Catalytic Gels for a Prebiotically-Relevant Asymmetric Aldol Reaction in Water: From Organocatalyst Design to Hydrogel Discovery and Back Again

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Contents

1. Materials and Instrumentation

Unless otherwise noted all compounds were bought from commercial suppliers and used without further purification. Where a solvent is described as "dry" it was purified by PureSolv alumina columns from Innovative Technologies. Melting points were determined using a Stuart SMP3 apparatus. Optical rotations were carried out using a JASCO-DIP370 polarimeter and $[\alpha]_D$ values are given in deg.cm^{3}g $^{-1}$dm^{-1}. Infra-red spectra were acquired on a ThermoNicolet Avatar 370 FT-IR spectrometer. Nuclear magnetic resonance spectra were recorded on a Jeol ECS-400, a Jeol 500 Avance III HD 500 or a Jeol AV500 at ambient temperature. Coupling constants (*J*) are quoted in Hertz. Mass spectrometry was performed by the University of York mass spectrometry service using electrospray ionisation (ESI). Thin layer chromatography was performed on glass-backed plates coated with Merck Silica gel 60 F254. The plates were developed using UV light, acidic aqueous ceric ammonium molybdate or basic aqueous potassium permanganate. Liquid chromatography was performed using forced flow (flash column) with the solvent systems indicated. The stationary phase was silica gel 60 (220–240 mesh) supplied by SigmaAldrich. Preparative Thin Layer Chromatography (PTLC) was carried out on 20x20 2000 micron silica plates with UV254 purchased from Uniplate. High Performance Liquid Chromatography (HPLC) was performed using an Agilent 1100 series instrument using the chiral columns indicated and a range of wavelengths from 210-280 nm for detection. Buffer solutions, pH 6 and pH 7 phosphate buffers, were purchased as ready-made solutions from Fisher Scientific. TEM images were obtained on a FEI Tecnai 12 G^2 fitted with a CCD camera. Fibre sizes were measured using the *ImageJ* software. SEM images were taken using a JEOL JSM-7600F field emission SEM. Rheology was measured on a Malvern Instruments Kinexus Pro+ Rheometer fitted with a 2 cm parallel plate geometry.

2. Gelation testing

2.1. L-Glutamine amide (1)

A known quantity of L-glutamine amide **1** (3 mg) was weighed into a 2.5 mL sample vial to which was added by solvent (0.1 mL). The vial was then heated until the compound dissolved.

The vial was then left to cool, 12 hours the tube inversion test was carried out to see if gelation had taken place.

2.2. L-Glutamine amide (1) and aldehyde to give Schiff base gelator (2)

To a known quantity of L-glutamine amide **1**, aldehyde (1 eq) was added followed by water (1 mL) to form a suspension. The suspension was heated until oil droplets appeared. The solution was left to cool. Inversion test was then used to establish if a gel had formed. These quantities were changed depending on what being studied.

2.3. 2-Benzylamino-N^1-dodecyl-L-glutamine amide (3)

Water (1 mL) was added to benzyl glutamine amide (**3**) (1 mg 2.48 μmol) to form a suspension. The suspension was heated until oil droplets appeared then immediately sonicated until the solution became white but no aggregates observed. The solution was left to cool. Inversion test was then used to establish if a gel had formed. This method was the same even on a larger scale of gel formation.

3. Gel Characterisation Methods

3.1. Electron Microscopy Sample Preparation

TEM Samples. The gels were prepared as described above. To prepare samples for TEM, a small portion of gel was removed with a spatula and 'drop-cast' onto a heat-treated copper TEM grip. Excess material was removed using filter paper and left to dry for 20 minutes prior to imaging. A uranyl acetate stain was used for contrast. Meg Stark at the Biology Technology Facility, University of York, carried this out.

SEM Samples. Gels were prepared as described above. Gels were then prepared for SEM by freeze-drying; Meg Stark at the Biology Technology Facility, University of York, using the method described below, carried this out. The gel was spread using a mounted needle on a

thin piece of copper shim (to act as support); excess liquid was removed with filter paper. The gel was frozen on the copper support by submersion in nitrogen slush (ca. -210°C); after this water was removed from the gel by lyophilising on a Peltier stage, with a maximum temperature of -50°C. Once dry, the gel was knocked off the shim with a mounted needle, and the shim was mounted on an SEM stub using a carbon sticky tab. The sample was then sputter-coated with a thin layer (< 12 nm) of gold/palladium coating to prevent sample charging, before SEM imaging.

3.2. Circular Dichroism

To glutamine amide (**1**) (1 mg, 3.19 mmol) was added 4-nitrobenzaldehyde (1 eq, 480 μg. 3.19 mmol) followed by water (1 mL). The solution was heated until boiling ca. 100°C. Whilst hot, an aliquot (450 μL) of the sample was taken and transferred to 1 mm pathlength quartz cuvette. The sample was left overnight to allow gel formation.

Water (1 mL) was added to benzylglutamine amide **3** (1 mg, 0.025 mmol). The solution was heated until boiling ca. 100°C then sonicated for 30 seconds. Whilst hot an aliquot (450 μL) of the sample was taken and transferred to 1 mm quartz cuvette. The sample was left overnight to allow gel formation.

3.3. Rheology

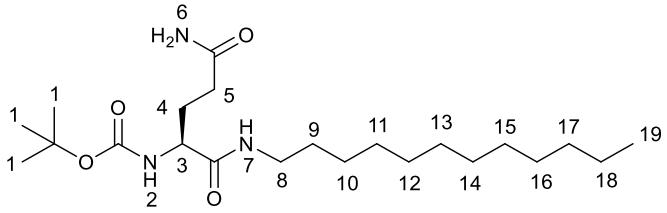
To glutamine amide (**1**) (1 mg, 3.19 mmol) was added 4-nitrobenzaldehyde (1 eq, 480 μg. 3.19 mmol) followed by water (1 mL). The solution was heated until boiling ca. 100°C. Whilst hot, the sample was transferred to a bottomless vial attached to a Petri dish with sealant. The sample was left over night to allow gel formation then transferred to the rheometer plate.

To glutamine amide (**1**) (2.99 mg, 8.61 mmol) was added benzaldehyde (1 eq, 1.01 mg. 8.61 mmol) followed by water (1 mL). The solution was heated until boiling ca. 100°C. Whilst hot, the sample was transferred to a bottomless vial attached to a Petri dish with sealant. The sample was left over night to allow gel formation then transferred to the rheometer plate.

Water (1 mL) was added to benzylglutamine amide (**3**) (4 mg, 0.01 mmol). The solution was heated until boiling ca. 100°C then sonicated for 30 seconds. Whilst hot, the sample was transferred to a bottomless vial onto the rheometer plate (pre-heated to 50°C). Once loaded, the rheometer plate was cooled to room temperature. The vial was held in place until the gel began to form, then left for half an hour before removal of the vial.

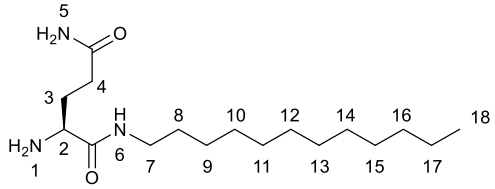
4. Synthesis and Characterisation

4.1. L-Boc-glutamine dodecylamine



Boc-Gln-OH (482 mg, 1.97 mmol) was dissolved in DCM (30 mL) and stirred at 0°C for 5 minutes. Then EDC (660 mg, 3.56 mmol) DMAP (239 mg, 1.97 mmol) and dodecylamine (362 mg, 1.97 mmol) were added. The mixture was stirred for 2 h at 0°C followed by stirring for 12 h at room temperature. The reaction mixture was then washed with 2 M hydrochloric acid solution (20 mL), water, 1 M NaOH (20 mL) and brine (20 mL). The organic solvent was dried over magnesium sulfate The organic solvent was removed in vacuo to yield a white solid. The organic solvent was removed *in vacuo* to yield a white solid (422.71 mg, 1.02 mmol, 52%). **Mp:** 109-110°C; **IR** ν_{max} (cm^{-1}): 3380w, 3319w, 3251w, 3196w, 3077w, 2922m, 2852m, 1962w, 1691s, 1653vs, 1619m, 1560m, 1515s, 1455m, 1415m, 1391m, 1364m, 1319m, 1286m, 1246s, 1168s, 1089w, 1058w, 1028w, 999w, 866w, 785w, 721w, 638m, 597m, 554m, 481w, 464w, 457w; **[α]D^{25}** (deg cm^3 g^{-1} dm^{-1}) -9.7; **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm; 7.71 (1H, br t, *J*=5.5 Hz, CO-H**7**), 7.26 (1H, br s, H**2**), 6.78 (2H, br t, *J*=14.7 Hz, H**6**), 3.81 (1H, q, *J*=8.7 Hz, H**3**), 1.98 - 2.13 (2H, m, H**5**), 3.13-2.93 (2H, m, H**8**), 1.86-1.58 (2H, m, H**4**), 1.41 (11H, m, H**1**, H**9**), 1.21 (20H, m, H**10-18**), 0.85 (3H, t, *J* = 8.2, H**19**); **^{13}C NMR** (400 MHz, DMSO-d_6) δ ppm: 173.79 (H_2N-**C**=O), 171.55 (HN-**C**=O), 155.28 (C-Boc **C**=O), 77.98 (Boc CH_3-**C**), 52.81 (C-3), 38.37 (C-5), 31.62 (C-4), 31.34 (C-8), 29.05 (**C**H_2), 28.85 (**C**H_2), 28.75 (**C**H_2), 27.87 (**C**H_2) 26.29 (C-4), 22.13 (C-18) 14.04 (C-19)**; ESI-MS** (m/z) calc. $C_{22}H_{43}N_3NaO_4$ 436.3146, found 436.3151 (100% $[M+Na]^+$).

4.2. L-Glutamine dodecylamine (1)



L-Boc-Gln amide (100 mg, 0.242 mmol) was added to a solution of 4 M HCl in dioxane (15 eq). Solvent was removed in vacuo to yield a white solid (75 mg, 0.241 mmol, 100%). The solid (75 mg) was then deprotonated using NaOH (1 M) and extracted with DCM to give the free amine **1** (40 mg, 0.127 mmol, 53%). **Mp**= 117-119°C; **IR** ν_{max} (cm^{-1}): 3411w, 3380w, 3321w, 3157w, 3079w, 2919m, 2850m, 1962m, 1691m, 1651vs, 1616m, 1548m, 1532m, 1518m, 1449s, 1429m, 1415m, 1392w, 1367m, 1321w, 1303w, 1284m, 1272m, 1248m, 1211w, 1169m, 1114w, 1100w, 1057w, 1039w, 1027w, 984w, 951vw, 935vw, 915w, 892w, 861w, 825w 802w, 792w, 773w, 755w, 730w, 719w, 666w, 631m, 596m, 581m, 561m, 546m, 539m, 494w, 484m, 464w, 457w; **$[\alpha]_D^{25}$** (deg cm^3 g^{-1} dm^{-1}) -25.2; **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 7.75 (1H, t, *J*=5.5 Hz, H_6), 7.24 and 6.70 (1H each, H_5), 3.05-2.85 (3H, m, $H_{7/2}$) 2.01-1.85 (2 H, m, H_4), 1.75-1.55 (2H, m, $H_{8/3}$), 1.50-1.40 (1H, m, H_3) 1.43-1.30 (2H, m, H_9), 1.26-1.20 (16H, m, $H_{10\text{-}17}$), 0.83 (3H, t, *J*=5.5 Hz, H_{18}); **^{13}C NMR** (400 MHz, DMSO-d_6) δ ppm: 174.77 (H_2N-**C**=O), 174.29 (NH-**C**=O), 54.48 (C-3), 38.29 (C-4), 31.77 (C-3), 31.34 (C-7), 31.26 (CH_2), 31.19 (CH_2), 29.06 (CH_2), 28.76 (CH_2), 26.44 (C-7), 22.14 (C-18) 14.09 (CH_2-CH_3); **ESI-MS** (m/z) calc. $C_{17}H_{36}N_3O_2$ 314.2802, found 314.2802 (100% $[M+H]^+$).

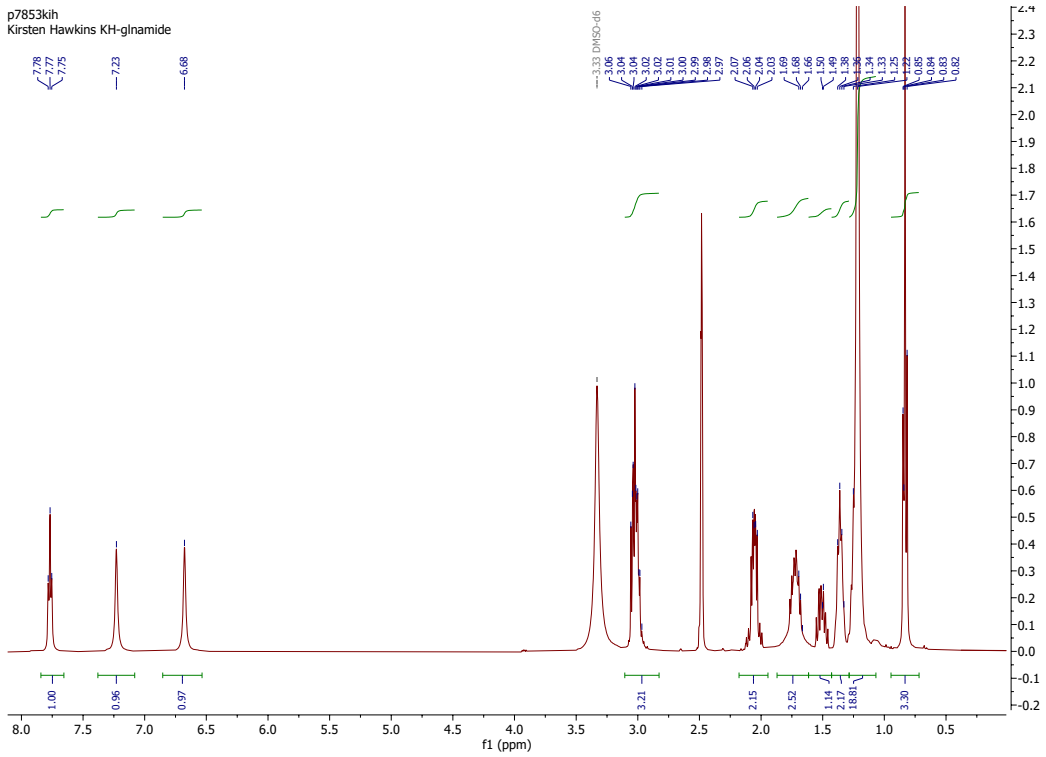


Fig. S1. ^{1}H NMR Spectrum of compound **1** in DMSO-d_6.

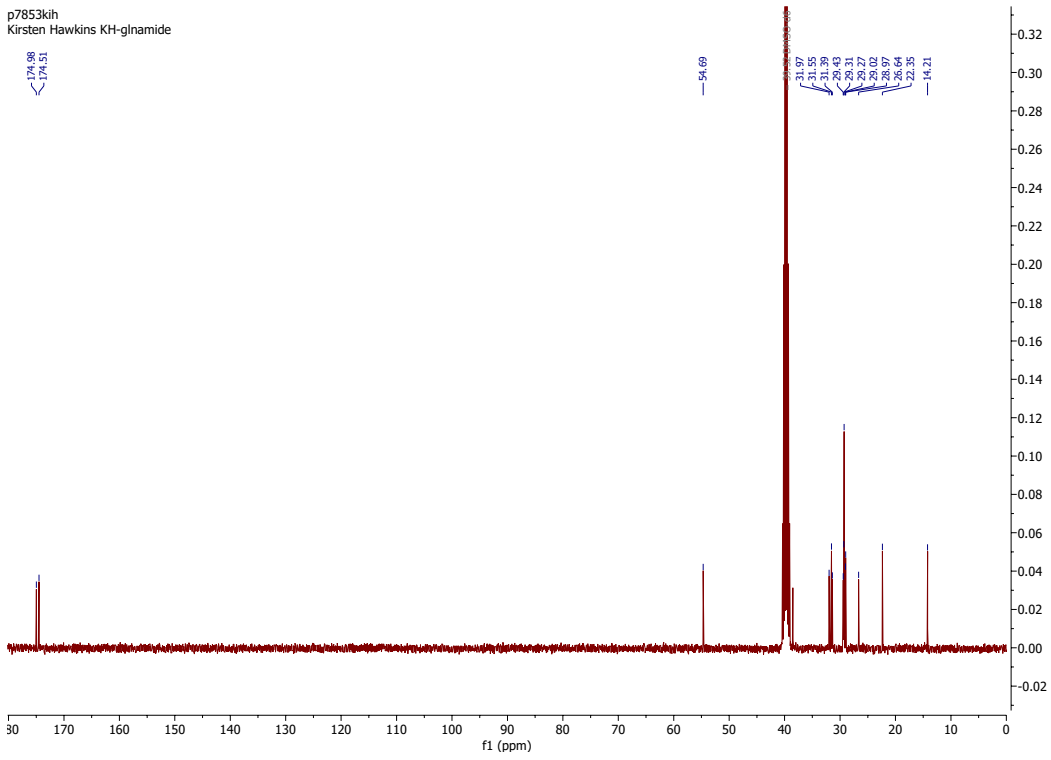
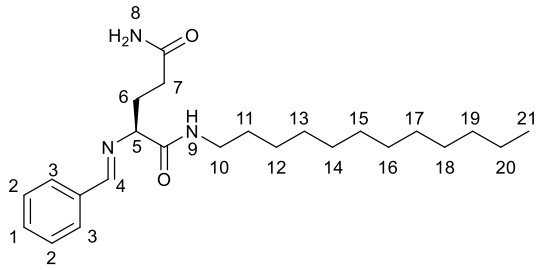


Fig. S2. ^{13}C NMR Spectrum of compound **1** in DMSO-d_6.

4.3. (*E*)-2-(benzylideneneamino)-N^1-dodecyl-L-glutamine amide (2a)



To L-glutamine amide (**1**) (351 mg, 1.23 mmol) was added benzaldehyde (0.14 mL, 1.35 mmol, 1.2 eq) followed by 100 mL of water. The suspension was sonicated for 2 minutes then heated until boiling or until fully dissolved to initiate gelation. The solution was then left to cool. Once the solution had gelled, it was extracted into DCM (3x 50 mL) the organic layer was removed *in vacuo* to yield a white solid (413.9 mg, 84% yield 1.03 mmol); **IR** ν_{max} (cm^{-1}): 3411w, 3298m, 2918s, 2872w, 2850m, 1649vs, 1639s, 1579w, 1547s, 1467m, 1451m, 1434m, 1410m, 1380w, 1338w, 1308m, 1236w, 1157w, 756m, 720w, 695s, 670m, 623m, 618m, 585m, 559m, 502w; **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm: 8.31 (1H, s, H$_{\mathbf{4}}$), 8.33 (2H, d, *J* = 8.9 Hz, H$_{\mathbf{3}}$), 7.63 (1H, t, *J* = 5.9 Hz, H$_{\mathbf{9}}$), 7.56-7.37 (3H, m, H$_{\mathbf{1\text{-}2}}$), 7.27 (1H, s broad, H$_{\mathbf{8}}$,), 6.72 (1H, s broad, H$_{\mathbf{8}}$,), 3.98-3.76 (1H, m, H$_{\mathbf{5}}$,), 3.31-3.02 (2H, m, H$_{\mathbf{10}}$,) 2.21-1.85 (2H, m, H$_{\mathbf{6}}$), 1.44-1.36 (2H, m, H$_{\mathbf{7}}$), 1.46-1.32 (2H, m, H$_{\mathbf{11}}$), 1.28-1.15 (20H, m, H$_{\mathbf{12\text{-}20}}$,), 0.84 (3H, t, *J* = 7.2 Hz, H$_{\mathbf{21}}$,), **^{13}C NMR** (400 MHz, DMSO-d_6) δ ppm 174.13 (NH$_2$-**C**=O), 171.00 (NH-**C**=O), 162.95 (C-4), 131.59 (**C** aromatic), 129.14 (**C** aromatic), 31.83 (C-7), 30.35 (C-6), 29.26 (**C**H$_2$), 26.86 (**C**H$_2$), 22.64 (**C**H$_2$-CH$_3$), 14.51 (terminal C**H**$_3$); **ESI-MS** (m/z) calc. $C_{24}H_{40}N_3O_2$ 402.3115 found 402.3117 (47% $[M+H]^+$) and calc. $C_{24}H_{39}N_3NaO_2$ 424.2934 found 424.2936 (100% [M+Na]).

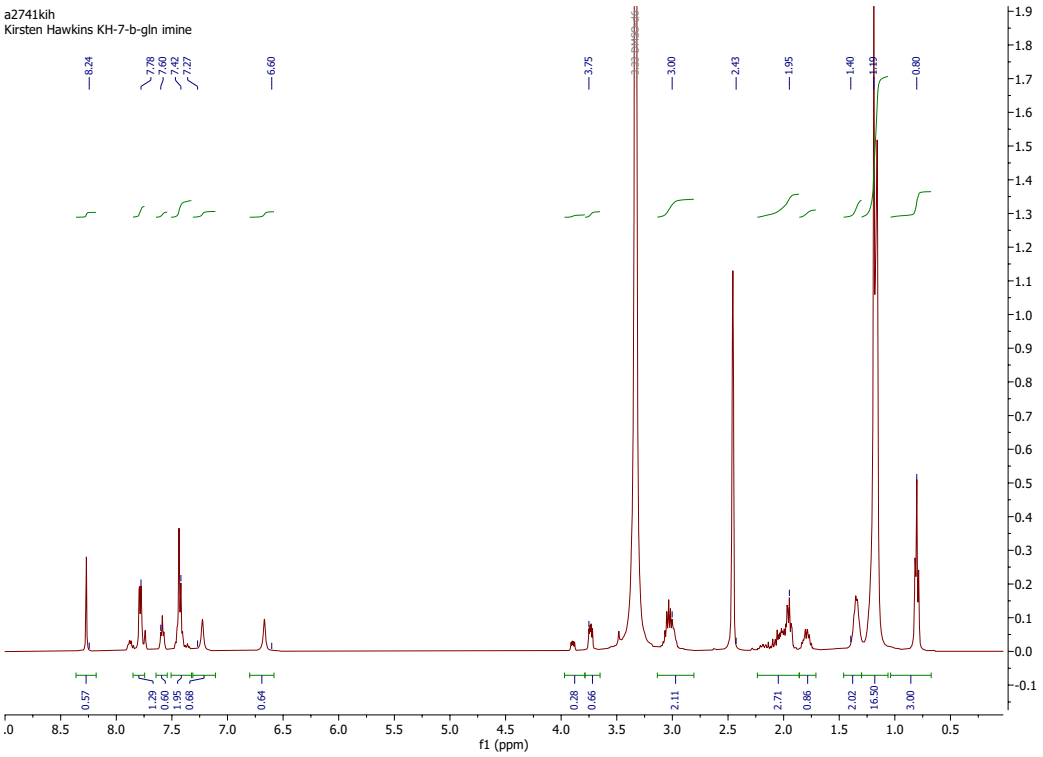


Fig. S3. ^{1}H NMR Spectrum of compound **2a** in DMSO-d_6.

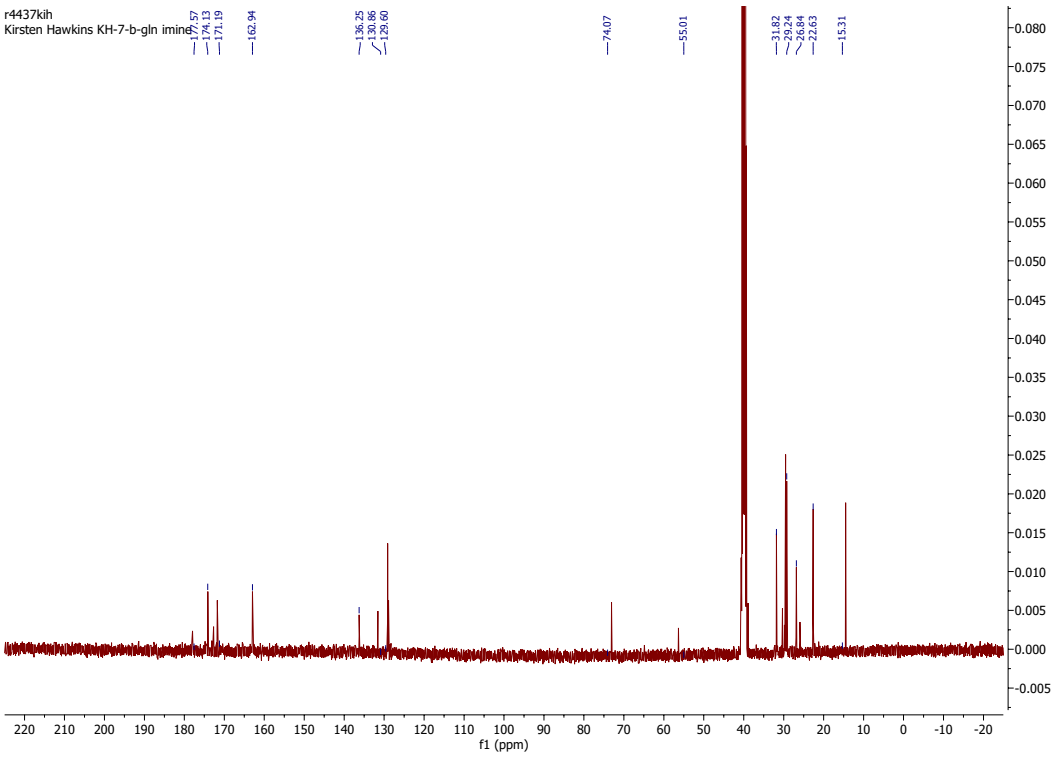
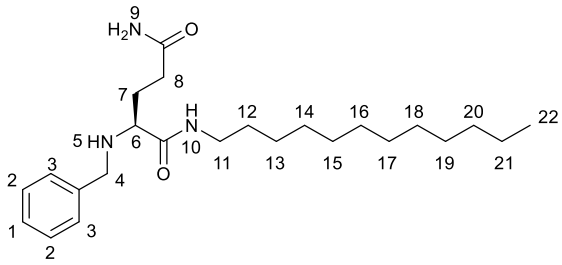


Fig. S4. ^{13}C NMR Spectrum of compound **2a** in DMSO-d_6.

4.4. 2-Benzylamino-N^1-dodecyl-L-glutamine amide (3)



To L-glutamine amide (**1**) (200 mg, 0.64 mmol) was added benzaldehyde (81 uL, 0.77 mmol, 1.2 eq) followed by 100 mL of water. The suspension was sonicated for 2 minutes then heated until boiling or until fully dissolved to initiate gelation. The solution was then left to cool. Once the solution had gelled, it was extracted into DCM (3 x 50 mL) the organic layer was removed *in vacuo* to yield a white solid. A methanol (10 mL) solution of sodium borohydride (10 eq) was added to the white solid. The solution was left to stir. Once TLC (90:10 DCM:MeOH) indicated that reduction of both residual aldehyde and the imine had taken place the solvent was removed *in vacuo*, then re-dissolved in DCM (20 mL) filtered and washed with ammonium chloride (NH_4Cl) solution. The organic layer was removed *in vacuo* to yield either a clear sticky oil or a white product. If a clear sticky oil was observed diethyl ether 20 mL was added then removed *in vacuo* to yield a white solid. (218 mg, 84% 0.54 mmol). **Mp** 90-91°C; **IR** ν_{max} (cm^{-1}): 3397m 3301m, 3213w, 2955m, 2919s, 2851s, 1655vs, 1640s, 1627s, 1551s, 1496w, 1466m, 1453m, 1415m, 1377m, 1344m, 1309w, 1276m, 1257m, 1247m, 1209w, 1153w, 1128w, 806w, 745m, 721m, 696s, 669s, 655s, 611s, 598s, 509m, 465m **$[\alpha]_D^{25}$** (deg cm^3 g^{-1} dm^{-1}) -4.6; **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm: 7.85 (1H, t, *J*= 5.7 Hz, H_{10}), 7.30 (2H, d, H_3), 7.26-7.19 (3H, m, H_{1-2}), 6.70 (2H, s, H_9), 3.65 (1H, d, *J*=13.2 Hz, H_4), 3.48 (1H, d, *J*=13.7 Hz H_4), 3.08 (2H, q, *J*=6.4 Hz, H_{11}), 2.91 (1H, t, *J*=6.6 Hz, H_6), 2.22-1.99 (2H, m, H_8), 1.77-1.58 (1H, m, H_7), 1.48-1.36 (2H, m, H_{12}), 1.23 (20H, m, H_{13-21}), 0.85 (3H, t, *J*=6.6 Hz, H_{22}); **^{13}C NMR** (400 MHz, DMSO-d_6) δ ppm 174.07 (NH_2-**C**=O), 173.58 (HN-**C**=O), 140.54 (**C** aromatic), 136.63 (**C** aromatic), 128.54 (**C** aromatic), 128.11 (**C** aromatic), 127.87 (**C** aromatic), 127.68 (**C** aromatic), 126.62 (**C** aromatic), 61.23 (Bnz-**C**H_2-NH-CH), 51.12 (Bnz-CH_2-NH-**C**H), 31.32 (**C**H_2 Chain), 29.22 (**C**H_2 Chain), 29.03 (**C**H_2 Chain), 28.74 (**C**H_2 Chain), 26.39 (**C**H_2 Chain), 22.12 (**C**H_2-CH_3), 13.99 (terminal C**H**$_3$); **ESI-MS** (m/z) calc. $C_{24}H_{42}N_3O_2$ found 404.3270 (100% $[M+H]^+$) and calc. $C_{24}H_{41}N_3NaO_2$ found 426.3091 (21% $[M+Na]^+$)

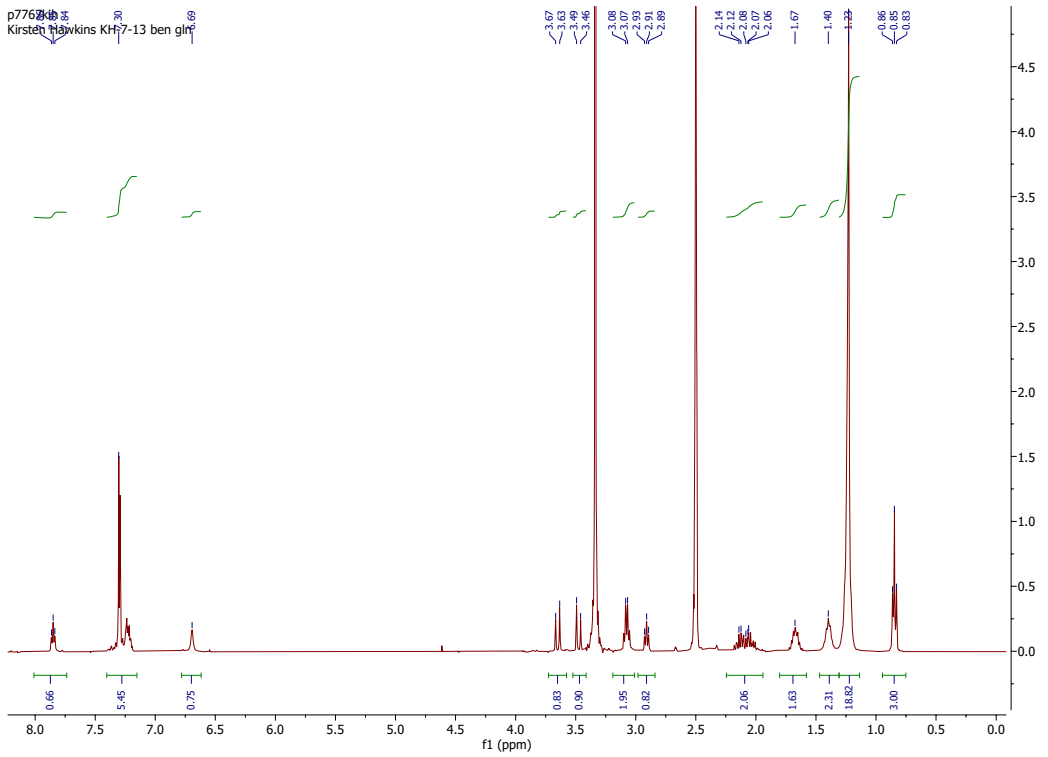


Fig. S5. ^{1}H NMR Spectrum of compound **3** in DMSO-d_6.

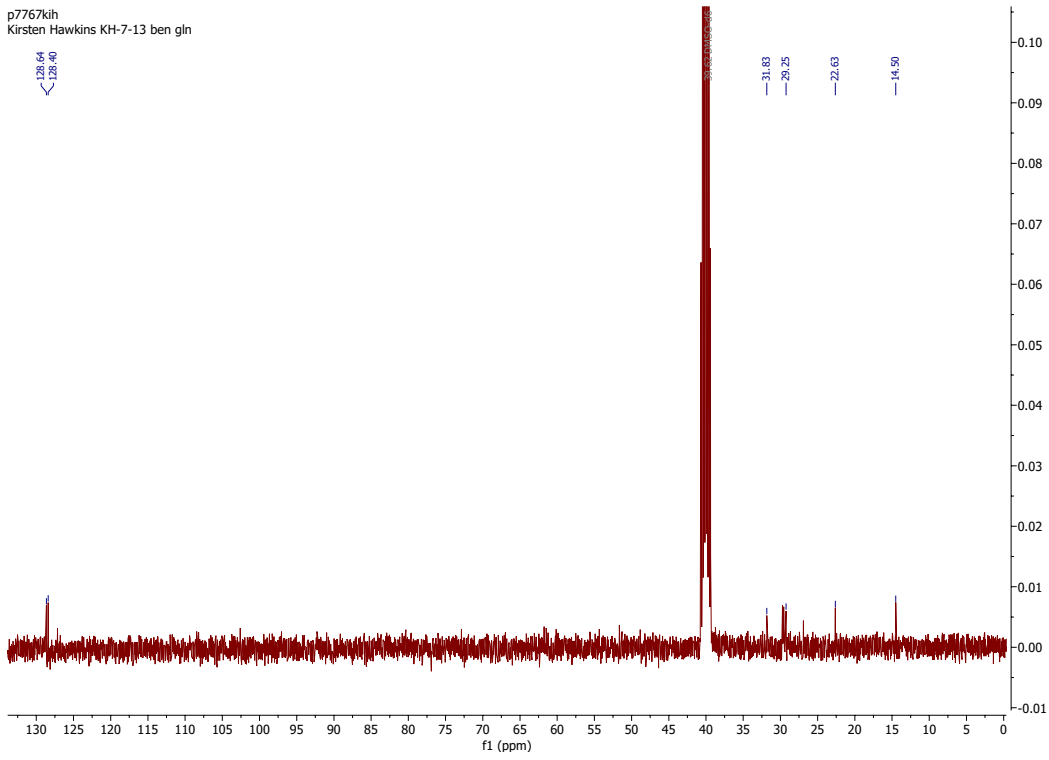
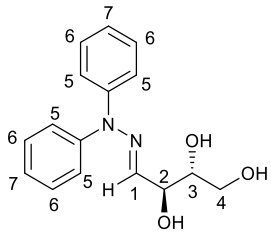


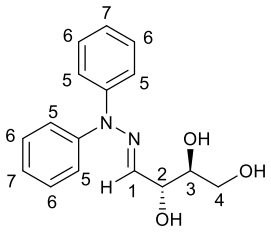
Fig. S6. ^{13}C NMR Spectrum of compound **3** in DMSO-d_6.

4.5. (*2R, 3S, E*)-4-(2,2-diphenylhydrazone)-butane-1,2,3-triol[1]



D-Erythrose (20 mg, 0.16 mmol) and *N,N*-diphenyl hydrazine (35 mg, 0.19 mmol) were dissolved in methanol (3 mL) and stirred for 45 minutes at room temperature before concentration *in vacuo*. Purification via flash column chromatography (95:5 DCM:methanol) gave a brown oil in a 19% yield (9.12 mg, 0.031 mmol). **IR** ν_{max} (cm^{-1}): 3308m, 3061w, 2927w, 2882w, 1589s, 1494vs, 1451m, 1410s, 1296s, 1212s, 1175m, 1155m, 1090s, 1070s, 1037s, 1002s, 939m, 887m, 782m, 748vs, 737s, 693vs, 654s, 630s, 618s, 566s, 507s, 456m; **^{1}H NMR** (400 MHz, CD_3OD) δ ppm: 7.37-7.34 (4H, m, H_6), 7.12 (2H, t, *J* = 7.4 Hz, H_7), 7.06 (4H, m, H_5), 6.54 (1H, d, *J* = 6.0 Hz,H_1), 4.24 (1H, dd, *J* = 6.0, 5.9 Hz, H_2), 3.67-3.60 (1H, m, H_3), 3.55-3.50 (2H, m, H_4); **^{13}C NMR** (400 MHz, CD_3OD) δ ppm: 145.2 (C-5), 139.2 (C-4), 130.7 (C-7), 125.4 (C-8), 123.5 (C-6), 75.5 (C-2), 73.7 (C3), 64.3 (C-1); **ESI-MS** (m/z) cal $C_{16}H_{18}N_2NaO_3$ 309.1210, found 309.1210 (100% $[M+H]^+$).

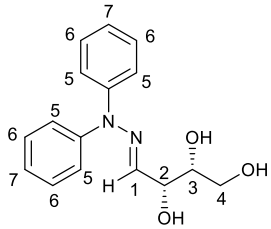
4.6. (*2S, 3R, E*)-4-(2,2-diphenylhydrazone)-butane-1,2,3-triol[1]



L-Erythrose (20 mg, 0.16 mmol) and *N,N*-diphenyl hydrazine 144 (35 mg, 0.19 mmol) were dissolved in methanol (3 mL) and stirred for 45 minutes at room temperature before concentration in vacuo. Purification via flash column chromatography (95:5 DCM:methanol) gave a brown oil in a 19% yield (9.12 mg, 0.031 mmol). **IR** ν_{max} (cm^{-1}): 3308m, 3061w, 2927w, 2882w, 1589s, 1494vs, 1451m, 1410s, 1296s, 1212s, 1175m, 1155m, 1090s, 1070s, 1037s, 1002s, 939m, 887m, 782m, 748vs, 737s, 693vs, 654s, 630s, 618s, 566s, 507s, 456m; **^{1}H NMR** (400 MHz, CD_3OD) δ ppm 7.37-7.34 (4H, m, H_6), 7.12 (2H, t, *J* = 7.4 Hz, H_7), 7.06 (4H, m, H_5), 6.54 (1H, d, *J* = 6.0 Hz,H_1), 4.24 (1H, dd, *J* = 6.0, 5.9 Hz, H_2), 3.67-3.60 (1H, m, H_3), 3.55-3.50

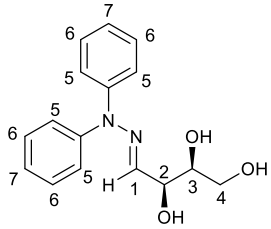
(2H, m, H_4); **^{13}C NMR** (400 MHz, CD_3OD) δ ppm: 145.2 (C-5), 139.2 (C-4), 130.7 (C-7), 125.4 (C-8), 123.5 (C-6), 75.5 (C-2), 73.7 (C3), 64.3 (C-1); **ESI-MS** (m/z) calc. $C_{16}H_{18}N_2NaO_3$ 309.1210, found 309.1210 (100% $[M+H]^+$).

4.7. (*2S, 3S, E*)-4-(2,2-diphenylhydrazone)-butane-1,2,3-triol[1]



L-Threose (20 mg, 0.16 mmol) and *N,N*-diphenyl hydrazine 144 (35 mg, 0.19 mmol) were dissolved in methanol (3 mL) and stirred for 45 minutes at room temperature before concentration in vacuo. Purification via flash column chromatography (95:5 DCM:methanol) gave a brown oil in a 68% yield (31 mg, 0.108 mmol). **IR** ν_{max} (cm^{-1}): 3308m, 3061w, 2927w, 2882w, 1589s, 1494vs, 1451m, 1410s, 1296s, 1212s, 1175m, 1155m, 1090s, 1070s, 1037s, 1002s, 939m, 887m, 782m, 748vs, 737s, 693vs, 654s, 630s, 618s, 566s, 507s, 456m; **^{1}H NMR** (400 MHz, CD_3OD) δ ppm: 7.35 (4H, dd, *J* =8.4 Hz, H_6), 7.18 (2H, t, *J* = 7.4 Hz, H_7), 7.05 (4H, m, H_5), 6.51 (1H, d, *J* = 5.7 Hz, H_1), 4.27 (1H, dd, *J* = 5.7, 4.4 Hz, H_2), 3.63 (1H, ddd, *J* = 8.0, 5.0, 4.4 Hz, H_3), 3.63 (2H, dd, *J*= 12.5, 5.0 Hz H_4); **^{13}C NMR** (400 MHz, CD_3OD) δ ppm: 145.2 (C-5), 139.2 (C-4), HRMS 130.7 (C-7), 125.4 (C-8), 123.5 (C-6), 75.5 (C-2), 73.7 (C3), 64.3 (C-1); **ESI-MS** (m/z) calc. $C_{16}H_{18}N_2NaO_3$ 309.1210, found 309.1210 (100% $[M+H]^+$).

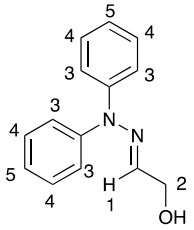
4.8. (*2R, 3R, E*)-4-(2,2-diphenylhydrazone)-butane-1,2,3-triol[1]



D-Threose (60 mg, 0.5 mmol) and *N,N*-diphenyl hydrazine (105 mg, 0.57 mmol mmol) were dissolved in methanol (3 mL) and stirred for 45 minutes at room temperature before concentration in vacuo. Purification via flash column chromatography (95:5 DCM:methanol) gave a brown oil in a 5.5% yield (8.12 mg, 0.091 mmol). **IR** ν_{max} (cm^{-1}): 3308m, 3061w, 2927w,

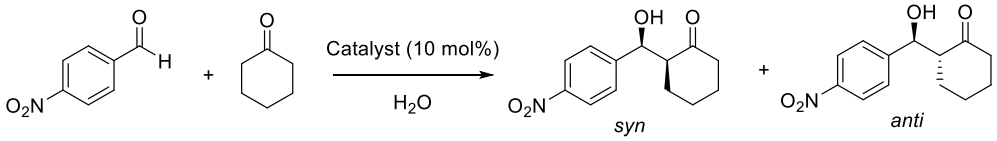
2882w, 1589s, 1494vs, 1451m, 1410s, 1296s, 1212s, 1175m, 1155m, 1090s, 1070s, 1037s, 1002s, 939m, 887m, 782m, 748vs, 737s, 693vs, 654s, 630s, 618s, 566s, 507s, 456m; **^{1}H NMR** (400 MHz, CD_3OD) δ ppm: 7.35 (4H, dd, *J* =8.4 Hz, H_6), 7.18 (2H, t, *J* = 7.4 Hz, H_7), 7.05 (4H, m, H_5), 6.51 (1H, d, *J* = 5.7 Hz, H_1), 4.27 (1H, dd, *J* = 5.7, 4.4 Hz, H_2), 3.63 (1H, ddd, *J* = 8.0, 5.0, 4.4 Hz, H_3), 3.63 (2H, dd, *J*= 12.5, 5.0 Hz H_4); **^{13}C NMR** (400 MHz, CD_3OD) δ ppm: 145.2 (C-5), 139.2 (C-4), HRMS 130.7 (C-7), 125.4 (C-8), 123.5 (C-6), 75.5 (C-2), 73.7 (C3), 64.3 (C-1); **ESI-MS** (m/z) calc. $C_{16}H_{18}N_2NaO_3$ 309.1210, found 309.1210 (100% $[M+H]^+$).

4.9. 2-(2,2-Diphenylhydrazone)-ethanol[1]



Glycolaldehyde dimer (30 mg, 0.25 mmol) and *N,N*-diphenyl hydrazine (55 mg, 0.3 mmol) were dissolved in methanol (3 mL) and stirred for 45 minutes at room temperature before concentration *in vacuo*. Purification via flash column chromatography (95:5 DCM:methanol) gave a brown oil in a 30 % crude yield (17 mg, 0.075 mmol). **^{1}H NMR** (400 MHz, CD_3OD) δ ppm: 7.40-7.37 (4H, m, H_5), 7.13-7.09 (2H, m, H_4), 7.03 (4H, d, *J*= 7.9 Hz, H_3), 6.49 (1H, t, *J* = 5.0 Hz, H_1), 4.15 (1H, d, *J* = 5.0 H_2), in agreement with that reported in literature.[2]

5. General Procedure for Solution Phase Catalysis of 4-Nitrobenzaldehyde and Cyclohexanone[3]



To a solution of catalyst (0.065 mmol) in water (20 mL) was added a solution of 4-nitrobenzaldehyde (98 mg, 6.5 mmol) in cyclohexanone (6.7 mL, 65 mmol). The reaction was left for a period of time (24, 48 or 72 h) with no stirring. After this time the reaction mixture was extracted with DCM then solvent was removed *in vacuo* to yield a yellow solid crude

material. The conversion of the reaction was determined by integrating the ^{1}H NMR of the crude reaction mixture using the aldehyde peak as a reference. The *syn*:*anti* ratio was determined by integrating the ^{1}H NMR of the crude reaction mixture and by comparing the CH-OH peaks. The enantiomeric excess of the crude product was analysed, via HPLC using a Chiralpak IB column (97:3 Hexane: IPA Flow rate 1 mL/min).

Syn diastereomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 8.21 (1H, d, *J*= 8.9 Hz, $H_{\mathbf{1}}$), 7.49 (1H, d, *J*= 8.4 Hz, $H_{\mathbf{2}}$), 5.49 (1 H, br. s, $H_{\mathbf{3}}$), 3.18 (1 H, br. s, OH), 2.66-2.59 (1 H, m, $H_{\mathbf{4}}$), 2.52-2.46 (1 H, m, $H_{\mathbf{8}}$), 2.45-2.35 (1 H, m, $H_{\mathbf{8}}$), 2.15-2.08 (1 H, m, $H_{\mathbf{7}}$), 1.89-1.82 (1H, m, $H_{\mathbf{6}}$), 1.76-1.65 (2 H, m, $H_{\mathbf{5}}$, $H_{\mathbf{7}}$), 1.63-1.47 (2 H, m, $H_{\mathbf{5}}$, $H_{\mathbf{6}}$); **^{13}C NMR** (400 MHz, CDCl3) δ ppm: 214.0 (C=O), 149.1 (Ar), 147.1 (C-N), 126.7 (2), 123.8 (1), 70.2 (3), 56.9 (4), 42.7 (8), 28.0 (7), 26.0 (5), 25.0 (6); **Chiral HPLC** *syn*-diastereomer: Enantiomer 1 t_R = 27.9 min, Enantiomer 2 t_R = 29.5 min.

Anti diastereomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 8.21 (1H, d, *J*=8.8 Hz, $H_{\mathbf{1}}$), 7.51 (1H, d, *J*= 8.4 Hz, $H_{\mathbf{2}}$), 4.89 (1H, dd, J=3.2 Hz, 8.35 Hz, $H_{\mathbf{3}}$), 4.08 (1 H, d, J=3.2 Hz, OH), 2.64-2.54 (1 H, m, $H_{\mathbf{4}}$), 2.53-2.46 (1 H, m, $H_{\mathbf{8}}$), 2.42-2.31 (1 H, m, $H_{\mathbf{8}}$), 2.15-2.08 (1 H, m, $H_{\mathbf{7}}$), 1.89-1.79(1 H, m, $H_{\mathbf{6}}$), 1.74-1.64 (1 H, m, $H_{\mathbf{5}}$,), 1.63-1.47 (2 H, m, $H_{\mathbf{5}}$, $H_{\mathbf{6}}$), 1.45-1.34 (1 H, m, $H_{\mathbf{7}}$); **Chiral HPLC** *anti*-diastereomer: Enantiomer 1 t_R = 34.7 min, Enantiomer 2 t_R = 43.3 min. Spectroscopic data are in agreement with the literature.[3]

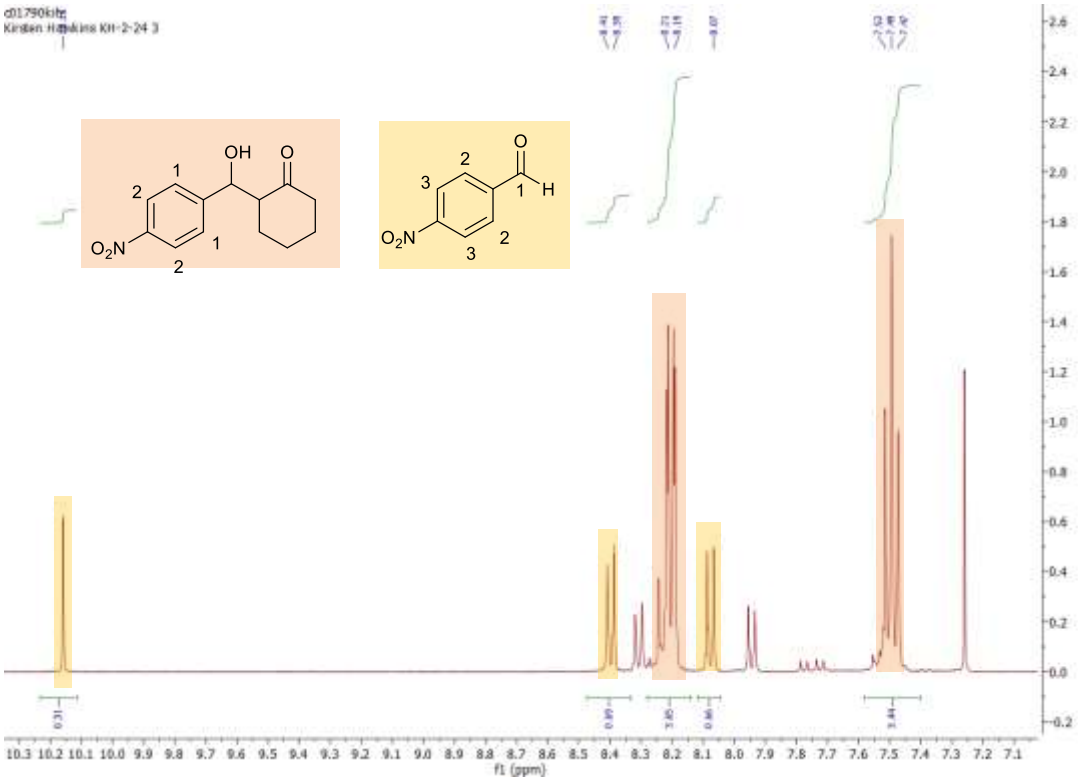


Fig. S7. Typical ^{1}H NMR Spectrum for solution phase catalysis of 4-nitrobenzaldehyde and cyclohexanone. Starting material key peak of 4-nitrobenzaldehyde: ^{1}H NMR (400 MHz, $CDCl_3$): 10.16 (1H, S, H_1), 8.41 (2H, d, *J* = 8.6 Hz, H_3), 8.07 (2H, d, *J* = 8.6 Hz, H_2) Product key peaks: ^{1}H NMR (400 MHz, $CDCl_3$): 8.21 (1H, d, *J*=8.8 Hz, H_2), 8.20 (1H, d, *J*= 8.9 Hz, H_2) 7.41 (1H, d, *J*=8.5 Hz, H_1) 7.48 (1H, d, *J*= 8.4 Hz, H_1).

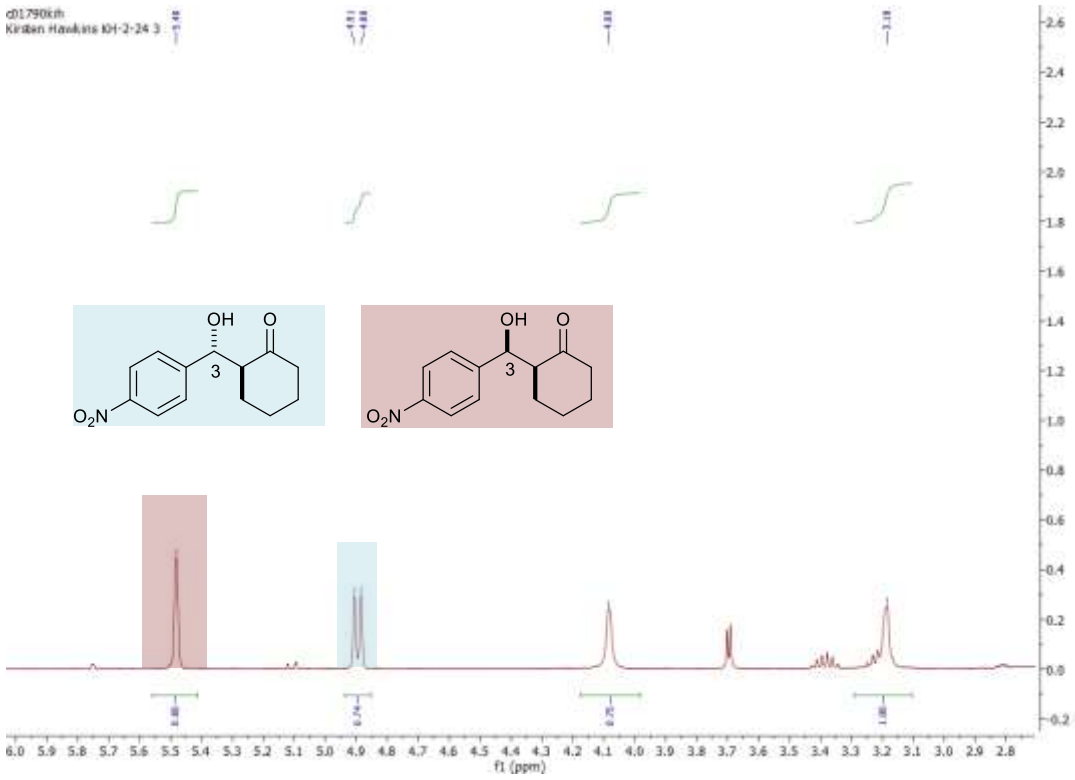


Fig. S8. Typical ^{1}H NMR Spectrum for solution phase catalysis of 4-nitrobenzaldehyde and cyclohexanone. *Syn* product key peaks: ^{1}H NMR $CDCl_3$: 5.49 (1H, br. s, H_3), 3.18 (1H, br. s, OH), *Anti* product key peaks: ^{1}H NMR $CDCl_3$: 4.89 (1H, dd, *J*=3.2 Hz, 8.35 Hz, H_3), 4.08 (1H, d, *J*=3.2 Hz, OH)

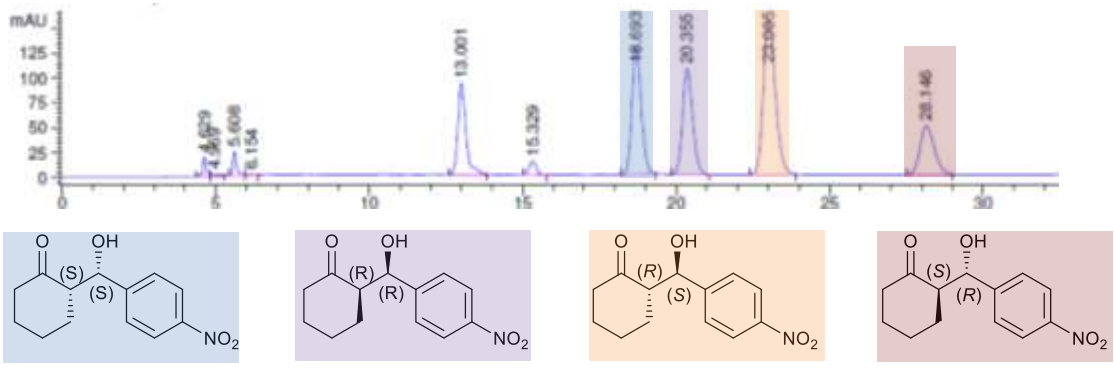


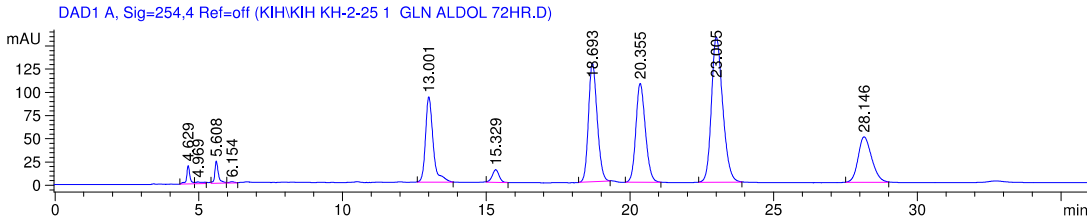
Fig. S9. HPLC trace of crude aldol condensation of 4-nitrobenzaldehyde and cyclohexanone. IB Chiral Pak, 1 mL/min, 97:3 Hexane: IPA

Table S1: Glutamine amide (**1**) catalysed aldol condensation of 4-nitrobenzaldehyde and cyclohexanone in water

Solvent	Time h	Conversion %	Crude NMR d.r anti:syn	Gel?
Water	24	45	2.07:1	In-situ
	24	33	2.22:1	In-situ
Water	48	100	1.57:1	In-situ
	48	68	1.59:1	In-situ
	48	100	1.16:1	In-situ
Water	72	99	1.07:1	In-situ
	72	100	1.71:1	In-situ
	72	99	1.33:1	In-situ

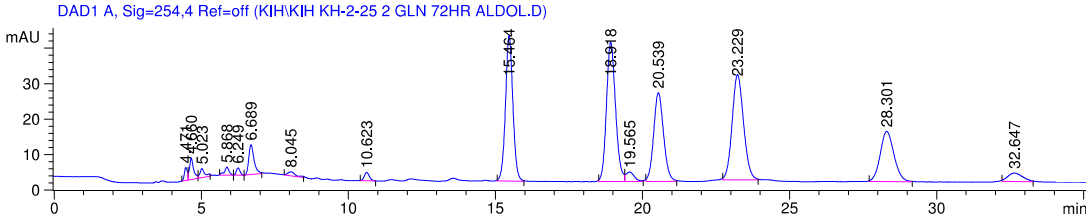
Table S2: L-Glutamine amide catalysis HPLC data

Solvent	Time h	Crude HPLC ee%	In situ gel?
Water	72	Syn 5% Anti 45%	Yes
Water	72	Syn 18% Anti 27%	Yes
Water	72	Syn 10% Anti 24%	Yes



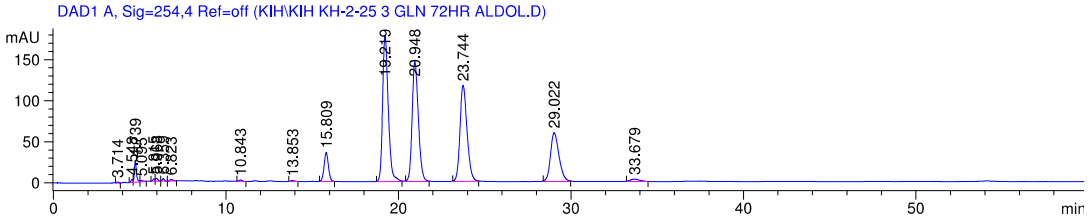
Peak	Retention time (min)	Peak area (%)
1	18.693	20.1493
2	20.355	18.3346
3	23.005	31.9384
4	28.146	12.0856

Figure S10: HPLC trace for aldol condensation of 4-nitrobenzaldehyde with cyclohexanone at 72 h run 1 catalysed by glutamine amide in solution phase



Peak	Retention time (min)	Peak area (%)
1	18.918	21.8651
2	20.539	15.1963
3	23.229	20.8279
4	28.301	11.9392

Figure S11: HPLC trace for aldol condensation of 4-nitrobenzaldehyde with cyclohexanone at 72 h run 2 catalysed by glutamine amide in solution phase

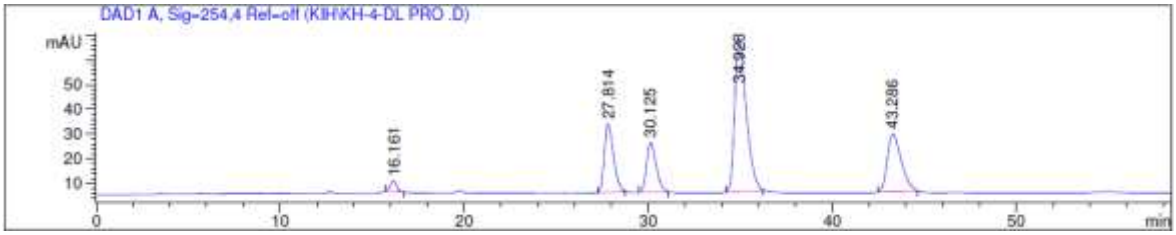


Peak	Retention time (min)	Peak area (%)
1	19.219	28.5837
2	20.948	25.7488
3	23.744	23.3859
4	29.022	14.2308

Figure S12: HPLC trace for aldol condensation of 4-nitrobenzaldehyde with cyclohexanone at 72 h run 3 catalysed by glutamine amide in solution phase

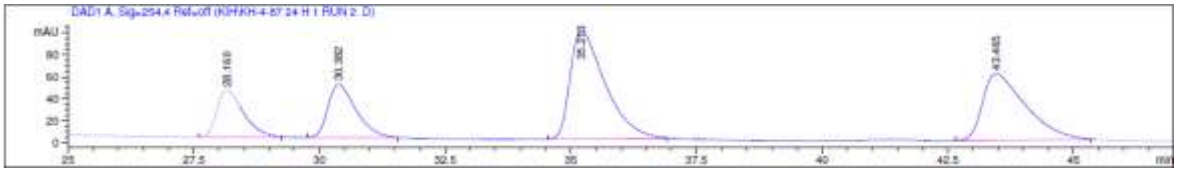
Table S3: Benzylglutamine amide catalysed aldol condensation of 4-nitrobenzaldehyde and cyclohexanone in solution in water

Entry	Time (h)	Conversion (%)	Crude NMR d.r anti:syn	Crude HPLC ee%
1	24	24	1.99 : 1.00	*Anti*: 16% *Syn*: 11%
2	24	21	1.95 : 1.00	*Anti*: 17% *Syn*: 7%
3	24	25	2.10 : 1.00	*Anti*: 16% *Syn*: 10%
4	48	24	2.14 :1.00	*Anti:* 22% *Syn*: 8%
5	48	46	2.20 : 1.00	*Anti*: 15% *Syn*: 7%
6	48	31	2.10 : 1.00	*Anti:* 23% *Syn*: 12%
7	72	42	1.98 :1.00	*Anti*: 15% *Syn*: 8%
8	72	53	2.11 : 1.00	*Anti*: 16% *Syn*: 6%
9	72	36	1.93 : 1.00	*Anti*: 16% *Syn*: 7%



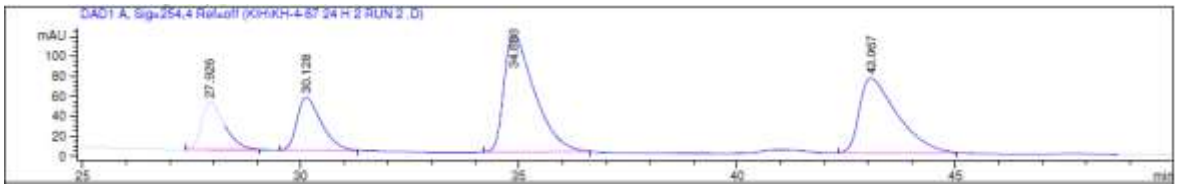
Peak	Retention time (min)	Peak area (%)
1	27.814	16.6655
2	30.125	12.8407
3	34.928	47.1505
4	43.286	21.5095

Figure S13: HPLC standard for the aldol condensation of 4-nitrobenzaldehyde and cyclohexanone using D/L proline as a catalyst



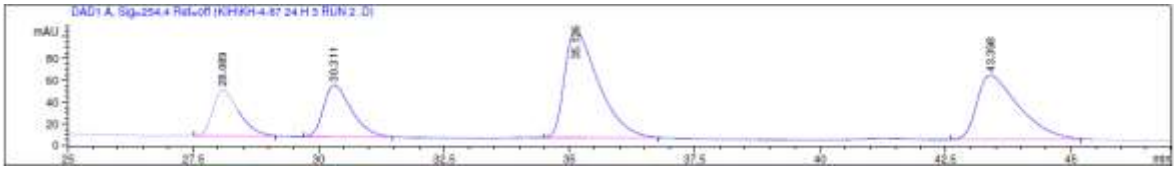
Peak	Retention time (min)	Peak area (%)
1	27.823	2.2277
2	30.058	2.8000
3	34.855	6.5108
4	42.927	4.7606

Figure S14: HPLC trace for aldol condensation of 4-nitrobenzaldehyde with cyclohexanone at 24 h run 1 catalysed by benzyl glutamine amide in solution phase



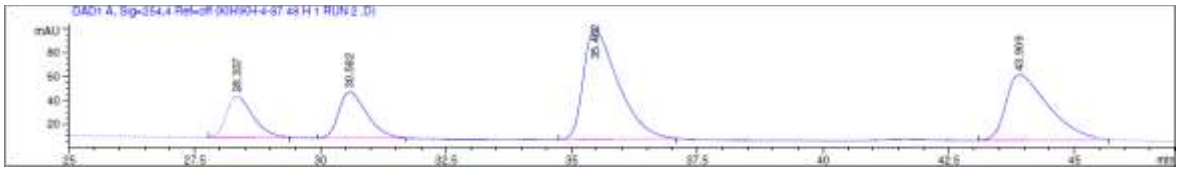
Peak	Retention time (min)	Peak area (%)
1	27.901	2.1275
2	30.157	2.4308
3	35.106	2.8400
4	43.363	2.8793

Figure S15: HPLC trace for aldol condensation of 4-nitrobenzaldehyde with cyclohexanone at 24 h run 2 catalysed by benzyl glutamine amide in solution phase



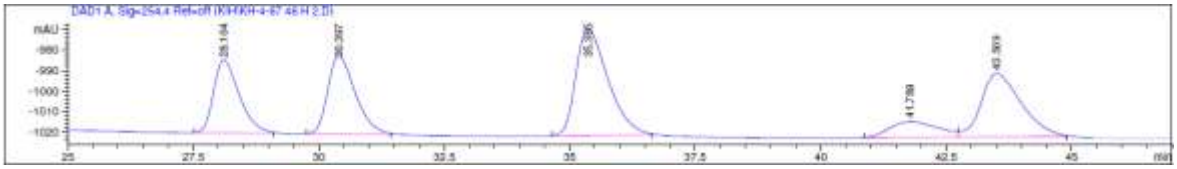
Peak	Retention time (min)	Peak area (%)
1	27.985	2.2724
2	30.231	2.7656
3	35.046	6.2312
4	43.093	4.5699

Figure S16: HPLC trace for aldol condensation of 4-nitrobenzaldehyde with cyclohexanone at 24 h run 3 catalysed by benzyl glutamine amide in solution phase



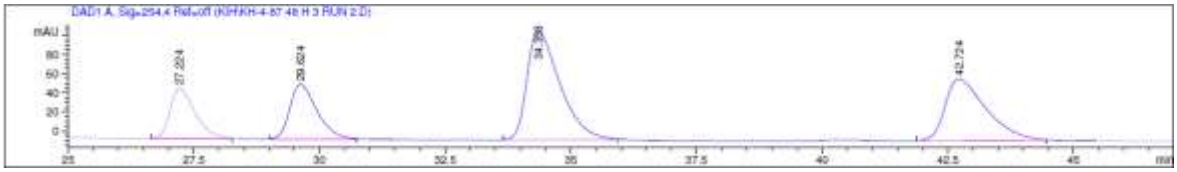
Peak	Retention time (min)	Peak area (%)
1	28.195	1.9041
2	30.471	2.2492
3	35.321	4.7004
4	43.421	3.0202

Figure S17: HPLC trace for aldol condensation of 4-nitrobenzaldehyde with cyclohexanone at 48 h run 1 catalysed by benzyl glutamine amide in solution phase



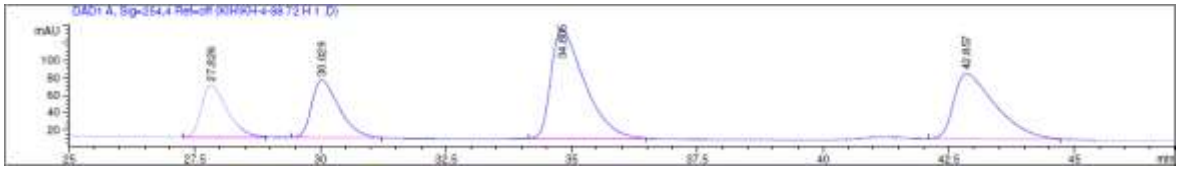
Peak	Retention time (min)	Peak area (%)
1	28.104	2.0422
2	30.397	2.3394
3	35.365	3.7423
4	43.509	2.7861

Figure S18: HPLC trace for aldol condensation of 4-nitrobenzaldehyde with cyclohexanone at 48 h run 2 catalysed by benzyl glutamine amide in solution phase



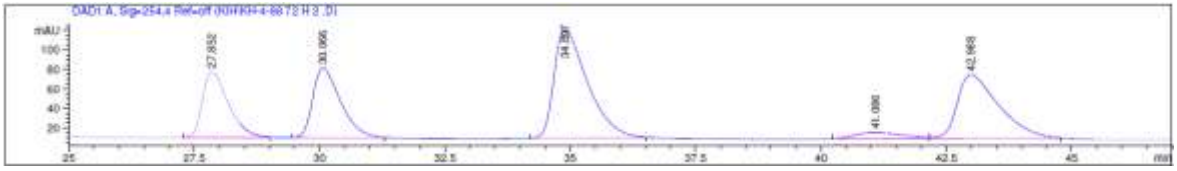
Peak	Retention time (min)	Peak area (%)
1	27.985	2.2724
2	30.231	2.7656
3	35.046	6.2312
4	43.093	4.5699

Figure S19: HPLC trace for aldol condensation of 4-nitrobenzaldehyde with cyclohexanone at 48 h run 3 catalysed by benzyl glutamine amide in solution phase



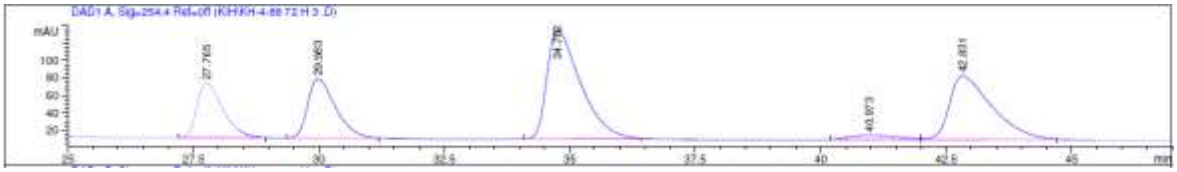
Peak	Retention time (min)	Peak area (%)
1	27.826	3.2861
2	30.029	3.8748
3	34.805	8.901
4	42.857	6.6407

Figure S20: HPLC trace for aldol condensation of 4-nitrobenzaldehyde with cyclohexanone at 72 h run 1 catalysed by benzyl glutamine amide in solution phase



Peak	Retention time (min)	Peak area (%)
1	27.852	5.8943
2	30.066	6.6581
3	34.897	12.4945
4	42.988	9.1192

Figure S21: HPLC trace for aldol condensation of 4-nitrobenzaldehyde with cyclohexanone at 72 h run 2 catalysed by benzyl glutamine amide in solution phase



Peak	Retention time (min)	Peak area (%)
1	27.765	4.1753
2	29.983	4.8244
3	34.762	10.6466
4	42.831	7.9042

Figure S22: HPLC trace for aldol condensation of 4-nitrobenzaldehyde with cyclohexanone at 72 h run 3 catalysed by benzyl glutamine amide in solution phase

Table S4: Benzylglutamine amide catalysed aldol condensation of 4-nitrobenzaldehyde and cyclohexanone in solution in buffered conditions in water.

Entry	Catalyst Present	Time h	pH	Conversion	Crude NMR dr *Anti:Syn*	Crude HPLC ee %
1	No	72	8.6	50%	2.00:1.00	*Anti :*1 *Syn* : 1
2	Yes	24	7	11%	1.88:1.00	*Anti:* 51 *Syn:* 16 *Anti:* 59 *Syn:* 19 *Anti:* 58 *Syn:* 18
3	Yes	24	4	5%	1.94:1.00	*Anti:* 72 *Syn:* 34 *Anti:* 73 *Syn:* 35 *Anti:* 74 *Syn:* 34
4	No	24	7	4%	1.98:1.00	*Anti:* 1 *Syn:* 1
5	No	24	4	0.3 %	0.84: 1.00	*Anti:* 1 *Syn:* 1

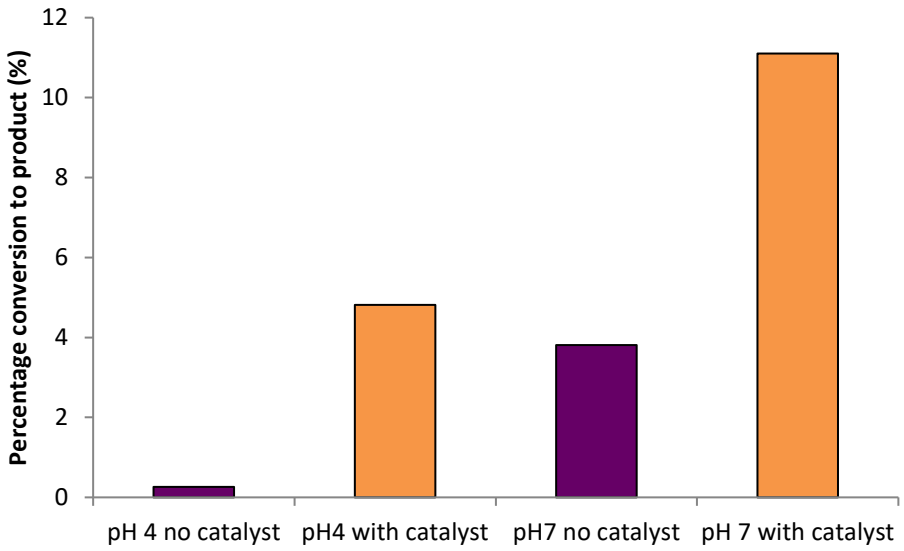


Figure S23: Graph showing percentage conversion of starting material to product after 24 h at different pH values, with or without catalyst.

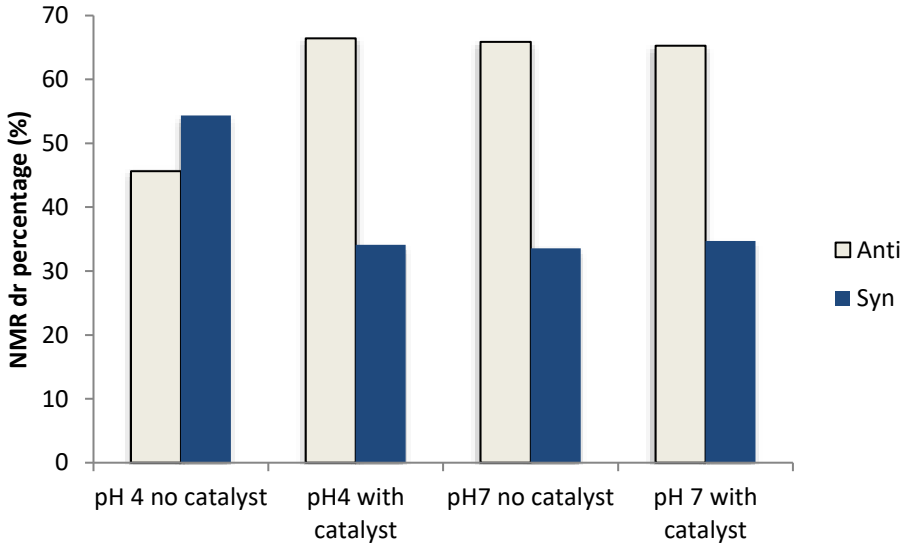


Figure S24: Graph showing percentages of *syn* and *anti* products after 24 h at different pH values, with and without catalyst

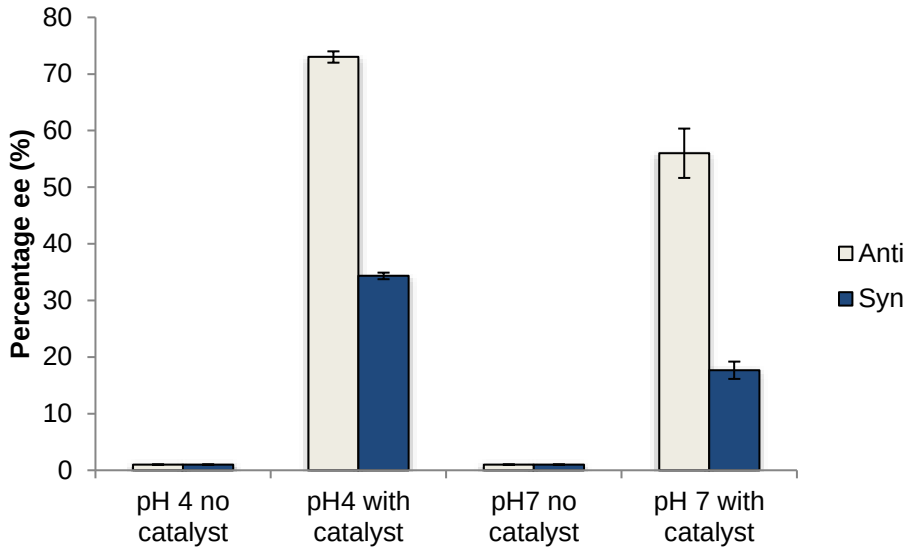
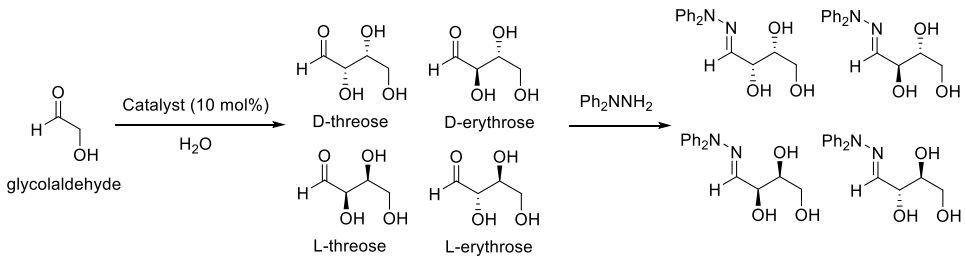
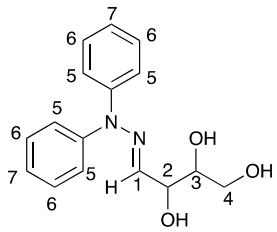


Figure S25: Graph showing *syn* and *anti* ee% after 24 h at different pH values, with and without catalyst.

6. General Procedure for the Dimerization of Glycolaldehyde on Hydrogel 3



To the surface of the benzylglutamine amide hydrogel **3** (20 mg, 49.6 μmol, 5 mL) was added glycolaldehyde (59 mg, 0.49 mmol) in water (200 μL) in 10 μL aliquots. After 48 h the reaction was stopped by removal of the water *in vacuo*. Once the water was removed, 1.2 eq of diphenyl hydrazone was added in methanol with 1-2 drops of acetic acid. The reaction was left to stir for 1 h at room temperature. After 1 h the solvent was removed to yield a brown oil. The crude oil was analysed by ^{1}H NMR to determine conversion of glycolaldehyde to tetrose sugars. The crude material was then purified by column chromatography (100 % DCM to 8:2 DCM:MeOH) and chiral HPLC was performed on an IC Chiral Pak column (90:10 Hexane:IPA, 40^{o}C, 1 mL/min)



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Erythrose hydrazone **^{1}H NMR** (400 MHz, CD_3OD) δ ppm 7.37-7.34 (4H, m, H_6), 7.12 (2H, t, *J* = 7.4 Hz, H_7), 7.06 (4H, m, H_5), 6.54 (1H, d, *J* = 6.0 Hz,H_1), 4.24 (1H, dd, *J* = 6.0, 5.9 Hz, H_2), 3.67-3.60 (1H, m, H_3), 3.55-3.50 (2H, m, H_4);

Threose hydrazone **^{1}H NMR** (400 MHz, CD_3OD) δ ppm: 7.35 (4H, dd, *J* =8.4 Hz, H_6), 7.18 (2H, t, *J* = 7.4 Hz, H_7), 7.05 (4H, m, H_5), 6.51 (1H, d, *J* = 5.7 Hz, H_1), 4.27 (1H, dd, *J* = 5.7, 4.4 Hz, H_2), 3.63 (1H, ddd, *J* = 8.0, 5.0, 4.4 Hz, H_3), 3.63 (2H, dd, *J*= 12.5, 5.0 Hz H_4);

Chiral HPLC: L-Erythrose hydrazone t_R = 18.414 min, D-Erythrose hydrazone t_R = 27.130 min, L-Threose hydrazone t_R = 34.082 min, D-Threose hydrazone t_R = 21.905 min

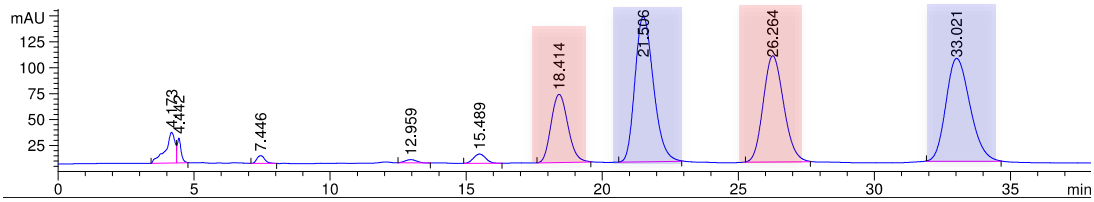


Figure S26: Mixed Hydrazone HPLC trace Chiralpak IC column (90:10 *n*-hexane: IPA) 40°C. D-erythrose hydrazone = 18.414 min, D-threose Hydrazone = 21.506 min, L-erythrose = 26.264 min, L-threose = 33.021 min

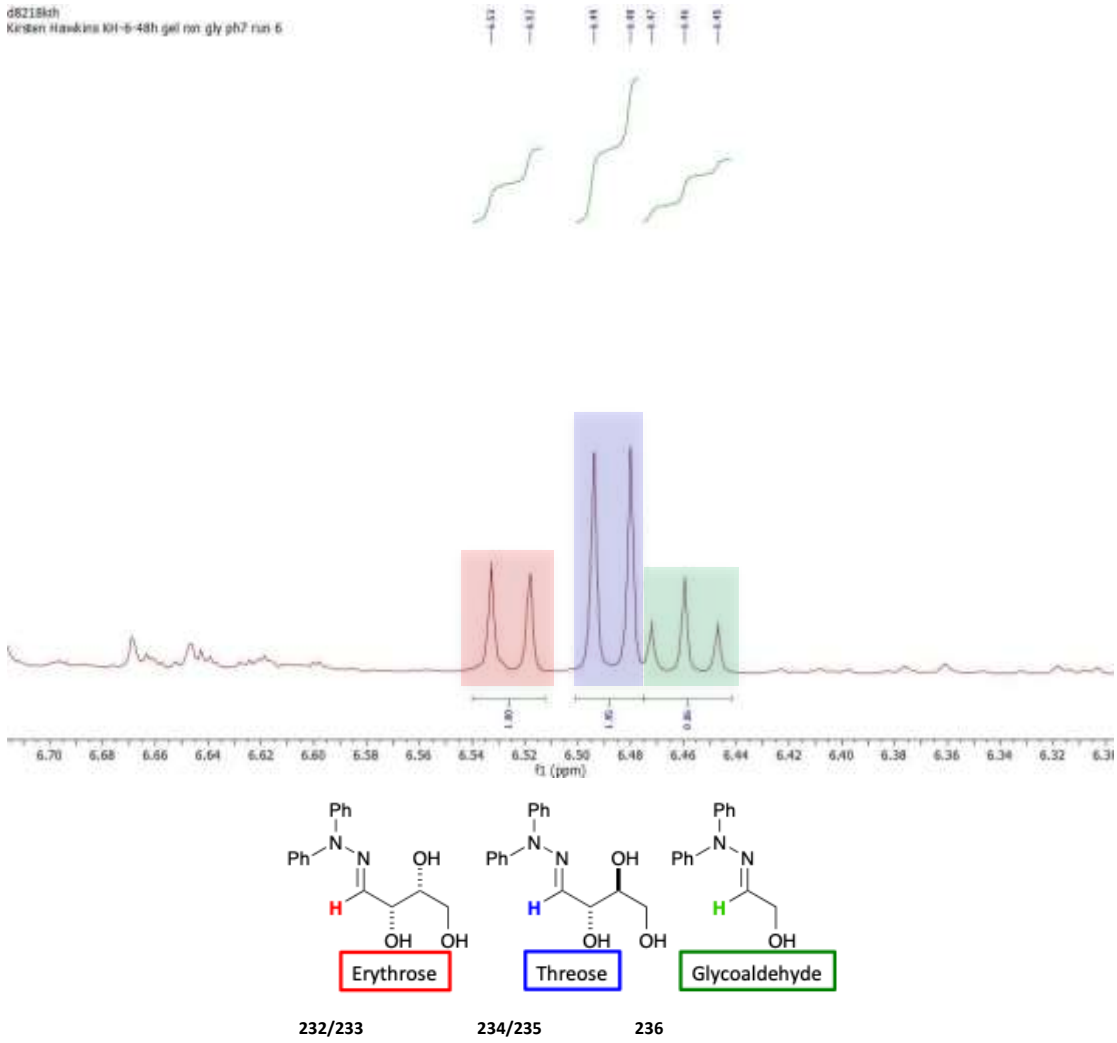
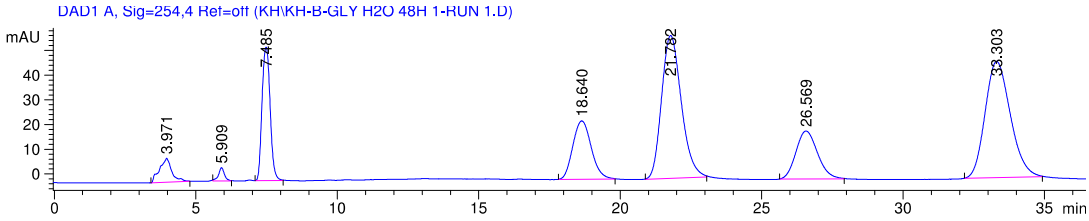
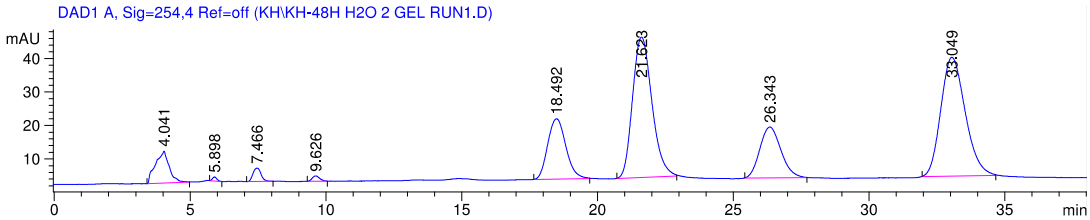


Figure S27: An authentic crude ^{1}H NMR of the dimerization of glycolaldehyde (**89**) on the benzylglutamine amide (**230**) gel. Protected as the hydrazone



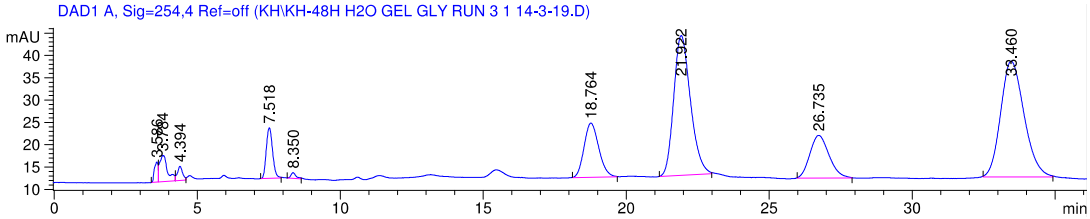
Peak	Retention time (min)	Peak area (%)
1	18.640	11.5690
2	21.782	30.2097
3	26.569	11.1212
4	33.303	31.5698

Figure S28: HPLC trace for dimerization of glycolaldehyde with benzylglutamine amide as a gel 48 h run 1



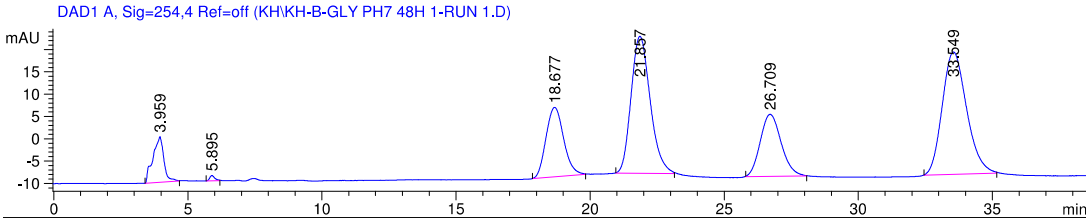
Peak	Retention time (min)	Peak area (%)
1	18.492	13.0411
2	21.623	32.3852
3	26.343	12.7896
4	33.049	34.6036

Figure S29: HPLC trace for dimerization of glycolaldehyde with benzylglutamine amide as a gel 48 h run 2



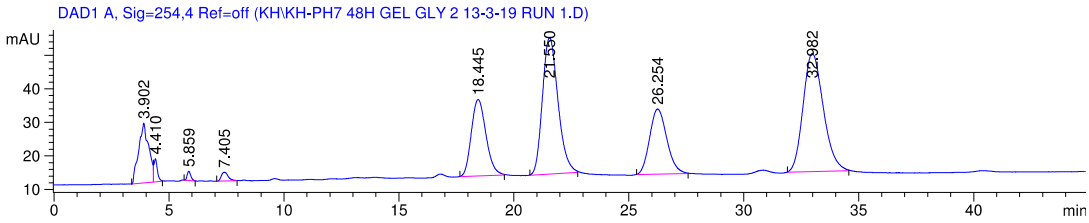
Peak	Retention time (min)	Peak area (%)
1	18.764	10.7850
2	21.922	31.7947
3	26.735	11.1461
4	33.460	36.8207

Figure S30: HPLC trace for dimerization of glycolaldehyde with benzylglutamine amide as a gel 48 h run 3



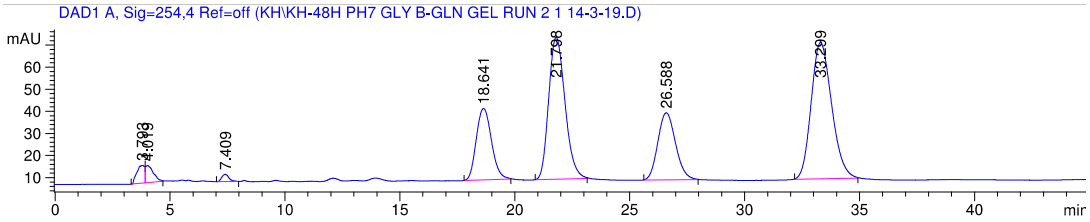
Peak	Retention time (min)	Peak area (%)
1	18.764	14.1906
2	21.922	30.2743
3	26.735	15.0206
4	33.460	34.5193

Figure S31: HPLC trace for dimerization of glycolaldehyde with benzylglutamine amide as a gel 48 h at pH 7 run 1



Peak	Retention time (min)	Peak area (%)
1	18.445	14.8551
2	21.550	28.2334
3	26.254	14.8500
4	34.982	31.7954

Figure S32: HPLC trace for dimerization of glycolaldehyde with benzylglutamine amide as a gel 48 h at pH 7 run 2



Peak	Retention time (min)	Peak area (%)
1	18.641	14.1279
2	21.798	30.0387
3	26.588	15.3826
4	33.299	36.2502

Figure S33: HPLC trace for dimerization of glycolaldehyde with benzylglutamine amide as a gel 48 h at pH 7 run 3

7. Characterisation of L-glutamine amide (1) and 4-nitrobenzaldehyde gel

Table S5: Identifying the minimum ratio of 4-nitrobenzaldehyde to glutamine amide (**1**) (1 mg, 3.16 mmol) required to form a hydrogel in water (1 mL). Gelation determined by tube inversion.

Entry	Equivalents of 4-nitrobenzaldehyde	Quantity of 4-nitrobenzaldehyde	Did it gel?
1	0.0	0 ug	No gel
2	0.1	50 μg ±5 μg	No gel
3	0.2	100 μg ±5 μg	No gel
4	0.3	140 μg ±5 μg	No gel
5	0.4	190 μg ±5 μg	No gel
6	0.5	240 μg ±5 μg	No gel
7	0.6	290 μg ±5 μg	Weak gel
8	0.7	340 μg ±5 μg	Gel
9	0.8	390 μg ±5 μg	Gel
10	0.9	440 μg ±5 μg	Gel
11	1.0	480 μg ±5 μg	Gel

Table S6: Varying the concentration of the 1:1 system to find the minimum gelation concentration (MGC) and most robust gel, 1 mL water.

Entry	Mass of glutamine amide	Equivalents of 4-nitrobenzaldehyde	Mass of 4-nitrobenzaldehyde	Did it gel?
1	0.50 mg	1.0	240 μg ±5 μg	Very Weak
2	1.00 mg	1.0	480 μg ±5 μg	Gel
3	2.00 mg	1.0	960 μg ±5 μg	Gel
4	3.00 mg	1.0	1.44 mg ±5 μg	Gel
5	4.00 mg	1.0	1.92 mg ±5 μg	Gel
6	5.00 mg	1.0	2.40 mg ±5 μg	Gel

Table S7: T_{gel} of glutamine amide (**1**) and 4-nitrobenzaldehyde hydrogel 1:1 (1 mL water)

Entry	Mass of glutamine amide	Equivalents of 4-nitrobenzaldehyde	T_{gel} / °C
1	1.00 mg	1.0	61 ± 0.5
2	2.00 mg	1.0	69 ± 0.5
3	3.00 mg	1.0	70 ± 0.5
4	4.00 mg	1.0	72 ± 0.5
5	5.00 mg	1.0	83 ± 0.5

Table S8: T_{gel} of glutamine amide (**1**) (1 mg, 3.16 mmol) and 4-nitrobenzaldehyde hydrogel with varying equivalents of 4-nitrobenzaldehyde (1 mL water)

Entry	Equivalents of 4-nitrobenzaldehyde	T_{gel} / °C
1	0.6	26 ± 0.5
2	0.7	76 ± 0.5
3	9.0	76 ± 0.5
4	10	62 ± 0.5

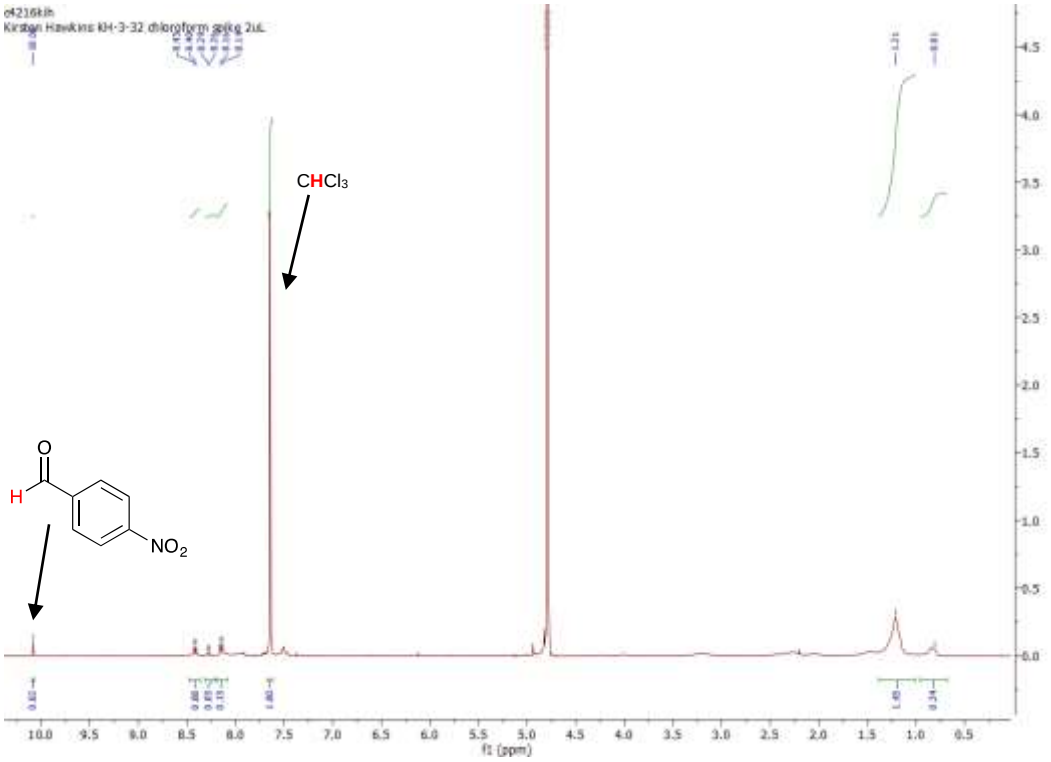


Figure S34: ^{1}H NMR of 4-nitrobenzaldehyde (**47**) (670 μg) and glutamine amide (**210**) (1.5mg) hydrogel with chloroform spike (2 μL). Obtained in D_2O (0.7 mL) 400 MHz

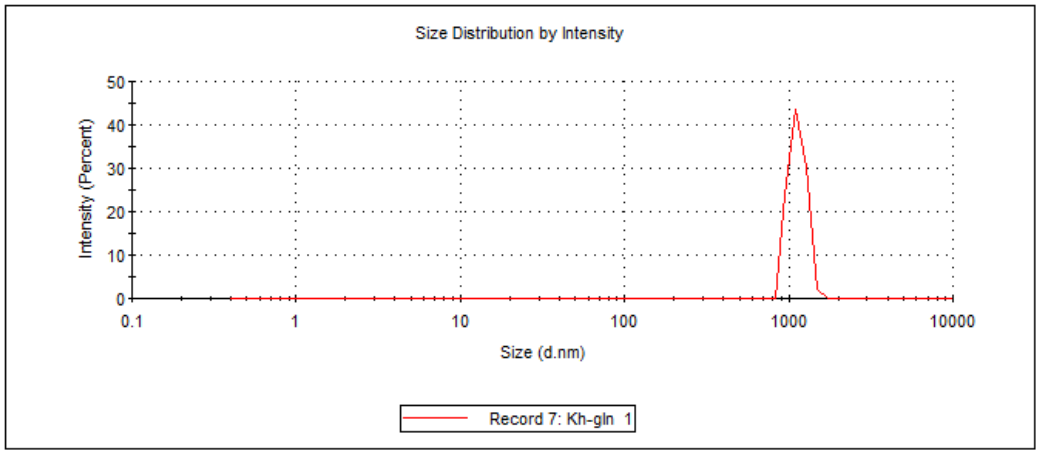


Figure S35: DLS data (size distribution by intensity) for glutamine amide (**1**) 1 mg/ mL.

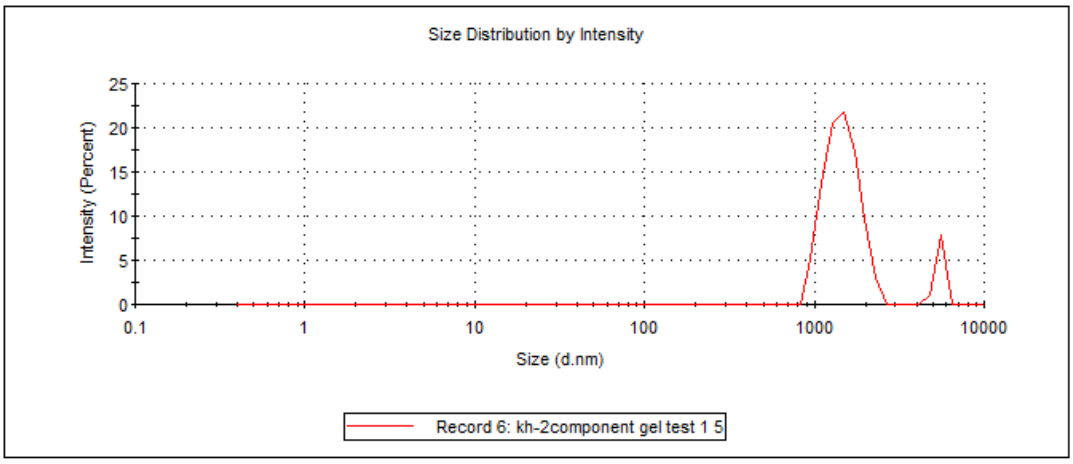


Figure S36: DLS (size distribution by intensity) of 1:1 glutamine amide (**1**) and 4-nitrobenzaldehyde in 1 mL water after standing for 5 h

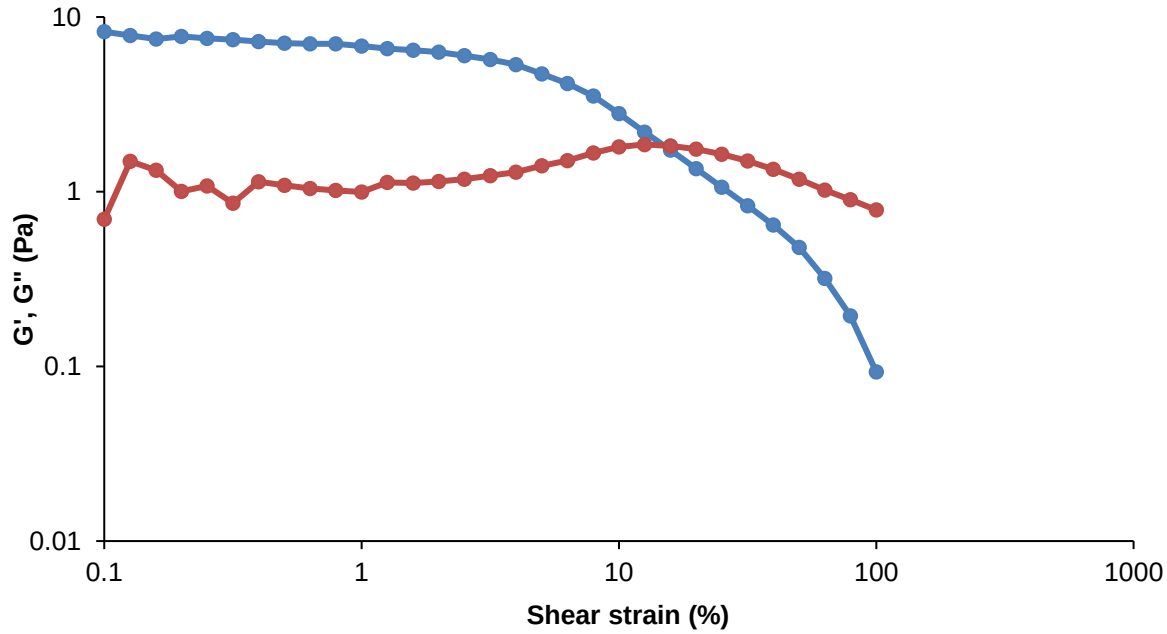


Figure S37: 4-Nitrobenzaldehye (480 μg) and glutamine amide (**1**) (1 mg) gel (1:1, 1 mL pH 2.9). Elastic (G', blue circles) and loss (G'', red circles) moduli of hydrogels with varying shear strain (frequency = 1 Hz). It is likely that the very soft nature of this gel reflects the low pH value at which this rheology was measured.

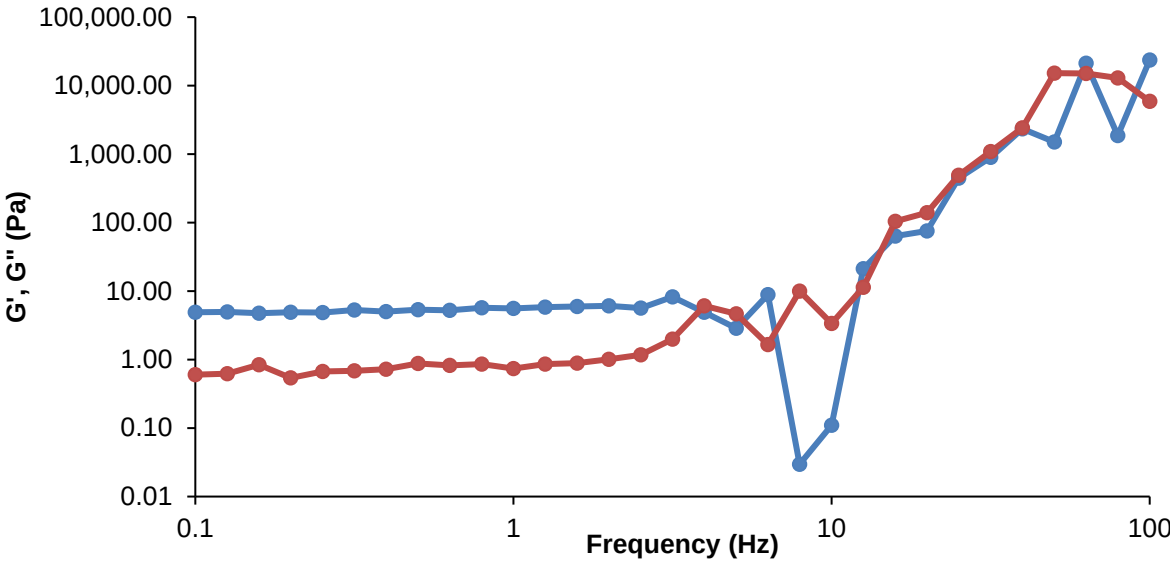


Figure S38: 4-Nitrobenzaldehyde and glutamine amide (**1**) gel (1:1, 1 mL, pH 2.9). Elastic (G', blue circles) and loss (G", red circles) moduli of hydrogels with varying frequency.

We also determined the rheology of the gel based on Schiff base **2a** formed. We were able to carry out this rheology at pH 7, and for purposes of direct comparison with gelator **3**, we measured the rheological performance at a total loading of 4 mg/mL (gutamine amide + benzaldehyde).

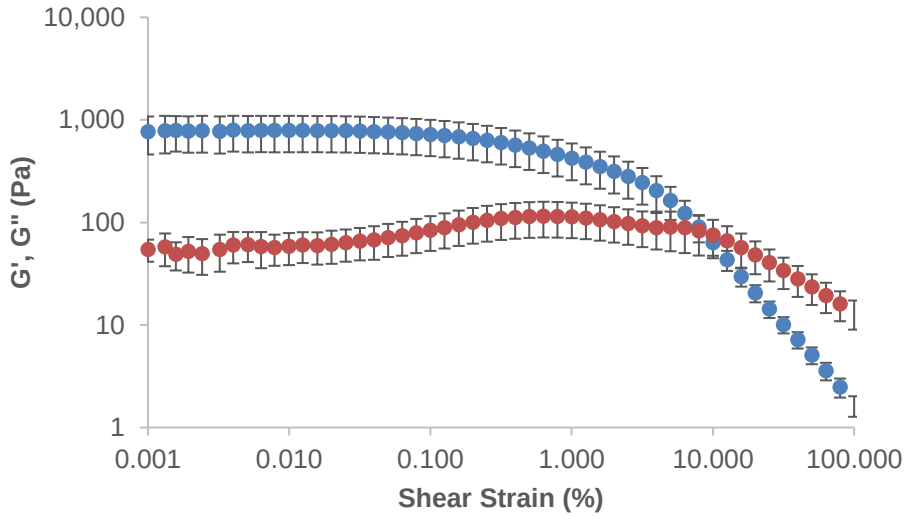


Figure S39: Glutamine amide (**1**) + benzaldehyde (1:1, total 4 mg in 1 mL water) gel. Elastic (G', blue circles) and loss (G'', red circles) moduli of hydrogels with varying shear strain (frequency = 1 Hz).

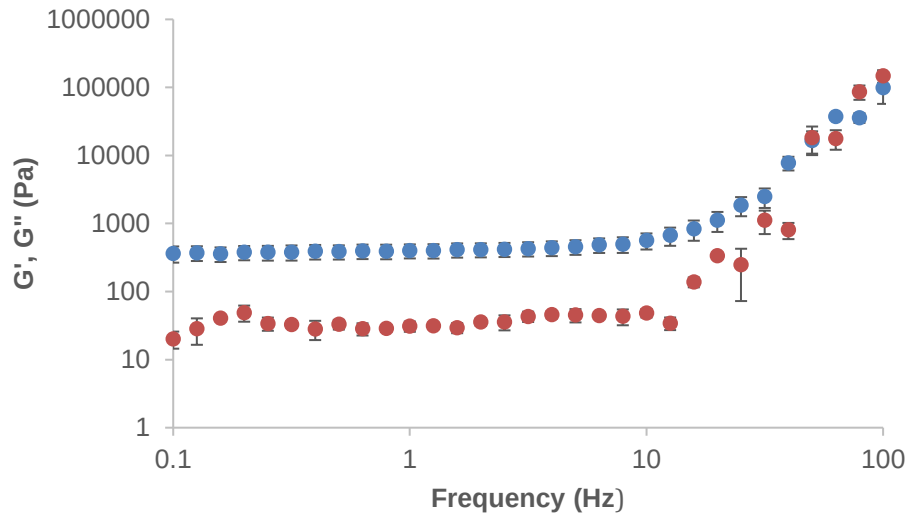


Figure S40: Glutamine amide (**1**) + benzaldehyde (1:1, total 4 mg in 1 mL water) gel. Elastic (G', blue circles) and loss (G'', red circles) moduli of hydrogels with varying frequency.

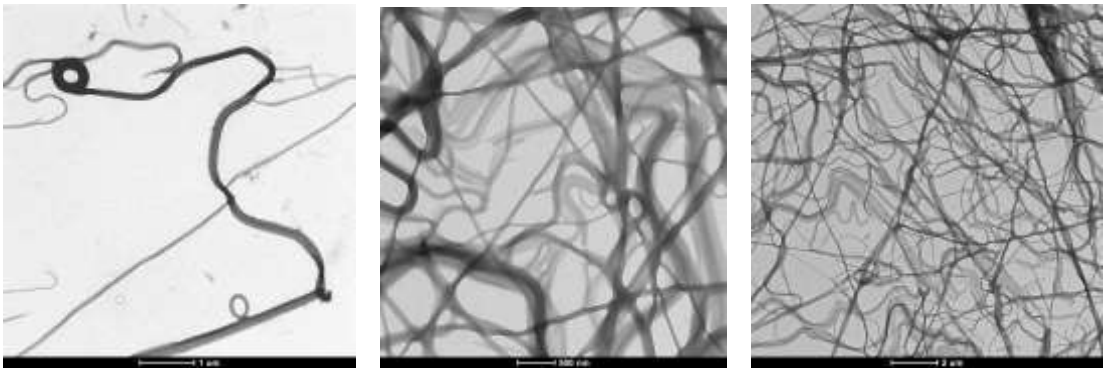


Figure S41: TEM image 1 mg / mL glutamine amide and 480 μg 4-nitrobenzaldehyde (1:1). Scale bars: (left) 1 μm, (middle) 500 nm, (right) 2 μm.

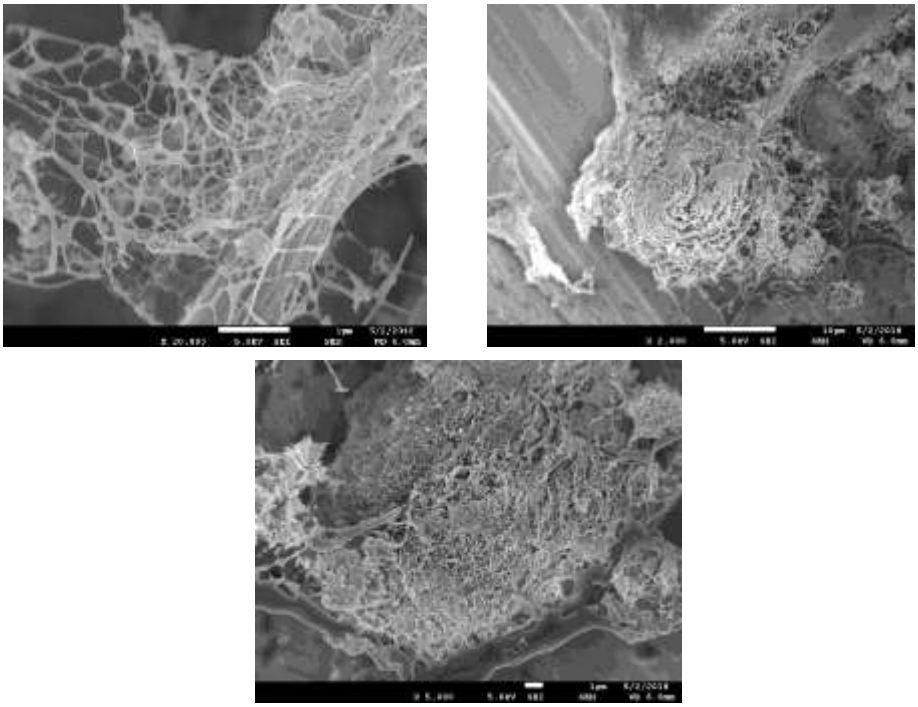


Figure S42: SEM images 1 mg / mL glutamine amide and 480 μg 4-nitrobenzaldehyde (1:1). Scale bars (top left) 1 mm, (top right) 10 μm, (bottom) 1 μm.

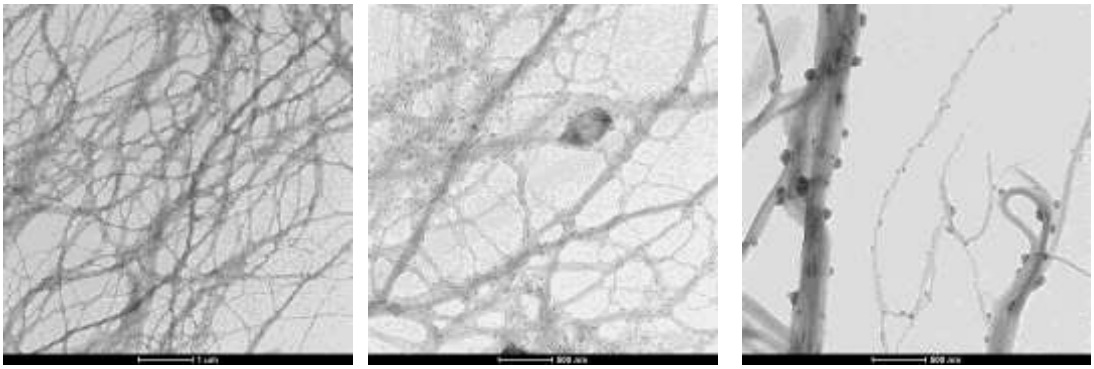


Figure S43: TEM images 2 mg / mL glutamine amide and 960 □g 4-nitrobenzaldehyde (1:1). Scale bars (left) 1 μm, (middle) 500 nm, (right) 500 nm.

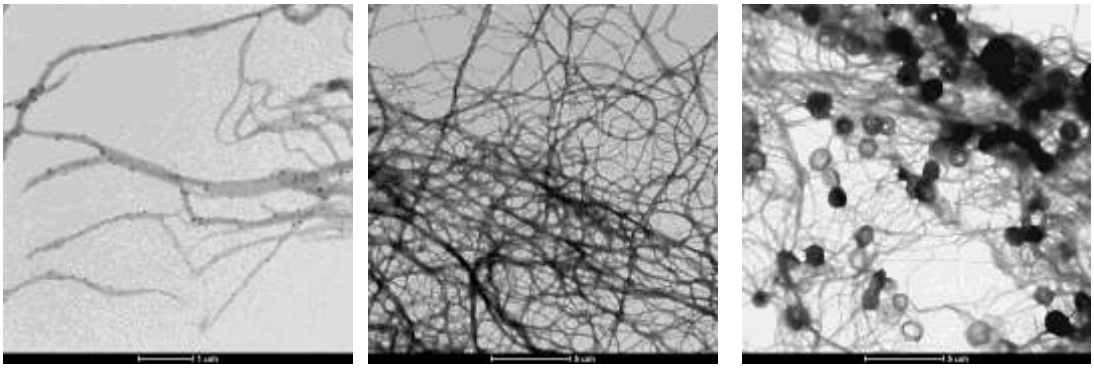


Figure S44: TEM images 3 mg / mL glutamine amide and 1.44 mg 4-nitrobenzaldehyde (1:1). Scale bars (left) 1 μm, (middle) 5 μm, (right) 5 μm.

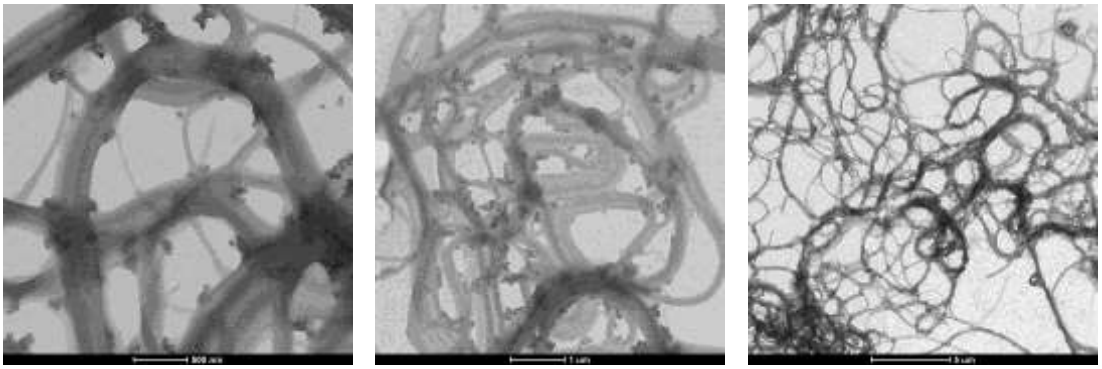


Figure S45: TEM images 5 mg / mL glutamine amide 2.4 mg 4-nitrobenzaldehyde (1:1). Scale bars (left) 500 nm, (middle) 1 μm, (right) 5 μm.

Table S9: HCl or NaOH adjusted solution pH screen for a 1:1 two-component system using glutamine amide (1 mg, 3.19 mmol) and 4-nitrobenzaldehyde (1 eq.) in 1 mL water.

Entry	Aldehyde equivalents used	pH	Result	
1	1	1.19	No gel	
2	1	1.92	No gel	
3	1	2.90	Gel	
4	1	3.98	Semi-gel	
5	1	5.16	Semi-gel	
6	1	5.80	Gel	
7	1	8.09	No	
8	1	9.00	No	

9	1	10.03	Yes	
10	1	11.03	Yes	
11	1	11.90	No	
12	1	13	No	

To learn about the thixotropic potential of the gel several investigations of injectability were carried out. Three methods of breaking the gel network down were tested, manually shaking, injecting (Fig. S42) and de-hydrating. Once broken down the system was allowed to heal in different ways (Table S10).

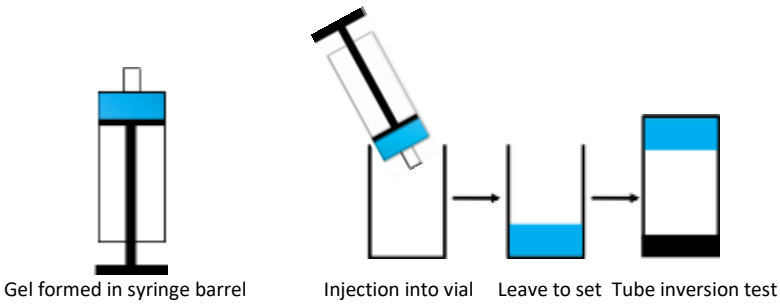
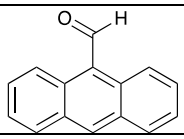
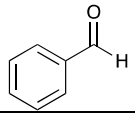
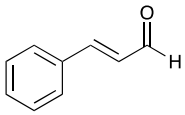
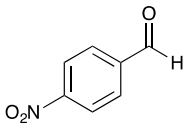
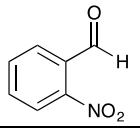
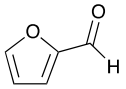
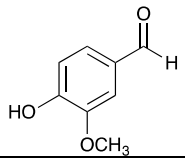
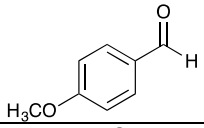
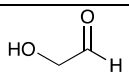
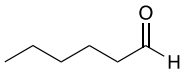


Figure S46: Testing injectability of gels

Table S10: Self-healing test of 4-nitrobenzaldehyde:glutamine amide gel (1:1, 3.16 μmol in 1 mL water). Times given are the times required to re-assemble a full sample-spanning gel capable of withstanding tube inversion.

Method of breaking gel network	**Method of re-healing gel**	**Did it form a gel? (1:1 gel system)**	**Time taken**
Shaking	Re-applying external stimuli (heat cool)	Yes	4-12 h
Shaking	Left to rest no external stimuli	Yes	12 h
Injecting	Left to rest no external stimuli	Yes	4-12 h
De-hydrating	Re-hydrating and external stimuli applied	No gel	N/A

Table S11: Aldehyde screen of the 1:1 two-component system with glutamine amide (**1**) (5 mg, 15.97 mmol) in 1mL H_2O.

Entry	Aldehyde	Structure	Result
1	9-Anthraldehyde		Gel
2	Benzaldehyde		Gel
3	Cinnamaldehyde		Gel
4	4-Nitrobenzaldehyde		Gel
5	2-Nitrobenzaldehyde		Gel
6	Furfural		Inconsistent gel
7	Vanillin		No gel
8	4-Methoxybenzaldehyde		No gel
9	Glycolaldehyde		No gel
10	Hexanal		No gel

^{1}H NMR Competition Assay. This experiment was performed at a glutamine amide loading of 5 mg/mL, with one equivalent of each of benzaldehyde and vanillin, in D_2O.

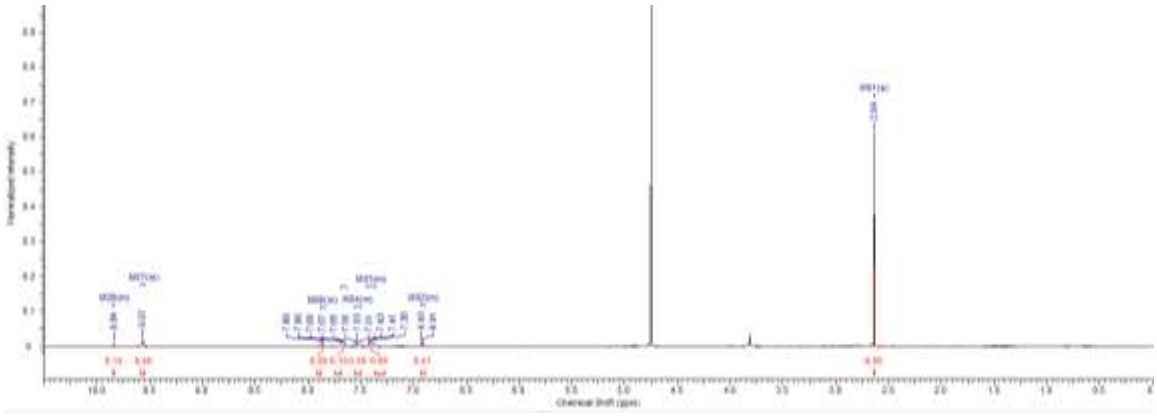


Figure S47: Full ^{1}H NMR spectrum of 1:1:1 glutamine amide:benzaldhyde:vanillin at a glutamine amide loading of 5 mg/mL, in D_2O with a spike of DMSO (2 μl). Key peaks: 9.85 ppm (benzaldehyde), 9.55 (vanillin) and 2.6 (DMSO).

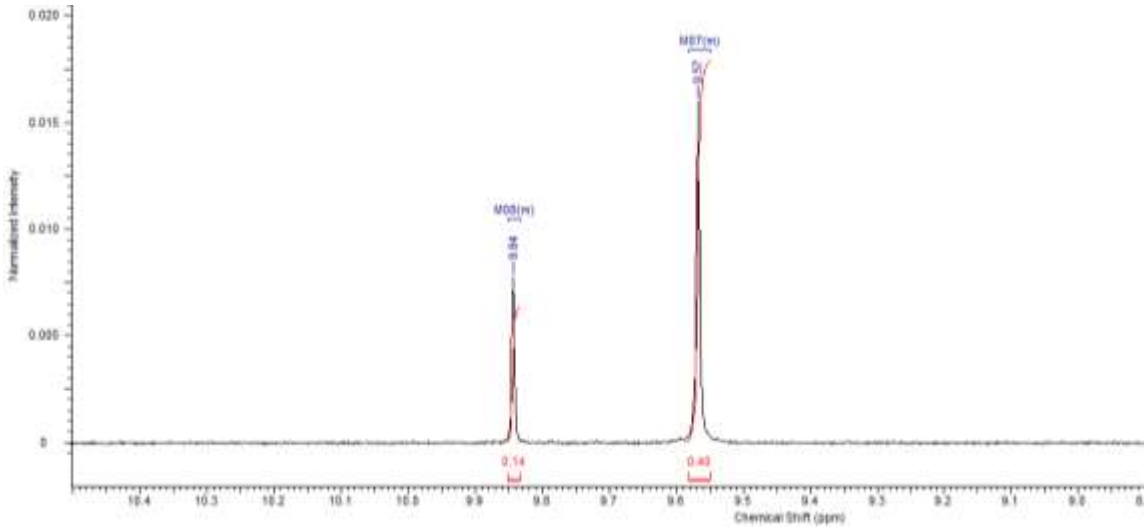
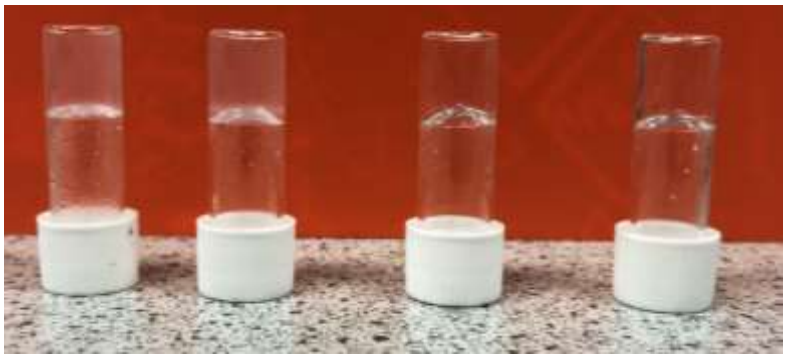


Figure S48: ^{1}H NMR spectrum focussed on the aldehyde region of 1:1:1 glutamine amide:benzaldhyde:vanillin at a glutamine amide loading of 5 mg/mL, in D_2O with a spike of DMSO (2 μl). Key peaks: 9.84 ppm (benzaldehyde) and 9.56 ppm (vanillin). Less benzaldehyde is visible in the ^{1}H NMR spectrum which indicates that more has been incorporated into the 'solid-like' gel nanofibres.

8. Characterisation of Benzyl Glutamine Amide (3) Gel



0.95 mg 0.85 mg 0.5 mg 0.3 mg

Figure S49: Minimum gelation concentration (loadings in mg mL^{-1}).

Table S12: Solvent screen of benzylglutamine amide (**3**) (3 mg / 0.1 mL)

Solvent	Did it gel?
Acetonitrile	Yes
Toluene	No
Cyclohexane	Yes
Ethyl acetate	No
THF	No

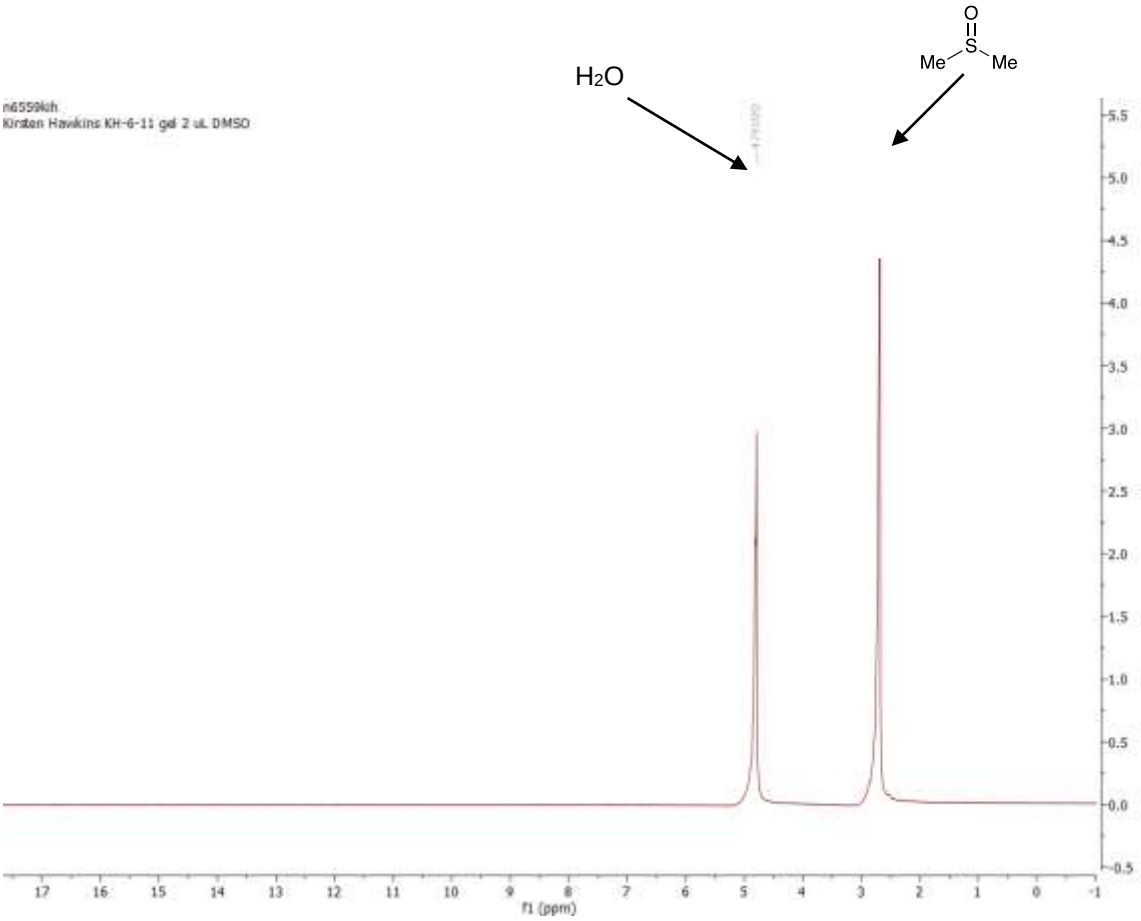


Figure S50: ^{1}H NMR of benzylglutamine amide (**3**) hydrogel. (0.7 mg in 0.7 mL D_2O, 2 µL DMSO).

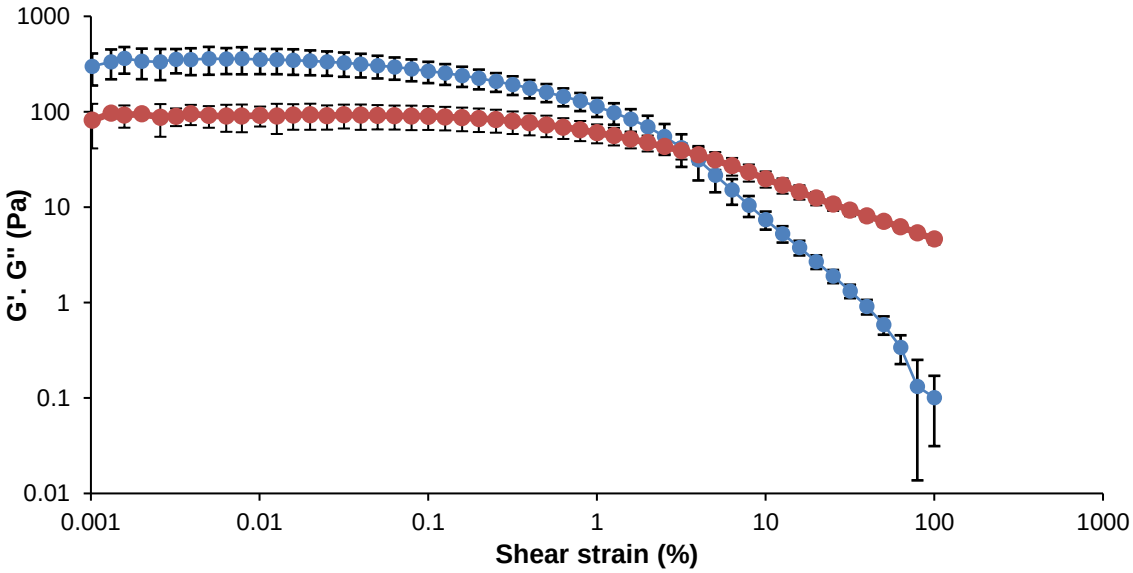


Figure S51: Benzylglutamine amide (**3**) gel (4 mg in 1 mL water). Elastic (G', blue circles) and loss (G'', red circles) moduli of hydrogels with varying shear strain (frequency = 1 Hz).

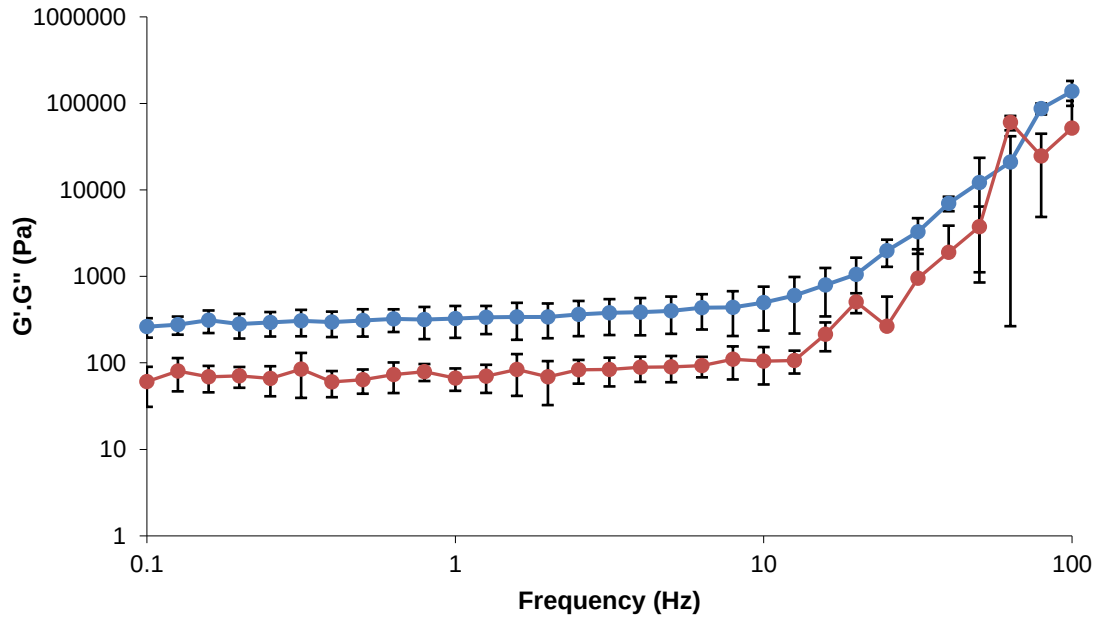


Figure S52: Benzylglutamine amide (**3**) gel 4 mg in 1 mL water. Elastic (G', blue circles) and loss (G", red circles) moduli of hydrogels with varying frequency.

9. References

1. Steer, A. M. Studies on the Prebiotic Origin of 2-Deoxy-D-ribose, *PhD Thesis*, University of York, **2017**.

2. Friestad, G. K.; Massari, S. E. Diastereoselective Vinyl Addition to Chiral Hydrazones via Tandem Thiyl Radical Addition and Silicon-Tethered Cyclization, *Org. Lett.*, **2000**, *2*, 4237–4240.

3. Rodriguez-Llansola, F.; Miravet, J. F.; Escuder, B. A Supramolecular Hydrogel as a Reusable Heterogeneous Catalyst for the Direct Aldol Reaction, *Chem. Commun.*, **2009**, 7303-7305.