Supplementary Information

Synthesis of Symmetric Bis(imidazole-4,5-dicarboxamides) Substituted with Amino Acids

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Experimental Section

General Methods. All apparatus were oven-dried and cooled in a desiccator. Reagent grade THF and CH_2Cl_2 were distilled from sodium benzophenone ketyl and CaH_2 , respectively, before use. All other reagents were purchased from commercial suppliers and used without purification. Thin-layer chromatography was done on 250 μm silica gel plates containing a fluorescent indicator and were visualized by using UV and I_2 as well as ninhydrin spray for amines. Melting points are uncorrected and elemental analyses were done by a contracting laboratory. ^1H and ^{13}C NMR spectra were measured at 400 and 50.3 MHz, respectively, in either CDCl_3 with CHCl_3 as the internal reference for ^1H (δ 7.26) and CDCl_3 as the internal reference for ^{13}C (δ 77.06) or in $\text{DMSO}-d_6$ with DMSO as the internal reference for ^1H (δ 2.50) and $\text{DMSO}-d_6$ as the internal reference for ^{13}C (δ 39.50).

Symmetric imidazole-4,5-dicarboxamides disubstituted with amino acid esters (2–8). General procedure. To a dry flask under argon was added **1** and 25 mL dry THF. To this stirred suspension at 0 °C were added 4 equiv of the appropriate amino acid ester hydrochloride salt followed by 6 equiv of diisopropylethylamine over 15 min. The solution was stirred at rt for 12 h before concentrating under vacuum to provide the crude product. The solid was dissolved in 25 mL of CH_2Cl_2 and extracted with 10% citric acid, 1 M NaHCO_3 , and brine. The organic layer was dried over MgSO_4 and stirred with approximately 200 mg of decolorizing carbon. The mixture was filtered, and the filtrate was concentrated under vacuum to yield the final product.

2. Synthesized from 0.239 g of **1** to yield 0.767 g (89%) of **2** as a foam consistent with known material:¹ mp 65–68 °C; ^1H NMR ($\text{DMSO}-d_6$) δ 13.36 (bs, 1 H), 11.28 (bs, 1 H), 8.51 (bs, 1 H), 7.85 (s, 1 H), 7.24 (bs, 10 H), 4.51–4.78 (m, 2 H), 2.93–3.36 (m, 4 H), 1.36 (bs, 18 H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 169.9, 163.0, 157.6, 137.0, 136.5, 132.5, 129.3, 128.2, 126.6, 81.0, 54.6, 53.8, 37.5, 36.4, 27.5; FAB MS m/z = 563 $[\text{M} + \text{H}]^+$. Anal. Calcd for $\text{C}_{31}\text{H}_{38}\text{N}_4\text{O}_6$: C, 66.17; H, 6.81; N, 9.96. Found: C, 66.16; H, 6.77; N, 9.60.

3. Synthesized from 0.400 g of **1** to yield 1.151 g (94%) of **3** as a foam: mp 68–71 °C; ^1H NMR (CDCl_3) δ 12.40 (bs, 1 H), 11.65 (bs, 1 H), 8.15 (bs, 1 H), 7.52 (s, 1 H), 7.26 (s, 10 H), 4.71–5.15 (m, 2 H), 3.73 (s, 6 H), 3.10–3.40 (m, 4 H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 171.5, 163.1, 157.7, 137.2, 136.6, 132.5, 129.2, 128.3, 127.7, 126.7, 54.1, 53.2, 52.2, 52.0, 37.2, 36.0; MS (ES⁺): m/z = 479 $[\text{M} + \text{H}]^+$. Anal. Calcd. for $\text{C}_{25}\text{H}_{26}\text{N}_4\text{O}_6$: C, 62.76; H, 5.48; N, 11.72. Found: C, 62.90; H, 5.41; N, 11.72.

4. Synthesized from 0.458 g of **1** to yield 1.112 g (93%) of **4** as a glassy solid: mp 54–56 °C; ^1H NMR ($\text{DMSO}-d_6$) δ 10.03 (bs, 2 H), 7.90 (s, 1 H), 4.42–4.61 (m, 2 H), 3.66 (s, 6 H), 1.50–1.93 (m, 6 H), 0.85–0.98 (m, 12 H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 172.4, 160.7, 136.6, 130.2, 52.0, 50.4, 24.4, 22.7, 21.2; FAB+ MS m/z = 411 $[\text{M} + \text{H}]^+$. Anal. Calcd. for $\text{C}_{19}\text{H}_{30}\text{N}_4\text{O}_6$: C, 55.60; H, 7.37; N, 13.65. Found: C, 55.51; H, 7.38; N, 13.56.

5. Synthesized from 0.492 g of **1** to yield 1.185 g (99%) of **5** as a sticky foam: ^1H NMR ($\text{DMSO}-d_6$) δ 13.44 (bs, 1 H), 11.14 (d, J = 8.0 Hz, 1 H), 8.37 (d, J = 8.8 Hz, 1 H), 7.92 (s, 1 H), 4.36–4.49 (m, 2 H), 3.68–3.69 (m, 6 H), 2.09–2.28 (m, 2 H), 0.91–1.01 (m, 12 H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 171.6, 171.4, 136.6, 158.0, 136.7, 132.3, 127.8, 57.7, 57.1, 52.1, 51.9, 19.0, 18.1, 17.6; FAB+ MS m/z = 383 $[\text{M} + \text{H}]^+$. Anal. Calcd. for $\text{C}_{17}\text{H}_{26}\text{N}_4\text{O}_6$: C, 53.40; H, 6.85; N, 14.65. Found: C, 53.53; H, 6.98; N, 14.56.

6. Synthesized from 0.576 g of **1** to yield 1.124 g (94%) of **6** as a sticky foam: ^1H NMR ($\text{DMSO}-d_6$) δ 10.1 (bs, 2 H), 7.90 (s, 1 H), 4.55 (p, 2 H), 3.66 (s, 6 H), 1.42 (d, 6 H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 172.6, 160.4, 136.6, 130.3, 52.1, 47.7, 17.1; FAB+ MS m/z = 327 $[\text{M} + \text{H}]^+$. Anal. Calcd. for $\text{C}_{13}\text{H}_{18}\text{N}_4\text{O}_6$: C, 47.85; H, 5.56; N, 17.17. Found: C, 48.08; H, 5.58; N, 17.14.

7. This synthesis has been previously described.² Synthesized from 0.575 g of **1** to yield 0.403 g (33%) of **7** as a crystalline solid following silica gel chromatography and crystallization from CH₂Cl₂/hexanes: mp 159–160 °C; ¹H NMR (DMSO-*d*₆) δ 13.40 (bs, 1 H), 11.20 (bs, 1 H), 9.00 (bs, 1 H), 7.91 (s, 1 H), 4.07–4.18 (m, 2 H), 1.15–1.24 (m, 6 H); ¹³C NMR (DMSO-*d*₆) δ 169.5, 136.7, 60.59, 40.95, 14.08; ES+ MS *m/z* = 327 [M + H]⁺. Anal. Calcd. for C₁₃H₁₈N₄O₆: C, 47.85; H, 5.56; N, 17.17. Found: C, 48.04; H, 5.35; N, 17.03.

8. Synthesized from 0.233 g of **1** to yield 0.512 g (89%) of **8** as a solid: mp 159–160 °C; ¹H NMR (DMSO-*d*₆) δ 13.35 (bs, 1 H), 11.20 (bs, 1 H), 8.90 (bs, 1 H), 7.89 (s, 1 H), 3.96–3.99 (m, 4 H), 1.42 (s, 18 H); ¹³C NMR (DMSO-*d*₆) δ 168.5, 136.5, 80.9, 41.6, 27.7; FAB+ MS *m/z* = 383 [M + H]⁺. Anal. Calcd. for C₁₇H₂₆N₄O₆: C, 53.40; H, 6.85; N, 14.65. Found: C, 53.31; H, 6.82; N, 14.41.

**5,10-Dioxo-5*H*,10*H*-diimidazo{1,5-*a*:1',5'-*d*}pyrazine-1,6-dicarbonyl amino acid esters (9–14).
General Procedures.**

Method A (9, 10). To a dry flask under argon was suspended 1.00 g (3.19 mmol) of **1** in 25 mL of dry THF. To this stirred solution at –78 °C was added 2 molar equiv of amino acid ester hydrochloride followed by 4 molar equiv of diisopropylethylamine over 15 min. The solution was held at –78 °C for 2 h and then stirred overnight at rt. Addition of 2 volume equiv of water yielded a precipitate of crude product that was collected by vacuum filtration and dissolved in 50 mL of CH₂Cl₂. This solution was dried over MgSO₄ and filtered. The final product precipitated upon the addition of hexanes and was collected by vacuum filtration.

Method B (11–14). As for Method A but in CH₂Cl₂ with pyridine as the base, and with the solution held at –78 °C for 30 min. before stirring 1 h at rt. Solids were removed by filtration through Celite and the filtrate was extracted against water (3×). The organic fraction was dried over MgSO₄, filtered, and concentrated. The residue was suspended in boiling EtOAc, stirred for 10 min, and cooled to 0 °C and the product solid collected by vacuum filtration.

9. Synthesized from 0.918 g of **1** with L-phenylalanine *tert*-butyl ester hydrochloride via Method A to yield 0.790 g (40%) of **9** as a solid: mp 179–180 °C (dec); ¹H NMR (DMSO-*d*₆) δ 9.02 (d, *J* = 8.8 Hz, 2 H), 9.00 (s, 2 H), 7.20–7.33 (m, 10 H), 4.64–4.72 (m, 4 H), 3.12–3.19 (m, 4 H), 1.37 (s, 18 H); ¹³C NMR (CDCl₃) δ 169.9, 158.7, 149.5, 143.8, 138.4, 136.9, 129.2, 128.3, 126.6, 120.6, 81.2, 54.4, 36.8, 27.5.

10. Synthesized from 0.917 g of **1** with L-isoleucine *tert*-butyl ester hydrochloride via Method A to yield 1.060 g (59%) of **10** as a solid: mp 191–193 °C (dec); the presence of conformational isomers was evident in the ¹H NMR spectrum; ¹H NMR (DMSO-*d*₆) δ 9.02–9.08 (m, 2 H), 4.36–4.48 (m, 2 H), 1.91–1.98 (m, 2 H), 1.42–1.46 (m, 18 H), 1.26–1.37 (m, 4 H), 0.88–1.00 (m, 12 H); ¹³C NMR (CDCl₃) δ 169.9, 158.8, 150.4, 144.2, 138.9, 120.3, 81.3, 57.1, 36.9, 27.7, 24.9, 15.5, 11.4.

11. This synthesis has been previously described.² Briefly, the compound was synthesized from 2.039 g of **1** with L-valine benzyl ester hydrochloride via Method B to yield 3.118 g (73%) of **11** as a solid consistent with known material: mp 183–186 °C; ¹H NMR (CDCl₃) δ 8.78 (d, *J* = 8.8 Hz, 2 H), 8.65 (s, 2 H), 7.33–7.38 (m, 10 H), 5.16–5.25 (m, 4 H), 4.86–4.89 (m, 2 H), 2.34–2.38 (m, 2 H), 0.98–1.02 (m, 12 H); ¹³C NMR (CDCl₃) δ 171.5, 158.1, 149.8, 147.1, 138.9, 135.5, 128.9, 128.8, 119.2, 67.6, 58.1, 31.6, 19.4, 17.9.

12. Synthesized from 1.017 g of **1** with L-valine ethyl ester hydrochloride via Method B to yield 1.342 g (77%) of **12** as a solid: mp 208–212 °C (dec); ¹H NMR (CDCl₃) δ 8.71 (s, 2 H), 8.69 (s, 2 H), 4.82–4.85 (m, 4 H), 4.22–4.30 (m, 4 H), 2.33–2.41 (m, 2 H), 1.30–1.34 (m, 6 H), 1.04–1.06 (m, 12 H); ¹³C NMR (CDCl₃) δ 171.4, 157.9, 149.5, 147.1, 138.8, 118.9, 61.7, 57.9, 31.5, 19.2, 17.9, 14.4; FAB MS *m/z* 531 [M + H]⁺.

13. Synthesized from 1.858 g of **1** with L-valine *tert*-butyl ester hydrochloride via Method B to yield 2.769 g (80%) of **13** as a solid: mp 177–180 °C; ¹H NMR (CDCl₃) δ 8.76 (d, *J* = 8.8 Hz, 2 H), 8.70 (s, 2 H), 4.76 (dd, *J* = 8.8 Hz, *J* = 8.8 Hz, m, 2 H), 2.32–2.36 (m, 2 H), 1.50 (s, 18 H), 1.04 (d, *J* = 6.8 Hz, 12 H); ¹³C NMR (CDCl₃) δ 170.8, 158.0, 149.7, 147.5, 139.0, 119.0, 82.7, 58.4, 31.9, 28.4, 19.4, 18.0.

14. Synthesized from 0.975 g of **1** with L-leucine benzyl ester hydrochloride via Method B to yield 1.144 g (54%) of **14** as a solid. mp 140–141 °C; ¹H NMR (CDCl₃) δ 8.65 (s, 2 H), 8.56 (d, *J* = 8.4 Hz, 2 H), 7.37 (bs, 10 H), 5.21 (s, 4 H), 4.92–4.97 (m, 2 H), 1.73–1.85 (m, 6 H), 0.96–0.99 (m, 12 H); ¹³C NMR (CDCl₃) δ 172.5, 157.9, 149.4, 147.1, 138.8, 135.6, 129.0, 128.8, 128.7, 119.2, 67.7, 51.8, 41.7, 25.3, 23.2, 22.3; FAB MS *m/z* 683 [*M* + *H*]⁺.

Amino acid Ester-substituted bis-imidazole-4,5-dicarboxamides (15–31). General Procedures.

Method C. To a dry flask under argon was added 1 molar equiv of an amino acid ester-substituted pyrazine in 5 mL of dry CH₂Cl₂. To this stirred solution at rt was added 1 molar equiv of the appropriate aliphatic diamine. The solution was stirred for 2 h at rt before adding 20 mL of MeOH. The solution was concentrated to approximately one-third the volume and the resulting precipitate collected by vacuum filtration. The solid was further dried under high vacuum.

Method D. The reaction was run as described for Method C. The solution was stirred for 2 h before extracting with 0.1 M HCl, water, 0.1 M NaOH, and water. The organic layer was dried over MgSO₄, filtered, and concentrated under vacuum to yield a viscous oil that solidified under high vacuum.

Method E. The reaction was run as described for Method C. The solution was stirred for 2 h before concentration under vacuum to a crude solid that was dissolved in 10 mL of boiling MeOH. Addition of 2 mL of water was followed by cooling to rt with stirring. After 3 h, the precipitated solids were collected and washed with cold MeOH and the process of dissolving in hot MeOH, adding water, and then stirring at rt was repeated. The final precipitate was washed with cold MeOH and dried under vacuum.

Method F. The reaction was run as described for Method C. The solution was stirred for 4 h at rt. The solution was extracted with 10% citric acid, 1 M NaHCO₃, and brine, dried over MgSO₄, filtered, and concentrated under vacuum to yield a crude product that was further purified by either precipitation or column chromatography.

Method G. The reaction was run as described for Method C. The solution was stirred for 2 h at rt before the solids were collected by filtration and washed with a 2 mL portion of CH₂Cl₂. To the filtrate was added an equal volume of hexane to further precipitate the product solid.

Method H. To a dry flask under nitrogen was added 1 molar equiv of an amino acid substituted pyrazine in 2 mL of dry CH₂Cl₂/THF (3:1). To this stirred solution at rt was added 1 molar equiv of ethylene glycol. The solution was refluxed for 20 h before the solids were collected by filtration and washed with a 2 mL portion of CH₂Cl₂ before drying under vacuum.

Method I. To a dry flask under argon was added the appropriate deprotected diamine-linked diamino acid trifluoroacetate salt in 25 mL dry THF. To this stirred solution was added 1 molar equiv of the appropriate amino acid substituted pyrazine followed by cooling to –78 °C and the dropwise addition of a THF solution containing 2 molar equiv of diisopropylethylamine. The ice bath was removed after 5 min, and the solution was stirred for 18 h at rt. The THF was removed under vacuum, and the residues were dissolved in EtOAc. The solution was extracted with 1 M HCl, 1 M NaOH, and brine, dried over MgSO₄, filtered, and concentrated under vacuum to yield the desired product.

- 15.** Synthesized from 0.101 g of **11** via Method C to yield 52 mg (47%) of **15** as a solid: mp 230–231 °C; ¹H NMR (DMSO-*d*₆) δ 13.24 (bs, 2 H), 11.54 (bs, 2 H), 8.85 (bs, 2 H), 7.83 (s, 2 H), 7.29–7.38 (m, 10 H), 5.12–5.19 (s, 4 H), 4.40–4.43 (m, 2 H), 3.48–3.56 (m, 4 H), 2.14–2.22 (m, 2 H), 0.89–0.91 (d, *J* = 7.2 Hz, 12 H); the carbonyl resonances were broad in the ¹³C NMR spectra; the ethylenediamine signals were masked and unobserved by the DMSO-*d*₆ signals; ¹³C NMR (DMSO-*d*₆) δ 171.0, 163.7, 158.4, 136.2, 135.9, 133.2, 128.4, 128.0, 127.9, 65.9, 57.7, 30.0, 19.0, 17.6; FAB MS *m/z* 715 [M + H]⁺.
- 16.** Synthesized from 0.102 g of **11** via Method D to yield 82 mg (69%) of **16** as a sticky solid. The imidazole and amide NHs were broad and conformationally averaged in the ¹H NMR spectrum: ¹H NMR (CDCl₃) δ 7.29–7.39 (m, 12 H), 5.16–5.28 (m, 4 H), 4.61–4.78 (m, 2 H), 3.46–3.60 (m, 4 H), 2.33–2.41 (m, 2 H), 1.77–1.84 (m, 4 H), 0.98–1.04 (m, 12 H); the carbonyl resonances were broad in the ¹³C NMR spectra; ¹³C NMR (CDCl₃) δ 171.3, ~160, 135.8, 128.9, 128.7, 67.3, 58.5, 39.8, 31.3, 27.2, 19.6, 18.3; FAB MS *m/z* 743 [M + H]⁺.
- 17.** Synthesized from 0.106 g of **11** via Method D to yield 85 mg (71%) of **17** as a solid: mp 185–187 °C; ¹H NMR (DMSO-*d*₆) δ 13.29 (bs, 2 H), 11.59 (bs, 2 H), 8.89 (bs, 2 H), 7.85 (s, 2 H), 7.28–7.37 (m, 10 H), 5.12–5.33 (m, 4 H), 4.42–4.44 (m, 2 H), 3.33–3.36 (m, 4 H), 2.17–2.23 (m, 2 H), 1.73–1.80 (m, 2 H), 0.93 (d, *J* = 6.8 Hz, 12 H); the carbonyl resonances were broad in the ¹³C NMR spectra; ¹³C NMR (CDCl₃) δ 171.0, 162.9, 158.9, 136.3, 135.9, 132.9, 128.4, 128.1, 127.9, 65.9, 57.8, 36.1, 30.0, 29.2, 19.1, 17.7; FAB MS *m/z* 729 [M + H]⁺.
- 18.** Synthesized from 0.100 g of **11** via Method C to yield 79 mg (67%) of **18** as a solid: mp 153–154 °C; ¹H NMR (DMSO-*d*₆) δ 13.22 (bs, 2 H), 11.62 (bs, 2 H), 8.68 (bs, 2 H), 7.84 (s, 2 H), 7.29–7.38 (m, 10 H), 5.12–5.19 (m, 4 H), 4.42–4.45 (m, 2 H), 3.26–3.44 (m, 4 H), 2.22–2.33 (m, 2 H), 1.50–1.52 (m, 4 H), 1.23–1.32 (m, 4 H), 0.93 (d, *J* = 6.8 Hz, 12 H); the carbonyl resonances were broad in the ¹³C NMR spectra; ¹³C NMR (CDCl₃) δ 171.0, ~160, 136.3, 135.9, 128.4, 128.1, 127.9, 66.0, 57.7, 57.6, 30.0, 28.9, 26.1, 19.0, 17.7; FAB MS *m/z* 771 [M + H]⁺.
- 19.** Synthesized from 0.101 g of **9** via Method E to yield 87 mg (73%) of **19** as a solid: mp 147–149 °C; ¹H NMR (CDCl₃) δ 13.24 (bs, 2 H), 11.66 (bs, 2 H), 8.63 (bs, 2 H), 7.81 (s, 2 H), 7.18–7.24 (m, 10 H), 4.58–4.61 (m, 2 H), 3.28–3.32 (m, 4 H), 3.08–3.16 (m, 4 H), 1.46–1.60 (m, 4 H), 1.32 (s, 18 H); the carbonyl resonances were unobserved in the ¹³C NMR spectra; ¹³C NMR (DMSO-*d*₆) δ 170.2, 136.7, 129.8, 128.8, 127.3, 40.2, 38.7, 29.1, 28.3, 26.7; FAB MS *m/z* 800 [M + H]⁺.
- 20.** Synthesized from 0.109 g of **11** via Method G to yield 73 mg (49%) of **20** as a solid: mp 184–188 °C; ¹H NMR (DMSO-*d*₆) δ 12.69 (bs, 2 H), 9.19 (bs, 2 H), 7.65 (s, 2 H), 7.29–7.39 (m, 10 H), 5.11–5.14 (m, 4 H), 4.36–4.53 (m, 2 H), 2.84–2.89 (m, 8 H), 2.16–2.33 (m, 2 H), 1.53–1.58 (m, 8 H), 1.24–1.33 (m, 8 H), 0.93–0.95 (m, 12 H), 0.84 (t, *J* = 7.2 Hz, 6 H); the carbonyl resonances were broad in the ¹³C NMR spectra; ¹³C NMR (DMSO-*d*₆) δ 171.5, ~162, ~161, 136.1, 135.0, 128.4, 128.0, 127.8, 65.6, 58.2, 46.5, 29.9, 27.5, 25.3, 25.1, 19.3, 19.2, 17.9, 13.5; FAB MS *m/z* 453 [M + H + Na]⁺².
- 21.** Synthesized from 0.256 g of **11** via Method F to yield 148 mg (49%) of **21** as a solid: mp 181–182 °C; ¹H NMR (CDCl₃) δ 13.34 (s, 2 H), 10.38 (s, 2 H), 7.86 (s, 2 H), 7.25–7.36 (m, 10 H), 5.13–5.19 (m, 4 H), 4.41–4.45 (m, 2 H), 3.94–4.00 (m, 1 H), 3.61–3.81 (m, 3 H), 3.49–3.56 (m, 4 H), 2.17–2.21 (m, 2 H), 1.12–1.26 (m, 4 H), 0.92–0.96 (m, 12 H); the carbonyl resonances and the ethylenediamine resonances show multiple signals in the ¹³C NMR spectra; ¹³C NMR (CDCl₃) δ 171.0, 165.5, 165.4, 165.2, 165.1, 158.8, 158.7, 135.9, 134.4, 134.3, 128.4, 128.1, 128.0, 66.0, 57.6, 47.2, 45.6, 45.2, 44.7, 44.4, 43.6, 42.1, 41.6, 30.0, 29.9, 19.0, 17.4, 17.2, 14.3, 14.2; FAB MS *m/z* 771 [M + H]⁺.

22. Synthesized from 0.504 g of **13** via a modified version of Method F to yield 0.256 g (42%) of **22** as a solid. The modification was to stir the solution at $-60\text{ }^{\circ}\text{C}$ for 2 h and then allowing it to warm to rt prior to extraction. The crude product was purified by silica gel column chromatography with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (98.5:1.5) as the eluant: mp $192\text{--}194\text{ }^{\circ}\text{C}$; conformational isomers were evident in the ^1H NMR spectrum; ^1H NMR ($\text{DMSO-}d_6$) δ 13.30 (bs, 2 H), 10.14–10.20 (m, 2 H), 7.83–7.88 (m, 2 H), 4.23–4.26 (m, 2 H), 3.47–3.99 (m, 8 H), 2.12–2.15 (m, 2 H), 1.40–1.41 (m, 18 H), 1.15–1.29 (m, 6 H), 0.92–0.97 (m, 12 H); ^{13}C NMR ($\text{DMSO-}d_6$) δ 170.1, 165.2, 158.6, 135.7, 134.2, 128.4, 80.7, 58.0, 47.2, 44.4, 30.1, 29.1, 27.6, 26.1, 19.2, 17.4, 14.2, 12.2; FAB MS m/z 703 $[\text{M} + \text{H}]^+$.

23. Synthesized from 0.504 g of **12** via a modified version of Method F to yield 0.173 g (28%) of **23** as a solid. The modification was to stir the solution at $-60\text{ }^{\circ}\text{C}$ for 2 h and then allowing it to warm to rt prior to extraction. The crude product was purified by silica gel column chromatography with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (98.5:1.5) as the eluant: mp $201\text{--}203\text{ }^{\circ}\text{C}$; ^1H NMR ($\text{DMSO-}d_6$) δ 13.27 (bs, 2 H), 10.23 (bs, 2 H), 7.82–7.84 (m, 2 H), 4.32–4.35 (m, 2 H), 4.09–4.14 (m, 4 H), 3.47–3.94 (m, 8 H), 2.11–2.18 (m, 2 H), 1.13–1.25 (m, 6 H), 0.93–0.95 (m, 12 H); the carbonyl resonances were broad in the ^{13}C NMR spectra; ^{13}C NMR ($\text{DMSO-}d_6$) δ 171.7, 164.9, 159.8, 135.0, 129.5, 128.9, 61.5, 59.1, 46.0, 42.7, 30.9, 19.7, 18.2, 14.6, 12.9; FAB MS m/z 647 $[\text{M} + \text{H}]^+$.

24. Synthesized from 1.028 g of **11** via a modified Method D to yield 0.983 g (85%) of **24** as a solid. The modification was to suspend the crude solid from extraction in boiling ethyl acetate for 30 min, cooling to $0\text{ }^{\circ}\text{C}$, filtering the solid, and washing the solid with cold ethyl acetate before drying under vacuum: mp $210\text{--}211\text{ }^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 13.33 (bs, 2 H), 10.25 (bs, 2 H), 7.85–7.89 (m, 2 H), 7.32–7.36 (m, 10 H), 5.15–5.19 (m, 4 H), 4.41–4.43 (m, 2 H), 3.71–4.03 (m, 8 H), 2.11–2.19 (m, 2 H), 0.92 (bs, 12 H); ^{13}C NMR (CDCl_3) δ 171.1, 163.7, 159.5, 135.5, 134.7, 133.6, 129.5, 128.5, 128.3, 128.2, 66.8, 60.4, 58.7, 52.9, 48.0, 47.3, 43.7, 43.0, 30.6, 19.3, 17.8, 14.1; FAB MS m/z 741 $[\text{M} + \text{H}]^+$.

25. Synthesized from 0.501 g of **14** via a modified version of Method F to yield 0.344 g (59%) of **25** as a solid. The modification was to stir the solution at $-60\text{ }^{\circ}\text{C}$ for 2 h and then allowing it to warm to rt prior to extraction. The crude product was purified by silica gel column chromatography with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (98.5:1.5) as the eluant: mp $171\text{--}173\text{ }^{\circ}\text{C}$; ^1H NMR ($\text{DMSO-}d_6$) δ 13.35 (bs, 2 H), 10.24 (bs, 2 H), 7.82–7.84 (m, 2 H), 7.13–7.37 (m, 10 H), 5.12–5.16 (m, 4 H), 4.49–4.58 (m, 2 H), 3.40–3.68 (m, 8 H), 1.58–1.74 (m, 6 H), 1.09–1.17 (m, 6 H), 0.85–0.90 (m, 12 H); the carbonyl resonances were broad in the ^{13}C NMR spectra; ^{13}C NMR ($\text{DMSO-}d_6$) δ 171.9, 171.8, 162.5, 158.6, 135.9, 128.4, 128.0, 127.8, 127.7, 66.0, 50.6, 47.0, 45.5, 44.7, 44.3, 24.4, 22.6, 21.5, 14.1, 12.3; FAB MS m/z 800 $[\text{M} + \text{H}]^+$.

26. Synthesized from 0.042 g of **25** by catalytic hydrogenation. To a solution of **25** in 10 mL of MeOH was added 40 mg of a 10% Pd/C catalyst under nitrogen. The mixture was shaken with 20 psi H_2 for 1 h. The solution was filtered through Celite to remove the catalyst and the MeOH was removed under vacuum to quantitatively yield **26** as a glass: mp $123\text{--}130\text{ }^{\circ}\text{C}$; ^1H NMR ($\text{DMSO-}d_6$) δ 13.08 (bs, 2 H), 12.72 (bs, 2 H), 19.92 (bs, 2 H), 7.81–7.88 (m, 2 H), 4.37–4.45 (m, 2 H), 3.17–3.88 (m, 8 H), 1.60 (bs, 6 H), 1.11–1.21 (m, 6 H), 0.87–0.90 (m, 12 H).

27. Synthesized from **11** via Method H to yield 0.069 g (49%) of **27** as a solid: mp $201\text{--}202\text{ }^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 13.53 (bs, 2 H), 10.17 (bs, 2 H), 7.85 (m, 2 H), 7.31–7.36 (m, 10 H), 5.13–5.20 (m, 4 H), 4.61–4.68 (m, 4 H), 4.32–4.34 (m, 2 H), 2.13–2.21 (m, 2 H), 0.86–0.90 (m, 12 H); ^{13}C NMR (CDCl_3) δ 170.7, 165.1, 157.7, 137.3, 135.8, 131.0, 129.5, 128.4, 128.1, 128.0, 66.1, 63.3, 57.6, 30.0, 25.1, 21.8, 18.9, 17.4, 10.9; FAB MS m/z 717 $[\text{M} + \text{H}]^+$.

28. Synthesized from 0.099 g of deprotected diamine-linked diamino acid trifluoroacetate salt and 0.109 g of **9** via Method I to yield 77 mg (46%) of **28** as a sticky glass. There was evidence of conformational isomers in the ^1H NMR spectrum: ^1H NMR ($\text{DMSO}-d_6$) δ 12.80 (bs, 2 H), 10.50 (bs, 2 H), 8.27 (bs, 2 H), 7.81 (s, 2 H), 7.16–7.24 (m, 20 H), 4.63–4.69 (m, 4 H), 3.60–3.80 (m, 4 H), 2.93–3.20 (m, 8 H), 1.34 (s, 18 H).

29. Synthesized from 0.100 g of deprotected diamine-linked diamino acid trifluoroacetate salt and 0.109 g of **9** via Method I to yield 69 mg (41%) of **29** as a sticky glass: There was evidence of conformational isomers in the ^1H NMR spectrum: ^1H NMR ($\text{DMSO}-d_6$) δ 13.30 (bs, 1 H), 13.22 (bs, 1 H), 11.30–11.31 (m, 1 H), 11.12–11.13 (m, 1 H), 8.41–8.43 (m, 1 H), 8.33–8.35 (m, 1 H), 8.18–8.22 (m, 1 H), 8.05–8.10 (m, 1 H), 7.80–7.83 (m, 1 H), 7.68–7.70 (m, 1 H), 7.10–7.27 (m, 20 H), 4.74–4.75 (m, 2 H), 4.56–4.59 (m, 2 H), 4.14 (bs, 2 H), 3.20–3.22 (m, 2 H), 2.78–3.20 (m, 8 H), 1.20–1.50 (m, 18 H), 0.85–0.89 (m, 2H).

30. Synthesized from 0.045 g of deprotected diamine-linked diamino acid trifluoroacetate salt and 0.045 g of **10** via Method I to yield 34 mg (45%) of **30** as a glass: mp 132–138 °C; there was evidence of conformational isomers in the ^1H NMR spectrum; ^1H NMR ($\text{DMSO}-d_6$) δ 13.28 (bs, 2 H), 11.11–11.13 (m, 2 H), 8.10–8.40 (m, 4 H), 7.82 (s, 2 H), 7.14–7.25 (m, 10 H), 4.75–4.77 (m, 1 H), 4.45–4.60 (m, 2 H), 4.29–4.32 (m, 1 H), 2.80–3.20 (m, 8 H), 1.80–1.90 (m, 2 H), 1.38–1.48 (m, 18 H), 1.18–1.30 (m, 4 H), 0.85–0.96 (m, 12 H).

31. Synthesized from 0.096 g of deprotected diamine-linked diamino acid trifluoroacetate salt and 0.096 g of **10** via Method I to yield 102 mg (61%) of **31** as a sticky glass. There was evidence of conformational isomers in the ^1H NMR spectrum: ^1H NMR ($\text{DMSO}-d_6$) δ 13.29 (bs, 2 H), 11.13 (bs, 2 H), 8.10–8.40 (m, 4 H), 7.83 (s, 2 H), 7.10–7.30 (m, 10 H), 4.60–4.80 (m, 2 H), 4.30–4.55 (m, 2 H), 2.95–3.15 (m, 8 H), 1.80–2.00 (m, 2 H), 1.20–1.50 (m, 28 H), 0.90 (bs, 12 H).

Synthesis of diamine-linked diamino acids. General Method. To a dry round-bottom flask under argon was added a Boc-protected amino acid in 5 mL of dry CH_2Cl_2 . To this stirred solution at 0 °C was added a water-soluble carbodiimide all at once followed by the dropwise addition of the liquid diamine. The solution was stirred for 12 h at rt before extracting with 10% citric acid, 1 M NaHCO_3 , and brine. The organic fraction was dried over MgSO_4 , filtered, and concentrated under vacuum to yield a crude product that was used without further purification.

Ethylenediamine-linked Boc-Phe-OH. Synthesized from 4.782 g of Boc-(*S*)-phenylalanine and 0.60 mL of ethylenediamine by the general method to yield 1.143 g (23%) of crude product: ^1H NMR (CDCl_3) δ 7.12–7.27 (m, 10 H), 5.90–6.08 (bs, 2 H), 5.15–5.25 (m, 2 H), 4.10–4.20 (m, 2 H), 2.88–3.20 (m, 8 H), 1.25–1.45 (m, 18 H); ^{13}C NMR (CDCl_3) δ 172.2, 155.5, 137.0, 129.7, 128.9, 127.2, 80.5, 56.4, 39.3, 28.6.

1,3-Propanediamine-linked Boc-Phe-OH. Synthesized from 2.000 g of Boc-(*S*)-phenylalanine and 0.32 mL of 1,3-propanediamine by the general method to yield 1.121 g (52%) of crude product: ^1H NMR ($\text{DMSO}-d_6$) δ 7.85 (bs, 2 H), 7.15–7.30 (m, 10 H), 6.85–6.95 (m, 2 H), 4.02–4.12 (m, 4 H), 2.70–3.05 (m, 6 H), 1.40–1.50 (m, 2 H), 1.20–1.33 (m, 18 H), 1.00–1.10 (m, 2 H); ^{13}C NMR (CDCl_3) δ 172.1, 155.9, 136.9, 129.6, 128.9, 127.1, 80.5, 77.5, 56.4, 38.7, 36.6, 28.5.

1,4-Butanediamine-linked Boc-Phe-OH. Synthesized from 2.020 g of Boc-(*S*)-phenylalanine and 0.38 mL of 1,4-butanediamine by the general method to yield 1.594 g (73%) of crude product: ^1H NMR (CDCl_3) δ 7.20–7.30 (m, 10 H), 6.45–6.55 (bs, 2 H), 5.25–5.45 (m, 2 H), 4.30–4.45 (m, 2 H), 3.15–3.25 (m, 2 H), 2.85–3.15 (m, 6 H), 1.15–1.45 (m, 22 H); ^{13}C NMR (CDCl_3) δ 171.9, 155.9, 137.1, 129.6, 128.8, 127.0, 80.4, 77.5, 56.3, 39.0, 28.5, 26.3.

Deprotection of the diamine-linked diamino acids. General Method. To a dry round-bottom flask under argon was added a diamine-linked diamino acid in dry dichloromethane. To this stirred solution at 0 °C was added trifluoroacetic acid dropwise. The solution was stirred for 2 h at rt before evaporating the solvent and acid under vacuum. The residues were dissolved in dichloromethane and concentrated under vacuum three separate times to yield an oil that was used without further purification.

Figure S1. ^1H NMR spectrum of **2** in $\text{DMSO}-d_6$.

2

13C OBSERVE
Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature
GEMINI-200 "gemin11"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 29.8 degrees
Acq. time 1.450 sec
Width 12500.0 Hz
17488 repetitions
OBSERVE C13, 50.2845991 MHz
DECOUPLE H1, 199.9795007 MHz
Power 39.00
continuously on
-VALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 32 hr, 55 min, 39 sec

Figure S2. ¹³C NMR spectrum of **2** in DMSO-*d*₆.

Figure S3. ^1H NMR spectrum of **3** in CDCl_3 .

3

Figure S4. ¹³C NMR spectrum of **3** in CDCl₃.

4

Figure S5. ¹H NMR spectrum of **4** in CDCl₃.

Figure S6. ^{13}C NMR spectrum of **4** in $\text{DMSO-}d_6$.

Figure S7. ^1H NMR spectrum of **5** in $\text{DMSO-}d_6$.

5

13C OBSERVE
Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature
GEMINI-200 "geminil"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 29.8 degrees
Acq. time 1.438 sec
Width 12500.0 Hz
5776 repetitions
OBSERVE C13, 50.2845987 MHz
DECUPLE H1, 199.9795087 MHz
Power 38 dB
Continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 32 hr, 55 min, 39 sec

Figure S8. ^{13}C NMR spectrum of **5** in $\text{DMSO}-d_6$.

Figure S9. ¹H NMR spectrum of **6** in DMSO-*d*₆.

Figure S10. ^{13}C NMR spectrum of **6** in $\text{DMSO-}d_6$.

Figure S11. ¹H NMR spectrum of **7** in DMSO-*d*₆.

13C OBSERVE
Pulse Sequence
Solvent: DMSO
Ambient temperature
GEMINI-200 "geminii"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 29.8 degrees
Acq. time 1.498 sec
Width 12500.0 Hz
16944 repetitions
OBSERVE C13, 50.2845980 MHz
DECOUPLE H1, 199.9795087 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 32 hr, 55 min, 39 sec

Figure S12. ^{13}C NMR spectrum of **7** in $\text{DMSO}-d_6$.

Figure S13. ^1H NMR spectrum of **8** in $\text{DMSO-}d_6$.

Figure S14. ¹³C NMR spectrum of **8** in DMSO-*d*₆.

Figure S15. ^1H NMR spectrum of **9** in $\text{DMSO-}d_6$.

Figure S16. ^{13}C NMR spectrum of **9** in $\text{DMSO}-d_6$.

Figure S17. ^1H NMR spectrum of **10** in $\text{DMSO-}d_6$.

13C OBSERVE
Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature
File: d136a.monophotBu#3-C13
GEMINI-200 "geminii"
PULSE SEQUENCE
Pulse 29.8 degrees
Acq. time 1.458 sec
Width 12500.0 Hz
24000 repetitions
OBSERVE C13, 50.2845995 MHz
DECOUPLE H1, 199.9795087 MHz
Power 30 dB
continuously on
VALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 2 hr, 34 min, 29 sec

Figure S18. ^{13}C NMR spectrum of **10** in $\text{DMSO-}d_6$.

Figure S19. ¹H NMR spectrum of **11** in CDCl₃.

Figure S20. ^{13}C NMR spectrum of **11** in CDCl_3 .

12

Figure S21. ¹H NMR spectrum of **12** in CDCl₃.

Figure S22. ¹³C NMR spectrum of **12** in CDCl₃.

Figure S24. ¹³C NMR spectrum of **13** in CDCl₃.

Figure S25. ¹H NMR spectrum of **14** in CDCl₃.

Figure S26. ¹³C NMR spectrum of **14** in CDCl₃.

Figure S27. ^1H NMR spectrum of **15** in $\text{DMSO-}d_6$.

Figure S28. ^{13}C NMR spectrum of **15** in $\text{DMSO-}d_6$.

STANDARD 1H OBSERVE

Pulse Sequence: s2pul
 Solvent: DMSO
 Ambient temperature
 UNITYplus-400 "pollux"
 PULSE SEQUENCE
 Relax. delay 1.000 sec
 Pulse 31.5 degrees
 Acq. time 2.000 sec
 Width 8000.0 Hz
 386 repetitions
 OBSERVE H1, 399.8430728 MHz
 DATA PROCESSING
 FT size 32768
 Total time 51 min, 23 sec

Figure S29. ^1H NMR spectrum of **16** in $\text{DMSO-}d_6$.

Figure S30. ¹³C NMR spectrum of **16** in CDCl₃.

Figure S31. ¹H NMR spectrum of **17** in DMSO-*d*₆.

Figure S32. ^{13}C NMR spectrum of **17** in DMSO- d_6 .

Figure S33. ^1H NMR spectrum of **18** in $\text{DMSO}-d_6$.

13C OBSERVE
Pulse Sequence: s2pul
Solvent: ~~acetone~~ **DMSO-*d*₆**
Ambient temperature
GEMINI-200 "gemin1"
PULSE SEQUENCE
Relax. delay 1.500 sec
Pulse 60.0 degrees
Acq. time 1.498 sec
Width 12500.0 Hz
42864 repetitions
OBSERVE C13, 50.2846652 MHz
DECOUPLE H1, 199.9785588 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 28 hr, 5 min, 23 sec

Figure S34. ^{13}C NMR spectrum of **18** in $\text{DMSO-}d_6$.

Figure S35. ^1H NMR spectrum of **19** in $\text{DMSO}-d_6$.

Figure S36. ¹³C NMR spectrum of **19** in CDCl₃.

Figure S37. ^1H NMR spectrum of **20** in $\text{DMSO-}d_6$.

Figure S38. ¹³C NMR spectrum of **20** in DMSO-*d*₆.

STANDARD 1H OBSERVE

Pulse Sequence: s2pul
 Solvent: DMSO
 Ambient temperature
 UNITYplus-400 "pollux"
 PULSE SEQUENCE
 Relax. delay 1.000 sec
 Pulse 31.5 degrees
 Acq. time 2.000 sec
 Width 8000.0 Hz
 64 repetitions
 OBSERVE H1, 399.8430709 MHz
 DATA PROCESSING
 FT size 32768
 Total time 3 min, 12 sec

Figure S39. ^1H NMR spectrum of **21** in $\text{DMSO-}d_6$.

Figure S40. ^{13}C NMR spectrum of **21** in $\text{DMSO-}d_6$.

22

Figure S41. ^1H NMR spectrum of **22** in $\text{DMSO}-d_6$.

22

13C OBSERVE
Pulse Sequence: szpul
Solvent: DMSO
Ambient temperature
File: al-2-261
GEMINI-200 "geminii"
PULSE SEQUENCE
Relax. delay 2.500 sec
Pulse 60.0 degrees
Acq. time 1.430 sec
Width 12500.0 Hz
21584 repetitions
OBSERVE C13, 50.2838700 MHz
DECOUPLE H1, 199.9795087 MHz
Power 30 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 17 hr, 54 min, 9 sec

Figure S42. ^{13}C NMR spectrum of **22** in $\text{DMSO-}d_6$.

23

Figure S43. ^1H NMR spectrum of **23** in $\text{DMSO-}d_6$.

23

13C OBSERVE
Pulse Sequence: szpul
Solvent: CDCl₃
Ambient temperature
File: al-2-263
GEMINI-200 "gemin1"
PULSE SEQUENCE
Relax. delay 2.000 sec
Pulse 60.0 degrees
Acq. time 1.498 sec
Width 12500.0 Hz
25824 repetitions
OBSERVE C13, 50.2843663 MHz
DECOUPLE H1, 199.9785588 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 29 hr, 8 min, 19 sec

Figure S44. ¹³C NMR spectrum of **23** in CDCl₃.

Figure S45. ^1H NMR spectrum of **24** in $\text{DMSO}-d_6$.

24

13C OBSERVE
Pulse Sequence: zgpg30
Solvent: DMSO
Ambient temperature
File: al-2-255
GEMINI-200 "geminil"
PULSE SEQUENCE
Relax. delay 2.500 sec
Pulse 60.0 degrees
Acq. time 1.498 sec
Width 12500.0 Hz
17500 repetitions
OBSERVE C13, 50.2645930 MHz
DECOUPLE H1, 199.9795007 MHz
Power 30 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 17 hr, 54 min, 9 sec

Figure S46. ¹³C NMR spectrum of **24** in DMSO-*d*₆.

25

Figure S47. ^1H NMR spectrum of **25** in $\text{DMSO-}d_6$.

26

Figure S48. ¹H NMR spectrum of **26** in DMSO-*d*₆.

Figure S49. ¹³C NMR spectrum of **26** in CDCl₃.

Figure S50. ¹H NMR spectrum of **27** in DMSO-*d*₆.

Figure S51. ^{13}C NMR spectrum of **27** in $\text{DMSO-}d_6$.

28

Figure S52. ¹H NMR spectrum of **28** in CDCl₃.

28

13C OBSERVE
Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature
File: h156a-013
GEMINI-200 "geminil"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 25.5 degrees
Acq. time 1.498 sec
Width 12500.0 Hz
11116 repetitions
OBSERVE C13, 50.2845972 MHz
DECOUPLE H1, 199.8795007 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 45 hr, 44 min, 24 sec

Figure S53. ¹³C NMR spectrum of **28** in DMSO-*d*₆.

29

Figure S55. ^{13}C NMR spectrum of **29** in $\text{DMSO-}d_6$.

30

STANDARD 1H OBSERVE

Pulse Sequence: s2pu1
 Solvent: CDCl3
 Ambient temperature
 UNITYplus-400 "pollux1"
 PULSE SEQUENCE
 Relax. delay 1.000 sec
 Pulse 30.0 degrees
 Acq. time 3.840 sec
 Width 8000.0 Hz
 72 repetitions
 OBSERVE H1, 399.8509442 MHz
 DATA PROCESSING
 Line broadening 0.3 Hz
 FT size 32768
 Total time 10 min, 20 sec

Figure S56. ^1H NMR spectrum of **30** in CDCl_3 .

30

13C OBSERVE
Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature
File: 0152
GEMINI-200 "gemin1"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 29.0 degrees
Acq. time 1.498 sec
Width 12500.0 Hz
180000 repetitions
OBSERVE C13, 50.2845987 MHz
DECOUPLE H1, 199.9795087 MHz
Power 30 dB
continuously on
VALT2-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
F1 size 65536
Total time 32 hr, 55 min, 39 sec

Figure S57. ^{13}C NMR spectrum of **30** in $\text{DMSO}-d_6$.

31

STANDARD 1H OBSERVE

Pulse Sequence: s2pu1
 Solvent: CDCl3
 Ambient temperature
 UNITYplus-400 "pollux1"
 PULSE SEQUENCE
 Relax. delay 1.000 sec
 Pulse 30.0 degrees
 Acq. time 3.840 sec
 Width 8000.0 Hz
 64 repetitions
 OBSERVE H1, 399.8509447 MHz
 DATA PROCESSING
 Line broadening 0.3 Hz
 FT size 32768
 Total time 10 min, 20 sec

Figure S58. ^1H NMR spectrum of **31** in CDCl_3 .

31

13C OBSERVE
Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature
GEMINI-230 "geminii"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 29.8 degrees
Acq. time 1.455 sec
Width 12500.0 Hz
250000 repetitions
OBSERVE C13, 50.2845372 MHz
DECOUPLE H1, 100.9795087 MHz
Power 30.00
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 45 hr, 44 min, 24 sec

Figure S59. ^{13}C NMR spectrum of **31** in $\text{DMSO-}d_6$.

Figure S60. ^1H NMR spectrum of the amide region for *N,N'*-dimethylimidazole-4,5-dicarboxamide in H_2O at select pH values.

HPLC Analysis of **2-8**, **15-19**, and **21-31**.

Method: Samples were prepared at a concentration of 1mg/mL in MeOH. Five microliters of the sample was eluted on a C18-RP column with a gradient of acetonitrile/water (1 mL/min flow rate). Compounds were detected at 218 nm (and 254 for one analysis shown below). The gradient used was as follows:

Time (min)	% CH ₃ CN	% H ₂ O
0	50	50
10	95	5
12	100	0
14	100	0
15	50	50

The suitability of this method for the analysis of these compounds was illustrated by a coinjection of homologs **15** and **16** with baseline separation (see below). The traces of these compounds injected separately as observed at 254 nm is included later in the supplementary information.

Figure S61. HPLC trace from the coinjection of compounds **15** and **16**, showing complete separation of the homologs.

Figure S62. HPLC trace of **2**.

Figure S63. HPLC trace of **3**.

Figure S64. HPLC trace of **4**.

Figure S65. HPLC trace of **5**.

Figure S66. HPLC trace of **6**.

Figure S67. HPLC trace of **7**.

Figure S68. HPLC trace of **8**.

Figure S69. HPLC trace of **15**.

Figure S70. HPLC trace of **16**.

Figure S71. HPLC trace of **17**.

Figure S72. HPLC trace of **18**.

Figure S73. HPLC trace of **19**.

Figure S74. HPLC trace of **21**.

Figure S75. HPLC trace of **22**.

Figure S76. HPLC trace of **23**.

Figure S77. HPLC trace of **24**.

Figure S78. HPLC trace of **25**.

Figure S79. HPLC trace of **26**.

Figure S80. HPLC trace of **27**.

Figure S81. HPLC trace of **28**.

Figure S82. HPLC trace of **29**.

Figure S83. HPLC trace of **30**.

Figure S84. HPLC trace of **31**.