Supporting Information

Spirocyclic and Bicyclic 8-Nitrobenzothiazinones for Tuberculosis with Improved Physicochemical and Pharmacokinetic Properties

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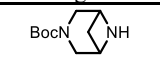
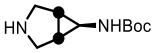
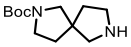
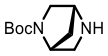
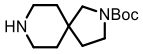
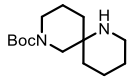
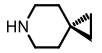
I. General

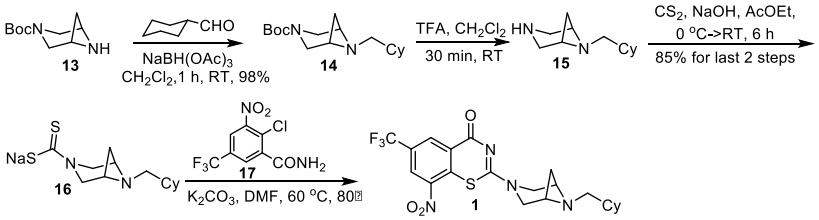
Unless otherwise noted, reagents and materials were obtained from commercial suppliers (Table S1) and were used without further purification. Solvents were dried by the appropriate drying agents prior to use. Anhydrous tetrahydrofuran and dichloromethane were obtained from commercial sources. All solvents used for routine isolation of products and for chromatography were reagent grade. Moisture- and air-sensitive reactions were carried out under an atmosphere of Argon. All reactions were monitored by thin layer chromatography (TLC) and column chromatography purification was performed using 230-400 mesh silica gel. NMR spectra were measured on Bruker AV400 spectrometer at 400 MHz or 300 MHz for ^{1}H spectra and at 100 MHz or 75 MHz for ^{13}C spectra using $CDCl_3$, CD_3OD and D_2O, and calibrated from the residual solvent signal. All final products were characterized by ^{1}H NMR, ^{13}C NMR and MS analyses. Except for the known compounds, all new compounds were also characterized and confirmed by HRMS. Melting points were determined on Yanaco MP-J3 microscope melting point apparatus.

Table S1. The key building blocks of target compounds and commercial suppliers

Building blocks	CAS No.	Catalog No.	Vendors
	1251017-66-9	KH-53707	3A Chemicals
	236406-55-6	AK-23563	Innochem-Beijing
	896464-16-7	PB00714	Innochem-Beijing
	134575-17-0	WXCD00110027	3A Chemicals
	236406-49-8	AK-24789	Innochem-Beijing
	198989-07-0	SCO-0295	Wuxi LabNetwork
	104102-70-3	WX100001	Wuxi LabNetwork
	858671-91-7	WXCD00120062	Wuxi LabNetwork
	336191-17-4	WXCD00100013	Wuxi LabNetwork
	1086394-59-3	38805	Wuxi LabNetwork
	1037834-62-0	WXCD00100641	Wuxi LabNetwork

II. Synthetic Procedures and Characterization Data

Scheme S1. Representative Synthesis of **1.**



General Procedure for the synthesis of intermediates 14a, 14c-d, and 16f-k. A solution of cyclohexane carboxaldehyde (2.02 mL, 16.64 mmol, 1.1 equiv) in CH_2Cl_2 (20 mL) was added to a solution of **13** (15.13 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) at room temperature. After 30 min, sodium triacetoxyborohydride (3.37 g, 15.9 mmol, 1.05 equiv) was added in portions and the mixture stirred at room temperature for 3 h. The reaction solution was quenched with saturated aqueous Na_2CO_3 (30 mL), extracted with CH_2Cl_2 (20 mL × 3), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford **14a-k**.

***tert*-Butyl 6-(cyclohexylmethyl)-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate (14a)**. The title compound was prepared from *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-3-carboxylate (0.50g, 2.52 mmol, 1.0 equiv) and cyclohexane carboxaldehyde (0.34 mL, 2.8 mmol, 1.1 equiv) using the general procedure for reductive amination to afford **14a** (0.72 g, 98%) as a white solid: R_f = 0.20 (5:1, EtOAc-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.75 (m, 2H), 3.53 (m, 2H), 3.26 (m, 2H), 2.49 (m, 1H), 2.15 (m, 2H), 1.64 (m, 5H), 1.46 (m, 1H), 1.44 (s, 9H), 1.17 (m, 4H), 0.83 (m, 2H);^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 79.6, 58.3, 52.1, 43.0, 42.3, 37.3, 31.9, 29.5, 28.5, 28.4, 26.6, 26.1; HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{17}H_{31}N_2O_2$ 295.2380, found 295.2385 (error 1.7 ppm).

***tert*-Butyl 7-(cyclohexylmethyl)-2,7-diazaspiro[3.5]nonane-2-carboxylate (14c)**. The title compound was prepared from 2-(tert- Butoxycarbonyl)-2,7-diazaspiro[3.5]nonane (0.50g, 2.21 mmol, 1.0 equiv) and cyclohexane carboxaldehyde (0.29 mL, 2.43 mmol, 1.1 equiv) using the general procedure for reductive amination to afford **14c** (0.66 g, 93%) as a white solid: R_f = 0.20 (5:1, EtOAc-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.63 (s, 4H), 2.69 (brs, 4H), 2.43 (d, J = 7.6 Hz, 2H), 1.93 (m, 4H), 1.69 (m, 5H), 1.43 (s, 9H), 1.19 (m, 4H), 0.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.5, 79.8, 64.2, 50.2, 34.2, 33.4, 32.8, 31.7, 29.8, 28.5, 26.3, 26.0; HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{19}H_{35}N_2O_2$: 323.2693; found: 323.2687 (error 1.9 ppm).

***tert*-Butyl 2-(cyclohexylmethyl)-2,7-diazaspiro[3.5]nonane-7-carboxylate (14d)**. The title compound was prepared from tert-Butyl 2,7-diazaspiro[3.5]nonane-7-carboxylate (0.50g, 2.21 mmol, 1.0 equiv) and cyclohexane carboxaldehyde (0.29 mL, 2.43 mmol, 1.1 equiv) using the general procedure for reductive amination to afford **14d** (0.67 g, 94%) as a white solid: R_f = 0.20 (5:1, EtOAc-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.62 (s, 4H), 3.29 (m, 4H), 2.77 (d, J = 6.9 Hz, 2H), 1.73 (m, 4H), 1.62 (m, 5H), 1.40 (s, 9H), 1.15 (m, 4H), 0.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.8, 80.0, 64.3, 63.4, 40.6, 35.3, 35.0, 34.2, 31.0, 29.8, 28.5, 26.0, 25.7; HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{19}H_{35}N_2O_2$: 323.2693; found: 323.2686 (error 2.2 ppm).

***tert*-Butyl 7-(cyclohexylmethyl)-2,7-diazaspiro[4.4]nonane-2-carboxylate (14f)**. The title compound was prepared from tert-Butyl 2,7-diazaspiro[4.4]nonane-2-carboxylate (0.50g, 2.21 mmol, 1.0 equiv) and cyclohexane carboxaldehyde (0.29 mL, 2.43 mmol, 1.1 equiv) using the general procedure for reductive amination to afford **14f** (0.65 g, 91%) as a white solid: R_f = 0.20 (5:1, EtOAc-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.33 (m, 4H), 2.59 (m, 4H), 2.29 (m, 2H), 1.80 (m, 6H), 1.69 (m, 3H), 1.44 (s, 9H), 1.19 (m, 4H), 0.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.8, 79.5, 63.8, 63.6, 57.5, 56.8, 54.6, 48.3, 47.5, 45.5, 45.1, 37.0, 35.1, 31.8, 29.8, 28.6, 26.6, 26.0; HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{19}H_{35}N_2O_2$: 323.2693; found: 323.2687 (error 1.9 ppm).

***tert*-Butyl 5-(cyclohexylmethyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (14g)**. The title compound was prepared from tert-Butyl 2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylate (0.50 g, 2.52 mmol, 1.0 equiv) and cyclohexane carboxaldehyde (0.34 mL, 2.77 mmol, 1.1 equiv) using the general procedure for reductive amination to afford **14g** (0.71 g, 96%) as a white solid: R_f = 0.20 (5:1, EtOAc-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.36 (s, 0.5H), 4.23 (s, 0.5H), 3.57 (m, 1.5H), 3.16 (m, 1.5H), 2.48 (m, 2H), 1.95 (m, 1H), 1.70 (m, 5H), 1.46 (s, 9H), 1.16 (m, 7H), 0.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3, 79.8, 61.9, 61.0, 60.9, 57.1, 48.5, 37.3, 36.6, 35.8, 31.8, 29.9, 28.7, 26.7, 26.2; HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{17}H_{31}N_2O_2$: 295.2380; found: 295.2383 (error 1.0 ppm).

***tert*-Butyl 6-(cyclohexylmethyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (14h)**. The title compound was prepared from tert-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate (0.50 g, 2.52 mmol, 1.0 equiv) and cyclohexane carboxaldehyde (0.34 mL, 2.77 mmol, 1.1 equiv) using the general procedure for reductive amination to afford **14h** (0.68 g, 91%) as a white solid: R_f = 0.20 (5:1, EtOAc-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.00 (s, 4H), 3.61 (s, 4H), 2.45 (d, J = 8.0 Hz, 2H), 1.69 (m, 5H), 1.42 (s, 9H), 1.18 (m, 4H), 0.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 79.9, 65.3, 64.2, 35.8, 33.3, 31.4, 29.9, 28.5, 26.3, 25.9, 21.8; HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{17}H_{31}N_2O_2$: 295.2380; found: 295.2375 (error 1.7 ppm).

***tert*-Butyl 5-(cyclohexylmethyl)-2,5-diazabicyclo[2.2.2]octane-2-carboxylate (14i)**. The title compound was prepared from tert butyl 2,5-diaza-bicyclo[2.2.2]octane-2-carboxylate (0.50 g, 2.36 mmol, 1.0 equiv) and cyclohexane carboxaldehyde (0.31 mL, 2.59 mmol, 1.1 equiv) using the general procedure for reductive amination to afford **14i** (0.67 g, 93%) as a white solid: R_f = 0.20 (5:1, EtOAc-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.95 (s, 0.5H), 3.82 (s, 0.5H), 3.60 (m, 1H), 3.18 (m, 1H), 2.89 (m, 1H), 2.84 (s, 1H), 2.73 (m, 1H), 2.31 (d, J = 7.0 Hz, 2H), 1.98 (m, 1H), 1.80-1.50 (m, 8H), 1.38 (s, 9H), 1.13 (m, 4H), 0.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.6, 79.3, 63.2, 57.2, 50.9, 46.9, 36.0, 31.7, 29.5, 28.5, 26.7, 26.1, 25.5, 23.9; HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{18}H_{33}N_2O_2$: 309.2537; found: 309.2535 (error 0.5 ppm).

***tert*-Butyl 2-(cyclohexylmethyl)-2,8-diazaspiro[4.5]decane-8-carboxylate (14j)**. The title compound was prepared from tert butyl 2,8-diazaspiro[4.5]decane-8-carboxylate (0.50 g, 2.08 mmol, 1.0 equiv) and cyclohexane carboxaldehyde (0.28 mL, 2.29

mmol, 1.1 equiv) using the general procedure for reductive amination to afford **14j** (0.66 g, 95%) as a white solid: R_f = 0.20 (5:1, EtOAc-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.39 (m, 2H), 3.30 (m, 2H), 2.84 (m, 2H), 2.62 (m, 2H), 2.44 (d, *J* = 6.9 Hz, 2H), 1.89 (m, 2H), 1.72 (m, 9H), 1.43 (s, 9H), 1.13 (m, 4H), 0.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.9, 79.5, 64.8, 63.3, 53.5, 44.2, 40.2, 37.0, 36.1, 35.6, 31.7, 29.5, 28.5, 26.0, 25.7; HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{20}H_{37}N_2O_2$: 337.2850; found: 337.2851 (error 0.4 ppm).

***tert*-Butyl 1-(cyclohexylmethyl)-1,8-diazaspiro[5.5]undecane-8-carboxylate (14k)**. The title compound was prepared from tert butyl 1,8-diazaspiro[5.5]undecan-8-carboxylate (0.50 g, 1.97 mmol, 1.0 equiv) and cyclohexane carboxaldehyde (0.26 mL, 2.16 mmol, 1.1 equiv) using the general procedure for reductive amination to afford **14k** (0.63 g, 92%) as a colorless oil: R_f = 0.20 (5:1, EtOAc-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.47 (s, 2H), 3.17 (m, 2H), 2.76-2.82 (m, 4H), 1.46-1.68 (m, 14H), 1.42 (s, 9H), 1.33 (m, 4H), 1.21 (m, 1H), 0.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1, 79.7, 65.6, 51.0, 50.3, 49.3, 44.7, 44.0, 41.0, 36.8, 36.1, 33.3, 30.6, 29.7, 28.5, 25.9, 21.0, 20.1, 19.2; HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{21}H_{39}N_2O_2$: 351.3006; found: 351.3008 (error 0.6 ppm).

General procedure for the synthesis of compounds 16a, 16c-d, and 16f-l. Compound **14** (2.04 mmol, 1.0 equiv) was dissolved in TFA/CH_2Cl_2 (v/v, 1:1) (20 mL) and the solution was stirred at 0 °C. After 30 min, the solvent was removed under vacumm to afford the crude **15**, which was used in the next step without further purification. To a pre-cooled mixture of crude **15** obtained above in EtOAc was added 30% aqueous NaOH (0.68 mL, 5.09 mmol, 2.5 equiv) followed by CS_2 (0.15 mL, 2.45 mmol, 1.2 equiv). The reaction mixture was stirred for 3 h at 0 °C, then at room temperature for another 3 h. The reaction mixture was filtered and the filter cake was washed by ethyl acetate and dried under vacumm to afford **16**.

Sodium 6-(cyclohexylmethyl)-3,6-diazabicyclo[3.1.1]heptane-3-carbodithioate (16a). The title compound was prepared from **14a** (0.60g, 2.04 mmol, 1.0 equiv), which was deprotected in TFA followed by substitution reaction with CS_2 (0.15 mL, 2.45 mmol, 1.2 equiv) using the general procedure to afford **16a** (0.51 g, 85%) as a white solid: ^{1}H NMR (400 MHz, CD_3OD): δ 4.12 (m, 2H), 3.70 (m, 2H), 2.90 (m, 1H), 2.47 (m, 1H), 2.24 (m, 1H), 2.08 (m, 1H), 1.75 (m, 5H), 1.43 (m, 1H), 1.28 (m, 4H), 0.95 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 207.4, 64.5, 60.4, 52.1, 38.4, 32.9, 30.7, 29.0, 27.2; HRMS (ESI+) *m/z* $[M - Na + 2H]^+$ calcd for $C_{13}H_{23}N_2S_2$: 271.1297; found: 271.1296 (error 0.4 ppm).

Sodium 7-(cyclohexylmethyl)-2,7-diazaspiro[3.5]nonane-2-carbodithioate (16c). The title compound was prepared from **14c** (0.66g, 2.04 mmol, 1.0 equiv), which was deprotected in TFA followed by substitution reaction with CS_2 (0.15 mL, 2.45 mmol, 1.2 equiv) using the general procedure to afford **16c** (0.54 g, 83%) as a white solid: ^{1}H NMR (400 MHz, CD_3OD): δ 3.85 (s, 4H), 2.42 (brs, 4H), 2.18 (d, *J* = 6.9 Hz, 2H), 1.78 (m, 4H), 1.69 (m, 4H), 1.56 (m, 1H), 1.26 (m, 4H), 0.92 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 208.9, 65.6, 63.6, 50.8, 34.8, 34.4, 31.7, 28.8, 26.3, 25.8; HRMS (ESI+) *m/z* $[M - Na + 2H]^+$ calcd for $C_{15}H_{27}N_2S_2$: 299.1610; found: 299.1608 (error 0.7 ppm).

Sodium 2-(cyclohexylmethyl)-2,7-diazaspiro[3.5]nonane-7-carbodithioate (16d). The title compound was prepared from **14d** (0.66g, 2.04 mmol, 1.0 equiv), which was deprotected in TFA followed by substitution reaction with CS_2 (0.15 mL, 2.45 mmol, 1.2 equiv) using the general procedure to afford **16d** (0.51 g, 79%) as a white solid: ^{1}H NMR (400 MHz, CD_3OD): δ 4.32 (m, 2H), 3.21 (s, 2H), 3.11 (s, 2H), 2.80 (m, 2H), 2.44 (d, *J* = 6.9 Hz, 1H), 2.38 (d, *J* = 6.9 Hz, 1H), 1.77 (m, 3H), 1.70 (m, 5H), 1.40 (m, 1H), 1.21 (m, 4H), 0.91 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 210.8, 66.7, 66.5, 64.6, 64.4, 41.9, 36.5, 36.4, 35.6, 34.7, 34.0, 33.5, 31.2, 26.1, 25.6; HRMS (ESI+) *m/z* $[M - Na + H]^+$ calcd for $C_{15}H_{26}N_2S_2$: 298.1537; found: 298.1537 (error 1.7 ppm).

Sodium 7-(cyclohexylmethyl)-2,7-diazaspiro[4.4]nonane-2-carbodithioate (16f). The title compound was prepared from **14f** (0.66g, 2.04 mmol, 1.0 equiv), which was deprotected in TFA followed by substitution reaction with CS_2 (0.15 mL, 2.45 mmol, 1.2 equiv) using the general procedure to afford **16f** (0.49 g, 74%) as a white solid: ^{1}H NMR (400 MHz, CD_3OD): δ 3.95 (m, 2H), 3.40 (m, 3H), 2.90 (m, 3H), 2.52 (m, 1H), 2.05 (m, 4H), 1.80 (m, 6H), 1.30 (m, 4H), 0.98 (m, 2H); HRMS (ESI+) *m/z* $[M - Na - CS_2 + 2H]^+$ calcd for $C_{14}H_{27}N_2$: 223.2169; found: 223.2159 (error 4.4 ppm).

Sodium 5-(cyclohexylmethyl)-2,5-diazabicyclo[2.2.1]heptane-2-carbodithioate (16g). The title compound was prepared from **14g** (0.60g, 2.04 mmol, 1.0 equiv), which was deprotected in TFA followed by substitution reaction with CS_2 (0.15 mL, 2.45 mmol, 1.2 equiv) using the general procedure to afford **16g** (0.49 g, 82%) as a white solid: ^{1}H NMR (400 MHz, CD_3OD): δ 5.46 (s, 1H), 4.05 (dd, *J* = 12.4 Hz, 2.0 Hz, 1H), 3.65 (s, 1H), 3.53 (dd, *J* = 12.4 Hz, 2.2 Hz, 1H), 3.03 (dd, *J* = 9.9 Hz, 2.2 Hz, 1H), 2.75 (d, *J* = 9.9 Hz, 1H), 2.48 (d, *J* = 6.7 Hz, 2H), 1.95 (m, 1H), 1.83 (m, 1H), 1.70 (m, 4H), 1.45 (m, 1H), 1.26 (m, 4H), 0.93 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 210.5, 63.9, 62.7, 61.0, 59.3, 55.7, 37.2, 35.4, 31.4, 31.3, 26.3, 25.7, 22.7; HRMS (ESI+) *m/z* $[M - Na + 2H]^+$ calcd for $C_{13}H_{22}N_2S_2$: 270.1224; found: 270.1224 (error 1.9 ppm).

Sodium 6-(cyclohexylmethyl)-2,6-diazaspiro[3.3]heptane-2-carbodithioate (16h). The title compound was prepared from **14h** (0.60g, 2.04 mmol, 1.0 equiv), which was deprotected in TFA followed by substitution reaction with CS_2 (0.15 mL, 2.45 mmol, 1.2 equiv) using the general procedure to afford **16h** (0.46 g, 77%) as a white solid: ^{1}H NMR (400 MHz, CD_3OD): δ 4.22 (s, 4H), 3.49 (s, 4H), 2.40 (d, *J* = 6.9 Hz, 2H), 1.71 (m, 4H), 1.40 (m, 1H), 1.24 (m, 4H), 0.92 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 210.3, 67.4, 65.6, 64.9, 37.6, 32.5, 30.9, 27.5, 27.0; HRMS (ESI+) *m/z* $[M - Na + 2H]^+$ calcd for $C_{13}H_{23}N_2S_2$: 271.1297; found: 271.1302 (error 1.8 ppm).

Sodium 5-(cyclohexylmethyl)-2,5-diazabicyclo[2.2.2]octane-2-carbodithioate (16i). The title compound was prepared from **14i** (0.63g, 2.04 mmol, 1.0 equiv), which was deprotected in TFA followed by substitution reaction with CS_2 (0.15 mL, 2.45 mmol, 1.2 equiv) using the general procedure to afford **16i** (0.54 g, 86%) as a white solid: ^{1}H NMR (400 MHz, CD_3OD): δ 5.67 (m, 1H), 4.16 (dt, *J* = 13.6, 2.7 Hz, 1H), 3.86 (dd, *J* = 13.6, 1.8 Hz, 1H), 2.93 (m, 3H), 2.41 (m, 2H), 2.06 (m, 1H), 1.96 (m, 1H), 1.75 (m, 6H), 1.44 (m, 1H), 1.26 (m, 4H), 0.90 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 208.1, 63.0, 56.1, 53.7, 52.4, 51.8, 36.0, 31.4, 26.4, 25.8, 23.6, 23.2; HRMS (ESI+) *m/z* $[M - Na + 2H]^+$ calcd for $C_{14}H_{24}N_2S_2$: 284.1375; found: 284.1383 (error 2.7 ppm).

Sodium 2-(cyclohexylmethyl)-2,8-diazaspiro[4.5]decane-8-carbodithioate (16j). The title compound was prepared from **14j** (0.69g, 2.04 mmol, 1.0 equiv), which was deprotected in TFA followed by substitution reaction with CS_2 (0.15 mL, 2.45 mmol, 1.2 equiv) using the general procedure to afford **16j** (0.55 g, 80%) as a white solid: ^{1}H NMR (400 MHz, CD_3OD): δ 3.12 (m, 3H), 2.76 (m, 1H), 2.62 (m, 2H), 2.40 (m, 1H), 2.14 (m, 1H), 2.00 (m, 1H), 1.79 (m, 10H), 1.54 (m, 1H), 1.43 (m, 1H), 1.28 (m, 4H), 0.95 (m, 2H); HRMS (ESI+) *m/z* $[M - Na - CS_2 + 2H]^+$ calcd for $C_{15}H_{29}N_2$: 237.2325; found: 237.2318 (error 3.1 ppm).

Sodium 1-(cyclohexylmethyl)-1,8-diazaspiro[5.5]undecane-8-carbodithioate (16k). The title compound was prepared from **14k** (0.71g, 2.04 mmol, 1.0 equiv), which was deprotected in TFA followed by substitution reaction with CS_2 (0.15 mL, 2.45 mmol, 1.2 equiv) using the general procedure to afford **16k** (0.54 g, 76%) as a white solid: ^{1}H NMR (400 MHz, CD_3OD): δ 3.63 (m, 1H), 3.45 (m, 1H), 3.13 (m, 2H), 2.97 (m, 4H), 2.72 (m, 2H), 1.84 (m, 4H), 1.60 (m, 9H), 1.28 (m, 4H), 0.96 (m, 2H); HRMS (ESI+) *m/z* $[M - Na - CS_2 + 2H]^+$ calcd for $C_{16}H_{31}N_2$: 251.2482; found: 251.2476 (error 2.3 ppm).

Sodium 6-azaspiro[2.5]octane-6-carbodithioate (16l). The title compound was prepared from **15l** (0.30g, 2.04 mmol, 1.0 equiv), which was deprotected in TFA followed by substitution reaction with CS_2 (0.15 mL, 2.45 mmol, 1.2 equiv) using the general procedure to afford **16l** (0.38 g, 87%) as a white solid: ^{1}H NMR (400 MHz, CD_3OD): δ 4.46 (m, 4H), 1.43 (m, 4H), 0.39 (s, 4H); HRMS (ESI+) *m/z* $[2M - 2Na + H]^+$ calcd for $C_{16}H_{25}N_2S_4$: 373.0895; found: 373.0884 (error 3.0 ppm).

General Procedure for the Synthesis of benzothiazinone analogs (1, 3-4, 6-12). A mixture of **16** (0.34 mmol, 1.0 equiv), **17** (0.11 g, 0.41 mmol, 1.2 equiv) and anhydrous K_2CO_3 (0.052 g, 0.38 mmol, 1.1 equiv) was stirred in anhydrous DMF (15 mL) at 60 °C. After 2 h, the reaction mixture was cooled down to room temperature and poured into ice-water. The product was extracted with CH_2Cl_2 (20 mL × 5). The organic layer was combined, washed by saturated brine (5 mL × 3) and dried by anhydrous sodium sulfate which was removed by filtration after 20 min. The solvent CH_2Cl_2 was removed under reduced pressure. Compound **1**, **6-9**, **11**, and **12** were purified by preparative HPLC employing and Xbridge C18 (30 mm × 2.1 mm, 3 µm). HPLC condition (solvent A = 0.07% TFA + H_2O, solvent B = acetonitrile), injection volume: 5 µL, flowrate: 0.8 mL/min,gradient elution: 0.00 min, 0% B; 5 min, 60% B; 6.4 min, 60% B; 6.41 min, 0% B; 7.00 min, 0% B. Compounds **3-4**, **10** was purified by flash column chromatography on silica gel with the indicated solvent system (petroleum ether/ethyl acetate 10:1–>5:1–>2:1–>1:1–>1:2–>1:10–>100% ethyl acetate).

2-((1*R*,5*S*)-6-(Cyclohexylmethyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)-8-nitro-6-(trifluoromethyl)-4*H*-benzo[*e*][1,3]thiazin-4-one (1). The title compound was prepared from **16a** (0.10 g, 0.34 mmol, 1.0 equiv) and **17** (0.11g, 0.41 mmol, 1.2 equiv) using the general procedure for cyclization to afford compound **1** (0.13 g, 80%) as a light yellow solid: mp 126-128 °C; R_f = 0.2 (1:2 Hexane-EtOAc); ^{1}H NMR (400 MHz, CD_3OD) δ 9.06 (s, 1H), 8.96 (s, 1H), 4.45 (m, 6H), 3.48 (m, 1H), 3.10 (m, 2H), 2.11 (d, *J* = 8.0 Hz, 1H), 1.80 (m, 4H), 1.72 (m, 1H), 1.31 (m, 4H), 1.10 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 168.1, 166.6, 145.8, 135.5, 133.7, 130.7 (q, *J* = 35.0 Hz), 127.6, 127.4, 124.1 (q, *J* = 271.0 Hz), 58.3, 35.9, 31.6, 26.9, 26.6, 18.4; HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{21}H_{24}F_3N_4O_3S$ 469.1516, found 469.1508 (error 1.7 ppm).

2-(7-(Cyclohexylmethyl)-2,7-diazaspiro[3.5]nonan-2-yl)-8-nitro-6-(trifluoromethyl)-4*H*-benzo[*e*][1,3]thiazin-4-one (3). The title compound was prepared from **16c** (0.11g, 0.34 mmol, 1.0 equiv) and **17** (0.11g, 0.41 mmol, 1.2 equiv) using the general procedure for cyclization to afford compound **3** (0.13 g, 78%) as a light yellow solid: mp 230° C decomposed; *Rf* = 0.2 (1:2 Hexane-EtOAc); ^{1}H NMR (600 MHz, CD_3OD): δ 8.99 (s, 1H), 8.88 (s, 1H), 4.15 (s, 2H), 4.10 (s, 2H), 2.68 (m, 4H), 2.40 (m, 2H), 2.02 (m, 4H), 1.81 (m, 2H), 1.75 (m, 2H), 1.70 (m, 1H), 1.36 (m, 2H), 1.24 (m, 2H), 0.97 (m, 2H); ^{13}C NMR (150 MHz, CD_3OD): δ 168.1, 164.7, 145.4, 136.0, 133.5, 130.1 (q, *J* = 34.5 Hz), 127.6, 127.2, 124.1 (q, *J* = 271.5 Hz), 66.1, 62.7, 61.1, 58.3,

53.6, 51.8, 36.5, 35.8, 34.8, 32.8, 27.5, 27.0, 18.4; HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{23}H_{28}F_3N_4O_3S$: 497.1829; found: 497.1829 (error 0.1 ppm).

2-(2-(Cyclohexylmethyl)-2,7-diazaspiro[3.5]nonan-7-yl)-8-nitro-6-(trifluoromethyl)-4*H*-benzo[*e*][1,3]thiazin-4-one (4). The title compound was prepared from **16d** (0.11g, 0.34 mmol, 1.0 equiv) and **17** (0.11g, 0.41 mmol, 1.2 equiv) using the general procedure for cyclization to afford compound **4** (0.13 g, 75%) as a light yellow solid: mp 238° C decomposed; R_f = 0.2 (1:2 Hexane-EtOAc); ^{1}H NMR (600 MHz, CD_3OD): δ 8.95 (s, 1H), 8.88 (s, 1H), 4.07 (m, 8H), 3.16 (d, J = 7.1 Hz, 2H), 2.09 (m, 4H), 1.78 (m, 4H), 1.70 (m, 1H), 1.30 (m, 4H), 1.06 (m, 2H); ^{13}C NMR (150 MHz, CD_3OD): δ 168.9, 164.6, 145.9, 135.9, 133.2, 130.3 (q, *J* = 34.9 Hz), 127.4, 127.3, 124.1 (q, *J* = 270.5 Hz), 64.8, 63.7, 58.3, 35.7, 35.5, 31.3, 26.9, 26.5, 18.4; HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{23}H_{28}F_3N_4O_3S$: 497.1829; found: 497.1833 (error 0.9 ppm).

2-(7-(Cyclohexylmethyl)-2,7-diazaspiro[4.4]nonan-2-yl)-8-nitro-6-(trifluoromethyl)-4*H*-benzo[*e*][1,3]thiazin-4-one (6). The title compound was prepared from **16f** (0.11g, 0.34 mmol, 1.0 equiv) and **17** (0.11g, 0.41 mmol, 1.2 equiv) using the general procedure for cyclization to afford compound **6** (0.12 g, 72%) as a light yellow solid: mp 95-97° C; R_f = 0.2 (1:2 Hexane-EtOAc); ^{1}H NMR (500 MHz, CD_3OD): δ 9.02 (s, 1H), 8.91 (s, 1H), 3.86 (m, 6H), 3.33 (m, 2H), 3.14 (m, 2H), 2.23 (m, 4H), 1.80 (m, 4H), 1.73 (m, 1H), 1.28 (m, 4H), 1.08 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 168.2, 163.3, 145.6, 136.1, 133.6, 130.2 (q, *J* = 34.7 Hz), 127.5, 127.3, 124.1 (q, *J* = 271.0 Hz), 63.5, 62.7, 62.1, 60.0, 58.3, 57.3, 55.7, 36.7, 35.8, 31.5, 26.9, 26.5; HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{23}H_{28}F_3N_4O_3S$: 497.1829; found: 497.1824 (error 1.0 ppm).

2-(5-(Cyclohexylmethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-8-nitro-6-(trifluoromethyl)-4*H*-benzo[*e*][1,3]thiazin-4-one (**7**). The title compound was prepared from **16g** (0.10g, 0.34 mmol, 1.0 equiv) and **17** (0.11g, 0.41 mmol, 1.2 equiv) using the general procedure for cyclization to afford compound **7** (0.13 g, 81%) as a light yellow solid: mp 121-124° C; R_f = 0.2 (1:2 Hexane-EtOAc); ^{1}H NMR (400 MHz, CD_3OD): δ 9.01 (s, 1H), 8.92 (s, 1H), 5.53 (s, 0.5H), 5.23 (s, 0.5H), 4.71 (m, 1H), 4.16 (m, 1H), 4.01 (m, 2H), 3.58 (m, 1H), 3.22 (m, 2H), 2.44 (m, 2H), 1.81 (m, 4H), 1.73 (m, 1H), 1.39-1.22 (m, 4H), 1.13-1.07 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 168.3, 164.3, 145.6, 135.7, 133.6, 130.5 (q, *J* = 34.7 Hz), 127.5, 127.4, 124.0 (q, *J* = 271.0 Hz), 61.9, 59.8, 58.9, 52.3, 35.5, 35.4, 31.5, 31.4, 26.9, 26.5, 26.4; HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{21}H_{24}F_3N_4O_3S$: 469.1516; found: 469.1512 (error 0.8 ppm).

2-(6-(Cyclohexylmethyl)-2,6-diazaspiro[3.3]heptan-2-yl)-8-nitro-6-(trifluoromethyl)-4*H*-benzo[*e*][1,3]thiazin-4-one (**8**). The title compound was prepared from **16h** (0.10g, 0.34 mmol, 1.0 equiv) and **17** (0.11g, 0.41 mmol, 1.2 equiv) using the general procedure for cyclization to afford compound **8** (0.12 g, 76%) as a light yellow solid: mp 176-179° C; R_f = 0.2 (1:2 Hexane-EtOAc); ^{1}H NMR (400 MHz, CD_3OD): δ 9.01 (s, 1H), 8.91 (s, 1H), 4.65 (m, 2H), 4.53 (m, 4H), 4.38 (m, 2H), 3.12 (d, *J* = 7.0 Hz, 2H), 1.76 (m, 4H), 1.63 (m, 1H), 1.28 (m, 4H), 1.05 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 168.1, 164.2, 145.5, 135.7, 133.7, 130.3 (q, J = 35.0 Hz), 127.6, 127.4, 124.1 (q, *J* = 270.0 Hz), 64.5, 62.5, 61.5, 36.0, 35.3, 31.2, 26.9, 26.4; HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{21}H_{24}F_3N_4O_3S$: 469.1516; found: 469.1515 (error 0.2 ppm).

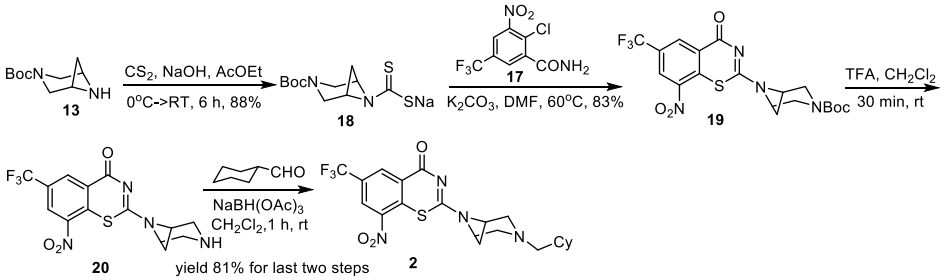
2-(5-(Cyclohexylmethyl)-2,5-diazabicyclo[2.2.2]octan-2-yl)-8-nitro-6-(trifluoromethyl)-4*H*-benzo[*e*][1,3]thiazin-4-one (**9**). The title compound was prepared from **16i** (0.11g, 0.34 mmol, 1.0 equiv) and **17** (0.11g, 0.41 mmol, 1.2 equiv) using the general procedure for cyclization to afford compound **1** (0.13 g, 77%) as a light yellow solid: mp 204-206° C; R_f = 0.2 (1:2 Hexane-EtOAc); ^{1}H NMR (400 MHz, CD_3OD): δ 9.01 (s, 1H), 8.92 (s, 1H), 5.45 (s, 0.5H), 4.79 (s, 0.5H), 4.30 (m, 1H), 4.08 (m, 2H), 3.27 (m, 3H), 2.43 (m, 1H), 2.20 (m, 3H), 1.83 (m, 5H), 1.72 (m, 1H), 1.35 (m, 2H), 1.25 (m, 2H), 1.10 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 168.3, 165.6, 145.8, 135.6, 133.5, 130.6 (q, *J* = 34.0 Hz), 127.7, 127.5, 124.0 (q, *J* = 270.0 Hz), 62.5, 56.7, 54.5, 47.5, 45.9, 34.8, 31.6, 31.5, 26.9, 26.5; HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{22}H_{26}F_3N_4O_3S$: 483.1672; found: 483.1668 (error 0.9 ppm).

2-(2-(Cyclohexylmethyl)-2,8-diazaspiro[4.5]decan-8-yl)-8-nitro-6-(trifluoromethyl)-4*H*-benzo[*e*][1,3]thiazin-4-one (**10**). The title compound was prepared from **16j** (0.12g, 0.34 mmol, 1.0 equiv) and **17** (0.11g, 0.41 mmol, 1.2 equiv) using the general procedure for cyclization to afford compound **10** (0.14 g, 79%) as a light yellow solid: mp 113-115° C; R_f = 0.2 (1:2 Hexane-EtOAc); ^{1}H NMR (300 MHz, CD_3OD): δ 8.97 (s, 1H), 8.89 (s, 1H), 3.97 (m, 4H), 3.80 (m, 1H), 3.68 (m, 1H), 3.11 (m, 3H), 2.22 (m, 1H), 2.07 (m, 1H), 1.87 (m, 10H), 1.32 (m, 4H), 1.08 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD): δ 168.9, 164.4, 145.9, 136.0, 133.1 (q, *J* = 3.0 Hz), 130.1 (q, *J* = 34.5 Hz), 127.4, 127.3, 124.1 (q, *J* = 270.0 Hz), 64.3, 63.5, 55.2, 42.3, 36.5, 35.8, 35.3, 31.8, 30.7, 30.5, 27.0, 26.5; HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{24}H_{30}F_3N_4O_3S$: 511.1985; found: 511.1989 (error 0.7 ppm).

2-(1-(Cyclohexylmethyl)-1,8-diazaspiro[5.5]undecan-8-yl)-8-nitro-6-(trifluoromethyl)-4*H*-benzo[*e*][1,3]thiazin-4-one (**11**). The title compound was prepared from **16k** (0.12g, 0.34 mmol, 1.0 equiv) and **17** (0.11g, 0.41 mmol, 1.2 equiv) using the general procedure for cyclization to afford compound **11** (0.14 g, 75%) as a light yellow solid: mp 121-123° C; R_f = 0.2 (1:2 Hexane-EtOAc); ^{1}H NMR (400 MHz, CD_3OD): δ 8.99 (s, 1H), 8.92 (s, 1H), 5.46 (brs, 0.5H), 4.76 (brs, 0.5H), 4.32 (m, 1H), 4.12 (m, 0.5H), 3.56 (m, 3H), 3.40 (m, 1.5H), 2.86 (m, 1H), 2.35 (m, 1H), 1.82 (m, 14H), 1.30 (m, 4H), 1.12 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 168.8, 166.1, 146.0, 135.8, 133.2, 130.6 (q, J = 36.7 Hz), 127.7, 127.3, 124.1 (q, J = 270.5 Hz), 66.2, 65.7, 58.5, 58.4, 51.4, 47.4, 36.1, 32.5, 32.2, 26.8, 26.6, 23.1, 22.0, 21.3, 19.2, 18.4; HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{25}H_{32}F_3N_4O_3S$: 525.2142; found: 525.2133 (error 1.7 ppm).

2-(6-azaspiro[2.5]octan-6-yl)-8-nitro-6-(trifluoromethyl)-4*H*-benzo[*e*][1,3]thiazin-4-one (**12**). The title compound was prepared from **16l** (0.07g, 0.34 mmol, 1.0 equiv) and **17** (0.11g, 0.41 mmol, 1.2 equiv) using the general procedure for cyclization to afford compound **12** (0.10 g, 83%) as a light yellow solid: mp 193-195° C; R_f = 0.2 (1:2 Hexane-EtOAc); ^{1}H NMR (400 MHz, CD_3OD): δ 8.95 (d, J = 2.10 Hz, 1H), 8.86 (d, J = 2.10 Hz, 1H), 4.08 (m, 4H), 1.59 (s, 4H), 0.50 (s, 4H); ^{13}C NMR (100 MHz, CD_3OD): δ 168.9, 164.1, 145.9, 136.2, 133.1, 130.1 (q, J = 35.0 Hz), 127.4, 127.3, 124.2 (q, J = 271.0 Hz), 35.9, 32.5, 18.7, 12.2; HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{16}H_{15}F_3N_3O_3S$: 386.0781; found: 386.0786 (error 1.4 ppm).

Scheme S2. Representative Synthesis of **2** using the alternative route



General Procedure for the synthesis of compound 18b and 18e. To a pre-cooled solution of **13** (5.04 mmol, 1.0 equiv) in EtOAc (10 mL) was added 30% aqueous sodium hydroxide (1.01 mL, 7.57 mmol, 1.5 equiv) followed by CS_2 (0.37 mL, 6.05 mmol, 1.2 equiv). The reaction mixture stirred for 3 h at 0 °C, then 3 h at room temperature. The reaction mixture was filtered and the filter cake was washed by EtOAc and dried under vacumm to afford **18**.

Sodium (1*R*,5*S*)-3-(*tert*-butoxycarbonyl)-3,6-diazabicyclo[3.1.1]heptane-6-carbodithioate (**18b**). The title compound was prepared from *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-3-carboxylate (1.00 g, 5.04 mmol, 1.0 equiv), by condensation with CS_2 (0.37 mL, 6.05 mmol, 1.2 equiv) using the general procedure to afford **18b** (1.31 g, 88%) as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 4.66 (m, 1H), 4.60 (m, 1H), 4.23 (t, J = 13.1 Hz, 2H), 3.44 (t, J = 13.1 Hz, 2H), 2.55 (m, 1H), 1.49 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 209.9, 158.0, 81.2, 63.7, 46.7, 46.2, 28.7, 27.0, 24.2; HRMS (ESI+) *m/z* $[M – Na - CS_2 + 2H]^+$ calcd for $C_{10}H_{19}N_2O_2$ 199.1441, found 199.1442 (error 0.5 ppm).

Sodium 6-((*tert*-butoxycarbonyl)amino)-3-azabicyclo[3.1.0]hexane-3-carbodithioate (**18e**). The title compound was prepared from *tert*-butyl *meso*-3-azabicyclo[3.1.0]hex-6-ylcarbamate (1.00 g, 5.04 mmol, 1.0 equiv), by condensation with CS_2 (0.37 mL, 6.05 mmol, 1.2 equiv) using the general procedure to afford **18e** (1.09 g, 73%) as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 4.32 (d, J = 13.2 Hz, 2H), 3.75 (d, J = 13.2 Hz, 2H), 2.15 (s, 1H), 1.77 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, CD_3OD) δ 208.7, 157.4, 78.8, 55.2, 34.1, 27.3, 24.7; HRMS (ESI+) *m/*z $[M – Na - CS_2 + 2H]^+$ calcd for $C_{10}H_{19}N_2O_2$ 199.1441, found 199.1440 (error 0.5 ppm).

General procedure for the synthesis of compounds 19b and 19e. A mixture of **18** (0.51 mmol, 1.0 equiv), **17** (0.22 g, 0.61 mmol, 1.2 equiv) and anhydrous K_2CO_3 (0.08 g, 0.56 mmol, 1.1 equiv) was stirred in anhydrous DMF (15 mL) at 60 ℃. After 2 h, the reaction mixture was cooled down to room temperature and poured into ice-water. The product was extracted with CH_2Cl_2 (20 mL × 5). The organic layer was combined, washed by saturated brine (5 mL × 3) and dried by anhydrous sodium sulfate which was removed by filtration after 20 minutes. The solvent CH_2Cl_2 was removed under reduced pressure. The product was purified by silica flash column chromatography.

***tert*-Butyl 6-(8-nitro-4-oxo-6-(trifluoromethyl)-4*H*-benzo[*e*][1,3]thiazin-2-yl)-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate** (**19b**). The title compound was prepared from **18b** (0.15g, 0.51 mmol, 1.0 equiv) and **17** (0.22g, 0.61 mmol, 1.2 equiv) using the

general procedure for cyclization to afford compound **19b** (0.20 g, 83%) as a light yellow solid: R_f = 0.3 (1:2 Hexane-EtOAc); ^{1}H NMR (400 MHz, CD_3OD): δ 8.99 (s, 1H), 8.89 (s, 1H), 4.94 (m, 1H), 4.88 (m, 1H), 4.02 (m, 2H), 3.74 (m, 2H), 2.97 (m, 1H), 1.87 (q, J = 9.2 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, CD_3OD): δ 166.8, 161.9, 144.0, 134.7, 132.1, 128.7 (q, J = 35.1 Hz), 126.2, 125.8, 122.7 (q, J = 270.0 Hz), 80.4, 62.3, 61.4, 29.3, 27.1; HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{19}H_{20}F_3N_4O_5S$: 473.1101; found: 473.1102 (error 0.2 ppm).

***tert*-Butyl (3-(8-nitro-4-oxo-6-(trifluoromethyl)-4*H*-benzo[*e*][1,3]thiazin-2-yl)-3-azabicyclo[3.1.0]hexan-6-yl)carbamate** (**19e**). The title compound was prepared from **18e** (0.15g, 0.51 mmol, 1.0 equiv) and **17** (0.22g, 0.61 mmol, 1.2 equiv) using the general procedure for cyclization to afford compound **19e** (0.18 g, 76%) as a light yellow solid: R_f = 0.3 (1:2 Hexane-EtOAc); ^{1}H NMR (400 MHz, CD_3OD): δ 9.00 (s, 1H), 8.89 (s, 1H), 4.22 (m, 1H), 4.01 (m, 2H), 3.86 (m, 2H), 2.03 (m, 1H), 1.97 (m, 1H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, CD_3OD): δ 166.7, 161.8, 144.1, 134.7, 132.0, 128.7 (q, J = 34.0 Hz), 126.1, 125.8, 122.7 (q, J = 270.0 Hz), 79.2, 51.9, 49.0, 29.3, 27.2; HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{19}H_{20}F_3N_4O_5S$: 473.1101; found: 473.1095 (error 1.3 ppm).

General procedure for the synthesis of benzothiazinone analogs (2 and 5). Compound **19** (0.42 mmol, 1.0 equiv) was dissolved in TFA/CH_2Cl_2 (10 mL) and the solution was stirred in ice-bath. After 30 minutes, the solvent was removed under vacumm to afford the crude **20**, which was used in the next step without further purification. The mixture of crude **20** and cyclohexane carboxaldehyde (0.06 mL, 0.47 mmol, 1.1 equiv) was stirred at room temperature. After 30 minutes, sodium triacetoxyborohydride (0.09 g, 0.44 mmol, 1.05 equiv) was added in portions and the mixture stirred at room temperature for 3 h. The reaction solution was quenched with saturated aqueous Na_2CO_3 (10 mL), extracted with CH_2Cl_2 (10 mL × 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica flash column chromatography to give the final compound.

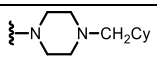
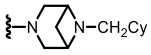
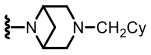
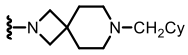
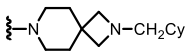
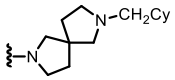
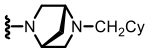
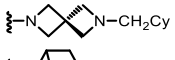
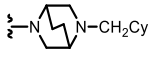
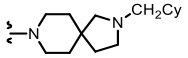
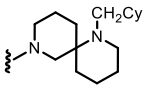
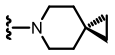
2-(3-(Cyclohexylmethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl)-8-nitro-6-(trifluoromethyl)-4*H*-benzo[*e*][1,3]thiazin-4-one (**2**). The title compound was prepared from **19b** (0.15g, 0.32 mmol, 1.0 equiv), which was deprotected in TFA followed by reductive amination with cyclohexane carboxaldehyde (0.04 mL, 0.35 mmol, 1.1 equiv) using the general procedure to afford **2** (0.12 g, 81%) as a light yellow solid: mp 122-124° C; R_f = 0.2 (1:2 Hexane-EtOAc); ^{1}H NMR (500 MHz, CD_3OD): δ 9.05 (d, J = 2.1 Hz, 1H), 8.95 (d, J = 2.1 Hz, 1H), 4.57 (m, 2H), 4.40 (m, 4H), 3.45 (m, 1H), 3.10 (m, 2H), 2.10 (d, J = 8.0 Hz, 1H), 1.79 (m, 4H), 1.72 (m, 1H), 1.30 (m, 4H), 1.08 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 168.1, 166.5, 145.8, 135.5, 133.7, 130.7 (q, J = 35.0 Hz), 127.6, 127.4, 124.1 (q, J = 270.0 Hz), 64.3, 64.0, 58.3, 36.0, 31.7, 26.9, 26.6, 18.4; HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{21}H_{24}F_3N_4O_3S$: 469.1516; found: 469.1521 (error 1.1 ppm).

2-(6-(Cyclohexylmethyl)-3,6-diazabicyclo[3.1.0]hexan-3-yl)-8-nitro-6-(trifluoromethyl)-4*H*-benzo[*e*][1,3]thiazin-4-one (**5**). The title compound was prepared from **19e** (0.15g, 0.32 mmol, 1.0 equiv), which was deprotected in TFA followed by reductive amination with cyclohexane carboxaldehyde (0.04 mL, 0.35 mmol, 1.1 equiv) using the general procedure to afford **2** (0.12 g, 80%) as a light yellow solid: mp 131-134° C; R_f = 0.2 (1:2 Hexane-EtOAc); ^{1}H NMR (300 MHz, CD_3OD): δ 8.98 (d, J = 2.1 Hz, 1H), 8.88 (d, J = 2.1 Hz, 1H), 4.25 (m, 1H), 4.03 (m, 1H), 3.95 (m, 2H), 2.86 (d, J = 7.0 Hz, 2H), 2.48 (m, 1H), 2.30 (m, 1H), 2.21 (m, 1H), 1.76 (m, 5H), 1.30 (m, 4H), 0.99 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD): δ 167.7, 163.0, 145.1, 136.0, 133.5, 130.2 (q, J = 35.3 Hz), 127.3, 127.0, 123.8 (q, J = 274.0 Hz), 56.2, 53.3, 50.4, 42.1, 37.1, 31.8, 27.2, 26.7, 23.9, 22.5; HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{21}H_{24}F_3N_4O_3S$: 469.1516; found: 469.1515 (error 0.2 ppm).

III. MIC Determination

The minimum inhibitory concentrations (MICs) of all compounds measured were determined by broth microdilution method with compounds added from DMSO stock solutions into supplemented 7H9 medium for a final concentration of 1% DMSO for all treatments. Compound stock solutions were prepared in DMSO and the final test concentrations ranged from 1024 nM to 1 nM. *M. tuberculosis* H37Rv, CDC1551, and Erdman were grown to mid-log (OD_{600} ~ 0.4-0.6) in 30-mL square bottles (Nalgene) containing supplemented 7H9 medium with tyloxapol (0.05% vol/vol), oleate-albumin-dextrose-catalase (OADC; Becton Dickinson 10% vol/vol), and glycerol (0.2% vol/vol). Cells were then inoculated into 96-well round bottom plates (Corning) containing 7H9 medium (100 μL/well) and compound to an initial OD_{600} of 0.001. Plates were incubated at 37°C, and growth was monitored at 7 and 10 days. Visual inspection was used to determine the minimum concentration of compound required to inhibit 90% of growth relative to that of the no drug control after a period of 10 days. Experiments were performed twice independently in triplicate.

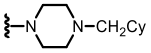
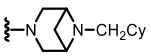
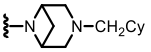
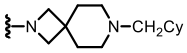
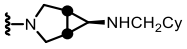
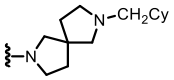
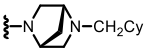
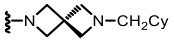
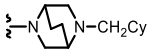
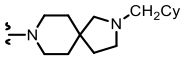
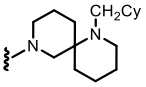
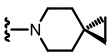
Table S2. MIC_{90} values against *M. tuberculosis strains* H37Rv, CDC1551, and Erdman.

		MIC_{90} (nM)		
Compounds	R	H37Rv	CDC1551	Erdman
PBTZ169		2	1	1
1		128	64	128
2		128	128	32
3		1024	512	512
4		512	512	512
5		32	16	16
6		256	256	128
7		64	64	64
8		256	256	128
9		32	32	32
10		128	128	64
11		1024	1024	1024
12		16	16	8

IV. Cell Cytotoxicity

The CellTiter-Glo Luminescence Assay (Promega, Madison, WI) was used to determine CC_{90}, the concentration that caused a 90% reduction in cell viability for each compound tested. Human hepatocellular carcinoma (HepG2) cells (ATCC: HB-8065) and African green monkey kidney (Vero) cells (ATCC: CCL-81) were grown in Dulbecco's MEM growth medium supplemented with 10% fetal bovine serum, 100 U/mL penicillin, and 100 µg/mL streptomycin at 37 °C and 5% CO_2 in a humidified incubator. Vero and HepG2 cells were used to seed white opaque 96-well plates at a density of 2×10^4 cells/well in a total volume of 100 uL MEM medium. Following an overnight incubation, a two-fold dilution series of compound stock solutions in DMSO were added to each well yielding final compound concentrations ranging from 100 µM to 0.78 µM and a final concentration of 1% DMSO in each well. Following 72 h of incubation, medium containing drug was aspirated and 50 µL of fresh medium was added with 50 µL of the Celltiter-Glo substrate. Further steps were performed according to instructions provided by the manufacturer. Cells were then shaken at 350 rpm for 2 min using an orbital shaker to lyse and incubated at room temperature for 10 min to stabilize signal. The luminescent signal was measured in a Synergy H1 Hybrid Multi-Mode Microplate Reader (BioTek). Data were fitted to the four-parameter Hill equation using GraphPad Prism v6.0 to determine $CC_{90} \pm SD$ values. Experiments were performed on three independent days in duplicate.

Table S3. Cytotoxicity of hits against Vero and HepG2 cell lines

		CC_{90} (µM)	
Compounds	R	Vero	HepG2
PBTZ169		>100 (127)[1]	>100
1		42 ± 14	>100
2		53 ± 13	73 ± 4
3		64 ± 13	64 ± 6
4		66 ± 9	39 ± 6
5		50 ± 7	24 ± 4
6		28 ± 6	28 ± 6
7		58 ± 13	34 ± 2
8		65 ± 10	44 ± 3
9		>100	>100
10		34 ± 4	28 ± 6
11		73 ± 15	>100
12		>100	>100

[1] IC_{50} value from Makarov, V.; Lechartier, B.; Zhang, M.; Neres, J.; van der Sar, A.M.; Raadsen, S.A.S.A.; Hartkoorn, R.C.; Ryabova, O.B.; Vocat, A.; Decosterd, L.A.; Widmer, N.; Buclin, T.; Bitter, W.; Andries, K.; Pojer, F.; Dyson, P.J.; Cole, S.T., Towards a new combination therapy for tuberculosis with next generation benzothiazinones. *EMBO Mol. Med.* **2014**, *6*, 372-383.

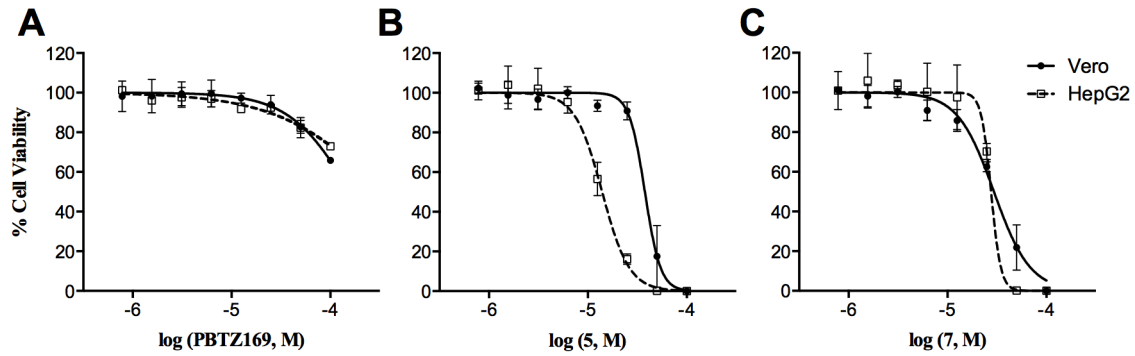


Figure S1. Representative growth inhibition curves of cytotoxicity experiments for (A) PBTZ169, (B) compound **5**, (C) compound **7**. (A-C) Vero and HepG2 cells were incubated with a range of drug concentrations for 72 h. Dose-response curves were plotted using GraphPad Prism v6.0. Each data point is mean ± SD of duplicate samples.

V. Aqueous Solubility Determination

Kinetic solubility was measured at pH 7.4 by adding a DMSO stock solution of compounds to a phosphate buffer saline solution (45 mM KH_2PO_4, 45 mM KOAc, 75 mM KCl, 45 mM ethanolamine, pH 7.4) in a total volume of 400 µL with a final DMSO concentration of 1% and the compounds quantifed by LC-MS/MS. Test compounds were initially dissolved in DMSO (PBTZ169: 10 mM; Compounds **5**, **7**, **9** and **12**: 50 mM). A total of 4 µL of stock solution of compounds at different concentration were mixed with 396 µL of the buffer in a microplate, which was shaken for 4 h at room temperature. The mixture was allowed to sit for 30 min at room temperature with a shaking and filtered through a 0.3 µm pore size membrane filter. The filtrate was diluted by 10× and 30×, and vortexed. The diluted solutions were analyzed by LC-MS/MS. A series of calibration compound solutions was prepared to generate a standard curve. The DMSO stock solutions were diluted to obtain 100 µL of a 200 µM solution of each compound, which was then used to prepare a 3-fold serial dilution series from 200 µM down to 0.003 µM (total 10 concentrations).

Chromatographic separation was performed on a Kinetex C18 100A column (30 mm x 3 mm, 2.6 µm) with a gradient mobile phase of acetonitrile/water containing 0.1% formic acid at 0.8 mL/min flow rate. LC condition: solvent A = H_2O (0.1% FA), solvent B = acetonitrile (0.1% FA). Gradient elution: 0.00 min, 95.0% A; 0.50 min, 95% A; 0.80 min, 5% A; 1.50 min, 5% A; 1.51 min, 95% A; 2.00 min, 95% A. The injection volume was 5 µL.

All analytes were analyzed by MS in postive ionization mode by Multiple Reaction Monitoring (MRM). To determine the fragmentation pattern and optimum MRM settings (**Table S4**), each analyte was infused (in 1:1 water:acetonitrile containing 0.1% Formic Acid) onto the MS by a syringe pump at a flow of 0.8 mL/min.

Table S4. Key fragmentation and optimized mass spectrometer conditions of PBTZ169, 5, 7, 9 and 12 in ESI negative mode.

Compounds	Precursor ion	Product ions	CE (v)	DP (v)
PBTZ169	457.1	343.8	35	116
5	470.1	179.0	27	91
7	469.1	355.8	39	146
9	483.1	369.9	39	166
12	386.1	303.8	37	141

Experiments were performed in a Sciex QTRAP 4500 instrument; CE = Collision Energy, DP = Declustering Potential.

VI. Microsomal Stability

Microsomal stability studies were conducted by BioDuro (Bejing, China). 100 μM of compounds in DMSO were prepared. 2.5 μL of solution was mixed with 197.5 μL liver microsome (0.5 mg/mL) (mouse and human) gently and preincubate at 37 °C for 5 min. The reaction was initiated by adding 50 μL NADPH working solution (5 mM). At each time point of 0, 5, 15, 30, 60 min, 30 μL of the reaction solution was taken out and quenched by adding 300 μL of internal standard (10 ng/mL tolbutamide) in 1:1 MeOH/MeCN. The mixture was centrifuged at 4000 rpm at 4 °C for 15 min. 100 μL of the supernant was mixed with 100 μL distilled water and then analyzed by LC-MS/MS. Midazolam, dextromethorphan, diclofenac, omeprazole, and phenacetin were used as controls.

VII. Protein Plasma Binding

The extent of plasma protein binding for each test compounds was determined by equilibrium dialysis. A 96-well Rapid Equilibrium Dialysis (RED) kit (ThermoFisher Scientific) with cassettes of compounds (pooling of compounds predialysis) was used to perform measurement (each run in duplicate). The plasma was centrifuged (15 min, 4000 rpm at 4 ^{o}C). Test compound was added to the plasma which was mixed and heated (1 mM, 1% [vol/vol] DMSO, 37 ^{o}C). Regenerated cellulose membranes (5000 Daltons, Harvard Apparatus) were soaked in phosphate buffer for 5 min and placed within Fast Micro-Equilibrium Dialyzers (Harvard Apparatus). Subsequently, the plasma containing compounds was added to the donor side of the single-use RED plate. Buffer was added to the other side. Equilibrium dialysis was undertaken by incubation (5 h, 37 ^{o}C) and samples were removed from each compartment for LC-MS/MS analysis.

VIII. In vivo Pharmacokinetic Analysis

Animal Care and Welfare Committee of Institute of Materia Medica, Chinese Academy of Medical Sciences approved all animal protocols (1 Xian nong tan Street, Xicheng District, Beijing, China; protocol #SYXK 2014-0023). All animal programs are in compliance with the Guide for the Care and Use of Laboratory Animals issued by Beijing Association on Laboratory Animal Care (BALAC). SPF male ICR mice weighing 26-27 g were divided into two groups with three mice each: one for oral administration and intravenous injection, separately. The tested compound was formulated at a concentration of 1.0 mg/mL for a dose of 10 mg/kg given orally (p.o.) and at 0.4 mg/mL for a dose of 2 mg/kg given intravenously (i.v.). The tested compound was formulated by 0.5% carboxymethyl cellulose for p.o. administration and 10%DMSO/50%PEG400/40%water with 2.9% HCl for i.v. administration, respectively. Plasma was harvested and stored at -80^{o}C until analyzed. Plasma samples were extracted with acetonitrile containing Terfenadine and Buspirone as internal standards. Analyte quantitation was performed by a LC/TSQ Quantum Access mass spectrometer (AB Sciex 5500). Chromatographic separation was performed on a Kinetex C18 100A column (30 mm x 3 mm, 2.6 μm) with a gradient mobile phase of acetonitrile/water containing 0.1% formic acid at 0.7 mL/min flow rate. LC condition: solvent A = 5 mM NH_4OAc (0.05% FA) + H_2O, solvent B = acetonitrile (0.1% FA). Gradient elution: 0.00 min, 82.0% A; 0.40 min, 82% A; 2.00 min, 5% A; 2.20 min, 5% A; 2.21 min, 82% A; 3.00 min, 82% A.

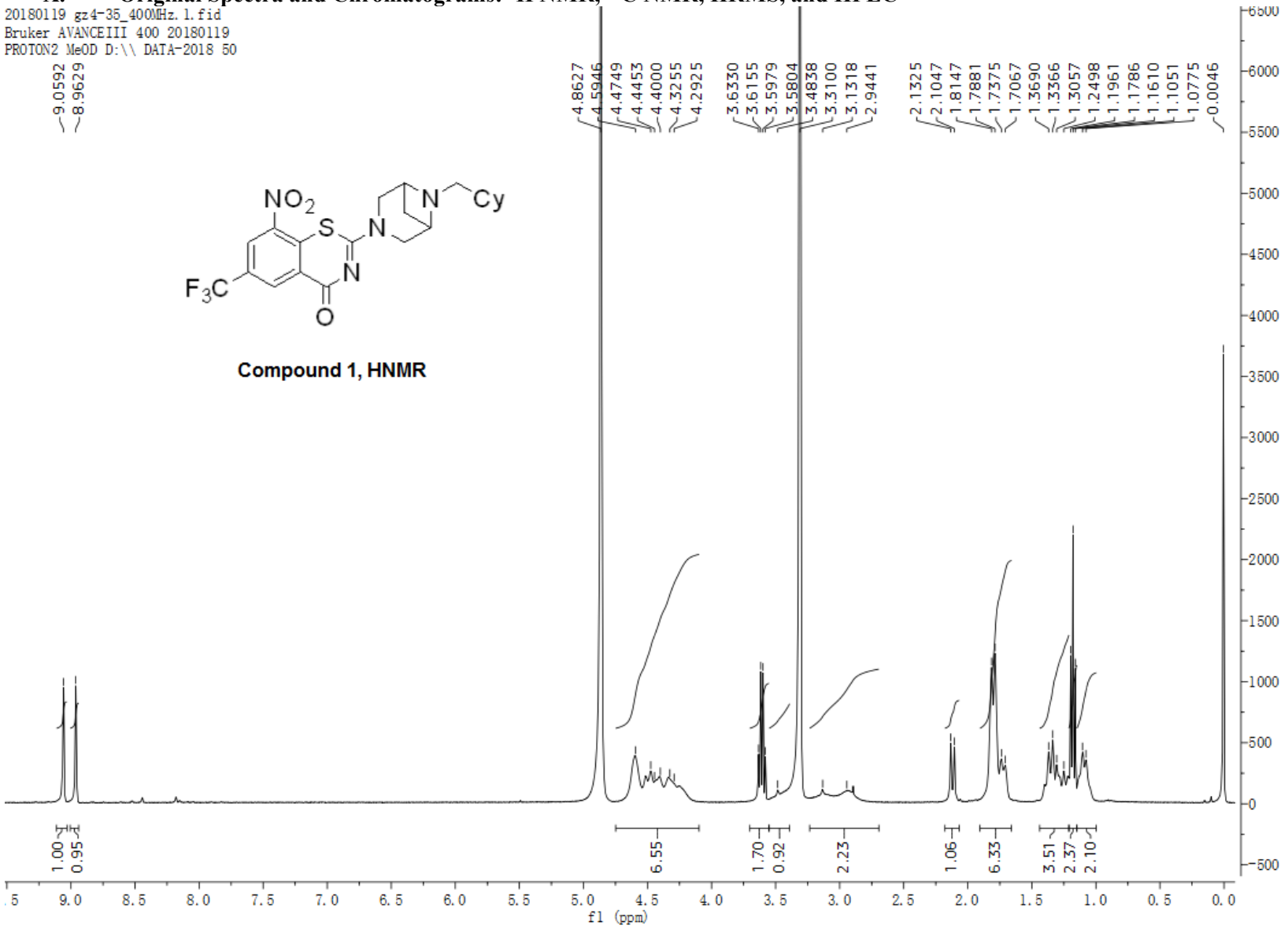
IX. HPLC Purity Determination

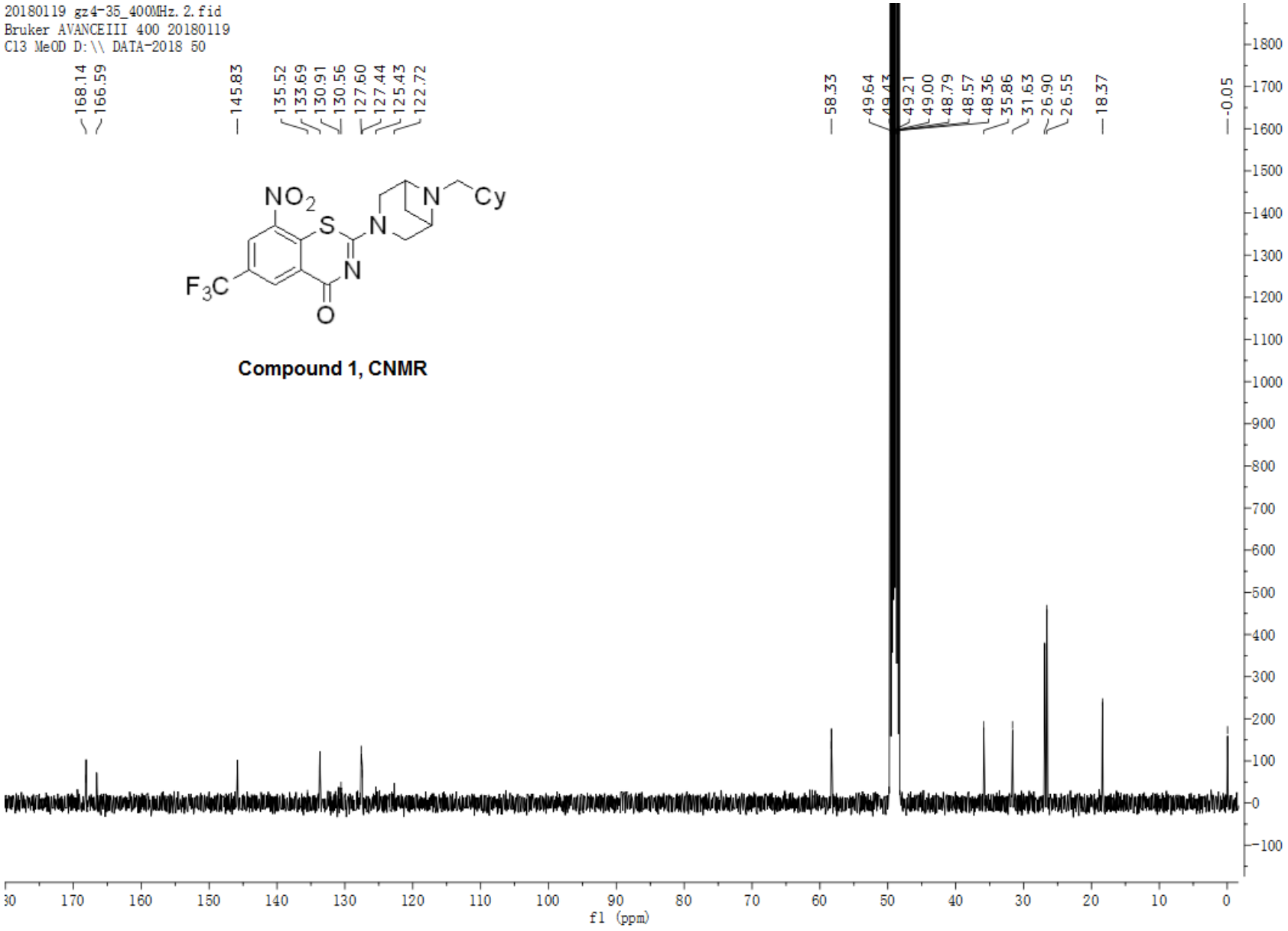
All samples were performed on a Shimadzu LCMS-2020 Series with LC20AD pumps and SPD M20A detector (220 nm and 254 nm) employing an Xbridge C18 column (30 mm × 2.1 mm, 3 μm) to determine purity (**Table S5**). HPLC condition (solvent A = 0.07% TFA + H_2O, solvent B = acetonitrile), injection volume: 5 μL, flowrate: 0.8 mL/min,gradient elution: 0.00 min, 0% B; 5 min, 60% B; 6.4 min, 60% B; 6.41 min, 0% B; 7.00 min, 0% B.

Table S5. The retention time, *k*' values and purities of target compounds

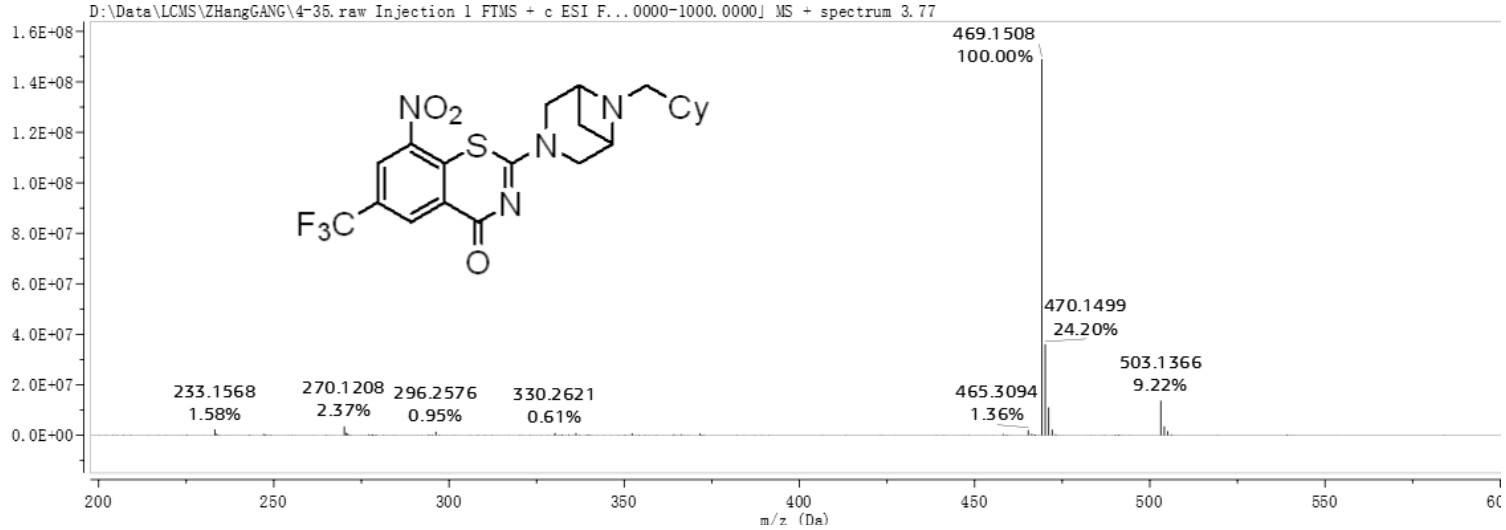
Compounds	Retention time (min)	*k*′ values	Purities (%)
1	3.35	12.4	99.8
2	3.63	12.4	92.8
5	3.77	14.1	95.6
6	3.72	14.5	99.5
7	3.53	11.7	100
8	3.49	13.5	99.4
9	3.39	12.0	99.8
11	3.58	10.2	99.7
12	5.05	17.7	100

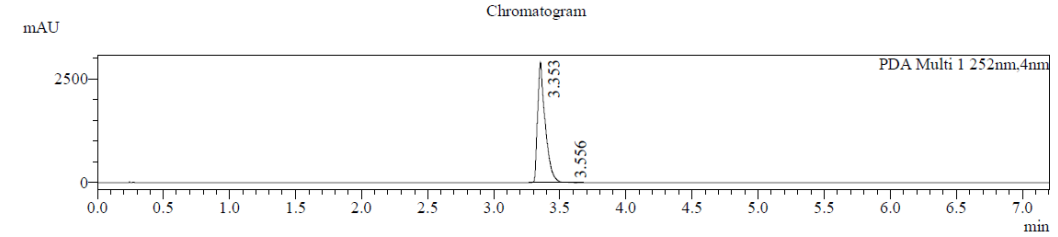
X. Original Spectra and Chromatograms: ^{1}H NMR, ^{13}C NMR, HRMS, and HPLC

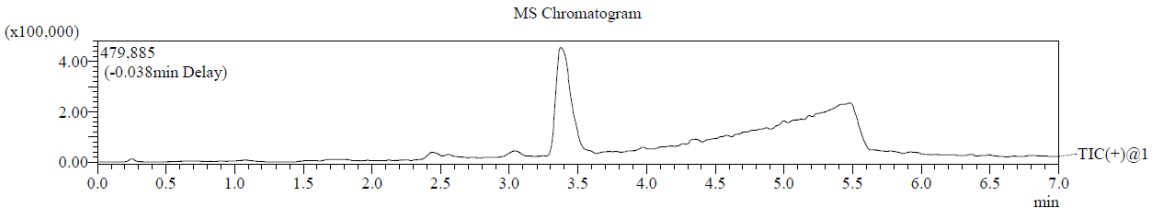




Compound 1, CNMR





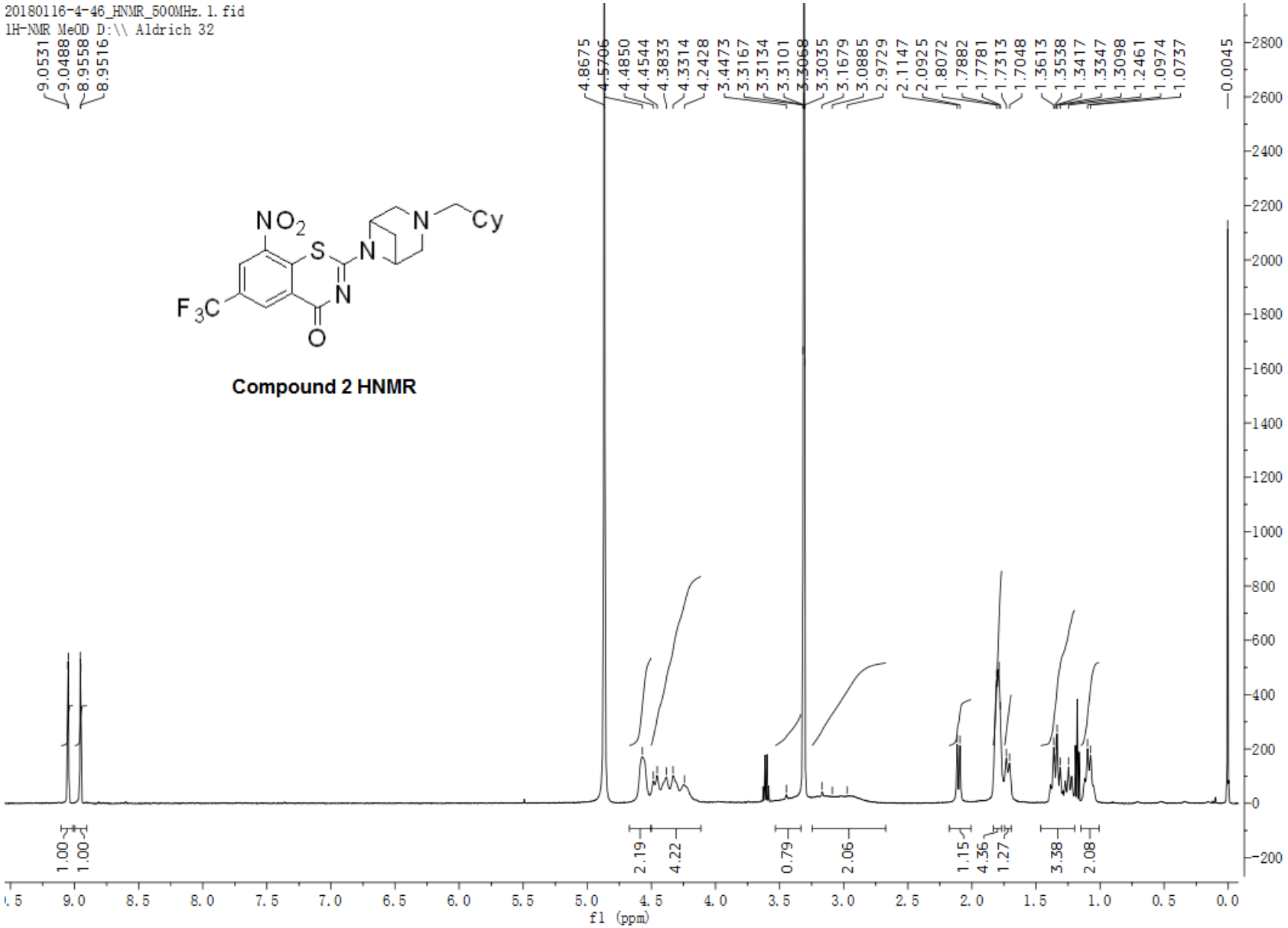


Integration Result

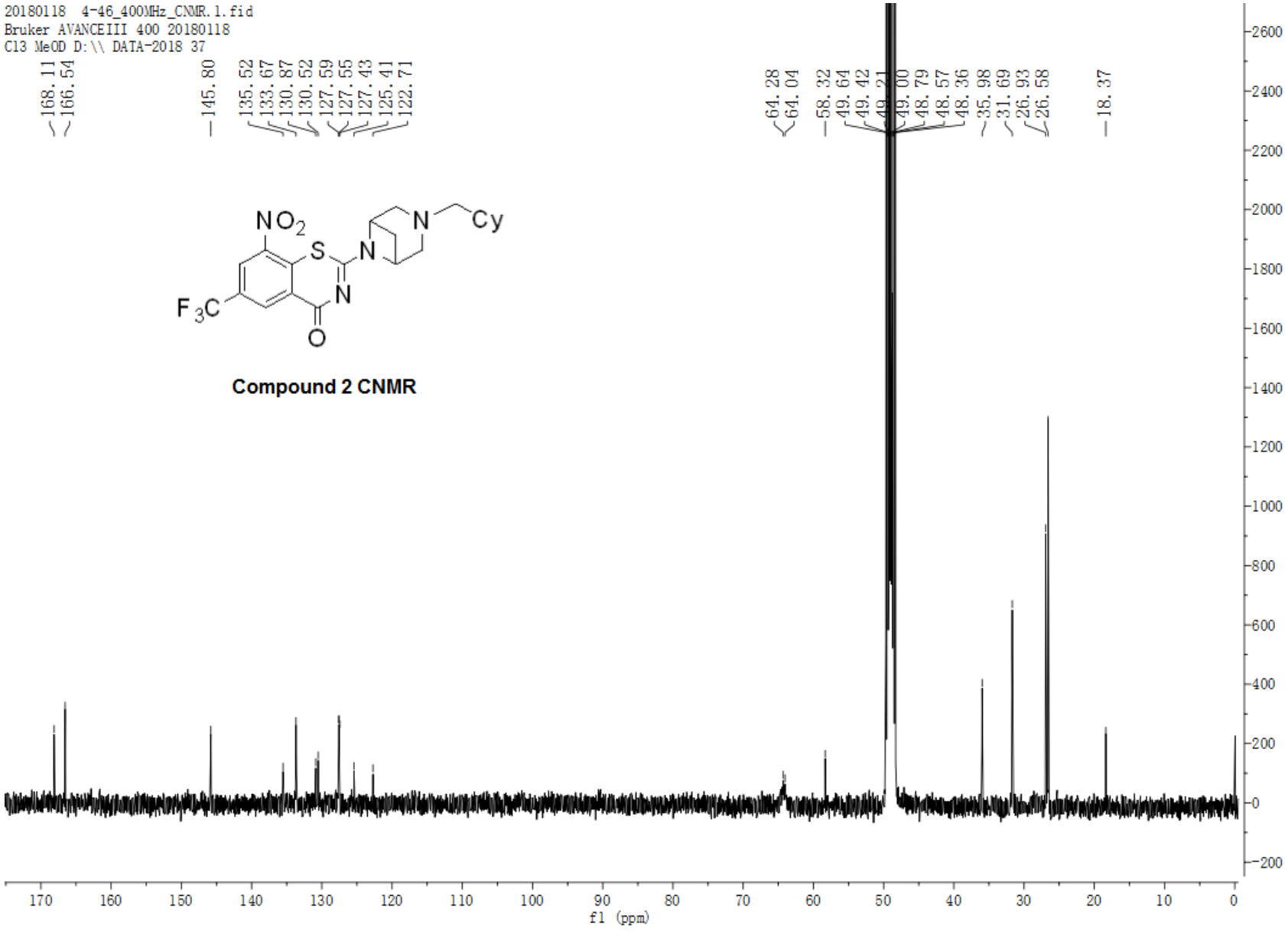
Peak Table

PDA Ch1 252nm

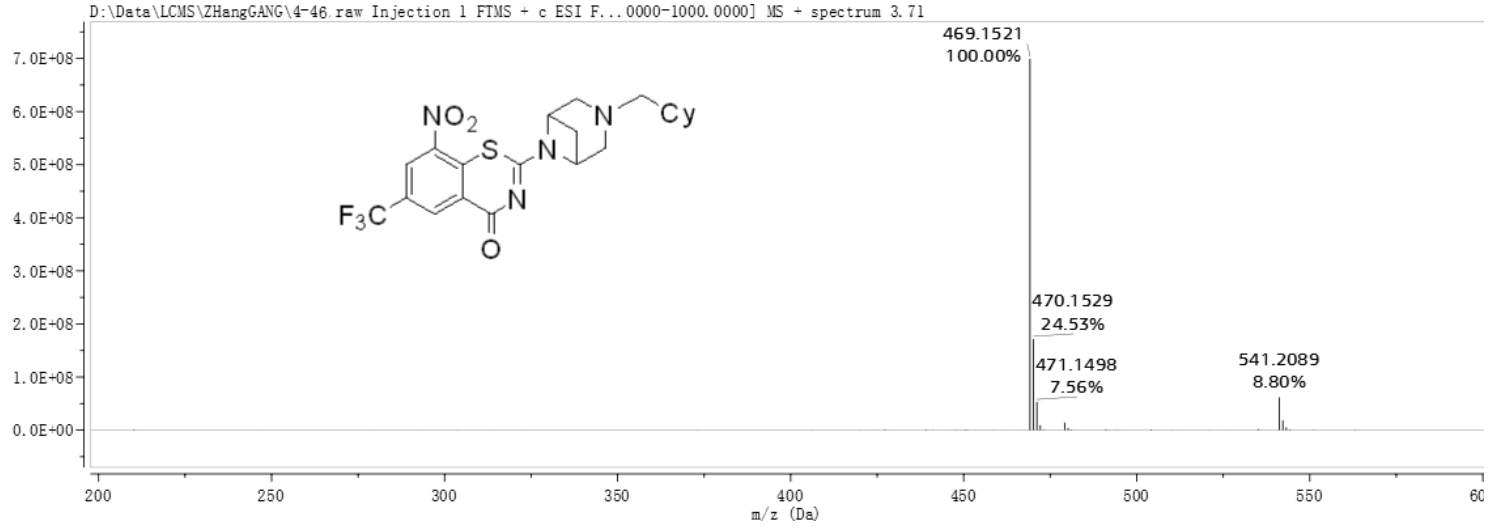
Peak#	Ret. Time	Height	Height%	USP Width	Area	Area%
1	3.353	2895445	99.745	0.120	11606444	99.832
2	3.556	7393	0.255	0.079	19506	0.168



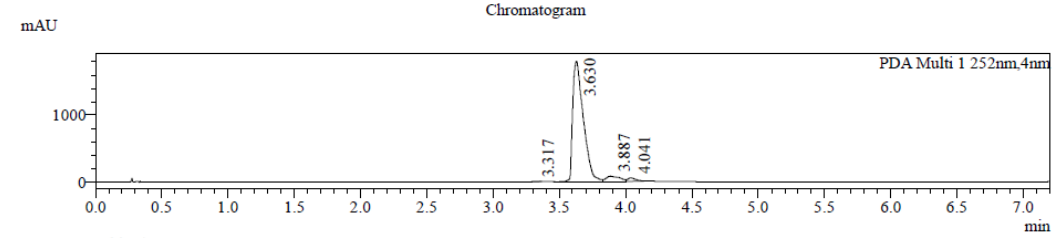
Compound 2 HNMR



Compound 2 CNMR

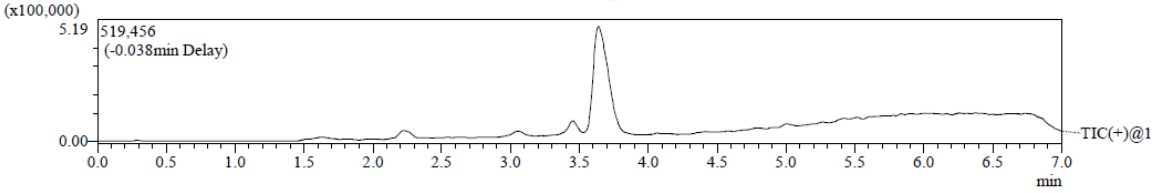


Chromatogram



1 PDA Multi 1 / 252nm,4nm

MS Chromatogram

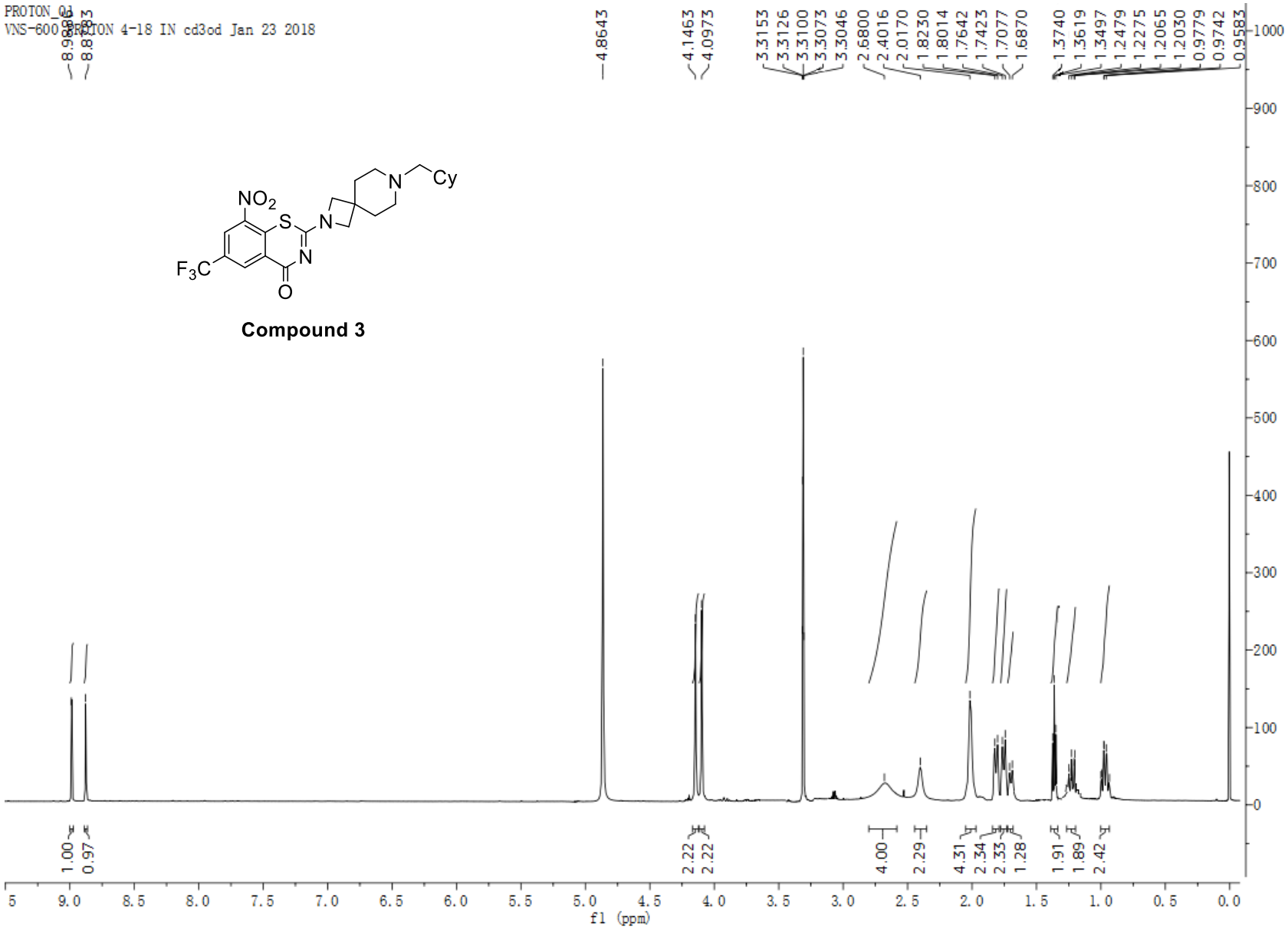


Integration Result

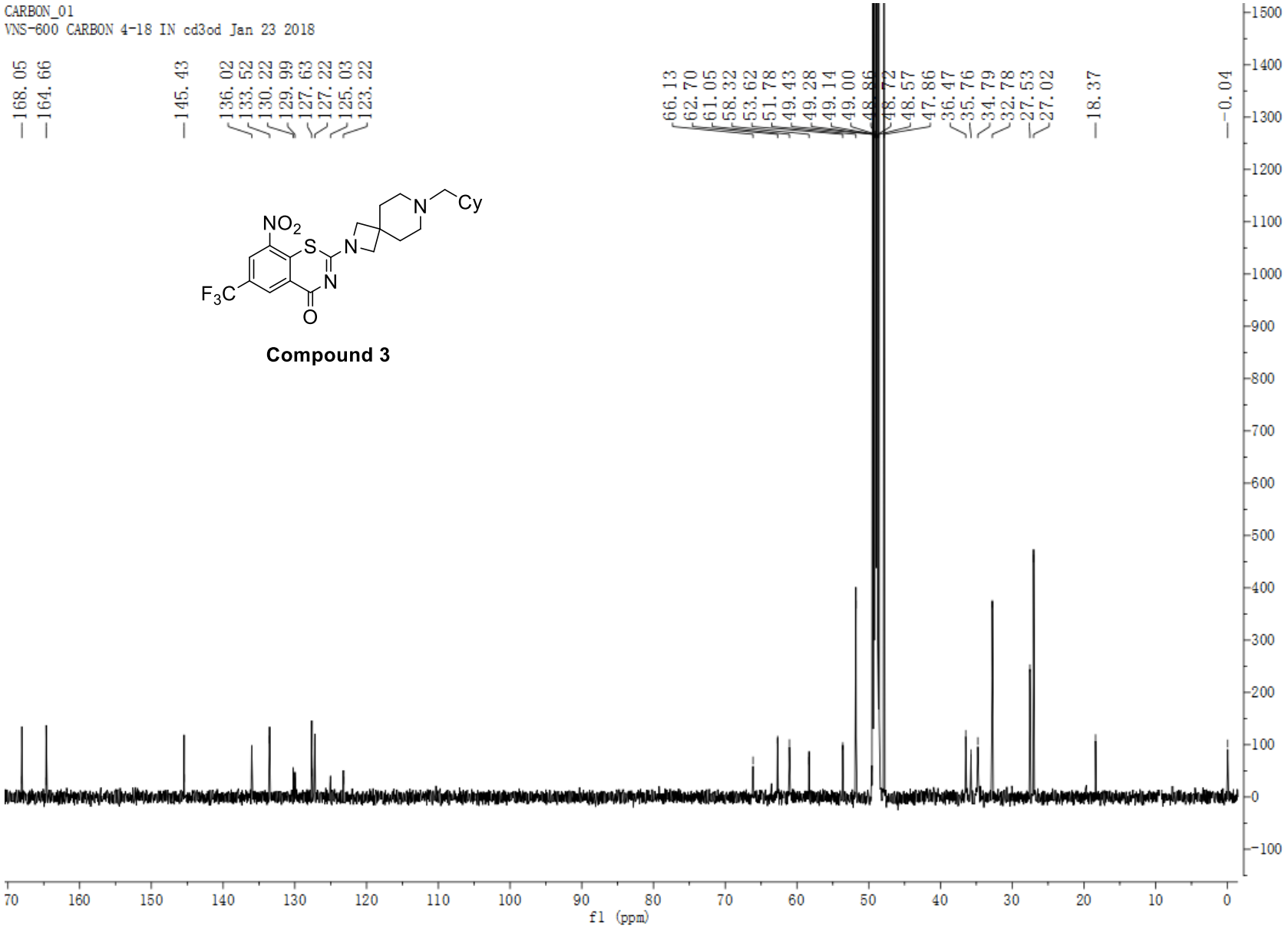
Peak Table

PDA Ch1 252nm

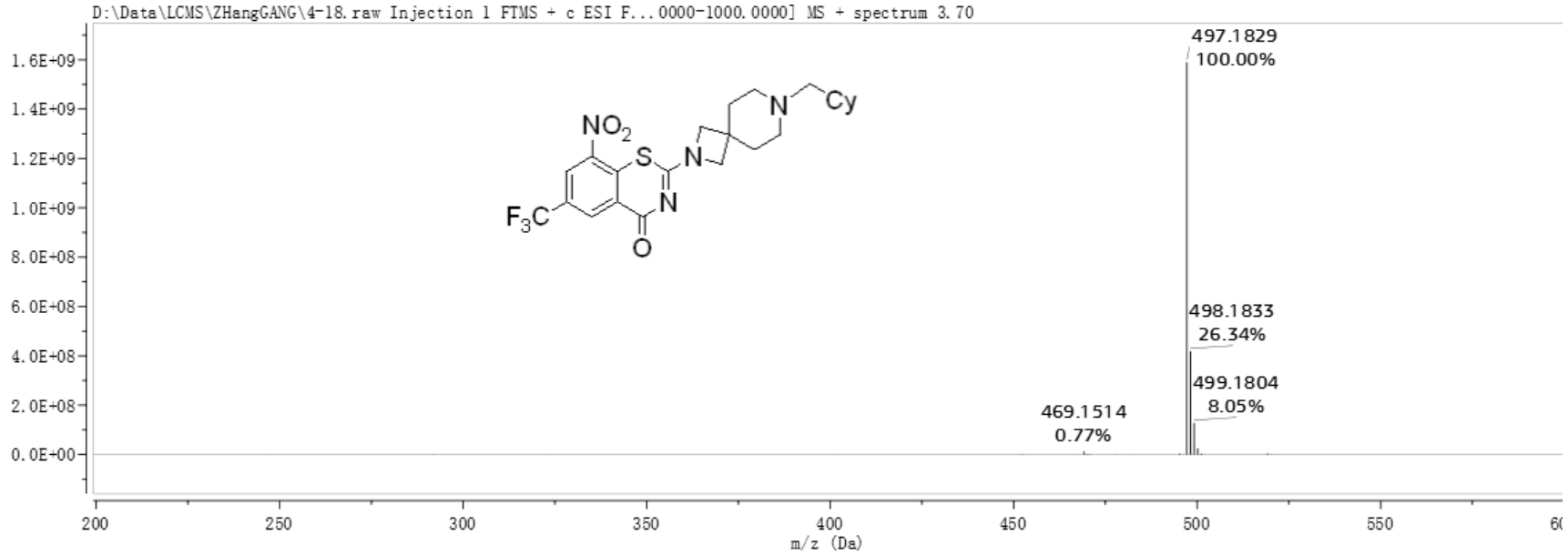
Peak#	Ret. Time	Height	Height%	USP Width	Area	Area%
1	3.317	3447	0.178	0.071	9167	0.085
2	3.630	1803441	93.294	0.157	10068627	92.866
3	3.887	78482	4.060	0.197	560780	5.172
4	4.041	47711	2.468	0.126	203546	1.877

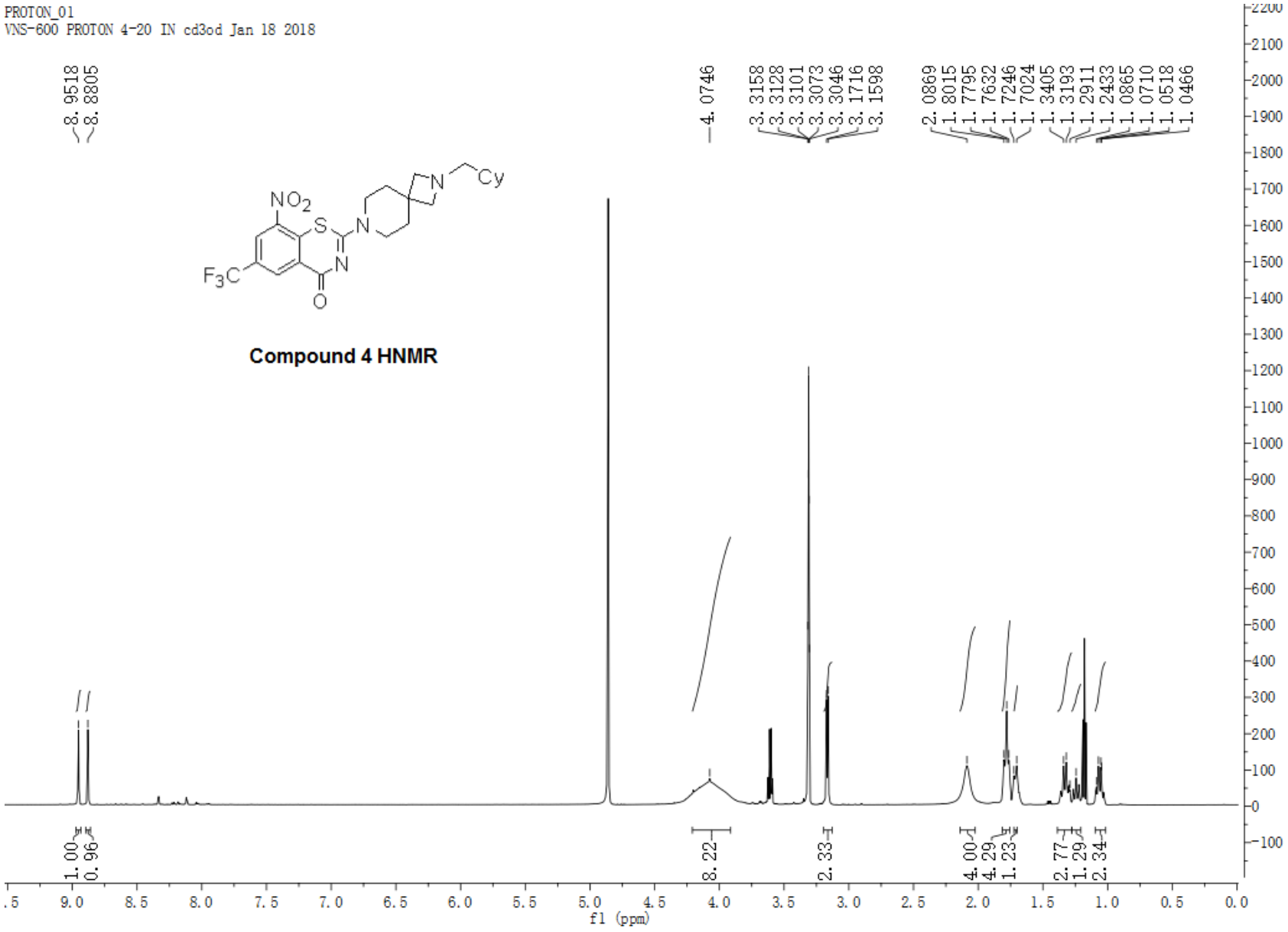

PROTON_01
VNS-600 PROTON 4-18 IN cd3od Jan 23 2018
8.9886
8.8793
4.8643
4.1463
4.0973
3.3153
3.3126
3.3100
3.3073
3.3046
2.6800
2.4016
2.0170
1.8230
1.8014
1.7642
1.7423
1.7077
1.6870
1.3740
1.3619
1.3497
1.2479
1.2275
1.2065
1.2030
0.9779
0.9742
0.9583
NO2
S
N
N
Cy
F3C
O
1.00
0.97
2.22
2.22
4.00
2.29
4.31
2.34
2.33
1.28
1.91
1.89
2.42
f1 (ppm)

Compound 3

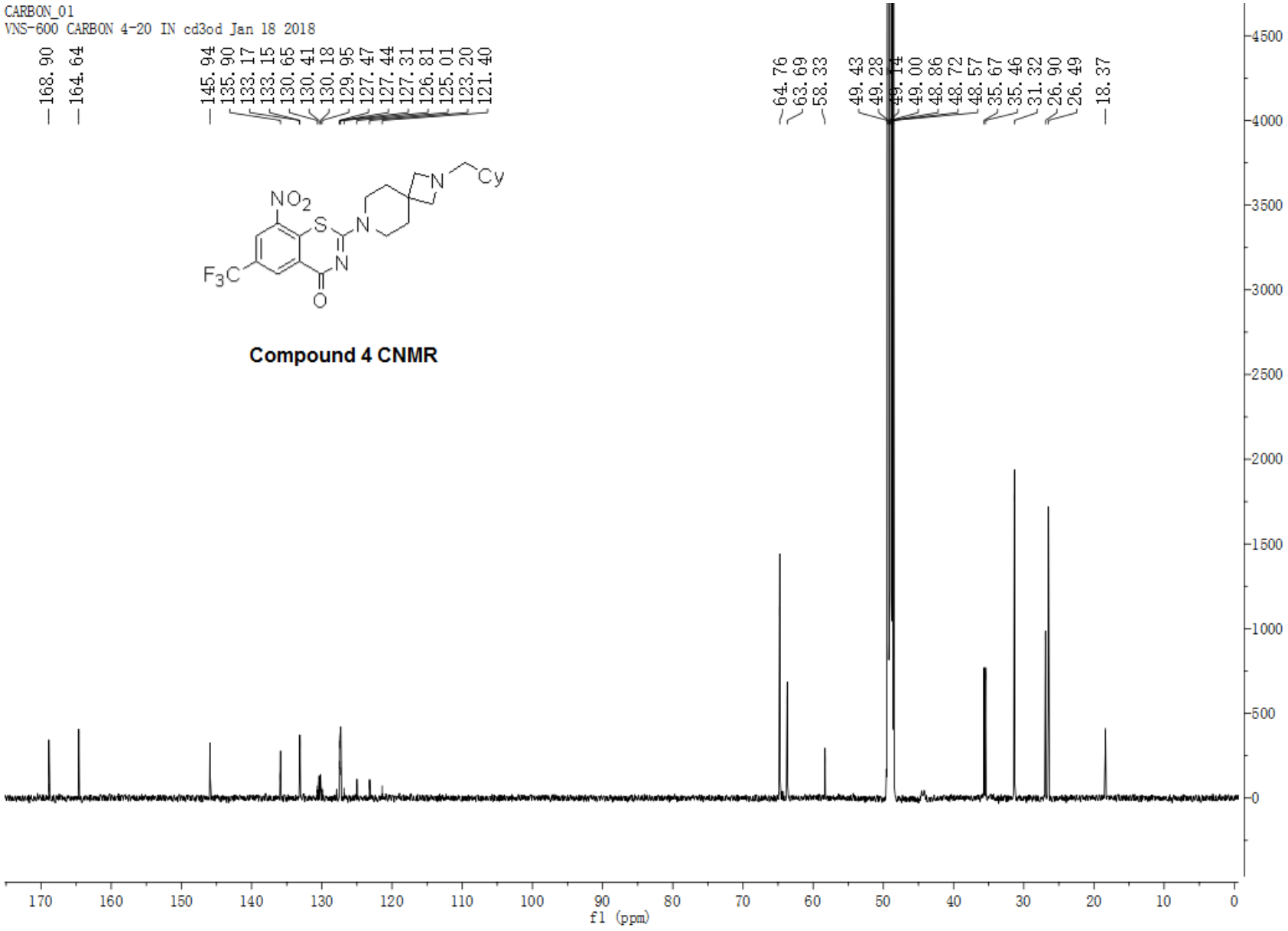

CARBON_01
VNS-600 CARBON 4-18 IN cd3od Jan 23 2018
168.05
164.66
145.43
136.02
133.52
130.22
129.99
127.63
127.22
125.03
123.22
66.13
62.70
61.05
58.32
53.62
51.78
49.43
49.28
49.14
49.00
48.86
48.72
48.57
47.86
36.47
35.76
34.79
32.78
27.53
27.02
18.37
0.04
NO2
S
N
N
Cy
F3C
N
O
f1 (ppm)

Compound 3

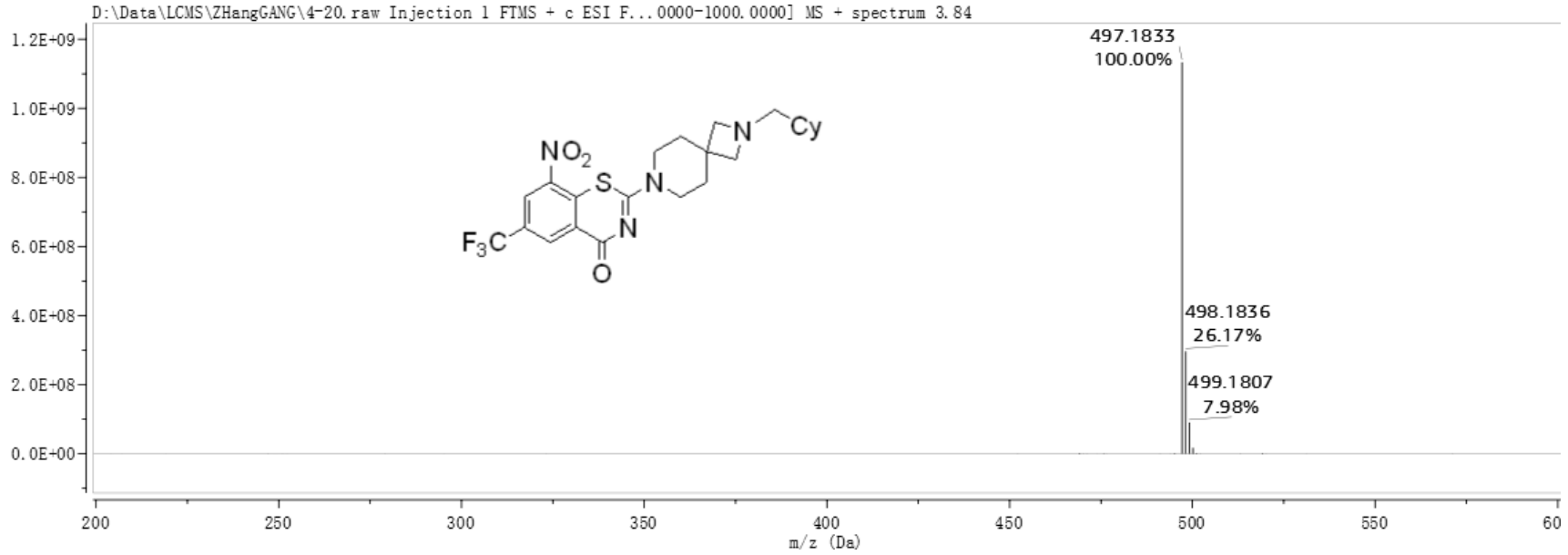

D:\Data\LCMS\ZHangGANG\4-18.raw Injection 1 FTMS + c ESI F...0000-1000.0000] MS + spectrum 3.70
497.1829
100.00%
498.1833
26.34%
499.1804
8.05%
469.1514
0.77%
NO2
S
N
N
Cy
F3C
N
O
1.6E+09
1.4E+09
1.2E+09
1.0E+09
8.0E+08
6.0E+08
4.0E+08
2.0E+08
0.0E+00
200
250
300
350
400
450
500
550
m/z (Da)

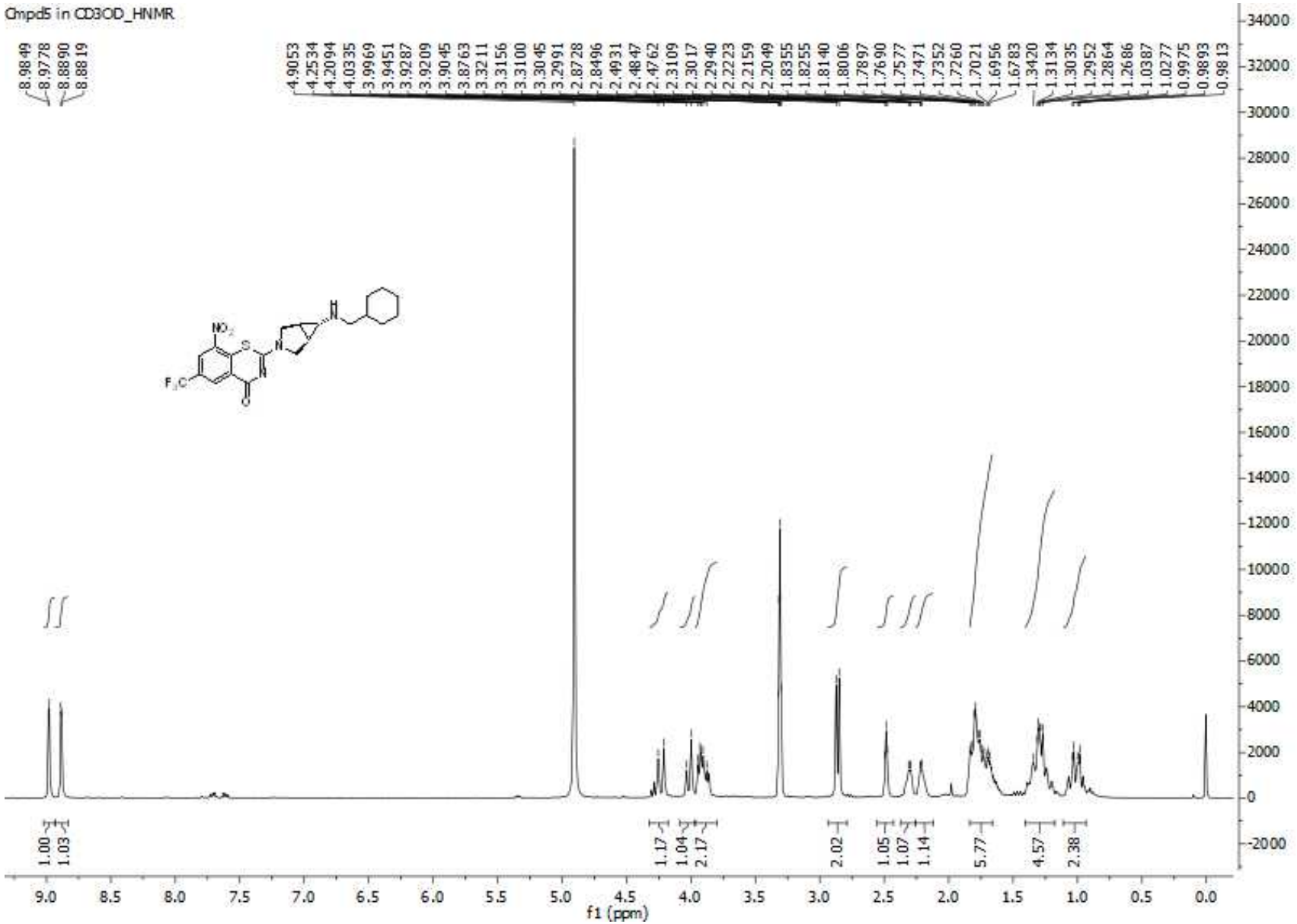


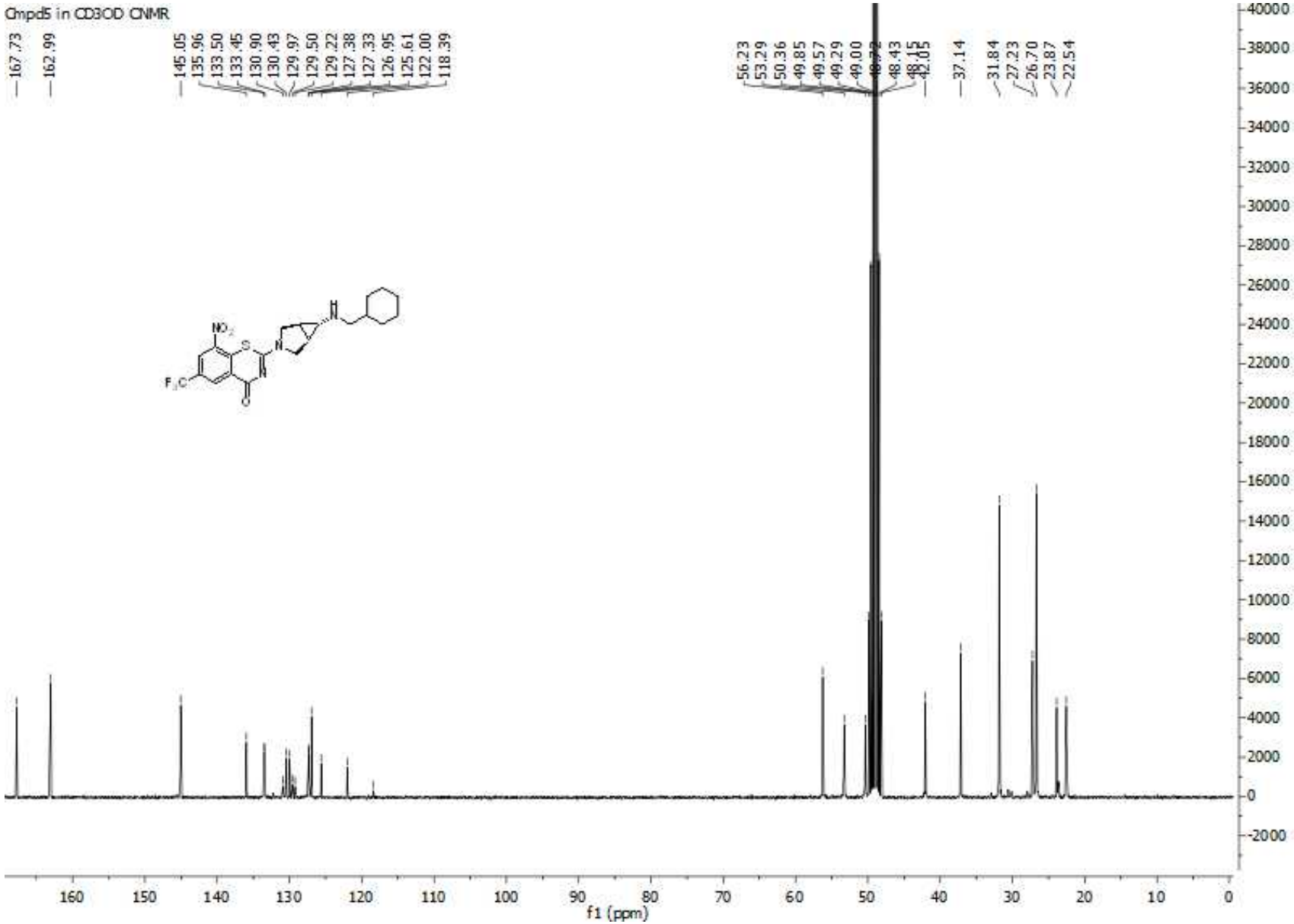
Compound 4 HNMR

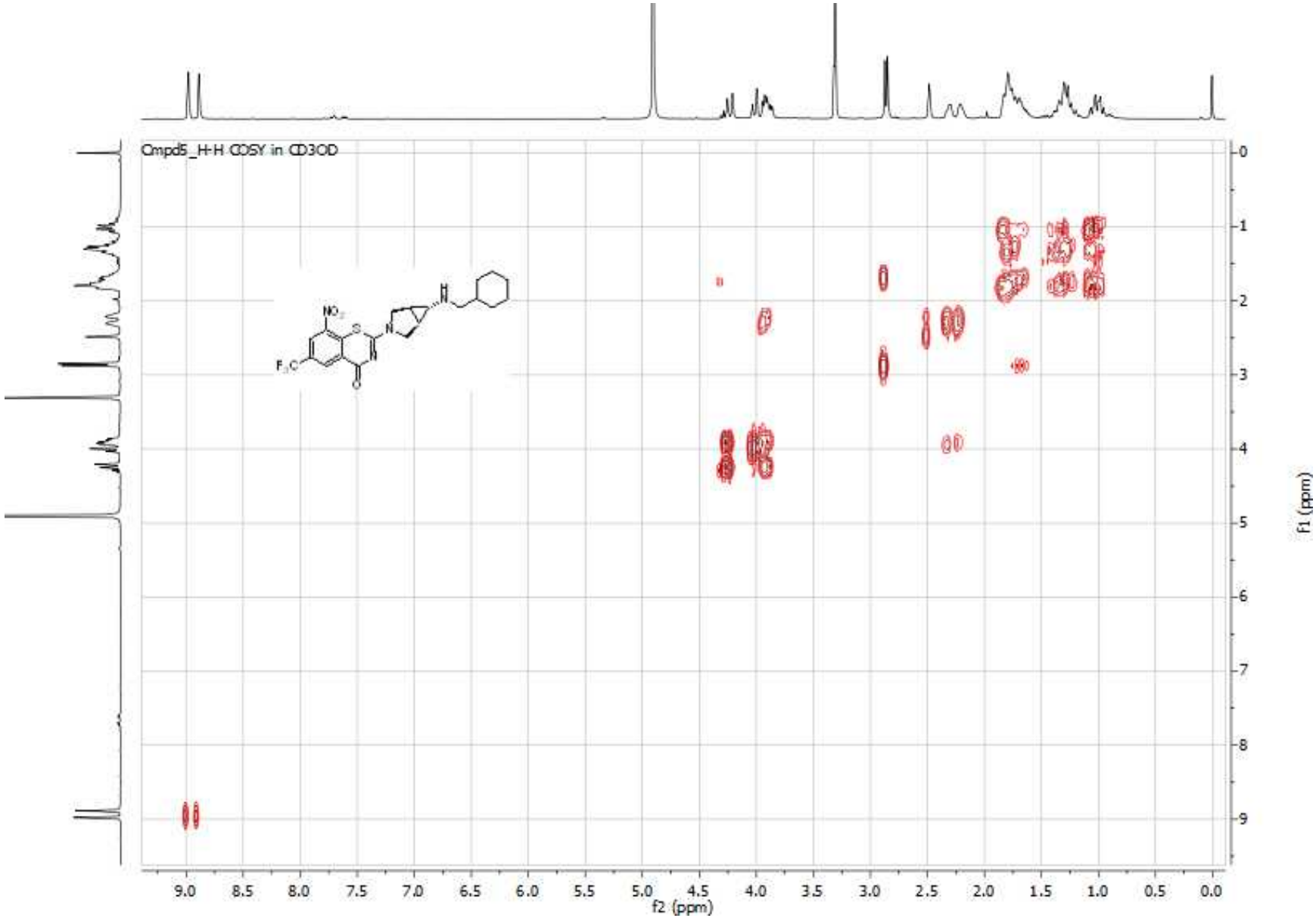


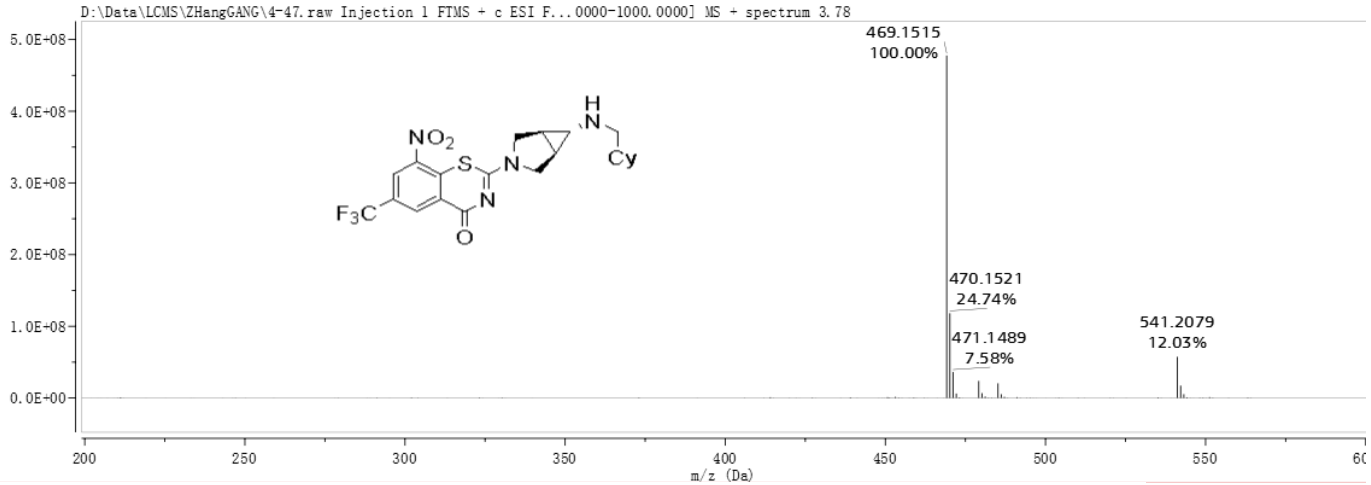
Compound 4 CNMR

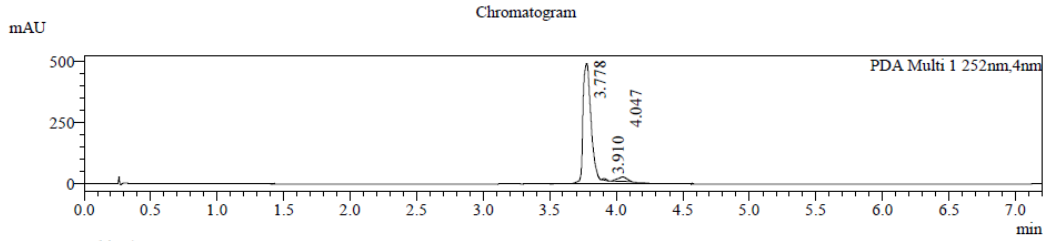

D:\Data\LCMS\ZHangGANG\4-20.raw Injection 1 FTMS + c ESI F...0000-1000.0000] MS + spectrum 3.84
497.1833
100.00%
498.1836
26.17%
499.1807
7.98%
NO2
S
N
N
Cy
F3C
O
1.2E+09
1.0E+09
8.0E+08
6.0E+08
4.0E+08
2.0E+08
0.0E+00
200
250
300
350
400
450
500
550
m/z (Da)

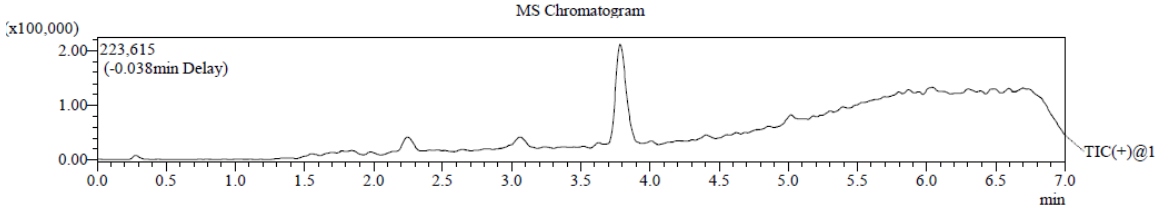

Cmpd5 in CD3OD_HNMR
8.9849
8.9778
8.8890
8.8819
4.9053
4.2534
4.2094
4.0335
3.9969
3.9451
3.9287
3.9209
3.9045
3.8763
3.3211
3.3156
3.3100
3.3045
3.2991
2.8728
2.8496
2.4931
2.4847
2.4762
2.3109
2.3017
2.2940
2.2223
2.2159
2.2049
1.8355
1.8255
1.8140
1.8006
1.7897
1.7690
1.7577
1.7471
1.7352
1.7260
1.7021
1.6956
1.6783
1.3420
1.3134
1.3035
1.2952
1.2864
1.2686
1.0387
1.0277
0.9975
0.9893
0.9813
1.00
1.03
1.17
1.04
2.17
2.02
1.05
1.07
1.14
5.77
4.57
2.38
f1 (ppm)


Cmpd5 in CD3OD CNMR
167.73
162.99
145.05
135.96
133.50
133.45
130.90
130.43
129.97
129.50
129.22
127.38
127.33
126.95
125.61
122.00
118.39
56.23
53.29
50.36
49.85
49.57
49.29
49.00
48.72
48.43
48.15
42.05
37.14
31.84
27.23
26.70
23.87
22.54
f1 (ppm)


Cmpd5_H-H COSY in CD3OD
f2 (ppm)
f1 (ppm)





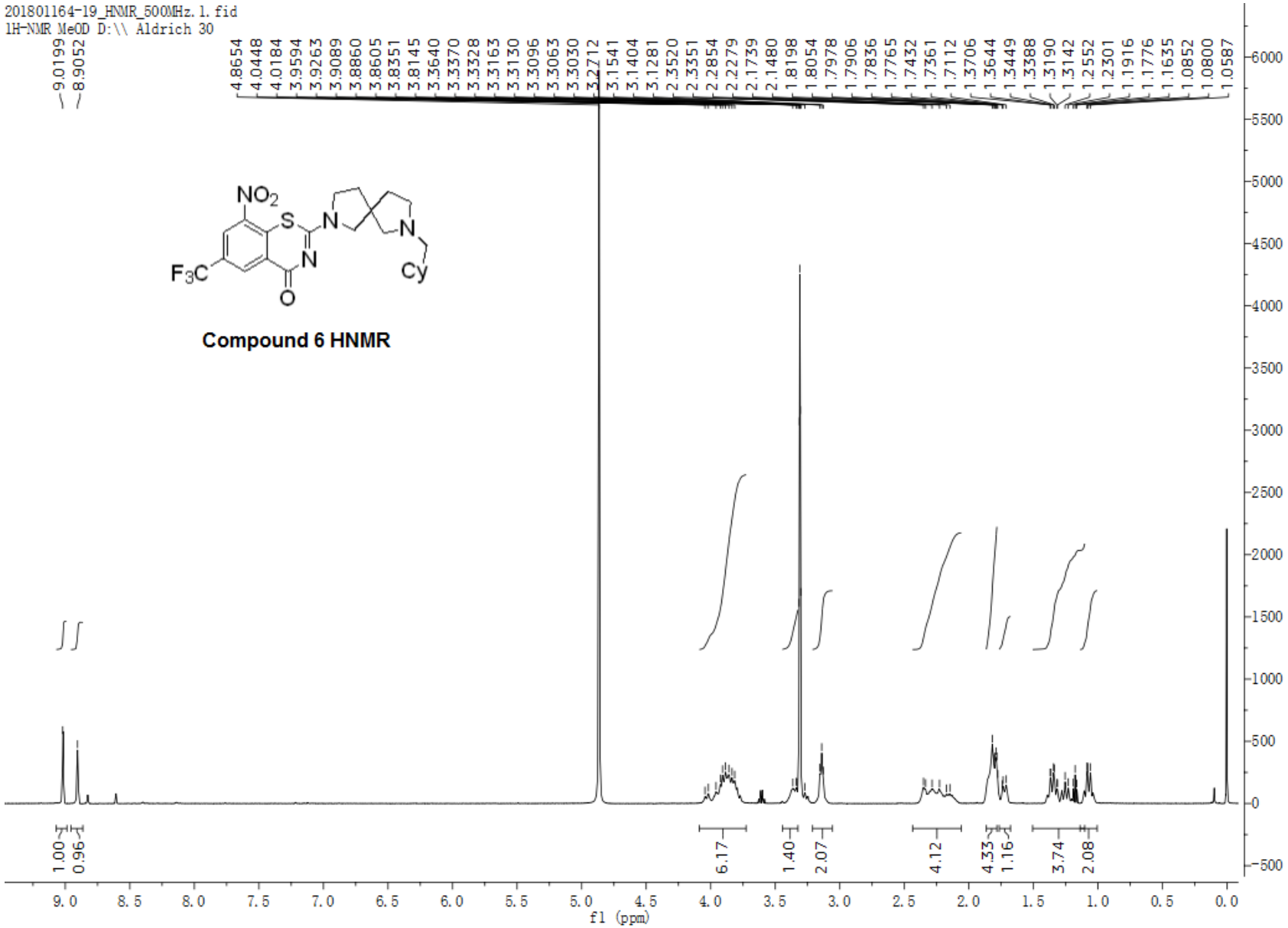


Integration Result

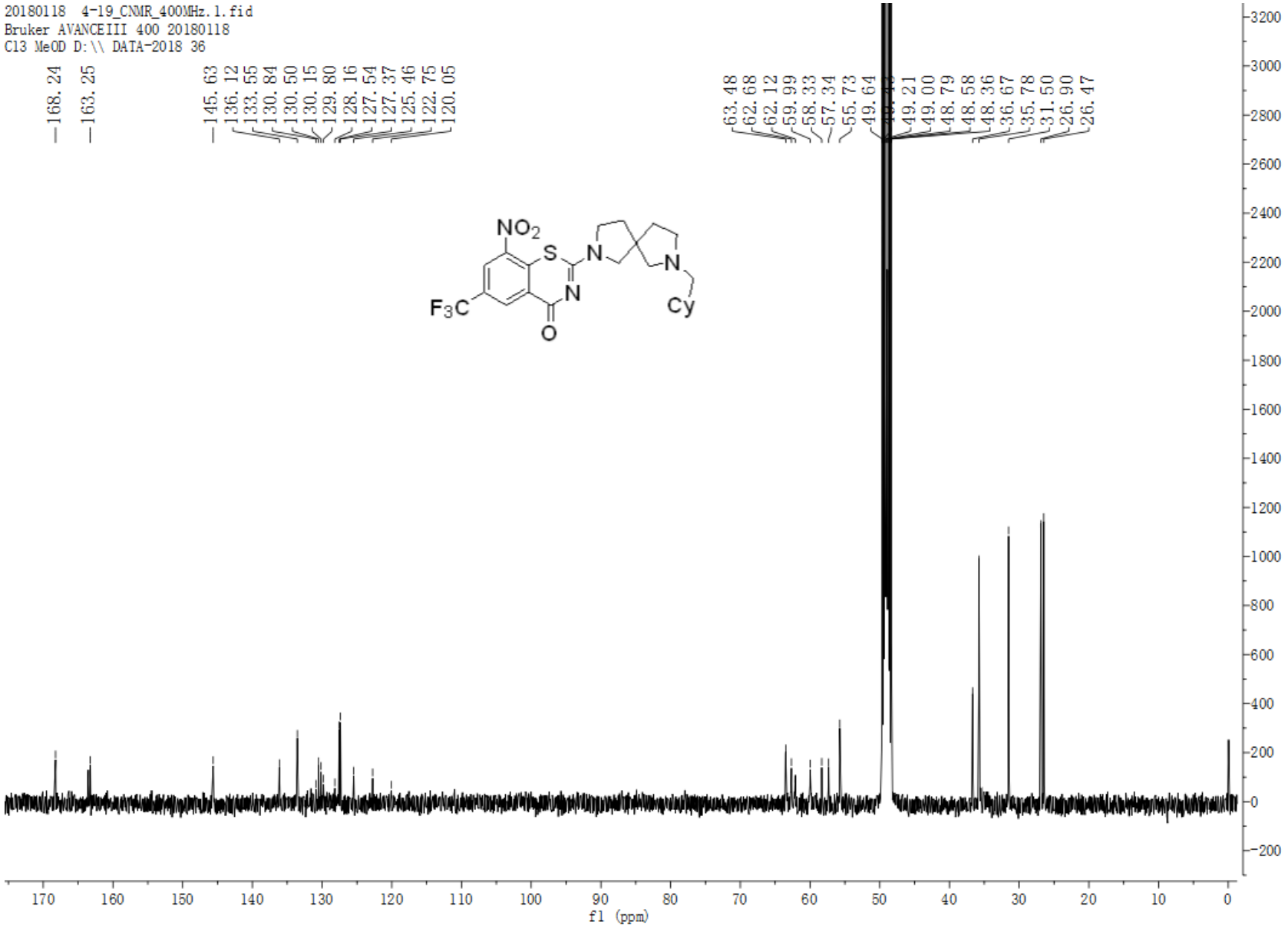
Peak Table

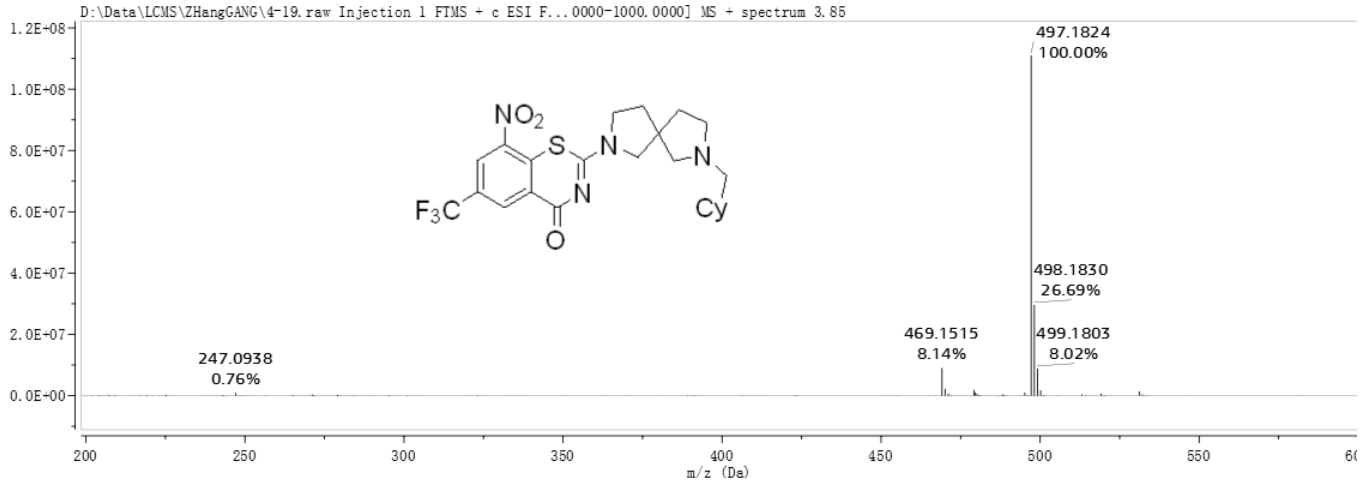
PDA Ch1 252nm

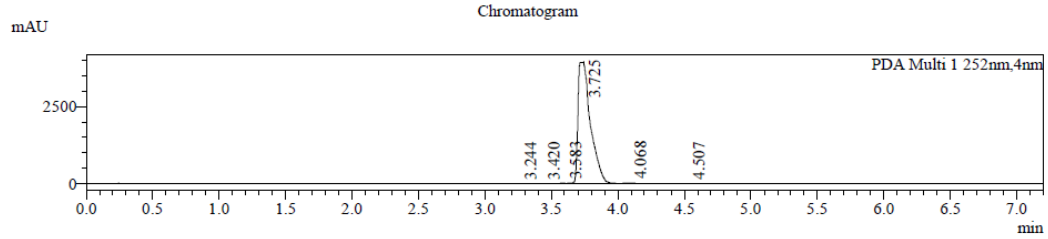
Peak#	Ret. Time	Height	Height%	USP Width	Area	Area%
1	3.778	490849	95.212	0.102	2224876	95.648
2	3.910	6546	1.270	0.051	12261	0.527
3	4.047	18137	3.518	0.188	88972	3.825



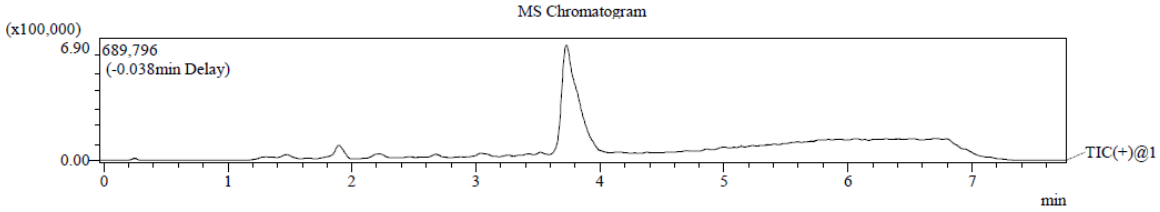
Compound 6 HNMR


20180118 4-19_CNMR_400MHz.1.fid
Bruker AVANCEIII 400 20180118
C13 MeOD D:\\ DATA-2018 36
168.24
163.25
145.63
136.12
133.55
130.84
130.50
130.15
129.80
128.16
127.54
127.37
125.46
122.75
120.05
63.48
62.68
62.12
59.99
58.33
57.34
55.73
49.64
49.21
49.00
48.79
48.58
48.36
36.67
35.78
31.50
26.90
26.47
NO2
S
N
N
N
F3C
O
Cy
f1 (ppm)





1 PDA Multi 1 / 252nm,4nm



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Integration Result

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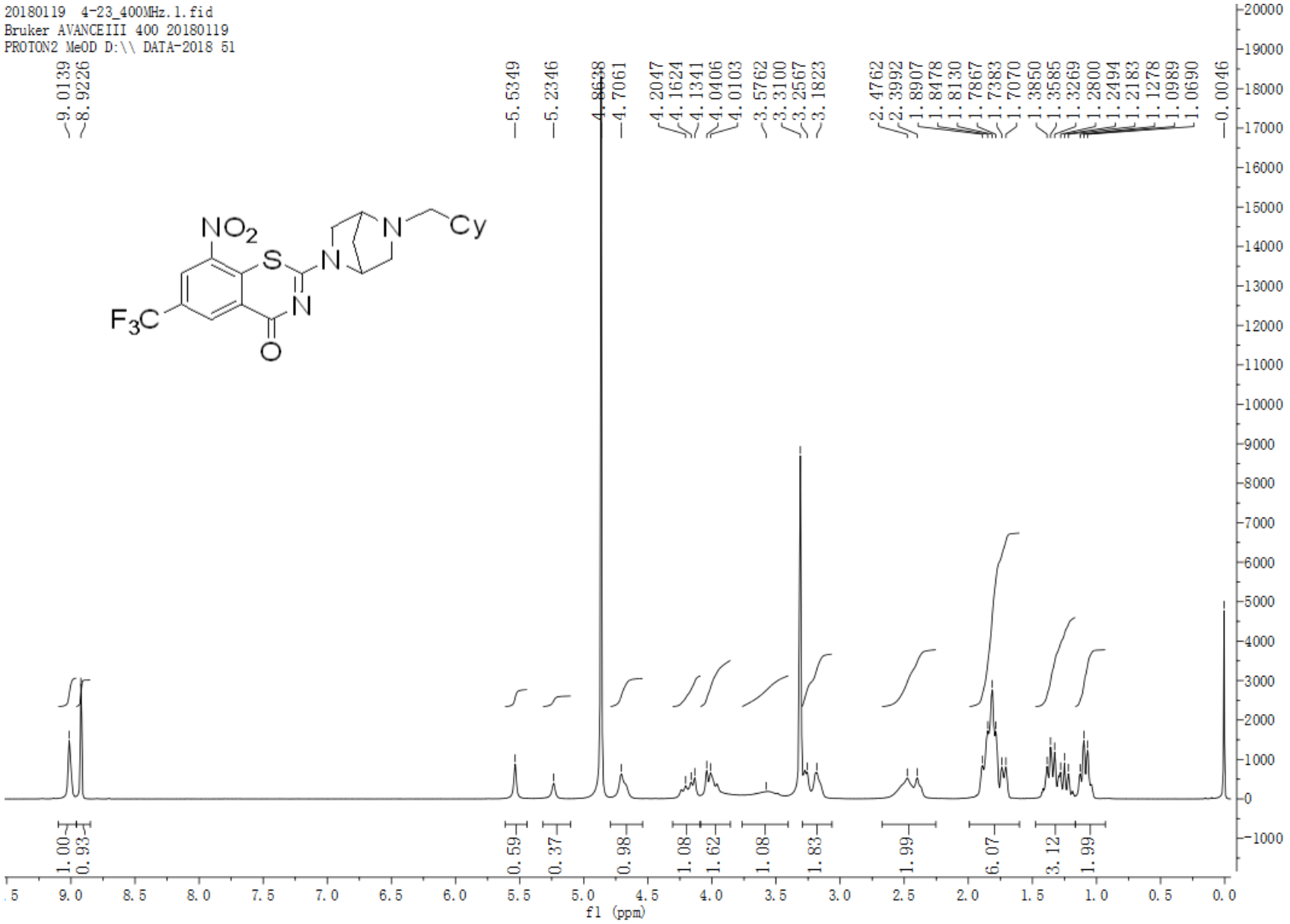
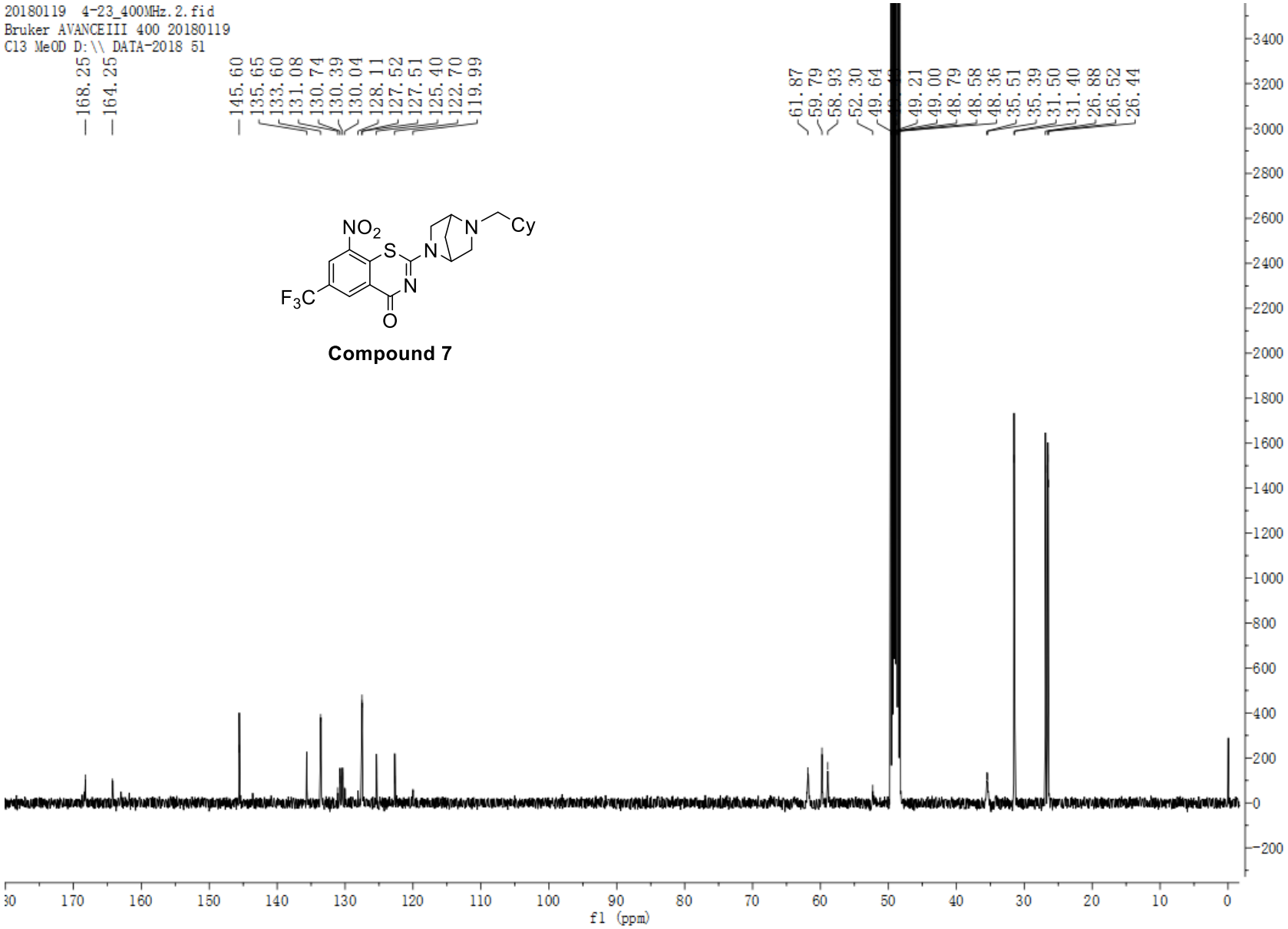
Peak Table

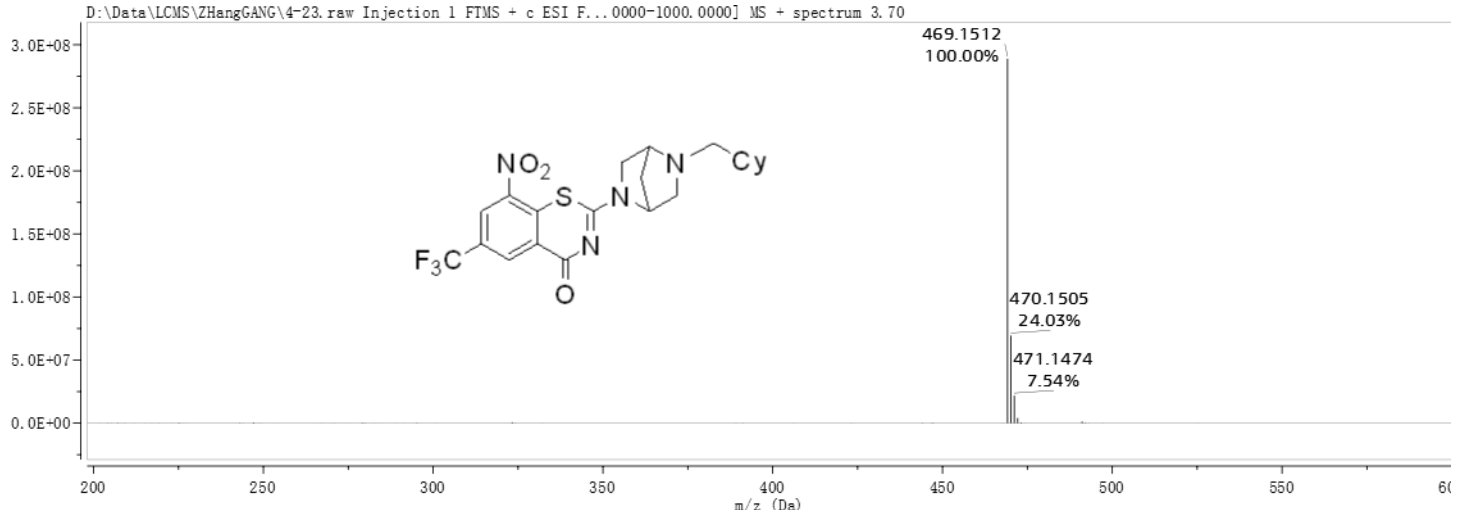
PDA Ch1 252nm

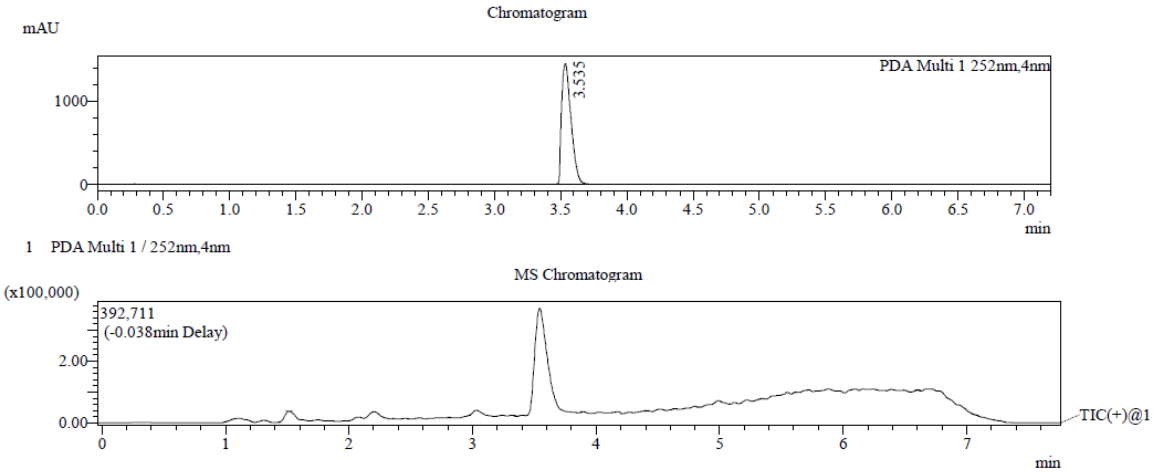
Peak#	Ret. Time	Height	Height%	USP Width	Area	Area%
1	3.244	3704	0.093	0.085	12091	0.047
2	3.420	2774	0.070	0.088	9693	0.038
3	3.583	7049	0.178	0.219	36530	0.142
4	3.725	3937287	99.350	0.132	25691594	99.580
5	4.068	9099	0.230	0.147	37313	0.145
6	4.507	3121	0.079	0.100	12836	0.050


20180119 4-23_400MHz.1.fid
Bruker AVANCEIII 400 20180119
PROTON2 MeOD D:\\ DATA-2018 51
9.0139
8.9226
5.5349
5.2346
4.8638
4.7061
4.2047
4.1624
4.1341
4.0406
4.0103
3.5762
3.3100
3.2567
3.1823
2.4762
2.3992
1.8907
1.8478
1.8130
1.7867
1.7383
1.7070
1.3850
1.3585
1.3269
1.2800
1.2494
1.2183
1.1278
1.0989
1.0690
0.0046
NO2
S
N
N
Cy
F3C
N
O
1.00
0.93
0.59
0.37
0.98
1.08
1.62
1.08
1.83
1.99
6.07
3.12
1.99
f1 (ppm)


20180119 4-23_400MHz.2.fid
Bruker AVANCEIII 400 20180119
C13 MeOD D:\\ DATA-2018 51
168.25
164.25
145.60
135.65
133.60
131.08
130.74
130.39
130.04
128.11
127.52
127.51
125.40
122.70
119.99
61.87
59.79
58.93
52.30
49.64
49.21
49.00
48.79
48.58
48.36
35.51
35.39
31.50
31.40
26.88
26.52
26.44
NO2
S
N
N
Cy
F3C
N
O
f1 (ppm)

Compound 7



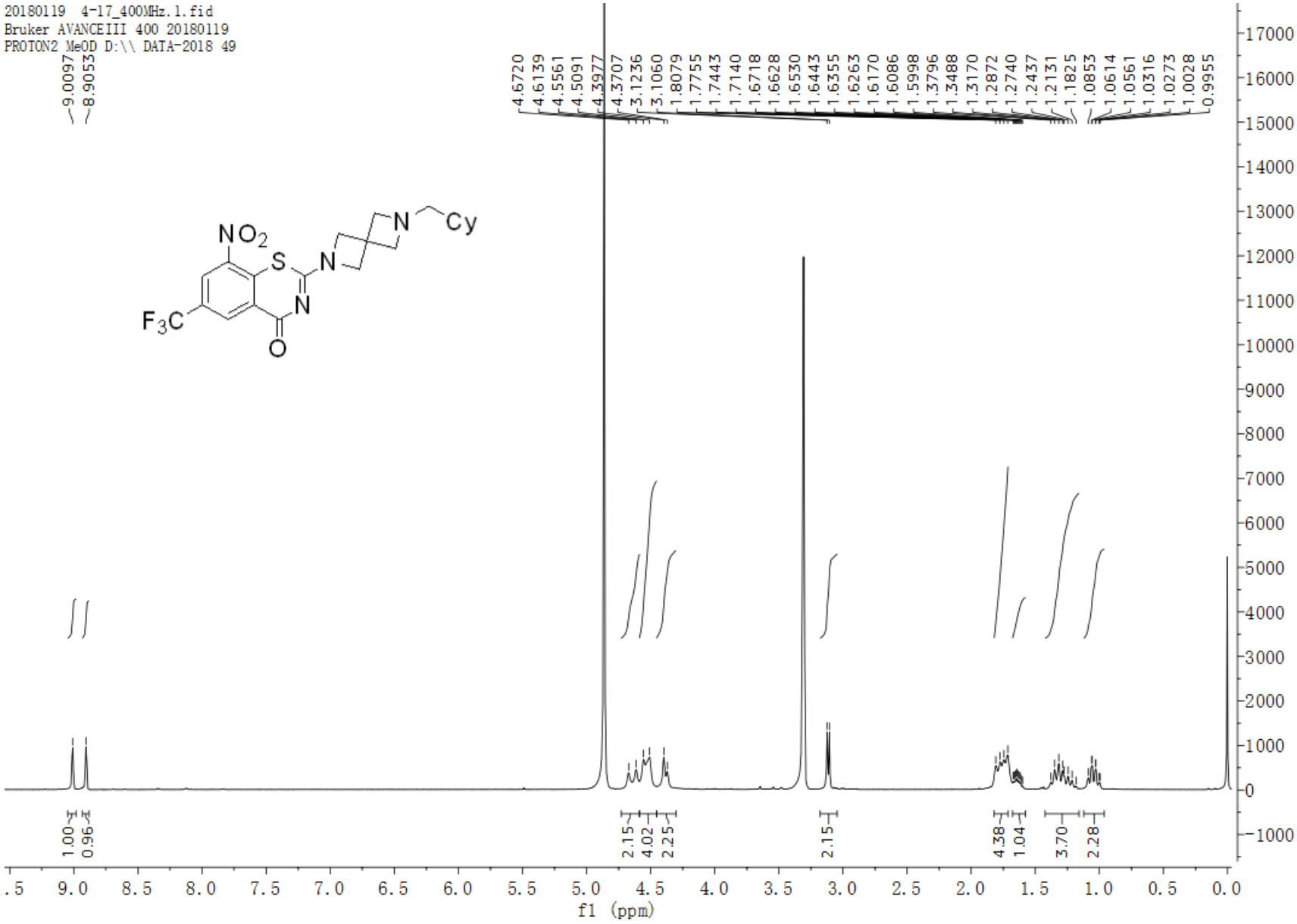


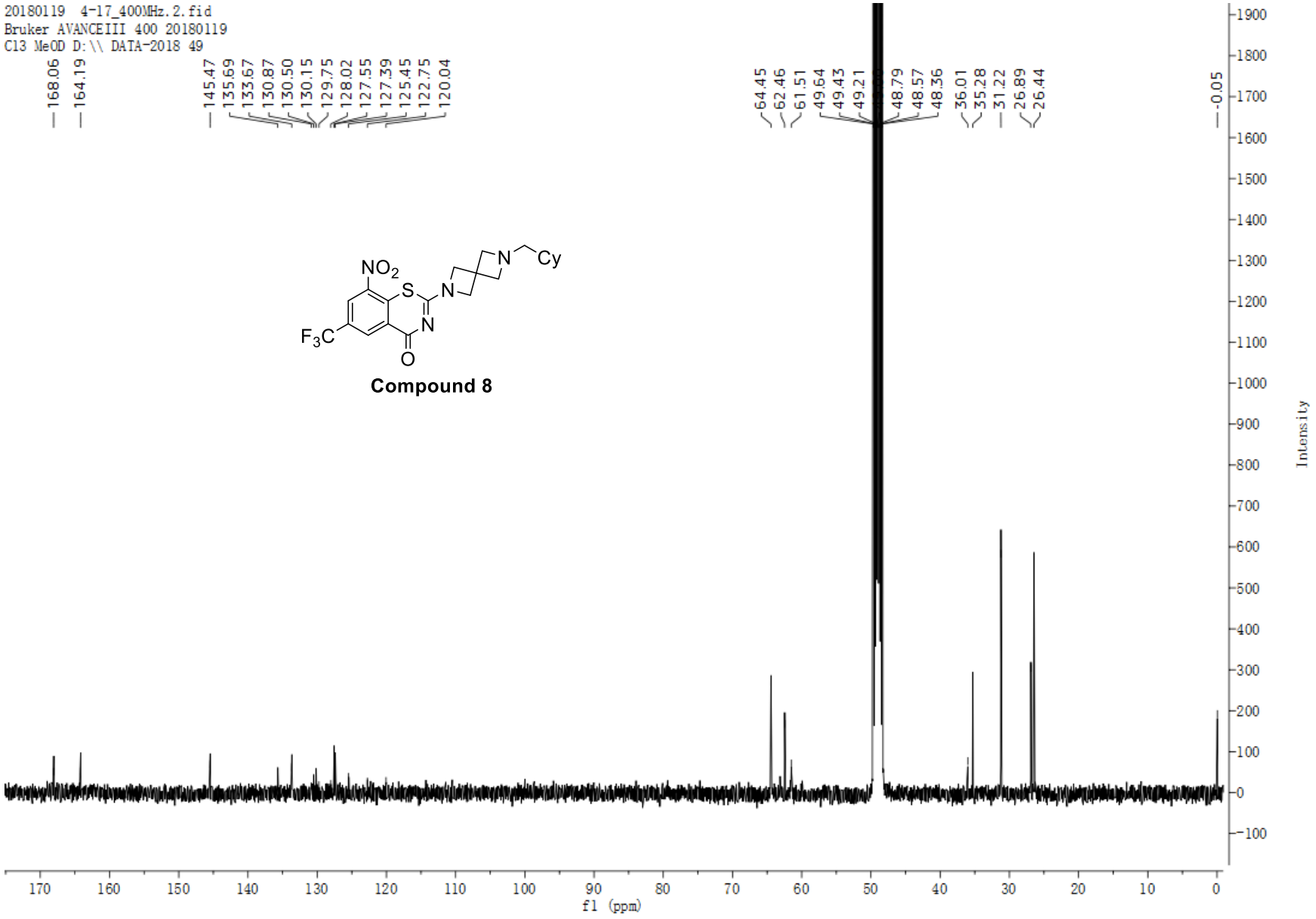
Integration Result

Peak Table

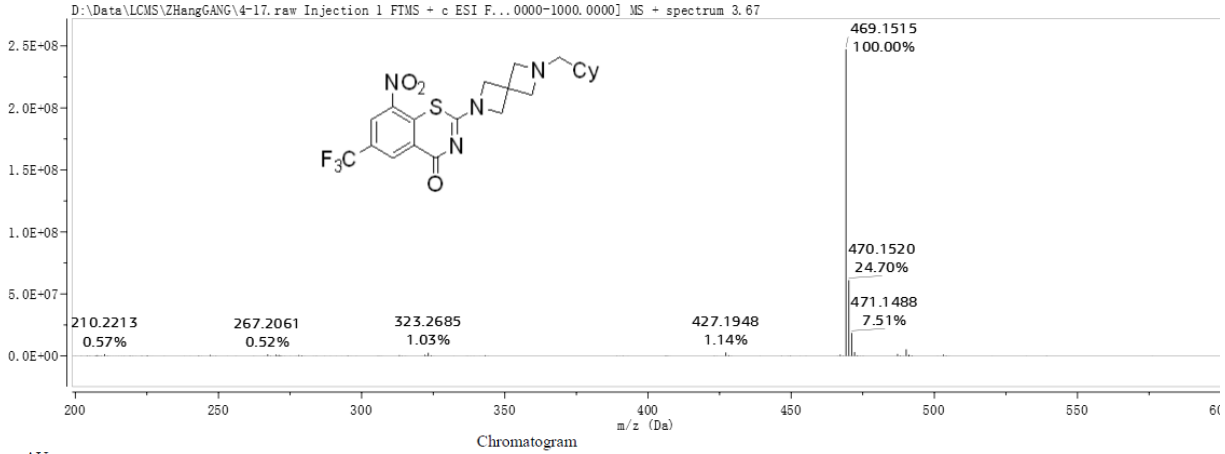
PDA Ch1 252nm

Peak#	Ret. Time	Height	Height%	USP Width	Area	Area%
1	3.535	1446812	100.000	0.139	7156847	100.000

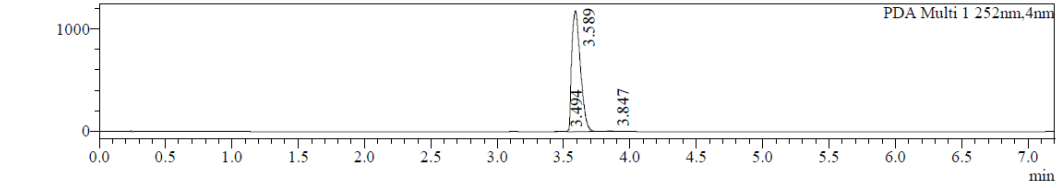

20180119 4-17_400MHz.1.fid
Bruker AVANCEIII 400 20180119
PROTON2 MeOD D:\\ DATA-2018 49
NO2
S
N
N
Cy
N
F3C
O
f1 (ppm)


20180119 4-17_400MHz.2.fid
Bruker AVANCEIII 400 20180119
C13 MeOD D:\\ DATA-2018 49
168.06
164.19
145.47
135.69
133.67
130.87
130.50
130.15
129.75
128.02
127.55
127.39
125.45
122.75
120.04
64.45
62.46
61.51
49.64
49.43
49.21
48.79
48.57
48.36
36.01
35.28
31.22
26.89
26.44
-0.05
NO2
S
N
N
Cy
F3C
N
O
Intensity
f1 (ppm)

Compound 8

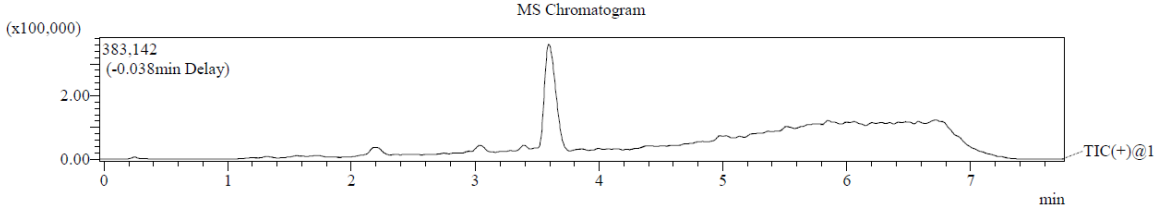


Chromatogram



1 PDA Multi 1 / 252nm,4nm

MS Chromatogram



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Integration Result

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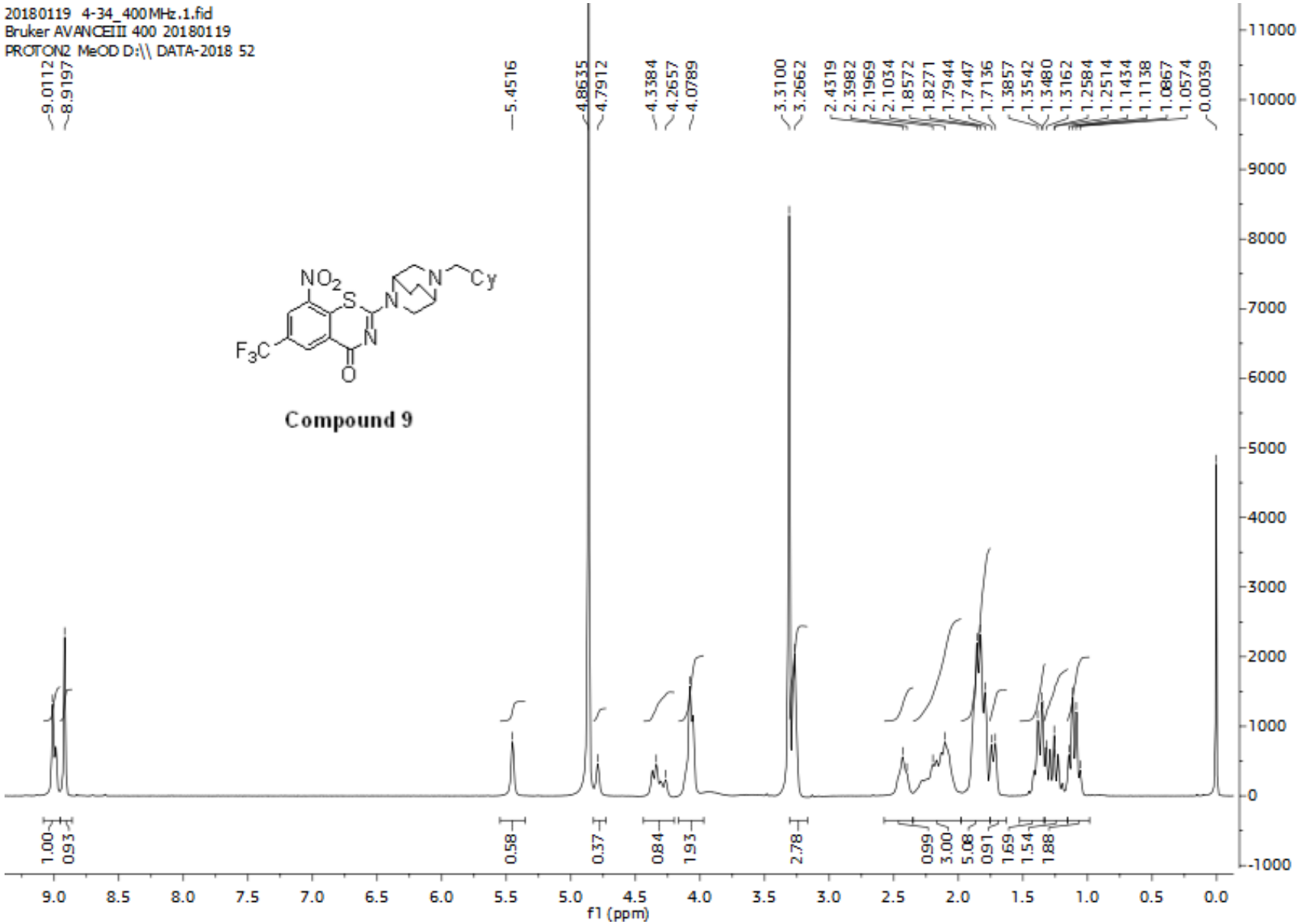
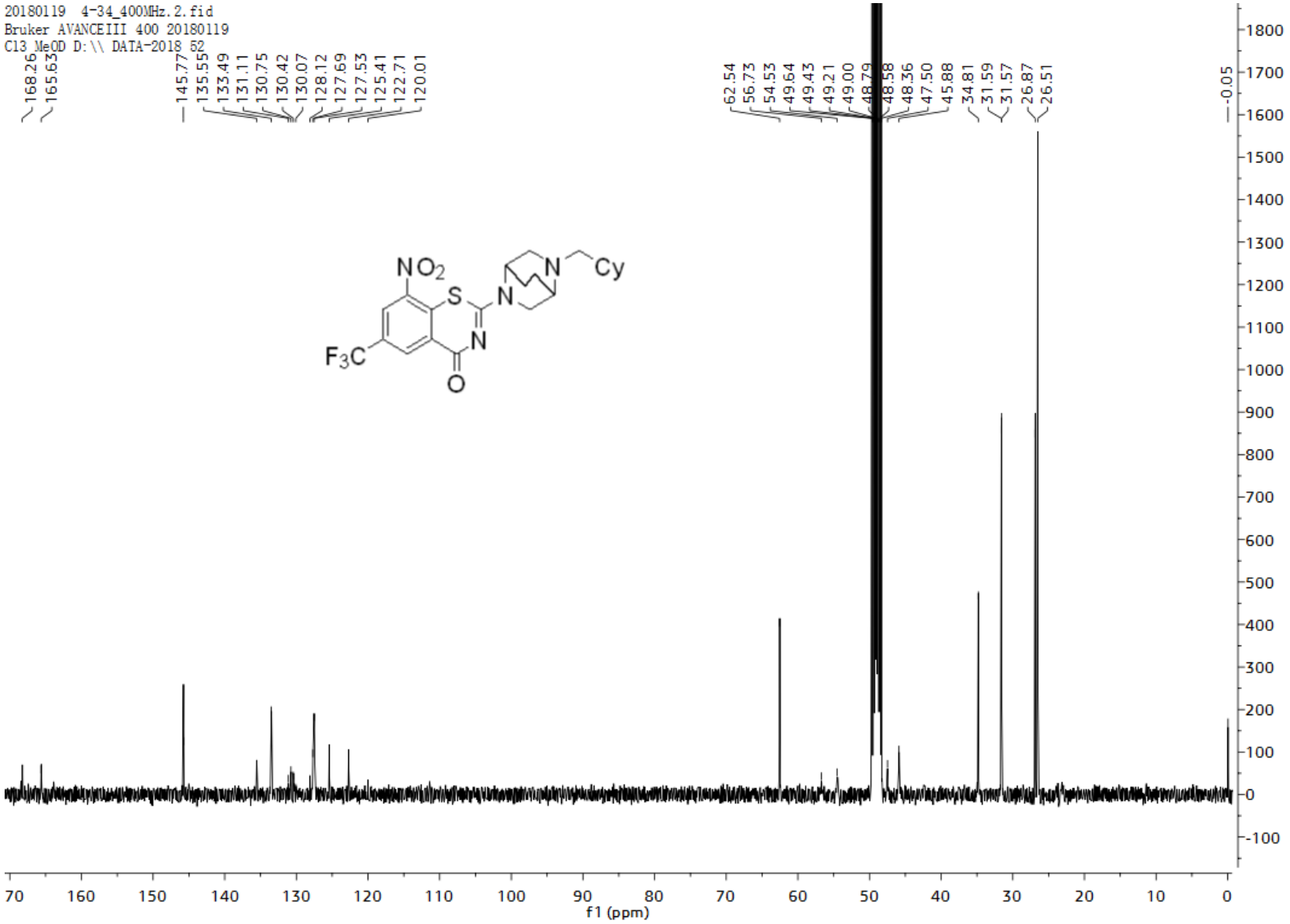
Peak Table

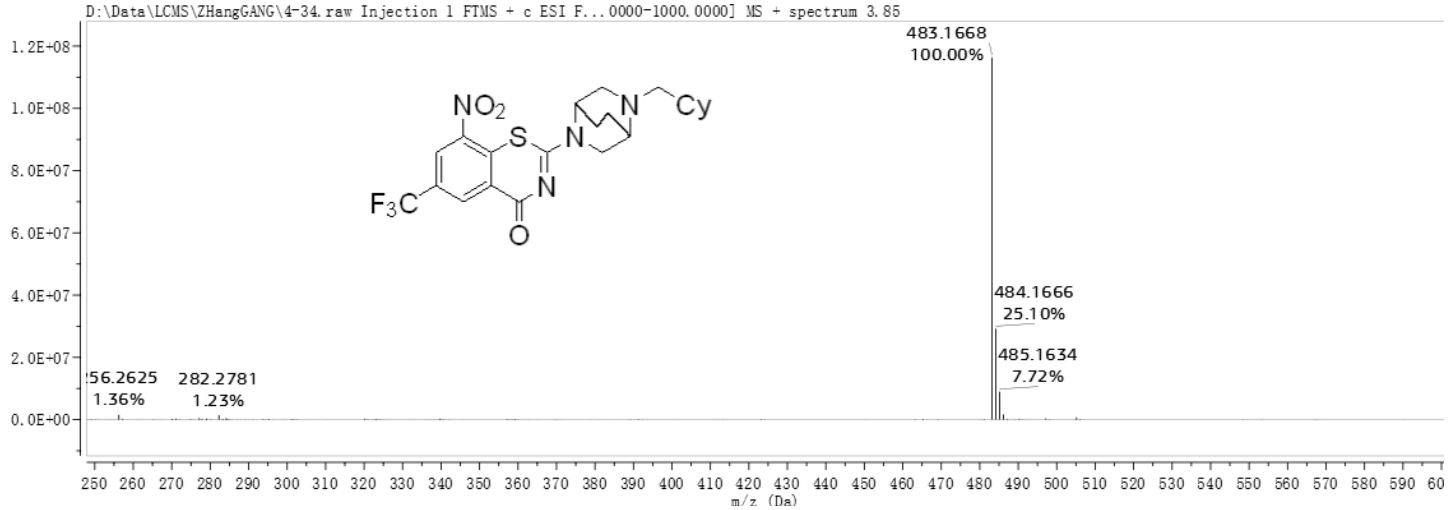
PDA Ch1 252nm

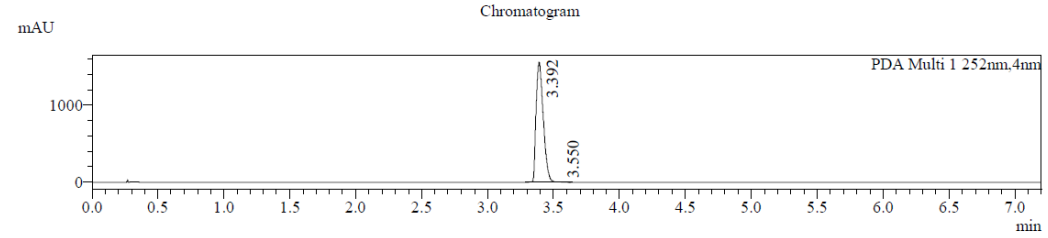
Peak#	Ret. Time	Height	Height%	USP Width	Area	Area%
1	3.494	4626	0.390	0.427	13732	0.257
2	3.589	1175438	99.146	0.122	5324586	99.478
3	3.847	5496	0.464	0.070	14213	0.266

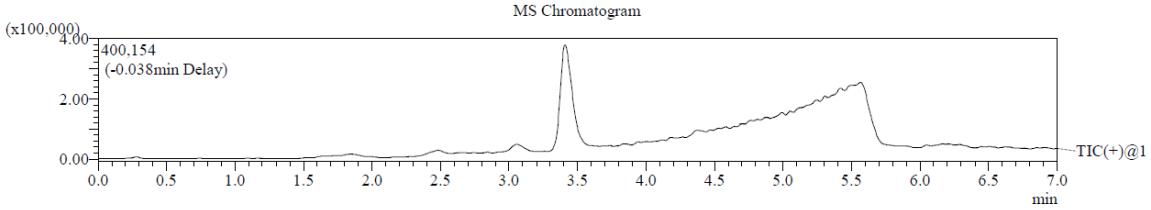

20180119 4-34_400MHz.1.fid
Bruker AVANCEIII 400 20180119
PROTON2 MeOD D:\\ DATA-2018 52
9.0112
8.9197
5.4516
4.8635
4.7912
4.3384
4.2657
4.0789
3.3100
3.2662
2.4319
2.3982
2.1969
2.1034
1.8572
1.8271
1.7944
1.7447
1.7136
1.3857
1.3542
1.3480
1.3162
1.2584
1.2514
1.1434
1.1138
1.0867
1.0574
0.0039
1.00
0.93
0.58
0.37
0.84
1.93
2.78
0.99
3.00
5.08
0.91
1.69
1.54
1.88
f1 (ppm)

Compound 9


20180119 4-34_400MHz.2.fid
Bruker AVANCEIII 400 20180119
C13 MeOD D:\\ DATA-2018 52
168.26
165.63
145.77
135.55
133.49
131.11
130.75
130.42
130.07
128.12
127.69
127.53
125.41
122.71
120.01
62.54
56.73
54.53
49.64
49.43
49.21
49.00
48.79
48.58
48.36
47.50
45.88
34.81
31.59
31.57
26.87
26.51
-0.05
NO2
S
N
N
Cy
N
F3C
O
f1 (ppm)





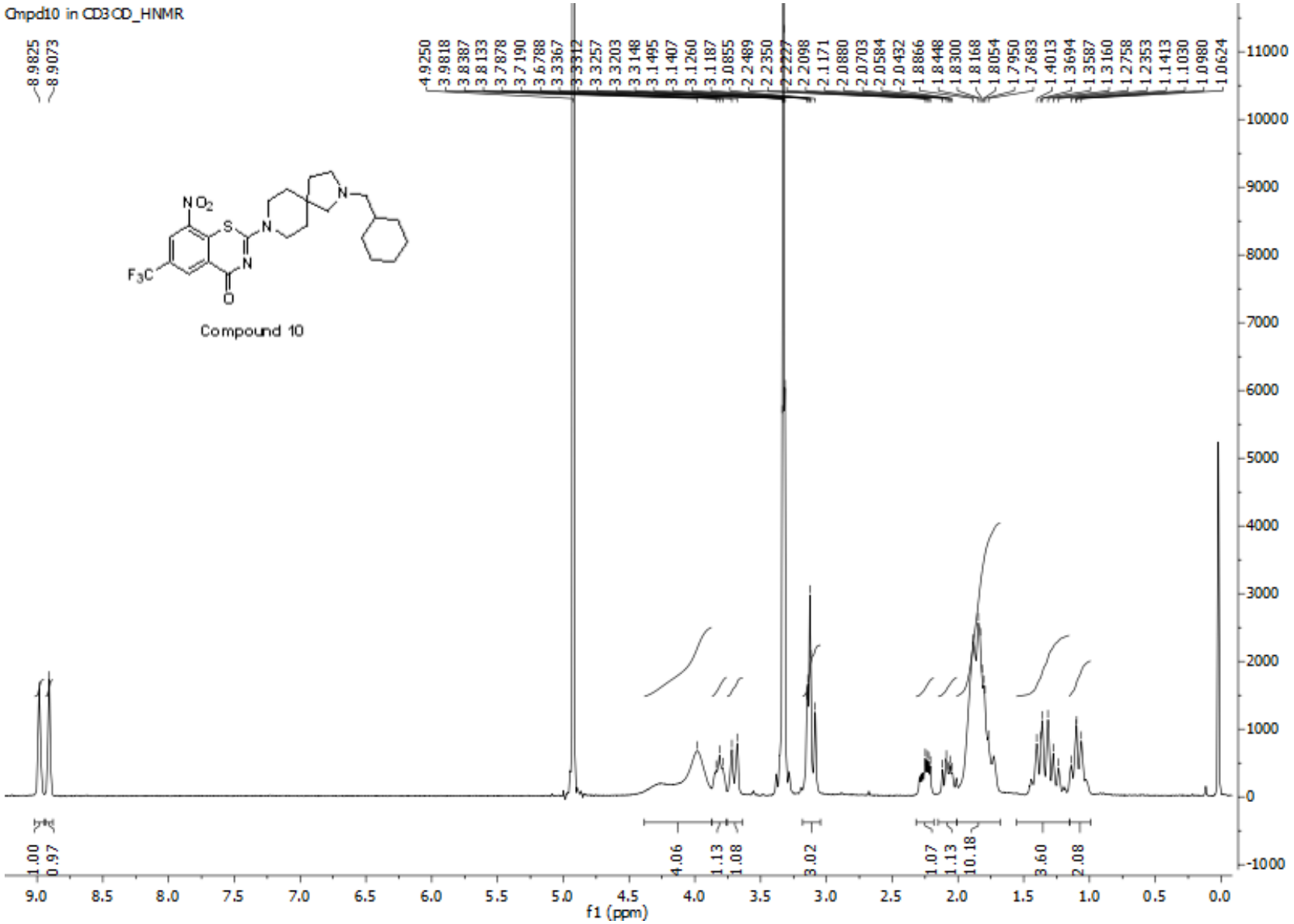


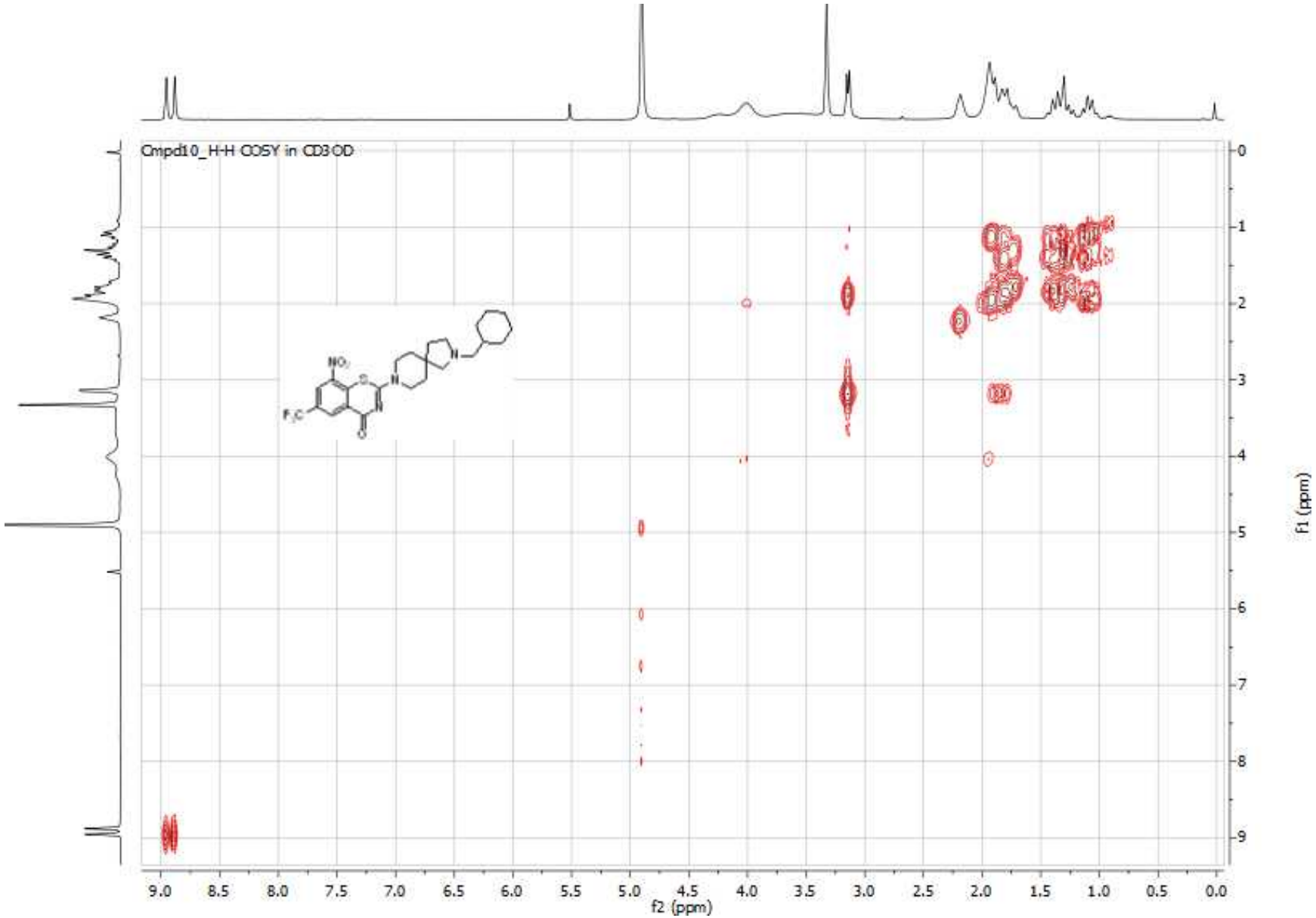
Integration Result

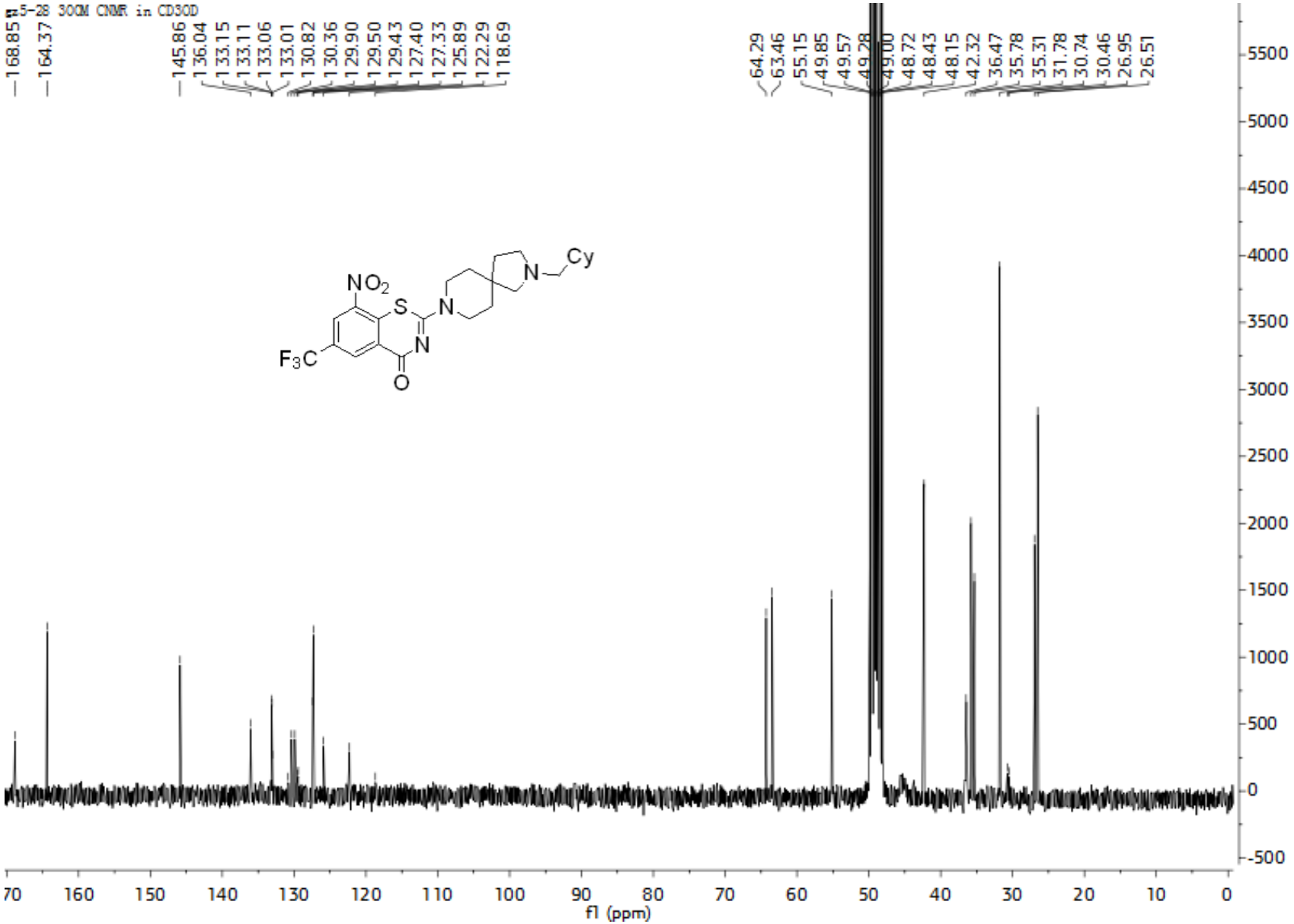
Peak Table

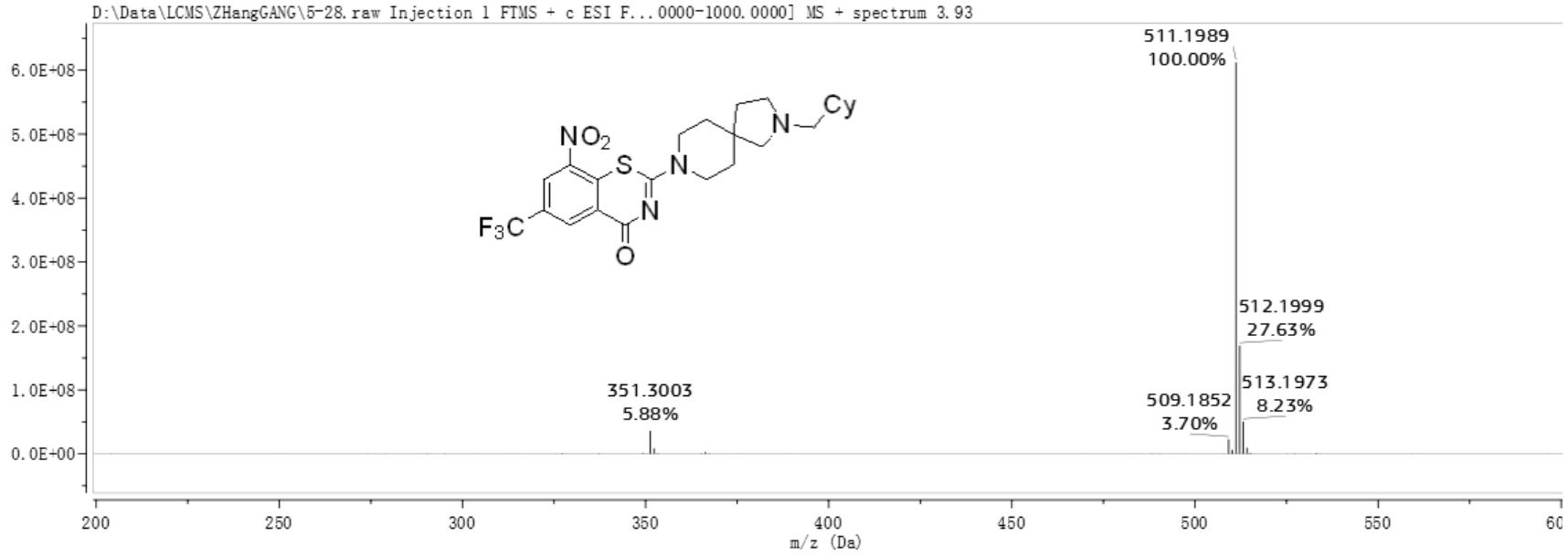
PDA Ch1 252nm

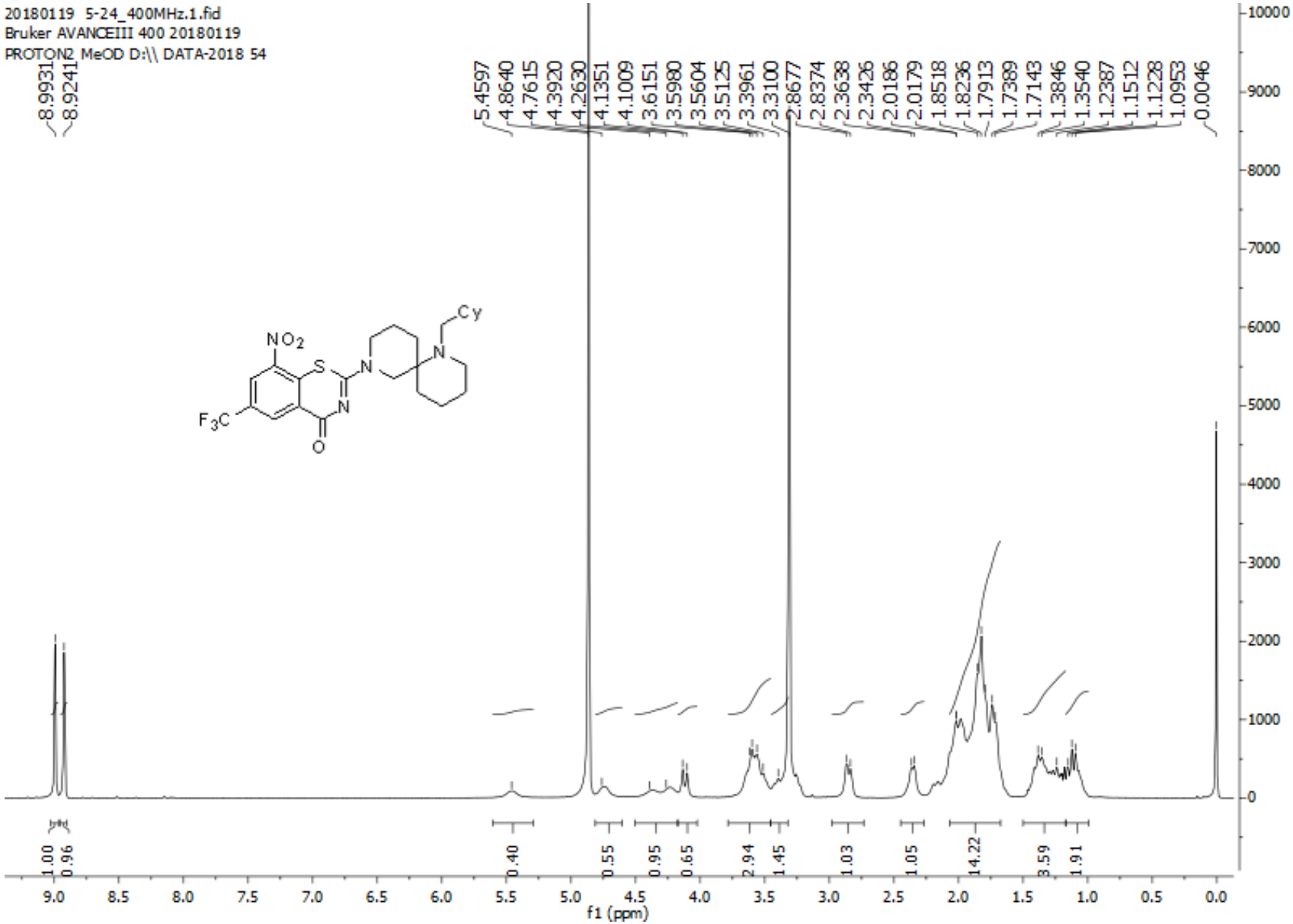
Peak#	Ret. Time	Height	Height%	USP Width	Area	Area%
1	3.392	1556476	99.770	0.106	5905816	99.817
2	3.550	3583	0.230	0.100	10843	0.183

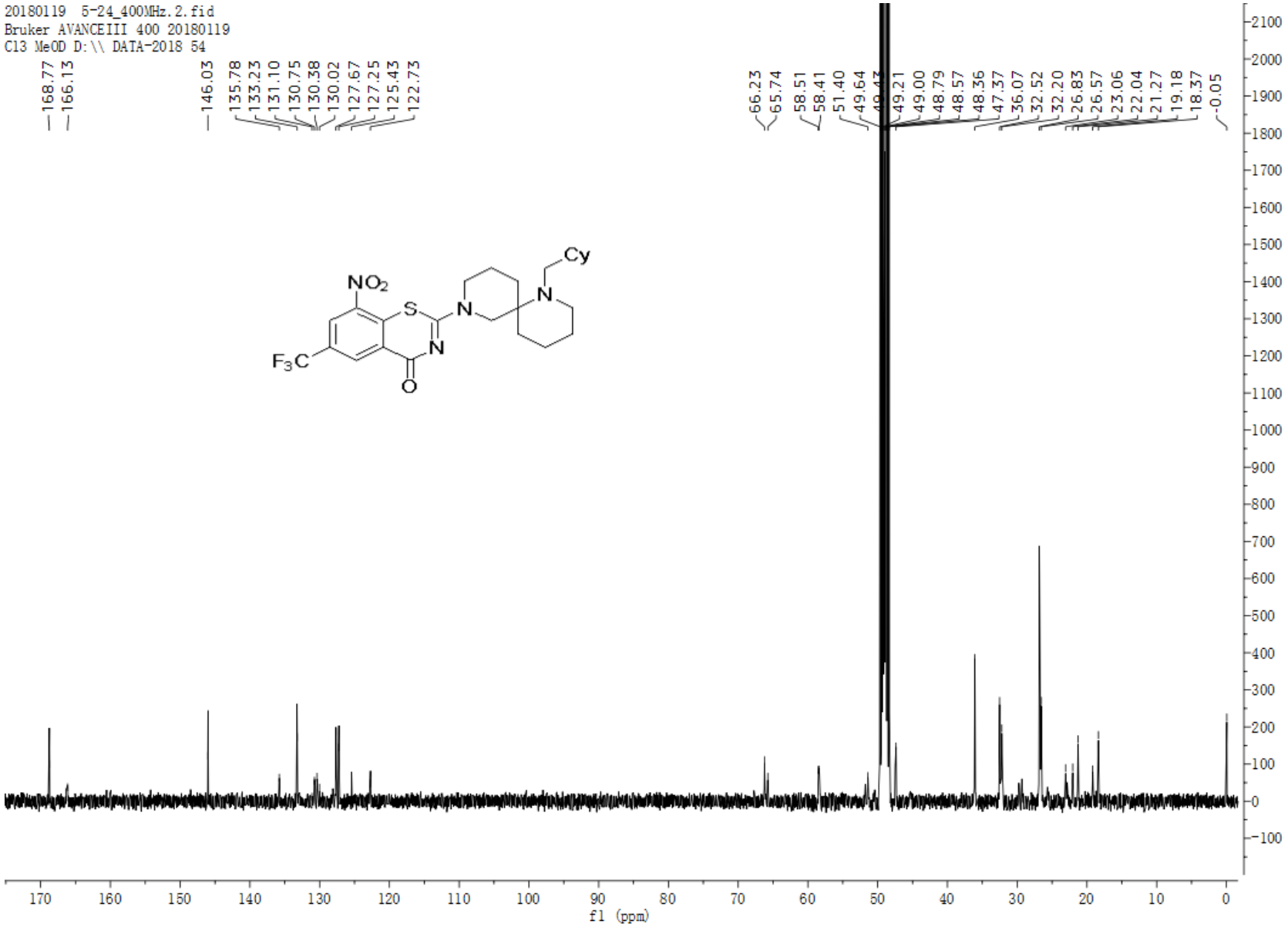

Cmpd10 in CD3OD_HNMR
Compound 10
f1 (ppm)

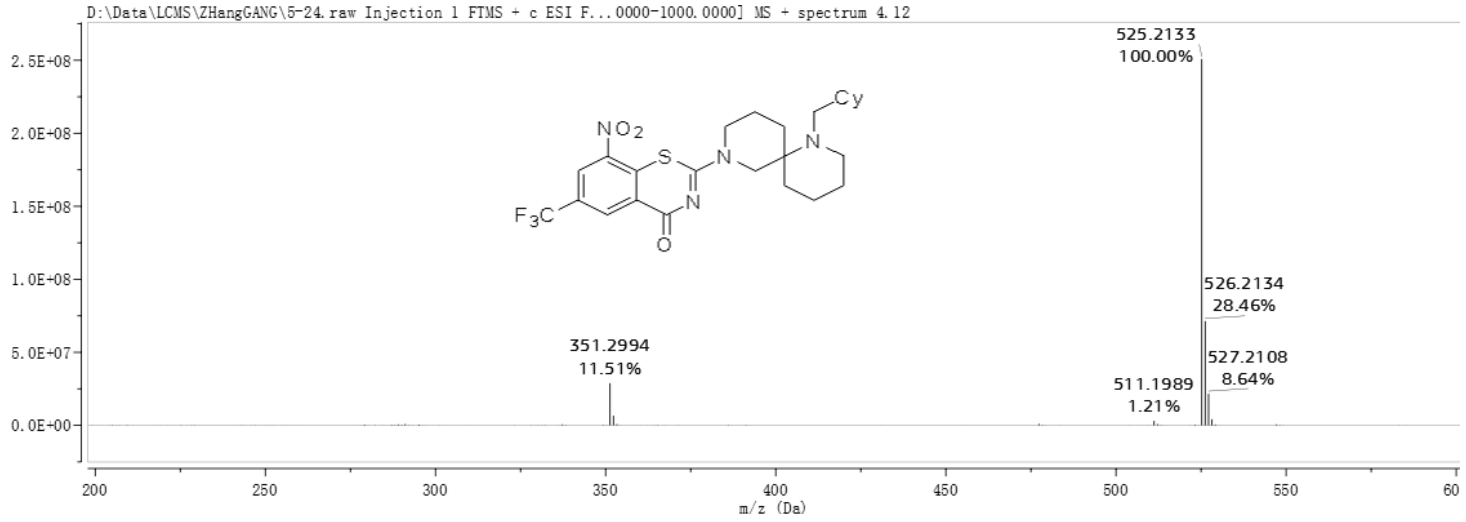

Cmpd10_H-H COSY in CD3OD
f2 (ppm)
f1 (ppm)


5-28 300M CNMR in CD3OD
168.85
164.37
145.86
136.04
133.15
133.11
133.06
133.01
130.82
130.36
129.90
129.50
129.43
127.40
127.33
125.89
122.29
118.69
64.29
63.46
55.15
49.85
49.57
49.28
49.00
48.72
48.43
48.15
42.32
36.47
35.78
35.31
31.78
30.74
30.46
26.95
26.51
NO2
S
N
N
Cy
N
F3C
O
f1 (ppm)

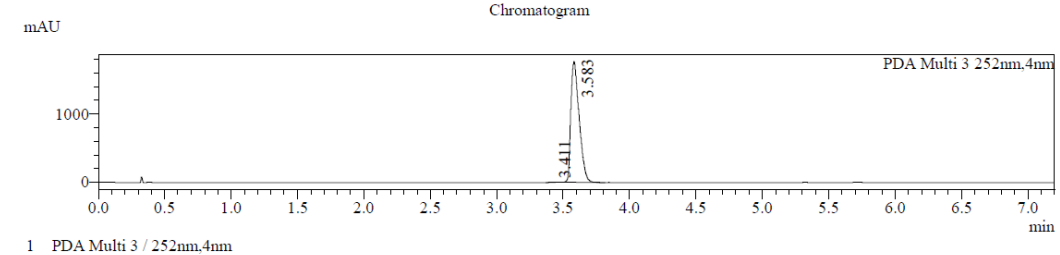

D:\Data\LCMS\ZHangGANG\5-28.raw Injection 1 FTMS + c ESI F...0000-1000.0000] MS + spectrum 3.93
511.1989
100.00%
512.1999
27.63%
513.1973
8.23%
509.1852
3.70%
351.3003
5.88%
NO2
S
N
N
Cy
N
F3C
O
6.0E+08
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
200
250
300
350
400
450
500
550
m/z (Da)


20180119 5-24_400MHz.1.fid
Bruker AVANCEIII 400 20180119
PROTON2 MeOD D:\\ DATA-2018 54
8.9931
8.9241
5.4597
4.8640
4.7615
4.3920
4.2630
4.1351
4.1009
3.6151
3.5980
3.5604
3.5125
3.3961
3.3100
2.8677
2.8374
2.3638
2.3426
2.0186
2.0179
1.8518
1.8236
1.7913
1.7389
1.7143
1.3846
1.3540
1.2387
1.1512
1.1228
1.0953
0.0046
NO2
S
N
N
Cy
F3C
N
O
1.00
0.96
0.40
0.55
0.95
0.65
2.94
1.45
1.03
1.05
14.22
3.59
1.91
f1 (ppm)


20180119 5-24_400MHz.2.fid
Bruker AVANCEIII 400 20180119
C13 MeOD D:\\ DATA-2018 54
168.77
166.13
146.03
135.78
133.23
131.10
130.75
130.38
130.02
127.67
127.25
125.43
122.73
66.23
65.74
58.51
58.41
51.40
49.64
49.21
49.00
48.79
48.57
48.36
47.37
36.07
32.52
32.20
26.83
26.57
23.06
22.04
21.27
19.18
18.37
-0.05
NO2
S
N
N
Cy
N
F3C
O
f1 (ppm)

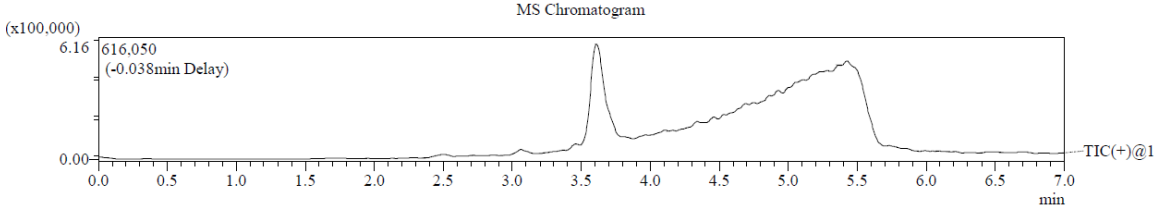


Chromatogram



1 PDA Multi 3 / 252nm,4nm

MS Chromatogram

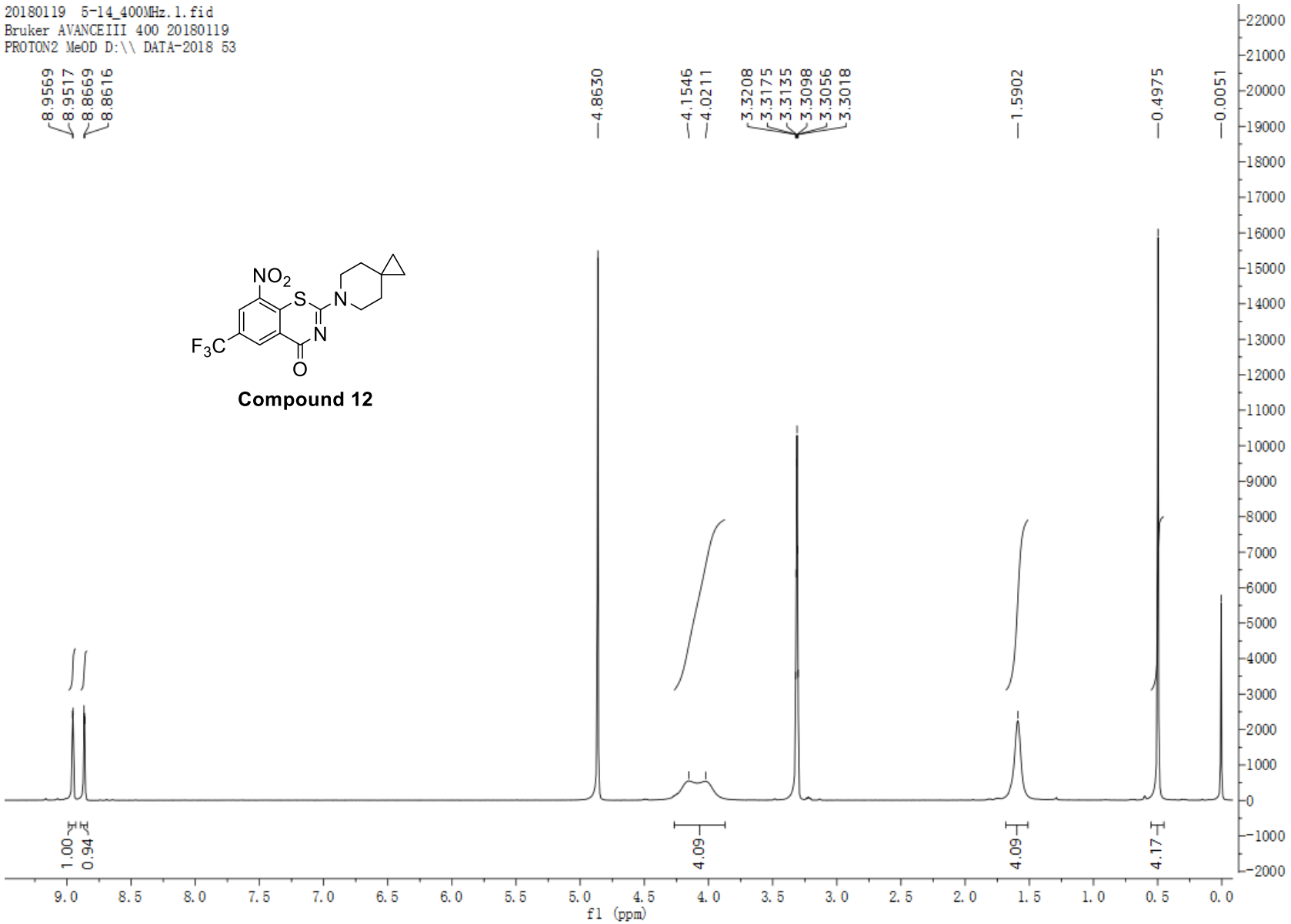


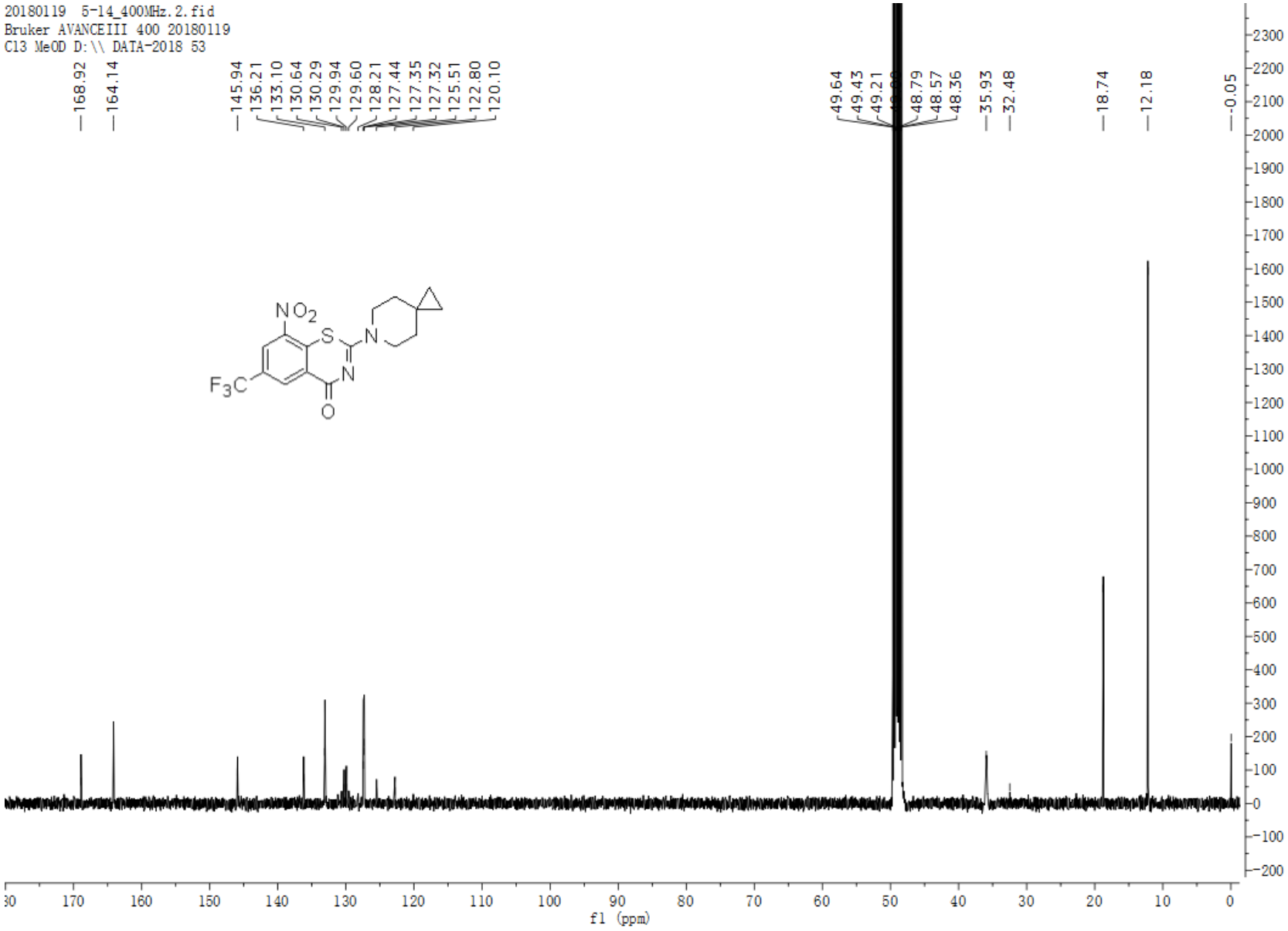
Integration Result

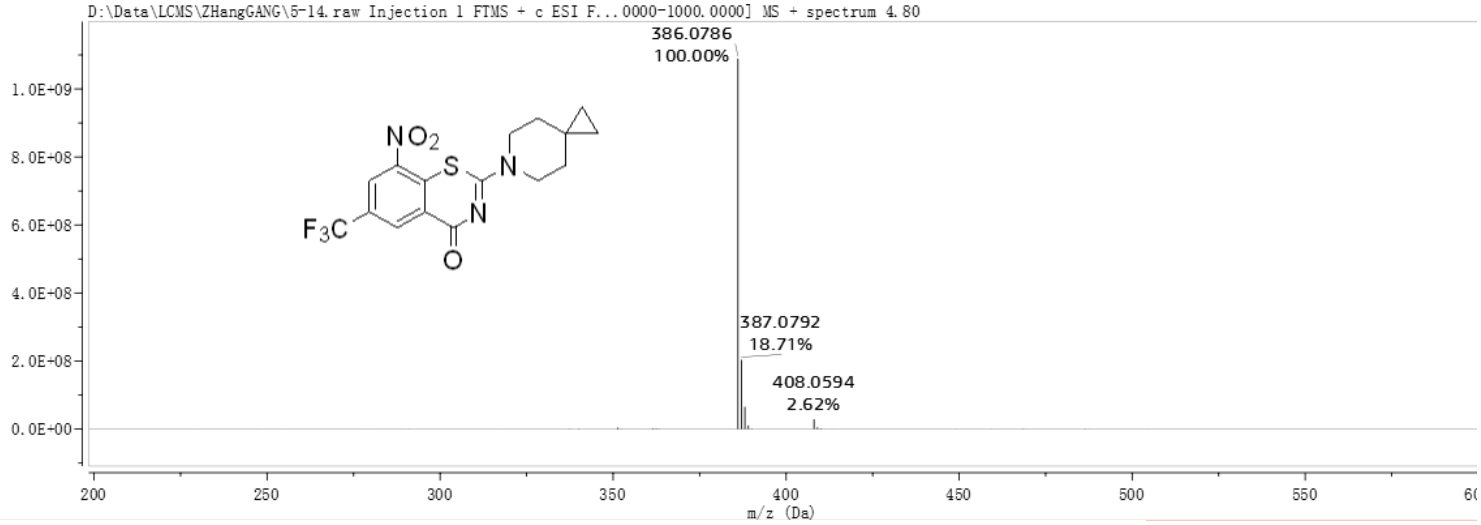
Peak Table

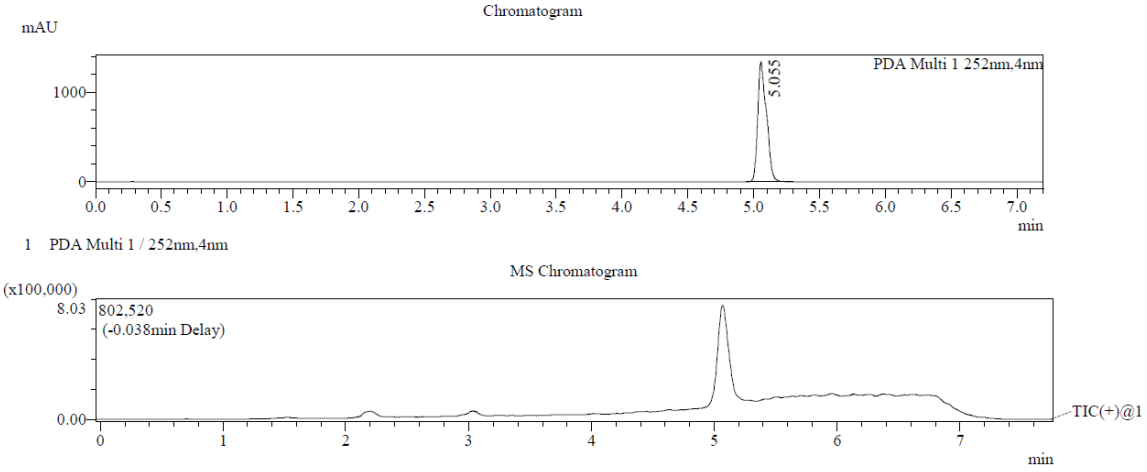
PDA Ch3 252nm

Peak#	Ret. Time	Height	Height%	USP Width	Area	Area%
1	3.411	4363	0.246	0.098	15834	0.204
2	3.583	1770441	99.754	0.124	7743232	99.796


20180119 5-14_400MHz.1.fid
Bruker AVANCEIII 400 20180119
PROTON2 MeOD D:\\ DATA-2018 53
8.9569
8.9517
8.8669
8.8616
4.8630
4.1546
4.0211
3.3208
3.3175
3.3135
3.3098
3.3056
3.3018
1.5902
0.4975
0.0051
NO2
S
N
N
F3C
O
Compound 12
1.00
0.94
4.09
4.09
4.17
f1 (ppm)


20180119 5-14_400MHz.2.fid
Bruker AVANCEIII 400 20180119
C13 MeOD D:\\ DATA-2018 53
168.92
164.14
145.94
136.21
133.10
130.64
130.29
129.94
129.60
128.21
127.44
127.35
127.32
125.51
122.80
120.10
49.64
49.43
49.21
48.79
48.57
48.36
35.93
32.48
18.74
12.18
-0.05
NO2
S
N
N
F3C
O
f1 (ppm)





Integration Result

Peak Table

PDA Ch1 252nm

Peak#	Ret. Time	Height	Height%	USP Width	Area	Area%
1	5.055	1332199	100.000	0.159	6168327	100.000