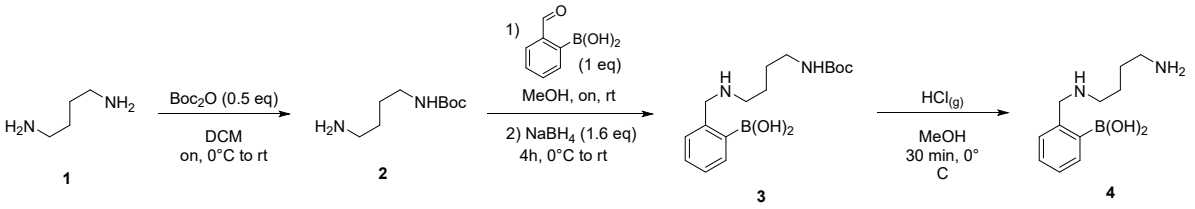
Supplementary information

Synthesis of wPBA

General synthetic pathway



Reagents, solvents and reaction conditions

Di-tert-butylcarbonate (Boc_2O), 1.4-diaminobutane, sodium tetraborohydride ($NaBH_4$) were all provided by Acros-Fisher. 2-(Formyl)phenylboronic acid and methanol (MeOH) were respectively supplied by Apollo Scientific and Merck (Darmstadt, Germany). Sulfuric acid (H_2SO_4) and sodium chloride (NaCl) were provided by VWR. The MB SPS-800-dry solvent system was used to dry dichloromethane. The reactions were carried out in glassware vessels which were either flame dried under vacuum or placed under argon stream for several minutes. Reactions were also performed under rigorous anhydrous conditions and argon stream/positive pressure of argon. Flash column chromatography was carried out using automatic Reveleris Büchi apparatus. Silica cartridges (4 g till 330 g, Büchi) were used with high purity grade of silica (40 µm).

Reaction monitoring and characterisation

All reactions were monitored by TLC on commercially available precoated plates (Kieselgel 60 F254), and the compounds were visualized with $KMnO_4$ solution [$KMnO_4$ (3 g), K_2CO_3 (20 g), NaOH (5% aq.; 5 mL), H_2O (300 mL)] and heating or by UV (254 nm) when possible.

Intermediate and final products were characterised by ^1H and ^{13}C NMR as well as ESI-TOF-HRMS.

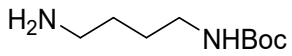
NMR studies

Intermediate and final products were characterised by ^1H and ^{13}C NMR. Spectra were recorded on a Bruker Avance 300 spectrometer fitted with a 5 mm i.d. BBO probe carefully tuned to the recording frequency of 300.13 MHz (for ^1H) and 75.47 MHz (for ^{13}C), the temperature of the probe was set at room temperature (around 293-294 K), on a Bruker Avance 400 spectrometer fitted with a 5 mm i.d. BBFO+ probe carefully tuned to the recording frequency of 400.13 MHz (for ^1H) and 100.61 MHz (for ^{13}C). The spectra are referenced to the solvent in which they were run (7.26 ppm for ^1H $CDCl_3$ and 77.16 ppm for ^{13}C $CDCl_3$, 2.50 ppm for ^1H DMSO-d_6 and 39.52 ppm for ^{13}C DMSO-d_6). Chemical shifts (δ) are given in ppm, and coupling constants (*J*) are given in Hz with the following splitting abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, qt = quintet, sx = sextuplet, sp = septuplet, m = massif and br = broad. All assignments were confirmed with the aid of two-dimensional ^1H, ^1H (COSY), or ^1H, ^{13}C (HSQC, HMBC) experiments using standard pulse programs.

ESI-TOF-HRMS investigations

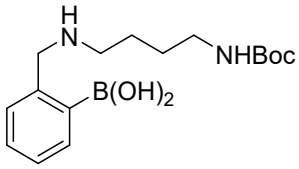
Intermediate and final products were characterised by electrospray (ESI)-time of flight (TOF) high resolution mass spectrometry (HRMS) measurements a Xevo G2-XS QTOF spectrometer (Waters, USA) in both positive and negative modes by direct introduction.

Synthesis of tert-Butyl (4-aminobutyl)carbamate :



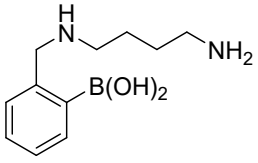
To a solution of diaminobutane (115.60 mmol, 10.36 mL) in dry DCM (100 mL) is added a solution of di-tert-butylcarbonate (57.80 mmol, 12.60 g) in dry DCM (90 mL) dropwise at 0°C. Reaction mixture is stirred at 0°C for 1h, then at room temperature overnight. The solution is diluted with DCM (200 mL). Iced-cold water is added and organic layers are extracted with DCM (3 times). Organic layers are washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude is purified by flash chromatography on silica gel (DCM/MeOH, 10/0 to 8/2, 1% Et_3N) to afford compound **2** (46.24 mmol, 8.69 g) with 40% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 4.80 (bs, 1H), 3.06-3.08 (m, 2H), 2.66-2.69 (m, 2H), 2.13 (bs, 2H), 1.42-1.51 (m, 4H), 1.39 (s, 9H) ; ^{13}C NMR (100 MHz, CDCl3): 156.1 (CO), 79.1 (C^{IV}), 41.6 (C_{al}), 40.4 (C_{al}), 30.49 (C_{al}), 28.5 (C_{al}), 28.5 (C_{al}), 28.5 (C_{al}), 27.5 (C_{al}) ; ESI(+)-TOF-HRMS *m/z* for $C_9H_{21}N_2O_2$ $[M + H]^+$: theoretical 189.1604, observed : 189.1603.

Synthesis of (2-(((4-((tert-Butoxycarbonyl)amino)butyl)amino)methyl)phenyl)boronic acid :



To a solution of tert-butyl(4-aminobutyl)carbamate (38.80 mmol, 7.30 g) in methanol (30 mL), is added 2-formylphenylboronic acid (38.80 mmol, 5.82 g) at room temperature, under argon atmosphere. The reaction mixture is stirred overnight at room temperature. Sodium borohydride (62.08 mmol, 2.35 g) is added carefully at 0°C. After total addition, the reaction mixture is stirred at room temperature until bubbles disappearance. Water and dichloromethane are added to the mixture. Organic layers are extracted with dichloromethane, dried over Na_2SO_4 and concentrated under reduced pressure to give compound **3** (37.05 mmol, 11.93 g) without further purification with 95% yield. ^{1}H NMR (400 MHz, MeOD): 7.43-7.45 (m, 1H), 7.13-7.21 (m, 3H), 4.00 (s, 2H), 3.10 (t, 2H), 2.85-2.89 (m, 2H), 1.71-1.79 (m, 2H), 1.50-1.57 (qt, 2H), 1.44 (s, 9H) ; ^{13}C NMR (100 MHz, MeOD): 158.5 (CO), 144.8 (C_{ar}), 142.4 (C_{ar}), 131.6 (C_{ar}), 128.2 (C_{ar}), 127.6 (C_{ar}), 124.1 (C_{ar}), 79.9 (C^{IV}), 55.0 (C_{al}), 48.6 (C_{al}), 40.8 (C_{al}), 28.8 (C_{al}), 28.8 (C_{al}), 28.8 (C_{al}), 28.6 (C_{al}), 25.2 (C_{al}) ; ESI(+)-TOF-HRMS *m/z* for $C_{18}H_{32}N_2O_4B$** $[M + H]^+$: theoretical 350.2487, observed : 350.2491.

Synthesis of (2-(((4-aminobutyl)amino)methyl)phenyl)boronic acid (wPBA):



To a solution of (2-(((4-((tert-butoxycarbonyl)amino)butyl)amino)methyl)phenyl)boronic acid (2.62 mmol, 0.84 g) in methanol (5 mL), hydrochloric acid gas is bubbled (from sulfuric acid over NaCl) at 0°C under argon atmosphere. Half an hour later, methanol is evaporated. The crude is dissolved in distilled water (15 mL) and an aqueous solution of sodium hydroxide (1 M) is added until pH 11. Water is co-evaporated with toluene. The crude is dissolved in dichloromethane, dried over Na_2SO_4 and concentrated under reduced pressure to afford the wished monomer **4** (1.89 mmol, 0.42 g) with 72% yield. ^{1}H NMR (400 MHz, MeOD): 7.40-7.43 (m, 1H), 7.15-7.23 (m, 3H), 4.03 (s, 2H), 2.96-3.00 (m, 2H), 2.89-2.93 (m, 2H), 1.82-1.90 (m, 2H), 1.69-1.77 (m, 2H) ; ^{13}C NMR (100 MHz, MeOD): 144.4 (C_{ar}), 142.7 (C_{ar}), 131.5 (C_{ar}), 128.4 (C_{ar}), 127.6 (C_{ar}), 124.1 (C_{ar}), 55.2 (C_{al}), 48.2 (C_{al}), 40.4 (C_{al}), 26.7 (C_{al}), 24.7 (C_{al}) ; ESI(+)-TOF-HRMS *m/z* for $C_{11}H_{16}N_2B$* $[M + H]^+$: theoretical 186.1451, observed : 186.1443.

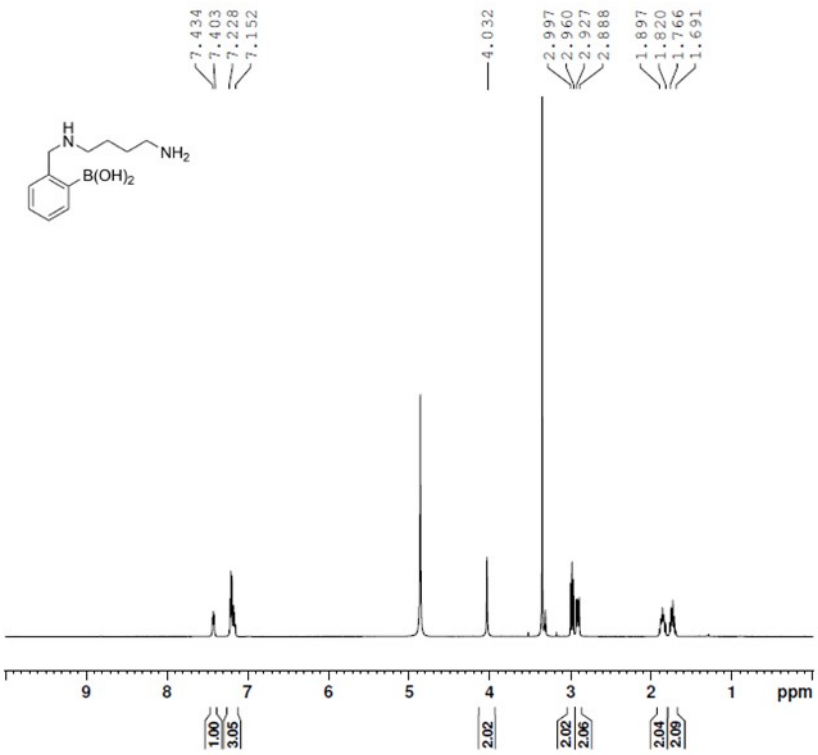


Figure S1. [1]H NMR spectrum of wPBA in MeOD.

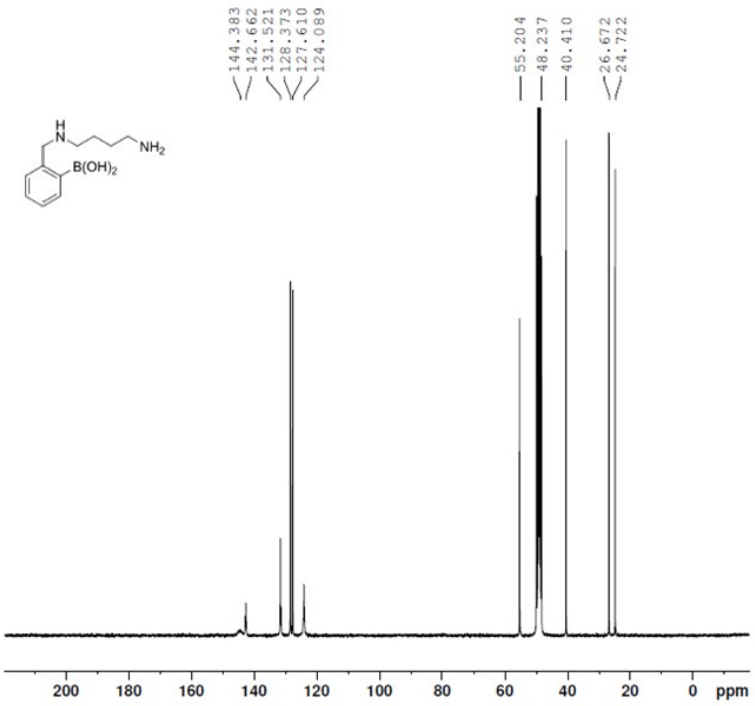


Figure S2. [13]C NMR spectrum of wPBA in MeOD.

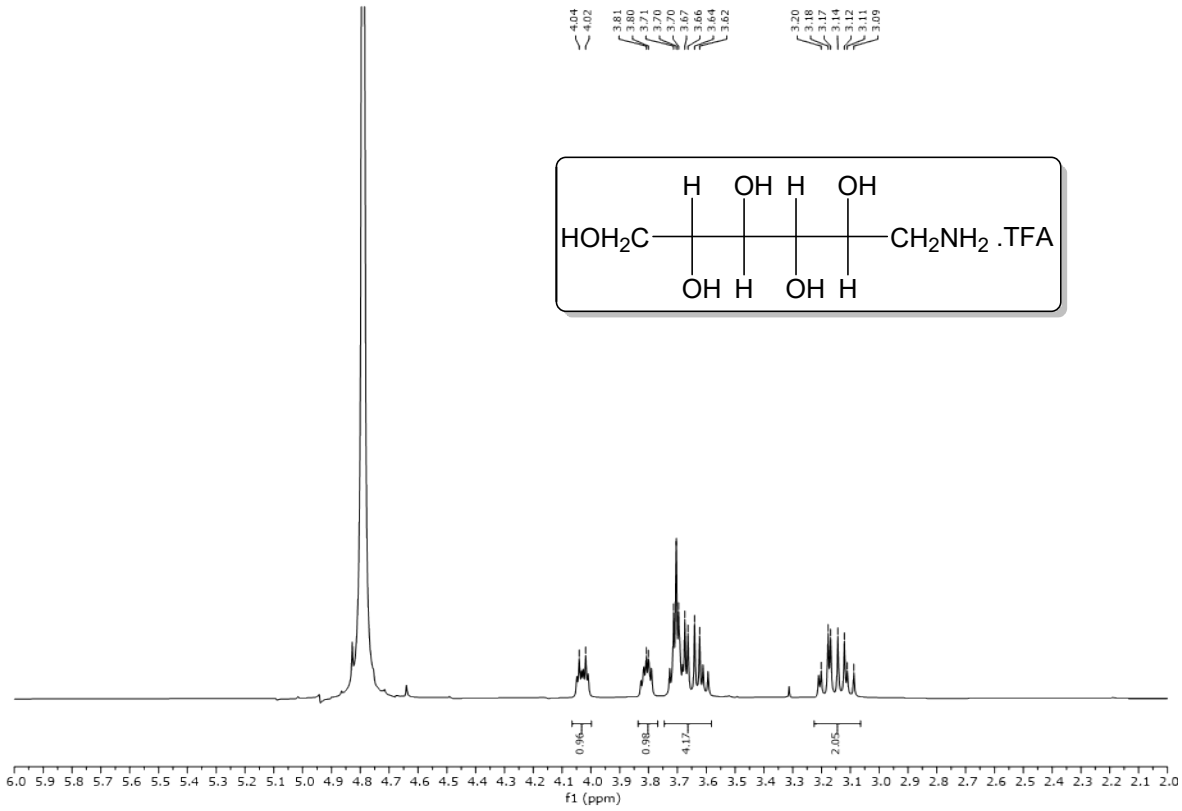


Figure S3. ^{1}H NMR spectrum of iditolamine in D_2O.

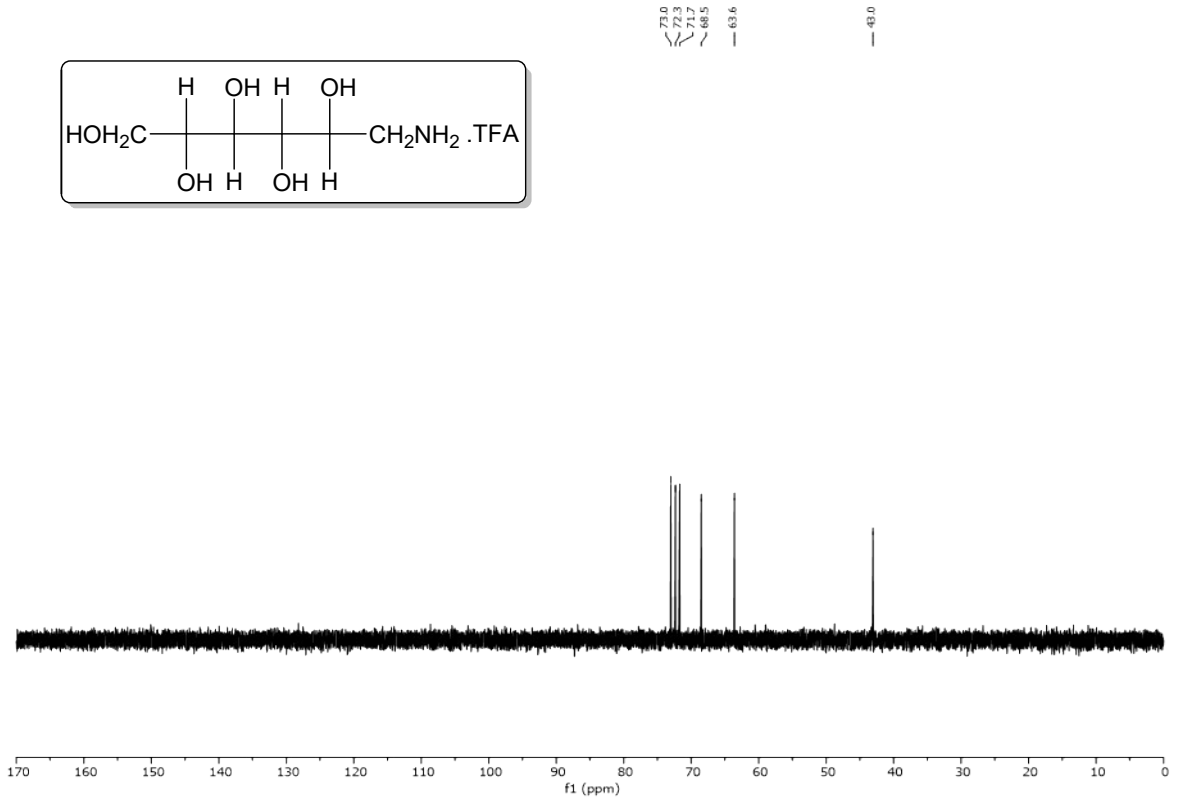


Figure S4: ^{13}C NMR spectrum of iditolamine in D_2O.

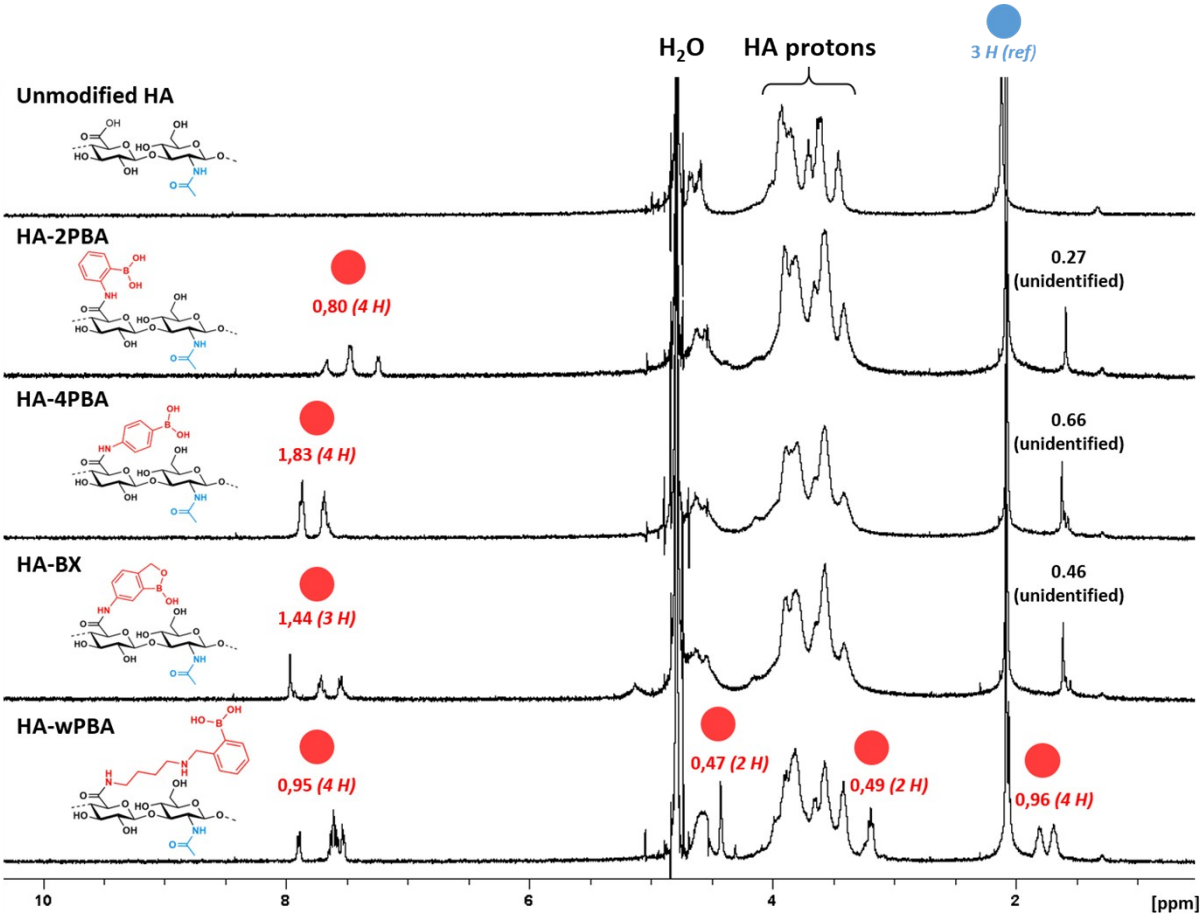


Figure S5. Representative ^{1}H NMR (400 MHz, D_2O) of HA, HA-2PBA, HA-4PBA, HA-BX and HA-wPBA, confirming the success of the syntheses. The 3 protons of the N-acetyl group of HA (blue circle, 2.1 ppm) served as a reference to calculate the degrees of substitution of HA-2PBA and HA-wPBA (red circles at 7.5-8 ppm, acounting for 3 or 4 protons). The grafting of 4PBA and BX repeatedly led to confusing substitution data via ^{1}H NMR (e.g., higher DS than the targeted values), which could not be explained. Thus, 4PBA-modified HA and BX-modified HA were characterized by another method (i.e., elemental analysis).

Table S1. Synthetic conditions for the synthesis of phenylboronic acid (PBA)-modified HA.

HA MW	Solvent	Activating agent	PBA	Substitution
300 kDa	0.1 M MES pH 5.5 (9 mL) + 1 mL DMSO	DMT-MM, 0.5 eq (34 mg; 0.124 mmol)	2PBA, 0.25 eq (11 mg; 0.062 mmol)	20% (^{1}H NMR)
			3PBA, 0.25 eq (8 mg; 0.062 mmol)	precipitate
			4PBA, 0.25 eq (11 mg; 0.062 mmol)	24% (EA)
			BX, 0.25 eq (13 mg; 0.062 mmol)	25% (EA)
100 kDa	0.1 M MES pH 5.5 (10 mL)	DMT-MM, 1 eq (69 mg; 0.248 mmol)	wPBA, 0.5 eq (28 mg; 0.124 mmol)	22% (^{1}H NMR)
300 kDa				24% (^{1}H NMR) 20% (EA)
100 kDa		DMT-MM, 2 eq (137 mg; 0.496 mmol)	wPBA, 1 eq (55 mg; 0.248 mmol)	40% (^{1}H NMR)
300 kDa				40% (^{1}H NMR)

All reactions were performed on 100 mg of HA (0.248 mmol of carboxylic acid). All equivalents were relative to the carboxylic acid groups of HA. ^{1}H NMR = proton nuclear magnetic resonance. EA = Elemental analysis.

Table S2. Synthetic conditions for the synthesis of diol-modified HA.

HA	Solvent	Activating agent	diol	Substitution
300 kDa	0.1 M MES pH 5.5 (10 mL)	DMT-MM, 1 eq (69 mg; 0.248 mmol)	Tris, 0.5 eq (15 mg; 0.124 mmol)	undetected
			Aminopropanediol, 0.5 eq (9.6 µL; 0. 124 mmol)	undetected
			Serinol, 0.5 eq (11 mg; 0.124 mmol)	undetected
			Glucosamine, 0.5 eq (27 mg; 0.124 mmol)	33% (TNBS) 29% (EA)
			Galactosamine, 0.5 eq (27 mg; 0.124 mmol)	32% (TNBS) 29% (EA)
			Fructosamine, 0.5 eq (27 mg, 0.124 mmol)	33% (TNBS) 37% (EA)
			Dulcitolamine, 0.5 eq (27 mg; 0.124 mmol)	26% (TNBS) 32% (EA)
			Iditolamine, 0.5 eq (24 mg; 0.124 mmol)	35% (TNBS)
			Dopamine, 0.5 eq (24 mg; 0.124 mmol)	undetected
100 kDa	0.1 M MES pH 5.5 (10 mL)	DMT-MM, 1 eq (69 mg; 0.248 mmol)	Glucamine, 0.5 eq (22 mg; 0.124 mmol)	33% (TNBS) 32% (EA)
300 kDa				33% (TNBS) 32% (EA)
100 kDa		DMT-MM, 2 eq (137 mg; 0.496 mmol)	Glucamine, 1 eq (45 mg, 0.248 mmol)	55% (TNBS) 52% (EA)
300 kDa				56% (TNBS) 52% (EA)

All reactions were performed on 100 mg of HA (0.248 mmol of carboxylic acid). All equivalents were relative to the carboxylic acid groups of HA. EA = Elemental analysis; TNBS = unreacted amine dosage using 2,4,6-trinitrobenzene sulfonic acid.

Table S3. Elemental analysis data of the investigated diol-modified HA, allowing to determine their degrees of substitution.

HA MW	Diol (eq)	%N	%C	N/C (m/m)	N/C (mol/mol)
300 kDa	4PBA (0.25 eq)	3.29	35.05	0.0939	0.0805
	BX (0.25 eq)	3.4	36.62	0.0929	0.0796
	wPBA (0.5 eq)	3.35	33.23	0.1008	0.0864
	glucosamine (0.5 eq)	3.456	36.176	0.0955	0.0819
	galactosamine (0.5 eq)	3.46	36.163	0.0957	0.08
	fructosamine (0.5 eq)	3.687	37.33	0.0988	0.0847
	dulcitolamine (0.5 eq)	3.62	37.36	0.0969	0.0831
100 kDa	glucamine (0.5 eq)	3.45	35.75	0.0965	0.0827
300 kDa		3.669	37.863	0.0969	0.0831
100 kDa	glucamine (1 eq)	3.97	38.38	0.1034	0.08866
300 kDa		3.72	35.92	0.1036	0.0888

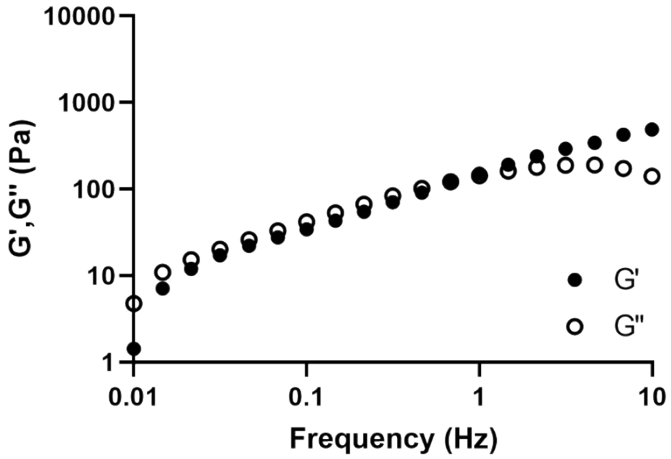


Figure S6. Frequency sweep of a wPBA/glucamine alginate hydrogels, at a total alginate concentration of 2% (w/v), using an alginate-wPBA:alginate-glucamine volume ratio of 1:1.

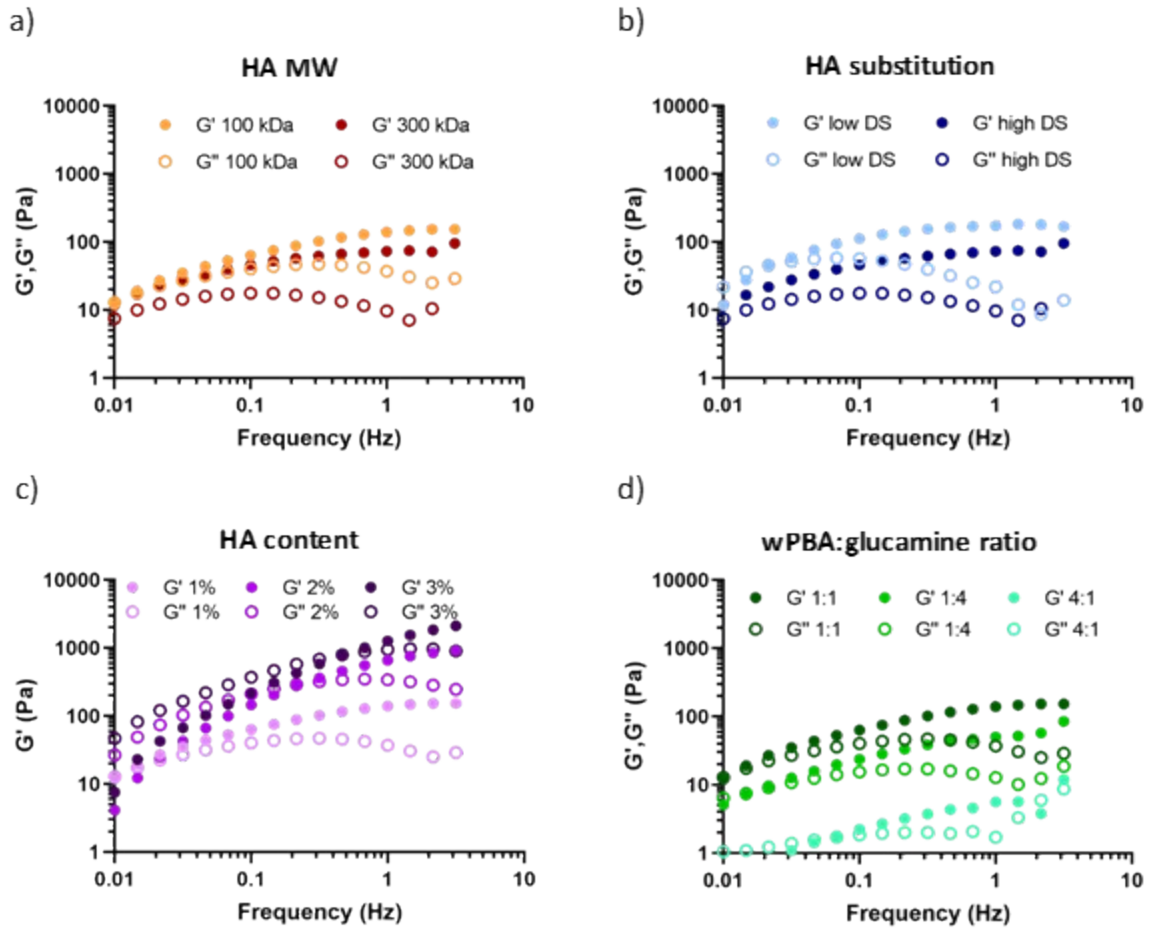


Figure S7. The influence of a) HA MW, b) HA DS, c) HA content, and d) wPBA:glucamine molar ratio on hydrogel shear elastic (*G′*) and loss (*G″*) moduli, evaluated using dynamic shear rheometry. Results on HA DS compared to low DS (HA-wPBA, 24%; HA-glucamine, 32%) and high DS (HA wPBA, 40%; HA-glucamine, 52%).

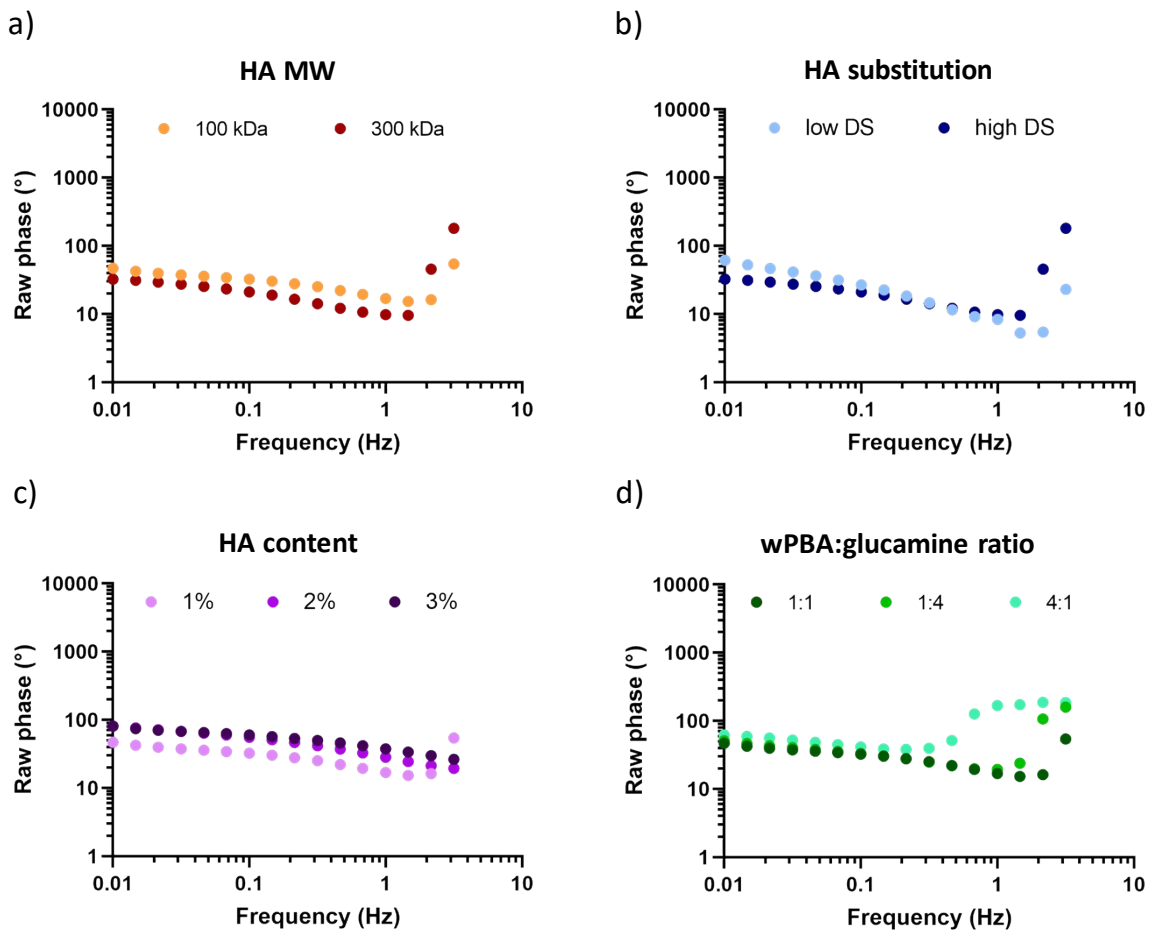


Figure S8. Raw phase data associated with Figure 2.

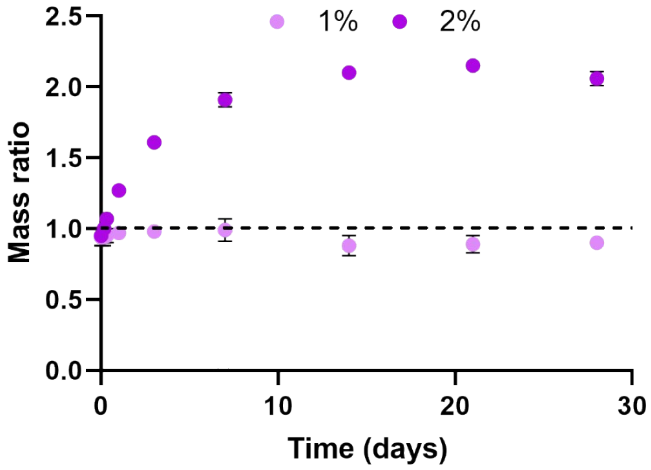


Figure S9. The influence of HA content of 300 kDa HA hydrogels (HA-wPBA: DS of 40%; HA-glucamine: DS of 52%) on the hydrogel stability/swelling. Data are shown as mean ± SD (n = 3).

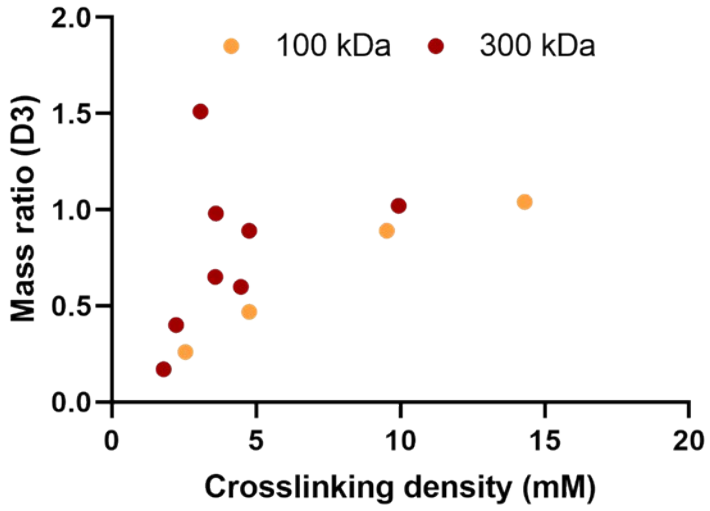


Figure S10. Swelling/shrinking behavior of immersed hydrogels as a function of the crosslinking density. Values show no obvious trend, suggesting no direct correlation. Data were extracted from the swelling/stability profiles presented in Figure 3, using the day-3 time point values.

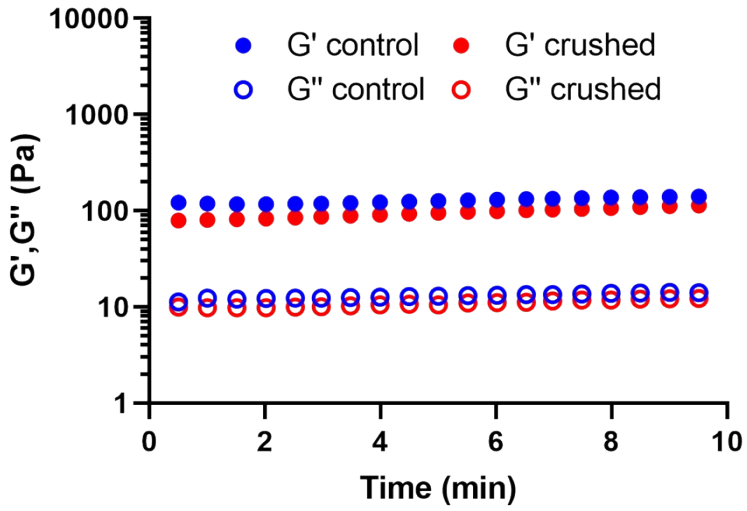


Figure S11. Rheological evaluation of a boronate ester-based hydrogel, before and after manual crushing, confirming its self-healing properties.

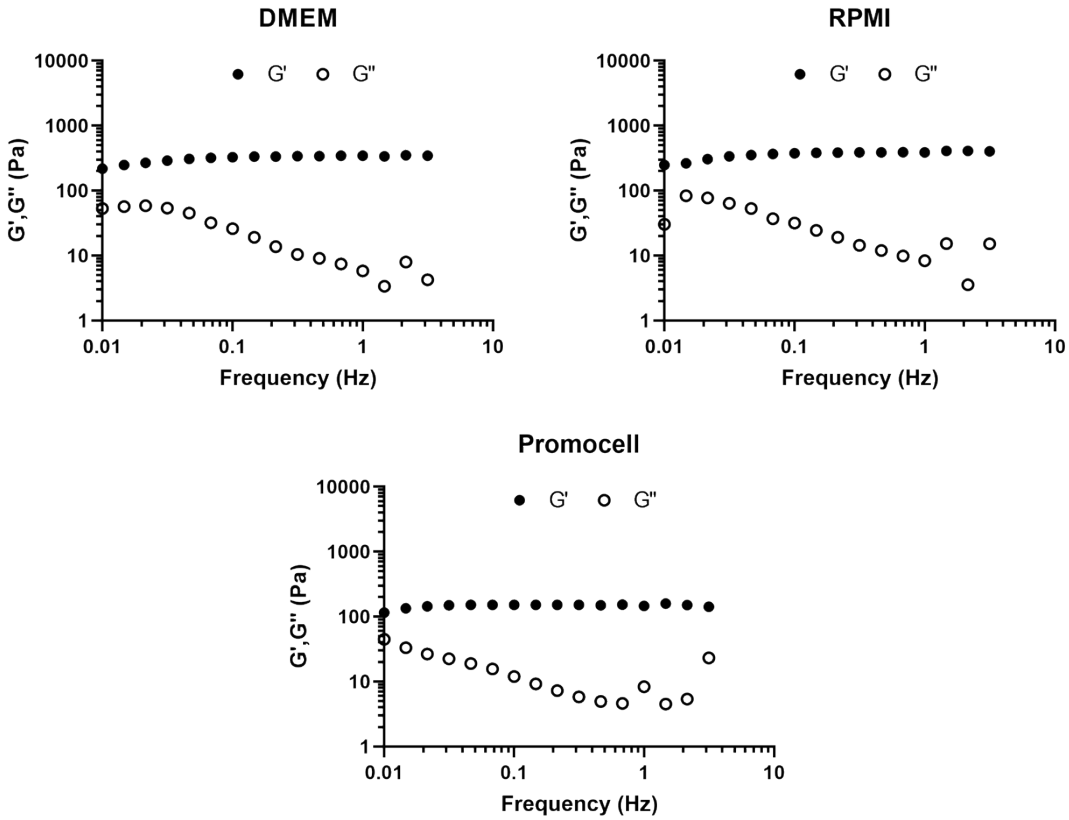


Figure S12. Our Boronate ester-based hydrogels can be obtained with a variety of cell culture media. Here, the use of DMEM, RPMI or Promocell led to successful gelation, and revealed a slight increase in the shear elastic modulus of the hydrogels in a culture medium-dependent manner.

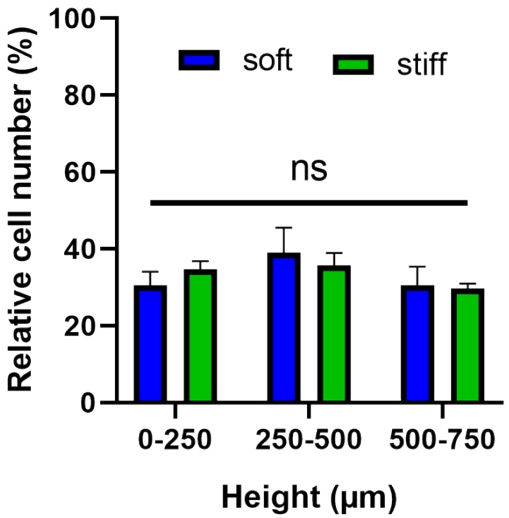


Figure S13. Relative cell distribution in the soft and stiff hydrogels, confirming homogenous cell encapsulation. The dashed line indicates the expected relative cell number in each of the three bins, which is 33%). Data are shown as mean ± SD (n = 3) with statistical significance determined using one-way ANOVA with a Tukey's post hoc test (ns : not significant).