Supporting information for the manuscript entitled

Malaria Box-inspired discovery of *N*-aminoalkyl-β-carboline-3-carboxamides, a novel orally-active class of antimalarials.

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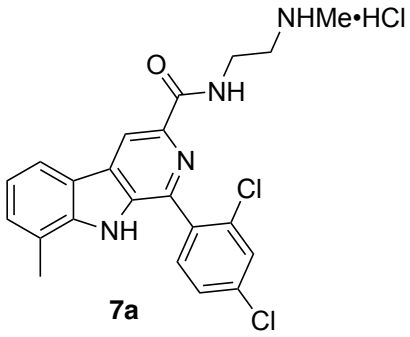
A. Synthetic procedures and tabulation of analytical data

General information

Compounds were purchased from Sigma-Aldrich, Alfa Aesar, Oakwood Chemicals, and Combi-Blocks, and were used without purification, unless otherwise noted. In particular, 7-methylindole (**8**), di-tert-butyl decarbonate, and *N*-boc-iodoalanine methyl ester (*R*)-**10**, were purchased from Oakwood Chemicals. Tryptophan methyl ester (*S*)-**25** was purchased from Sigma-Aldrich. *N*-boc-iodoalanine methyl ester (*S*)-**10**, and iodobenzene diacetate were purchased from Combi-Blocks.

^{1}H NMR spectra were recorded at 400 or 500 MHz; the corresponding ^{13}C NMR resonant frequencies were 101 and 126 MHz respectively. All compounds submitted for bioassay were judged to be ≥95% pure by ^{1}H NMR spectroscopy. Optical rotations were obtained using a JASCO P-2000 polarimeter. HRMS of compounds were obtained using Waters Synapt G2-S interfaced with a Waters Acquity I-class UPLC and Agilent 6220 AM TOF LC/MS.

Synthesis Procedures and Analytical Data



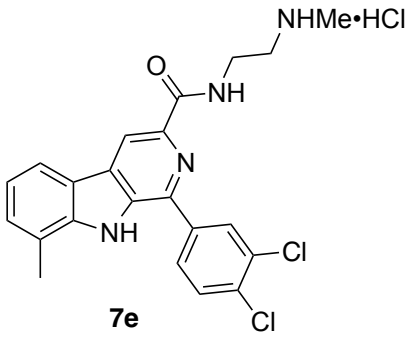
7a

*1-(2,4-dichlorophenyl)-8-methyl-N-(2-(methylamino)ethyl)-9H-pyrido[3,4-b]indole-3-carboxamide hydrochloride (***7a***)*

To a 1 dram vial were added methyl 1-(2,4-dichlorophenyl)-8-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **14a** (30 mg, 0.078 mmol) and a magnetic stirbar. The vial was sealed with a rubber septum and purged with N_2 for 5 minutes. *N*^{1}-methylethane-1,2-diamine (0.04 mL, d = 0.85 g/mL, 0.39 mmol, 5 equiv) was added via syringe, the mixture was stirred at rt for 5 minutes, and then heated to 90 °C for 22 h, at which point TLC indicated complete consumption of **14a**. The reaction was allowed to cool to rt, then placed in an ice bath, and ice-cold water (~1 mL) was added to precipitate the product. The resulting mixture was stirred at r.t. for another 5 minutes and the solid was collected by vacuum filtration, and washed with cold water, and air-dried obtain the free base of **7a** (28 mg, 84% yield). A portion of this material (14.8 mg) was dissolved in 0.1 M HCl in methanol (0.4 mL, prepared from 12 N HCl (aq)), concentrated *in vacuo*. The salt was again dissolved in methanol (~1 mL) and concentrated *in vacuo* to remove residual water. The solid was triturated with toluene and dried overnight to obtain **7a** (as the depicted HCl salt, 15 mg, 93% yield) as a bright yellow solid.

^{1}H NMR (500 MHz, CD_3OD) δ 8.94 (s, 1H), 8.13 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.74 (d, *J* = 2.1 Hz, 1H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.58 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.42 (dt, *J* = 7.2, 1.1 Hz, 1H), 7.28 (app t, *J* = 7.6 Hz, 1H), 3.79 (t, *J* = 5.6 Hz, 2H), 3.28 (t, *J* = 5.6 Hz, 2H), 2.75 (s, 3H), 2.58 (s, 3H).

^{13}C NMR (free base, 126 MHz, CD_3OD) δ 168.9, 142.7, 140.8, 139.3, 137.4, 136.9, 136.6, 135.9, 134.2, 131.8, 131.0, 130.7, 128.7, 123.6, 122.5, 122.1, 120.2, 115.4, 50.9, 37.2, 33.8, 17.4.
HRMS (ESI+) calculated for $C_{22}H_{21}Cl_2N_4O$ $[M+H]^+$: 427.1087, found 427.1089



7e

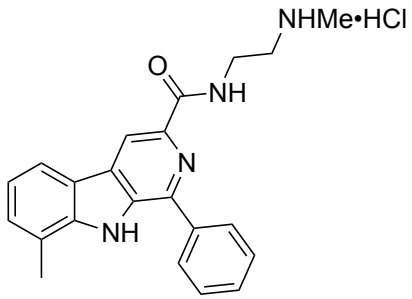
*1-(3,4-dichlorophenyl)-8-methyl-N-(2-(methylamino)ethyl)-9H-pyrido[3,4-b]indole-3-carboxamide hydrochloride (***7e***)*

To an oven-dried 25 mL RBF were added methyl 1-(3,4-dichlorophenyl)-8-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **14e** (250 mg, 0.649 mmol) and a magnetic stirbar. The flask was sealed with a rubber septum and purged with N_2 for 5 minutes. *N*^{1}-methylethane-1,2-diamine (0.283 mL, d = 0.85 g/mL, 0.25 mmol, 5 equiv) was added via syringe, the mixture was stirred at rt for 5 minutes, and then heated to 90 °C for 22 h, at which point TLC indicated complete consumption of **2**. The reaction was allowed to cool to rt, then placed in an ice bath, and ice-cold water (~3 mL) was added to precipitate the product. The resulting mixture was stirred at r.t. for another 5 minutes and the solid was collected by vacuum filtration, and washed with cold water, and air-dried obtain the free base of **7e** (240 mg, 87% yield). A portion of this material (204 mg) was dissolved in 0.1 M HCl in methanol (4.8 mL, prepared from 12 N HCl (aq)), concentrated *in vacuo*. The salt was again dissolved in methanol (5 mL) and concentrated *in vacuo* to remove residual water. The solid was triturated with toluene and dried overnight to obtain **7e** (as the depicted HCl salt ,185 mg, 86% recovered).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.54 (s, 1H), 9.01 (t, J = 6.1 Hz, 1H), 8.86 (s, 1H), 8.61 (br s, 1H), 8.34 (d, J = 2.0 Hz, 1H), 8.27 (d, J = 7.9 Hz, 1H), 8.13 (dd, J = 8.3, 2.0 Hz, 1H), 7.90 (d, J = 8.3 Hz, 1H), 7.43 (dt, J = 7.1, 1.1 Hz, 1H), 7.26 (app t, J = 7.9, 7.2 Hz, 1H), 3.69 (app q, J = 6.0 Hz, 2H), 3.18 – 3.12 (m, 2H), 2.64 (s, 3H), 2.60 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 165.60, 141.07, 139.69, 138.72, 138.10, 134.83, 131.62, 131.54, 131.01, 130.97, 130.76, 129.59, 129.39, 122.42, 121.21, 120.76, 119.50, 113.85, 48.43, 35.63, 32.79, 17.45.

HRMS (ESI+) calculated for $C_{22}H_{21}Cl_2N_4O$ $[M+H]^+$: 427.1087, found 427.1081



7f

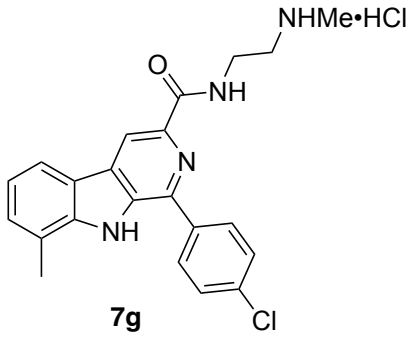
*8-methyl-N-(2-(methylamino)ethyl)-1-phenyl-9H-pyrido[3,4-b]indole-3-carboxamide hydrochloride (**7f**)*

To a 1 dram vial were added methyl 8-methyl-1-phenyl-9H-carbazole-3-carboxylate **14f** (50 mg, 0.158 mmol) and a magnetic stirbar. The vial was sealed with a rubber septum and purged with N_2 for 5 minutes. *N*^{1}-methylethane-1,2-diamine (0.07 mL, d = 0.85 g/mL, 0.79 mmol, 5 equiv) was added via syringe, the mixture was stirred at rt for 5 minutes, and then heated to 90 °C for 22 h, at which point TLC indicated complete consumption of **14f**. The reaction was allowed to cool to rt, then placed in an ice bath, and ice-cold water (~1 mL) was added to precipitate the product. The resulting mixture was stirred at r.t. for another 5 minutes and the solid was collected by vacuum filtration, and washed with cold water, and air-dried obtain the free base of **7f** (42 mg, 75% yield). A portion of this material (21.1 mg) was dissolved in 0.1 M HCl in methanol (0.8 mL, prepared from 12 N HCl (aq)), concentrated *in vacuo*. The salt was again dissolved in methanol (~1 mL) and concentrated *in vacuo* to remove residual water. The solid was triturated with toluene and dried overnight to obtain **7f** (as the depicted HCl salt, 21.1 mg, 92% recovered) as a bright yellow solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.4 (s, 1H), 9.0 (t, J = 6.1 Hz, 1H), 8.8 (s, 1H), 8.7 (br s, 2H), 8.2 (d, J = 7.8 Hz, 1H), 8.2 (d, J = 7.1 Hz, 2H), 7.6 (app t, J = 7.5 Hz, 2H), 7.6 (app t, J = 7.4 Hz, 1H), 7.4 (dt, J = 7.1, 1.0 Hz, 1H), 7.3 (app t, J = 7.5 Hz,1H), 3.7 (app q, J = 6.1 Hz, 2H), 3.2 (app quint, J = 6.0 Hz, 2H), 2.6 (s, 3H), 2.6 (t, J = 5.5 Hz, 3H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 165.7, 141.3, 141.0, 139.5, 137.6, 134.8, 130.7, 129.4, 129.1, 129.0, 128.7, 122.5, 121.3, 120.6, 119.4, 113.1, 48.4, 35.6, 32.7, 17.5.

HRMS (ESI+) calculated for $C_{22}H_{23}N_4O$ $[M+H]^+$: 359.1866, found : 359.1862



7g

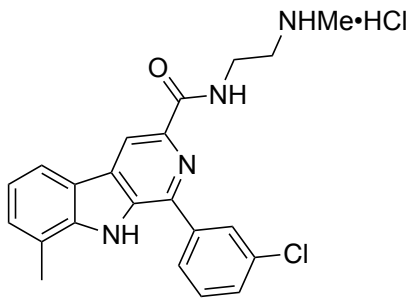
*1-(4-chlorophenyl)-8-methyl-N-(2-(methylamino)ethyl)-9H-pyrido[3,4-b]indole-3-carboxamide hydrochloride (**7g**)*

To a 1 dram vial were added methyl 1-(4-chlorophenyl)-8-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **14g** (50 mg, 0.143 mmol) and a magnetic stirbar. The vial was sealed with a rubber septum and purged with N_2 for 5 minutes. N^1-methylethane-1,2-diamine (0.06 mL, d = 0.85 g/mL, 0.71 mmol, 5 equiv) was added via syringe, the mixture was stirred at rt for 5 minutes, and then heated to 90 °C for 22 h, at which point TLC indicated complete consumption of **14g**. The reaction was allowed to cool to rt, then placed in an ice bath, and ice-cold water (~1 mL) was added to precipitate the product. The resulting mixture was stirred at r.t. for another 5 minutes and the solid was collected by vacuum filtration, and washed with cold water, and air-dried obtain the free base of **7g** (38 mg, 68% yield). A portion of this material (36 mg) was dissolved in 0.1 M HCl in methanol (1.0 mL, prepared from 12 N HCl (aq)), concentrated *in vacuo*. The salt was again dissolved in methanol (~1 mL) and concentrated *in vacuo* to remove residual water. The solid was triturated with toluene and dried overnight to obtain **7g** (as the depicted HCl salt, 25 mg, 64% yield) as bright yellow solid.

^{1}H NMR (400 MHz, CD_3OD) δ 8.82 (s, 1H), 8.15 – 8.05 (m, 3H), 7.67 – 7.60 (m, 2H), 7.41 (dt, *J* = 7.2, 1.1 Hz, 1H), 7.27 (ddd, *J* = 7.7, 7.2, 0.4 Hz, 1H), 3.85 – 3.78 (m, 2H), 3.31 – 3.24 (m, 2H), 2.76 (s, 3H), 2.64 (s, 3H).

^{13}C NMR (126 MHz, CD_3OD) δ 169.3, 142.6, 142.3, 140.2, 137.9, 136.7, 136.1, 132.5, 131.6, 130.7, 130.0, 123.8, 122.9, 122.1, 120.0, 114.6, 51.0, 37.4, 34.0, 17.4.

HRMS (ESI+) calculated for $C_{22}H_{22}ClN_4O$ $[M+H]^+$: 393.1477, found 393.1472



7h

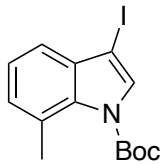
*1-(3-chlorophenyl)-8-methyl-N-(2-(methylamino)ethyl)-9H-pyrido[3,4-b]indole-3-carboxamide hydrochloride (***7h***)*

To a 1 dram vial were added methyl 1-(3-chlorophenyl)-8-methyl-9H-pyrido[3,4-b]indole-3-carboxylate **14h** (50 mg, 0.143 mmol) and a magnetic stirbar. The vial was sealed with a rubber septum and purged with N_2 for 5 minutes. *N*^{1}-methylethane-1,2-diamine (0.07 mL, d = 0.85 g/mL, 0.71 mmol, 5 equiv) was added via syringe, the mixture was stirred at rt for 5 minutes, and then heated to 90 °C for 22 h, at which point TLC indicated complete consumption of **14h**. The reaction was allowed to cool to rt, then placed in an ice bath, and ice-cold water (~1 mL) was added to precipitate the product. The resulting mixture was stirred at r.t. for another 5 minutes and the solid was collected by vacuum filtration, and washed with cold water, and air-dried obtain the free base of **7h** (45 mg, 80% yield). A portion of this material (17.5 mg) was dissolved in 0.1 M HCl in methanol (0.45 mL, prepared from 12 N HCl (aq)), concentrated *in vacuo*. The salt was again dissolved in methanol (~1 mL) and concentrated *in vacuo* to remove residual water. The solid was triturated with toluene and dried overnight to obtain **7h** (as the depicted HCl salt, 18.7 mg, 98% recovered) as dark yellow solid.

^{1}H NMR (400 MHz, CD_3OD) δ 9.05 (s, 1H), 8.19 (dt, *J* = 7.8, 1.0 Hz, 1H), 8.09 -8.09 (m, 1H), 8.02 – 7.95 (m, 1H), 7.70 – 7.65 (m, 2H), 7.51 (dt, *J* = 7.2, 1.1 Hz, 1H), 7.37 (app t, *J* = 7.6 Hz,1H), 3.88 – 3.83 (m, 2H), 3.37 – 3.33 (m, 2H), 2.79 (s, 3H), 2.66 (s, 3H).

^{13}C NMR (126 MHz, DMSO) δ 164.6, 141.1, 140.1, 139.7, 139.5, 134.7, 133.5, 131.0, 130.5, 129.4, 128.8(2 accidental equivalent peaks), 127.7, 122.4, 121.3, 120.6, 119.4, 113.3, 50.9, 38.6, 36.0, 17.5.

HRMS (ESI+) calculated for $C_{22}H_{22}ClN_4O$ $[M+H]^+$: 393.1477, found : 393.1475



9

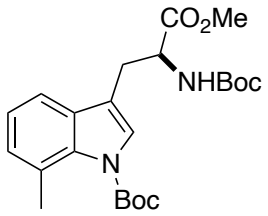
*Tert-butyl 3-iodo-7-methyl-1H-indole-1-carboxylate(**9**)*

A literature procedure for synthesis of *tert*-butyl 3- iodo-1*H*-indole-1-carboxylate was followed. To a solution of 7-bromo-1H-indole (2.0 g, 15.25 mmol) in DMF (20 mL) was added iodine (3.88 g, 15.4 mmol, 3.9 equiv.) and potassium hydroxide (2.14 g, 38.12 mmol, 2.5 equiv.). The reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was then poured into 400 mL of ice water containing saturated aqueous sodium thiosulfate. The mixture was placed in an ice bath for 2 hours to ensure the complete precipitation. The precipitate was filtered, washed with ice water and dried in vacuo to obtain crude product as a brownish solid. It was used in the next step without further purification. The obtained solid was dissolved in CH_2Cl_2 (20 mL). 4-Dimethylaminopyridine (128 mg, 1.05 mmol, 10 mol%) and di-tert-butyl dicarbonate (3.43 g, 15.7 mmol, 1.5 equiv.) was then added to the solution. The reaction mixture was stirred at room temperature for 24 hours. The mixture was then washed with 1 M HCl (300 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (1: 4 CH_2Cl_2/ hexanes) to give **9** (2.39 g, 44% over two steps) as an off-white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.29 – 7.22 (m, 2H), 7.19 – 7.18 (m, 1H), 2.65 (s, 3H), 1.65 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.6, 134.5, 133.4, 132.3, 128.9, 125.6, 123.9, 119.5, 84.1, 65.8, 28.2, 22.1.

HRMS (ESI+) calculated for $C_{14}H_{17}INO_2$ $[M+H]^+$: 358.0298, found : 358.0267



(*S*)-**11**

*tert-butyl (S)-3-(2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-7-methyl-1H-indole-1-carboxylate((S)-**11**)*

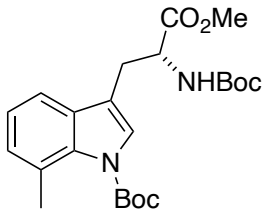
Based on the procedure of Ross et al.[1] Zinc dust (274 mg, 4.2 mmol, 3 equiv.) was added to a flame-dried, nitrogen-purged two neck round-bottomed flask. Dry DMF (1.4 mL) was added via syringe, followed by a catalytic amount of iodine (52.91 mg, 0.21 mmol, 15 mol%). A color change of the DMF was observed from colorless to yellow and back again. Methyl (*R*)-2-((tert-butoxycarbonyl)amino)-3-iodopropanoate (460.72 mg, 1.40 mmol, 1.0 equiv.) was added immediately, followed by a catalytic amount of iodine (52.91 mg, 0.21 mmol, 15 mol%). The solution was stirred at room temperature; successful zinc insertion is accompanied by a noticeable exotherm. The solution of organozinc reagent was allowed to cool to room temperature before use. Pd_2dba_3 (32.05 mg, 0.035 mmol, 2.5 mol%), SPhos (28.73 mg, 0.070 mmol, 5.0 mol%), and the tert-butyl 3-iodo-7-methyl-1H-indole-1-carboxylate **9** (650 mg, 1.82 mmol, 1.3 equiv.) were added to the solution of organozinc reagent and the mixture was stirred at room temperature for 41 hours, under a positive pressure of nitrogen. The crude reaction mixture was applied directly to a silica gel column (9:1 Hexanes/Ethyl acetate) to afford the purified cross-coupled product (*S*)-**11** (372 mg, 83%) as a brown solid. ^{1}H NMR analysis indicated ~90% purity, which proved sufficient for the subsequent steps.

$[\alpha]_D^{23} = +19.7\ (c = 5.00, \mathrm{MeOH})$

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 2H), 7.15 (app t, *J* = 7.6 Hz, 1H), 7.10 (d, *J* = 7.3 Hz, 1H), 5.08 (d, *J* = 8.1 Hz, 1H), 4.64 (app q, *J* = 6.5 Hz, 1H), 3.68 (s, 3H), 3.26 – 3.11 (m, 2H), 2.62 (s, 3H), 1.63 (s, 9H), 1.44 – 1.44 (m, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 155.2, 149.5, 135.1, 132.0, 128.1, 126.5, 125.6, 123.2, 116.5, 114.9, 83.4, 80.06, 53.8, 52.4, 28.5, 28.2, 22.3.

HRMS (ESI+) calculated for $C_{23}H_{33}N_2O_6$ $[M+H]^+$: 433.2333, found : 433.2337



(*R*)-**11**

*tert-butyl (R)-3-(2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-7-methyl-1H-indole-1-carboxylate((R)-**11**)*

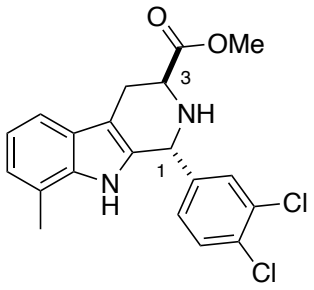
Based on the procedure of Ross et al.[1] Zinc dust (274 mg, 4.2 mmol, 3.0 equiv.) was added to a flame-dried, nitrogen-purged two neck round-bottomed flask. Dry DMF (1.4 mL) was added via syringe, followed by a catalytic amount of iodine (52.91 mg, 0.21 mmol, 15 mol%). A color change of the DMF was observed from colorless to yellow and back again. Methyl (*S*)-2-((tert-butoxycarbonyl)amino)-3-iodopropanoate (460.72 mg, 1.40 mmol, 1.0 equiv.) was added immediately, followed by a catalytic amount of iodine (52.91 mg, 0.21 mmol, 15 mol%). The solution was stirred at room temperature; successful zinc insertion is accompanied by a noticeable exotherm. The solution of organozinc reagent was allowed to cool to room temperature before use. Pd_2dba_3 (32.05 mg, 0.035 mmol, 2.5 mol%), SPhos (28.73 mg, 0.070 mmol, 5 mol%), and the tert-butyl 3-iodo-7-methyl-1H-indole-1-carboxylate **9** (650 mg, 1.82 mmol, 1.3 equiv.) were added to the solution of organozinc reagent and the mixture was stirred at room temperature for 41 hours, under a positive pressure of nitrogen. The crude reaction mixture was applied directly to a silica gel column (9:1 Hexanes/Ethyl acetate) to afford the purified cross-coupled product (*R*)-**11** (383 mg, 86%) as a brown solid. ^{1}H NMR analysis indicated ~90% purity, which proved sufficient for the subsequent steps.

$[\alpha]_D^{23} = -22.4\ (c = 5.00, \mathrm{MeOH})$

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 2H), 7.15 (app t, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 7.3 Hz, 1H), 5.08 (d, *J* = 8.0 Hz, 1H), 4.67 – 4.60 (m, 1H), 3.68 (s, 3H), 3.19 – 3.18 (m, 2H), 2.62 (s, 3H), 1.62 (s, 9H), 1.44 -.1.44(m, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 155.2, 149.5, 135.1, 132.0, 128.1, 126.5, 125.6, 123.2, 116.5, 114.9, 83.4, 80.1, 53.8, 52.4, 28.5, 28.2, 22.3.

HRMS (ESI+) calculated for $C_{23}H_{33}N_2O_6$ $[M+H]^+$: 433.2333, found : 433.2336



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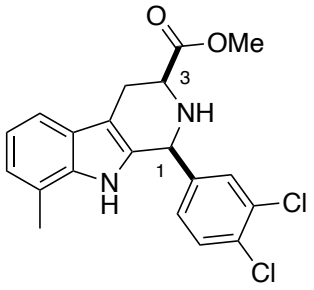


(1*R*,3*S*)-**12e** (1*S*,3*S*)-**12e**

Methyl (1R,3S)-1-(3,4-dichlorophenyl)-8-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate ((1*R*,3*S*)-**12e***) & methyl (1S,3S)-1-(3,4-dichlorophenyl)-8-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (*(1*S*,3*S*)-**12e***)*

Tert-butyl (*S*)-3-(2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-7-methyl-1H-indole-1-carboxylate ***S*-11**(364 mg, 0.896 mmol, 1.0 equiv.) was dissolved in 12 mL of dichloro methane. To the solution were trifluoroacetic acid (0.61 mL, 7.89 mmol, 8.81 equiv.) and the reaction mixture was stirred at room temperature for 13 hours. The solvent was evaporated, the crude product diluted with EtOAc and washed with saturated $NaHCO_3$-solution and brine. The organic layer was dried over Na_2SO_4 and evaporated in vacuo methyl (*S*)-2-amino-3-(7-methyl-1*H*-indol-3-yl)propanoate, a brown oil were obtained. This compound was used for next reaction without further purification.

To a solution of methyl (*S*)-2-amino-3-(7-methyl-1*H*-indol-3-yl)propanoate (195 mg, 0.841 mmol, 1.00 equiv.) in dichloromethane (8 mL) was 1.5 g of a 4 Å MS. To this 3,4-dichlorobenzaldehyde (162 mg, 0.92 mmol, 1.01 eq.) was added and stirred for 24 hours at room temperature. The reaction was cooled to 0 °C, TFA (0.13 mL, 193 mg, 1.68 mmol, 2.00 eq.) was added dropwise and it was stirred for 48 hours at room temperature. The reaction was cooled to 0 °C, a saturated $NaHCO_3$-solution and EtOAc was added and stirred for an hour at 0 °C. The mixture was extracted with EtOAc, the combined organic layers were dried over Na_2SO_4, evaporated in vacuo and purified by flash chromatography (DCM:Hex:EtOAc = 5:5:1) to obtain 124 mg, 39% of the *cis*-product ((1*S*,3*S*)-**12e**) and 68 mg, 22%) of the *trans*-product ((1*R*,3*S*)-**12e**).

methyl (1S,3S)-1-(3,4-dichlorophenyl)-8-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate ((1*S*,3*S*)-**12e***)*

$[\alpha]_D^{22} = -80.1\ (c = 1.08, \mathrm{MeOH})$

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 2.0 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.27 – 7.24 (m, 1H), 7.23 (br s, 1H), 7.07 (app t, *J* = 7.5 Hz, 1H), 6.99 (dt, *J* = 7.2, 1.0 Hz, 1H), 5.24 (t, *J* = 2.2 Hz, 1H), 3.94 (dd, *J* = 11.1, 4.1 Hz, 1H), 3.82 (s, 3H), 3.22 (ddd, *J* = 15.1, 4.1, 1.9 Hz, 1H), 3.00 (ddd, *J* = 15.1, 11.1, 2.6 Hz, 1H), 2.38 (s, 3H), 1.57 (br s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 141.3, 136.0, 133.3, 133.1, 132.9, 131.1, 130.9, 128.2, 126.6, 123.2, 120.4, 120.3, 116.2, 110.3, 57.9, 56.8, 52.5, 25.8, 16.8.

HRMS (ESI+) calculated for $C_{20}H_{19}Cl_2N_2O_2$ $[M+H]^+$: 389.0818, found : 389.0820

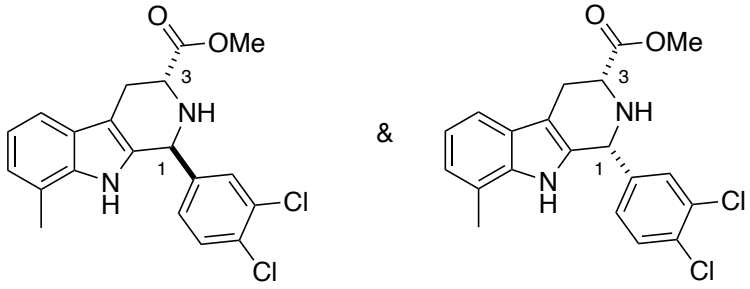
methyl (1R,3S)-1-(3,4-dichlorophenyl)-8-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate ((1*R*,3*S*)-**12e***)*

$[\alpha]_D^{23} = +20.0$ (c = 2.65, MeOH)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.40 (m, 4H), 7.15 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.10 – 7.06 (app t, *J* = 7.4 Hz, 1H), 7.00 (dt, *J* = 7.2, 1.0 Hz, 1H), 5.40 (d, *J* = 1.5 Hz, 1H), 3.93 (dd, *J* = 6.7, 5.4 Hz, 1H), 3.72 (s, 3H), 3.26 (ddd, *J* = 15.5, 5.4, 1.5 Hz, 1H), 3.12 (ddd, *J* = 15.5, 6.7, 1.5 Hz, 1H), 2.40 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 142.3, 135.7, 132.8, 132.1, 131.6, 130.6, 130.3, 127.7, 126.3, 123.0, 120.1, 119.9, 116.0, 109.3, 53.9, 52.4, 52.1, 24.6, 16.6.

HRMS (ESI+) calculated for $C_{20}H_{19}Cl_2N_2O_2$ $[M+H]^+$: 389.0818, found : 389.0823



(1*S*,3*R*)-**12e** (1*R*,3*R*)-**12e**

*Methyl (1S,3R)-1-(3,4-dichlorophenyl)-8-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate ((1S,3R)-**12e**) & methyl (1R,3R)-1-(3,4-dichlorophenyl)-8-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (*(1*R*,3*R*)-**12e***)*

Tert-butyl (*R*)-3-(2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-7-methyl-1H-indole-1-carboxylate ***R*-11** (436 mg, 1.01 mmol, 1.0 equiv.) was dissolved in 12 mL of dichloro methane.

To the solution were trifluoroacetic acid (0.68 mL, 8,87 mmol, 8.81 equiv.) and the reaction mixture was stirred at room temperature for 13 hours. The solvent was evaporated, the crude product diluted with EtOAc and washed with saturated $NaHCO_3$-solution and brine. The organic layer was dried over Na_2SO_4 and evaporated in vacuo methyl (*R*)-2-amino-3-(7-methyl-1*H*-indol-3-yl)propanoate, a brown oil were obtained. This compound was used for next reaction without further purification.

To a solution of methyl (*R*)-2-amino-3-(7-methyl-1*H*-indol-3-yl)propanoate (222 mg, 0.956 mmol, 1.00 equiv.) in dichloromethane (8 mL) was 1.5 g of a 4 Å MS. To this 3,4-dichlorobenzaldehyde (184 mg, 1.05 mmol, 1.01 eq.) was added and stirred for 24 hours at room temperature. The reaction was cooled to 0 °C, TFA (0.15 mL, 220 mg, 1.91 mmol, 2.00 eq.) was added dropwise and it was stirred for 48 hours at room temperature. The reaction was cooled to 0 °C, a saturated $NaHCO_3$-solution and EtOAc was added and stirred for an hour at 0 °C. The mixture was extracted with EtOAc, the combined organic layers were dried over Na_2SO_4, evaporated in vacuo and purified by flash chromatography (DCM:Hex:EtOAc = 5:5:1) to obtain 110 mg, 31% of the *cis*-product ((1*R*,3*R)*-**12e**) and 57 mg, 16%) of the *trans*-product ((1*S*,3*R)*-**12e**).

*methyl (1R,3R)-1-(3,4-dichlorophenyl)-8-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate ((1R,3R)-**12e**)*

$[\alpha]_D^{22} = +87.8\ (c = 1.01, MeOH)$

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 2.0 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.25 (m, 1H), 7.22 (br s, 1H), 7.07 (app t, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 7.3 Hz, 1H), 5.24 (t, *J* = 2.2 Hz, 1H), 3.94 (dd, *J* = 11.1, 4.1 Hz, 1H), 3.82 (s, 3H), 3.22 (ddd, *J* = 15.1, 4.2, 1.9 Hz, 1H), 3.00 (ddd, *J* = 15.1, 11.1, 2.6 Hz, 1H), 2.38 (s, 3H), 1.55 (br s, 1H).

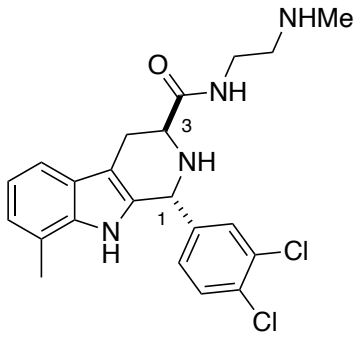
^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 141.3, 136.0, 133.3, 133.1, 132.9, 131.1, 130.9, 128.2, 126.6, 123.2, 120.4, 120.3, 116.2, 110.3, 57.9, 56.8, 52.5, 25.8, 16.8.

HRMS (ESI+) calculated for $C_{20}H_{19}Cl_2N_2O_2$ $[M+H]^+$: 389.0818, found : 389.0822

*methyl (1R,3R)-1-(3,4-dichlorophenyl)-8-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate ((1S,3R)-**12e**)*

$[\alpha]_D^{23} = -23.7\ (c = 2.53, MeOH)$

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.39 (m, 4H), 7.15 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.10 (app t, , *J* = 7.7 Hz, 1H), 7.00 (dt, *J* = 7.2, 1.0 Hz, 1H), 5.40 (app s, 1H), 3.93 (dd, *J* = 6.7, 5.4 Hz, 1H), 3.72 (s, 3H), 3.26 (ddd, *J* = 15.5, 5.4, 1.3 Hz, 1H), 3.12 (ddd, *J* = 15.5, 6.7, 1.6 Hz, 1H), 2.40 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2, 142.5, 135.9, 133.1, 132.4, 131.9, 130.8, 130.5, 128.0, 126.5, 123.2, 120.4, 120.2, 116.2, 109.6, 54.2, 52.7, 52.4, 24.8, 16.8.
HRMS (ESI+) calculated for $C_{20}H_{19}Cl_2N_2O_2$ $[M+H]^+$: 389.0818, found : 389.0817



(1*R*,3*S*)-**13e**

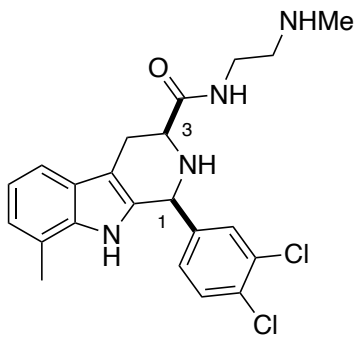
(1R,3S)-1-(3,4-dichlorophenyl)-8-methyl-N-(2-(methylamino)ethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide((1*R*,3*S*)-**13e***)*

Methyl (1*R*,3*S*)-1-(3,4-dichlorophenyl)-8-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (1*R*,3*S)*-**12e** (62 mg, 0.159 mmol, 1.00 eq.) was dissolved in 5 mL of methanol and added N^1-methylethane-1,2-diamine (0.07 mL, d = 0.85 g/mL, 0.795 mmol, 5 equiv) and stirred at 65°C overnight. The solvent was evaporated, and the crude product was extracted with DCM and H_2O, the combined organic layers were dried over Na_2SO_4, evaporated in vacuo and purified by flash chromatography (9:1 DCM/MeOH with 5 drops of NH_4OH in 10 mL solution) to obtain (1*R*,3*S*)-**13e** (45 mg, 66%) as a pale yellowish solid.

$[\alpha]_D^{23} = -8.75\ (c = 0.265, CHCl_3)$

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.43 – 7.38 (m, 2H), 7.23 (t, *J* = 5.7 Hz, 1H), 7.14 – 7.09 (m, 2H), 7.05 (dt, *J* = 7.2, 1.1 Hz, 1H), 5.27 (s, 1H), 3.57 (dd, *J* = 10.1, 4.9 Hz, 1H), 3.47 – 3.42 (m, 1H), 3.37 – 3.30 (m, 2H), 2.92 (ddd, *J* = 16.0, 10.1, 1.5 Hz, 1H), 2.77 (t, *J* = 5.9 Hz, 2H), 2.47 (s, 3H), 2.46 (s, 3H), 2.03 (br s, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 141.9, 136.0, 132.9, 132.2, 131.7, 130.7, 130.6, 128.1, 126.6, 123.4, 120.4, 120.2, 116.5, 111.6, 54.6, 52.4, 50.7, 38.4, 35.9, 25.1, 16.8.

HRMS (ESI+) calculated for $C_{22}H_{25}Cl_2N_4O$ $[M+H]^+$: 431.1400, found : 431.1400



(1*S*,3*S*)-**13e**

(1S,3S)-1-(3,4-dichlorophenyl)-8-methyl-N-(2-(methylamino)ethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide((1*S*,3*S*)-**13e***)*

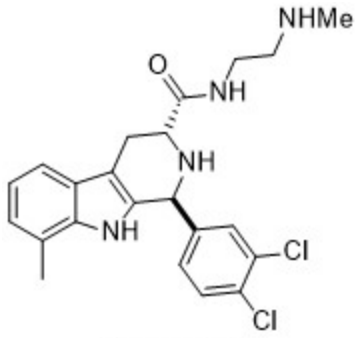
Methyl (1*S*,3*S*)-1-(3,4-dichlorophenyl)-8-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (1*S*,3*S)*-**12e** (88 mg, 0.226 mmol, 1.00 eq.) was dissolved in 5 mL of methanol and added N^1-methylethane-1,2-diamine (0.1 mL, d = 0.85 g/mL, 1.131 mmol, 5 equiv) and stirred at 65°C overnight. The solvent was evaporated, and the crude product was extracted with DCM and H_2O, the combined organic layers were dried over Na_2SO_4, evaporated in vacuo and purified by flash chromatography (9:1 DCM/MeOH with 5 drops of NH_4OH in 10 mL solution) to obtain (1*S*,3*S*)-**13e)** (30 mg, 31%) as a pale yellowish solid. Also, obtained a free base of 1-(3,4-dichlorophenyl)-8-methyl-N-(2-(methylamino)ethyl)-9H-pyrido[3,4-b]indole-3-carboxamide hydrochloride (**7e**) (17 mg, 17%)as an off-white solid

$[\alpha]_D^{22} = -68.2\ (c = 0.367, CHCl_3)$

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.40 (d, *J* = 2.1 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.14 – 7.08 (m, 2H), 7.05 (app t, *J* = 8.5 Hz, 1H), 6.98 (dt, *J* = 7.2, 1.0 Hz, 1H), 5.02 (app s, 1H), 3.82 (dd, *J* = 11.2, 4.2 Hz, 1H), 3.62 (d, *J* = 7.5 Hz, 2H), 3.26 (ddd, *J* = 15.2, 4.2, 1.8 Hz, 1H), 3.11 – 2.94 (m, 3H), 2.63 (s, 3H), 2.36 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.73, 141.38, 135.91, 133.00, 132.98, 132.60, 130.98, 130.95, 128.40, 126.67, 123.24, 120.33, 120.25, 116.31, 110.66, 58.29, 57.57, 49.27, 35.75, 33.50, 25.72, 16.86.

HRMS (ESI+) calculated for $C_{22}H_{25}Cl_2N_4O$ $[M+H]^+$: 431.1400, found : 431.1397



(1*S*,3*R*)-**13e**

(1S,3R)-1-(3,4-dichlorophenyl)-8-methyl-N-(2-(methylamino)ethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide((1*S*,3*R*)-**13e***)*

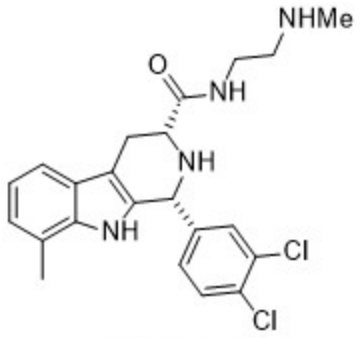
Methyl (1*S*,3*R*)-1-(3,4-dichlorophenyl)-8-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (1*S*,3*R)*-**12e** (57 mg, 0.143 mmol, 1.00 eq.) was dissolved in 5 mL of methanol and added N^1-methylethane-1,2-diamine (0.06 mL, d = 0.85 g/mL, 0.719 mmol, 5 equiv) and stirred at 65°C overnight. The solvent was evaporated, and the crude product was extracted with DCM and H_2O, the combined organic layers were dried over Na_2SO_4, evaporated in vacuo and purified by flash chromatography (9:1 DCM/MeOH with 5 drops of NH_4OH in 10 mL solution) to obtain (1*S*,3*R*)-**13e** (41 mg, 67%) as a pale yellowish solid.

$[\alpha]_D^{23} = +10.5\ (c = 0.260, CHCl_3)$

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.40 – 7.37 (m, 2H), 7.24 (t, *J* = 5.7 Hz, 1H), 7.10 – 7.06 (m, 2H), 7.02 (dt, *J* = 7.1, 1.1 Hz, 1H), 5.24 (s, 1H), 3.54 (dd, *J* = 10.0, 4.9 Hz, 1H), 3.48 – 3.42 (m, 1H), 3.35 – 3.27 (m, 2H), 2.96 – 2.88 (m, 1H), 2.78 (t, *J* = 5.7 Hz, 2H), 2.46 (s, 3H), 2.43 (s, 3H), 2.14 (br s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 141.9, 136.0, 132.9, 132.2, 131.7, 130.7, 130.6, 128.2, 126.6, 123.4, 120.4, 120.2, 116.4, 111.5, 54.6, 52.4, 50.7, 38.3, 35.8, 25.0, 16.8.

HRMS (ESI+) calculated for $C_{22}H_{25}Cl_2N_4O$ $[M+H]^+$: 431.1400, found : 431.1407



(1*R*,3*R*)-**13e**

(1R,3R)-1-(3,4-dichlorophenyl)-8-methyl-N-(2-(methylamino)ethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide((1*R*,3*R*)-**13e***)*

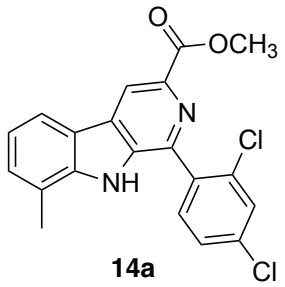
Methyl (1*R*,3*R*)-1-(3,4-dichlorophenyl)-8-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (1*R*,3*R)*-**12e** (102 mg, 0.262 mmol, 1.00 eq.) was dissolved in 5 mL of methanol and added N^1-methylethane-1,2-diamine (0.12 mL, d = 0.85 g/mL, 1.31 mmol, 5 equiv) and stirred at 65°C overnight. The solvent was evaporated, and the crude product was extracted with DCM and H_2O, the combined organic layers were dried over Na_2SO_4, evaporated in vacuo and purified by flash chromatography (9:1 DCM/MeOH with 5 drops of NH_4OH in 10 mL solution) to obtain (1*R*,3*R*)-**13e** (67 mg, 61%) as a pale yellowish solid. Also, obtained a free base of 1-(3,4-dichlorophenyl)-8-methyl-N-(2-(methylamino)ethyl)-9H-pyrido[3,4-b]indole-3-carboxamide hydrochloride (**7e**) (15 mg, 14%)as an off-white solid.

$[\alpha]_D^{22} = +70.3\ (c = 0.367, CHCl_3)$

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (m, 2H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.28 (br s, 1H), 7.20 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.13 – 7.05 (m, 2H), 7.00 (d, *J* = 7.3 Hz, 1H), 5.20 (app s, 1H), 3.75 (dd, *J* = 11.1, 4.3 Hz, 1H), 3.49 – 3.30 (m, 3H), 2.89 (ddd, *J* = 15.6, 11.2, 2.7 Hz, 1H), 2.76 (t, *J* = 6.0 Hz, 2H), 2.44 (s, 3H), 2.38 (s, 3H), 1.73 (br s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.2, 136.0, 133.4, 133.0(2 accidental equivalent peaks), 131.2, 130.8, 128.1, 126.7, 123.3, 120.4, 120.3, 116.4, 111.4, 58.2(2 accidental equivalent peaks), 51.0, 38.8, 36.3, 25.9, 16.8.

HRMS (ESI+) calculated for $C_{22}H_{25}Cl_2N_4O$ $[M+H]^+$: 431.1400, found : 431.1402



14a

*methyl 1-(2,4-dichlorophenyl)-8-methyl-9H-pyrido[3,4-b]indole-3-carboxylate (***14a***)*

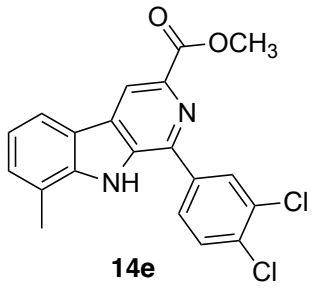
A 150 mL RBF was charged with (±)-7-methyltryptophan methyl ester ((±)-**24**, 3.0 g, 11.16 mmol), 4 Å molecular sieves (7 g, powder form), 2,4-dichlorobenzaldehyde (1.97 g, 11.27 mmol, 1.0 equiv), and CH_2Cl_2 (30 mL), capped with a septum and purged with nitrogen. After stirring at rt for 36 h, the reaction was cooled to 0 °C, and TFA (1.79 mL, 2.6 g, 22.3 mmol, 2 equiv) was added dropwise. After stirring for an additional 48 h TLC indicated complete consumption of imine intermediate, and the reaction mixture was basified with saturated aq. sodium bicarbonate (30 mL). The molecular sieves were removed by filtration, and the remaining mixture was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine, dried with sodium sulfate, concentrated *in vacuo*, and purified by silica column chromatography using 5:5:1 Hexanes/DCM/EtOAc to give the *cis*- and *trans*- methyl 1-(2,4-dichlorophenyl)-8-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate in a 2:1 ratio (yield cis- 1.3 g, 30%, trans- 580 mg, 14%) as bright yellow solids.

A 100-mL round-bottomed flask was charged with a portion of the *cis* diastereomer of (580 mg, 1.48 mmol), iodobenzene diacetate (959 mg, 2.98 mmol, 2.0 equiv) and DMF (3 mL). The mixture was stirred at r.t. under N_2 for 6 h until completion was indicated by TLC. After completion, the reaction mixture was neutralized with aq. sodium bicarbonate (~12 mL). The mixture was extracted with EtOAc (3 x 15 mL), the combined organic phases washed with brine, dried with sodium sulfate, and concentrated *in vacuo*. The crude product was triturated with toluene (3 x 2 mL), vacuum filtered, and air dried to give **14a** (326 mg, 57%) as a pale brown solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.51 (s, 1H), 8.98 (s, 1H), 8.27 (d, J = 7.9 Hz, 1H), 7.86 (dd, J = 1.5, 0.9 Hz, 1H), 7.67 – 7.62 (m, 2H), 7.41 (dt, J = 7.1, 1.0 Hz, 1H), 7.25 (dd, J = 7.9, 7.1 Hz, 1H), 3.91 (s, 3H), 2.56 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 165.89, 140.65, 140.34, 136.24, 135.72, 135.70, 134.28, 134.08, 133.25, 129.51, 129.08, 129.01, 127.50, 122.10, 120.88, 120.68, 119.54, 117.45, 52.07, 17.42.

HRMS (ESI+) calculated for $C_{20}H_{15}Cl_2N_2O_2$ $[M+H]^+$: 385.0505, found 385.0508.



14e

*methyl 1-(3,4-dichlorophenyl)-8-methyl-9H-pyrido[3,4-b]indole-3-carboxylate (***14e***)*

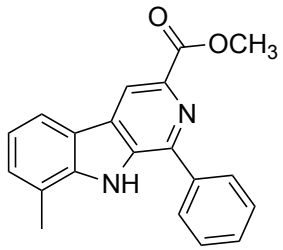
A 150 mL RBF was charged with (±)-7-methyltryptophan methyl ester ((±)-**24**, 2.0 g, 7.4 mmol), 4 Å molecular sieves (4.5 g, powder form), 3,4-dichlorobenzaldehyde (1.32 g, 7.5 mmol, 1.0 equiv), and CH_2Cl_2 (20 mL), capped with a septum and purged with nitrogen. After stirring at rt for 36 h, the reaction was cooled to 0 °C, and TFA (1.2 mL, 1.7 g, 14.9 mmol, 2 equiv) was added dropwise. After stirring for an additional 48 h TLC indicated complete consumption of imine intermediate, and the reaction mixture was basified with saturated aq. sodium bicarbonate (20 mL). The molecular sieves were removed by filtration, and the remaining mixture was extracted with EtOAc (3 x 40 mL). The combined organic phases were washed with brine, dried with sodium sulfate, concentrated *in vacuo*, and purified by silica plug wash (5:5:1 Hexanes/DCM/EtOAc) to give mixture of *cis*- and *trans*- diastereomers of methyl 1-(3,4-dichlorophenyl)-8-methyl-2,3,4,9-tetrahydro-1*H* -pyrido[3,4-*b*]indole-3-carboxylate in 1:2 ratio (yield 1.9 g, 66%).

To an oven-dried 100 mL RBF was added a portion of this mixture (1.0 g, 2.57 mmol), iodobenzene diacetate (1.65 g, 5.14 mmol, 2.0 equiv) and DMF (5.5 mL). The mixture was stirred at r.t. under N_2 for 6 h until completion was indicated by TLC. After completion, the reaction mixture was neutralized with aq. sodium bicarbonate (~15 mL). The mixture was extracted with EtOAc (3 x 20 mL), the combined organic phases washed with brine, dried with sodium sulfate, and concentrated *in vacuo*. The crude product was triturated with toluene (3 x 4 mL), vacuum filtered, and air dried to give **14e** (616 mg, 68%) as a pale brown solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.61 (s, 1H), 8.94 (d, J = 0.5 Hz, 1H), 8.28 (d, J = 7.9 Hz, 1H), 8.16 (d, J = 2.0 Hz, 1H), 7.97 (dd, J = 8.3, 2.0 Hz, 1H), 7.90 (d, J = 8.3 Hz, 1H), 7.43 (dt, J = 7.2, 1.1 Hz, 1H), 7.27 (app t, J = 7.5 Hz,1H), 3.94 (s, 3H), 2.63 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 165.9, 140.9, 140.1, 138.2, 136.8, 135.1, 131.6, 131.4, 130.8(2 accidental equivalent peaks), 130.3, 129.6, 129.3, 122.5, 121.1, 120.9, 119.5, 117.2, 52.2, 17.5.

HRMS (ESI+) calculated for $C_5Cl_2N_2O_2$ $[M+H]^+$: 385.0505, found 385.0500



14f

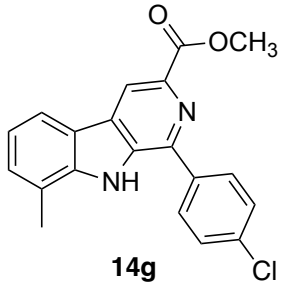
*methyl 8-methyl-1-phenyl-9H-carbazole-3-carboxylate(***14f***)*

A 150 mL RBF was charged with (±)-7-methyltryptophan methyl ester (±)-**24**, 500.0 mg, 1.86 mmol), 4 Å molecular sieves (3.0 g, powder form), benzaldehyde (0.181 mL, d = 1.04 g/mL, 1.77 mmol, 0.95 equiv), and CH_2Cl_2 (15 mL), capped with a septum and purged with nitrogen. After stirring at rt for 24 h, the reaction was cooled to 0 °C, and TFA (0.285 mL, 424 mg, 3.72 mmol, 2 equiv) was added dropwise. After stirring for an additional 48 h TLC indicated complete consumption of imine intermediate, and the reaction mixture was basified with saturated aq. sodium bicarbonate (12 mL). The molecular sieves were removed by filtration, and the remaining mixture was extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with brine, dried with sodium sulfate, concentrated *in vacuo*, and purified by silica plug wash (5:5:1 Hexanes/DCM/EtOAc) to give mixture of *cis*- and *trans*- diastereomers of methyl 8-methyl-1-phenyl-2,3,4,9-tetrahydro-1H-carbazole-3-carboxylate in 2:1 ratio (yield 383 mg, 65%).

To an oven-dried 100 mL RBF was added a portion of this mixture (238 mg, 0.742 mmol), iodobenzene diacetate (478.54 mg, 1.49 mmol, 2.0 equiv) and DMF (2.0 mL). The mixture was stirred at r.t. under N_2 for 6 h until completion was indicated by TLC. After completion, the reaction mixture was neutralized with aq. sodium bicarbonate (~10 mL). The mixture was extracted with EtOAc (3 x 15 mL), the combined organic phases washed with brine, dried with

sodium sulfate, and concentrated *in vacuo*. The crude product was triturated with toluene (3 x 2 mL), vacuum filtered, and air dried to give **14f** (146 mg, 62%) as a pale yellowish white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.51 (s, 1H), 8.89 (s, 1H), 8.25 (dt, J = 7.8, 1.0 Hz, 1H), 8.05 – 8.00 (m, 2H), 7.68 – 7.53 (m, 3H), 7.40 (dt, J = 7.2, 1.0 Hz, 1H), 7.25 (app t, J = 7.5 Hz, 1H), 3.93 (s, 3H), 2.64 (s, 3H).
^{13}C NMR (101 MHz, DMSO-d_6) δ 166.06, 142.71, 140.87, 137.79, 136.85, 135.06, 129.95, 129.39, 128.94, 128.92, 128.66, 122.56, 121.24, 120.72, 119.31, 116.53, 52.06, 17.47
HRMS (ESI+) calculated for $C_{20}H_{17}N_2O_2$ $[M+H]^+$: 317.1285, found : 317.1283



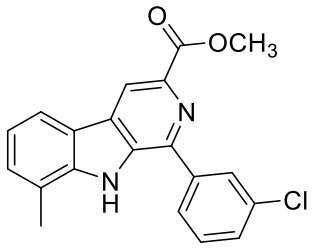
14g

*methyl 1-(4-chlorophenyl)-8-methyl-9H-pyrido[3,4-b]indole-3-carboxylate (***14g***)*

A 150 mL RBF was charged with (±)-7-methyltryptophan methyl ester (±)-**24 (**1.88 g, 7.01 mmol), 4 Å molecular sieves (3.0 g, powder form), 4-chloro benzaldehyde (1.42 g, 10.10 mmol, 1.4 equiv), and CH_2Cl_2 (25 mL), capped with a septum and purged with nitrogen. After stirring at rt for 50 h, the reaction was cooled to 0 °C, and TFA (1.54 mL, 2.29 g, 20.0 mmol, 2.8 equiv) was added dropwise. After stirring for an additional 50 h TLC indicated complete consumption of imine intermediate, and the reaction mixture was basified with saturated aq. sodium bicarbonate (10 mL). The molecular sieves were removed by filtration, and the remaining mixture was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine, dried with sodium sulfate, concentrated *in vacuo*, and purified by silica plug wash (5:5:1 Hexanes/DCM/EtOAc) to give only *cis*- diastereomer of methyl 1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (yield 434 mg, 16%).
To an oven-dried 100 mL RBF was added this compound (434 mg, 1.27 mmol), iodobenzene diacetate (820.5 mg, 2.55 mmol, 2.0 equiv) and DMF (4.0 mL). The mixture was stirred at r.t. under N_2 for 6 h until completion was indicated by TLC. After completion, the reaction mixture

was neutralized with aq. sodium bicarbonate (~10 mL). The mixture was extracted with EtOAc (5 x 100 mL), the combined organic phases washed with brine, dried with sodium sulfate, and concentrated *in vacuo*. The crude product was triturated with toluene (3 x 2 mL), vacuum filtered, and air dried to give **14g** (275 mg, 64%) as a pale brownish white solid

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.51 (s, 1H), 8.90 (s, 1H), 8.25 (d, J = 7.8 Hz, 1H), 8.05 – 7.99 (m, 2H), 7.71 – 7.66 (m, 2H), 7.41 (app d, J = 7.2 Hz, 1H), 7.25 (app t, J = 7.5 Hz, 1H), 3.93 (s, 3H), 2.63 (s, 3H).
^{13}C NMR (101 MHz, DMSO-d_6) δ 166.0, 141.4, 140.9, 136.9, 136.5, 135.0, 133.7, 130.8, 130.1, 129.5, 128.7, 122.5, 121.2, 120.8, 119.4, 116.8, 52.1, 17.4.
HRMS (ESI+) calculated for $C_{20}H_{16}ClN_2O_2$ $[M+H]^+$: 351.0895, found : 351.0887



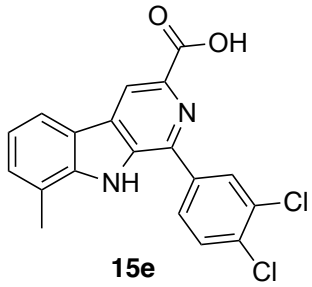
14h

*methyl 1-(3-chlorophenyl)-8-methyl-9H-pyrido[3,4-b]indole-3-carboxylate (**14h**)*

A 150 mL RBF was charged with (±)-7-methyltryptophan methyl ester (±)-**24**, 500.0 mg, 1.86 mmol), 4 Å molecular sieves (3.0 g, powder form), 3-chlorobenzaldehyde (0.2 mL, d = 1.24 g/mL, 1.77 mmol, 0.95 equiv), and CH_2Cl_2 (15 mL), capped with a septum and purged with nitrogen. After stirring at rt for 24 h, the reaction was cooled to 0 °C, and TFA (0.285 mL, 424 mg, 3.72 mmol, 2 equiv) was added dropwise. After stirring for an additional 48 h TLC indicated complete consumption of imine intermediate, and the reaction mixture was basified with saturated aq. sodium bicarbonate (12 mL). The molecular sieves were removed by filtration, and the remaining mixture was extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with brine, dried with sodium sulfate, concentrated *in vacuo*, and purified by silica plug wash (5:5:1 Hexanes/DCM/EtOAc) to give mixture of *cis*- and *trans*- diastereomers of methyl 1-(3-chlorophenyl)-8-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate 2:1 ratio (yield 404 mg, 61%).

To an oven-dried 100 mL RBF was added a portion of this mixture (265 mg, 0.747 mmol), iodobenzene diacetate (481.10 mg, 1.49 mmol, 2.0 equiv) and DMF (2.0 mL). The mixture was stirred at r.t. under N_2 for 6 h until completion was indicated by TLC. After completion, the reaction mixture was neutralized with aq. sodium bicarbonate (~10 mL). The mixture was extracted with EtOAc (3 x 15 mL), the combined organic phases washed with brine, dried with sodium sulfate, and concentrated *in vacuo*. The crude product was triturated with toluene (3 x 2 mL), vacuum filtered, and air dried to give **14h** (171 mg, 65%) as a pale yellowish white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.60 (s, 1H), 8.92 (s, 1H), 8.26 (d, J = 7.8 Hz, 1H), 8.00 – 7.95 (m, 2H), 7.69 – 7.61 (m, 2H), 7.42 (dt, J = 7.2, 1.1 Hz, 1H), 7.26 (app t, J = 7.5 Hz, 1H), 3.94 (s, 3H), 2.64 (s, 3H).
^{13}C NMR (101 MHz, DMSO-d_6) δ 165.9, 141.1, 140.9, 139.8, 136.8, 135.0, 133.3, 130.6, 130.2, 129.5, 128.8, 128.6, 127.7, 122.5, 121.2, 120.8, 119.4, 117.0, 52.1, 17.5.
HRMS (ESI+) calculated for $C_{20}H_{16}ClN_2O_2$ $[M+H]^+$: 351.0895, found 351.0893



15e

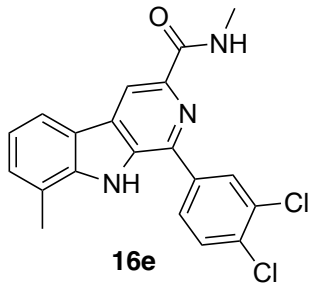
*1-(3,4-dichlorophenyl)-8-methyl-9H-pyrido[3,4-b]indole-3-carboxylic acid (***15e***)*

To a 6 dram vial were added methyl 1-(3,4-dichlorophenyl)-8-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **14e** (30 mg, 0.078 mmol) and a magnetic stirbar. To this ethanol (3 mL) and aq. KOH (20%, 2 mL) was added, the mixture was stirred at rt for 5 minutes, and then heated to 95 °C for 4 h, at which point TLC indicated complete consumption of **14e**. The reaction was allowed to cool to rt, then added aq. HCl (3 mL, 6 M) to precipitate the product. The resulting mixture was stirred at r.t. for another 5 minutes and the solid was collected by vacuum filtration, and washed with cold water, and air-dried obtain **15e** (22 mg, 76% yield) as an off-white solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.59 (s, 1H), 8.92 (s, 1H), 8.27 – 8.25 (m, 2H), 8.03 (dd, J = 8.3, 2.1 Hz, 1H), 7.89 (d, J = 8.3 Hz, 1H), 7.42 (dt, J = 7.2, 1.2 Hz, 1H), 7.26 (app t, J = 7.5 Hz, 1H), 2.64 (s, 3H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 166.6, 141.0, 139.6, 138.1, 137.5, 135.0, 131.5, 131.4, 131.0, 130.7, 130.6, 129.6, 129.3, 122.4, 121.1, 120.8, 119.5, 116.8, 17.4.

HRMS (ESI+) calculated for $C_{19}H_{13}Cl_2N_2O_2$ $[M+H]^+$: 371.0349, found 371.0341



16e

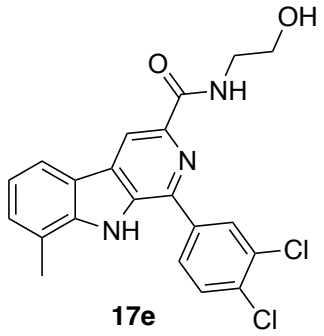
*1-(3,4-dichlorophenyl)-N,8-dimethyl-9H-pyrido[3,4-b]indole-3-carboxamide (***16e***)*

To a sealed tube were added methyl 1-(3,4-dichlorophenyl)-8-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **14e** (30 mg, 0.078 mmol), ethanol (1.5 mL), methylamine (0.2 mL, d = 0.7 g/mL, 3.86 mmol, 50 equiv), and a magnetic stirbar. The tube was purged with N_2, and sealed with its cap. The mixture was stirred at rt for 5 minutes, and then heated to 65 °C for 67 h, at which point TLC indicated complete consumption of **14e**. The reaction was allowed to cool to rt, then concentrated *in vacuo* to obtain **16e** (17 mg, 62% yield) as an off-white solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.47 (s, 1H), 8.81 (s, 1H), 8.73 (d, J = 4.8 Hz, 1H), 8.37 (d, J = 2.1 Hz, 1H), 8.25 (d, J = 7.8 Hz, 1H), 8.13 (dd, J = 8.3, 2.1 Hz, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.41 (dt, J = 7.1, 1.1 Hz, 1H), 7.24 (app t, J = 7.5 Hz, 1H), 2.91 (d, J = 4.8 Hz, 3H), 2.63 (s, 3H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 165.2, 141.1, 140.3, 138.6, 138.2, 134.6, 131.5, 131.1, 131.0(2 accidental equivalent peaks), 130.7, 129.5, 129.3, 122.3, 121.3, 120.7, 119.5, 113.4, 26.1, 17.4.

HRMS (ESI+) calculated for $C_{20}H_{16}Cl_2N_3O$ $[M+H]^+$: 384.0665, found 384.0670



17e

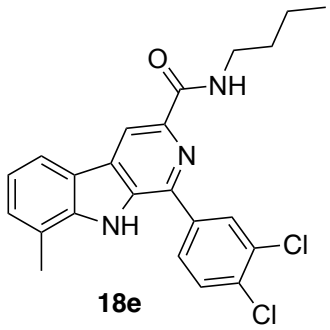
*1-(3,4-dichlorophenyl)-N-(2-hydroxyethyl)-8-methyl-9H-pyrido[3,4-b]indole-3-carboxamide(***17e***)*

To a 1 dram vial were added methyl 1-(3,4-dichlorophenyl)-8-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **14e** (30.0 mg, 0.078 mmol) and a magnetic stirbar. The vial was sealed with a rubber septum and purged with N_2 for 5 minutes. ethanolamine (0.03 mL, d = 1.01 g/mL, 0.39 mmol, 5 equiv) was added via syringe, the mixture was stirred at rt for 5 minutes, and then heated to 90 °C for 22 h, at which point TLC indicated complete consumption of **14e**. The reaction was allowed to cool to rt, then placed in an ice bath, and ice-cold water (~1 mL) was added to precipitate the product. The resulting mixture was stirred at r.t. for another 5 minutes and the solid was collected by vacuum filtration, and washed with cold water, and air-dried obtain **17e** (24 mg, 74% yield) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.48 (s, 1H), 8.84 (s, 1H), 8.71 (t, *J* = 6.0 Hz, 1H), 8.32 (d, *J* = 2.1 Hz, 1H), 8.25 (ddd, *J* = 7.9, 1.2, 0.7 Hz, 1H), 8.09 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.41 (dt, *J* = 7.2, 1.2 Hz, 1H), 7.24 (app t, *J* = 7.6 Hz, 1H), 4.83 (t, *J* = 5.4 Hz, 1H), 3.60 – 3.54 (m, 2H), 3.50 – 3.44 (m, 2H), 2.63 (s, 3H).

^{13}C NMR (126 MHz, CD_3OD) δ 164.66, 141.08, 140.07, 138.65, 138.18, 134.75, 131.57, 131.51, 131.03, 130.98, 130.78, 129.52, 129.32, 122.36, 121.24, 120.69, 119.50, 113.57, 60.00, 41.68, 17.44.

HRMS (ESI+) calculated for $C_{21}H_{18}Cl_2N_3O_2$ $[M+H]^+$: 414.0771, found 414.0768.



18e

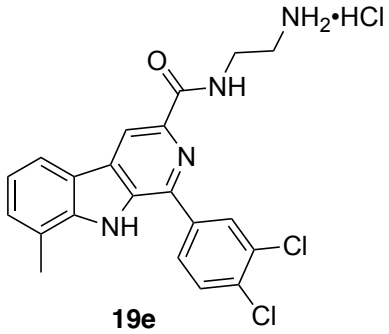
*N-butyl-1-(3,4-dichlorophenyl)-8-methyl-9H-pyrido[3,4-b]indole-3-carboxamide (***18e***)*

To a 1 dram vial were added methyl 1-(3,4-dichlorophenyl)-8-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **14e** (40 mg, 0.103 mmol) and a magnetic stirbar. The vial was sealed with a rubber septum and purged with N_2 for 5 minutes. Butylamine (0.08 mL, d = 0.74 g/mL, 0.82 mmol, 8 equiv) was added via syringe, the mixture was stirred at rt for 5 minutes, and then heated to 60 °C for 36 h, at which point TLC indicated complete consumption of **14e**. The reaction was allowed to cool to rt, then placed in an ice bath, and ice-cold water (~1 mL) was added to precipitate the product. The resulting mixture was stirred at r.t. for another 5 minutes and the solid was collected by vacuum filtration, and washed with cold water, and air-dried obtain **18e** (19 mg, 43% yield) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (s, 1H), 8.71 (t, J = 6.2 Hz, 1H), 8.35 (d, J = 2.1 Hz, 1H), 8.24 (dt, J = 7.8, 1.0 Hz, 1H), 8.13 (dd, J = 8.3, 2.1 Hz, 1H), 7.89 (d, J = 8.3 Hz, 1H), 7.41 (dt, J = 7.1, 1.1 Hz, 1H), 7.24 (app t, J = 7.5 Hz, 1H), 3.44 – 3.35 (m, 2H), 2.63 (s, 3H), 1.57 (app quint, J = 7.3 Hz, 2H), 1.36 (app h, J = 7.4 Hz, 2H), 0.93 (t, J = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 164.55, 141.17, 140.28, 138.57, 138.22, 134.78, 131.53, 131.49, 131.07, 131.03, 130.74, 129.48, 129.37, 122.38, 121.26, 120.64, 119.47, 113.51, 38.62, 31.73, 19.78, 17.45, 13.84.

HRMS (ESI+) calculated for $C_{23}H_{22}Cl_2N_3O$ $[M+H]^+$: 426.1134, found 426.1124



19e

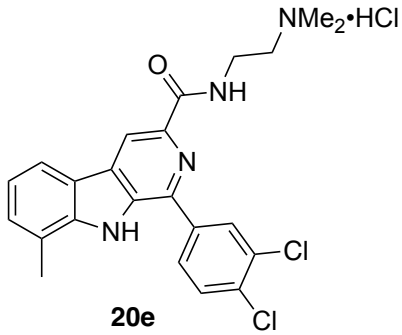
*N-(2-aminoethyl)-1-(3,4-dichlorophenyl)-8-methyl-9H-pyrido[3,4-b]indole-3-carboxamide hydrochloride (***19e***)*

The free base of compound **19e** was prepared similarly to that of **7e** described above, using methyl 1-(3,4-dichlorophenyl)-8-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **14e** (50 mg, 0.130 mmol), ethane-1,2-diamine (0.05 mL, d = 0.9 g/mL, 0.650 mmol, 5 equiv) affording 47 mg, 87% yield as an off-white powder. A portion of this material (19.6 mg) was dissolved in 0.1 M HCl in methanol (0.48 mL, prepared from 12 N HCl (aq)), concentrated *in vacuo*. The salt was again dissolved in methanol (1 mL) and concentrated *in vacuo* to remove residual water. The solid was triturated with toluene and dried overnight to obtain **19e** (as the depicted HCl salt, 19 mg, 90% yield) as bright yellow solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.53 (s, 1H), 9.00 (t, J = 6.2 Hz, 1H), 8.86 (s, 1H), 8.35 (d, J = 2.1 Hz, 1H), 8.26 (d, J = 7.8 Hz, 1H), 8.14 (dd, J = 8.4, 2.1 Hz, 1H), 8.09 – 8.03 (br m, 2H), 7.89 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 7.2 Hz, 1H), 7.25 (app t, J = 7.6 Hz, 1H), 3.65 (q, J = 6.3 Hz, 2H), 3.04 (q, J = 6.0 Hz, 2H), 2.64 (s, 3H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 165.43, 141.03, 139.69, 138.64, 138.02, 134.76, 131.54, 131.46, 130.95, 130.67, 129.51, 129.35, 122.35, 121.17, 120.69, 119.40, 113.72, 36.89, 17.36.

HRMS (ESI+) calculated for $C_{21}H_{19}Cl_2N_4O$ $[M+H]^+$: 413.0930, found 413.0911.

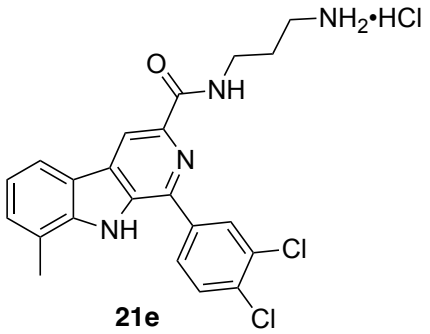


20e

*1-(3,4-dichlorophenyl)-N-(2-(dimethylamino)ethyl)-8-methyl-9H-pyrido[3,4-b]indole-3-carboxamide hydrochloride (***20e***)*

To a 1 dram vial were added methyl 1-(3,4-dichlorophenyl)-8-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **14e** (40 mg, 0.103 mmol) and a magnetic stirbar. The vial was sealed with a rubber septum and purged with N_2 for 5 minutes. N^1,N^1-dimethylethane-1,2-diamine (0.06 mL, d = 0.807 g/mL, 0.52 mmol, 5 equiv) was added via syringe, the mixture was stirred at rt for 5 minutes, and then heated to 90 °C for 22 h, at which point TLC indicated complete consumption of **14e**. The reaction was allowed to cool to rt, then placed in an ice bath, and ice-cold water (~1 mL) was added to precipitate the product. The resulting mixture was stirred at r.t. for another 5 minutes and the solid was collected by vacuum filtration, and washed with cold water, and air-dried obtain the free base of **20e** (43 mg, 93% yield). A portion of this material (20 mg) was dissolved in 0.1 M HCl in methanol (0.44 mL, prepared from 12 N HCl (aq)), concentrated *in vacuo*. The salt was again dissolved in methanol (~1 mL) and concentrated *in vacuo* to remove residual water. The solid was triturated with toluene and dried overnight to obtain **20e** (as the depicted HCl salt, 20.9 mg, 96% yield) as bright yellow solid.

^{1}H NMR (500 MHz, CD_3OD) δ 8.83 (s, 1H), 8.27 (d, *J* = 2.1 Hz, 1H), 8.09 (d, *J* = 7.9 Hz, 1H), 8.04 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.27 (app t, *J* = 7.6 Hz, 1H), 3.90 (t, *J* = 5.8 Hz, 2H), 3.46 (t, *J* = 5.8 Hz, 2H), 3.01 (s, 6H), 2.65 (s, 3H).
^{13}C NMR (126 MHz, CD_3OD) δ 169.2, 142.7, 141.0, 140.2, 139.6, 136.7, 134.0, 133.8, 132.8, 132.1, 131.9, 130.9, 129.8, 123.8, 122.8, 122.3, 120.0, 115.1, 59.0, 44.0, 36.1, 17.5.
HRMS (ESI+) calculated for $C_{23}H_{23}Cl_2N_4O$ $[M+H]^+$: 441.1243, found 441.1245



21e

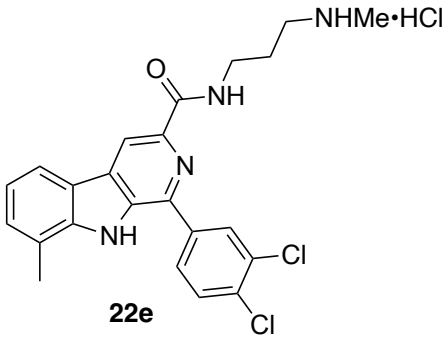
*N-(3-aminopropyl)-1-(3,4-dichlorophenyl)-8-methyl-9H-pyrido[3,4-b]indole-3-carboxamide hydrochloride (***21e***)*

The free base of compound **21e** was prepared similarly to **1** described above, using methyl 1-(3,4-dichlorophenyl)-8-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **14e** (50 mg, 0.130 mmol), propane-1,3-diamine (0.06 mL, d = 0.89 g/mL, 0.650 mmol, 5 equiv) affording 46 mg, 83% yield as an off-white powder. A portion of this material (21.2 mg) was dissolved in 0.1 M HCl in methanol (0.49 mL, prepared from 12 N HCl (aq)), concentrated *in vacuo*. The salt was again dissolved in methanol (1 mL) and concentrated *in vacuo* to remove residual water. The solid was triturated with toluene and dried overnight to obtain **21e** (as the depicted HCl salt, 18 mg, 78% yield) as bright yellow solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.5 (s, 1H), 9.0 (t, J = 6.3 Hz, 1H), 8.8 (s, 1H), 8.3 (d, J = 2.0 Hz, 1H), 8.2 (d, J = 7.8 Hz, 1H), 8.1 (dd, J = 8.3, 2.0 Hz, 1H), 8.0 (br app s, 3H), 7.9 (d, J = 8.3 Hz, 1H), 7.4 (d, J = 7.1 Hz, 1H), 7.2 (t, J = 7.5 Hz, 1H), 3.5 (q, J = 6.5 Hz, 2H), 2.8 (q, J = 6.7 Hz, 2H), 2.6 (s, 3H), 1.9 (app quint, J = 7.0 Hz, 2H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 165.16, 141.03, 139.87, 138.66, 138.04, 134.72, 131.52, 131.44, 130.97, 130.65, 129.48, 129.34, 122.32, 121.16, 120.65, 119.37, 113.56, 36.77, 35.91, 27.64, 17.34.

HRMS (ESI+) calculated for $C_{22}H_{21}Cl_2N_4O$ $[M+H]^+$: 427.1087, found 427.1061.



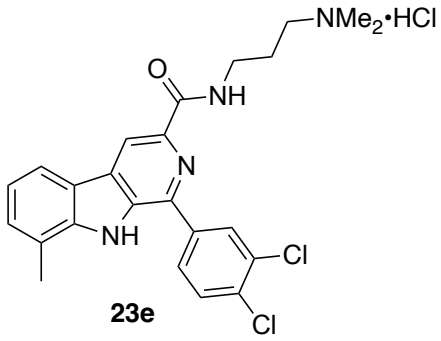
22e

*1-(3,4-dichlorophenyl)-8-methyl-N-(3-(methylamino)propyl)-9H-pyrido[3,4-b]indole-3-carboxamide hydrochloride (***22e***)*

To a 1 dram vial were added methyl 1-(3,4-dichlorophenyl)-8-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **14e** (30 mg, 0.078 mmol) and a magnetic stirbar. The vial was sealed with a rubber septum and purged with N_2 for 5 minutes. N^1-methylpropane-1,3-diamine (0.04 mL, d = 0.84

g/mL, 0.39 mmol, 5 equiv) was added via syringe, the mixture was stirred at rt for 5 minutes, and then heated to 90 °C for 22 h, at which point TLC indicated complete consumption of **14e**. The reaction was allowed to cool to rt, then placed in an ice bath, and ice-cold water (~1 mL) was added to precipitate the product. The resulting mixture was stirred at r.t. for another 5 minutes and the solid was collected by vacuum filtration, and washed with cold water, and air-dried obtain the free base of **7** (27 mg, 77% yield). A portion of this material (14.3 mg) was dissolved in 0.1 M HCl in methanol (0.33 mL, prepared from 12 N HCl (aq)), concentrated *in vacuo*. The salt was again dissolved in methanol (~1 mL) and concentrated *in vacuo* to remove residual water. The solid was triturated with toluene and dried overnight to obtain **22e** (as the depicted HCl salt 9.0 mg, 58% yield) as a bright yellow solid.

^{1}H NMR (400 MHz, CD_3OD) δ 8.84 (s, 1H), 8.27 (d, *J* = 2.1 Hz, 1H), 8.11 (ddd, *J* = 7.9, 1.2, 0.7 Hz, 1H), 8.04 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.43 (dt, *J* = 7.2, 1.0 Hz, 1H), 7.28 (app t, *J* = 7.5 Hz, 1H), 3.62 (t, *J* = 6.5 Hz, 2H), 3.08 (t, *J* = 7.2 Hz, 2H), 2.74 (s, 3H), 2.65 (s, 3H), 2.04 (app quin, *J* = 6.9 Hz, 2H).
^{13}C NMR (126 MHz, CD_3OD) δ 168.05, 142.66, 140.80, 140.76, 139.71, 136.53, 133.88, 133.77, 132.82, 132.02, 131.80, 130.75, 129.74, 123.69, 122.88, 122.10, 120.01, 114.58, 49.74, 38.22, 35.81, 30.02, 17.45.
HRMS (ESI+) calculated for $C_{23}H_{23}Cl_2N_4O$ $[M+H]^+$: 441.1243, found 441.1238



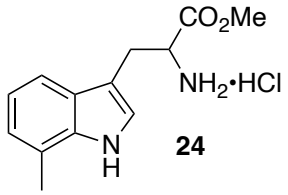
23e

*1-(3,4-dichlorophenyl)-N-(3-(dimethylamino)propyl)-8-methyl-9H-pyrido[3,4-b]indole-3-carboxamide hydrochloride (***23e***)*

To a 1 dram vial were added methyl 1-(3,4-dichlorophenyl)-8-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **14e** (50 mg, 0.13 mmol) and a magnetic stirbar. The vial was sealed with a rubber septum and purged with N_2 for 5 minutes. N^1,N^1-dimethylpropane-1,3-diamine (0.11 mL, d = 0.81

g/mL, 0.91 mmol, 7 equiv) was added via syringe, the mixture was stirred at rt for 5 minutes, and then heated to 70 °C for 30 h, at which point TLC indicated complete consumption of **14e**. The reaction was allowed to cool to rt, then placed in an ice bath, and ice-cold water (~1 mL) was added to precipitate the product. The resulting mixture was stirred at r.t. for another 5 minutes and the solid was collected by vacuum filtration, and washed with cold water, and air-dried obtain the free base of **23e** (23 mg, 39% yield). A portion of this material (10 mg) was dissolved in 0.1 M HCl in methanol (0.22 mL, prepared from 12 N HCl (aq)), concentrated *in vacuo*. The salt was again dissolved in methanol (~1 mL) and concentrated *in vacuo* to remove residual water. The solid was triturated with toluene and dried overnight to obtain **23e** (as the depicted HCl salt 9.0 mg, 84% yield) as a bright yellow solid.

^{1}H NMR (400 MHz, CD_3OD) δ 8.89 (s, 1H), 8.27 (d, *J* = 2.1 Hz 1H), 8.13 (ddd, *J* = 7.9, 1.1, 0.7 Hz, 1H), 8.03 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.45 (dt, *J* = 7.2, 1.1 Hz, 1H), 7.30 (app t, *J* = 7.6 Hz, 1H), 3.63 (t, *J* = 6.5 Hz, 2H), 3.24 (t, *J* = 7.6 Hz, 2H), 2.94 (s, 6H), 2.66 (s, 3H), 2.11 (app quin, *J* = 7.1 Hz, 3H)
^{13}C NMR (free base, 101 MHz, CD_3OD) 167.8, 142.6, 140.9, 140.6, 139.7, 136.4, 133.8, 133.7, 132.8, 131.9, 131.7, 130.7, 129.7, 123.6, 122.8, 122.0, 120.0, 114.5, 58.5, 45.5, 39.0, 28.2, 17.4.
HRMS (ESI+) calculated for $C_{24}H_{25}Cl_2N_4O$ $[M+H]^+$: 455.1400, found 455.1395



24

7-methyltryptophan methyl ester hydrochloride ((±)-**24***)*

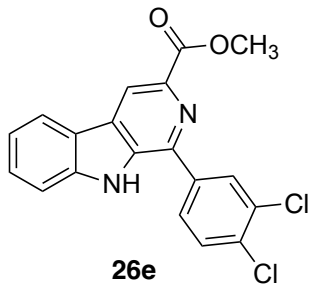
Based on a literature procedure for 7-bromotryptophan methyl ester.[2] 7-methylindole (3.5 g, 26.7 mmol), *dl*-serine (5.6 g, 53.3 mmol, 2 equiv), were combined with acetic acid (75 mL) and acetic anhydride (16.3 mL, d = 1.08 g/mL, 159.7 mmol, 6.0 equiv) and the mixture was allowed to stir at room temperature under nitrogen for 10 minutes and then heated to 75 °C for 3 h. The mixture was then cooled down and diluted with Et_2O (150 mL). 30% NaOH (aq.) (50 ml) was added until the pH was completely basic. The water layer was further washed with diethyl ether (3×150 mL). The mixed organic extracts were further extracted with 1 M NaOH (aq.) (2×40 mL). This aqueous

basic extract was mixed with the previous basic extract mixture, a small amount of $Na_2S_2O_4$ were added and the mixture was cooled down in an ice bath. Subsequently, conc. HCl, were added until the pH was acidic. The organic layer was extracted with EtOAc (4×150 mL). The combined organic extracts were washed with brine (2×20 mL), dried over sodium sulfate and concentrated in vacuo. Further, this residue dissolved in 1 M NaOH (aq.) (50 mL), and precipitated out using addition of conc. HCl (6 mL). This precipitate was filtered using sintered Buchner funnel and dried affording crude N_α-acetyl-7-methyltryptophan (5.67 g, 83%). To a 0.2 M methanol solution of a portion of this material (1.63g, 6.26 mmol) at 0 °C was added thionyl chloride (2.49 mL, 4.09 g, 34.43 mmol, 5.5 equiv) dropwise. The mixture was warmed up to room temperature and then heated to 70 °C under reflux for 52 h. The mixture was cooled down and concentrated in vacuo. Et_2O (30 mL) were added and the mixture were stirred for 30 min. The emulsion was filtered and washed numerous times with Et_2O until the solid was not sticky. The solid was air dried to afford tryptophan methyl ester. hydrochloride salt **24** (1.38g, 69% yield over two steps) as a dark red solid.

^{1}H NMR (400 MHz, CD_3OD) δ 7.37 (ddd, J = 7.8, 1.4, 0.7 Hz, 1H), 7.21 (s, 1H), 7.01 – 6.92 (m, 2H), 4.32 (dd, J = 7.3, 5.5 Hz, 1H), 3.79 (s, 3H), 3.45 (ddd, J = 15.1, 5.5, 0.8 Hz, 1H), 3.35 (ddd, J = 15.1, 7.3, 0.7 Hz, 1H), 2.49 (s, 3H).

^{13}C NMR (101 MHz, CD_3OD) δ 170.8, 137.7, 127.8, 125.4, 123.4, 122.2, 120.6, 116.5, 107.8, 54.6, 53.6, 27.7, 16.9.

HRMS (ESI+) calculated for $C_{13}H_{17}N_2O_2$ $[M+H]^+$: 233.1285, found 233.1318



26e

*methyl 1-(3,4-dichlorophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate (***26e***)*

A 150 mL RBF was charged with L-tryptophan methyl ester, (1.50 g, 5.89 mmol), 4 Å molecular sieves (3.7 g, powder form), 3,4-dichlorobenzaldehyde (1.0 g, 5.95 mmol, 0.95 equiv), and CH_2Cl_2 (20 mL), capped with a septum and purged with nitrogen. After stirring at rt for 23 h, the reaction

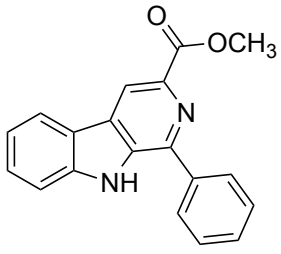
was cooled to 0 °C, and TFA (0.91 mL, 1.34 g, 11.8 mmol, 2 equiv) was added dropwise. After stirring for an additional 48 h TLC indicated complete consumption of imine intermediate, and the reaction mixture was basified with saturated aq. sodium bicarbonate (22 mL). The molecular sieves were removed by filtration, and the remaining mixture was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine, dried with sodium sulfate, concentrated *in vacuo*, and purified by silica plug wash (5:5:1 Hexanes/DCM/EtOAc) to give *cis*- and *trans*-diastereomers of methyl 1-(3,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (yields -*cis* 1.7 g, 76%, -*trans* 450 mg, 19%).

To an oven-dried 250 mL RBF was added a portion of methyl (1*S*,3*S*)-1-(3,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (900 mg, 2.39 mmol), iodobenzene diacetate (1.54 g, 4.80 mmol, 2.0 equiv) and DMF (5 mL). The mixture was stirred at r.t. under N_2 for 6 h until completion was indicated by TLC. After completion, the reaction mixture was neutralized with aq. sodium bicarbonate (~20 mL). The mixture was extracted with EtOAc (3 x 20 mL), the combined organic phases washed with brine, dried with sodium sulfate, and concentrated *in vacuo*. The crude product was triturated with toluene (3 x 2 mL), vacuum filtered, and air dried to give **26e** (683 mg, 77%) as a brownish white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.07 (s, 1H), 8.97 (s, 1H), 8.45 (dt, J = 8.0, 1.1 Hz, 1H), 8.21 (d, J = 2.1 Hz, 1H), 8.01 (dd, J = 8.3, 2.1 Hz, 1H), 7.90 (d, J = 8.3 Hz, 1H), 7.70 (dt, J = 8.2, 1.1 Hz, 1H), 7.63 (ddd, J = 8.2, 7.0, 1.1 Hz, 1H), 7.35 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H), 3.94 (s, 3H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 165.8, 141.6, 139.4, 138.0, 136.7, 134.6, 131.7, 131.6, 131.0, 130.4, 129.7, 129.0, 128.9, 122.2, 121.1, 120.6, 117.3, 112.7, 52.1.

HRMS (ESI+) calculated for $C_{19}H_{13}Cl_2N_2O_2$ $[M+H]^+$: 371.0349, found 371.0349



26f

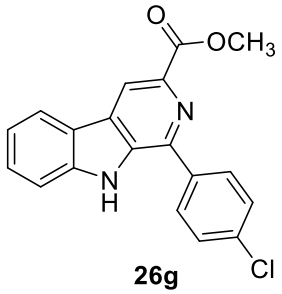
*methyl 1-phenyl-9H-pyrido[3,4-b]indole-3-carboxylate (***26f***)*

A 250 mL RBF was charged with L-tryptophan methyl ester, (1.00 g, 3.92 mmol), 4 Å molecular sieves (3.25 g, powder form), benzaldehyde (375 mg, 0.363 mL, 3.53 mmol, 0.90 equiv), and

CH_2Cl_2 (17 mL), capped with a septum and purged with nitrogen. After stirring at rt for 24 h, the reaction was cooled to 0 °C, and TFA (0.60 mL, 895 mg, 7.8 mmol, 2 equiv) was added dropwise. After stirring for an additional 24 h TLC indicated complete consumption of imine intermediate, and the reaction mixture was basified with saturated aq. sodium bicarbonate (15 mL). The molecular sieves were removed by filtration, and the remaining mixture was extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with brine, dried with sodium sulfate, concentrated *in vacuo*, and purified by silica plug wash (5:5:4 Hexanes/DCM/EtOAc) to give mixture of diastereomers of methyl 1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (yield 1.1 g, 91%). A portion of the material was oxidized as described in the literature:[3] methyl 1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (500.0 mg, 1.63 mmol), iodobenzene diacetate (1.08 g, 3.34 mmol, 2.0 equiv) and DMF (3 mL). Obtained **26f** (349 mg, 71%) as a brown solid. The ^{1}H NMR data matched the literature.[3]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 (s, 1H), 8.44 (d, J = 7.9 Hz, 1H), 8.05 – 8.00 (m, 2H), 7.64 (m, 5H), 7.34 (app t, J = 7.4 Hz, 1H), 3.94 (s, 3H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 166.06, 142.10, 141.46, 137.51, 136.66, 134.56, 129.16, 129.00, 128.80, 128.69, 128.61, 122.02, 121.11, 120.42, 116.70, 112.77, 52.06.



26g

*methyl 1-(4-chlorophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate (**26g**)*

A 100 mL RBF was charged with L-tryptophan methyl ester, (500 g, 1.96 mmol), 4 Å molecular sieves (3.0 g, powder form), 3-chlorobenzaldehyde (261 mg, 1.86 mmol, 0.95 equiv), and CH_2Cl_2 (15 mL), capped with a septum and purged with nitrogen. After stirring at rt for 24 h, the reaction was cooled to 0 °C, and TFA (0.31 mL, 448.0 mg, 3.93 mmol, 2 equiv) was added dropwise. After stirring for an additional 48 h TLC indicated complete consumption of imine intermediate, and the reaction mixture was basified with saturated aq. sodium bicarbonate (12 mL). The molecular sieves were removed by filtration, and the remaining mixture was extracted with EtOAc (3 x 15 mL).

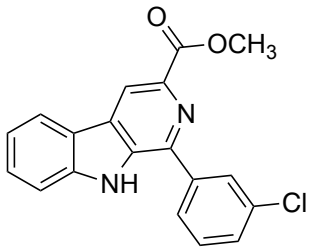
The combined organic phases were washed with brine, dried with sodium sulfate, concentrated *in vacuo*, and purified by silica plug wash (5:5:1 Hexanes/DCM/EtOAc) to give mixture of diastereomers of methyl 1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (yield 444 mg, 67%).

To an oven-dried 100 mL RBF was added the mixture of diastereomers of methyl 1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (444.0 mg, 1.30 mmol), iodobenzene diacetate (839.0 mg, 2.61 mmol, 2.0 equiv) and DMF (3 mL). The mixture was stirred at r.t. under N_2 for 6 h until completion was indicated by TLC. After completion, the reaction mixture was neutralized with aq. sodium bicarbonate (~15 mL). The mixture was extracted with EtOAc (3 x 15 mL), the combined organic phases washed with brine, dried with sodium sulfate, and concentrated *in vacuo*. The crude product was triturated with toluene (3 x 2 mL), vacuum filtered, and air dried to give **26g** (334 mg, 76%) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.98 (s, 1H), 8.95 (s, 1H), 8.44 (d, J = 7.9 Hz, 1H), 8.09 – 8.01 (m, 2H), 7.70 (m, 3H), 7.62 (app t, J = 7.6 Hz, 1H), 7.34 (app t, J = 7.5 Hz, 1H), 3.94 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 165.97, 141.51, 140.78, 136.71, 136.30, 134.56, 133.77, 130.44, 129.42, 128.85, 128.83, 122.11, 121.11, 120.54, 116.97, 112.75, 52.10.

HRMS (ESI+) calculated for $C_{19}H_{14}ClN_2O_2$ $[M+H]^+$: 337.0738, found 337.0738



26h

*methyl 1-(3-chlorophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate (***26h***).*

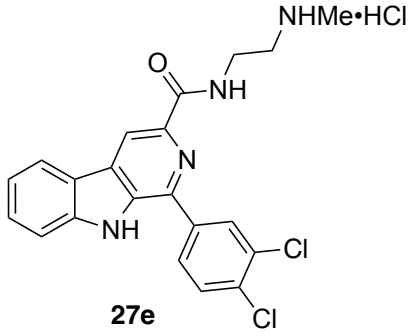
A 150 mL RBF was charged with L-tryptophan methyl ester hydrochloride salt (2.0 g, 7.9 mmol), 4 Å molecular sieves (4.0 g, powder form), 3-chloro benzaldehyde (0.800 mL, d = 1.24 g/mL , 7.9 mmol, 1.0 equiv), and CH_2Cl_2 (17 mL), capped with a septum and purged with nitrogen. After stirring at rt for 20 h, TFA (1.23 mL, d = 1.18 g/mL, 15.8 mmol, 2 equiv) was added dropwise. After stirring for an additional 18 h. TLC indicated complete consumption of imine intermediate, and the reaction mixture was basified with saturated aq. sodium bicarbonate (20 mL). The molecular sieves were removed by filtration, and the remaining mixture was extracted with EtOAc

(4 x 40 mL). The combined organic phases were washed with brine, dried with sodium sulfate, concentrated *in vacuo*, and purified by silica plug wash (5:5:1 Hexanes/DCM/EtOAc) to give mixture of *cis*- and *trans*- diastereomers (yield 2.5 g, 92%). To another oven-dried 100 mL RBF were added this mixture (520 mg, 1.53 mmol), iodobenzene diacetate (983 mg, 3.05 mmol, 2.0 equiv) and DMF (3 mL). The mixture was stirred at r.t. under N_2 for 5 h until completion was indicated by TLC. After completion, the reaction mixture was neutralized with aq. sodium bicarbonate (~14 mL). The mixture was extracted with EtOAc (3 x 15 mL), the combined organic phases washed with brine, dried with sodium sulfate, and concentrated *in vacuo*. The crude product was triturated with toluene (3 x 2 mL), vacuum filtered, and air dried to give **26h** (463 mg, 90%) as a pale brown solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.04 (s, 1H), 8.96 (s, 1H), 8.45 (d, J = 7.9 Hz, 1H), 8.17 – 7.96 (m, 2H), 7.75 – 7.57 (m, 4H), 7.35 (app t, J = 7.5 Hz, 1H), 3.94 (s, 3H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 166.0, 141.6, 140.4, 139.5, 136.7, 134.6, 133.6, 130.7, 129.6, 128.9, 128.3, 127.3, 122.2, 121.1, 120.6, 117.2, 112.8, 52.2.

HRMS (ESI+) calculated for $C_{19}H_{14}ClN_2O_2$ $[M+H]^+$: 337.0738, found: 337.0731.



27e

1-(3,4-dichlorophenyl)-N-(2-(methylamino)ethyl)-9H-pyrido[3,4-b]indole-3-carboxamide hydrochloride(**27e*)***

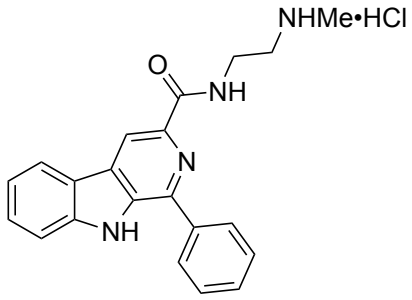
To a 1 dram vial were added methyl 1-(3,4-dichlorophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **26e** (30.0 mg, 0.081 mmol) and a magnetic stirbar. The vial was sealed with a rubber septum and purged with N_2 for 5 minutes. *N*^{1}-methylethane-1,2-diamine (0.03 mL, d = 0.85 g/mL, 0.32 mmol, 4 equiv) was added via syringe, the mixture was stirred at rt for 5 minutes, and then heated to 80 °C for 23 h, at which point TLC indicated complete consumption of **26e**. The reaction was allowed to cool to rt, then placed in an ice bath, and ice-cold water (~1 mL) was added to precipitate the product. The resulting mixture was stirred at r.t. for another 5 minutes and the solid was collected

by vacuum filtration, and washed with cold water and hexane, and air-dried to obtain the free base of **27e** (30 mg, 90% yield) as an off-white solid. A portion of this material (9.7 mg) was dissolved in 0.1 M HCl in methanol (0.3 mL, prepared from 12 N HCl (aq)), concentrated *in vacuo*. The salt was again dissolved in methanol (1 mL) and concentrated *in vacuo* to remove residual water. The solid was triturated with toluene and dried overnight to obtain **27e** (as the depicted HCl salt, 9.5 mg, 89% yield) as bright yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.02 (s, 1H), 9.03 (t, J = 6.1 Hz, 1H), 8.90 (s, 1H), 8.61 (br s, 2H), 8.45 (d, J = 7.8 Hz, 1H), 8.39 (d, J = 2.0 Hz, 1H), 8.23 – 8.10 (m, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.67 – 7.58 (m, 1H), 7.34 (t, J = 7.9 Hz, 1H), 3.68 (m, 2H), 3.21 – 3.10 (m, 2H), 2.61 (t, J = 5.4 Hz, 3H).

^{13}C NMR (Free Base, 126 MHz, CD_3OD) δ 168.2, 143.3, 140.7, 140.2, 139.5, 136.1, 134.0, 132.2, 131.9, 131.7, 130.1, 129.4(2 accidental equivalent peaks), 122.9, 122.6, 121.8, 114.7, 113.5, 51.8, 39.7, 35.8.

HRMS (ESI+) calculated for $C_{21}H_{19}Cl_2N_4O$ $[M+H]^+$: 413.0930, found 413.0935

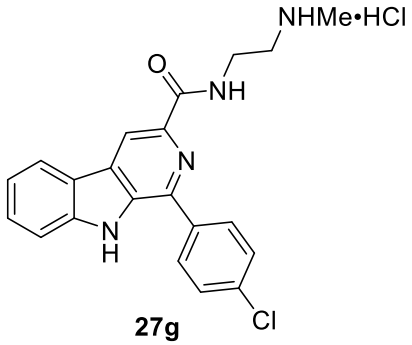


27f

*N-(2-(methylamino)ethyl)-1-phenyl-9H-pyrido[3,4-b]indole-3-carboxamide hydrochloride (***27f***)*

To a 1 dram vial were added methyl 1-phenyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **26f** (30 mg, 0.099 mmol) and a magnetic stirbar. The vial was sealed with a rubber septum and purged with N_2 for 5 minutes. *N*^{1}-methylethane-1,2-diamine (0.05 mL, d = 0.85 g/mL, 0.50 mmol, 5 equiv) was added via syringe, the mixture was stirred at rt for 5 minutes, and then heated to 90 °C for 22 h, at which point TLC indicated complete consumption of **26f**. The reaction was allowed to cool to rt, then placed in an ice bath, and ice-cold water (~1 mL) was added to precipitate the product. The resulting mixture was stirred at r.t. for another 5 minutes and the solid was collected by vacuum filtration, and washed with cold water, and air-dried obtain the free base of **27f** (25 mg, 73% yield). A portion of this material (15.3 mg) was dissolved in 0.1 M HCl in methanol (0.45 mL, prepared

from 12 N HCl (aq)), concentrated *in vacuo*. The salt was again dissolved in methanol (~1 mL) and concentrated *in vacuo* to remove residual water. The solid was triturated with toluene and dried overnight to obtain **27f** (as the depicted HCl salt, 15.7 mg, 93% yield) as bright yellow solid.
^{1}H NMR (500 MHz, CD_3OD) δ 8.83 (s, 1H), 8.27 (d, *J* = 7.9 Hz, 1H), 8.10 (d, *J* = 8.7 Hz, 1H), 7.70 – 7.53 (m, 5H), 7.34 (t, *J* = 7.5 Hz, 1H), 3.83 (t, *J* = 5.6 Hz, 2H), 3.29 (t, *J* = 5.3 Hz, 2H), 2.76 (s, 3H).
^{13}C NMR (126 MHz, CD_3OD) δ 169.50, 143.29, 143.26, 140.07, 139.14, 136.39, 131.60, 130.24, 130.00, 129.96, 129.79, 122.94, 122.55, 121.71, 114.43, 113.58, 51.05, 37.35, 33.93.
HRMS (ESI+) calculated for $C_{21}H_{21}N_4O$ $[M+H]^+$: 345.1710, found 345.1720



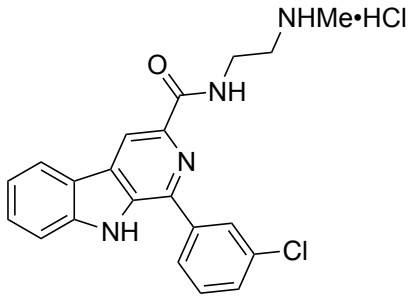
27g

1-(4-chlorophenyl)-N-(2-(methylamino)ethyl)-9H-pyrido[3,4-b]indole-3-carboxamide hydrochloride

Free base of compound **27g** was prepared similarly to **27e** described above, using methyl 1-(4-chlorophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate **26g** (50 mg, 0.149 mmol), *N*^{1}-methylethane-1,2-diamine (0.07 mL, d = 0.85 g/mL, 0.742 mmol, 5 equiv) affording **27g** free base (48 mg, 89% yield) as an off-white powder. A portion of this material (19.9mg) was dissolved in 0.1 M HCl in methanol (0.53 mL, prepared from 12 N HCl (aq)), concentrated *in vacuo*. The salt was again dissolved in methanol (1 mL) and concentrated *in vacuo* to remove residual water. The solid was triturated with toluene and dried overnight to obtain **27g** (as the depicted HCl salt, 20.0 mg, 92% recovered) as a yellowish brown solid.
^{1}H NMR (500 MHz, DMSO-d_6) δ 11.97 (s, 1H), 9.02 (t, *J* = 6.2 Hz, 1H), 8.87 (br s, 1H), 8.83 – 8.74 (m, 2H), 8.43 (d, *J* = 7.9 Hz, 1H), 8.26 – 8.21 (m, 2H), 7.71 (m, 3H), 7.61 (app t, *J* = 7.7 Hz, 1H), 7.3 (app t, *J* = 7.5 Hz, 1H), 3.70 (app q, *J* = 6.0 Hz, 2H), 3.15 (app quint, *J* = 6.0 Hz, 2H), 2.59 (t, *J* = 5.4 Hz, 3H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 165.7, 141.7, 139.4, 139.3, 136.2, 134.3, 133.8, 130.7, 130.1, 128.9, 128.8, 122.1, 121.2, 120.4, 113.6, 112.7, 48.3, 35.6, 32.7.

HRMS (ESI+) calculated for $C_{21}H_{20}ClN_4O$ $[M+H]^+$: 379.1320, found 379.1320



27h

*1-(3-chlorophenyl)-N-(2-(methylamino)ethyl)-9H-pyrido[3,4-b]indole-3-carboxamide hydrochloride (***27h***)*

Free base of compound **27h** was prepared similarly to **27e** described above, using methyl 1-(3-chlorophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **26h** (50 mg, 0.149 mmol), N^1-methylethane-1,2-diamine (0.07 mL, d = 0.85 g/mL, 0.742 mmol, 5 equiv) affording **27h** free base (54 mg, 95% yield) as a pale brown powder. A portion of this material (20.2 mg) was dissolved in 0.1 M HCl in methanol (0.53 mL, prepared from 12 N HCl (aq)), concentrated *in vacuo*. The salt was again dissolved in methanol (1 mL) and concentrated *in vacuo* to remove residual water. The solid was triturated with toluene and dried overnight to obtain **27h** (as the depicted HCl salt, 20.0 mg, 89% yield) as a yellowish brown solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.98 (s, 1H), 9.01 (t, J = 6.1 Hz, 1H), 8.88 (s, 1H), 8.70 (br s, 2H), 8.44 (d, J = 7.9 Hz, 1H), 8.19 (app t, J = 1.8 Hz, 1H), 8.13 (dt, J = 7.5, 1.5 Hz, 1H), 7.72 – 7.60 (m, 4H), 7.33 (app t, J = 7.5 Hz, 1H), 3.70 (app q, J = 6.1 Hz, 2H), 3.15 (m, 2H), 2.60 (t, J = 5.4 Hz, 3H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 165.6, 141.6, 139.5, 139.4, 139.0, 134.3, 133.7, 130.6, 130.1, 128.9, 128.8, 128.4, 127.4, 122.0, 121.1, 120.3, 113.7, 112.7, 48.3, 35.6, 32.7.

HRMS (ESI+) calculated for $C_{21}H_{20}ClN_4O$ $[M+H]^+$: 379.1320, found 379.1292.

B. Procedures for *in vitro* antimalarial and cytotoxicity assays

Parasite Culture. *P. falciparum* strains Dd2 (MRA-150, resistant to chloroquine, pyrimethamine and mefloquine), 3D7 (MRA-102, drug-sensitive) and W2 (MRA-157, resistant to chloroquine

and sensitive to mefloquine) were obtained from MR4 Malaria Reagent Repository (ATCC, Manassas, VA), a part of the BEI Resources Repository (NIAID, NIH). The Dd2-KAE609 resistant strain was a gift from Dr. Elizabeth Winzeler.[4] The field strain 4G (dihydroartemisinin- and chloroquine-resistant) was a gift of Dr. Dennis Kyle.[5] Parasites were maintained in O-positive human erythrocytes (Interstate Blood Bank Inc., Memphis, Tennessee) at 5% hematocrit in RPMI 1640 medium supplemented with 5 g/L Albumax I (Gibco Life Technologies), 2 g/L glucose (Sigma-Aldrich), 2.3 g/L sodium bicarbonate (Sigma-Aldrich), 370 μM hypoxanthine (Sigma-Aldrich), 25 mM HEPES, and 20 mg/L gentamicin (Gibco Life Technologies). The parasites were kept at 37°C under reduced-oxygen conditions (5% CO2, 5% O_2, and 90% N_2).

Growth inhibition and metabolic rescue by isopentenyl diphosphate (IPP) supplementation assays. The antimalarial effect of test compounds was evaluated against asexual blood stages of *P. falciparum* parasites using the SYBR green I assay as described previously.[6] The antimalarial activity of MMV008138 analogs was first evaluated against asexual parasites using four-point dilutions ranging from 10 μM to 1.25 μM. For active compounds, the half maximal effective concentration (EC_{50}) was determined using ten-point dilutions at concentrations ranging from 5-10 μM to 0.005-0.01 μM in constant 0.1% DMSO (vehicle). The percentage of growth was normalized to that of untreated control parasites in the presence of 0.1% DMSO. Background determinations were made using uninfected erythrocytes. Two or more independent experiments in duplicate were performed. The EC_{50} values were calculated with GraphPad Prism 9 (GraphPad Software Ltd.) using nonlinear regression curve fitting with variable slope (four parameters) and represent the average and their standard error of the mean (S.E.M.). To assess whether compounds were specifically targeting the apicoplast, the recovery of growth in the presence of inhibitor and IPP was performed as described previously.[6] Briefly, parasites were grown in the presence or absence of 200 μM IPP along with a serial dilution (10 μM to 0.01 μM) or single concentration (10 or 20 μM) of test compounds. All conditions were set in 96-well half area plates using highly synchronous ring-stage parasite cultures (100 μL/well at 1% hematocrit and 1% parasitemia) and incubated for 72 h under normal culture conditions. Parasite growth was measured by the SYBR green I assay.

***In vitro* cytotoxicity against HEK293 cells.** Compound **7e•**HCl was evaluated against the HEK293 (Human Embryonic Kidney) normal cell line. Briefly, 10,000 HEK293 cells per well were plated in a clear bottom 96 well plate. After allowing the cells to adhere, the media was

replaced with 100 μL of media containing varying amounts of **7e•**HCl and incubated for 24 hours. Then, 10 μL of resazurin sodium salt (Sigma) at 0.125 mg/mL was added to each well and incubated for 8 h. Cell viability was determined by measuring the fluorescence at 585 nm after excitation at 540 nm. Epoxomicin was used as control (EC_{50} = 400 nM). The half maximal cytotoxic concentration (CC_{50}) was determined using ten-point dilutions at concentrations ranging from 50 μM to 0.4 μM in constant 0.1% DMSO (vehicle) from three independent experiments in duplicate were performed. The percentage of growth was normalized to that of untreated control cells in the presence of 0.2% DMSO. The CC_{50} values were calculated with GraphPad Prism 9 (GraphPad Software Ltd.) using nonlinear regression curve fitting with variable slope (four parameters) and represent the average and their standard error of the mean (S.E.M.).

***Escherichia coli* growth inhibition assays.** The effect of **7e•**HCl against *E. coli*, strain BL21(DE3), was evaluated as describe previously.[7] Briefly, an overnight culture of *E. coli* cultivated at 37 ºC at 200 rpm agitation was diluted to an OD600 of ~0.6 the culture and inoculated into a culture tube containing **7e•**HCl previously diluted in LB broth medium at three final concentrations (500 μM, 250 μM, and 125 μM). The final DMSO concentration was 5%. Cultures were incubated for 18 h at 37 ºC and 200 rpm agitation. The following controls were performed: 100 μM fosmidomycin (FOS) treatment which targets the MEP pathway in *E. coli*, media without inoculum, 5% DMSO (vehicle), and control with inoculum alone (untreated). After 18h incubation, bacteria growth was measured using a cell density meter. The percentage of growth was normalized to that of untreated control bacteria and potential inhibition of growth of **7e•**HCl was determined by comparison to the 5% DMSO control, which does not affect *E. coli* growth, as we described previously.[7]

C. *In vitro* ADME-Tox Assays performed by Contract Research Organizations

[^{3}H]-Hypoxanthine incorporation assay (Table 4, entry 6)

This standard 48 h assay was performed by GSK Tres Cantos (Spain), using 3D7A strain *P. falciparum*, with initial parasitemia of 0.5% and hematocrit 2%.

Lactate dehydrogenase inhibition assay (Table 4, entry 7)

This standard 72 h assay was performed by TCGLS (Kolkata, India) on 3D7 strain *P. falciparum*.

Primary human hepatocytes cytotoxicity assay (Table 4, entry 9)

This assay was performed by TropIQ Health Sciences by DAPI staining as described previously.[8]

hERG inhibition assay (Table 4, entry 11)

This assay was performed by Pharmaron by manual patch-clamp,using 8 concentrations of drug in HEK-293 cells stably transfected with the hERG gene.

Mini-Ames panel (Table 4, entry 12)

This assay was performed by Sequani (Ledbury, England, UK). The test compound **7e**•HCl did not induce mutations in two histidine-dependent auxotrophic mutants of *Salmonella typhimurium*, strains TA98 and TA100.

Log D (Table 4, entry 15)

This assay was performed by Pharmaron at 10 mM, using LC/MS to quantitate partitioning between 1-octanol and pH 7.4 PBS.

PBS solubility (Table 4, entry 16)

Thermodynamic solubility at pH 7.4 was determined by Pharmaron, using LC/MS for quantitation.

Plasma protein binding (mouse) (Table 4, entry 17)

This assay was performed by Pharmaron, using mixed gender CD-1 mouse plasma, equilibrium dialysis, and LC/MS for quantitation.

Mouse Plasma stability (Table 4, entry 18)

This assay was performed by Pharmaron, using mixed gender CD-1 mouse plasma, and LC/MS for quantitation.

Mouse microsomal stability and Cl_{int} (Table 4, entries 19-20)

This assay was performed by Pharmaron, using pooled male CD-1 mouse liver microsomes. With added NADPH, 37% loss of parent was observed over 60 min. Without added NADPH, less than 4% parent was lost over 60 min. LC/MS was used for quantitation.

D. Protocol for *in vivo* efficacy study of 7e•HCl in *Plasmodium berghei*-infected mice

Efficacy of **7e**•HCl in *P. berghei*-infected mice was determined at the Anti-Infectives Core Facility, Department of Microbiology, Grossman School of Medicine, New York University.

Protocol

Three groups of five female Swiss Webster mice weighing 25 to 30 g were used for vehicle control, **7e**•HCl treatment (PO, 40 mg/kg/d) and the positive control chloroquine (PO, 40 mg/kg/d). Mice were infected via intraperitoneal (i.p.) injection with 10^3 *Plasmodium berghei* ANKA expressing luciferase (PbGFP-Luccon) obtained from a donor infected mouse.[9] On day 3 after infection, mice

were anesthetized by inhalation of isofluorane and injected via i.p. with 150 mg/kg of luciferase substrate dissolved in PBS (D-Luciferin Potassium Salt, Gold Biotechnology). Mice were imaged 5 to 10 min after injection of luciferin using an IVIS imager (Lumina II In Vivo Imaging System; Perkin-Elmer). The data acquisition and analysis were performed with LivingImage (Xenogen). Accumulated light intensity was measured in each mouse to determine the baseline infection levels before treatment. Mice were then started on a four-day course of treatment (once per day by oral gavage). The control group was treated with vehicle (0.5% (hydroxypropyl)methyl cellulose, 0.5% Tween-80) and the drug-treated groups received the experimental compound or chloroquine at 40 mg/kg body weight. On days 5 and 7 post-infection, mice were imaged as described above and images are shown in Figure 3. Total average luminescence for each group is shown below.

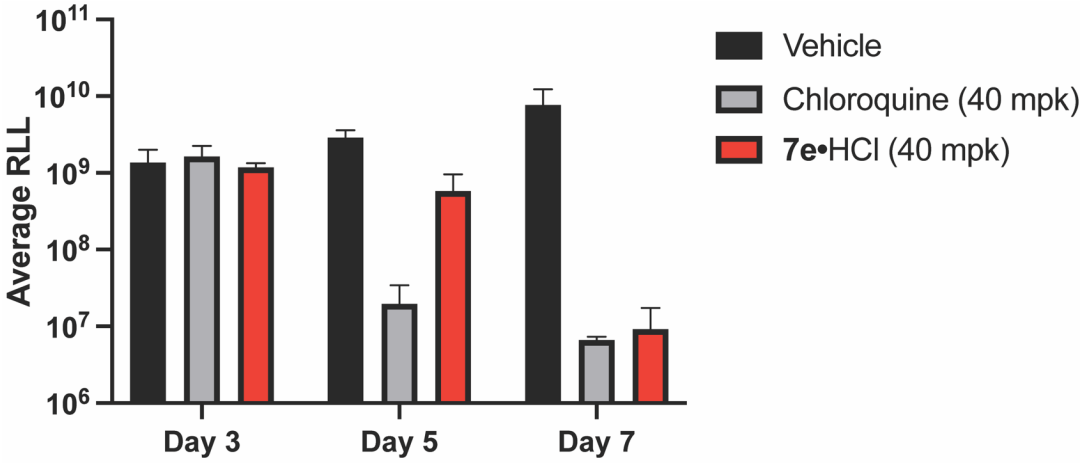


Figure S1. Relative levels of luminescence (indirect parasitemia) of each treatment group. Note that for the vehicle control, three of the five infected mice died by Day 7 (see Figure 3). As shown above, on day 7 post-infection both the **7e**•HCl and chloroquine-treated groups showed approximately 100-fold reduction in luminescence relative to the vehicle control.

E. Pharmacokinetics protocol and exposure vs time data for 7e•HCl in rats

Pharmacokinetic analysis of **7e**•HCl in rats was performed by TCGLS (Kolkata, India). Three rats (250 ± 50 g each) were used for oral (40 mg/kg, gavage, conscious) and IV (10 mg/kg, lateral tail vein with anesthesia), administration. The vehicle for both routes was 40% PEG400, 10% ethanol, and 50% PBS. Stock concentrations were 8.0 and 5.0 mg/mL (oral and IV respectively), and rats

were dosed at 5.0 and 2.0 mL/kg (oral and IV respectively). Key pharmacokinetic parameters are shown in Table S1, and plots of plasma concentration vs time for all 6 rats are shown in Figure S2.

Table S1. Key pharmacokinetic parameters for **7e**•HCl

Route (dose)	Parameter	Value
IV (10 mg/kg)	$t_{1/2}$ (h)	5.96 ± 0.62
	C_{max} (μg/mL)	0.66 ± 0.07
	C_0 (μg/mL)	0.78 ± 0.10
	t_{last} (h)	24
	C_{min} (μg/mL)	0.0217 ± 0.002
	C_{max}/C_{min}	30.5 ± 3.5
	$AUC_{0\text{-}24h}$ (μg/mL)	3.25 ± 0.41
	$AUC_{0\text{-}inf}$ (μg/mL)	3.44 ± 0.38
	V_d (L/kg)	21.8 ± 4.1
PO (40 mg/kg)	$t_{1/2}$ (h)	7.74 ± 1.38
	t_{max} (h)	8.0
	C_{max} (μg/mL)	0.34 ± 0.01
	t_{last} (h)	24
	C_{min} (μg/mL)	0.003 ± 0.002
	C_{max}/C_{min}	164 ± 90
	$AUC_{0\text{-}24h}$ (μg/mL)	4.61 ± 0.33
	$AUC_{0\text{-}inf}$ (μg/mL)	5.56 ± 0.76

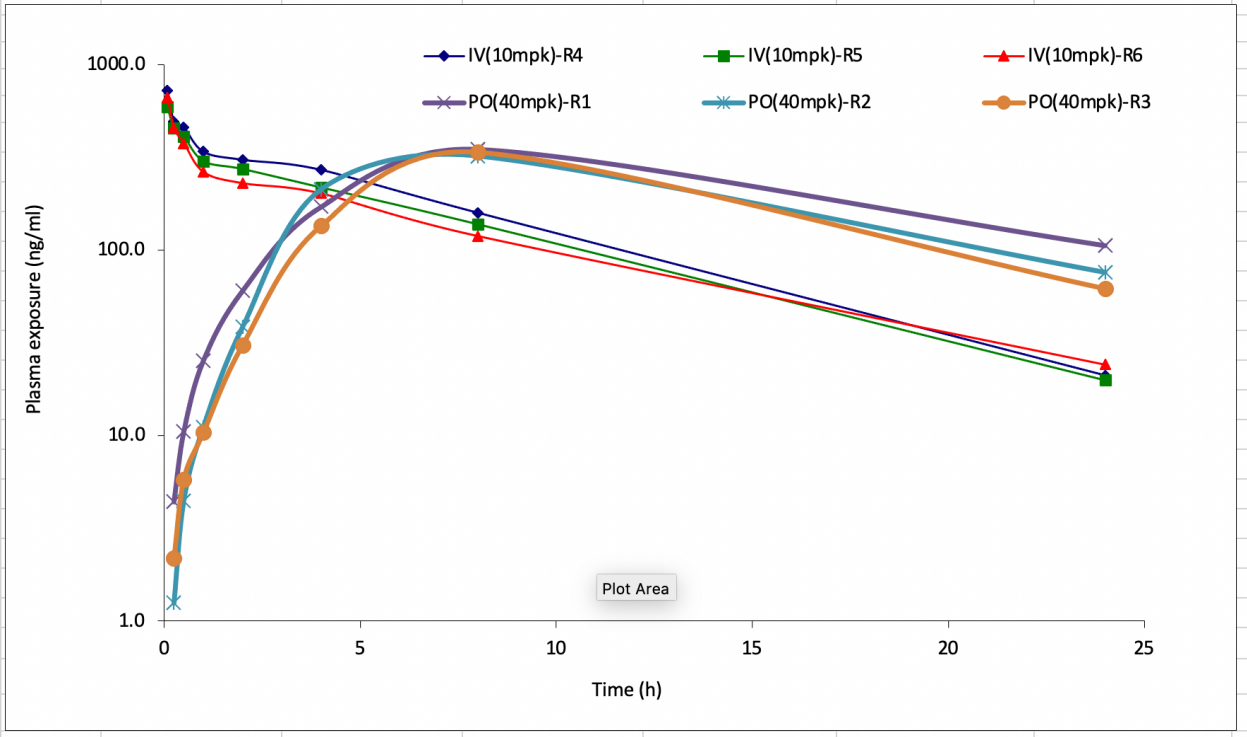


Figure S2. Plasma exposure vs time for oral (40 mg/kg, rats 1-3) and IV (10 mg/kg, rats 4-6) administration of **7e**•HCl.

F. References

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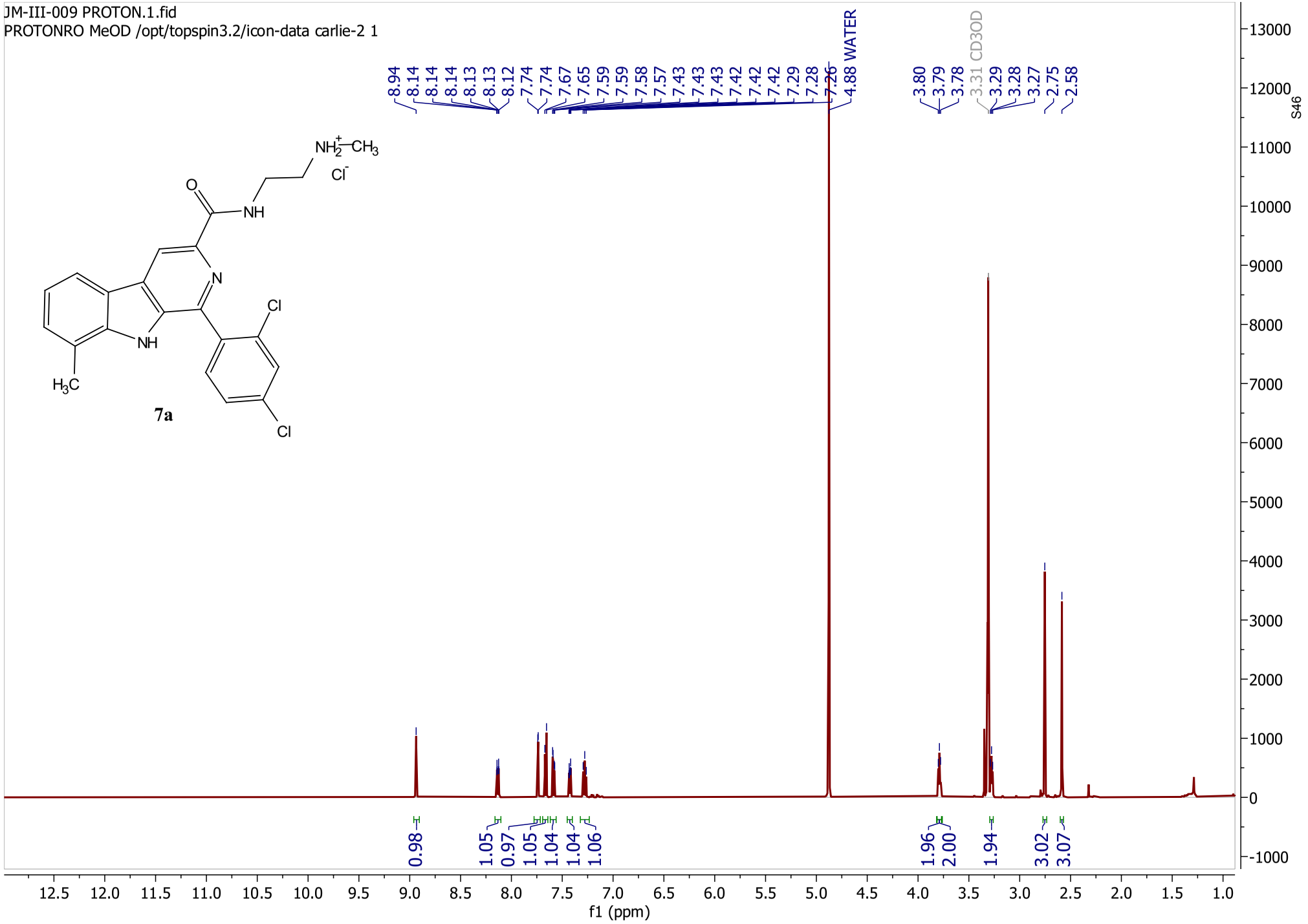
G. NMR Spectra for all tested compounds.

See following pages.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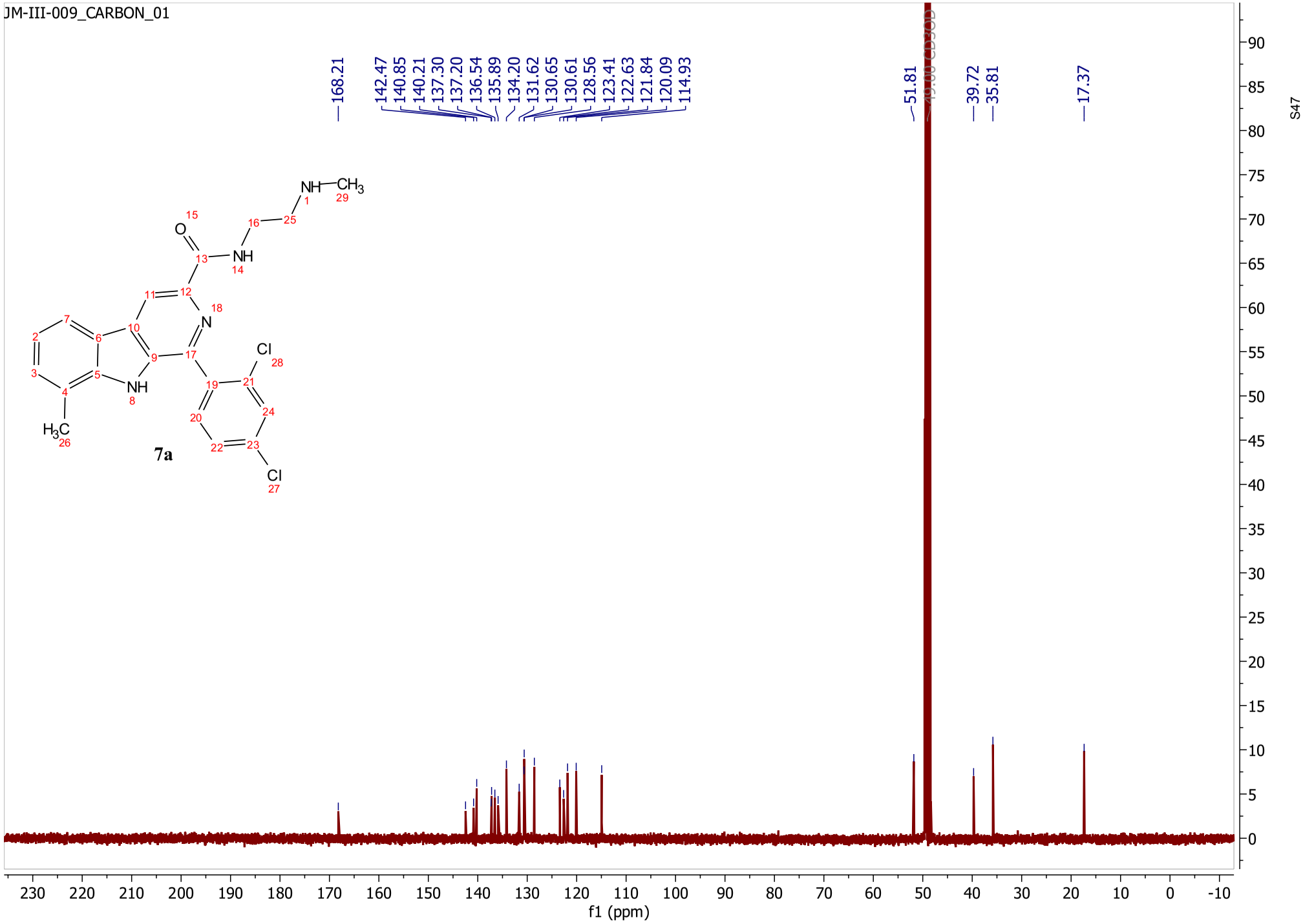
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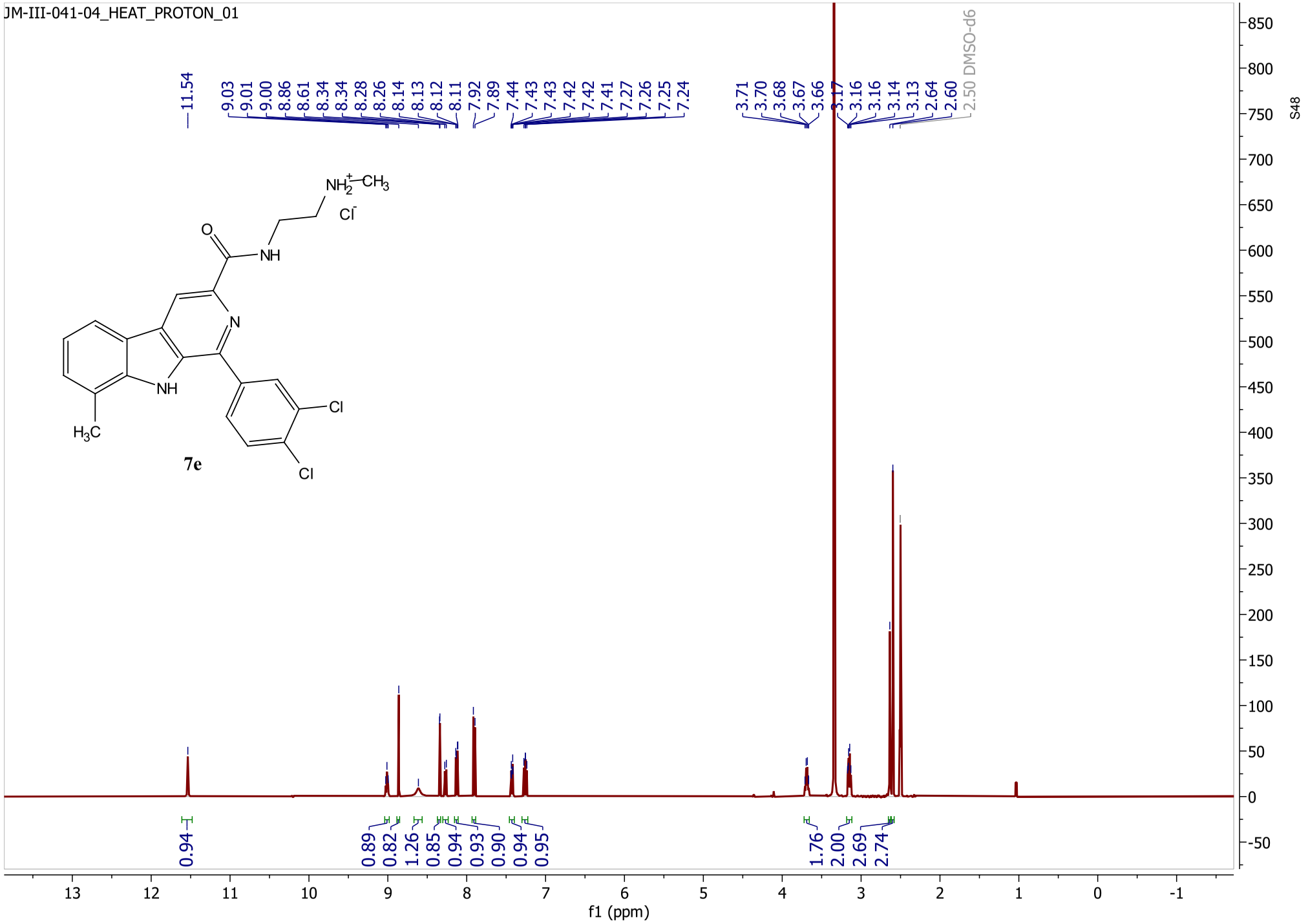
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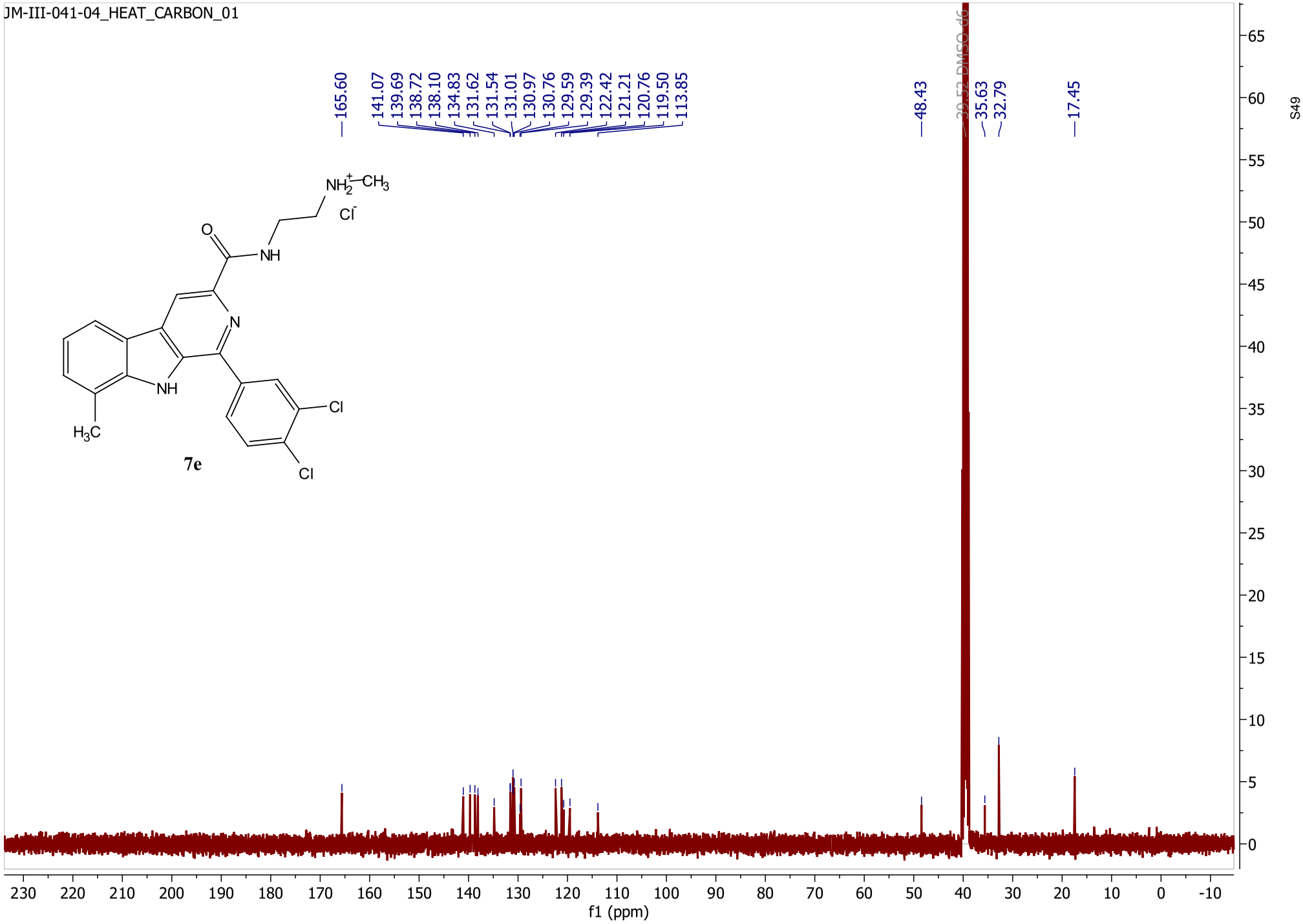
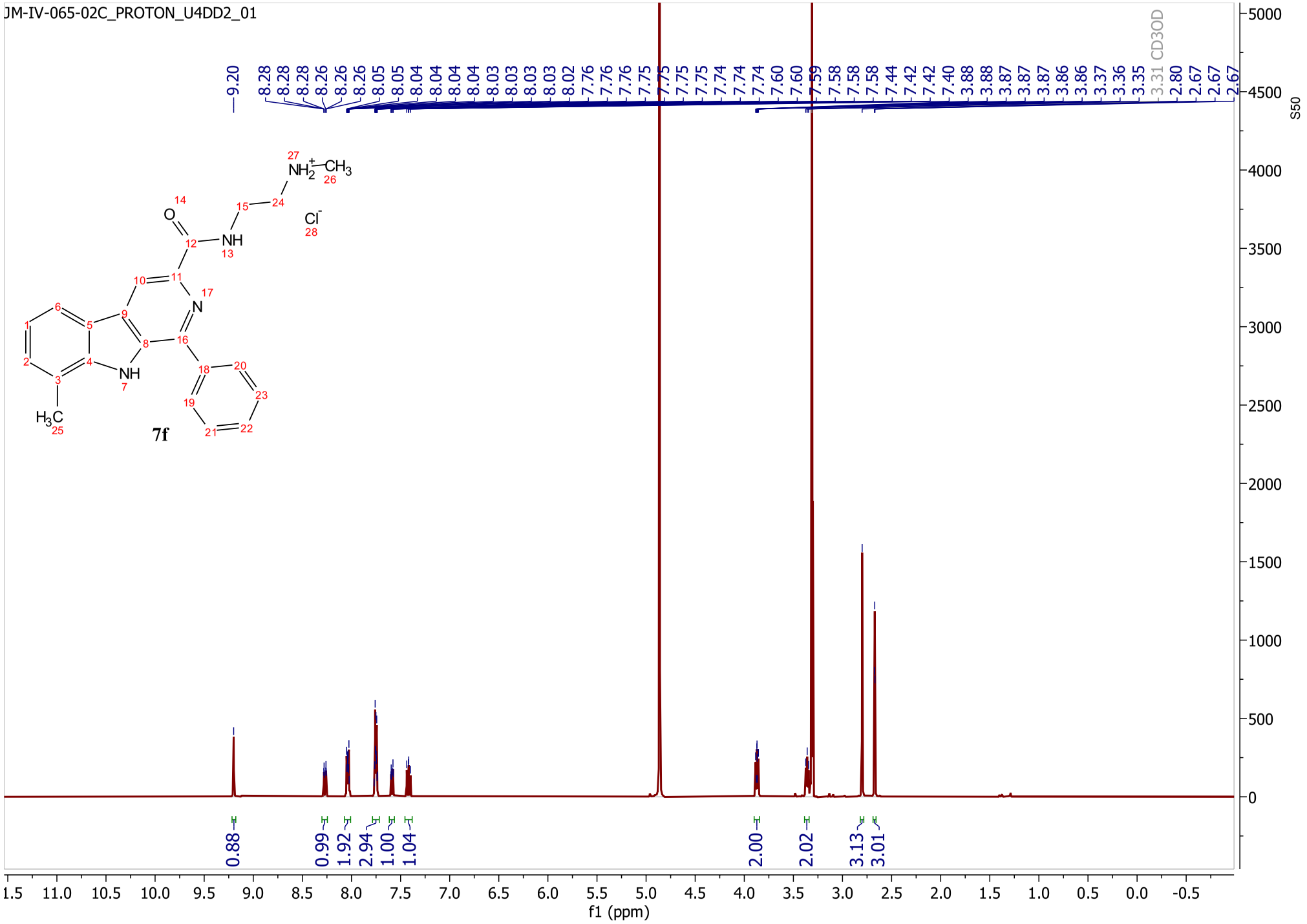
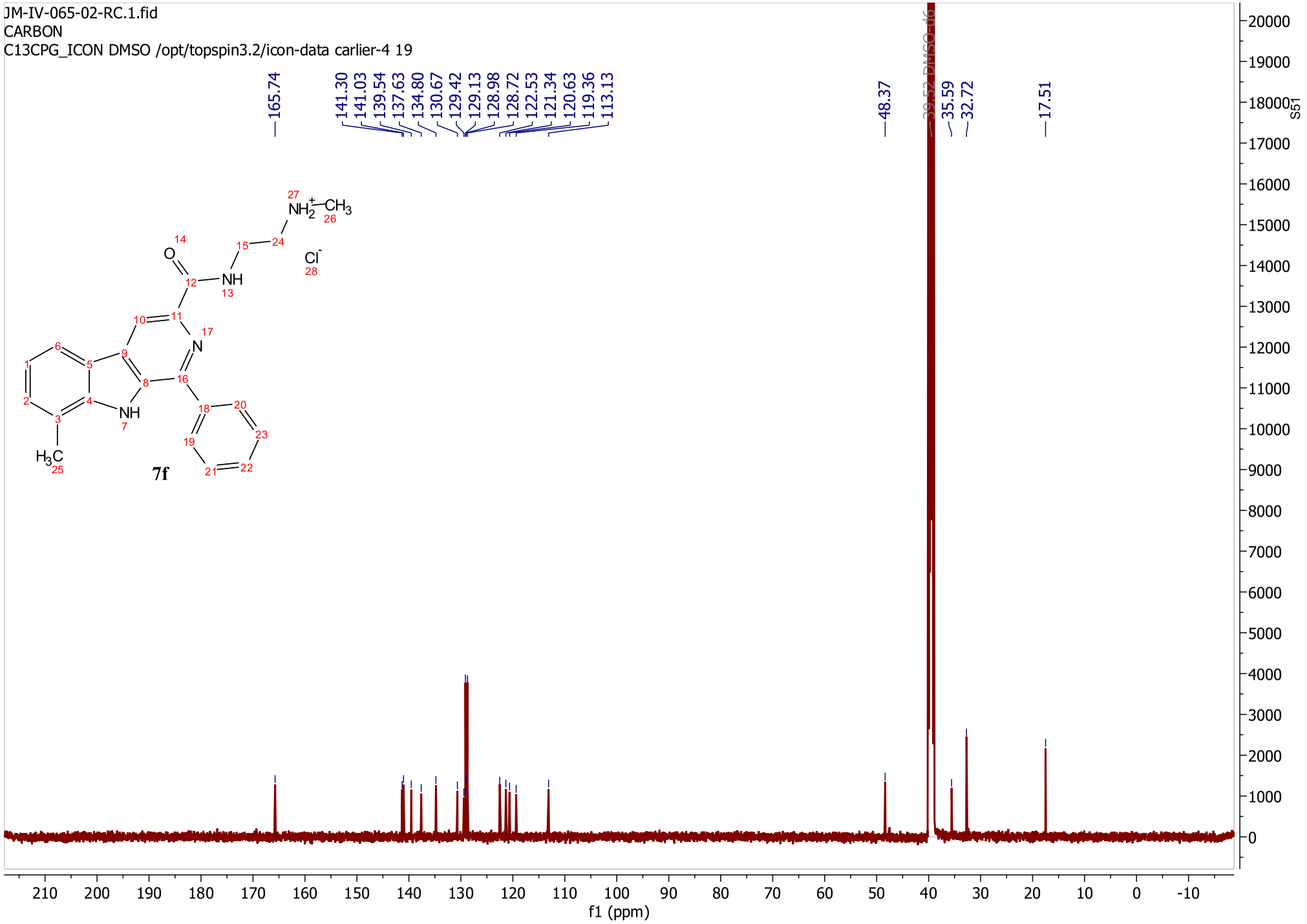
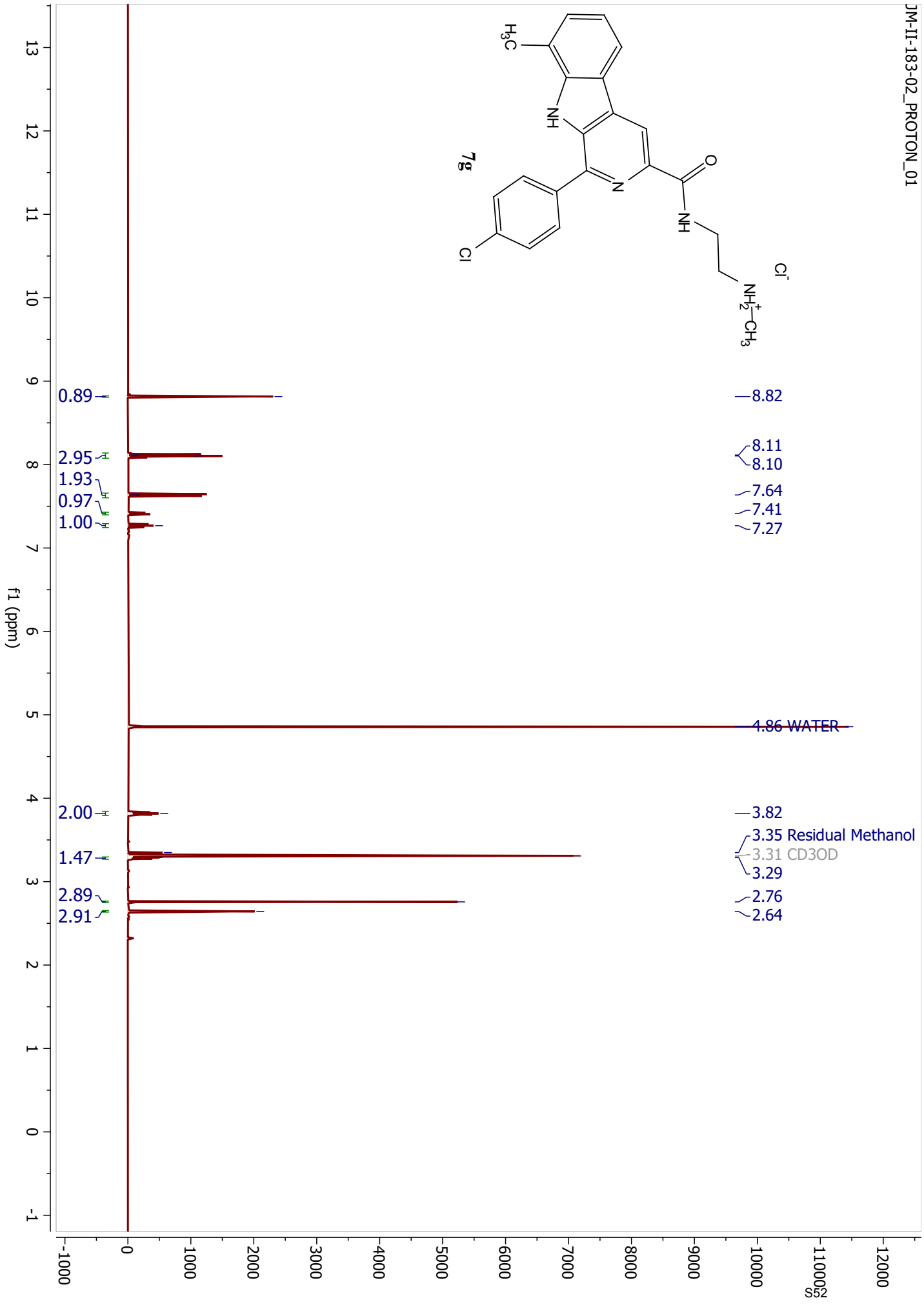
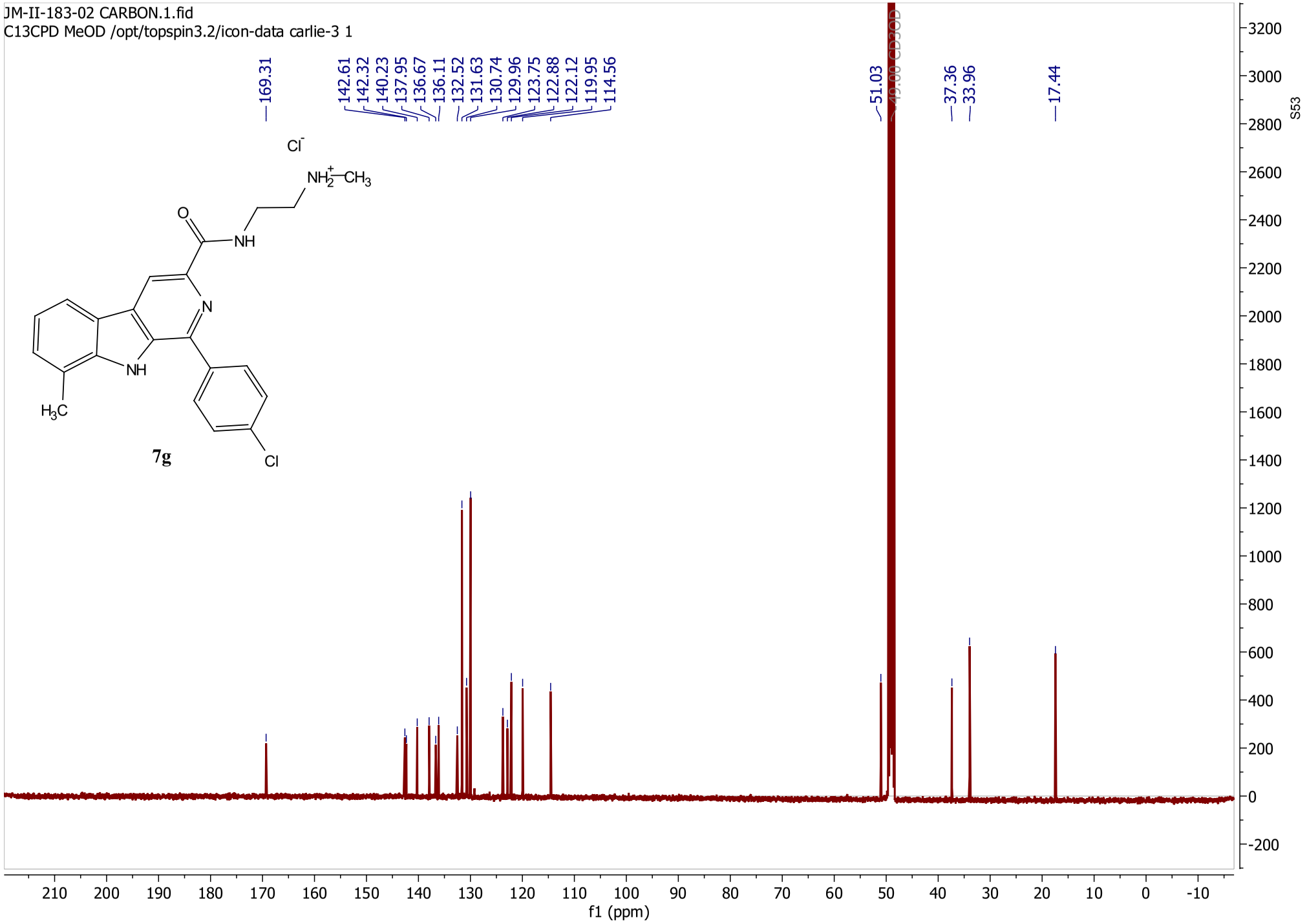
9.00
8.86
8.61
8.34
8.34
8.28
8.26
8.14
8.13
8.12
8.11
7.92
7.89
7.44
7.43
7.43
7.42
7.42
7.41
7.27
7.26
7.25
7.24
3.71
3.70
3.68
3.67
3.66
3.17
3.16
3.16
3.14
3.13
2.64
2.60
2.50 DMSO-d6
NH2+—CH3
Cl-
O
NH
N
NH
H3C
Cl
Cl
7e
0.94
0.89
0.82
1.26
0.85
0.94
0.93
0.90
0.94
0.95
1.76
2.00
2.69
2.74
f1 (ppm)
S48

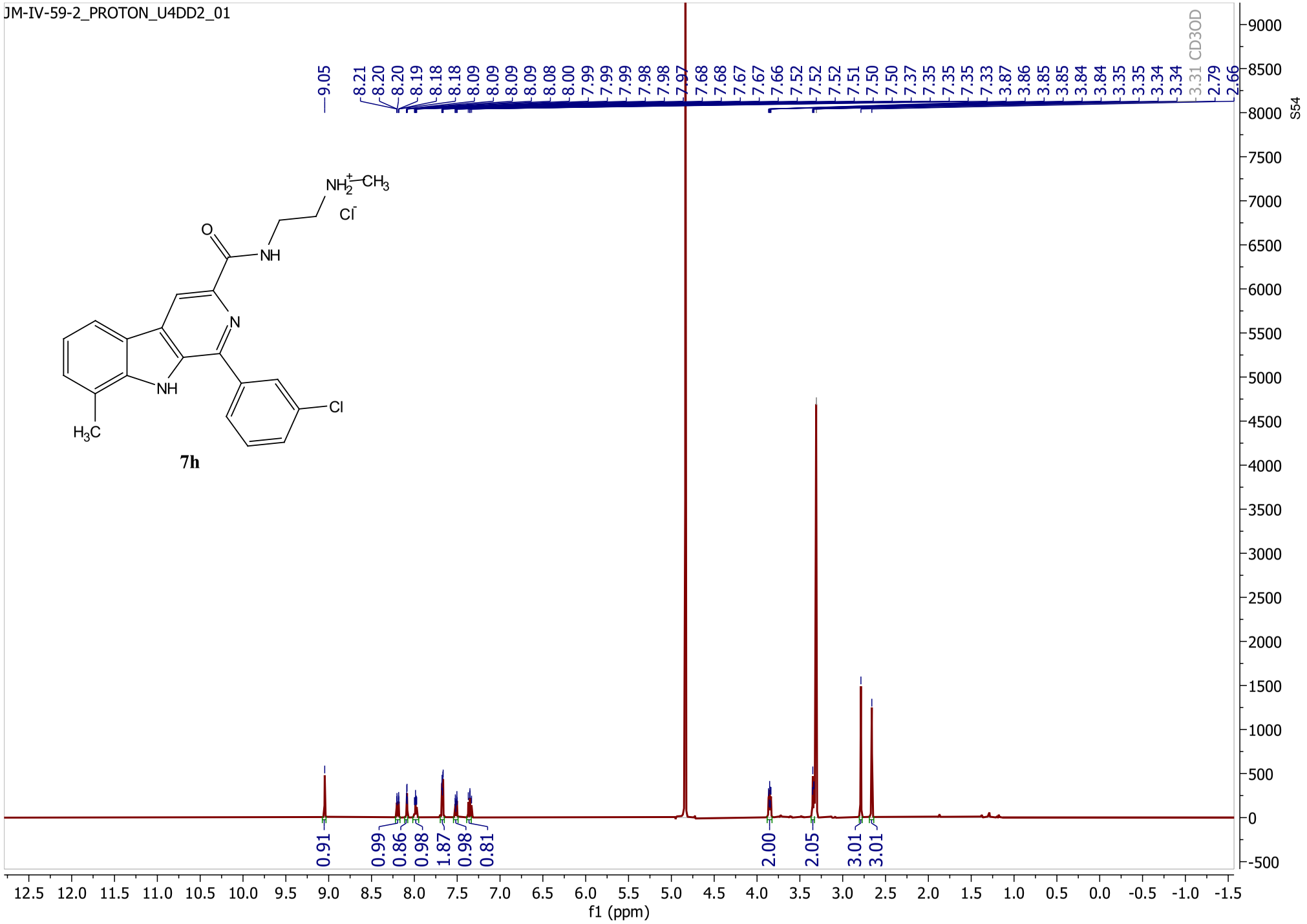

JM-III-041-04_HEAT_CARBON_01
165.60
141.07
139.69
138.72
138.10
134.83
131.62
131.54
131.01
130.97
130.76
129.59
129.39
122.42
121.21
120.76
119.50
113.85
48.43
39.52 DMSO-d6
35.63
32.79
17.45
NH2+ CH3
Cl-
O
NH
N
NH
H3C
Cl
Cl
7e
S49
f1 (ppm)

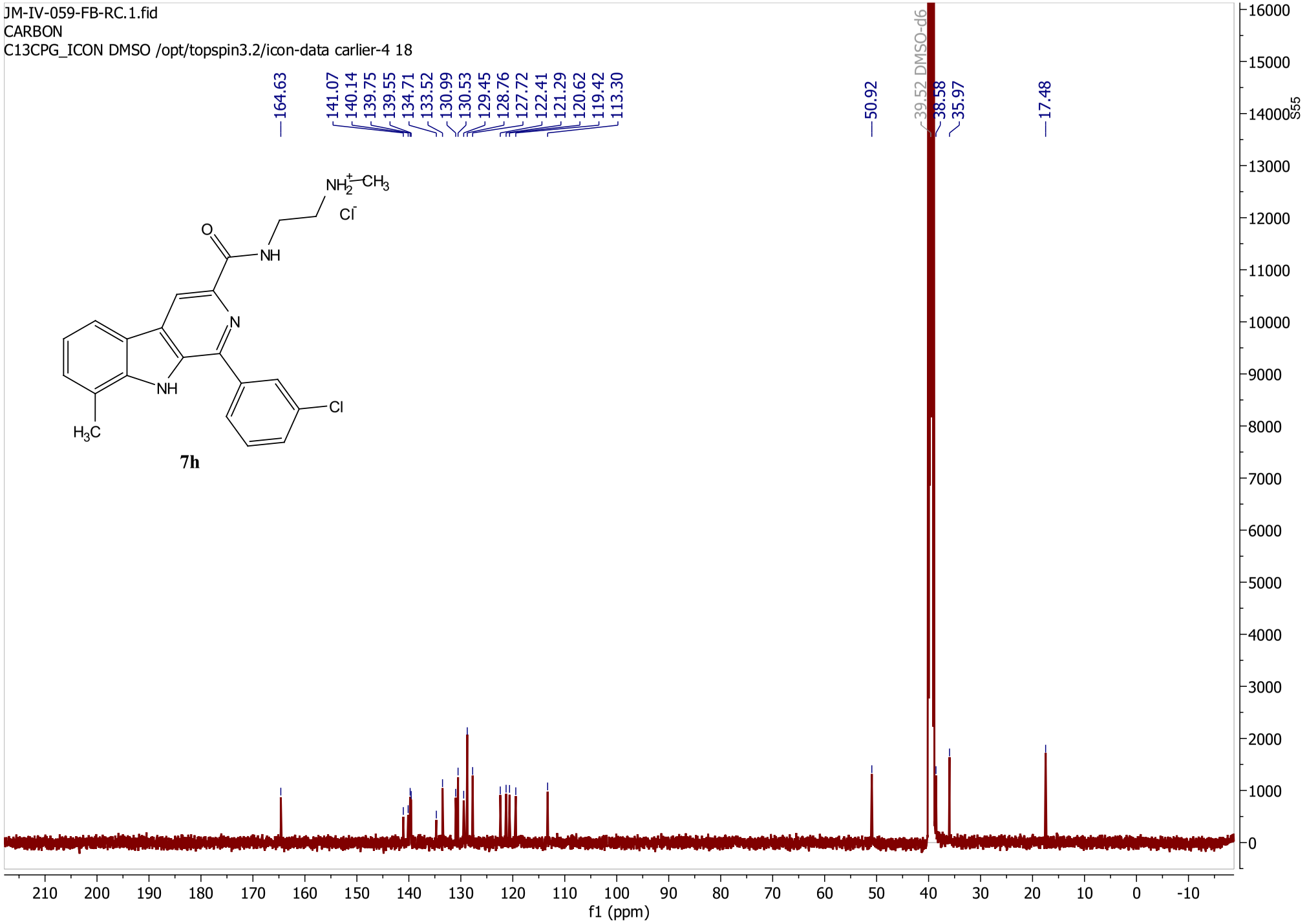

JM-IV-065-02C_PROTON_U4DD2_01
9.20
8.28 8.28 8.28 8.26 8.26 8.26 8.05 8.05 8.04 8.04 8.04 8.04 8.03 8.03 8.03 8.03 8.02 7.76 7.76 7.76 7.75 7.75 7.75 7.75 7.74 7.74 7.74 7.60 7.60 7.59 7.58 7.58 7.58 7.44 7.42 7.42 7.40 3.88 3.88 3.87 3.87 3.87 3.86 3.86 3.37 3.36 3.35 3.31 CD3OD 2.80 2.67 2.67 2.67
S50
7f
0.88 0.99 1.92 2.94 1.00 1.04 2.00 2.02 3.13 3.01
f1 (ppm)

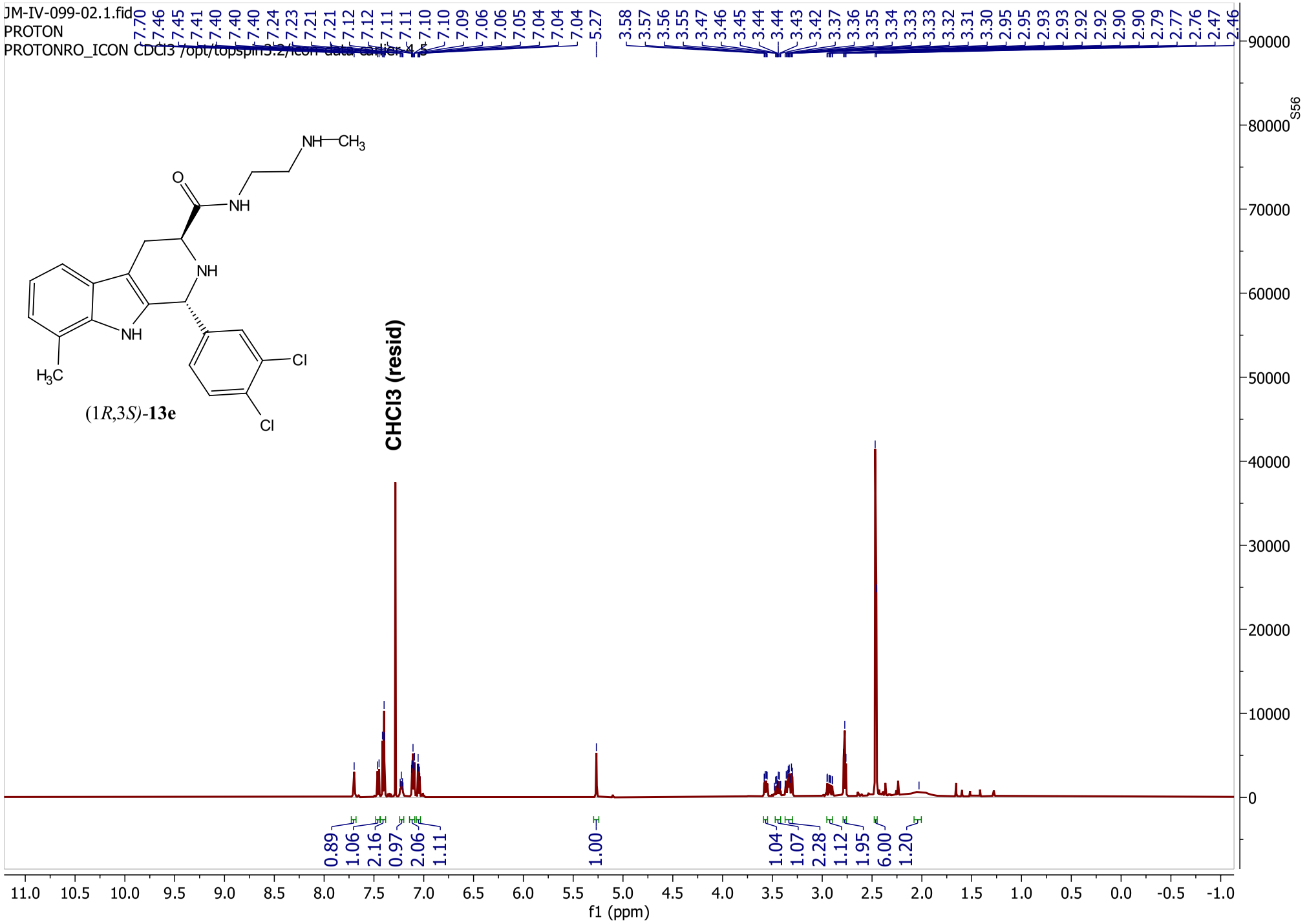

JM-IV-065-02-RC.1.fid
CARBON
C13CPG_ICON DMSO /opt/topspin3.2/icon-data carlier-4 19
165.74
141.30
141.03
139.54
137.63
134.80
130.67
129.42
129.13
128.98
128.72
122.53
121.34
120.63
119.36
113.13
48.37
39.52 DMSO-d6
35.59
32.72
17.51
S51
7f
f1 (ppm)

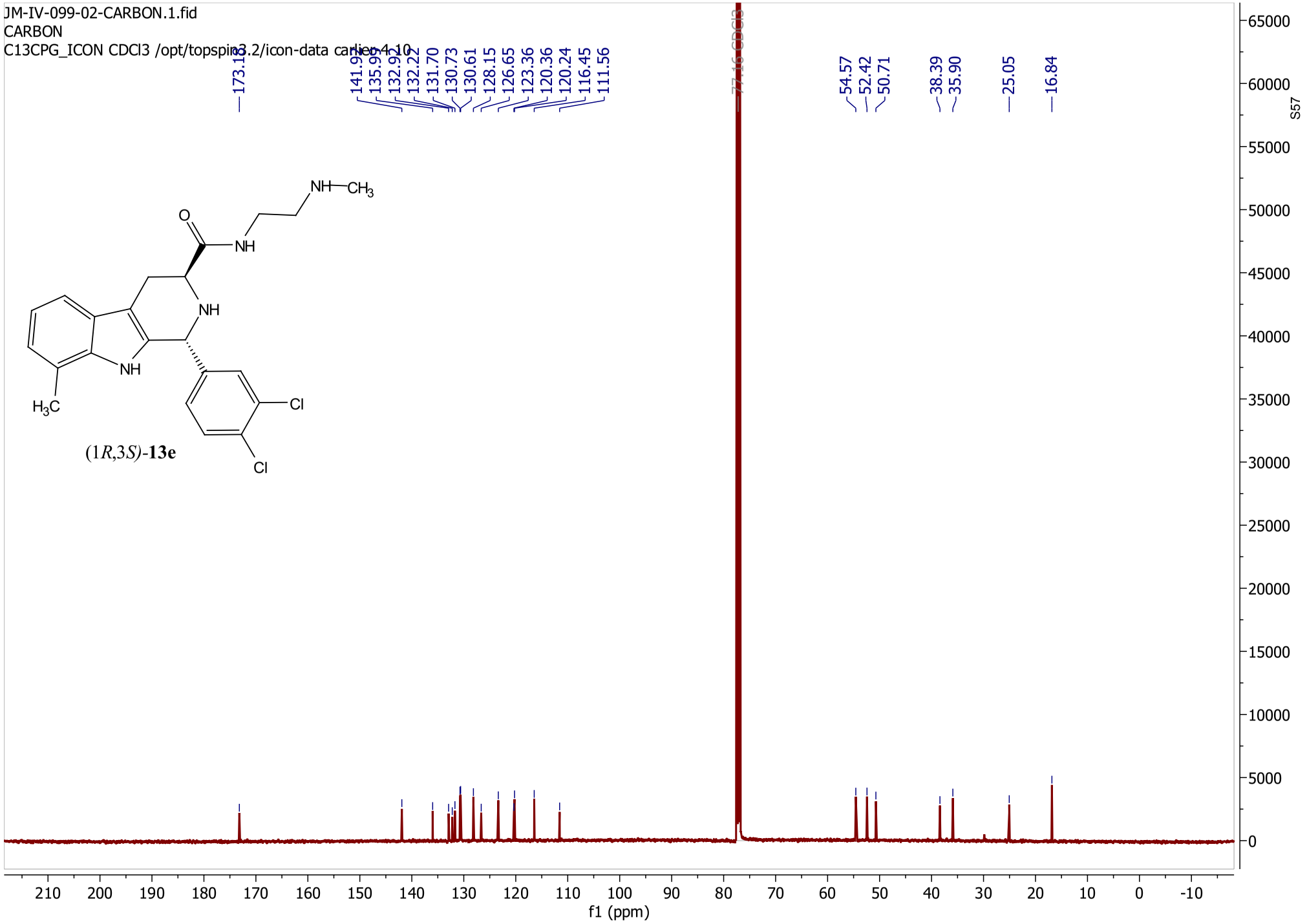

JM-II-183-02_PROTON_01
7g
f1 (ppm)
0.89
2.95
1.93
0.97
1.00
2.00
1.47
2.89
2.91
8.82
8.11
8.10
7.64
7.41
7.27
4.86 WATER
3.82
3.35 Residual Methanol
3.31 CD3OD
3.29
2.76
2.64

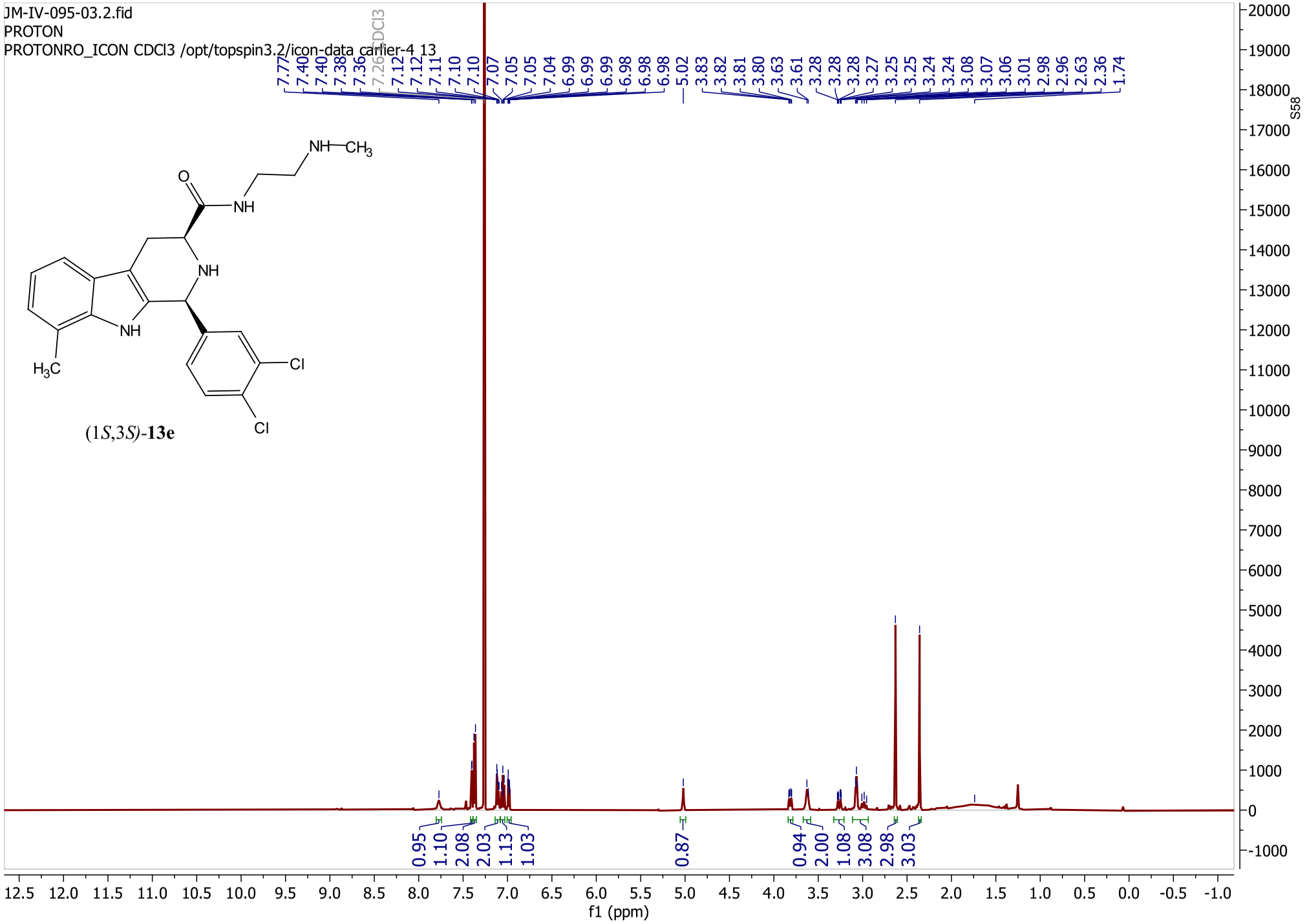

JM-II-183-02 CARBON.1.fid
C13CPD MeOD /opt/topspin3.2/icon-data carlie-3 1
169.31
142.61
142.32
140.23
137.95
136.67
136.11
132.52
131.63
130.74
129.96
123.75
122.88
122.12
119.95
114.56
51.03
49.00 CD3OD
37.36
33.96
17.44
S53
Cl-
NH2+—CH3
O
NH
N
NH
H3C
Cl
7g
f1 (ppm)

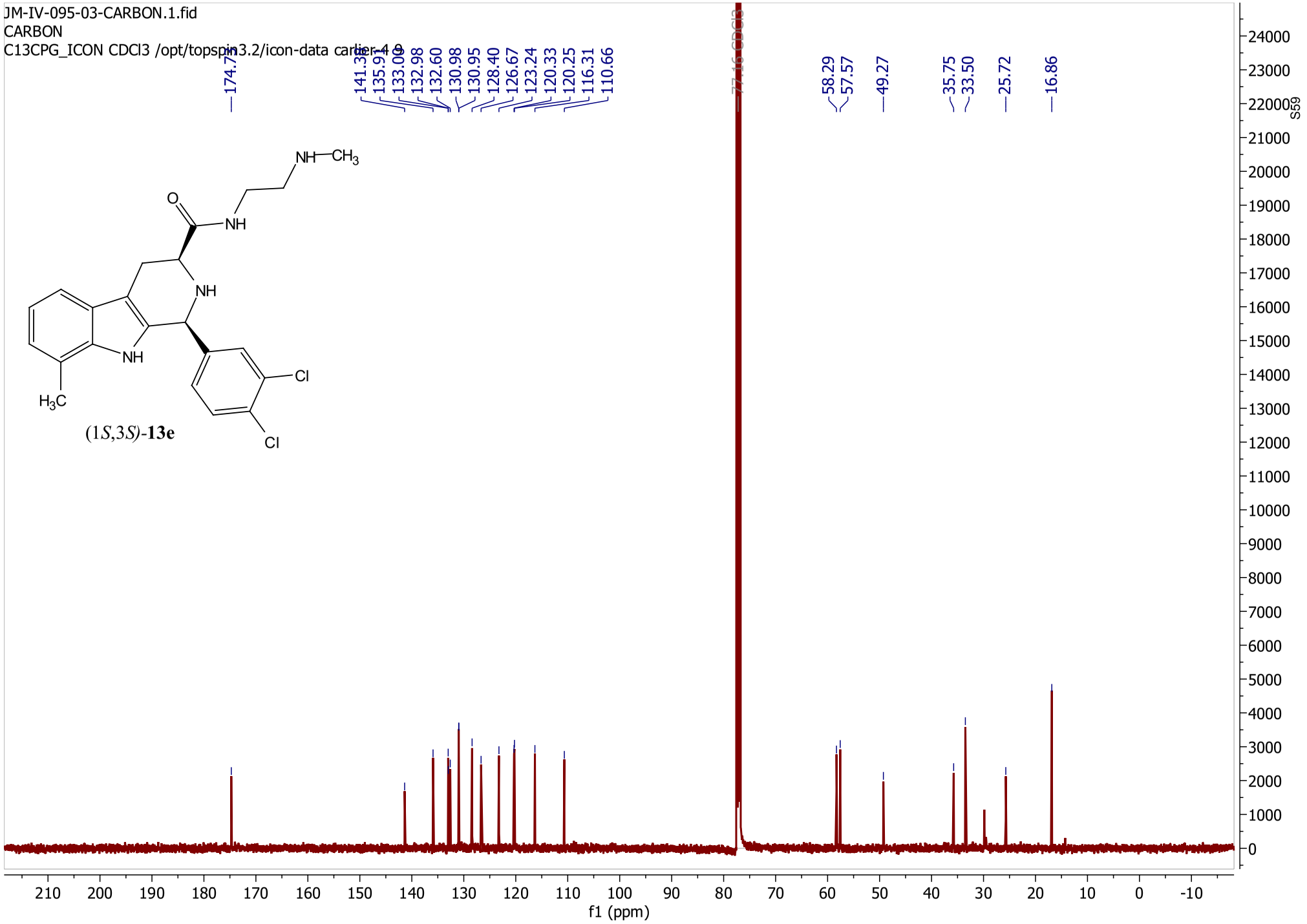

JM-IV-59-2_PROTON_U4DD2_01
9.05
8.21
8.20
8.20
8.19
8.18
8.18
8.09
8.09
8.09
8.09
8.08
8.00
7.99
7.99
7.99
7.98
7.98
7.97
7.68
7.68
7.67
7.67
7.66
7.52
7.52
7.52
7.51
7.50
7.50
7.37
7.35
7.35
7.35
7.33
3.87
3.86
3.85
3.85
3.84
3.84
3.35
3.35
3.34
3.34
3.31 CD3OD
2.79
2.66
NH2+ CH3
Cl-
O
NH
N
NH
Cl
H3C
7h
0.91
0.99
0.86
0.98
1.87
0.98
0.81
2.00
2.05
3.01
3.01
f1 (ppm)
S54

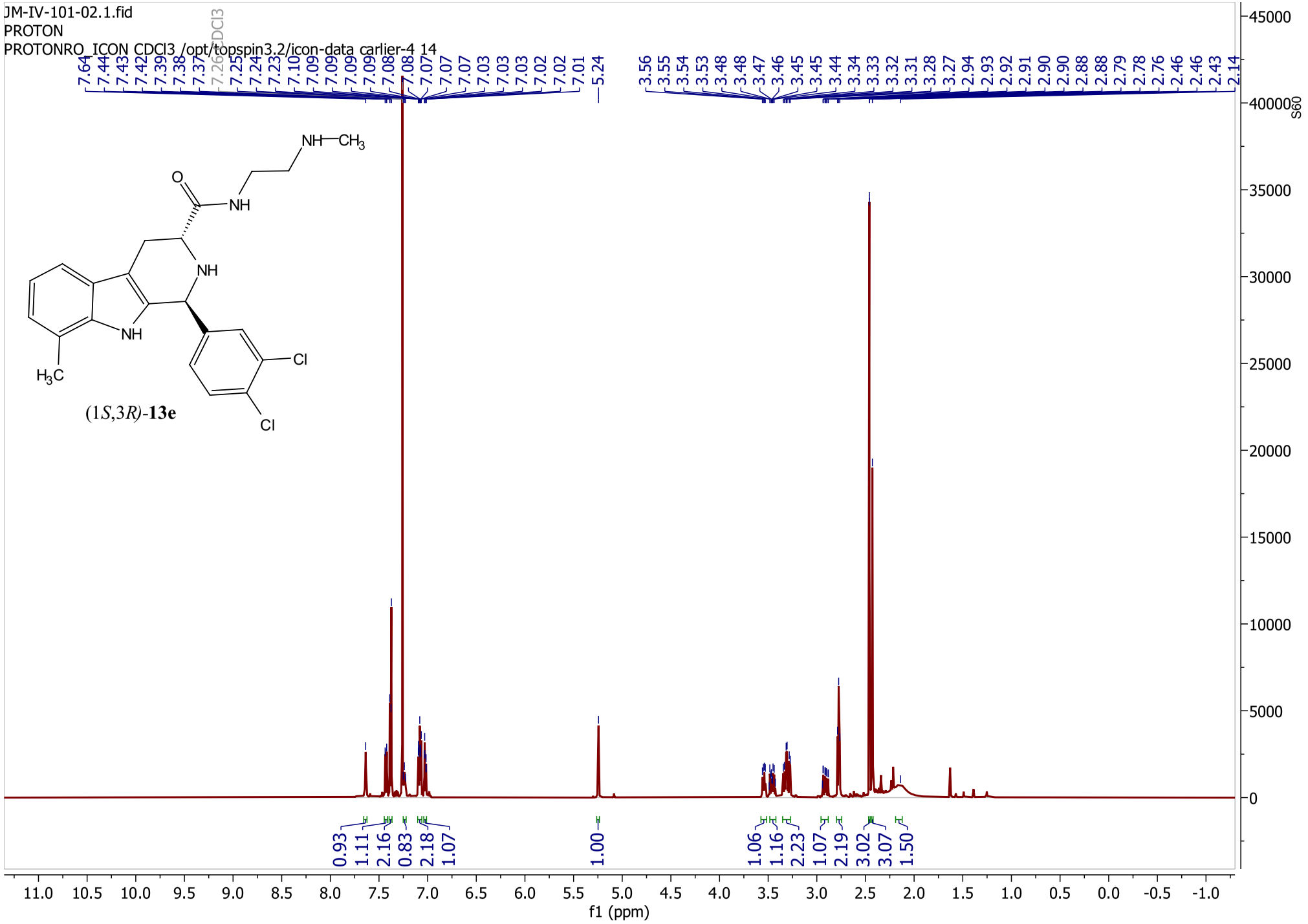

JM-IV-059-FB-RC.1.fid
CARBON
C13CPG_ICON DMSO /opt/topspin3.2/icon-data carlier-4 18
164.63
141.07
140.14
139.75
139.55
134.71
133.52
130.99
130.53
129.45
128.76
127.72
122.41
121.29
120.62
119.42
113.30
50.92
39.52 DMSO-d6
38.58
35.97
17.48
S55
NH2+ CH3
Cl-
O
NH
N
NH
Cl
H3C
7h
f1 (ppm)

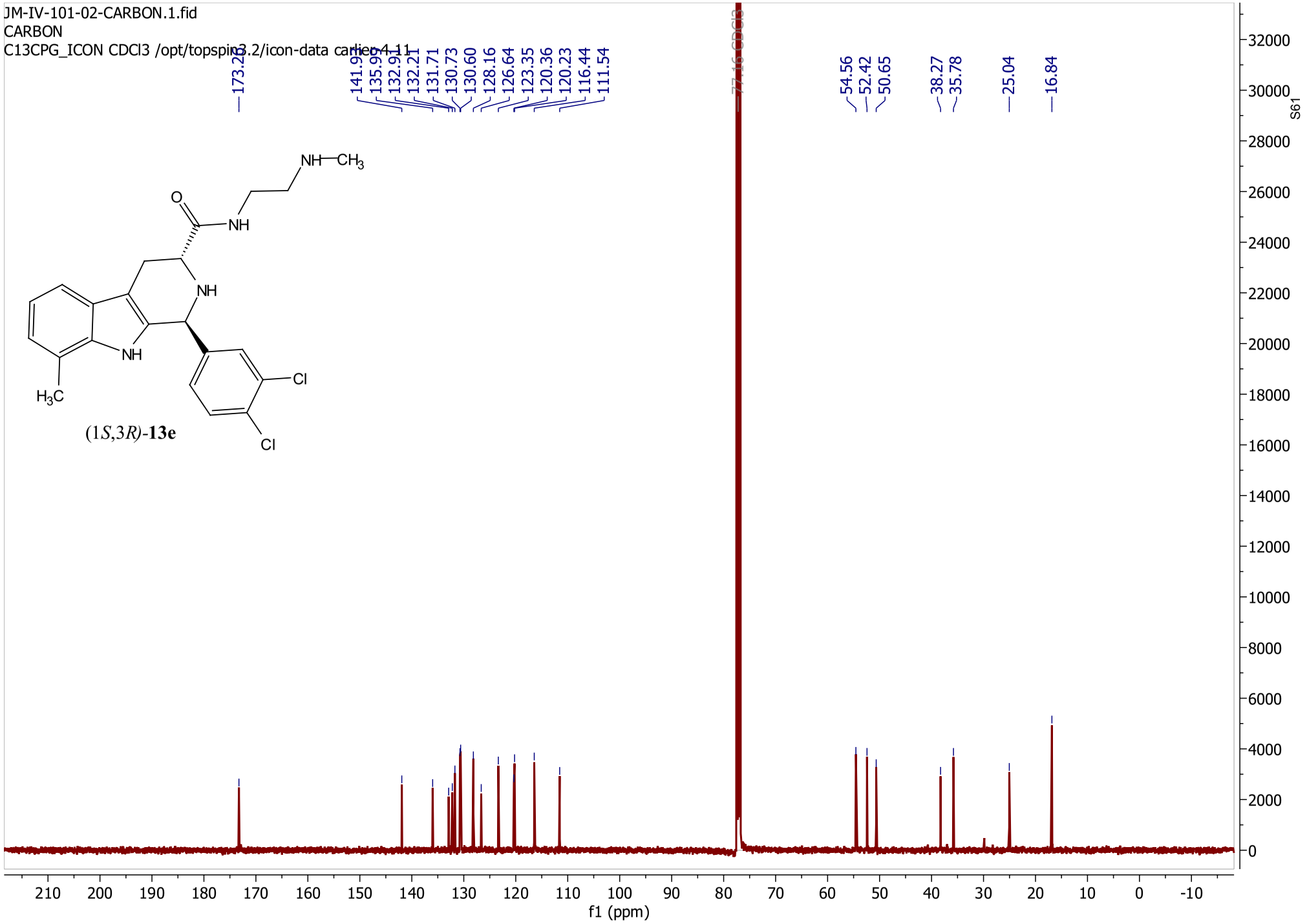

JM-IV-099-02.1.fid
PROTON
PROTONRO_ICON CDCl3 /opt/topspin3.2/
7.70 7.46 7.45 7.41 7.40 7.40 7.40 7.24 7.23 7.21 7.21 7.12 7.12 7.11 7.11 7.10 7.10 7.09 7.06 7.06 7.05 7.04 7.04 7.04 5.27
3.58 3.57 3.56 3.55 3.47 3.46 3.45 3.44 3.44 3.43 3.42 3.37 3.36 3.35 3.34 3.33 3.33 3.32 3.31 3.30 2.95 2.95 2.93 2.93 2.92 2.92 2.90 2.90 2.79 2.77 2.76 2.47 2.46
NH
CH3
O
NH
NH
NH
H3C
Cl
Cl
(1R,3S)-13e
CHCl3 (resid)
S56
0.89 1.06 2.16 0.97 2.06 1.11 1.00 1.04 1.07 2.28 1.12 1.95 6.00 1.20
f1 (ppm)

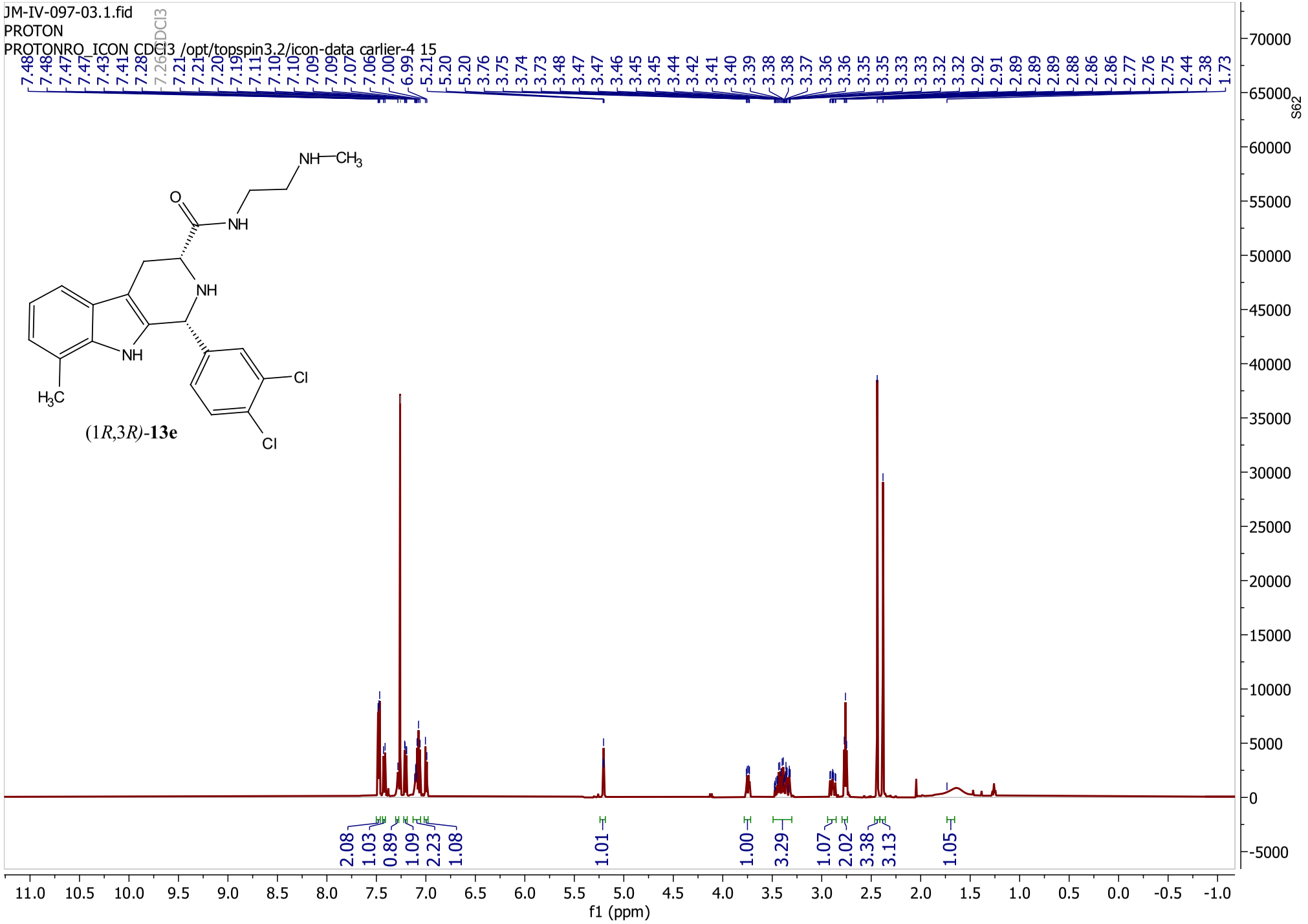

JM-IV-099-02-CARBON.1.fid
CARBON
C13CPG_ICON CDCl3 /opt/topspin3.2/icon-data carlier 4 10
173.15
141.92
135.99
132.92
132.22
131.70
130.73
130.61
128.15
126.65
123.36
120.36
120.24
116.45
111.56
77.16 CDCl3
54.57
52.42
50.71
38.39
35.90
25.05
16.84
NH—CH3
O
NH
NH
NH
H3C
Cl
Cl
(1R,3S)-13e
S57
f1 (ppm)

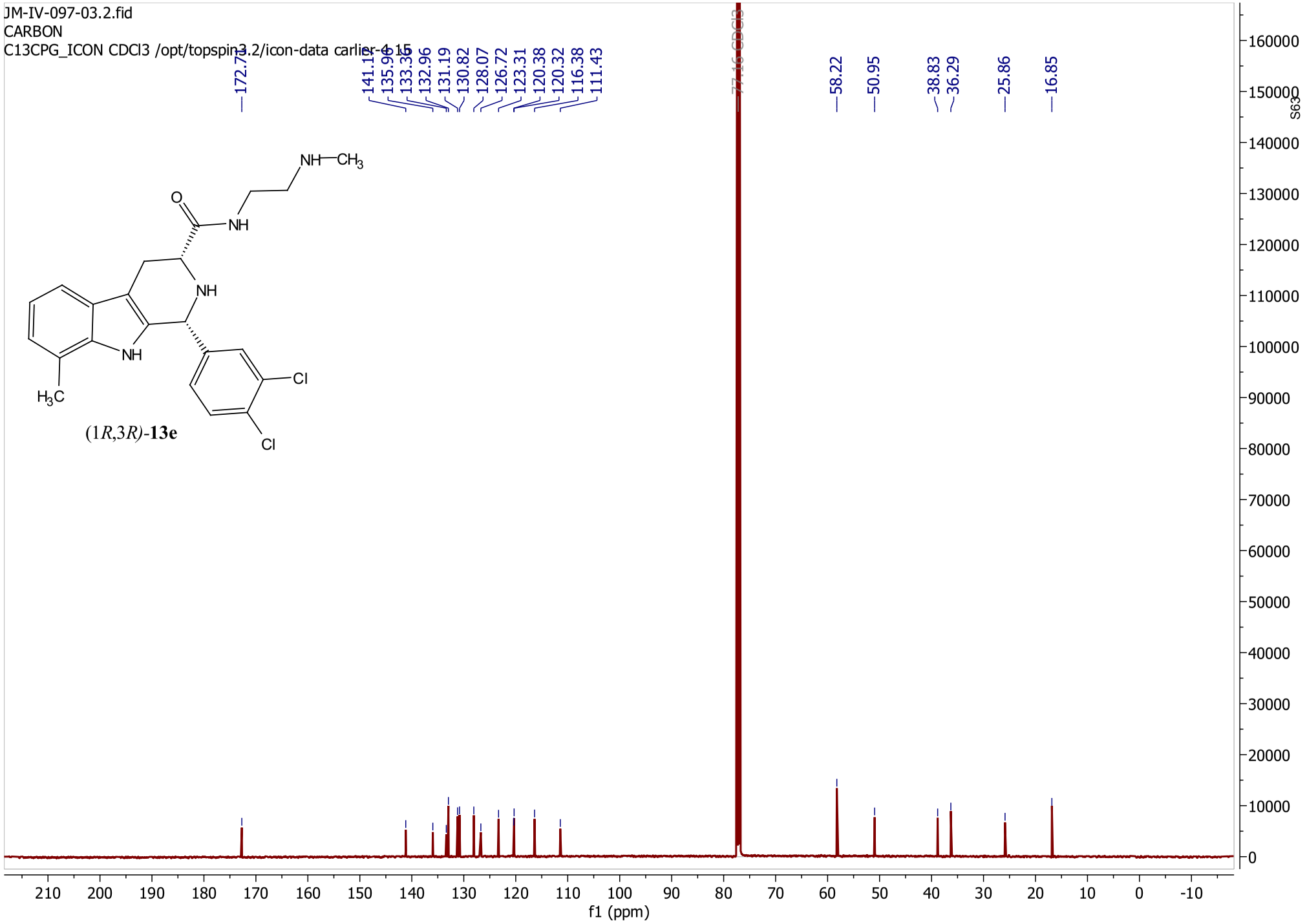

JM-IV-095-03.2.fid
PROTON
PROTONRO_ICON CDCl3 /opt/topspin3.2/icon-data carlier-4 13
CDCl3
7.77 7.40 7.40 7.38 7.36 7.26 7.12 7.12 7.11 7.10 7.10 7.07 7.05 7.05 7.04 6.99 6.99 6.99 6.98 6.98 6.98 5.02 3.83 3.82 3.81 3.80 3.63 3.61 3.28 3.28 3.28 3.27 3.25 3.25 3.24 3.24 3.08 3.07 3.06 3.01 2.98 2.96 2.63 2.36 1.74
NH
CH3
O
NH
NH
NH
H3C
Cl
Cl
(1S,3S)-13e
0.95 1.10 2.08 2.03 1.13 1.03 0.87 0.94 2.00 1.08 3.08 2.98 3.03
S58
f1 (ppm)

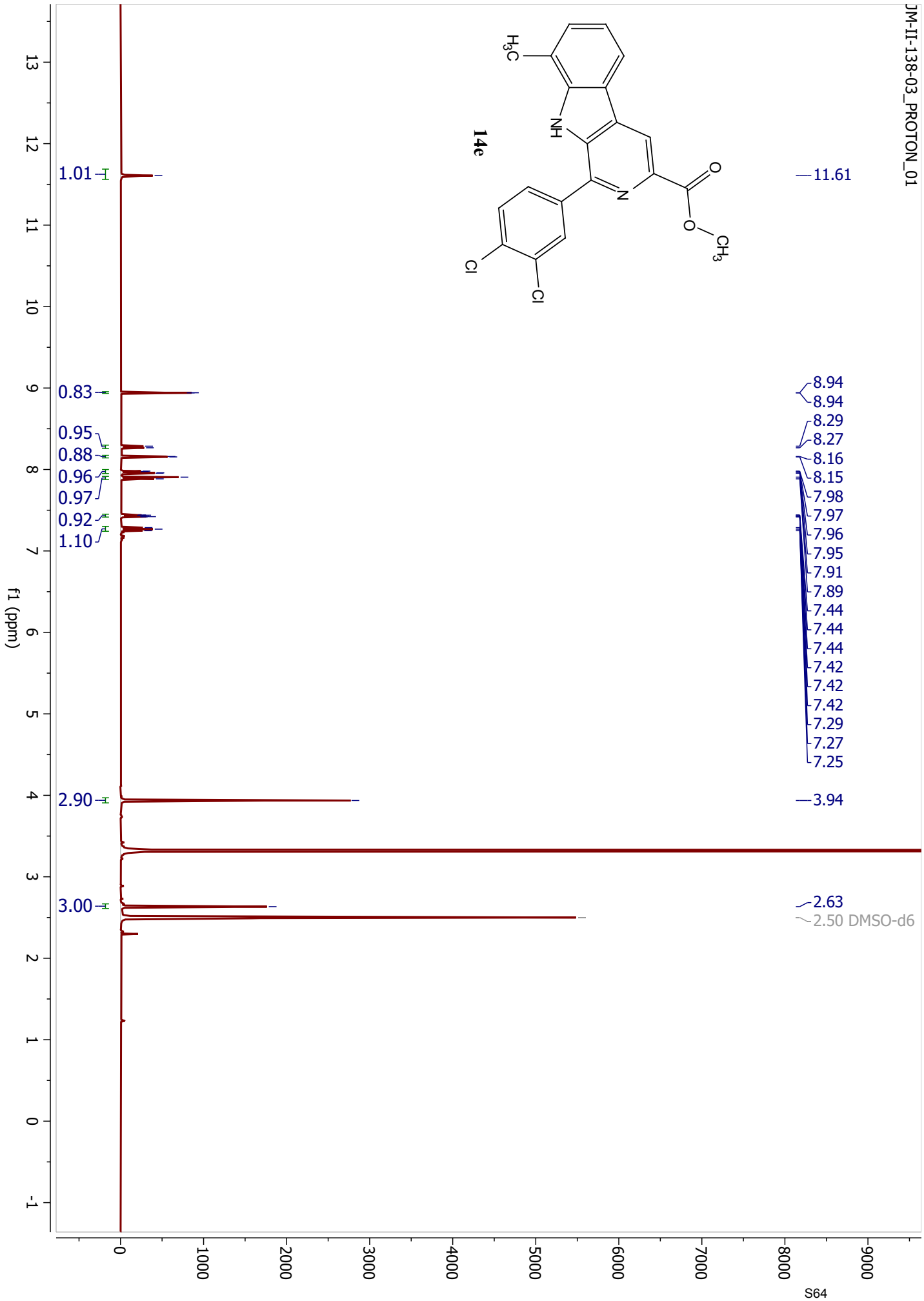

JM-IV-095-03-CARBON.1.fid
CARBON
C13CPG_ICON CDCl3 /opt/topspin3.2/icon-data cardiet-4 9
174.79
141.38
135.94
133.09
132.98
132.60
130.98
130.95
128.40
126.67
123.24
120.33
120.25
116.31
110.66
77.16 CDCl3
58.29
57.57
49.27
35.75
33.50
25.72
16.86
NH
CH3
O
NH
NH
NH
Cl
Cl
H3C
(1S,3S)-13e
S59
f1 (ppm)

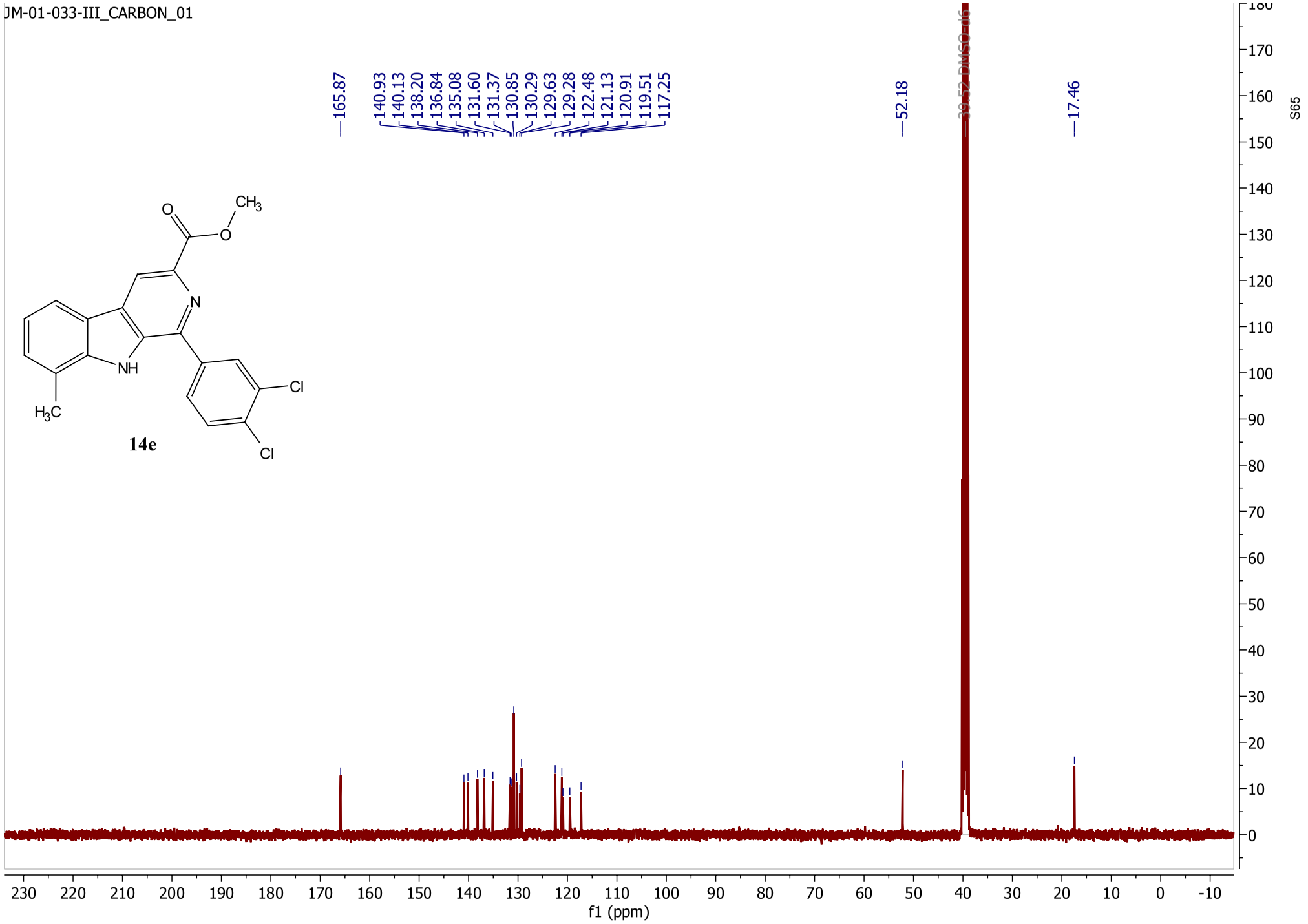

JM-IV-101-02.1.fid
PROTON
PROTONRO_ICON CDCl3 /opt/topspin3.2/icon-data carlier-4 14
CDCl3
7.64 7.44 7.43 7.42 7.39 7.38 7.37 7.26 7.25 7.24 7.23 7.10 7.09 7.09 7.09 7.09 7.08 7.08 7.07 7.07 7.07 7.03 7.03 7.03 7.02 7.02 7.01 5.24
3.56 3.55 3.54 3.53 3.48 3.48 3.47 3.46 3.45 3.45 3.44 3.34 3.33 3.32 3.31 3.28 3.27 2.94 2.93 2.92 2.91 2.90 2.90 2.88 2.88 2.79 2.78 2.76 2.46 2.46 2.43 2.14
NH—CH3
O
NH
NH
NH
H3C
Cl
Cl
(1S,3R)-13e
0.93 1.11 2.16 0.83 2.18 1.07 1.00 1.06 1.16 2.23 1.07 2.19 3.02 3.07 1.50
f1 (ppm)
S60


JM-IV-101-02-CARBON.1.fid
CARBON
C13CPG_ICON CDCl3 /opt/topspin3.2/icon-data carlier 4 11
173.20
141.95
135.99
132.91
132.21
131.71
130.73
130.60
128.16
126.64
123.35
120.36
120.23
116.44
111.54
77.16 CDCl3
54.56
52.42
50.65
38.27
35.78
25.04
16.84
NH—CH3
O
NH
NH
NH
H3C
Cl
Cl
(1S,3R)-13e
S61
f1 (ppm)

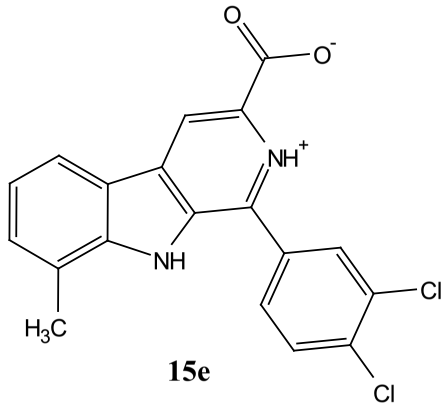

JM-IV-097-03.1.fid
PROTON
PROTONRO_ICON CDCl3 /opt/topspin3.2/icon-data carlier-4 15
7.48 7.48 7.47 7.47 7.43 7.41 7.28 7.26 CDCl3 7.21 7.21 7.20 7.19 7.11 7.10 7.10 7.09 7.09 7.07 7.06 7.00 6.99 5.21 5.20 5.20 3.76 3.75 3.74 3.73 3.48 3.47 3.47 3.46 3.45 3.45 3.44 3.42 3.41 3.40 3.39 3.38 3.38 3.37 3.36 3.36 3.35 3.35 3.33 3.33 3.32 3.32 2.92 2.91 2.89 2.89 2.89 2.88 2.86 2.86 2.77 2.76 2.75 2.44 2.38 1.73
S62
NH—CH3
O
NH
NH
NH
H3C
Cl
Cl
(1R,3R)-13e
2.08 1.03 0.89 1.09 2.23 1.08 1.01 1.00 3.29 1.07 2.02 3.38 3.13 1.05
f1 (ppm)


JM-IV-097-03.2.fid
CARBON
C13CPG_ICON CDCl3 /opt/topspin3.2/icon-data carlier-4 15
172.77
141.12
135.96
133.36
132.96
131.19
130.82
128.07
126.72
123.31
120.38
120.32
116.38
111.43
77.16 CDCl3
58.22
50.95
38.83
36.29
25.86
16.85
NH—CH3
O
NH
NH
NH
H3C
Cl
Cl
(1R,3R)-13e
S63
f1 (ppm)

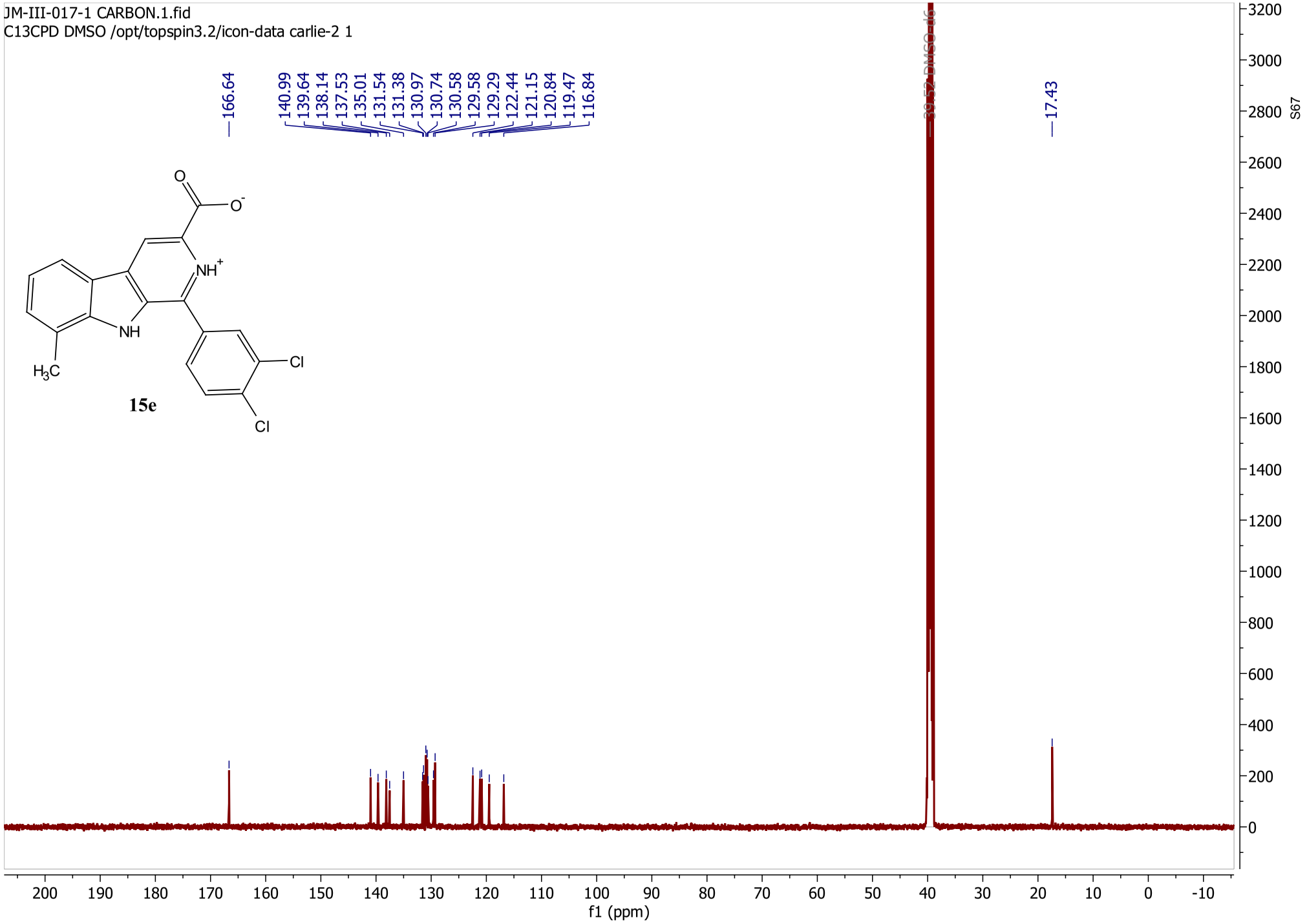

JM-II-138-03_PROTON_01
14e
H3C
NH
N
O
O
CH3
Cl
Cl
1.01
0.83
0.95
0.88
0.96
0.97
0.92
1.10
2.90
3.00
11.61
8.94
8.94
8.29
8.27
8.16
8.15
7.98
7.97
7.96
7.95
7.91
7.89
7.44
7.44
7.44
7.42
7.42
7.42
7.29
7.27
7.25
3.94
2.63
2.50 DMSO-d6
f1 (ppm)
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
0
1000
2000
3000
4000
5000
6000
7000
8000
9000

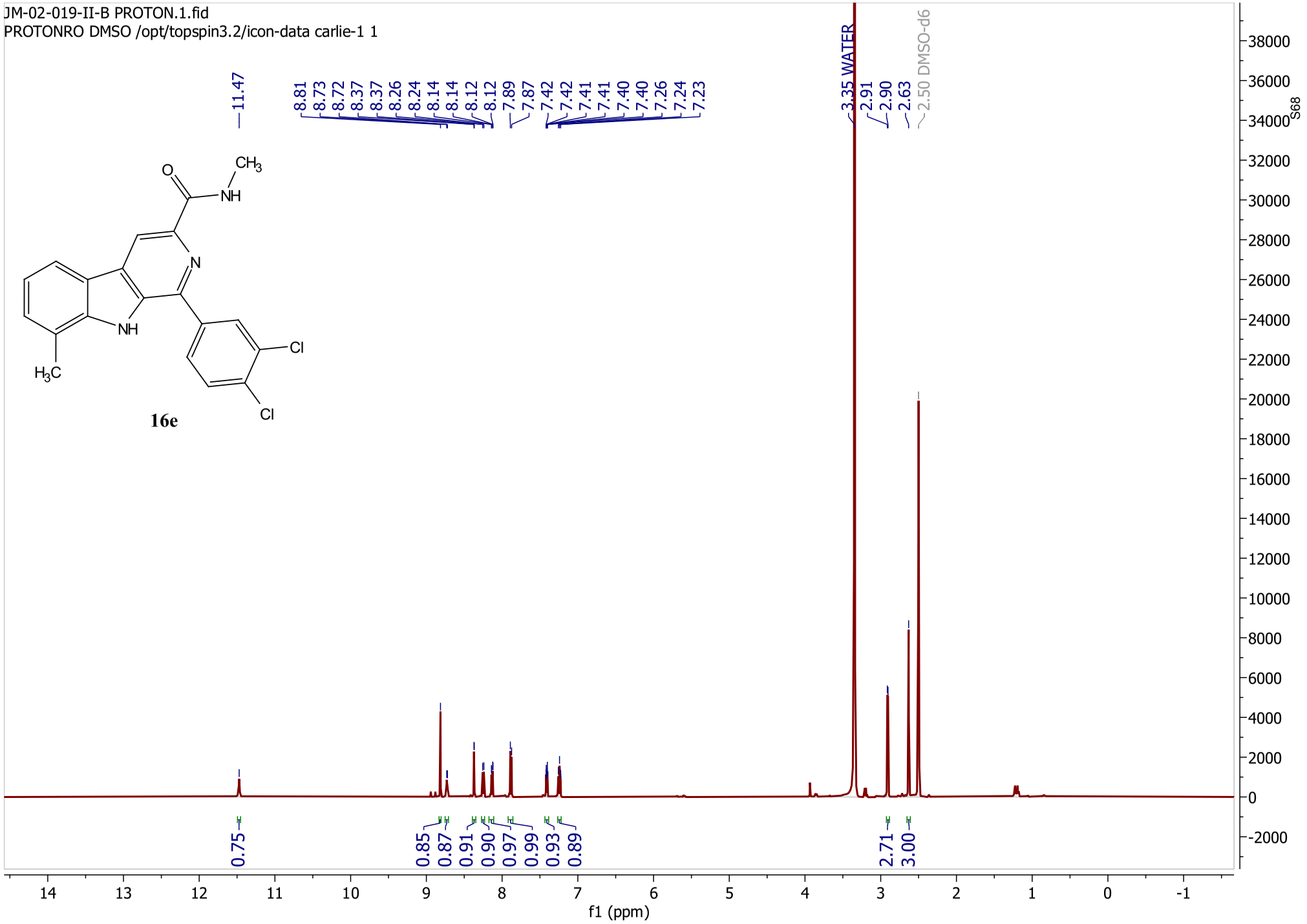

JM-01-033-III_CARBON_01
165.87
140.93
140.13
138.20
136.84
135.08
131.60
131.37
130.85
130.29
129.63
129.28
122.48
121.13
120.91
119.51
117.25
52.18
39.52 DMSO-d6
17.46
O
O
CH3
N
NH
H3C
Cl
Cl
14e
S65
f1 (ppm)

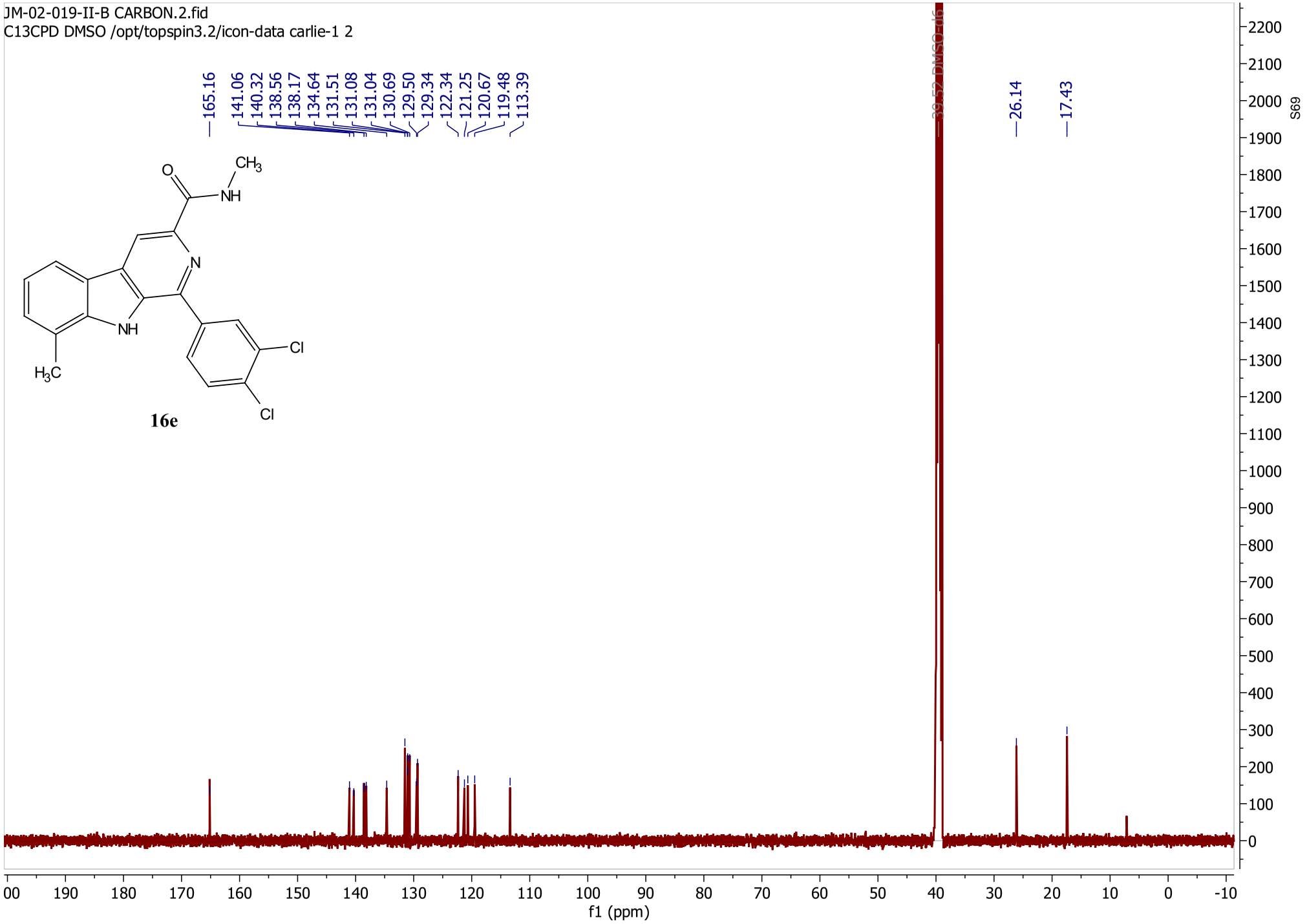
JM-III-017-1.1.fid
PROTONRO DMSO /opt/topspin3.2/icon-data carlie-2 1

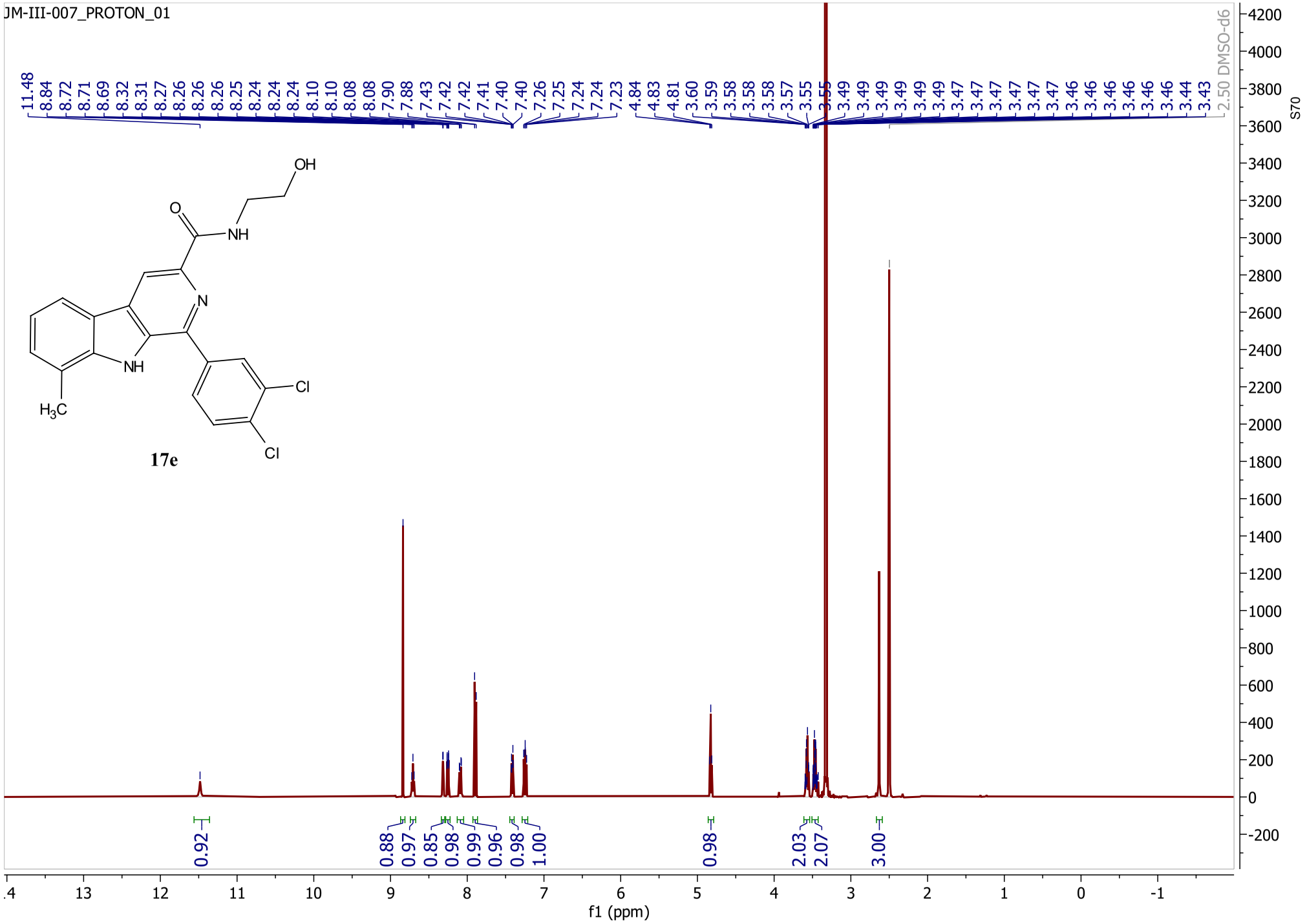


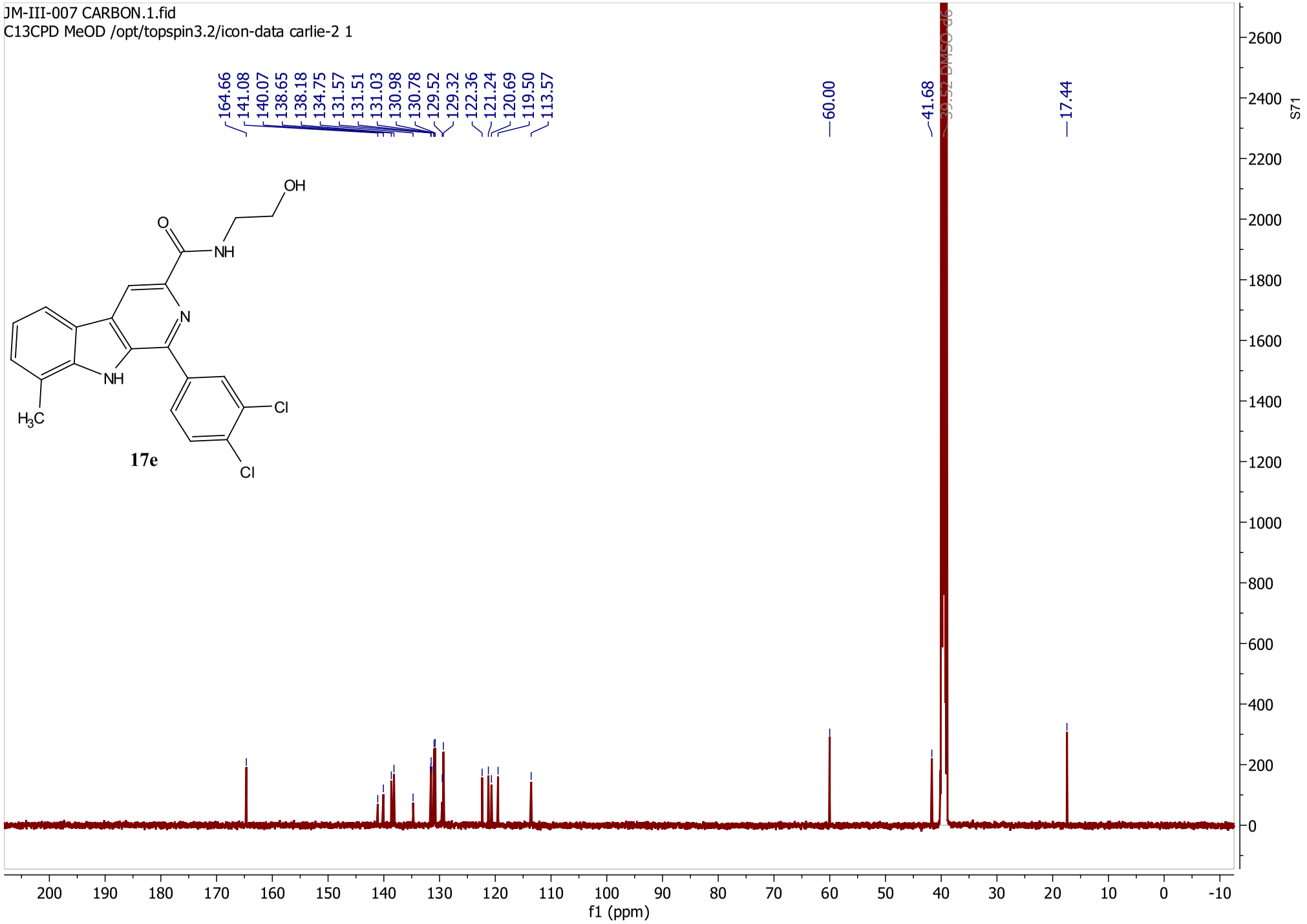
15e

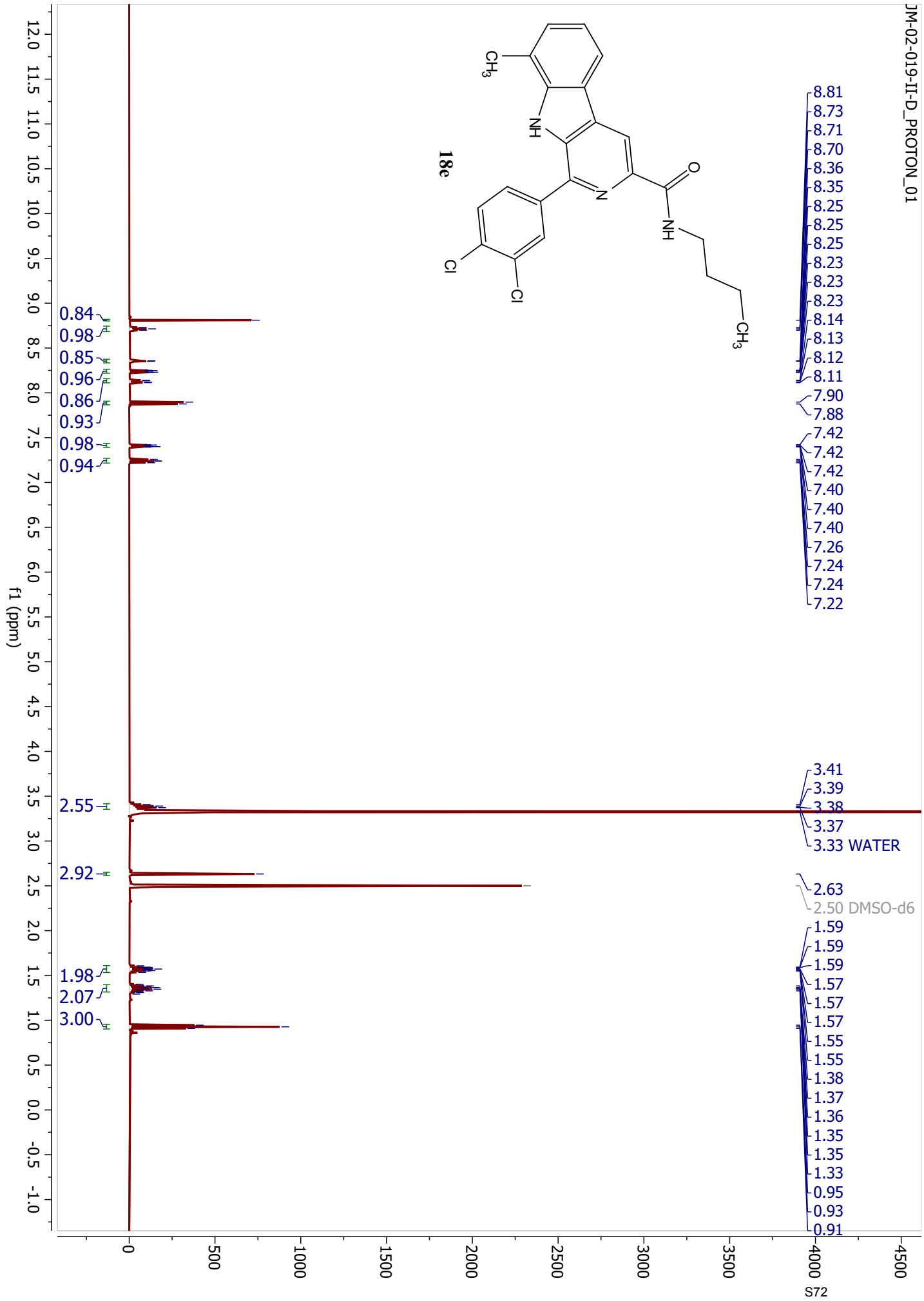

JM-III-017-1 CARBON.1.fid
C13CPD DMSO /opt/topspin3.2/icon-data carlie-2 1
166.64
140.99
139.64
138.14
137.53
135.01
131.54
131.38
130.97
130.74
130.58
129.58
129.29
122.44
121.15
120.84
119.47
116.84
39.52 DMSO-d6
17.43
O
O-
NH+
NH
H3C
Cl
Cl
15e
S67
f1 (ppm)

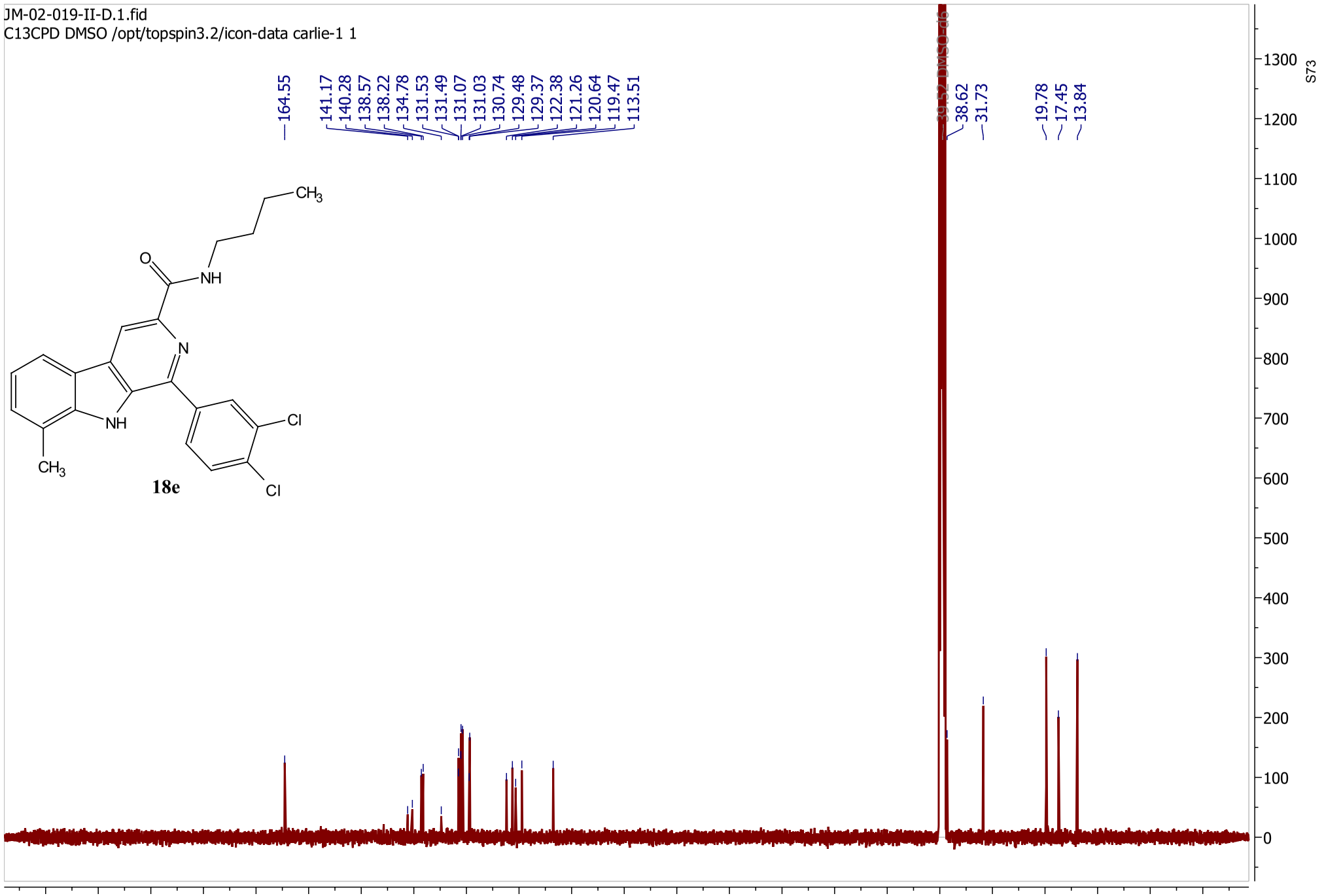

JM-02-019-II-B PROTON.1.fid
PROTONRO DMSO /opt/topspin3.2/icon-data carlie-1 1
11.47
8.81
8.73
8.72
8.37
8.37
8.26
8.24
8.14
8.14
8.12
8.12
7.89
7.87
7.42
7.42
7.41
7.41
7.40
7.40
7.26
7.24
7.23
3.35 WATER
2.91
2.90
2.63
2.50 DMSO-d6
S68
O
NH
CH3
N
NH
H3C
Cl
Cl
16e
0.75
0.85
0.87
0.91
0.90
0.97
0.99
0.93
0.89
2.71
3.00
f1 (ppm)

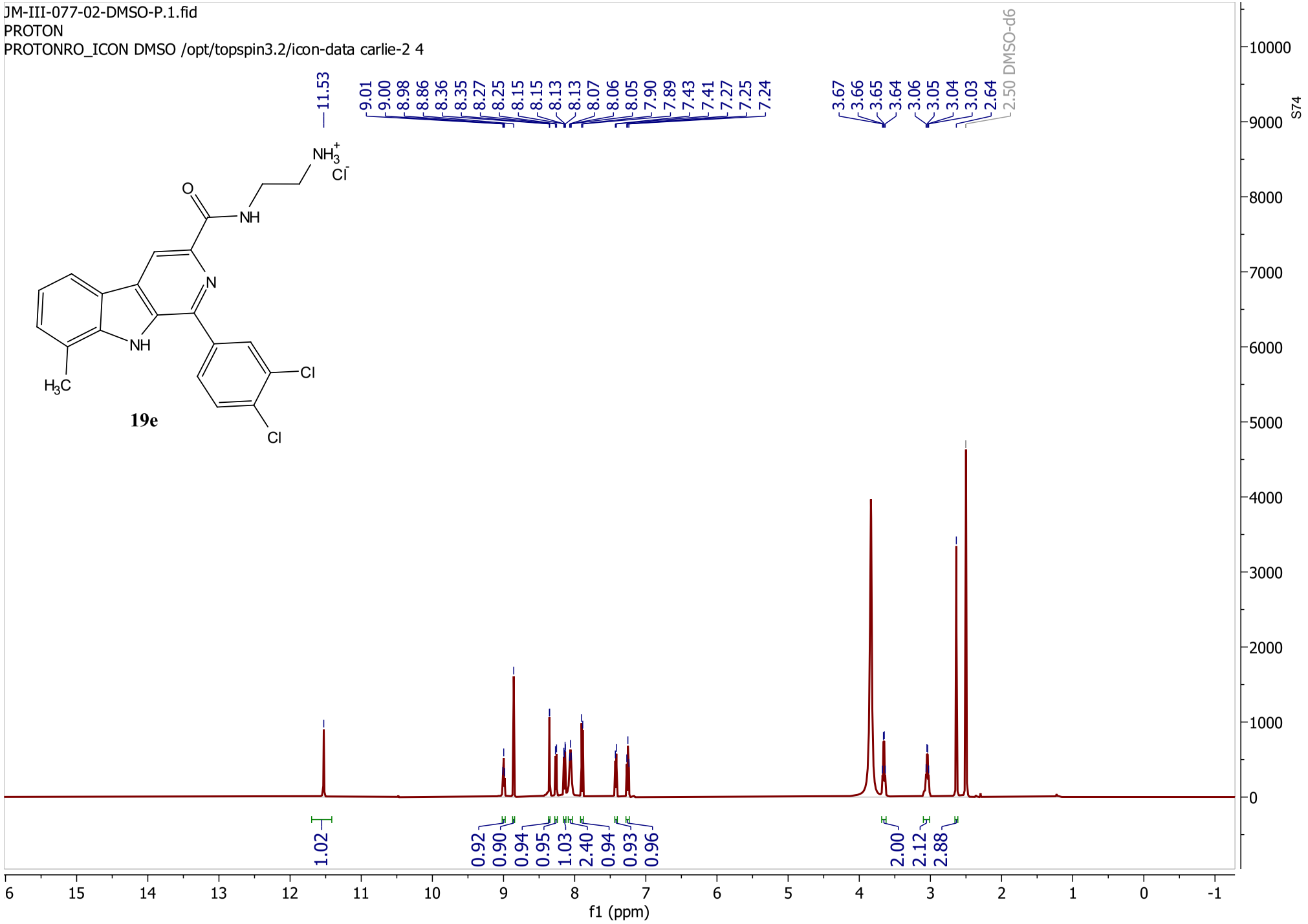

JM-02-019-II-B CARBON.2.fid
C13CPD DMSO /opt/topspin3.2/icon-data carlie-1 2
165.16
141.06
140.32
138.56
138.17
134.64
131.51
131.08
131.04
130.69
129.50
129.34
122.34
121.25
120.67
119.48
113.39
39.52 DMSO-d6
26.14
17.43
O
CH3
NH
N
NH
H3C
Cl
Cl
16e
S69
f1 (ppm)

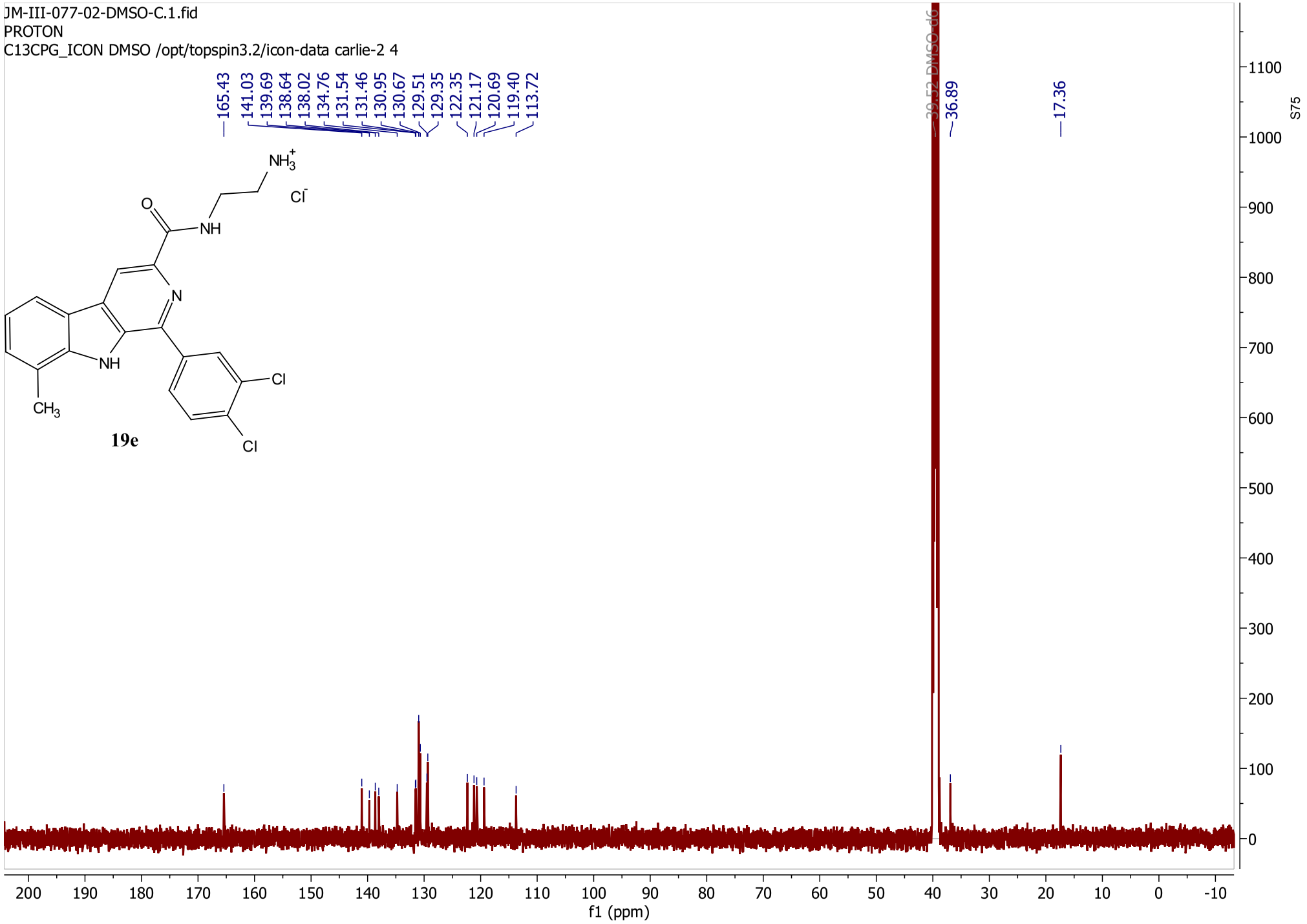

JM-III-007_PROTON_01
11.48
8.84
8.72
8.71
8.69
8.32
8.31
8.27
8.26
8.26
8.26
8.25
8.24
8.24
8.24
8.10
8.10
8.08
8.08
7.90
7.88
7.43
7.42
7.42
7.41
7.40
7.40
7.26
7.25
7.24
7.24
7.23
4.84
4.83
4.81
3.60
3.59
3.58
3.58
3.58
3.57
3.55
3.55
3.49
3.49
3.49
3.49
3.49
3.49
3.47
3.47
3.47
3.47
3.47
3.47
3.46
3.46
3.46
3.46
3.46
3.46
3.44
3.43
2.50 DMSO-d6
S70
OH
O
NH
N
NH
H3C
Cl
Cl
17e
0.92
0.88
0.97
0.85
0.98
0.99
0.96
0.98
1.00
0.98
2.03
2.07
3.00
f1 (ppm)

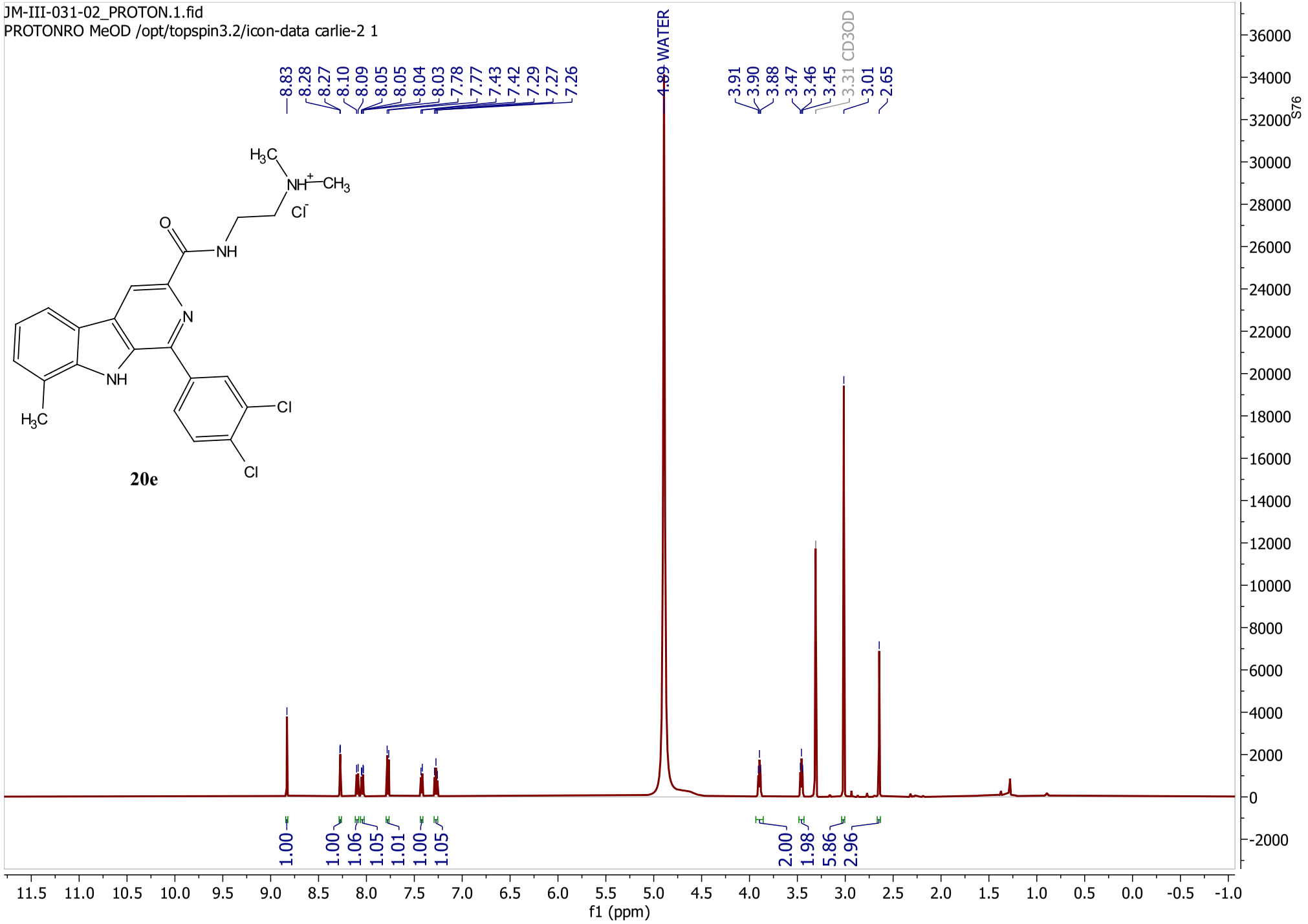

JM-III-007 CARBON.1.fid
C13CPD MeOD /opt/topspin3.2/icon-data carlie-2 1
164.66
141.08
140.07
138.65
138.18
134.75
131.57
131.51
131.03
130.98
130.78
129.52
129.32
122.36
121.24
120.69
119.50
113.57
60.00
41.68
39.52 DMSO-d6
17.44
OH
O
NH
N
NH
H3C
Cl
Cl
17e
S71
f1 (ppm)

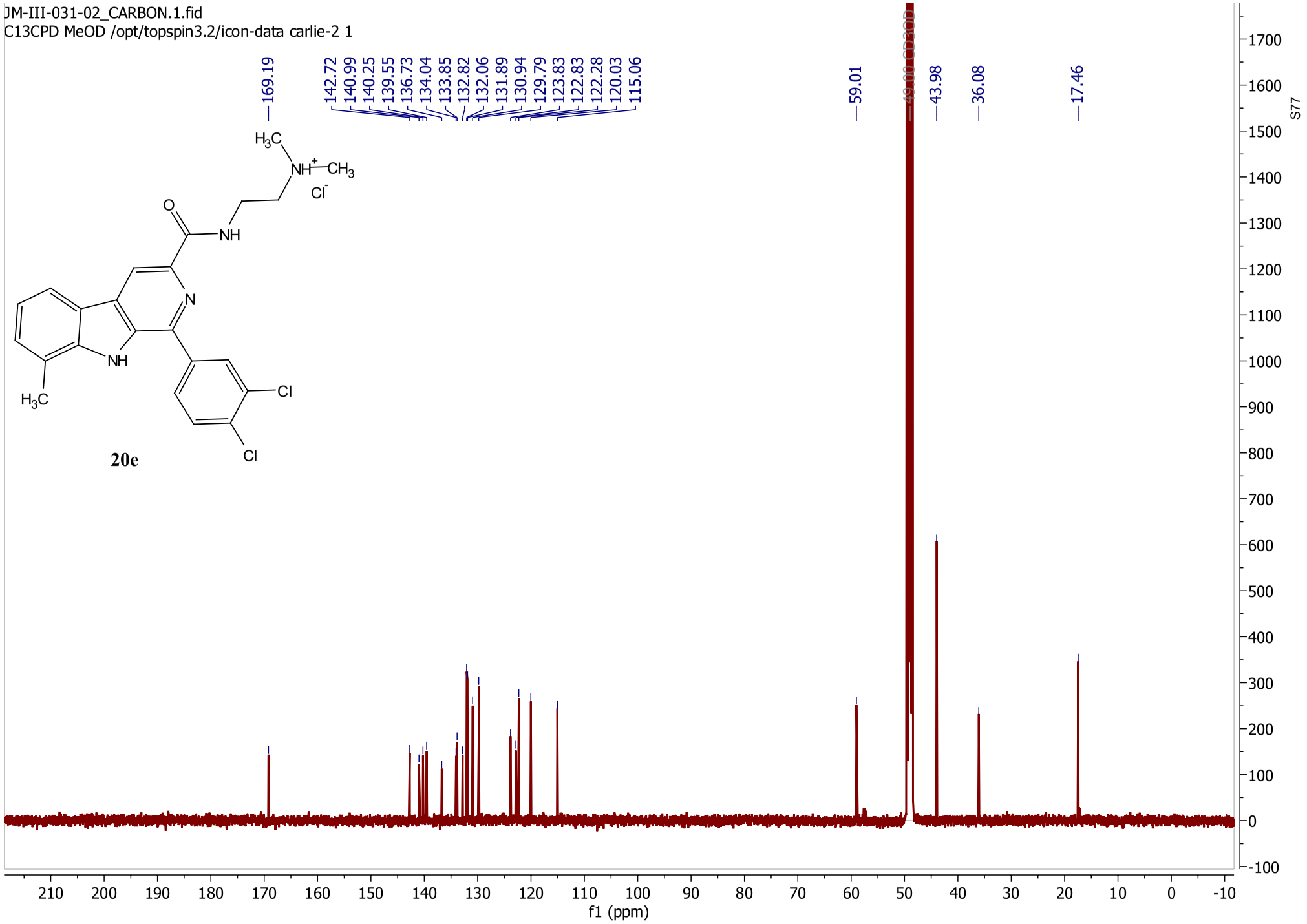

JM-02-019-II-D_PROTON_01
18e
f1 (ppm)
0.84
0.98
0.85
0.96
0.86
0.93
0.98
0.94
2.55
2.92
1.98
2.07
3.00
8.81
8.73
8.71
8.70
8.36
8.35
8.25
8.25
8.25
8.23
8.23
8.23
8.14
8.13
8.12
8.11
7.90
7.88
7.42
7.42
7.42
7.40
7.40
7.40
7.26
7.24
7.24
7.22
3.41
3.39
3.38
3.37
3.33 WATER
2.63
2.50 DMSO-d6
1.59
1.59
1.59
1.57
1.57
1.57
1.55
1.55
1.38
1.37
1.36
1.35
1.35
1.33
0.95
0.93
0.91


JM-02-019-II-D.1.fid
C13CPD DMSO /opt/topspin3.2/icon-data carlie-1 1
164.55
141.17
140.28
138.57
138.22
134.78
131.53
131.49
131.07
131.03
130.74
129.48
129.37
122.38
121.26
120.64
119.47
113.51
39.52 DMSO-d6
38.62
31.73
19.78
17.45
13.84
CH3
O
NH
N
NH
CH3
Cl
Cl
18e
S73
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0

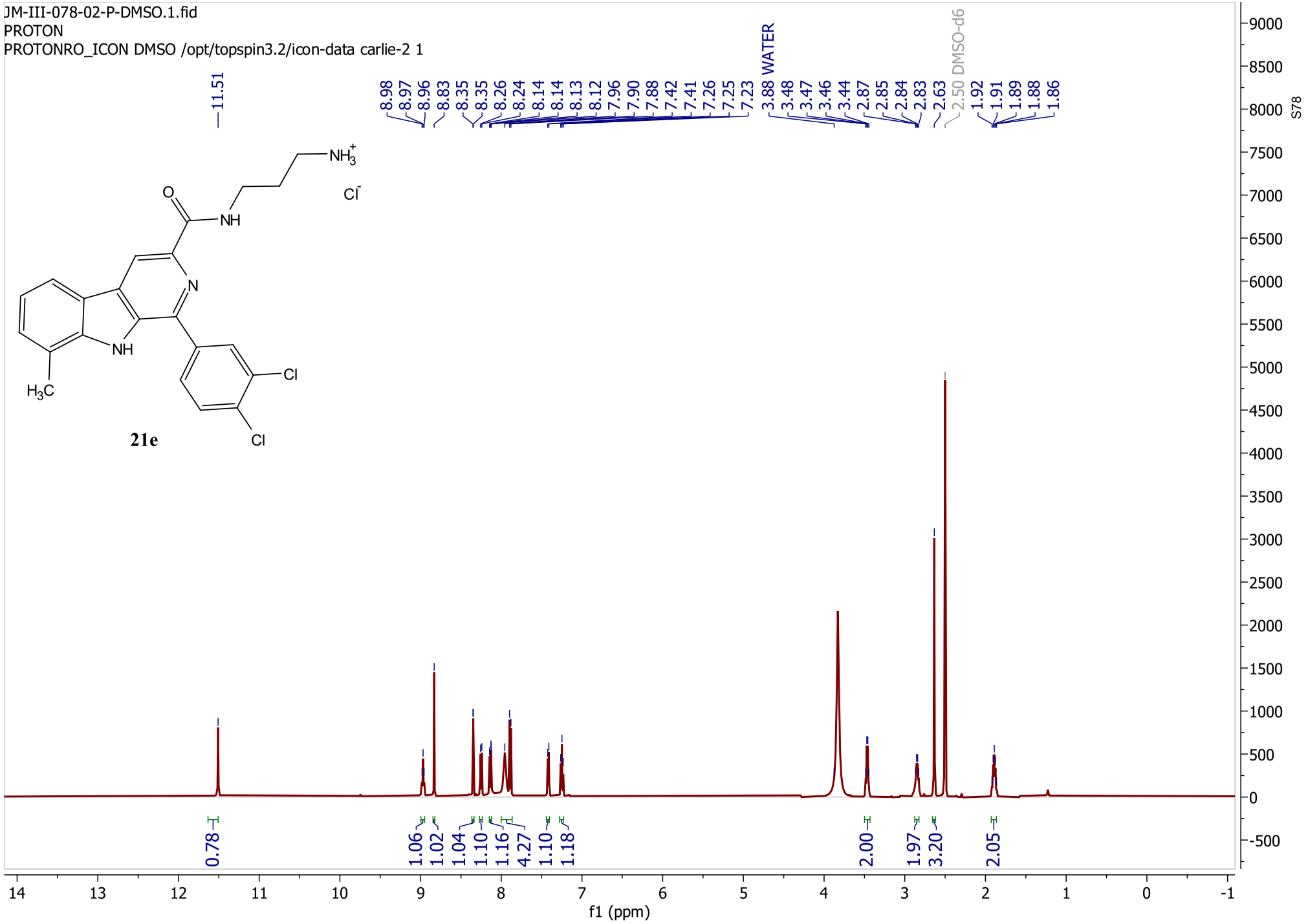

JM-III-077-02-DMSO-P.1.fid
PROTON
PROTONRO_ICON DMSO /opt/topspin3.2/icon-data carlie-2 4
11.53
9.01
9.00
8.98
8.86
8.36
8.35
8.27
8.25
8.15
8.15
8.13
8.13
8.07
8.06
8.05
7.90
7.89
7.43
7.41
7.27
7.25
7.24
3.67
3.66
3.65
3.64
3.06
3.05
3.04
3.03
2.64
2.50 DMSO-d6
NH3+
Cl-
O
NH
N
NH
H3C
Cl
Cl
19e
1.02
0.92
0.90
0.94
0.95
1.03
2.40
0.94
0.93
0.96
2.00
2.12
2.88
f1 (ppm)
S74

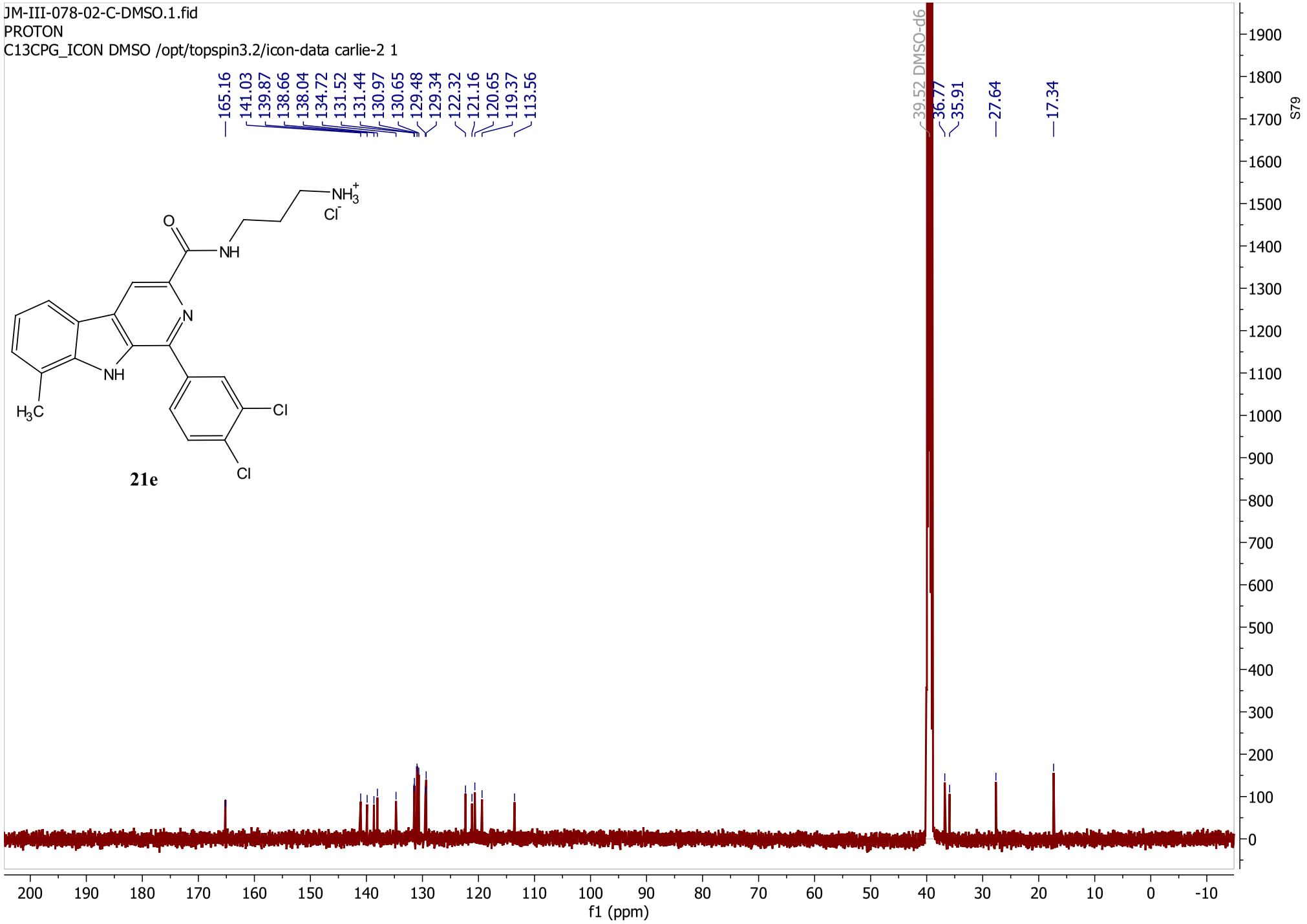

JM-III-077-02-DMSO-C.1.fid
PROTON
C13CPG_ICON DMSO /opt/topspin3.2/icon-data carlie-2 4
165.43
141.03
139.69
138.64
138.02
134.76
131.54
131.46
130.95
130.67
129.51
129.35
122.35
121.17
120.69
119.40
113.72
39.52 DMSO-d6
36.89
17.36
NH3+
Cl-
O
NH
N
NH
CH3
Cl
Cl
19e
S75
f1 (ppm)

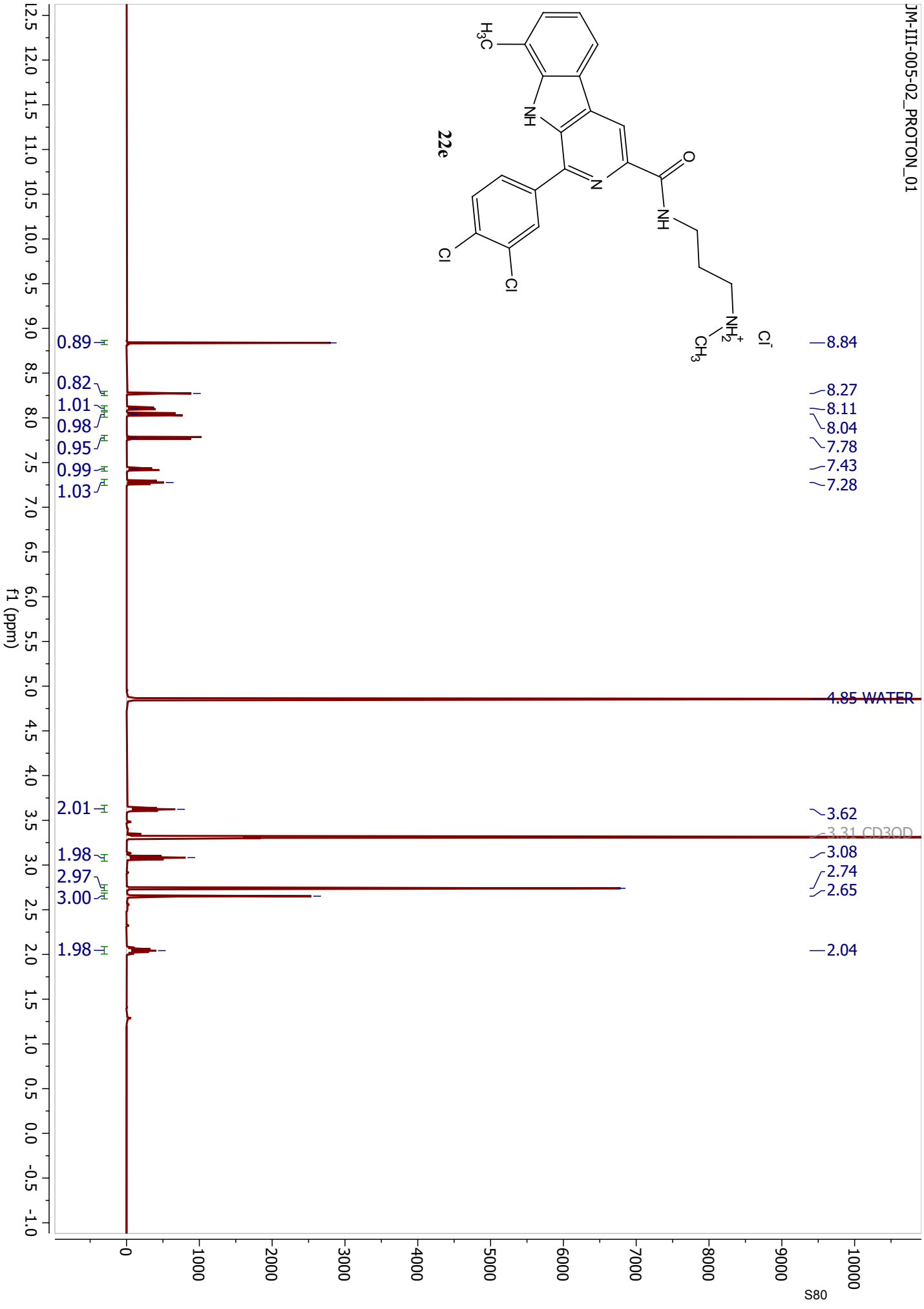

JM-III-031-02_PROTON.1.fid
PROTONRO MeOD /opt/topspin3.2/icon-data carlie-2 1
8.83
8.28
8.27
8.10
8.09
8.05
8.05
8.04
8.03
7.78
7.77
7.43
7.42
7.29
7.27
7.26
4.89 WATER
3.91
3.90
3.88
3.47
3.46
3.45
3.31 CD3OD
3.01
2.65
S76
H3C
NH+
CH3
Cl-
O
NH
N
NH
H3C
Cl
Cl
20e
1.00
1.00
1.06
1.05
1.01
1.00
1.05
2.00
1.98
5.86
2.96
f1 (ppm)

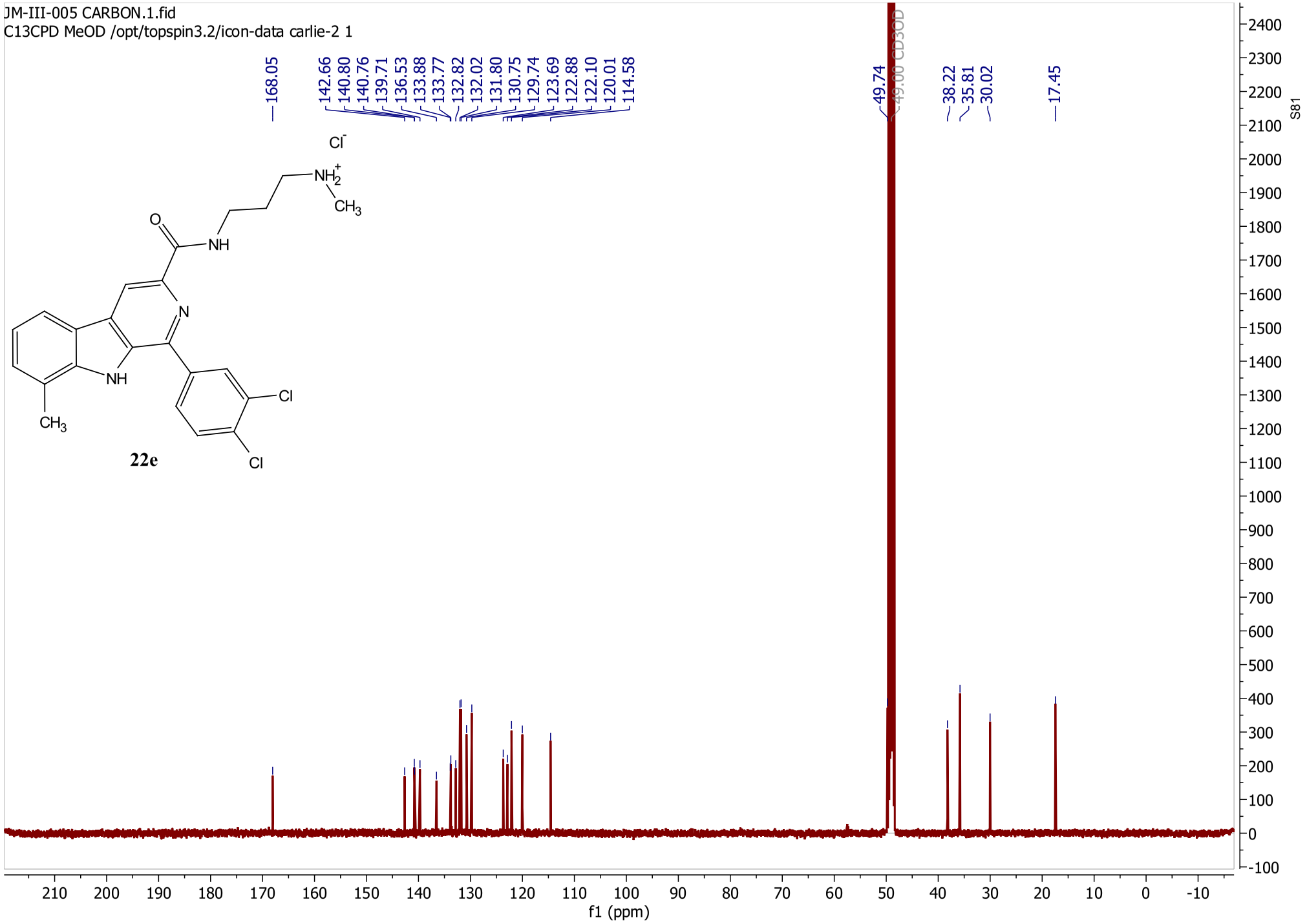

JM-III-031-02_CARBON.1.fid
C13CPD MeOD /opt/topspin3.2/icon-data carlie-2 1
169.19
142.72
140.99
140.25
139.55
136.73
134.04
133.85
132.82
132.06
131.89
130.94
129.79
123.83
122.83
122.28
120.03
115.06
59.01
49.00 CD3OD
43.98
36.08
17.46
S77
f1 (ppm)

20e

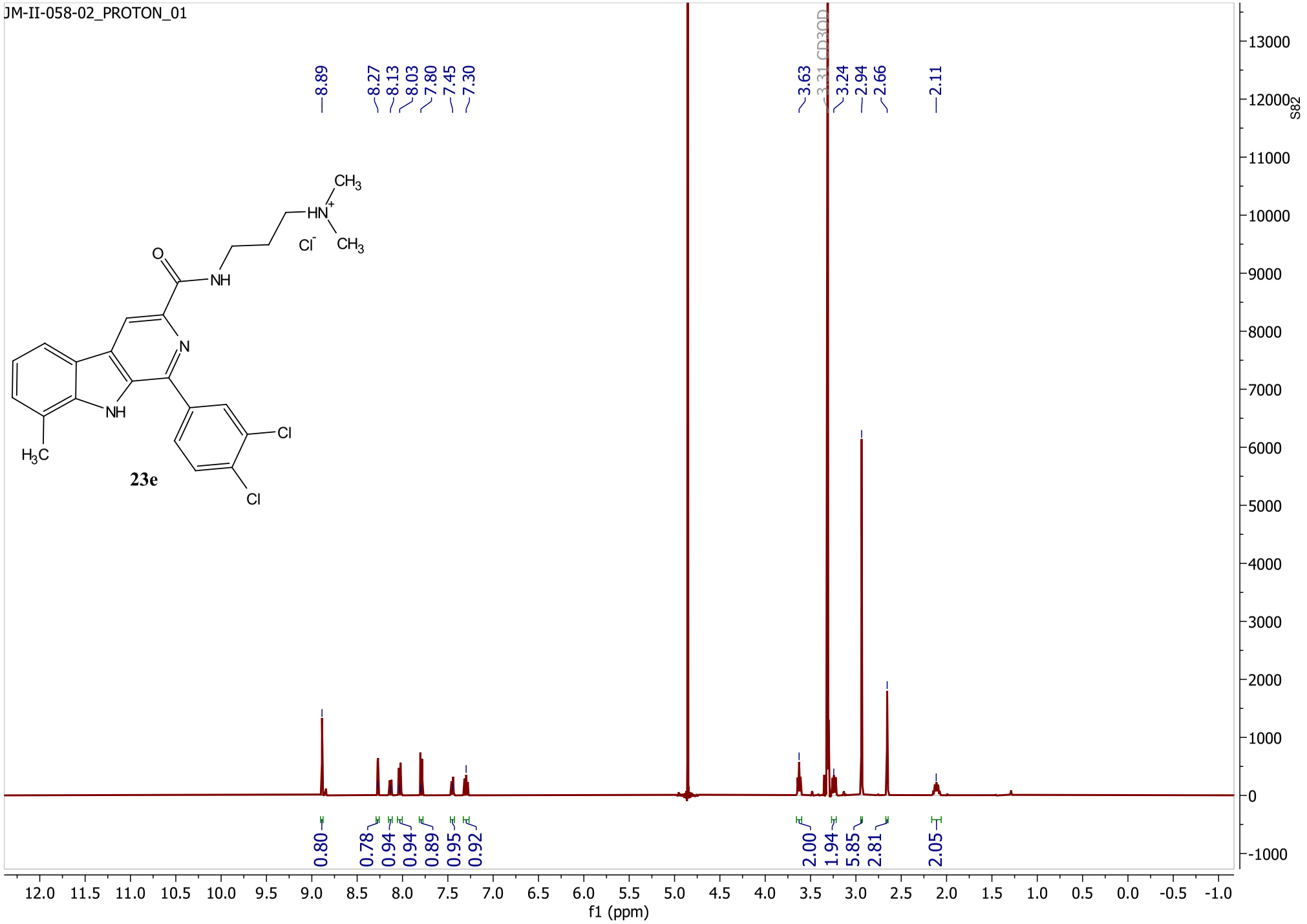

JM-III-078-02-P-DMSO.1.fid
PROTON
PROTONRO_ICON DMSO /opt/topspin3.2/icon-data carlie-2 1
11.51
8.98
8.97
8.96
8.83
8.35
8.35
8.26
8.24
8.14
8.14
8.13
8.12
7.96
7.90
7.88
7.42
7.41
7.26
7.25
7.23
3.88 WATER
3.48
3.47
3.46
3.44
2.87
2.85
2.84
2.83
2.63
2.50 DMSO-d6
1.92
1.91
1.89
1.88
1.86
NH3+
Cl-
O
NH
N
NH
H3C
Cl
Cl
21e
0.78
1.06
1.02
1.04
1.10
1.16
4.27
1.10
1.18
2.00
1.97
3.20
2.05
f1 (ppm)
S78

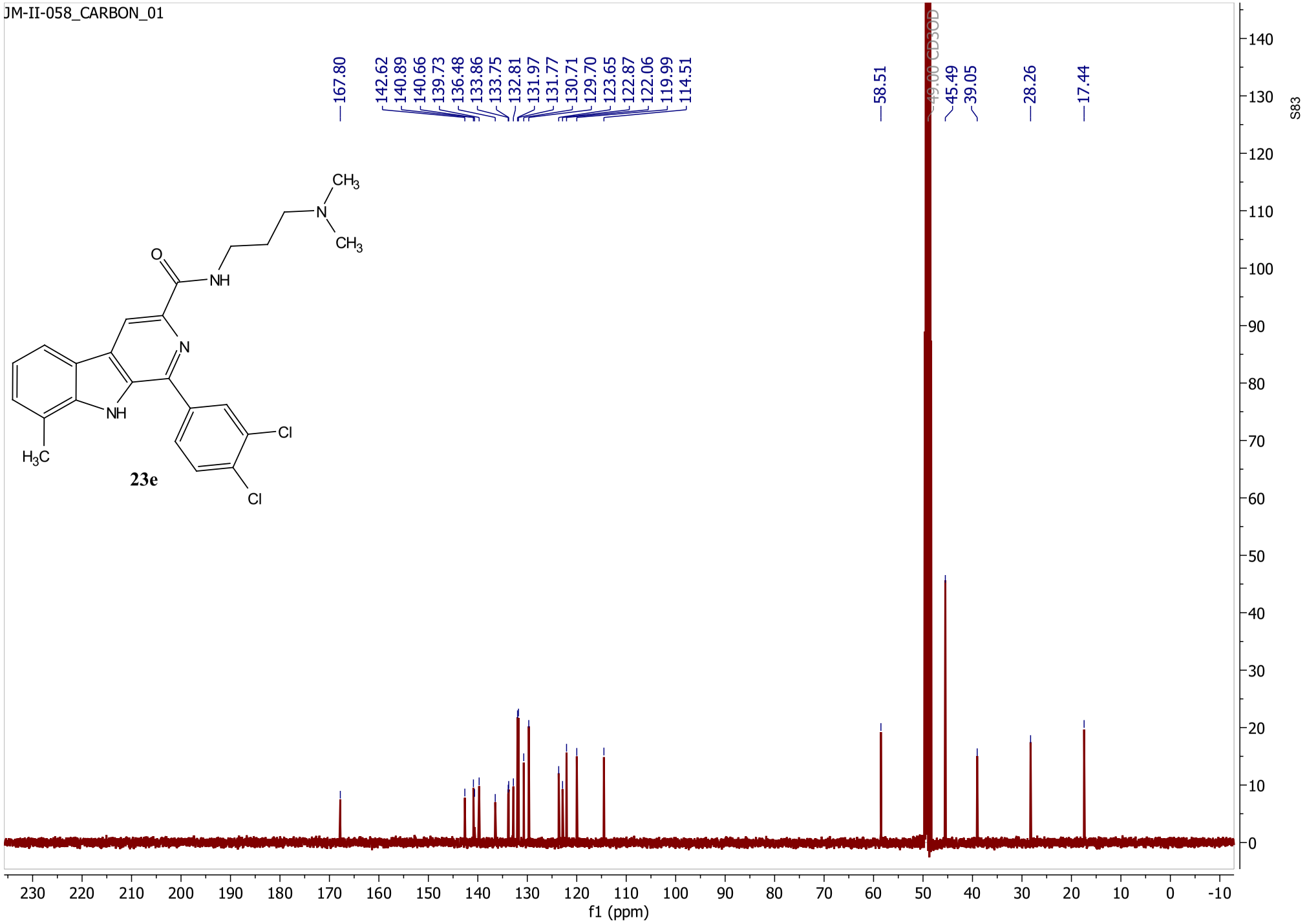

JM-III-078-02-C-DMSO.1.fid
PROTON
C13CPG_ICON DMSO /opt/topspin3.2/icon-data carlie-2 1
165.16
141.03
139.87
138.66
138.04
134.72
131.52
131.44
130.97
130.65
129.48
129.34
122.32
121.16
120.65
119.37
113.56
39.52 DMSO-d6
36.77
35.91
27.64
17.34
S79
21e
f1 (ppm)

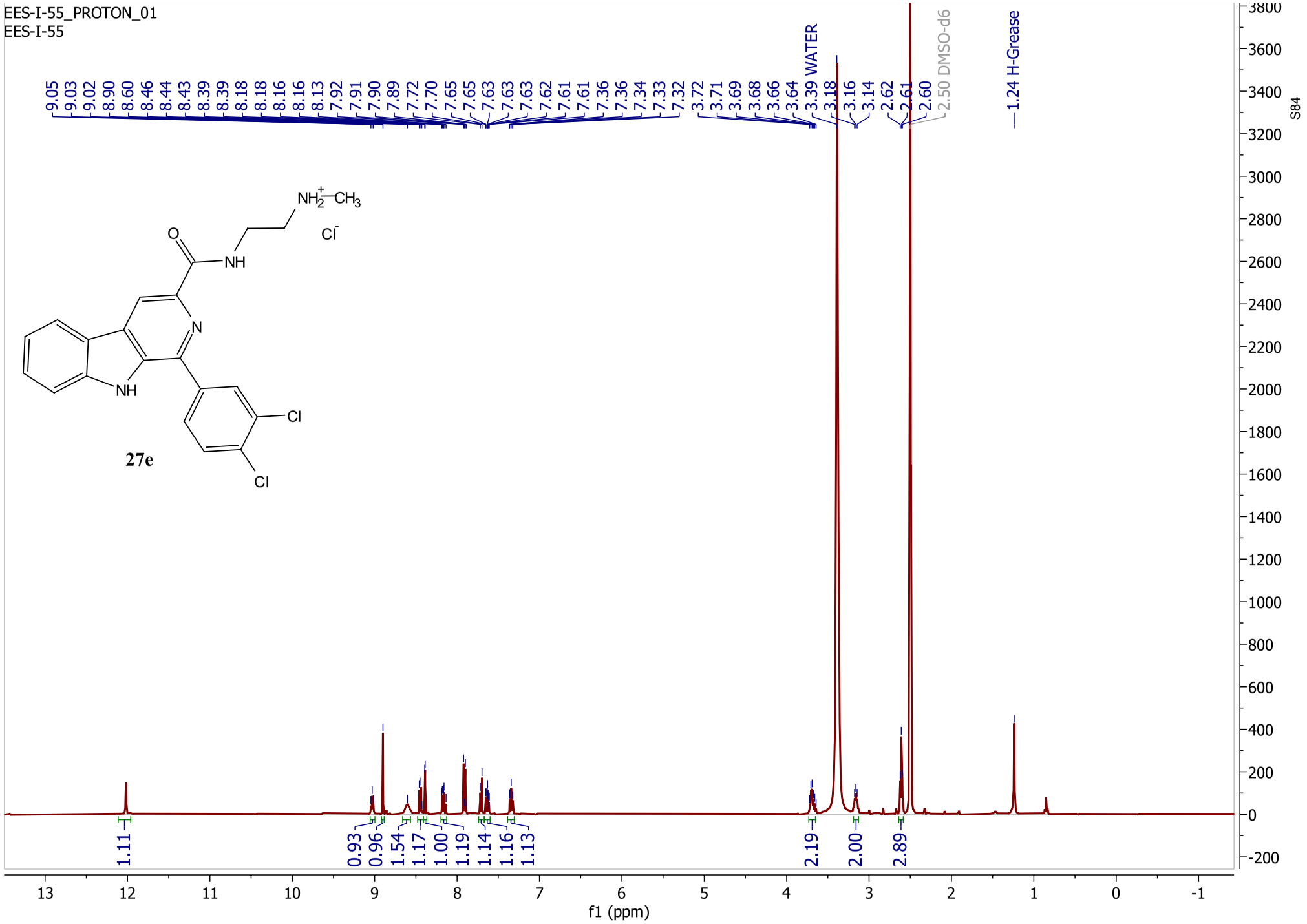

JM-III-005-02_PROTON_01
22e
H3C
NH
N
O
NH
Cl
Cl
NH2+
CH3
Cl-
0.89
0.82
1.01
0.98
0.95
0.99
1.03
2.01
1.98
2.97
3.00
1.98
8.84
8.27
8.11
8.04
7.78
7.43
7.28
4.85 WATER
3.62
3.31 CD3OD
3.08
2.74
2.65
2.04
f1 (ppm)
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
0 1000 2000 3000 4000 5000 6000 7000 8000 9000 10000

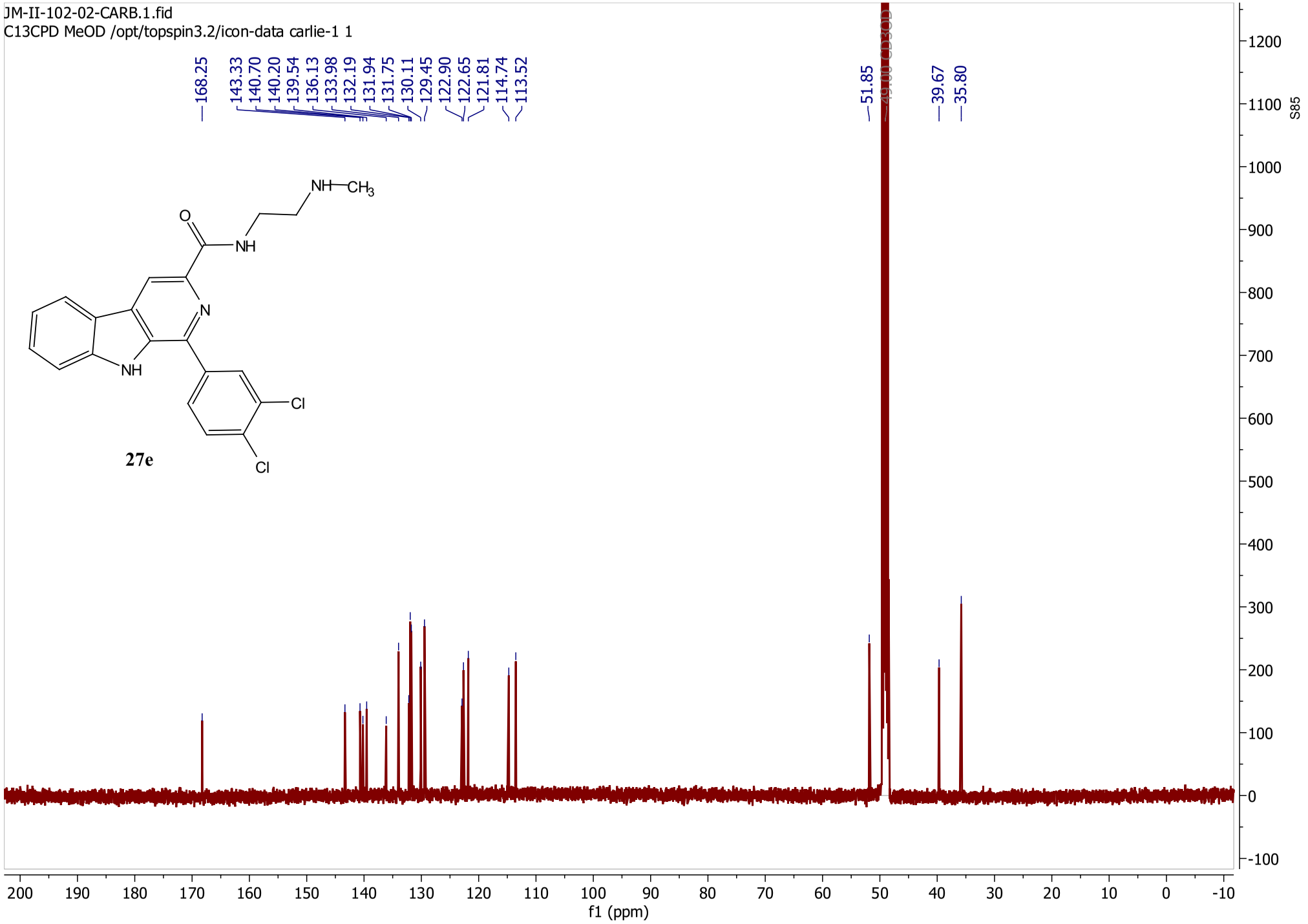

JM-III-005 CARBON.1.fid
C13CPD MeOD /opt/topspin3.2/icon-data carlie-2 1
168.05
142.66
140.80
140.76
139.71
136.53
133.88
133.77
132.82
132.02
131.80
130.75
129.74
123.69
122.88
122.10
120.01
114.58
49.74
49.00 CD3OD
38.22
35.81
30.02
17.45
S81
f1 (ppm)

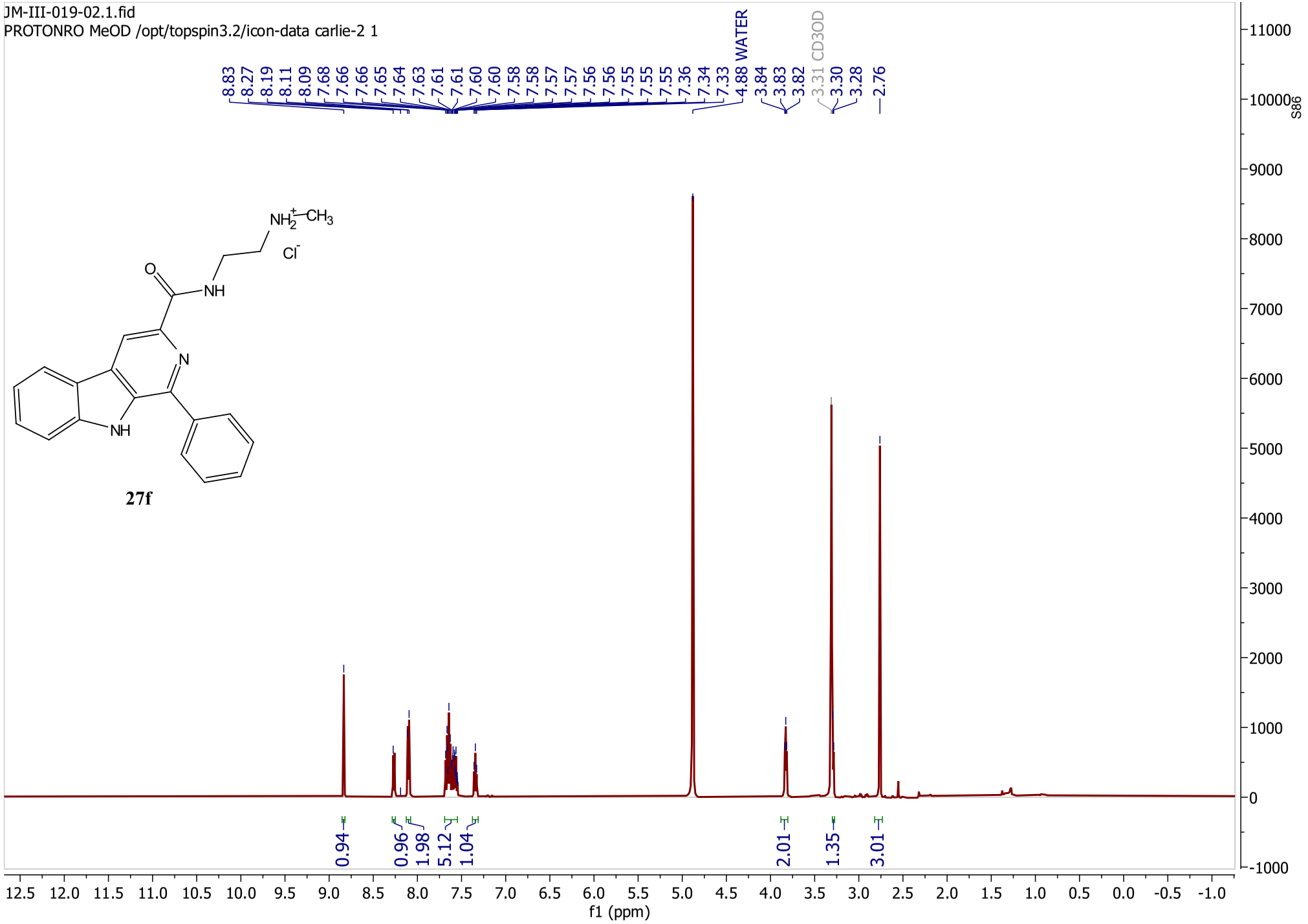
22e

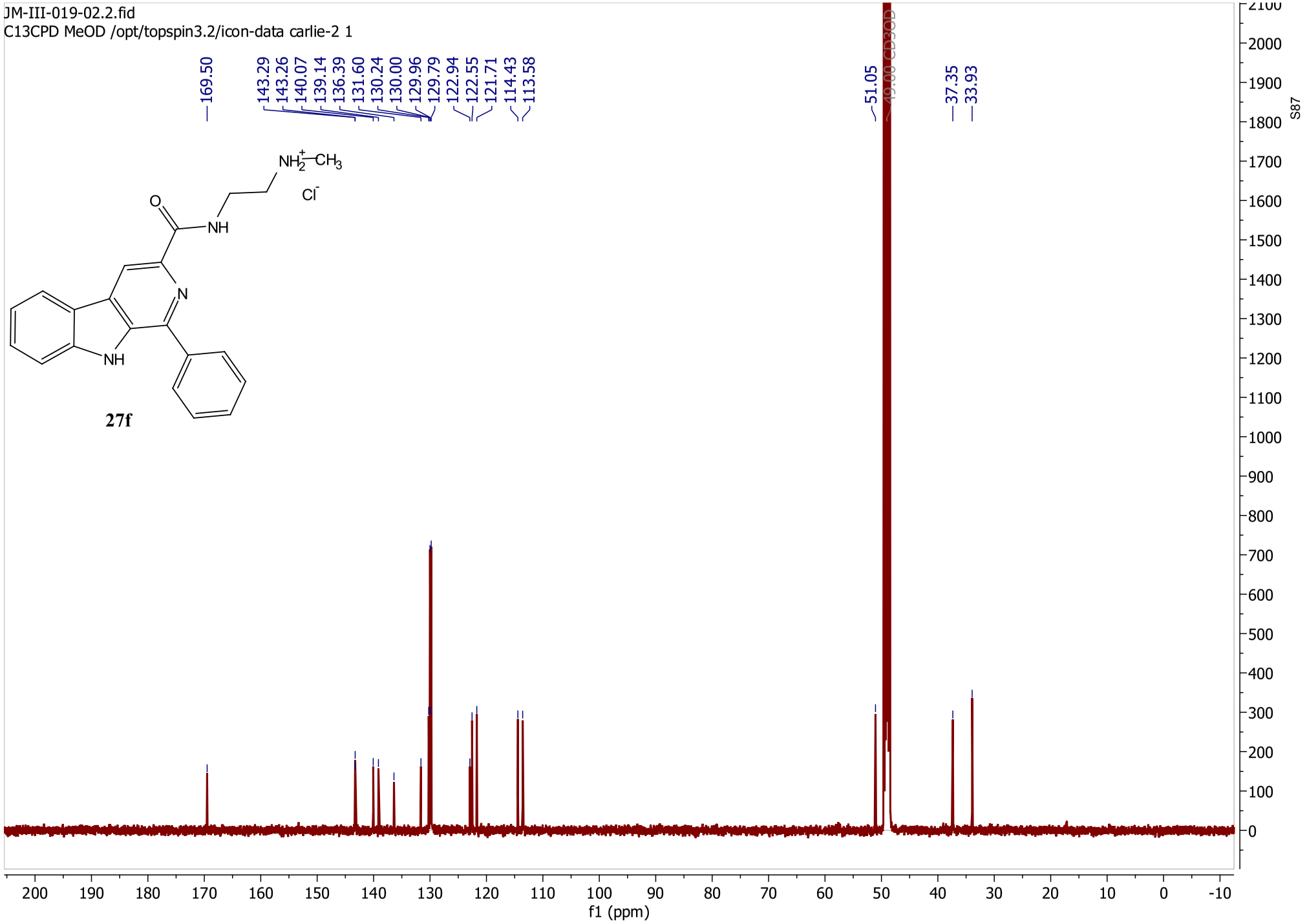

JM-II-058-02_PROTON_01
8.89
8.27
8.13
8.03
7.80
7.45
7.30
3.63
3.31 CD3OD
3.24
2.94
2.66
2.11
S82
23e
0.80
0.78
0.94
0.94
0.89
0.95
0.92
2.00
1.94
5.85
2.81
2.05
f1 (ppm)

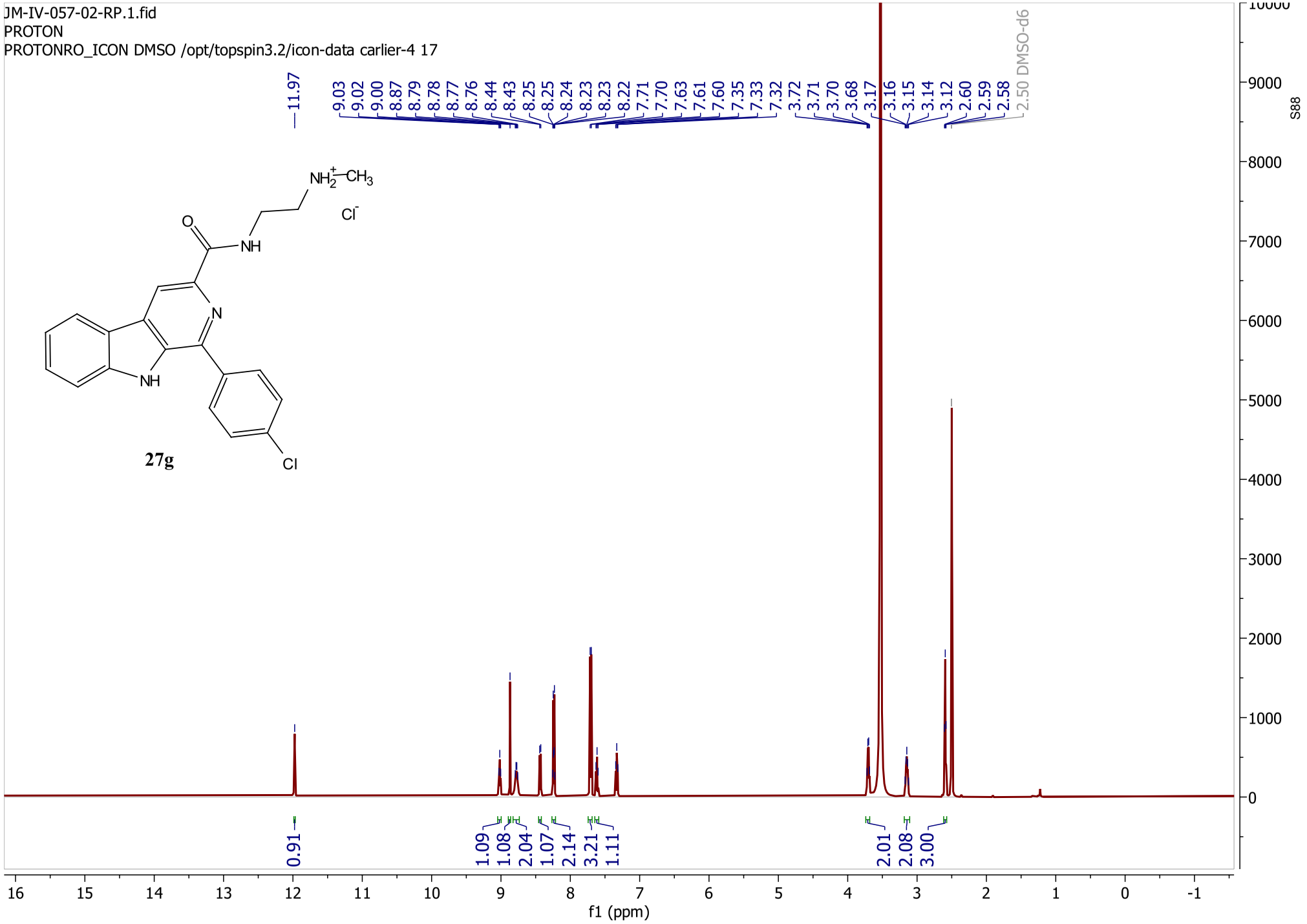

JM-II-058_CARBON_01
167.80
142.62
140.89
140.66
139.73
136.48
133.86
133.75
132.81
131.97
131.77
130.71
129.70
123.65
122.87
122.06
119.99
114.51
58.51
49.00 CD3OD
45.49
39.05
28.26
17.44
S83
23e
f1 (ppm)

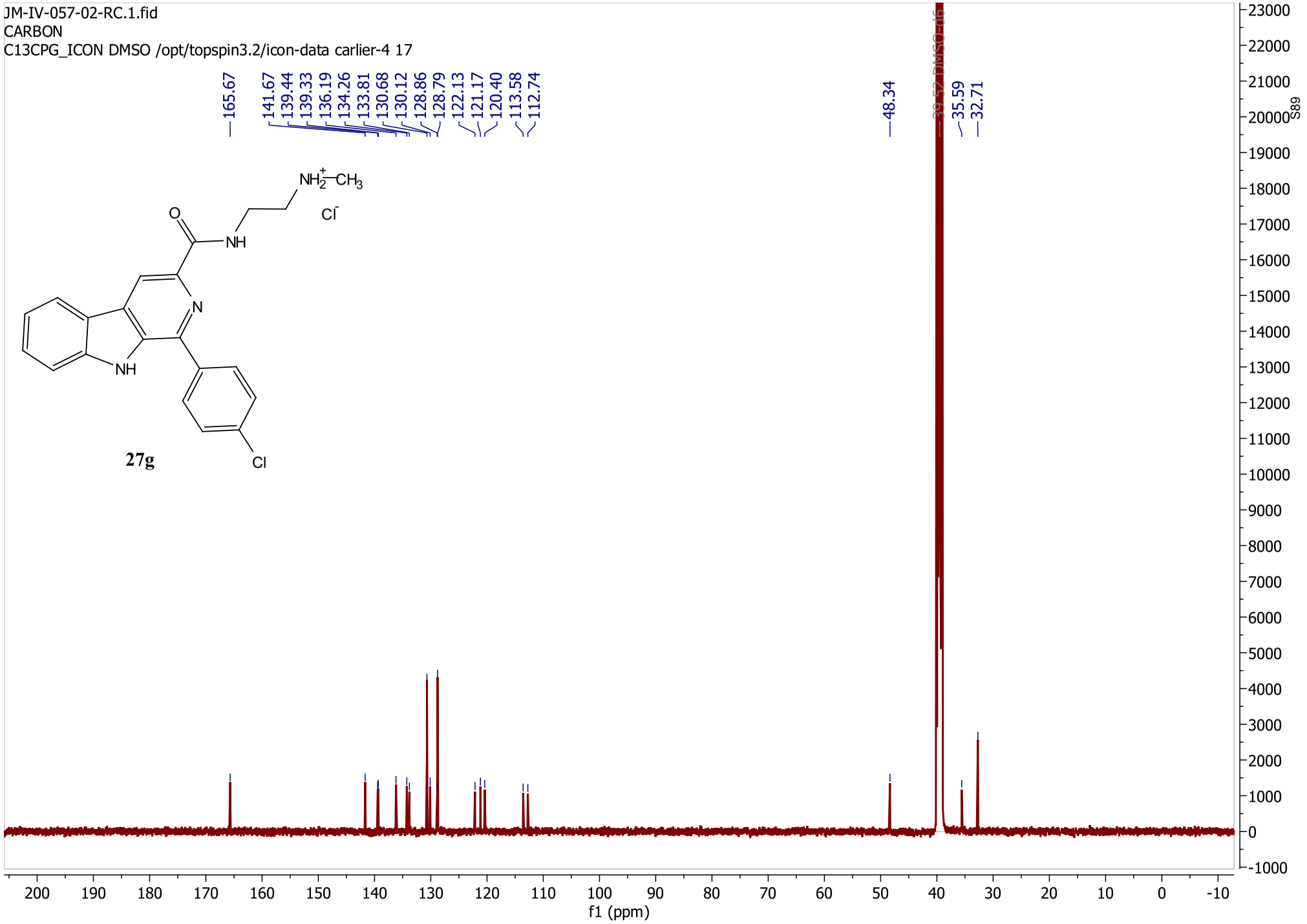

EES-I-55_PROTON_01
EES-I-55
9.05 9.03 9.02 8.90 8.60 8.46 8.44 8.43 8.39 8.39 8.18 8.18 8.16 8.16 8.13 7.92 7.91 7.90 7.89 7.72 7.70 7.65 7.65 7.63 7.63 7.63 7.62 7.61 7.61 7.36 7.36 7.34 7.33 7.32 3.72 3.71 3.69 3.68 3.66 3.64 3.39 WATER 3.18 3.16 3.14 2.62 2.61 2.60 2.50 DMSO-d6 1.24 H-Grease
S84
NH2+ CH3
Cl-
O
NH
N
NH
Cl
Cl
27e
1.11 0.93 0.96 1.54 1.17 1.00 1.19 1.14 1.16 1.13 2.19 2.00 2.89
f1 (ppm)

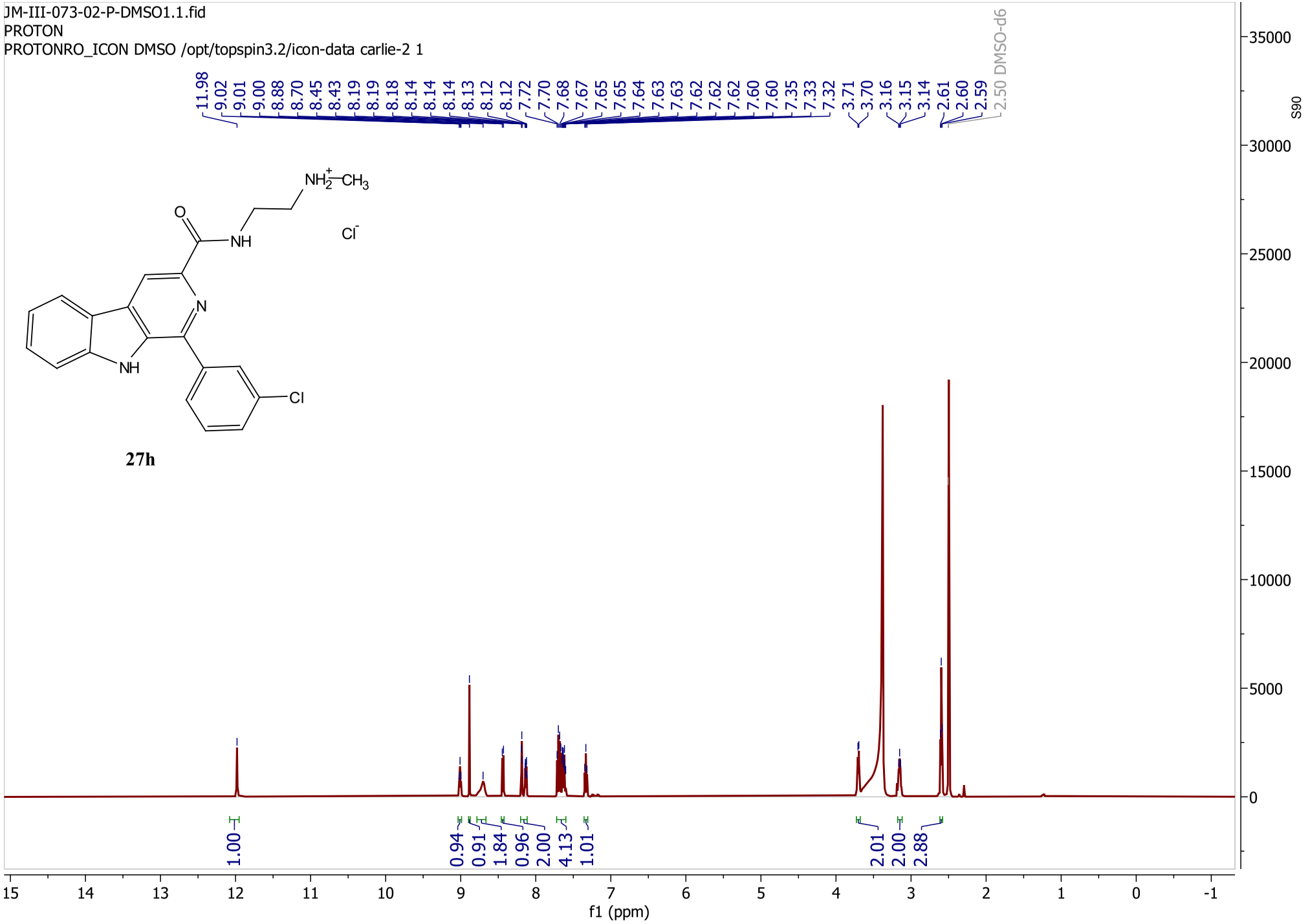

JM-II-102-02-CARB.1.fid
C13CPD MeOD /opt/topspin3.2/icon-data carlie-1 1
168.25
143.33
140.70
140.20
139.54
136.13
133.98
132.19
131.94
131.75
130.11
129.45
122.90
122.65
121.81
114.74
113.52
51.85
49.00 CD3OD
39.67
35.80
NH—CH3
O
NH
N
NH
Cl
Cl
27e
S85
f1 (ppm)

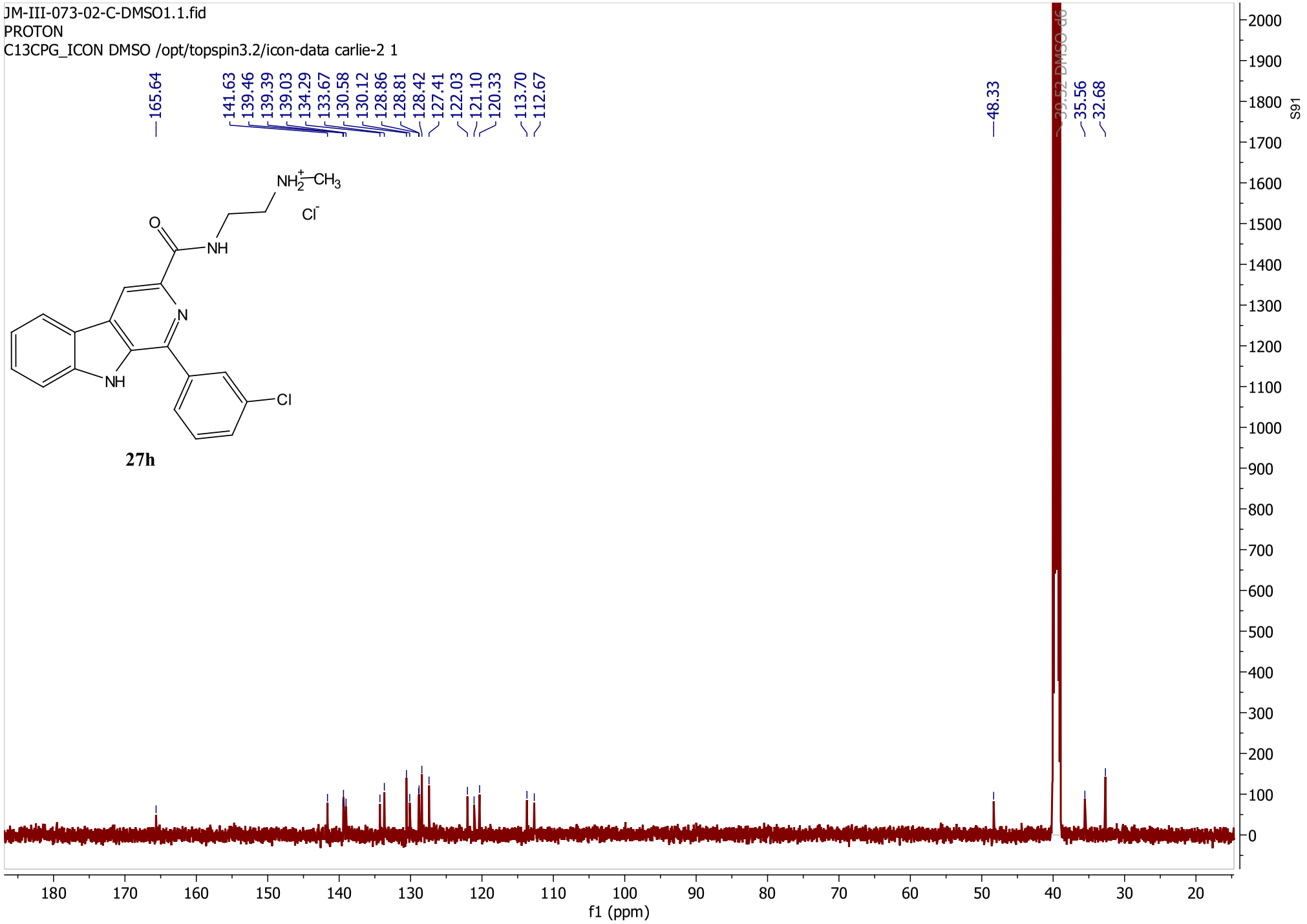

JM-III-019-02.1.fid
PROTONRO MeOD /opt/topspin3.2/icon-data carlie-2 1
8.83
8.27
8.19
8.11
8.09
7.68
7.66
7.66
7.65
7.64
7.63
7.61
7.61
7.60
7.60
7.58
7.58
7.57
7.57
7.56
7.56
7.55
7.55
7.55
7.36
7.34
7.33
4.88 WATER
3.84
3.83
3.82
3.31 CD3OD
3.30
3.28
2.76
NH2+ CH3
Cl-
O
NH
N
NH
27f
0.94
0.96
1.98
5.12
1.04
2.01
1.35
3.01
f1 (ppm)
S86


JM-III-019-02.2.fid
C13CPD MeOD /opt/topspin3.2/icon-data carlie-2 1
169.50
143.29
143.26
140.07
139.14
136.39
131.60
130.24
130.00
129.96
129.79
122.94
122.55
121.71
114.43
113.58
51.05
49.00 CD3OD
37.35
33.93
NH2+—CH3
Cl-
O
NH
N
NH
27f
S87
f1 (ppm)


JM-IV-057-02-RP.1.fid
PROTON
PROTONRO_ICON DMSO /opt/topspin3.2/icon-data carlier-4 17
11.97
9.03
9.02
9.00
8.87
8.79
8.78
8.77
8.76
8.44
8.43
8.25
8.25
8.24
8.23
8.23
8.22
7.71
7.70
7.63
7.61
7.60
7.35
7.33
7.32
3.72
3.71
3.70
3.68
3.17
3.16
3.15
3.14
3.12
2.60
2.59
2.58
2.50 DMSO-d6
S88
NH2+—CH3
Cl-
O
NH
N
NH
Cl
27g
0.91
1.09
1.08
2.04
1.07
2.14
3.21
1.11
2.01
2.08
3.00
f1 (ppm)


JM-IV-057-02-RC.1.fid
CARBON
C13CPG_ICON DMSO /opt/topspin3.2/icon-data carlier-4 17
165.67
141.67
139.44
139.33
136.19
134.26
133.81
130.68
130.12
128.86
128.79
122.13
121.17
120.40
113.58
112.74
48.34
39.52 DMSO-d6
35.59
32.71
S89
NH2+—CH3
Cl-
O
NH
N
NH
Cl
27g
f1 (ppm)


JM-III-073-02-P-DMSO1.1.fid
PROTON
PROTONRO_ICON DMSO /opt/topspin3.2/icon-data carlie-2 1
11.98
9.02
9.01
9.00
8.88
8.70
8.45
8.43
8.19
8.19
8.18
8.14
8.14
8.14
8.13
8.12
8.12
7.72
7.70
7.68
7.67
7.65
7.65
7.64
7.63
7.63
7.62
7.62
7.62
7.60
7.60
7.35
7.33
7.32
3.71
3.70
3.16
3.15
3.14
2.61
2.60
2.59
2.50 DMSO-d6
S90
NH2+—CH3
Cl-
O
NH
N
NH
Cl
27h
1.00
0.94
0.91
1.84
0.96
2.00
4.13
1.01
2.01
2.00
2.88
f1 (ppm)


JM-III-073-02-C-DMSO1.1.fid
PROTON
C13CPG_ICON DMSO /opt/topspin3.2/icon-data carlie-2 1
165.64
141.63
139.46
139.39
139.03
134.29
133.67
130.58
130.12
128.86
128.81
128.42
127.41
122.03
121.10
120.33
113.70
112.67
48.33
39.52 DMSO-d6
35.56
32.68
NH2+ CH3
Cl-
O
NH
N
NH
Cl
27h
S91
f1 (ppm)