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Synthesis of 3-imino-1-benzazepines by the cyanide-incorporating heterocyclization of (2-benzylaminobenzylidene)malonates

Dmitrii S. Ivanov, Marina V. Molchanova, Aleksander Yu. Smirnov, Andrey A. Mikhaylov, Pavel N. Solyev and Mikhail S. Baranov

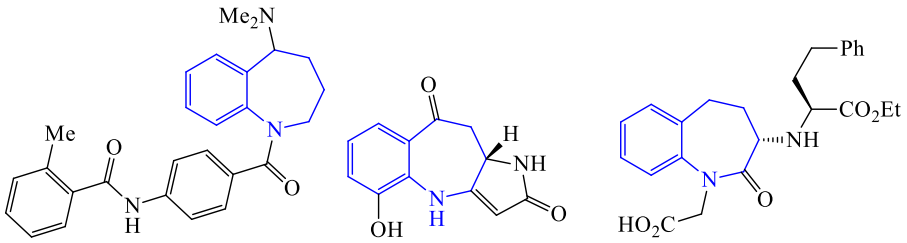
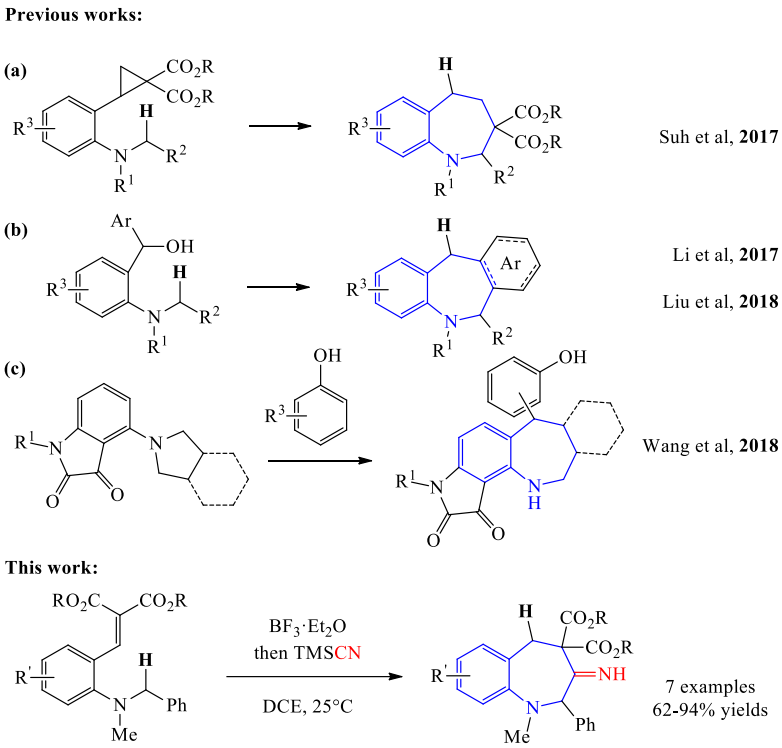


Figure S1 Representative biologically active 1-benzazepine derivatives.

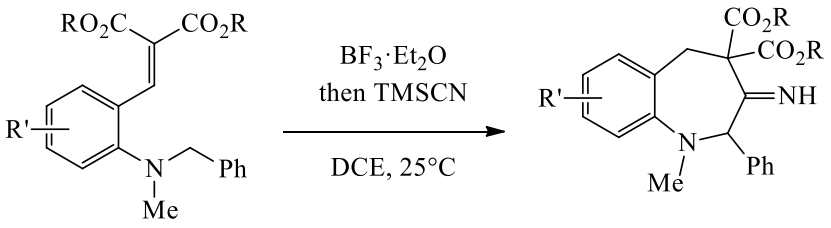


Scheme S1 Literature syntheses of some 1-benzazepines *vs*. those of the current work

S1. Reagents and methods.

^{1}H and ^{13}C NMR spectra were acquired on Bruker Avance III (700 and 176 MHz, respectively), Bruker Avance III 800 (800 and 201 MHz, respectively), and Bruker Fourier 300 (300 and 75 MHz, respectively) spectrometers in DMSO-*d*$_6$ (TMS or the residual solvent signals (2.50 ppm for ^{1}H nuclei, 39.5 ppm for ^{13}C nuclei) served as internal standard) or $CDCl_3$ (the residual solvent signals served as internal standards (7.26 ppm for ^{1}H nuclei, 77.2 ppm for ^{13}C nuclei)). High-resolution mass spectra were recorded on a Sciex TripleTOF 5600+ instrument, electrospray ionization. The infrared absorption spectra were registered using an FT-801 Fourier IR spectrometer (Simex, Russia) in the range of 500–4000 cm^{-1} using ATR technique (ATR = attenuated total reflection). Spectra were recorded with a scan number of 36 with a resolution of 4 cm^{-1}. The results were presented as an averaged (or levelled) spectrum. ZaIR 3.5 software (Simex) was used to carry out baseline correction and normalization of FTIR spectra. A background measurement was taken for every sample processed. Peaks corresponding to CO_2 were not removed (663-674 cm^{-1} and 2290-2390 cm^{-1}).The absorption bands are reported as follows: vs. = very strong, s = strong, m = middle, w = weak, vw = very weak. Melting points were determined on an SMP 30 instrument. Reagents supplied by Acros Organics were used without additional purification; freshly distilled solvents were used for the reactions. Compounds **1a-f**, **2a-f, 2′a, 2″a** were obtained from commercially available reagents using a literature method.[S1] The spectral characteristics of compounds **1a-b**,[S2] **1c**,[S1] **1d**,[S2] **1e**,[S2] **1h**,[S3] **2a**,[S4] **2b-e**,[S1] **2′a, 2″a**,[S5] **2f**[S1] coincided with the literature data.

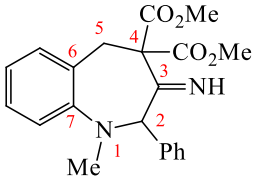
S2. General synthetic procedure for 3-imino-1-methyl-2-phenyl-1,2,3,5-tetrahydro-4*H*-benzazepine-4,4-dicarboxylates 3a.



2a-g **3a-g**

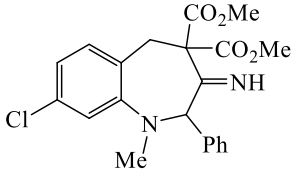
The corresponding 2-[2-(*N*-benzyl-*N*-methylamino)benzylidene]malonate **2** (0.5 mmol) dissolved in 1,2-dichloroethane (2 mL), $BF_3 \cdot Et_2O$ (177 mg, 1.25 mmol, 154 μL) was added, and the mixture was stirred for 12 h (overnight) at 25 °C. Then Me_3SiCN (99 mg, 1 mmol, 125 μL) was added, and the mixture was stirred for 30 min at 25 °C. The reaction progress was monitored by TLC (eluent hexane – EtOAc, 3:1). After the disappearance of substrate **2**, the reaction mixture was diluted with 50 mL of EtOAc, treated with a mixture of 15 mL of sat. aq. $NaHCO_3$ solution and 15 mL of sat. aq. KCl solution, then 2×30 ml of sat. aq. KCl solution, dried over Na_2SO_4, evaporated. The product was isolated by flash chromatography (gradient eluent hexane – EtOAc 9:1 vol, then 3:1 vol). In the case of the impurity's **4** presence, the product was additionally purified by flash chromatography (eluent hexane – CH_2Cl_2 1:1 vol, then 1:3 vol).

Dimethyl 3-imino-1-methyl-2-phenyl-1,2,3,5-tetrahydro-4*H*-1-benzazepine-4,4-dicarboxylate (3a).



Yield 161 mg (88%), pale yellow oil (R_f = 0.35 for eluent hexane – EtOAc 3:1 vol). ^{1}H NMR (800 MHz, DMSO-d_6) δ: 7.55 – 7.51 (2H, m, Ph), 7.50 – 7.47 (2H, m, Ph), 7.44 – 7.41 (2H, m, Ph, H-6 Ar), 7.29 – 7.26 (1H, m, H-8 Ar), 7.16 – 7.13 (1H, m, H-7 Ar), 7.03 – 7.00 (1H, m, H-9 Ar), 5.66 (1H, s, N-C<u>H</u>-Ph), 3.93 (6H, s, $COOCH_3$), 3.62 – 3.58 (2H, m, Ar-C<u>H</u>$_2$), 2.58 (3H, s, N-CH_3). ^{13}C NMR (201 MHz, DMSO-d_6) δ: 173.2 (<u>C</u>OOMe), 148.3 (C-10), 135.6 (C-11), 133.8 (C=NH), 128.9 (*m*-C Ph), 128.8 (*p*-C Ph), 127.9 (*o*-C Ph), 127.7 (C-9), 127.0 (C-8), 125.7 (C-7), 122.5 (C-6), 117.3 (*i*-C Ph), 78.3 (<u>C</u>(COOMe)$_2$), 60.3 (N-<u>C</u>H-Ph), 56.1 (COO<u>C</u>H$_3$), 37.6 (br. s., N-<u>C</u>H$_3$), 21.7 (Ar-<u>C</u>H$_2$). HRMS (ESI), *m/z*: 366.1655 $[M+H]^+$, (calc. for $C_{21}H_{23}N_2O_4^+$, *m/z*: 367.1652). ^{1}H-^{13}C HSQC (the most important cross peaks): H^5-C^5. ^{1}H-^{13}C HMBC (the most important cross peaks): H^5-C^3. IR (ATR diamond, ν/cm^{-1}): 529, 627, 671, 696, 718, 731, 758, 774, 799, 916, 941, 1036, 1076, 1121, 1186, 1225, 1277, 1339, 1377, 1391, 1447, 1503, 1607 (C=NH), 1734 (C=O), 2851, 2952, 3033, 3064.

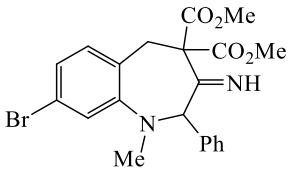
Dimethyl 8-chloro-3-imino-1-methyl-2-phenyl-1,2,3,5-tetrahydro-4*H*-1-benzazepine-4,4-dicarboxylate (3b).



Yield 120 mg (86%), colorless oil (R_f = 0.30 for eluent hexane – EtOAc 3:1 vol). ^{1}H NMR (800 MHz, DMSO-d_6) δ: 7.53 – 7.51 (2H, m, *o*-H Ph), 7.50 – 7.47 (2H, m, *m*-H Ph), 7.45 – 7.42 (1H, m, *p*-H Ph), 7.41 (1H, d, *J* = 2.2 Hz, H-9 Ar), 7.21 (1H, dd, *J* = 8.3 Hz, 2.2 Hz, H-7 Ar), 7.07 (1H, d, *J* = 8.3 Hz, H-6 Ar), 5.74 (1H, s, N-C<u>H</u>-Ph), 3.93 (6H, s, $COOCH_3$), 3.58 – 3.52 (2H, m, Ar-C<u>H</u>$_2$), 2.57 (3H, s, N-CH_3). ^{13}C NMR (201 MHz, DMSO-d_6) δ: 173.1 (<u>C</u>OOMe), 149.6 (Ar), 134.8 (Ar), 133.4 (C=NH), 131.0 (Ar), 129.8 (Ar), 129.0 (Ar), 129.0 (Ar), 127.7 (Ar), 125.6 (Ar), 122.7 (Ar), 117.1 (Ar), 78.0

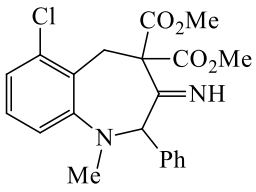
(C(COOMe)$_2$), 59.9 (COOCH$_3$), 56.1 (N-CH-Ph), 38.0 (уш. с., N-CH$_3$), 21.5 (Ar-CH$_2$). HRMS (ESI), *m/z*: 401.1261 [M+H]$^+$, (calc. for $C_{21}H_{22}ClN_2O_4^+$, *m/z*: 401.1263).

Dimethyl 8-bromo-3-imino-1-methyl-2-phenyl-1,2,3,5-tetrahydro-4*H*-1-benzazepine-4,4-dicarboxylate (3c).



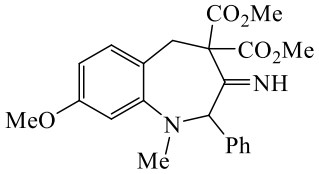
Yield 172 mg (77%), colorless oil (R_f = 0.30 for eluent hexane – EtOAc 3:1 vol). ^{1}H NMR (800 MHz, $CDCl_3$) *δ*: 7.62 – 7.54 (3H, m, Ar), 7.49 – 7.40 (3H, m, Ar), 7.29 – 7.26 (1H, m, Ar), 6.88 (1H, d, *J* = 8.3, H-6 Ar), 5.16 (1H, s, N-CH-Ph), 3.95 (6H, s, COOCH$_3$), 3.65 – 3.52 (2H, m, Ar-CH$_2$), 2.65 (3H, s, N-CH$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 173.9 (COOMe), 150.0 (Ar), 134.4 (C=NH), 133.1 (Ar), 129.7 (Ar), 129.5 (Ar), 129.4 (Ar), 129.2 (Ar), 127.8 (Ar), 126.4 (Ar), 120.8 (Ar), 116.3 (Ar), 77.9 (C(COOMe)$_2$), 61.3 (COOCH$_3$), 56.0 (N-CH-Ph), 37.4 (Ar-CH$_2$-C), 22.3 (N-CH$_3$). HRMS (ESI), *m/z*: 445.0757 [M+H]$^+$, (calc. for $C_{21}H_{22}BrN_2O_4^+$, *m/z*: 445.0757).

Dimethyl 6-chloro-3-imino-1-methyl-2-phenyl-1,2,3,5-tetrahydro-4*H*-1-benzazepine-4,4-dicarboxylate (3d).



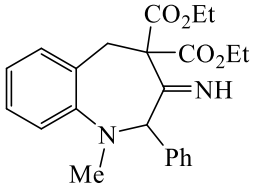
Yield 124 mg (62%), white solid, m. p. 95°C (R_f = 0.35 for eluent hexane – EtOAc 3:1 vol). ^{1}H NMR (800 MHz, DMSO-*d*$_6$) *δ*: 7.33 – 7.29 (3H, m, Ar), 7.13 – 7.10 (1H, m, Ar), 7.02 – 6.99 (2H, m, Ar), 6.72 (1H, d, *J* = 7.9 Hz, Ar), 6.62 (1H, d, *J* = 8.4 Hz, Ar), 5.12 (1H, s, N-CH-Ph), 3.67 – 3.65 (2H, m, Ar-CH$_2$), 3.60 – 3.57 (6H, m, COOCH$_3$), 2.88 (3H, s, N-CH$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 173.5 (COOMe), 148.8 (Ar), 135.5 (C=NH), 133.6 (Ar), 129.3 (Ar), 129.1 (Ar), 128.3 (Ar), 127.8 (Ar), 127.5 (Ar), 126.1 (Ar), 122.8 (Ar), 116.8 (Ar), 78.7 (C(COOMe)$_2$), 65.5 (COOCH$_3$), 61.8 (COOCH$_3$), 37.2 (N-CH-Ph), 22.3 (Ar-CH$_2$), 14.4 (N-CH$_3$). HRMS (ESI), *m/z*: 401.1263 [M+H]$^+$, (calc. for $C_{21}H_{22}ClN_2O_4^+$, *m/z*: 401.1263).

Dimethyl 3-imino-8-methoxy-1-methyl-2-phenyl-1,2,3,5-tetrahydro-4*H*-1-benzazepine-4,4-dicarboxylate (3e).



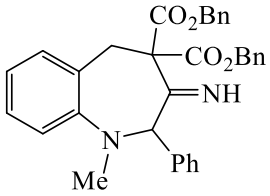
Yield 186 mg (94%), colorless oil (R_f = 0.20 for eluent hexane – EtOAc 3:1 vol). ^{1}H NMR (800 MHz, $CDCl_3$) *δ*: 7.63 – 7.60 (2H, m, *o*-H Ph), 7.47 – 7.43 (2H, m, *m*-H Ph), 7.43 – 7.40 (1H, m, *p*-H Ph), 7.06 (1H, d, *J* = 2.6 Hz, H-9 Ar), 6.92 (1H, d, J = 8.5 Hz, H-6 Ar), 6.70 (1H, dd, J = 8.5, 2.6, H-7 Ar), 5.19 (1H, s, N-CH-Ph), 3.94 (6H, s, COOCH$_3$), 3.82 (3H, s, OCH$_3$), 3.66 – 3.52 (2H, m, Ar-CH$_2$), 2.64 (3H, s, N-CH$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 173.9 (COOMe), 159.1 (Ar), 149.8 (Ar), 133.6 (C=NH), 129.3 (Ar), 129.1 (Ar), 128.9 (Ar), 127.8 (Ar), 127.0 (Ar), 116.8 (Ar), 111.4 (Ar), 109.2 (Ar), 78.7 (C(COOMe)$_2$), 61.5 (N-CH-Ph), 55.8 (COOCH$_3$), 55.5 (Ar-OCH$_3$), 37.3 (Ar-CH$_2$), 21.8 (N-CH$_3$). HRMS (ESI), *m/z*: 397.1760 [M+H]$^+$, (calc. for $C_{22}H_{25}N_2O_5^+$, *m/z*: 397.1758).

Diethyl 3-imino-1-methyl-2-phenyl-1,2,3,5-tetrahydro-4*H*-1-benzazepine-4,4-dicarboxylate (3′a).



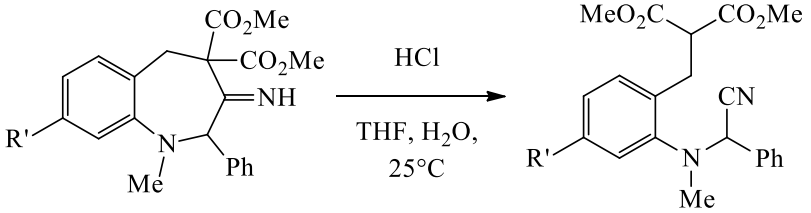
Yield 158 mg (79%), pale yellow oil (R_f = 0.40 for eluent hexane – EtOAc 3:1 vol). ^{1}H NMR (800 MHz, $CDCl_3$) δ: 7.65 – 7.60 (2H, m, Ar), 7.50 – 7.48 (1H, m, Ar), 7.47 – 7.44 (2H, m, Ar), 7.43 – 7.40 (1H, m, Ar), 7.28 – 7.26 (1H, m, Ar), 7.16 – 7.14 (1H, m, Ar), 7.05 – 7.02 (1H, m, Ar), 5.21 (1H, s, N-C<u>H</u>-Ph), 4.41 – 4.36 (4H, m, COOC<u>H</u>$_2$CH$_3$), 3.72 – 3.62 (2H, m, Ar-C<u>H</u>$_2$), 2.66 (3H, s, N-CH$_3$), 1.26 (6H, t, J = 7.1 Hz, COOCH$_2$C<u>H</u>$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.5 (<u>C</u>OOMe), 148.8 (Ar), 135.5 (C=NH), 133.6 (Ar), 129.3 (Ar), 129.1 (Ar), 128.3 (Ar), 127.8 (Ar), 127.5 (Ar), 126.1 (Ar), 122.8 (Ar), 116.8 (Ar), 78.7 (<u>C</u>(COOMe)$_2$), 65.5 (COO<u>C</u>H$_2$CH$_3$), 61.8 (N-<u>C</u>H-Ph), 37.2 (Ar-<u>C</u>H$_2$), 22.3 (N-<u>C</u>H$_3$), 14.4 (COOCH$_2$<u>C</u>H$_3$). HRMS (ESI), *m/z*: 395.1965 $[M+H]^+$, (calc. for $C_{23}H_{27}N_2O_4^+$, *m/z*: 395.1965).

Dibenzyl 3-imino-1-methyl-2-phenyl-1,2,3,5-tetrahydro-4*H*-1-benzazepine-4,4-dicarboxylate (3″a).



Yield 210 mg (81%), pale yellow oil (Rf = 0.40 for eluent hexane – EtOAc 3:1 vol). ^{1}H NMR (800 MHz, $CDCl_3$) δ: 7.44 – 7.38 (4H, m, Ar), 7.36 – 7.33 (3H, m, Ar), 7.32 – 7.29 (2H, m, Ar), 7.29 – 7.27 (3H, m, Ar), 7.25 – 7.23 (2H, m, Ar), 7.16 – 7.13 (4H, m, Ar), 7.10 – 7.07 (1H, m, Ar), 6.98 – 6.95 (1H, m, Ar), 5.32 (4H, m, COOC<u>H</u>$_2$Ph), 4.82 (1H, s, N-C<u>H</u>-Ph), 3.64 (2H, m, Ar-C<u>H</u>$_2$-C), 2.42 (3H, s, N-CH$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.4 (<u>C</u>OOMe), 148.9 (уш. с., Ar), 135.5 (C=NH), 133.6 (Ar), 133.5 (Ar), 129.3 (Ar), 129.1 (Ar), 128.9 (Ar), 128.6 (Ar), 128.3 (Ar), 127.7 (Ar), 127.4 (Ar), 126.2 (Ar), 122.8 (Ar), 116.8 (Ar), 79.6 (<u>C</u>(COOMe)$_2$), 71.0 (COO<u>C</u>H$_2$Ph), 61.5 (N-<u>C</u>H-Ph), 37.0 (Ar-<u>C</u>H$_2$-C), 22.0 (N-<u>C</u>H$_3$). HRMS (ESI), *m/z*: 519.2278 $[M+H]^+$ (calc. for $C_{33}H_{31}N_2O_4^+$, *m/z*: 519.2278).

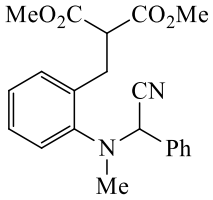
S3. General synthetic procedure for dimethyl 2-{2-[*N*-(1-cyano-1-phenylmethyl)-*N*-methylamino]benzyl}malonates 4.



3a-c **4a-c**

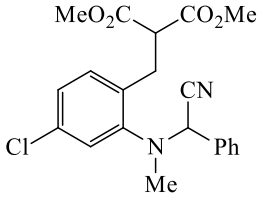
The corresponding 3-imino-1-methyl-2-phenyl-1,2,3,5-tetrahydro-4*H*-1-benzazepine-4,4-dicarboxylate **3a–c** (0.2 mmol) was dissolved in THF (2 mL), 3 M aq. HCl (2 mL) was added, and the mixture was stirred for 6 h. The reaction progress was monitored by TLC (eluent CH_2Cl_2). After the disappearance of substrate **3a–c**, the reaction mixture was diluted with 50 mL EtOAc, treated with 2×30 mL saturated aq. KCl, dried over Na_2SO_4 and evaporated. The product was isolated by flash chromatography (eluent hexane – DCM 1:1 vol., then 1:3 vol.).

Dimethyl 2-{2-[*N*-(1-cyano-1-phenylmethyl)-*N*-methylamino]benzyl}malonate (4a).



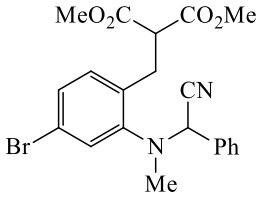
Yield 64 mg (87%), colorless oil (Rf = 0.35 for eluent hexane – CH_2Cl_2 1:3 vol). ^{1}H NMR (800 MHz, DMSO-d_6) δ: 7.55 – 7.52 (2H, m, *o*-H Ph), 7.50 – 7.47 (2H, m, *m*-H Ph), 7.46 – 7.42 (2H, m, *p*-H Ph and Ar), 7.34 – 7.31 (1H, m, Ar), 7.25 – 7.22 (1H, m, Ar), 7.19 – 7.16 (1H, m, Ar), 5.70 (1H, s, N-C<u>H</u>-Ph), 4.00 - 3.96 (1H, m, C<u>H</u>(COOMe)$_2$), 3.63 (3H, s, COOCH_3), 3.58 (3H, s, COOCH_3), 3.35 – 3.31 (1H, m, Ar-C<u>H$_2$</u>-CH), 3.13 (1H, dd, J = 14.3, 8.6, Ar-S<u>H$_2$</u>-CH), 2.53 (3H, s, N-CH_3). ^{13}C NMR (201 MHz, DMSO-d_6) δ: 168.9 (<u>C</u>OOMe), 148.9 (Ar), 134.1 (Ar), 133.6 (Ar), 130.3 (Ar), 128.9 (Ar), 128.9 (Ar), 127.9 (Ar), 127.6 (Ar), 125.9 (Ar), 123.2 (Ar), 117.0 (CN), 60.9 (<u>C</u>H-CN), 52.4, 52.3, 51.3, 37.3 (N-<u>C</u>H$_3$), 29.9 (Ar-<u>C</u>H$_2$). HRMS (ESI), *m/z*: 367.1652 $[M+H]^+$ (calc. for $C_{21}H_{23}N_2O_4^+$, *m/z*: 367.1652). IR (ATR diamond, ν/cm^{-1}): 505, 519, 544, 602, 631, 654, 696, 731, 749, 762, 777, 841, 914, 940, 1024, 1046, 1078, 1117, 1150, 1196, 1227, 1264, 1294, 1337, 1372, 1433, 1449, 1493, 1599, 1678, 1730 (C=O), 2849, 2952, 3031, 3064.

Dimethyl 2-{4-chloro-2-[*N*-(1-cyano-1-phenylmethyl)-*N*-methylamino]benzyl}malonate (4b).



Yield 66 mg (82%), colorless oil (Rf = 0.35 for eluent hexane – CH_2Cl_2 1:3 vol). ^{1}H NMR (800 MHz, DMSO-d_6) δ: 7.54 – 7.48 (4H, m, *o*-H и *m*-H Ph), 7.47 – 7.44 (1H, m, *p*-H Ph), 7.42 (1H, d, J = 2.2, H-9 Ar), 7.30 (1H, d, J = 8.3, H-6 Ar), 7.26 (1H, dd, J = 8.3, 2.2, H-7 Ar), 5.76 (1H, s, N-C<u>H</u>-Ph), 4.01 - 3.98 (1H, m, C<u>H</u>(COOMe)$_2$), 3.63 (3H, s, COOCH_3), 3.59 (3H, s, COOCH_3), 3.29 – 3.25 (1H, m, Ar-C<u>H$_2$</u>-CH), 3.16 – 3.10 (1H, m, Ar-S<u>H$_2$</u>-CH), 2.52 (3H, s, N-CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 168.9 (<u>C</u>OOMe), 150.2 (Ar), 133.2 (Ar), 131.9 (Ar), 131.8 (Ar), 129.1 (Ar), 129.0 (Ar), 127.6 (Ar), 125.9 (Ar), 123.3 (Ar), 116.8 (<u>C</u>N), 60.6 (<u>C</u>H-CN), 52.5, 52.4, 51.1, 37.3 (N-<u>C</u>H$_3$), 29.3 (Ar-<u>C</u>H$_2$). HRMS (ESI), *m/z*: 401.1262 $[M+H]^+$ (calc. for $C_{21}H_{22}ClN_2O_4^+$, *m/z*: 401.1263).

Dimethyl 2-{4-bromo-2-[*N*-(1-cyano-1-phenylmethyl)-*N*-methylamino]benzyl}malonate (4c).



Yield 80 mg (90%), colorless oil (Rf = 0.35 for eluent hexane – DCM 1:3 vol). NMR ^{1}H NMR (800 MHz, $CDCl_3$) δ: 7.63 (1H, d, J = 2.0, H-9 Ar), 7.62 – 7.59 (2H, m, *o*-H Ph), 7.46 – 7.40 (3H, m, *p*-H and *m*-H Ph), 7.31 (1H, dd, J = 8.2, 2.0, H-7 Ar), 7.09 (1H, d, J = 8.2, H-6 Ar), 5.17 (1H, s, N-C<u>H</u>-Ph), 3.87 (1H, dd, J = 9.0, 6.8, C<u>H</u>(COOMe)$_2$), 3.73 (3H, s, COOCH_3), 3.66 (3H, s, COOCH_3), 3.31 (1H, dd, J = 14.3, 6.8, Ar-C<u>H$_2$</u>-CH), 3.23 (1H, dd, J = 14.3, 9.0, Ar-C<u>H$_2$</u>-CH), 2.63 (3H, s, N-CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.2 (<u>C</u>OOMe), 150.5 (Ar), 133.1 (Ar), 132.8 (Ar), 132.1 (Ar), 129.8 (Ar), 129.5 (Ar), 129.2 (Ar), 128.0 (Ar), 127.5 (Ar), 121.8 (Ar), 116.2 (<u>C</u>N), 62.00 (<u>C</u>H-CN), 52.9, 52.8, 51.8, 37.4 (N-<u>C</u>H$_3$), 30.4 (Ar-<u>C</u>H$_2$). HRMS (ESI), *m/z*: 445.0757 $[M+H]^+$ (calc. for $C_{21}H_{22}BrN_2O_4^+$, *m/z*: 445.0757).

S4. References.

S1. E. R. Zaitseva, D. S. Ivanov, A. Y. Smirnov, A. A. Mikhaylov, N. S. Baleeva and M. S. Baranov, *Molecules*, 2022, **27**, 5270; https://www.mdpi.com/1420-3049/27/16/5270.

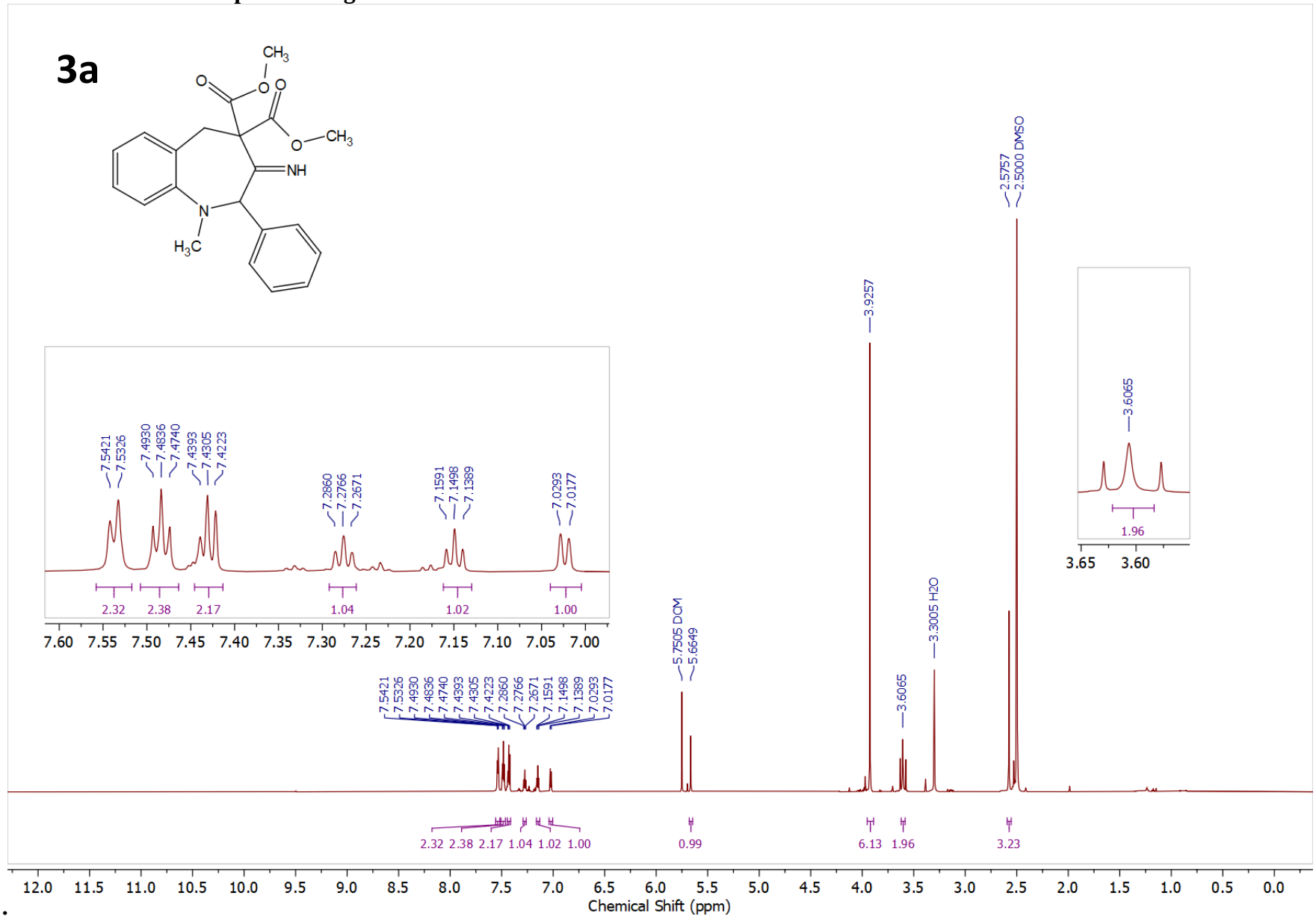
S2. P. Yang, W. Xu, R. Wang, M. Zhang, C. Xie, X. Zeng and M. Wang, *Org. Lett.*, 2019, **21**, 3658; https://pubs.acs.org/doi/abs/10.1021/acs.orglett.9b01093.

S3. K. A. Krasnov, V. G. Kartsev and V. N. Khrustalev, *Mendeleev Commun.*, 2006, **16**, 52; https://doi.org/10.1070/MC2006v016n01ABEH002216.

S4. S. Murarka, C. Zhang, M. D. Konieczynska and D. Seidel, *Org. Lett.*, 2009, **11**, 129; https://pubs.acs.org/doi/abs/10.1021/ol802519r.

S5. W. Cao, X. Liu, W. Wang, L. Lin and X. Feng, *Org. Lett.*, 2011, **13**, 600; https://pubs.acs.org/doi/abs/10.1021/ol1028282.

S5. NMR and HRMS spectra images



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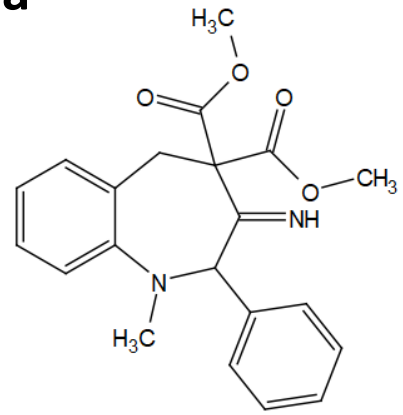
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O
O
O
O
CH3
NH
N
H3C

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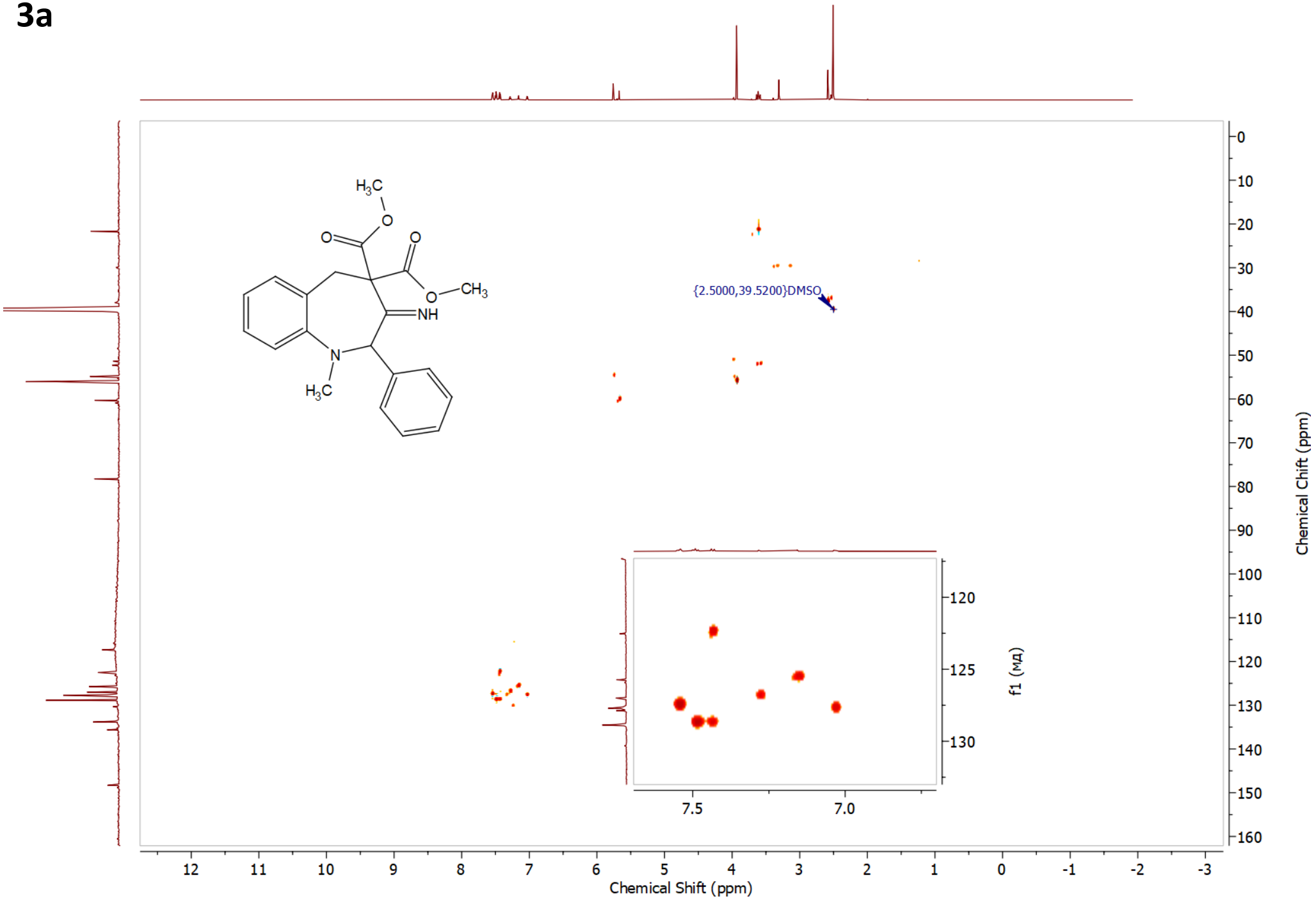
128.8417
127.8823
127.7149
127.0029
125.7287
122.5320
37.9199
39.5200 DMSO
37.9199
173.1861
148.3192
135.6247
133.8436
128.8726
128.8417
127.7149
127.0029
117.3253
78.2505
60.2940
56.0569
54.8520 DCM
21.6550
Chemical Shift (ppm)

3a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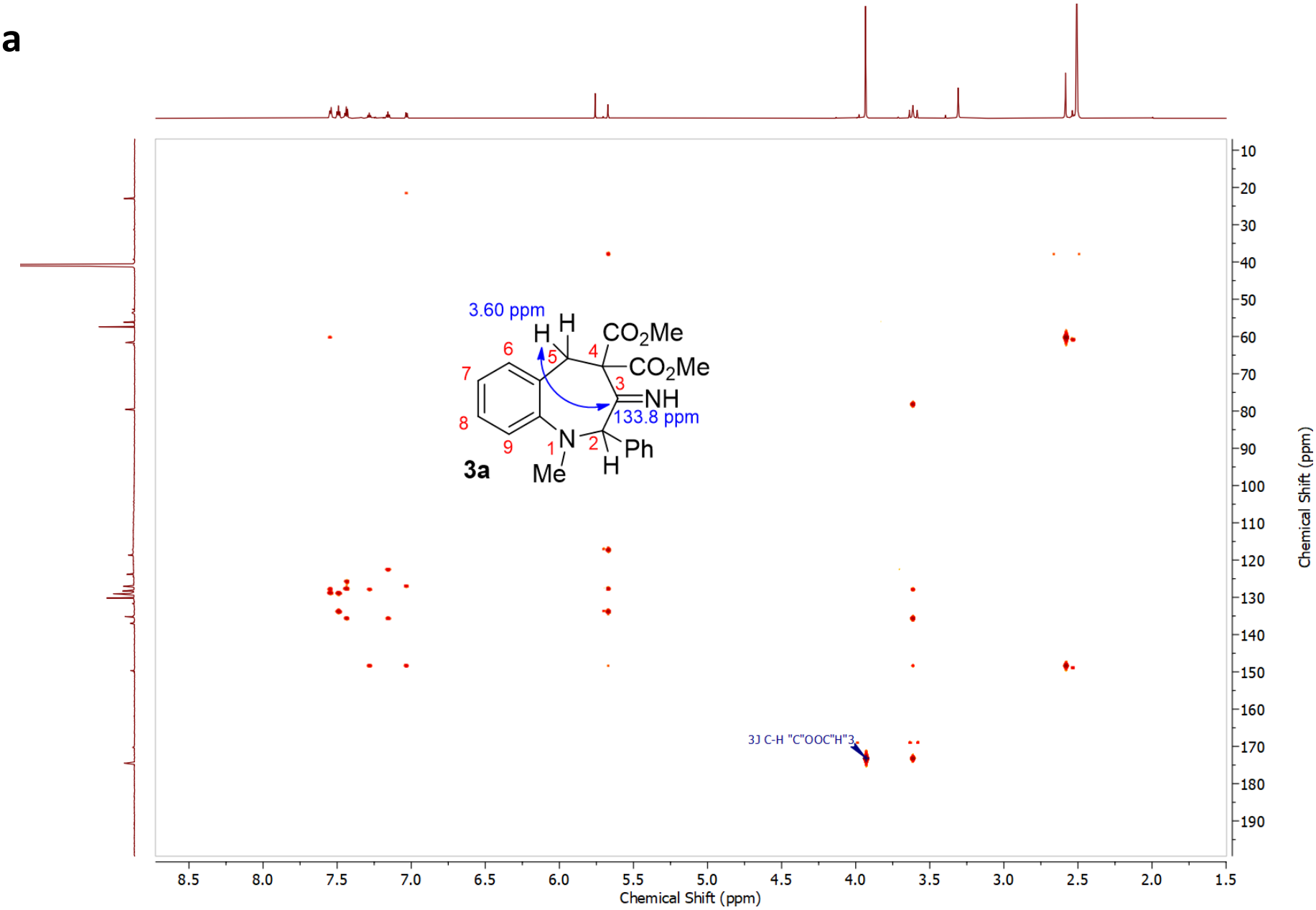
Chemical Shift (ppm)
Chemical Chift (ppm)
f1 (мд)

3a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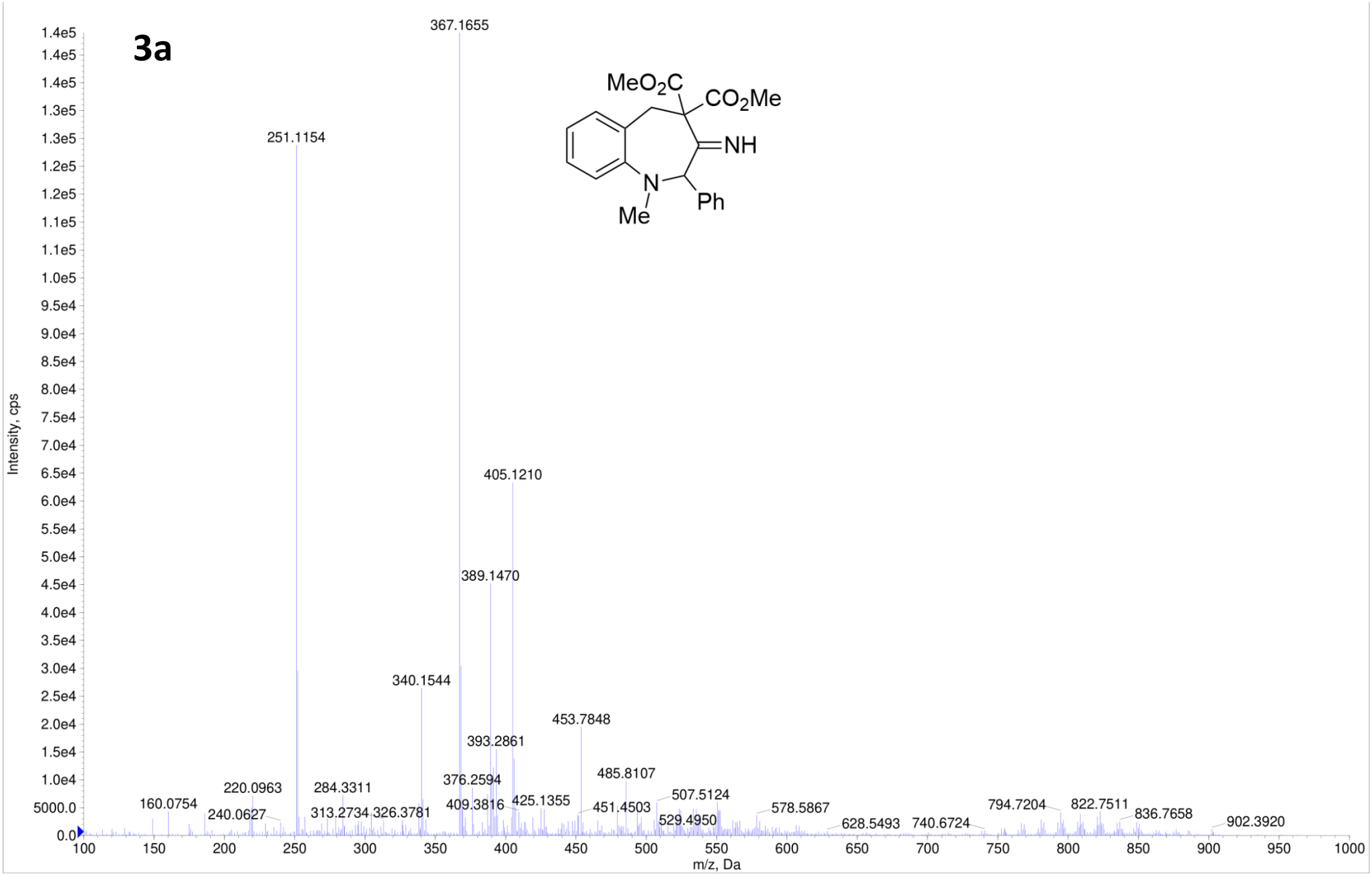
133.8 ppm
3J C-H "C"OOC"H"3
3a
Chemical Shift (ppm)
Chemical Shift (ppm)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NH
N
Me
Ph
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m/z, Da
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389.1470
340.1544
453.7848
393.2861
485.8107
376.2594
220.0963
284.3311
160.0754
240.0627
313.2734
326.3781
409.3816
425.1355
451.4503
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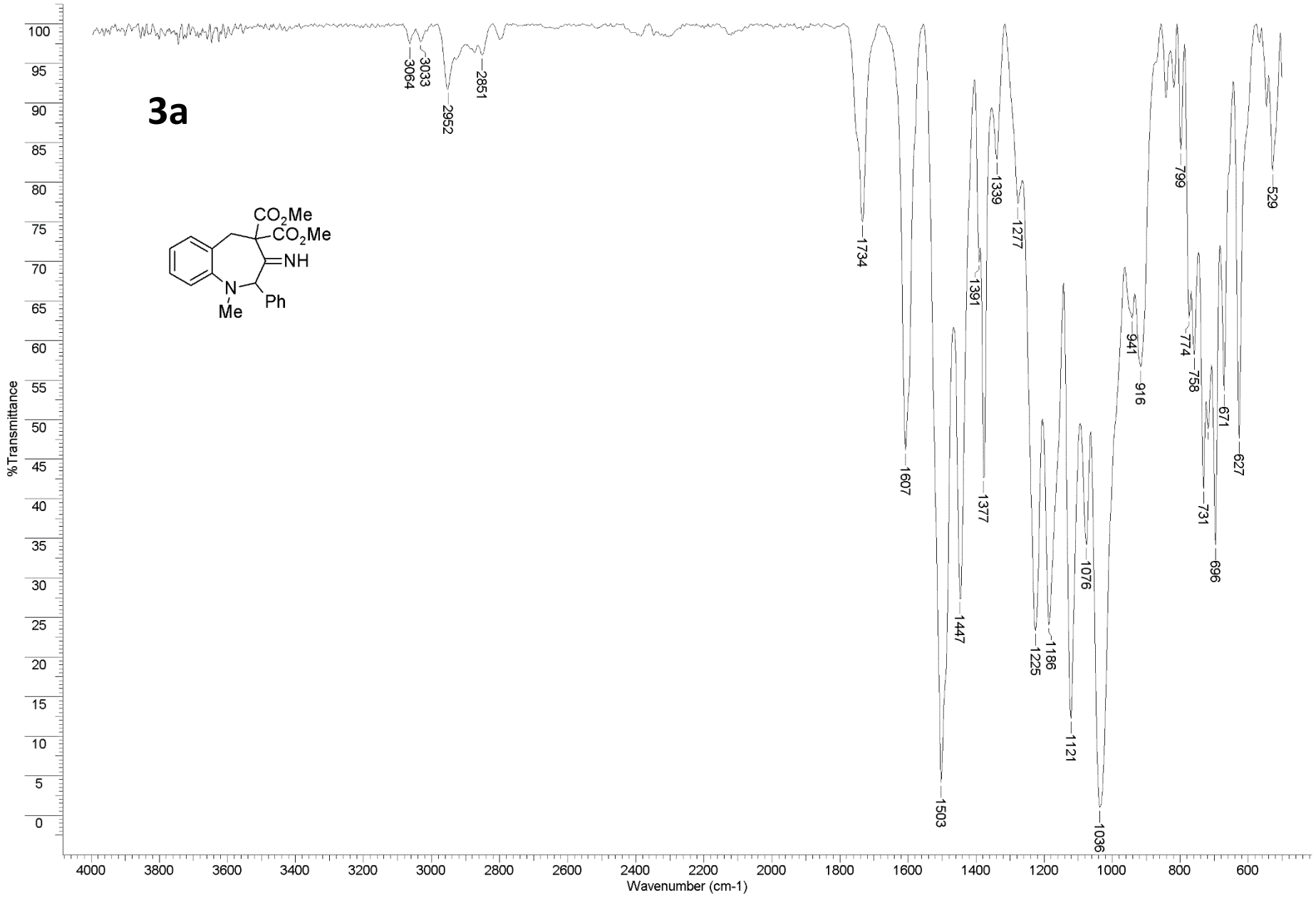
902.3920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CO2Me
CO2Me
NH
N
Me
Ph
%Transmittance
Wavenumber (cm-1)
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3033
2952
2851
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1607
1503
1447
1391
1377
1339
1277
1225
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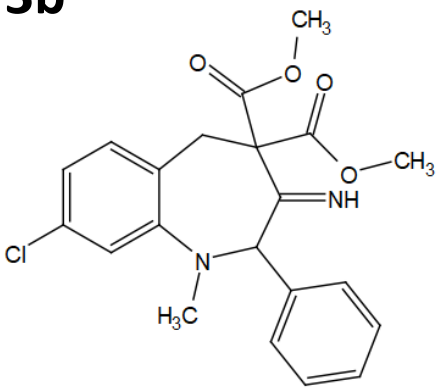
1076
1036
941
916
799
774
758
731
696
671
627
529

3b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O
O
CH3
NH
Cl
N
H3C

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7.4422
7.4332
7.4088
7.4061
7.2212
7.2185
7.2108
7.2080
7.0765
7.0661
1.99
2.13
1.02
1.02
1.00
1.00
7.55
7.50
7.45
7.40
7.35
7.30
7.25
7.20
7.15
7.10
7.05
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2.5695
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3.2984 H2O
5.7504 DCM
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2.88
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1.99
3.60
3.55
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11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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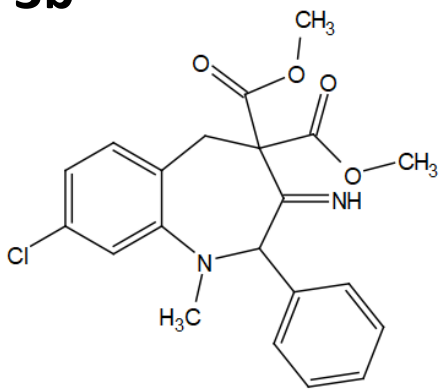
0.0
Chemical Shift (ppm)

3b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O
O
O
CH3
NH
Cl
N
H3C

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38.0039
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133.4225
130.9699
129.7852
129.0098
128.9715
127.7222
125.6374
173.1075
149.6044
134.8198
133.4225
130.9699
129.7852
129.0098
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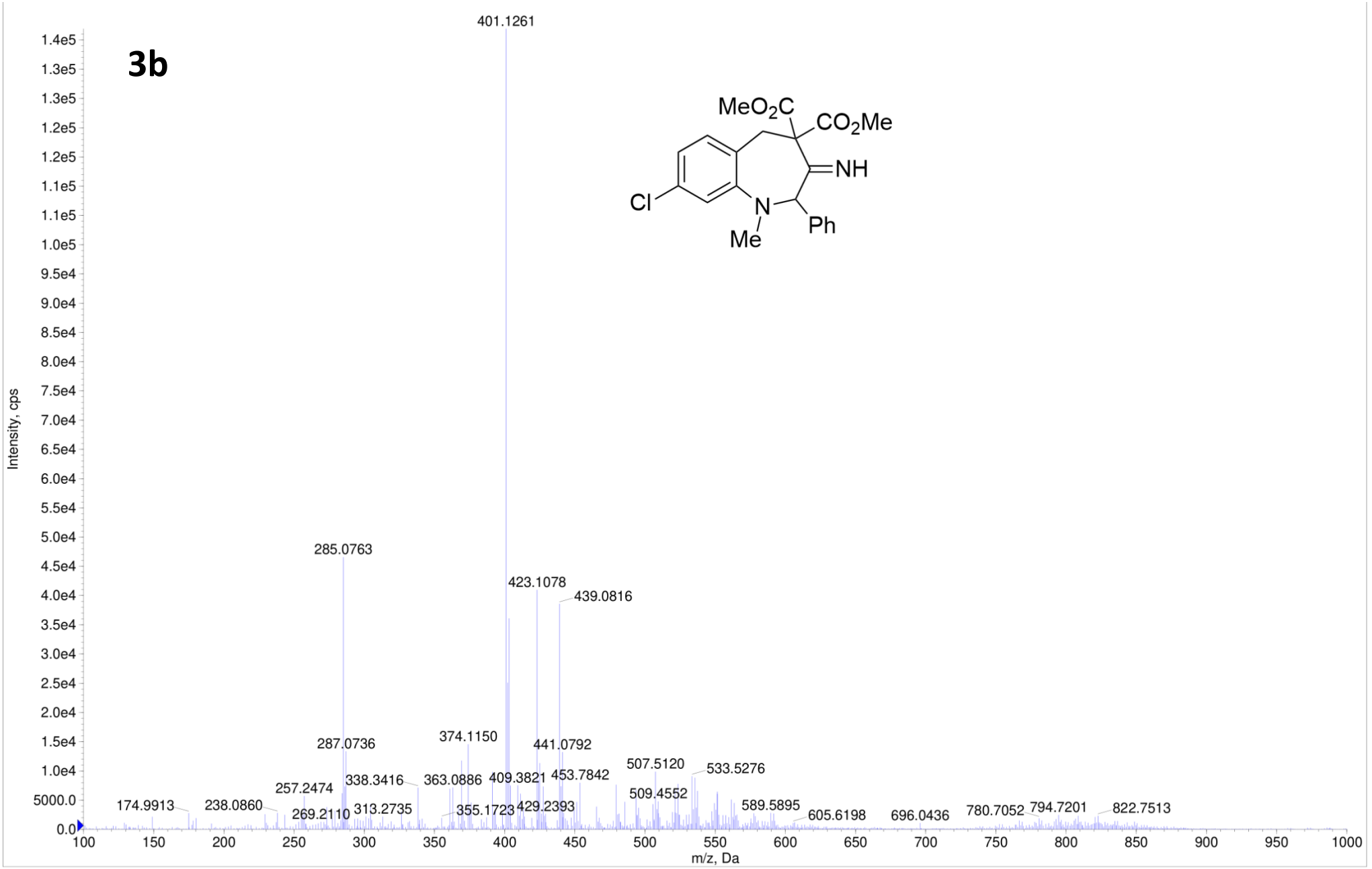
Chemical Shift (ppm)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Cl
N
Ph
Me
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533.5276
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338.3416
363.0886
409.3821
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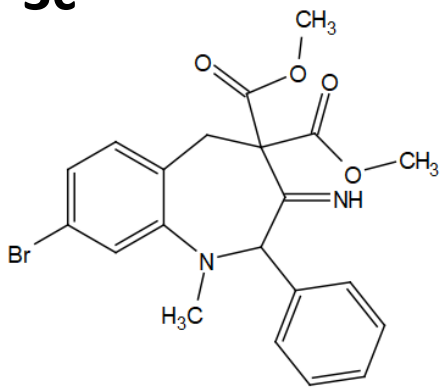
Intensity, cps
m/z, Da

3c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O
O
CH3
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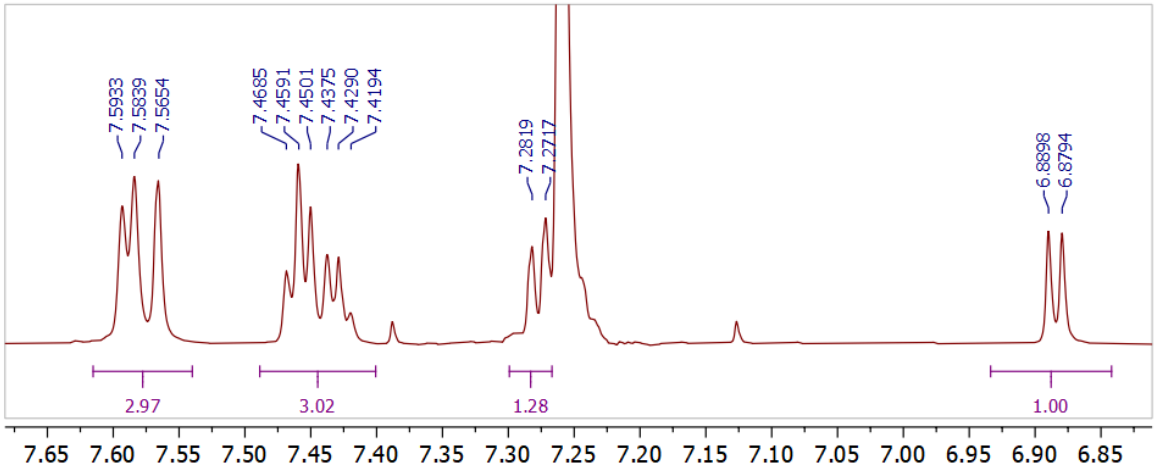
Br
N
H3C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7.4290
7.4194
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7.2717
6.8898
6.8794
2.97
3.02
1.28
1.00
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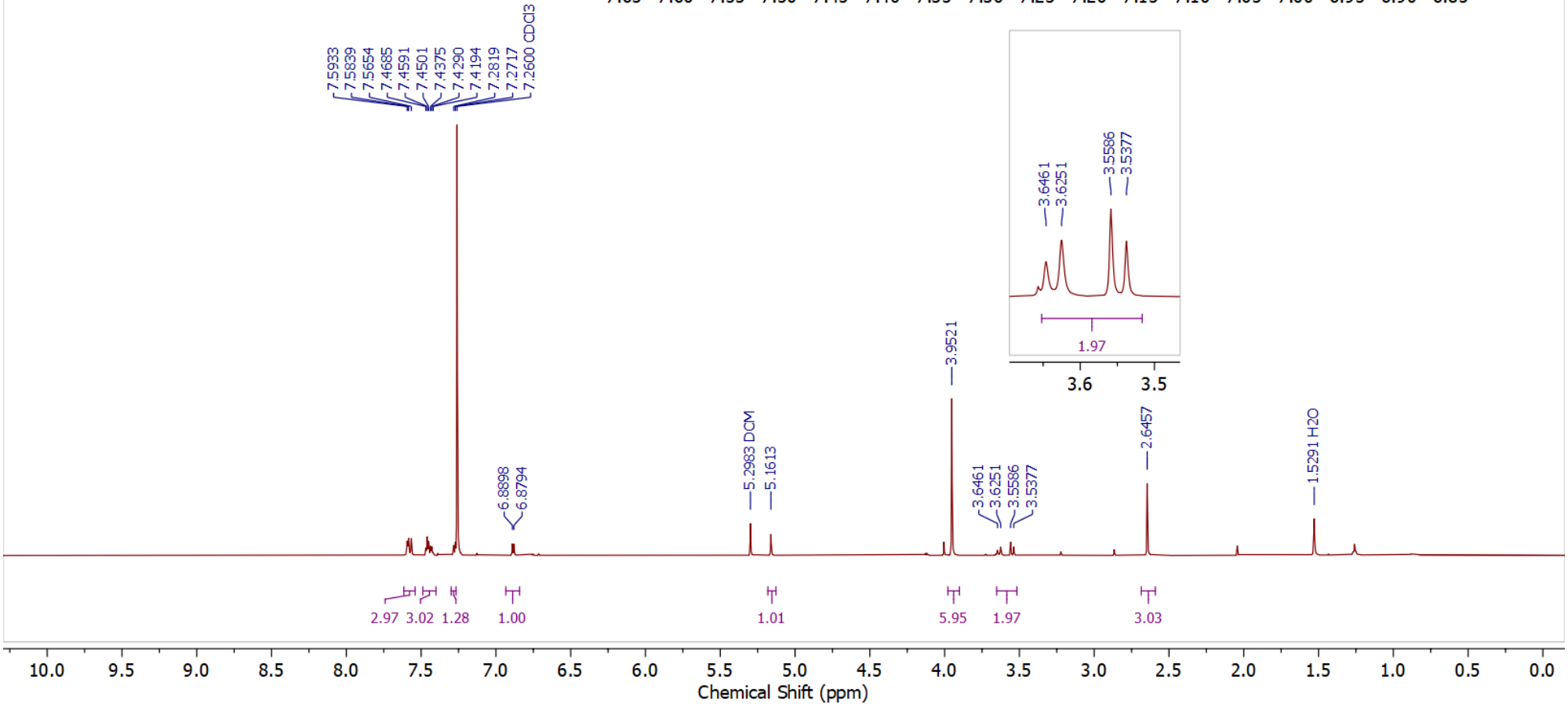
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7.5839
7.5654
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7.4591
7.4501
7.4375
7.4290
7.4194
7.2819
7.2717
7.2600 CDCl3
6.8898
6.8794
5.2983 DCM
5.1613
3.9521
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3.6251
3.5586
3.5377
2.6457
1.5291 H2O
2.97 3.02 1.28 1.00
1.01
5.95
1.97
3.03
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
Chemical Shift (ppm)

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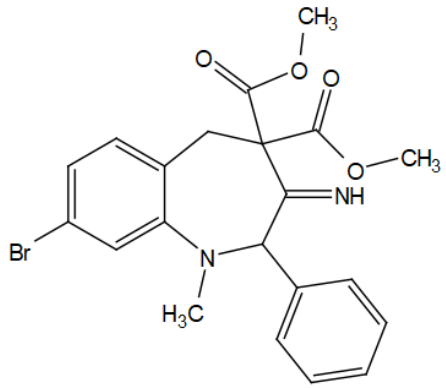
3.5377
1.97
3.6 3.5

3c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O
CH3
NH
Br
N
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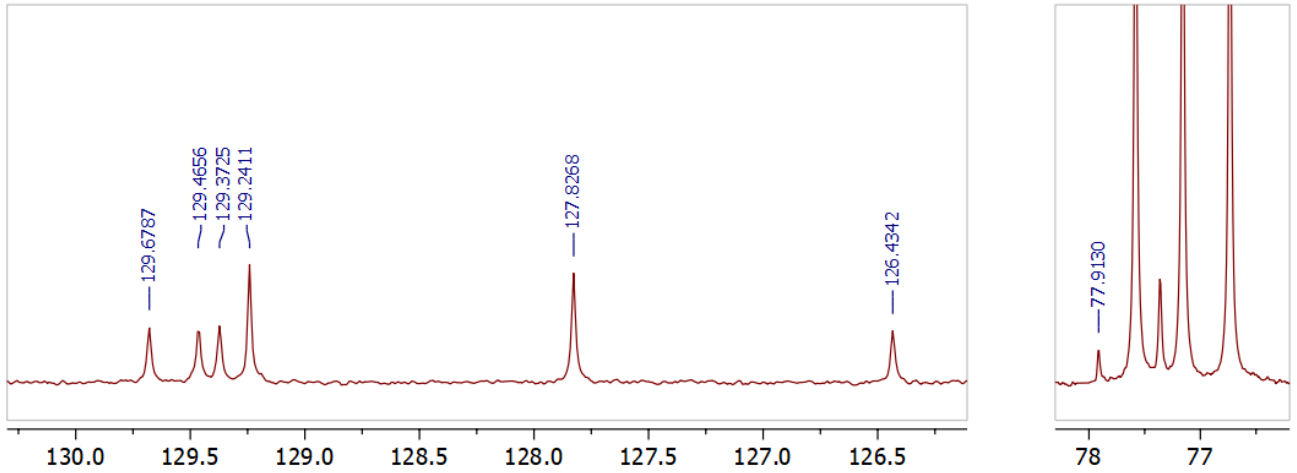
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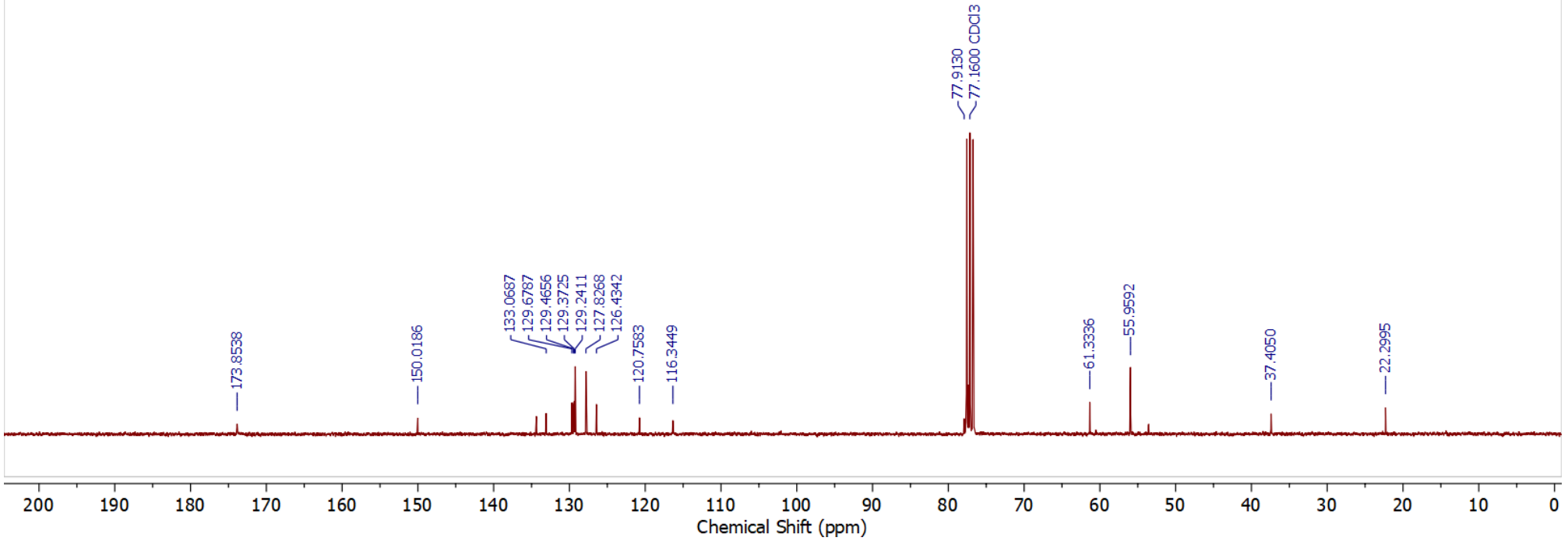
126.5
78
77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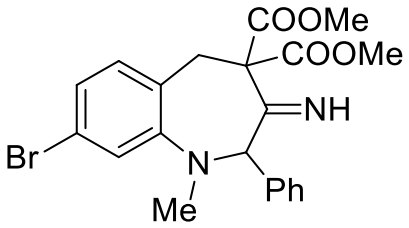
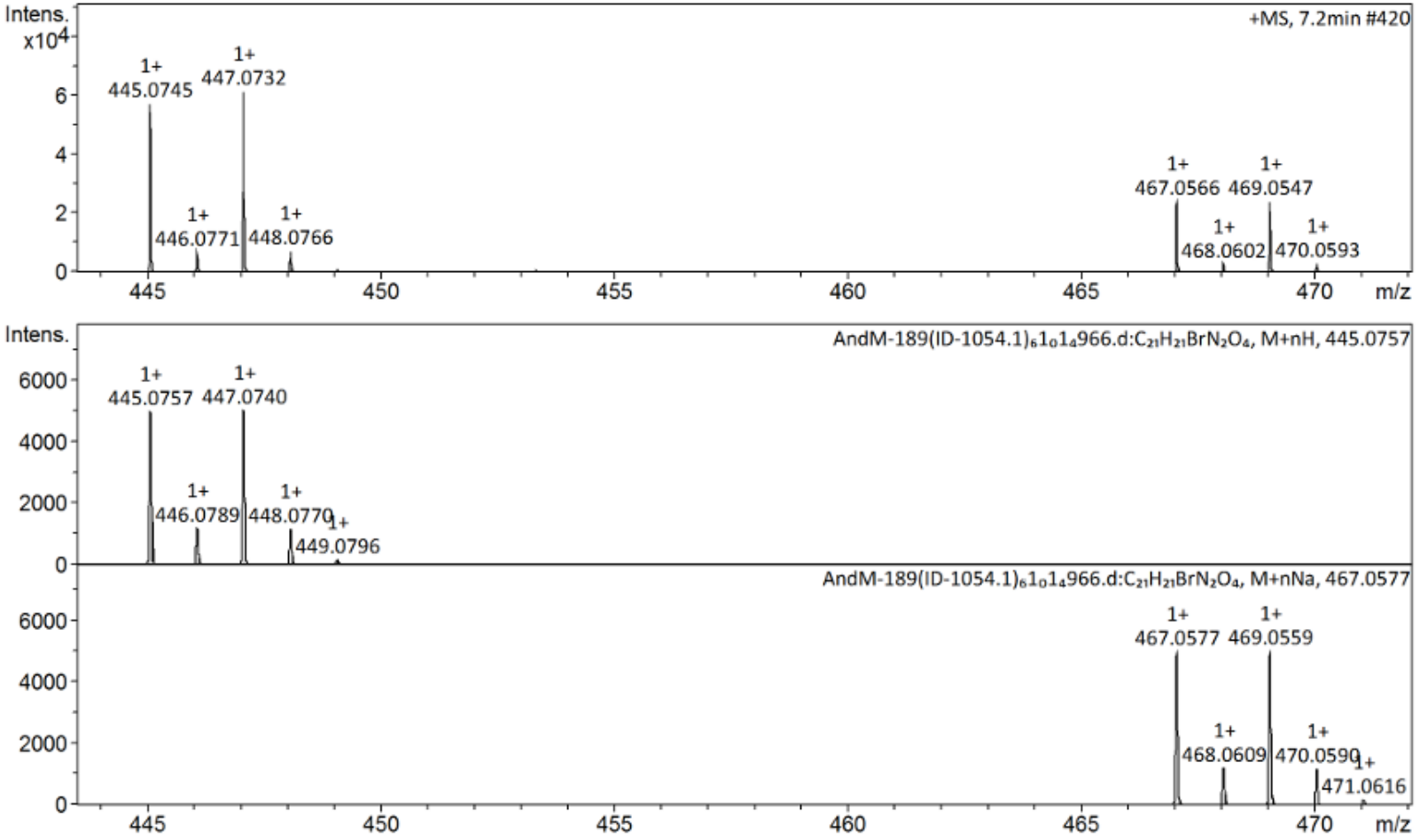
Chemical Shift (ppm)

3c


COOMe
COOMe
NH
Br
N
Ph
Me


Intens.
x10^4
+MS, 7.2min #420
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1+ 447.0732
1+ 446.0771
1+ 448.0766
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1+ 469.0547
1+ 468.0602
1+ 470.0593
m/z
Intens.
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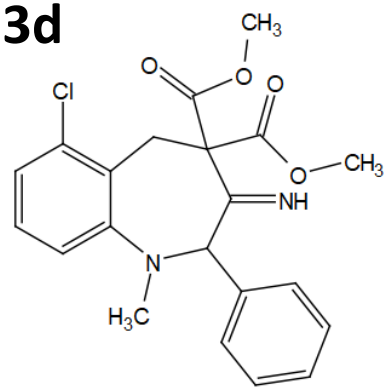
m/z

3d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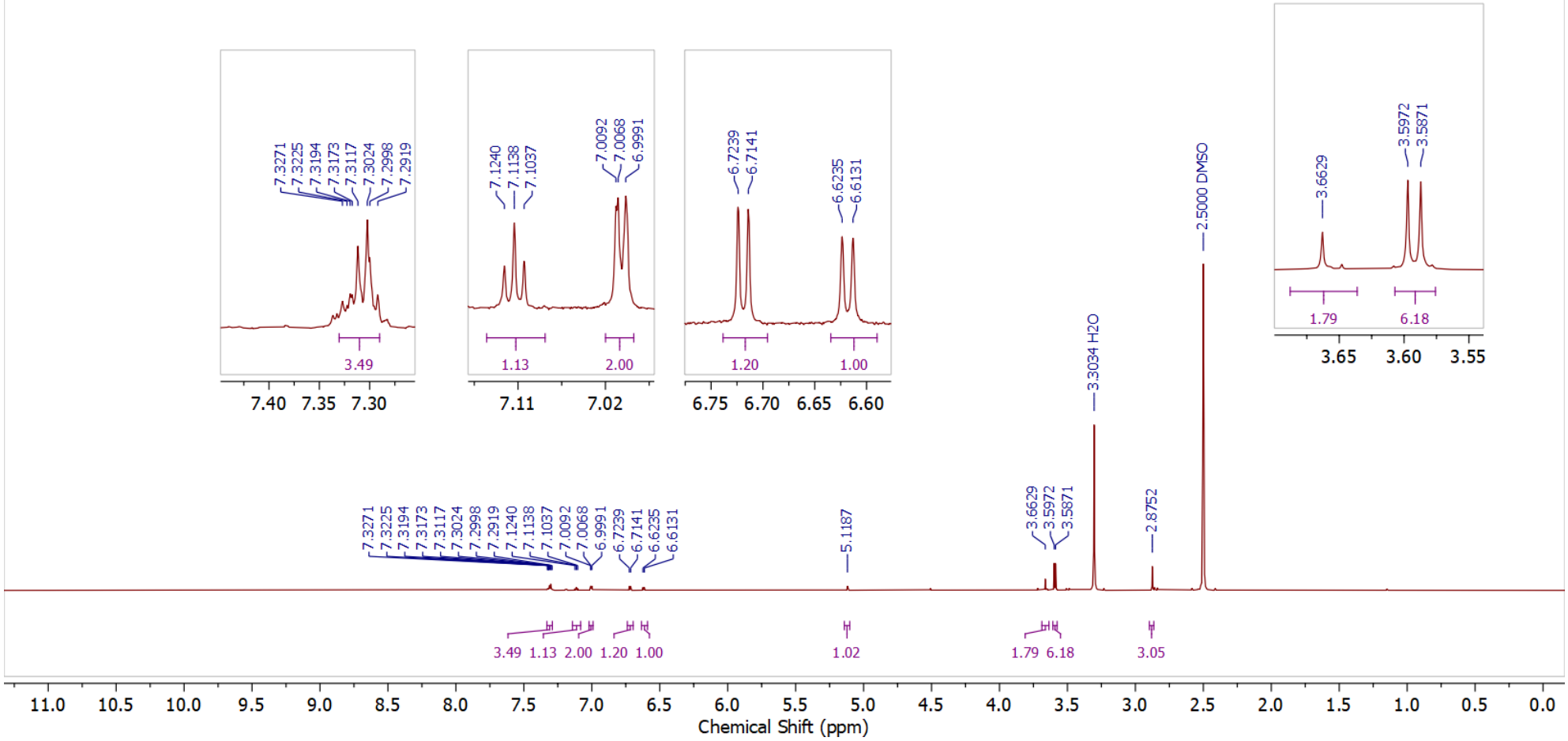
O
CH3
NH
N
H3C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5.1187
3.6629
3.5972
3.5871
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2.8752
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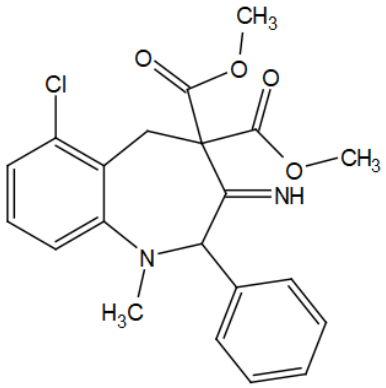
3.05
Chemical Shift (ppm)

3d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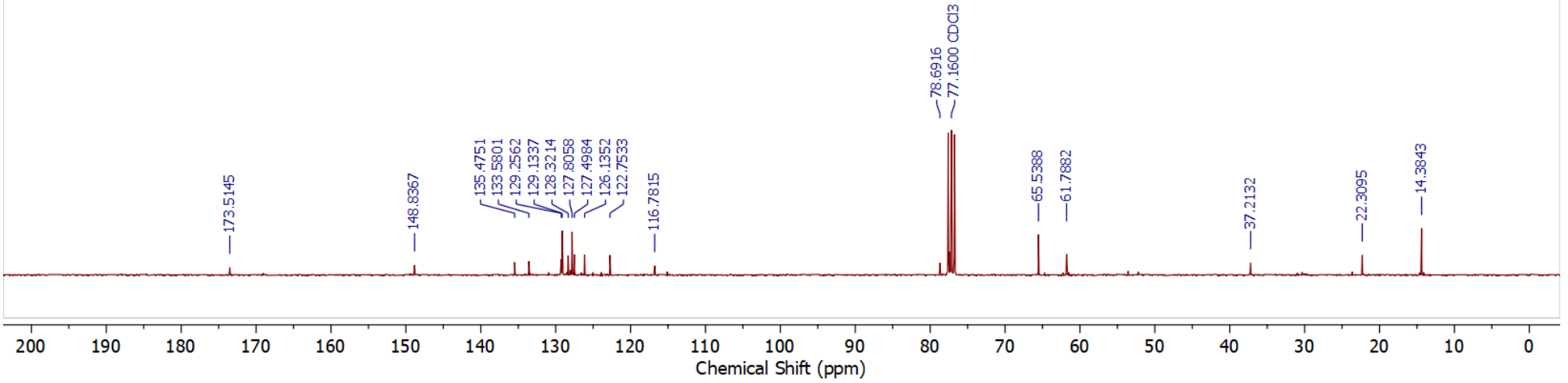
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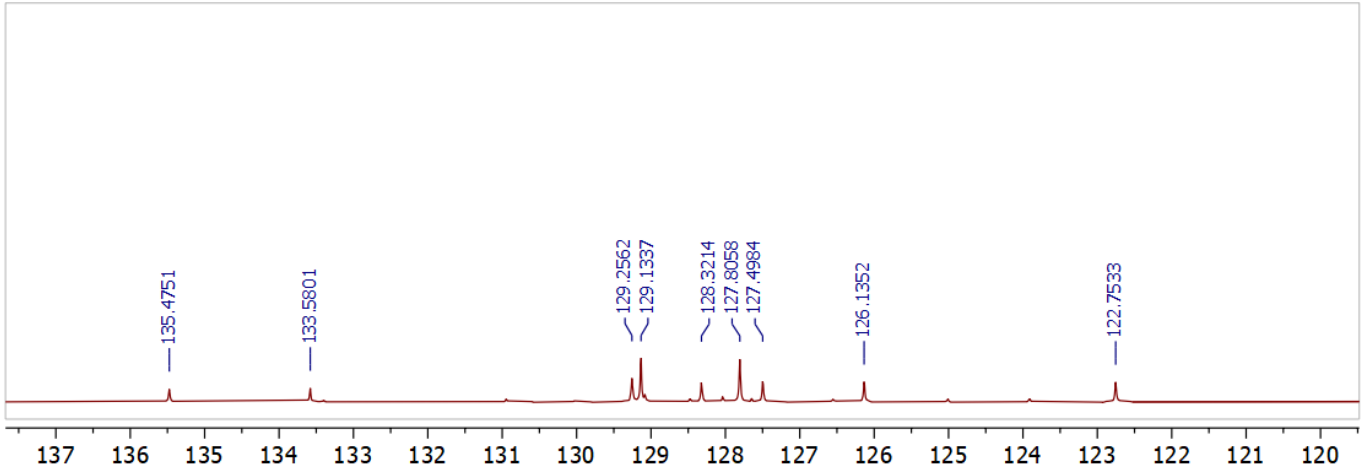
Chemical Shift (ppm)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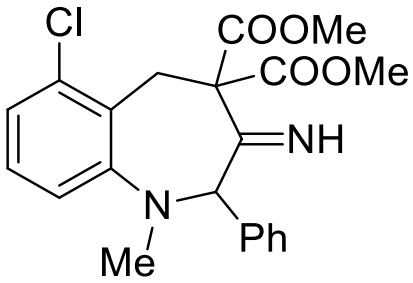
3d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COOMe
NH
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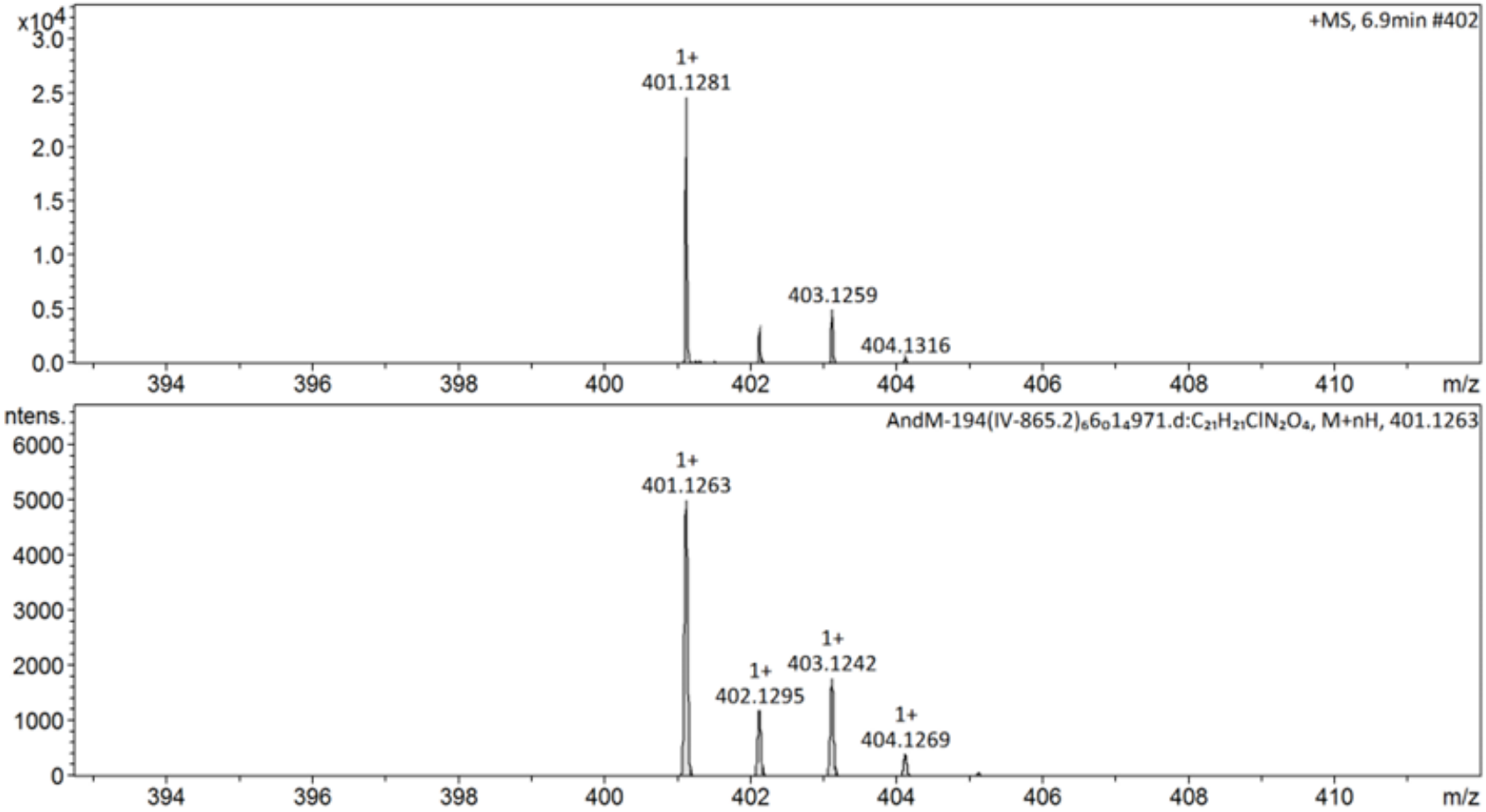
Me
Ph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2.0
1.5
1.0
0.5
0.0
+MS, 6.9min #402
1+
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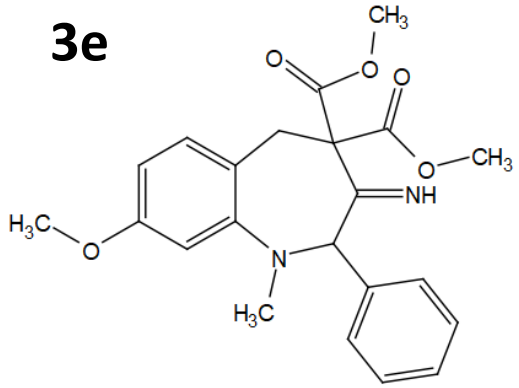
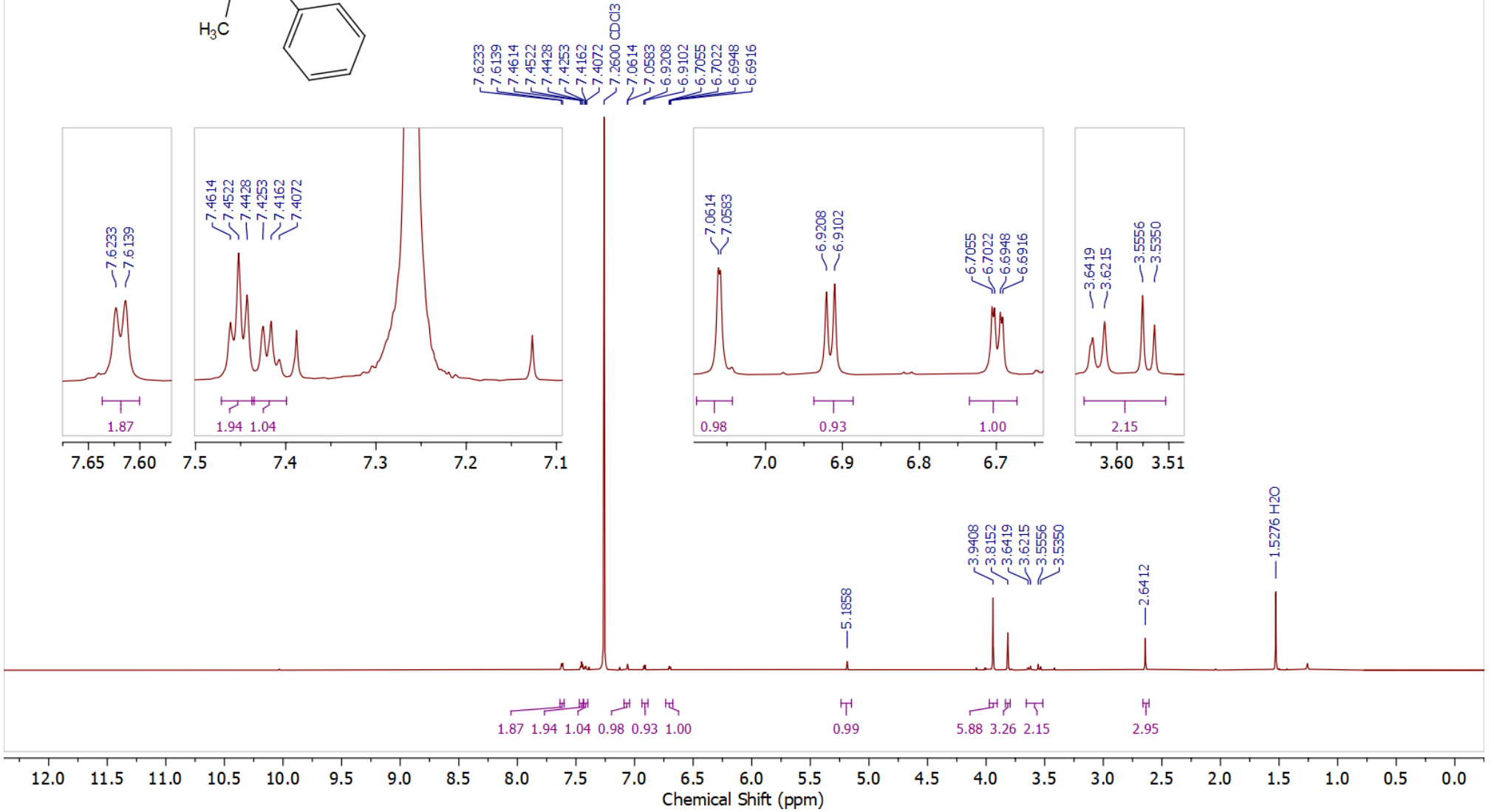
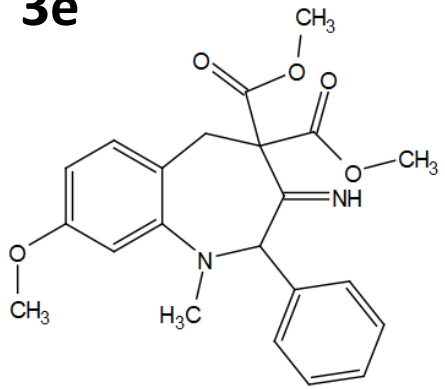
403.1259
404.1316
394
396
398
400
402
404
406
408
410
m/z
ntens.
6000
5000
4000
3000
2000
1000
0
AndM-194(IV-865.2)₆6₀1₄971.d:C₂₁H₂₁ClN₂O₄, M+nH, 401.1263
1+
401.1263
1+
402.1295
1+
403.1242
1+
404.1269
394
396
398
400
402
404
406
408
410
m/z

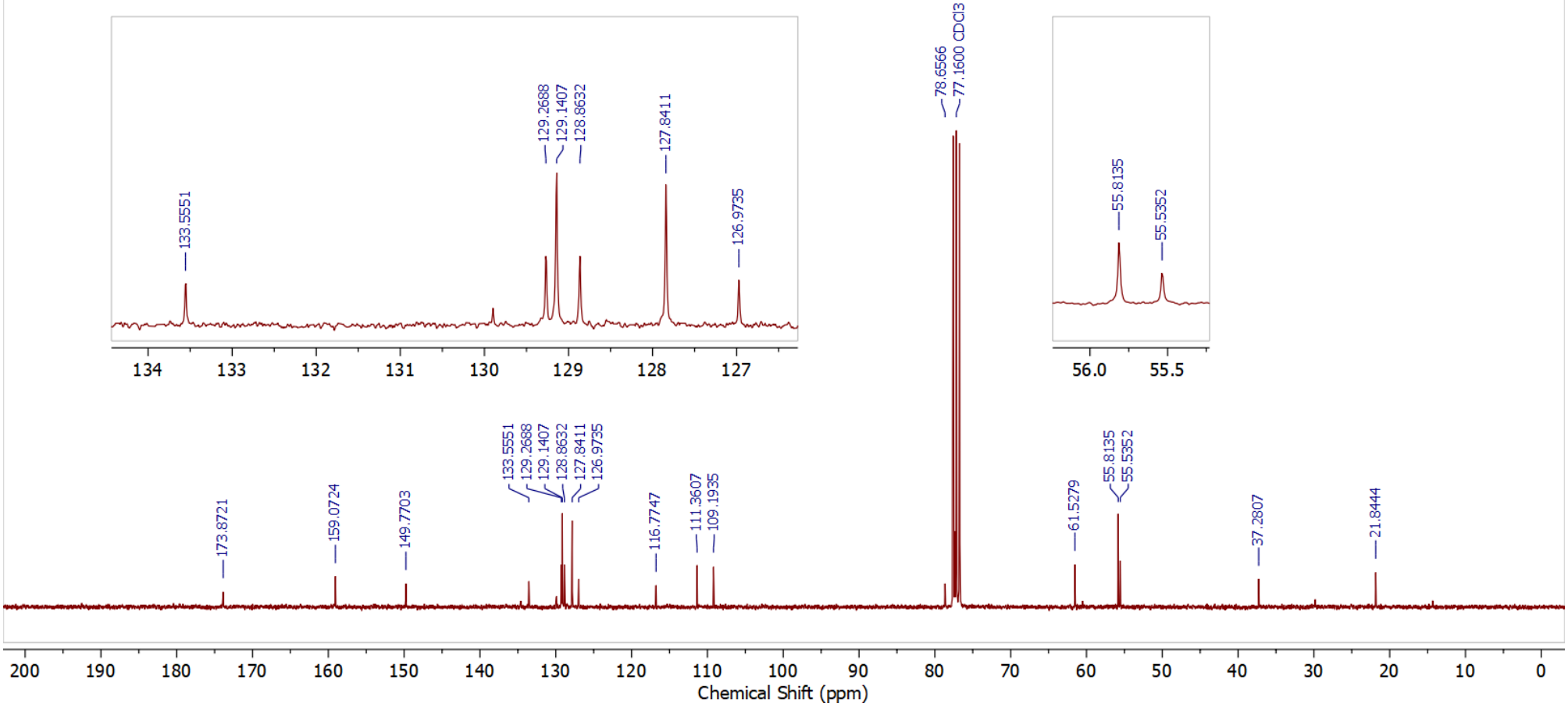
3e

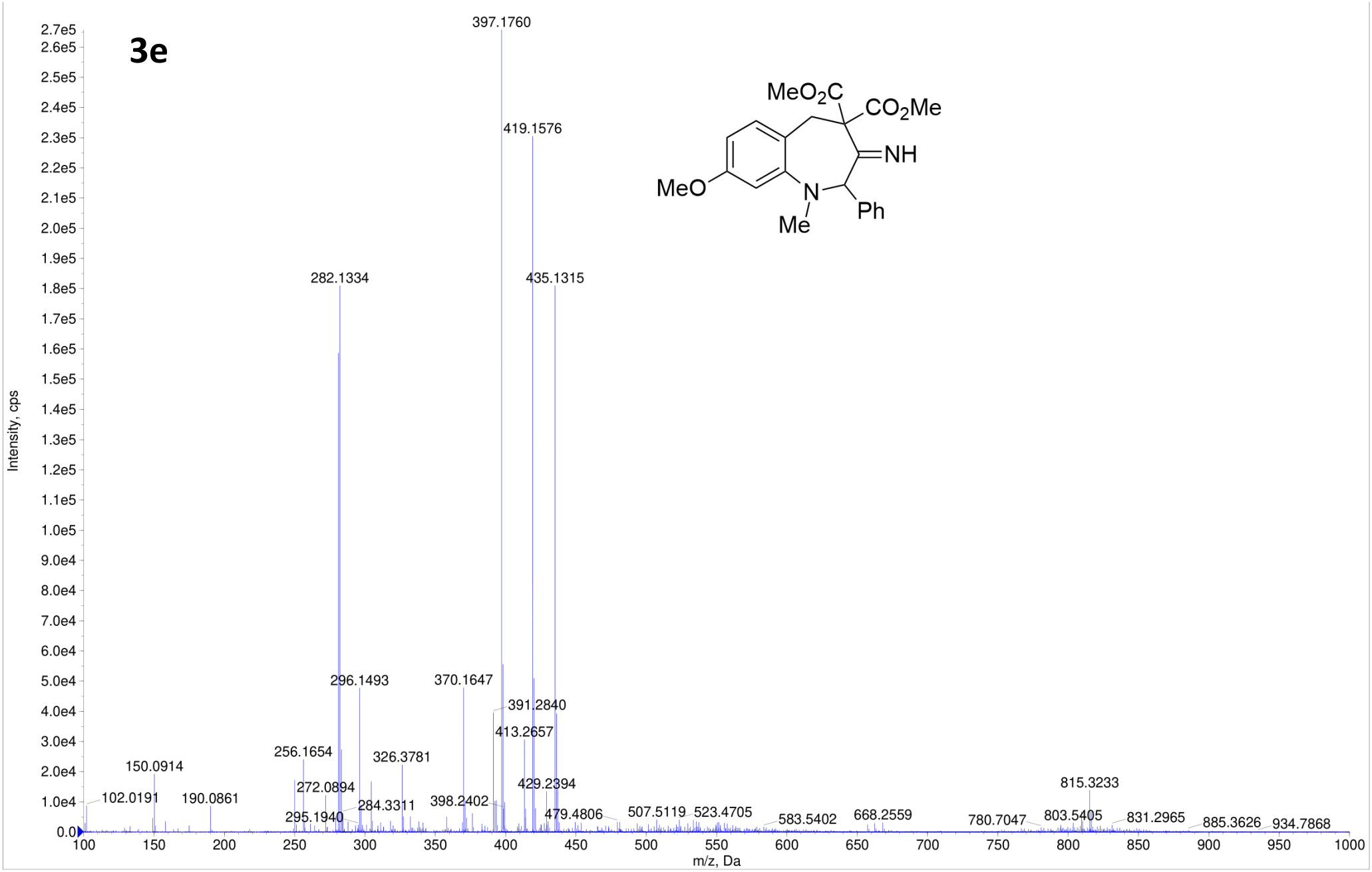

CH3
O
O
O
O
CH3
NH
H3C
O
N
H3C

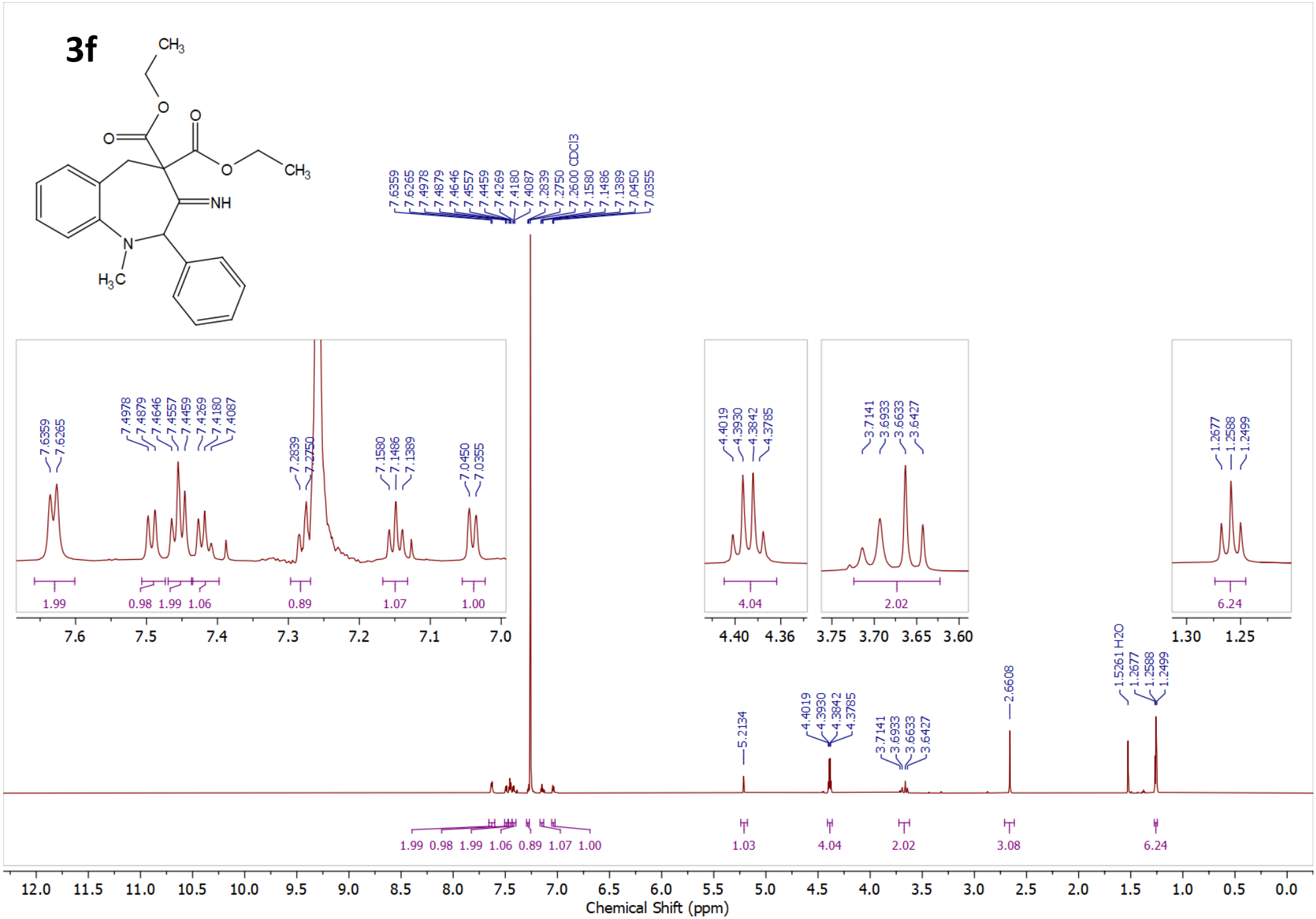

7.6233
7.6139
7.4614
7.4522
7.4428
7.4253
7.4162
7.4072
7.2600 CDCl3
7.0614
7.0583
6.9208
6.9102
6.7055
6.7022
6.6948
6.6916
3.6419
3.6215
3.5556
3.5350
5.1858
3.9408
3.8152
3.6419
3.6215
3.5556
3.5350
2.6412
1.5276 H2O
1.87
1.94
1.04
0.98
0.93
1.00
0.99
5.88
3.26
2.15
2.95
Chemical Shift (ppm)

3e

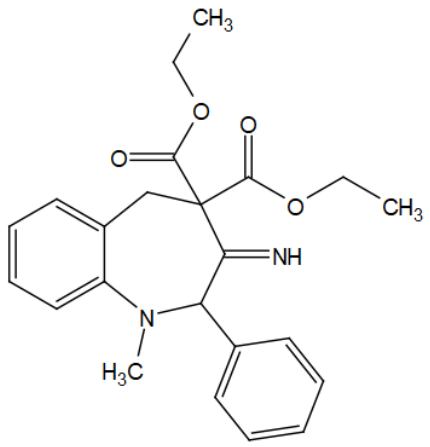

CH3
O
O
O
O
CH3
NH
O
CH3
N
H3C


133.5551
129.2688
129.1407
128.8632
127.8411
126.9735
78.6566
77.1600 CDCl3
55.8135
55.5352
173.8721
159.0724
149.7703
133.5551
129.2688
129.1407
128.8632
127.8411
126.9735
116.7747
111.3607
109.1935
61.5279
55.8135
55.5352
37.2807
21.8444
Chemical Shift (ppm)


3e
397.1760
419.1576
282.1334
435.1315
296.1493
370.1647
391.2840
413.2657
256.1654
326.3781
150.0914
272.0894
429.2394
102.0191
190.0861
284.3311
398.2402
295.1940
479.4806
507.5119
523.4705
583.5402
668.2559
780.7047
803.5405
815.3233
831.2965
885.3626
934.7868
MeO2C
CO2Me
NH
MeO
N
Me
Ph
Intensity, cps
m/z, Da

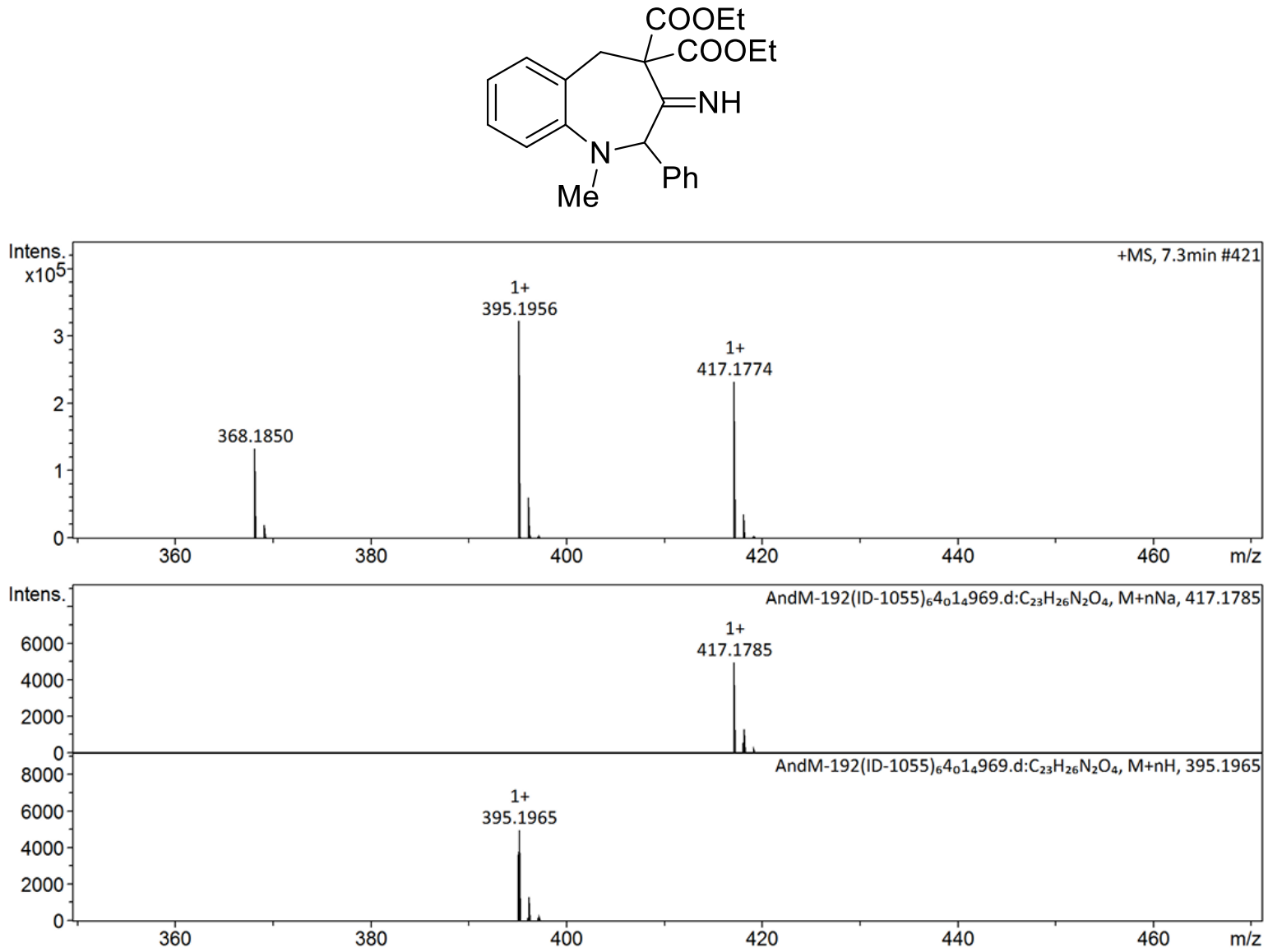

3f
CH3
O
O
O
O
CH3
NH
N
H3C
7.6359
7.6265
7.4978
7.4879
7.4646
7.4557
7.4459
7.4269
7.4180
7.4087
7.2839
7.2750
7.2600 CDCl3
7.1580
7.1486
7.1389
7.0450
7.0355
4.4019
4.3930
4.3842
4.3785
3.7141
3.6933
3.6633
3.6427
1.2677
1.2588
1.2499
1.5261 H2O
2.6608
5.2134
1.99 0.98 1.99 1.06 0.89 1.07 1.00
1.03
4.04
2.02
3.08
6.24
Chemical Shift (ppm)

3f

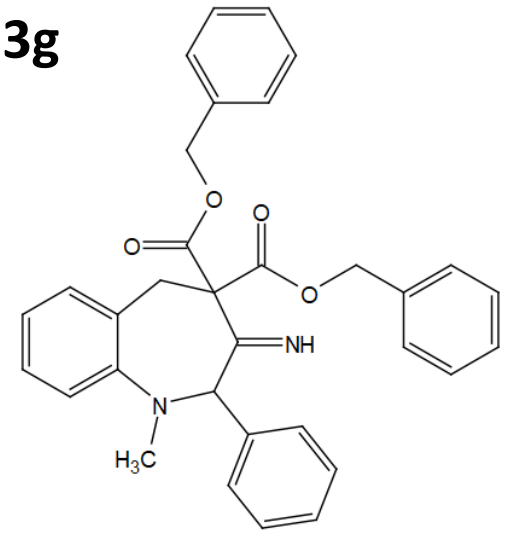

CH3
O
O
O
O
CH3
NH
N
H3C

78.6915
77.1600 CDCl3
129.2563
129.1376
128.3224
127.8062
127.4986
126.1356
135.4756
133.5845
129.2563
129.1376
128.3224
127.8062
127.4986
126.1356
122.7537
65.5380
61.7908
14.3838
37.2147
22.3101
173.5140
148.8372
116.7815
130
129
128
127
126
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

3f

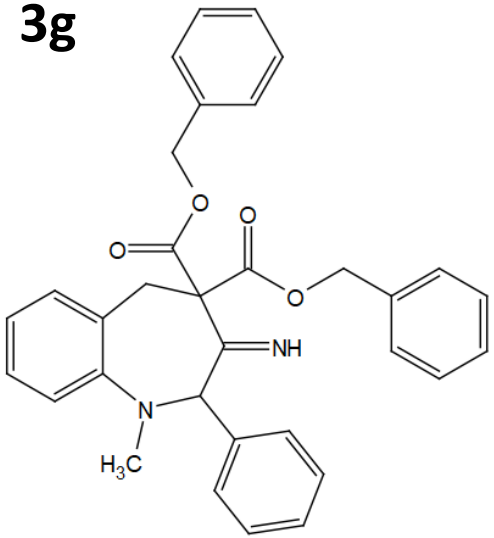

COOEt
COOEt
NH
N
Me
Ph
Intens.
x10^5
+MS, 7.3min #421
1+
395.1956
1+
417.1774
368.1850
m/z
AndM-192(ID-1055)640141969.d:C23H26N2O4, M+nNa, 417.1785
1+
417.1785
AndM-192(ID-1055)640141969.d:C23H26N2O4, M+nH, 395.1965
1+
395.1965

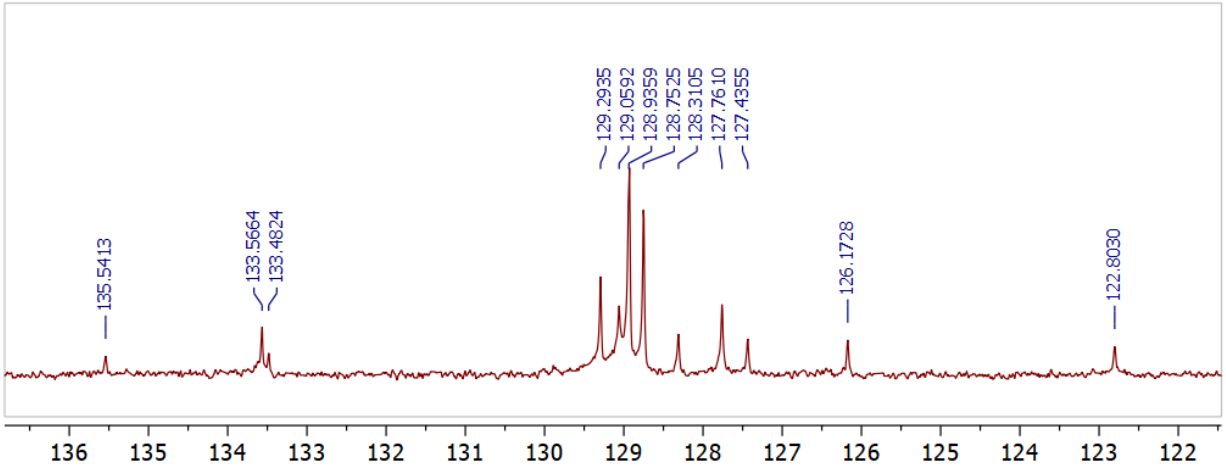
3g

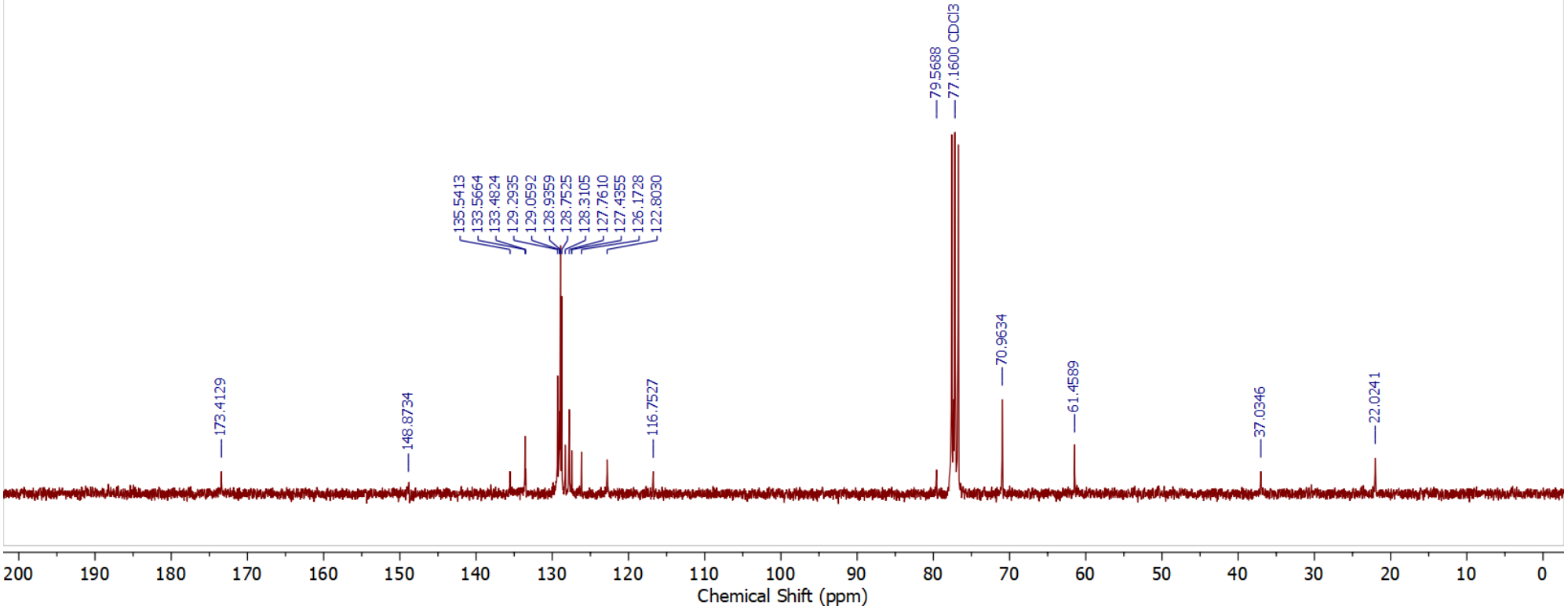

O
O
O
O
NH
N
H3C

7.4231
7.4148
7.3880
7.3534
7.3495
7.3452
7.3198
7.3098
7.3014
7.2824
7.2732
7.2600 CDCl3
7.2481
7.2420
7.2347
7.1518
7.1417
7.0951
7.0860
7.0767
6.9737
6.9641
5.3383
5.3233
5.3161
5.2989 DCM
3.6359
4.8249
2.4158
1.5302 H2O
4.29
3.24
2.13
3.44
2.16
4.03
1.13
1.00
3.99
1.99
4.01
1.05
1.99
3.11
Chemical Shift (ppm)

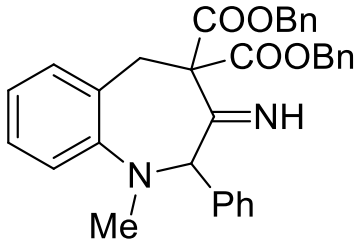
3g

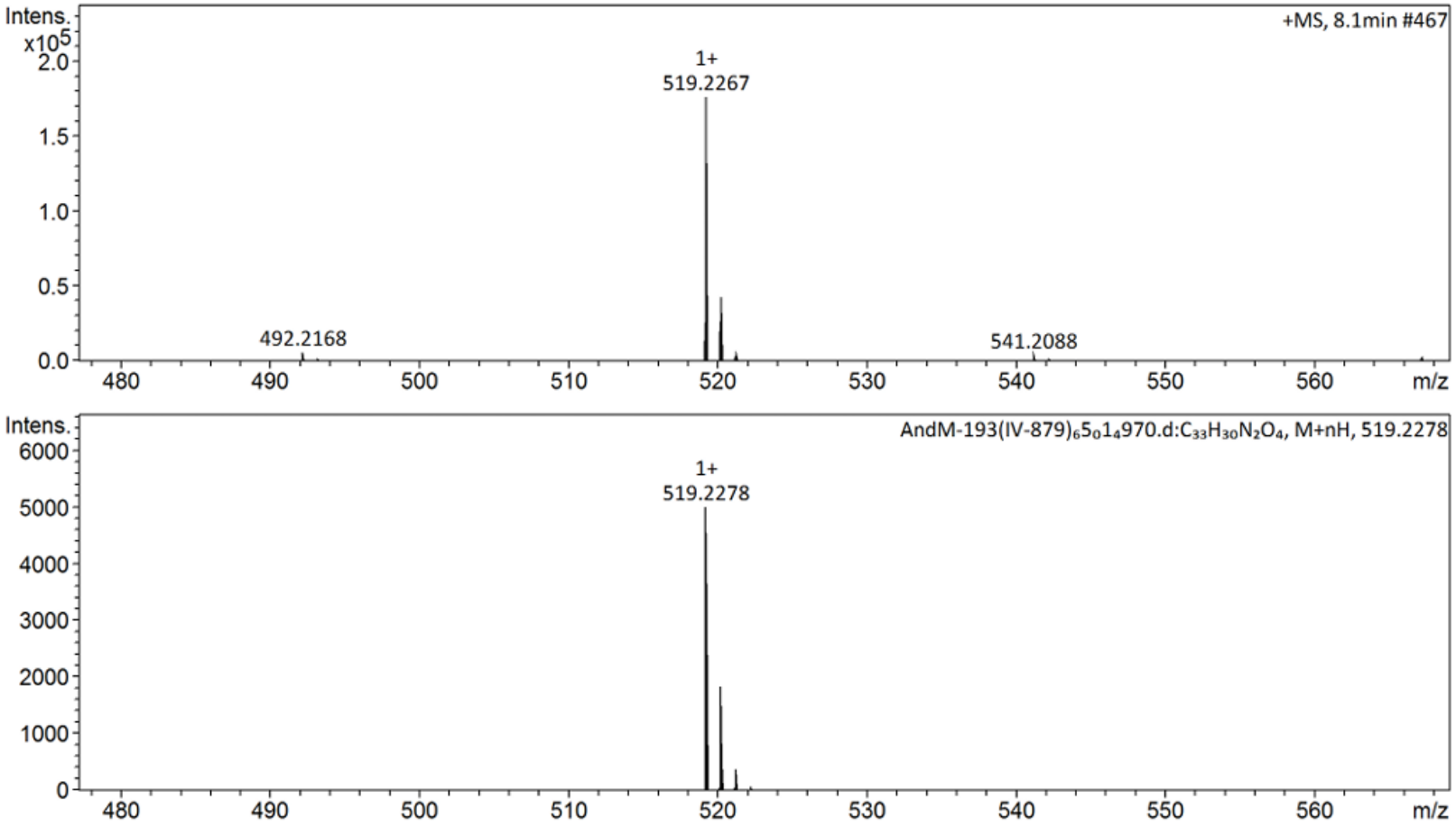

O
O
O
O
NH
N
H_3C

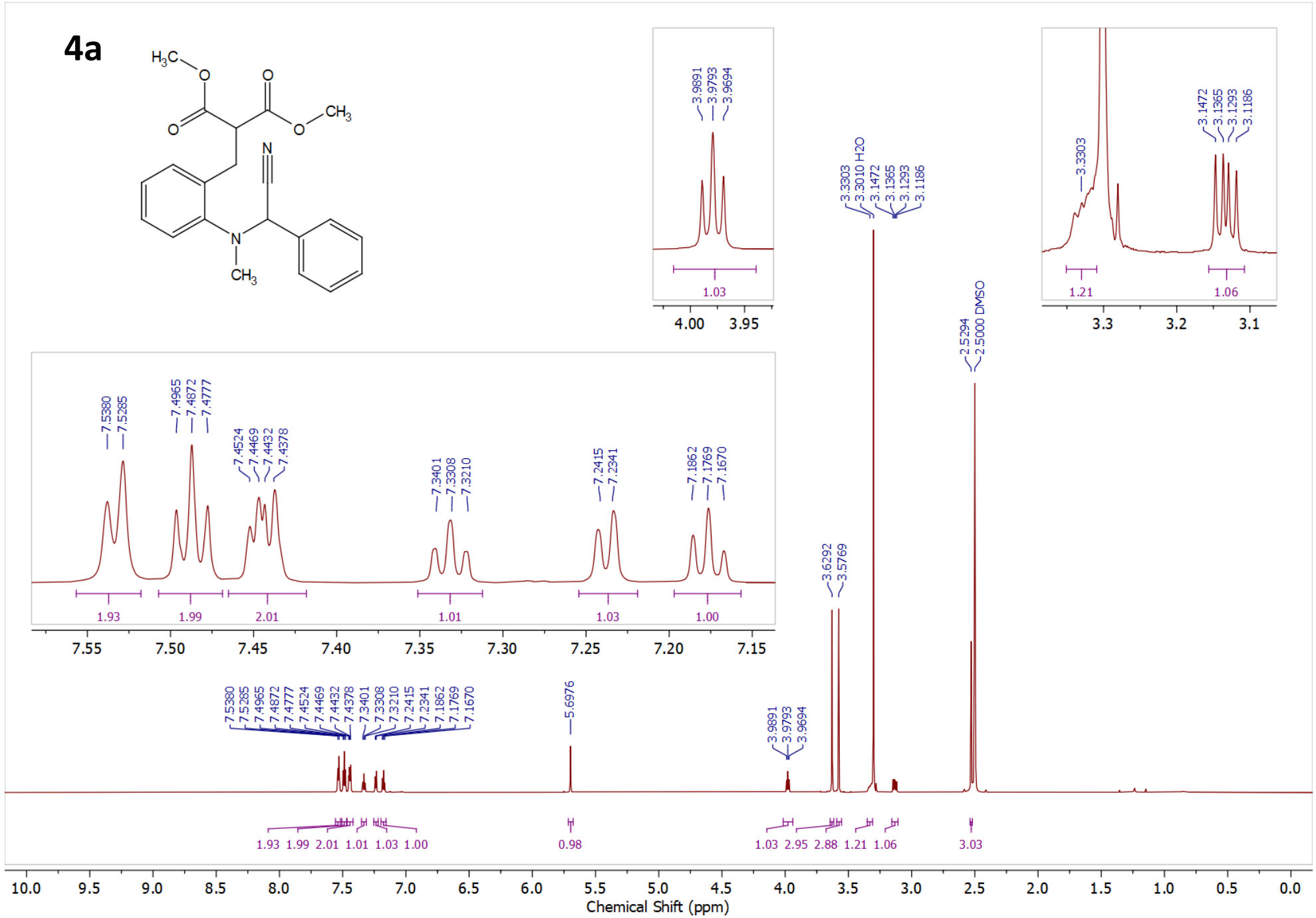

135.5413
133.5664
133.4824
129.2935
129.0592
128.9359
128.7525
128.3105
127.7610
127.4355
126.1728
122.8030
136
135
134
133
132
131
130
129
128
127
126
125
124
123
122


173.4129
148.8734
135.5413
133.5664
133.4824
129.2935
129.0592
128.9359
128.7525
128.3105
127.7610
127.4355
126.1728
122.8030
116.7527
79.5688
77.1600 CDCl3
70.9634
61.4589
37.0346
22.0241
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

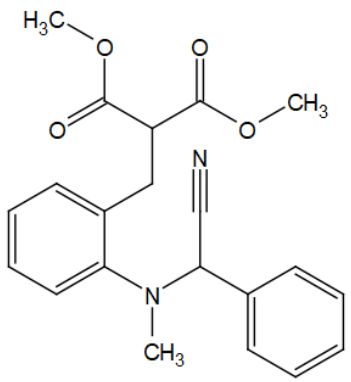
3g


COOBn
COOBn
NH
N
Me
Ph

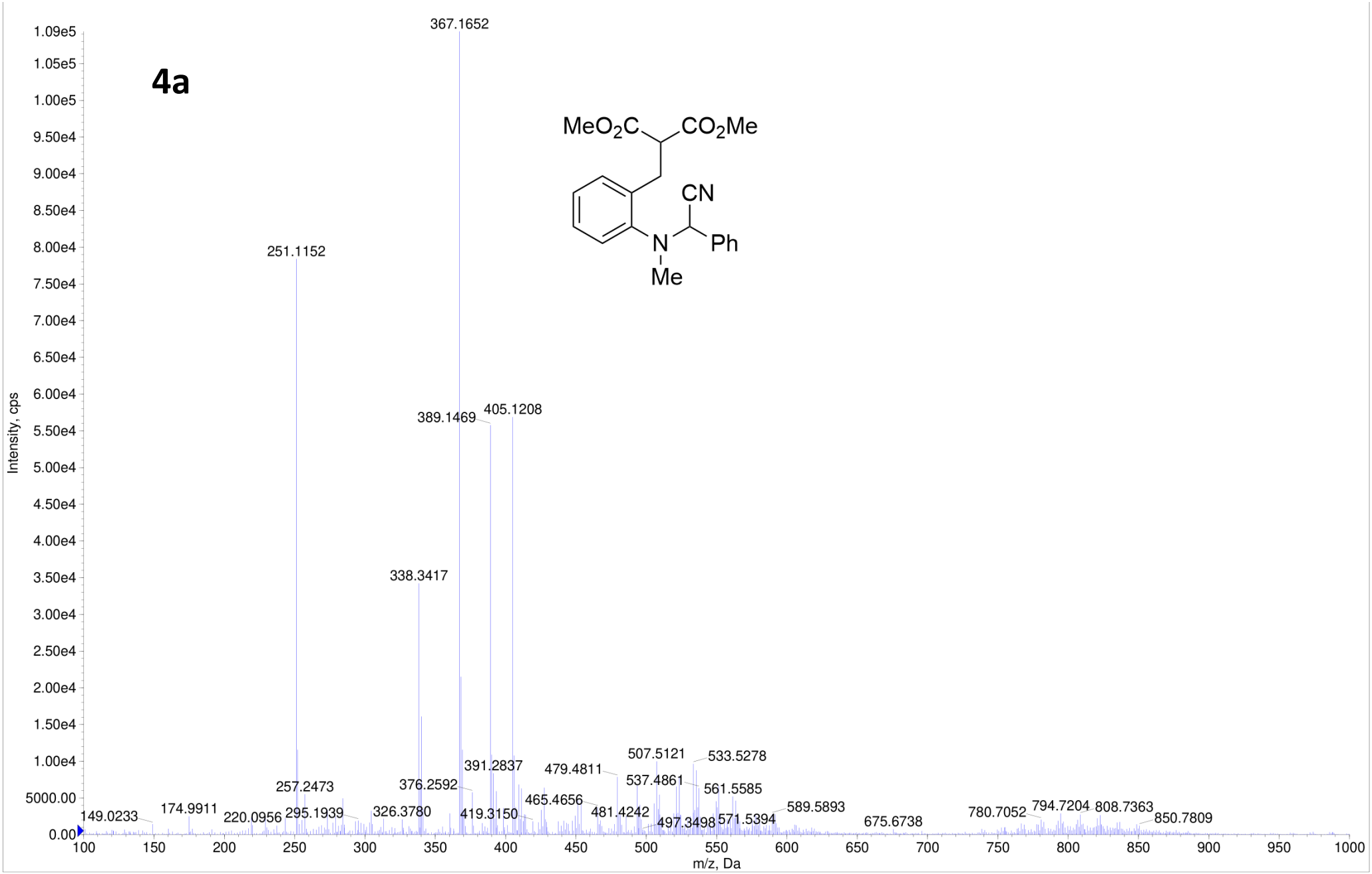

Intens.
x10^5
2.0
1.5
1.0
0.5
0.0
+MS, 8.1min #467
1+
519.2267
492.2168
541.2088
480
490
500
510
520
530
540
550
560
m/z
Intens.
6000
5000
4000
3000
2000
1000
0
AndM-193(IV-879)65014970.d:C33H30N2O4, M+nH, 519.2278
1+
519.2278
480
490
500
510
520
530
540
550
560
m/z

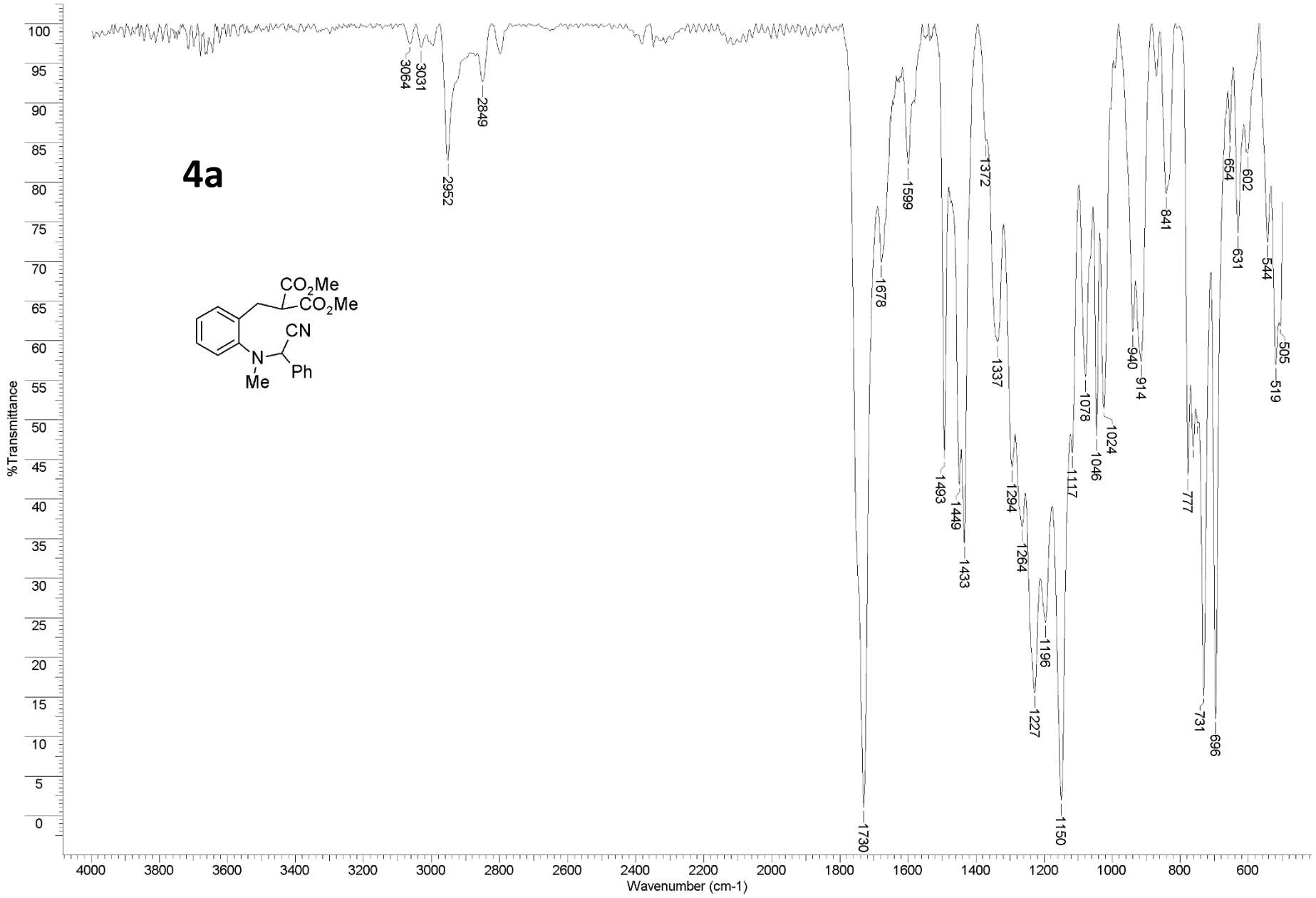

4a
H3C
O
O
O
O
CH3
N
N
CH3
3.9891
3.9793
3.9694
1.03
4.00
3.95
3.3303
3.3010 H2O
3.1472
3.1365
3.1293
3.1186
2.5294
2.5000 DMSO
3.6292
3.5769
3.1472
3.1365
3.1293
3.1186
3.3303
1.21
1.06
3.3
3.2
3.1
7.5380
7.5285
7.4965
7.4872
7.4777
7.4524
7.4469
7.4432
7.4378
7.3401
7.3308
7.3210
7.2415
7.2341
7.1862
7.1769
7.1670
1.93
1.99
2.01
1.01
1.03
1.00
7.55
7.50
7.45
7.40
7.35
7.30
7.25
7.20
7.15
5.6976
0.98
1.03 2.95 2.88 1.21 1.06
3.03
1.93 1.99 2.01 1.01 1.03 1.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Chemical Shift (ppm)

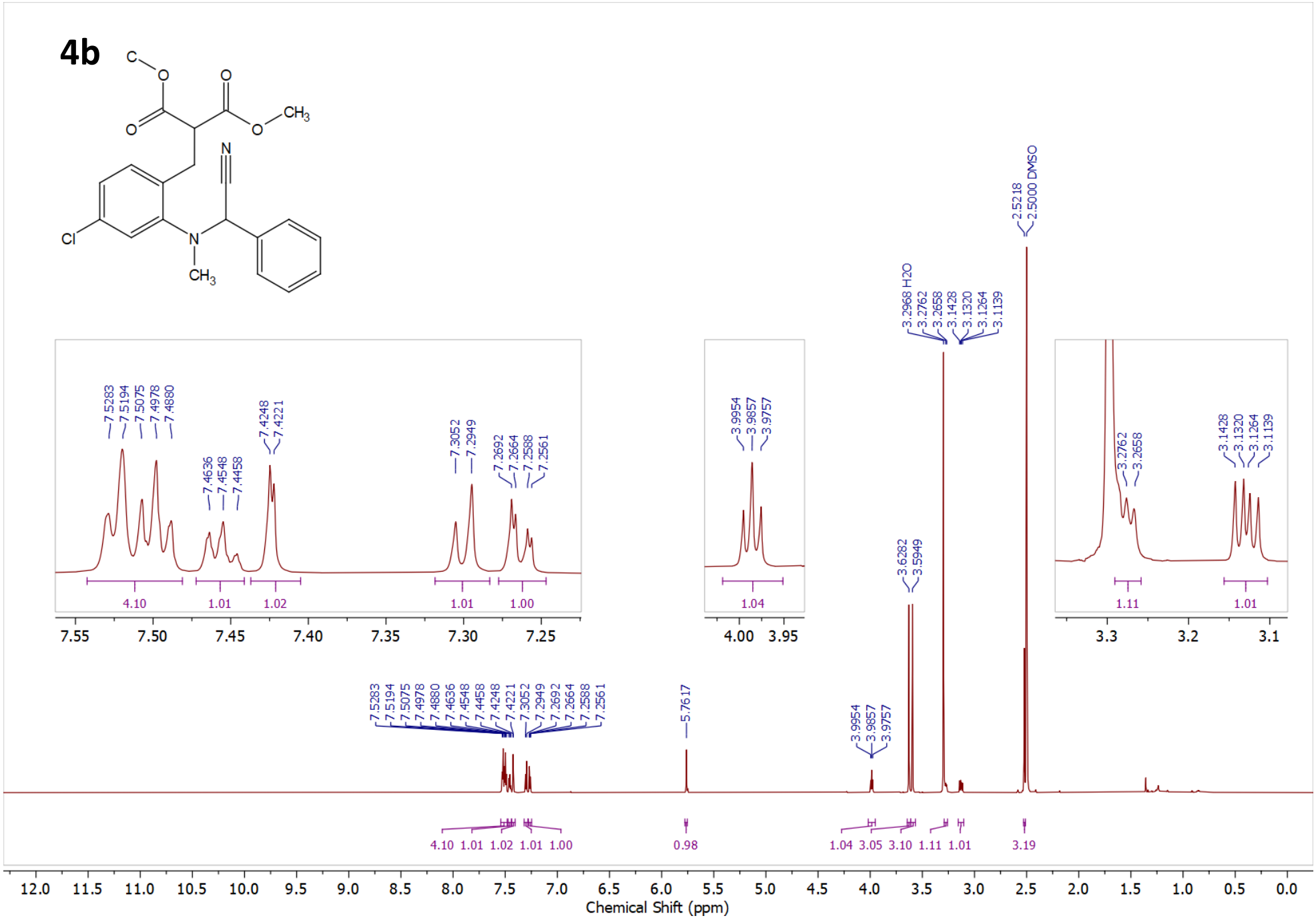
4a

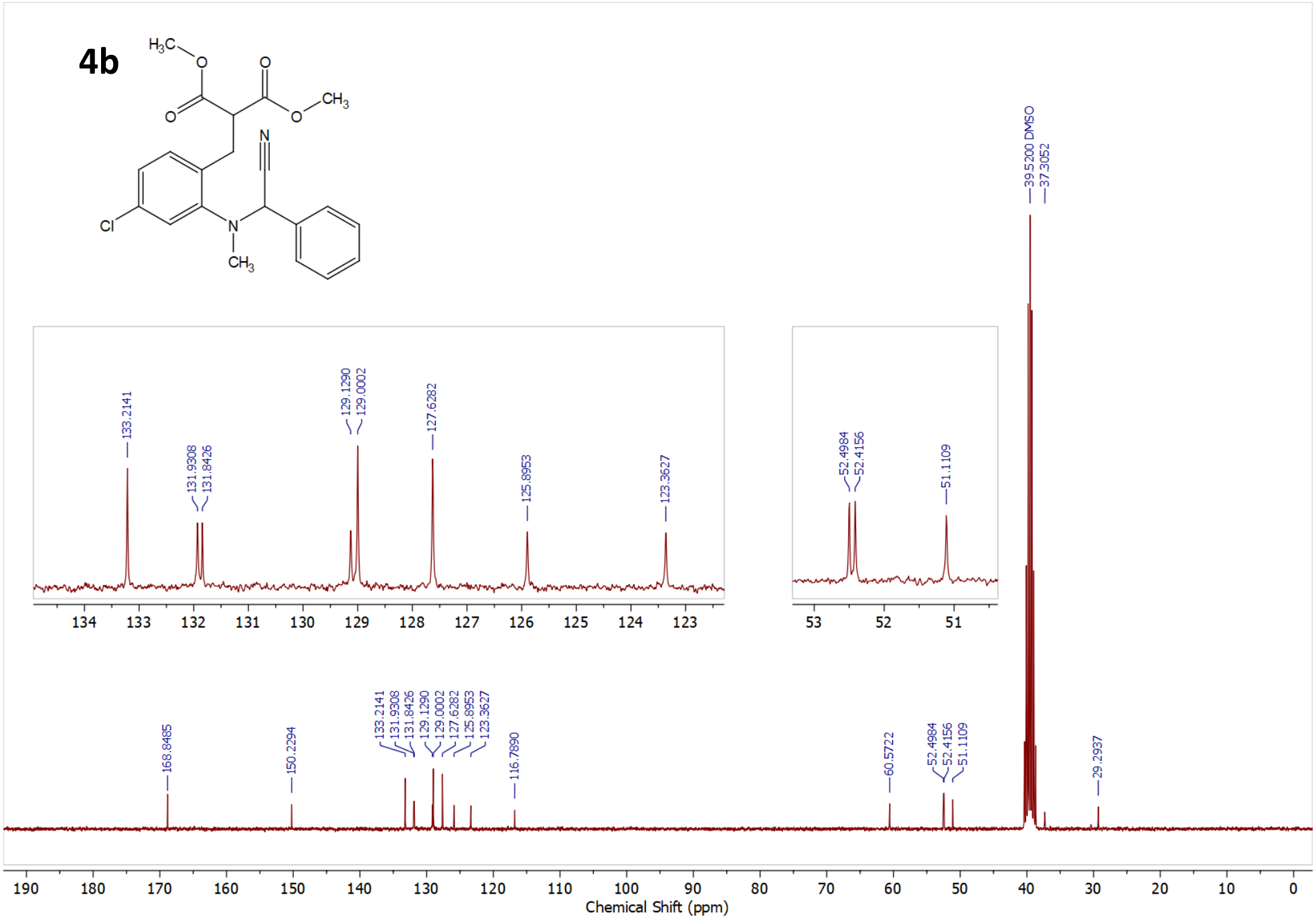

H3C
O
O
O
O
CH3
N
N
CH3

39.5200 DMSO
37.2872
134.0751
133.6177
130.3131
128.9356
128.8658
127.8588
127.6190
125.9281
52.4009
52.2855
51.3276
37.2872
168.9296
148.8522
134.0751
133.6177
130.3131
128.9356
128.8658
127.8588
127.6190
125.9281
123.1684
117.0088
60.8749
52.4009
52.2855
51.3276
29.8862
Chemical Shift (ppm)

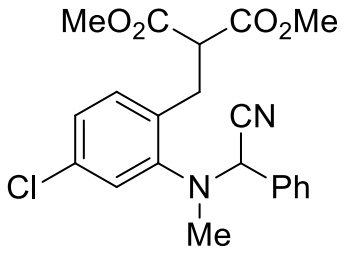

4a
MeO2C
CO2Me
CN
N
Ph
Me
Intensity, cps
m/z, Da
367.1652
251.1152
389.1469
405.1208
338.3417
391.2837
479.4811
507.5121
533.5278
537.4861
561.5585
257.2473
376.2592
465.4656
589.5893
149.0233
174.9911
220.0956
295.1939
326.3780
419.3150
481.4242
497.3498
571.5394
675.6738
780.7052
794.7204
808.7363
850.7809

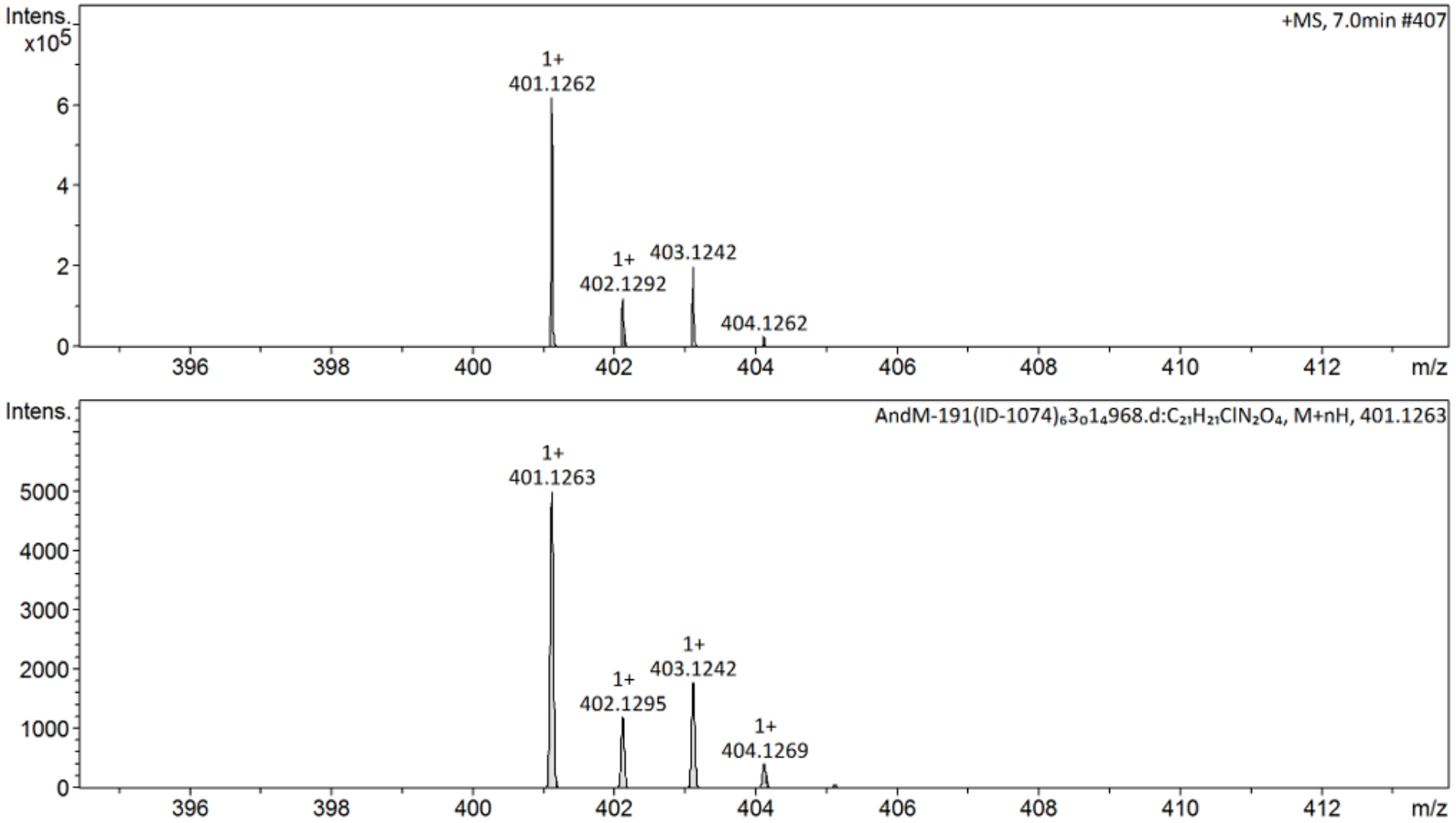

4a
CO2Me
CO2Me
CN
N
Me
Ph
%Transmittance
Wavenumber (cm-1)
3064
3031
2952
2849
1730
1678
1599
1493
1449
1433
1372
1337
1294
1264
1227
1196
1150
1117
1078
1046
1024
940
914
841
777
731
696
654
631
602
544
519
505


4b
Cl
N
CH3
7.5283
7.5194
7.5075
7.4978
7.4880
7.4636
7.4548
7.4458
7.4248
7.4221
7.3052
7.2949
7.2692
7.2664
7.2588
7.2561
3.9954
3.9857
3.9757
3.6282
3.5949
3.2968 H2O
3.2762
3.2658
3.1428
3.1320
3.1264
3.1139
2.5218
2.5000 DMSO
5.7617
4.10 1.01 1.02 1.01 1.00
0.98
1.04 3.05 3.10 1.11 1.01
3.19
Chemical Shift (ppm)

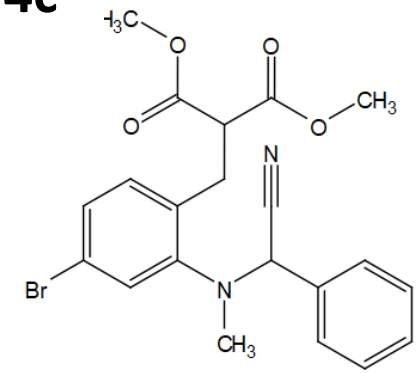

4b
H3C
O
O
O
O
CH3
N
Cl
N
CH3
133.2141
131.9308
131.8426
129.1290
129.0002
127.6282
125.8953
123.3627
52.4984
52.4156
51.1109
39.5200 DMSO
37.3052
168.8485
150.2294
116.7890
60.5722
29.2937
Chemical Shift (ppm)

4b

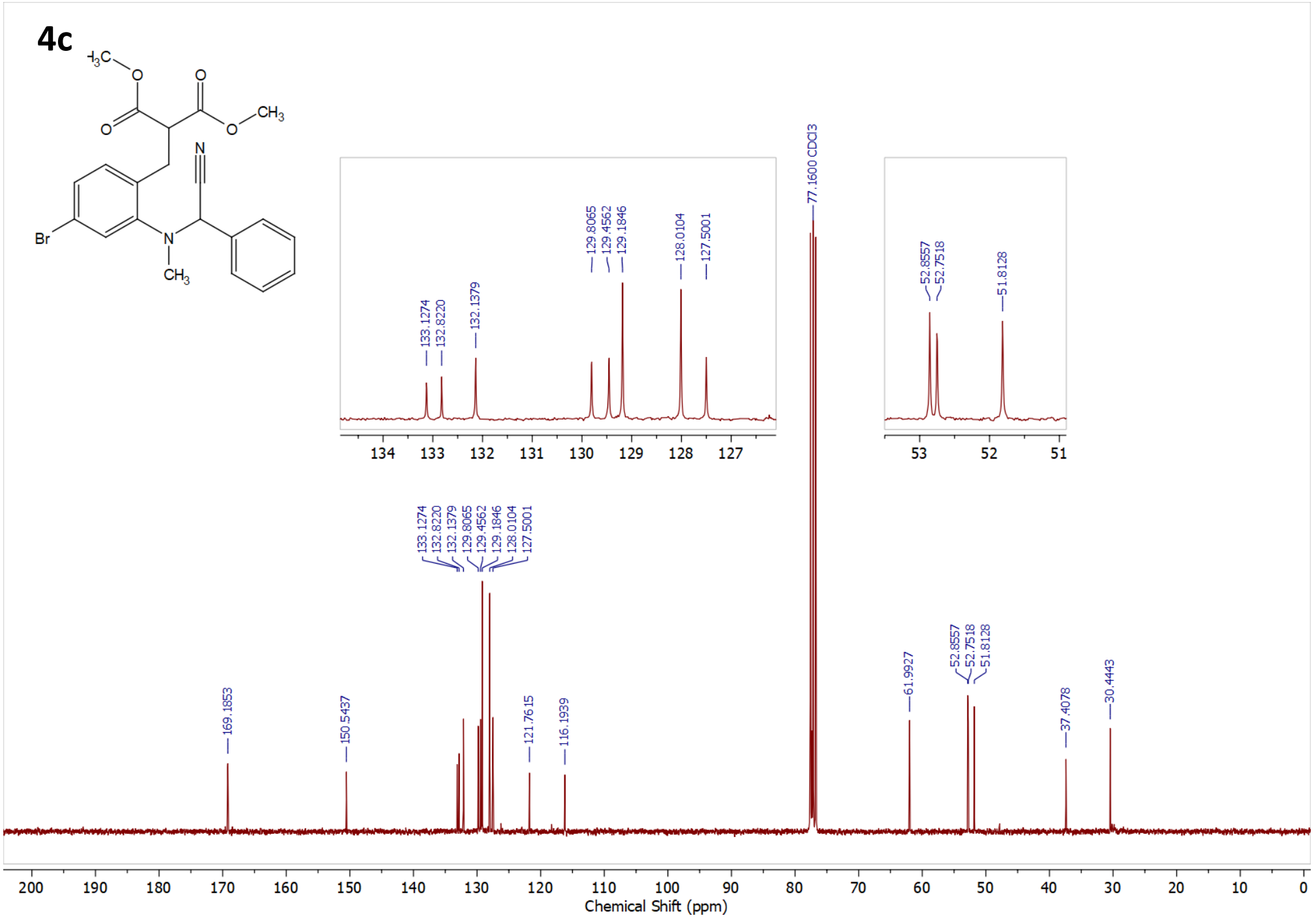

MeO2C
CO2Me
CN
Cl
N
Ph
Me


Intens.
x10^5
+MS, 7.0min #407
1+
401.1262
1+
402.1292
403.1242
404.1262
396
398
400
402
404
406
408
410
412
m/z
Intens.
AndM-191(ID-1074)63014968.d:C21H21ClN2O4, M+nH, 401.1263
1+
401.1263
1+
402.1295
1+
403.1242
1+
404.1269
396
398
400
402
404
406
408
410
412
m/z

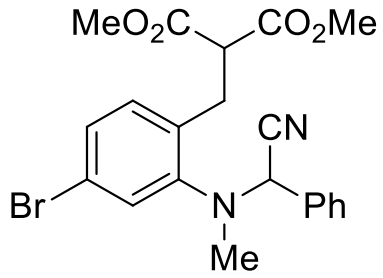
4c

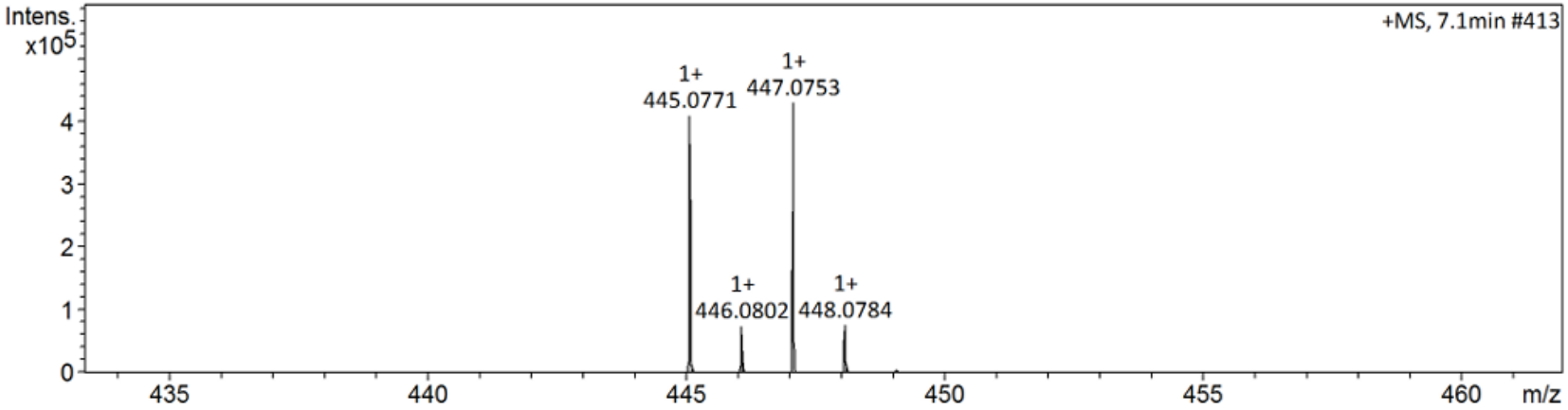

H3C
O
O
O
O
CH3
N
Br
N
CH3

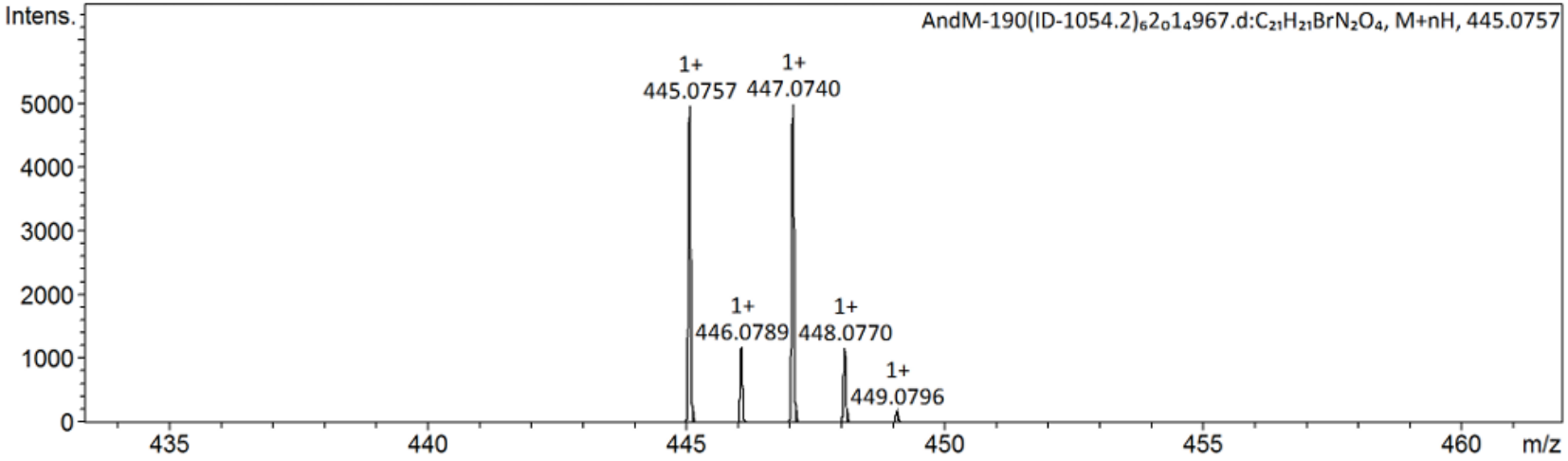
7.6293
7.6268
7.6146
7.6052
7.4547
7.4444
7.4349
7.4242
7.4155
7.4065
7.3120
7.3096
7.3018
7.2993
7.2600 CDCl3
7.0909
7.0807
0.94 1.97 3.03 1.01 1.00
3.8797
3.8711
3.8684
3.8599
0.99
3.3229
3.3145
3.3050
3.2965
3.2466
3.2353
3.2287
3.2174
0.98 1.03
5.1668
3.7258
3.6564
2.6312
1.5343 H2O
0.99 3.14 2.92 0.98 1.03
3.04
Chemical Shift (ppm)


4c
Br
N
CH3
O
O
O
O
CH3
H3C
N
CH3
77.1600 CDCl3
133.1274
132.8220
132.1379
129.8065
129.4562
129.1846
128.0104
127.5001
52.8557
52.7518
51.8128
169.1853
150.5437
121.7615
116.1939
61.9927
37.4078
30.4443
Chemical Shift (ppm)

4c


MeO2C
CO2Me
CN
Br
N
Ph
Me


Intens.
x10^5
+MS, 7.1min #413
1+
445.0771
1+
447.0753
1+
446.0802
1+
448.0784
435
440
445
450
455
460
m/z


Intens.
AndM-190(ID-1054.2)620140967.d:C21H21BrN2O4, M+nH, 445.0757
1+
445.0757
1+
447.0740
1+
446.0789
1+
448.0770
1+
449.0796
435
440
445
450
455
460
m/z