A *cis* Amide Bond Surrogate Incorporating 1,2,4-Triazole

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A novel *cis* amide bond surrogate incorporating 1,2,4-triazole was designed and synthesized by the reaction of a thionotripeptide, formic hydrazide, and mercury(II) acetate. This method of surrogate formation was also applicable to a cyclic thionopeptide.

The peptide analogues into which a *cis* amide bond surrogate has been incorporated are useful for the studies of the active conformation and/or the topology of the active site of original peptides. 1,5-Disubstituted tetrazole is known as a *cis* amide bond surrogate (Figure 1),[1,2] and it has been incorporated into bradykinin,[3] CCK-B receptor ligands,[4] somatostatin,[5] leucine-enkephalin,[6] and TRH analogues[7] for their biological activity studies. Tetrazole is a good *cis* amide bond surrogate. However, it can be formed only in dipeptides, and the elongation of the peptide chains by addition of amino acid residues or peptides at the N-terminus is not easy, as it readily forms a diketopiperazine ring.[2,3] We considered that 1,2,4-triazole might make a good *cis* amide bond surrogate, as it is formed via an easily accessible thionopeptide. The present paper describes preparation of several triazole surrogate-containing peptides via their thionopeptides.

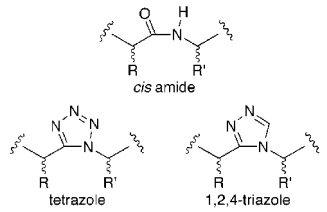
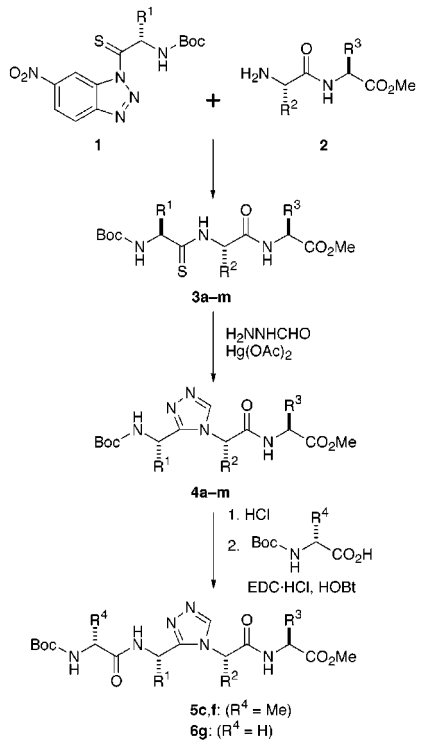


Figure 1.

Thionopeptides are known to be readily prepared by the reaction of benzotriazole thioacylating agents with amino acid esters.[8] By using this method, as shown in Scheme 1, thionotripeptides **3a**−**m** were prepared from benzotriazole thioacylating agents **1** and dipeptide esters **2** in moderate to excellent yields. When thionotripeptide **3a** was treated with 5 equiv of formic hydrazide and 1.5 equiv of mercury(II) acetate in acetonitrile at room temperature for 2 h, triazolotripeptide **4a** was obtained in 67% yield. The presence of the triazole ring in **4a** was confirmed by the characteristic resonances of the methine proton (*δ* 8.28, br s, 1H) and the methine (*δ* 141.56) and quaternary (*δ* 154.57) carbons of the triazole ring in the NMR spectra. Triazolotripeptides have an advantage over their dipeptide analogues in that they do not form diketopiperazine during the extension reaction of the peptide chain at the N-terminus. In the same manner, thionotripeptides **3b**−**m** were converted into their triazolotripeptides **4b**−**m** (Table 1). This method was found to be satisfactory for those thionopeptides having oxidation-sensitive residues such as unprotected tryptophan (entry 5), methionine (entry 8), and tyrosine (entry 9). The side chains of the thionoamino acid residues in tripeptides appear to affect the yields of triazoles. When the thionotripeptides contain thionovaline residue, the yields of triazoles were quite low (entries 10 and 11),

Scheme 1[a]



[a] R^1, R^2, R^3: See Table 1

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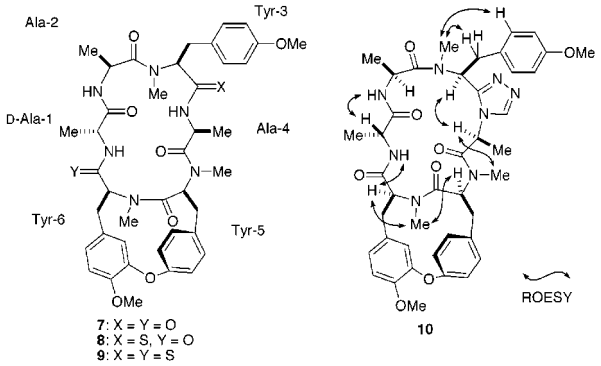

Figure 2.

which may be attributed to the adjacent bulky isopropyl group that hinders formic hydrazide from approaching the thiocarbonyl group. Under the reaction conditions used in the present experiment, no epimeric analogues were detected.

Elongation of the amino acid chains at the N-terminus of triazolopeptides was feasible, although it required a rather long reaction time of 1−5 days. Triazolopeptide **4c** was deprotected with 4 M HCl in dioxane, and then it was subjected to a coupling reaction with *N*-Boc-D-alanine, using 1-ethyl-3-(3′-(dimethylamino)propyl)carbodiimide·HCl (EDC·HCl) and 1-hydroxybenzotriazole (HOBt) in chloroform to afford tetrapeptide **5c** in 86% yield. In the same manner, **4f** and **4g** were converted into the corresponding tetrapeptides **5f** and **6g**, in yields of 81% and 82%, respectively. The structure of peptide **5f** was confirmed by X-ray crystallography.

This method of surrogate formation is also applicable to cyclic thionopeptides. Those cyclic thionopeptides were readily prepared by treating the cyclic peptides with a thionating reagent. A number of such cyclic thionopeptides have been prepared from biologically important cyclic peptides.[9] When a triazole unit is incorporated into cyclic peptide backbones, however, the conformational features of the surrogate-containing cyclic peptide analogues may be different from those of the original peptides. For example, treatment of RA-VII (**7**), an antitumor bicyclic hexapeptide, with Lawesson's reagent afforded thioamide **8** and bis(thioamide) **9** in 80% and 3% yield, respectively[10] (Figure 2). When **8** was treated with formic hydrazide under the same conditions for 72 h, triazole **10** was obtained in 48% yield, in which the peptide bond between Tyr-3 and Ala-4 is modified to *cis*. The ^{1}H NMR spectrum of **10** showed that, in $CDCl_3$ at 315 K, **10** exists in two stable conformers in a ratio of 83:17. In the ROESY spectrum of **10**, in the major conformer, cross-peaks were observed between D-Ala-1 H_α/Ala-2 NH, Tyr-3 H_α/Ala-4 H_α, Ala-4 H_α/Tyr-5 NMe, Tyr-5 H_α/Tyr-6 NMe, Tyr-6 NMe/Tyr-6 H_α, and Tyr-6 H_α/D-Ala-1 NH. Accordingly, the peptide bonds between D-Ala-1/Ala-2, Ala-2/Tyr-3, Tyr-3/Ala-4, Ala-4/Tyr-5, Tyr-5/Tyr-6, and Tyr-6/D-Ala-1 in the major conformer of **10** were determined to be *trans*, *cis*, *cis*, *trans*, *trans*, and *trans*, respectively,[11] which are *trans*, *trans*, *trans*, *trans*, *cis*, and *trans*, respectively, in the original peptide **7**.[12] Peptides with conformational features of this type are not known in the natural peptides of RA-series.

Table 1. Triazoles 4a−m from Thionopeptides 3a−m

entry	substrate	R^1	R^2	R^3	yield (%) of **4**
1	**3a**	Me	Me	Bn	67
2	**3b**	Me	Bn	Me	69
3	**3c**	Me	H	Bn	87
4	**3d**	Me	*i*-Pr	Bn	61
5	**3e**	Me	Me	indol-3-yl-methyl	59
6	**3f**	Bn	Me	Bn	56
7	**3g**	Bn	Bn	Me	75
8	**3h**	Bn	2-(methyl-sulfanyl)ethyl	Bn	65
9	**3i**	Bn	Me	4-hydroxy-benzyl	65
10	**3j**	*i*-Pr	*i*-Pr	Bn	13
11	**3k**	*i*-Pr	Me	Bn	18
12	**3l**	H	Me	Bn	59
13	**3m**	H	Bn	Me	60

This new approach provides an efficient and practical method for preparing a *cis* amide bond surrogate, which may be of great value to peptide chemistry.

Experimental Section

General. THF was prepared by distillation over sodium metal. Melting points are recorded uncorrected. ^{1}H and ^{13}C NMR spectra were obtained at 300 K, unless otherwise noted. ^{1}H chemical shifts in $CDCl_3$, methanol-d_4, and DMSO-d_6 were referenced to residual $CHCl_3$ (7.26 ppm), CD_2HOD (3.31 ppm), and CD_2HSOCD_3 (2.50 ppm); ^{13}C chemical shifts were referenced to the solvent ($CDCl_3$, 77.03 ppm; methanol-d_4, 49.0 ppm; DMSO-d_6, 39.5 ppm).

Benzotriazole Thioacylating Agent 1 (R^1 = H). This compound was prepared according to the general procedure reported in ref 8 via α-*N*-Boc-glycine 2-amino-5-nitroanilide and α-*N*-Boc-glycine 2-amino-5-nitrothioanilide. Yield 88%; orange amorphous powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (d, 1H, J = 2.0 Hz), 8.45 (dd, 1H, J = 8.9, 2.0 Hz), 8.32 (d, 1H, J = 8.9 Hz), 5.44 (br s, 1H), 5.15 (d, 2H, J = 6.1 Hz), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.33, 155.76, 149.62, 148.81, 131.88, 122.18, 121.53, 112.53, 80.54, 52.80, 28.33; IR (KBr) ν_{max} 3364, 2981, 2924, 1698, 1531, 1349, 1274, 1262, 1175, 1053, 999, 798, 735 cm^{-1}; negative-FABMS *m*/*z* 336 [M − H]$^-$.

α-*N*-Boc-glycine 2-amino-5-nitroanilide: yield 85%; yellow crystalline powder, mp 178−179 °C (hexane−EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.27 (s, 1H), 8.11 (s, 1H), 7.86 (dd, 1H, J = 9.0, 2.4 Hz), 7.05 (m, 1H), 6.75 (d, 1H, J = 9.0 Hz), 6.46 (s, 2H), 3.76 (d, 2H, J = 5.6 Hz), 1.39 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.28, 156.27, 149.78, 135.63, 123.37, 122.26, 121.24, 113.73, 78.50, 43.88, 28.32; IR (KBr)

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(11) No ROESY correlation was detected between Ala-2 H_α/Tyr-3 H_α, because the resonance of these protons had the same chemical shifts, but the peptide bond between Ala-2/Tyr-3 was assigned to *cis*. ROESY cross-peaks observed between Tyr-3 NMe/Tyr-3 H_β and Tyr-3 NMe/Tyr-3 H_δ, and the absence of cross-peaks between Ala-2 H_α/Tyr-3 NMe, Tyr-3 NMe/Tyr-3 H_α, and Ala-2 Me/Tyr-3 NMe may provide collateral evidence for the *cis* amide configuration between Ala-2/Tyr-3.

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ν_{max} 3385, 3350, 3293, 1698, 1680, 1624, 1587, 1528, 1480, 1308, 1167 cm^{-1}; FABMS *m/z* 311 $[M + H]^+$. Anal. Calcd for $C_{13}H_{18}N_4O_5$: C, 50.32; H, 5.85; N, 18.06. Found: C, 50.25; H, 5.86; N, 17.98.

α-*N*-Boc-Glycine 2-amino-5-nitrothioanilide: yield 81%; yellow crystalline powder, mp 158−159 °C (ether); ^1H NMR (400 MHz, DMSO-d_6) δ 10.92 (br s, 1H), 7.94 (dd, 1H, J = 9.1, 2.6 Hz), 7.90 (d, 1H, J = 2.6 Hz), 7.13 (br s, 1H), 6.79 (d, 1H, J = 9.1 Hz), 6.42 (s, 2H), 4.10 (d, 2H, J = 5.8 Hz), 1.41 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 202.97, 155.95, 150.72, 135.38, 124.97, 124.81, 122.48, 113.97, 78.69, 51.52, 28.19; IR (KBr) ν_{max} 3349, 1668, 1634, 1515, 1490, 1390, 1333, 1304, 1250, 1160 cm^{-1}; negative-FABMS *m/z* 325 $[M - H]^-$. Anal. Calcd for $C_{13}H_{18}N_4O_4S$: C, 47.84; H, 5.56; N, 17.17. Found: C, 47.66; H, 5.60; N, 16.94.

General Procedure for Reaction of Benzotriazole Thioacylating Agents 1 with Dipeptides 2. Formation of Thionotripeptides 3a−m. *N*-Boc-protected dipeptide methyl ester (1.0 mmol) was treated with 4 M HCl in dioxane (4.0 mL) at room temperature for 1 h. The mixture was evaporated to dryness to give a residue, which was dissolved in THF (5 mL), and triethylamine (0.14 mL, 1.01 mmol) was added to the solution at 0 °C. This solution was added dropwise to a cooled solution (0 °C) of thioacylating agents **1** (1.0 mmol) in 15 mL of THF, and the mixture was stirred at this temperature for 20 min. The solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, $CHCl_3$/hexane/MeOH, 10/10/1 then MPLC, silica gel, EtOAc/hexane, 2/3) to provide thionotripeptides **3a**−**m**.

Boc-AlaΨ[CS-NH]Ala-Phe-OMe (3a): yield 91%; amorphous solid; $[\alpha]^{24}_D$ −74.1° (c = 0.91, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 8.51 (br d, 1H, J = 6.0 Hz), 7.32−7.21 (m, 3H), 7.09 (d-like, 2H, J = 8.1 Hz), 6.45 (br d, 1H, J = 7.1 Hz), 5.18 (br d, 1H, J = 6.3 Hz), 4.98 (m, 1H), 4.85 (m, 1H), 4.43 (m, 1H), 3.72 (s, 3H), 3.17−3.05 (m, 2H), 1.48−1.37 (m, 6H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.21, 171.71, 170.76, 155.16, 135.47, 129.18, 128.52, 127.07, 80.13, 55.98, 53.88, 53.42, 52.37, 37.74, 28.22, 21.76, 17.13; IR (film) ν_{max} 3306, 2979, 1734, 1685, 1518, 1444, 1367, 1218, 1168, 757 cm^{-1}; FABMS *m/z* 460 $[M + Na]^+$, 438 $[M + H]^+$. Anal. Calcd for $C_{21}H_{31}N_3O_5S$: C, 57.65; H, 7.14; N, 9.60. Found: C, 57.48; H, 7.31; N, 9.38.

Boc-AlaΨ[CS-NH]Phe-Ala-OMe (3b): yield 83%; amorphous solid; $[\alpha]^{24}_D$ −15.3° (c = 0.75, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (br d, 1H, J = 7.2 Hz), 7.32−7.22 (m, 5H), 6.24 (br s, 1H), 5.20 (m, 1H), 5.11 (d, 1H, J = 6.2 Hz), 4.50−4.41 (m, 2H), 3.70 (s, 3H), 3.35 (dd, 1H, J = 13.8, 5.0 Hz), 3.08 (dd, 1H, J = 13.8, 8.0 Hz), 1.42 (d, 3H, J = 6.9 Hz), 1.39 (s, 9H), 1.30 (d, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.80, 172.39, 168.96, 155.18, 135.92, 129.36, 128.69, 127.23, 80.51, 59.04, 57.53, 52.42, 48.35, 36.95, 28.20, 21.56, 17.98; IR (film) ν_{max} 3308, 2979, 1741, 1685, 1515, 1454, 1367, 1244, 1217, 1164, 756 cm^{-1}; FABMS *m/z* 460 $[M + Na]^+$, 438 $[M + H]^+$. Anal. Calcd for $C_{21}H_{31}N_3O_5S$: C, 57.65; H, 7.14; N, 9.60. Found: C, 57.37; H, 7.04; N, 9.35.

Boc-AlaΨ[CS-NH]Gly-Phe-OMe (3c): yield 92%; amorphous solid; $[\alpha]^{24}_D$ −6.7° (c = 0.77, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (br s, 1H), 7.33−7.21 (m, 3H), 7.09 (d-like, 2H, J = 8.1 Hz), 6.31 (br s, 1H), 5.13 (br s, 1H), 4.89 (m, 1H), 4.50 (m, 1H), 4.32 (dd, 1H, J = 17.5, 4.7 Hz), 4.24 (dd, 1H, J = 17.5, 4.6 Hz), 3.74 (s, 3H), 3.15 (dd, 1H, J = 13.9, 5.7 Hz), 3.11 (dd, 1H, J = 13.9, 6.1 Hz), 1.46 (d, 3H, J = 6.9 Hz), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.04, 171.83, 167.01, 155.26, 135.55, 129.19, 128.59, 127.15, 80.24, 56.25, 53.45, 52.49, 48.29, 37.78, 28.28, 21.88; IR (film) ν_{max} 3310, 2979, 1738, 1686, 1521, 1444, 1367, 1247, 1219, 1168, 757 cm^{-1}; FABMS *m/z* 446 $[M + Na]^+$, 424 $[M + H]^+$. Anal. Calcd for $C_{20}H_{29}N_3O_5S$: C, 56.72; H, 6.90; N, 9.92. Found: C, 56.54; H, 7.01; N, 9.74.

Boc-AlaΨ[CS-NH]Val-Phe-OMe (3d): yield 88%; amorphous solid; $[\alpha]^{24}_D$ −96.4° (c = 0.56, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (br d, 1H, J = 7.6 Hz), 7.32−7.20 (m, 3H), 7.10 (d-like, 2H, J = 8.2 Hz), 6.26 (d, 1H, J = 7.6 Hz), 5.10 (br s, 1H), 4.90−4.81 (m, 2H), 4.42 (m, 1H), 3.72 (s, 3H), 3.16−3.05 (m, 2H), 2.29 (m, 1H), 1.45 (d, 3H, J = 6.9 Hz), 1.43 (s, 9H), 0.97 (d, 3H, J = 6.9 Hz), 0.94 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.85, 171.52, 169.31, 155.28, 135.39, 129.25, 128.62, 127.13, 80.18, 63.82, 56.23, 53.23, 52.31, 37.72, 30.60, 28.24, 21.48, 18.70, 18.42; IR (film) ν_{max} 3307, 2974, 2933, 1733, 1686, 1663, 1520, 1497, 1440, 1367, 1218, 1168, 757 cm^{-1}; FABMS *m/z* 488 $[M + Na]^+$, 466 $[M + H]^+$. Anal. Calcd for $C_{23}H_{35}N_3O_5S$: C, 59.33; H, 7.58; N, 9.02. Found: C, 59.05; H, 7.66; N, 8.83.

Boc-AlaΨ[CS-NH]Ala-Trp-OMe (3e): yield 73%; amorphous solid; $[\alpha]^{26}_D$ −64.1° (c = 0.39, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (br d, 1H, J = 6.6 Hz), 8.21 (s, 1H), 7.49 (d, 1H, J = 7.8 Hz), 7.34 (d, 1H, J = 8.0 Hz), 7.18 (t, 1H, J = 7.9 Hz), 7.11 (t, 1H, J = 7.9 Hz), 7.00 (d, 1H, J = 2.3 Hz), 6.48 (br d, 1H, J = 7.1 Hz), 5.09 (br s, 1H), 4.98 (m, 1H), 4.89 (m, 1H), 4.39 (m, 1H), 3.70 (s, 3H), 3.36−3.26 (m, 2H), 1.44 (s, 9H), 1.43 (d, 3H, J = 6.8 Hz), 1.39 (d, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.71, 172.15, 170.81, 155.30, 136.12, 127.45, 123.45, 122.10, 119.62, 118.37, 111.39, 109.20, 80.52, 56.76, 53.96, 53.14, 52.55, 28.29, 27.56, 21.65, 17.26; IR (film) ν_{max} 3320, 2979, 2932, 1734, 1685, 1519, 1442, 1367, 1216, 1166, 756 cm^{-1}; FABMS *m/z* 499 $[M + Na]^+$, 477 $[M + H]^+$. Anal. Calcd for $C_{23}H_{32}N_4O_5S$: C, 57.96; H, 6.77; N, 11.76. Found: C, 57.58; H, 6.76; N, 11.45.

Boc-PheΨ[CS-NH]Ala-Phe-OMe (3f): yield 90%; amorphous solid; $[\alpha]^{24}_D$ −32.5° (c = 0.78, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (br d, 1H, J = 6.7 Hz), 7.33−7.16 (m, 8H), 7.08 (d-like, 2H, J = 8.2 Hz), 6.21 (d, 1H, J = 7.6 Hz), 5.17 (br s, 1H), 4.86 (m, 1H), 4.77 (m, 1H), 4.60 (m, 1H), 3.71 (s, 3H), 3.22−3.10 (m, 2H), 3.08 (d, 2H, J = 5.9 Hz), 1.40 (s, 9H), 1.38 (d, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.71, 171.67, 170.42, 155.11, 136.39, 135.52, 129.20, 129.15, 128.61, 128.51, 127.18, 126.91, 80.37, 62.08, 53.84, 53.49, 52.41, 41.63, 37.73, 28.20, 17.20; IR (film) ν_{max} 3302, 2979, 1731, 1686, 1454, 1440, 1366, 1217, 1169, 756, 700 cm^{-1}; FABMS *m/z* 536 $[M + Na]^+$, 514 $[M + H]^+$. Anal. Calcd for $C_{27}H_{35}N_3O_5S$: C, 63.14; H, 6.87; N, 8.18. Found: C, 63.11; H, 6.97; N, 8.03.

Boc-PheΨ[CS-NH]Phe-Ala-OMe (3g): yield 88%; amorphous solid; $[\alpha]^{24}_D$ −4.3° (c = 0.67, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (br s, 1H), 7.33−7.18 (m, 8H), 7.17−7.09 (m, 2H), 6.06 (br s, 1H), 5.13−5.04 (m, 2H), 4.62 (m, 1H), 4.39 (m, 1H), 3.69 (s, 3H), 3.37 (dd, 1H, J = 13.5, 4.4 Hz), 3.17 (m, 2H), 2.84 (dd, 1H, J = 13.5, 8.3 Hz), 1.33 (s, 9H), 1.26 (d, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.30, 172.22, 168.52, 155.09, 136.13, 135.81, 129.33, 129.14, 128.69, 127.23, 127.20, 80.57, 63.02, 59.03, 52.35, 48.31, 41.08, 36.81, 28.10, 17.93; IR (film) ν_{max} 3305, 2979, 1717, 1685, 1508, 1498, 1454, 1367, 1217, 1164, 756, 700 cm^{-1}; FABMS *m/z* 536 $[M + Na]^+$, 514 $[M + H]^+$. Anal. Calcd for $C_{27}H_{35}N_3O_5S$: C, 63.14; H, 6.87; N, 8.18. Found: C, 62.90; H, 7.01; N, 8.05.

Boc-PheΨ[CS-NH]Met-Phe-OMe (3h): yield 62%; amorphous solid; $[\alpha]^{26}_D$ −12.6° (c = 0.47, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (br d, 1H, J = 7.1 Hz), 7.35−7.09 (m, 10H), 6.65 (d, 1H, J = 7.8 Hz), 5.19 (br d, 1H, J = 6.9 Hz), 5.05, (m, 1H), 4.75 (m, 1H), 4.59 (m, 1H), 3.71 (s, 3H), 3.23−3.02 (m, 4H), 2.53 (m, 2H), 2.15 (m, 1H), 2.03 (s, 3H), 1.98 (m, 1H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.73, 171.33, 169.09, 155.11, 136.31, 135.50, 129.18, 129.14, 128.76, 128.63, 127.29, 127.03, 80.47, 62.63, 56.96, 53.50, 52.34, 41.39, 37.61, 29.61, 29.58, 28.23, 14.80; IR (film) ν_{max} 3282, 2978, 1741, 1685, 1509, 1497, 1438, 1366, 1217, 1167, 755, 700 cm^{-1}; FABMS *m/z* 596 $[M + Na]^+$, 574 $[M + H]^+$. Anal. Calcd for $C_{29}H_{39}N_3O_5S_2 \cdot 0.25H_2O$: C, 60.23; H, 6.80; N, 7.27. Found C, 60.13; H, 6.88; N, 7.12.

Boc-PheΨ[CS-NH]Ala-Tyr-OMe (3i): yield 48%; amorphous solid; $[\alpha]^{26}_D$ −21.0° (c = 0.41, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (br d, 1H, J = 6.7 Hz), 7.30−7.16 (m, 5H), 6.92 (d-like, 2H, J = 8.4 Hz), 6.75 (d-like, 2H, J = 8.4 Hz), 6.44 (d, 1H, J = 7.9 Hz), 5.18 (br d, 1H, J = 7.5 Hz), 4.88 (m, 1H), 4.74 (m, 1H), 4.64 (br m, 1H), 3.74 (s, 3H), 3.18 (d-like, 2H, J = 6.3 Hz), 3.04−2.92 (m, 2H), 1.39 (s, 9H), 1.36 (d, 3H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.44, 172.02, 170.67, 155.40, 136.27, 130.41, 129.22, 128.64, 127.09, 126.90, 115.73, 80.85, 62.34, 54.01, 53.82, 52.59, 41.47, 37.08, 28.23, 17.29; IR (film) ν_{max} 3309, 2979, 1732, 1684, 1516, 1442, 1367,

1219, 1170, 756 cm^{-1}; FABMS *m/z* 552 $[M + Na]^+$, 530 $[M + H]^+$. Anal. Calcd for $C_{27}H_{35}N_3O_6S \cdot 0.2H_2O$: C, 60.81; H, 6.62; N, 7.88. Found C, 60.81; H, 6.90; N, 7.51.

Boc-ValΨ[CS-NH]Val-Phe-OMe (3j): yield 91%; amorphous solid; $[\alpha]^{24}_D$ −93.9° (*c* = 0.67, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, 1H, *J* = 8.1 Hz), 7.33−7.21 (m, 3H), 7.11 (d-like, 2H, *J* = 8.2 Hz), 6.31 (d, 1H, *J* = 7.7 Hz), 5.18 (br d, 1H, *J* = 7.9 Hz), 4.93−4.83 (m, 2H), 4.07 (m, 1H), 3.73 (s, 3H), 3.11 (d, 2H, *J* = 5.9 Hz), 2.38−2.23 (m, 2H), 1.44 (s, 9H), 1.01−0.88 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.76, 171.49, 169.21, 155.63, 135.36, 129.23, 128.63, 127.16, 79.95, 66.81, 63.79, 53.27, 52.31, 37.74, 33.04, 30.57, 28.24, 19.58, 18.65, 18.53, 17.90; IR (film) ν_{max} 3310, 2966, 1734, 1715, 1687, 1665, 1497, 1367, 1218, 1170, 1012, 757, 700 cm^{-1}; FABMS *m/z* 516 $[M + Na]^+$, 494 $[M + H]^+$. Anal. Calcd for $C_{25}H_{39}N_3O_5S$: C, 60.83; H, 7.96; N, 8.51. Found: C, 60.54; H, 7.99; N, 8.35.

Boc-ValΨ[CS-NH]Ala-Phe-OMe (3k): yield 91%; amorphous solid; $[\alpha]^{26}_D$ −70.6° (*c* = 0.57, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, 1H, *J* = 6.9 Hz), 7.32−7.21 (m, 3H), 7.09 (d-like, 2H, *J* = 8.2 Hz), 6.33 (d, 1H, *J* = 8.6 Hz), 5.18 (br s, 1H), 4.99 (m, 1H), 4.84 (m, 1H), 4.07 (m, 1H), 3.73 (s, 3H), 3.17−3.06 (m, 2H), 2.28 (m, 1H), 1.46 (d, 3H, *J* = 7.0 Hz), 1.44 (s, 9H), 0.92 (d, 3H, *J* = 6.4 Hz), 0.91 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.88, 171.74, 170.69, 155.62, 135.44, 129.22, 128.58, 127.14, 80.00, 66.13, 53.85, 53.51, 52.42, 37.81, 33.58, 28.29, 19.56, 17.75, 17.27; IR (film) ν_{max} 3304, 2976, 1733, 1686, 1499, 1446, 1390, 1367, 1218, 1170, 757, 701 cm^{-1}; FABMS *m/z* 488 $[M + Na]^+$, 466 $[M + H]^+$. Anal. Calcd for $C_{23}H_{35}N_3O_5S$: C, 59.33; H, 7.58; N, 9.02. Found: C, 59.11; H, 7.59; N, 8.84.

Boc-GlyΨ[CS-NH]Ala-Phe-OMe (3l): yield 71%; amorphous solid; $[\alpha]^{24}_D$ −62.4° (*c* = 0.44, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (br s, 1H), 7.33−7.21 (m, 3H), 7.10 (d-like, 2H, *J* = 8.2 Hz), 6.43 (br d, 1H, *J* = 7.8 Hz), 5.12 (br s, 1H), 5.00 (m, 1H), 4.86 (m, 1H), 4.17 (dd, 1H, *J* = 17.2, 6.2 Hz), 4.11 (dd, 1H, *J* = 17.2, 6.2 Hz), 3.74 (s, 3H), 3.14 (dd, 1H, *J* = 14.0, 5.6 Hz), 3.09 (dd, 1H, *J* = 14.0, 6.4 Hz), 1.46 (s, 9H), 1.45 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.56, 171.62, 170.60, 156.09, 135.53, 129.27, 128.61, 127.17, 80.76, 53.82, 53.38, 52.45, 51.88, 37.81, 28.23, 17.08; IR (film) ν_{max} 3315, 2979, 1682, 1523, 1444, 1367, 1276, 1248, 1217, 1167, 757, 702 cm^{-1}; FABMS *m/z* 446 $[M + Na]^+$, 424 $[M + H]^+$. Anal. Calcd for $C_{20}H_{29}N_3O_5S$: C, 56.72; H, 6.90; N, 9.92. Found: C, 56.36; H, 7.01; N, 9.72.

Boc-GlyΨ[CS-NH]Phe-Ala-OMe (3m): yield 67%; amorphous solid; $[\alpha]^{24}_D$ +6.9° (*c* = 0.42, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 8.63 (br d, 1H, *J* = 6.6 Hz), 7.34−7.23 (m, 5H), 6.05 (br s, 1H), 5.19 (m, 1H), 5.13 (br s, 1H), 4.46 (m, 1H), 4.24−4.12 (m, 2H), 3.71 (s, 3H), 3.36 (dd, 1H, *J* = 13.7, 5.0 Hz), 3.05 (dd, 1H, *J* = 13.7, 8.4 Hz), 1.44 (s, 9H), 1.31 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.65, 172.41, 168.95, 156.06, 135.83, 129.33, 128.70, 127.21, 80.73, 59.34, 52.44, 52.07, 48.33, 37.14, 28.21, 18.06; IR (film) ν_{max} 3317, 2979, 1741, 1723, 1668, 1520, 1454, 1367, 1275, 1247, 1217, 1163, 756, 701 cm^{-1}; FABMS *m/z* 446, $[M + Na]^+$, 424 $[M + H]^+$. Anal. Calcd for $C_{20}H_{29}N_3O_5S$: C, 56.72; H, 6.90; N, 9.92. Found: C, 56.44; H, 7.07; N, 9.68.

General Procedure for Preparation of Triazoles 4a−m from Thionotripeptides 3a−m. To a suspension of thionotripeptides **3a**−**m** (0.16 mmol) and formic hydrazide (48.0 mg, 0.80 mmol) in MeCN (0.5 mL) was added mercury(II) acetate (76.5 mg, 0.24 mmol), and the mixture was stirred at room temperature for 2 h. Water (10 mL) was added to the mixture, and the mixture was extracted with $CHCl_3$ (3 × 10 mL). The $CHCl_3$ extract was washed with brine (5 mL), dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo. The residue was chromatographed (MPLC, silica gel, hexane/$CHCl_3$/MeOH, 15:15:1) to provide triazoles **4a**−**m**.

Data for 4a: colorless crystalline powder, mp 191−192 °C ($CHCl_3$−isopropyl ether); $[\alpha]^{24}_D$ −7.5° (*c* = 0.56, MeOH); ^1H NMR (500 MHz, $CDCl_3$) δ 8.28 (br s, 1H), 7.98 (br s, 1H), 7.23−7.16 (m, 3H), 7.10−6.97 (m, 2H), 6.44 (br s, 1H), 5.63 (br m, 1H), 5.03 (br m, 1H), 4.82 (m, 1H), 3.72 (s, 3H), 3.19 (dd, 1H, *J* = 13.8, 5.4 Hz), 2.92 (m, 1H), 1.73 (br s, 3H), 1.64 (d, 3H, *J* = 6.7 Hz), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.43, 167.88, 155.64, 154.57, 141.56, 135.87, 128.92, 128.52, 126.94, 80.45, 53.61, 52.96, 52.27, 41.30, 37.66, 28.21, 19.94, 19.32; IR (KBr) ν_{max} 3276, 3213, 2981, 1756, 1709, 1698, 1531, 1523, 1455, 1366, 1268, 1250, 1217, 1201, 1173, 1064, 761, 705 cm^{-1}; FABMS *m/z* 446 $[M + H]^+$. Anal. Calcd for $C_{22}H_{31}N_5O_5$: C, 59.31; H, 7.01; N, 15.72. Found: C, 59.25; H, 7.02; N, 15.64.

Data for 4b: colorless crystalline powder, mp 199−200 °C ($CHCl_3$−isopropyl ether); $[\alpha]^{25}_D$ −38.7° (*c* = 1.00, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (br s, 1H), 7.98 (br s, 1H), 7.29−7.19 (m, 3H), 7.01−6.92 (m, 2H), 5.88 (br s, 1H), 5.60 (br d, 1H, *J* = 9.8 Hz), 4.55 (m, 1H), 4.12 (m, 1H), 3.77 (s, 3H), 3.40 (dd, 1H, *J* = 14.3, 3.3 Hz), 3.20 (dd, 1H, *J* = 14.3, 12.0 Hz), 1.37 (d, 3H, *J* = 7.3 Hz), 1.33 (s, 9H), 0.94 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.47, 167.41, 155.60, 155.35, 140.84, 135.36, 129.03, 128.95, 127.38, 80.38, 58.72, 52.36, 48.37, 40.27, 39.80, 28.20, 18.52, 17.53; IR (KBr) ν_{max} 3261, 2983, 1743, 1672, 1549, 1509, 1454, 1367, 1316, 1284, 1252, 1210, 1181, 1074, 1062, 752, 702 cm^{-1}; FABMS *m/z* 446 $[M + H]^+$. Anal. Calcd for $C_{22}H_{31}N_5O_5$: C, 59.31; H, 7.01; N, 15.72. Found: C, 59.13; H, 6.94; N, 15.68.

Data for 4c: amorphous solid; $[\alpha]^{24}_D$ +17.4° (*c* = 1.99, MeOH); ^1H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.84 (br d, 1H, *J* = 5.5 Hz), 7.29−7.18 (m, 3H), 7.11 (d-like, 2H, *J* = 8.3 Hz), 5.70 (br d, 1H, *J* = 7.5 Hz), 5.01 (m, 1H), 4.90−4.68 (m, 3H), 3.70 (s, 3H), 3.18 (dd, 1H, *J* = 13.9, 5.5 Hz), 3.05 (dd, 1H, *J* = 13.9, 8.1 Hz), 1.62 (d, 3H, *J* = 6.9 Hz), 1.39 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.61, 165.48, 155.76, 155.54, 144.44, 136.02, 129.09, 128.48, 126.97, 80.10, 53.92, 52.31, 46.63, 41.24, 37.45, 28.22, 19.74; IR (film) ν_{max} 3222, 2980, 1745, 1692, 1512, 1497, 1455, 1367, 1250, 1215, 1166, 755, 701 cm^{-1}; FABMS *m/z* 432 $[M + H]^+$; HRFABMS calcd for $C_{21}H_{30}N_5O_5$ 432.2247, found 432.2273.

Data for 4d: colorless crystalline powder, mp 214−215 °C ($CHCl_3$−isopropyl ether); $[\alpha]^{24}_D$ −11.8° (*c* = 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.37 (br s, 1H), 8.02 (br s, 1H), 7.22−7.13 (m, 3H), 7.05−6.95 (m, 2H), 6.44 (br s, 1H), 5.13−4.91 (m, 2H), 4.78 (m, 1H), 3.71 (s, 3H), 3.16 (dd, 1H, *J* = 13.5, 5.5 Hz), 2.93 (m, 1H), 2.39 (m, 1H), 1.74 (br s, 3H), 1.40, (s, 9H), 1.11 (d, 3H, *J* = 6.5 Hz), 0.74 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.26, 167.37, 155.72, 155.23, 141.59, 135.82, 128.87, 128.50, 126.95, 80.56, 63.51, 53.80, 52.20, 41.06, 37.72, 32.07, 28.25, 19.88, 19.16, 18.25; IR (KBr) ν_{max} 3259, 2978, 1753, 1714, 1689, 1574, 1533, 1520, 1367, 1300, 1268, 1252, 1216, 1202, 1171, 1061, 703 cm^{-1}; FABMS *m/z* 474 $[M + H]^+$. Anal. Calcd for $C_{24}H_{35}N_5O_5$: C, 60.87; H, 7.45; N, 14.79. Found: C, 60.69; H, 7.42; N, 14.64.

Data for 4e: colorless crystalline powder, mp 223−224 °C ($CHCl_3$−isopropyl ether); $[\alpha]^{26}_D$ −8.2° (*c* = 0.45, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.05 (br s, 1H), 7.47 (d-like, 2H, *J* = 7.8 Hz), 7.35 (d, 1H, *J* = 8.0 Hz), 7.14 (t, 1H, *J* = 7.9 Hz), 7.06 (t, 1H, *J* = 7.9 Hz), 6.69 (br s, 1H), 5.97 (br s, 1H), 5.38 (br s, 1H), 4.99−4.81 (m, 2H), 3.74 (s, 3H), 3.35 (dd, 1H, *J* = 14.7, 4.7 Hz), 3.09 (m, 1H), 1.62−1.52 (m, 6H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.02, 169.14, 155.05, 154.39, 143.29, 136.28, 127.13, 123.87, 121.20, 118.61, 118.04, 111.64, 108.97, 78.62, 53.65, 52.42, 52.05, 41.85, 28.24, 27.33, 19.75, 19.40; IR (KBr) ν_{max} 3284, 2979, 1747, 1712, 1680, 1524, 1251, 1219, 1201, 1169, 1063, 741 cm^{-1}; FABMS *m/z* 485 $[M + H]^+$. Anal. Calcd for $C_{24}H_{32}N_6O_5$: C, 59.49; H, 6.66; N, 17.34. Found: C, 59.37; H, 6.64; N, 17.29.

Data for 4f: colorless crystalline powder, mp 209−210 °C ($CHCl_3$−isopropyl ether); $[\alpha]^{24}_D$ +18.0° (*c* = 0.41, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.69 (d, 1H, *J* = 8.4 Hz), 7.24−7.15 (m, 6H), 7.09−7.02 (m, 2H), 6.93−6.86 (m, 2H), 6.22 (br s, 1H), 4.92 (m, 1H), 4.83−4.72 (m, 2H), 3.70 (s, 3H), 3.59 (m, 1H), 3.37 (dd, 1H, *J* = 12.7, 5.1 Hz), 3.10 (dd, 1H, *J* = 13.7, 5.2 Hz), 2.79 (dd, 1H, *J* = 13.7, 9.7 Hz), 1.39 (s, 9H), 0.77 (br d, 3H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.30, 167.49, 155.81, 153.57, 140.59, 135.89, 129.25, 128.73, 128.65, 128.51, 127.10, 126.78, 80.65, 68.17, 53.72, 52.55, 52.13, 47.75, 40.52, 37.59, 28.13, 22.72, 17.58; IR (KBr) ν_{max} 3279, 3222, 3032, 2981, 1759, 1738, 1710, 1694, 1570, 1520, 1498, 1455, 1391, 1366, 1290, 1249, 1196, 1170, 1010, 751, 698

cm^{-1}; FABMS *m/z* 522 $[M + H]^+$. Anal. Calcd for $C_{28}H_{35}N_5O_5$: C, 64.47; H, 6.76; N, 13.43. Found: C, 64.24; H, 6.80; N, 13.29.

Data for 4g: amorphous solid; $[\alpha]^{24}_D$ +1.6° (*c* = 0.74, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.71 (br s, 1H), 7.29−7.15 (m, 6H), 7.02−6.94 (m, 4H), 5.55 (br s, 1H), 5.34 (br m, 1H), 4.54−4.43 (m, 2H), 3.72 (s, 3H), 3.32 (dd, 1H, *J* = 14.0, 5.5 Hz), 3.14 (dd, 1H, *J* = 14.0, 9.8 Hz), 2.79 (dd, 1H, *J* = 14.0, 9.8 Hz), 2.41 (dd, 1H, *J* = 14.0, 5.6 Hz), 1.31 (d, 3H, *J* = 7.2 Hz), 1.27 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.31, 167.07, 155.84, 154.33, 141.12, 136.25, 135.31, 129.05, 128.92, 128.53, 127.39, 126.91, 80.51, 58.70, 52.31, 48.37, 45.83, 39.53, 38.63, 28.07, 17.49; IR (film) ν_{max} 3317, 2981, 1746, 1679, 1549, 1523, 1454, 1367, 1253, 1217, 1168, 753, 700 cm^{-1}; FABMS *m/z* 522 $[M + H]^+$; HRFABMS calcd for $C_{28}H_{36}N_5O_5$ 522.2716, found 522.2700.

Data for 4h: colorless fine needles, mp 164−166 °C ($MeOH-H_2O$); $[\alpha]^{25}_D$ +10.0° (*c* = 0.66, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (br s, 1H), 7.86 (br d, 1H, *J* = 6.5 Hz), 7.27−7.12 (m, 8H), 6.97 (br s, 2H), 6.27 (br s, 1H), 5.27 (br s, 1H), 5.09 (m, 1H), 4.75 (m, 1H), 3.70 (s, 3H), 3.57 (br m, 1H), 3.41 (dd, 1H, *J* = 13.1, 6.8 Hz), 3.11 (dd, 1H, *J* = 13.7, 5.5 Hz), 2.88 (dd, 1H, *J* = 13.7, 8.8 Hz), 2.27−2.11 (m, 4H), 1.99 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.09, 166.80, 155.80, 153.73, 141.05, 135.99, 135.73, 129.29, 128.79, 128.66, 128.57, 127.15, 126.94, 80.75, 55.50, 53.81, 52.20, 47.09, 40.09, 37.64, 31.92, 29.49, 28.16, 15.35; IR (KBr) ν_{max} 3231, 3028, 1734, 1708, 1696, 1523, 1282, 1254, 1170, 1015, 697 cm^{-1}; FABMS *m/z* 582 $[M + H]^+$. Anal. Calcd for $C_{30}H_{39}N_5O_5S$: C, 61.94; H, 6.76; N, 12.04. Found C, 61.84; H, 6.73; N, 11.97.

Data for 4i: colorless fine needles, mp 182−183 °C ($MeOH-H_2O$); $[\alpha]^{25}_D$ +23.3° (*c* = 0.50, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 8.22 (br s, 1H), 7.29−7.18 (m, 3H), 7.10 (br d, 2H, *J* = 6.5 Hz), 6.83 (br d, 2H, *J* = 8.5 Hz), 6.64 (d-like, 2H, *J* = 8.5 Hz), 5.03 (dd, 1H, *J* = 10.1, 6.0 Hz), 4.88 (m, 1H), 4.56 (dd, 1H, *J* = 8.7, 5.8 Hz), 3.69 (s, 3H), 3.33 (dd, 1H, 12.9, 6.0 Hz), 3.21 (dd, 1H, *J* = 12.9, 10.1 Hz), 3.00 (dd, 1H, *J* = 13.8, 5.8 Hz), 2.89 (dd, 1H, *J* = 13.8, 8.7 Hz), 1.40 (s, 9H), 0.95 (br d, 3H, *J* = 5.7 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 173.17, 170.13, 157.53, 157.36, 156.14, 143.00, 137.66, 131.06, 130.62, 129.72, 128.40, 128.13, 116.39, 81.02, 55.87, 54.12, 52.71, 48.86, 41.44, 37.56, 28.69, 18.45; IR (KBr) ν_{max} 3388, 3359, 3327, 2979, 1745, 1692, 1671, 1517, 1455, 1443, 1368, 1270, 1246, 1208, 1172, 704 cm^{-1}; FABMS *m/z* 538 $[M + H]^+$. Anal. Calcd for $C_{28}H_{35}N_5O_6$: C, 62.55; H, 6.56; N, 13.03. Found C, 62.32; H, 6.61; N, 12.80.

Data for 4j: amorphous solid; $[\alpha]^{25}_D$ −7.0° (*c* = 0.34, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.85 (br s, 1H), 7.23−7.11 (m, 3H), 7.08−6.94 (m, 2H), 6.19 (br s, 1H), 4.95 (br s, 1H), 4.69 (m, 1H), 4.52 (br t, 1H, *J* = 8.4 Hz), 3.68 (s, 3H), 3.13 (dd, 1H, *J* = 13.7, 6.1 Hz), 2.96 (dd, 1H, *J* = 13.7, 8.1 Hz), 2.60 (m, 1H), 2.40 (m, 1H), 1.40, (s, 9H), 1.15 (d, 3H, *J* = 6.2 Hz), 1.10 (d, 3H, *J* = 6.3 Hz), 0.86−0.74 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.17, 167.59, 156.46, 154.17, 141.84, 135.90, 128.90, 128.52, 127.02, 80.55, 63.66, 54.12, 52.23, 51.42, 37.81, 32.41, 31.81, 28.34, 20.37, 19.15, 19.05, 18.79; IR (film) ν_{max} 3220, 2968, 1748, 1712, 1685, 1518, 1366, 1281, 1173, 1008, 757, 699 cm^{-1}; FABMS *m/z* 502 $[M + H]^+$; HRFABMS calcd for $C_{26}H_{40}N_5O_5$ 502.3029, found 502.3036.

Data for 4k: colorless crystalline powder, mp 207 °C ($CHCl_3$−isopropyl ether); $[\alpha]^{24}_D$ −7.9° (*c* = 0.32, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.92 (br d, 1H, *J* = 5.4 Hz), 7.25−7.18 (m, 3H), 7.00−6.92 (m, 2H), 6.34 (br s, 1H), 5.41 (m, 1H), 4.82 (m, 1H), 4.41 (br t, 1H, *J* = 8.9 Hz), 3.72 (s, 3H), 3.15 (dd, 1H, *J* = 13.7, 5.2 Hz), 2.83 (dd, 1H, *J* = 13.7, 9.6 Hz), 2.63 (br m, 1H), 1.59 (d, 3H, *J* = 6.9 Hz), 1.40 (s, 9H), 1.17 (d, 3H, *J* = 6.5 Hz), 0.77 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.36, 167.55, 156.42, 154.06, 140.83, 135.97, 128.86, 128.62, 126.93, 80.58, 53.87, 52.71, 52.26, 51.72, 37.80, 32.07, 28.24, 19.66, 19.58, 18.97; IR (KBr) ν_{max} 3239, 2974, 1740, 1714, 1695, 1536, 1519, 1365, 1280, 1247, 1227, 1199, 1169, 1011, 754, 701 cm^{-1}; FABMS *m/z* 474 $[M + H]^+$. Anal. Calcd for $C_{24}H_{35}N_5O_5$: C, 60.87; H, 7.45; N, 14.79. Found: C, 60.69; H, 7.27; N, 14.54.

Data for 4l: amorphous solid; $[\alpha]^{24}_D$ −1.7° (*c* = 0.34, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (br s, 1H), 7.99 (br s, 1H), 7.23−7.16 (m, 3H), 7.13−7.06 (m, 2H), 6.40 (br s, 1H), 5.65 (q, 1H, *J* = 6.9 Hz), 4.82 (m, 1H), 4.62−4.49 (m, 2H), 3.74 (s, 3H), 3.23 (dd, 1H, *J* = 14.0, 5.5 Hz), 3.02 (dd, 1H, *J* = 14.0, 8.8 Hz), 1.68 (d, 3H, *J* = 6.9 Hz), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.54, 168.36, 156.43, 151.22, 142.25, 135.93, 129.07, 128.56, 127.11, 80.61, 53.67, 53.45, 52.30, 37.68, 34.82, 28.34, 18.99; IR (film) ν_{max} 3224, 2980, 1745, 1692, 1525, 1500, 1366, 1277, 1251, 1216, 1170, 861, 755, 701 cm^{-1}; FABMS *m/z* 432 $[M + H]^+$; HRFABMS calcd for $C_{21}H_{30}N_5O_5$ 432.2247, found 432.2249.

Data for 4m: colorless crystalline powder, mp 172 °C ($CHCl_3$−isopropyl ether); $[\alpha]^{25}_D$ −8.6° (*c* = 1.01, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.28 (br d, 1H, *J* = 5.5 Hz), 7.23−7.10 (m, 3H), 6.95−6.85 (m, 2H), 6.16 (br m, 1H), 5.61 (dd, 1H, *J* = 10.7, 4.5 Hz), 4.54 (m, 1H), 3.94−3.67 (m, 2H), 3.75 (s, 3H), 3.38 (dd, 1H, *J* = 14.0, 4.5 Hz), 3.16 (dd, 1H, *J* = 14.0, 10.7 Hz), 1.37 (d, 3H, *J* = 7.2 Hz), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.50, 167.71, 156.18, 151.62, 142.46, 134.96, 128.83, 128.55, 127.20, 79.89, 58.76, 52.23, 48.31, 40.39, 34.11, 28.16, 17.35; IR (KBr) ν_{max} 3422, 3209, 3144, 2984, 1740, 1684, 1570, 1511, 1278, 1163, 1061, 747, 702 cm^{-1}; FABMS *m/z* 432 $[M + H]^+$; HRFABMS calcd for $C_{21}H_{30}N_5O_5$ 432.2247, found 432.2239.

Triazolotetrapeptide 5c. Compound **4c** was added to 4 M HCl in dioxane (1.0 mL) at room temperature and stirred for 1 h, and then the solvent was removed in vacuo. The residue was dissolved in $CHCl_3$ (0.5 mL), and *N*-Boc-D-alanine (138 mg, 0.073 mmol) and HOBt (9.9 mg, 0.073 mmol) were added to the solution. After dropwise addition of triethylamine (10.2 μL, 0.073 mmol), EDC·HCl (14.0 mg, 0.073 mmol) was added to the solution, and the mixture was stirred at room temperature for 1 day. Water (10 mL) was added to the solution, and the mixture was extracted with $CHCl_3$ (3 × 10 mL). The $CHCl_3$ layer was washed with brine (5 mL), dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo. The residue was chromatographed (MPLC, silica gel, $CHCl_3$/EtOAc/MeOH, 15/2/1) to provide **5c** (27.2 mg, 86%) as an amorphous solid; $[\alpha]^{24}_D$ +18.8° (*c* = 0.88, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.08 (d, 1H, *J* = 7.7 Hz), 7.89 (d, 1H, *J* = 8.0 Hz), 7.30−7.19 (m, 3H), 7.16 (d-like, 2H, *J* = 8.2 Hz), 5.44 (br s, 1H), 5.26 (m, 1H), 4.94−4.80 (m, 2H), 4.77 (m, 1H), 4.13 (m, 1H), 3.71 (s, 3H), 3.20 (dd, 1H, *J* = 14.0, 5.5 Hz), 3.08 (dd, 1H, *J* = 14.0, 8.3 Hz), 1.66 (d, 3H, *J* = 7.0 Hz), 1.40 (s, 9H), 1.31 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.45, 171.62, 165.65, 155.41, 154.78, 144.63, 136.07, 129.04, 128.44, 126.93, 79.74, 54.03, 52.28, 50.30, 46.57, 39.73, 37.33, 28.19, 19.07, 18.28; IR (film) ν_{max} 3286, 2981, 1744, 1691, 1523, 1454, 1367, 1249, 1218, 1168, 756, 701 cm^{-1}; FABMS *m/z* 503 $[M + H]^+$; HRFABMS calcd for $C_{24}H_{35}N_6O_6$ 503.2618, found 503.2603.

Triazolotetrapeptide 5f. As described for **5c**, **4f** provided **5f** (81%) as colorless fine needles, mp 201−202 °C ($CHCl_3$−isopropyl ether); $[\alpha]^{26}_D$ +13.6° (*c* = 0.59, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (br s, 1H), 8.03 (br s, 1H), 7.99 (s, 1H), 7.24−7.03 (m, 8H), 6.88−6.80 (m, 2H), 5.40 (br s, 1H), 5.14 (m, 1H), 4.96 (m, 1H), 4.68 (m, 1H), 4.24 (br m, 1H), 3.69 (s, 3H), 3.50 (dd, 1H, *J* = 12.9, 10.1 Hz), 3.40 (dd, 1H, *J* = 12.9, 6.0 Hz), 3.07 (dd, 1H, *J* = 13.8, 5.5 Hz), 2.89 (dd, 1H, *J* = 13.8, 8.5 Hz), 1.41 (s, 9H), 1.19 (d, 3H, *J* = 7.0 Hz), 0.97 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.94, 171.52, 167.68, 155.46, 153.01, 140.99, 136.08, 135.95, 129.33, 128.78, 128.49, 127.24, 126.78, 80.21, 53.97, 52.84, 52.35, 49.86, 46.67, 39.82, 37.34, 28.32, 18.49, 18.19; IR (KBr) ν_{max} 3267, 2979, 1745, 1722, 1687, 1657, 1558, 1507, 1455, 1366, 1244, 1221, 1171, 702 cm^{-1}; FABMS *m/z* 593 $[M + H]^+$. Anal. Calcd for $C_{31}H_{40}N_6O_6$: C, 62.82; H, 6.80; N, 14.18. Found: C, 63.03; H, 6.85; N, 14.04. Crystal data for **5f**: $C_{31}H_{40}N_6O_6$, *M* = 592.70, 0.4 × 0.2 × 0.1 mm^3, monoclinic, $P2_1$, *a* = 13.992 (3), *b* = 10.865 (4), *c* = 10.575 (2) Å, β = 90.55 (2)°, *V* = 1607.6 (7) $Å^3$, *T* = 298 K, *Z* = 2, μ(Cu Kα) = 6.705 mm^{-1}, 3507 reflections measured, 3067 unique reflections (R_{int} = 0.027), *R* = 0.048, *Rw* = 0.072. The structure was solved by direct methods and expanded using Fourier techniques.

Triazolotetrapeptide 6g. As described for **5c**, **4g** provided **6g** (82%) by using *N*-Boc-glycine as an amorphous solid; $[\alpha]^{24}_D$ −14.6° (*c* = 0.77, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.99 (br s, 1H), 7.93 (br d, 1H, *J* = 6.1 Hz), 7.32−7.14 (m, 6H), 7.01 (d-like, 2H, *J* = 7.0 Hz), 6.96 (d-like, 2H, *J* = 6.8 Hz), 5.44 (br s, 1H), 5.37 (m, 1H), 4.73 (m, 1H), 4.42 (m, 1H), 3.71 (s, 3H), 3.69 (m, 1H), 3.57 (dd, 1H, *J* = 17.2, 5.1 Hz), 3.34 (dd, 1H, *J* = 13.9, 5.3 Hz), 3.26 (dd, 1H, *J* = 13.9, 9.7 Hz), 2.85 (dd, 1H, *J* = 13.9, 9.9 Hz), 2.62 (m, 1H), 1.36 (s, 9H), 1.33 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.51, 170.73, 167.05, 155.88, 153.99, 141.45, 136.30, 135.34, 129.06, 128.96, 128.55, 127.48, 127.00, 79.89, 58.99, 52.36, 48.57, 45.08, 43.39, 39.63, 38.21, 28.22, 17.11; IR (film) ν_{max} 3286, 2980, 1745, 1685, 1540, 1499, 1455, 1367, 1281, 1247, 1217, 1171, 754, 701 cm^{-1}; FABMS *m*/*z* 579 $[M + H]^+$; HRFABMS calcd for $C_{30}H_{39}N_6O_6$ 579.2931, found 579.2917.

Triazole Analogue of RA-VII 10. To a suspension of thioamide **8** (40.3 mg, 0.0512 mmol) and formic hydrazide (15.4 mg, 0.256 mmol) in MeCN (0.25 mL) was added mercury(II) acetate (24.5 mg, 0.0769 mmol), and the mixture was stirred at room temperature for 72 h. Water (10 mL) was added to the mixture, and the mixture was extracted with $CHCl_3$ (2 × 10 mL). The $CHCl_3$ extract was washed with brine (5 mL), dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo. The residue was chromatographed (MPLC, silica gel, $CHCl_3$/EtOAc/MeOH, 20:2:1) to provide triazole **10** (19.4 mg, 48%) as a crystalline powder, mp > 300 °C (MeOH); $[\alpha]^{23}_D$ −124° (*c* = 0.16, $CHCl_3$); ^{1}H NMR (500 MHz, 315 K, $CDCl_3$, major conformer) δ 8.13 (s), 7.51 (dd, 1H, *J* = 8.6, 2.1 Hz), 7.48 (d, 1H, *J* = 9.2 Hz), 7.24 (dd, 1H, *J* = 8.3, 2.1 Hz), 7.21 (dd, 1H, *J* = 8.3, 2.1 Hz), 7.10 (d-like, 2H, *J* = 8.6 Hz), 7.03 (dd, 1H, *J* = 8.6, 2.1 Hz), 6.82 (d-like, 2H, *J* = 8.6 Hz), 6.74 (d, 1H, *J* = 8.2 Hz), 6.62 (dd, 1H, *J* = 8.2, 1.9 Hz), 6.16 (d, 1H, *J* = 6.8 Hz), 5.99 (dd, 1H, *J* = 12.2, 4.4 Hz), 5.77 (q, 1H, *J* = 6.6 Hz), 5.30−5.23 (m, 2H), 4.63 (d, 1H, *J* = 1.9 Hz), 4.50 (m, 1H), 3.91 (s, 3H), 3.76 (s, 3H), 3.71 (dd, 1H, *J* = 13.8, 7.6 Hz), 3.39−3.31 (m, 2H), 3.07−3.00 (m, 3H), 2.99 (s, 3H), 2.91 (dd, 1H, *J* = 14.4, 3.9 Hz), 2.81 (m, 1H), 2.75 (s, 3H), 2.33 (s, 3H), 1.42 (d, 3H, *J* = 6.6 Hz), 1.31 (d, 3H, *J* = 6.7 Hz), 0.99 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, 315 K, $CDCl_3$, major conformers) δ 172.94, 172.86, 168.44, 167.97, 167.94, 159.25, 158.23, 152.24, 149.79, 146.84, 141.25, 133.84, 131.95, 131.15, 130.51, 130.42, 128.21, 127.44, 124.01, 121.83, 119.62, 114.73, 112.48, 68.79, 56.30, 55.37, 54.34, 53.74, 51.39, 49.23, 43.43, 41.12, 38.01, 34.70, 32.12, 29.31, 29.22, 20.23, 20.10, 19.07; IR (KBr) ν_{max} 3377, 3308, 2979, 2935, 1656, 1630, 1515, 1499, 1443, 1412, 1267, 1251, 1215, 1129, 1091 cm^{-1}; FABMS *m*/*z* 795 $[M + H]^+$; HRFABMS calcd for $C_{42}H_{51}N_8O_8$ 795.3830, found 795.3814.

Supporting Information Available: ^{1}H NMR spectra of **1** (R^1 = H), precursors of **1**, **3a**−**m**, **4a**−**m**, **5c**,**f**, **6g**, and **10**, and X-ray data and an ORTEP diagram of **5f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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