Supporting Information

Self-crosslinking smart hydrogels through direct complexation between benzoxaborole derivatives and diols from hyaluronic acid

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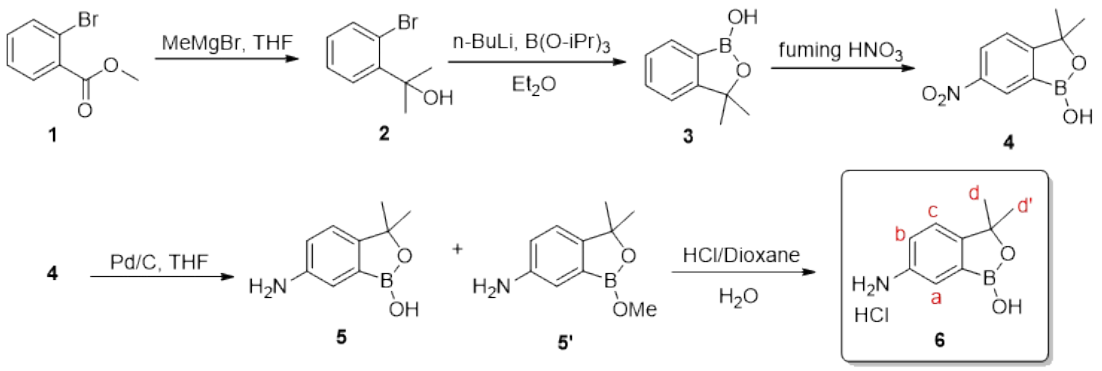
1. Synthesis of aminobenzoxaborole (BOR-NH_2) compounds

Except 6-aminobenzoxaborole (6ABOR) which is commercially available, the other custom-made aminobenzoxaborole compounds were synthesized in four to seven steps, as described below. Among them, four derivatives (DM6ABOR, 7ABOR, 5ABOR and 4ABOR) have already been reported in literature,[1–6] whereas the others (DMF6ABOR, F6ABOR, DM7ABOR, DM5ABOR and DM4ABOR) are novel molecules.

6-amino-3,3-dimethylbenzo-3H-benzo[c][1,2]oxaborol-1-ol (DM6ABOR) hydrochloride



Synthesis of **2**: To a solution of **1** (5.0 g, 23 mmol) in anhydrous THF (80 mL), MeMgBr (23 mL, 3 M) was added dropwise at 0 °C and the reaction was allowed to room temperature for 4 h. The mixture was poured by saturated NH_4Cl, extracted with ethyl acetate (3 x 100 mL), washed with brine (2 x 100 mL), dried over Na_2SO_4 and concentrated to yield crude, which was purified by flash column chromatography to give compound **2** (2.6 g, 52 %) as a colorless oil.

Synthesis of **3**: To a solution of n-BuLi (21 mL, 2.5 M) in Et_2O (50 mL) was added dropwise a solution of compound **2** (5.0 g, 23.36 mmol) in Et_2O (50 mL) at -75 °C and stirred for 2 h. Triisopropyl borate was added dropwise and the reaction was allowed to room temperature overnight. The mixture was poured by saturated NH4Cl, extracted with ethyl acetate (3 x 500 mL), washed with brine (2 x 100 mL), dried over Na_2SO_4 and concentrated to yield crude, which was purified by flash column chromatography to give compound **3** (2.0 g, 80 % pure) as a colorless oil, which was used to next step directly.

Synthesis of **4**: A solution of compound **3** in $PhNO_3$ was added to fuming HNO_3 and stirred at -40 °C for 2 h. The mixture was poured onto ice-water and extracted with ethyl acetate (3 x 500

mL), washed with brine (2 x 50 mL), dried over Na_2SO_4 and concentrated to yield crude, which was purified by flash column chromatography (eluent: 10 % to 17 % ethyl acetate) to give compound **4** (0.6 g) as a yellow solid.

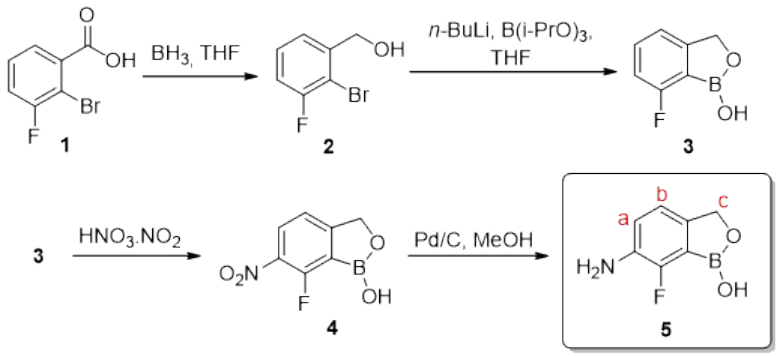
Synthesis of **5**: A mixture of compound **4** (120 mg, crude) and Pd/C (50 mg) in THF (10 mL) was stirred at room temperature overnight under H_2 atmosphere. The mixture was filtered and the residue was concentrated to dryness to give crude (300 mg), which was purified by preparative-TLC to give a mixture of compound **5/5'** (70 mg, confirmed by ^{1}H NMR).

Synthesis of **6** (**DM6ABOR**): A mixture of compound **5/5'** (70 mg, crude) in HCl/dioxane and H_2O was stirred at room temperature overnight. The solution was removed under reduced pressure to give compound **6** (80 mg, 98 % pure) as an off white solid.

^{1}H NMR (400 MHz, DMSO-*d6*, 298 K): δ (ppm) 9.32 (br, 1H), 7.63 (s, 1H, **Ha**), 7.53-7.51 (d, 1H, **Hc**), 7.42-7.40 (d, 1H, **Hb**), 1.43 (s, 6H, **Hd-Hd'**).

LC-MS (MS, *m/z*): 178.4 $[M + H]^+$.

6-amino-7-fluorobenzo[c][1,2]oxaborol-1(3H)-ol (F6ABOR)



Synthesis of **2**: To a solution of **1** (120 g, 547.9 mmol) in anhydrous THF (1200 mL) was added BH_3.THF (1638 mL, 1643.8 mmol, 3.0 eq) at 0 °C. After stirring for 30 min at 0 °C, the mixture was warmed to room temperature and stirred for 16 h. HPLC indicated SM was disappeared, the reaction mixture was cooled to 0 °C and was carefully quenched with addition of 2000 mL of H_2O. The mixture was then extracted with EtOAc (3 x 400 mL). The organic layer was dried and concentrated in vacuum to give **2** (108 g, crude) as a white solid.

Synthesis of **3**: To a solution of **2** (108 g, 525.7 mmol, 1 eq) and triisopropyl borate (197.7 g, 224.2 mmol, 2 eq) in anhydrous THF (2600 mL) at N_2 atmosphere, n-BuLi (2.5 M in hexane, 470.7 mL, 1177.7 mmol, 2.2 eq) was added dropwise at -78 °C. Then, the mixture was allowed to warm to room temperature and stirred overnight under N_2. HPLC indicated that the reaction was completed and 1 M HCl (30 mL) was added in the medium followed by extraction with EtOAc (3 x 1000 mL). The organic phase was washed with brine, dried and concentrated under vacuum to give a crude residue, which was purified by silica gel column chromatography to afford **3** (8.0 g, 47 %) as a yellow powder.

^{1}H NMR (300 MHz, DMSO-*d6*, 298 K): δ (ppm) 9.25 (br, 1H), 7.57-7.50 (m, 1H), 7.24 (d, J = 7.2 Hz, 1H), 7.04 (t, J = 8.1 Hz, 1H), 5.01 (s, 2H).

Synthesis of **4**: To a pre-cooled fuming HNO_3 (24 mL), **3** (8.0 g, 52.6 mmol, 1 eq) was added as a solid in potions with the aid of -30 °C cooler. After the completion of addition, the reaction mixture was stirred for 1 h to give a yellow slurry, quenched by the addition of crushed ice (400 g) at the same temperature, and warmed to room temperature slowly. The final yellow suspension was filtrated, washed to pH 6-7 with water to give crude compound **4**, which was purified by silica gel column chromatography to afford **4** (2.7 g, 26.2 %) as a white powder solid.

^{1}H NMR (300 MHz, DMSO-*d6*, 298 K): δ (ppm) 8.43-8.24 (m, 1H), 7.48-7.37 (m, 1H), 5.37 (s, 2H).

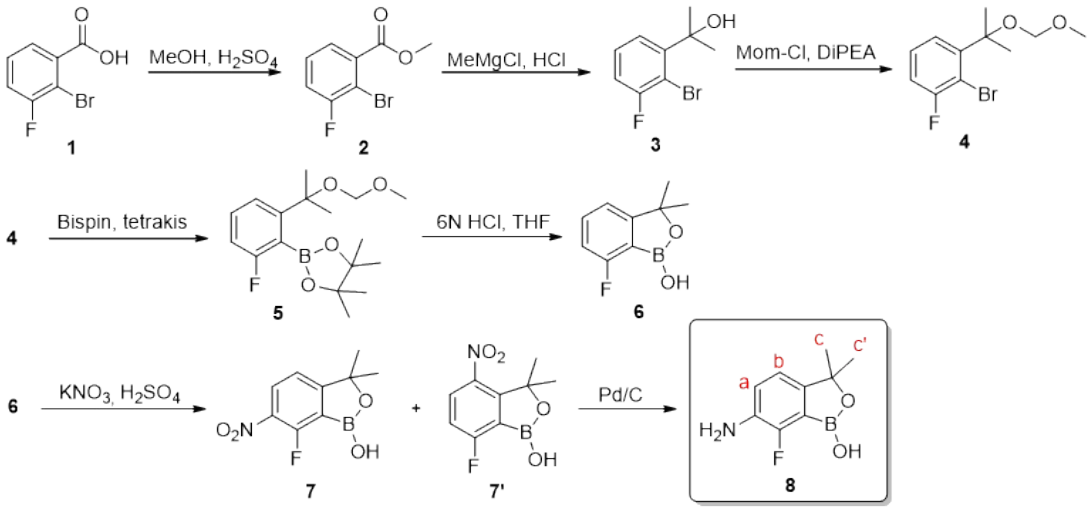
LC-MS (MS, *m/z*): 198.1 $[M + H]^+$.

Synthesis of **5** (**F6ABOR**): Pd/C (0.27 g) was added to a solution of **4** (2.7 g, 13.7 mmol, 1.0 eq) in THF (27 mL) under N_2 and the suspension was degassed under vacuum and purged with H_2 for three times. The reaction medium was stirred at 25 °C for 2 h under H_2. Thin layer chromatography (eluent: petroleum ether/ethyl acetate 1:1) indicated that the reaction was completed. The reaction mixture was then filtered to remove Pd/C and the filtrate was concentrated to dryness to give **5** (1.7 g, 77 %).

^{1}H NMR (300 MHz, DMSO-*d6*, 298 K): δ (ppm) 9.04 (s, 1H), 6.79-6.73 (m, 1H, **Hb**), 6.68-6.63 (m, 1H, **Ha**), 4.90 (br, 2H), 4.78 (s, 2H, **Hc**).

LC-MS (MS, *m/z*): 168.1 $[M + H]^+$.

6-amino-7-fluoro-3,3-dimethylbenzo[c][1,2]oxaborol-1(3H)-ol (DMF6ABOR)



Synthesis of **2**: To a stirred solution of **1** (50 g, 0.229 mol) in methanol (500 mL) cooled to 5°C, H_2SO_4 (50 mL) was added dropwise below 10 °C under N_2. The reaction mixture was stirred at 85 °C for 16 h and the formation of product was observed by thin layer chromatography. The reaction mixture was completely concentrated and cooled to get solid, diluted with water and stirred for 15 min, filtered and then dried to give 50 g (94 %) of **2** as a white solid.

Synthesis of **3**: To a solution of **2** (50 g, 0.215 mol) in THF (1000 mL) cooled to 5 °C, CH_3MgCl (3 M in THF, 287 mL, 0.862 mol) was added dropwise at 10 °C under N_2. The mixture was

stirred at room temperature for 2 h and quenched with 500 mL of saturated NH_4Cl solution. The mixture was extracted with ethyl acetate and the combined organic layer was washed with brine, dried over sodium sulfate and concentrated under vacuum to provide yellow oil. The crude product was purified by column chromatography (silica gel; eluent: ethyl acetate/hexane, 70:30) to afford 38 g (76 %) of **3** as a colorless liquid.

Synthesis of **4**: To a solution of **3** (38 g, 0.163 mol) in THF (700 mL) DIPEA (84.5 g, 0.655 mol) and Mom-Cl (26.0 g, 0.326 mol) were added successively, followed by reaction mixture heating to 75 °C under stirring for 16 h under N_2. The product formation was observed by TLC. The reaction mixture was concentrated completely, diluted with water (400 mL) and extracted with ethyl acetate (3 x 50 mL). Combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to get the crude product, which was purified by column chromatography (silica gel; eluent: ethyl acetate:hexane, 10:90) to afford **4** (30 g, 63 %) as a colorless liquid.

Synthesis of **5**: BISPIN (41.2 g, 0.162 mol) and potassium acetate (26.5 g, 0.270 mol) were added to a solution of **4** (30 g, 0.108 mol) in dioxane (600 mL), degassed with argon for 10 min. $Pd(PPh_3)_4$ (8.78 g, 0.010 mol) was then added the reaction medium was degassed for more 5 min followed by heating to 110 °C and stirred for 24 h under N_2. A color change of the reaction mixture from yellow to black indicated the completion of the reaction as observed by TLC. The medium was filtered through celite and the filtrate was concentrated to give **5** (40 g, crude) as a black gum crude which was used directly in the next step without further purification.

Synthesis of **6**: To a solution of **5** (40 g, 0.123 mmol) in THF (200 mL) was added 6 N HCl (200 mL) followed by reaction stirring at room temperature for 4 h. After confirming formation of product by thin layer chromatography, the reaction mixture was concentrated and basified with a NaOH solution until pH 9 and extracted with EtOAc (2 x 200 mL). An aqueous layer was acidified until pH 2 and extracted with ethyl acetate (3 x 50 mL). Combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to afford **6** (12 g, 51 %, LC-MS 80 %) as a yellow gum.

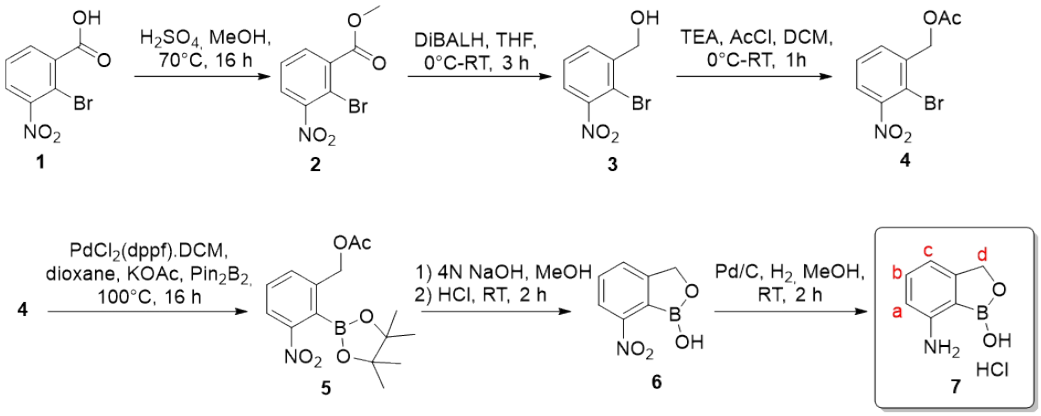
Synthesis of **7**: KNO_3 (6.73 g, 0.066 mol) was added to a solution of **6** (12 g, 0.066 mol) in H_2SO_4 (100 mL) at 0 °C and stirred for 1 h under nitrogen. The reaction mixture was diluted with ice water (400 mL) and extracted with ethyl acetate (3 x 200 mL). Combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to give **7/7'** (10 g, 66 %, LC-MS 80 %) as a yellow solid containing a mixture of positional isomers.

Synthesis of **8** (**DMF6ABOR**): To a solution of **7/7'** (8 g, 0.046 mol) in methanol (100 mL) was added 10 % Pd/C (2 g) and stirred at room temperature for 16 h under hydrogen atmosphere. After observation of product formation by thin layer chromatography, the reaction mixture was filtered through celite and the filtrate was concentrated. The crude product was then purified by column chromatography (silica gel; eluent: ethyl acetate:hexane, 25:75) to give **8** (3.0 g, 90 %) as a yellow solid as a mixture of positional isomers purified by preparative HPLC and recovered by lyophilization to afford 1.16 g of an off-white solid.

^{1}H NMR (400 MHz, DMSO-*d6*, 298 K): δ (ppm) 6.90-6.88 (d, 2H, **Hb-Ha**), 4.93 (s, 2H), 1.39 (s, 6H, **Hc-Hc'**).

LC-MS (MS, *m/z*): 195.97 $[M + H]^+$.

7-aminobenzo[c][1,2]oxaborol-1(3H)-ol (7ABOR) hydrochloride



Synthesis of **2**: To a stirred solution of **1** (40 g, 162.6 mmol, 1.0 eq) in MeOH (400 mL), H_2SO_4 (20 mL) was added dropwise through addition of funnel at 0 °C. After completion of the addition, the medium was heated to 70 °C and stirred for 16 h. The progress of the reaction was monitored by TLC (40 % EtOAc in n-hexane). After completion of the reaction, the mixture was fully evaporated under reduced pressure to get a residue. Water (1.5 L) was added to the resulting residue and stirred for 10 min followed by filtration of the solid and drying to get **2** (40.0 g, 94.6 %) as a yellow solid.

^{1}H NMR (400 MHz, DMSO-*d6*, 298 K): δ (ppm) 7.85 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.76 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 3.98 (s, 3H).

LC-MS (ES, *m/z*): no ionization.

Synthesis of **3**: To a stirred solution of **2** (40 g, 153.82 mmol, 1.0 eq) in THF (400 mL) was added DIBALH (138 mL, 230.73 mmol, 1.5 eq) dropwise at 0 °C over a period of 45 minutes. After completion of addition, the reaction mixture was slowly warmed to room temperature and stirred for 3 h. The progress of the reaction was monitored by TLC (40 % EtOAc in n-hexane) and, after completion of the reaction, the medium was cooled to 0 °C, quenched with saturated ammonium chloride solution (150 mL) and extracted with ethyl acetate (2 x 500 mL). The combined organic layer was washed with saturated brine solution (200 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to get crude compound. The crude product was purified by flash column chromatography using 100-200 mesh silica gel, eluted with 20 % ethyl acetate in petroleum ether to afford **3** (35.0 g, 98.06 %) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-*d6*, 298 K): δ (ppm) 7.77 (d, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 1H), 4.84 (s, 2H), 2.08 (s, 1H, OH).

Synthesis of **4**: TEA (62.5 mL, 452.50 mmol, 3.0 eq) and AcCl (21.5 mL, 301.67 mmol, 2.0 eq) were sequentially added to a stirred solution of **3** (35 g, 150.83 mmol, 1.0 eq) in DCM (350 mL) at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred for 1 h. Then, the medium was diluted with DCM (500 mL) and washed with water (500 mL) followed by saturated brine solution (500 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to get a crude compound, which was purified by flash column chromatography using 100-200 mesh silica gel and eluted with 15 % ethyl acetate in petroleum ether to give **4** (30.0 g, 72.5%) as a pale yellow solid.

^{1}H NMR (400 MHz, DMSO-*d6*, 298 K): δ (ppm) 7.67 (d, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 7.2 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 5.26 (s, 2H), 2.17 (s, 3H).

LC-MS (ES, *m/z*): 276.14 $[M + H]^+$.

Synthesis of **5**: Compound **4** (5.0 g, 18.34 mmol, 1.0 eq), Pin_2B_2 (6.94 g, 27.36 mmol, 1.5 eq), AcOK (5.40 g, 55.02 mmol, 3.0 eq) were then taken in 1,4-dioxane (50 mL) degassed with argon for 10 minutes. $PdCl_2(dppf)_2$ (1.49 g, 1.834 mmol, 0.1 eq) was added to the reaction mixture, degassed for 5 minutes, heated to 100 °C and stirred for 16 h. The progress of the reaction was monitored by TLC (10 % EtOAc in n-hexane). The reaction mixture was filtered through celite and the filtrate was evaporated under vacuum to obtain a crude product which was purified by flash column chromatography (silica gel; eluent: 20 % ethyl acetate in petroleum ether) to afford **5** (3.50 g, 59.82 %) as a pale brown solid.

^{1}H NMR (400 MHz, DMSO-*d6*, 298 K): δ (ppm) 8.15 (d, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 5.20 (s, 2H), 2.10 (s, 3H), 1.45 (s, 12H).

LC-MS (ES, *m/z*): 322.18 $[M + H]^+$.

Synthesis of **6**: To a solution of **5** (2.5 g, 7.78 mmol, 1.0 eq) in methanol (25 mL), a 4 N NaOH solution was added dropwise at 0 °C. After completion of addition, reaction mixture was warmed to room temperature and stirred for 2 h. The progress of the reaction was monitored by TLC (70 % EtOAc in n-hexane) and the completed reaction mixture was cooled to 0 °C followed by adding a 6 N HCl solution (4.5 mL) dropwise. The recovered solid was filtered and dried to give **6** (600 mg, 43.47 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d6*, 298 K): δ (ppm) 8.94 (s, 1H, OH), 8.02 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 7.82 Hz, 1H), 7.75 (t, *J* = 7.6 Hz, 1H), 5.09 (s, 2H).

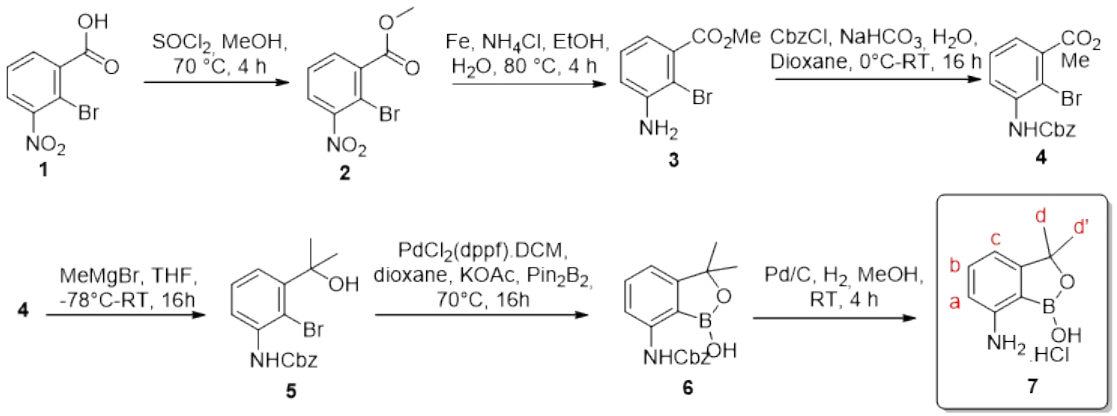
LC-MS (ES, *m/z*): 179.9 $[M + H]^+$.

Synthesis of **7** (**7ABOR**): Pd/C (2.50 g) was added to a solution of **6** (3.5 g, 19.56 mmol, 1.0 eq) in MeOH (25 mL) under N_2 and the reaction medium was hydrogenated under 50 psi at room temperature for 4 h. The reaction was monitored by TLC (50 % EtOAc in hexane). Then, the medium was filtered through celite and washed with MeOH (100 mL). The combined filtrate was evaporated under reduced pressure to afford the final compound as a free amine. This was converted to its corresponding HCl salt in 1,4-dioxane (20 mL) with addition of 4 M HCl in 1,4-dioxane (10 mL) under stirring for 1 h. The reaction mixture was fully evaporated under vacuum to give a crude product which was washed with 50 % ethyl acetate in petroleum ether (100 mL) and filtered the solid to give **7** (2.5 g, 85.91 %) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-*d6*, 298 K): δ (ppm) 7.42 (t, *J* = 7.6 Hz, 1H, **Hc**), 7.13 (d, *J* = 7.2 Hz, 1H, **Hb**), 7.04 (d, *J* = 7.6 Hz, 1H, **Ha**), 4.97 (2H, s, **Hd**).

LC-MS (ES, *m/z*): 150.2 $[M + H]^+$.

7-amino-3,3-dimethylbenzo[c][1,2]oxaborol-1(3H)-ol (DM7ABOR) hydrochloride



Synthesis of **2**: To a stirred solution of compound **1** (70 g, 284.5 mmol, 1.0 eq) in MeOH (750 mL) was added $SOCl_2$ (30.97 mL, 426.8 mmol, 1.5 eq) dropwise through addition funnel at 0 °C. The reaction mixture was then heated to 70 °C and stirred for 4 h. The progress of the reaction was monitored by TLC (20 % EtOAc in n-hexane). After completion of the reaction, the reaction mixture was fully evaporated under reduced pressure to get residue. Water (1.5 L) was added to the resulting residue with stirring for 10 min. The solid was then filtered and dried to obtain **2** (72.0 g, 97.3 %) as an off white solid.

^{1}H NMR (400 MHz, DMSO-*d6*, 298 K): δ (ppm) 7.85 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.76 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 3.98 (s, 3H).

LC-MS (ES, *m/z*): no ionization.

Synthesis of **3**: To a stirred solution of compound **2** (72 g, 276.92 mmol, 1.0 eq) in EtOH/water (720 mL, 1:1) were added Fe (77.33 g, 1384.6 mmol, 5.0 eq) and NH_4Cl (118.4 g, 2215 mmol, 8.0 eq) at rt. The reaction medium was heated to 80 °C and stirred for 4 h. The progress of the reaction was monitored by TLC (40 % EtOAc in n-hexane). After completion of the reaction, the medium was cooled to rt, filtered through celite bed and the filtrate was evaporated under reduced pressure to give a residue, which was portioned between water (2.0 L) and ethyl acetate (2.0 L). The organic layer was washed with saturated brine solution (500 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to give the crude compound **3** (62.0 g, 98.4 %) as a brown liquid.

^{1}H NMR (400 MHz, DMSO-*d6*, 298 K): δ (ppm) 7.12 (t, *J* = 8.0 Hz, 1H), 6.93 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.80 (dd, *J* = 7.6, 1.6 Hz, 1H), 5.58 (s, 2H), 3.81 (s, 3H).

LC-MS (ES, *m/z*): 229.8 $[M + H]^+$.

Synthesis of **4**: To a stirred solution of **3** (62 g, 271.92 mmol, 1.0 eq) in 1,4-dioxane/water (640 mL, 1:1) were added $NaHCO_3$ (68.52 g, 815.76 mmol, 3.0 eq) and CbzCl (57.98 mL, 407.88 mmol, 1.5 eq) sequentially at 0 °C, and the reaction mixture was slowly warmed to rt under stirring for 16 h. The progress of the reaction was monitored by TLC (20 % EtOAc in n-hexane). After completion of the reaction, the medium was diluted with ethyl acetate (1500 mL) washed with water (1500 mL) followed by saturated brine solution (500 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to get a crude compound which was purified by flash column chromatography using 100-200 mesh silica gel, eluted with

10 % ethyl acetate in petroleum ether to afford compound **4** (65.0 g, 65.8 %) as an off white solid.

^{1}H NMR (400 MHz, DMSO-*d6*, 298 K): δ (ppm) 9.25 (s, 1H, NH), 7.67 (dd, *J* = 7.6, 2.4 Hz, 1H), 7.49-7.33 (m, 7H), 5.16 (s, 2H), 3.86 (s, 3H).

LC-MS (ES, *m/z*): 365.9 [M + H]+.

Synthesis of **5**: To a stirred solution of **4** (40.0 g, 110.19 mmol, 1.0 eq) in THF (400 mL) was added 2.5 M MeMgBr (440.4 mL, 1101 mmol, 10 eq) in diethyl ether dropwise over a period of 30 min at -78 °C (temperature maintained for 1 h). After 1 h, the reaction mixture was slowly warmed to rt and stirred for 16 h. The progress of the reaction was monitored by TLC (40 % EtOAc in n-hexane). After completion of the reaction, the medium was quenched with saturated NH_4Cl solution (1000 mL) at 0 °C and extracted with EtOAc (2 x 750 mL). The combined organic layer was washed with saturated brine solution (500 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to get a crude compound. The crude product was purified by flash column chromatography using 100-200 mesh silica gel, eluted with 25 % ethyl acetate in petroleum ether to give **5** (24.0 g, 60 %) as a brown solid.

^{1}H NMR (400 MHz, DMSO-*d6*, 298 K): δ (ppm) 8.98 (m, 1H, NH), 7.71 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.41-7.30 (m, 7H), 5.13 (s, 2H), 1.63 (s, 6H).

Synthesis of **6**: Compound **5** (24.0 g, 66.11 mmol, 1.0 eq), Pin_2B_2 (22.4 g, 99.17 mmol, 1.5 eq) and AcOK (19.46 g, 198.3 mmol, 3.0 eq) were taken in 1,4-dioxane (250 mL) and degassed with argon for 10 minutes. $PdCl_2(dppf)_2$ (4.83 g, 6.611 mmol, 0.1 eq) was added to the reaction mixture, degassed by additional 5 minutes and then heated to 70 °C under stirring for 16 h. The progress of the reaction was monitored by TLC (40 % EtOAc in n-hexane). After completion of the reaction, the medium was filtered through celite pad and the filtrate was evaporated under vacuum to obtain a crude compound, which was purified by flash column chromatography using 100-200 mesh silica gel and eluted with 20 % ethyl acetate in petroleum ether to afford **6** (12.0 g, 58.53 %) as a brown solid.

^{1}H NMR (400 MHz, DMSO-*d6*, 298 K): δ (ppm) 9.25 (s, 1H, NH), 8.22 (s, 1H, OH), 7.75 (d, *J* = 7.6 Hz, 1H), 7.45-7.34 (m, 6H), 7.07 (d, *J* = 7.6 Hz, 1H), 5.17 (s, 2H), 1.43 (s, 6H).

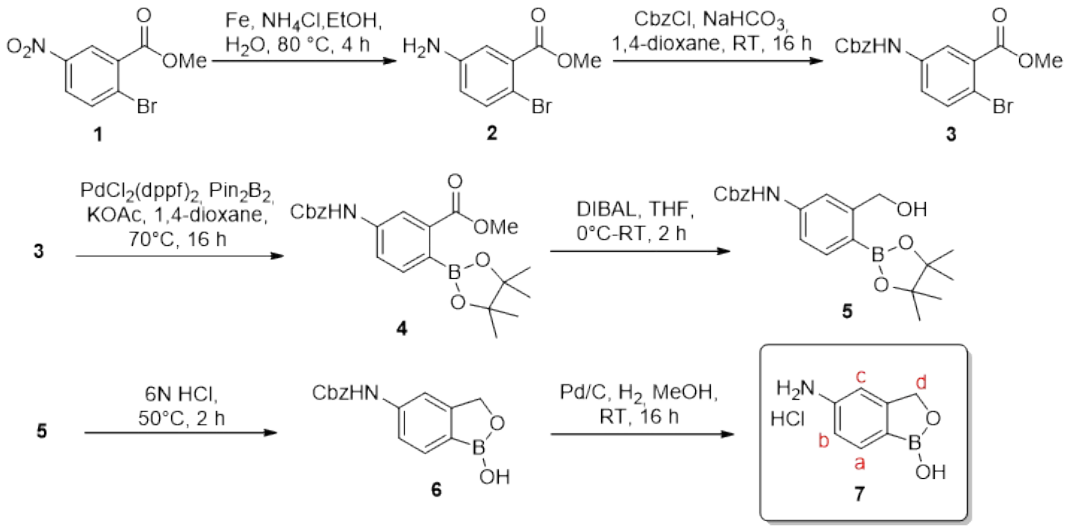
LC-MS (ES, *m/z*): 312.14 $[M + H]^+$.

Synthesis of **7** (**DM7ABOR**): Pd/C (1.20 g) was added to a solution of compound **6** (12.0 g, 38.58 mmol, 1.0 eq) in MeOH (120 mL) under nitrogen atmosphere, and the reaction mixture was hydrogenated under 50 psi at rt for 4 h. The progress of the reaction was monitored by TLC (50 % EtOAc in n-hexane). After completion of the reaction, the medium was filtered through celite pad and washed with MeOH (200 mL). The combined filtrate was evaporated under reduced pressure to afford the final compound as a free amine. The amine was converted to its corresponding HCl by taking the crude compound in DCM (120 mL) with addition of 4M HCl in 1,4-dioxane (120 mL) under stirring for 1 h. The reaction mixture was fully evaporated under reduced pressure to get the crude compound, which was washed with 30 % ethyl acetate in petroleum ether (150 mL) and filtered the solid to give **7** as HCl salt (3.4 g, 41.4 %) as an off white solid.

^{1}H NMR (400 MHz, DMSO-*d6*, 298 K): δ (ppm) 7.43 (t, *J* = 7.6 Hz, 1H, **Hc**), 7.18 (d, *J* = 6.8 Hz, 1H, **Hb**), 7.05 (d, *J* = 7.6 Hz, 1H, **Ha**), 1.44 (6H, s, **Hd-Hd'**).

LC-MS (ES, *m/z*): 178.26 $[M + H]^+$.

5-aminobenzo[c][1,2]oxaborol-1(3H)-ol (5ABOR) hydrochloride



Synthesis of **2**: To a stirred solution of compound **1** (40 g, 55.03 mmol, 1.0 eq) in EtOH/water (500 mL, 1:1) were added Fe (43.29 g, 775.1 mmol, 5.0 eq) and NH_4Cl (66.34 g, 1240 mmol, 8.0 eq) at rt. The reaction mixture was heated to 80 °C and stirred for 16 h. The progress of the reaction was monitored by TLC (20 % EtOAc in n-hexane). After completion of the reaction, the medium was cooled to rt, filtered the through celite bed and the filtrate was evaporated under reduced pressure to give a residue. The resulting residue was portioned between water (1.0 L) and ethyl acetate (1.0 L). The organic layer was washed with saturated brine solution (500 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to get crude compound **2** (33.0 g, 93.4 %) as a brown liquid.

^{1}H NMR (400 MHz, DMSO-*d6*, 298 K): δ (ppm) 7.28 (d, *J* = 8.8 Hz, 1H), 6.94 (d, *J* = 2.4 Hz, 1H), 6.63 (dd, *J* = 8.8, 3.2 Hz, 1H), 5.52 (s, 2H, NH2), 3.80 (s, 3H).

LC-MS (ES, *m/z*): 231.97 $[M + H]^+$.

Synthesis of **3**: To a solution of compound **2** (33 g, 144.12 mmol, 1.0 eq) in THF/water (400 mL, 1:1) were added $NaHCO_3$ (36.31 g, 432.37 mmol, 3.0 eq) and CbzCl (29.50 g, 172.94 mmol, 1.5 eq) successively at 0 °C. The reaction mixture was slowly warmed to rt and stirred for 16 h. The progress of the reaction was monitored by TLC (20 % EtOAc in *n*-hexane). After completion of the reaction, the medium was diluted with ethyl acetate (1000 mL) and washed with water (1000 mL) followed by saturated brine solution (500 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to obtain a crude compound. The crude product was purified by flash column chromatography using 100-200 mesh silica gel eluted with 10 % ethyl acetate in petroleum ether to give **3** (35.0 g, 67 %) as an off white solid.

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ (ppm) 10.09 (s, 1H, NH), 7.95 (d, *J* = 2.4 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.52 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.44-7.34 (m, 5H), 5.16 (s, 2H), 3.85 (s, 3H).

LC-MS (ES, *m/z*): 362.07 $[M + H]^+$.

Synthesis of **4**: Compound **3** (30.0 g, 82.41 mmol, 1.0 eq), Pin_2B_2 (31.1 g, 253.94 mmol, 1.5 eq) and AcOK (24.0 g, 247.25 mmol, 3.0 eq) were taken in 1,4-dioxane (300 mL). The reaction mixture was degassed with argon for 10 minutes. Then, $PdCl_2(dppf)_2$ (6.69 g, 8.241 mmol, 0.1 eq) was added and the medium was degassed by additional 5 minutes, heated to 70 °C and stirred for 16 h. The progress of the reaction was monitored by TLC (30 % EtOAc in *n*-hexane). After completion of the reaction, the reaction mixture was filtered through celite pad, washed with ethyl acetate (200 mL) and the filtrate was evaporated under vacuum to get a crude compound. This was purified by flash column chromatography using 100-200 mesh silica gel eluted with 20 % ethyl acetate in petroleum ether to afford **4** (30.0 g, 79.43 %) as an off white solid.

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ (ppm) 10.03 (s, 1H, NH), 8.02 (d, J = 2.0 Hz, 1H), 7.64 (dd, J = 8.4, 2.0 Hz, 1H), 7.44-7.32 (m, 6H), 5.16 (s, 2H), 3.82 (s, 3H), 1.29 (s, 12H).

LC-MS (ES, *m/z*): 412.13 $[M + H]^+$.

Synthesis of **5** and **6**:
To a solution of **4** (30.0 g, 72.9 mmol, 1.0 eq) in DCM (180 mL) was added 20 % DIBAL in toluene (150 mL) dropwise through addition funnel at 0 °C. After completion of the addition, the medium was slowly warmed to rt and stirred for 2 h. The progress of the reaction was monitored by TLC (40 % EtOAc in *n*-hexane) until formation of **5**. After completion of the reaction, 6 N HCl (200 mL) was added dropwise at 0 °C and the reaction mixture was heated to 50 °C under stirring for 2 h. The reaction medium was then diluted with ethyl acetate (600 mL), washed with water (500 mL) followed by saturated brine solution (200 mL), dried over anhydrous sodium sulfate and evaporated under vacuum to obtain a crude compound. The crude product was purified by flash column chromatography using 100-200 mesh silica gel, eluted with 30 % ethyl acetate in petroleum ether to give compound **6** (13.0 g, 62.95 %) as a light brown solid.

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ (ppm) 9.92 (s, 1H, NH), 8.98 (s, 1H, OH), 7.61-7.57 (m, 2H), 7.44-7.20 (m, 6H), 5.14 (s, 2H), 4.92 (s, 2H).

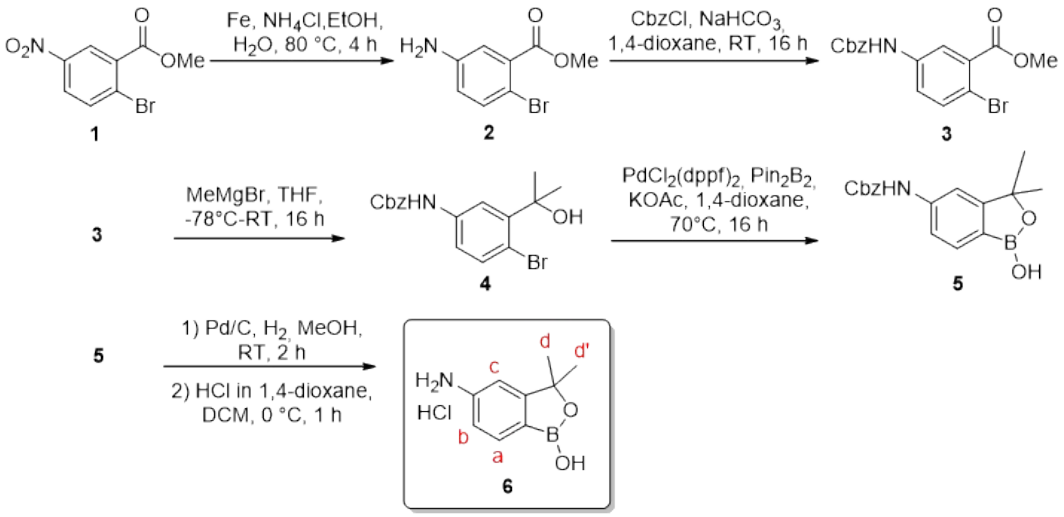
LC-MS (ES, *m/z*): 284.05 $[M + H]^+$.

Synthesis of **7** (**5ABOR**): Pd/C (13.0 g) was added to a solution of **6** (13.0 g, 45.9 mmol, 1.0 eq) in MeOH (260 mL) under N_2 atmosphere and the reaction mixture was hydrogenated under 50 psi at rt for 16 h. The progress of the reaction was monitored by TLC (50 % EtOAc in hexane). After completion of the reaction, the medium was filtered through celite pad and washed with MeOH (400 mL). The combined filtrate was evaporated under reduced pressure to afford the final compound as free amine. It was converted to the corresponding HCl salt in diethyl ether (100 mL) with addition of 4 M HCl in 1,4-dioxane (100 mL) under stirring for 1 h. The reaction mixture was fully evaporated under reduced pressure to get crude compound. The crude product was washed with 50 % ethyl acetate in diethyl ether (100 mL) and the solid was filtered to give the final compound as HCl salt (4.4 g, 51.82 %) as an off white solid.

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ (ppm) 7.71 (d, J = 7.6 Hz, 1H, **Ha**), 7.17 (s, 1H, **Hc**), 7.12 (d, J = 8.0 Hz, 1H, **Hb**), 4.97 (2H, s, **Hd**).

LC-MS (ES, *m/z*): 150.2 $[M + H]^+$.

5-amino-3,3-dimethylbenzo[c][1,2]oxaborol-1(3H)-ol (DM5ABOR) hydrochloride



Synthesis of **2**: To a stirred solution of **1** (40 g, 55.03 mmol, 1.0 eq) in EtOH/water (500 mL, 1:1), were added Fe (43.29 g, 775.1 mmol, 5.0 eq) and NH_4Cl (66.34 g, 1240 mmol, 8.0 eq) at RT. The reaction mixture was heated to 80 °C and stirred for 16 h. The progress of the reaction was monitored by TLC (20 % EtOAc in *n*-hexane). After completion of the reaction, the medium was cooled to RT, filtered through celite bed and the filtrate was evaporated under reduced pressure to give a residue, which was was portioned between water (1.0 L) and ethyl acetate (1.0 L). The organic layer was washed with saturated brine solution (500 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain crude compound **2** (33.0 g, 93.4 %) as a brown liquid.

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ (ppm) 7.28 (d, J = 8.8 Hz, 1H), 6.94 (d, J = 2.4 Hz, 1H), 6.63 (dd, J = 8.8, 3.2 Hz, 1H), 5.52 (s, 2H, NH_2), 3.80 (s, 3H).

LC-MS (ES, *m/z*): 231.97 $[M + H]^+$.

Synthesis of **3**: To a solution of compound **2** (33 g, 144.12 mmol, 1.0 eq) in THF/water (400 mL, 1:1), were added $NaHCO_3$ (36.31 g, 432.37 mmol, 3.0 eq) and CbzCl (29.50 g, 172.94 mmol, 1.5 eq) successively at 0 °C. The reaction mixture was slowly warmed to RT and stirred for 16 h. The progress of reaction was monitored by TLC (20 % EtOAc in *n*-hexane). After completion of the reaction, the medium was diluted with ethyl acetate (1000 mL) washed with water (1000 mL) followed by saturated brine solution (500 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to get crude compound. Crude product was purified by flash column chromatography using 100-200 mesh silica gel, eluted with 10 % ethyl acetate in petroleum ether to afford **3** (35.0 g, 67 %) as an off white solid.

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ (ppm) 10.09 (s, 1H, NH), 7.95 (d, J = 2.4 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.52 (dd, J = 8.8, 2.4 Hz, 1H), 7.44-7.34 (m, 5H), 5.16 (s, 2H), 3.85 (s, 3H).

LC-MS (ES, *m/z*): 262.07 $[M + H]^+$.

Synthesis of **4**: To a stirred solution of **3** (35.0 g, 96.41 mmol, 1.0 eq) in THF (350 mL) was added 2.5 M MeMgBr (385.6 mL, 964.1 mmol, 10 eq) in diethyl ether dropwise over a period

of 30 min at -78 °C (temperature maintained for 1 h). After 1 h, the reaction mixture was slowly warmed to RT and stirred for 16 h. The progress of the reaction was monitored by TLC (40 % EtOAc in *n*-hexane). After completion of the reaction, the medium was quenched with saturated NH_4Cl solution (1000 mL) at 0 °C and extracted with EtOAc (2 x 750 mL). The combined organic layer was washed with saturated brine solution (500 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to get crude compound. The crude product was purified by flash column chromatography using 100-200 mesh silica gel, eluted with 25 % ethyl acetate in petroleum ether to give compound **4** (25.0 g, 71.4 %) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ (ppm) 9.82 (s, 1H, NH), 7.97 (d, J = 2.8 Hz, 1H), 7.46-7.30 (m, 7H), 5.19 (s, 1H, OH), 5.15 (s, 2H), 1.58 (s, 6H).

LC-MS (ES, *m/z*): 362.01 $[M + H]^+$.

Synthesis of **5**: Compound **4** (25.0 g, 68.87 mmol, 1.0 eq), Pin_2B_2 (26.23 g, 103.3 mmol, 1.5 eq) and AcOK (20.27 g, 206.6 mmol, 3.0 eq) were taken in 1,4-dioxane (250 mL). The reaction medium was degassed with argon for 10 minutes. Then, $PdCl_2(dppf)_2$ (5.0 g, 6.88 mmol, 0.1 eq) was added, the reaction mixture was degassed by additional 5 minutes, heated to 70 °C and stirred for 16 h. The progress of the reaction was monitored by TLC (40 % EtOAc in *n*-hexane). After completion of the reaction, the medium was filtered through celite pad and the filtrate was evaporated under vacuum to afford a crude compound. The crude product was purified by flash column chromatography using 100-200 mesh silica gel, eluted with 20 % ethyl acetate in petroleum ether to give **5** (17.0 g, 79.43 %) as a brown solid.

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ (ppm) 9.95-9.90 (m, 1H, NH), 8.83 (s, 1H, OH), 7.59-7.49 (m, 2H), 7.44-7.29 (m, 6H), 5.16 (s, 2H), 1.40 (s, 6H).

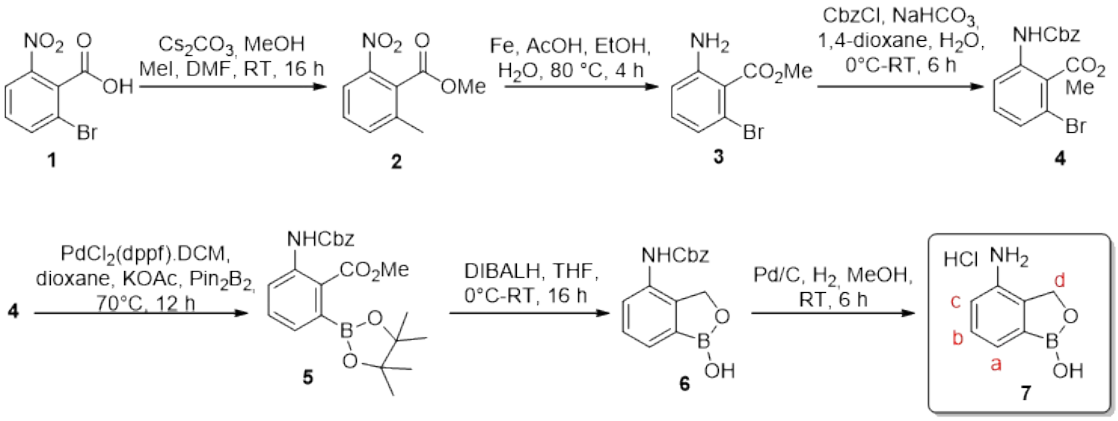
LC-MS (ES, *m/z*): 310.19 $[M + H]^+$.

Synthesis of **6** (**DM5ABOR**): Pd/C (1.70 g) was added to a solution of **5** (17.0 g, 54.63 mmol, 1.0 eq) in MeOH (200 mL) under N_2 and the reaction was hydrogenated under 50 psi for 16 h. The progress of the reaction was monitored by TLC (50 % EtOAc in *n*-hexane). After completion of the reaction, the medium was filtered through celite pad and washed with MeOH (300 mL). The combined filtrate was evaporated under reduced pressure to afford final compound as free amine. Compound was converted to its corresponding HCl salt in DCM (170 mL) with addition of 4 M HCl in 1,4-dioxane (170 mL) under stirring for 1 h. The reaction mixture was fully evaporated under reduced pressure to obtain a crude compound, which was washed with 30 % ethyl acetate in petroleum ether to give **6** as HCl salt (6.2 g, 53.12 %) as an off white solid.

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ (ppm) 7.60 (d, J = 8.0 Hz, 1H, **Ha**), 7.03 (s, 2H, **Hc-Hb**), 1.42 (6H, s, **Hd-Hd'**).

LC-MS (ES, *m/z*): 178.26 $[M + H]^+$.

4-aminobenzo[c][1,2]oxaborol-1(3H)-ol (4ABOR) hydrochloride



Synthesis of **2**: To a stirred solution of **1** (110 g, 447.15 mmol, 1.0 eq) in MeOH (1000 mL), Cs_2CO_3 (72.8 g, 223.5 mmol, 0.5 eq) was added at RT under stirring for 30 min. The reaction mixture was fully evaporated under reduced pressure to get a residue. To the resulting residue taken in DMF (1000 mL), was added MeI (33.4 mL, 141.94 mmol, 1.2 eq) dropwise through addition funnel at 0 °C, the reaction mixture was slowly warmed to RT and stirred for 16 h. The progress of the reaction was monitored by TLC (25 % EtOAc in *n*-hexane). After completion of the reaction, the medium was diluted with ice cooled water (1.5 L), the solid was filtered and dried to afford **2** (110 g, 94 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ (ppm) 8.17 (d, J = 7.6 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 4.02 (s, 3H).

LC-MS (ES, *m/z*): 259.92 $[M + H]^+$.

Synthesis of **3**: To a solution of compound **2** (110 g, 424.7 mmol, 1.0 eq) in EtOH (2.0 L), were added AcOH (550 mL) followed by Fe (118.1 g, 2123.5 mmol, 5.0 eq) at RT. The reaction mixture was heated to 80 °C and stirred for 4 h. The progress of the reaction was monitored by TLC (25 % EtOAc in *n*-hexane). After completion of the reaction, the medium was fully evaporated under reduced pressure to give a residue. The resulting residue was diluted with water (1.5 L), basified with $NaHCO_3$ and extracted with ethyl acetate (1 L x 2). The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain the crude compound **3** (80.0 g, 82.2 %) as a brown liquid.

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ (ppm) 7.01 (d, J = 8.0 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 5.64 (s, 2H, NH_2), 3.82 (s, 3H).

LC-MS (ES, *m/z*): 229.9 $[M + H]^+$.

Synthesis of **4**: $NaHCO_3$ (29.2 g, 349.39 mmol, 2.0 eq) and CbzCl (37.5 mL, 262.04 mmol, 1.5 eq) were sequentially added to a stirred solution of **3** (40 g, 174.69 mmol, 1.0 eq) in THF/water (800 mL, 1:1) at 0 °C. The reaction mixture was slowly warmed to RT and stirred for 6 h. The progress of the reaction was monitored by TLC (20 % EtOAc in *n*-hexane). After completion of the reaction, the medium was diluted with ethyl acetate (1000 mL) and washed with water (1000 mL) followed by saturated brine solution (500 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to get crude compound. Crude product

was purified by flash column chromatography using 100-200 mesh silica gel, eluted with 10 % ethyl acetate in petroleum ether to afford **4** (50.0 g, 78.8 %) as a yellow liquid.
^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ (ppm) 9.57 (s, 1H, NH), 7.48 (d, J = 8.4 Hz, 2H), 7.40-7.20 (m, 6H), 5.16 (s, 2H), 3.76 (s, 3H).

LC-MS (ES, *m/z*): 362.05 $[M + H]^+$.

Synthesis of **5**: Compound **4** (50.0 g, 137.36 mmol, 1.0 eq), Pin_2B_2 (41.8 g, 164.83 mmol, 1.5 eq) and AcOK (40.3 g, 412.08 mmol, 3.0 eq) were taken in 1,4-dioxane (500 mL). The reaction medium was degassed with argon for 10 min. $PdCl_2(dppf)_2$.DCM (5.60 g, 6.86 mmol, 0.05 eq) was added to the reaction mixture, degassed by additional 5 minutes, heated to 70 °C and stirred for 12 h. The progress of the reaction was monitored by TLC (30 % EtOAc in *n*-hexane). After completion of the reaction, the medium was filtered through celite pad, washed with ethyl acetate (500 mL) and the filtrate was evaporated under vacuum to give a crude compound. The crude product was purified by flash column chromatography using 100-200 mesh silica gel, eluted with 20 % ethyl acetate in petroleum ether to afford **5** (40.0 g, 70.67 %) as an off white solid.

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ (ppm) 9.59 (s, 1H, NH), 7.81 (d, J = 8.0 Hz, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.42-7.34 (m, 5H), 7.25-7.23 (m, 1H), 5.14 (s, 2H), 3.75 (s, 3H), 1.28 (s, 12H).

LC-MS (ES, *m/z*): 412.18 $[M + H]^+$.

Synthesis of **6**: To a solution of **5** (40.0 g, 97.32 mmol, 1.0 eq) in DCM (500 mL), was added 20 % DIBALH in toluene (200 mL) dropwise through addition funnel at 0 °C. The reaction mixture was then slowly warmed to RT and stirred for 2 h. The progress of the reaction was monitored by TLC (40 % EtOAc in *n*-hexane). After completion of the reaction, 6 N HCl (200 mL) was added dropwise at 0 °C, and the medium was heated to 50 °C under stirring for 2 h (reaction also monitored by TLC). After completion of the reaction, the medium was diluted with DCM (500 mL), washed with water (500 mL) followed by saturated brine solution (200 mL), dried over anhydrous sodium sulfate and evaporated under vacuum to obtain a crude compound. The crude product was purified by flash column chromatography using 100-200 mesh silica gel, eluted with 40-50 % ethyl acetate in petroleum ether to give **6** (16.0 g, 58.18 %) as an off white solid.

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ (ppm) 9.32 (s, 1H, NH), 9.14 (s, 1H, OH), 7.62 (d, J = 8.0 Hz, 1H), 7.48-7.30 (m, 7H), 5.15 (s, 2H), 4.97 (s, 2H).

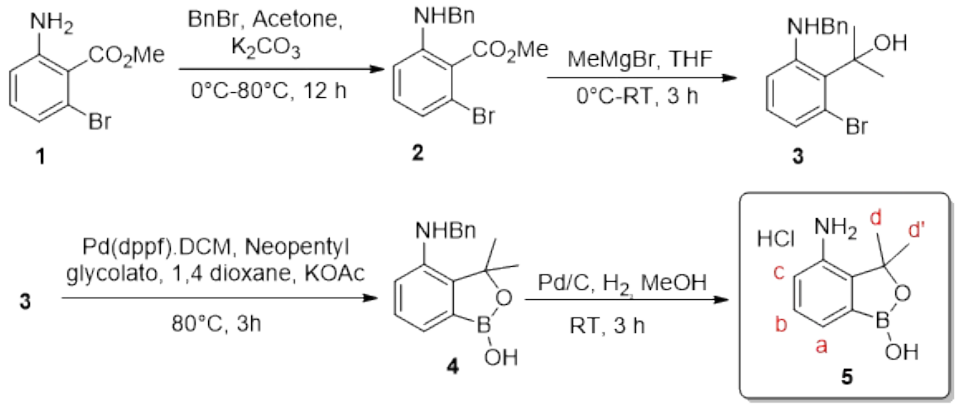
LC-MS (ES, *m/z*): 284.08 $[M + H]^+$.

Synthesis of **7** (**4ABOR**): Pd/C (13.0 g) was added to a solution of **6** (16.0 g, 56.5 mmol, 1.0 eq) in MeOH (300 mL) under nitrogen atmosphere. The reaction mixture was hydrogenated under 50 psi at RT for 6 h. The progress of the reaction was monitored by TLC (50 % EtOAc in *n*-hexane). After completion of the reaction, the medium was filtered through celite pad and washed with MeOH (400 mL). The combined filtrate was evaporated under reduced pressure to afford the final compound as free amine. It was converted to its corresponding HCl salt in diethyl ether (100 mL) with addition of 4 M HCl in 1,4-dioxane (100 mL) under stirring for 1 h. The reaction mixture was fully evaporated under reduced pressure to get crude compound. The crude product was washed with 30 % acetone in ethyl acetate (100 mL) and the solid was filtered to give the final compound **7** as HCl salt (6.1 g, 71.25 %) as an white solid.

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ (ppm) 7.61 (d, J = 7.2 Hz, 1H, **Ha**), 7.41-7.34 (m, 2H, **Hb-Hc**), 5.07 (2H, s, **Hd**).

LC-MS (ES, *m/z*): 150.1 $[M + H]^+$.

4-amino-3,3-dimethylbenzo[c][1,2]oxaborol-1(3H)-ol (DM4ABOR) hydrochloride



Synthesis of **2**: K_2CO_3 (57.4 g, 416 mmol) was added to a solution of **1** (48 g, 208 mmol) in acetone (500 mL) and the reaction medium was stirred at RT for 15 min. BnBr (53.35 g, 213 mmol) was then added and the medium was stirred at RT for 12 h. The reaction progress was monitored by TLC (25 % EtOAc in *n*-hexane). After completion of the reaction, the reaction mixture was quenched with water (250 mL) and extracted with ethyl acetate (1 L). Combined organic layers were washed with saturated $NaHCO_3$ solution (250 mL) and brine solution (250 mL), dried over sodium sulfate and concentrated under reduced pressure to afford the crude compound **2** as a brown gummy. The crude product was purified by silica gel column chromatography (60-120 mesh) initially eluted with 5-7 % ethyl acetate in petroleum ether. The collected fractions were combined and concentrated under reduced pressure to obtain **2** (40 g, 59 %) as a pale yellow liquid.

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ (ppm) 7.32-7.29 (m, 2H), 7.28-7.20 (m, 3H), 7.07-6.98 (m, 1H), 6.91-6.89 (dd, J = 7.6 Hz, 0.8 Hz, 1H), 6.56-6.53 (dd, J = 7.6 Hz, 0.8 Hz, 1H), 6.15 (s, 1H), 4.36 (s, 2H), 3.92 (s, 3H).

LC-MS (ES, *m/z*): 320.06 $[M + H]^+$.

Synthesis of **3**: To a solution of **2** (40 g, 125 mmol) in THF (500 mL) was added MeMgBr (400 mL) dropwise over the period of 30 min at 0 ºC. The medium was stirred at 0 ºC for 15 min and then at RT for 16 h. The reaction progress was monitored by TLC (25 % EtOAc in *n*-hexane). After completion of the reaction, the reaction mixture was quenched with saturated ammonium chloride solution (600 mL) and extracted with ethyl acetate (3 x 500 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to afford crude compound **3**, which was washed with pentane and dried to give **3** (35 g, 87 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): 7.34-7.26 (m, 5H), 6.96-6.93 (dd, J = 8.0 Hz, 1.2 Hz, 1H), 6.84-6.80 (t, J = 8.4 Hz, 1H), 6.56-6.54 (d, J = 8.4 Hz, 1H), 4.30 (s, 2H), 1.92 (s, 6H).

LC-MS (ES, *m/z*): 320.09 $[M + H]^+$.
Synthesis of **4**: To a solution of **3** (35 g, 109 mmol), neopentyl glycolato diborane (37.03 g, 163 mmol) and KOAc (32.1 g, 327 mmol), $Pd(dppf)Cl_2$.DCM (4.45 g, 5.45 mmol) in 1,4 dioxane (350 mL) was added and heated to 70 °C for 6 h under N_2. The reaction progress was monitored by TLC (25 % EtOAc in *n*-hexane). After completion of the reaction, the medium was filtered through celite bed and washed with ethyl acetate (2 x 200 mL) and the filtrate was evaporated under vacuum to get crude compound **4** as a brown gummy. The crude product was purified by silica gel column chromatography (100-200 mesh) initially eluted with 5-7 % ethyl acetate in petroleum ether and the collected fractions were combined and concentrated under reduced pressure to give **4** (20 g, 68 %) as a pale yellow liquid.

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): 7.37-7.26 (m, 5H), 7.22-7.16 (m, 1H), 7.10-7.05 (m, 1H), 6.74-6.67 (m, 1H), 4.39 (s, 2H), 1.63 (s, 6H).

LC-MS (ES, *m/z*): 268.22 $[M + H]^+$.

Synthesis of **5** (**DM4ABOR**): To a stirred solution of **4** (20 g, 74.9 mmol) in methanol (200 mL), was added Pd/C (10 g) in one charge wet with ethyl acetate. The reaction was hydrogenated at 30 psi (balloon pressure). The reaction progress was monitored by TLC (40 % EtOAc in *n*-hexane). After completion of the reaction, the reaction medium was filtered through celite bed, washed with methanol (2 x 100 mL) and the filtrate was evaporated under vacuum to get crude compound **5** as a brown gummy. The crude product was washed with diethyl ether (2 x 200 mL) followed by addition of 4 M HCl in dioxane under stirring for 1 h. The reaction medium was then evaporated under vacuum to afford **5** (12.218 g, 77 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): 8.07 (br, 1H), 7.53-7.22 (m, 3H, **Ha-Hb-Hc**), 5.32 (br, 3H), 1.54 (s, 6H, **Hd-Hd'**).

LC-MS (ES, *m/z*): 178.26 $[M + H]^+$.

2. ^{1}H NMR characterization of HA-BOR derivatives synthesized (M_w = 100 kg mol^{-1})

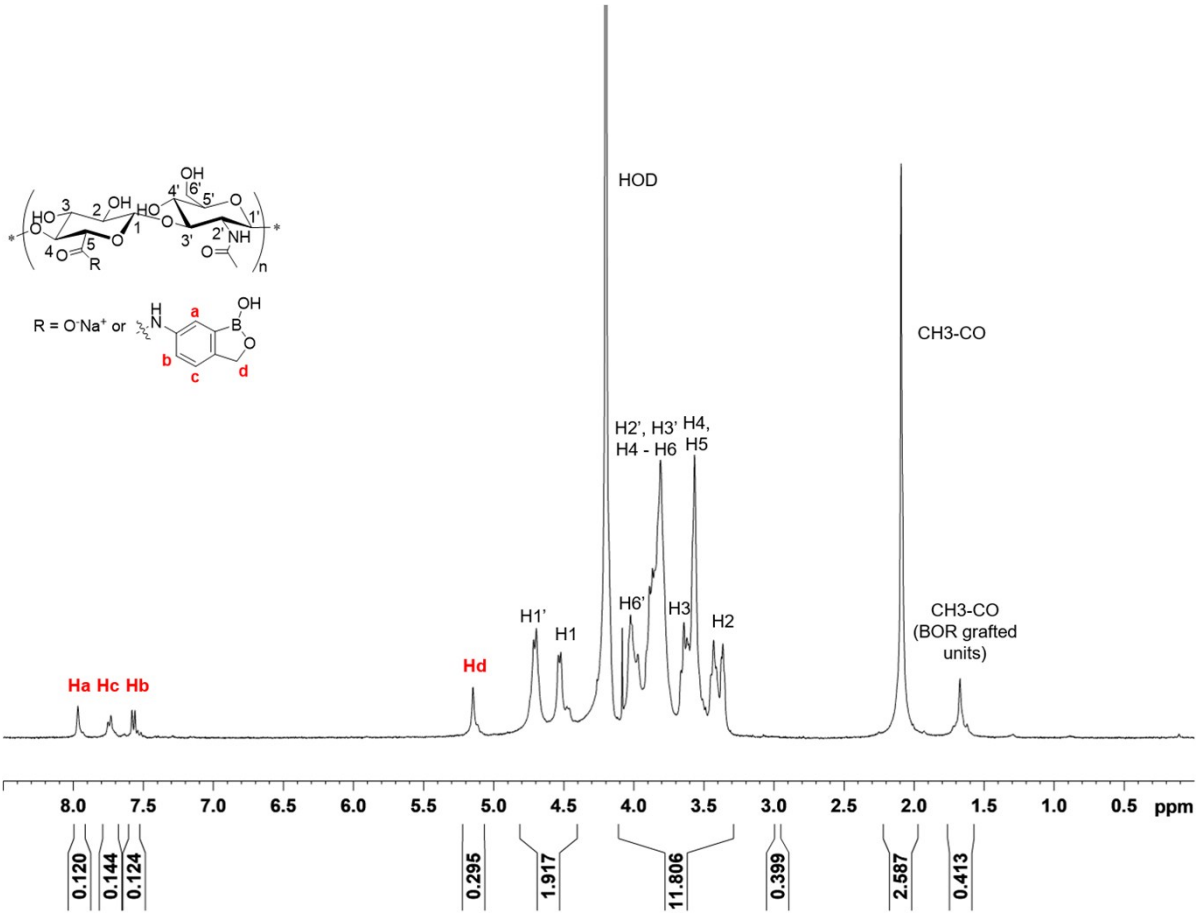


Figure S1. ^{1}H NMR spectrum (400 MHz, D_2O, 6 mg.mL^{-1}, 80 °C) of HA100-6ABOR.

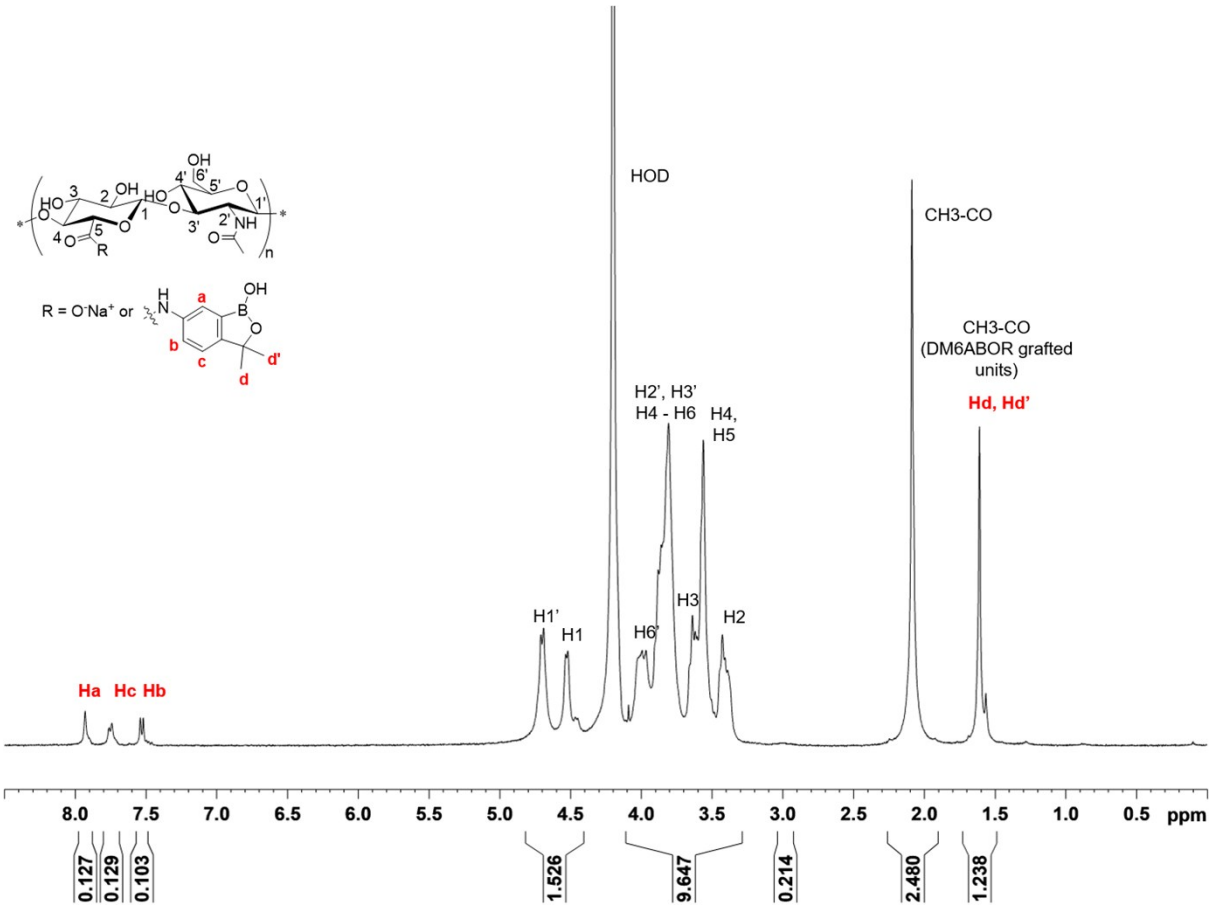


Figure S2. ^{1}H NMR spectrum (400 MHz, D_2O, 6 mg.mL^{-1}, 80 °C) of HA100-DM6ABOR.

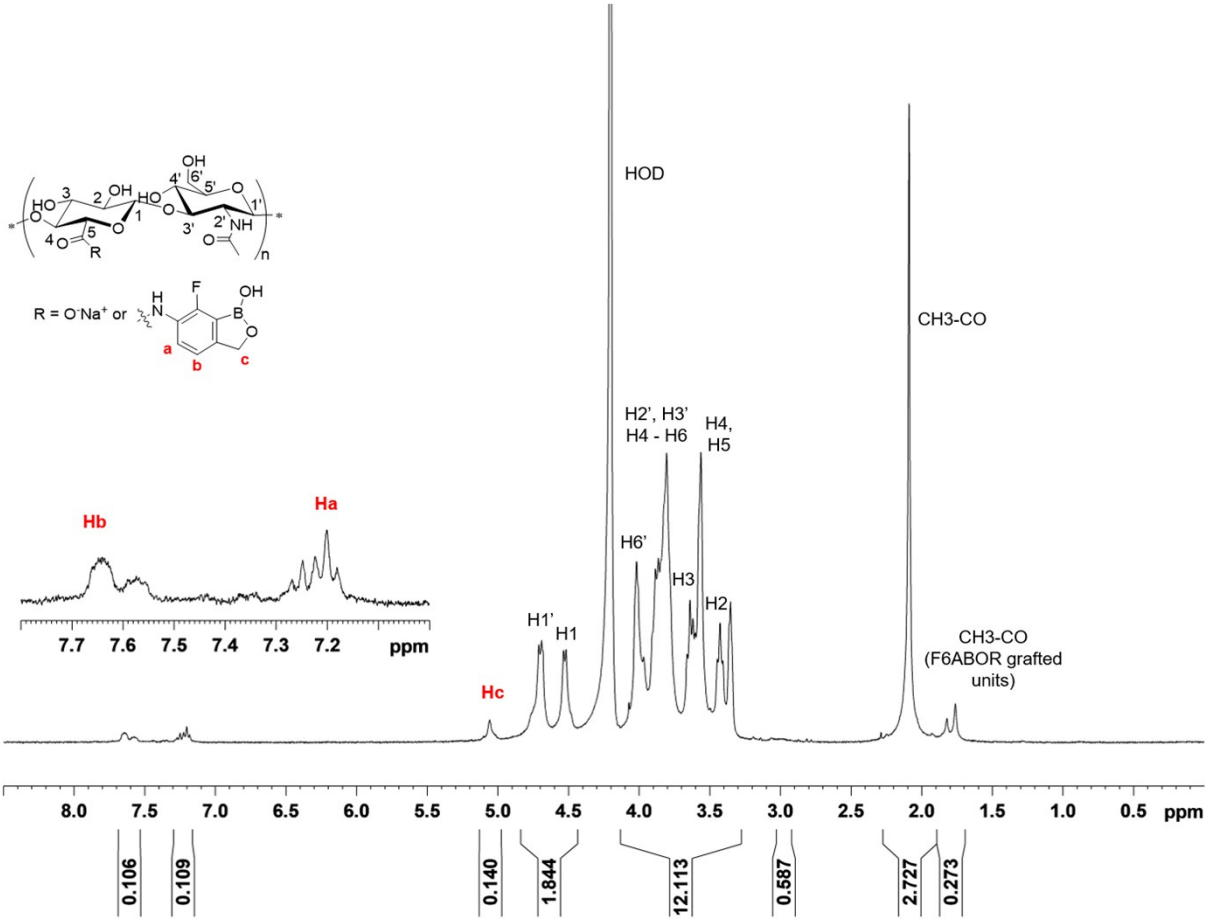


Figure S3. ^{1}H NMR spectrum (400 MHz, D_2O, 6 mg.mL^{-1}, 80 °C) of HA100-F6ABOR.

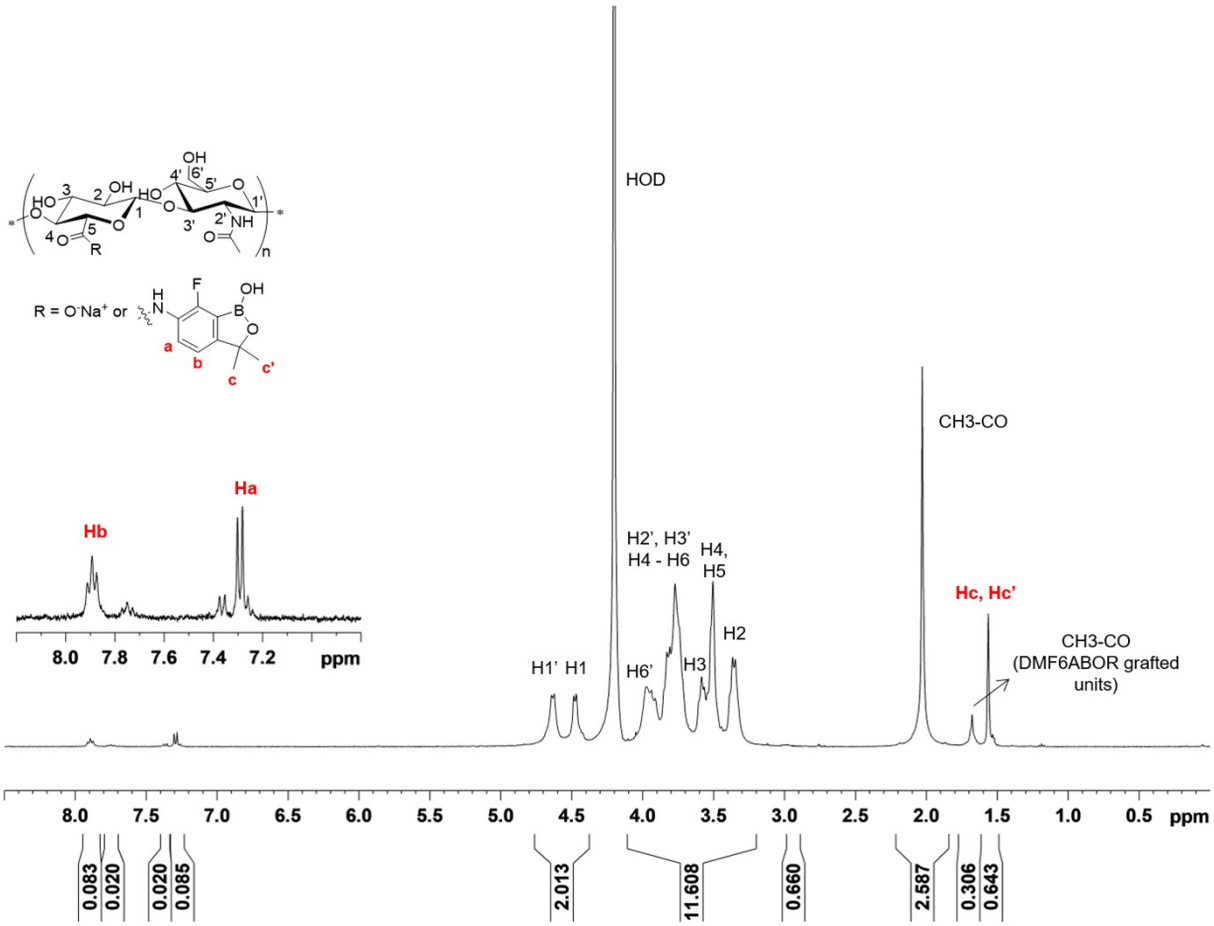


Figure S4. ^{1}H NMR spectrum (400 MHz, D_2O, 6 mg.mL^{-1}, 80 °C) of HA100-DMF6ABOR.

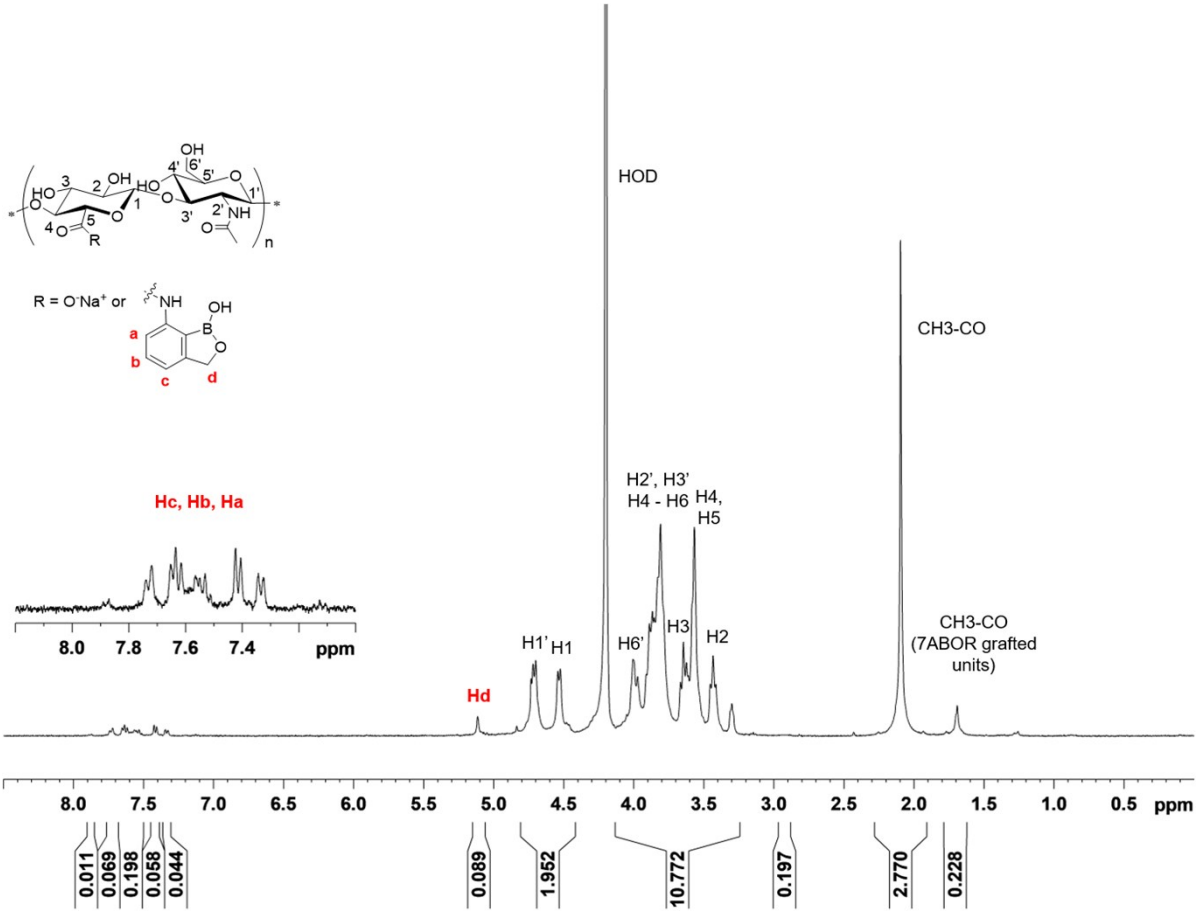


Figure S5. ^{1}H NMR spectrum (400 MHz, D_2O, 6 mg.mL^{-1}, 80 °C) of HA100-7ABOR.

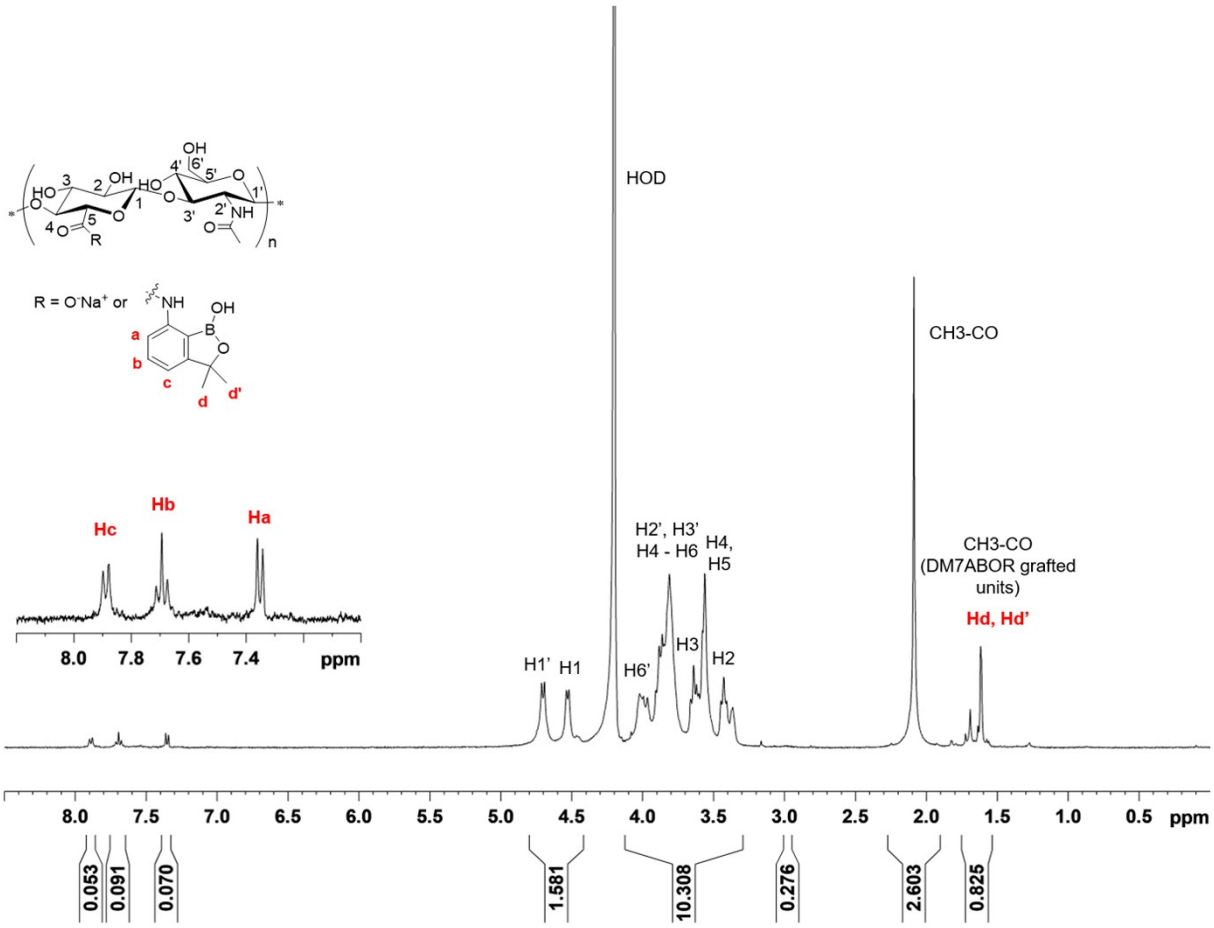


Figure S6. ^{1}H NMR spectrum (400 MHz, D_2O, 6 mg.mL^{-1}, 80 °C) of HA100-DM7ABOR.

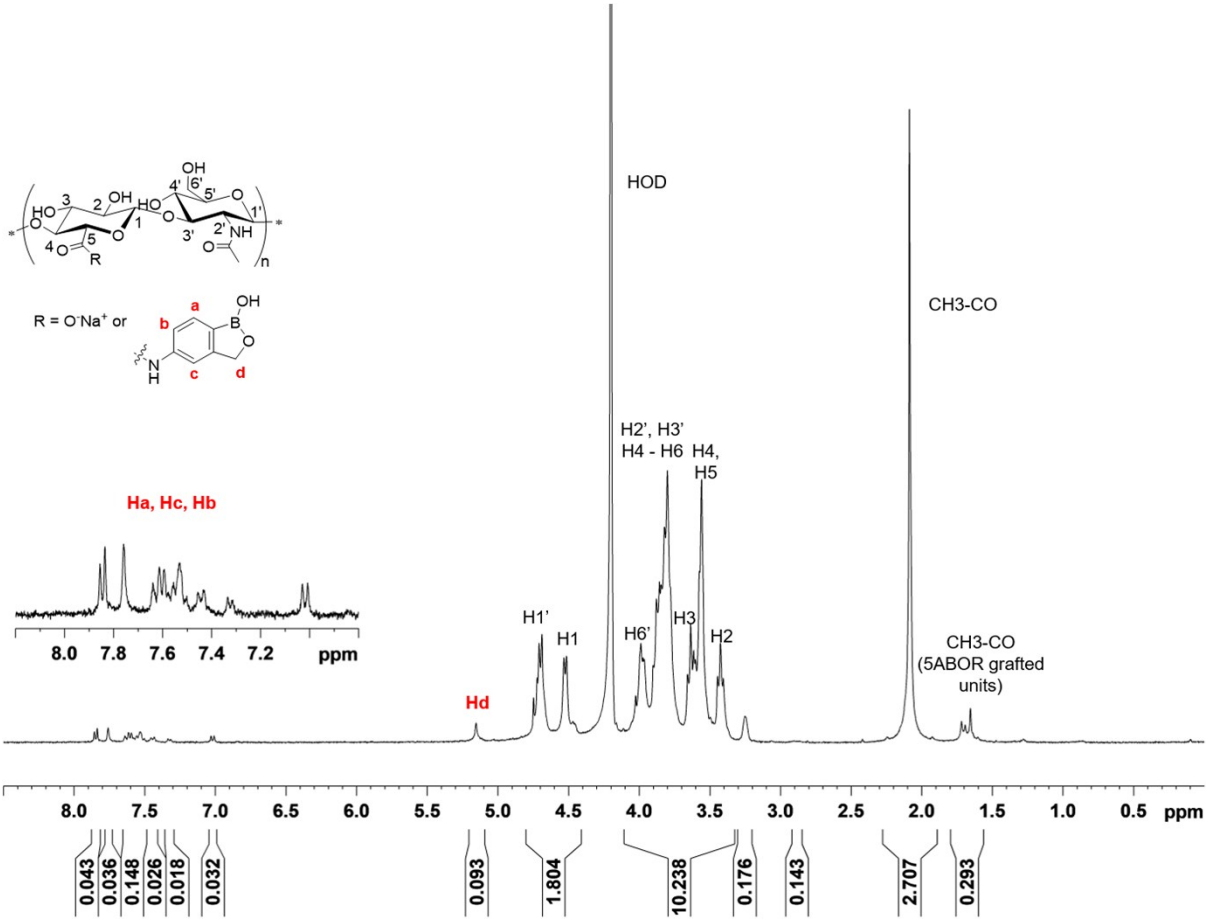


Figure S7. ^{1}H NMR spectrum (400 MHz, D_2O, 6 mg.mL^{-1}, 80 °C) of HA100-5ABOR.

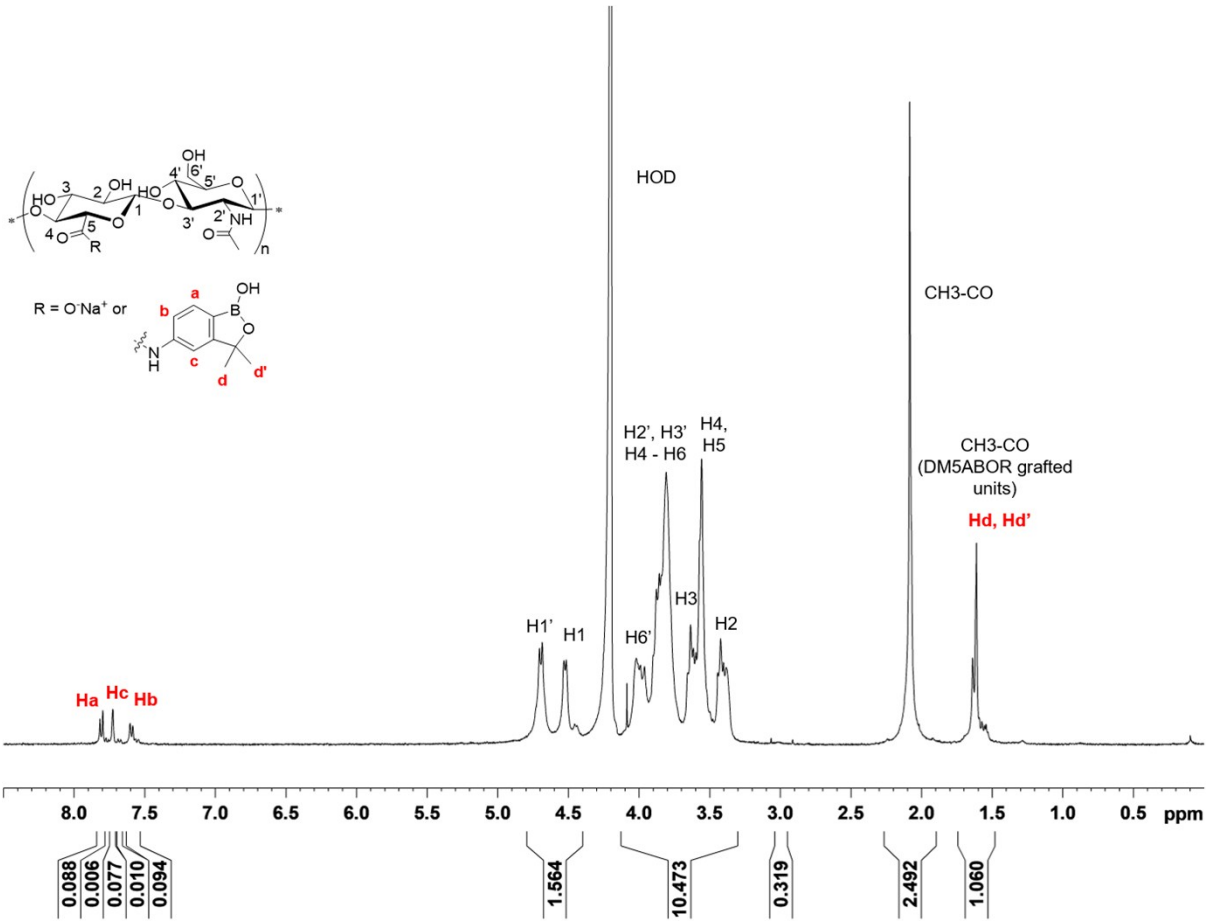


Figure S8. ^{1}H NMR spectrum (400 MHz, D_2O, 6 mg.mL^{-1}, 80 °C) of HA100-DM5ABOR.

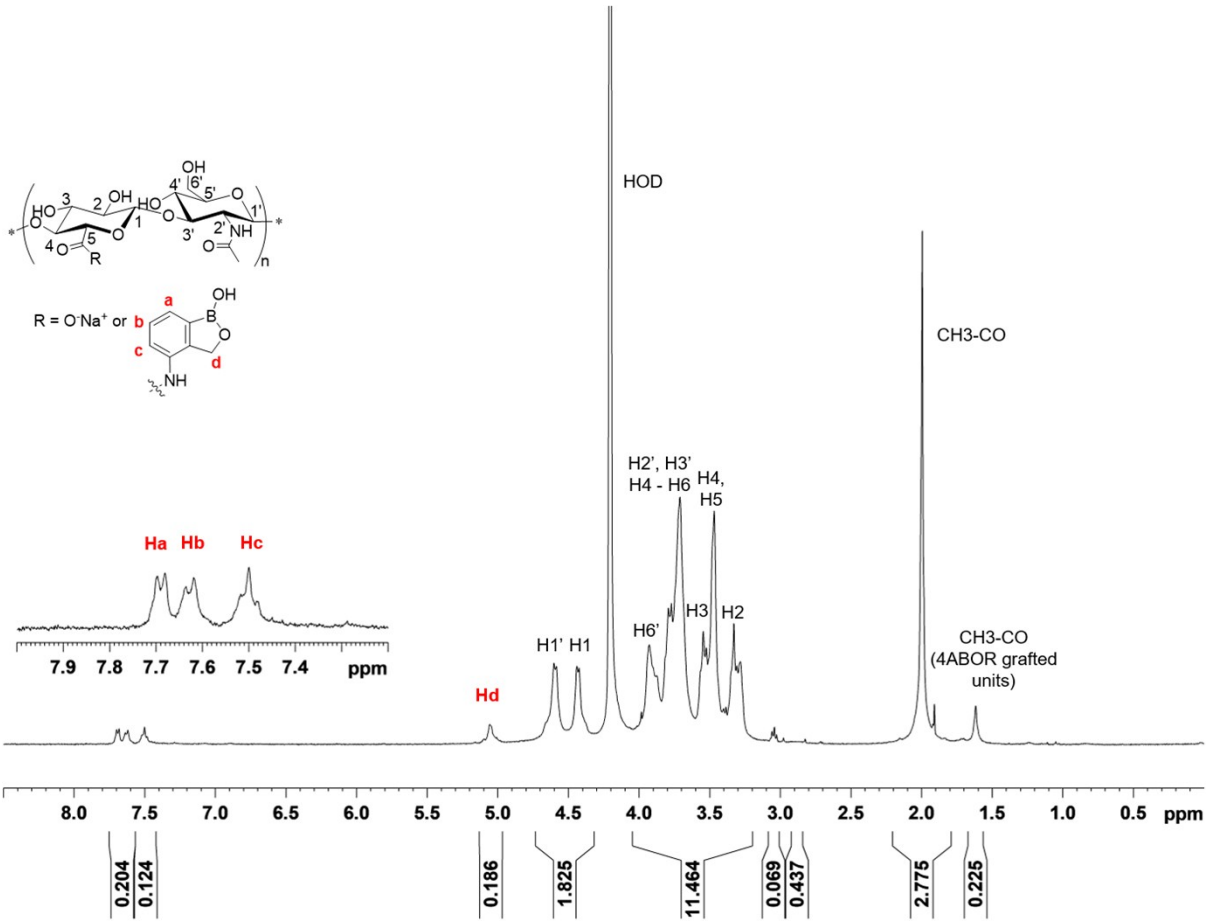
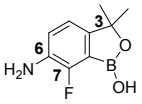
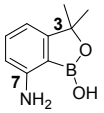


Figure S9. ^{1}H NMR spectrum (400 MHz, D_2O, 6 mg.mL^{-1}, 80 °C) of HA100-4ABOR.

3. Summary of HA-BOR derivatives synthesized (M_w = 360 kg mol^{-1})

Table S1. Summary of the syntheses of HA360-BOR conjugates.

Entry	Derivative	Structure	Time of reaction (h)	DS[a)]	Coupling NMR (%)
1	DMF**6**ABOR		46	0.1	67
2	DM**7**ABOR		44	0.1	67

[a)]Determined by ^{1}H NMR spectroscopy at 80 °C in D_2O.

4. ^{1}H NMR characterization of HA-BOR derivatives synthesized (M_w = 360 kg mol^{-1})

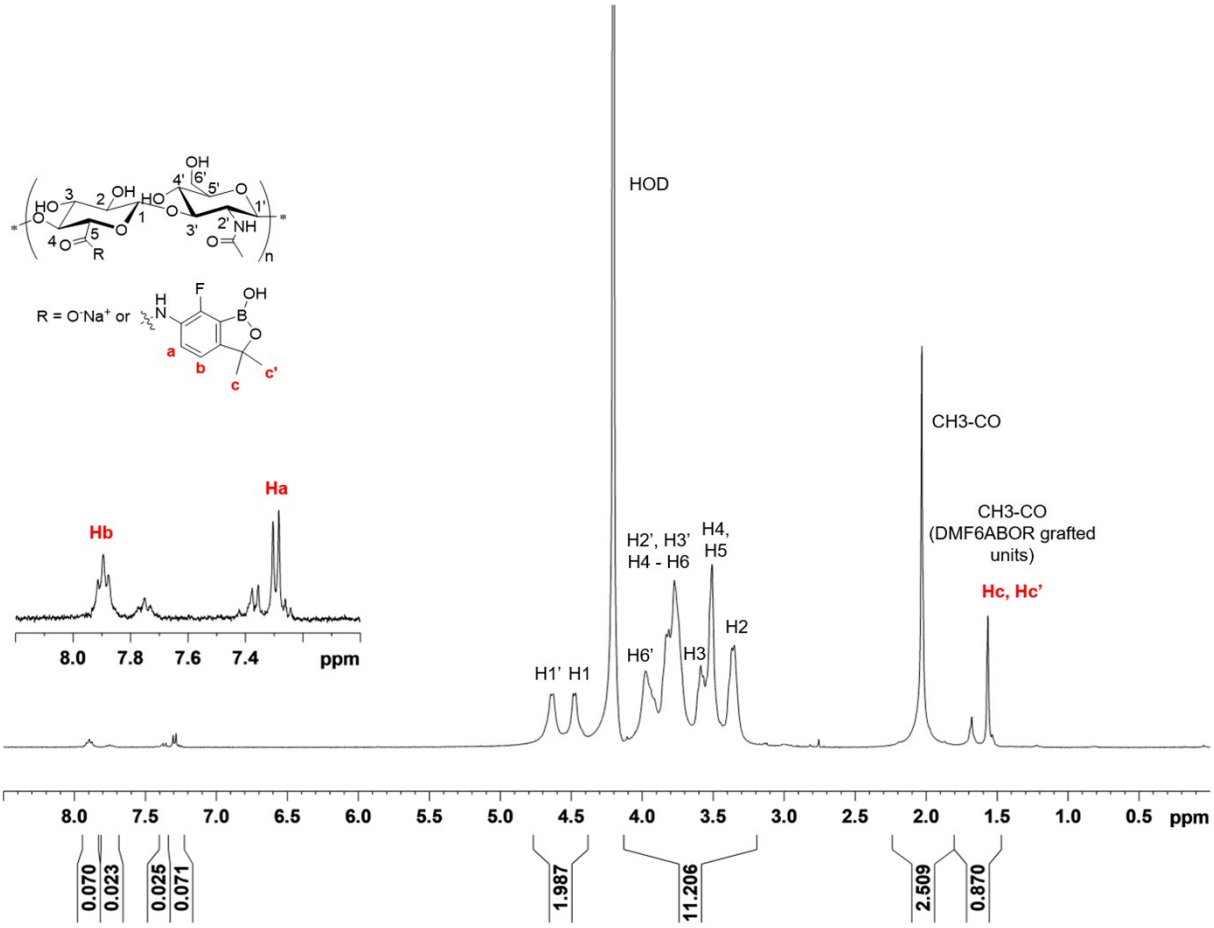


Figure S10. ^{1}H NMR spectrum (400 MHz, D_2O, 6 mg.mL^{-1}, 80 °C) of the HA360-DMF6ABOR derivative.

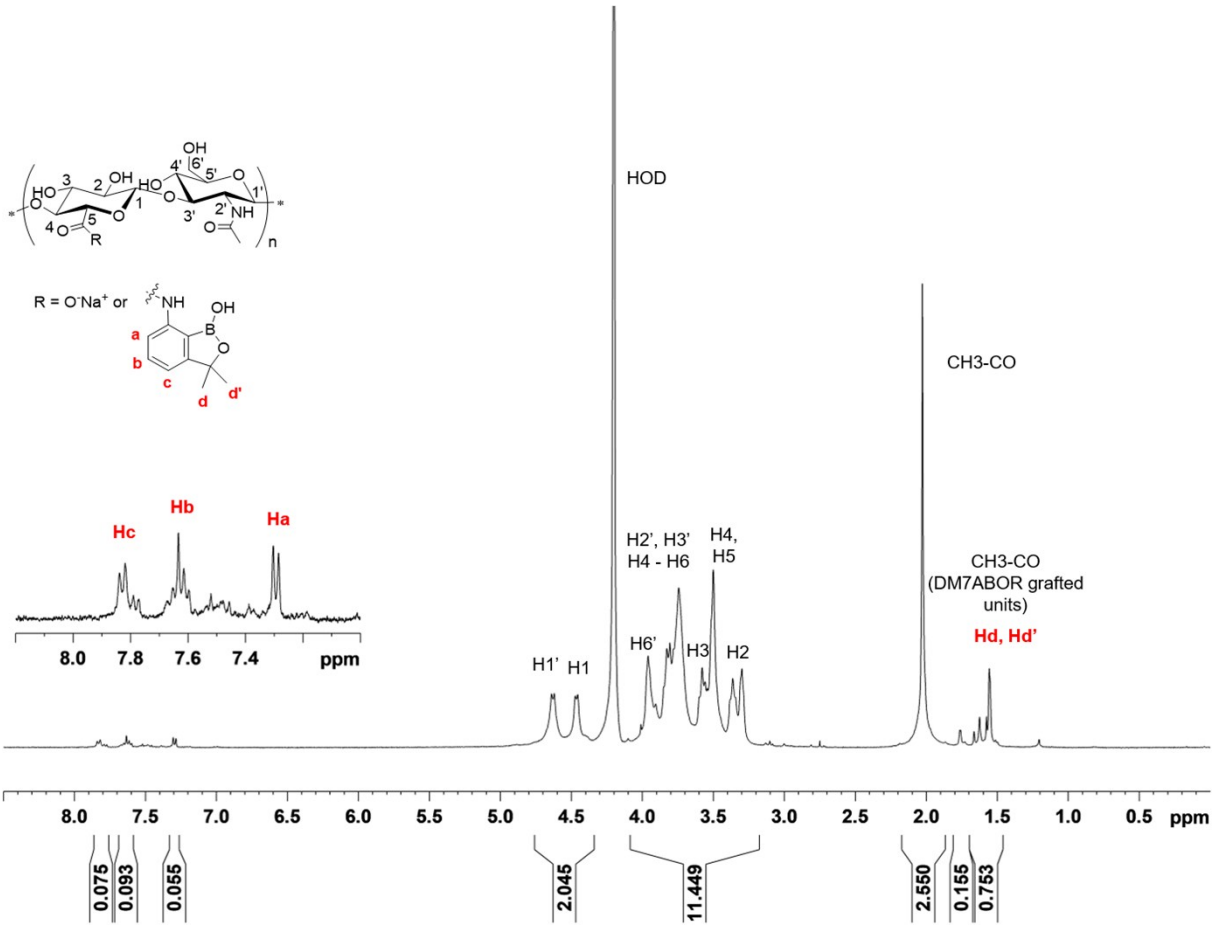


Figure S11. ^{1}H NMR spectrum (400 MHz, D_2O, 6 mg.mL^{-1}, 80 °C) of the HA360-DM7ABOR derivative.

5. Determination of the pK_a of free 6ABOR, DMF6ABOR and DM7ABOR derivatives by ^{11}B NMR spectroscopy

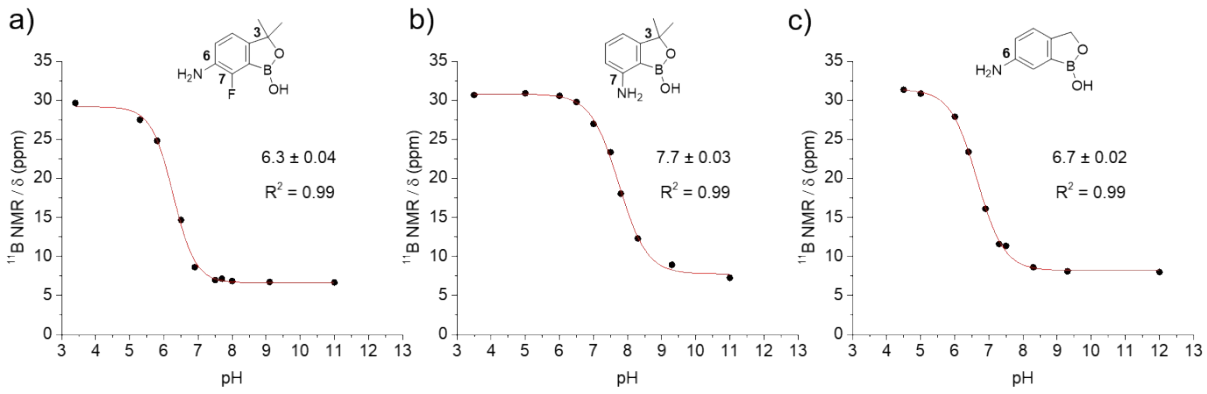


Figure S12. Determination of the pK_a of free (a) 6ABOR, (b) DMF6ABOR and (c) DM7ABOR derivatives by ^{11}B NMR titration as a function of pH (curve fitting using Boltzmann equation).

6. MD simulations of two possible complexes formed between DMF6ABOR and diol pairs from HA

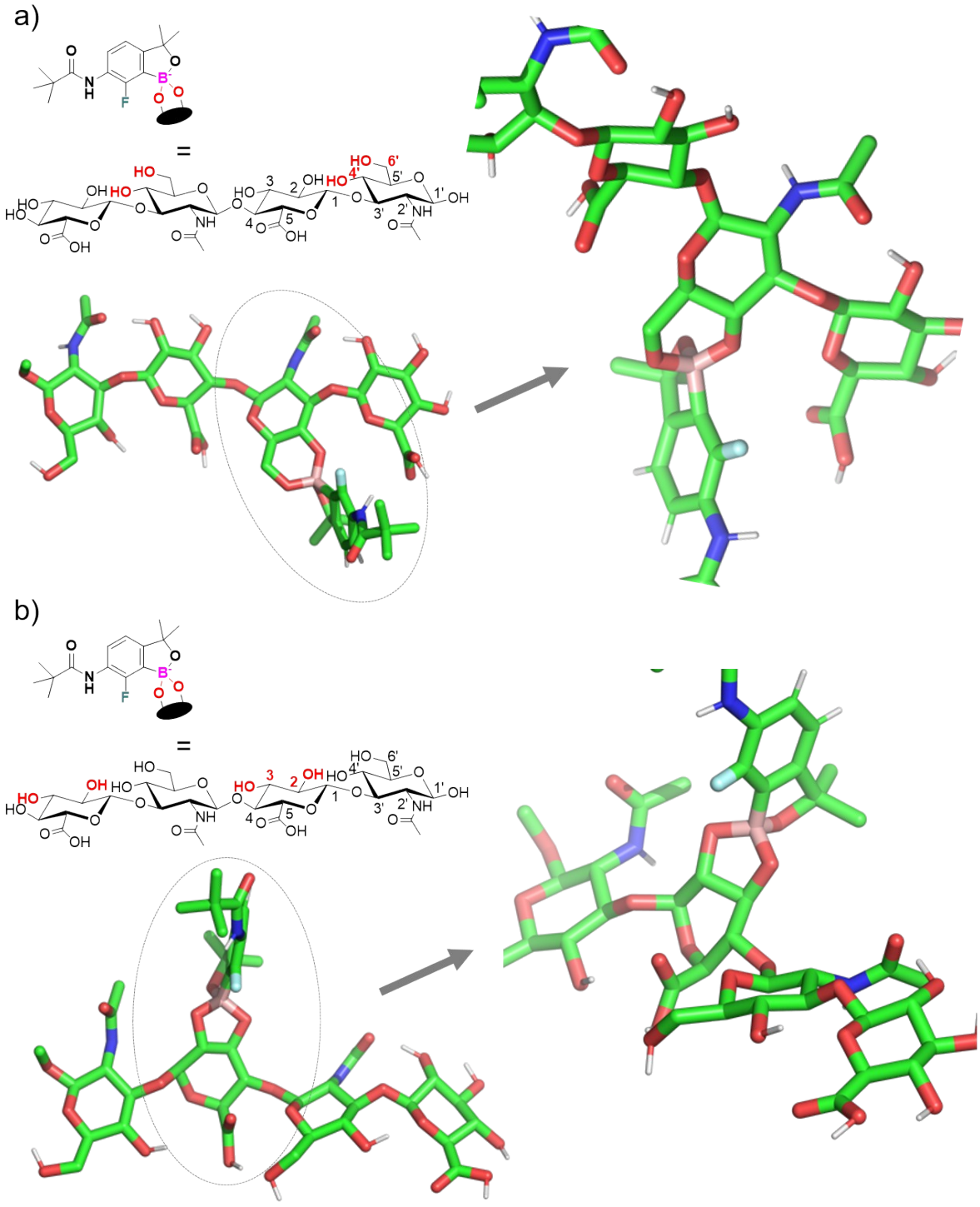


Figure S13. Force field energy minimized structures of two possible complexes for DMF6ABOR and HA (with 2 repeating disaccharide units): (a) DMF6ABOR bound to the C-4/C-6 diol of the D-GlcNAc unit, and (b) DMF6ABOR bound to the C-2/C-3 diol pair of D-Glc. For the simulations, the complexes were first solubilized in spc water and energy minimized (GROMACS, Gromos54a7 ff).

7. Methodology for determining K_a by ^{1}H NMR Spectroscopy

The procedure to determine values of K_a was adapted from previous studies using free boronic acids and saccharides.[7,8] This method consisted in assuming that a boronic acid (B) and a saccharide (S) bind in one modality, BS:

$$B + S \rightleftarrows BS$$

$$K_a = \frac{[BS]}{[B].[S]} \qquad (1)$$

Where [B], [S] and [BS] are the molar concentrations of free boronic acid, free saccharide and complex, respectively.

To calculate K_a, the [BS]/[B] ratio was determined by digital integration of aryl protons of the boronic acid/saccharide complex and of the free boronic acid, allowing to calculate [B], [BS] and [S], as follows:

$$[B] = \frac{[B]_0}{\frac{[BS]}{[B]} + 1} \qquad (2)$$

Where $[B]_0$ is the initial concentration of boronic acid added in the NMR tube, and

$$[BS] = \frac{[BS]}{[B]}[B] \qquad (3)$$

$$[S] = [S]_0 - [BS] \qquad (4)$$

Where $[S]_0$ is the initial concentration of saccharide added in the NMR tube.

Procedure for the preparation of samples for NMR analysis

Stock solutions of free DMF6ABOR (DM7ABOR) and free D-fructose (native HA100) were prepared by solubilization in distilled water. When necessary, the pH was carefully adjusted to 7.4 by adding 1 M NaOH, using a pH-meter, and water was added to get a concentration of 4 mM. Then, the solutions were diluted with 0.02 M PBS pH 7.4 in order to obtain a final concentration of 2 mM DMF6ABOR (DM7ABOR) or D-fructose (native HA100) in 0.01 M PBS at pH 7.4. The solutions of complexes were then prepared by mixing various volumes of a stock solution of DMF6ABOR (DM7ABOR) with a stock solution of D-fructose (native HA100). This generated mixtures of pH 7.4 (± 0.1), with a molar ratio of DMF6ABOR (DM7ABOR)/saccharide at a range of 0.3 to 1.5. Water was removed by freeze-drying and the samples were properly dissolved in D_2O prior to NMR analysis. Each value of K_a was determined from two experiments of titration using freshly prepared solutions. ^{1}H NMR titration was performed with at least 6 different concentrations at 25 °C.

Procedure for determining the chemical shifts of aryl protons in bound and free boronic acids

^{1}H NMR spectra of DMF6ABOR and DM7ABOR alone were first recorded (spectra (a) in Figure S12, S14, S16 and S18). Second, ^{1}H NMR spectra of DMF6ABOR and DM7ABOR in presence of excess free saccharide (D-fructose or native HA100 to induce 100 % complex formation are acquired (spectra (b) in Figure S12, S14, S16 and S18). Comparison of spectra

(a) and (b) allows the assignment of the aryl protons in bound and free aminobenzoxaboroles. This analysis was then used to interpret the spectra from the titrations with D-fructose or native HA100; spectra (c) in Figure S12, S14, S16 and S18.

8. Determination of K_a by ^{1}H NMR for 6ABOR and D-fructose

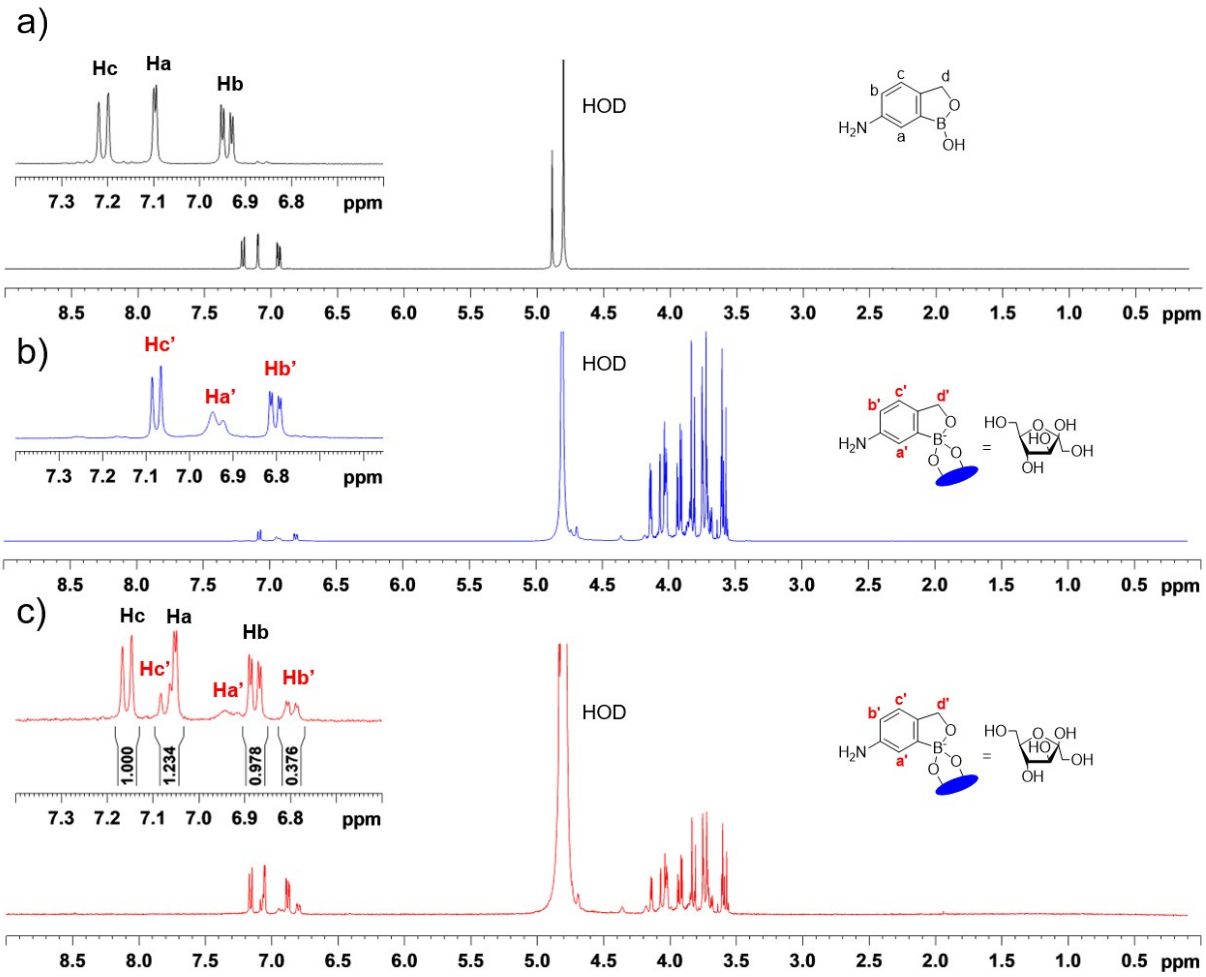


Figure S14. ^{1}H NMR spectra in 0.01 M deuterated PBS pH 7.4 at 25 °C of ABOR alone (15 mM) (a), ABOR (15 mM) in the presence of excess D-fructose (150 mM) (b) and ABOR (15 mM) with D-fructose (15 mM) (c). The [BS]/[B] ratio was calculated from the digital integration of Hc (free ABOR) and Hb' (complexed ABOR) signals.

9. Determination of K_a by ITC for 6ABOR and D-fructose

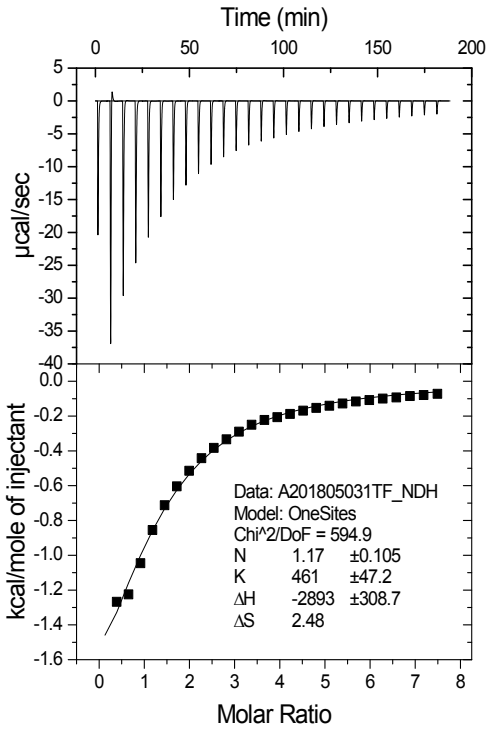


Figure S15. Calorimetric titration of 6ABOR (2 mM) with D-fructose (75 mM) in 0.01 M PBS (pH 7.4, 25 °C).

10. Determination of K_a by ^{1}H NMR for DMF6ABOR and D-fructose

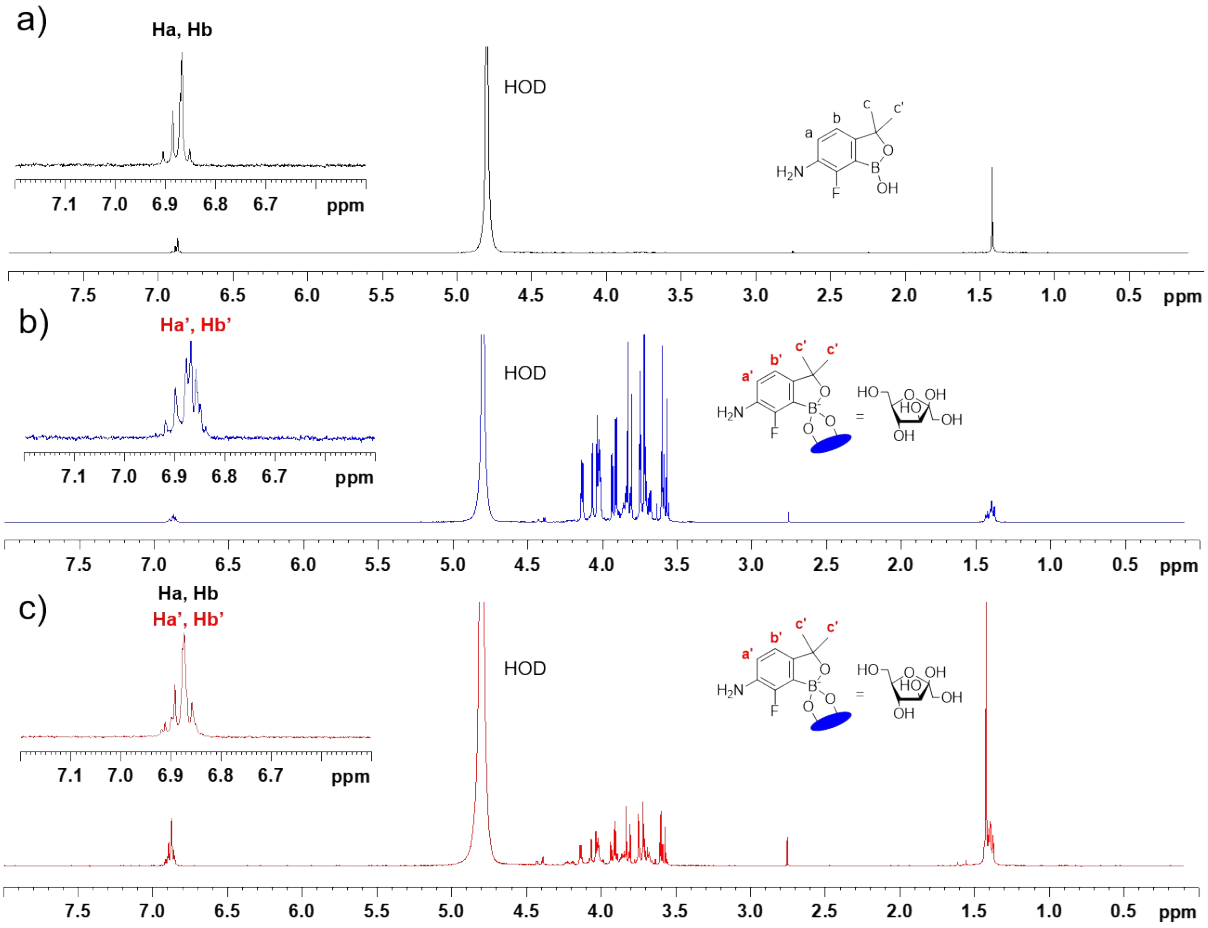


Figure S16. ^{1}H NMR spectra in 0.01 M deuterated PBS pH 7.4 at 25 °C of DMF6ABOR alone (1 mM) (a), DMF6ABOR (1 mM) in the presence of excess D-fructose (10 mM) (b), and DMF6ABOR (1 mM) with D-fructose (1 mM) (c). K_a was not measured because the aromatic signals (7-8 ppm) of bound and unbound forms of DMF6ABOR were not sufficiently separated to be integrated.

11. Determination of K_a by ITC for DMF6ABOR and D-fructose

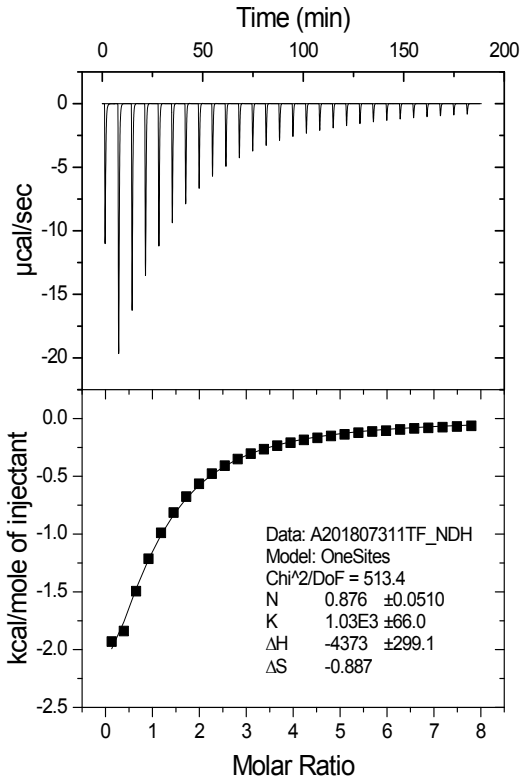


Figure S17. Calorimetric titration of DMF6ABOR (1 mM) with D-fructose (37.5 mM) in 0.01 M PBS (pH 7.4, 25 °C).

12. Determination of K_a by ^{1}H NMR for DM7ABOR and D-fructose

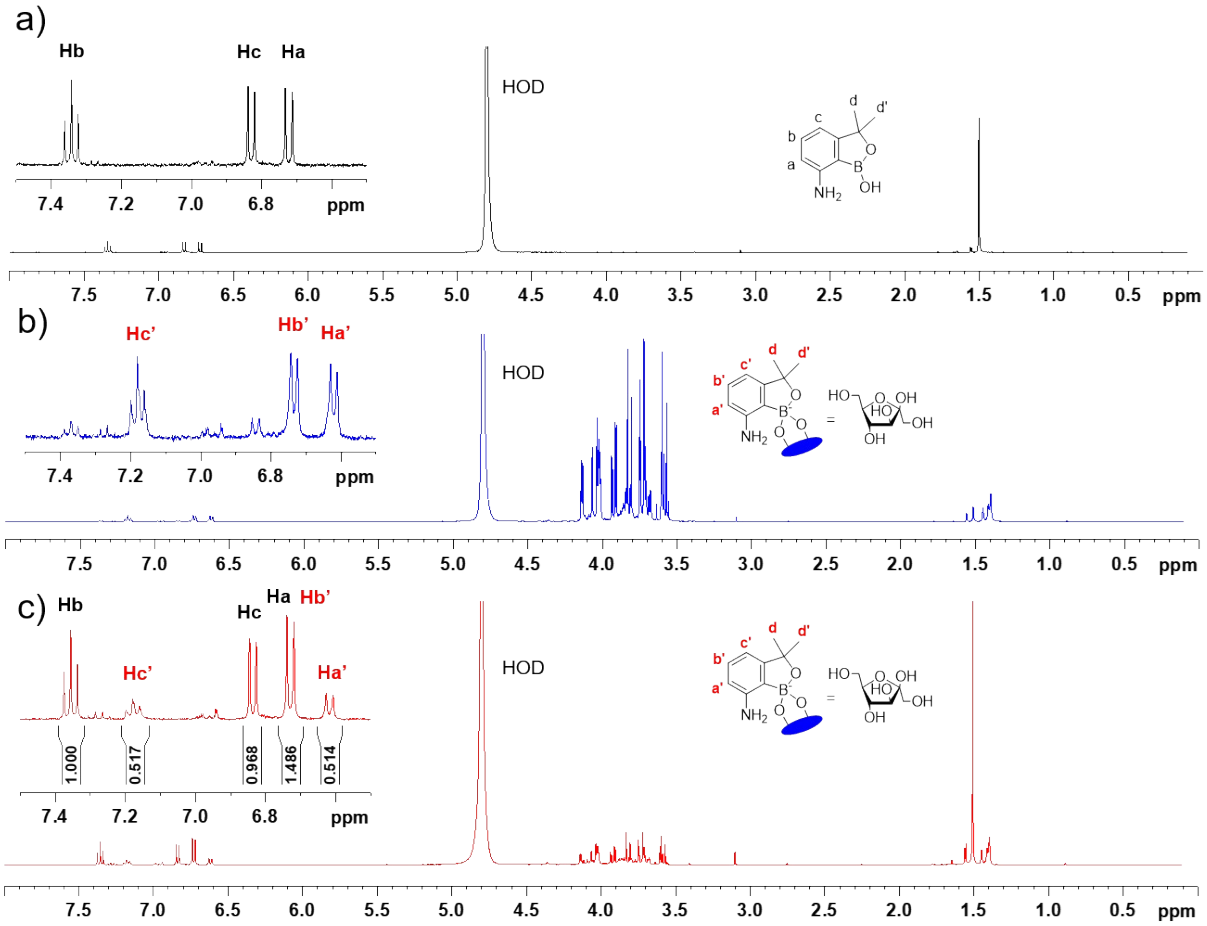


Figure S18. [1]H NMR spectra in 0.01 M deuterated PBS pH 7.4 at 25 °C of DM7ABOR alone (1 mM) (a), DM7ABOR (1 mM) in the presence of excess D-fructose (10 mM) (b), and DM7ABOR (1 mM) with D-fructose (1 mM) (c). The [BS]/[B] ratio was calculated from the digital integration of Hb (free DM7ABOR) and Ha' or Hc' (complexed DM7ABOR) signals.

13. Determination of K_a by ITC for DM7ABOR and D-fructose

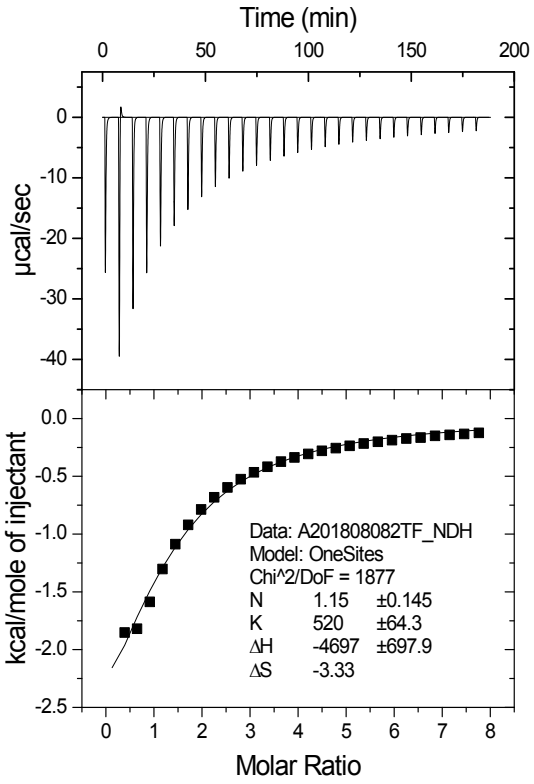


Figure S19. Calorimetric titration of DM7ABOR (1.5 mM) with D-fructose (56 mM) in 0.01 M PBS (pH 7.4, 25 °C).

14. Determination of K_a by ^{1}H NMR for DMFF6ABOR and native HA

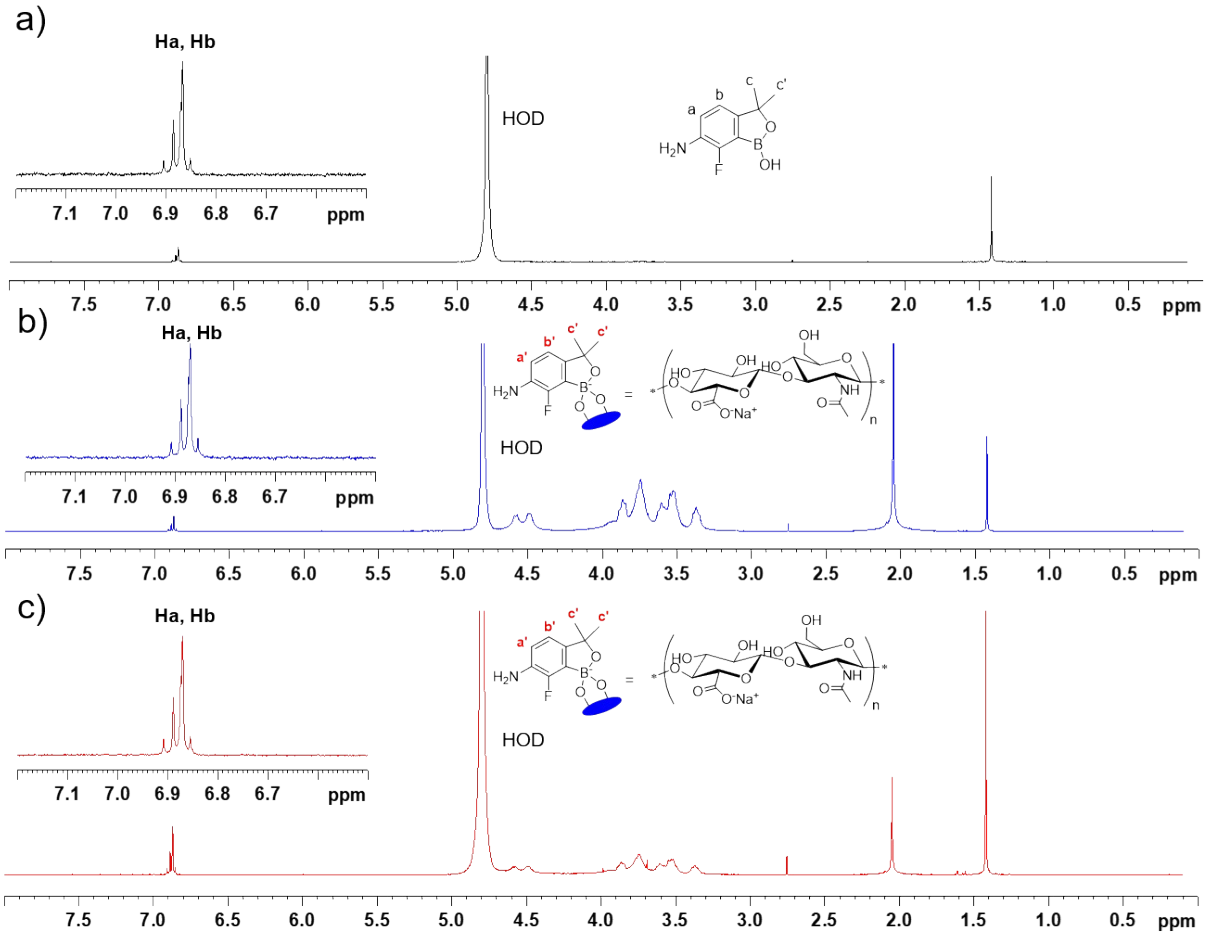


Figure S20. ^{1}H NMR spectra in 0.01 M deuterated PBS pH 7.4 at 25 °C of DMF6ABOR alone (1 mM) (a), DMF6ABOR (1 mM) in the presence of excess native HA (10 mM of HA disaccharide) (b), and DMF6ABOR (1 mM) with native HA (1 mM of HA disaccharide) (c). K_a was not measured because only the unbound form of DMF6ABOR was observed at 25 °C (rapid exchange dynamics relative to NMR time-scale).

15. Self-healing characterization of a hydrogel based on HA100-DMF6ABOR

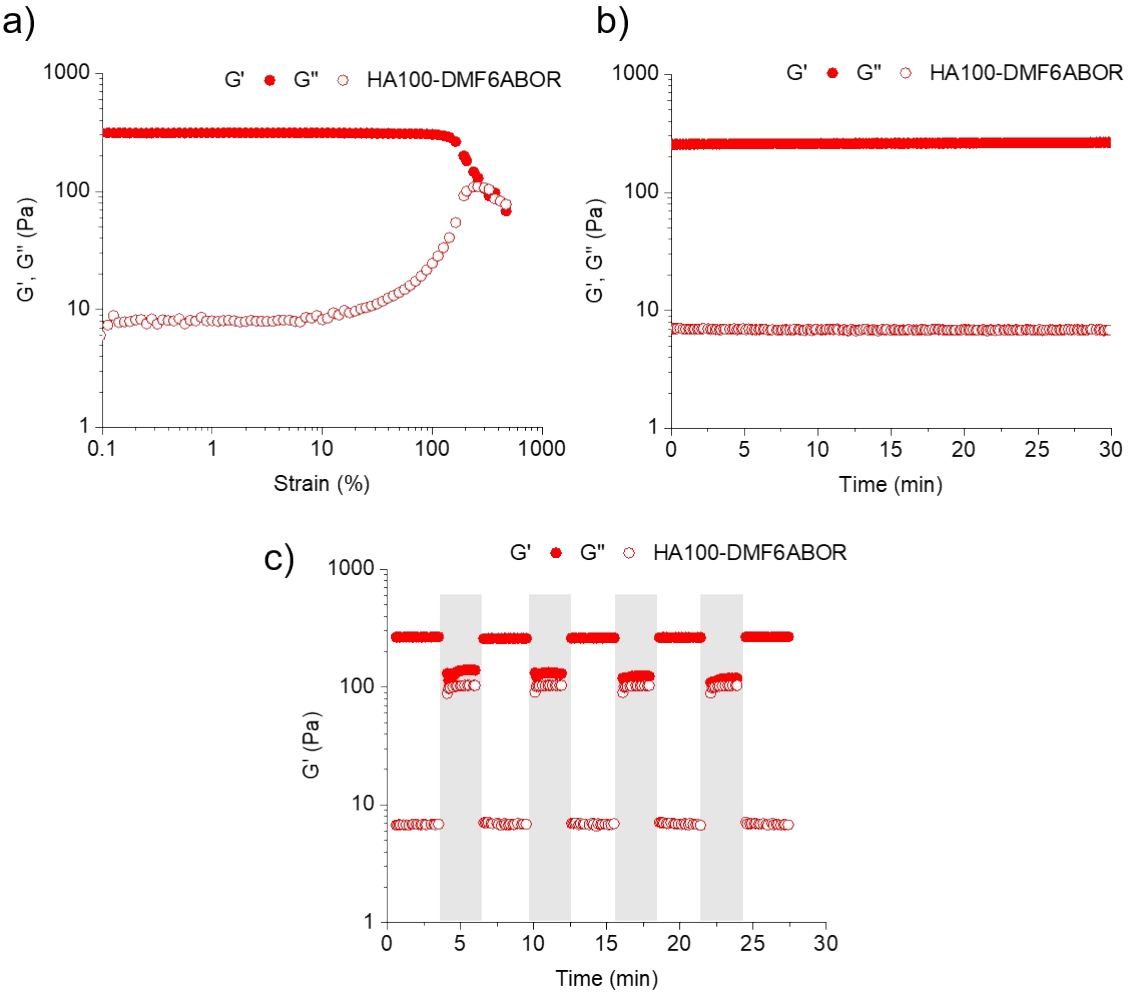


Figure S21. Self-healing of the HA100-DMF6ABOR hydrogel after failure. (a) Variation of G' and G" when increasing strain, followed by (b) the linear recovery of the moduli when strain was reduced. The gel fractured at a strain of, approximately, 300 % and immediately recovered its moduli when strain was reduced to 5 %. (c) Four cycles of recovery from strain-induced breakdowns at physiological pH: a strain above the linear viscoelastic region (shaded regions, 250 % of strain) was applied for 2 min, followed by linear recovery measurements during 3 min (unshaded regions, 5 % of strain).

16. DMF6ABOR model used for molecular dynamics (MD) studies

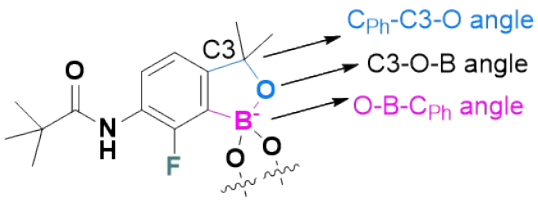


Figure S22. DMF6ABOR model containing a *tert*-butyl group to simulate the HA chain used for MD calculations. The arrows indicate the angles of the oxaborole ring that are impacted by the *gem*-dimethyl group.

17. Investigation of the molecular geometry of the complexes formed between HA diols and grafted DMF6ABOR (DM7ABOR) by MD simulations

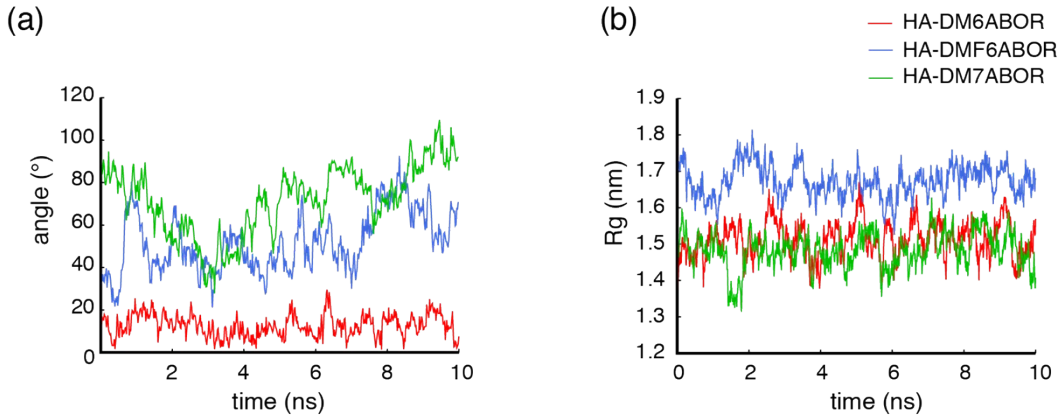


Figure S23. Conformational analysis of MD-simulated molecules with different cross-linkers: (a) angles between end-to-end vectors of HA chains, and (b) radii of gyration (Rg) of each molecule as a function of simulation time. The conformational parameters were extracted from the last 10 ns of production MD trajectories.

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