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

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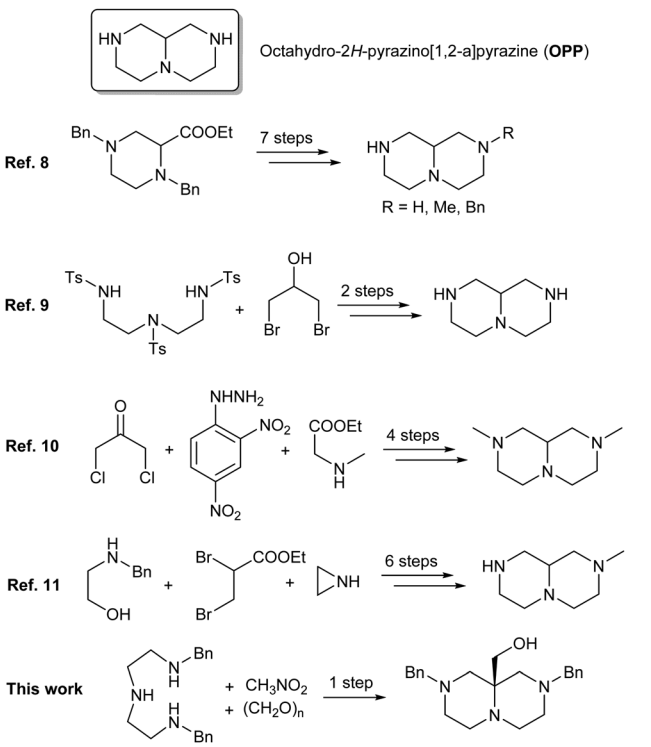
An unexpected nitro group displacement during a nitro-Mannich reaction led to the one-pot formation of the octahydro-2*H*-pyrazino[1,2-*a*]pyrazine core, representing the shortest access to date to this pharmacologically relevant heterobicyclic system. A mechanistic hypothesis is suggested and supported by specific experiments and HRMS analysis of reaction mixtures.

The heterobicyclic core of octahydro-2*H*-pyrazino[1,2-*a*]pyrazines (OPPs) (Scheme 1) is the subject of an increasing number of medicinal chemistry studies, focused on its pharmacophoric properties. OPPs have been extensively investigated as putative β-turn mimetics[1,2] and as 5-HT2C receptor agonists.[3] OPP derivatives were patented as IgE inhibitors,[4] while inhibitor activity was ascribed to OPPs against renal outer medullary potassium channel (ROMK),[5] ubiquitin specific peptidase 30 (USP30)[6] and the important lung adenocarcinoma-related mutant oncogene $KRAS^{G12C}$.[7]

The synthesis of the OPP framework is not straightforward, and the few procedures reported in the literature usually require several steps. Gubert *et al.*[8] described a 7-step synthesis of the unsubstituted OPP, starting from ethyl 1,4-dibenzylpiperazine-2-carboxylate, while Wu *et al.* reported a transannular reaction leading to the unsubstituted OPP during the HBr-mediated detosylation of 1,4,7-tritosyl-1,4,7-triazadecan-9-ol for which fractional crystallization is required to separate the native OPP from the 10-membered monocyclic isomeric byproduct.[9]

Different approaches have been developed for the preparation of octahydro-2*H*-pyrazino[1,2-*a*]-pyrazinones (including -diones and -triones), with the eventual need for an additional reduction step to access the fully reduced OPP. An early approach involves 4 steps, starting from 1,3-dichloroacetone, 2,4-dinitrophenylhydrazine and sarcosine ethyl ester and leading to *N*-methyl-octahydro-2*H*-pyrazino[1,2-*a*]pyrazine.[10] A 6-step preparation of the same derivative starting from *N*-benzylethanolamine was reported in 1977 by Beim and Day.[11] Peptide synthesis approaches were employed for the preparation of the OPP core, sequentially forming the piperazine rings by *ex novo* lactamization of α-amino acid precursors, either by solution-phase[12] or by solid-phase[2] protocols.



Scheme 1 Octahydro-2*H*-pyrazino[1,2-*a*]pyrazine (OPP) and former synthetic accesses.

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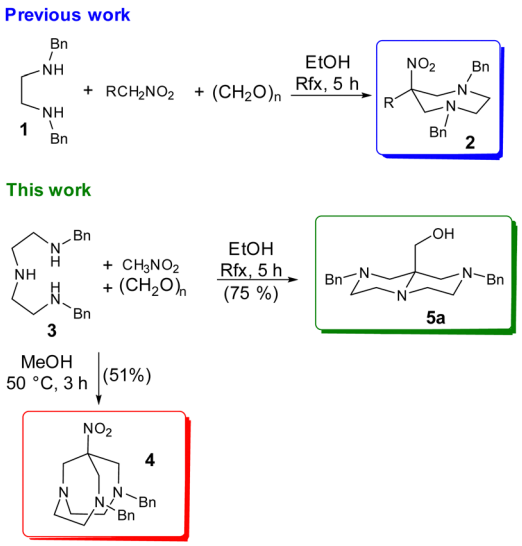
† Electronic supplementary information (ESI) available. CCDC 2327990 (**5a**). For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4cc03596h



Scheme 2 Preparation of compounds **2**, **4** and **5a** by nitro-Mannich reaction.

The first piperazine ring of OPPs was alternatively accessed through the Castagnoli–Cushman reaction of cyclic anhydrides with imines.[1]

The nitro-Mannich reaction is a well-established C–C bond forming transformation leading to useful synthons bearing vicinal nitrogen-based functional groups.[13] Our research group has routinely employed the nitro-Mannich reaction for the synthesis of precursors of mesocyclic chelating agents, by reacting a vicinal secondary diamine (*e.g.*: *N*,*N*′-dibenzyl-1,2-ethylenediamine, **1**) with formaldehyde and a suitable nitroalkane (Scheme 2).[14]

In continuation of our studies on functionalized analogues of mesocyclic chelating agents, we explored the reactivity of a secondary triamine, observing an unexpected behaviour, dependent on the reaction conditions. When *N*,*N*″-dibenzyldiethylenetriamine **3**[15] is refluxed in ethanol with nitromethane and *para*-formaldehyde, a vigorous evolution of a red-brown gas (identified as NO_2 by absorption in aqueous NaOH solution, the latter tested positive to nitrite by semiquantitative nitrite-test strips) occurred and the formation of a main product was observed by TLC analysis. This product was isolated in 75% yield as a white solid and to our surprise its NMR and MS spectra are not compatible to the expected nitro-Mannich product **4** (Scheme 2). The NMR spectra suggest a symmetric structure, lacking the nitro group as confirmed by IR and HRMS analysis, the latter providing the molecular formula $C_{22}H_{29}N_3O$ (Fig. S7–S12, S27 and S29, ESI†).

Crystallization from diethyl ether provided single crystals suitable for X-ray diffractometric analysis (Fig. 1 and Table S3, ESI†), which identified the new compound as (2,8-dibenzylocta-hydro-9*aH*-pyrazino[1,2-*a*]pyrazin-9*a*-yl)-methanol **5a** (Scheme 2 and Fig. 1).

The unexpected elimination of the nitro group and the concomitant formation of compound **5a** prompted us to investigate the mechanism of this unprecedented reaction.

The nitro group is known to act as a leaving group,[16,17] for example in β-eliminations,[18] generally triggered by the presence of an acidic hydrogen in the β-position, and in $S_{RN}1$ substitutions,[19] requiring a radical-stabilising substitution pattern.

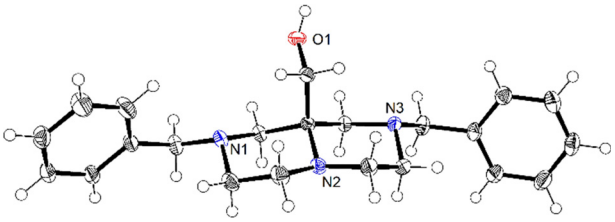


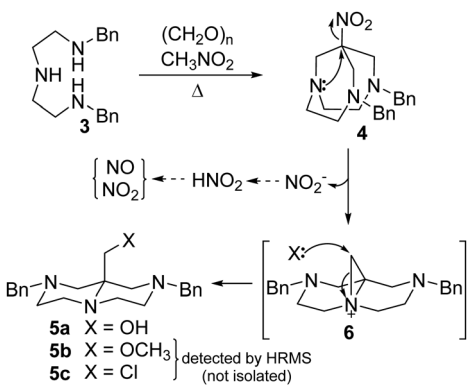
Fig. 1 ORTEP representation of the crystal structure of compound **5a**, obtained by SC-XRD analysis. Ellipsoids are represented with 50% probability. Color codes: C, gray; N, blue; O, red; H, light gray.

Compound **5a** may be originated by the loss of the nitro group from the expected nitro-Mannich product **4** preformed under the reaction conditions or directly by an alternative pathway. The expected nitro-Mannich product **4** is in fact detected in the reaction mixture and can be isolated in 51% yield by running the reaction under milder conditions (methanol, 50 °C), along with minor amounts of **5a** (Scheme 2).

The comparison between the molecular formula of compounds **4** and **5a** points to the loss of the nitro group and the following introduction of a hydroxyl group. The clear change in connectivity may be traced back to a rearrangement process, likely concomitant with the loss of the nitro group. The complete loss of the nitro group strongly suggested by the copious evolution of gaseous NO_2 points to an intermolecular origin of the incoming OH group, presumably ascribed to H_2O, either adventitious or produced by the initial nitro-Mannich steps (3 eq. of H_2O are generated in the condensation **3** + $3CH_2O$ + CH_3NO_2 → **4** + $3H_2O$).

A possible reaction mechanism for this unprecedented transformation is proposed in Scheme 3.

The nitrotriamine **4** is initially formed by a classic nitro-Mannich condensation. On heating, compound **4** undergoes an intramolecular nucleophilic displacement of the nitro group by the central nitrogen atom, leading to the intermediate tricyclic aziridinium ion **6**. Nucleophilic ring opening of the strained three-membered ring takes place at its unhindered methylene group, leading to compound **5a**, with the role of the nucleophile played by water formed during the condensation step. The nitro



Scheme 3 Proposed mechanism for the formation of compound **5a** and two side products **5b** and **5c**, detected by HRMS.

group acts as the leaving group and is lost as NO_2^-, the latter in equilibrium with the highly unstable nitrous acid, finally undergoing decomposition to nitrogen oxides (Scheme 3).

To assess the role of water, triamine **3**, *para*-formaldehyde and nitromethane were heated in an aprotic solvent (THF), kept dry by an excess of preactivated 3 Å molecular sieves. TLC analysis of the reaction mixture clearly showed the formation of **4**, the total absence of **5a** and the formation of minor amounts of highly polar compounds. The reaction mixture was then cooled to room temperature and filtered under vacuum to remove the molecular sieves. Water was added, and the solution refluxed for additional 4 hours. TLC analysis showed the progressive formation of **5a**, confirming the direct role of water in this reaction.

Careful analysis by HPLC-HRMS of the reaction mixture run in methanol (Scheme 2) and leading to **4** allowed to detect two additional compounds (**5b** and **5c**), identified on the base of their molecular weight and fragmentation patterns (Fig. S16, ESI†). The methoxy derivative **5b** likely arises from solvolytic ring opening of aziridinium **6**. The formation of compound **5c** could be ascribed to the presence of residual chloride ions in the starting triamine **3**, as the latter is prepared and isolated as the trihydrochloride following a literature procedure.[15]

A rational underlying the unusual nucleophilic displacement may be proposed on the base of stereoelectronic effects. The instability of nitrotriamine **4** on heating could arise from the possibility for this flexible bicyclic structure to undergo a pyramidal inversion of the (central) nitrogen atom, leading its lone pair free to flip outward/inward (Scheme 4). The lone pair, once directed inward, can approach the carbon atom bearing the nitro group to start the nucleophilic displacement *en route* to the intermediate aziridinium **6**.

Obviously, pyramidal inversion of the nitrogen atom is precluded in the nitrotriamines **7**[20] and **8**[21] (Scheme 4), previously reported in the literature, as they are stable at temperatures higher than those involved in the formation of **5** (compound **7** decomposes only at $T > 260$ °C while compound **8** withstands recrystallization from boiling 1-butanol (bp 117.7 °C) and sublimes unchanged at 191–192 °C).

A similar nitro group displacement could be expected in monocyclic nitrodiamines **2a–b**[22,23] (Scheme 4), as they are free to undergo pyramidal inversion of the nitrogen atoms. However, compounds **2a–b** are stable under the reaction conditions (*i.e.* refluxing ethanol), actually employed for their synthesis in almost quantitative yield. Nevertheless, HRMS of **2a–b** clearly shows fragmentation peaks corresponding to the formation of the bicyclic aziridinium ion with loss of the nitro group in the mass spectrometer ion source (Fig. S17 and S18, ESI†), supporting the possibility of this reaction pathway. The lower propensity of the monocyclic nitrodiamines **2a–b** to the loss of the nitro group could be explained by the need for assuming high energy conformations to allow the nitrogen lone pair to approach the C–NO_2 carbon atom, while the bicyclic structure of **4**, when in the "in" conformation, forces the lone pair correctly pointed towards the σ^*_{C-N} orbital.

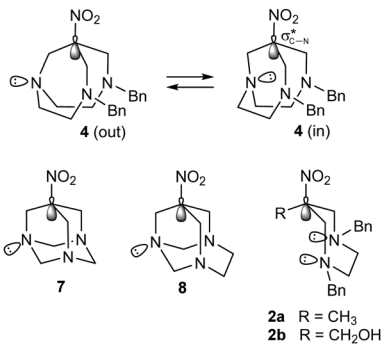
The easy access to the OPP core represented by this unexpected transformation paves the way for the preparation of a wide range of OPP derivatives, taking advantage of the functionalization pattern of compound **5a**.

We demonstrated the versatility of the latter in accessing the OPP chemical space with a series of simple reactions, summarized in Scheme 5.

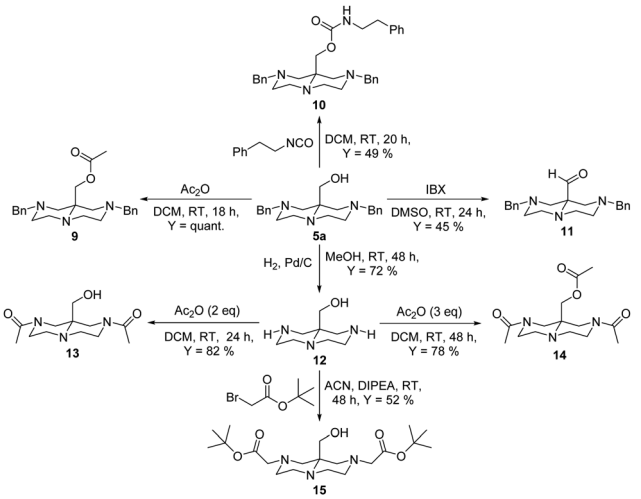
The OH-group of compound **5a** shows the expected reactivity of a primary alcohol. Quantitative acetylation to **9** is obtained by treatment with acetic anhydride in DCM at r.t., while reaction in the same conditions with 2-phenethyl isocyanate provides the carbamate **10**. The reaction of **5a** with IBX in DMSO leads to the oxidation to the interesting triaminoaldehyde **11** in 45% yield.

Synthetic work on the distal nitrogen atoms of **5a** requires their preliminary debenzylation, cleanly obtained by catalytic hydrogenolysis in methanol at r.t., to give compound **12**. Selective acylation of the resulting secondary amines is achieved by treatment with stoichiometric acetic anhydride in DCM at r.t., quantitatively yielding diacetamide **13**. An additional equivalent of acetic anhydride in the same experimental conditions allows exhaustive acylation of the secondary amines and of the primary alcoholic group to give the diamidoester **14** in 78% yield.

Treatment of compound **12** with an alkylating agent (*t*-butyl bromoacetate) in acetonitrile in the presence of DIPEA at r.t.



Scheme 4 Nitrodiamines and nitrotriamines discussed in the text.



Scheme 5 OPP derivatives obtained by post-synthetic transformations of compound **5a**.

leads to the alkylation of the secondary amines, yielding the highly functionalized triaminohydroxydiester **15** in 52% yield.

Finally, the reaction of 1,4,7-trimethyldiethylenetriamine with nitromethane and *para*-formaldehyde in refluxing ethanol for 5 h, the same conditions leading to the formation of compound **5a**, formed a complex mixture, possibly due to an extensive polymerization.

The reaction described in this manuscript represents an unprecedented, simple and efficient approach to pharmacologically relevant octahydro-2*H*-pyrazino[1,2-*a*]pyrazines (OPPs).

A possible mechanism for this transformation involving a combination of nitro-group displacement-rearrangement is proposed and supported by preliminary experimental data.

The functionalized OPP obtained by this unexpected transformation has been converted to a series of OPP derivatives, demonstrating its versatility.

The nitro-Mannich-rearrangement sequence described in this manuscript represents a short and efficient synthesis to OPPs core and a useful entry into the chemical space of this pharmacologically relevant heterobicyclic compounds.

Data availability

The data supporting this article have been included as a part of ESI.† CCDC 2327990 (**5a**) contain the supplementary crystallographic data for this paper.

Conflicts of interest

There are no conflicts to declare.

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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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Table of contents

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

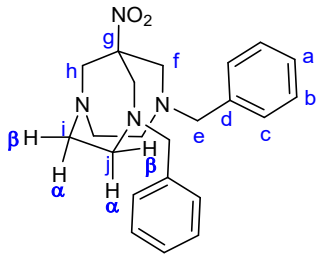
once with saturated aqueous solution of sodium carbonate, dried over sodium carbonate and sodium sulphate, filtered and the solvent was removed under vacuum. The product was crystallised from diethyl ether (5 mL) at 4 °C for 15 h and the solid was recovered by vacuum filtration, washed with diethyl ether 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**.

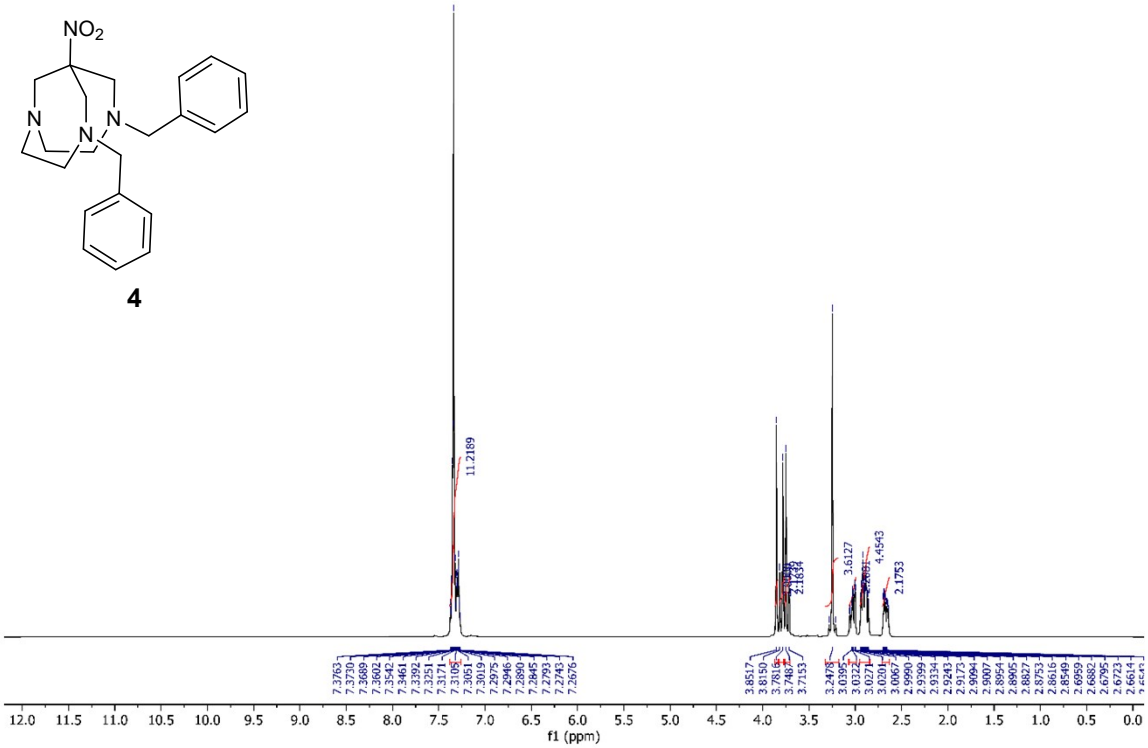


Figure S1. ^{1}H NMR spectrum of compound **4**.

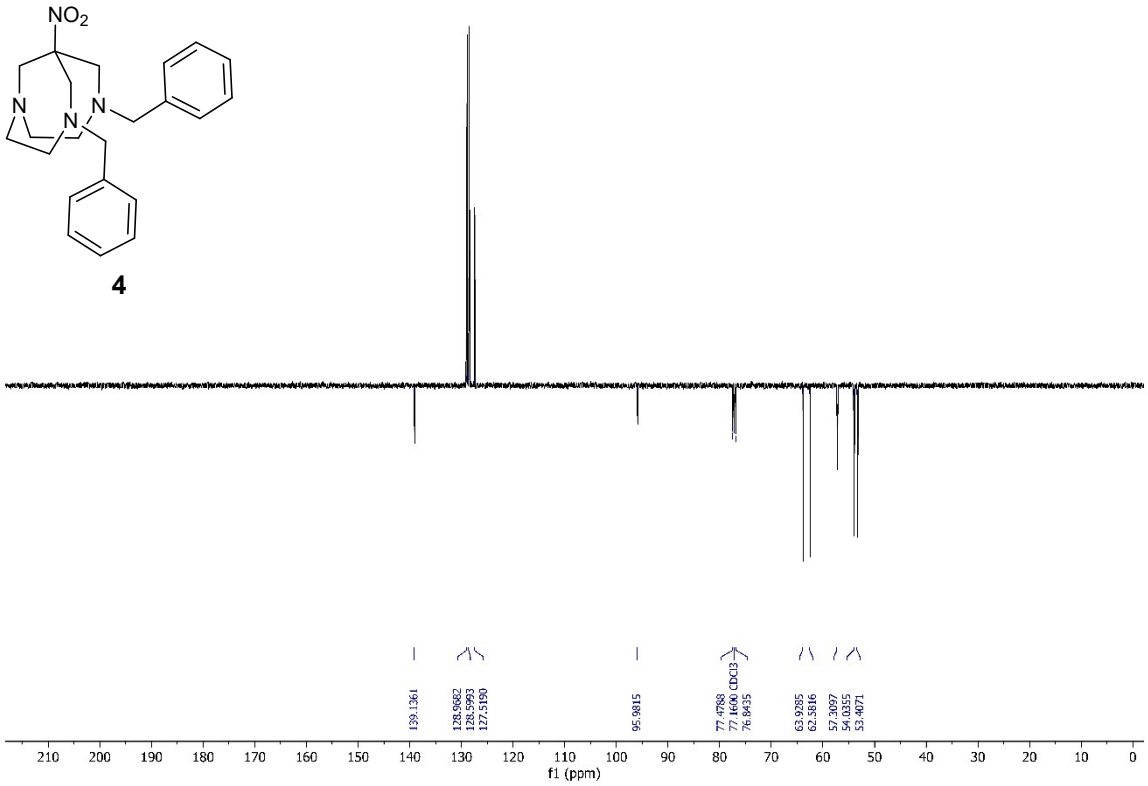


Figure S2. ^{13}C APT NMR spectrum of compound **4**.

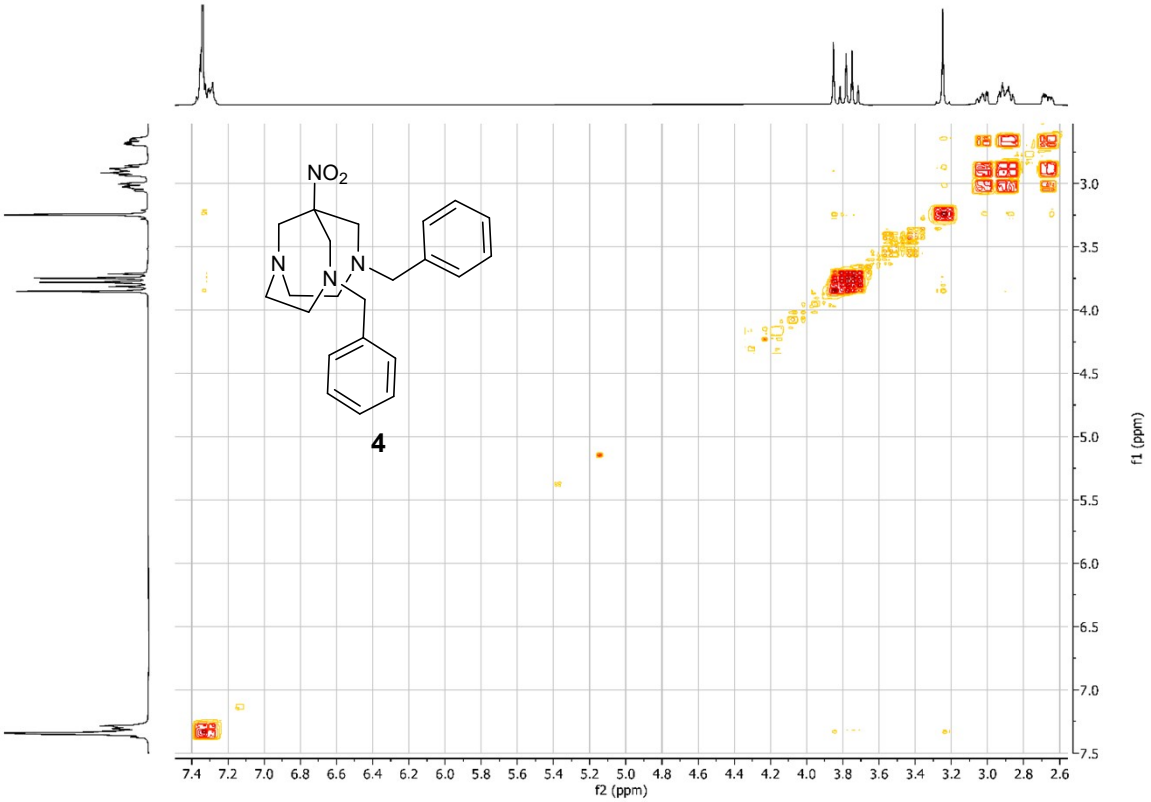


Figure S3. $^{1}H - {}^{1}H$ COSY spectrum of compound **4**.

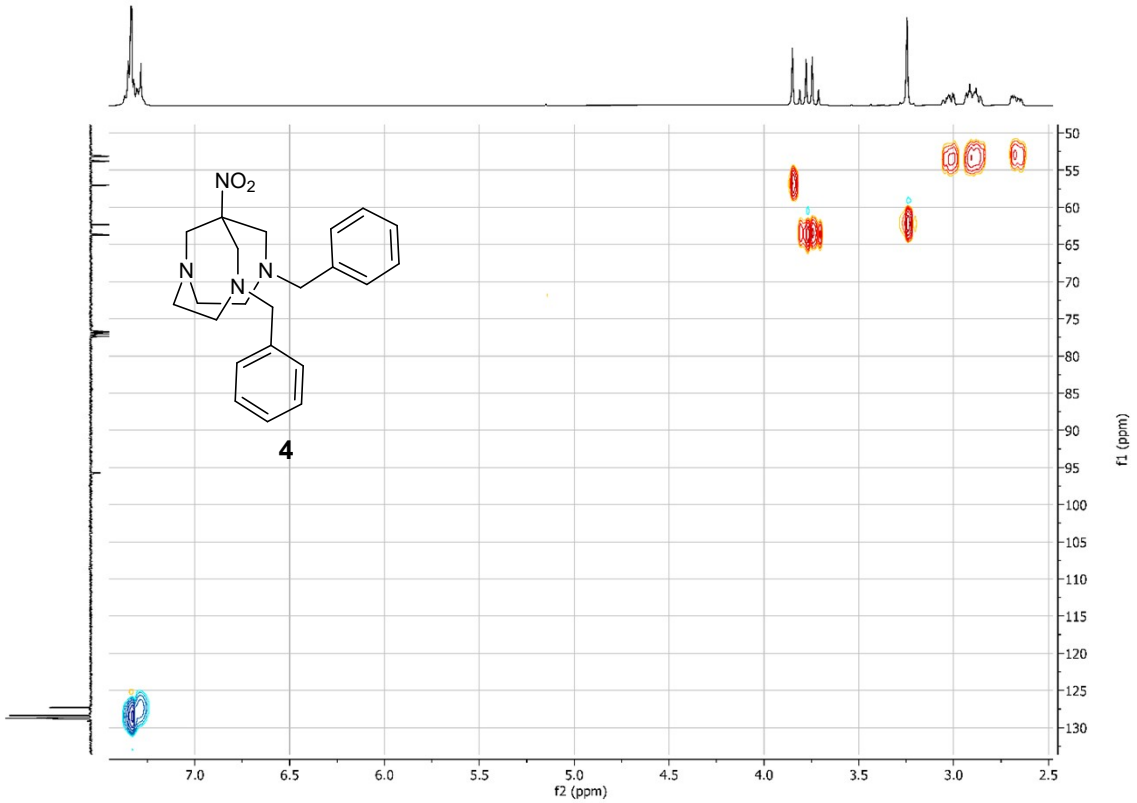


Figure S4. $^{1}H - {}^{13}C$ HSQC spectrum of compound **4**.

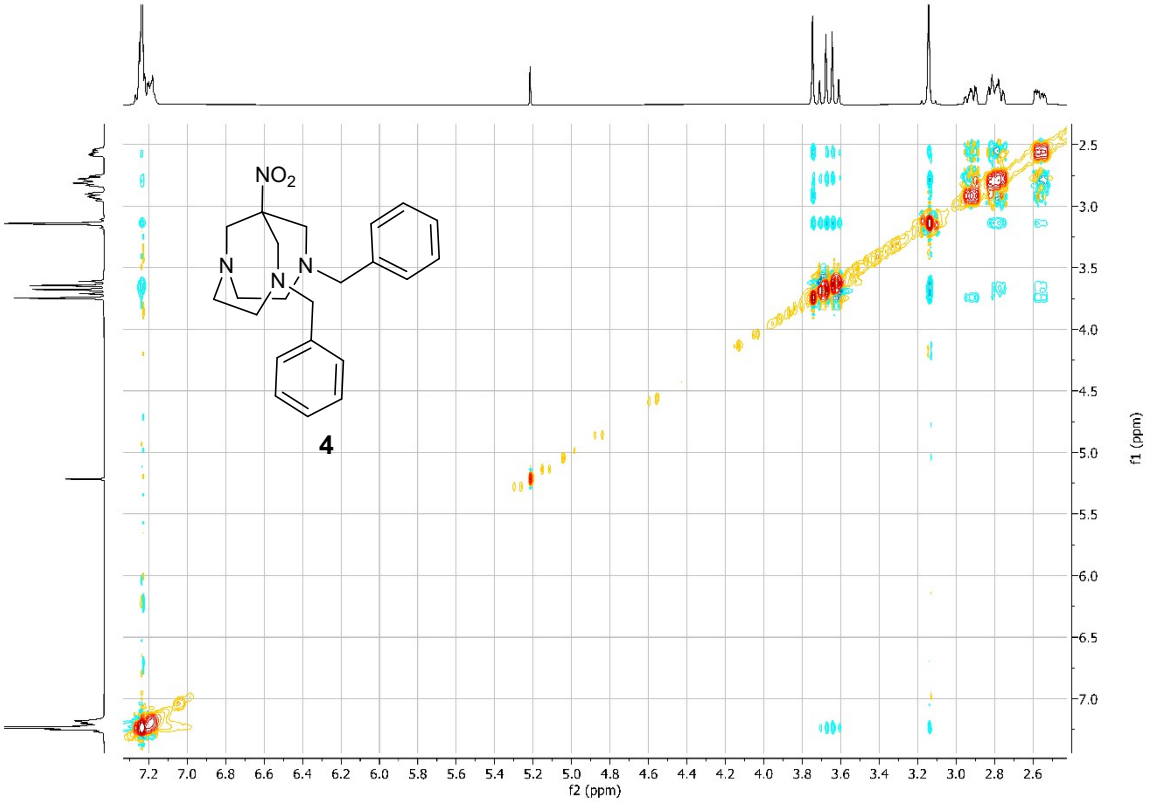


Figure S5. $^{1}H - {}^{1}H$ NOESY spectrum of compound **4**.

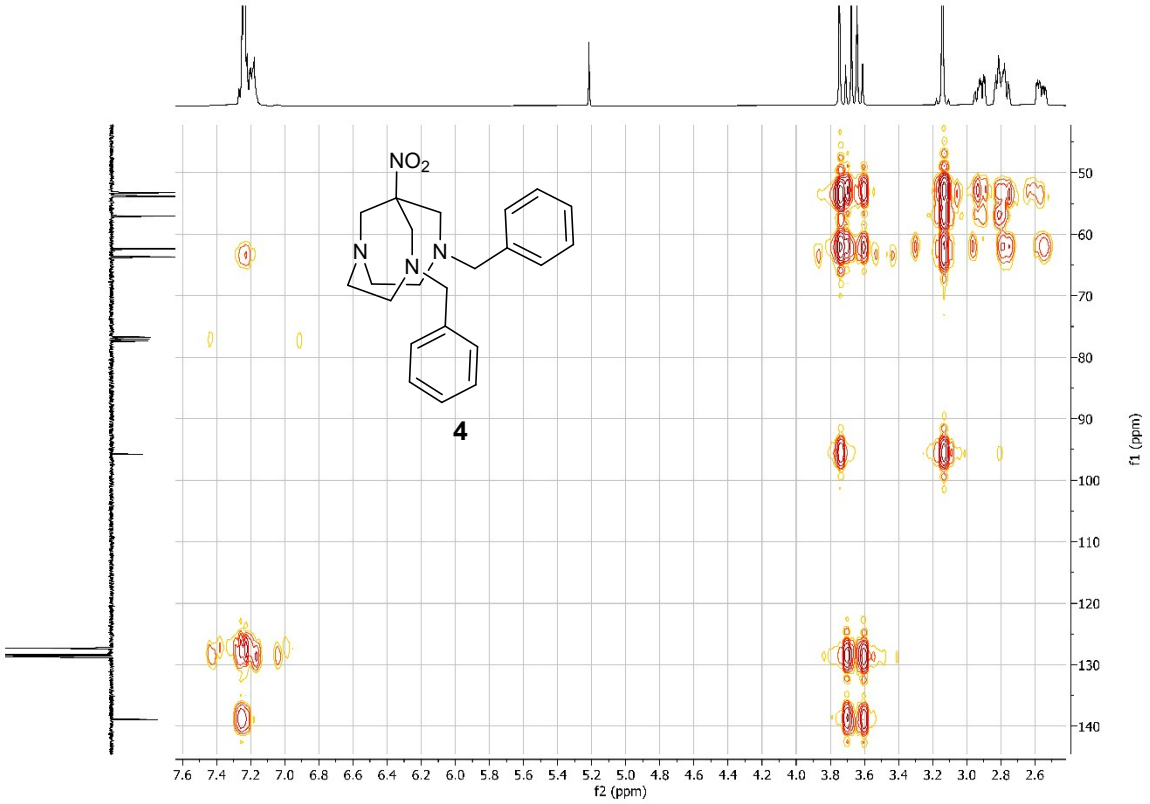
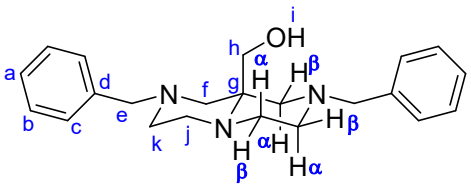


Figure S6. $^{1}H - {}^{13}C$ HMBC spectrum of compound **4**.



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**.

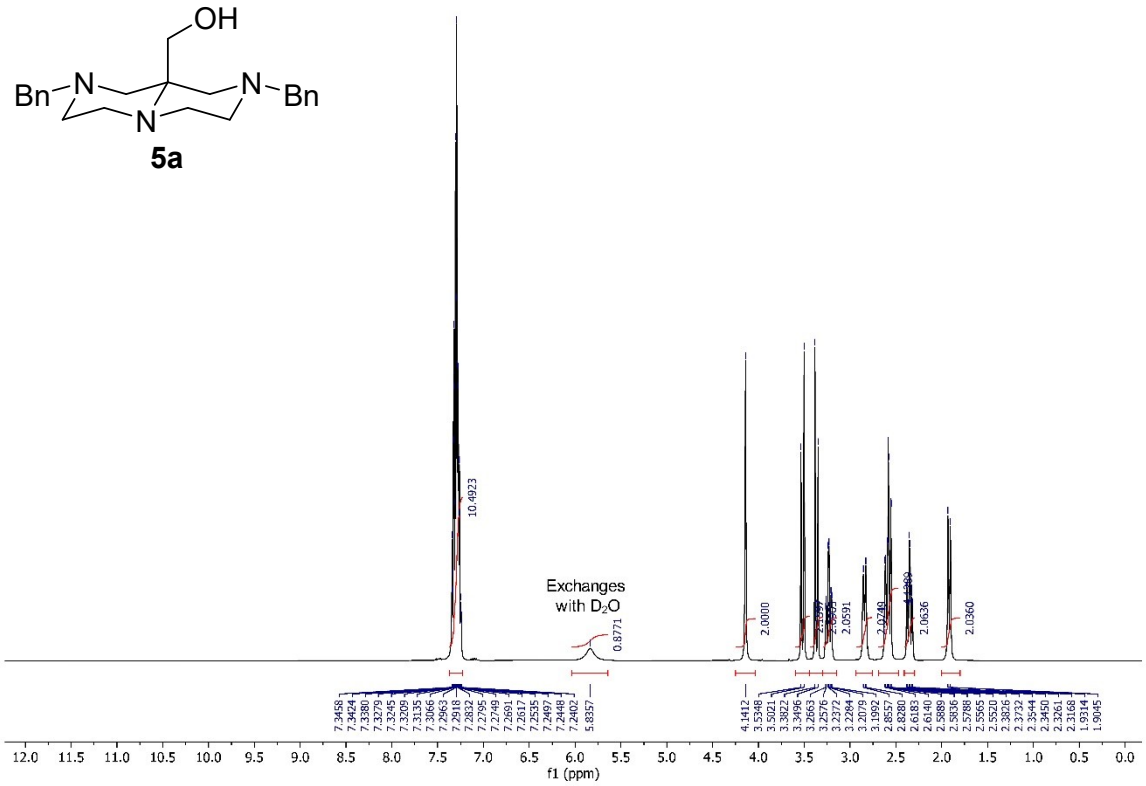


Figure S7. ^{1}H NMR spectrum of compound **5a**.

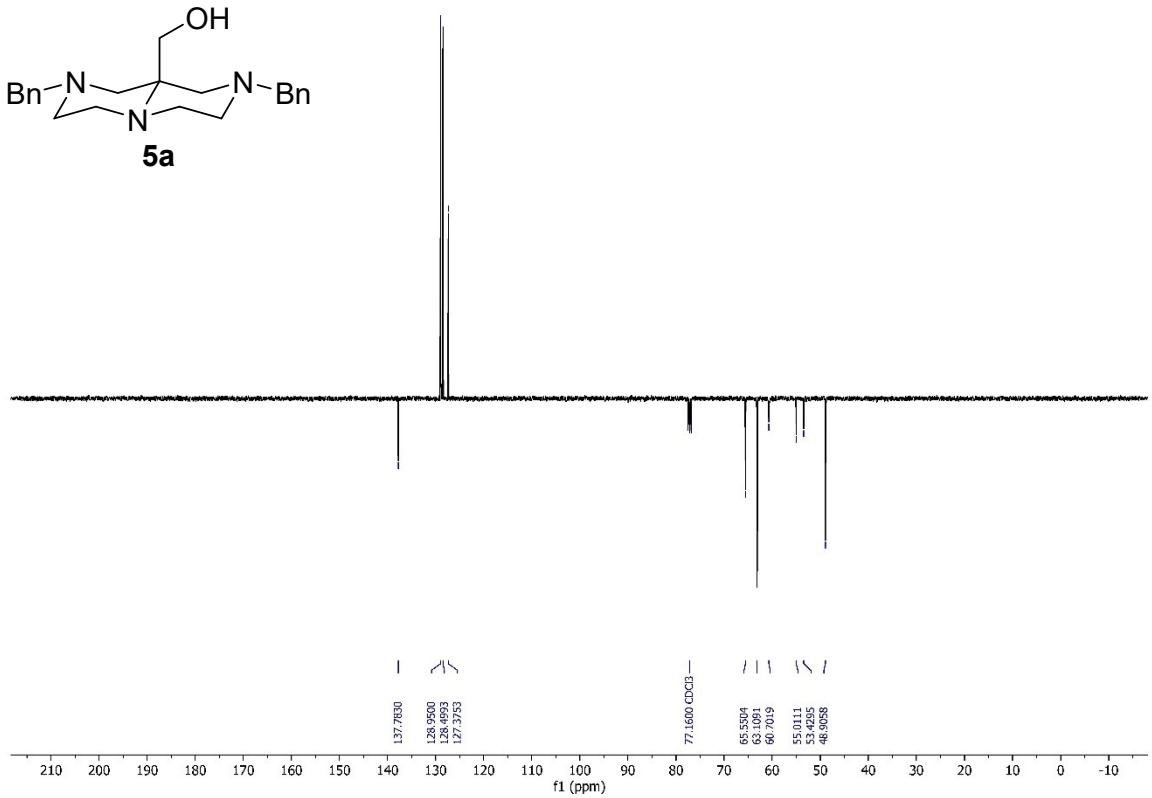


Figure S8. ^{13}C APT NMR spectrum of compound **5a**.

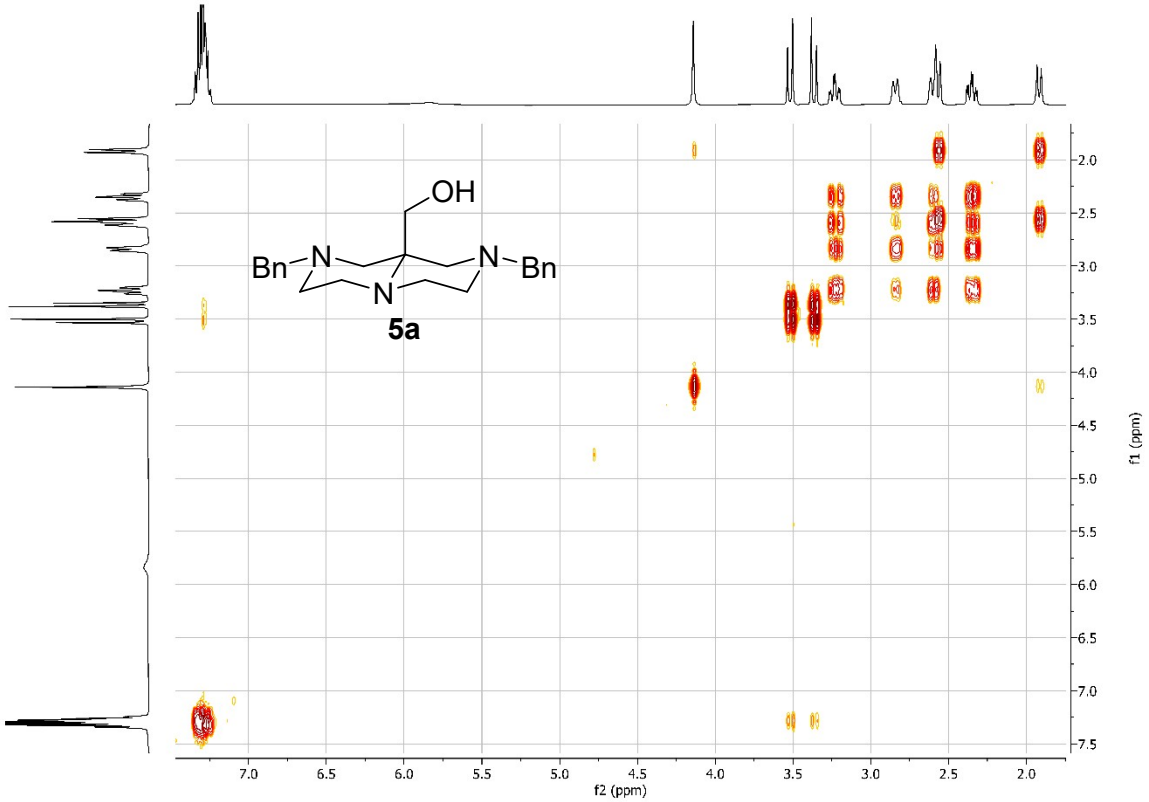


Figure S9. $^{1}H - {}^{1}H$ COSY spectrum of compound **5a**.

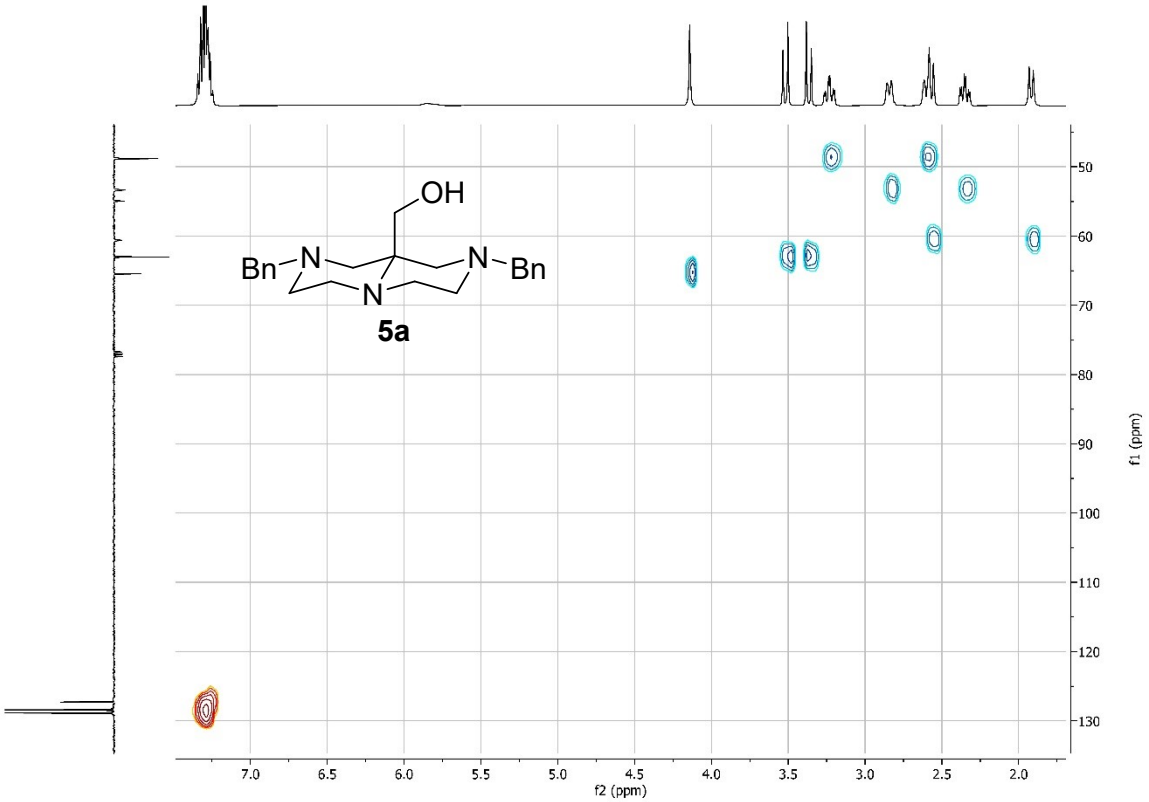


Figure S10. $^{1}H - {}^{13}C$ HSQC spectrum of compound **5a**.

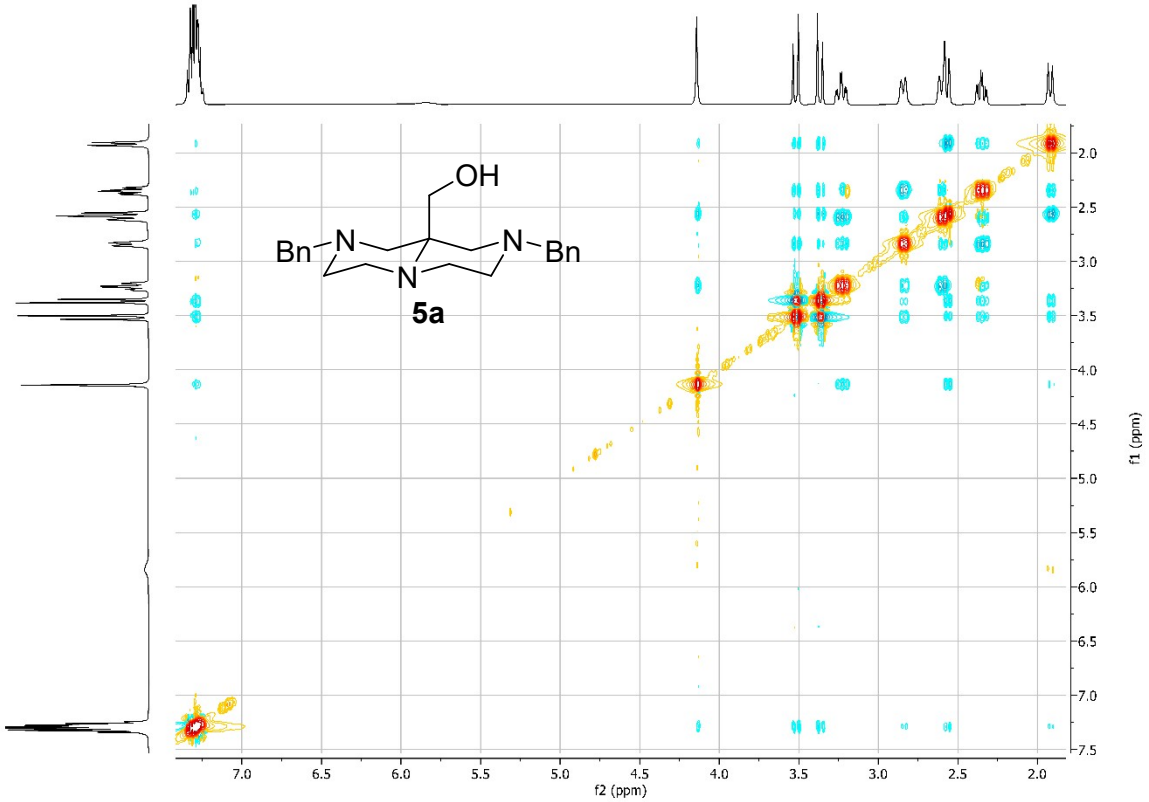


Figure S11. ^{1}H – ^{1}H NOESY spectrum of compound **5a**.

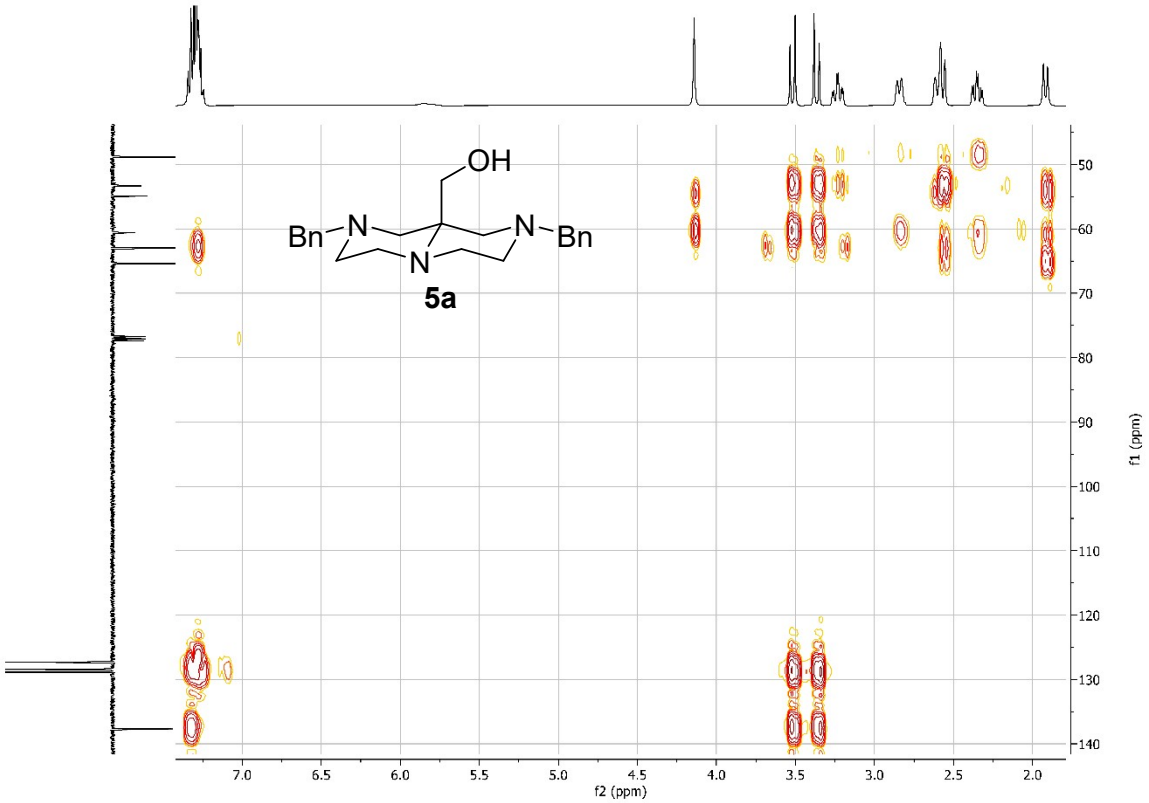


Figure S12. ^{1}H – ^{13}C HMBC spectrum of compound **5a**.

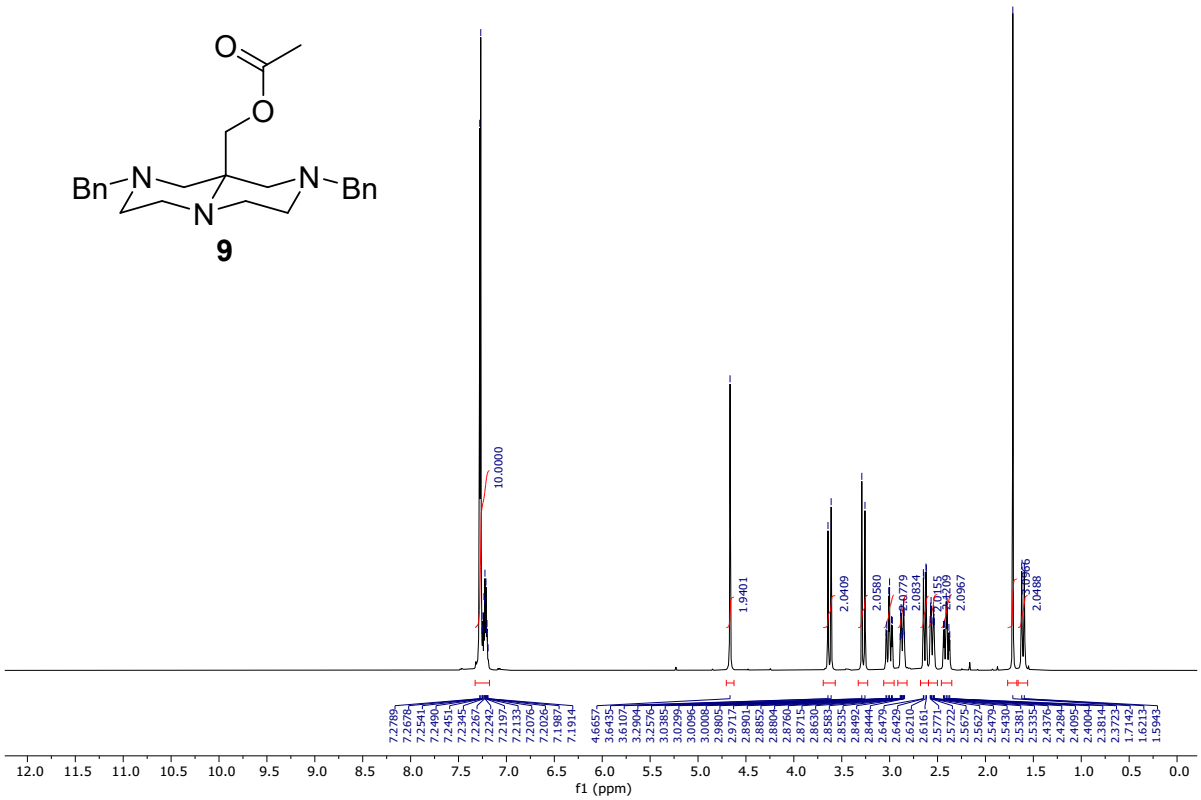


Figure S13. ^{1}H NMR spectrum of compound **9**.

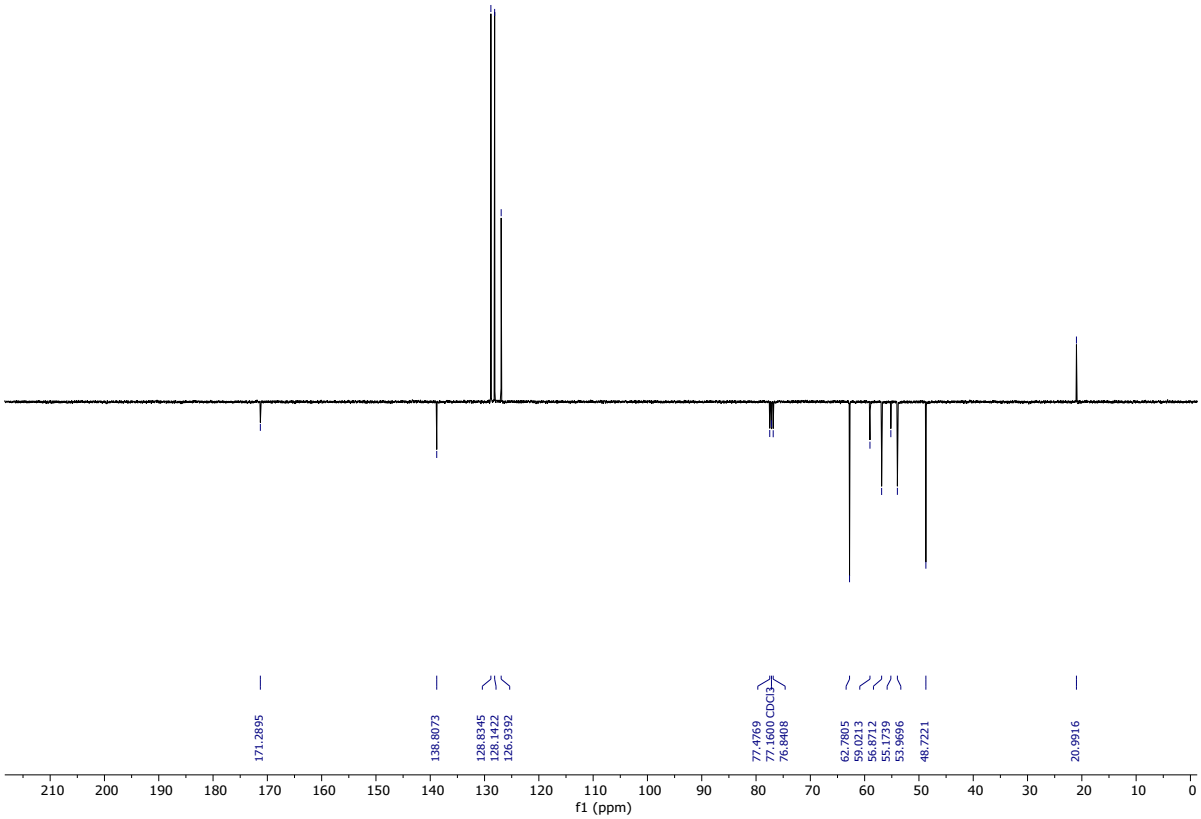


Figure S14. ^{13}C APT NMR spectrum of compound **9**.

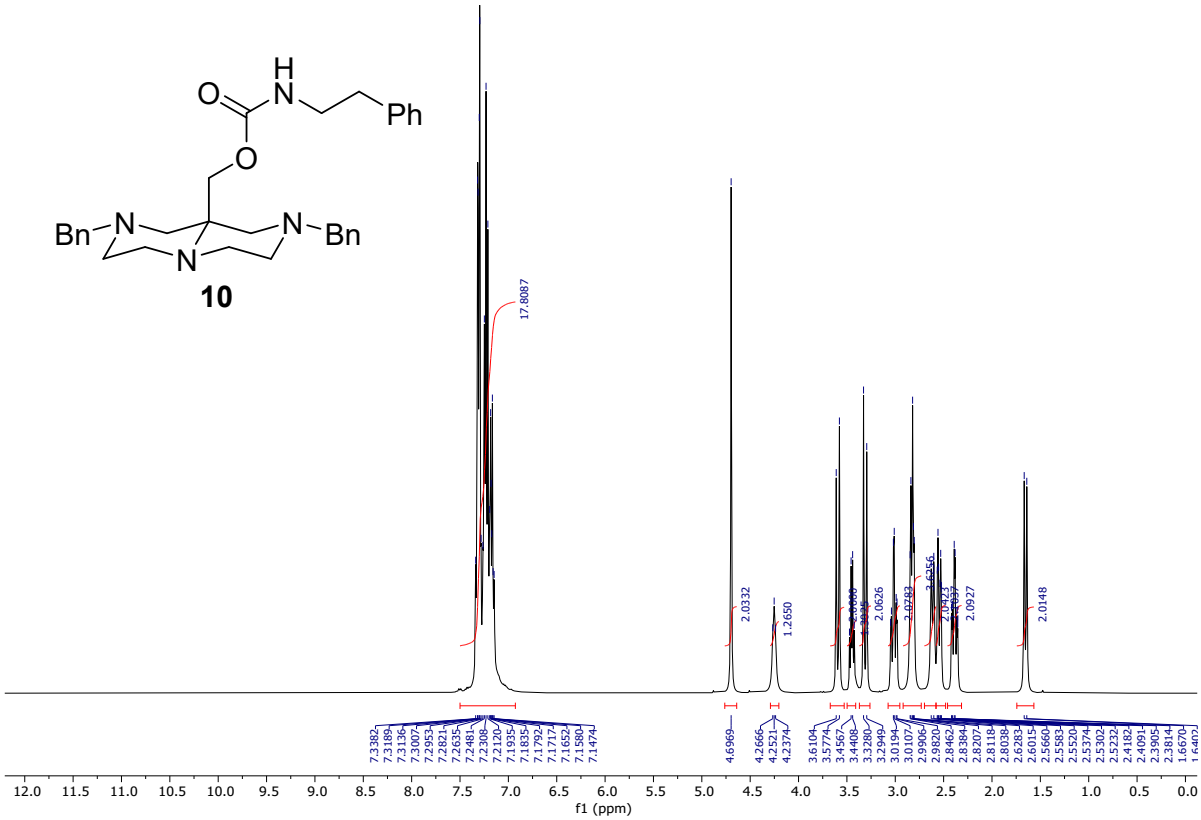


Figure S15. ^{1}H NMR spectrum of compound **10**.

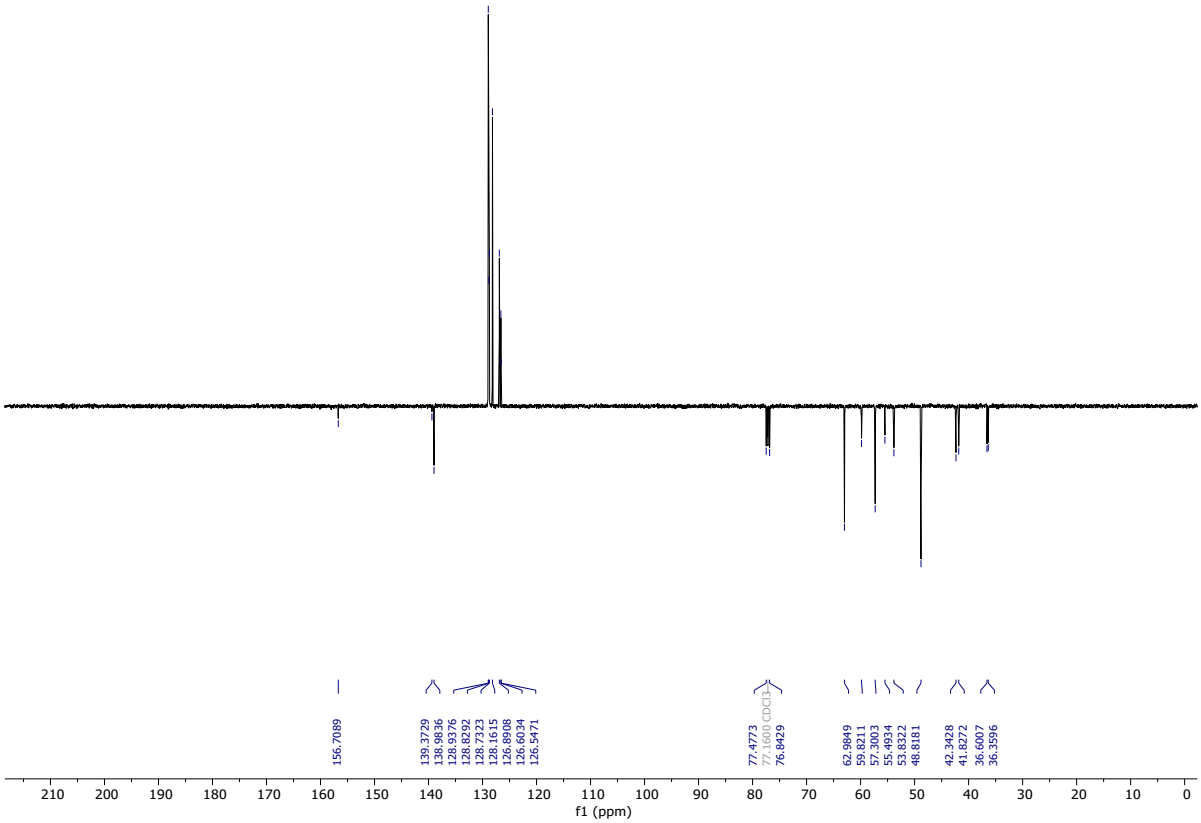


Figure S16. ^{13}C APT NMR spectrum of compound **10**.

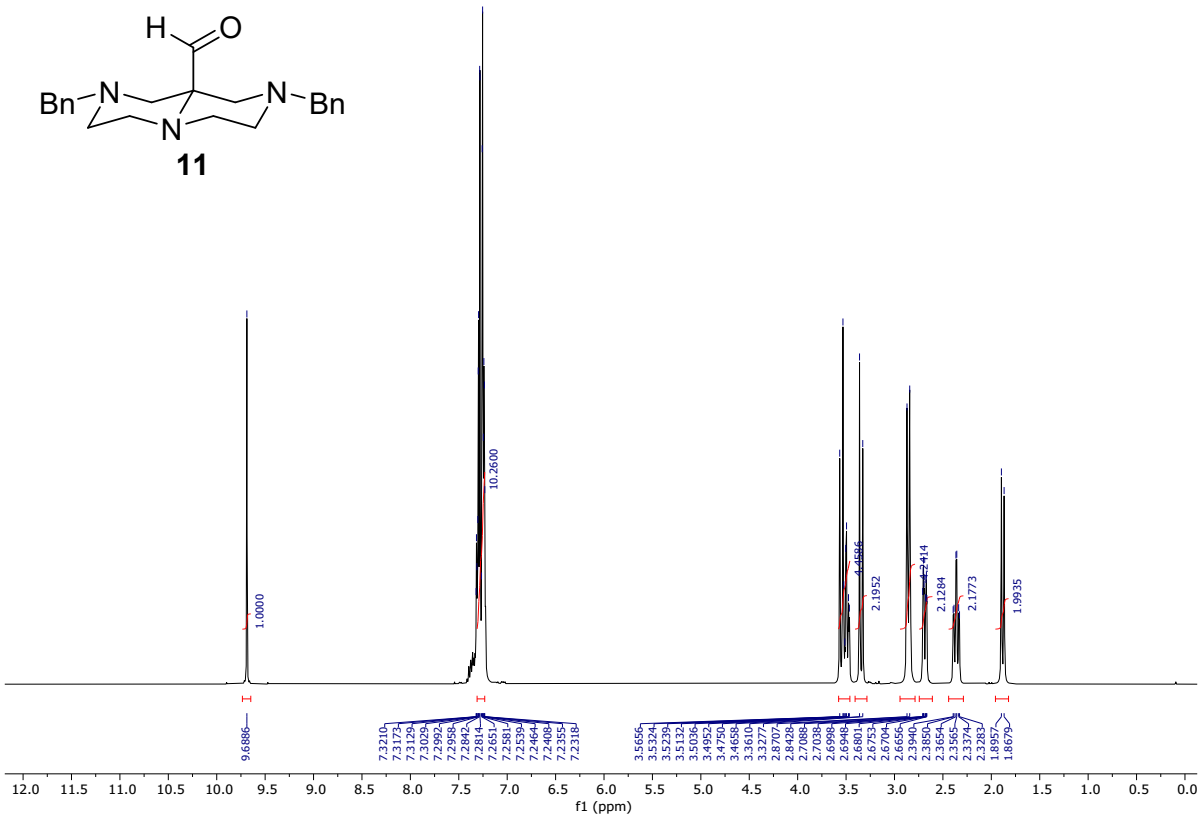


Figure S17. ^{1}H NMR spectrum of compound **11**.

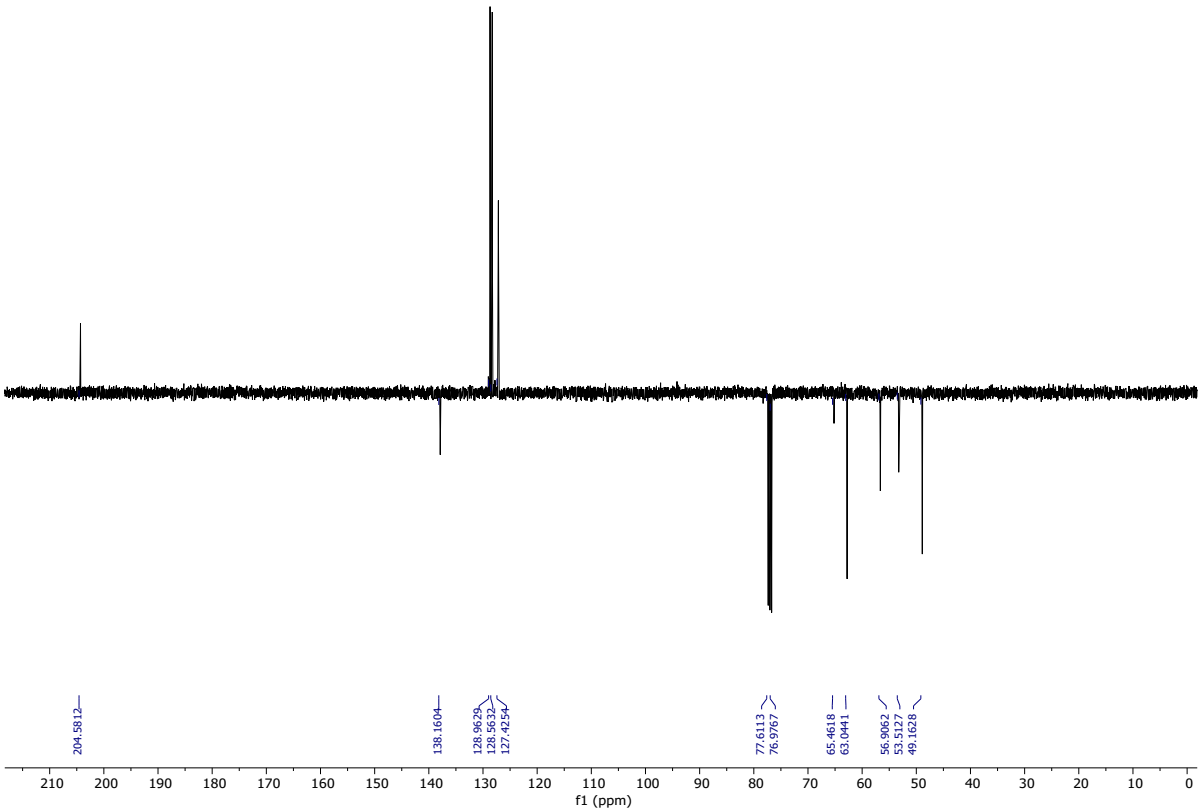


Figure S18. ^{13}C APT NMR spectrum of compound **11**.

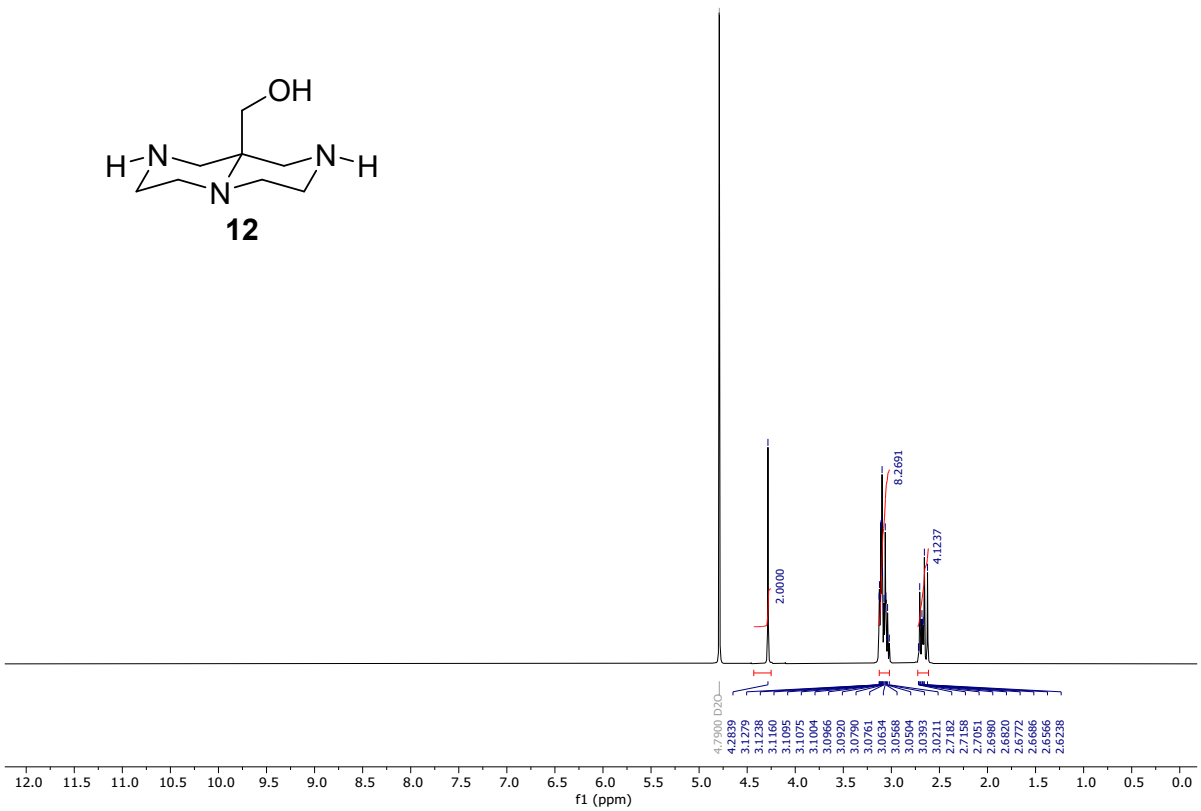


Figure S19. ^{1}H NMR spectrum of compound **12**.

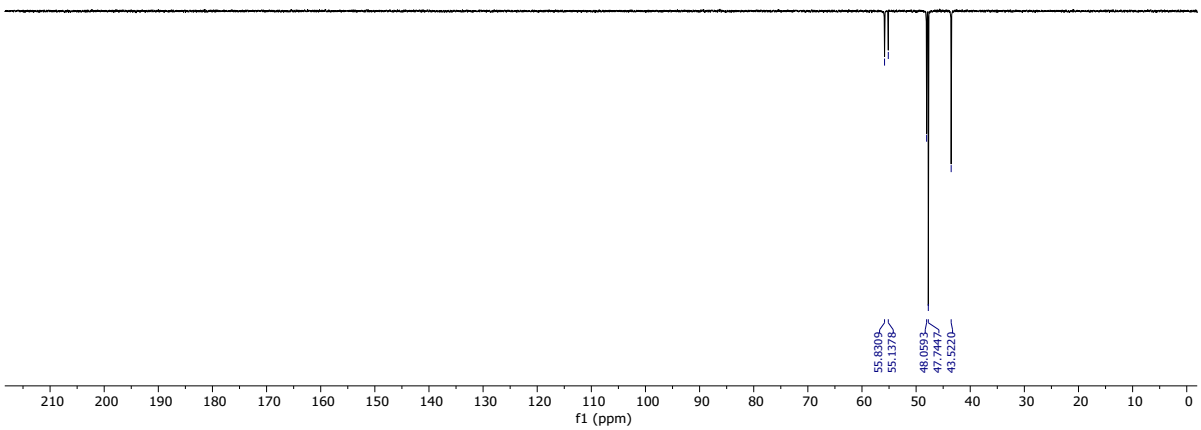


Figure S20. ^{13}C APT NMR spectrum of compound **12**.

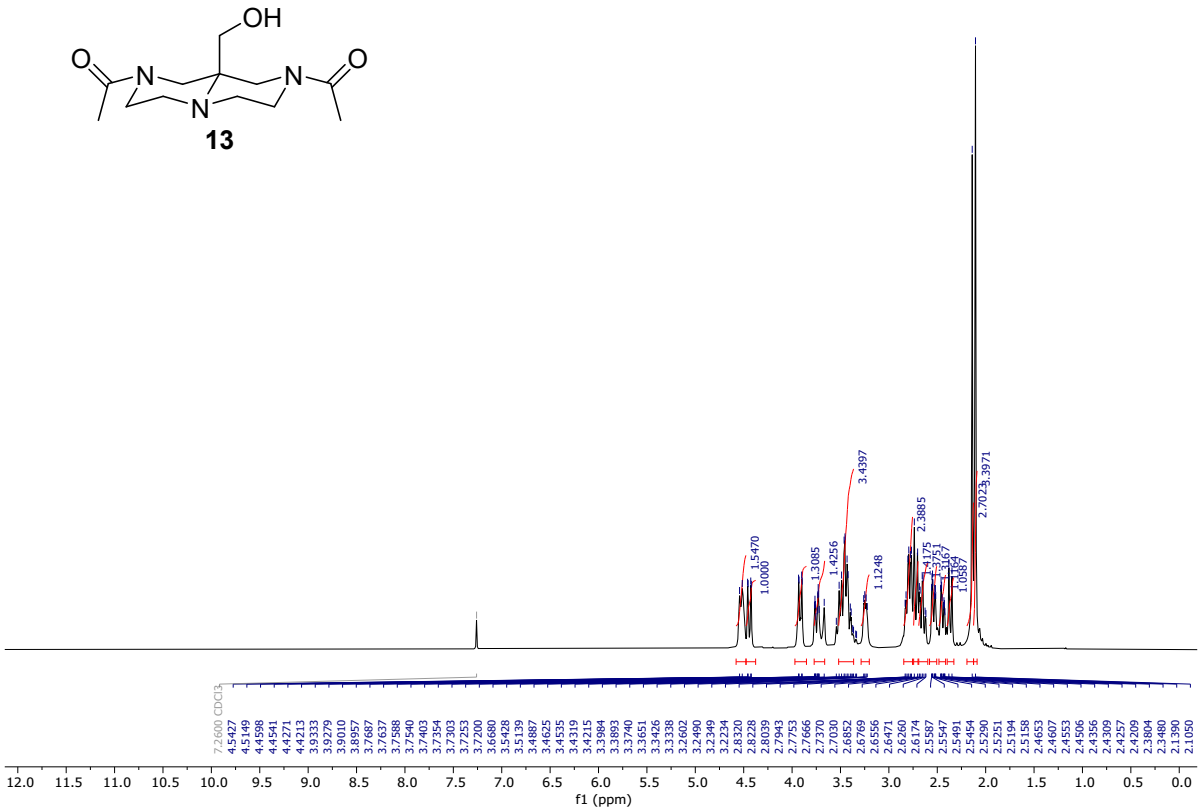


Figure S21. ^{1}H NMR spectrum of compound **13**.

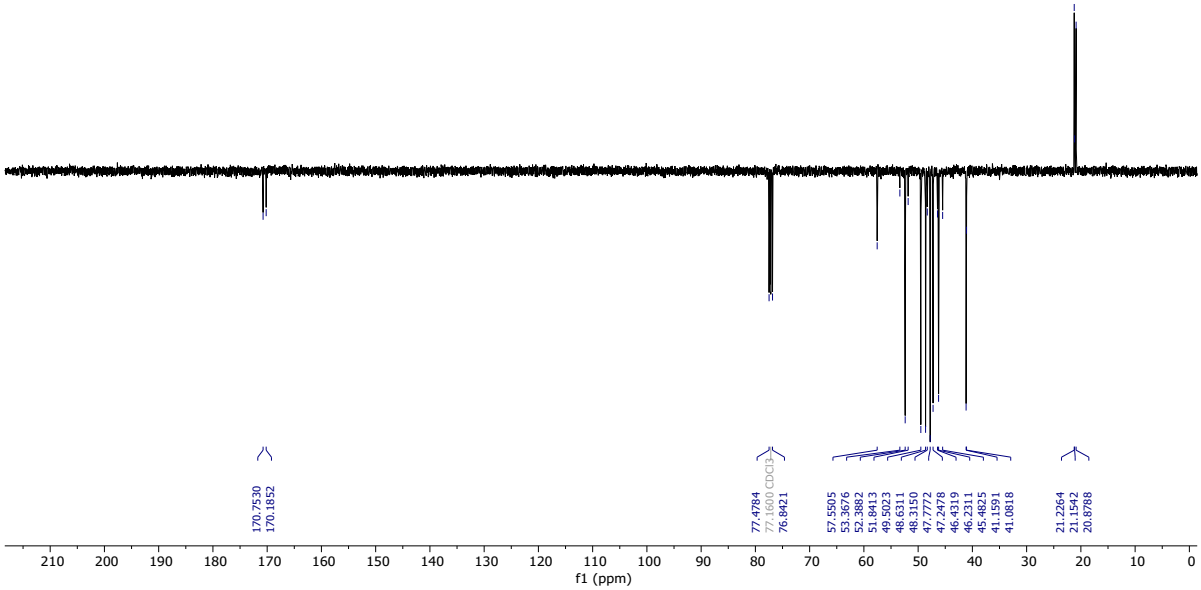
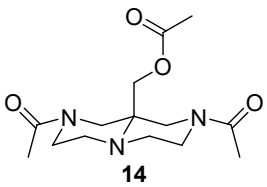


Figure S22. ^{13}C APT NMR spectrum of compound **13**.



14

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

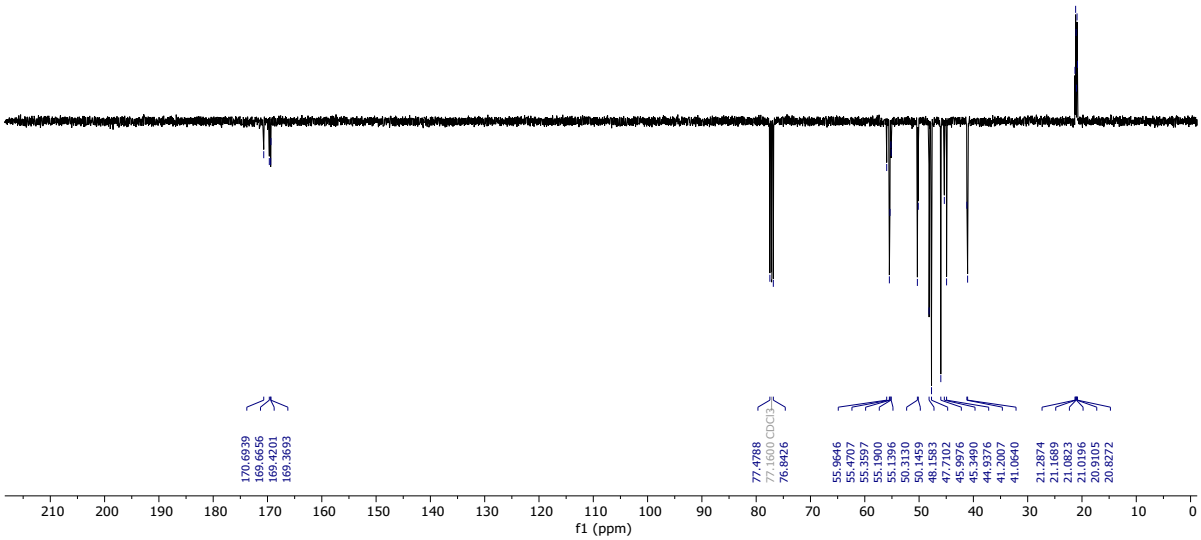


Figure S24. ^{13}C APT NMR spectrum of compound **14**.

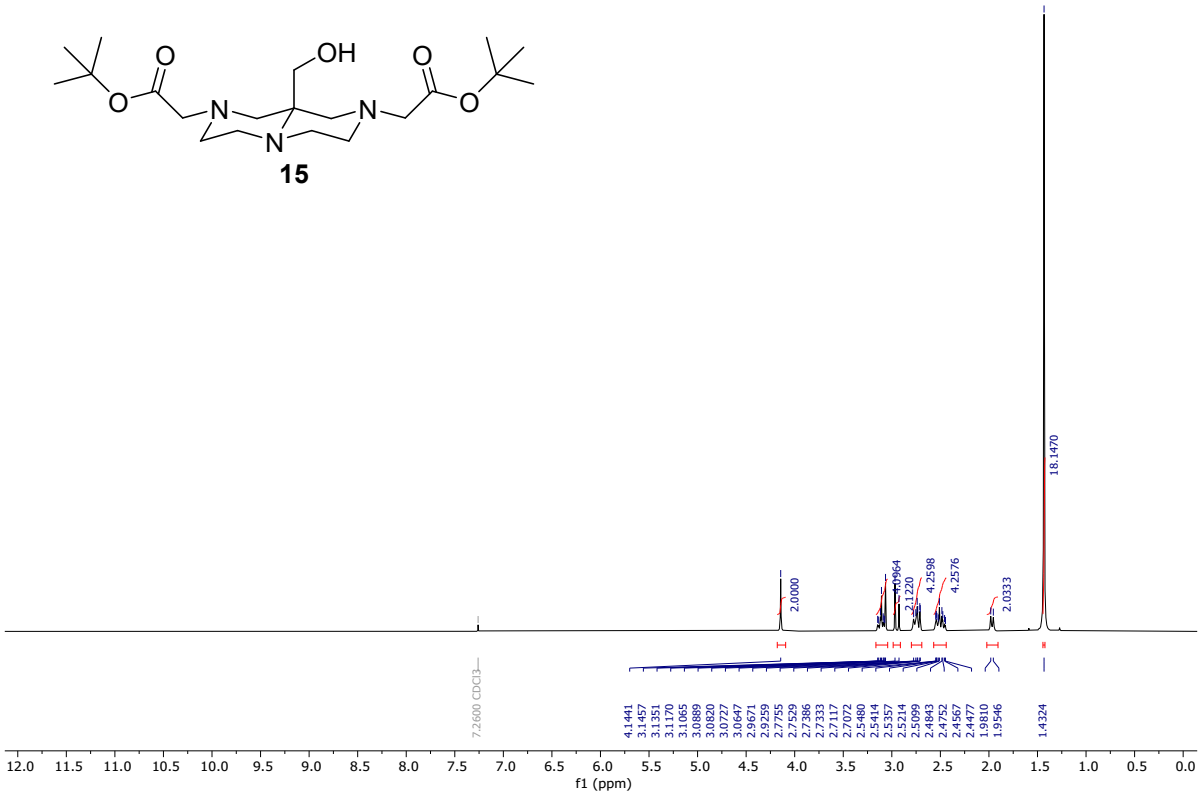


Figure S25. ^{1}H NMR spectrum of compound **15**.

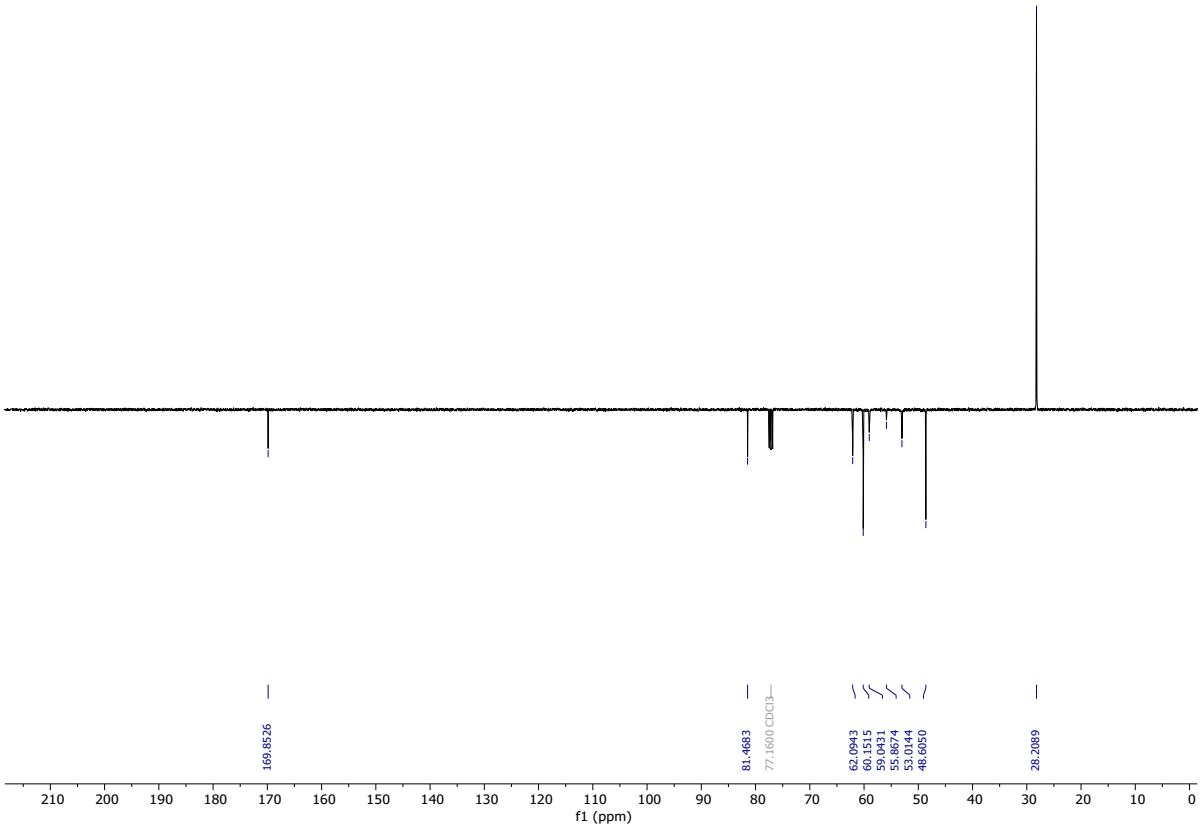


Figure S26. ^{13}C APT NMR spectrum of compound **15**.

FT-IR analysis compound 5a

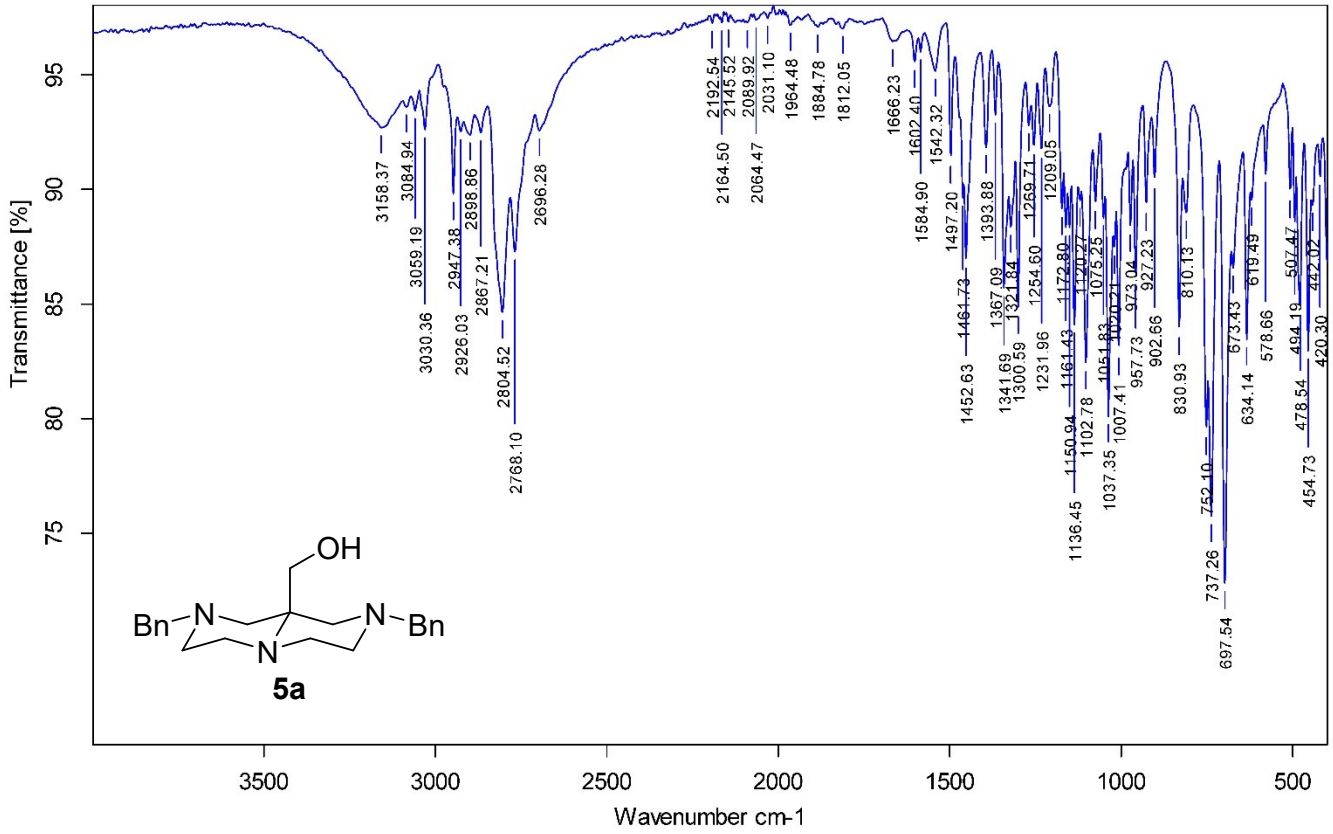


Figure S27. FT-IR spectrum of compound **5a**.

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**)

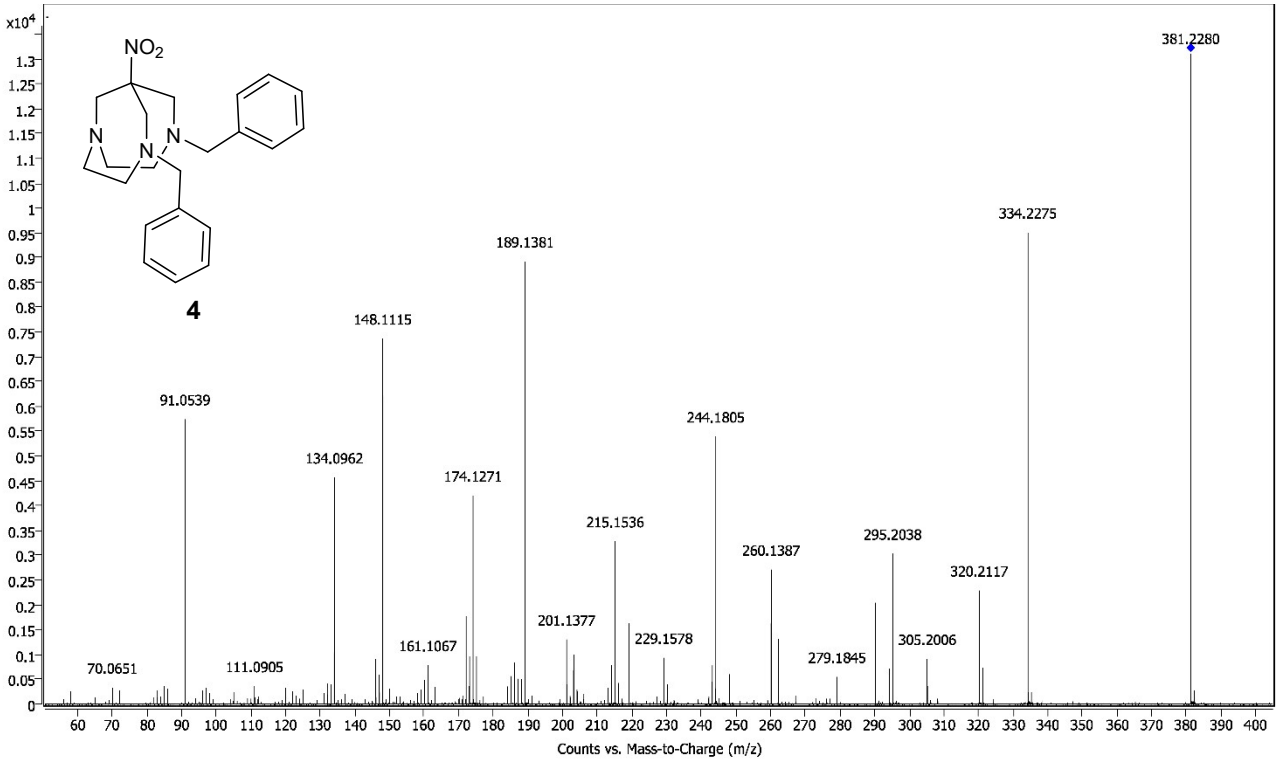


Figure S28. HRMS spectrum of compound **4**.

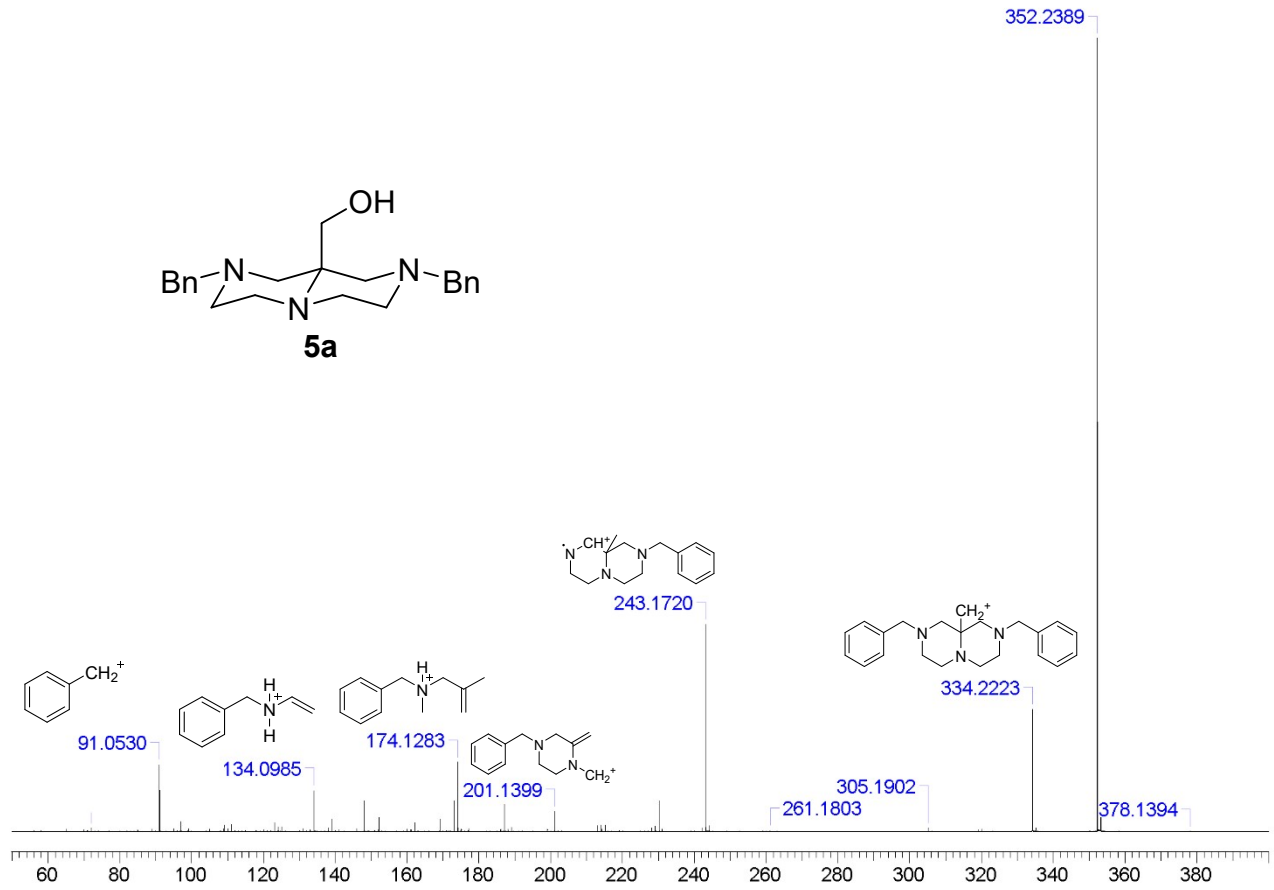


Figure S29. HRMS spectrum of compound **5a**.

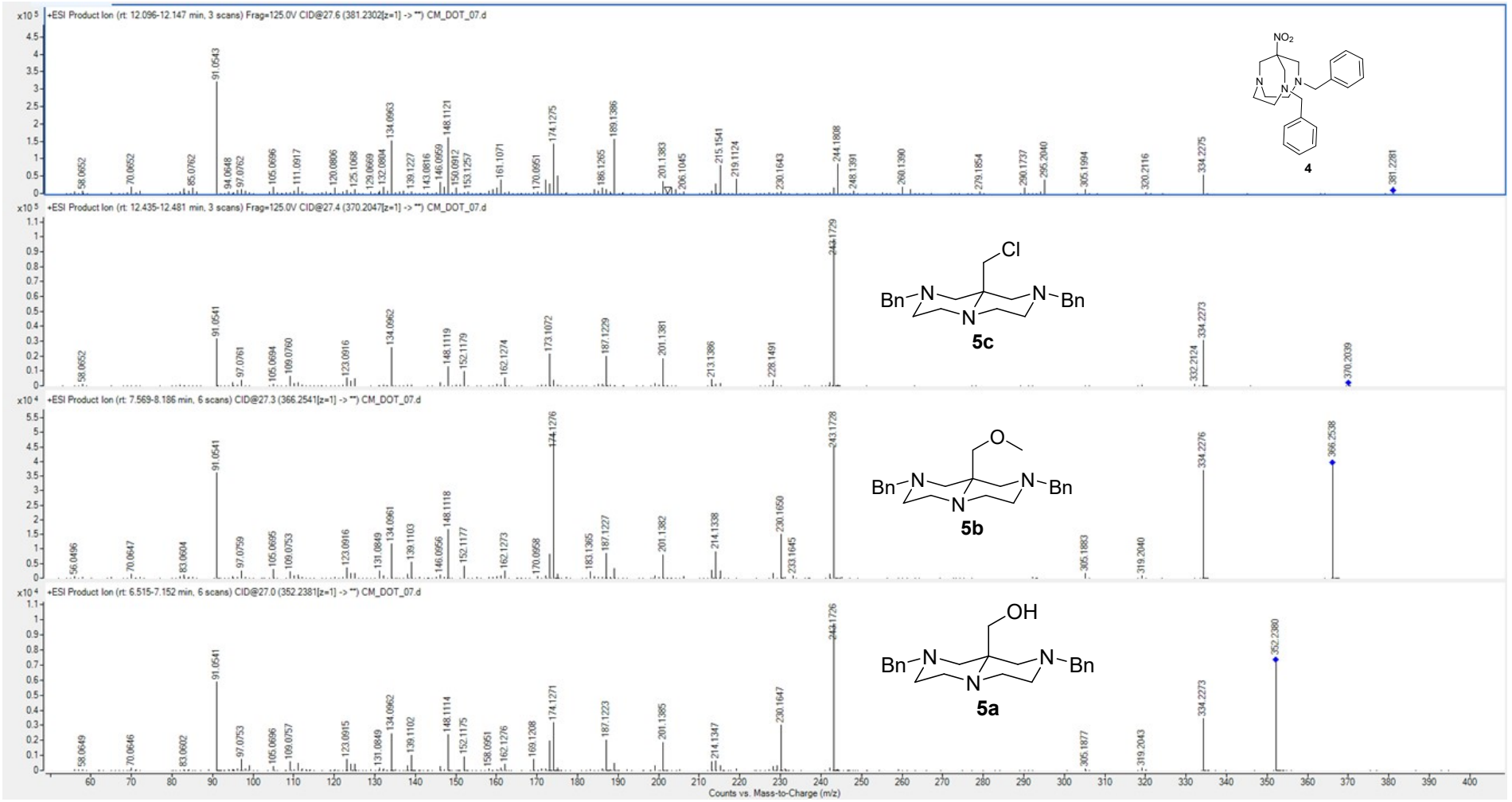


Figure S30. Superimposition of HRMS spectra of compound, from top to bottom, **4**, **5c**, **5b** and **5a**.

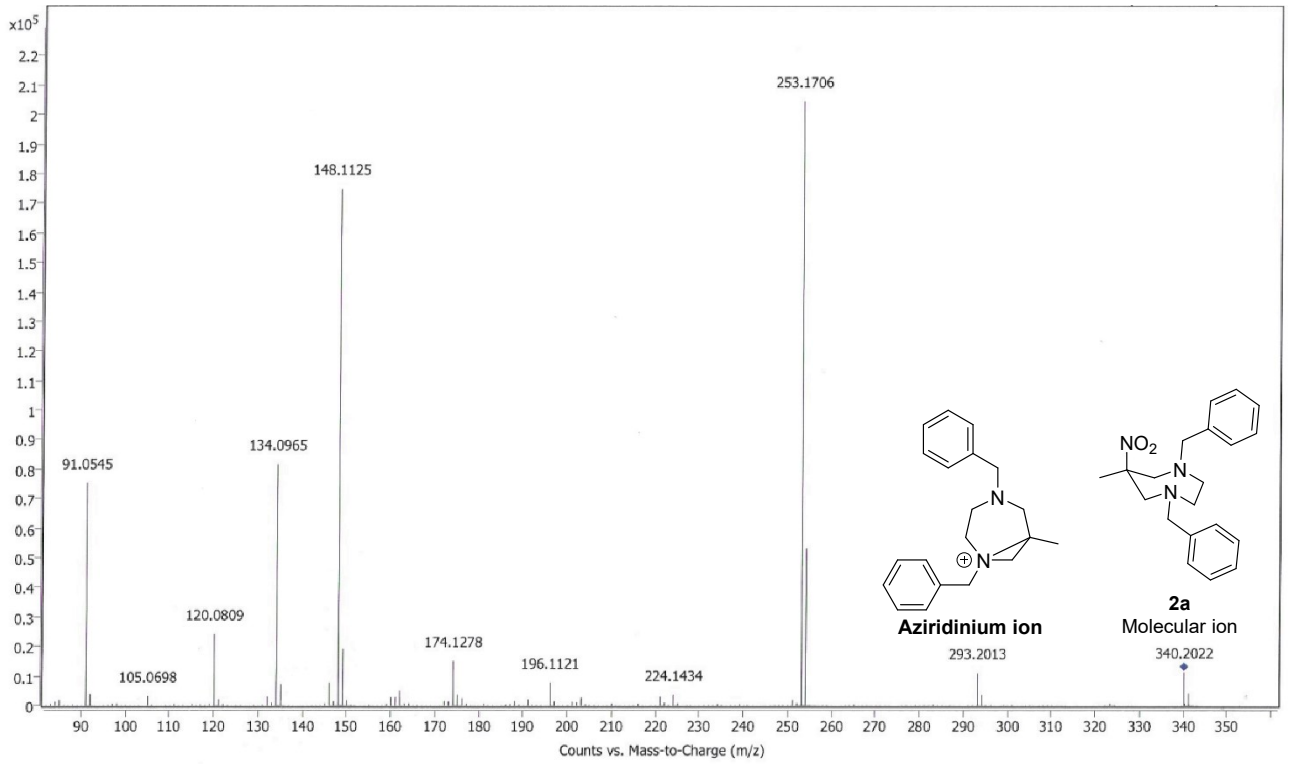


Figure S31. HRMS spectrum of compound **2a**.

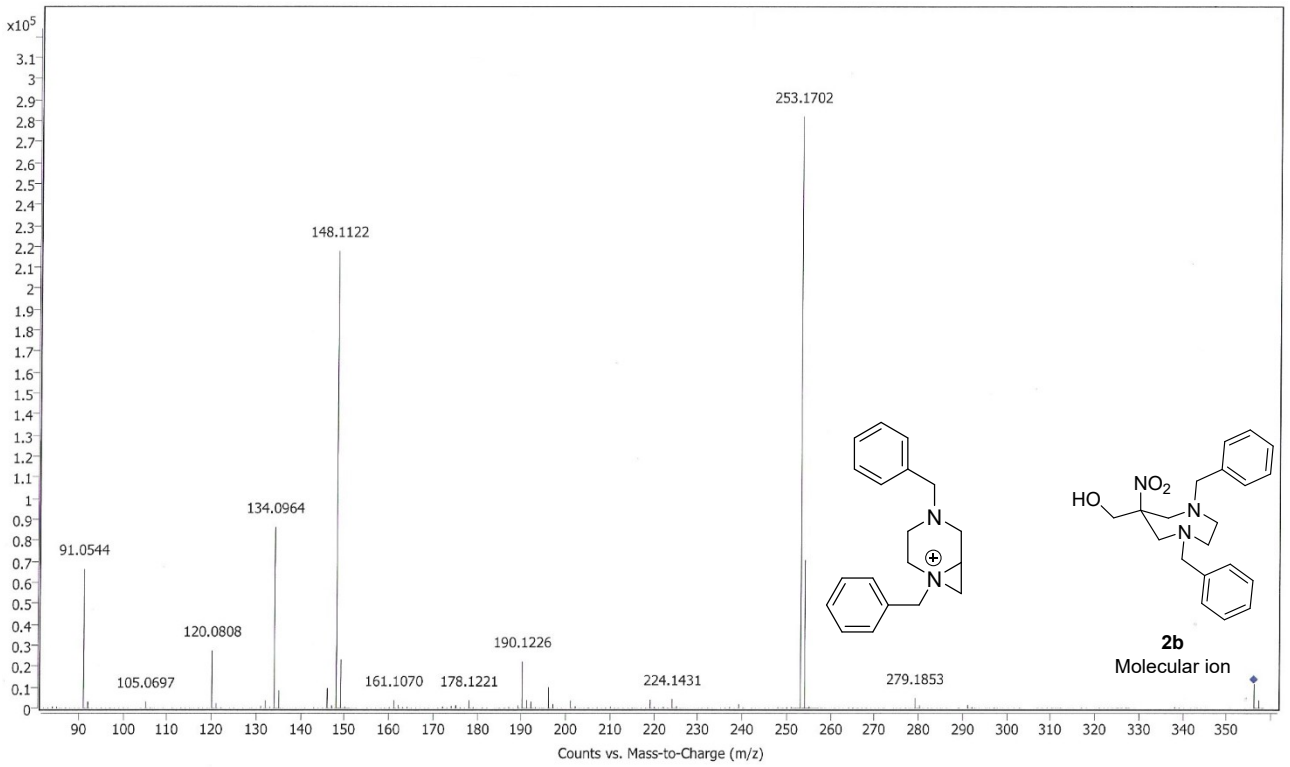


Figure S32. HRMS spectrum of compound **2b**.

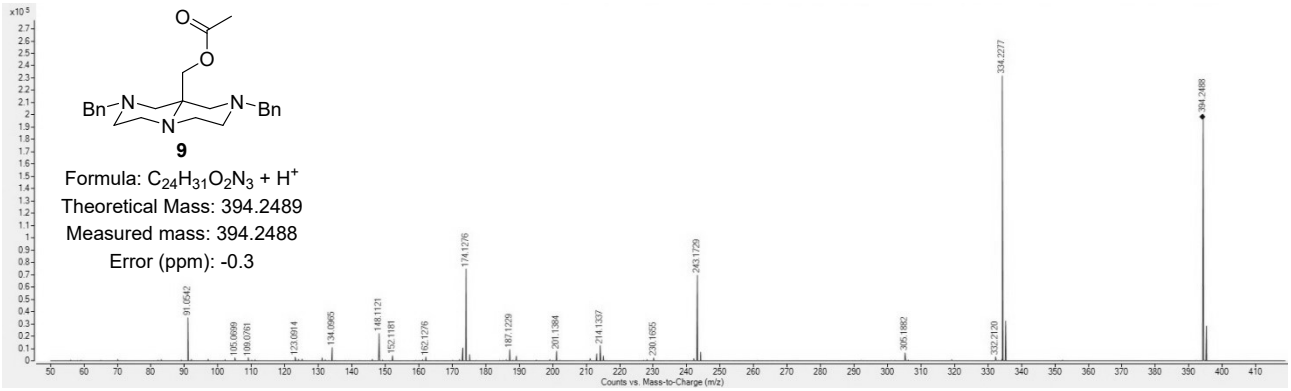


Figure S33. HRMS spectrum of compound **9**.

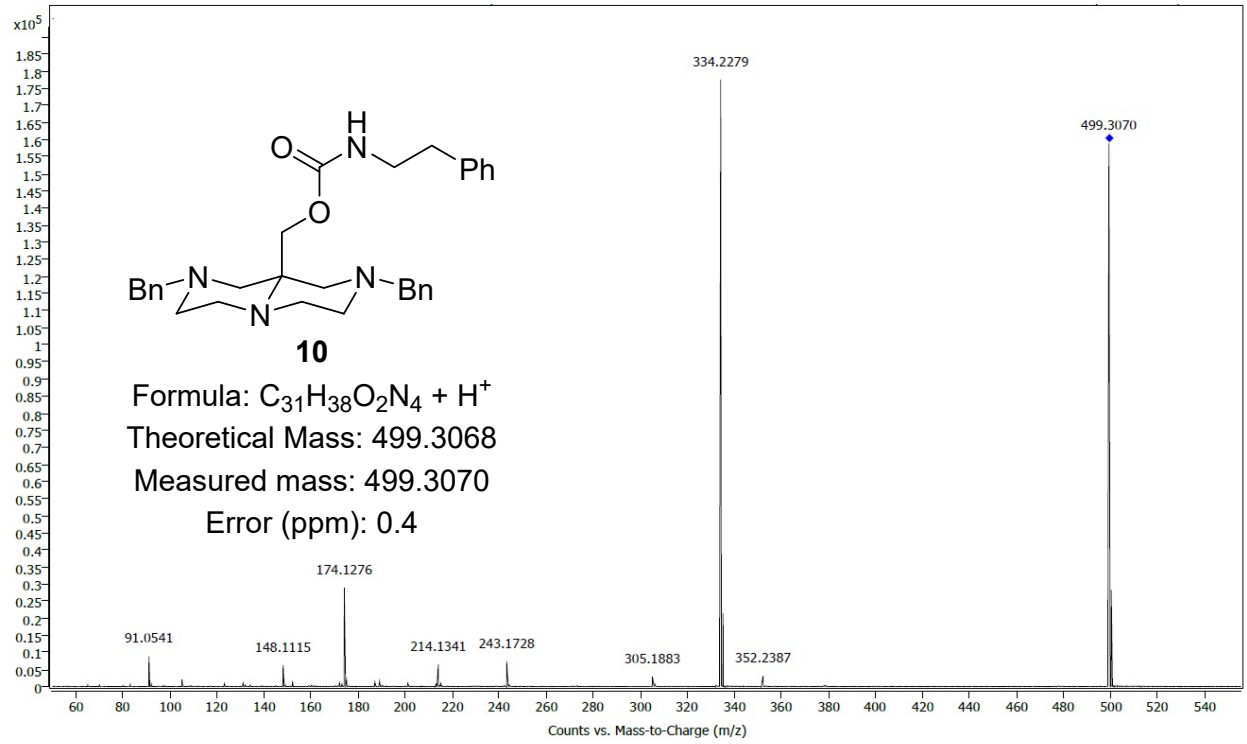


Figure S34. HRMS spectrum of compound **10**.

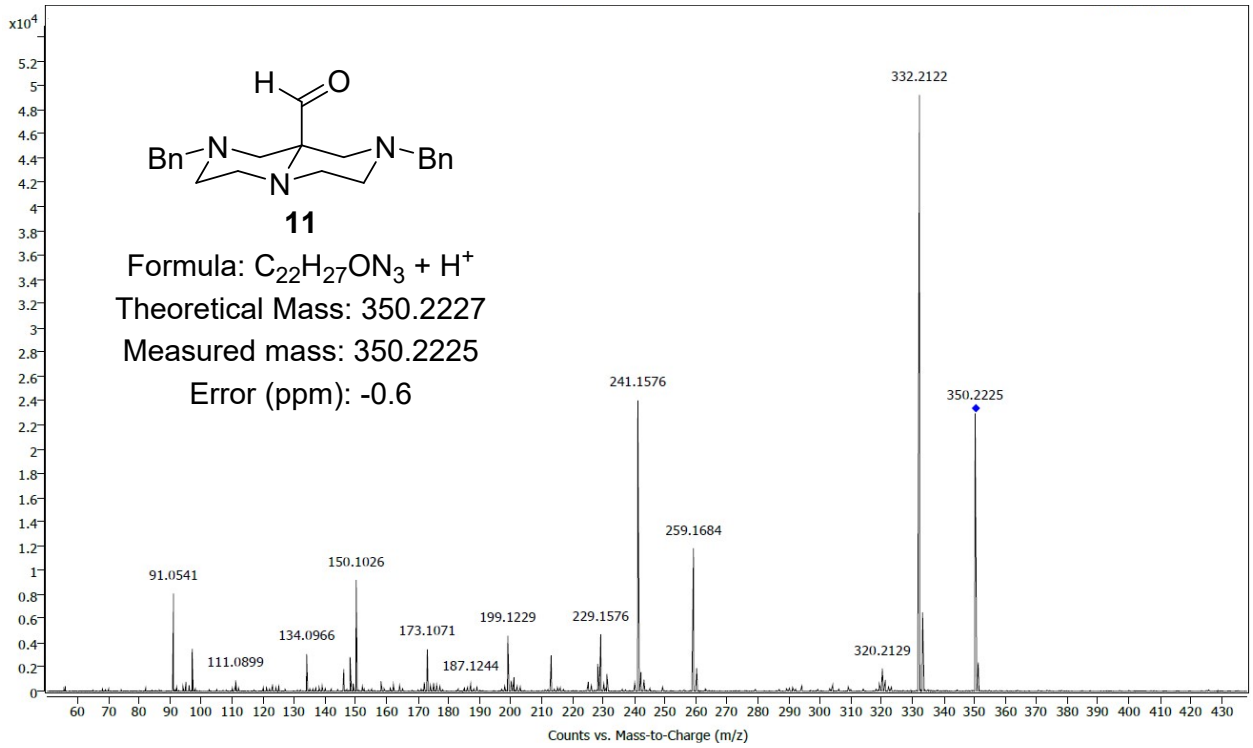


Figure S35. HRMS spectrum of compound **11**.

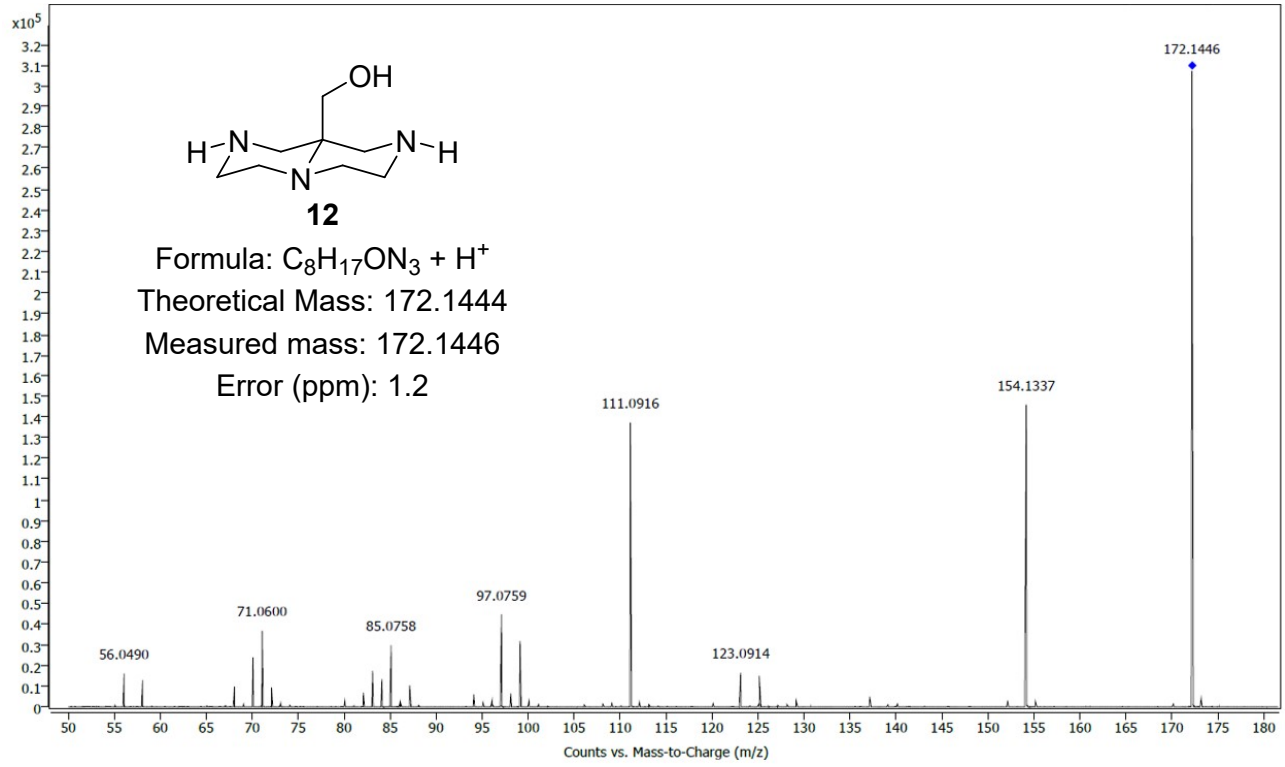


Figure S36. HRMS spectrum of compound **12**.

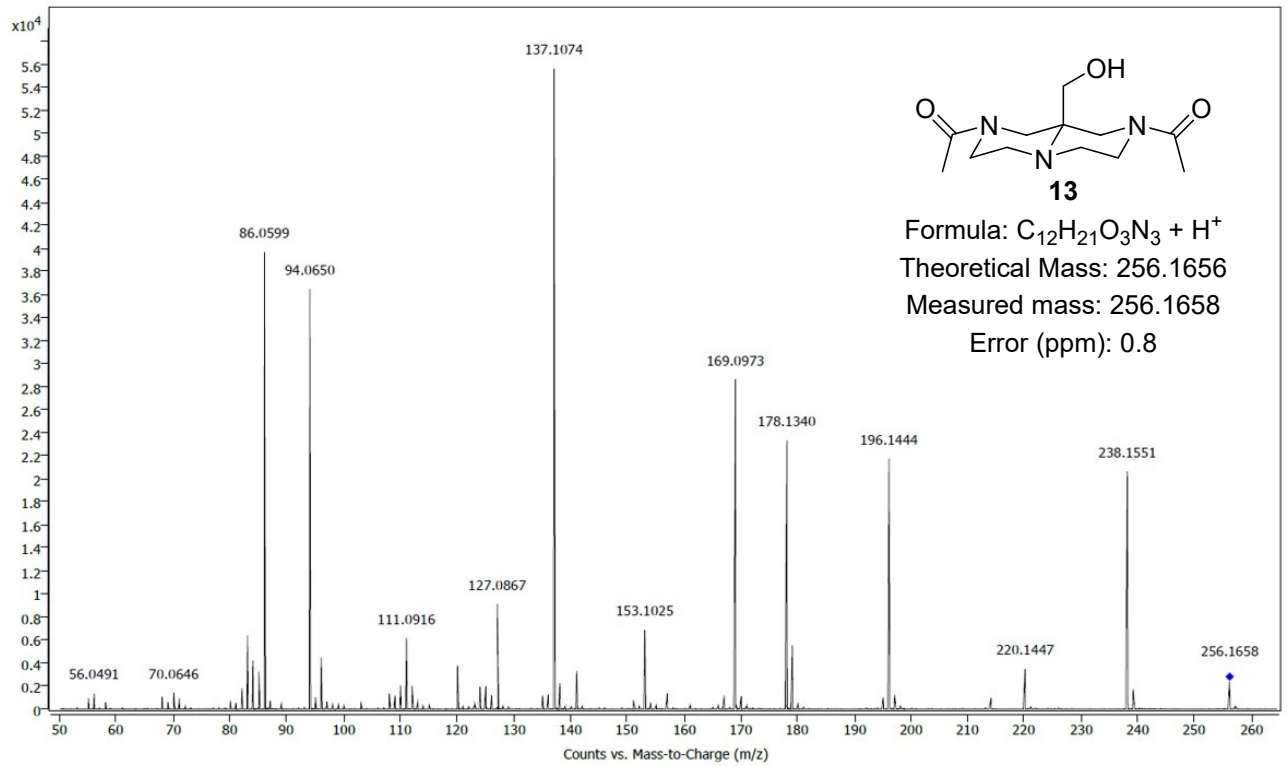


Figure S37. HRMS spectrum of compound **13**.

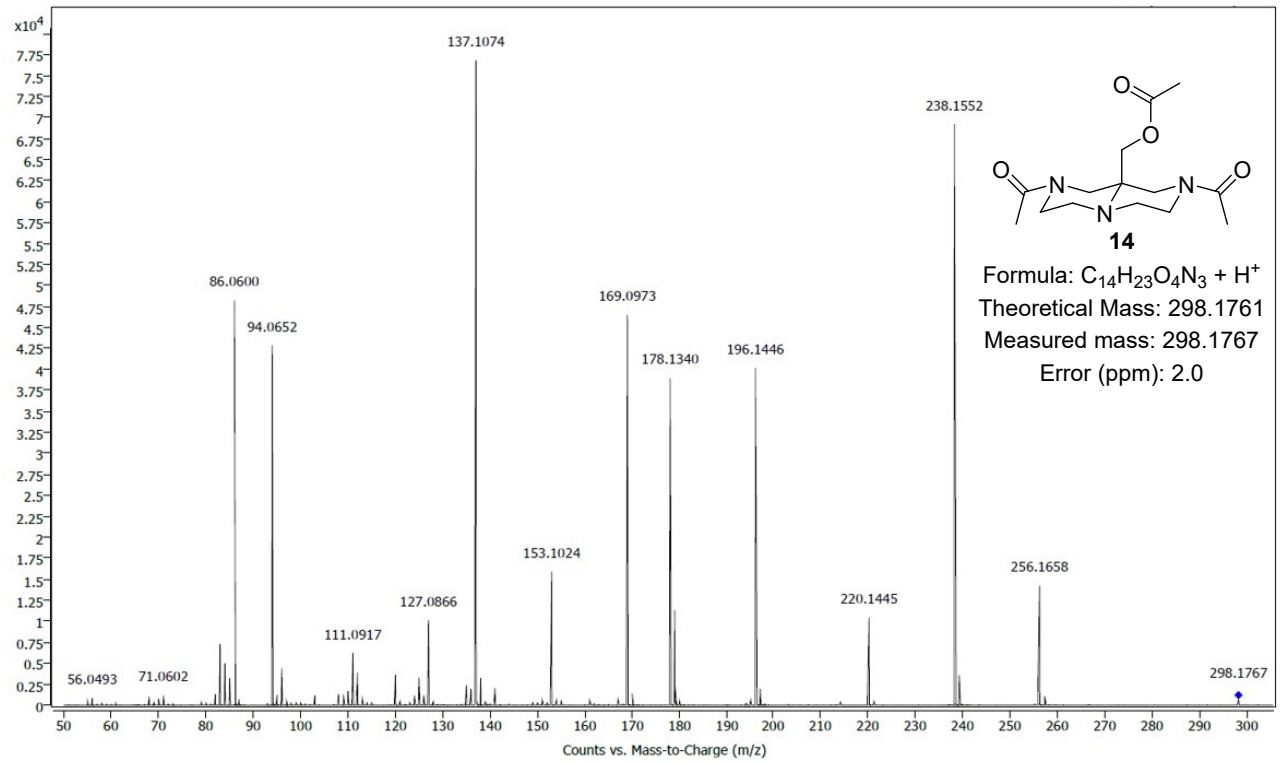


Figure S38. HRMS spectrum of compound **14**.

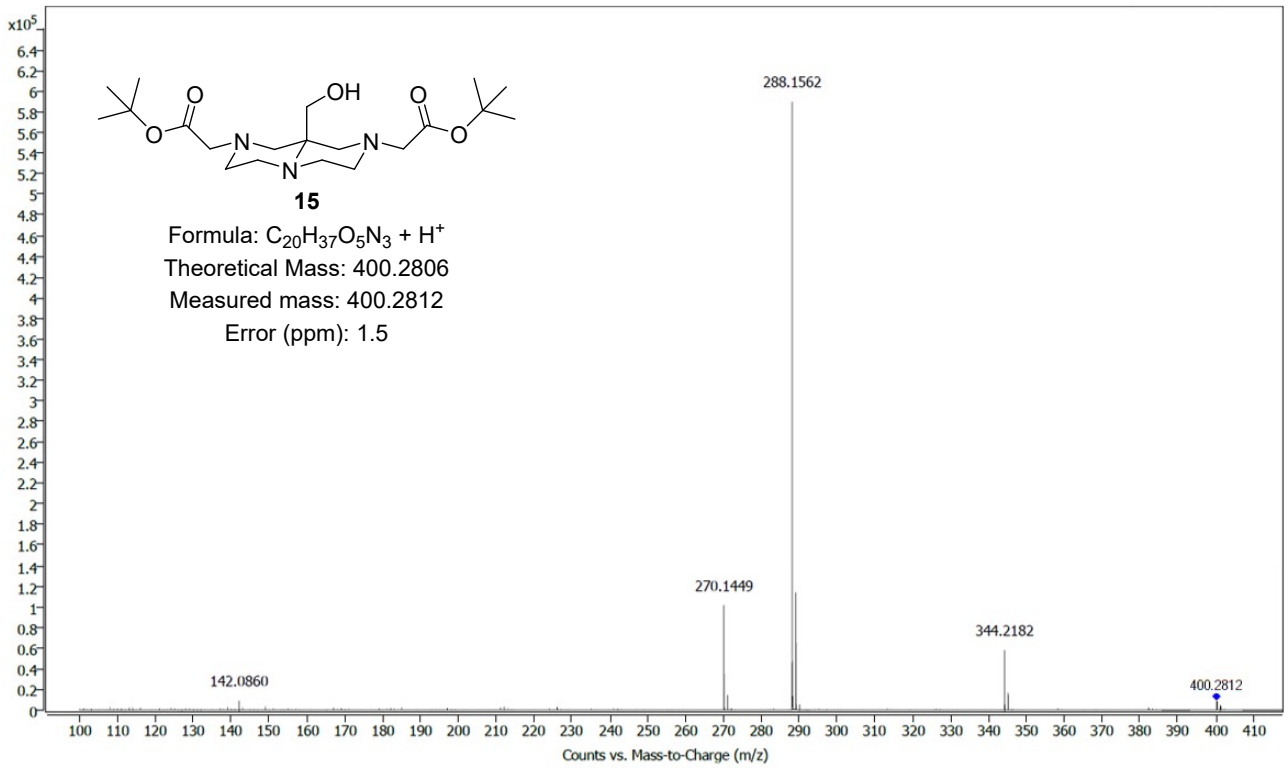


Figure S39. HRMS spectrum of compound **15**.

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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