Supporting information I

Synthesis of peptoid based small molecular gelators from multiple component reaction

Hari P. R. Mangunuru, Hao Yang, Guijun Wang*

Experimental section

General Methods:

Reagents and solvents were obtained from commercial suppliers (Sigma-Aldrich, Acros, Fisher etc.) and used directly without any purifications. All reactions, unless otherwise noted were carried out in oven dried glassware under nitrogen atmosphere. Combiflash chromatography was carried out using silicycle 230-400 mesh silcagel. Thin-layer chromatography (TLC) analysis was performed with Merck Kieselgel 60 F 254 plates, and visualized using UV light and phosphomolybdic (PMA) staining. ¹H NMR and proton-decoupled ¹³C NMR spectra were obtained with Bruker 400 MHz spectrometers in CDCl₃ with TMS as an internal standard. Proton and carbon spectra chemical shifts were reported using TMS and CDCl₃ as internal standard at 0 ppm and at 77.23 ppm, respectively.

General procedure using compound 16 as an example:

Benzyl amine (50 mg, 0.46 mmol) was added to a solution of paraformaldehyde (0.013 g, 0.46 mmol) in methanol (6 mL), the solution was stirred at room temperature for 1h. Then benzoic acid (0.055 g, 0.46 mmol) was added followed by cyclohexyl isocyanide (0.051 g, 0.46 mmol). The reaction was monitored using TLC which indicated completion after 24h. The reaction mixtrure was diluted with DCM (15 mL), washed with water (10 mL), the organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified using 60% EtOAc:Hexane. The desired product was obtained as a white solid (0.145 g) in 88% of yield.

All other compounds were synthesized by a similar procedure. The following are their characterization data.

N-benzyl-N-(2-(cyclohexylamino)-2-oxoethyl)acetamide (14)



The pure compound was obtained as a white solid with 0.112 g (83 %), m.p. 122.0-124.0 °C .¹H NMR (400 MHz, CDCl₃): (mixture of rotamers) δ 0.82 (m, 2H), 1.07 (m, 4H), 1.26 (m, 4H),1.59 (m, 7H), 1.75 (m, 3H), 2.05 (s, 1H), 2.13 (s, 3H), 3.62 (m, 1H), 3.82 (s, 1H), 3.85 (s, 2H), 4.54 (s, 1H), 4.58 (s, 2H), 5.47 (d, *J* = 7.26 Hz, 1H), 6.15 (d, *J* = 7.26 Hz, 1H), 7.08 (m, 2H), 7.20-7.31 (m, 6H). ¹³C (100 MHz, CDCl₃): (mixture of rotamers) δ 21.4, 21.7, 24.7, 24.8, 25.3, 25.5, 32.7, 32.8, 48.1, 48.2, 50.5, 50.7, 52.5, 53.3, 126.6, 127.9, 128.0, 128.6, 129.0, 129.1, 135.8, 137.0, 166.8, 167.9, 171.5, 171.9. HRMS (ESI+) calcd for C₁₇H₂₄N₂O₂ [M+Na]+, 311.1729; found 311.1727.

N-benzyl-N-(2-(cyclohexylamino)-2-oxoethyl)pent-4-ynamide (15)



The pure compound was obtained as a white solid with 0.109 g (71 %), m.p. 138.0-140.0 °C. ¹H NMR (400 MHz, CDCl₃): (mixture of rotamers) δ 0.93 (qd, J = 11.8 Hz, 1H), 1.14 (m, 3H), 1.34 (m, 3H), 1.68 (m, 6H), 1.87 (m, 2H), 1.99 (m, 1H), 2.58 (m, 2H), 2.69 (m, 2H), 3.71 (m, 1H), 3.92 (s, 1H), 3.97 (s, 2H), 4.65 (s, 1H), 4.70 (s, 2H), 5.58 (d, J = 8.0 Hz, 1H), 6.24 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 7.3 Hz, 2H), 7.34 (m, 5H). ¹³C (100 MHz, CDCl₃): (mixture of rotamers) δ 14.5, 14.7, 24.7, 24.8, 25.3, 25.5, 31.9, 32.3, 32.8, 32.9, 48.1, 48.4, 50.7, 50.9, 51.5, 52.4, 69.0, 69.1, 126.5, 127.9, 128.0, 128.6, 129.0, 135.6, 136.8, 166.7, 167.7, 171.9, 172.4. HRMS (ESI+) calcd for C₂₀H₂₆N₂O₂ [M+Na]+, 349.1886; found 349.1884.

N-benzyl-N-(2-(cyclohexylamino)-2-oxoethyl)benzamide (16)



The pure compound was obtained as a white solid with 0.145 g (88 %), m.p. 104.0-106.0 °C. ¹H NMR (400 MHz, CDCl₃): (mixture of rotamers) δ 1.10 (m, 4H),1.28 (m, 3H), 1.60 (m, 4H),1.78 (m, 3H), 3.66 (m, 2H), 3.96 (s, 2H), 4.57 (s, 2H), 4.72 (s, 1H), 5.59 (br, 1H), 6.29 (br, 1H), 7.11(m, 2H), 7.22-7.41 (m, 15H). ¹³C (100 MHz, CDCl₃): (mixture of rotamers) δ 24.7, 25.5, 32.9, 48.1, 49.4, 54.0, 126.8, 127.1, 127.9, 128.6, 128.9, 130.1, 135.2, 135.9, 167.7, 172.9. HRMS (ESI+) calcd for C₂₂H₂₆N₂O₂ [M+Na]⁺, 373.1886 found 373.1882.

N-benzyl-4-bromo-N-(2-(cyclohexylamino)-2-oxoethyl)benzamide (17)



The pure compound was obtained as a white solid with 0.165 g (82 %), m.p. 168.0-170.0 °C. ¹H NMR (400 MHz, CDCl₃): (mixture of rotamers) δ 1.06 (m, 5H), 1.26 (m, 4H), 1.58 (m, 6H), 1.77 (m, 4H), 3.65 (m, 2H), 3.93 (s, 2H), 4.54(s, 2H), 4.66 (s, 1H), 5.78(br. s, 1H), 6.22 (br. s, 1H), 7.18-7.33 (m, 9H), 7.43 (d, *J* = 7.5 Hz, 2H). ¹³C (100 MHz, CDCl₃): (mixture of rotamers) δ 24.7, 25.4, 32.9, 48.2, 48.4, 49.2, 49.7, 51.7, 54.0, 124.5, 127.0, 127.9, 128.6, 128.9, 131.8, 134.1, 135.8, 167.3, 171.8. HRMS (ESI+) calcd for C₂₂H₂₅N₂O₂Br [M+Na]+, 451.0991; found 451.0997.

N-benzyl-N-(2-(cyclohexylamino)-2-oxoethyl)-4-nitrobenzamide (18)



The pure compound was obtained as a white solid with 0.162 g (87 %), m.p. 190.0-192.0 °C. ¹H NMR (400 MHz, CDCl₃): (mixture of rotamers) δ 1.10 (m, 10H), 1.67 (m, 10H), 3.59 (s, 1H), 3.68 (m, 2H), 3.98 (s, 2H), 4.52 (s, 2H), 4.73 (s, 1H), 5.22 (s, 1H), 5.89 (d, *J* = 4.8 Hz, 1H), 7.08 (d, *J* = 6.5 Hz, 2H), 7.28 (m, 7H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 7.5 Hz, 2H), 8.17 (m, 2H). ¹³C (100 MHz, CDCl₃): (mixture of rotamers) δ 24.7, 25.3, 25.4, 25.5, 30.5, 33.0, 48.4, 48.9, 53.9, 123.9, 126.9, 127.9, 128.0, 128.1, 128.2, 128.6, 128.7, 129.0, 129.1, 135.3, 141.4, 148.6, 166.8, 170.6. HRMS (ESI+) calcd for C₂₂H₂₅N₃O₄ [M+Na]+, 418.1737; found 418.1741.

(R)-4-bromo-N-(2-(cyclohexylamino)-2-oxoethyl)-N-(1-phenylethyl)benzamide (19)



The pure compound was obtained as a white solid with 0.131 g (71 %), m.p. 140.0-142.0 °C. ¹H NMR (400 MHz, CDCl₃): (mixture of rotamers) δ 1.09 (m, 3H), 1.27 (m, 3H), 1.48 (m, 2H), 1.55 (s, 2H), 1.56 (s, 3H), 1.75 (m, 2H), 3.37 (m, 2H), 3.63 (s, 3H), 4.15 (d, *J* = 14.6 1H), 4.50 (s, 1H), 6.40 (br. s, 1H), 7.13 (br, 1H), 7.23 (m, 2H), 7.27 (m, 5H), 7.50 (m, 2H). ¹³C (100 MHz, CDCl₃): (mixture of rotamers) δ 17.9, 24.6, 25.5, 32.7, 32.8, 47.1, 48.0, 57.6, 64.2, 124.2, 126.7, 127.0, 128.0, 128.7, 128.9, 132.0, 134.7, 139.1, 168.3, 171.8. HRMS (ESI+) calcd for C₂₃H₂₇N₂O₂Br [M+Na]+, 465.1148; found 465.1156.

N-(4-methoxybenzyl)-4-bromo-N-(2-(cyclohexylamino)-2-oxoethyl)benzamide (20)



The pure compound was obtained as a white solid with 0.132 g (79 %), m.p. 174.0-176.0 °C. ¹H NMR (400 MHz, CDCl₃): (mixture of rotamers) δ 1.09 (m, 4H), 1.29 (q, *J* = 12.0 Hz, 3H), 1.58 (m, 5H), 1.79 (m, 3H), 3.67 (m, 2H), 3.73 (s, 3H), 3.93 (s, 2H), 4.48 (s, 2H), 4.64 (s, 1H), 6.11 (d, 1H), 6.80 (d, *J* = 8.3 Hz, 2H), 7.00 (d, *J* = 5.3 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 7.8 Hz, 2H).¹³C (100 MHz, CDCl₃): (mixture of rotamers) δ 24.71, 24.74, 25.4, 48.2, 49.2, 53.5, 55.3, 114.3, 124.5, 128.4, 128.6, 131.8, 159.4, 167.4, 171.7. HRMS (ESI+) calcd for C₂₃H₂₇N₂O₃Br [M+Na]+, 481.1097; found 481.1103.

Ethyl 2-(2-(N-(4-methoxybenzyl)-4-bromobenzamido)acetamido)acetate (21)



The pure compound was obtained as a white solid with 0.112 g (66 %), m.p. 123.0-125.0 °C. ¹H NMR (400 MHz, CDCl₃): (mixture of rotamers)) δ 1.23 (m, 3H), 3.82 (s, 3H), 4.02 (d, *J* = 5.3 Hz, 2H), 4.12 (br, s, 2H), 4.24 (q, *J* = 7.0 Hz, 2H), 4.57 (br, 2H), 6.89 (m, 2H), 7.13 (d, *J* = 5.0 Hz, 2H), 7.43 (m, 2H), 7.56 (d, *J* = 8.0 Hz, 2H). ¹³C (100 MHz, CDCl₃): (mixture of rotamers) δ 14.1, 41.2, 48.4, 53.4, 55.3, 61.6, 114.3, 124.5, 128.4, 128.7, 131.8, 134.0, 134.1, 158.2, 159.4, 168.6, 169.6, 171.9. HRMS (ESI+) calcd for C₂₁H₂₃BrN₂O₅ [M+Na]+ , 485.0682; found 485.0680.





The pure compound was obtained as a light yellow oil with 0.134 g (81 %). ¹H NMR (400 MHz, CDCl₃): (mixture of rotamers) δ 1.22 (m, 3H), 3.67 (s, 2H), 3.91 (d, *J* = 3.5 Hz, 2H), 4.04 (br, s, 2H), 4.13 (q, J = 7.0 Hz, 2H), 4.57 (br. s, 2H), 4.74 (s, 1H), 6.90 (s, 1H), 7.12 (s, 2H), 7.21-7.35 (m, 8H), 7.44 (m, 2H). ¹³C (100 MHz, CDCl₃): (mixture of rotamers) δ 14.2, 41.0, 41.2, 48.6, 52.3, 53.9, 61.5, 126.9, 127.1, 127.9, 128.6, 128.9, 130.2, 135.1, 135.8, 168.9, 169.6, 173.0. HRMS (ESI+) calcd for; C₂₀H₂₂N₂O₄ [M+Na]+, 377.1471; found 377.1471.

Ethyl 2-(2-(N-(4-methoxybenzyl)benzamido)acetamido)acetate (23)



The pure compound was obtained as a white solid with 0.094 g (67 %), m.p. 94.0-96.0 °C. ¹H NMR (400 MHz, CDCl₃): (mixture of rotamers) δ 1.22 (m, 3H), 3.72 (s, 3H), 3.92 (d, *J* = 5.3 Hz, 2H), 4.04 (br, s, 2H), 4.13 (q, J = 7.0 Hz, 2H), 4.57 (br, 2H),6.79 (d, *J* = 8.5 Hz, 2H), 6.99 (m, 1H), 7.03 (d, *J* = 5.5 Hz, 2H), 7.34 (m, 3H), 7.44 (m, 2H). ¹³C (100 MHz, CDCl₃): (mixture of rotamers) δ 14.1, 41.2, 48.4, 53.4, 55.3, 61.5, 114.2, 126.9, 127.5, 128.3, 128.6, 130.0, 130.1, 133.1, 135.2, 159.3, 168.9, 169.6, 172.9. HRMS (ESI+) calcd for C₂₁H₂₄N₂O₅ [M+Na]+, 407.1577; found 407.1575.

N-(2-(cyclohexylamino)-2-oxoethyl)-N-(8-hydroxy-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)benzamide (24)



The pure compound was obtained as a white solid with 0.083 g (89 %), m.p. 261.0-263.0 °C. ¹H NMR (400 MHz, CDCl₃): δ 1.08 (m, 3H), 1.27 (m, 2H), 1.58 (m, 3H), 1.87 (dd, J = 18.6, 14.1Hz, 2H), 3.30 (s, 3H), 3.46 (t, J = 9.2 Hz, 1H), 3.59 (m, 1H), 3.72 (m, 2H), 3.90 (dd, J = 10.0, 3.5 Hz, 1H), 4.12 (m, 2H), 4.17 (d, J = 4.8 Hz, 2H), 4.45 (d, J = 3.5 Hz, 1H), 5.44 (s, 1H), 5.83 (d, J = 8.0 Hz, 1H), 6.49 (d, J = 1.5 Hz, 1H), 7.26 (dd, J = 5.0, 1.8 Hz, 3H), 7.33 (d, J = 8.3 Hz, 2H), 7.42 (m, 2H), 7.50 (d, J = 8.3 Hz, 2H).¹³C (100 MHz, CDCl₃): δ 24.6,25.4, 32.9, 47.6, 49.0, 55.2, 62.7, 63.3, 66.6, 68.7, 80.9, 100.8, 101.7, 124.1, 126.3, 128.2, 128.8, 129.0, 132.0, 134.0, 137.1, 169.7, 172.5. HRMS (ESI+) calcd for C₂₉H₃₆N₂O₇ [M+Na]+, 547.2414; found 547.2420.

4-Bromo-N-(2-(cyclohexylamino)-2-oxoethyl)-N-(8-hydroxy-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)benzamide (25)



The pure compound was obtained as a white solid with 0.098 g (91 %), m.p. 291.0-293.0 °C. ¹H NMR (400 MHz, CDCl₃): δ 1.1 (m, 3H), 1.26 (m, 2H), 1.53 (m, 1H), 1.62 (m, 2H), 1.87 (m, 2H),

3.31 (s, 3H), 3.48 (m, 1H), 3.62 (m, 1H), 3.73 (m, 2H), 3.84 (dd, J = 9.9, 3.6 Hz, 1H), 4.15 (m, 4H), 4.44 (d, J = 3.5 Hz, 1H), 5.46 (s, 1H), 5.78 (d, J = 8.0 Hz, 1H), 6.49 (d, J = 1.5 Hz, 1H), 7.27 (dd, J = 5.0, 1.8 Hz, 3H), 7.33 (d, J = 8.3, 2H), 7.42 (m, 2H), 7.50 (d, J = 8.3 Hz, 2H). ¹³C (100 MHz, CDCl₃): δ 24.7, 25.4, 32.84, 32.89, 47.6, 48.9, 55.2, 62.6, 63.3, 66.7, 68.7, 80.9, 100.9, 101.7, 126.3, 127.0, 128.2, 128.7, 129.0, 129.7, 135.2, 137.1, 169.9, 173.5. HRMS (ESI+) calcd for C₂₉H₃₅N₂O₇Br [M+Na]+, 625.1519; found 625.1530.

Ethyl-2-(2-(4-bromo-N-(8-hydroxy-6-methoxy-2-phenyl-hexahydropyrano[3,2-d][1,3]dioxin-7-yl)benzamido)acetamido)acetate (26)



The pure compound was obtained as a white solid with 0.065 g (61 %), m.p. 207.0-209.0 °C. ¹H NMR (400 MHz, CDCl₃): δ 1.26 (m, 3H), 3.31 (s, 3H), 3.44 (m, 1H), 3.61 (m, 1H), 3.73 (m,1H), 3.82 (dd, *J* = 10.0, 3.5 Hz, 1H), 3.90 (dd, *J* = 18.3, 3.3 Hz, 1H), 4.08 (m, 2H), 4.15 (m, 4H), 4.32 (m, 2H), 4.47 (d, *J* = 3.5 Hz, 1H), 5.44 (s, 1H), 6.05 (d, *J* = 2.0 Hz, 1H), 6.66 (m 1H), 7.26 (dd, *J* = 4.9, 1.9 Hz, 3H), 7.21 (d, *J* = 8.3 Hz, 2H), 7.40 (m, 2H), 7.50 (d, *J* = 8.3 Hz, 2H). ¹³C (100 MHz, CDCl₃): δ 14.1, 41.6, 47.0, 55.2, 61.8, 62.5, 63.3, 66.6, 68.7, 81.0, 100.7, 100.8, 124.2, 126.3, 128.2, 128.8, 129.1, 132.0, 134.0, 137.0, 169.6, 170.9, 172.6. HRMS (ESI+) calcd for C₂₇H₃₁BrN₂O₉ [M+Na]+, 629.1105; found 629.1103.

Compound	DMSO:H ₂ O (1:2) mg/mL	T1 (°C)	T2 (°C)	T3 (°C)
15	20.0	95	100	110
17	5.0	78	80	90
18	10.0	91	95	110
20	6.6	91	110	120
21	2.0	70	75	81
23	20.0	50	52	58
26	6.6	110	118	128

Table S1 The melting point range for the gels in DMSO: $H_2O(1:2)$

The melting points were measured at their minimum gelation contractions in DMSO:H₂O (1:2, volume ratio). T1 is the temperature of the initial melting, T2 is the temperature when the gel is estimated half melted, and T3 is the temperature when the gel turned to clear. The melting temperature of the gel is estimated based on the disappearance of the opaqueness of the initial gels. In general, a compound was dissolved in a small vial at their minimum gelation concentrations and then transferred into a small tube (such as NMR tube) using a pipette while it was still warm. The tube was then sonicated and cooled till a stable gel is reformed. The tube was immersed in oil bath and the temperature of the solid phase to liquid phase transition was monitored using a thermometer.

Supporting information II

Synthesis of peptoid based small molecular gelators from multiple component reaction

Hari P. R. Mangunuru, Hao Yang, Guijun Wang*

Table of content	1
¹ H NMR & ¹³ C NMR for compound 14	2
¹ H NMR & ¹³ C NMR for compound 15	3
¹ H NMR & ¹³ C NMR for compound 16	4
¹ H NMR & ¹³ C NMR for compound 17	5
¹ H NMR & ¹³ C NMR for compound 18	5
¹ H NMR & ¹³ C NMR for compound 19	7
¹ H NMR & ¹³ C NMR for compound 20 S8	8
¹ H NMR & ¹³ C NMR for compound 21	9
¹ H NMR & ¹³ C NMR for compound 22	10
¹ H NMR & ¹³ C NMR for compound 23	11
¹ H NMR & ¹³ C NMR for compound 24	12
¹ H NMR & ¹³ C NMR for compound 25	13
¹ H NMR & ¹³ C NMR for compound 26	14



¹H NMR (400 MHz, CDCl₃): (mixture of rotamers), ¹³C (100 MHz, CDCl₃): (mixture of rotamers) for compound **14.**



¹H NMR (400 MHz, CDCl₃): (mixture of rotamers), ¹³C (100 MHz, CDCl₃): (mixture of rotamers) for compound **15.**



¹H NMR (400 MHz, CDCl₃): (mixture of rotamers), ¹³C (100 MHz, CDCl₃): (mixture of rotamers) for compound **16**.



¹H NMR (400 MHz, CDCl₃): (mixture of rotamers), ¹³C (100 MHz, CDCl₃): (mixture of rotamers) for compound **17**



compound 18



compound 19







¹H NMR (400 MHz, CDCl₃): (mixture of rotamers), ¹³C (100 MHz, CDCl₃): (mixture of rotamers) for compound **22**



 $\text{compound}\ 23$



 ^1H NMR (400 MHz, CDCl_3), ^{13}C (100 MHz, CDCl_3) for compound 24

 1 H NMR (400 MHz, CDCl₃), 13 C (100 MHz, CDCl₃) for compound **25**

 ^1H NMR (400 MHz, CDCl_3), ^{13}C (100 MHz, CDCl_3) for compound 26