Electronic Supplementary Material (ESI)

for

A serendipitous one-pot synthesis of the octahydro-2*H*-pyrazino[1,2-a]pyrazine core

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Materials and methods

Solvents and starting materials were purchased from Merck or TCI and used without further purification. All aqueous solutions were prepared from ultrapure laboratory grade water (18 MΩ· cm) obtained from Millipore/MilliQ purification system. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz on a Bruker Avance Neo 400 spectrometer. Chemical shifts are reported in ppm with the protic impurities of the deuterated solvent as the internal reference. Mass spectra were obtained with a Thermo Finningan LCQ-Deca XP-PLUS ion trap spectrometer equipped with an electrospray source. High resolution mass spectra were registered on a ThermoScientific Q-Exactive Plus spectrometer and on an Agilent, Q-ToF G6545B. TLC were performed with silica gel (MN Kieselgel 60F254) and visualized by UV or sprayed with Dragendorff reagent or alkaline $KMnO_4$. Column chromatography was carried out on Macherey-Nagel Silica gel 60 (0.063-0.200 mm). Macherey – Nagel Quantofix Nitrate Nitrite semi-quantitative test strips were used to identify the gas evolved during the formation of **5a**. Compounds **3**,[1] **2a**[2] and **2b**[3] were prepared as reported in the literature.

Synthetic procedures

4,8-Dibenzyl-6-nitro-1,4,8-triazabicyclo[4.4.1]undecane (4). Compound **3** (4.80 g, 46.5 mmol) was dissolved in methanol (20 mL) and nitromethane (0.9 mL, 46.5 mmol) and paraformaldehyde (2.54 g, 84.7 mmol) were added with stirring. The mixture was heated at 50 °C for 3 h and periodically analysed by TLC (Petroleum ether/EtOAc 5:5 and DCM/MeOH 9:1). The product was isolated by gravity column chromatography on silica gel using as eluent a mixture of petroleum ether/EtOAc 10:0 - 5:5 obtaining compound **4** (3.27 g, 51 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.38 - 7.26 (m, 10H), 3.85 (s, 2H), 3.80 (d, J = 13.4 Hz, 2H), 3.73 (d, J = 13.4 Hz, 2H), 3.25 (br s, 4H), 3.03 (ddd, J = 13.3, 8.3, 2.8 Hz, 2H), 2.95 - 2.84 (m, 4H), 2.67 (ddd, J = 13.6, 6.5, 2.9 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 139.1 (C), 129.0 (CH), 128.6 (CH), 127.5 (CH), 96.0 (C), 63.9 (CH_2), 62.6 (CH_2), 57.3 (CH_2), 54.0 (CH_2), 53.4 (CH_2) ppm. HRMS (ESI^+): m/z = 381.2280 (100 %, $[M+H]^+$). Calc. For $C_{22}H_{28}O_2N_4+H^+$: 381.2285.

(2,8-Dibenzyloctahydro-9a*H*-pyrazino[1,2-*a*]pyrazin-9a-yl)methanol (5a). Compound **3** (8.00 g, 28.2 mmol) was dissolved in ethanol (70 mL) and nitromethane (1.5 mL, 28.2 mmol) and paraformaldehyde (4.24 g, 141 mmol) were added with stirring. The mixture was refluxed for 5 h, checked by TLC (DCM/MeOH 9:1), cooled to 0 °C, acidified with 8.2 mL of 37 % aqueous HCl and dried under vacuum. The residue was taken up with water, 1.4 g of activated charcoal were added, the mixture was stirred and refluxed for 5 min, vacuum filtered while hot and the solid was washed with water. The filtrate was extracted three times with DCM, which was discarded, the aqueous phase was basified with Na_2CO_3 and extracted three times with ether. The pooled ethereal phases were dried over Na_2CO_3 and Na_2SO_4 and the solvent was removed under vacuum. The residue was taken up with 70 mL of *i*-PrOH, cooled to 0 °C and 48 % aqueous HBr (12.8 mL) was added dropwise in 10 min with stirring. Then the mixture was refluxed until a solution was obtained, filtered while hot and left at RT for 3 h and at 0 °C for 18 h. White crystals were formed, which were vacuum filtered, washed with *i*-PrOH, Et_2O and dried under vacuum. A second crop was obtained from the mother liquors by evaporating half the solvent, cooling at 0 °C for 18 h, vacuum filtering and washing the solid with *i*-PrOH and Et_2O. The two crops were pooled, suspended in sodium carbonate saturated aqueous solution and dichloromethane and the aqueous layer was extracted three times with DCM. The pooled organic layers were dried over sodium sulphate and sodium carbonate, filtered and the solvent was removed under vacuum to give compound **5a** (7.40 g, 75 %) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.35 - 7.24 (m, 10H), 5.84 (br s, 1H), 4.14 (s, 2H), 3.52 (d, J = 13.1 Hz, 2H), 3.37 (d, J = 13.1 Hz, 2H), 3.23 (td, J = 11.7, 3.5 Hz, 2H), 2.84 (d, J = 11.1 Hz, 1H), 2.69 -2.47 (m, 4H), 2.35 (td, J = 11.3, 3.8 Hz, 2H), 1.92 (d, J = 10.8 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 137.8 (C), 129.0 (CH), 128.5 (CH), 127.4 (CH), 65.6 (CH_2), 63.1 (CH_2), 60.7 (CH_2), 55.0 (C), 53.4 (CH_2), 48.9 (CH_2) ppm. IR (neat): 3158, 3030, 2926, 2804, 2768, 1452, 1136, 1037, 737, 697 cm^{-1}. HRMS (ESI^+): m/z = 352.23789 (100%, $[M+H]^+$). Calc. For $C_{22}H_{29}ON_3+H^+$: 352.23834.

(2,8-Dibenzyloctahydro-9a*H*-pyrazino[1,2-*a*]pyrazin-9a-yl)methyl acetate (9). Compound **5a** (175 mg, 0.498 mmol) was dissolved in dichloromethane (1 mL) and acetic anhydride (60 µL, 0.647 mmol) was added dropwise with stirring. The resulting solution was left at room temperature for 18 hours and checked

periodically by TLC (EtOAc 100 %). The mixture was washed once with saturated aqueous solution of sodium carbonate, dried over sodium carbonate and sodium sulphate, filtered and the solvent was removed under vacuum to yield compound **9** (quant., 196 mg) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$,298 K) δ 7.33 – 7.18 (m, 10H), 4.67 (s, 2H), 3.63 (d, *J* = 13.1 Hz, 2H), 3.27 (d, *J* = 13.2 Hz, 2H), 3.01 (td, *J* = 11.6, 3.5 Hz, 2H), 2.87 (dp, *J* = 10.9, 1.9 Hz, 2H), 2.63 (dd, *J* = 10.7, 2.0 Hz, 2H), 2.56 (ddd, *J* = 11.7, 3.8, 1.9 Hz, 2H), 2.40 (td, *J* = 11.2, 3.7 Hz, 2H), 1.71 (s, 3H), 1.61 (d, *J* = 10.8 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 171.3 (C), 138.8 (C), 128.8 (CH), 128.1 (CH), 126.9 (CH), 62.8 (CH_2), 59.0 (CH_2), 56.9 (CH_2), 55.2 (C), 54.0 (CH_2), 48.7 (CH_2), 21.0 (CH_3) ppm. HRMS (ESI$^+$): *m*/z = 394.2488 ([M+H]$^+$). Calc. For $C_{24}H_{31}O_2N_3$+H$^+$: 394.2489.

(2,8-Dibenzyloctahydro-9a*H*-pyrazino[1,2-*a*]pyrazin-9a-yl)methyl 2-phenethylcarbamate (10). Compound **5a** (170 mg, 0.484 mmol) was dissolved in dichloromethane (1 mL) and 2-phenethyl isocyanate (0.1 mL, 0.726 mmol) was added dropwise with stirring. The resulting solution was left at room temperature for 20 hours and checked periodically by TLC (EtOAc 100 %). The mixture was dried under vacuum, the residue was triturated with petroleum ether, filtered under vacuum and washed with petroleum ether. The product was purified by crystallisation from diethyl ether at 4 °C, recovered by vacuum filtration, washed with diethyl ether and petroleum ether, dried under vacuum and obtained as white crystals (118 mg, 49 %). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.34 – 7.15 (m, 15H), 4.70 (s, 2H), 4.25 (t, *J* = 5.8 Hz, 1H), 3.59 (d, *J* = 13.2 Hz, 2H), 3.45 (q, *J* = 6.7 Hz, 1H), 3.31 (d, *J* = 13.2 Hz, 2H), 3.02 (td, *J* = 11.5, 3.5 Hz, 2H), 2.85 – 2.80 (m, 4H), 2.61 (d, *J* = 10.7 Hz, 2H), 2.54 (dt, *J* = 11.5, 2.9 Hz, 2H), 2.39 (td, *J* = 11.1, 3.7 Hz, 2H), 1.65 (d, *J* = 10.7 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K) signals are referred to the main rotamer, δ 156.7 (C), 139.4 (C), 139.0 (C), 128.9 (CH), 128.8 (CH), 128.7 (CH), 126.9 (CH), 126.6 (CH), 126.5 (CH), 63.0 (CH_2), 59.8 (CH_2), 57.3 (CH_2), 55.5 (C), 53.8 (CH_2), 48.8 (CH_2), 42.34 (CH_2), 36.60 (CH_2) ppm. HRMS (ESI$^+$): *m*/z = 499.3070 ([M+H]$^+$). Calc. For $C_{31}H_{38}O_2N_4$+H$^+$: 499.3068.

2,8-dibenzyloctahydro-9a*H*-pyrazino[1,2-*a*]pyrazine-9a-carbaldehyde (11). Compound **5a** (180 mg, 0.512 mmol) was dissolved in dimethyl sulfoxide (2 mL) and 2-iodoxybenzoic acid (287 mg, 1.02 mmol) was added. At first a solution was obtained, but, as the reaction proceeds, a copious crystalline precipitate was formed. The mixture was stirred at room temperature for 24 h and checked periodically by TLC (EtOAc). The reaction was quenched in a sodium carbonate saturated solution, which was extracted trice with diethyl ether. The combined organic phases were dried over sodium sulphate, filtered and the solvent was removed under vacuum. The product was purified by crystallisation from diethyl ether at 4 °C, recovered by vacuum filtration, washed with diethyl ether and petroleum ether, dried under vacuum and obtained as off-white crystals (80.7 mg, 45 %). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 9.69 (s, 1H), 7.32 – 7.23 (m, 10H), 3.57 – 3.47 (m, 4H), 3.34 (d, *J* = 13.3 Hz, 2H), 2.86 (d, *J* = 11.2 Hz, 4H), 2.69 (ddd, *J* = 11.7, 3.7, 2.0 Hz, 2H), 2.36 (td, *J* = 11.4, 3.6 Hz, 2H), 1.88 (d, *J* = 11.1 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 204.5 (CH), 138.0 (C), 128.8 (CH), 128.4 (CH), 127.3 (CH), 65.3 (C), 62.9 (CH_2), 56.8 (CH_2), 53.4 (CH_2), 49.0 (CH_2) ppm. HRMS (ESI$^+$): *m*/z = 350.2225 ([M+H]$^+$). Calc. For $C_{22}H_{27}ON_3$+H$^+$: 350.2227.

(Octahydro-9a*H*-pyrazino[1,2-*a*]pyrazin-9a-yl)methanol (12). Compound **5a** (2.00 g, 5.69 mmol) was dissolved in methanol (20 mL) and palladium on carbon (10 %, wet 50% water, 500 mg) was added. The mixture was stirred under hydrogen atmosphere (10 bar) at room temperature for 48 h and checked periodically by TLC (EtOAc 100 % and DCM/MeOH/NH_3 6:4:1). The mixture was filtered under vacuum through Celite, the filter cake was thoroughly washed with methanol and discarded, while the filtrate was dried under vacuum. The product was purified by crystallization from acetonitrile at 4 °C and it was recovered by vacuum filtration, washed with acetonitrile, diethyl ether and petroleum ether, dried under vacuum and obtained as off-white yellowish crystals (699 mg, 72 %). ^{1}H NMR (400 MHz, D_2O, 323 K) δ 4.28 (s, 2H), 3.13 – 3.02 (m, 8H), 2.72 – 2.62 (m, 4H) ppm. ^{13}C NMR (101 MHz, D_2O, 323 K) δ 55.8 (C), 55.1 (CH_2), 48.1 (CH_2), 47.7 (CH_2), 43.5 (CH_2) ppm. HRMS (ESI$^+$): *m*/z = 172.1446 ([M+H]$^+$). Calc. For $C_8H_{17}ON_3$+H$^+$: 172.1444.

(2,8-Diacetyloctahydro-9a*H*-pyrazino[1,2-*a*]pyrazin-9a-yl)methanol (13). Compound **12** (105 mg, 0.613 mmol) was dissolved in dichloromethane (2 mL) and acetic anhydride (130 µL, 1.35 mmol) was added with stirring. The reaction was left at RT for 24 h and checked by TLC (DCM/MeOH 9:1). The mixture was washed

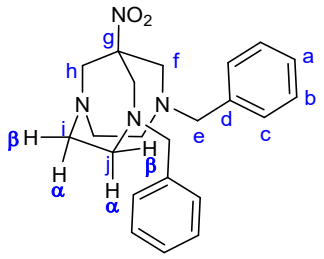
once with saturated aqueous solution of sodium carbonate, dried over sodium carbonate and sodium sulphate, filtered and the solvent was removed under vacuum. The product was crystallised from diethyl ether (5 mL) at 4 °C for 15 h and the solid was recovered by vacuum filtration, washed with diethyl ether and petroleum ether and dried under vacuum to give compound **13** (129 mg, 82 %) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) signals are referred to the main rotamer, δ 4.53 (d, J = 11.1 Hz, 1H), 4.44 (dd, J = 13.1, 2.3 Hz, 1H), 3.91 (dd, J = 12.9, 2.2 Hz, 1H), 3.77 – 3.67 (m, 1H), 3.54 – 3.33 (m, 3H), 3.24 (dd, J = 10.2, 4.6 Hz, 1H), 2.80 (td, J = 11.2, 3.6 Hz, 2H), 2.72 (d, J = 13.6 Hz, 1H), 2.65 (td, J = 11.9, 3.4 Hz, 1H), 2.54 (dd, J = 11.8, 3.8, 1.5 Hz, 1H), 2.44 (ddd, J = 11.8, 3.9, 1.8 Hz, 1H), 2.36 (d, J = 13.0 Hz, 1H), 2.14 (s, 3H), 2.11 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K) signals are referred to the main rotamer, δ 170.8 (C), 170.2 (C), 57.6 (C), 52.4 (CH_2), 49.5 (CH_2), 48.6 (CH_2), 47.8 (CH_2), 47.3 (CH_2), 46.2 (CH_2), 41.2 (CH_2), 21.2 (CH_3), 20.9 (CH_3) ppm. HRMS (ESI$^+$): m/z = 256.1658 ([M+H]$^+$). Calc. For $C_{12}H_{21}O_3N_3$+H$^+$: 256.1656.

(2,8-Diacetyloctahydro-9a*H*-pyrazino[1,2-*a*]pyrazin-9a-yl)methyl acetate (14). Compound **12** (102 mg, 0.596 mmol) was dissolved in dichloromethane (2 mL) and acetic anhydride (170 µL, 1.79 mmol) was added with stirring. The reaction was left at RT for 48 h and checked by TLC (DCM/MeOH 9:1). The mixture was washed once with saturated aqueous solution of sodium carbonate, dried over sodium carbonate and sodium sulphate, filtered and the solvent was removed under vacuum. The product was crystallised from petroleum ether (5 mL) at 4 °C for 17 h and the solid was recovered by vacuum filtration, washed with petroleum ether and dried under vacuum to yield compound **14** (138 mg, 78 %) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) signals are referred to the main rotamer, δ 4.58 (dd, J = 12.7, 2.1 Hz, 2H), 4.36 (d, J = 11.4 Hz, 1H), 4.15 (d, J = 64.2 Hz, 1H), 3.93 (d, J = 11.1 Hz, 1H), 3.87 – 3.80 (m, 1H), 3.77 – 3.72 (m, 1H), 3.35 (tt, J = 12.4, 3.6 Hz, 1H), 2.90 – 2.73 (m, 3H), 2.60 – 2.56 (m, 2H), 2.36 (dd, J = 12.8, 3.8 Hz, 1H), 2.11 – 2.03 (m, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K) signals are referred to the main rotamer, δ 170.7 (C), 169.7 (C), 169.4 (C), 56.0 (C) , 55.5 (CH_2), 55.4 (CH_2), 50.3 (CH_2), 47.7 (CH_2), 46.0 (CH_2), 44.9 (CH_2), 41.1 (CH_2), 21.2 (CH_3), 21.1 (CH_3), 20.9 (CH_3) ppm. HRMS (ESI$^+$): m/z = 298.1767 ([M+H]$^+$). Calc. For $C_{14}H_{23}O_4N_3$+H$^+$: 298.1761.

Di-*tert*-butyl 2,2'-(9a-(hydroxymethyl)hexahydro-2*H*-pyrazino[1,2-*a*]pyrazine-2,8(1*H*)-diyl)diacetate (15). Compound **12** (101 mg, 0.590 mmol) was dissolved in acetonitrile (2 mL) and *N*,*N*-diisopropylethylamine (DIPEA) (310 µL, 1.77 mmol) was added with stirring and the mixture was cooled to 0 °C. Then, *tert*-butyl bromoacetate (190 µL, 1.30 mmol) was added in 5 minutes, the mixture was left at room temperature for 48 h and checked by TLC (EtOAc 100 %). The mixture was dried under vacuum and the product was purified by gravity column chromatography on silica gel (eluent: EtOAc 100%) to give compound **15** (123 mg, 52 %) as a brownish oil. ^{1}H NMR (400 MHz, CDCl3, 298 K) δ 4.14 (s, 2H), 3.15 – 3.06 (m, 4H), 2.95 (d, J = 16.5 Hz, 2H), 2.78 – 2.70 (m, 4H), 2.55 – 2.45 (m, 4H), 1.97 (d, J = 10.6 Hz, 2H), 1.43 (s, 18H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 169.9 (C), 81.5 (C), 62.1 (CH_2), 60.2 (CH_2), 59.0 (CH_2), 55.9 (C), 53.0 (CH_2), 48.6 (CH_2), 28.2 (CH_3) ppm. HRMS (ESI$^+$): m/z = 400.2812 ([M+H]$^+$). Calc. For $C_{20}H_{37}O_5N_3$+H$^+$: 400.2806.

NMR assignment of compound 4 and 5a

The ^{1}H and ^{13}C NMR spectra of compound **4** (**Figure S1 - S6**) and **5a** (**Figure S7 – S12**), acquired at 298 K using respectively the standard parameter sets zg30, jmod, cosygpppqf, hsqcedetgpsisp, noesygpphpp and hmbcgplpndqf were assigned as reported in **Tables S1 – S2**.



4

Atom	Type	Proton	Carbon
a	CH	7.38 – 7.26	127.5
b	CH		129.0
c	CH		128.6
d	C	-	139.1
e	CH_2	3.77	63.9
f	CH_2	3.25	62.6
g	C	-	96.0
h	CH_2	3.85	57.3
i	CH_2	α 2.90, β 3.03	54.0
j	CH_2	α 2.88, β 2.67	53.4

Table S1. NMR full assignment of signals of compound **4**.

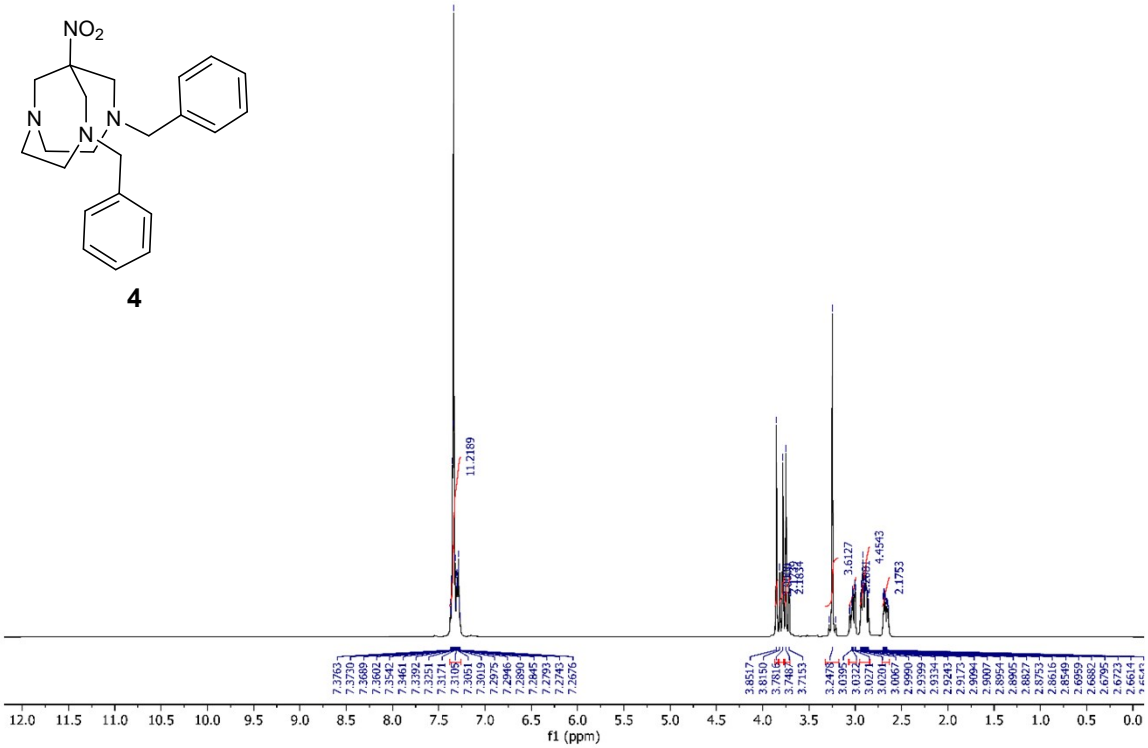


Figure S1. ^{1}H NMR spectrum of compound **4**.

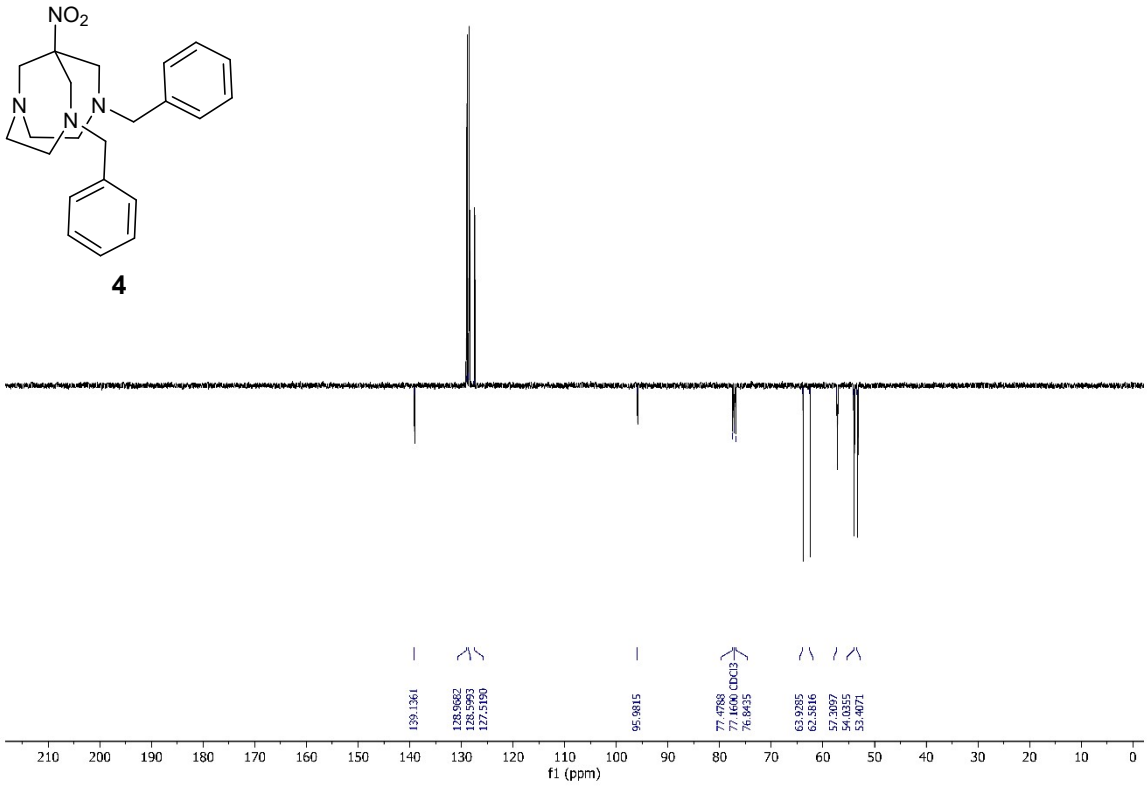


Figure S2. ^{13}C APT NMR spectrum of compound **4**.

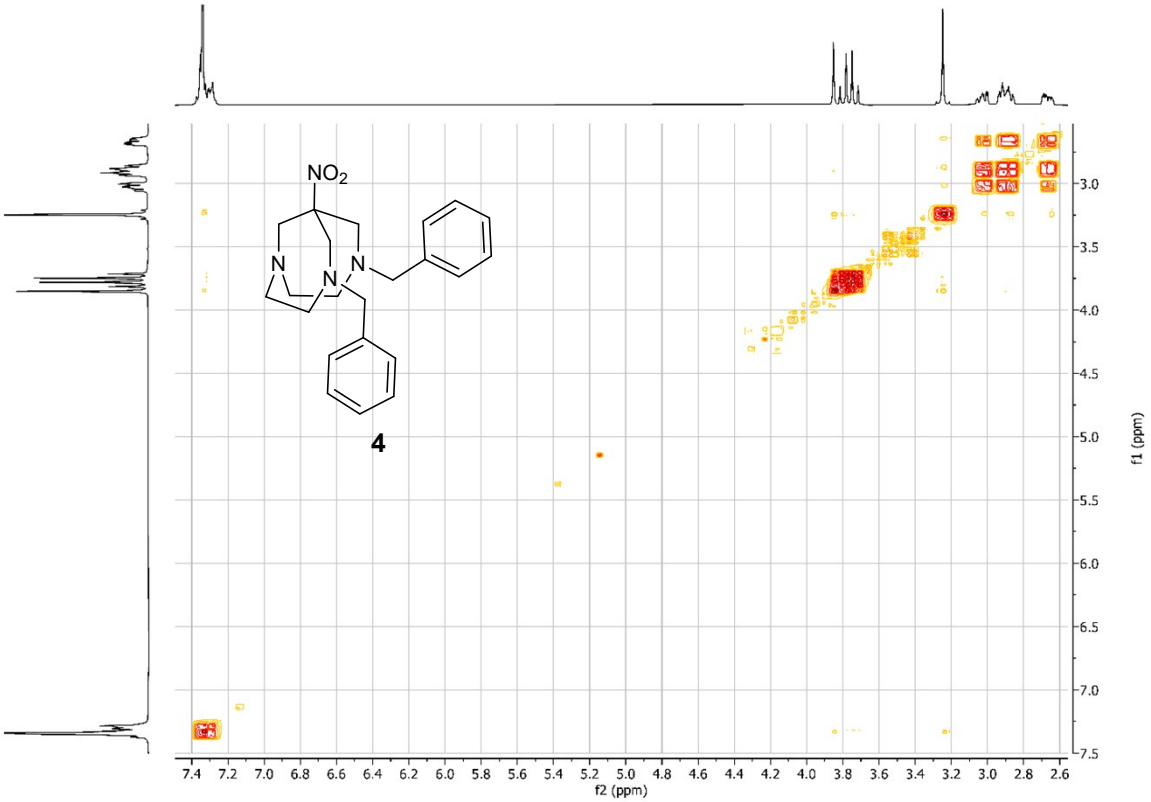


Figure S3. $^{1}H - {}^{1}H$ COSY spectrum of compound **4**.

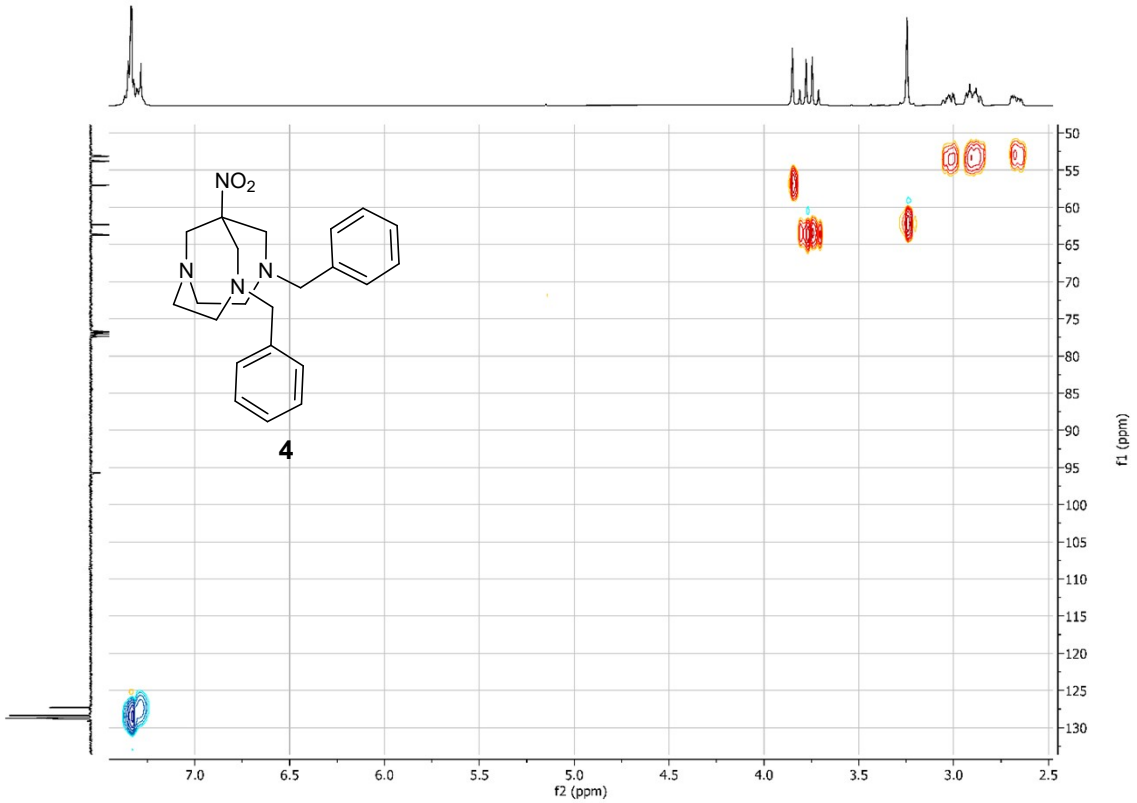


Figure S4. $^{1}H - {}^{13}C$ HSQC spectrum of compound **4**.

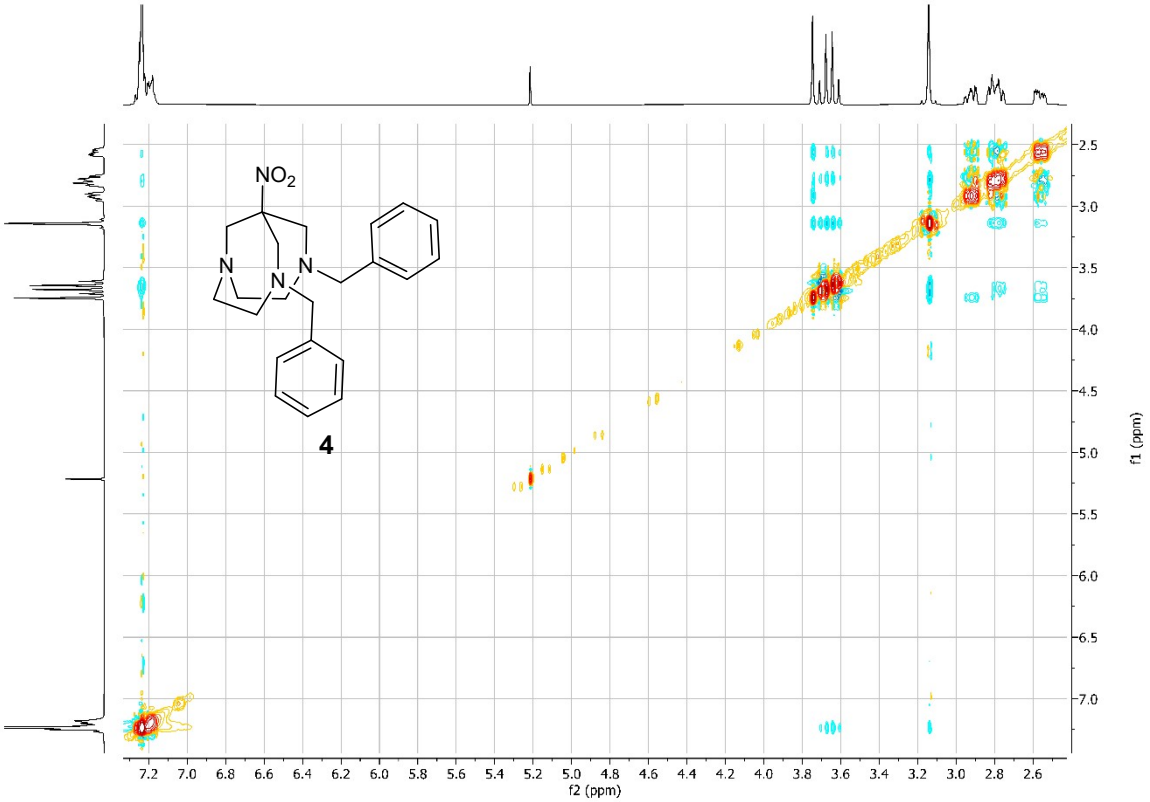


Figure S5. $^{1}H - {}^{1}H$ NOESY spectrum of compound **4**.

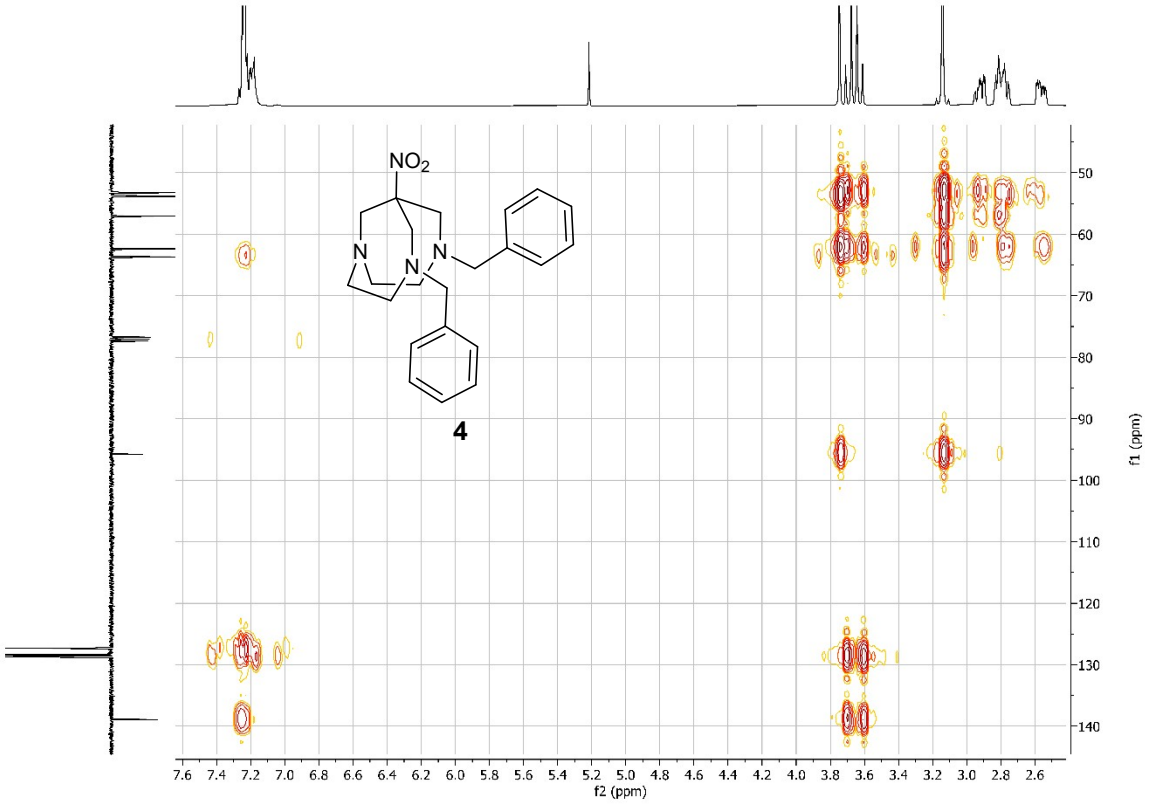
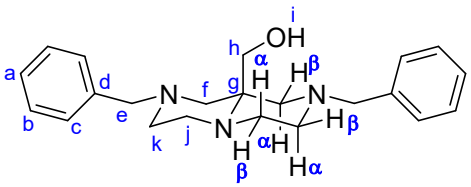


Figure S6. $^{1}H - {}^{13}C$ HMBC spectrum of compound **4**.



5a

Atom	Type	Proton	Carbon
a	CH	7.35 – 7.24	127.4
b	CH		129.0
c	CH		128.5
d	C	-	137.8
e	CH_2	3.52, 3.37	63.1
f	CH_2	α 1.92, β 2.55	60.7
g	C	-	55.0
h	CH_2	4.14	65.6
i	OH	5.84	-
j	CH_2	α 3.23, β 2.59	48.9
k	CH_2	α 2.35, β 2.84	53.4

Table S2. NMR full assignment of signals of compound **5a**.

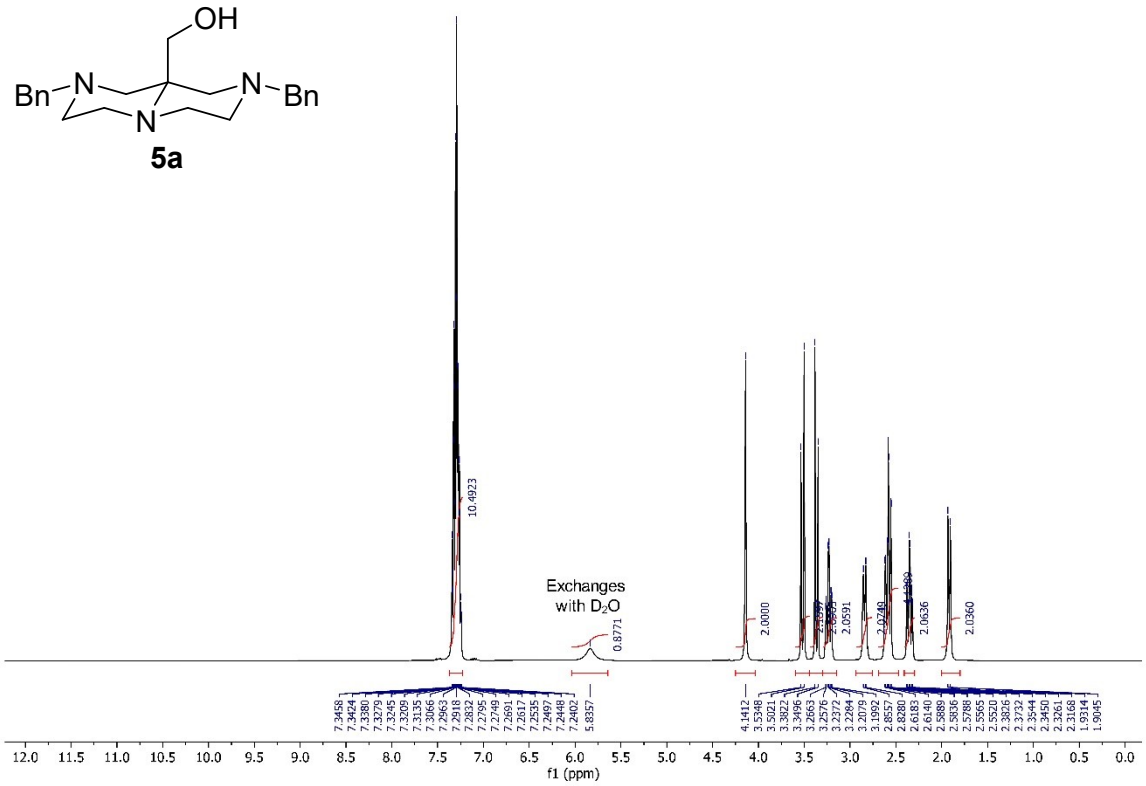


Figure S7. ^{1}H NMR spectrum of compound **5a**.

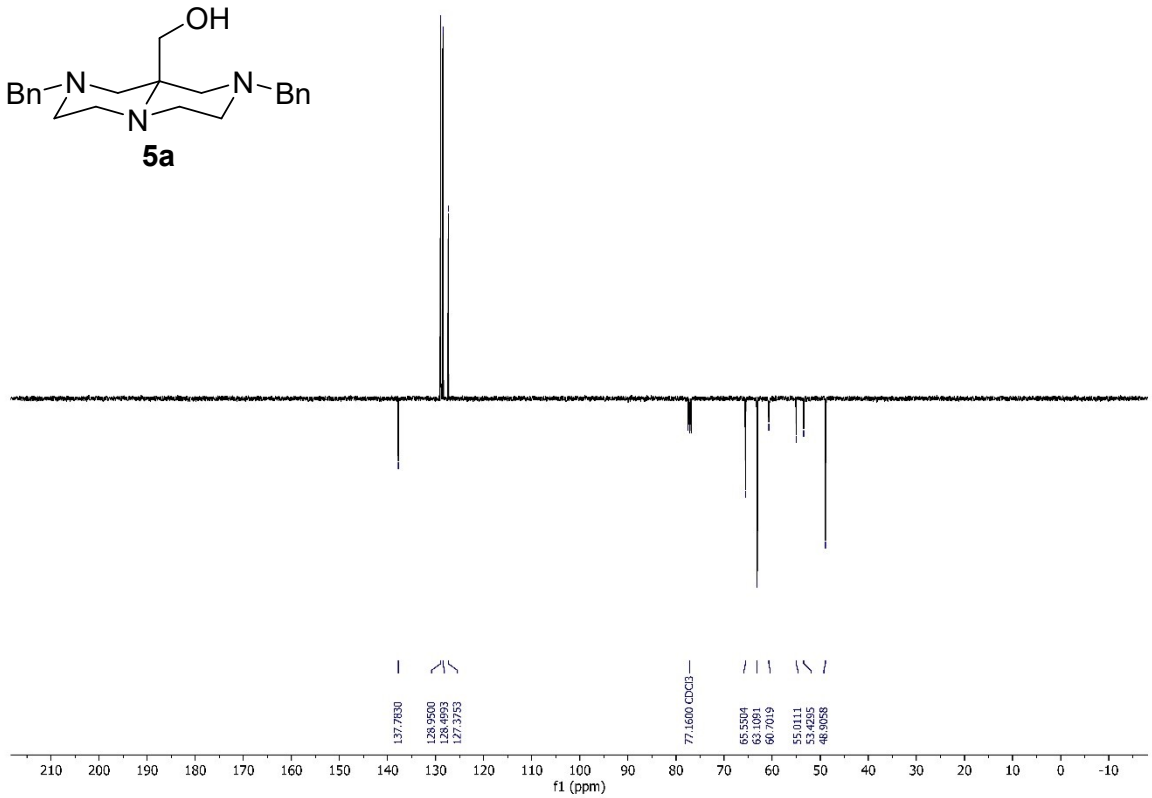


Figure S8. ^{13}C APT NMR spectrum of compound **5a**.

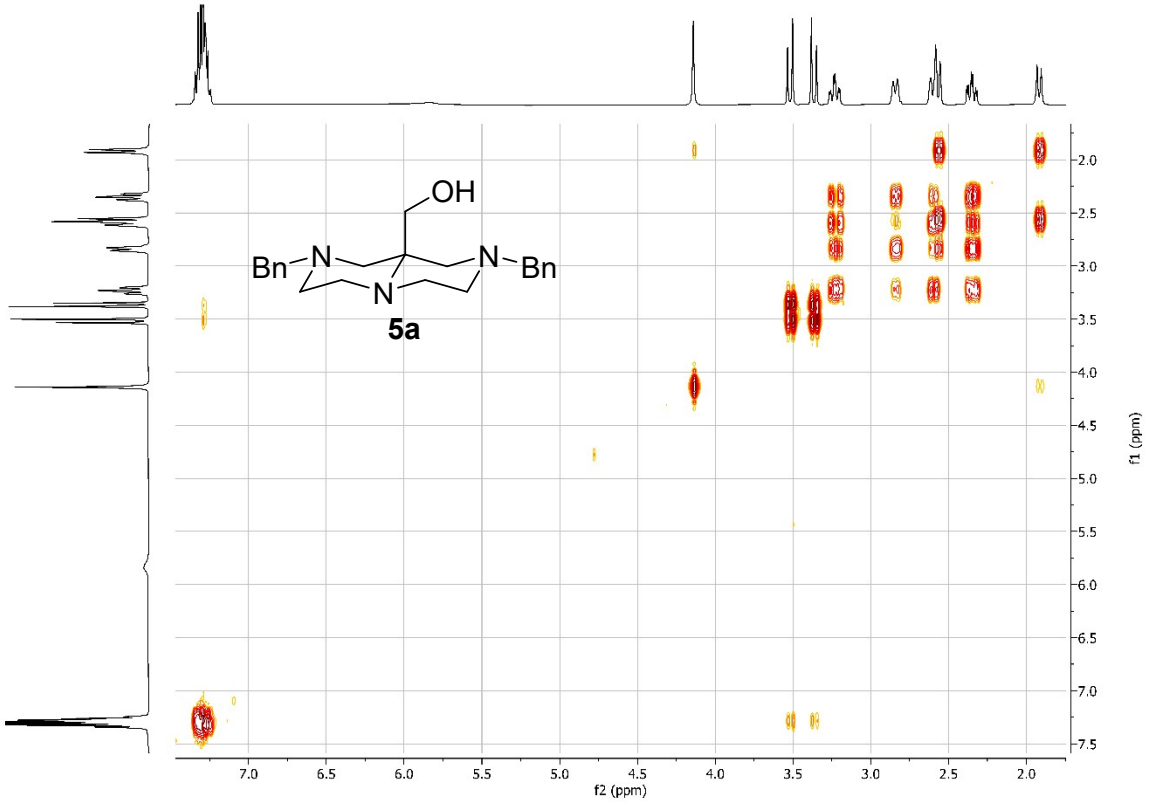


Figure S9. $^{1}H - {}^{1}H$ COSY spectrum of compound **5a**.

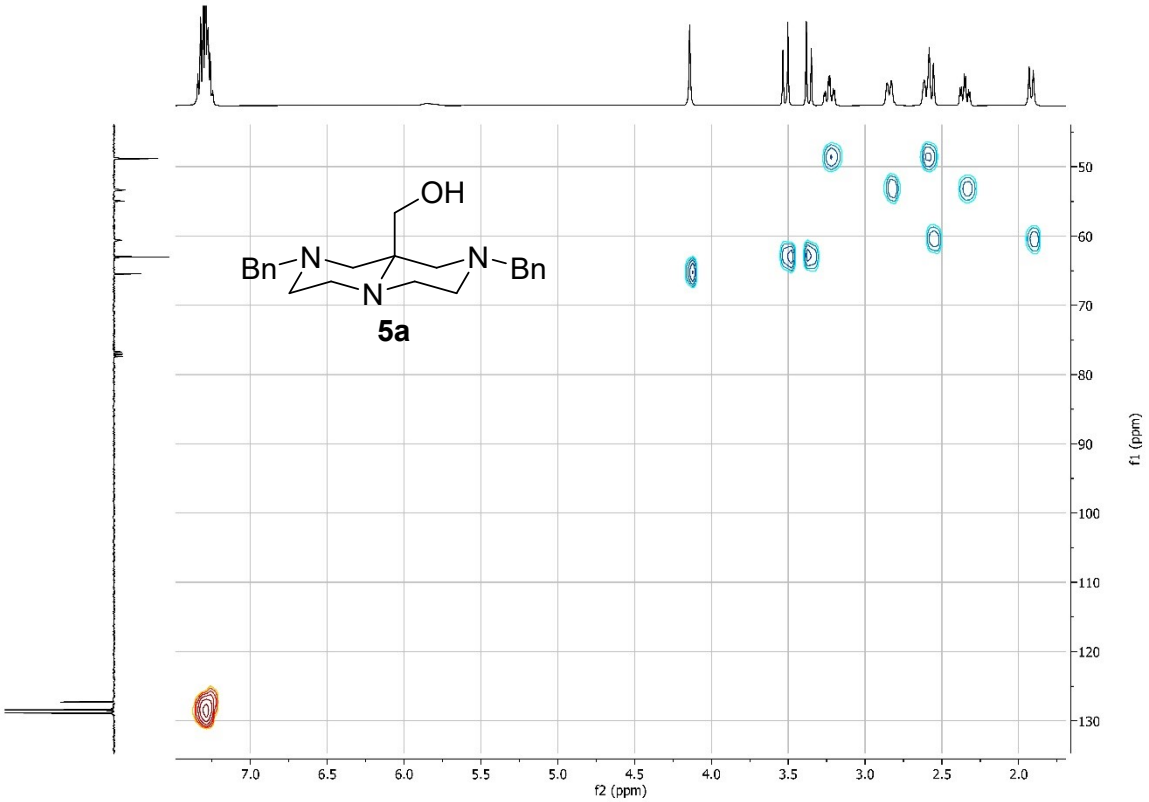


Figure S10. $^{1}H - {}^{13}C$ HSQC spectrum of compound **5a**.

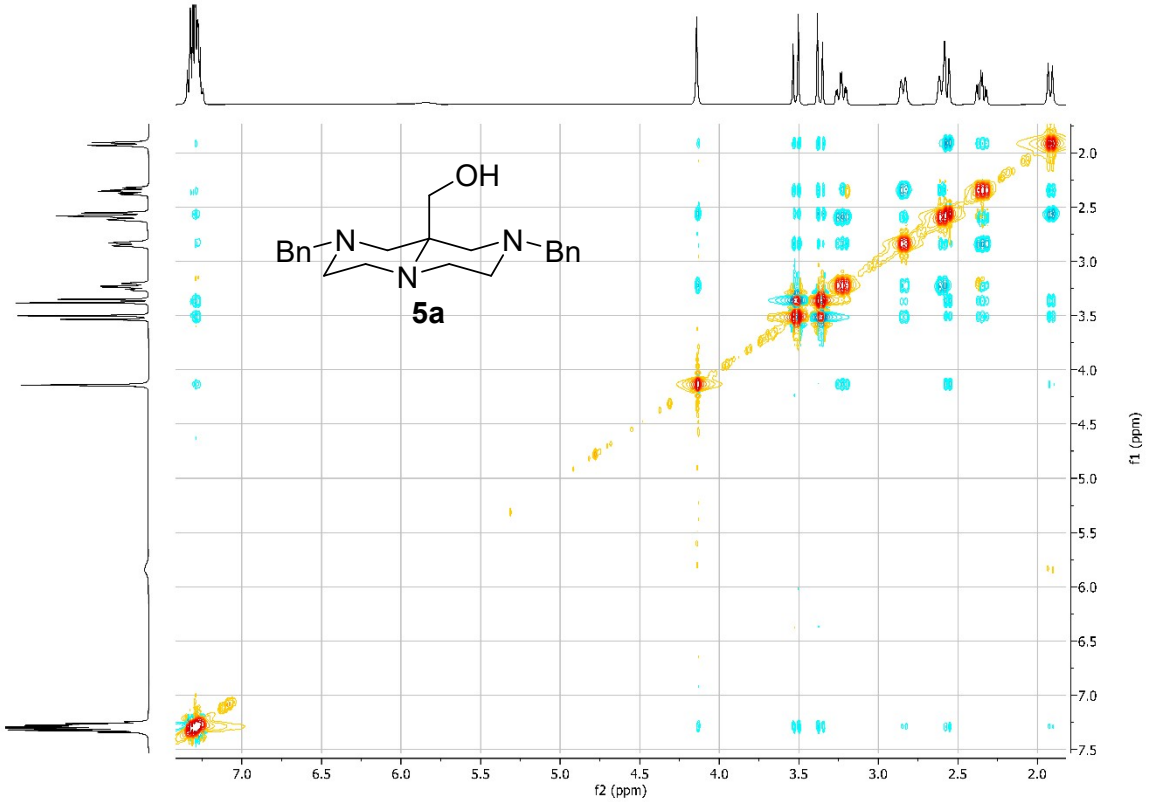


Figure S11. ^{1}H – ^{1}H NOESY spectrum of compound **5a**.

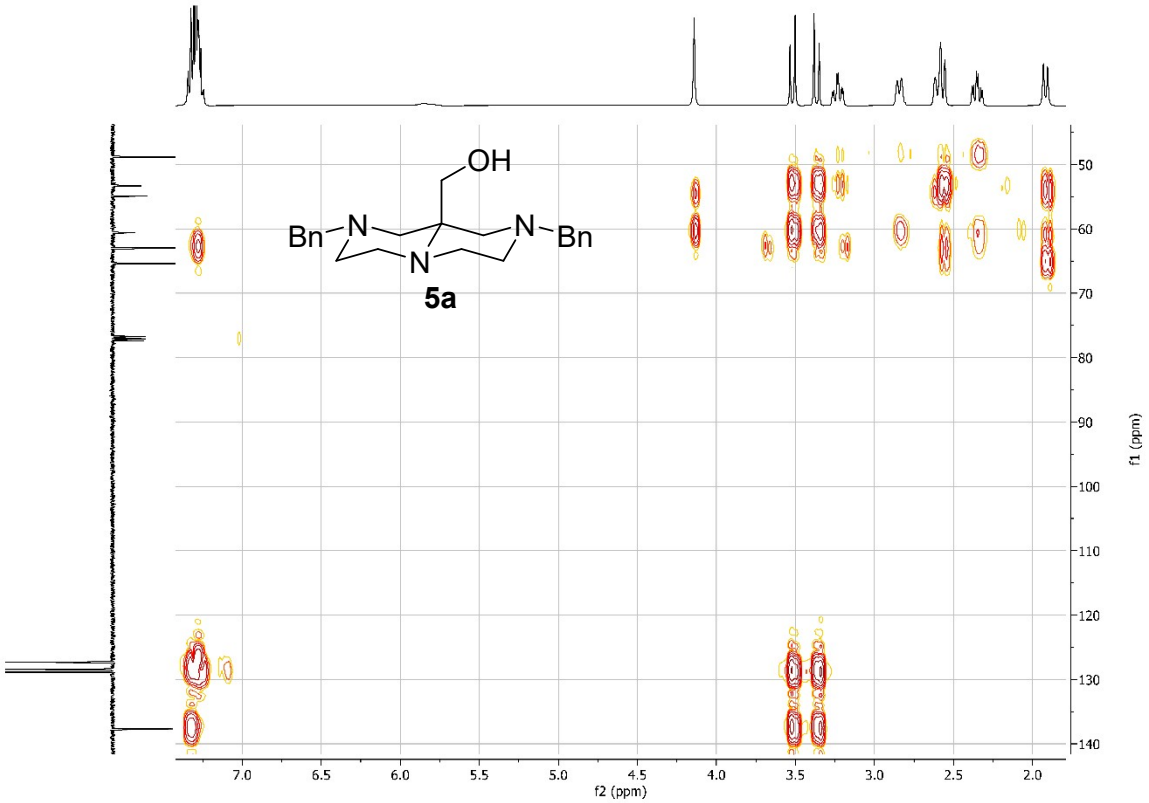


Figure S12. ^{1}H – ^{13}C HMBC spectrum of compound **5a**.

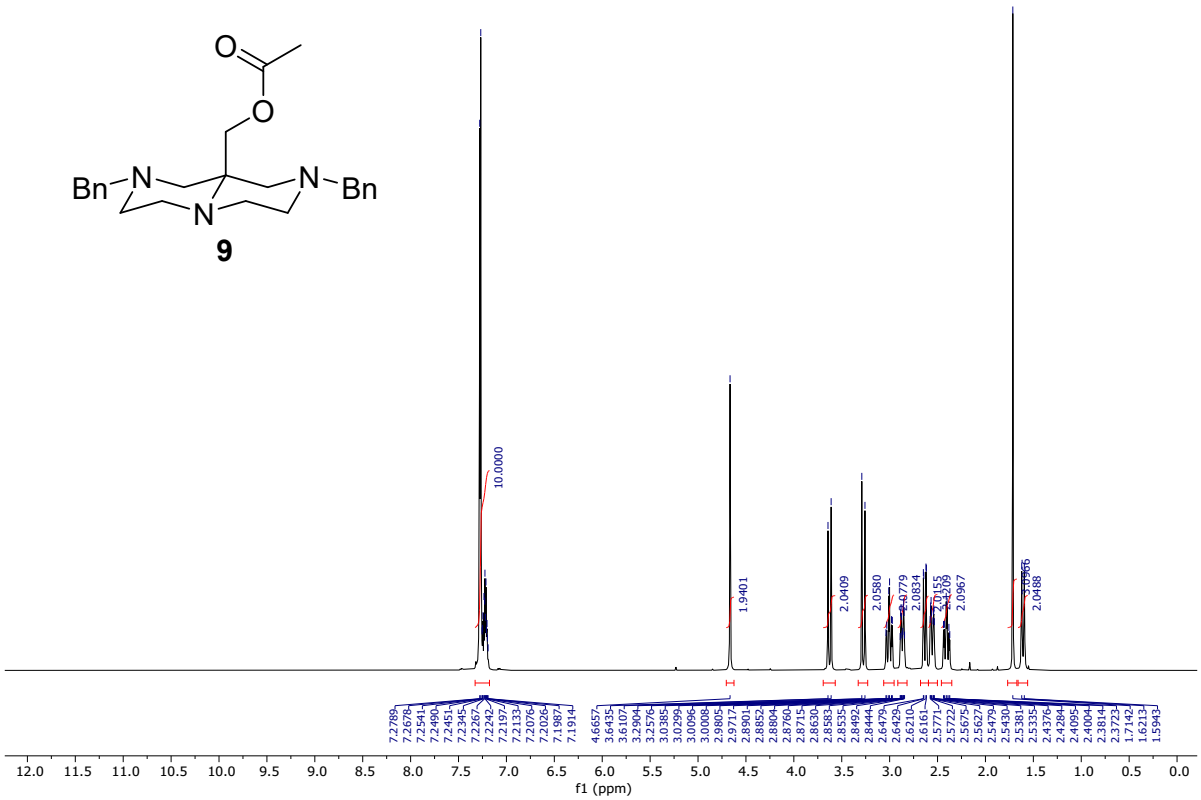


Figure S13. ^{1}H NMR spectrum of compound **9**.

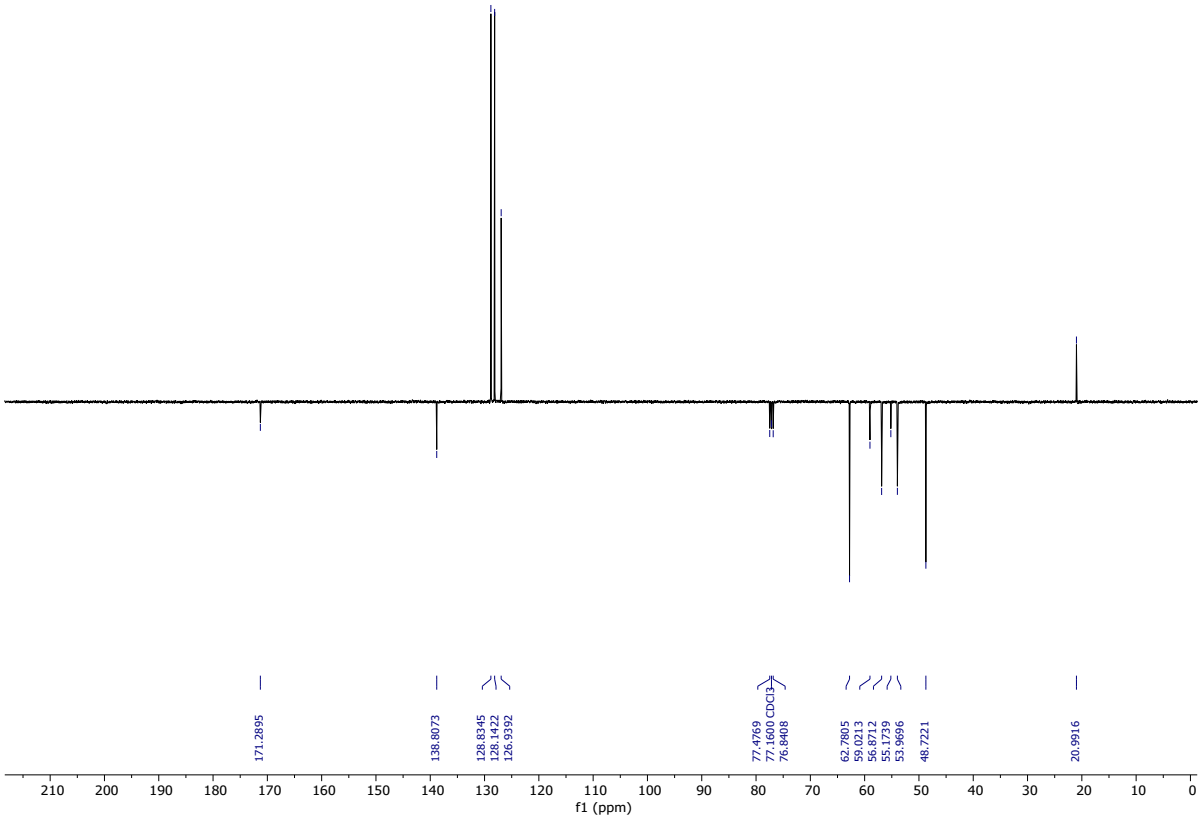


Figure S14. ^{13}C APT NMR spectrum of compound **9**.

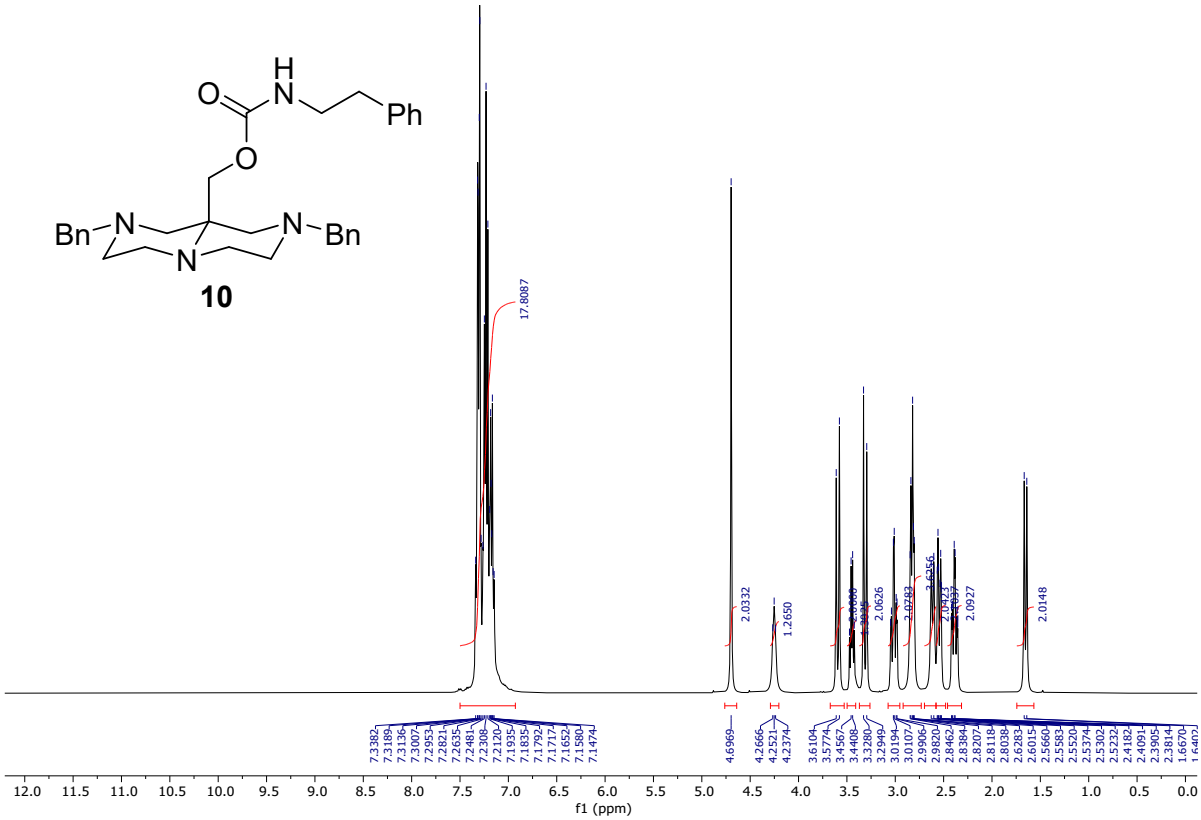


Figure S15. ^{1}H NMR spectrum of compound **10**.

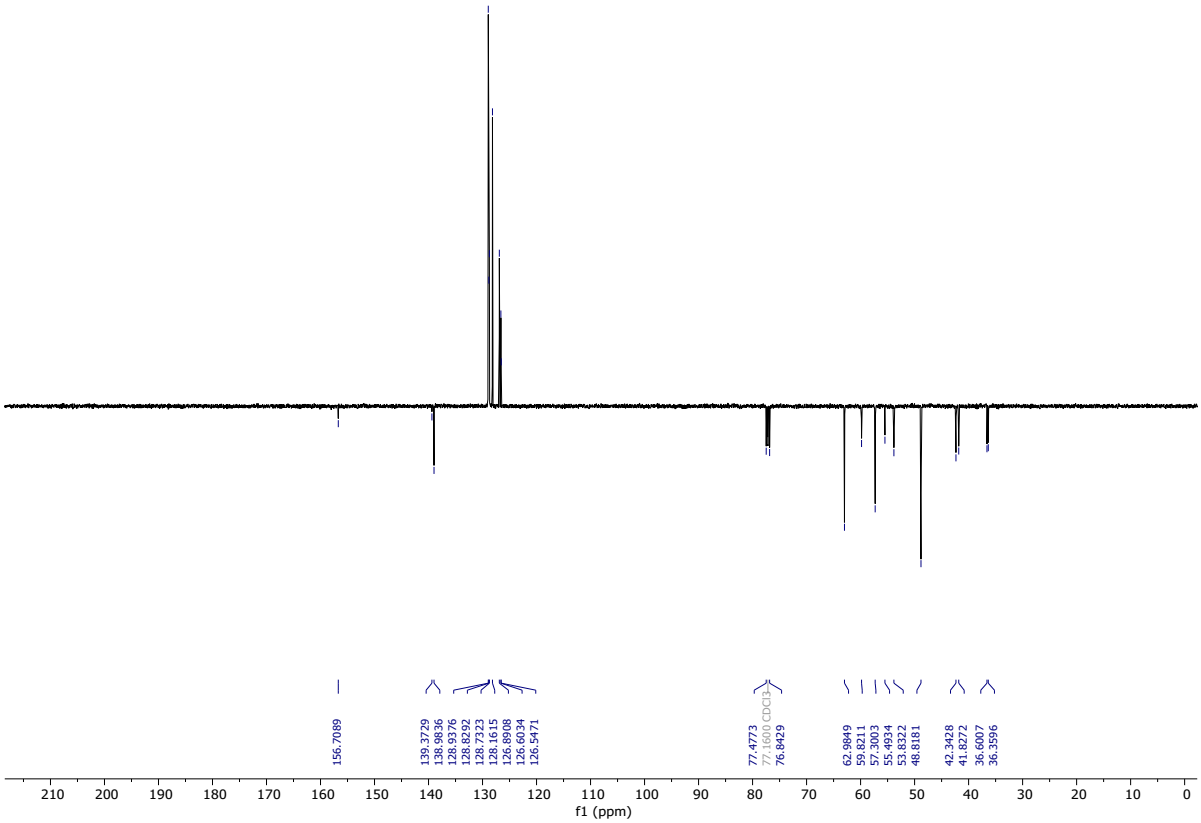


Figure S16. ^{13}C APT NMR spectrum of compound **10**.

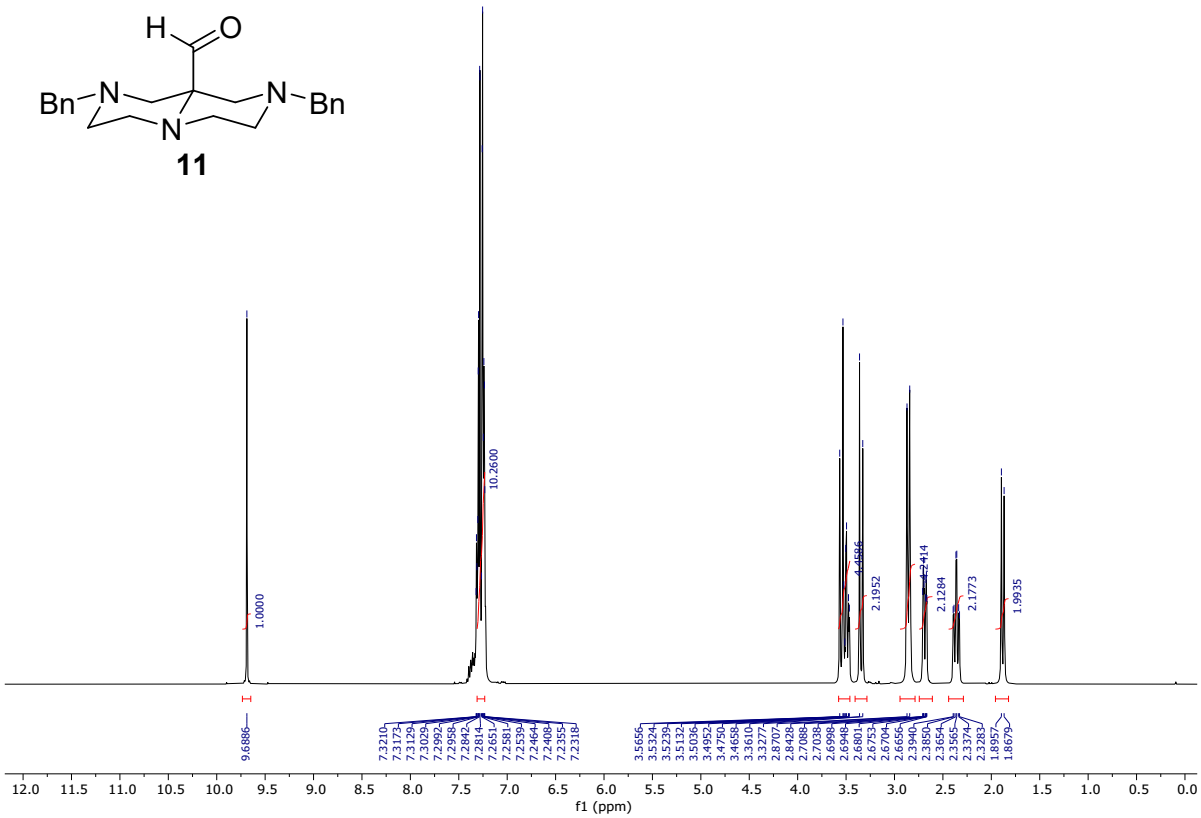


Figure S17. ^{1}H NMR spectrum of compound **11**.

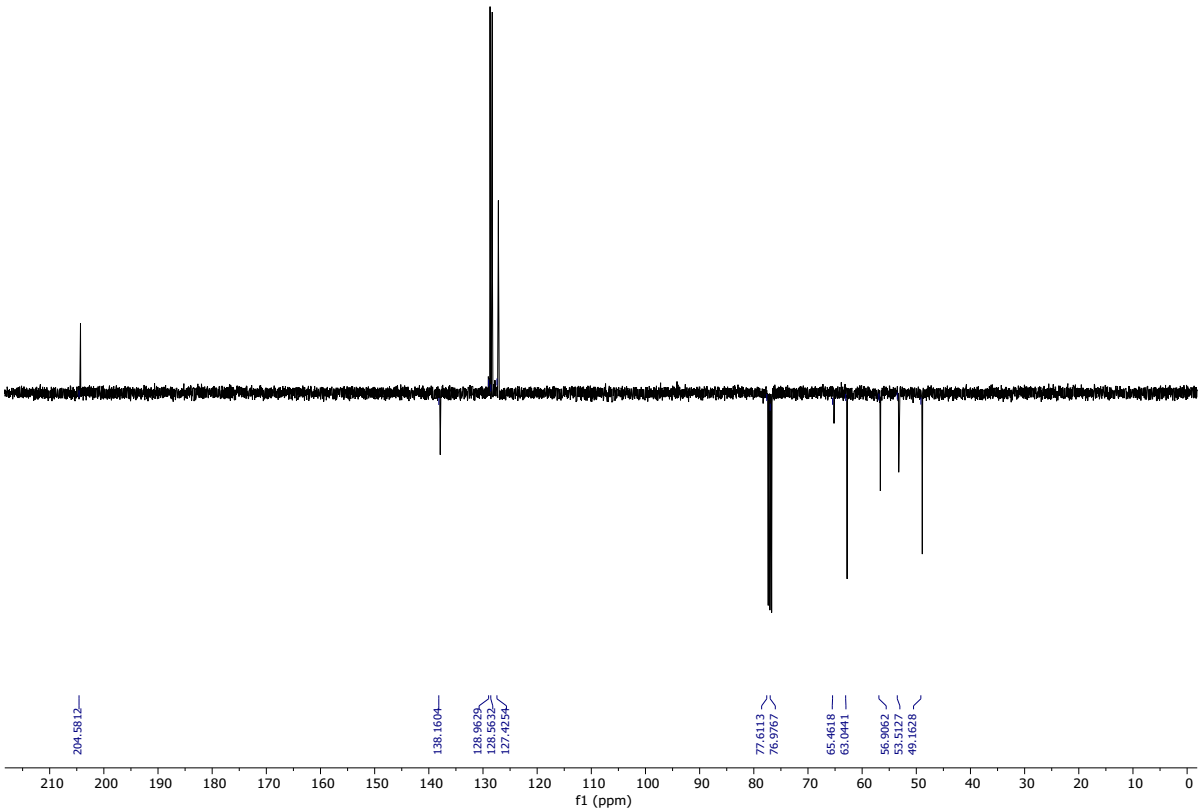


Figure S18. ^{13}C APT NMR spectrum of compound **11**.

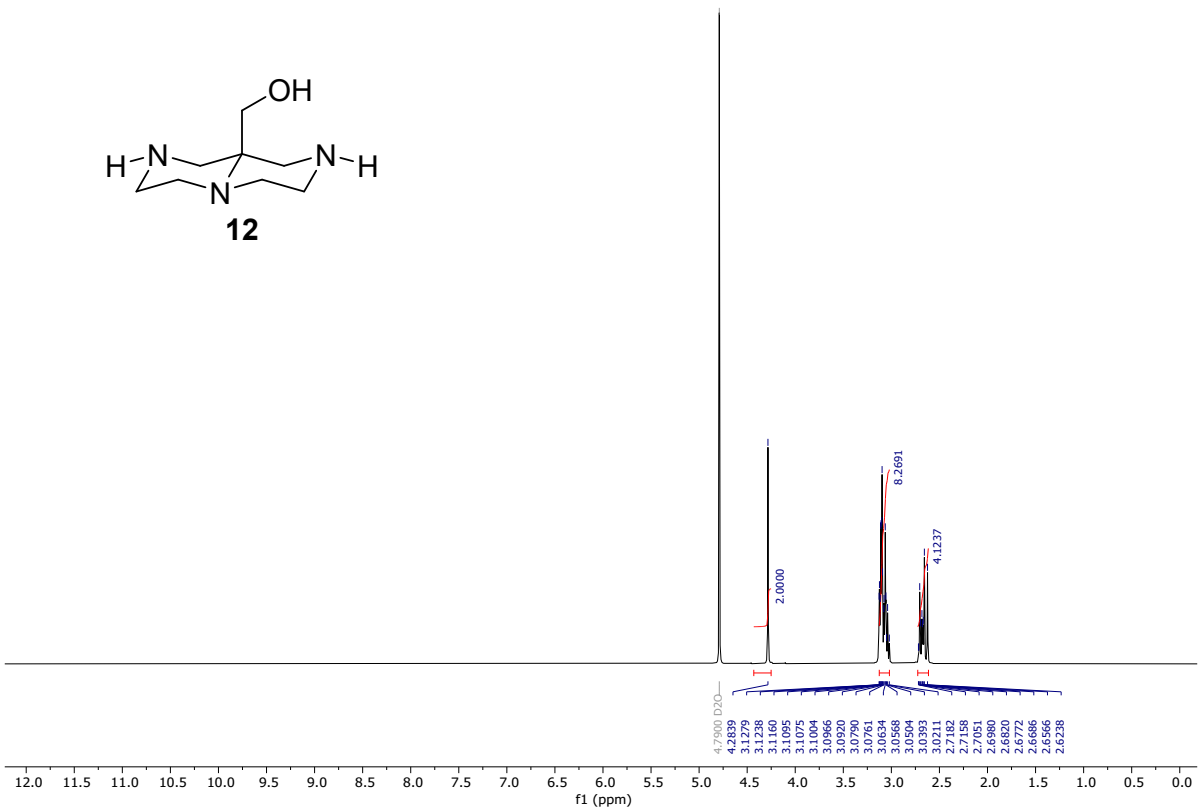


Figure S19. ^{1}H NMR spectrum of compound **12**.

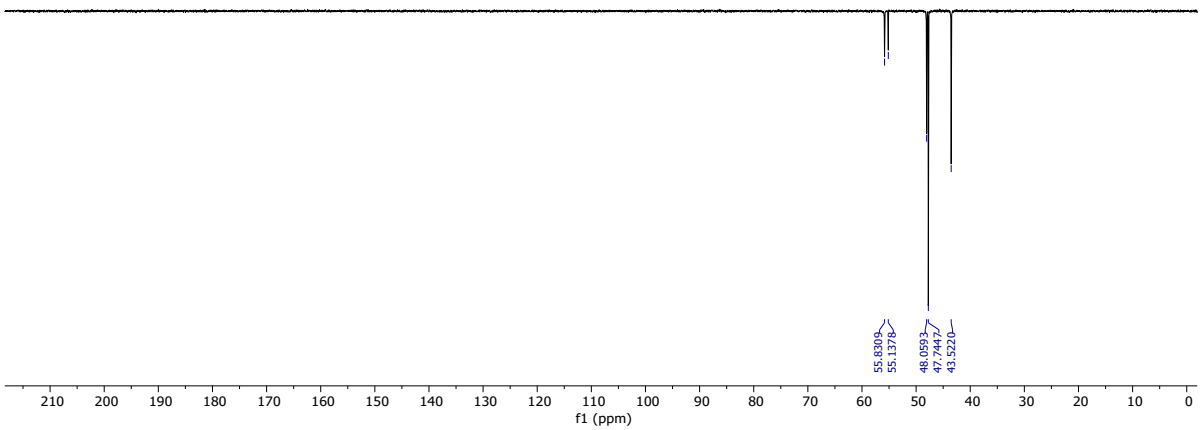


Figure S20. ^{13}C APT NMR spectrum of compound **12**.

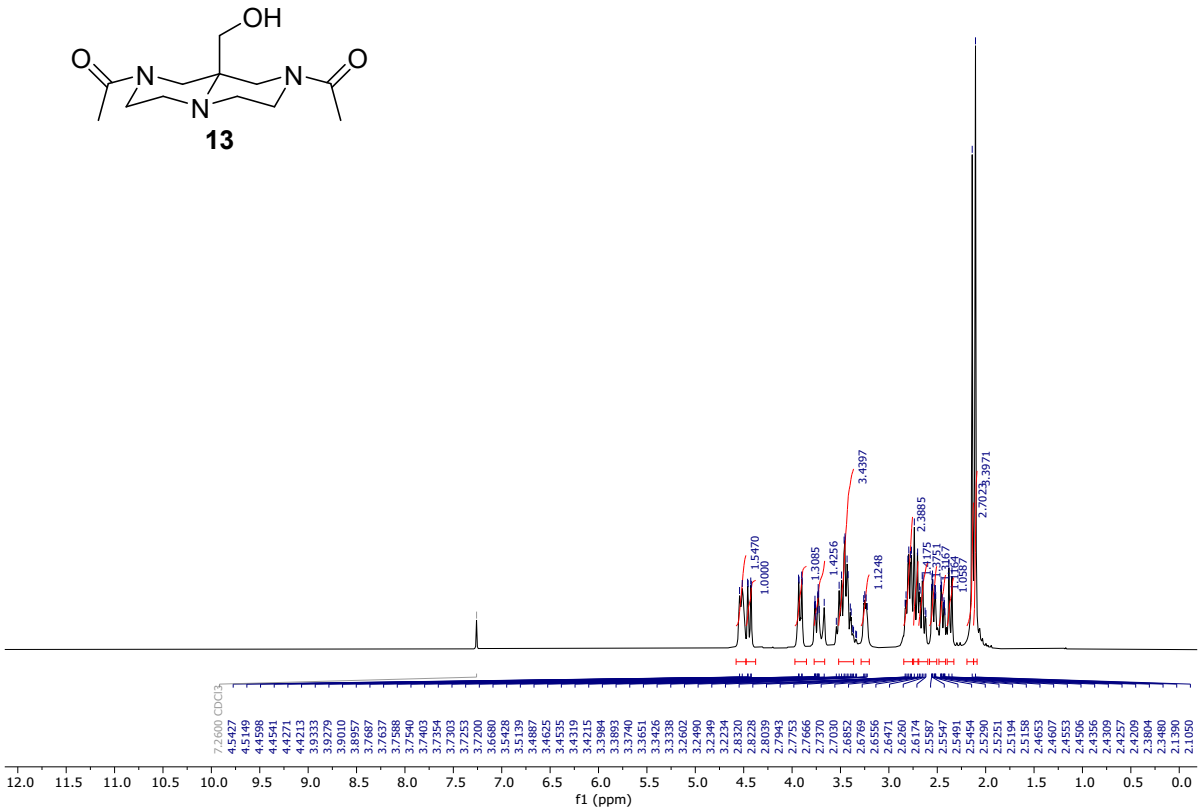


Figure S21. ^{1}H NMR spectrum of compound **13**.

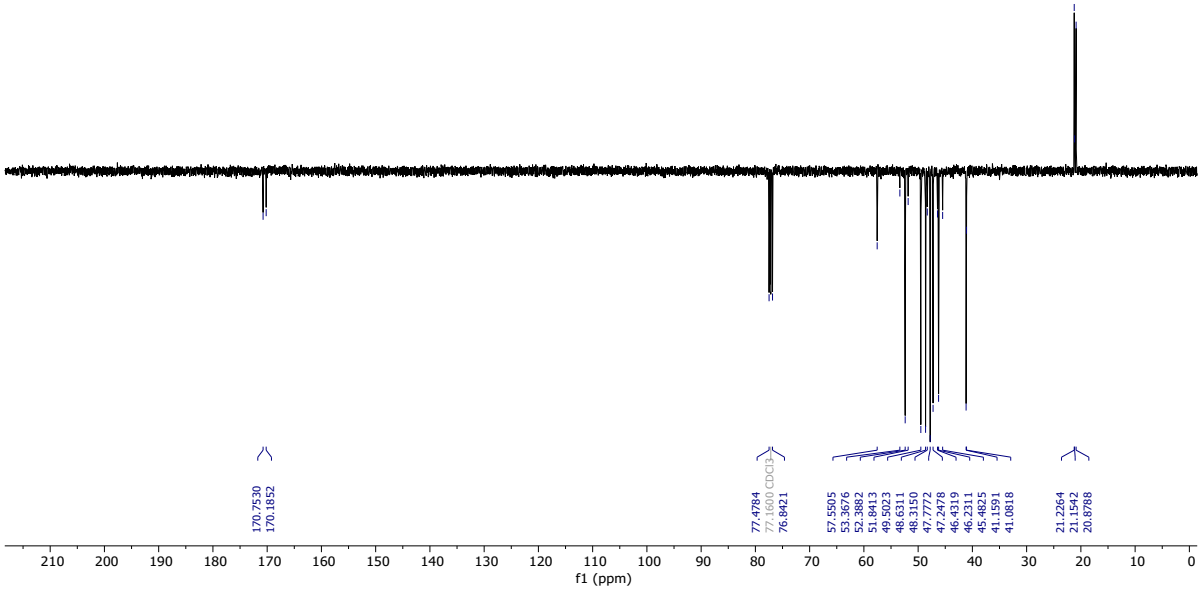


Figure S22. ^{13}C APT NMR spectrum of compound **13**.

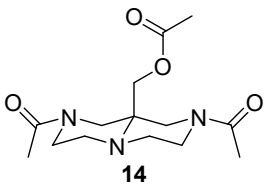


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Figure S23. ^{1}H NMR spectrum of compound **14**.

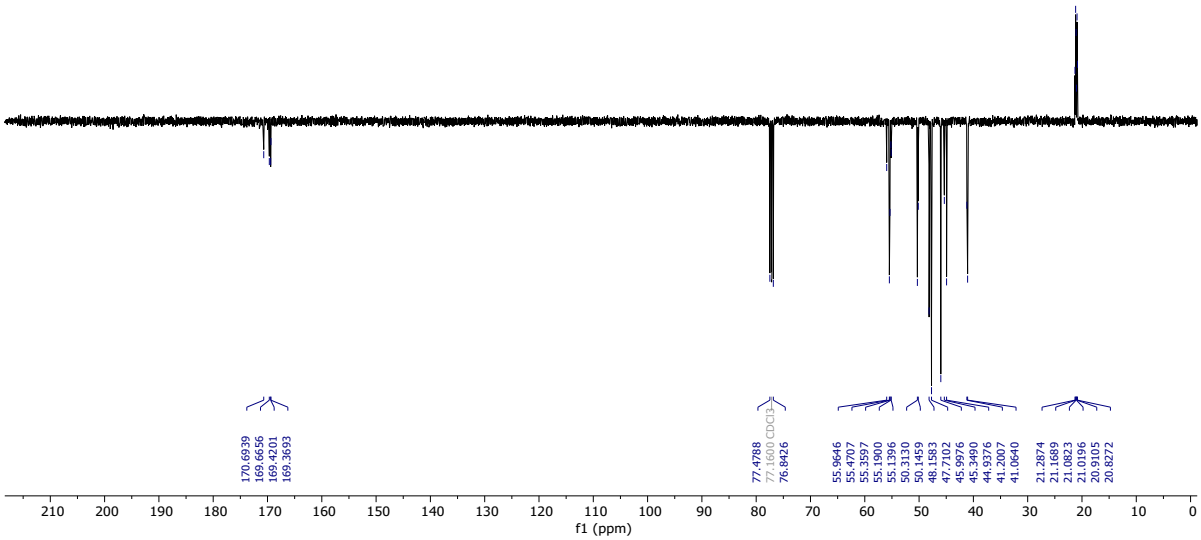

Figure S24. ^{13}C APT NMR spectrum of compound **14**.

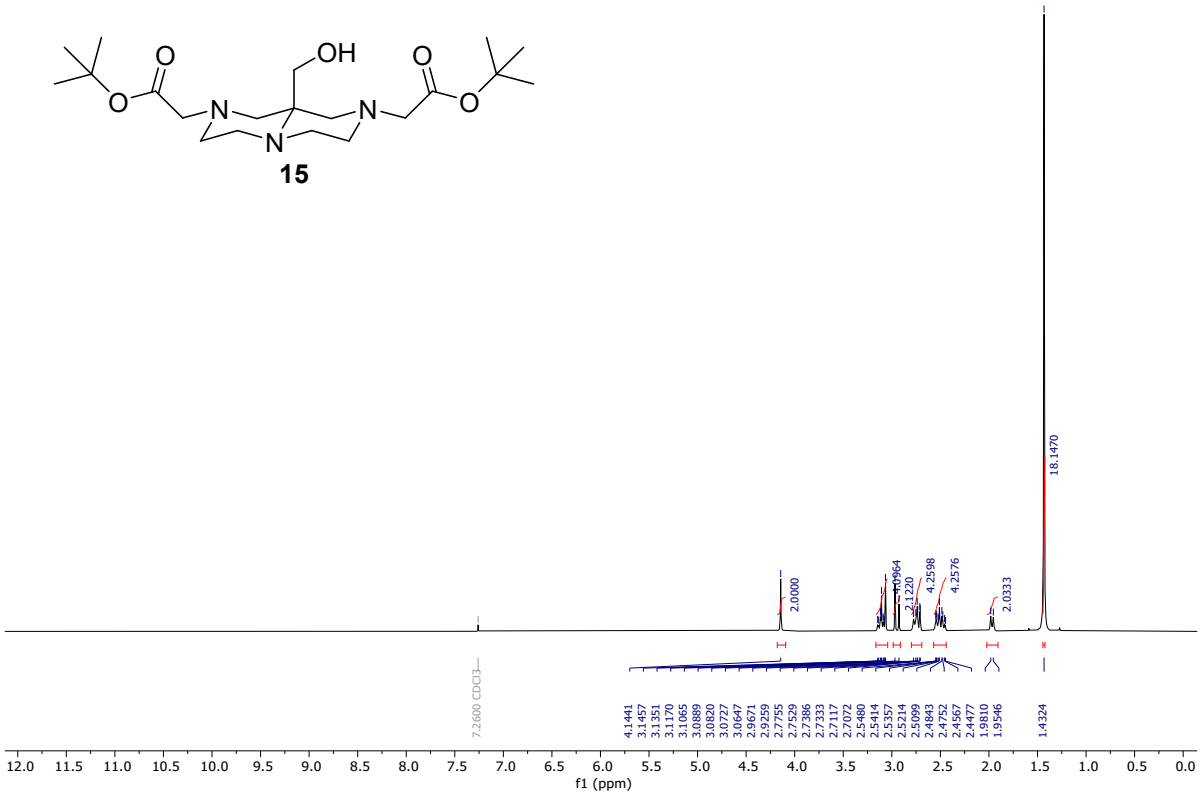

Figure S25. ^{1}H NMR spectrum of compound **15**.

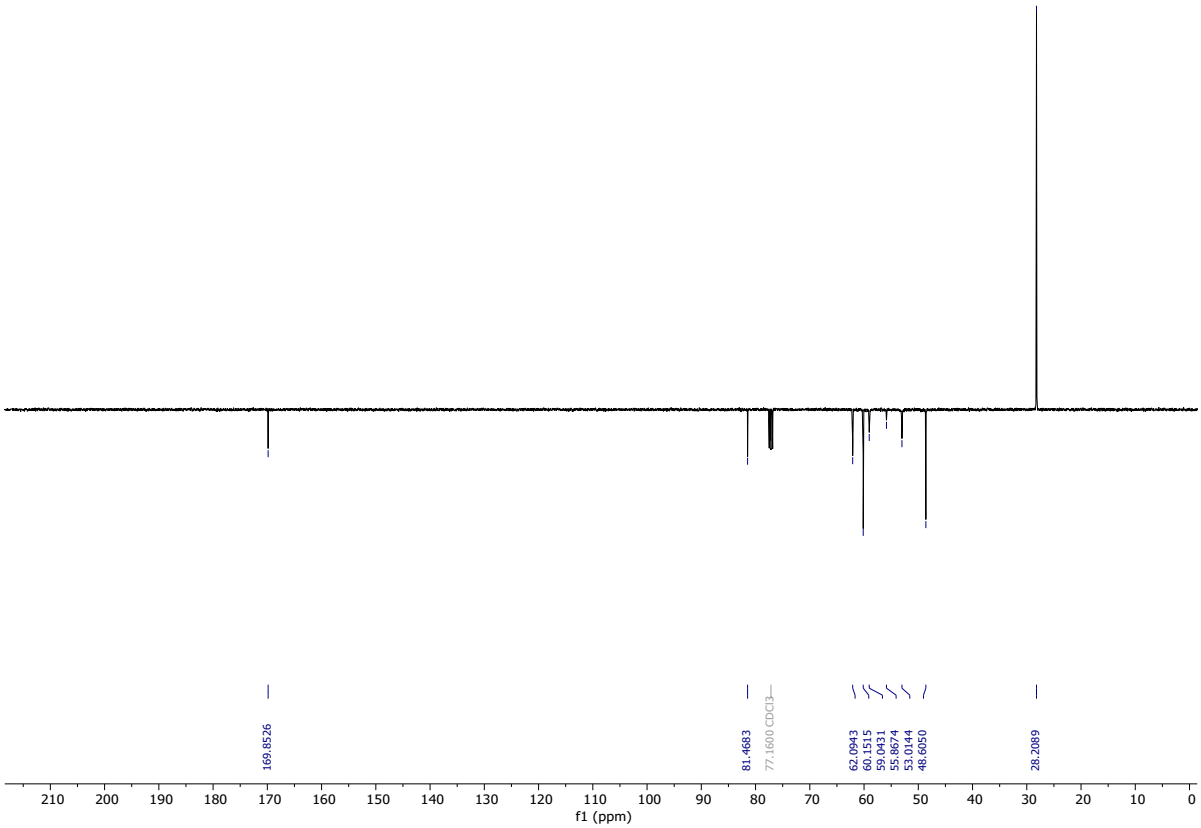

Figure S26. ^{13}C APT NMR spectrum of compound **15**.

FT-IR analysis compound 5a

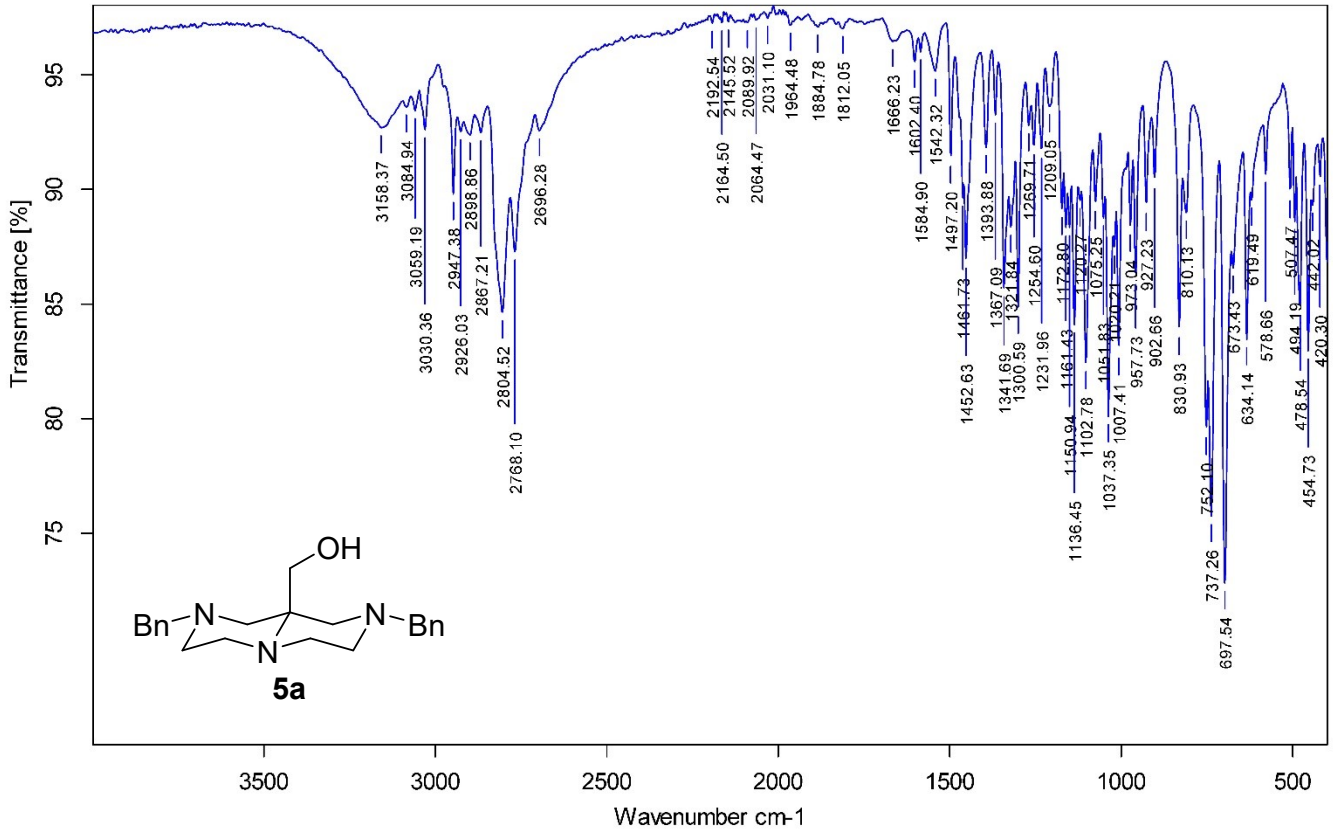

Figure S27. FT-IR spectrum of compound **5a**.

HRMS analysis

The HMRS analysis of compound **4** confirmed the mass of $[M+H]^+$ = 381.2280 m/z (ESI^+). The main signals obtained by fragmentation of the $[M+H]^+$ species of compound **4** are an initial loss of a NO_2 group (334.2275 m/z) followed by a loss of a tropylium cation (244.1808 m/z). **(Figure S28)**
The analysis of compound **5a** confirmed the mass of $[M+H]^+$ = 352.2389 m/z (ESI^+). The main signals obtained by fragmentation (CID 20 eV) of the $[M+H]^+$ species of compound **5a** are a first dehydration (334.2223 m/z) followed by a loss of a tropylium cation (243.1720 m/z). The mass region between 230 m/z and 130 m/z there are fragmentations involving the opening of the OPP ring. (**Figure S29**)

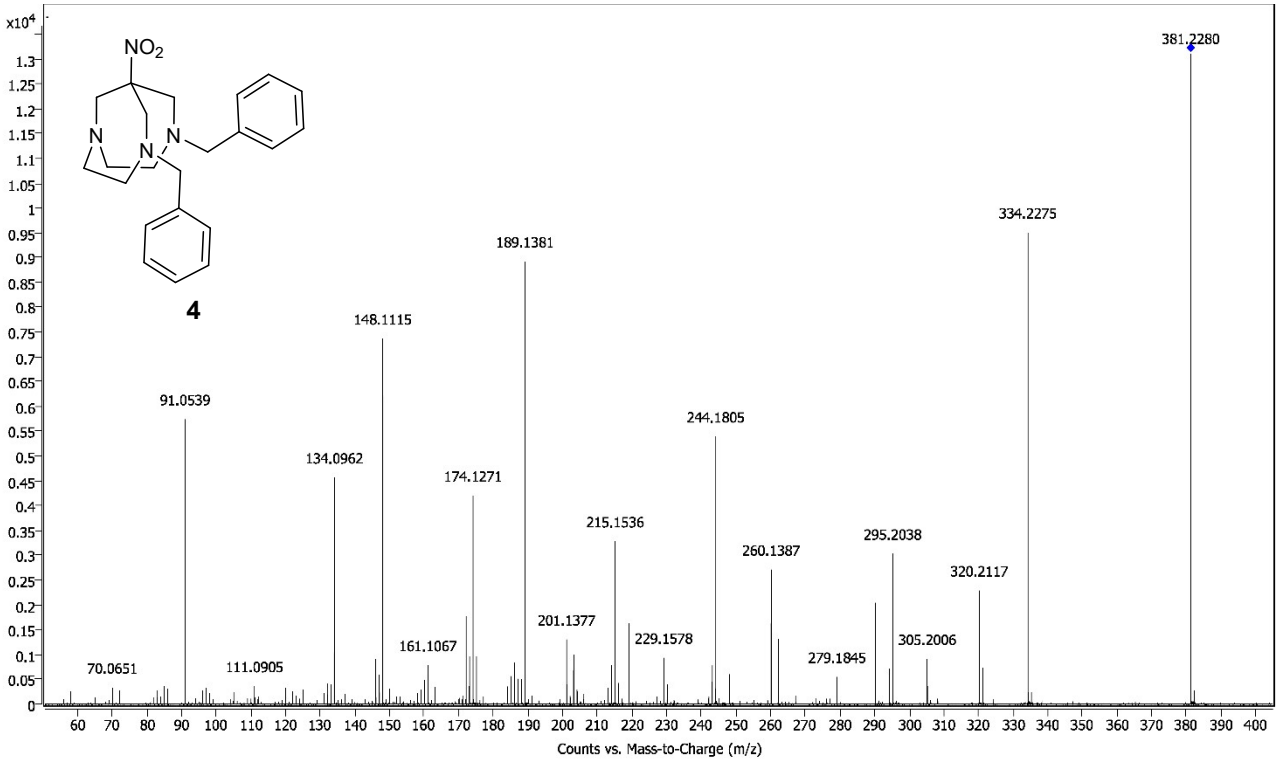

Figure S28. HRMS spectrum of compound **4**.

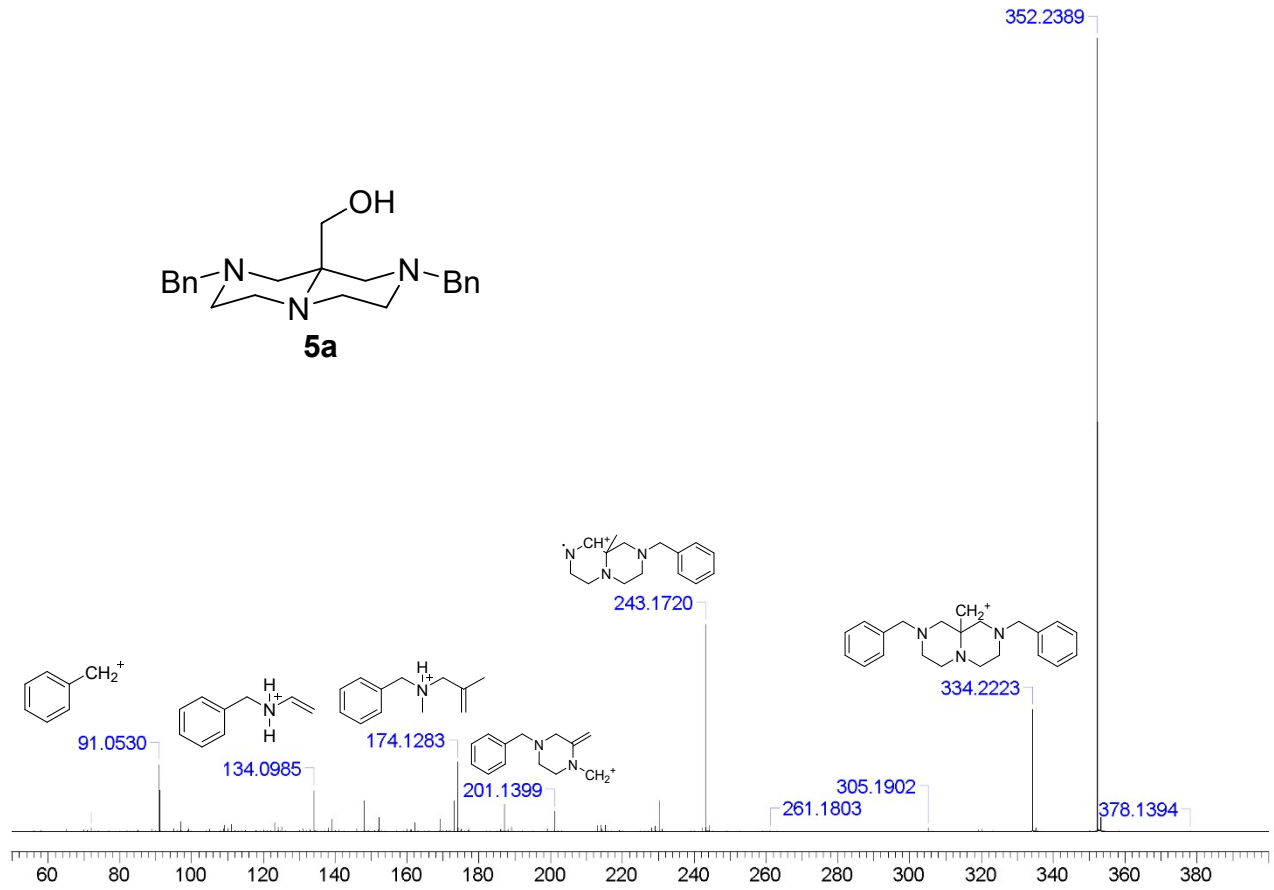

Figure S29. HRMS spectrum of compound **5a**.

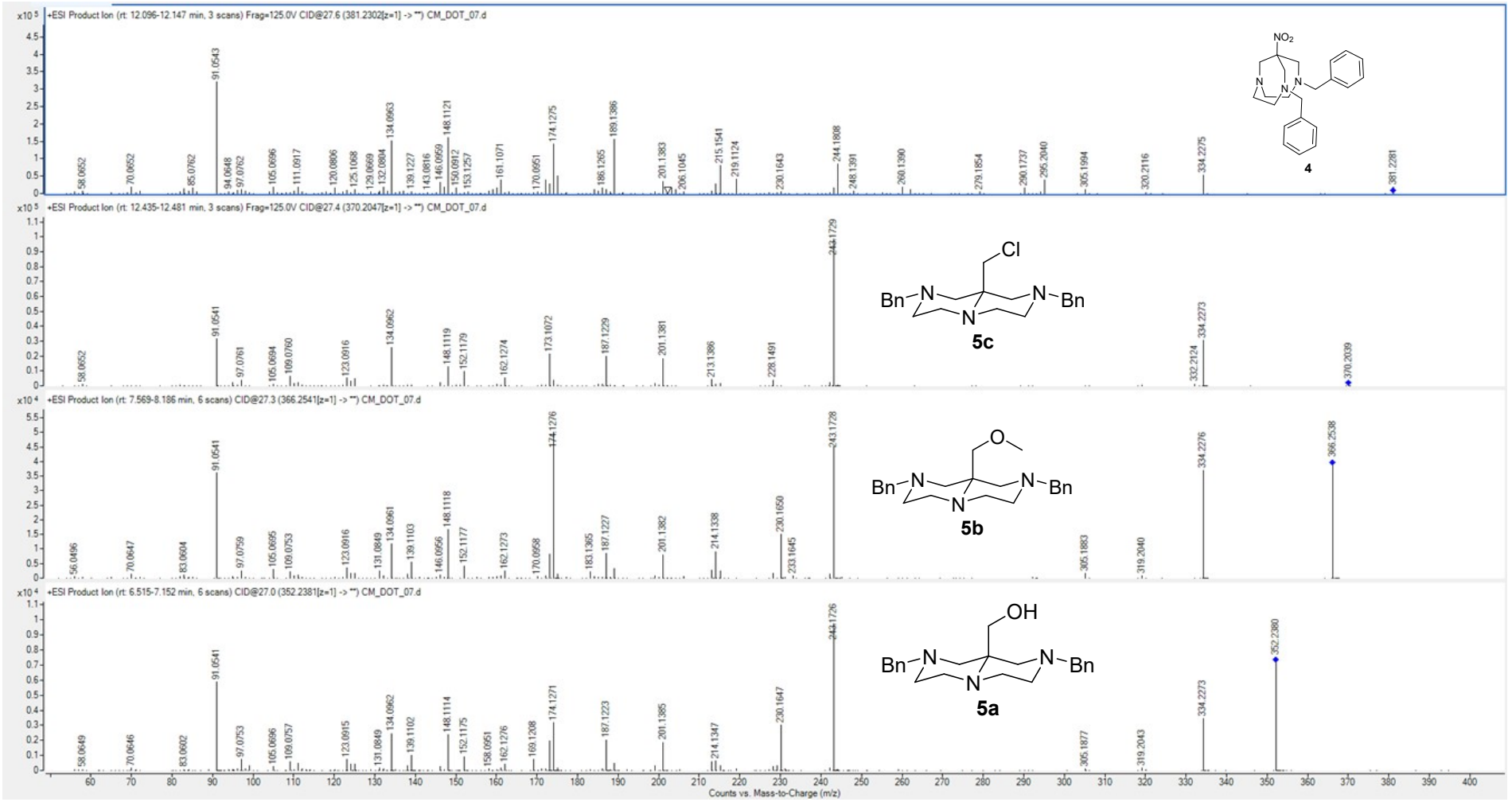

Figure S30. Superimposition of HRMS spectra of compound, from top to bottom, **4**, **5c**, **5b** and **5a**.

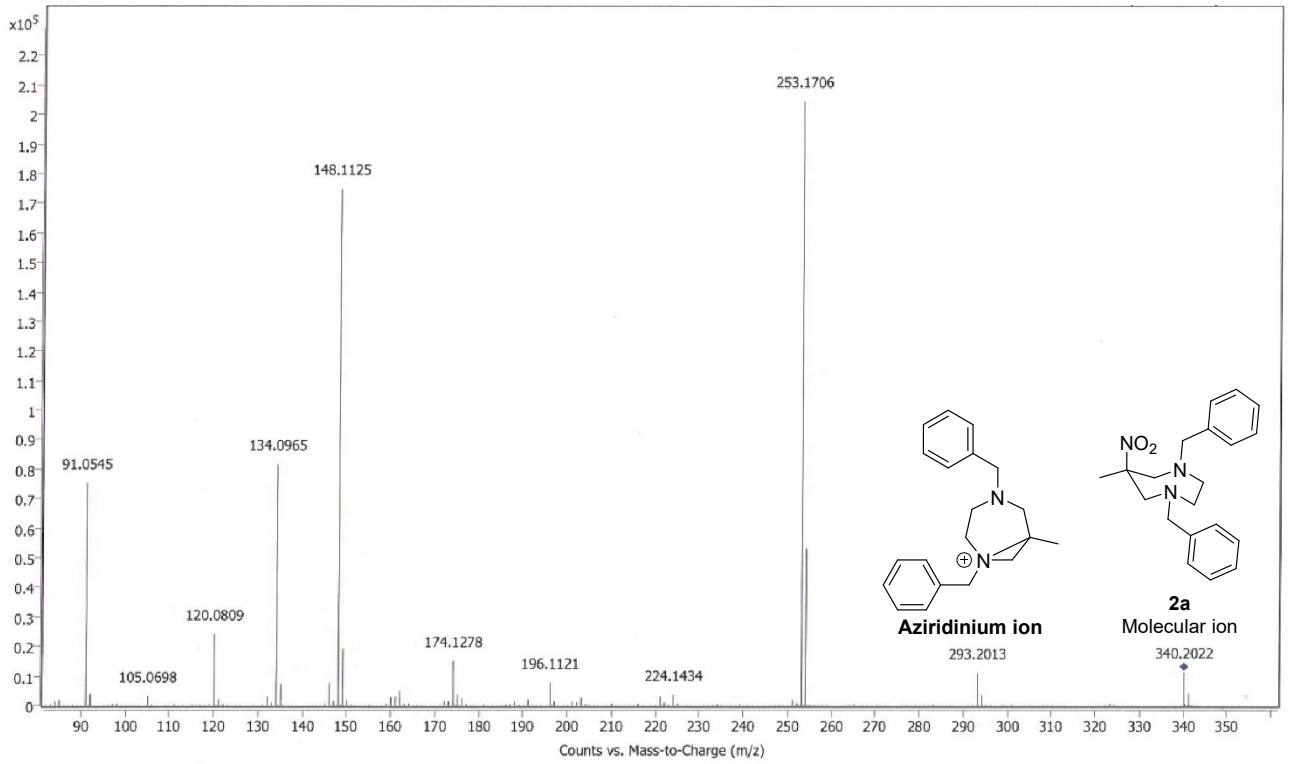

Figure S31. HRMS spectrum of compound **2a**.

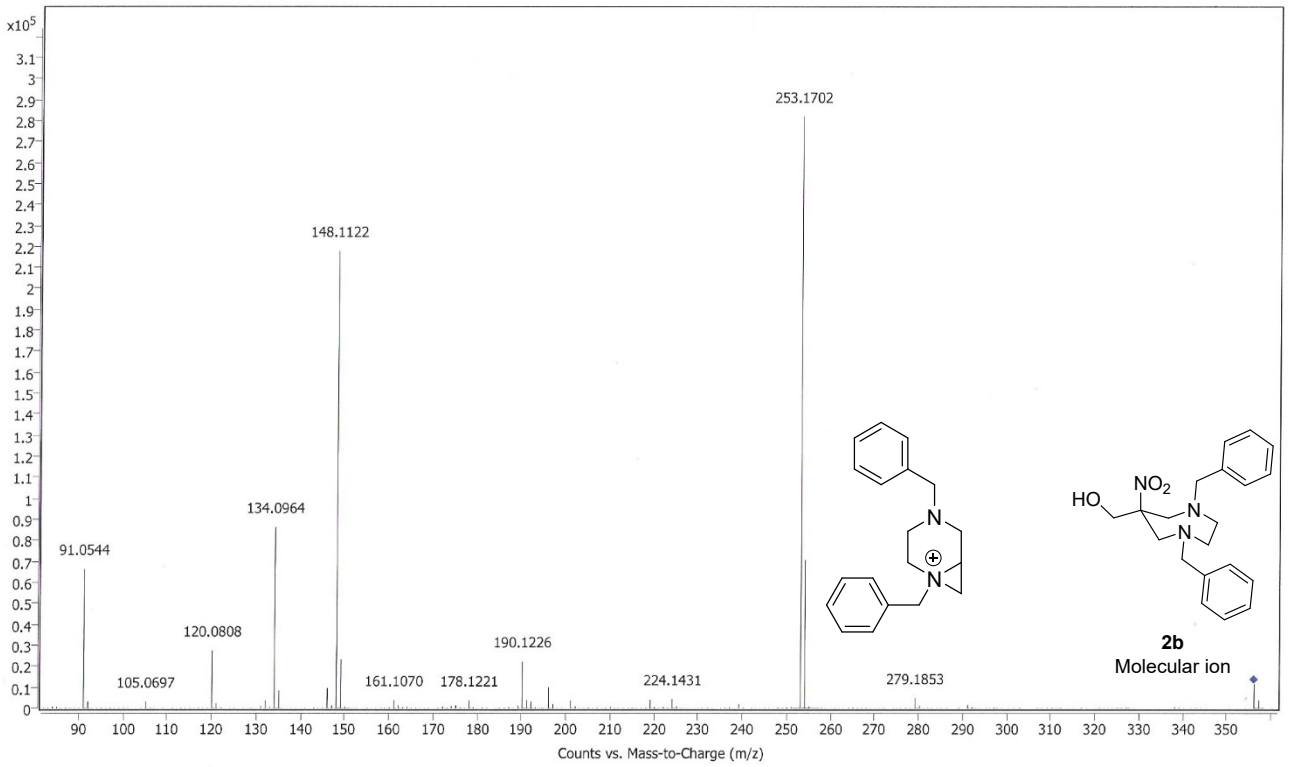

Figure S32. HRMS spectrum of compound **2b**.

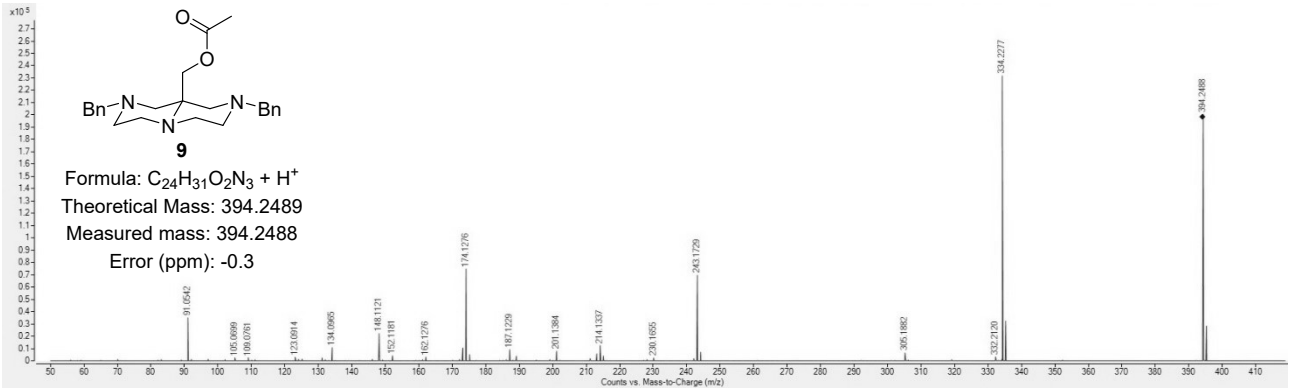

Figure S33. HRMS spectrum of compound **9**.

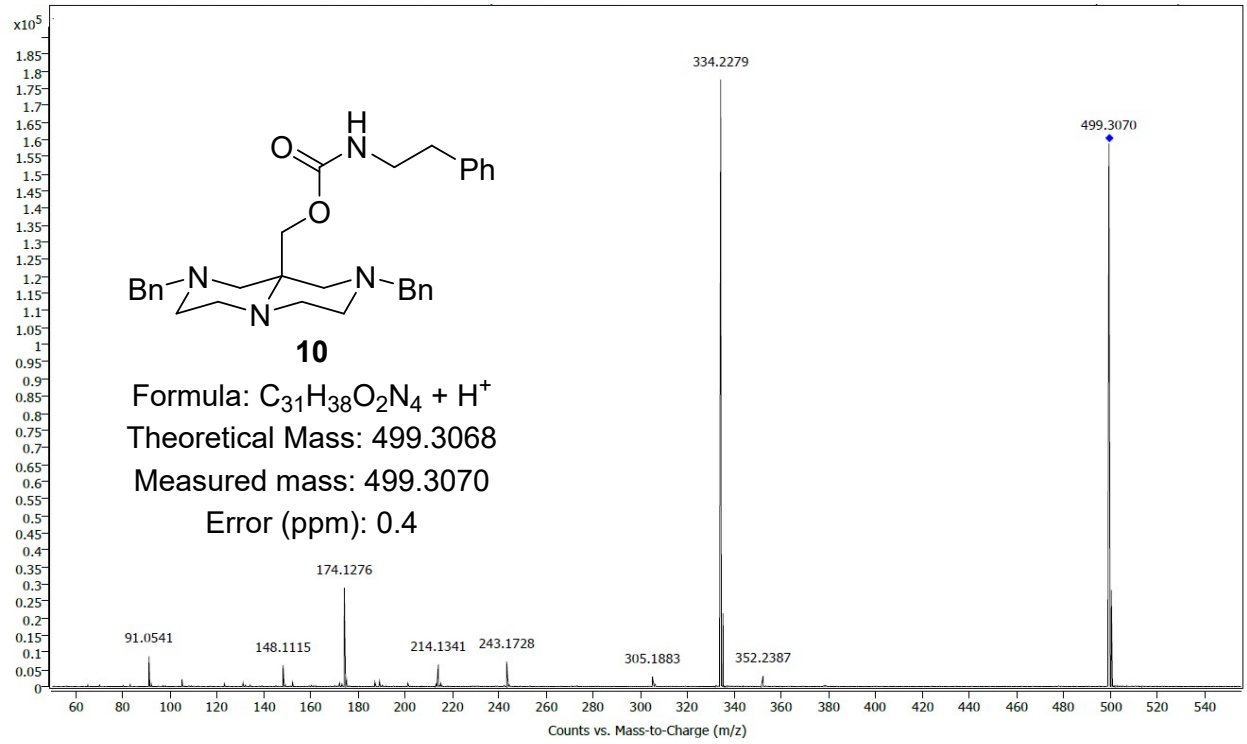

Figure S34. HRMS spectrum of compound **10**.

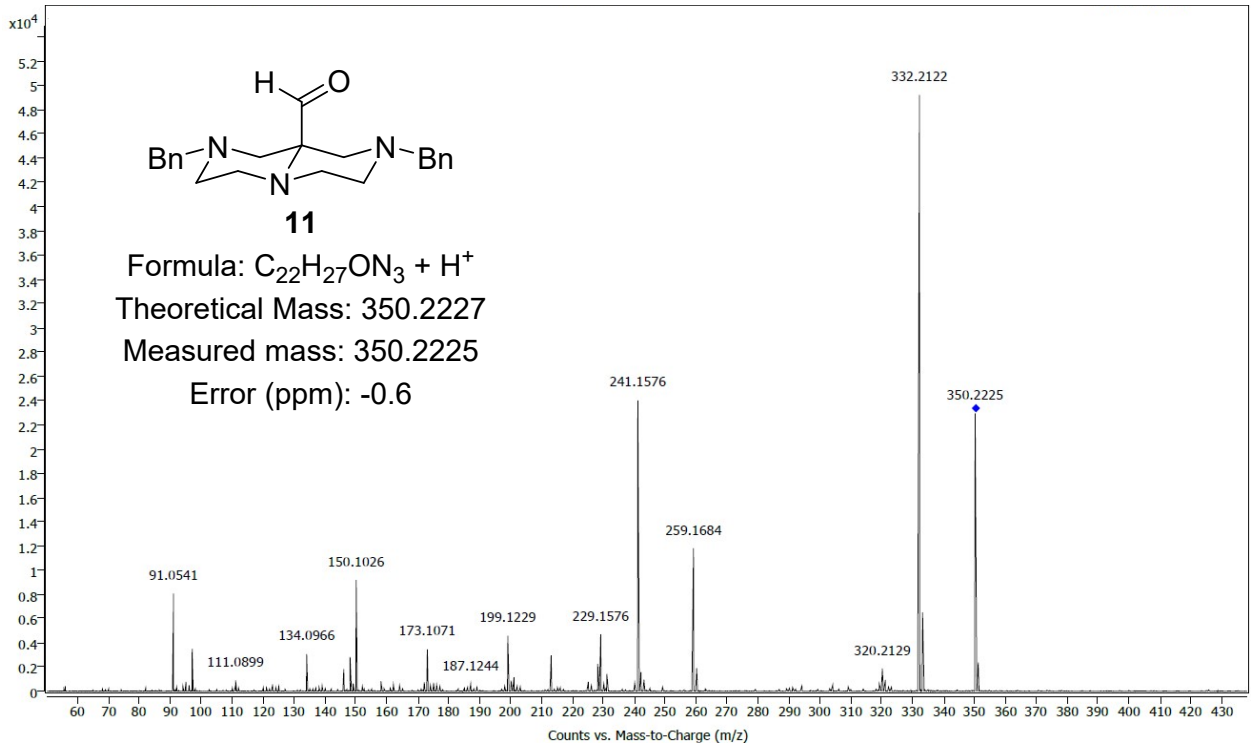

Figure S35. HRMS spectrum of compound **11**.

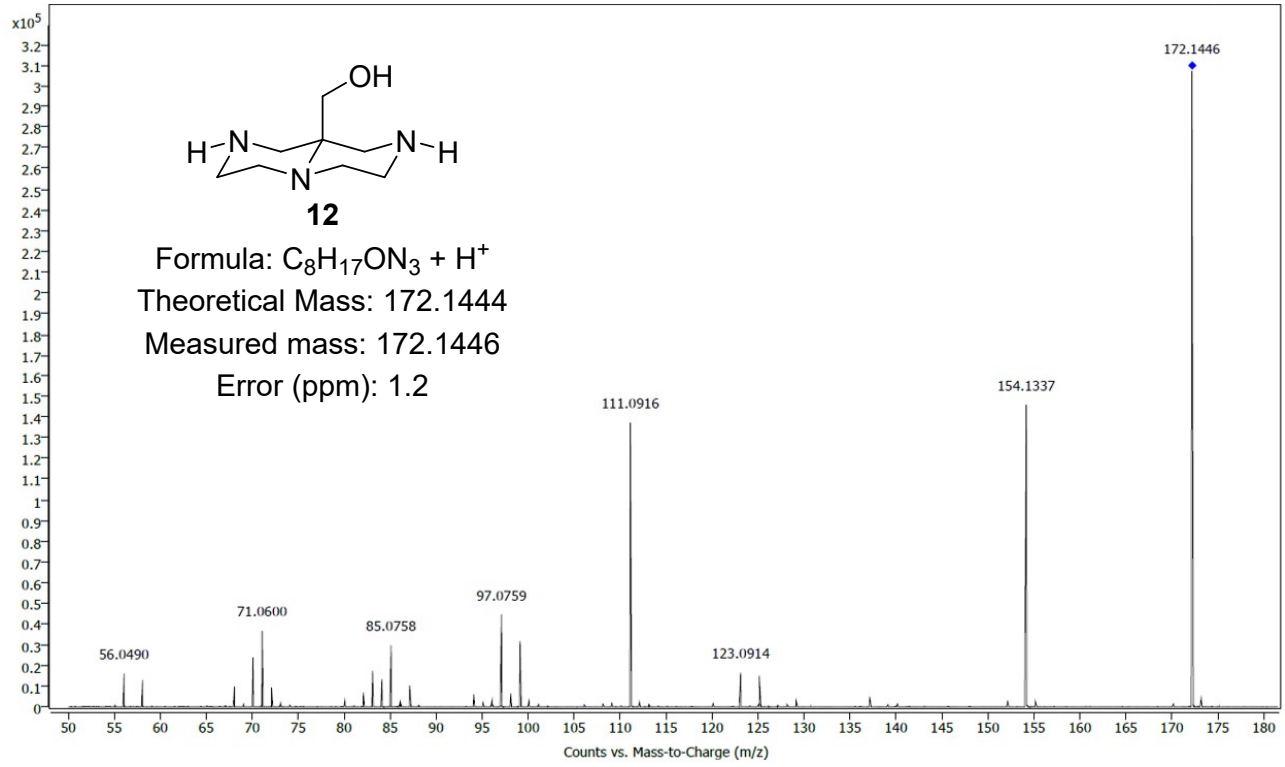

Figure S36. HRMS spectrum of compound **12**.

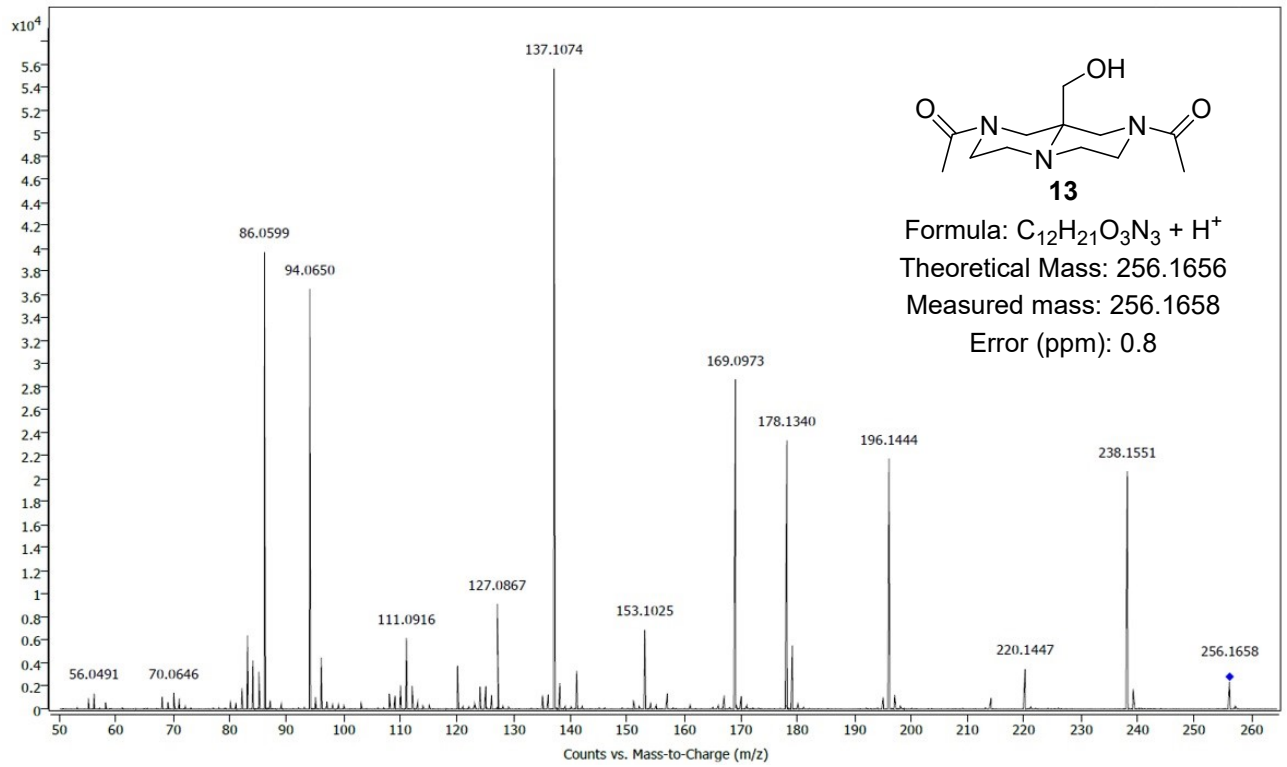

Figure S37. HRMS spectrum of compound **13**.

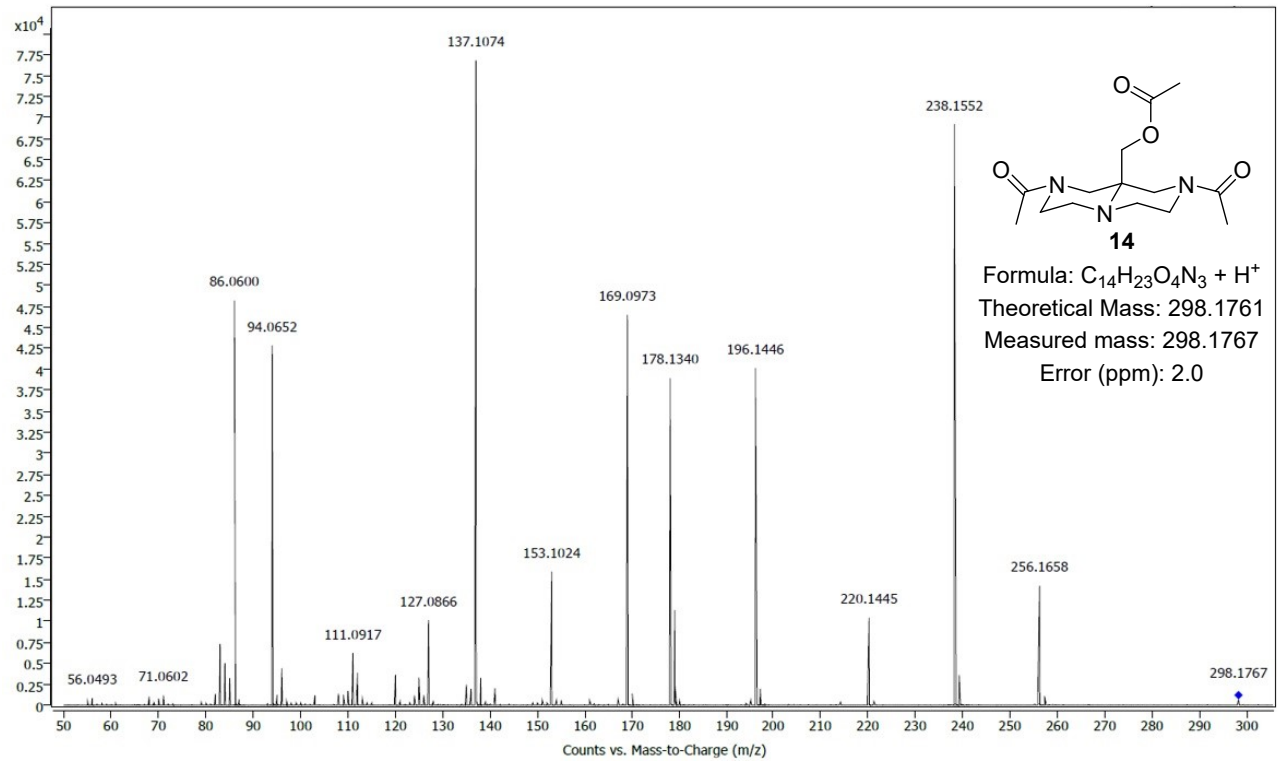

Figure S38. HRMS spectrum of compound **14**.

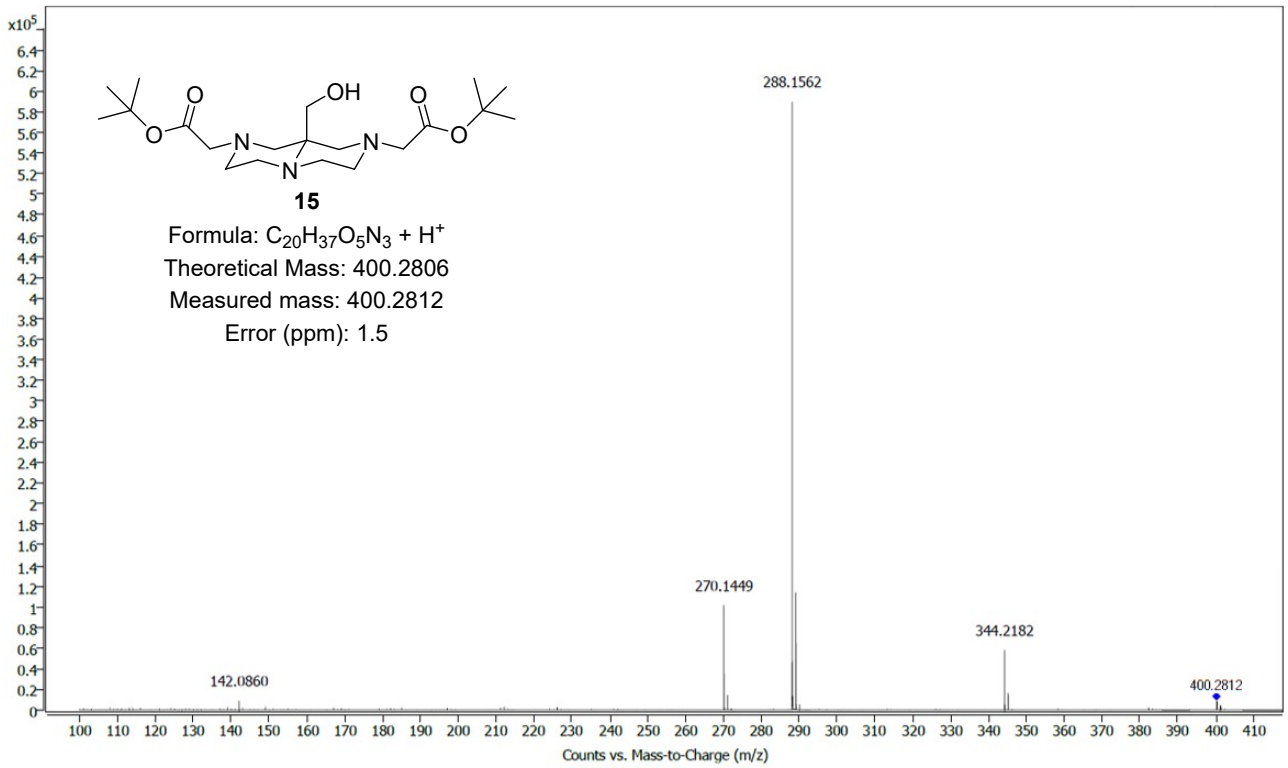

Figure S39. HRMS spectrum of compound **15**.

SC-XRD analysis

Single crystal X-ray diffraction (SC-XRD) data were collected with a Smart APEXII CCD area-detector diffractometer (BRUKER). The radiation source was a molybdenum anode (Mo-K_α, λ = 0.71073 Å) with the generator working at 50 kV and 30 mA. The data reduction was carried out with CrysAlis Pro[4] version 1.171.42.60a using an empirical absorption correction with spherical harmonics (SCALE3 ABSPACK). The structure was solved by dual space methods with SHELXT-2015[5] and refined with SHELXL-2019[6] using the WinGX program suite.[7] Structure refinement was done using full-matrix least-square routines against F^2. Hydrogen atoms on heteroatoms were refined semi-freely. All remaining hydrogen atoms were refined on idealized positions. The picture was generated with the programs DIAMOND 4.0.[8] CCDC 2327990 (**5a**) contain the supplementary crystallographic data for this paper. These data and additional information can be obtained free of charge via https://summary.ccdc.cam.ac.uk/structure-summary-form (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.uk).

Table S3. Summary of crystallographic data for compound **5a**.

Compound	**5a**
CCDC No.	2327990
Formula	$C_{22}H_{29}N_3O$
Formula weight	351.48
Crystal system	Monoclinic
Space group	$P2_1/n$
a [Å]	10.2333(3)
b [Å]	10.3310(2)
c [Å]	18.6080(4)
α [°]	90
β [°]	91.011(2)
γ [°]	90
V [Å^3]	1966.94(8)
Z	4
Radiation type	Mo-Kα
Temp. [K]	150(2)
$\rho_{(calcd)}$ [g·cm^{-3}]	1.187
μ [mm^{-1}]	0.074
F(000)	760
Cryst. size [mm^3]	0.370 x 0.350 x 0.290
θ range [°]	2.189-31.466
Limiting indices	-14<=h<=14 -14<=k<=14 -27<=l<=25
Reflections collected/unique[a]	21745 / 6066 [R(int) = 0.0098]
Data/restraints/param	6066 / 0 / 237
Completeness to θ = 25.242° [%]	100.0
Max. and min. transmission	1.00000 and 0.87431
Final R indices (I > 2σ(I))[b]	R_1 = 0.0409, wR_2 = 0.1111
R indices (all data)	R_1 = 0.0447, wR_2 = 0.1143
Absolute Structure Parameter	–
Goodness of fit[c] on F^2	1.031
Largest diff. peak and hole [Å^{-3}]	0.385 and -0.260

[a] $R_{int} = \Sigma|F_o^2 - F_o^2(mean)|/\Sigma F_o^2$, [b] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$, [c] GooF = $\{S/(n-p)\}^{1/2} = \{\Sigma[w(F_o^2 - F_c^2)^2]/(n-p)\}^{1/2}$.

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1) C. Galaup, J.-M. Couchet, S. Bedel, P. Tisnès and C. Picard, *J. Org. Chem.*, 2005, **70**, 2274–2284.
2) S. Aime, L. Calabi, C. Cavallotti, E. Gianolio, G. B. Giovenzana, P. Losi, A. Maiocchi, G. Palmisano and M. Sisti, *Inorg. Chem.*, 2004, **43**, 7588–7590.
3) G. Gugliotta, M. Botta, G. B. Giovenzana and L. Tei, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 3442–3444.
4) Agilent, CrysAlis PRO, Agilent Technologies Ltd, Yarnton, Oxfordshire, England, **2019**.
5) Sheldrick, G. M. (2015). Acta Cryst. A71, 3-8.
6) Sheldrick, G. M. (2015). Acta Cryst. C71, 3-8.
7) Farrugia, L. J. (2012). J. Appl. Cryst. 45, 849-854.
8) Diamond - Crystal and Molecular Structure Visualization, Crystal Impact - Dr. H. Putz & Dr. K. Brandenburg GbR, Kreuzherrenstr. 102, 53227 Bonn, Germany, https://www.crystalimpact.de/diamond.