A Convergent Synthesis of New β-Turn Mimics by Click Chemistry

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Supporting Information

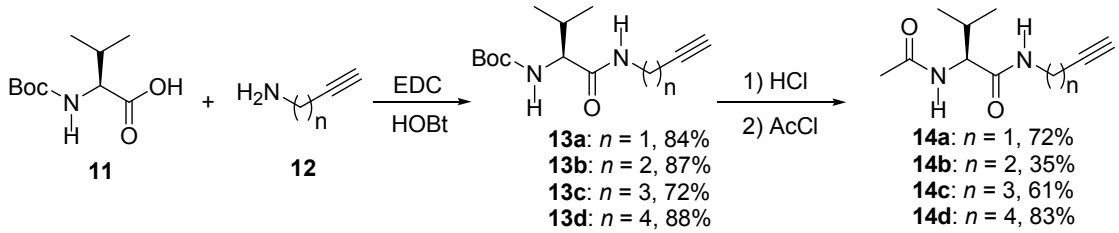
Part I. Experimental Section

Part II. Figures and Schemes

Part I. Experimental Section

General Experimental Details: ^{1}H NMR spectra were recorded at 500 and 600 MHz and ^{13}C NMR were recorded at 125 and 150 MHz on Bruker instruments. ^{1}H and ^{13}C NMR chemical shifts are reported as δ values in ppm relative to TMS or residual solvent: $CDCl_3$ (7.27 ppm for ^{1}H and 77 ppm for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet), integration and coupling constants in Hertz (Hz). Multiplets (m) are reported over the range (ppm) which they appear at the indicated field strength. Mass spectral data were obtained on a Micromass Autospec specrometer. All commercial reagents were used as received with the following exceptions: The solvents CH_2Cl_2 and THF were obtained from an alumina filtration system according to the method described by Grubbs.[1] Flash chromatograph was performed using forced flow of the indicated solvent system on Fisher silica gel 60 (230–400 mesh). Moisture sensitive reactions were performed under nitrogen atmosphere using flame-dried glassware and standard syringe/septa techniques. Alkynylamines **12** [2] and azidoalkanoic acids **17** [3] were prepared according to the literature procedures. Cycloadditions of alkynes to azides were performed according to the procedures reported by Sharpless and coworkers.[4]

Synthesis of acetylamino-*N*-alkynylamidovaline 14



13a. A solution of Boc-Val-OH **11** (3.87 g, 17.8 mmol), EDC (3.27 g, 17.8 mmol), and HOBt (2.53 g, 18.7 mmol) in CH_2Cl_2 was cooled to 0 ^{o}C. To this solution was added DIPEA (4.60 g, 35.6 mmol) then prop-2-ynylamine **12a** (0.98 g, 17.8 mmol). The solution was allowed to warm to rt and stir overnight. The reaction mixture was purified by flash chromatography using a mixture of CH_2Cl_2 and EtOAc (6/1) to give 3.78 g (14.9 mmol, 84%) of **13a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (d, *J* = 6.6, 3H), 0.97 (d, *J* = 6.6, 3H), 1.45 (s, 9H), 2.13–2.21 (m, 1H), 2.23 (t, *J* = 2.6, 1H), 3.90 (dd, *J* = 8.6, 6.2, 1H), 4.02–4.10 (m, 2H), 5.00 (br s, 1H), 6.15 (br s, 1H); MS (ESI), *m/z* calcd for $[C_{13}H_{22}N_2O_3 + Na]^+$ = 277.15; found 277.12.

13b. But-3-ynylamine (**12b**) hydrochloride (1.08 g, 10.2 mmol) was dissolved in 10 mL of 10 % NaOH. The solution was extracted with CH_2Cl_2 (10 mL x 3) and combined organic layers were dried over $MgSO_4$. A solution of Boc-Val-OH **11** (2.22 g, 10.2 mmol), EDC (2.15 g, 11.2 mmol), and HOBt (1.65 g, 12.2 mmol) in CH_2Cl_2 was cooled to 0 ^{o}C. To this solution was added DIPEA (3.96 g, 30.6

mmol) then but-3-ynylamine prepared as above. The solution was allowed to warm to rt and stir overnight. The reaction mixture was purified by flash chromatography using a mixture of CH_2Cl_2 and EtOAc (6/1→5/1) to give 2.38 g (8.87 mmol, 87%) of **13b**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.92 (d, *J* = 6.6, 3H), 0.96 (d, *J* = 6.6, 3H), 1.45 (s, 9H), 2.00 (t, *J* = 2.6, 1H), 2.12–2.19 (m, 1H), 2.42 (td, *J* = 6.9, 2.6, 2H), 3.37–3.43 (m, 1H), 3.46–3.52 (m, 1H), 3.89 (dd, *J* = 8.6, 6.1, 1H), 5.01 (br s, 1H), 6.19 (br s, 1H); MS (ESI), *m/z* calcd for $[C_{14}H_{24}N_2O_3 + Na]^+$ = 291.2; found 291.2.

13c. A solution of Boc-Val-OH **11** (1.57 g, 7.22 mmol), EDC (1.45 g, 7.22 mmol), and HOBt (1.07 g, 7.94 mmol) in CH_2Cl_2 was cooled to 0 ^{o}C. To this solution was added DIPEA (1.86 g, 14.4 mmol) then pent-4-ynylamine **12c** (0.600 g, 7.22 mmol). The solution was allowed to warm to rt and stir overnight. The reaction mixture was purified by flash chromatography using a mixture of CH_2Cl_2 and EtOAc (6/1) to give 1.46 g (5.18 mmol, 72%) of **13c**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.92 (d, *J* = 6.6, 3H), 0.96 (d, *J* = 6.6, 3H), 1.45 (s, 9H), 1.73–1.78 (m, 2H), 2.00 (t, *J* = 2.6, 1H), 2.13–2.20 (m, 1H), 2.26 (td, *J* = 6.9, 2.6, 2H), 3.37–3.43 (m, 2H), 3.73–3.77 (m, 1H), 5.00 (br s, 1H), 6.09 (br s, 1H); MS (ESI), *m/z* calcd for $[C_{15}H_{26}N_2O_3 + Na]^+$ = 305.2; found 305.0.

13d. A solution of Boc-Val-OH **11** (1.10 g, 5.05 mmol), EDC (1.02 g, 5.30 mmol), and HOBt (0.75 g, 5.6 mmol) in CH_2Cl_2 was cooled to 0 ^{o}C. To this solution was added DIPEA (1.31 g, 10.1 mmol) then hex-5-ynylamine **12d** (0.491 g, 5.05 mmol). The solution was allowed to warm to rt and stir overnight. The reaction mixture was purified by flash chromatography using a mixture of CH_2Cl_2 and EtOAc (6/1) to give 1.31 g (4.43 mmol, 88%) of **13d**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.92 (d, *J* = 6.6, 3H), 0.96 (d, *J* = 6.6, 3H), 1.45 (s, 9H), 1.53–1.59 (m, 2H), 1.62–1.68 (m, 2H), 1.96 (t, *J* = 2.6, 1H), 2.10–2.20 (m, 1H), 2.21–2.25 (m, 2H), 3.28–3.32 (m, 2H), 3.81–3.85 (m, 1H), 5.01 (br s, 1H), 5.93 (br s, 1H); MS (ESI), *m/z* calcd for $[C_{16}H_{28}N_2O_3 + Na]^+$ = 319.20; found 319.15.

14a. A solution of **13a** (0.938 g, 3.69 mmol) in CH_2Cl_2 was cooled to 0 ^{o}C. To this solution was added 10 mL of 4 M HCl in dioxane. The solution was allowed to warm to rt and stir 3 h. The solution was concentrated in vacuo and diluted with CH_2Cl_2 (20 mL). To this solution was added triethylamine (10 mL) then cooled to –78 ^{o}C. Acetic anhydride (50 mL) was added slowly and the solution was allowed to warm to rt and stir overnight. The reaction mixture was concentrated in vacuo and white solid was filtrated then recrystlallized in hexanes/CH_2Cl_2 to give 0.524 g (2.67 mmol, 72%) of **14a**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.83 (dd, *J* = 6.8, 1.7, 6H), 1.86 (s, 3H), 1.88–1.94 (m, 1H), 3.07 (t, *J* = 2.5, 1H), 3.78–3.92 (m, 2H), 4.09 (dd, *J* = 8.9, 7.2, 1H), 7.88 (d, *J* = 9.0, 1H), 8.39 (t, *J* = 5.4, 1H); MS (ESI), *m/z* calcd for $[C_{10}H_{16}N_2O_2 + Na]^+$ = 219.2; found 219.1.

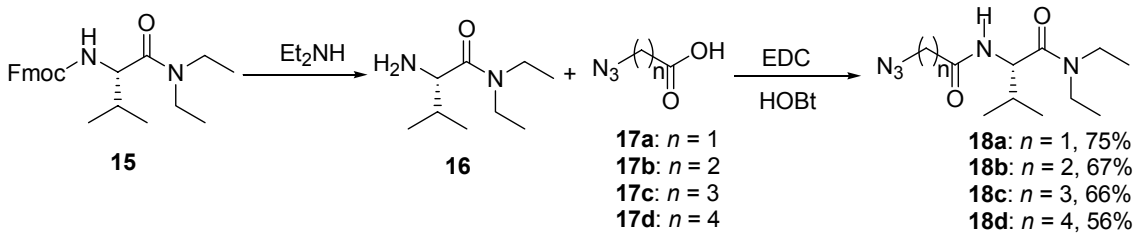
14b. A solution of **13b** (0.69 g, 2.6 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 ^{o}C. To this solution was added 20 mL of 4 M HCl in dioxane. The solution was allowed to warm to rt and stir 3 h. The solution was concentrated in vacuo and

diluted with CH_2Cl_2. To this solution was added triethylamine (5 mL) and cooled to 0 ^oC. Acetyl chloride (0.50 mL, 7.1 mmol) was added slowly at 0 ^oC. The solution was allowed to warm to rt and stir overnight. The reaction mixture was washed with H_2O (50 mL) and extracted with EtOAc (50 mL x 2). Combined organic layers were washed with water, dried over $MgSO_4$ then concentrated in vacuo. The reaction mixture was purified by flash chromatography using a mixture of CH_2Cl_2 and EtOAc (1/5) to give 0.19 g (0.90 mmol, 35%) of **14b**. ^1H NMR (600 MHz, $CDCl_3$) δ 0.97 (dd, *J* = 6.7, 1.2, 6H), 2.03 (t, *J* = 5.3, 1H), 2.04 (s, 3H), 2.06–2.10 (m, 1H), 2.40–2.44 (m, 2H), 3.34–3.38 (m, 1H), 3.48–3.54 (m, 1H), 4.20 (dd, *J* = 8.7, 7.0, 1H), 6.04 (br s, 1H), 6.05 (br s, 1H); MS (ESI), *m/z* calcd for $[C_{11}H_{18}N_2O_2 + Na]^+$ = 233.2; found 233.1.

14c. A solution of **13c** (1.46 g, 5.18 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 ^oC. To this solution was added 20 mL of 4 M HCl in dioxane. The solution was allowed to warm to rt and stir 3 h. The solution was concentrated in vacuo and diluted with CH_2Cl_2. To this solution was added triethylamine (5 mL) and cooled to 0 ^oC. Acetyl chloride (0.55 mL, 7.8 mmol) was added slowly at 0 ^oC. The solution was allowed to warm to rt and stir overnight. The reaction mixture was washed with H_2O (50 mL) and dried over $MgSO_4$ then concentrated in vacuo. The reaction mixture was purified by flash chromatography using a mixture of CH_2Cl_2 and EtOAc (1/3→1/4) to give 0.713 g (3.18 mmol, 61%) of **14c**. ^1H NMR (600 MHz, $CDCl_3$) δ 0.96 (dd, *J* = 6.7, 2.0, 6H), 1.72–1.80 (m, 2H), 2.01 (t, *J* = 2.7, 1H), 2.04 (s, 3H), 2.04–2.10 (m, 1H), 2.26 (td, *J* = 6.9, 2.7, 2H), 3.34–3.46 (m, 2H), 4.15 (dd, *J* = 8.7, 7.2, 1H), 6.01 (br s, 1H), 6.05 (d, *J* = 8.4, 1H); MS (ESI), *m/z* calcd for $[C_{12}H_{20}N_2O_2 + Na]^+$ = 247.2; found 247.1.

14d. A solution of **13d** (1.30 g, 4.38 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 ^oC. To this solution was added 40 mL of 4 M HCl in dioxane. The solution was allowed to warm to rt and stir 3 h. The solution was concentrated in vacuo and diluted with CH_2Cl_2. To this solution was added triethylamine (5 mL) and cooled to 0 ^oC. Acetyl chloride (0.50 mL, 7.1 mmol) was added slowly at 0 ^oC. The solution was allowed to warm to rt and stir overnight. The reaction mixture was washed with H_2O (50 mL) and extracted with EtOAc (50 mL x 2). Combined organic layers were washed with water, dried over $MgSO_4$ then concentrated in vacuo. The reaction mixture was purified by flash chromatography using a mixture of CH_2Cl_2 and EtOAc (1/6) to give 0.862 g (3.62 mmol, 83%) of **14d**. ^1H NMR (600 MHz, $CDCl_3$) δ 0.96 (dd, *J* = 6.7, 1.4, 6H), 1.53–1.59 (m, 2H), 1.62–1.68 (m, 2H), 1.96 (t, *J* = 2.6, 1H), 2.03 (s, 3H), 2.04–2.10 (m, 1H), 2.23 (td, *J* = 6.9, 2.6, 2H), 3.21–3.28 (m, 1H), 3.30–3.37 (m, 1H), 4.18 (dd, *J* = 8.7, 7.4, 1H), 6.10 (br s, 1H), 6.16 (d, *J* = 8.7, 1H); MS (ESI), *m/z* calcd for $[C_{13}H_{22}N_2O_2 + Na]^+$ = 261.2; found 261.1.

Synthesis of 18



18a. A solution of **15** (0.975 g, 2.47 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C. To this solution was added Et_2NH (10 mL). The solution was allowed to warm to rt and stir 2 h to give **16**. The solution was concentrated in vacuo and diluted with CH_2Cl_2. A separate solution of **17a** (0.28 g, 2.7 mmol), EDC (0.50 g, 2.6 mmol), and HOBt (0.37 g, 2.7 mmol) in CH_2Cl_2 was cooled to 0 °C. To this solution was added DIPEA (0.64 g, 4.9 mmol), then a solution of **16** in CH_2Cl_2 prepared as above. The solution was allowed to warm to rt and stir overnight. The reaction mixture was purified by flash chromatography using a mixture of CH_2Cl_2 and EtOAc (8/1→6/1) to give 0.471 g (1.84 mmol, 75%) of **18a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (d, *J* = 6.8, 3H), 0.97 (d, *J* = 6.8, 3H), 1.14 (t, *J* = 7.1, 3H), 1.24 (t, *J* = 7.1, 3H), 1.98–2.07 (m, 1H), 3.13–3.21 (m, 1H), 3.31–3.39 (m, 1H), 3.45–3.53 (m, 1H), 3.60–3.68 (m, 1H), 3.93–4.06 (m, 2H), 4.77 (dd, *J* = 9.2, 6.4, 1H), 6.94 (d, *J* = 8.5, 1H); MS (ESI), *m/z* calcd for $[C_{11}H_{21}N_5O_2 + Na]^+$ = 278.16; found 278.12.

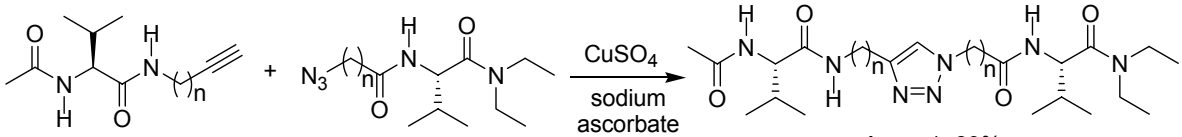
18b. A solution of **15** (2.12 g, 5.37 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C. To this solution was added Et_2NH (10 mL). The solution was allowed to warm to rt and stir 3 h to give **16**. The solution was concentrated in vacuo and diluted with CH_2Cl_2. A separate solution of **17b** (0.70 g, 6.0 mmol), EDC (1.10 g, 5.8 mmol), and HOBt (0.80 g, 6.0 mmol) in CH_2Cl_2 was cooled to 0 °C. To this solution was added DIPEA (1.40 g, 10.8 mmol), then a solution of **16** in CH_2Cl_2 prepared as above. The solution was allowed to warm to rt and stir overnight. The reaction mixture was purified by flash chromatography using a mixture of CH_2Cl_2 and EtOAc (2/1→1/1) to give 0.98 g (3.64 mmol, 67%) of **18b**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (d, *J* = 6.8, 3H), 0.97 (d, *J* = 6.8, 3H), 1.14 (t, *J* = 7.2, 3H), 1.24 (t, *J* = 7.2, 3H), 1.97–2.02 (m, 1H), 2.48 (t, *J* = 6.4, 2H), 3.13–3.21 (m, 1H), 3.31–3.39 (m, 1H), 3.45–3.53 (m, 1H), 3.58–3.68 (m, 3H), 4.80 (dd, *J* = 9.1, 6.6, 1H), 6.36 (d, *J* = 9.0, 1H); MS (ESI), *m/z* calcd for $[C_{12}H_{23}N_5O_2 + Na]^+$ = 292.2; found 292.1.

18c. A solution of **15** (1.28 g, 3.25 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C. To this solution was added Et_2NH (10 mL). The solution was allowed to warm to rt and stir 3 h to give **16**. The solution was concentrated in vacuo and diluted with CH_2Cl_2. A separate solution of **17c** (0.46 g, 3.6 mmol), EDC (0.65 g, 3.4 mmol), and HOBt (0.48 g, 3.6 mmol) in CH_2Cl_2 was cooled to 0 °C. To this solution was added DIPEA (0.84 g, 6.5 mmol), then a solution of **16** in CH_2Cl_2 prepared as

above. The solution was allowed to warm to rt and stir overnight. The reaction mixture was purified by flash chromatography using a mixture of CH_2Cl_2 and EtOAc (2/1→1/1) to give 0.61 g (2.2 mmol, 66%) of **18c**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (d, *J* = 6.8, 3H), 0.96(d, *J* = 6.8, 3H), 1.13 (t, *J* = 7.2, 3H), 1.24 (t, *J* = 7.2, 3H), 1.90–2.02 (m, 3H), 2.32 (td, *J* = 7.5, 1.5, 2H), 3.13–3.21 (m, 1H), 3.32–3.40 (m, 3H), 3.45–3.53 (m, 1H), 3.58–3.65 (m, 1H), 4.77 (dd, *J* = 9.1, 6.6, 1H), 6.22 (d, *J* = 8.8, 1H); MS (ESI), *m/z* calcd for $[C_{13}H_{25}N_5O_2 + Na]^+$ = 306.2; found 306.1.

18d. A solution of **15** (1.15 g, 2.92 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C. To this solution was added Et_2NH (5 mL). The solution was allowed to warm to rt and stir 3 h to give **16**. The solution was concentrated in vacuo and diluted with CH_2Cl_2. A separate solution of **17d** (0.46 g, 3.2 mmol), EDC (0.59 g, 3.1 mmol), and HOBt (0.44 g, 3.2 mmol) in CH_2Cl_2 was cooled to 0 °C. To this solution was added DIPEA (0.76 g, 5.8 mmol), then a solution of **16** in CH_2Cl_2 prepared as above. The solution was allowed to warm to rt and stir overnight. The reaction mixture was purified by flash chromatography using a mixture of CH_2Cl_2 and EtOAc (2/1→1/1) to give 0.49 g (1.6 mmol, 56%) of **18d**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (d, *J* = 6.8, 3H), 0.96(d, *J* = 6.8, 3H), 1.13 (t, *J* = 7.2, 3H), 1.25 (t, *J* = 7.2, 3H), 1.60–1.67 (m, 2H), 1.70–1.76 (m, 2H), 1.96–2.02 (m, 1H), 2.26 (t, *J* = 7.3, 2H), 3.13–3.21 (m, 1H), 3.28–3.32 (m, 2H), 3.34–3.44 (m, 1H), 3.45–3.53 (m, 1H), 3.58–3.65 (m, 1H), 4.77 (dd, *J* = 9.1, 6.7, 1H), 6.19 (d, *J* = 8.5, 1H); MS (ESI), *m/z* calcd for $[C_{14}H_{27}N_5O_2 + Na]^+$ = 320.2; found 320.2.

Synthesis of tetrapeptide triazoles 1–4



14a: *n* = 1
14b: *n* = 2
14c: *n* = 3
14d: *n* = 4

18a: *n* = 1
18b: *n* = 2
18c: *n* = 3
18d: *n* = 4

1: *n* = 1, 80%
2: *n* = 2, 35%
3: *n* = 3, 65%
4: *n* = 4, 67%

Triazole 1. To a suspension of azide **18a** (0.38 g, 1.5 mmol) and alkyne **14a** (0.29 g, 1.5 mmol) in a 1:1 mixture of H_2O and *tert*-butyl alcohol (6 mL) was added sodium ascorbate (0.15 mmol, 0.15 mL of freshly prepared 1 M solution in H_2O), followed by copper(II) sulfate (2.4 mg, 0.015 mmol, in 0.1 mL of H_2O). The heterogeneous mixture was stirred vigorously overnight. The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography using a mixture of CH_2Cl_2 and EtOAc (1/6) → CH_2Cl_2 and MeOH (9/1) to give 0.54 g (1.2 mmol, 80%) of **1**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90–0.98 (m, 12H), 1.12 (t, *J* = 7.1, 3H), 1.23 (t, *J* = 7.1, 3H), 1.98 (s, 3H), 2.00–2.12 (m, 2H), 3.10–3.20 (m, 1H), 3.34–3.50 (m, 2H), 3.56–3.64 (m, 1H), 4.36–4.46 (m, 2H), 4.66 (dd, *J* = 15.3, 6.5, 1H), 4.73 (dd, *J* = 8.9, 6.8, 1H), 4.98 (q, *J* = 15.9, 2H), 6.93 (d, *J* = 9.0, 1H), 7.54 (br s, 1H), 7.58 (s, 1H), 7.68 (d, *J* = 10.1, 1H); HRMS (ESI), *m/z* calcd for $[C_{21}H_{37}N_7O_4 + Na]^+$ = 474.2805; found 474.2812.

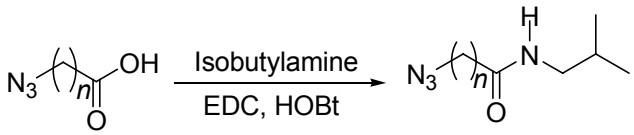
Triazole 2. To a suspension of azide **18b** (0.50 g, 1.8 mmol) and alkyne **14b** (0.38 g, 1.8 mmol) in a 1:1 mixture of H_2O and *tert*-butyl alcohol (6 mL) was added sodium ascorbate (0.18 mmol, 0.18 mL of freshly prepared 1 M solution in H_2O), followed by copper(II) sulfate (2.8 mg, 0.018 mmol, in 0.1 mL of H_2O). The heterogeneous mixture was stirred vigorously overnight. The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography using a mixture of CH_2Cl_2 and EtOAc (1/6) → CH_2Cl_2 and MeOH (6/1) to give 0.30 g (0.63 mmol, 35%) of **2**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88–0.96 (m, 12H), 1.08 (t, *J* = 7.2, 3H), 1.27 (t, *J* = 7.2, 3H), 1.92–1.98 (m, 2H), 2.04 (s, 3H), 2.68 (dt, *J* = 14.7, 4.0, 1H), 2.81–2.85 (m, 1H), 3.02–3.12 (m, 2H), 3.13–3.21 (m, 2H), 3.40–3.46 (m, 2H), 3.54–3.60 (m, 1H), 3.82–3.88 (m, 1H), 4.38 (t, *J* = 9.2, 1H), 4.43 (dt, *J* = 13.9, 4.2, 1H), 4.59 (t, *J* = 8.3, 1H), 4.90 (t, *J* = 11.5, 1H), 6.31 (d, *J* = 9.3, 1H), 7.31 (s, 1H), 7.63 (d, *J* = 8.6, 1H), 8.03 (br s, 1H); HRMS (ESI), *m/z* calcd for $[C_{23}H_{41}N_7O_4 + Na]^+$ = 502.3118; found 502.3127.

Triazole 3. To a suspension of azide **18c** (0.57 g, 2.0 mmol) and alkyne **14c** (0.45 g, 2.0 mmol) in a 1:1 mixture of H_2O and *tert*-butyl alcohol (8 mL) was added sodium ascorbate (0.20 mmol, 0.2 mL of freshly prepared 1 M solution in H_2O), followed by copper(II) sulfate (3.2 mg, 0.02 mmol, in 0.1 mL of H_2O). The heterogeneous mixture was stirred vigorously overnight. The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography using a mixture of CH_2Cl_2 and EtOAc (1/6) → CH_2Cl_2 and MeOH (9/1) to give 0.66 g (1.3 mmol, 65%) of **3**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94–0.98 (m, 12H), 1.12 (t, *J* = 7.2, 3H), 1.26 (t, *J* = 7.2, 3H), 1.84–1.98 (m, 2H), 2.04 (s, 3H), 2.04–2.12 (m, 2H), 2.16–2.28 (m, 4H), 2.77 (t, *J* = 6.0, 2H), 3.12–3.28 (m, 3H), 3.42–3.58 (m, 3H), 4.11 (t, *J* = 8.9, 1H), 4.32–4.44 (m, 2H), 4.78 (t, *J* = 8.7, 1H), 6.21 (br s, 1H), 7.39 (s, 1H), 7.67 (d, *J* = 9.2, 1H), 7.83 (d, *J* = 8.9, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 12.85, 14.67, 18.28, 18.62, 19.45, 19.49, 21.80, 22.84, 26.15, 28.62, 30.64, 31.71, 32.20, 37.22, 40.65, 42.42, 49.33, 53.94, 59.60, 122.45, 146.23, 170.79, 171.52, 172.02; HRMS (ESI), *m/z* calcd for $[C_{25}H_{45}N_7O_4 + Na]^+$ = 530.3431; found 530.3442.

Triazole 4. To a suspension of azide **18d** (0.46 g, 1.5 mmol) and alkyne **14d** (0.376 g, 1.5 mmol) in a 1:1 mixture of H_2O and *tert*-butyl alcohol (6 mL) was added sodium ascorbate (0.15 mmol, 0.15 mL of freshly prepared 1 M solution in H_2O), followed by copper(II) sulfate (2.5 mg, 0.015 mmol, in 0.1 mL of H_2O). The heterogeneous mixture was stirred vigorously overnight. The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography using a mixture of CH_2Cl_2 and MeOH (18/1→9/1) to give 0.55 g (1.0 mmol, 67%) of **4**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.90–0.98 (m, 12H), 1.11 (t, *J* = 7.1, 3H), 1.23 (t, *J* = 7.1, 3H), 1.51–1.59 (m, 2H), 1.60–1.68 (m, 2H), 1.68–1.76 (m, 2H), 1.89–1.97 (m, 2H), 1.98–1.02 (m, 1H), 2.02 (s, 3H), 2.04–2.08 (m, 1H), 2.21–2.31 (m, 2H), 2.75 (t, *J* = 7.0, 2H), 3.14–3.22 (m, 2H), 3.30–3.38 (m, 1H), 3.38–3.44 (m, 1H), 3.44–3.52 (m, 1H), 3.54–3.60 (m, 1H), 4.24 (dd, *J* = 8.8, 7.4, 1H), 4.34 (t, *J* = 6.9, 2H), 4.74 (dd, *J* = 9.1, 7.0, 1H), 6.29 (d, *J* = 8.6, 1H), 6.51

(d, *J* = 9.1, 1H), 6.55 (br s, 1H), 7.31 (s, 1H); HRMS (ESI), *m/z* calcd for $[C_{27}H_{49}N_7O_4 + Na]^+$ = 558.3744; found 558.3746.

Synthesis of Azido-*N*-isopropylamide 19



17a: n = 1
17b: n = 2
17c: n = 3
17d: n = 4

19a: n = 1, 71%
19b: n = 2, 41%
19c: n = 3, 45%
19d: n = 4, 52%

19a. A solution of 2-azidoacetic acid **17a** (2.19 g, 21.7 mmol), EDC (4.15 g, 21.7 mmol), and HOBt (2.92 g, 21.7 mmol) in CH_2Cl_2 was cooled to 0 °C. To this solution was added DIPEA (7.5 mL, 43.6 mmol) then isopropylamine (1.58 g, 21.7 mmol). The solution was allowed to warm to rt and stir overnight. The reaction mixture was purified by flash chromatography using a mixture of CH_2Cl_2 and EtOAc (1/0→3/1) to give 2.32 g (15.3 mmol, 71%) of **19a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (d, *J* = 6.7, 6H), 1.78–1.84 (m, 1H), 3.13 (t, *J* = 6.5, 2H), 4.01 (s, 2H), 6.38 (br s, 1H); MS (ESI), *m/z* calcd for $[C_6H_{12}N_4O + Na]^+$ = 179.09; found 179.08.

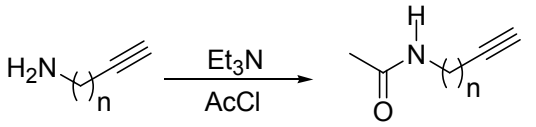
19b. A solution of 3-azidopropinoic acid **17b** (4.00 g, 34.7 mmol), EDC (6.65 g, 34.7 mmol), and HOBt (4.69 g, 34.7 mmol) in CH_2Cl_2 was cooled to 0 °C. To this solution was added DIPEA (12 mL, 69.4 mmol) then isopropylamine (2.54 g, 34.7 mmol). The solution was allowed to warm to rt and stir overnight. The reaction mixture was purified by flash chromatography using a mixture of CH_2Cl_2 and EtOAc (1/0→5/1) to give 2.40 g (14.1 mmol, 41%) of **19b**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (d, *J* = 6.8, 6H), 1.74–1.83 (m, 1H), 2.43 (t, *J* = 6.4, 2H), 3.11 (t, *J* = 6.6, 2H), 3.63 (t, *J* = 6.4, 2H), 5.78 (br s, 1H); MS (ESI), *m/z* calcd for $[C_7H_{14}N_4O + Na]^+$ = 193.11; found 193.09.

19c. A solution of 4-azidobutyric acid **17c** (4.54 g, 35.2 mmol), EDC (6.75 g, 35.2 mmol), and HOBt (4.75 g, 35.2 mmol) in CH_2Cl_2 was cooled to 0 °C. To this solution was added DIPEA (12 mL, 70.4 mmol) then isopropylamine (2.57 g, 35.2 mmol). The solution was allowed to warm to rt and stir overnight. The reaction mixture was purified by flash chromatography using a mixture of CH_2Cl_2 and EtOAc (1/0→5/1) to give 2.90 g (15.7 mmol, 45%) of **19c**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (d, *J* = 6.8, 6H), 1.73–1.79 (m, 1H), 1.90–1.96 (m, 2H), 2.28 (t, *J* = 7.2, 2H), 3.08 (t, *J* = 6.3, 2H), 3.35 (t, *J* = 6.5, 2H), 5.73 (br s, 1H); MS (ESI), *m/z* calcd for $[C_8H_{16}N_4O + Na]^+$ = 207.12; found 207.10.

19d. A solution of 5-azidopentanoic acid **17d** (3.58 g, 25.0 mmol), EDC (4.79 g, 25.0 mmol), and HOBt (3.38 g, 25.0 mmol) in CH_2Cl_2 was cooled to 0 °C. To this solution was added DIPEA (6.5 g, 50.0 mmol) then isopropylamine (1.83 g, 25.0

mmol). The solution was allowed to warm to rt and stir overnight. The reaction mixture was purified by flash chromatography using a mixture of CH_2Cl_2 and EtOAc (1/0→4/1) to give 2.57 g (12.9 mmol, 52%) of **19d**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (d, J = 6.7, 6H), 1.60–1.66 (m, 2H), 1.70–1.80 (m, 3H), 2.22 (t, J = 7.2, 2H), 3.08 (t, J = 6.1, 2H), 3.30 (t, J = 6.8, 2H), 5.62 (br s, 1H); MS (ESI), *m/z* calcd for $[C_9H_{18}N_4O + Na]^+$ = 221.14; found 221.13.

Synthesis of N-alkynylacetamide 20



12a: n = 1
12b: n = 2
12c: n = 3
12d: n = 4

20a: n = 1, 59%
20b: n = 2, 34%
20c: n = 3, 28%
20d: n = 4, 41%

20a. To a solution of prop-2-ynylamine **12a** (5.05 g, 91.7 mmol) and triethylamine (18.7 g, 183 mmol) in ether was added an ether solution of acetyl chloride (7.92 g, 101 mmol) at 0 ^{o}C dropwise. The solution was allowed to warm to rt and stir overnight. The reaction mixture was washed with H_2O (100 mL) and extracted with CH_2Cl_2 (100 mL x 3). Combined organic layers were washed with water, dried over $MgSO_4$ then concentrated in vacuo. Purification was carried out by flash chromatography (CH_2Cl_2/EtOAc = 2/1) to give 5.27 g (54.3 mmol, 59%) of **20a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.02 (s, 3H), 2.24 (t, J = 2.6, 2H), 4.04–4.09 (m, 2H), 5.73 (br s, 1H).

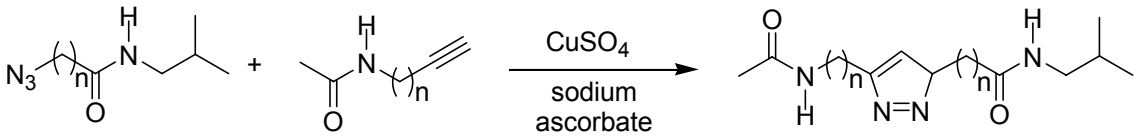
20b. But-3-ynylamine (**12b**) hydrochloride (1.64 g, 15.5 mmol) was dissolved in 10 mL of 10 % NaOH. The solution was extracted with CH_2Cl_2 (10 mL x 3) and combined organic layers were dried over $MgSO_4$ to give **12b**. To this solution was added triethylamine (3.6 g, 31 mmol) in ether and then acetyl chloride (7.92 g, 101 mmol) at 0 ^{o}C dropwise. The solution was allowed to warm to rt and stir overnight. The reaction mixture was washed with H_2O (50 mL) and extracted with EtOAc (50 mL x 2). Combined organic layers were washed with water, dried over $MgSO_4$ then concentrated in vacuo. Purification was carried out by flash chromatography (CH_2Cl_2/MeOH = 18/1→9/1) to give 0.58 g (5.22 mmol, 34%) of **20b**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.01 (s, 3H), 2.01–2.04 (m, 1H), 2.42 (td, J = 5.8, 2.0, 2H), 3.43 (q, J = 6.9, 2H), 5.78 (br s, 1H); MS (ESI), *m/z* calcd for $[C_6H_9NO + H]^+$ = 112.1; found 112.1.

20c. To a solution of pent-4-ynylamine **12c** (0.816 g, 9.81 mmol) and triethylamine (3.00 g, 29.4 mmol) in ether was added acetyl chloride (0.925 g, 11.8 mmol) at 0 ^{o}C dropwise. The solution was allowed to warm to rt and stir overnight. The reaction mixture was washed with H_2O (50 mL) and extracted with EtOAc (50 mL x 3). Combined organic layers were washed with water, dried over $MgSO_4$ then concentrated in vacuo. Purification was carried out by flash chromatography (CH_2Cl_2/EtOAc = 1/0→4/1) to give 0.340 g (2.72 mmol, 28%) of

20c. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.72–1.78 (m, 2H), 1.98–2.04 (m, 4H), 2.26 (td, *J* = 6.9, 2.6, 2H), 3.43 (q, *J* = 6.6, 2H), 5.82 (br s, 1H); MS (ESI), *m/z* calcd for $[C_7H_{11}NO + Na]^+$ = 148.1; found 148.0.

20d. To a solution of hex-5-ynylamine **12d** (1.27 g, 9.50 mmol) and triethylamine (4.85 g, 47.5 mmol) in ether was added acetyl chloride (0.82 g, 10.5 mmol) at 0 ^oC dropwise. The solution was allowed to warm to rt and stir overnight. The reaction mixture was washed with H_2O (50 mL) and extracted with ether (50 mL x 3). Combined organic layers were washed with water, dried over $MgSO_4$ then concentrated in vacuo. Purification was carried out by flash chromatography (CH_2Cl_2/EtOAc = 1/0→4/1) to give 0.54 g (3.88 mmol, 41%) of **20d**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52–1.66 (m, 4H), 1.96 (t, *J* = 2.6, 1H), 2.00 (s, 3H), 2.22 (td, *J* = 6.9, 2.6, 2H), 3.27 (q, *J* = 6.4, 2H), 5.65 (br s, 1H); MS (ESI), *m/z* calcd for $[C_8H_{13}NO + Na]^+$ = 162.1; found 162.1.

Synthesis of diamide triazole 5–8



19a: *n* = 1
19b: *n* = 2
19c: *n* = 3
19d: *n* = 4

20a: *n* = 1
20b: *n* = 2
20c: *n* = 3
20d: *n* = 4

5: *n* = 1, 47%
6: *n* = 2, 49%
7: *n* = 3, 37%
8: *n* = 4, 19%

Triazole 5. To a suspension of azide **19a** (0.94 g, 6.0 mmol) and alkyne **20a** (0.58 g, 6.0 mmol) in a 1:1 mixture of H_2O and *tert*-butyl alcohol (12 mL) was added sodium ascorbate (0.6 mmol, 0.6 mL of freshly prepared 1 M solution in H_2O), followed by copper(II) sulfate (9.6 mg, 0.06 mmol, in 0.1 mL of H_2O). The heterogeneous mixture was stirred vigorously overnight. The reaction mixture was concentrated in vacuo. The residue was purified by precipitation from water to give 0.72 g (2.8 mmol, 47%) of **5**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (d, *J* = 6.7, 6H), 1.72–1.78 (m, 1H), 2.02 (s, 3H), 3.10 (t, *J* = 6.4, 2H), 4.54 (d, *J* = 5.4, 2H), 5.03 (s, 2H), 6.05 (br s, 1H), 6.19 (br s, 1H), 7.73 (s, 1H); HRMS (ESI), *m/z* calcd for $[C_{11}H_{19}N_5O_2 + Na]^+$ = 276.1436; found 276.1437.

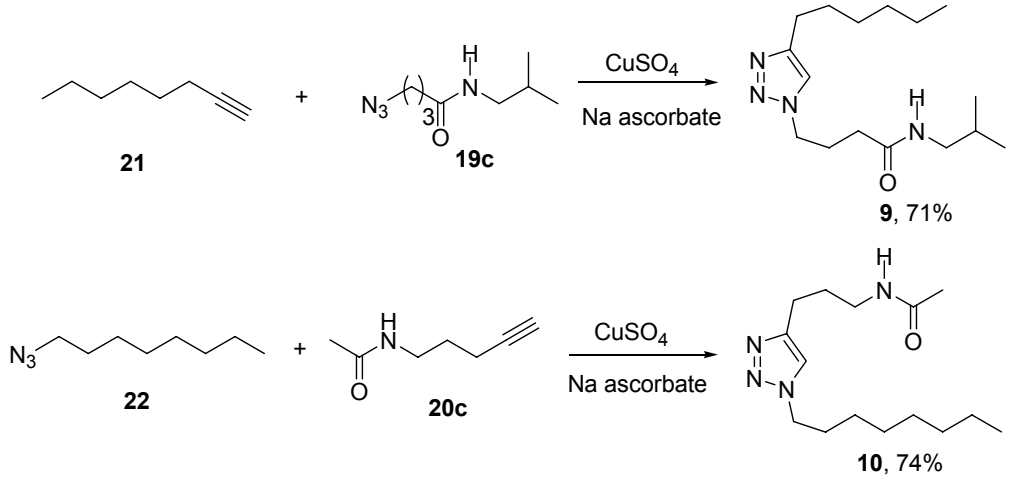
Triazole 6. To a suspension of azide **19b** (0.85 g, 5.0 mmol) and alkyne **20b** (0.55 g, 5.0 mmol) in a 1:1 mixture of H_2O and *tert*-butyl alcohol (10 mL) was added sodium ascorbate (0.5 mmol, 0.5 mL of freshly prepared 1 M solution in H_2O), followed by copper(II) sulfate (8.0 mg, 0.05 mmol, in 0.1 mL of H_2O). The heterogeneous mixture was stirred vigorously overnight. The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography using a mixture of CH_2Cl_2 and MeOH (5/1 → 3/1) to give 0.69 g (2.5 mmol, 49%) of **6**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.85 (d, *J* = 6.7, 6H), 1.68–1.74 (m, 1H), 1.97 (s, 3H), 2.81 (t, *J* = 6.2, 2H), 2.88 (t, *J* = 6.3, 2H), 3.06 (t, *J* = 6.4, 2H), 3.58 (q, *J* = 6.1, 2H), 4.68 (t, *J* = 6.1, 2H), 5.57 (br s, 1H), 6.21 (br s,

1H), 7.46 (s, 1H); HRMS (ESI), *m/z* calcd for $[C_{13}H_{23}N_5O_2 + Na]^+$ = 304.1750; found 304.1742.

Triazole 7. To a suspension of azide **19c** (0.50 g, 2.7 mmol) and alkyne **20c** (0.34 g, 2.7 mmol) in a 1:1 mixture of H_2O and *tert*-butyl alcohol (6 mL) was added sodium ascorbate (0.3 mmol, 0.3 mL of freshly prepared 1 M solution in H_2O), followed by copper(II) sulfate (4.8 mg, 0.03 mmol, in 0.1 mL of H_2O). The heterogeneous mixture was stirred vigorously overnight. The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography using a mixture of CH_2Cl_2 and MeOH (5/1 → 2/1) to give 0.31 g (1.0 mmol, 37%) of **7**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (d, *J* = 7.0, 6H), 1.76–1.82 (m, 1H), 1.87–1.93 (m, 2H), 2.00 (s, 3H), 2.14–2.18 (m, 2H), 2.20–2.25 (m, 2H), 2.78 (t, *J* = 6.9, 2H), 3.09 (t, *J* = 6.2, 2H), 3.27 (q, *J* = 6.4, 2H), 4.42 (t, *J* = 6.1, 2H), 5.80 (br s, 1H), 6.28 (br s, 1H), 7.39 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.13, 22.63, 23.26, 26.11, 28.43, 28.79, 32.44, 38.39, 46.94, 49.29, 170.27, 171.46; HRMS (ESI), *m/z* calcd for $[C_{15}H_{27}N_5O_2 + Na]^+$ = 332.2062; found 332.2060.

Triazole 8. To a suspension of azide **19d** (0.59 g, 3.0 mmol) and alkyne **20d** (0.42 g, 3.0 mmol) in a 1:1 mixture of H_2O and *tert*-butyl alcohol (6 mL) was added sodium ascorbate (0.3 mmol, 0.3 mL of freshly prepared 1 M solution in H_2O), followed by copper(II) sulfate (4.8 mg, 0.03 mmol, in 0.1 mL of H_2O). The heterogeneous mixture was stirred vigorously overnight. The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography using a mixture of CH_2Cl_2 and MeOH (1/0 → 8/1) to give 0.19 g (0.56 mmol, 19%) of **8**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (d, *J* = 6.7, 6H), 1.52–1.58 (m, 2H), 1.61–1.69 (m, 2H), 1.69–1.75 (m, 2H), 1.75–1.79 (m, 1H), 1.92–2.00 (m, 2H), 2.02 (s, 3H), 2.20 (t, *J* = 7.4, 2H), 2.74 (t, *J* = 7.3, 2H), 3.07 (t, *J* = 6.5, 2H), 3.26 (q, *J* = 6.0, 2H), 4.35 (t, *J* = 6.9, 2H), 5.60 (br s, 1H), 5.84 (br s, 1H), 7.31 (s, 1H); HRMS (ESI), *m/z* calcd for $[C_{17}H_{31}N_5O_2 + Na]^+$ = 360.2375; found 360.2379.

Synthesis of control triazoles 9 and 10



Control Triazole 9. To a suspension of azide **19c** (0.55 g, 3.0 mmol) and 1-octyne **21** (0.33 g, 3.0 mmol) in a 1:1 mixture of H_2O and *tert*-butyl alcohol (6 mL) was added sodium ascorbate (0.3 mmol, 0.3 mL of freshly prepared 1 M solution in H_2O), followed by copper(II) sulfate (4.8 mg, 0.03 mmol, in 0.1 mL of H_2O). The heterogeneous mixture was stirred vigorously overnight. The reaction mixture was concentrated in vacuo. The residue was purified by precipitation from water to give 0.63 g (2.1 mmol, 71%) of **9**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.86–0.92 (m, 3H), 0.93 (d, *J* = 6.7, 6H), 1.28–1.38 (m, 6H), 1.64–1.70 (m, 2H), 1.74–1.82 (m, 1H), 2.14–2.18 (m, 2H), 2.18–2.24 (m, 2H), 2.71 (t, *J* = 7.7, 2H), 3.10 (t, *J* = 6.1, 2H), 4.41 (t, *J* = 6.2, 2H), 5.77 (br s, 1H), 7.30 (s, 1H); HRMS (ESI), *m/z* calcd for $[C_{16}H_{30}N_4O + Na]^+$ = 317.2317; found 317.2323.

Control Triazole 10. To a suspension of 1-azidooctane **22** (0.22 g, 1.4 mmol) and alkyne **20c** (0.18 g, 1.4 mmol) in a 1:1 mixture of H_2O and *tert*-butyl alcohol (3 mL) was added sodium ascorbate (0.14 mmol, 0.14 mL of freshly prepared 1 M solution in H_2O), followed by copper(II) sulfate (2.2 mg, 0.014 mmol, in 0.1 mL of H_2O). The heterogeneous mixture was stirred vigorously overnight. The reaction mixture was concentrated in vacuo. The residue was purified by precipitation from water to give 0.29 g (1.0 mmol, 74%) of **10**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.5, 3H), 1.22–1.36 (m, 10H), 1.86–1.92 (m, 4H), 1.98 (s, 3H), 2.78 (t, *J* = 7.2, 2H), 3.31 (t, *J* = 6.5, 2H), 4.31 (t, *J* = 7.5, 2H), 5.91 (br s, 1H), 7.34 (s, 1H); HRMS (ESI), *m/z* calcd for $[C_{15}H_{28}N_4O + Na]^+$ = 303.2161; found 303.2163.

Part II. Figures and Schemes

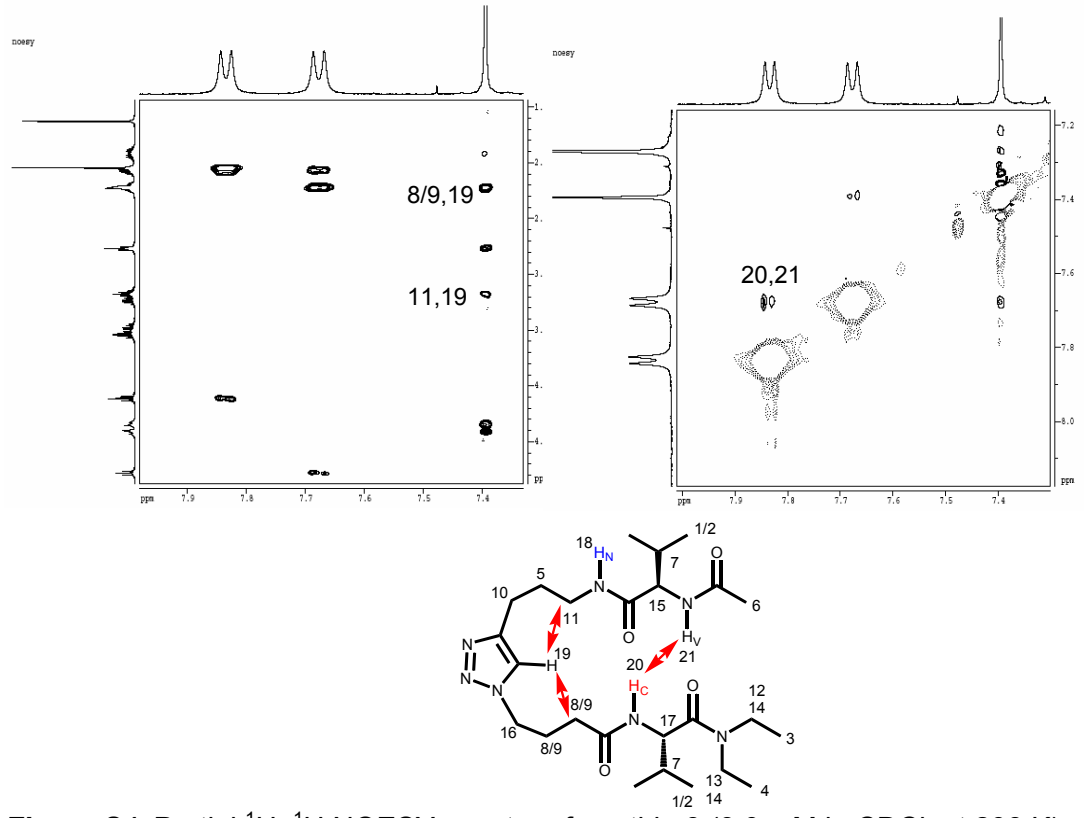


Figure S1. Partial $^{1}H–^{1}H$ NOESY spectra of peptide **3** (3.0 mM in $CDCl_3$ at 298 K).

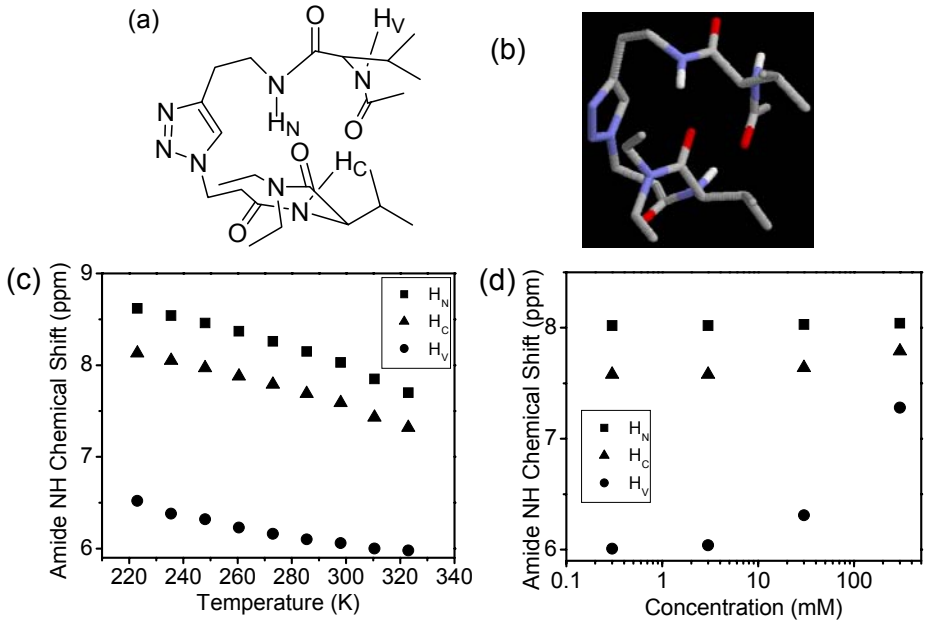


Figure S2. (a) Proposed chemical structures of peptide **2**; (b) an energy-minimized structure (MacroModel 6.0 Amber* force field); (c) temperature dependence of the amide proton chemical shifts for 3.0 mM solution of peptide **2** in $CDCl_3$; and (d) concentration dependence of the amide proton chemical shifts of peptide **2** in $CDCl_3$ at 298 K.

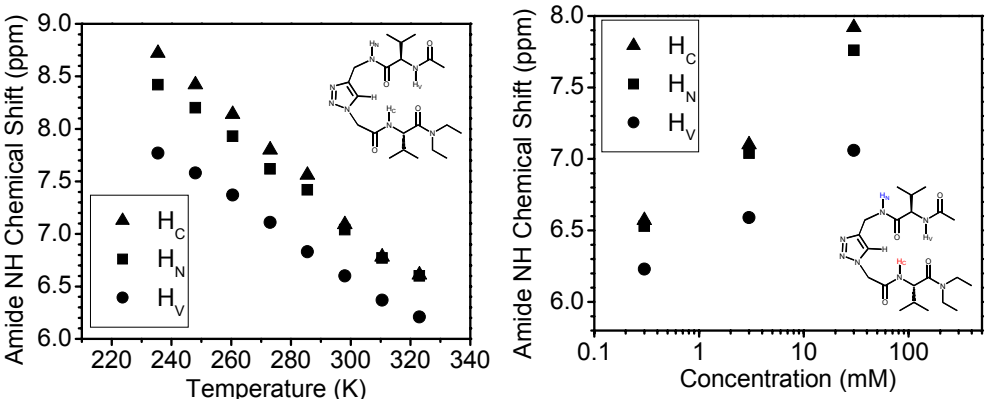


Figure S3. Temperature (left, 3.0mM) and concentration (at 298 K) dependence of the amide proton chemical shifts of peptide **1** in $CDCl_3$.

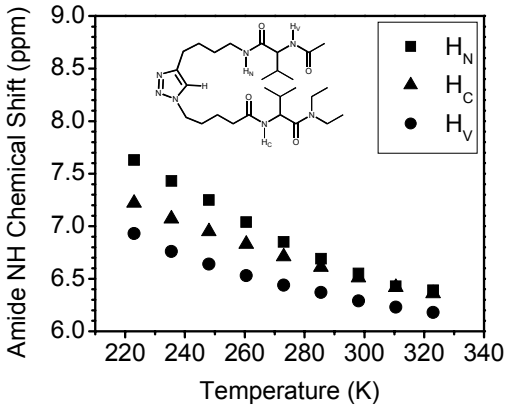
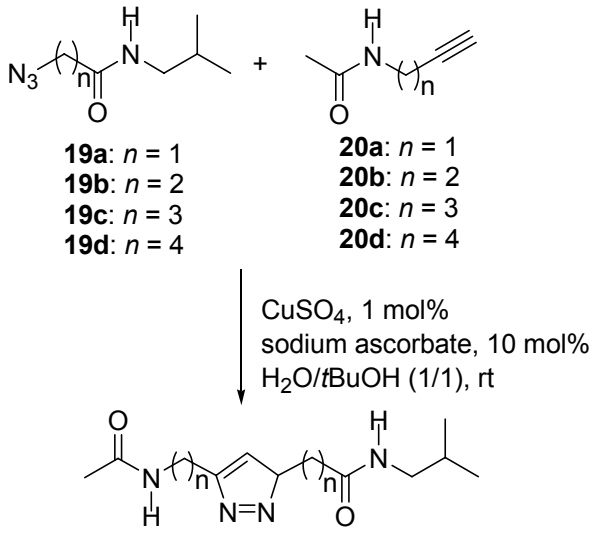


Figure S4. Temperature dependence of the amide proton chemical shifts of peptide **4** (3.0 mM in $CDCl_3$).



Scheme S1. Synthesis of 1,2,3-Triazole Based Amides with Linkers of Different Lengths

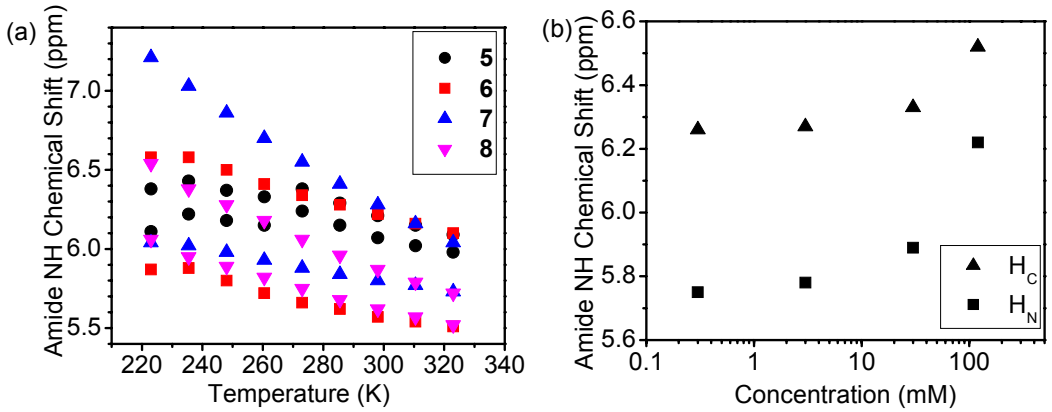


Figure S5. (a) Temperature dependence of the amide NH proton chemical shifts for 3.0 mM solutions of peptides **5**–**8** in $CDCl_3$; (b) concentration dependence of the amide NH proton chemical shifts for the solution of peptide **7** in $CDCl_3$ at 298 K.

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