Supporting Information for

Carborane pendants increase the potency of bis-substituted cyclam derivatives against *Mycobacterium tuberculosis*

Nicholas Smith,[a] Diana Quan,[b,c] Gayathri Nagalingam,[b,c] James A. Triccas,[b,c] Louis M. Rendina[a,d,e] and Peter J. Rutledge[a,e]

[a.] School of Chemistry, The University of Sydney, Sydney, NSW 2006, Australia

[b.] Sydney Institute of Infectious Diseases, Charles Perkins Centre, The University of Sydney, Sydney, NSW 2006, Australia

[c.] School of Medical Sciences, The University of Sydney, Sydney, NSW 2006, Australia

[d.] The University of Sydney Nano Institute (Sydney Nano), The University of Sydney, Sydney, NSW 2006 Australia

[e.] Corresponding authors: Professor Peter J. Rutledge, peter.rutledge@sydney.edu.au, +61 2 9351 5020 and Professor Louis M. Rendina, louis.rendina@sydney.edu.au, +61 2 9351 4781

Contents

1. General Procedures

Synthesis

Anhydrous solvents were collected from a PureSolv MD7 solvent purification system containing activated alumina and copper columns. 1,2-*closo*-carborane and *nido*-decaborane(14) were purchased from Boron Specialties LLC (US) and Katchem (Czech Republic), respectively, while all other commercially available reagents and solvents were purchased from Sigma Aldrich, Alfa Aesar, Combi-Blocks, and Merck. Automated flash column chromatography was performed on a Biotage Isolera Spektra One using Biotage SNAP KP-Sl cartridges filled with silica gel 60 LR, 0.04-0.06 mm (230-400 mesh ASTM). ^{1}H and $^{11}B\{^{1}H\}$ NMR spectra were recorded on Bruker Advance DPX 300 and 500 MHz spectrometers. Chemical shifts are reported relative to tetramethylsilane (0 ppm) or residual solvent resonance as internal standards. All low resolution ESI-MS and APCI-MS data were recorded on a Finnigan LCQ mass spectrometer. High resolution ESI-MS data were recorded on a Thermo Velos Pro Orbitrap mass spectrometer *via* syringe infusion on the Ion-Max Electrospray ionisation source. Infrared spectra were recorded on a Bruker ALPHA FT-IR spectrometer. Syntheses of compounds **7**[1], **11**[2], **12**[3] and **16**[4] have been reported previously and characterization data collected during this study for each of these compounds were in accordance with the reported literature values.

Bacterial Growth Conditions

Mycobacterial strain (*M. tuberculosis H37Rv*) was grown at 37°C to log phase ($OD_{600\ nm}$ between 0.6-0.8) in 7H9 media containing albumin, dextrose and catalase, 20% Tween 80 and 50% glycerol.

Resazurin Assay of Growth Inhibition

The minimal inhibitory concentration (MIC) of each compound was determined using a modified resazurin viability assay. All compounds were initially prepared at 10 mM stock solutions in 100% DMSO and then adjusted to the required concentration in diluent (0.1% DMSO). Compounds (0.1-100 μM) were added to wells in 2-fold dilutions and incubated with bacteria previously diluted to $OD_{600\ nm}$ of approximately 0.001. Compounds and bacteria were incubated in complete 7H9 media at 37°C in a humidified 5% CO_2 incubator for 4 days. Resazurin and Tween 80 (1:1) was then added and incubated at 37°C for a further 24 hours. MICs were calculated by detection of fluorescence at 590 nm using a FLUOstar Omega microplate reader (BMG, Labtech).

Safety note: Decaborane(14), sodium azide and organic azides are hazardous and potentially explosive materials. Only small amounts of these materials should be prepared, and these should be handled with caution.

2. Synthesis and Characterisation Data

*Di-tert-butyl 4,11-bis(closo-1,2-carboran-1-ylmethyl)-1,4,8,11-tetrazacyclotetradecane-1,8-dicarboxylate (**8**)*

A solution of compound **7** (100 mg, 0.21 mmol) in toluene (5 mL) was added dropwise to a solution of *nido*-decaborane(14) (39 mg, 0.32 mmol) and CH_3CN (0.1 mL) in toluene (20 mL). The reaction mixture was heated to reflux and stirred for 24 h. The reaction was quench with MeOH (10 mL) and allowed to stir for a further 24 h. The crude mixture was concentrated under reduced pressure and purified by column chromatography with 10% NH_3 in MeOH and DCM (1:9) to obtain product **8** as a yellow powder (90 mg, 60% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10-3.25 (br m, 20H), 1.47 (s, 18H), 1.73 (t, 4H, J 7.3), 2.57 (t, 4H, J 6.6), 2.65 (t, 4H, J 6.1), 3.04-3.20 (m, 12H), 3.80 (s, 2H). ^{11}B{^{1}H} NMR (500 MHz, $CDCl_3$): δ = -2.52 (s, 2B), -5.04 (s, 2B), -9.18 (s, 4B), -11.54 (s, 4B), -13.00 (s, 8B). LRMS (ESI+) $[M+Na]^+$ *m/z* = 736.76.

*1,8-Bis(closo-1,2-carboran-1-ylmethyl)-1,4,8,11-tetrazacyclotetradecane·2HCl (**9**)*

Hydrochloric acid (4.0 M in dioxane, 2.0 mL, 2.0 mmol) was added to a solution of compound **8** (35 mg, 0.049 mmol) in dioxane (5 mL) and stirred at room temperature for 4 hours. The solvent was evaporated off and the crude material was triturated with ice-cold ethyl acetate (2 x 10 mL) to obtain product **9** as a colourless powder (28 mg, 97% yield). ^{11}B{^{1}H} NMR (500 MHz, DMSO): δ = -2.70 (s, 2B), -4.92 (S, 2B), -9.37 (S, 4B), -12.07 (S, 4B), -12.74 (S, 8B). FTIR: ν_{max} cm^{-1} 2985, 2749, 2583, 2342, 1727, 1436, 1140, 1068, 898, 721. LRMS (ESI+) $[M-2Cl-H]^+$ *m/z* = 514.63. HRMS (ESI+) $[M-2Cl-H]^+$: *m/z calcd for* $C_{16}H_{49}B_{20}N_4^+$ 514.59222 *found* 514.59206.

Cesium 1,8-bis(7,8-dicarba-nido-undecaborate-7-ylmethyl)-1,4,8,11-tetrazacyclotetradecane (Cs_2·**10**)*

A mixture of CsF (42 mg, 0.28 mmol) and **9** (32 mg, 0.06 mmol) in EtOH (10 mL) was heated to reflux under nitrogen and stirred for 24 h. The solvent was evaporated off and the crude material was dissolved in acetone (30 mL). Insoluble borate impurities were removed by centrifugation and the supernatant was concentrated under reduced pressure to obtain compound Cs_2·**10** as a colourless powder (39 mg, 95% yield). ^{1}H NMR (500 MHz, acetone-d_6): δ = -3.12 (br s, 2H), -0.23-3.76 (br m, 16H), 1.16 (s, 2H), 1.65-1.75 (m, 4H), 2.13-2.30 (m, 2H), 2.42-2.53 (m, 2H), 2.59 (s, 2H), 2.68 (d, 2H, J 12.2), 2.76 (d, 2h, J 13.0), 2.83-2.98 (m, 6H), 3.02-3.07 (m, 2H), 3.14-3.26 (m, 2H). ^{11}B{^{1}H} NMR (500 MHz, acetone-d_6): δ = -10.16 (s, 2B), -12.35 (S, 2B), -13.39 (S, 2B), -15.32 (S, 2B), -19.74 (S, 4B), -20.62 (S, 2B), -32.27 (S, 2B), -36.67 (S, 2B). FTIR: ν_{max} cm^{-1} 2920, 2835, 2502, 1587, 1451, 1364, 1117, 1023, 974. LRMS (ESI-) $[M-2Cs+H]^-$ *m/z* = 492.56. HRMS (ESI-) $[M-2Cs+H]^-$: *m/z calcd for* $C_{16}H_{49}B_{18}N_4^-$ 492.57468 *found* 492.57480.

*Di-tert-butyl 4,11-bis(2-(closo-1,2-carboran-1-ylmethyl-1,2,3-triazol-1-yl)ethyl)-1,4,8,11-tetraazacyclo-tetradecane-1,8-dicarboxylate (**13**)*

A mixture of $CuSO_4$·$5H_2O$ (3.5 mg, 0.014 mmol) and sodium ascorbate (3.5 mg, 0.018 mmol) in H_2O (5 mL) was added to a mixture of **11** (80 mg, 0.440 mmol) and **12** (29 mg, 0.055 mmol) in THF (10 mL) and stirred at reflux under nitrogen for 16 h. The reaction mixture was quenched with the addition of NH_4Cl (sat, 5 mL) and the crude product was extracted with DCM (2 x 10 mL). Organic phases were combined, dried over $MgSO_4$

and concentrated under reduced pressure. The product was isolated by column chromatography with 10% NH_3 in MeOH and DCM (1:9) to obtain product **13** as a yellow oil (39 mg, 81% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.36-3.45 (m, 20H), 1.45 (s, 18H), 1.59 (qn, 4H, J 7.7), 2.47 (t, 4H, 6.3), 2.54-2.63 (m, 4H), 2.91 (t, 4H, J 6.1), 3.09-3.23 (m, 8H), 3.66 (s, 4H), 3.92 (s, 2H), 4.36 (t, 4H, J 6.0), 7.52 (s, 2H). ^{11}B{^{1}H} NMR (500 MHz, $CDCl_3$): δ = -1.95 (s, 3B), -5.43 (s, 2B), -9.34 (s, 5B), -10.95 (s, 4B), -12.60 (s, 6B). FTIR: ν_{max} cm^{-1} 2924, 2586, 1684, 1367, 1246, 1156, 1089, 1020, 913, 774, 532. LRMS (ESI+) $[M+H]^+$ *m/z* = 904.85, $[M+Na]^+$ *m/z* = 926.81.

*1-8-Bis(2-(closo-1,2-carboran-1-ylmethyl-1,2,3-triazol-1-yl)ethyl)-1,4,8,11-tetraazacyclotetradecane ·2HCl (***14***)*

HCl (4.0 M in dioxane, 2.0 mL, 2.0 mmol) was added to a solution of **13** (35 mg, 0.049 mmol) in dioxane (5 mL) and the resulting mixture stirred at room temperature for 4 h. The solvent was evaporated and the crude material triturated with ice-cold ethyl acetate (2 x 10 mL) to obtain product **14** as a white powder (24 mg, 82% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.37-3.67 (br m, 20H), 1.91 (s, 6H), 2.65 (s, 4H), 2.87 (s, 4H), 3.03 (s, 8H), 3.17 (s, 6H), 4.57 (s, 4H), 5.17 (s, 2H), 8.20 (s, 2H), 8.74 (s, 4H). ^{11}B{^{1}H} NMR (500 MHz, DMSO): δ = -3.21 (s, 2B), -6.03 (s, 2B), -9.71 (s, 4B), -11.81 (s, 6B), -12.80 (s, 6B). FTIR: ν_{max} cm^{-1} 2934, 2580, 1435, 1062, 778, 721. LRMS (ESI+) $[M-2Cl-H]^+$ *m/z* = 704.76. HRMS (ESI+) $[M-2Cl-H]^+$: *m/z calcd for* $C_{24}H_{59}B_{20}N_{10}^+$ 703.69252 *found* 703.69320.

Cesium 1,8-bis(2-(7,8-dicarba-nido-undecaborate-7-ylmethyl-1,2,3-triazol-1-yl)ethyl)-1,4,8,11-tetraazacyclotetradecane (Cs_2·**15***)*

A mixture of CsF (20 mg, 0.126 mmol) and **14** (30 mg, 0.039 mmol) in EtOH (10 mL) was heated to reflux under nitrogen and stirred for 24 h. The solvent was evaporated off and the crude material was dissolved in acetone (30 mL). Insoluble borate impurities were removed by centrifugation and the supernatant was concentrated under reduced pressure to obtain compound Cs_2·**15** as a colourless powder (33 mg, 89% yield). ^{1}H NMR (500 MHz, acetone-d_6): δ = -2.87 (br s, 2H), -0.38-3.43 (br m, 16H), 1.74 (s, 6H), 2.09 (s, 2H), 2.15 (s, 2H), 2.64-2.68 (m, 4H), 2.85 (s, 4H), 2.92-2.97 (m, 8H), 3.03 (d, 6H, J15.4), 4.61-4.64 (m, 4H), 7.86 (s, 2H). ^{11}B{^{1}H} NMR (500 MHz, acetone-d_6): δ = -10.34 (s, 2B), -10.95 (s, 2B), -13.54 (s, 2B), -15.99 (s, 2B), -18.93 (s, 4B), -21.83 (s, 2B), -33.24 (s, 2B), -36.85 (s, 2B). LRMS (ESI-) $[M-2Cs+H]^-$ *m/z* = 682.85. HRMS (ESI-) $[M-2Cs+H]^-$: *m/z calcd for* $C_{24}H_{59}B_{18}N_{10}^-$ 682.67138 *found* 682.67148.

*(E)-2-(5-Bromopent-3-en-1-yl)-1,2-closo-carborane (***17***)*

A solution of **16** (219 mg, 1.10 mmol) in anhydrous DCM (5 mL) was added dropwise to a mixture of Grubbs 2nd generation catalyst (36 mg, 4 mol%, 0.04 mmol) and allyl bromide (0.2 mL, 280 mg, 2.31 mmol) in anhydrous DCM (10 mL). The reaction mixture was stirred at room temperature under nitrogen for 4 h. The crude mixture was concentrated under reduced pressure and the product was isolated by column chromatography with hexane (100%) to obtain product **17** as a clear oil (119 mg, 37% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04-3.28 (m, 10H), 2.17-2.36 (m, 4H), 3.58 (s, 1H), 3.87-3.93 (m, 2H), 5.61-5.85 (m, 2H).

FTIR: ν_{max} cm^{-1} 3061, 2959, 2570, 1662, 1449, 1202, 962, 721, 589. LRMS (APCI+) $[M\text{-}Br+H]^+$ *m/z* = 211.23 (debromination). HRMS (APCI+) $[M\text{-}Br+H]^+$: *m/z calcd for* $C_7H_{19}B_{10}^+$ 212.24844 *found* 212.24848.

*1,8-Bis((E)-5-closo-1,2-carboran-1-ylpent-2-en-1-yl)-1,4,8,11-tetraazatetradecane (***19***)*

A solution of **17** (119 mg, 0.41 mmol) in anhydrous CH_3CN (5 mL) was added to a solution of bridged cyclam **18** (34 mg, 0.15 mmol) in anhydrous CH_3CN (10 mL). The reaction mixture was stirred at room temperature for 24 h, monitored by TLC and ESI-MS. The precipitate was filtered and washed with ice cold CH_3CN (2 x 20 mL). The crude product was then dissolved in MeOH (20 mL) and stirred with NaOH (2.5 M, 1 mL, 1 mmol) at room temperature for an additional 1 h. The crude mixture was concentrated under reduced pressure and the product was isolated by column chromatography with 10% NH_3 in MeOH and DCM (1:9) to obtain product **19** as a colourless powder (70 mg, 74% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20-3.40 (br m, 20H), 1.33 (s, 2H), 1.61 (p, 2H, J 3.0), 1.86-2.00 (m, 6H), 2.21-2.29 (m, 4H), 2.41 (t, 2H, J 4.2), 2.58 (t, 4H, J 5.2), 2.66-2.77 (m, 4H), 2.88-2.98 (m, 6H), 3.15-3.21 (m, 2H), 3.41 (t, 2H, J 6.0), 3.99 (s, 2H), 5.47-5.66 (m, 4H). FTIR: ν_{max} cm^{-1} 2926, 2588, 1672, 1456, 1183, 1138, 1020, 918, 722. LRMS (ESI+) $[M]^{2+}$ *m/z* = 323.85 (bridged). LRMS (ESI+) $[M+H]^+$ *m/z* = 622.76 (free base). HRMS (ESI+) $[M+H]^+$: *m/z calcd for* $C_{24}H_{61}B_{20}N_4^+$ 621.68985 *found* 621.68993.

Cesium 1,8-bis((E)-7,8-dicarba-nido-undecaborate-7-ylpent-2-en-1-yl)-1,4,8,11-tetraazacyclotetradecane (Cs_2·**20***)*

A mixture of CsF (20 mg, 0.126 mmol) and **19** (30 mg, 0.048 mmol) in EtOH (10 mL) was heated to reflux under nitrogen and stirred for 24 h. The solvent was evaporated off and the crude material was dissolved in acetone (30 mL). Insoluble borate impurities were removed by centrifugation and the supernatant was concentrated under reduced pressure to obtain compound Cs_2·**20** as a colourless powder (40 mg, 96% yield). ^{1}H NMR (500 MHz, Acetone-d_6): δ = -2.65 (br s, 2H), -0.34-2.75 (br m, 16H), 1.19 (s, 2H), 1.49-1.56 (m, 2H), 1.65 (s, 2H), 1.67-1.75 (m, 6H), 2.14-2.23 (m, 4H), 2.49-2.56 (m, 8H), 2.64 (dt, 6H, J 15.5, 5.3), 3.07 (d, 4H, J 6.6), 5.48 (dt, 2H, J 15.3, 6.7), 5.61 (dt, 2H, J 15.3, 6.7). ^{11}B{^{1}H} NMR (500 MHz, Acetone-D6): δ = -11.15 (s, 5B), -14.20 (s, 2B), -17.33 (s, 2B), -18.48 (s, 4B), -22.40 (s, 1B), -33.54 (s, 2B), -37.45 (s, 2B). FTIR: ν_{max} cm^{-1} 2914, 2830, 2506, 1615, 1448, 1354, 1025, 972. LRMS (ESI-) $[M\text{-}2Cs+H]^-$ *m/z* = 600.74. HRMS (ESI-) $[M\text{-}2Cs+H]^-$: *m/z calcd for* $C_{24}H_{61}B_{18}N_4^-$ 600.66857 *found* 600.66881.

3. ^{1}H and $^{11}B\{^{1}H\}$ NMR Spectra of Novel Compounds

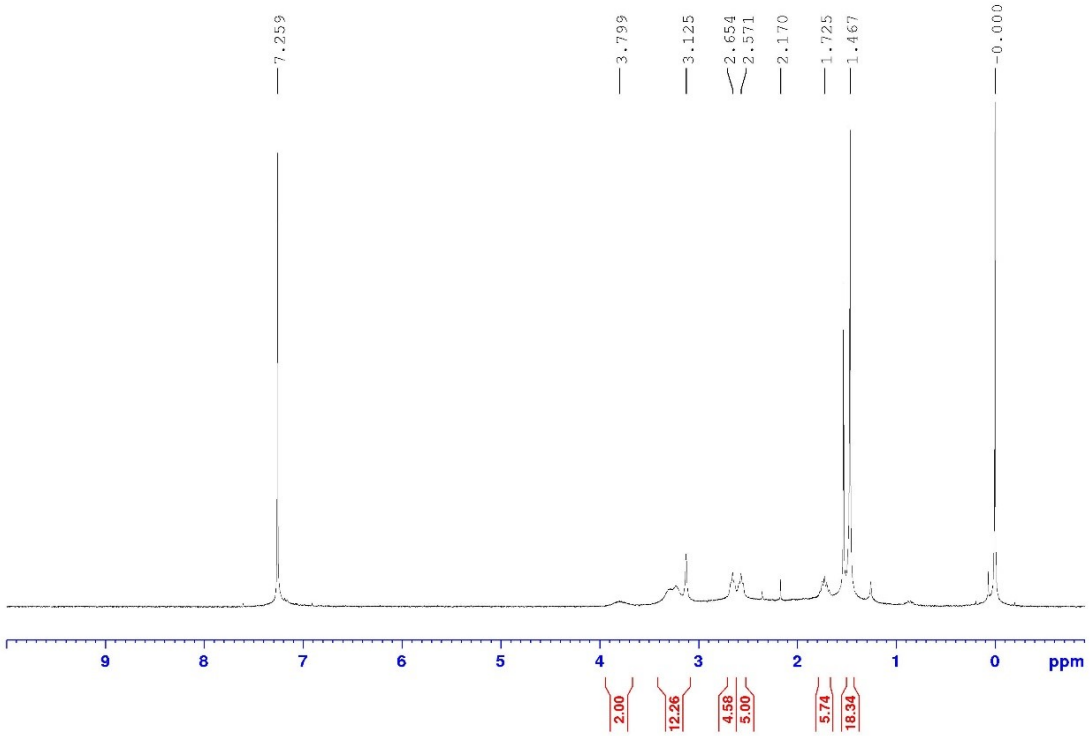

Figure S1. ^{1}H NMR spectrum of compound **8** in $CDCl_3$.

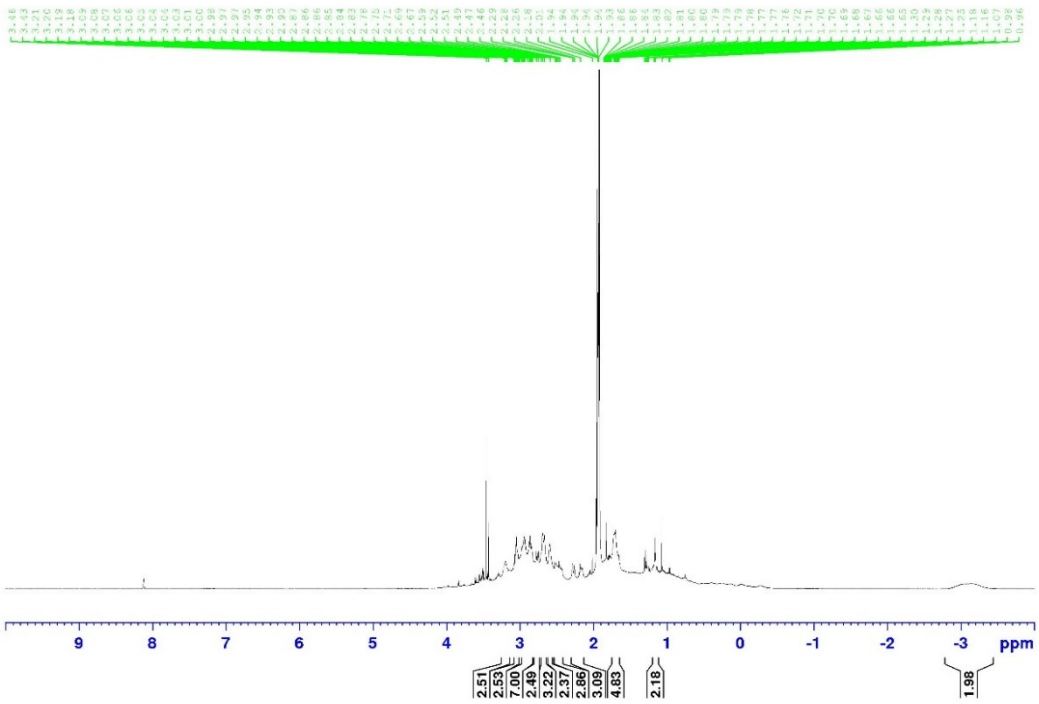

Figure S2. ^{1}H NMR spectrum of compound Cs_2·**10** in d_6-acetone.

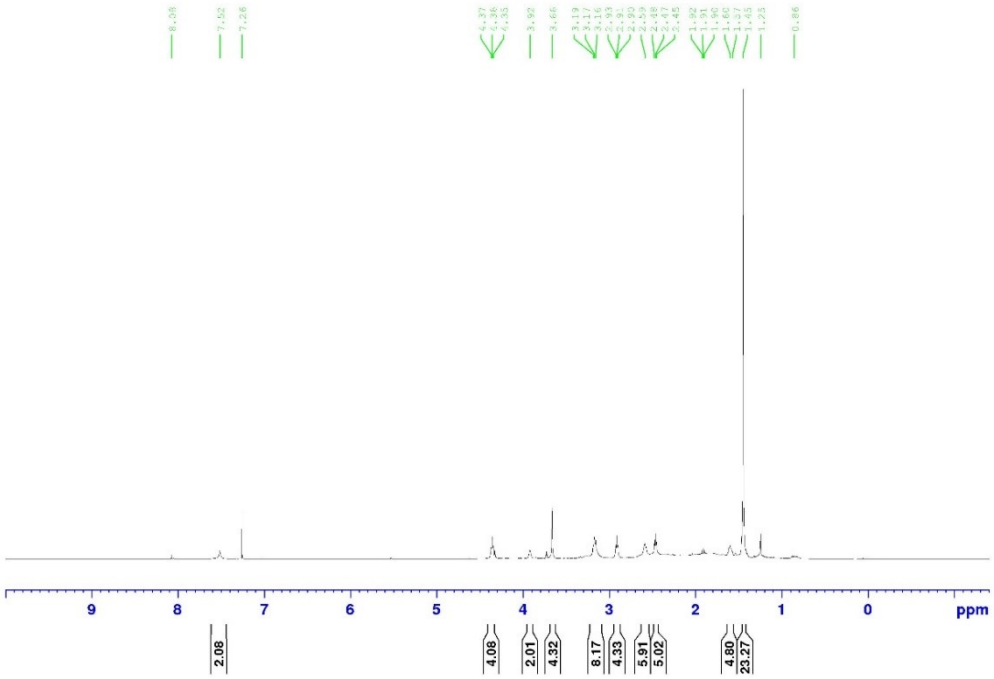

Figure S3. ^{1}H NMR spectrum of compound **13** in $CDCl_3$.

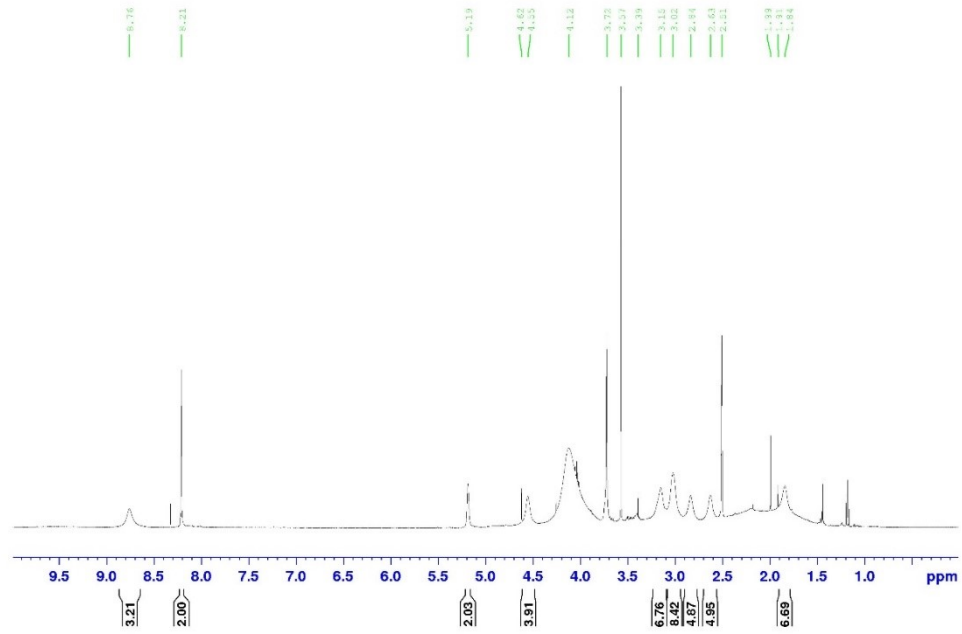

Figure S4. ^{1}H NMR spectrum of compound **14** in d_6-DMSO.

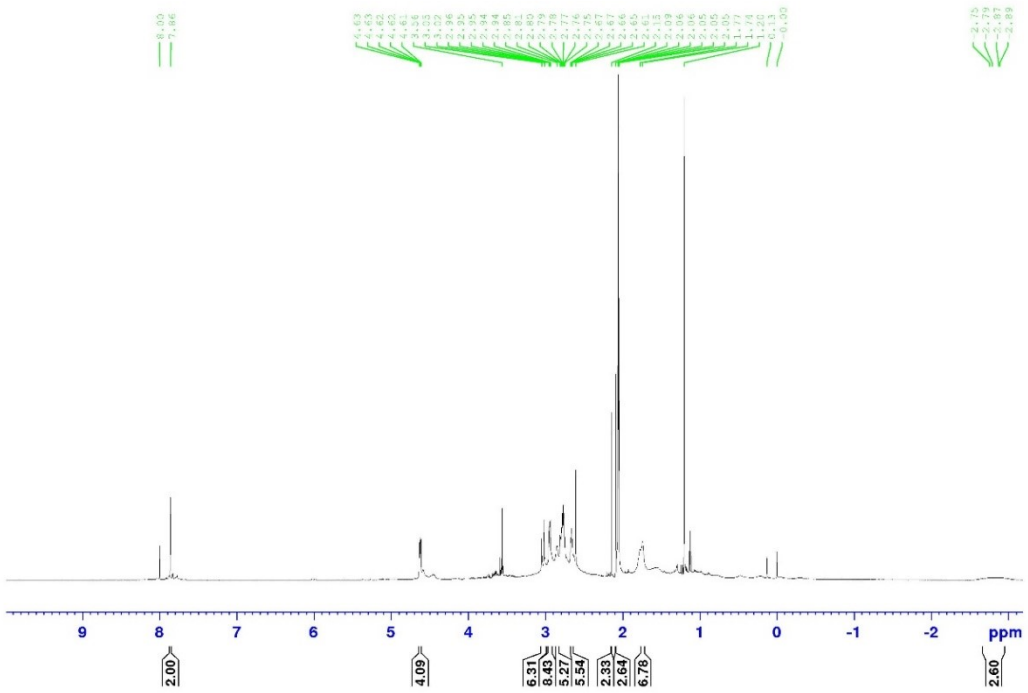

Figure S5. ^{1}H NMR spectrum of compound Cs_2·**15** in d_6-acetone.

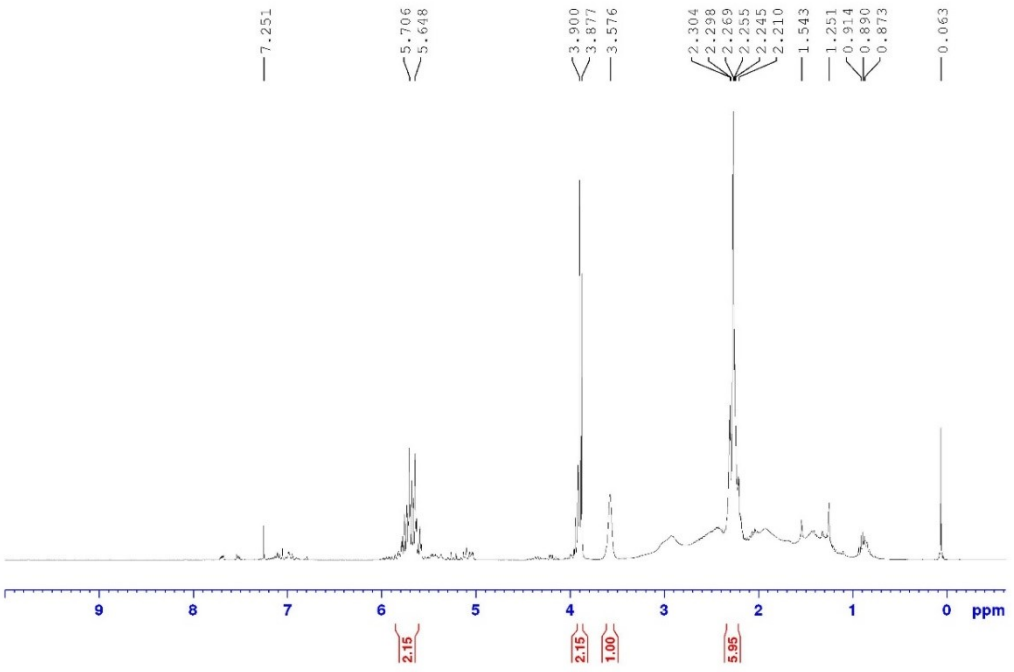

Figure S6. ^{1}H NMR spectrum of compound **17** in $CDCl_3$.

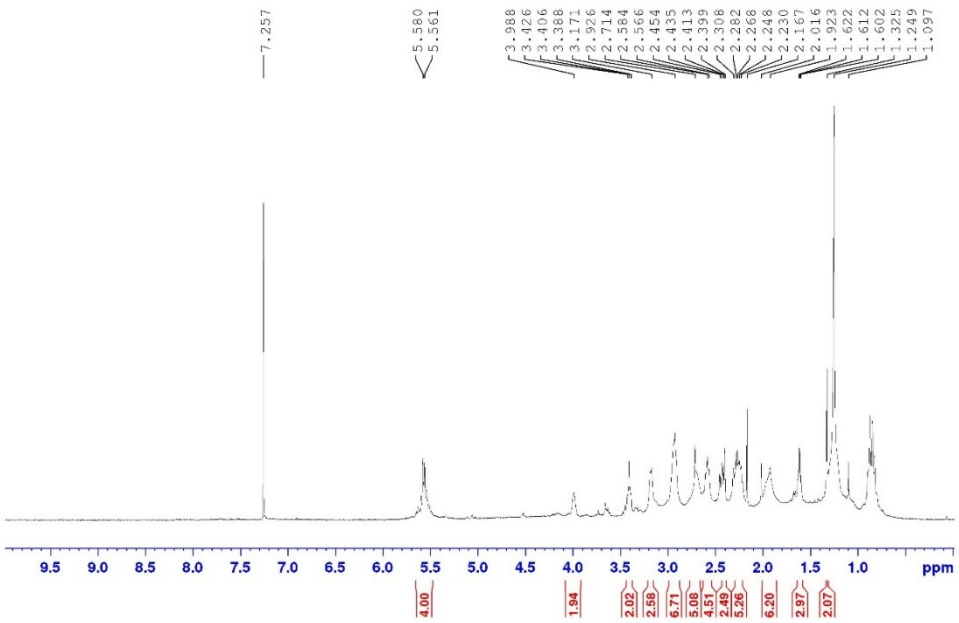

Figure S7. ^{1}H NMR spectrum of compound **19** in $CDCl_3$.

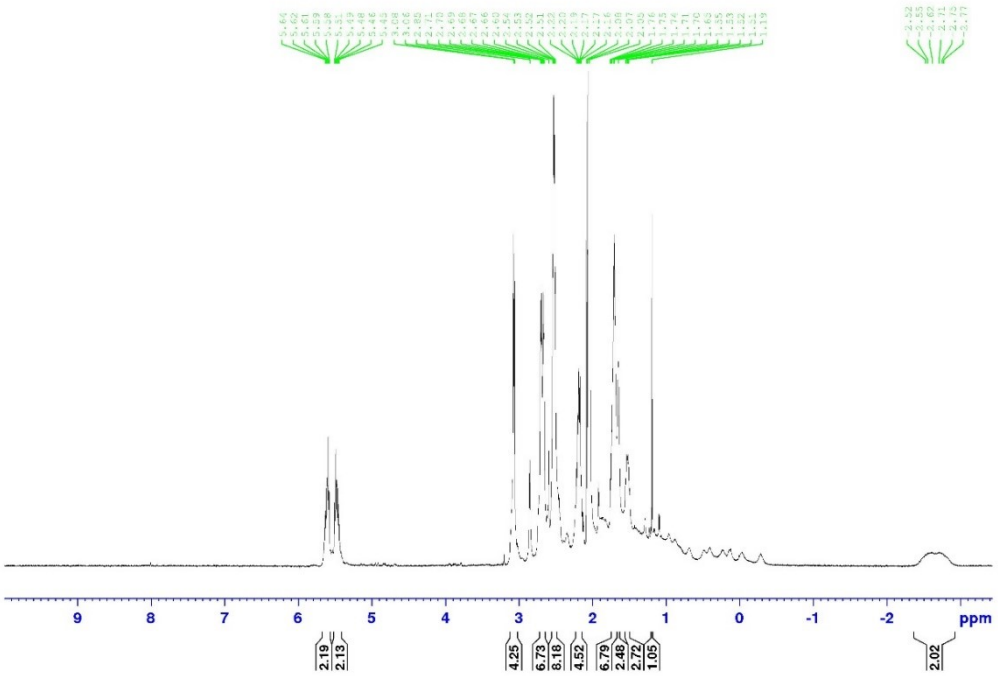

Figure S8. ^{1}H NMR spectrum of compound Cs_2·**20** in d_6-acetone.

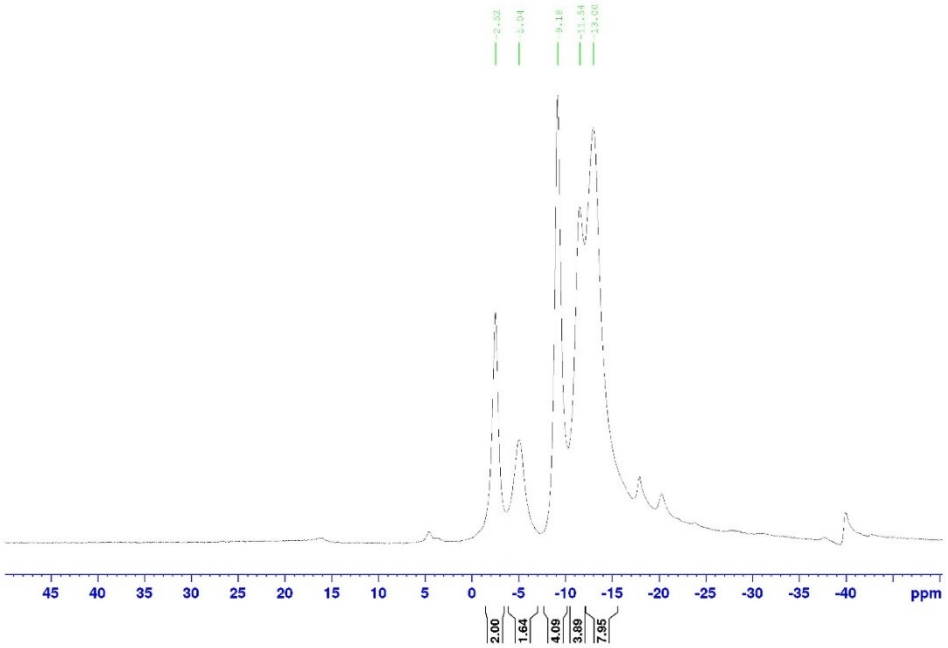

Figure S9. $^{11}B\{^{1}H\}$ NMR spectrum of compound **8** in $CDCl_3$.

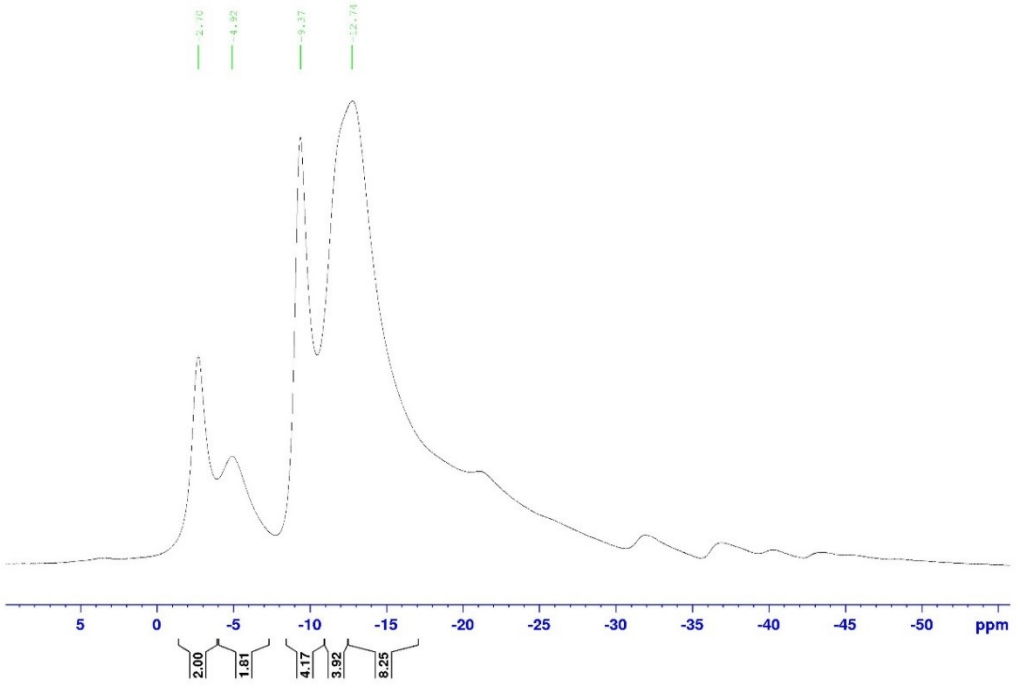

Figure S10. $^{11}B\{^{1}H\}$ NMR spectrum of compound **9** in d_6-DMSO.

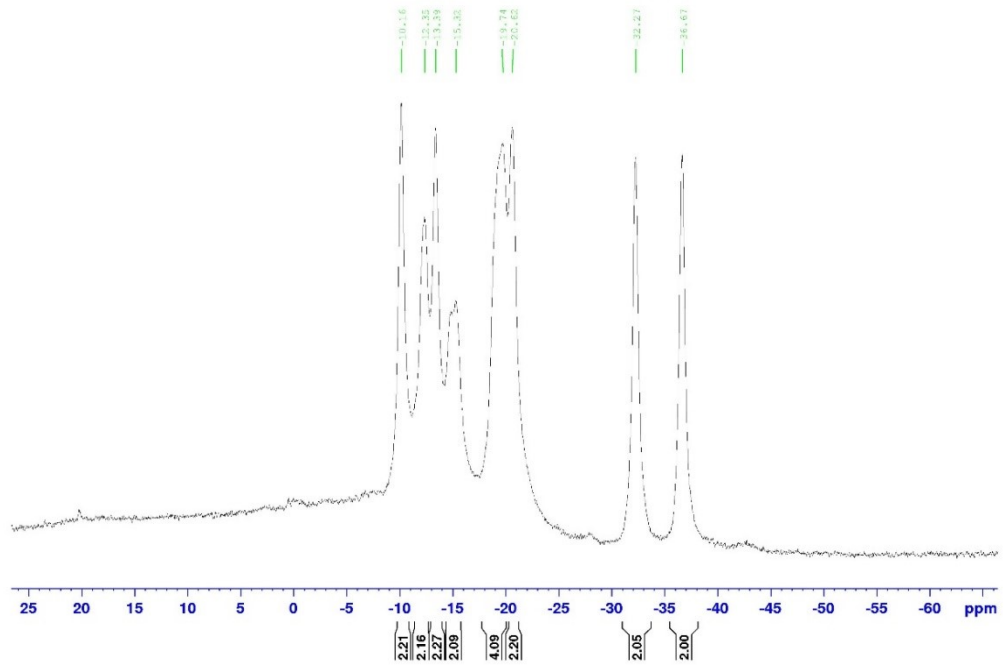

Figure S11. $^{11}B\{^{1}H\}$ NMR spectrum of compound Cs_2·**10** in d_6-acetone.

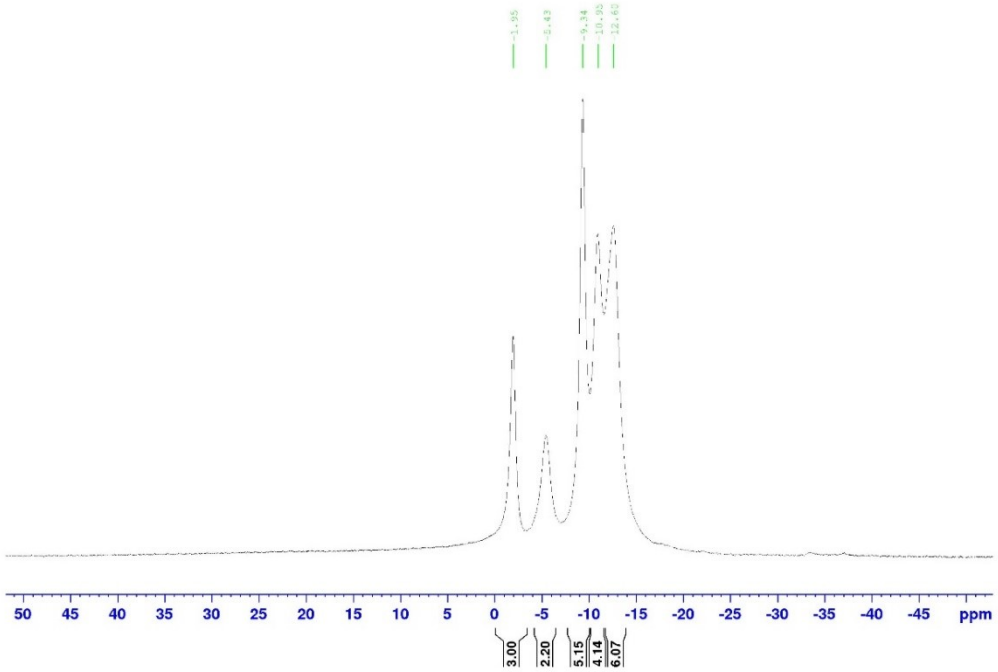

Figure S12. $^{11}B\{^{1}H\}$ NMR spectrum of compound **13** in $CDCl_3$.

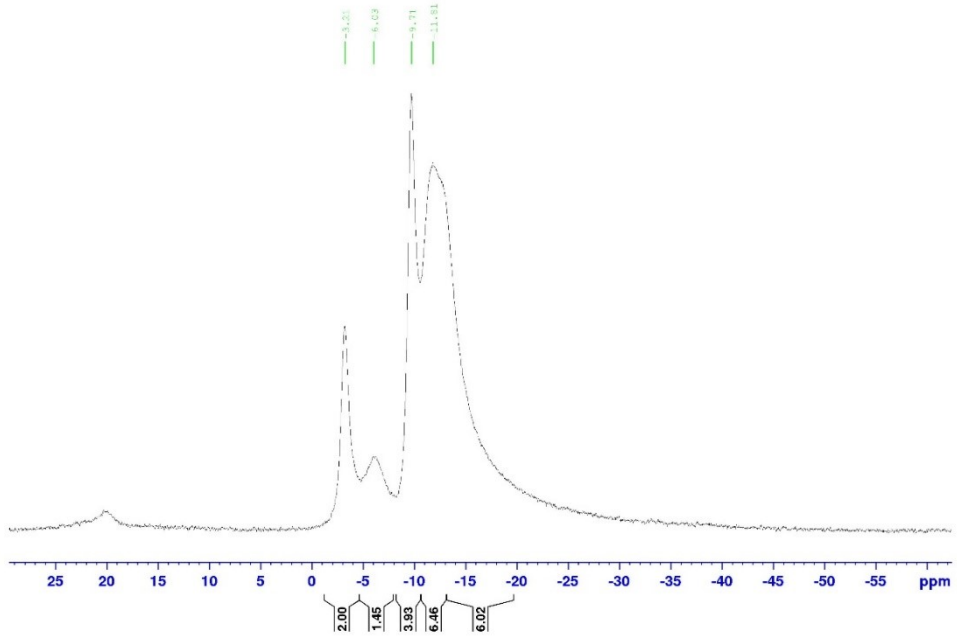

Figure S13. $^{11}B\{^{1}H\}$ NMR spectrum of compound **14** in d_6-DMSO.

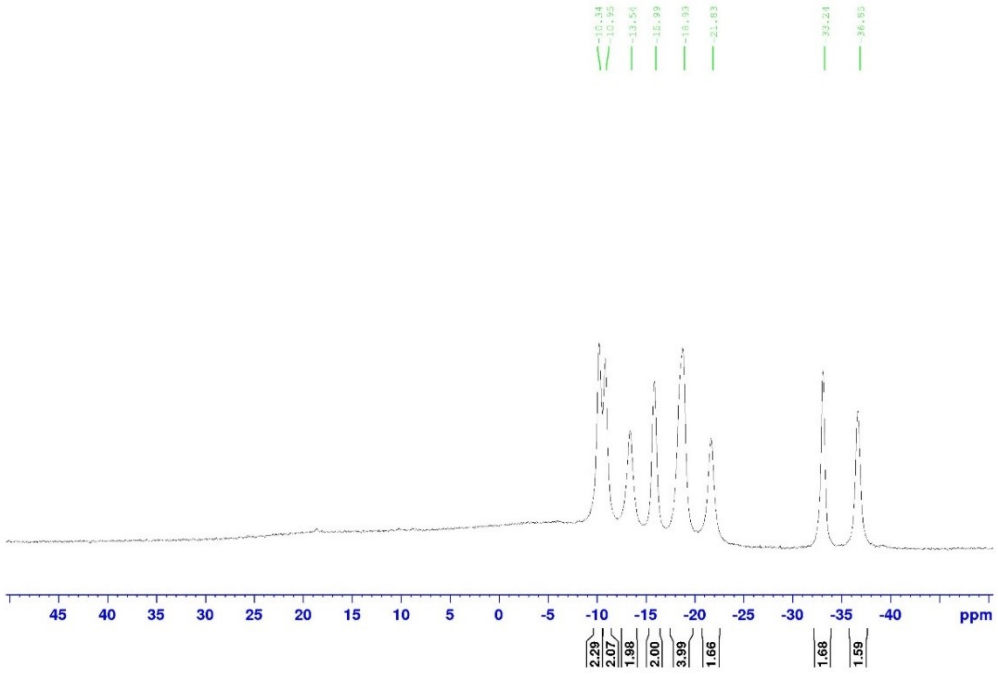

Figure S14. $^{11}B\{^{1}H\}$ NMR spectrum of compound Cs_2·**15** in d_6-acetone.

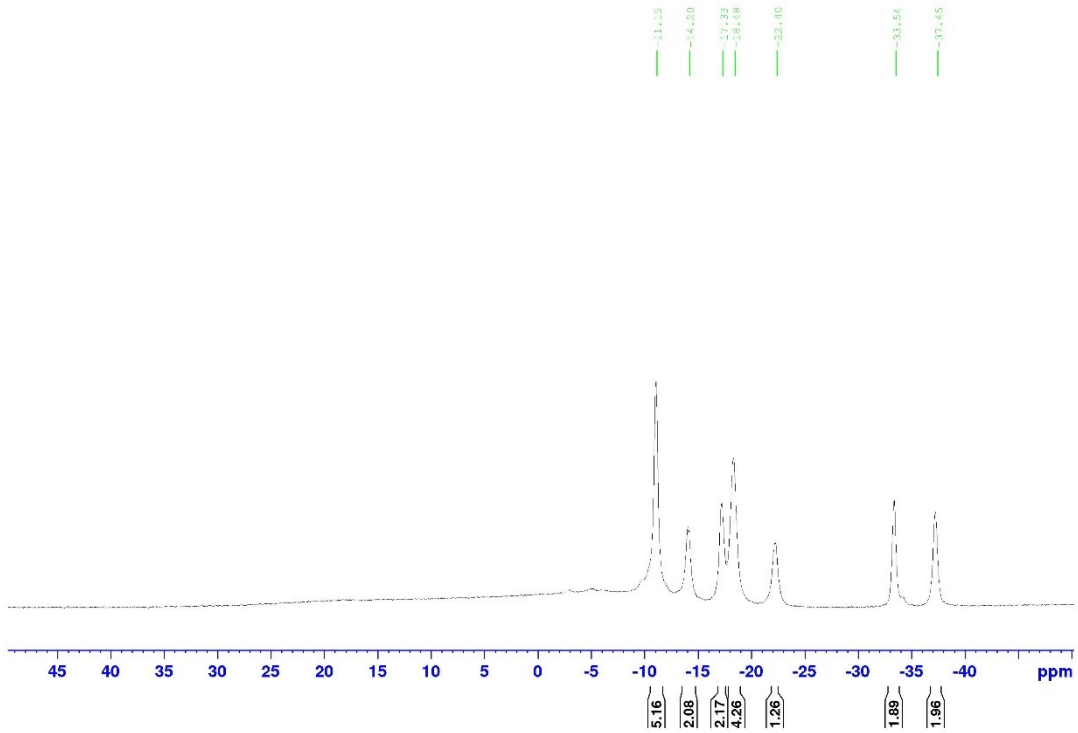

Figure S15. $^{11}B\{^{1}H\}$ NMR spectrum of compound Cs_2·**20** in d_6-acetone.

4. High- and Low-Resolution Mass Spectra

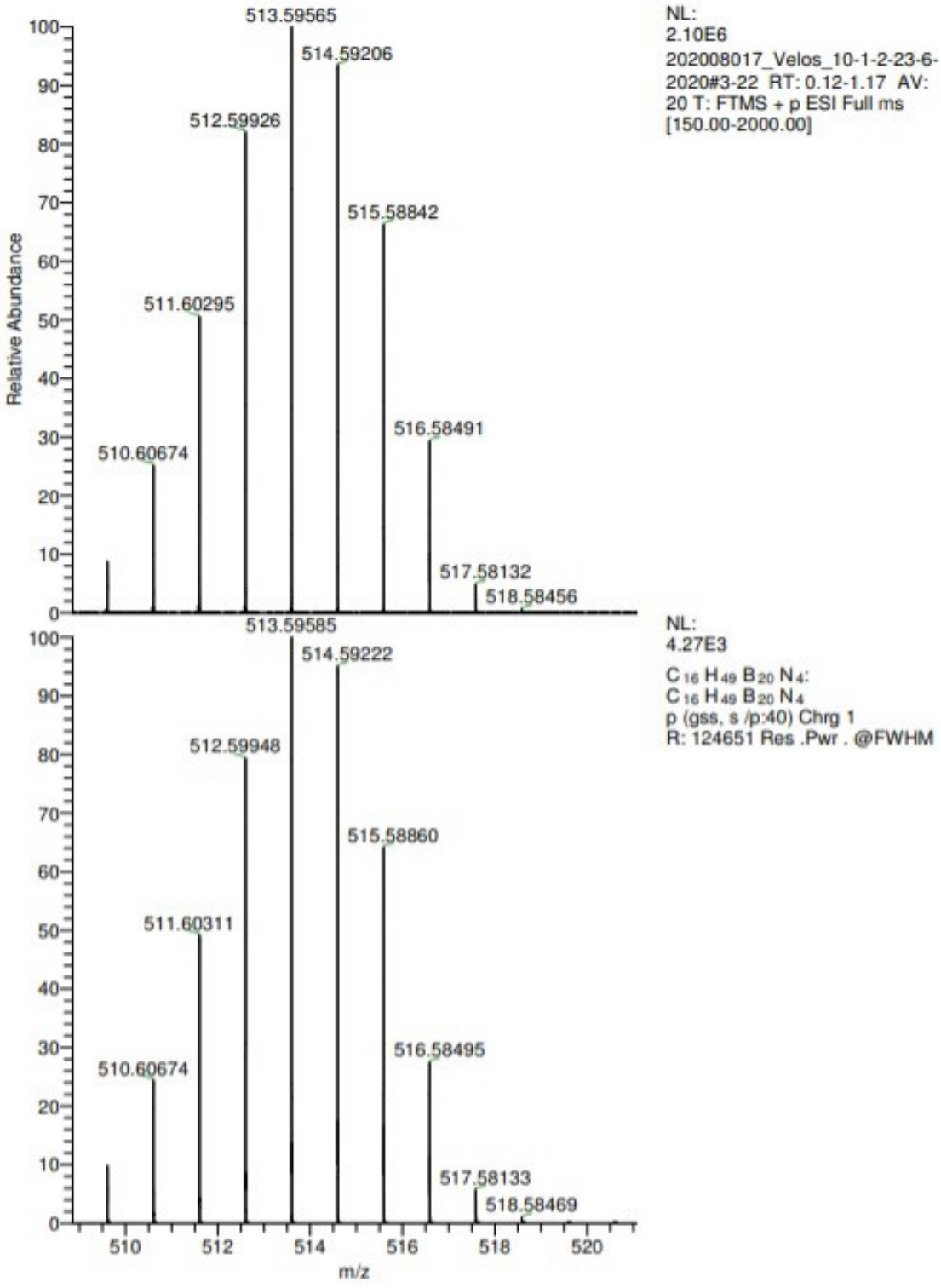

Figure S16. HRMS spectrum of compound **9** *m/z calcd for* $C_{16}H_{49}B_{20}N_4^+$ 514.59222 *found* 514.59206.

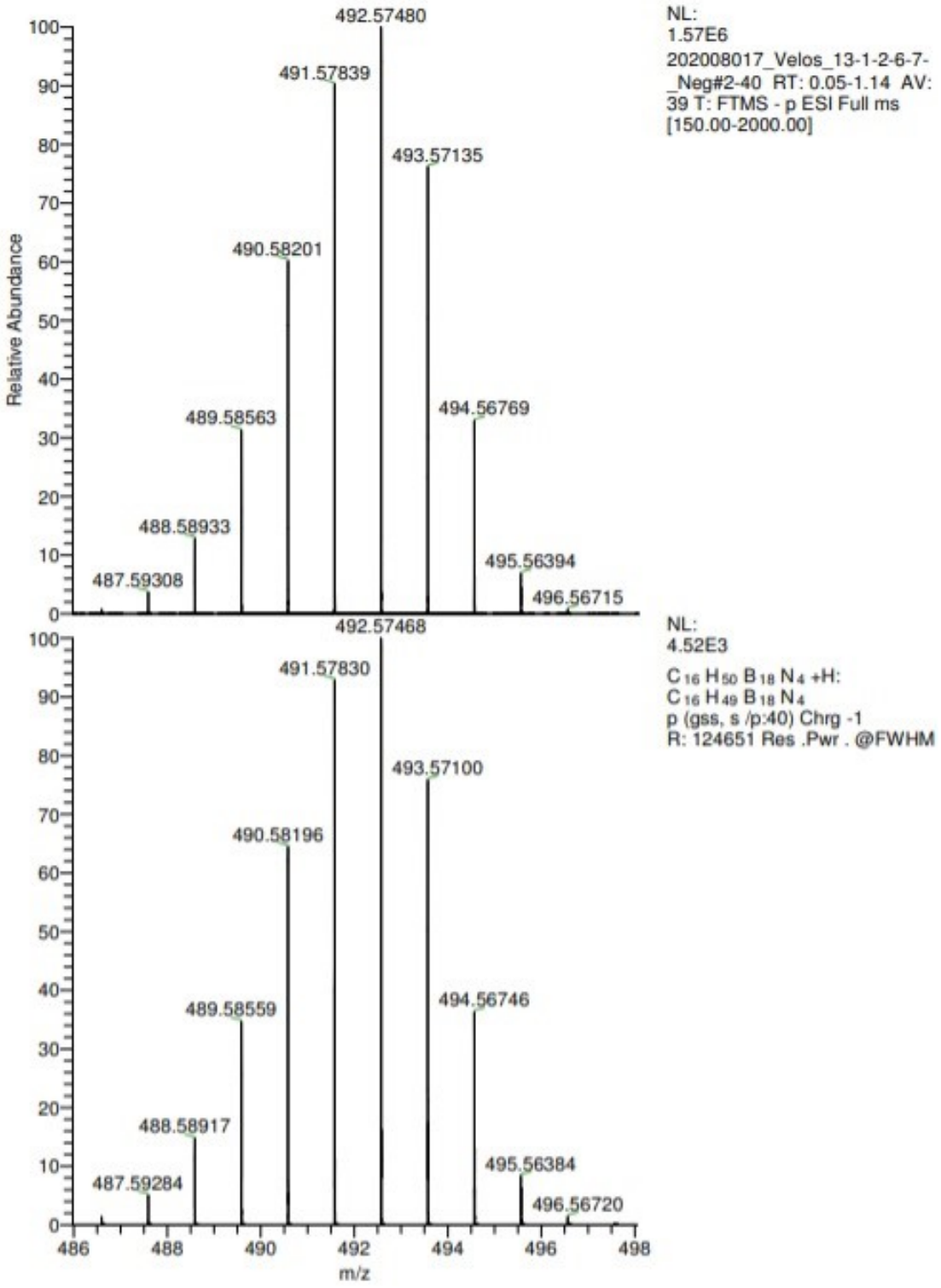

Figure S17. HRMS spectrum of compound Cs_2·**10** *m/z calcd for* $C_{16}H_{49}B_{18}N_4^-$ 492.57468 *found* 492.57480.

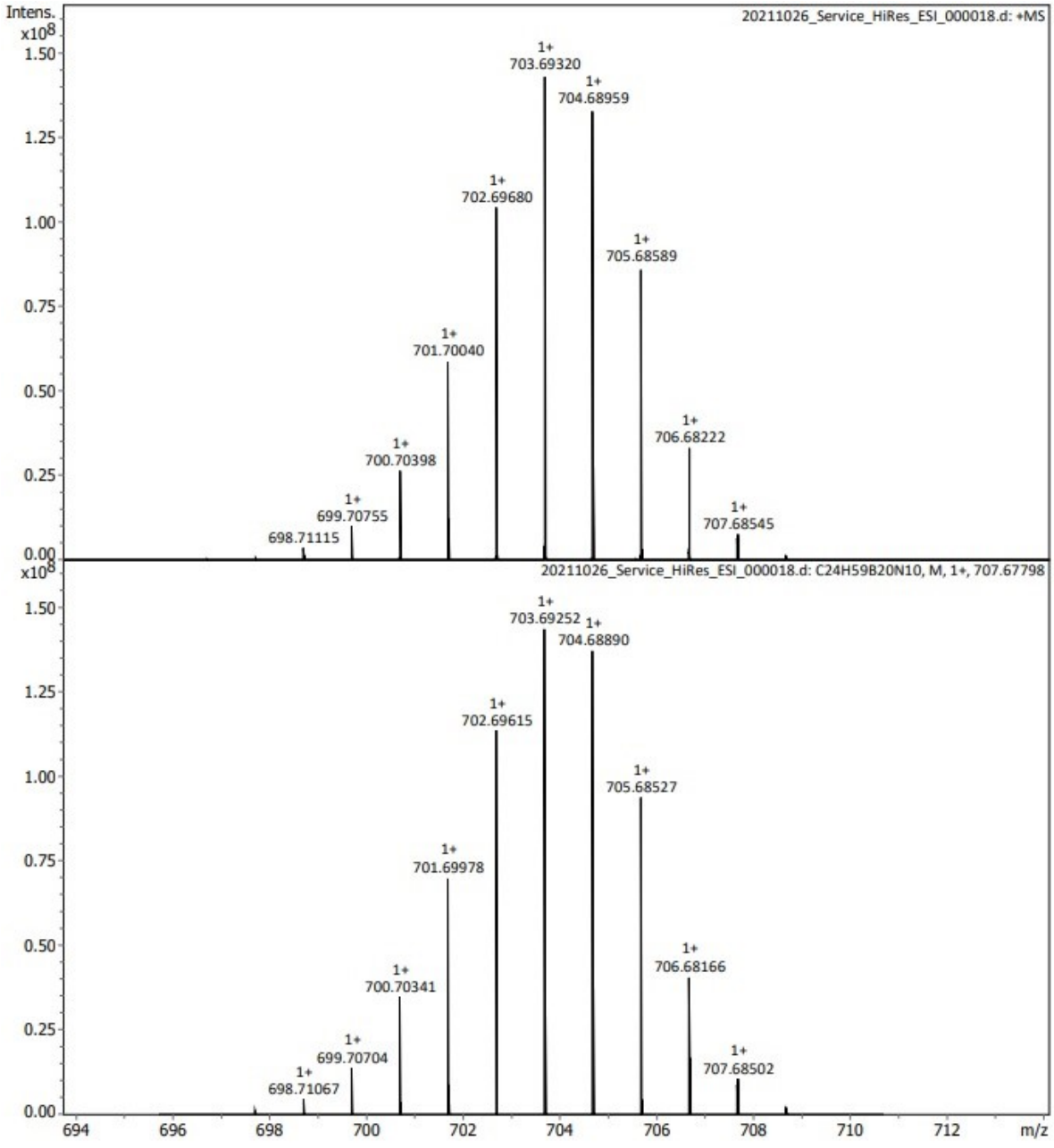

Figure S18. HRMS spectrum of compound **14** *m/z calcd for* $C_{24}H_{59}B_{20}N_{10}^{+}$ 703.69252 *found* 703.69320.

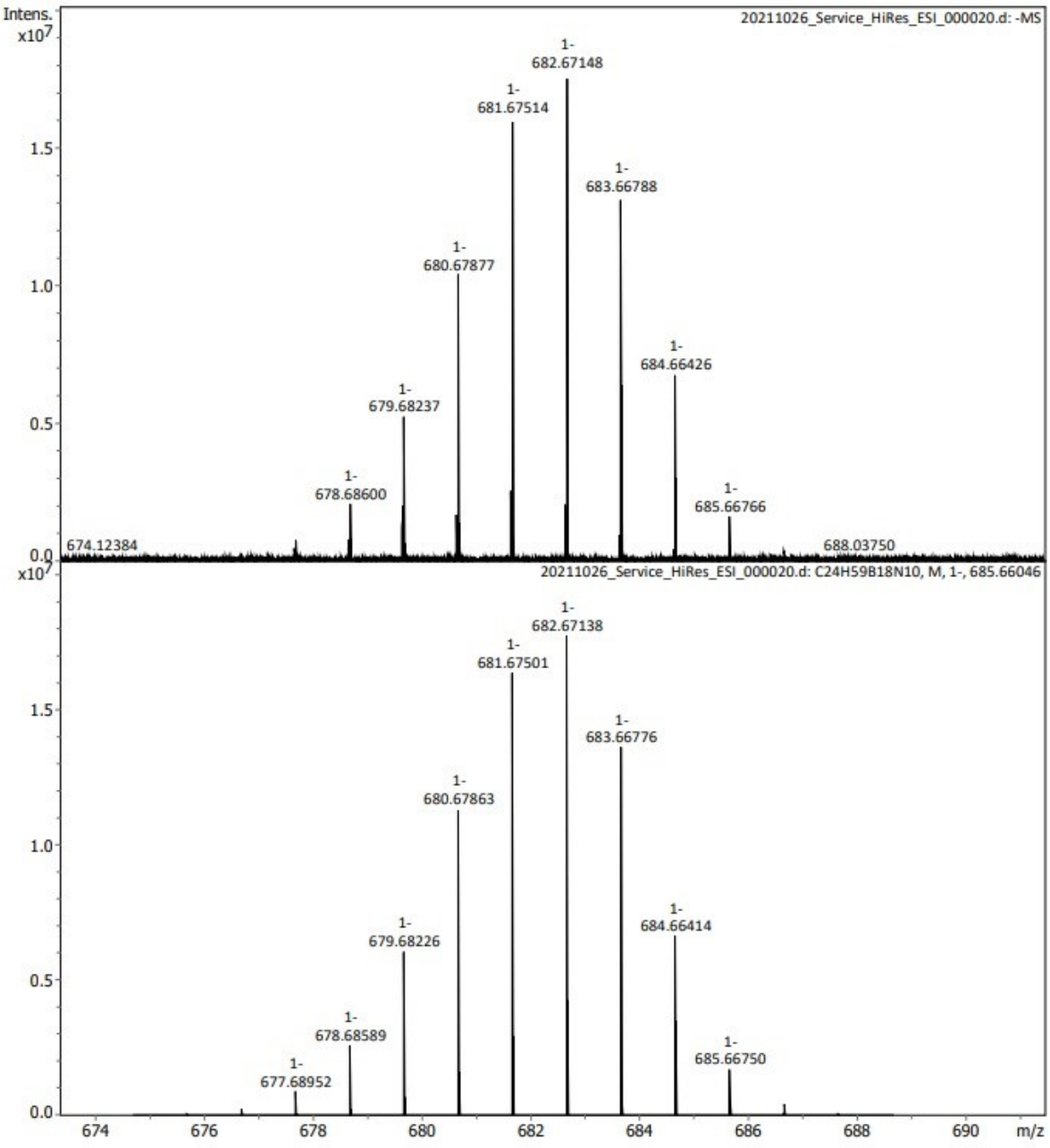

Figure S19. HRMS spectrum of compound Cs_2·**15** *m/z calcd for* $C_{24}H_{59}B_{18}N_{10}^-$ 682.67138 *found* 682.67148.

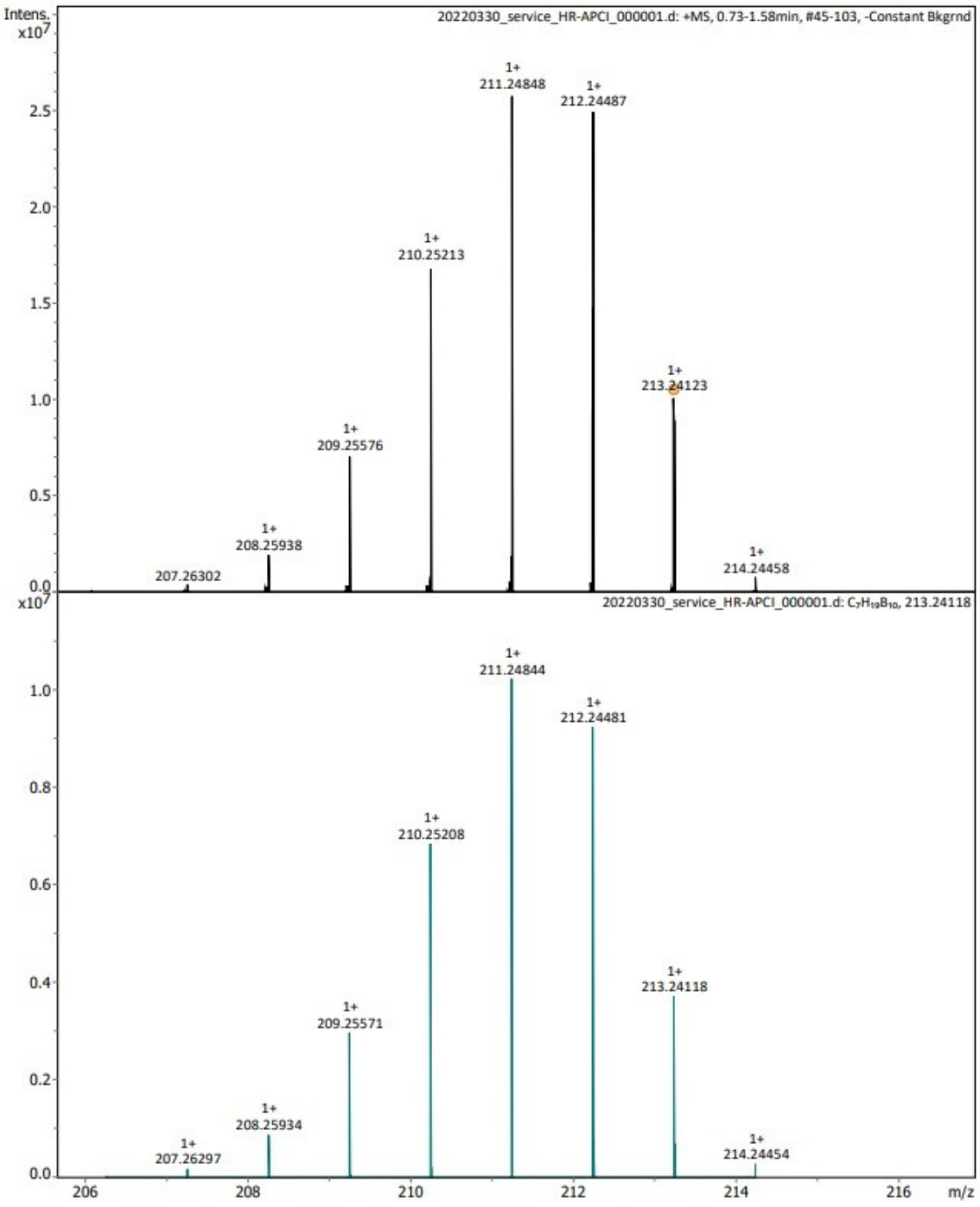

Figure S20. HRMS spectrum of compound **17** *m/z calcd for* $C_7H_{19}B_{10}^+$ 212.24844 *found* 212.24848.

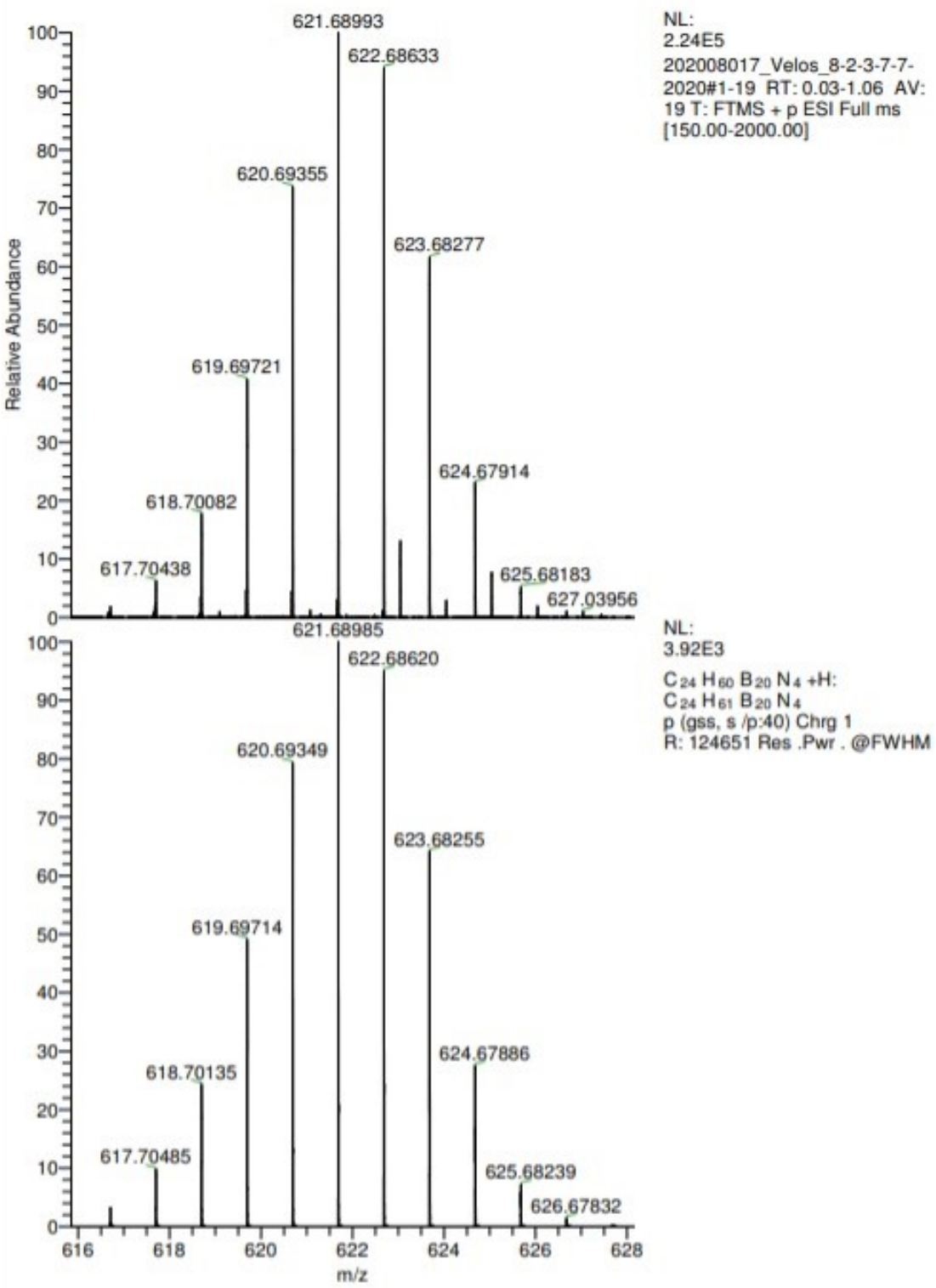

Figure S21. HRMS spectrum of compound **19** *m/z calcd for* $C_{24}H_{61}B_{20}N_4^+$ 621.68985 *found* 621.68993.

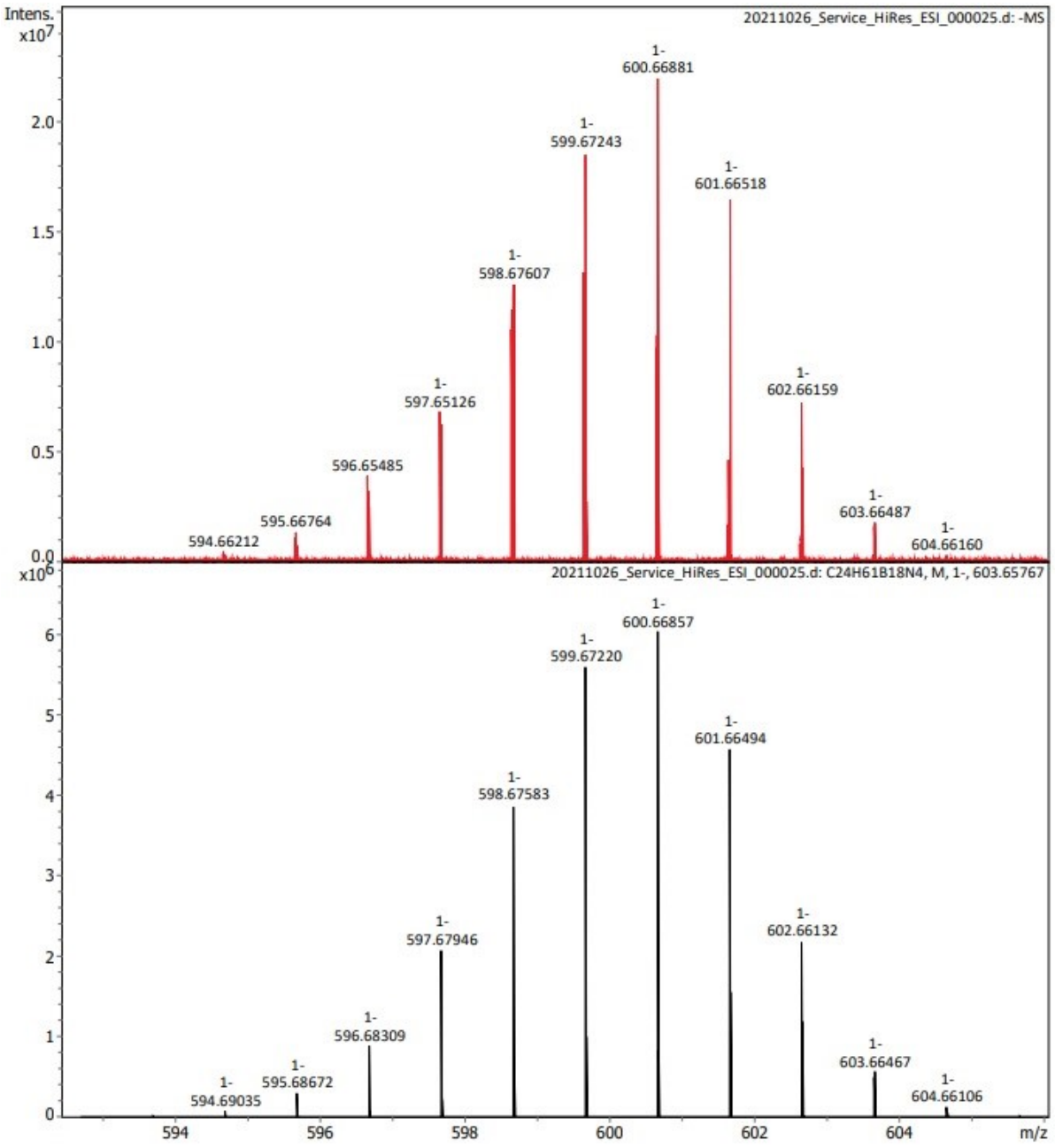

Figure S22. HRMS spectrum of compound Cs_2·**20** *m/z calcd for* $C_{24}H_{61}B_{18}N_4^-$ 600.66857 *found* 600.66881.

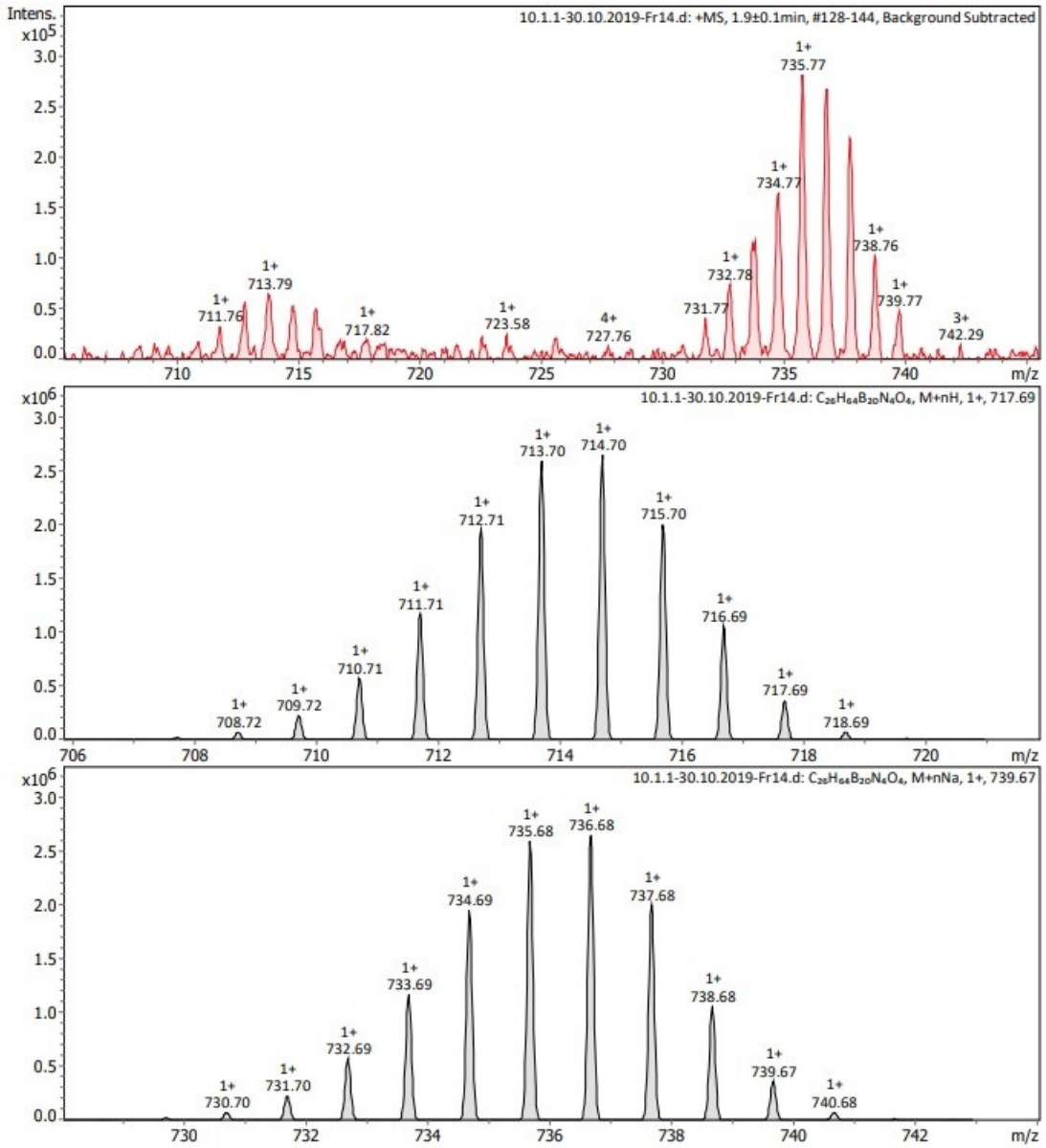

Figure S23. LRMS spectrum of compound **8** *m/z calcd for* $C_{26}H_{65}B_{20}N_4O_4^+$ 714.70 *found* 713.79 and *calcd for* $C_{26}H_{64}B_{20}N_4O_4Na^+$ 735.68 *found* 735.77.

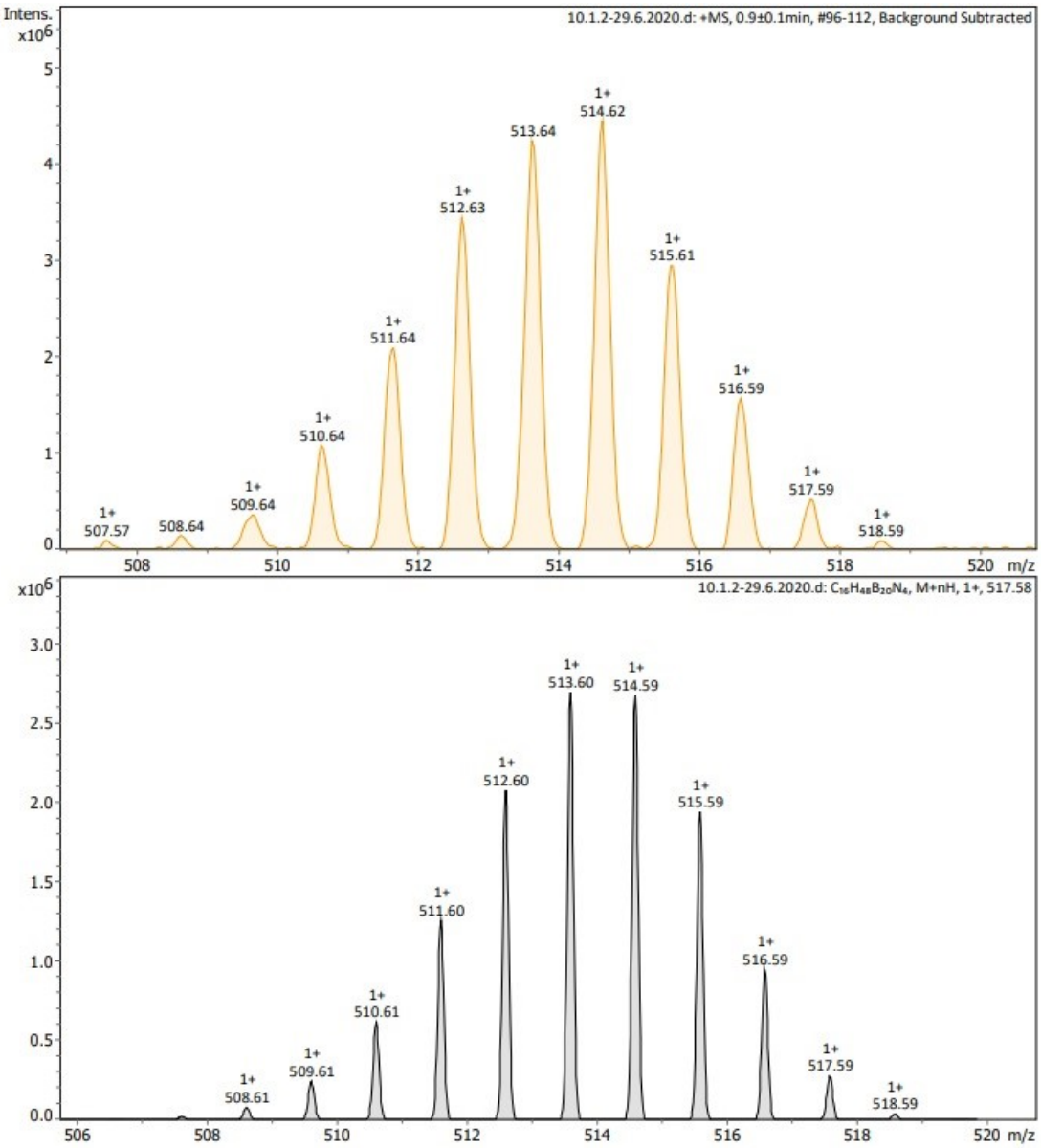

Figure S24. LRMS spectrum of compound **9** *m/z calcd for* $C_{16}H_{49}B_{20}N_4^+$ 514.59 *found* 514.62.

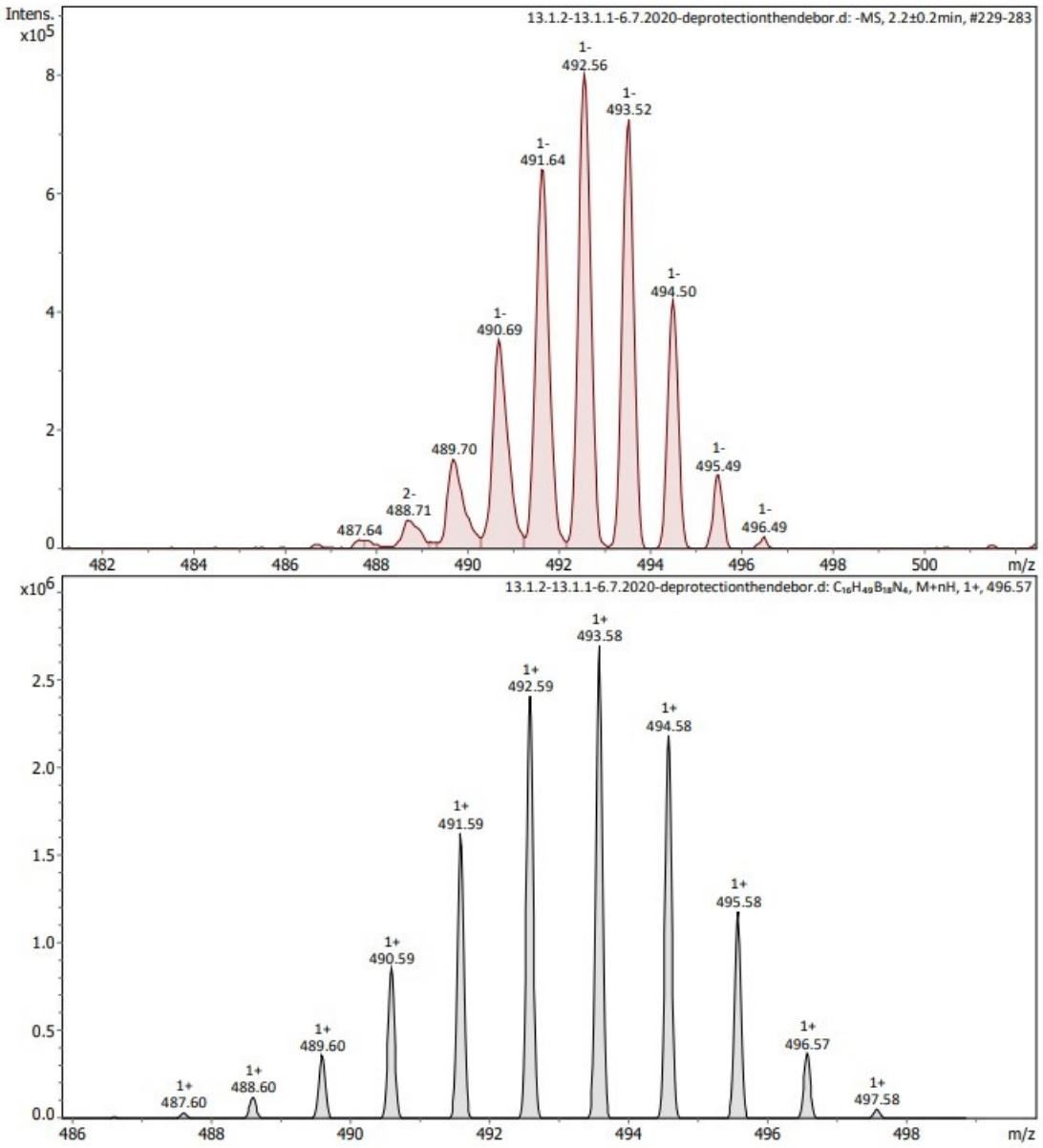

Figure S25. LRMS spectrum of compound Cs_2·**10** *m/z calcd for* $C_{16}H_{49}B_{18}N_4^-$ 493.58 *found* 492.56.

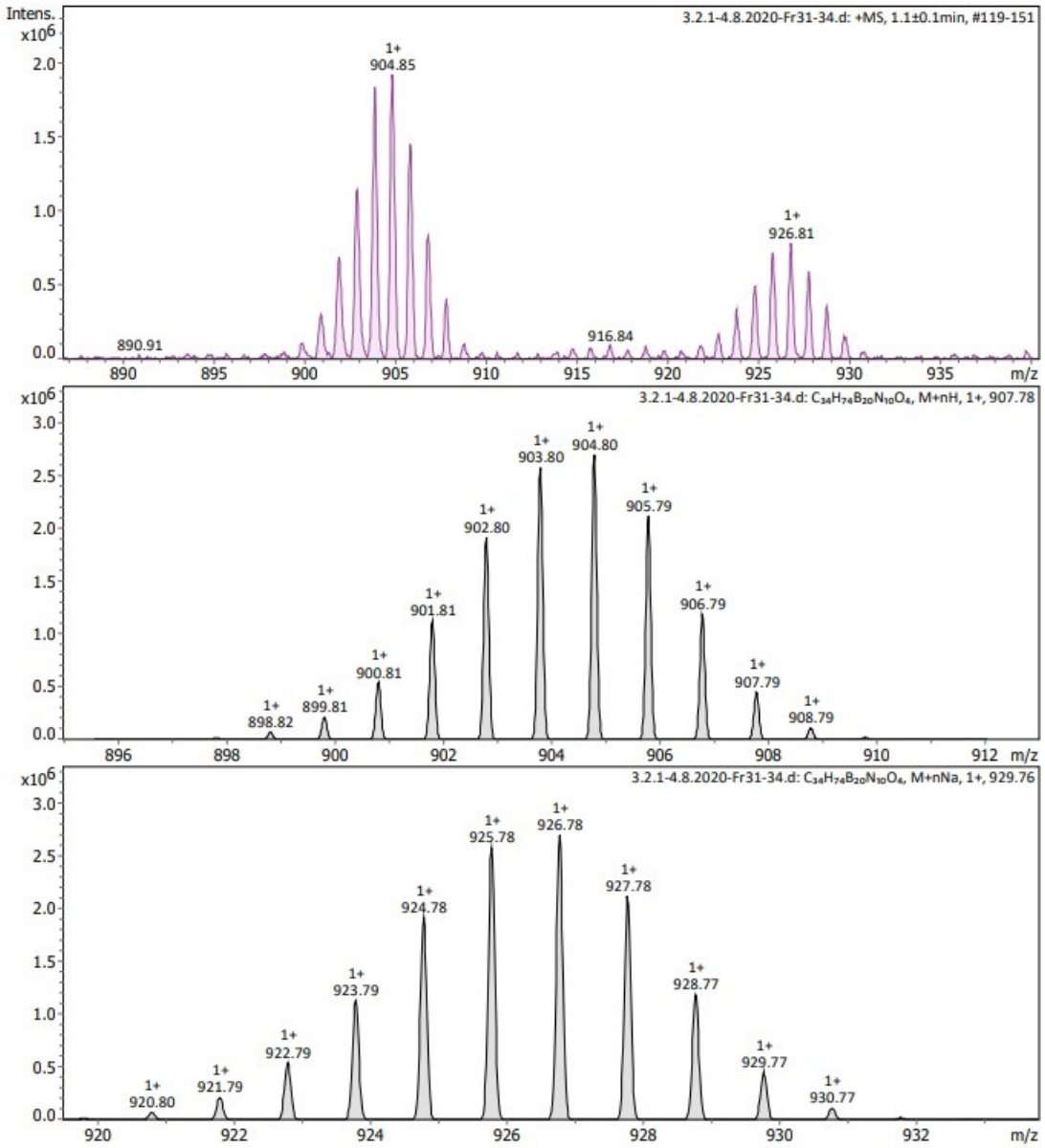

Figure S26. LRMS spectrum of compound **13** *m/z calcd for* $C_{34}H_{75}B_{20}N_{10}O_4^+$ 904.80 *found* 904.85 and *calcd for* $C_{34}H_{75}B_{20}N_{10}O_4Na^+$ 926.78 *found* 926.81.

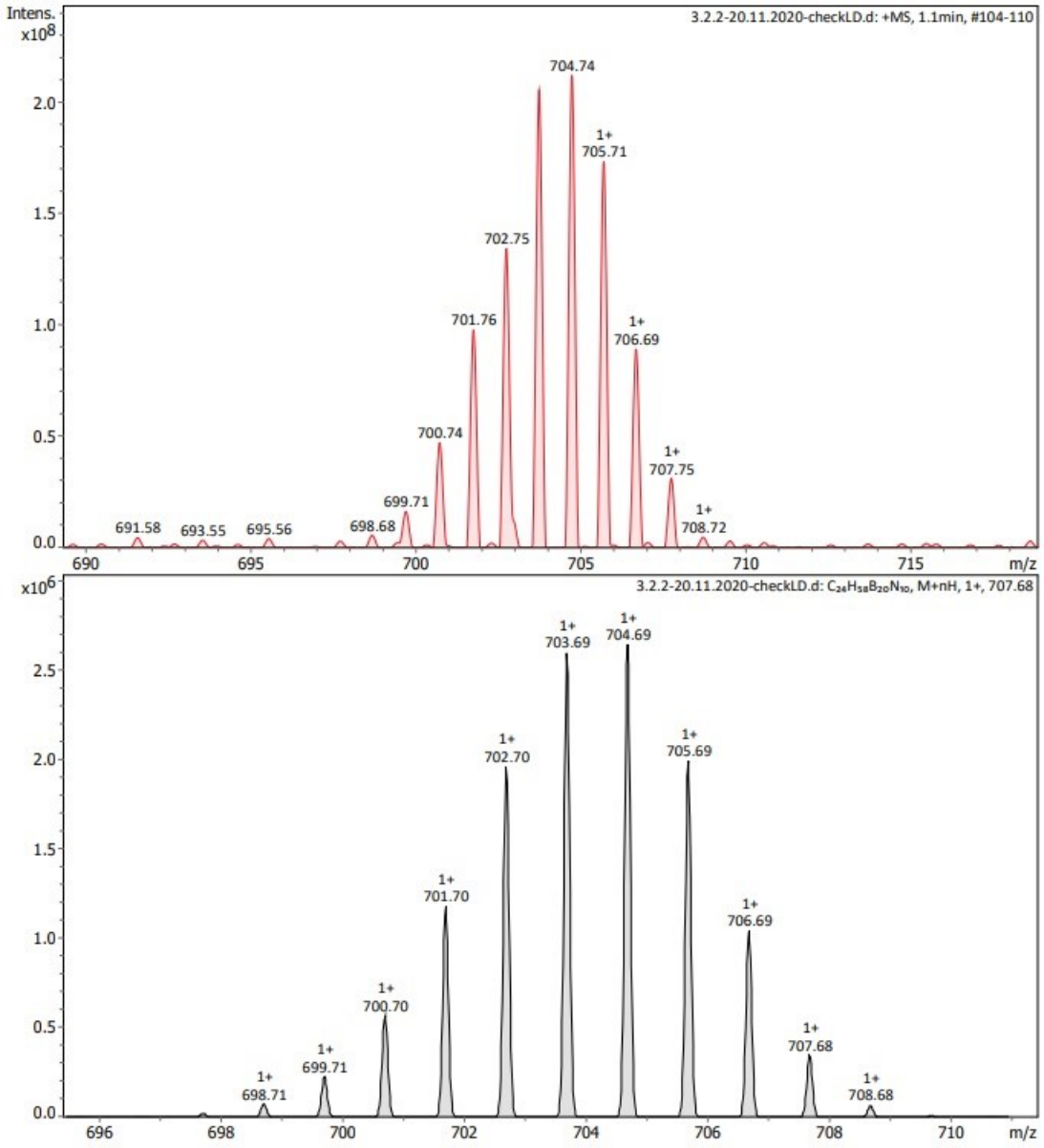

Figure S27. LRMS spectrum of compound **14** *m/z calcd for* $C_{24}H_{59}B_{20}N_{10}^{+}$ 704.69 *found* 704.74.

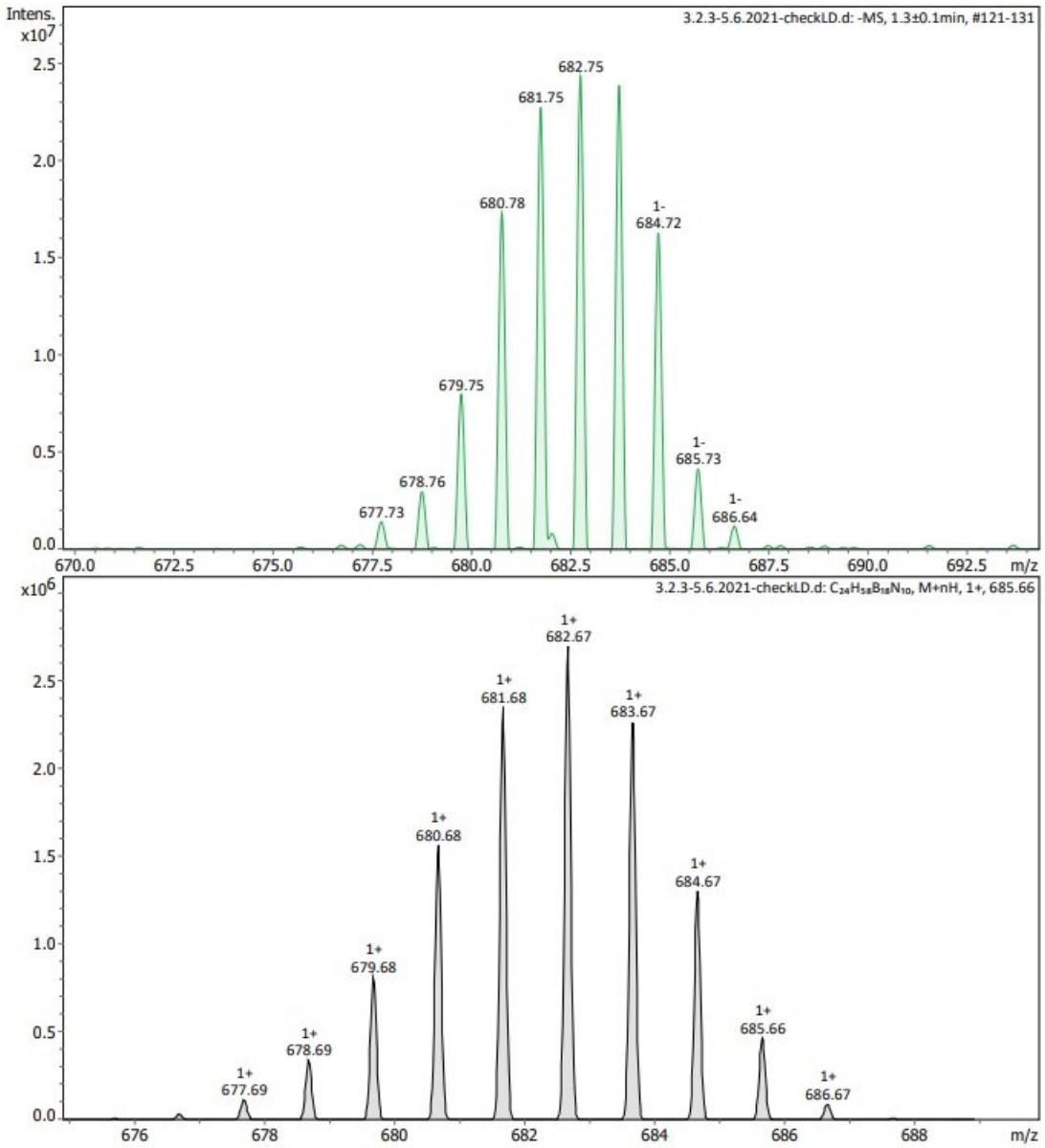

Figure S28. LRMS spectrum of compound Cs_2·**15** *m/z calcd for* $C_{24}H_{59}B_{18}N_{10}^-$ 682.67 *found* 682.75.

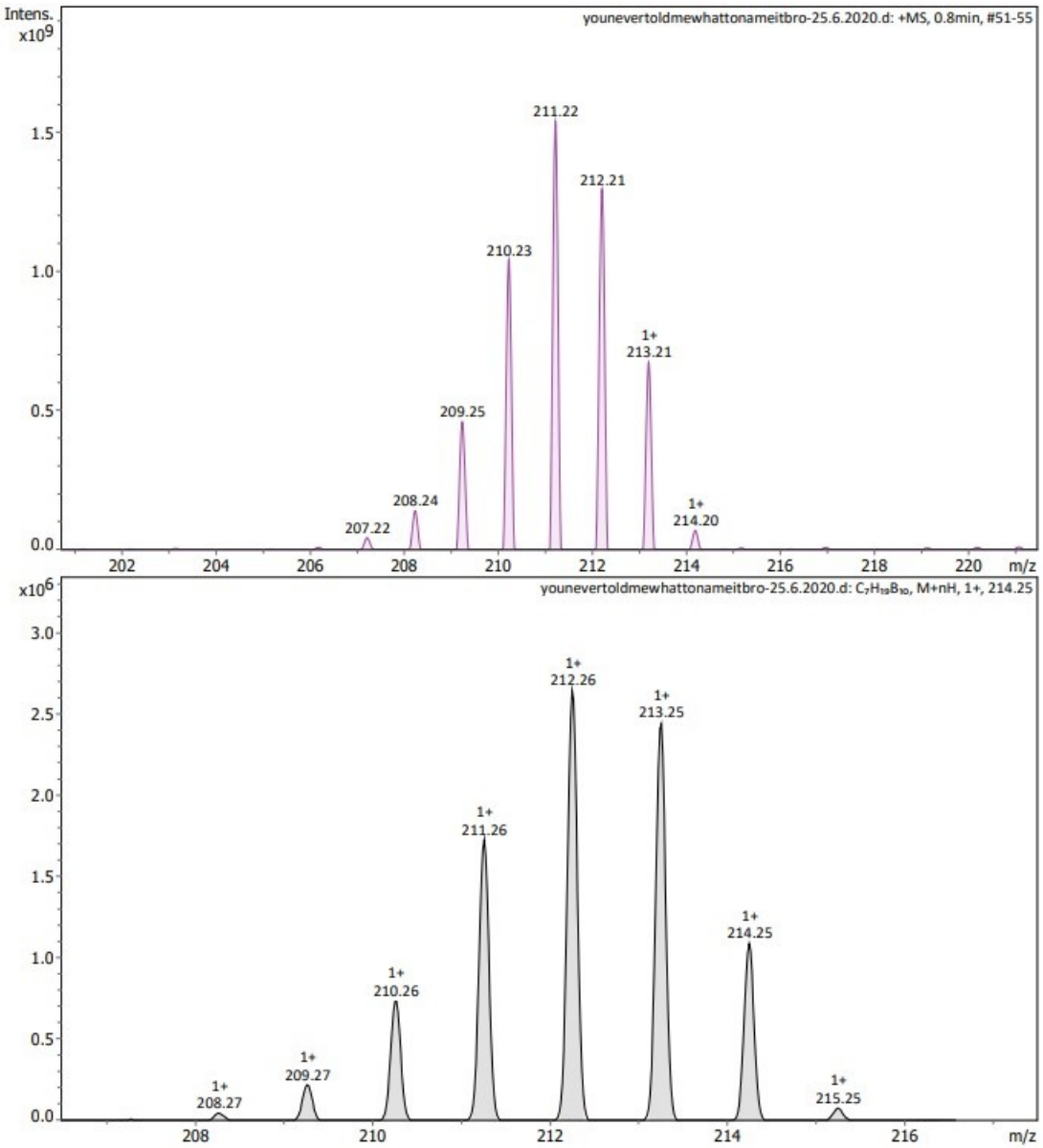

Figure S29. LRMS spectrum of compound **17** *m/z calcd for* $C_7H_{19}B_{10}^+$ 212.26 *found* 211.22.

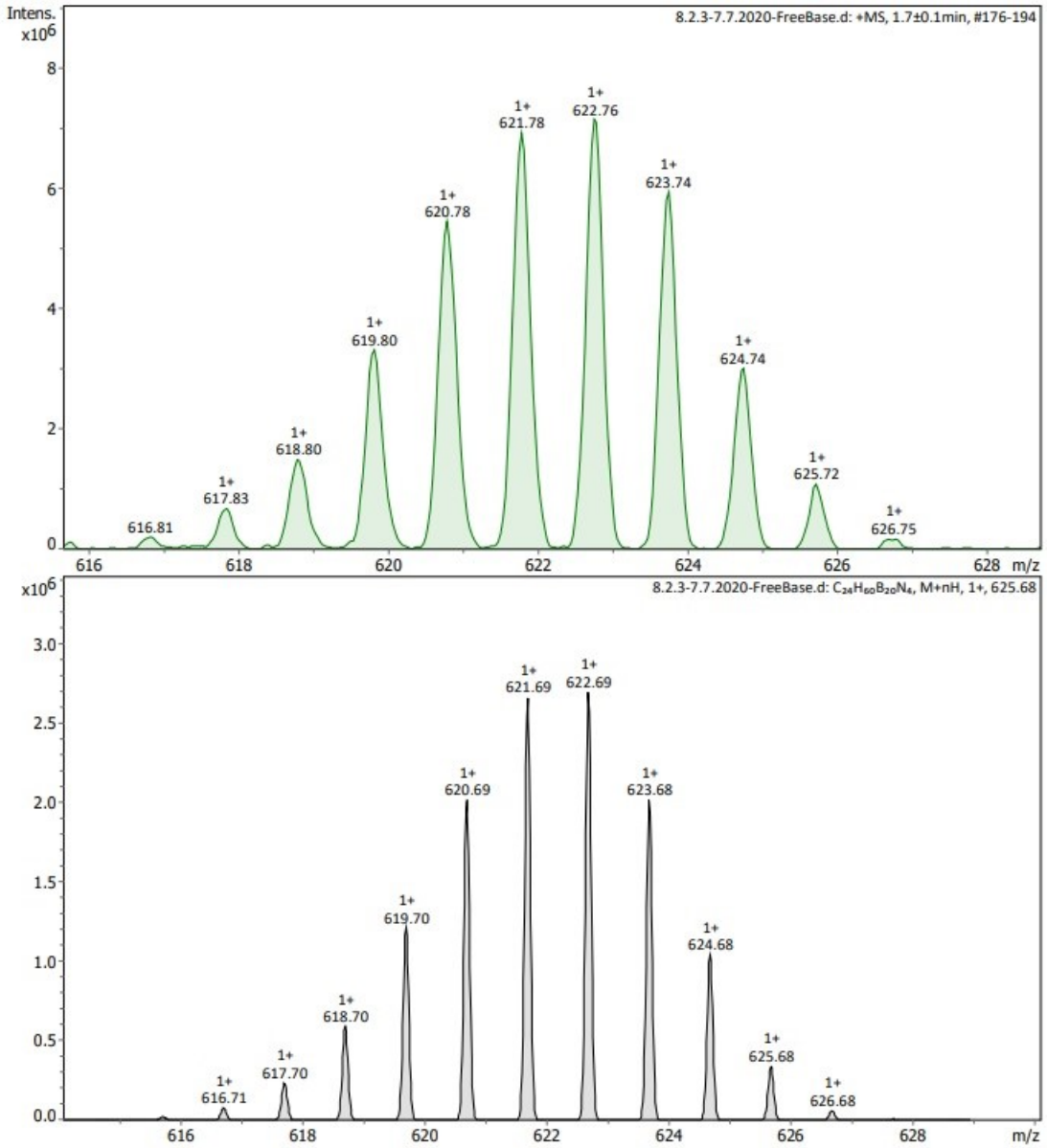

Figure S30. LRMS spectrum of compound **19** *m/z calcd for* $C_{24}H_{61}B_{20}N_4^+$ 622.69 *found* 622.76.

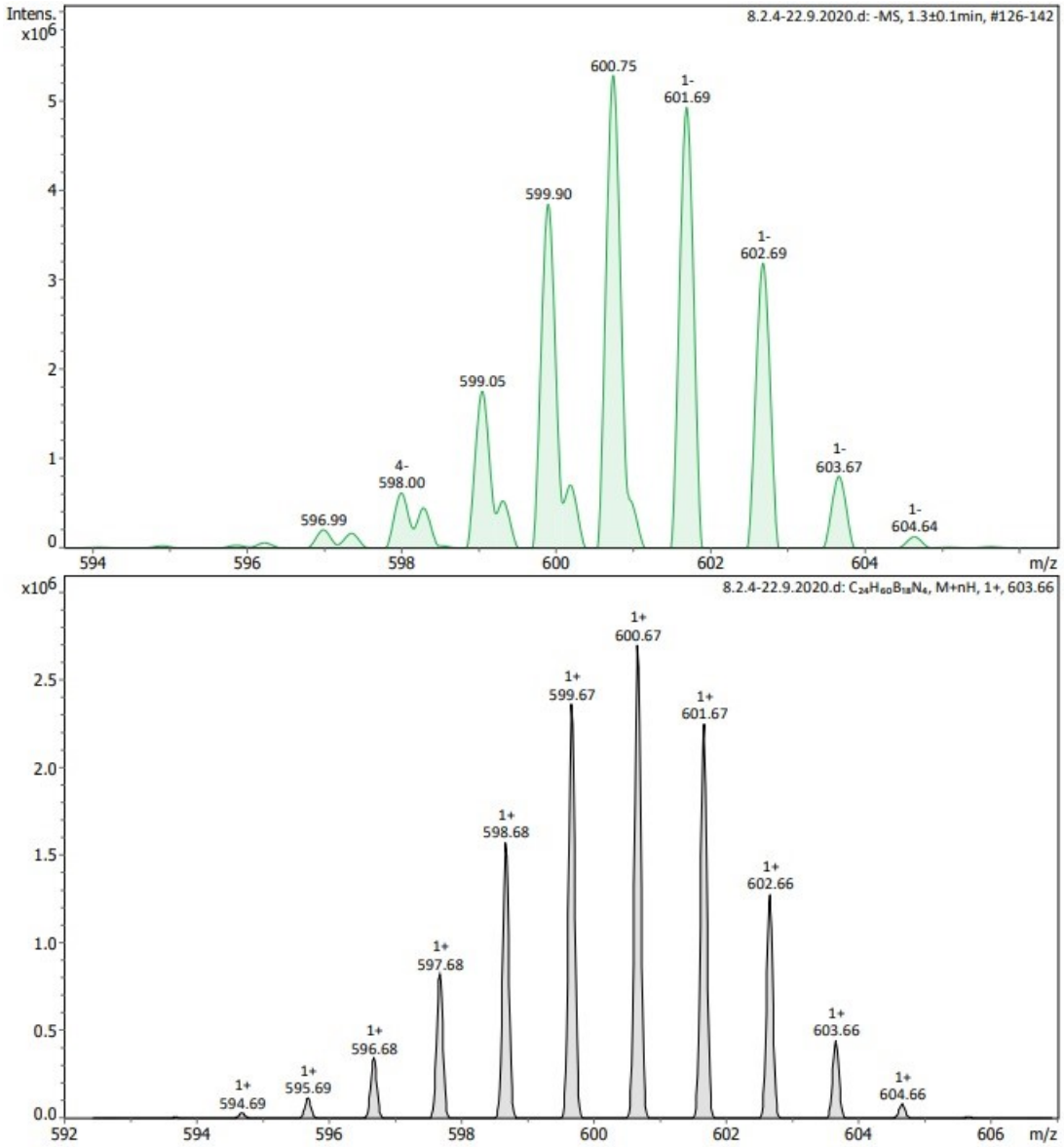

Figure S31. LRMS spectrum of compound Cs_2·**20** *m/z calcd for* $C_{24}H_{61}B_{18}N_4^-$ 600.67 *found* 600.75.

5. References

1 M. Yu, G. Nagalingam, S. Ellis, E. Martinez, V. Sintchenko, M. Spain, P. J. Rutledge, M. H. Todd and J. A. Triccas, *Journal of Medicinal Chemistry*, 2016, **59**, 5917–5921.

2 C. di Meo, L. Panza, F. Campo, D. Capitani, L. Mannina, A. Banzato, M. Rondina, A. Rosato and V. Crescenzi, *Macromolecular Bioscience*, 2008, **8**, 670–681.

3 J. K. H. Wong, S. Ast, M. Yu, R. Flehr, A. J. Counsell, P. Turner, P. Crisologo, M. H. Todd and P. J. Rutledge, *ChemistryOpen*, 2016, **5**, 375–385.

4 F. A. Gomez and M. F. Hawthorne, *Journal of Organic Chemistry*, 1992, **57**, 1384-1390.