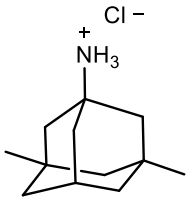
Supplementary Note. Chemical Synthesis and Characterization

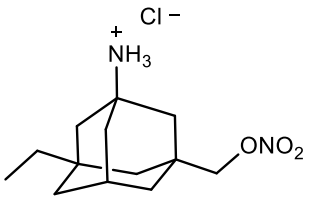
General Information

Reaction progress of non-UV active intermediates was followed by thin layer chromatography (TLC) eluting with EtOAc/hexane or MeOH/DCM. Non-amine containing molecules were visualized with Ammonium Molybdate Reagent 1 from Ricca or 5% sulfuric acid/ethanol stains by gently heating with a heat gun. Amine containing molecules were visualized using Dragendorff's stain. Flash chromatography was performed using an Isco Companion (Teledyne-Isco) and prepacked silica columns (Silicycle). Solvents were purchased from Fisher Scientific and Acros Organics. Solvents, including anhydrous solvents, were used as received. Reagent chemicals were purchased from Sigma Aldrich, Fisher Scientific, and AK Scientific and used as received. Adamantane precursors were purchased from AK Scientific, Alfa Aesar, Combiblocks and Enamine and used as received. Purity of final products was determined by HPLC measuring UV absorption at 210 nm, TLC (as described above), and 1H NMR. LCMS was obtained using a Waters Micromass ZQ with a 2695 Separation Module, and a 2996 Photodiode Array running Empower 2 software. 1H and 13C NMR were performed by Numega Resonance Lab, San Diego, CA using Bruker AV-500 or Avance II 500 MHz NMR's. High resolution mass spectra were obtained at Scripps Research, San Diego, CA using an Agilent 6230 TOF LC/MS System a with Dual AJS ESI or Dual ESI source. Acquisition was performed using Agilent MassHunter Workstation Data Acquisition Version B.08.00. Data processing was performed using Agilent MassHunter Workstation Qualitative Analysis Navigator Version B.08.00.



NMT1 (Memantine)

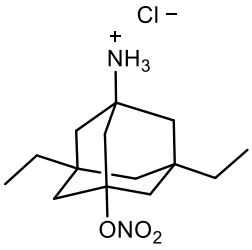
(1r,3R,5S,7r)-3,5-Dimethyladamantan-1-amine hydrochloride (NMT1) was purchased from AK Scientific (memantine hydrochloride, 98% purity) and used as received.



NMT2

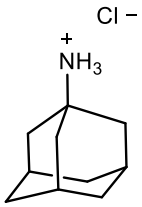
((1R,3S,5R,7S)-3-Amino-5-ethyladamantan-1-yl)methyl nitrate hydrochloride (NMT2) was synthesized as the racemate according to literature[1] procedure (>98% purity). ^{1}HNMR (500 MHz, DMSO) δ 8.23 (br s, 3H), 4.29 (s, 2H), 2.22 (m, 1H), 1.70 (br s, 2H), 1.615 (dd, *J* = 11.7,

26.6 Hz, 2H), 1.475 (dd, *J* = 11.8, 26.3 Hz, 2H), 1.43 (br s, 2H), 1.33 (m, 2H), 1.235 (dd, *J* = 12.5, 26.0 Hz, 2H), 1.19 (dd, *J* = 7.4, 19.9 Hz, 2H), 0.77 (t, *J* = 7.4 Hz, 3H); ^{13}CNMR (500 MHz, DMSO) δ 80.43, 51.84, 43.46, 41.14, 40.82, 40.10, 38.86, 38.81, 36.31, 35.26, 34.57, 34.05, 28.14, 6.91; HRMS(ESI+) calcd for C13H22N2O3 $[M+H]^+$ m/z 255.1703, found 255.1698



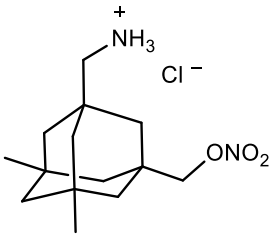
NMT3 (NitroSynapsin)

(1s,3r,5R,7S)-3-Amino-5,7-diethyladamantan-1-yl nitrate hydrochloride (NMT3) was synthesized according to literature[2] procedure (>98% purity). ^{1}HNMR (500 MHz, DMSO) δ 8.50 (br s, 3H), 2.21 (s, 2H), 1.73 (dd, *J* = 12.02, 17.02 Hz, 4H), 1.57 (d, *J* = 11.8 Hz, 2H), 1.48 (d, *J* = 11.8 Hz, 2H), 1.30 (dd, *J* = 7.56, 22.7 Hz, 4H), 1.21 (d, *J* = 12.8 Hz, 1H), 1.09 (d, *J* = 12.8 Hz, 1H), 0.79 (t, *J* = 7.45 Hz, 6H); ^{13}CNMR (500 MHz, DMSO) δ 90.58, 53.77, 42.88, 42.40, 41.42, 41.04, 36.76, 33.77, 7.11; HRMS(ESI+) calcd for C13H22N2O3 $[M+H]^+$ m/z 269.1860, found 269.1865



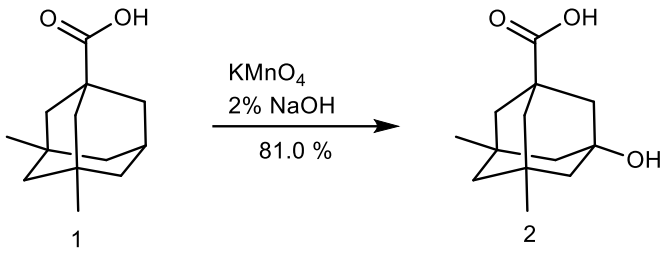
NMT4 (Amantadine)

(3s,5s,7s)-Adamantan-1-amine (NMT4) was purchased from Ak Scientific (amantadine hydrochloride, 99% purity) and used as received.

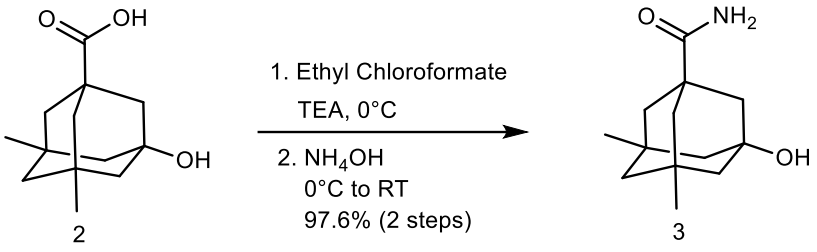


NMT5

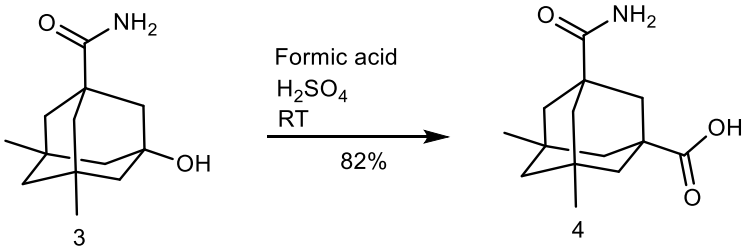
((1s,3r,5R,7S)-3-(Aminomethyl)-5,7-dimethyladamantan-1-yl)methyl nitrate hydrochloride (NMT5) was synthesized according to the following procedure (>98% purity).



Compound 2 was synthesized according to literature[3] procedure and isolated as a white solid (4.7 g, 81% yield). ^{1}HNMR (500 MHz, DMSO) δ 12.0 (br s, 1H), 5.4 (s, 1H), 1.5 (s, 2H), 1.32 (dd, *J* = 12.4, 23.6 Hz, 4H), 1.22 (dd, *J* = 11.6, 18.4 Hz, 4H), 1.03 (s, 2H), 0.85 (s, 6H)

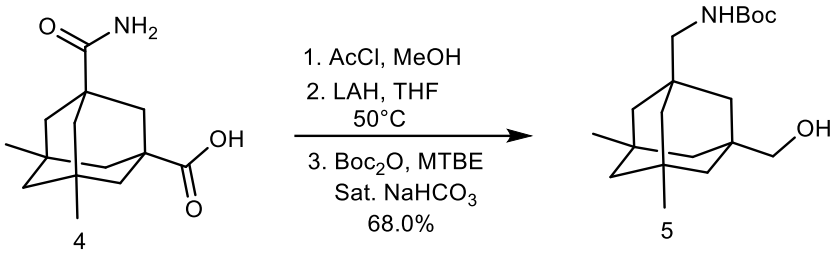


A solution of 2 (4.1 g, 18.3 mmol) in anhydrous THF (50 mL) was chilled over an ice bath, under argon, with stirring. Triethylamine (3.1 mL, 22.0 mmol) was added rapidly via syringe followed by a drop-wise addition of ethyl chloroformate (2.1 mL, 22.0 mmol). The mixture was stirred for 1 hr and ammonium hydroxide (3 mL) was added dropwise over 1-2 minutes. The ice bath was removed, and the stirring was continued for an additional 2 hr. The mixture was concentrated on a rotovap to remove THF. The residue was diluted with ethyl acetate, washed with 1 N HCl, saturated sodium bicarbonate solution, and brine. The layers were separated, and the organic layer was dried over sodium sulfate and concentrated to a white solid which was dried overnight under high vacuum. (4.0 g, 97.6% yield), MS(ESI+) m/z 224.22 $[M+H]^{+}$

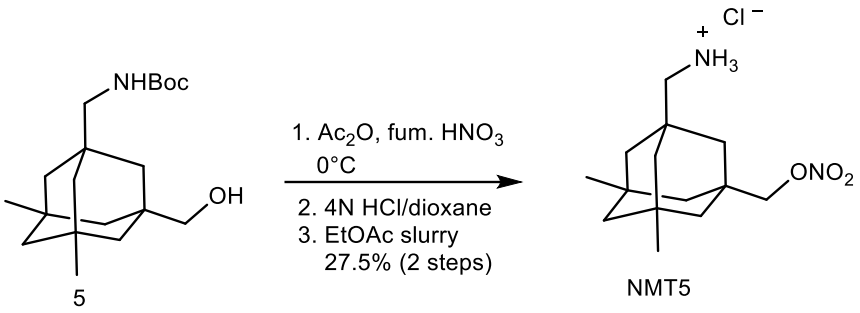


Compound 3 was added to concentrated sulfuric acid (30 mL) and stirred at room temperature until dissolved. Formic acid (98%, 6 mL) was charged to an addition funnel and added dropwise over 5 hr with stirring. Gas was evolved during the addition. The mixture was stirred an

additional 3 hr until starting material was consumed. The mixture was poured onto ice while stirring with a glass rod and left to stand until ice had melted. The solid precipitate was collected by filtering through a sintered glass frit. The filter cake was washed 3x with DI water and dried in a vacuum oven at 40 °C overnight to give the product as a white solid. (3.7 g, 82% yield). ^{1}HNMR (500 MHz, DMSO) δ 12.08 (br s, 1H), 7.01 (s, 1H), 6.71 (s, 1H), 1.67 (s, 2H), 1.41-1.33 (m, 8H), 1.08 (s, 2H), 0.84 (s, 6H); MS(ESI+) m/z 252.15 $[M+H]^{+}$



A solution of 4 (3.7 g, 14.7 mmol) in dry methanol (100 mL) was chilled over an ice bath, under an atmosphere of argon. Acetyl chloride (1.2 mL) was added dropwise with stirring. The mixture was stirred overnight allowing the ice bath to warm to RT. The mixture was chilled over an ice bath and treated with acetyl chloride (1 mL) dropwise with stirring. The ice bath was removed, and the mixture was stirred for 3 hr. The mixture was concentrated by rotovap, and the residue was dissolved in THF/heptane and concentrated by rotovap. The THF/heptane co-distillation was repeated once more. The residue was dissolved in dry THF (250 mL) and a reflux condenser with drierite column was attached. Lithium aluminum hydride pellets (2.5 g, 63.2 mmol) were added one at a time with stirring. After the pellets were dissolved, the reaction was heated to 50 °C overnight. The mixture was chilled over an ice bath and carefully quenched with sodium sulfate decahydrate until no more hydrogen was evolved. Diethyl ether (250 mL) was added, and the mixture was stirred at RT for 3 hr until a white filtrable precipitate was obtained. The mixture was filtered through a glass frit containing a layer of celite and washed 2x with diethyl ether. The solvent was evaporated by rotovap. The residue was dissolved in MTBE (50 mL). Boc anhydride (3.4 g, 15.7 mmol) and saturated sodium bicarbonate solution (50 mL) were added sequentially. The mixture was stirred overnight. A precipitate had formed which was isolated by filtering the mixture through a glass frit. The layers of the filtrate were separated, and the MTBE layer was concentrated to a solid and combined with the earlier isolated filter cake. The material was purified by flash chromatography on silica gel eluting with a gradient of 30% to 40% ethyl acetate/hexane. The fractions were concentrated by rotovap and dried under high vacuum overnight to give the product as a white solid (3.2g, 68.0% yield over 3 steps). ^{1}HNMR (500 MHz, DMSO) δ 6.66 (br t, *J* = 5.4 Hz, 1H), 4.31 (t, *J* = 6.4 Hz, 1H), 3.01 (d, *J* = 5.4 Hz, 1H), 2.68 (d, *J* = 6.4 Hz, 1H), 1.37 (s, 9H), 0.99 (br d, *J* = 11.9 Hz, 12H), 0.80 (s, 6H); MS(ESI+) m/z 324.36 $[M+H]^{+}$



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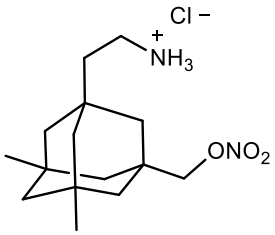
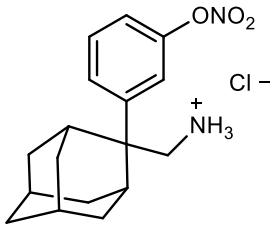
NMT5

A solution of 5 (3.2 g, 10 mmol) in dichloromethane was chilled over ice, under an atmosphere of argon. A chilled solution of acetyl nitrite was prepared by adding fuming nitric acid (2 mL) dropwise to ice cold acetic anhydride (3 mL) with stirring. The acetyl nitrite solution (4.87 mL) was added as 1 mL portions, rapidly added, while maintaining the bulk in the ice bath to avoid warming. Acetyl nitrite degrades exothermically as it warms to RT. The reaction was stirred for 15 min following the acetyl nitrite addition and was quenched by pouring into ice cold sodium bicarbonate solution (100 mL). The mixture was stirred for 1 hr and allowed to warm to RT. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined layers were washed with brine and dried by stirring with sodium sulfate. The solvent was evaporated by rotovap and concentrated to a residue which was passed through a plug of silica eluting with 20% ethyl acetate/hexane. The solvent was evaporated by rotovap, and the residue was treated with 4 N HCl/dioxane (20mL). The mixture was swirled to dissolve and allowed to stand for 3 hr until starting material was consumed. Heptane (20 mL) was added, and the solvent was removed by rotovap at 40 °C. The residue was triturated with ethyl acetate and the resulting slurry was stirred for 1 hr at RT. The precipitate was collected by vacuum filtration through a glass frit and dried under high vacuum overnight to give the product as a white solid (835 mg, 27.5% yield over 2 steps). >98% purity. ^{1}HNMR (500 MHz, DMSO) δ 7.90 (s, 3H), 4.24 (s, 2H), 2.56 (s, 2H), 1.25 (s, 2H), 1.16 (m, 8H), 1.07 (m, 2H), 0.85 (s, 6H); ^{13}CNMR (500 MHz, DMSO) δ 81.06, 49.49, 48.82, 44.35, 43.68, 38.93, 35.13, 33.82, 30.86, 29.76; HRMS(ESI+) calcd for C14H24N2O3 $[M+H]^+$ m/z 269.1860, found 269.1867



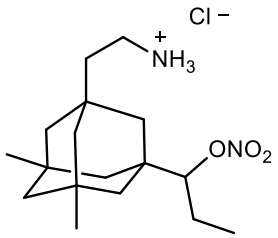
NMT6

((1s,3r,5R,7S)-3-(2-Aminoethyl)-5,7-dimethyladamantan-1-yl)methyl nitrate hydrochloride (NMT6) was synthesized according to literature[4] procedure (>98% purity). ^{1}HNMR (500 MHz, DMSO) δ 7.77 (br s, 3H), 4.23 (s, 2H), 2.75 (m, 2H), 1.40 (m, 2H), 1.16 (m, 6H), 1.08 (m, 6H), 0.83 (s, 6H); ^{13}CNMR (500 MHz, DMSO) δ 81.24, 49.71, 47.03, 43.89, 35.25, 34.30, 31.02, 29.81; HRMS(ESI+) calcd for C15H26N2O3 $[M+H]^+$ m/z 283.2016, found 283.2023



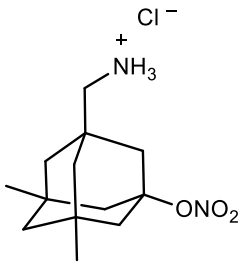
NMT7

3-((1r,3r,5r,7r)-2-(Aminomethyl)adamantan-2-yl)phenyl nitrate hydrochloride (NMT7) was synthesized according to literature[4] procedure (>98% purity). ^{1}HNMR (500 MHz, DMSO) δ 7.93 (d, *J* = 8.8 Hz, 1H), 7.16 (d, *J* = 1.6 Hz, 1H), 7.01 (dd, *J* = 1.6, 8.8 Hz, 1H), 3.20 (br d, *J* = 13.3 Hz, 1H), 3.06 (br d, *J* = 13.2 Hz, 1H), 2.53-2.46 (m, 2H (overlaps DMSO)), 2.12(br d, *J* = 13.1 Hz, 2H), 1.91 (br s, 1H), 1.8-1.5 (m, 9H); ^{13}CNMR (500 MHz, DMSO) δ 152.84, 150.82, 134.81, 125.77, 118.62, 117.97, 46.09, 45.40, 37.70, 32.95, 32.77, 31.88, 30.60, 29.93, 26.88, 26.16; HRMS(ESI+) calcd for C17H22N2O3 $[M+H]^{+}$ m/z 303.1703, found 303.1700



NMT8

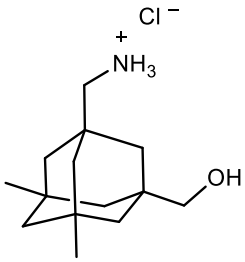
1-((1s,3r,5R,7S)-3-(2-Aminoethyl)-5,7-dimethyladamantan-1-yl)propyl nitrate hydrochloride (NMT8) was synthesized as the racemate according to literature[4] procedure (>96% purity). ^{1}HNMR (500 MHz, DMSO) δ 7.76 (br s, 3H), 4.85 (dd, *J* = 2.6, 10.5 Hz, 2H), 2.77-2.73 (m, 2H), 1.80-1.76 (m, 1H), 1.56-1.51 (m, 1H), 1.40-1.37 (m, 2H), 1.19-1.03 (m, 12H), 0.89 (t, *J* = 7.3 Hz, 3H), 0.82 (s, 6H); ^{13}CNMR (500 MHz, DMSO) δ 93.18, 49.70, 47.01, 42.92, 40.42, 34.28, 33.20, 31.06, 29.93, 20.34, 10.47; HRMS(ESI+) calcd for C17H30N2O3 $[M+H]^{+}$ m/z 311.2329, found 311.2320



NMT9

(1s,3r,5R,7S)-3-(Aminomethyl)-5,7-dimethyladamantan-1-yl nitrate hydrochloride (NMT9) was synthesized according to literature[4] procedure (>98% purity). ^{1}HNMR (500 MHz, DMSO) δ 8.06 (br s, 3H), 2.65 (br s, 2H), 1.84 (br s, 2H), 1.72 (dd, *J* = 11.6, 16.2 Hz, 4H), 1.30 (d, *J* = 12.3 Hz,

2H), 1.22-1.17 (m, 3H), 1.10 (d, *J* = 12.6 Hz, 1H), 0.92 (s, 6H); ^{13}CNMR (500 MHz, DMSO) δ 92.01, 48.53, 48.02, 43.92, 36.74, 33.92, 29.02; HRMS(ESI+) calcd for C13H22N2O3 $[M+H]^+$ m/z 255.1703, found 255.1706



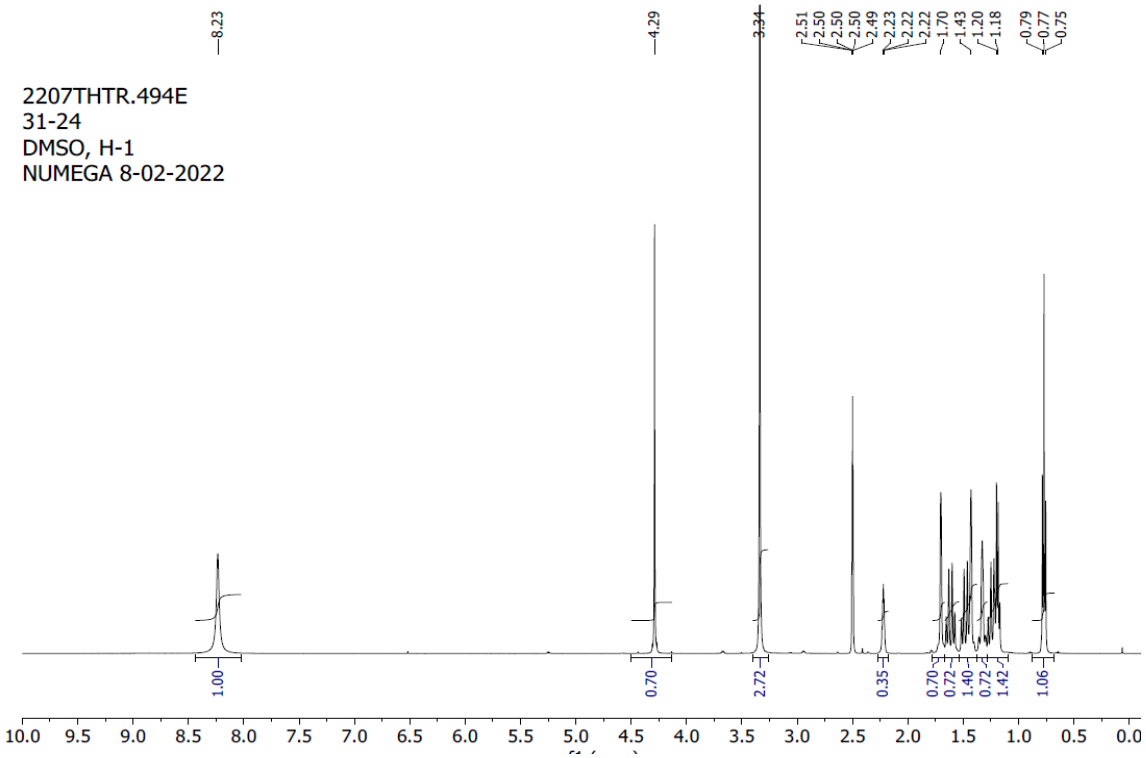
NMT5 metabolite

((1s,3r,5R,7S)-3-(aminomethyl)-5,7-dimethyladamantan-1-yl)methanol hydrochloride (NMT5 metabolite) was synthesized according to the following procedure (>98% purity).

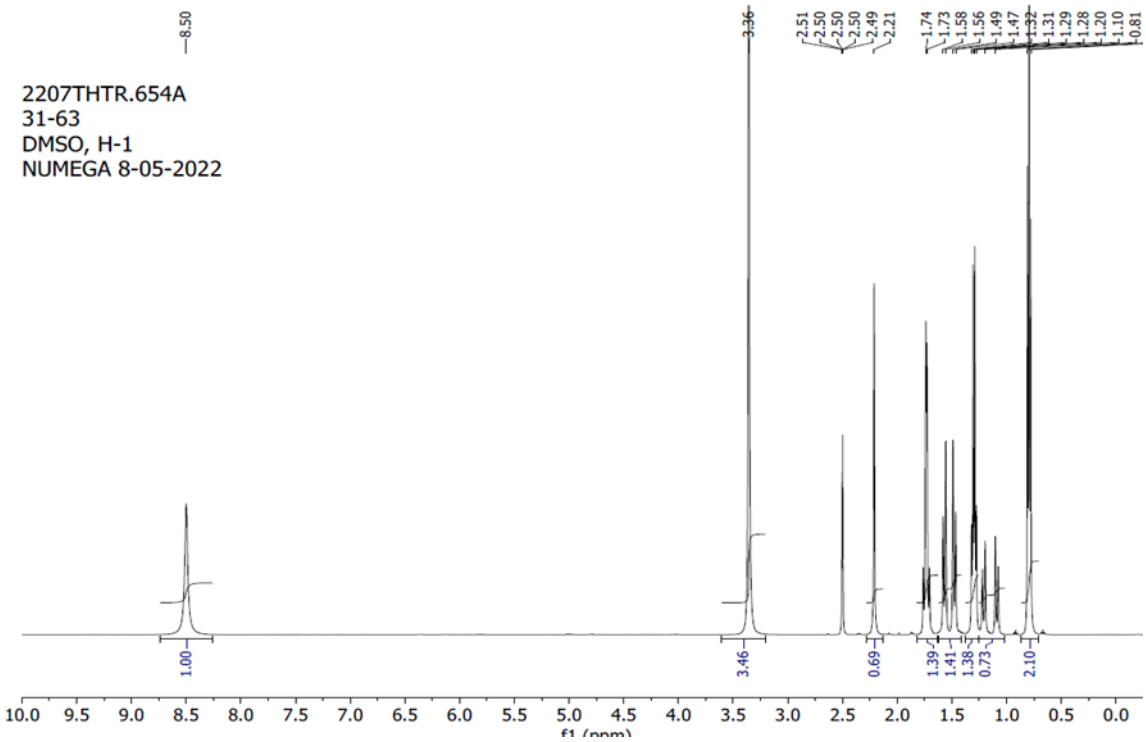
Compound 5 (100 mg, 0.3 mmol) was treated with 4N HCl/dioxane (1 mL) and stirred at room temperature for 3 hr. The solvent was removed by rotovap. The residue was triturated with ethyl acetate and the slurry was stirred for 2 hr. The product was collected by vacuum filtration onto a glass frit and dried in a vacuum oven at 40 °C overnight to give the product as a white solid. (55 mg, 71% yield). (>98% purity) ^{1}HNMR (500 MHz, DMSO) δ 7.80 (br s, 3H), 4.45 (t, *J* = 5.3 Hz, 1H), 3.045 (d, *J* = 5.2 Hz, 2H), 2.54 (s, 2H), 1.11 (br s, 6H), 1.04 (br s, 6H), 0.83 (s, 6H); ^{13}CNMR (500 MHz, DMSO) δ 70.75, 50.12, 49.22, 44.93, 44.57, 36.62, 33.93, 31.01, 30.08; HRMS(ESI+) calcd for C14H25NO $[M+H]^+$ m/z 224.2009, found 224.2005

References

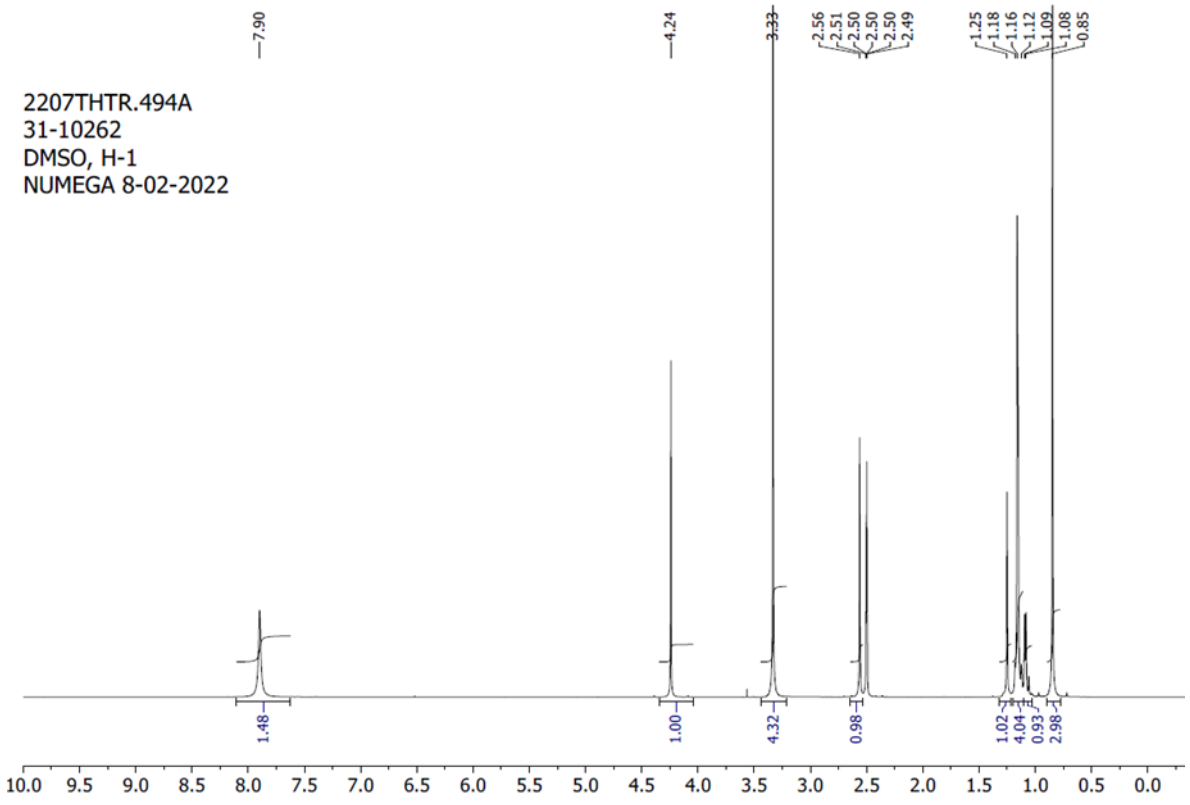
1. Liu, Z. *et al*. Synthesis and biological evaluation of memantine nitrates as a potential treatment for neurodegenerative diseases. *Med. Chem. Commun.* **8**, 135-147 (2016).
2. Wang, Y. *et al*. Aminoadamantane Derivatives as Therapeutic Agents. US644702B1 (2002).
3. Anderson, G. L. *et al*. Novel Synthesis of 3-Fluoro-1-Aminoadamantane and Some of its Derivatives. *Syn. Comm*. **18**, 1967-1974 (1988).
4. Becker, C. K. *et al*. Aminoadamantyl nitrate compounds and their use to treat CNS disorders. US20200377444A1 (2020).



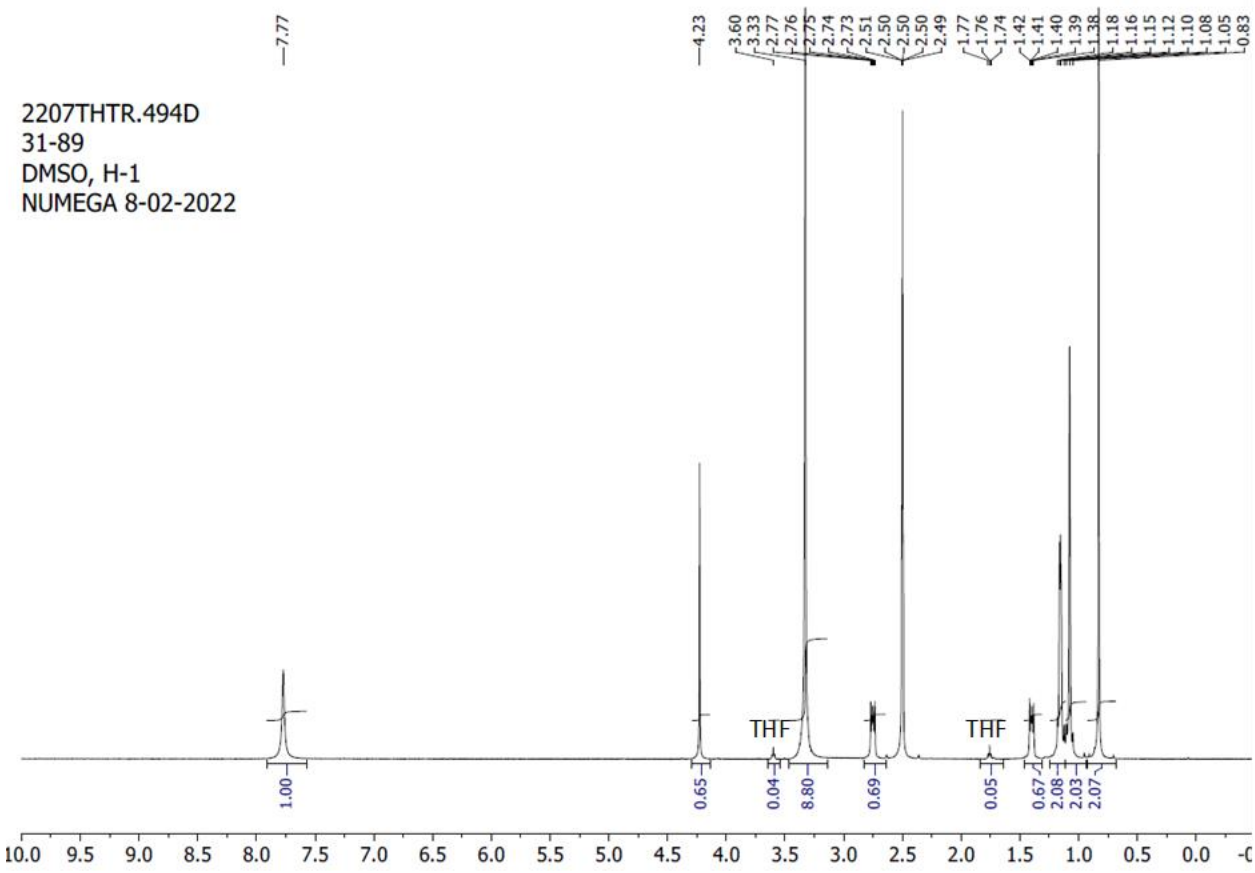
Supplementary Fig. 1. ^{1}H NMR Spectra of NMT2.



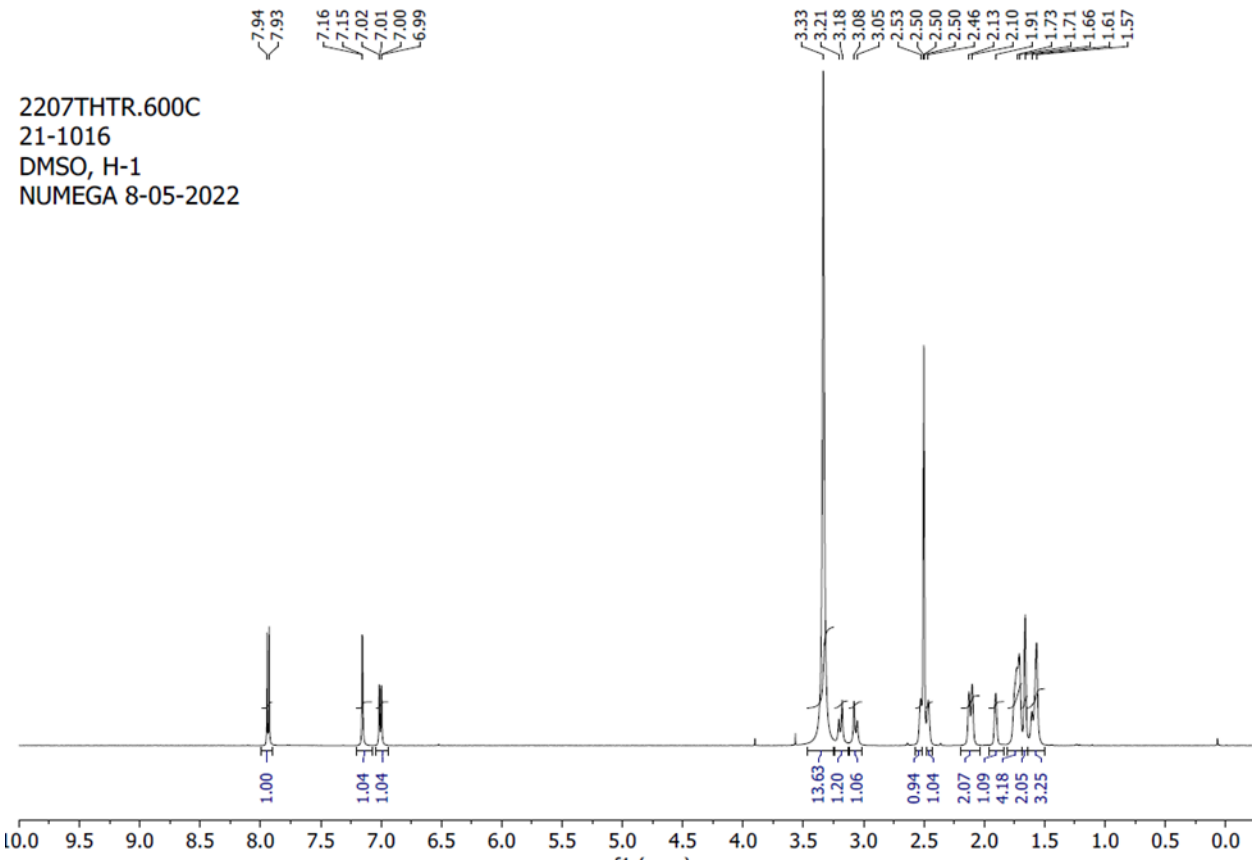
Supplementary Fig. 2. ^{1}H NMR Spectra of NMT3.



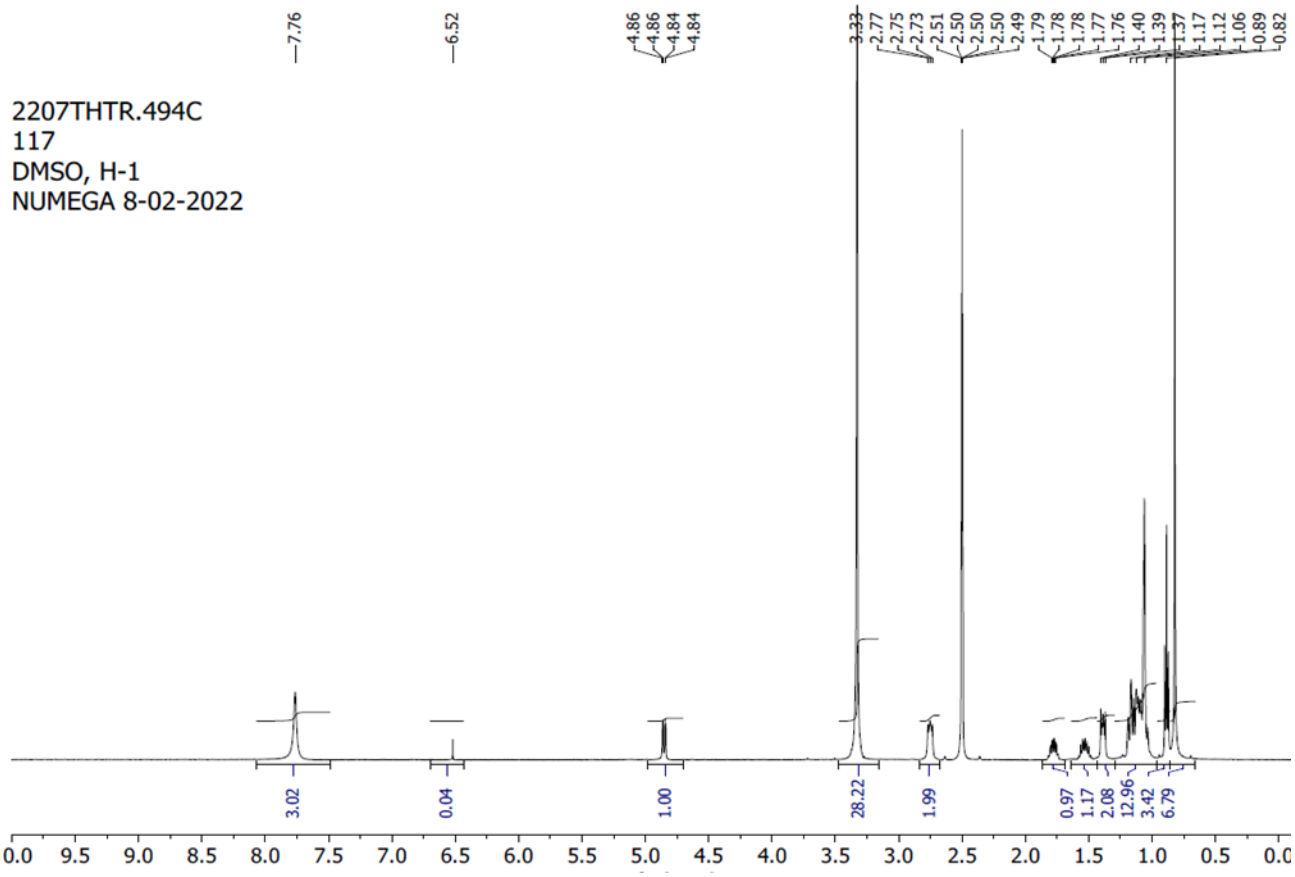
Supplementary Fig. 3. ^{1}H NMR Spectra of NMT5.



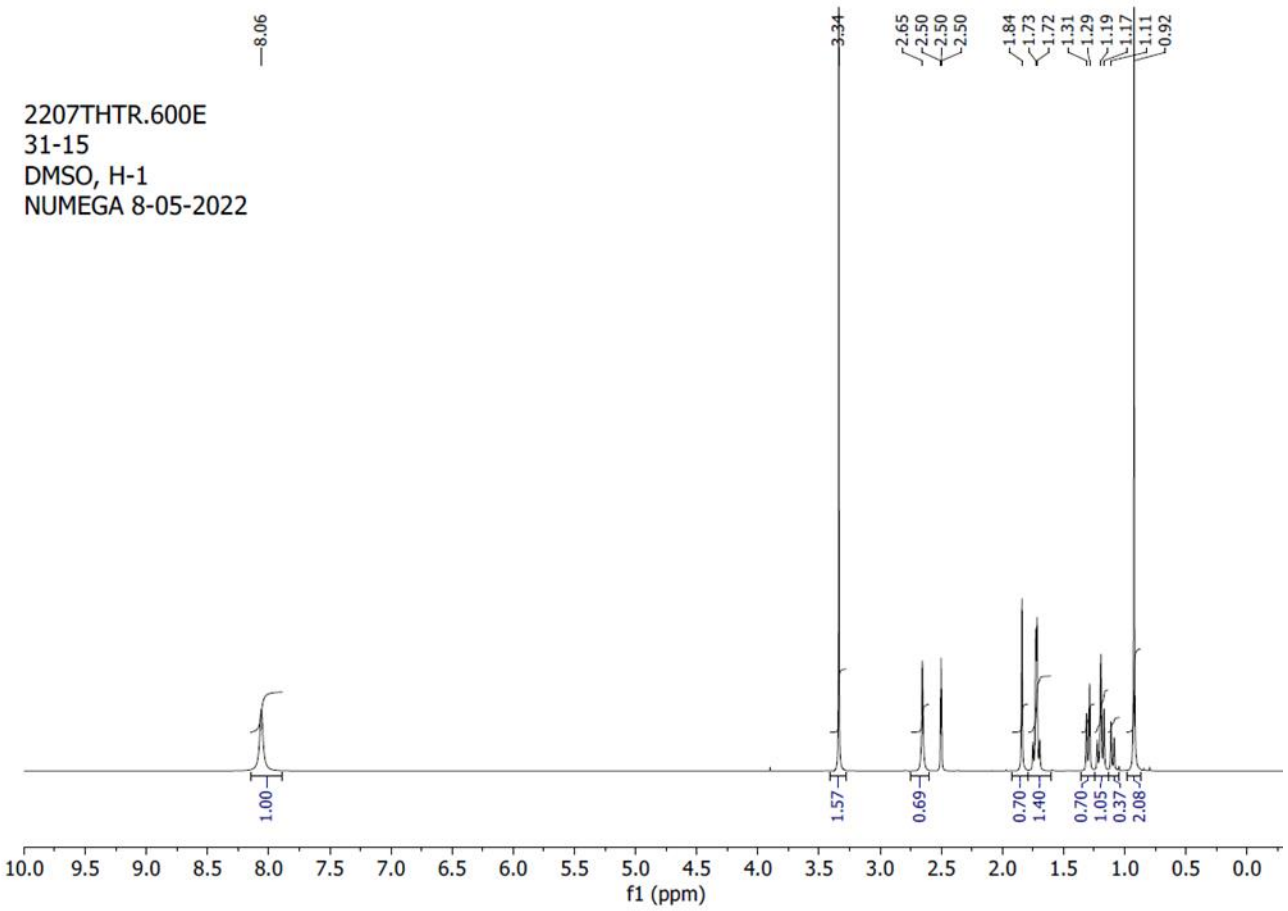
Supplementary Fig. 4. ^{1}H NMR Spectra of NMT6.



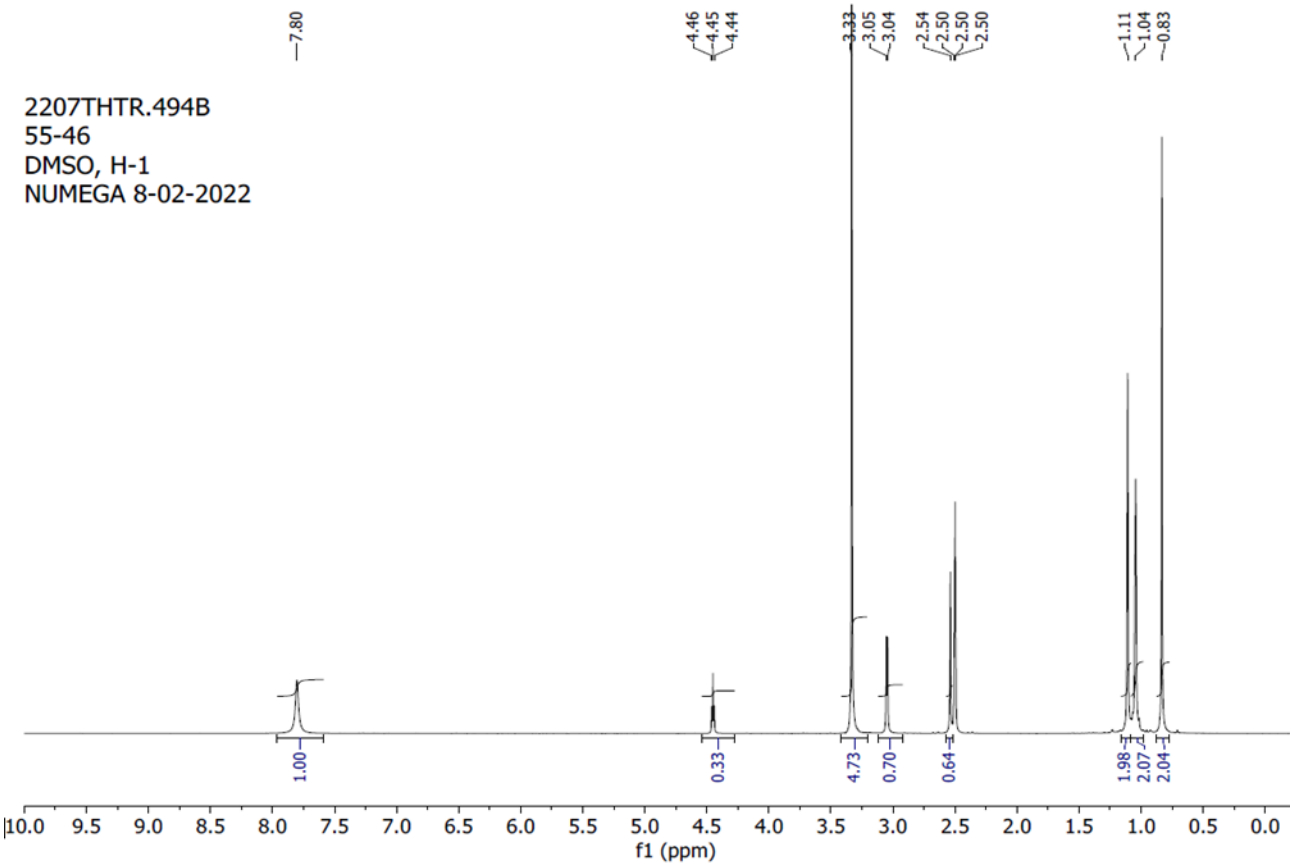
Supplementary Fig. 5. ^{1}H NMR Spectra of NMT7.



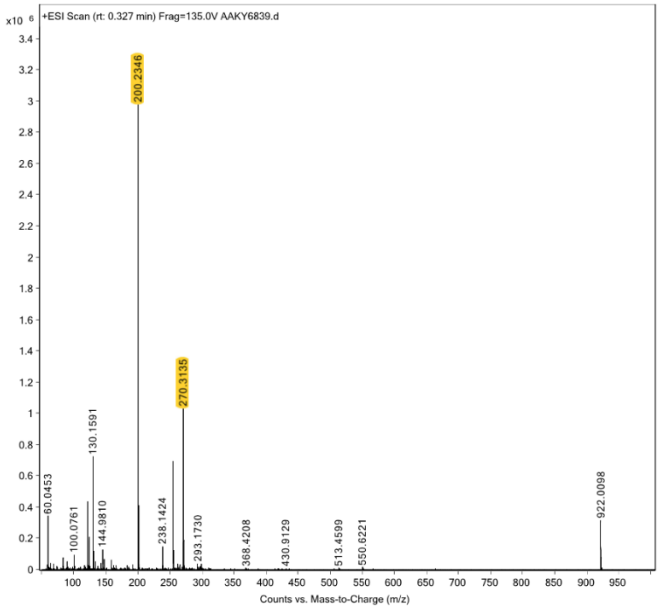
Supplementary Fig. 6. ^{1}H NMR Spectra of NMT8.

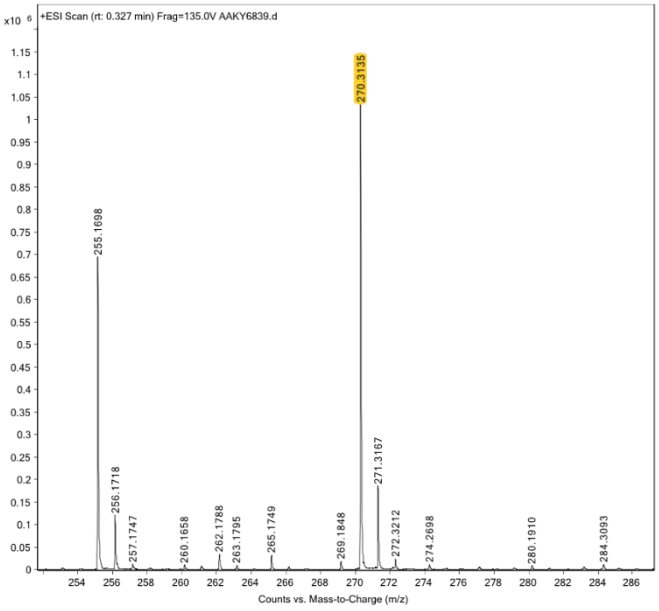


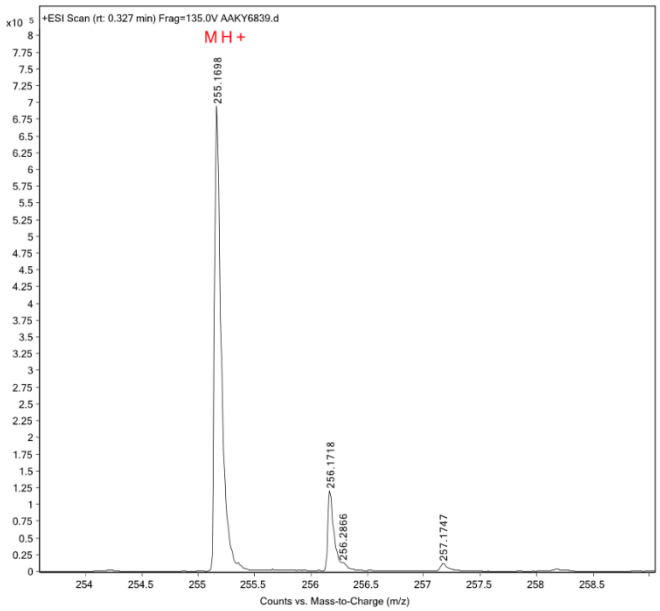
Supplementary Fig. 7. ^{1}H NMR Spectra of NMT9.



Supplementary Fig. 8. ^{1}H NMR Spectra of NMT5-metabolite.

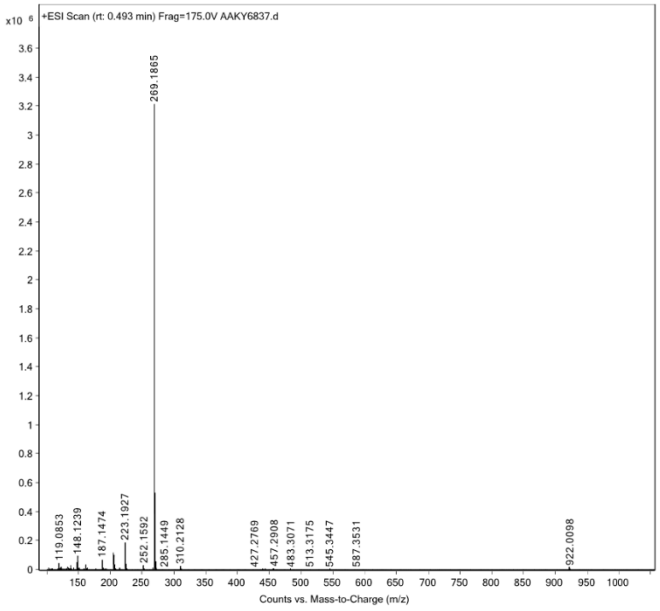


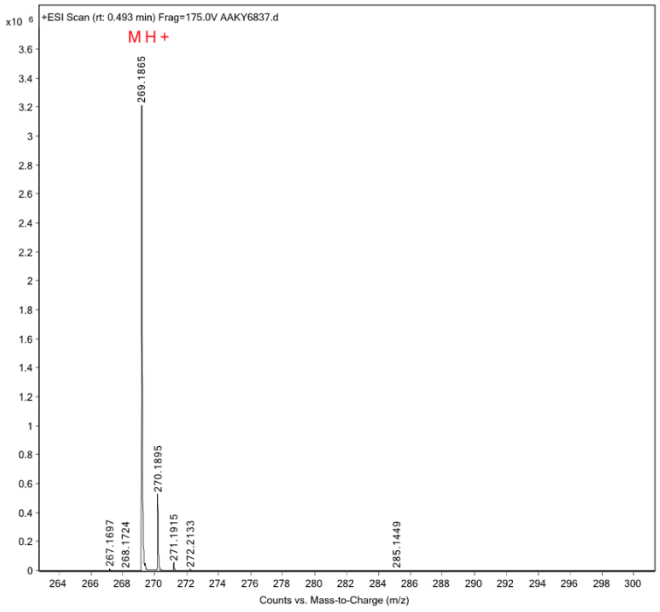


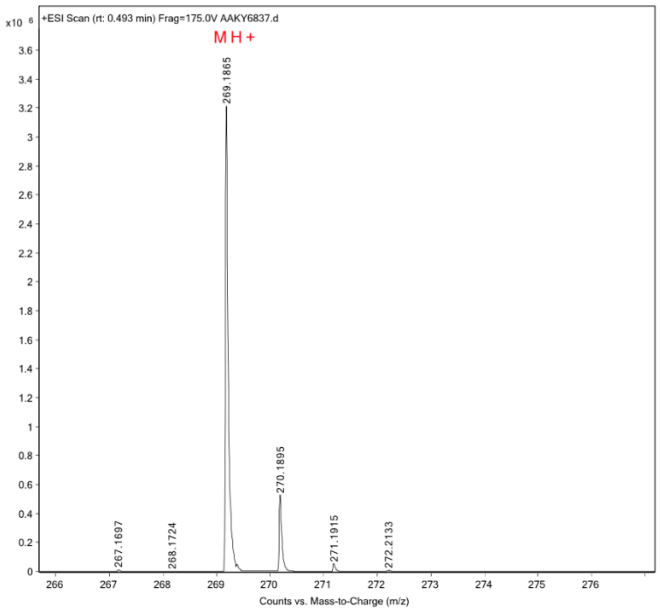


Yellow highlights indicated background ions from solvent.

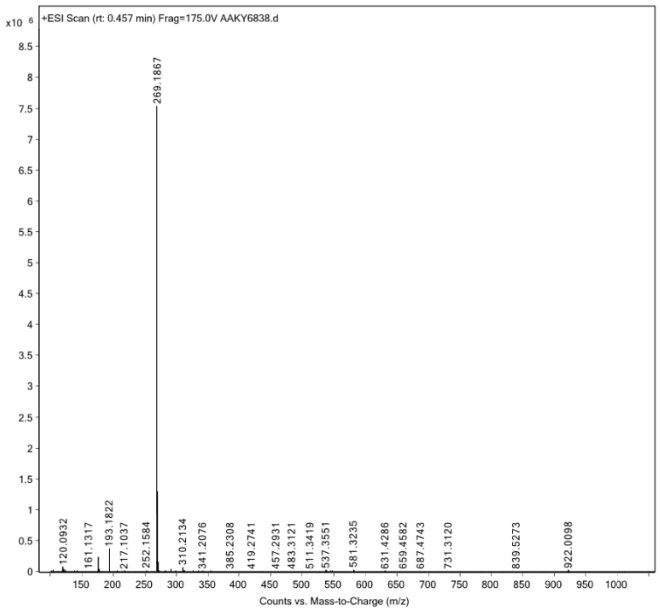
Supplementary Fig. 9. HRMS of NMT2.

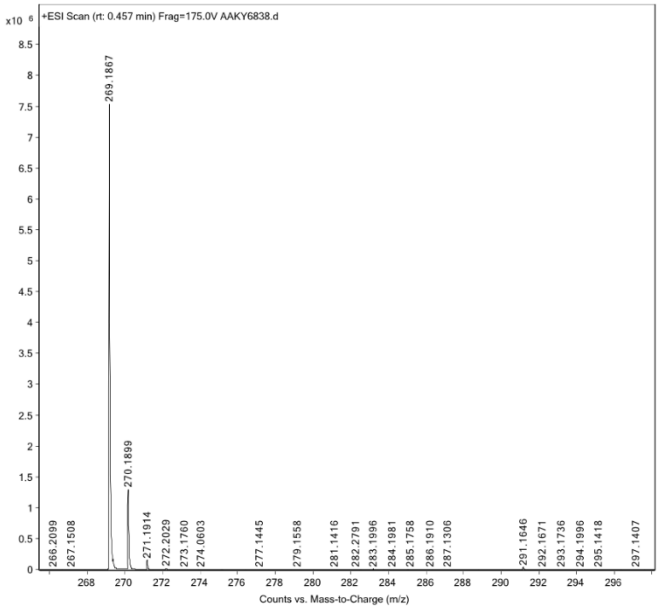


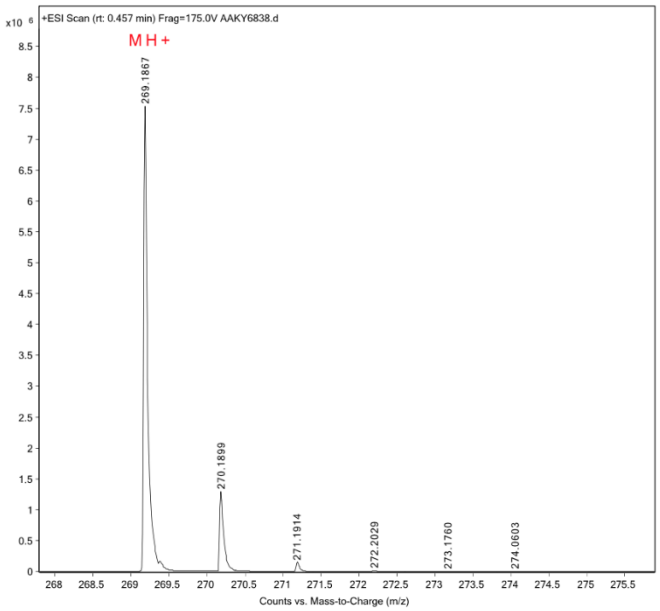




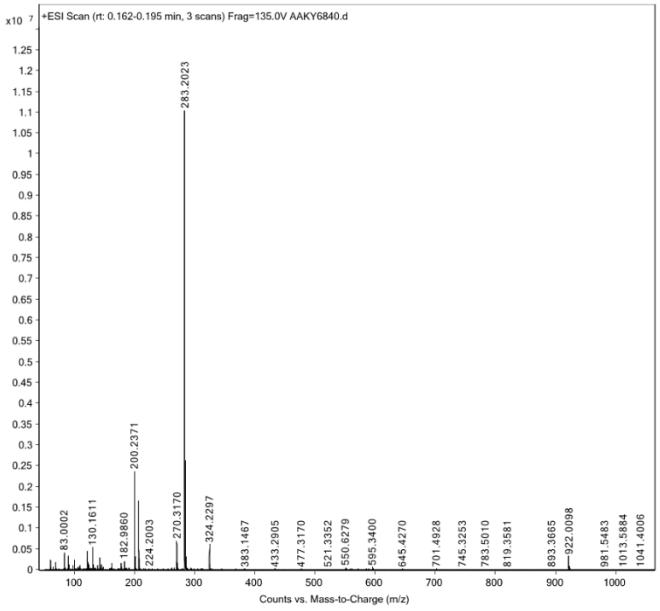
Supplementary Fig. 10. HRMS of NMT3.

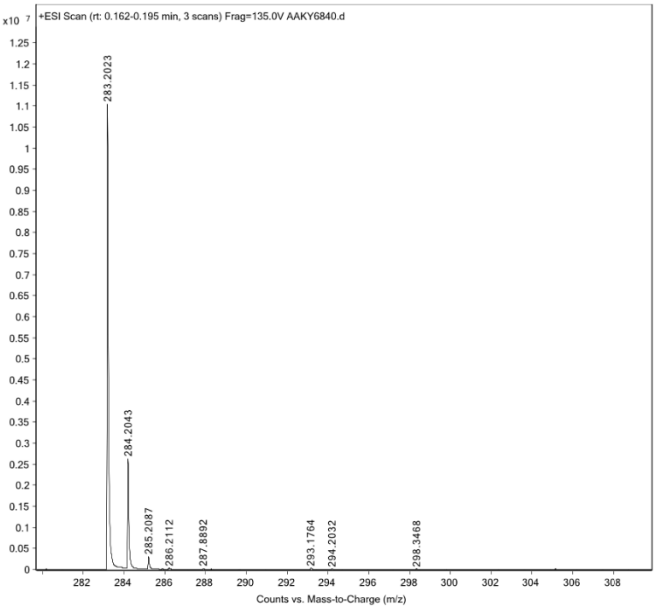


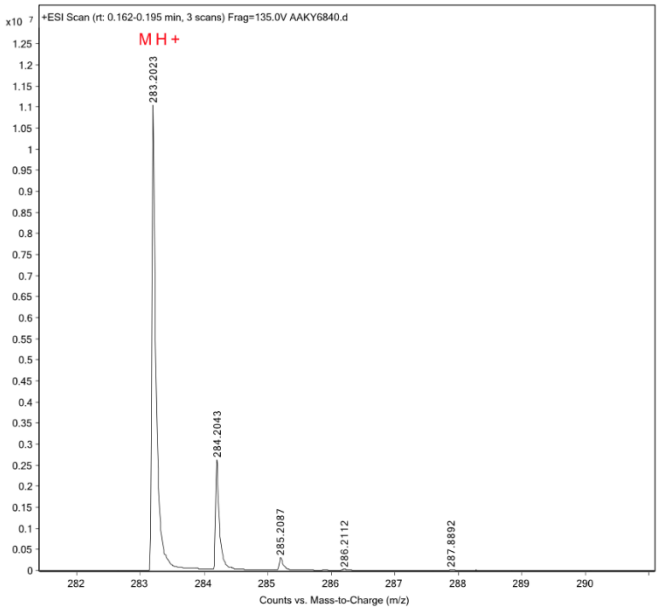




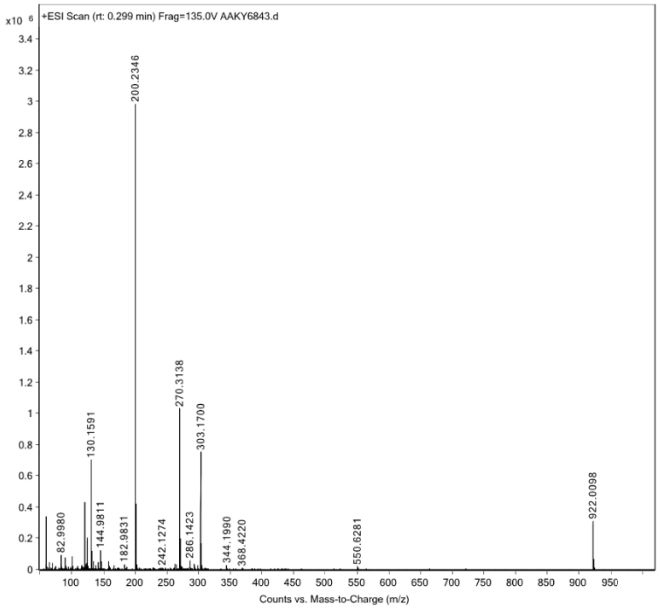
Supplementary Fig. 11. HRMS of NMT5.

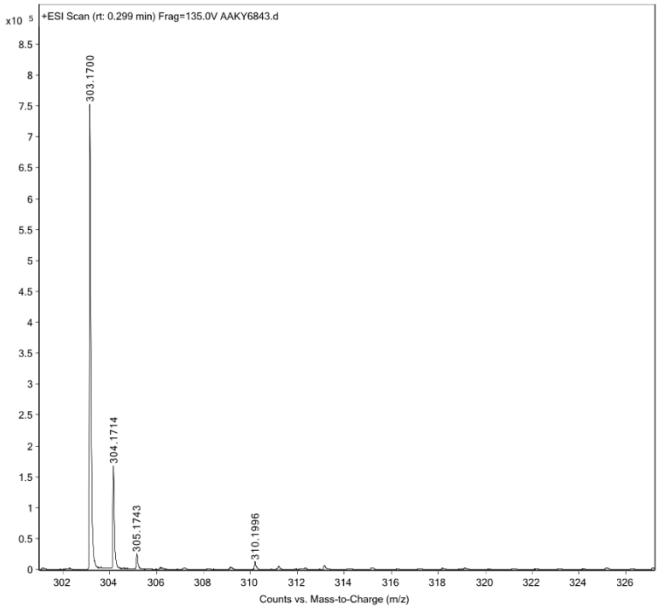


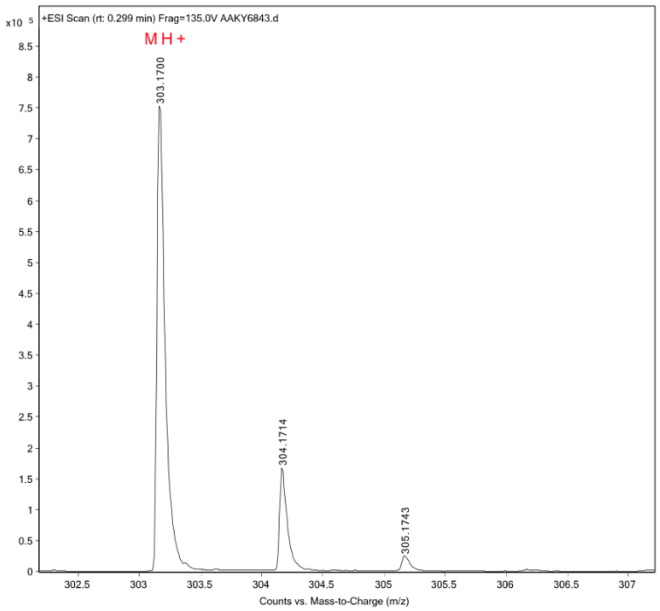




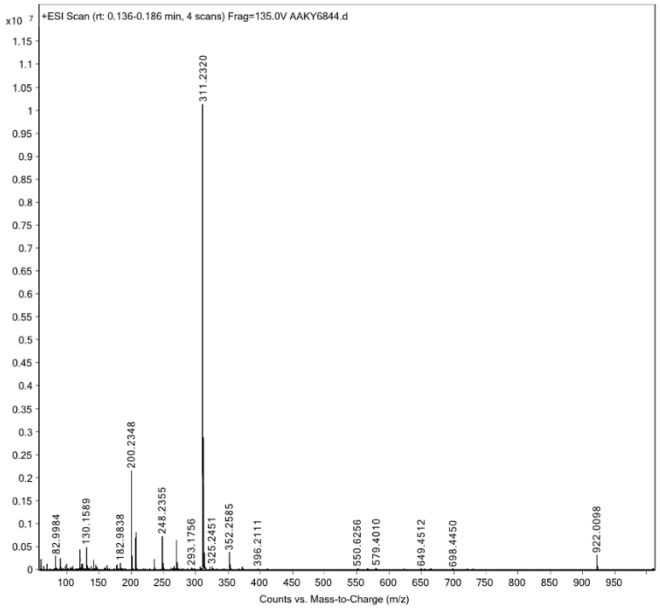
Supplementary Fig. 12. HRMS of NMT6.

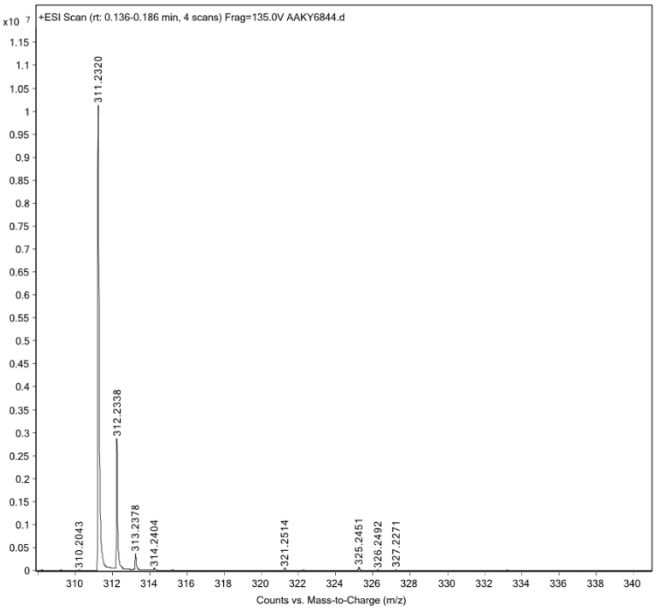


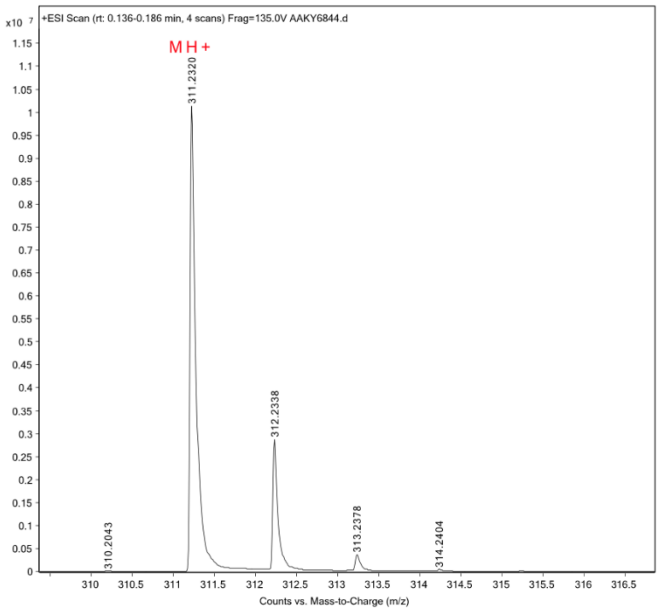




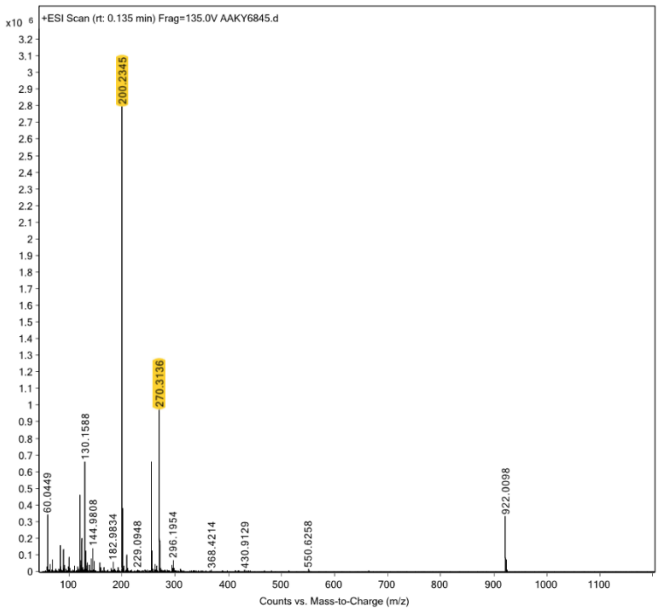
Supplementary Fig. 13. HRMS of NMT7.

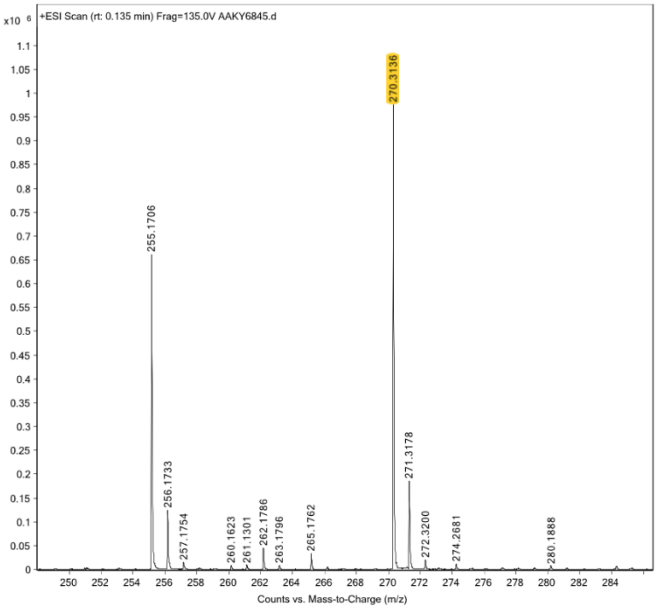


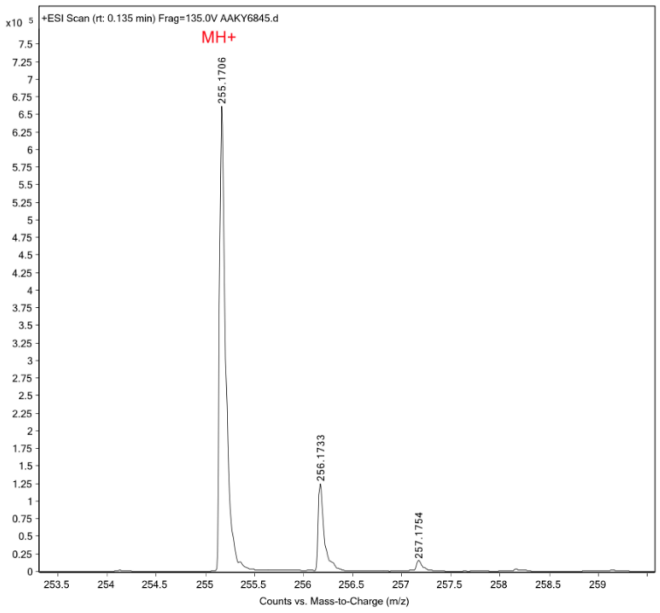




Supplementary Fig. 14. HRMS of NMT8.

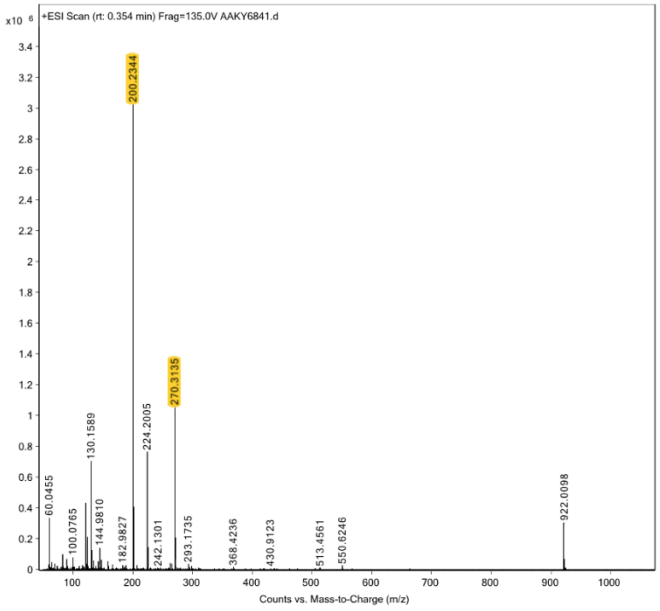


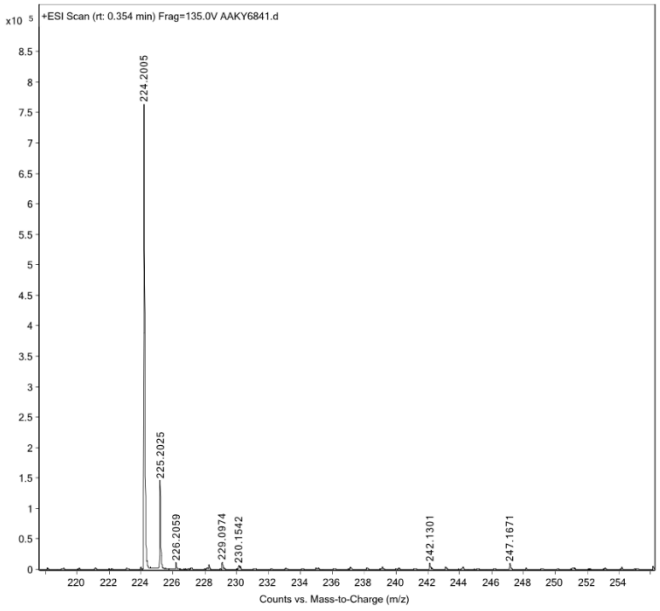


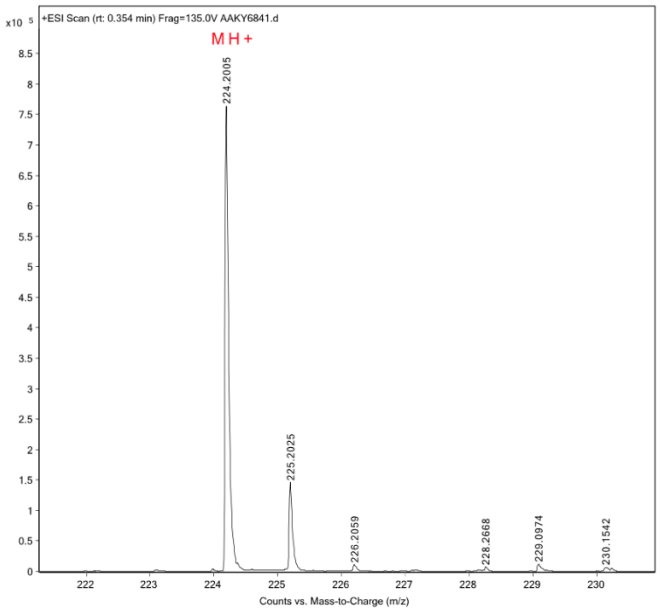


Yellow highlights indicated background ions from solvent.

Supplementary Fig. 15. HRMS of NMT9.







Yellow highlights indicated background ions from solvent.

Supplementary Fig. 16. HRMS of NMT5-metabolite.