Supporting Information

Oxa-, Thia-, Heterocycle and Carborane Analogs of SQ109: Bacterial and Protozoal Cell Growth Inhibitors

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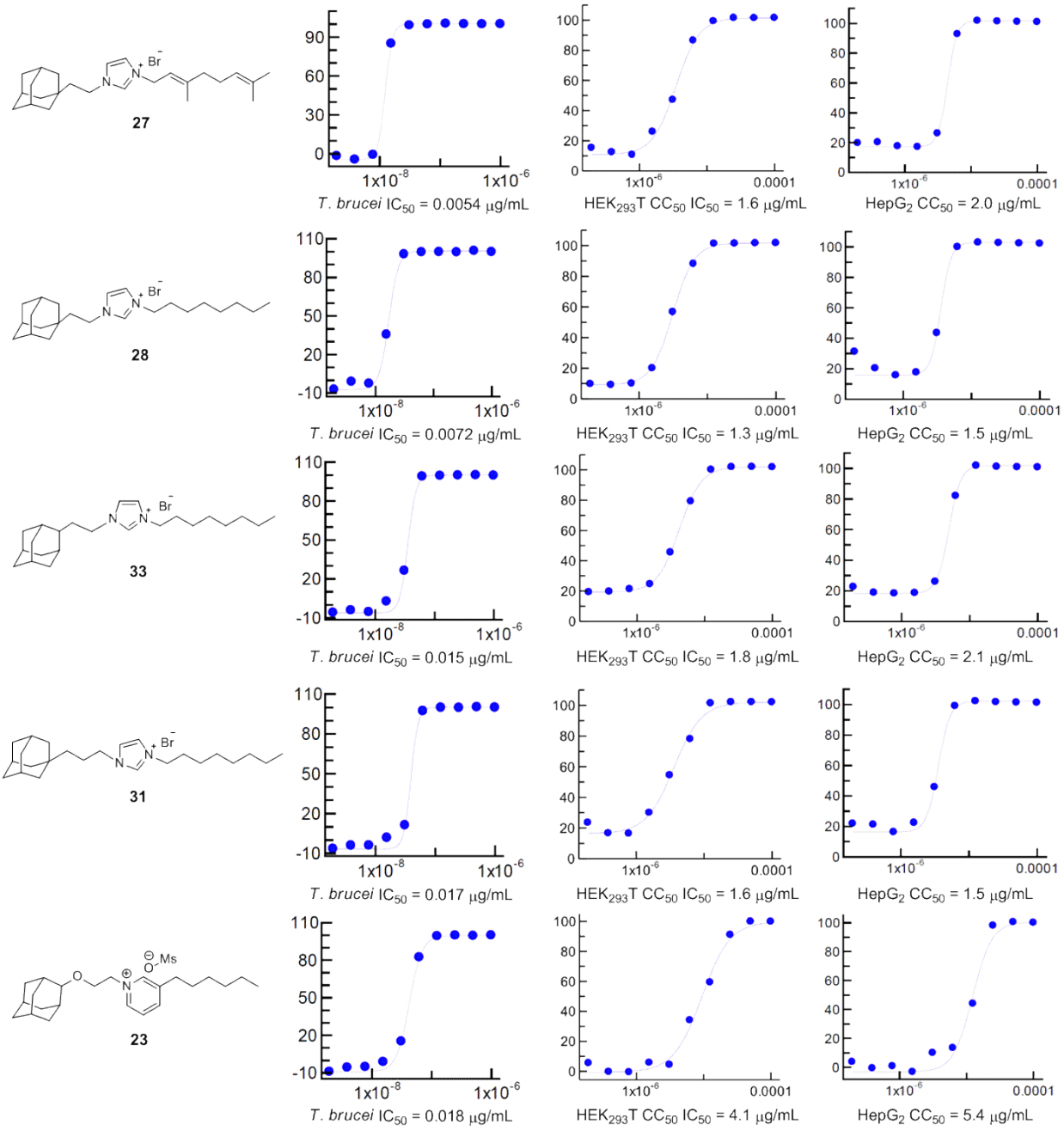


Figure S1. Dose-response curves for the top five *T. brucei* cell growth inhibitors and their corresponding effects on HEK293T and HepG2 cell growth.

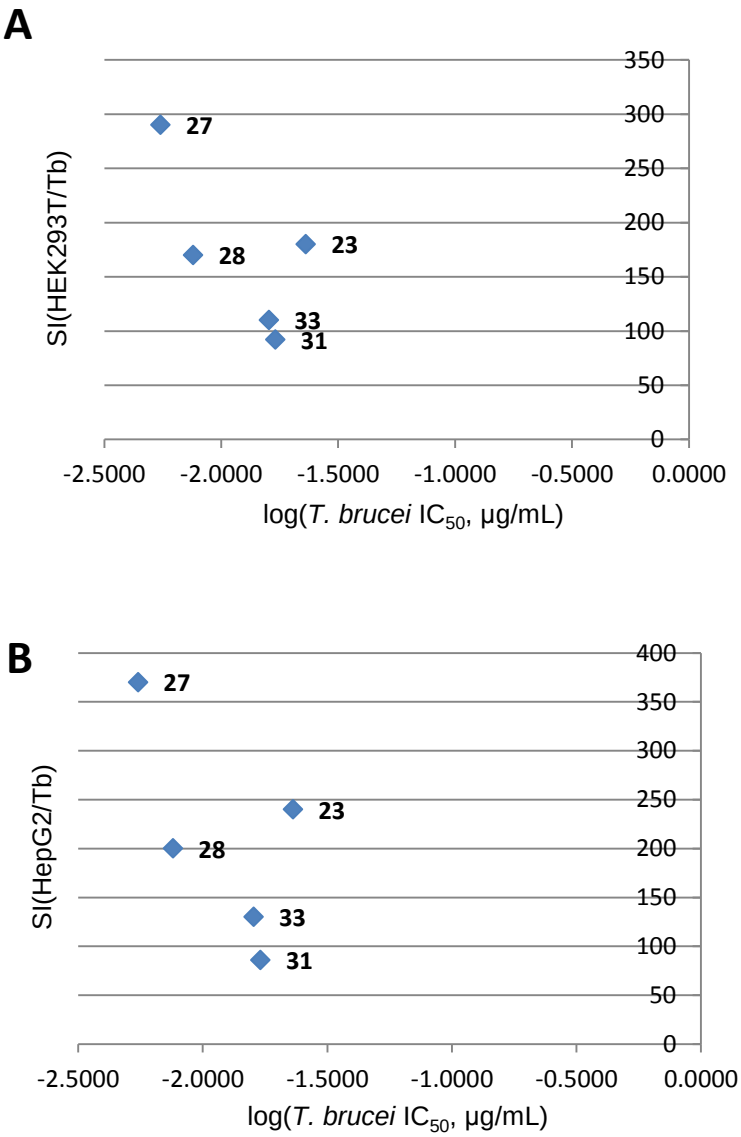


Figure S2. A. Plot of selectivity index (HEK293T CC_{50}/*T. brucei* IC_{50}) *versus* log(*T. brucei* IC_{50}, µg/mL). B. Plot of selectivity index (HepG2 CC_{50}/*T. brucei* IC_{50}) *versus* log(*T. brucei* IC_{50}, µg/mL).

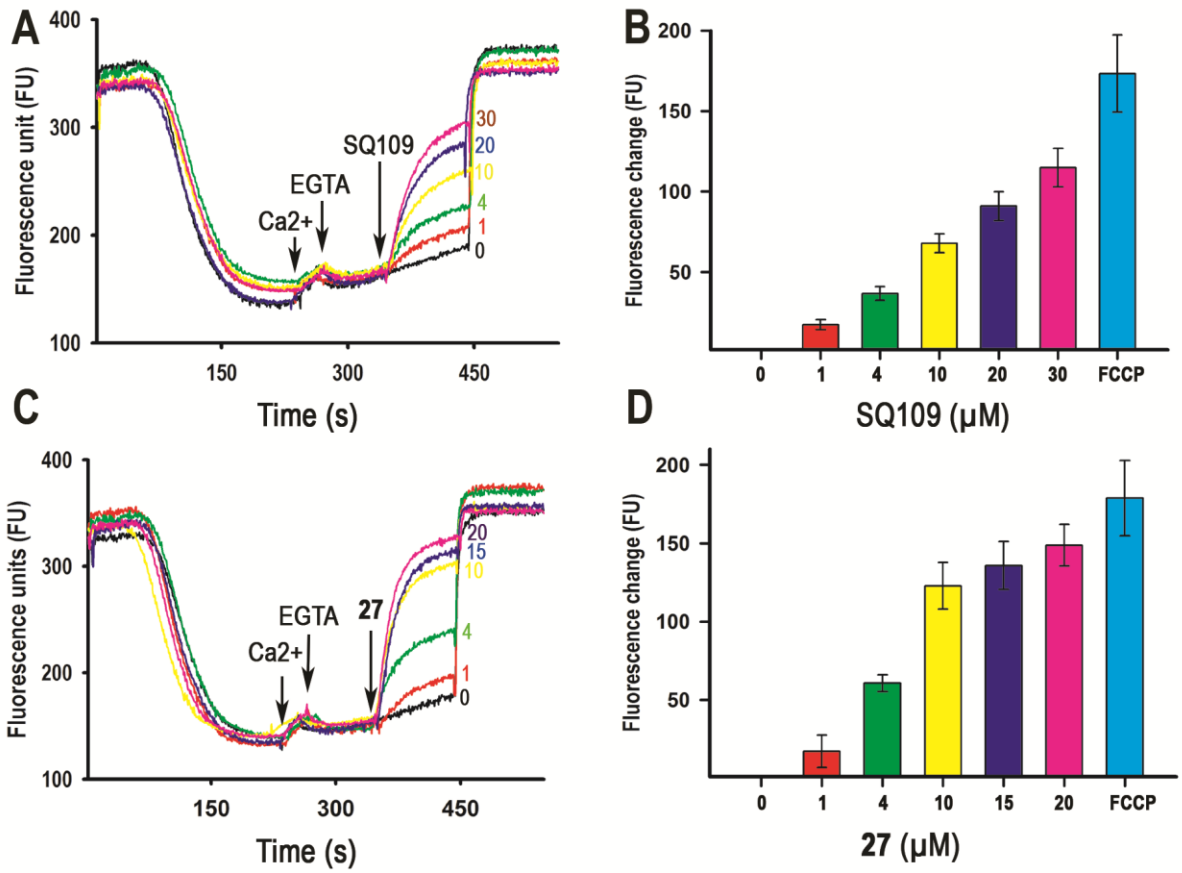


Figure S3. Effects of SQ109 (**2**) or **27** on the mitochondrial membrane potential of digitonin-permeabilized *T. brucei* procyclic forms. PCF trypanosomes (5 x 10^7 cells) were added to reaction buffer (2.4 mL) containing 2 mM succinate and 5 μM safranine, and the reaction initiated by addition of 50 μM digitonin. (A, C) $CaCl_2$ (12 μM), EGTA (200 μM), various concentrations of SQ109 (A) or **27** (C), and 8 μM FCCP were added where indicated. (B, D) Changes in safranine fluorescence after addition of SQ109 (1-30 μM, 0.33-10 μg/mL), **27** (1-20 μM, 0.45-9.0 μg/mL) or FCCP (8 μM), as shown in (A, C), respectively. The results are means ± SD of three independent experiments.

METHODS

Cell growth inhibition assays: Cell Lines. *Mycobacterium tuberculosis* H37Rv, *Mycobacterium tuberculosis* Erdman, *Mycobacterium smegmatis* ATCC 700084, *Bacillus subtilis* subsp. *subtilis* ATCC 6051, *E. coli* ATCC 29425, and *Saccharomyces cerevisiae* ATCC 208352 were purchased from the American Type Culture Collection. *Trypanosoma brucei brucei* strain 427 (bloodstream form) was cultivated at 37 ℃ with a 5% CO_2 atmosphere in HMI-9 medium supplemented with 10% fetal bovine serum (FBS). *T. brucei* was subcultured every 3 or 4 d and maintained until the twentieth passage. The HEK293T, human embryonic kidney, and HepG2, the hepatocellular carcinoma cell line used in the cytotoxicity test was cultivated at 37 ℃ with a 5% CO_2 atmosphere in Dulbecco's modified Eagle's medium supplemented with 10% FBS.

***M. tuberculosis* H37Rv Growth Inhibition Assay**. The compounds were assayed for inhibition of *M. tuberculosis* H37Rv cell growth as described previously[1]. In brief, cell growth MIC values were estimated visually by using series 2-fold inhibitor dilutions, in duplicate.

***M. tuberculosis* Erdman Growth Inhibition Assay**. The compounds were assayed for inhibition of *M. tuberculosis* Erdman cell growth as described previously[2]. In brief, cell growth inibition MIC values were estimated visually by using series 2-fold inhibitor dilutions, in duplicate.

***E. coli* ATCC 29425 Growth Inhibition Assay**. IC_{50} values for *E. coli* growth inhibition were determined by using a broth microdilution method. An overnight culture of *E. coli* was diluted 50-fold into fresh Luria−Bertani (LB) broth and incubated to an OD_{600} of ~0.4. The culture was then diluted 500-fold into fresh LB medium and 100 μL inoculated into each well of a 96-well flat-bottom culture plate (Corning Inc., Corning, NY). The starting concentration of each compound was 200 μg/mL, and this was 2×serially diluted to 0.19 μg/mL. Plates were incubated for 3 h at 37 ℃ to midexponential phase. An MTT ((3-(4,5-dimethylthiazol-2-yl)-2,5-

diphenyltetrazolium bromide) cell proliferation assay (ATCC) was then carried out to obtain bacterial viability dose−response curves. Briefly, 10 μL of MTT reagent was added into each well, followed by incubation for 2−4 h until a purple precipitate was visible. Then, 100 μL of detergent reagent was added, and the plates were incubated in the dark at 22 ℃ for 2 h. Absorbance was measured at 570 nm and a nonlinear regression analysis carried out using Origin 6.1 software. The average error was 11%.

***B. subtilis* ATCC® 6051TM growth inhibition assay**. A 16 h culture of *B. subtilis* was diluted 50-fold into fresh Luria-Bertani (LB) broth and incubated to an OD_{600} of ~ 0.4. The culture was then diluted 500-fold into fresh LB medium and 100 μL were inoculated into a 96 well flat bottom culture plate (Corning Inc., Corning, NY). The starting concentration of each compound was 0.5 μg/mL and was then serial diluted. Plates were incubated for 12-16 h at 37 ℃. The absorbance was recorded at 570 nm. A non-linear regression analysis was carried out on the data obtained using Origin 6.1. The average error was 9%.

***S. cerevisiae* growth inhibition assay**. The protocol was the same as with the *B. subtilis* assay protocol except that YPD medium was used and the 96-well plate was incubated for 36 h instead of 12-16 h. A non-linear regression analysis was carried out on the data obtained using Origin 6.1. The average error was 14%.

M. smegmatis ATCC 700084 **growth inhibition assay**. The protocol was the same as with the *B. subtilis* assay protocol except that 7H9/ADC (9:1) medium was used. A non-linear regression analysis was carried out on the data obtained using Origin 6.1. The average error was 9%.

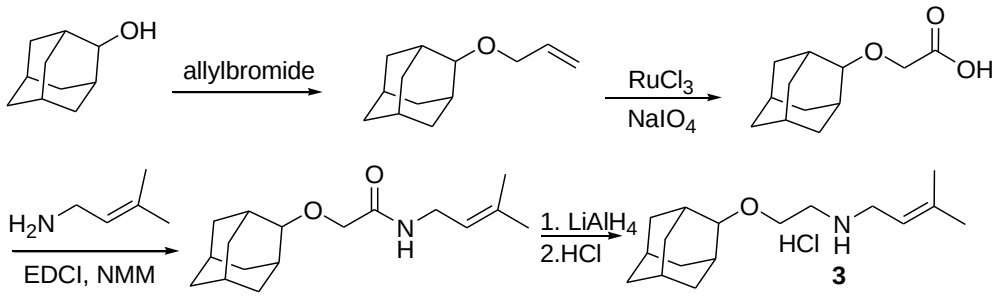
Analysis of mitochondrial membrane potential. We monitored the mitochondrial membrane potential spectrofluorometrically using safranine as the probe[3,4]. The reaction buffer contained

125 mM sucrose, 65 mM KCl, 10 mM Na-Hepes-KOH buffer, pH 7.2, 1 mM $MgCl_2$, 2.5 mM potassiumphosphate, and 5 μM safranine. *T. brucei* BSF (2 x 10^8 cells) were added to the reaction buffer (2.0) containing 1 mM ATP, 200 μM EGTA and 500 μM sodium orthovanadate, and the reaction was started by addition of 40 μM digitonin. PCF (5 x 10^7 cells) were added to the reaction buffer (2.4 ml) containing 2 mM succinate and the reaction started by addition of 50 μM digitonin. Incubations were at 28 ^oC (PCF) or 37 ℃ (BSF). Drugs, ADP (10 μM), oligomycin (Oligo, 2 μg/ml), $CaCl_2$ (12 μM), EGTA (200 μM), and FCCP (8 μM) where added where indicated. Fluorescence changes were monitored using a Hitachi 4500 spectrofluorometer (excitation wavelength = 496 nm; emission wavelength = 586 nm).

Mammalian cell cytotoxicity assay. For evaluation of mammalian cell cytotoxicity, HEK293T and HepG2 cells were cultured at 37 ℃ with 5% CO_2 in Dulbecco's modified eagle medium containing 10% FBS. HEK293T and HepG2 cells were diluted to 8 X 10^4/mL and 4 X 10^4/mL, respectively, and were seeded in 384 well plates. The compounds at 2-fold dilution in 10-points concentration were tested and incubated for 72 h. To determine viability, 10 μL of a 280 μM solution of resazurin sodium salt (final concentration, 40 μM of resazurin) was added to each well for 5 h. To assess cell viability, resazurin reduction was measured with a Victor 3^{TM} fluorimeter at an excitation wavelength of 530 nm and emission of 590 nm. Chloropromazine was used as a reference drug and DMSO 1% was used as a drug-negative control.

Synthesis and Characterization of Compounds

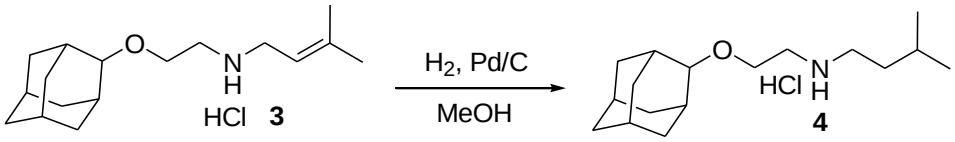
_N_-(2-(((1_r_,3_r_,5_r_,7_r_)-Adamantan-2-yl)oxy)ethyl)-3-methylbut-2-en-1-amine hydrochloride (3)



To a suspension of NaH (washed with and dried from hexane, 368 mg, 16 mmol) in THF (30 mL) was added 2-adamantanol (1.5 g, 10 mmol) at 0 ^{o}C. Stirring was continued for 30 min at 25 ^{o}C, then allyl bromide (1.8 g, 15 mmol) was added. Stirring was continued for 3h at 25 ^{o}C, then the reaction was quenched by adding saturated aqueous NH_4Cl. Upon separation and concentration under reduced pressure using a rotary evaporator, the residue was purified by silica gel column chromatography using 5% EtOAc in hexane as eluent to afford the allyl ether (1.4 g, 75%). To a suspension of the allyl ether (1.4 g, 7.5 mmol) in MeCN/H_2O/ethyl acetate (1/2/1, 35 mL) was added $NaIO_4$ (8.42 g, 40 mmol), then $RuCl_3 \cdot H_2O$ (110 mg, 0.5 mmol). After stirring for 10 h at 25 ^{o}C, ethyl acetate (40 mL) was added. Separation and concentration of the organic phase under reduced pressure gave the crude acid (1.3 g, 84%). To a solution of crude acid (210 mg, 1 mmol), isopentenylamine (102 mg, 1.2 mmol), EDCI (228 mg, 1.2 mmol) and HOAT (164 mg, 1.2 mmol) in dry THF/DMF (2 mL/2 mL) was added *N*-methylmorpholine (505 mg, 5 mmol) at 0 ^{o}C with stirring. Stirring was continued for 2 h at 25 ^{o}C. The reaction mixture was distributed between saturated aqueous NH_4Cl and hexane. The hexane phase was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure to give a residue. Purification of the residue with flash chromatography (SiO_2, hexane/ethyl acetate = 10/1) gave the amide (226 mg, yield: 82%). To a solution of the amide (200 mg, 0.72 mmol) in dry ethyl ether (6 mL) was added $LiAlH_4$ (76 mg, 2 mmol) under N_2. Stirring was continued for 10 h at reflux, the reaction flask was then cooled in an ice-bath and the reaction quenched by adding aqueous ammonium hydroxide (37%, 0.2 mL).

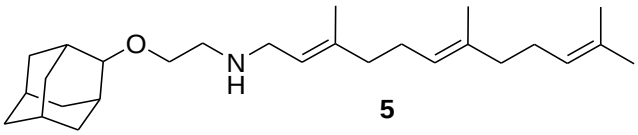
Vigorous stirring was continued for 20 min. Upon separation and concentration under reduced pressure, the residue was purified by using silica gel column chromatography (using NH_4OH (37%)/MeOH/EtOAc = 1/5/100 as eluent) to afford the product (134 mg, 71%). The HCl salt was obtained by neutralizing the amine with HCl in toluene in quantitative yield. The purity of the product was determined by qNMR: 98.5%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 9.31 (s, 2H), 5.38 (m, 1H), 3.77 (t, J = 5.3 Hz, 2H), 3.68 (m, 2H), 3.45 (s, 1H), 3.07 (m, 2H), 1.96-1.40 (m, 20H). HRMS (ESI) m/z $[M + H]^+$ calculated for $[C_{17}H_{30}NO]^+$ 264.2327, found 264.2342.

***N*-(2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)oxy)ethyl)-3-methylbutan-1-amine hydrochloride (4)**



To a solution of amine **3** (HCl salt, 60 mg, 0.2 mmol) in MeOH (4 mL) was added palladium on charcoal (5%, 15 mg) under N_2. Stirring was continued for 1 h at 22 ^{o}C after switching the reaction atmosphere from N_2 to H_2 using a hydrogen balloon. The reaction mixture was passed through a Celite pad, then the filtrate was evaporated under reduced pressure to give the product as a white powder (55 mg, 90%). The purity of the product was determined by qNMR: 93.2%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 9.44 (s, 2H), 3.87 (t, J = 5.2 Hz, 2H), 3.51 (s, 1H), 3.22 (t, J = 5.2 Hz, 2H), 3.15 (dt, J = 7.0, 4.0 Hz, 2H), 2.15 – 1.33 (m, 17H), 0.94 (s, 3H), 0.93 (s, 3H). HRMS (ESI) m/z $[M + H]^+$ calculated for $[C_{17}H_{32}NO]^+$ 266.2484, found 266.2459.

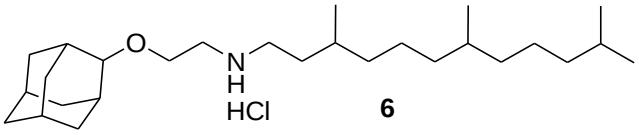
(2*E*,6*E*)-*N*-(2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)oxy)ethyl)-3,7,11-trimethyldo-deca-2,6,10-trien-1-amine (5)



5 was made by following the protocol used for **3**. Purity of the product was determined by

qNMR: 93.8%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 5.28 (m, 1H), 5.10 (m, 2H), 3.56 (t, J = 5.2 Hz, 2H), 3.43 (s, 1H), 3.28 (d, J = 6.8 Hz, 2H), 2.80 (t, J = 5.2 Hz, 2H), 2.11-1.45 (m, 22H), 1.65 (s, 3 h), 1.65 (s, 3H), 1.0 (s, 6H). HRMS (ESI) m/z $[M + H]^+$ calculated for $[C_{27}H_{46}NO]^+$ 400.3579, found 400.3573.

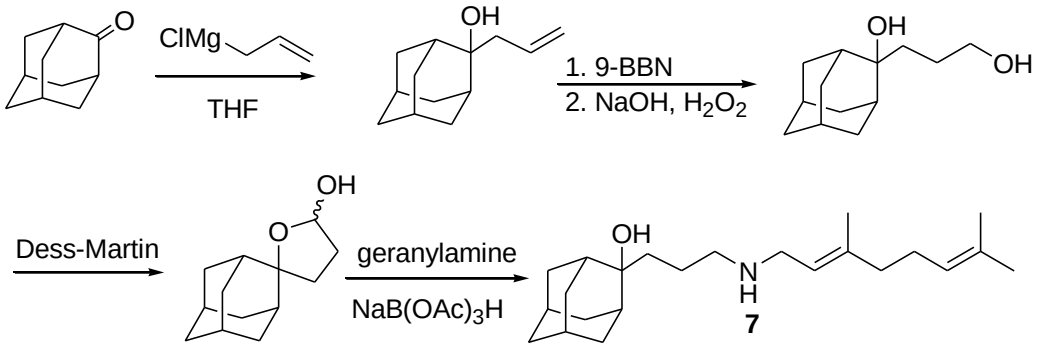
***N*-(2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)oxy)ethyl)-3,7,11-trimethyldodecan-1-amine hydrochloride (6)**



6

6 was made by following the protocol used for **4**. Purity of the product was determined by qNMR: 96.4%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 9.40 (s, 2H), 3.87 (s, 2H), 3.51 (s, 2H), 3.30 – 3.05 (m, 4H), 2.05 – 0.97 (m, 31H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 6H), 0.84 (d, J = 6.6 Hz, 3H). HRMS (ESI) m/z $[M + H]^+$ calculated for $[C_{27}H_{52}NO]^+$ 406.4049, found 406.4035.

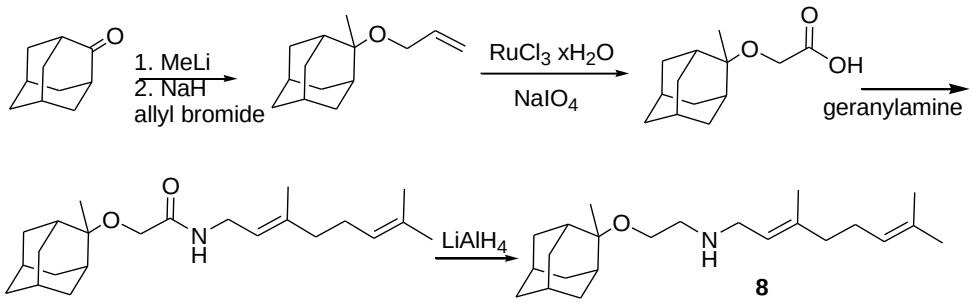
(1*r*,3*r*,5*r*,7*r*)-2-(3-(((*E*)-3,7-Dimethylocta-2,6-dien-1-yl)amino)propyl)adamantan-2-ol (7)



To a solution of 2-adamantanone (300 mg, 2 mmol) in dry THF (7 mL) was added allylmagnesium chloride (2 M in THF, 1.1 mL) dropwise at 0 ^{o}C with stirring. Stirring was continued for 30 min at 0 ^{o}C and 30 min at 25 ^{o}C. The reaction mixture was diluted with ethyl

acetate and quenched with saturated aqueous NH_4Cl. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give the crude olefin. To a solution of the crude olefin in dry THF (7 mL) was added 9-BBN (0.5 M in THF, 4.4 mL) dropwise. Stirring was continued for 30 min at 0 ^oC and 1 h at 25 ^oC. The reaction flask was then placed in an ice-bath and NaOH (3N in H_2O, 3 mL) and H_2O_2 (30% in water, 0.68 mL) added, sequentially. Stirring was continued for 30 min at 0 ^oC and 1 h at 25 ^oC. The reaction mixture was then diluted with ethyl acetate and quenched with saturated aqueous $Na_2S_2O_3$ at 0 ^oC. The organic phase was dried over Na_2SO_4 and then evaporated under reduced pressure to give the crude diol. To a solution of the crude diol in DCM (7 mL) was added Dess-Martin periodinane (848 mg) at 0 ^oC. Stirring was continued for 30 min at 0 ^oC and 1 h at 25 ^oC. The residue from the reduced-pressure evaporation was purified by using flash chromatography (SiO_2, hexane/ethyl acetate = 6/1) to give the hemiacetal (203 mg, 49%). To a solution of the hemiacetal (166 mg, 0.8 mmol) in dry DCM (5 mL) was added geranylamine (122 mg, 0.8 mmol) and sodium triacetoxyborohyride (424 mg, 2 mmol). Stirring was continued for 12 h at 25 ^oC. The reaction was quenched by adding saturated aqueous $NaHCO_3$ (5 mL). The organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give a residue. Purification of the residue with flash chromatography (SiO_2, chloroform/ methanol = 8/1) gave the product **7** (177 mg, 64%). Purity of the product was determined by qNMR: 93.3%. ^1H NMR (500 MHz, chloroform-d_1) 5.26 (t, J = 10.0 Hz, 1H), 5.08 (t, J = 10.0 Hz, 1H), 3.26 (d, J = 6.9 Hz, 2H), 2.69 (t, J = 6.1 Hz, 2H), 2.28 (dd, J = 11.8, 3.5 Hz, 2H), 2.09-1.51 (m, 23H), 2.64 (s, 3H), 1.60 (s, 3H). HRMS (ESI) m/z $[M + H]^+$ calculated for $[C_{23}H_{40}NO]^+$ 346.3110, found 346.3113.

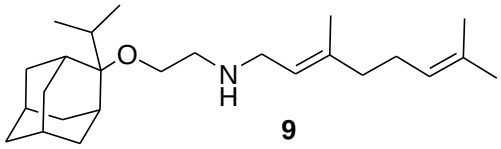
(*E*)-3,7-Dimethyl-*N*-(2-(((1*r*,3*r*,5*r*,7*r*)-2-methyladamantan-2-yl)oxy)ethyl)-octa-2,6-dien-1-amine (8)



To a solution of 2-adamantanone (150 mg, 1 mmol) in dry THF (4 mL) was added methyl lithium (1.6 M in diethyl ether, 0.8 mL) dropwise at 0 ^{o}C, with stirring. Stirring was continued for 30 min at 0 ^{o}C and the reaction quenched by adding saturated aqueous NH_4Cl. The organic phase was separated, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give the crude alcohol. To a solution of crude alcohol and allyl bromide (360 mg, 3 mmol) in dry DMF (3 mL) was added NaH (washed with and dried from hexane, 46 mg) at 0 ^{o}C with stirring. Stirring was continued for 1 h at 0 ^{o}C. The reaction mixture was distributted between saturated aqueous NH_4Cl and hexane. The hexane phase was separated and dried over anhydrous Na_2SO_4 then evaporated under reduced pressure to give the crude olefin. To a solution of crude olefin in ethyl acetate/MeCN and deionized water (5 mL/5 mL/5 mL) was added $RuCl_3$ hydrate (10 mg, 0.05 mmol) and $NaIO_4$ (428 mg, 2 mmol) at 0 ^{o}C. Vigorous stirring was continued for 20 min at 0 ^{o}C and for 4 h at 25 ^{o}C. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give the crude acid. To a solution of the crude acid, geranylamine (153 mg, 1 mmol), EDCI (191 mg, 1 mmol) and HOAT (136 mg, 1 mmol) in dry THF/DMF (2 mL/2 mL) was added *N*-methylmorpholine (505 mg, 5 mmol) at 0 ^{o}C with stirring. Stirring was continued for 2 h at 25 ^{o}C. The reaction mixture was distributed between saturated aqueous NH_4Cl and hexane. The hexane phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give a residue. Purification of the residue with flash chromatography (SiO_2, hexane/ethyl acetate = 10/1) gave the amide (147 mg, yield: 41%). To a solution of the amide

(108 mg, 0.3 mmol) in dry diethyl ether (3 mL) was added $LiAlH_4$ (38 mg, 1 mmol) under N_2. Stirring was continued for 10 h at reflux, the reaction flask cooled in an ice-bath and the reaction quenched by adding aqueous ammonium hydroxide (37%, 0.2 mL). Vigorous stirring was continued for 20 min. Upon separation and concentration under reduced pressure, the residue was purified by silica gel column chromatography (using NH_4OH (37%)/MeOH/EtOAc = 1/5/100 as eluent) to afford the product **8** (69 mg, 67%). Purity of the product was determined by qNMR: 98.9%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 5.27 (t, J = 5.9 Hz, 1H), 5.09 (t, J = 7.2 Hz, 1H), 3.45 (t, J = 5.3 Hz, 2H), 3.26 (d, J = 6.8 Hz, 2H), 2.77 (t, J = 5.3 Hz, 2H), 2.20 – 1.37 (m, 18H), 1.67 (s, 3H), 1.64 (s, 3H), 1.60 (s, 3H), 1.26 (s, 3H). HRMS (ESI) m/z $[M + H]^+$ calculated for $[C_{23}H_{40}NO]^+$ 346.3110, found 346.3098.

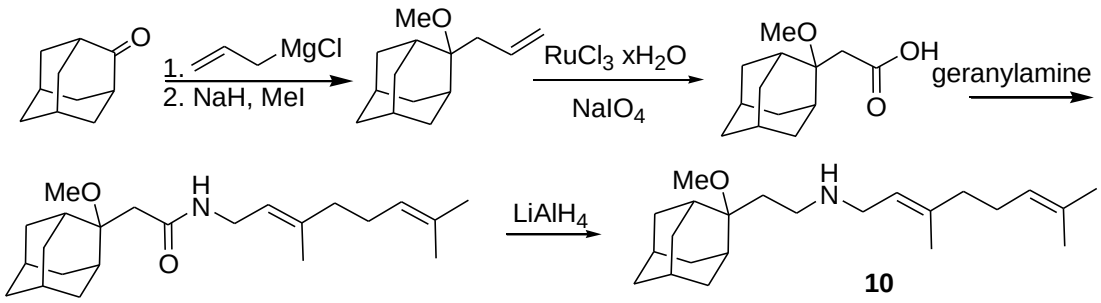
***(E)*-*N*-(2-(((1*r*,3*r*,5*r*,7*r*)-2-Isopropyladamantan-2-yl)oxy)ethyl)-3,7-dimethylocta-2,6-dien-1-amine (9)**



9

9 was made by following the protocol used for **8**. Purity of the product was determined by qNMR: 98.2%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 5.28 ((t, J = 5.0 Hz, 1H), 5.10 (t, J = 5.0 Hz,, 1H), 3.55 (t, J = 5.2 Hz, 2H), 3.43 (s, 1H), 3.26 (d, J = 6.7 Hz, 2H), 2.79 (t, J = 5.2 Hz, 2H), 2.19 – 1.35 (m, 25H), 1.68 (s, 3H), 1.64 (s, 3H), 1.60 (s, 3H). HRMS (ESI) m/z $[M + H]^+$ calculated for $[C_{25}H_{44}NO]^+$ 374.3423, found 374.3432.

(*E*)-*N*-(2-((1*r*,3*r*,5*r*,7*r*)-2-Methoxyadamantan-2-yl)ethyl)-3,7-dimethylocta-2,6-dien-1-amine (10)

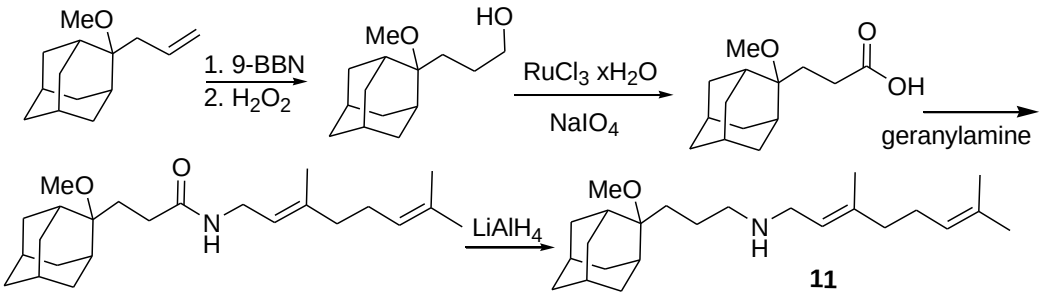


10

To a solution of 2-adamantanone (150 mg, 1 mmol) in dry THF (4 mL) was added allylmagnesium chloride (2.0 M in THF, 0.6 mL) dropwise at 0 ^{o}C with stirring. Stirring was continued for 30 min at 0 ^{o}C and the reaction quenched by adding saturated aqueous NH_4Cl. The organic phase was separated, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give the crude alcohol. To a solution of the crude alcohol and MeI (426 mg, 3 mmol) in dry DMF (3 mL) was added NaH (washed with and dried from hexane, 46 mg) at 0 ^{o}C with stirring. Stirring was continued for 1 h at 0 ^{o}C. The reaction mixture was distributed between saturated aqueous NH_4Cl and hexane. The hexane phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give the crude olefin. To a solution of crude olefin in ethyl acetate/MeCN and deionized water (5 mL/5 mL/5 mL) was added $RuCl_3$ hydrate (10 mg, 0.05 mmol) and $NaIO_4$ (428 mg, 2 mmol) at 0 ^{o}C. Vigorous stirring was continued for 20 min at 0 ^{o}C and for 4 h at 25 ^{o}C. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give the crude acid. To a solution of the crude acid, geranylamine (153 mg, 1 mmol), EDCI (191 mg, 1 mmol) and HOAT (136 mg, 1 mmol) in dry THF/DMF (2 mL/2 mL) was added *N*-methylmorpholine (505 mg, 5 mmol) at 0 ^{o}C with stirring. Stirring was continued for 2 h at 25 ^{o}C. The reaction mixture was distributed between saturated aqueous NH_4Cl and hexane. The hexane phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give a residue. Purification of the residue with flash chromatography (SiO_2, hexane/ethyl acetate = 10/1) gave the amide (155 mg, yield: 41%). To a solution of the amide

(108 mg, 0.3 mmol) in dry diethyl ether (3 mL) was added $LiAlH_4$ (38 mg, 1 mmol) under N_2. Stirring was continued for 10 h at reflux, the reaction flask cooled in an ice-bath and the reaction quenched by adding aqueous ammonium hydroxide (37%, 0.2 mL). Vigorous stirring was continued for 20 min. Upon separation and concentration under reduced pressure, the residue was purified by silica gel column chromatography (using NH_4OH (37%)/MeOH/EtOAc = 1/5/100 as eluent) to afford the product **10** (74 mg, 67%). Purity of the product was determined by qNMR: 90.1%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 5.27 (t, J = 5.3 Hz, 1H), 5.10 (t, J = 5.0 Hz,, 1H), 3.23 (d, J = 6.8 Hz, 2H), 3.16 (s, 3H), 2.63 (t, J = 10.0 Hz, 2H), 2.11-1.4 (m, 18H), 1.68 (s, 3H), 1.64 (s, 3H), 1.60 (s, 3H). HRMS (ESI) m/z $[M + H]^+$ calculated for $[C_{23}H_{40}NO]^+$ 346.3110, found 346.31094.

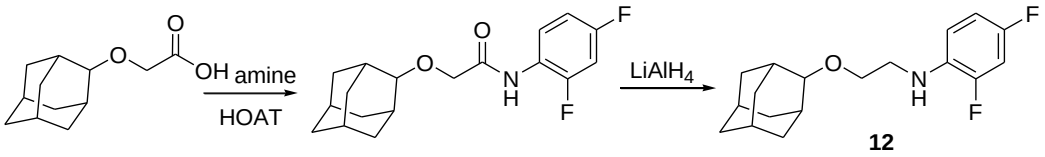
(*E*)-*N*-(3-((1*r*,3*r*,5*r*,7*r*)-2-Methoxyadamantan-2-yl)propyl)-3,7-dimethylo-cta-2,6-dien-1-amine (11)



11 was made following the protocol used for **10**. The only modification was that hydroboration-oxidation of the olefin was carried out prior to sodium periodate oxidation. To a solution of the olefin (171 mg, 0.83 mmol) in dry THF (2 mL) was added 9-BBN (0.5 M in THF, 2 mL, 1 mmol) under N_2 at 0 ^{o}C. Stirring was continued for 2 h at 0 ^{o}C, then aqueous NaOH (3N, 1 mL) and H_2O_2 (30% in water, 0.18 mL, 1.66 mmol) was added, sequentially. Vigorous stirring was continued for 30 min at 0 ^{o}C and for 1 h at 25 ^{o}C, and then ethyl acetate (4 ml) and saturated aqueous $Na_2S_2O_3$ was added, with stirring. The organic phase was separated and evaporated

under reduced pressure to give the crude alcohol. Purity of the product was determined by qNMR: 94.1%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 5.26 (t, J = 5.0 Hz, 1H), 5.10 (t, J = 5.0 Hz, 1H), 3.23 (d, J = 6.8 Hz, 2H), 3.12 (s, 3H), 2.61 (t, J = 7.2 Hz, 2H), 2.11-1.45 (m, 22H), 1.68 (s, 3H), 1.64 (s, 3H), 1.60 (s, 3H). HRMS (ESI) m/z $[M + H]^+$ calculated for $[C_{24}H_{42}NO]^+$ 360.3266, found 360.3253.

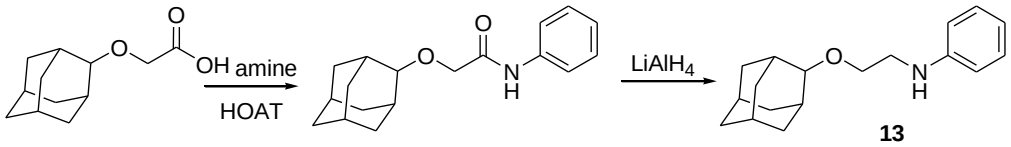
***N*-(2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)oxy)ethyl)-2,4-difluoroaniline (12)**



12

12 was made by following the protocol used for **3**. Purity of the product was determined by qNMR: 98.1%. ^{1}H NMR (500 MHz, chloroform-d_1) 7.76 (m, 1H), 6.93 (m, 2H), 3.7 (t, J = 5.2 Hz, 2H), 3.55 (t, J = 5.2 Hz, 2H), 3.40 (s, 1H) 1.92-1.41 (m, 14H). HRMS (ESI) m/z $[M + H]^+$ calculated for $[C_{18}H_{24}F_2NO]^+$ 308.1826, found 308.1850.

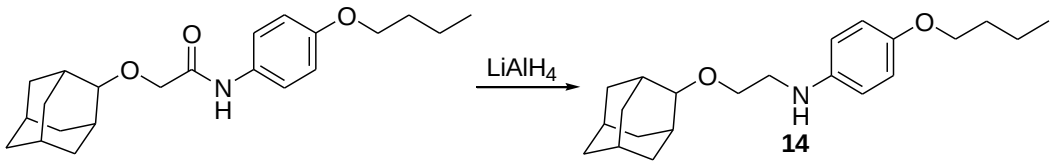
***N*-(2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)oxy)ethyl)aniline (13)**



13

13 was made by following the protocol used for **3**. Purity of the product was determined by qNMR: 95.0%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 7.62 (m, 2H), 7.39 (m, 3H), 3.71 (t, J = 5.6 Hz, 2H), 3.50 (t, J = 5.5 Hz, 2H), 3.36 (s, 1H), 1.96-1.39 (m, 14H). HRMS (ESI) m/z $[M + H]^+$ calculated for $[C_{18}H_{26}NO]^+$ 272.2014, found 272.2008.

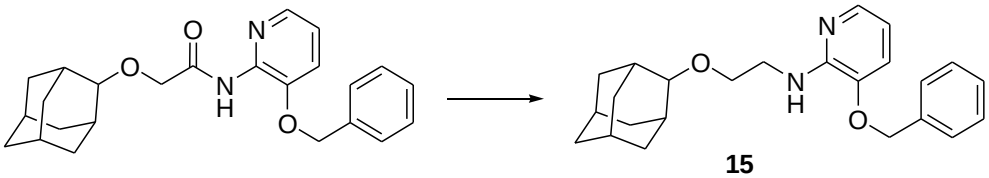
***N*-(2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)oxy)ethyl)-4-butoxyaniline (14).**



14

14 was made by following the protocol used for **3**. Purity of the product was determined by qNMR: 99.5%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 6.78 (d, J = 8.8 Hz, 2H), 6.62 (d, J = 8.8 Hz, 2H), 3.89 (t, J = 6.6 Hz, 2H), 3.64 (t, J = 5.2 Hz, 2H), 3.44 (m, 1H), 3.24 (t, J = 5.2 Hz, 2H), 2.07 – 1.37 (m, 18H), 0.96 (t, J = 7.4 Hz, 3H). HRMS (ESI) m/z $[M + H]^+$ calculated for $[C_{22}H_{34}NO]^+$ 344.2590, found 344.2601.

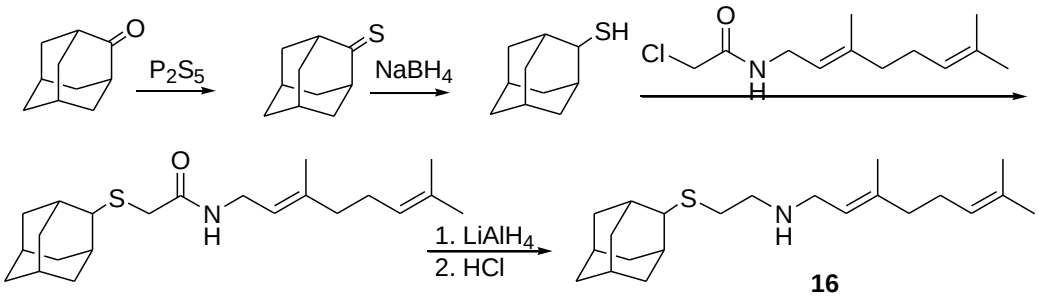
***N*-(2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)oxy)ethyl)-3-(benzyloxy)pyridin-2-amine (15).**



15

15 was made by following the protocol used for **3**. Purity of the product was determined by qNMR: 95.4%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 7.77 (dd, J = 4.8, 1.6 Hz, 1H), 7.41 – 7.33 (m, 2H), 7.24 (d, J = 7.8 Hz, 2H), 7.21 – 7.15 (m, 1H), 7.11 (dd, J = 7.8, 1.7 Hz, 1H), 6.81 (dd, J = 7.8, 4.8 Hz, 1H), 4.64 (s, 2H), 3.48 (dd, J = 5.4, 4.1 Hz, 2H), 3.44 (s, 1H), 3.37 (t, J = 4.8 Hz, 2H), 2.14 – 1.50 (m, 14H). HRMS (ESI) m/z $[M + H]^+$ calculated for $[C_{24}H_{31}N_2O_2]^+$ 379.2386, found 379.2389.

(*E*)-*N*-(2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)thio)ethyl)-3,7-dimethylocta-2,6-dien-1-amine (16).

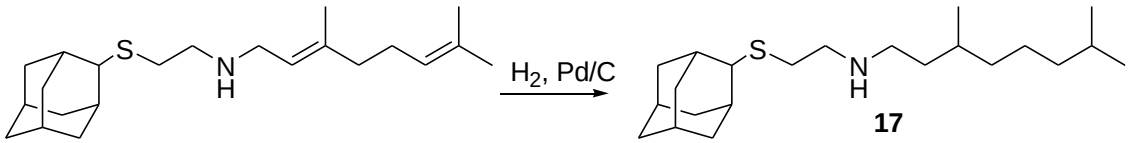


16

Thio-adamantanol was made according to a reported protocol[5]. To a stirred solution of geranylamine (153 mg, 1.0 mmol) in $CHCl_3$ (3 mL), chloroacetyl chloride (167 mg, 1.5 mmol) was added drop-wise at 0 ^{o}C. Then water (2 mL) was added followed by K_2CO_3 (414 mg, 3.0

mmol). A catalytic amount of tetrabutylammonium hydrogen sulfate was added to the reaction mixture which was then stirred for 4 h. After completion of the reaction, as monitored by TLC, the organic layer was separated and dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residual mass was purified by silica gel column chromatography using 25% EtOAc in hexane as eluent to afford the chloroacetamide (183 mg, 80%). To a solution of 2-(thio)adamantanol (84 mg, 0.5 mmol) in dry THF (3 mL) was added NaH (washed with and dried from hexane, 23 mg, 1 mmol) at 0 ^oC with stirring. After stirring for 30 min at 22 ^oC, the chloroacetamide (115 mg, 0.5mmol) was added. Stirring was continued for 12 h at 22 ^oC, then the reaction was quenched by adding saturated aqueous NH_4Cl. Upon separation and concentration under reduced pressure, the residue was purified by silica gel column chromatography using 25% EtOAc in hexane as eluent to afford the 2-(adamantanylthio) acetamide (152 mg, 84%). To a suspension of $LiAlH_4$ (38 mg, 1 mmol) in dry THF (2 mL) was added 2-(adamanta-nylthio)acetamide (121 mg, 0.33 mmol) at 25 ^oC. Stirring was continued for 5 h at refluxing, the reaction mixture cooled in an ice-bath and quenched by adding aqueous ammonium hydroxide (37%, 0.3 mL). Vigorous stirring was continued for 20 min. Upon separation and concentration under reduced pressure, the residue was purified by silica gel column chromatography (using NH_4OH (37%)/MeOH/EtOAc = 1/5/100 as eluent) to afford the product **16** (89 mg, 78%). The HCl salt was obtained by neutralizing the amine with HCl in toluene with a quantitative yield. Purity of the product was determined by qNMR: 92.0%. ^1H NMR (500 MHz, chloroform-d_1): δ 9.60 (s, 2H), 5.41 (m, 1H), 5.04 (m, 1H), 3.65 (m, 2H), 3.02 (m, 5H), 2.26 – 1.36 (m, 27H). HRMS (ESI) m/z $[M + H]^+$ calculated for $[C_{22}H_{38}NS]^+$ 348.2725, found 348.2726.

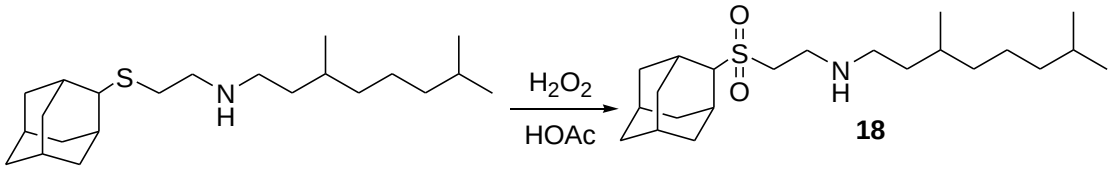
***N*-(2-(((1*r*,3*r*,5r,7*r*)-Adamantan-2-yl)thio)ethyl)-3,7-dimethyloctan-1-amine (17).**



17

To a solution of the unsaturated amine **16** (30 mg) in methanol (2 mL) was added palladium on charcoal (10%, 30 mg) under N_2. Stirring was continued for 1 h at 25 ^oC after switching the reaction atmosphere from N_2 to H_2 using a hydrogen balloon. Filtration and evaporation gave the product **17** (25 mg, 83%). Purity of the product was determined by qNMR: 97.9%. ^1H NMR (500 MHz, chloroform-*d*$_1$): 3.04 (s, 1H), 2.80 (t, *J* = 6.5 Hz, 2H), 2.69 (t, *J* = 6.5 Hz, 2H), 2.62 (m, 2H), 2.16 (d, *J* = 12.7 Hz, 2H), 2.13 (s, 1H), 1.96-1.10 (m, 24H), 0.88-0.86 (m, 9H). HRMS (ESI) m/z $[M + H]^+$ calculated for $[C_{22}H_{42}NS]^+$ 352.3038, found 352.3030.

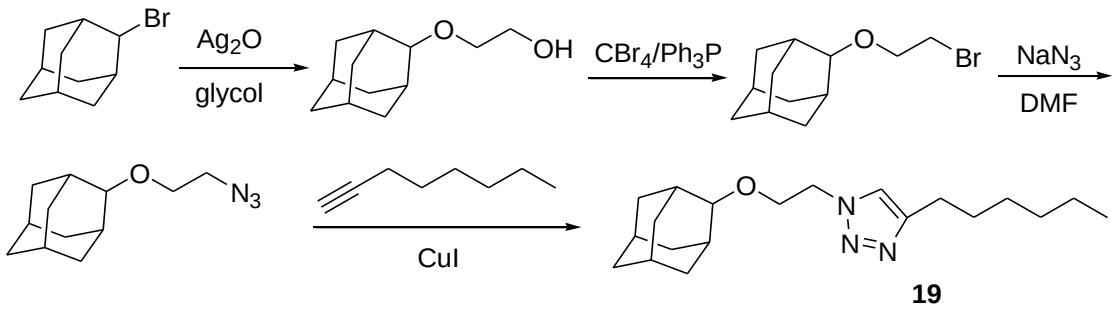
***N*-(2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)sulfonyl)ethyl)-3,7-dimethyloctan-1-amine (18).**



18

To a solution of the thioether **17** (50 mg, 0.14 mmol) in HOAc (1 mL) was added H_2O_2 (30% in water, 79 mg) at 0 ^oC with stirring, then ethyl acetate (5 mL) and water (5 mL) was added. Stirring was continued for 12 h at 25 ^oC. Solid $NaHCO_3$ was added in portion until no bubbling was observed. The ethyl acetate phase was separated, washed with saturated aqueous $Na_2S_2O_3$, dried over anhydrous Na_2SO_4, and then evaporated under reduced pressure to give a residue. Purification of the residue with flash chromatography (SiO_2, chloroform/MeOH = 6/1) gave the product **18** (30 mg, yield: 57%). Purity of the product was determined by qNMR: 98.7%. ^1H NMR (500 MHz, chloroform-*d*$_1$) δ 3.28 (s, 1H), 3.14 (s, 4H), 2.62 (m, 2H), 2.53 (d, *J* = 3.8 Hz, 2H), 2.46 (dd, *J* = 13.3, 3.2 Hz, 2H), 1.96 (dt, *J* = 11.5, 3.1 Hz, 4H), 1.83 – 1.02 (m, 18H), 0.86 (m, 9H). HRMS (ESI) m/z $[M + H]^+$ calculated for $[C_{22}H_{42}NO_2S]^+$ 384.2936, found 384.2936.

1-(2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)oxy)ethyl)-4-hexyl-1*H*-1,2,3-triazole (19).

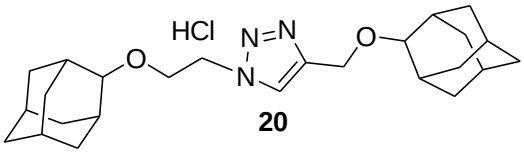


19

A mixture of 2-adamantyl bromide (215 mg, 1 mmol), Ag_2SO_4 (310 mg, 1 mmol) and ethylene glycol (1 ml) was heated for 1.5 h at 90 ^oC. The reaction mixture was then distributed between ethyl acetate and water. The ethyl acetate phase was separated and dried over anhydrous Na_2SO_4 then evaporated under reduced pressure to give a residue. Purification of the residue with flash chromatography (SiO_2, hexane/ethyl acetate = 6/1) gave the alcohol product (110 mg, yield: 56%). To a solution of the alcohol (98 mg, 0.5 mmol) in dry DCM (3 mL) was added Ph_3P (183 mg, 0.7 mmol) and CBr_4 (232 mg, 0.7 mmol) at 0 ^oC with stirring. Stirring was continued for 30 min at 0 ^oC and 2 h at 25 ^oC. The reaction mixture was then concentrated and purified by using flash chromatography (SiO_2, hexane/ethyl acetate = 20/1) to give the bromide product (117 mg, yield: 91%). A mixture of the bromide product (103 mg, 0.4 mmol), NaN_3 (65 mg, 1 mmol) and DMF (1.5 mL) was heated for 1 h at 80 ^oC. The reaction mixture was then distributed between hexane and water. The hexane phase was separated and dried over anhydrous Na_2SO_4, then evaporated under reduced pressure to give the azide (83 mg, yield 95%). A mixture of the azide (44 mg, 0.2 mmol), CuI (7 mg, 0.04 mmol), 1-octyne (22 mg, 0.2 mmol) and sodium ascorbate (98 mg, 0.5 mmol) in H_2O/DCM (1 mL/2 mL) was then stirred for 12 h at 25 ^oC. The organic phase was concentrated and purified by using flash chromatography (SiO_2, hexane/ethyl acetate = 8/1) to give the product **19** (48 mg, yield: 72%). The HCl salt was obtained by neutralizing the triazole with HCl in toluene with quantitative yield. Purity of the product was determined by

qNMR: 99.5%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 7.58 (s, 1H), 4.57 (t, J = 4.9 Hz, 2H), 3.80 ((t, J = 4.9 Hz, 3H), 3.41 (s, 1H), 2.80 (t, J = 7.7 Hz, 2H), 2.02 – 1.22 (m, 22H), 0.88 ((t, J = 5.0 Hz, 3H). HRMS (ESI) m/z $[M + H]^+$ calculated for $[C_{20}H_{34}N_3O]^+$ 332.2702, found 332.2698.

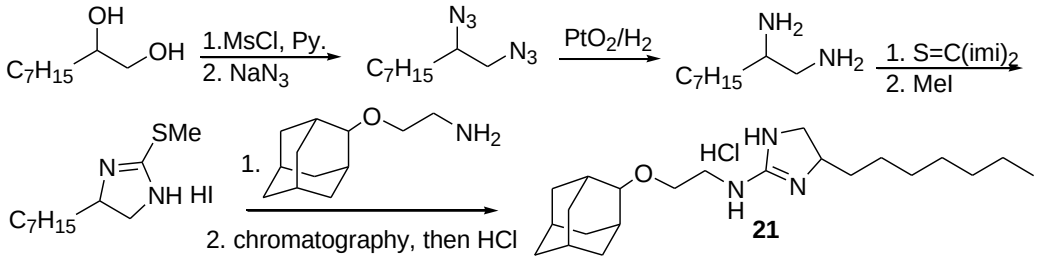
1-(2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)oxy)ethyl)-4-((((1*r*,3*r*,5*r*,7*r*)-adama-ntan-2-yl)oxy)methyl)-1*H*-1,2,3-triazole hydrochloride (20).



20

20 was made by following the protocol used for **19**. Purity of the product was determined by qNMR: 95.9%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 7.89 (s, 1H), 4.77 (s, 2H), 4.61 (t,J = 5.0 Hz, 2H), 3.82 (t, J = 4.9 Hz, 2H), 3.59 (s, 1H), 3.42 (s, 1H), 2.23 – 1.34 (m, 28H). HRMS (ESI) m/z $[M + H]^+$ calculated for $[C_{25}H_{38}N_3O_2]^+$ 412.2964, found 412.2961.

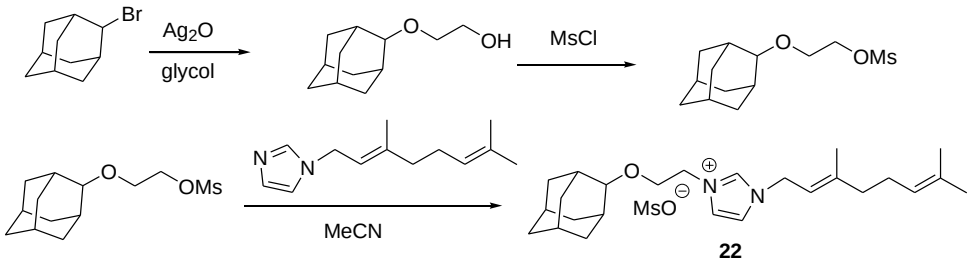
***N*-(2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)oxy)ethyl)-4-heptyl-4,5-dihydro-1*H*-imidazol-2-amine hydroiodide (21).**



To a solution of 1,2-nonanediol (320 mg, 2 mmol) in dry DCM (6 mL) was added pyridine (480 mg, 6 mmol) and MsCl (342 mg, 3 mmol) at 0 ^{o}C with stirring. Stirring was continued for 1 h at 0 ^{o}C then the reaction was quenched by adding saturated aqueous $NaHCO_3$. The DCM phase was separated and concentrated to give the crude dimesylate. A mixture of the the crude dimesylate and NaN_3 (260 mg, 4 mmol) in DMF (4 mL) was heated at 80 ^{o}C for 2 h. The resulting mixture was distributed between hexane and water. The hexane phase was separated and dried over

anhydrous Na_2SO_4 and solvents removed under reduced pressure to give the diazide. A mixture of diazide and PtO_2 (40 mg, 0.1 mmol) in MeOH (4 mL) was stirred under H_2 for 2 h at 25 ^oC. Filtration and evaporation gave the diamine (227 mg, 72%). To a solution of the diamine (227 mg, 1.44 mmol) in dry DCM was added 1,1'-thiocarbonyldiimidazole (356 mg, 2 mmol) at 0 ^oC. Stirring was continued for 2 h at 25 ^oC. The reaction mixture was purified by using flash chromatography (SiO_2, hexane/ethyl acetate = 6/1) to give the thiourea (216 mg, yield: 75%). A solution of the thiourea (216 mg, 1.08 mmol) and MeI (426 mg, 3 mmol) in methanol (4 mL) was refluxed for 4h. The solution was evaporated to give methylthioimidazole which was used in the next step. The amine (38 mg, 0.2 mmol) and methylthioimidazole (69 mg, 0.2 mmol) were refluxed in isopropanol (2 mL) for 2 h. The reaction mixture was concentrated and purified with flash chromatography (SiO_2, $CHCl_3$/MeOH/Et_3N = 100/10/5) to give **21** (64 mg). The HCl salt of **21** was obtained by neutralizing it with HCl in toluene. Purity of the product was determined by qNMR: 95.6%. ^1H NMR (500 MHz, chloroform-d_1) δ 8.99 (s, 1H), 8.42 (d, 1H), 7.05 (d, 1H), 4.51 – 3.80 (m, 2H), 3.74 – 3.57 (m, 2H), 3.53 (s, 1H), 3.49 – 3.10 (m, 3H), 2.09 – 1.66 (m, 11H), 1.62 – 1.15 (m, 15H), 0.89 (t, J = 5.0 Hz, 1H). HRMS (ESI) m/z $[M + H]^+$ calculated for $[C_{22}H_{40}N_3O]^+$ 362.3171, found 362.3171.

3-(2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)oxy)ethyl)-1-((*E*)-3,7-dimethylocta-2,6-dien-1-yl)-1*H*-imidazol-3-ium methanesulfonate (22).

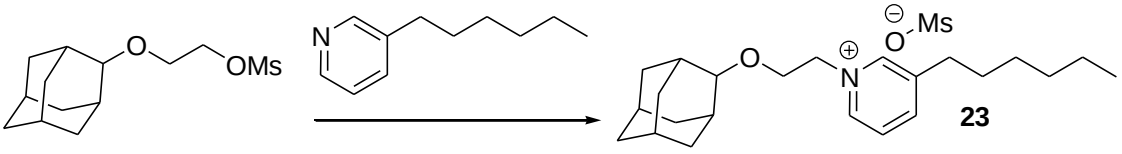


22

A mixture of 2-adamantyl bromide (215 mg, 1 mmol), Ag_2SO_4 (310 mg, 1 mmol) and ethylele

glycol (1 mL) was heated for 1.5 h at 90 ^{o}C. The reaction mixture was distributed between ethyl acetate and water. The ethyl acetate phase was separated and dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure to give the residue. Purification of the residue with flash chromatography (SiO_2, hexane/ethyl acetate = 6/1) gave the alcohol product (110 mg, yield: 56%). To a solution of the alcohol (110 mg, 0.56 mmol) in dry CH_2Cl_2 (3 mL) was added pyridine (158 mg, 2 mmol) and MsCl (91 mg, 0.8 mmol) at 0 ^{o}C with stirring. After stirring was continued for 2 h at 0 ^{o}C, all volatile components was removed under reduced pressure. The residue was purified by using flash chromatography (silica gel, hexane/ethyl acetate = 10/1) to give mesylate (146 mg, 95%). A mixture of the mesylate (27 mg, 0.1 mmol) and geranylimidazole (20 mg, 0.1 mmol) in MeCN (2 mL) was refluxed for 5 h. Evaporation gave a quantitative yield of the product **22**. Purity of the product was determined by qNMR: 91.7%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 9.96 (s, 1H), 7.47 (s, 1H), 7.08 (s, 1H), 5.37 (m, 1H), 5.03 (m, 1H), 4.88 (d, J = 7.5 Hz, 2H), 4.56 (m, 2H), 3.80 (m, 2H), 3.44 (s, 1H), 2.79 (s, 3H), 2.36 – 1.26 (m, 18H), 1.79 (s, ,3H), 1.68 (s, 3H), 1.60 (s, 3H). HRMS (ESI) m/z $[M]^{+}$ calculated for $[C_{25}H_{39}N_2O]^{+}$ 383.3062, found 383.3066.

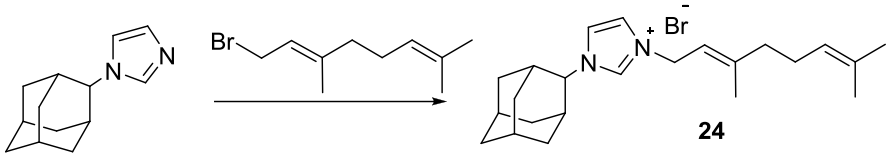
1-(2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)oxy)ethyl)-3-hexylpyridin-1-ium methanesulfonate (23).



23

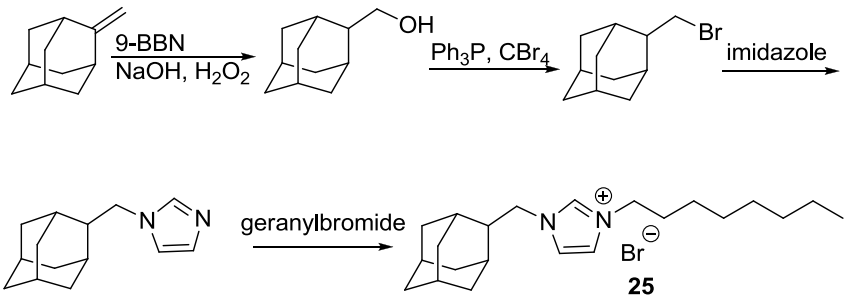
23 was made by following to the protocol used for **22**. Purity of the product was determined by qNMR: 96.11%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 8.98 (m, 1H), 8.74 (s, 1H), 8.24 (d, J = 7.9, Hz, 1H), 7.99 (dd, J = 8.0, 6.0 Hz, 1H), 4.91 (t, J = 5.5 Hz, 2H), 3.91 (J = 5.5 Hz, 2H), 3.42 (s, 1H), 2.85 (t, J = 7.5 Hz, 2H), 2.75 (s, 3H), 2.03 – 1.11 (m, 22H), 0.90 (m, 3H). HRMS (ESI) m/z $[M]^{+}$ calculated for $[C_{23}H_{36}NO]^{+}$ 342.2797, found 342.2785.

1-((1r,3*r*,5*r*,7*r*)-Adamantan-2-yl)-3-((*E*)-3,7-dimethylocta-2,6-dien-1-yl)-1*H*-imidazol-3-ium bromide (24).



1-(1-Adamantyl)-1*H*-imidazole was made according to a reported protocol[6]. A mixture of adamantly-imidazole (40 mg, 0.2 mmol) and geranyl bromide (44 mg, 0.2 mmol) in DCM (0.5 mL) was stirred for 12 h at 25 ^{o}C. The solid resulting from evaporation was thoroughly washed with hexane to give the product **24** (50 mg, yield: 59%). Purity of the product was determined by qNMR: 91.7%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.65 (s, 1H), 5.40 (t, *J* = 7.7 Hz, 1H), 5.17 (d, *J* = 7.6 Hz, 2H), 5.04 (s, 1H), 4.39 (s, 2H), 2.73 (s, 3H). HRMS (ESI) m/z $[M]^{+}$ calculated for $[C_{23}H_{35}N_2O]^{+}$ 339.2800, found 339.2797.

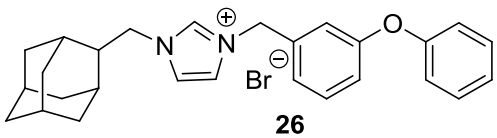
1-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)methyl)-3-octyl-1*H*-imidazol-3-ium bromide (25).



To a solution of methyleneadamantane[7] (296 mg, 2 mmol) in dry THF was added 9-BBN (0.5 M in THF, 4.4 mL) dropwise. Stirring was continued for 30 min at 0 ^{o}C and 1 h at 25 ^{o}C. The reaction flask was cooled in an ice-bath. To the resulting reaction mixture was added NaOH (3N in H_2O, 3 mL) and H_2O_2 (30% in water, 0.68 mL). Stirring was continued for 30 min at 0 ^{o}C and 1h at 25 ^{o}C. The reaction mixture was diluted with ethyl acetate and quenched with saturated aqueous Na_2SO_3 at 0 ^{o}C. The organic phase was dried over Na_2SO_4 and solvents removed under

reduced pressure to give the crude hydroxymethyladamantane. To a solution of the 2-hydroxymethyladamantane in DCM (6 mL) was added Ph_3P (524 mg, 2 mmol) and CBr_4 (662 mg, 2 mmol) at 0 ^oC with stirring. Stirring was continued for 30 min at 0 ^oC and for 2 h at 25 ^oC. The reaction mixture was concentrated and purified by using flash chromatography (SiO_2, hexane/ethyl acetate = 20/1) to give the bromide product (274 mg, yield: 61%). To a solution of imidazole (134 mg, 2 mmol) in dry THF (7 mL) was added NaH (washed with hexane, 58 mg, 2.5 mmol) at 0 ^oC with stirring. Stirring was continued for 20 min at 25 ^oC and 30 min at 50 ^oC. To the resulting solution was added bromomethyladamantane (229 mg, 1 mmol) at 25 ^oC, with stirring. Stirring was continued for 24 h at 50 ^oC. The reaction mixture was diluted with ethyl acetate and quenched with saturated aqueous NH_4Cl. The organic phase was separated and concentrated to give a residue. The residue was purified by using flash chromatography (SiO_2, ethyl acetate, 140 mg, 65%) to give the adamantanylmethylimidazole. A solution of adamantanylmethylimidazole (44 mg, 0.2 mmol) in octyl bromide (0.2 mL) was stirred for 4 h at 80 ^oC. To the reaction mixture was added 4 mL of hexane and the resulting precipitate was washed with hexane, three times, to give the product **25** (46 mg, yield: 56%). Purity of the product was determined by qNMR: 91.5%. ^1H NMR (500 MHz, Chloroform-*d*) δ 10.76 (s, 1H), 7.22 (s, 1H), 7.18 (s, 1H), 4.48 (d, *J* = 8.1 Hz, 2H), 4.38 (t, *J* = 7.5 Hz, 2H), 2.25 (t, *J* = 8.2 Hz, 1H), 2.10 – 1.07 (m, 26H), 0.87 (t, *J* = 6.9 Hz, 3H). HRMS (ESI) m/z $[M]^+$ calculated for $[C_{22}H_{37}N_2]^+$ 329.2957, found 329.2947.

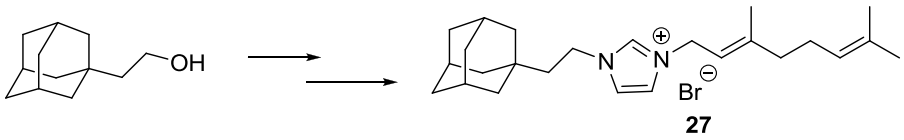
1-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)methyl)-3-(3-phenoxybenzyl)-1*H*-imidazol-3-ium bromide (26).



26

26 was made by following the protocol used for **25**. Purity of the product was determined by qNMR: 99.1%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 10.86 (s, 1H), 7.39 – 7.31 (m, 3H), 7.24 – 7.19 (m, 1H), 7.19 – 7.10 (m, 3H), 7.04 – 6.92 (m, 4H), 5.64 (s, 2H), 4.41 (d, J = 8.0 Hz, 2H), 2.24 (t, J = 8.1 Hz, 1H), 2.02 – 1.57 (m, 14H). HRMS (ESI) m/z $[M]^+$ calculated for $[C_{27}H_{31}N_2O]^+$ 399.2436, found 399.2430.

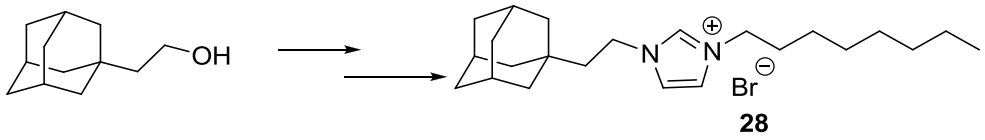
1-(2-((3*r*,5*r*,7*r*)-Adamantan-1-yl)ethyl)-3-((*E*)-3,7-dimethylocta-2,6-dien-1-yl)-1*H*-imidazol-3-ium bromide (27).



27

27 was made by following the protocol used for **25** using 1-(1-hydroxy-ethyl) adamantane as the starting material which is commercial available. Purity of the product was determined by qNMR: 91.9%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 10.67 (s, 1H), 7.24 (s, 1H), 7.18 (s, 1H), 5.50 – 5.28 (m, 1H), 5.03 (m, 1H), 5.01 (d, J = 7.5 Hz, 2H), 4.49 – 4.19 (m, 2H), 2.17 – 1.22 (m, 21H), 1.60 (s, 3H), 1.57 (s, 6H). HRMS (ESI) m/z $[M]^+$ calculated for $[C_{25}H_{39}N_2]^+$ 367.3113, found 367.3128.

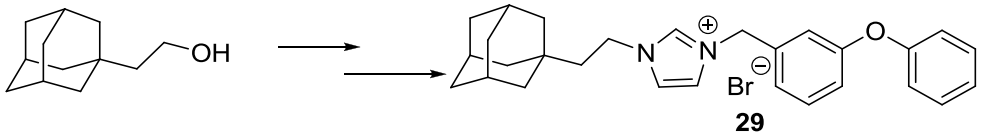
1-(2-((3*r*,5*r*,7*r*)-Adamantan-1-yl)ethyl)-3-octyl-1*H*-imidazol-3-ium bromide (28).



28

28 was made by following the protocol used for **25** using 1-(1-hydroxy-ethyl) adamantane as the starting material. Purity of the product was determined by qNMR: 98.1%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 10.80 (s, 1H), 7.21 (m, 2H), 4.36 (m, 4H), 2.18 – 1.80 (m, 5H), 1.83 – 1.59 (m, 12H), 1.43 – 1.10 (m, 10H), 0.87 (t, J = 6.8 Hz, 3H). HRMS (ESI) m/z $[M]^+$ calculated for $[C_{23}H_{39}N_2]^+$ 343.3113, found 343.3111.

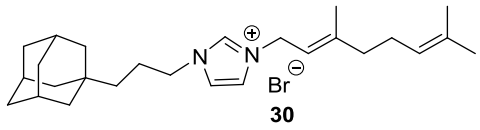
1-(2-((3*r*,5*r*,7*r*)-Adamantan-1-yl)ethyl)-3-(3-phenoxybenzyl)-1*H*-imidazol-3-ium bromide (29).



29

29 was made by following the protocol used for **26** using 1-(1-hydroxy-ethyl) adamantane as starting material. Purity of the product was determined by qNMR: 91.0%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 10.83 (t, J = 1.6 Hz, 1H), 7.42 – 7.28 (m, 3H), 7.25 – 7.10 (m, 4H), 7.06 – 6.90 (m, 4H), 5.63 (s, 2H), 4.38 – 4.16 (m, 2H), 2.17 – 1.44 (m, 17H). HRMS (ESI) m/z $[M]^+$ calculated for $[C_{28}H_{33}N_2O]^+$ 413.2593, found 413.2595.

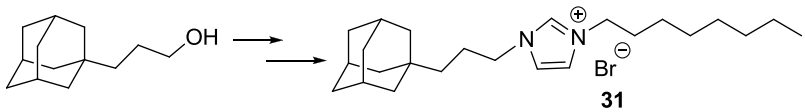
1-(3-((3*r*,5*r*,7*r*)-Adamantan-1-yl)propyl)-3-((*E*)-3,7-dimethylocta-2,6-dien-1-yl)-1*H*-imidazol-3-ium bromide (30).



30

30 was made by following the protocol used for **25** using 1-(3-hydroxy-propyl)adamantane[8] as starting material. Purity of the product was determined by qNMR: 90.9%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 10.61 (s, 1H), 7.21 (s, 1H), 7.16 (s, 1H), 5.38 (m, , 1H), 5.03 (t, m , 1H), 5.01 (d, J = 10.0 Hz, 2H), 4.30 (t, J = 7.5 Hz, 2H), 1.52 (m, 23H), 1.60 (s, 3), 1.44 (s, 6H). HRMS (ESI) m/z $[M]^+$ calculated for $[C_{26}H_{41}N_2]^+$: 381.3270, found : 381.3267.

1-(3-((3*r*,5*r*,7*r*)-Adamantan-1-yl)propyl)-3-octyl-1*H*-imidazol-3-ium bromide (31).

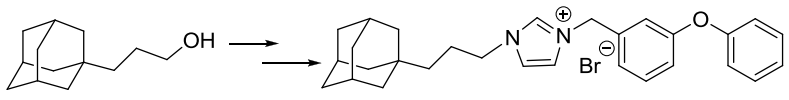


31

31 was made by following the protocol used for **25** using 1-(3-hydroxy-propyl) adamantaneas[8] starting material. Purity of the product was determined by qNMR: 97.2%. ^{1}H NMR (500 MHz,

chloroform-d_1) δ 10.76 (s, 1H), 7.22 (s, 2H), 4.36 (t, J = 7.5 Hz, 2H), 4.32 (t, J = 7.5 Hz, 2H), 2.03 – 1.17 (m, 15H), 1.12 – 1.01 (m, 2H), 0.87 (t, J = 6.8 Hz, 3H). HRMS (ESI) m/z $[M]^+$ calculated for $[C_{24}H_{41}N_2]^+$ 357.3270, found 357.3258.

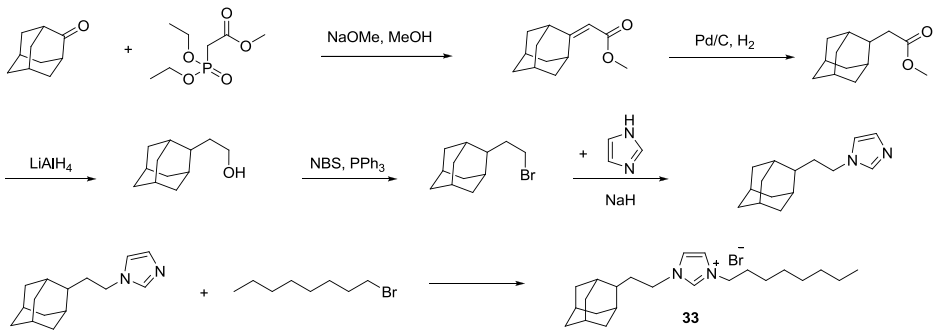
1-(3-((3*r*,5*r*,7*r*)-Adamantan-1-yl)propyl)-3-(3-phenoxybenzyl)-1*H*-imidazol-3-ium bromide (32).



32

32 was made by following the protocol used for **26** using 1-(3-hydroxy-propyl)adamantane[8] as starting material. Purity of the product was determined by qNMR: 90.1%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 10.90 (s, 1H), 7.35 (m, 3H), 7.24 – 7.11 (m, 3H), 6.99 (m, 5H), 5.62 (s, 2H), 4.27 (t, J = 7.5 Hz, 2H), 1.96 – 1.38 (m, 17H), 1.071 (m, 2H). HRMS (ESI) m/z $[M]^+$ calculated for $[C_{29}H_{35}N_2O]^+$ 427.2749, found 427.2754.

1-(3-((3*r*,5*r*,7*r*)-Adamantan-2-yl)propyl)-3-octyl-1*H*-imidazol-3-ium bromide (33)

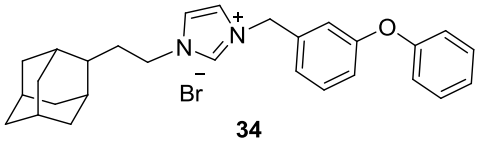


To a solution of 2-adamantanone (5 g, 33.28 mmol) in 32 mL of methanol was added methyl 2-diethoxyphosphoacetate (9 mL, 49.68 mmol). The reaction mixture was cooled at 0 ^{o}C and into it was slowly added sodium methoxide (solution of 30% wt in methanol). The mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the crude was treated with ethyl acetate and water. The organic layer was dried over Na_2SO_4 and the

solvent was removed under reduced pressure. The crude was purified by using column chromatography (silica gel, eluting with hexane/ethyl acetate 90:1) to give the unsaturated ester as a solid (6.41 g, 90%)**.** To a solution of the unsaturated ester (6.4 g, 31.07 mmol) in methanol (100 mL) was added ammonium formiate (7.8 g, 124.33 mmol), then was added palladium on charcoal (0.6 g, 10%) under nitrogen. The reaction mixture was stirred at room temperature for 3 h. Solvents were removed under reduced pressure. The crude was treated with water and ethyl acetate, and the organic layer was separated, dried over Na_2SO_4 and solvent removed under reduced pressure. The ester product was obtained as a colourless oil (6.2 g, 95%). To a solution of lithium aluminum hydride (1.58 g, 41.63 mmol) in anhydrous tetrahydrofuran (THF) was slowly added a solution of the ester (6.2 g, 29.76 mmol) in THF (55 mL). The reaction mixture was stirred at room temperature overnight. Then water (12 mL), sodium hydroxide 4N (12 mL) and finally water (36 mL) were added into the solution at 0 ^oC. The mixture was stirred for some minutes and the resulting salts were filtered through a pad of celite washing with ethyl acetate (100 mL). The crude was treated with water and CH_2Cl_2 and the organic layer was separated, dried over Na_2SO_4 and solvents removed under reduced pressure to give the alcohol product as an oil (4.83 g, 90%). To a solution of the alcohol (4.8 g, 26 mmol) in 100 mL CH_2Cl_2 was added triphenylphosphine (13.6 g, 52 mmol). The reaction mixture was stirred at room temperature while N-bromosuccinimide (NBS, 6.9 g, 39 mmol) was added in small portions. The mixture was stirred overnight and then washed with water and extracted with hexane. The organic layer was separated, dried over Na_2SO_4 and solvents removed under reduced pressure to give the bromide product as a light yellow solid (6.0 g, 95%). Imidazole (1.0 g, 15 mmol) was dissolved in THF (30 mL) and NaH (240 mg, 10 mmol) was added. The reaction mixture was stirred at room temperature for 30 minutes and then the bromide product (1.2 g, 5 mmol) was added. The

reaction mixture was then heated to 80 ^{o}C and stirred overnight. The reaction was quenched with water and the mixture extracted with diethyl ether. The organic layer was separated, dried over Na_2SO_4 and solvents removed under reduced pressure. The crude product was purified by silica flash chromatography (silica gel, hexane/ethyl acetate 2:1). The imidazole product was obtained as light yellow solid (0.6 g, 50%). The imidazole product was dissolved in 1-bromooctane and the reaction mixture stirred overnight under nitrogen at 80 ^{o}C. The reaction mixture was treated with hexane and a white precipitate formed. The mixture was centrifuged and the solution discarded. The white precipitate was washed three times with hexane and gave the product **33** as a white solid. Purity of the product was determined by qNMR: 98.9%. ^{1}H NMR (500 MHz, chloroform-*d*$_1$) δ 10.638 (s, 1H), 7.35 (d, J = 10.5 Hz, 1H), 7.34 (d, J = 10.5 Hz 1H), 4.33 (m, 4H), 2.06 (m, 2H), 1.92-1.82 (m, 12H), 1.68 (m, 2H), 1.55 (m, 1H), 1.31-1.21 (m, 12H), 0.85 (t, J = 7.0 Hz, 3H). HRMS (ESI): m/z $[M + H]^+$ calculated for $[C_{23}H_{29}N_2]^+$ 343.3113, found 343.3119.

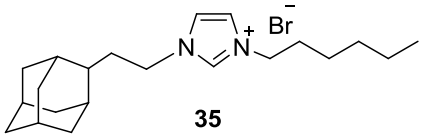
1-(3-((3*r*,5*r*,7*r*)-Adamantan-1-yl)propyl)-3-(3-phenoxybenzyl)-1*H*-imidazol-3-ium bromide (34).



34

34 was made by following the protocol used for **33**. Purity of the product was determined by qNMR: 100%. ^{1}H NMR (500 MHz, chloroform-*d*$_1$) δ 10.77 (s, 1H), 7.33-6.90 (m, 11H), 5.62 (s, 2H), 4.29 (t, J = 7.5 Hz, 2H), 1.92-1.82 (m, 12H), 1.68 (m, 2H), 1.55 (m, 1H). HRMS (ESI) m/z $[M]^+$ calculated for $[C_{28}H_{33}N_2O]^+$ 413.2593, found 413.2586.

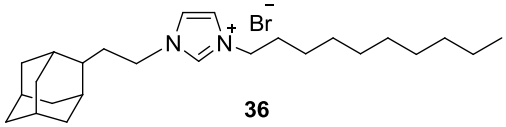
1-(3-((3*r*,5*r*,7*r*)-Adamantan-2-yl)propyl)-3-hexyl-1*H*-imidazol-3-ium bromide (35)



35

35 was made by following the protocol used for **33**. Purity of the product was determined by qNMR: 98.9%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 10.86 (s, 1H), 7.35 (d, J = 10.5 Hz, 1H), 7.26 (d, J = 10.5 Hz 1H), 4.37 (m, 4H), 2.06 (m, 2H), 1.92-1.82 (m, 12H), 1.68 (m, 2H), 1.55 (m, 1H), 1.31-1.21 (m, 8H), 0.85 (t, J = 7.0 Hz, 3H). HRMS (ESI): m/z $[M + H]^+$ calculated for $[C_{21}H_{35}N_2]^+$ 315.2830, found 315.2834.

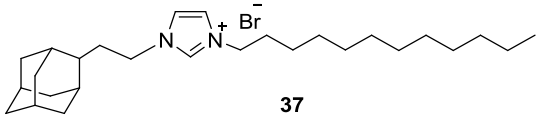
1-(3-((3*r*,5*r*,7*r*)-Adamantan-2-yl)propyl)-3-decyl-1*H*-imidazol-3-ium bromide (36)



36

36 was made by following the protocol used for **33**. Purity of the product was determined by qNMR: 96.4%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 10.86 (s, 1H), 7.35 (d, J = 10.5 Hz, 1H), 7.26 (d, J = 10.5 Hz 1H), 4.37 (m, 4H), 2.06 (m, 2H), 1.92-1.82 (m, 12H), 1.68 (m, 2H), 1.55 (m, 1H), 1.31-1.21 (m, 16H), 0.85 (t, J = 7.0 Hz, 3H). HRMS (ESI): m/z $[M + H]^+$ calculated for $[C_{25}H_{43}N_2]^+$ 371.3426, found 371.3430.

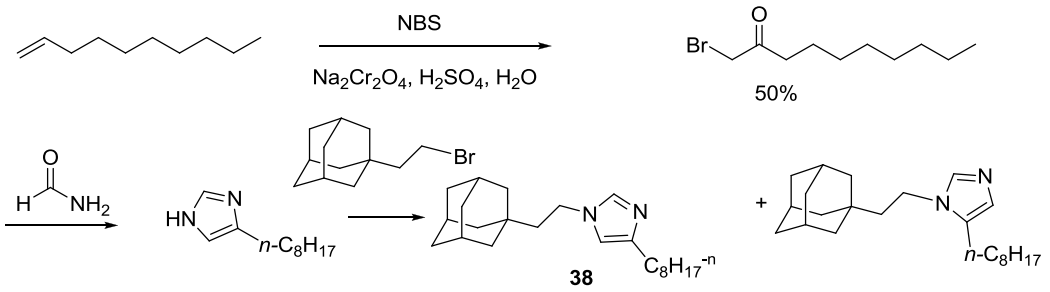
1-(3-((3*r*,5*r*,7*r*)-Adamantan-2-yl)propyl)-3-dodecyl-1*H*-imidazol-3-ium bromide (37)



37

37 was made by following the protocol used for **33**. Purity of the product was determined by qNMR: 99.9%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 10.85 (s, 1H), 7.35 (d, J = 10.5 Hz, 1H), 7.26 (d, J = 10.5 Hz 1H), 4.37 (m, 4H), 2.06 (m, 2H), 1.92-1.82 (m, 12H), 1.68 (m, 2H), 1.55 (m, 1H), 1.31-1.21 (m, 20H), 0.85 (t, J = 7.0 Hz, 3H). HRMS (ESI): m/z $[M + H]^+$ calculated for $[C_{27}H_{47}N_2]^+$ 399.3734, found 399.3739.

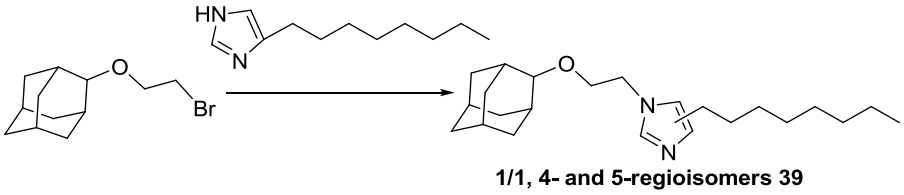
1-(2-((3*r*,5*r*,7*r*)-Adamantan-1-yl)ethyl)-4-octyl-1*H*-imidazole (38).



To a solution of dec-1-ene (5 g, 36 mmol) in DMSO (100 ml) and water (2.5 mL) was added NBS (18 g, 101 mmol) at 25 ^{o}C with stirring. Stirring was continued for 4 h at 40 ^{o}C. Water (250 mL) was added to the mixture which was then extracted with ether; the ether extracts were washed with water, dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure to yield the crude bromohydrin. To a solution of the bromohydrin in acetone (25 mL) was added dropwise with stirring at 25 ^{o}C a solution of sodium dichromate (3.5 g, 12.5 mmol) in concentrated sulfuric acid (2.5 mL) plus water (15 mL). Stirring was continued for 1.5 h at 25 ^{o}C. Diethyl ether (25 mL) was added and the mixture stirred for a further 1 h. The ether layer was then separated, washed with water, dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure to give 1-bromodecan-2-one (4.23 g, yield: 50%). Under N_2, the bromo-ketone (1.16 g in a minimal amount of hexane) was added to preheated formamide (10 mL, 180 ^{o}C), dropwise. The hexane rapidly evaporated and stirring was continued for 2 h at 180 ^{o}C. The reaction mixture cooled to 25 ^{o}C and then distributed between toluene and aqueous NaOH (3N). The toluene phase was separated, dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure to give a residue. The residue was purified by using flash chromatography (SiO_2, ethyl acetate) to give 4-octanylimidazole (693 mg, yield: 77%). To a solution of 4-octanylimidazole (90 mg, 0.5 mmol) in dry THF (3 mL) was added NaH (washed with and dried from hexane, 16 mg, 0.7 mmol) at 0 ^{o}C, with stirring. Stirring was continued for 20 min at 25 ^{o}C

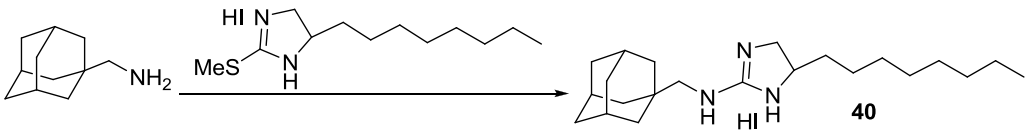
and 30 min at 50 ^{o}C. To the resulting solution was added bromomethyladamantane (114 mg, 0.5 mmol) at 25 ^{o}C, with stirring. Stirring was continued for 12 h at 60 ^{o}C. The reaction mixture was diluted with ethyl acetate and quenched with saturated aqueous NH_4Cl. The organic phase was separated and concentrated to give a residue. Purification of the residue with flash chromatography (SiO_2, ethyl acetate) gave the product **38** (27 mg, yield: 16%, Purity of the product was determined by qNMR: 92.2%). ^{1}H NMR (500 MHz, chloroform-*d*$_1$) δ 7.42 (s, 1H), 6.61 (s, 1H), 3.92 – 3.82 (m, 2H), 2.54 (t, *J* = 7.7 Hz, 2H), 2.05 – 0.76 (m, 32H). HRMS (ESI) m/z $[M + H]^+$ calculated for $[C_{23}H_{39}N_2]^+$ 343.3113, found 343.3118.

1-(2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)oxy)ethyl)-5-octyl-1*H*-imidazole and 1-(2-(((1*r*,3*r*,5*r*,7*r*)-adamantan-2-yl)oxy)ethyl)-4-octyl-1H-imidazole (39, as a 1/1 mixture).



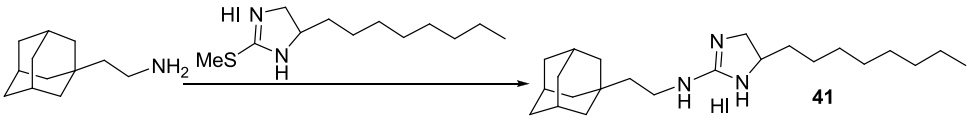
39 was made by following the protocol used for **38** but using (1*r*,3*r*,5*r*,7*r*)-2-(2-bromoethoxy)adamantane as the alkylation reagent. Purity of the product was determined by qNMR: 91.5%. ^{1}H NMR (500 MHz, chloroform-*d*$_1$) δ 1/1 regioisomer: 7. 60 (s, 1H), 7.53 (s, 1H), 6.77 (s, 1H),6.72 (s, 1H), 4.05 (t, *J* = 5.2 Hz, 2H), 4.02 (t, *J* = 5.3 Hz, 2H), 3.65 (m, 4H), 3.38 (m, 2H), 2.55 (m,4H), 2.01 – 1.14 (m, 52H), 0.88 (m, 6H). HRMS (ESI) m/z $[M + H]^+$ calculated for $[C_{23}H_{39}N_2O]^+$ 359.3062, found 359.3056.

***N*-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)methyl)-5-octyl-4,5-dihydro-1*H*-imidazol-2-amine hydroiodide (40).**



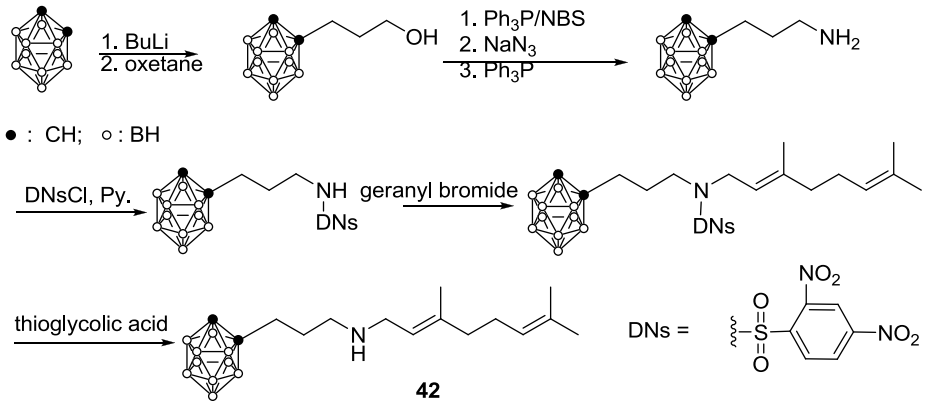
40 was made by following the protocol used for **21**. Purity of the product was determined by qNMR: 92.4%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 4.02-3.15 (m, 5H), 2.01-1.26 (m, 28 H), 0.88 (t, J = 6.9 Hz, 3H). HRMS (ESI) m/z $[M + H]^+$ calculated for $[C_{22}H_{40}N_3]^+$ 346.3222, found 346.3218.

***N*-(2-((3*r*,5*r*,7*r*)-Adamantan-1-yl)ethyl)-5-octyl-4,5-dihydro-1*H*-imidazol-2-amine hydroiodide (41).**



41 was made by following the protocol used for **21**. Purity of the product was determined by qNMR: 95.4%. ^{1}H NMR (500 MHz, chloroform-d_1) 4.45 and 4.28 (broad, 2H), 3.75 (m, 1H), 3.57 (t, J = 10.0 Hz, 2H), 3.12 (t, J = 10.0 Hz, 2H), 2.66 and 2.56 (broad, 2H), 1.91-1.24 (m, 28H), 0.86 (m, 3H). HRMS (ESI) m/z $[M + H]^+$ calculated for $[C_{23}H_{42}N_3]^+$ 360.3379, found 360.3368.

(*E*)-*N*-(3-(1'-(1',2'-Dicarbaclosododecaboranyl))propyl)-3,7-dimethylocta-2,6-dien-1-amine (42).

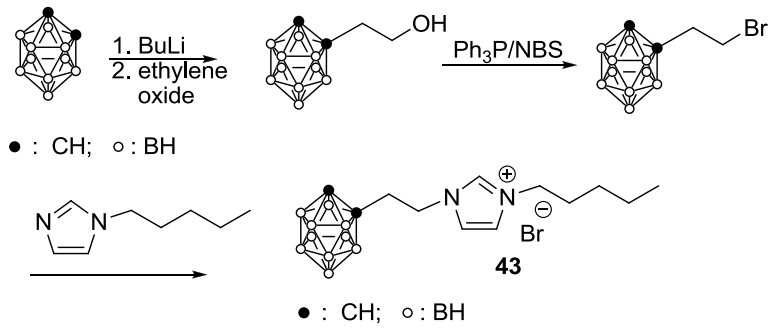


To a solution of *o*-carborane (268 mg, 2 mmol) in dry THF (6 mL, 2 mmol) was added BuLi (1.6 M in hexane, 1.25 mL, 2 mmol) at -78 ^{o}C under N_2. Stirring was continued for 30 min, then

trimethylene oxide (0.2 mL, 3 mmol) was added, dropwise. After stirring for 1 h at 0 ^{o}C, the reaction was quenched by adding saturated aqueous NH_4Cl (2 mL). The aqueous phase was extracted with ethyl acetate (3 mL x 3), then solvents were removed from the combined organic phase under reduced pressure and the residue purified by using flash chromatography (silica gel, hexane/ethyl acetate = 5/1) to give the carboranylpropyl alcohol (311 mg, 81%). To a solution of the carboranylpropyl alcohol (297 mg, 1.5 mmol) in dry CH_2Cl_2 (5 mL) was added Ph_3P (524 mg, 2 mmol) followed by NBS (356 mg, 2 mmol). After stirring for 3 h at 0 ^{o}C, all volatile components were removed under reduced pressure. The reaction residue was purified by using flash chromatography (silica gel, hexane/ethyl acetate = 15/1) to give the bromopropyl product (287 mg, 75%). To a solution of the carboranylpropyl bromide (256 mg, 1 mmol) in DMF (2 mL) was added NaN_3 (130 mg, 2 mmol), and the resulting solution was stirred for 3 h at 100 ^{o}C. The reaction mixture cooled to room temperature and distributed between ethyl acetate/water (10 mL/10 mL). The ethyl acetate phase was separated and washed with water (5 mL x 3), then solvent was removed under reduced pressure to give the crude carboranylpropyl azide. To a solution of the above crude azide in THF/H_2O (5 mL/0.5 mL) was added Ph_3P (314 mg, 1.2 mmol). Stirring was continued for 10 h at 25 ^{o}C, and then solvents were removed under reduced pressure. Flash chromatography (silica gel, $CHCl_3$/MeOH = 10/1) of the residue gave the carboranylpropylamine (99 mg, 52%). To a solution of the carboranylpropylamine (99 mg, 0.52 mmol) in dry CH_2Cl_2 (2 mL) was added Et_3N (0.14 mL, 1 mmol) and 2,4-dinitrobenzensulfonyl chloride (186 mg, 0.7 mmol) at 0 ^{o}C. Stirring was continued for 2 h at 0 ^{o}C and then solvents were removed under reduced pressure. Flash chromatography (silica gel, hexane/ethyl acetate = 10/1) of the residue gave carboranylpropyl dinitrobenzensulfonyl amine (120 mg, 55%). To a solution of carboranylpropyl dinitrobenzensulfonyl amine (120 mg, 0.28 mmol) in DMF (2 mL)

was added geranyl bromide (73 mg, 0.34 mmol) and K_2CO_3 (47 mg, 0.34 mmol) with stirring. Stirring was continued for 1 h at 60 ^oC, then the reaction mixture was cooled to room temperature. The reaction mixture was distributed between ethyl acetate/water (10 mL/10 mL) and the ethyl acetate phase was separated, dried over Na_2SO_4 and solvents removed under reduced pressure to give the crude trisubstituted amine product. To a solution of the trisubstituted amine in CH_2Cl_2 was added thioglycolic acid (26 mg, 0.28 mmol) and Et_3N (84 mg, 0.84 mmol) at 0 ^oC. Stirring was continued for 1 h at 25 ^oC. The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The CH_2Cl_2 phase was separated, dried over Na_2SO_4 and solvents removed under reduced pressure to give the crude product **42**. Flash chromatography (silica gel, $CHCl_3$/MeOH = 10/1) of the residue gave the desired product as a pale yellow oil (17 mg, 18%). To a solution of amine in toluene (1 mL) was added trifluoroacetic acid (TFA) (10 mg) at 0 ^oC. All the volatile components were then removed to give the TFA salt of the amine in quantitative yield. Purity of the product was determined by qNMR: 96.0%. ^1H NMR (500 MHz, chloroform-*d*$_1$) δ 5.23 (m, 1H), 5.05 (m, 1H), 3.67 (s, 1H), 3.40 (d, J = 7.2 Hz, 2H), 2.74 (t, J = 6.9 Hz, 2H), 2.75-1.65 (m, 16) 2.33 (m, 2H), 1.67 (s, 6H), 1.60 (s, 3H). HRMS (ESI) m/z $[M + H]^+$ calculated for $[C_{15}H_{36}B_{10}N]^+$ 340.3778, found 340.3803.

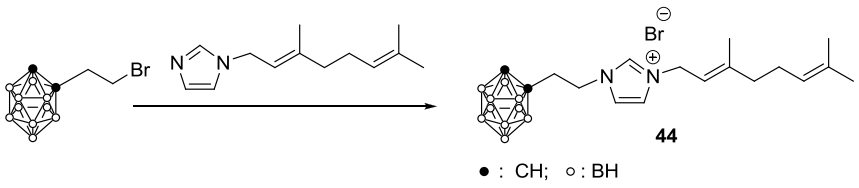
1-(-(1'-(1',2'-Dicarbaclosododecaboranyl))ethyl)-3-pentyl-1*H*-imidazol-3-ium bromide (43).



To a solution of *o*-carborane (268 mg, 2 mmol) in dry THF (6 mL, 2 mmol) was added BuLi (1.6 M in hexane, 1.25 mL, 2 mmol) at -78 ^oC under N_2. Stirring was continued for 30 min, then

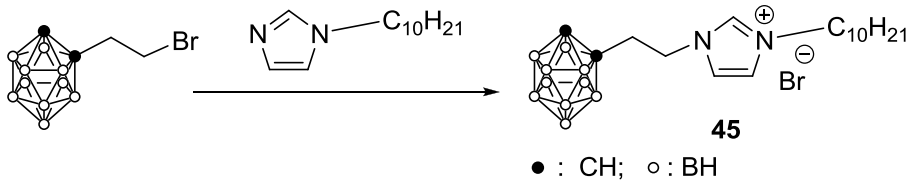
ethylene oxide (1.2 M in THF, 2.5 mL, 3 mmol) was added dropwise. Stirring was continued for 1 h at 0 ^{o}C, then the reaction was quenched by adding saturated aqueous NH_4Cl (2 mL). The aqueous phase was extracted with ethyl acetate (3 mL x 3) and the combined organic phase was dried over Na_2SO_4 and solvents removed under reduced pressure. The residue was purified by using flash chromatography (silica gel, hexane/ethyl acetate = 5/1) to give the carboranylethyl alcohol (303 mg, 85%). To a solution of the carboranylethyl alcohol (303 mg, 1.7 mmol) in dry CH_2Cl_2 (5 mL) was added Ph_3P (524 mg, 2 mmol) followed by NBS (356 mg, 2 mmol). Stirring was continued for 3 h at 0 ^{o}C, then all volatile components were removed under reduced pressure. The residue was purified by flash chromatography (silica gel, hexane/ethyl acetate = 15/1) to give the bromide product (328 mg, 80%). A mixture of the carboranylethyl bromide product (33 mg, 0.1 mmol), *N*-pentylimidazole (14 mg, 0.1 mmol) and chloroform (0.5 mL) was heated for 3 h at 120 ^{o}C in the sealed tube. The reaction mixture was cooled to room temperature and all volatile components removed under reduced pressure. The residue was purified by flash chromatography (silica gel, $CHCl_3$/MeOH = 10/1) to give the product **43** (30 mg, 65%). Purity of the product was determined by qNMR: 92.5%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 10.60 (s, 1H), 7.52 (s, 1H), 7.20 (s, 1H), 5.11 (s, 1H), 4.58 (t, J = 10.0 Hz, 2H), 4.20 (t, J = 7.5 Hz, 2H), 3.22 (t, J = 10.0 Hz,, 2H), 2.80 – 1.71 (m, 10H), 1.93 (m, 2H), 1.36 (m, 4H), 0.92 (t, J = 7.0 Hz, 3H). HRMS (ESI) m/z $[M]^+$ calculated for $[C_{12}H_{29}B_{10}N_2]^+$ 311.3261, found 311.3232.

(*E*)-1-(-(1'-(1',2'-Dicarbaclosododecaboranyl))ethyl)-3-(3,7-dimethylocta-2,6-dien-1-yl)-1*H*-imidazol-3-ium (44).



44 was made by following the protocol used for **43**. Purity of the product was determined by qNMR: 91.6%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 10.32 (s, 1H), 7.49(s, 1H), 7.14 (s, 1H), 5.37 (m, 1H), 5.09 (s, 1H), 5.04 (s, 1H), 4.81 (d, J = 7.5 Hz, 2H), 4.61 – 4.49 (m, 2H), 3.27 – 3.10 (m, 2H), 2.69-1.25 (m, 14H), 1.80 (s, 3H), 1.60 (s, 3H), 1.54 (s, 3H). HRMS (ESI) m/z $[M]^+$ calculated for $[C_{17}H_{35}B_{10}N_2]^+$ 377.3731, found 377.3772.

3-Decyl-1-(-(1'-(1',2'-dicarbaclosododecaboranyl))ethyl)-1*H*-imidazol-3-ium bromide (45).

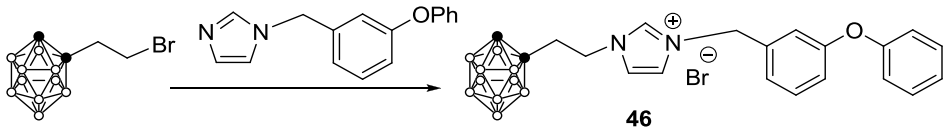


45

● : CH; ○ : BH

45 was made by following the protocol used for **43**. Purity of the product was determined by qNMR: 96.6%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 10.58 (s, 1H), 7.55 (s, 1H), 7.20 (s, 1H), 5.13 (s, 1H), 4.70 – 4.45 (m, 2H),4.19 (t, J = 7.5 Hz, 2H), 3.33 – 3.03 (m, 2H), 2.75 - 1.89 (m, 10H), 1.924 (m, 2H), 1.30 - 1.25 (m, 14H), 0.88 (t, J = 6.8 Hz, 3H). HRMS (ESI) m/z $[M]^+$ calculated for $[C_{17}H_{35}B_{10}N_2]^+$ 381.4044, found 381.4071.

1-(-(1'-(1',2'-Dicarbaclosododecaboranyl))ethyl)-3-(3-phenoxybenzyl)-1*H*-imidazol-3-ium bromide (46).

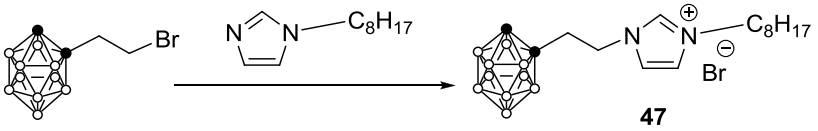


46

● : CH; ○ : BH

46 was made by following the protocol used for **43**. Purity of the product was determined by qNMR: 93.4%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 10.62 (s, 1H), 7.51 – 6.85 (m, 11H), 5.38 (s, 2H), 5.04 (s, 1H), 4.56 (d, J = 3.7 Hz, 2H), 3.21 (d, J = 7.9 Hz, 2H) 2.77-1.52 (m, 10H). HRMS (ESI) m/z $[M]^+$ calculated for $[C_{20}H_{29}B_{10}N_2O]^+$ 423.3210, found 423.3205.

1-(-(1'-(1',2'-Dicarbaclosododecaboranyl))ethyl)-3-octyl-1*H*-imidazol-3-ium bromide (47).

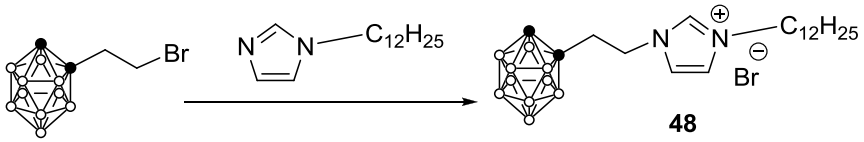


47

● : CH; ○ : BH

47 was made by following the protocol used for **43**. Purity of the product was determined by qNMR: 97.2%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 10.55 (s, 1H), 7.49 (d, J = 1.6 Hz, 1H), 7.19 (d, J = 1.5 Hz, 1H), 5.08 (s, 1H), 4.57 (m, 2H), 4.20 (t, J = 7.6 Hz, 2H),3.20 (dd, J = 9.8, 6.9 Hz, 2H), 2.75 - 1.70 (m, 10H), 1.91 (m, 2H), 1.49 – 1.12 (m, 10H), 0.88 (t, J = 6.8 Hz, 3H). HRMS (ESI) m/z $[M]^+$ calculated for $[C_{15}H_{35}B_{10}N_2]^+$ 353.3731, found 353.3765.

1-(-(1'-(1',2'-Dicarbaclosododecaboranyl))ethyl)-3-dodecyl-1*H*-imidazol-3-ium bromide (48).

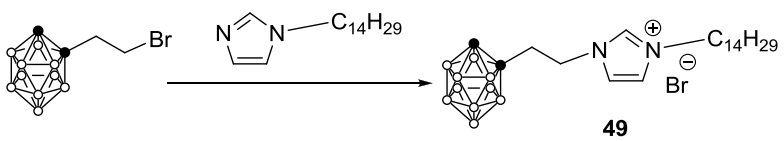


48

● : CH; ○ : BH

48 was made by following the protocol used for **43**. Purity of the product was determined by qNMR: 95.0%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 10.72 (s, 1H), 7.36(s, 1H), 7.17 (s, 1H), 5.10 (s, 1H), 4.68 – 4.39 (m, 2H), 4.19 (t, J = 7.6 Hz, 2H), 3.23 (dd, J = 9.8, 7.1 Hz, 2H), 2.75-1.75 (m, 10H), 1.94 (m, 2H), 1.34 – 1.25 (m, 18H), 0.88 (t, J = 6.8 Hz, 3H). HRMS (ESI) m/z $[M]^+$ calculated for $[C_{19}H_{43}B_{10}N_2]^+$ 409.4357, found 409.4376.

1-(-(1'-(1',2'-Dicarbaclosododecaboranyl))ethyl)-3-tetradecyl-1*H*-imidazol-3-ium bromide (49).



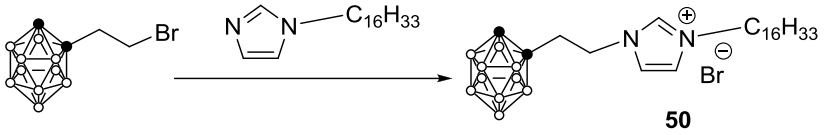
49

● : CH; ○ : BH

49 was made by following the protocol used for **43**. Purity of the product was determined by

qNMR: 92.6%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 10.56 (s, 1H), 7.48 (s, 1H), 7.19 (s, 1H), 5.10 (s, 1H), 457 (m, 2H), 4.20 (t, J = 7.5 Hz, 2H), 3.21 (m, 2H), 2.75-1.75 (m, 10H), 1.90 (m, 2H), (m, 22H), 0.88 (t, J = 6.8 Hz, 3H). HRMS (ESI) m/z $[M]^+$ calculated for $[C_{21}H_{47}B_{10}N_2]^+$ 437.4670, found 437.4689.

1-(-(1'-(1',2'-Dicarbaclosododecaboranyl))ethyl)-3-hexadecyl-1*H*-imidazol-3-ium bromide (50).



50

● : CH; ○ : BH

50 was made by following the protocol used for **43**. Purity of the product was determined by qNMR: 96.1%. ^{1}H NMR (500 MHz, chloroform-d_1) δ 10.61 (s, 1H), 7.49 (s, 1H), 7.19 (s, 1H), 5.12 (s, 1H), 4.58 (m, 2H), 4.19 (t, J = 7.5 Hz, 2H), 3.22 (m, 2H), 2.75 - 1.75 (m, 10H), 1.92 (m, 2 H), 2.68-1.25 (m, 26H), 0.88 (t, J = 6.8 Hz, 3H). HRMS (ESI) m/z $[M]^+$ calculated for $[C_{23}H_{51}B_{10}N_2]^+$ 465.4983, found 465.4977.

Figure S1. qNMR spectrum of compound **3**.

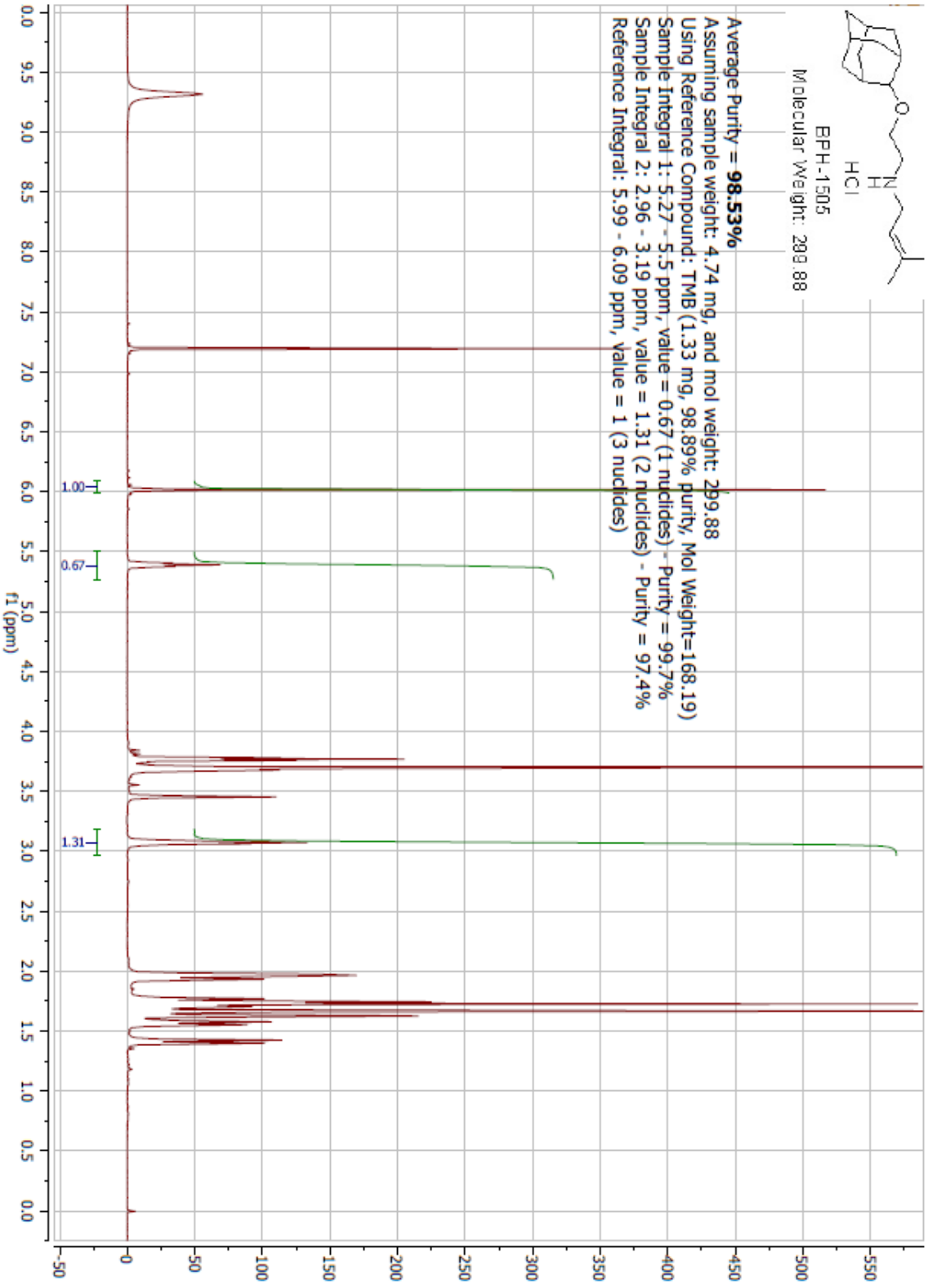


Figure S2. qNMR spectrum of compound **4**.

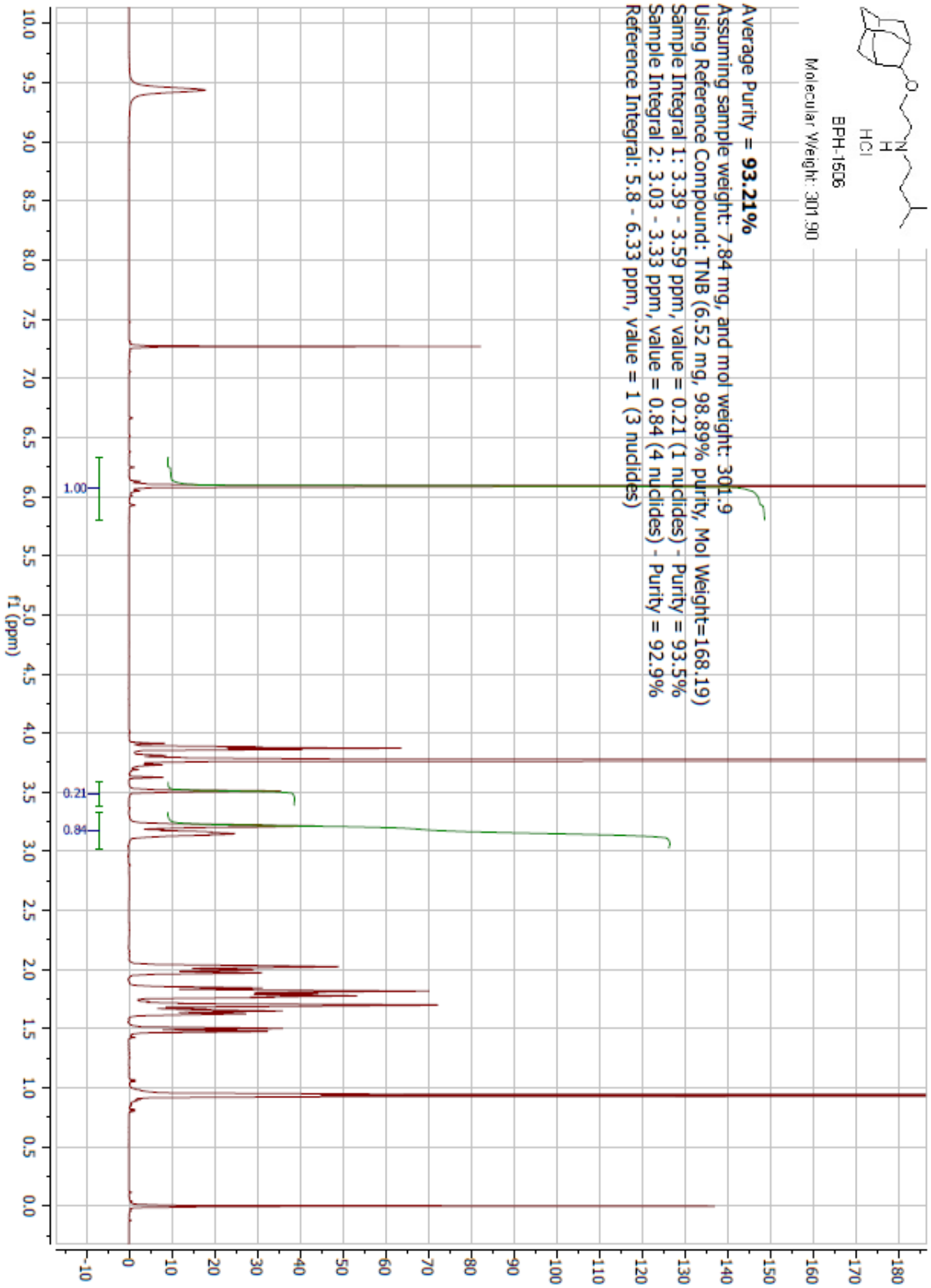


Figure S3. qNMR spectrum of compound **5**.

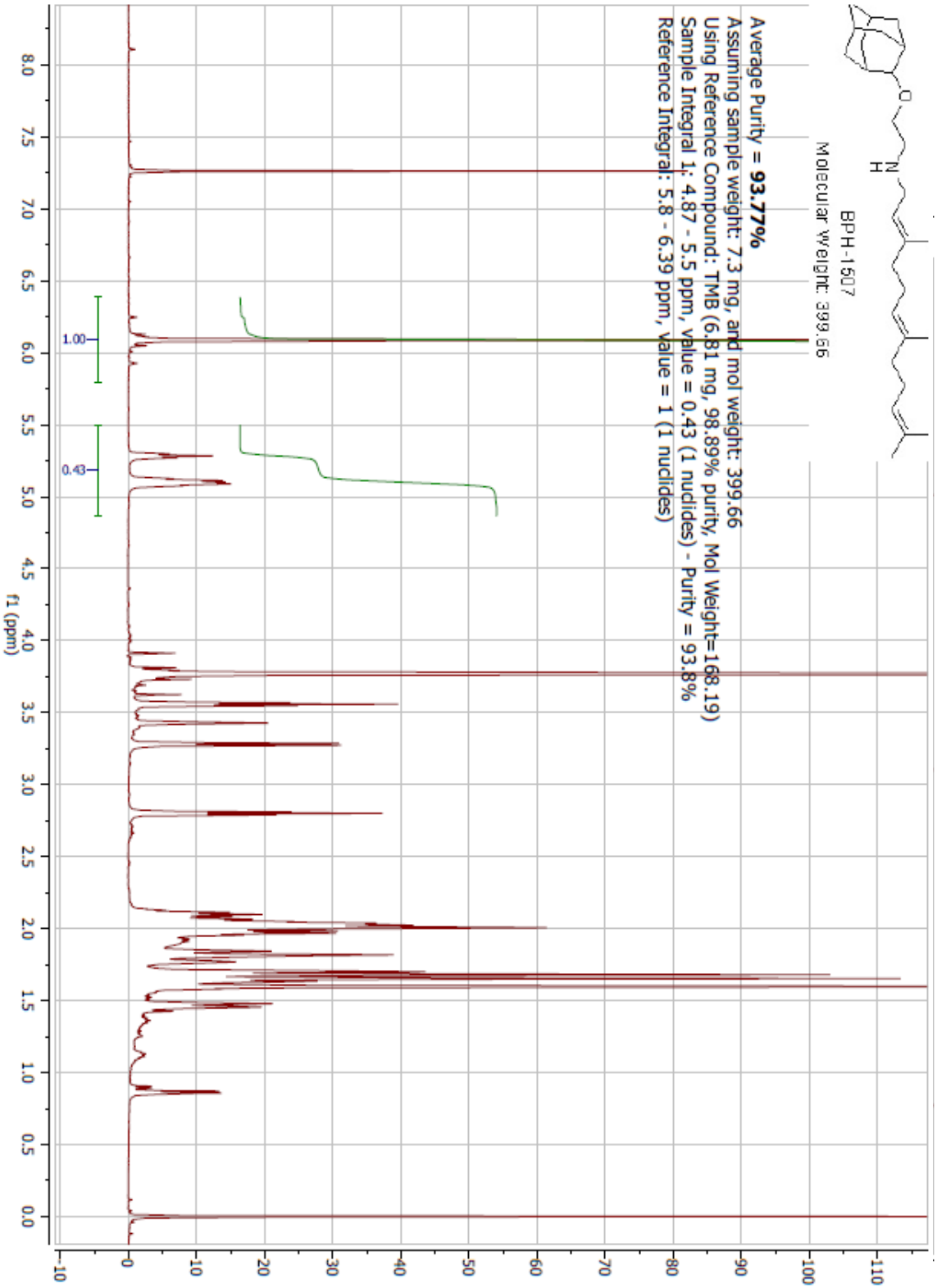


Figure S4. qNMR spectrum of compound **6**.

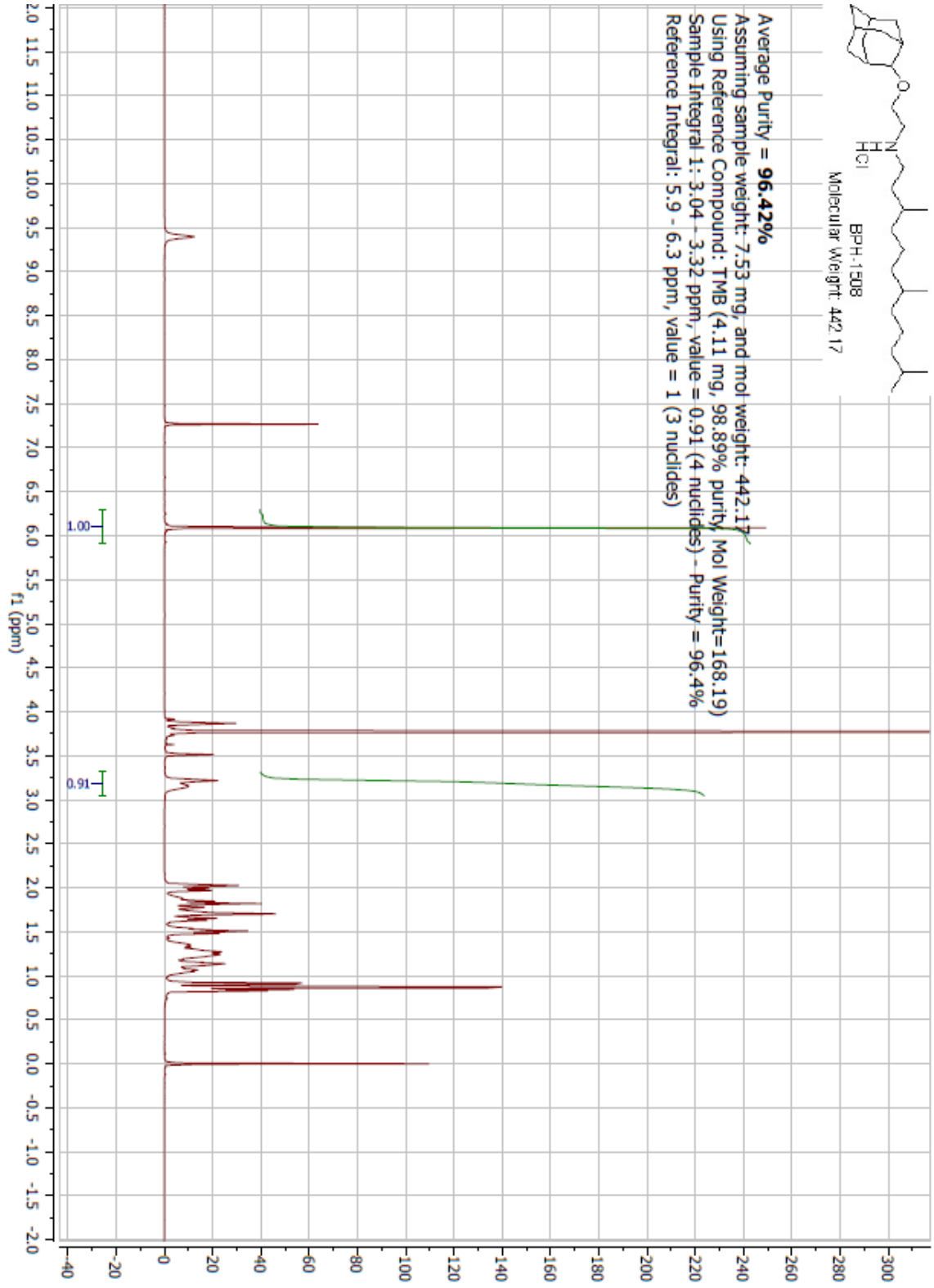


Figure S5. qNMR spectrum of compound **7**.

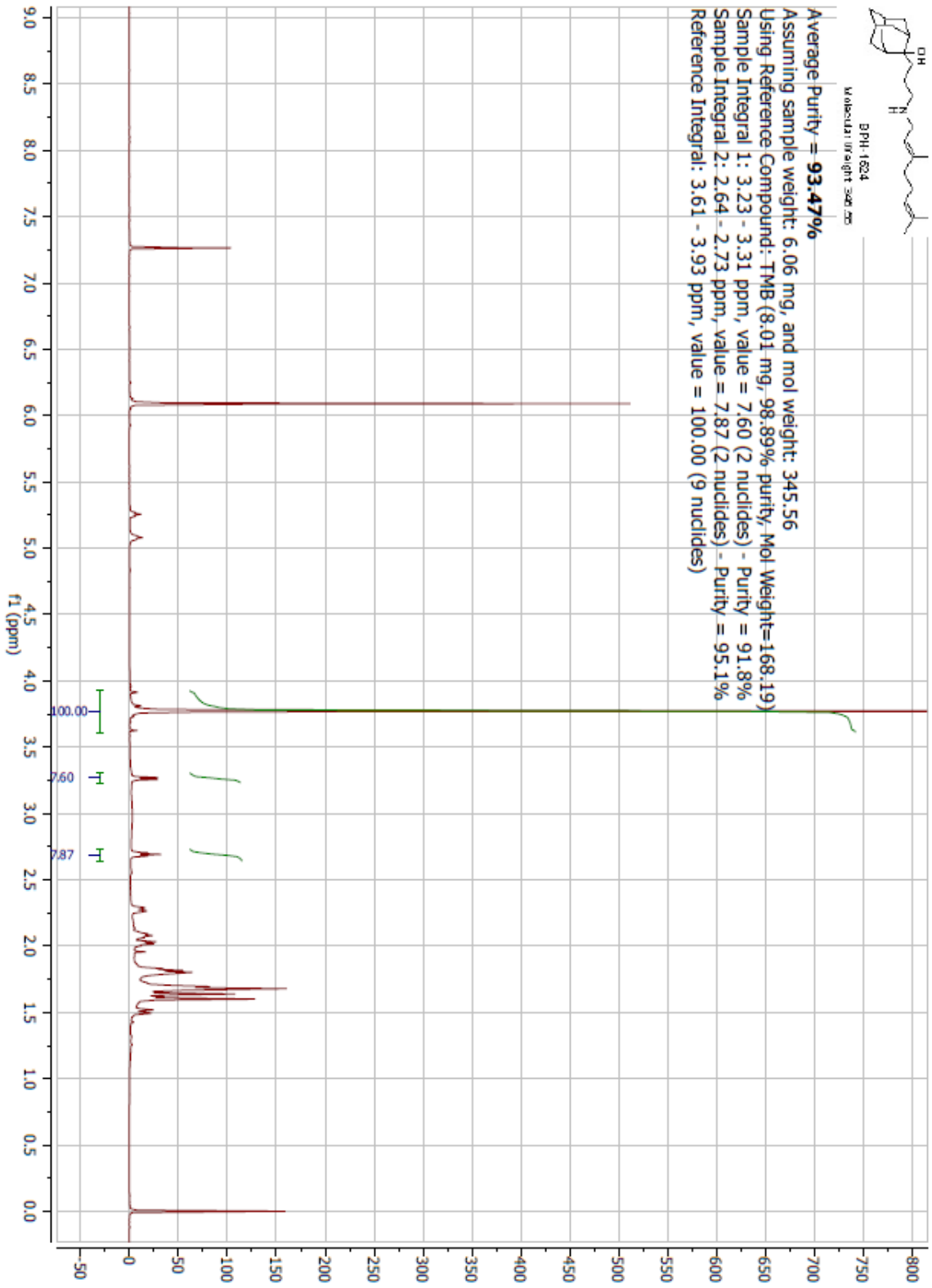


Figure S6. qNMR spectrum of compound **8.**

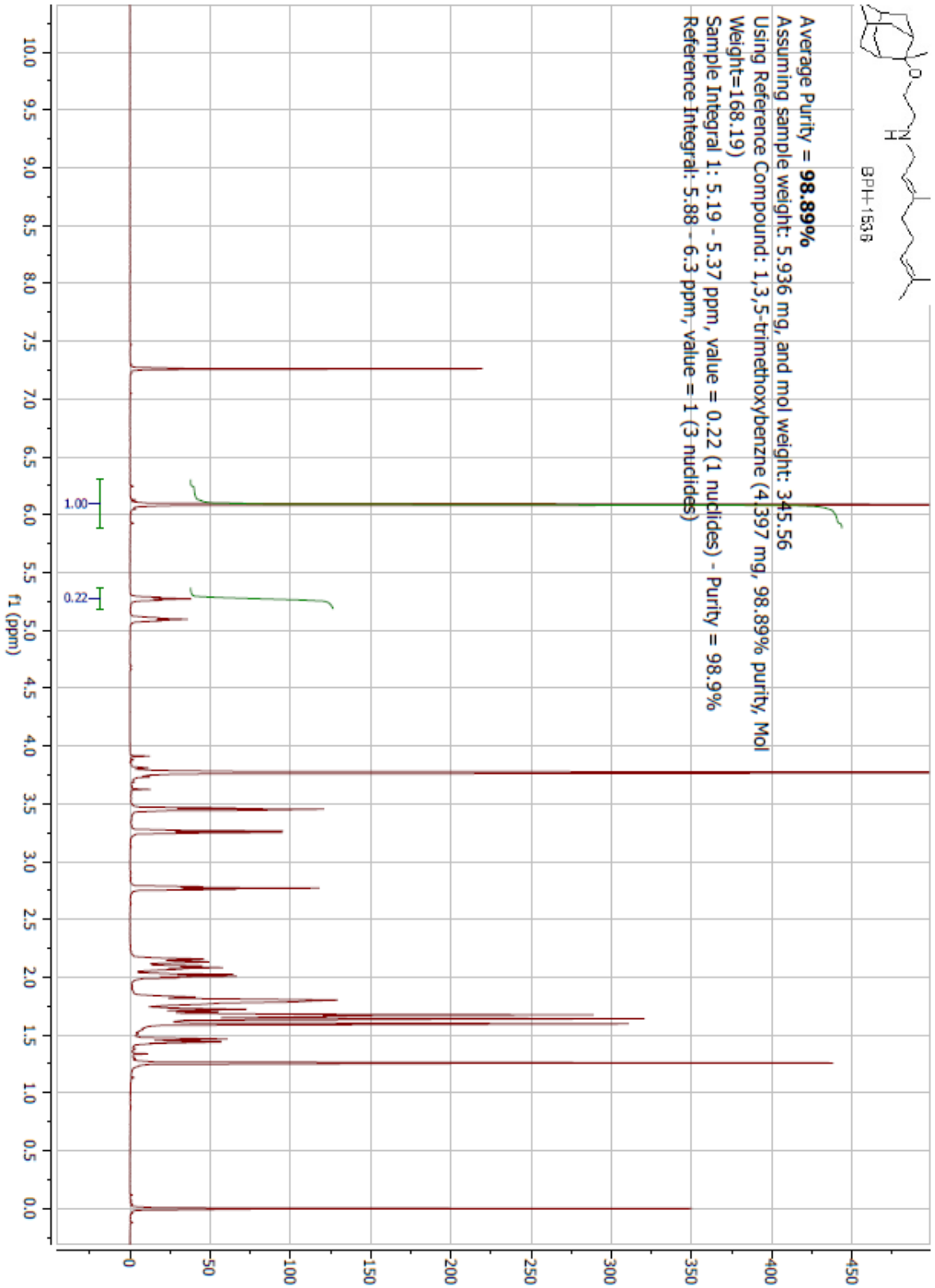


Figure S7. qNMR spectrum of compound **9.**

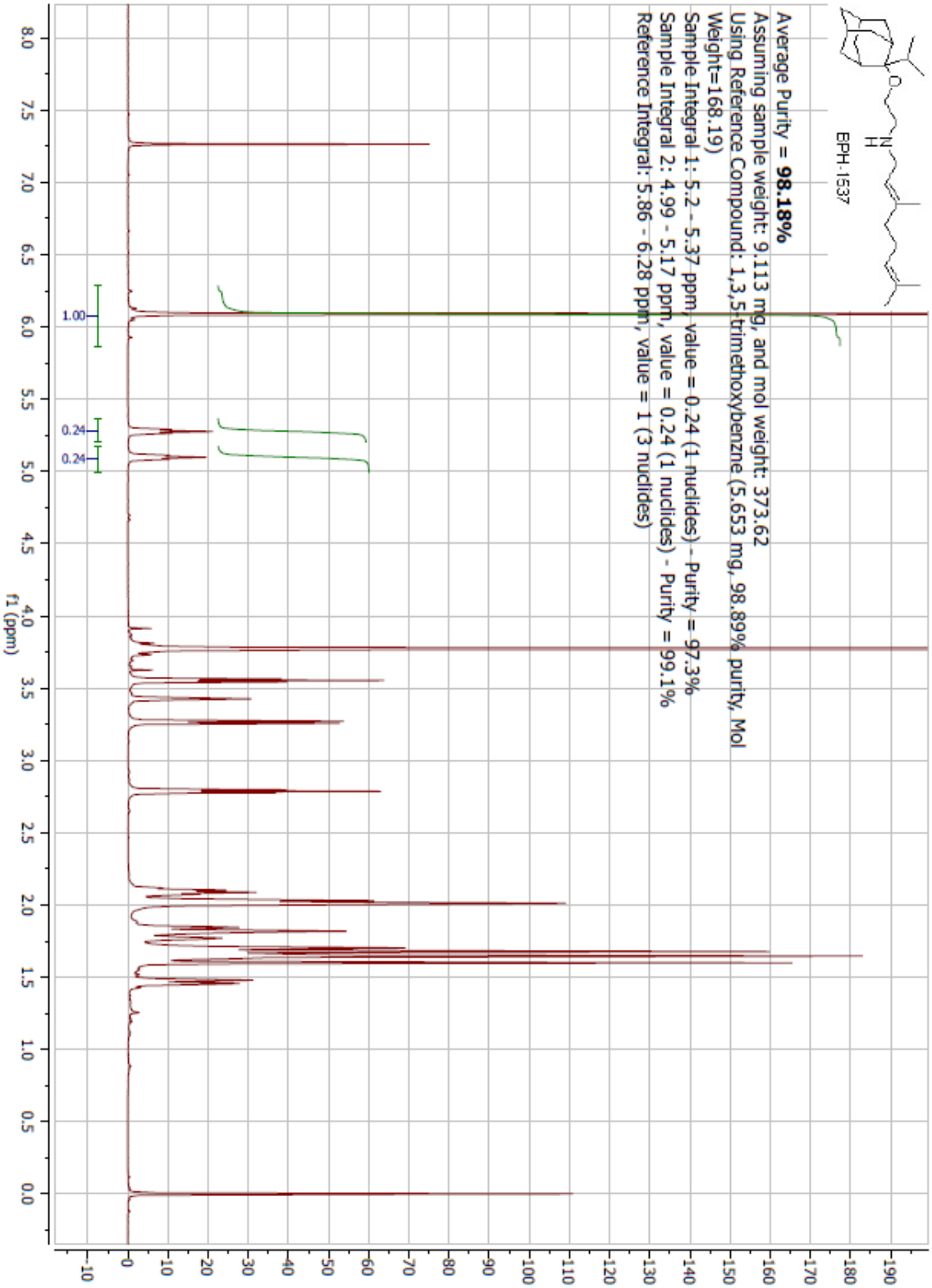


Figure S8. qNMR spectrum of compound **10.**

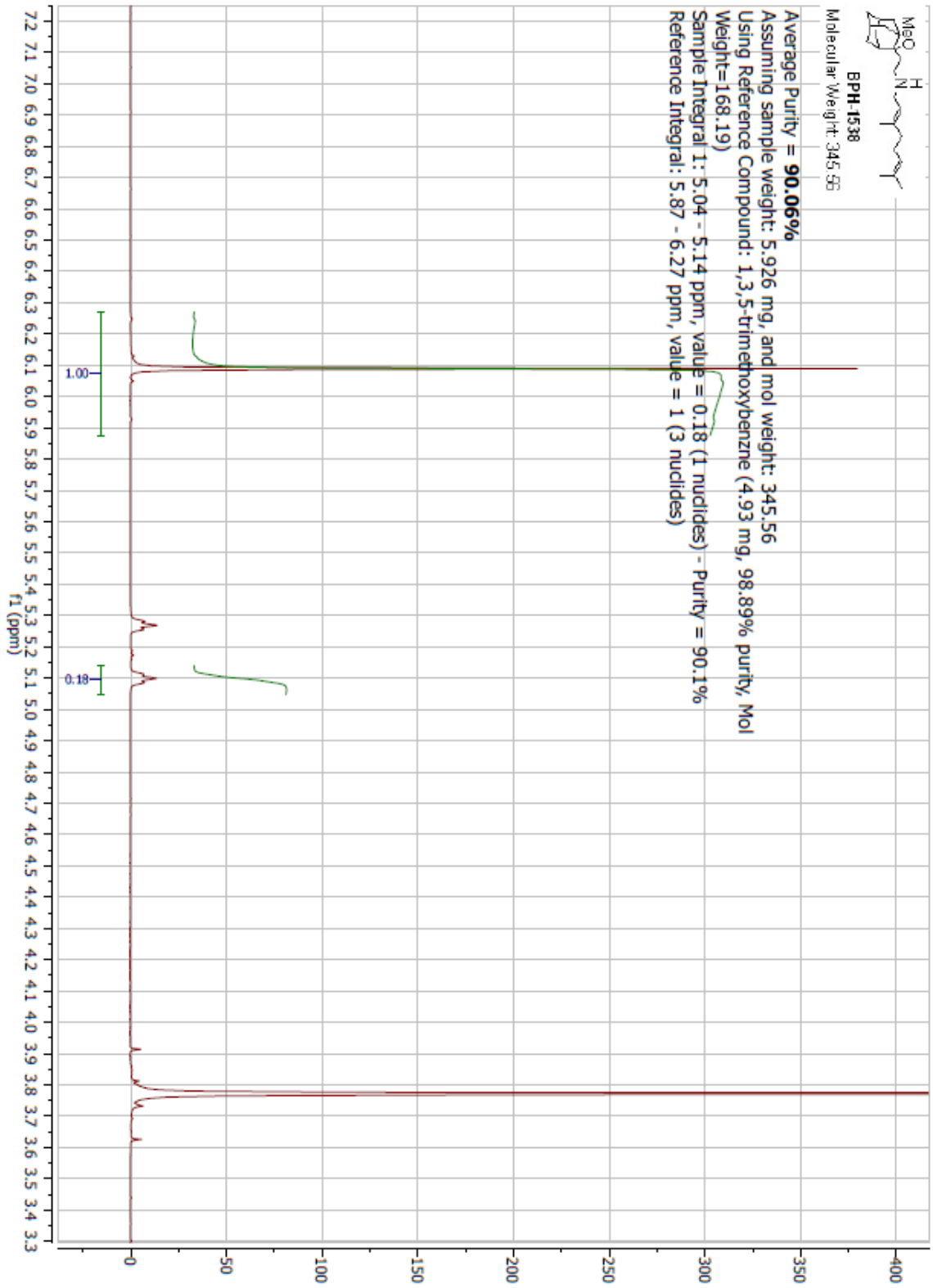


Figure S9. qNMR spectrum of compound **11**.

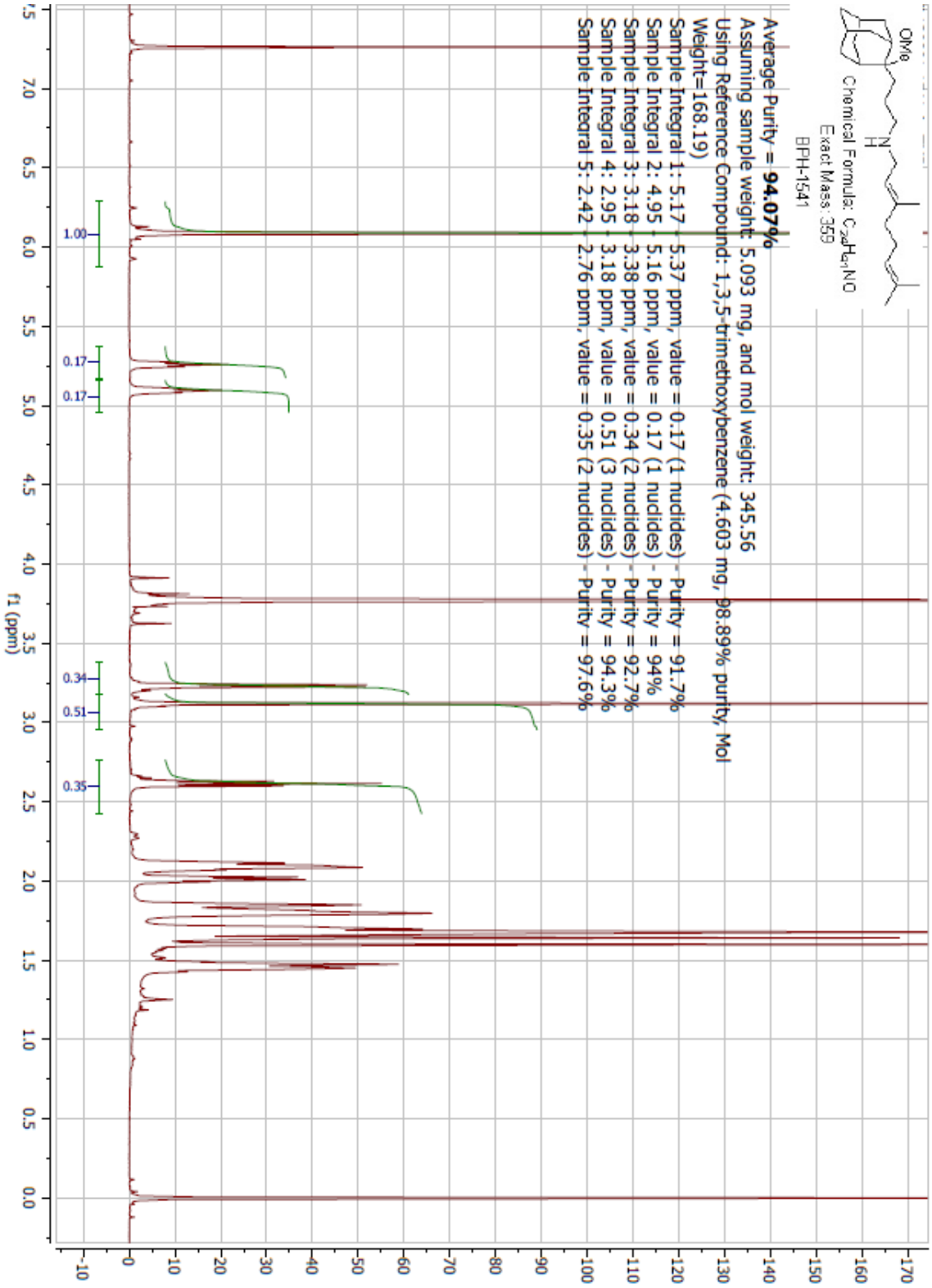


Figure S10. qNMR spectrum of compound **12**.

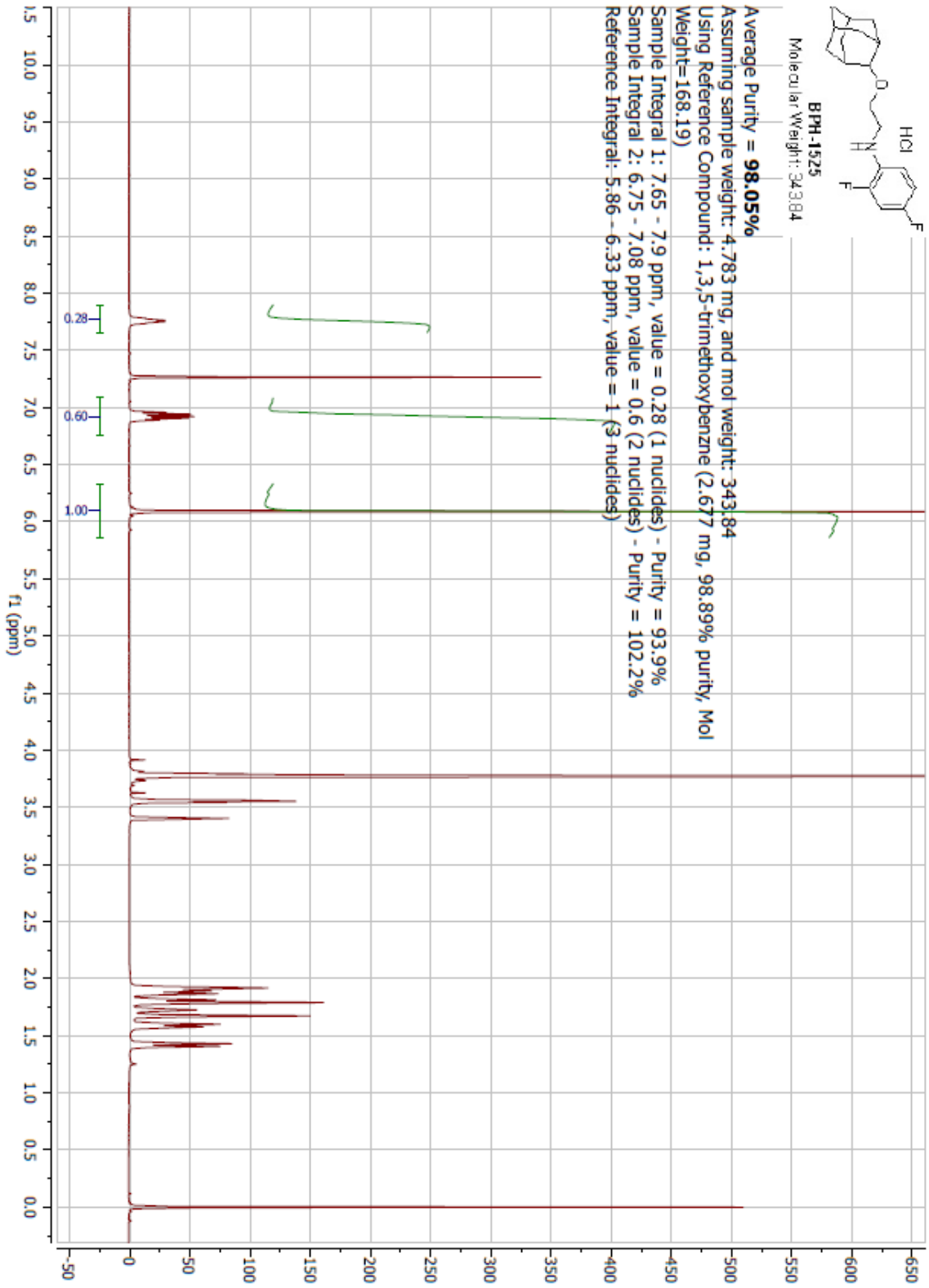


Figure S11. qNMR spectrum of compound **13**.

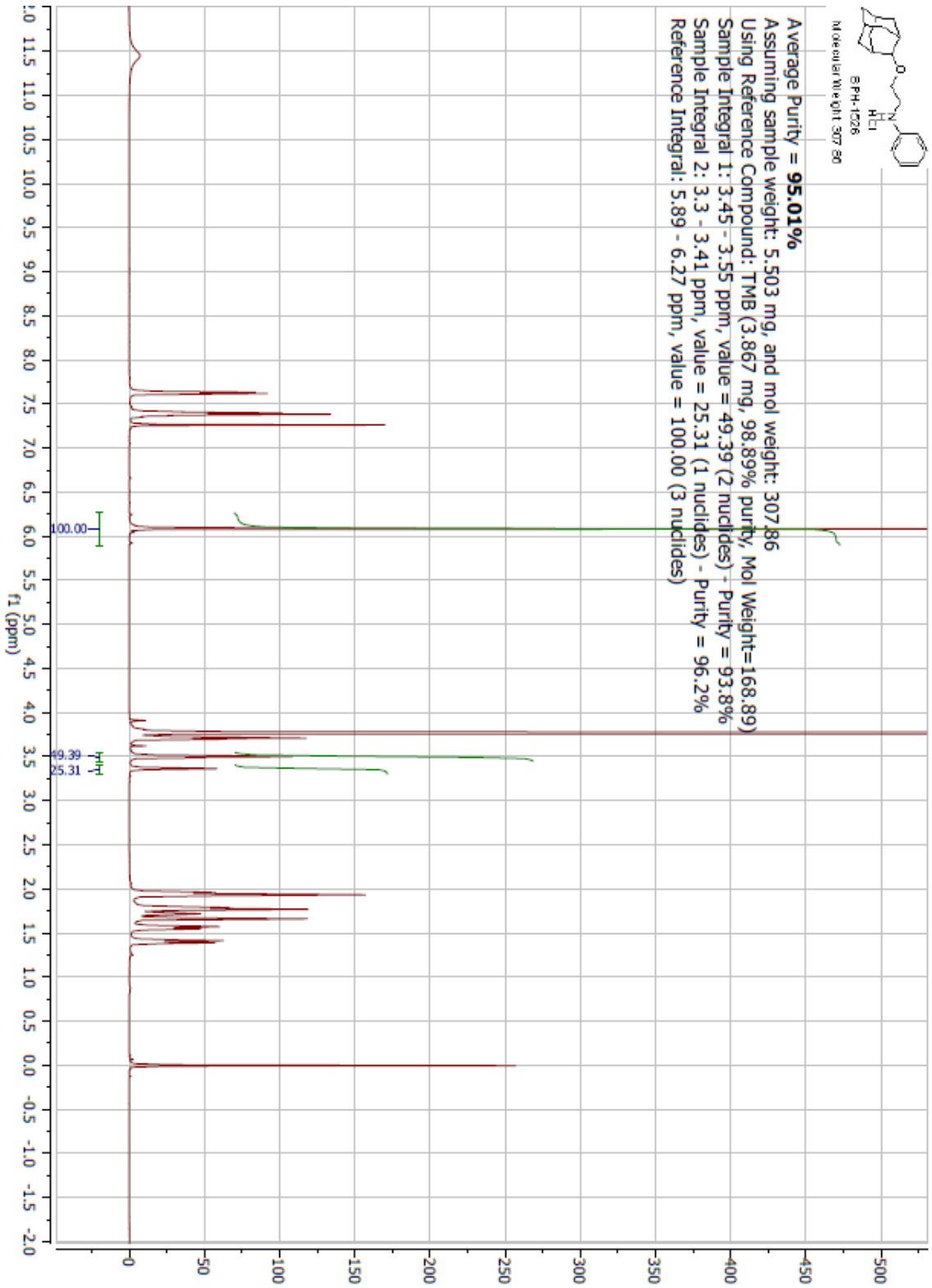


Figure S12. qNMR spectrum of compound **14**.

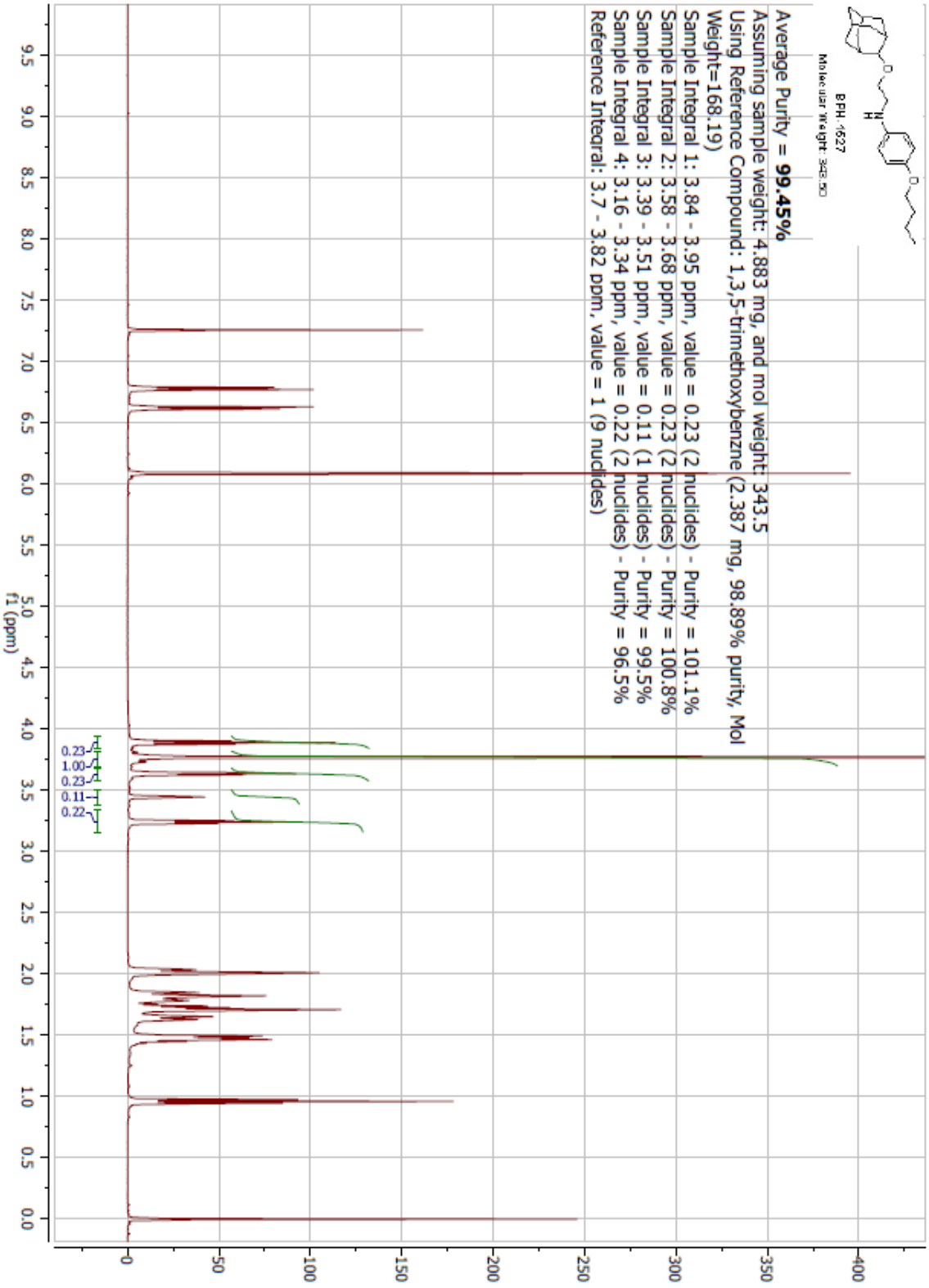


Figure S13. qNMR spectrum of compound **15**.

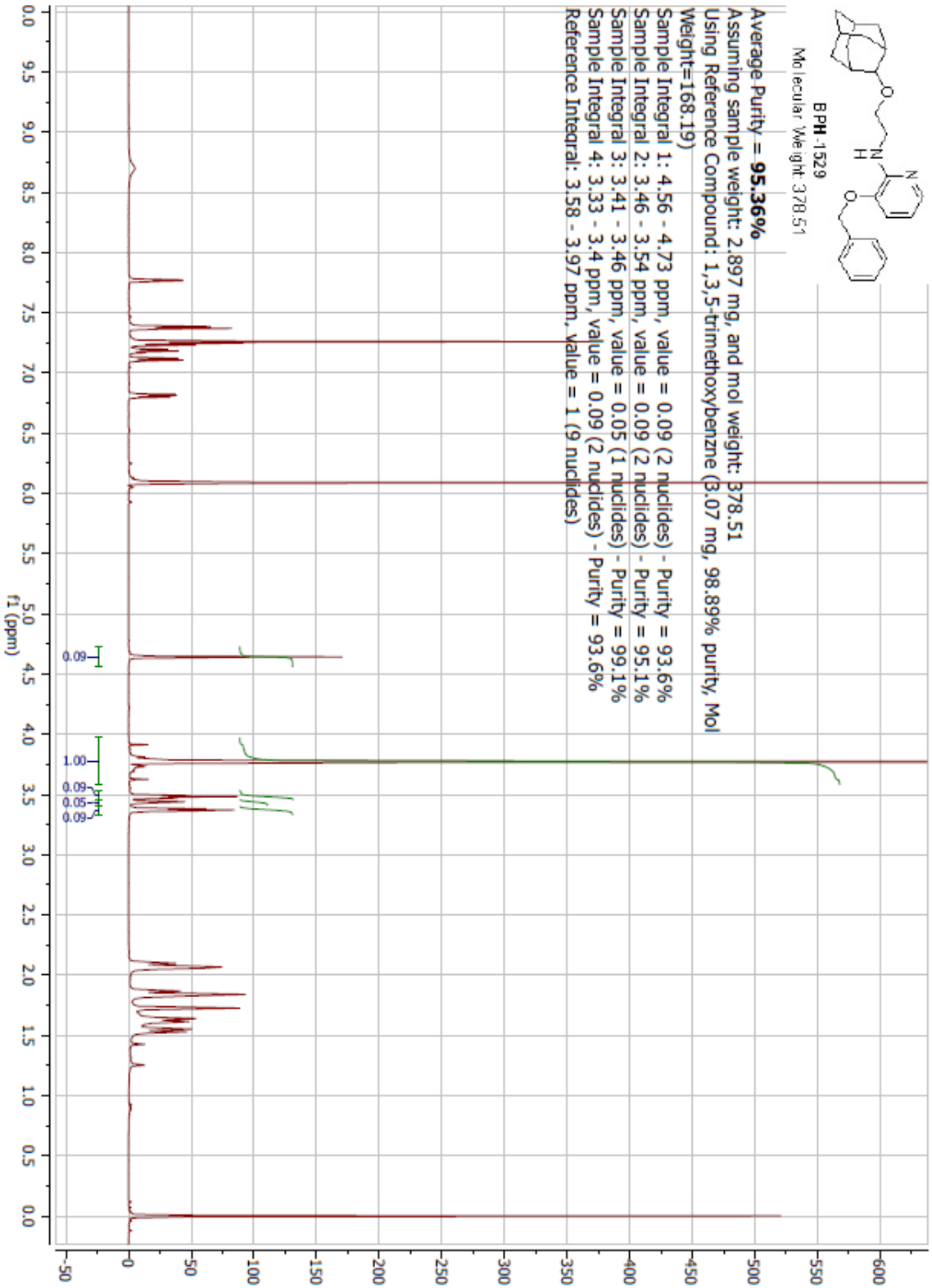


Figure S14. qNMR spectrum of compound **16**.

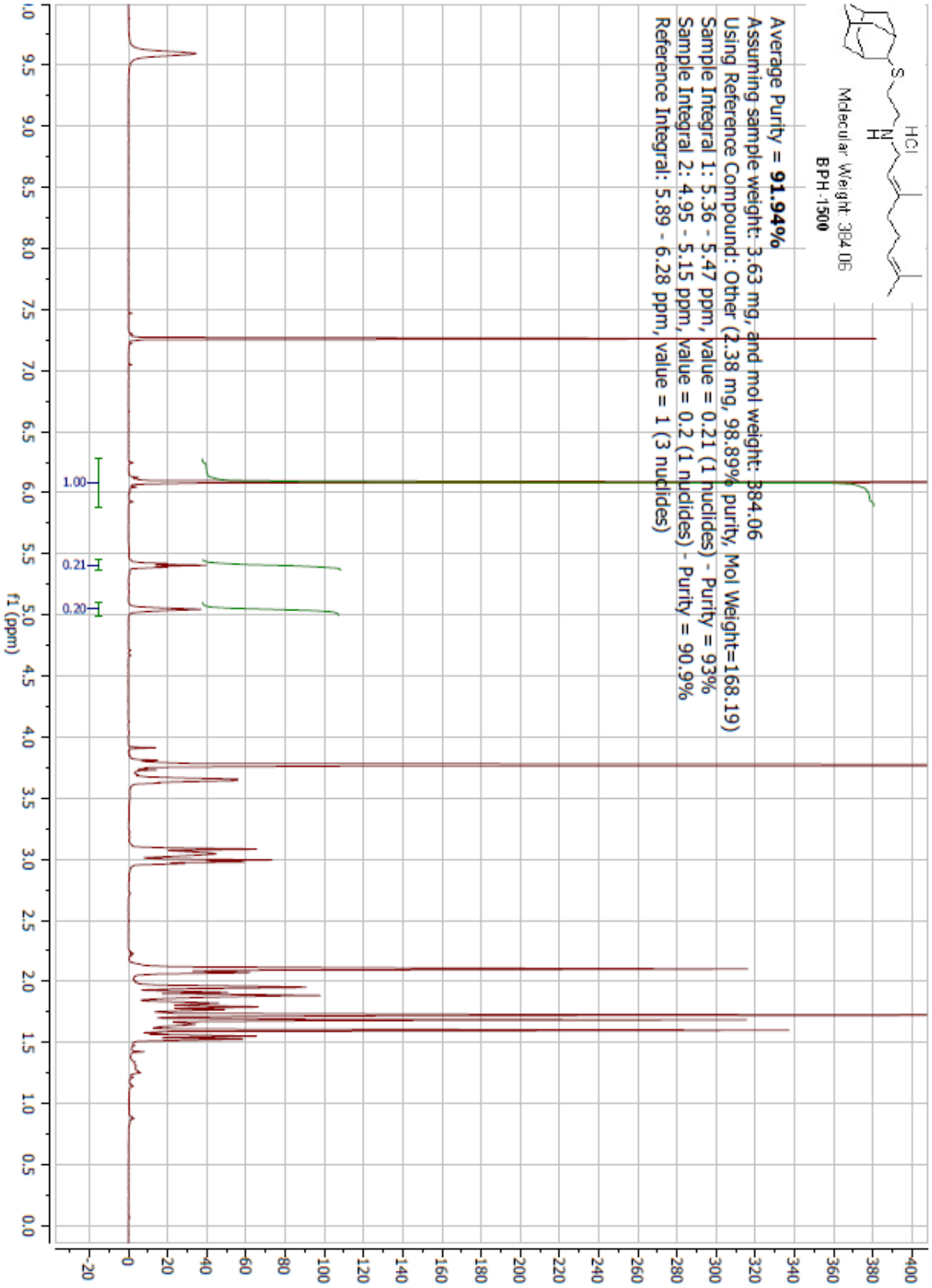


Figure S15. qNMR spectrum of compound **17**.

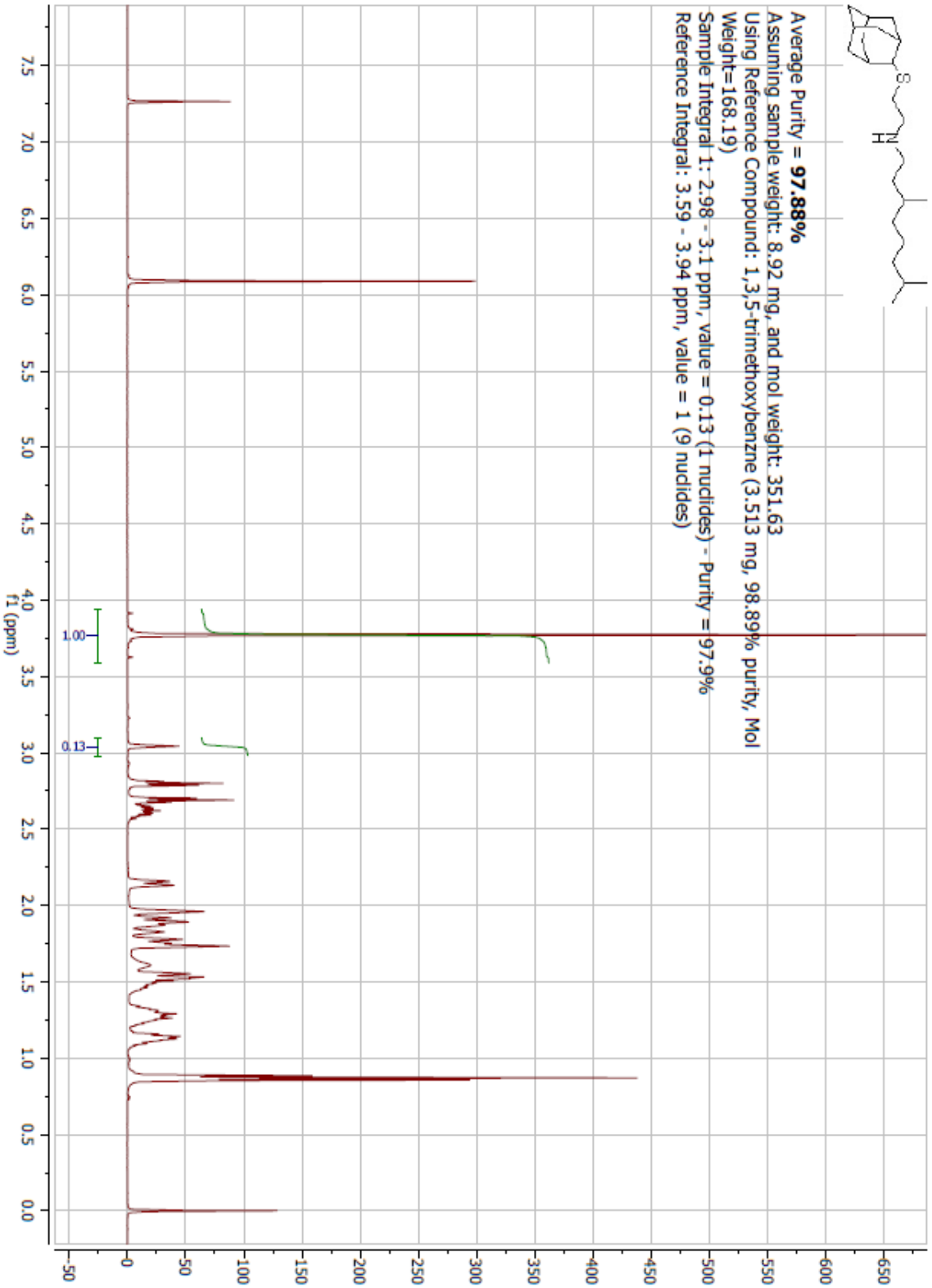


Figure S16. qNMR spectrum of compound **18**.

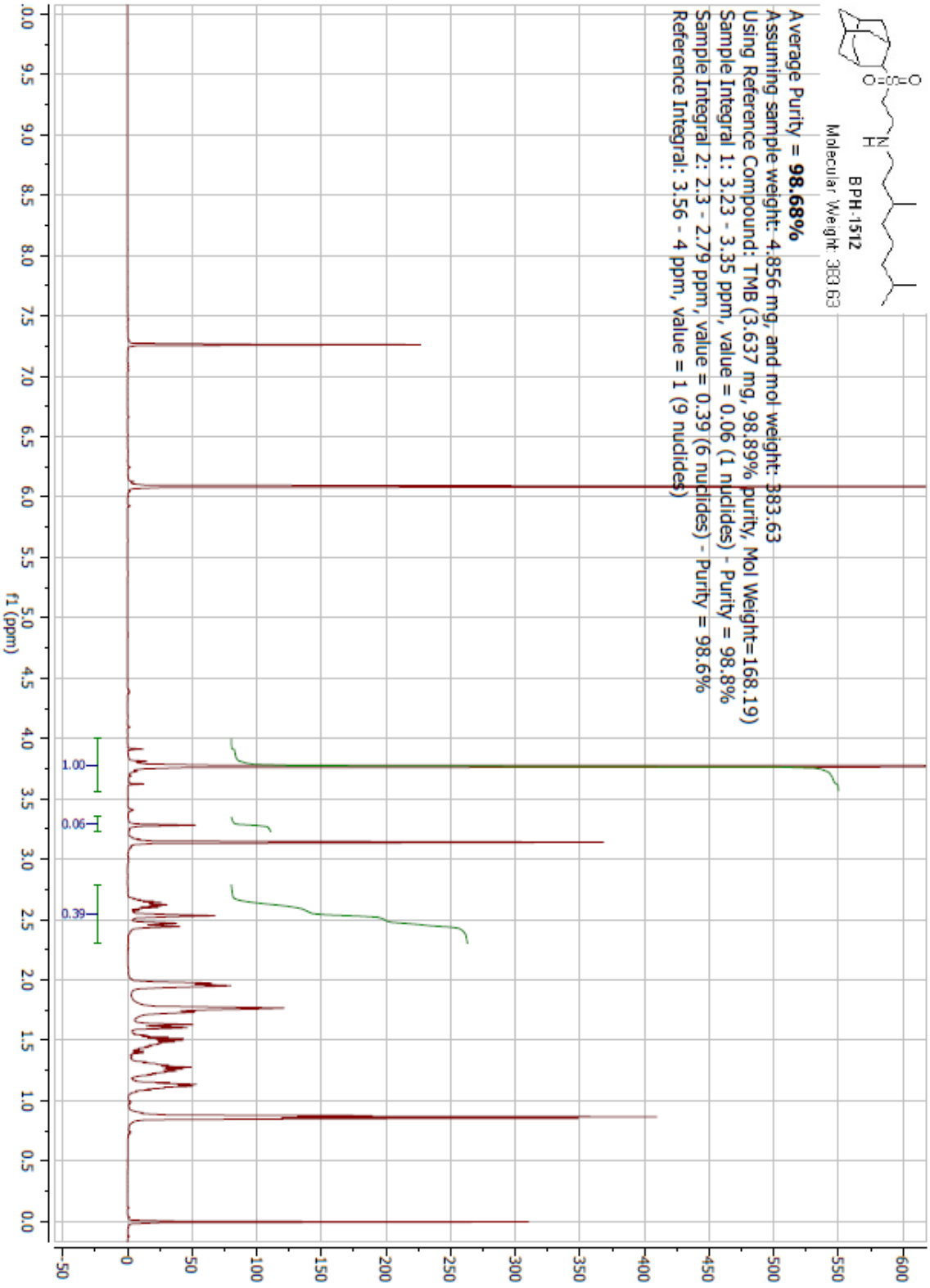


Figure S17. qNMR spectrum of compound **19**.

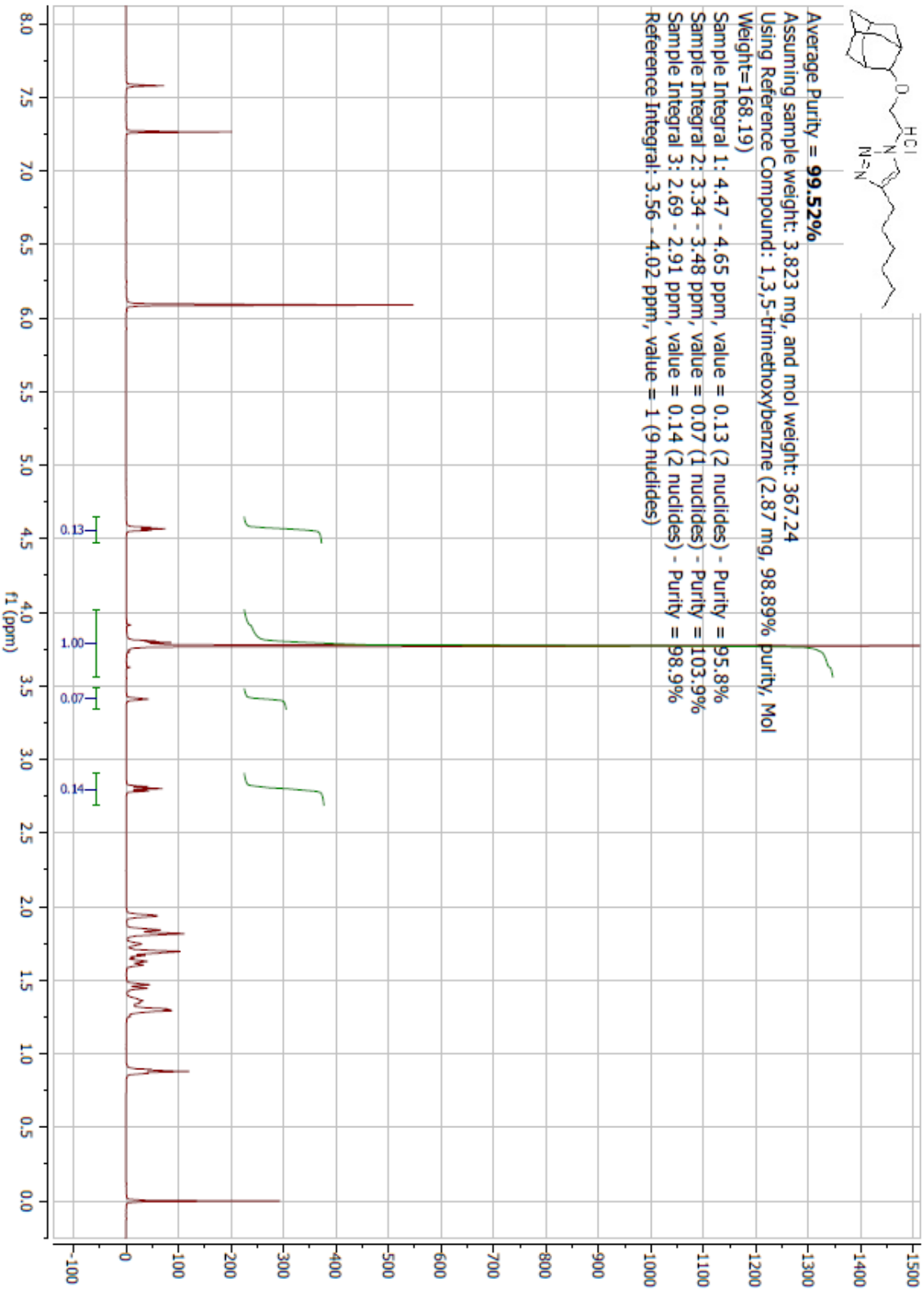


Figure S18. qNMR spectrum of compound **20**.

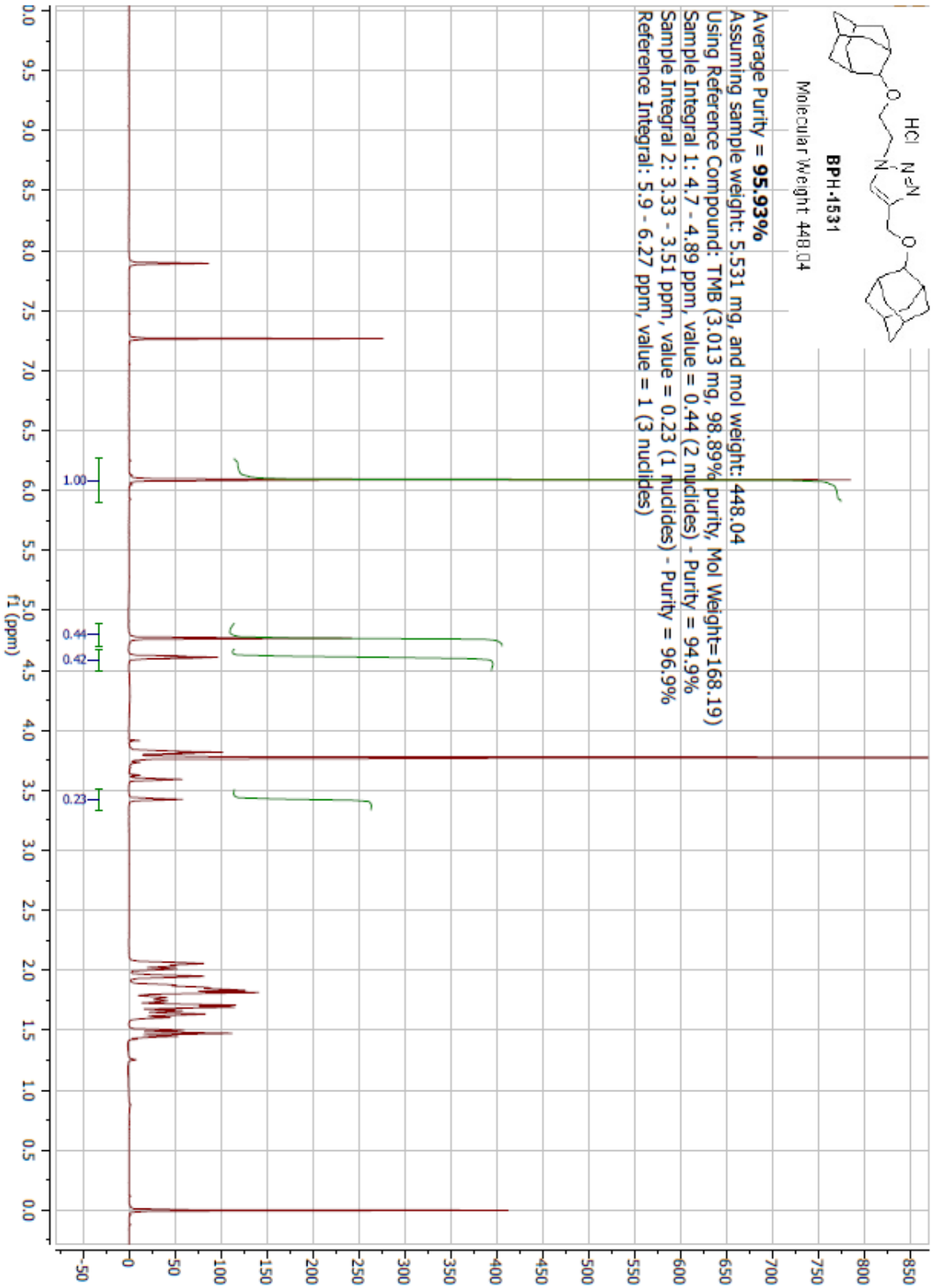


Figure S19. qNMR spectrum of compound **21**.

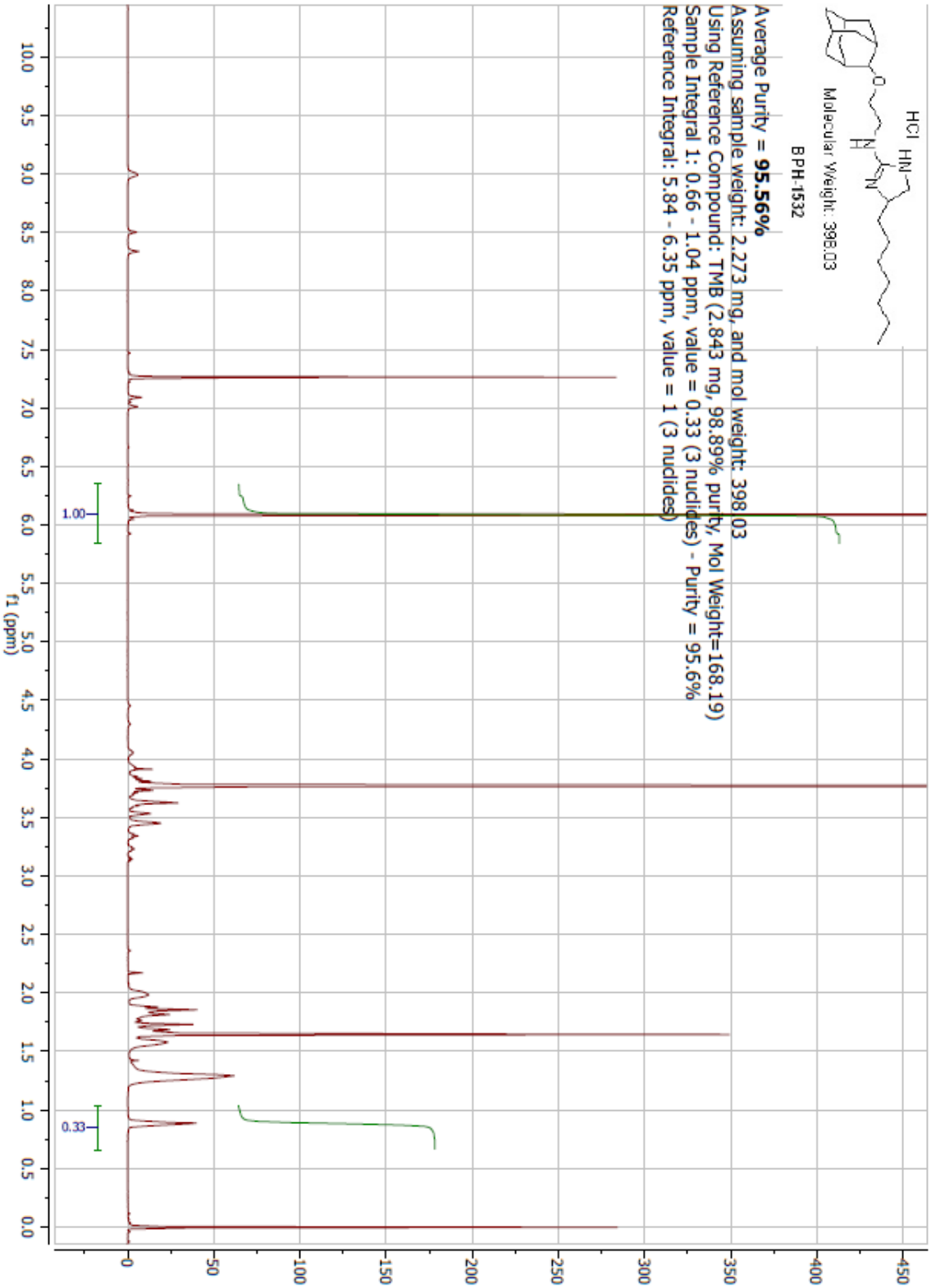


Figure S20. qNMR spectrum of compound **22.**

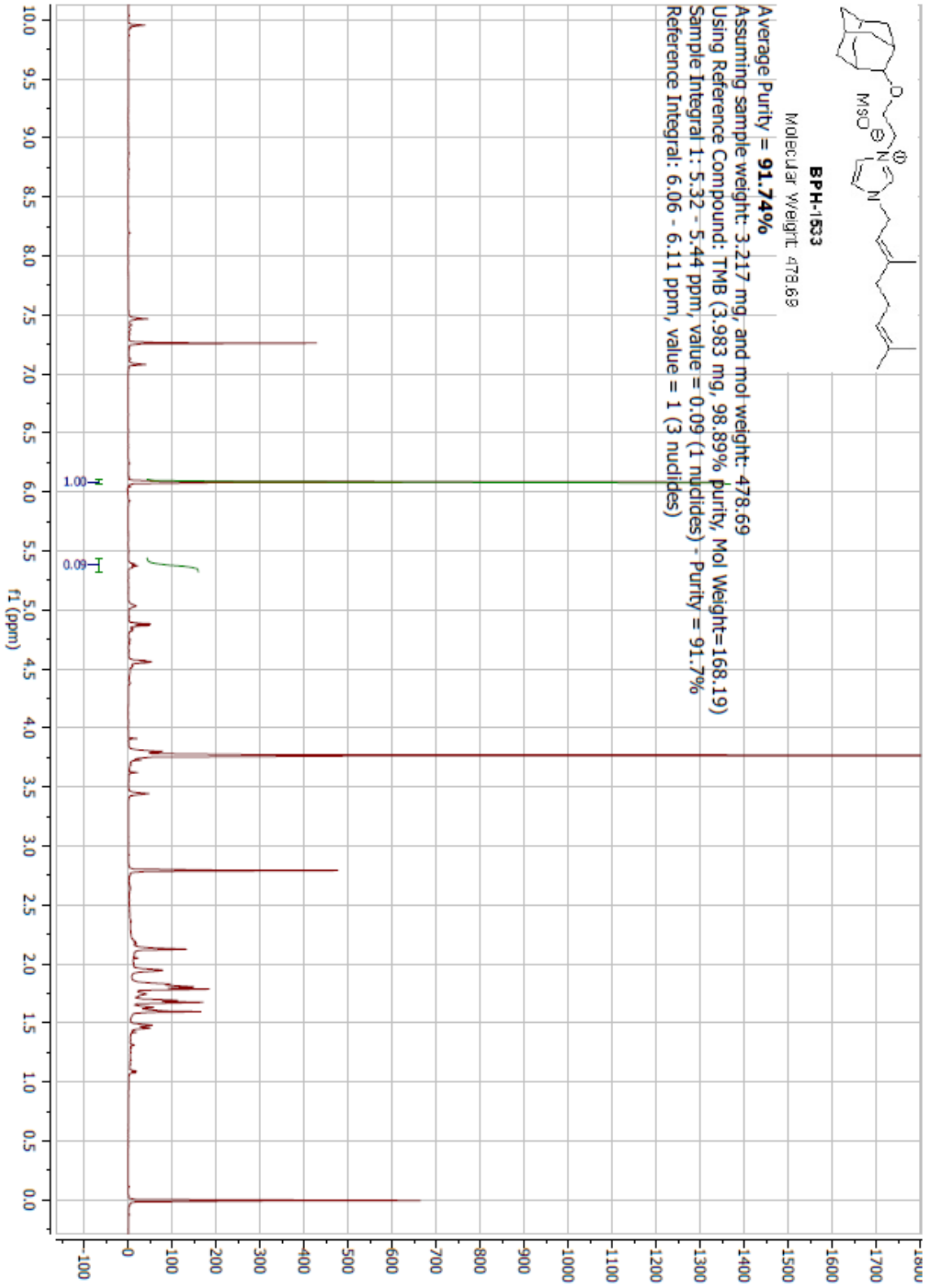


Figure S21. qNMR spectrum of compound **23**.

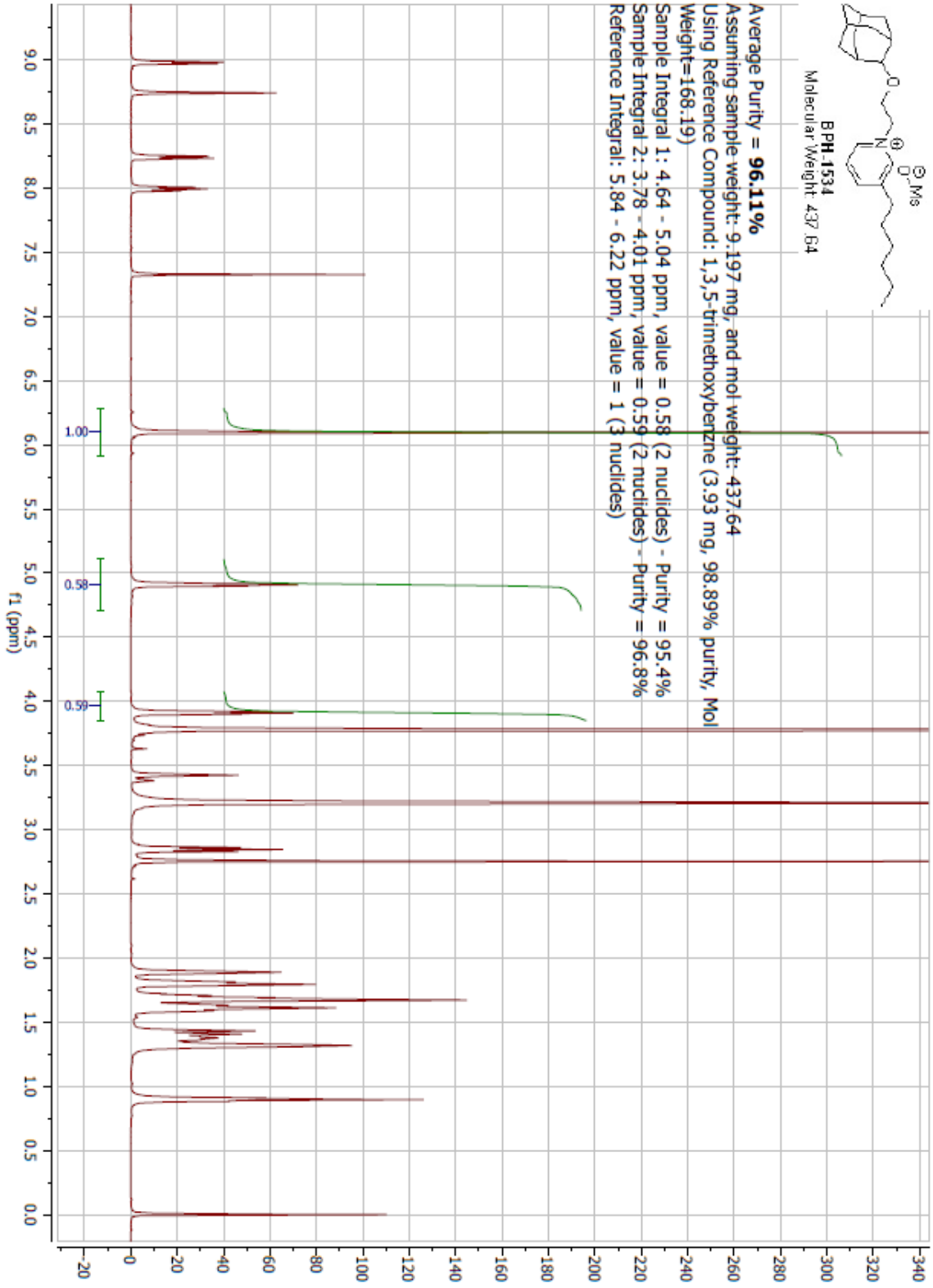


Figure S22. qNMR spectrum of compound **24**.

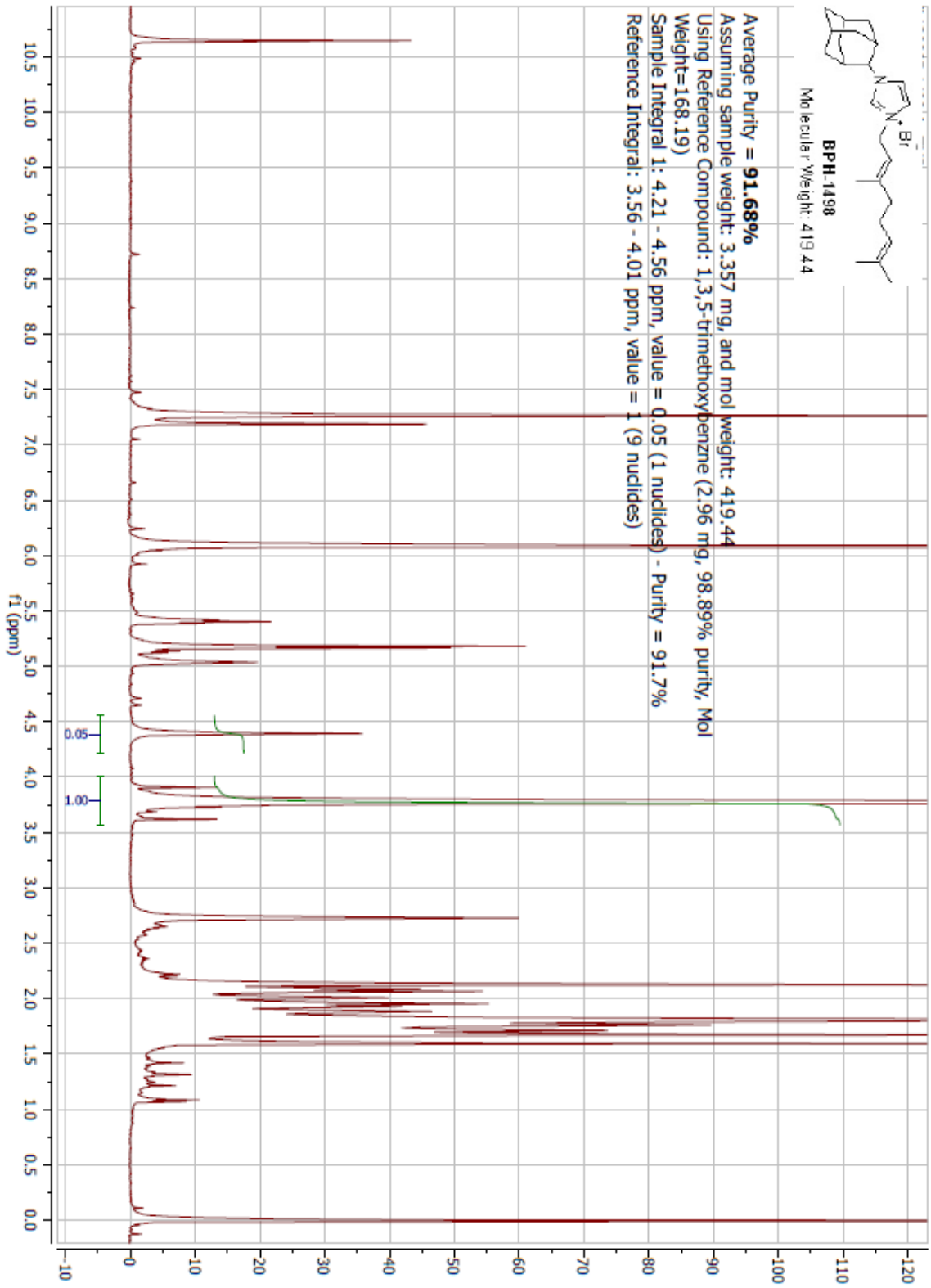


Figure S23. qNMR spectrum of compound **25**.

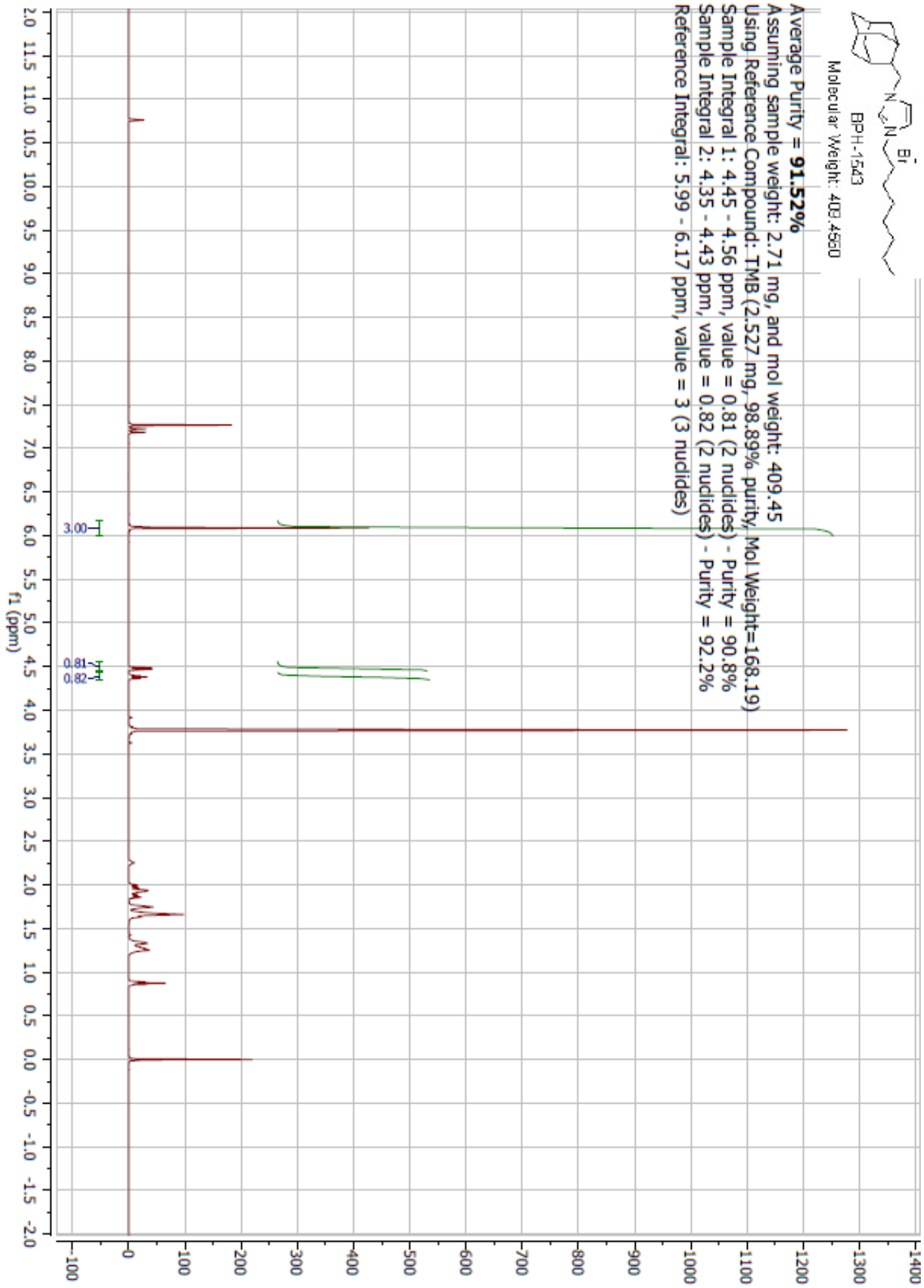


Figure S24. qNMR spectrum of compound **26**.

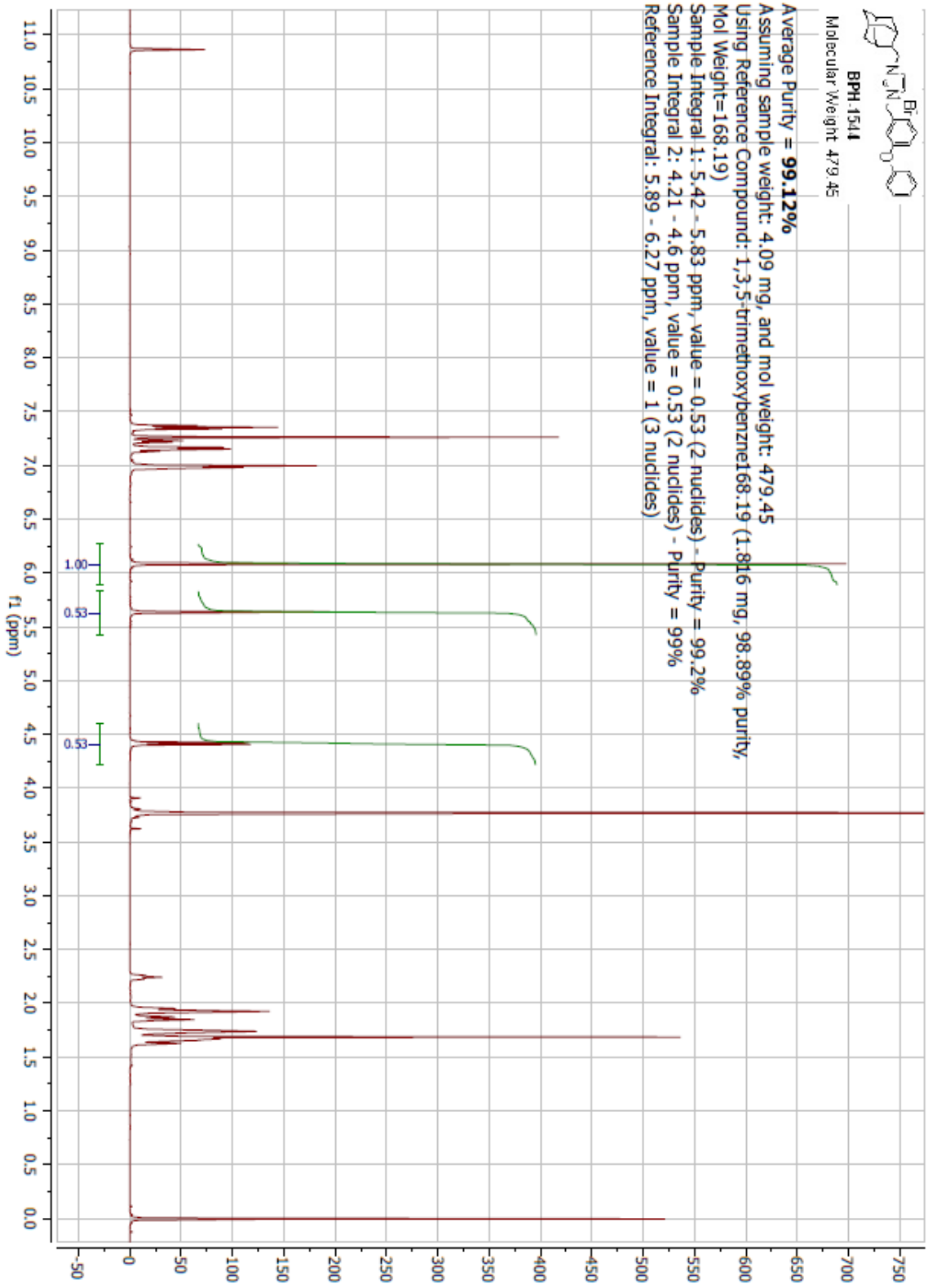


Figure S25. qNMR spectrum of compound **27**.

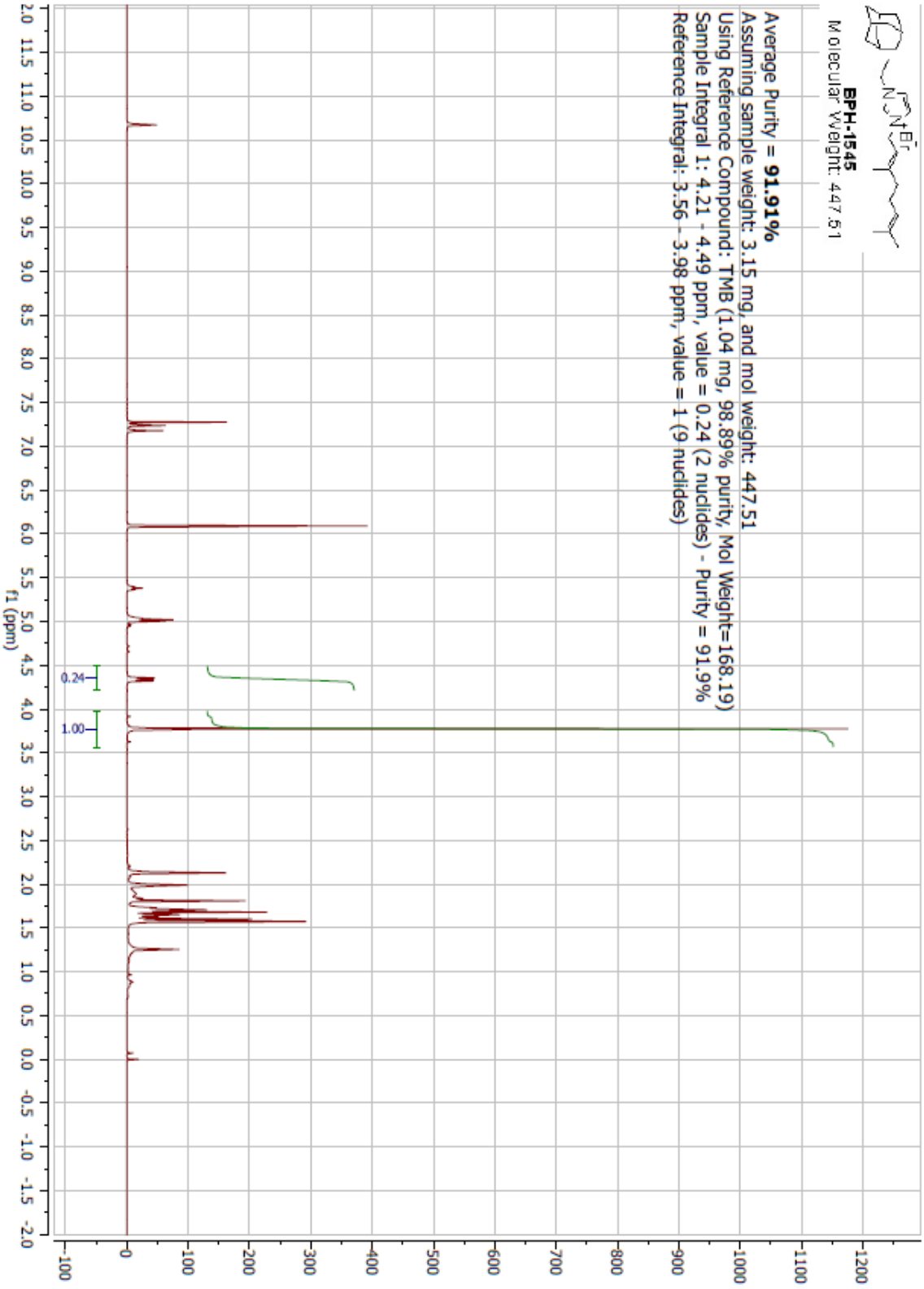


Figure S26. qNMR spectrum of compound **28**.

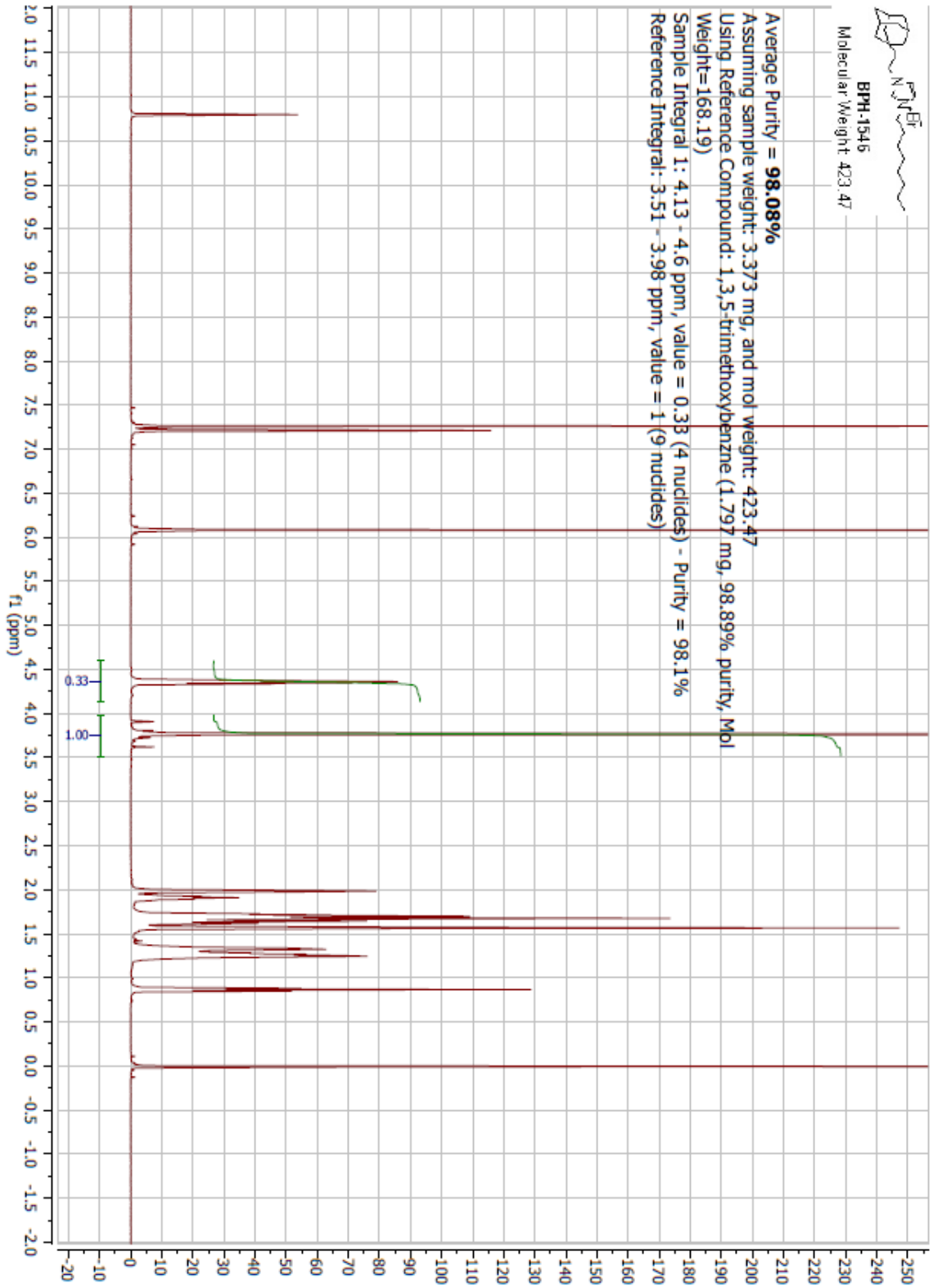


Figure S27. qNMR spectrum of compound **29**.

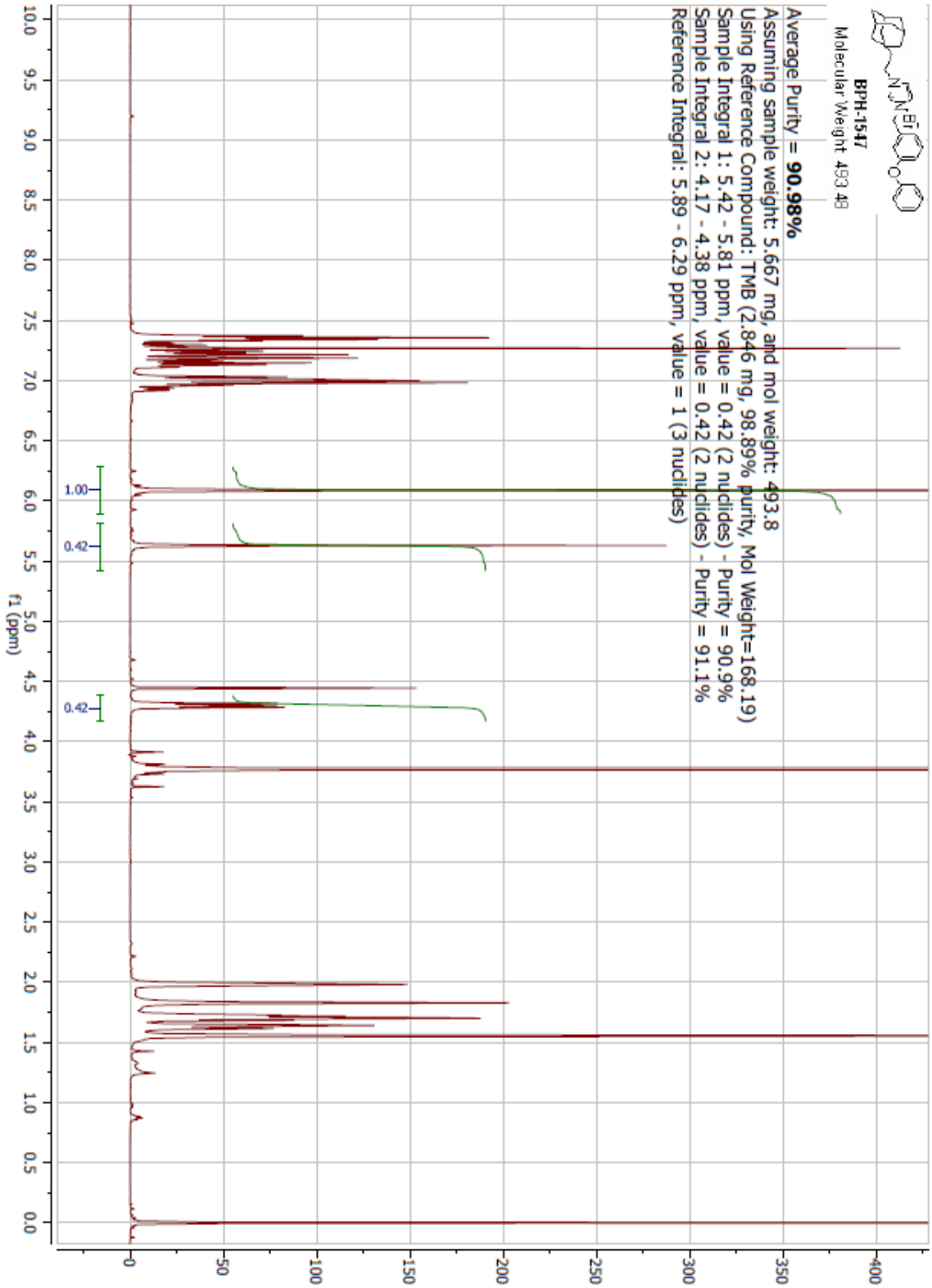


Figure S28. qNMR spectrum of compound **30**.

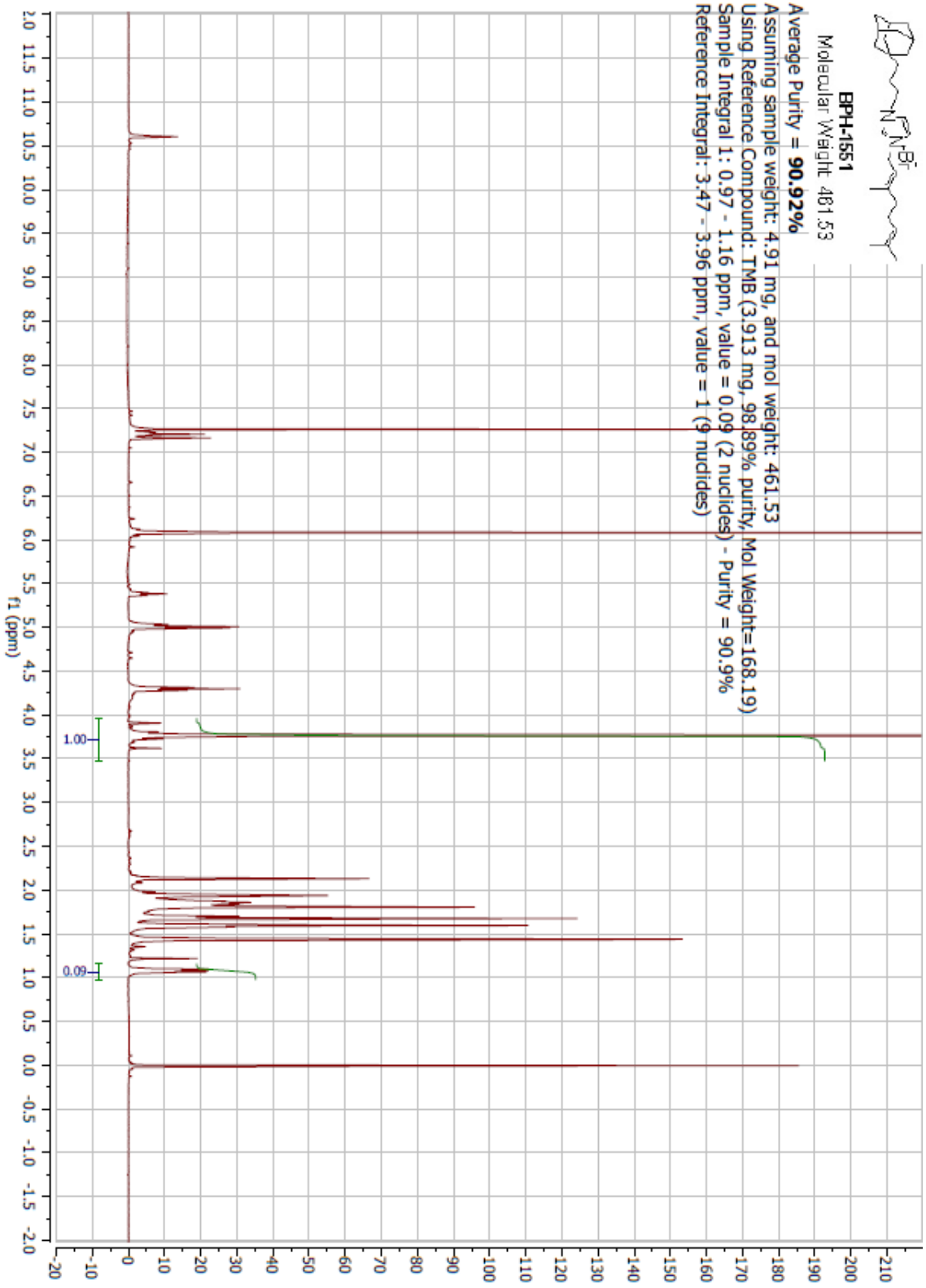


Figure S29. qNMR spectrum of compound **31**.

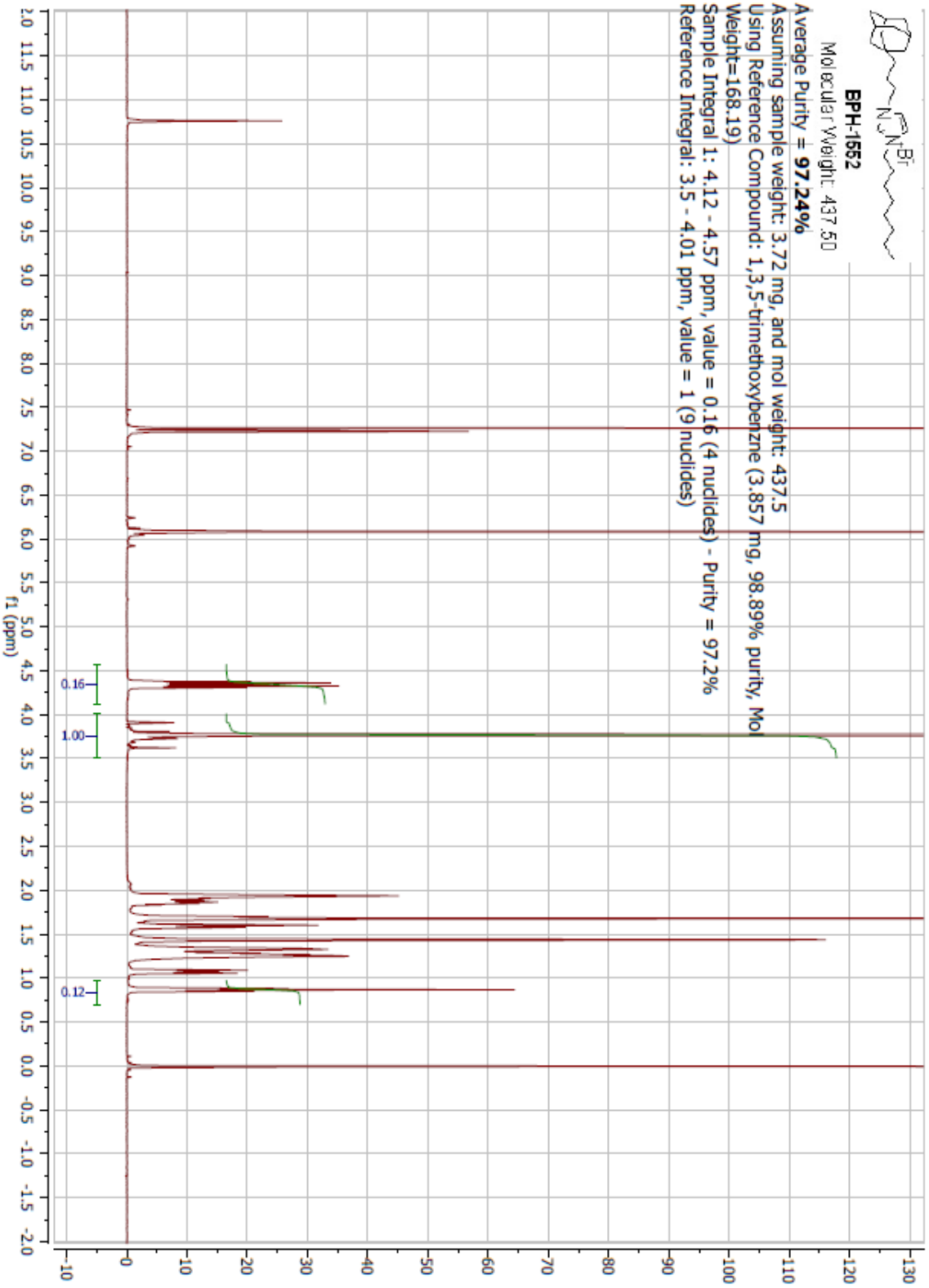


Figure S30. qNMR spectrum of compound **32.**

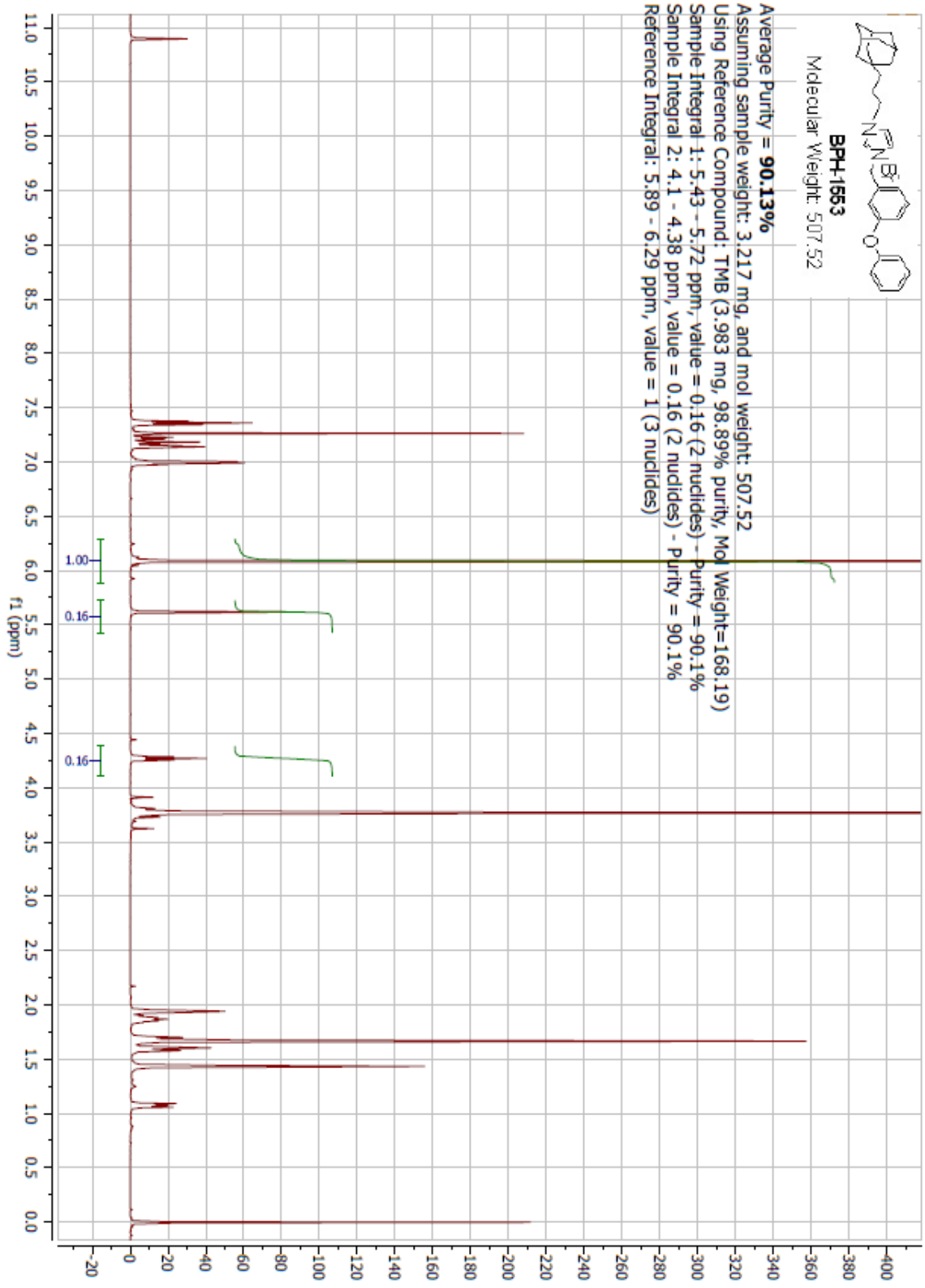


Figure S31. qNMR spectrum of compound **33**.

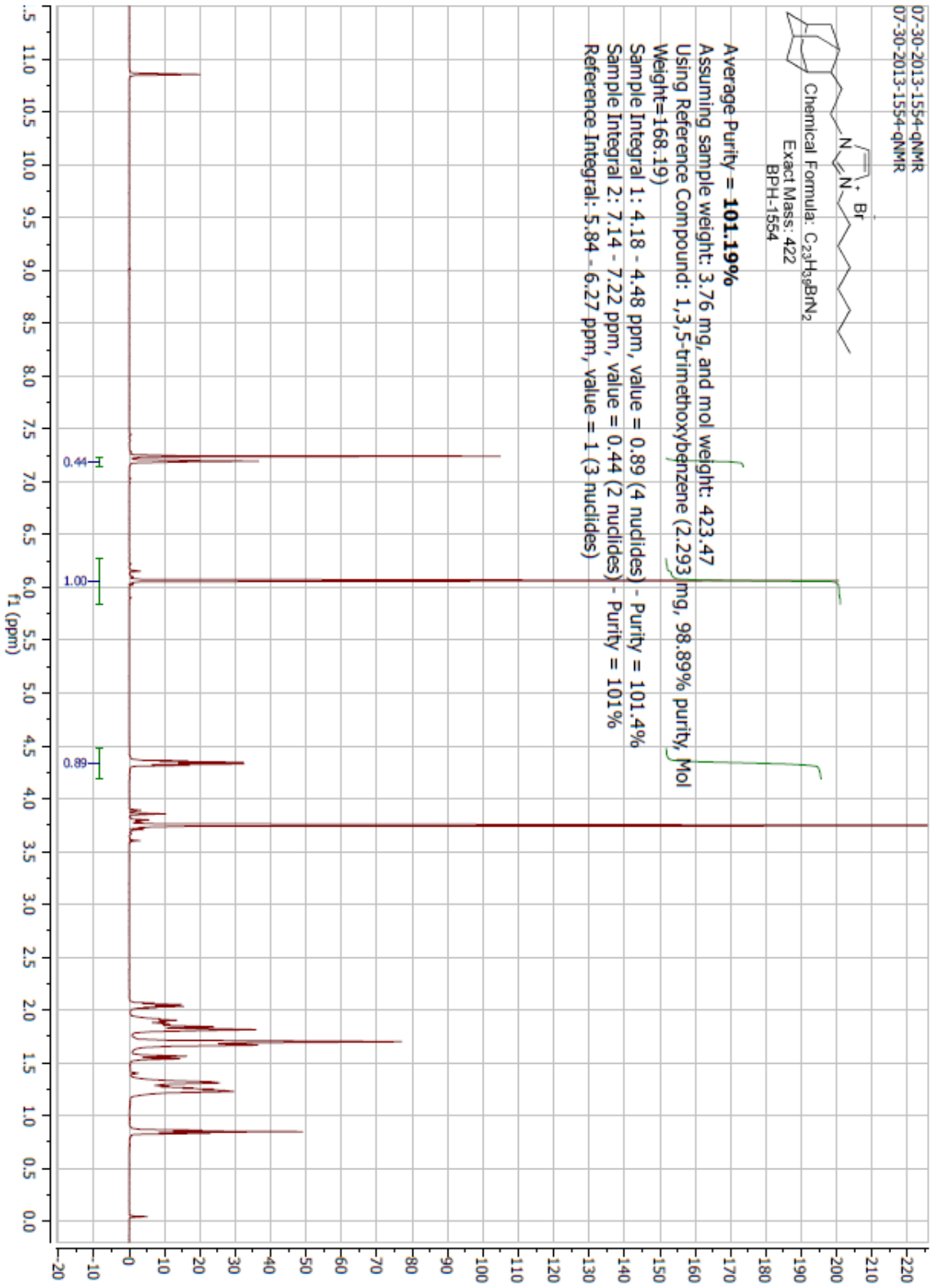


Figure S32. qNMR spectrum of compound **34**.

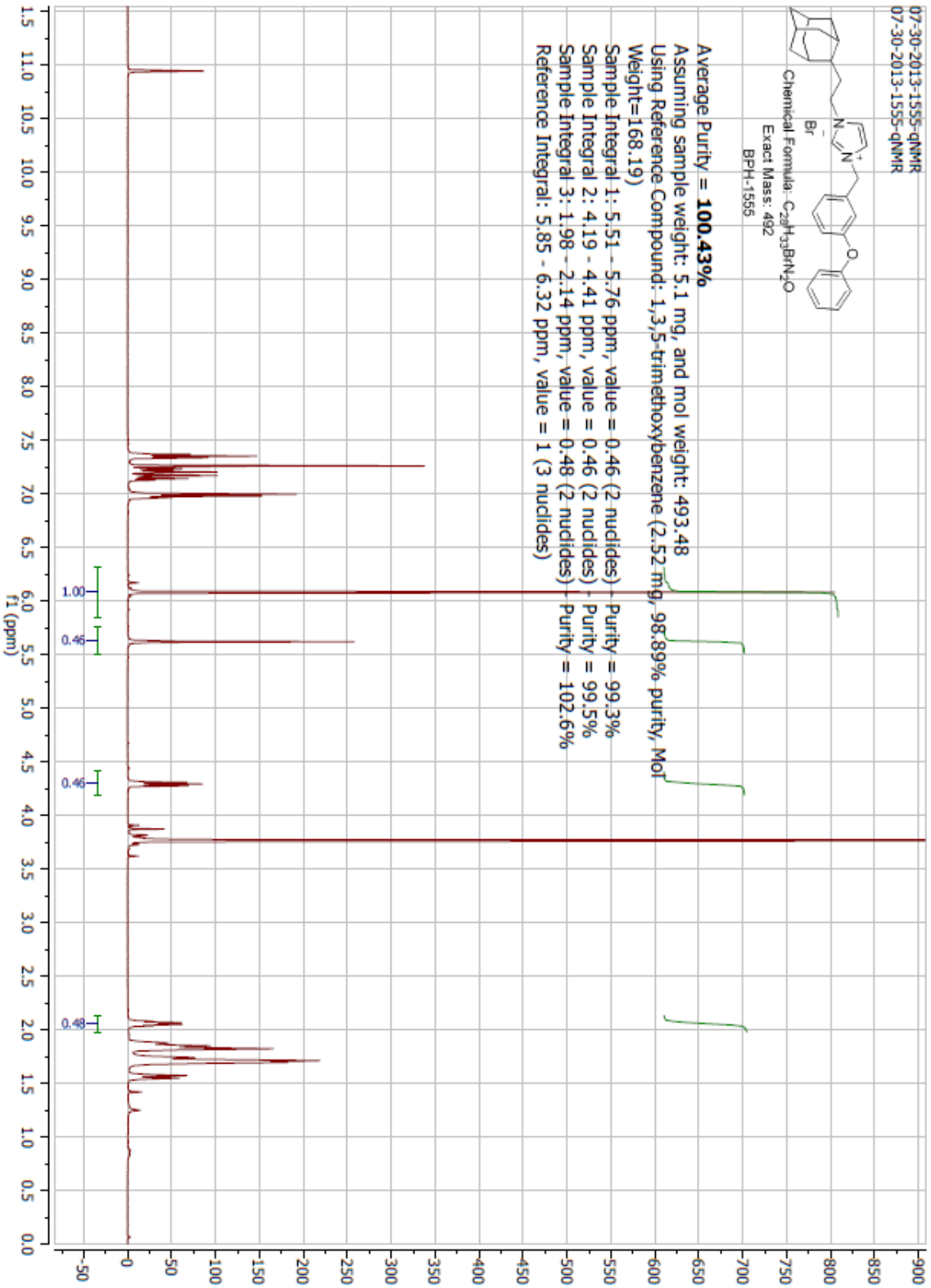


Figure S33. qNMR spectrum of compound **35**.

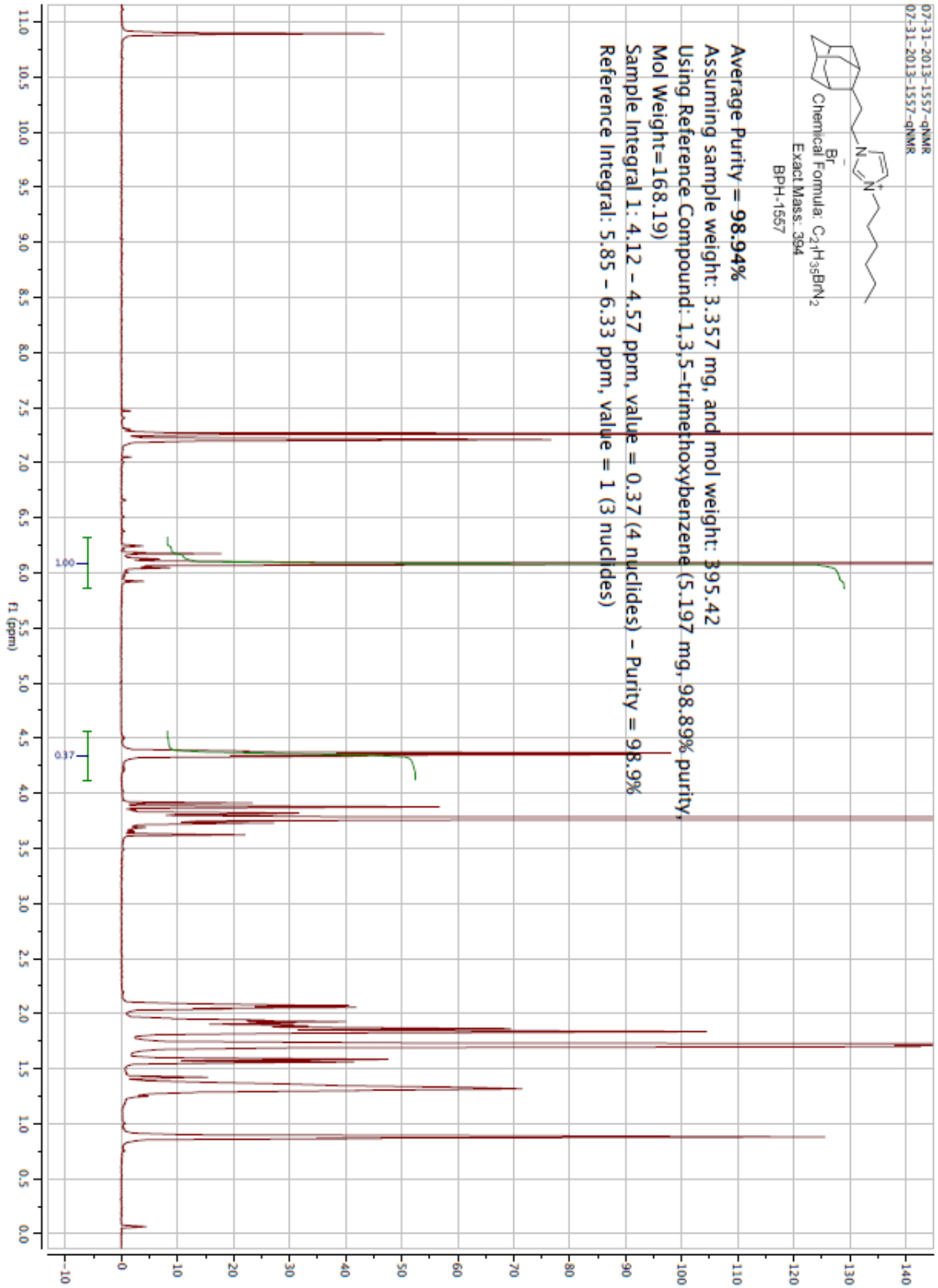


Figure S34. qNMR spectrum of compound **36**.

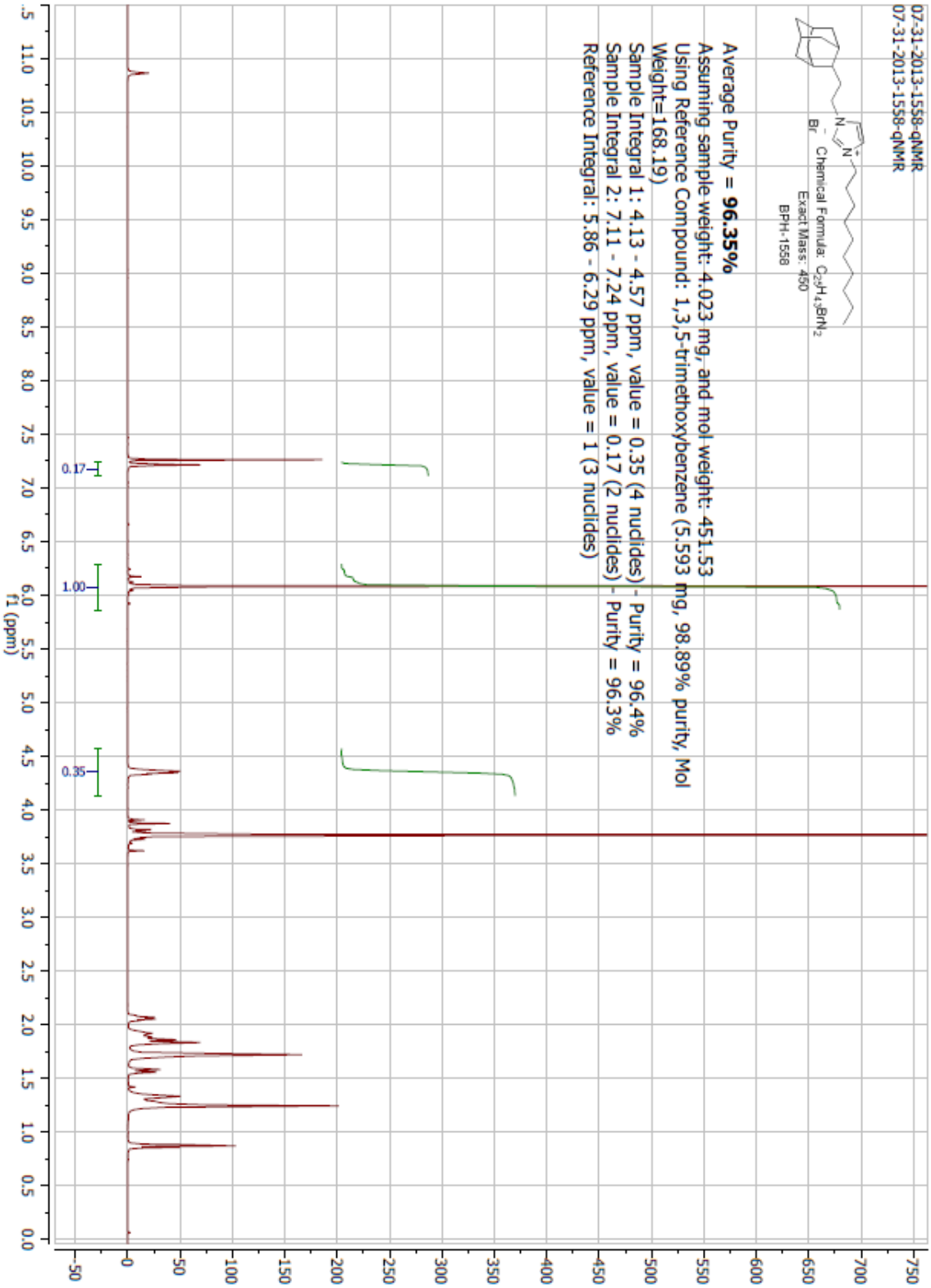


Figure S35. qNMR spectrum of compound **37**.

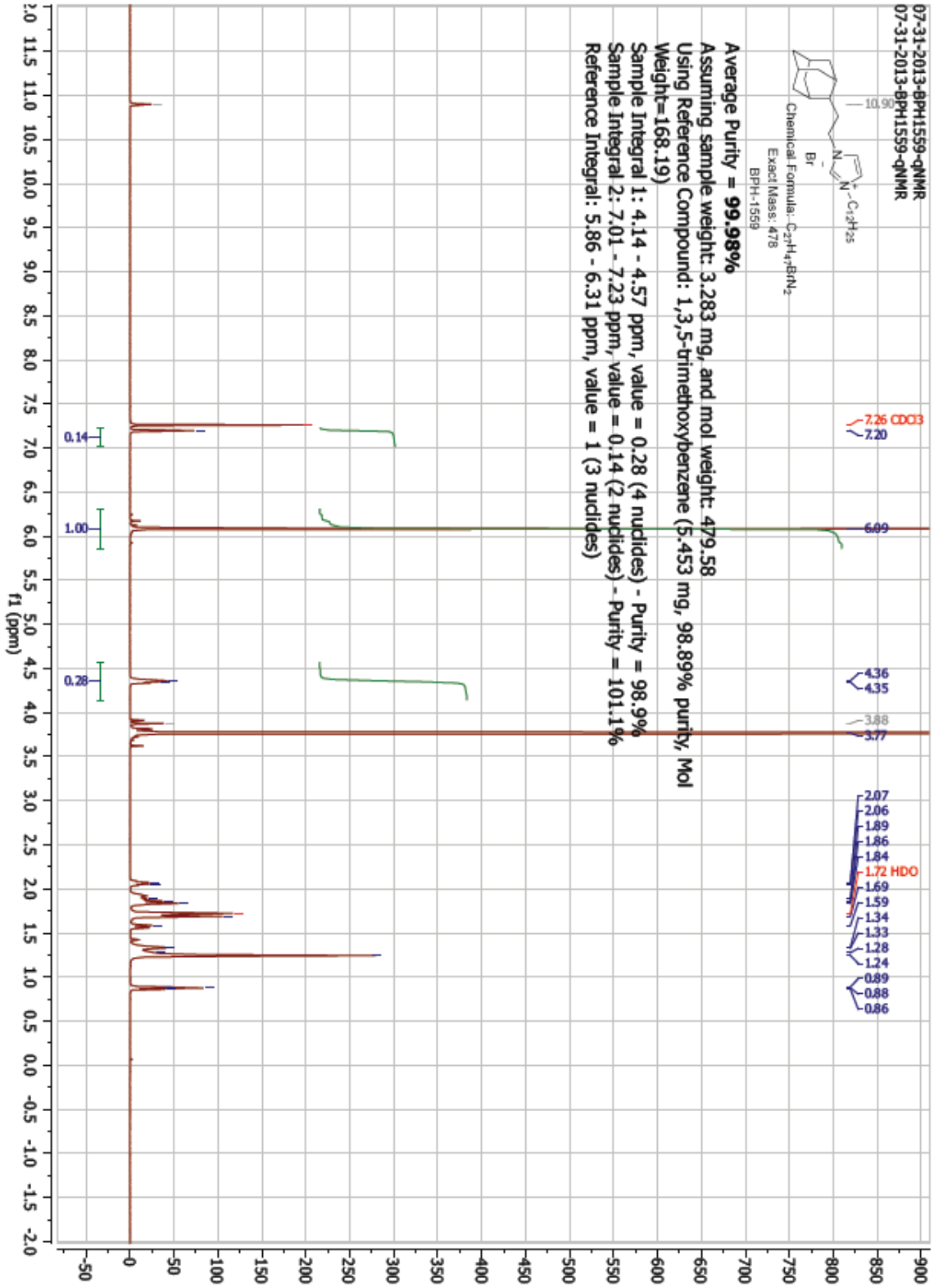


Figure S36. qNMR spectrum of compound **38**.

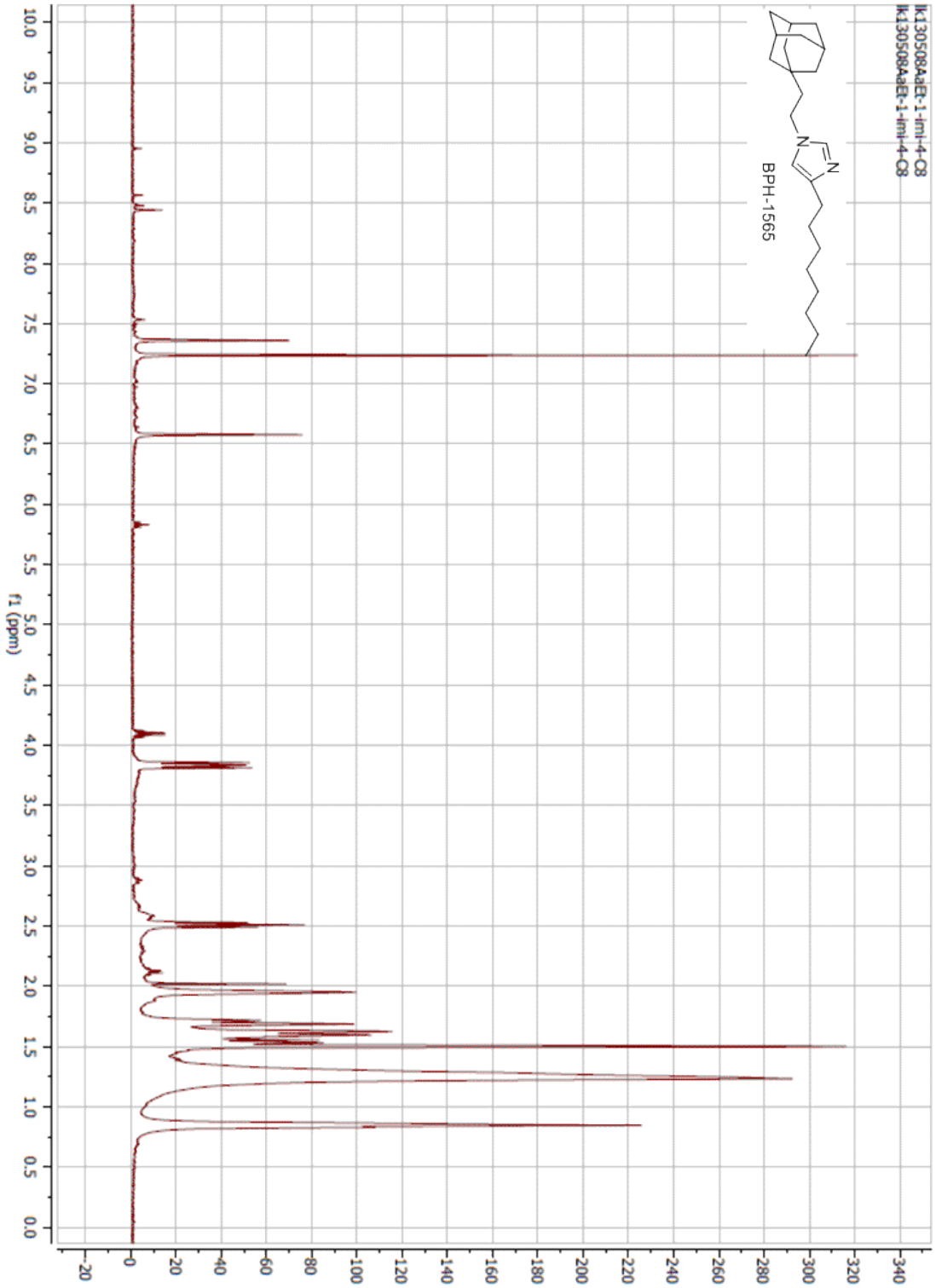


Figure S37. qNMR spectrum of compound **39**.

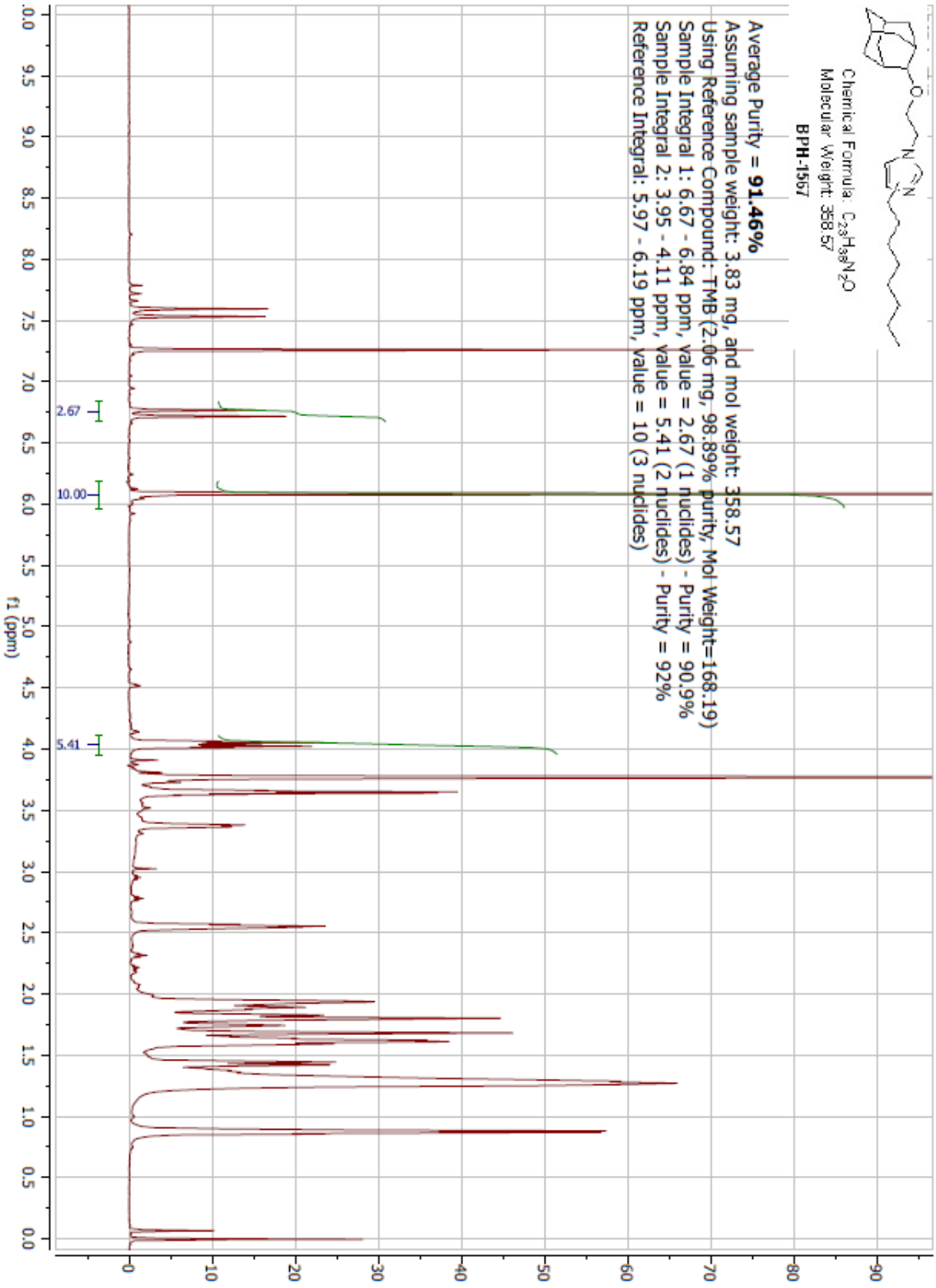


Figure S38. qNMR spectrum of compound **40**.

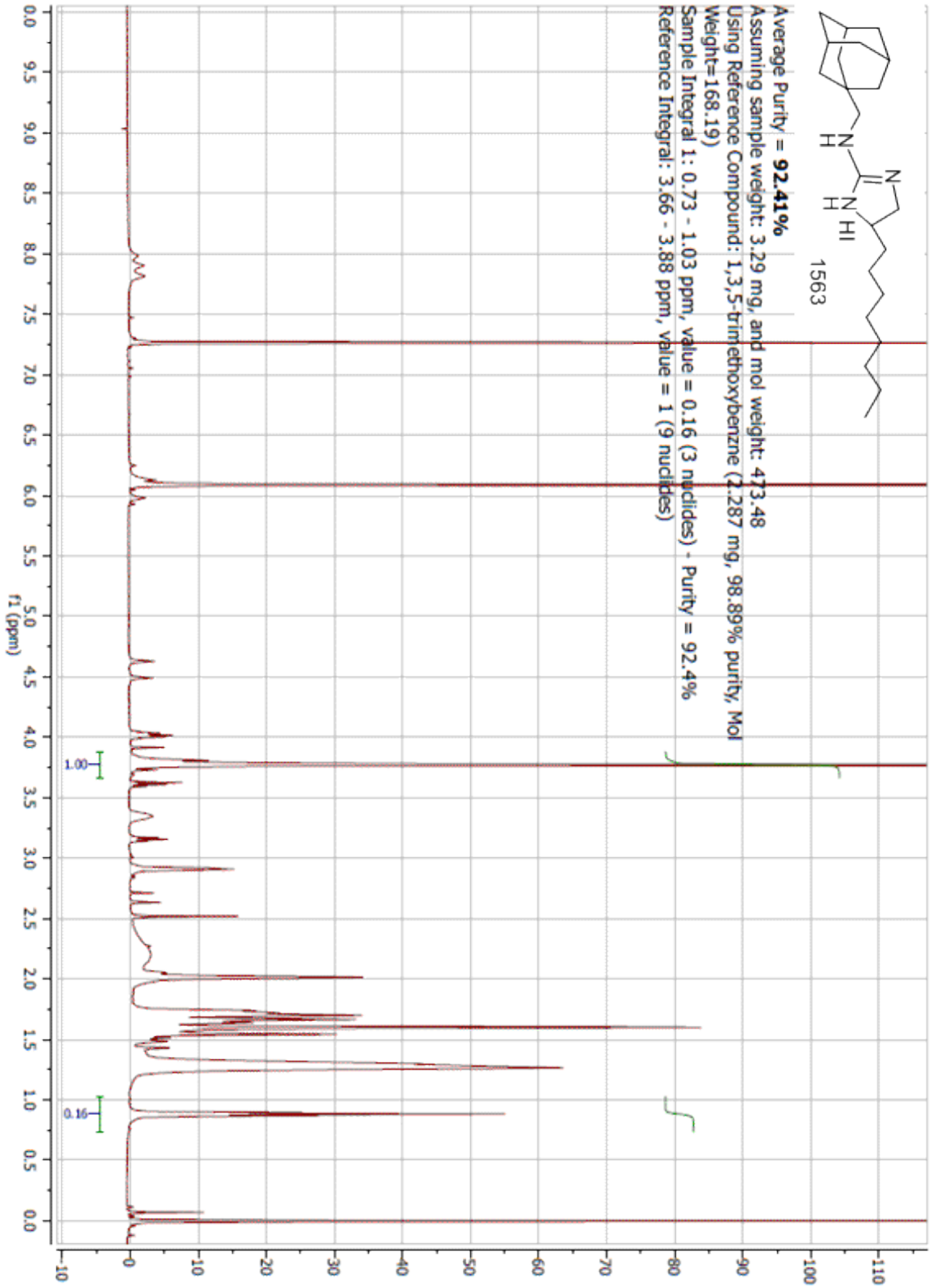


Figure S39. qNMR spectrum of compound **41**.

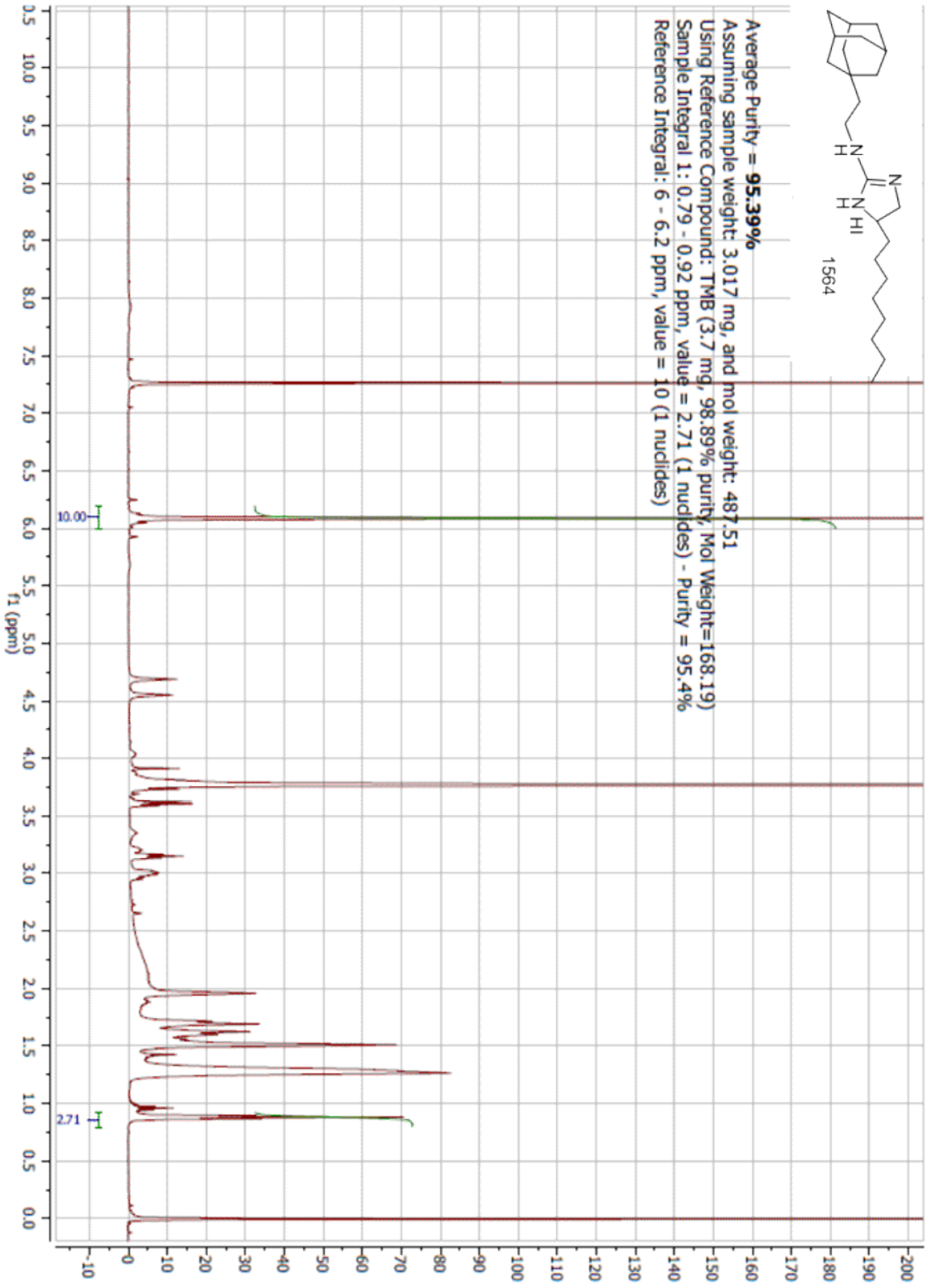


Figure S40. qNMR spectrum of compound **42.**

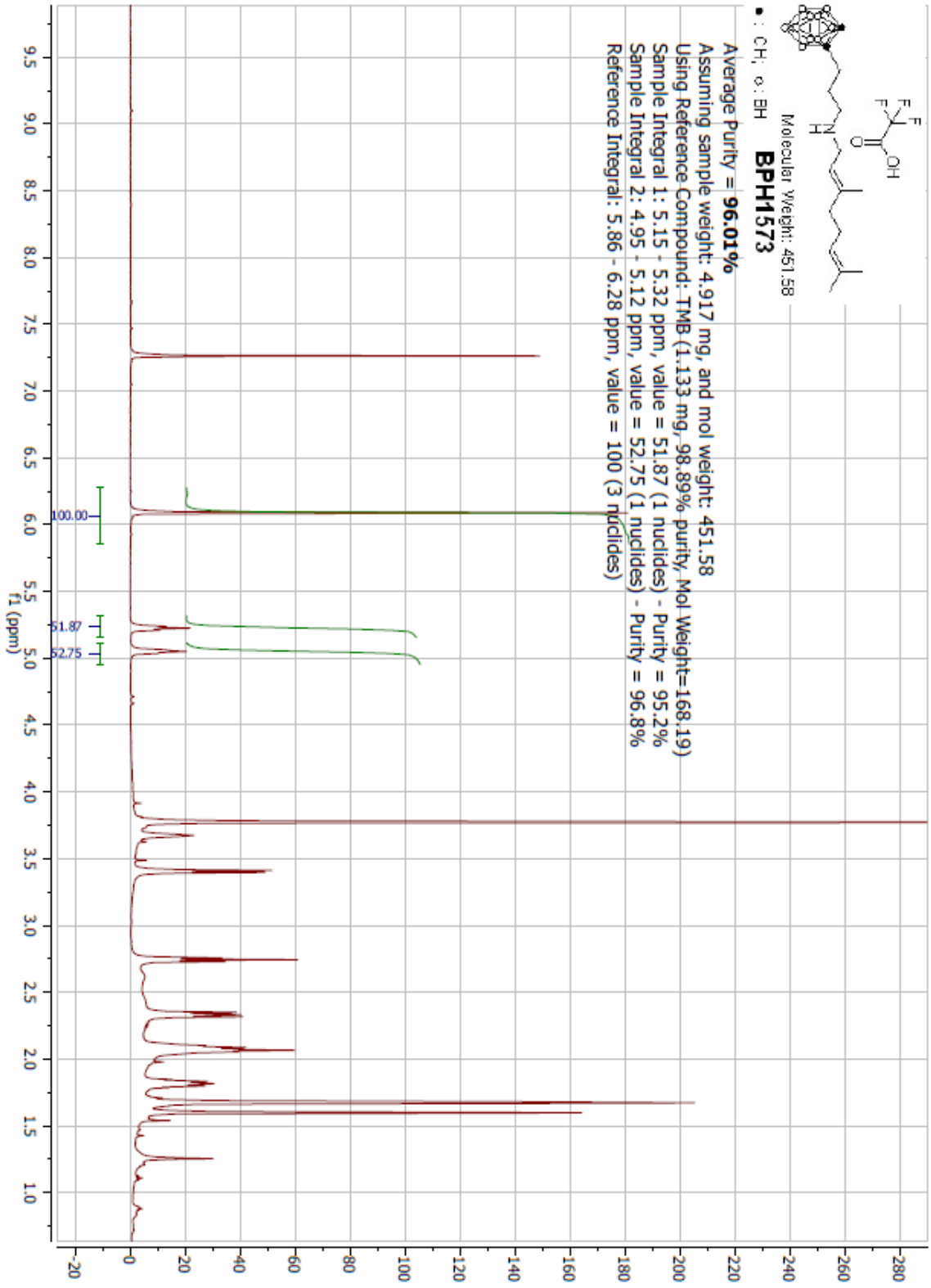


Figure S41. qNMR spectrum of compound **43**.

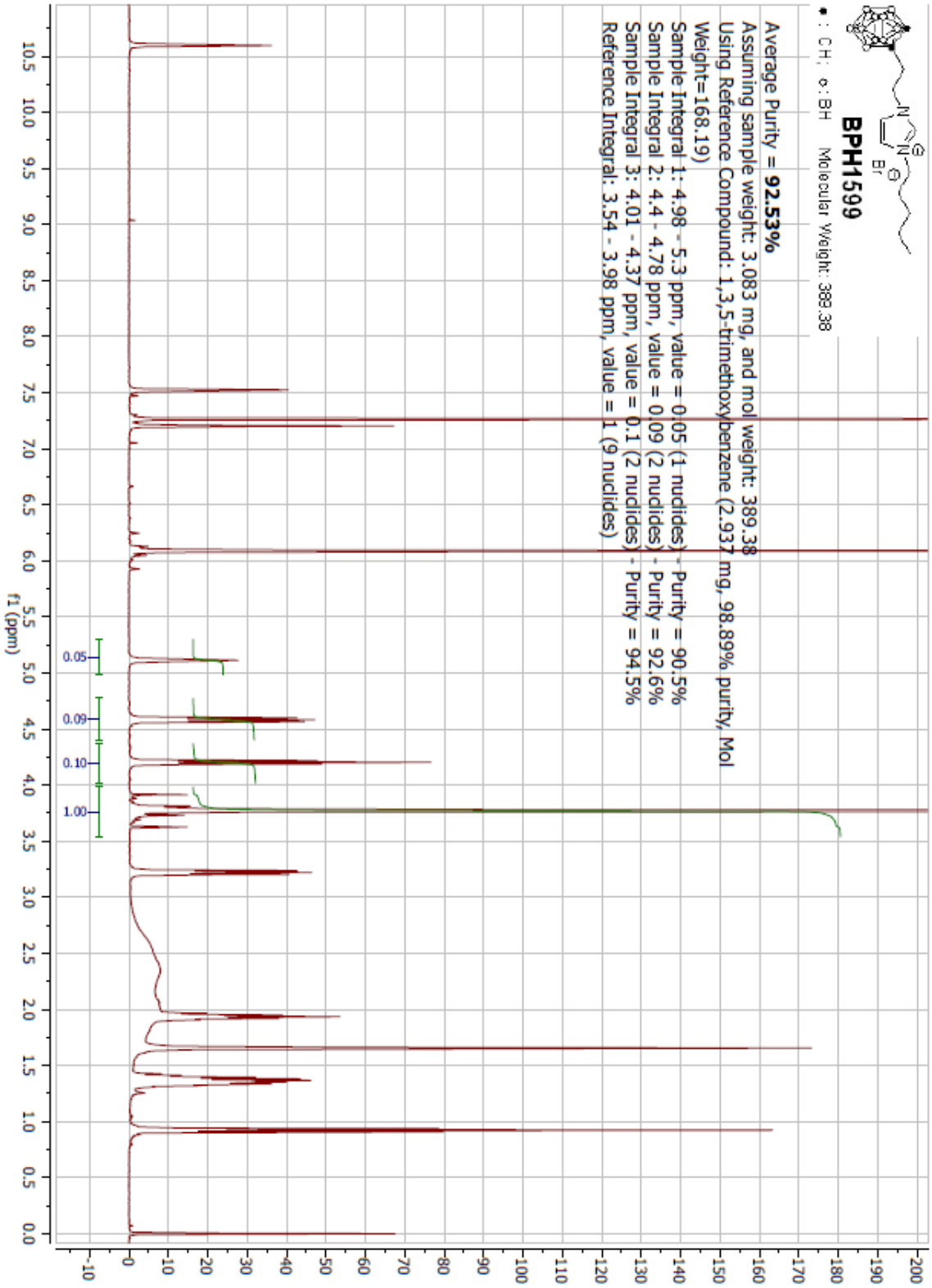


Figure S42. qNMR spectrum of compound **44**.

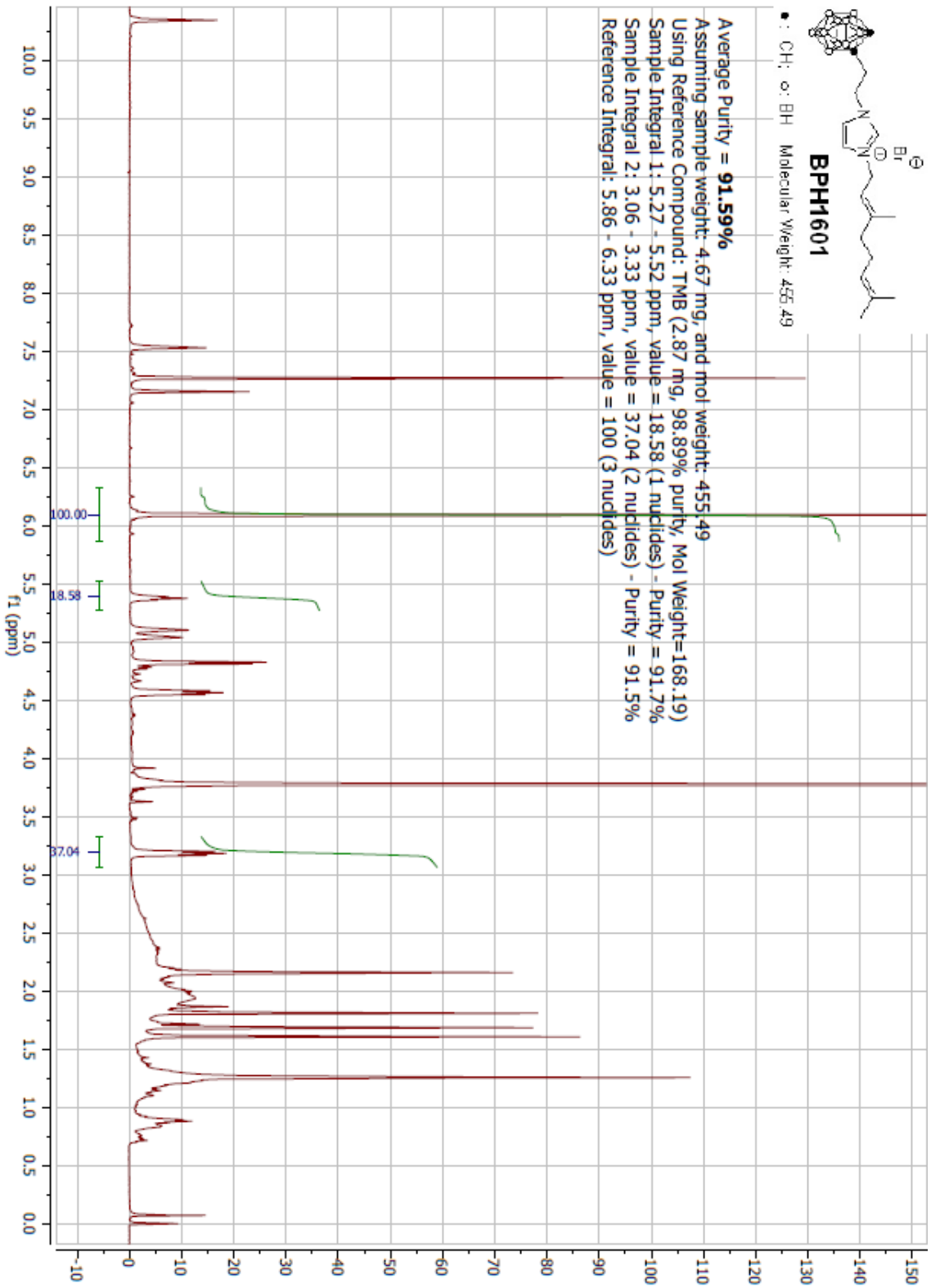


Figure S43. qNMR spectrum of compound **45**.

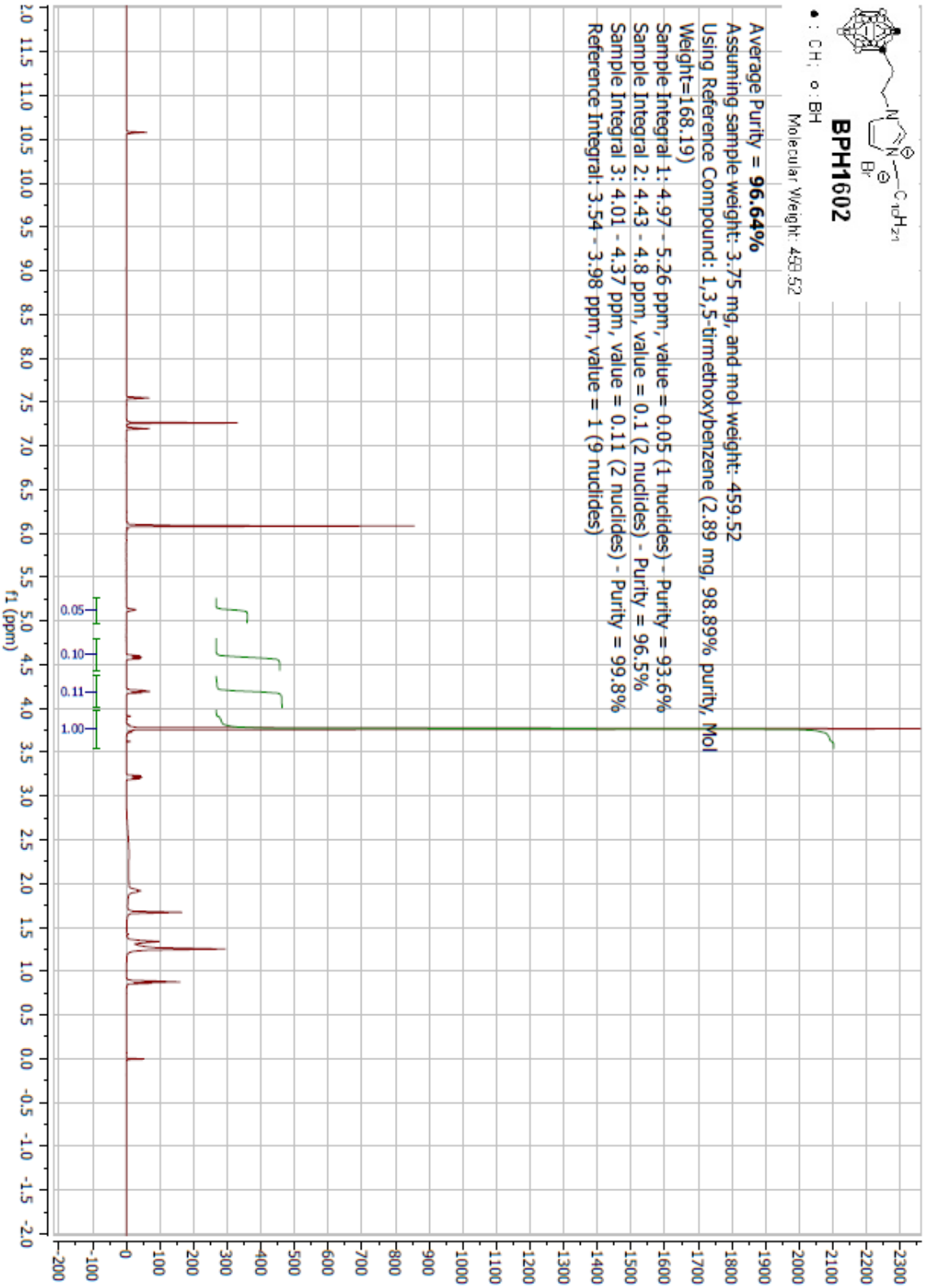


Figure S44. qNMR spectrum of compound **46**.

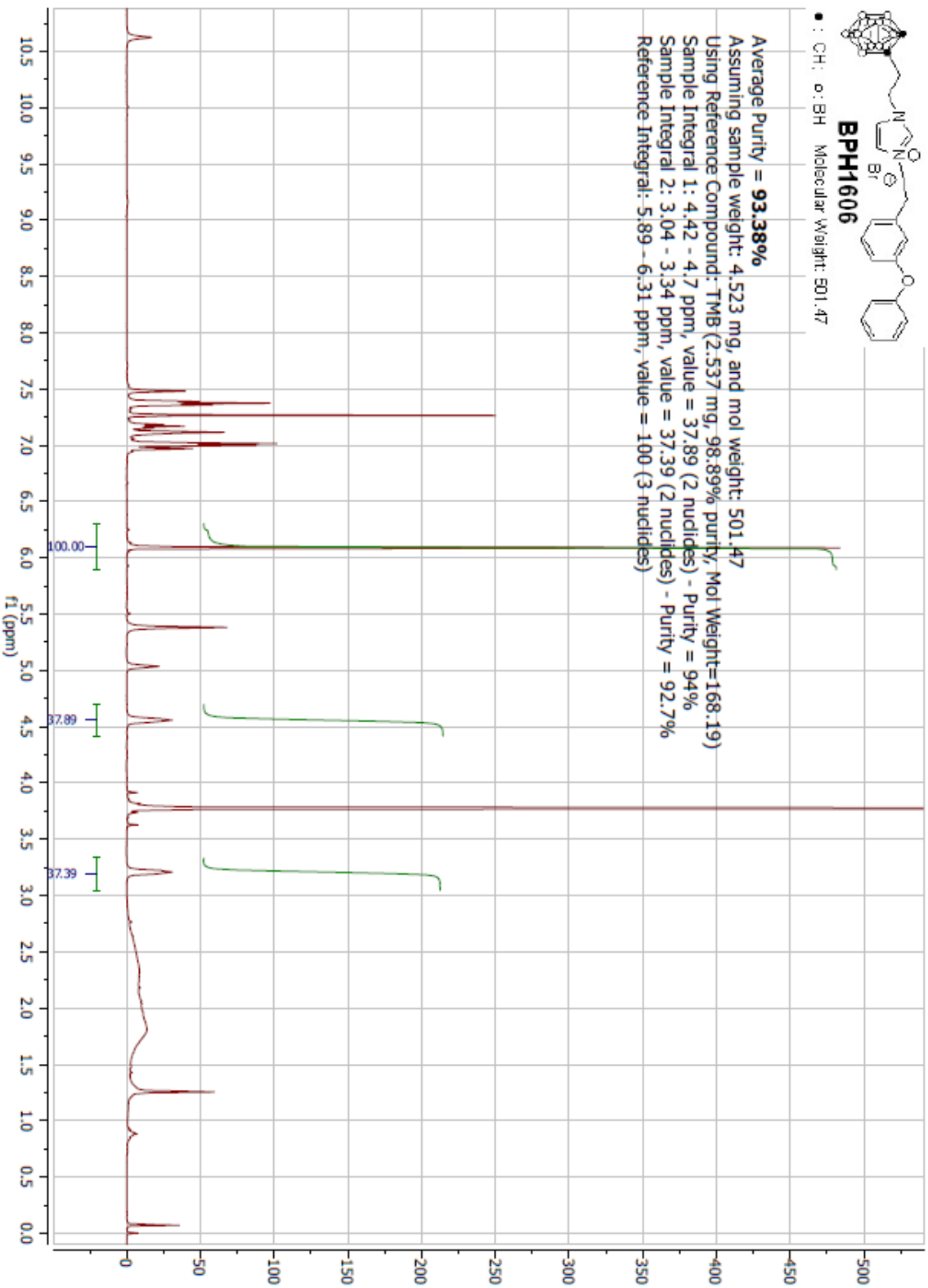


Figure S45. qNMR spectrum of compound **47**.

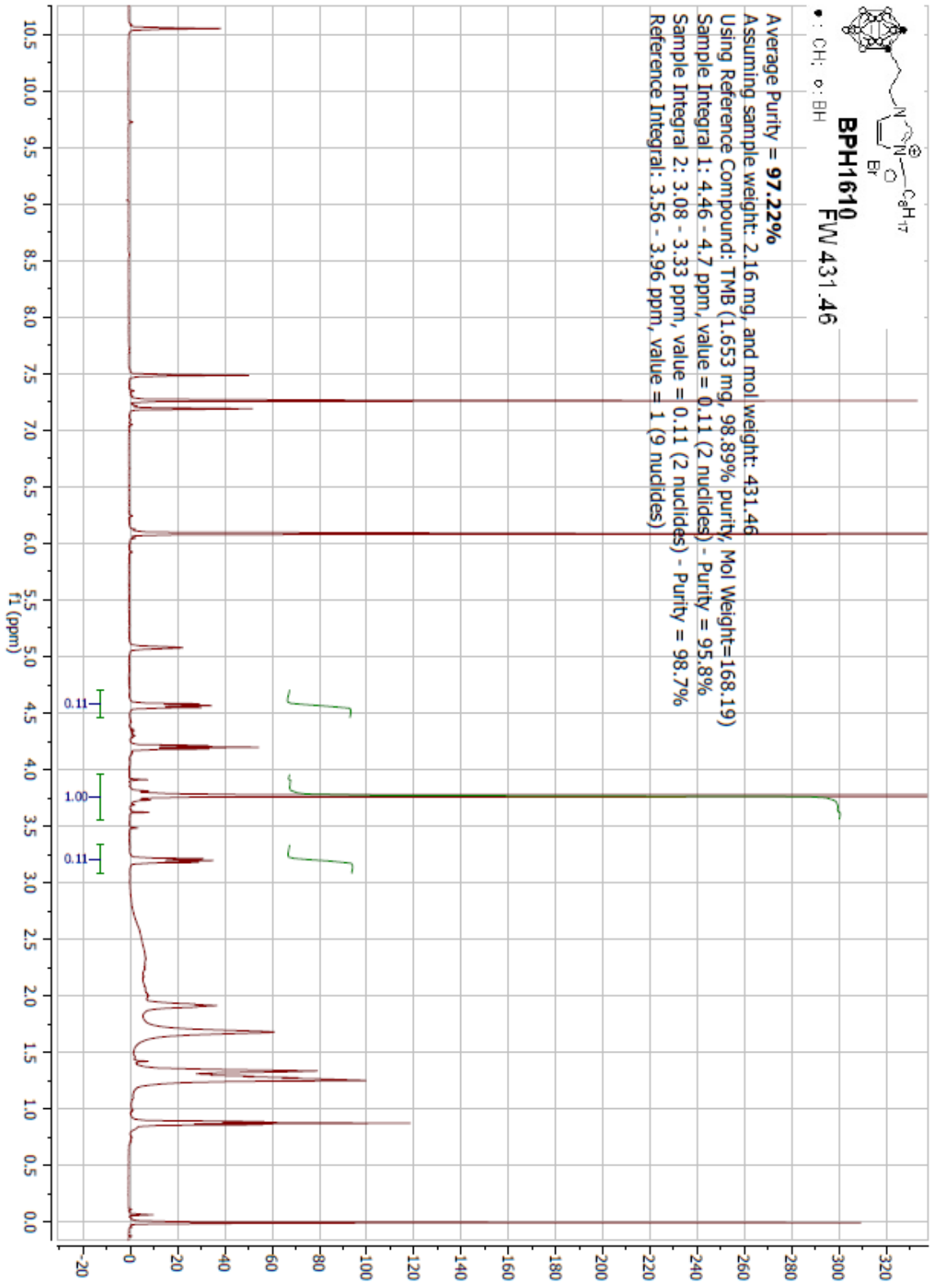


Figure S46. qNMR spectrum of compound **48**.

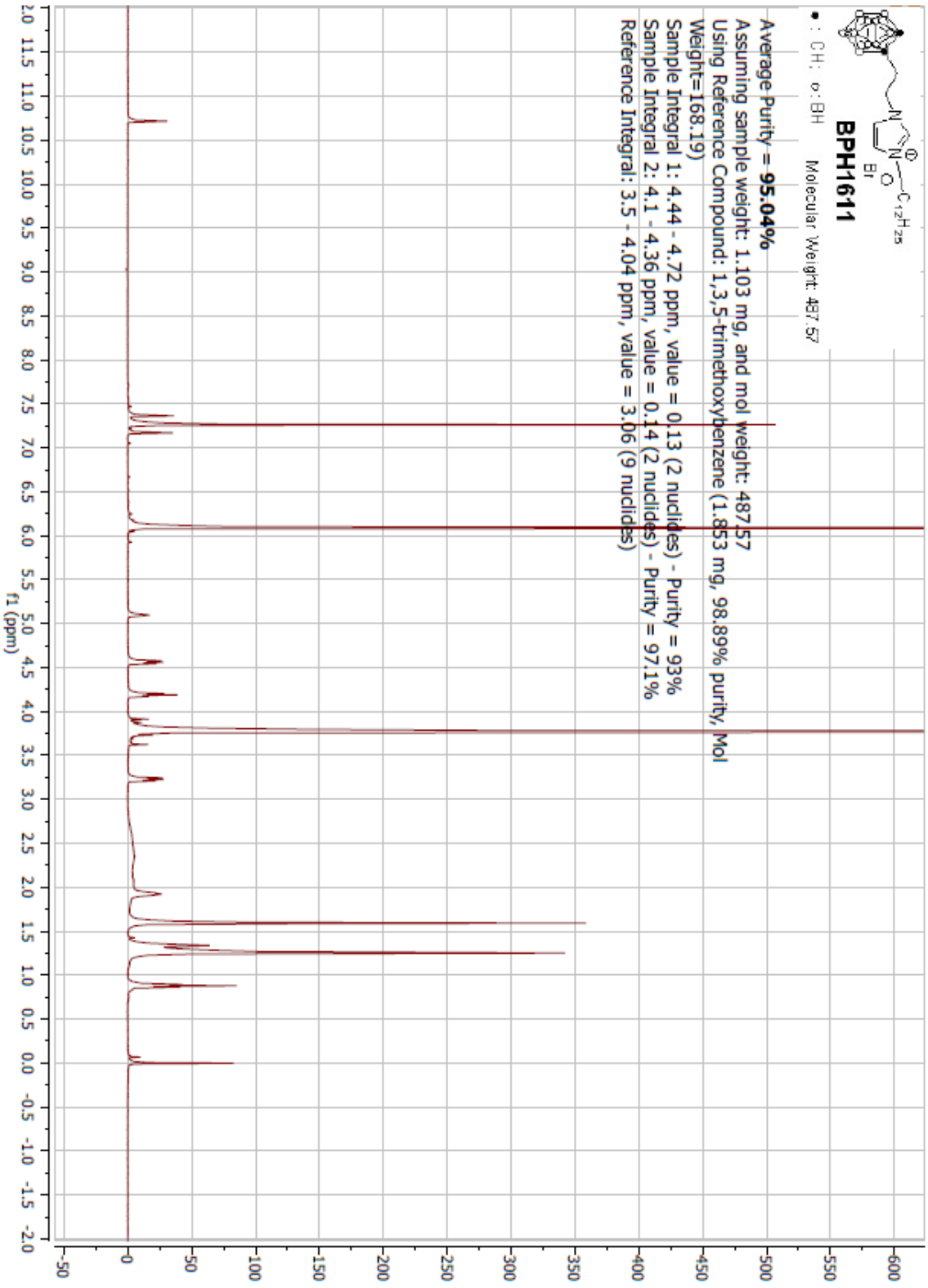


Figure S47. qNMR spectrum of compound **49**.

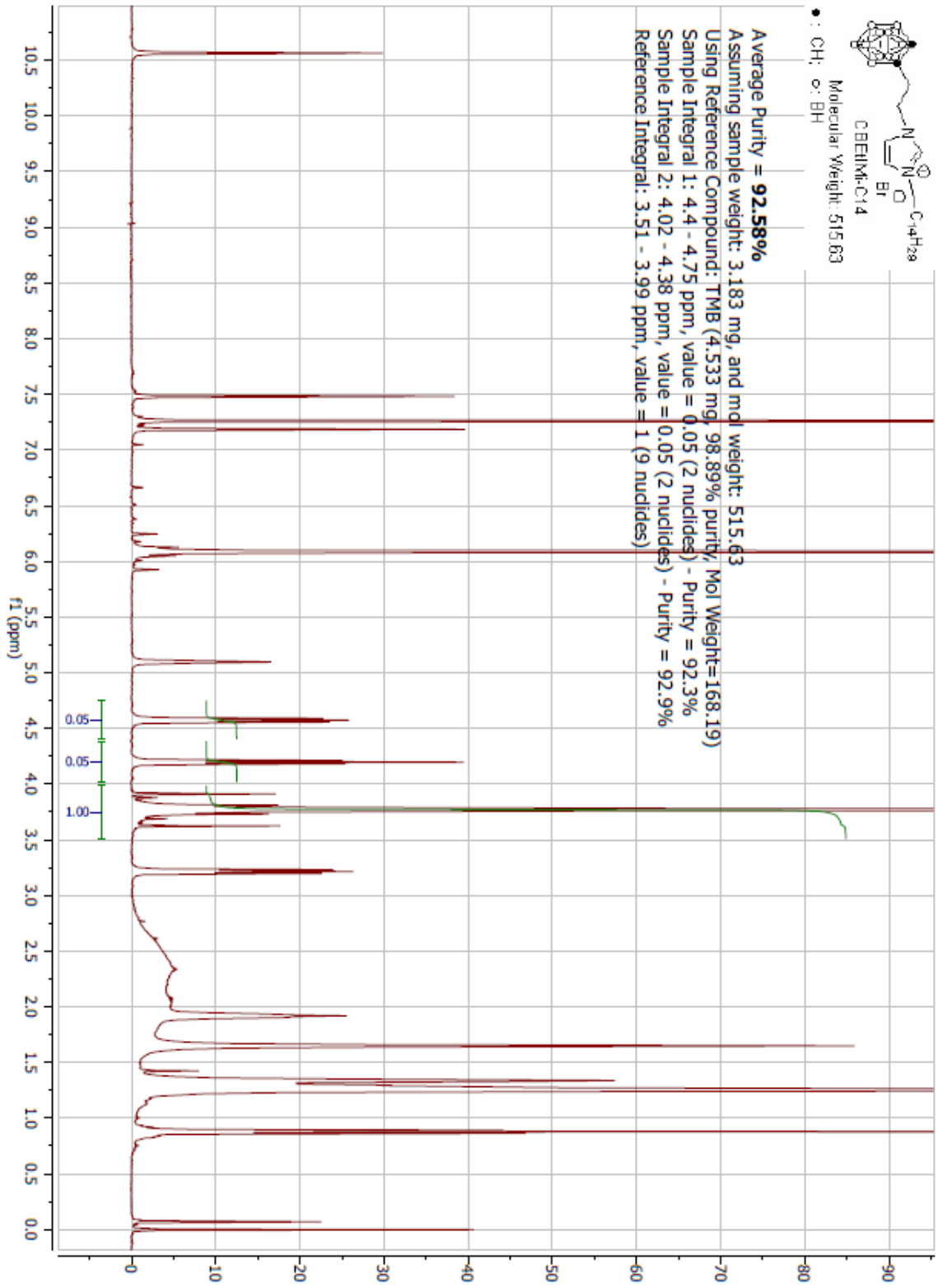
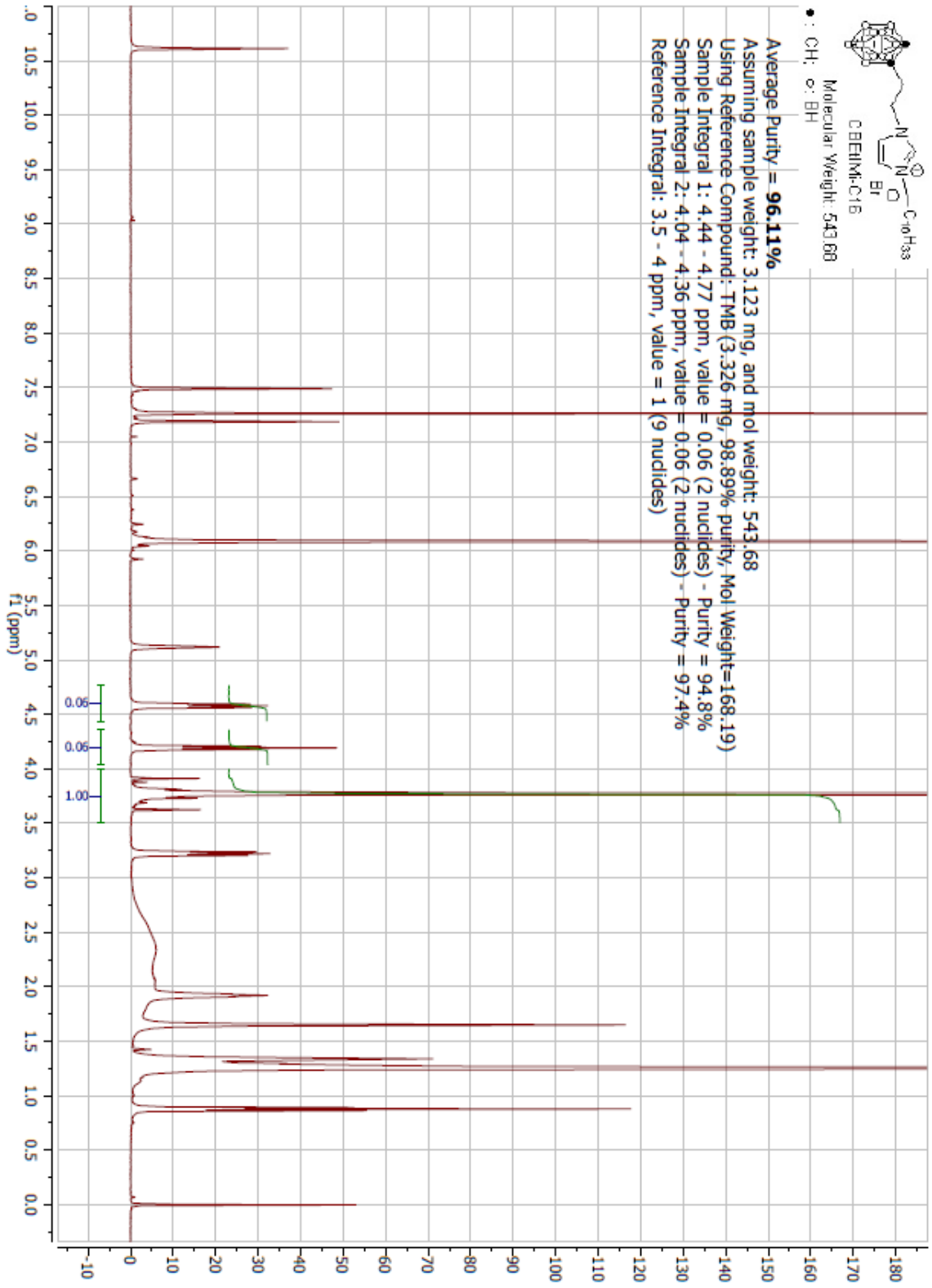


Figure S48. qNMR spectrum of compound **50**.



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