmin, 30-700 μM H-D-Lys(∂-Cbo)-Pro-Arg-pNA for protein Ca, 30-1000 μM CH_3SO_2-D-CHT-Gly-Arg-pNA for tPA, 70-3000 μM H-D-Nle-HHT-Lys-pNA for streptokinase, 30-1000 μM Cbo-L-Glu(∂-t-BuO)-Gly-Arg-pNA for urokinase, 0.1-2 mM MeOSuc-Ala-Ala-Pro-Val-pNA for leukocyte elastase, and 30-700 μM MeO-CO-D-CHG-Gly-Arg-pNA for factor Xa). The enzyme reaction is started by the addition of enzyme (E: 0.9 nM human α-thrombin, 3.2 units/mL bovine trypsin, 1.4 μg/mL (0.49 CU) human plasmin, 3.6 mM activated human protein C, 724 IU/mL Bowes melanoma 2-chain tPA activity standard, 15.1 IU/mL streptokinase in the presence of 6.5 μg/mL Lys-type human plasminogen, 150 IU/mL human high MW urokinase, 27 nM human leukocyte elastase, 20 nkat/mL human factor Xa). Data is collected over a period of 30 min and the initial rate of substrate hydrolysis [V_0 (mOD/min)] is calculated. Following Michaelis-Menten kinetics, the affinity of the enzyme for the substrate, in the absence of the inhibitor (K_m) and in the presence of an inhibitor (K_p), is determined to be the negative inverse x-intercept of Lineweaver-Burk plots. The dissociation constant for inhibition (K_i) is calculated using the following equation: $K_i = (K_m*[I])/(K_p-K_m)$ as described by Morrison.[70]

For determination of IC_{50} values the rate of increase in absorbance at 405 nM due to hydrolysis of synthetic chromogenic peptide substrates is measured in the presence and absence of inhibitors (I) with a microplate reader at 37 °C. The enzyme reaction is started by the addition of enzyme. Data is collected over a period of 30 min and the initial rate of substrate hydrolysis (V_0 (mOD/min)) is calculated. Inhibition is calculated by comparison with wells containing no inhibitor (vehicle) and IC_{50} values are determined using a four parameter fit logistics model.

For determination of slow (tight) binding K_i values enzyme (0.09 nM human alpha-thrombin) and inhibitor are preincubated for 4 h. The enzyme reaction is started by the addition of synthetic chromogenic peptide substrate (50 μM H-D-HHT-L-Ala-L-Arg-pNA). The rate of increase in absorbance at 405 nM due to substrate hydrolysis is measured in the presence and absence of inhibitors (I) with a microplate reader at 37 °C. Data is collected over a period of 4 h and the initial rate of substrate hydrolysis [V_0 (mOD/min)] is calculated. The dissociation constant for inhibition (K_i) is calculated using methods for tight binding inhibitors described by Morrison.[70]

Enzyme Selectivity K_i Values[a]

cmpd[b]	trypsin	fXa	plasmin	prot Ca	SK	tPA	uPA
3	3.1 ± 0.7 (9)	450 ± 100 (4)	2200 ± 300 (5)	3600 ± 700 (5)	1200 ± 200 (6)	62 ± 14 (6)	4400 ± 200 (3)
4	2.7 ± 1.2 (5)	1200 ± 300 (3)	770 ± 100 (3)	4700 ± 1200 (3)	420 ± 200 (2)	41 ± 16 (3)	17000 ± 4000 (3)
68	31 ± 13 (3)	490 ± 80 (3)	140 ± 20 (3)	2300 ± 700 (3)	990 ± 210 (3)	59 ± 9 (3)	2300 ± 300
1b	9.1 ± 3.7 (9)	95000 ± 25000 (6)	500 ± 80 (9)	1300 ± 300 (9)	1300 ± 400 (4)	1,400 ± 200 (12)	2300 ± 700 (3)
argbn	4600 ± 800 (10)	390000 ± 140000 (3)	400 ± 40 (3)	530 ± 180 (2)	>100000 (1)	370000 ± 100000 (3)	9500000 (1)

[a] K_i values are given in nM (mean ± standard error) and the number of experiments (N) is in parentheses. Abbreviations: fXa = factor Xa, prot. Ca = activated protein C, SK = streptokinase, tPA = two-chain tissue-type plasminogen activator, uPA = two-chain urokinase-type plasminogen activator. [b] Compound **1b** is efegatran and "argbn" is argatroban.

Hemodynamic Assessment in Anesthetized Guinea Pigs

Materials and Methods. Male guinea pigs (400-900 g, Hartley strain, Covance Inc., Denver PA) were anesthetized with a combination of ketamine HCl (90 mg/kg, Ketaset, Fort Dodge, Fort Dodge, IA) and xylazine HCl (12 mg/kg, Anased, Lloyd Laboratories, Shenandoah, IA) or ketamine HCl-xylazine HCl solution (RBI, Natick, MA) at 1 mL/kg given by intraperitoneal injection. The ventral neck was shaved and a mid-line incision was made to expose and isolate the vessels. The left jugular vein was canulated for administration of test compounds. Both carotid arteries were isolated and the left carotid was canulated with a 2F Mikro-tip® catheter transducer (Millar Instruments Inc., Houston, TX) for blood pressure and heart rate measurements. A 24 gauge x 0.75 in needle/catheter unit with luer hub (Angiocath®, Becton-Dickenson, Sandy, UT) attached to a saline filled 1-mL syringe was used to canulate the right carotid artery for blood sampling. Needle electrodes were attached to the appropriate limbs to record a lead II ECG. The data were continuously collected using a physiological recorder and BioWindows data acquisition and analysis software (Modular Instruments Inc., Malvern, PA).

Blood Cell Counts. During the control period an initial blood sample was taken to establish baseline blood cell counts. Additional blood samples were taken 10 min after each subsequent drug infusion. For each blood sample, 2-3 drops of blood was allowed to flow freely to clear the catheter, then 0.25 mL of non-anticoagulated blood was withdrawn and 0.25 mL of saline was pushed back thru the catheter to clear it of blood. The blood was dispensed into a microtainer® tube containing EDTA (Becton Dickenson, Franklin Lakes, NJ) and was placed on a rocker for at least five min before reading on a SYSMEX K-1000 differential cell counter (TOA Medical Electronics Co., Ltd., Kobe, Japan) for red blood cells (RBC), white blood cells (WBC), hematocrit, and platelets

Drug Administration. Solutions of compounds under study were made fresh for each experiment: dissolved in saline and administered in solution at a rate of 0.2 mL/min for 5 min using a Syringe Infusion Pump 22 (Harvard Apparatus, South Natick, MA). Concentration varied according to the animal weight and the drug dose. Each dose was given in 1 ml total volume over 5 min and the guinea pigs were allowed 10 min for the drug to equilibrate in the blood. In experiments where blood was analyzed, the blood sample was taken 10 min after the end of each infusion and the animals were allowed additional time to stabilize before administering the next dose. Most compounds were administered at 1, 3, and 10 mg/kg. Compound **3** was administered at doses of 0.3, 1.0 and 3.0 mg/kg whereas efegatran (**1b**) was administered at doses of 10, 18, 30, and 60 mg/kg.

Calculation of ED_{-25}. The dose to elicit a 25% decrease in mean arterial blood pressure was interpolated using regression analysis of the linear portion of the dose-response-curve. All calculations were conducted using Excel (Microsoft, version 7.0).

Canine Arteriovenous Shunt Antithrombotic Model

The canine arteriovenous shunt model was used to study the antithrombotic efficacy of **4** and **68** in comparison to **3** and the reference thrombin inhibitor efegatran (**1b**) and heparin. In this model, a thrombus (platelet/fibrin/red blood cell mixture in composition) forms on a section of silk thread placed in an extracorporeal shunt between the femoral artery and vein. Antithrombotic efficacy is indicated by decreases in the weight of thrombus formed in 20 min of exposure to flowing blood.

Surgical Preparation. Adult mongrel dogs of either sex (11-16.8 kg) were anesthetized with pento-barbital sodium (35 mg/kg, i.v.) and ventilated (Harvard Apparatus, Model 613, South Natick, MA) with room air via an endotracheal tube (15 strokes/min, 25 mL/kg). For arterial pressure determination, the left carotid artery was cannulated with a saline filled polyethylene catheter (PE-200) and connected to

a Statham pressure transducer (P23ID, Oxnard,CA). Mean arterial blood pressure was calculated using the formula 1/3 systolic + 2/3 diastolic blood pressure. Heart rate was monitored using a cardiotachometer (Biotach, Gould Electronics, Cleveland, OH) triggered from a lead II electrocardiogram generated by limb leads. A jugular vein was cannulated (PE-200) for drug administration. The left femoral artery and the left femoral vein were cannulated with silicon treated (Sigmacote®, Sigma Chemical Co., St. Louis, MO), saline-filled polyethylene tubing (PE-200) and connected with a 6-cm section of silicon treated tubing (PE-240) to form an extracorporeal arteriovenous shunt (AV shunt). Shunt patency was monitored using a Doppler flow system (model VF-1, Crystal Biotech Inc., Hopkinton, MA) and flowprobe (2.0-2.8 mm, Titronics Med. Inst., Iowa City, IA) placed proximal to the shunt. Parameters were monitored continuously on a polygraph recorder (Gould TA4000, Oxnard CA) at a paper speed of 10 mm/min.

Experimental Protocol. On completion of a 15-min post-surgical stabilization period, an occlusive thrombus was formed by the introduction of a thrombogenic surface (0 braided silk thread, 6 cm in length, Ethicon Inc., Somerville, NJ) into the shunt. Four consecutive 15-min shunt periods were used to test the effects of vehicle infusion and three doses of test compound or vehicle. Compounds **4**, **68**, **3**, efegatran (**1b**), heparin, and saline (0.9%) were administered as a bolus plus maintenance infusion beginning 5 min before insertion of the thrombogenic surface and continued for an additional 15 min. At the end of each 15-min shunt period the silk was carefully removed and weighed. A fifth shunt immediately following the total cumulative treatment dose was used to assess patency duration as indicated by time to total occlusion. Thrombus weight was calculated by subtracting the weight of the silk (9 mg) prior to placement from the total wet weight of the silk on removal from the shunt. Arterial blood was withdrawn prior to the first shunt and near the end of each shunt period for determination of gamma-thrombin, collagen and ADP-induced platelet aggregation in platelet rich plasma (PRP), thrombin time (TT), activated partial thromboplastin time (aPTT), prothrombin time (PT), activated clotting time (ACT) and platelet count. Template bleeding time was performed beginning 10 min into each shunt period.

Hematologic Studies. Platelet rich plasma was obtained from citrated whole blood (1:9) centrifuged at 500 rpm for 10 min (Beckman GS-6, Palo Alto, CA). PRP platelet count determinations were performed using a Sysmex™ K1000 (Baxter Laboratories, McGraw Park, IL). γ-thrombin, collagen and ADP-induced platelet aggregation were measured using an aggregation profiler (Bio/Data Model PAP-4, Horsham, PA) by recording the change in light transmission through a stirred (1130 rpm) sample of PRP maintained at 37°C. Aggregation was induced with γ-thrombin (0.33 μM/cuvette final concentration), collagen (0.02 μg/μL final concentration) or ADP (20 μM/cuvette final concentration) added to a 300-μL sample of PRP adjusted to 300,000 platelets/μL. Aggregation was monitored via changes in light transmission recorded over 5 min. TT, aPTT and PT were determined using a microsample coagulation analyzer (Instrument Laboratory ACL 100, Milano, Italy). ACT was determined using a whole blood microcoagulation analyzer (Hemochron® Jr., International Technidyne Corp., Edison, NJ). Template bleeding time was performed by making an incision into the gum (Surgicutt, ITC Corp., Edison, NJ) and the time to clot formation monitored. Platelet count determinations were performed on whole blood collected in 0.75-mL microvette (1.6 mg of EDTA/mL, Sarstedt, Germany) using a Sysmex™ K1000.

Test Compounds. Compounds **4**, **68**, **3**, and efegatran (**1b**) were administered as a bolus plus maintenance infusion based on an estimated plasma half life of 30 min. The bolus-loading dose was given over 1 min and the maintenance infusion over the remaining 19 min of each 20-min drug-dosing period. Total doses of **4** (0.03, 0.1 and 0.3 mg/kg) were apportioned as bolus + infusions of 0.0208 mg/kg + 0.0005 mg/kg/min, 0.0423 mg/kg + 0.0015 mg/kg/min and 0.1197 mg/kg + 0.0042 mg/kg/min. Total doses of **68**, **3**, and efegatran (**1b**) (0.1, 0.3, and 1.0 mg/kg) were apportioned as 0.0695 mg/kg + 0.0016 mg/kg/min, 0.1178 mg/kg + 0.0043 mg/kg/min, and 0.4294 mg/kg + 0.0142 mg/kg/min. Heparin was

administered as a bolus loading dose given over 2 min and a maintenance infusion over the remaining 18 min of each 20-min drug dosing period. Total doses of heparin (35, 350, and 695 U/kg) were apportioned as 30 U/kg + 15 U/kg/h, 100 U/kg + 50 U/kg/h and 300 U/kg + 150 U/kg/h. Vehicle for **4**, **68**, **3**, and efegatran (**1b**) and heparin was saline.

Statistical Analysis. All values are expressed as the mean and standard error of the mean. Statistical significance of the change was assessed based on change from baseline using analysis of variance and Student's t-test. Differences were considered significant when $p < 0.05$.

Rabbit Deep Vein Thrombosis Model

The rabbit deep vein thrombosis model was used to study the antithrombotic efficacy of **4** and **68** in comparison to **3**, the reference thrombin inhibitor efegatran (**1b**) and heparin. In this model, a thrombus (mainly fibrin in composition) forms in a section of vena cava. Antithrombotic efficacy is indicated by decreases in the weight of thrombus formed after a 10-min period.

Materials and Methods. Male rabbits (New Zealand White, 1.5-2.8 kg, Hazleton Res. Product Inc.) were sedated with a combination of ketamine (35 mg/kg, i.m.) and xylazine (5 mg/kg, i.m.). The rabbits were anesthetized via intravenous administration of sodium pentobarbital (20 mg/kg, i.v.) using an ear vein. Additional amounts of sodium pentobarbital were administered as necessary during the course of the experiment to maintain a level plane of anesthesia.

Surgical Preparation. A cannula was introduced into the right femoral vein for administering thromboplastin (T7910, Sigma, St. Louis, MO). A second cannula was introduced into the right femoral artery for removing blood samples and measuring blood pressure and heart rate, which was taken from the blood pressure pulse. The inferior vena cava was exposed via a mid-line incision and isolated between the renal veins and the bifurcation of the inferior vena cava. Two separate pieces of thread were placed under this section of vena cava 5.5 cm apart. A heating lamp was used for keeping animal core temperature consistent and standard lead II ECG was monitored with limb electrodes.

Drug Administration. Compounds **4**, **68** and **3** were administered intravenously through a marginal ear vein 5 min before introducing stasis of the vena cava. The compounds were administered as a bolus injection (60% of total dose in 1 mL of vehicle), followed by infusion (40% of total dose in 2 mL of vehicle) infused at the rate of 8 mL/h.

Blood Sampling. A 1-mL blood sample was taken from the femoral artery 4 min after start of compound administration. Two drops of whole blood were used for activated clotting time (ACT) measurement (Hemochron, model HE-JR, International Technidyne Corp., Edison, NJ). Platelet and cell counts were read on a SYSMEX K-1000 differential cell counter (TOA Medical Electronics Co., Ltd., Kobe Japan). The remainder of the whole blood sample was centrifuged (Eppendorf, model 5415C) at 10,000 rpm for 8 min. The serum was frozen immediately for aPTT, PT, and TT coagulation measurements.

Thrombus Weight Determination. Thromboplastin (0.1 mL/kg) was injected by bolus via the right femoral vein. Stasis was accomplished by first tying the proximal thread on the vena cava followed immediately by the distal. Total time between thromboplastin injection and tying both treads was 18 s. The stasis was maintained for 10 min and the thrombus was harvested by cutting the vena cava longitudinally. The thrombus was carefully removed, blotted on filter paper to remove blood and weighed immediately.

Table of Microanalytical Data[a]

cmpd	%C	%H	%N	%F	%water (KF)
3	47.38/47.75	4.74/4.64	11.86/11.98	15.86/15.71	1.74/1.92
4	45.54/45.59	4.44/4.47	10.93/10.76	15.89/15.60	2.01/2.09
5	46.46/46.22	4.55/4.59	11.96/12.02	16.40/16.01	1.87/1.60
6	46.77/46.42	4.67/4.67	11.86/11.82	16.77/16.69	2.40/2.54
7	42.48/42/75	3.81/3.85	10.67/10.66	24.29/24.12	2.45/2.61
8	44.81/44.92	5.03/5.03	10.76/10.80	18.76/18.83	1.48/1.37
9	50.57/50.77	5.12/5.03	12.98/13.17	10.56/10.39	2.38/2.70
10	46.44/46.54	5.08/4.99	11.85/11.66	10.33/10.67	3.48/3.81
11	45.67/45.28	4.69/4.46	11.23/11.00	16.97/16.91	
12	44.35/44.48	5.20/5.05	10.65/10.96	15.47/15.83	3.91/3.80
13	50.45/50.20	4.95/4.78	10.69/10.70	13.99/13.62	3.73/3.34
14	52.96/53.27	5.02/5.13	10.15/10.34		3.81/3.86
15	44.88/44.49	5.03/4.93	13.08/12.98		2.88/2.64
16	46.21/45.96	5.63/5.71	12.17/12.07	14.15/14.39	4.47/4/41
17[b]	44.69/44.37	5.26/4.89	11.92/11.75	15.94/15.80	3.94/3.11
18[b]	49.10/48.70	4.38/4.22	10.79/10.63	16.18/15.78	1.88/1.37
19	54.00/54.10	4.49/4.66	10.79/10.98	10.98/11.06	1.39/1.43
20	44.94/45.03	5.02/4.71	13.91/13.84	12.27/12.29	4.18/4.08
22	41.39/41.04	4.12/3.97	14.50/14.84	15.60/15.49	2.66/2.26
24	42.14/42.30	4.49/4.20	13.53/13.18	17.43/17.63	2.61/2.58
25[b]	47.27/46.89	4.98/5.06	11.84/12.11	15.82/16.22	1.74/2.76
26	47.11/46.76	4.90/4.95	11.36/11.56	15.99/15.62	2.67/2.28
27	44.01/44.11	4.56/4.34	10.57/10.96		3.88/3.80
28[b]	46.92/46.59	5.05/5.00	11.40/11.17	15.24/15.16	3.98/3.40
29	47.72/47.58	4.95/4.89	11.59/11.58	15.50/15.69	2.34/2.36
30	47.82/47.45	4.93/4.83	11.62/11.47	15.53/15.60	2.13/1.84

Table of Microanalytical Data[a] (contd)

cmpd	%C	%H	%N	%F	%water (KF)
31	51.14/50.95	4.50/4.39	9.80/9.60	14.96/14/66	2.10/1.72
32	50.14/49.95	4.48/4.44	9.53/9.38	15.52/15.63	2.86/2.87
33	50.31/50.06	4.54/4.42	9.62/9.49	15.00/15.00	3.30/3.53
34	48.65/48.87	5.07/5.13	11.15/11.40	14.91/14.88	3.07/3.05
35[b]	48.63/48.96	4.89/4.93	11.03/11.08	16.02/16.14	1.62/3.20
36	49.25/49.59	5.00/5.09	11.29/11.31	15.10/15.12	1.87/2.15
37	49.23/49.44	5.00/5.05	8.86/8.87	15.86/15.69	2.27/2.31
38	49.83/49.80	5.15/5.05	9.08/8.98	14.78/14.72	2.80/2.78
39[c]	48.93/48.90	5.12/4.92	8.59/8.51	14.69/14.51	2.21/1.98
40[d]	48.95/48.90	5.06/4.98	8.57/8.51	15.00/14.79	1.76/1.63
41[b,e]	49.61/49.53	5.24/5.30	8.12/8.01	15.21/15.02	3.55/2.46
42[f]	50.02/49.88	5.26/5.47	8.20/8.19	15.16/15.26	3.38/3.43
43	52.18/52.16	5.33/5.17	7.85/7.87	11.98/11.58	2.77/2.45
44	54.51/54.60	5.33/5.38	8.20/8.18	12.52/12.28	0.79/0.60
45	56.38/56.62	4.86/4.48	7.73/7.61	11.80/11.48	1.74/1.76
46	46.94/46.87	5.23/5.15	11.76/11.41	15.72/15.58	4.32/4.49
47	46.94/46.84	5.23/5.07	11.76/11.69	15.72/15.37	4.32/4.45
48[b]	41.78/41.80	4.29/4.05	9.47/9.49	22.03/22.10	2.61/0.92
49	41.05/40.86	4.22/3.85	9.18/9.16	22.69/22.30	2.95/1.40
50	44.63/44.38	44.63/44.38	11.57/11.85		4.78/4.83
51	47.80/47.68	4.91/4.82	9.89/9.74	16.10/15.81	3.18/3.18
52[g]	40.99/40.64	4.42/4.62	11.66/12.09		2.06/1.75
53	43.59/43.66	4.30/4.37	11.45/11.45		1.84/1.84
54	43.54/43.25	4.34/4.47	10.98/11.14	22.23/22.01	1.76/1.86
55	41.97/42.26	4.25/4.42	9.52/9.87		3.93/4.27
56	45.08/45.05	4.93/4.79	12.30/12.57		5.93/5.99

Table of Microanalytical Data[a] (contd)

cmpd	%C	%H	%N	%F	%water (KF)
57	44.88/44.49	5.03/4.93	13.08/12.98		2.88/2.64
58	41.93/41.59	4.56/4.53	11.41/11.84		3.56/3.40
59	44.08/44.25	4.95/4.68	11.39/11.29		3.14/3.29
60	47.55/47.20	4.91/5.19	11.61/12.02		2.24/2.56
61	45.55/45.71	5.11/5.31	11.20/11.34	16.93/17.16	2.88/2.96
62	45.93/45.60	4.26/4.03	9.63/9.70	19.38/19.06	2.30/1.96
63	46.20/46.33	4.94/4.72	11.22/11.42		3.61/3.68
64	46.83/46.79	4.79/4.79	11.95/12.15		3.29/3.29
65	43.93/43.97	4.25/4.22	10.55/10.82	20.44/20.57	2.13/2.22
67	42.61/42.16	4.65/4.35	11.42/11.45	16.85/16.19	5.87/5.37
68	45.53/45.51	4.68/4.53	10.62/10.54	15.43/15.19	3.32/3.39
69	49.72/49.95	5.19/5.10	8.43/8.47	15.09/14.88	3.90/4.10
70	49.97/50.18	5.38/5.35	8.62/8.48	9.82/9.52	3.32/3.37
73	56.82/56.61	5.53/5.21	10.46/10.15	10.64/10.46	0.67/0.72
74	47.63/47.95	5.03/5.00	12.81/13.00	8.71/9.04	2.35/2.31
75	48.76/48.85	5.79/5.59	11.64/11.74	10.82/11.08	1.92/2.32
76	44.90/44.64	4.89/4.70	11.24/10.96	8.50/8.39	2.06/2.09
77	48.08/48.18	4.50/4.26	11.54/11.57	10.26/9.98	1.48/1.54
78[h]	47.38/46.98	4.48/4.07	12.05/12.24	16.37/15.97	0.38/0.78

a. The values presented are calcd/found for the standard molecular formulas with the salts and solvates given in Table 1. The water composition was determined by Karl-Fischer analysis. b. Karl-Fischer analysis is out of range. c. Bromine analysis was 2.65/2.99. d. Bromine analysis was 2.64/2.86. e. Bromine analysis is out of range; 0.83/0.50. f. Bromine analysis was 0.47/0.49. g. Nitrogen analysis is out of range. h. Hydrogen analysis is out of range.