Design, Synthesis and Identification of Silicon Incorporated Oxazolidinone Antibiotics with Improved Brain Exposure

B. Seetharamsingh, Remya Ramesh, Santoshkumar S. Dange, Pankaj V. Khairnar, Smita Singhal, Dilip Upadhyay, Sridhar Veeraraghavan, Srikant Viswanadha, Swaroop Vakkalanka and D. Srinivasa Reddy*

*Corresponding author:
Dr. D. Srinivasa Reddy
National Chemical Laboratory (CSIR, India),
Division of Organic Chemistry,
Dr. Homi Bhabha Road,
Pune 411008, Maharashtra,
India.
E-mail: ds.reddy@ncl.res.in
Tel. +91 20 25902445
Fax. +91 20 25902629

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1. General

All reactions were carried out in oven-dried glassware under a positive pressure of argon or nitrogen unless otherwise mentioned with magnetic stirring. Air sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus *via* rubber septa. All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such without further purification. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F254). Visualization was accomplished with either UV light, iodine adsorbed on silica gel or by immersion in ethanolic solution of phosphomolybdic acid (PMA), *para*-anisaldehyde, 2,4-DNP strain, $KMnO_4$, ninhydrin solution followed by heating on a heat gun for ~15 sec. Column chromatography was performed on silica gel (100-200 or 230-400 mesh size). Deuterated solvents for NMR spectroscopic analyses were used as received. All ^{1}H NMR and ^{13}C NMR spectra were obtained using a 200 MHz, 400 MHz, 500 MHz spectrometer. Coupling constants were measured in Hertz. All chemical shifts were quoted in (δ) ppm and referenced to internal signals of residual solvent peak ($CDCl_3$ ^{1}H δ 7.26, ^{13}C δ 77.0) as a reference standard. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. HRMS (ESI) were recorded on ORBITRAP mass analyser (Thermo Scientific, Q Exactive). Mass spectra were measured with ESI ionization in MSQ LCMS mass spectrometer. Infrared (IR) spectra were recorded on a FT-IR spectrometer as a thin film. Chemical nomenclature was generated using ChemBioDraw Ultra. Optical rotation values were recorded on P-2000 polarimeter at 589 nm. Melting points were recorded on melting point instrument. Purity of products was determined by reverse phase HPLC analysis using Agilent technologies 1200 series; column: ZORBAX Eclipse XBD-C-18 (4.6 x 250 mm, 5 μ). Flow rate 1.00 mL/min, UV 254 nm; using mobile phases, Method A: 80/20 CH_3OH/H_2O for 20 min; Method B: 70/30 CH_3CN/H_2O for 20 min; Method C: 95/05 CH_3OH/H_2O for 20 min.

2. Experimental Procedures

Bis(bromoethyl)dimethylsilane: HBr gas was bubbled through a solution of dimethyl divinylsilane (10.0 g, 89.28 mmol), and dibenzoylperoxide (100 mg), in heptane (100 mL) at 0 ˚C for 30 min, RM was allowed to stir at rt for 18 h, water (200 mL), was added to reaction mixture separated the organic layer. The heptane layer was washed with 2*N* aqueous NaOH

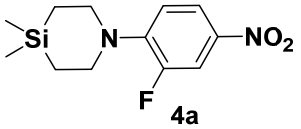
(2 x 100 mL), brine (100 mL) dried over anhydrous Na_2SO_4, concentrated *in vacuo,* to obtain product as a yellow liquid (24.5 g) in 100% yield.

1-Benzyl-4,4-dimethyl-1,4-azasilinane (2a):[1] Benzylamine (20 mL, 182 mmol) and Et_3N (15.2 mL, 109 mmol) were added to a solution of bis(bromoethyl) dimethylsilane (10 g, 36.5 mmol) in $CHCl_3$ (100 mL). The mixture was then refluxed for 16 h. The reaction mixture was cooled to rt, 5% NaOH solution (150 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). It was then washed with brine (200 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The product was purified by column chromatography on silica gel (230-400) using hexane- EtOAc (8:2) mixtures to obtain the product as a light yellow liquid (4.3 g) in 54% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33-7.25 (m, 5 H), 3.56 (s, 2 H), 2.68 (t, J = 6.3 Hz, 4 H), 0.75 (t, J = 6.3 Hz, 4 H), 0.04 (s, 6 H).

4,4-Dimethyl-1,4-azasilinane hydrochloride (3a):[1] To a solution of 1-benzyl-4,4-dimethyl-1,4-azasilinane **2a** (2.3 g, 10.5 mmol) in EtOH was added 6*N* HCl (10.5 mmol) and the solvent was removed under reduced pressure. The reaction mixture was coevaporated with EtOH (2 x 10 mL) and recrystallized from EtOH- Diethyl ether.

To slurry of 10% Pd/C (0.20 g) in EtOH (20 mL) was added the compound obtained above as a solution in ethanol (20 mL) dropwise and stirred at room temperature under hydrogen atmosphere for 20 h. The reaction mixture was filtered through celite, washed with MeOH (3 x 20 mL). The filtrate was concentrated under reduced pressure to give viscous oil which was triturated with diethyl ether to obtain the product as a white solid (950 mg) in 70% yield.

Compound **3b**[2] was prepared using the similar procedure employed for **3a**.

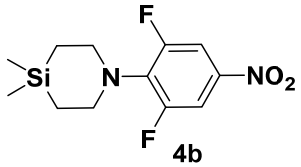


4a

1-(2-Fluoro-4-nitrophenyl)-4,4-dimethyl-1,4-azasilinane (4a): To a solution of 4,4-dimethyl-1,4-azasilinane hydrochloride (635 mg, 3.85 mmol) in EtOAc (10 mL) was added triethylamine (973 mg, 9.63 mmol) and stirred at rt for 10 min, the reaction mixture was cooled to 0 ˚C and 3, 4-difluoronitrobenzene (612 mg, 3.85 mmol) was added dropwise and allowed to stir at rt for 6 h, H_2O (20 mL) was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the solvent was removed under

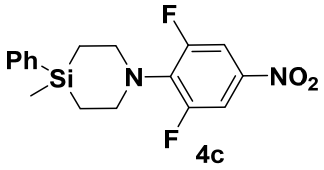
reduced pressure. Column chromatography on silica gel (230-400) using hexane gave the compound **4a** (721 mg, 69%) as yellow solid; IR υ_{max}(film): 2948, 2894, 1603, 1523, 1492, 1400, 1342, 1223 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 9.1, 2.6 Hz, 1 H), 7.86 (dd, *J* = 14.3, 2.8 Hz, 1 H), 6.87 (t, *J* = 9.0 Hz, 1 H), 3.70-3.67 (m, 4 H), 0.91- 0.85 (m, 4 H), 0.12 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2 (d, *J* = 246.7 Hz), 144.4 (d, *J* = 6.9 Hz), 137.8 (d, *J* = 9.2 Hz), 121.4 (d, *J* = 2.3 Hz), 115.9 (d, *J* = 4.6 Hz), 113.1 (*J* = 27.7 Hz), 49.3 (2 C), 13.7 (2 C), -2.8 (2 C); Mp: 70-72 °C; HRMS (ESI): *m*/*z* calculated for $C_{12}H_{18}FN_2O_2Si$ $[M+H]^+$ 269.1120 found 269.1123.

Compounds **4b** and **4c** were prepared using the similar procedure employed for **4a**.



4b

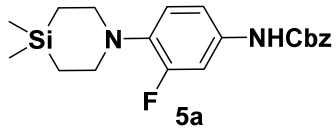
1-(2,6-Difluoro-4-nitrophenyl)-4,4-dimethyl-1,4-azasilinane (4b): Yield 86%; IRυ_{max}(film): 2894, 1603, 1523, 1492, 1400, 1342, 1223 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77-7.69 (m, 2 H), 3.51 (t, *J* = 6.3 Hz, 4 H), 0.90 (t, *J* = 6.3 Hz, 4 H), 0.12 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0 (dd, *J* = 248.5, 8.4 Hz, 2 C), 139.0 (d, *J* = 11.0 Hz), 136.7 (t, *J* = 12.4 Hz), 108.9 (m, 2 C), 51.0 (2 C), 15.1 (2 C), -3.1 (2 C); Mp: 165-168 °C; HRMS (ESI): *m*/*z* calculated for $C_{12}H_{17}F_2N_2O_2Si$ $[M+H]^+$ 287.1022 found 287.1018.



4c

1-(2,6-Difluoro-4-nitrophenyl)-4-methyl-4-phenyl-1,4-azasilinane (4c):

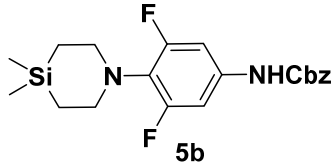
Yield 70%; IRυ_{max}(film): 1606, 1515, 1335 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.73 (m, 2 H), 7.59-7.56 (m, 2 H), 7.41-7.40 (m, 3 H), 3.60 (t, *J* = 6.0 Hz, 4 H), 1.34-1.27 (m, 2 H), 1.14-1.08 (m, 2 H), 0.39 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2 (dd, *J* = 248.9 Hz, 8.2 Hz, 2 C), 139.0 (t, *J* = 11.5 Hz), 136.9, 136.6 (t, *J* = 13.0 Hz), 133.8 (2 C), 129.5, 128.0 (2 C), 108.9 (m, 2 C), 51.0 (2 C), 13.9 (2 C), -4.0 (2 C); Mp: 84-86 °C; HRMS (ESI): *m*/*z* calculated for $C_{17}H_{19}F_2N_2O_2Si$ $[M+H]^+$ 349.1208 found 349.1206.



5a

Benzyl 4-(4, 4-dimethyl-1,4-azasilinan-1-yl)-3-fluorophenylcarbamate (5a): To a solution of Compound **4a** (610 mg, 2.28 mmol) in THF (30 mL) was added 10% Pd/C (~50 mg) and hydrogenated under a pressure of 35 psi in a parr hydrogenator at rt for 8 h. The reaction mixture was filtered through a pad of celite. To the filtrate, $NaHCO_3$ (420 mg, 5.01 mmol) in 5 mL water, CbzCl (427 mg, 2.5 mmol) were added at 0 ˚C and stirred at rt for 5 h, water (10 mL) was added and the aqueous layer was extracted with EtOAc (3 x 10 mL), combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography over 230-400 mesh silica gel (5-10% EtOAc/Petroleum ether) to afford compound **5a** (690 mg, 82%) as light yellow solid. IRυ_{max}(film): 3317, 2953, 2803, 1706, 1594, 1521, 1271 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.33 (m, 5 H), 7.25-7.21 (m, 1 H), 6.92-6.88 (m, 2 H), 6.73 (bs, 1 H), 5.18 (s, 2 H), 3.28 (t, *J* = 6.3 Hz, 4 H), 0.91 (t, *J* = 6.3 Hz, 4 H), 0.11 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3 (d, *J* = 245.1 Hz), 153.4, 137.7 (d, *J* = 9.2 Hz), 136.0, 131.8 (d, *J* = 8.5 Hz), 128.5 (2 C), 128.3, 128.2 (2 C), 120.1 (d, *J* = 3.8 Hz), 114.4, 107.8 (d, *J* = 26.0 Hz), 69.9, 51.2 (2 C), 14.4 (2 C), -3.0 (2 C); Mp: 80-82 °C; HRMS (ESI):*m*/*z* calculated for $C_{20}H_{26}FN_2O_2Si$ $[M+H]^+$ 373.1742 found 373.1742.

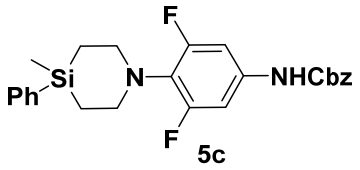
Compounds 5**b** and **5c** were prepared from **4b** and **4c** using the similar procedure employed for **5a**.



5b

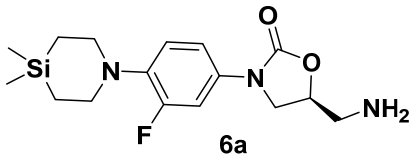
Benzyl4-(4,4-dimethyl-1,4-azasilinan-1-yl)-3,5-difluorophenylcarbamate (5b): Yield 69%; IRυ_{max}(film): 3317, 2953, 2803, 1706, 1594, 1521 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.34 (m, 5 H), 6.97-6.83 (m, 2 H), 6.58 (bs, 1 H), 5.18 (s, 2 H), 3.28 (t, *J* = 6.1 Hz, 4 H), 0.87 (t, *J* = 6.1 Hz, 4 H), 0.11 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8 (dd, *J* = 245.9 Hz, 9.3 Hz, 2 C), 153.0, 135.7, 133.3 (t, *J* = 13.5 Hz), 128.6 (2 C), 128.4, 128.3 (2 C), 127.7

(t, *J* = 14.6 Hz), 102.7 (d, *J* = 27.0 Hz), 67.2, 51.8 (2 C), 15.4 (2 C), -3.0 (2 C); Mp: 71-73 °C; HRMS (ESI):*m*/*z* calculated for $C_{20}H_{25}F_2N_2O_2Si$ $[M+H]^+$ 391.1648 found 391.1647.



5c

Benzyl 3,5-difluoro-4-(4-methyl-4-phenyl-1,4-azasilinan-1-yl) phenylcarbamate (5c): Yield 71%; IRυ_{max}(film): 3325, 2925, 2827, 1741, 1707, 1598, 1509, 1429 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66-7.63 (m, 2 H), 7.45-7.37 (m, 8 H), 6.97 (d, *J* = 10.0 Hz, 2 H), 6.95 (s, 1 H), 5.22 (s, 2 H), 3.43 (t, *J* = 5.8 Hz, 4 H), 1.35-1.29 (m, 2 H), 1.14-1.08 (m, 2 H), 0.42 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8 (dd, *J* = 245.9, 9.3 Hz, 2 C), 153.1, 137.8, 135.7, 133.8, 133.5 (t, *J* = 13.9 Hz, 2 C), 129.1, 128.6, 128.4, 128.3, 127.9, 126.1 (t, *J* = 14.1 Hz, 2 C), 102.6 (d, *J* = 27.0 Hz, 2 C), 67.2, 51.7 (2 C), 14.2 (2 C), -4.1; Mp: 85-87 °C; HRMS (ESI):*m*/*z* calculated for $C_{25}H_{27}F_2N_2O_2Si$ $[M+H]^+$ 453.1804 found 453.1801.



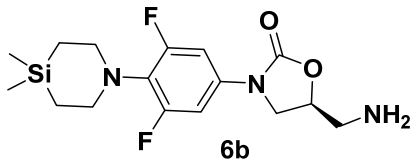
6a

(*S*)-5-(Aminomethyl)-3-(4-(4,4-dimethyl-1,4-azasilinan-1-yl)-3-fluorophenyl)oxazolidin-2-one (6a): To a solution of **5a** (1.20 g, 3.23 mmol) and (*S*)-*tert*-butyl 3-chloro-2-hydroxypropylcarbamate[3] (1.35 g, 6.47 mmol) in DMF (10 mL) was added LiO^tBu (1.03 g, 12.94 mmol) at 0 ˚C. The mixture was stirred at rt for 48 h. Saturated aqueous NH_4Cl was added, the organic phase was extracted with EtOAc (3 x 20 mL) and washed with brine solution, dried and concentrated under reduced pressure.

The crude residue was dissolved in CH_2Cl_2-TFA mixture (8:2) 20 mL and stirred at rt for 3 h, reaction mixture was concentrated and dissolved in water, the aqueous layer was washed with diethyl ether (2 x 50 mL), basified with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (2 x 50 mL), and the CH_2Cl_2 layer was dried and concentrated. The crude was purified by column chromatography on silica gel (230-400) using hexanes- EtOAc mixtures (2:8) to obtain the product as an off-white solid (500 mg) in 45% (brsm) over 2 steps. IRυ_{max}(film): 3685, 3021, 2955, 2809, 2401, 1747, 1515, 1416, 1219 cm^{-1}; ^1H NMR (400

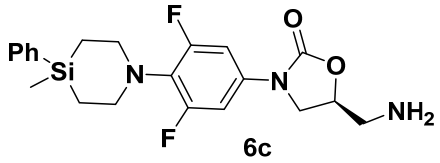
MHz, $CDCl_3$) δ 7.36 (dd, *J* = 14.2 Hz, 2.3 Hz, 1 H), 7.09 (dd, *J* = 8.8 Hz, 1.7 Hz, 1 H), 6.96 (t, *J* = 9.5 Hz, 1 H), 4.72-4.59 (m, 1 H), 4.00 (t, *J* = 8.3 Hz, 1 H), 3.79 (dd, *J* = 8.7 Hz, 6.8 Hz, 1 H), 3.30 (t, *J* = 6.2 Hz, 4 H), 3.10-3.05 (m, 1 H), 2.97-2.92 (m, 1 H), 1.52 (bs, 2 H) 0.90 (t, *J* = 6.2 Hz, 4 H), 0.09 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0 (d, *J* = 245.1 Hz), 154.6, 137.9 (d, *J* = 9.2 Hz), 132.0 (d, *J* = 10.3 Hz), 119.9 (d, *J* = 4.3 Hz), 113.7 (d, *J* = 3.2 Hz), 107.3 (d, *J* = 26.9 Hz), 73.8, 50.9 (2 C), 47.7, 45.0, 14.3 (2 C), -3.0 (2 C); Mp = 94-96 °C; HRMS (ESI):*m*/*z* calculated for $C_{16}H_{25}FN_3O_2Si$ $[M+H]^+$ 338.1695 found 338.1695; $[\alpha]_D^{26}$ – 34.7 (*c* 0.19, MeOH); HPLC: 97.24% t_R = 3.33 min (method C).

Compounds **6b** and **6c** were prepared from **5b** and **5c** using the similar procedure employed for **6a**.



6b

(*S*)-5-(Aminomethyl)-3-(4-(4,4-dimethyl-1,4-azasilinan-1-yl)-3,5-difluorophenyl) oxazolidin-2-one (6b): Yield 52% (brsm); IRυ_{max}(film): 3685, 3021, 2955, 2809, 2401, 1747, 1515, 1416 cm^{-1}; ^{1}H NMR (400 MHz, MeOD) δ 7.17-7.10 (m, 2 H), 4.95-4.88 (m, 1 H), 4.16 (t, *J* = 9.3 Hz, 1 H), 3.75 (dd, *J* = 9.1 Hz, 6.3 Hz, 1 H), 3.37-3.31 (m, 2 H), 3.28-3.24 (m, 4 H), 0.84 (t, *J* = 6.3 Hz, 4 H), 0.07 (s, 6 H); ^{13}C NMR (100 MHz, MeOD) δ 160.1 (dd, *J* = 244.3, 10.3 Hz, 2 C), 155.2, 135.3 (d, *J* = 13.9 Hz), 128.0, 103.6 (m, 2 C), 71.1, 52.9 (2 C), 48.8, 43.4, 16.4 (2 C), -3.0 (2 C); Mp = 180-182 °C; HRMS (ESI):*m*/*z* calculated for $C_{16}H_{24}F_2N_3O_2Si$ $[M+H]^+$ 356.1600 found 356.1593; $[\alpha]_D^{26}$ –25.15 (*c* 1.05, MeOH); HPLC: 97.13% t_R = 3.58 min (method C).

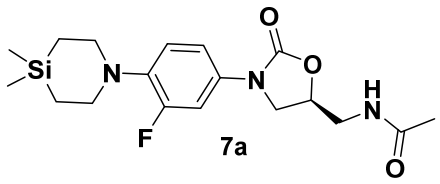


6c

(*S*)-5-(Aminomethyl)-3-(3,5-difluoro-4-(4-methyl-4-phenyl-1,4-azasilinan-1-yl)phenyl)oxazolidin-2-one (6c): Yield 60% (brsm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.55 (m, 2 H), 7.39-7.36 (m, 3 H), 7.10-7.03 (m, 2 H), 4.78-4.67 (m, 1 H), 3.97 (t, *J* = 8.7 Hz, 1 H), 3.78 (dd, *J* = 8.5 Hz, 6.8 Hz, 1 H), 3.36 (t, *J* = 6.2 Hz, 4 H), 3.19-3.14 (m, 1 H), 3.05-

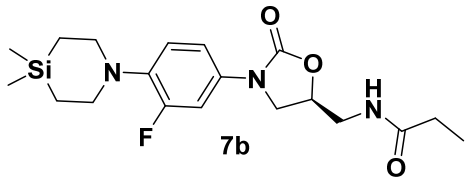
2.96 (m, 1 H), 2.26 (bs, 2 H), 1.29-1.20 (m, 2 H), 1.07-1.01 (m, 2 H), 0.35 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6 (dd, *J* = 245.9, 9.0 Hz, 2 C), 154.3, 137.8, 133.9 (2 C), 133.5 (t, *J* = 13.5 Hz), 129.1, 127.9 (2 C), 126.6 (t, *J* = 14.3 Hz), 102.2 (m, 2 C), 73.3, 51.7 (2 C), 47.5, 44.6, 14.3 (2 C), -4.0; Mp: 71-73 °C; HRMS (ESI):*m*/*z* calculated for $C_{21}H_{26}F_2N_3O_2Si$ $[M+H]^+$ 418.1757 found 418.1766; $[\alpha]_D^{26}$ –0.87 (*c* 0.98, $CHCl_3$); HPLC: 96.34% t_R = 3.26 min (method C).

General Procedure for the preparation of amides: To solution of **6a** or **6b** or **6c** (0.5 mmol) and DIPEA (1 mmol) in dry THF (4.0 mL), was added acid chloride (0.6 mmol) at 0 ˚C, and stirred at rt for 3 h, Saturated aqueous solution of $NaHCO_3$ (5.0 mL) was added to the reaction mixture and extracted with EtOAc (2 x 5 mL), the organic layer was washed with brine, dried and concentrated. The product was purified by column chromatography on silica gel using hexanes- EtOAc mixtures to obtain the product as an off-white solid.



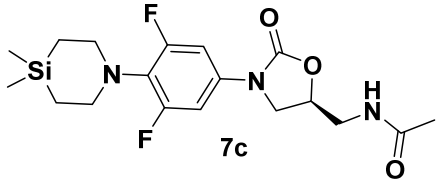
7a

(*S*)-N-((3-(4-(4,4-Dimethyl-1,4-azasilinan-1-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (7a): Yield 72%; IRυ_{max}(film): 2401, 1759, 1675, 1519, 1216 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 13.8 Hz, 1 H), 7.02-6.94 (m, 2 H), 6.52 (t, *J* = 5.8 Hz, 1 H), 4.78-4.72 (m, 1 H), 3.99 (t, *J* = 9.04 Hz, 1 H), 3.73 (dd, *J* = 9.0 Hz, 6.8 Hz, 1 H), 3.69-3.58 (m, 2 H), 3.31 (t, *J* = 5.5 Hz, 4 H), 2.01 (s, 3 H), 0.89 (t, *J* = 5.5 Hz, 4 H), 0.10 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 155.0 (d, *J* = 244.3 Hz), 154.5, 138.1 (d, *J* = 9.3 Hz), 131.4, 119.9, 114.0 (d, *J* = 3.1 Hz), 107.6 (d, *J* = 27.1 Hz), 71.9, 50.9 (2 C), 47.7, 41.9, 23.0, 14.3 (2 C), -3.0 (2 C); Mp = 123-126 °C; HRMS (ESI):*m*/*z* calculated for $C_{18}H_{27}FN_3O_3Si$ $[M+H]^+$ 380.1800, found 380.1814; $[\alpha]_D^{26}$ –4.16 (*c* 0.38, $CHCl_3$); HPLC: 99.03% t_R = 5.1 min (method A).



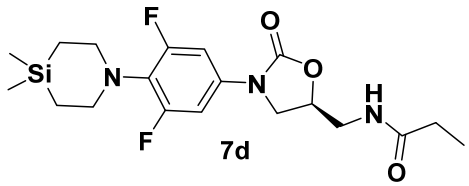
7b

(*S*)-N-((3-(4-(4,4-Dimethyl-1,4-azasilinan-1-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl) methyl)propionamide (7b): Yield 69%; IRυ_{max}(film): 3449, 2401, 1753, 1672, 1516 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 14.2 Hz, 2.1 Hz, 1 H), 7.01-6.91 (m, 2 H), 6.35 (t, *J* = 6.0 Hz, 1 H), 4.77-4.71 (m, 1 H), 3.99 (t, *J* = 9.2 Hz, 1 H), 3.72 (dd, *J* = 9.1, 6.0 Hz, 1 H), 3.66-3.62 (m, 2 H), 3.30 (t, *J* = 6.2 Hz, 4 H), 2.22 (q, *J* = 7.6 Hz, 2 H), 1.12 (t, *J* = 7.6 Hz, 3 H), 0.92-0.86 (m, 4 H), 0.09 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 155.0 (d, *J* = 245.1 Hz), 154.5, 138.2 (d, *J* = 9.3 Hz), 131.5 (d, *J* = 10.8 Hz), 119.8 (d, *J* = 3.8 Hz), 113.9 (d, *J* = 3.1 Hz), 107.5 (d, *J* = 27.0 Hz), 71.9, 50.9 (2 C), 47.7, 41.8, 29.4, 14.3 (2 C), 9.7, -3.0 (2 C); Mp = 135-137 °C; HRMS (ESI):*m*/*z* calculated for $C_{19}H_{29}FN_3O_3Si$ $[M+H]^+$ 394.1957, found 394.1957; $[\alpha]_D^{26}$ –2.68 (*c* 1.05, $CHCl_3$); HPLC: 95.38%, t_R = 6.02 min (method A).



7c

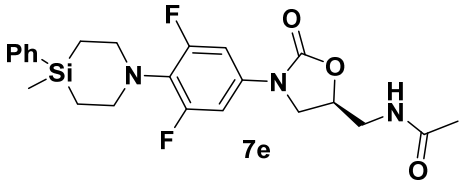
(*S*)-N-((3-(4-(4,4-Dimethyl-1,4-azasilinan-1-yl)-3,5-difluorophenyl)-2-oxooxazolidin-5-yl) methyl)acetamide (7c): Yield 62%; IRυ_{max}(film): 2400, 1757, 1675 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04-6.98 (m, 2 H), 6.00 (bs, 1 H), 4.79-4.73 (m, 1 H), 3.97 (t, *J* = 8.7 Hz, 1 H), 3.73-3.67 (m, 2 H), 3.63-3.56 (m, 1 H), 3.29 (t, *J* = 6.0 Hz, 4 H), 2.01 (s, 3 H), 0.86 (t, *J* = 6.0 Hz, 4 H), 0.09 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 158.6 (dd, *J* = 245.9 Hz, 9.3 Hz, 2 C), 154.1, 133.0 (t, *J* = 14.1 Hz), 127.0 (t, *J* = 14.4 Hz), 102.4 (m, 2 C), 71.9, 51.7 (2 C), 47.4, 41.8, 23.0, 15.4 (2 C), -3.0 (2 C); Mp = 136-139 °C; HRMS (ESI):*m*/*z* calculated for $C_{18}H_{26}F_2N_3O_3Si$ $[M+H]^+$ 398.1706, found 398.1718; $[\alpha]_D^{26}$ –14.44 (*c* 1.05, $CHCl_3$); HPLC: 95.28% t_R = 3.44 min (method C).



7d

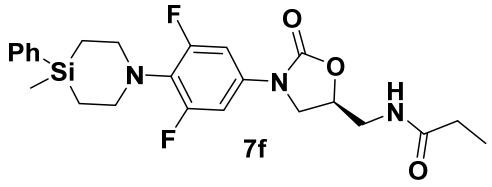
(*S*)-N-((3-(4-(4,4-Dimethyl-1,4-azasilinan-1-yl)-3,5-difluorophenyl)-2-oxooxazolidin-5-yl) methyl)propionamide (7d): Yield 63%; IRυ_{max}(film): 2925, 2401, 1753, 1671, 1510 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06-6.98 (m, 2 H), 6.30 (t, *J* = 5.8 Hz, 1 H), 4.78-4.74 (m, 1

H), 3.97 (t, *J* = 9.0 Hz, 1 H), 3.71 (dd, *J* = 9.2, 6.5 Hz, 1 H), 3.67-3.64 (m, 2 H), 3.28 (t, *J* = 6.0 Hz, 4 H), 2.24 (q, *J* = 7.6 Hz, 2 H), 1.12 (t, *J* = 7.6 Hz, 3 H), 0.85 (t, *J* = 6.0 Hz, 4 H), 0.09 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 158.6 (dd, *J* = 245.8, 9.2 Hz, 2 C), 154.1, 133.0 (t, *J* = 13.9 Hz), 127.0 (d, *J* = 14.6 Hz), 102.2 (m, 2 C), 71.9, 51.7 (2 C), 47.4, 41.7, 29.4, 15.4 (2 C), 9.7, -3.0 (2 C); Mp = 144-146 °C; HRMS (ESI):*m*/*z* calculated for $C_{19}H_{28}F_2N_3O_3Si$ $[M+H]^+$ 412.1863, found 412.1850; $[\alpha]_D^{26}$ –35.79 (*c* 0.21, $CHCl_3$); HPLC: 95.36% t_R = 9.12 min (method B).



7e

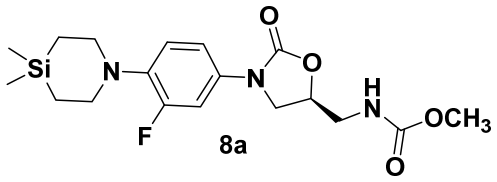
(*S*)-N-((3-(3,5-Difluoro-4-(4-methyl-4-phenyl-1,4-azasilinan-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (7e): Yield 72%; IRυ_{max}(film): 3307, 2926, 1753, 1655, 1511 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.61-7.57 (m, 2 H), 7.40-7.37 (m, 3 H), 7.13-6.98 (m, 2 H), 6.08 (t, *J* = 6.5 Hz, 1 H), 4.83-4.71 (m, 1 H), 3.98 (t, *J* = 8.8 Hz, 1 H), 3.74-3.60 (m, 3 H), 3.38 (t, *J* = 6.2 Hz, 4 H), 2.03 (s, 3 H), 1.34-1.20 (m, 2 H), 1.12-0.99 (m, 2 H), 0.36 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.4, 158.5 (dd, *J* = 245.9, 9.0 Hz, 2 C), 154.2, 137.7, 133.8 (2 C), 133.1 (t, *J* = 13.5 Hz), 129.1, 127.8 (2 C), 126.8 (t, *J* = 14.3 Hz), 102.2 (m, 2 C), 72.0, 51.6 (2 C), 47.3, 41.7, 22.9, 14.2 (2 C), -4.1; Mp = 112-114 °C; HRMS (ESI):*m*/*z* calculated for $C_{23}H_{28}F_2N_3O_3Si$ $[M+H]^+$ 460.1863, found 460.1863; $[\alpha]_D^{26}$ –15.37 (*c* 0.25, $CHCl_3$); HPLC: 98.62% t_R = 8.82 min (method A).



7f

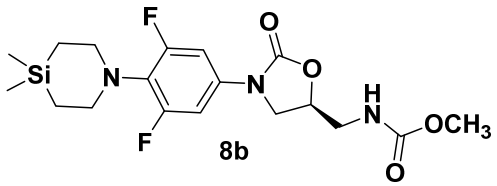
(*S*)-N-((3-(3,5-Difluoro-4-(4-methyl-4-phenyl-1,4-azasilinan-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)propionamide (7f): Yield 76%; IRυ_{max}(film): 3265, 3069, 2926, 1740, 1649, 1510, 1449, 1426 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.61-7.56 (m, 2 H), 7.40-7.37 (m, 3 H), 7.13-6.98 (m, 2 H), 5.97 (t, *J* = 6.0 Hz, 1 H), 4.82-4.69 (m, 1 H), 3.98 (t, *J* = 9.0 Hz, 1 H), 3.75-3.62 (m, 3 H), 3.38 (t, *J* = 6.2 Hz, 4 H), 2.22 (q, *J* = 7.6 Hz, 2 H), 1.34-0.99 (m, 7 H), 0.36 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.1, 158.5 (dd, *J* = 246.2, 9.1

Hz, 2 C), 154.2, 137.7, 133.8 (2 C), 133.1 (t, *J* = 13.2 Hz), 129.1, 127.8 (2 C), 126.8 (t, *J* = 14.3 Hz), 102.2 (m, 2 C), 72.0, 51.6 (2 C), 47.4, 41.7, 29.4, 14.2 (2 C), 9.7, -4.1; Mp = 123-125°C; HRMS (ESI):*m*/*z* calculated for $C_{24}H_{30}F_2N_3O_3Si$ $[M+H]^+$ 474.2019, found 474.2033; $[\alpha]_D^{26}$ –17.09 (*c* 0.47, $CHCl_3$); HPLC: 96.44% t_R = 11.68 min (method A).



8a

(*S*)-Methyl((3-(4-(4,4-dimethyl-1,4-azasilinan-1-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl) methyl)carbamate (8a): To a solution of amine **6a** (150 mg, 0.44 mmol) in CH_2Cl_2 (5.0 mL) was added Et_3N (0.18 mL, 1.34 mmol), CDI (108 mg, 0.67 mmol) and stirred at rt for 4 h, the reaction mixture was then concentrated to one third of its volume. To the crude MeOH (5 mL) and CH_2Cl_2 (5 mL) were added and stirred at rt for 24 h. The product was purified by column chromatography on silica gel (230-400) using hexanes- EtOAc (6:4) mixtures to obtain the product (65 mg, 37%) as an off-white solid. IRυ_{max}(film): 3684, 3450, 2401, 1755, 1725, 1515 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 13.8 Hz, 1.9 Hz, 1 H), 7.09-6.91 (m, 2 H), 5.42 (t, *J* = 5.8 Hz, 1 H), 4.80-4.68 (m, 1 H), 3.99 (t, *J* = 9.0 Hz, 1 H), 3.79-3.75 (m, 1 H), 3.66 (s, 3 H), 3.62-3.47 (m, 2 H), 3.29 (t, *J* = 6.0 Hz, 4 H), 0.88 (t, *J* = 6.0 Hz, 4 H), 0.09 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 154.9 (d, *J* = 245.7 Hz), 154.3, 138.0 (d, *J* = 9.5 Hz), 131.5 (d, *J* = 10.4 Hz), 119.8 (d, *J* = 4.2 Hz), 113.9 (d, *J* = 2.9 Hz), 107.5 (d, *J* = 26.8 Hz), 71.7, 52.5, 50.9 (2 C), 47.5, 43.5, 14.3 (2 C), -3.0 (2 C); Mp = 152-154 °C; HRMS (ESI):*m*/*z* calculated for $C_{18}H_{27}FN_3O_4Si$ $[M+H]^+$ 396.1749, found 396.1760; $[\alpha]_D^{26}$ +5.96 (*c* 0.26, $CHCl_3$); HPLC: 98.81% t_R = 7.09 min (method A).



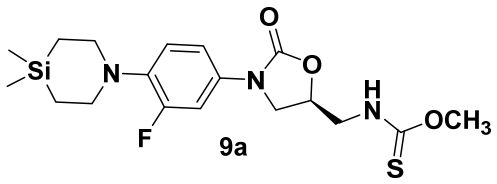
8b

Compound **8b** was prepared from **6b** using the similar procedure employed for **8a**.

(*S*)-Methyl (3-(4-(4,4-dimethyl-1,4-azasilinan-1-yl)-3,5-difluorophenyl)-2-oxooxazolidin-5-yl)methylcarbamate (8b): Yield 55%; IRυ_{max}(film): 2924, 1746, 1512, 1250 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.07-7.01 (m, 2 H), 5.30 (bs, 1 H), 4.77-4.72 (m, 1 H), 3.97 (t, *J* =

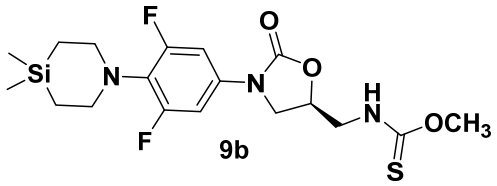
8.8 Hz, 1 H), 3.73 (t, *J* = 7.3 Hz, 1 H), 3.67 (s, 3 H), 3.61-3.49 (m, 2 H), 3.28 (t, *J* = 6.1 Hz, 4 H), 0.86 (t, *J* = 6.1 Hz, 4 H), 0.09 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7 (dd, *J* = 246.2, 9.3 Hz, 2 C), 157.5, 153.9, 133.1 (t, *J* = 13.2 Hz), 127.0 (t, *J* = 14.4 Hz), 102.3 (m, 2 C), 71.8, 52.6, 51.7 (2 C), 47.3, 43.6, 15.5 (2 C), -3.0 (2 C); Mp = 117-119 °C; HRMS (ESI):*m*/*z* calculated for $C_{18}H_{26}F_2N_3O_4Si$ $[M+H]^+$ 414.1655, found 414.1655; $[\alpha]_D^{26}$ +13.27 (*c* 0.11, $CHCl_3$); HPLC: 99.50% t_R = 10.95 min (method B).

Preparation of methyl thiocarbamate and thiourea analogs[4, 5] (9a, 9b, 9c & 9d):



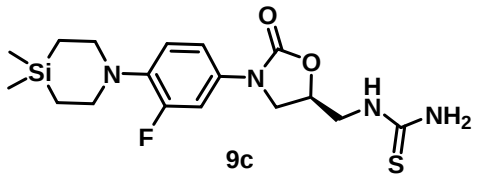
9a

(*S*)-O-Methyl((3-(4-(4,4-dimethyl-1,4-azasilinan-1-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl)methyl)carbamothioate (9a): To a solution of amine **6a** (150 mg, 0.45 mmol) in CH_2Cl_2 (5 mL) was added saturated aqueous $NaHCO_3$ (2 mL), cooled to 0 ˚C and added $CSCl_2$ (0.04 mL, 0.58 mmol), and stirred at rt for 3 h, the CH_2Cl_2 layer was separated and aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL), combined organic layers were washed with brine, dried and concentrated. Crude was dissolved in MeOH (5 mL) and refluxed for overnight, reaction mixture was concentrated under reduced pressure and dissolved in EtOAc, washed with saturated aqueous $NaHCO_3$, dried and concentrated. The crude was purified by column chromatography on silica gel (230-400) using hexane- EtOAc (1:1) mixtures to obtain the product (75 mg, 40%) as an off-white solid. IRυ_{max}(film): 3685, 3400, 2953, 2401, 1755, 1515 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 13.9 Hz, 1.9 Hz, 1 H), 7.07-6.91 (m, 2 H), 6.87 (t, *J* = 6.2 Hz, 1 H), 4.92-4.86 (m, 1 H), 4.08-4.03 (m, 2 H), 4.00 (s, 3 H), 3.97-3.91 (m, 1 H), 3.82-3.78 (m, 1 H), 3.31 (t, *J* = 6.2 Hz, 4 H), 0.89 (t, *J* = 6.2 Hz, 4 H), 0.10 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 154.2, 155.0 (d, *J* = 245.8 Hz), 138.2 (d, *J* = 9.4 Hz), 131.4 (d, *J* = 10.8 Hz), 119.9 (d, *J* = 3.8 Hz), 114.0 (d, *J* = 3.2 Hz), 107.6 (d, *J* = 26.8 Hz), 77.21, 71.2, 57.7, 50.9 (2 C), 47.6 (d, *J* = 2.3 Hz), 14.3 (2 C), -3.0 (2 C); Mp = 123-126 °C; HRMS (ESI):*m*/*z* calculated for $C_{18}H_{27}FN_3O_3SSi$ $[M+H]^+$ 412.1521, found 412.1509; $[\alpha]_D^{26}$ +32.24 (*c* 1.13, $CHCl_3$); HPLC: 99.17% t_R = 11.66 min (method A).



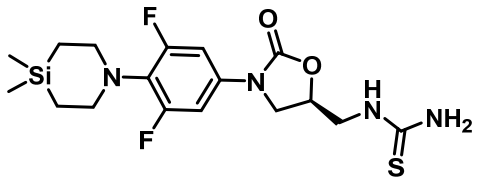
9b

(*S*)-O-Methyl(3-(4-(4,4-dimethyl-1,4-azasilinan-1-yl)-3,5-difluorophenyl)-2-oxooxazolidin-5-yl)methylcarbamothioate (9b): Yield 33%**;** IRυ_{max}(film): 3400, 3292, 2831, 2401, 1759, 1635, 1511, 1449 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12-6.97 (m, 2 H), 6.76 (t, *J* = 6.1 Hz, 1 H), 4.97-4.85 (m, 1 H), 4.13-3.93 (m, 6 H), 3.79 (dd, *J* = 9.0 Hz, 7.0 Hz, 1 H), 3.29 (t, *J* = 6.3 Hz, 4 H), 0.87 (t, *J* = 6.3 Hz, 4 H), 0.10 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 158.7 (dd, *J* = 245.9, 10.3 Hz, 2 C), 153.8, 133.0 (t, *J* = 12.8 Hz), 127.1 (t, *J* = 14.6 Hz), 102.4 (m, 2 C), 71.2, 57.8, 51.7 (2 C), 47.4, 47.3, 15.4 (2 C), -3.0 (2 C); Mp = 141-143 °C; HRMS (ESI):*m*/*z* calculated for $C_{18}H_{26}F_2N_3O_3SSi$ $[M+H]^+$ 430.1427, found 430.1440; $[\alpha]_D^{26}$ +46.47 (*c* 0.21, $CHCl_3$); HPLC: 98.60% t_R = 18.78 min (method B).



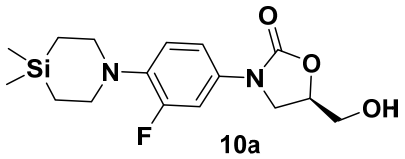
9c

(*S*)-1-((3-(4-(4,4-Dimethyl-1,4-azasilinan-1-yl)-3-fluorophenyl)-2-oxooxazolidin-5-l)methyl)thiourea (9c): Yield 78%; IRυ_{max}(film): 3405, 3294, 2839, 2401, 1759, 1630 cm^{-1}; ^1H NMR (400 MHz, DMSO-D_6) δ 7.93 (t, *J* = 6.0 Hz, 1 H), 7.27-7.00 (broad peak for 2 H merged with multiplet at 7.13-7.03), 7.43 (dd, *J* = 15.1, 2.2 Hz, 1 H), 7.13-7.03 (m, 2 H), 4.85-4.77 (m, 1 H), 4.07 (t, *J* = 8.7 Hz, 1 H), 3.72-3.85 (m, 3 H), 3.26 (t, *J* = 6.4 Hz, 4 H), 0.82 (t, *J* = 6.1 Hz, 4 H), 0.09 (s, 6 H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 184.0, 153.1 (d, *J* = 242.5 Hz), 154.0, 136.9 (d, *J* = 8.6 Hz), 132.1 (d, *J* = 10.5 Hz), 120.1 (d, *J* = 3.8 Hz), 114.1 (d, *J* = 2.9 Hz), 106.7 (d, *J* = 25.8 Hz), 71.6, 50.3 (2 C), 47.0, 46.5, 13.9 (2 C), -2.9 (2 C). HRMS (ESI): *m*/*z* calculated for $C_{17}H_{26}FN_4O_2SSi$ $[M+H]^+$ 397.1524 found 397.1527; $[\alpha]_D^{27}$ – 1.42 (*c* 0.28, DMSO); HPLC: 98.21% t_R = 5.5 min (method A).



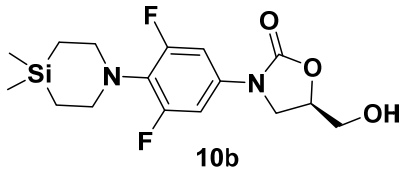
9d

(*S*)-1-((3-(4-(4,4-Dimethyl-1,4-azasilinan-1-yl)-3,5-difluorophenyl)-2-oxooxazolidin-5-yl)methyl)thiourea (9d): Yield 74%; IRυ_{max}(film): 3405, 3294, 2839, 2401, 1750, 1634 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-D_6) δ 7.91 (t, *J* = 6.0 Hz, 1 H), 7.40-7.05 (broad peak for 2 H, merged with doublet at 7.23), 7.23 (d, *J* = 10.8 Hz, 2 H), 4.90-4.80 (m, 1 H), 4.08 (t, *J* = 8.5 Hz, 1 H), 3.85-3.72 (m, 3 H), 3.23 (t, *J* = 5.2 Hz, 4 H), 0.82 (t, *J* = 5.2 Hz, 4 H), 0.10 (s, 6 H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 184.2, 158.3 (dd, *J* = 244.3, 9.3 Hz, 2 C), 154.0, 134.6 (t, *J* = 14.6 Hz), 125.6 (t, *J* = 14.6 Hz), 102.2 (m, 2 C), 71.9, 51.6 (2 C), 47.0, 46.7, 15.3 (2 C), -2.8 (2 C); $C_{17}H_{25}F_2N_4O_2SSi$ $[M+H]^+$ 415.1430 found 415.1432; $[\alpha]_D^{27}$ –3.97 (*c* 0.33, DMSO); HPLC: 99.21% t_R = 8.4 min (method B).



10a

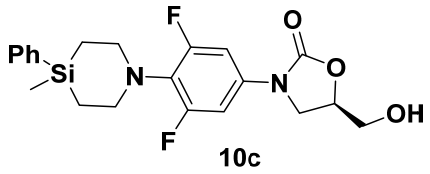
(*R*)-3-(4-(4,4-Dimethyl-1,4-azasilinan-1-yl)-3-fluorophenyl)-5-hydroxymethyl)oxazolidin-2-one (10a): To compound **5a** (800 mg, 2.15 mmol) in dry THF (5 mL) at –78 °C was added n-BuLi 1.6 M in hexane (2.4 mL, 3.87 mmol), stirred for 30 min, (*R*)-glycidylbutyrate (0.6 mL, 3.87 mmol) was added drop wise at –78 °C, and allowed to stir at RT for overnight, reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) extracted with EtOAc (2 x 5 mL), organic layer was washed with brine (5 mL), dried, concentrated. The product was purified by column chromatography on silica gel (230-400) using hexane- EtOAc (4:6) mixtures to obtain the product (420 mg, 58%) as an off-white solid. IRυ_{max}(film): 3407, 2953, 2922, 1738, 1517, 1418, 1384 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 14.4 Hz, 2.4 Hz, 1 H), 7.05 (dd, *J* = 9.4 Hz, 2.3 Hz, 1 H), 6.96-6.92 (m, 1 H), 4.73-4.68 (m, 1 H), 3.98-3.87 (m, 3 H), 3.74-3.69 (m, 1 H), 3.30 (t, *J* = 6.2 Hz, 4 H), 0.89 (t, *J* = 6.2 Hz, 4 H), 0.11 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1 (d, *J* = 243.5 Hz), 154.9, 138.0 (d, *J* = 6.9 Hz), 131.8 (d, *J* = 10.1 Hz), 119.9 (d, *J* = 4.1 Hz), 114.0 (d, *J* = 3.4 Hz), 107.5 (d, *J* = 26.7 Hz), 72.9, 62.6, 51.0 (2 C), 46.5, 14.3 (2 C), -3.0 (2 C); Mp = 126-129 °C; HRMS (ESI):*m*/*z* calculated for $C_{16}H_{24}FN_2O_3Si$ $[M+H]^+$ 339.1535,found 339.1547; $[\alpha]_D^{25.6}$ –32.45 (*c* 1.05, $CHCl_3$); HPLC: 96.39% t_R = 5.8 min (method B).



10b

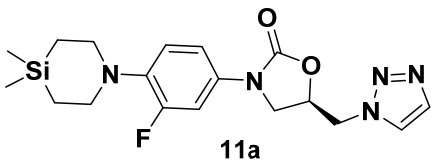
Compounds **10b** and **10c** were prepared from **5b** and **5c** using the similar procedure employed for **10a.**

(*R*)-3-(4-(4,4-Dimethyl-1,4-azasilinan-1-yl)-3,5-difluorophenyl)-5-(hydroxymethyl)oxazolidin-2-one (10b): Yield 62% (brsm); IRυ_{max}(film): 3401, 2401, 1754, 1511, 1252 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.11-7.03 (m, 2 H), 4.76-4.70 (m, 1 H), 4.01-3.89 (m, 3 H), 3.74 (dd, *J* = 12.5, 3.8, 1 H), 3.29 (t, *J* = 6.0 Hz, 4 H), 0.87 (t, *J* = 6.0 Hz, 4 H), 0.10 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7 (dd, *J* = 245.6, 9.7 Hz, 2 C), 154.3, 133.3 (t, *J* = 13.6 Hz), 126.9 (t, *J* = 14.7 Hz), 102.2 (m, 2 C), 72.7, 62.7, 51.8 (2 C), 46.2, 15.5 (2 C), -3.0 (2 C); Mp = 126-128 °C; HRMS (ESI): *m*/*z* calculated for $C_{16}H_{23}F_2N_2O_3Si$ $[M+H]^+$ 357.1441 found 357.1451; $[\alpha]_D^{26}$ –56.73 (*c* 0.26, $CHCl_3$); HPLC: 99.02% t_R = 8.82 min (method B).



10c

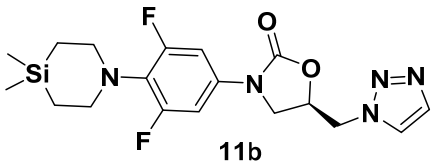
(*R*)-3-(3,5-Difluoro-4-(4-methyl-4-phenyl-1,4-azasilinan-1-yl)phenyl)-5-(hydroxymethyl)oxazolidin-2-one (10c): Yield 53% (brsm); IRυ_{max}(film): 3423, 2931, 2833, 1709, 1635, 1514 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61-7.56 (m, 2 H), 7.40-7.37 (m, 3 H), 7.11-7.04 (m, 2 H), 4.76-4.71 (m, 1 H), 4.01-3.89 (m, 3 H), 3.74 (dd, *J* = 12.5, 3.5 Hz, 1 H), 3.38 (m, 4 H), 2.66 (bs, 1 H), 1.30-1.23 (m, 2 H), 1.09-1.03 (m, 2 H), 0.36 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.65 (dd, *J* = 246.6, 10.2 Hz, 2 C), 154.4, 137.8, 133.9 (2 C), 133.4 (t, *J* = 13.1 Hz), 129.2, 127.9 (2 C), 126.7 (t, *J* = 13.9 Hz), 102.2 (m, 2 C), 72.8, 62.6, 51.7 (2 C), 46.1, 14.2 (2 C), -4.0; Mp = 105-107 °C; HRMS (ESI): *m*/*z* calculated for $C_{21}H_{25}F_2N_2O_3Si$ $[M+H]^+$ 419.1597 found 419.1609; $[\alpha]_D^{26}$ –48.53 (*c* 0.14, $CHCl_3$); HPLC: 96.97% t_R = 10.56 min (method B).



11a

(*R*)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(4-(4,4-dimethyl-1,4-azasilinan-1-yl)-3-fluorophenyl)oxazolidin-2-one (11a): To a solution of hydroxyl compound **10a** (200 mg, 0.59 mmol) in CH_2Cl_2 (5.0 mL) was added Et_3N (0.16 mL, 1.18 mmol) followed by methanesulfonylchloride (0.07 mL, 0.89 mmol) at 0 °C, stirred at rt for 2 h, reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (5 mL)**,** extracted with CH_2Cl_2 (3 x 5 mL), combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The crude mesyl compound obtained above was dissolved in DMF (5.0 mL), NaN_3 (78 mg, 1.2 mmol) was added and stirred at 80 °C for 4 h, water (10 mL) was added and extracted with diethyl ether (3 x 5 mL) combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure.

To the crude azido compound (0.60 mmol) obtained from above reaction were added 1,4-dioxane (4.0 mL), norbornadiene (0.31 mL, 3.03 mmol) and refluxed for 5 h, Water (5 mL) was added, layers were separated, aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL), dried, concentrated. The product was purified by column chromatography on silica using hexane- EtOAc mixtures to obtain the product (60 mg, 26 % over 3 steps) as a brown solid. IRυ_{max}(film): 2401, 1760, 1515, 1216 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1 H), 7.73 (s, 1 H), 7.21-7.18 (m, 1 H), 6.94-6.90 (m, 2 H), 5.05-4.99 (m, 1 H), 4.77-4.75 (m, 2 H), 4.10 (t, *J* = 9.0 Hz, 1 H), 3.85 (dd, *J* = 9.4 Hz, 6.2 Hz, 1 H), 3.30 (t, *J* = 6.2 Hz, 4 H), 0.87 (t, *J* = 6.2 Hz, 4 H), 0.09 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8 (d, *J* = 245.5 Hz), 153.5, 138.4 (d, *J* = 9.0 Hz), 134.5, 130.6 (d, *J* = 10.1 Hz), 125.0, 119.8 (d, *J* = 4.1 Hz), 114.4 (d, *J* = 3.3 Hz), 107.8 (d, *J* = 26.7 Hz), 70.3, 52.0, 50.8 (2 C), 47.5, 14.2 (2 C), -3.0 (2 C); Mp = 165-168 °C; HRMS (ESI):*m*/*z* calculated for $C_{18}H_{25}FN_5O_2Si$ $[M+H]^+$ 390.1756, found 390.1756; $[\alpha]_D^{26}$ –16.01 (*c* 0.27, $CHCl_3$); HPLC: 95.66% t_R = 5.8 min (method B).



11b

Compound **11b** was prepared from **10b** using the similar procedure employed for **11a**.

(*R*)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(4-(4,4-dimethyl-1,4-azasilinan-1-yl)-3,5-difluorophenyl)oxazolidin-2-one(11b): Yield 40% (over 3 steps); IRυ_{max}(film): 2401, 1767, 1635, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1 H), 7.73 (s, 1 H), 6.95-6.89 (m, 2 H), 5.07-5.02 (m, 1 H), 4.81-4.73 (m, 2 H), 4.09 (t, *J* = 9.2 Hz, 1 H), 3.85 (dd, *J* = 9.1 Hz, 6.3 Hz, 1 H), 3.27 (t, *J* = 5.8 Hz, 4 H), 0.85 (t, *J* = 5.8 Hz, 4 H), 0.09 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6 (dd, *J* = 246.1, 9.4 Hz, 2 C), 153.1, 134.5, 132.3 (t, *J* = 13.6 Hz), 127.4 (t, *J* = 14.1 Hz), 125.0, 102.5 (m, 2 C), 70.3, 51.9, 51.6 (2 C), 47.2, 15.4 (2 C), -3.0 (2 C); Mp = 149-151 °C; HRMS (ESI): *m*/*z* calculated for $C_{18}H_{24}F_2N_5O_2Si$ $[M+H]^+$ 408.1662 found 408.1649; $[\alpha]_D^{26}$ –40.66 (*c* 0.48, $CHCl_3$); HPLC: 94.95% t_R = 8.5 min (method B).

3. Biological assay methods

3.1. Determination of MIC

The strains in the MIC panel are either from ATCC or clinical isolates in the RCI culture collection. MIC (minimum inhibitory concentration) of NCEs was determined by Microbroth dilution method against facultative bacteria as per CLSI guidelines M7-A7.

3.1.1 Method

Microbroth dilution method

3.1.2. Medium

Cation adjusted Mueller Hinton II Broth (MHB-BD); *staphylococci spp*., *enterococci spp*.

3.1.3. Preparation of compounds

1 mg/mL of stock solution of compounds and standard drugs are prepared in dimethylsulfoxide/distilled water/solvent and further 2 fold dilutions are done in 96 well U bottom microtiter plates as per CLSI guidelines.

3.1.4. Inoculum preparation

Saline suspensions are prepared from three-four isolated bacterial colonies taken from cultures grown on TSA (Tryptic Soya Agar) for 18-24 h.

The turbidity of the suspension is adjusted to 0.5 McFarland standard (~1.5 X 10^8 CFU/mL). Cultures are diluted 100 times in MHB and 50 µL of diluted culture broth is added in wells already containing 50 µL of broth containing diluted compounds and growth well (positive control) to get approximately 3-7 x 10^5 CFU/mL. Cultures are randomly selected for CFU determination of inoculum suspensions. Micro titer plates are then incubated overnight at 35-37 ˚C in ambient air BOD.

3.1.5. End Point determination of MIC

MIC is recorded as the micro dilution well with lowest concentration of the drug at which there is complete disappearance of growth of the organism in comparison to positive control (growth well) as detected by the unaided eye.

3.1.6. Quality Control Strains

Staphylococcus aureus ATCC 29213

Enterococcus faecalis ATCC 29212

Table 1. Antibacterial activity of silicon compounds MIC_{90} (µg/mL)

Strain	6a	6b	6c	7a	7b	7c	7d	7e	7f	8a	8b	9a	9b	9c	9d	10a	10b	10c	11a	11b	LZD
S.aureus ATCC 25923	>32	16	>32	16	32	8	8	>32	>32	8	4	4	>32	ND	ND	>32	>32	32	16	>32	2
S.aureus ATCC 13709 Smith	>32	16	>32	16	32	8	>32	>32	>32	16	16	4	>32	4	>32	>32	>32	>32	32	>32	2
S.aureus ATCC 29213	>32	16	>32	16	32	>16	>32	>32	>32	>32	16	4	>32	4	>32	>32	>32	>32	32	>32	4
MRSA ATCC 43300	>32	16	32	16	32	>32	16	32	32	16	16	4	>32	<2	>32	>32	>32	32	16	>32	2
MRSA 562	>32	16	>32	16	32	8	8	>32	>32	16	16	4	>32	ND	ND	>32	16	32	16	32	2
S.aureus 2 (PVL+ve)	>32	16	>32	16	32	>32	8	>32	>32	16	16	4	>32	ND	ND	>32	>32	16	16	32	2
S.aureus ATCC Newman 25904	>32	16	>32	16	32	>32	16	>32	>32	16	16	4	>32	ND	ND	>32	>32	32	16	>32	2
MRSA ATCC BAA 39	>32	16	>32	16	16	8	32	>32	>32	8	8	4	>32	ND	ND	>32	16	32	16	>32	1
S.aureus DB00026	>32	16	>32	16	32	>32	>32	>32	>32	16	16	8	>32	ND	ND	>32	32	32	32	>32	1
MRSA 252 BAA 1720	>32	16	>32	16	32	>32	32	>32	>32	8	8	4	>32	ND	ND	32	>32	16	8	>32	2
S.epidermidis ATCC 14990	32	16	32	8	8	4	16	>32	>32	8	8	2	>32	<2	<2	32	16	16	16	32	1
MRSE ATCC 35984	>32	16	32	8	16	8	32	>32	>32	8	8	1	16	<2	<2	32	32	8	8	32	0.5
E.faecalis ATCC 29212	16	16	32	16	32	8	32	>32	>32	32	32	4	>32	4	>32	32	>32	32	16	32	1
E.faecalis ATCC 51299 (VRE&HLAR)	32	16	32	16	16	8	8	>32	>32	16	16	2	>32	<2	>32	>32	>32	16	16	32	1
E.faecalis ATCC 19433	32	16	32	16	32	16	32	>32	>32	32	32	8	>32	ND	ND	32	>32	32	32	32	2
E.faecium ATCC 19434	32	16	32	16	16	8	32	>32	>32	16	16	4	>32	4	>32	>32	16	32	32	>32	2
E.faecium ATCC 49224	32	16	32	8	8	8	32	32	>32	16	32	4	>32	4	>32	>32	8	16	32	>32	4

E.faecium ATCC 35667	32	8	32	8	16	8	32	32	32	8	8	2	>32	ND	ND	32	32	16	16	16	1
E.coli 7632	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	ND	ND	>32	>32	>32	>32	>32	>32
S.aureus FDA 209P	>32	16	>32	8	16	8	8	>32	>32	16	8	4	>32	ND	ND	32	16	16(ppt)	16	32	2
S.aureusA TCC 49775 PVL +ve	>32	16	>32	16	32	16	32	>32	>32	32	16	8	>32	ND	ND	>32	>32	32	32	>32	2
S.aureusA TCC 700699 Mu50	>32	16	>32	8	16	8	16	>32	>32	16	8	4	>32	ND	ND	32	8	8(ppt)	16	>32	1
MRSA 0-2657	>32	16	>32	8	16	8	16	>32	>32	16	8	4	>32	ND	ND	>32	>32	16	16	>32	2
MRSA DB 00026	>32	16	>32	16	32	8	32	>32	>32	32	32	4	>32	ND	ND	>32	>32	16(ppt)	32	32	2
S.aureus 13709 LNZ mutant	>32	32	>32	>16	>32	>16	>32	>32	>32	>32	>32	>32	>32	ND	ND	>32	>32	>32	>32	>32	>16
S.epidermidis ATCC 12228	>32	32	>32	8	8	4	8	>32	>32	16	8	4	>32	ND	ND	>32	>32	16	32	16	1
MRSE ATCC 35983	>32	32	>32	8	16	4	32	>32	>32	32	32	4	>32	ND	ND	32	>32	16	16	32	2
S.epidermis St 358	>32	16	>32	8	16	8	32	>32	>32	16	16	4	>32	ND	ND	32	>32	16(ppt)	16	32	2
E.faecalis SP 346 VRE	>32	16	>32	16	32	8	16	>32	>32	32	32	8	>32	ND	ND	>32	>32	32	32	16	2
E.faecium 6A VRE	32	8	>32	16	16	4	8	>32	>32	16	4	4	>32	ND	ND	32	8	8	16	4	2
E.faecium 134 VRE	>32	16	>32	16	32	8	32	>32	>32	32	32	4	>32	ND	ND	>32	>32	32	32	32	2
E.faecium 06076 VRE	>32	16	>32	16	32	8	>32	>32	>32	32	>32	4	>32	ND	ND	>32	>32	>32	>32	>32	2
E.faecium ATCC 3567	32	8	>32	16	16	16	32	32	>32	16	16	4	>32	ND	ND	>32	32	8	32	32	2

3.2. *In vitro* metabolic stability[6,7]

10 mM of standard solution was prepared in DMSO. 1 mM of working solution-1 was prepared in Acetonitrile from the standard solution, 50 µM of working solution-2 was prepared in Acetonitrile, water mixture (1:1) from the working solution-1. 98µL of cocktail mixture (buffer, microsomes and cofactor) was transferred in a pre labelled micro centrifuge tube, 2 µL of working solution (50 µM in ACN: Water) was added in to the cocktail mixture. Samples were incubated at 37 °C for 15, 30, 45 and 60 minutes time intervals. After incubation, samples were terminated with 200 µL of methanol containing internal standard. Then the samples were Vortexed in a table top vortexer for 5 min and centrifuged at 14000 RPM for 5 minutes. Supernatant samples were subjected to LC-MS/MS analysis.

3.3. *In vitro* Plasma stability[8]

10 mM of standard solution was prepared in DMSO. 1 mM of working solution-1 was prepared in Acetonitrile from the standard solution, 50 µM of working solution-2 was

prepared in Acetonitrile, water mixture (1:1) from the working solution-1. 98 µL of test system was transferred in a pre labelled micro centrifuge tube, 2 µL of working solution (50 µM in ACN: Water) was added in to the cocktail mixture. Samples were incubated at 37°C for 60 minutes time intervals. After incubation samples were terminated with 200 µL of methanol containing internal standard. Samples were Vortexed in a table top vortexer for 5 min and centrifuged at 14000 RPM for 5 minutes, supernatant samples were subjected to LC-MS/MS analysis.

3.4. Plasma Protein Binding (Equilibrium dialysis method)[8]

745µL of plasma was transferred into 2 mL micro centrifuge tube. To that 5µL of Test compound (150 µM) was added, samples were mixed in the table top vortexer for 2 minutes. 50 µL plasma (n=2) was transferred in a pre labelled 1.5 mL micro centrifuge tube treated as 0 hour sample. Remaining 650 µL plasma sample were incubated for 30 minutes at 37 °C in a water bath, after 30 minute incubation 50 µL plasma (n=2) was removed in a pre labelled 1.5mL micro centrifuge tube treated as 0.5 hour sample. 200 µL of plasma sample (n=2) was transferred into the sample chamber which is indicated by the red ring, RED insert was placed into the base plate and 350 µL of buffer was transferred into the buffer chamber. Plates were incubated at 37 °C at approximately 100 RPM on an orbital shaker or 20 RPM on an up-and-down shaker for 4 hours. 50 µL of post dialysis sample from the buffer and the plasma chambers were transferred into pre labelled micro centrifuged tube. 50 µL of plasma to the buffer samples and an equal volume of buffer (KH_2PO_4 Buffer pH 7.4) were added to the collected plasma samples. 150 µL of methanol containing internal standard (Tolbutamide 250 ng/mL) was added to precipitate the protein and release compound. Samples were vortexed for 3 minutes in a table top vortexer and centrifuge for 5 minutes at 14,000 RPM, Supernatant were subjected to LC-MS/MS analysis.

3.5. *In vitro* Solubility

10 mM of standard solution was prepared in DMSO, 5 mM of working solution-1 was prepared in DMSO from the standard solution. 495 µL of Buffer (1.2, 2.2, 4.5, 7.4 and 10.2 pH) was transferred in a pre labelled micro centrifuge tube. 5 µL of working solution (5 mM) was added in to the test system. Samples were Vortexed in a table top vortexer for 5 min and centrifuged at 14000 RPM for 5 minutes; supernatant samples were subjected to HPLC analysis.

3.6. SD oral PK in mice and Rat

All animals were fasted overnight (12 hours) before dosing and continued till 4.0 hours after administration of test item. The blood samples (all collections each of 150 µL from each animal) were collected according to the sampling schedule from orbital sinus into the micro centrifuge tube containing Dipotassium EDTA as an anticoagulant. Blood samples were centrifuged immediately with a speed of 1000 g for 10 min at 4 °C and separated plasma samples were frozen at below –80 °C and stored until analysis, the plasma concentrations of test item in all samples were analyzed by LC-MS/MS method. Pharmacokinetic parameters viz. C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, $t_{½}$, K_{el}, VZ_F and CLZ_F were estimated for the above concentrations by using WinNonlin software.

Table 2. Pharmacokinetics of Linezolid and 7a in Mice.

Route		**IV**		**Oral**	
Dose	mg/kg	1		10	
N		3		3	
Compound		**LZD**	**7a**	**LZD**	**7a**
C_{0}	µg/mL	1.67	0.89	-	-
C_{max}	µg/mL	1.55	0.83	6.39	2.17
AUC_{0-t}	µg.hr/mL	0.66	0.32	16.85	3.88
AUC_{0-inf}	µg.hr/mL	0.68	0.33	16.94	3.89
T_{max}	hr	-	-	0.25	0.25
$t_{½}$	hr	0.36	0.32	1.01	0.76
K_{el}	hr^{-1}	1.95	2.18	0.69	0.91
V_{z}	L/kg	0.76	1.41	-	-
Cl_{z}	mL/min/kg	24.61	50.98	-	-
% BA				100%	100%

3.7 Brain PK (pharmacokinetics)

Female BALB/c mice weighing 20 to 40 g were used as test system in this study. They were housed in a temperature (22±1°C) and relative humidity (55±10 %) controlled room and were exposed to a controlled 12-hr light / dark cycle and allowed free access to food and water. All animal experimental protocols and procedures were approved by institutional animal ethics. The details of number of groups, route of administration, formulation details, strength of the formulation etc are shown in table 3.

Table 3.

Animal no. and Sex	No of Groups	Route of administration	Vehicle	Test Item Dose level [mg/kg b.wt]	Volume of administration [mL/kg b.wt]	Strength of formulation [mg/mL]
16 F (F1-F16)	5 (each comprises of 2 animals)	p.o.	1% Polysorbate-80 + 99% Methyl Cellulose pH2.2 (4000cps; 0.5 % w/v)	10	10	1.0

3.7.1. Preparation of formulation

All the formulations were prepared just before administration.

Preparation of the Oral Suspension:

Test item was weighed and transferred it in to a mortar and triturated, 1% Polysorbate 80 (of the final suspension) was added to the mortar and the test item was triturated to get a smooth paste, 99% Methyl cellulose (MC 4000cps, 0.5% w/v) was added in gravimetric dilution fashion and triturated well to get a fine suspension, the suspension was sonicated for 5 min to get a uniform suspension.

3.7.2. Administration of test item

The oral suspension was administered to one group of 15 animals through oral gavage and the intravenous solution was administered to another group of 10 animals through lateral tail vein injection as per the standard procedures.

3.7.3. Sampling schedule

The blood samples (all collections each of 150 µL from each animal) were collected according to the sampling schedule from orbital sinus into the microfuge tubes containing DipotassiumEDTA as an anticoagulant. Blood samples were centrifuged immediately with a speed of 1000 g for 10 min at 4°C and separated plasma and brain samples were frozen at below -80°C and stored until analysis. The details are shown in table 4.

Table 4.

Route of administration	Sampling schedule		Total no. of Sampling points	Total no of Samples
	Animal No.	Sampling points		
p.o	F1, F2	0.25 hr post dose	8	16 +16
	F3, F4	0.5 hr post dose		
	F5, F6	1.0 hr post dose		
	F7, F8	2.0 hr post dose		
	F9, F10	4.0 hr post dose		
	F11, F12	6.0 hr post dose		
	F13, F14	8.0 hr post dose		
	F15, F16	24.0 hr post dose		

3.7.4. Brain homogenation

20% Brain homogenate were prepared in (Methanol: water 1:1).

Table 5. Comparison of brain-plasma PK of 7a, 7c, 9a and linezolid

	7a	**7a**	**7a**	**7c**	**7c**	**7c**	**9a**	**9a**	**9a**	**LZD**	**LZD**	**LZD**
Route	Brain	Plasma	Brain/ Plasma Ratio	Brain	Plasma	Brain/ Plasma Ratio	Brain	Plasma	Brain/ Plasma Ratio	Brain	Plasma	Brain/ Plasma Ratio
Dose	10	10		10	10	10	10	10		10	10	
N	2	2		2	2	2	2	2		2	2	
C_{max}	1.33	1.05	1.27	5.58	2.02	2.76	1.47	0.37	3.96	0.45	3.65	0.12
AUC_{0-t}	3.01	1.78	1.69	14.74	5.80	2.54	3.11	0.87	3.57	0.83	7.58	0.11
AUC_{0-inf}	3.05	1.80	1.69	16.44	6.21	2.65	3.24	0.93	3.49	0.90	7.70	0.12
T_{max}	0.25	0.25		1.00	1.00		0.5	0.5		0.50	0.50	
$t_{½}$	1.35	1.28		2.66	1.88		1.56	1.89		1.03	1.30	
K_{el}	0.51	0.54								0.67	0.53	

V_z	6.39	10.24								16.62	2.43	
Cl_z	54.70	92.49								186.09	21.63	

Units for brain: C_{max} = µg/g, AUC $_{0\text{-}t}$ = µg.hr/g, AUC $_{0\text{-}inf}$ = µg.hr/g, T_{max} = hr, $t_{1/2}$ = hr, K_{el} = hr^{-1}, V_z = L/kg, Cl_z = ml/min/kg.

Units for Plasma: C_{max} = µg/ml, AUC $_{0\text{-}t}$ = µg.hr/ml, AUC $_{0\text{-}inf}$ = µg.hr/ml, T_{max} = hr, $t_{1/2}$ = hr, K_{el} = hr^{-1}, V_z = L/kg, Cl_z = ml/min/kg.

3.8. Cytotoxicity of compounds 7a, 7c and 9a in liver cancer and normal epithelial cells:

Objective: To determine the cytotoxicity of compounds **7a**, **7c** and **9a** following 24 h incubation with human hepatoma (HepG2) and tracheal epithelial cells (HTEpiC). The HepG2 hepatoma cells behave and retain most characteristics of normal hepatocytes. These cells are therefore used commonly as a surrogate of normal cells to measure altered functional activity and cytotoxicity in response to therapeutic agents.

Method: Cells were plated at 5000 per well in a 96-well plate, treated with appropriate concentrations of compounds, and incubated for 24 h at 37 ˚C in a 5% CO_2/95% air incubator. Viability of cells was determined by estimating the amount of soluble formazan (in DMSO) formed after addition of 100 µg MTT and 3.5 h incubation at 37 ˚C. Media was removed and the crystals were dissolved in 150 µL DMSO. Absorbance was measured at 560 nm with a background correction at 640 nm on Fluostar Omega (BMG Labtech, USA). IC_{50} were calculated using GraphPad Prism 6.0 (La Jolla, USA) by fitting the data in a non-linear regression model with variable slope. Data were expressed as Mean ±SEM.

Results: Compounds **7c** and **9a** were non-toxic at >10 µM concentration in both HepG2and HTEpiCcells. However, the IC_{50} of compound **7a** incubation was 9 µM in HepG2 cells and 5 µM in HTEpiC cells.

Conclusion: While compounds **7c** and **9a** were relatively non-toxic in the cell lines tested, compound **7a** displayed cytotoxicity with IC_{50}<10 µM.

4. References

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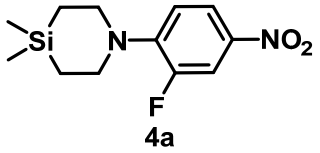
^{1}H NMR spectrum of Compound 4a (CDCl$_3$, 400 MHz)



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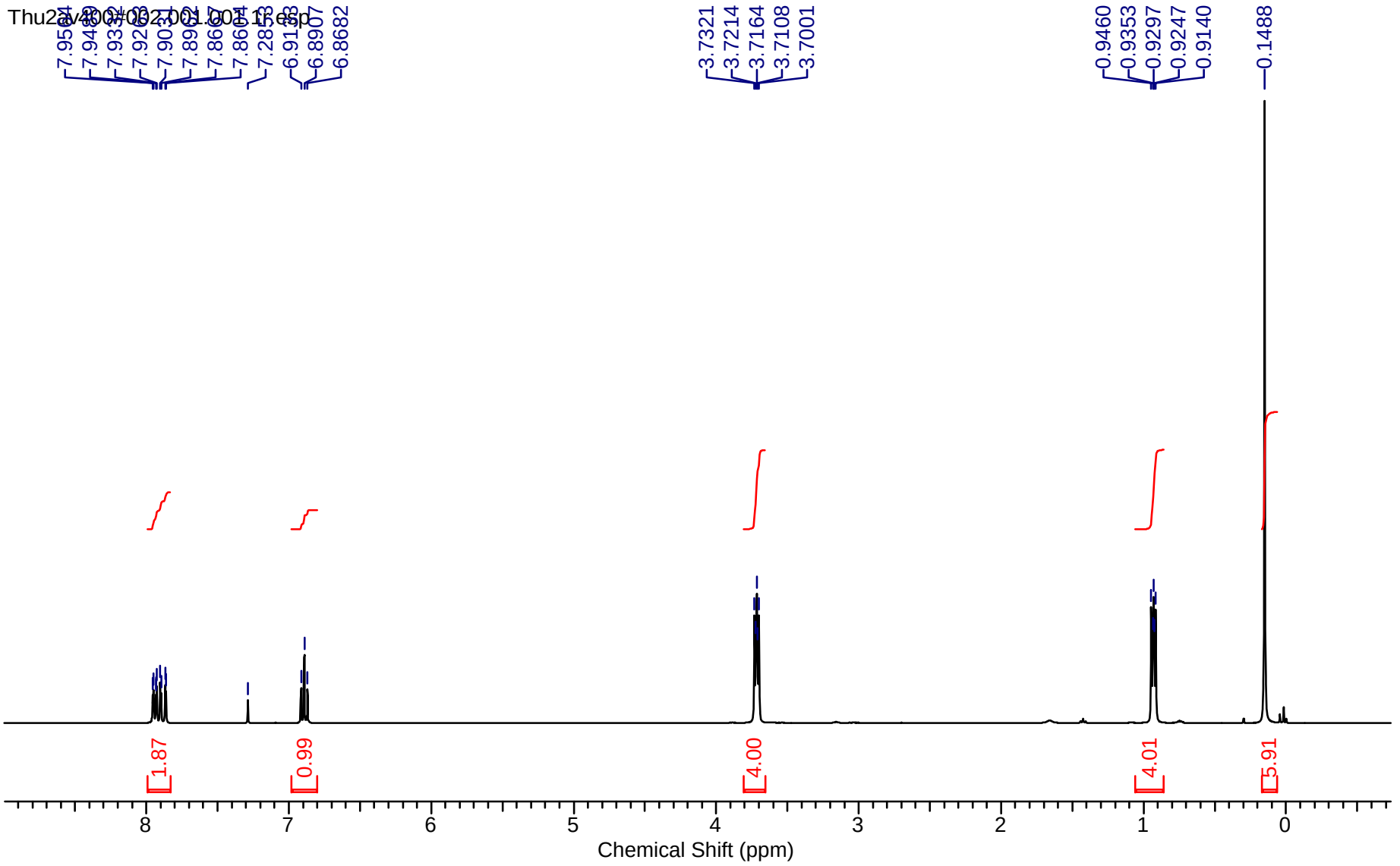
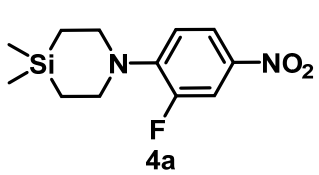
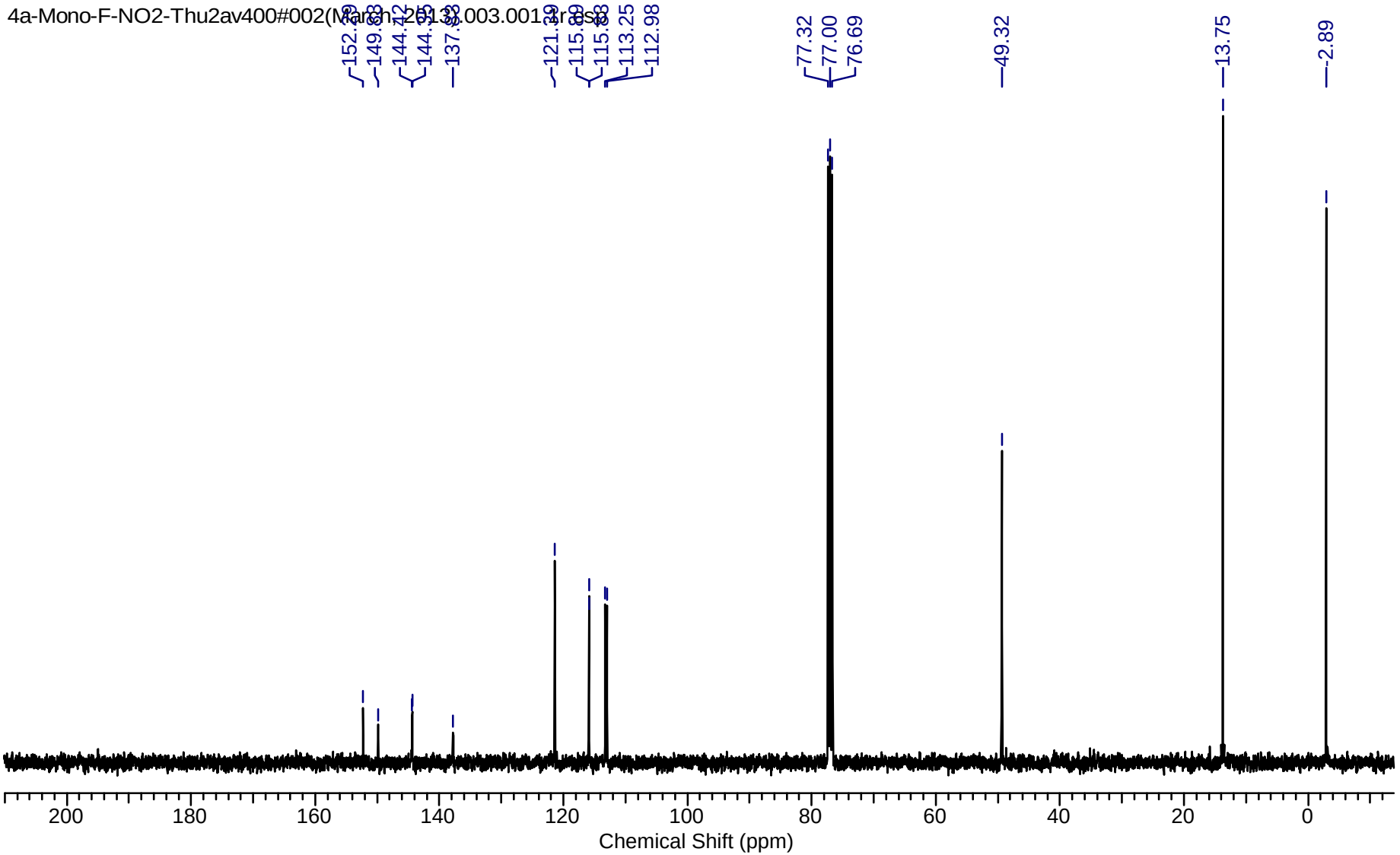
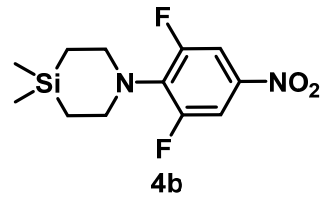




4a

^{13}C NMR spectrum of Compound 4a ($CDCl_3$, 100 MHz)





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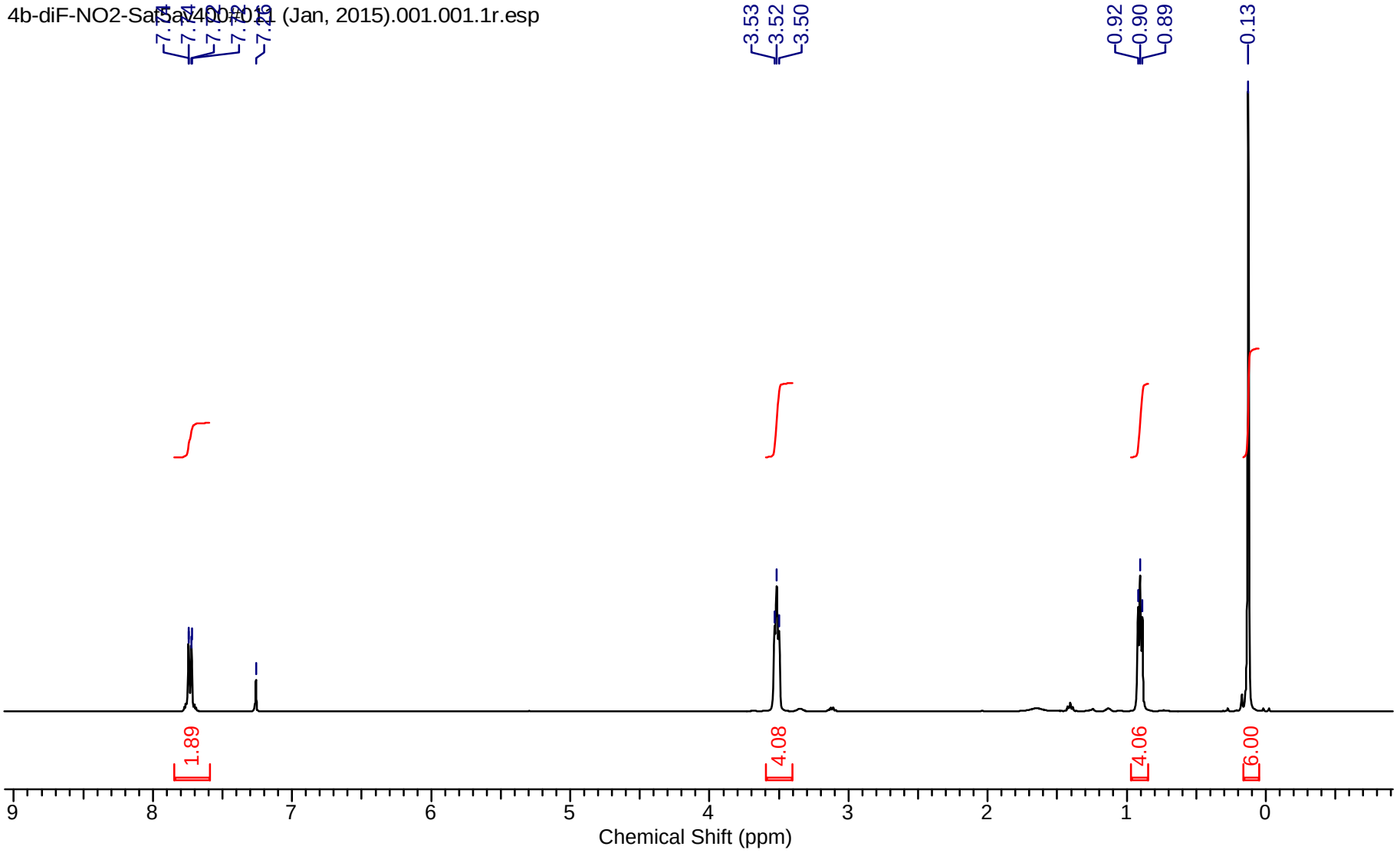
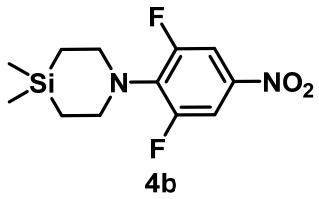
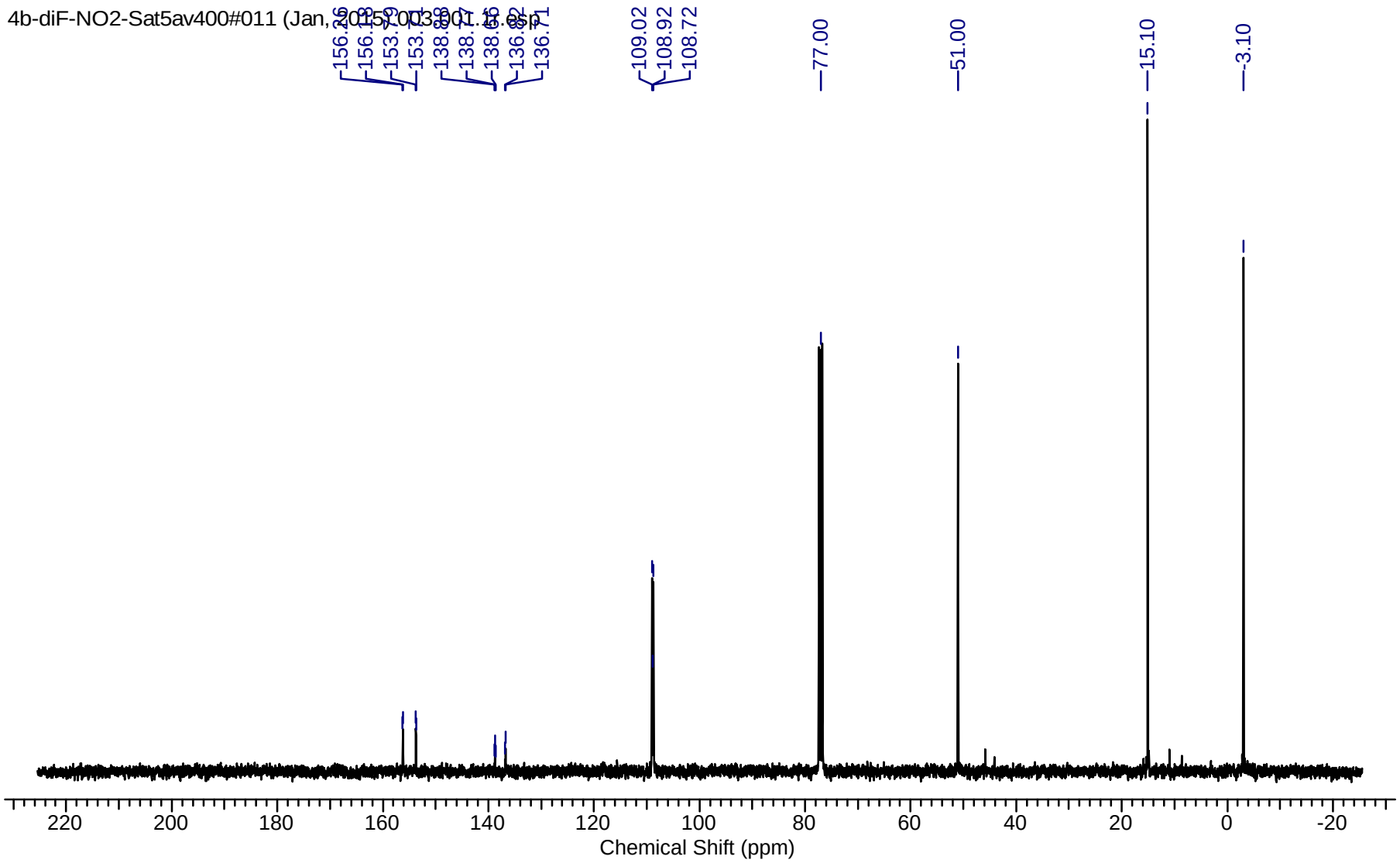




4b

^{13}C NMR spectrum of Compound 4b ($CDCl_3$, 100 MHz)



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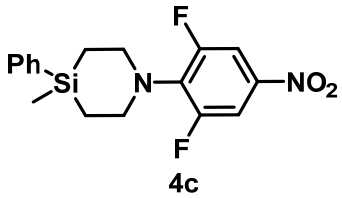

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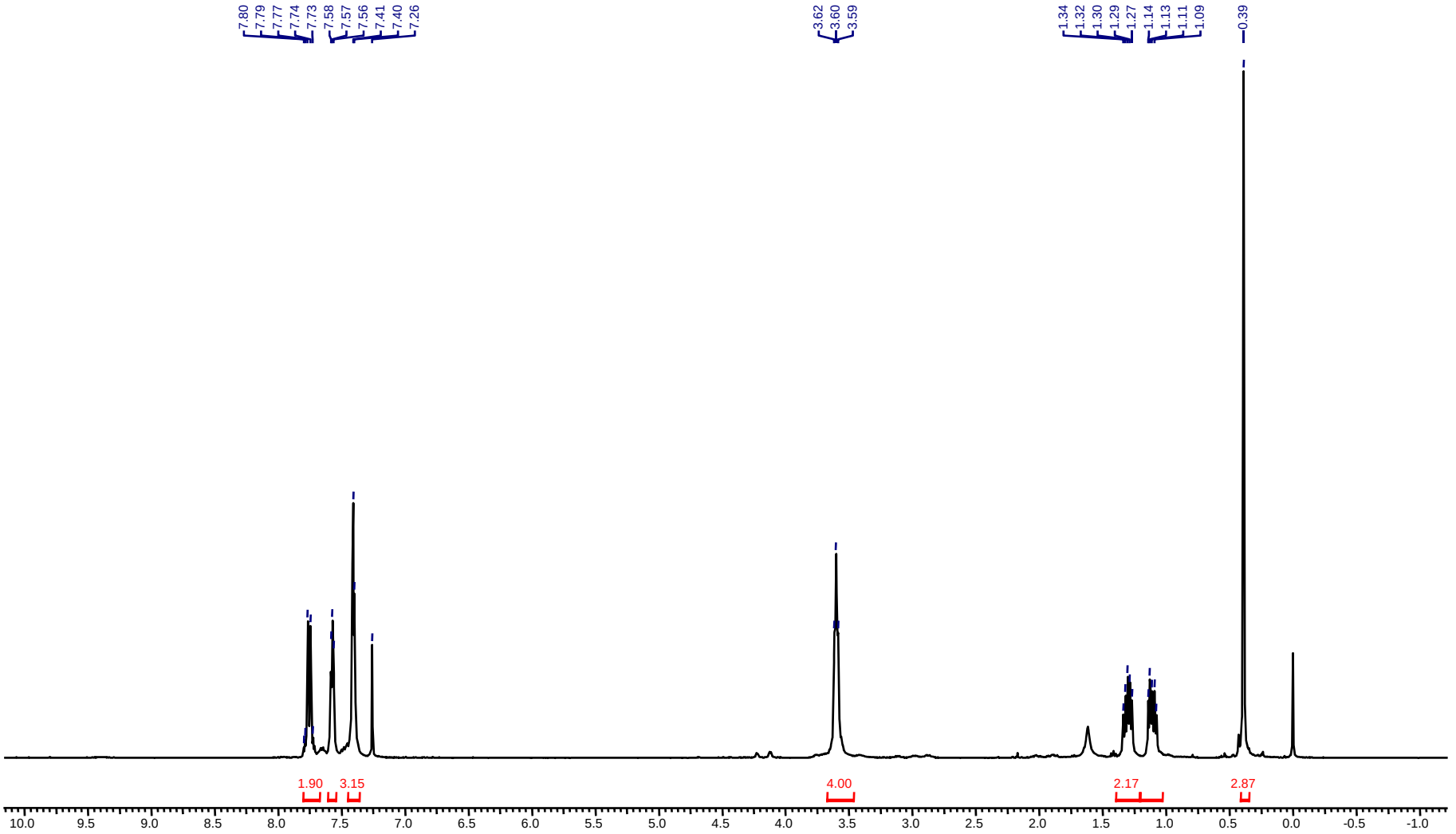

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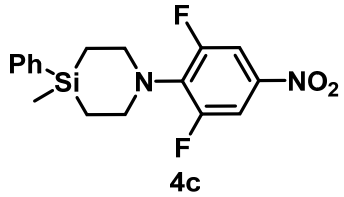

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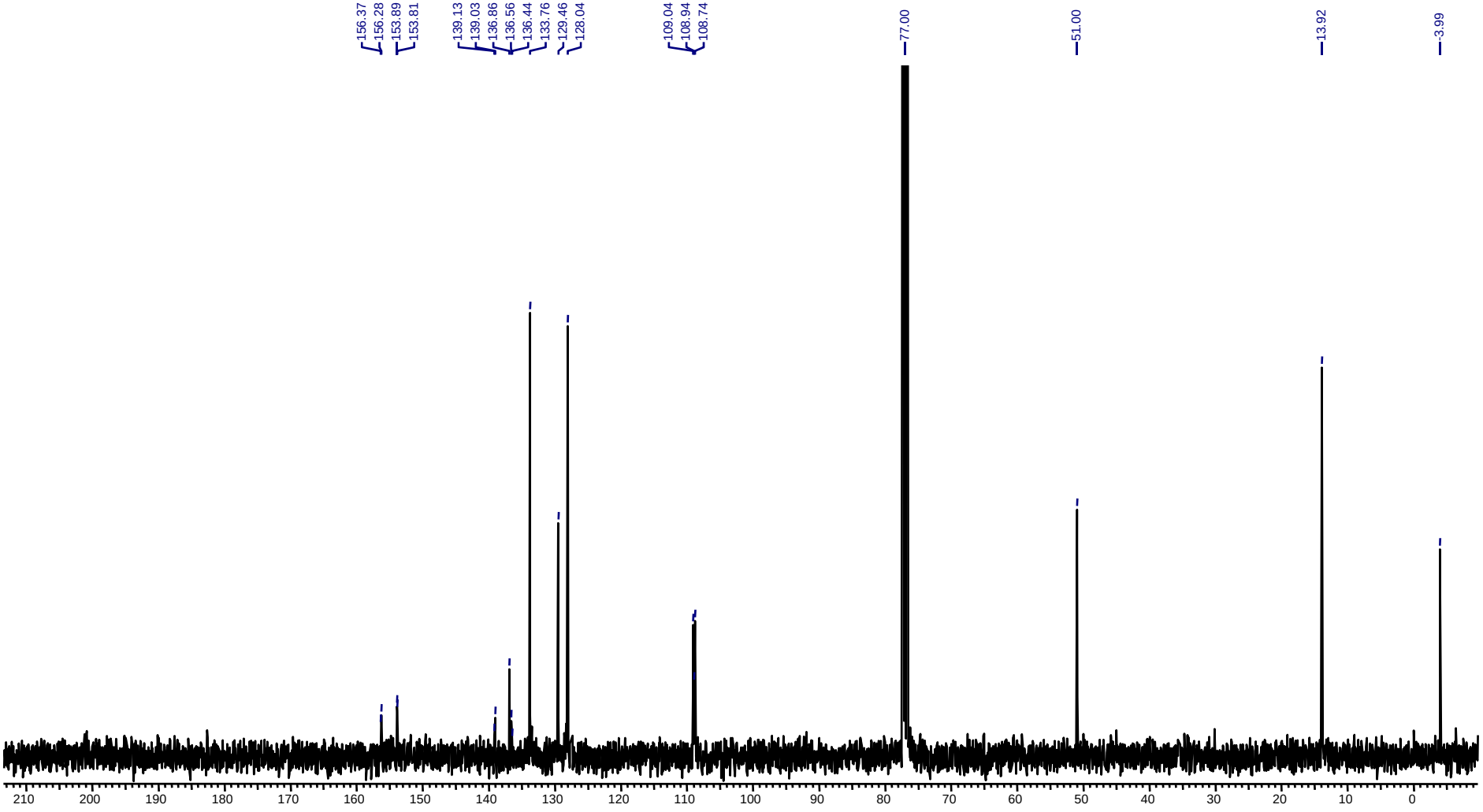

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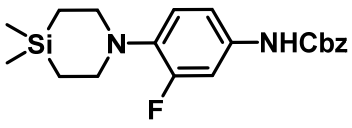
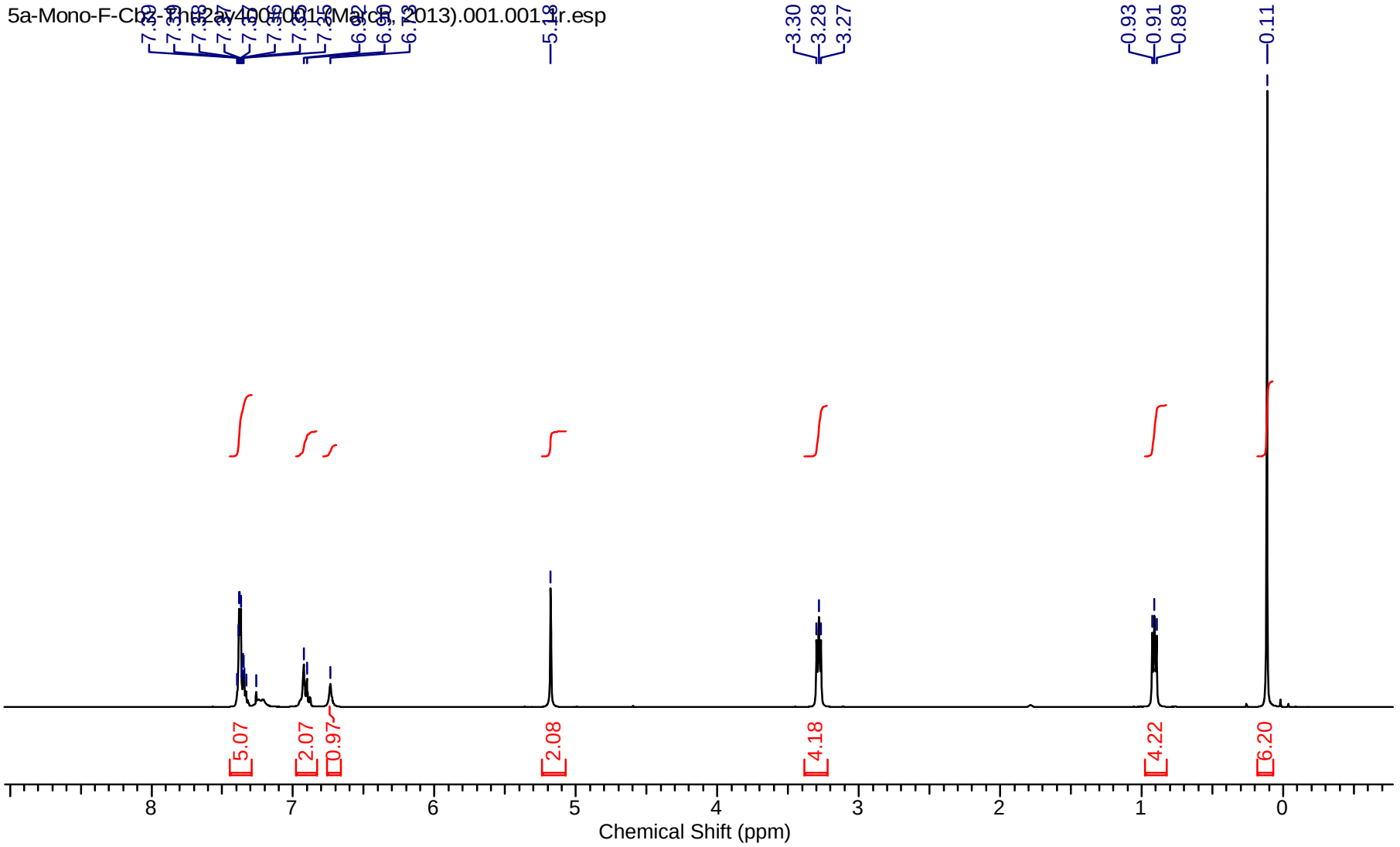
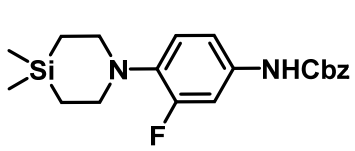


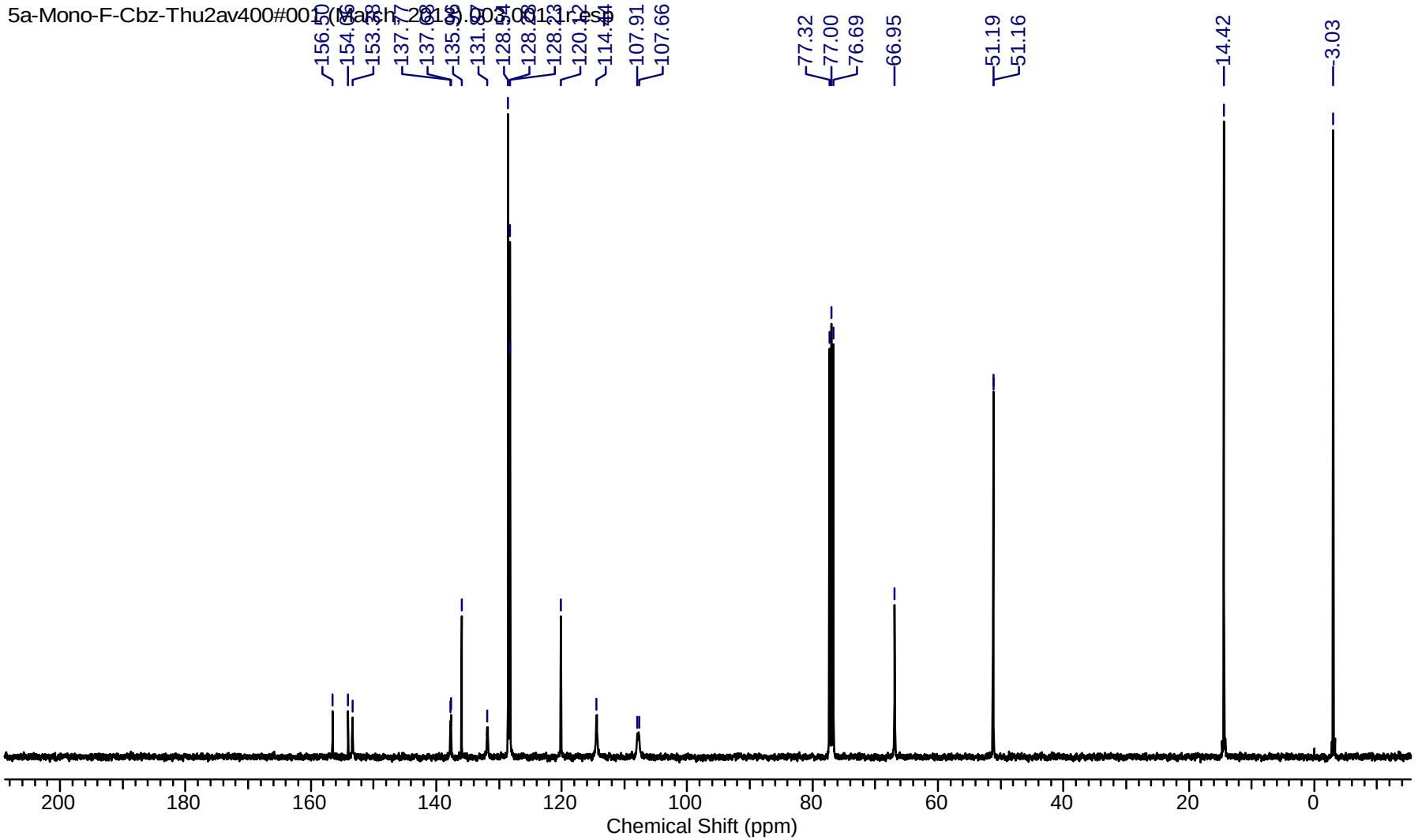
5a





5a

^{13}C NMR spectrum of Compound 5a ($CDCl_3$, 100 MHz)



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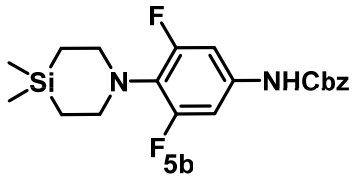
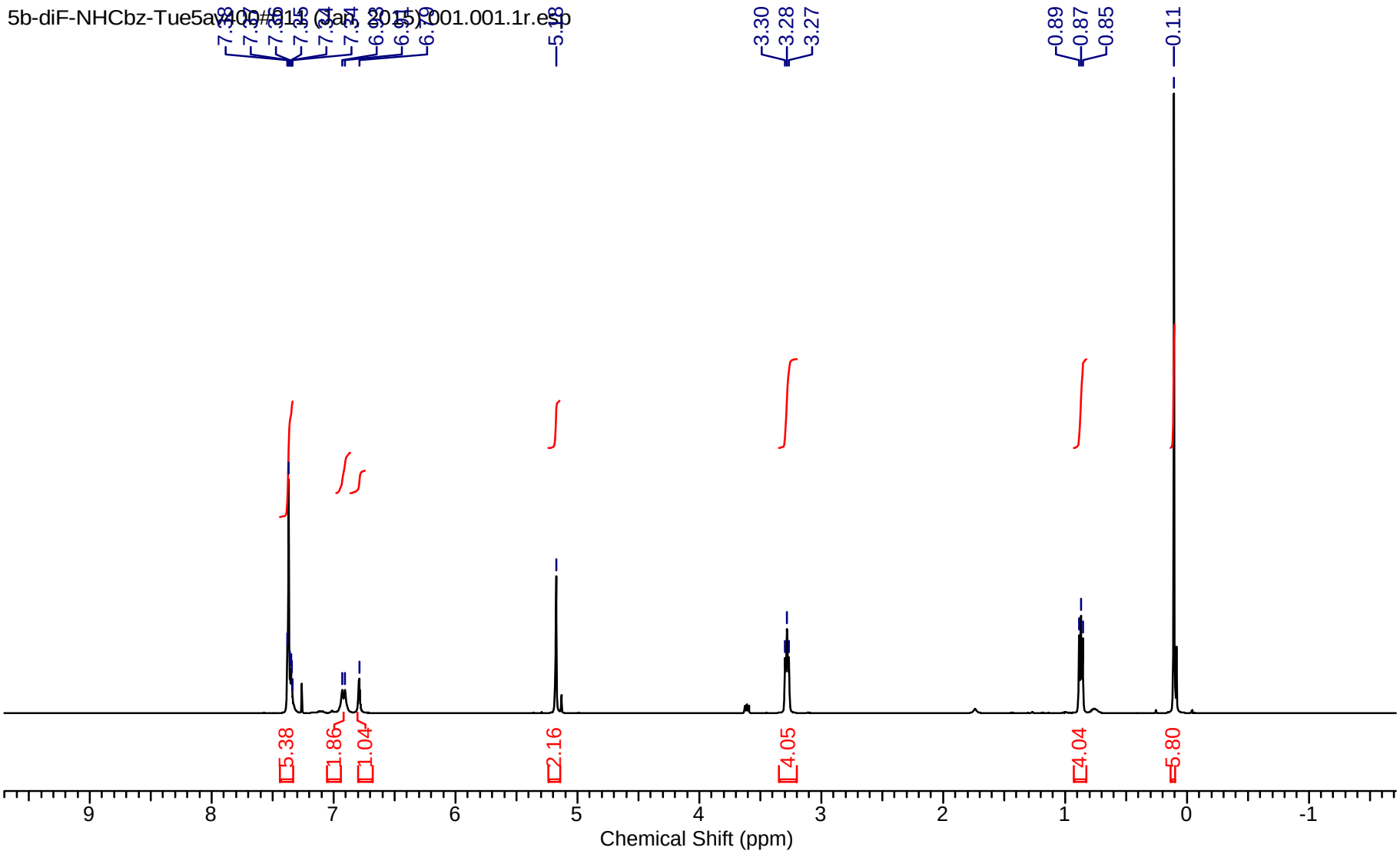
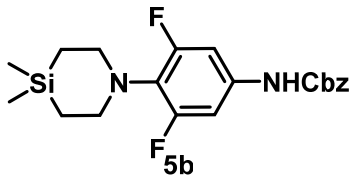
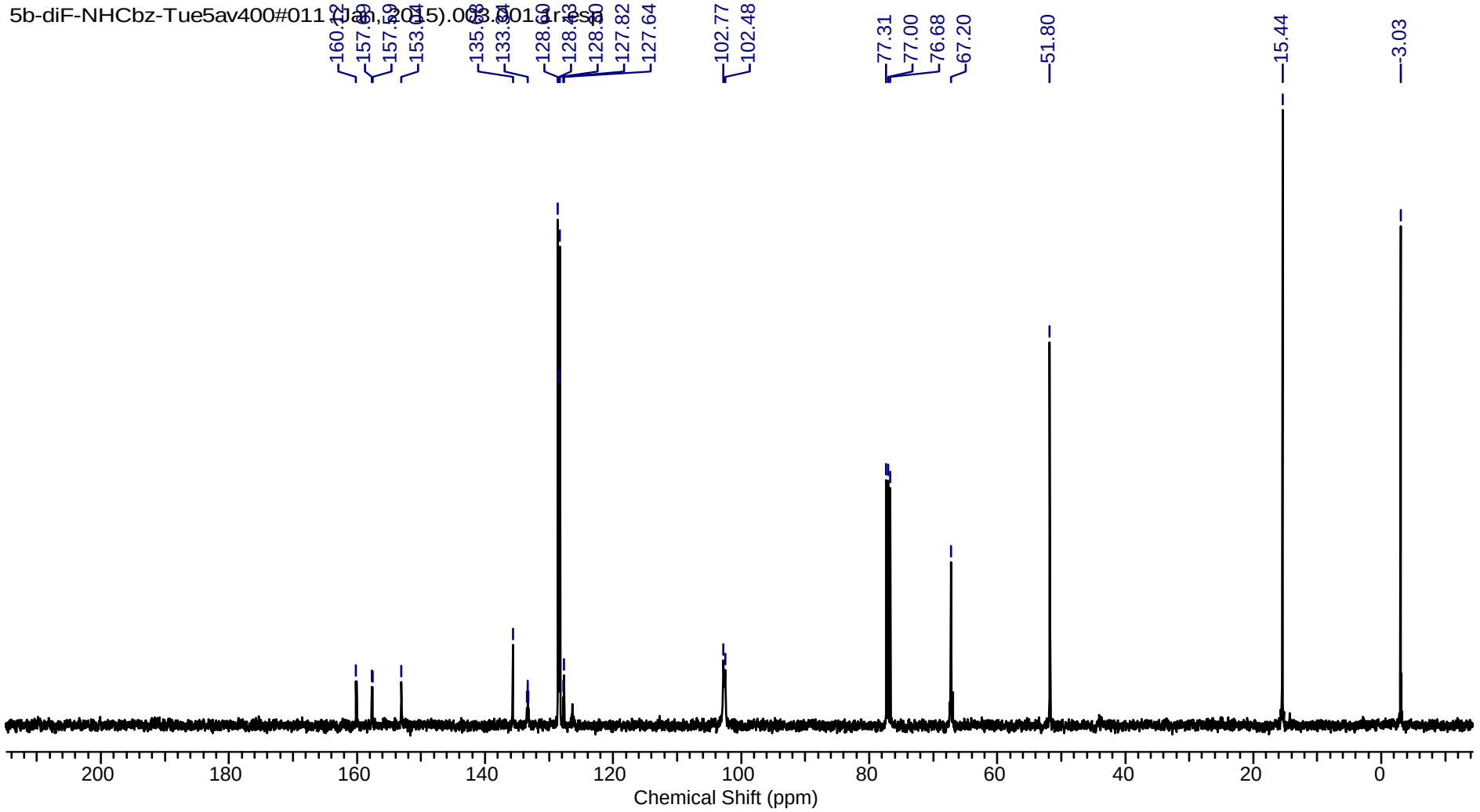




^{13}C NMR spectrum of Compound 5b ($CDCl_3$, 100 MHz)





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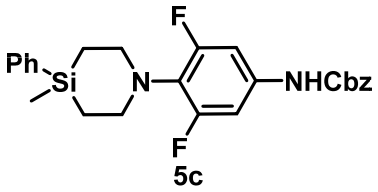

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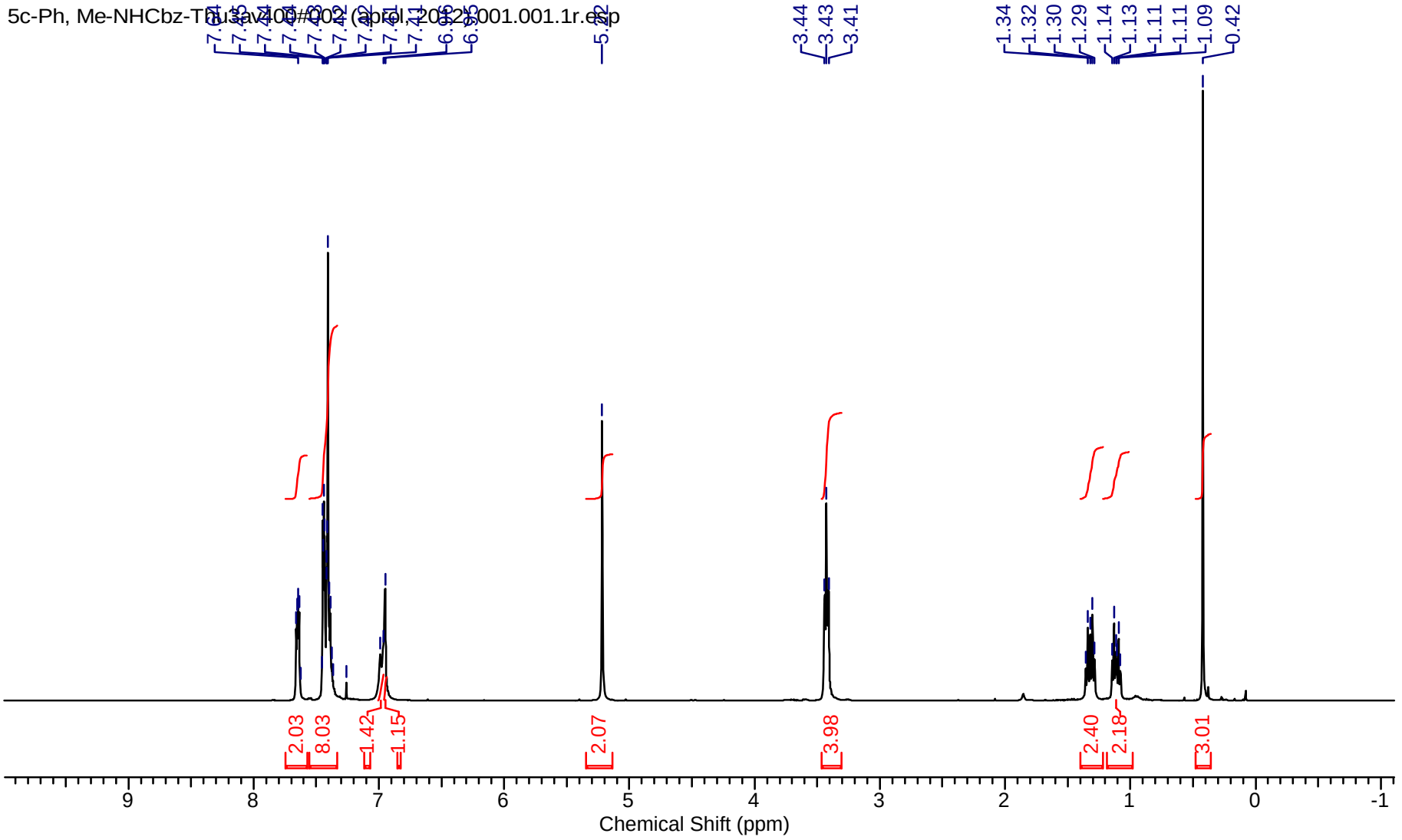
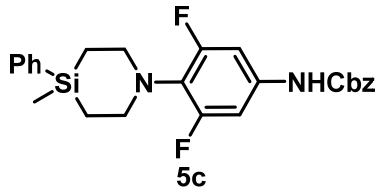
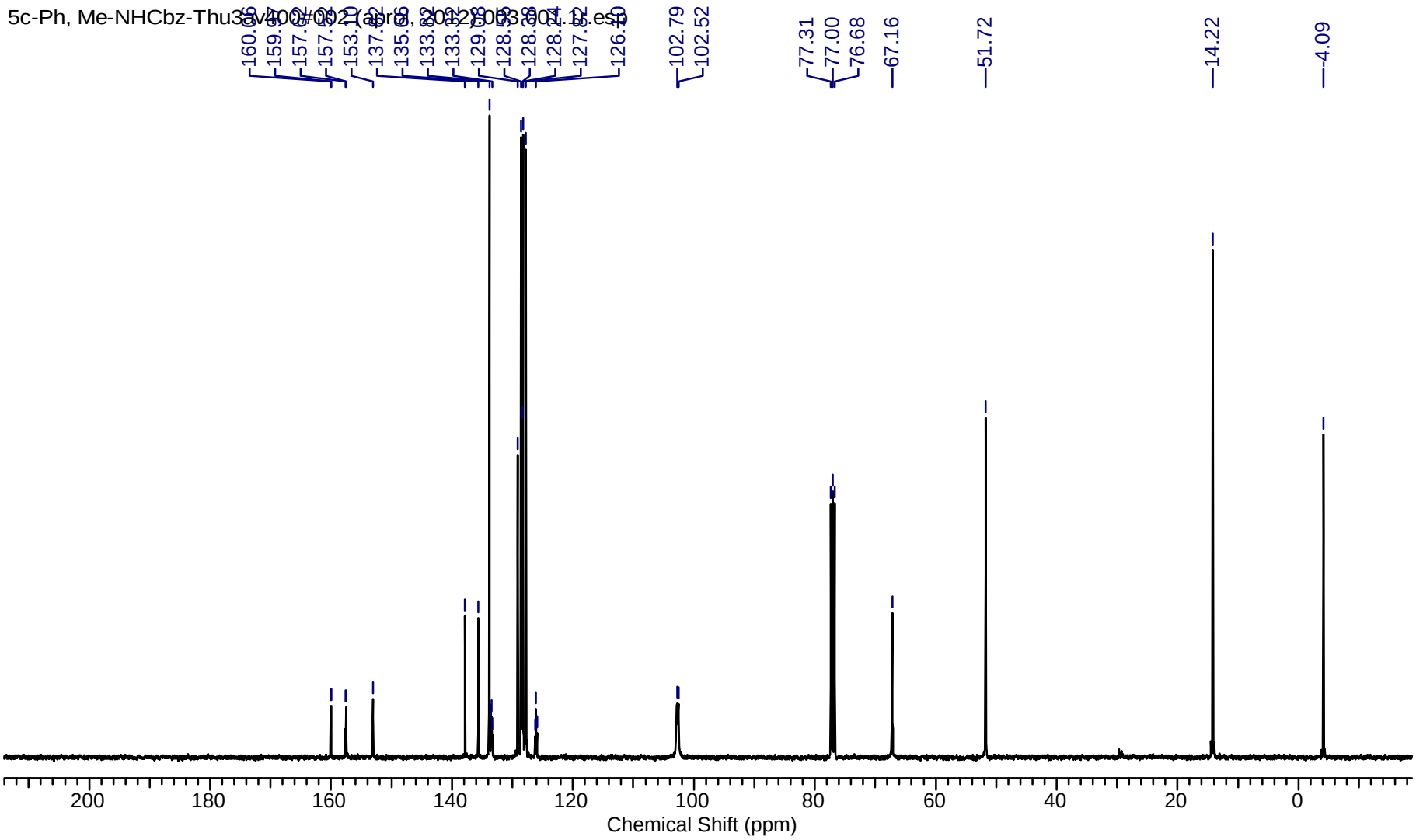
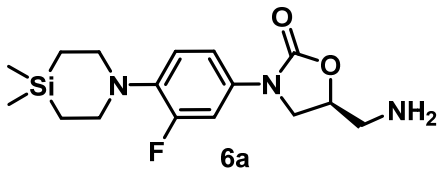




^{13}C NMR spectrum of Compound 5c ($CDCl_3$, 100 MHz)



^{1}H NMR spectrum of Compound 6a ($CDCl_3$, 400 MHz)



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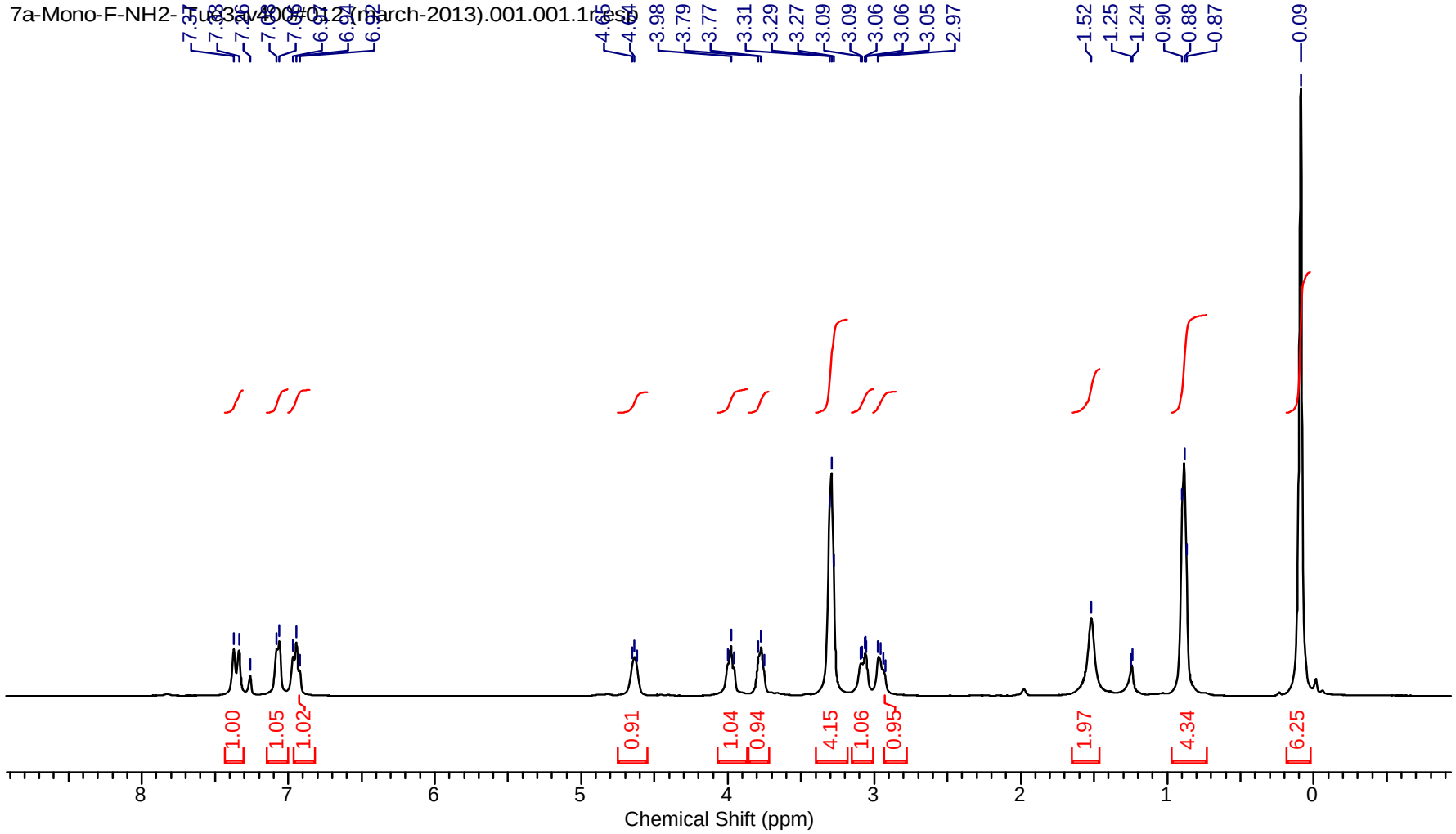

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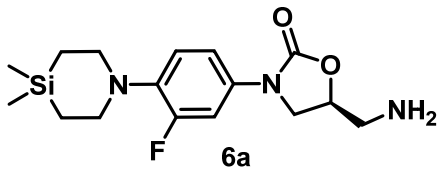

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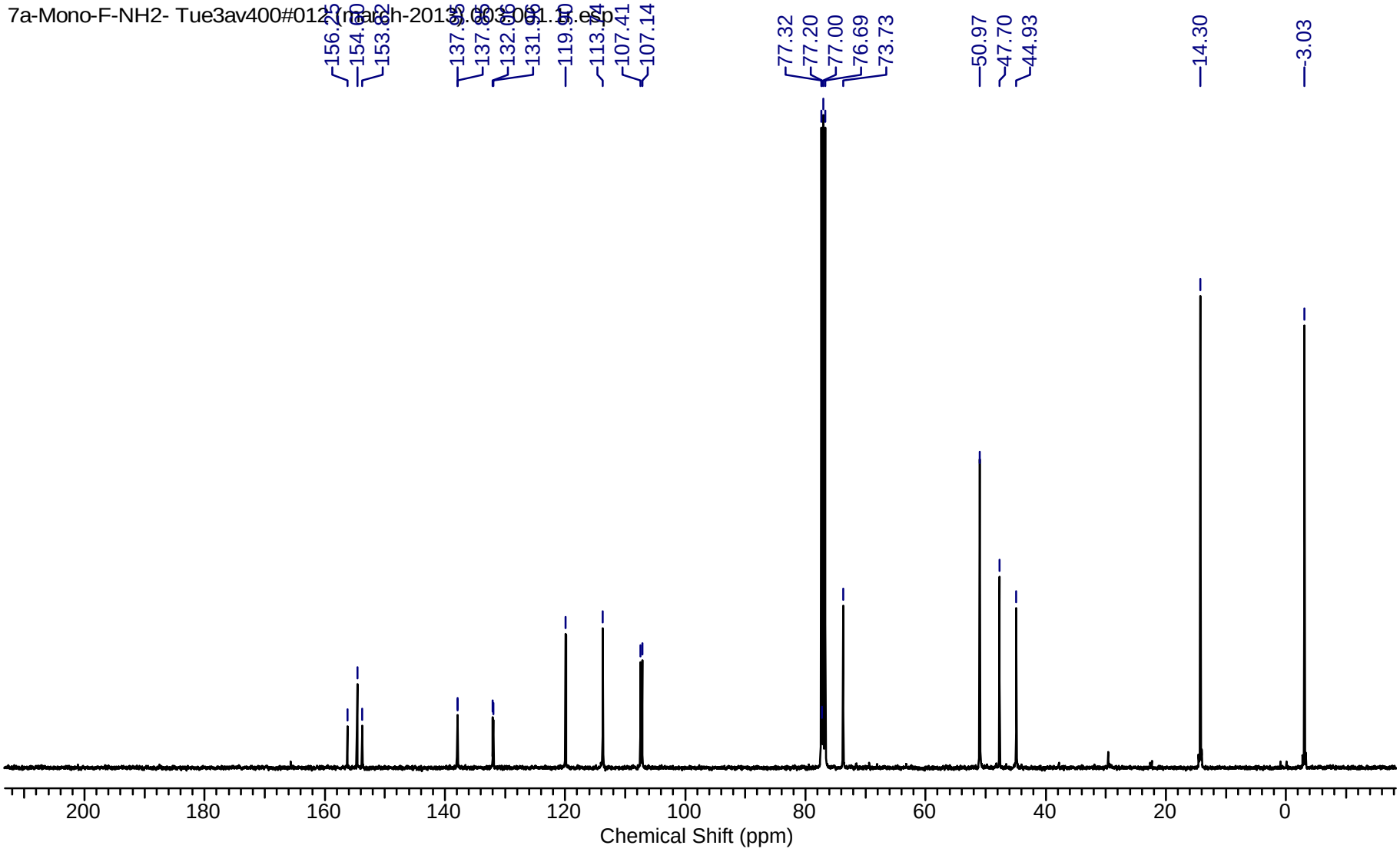

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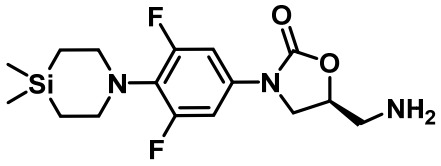

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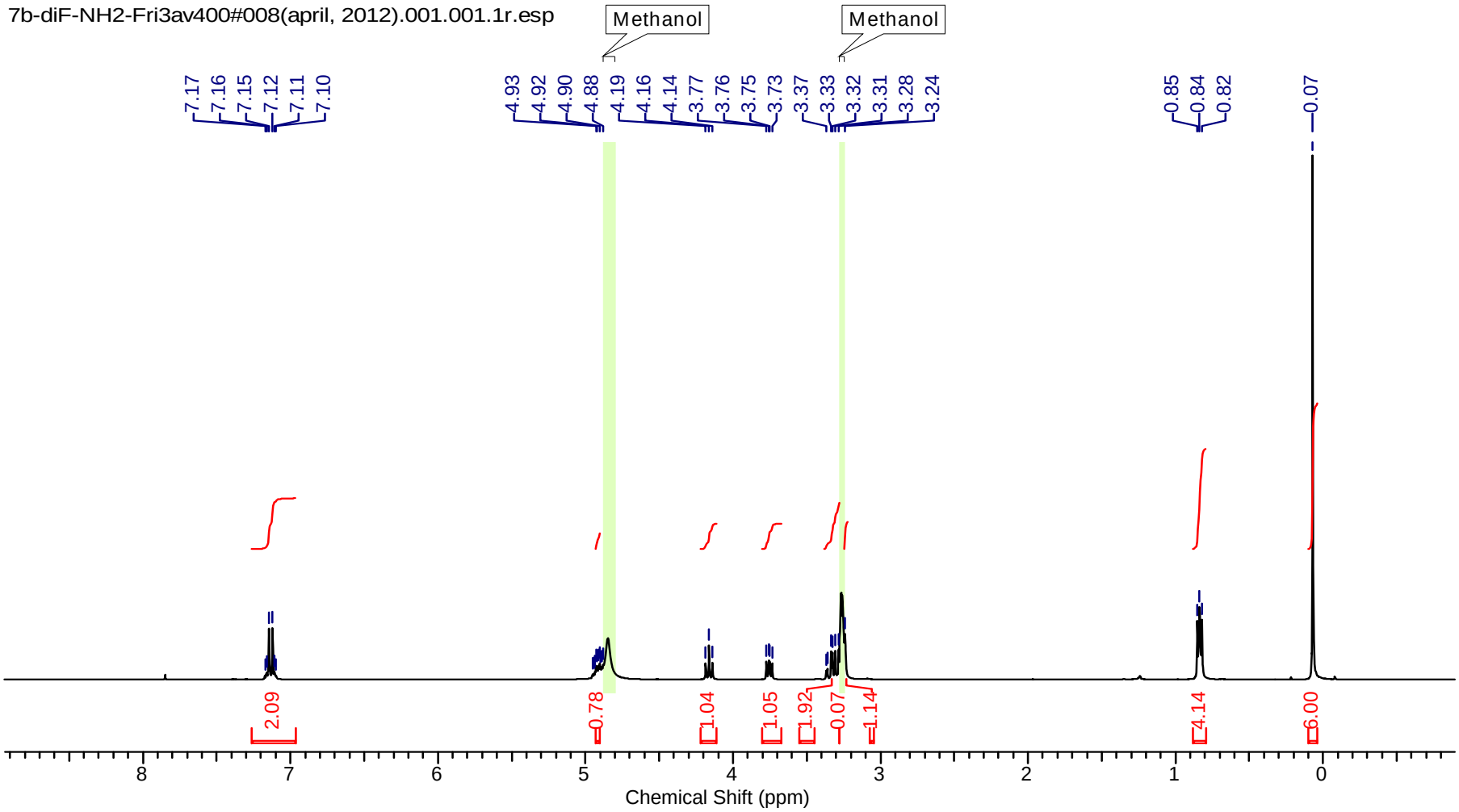
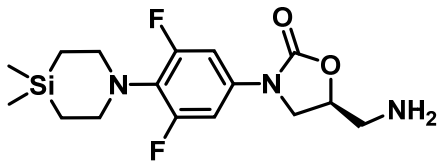


^{13}C NMR spectrum of Compound 6b (CD_3OD, 100 MHz)



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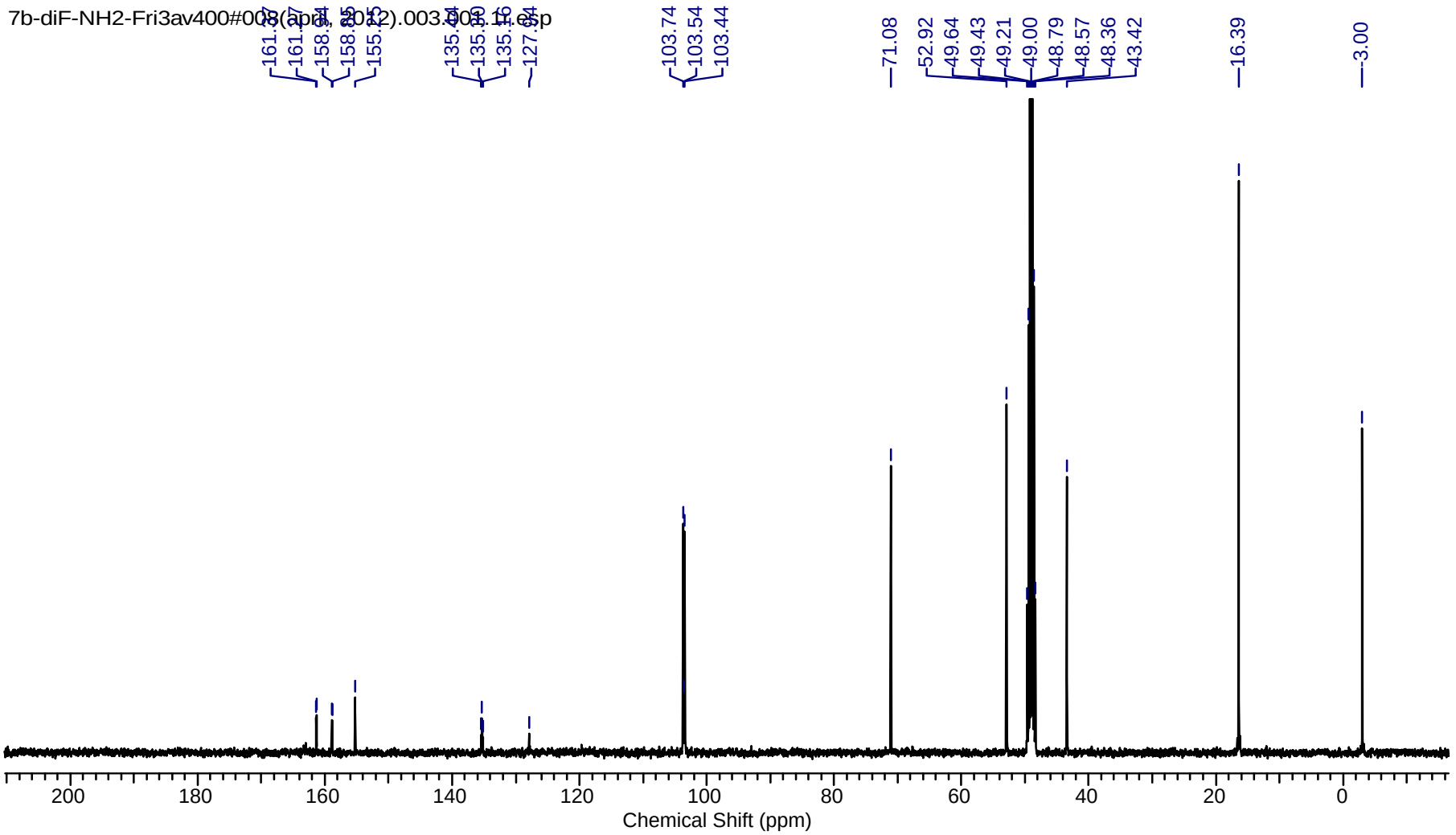

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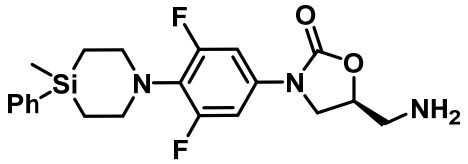

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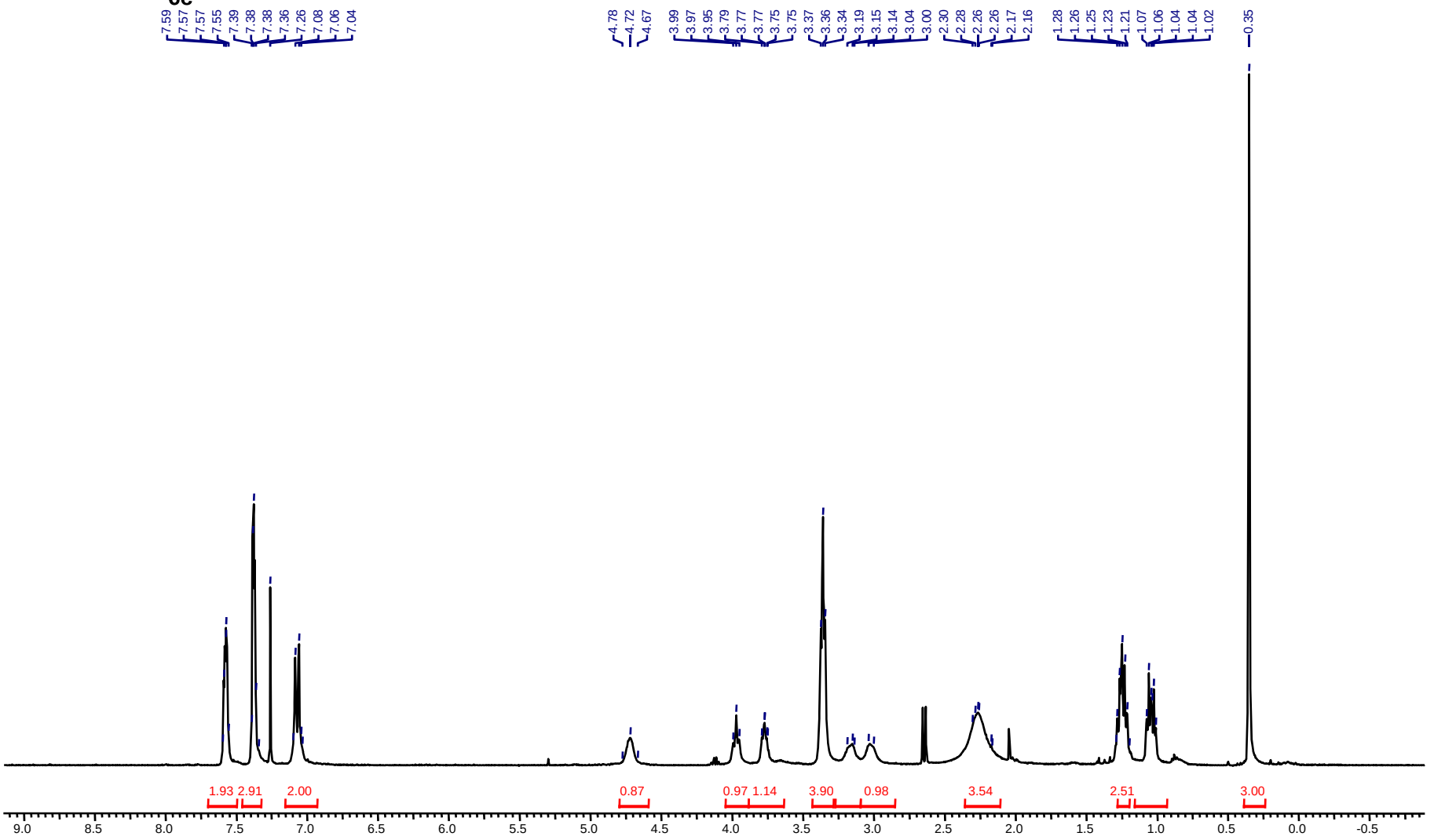
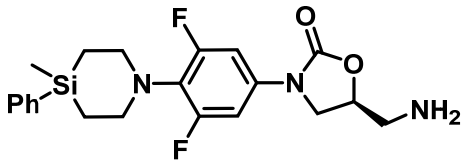


^{13}C NMR spectrum of Compound 6c ($CDCl_3$, 100 MHz)



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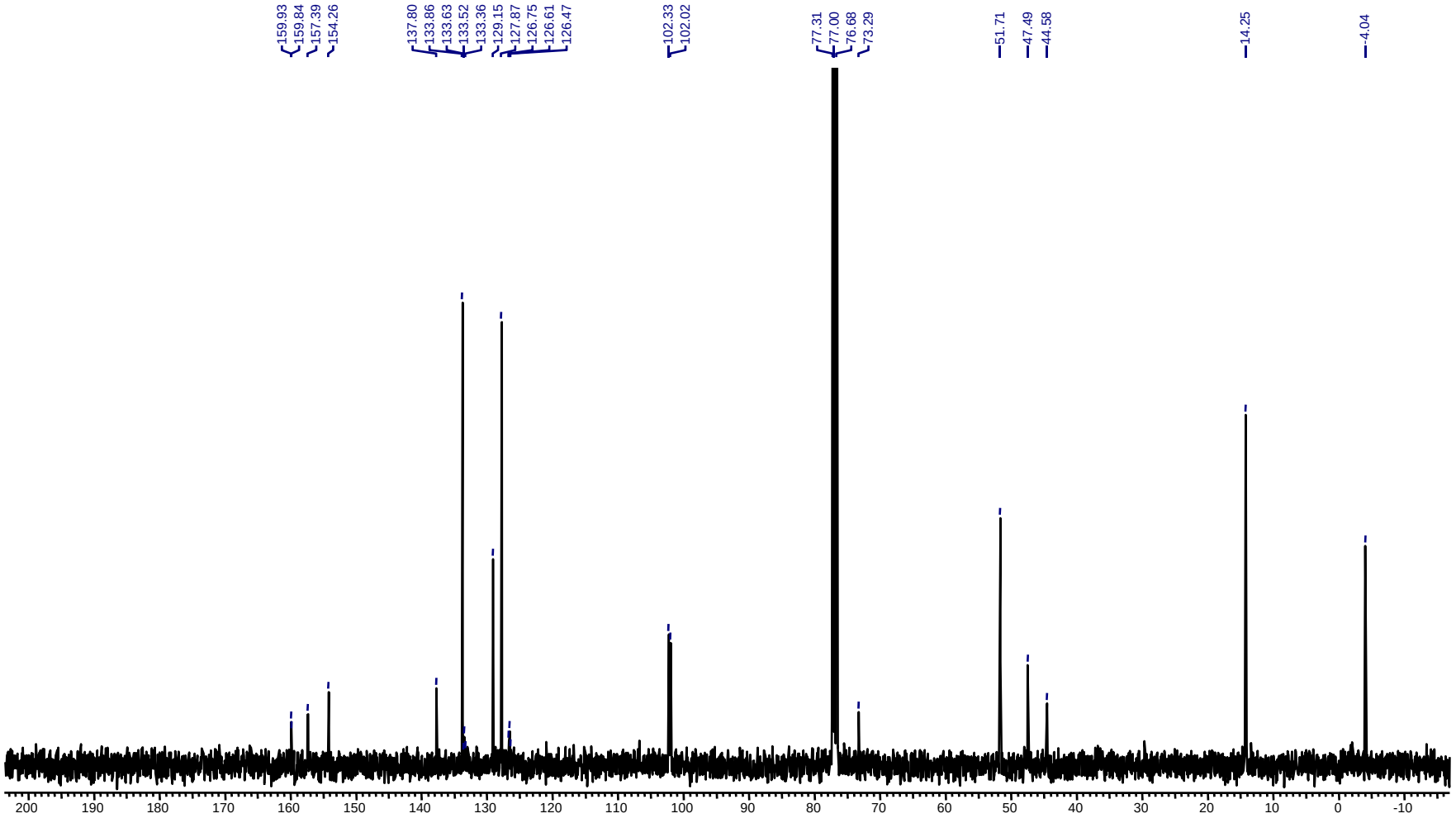

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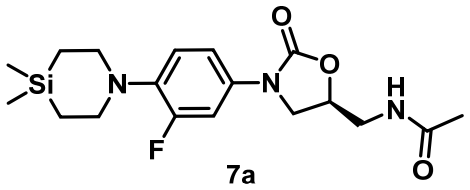
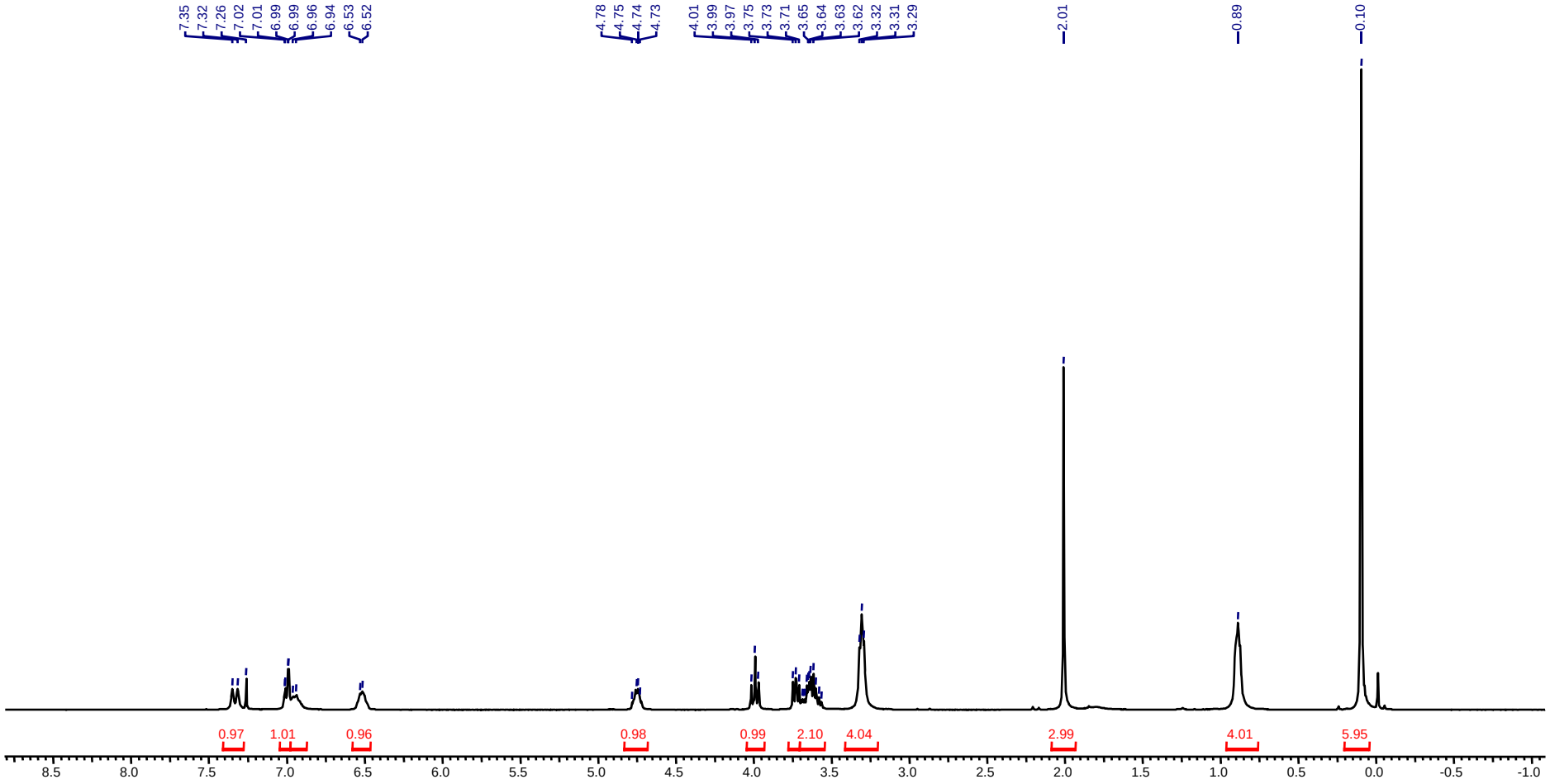
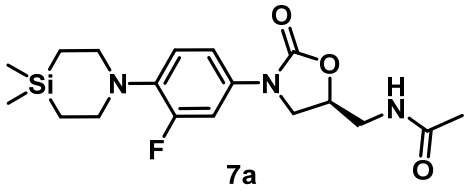


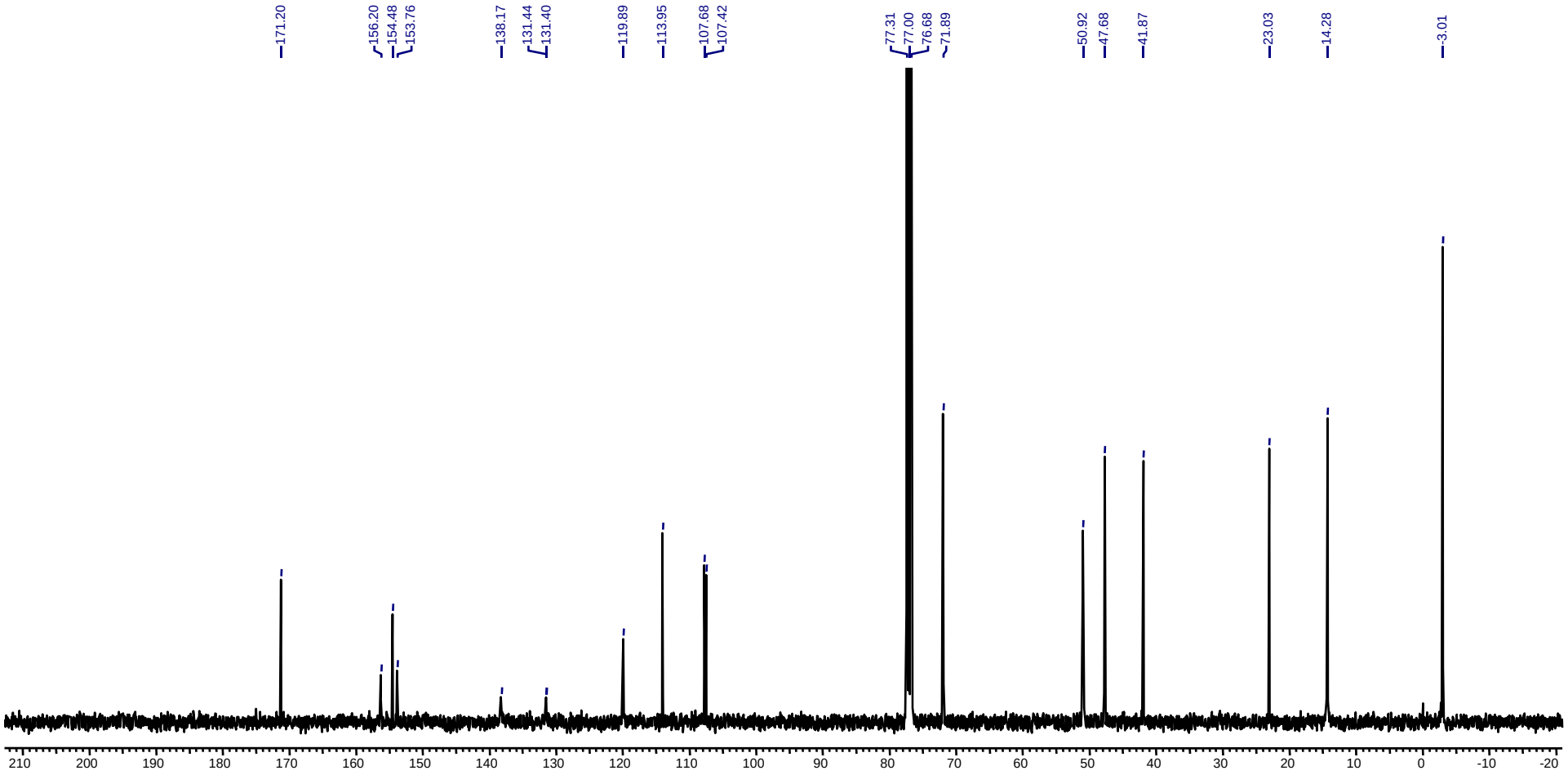
7a



^{13}C NMR spectrum of Compound 7a ($CDCl_3$, 100 MHz)



7a



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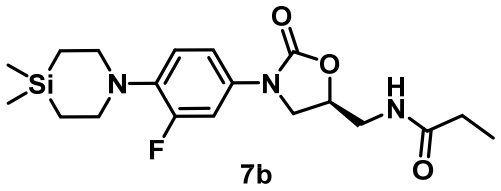

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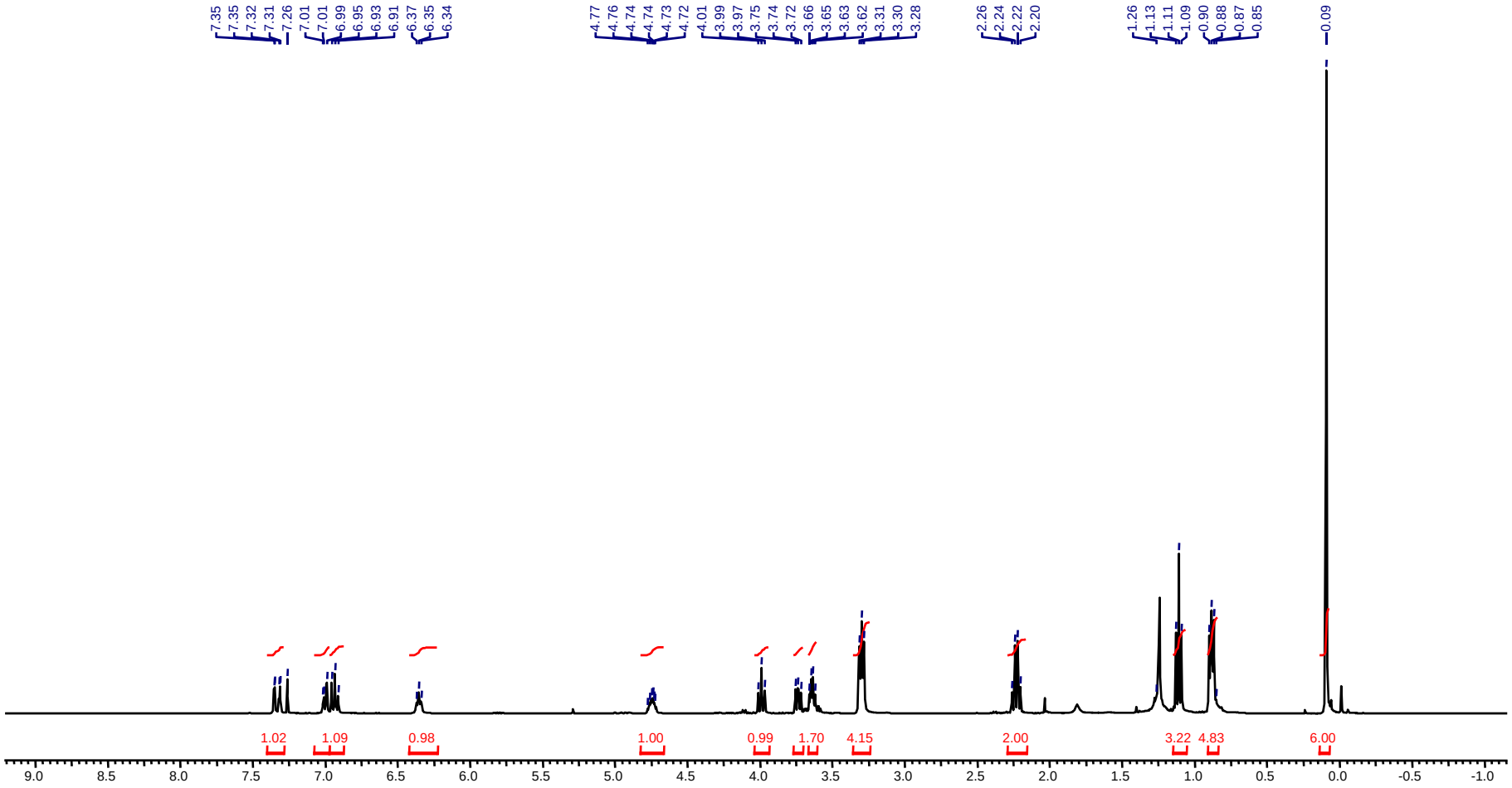
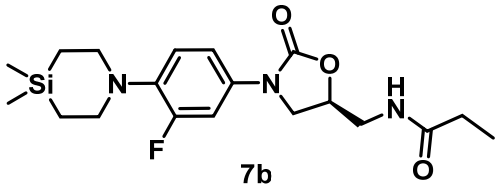
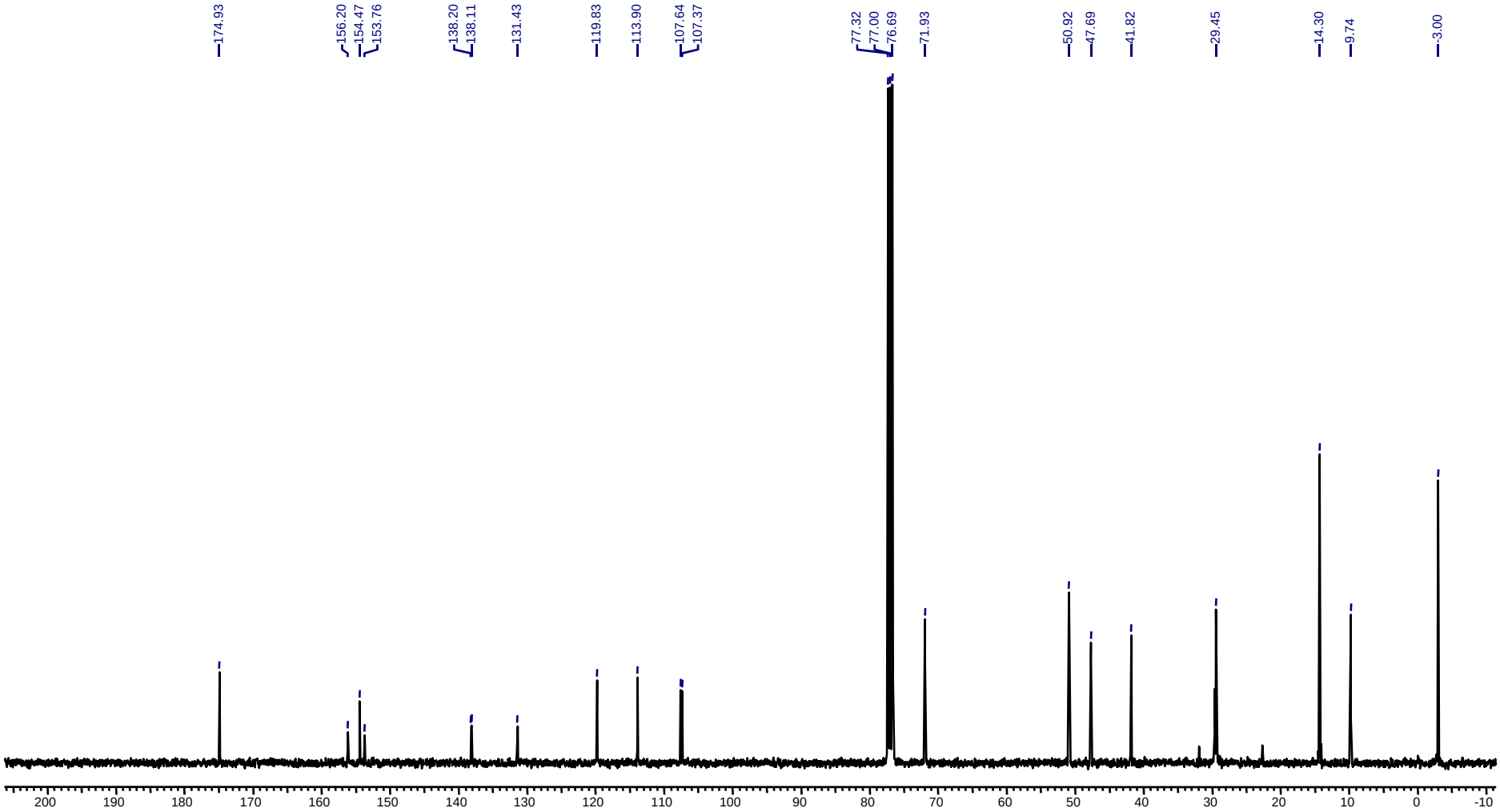


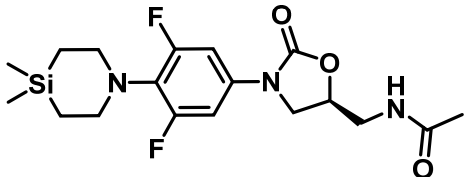
^{13}C NMR spectrum of Compound 7b ($CDCl_3$, 100 MHz)



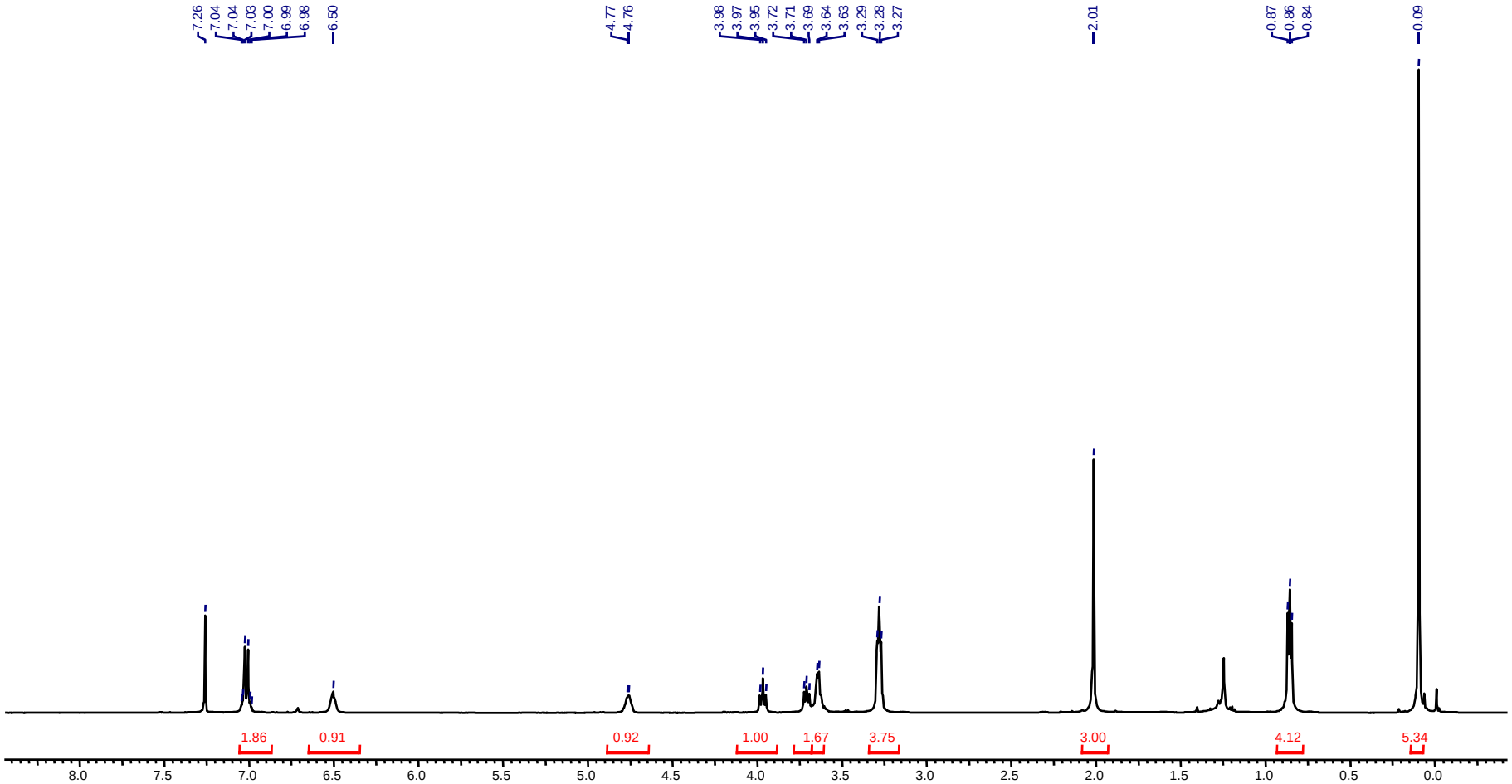
7b



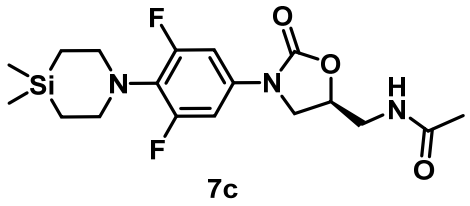
^{1}H NMR spectrum of Compound 7c (CDCl$_3$, 500 MHz)



7c



^{13}C NMR spectrum of Compound 7c ($CDCl_3$, 125 MHz)



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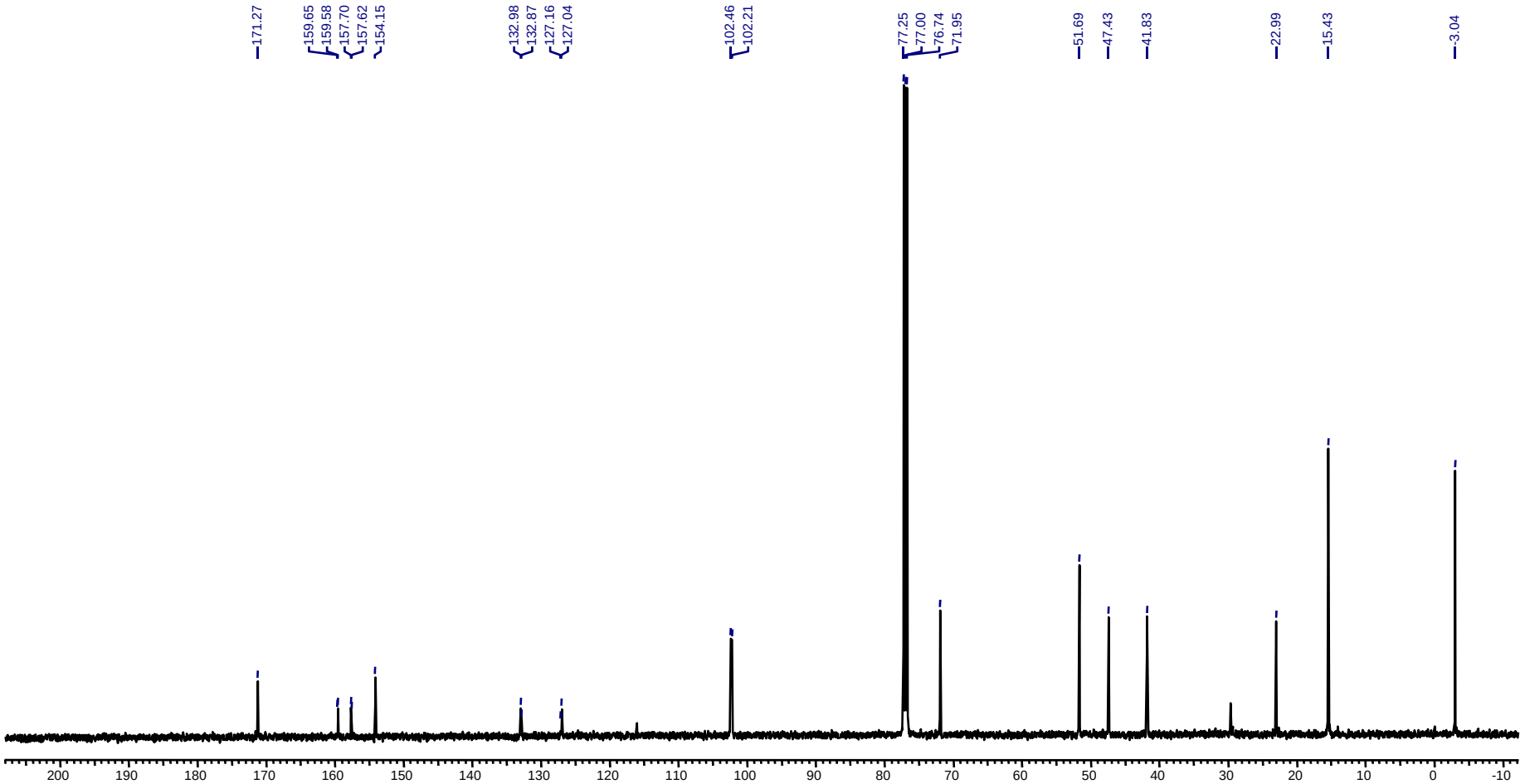
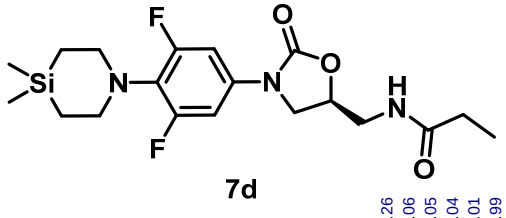
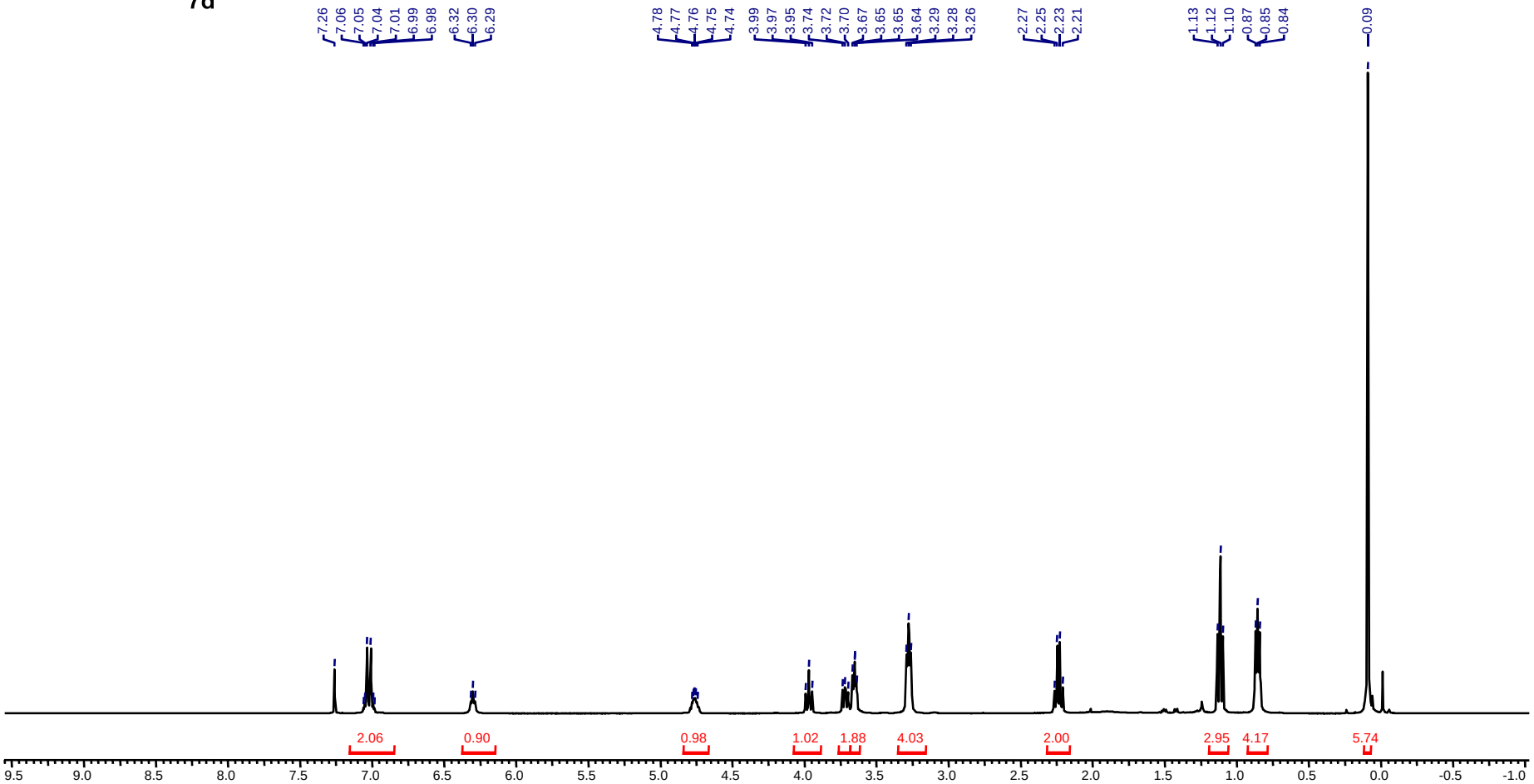


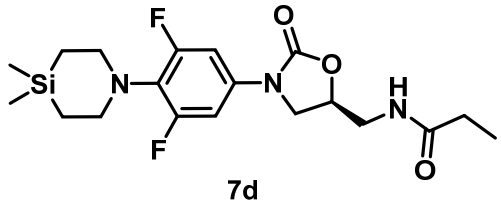
^{1}H NMR spectrum of Compound 7d (CDCl$_3$, 400 MHz)



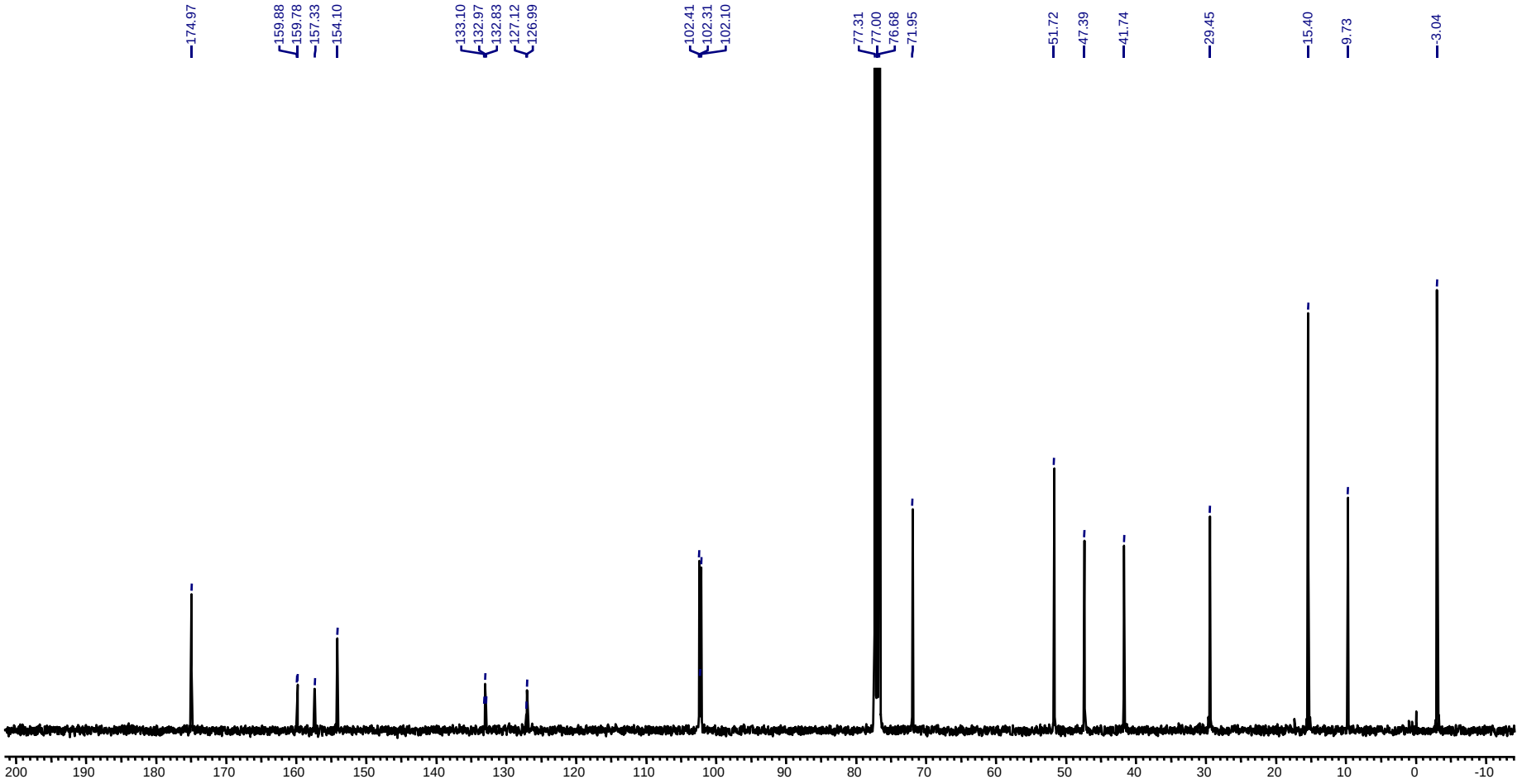
7d



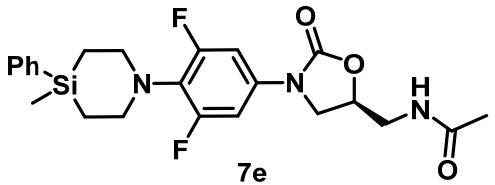
^{13}C NMR spectrum of Compound 7d ($CDCl_3$, 100 MHz)



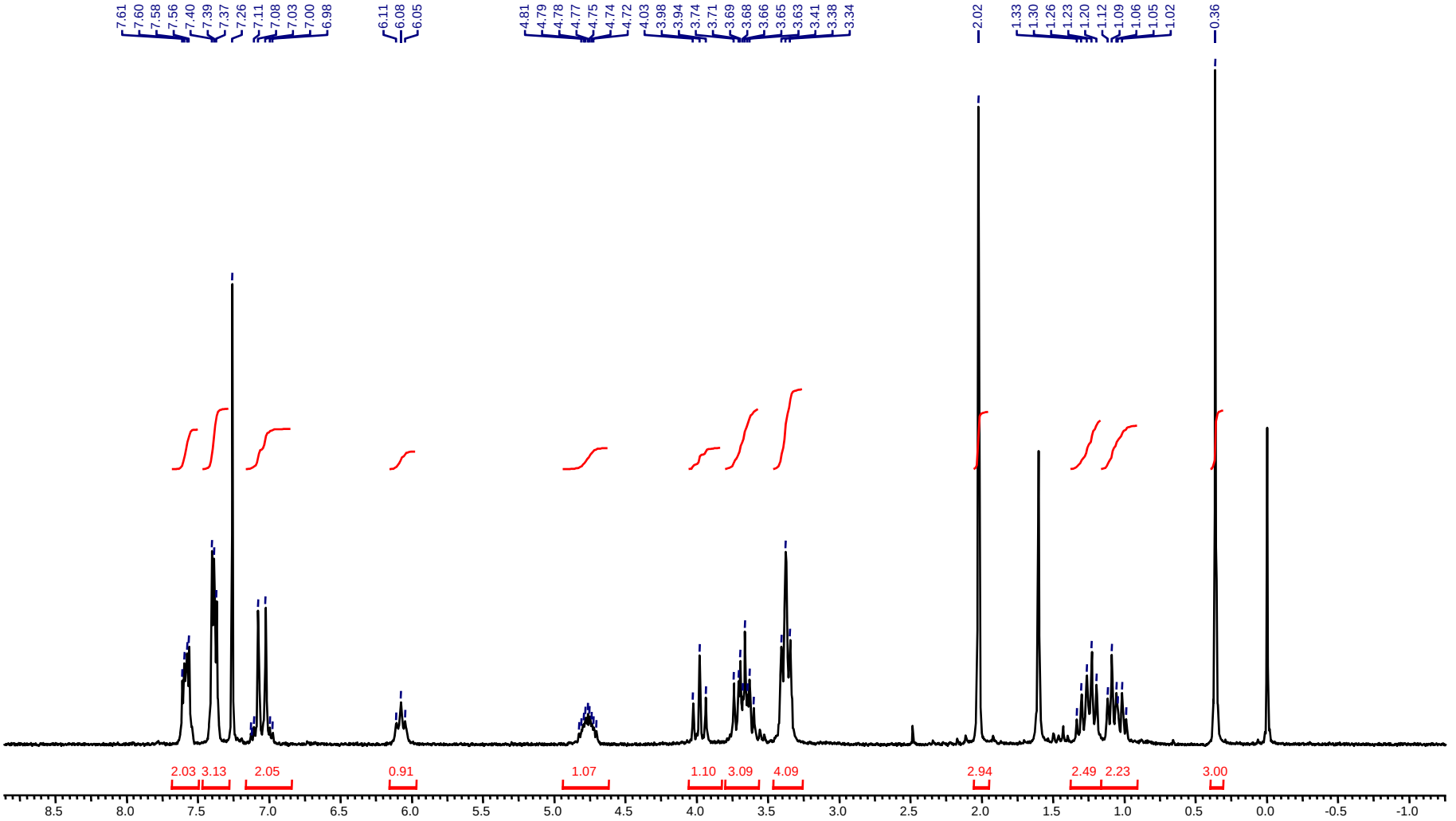
7d



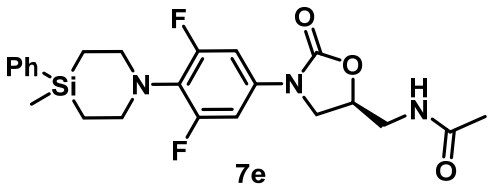
^{1}H NMR spectrum of Compound 7e ($CDCl_3$, 200 MHz)

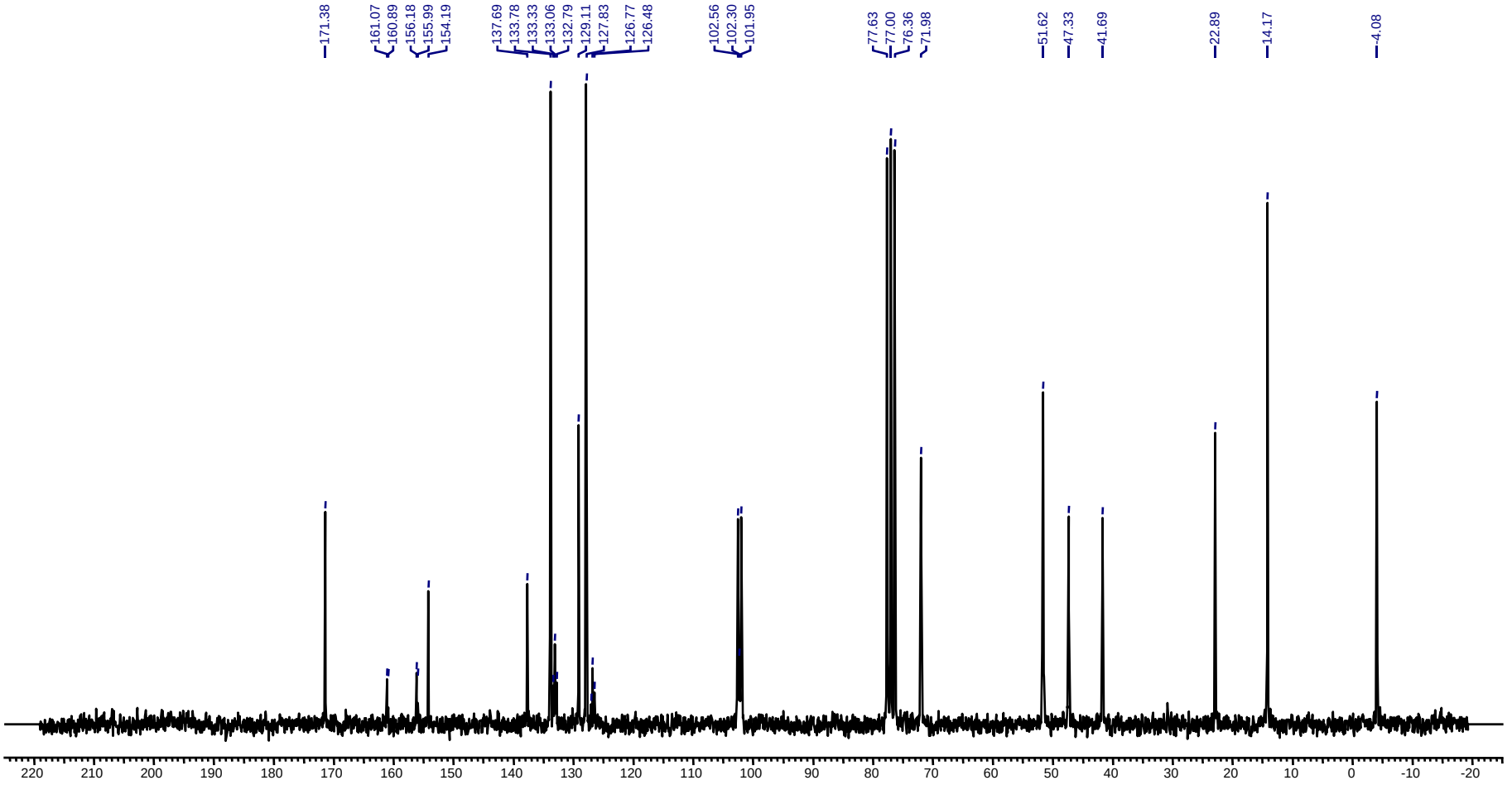


7e

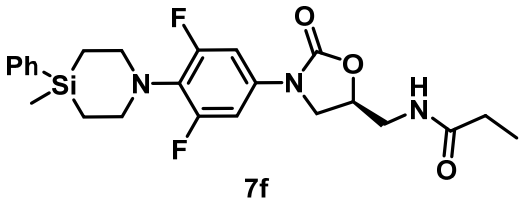


^{13}C NMR spectrum of Compound 7e (CDCl$_3$, 50 MHz)

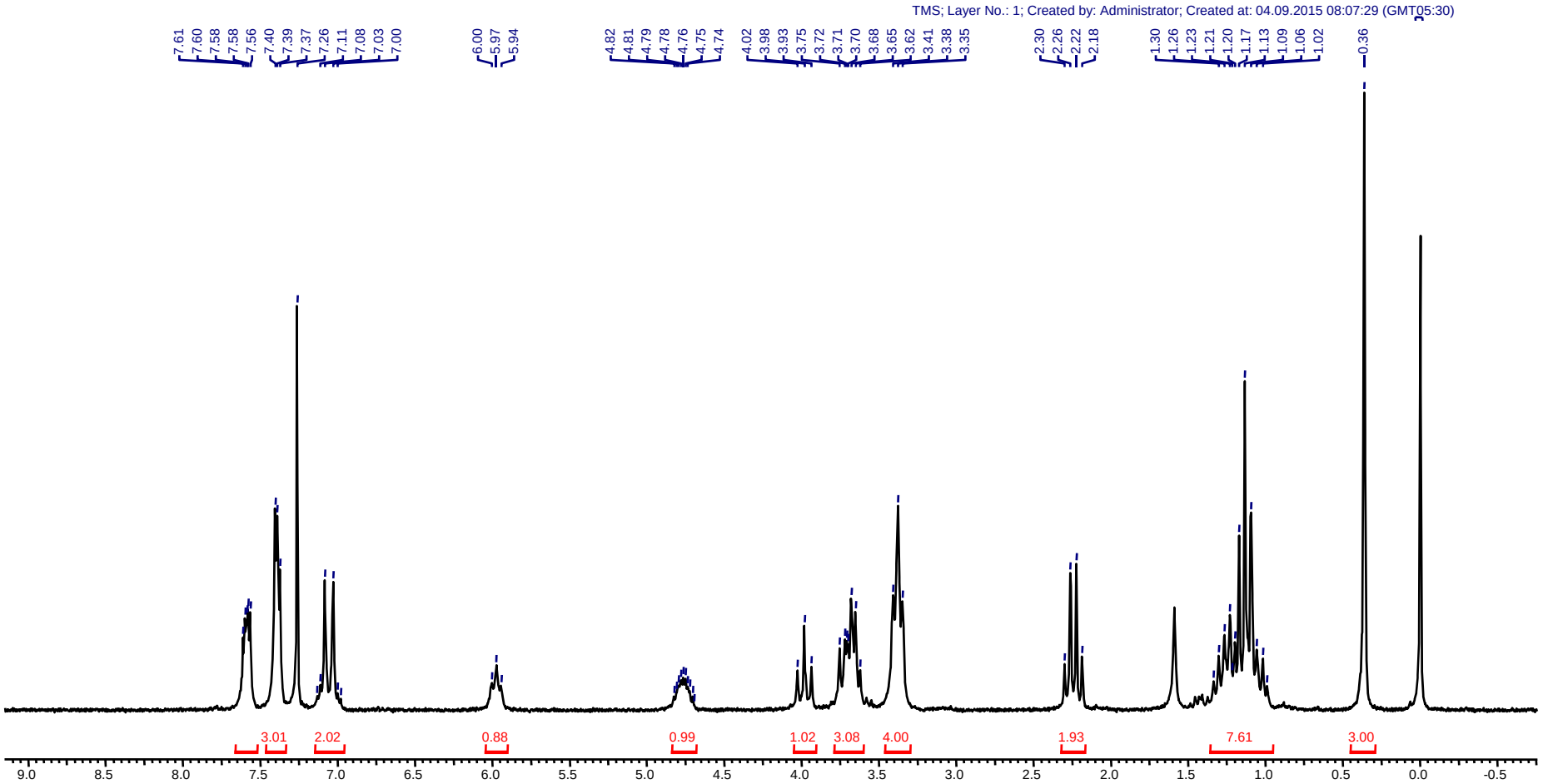




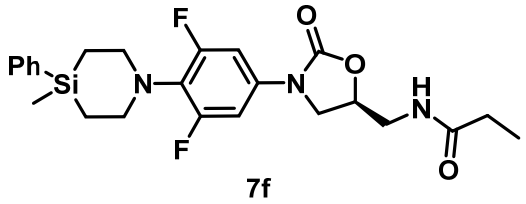
^{1}H NMR spectrum of Compound 7f (CDCl$_3$, 200 MHz)



7f



^{13}C NMR spectrum of Compound 7f (CDCl$_3$, 50 MHz)



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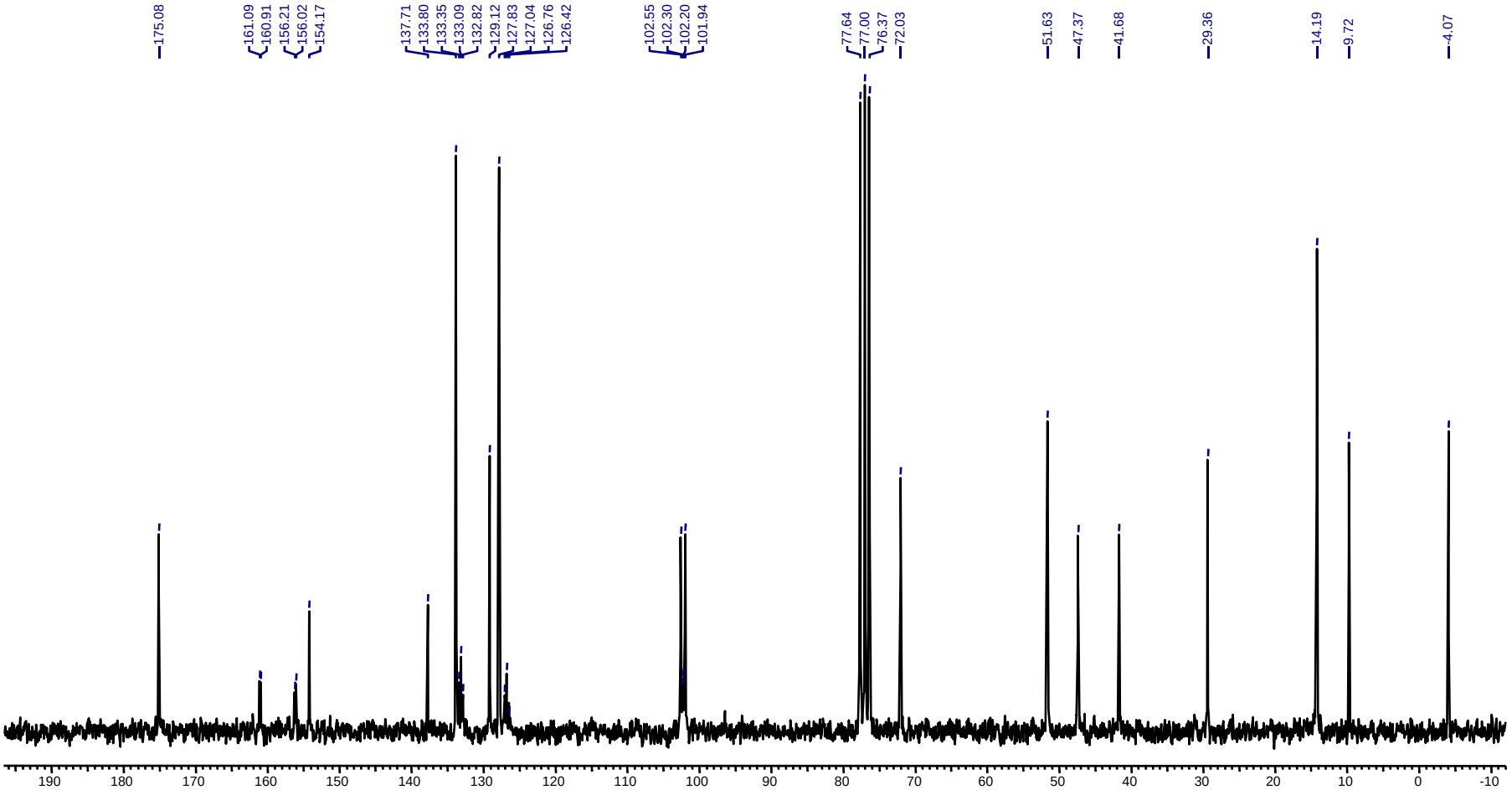
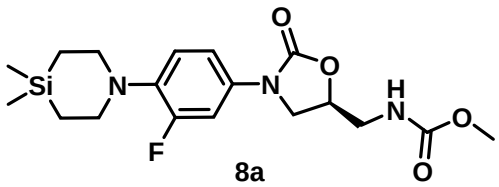
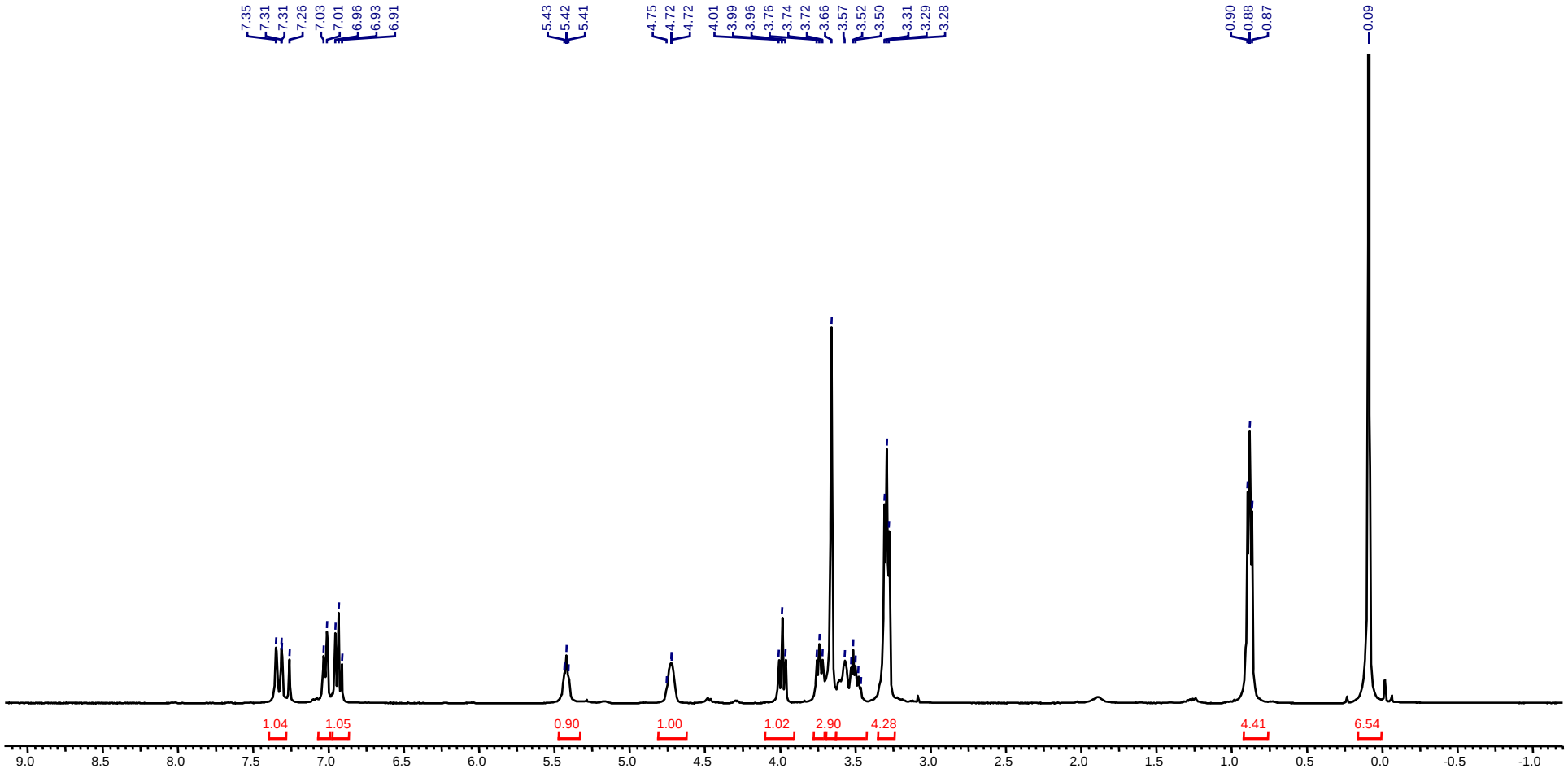


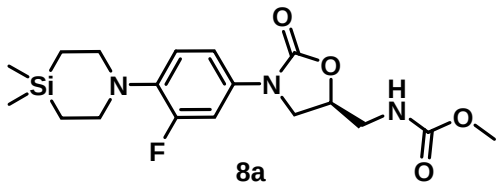
^{1}H NMR spectrum of Compound 8a ($CDCl_3$, 400 MHz)



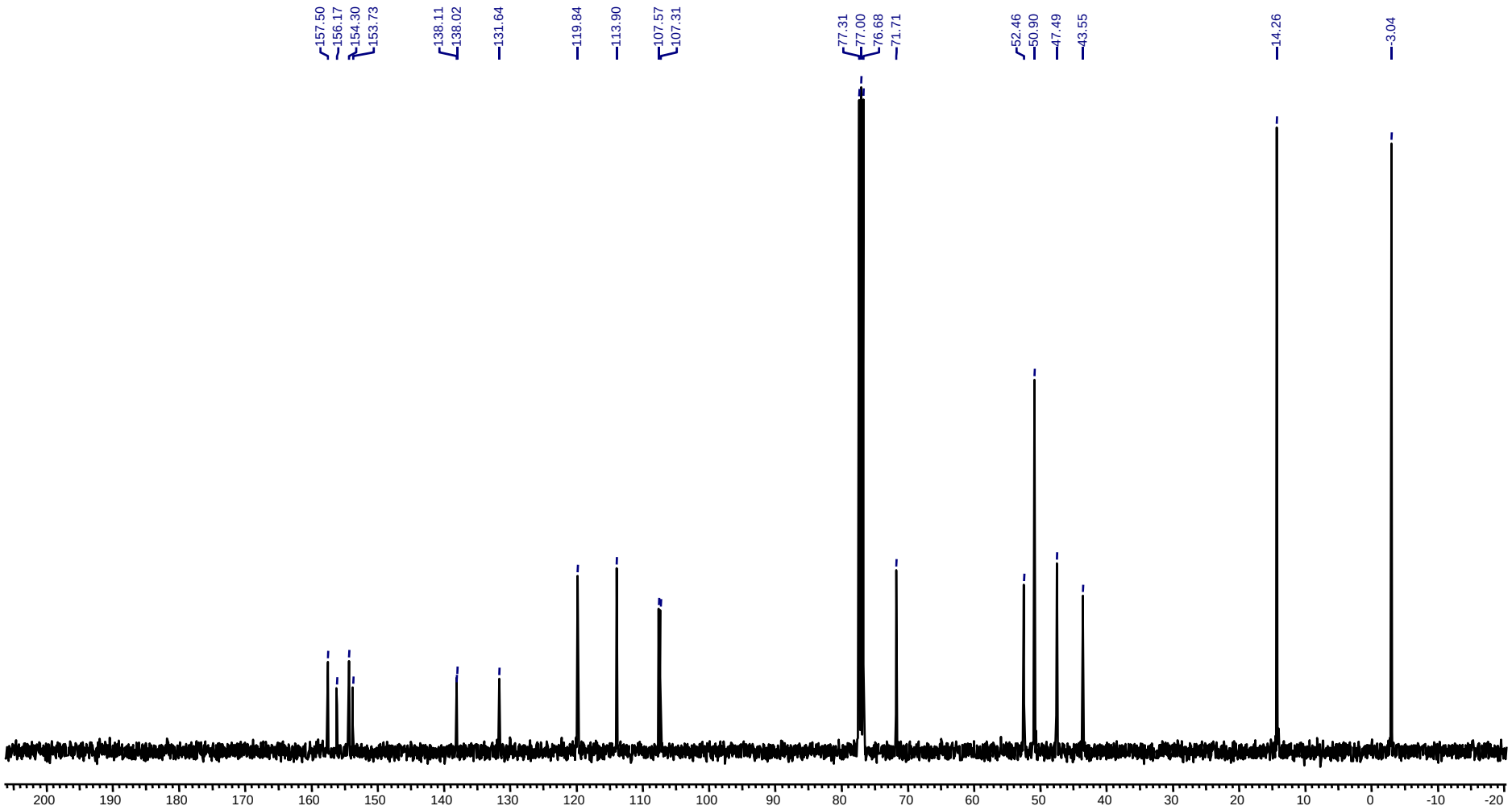
8a



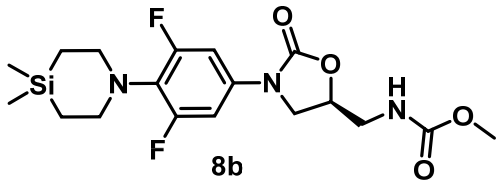
^{13}C NMR spectrum of Compound 8a ($CDCl_3$, 100 MHz)

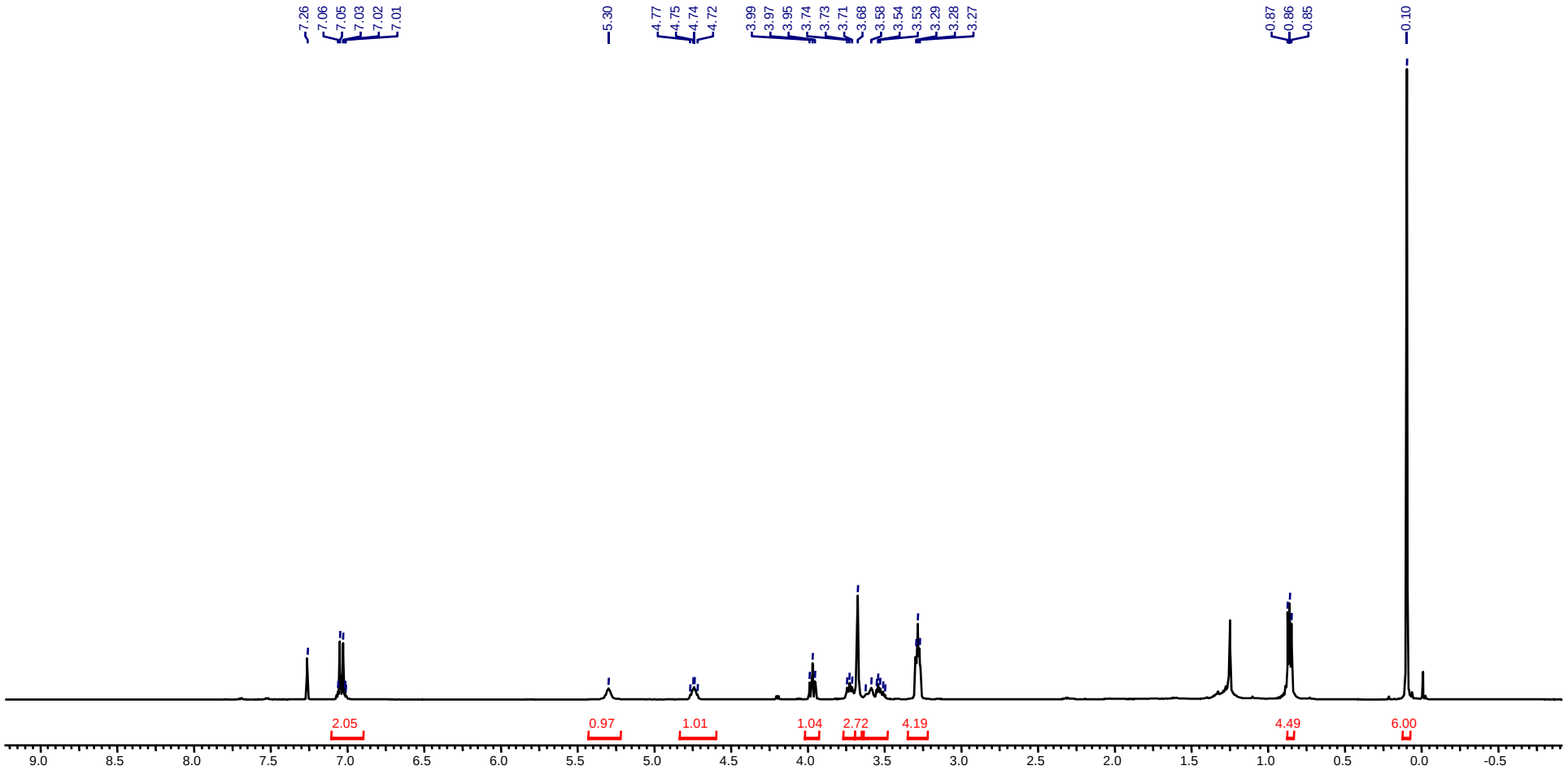


8a

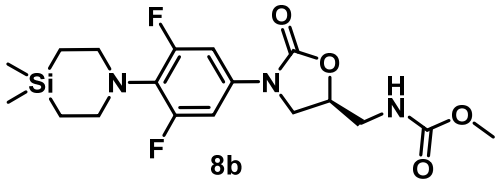


^{1}H NMR spectrum of Compound 8b ($CDCl_3$, 500 MHz)

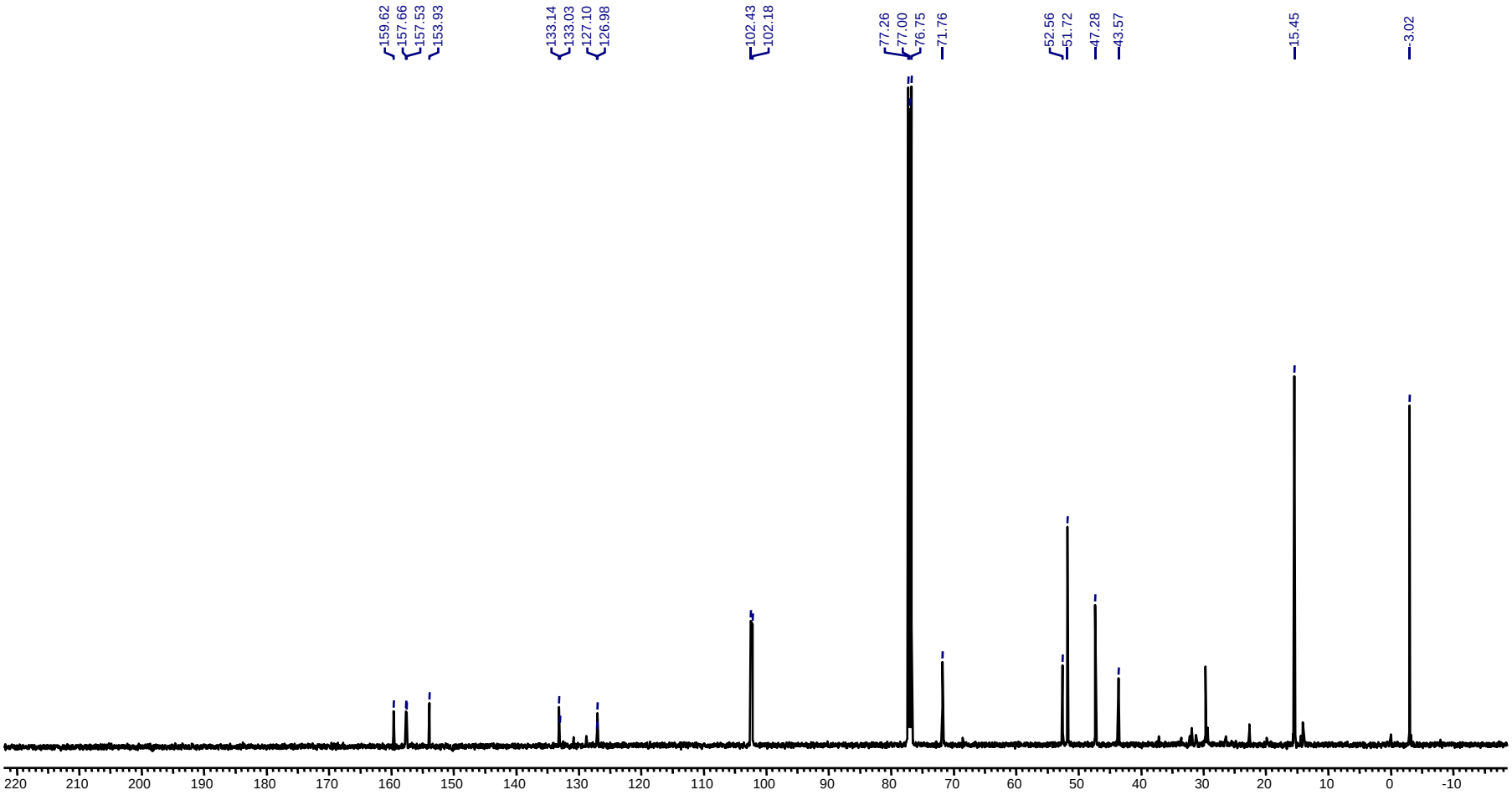




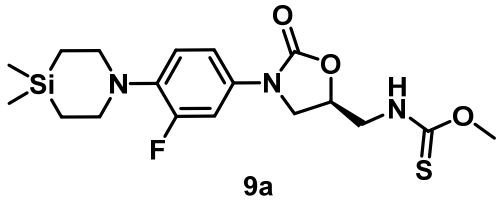
^{13}C NMR spectrum of Compound 8b ($CDCl_3$, 125 MHz)



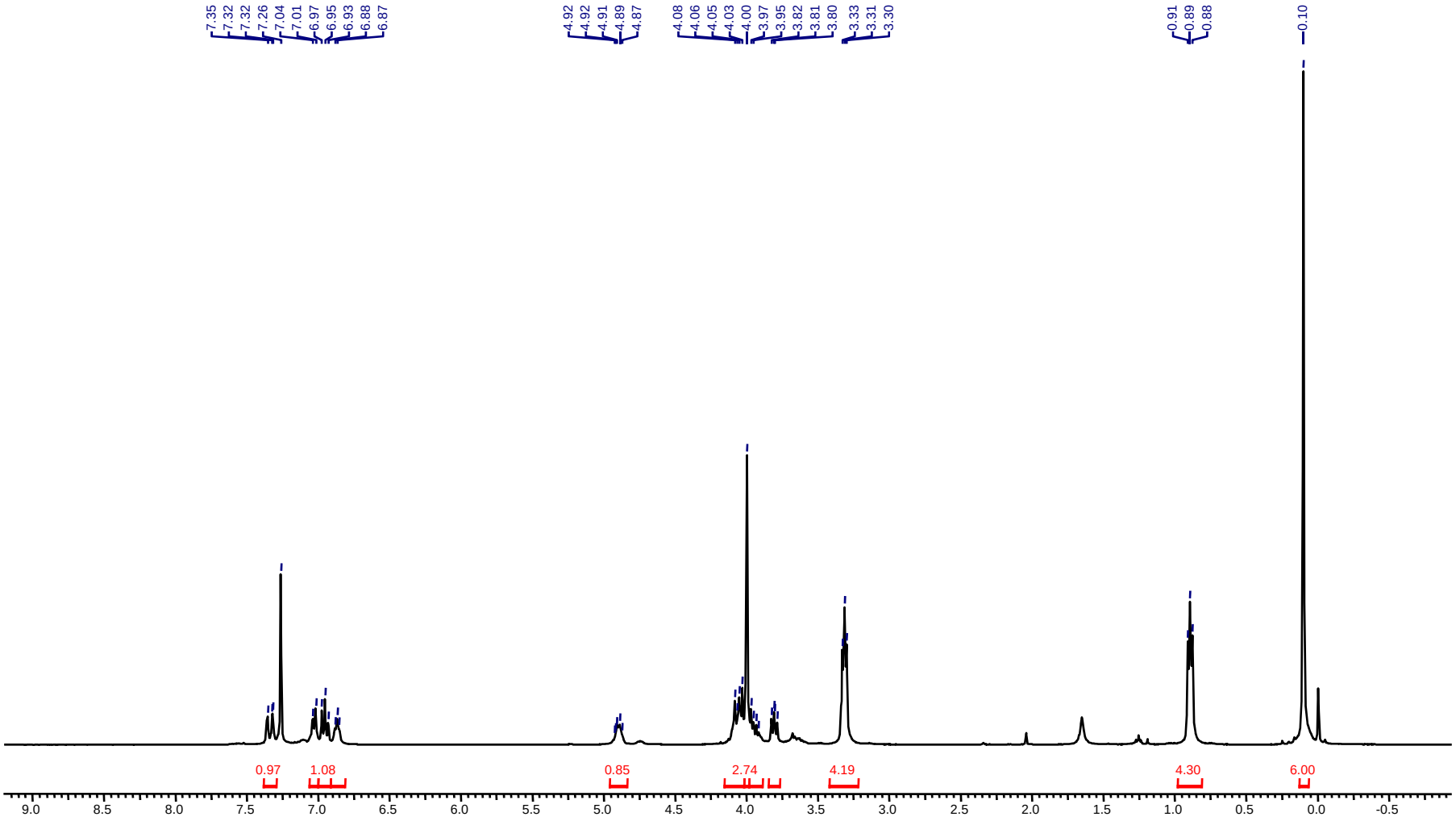
8b



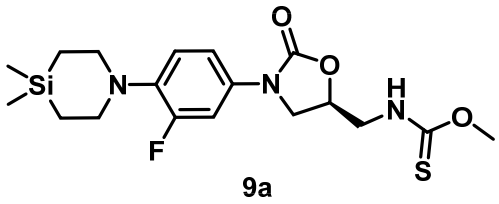
^{1}H NMR spectrum of Compound 9a (CDCl$_3$, 400 MHz)



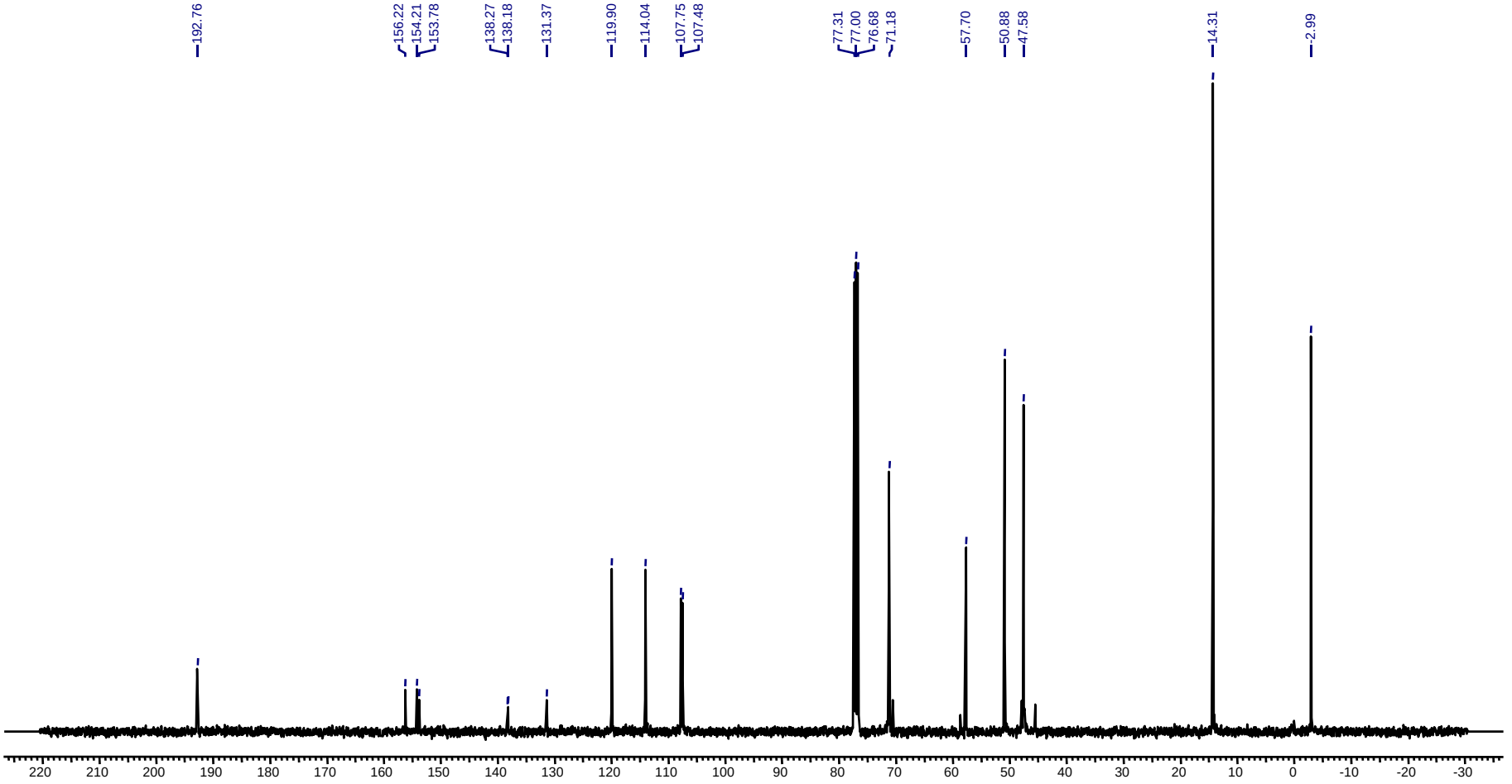
9a



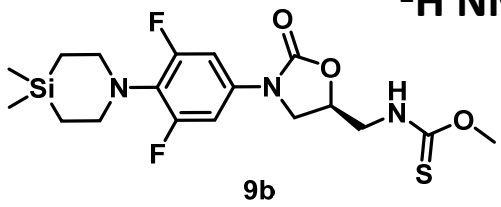
^{13}C NMR spectrum of Compound 9a ($CDCl_3$, 100 MHz)



9a



^{1}H NMR spectrum of Compound 9b (CDCl$_3$, 400 MHz)



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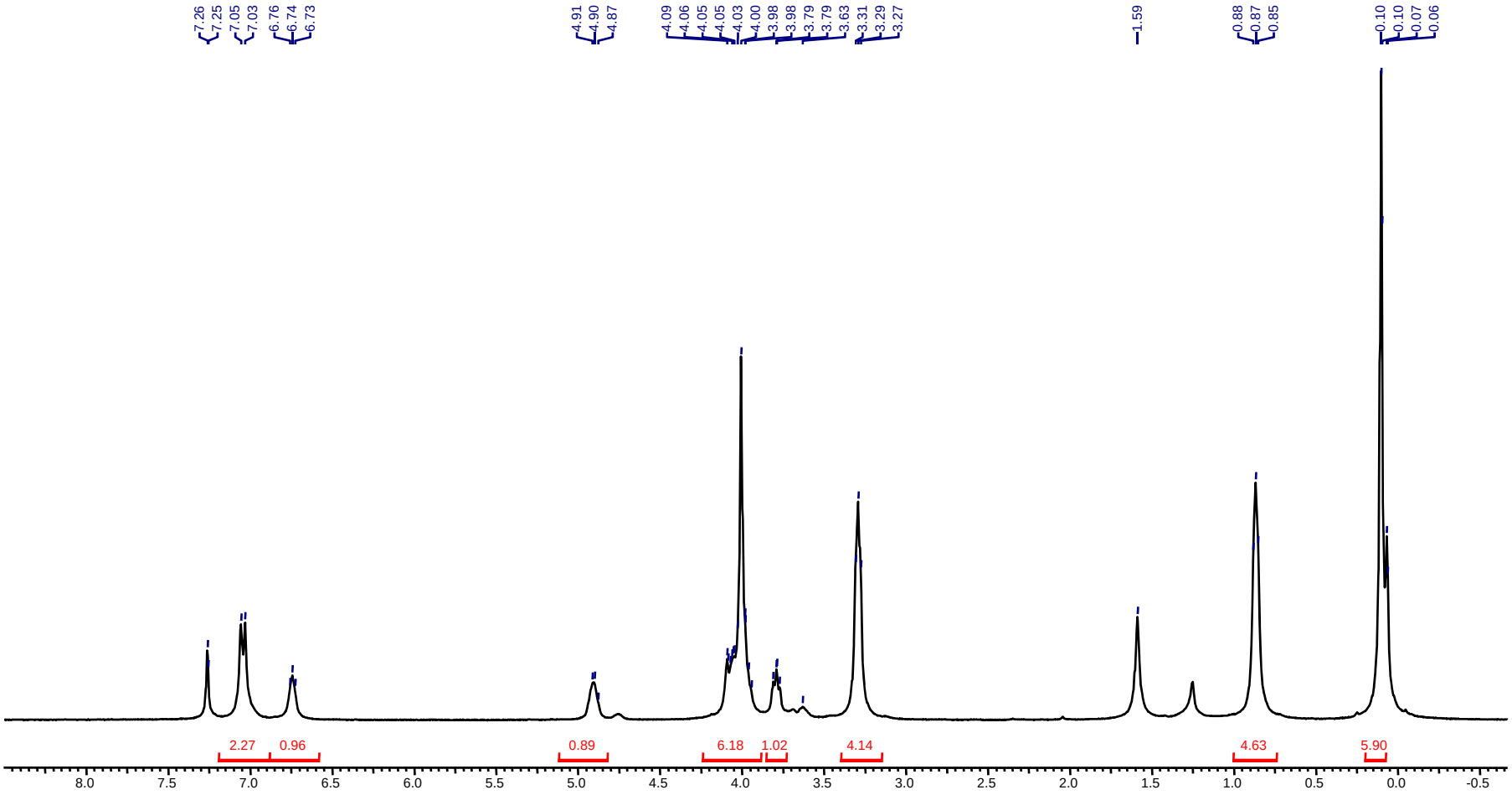
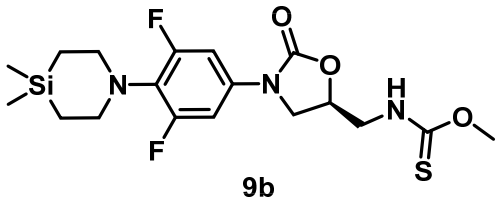


^{13}C NMR spectrum of Compound 9b ($CDCl_3$, 100 MHz)



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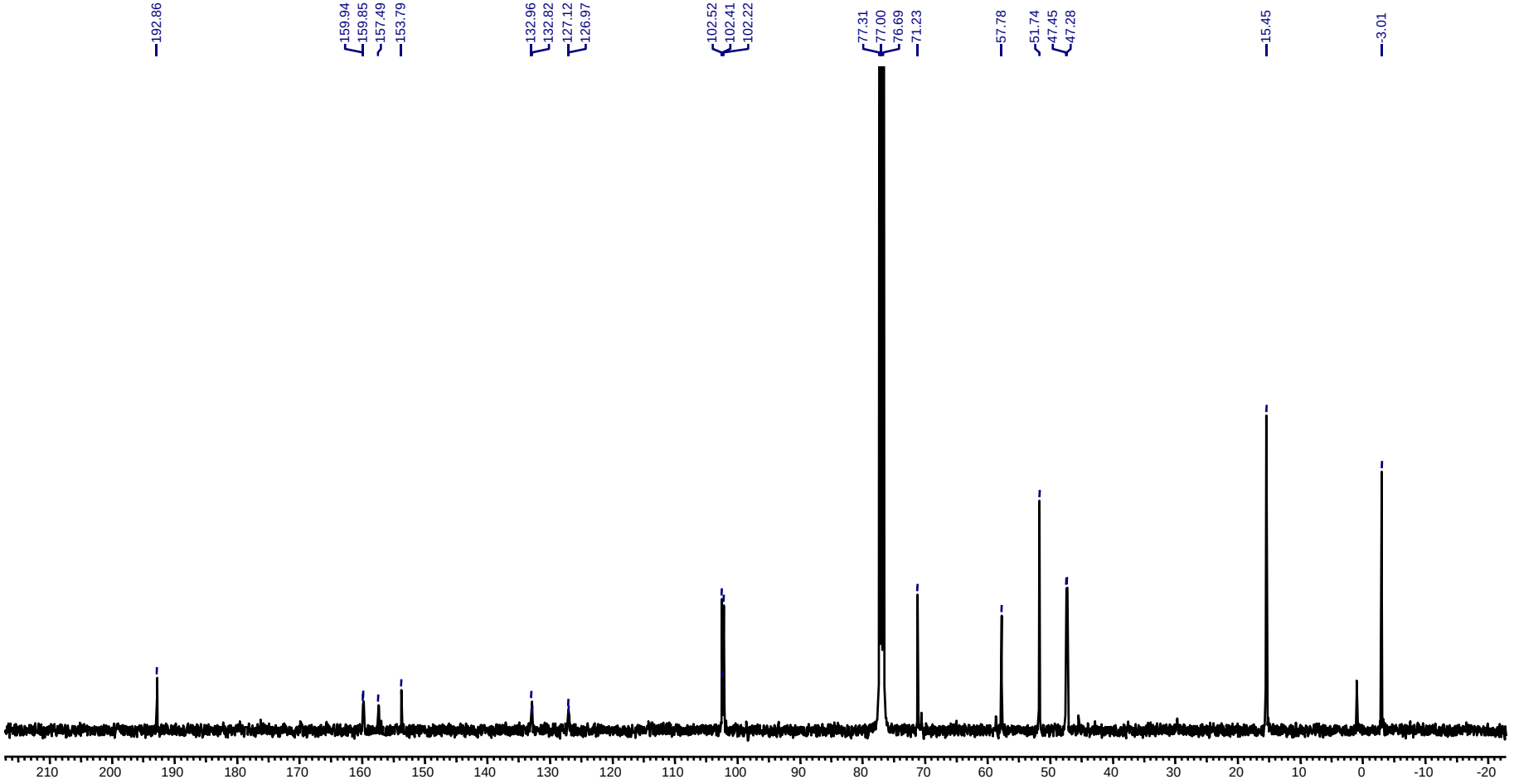
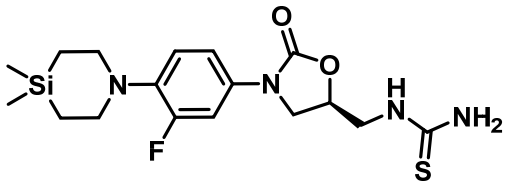
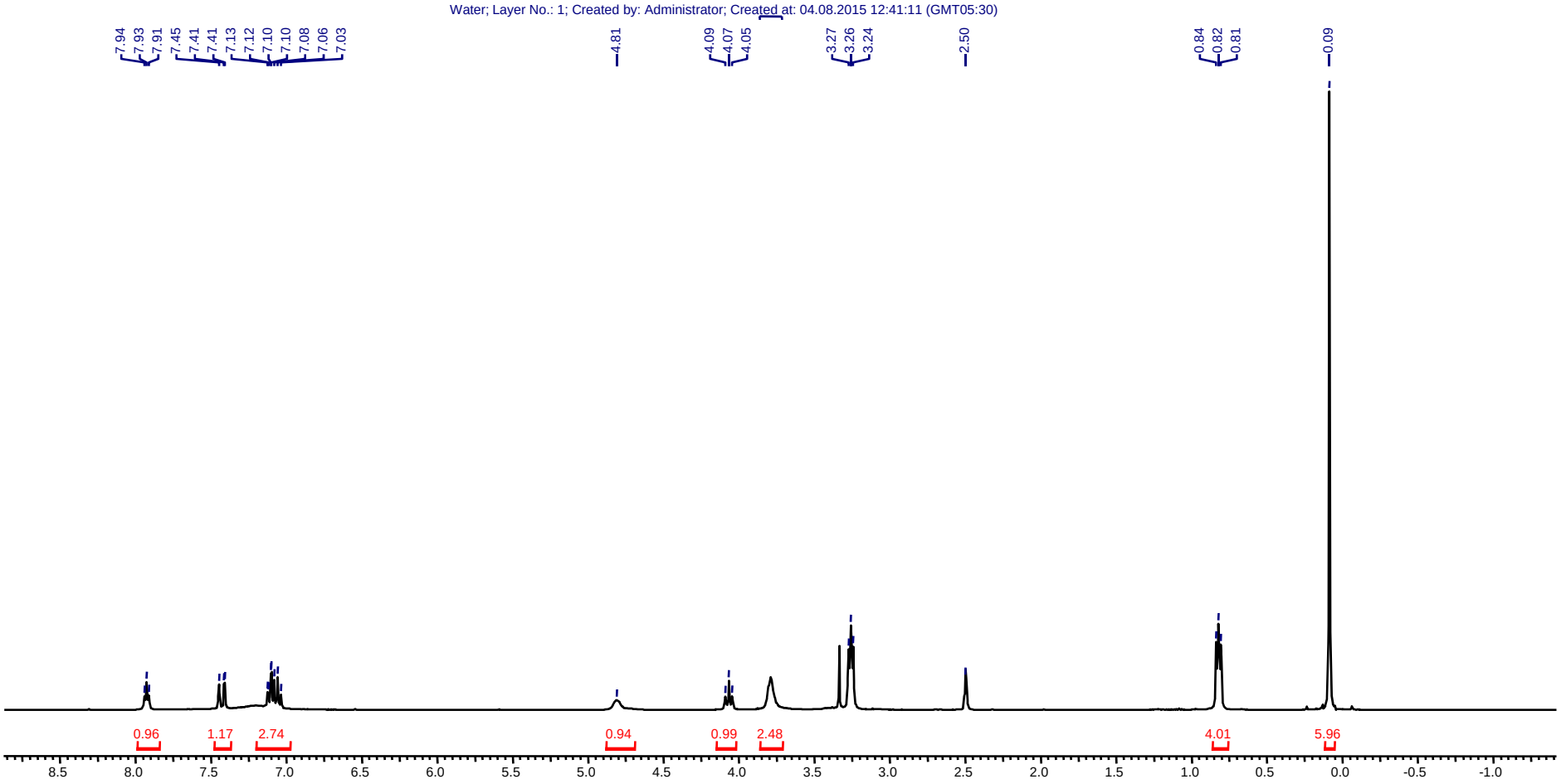


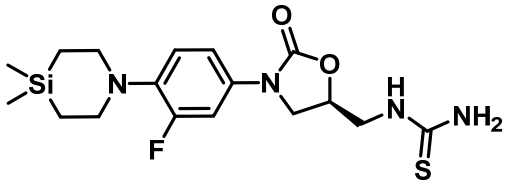
^{1}H NMR spectrum of Compound 9c (DMSO-d_6, 400 MHz)



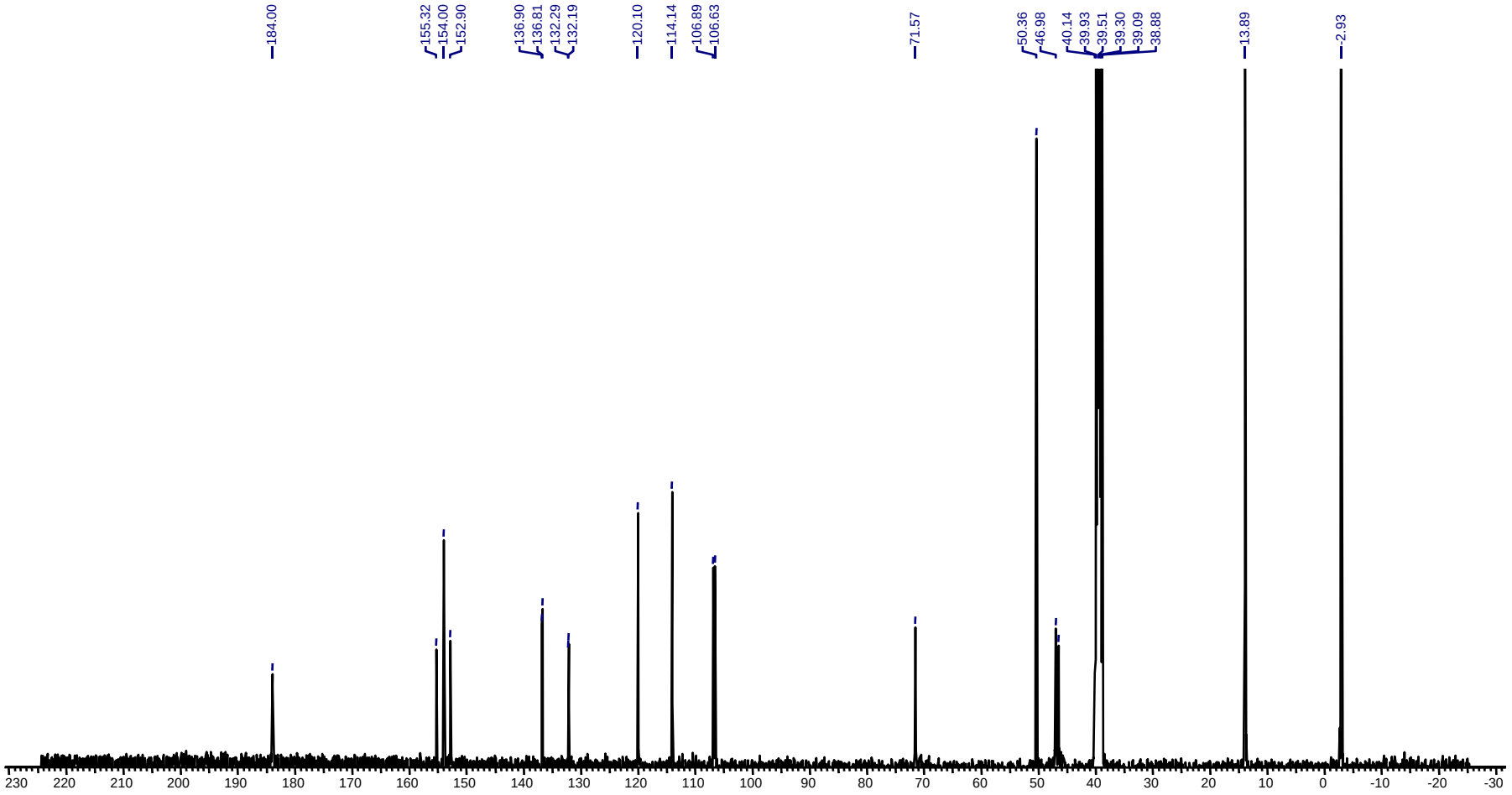
9c



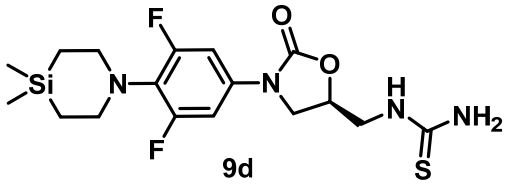
^{13}C NMR spectrum of Compound 9c (DMSO-d_6, 100 MHz)



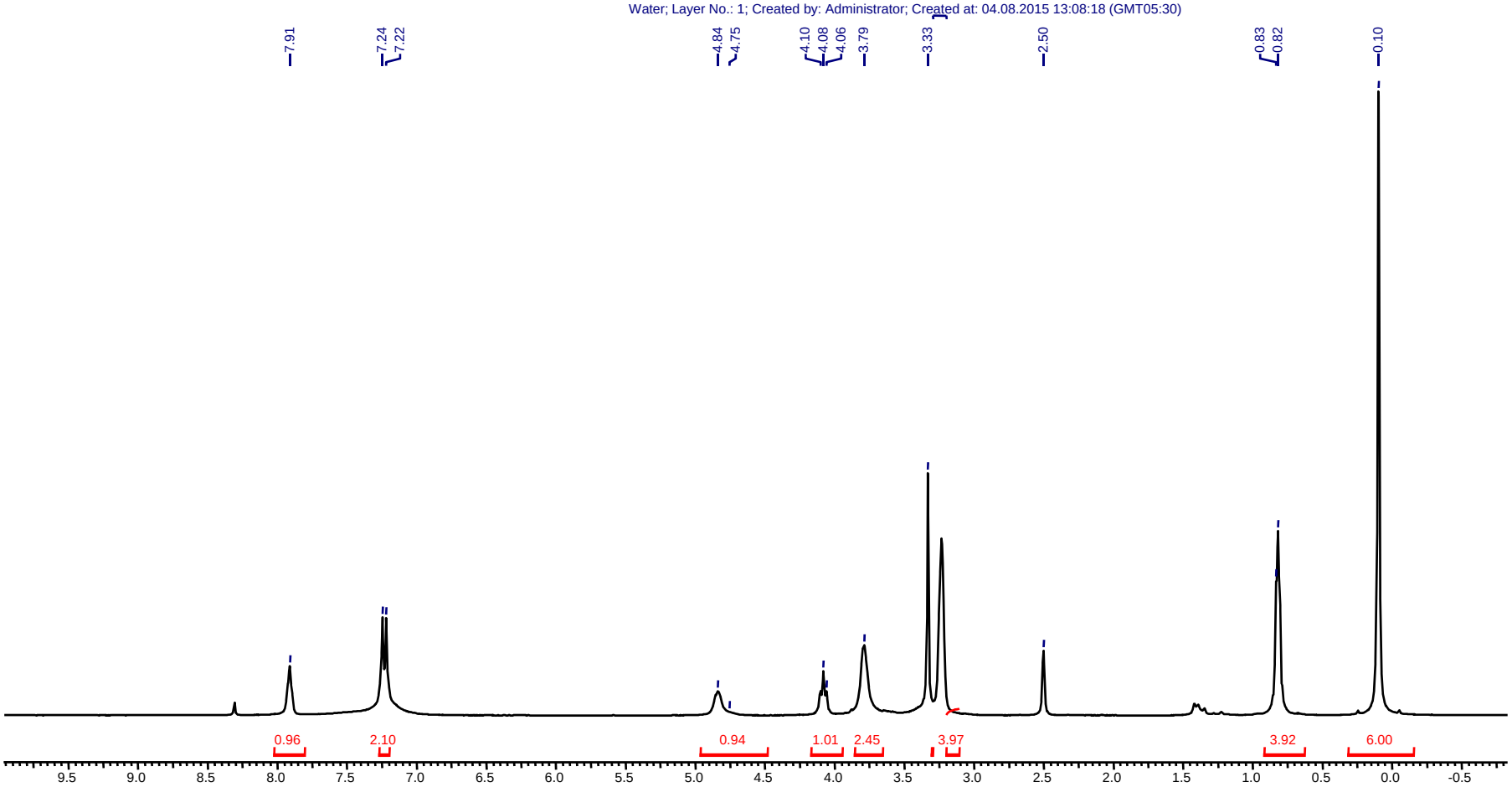
9c



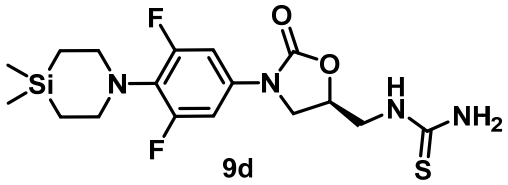
^{1}H NMR spectrum of Compound 9d (DMSO-d_6, 400 MHz)



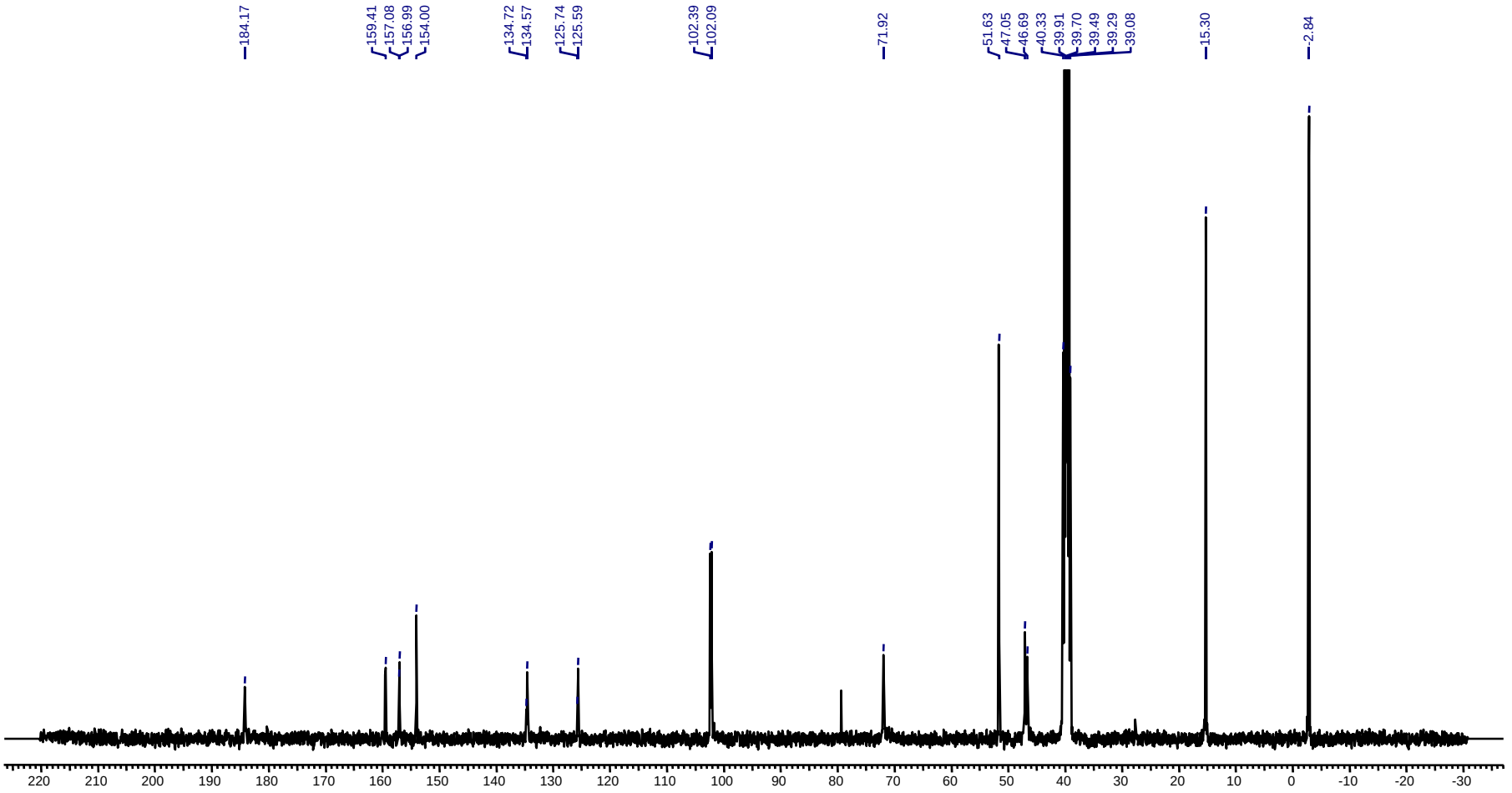
9d



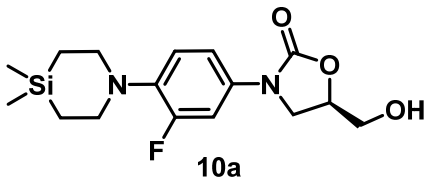
^{13}C NMR spectrum of Compound 9d (DMSO-d_6, 100 MHz)



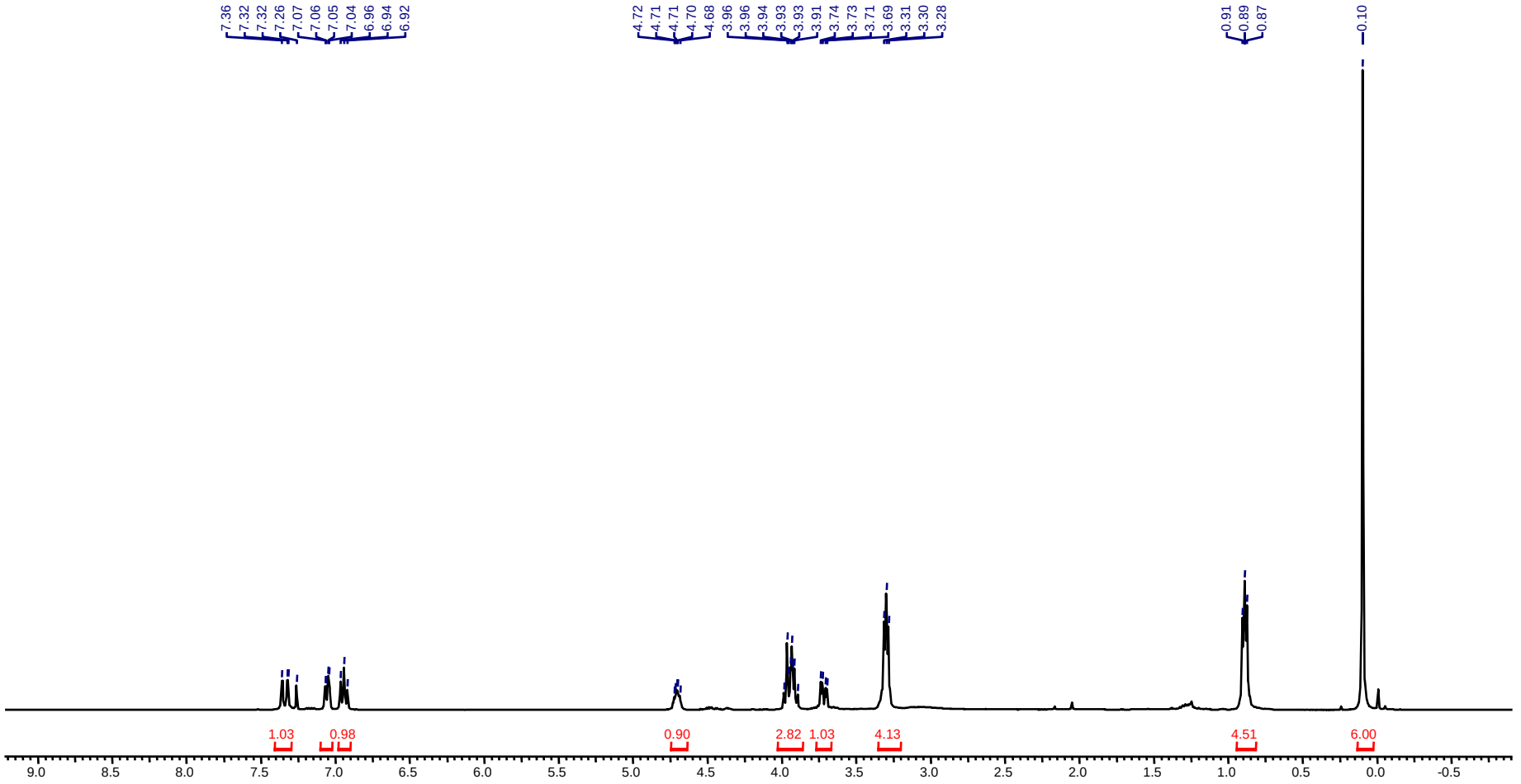
9d



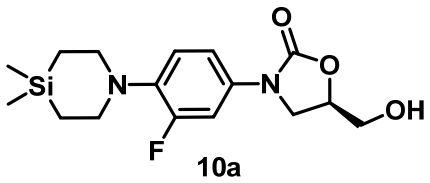
^{1}H NMR spectrum of Compound 10a ($CDCl_3$, 400 MHz)



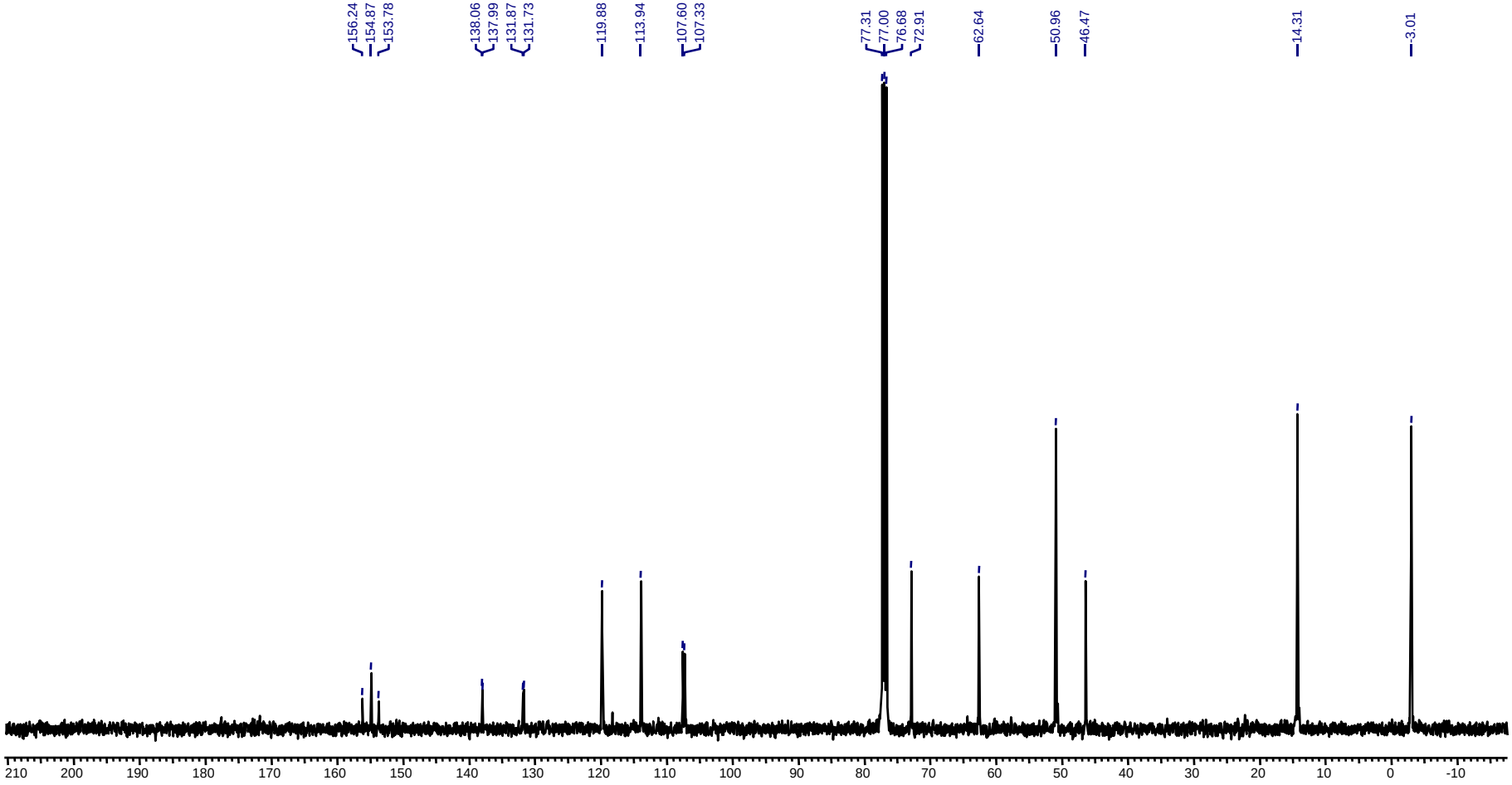
10a



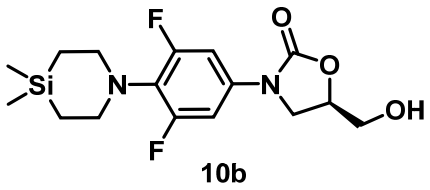
^{13}C NMR spectrum of Compound 10a ($CDCl_3$, 100 MHz)



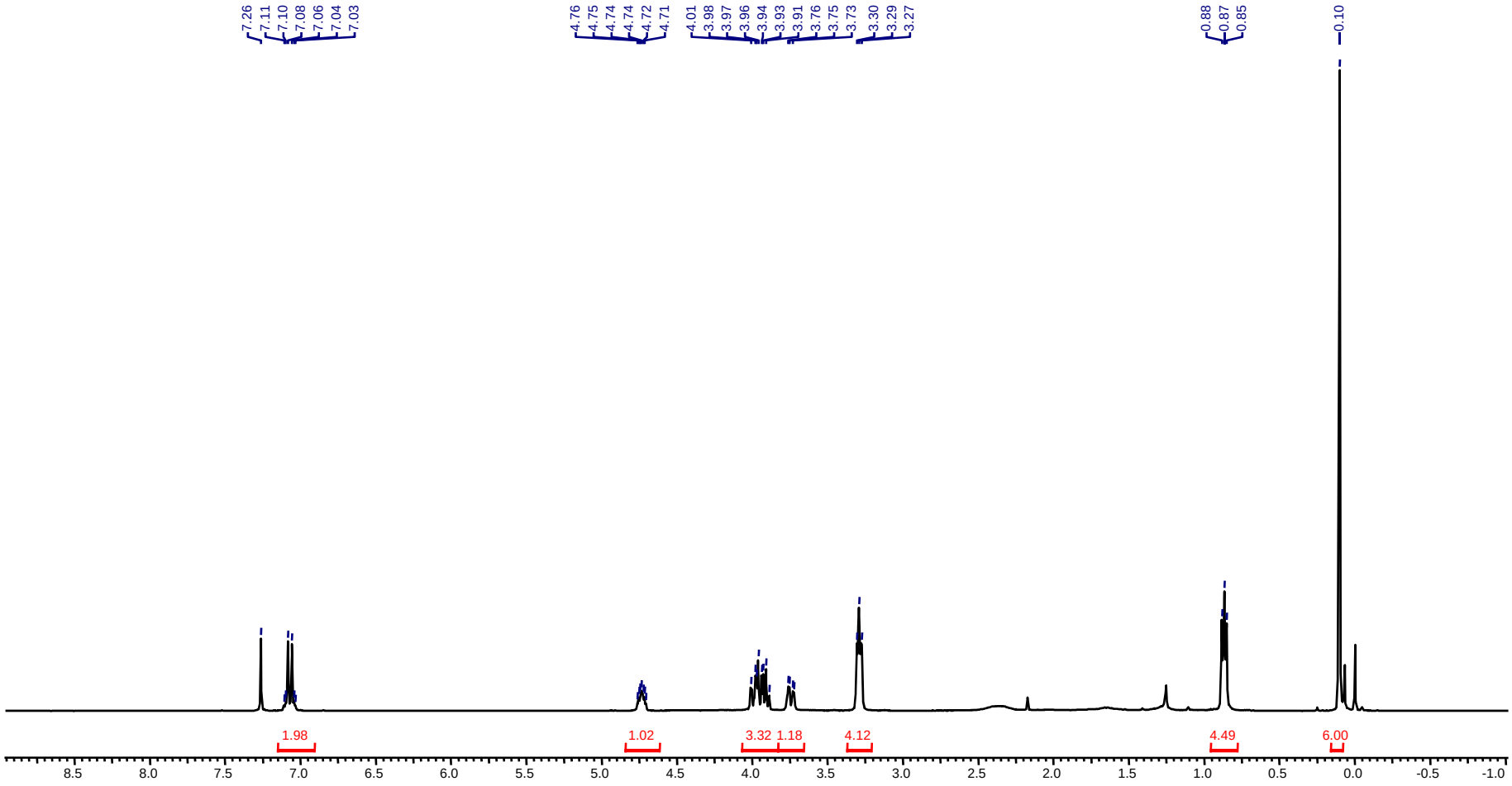
10a



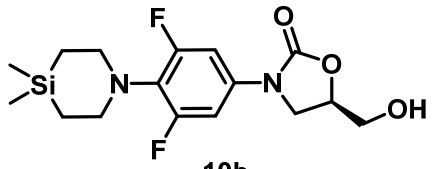
^{1}H NMR spectrum of Compound 10b ($CDCl_3$, 400 MHz)



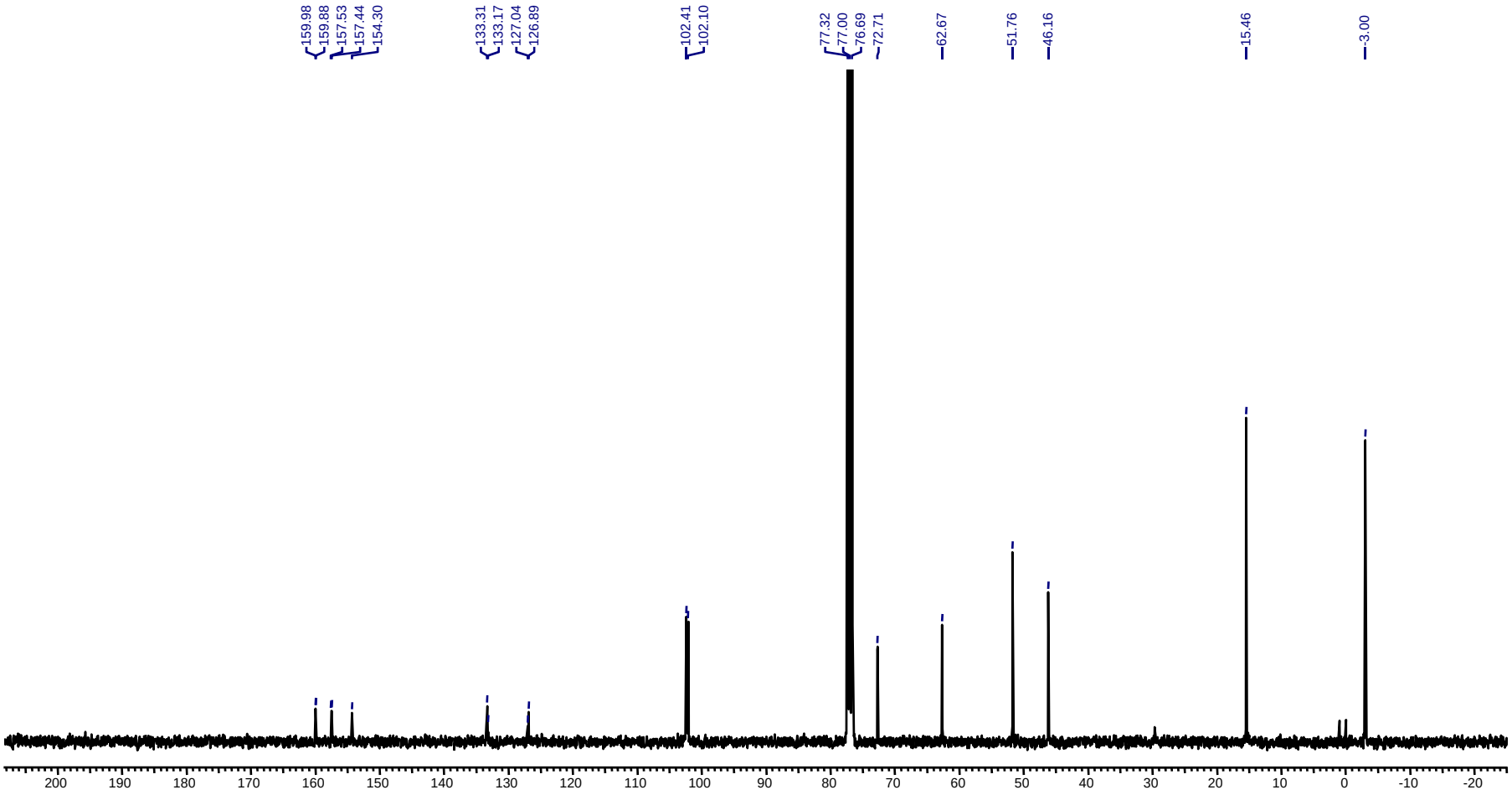
10b



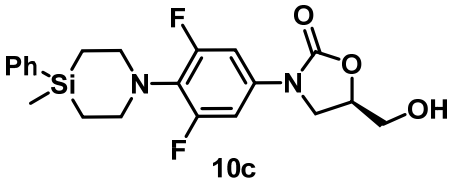
^{13}C NMR spectrum of Compound 10b ($CDCl_3$, 100 MHz)



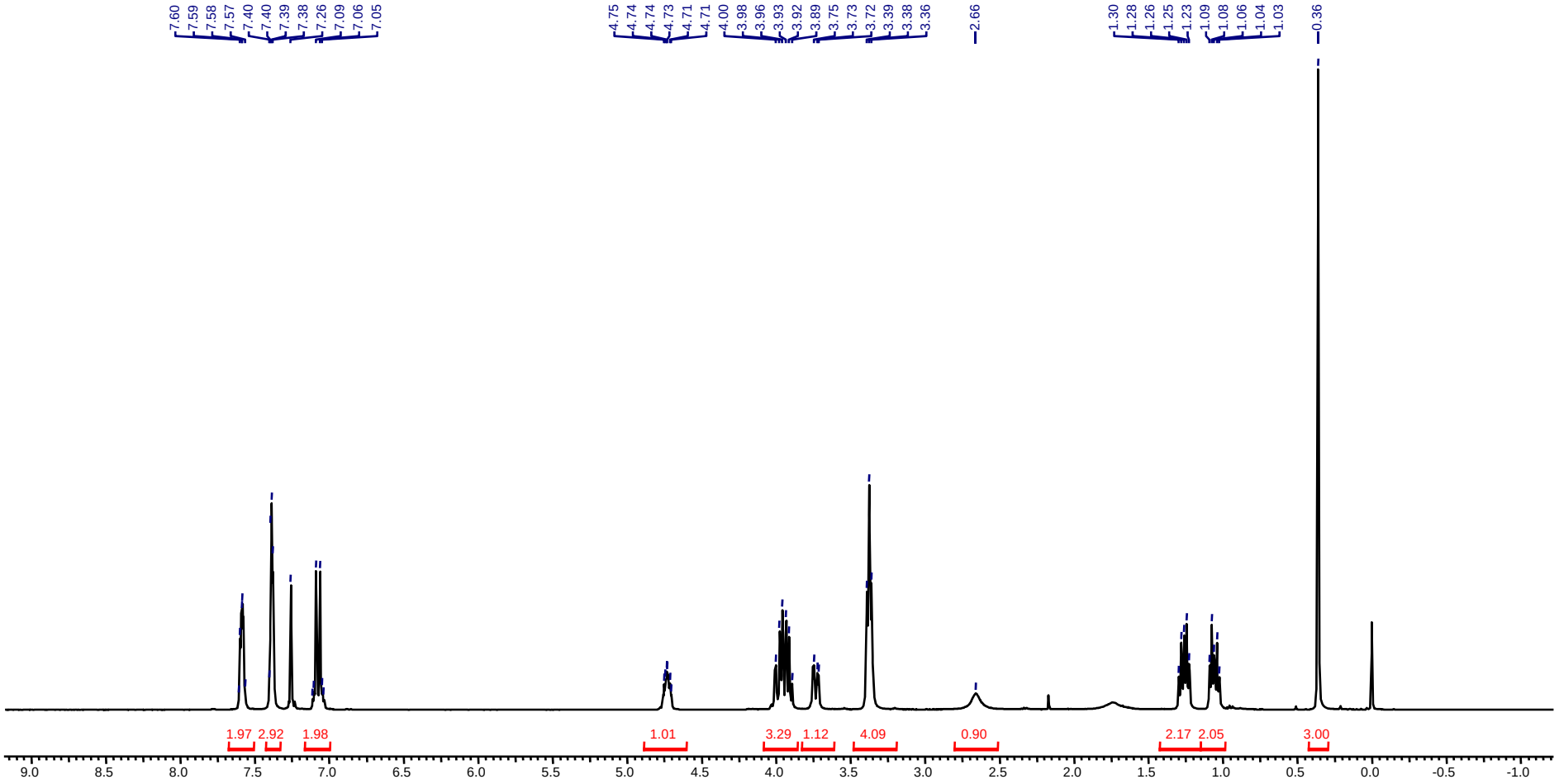
10b



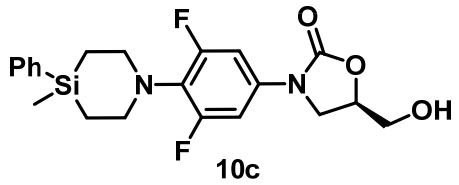
^{1}H NMR spectrum of Compound 10c (CDCl$_3$, 400 MHz)



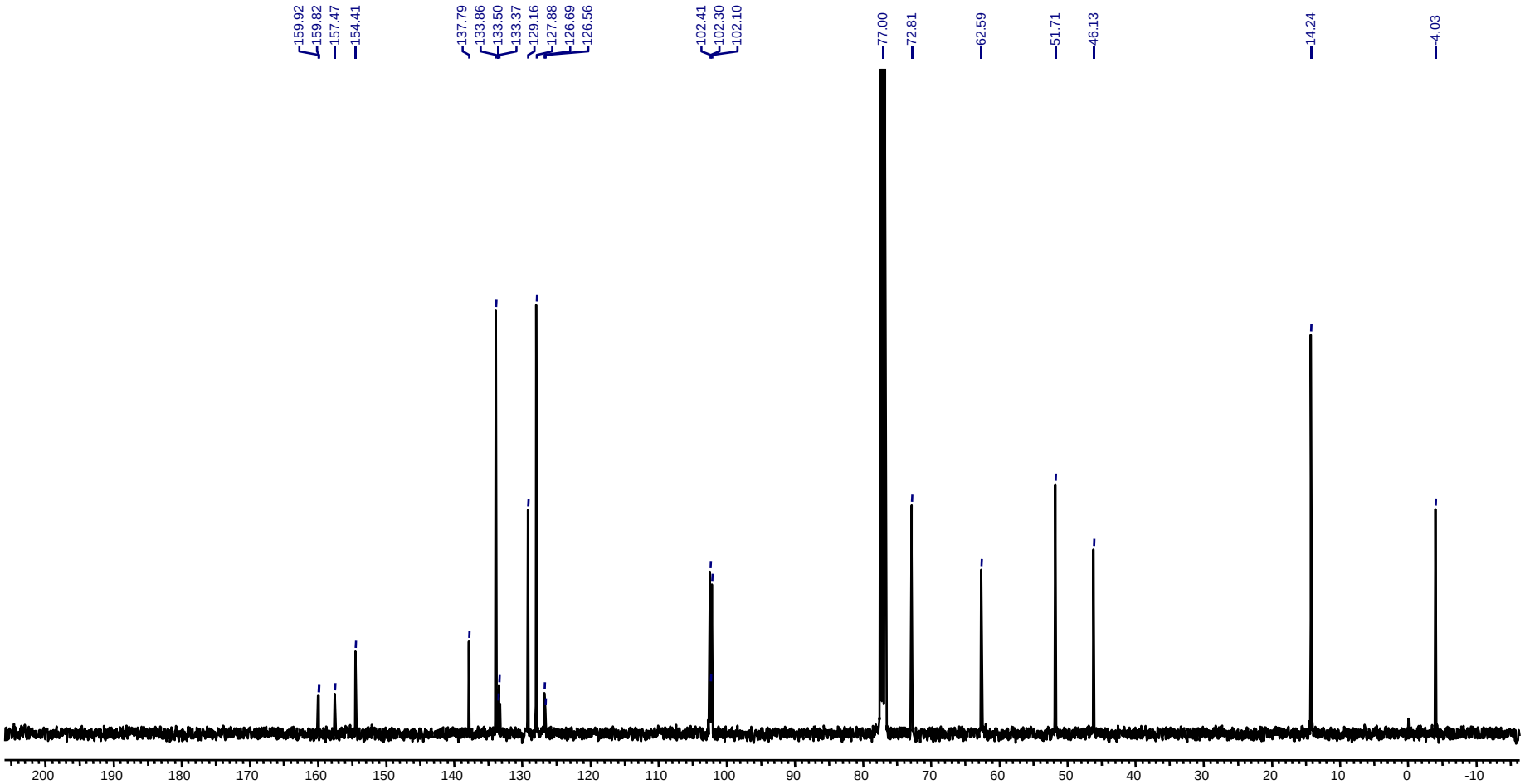
10c



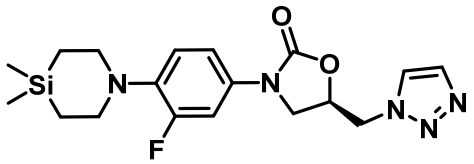
^{13}C NMR spectrum of Compound 10c ($CDCl_3$, 100 MHz)



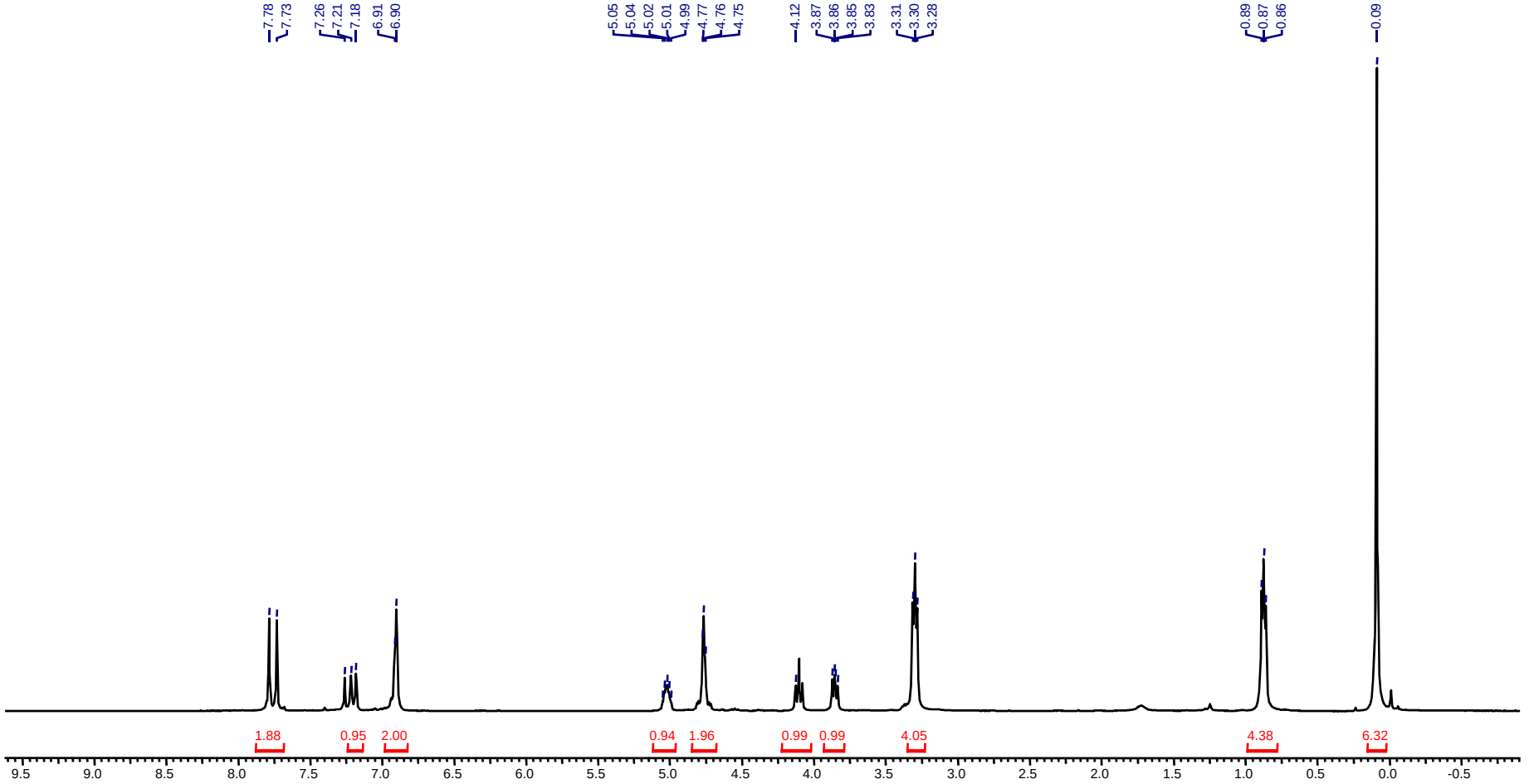
10c



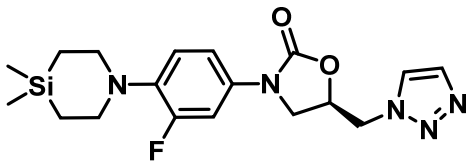
^{1}H NMR spectrum of Compound 11a ($CDCl_3$, 400 MHz)



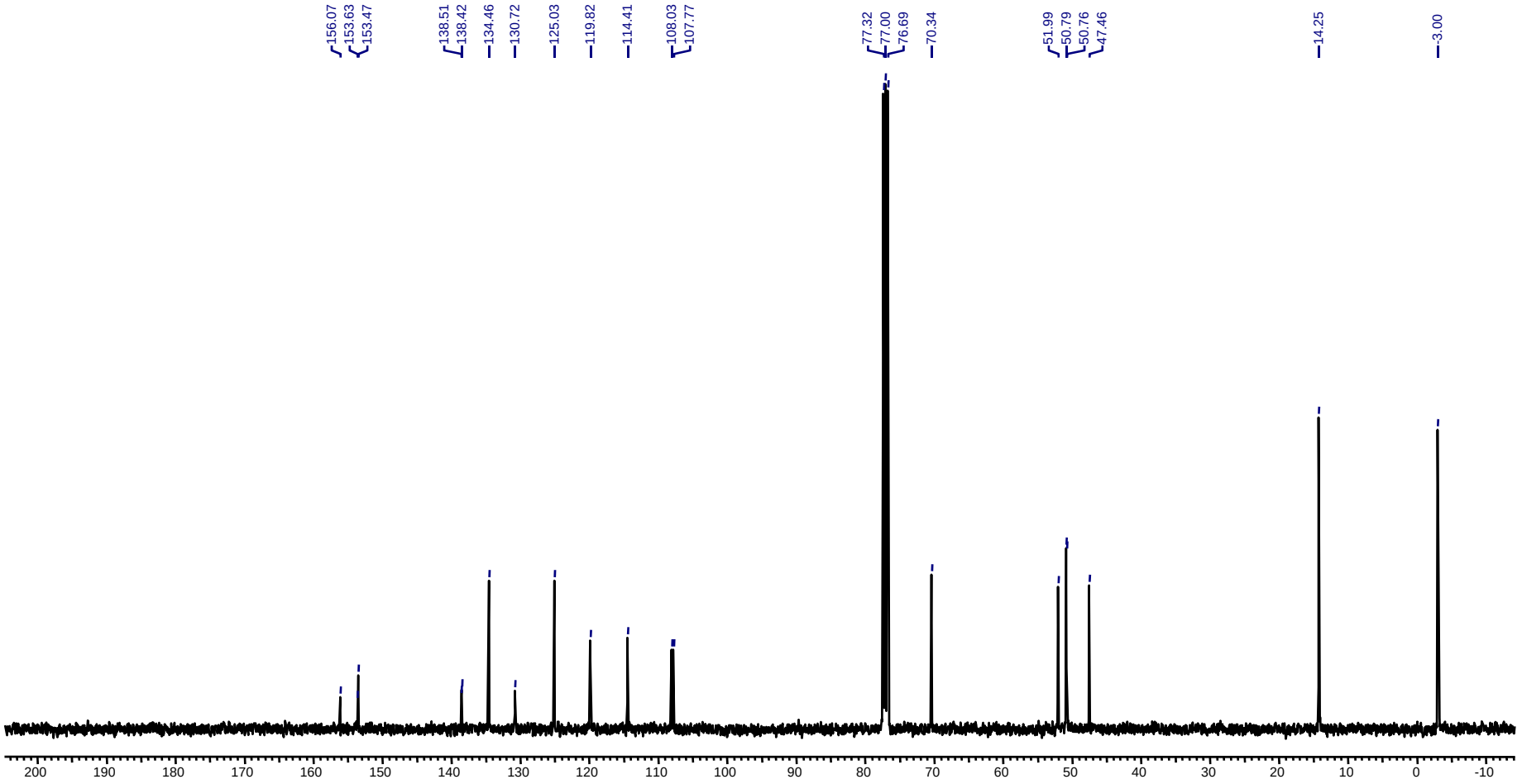
11a



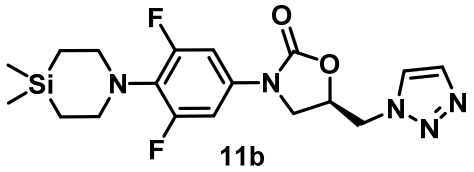
^{13}C NMR spectrum of Compound 11a ($CDCl_3$, 100 MHz)



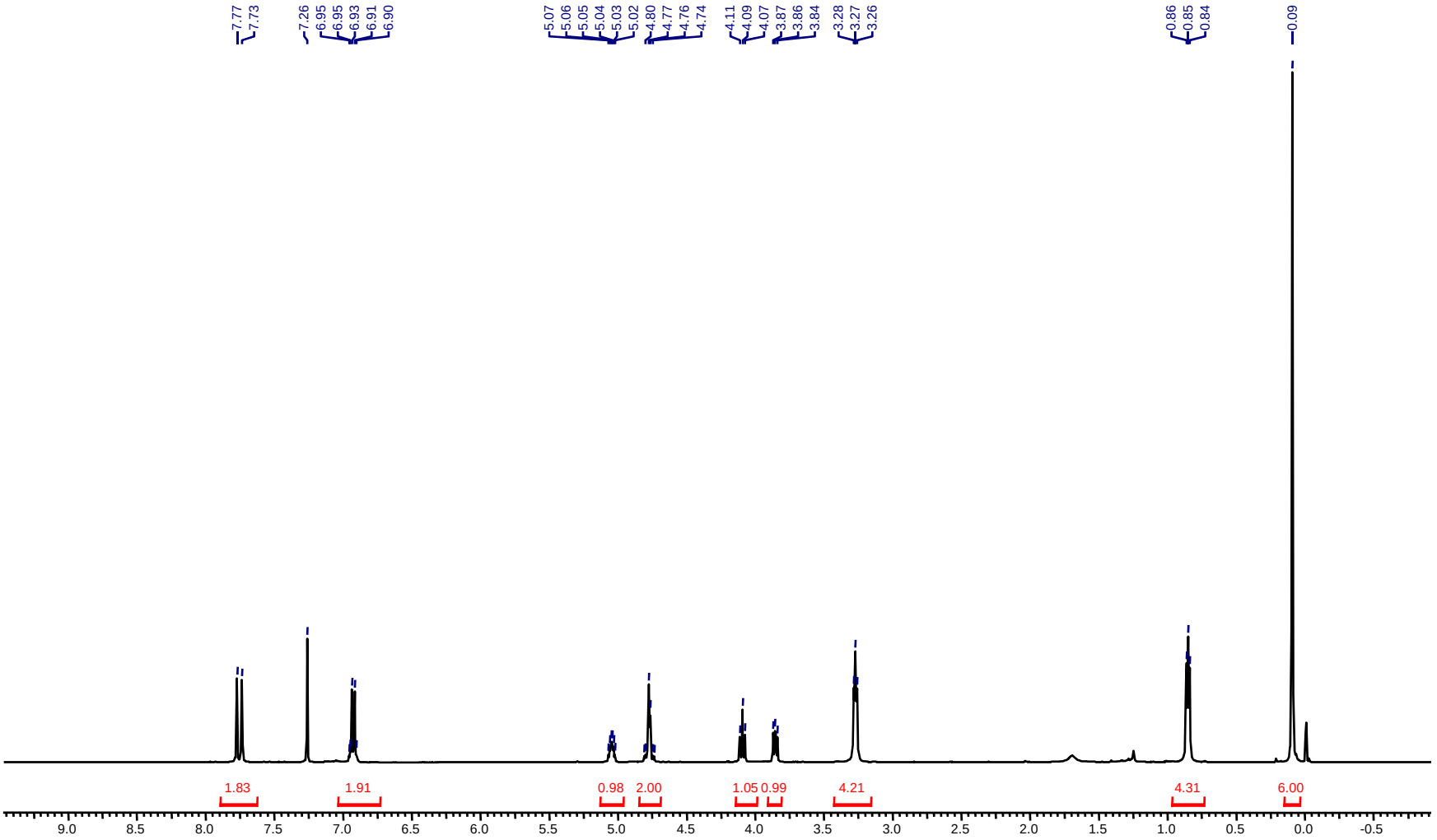
11a



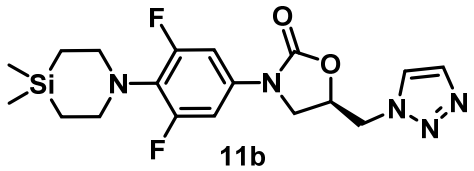
^{1}H NMR spectrum of Compound 11b ($CDCl_3$, 500 MHz)



11b



^{13}C NMR spectrum of Compound 11b ($CDCl_3$, 125 MHz)



11b