Supporting Information

The application of nitroimidazole-carbobane modified phenylalanine derivatives as dual-target B-carriers in Boron Neutron Capture Therapy

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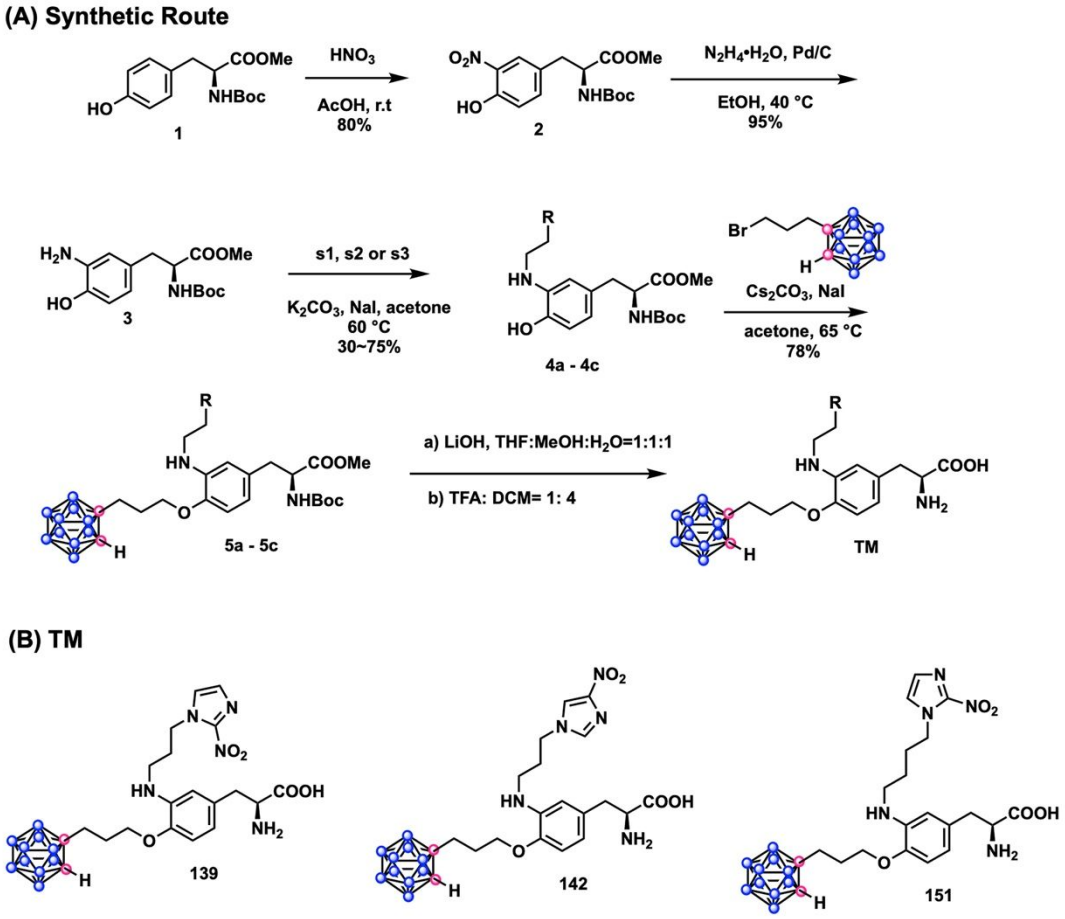
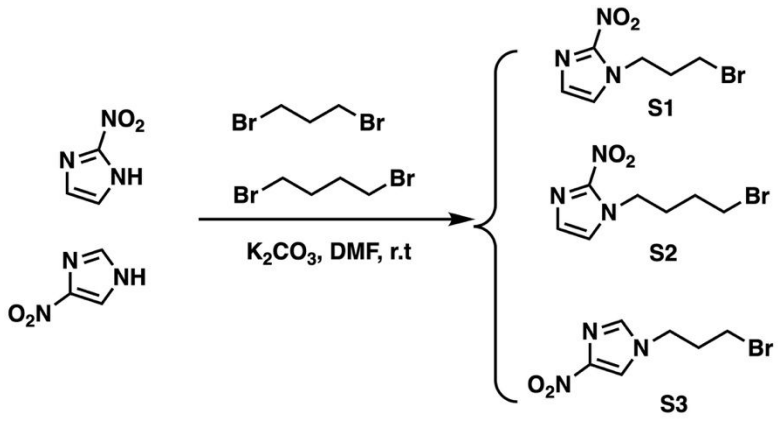
1. Synthesis



Scheme 1 synthetic route

1.1 Sythesis of nitroimidazole derivatives



Scheme 2 Synthesis of nitroimidazole derivatives

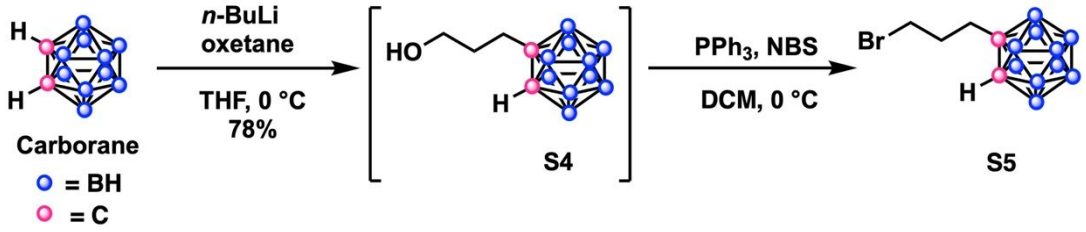
General process for the synthesis of nitroimidazole derivatives are described in **Scheme 1**. 2-nitroimidazole (200 mg, 1.77 mmol) was dissolved in 3 mL anhydrous DMF and K_2CO_3 (489 mg, 3.54 mmol). The reaction was carried out for 5 minutes at

room temperature. Then, 1,3-dibromopropane (0.72 ml, 7.07 mmol) was added dropwise to the reaction flask, and the reaction was allowed to proceed overnight at room temperature. After the reaction was completed, it was extracted with water (15 ml) and ethyl acetate (15 ml*3), and the organic phase was combined and extracted twice with 20 ml of saturated NaCl solution. The organic phase was collected by distillation under reduced pressure to give a crude material, which was purified by column chromatography (PE: EA = 1:1) to give a white solid compound **S1**, 320 mg, yield 77%. ^{1}H NMR (600 MHz, Chloroform-d) δ 7.21 (s, 1H), 7.17 (s, 1H), 4.63 (t, *J* = 6.1 Hz, 2H), 3.38 (t, *J* = 5.9 Hz, 2H), 2.45 – 2.38 (m, 2H).

S2 (400 MHz, Chloroform-d) δ7.19 (s, 1H), 7.14 (s, 1H), 4.52 (t, *J* = 7.5 Hz, 2H), 3.42 (t,J= 6.4 Hz, 2H), 2.08-2.00 (m, 2H), 1.93-1.82 (m, 2H)

S3 (400 MHz, Chloroform-d): δ7.81 (d, *J* = 1.3 Hz, 1H), 7.49 (d, *J*= 0.9 Hz, 1H), 4.30 (t, *J* = 6.1 Hz, 2H), 3.37 (t, *J* = 6.0 Hz, 2H), 2.45- 2.32 (m, 2H).

1.2 Synthesis of S5



Scheme 3 Synthesis route of S5

Carborane (300 mg, 2.08 mmol) was firstly dissolved in 2 ml of dry THF, then *n*-BuLi (1.56 ml, 2.5 mmol, 1.6 M in THF) was slowly added dropwise thereto at 0 °C. The reaction was warm to room temperature for about 30 minutes. Then the oxetane (0.27 ml, 4.16 mmol) was slowly added into the reaction at 0 °C, and the mixture was reacted at room temperature for 3 hours. After the TLC test showed disappearance of the starting material, the reaction was quenched by the addition of 5 ml of a saturated aqueous solution of NH_4Cl. An additional 30 ml of water was added and extracted 3 times with 30 ml of ethyl acetate. The organic phase was collected and extracted once more with 30 ml of saturated brine. The combined organic phases were evaporated under reduced pressure to give Compound **S4**, yield 78%. Then **S4** (50 mg, 0.25 mmol)

was dissolved in 2 mL of dry DCM. PPh_3 (130 mg, 0.5 mmol) and NBS (88 mg, 0.5 mmol) were added into the solvent at 0 ° C. TLC monitoring showed the disappearance of the starting material. The reaction mixture was subjected to distillation under reduced pressure and purified by column chromatography (PE: EA = 10:1) to give a pale yellow oily liquid compound **S5**, 62 mg, yield: 95%. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 3.59 (s, 1H), 3.37 (t, *J* = 6.2 Hz, 2H), 2.44 – 2.33 (m, 2H), 2.07-2.02 (m, 2H), 2.67-1.82 (m, 10H).

1.3 Synthesis of methyl (*S*)-2-((*tert*-butoxycarbonyl) amino)-3-(4-hydroxy-3-nitrophenyl) propanoate (compound 2)

Compound methyl (*tert*-butoxycarbonyl)-*L*-tyrosinate (500 mg, 1.69 mmol) was disscolved in AcOH (3 ml). The nitric acid was added into the solution, and the mixture was stirred for 2 hours at room temperature. Reaction progress was monitored by TLC. Then Saturated aqueous solution of sodium bicarbonate was added until the pH was at 7. The mixture was washed with EtOAc (15 ml *4). Then combined organic phases was dried over Na_2SO_4 and concentrated. The residue was purified by flash silica gel chromatography (PE: EA= 8:1) to afford yellow solid product 2.^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.84-7.90 (m, 1H), 7.37 (dd, *J* = 2.1, 8.5 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 4.57 (d, *J* = 6.1 Hz, 1H), 3.76 (s, 3H), 3.16 - 3.02 (m, 2H), 1.42 (s, 9H).

1.4 Synthesis of methyl (*S*) – 3 - (3– amino - 4- hydroxyphenyl)- 2- ((*tert*-butoxycarbonyl) amino) propanoate (compound 3)

Compound 2 (100 mg, 0.29 mmol) was dissolved in 5 ml ethanol, hydrazine hydrate (0.18 ml, 2.9 mmol) and Pd/C (10 mg, 10%) were added to the reaction under nitrogen. The reaction was carried out at 40 ° C for about 3 hours. After the disappearance of the starting material, Pd/C was removed by filtration with celite, and concentrated the filtrate under reduced pressure to give a white solid, 87 mg, yield 95%. 1H NMR (600 MHz, Chloroform-d) δ 6.61 (d, *J* = 7.4 Hz, 1H), 6.50 (s, 1H), 6.38 (d, *J* = 7.2 Hz, 1H), 5.05 (d, *J* = 8.1 Hz, 1H), 4.49 (q, *J* = 6.1 Hz, 1H), 3.70 (s, 3H), 2.91 (hept, *J* = 6.1 Hz, 2H), 1.41 (s, 9H).

1.5 General procedure A for compound 4a, 4b, 4c

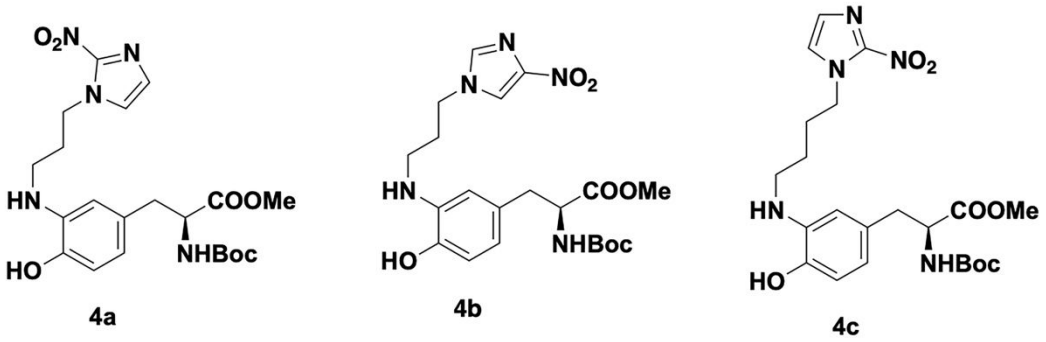


Figure S1 compound **4a**, **4b**, **4c**

To a solution of compound **3** (280 mg, 0.9 mmol) in 10 ml acetone was added 1-(3-bromopropyl)-2-nitro-1*H*-imidazole (316 mg, 1.35 mmol), K_2CO_3 (373 mg, 2.7 mmol) and NaI (391 mg, 2.7 mmol), the resulting mixture was stirred at 60 ℃ for 24 hours. After the completion of the reaction, the acetone was evaporated under reduced pressure, and the crude material was extracted with water (50 ml) and ethyl acetate (60 ml*3). The crude product was subjected to silica gel column chromatography (PE: EA = 5:1) to give a yellow solid compound **4a**, 310 mg, yield 75%.^{1}H NMR (500 MHz, DMSO-d_6) δ 9.08 (s, 1H), 7.71 (s, 1H), 7.19 (s, 1H), 7.09 (d, J = 7.9 Hz, 1H), 6.55 (d, J = 7.8 Hz, 1H), 6.35 (s, 1H), 6.27 (d, J = 7.7 Hz, 1H), 4.68 (d, J = 6.3 Hz, 1H), 4.48 (d, J = 7.1 Hz, 2H), 4.09 (d, J = 7.5 Hz, 1H), 3.60 (s, 4H), 3.08 (t, J = 6.5 Hz, 2H), 2.80 (dd, J = 14.4, 5.3 Hz, 1H), 2.72 – 2.64 (m, 1H), 2.09 (d, J = 6.1 Hz, 2H), 1.33 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.85, 155.29, 144.65, 142.84, 136.94, 128.27, 127.82, 127.72, 116.27, 113.12, 110.53, 78.16, 55.59, 51.61, 47.62, 39.92, 36.48, 29.35, 28.11, 27.82. MS data for $C_{21}H_{29}N_5O_7$ $[M+H]^+$ found 464.21908.

4b. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.09 (s, 1H), 8.47 (d, J = 1.6 Hz, 1H), 7.89 (s, 1H), 7.07 (d, J = 8.0 Hz, 1H), 6.54 (d, J = 7.8 Hz, 1H), 6.33 (d, J = 2.1 Hz, 1H), 6.26 (dd, J = 7.9, 1.9 Hz, 1H), 4.71 (t, J = 6.0 Hz, 1H), 4.16 (t, J = 7.1 Hz, 2H), 4.08 (td, J = 8.7, 5.5 Hz, 1H), 3.58 (s, 3H), 3.04 (q, J = 6.5 Hz, 2H), 2.73 (ddd, J = 61.3, 13.9, 7.5 Hz, 2H), 2.13 – 2.02 (m, 2H), 1.31 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.86, 155.32, 147.01, 142.84, 137.43, 136.94, 128.29, 121.60, 116.28, 113.13, 110.52, 78.19,

55.59, 51.62, 45.58, 36.48, 29.63, 28.12. MS data for $C_{21}H_{29}N_5O_7$ $[M+H]^+$ found 464.22074.

4c ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.11 (s, 1H), 6.61 (s, 1H), 6.36 (s, 1H), 6.32 (d, *J* = 7.2 Hz, 1H), 5.02 (d, *J* = 7.9 Hz, 1H), 4.49 (dt, *J* = 11.2, 5.1 Hz, 1H), 4.42 (t, *J* = 7.3 Hz, 2H), 3.70 (s, 3H), 3.14 (d, *J* = 7.0 Hz, 2H), 3.00 – 2.88 (m, 2H), 2.01 – 1.90 (m, 2H), 1.65 (q, *J* = 7.1, 6.3 Hz, 2H), 1.40 (s, 10H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.90, 155.45, 144.76, 143.13, 136.73, 128.42, 126.22, 118.37, 115.80, 115.45, 114.41, 112.48, 80.18, 77.36, 54.76, 52.35, 50.20, 43.52, 38.09, 29.80, 26.17. MS data for $C_{22}H_{31}N_5O_7$ $[M+H]^+$ found 478.22950.

1.6 General procedure B for 5a, 5b, 5c

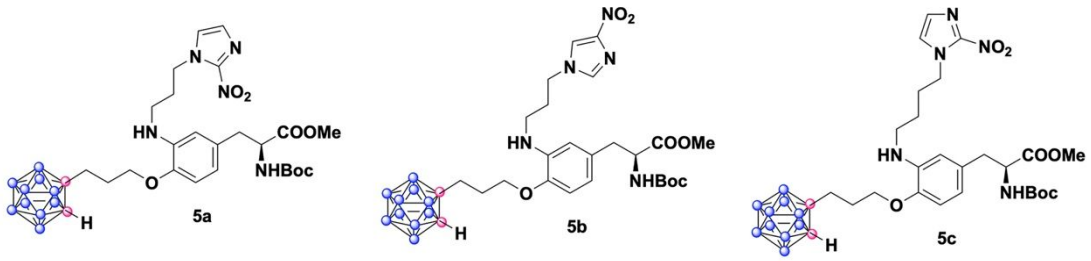


Figure S2 comound **5a**, **5b**, **5c**

Compound **4a** (20 mg, 0.04 mmol) and carborane bromide (17 mg, 0.06 mmol) were dissolved in 3 ml of dry acetone, and cesium carbonate (42 mg, 0.12 mmol) and sodium iodide (19 mg, 0.12 mmol) were added at room temperature. Then reacted at 65 ° C under nitrogen atmosphere for 24 h. TLC monitoring showed the disappearance of starting material. After extraction with water (15 ml) and ethyl acetate (15 ml*3), the organic phase was collected and separated by silica gel column chromatography (PE: EA = 1:1) to give the desired product **5a** total 17 mg, yield 63%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.15 (d, J = 9.4 Hz, 2H), 6.61 (d, *J* = 8.1 Hz, 1H), 6.40 (d, *J* = 8.0 Hz, 1H), 6.30 (s, 1H), 4.94 (d, *J* = 7.8 Hz, 1H), 4.58 (t, *J* = 7.1 Hz, 2H), 4.56 – 4.49 (m, 1H), 3.94 (t, *J* = 5.6 Hz, 2H), 3.86 (s, 1H), 3.71 (s, 3H), 3.21 (t, *J* = 5.9 Hz, 2H), 3.02 – 2.91 (m, 2H), 2.50 – 2.43 (m, 2H), 2.05 – 1.97 (m, 2H), 2.73-1.59 (m, 10H, BH), 1.40 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-d) δ 172.69, 155.27, 144.95, 137.58, 132.16, 129.29, 128.90, 126.26, 117.80, 110.87, 110.62, 80.01, 74.85, 66.97, 61.93, 54.63,

52.28, 48.92, 48.06, 40.23, 38.12, 35.17, 34.85, 31.55, 30.45, 30.32, 29.80, 29.30, 28.44. MS data for $C_{26}H_{45}B_{10}N_5O_7$ $[M+Na]^+$ found 671.42016.

5b. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.79 (s, 1H), 7.46 (s, 1H), 6.60 (d, *J* = 8.1 Hz, 1H), 6.41 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.31 (s, 1H), 4.97 (d, *J* = 7.7 Hz, 1H), 4.53 (d, *J* = 6.9 Hz, 1H), 4.17 (t, *J* = 6.8 Hz, 2H), 3.91 (t, *J* = 6.1 Hz, 2H), 3.79 (s, 1H), 3.70 (s, 3H), 3.23 (t, *J* = 6.3 Hz, 2H), 2.96 (ddd, *J* = 36.1, 13.8, 6.0 Hz, 2H), 2.44 – 2.36 (m, 2H), 2.25 – 2.17 (m, 2H), 1.98 (dq, *J* = 11.9, 6.0 Hz, 2H), 2.8-1.6 (m,10H, BH), 1.40 (s, 9H).^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.69, 155.26, 144.89, 137.30, 136.18, 132.15, 129.44, 119.42, 118.10, 110.94, 110.78, 80.01, 74.71, 66.93, 61.74, 54.61, 52.30, 46.42, 40.52, 38.18, 35.03, 31.54, 30.31, 30.14, 29.79, 29.19, 28.42. MS data for $C_{26}H_{45}B_{10}N_5O_7$ $[M+H]^+$ found 649.43828.

5c. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.18 – 7.06 (m, 2H), 6.79 (m, 1H), 6.59 (d, J = 8.1 Hz, 1H), 6.38 (ddd, J = 8.1, 4.3, 1.9 Hz, 1H), 4.94 (d, J = 9.1 Hz, 1H), 4.60 – 4.44 (m, 2H), 4.34 (t, J = 7.2 Hz, 1H), 4.17 – 3.97 (m, 2H), 3.74 (s, 1H), 3.71 (s, 3H), 3.25 – 3.07 (m, 2H), 2.97 (d, J = 5.9 Hz, 2H), 2.51 – 2.40 (m, 2H), 1.98 (dt, J = 9.8, 5.1 Hz, 2H), 1.88 – 1.78 (m, 2H), 1.70 (dt, J = 13.1, 6.5 Hz, 3H), 12.6 – 1.6 (m, 10H, BH), 1.41 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.70, 147.23, 128.67, 128.46, 126.15, 124.61, 124.10, 119.23, 110.79, 66.94, 61.65, 52.29, 50.21, 42.83, 35.14, 35.00, 34.82, 34.66, 32.12, 31.57, 30.33, 29.82, 29.24, 28.46, 28.34. MS data for $C_{27}H_{47}B_{10}N_5O_7$ $[M+Na]^+$ found 685.43625.

1.7 General procedure C for B139, B142, B151

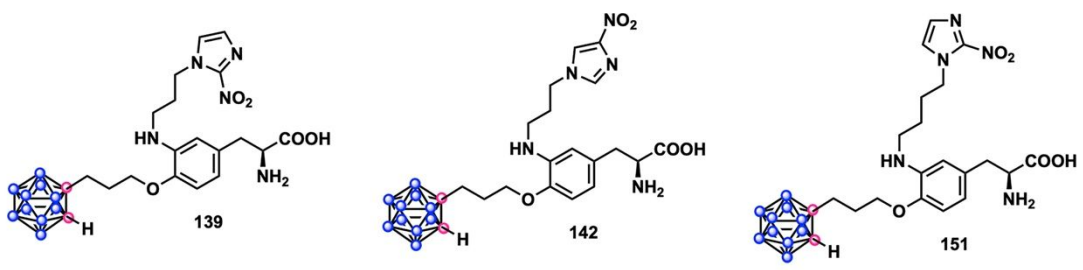


Figure S3 Target molecule B139, B142, B151

To a solution of compound 5a (35 mg, 0.067 mmol) in 2 ml MeOH was added LiOH

(10 mg, 0.42mmol in 3 ml H_2O). The resulting mixture was stirred at 45 ℃ for 15 hours. After the starting materials was disappeared, 1M HCl was added into the mixture to adjust the pH to acidity. Then extracted with 20 ml of ethyl acetate and dried by Na_2SO_4. The residue was concentrated and used to next step without further purification. The residue was dissolved in 1.8 ml DCM, then 0.3 ml TFA was added dropwise under ice bath conditions. After the starting material was completely reacted monitored by TLC and the solvent was distilled off under reduced pressure to afford B139, 12 mg, yield 42% (over 2 steps). ^{1}H NMR (500 MHz, DMSO-d6) δ 7.70 (s, 1H), 7.19 (s, 1H), 6.72 (d, J = 8.1 Hz, 1H), 6.48 (s, 1H), 6.45 (d, J = 7.6 Hz, 1H), 5.17 (s, 1H), 4.47 (t, J = 7.2 Hz, 1H), 4.09 (d, J = 5.9 Hz, 1H), 3.90 (t, J = 6.1 Hz, 2H), 3.13 (t, J = 6.8 Hz, 2H), 2.98 (ddp, J = 20.9, 14.1, 7.3, 6.7 Hz, 2H), 2.50 – 2.44 (m, 2H), 2.09 (q, J = 7.0 Hz, 2H), 1.90 (dt, J = 11.4, 5.9 Hz, 2H), 2.91-1.50 (m, 10H, BH). ^{13}C NMR (126 MHz, DMSO-d6) δ 171.01, 145.55, 145.16, 137.87, 128.38, 128.17, 127.84, 117.73, 111.79, 111.62, 79.66, 76.71, 67.33, 63.75, 53.87, 47.97, 36.17, 34.01, 29.60, 29.31. MS data for $C_{20}H_{35}B_{10}N_5O_5$ $[M+H]^+$ found 534.37234.

B142 ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.44 (s, 1H), 8.30 (s, 1H), 8.21 (d, J = 5.1 Hz, 3H), 7.88 (s, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.30 (d, J = 7.9 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.52 – 6.43 (m, 2H), 5.20 (s, 1H), 4.15 (t, J = 7.0 Hz, 2H), 4.10 (s, 1H), 3.89 (t, J = 6.1 Hz, 2H), 3.11 (t, J = 6.8 Hz, 2H), 2.97 (dtd, J = 21.0, 14.2, 12.7, 6.2 Hz, 3H), 2.47 (d, J = 8.8 Hz, 2H), 2.09 (p, J = 6.9 Hz, 3H), 1.93 – 1.85 (m, 3H), 2.89-1.50 (10H, BH). 13C NMR (126 MHz, DMSO-d6) δ 170.55, 147.04, 145.15, 137.40, 129.57, 127.36, 126.13, 123.94, 121.58, 117.45, 111.40, 79.19, 76.23, 66.87, 63.24, 53.40, 45.54, 35.66, 33.50, 29.22, 28.83. MS data for $C_{20}H_{35}B_{10}N_5O_5$ $[M+H]^+$ found 534.37273.

B151 ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (s, 1H), 7.23 – 7.14 (m, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 6.59 (s, 1H), 6.55 (d, *J* = 6.2 Hz, 1H), 5.19 (s, 1H), 4.32 (t, *J* = 7.0 Hz, 2H), 4.11 (s, 1H), 3.94 (dt, *J* = 23.4, 6.1 Hz, 2H), 3.13 (t, *J* = 6.9 Hz, 2H), 3.04 (d, *J* = 6.6 Hz, 2H), 2.37 – 2.24 (m, 2H), 1.94 – 1.86 (m, 5H), 1.73 (dt, *J* = 14.9, 7.3 Hz, 2H), 1.59 (q, *J* = 7.5 Hz, 2H), 2.8 – 1.5 (m, 10H, BH) . ^{13}C NMR (151 MHz, DMSO-d_6) δ 144.61, 144.51, 127.93, 127.91, 127.88, 127.82, 118.84, 116.90, 114.96, 113.02, 81.58,

70.35, 66.65, 63.26, 53.39, 49.22, 39.10, 35.32, 33.47, 29.64, 28.81, 27.38. MS data for $C_{21}H_{37}B_{10}N_5O_5$ $[M+H]^+$ found 549.4

2. NMR and HRMS

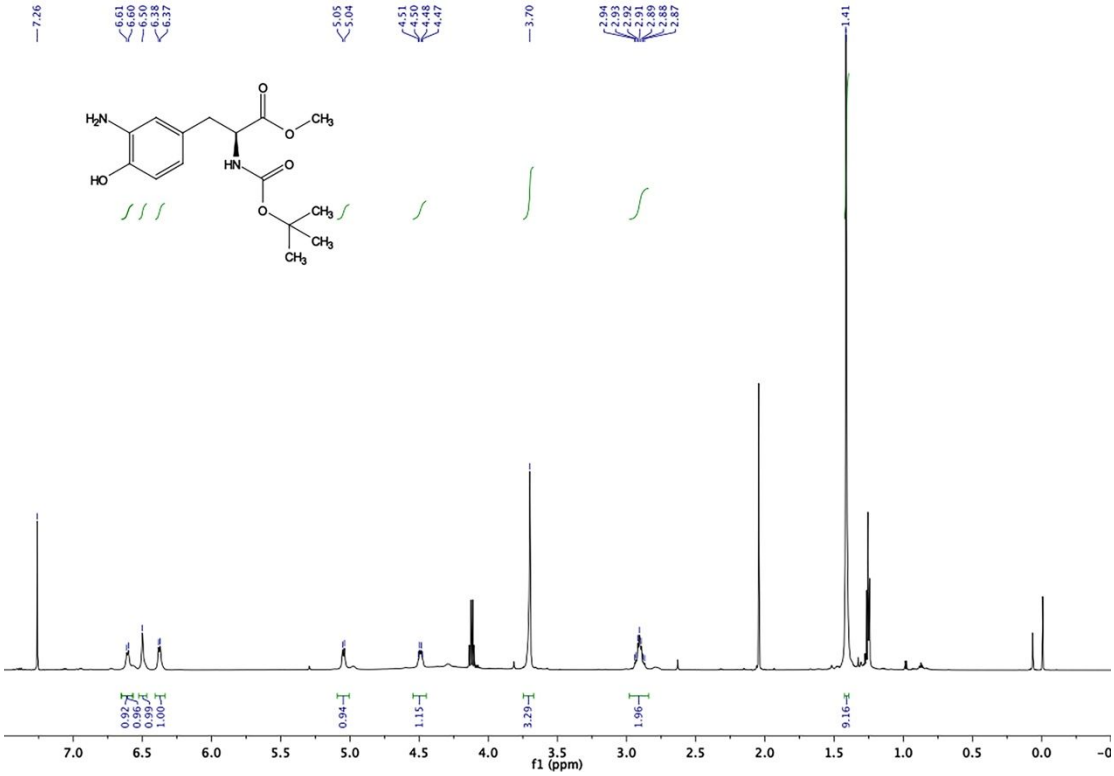


Figure S4 ^{1}H-NMR of compound **3** in $CDCl_3$

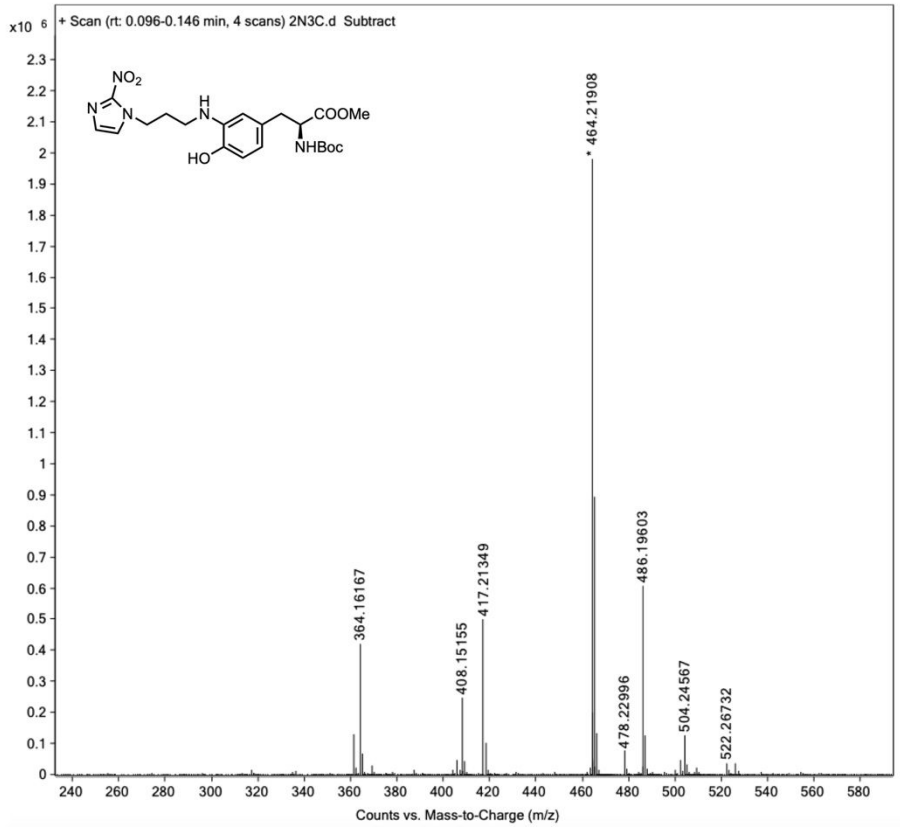


Figure S5 HRMS of **4a** (M+H)

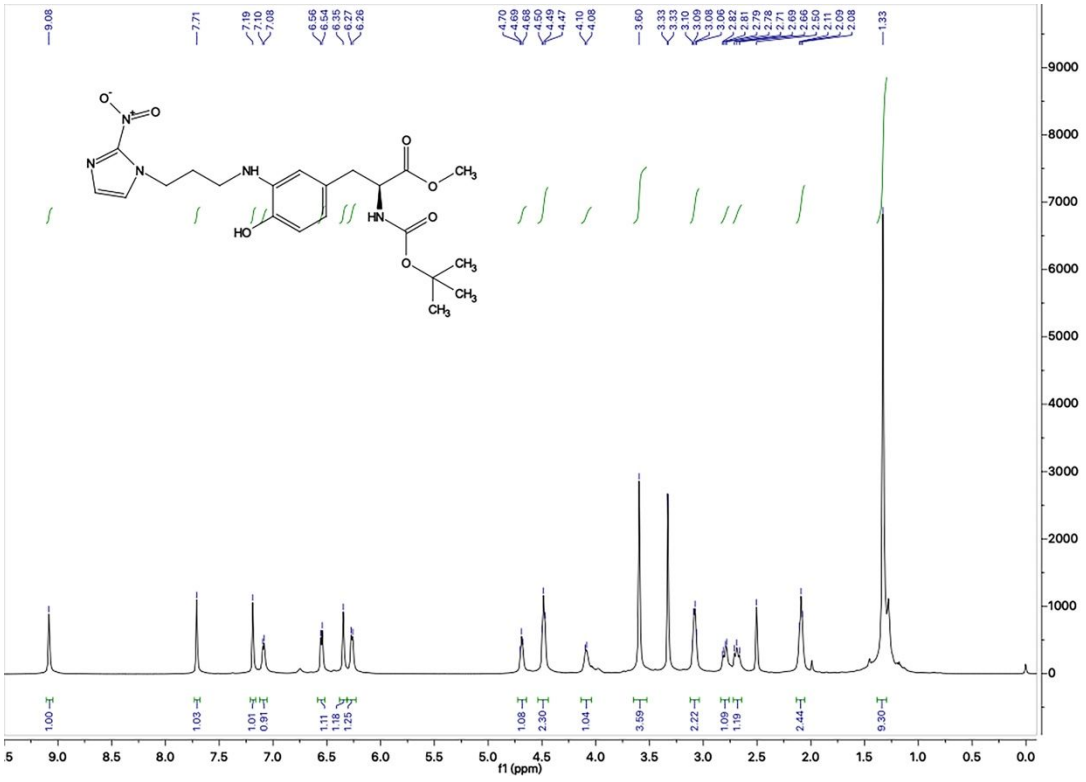


Figure S6 ^{1}H-NMR of compound **4a** in *d*-DMSO

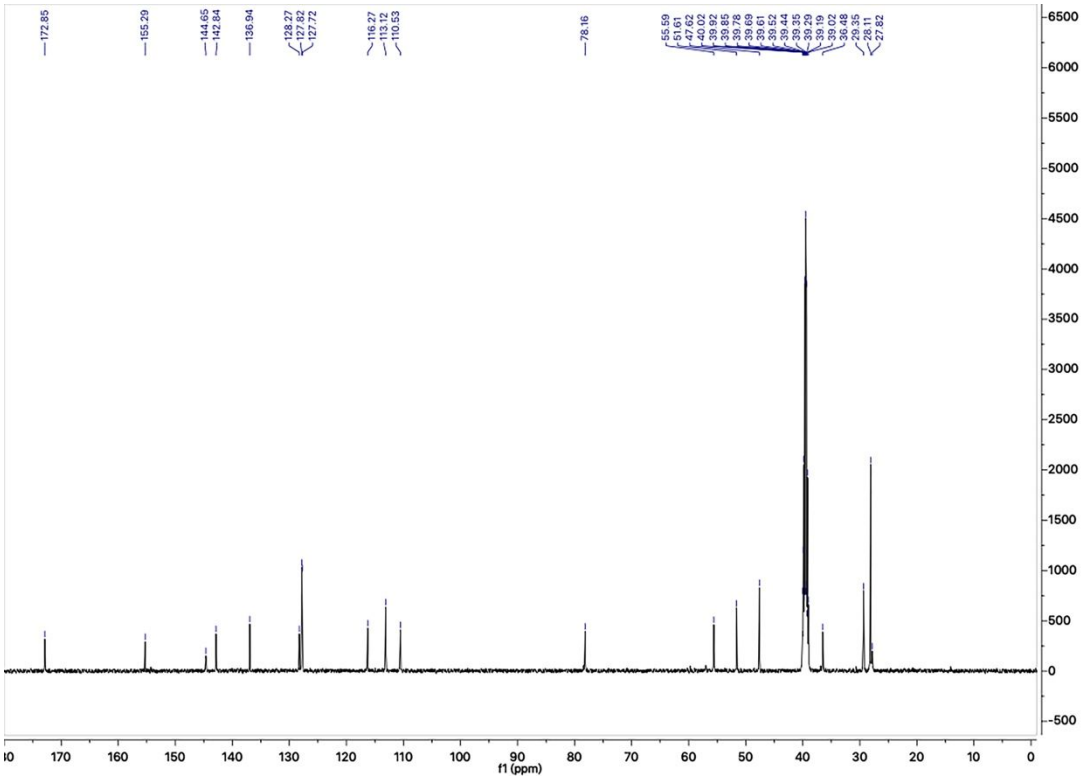


Figure S7 ^{13}C-NMR of compound **4a** in *d*-DMSO

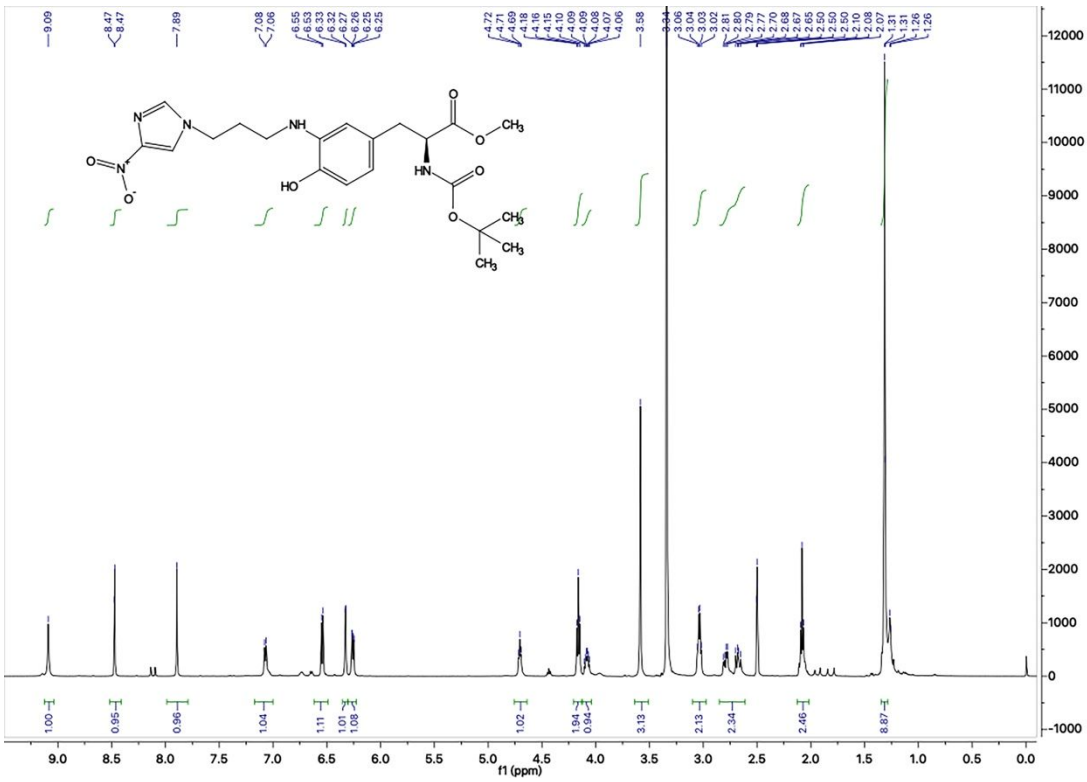


Figure S8 ^{1}H-NMR of **4b** in *d*-DMSO

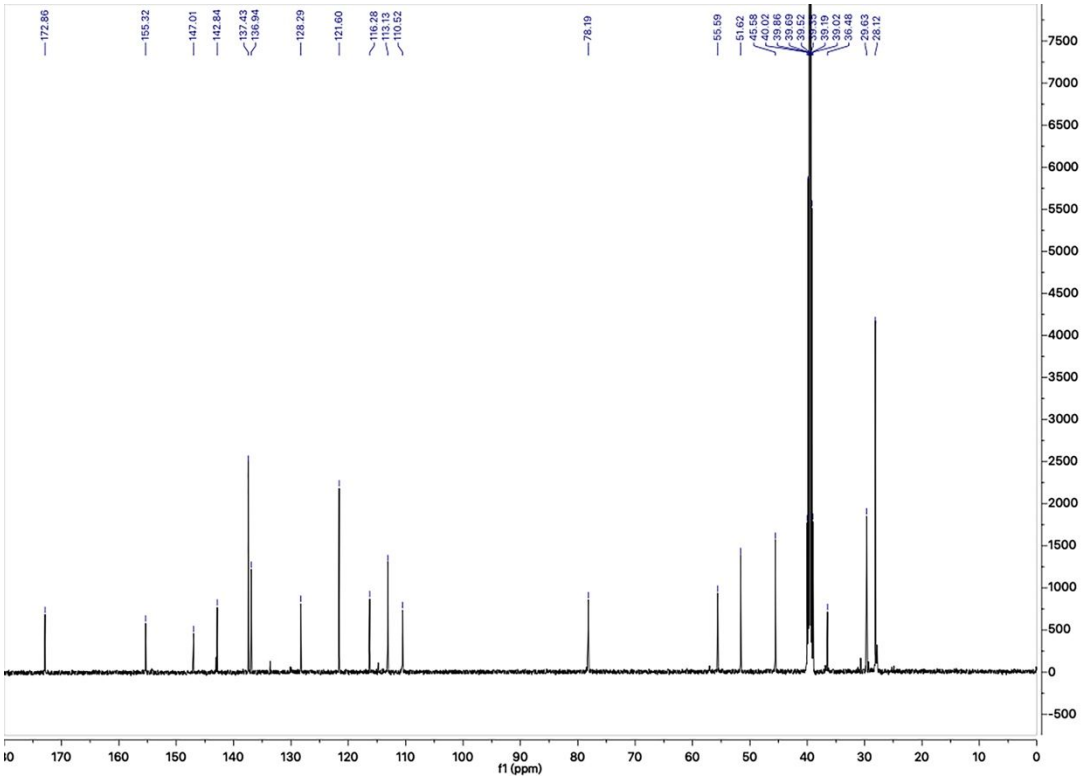


Figure S9 ^{13}C-NMR of **4b** in *d*-DMSO

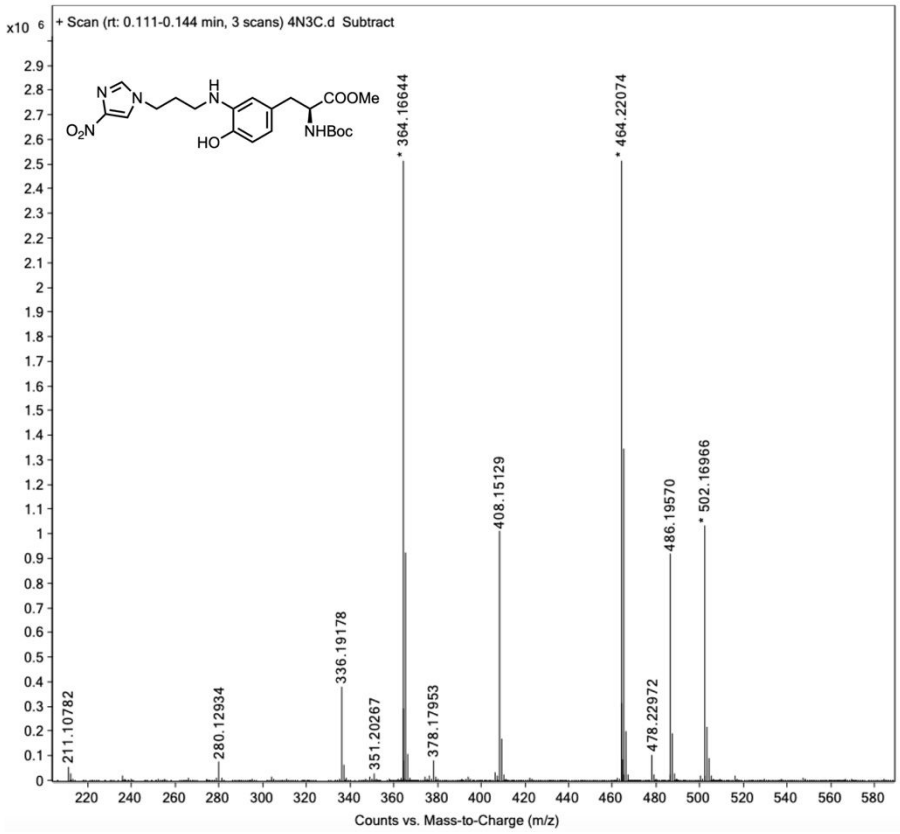


Figure S10 HRMS of **4b** (M+H)

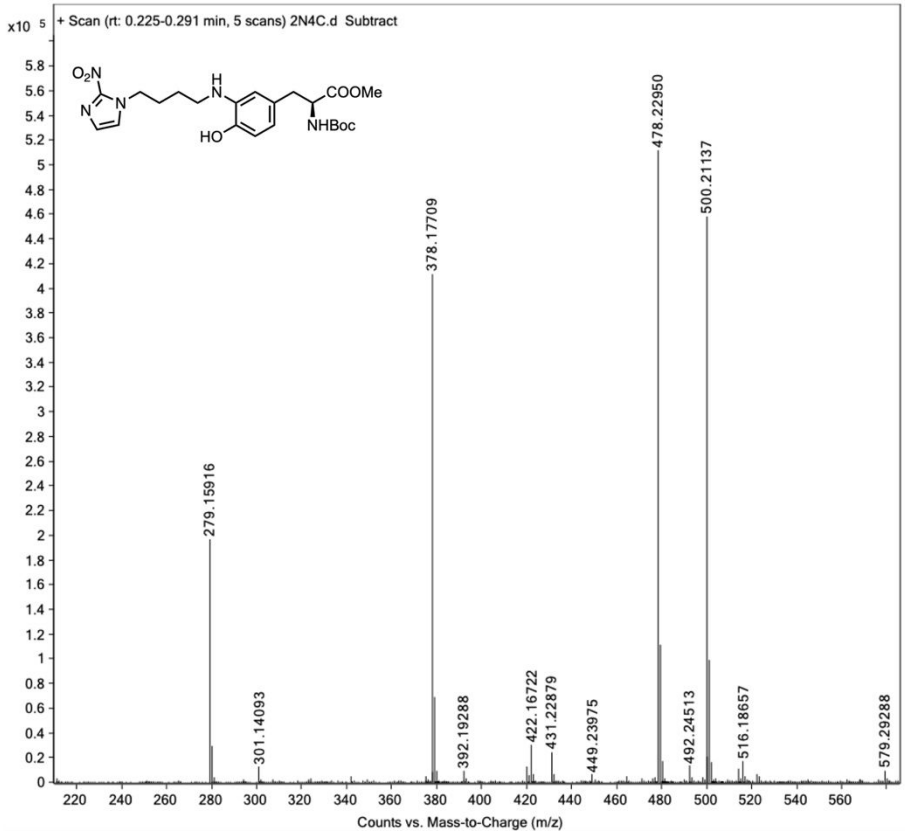


Figure S11 HRMS of **4c** (M+H)

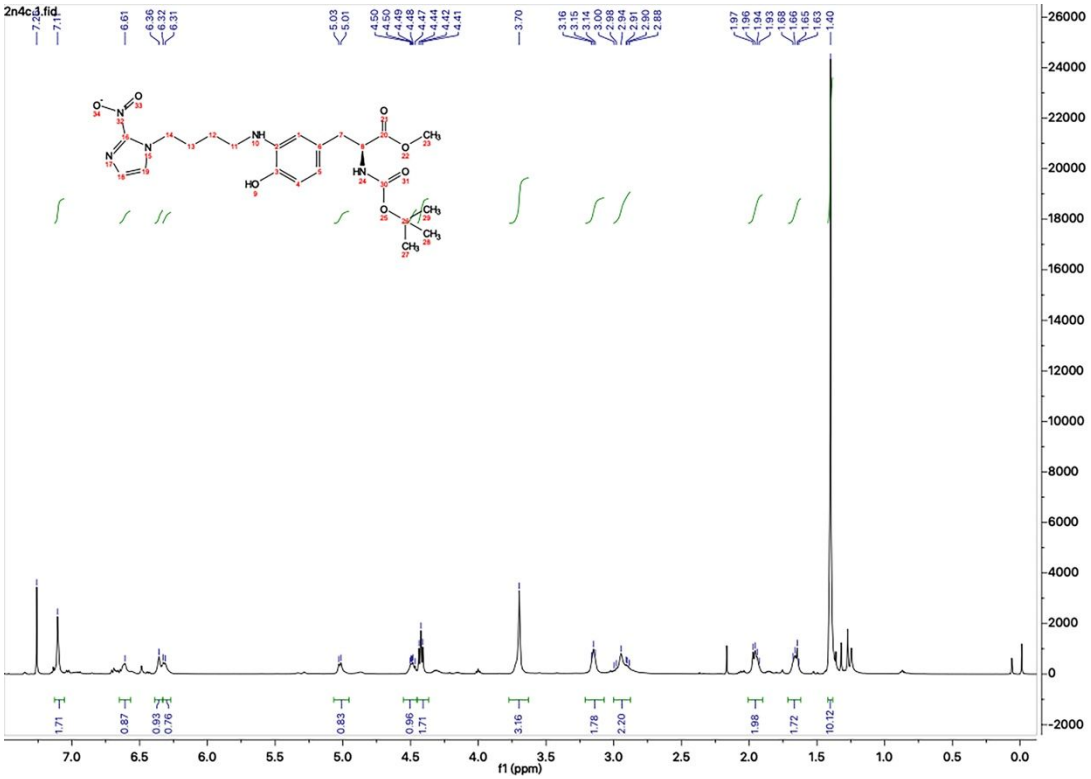


Figure S12 ^{1}H-NMR of **4c** in $CDCl_3$

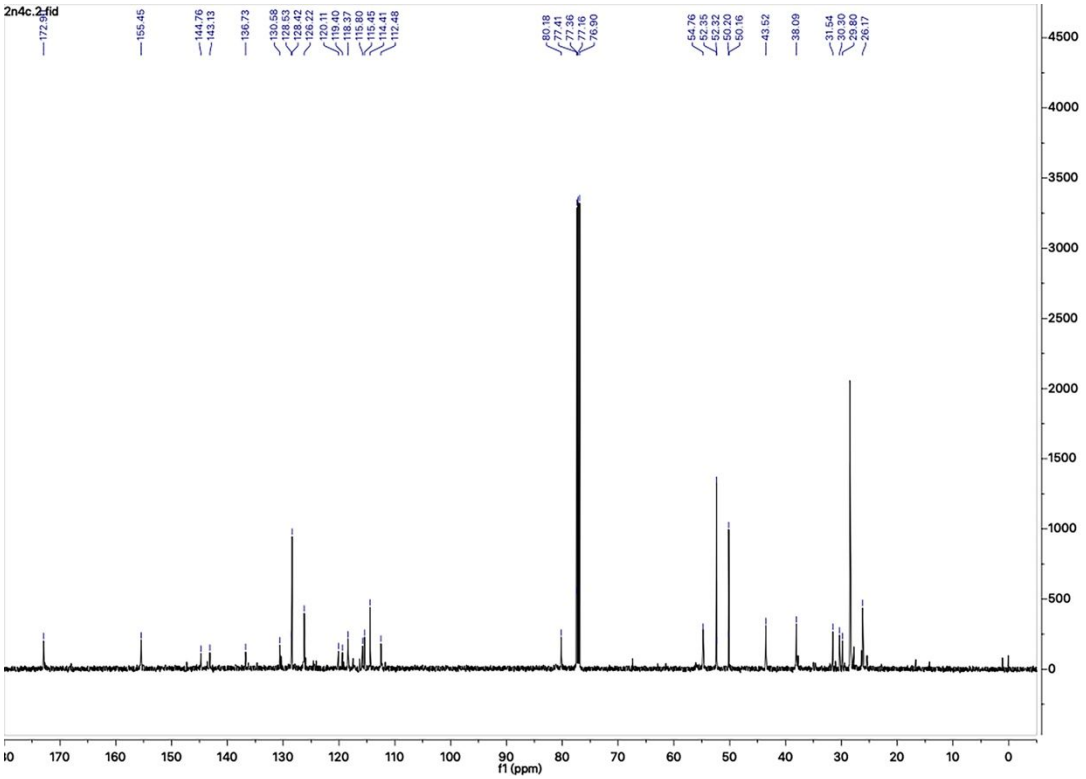


Figure S13 ^{13}C-NMR of **4c** in $CDCl_3$

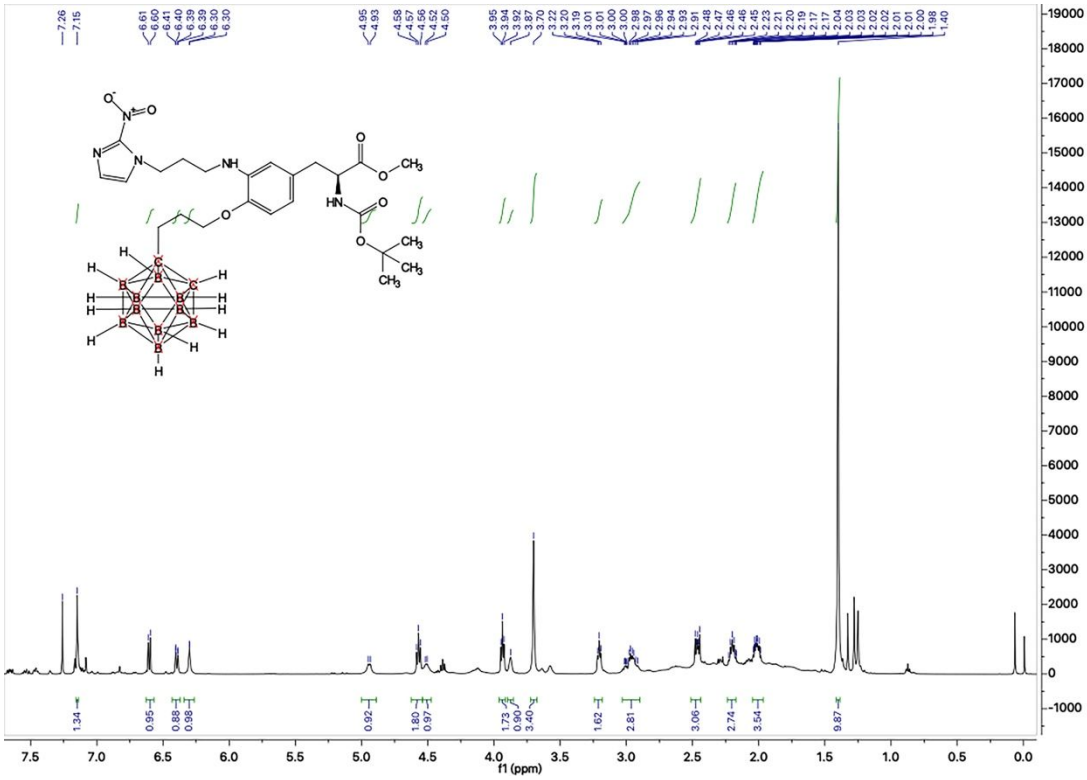


Figure S14 ^{1}H-NMR of **5a** in $CDCl_3$

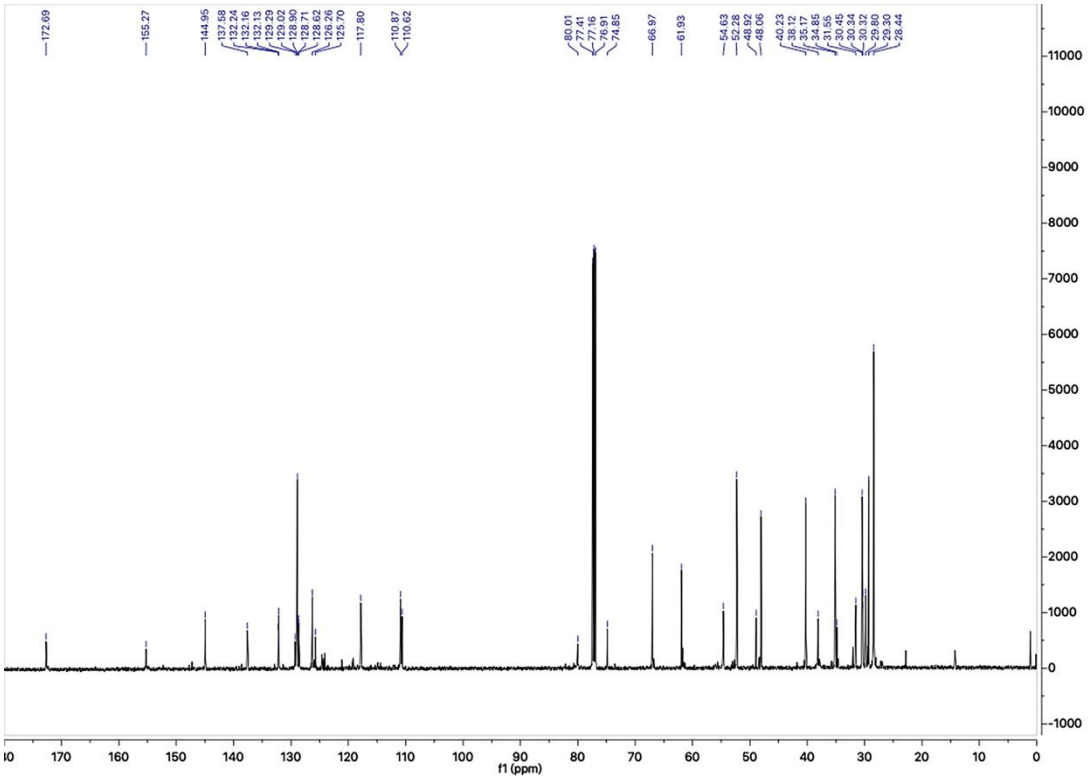


Figure S15 ^{13}C-NMR of **5a** in $CDCl_3$

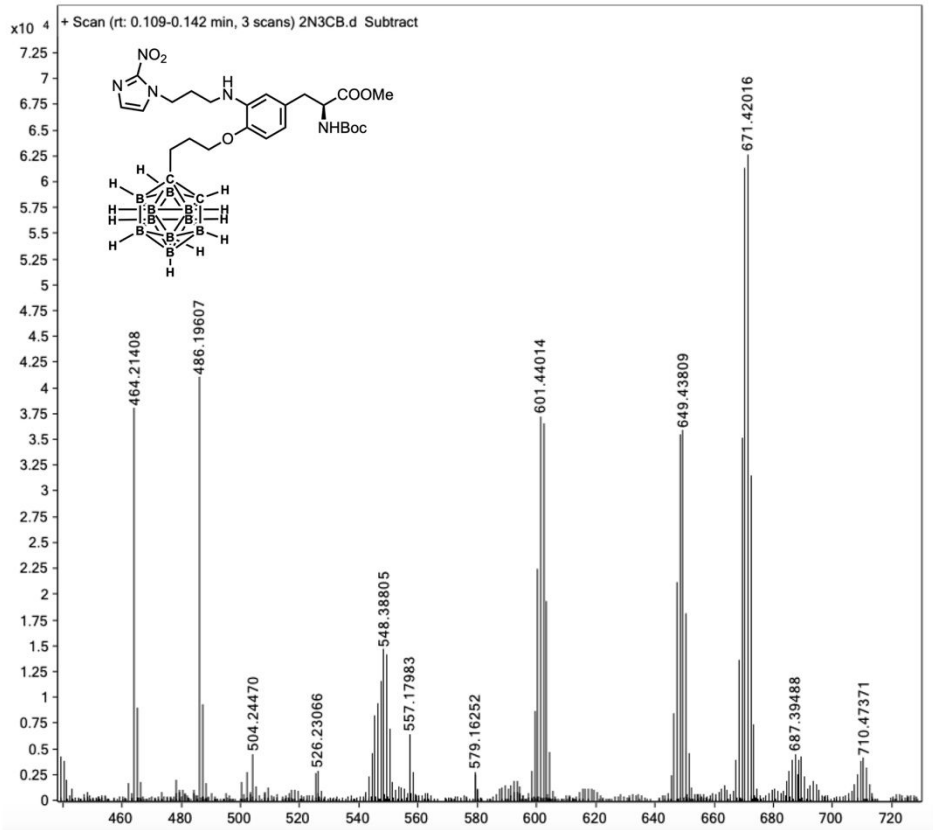


Figure S16 HRMS of **5a** (M+H, M+Na)

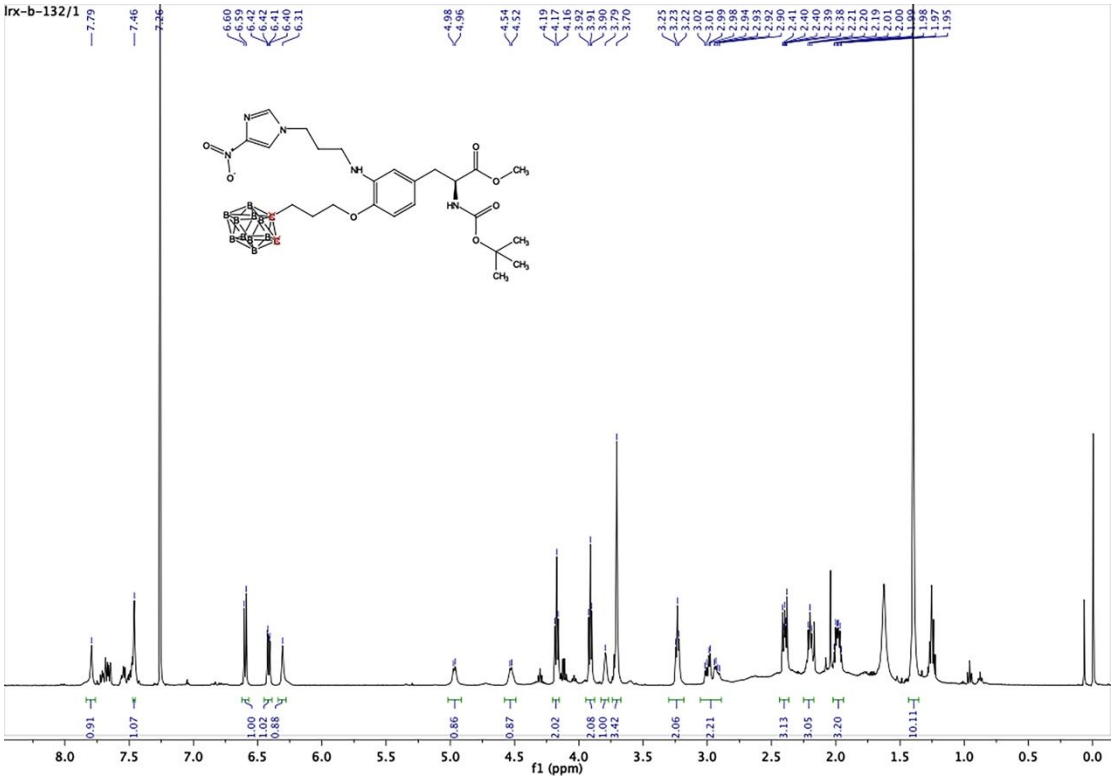


Figure S17 ^{1}H-NMR of **5b** in $CDCl_3$

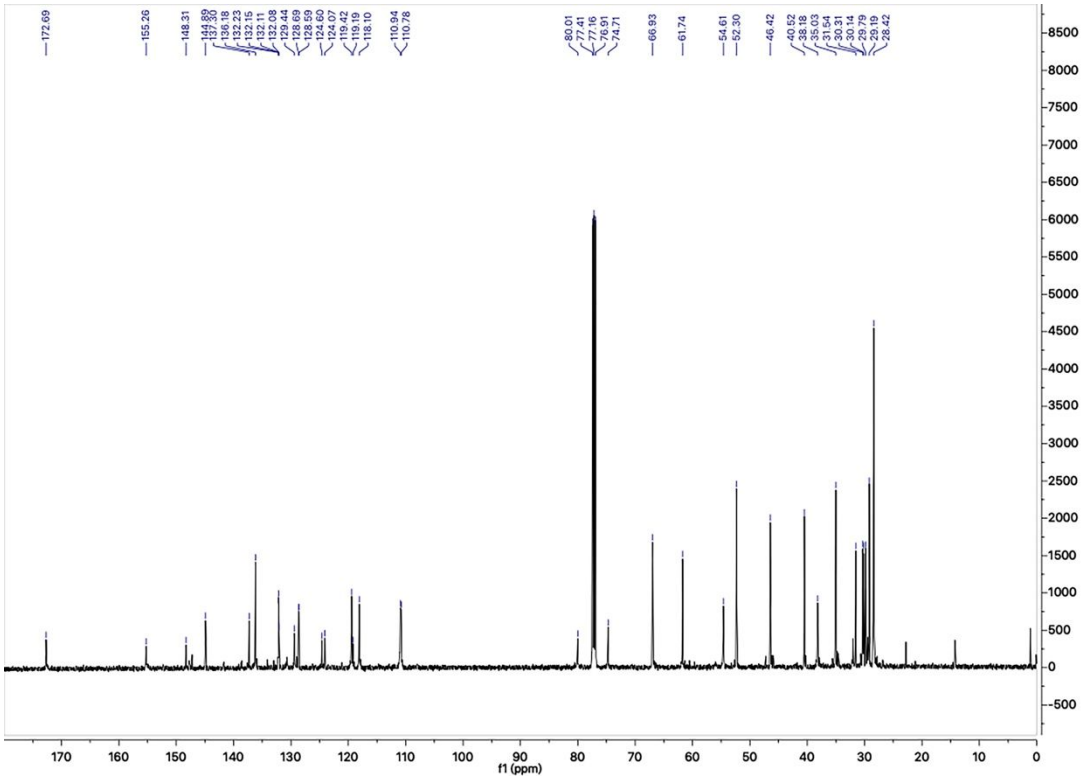


Figure S18 ^{13}C-NMR of **5b** in $CDCl_3$

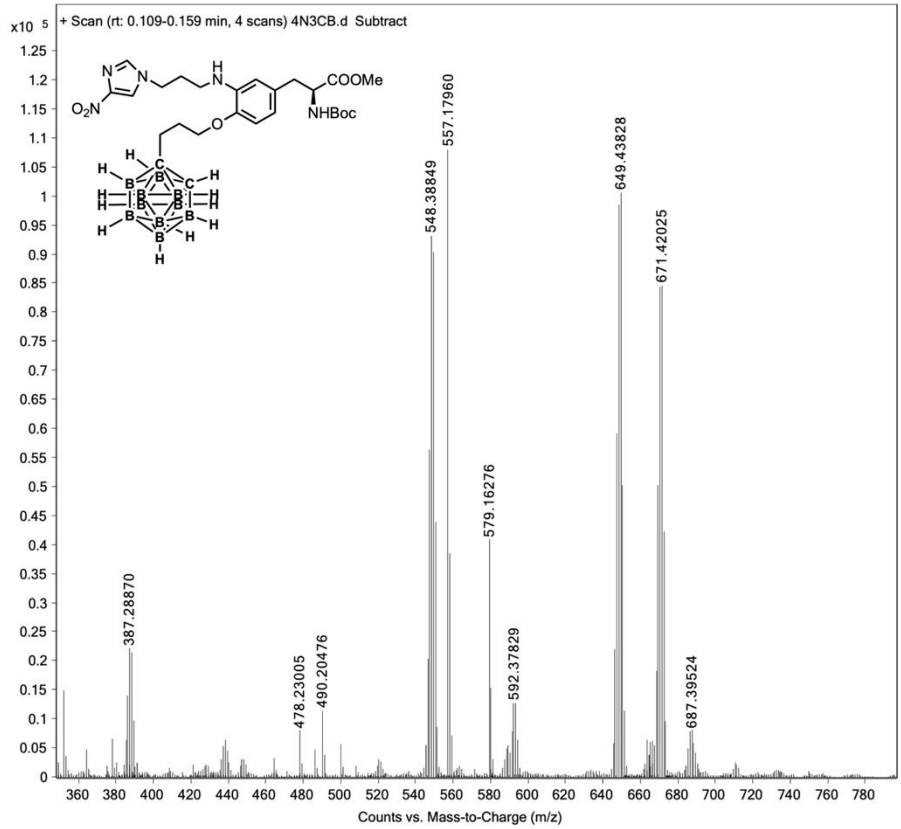


Figure S19 HRMS of **5b** (M+H, M+Na)

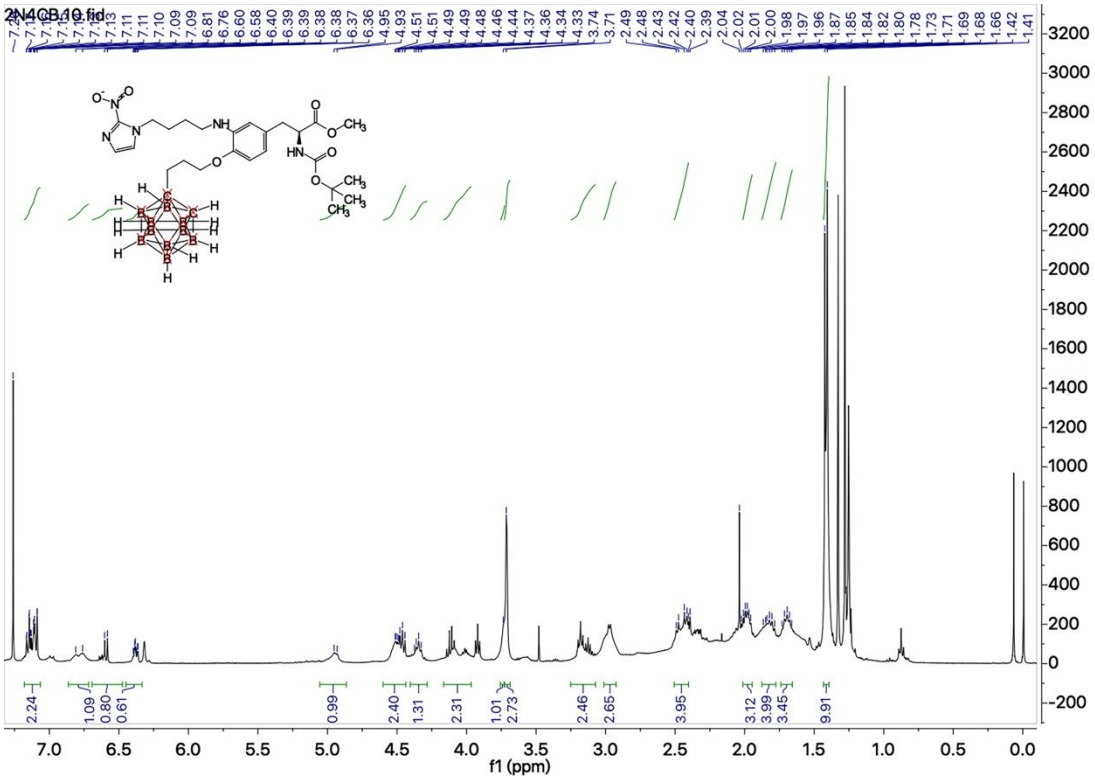


Figure S20 ^{1}H-NMR of 5c in $CDCl_3$

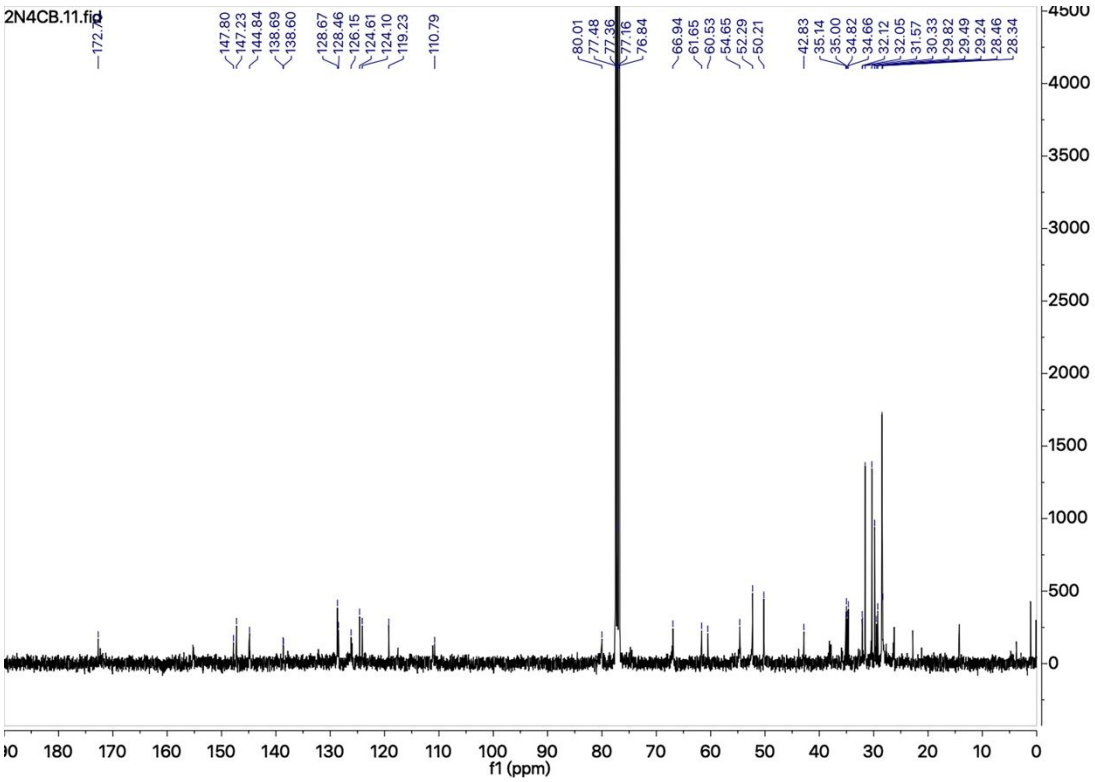


Figure S21 ^{13}C-NMR of 5c in $CDCl_3$

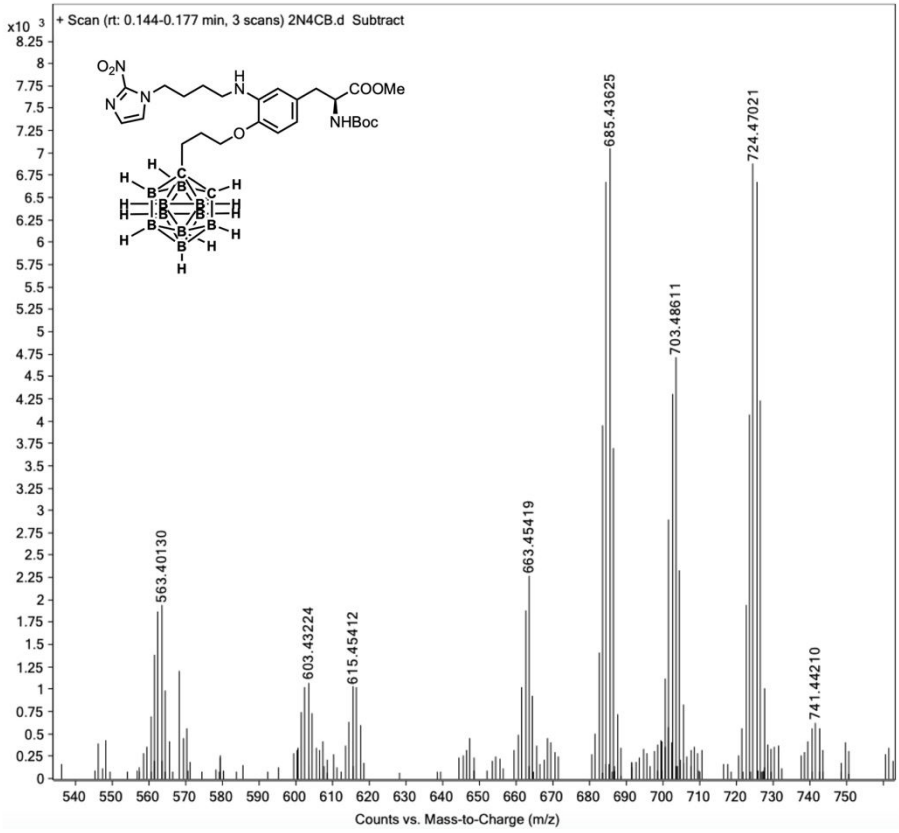


Figure S22 HRMS of **5c** (M+H, M+Na)

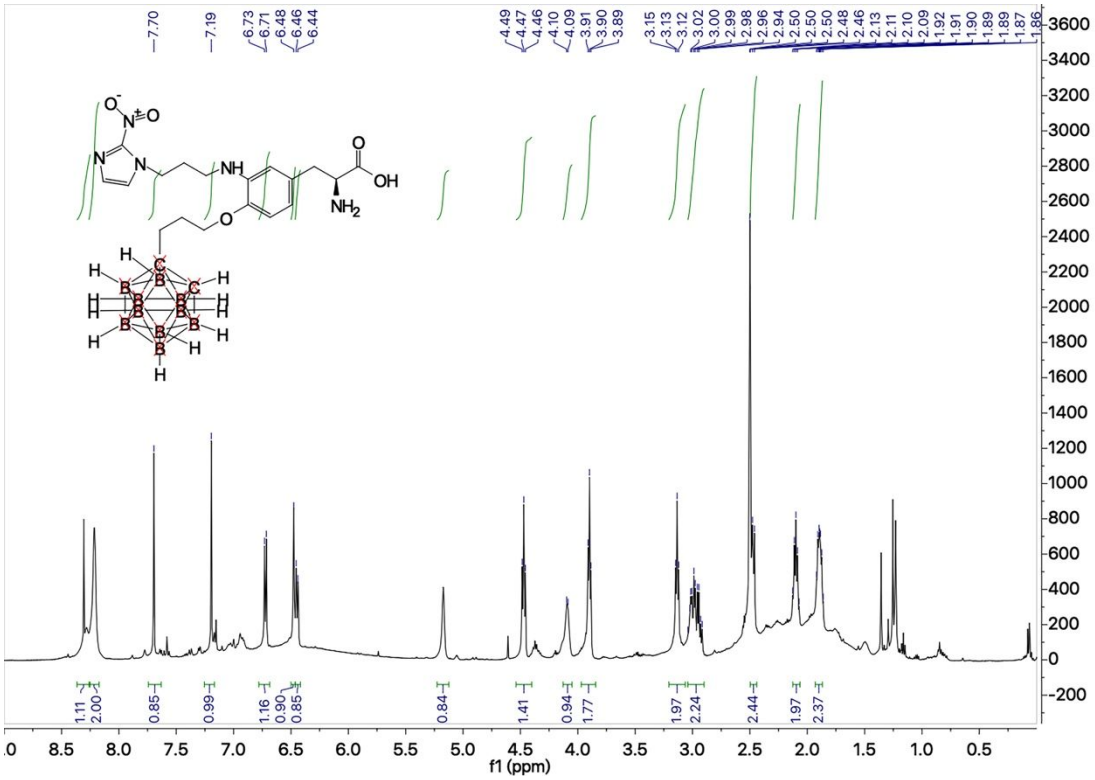


Figure S23 ^{1}H-NMR of **B139** in *d*-DMSO

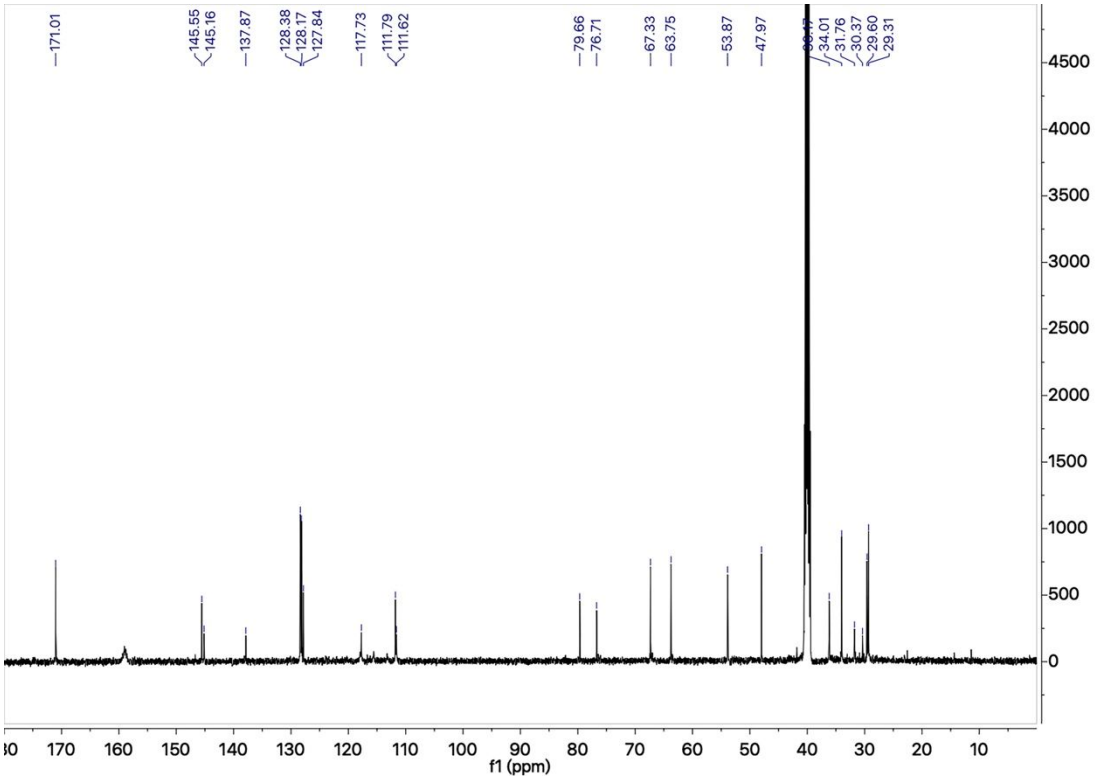


Figure S24 ^{13}C-NMR of **B139** in *d*-DMSO

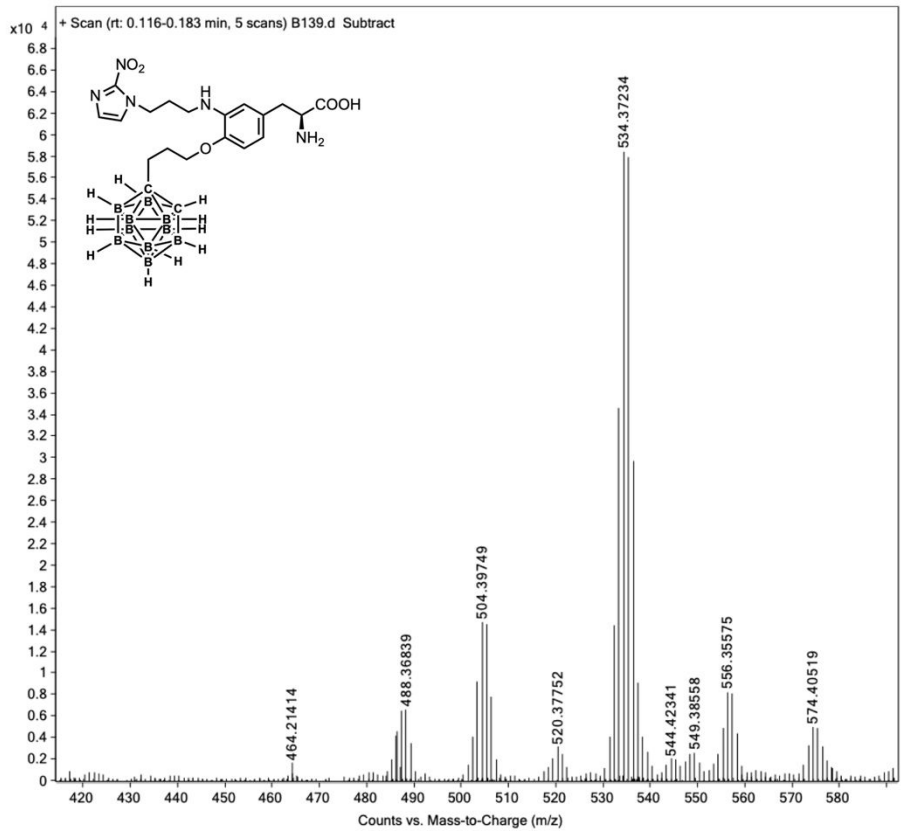


Figure S25 HRMS of **B139** (M+H)

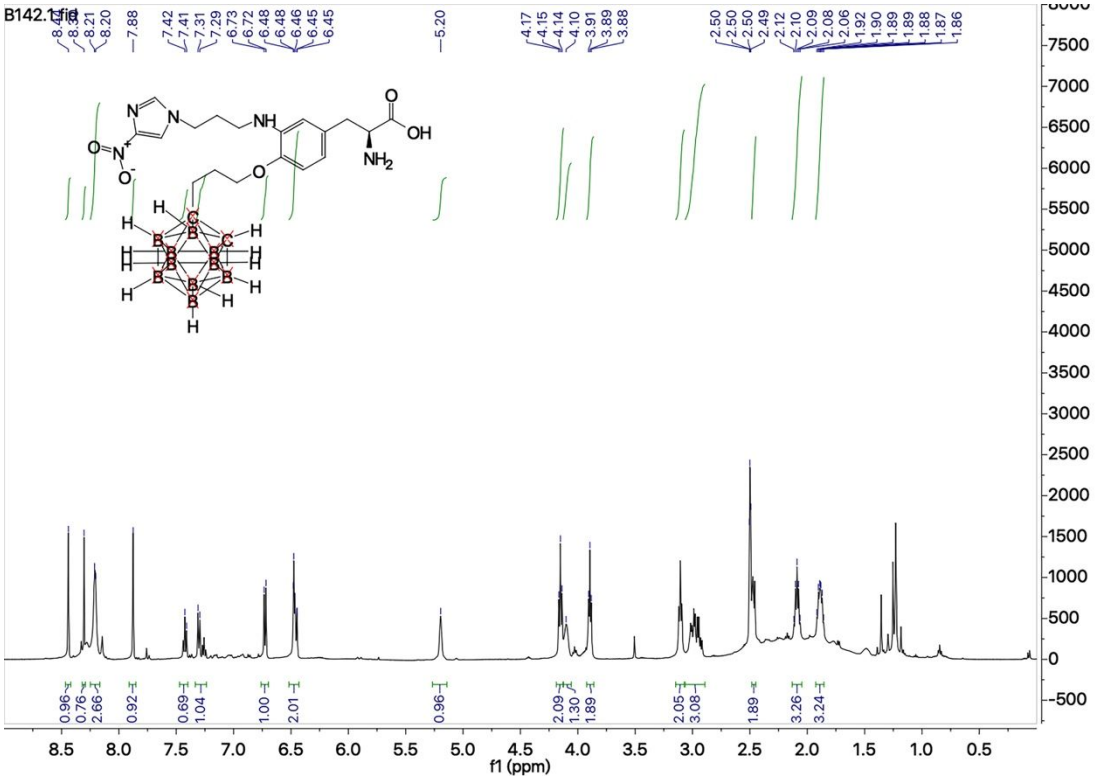


Figure S26 ^{1}H-NMR of **B142** in *d*-DMSO

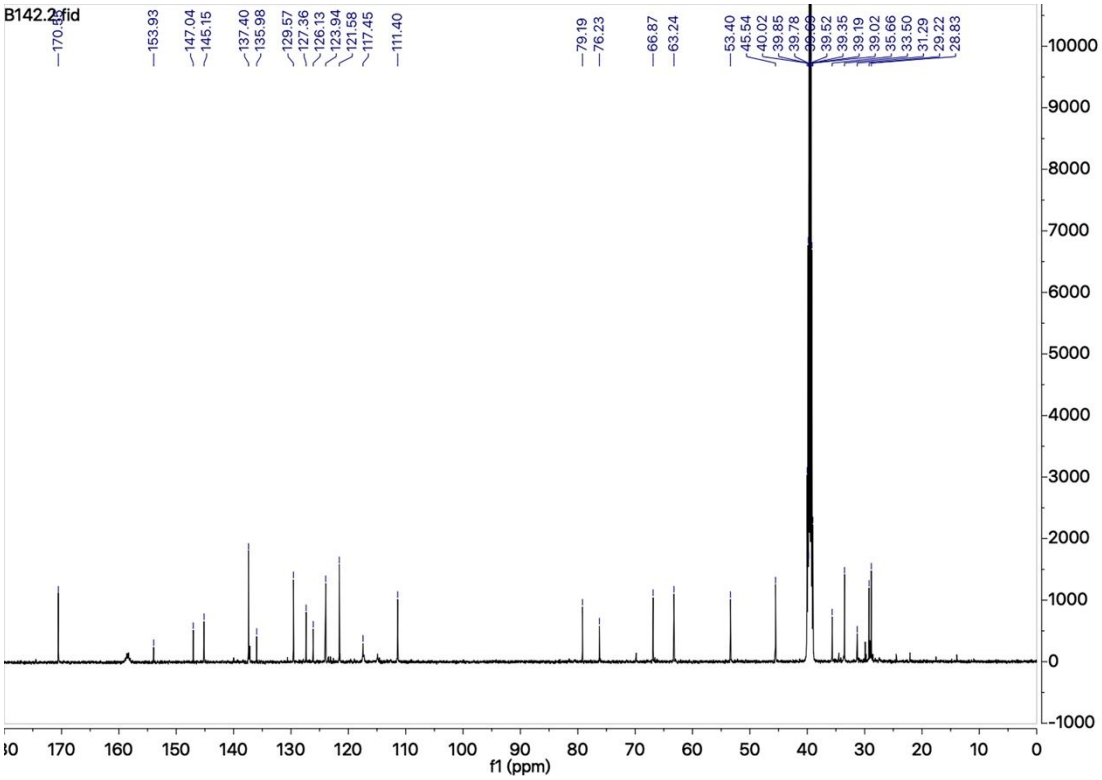


Figure S27 ^{13}C-NMR of **B142** in *d*-DMSO

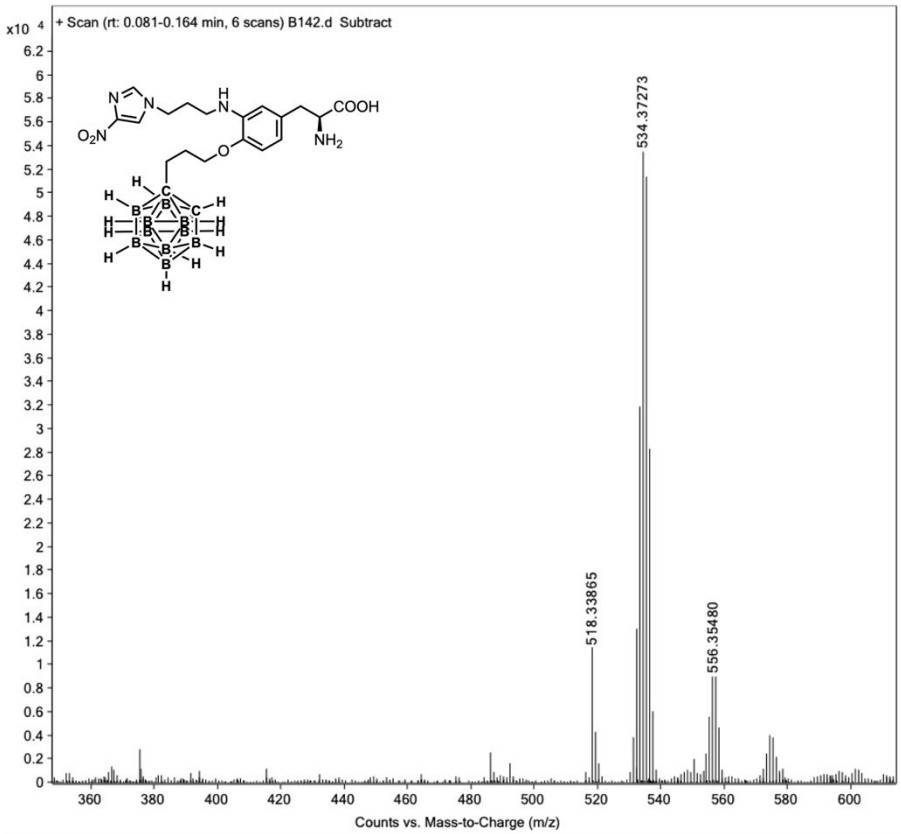


Figure S28 HRMS of **B142** (M+H)

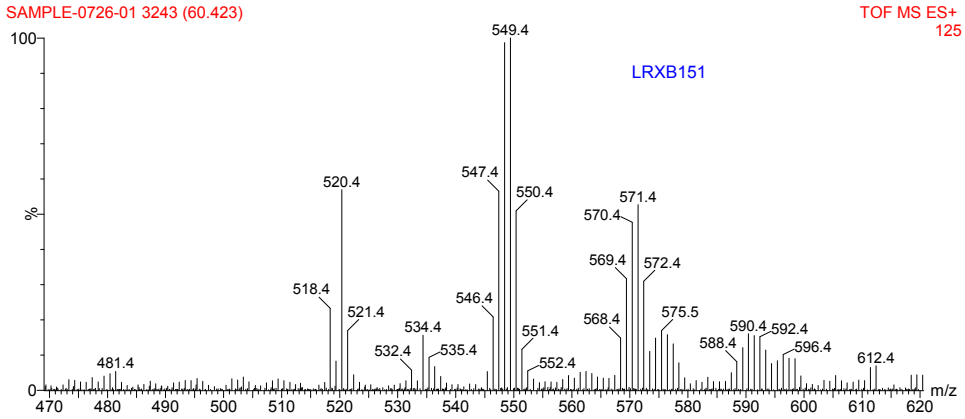


Figure S29 MS of **B151** (M+H, M+Na)

3. Standard Curve for detection boron using ICP-OES for Figure 7

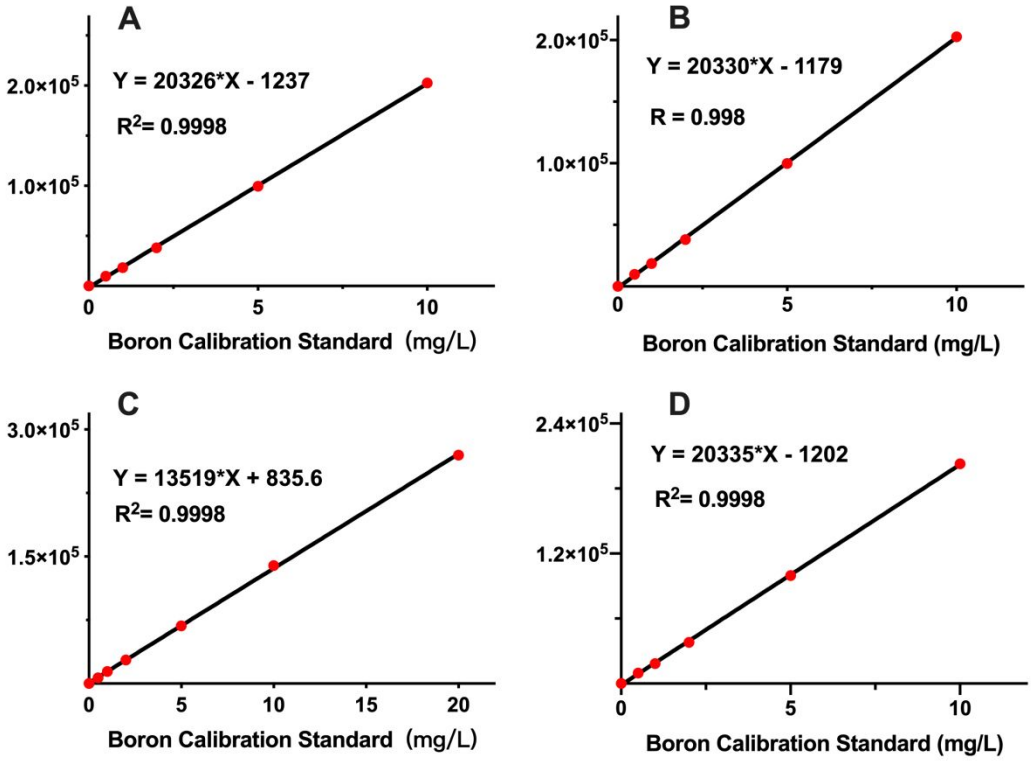


Figure S30 Standard Curve for detection boron using ICP-OES. (A) Standard Curve of Fig 7A; (B) Standard Curve of Fig 7B and Fig 7C; (C) Standard curve of Fig 7D, for U87 and MCF-7 cells; (D) Standard curve of Fig 7D, for SAS cell.

4. Time-dependence of uptake of B139 in different tumor cells

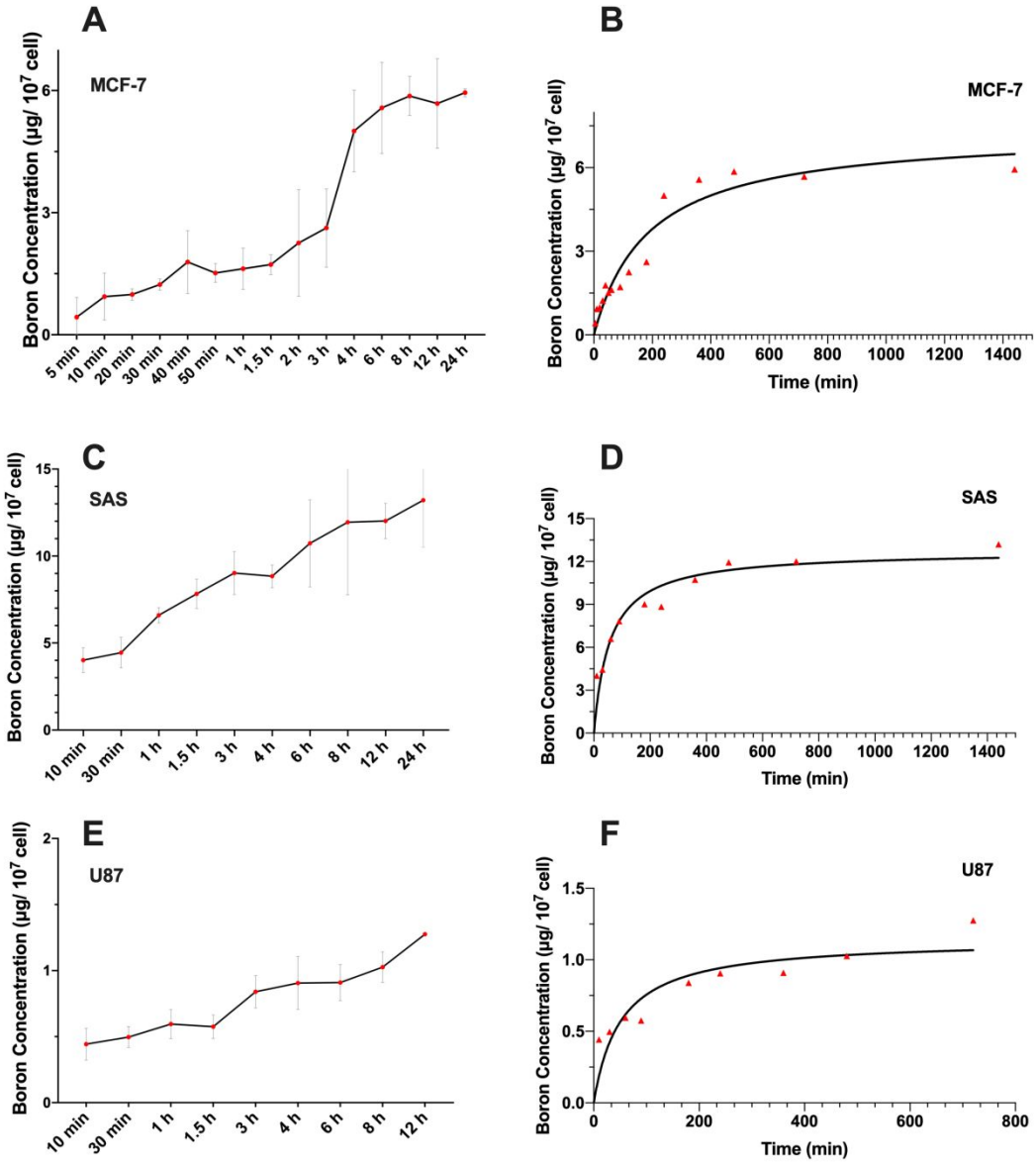


Figure S31 Time-Dependence of the uptake of B139 in tumor cells. (A), (C) and (E) are the boron uptake of B139 (300 μM) in MCF-7, SAS and U87 cells in different time. (B), (D) and (F) are the nonlinear curve fit of (A), (C) and (E).

5.

T**able S1** A brief literature overview of the dosage of BPA and BSH in the treatment

No.	Tumor-Bearing Mice	Dose of BPA	Dose of BSH	Ref
1	L929 (wt); L929 TK1(-)	100 μg B/ mouse[a]	/	1
2	Colon 26	/	30 mg B/kg	2
3	Colon 26	/	35 mg B/kg	3
4	D54 glioma	23.3 mg /kg[a]	/	4
5	U87	/	35 mg B/kg[b] (0.7 mg B/ mouse)	5
6	melanoma	/	200 mg/kg	6
7	ARO	350 mg	/	7
9	M2R melanoma	/	10 mg/kg[b], (0.2 mg B/ mouse)	8
10	SCCVII tumor	75 mg/kg	/	9

[a] Intratumoral injection

[b] The weight of one mouse is calculated as 20 g

The dosage of B139 for the treatment is 100 mg/kg, which equals to 18.7 mg B/kg or 0.37 mg B/ mouse, and was administered via tail vein injection.

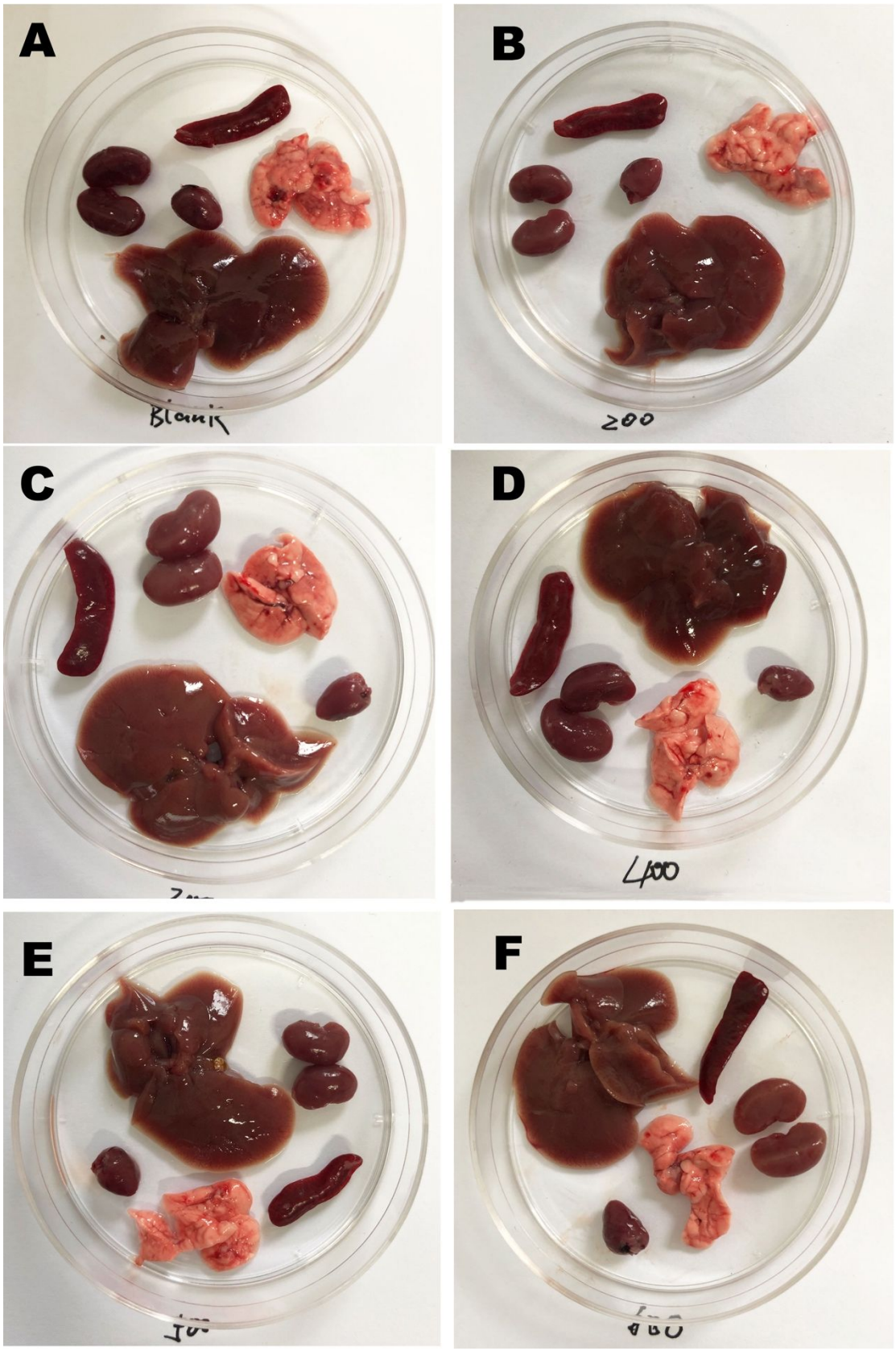


Figure S32 Organ anatomy after dissection of mice in different dose groups

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