Electronic Supplementary Material (ESI) for Soft Matter.
This journal is © The Royal Society of Chemistry 2020

ELECTRONIC SUPPLEMENTARY INFORMATION

Hybrid GMP-polyamine hydrogels as new biocompatible materials for drug encapsulation

Alberto Lopera,[a] Juan A. Aguilar,[b] Raquel Belda,[b] Begoña Verdejo,[a] Jonathan W. Steed,[b] and Enrique García-España[a]

[a] *Departamento de Química Inorgánica, Instituto de Ciencia Molecular, Universidad de Valencia, Calle Catedrático José Beltrán 2, 46980 Paterna, Valencia (Spain). E-mail: alberto.lopera@uv.es, enrique.garcia-es@uv.es*

[b] *Department of Chemistry, Durham University, South Road, DH1 3LE Durham (United Kingdom).*

Figure S1. Distribution diagram of **L1** as a function of the pH. [**L1**] = $1.0 \cdot 10^{-3}$ M.

Figure S2. Distribution diagram of **L2** as a function of the pH. [**L2**] = $1.0 \cdot 10^{-3}$ M.

Figure S3. Distribution diagram of **L3** as a function of the pH. [**L3**] = $1.0 \cdot 10^{-3}$ M.

Figure S4. Distribution diagram of **L4** as a function of the pH. [**L4**] = $1.0 \cdot 10^{-3}$ M.

Figure S5. Distribution diagram of **L5** as a function of the pH. [**L5**] = $1.0 \cdot 10^{-3}$ M.

Figure S6. Distribution diagram of the system GMP-**L1** as a function of the pH. [GMP] = [**L1**] = $1.0 \cdot 10^{-3}$ M.

Figure S7. Distribution diagram of the system GMP-**L2** as a function of the pH. [GMP] = [**L2**] = $1.0 \cdot 10^{-3}$ M.

Figure S8. Distribution diagram of the system GMP-**L3** as a function of the pH. [GMP] = [**L3**] = $1.0 \cdot 10^{-3}$ M.

Figure S9. Distribution diagram of the system GMP-**L4** as a function of the pH. [GMP] = [**L4**] = $1.0 \cdot 10^{-3}$ M.

Figure S10. Distribution diagram of the system GMP-**L5** as a function of the pH. [GMP] = [**L5**] = $1.0 \cdot 10^{-3}$ M.

Figure S11. Plot of the values of the logarithms of the effective constants for the interaction of **L1**-**L5** with GMP. [**L1**-**L5**] = [GMP] = $1.0 \cdot 10^{-3}$ M.

Figure S12. Oscillatory stress sweep experiments for the GMP-**L1** system. G': Filled circles. G'': Empty circles. GMP:**L1** molar ratios: 3:1 (purple), 4:1 (green), 5:1 (blue), 10:1 (red) and 30:1 (orange).

Figure S13. Oscillatory stress sweep experiments for the GMP-**L2** system. G': Filled circles. G'': Empty circles. GMP:**L2** molar ratios: 3:1 (purple), 4:1 (green), 5:1 (blue) and 10:1 (red).

Figure S14. Oscillatory stress sweep experiments for the GMP-**L3** system. G': Filled circles. G'': Empty circles. GMP:**L3** molar ratios: 3:1 (purple), 4:1 (green), 5:1 (blue), 10:1 (red), 30:1 (orange) and 50:1 (grey).

Figure S15. Oscillatory stress sweep experiments for the GMP-**L5** system. G': Filled circles. G'': Empty circles. GMP:**L5** molar ratios: 4:1 (green), 5:1 (blue), 10:1 (red), 30:1 (orange) and 50:1 (grey).

Figure S16. Evolution of the ^{1}H NMR signals for the system GMP-**L1** employing the optimal conditions for hydrogel formation deduced from rheology: GMP:**L1** 3:1 molar ratio. H1' signal from the GMP molecule (purple). H4 signal from the polyamine (green).

Figure S17. Evolution of the ^{1}H NMR signals for the system GMP-**L2** employing the optimal conditions for hydrogel formation deduced from rheology: GMP:**L2** 3:1 molar ratio. H1' signal from the GMP molecule (purple). H4 signal from the polyamine (green).

Figure S18. Evolution of the ^{1}H NMR for the system GMP-**L3** employing the optimal conditions for hydrogel formation deduced from rheology: GMP:**L3** 4:1 molar ratio. H1' signal from the GMP molecule (purple). H4 signal from the polyamine (green).

Figure S19. Evolution of the ^{1}H NMR for the system GMP-**L5** employing the optimal conditions for hydrogel formation deduced from rheology: GMP:**L5** 5:1 molar ratio. H1' signal from the GMP molecule (purple). H4 signal from the polyamine (green).

Figure S20. Oscillatory stress sweep experiments for the GMP-**L1**-Isoniazid system. G': Filled circles. G'': Empty circles. GMP:**L1** in 3:1 molar ratio in the absence of isoniazid (blue), having 1 mg of isoniazid per mL of hydrogel (green) and having 10 mg of isoniazid per mL of hydrogel (orange).

Figure S21. Oscillatory stress sweep experiments for the GMP-**L2**-Isoniazid system. G': Filled circles. G'': Empty circles. GMP:**L2** in 3:1 molar ratio in the absence of isoniazid (blue) and having 1 mg of isoniazid per mL of hydrogel (green).

Figure S22. Oscillatory stress sweep experiments for the GMP-**L3**-Isoniazid system. G': Filled circles. G'': Empty circles. GMP:**L3** in 4:1 molar ratio in the absence of isoniazid (blue), having 1 mg of isoniazid per mL of hydrogel (green) and having 10 mg of isoniazid per mL of hydrogel (orange).

Figure S23. Oscillatory stress sweep experiments for the GMP-**L5**-Isoniazid system. G': Filled circles. G'': Empty circles. GMP:**L5** in 5:1 molar ratio in the absence of isoniazid (blue) and having 1 mg of isoniazid per mL of hydrogel (green).

Figure S24. (a) ^{1}H NMR spectrum of **L1** in D_2O. (b) ^{13}C NMR spectrum of **L1** in D_2O.

Figure S25. (a) ^{1}H NMR spectrum of **L2** in D_2O. (b) ^{13}C NMR spectrum of **L2** in D_2O.

Figure S26. (a) ^{1}H NMR spectrum of **L3** in D_2O. (b) ^{13}C NMR spectrum of **L3** in D_2O.

Figure S27. (a) ^{1}H NMR spectrum of **L4** in D_2O. (b) ^{13}C NMR spectrum of **L4** in D_2O.

Figure S28. (a) ^{1}H NMR spectrum of **L5** in D_2O. (b) ^{13}C NMR spectrum of **L5** in D_2O.

Figure S29. Mass spectrum of **L1** in H_2O.

Figure S30. Mass spectrum of **L2** in H_2O.

Figure S31. Mass spectrum of **L3** in H_2O.

Figure S32. Mass spectrum of **L4** in H_2O.

Figure S33. Mass spectrum of **L5** in H_2O.

Table S1. Logarithms of the stability constants for the interaction of GMP with the receptors **L1**-**L5**, determined in 0.15 M NaCl at 298.0 ± 0.1 K.

Table S2. Rheological properties of the hybrid hydrogels at different GMP:polyamine molar ratios for the system GMP-**L1**.

Table S3. Rheological properties of the hybrid hydrogels at different GMP:polyamine molar ratios for the system GMP-**L2**.

Table S4. Rheological properties of the hybrid hydrogels at different GMP:polyamine molar ratios for the system GMP-**L3**.

Table S5. Rheological properties of the hybrid hydrogels at different GMP:polyamine molar ratios for the system GMP-**L5**.

Table S6. Rheological properties of the hybrid hydrogels for the system GMP-**L1**-Isoniazid at GMP:**L1** 3:1 molar ratio in the absence and in the presence of different amounts of isoniazid.

Table S7. Rheological properties of the hybrid hydrogels for the system GMP-**L2**-Isoniazid at GMP:**L2** 3:1 molar ratio in the absence and in the presence of different amounts of isoniazid.

Table S8. Rheological properties of the hybrid hydrogels for the system GMP-**L3**-Isoniazid at GMP:**L3** 4:1 molar ratio in the absence and in the presence of different amounts of isoniazid.

Table S9. Rheological properties of the hybrid hydrogels for the system GMP-**L5**-Isoniazid at GMP:**L5** 5:1 molar ratio in the absence and in the presence of different amounts of isoniazid.

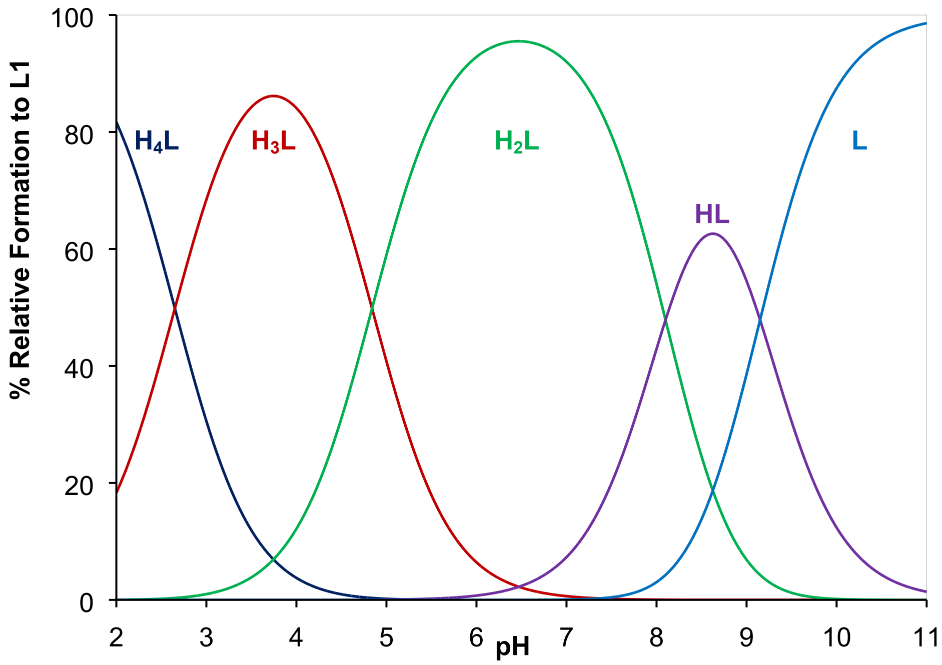

Figure S1. Distribution diagram of **L1** as a function of pH. [**L1**] = 1.0·10^{-3} M.

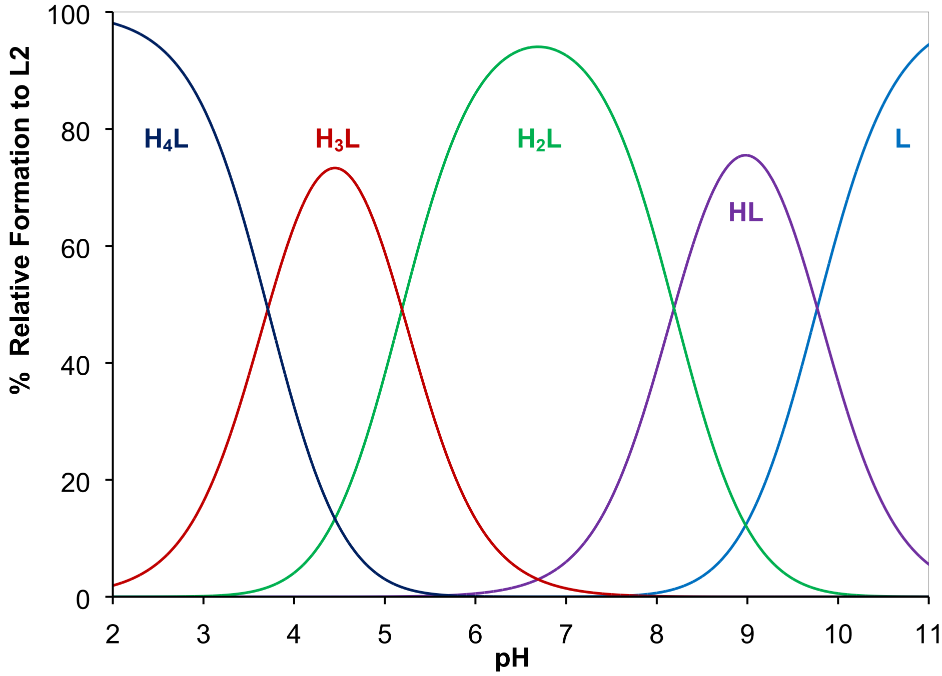

Figure S2. Distribution diagram of **L2** as a function of pH. [**L2**] = 1.0·10^{-3} M.

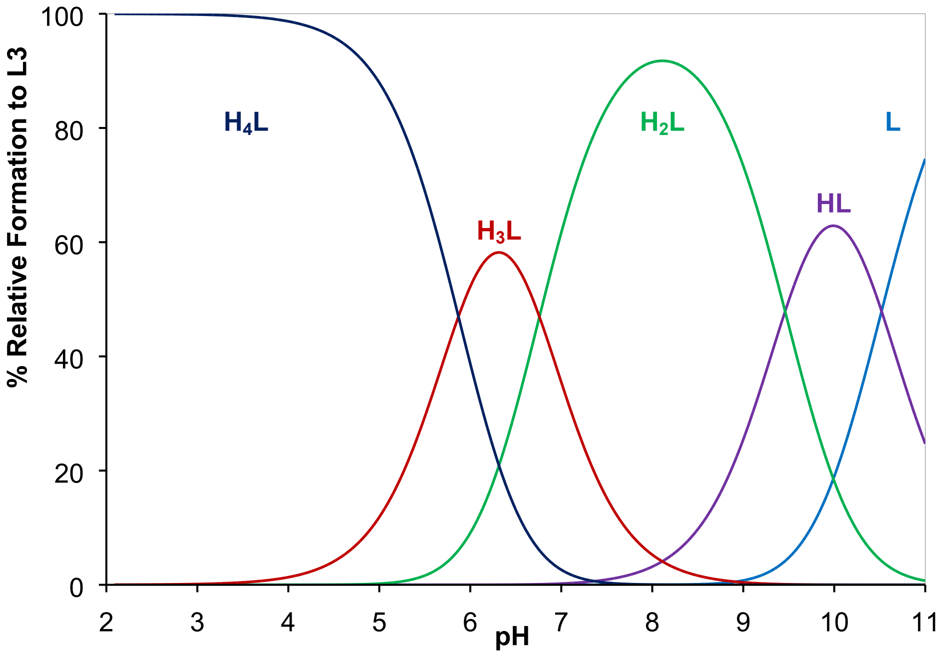

Figure S3. Distribution diagram of **L3** as a function of pH. [**L3**] = 1.0·10^{-3} M.

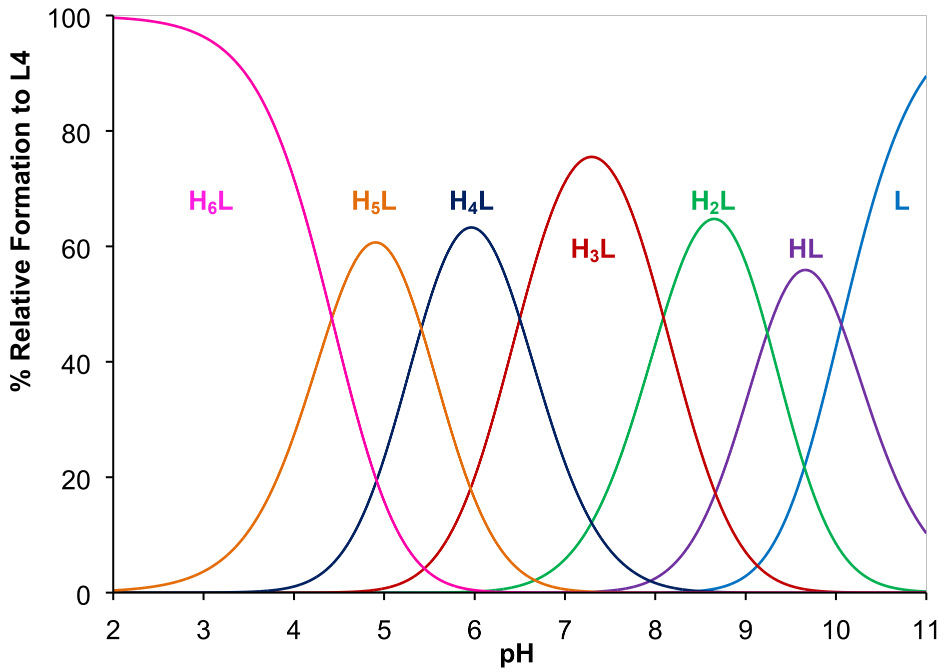

Figure S4. Distribution diagram of **L4** as a function of pH. [**L4**] = 1.0·10^{-3} M.

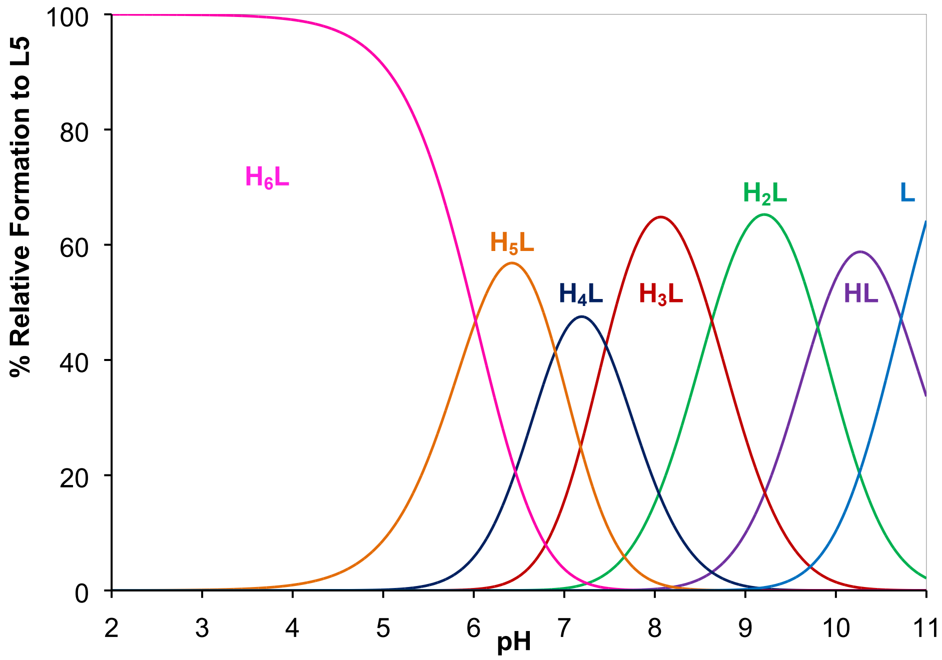

Figure S5. Distribution diagram of **L5** as a function of pH. [**L5**] = 1.0·10^{-3} M.

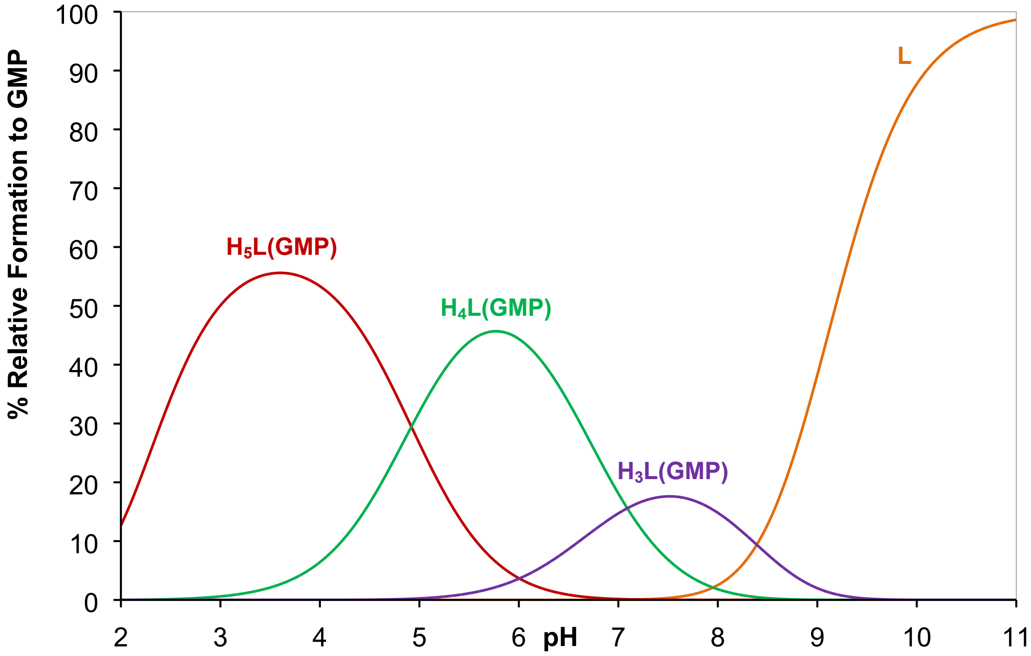

Figure S6. Distribution diagram of the system GMP-**L1** as a function of pH. [GMP] = [**L1**] = $1.0 \cdot 10^{-3}$ M.

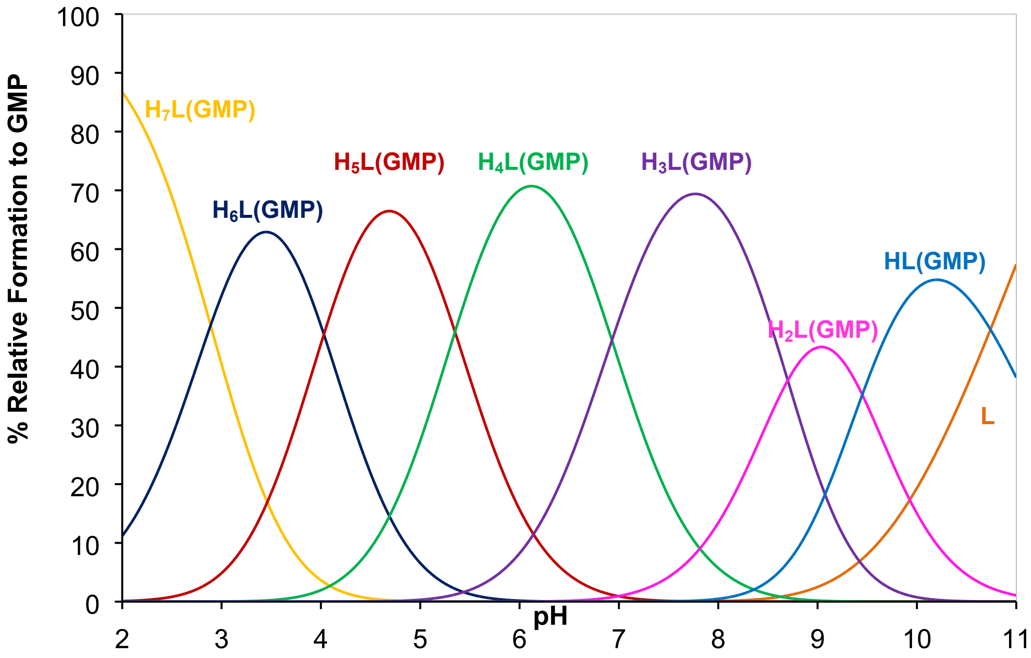

Figure S7. Distribution diagram of the system GMP-**L2** as a function of pH. [GMP] = [**L2**] = $1.0 \cdot 10^{-3}$ M.

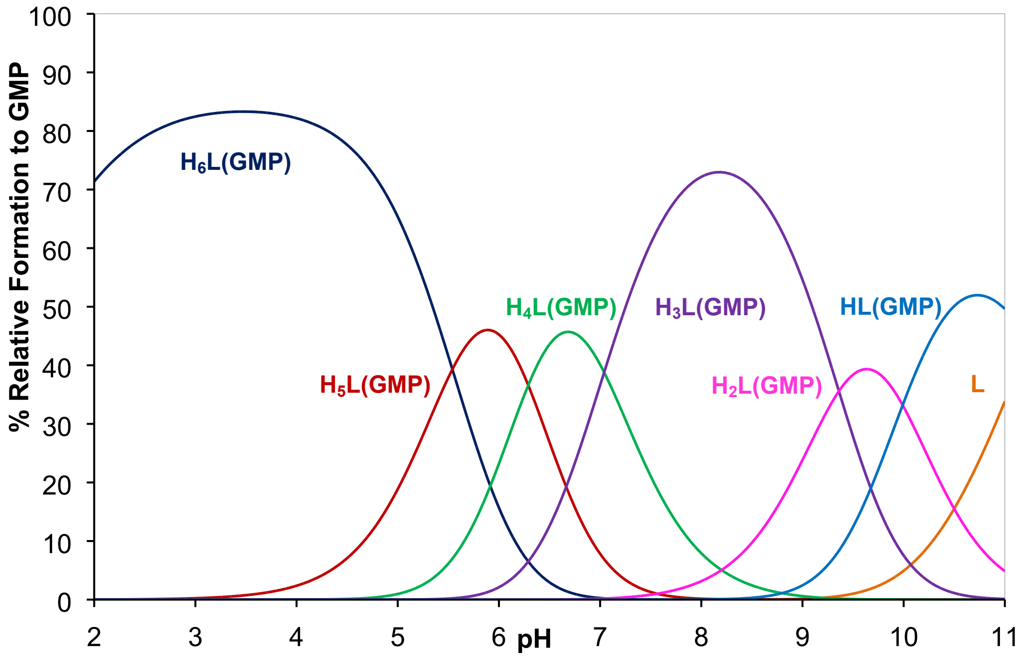

Figure S8. Distribution diagram of the system GMP-**L3** as a function of pH. [GMP] = [**L3**] = $1.0·10^{-3}$ M.

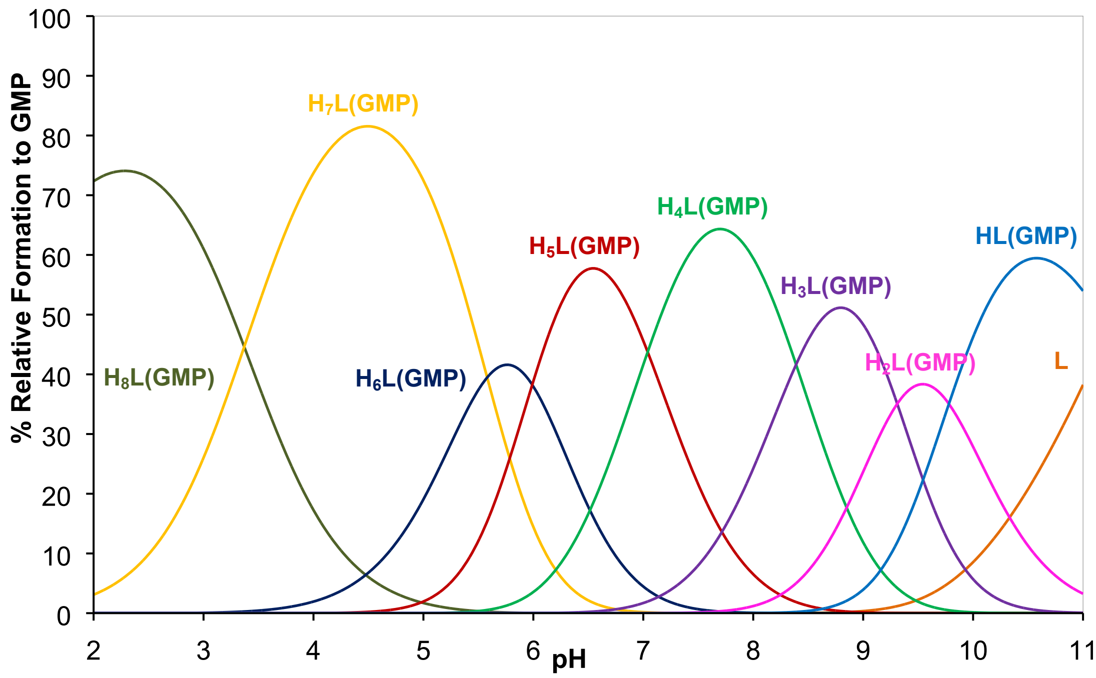

Figure S9. Distribution diagram of the system GMP-**L4** as a function of pH. [GMP] = [**L4**] = $1.0·10^{-3}$ M.

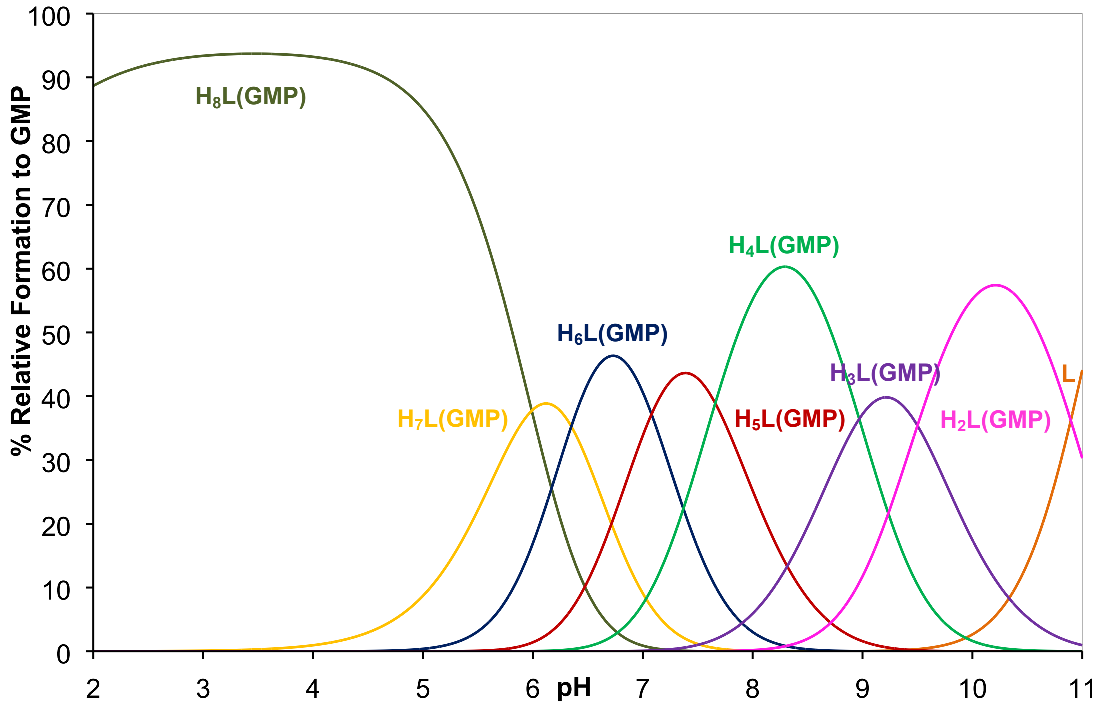

Figure S10. Distribution diagram of the system GMP-**L5** as a function of pH. [GMP] = [**L5**] = $1.0 \cdot 10^{-3}$ M.

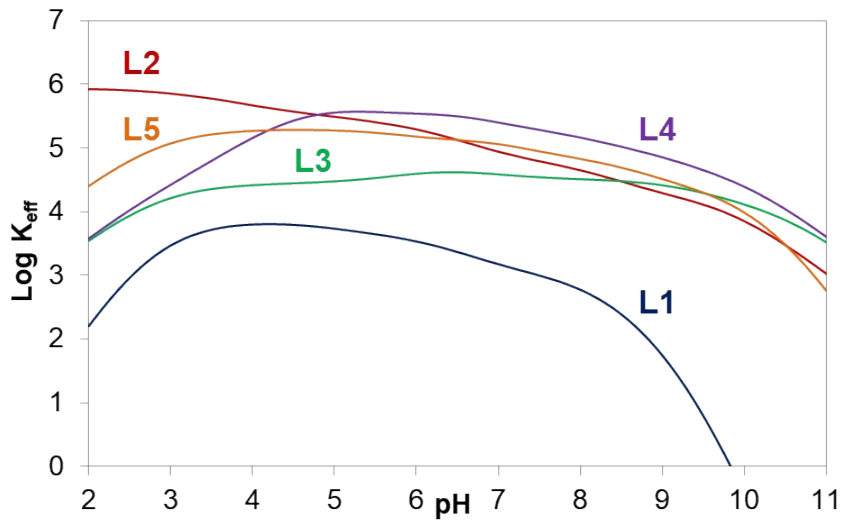

Figure S11. Plot of the values of the logarithms of the effective constants for the interaction of **L1**-**L5** with GMP. [**L1**-**L5**] = [GMP] = $1.0 \cdot 10^{-3}$ M.

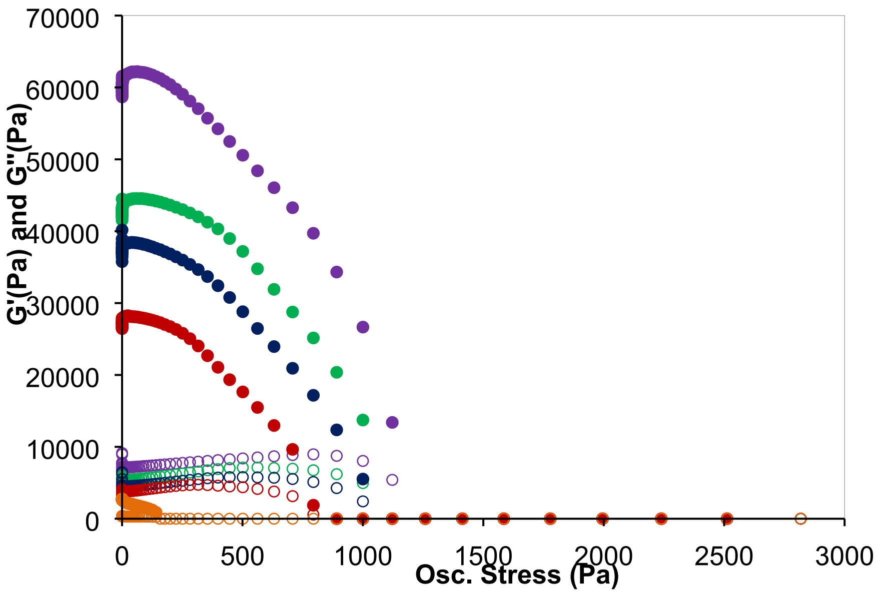

Figure S12. Oscillatory stress sweep experiments for the GMP-**L1** system. G': Filled circles. G'': Empty circles. GMP:**L1** molar ratios: 3:1 (purple), 4:1 (green), 5:1 (blue), 10:1 (red) and 30:1 (orange).

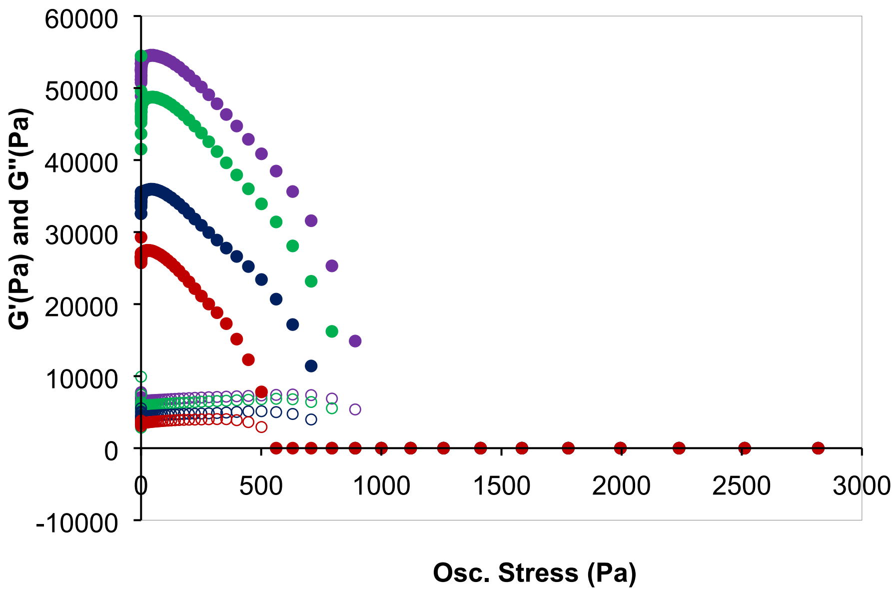

Figure S13. Oscillatory stress sweep experiments for the GMP-**L2** system. G': Filled circles. G'': Empty circles. GMP:**L2** molar ratios: 3:1 (purple), 4:1 (green), 5:1 (blue) and 10:1 (red).

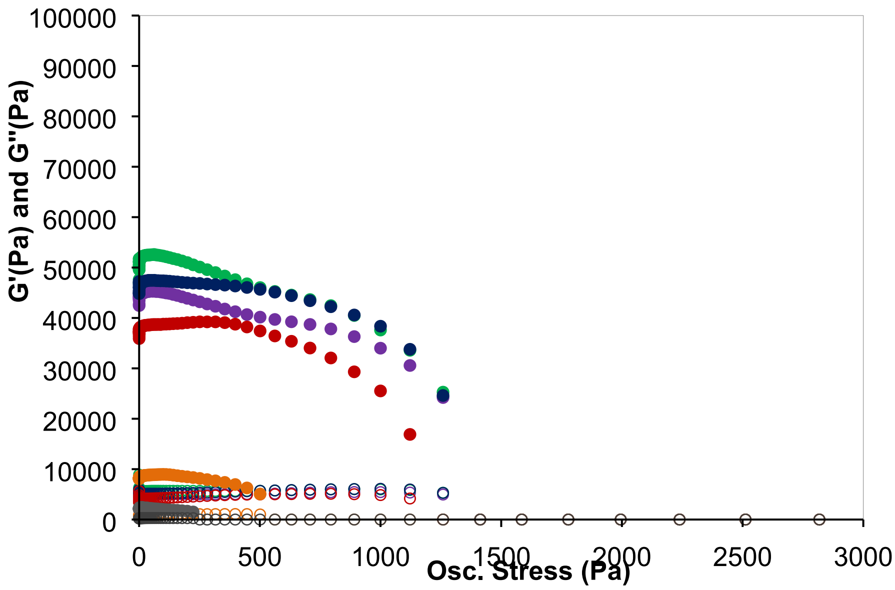

Figure S14. Oscillatory stress sweep experiments for the GMP-**L3** system. G': Filled circles. G'': Empty circles. GMP:**L3** molar ratios: 3:1 (purple), 4:1 (green), 5:1 (blue), 10:1 (red), 30:1 (orange) and 50:1 (grey).

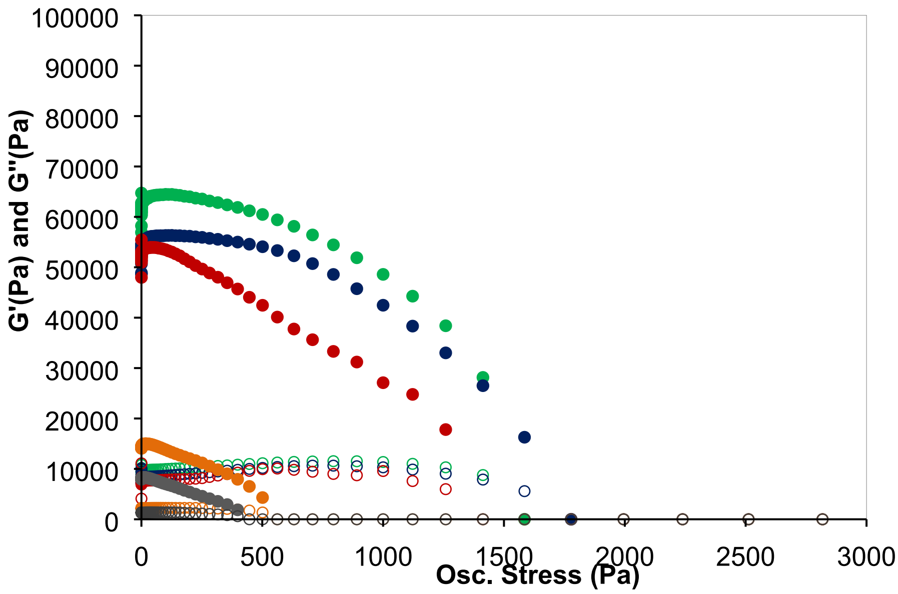

Figure S15. Oscillatory stress sweep experiments for the GMP-**L5** system. G': Filled circles. G'': Empty circles. GMP:**L5** molar ratios: 4:1 (green), 5:1 (blue), 10:1 (red), 30:1 (orange) and 50:1 (grey).

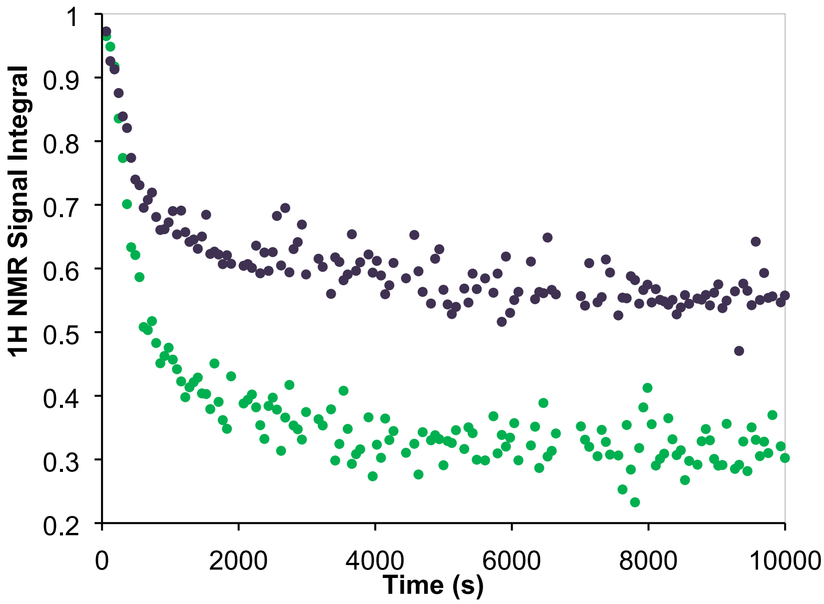

Figure S16. Evolution of the ^{1}H NMR signals for the system GMP-**L1** employing the optimal conditions for hydrogel formation deduced from rheology: GMP:**L1** 3:1 molar ratio. H1' signal from the GMP molecule (purple). H4 signal from the polyamine (green).

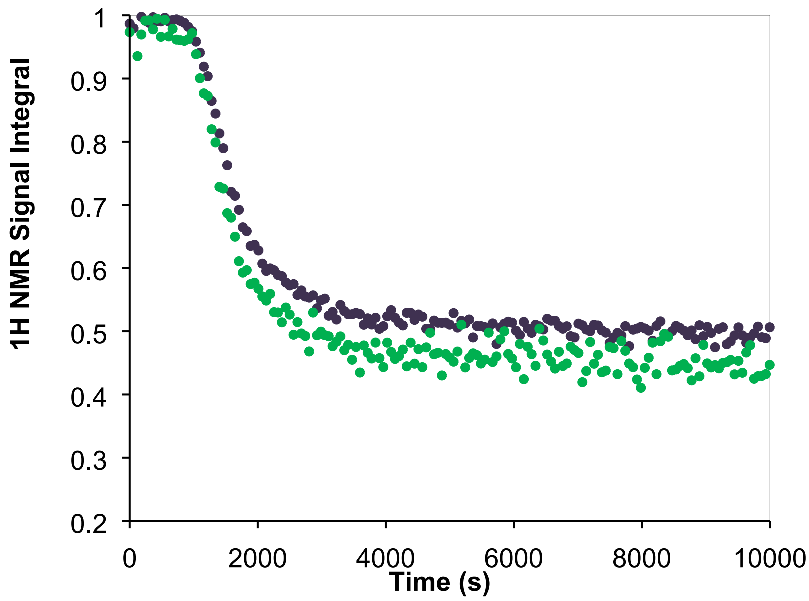

Figure S17. Evolution of the ^{1}H NMR signals for the system GMP-**L2** employing the optimal conditions for hydrogel formation deduced from rheology: GMP:**L2** 3:1 molar ratio. H1' signal from the GMP molecule (purple). H4 signal from the polyamine (green).

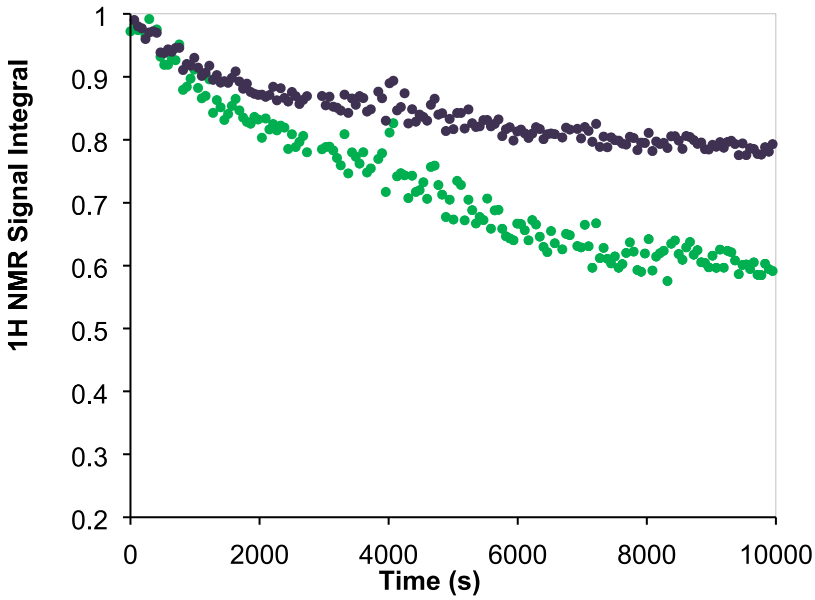

Figure S18. Evolution of the ¹H NMR signals for the system GMP-**L3** employing the optimal conditions for hydrogel formation deduced from rheology: GMP:**L3** 4:1 molar ratio. H1' signal from the GMP molecule (purple). H4 signal from the polyamine (green).

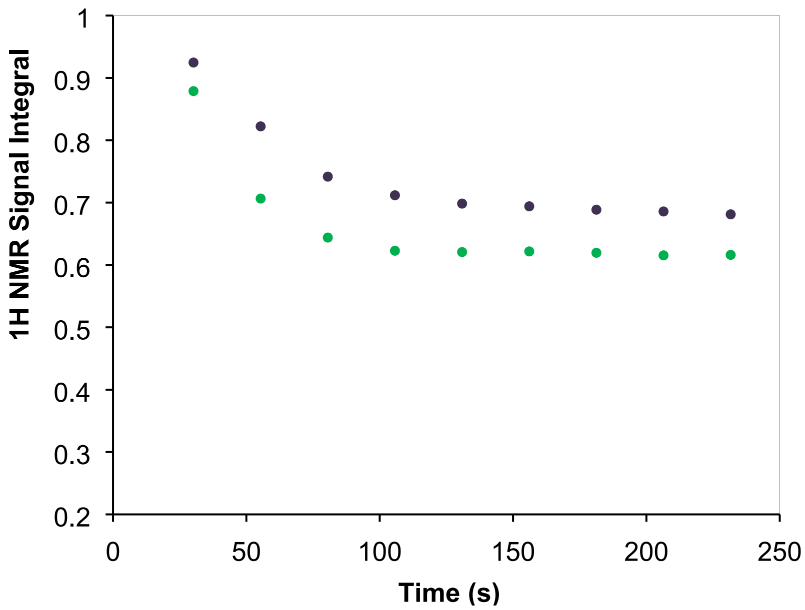

Figure S19. Evolution of the ¹H NMR signals for the system GMP-**L5** employing the optimal conditions for hydrogel formation deduced from rheology: GMP:**L5** 5:1 molar ratio. H1' signal from the GMP molecule (purple). H4 signal from the polyamine (green).

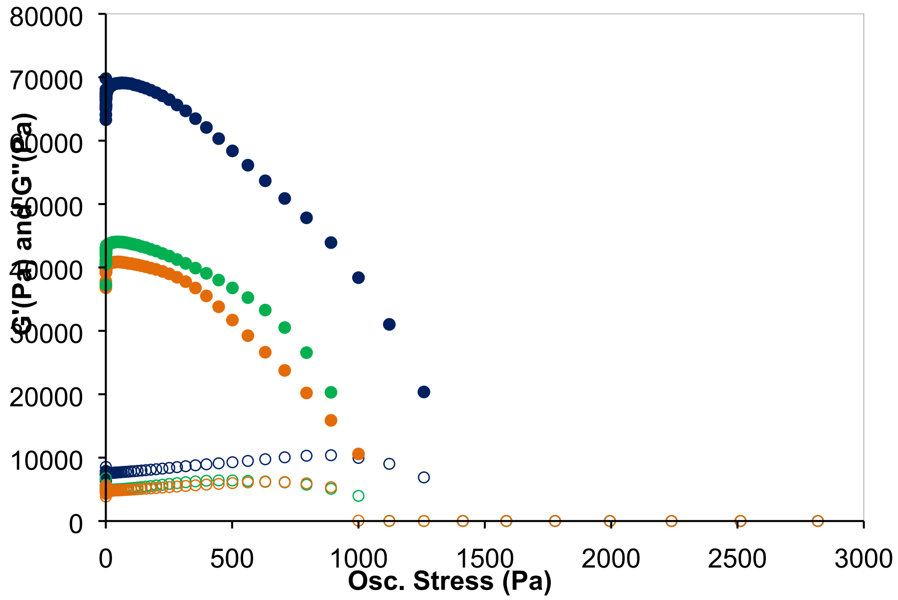

Figure S20. Oscillatory stress sweep experiments for the GMP-**L1**-Isoniazid system. G': Filled circles. G'': Empty circles. GMP:**L1** in 3:1 molar ratio in the absence of isoniazid (blue), having 1 mg of isoniazid per mL of hydrogel (green) and having 10 mg of isoniazid per mL of hydrogel (orange).

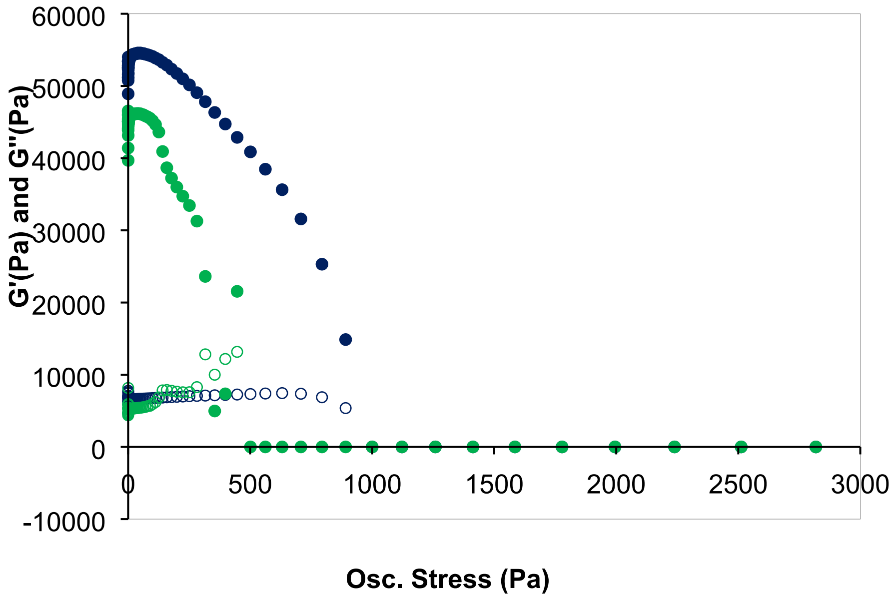

Figure S21. Oscillatory stress sweep experiments for the GMP-**L2**-Isoniazid system. G': Filled circles. G'': Empty circles. GMP:**L2** in 3:1 molar ratio in the absence of isoniazid (blue) and having 1 mg of isoniazid per mL of hydrogel (green).

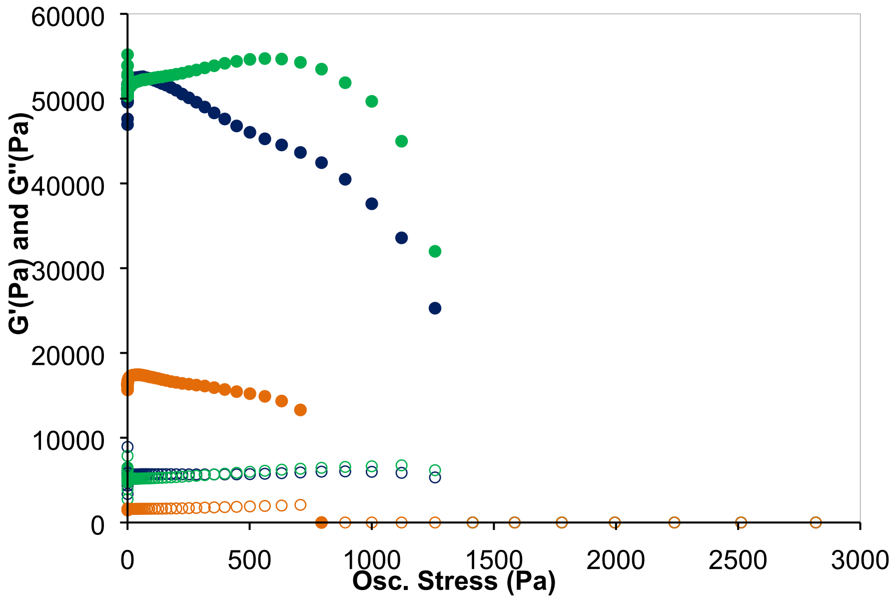

Figure S22. Oscillatory stress sweep experiments for the GMP-**L3**-Isoniazid system. G': Filled circles. G'': Empty circles. GMP:**L3** in 4:1 molar ratio in the absence of isoniazid (blue), having 1 mg of isoniazid per mL of hydrogel (green) and having 10 mg of isoniazid per mL of hydrogel (orange).

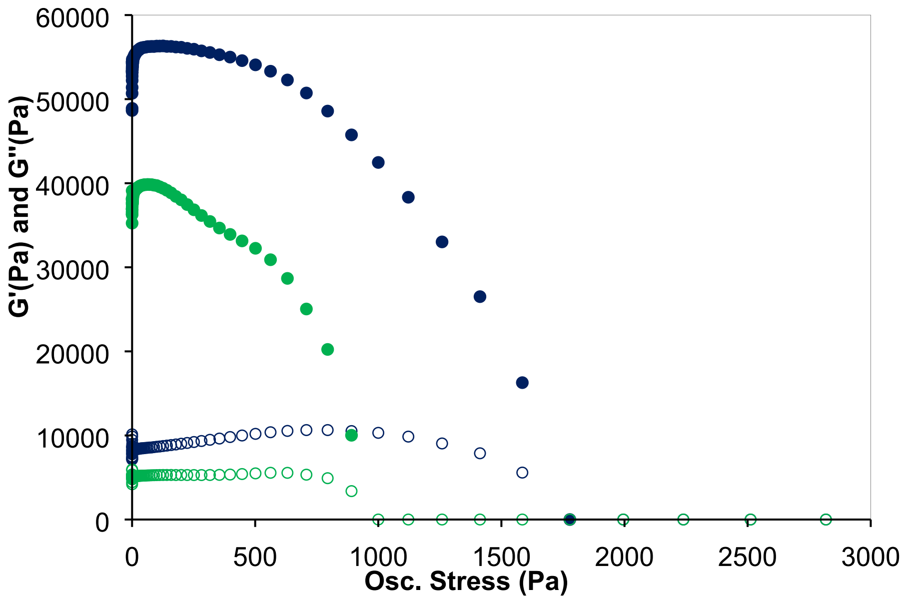

Figure S23. Oscillatory stress sweep experiments for the GMP-**L5**-Isoniazid system. G': Filled circles. G'': Empty circles. GMP:**L5** in 5:1 molar ratio in the absence of isoniazid (blue) and having 1 mg of isoniazid per mL of hydrogel (green).

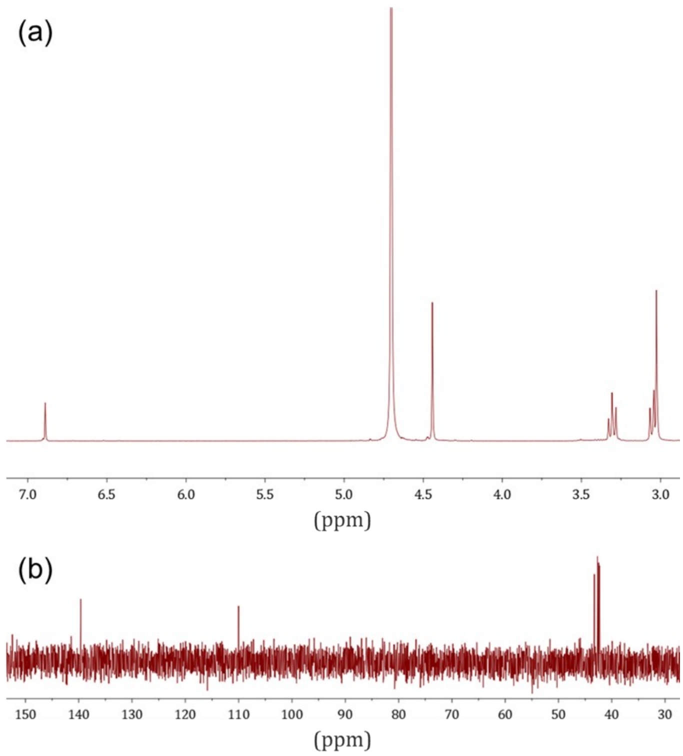

Figure S24. (a) [1]H NMR spectrum of **L1** in D_2O. (b) [13]C NMR spectrum of **L1** in D_2O.

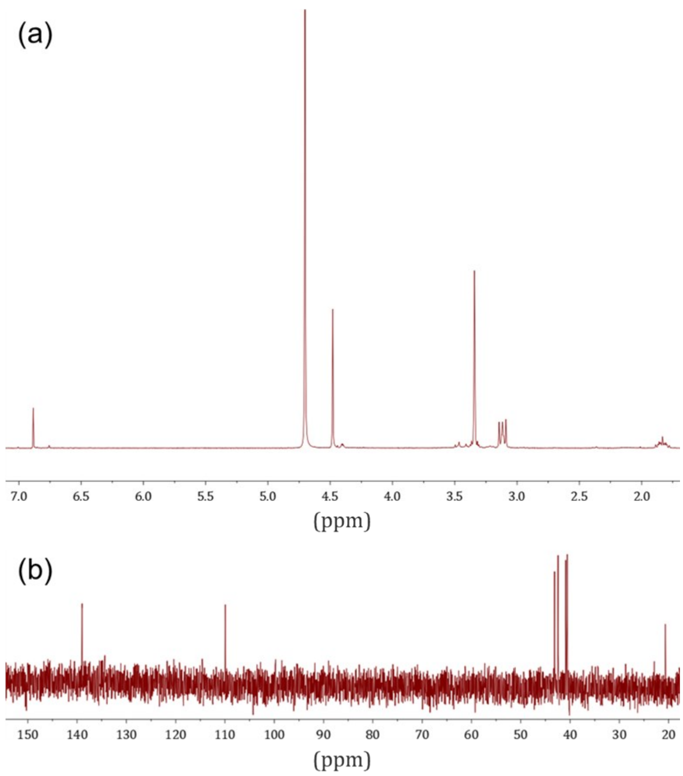

Figure S25. (a) [1]H NMR spectrum of **L2** in D_2O. (b) [13]C NMR spectrum of **L2** in D_2O.

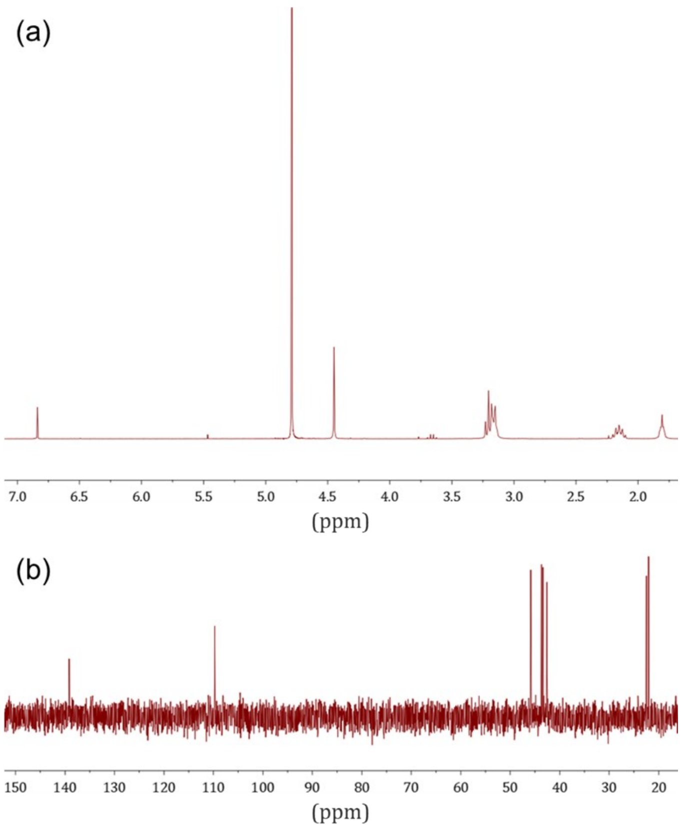

Figure S26. (a) ^{1}H NMR spectrum of **L3** in D_2O. (b) ^{13}C NMR spectrum of **L3** in D_2O.

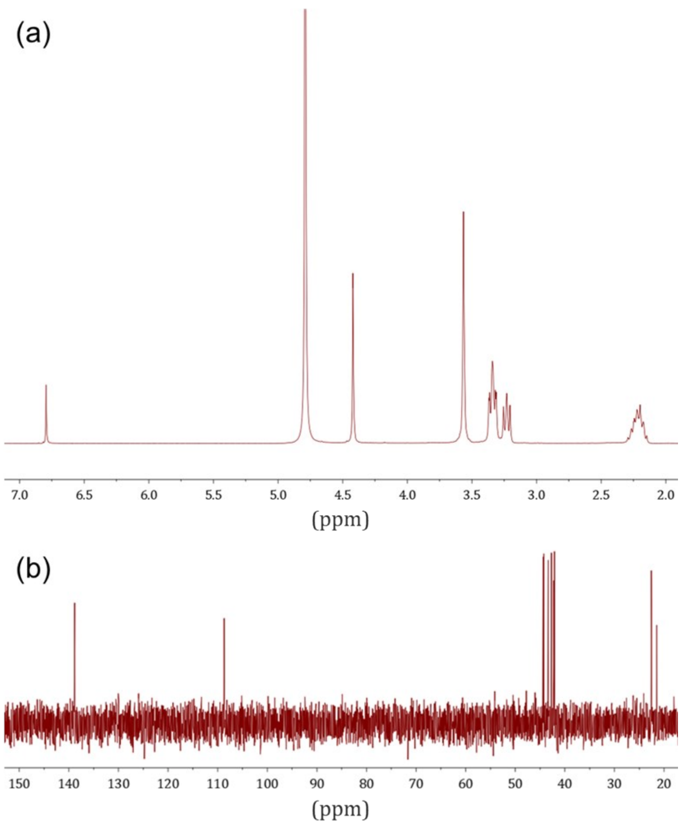

Figure S27. (a) ^{1}H NMR spectrum of **L4** in D_2O. (b) ^{13}C NMR spectrum of **L4** in D_2O.

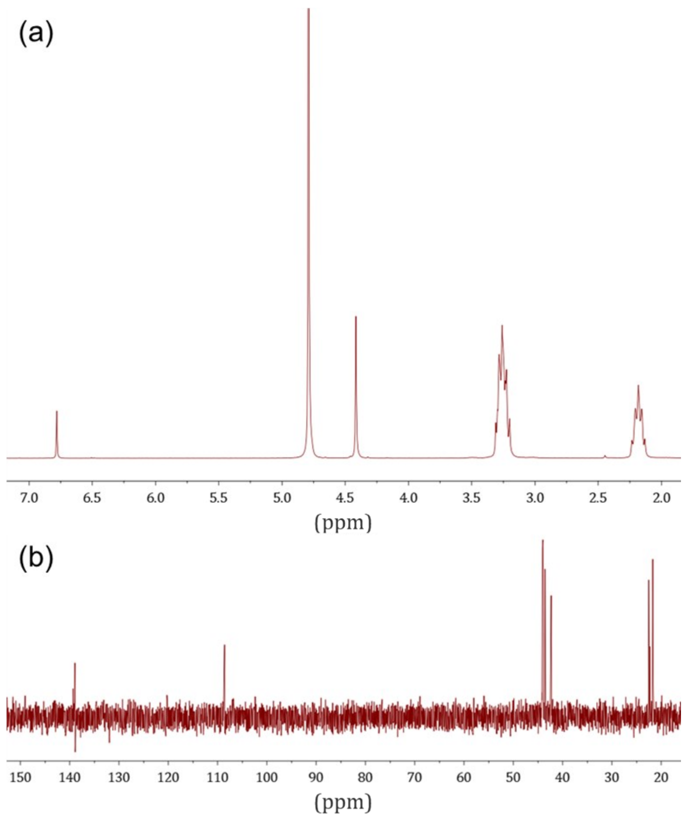

Figure S28. (a) ^{1}H NMR spectrum of **L5** in D_2O. (b) ^{13}C NMR spectrum of **L5** in D_2O.

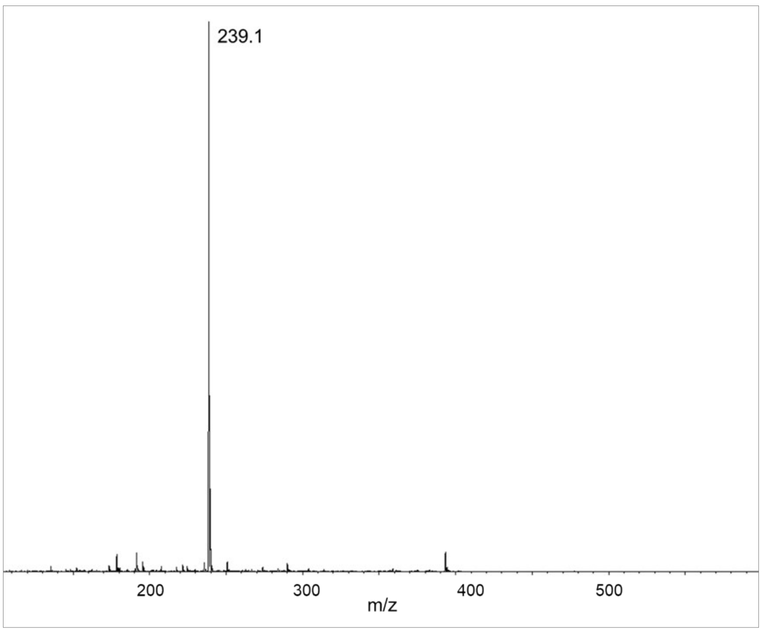

Figure S29. Mass spectrum of **L1** in H_2O.

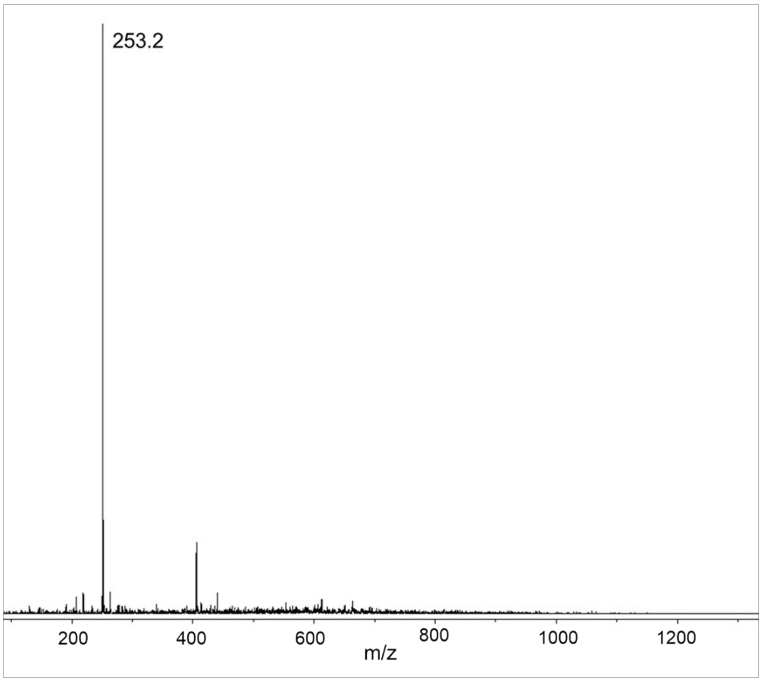

Figure S30. Mass spectrum of **L2** in H_2O.

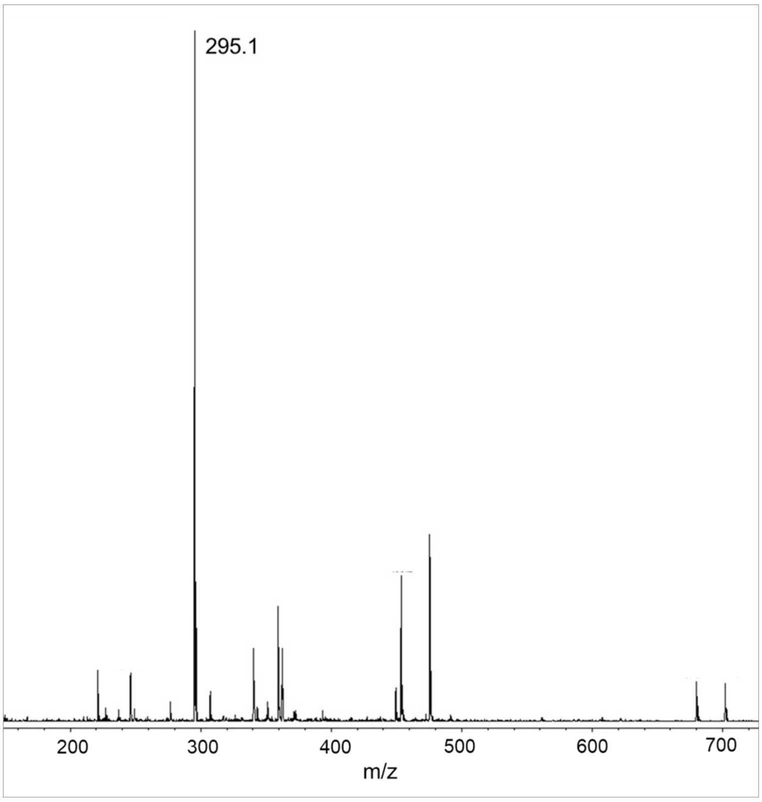

Figure S31. Mass spectrum of **L3** in H_2O.

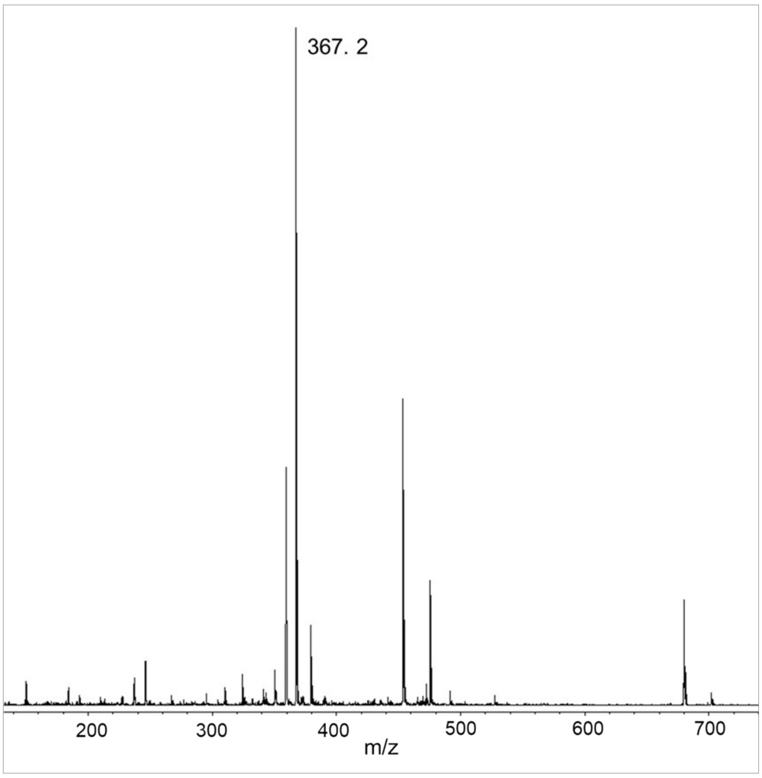

Figure S32. Mass spectrum of **L4** in H_2O.

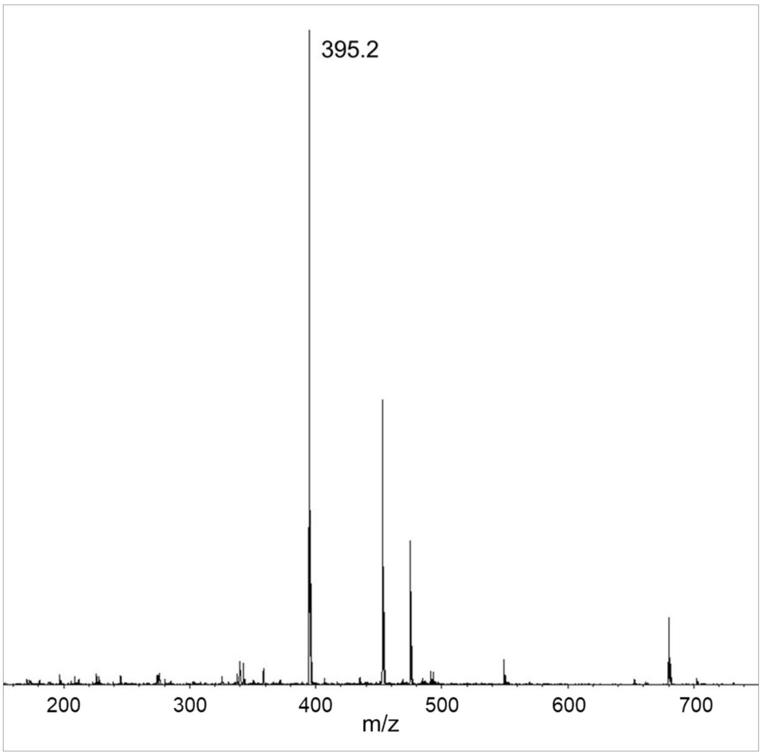

Figure S33. Mass spectrum of **L5** in H_2O.

Table S1. Logarithms of the stability constants for the interaction of GMP with the receptors **L1-L5**, determined in 0.15 M NaCl at 298.0 ± 0.1 K.

Reaction	L1	L2	L3	L4	L5
$HL + H_{-1}G \rightleftharpoons LG$[a]	-	4.28(5)	4.10(6)	4.58(5)	-
$HL + G \rightleftharpoons HLG$	-	4.26(3)	4.60(5)	4.89(3)	4.78(1)
$H_2L + G \rightleftharpoons H_2LG$	-	4.78(4)	4.51(5)	4.97(4)	4.49(1)
$H_2L + HG \rightleftharpoons H_3LG$	3.02(7)[b]	5.41(4)	-	-	-
$H_3L + G \rightleftharpoons H_3LG$	-	5.61(4)	4.79(5)	5.28(4)	4.83(1)
$H_2L + H_2G \rightleftharpoons H_4LG$	3.65(5)	-	-	-	-
$H_3L + HG \rightleftharpoons H_4LG$	-	5.54(4)	4.77(5)	-	-
$H_4L + G \rightleftharpoons H_4LG$	-	-	-	5.80(4)	5.03(2)
$H_3L + H_2G \rightleftharpoons H_5LG$	3.87(3)	-	-	-	-
$H_4L + HG \rightleftharpoons H_5LG$	-	5.89(4)	4.44(5)	5.54(4)	-
$H_5L + G \rightleftharpoons H_5LG$	-	-	-	-	5.26(2)
$H_4L + H_2G \rightleftharpoons H_6LG$	-	5.94(4)	-	-	-
$H_5L + HG \rightleftharpoons H_6LG$	-	-	-	5.68(4)	5.26(3)
$H_6L + HG \rightleftharpoons H_7LG$	-	-	-	4.45(6)	5.30(2)

(a) Charges omitted. (b) Values in parenthesis show standard deviation in the last significant figure.

Table S2. Rheological properties of the hybrid hydrogels at different GMP:polyamine molar ratios for the system GMP-**L1**.

GMP:L1 Molar Ratio	Estimated Charge	G' (Pa)	G"(Pa)	γ (Pa)
3:1	0	65000	7300	1190
4:1	-1	43000	5300	1000
5:1	-2	44000	5200	1000
6:1	-3	41000	4600	890
8:1	-5	32000	3900	790
10:1	-7	30000	4000	790
12:1	-9	22000	2800	560
30:1	-27	2400	300	140

Table S3. Rheological properties of the hybrid hydrogels at different GMP:polyamine molar ratios for the system GMP-**L2**.

GMP:L2 Molar Ratio	Estimated Charge	G' (Pa)	G"(Pa)	γ (Pa)
3:1	0	50000	6100	890
4:1	-1	48000	5900	790
5:1	-2	33000	4000	710
6:1	-3	30000	3800	670
8:1	-5	30000	3900	670
10:1	-7	26000	3400	500

Table S4. Rheological properties of the hybrid hydrogels at different GMP:polyamine molar ratios for the system GMP-**L3**.

GMP:L3 Molar Ratio	Estimated Charge	G' (Pa)	G"(Pa)	γ (Pa)
3:1	+1	45000	5000	1260
4:1	0	49000	5400	1260
5:1	-1	47000	5100	1260
6:1	-2	43000	4800	1260
8:1	-4	43000	4800	1120
10:1	-6	40000	4300	1120
12:1	-8	30000	3100	1000
30:1	-26	8600	860	500
50:1	-46	2700	320	250

Table S5. Rheological properties of the hybrid hydrogels at different GMP:polyamine molar ratios for the system GMP-**L5**.

GMP:L5 Molar Ratio	Estimated Charge	G' (Pa)	G"(Pa)	γ (Pa)
4:1	+1	65000	10000	1590
5:1	0	60000	9100	1780
6:1	-1	60000	9200	1410
8:1	-3	56000	9000	1410
10:1	-5	54000	7700	1260
12:1	-7	39000	5600	950
30:1	-25	15000	2200	530
50:1	-45	7700	1300	380

Table S6. Rheological properties of the hybrid hydrogels for the system GMP-**L1**-Isoniazid at GMP:**L1** 3:1 molar ratio in the absence and in the presence of different amounts of isoniazid.

GMP:L1 Molar Ratio	Isoniazid (mg/mL)	G' (Pa)	G"(Pa)	γ (Pa)
3:1	**0**	65000	7300	1190
3:1	**1**	46000	5300	1060
3:1	**10**	42000	4600	950

Table S7. Rheological properties of the hybrid hydrogels for the system GMP-**L2**-Isoniazid at GMP:**L2** 3:1 molar ratio in the absence and in the presence of different amounts of isoniazid.

GMP:L2 Molar Ratio	Isoniazid (mg/mL)	G' (Pa)	G"(Pa)	γ (Pa)
3:1	**0**	50000	6100	890
3:1	**1**	46000	5300	450
3:1	**10**	-	-	-

Table S8. Rheological properties of the hybrid hydrogels for the system GMP-**L3**-Isoniazid at GMP:**L3** 4:1 molar ratio in the absence and in the presence of different amounts of isoniazid.

GMP:L3 Molar Ratio	Isoniazid (mg/mL)	G' (Pa)	G"(Pa)	γ (Pa)
4:1	**0**	49000	5400	1260
4:1	**1**	52000	5200	1260
4:1	**10**	18000	1700	790

Table S9. Rheological properties of the hybrid hydrogels for the system GMP-**L5**-**I**soniazid at GMP:**L5** 5:1 molar ratio in the absence and in the presence of different amounts of isoniazid.

GMP:L5 Molar Ratio	**Isoniazid (mg/mL)**	**G' (Pa)**	**G''(Pa)**	**γ (Pa)**
5:1	**0**	60000	9100	1780
5:1	**1**	52000	5200	1260
5:1	**10**	-	-	-