Electronic Supplementary Material (ESI) for Chemical Communications

A tandem Friedel-Crafts based method for the construction of tricyclic pyrroloquinoline skeleton and its application to the synthesis of ammosamide B

Yohei Takayama,[a] Tatsuya Yamada,[b] Shinya Tatekabe,[a] Kazuo Nagasawa[a]

[a] Department of Biotechnology and Life Science Faculty of Technology,Tokyo University of Agriculture and Technology, 2-24-16 Nakamachi, Koganei, Tokyo 184-8588 (Japan), Tel & Fax: (+81) 42-388-7295; E-mail: knaga@cc.tuat.ac.jp

[b] Department of Medicinal and Life Science Faculty of Pharmaceutical Sciences, Tokyo University of Science, Noda, Chiba 278-8510, Japan.

CONTENTS

1) General……S3

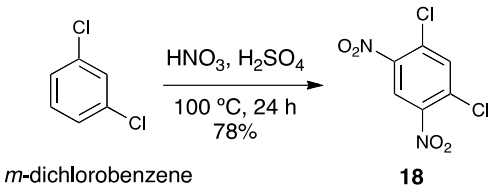
2) Experimental Section……S3

3) ^{1}H-NMR, ^{13}C-NMR spectra of compound **18**, **7**, **11**, **12**, **13**, **14**, **15**, **16**, **17**, **2**……S9

1) General

Flash chromatography was performed on Silica gel 60 (spherical, particle size 40 ~ 100 μm; Kanto). ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-AL 300, JNM-ECX 400, and JNM-ECA 500. The spectra are referenced internally according to residual solvent signals of $CDCl_3$ (^{1}H NMR; δ = 7.26 ppm, ^{13}C NMR; δ = 77.0 ppm), acetone-d6 (^{1}H NMR; δ = 2.05 ppm, ^{13}C NMR; δ = 29.8 ppm), DMSO-d6 (^{1}H NMR; δ = 2.50 ppm, ^{13}C NMR; δ = 39.5 ppm). Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet; br, broad), integration, coupling content (Hz). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). Mass spectra were recorded on a JEOL JMS-T100LC spectrometer with ESI-MS mode using methanol as solvent.

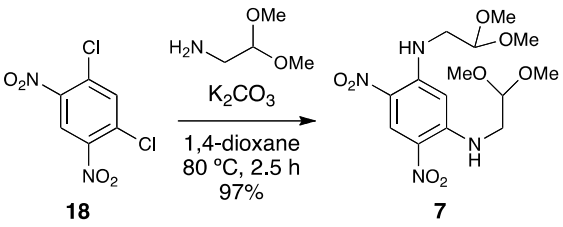
2) Experimental Section



m-dichlorobenzene **18**

Dichloro dinitro benzene **18**

To a solution of nitric acid (150 mL) and sulfuric acid (80 mL) at 0 °C was added a solution of *m*-dichlorobenzene (15 mL, 132.65 mmol) dropwise via pipette. The mixture was heated at 100 °C for 24 h, poured into ice-cold water, and extracted with EtOAc. The combined extracts were washed with water, saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in EtOAc, added *n*-hexane and precipitate was formed. This precipitate was collected with filtration using filter paper, to give **18** as a light yellow solid (24.49 g, 103.32 mmol 78%). Spectral data for **18**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.84 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.5, 135.2, 132.4, 123.3;

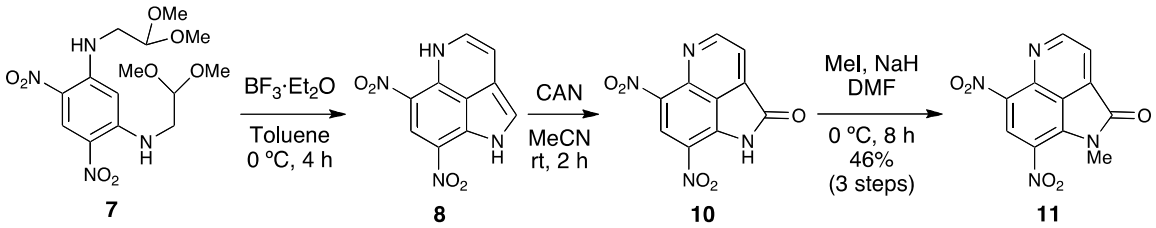


18 **7**

Bis-amino bis-nitro substituted benzene **7**

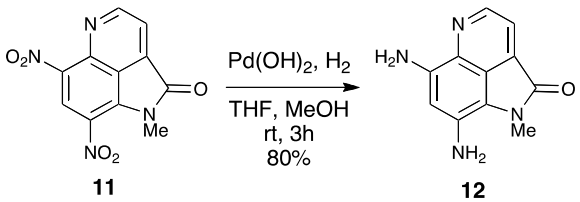
To a solution of dichloro dinitro benzene **18** (6.00 g, 25.3 mmol) in 1,4-dioxane (150 mL) was added K_2CO_3 (17.5 g, 126.5 mmol) and aminoacetoaldehyde dimethyl acetal (11 mL, 101.3 mmol) at room

temperature under N_2 atmosphere. The mixture was heated at 80 °C for 2.5 h, cooled at room temperature. The reaction mixture was added saturated aqueous NH_4Cl and H_2O, and precipitate was formed. This precipitate was collected with filtration using filter paper, to give **7** as a yellow solid (9.13 g, 24.4 mmol 97%). Spectral data for **7**: ^{1}H NMR (500 MHz, DMSO-d6) δ 8.95 (s, 1H), 8.35 (t, *J* = 5.2 Hz, 2H), 6.02 (s, 1H), 4.69 (t, *J* = 5.2 Hz, 2H), 3.54 (t, *J* = 5.2 Hz, 4H), 3.37 (s, 12H); ^{13}C NMR (125 MHz, DMSO-d6) δ 148.0, 128.5, 123.6, 101.6, 91.6, 53.8, 44.3; HRMS (ESI, *M* + Na^+) calcd for $C_{14}H_{22}N_4NaO_8$ 397.1335, found 397.1325.



N-methyl oxyindole **11**

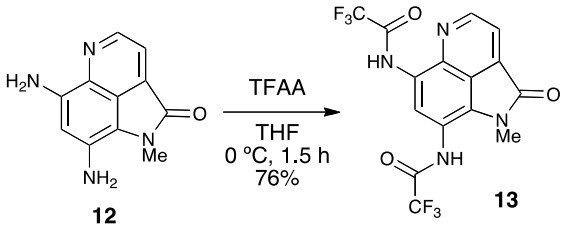
To a solution of bis-amino bis-nitro substituted benzene **7** (2.00 g, 5.35 mmol) in toluene (50 mL) was added $BF_3{\cdot}Et_2O$ (5.0 mL, 39.8 mmol) dropwise via pipette at 0 ºC under Ar atmosphere. After 3 h, the reaction mixture was added saturated aqueous $NaHCO_3$ and the organic layer was extracted with EtOAc. The extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. To a solution of the residue in MeCN (50 mL) was added CAN (3.06 g, 5.58 mmol) at room temperature for 2 h. The mixture was added saturated aqueous $NaHCO_3$ and extracted with EtOAc. The extracted were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. To a solution of residue in DMF (40 mL) was added NaH (71.6 mg, 1.79 mmol) and MeI (110 μL, 1.77 mmol) at 0 ºC under Ar atmosphere. After 8 h, the reaction mixture was added saturated aqueous NH_4Cl and the organic layer was extracted with EtOAc. The extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo.* The residue was chromatographed on silica gel ($CHCl_3$/MeOH = 1:0 to 50:1) to give **11** as a yellow solid (679 mg, 2.48 mmol, 46%). Spectral data for **11**: ^{1}H NMR (500 MHz, DMSO-d6) *δ* 9.53 (d, *J* = 4.5 Hz 1H), 8.97 (s, 1H), 8.31. (d, *J* = 4.5 Hz 1H), 3.50 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d6) *δ* 167.9, 158.4, 140.7, 138.5, 137.6, 133.0, 127.6, 126.6, 122.4, 120.3, 30.2; HRMS (ESI, *M* + H^+) calcd for $C_{11}H_7N_4O_5$ 275.0416, found 275.0466.



Aniline **12**

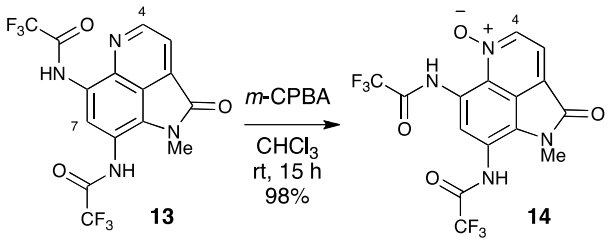
To a solution of *N*-methyl oxyindole **11** (257 mg, 0.94 mmol) in THF (10 mL) and MeOH (10 mL)

was added 20% $Pd(OH)_2$ (26 mg), and the reaction mixture was stirred at room temperature under an atmosphere of hydrogen gas (balloon). After 3 h, the reaction mixture was filtered through a pad of celite and eluted with EtOAc. The filtrates were concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 20:1 to 10:1) to give **12** as a purple solid (160 mg, 0.75 mmol, 80%). Spectral data for **12**: ^{1}H NMR (500 MHz, DMSO-d6) δ 8.64 (d, J = 4.5 Hz, 1H), 7.78 (d, J = 4.5 Hz, 1H), 6.19 (s, 1H), 5.87 (br, 2H), 5.86 (br, 2H), 3.53 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d6) δ 164.1, 143.5, 143.2, 134.8, 134.6, 129.4, 120.2, 117.5, 106.0, 101.9, 28.4; HRMS (ESI, M + Na^+) calcd for $C_{11}H_{10}N_4NaO$ 237.0752, found 237.0783.



Bis-trifluoroacetamide **13**

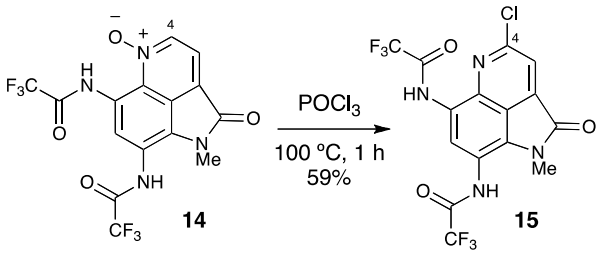
To a solution of aniline **12** (267 mg, 1.25 mmol) in THF (12 mL) was added TFAA (700 μL) dropwise via pipette at 0 ºC. After 1.5 h, the reaction mixture was added H_2O and the organic layer was extracted with EtOAc. The extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel column chromatography ($CHCl_3$ 100%) to give **13** as yellow solid (386 mg, 0.95 mmol, 76%). Spectral data for **13**: ^{1}H NMR (500 MHz, acetone-d6) δ 10.66 (br, 1H), 10.10 (br, 1H), 9.13 (d, J = 4.5 Hz, 1H), 8.33 (s, 1H), 7.90 (d, J = 4.5 Hz, 1H), 3.49 (s, 3H); ^{13}C NMR (125 MHz, acetone-d6) δ 166.9, 158.1 (q, J = 37.2 Hz), 155.5 (q, J = 37.2 Hz), 153.7, 137.5, 134.5, 132.9, 128.4, 122.3, 120.7, 119.5, 117.0 (q, J = 287.9 Hz), 116.7 (q, J = 287.9 Hz), 114.8, 27.8; HRMS (ESI, M + Na^+) calcd for $C_{15}H_8F_6N_4NaO_3$ 429.0398, found 429.0392.



N-oxide **14**

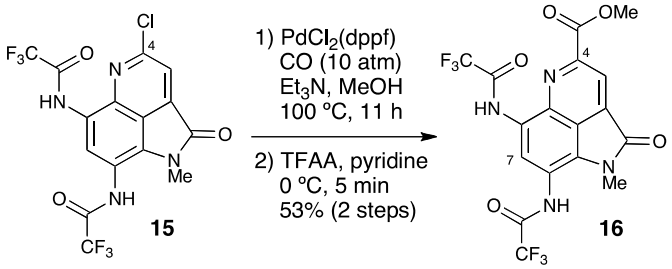
To a solution of bis-trifluoroacetamide **13** (190 mg, 0.47 mmol) in $CHCl_3$ (5 mL) was added *m*-CPBA (528 mg, 2.35 mmol) at room temperature. After 15 h, the reaction mixuture was added H_2O and the organic layer was extracted with $CHCl_3$. The water layer was extracted with EtOAc. The extracted were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The

residue was chromatographed on silica gel ($CHCl_3$/MeOH = 1:0 to 50:1) to give **14** as an orange solid (194 mg, 0.46 mmol, 98%). Spectral data for **14**: ^{1}H NMR (500 MHz, acetone-d6) δ 10.74 (br, 1H), 8.71 (s, 1H), 8.62 (s, 1H), 8.04 (s, 1H), 3.52 (s, 3H); ^{13}C NMR (125 MHz, acetone-d6) δ 165.1, 158.0 (q, J = 38.4 Hz), 154.8 (q, J = 38.4 Hz), 142.0, 132.1, 128.6, 126.7, 124.9, 124.5, 121.7, 120.8, 116.9 (q, J = 287.9 Hz), 116.8, 116.6 (q, J = 287.9 Hz), 27.9; HRMS (ESI, M + Na^+) calcd for $C_{15}H_8F_6N_4NaO_4$ 445.0347, found 445.0313.



C4 chlorine compound **15**

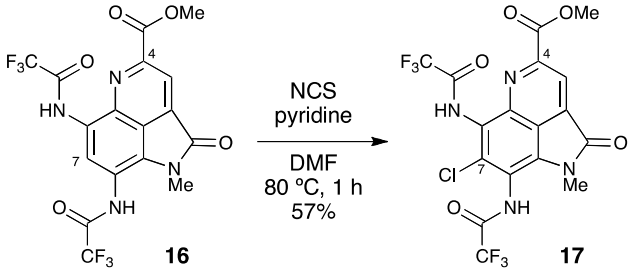
To a solution of *N*-oxide **14** (91.5 mg, 0.22 mmol) in $POCl_3$ (2 mL) was heated at 100 ºC under N_2 atmosphere. After 1 h, the reaction mixture was cooled to 0 ºC, poured into ice-cold water, and the organic layer was extracted with EtOAe. The extracted were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel ($CHCl_3$ 100%) to give **15** as a yellow solid (57.0 mg, 0.13 mmol, 59%). Spectral data for **15**: ^{1}H NMR (500 MHz, acetone-d6) δ 10.74 (br, 1H), 10.31 (br, 1H), 8.36 (s, 1H), 8.02 (s, 1H), 3.51 (s, 3H); ^{13}C NMR (125 MHz, acetone-d6) δ 165.8, 158.0 (q, J = 38.4 Hz), 155.9 (q, J = 38.4 Hz), 153.8, 138.2, 137.5, 133.3, 127.7, 125.2, 121.2, 120.2, 117.0 (q, J = 287.9 Hz), 116.7 (q, J = 287.9 Hz), 115.6, 28.0; HRMS (ESI, M + Na^+) calcd for $C_{15}H_7ClF_6N_4NaO_3$ 463.0009, found 462.9996.



Methyl ester **16**

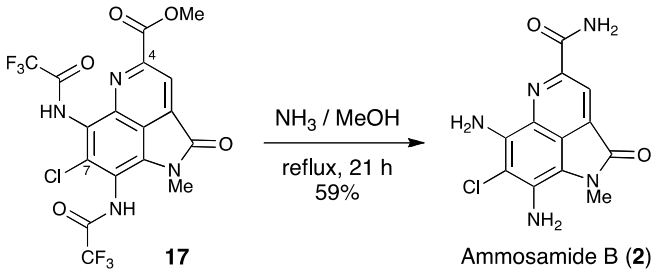
To a solution of C4 chlorine compound **15** (133 mg, 0.30 mmol) in MeOH (3 mL) was added Et_3N (220 μL, 1.59 mmol) dropwise via pipette and $PdCl_2$(dppf) (25.4 mg, 0.031 mmol) at room temperature, and the vessel was pressurized to 10 atm with CO gas and heated to 100 ºC. After 11 h, the reaction mixture was cooled to room temperature and reduced the pressure. The reaction mixture was added EtOAc and H_2O and the organic layer was extracted with EtOAc. The water layer was extracted with EtOAc. The extracts were washed with brine, dried over $MgSO_4$, filtered,

and concentrated *in vacuo*. To a solution of residue in pyridine (5 mL) was added TFAA (3 mL) dropwise via pippete at 0 ºC. After 5 min, the reaction mixture was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 1:0 to 100:1) to give **16** as orange solid (73 mg, 0.16 mmol, 53%). Spectral data for **16**: ^{1}H NMR (400 MHz, acetone-d6) δ 8.58 (s, 1H), 8.48 (s, 1H), 4.07 (s, 1H), 3.55 (s, 3H); ^{13}C NMR (125 MHz, acetone-d6) δ 166.3, 165.1, 158.0 (q, J = 38.4 Hz), 155.7 (q, J = 38.4 Hz), 151.3, 137.0, 136.1, 132.4, 129.1, 123.3, 122.2, 119.5, 117.0 (q, J = 286.7 Hz), 116.7, 116.7 (q, J = 286.7 Hz), 53.6, 28.0; HRMS (ESI, M - H^+) calcd for $C_{17}H_9F_6N_4O_5$ 463.0477, found 463.04300.



C7 chlorine compound **17**

To a solution of methyl ester **16** (10.7 mg, 0.023 mmol) in DMF (1 mL) was added pyridine (100 μL) dropwise via pipette and NCS (9.5 mg, 0.071 mmol), and the reaction mixture was heated to 80 ºC. After 1 h, the reaction mixture was cooled to room temperature and added EtOAc and H_2O and the organic layer was extracted with EtOAc. The water layer was extracted with EtOAc. The extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 100:1) to give **17** as a yellow solid (6.3 mg, 0.013 mmol, 57%). Spectral data for **17**: ^{1}H NMR (400 MHz, acetone-d6) δ 10.74 (br, 1H), 9.89 (br, 1H), 8.56 (s, 1H), 4.03 (s, 3H), 3.54 (s, 3H); ^{13}C NMR (125 MHz, acetone-d6) δ 178.9, 166.7, 165.3, 158.2 (q, J = 37.2 Hz), 156.8 (q, J = 37.2 Hz), 153.9, 141.6, 139.2, 138.3, 136.6, 121.7, 119.5, 117.1 (q, J = 287.9 Hz), 116.9 (q, J = 287.9 Hz), 113.9, 53.5, 27.8; HRMS (ESI, M - H^+) calcd for $C_{17}H_8ClF_6N_4O_5$ 497.0087, found 497.0057.



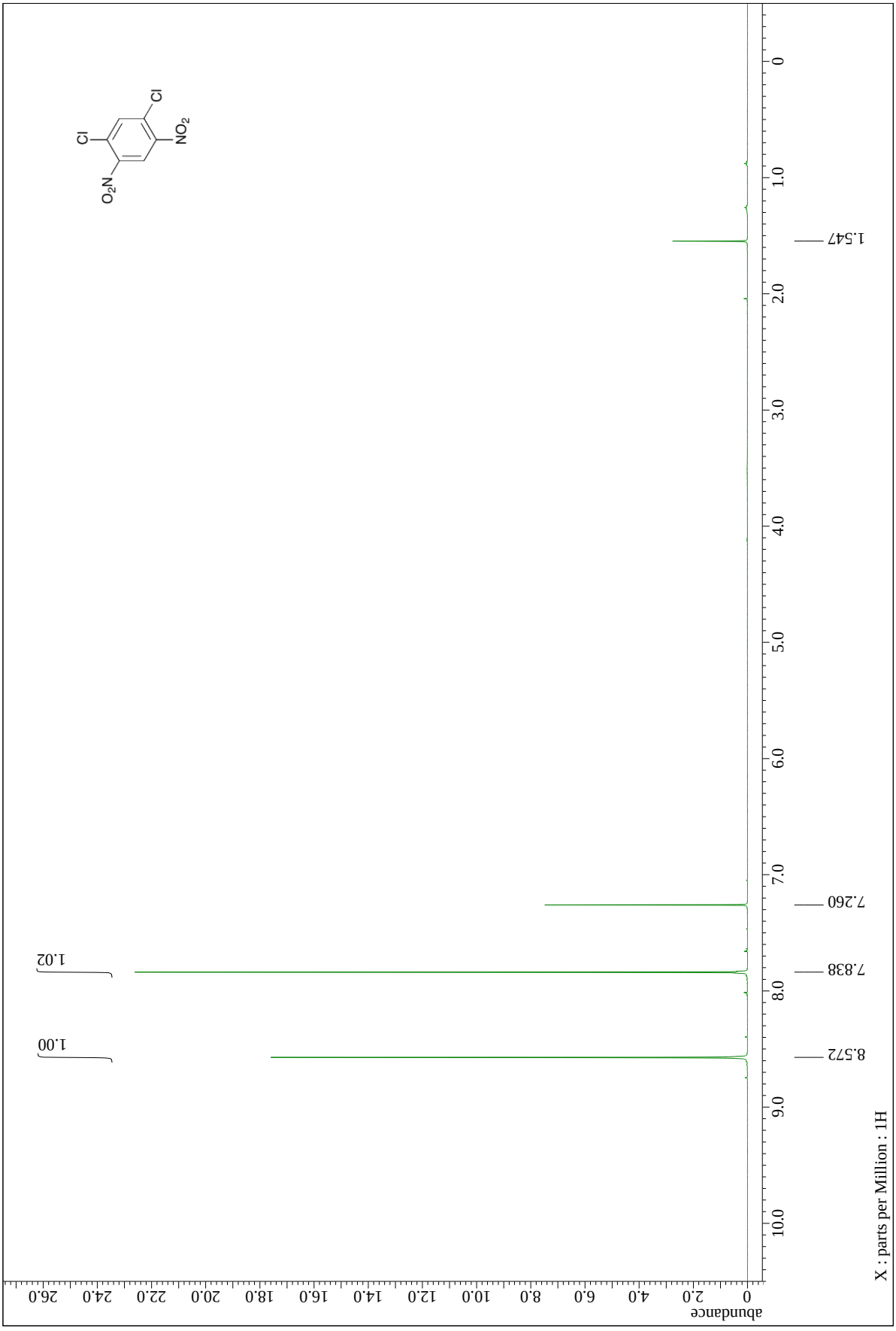
Ammosamide B (**2**)

To a solution of C7 chlorine compound **17** (5.5 mg, 0.011 mmol) in 4% NH_3/MeOH solution (2mL) was heated at reflux. The reaction mixture was stirred for 21 h and then concentrated *in vacuo*.

The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 50:1 to 10:1) to give **2** as a purple solid (1.9 mg, 0.013 mmol, 59%). Spectral data for **2**: ^{1}H NMR (400 MHz, DMSO-d6) δ 8.88 (br, 1H), 8.35 (s, 1H), 7.63 (br, 1H), 6.69 (br, 2H), 6.14 (br, 2H), 3.59 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d6) δ 166.1, 164.0, 144.7, 140.5, 132.4, 130.8, 130.6, 119.1, 115.3, 106.3, 104.5, 28.6; HRMS (ESI, M - H^+) calcd for $C_{12}H_9ClN_5O_2$ 290.0445, found 290.0416.

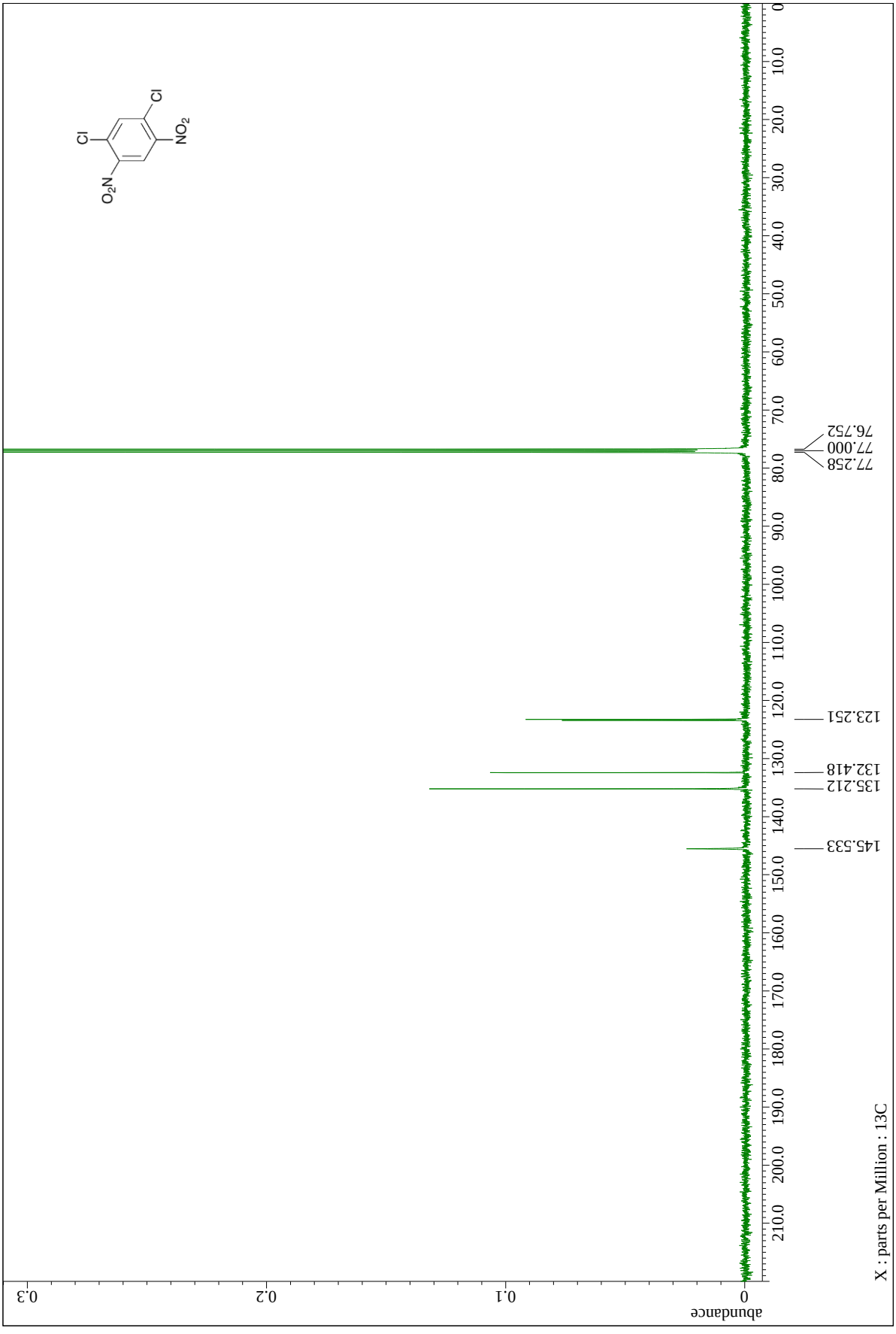
Dichloro dinitrobenzene **18**

^{1}H-NMR (500 MHz $CDCl_3$)



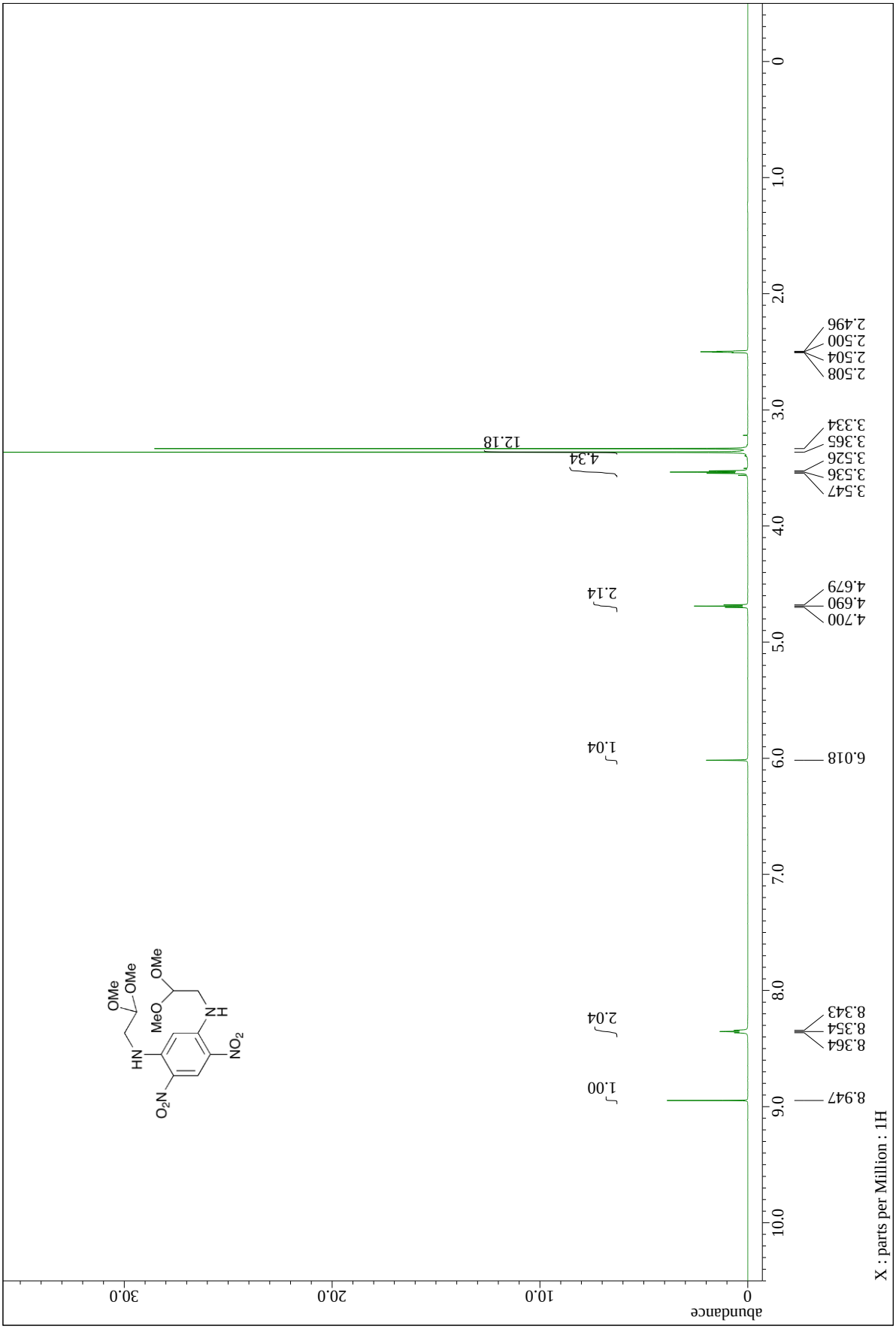
Dichloro dinitrobenzene **18**

^{13}C-NMR (125 MHz $CDCl_3$)



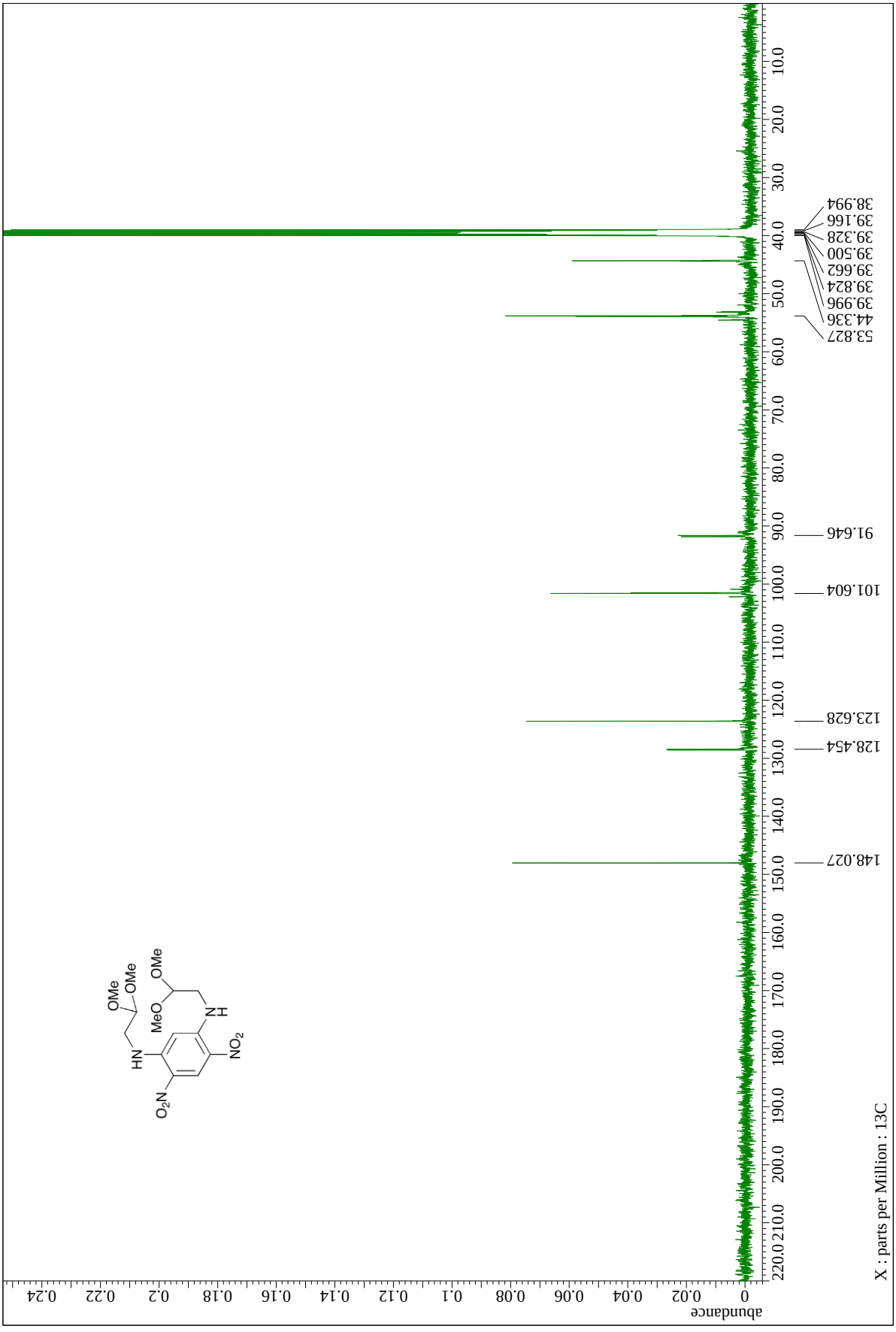
Tetra-aminosubstituted benzene **7**□

^{1}H-NMR (500 MHz DMSO-d6)□



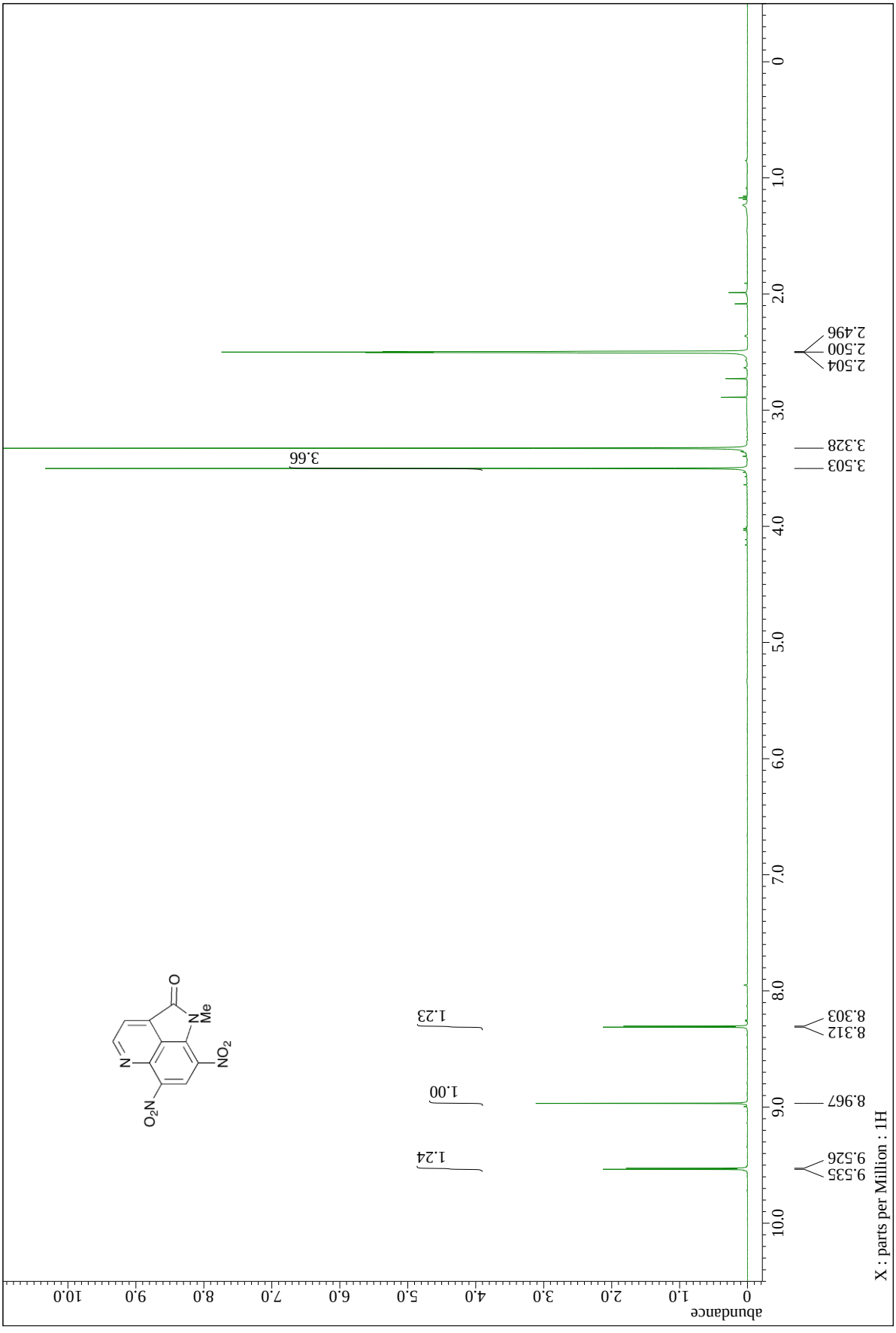
Tetra-aminosubstituted benzene **7**□

^{13}C-NMR (125 MHz DMSO-d6)□



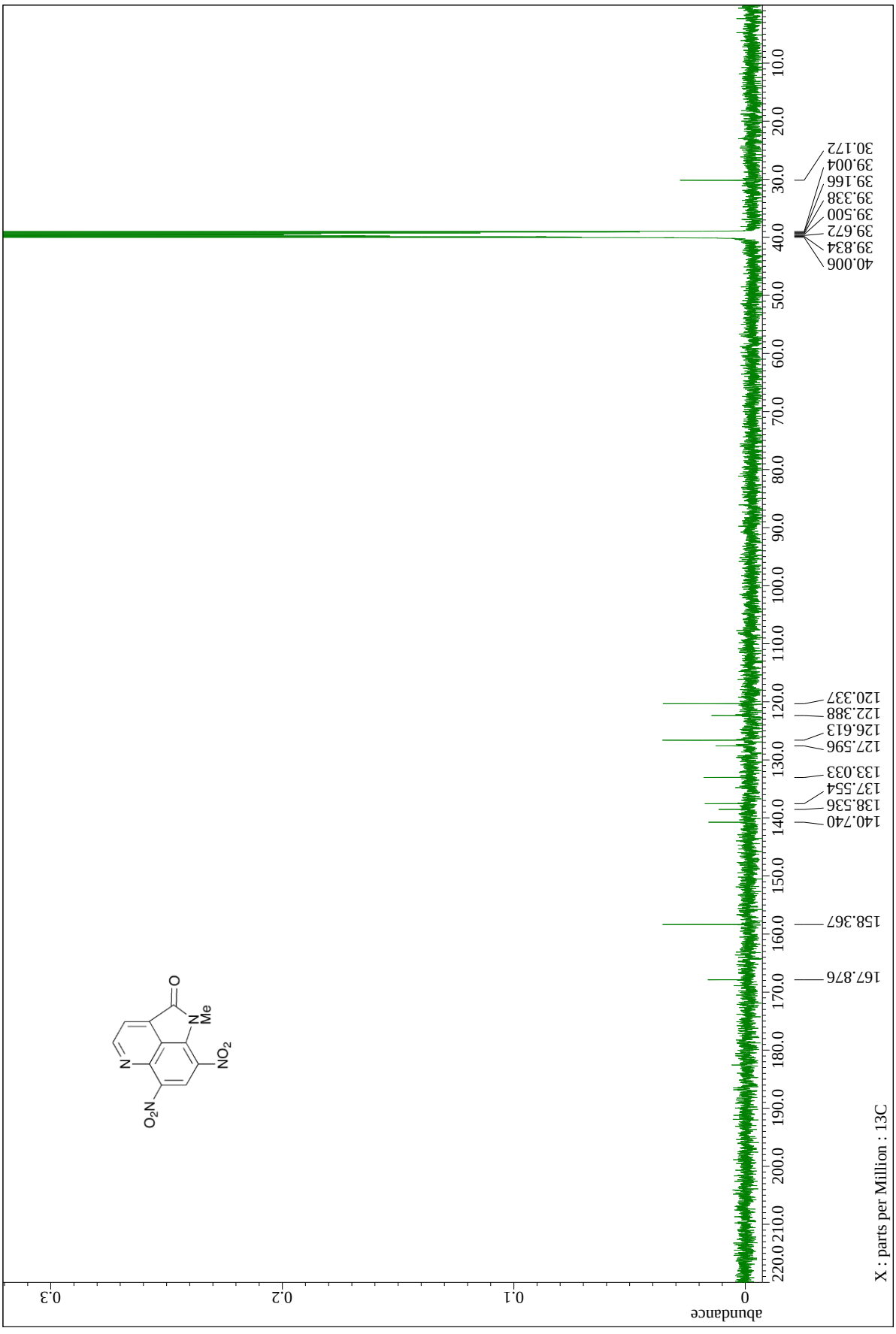
N-methyl oxyindole **11** □

^{1}H-NMR (500 MHz DMSO-d6)□



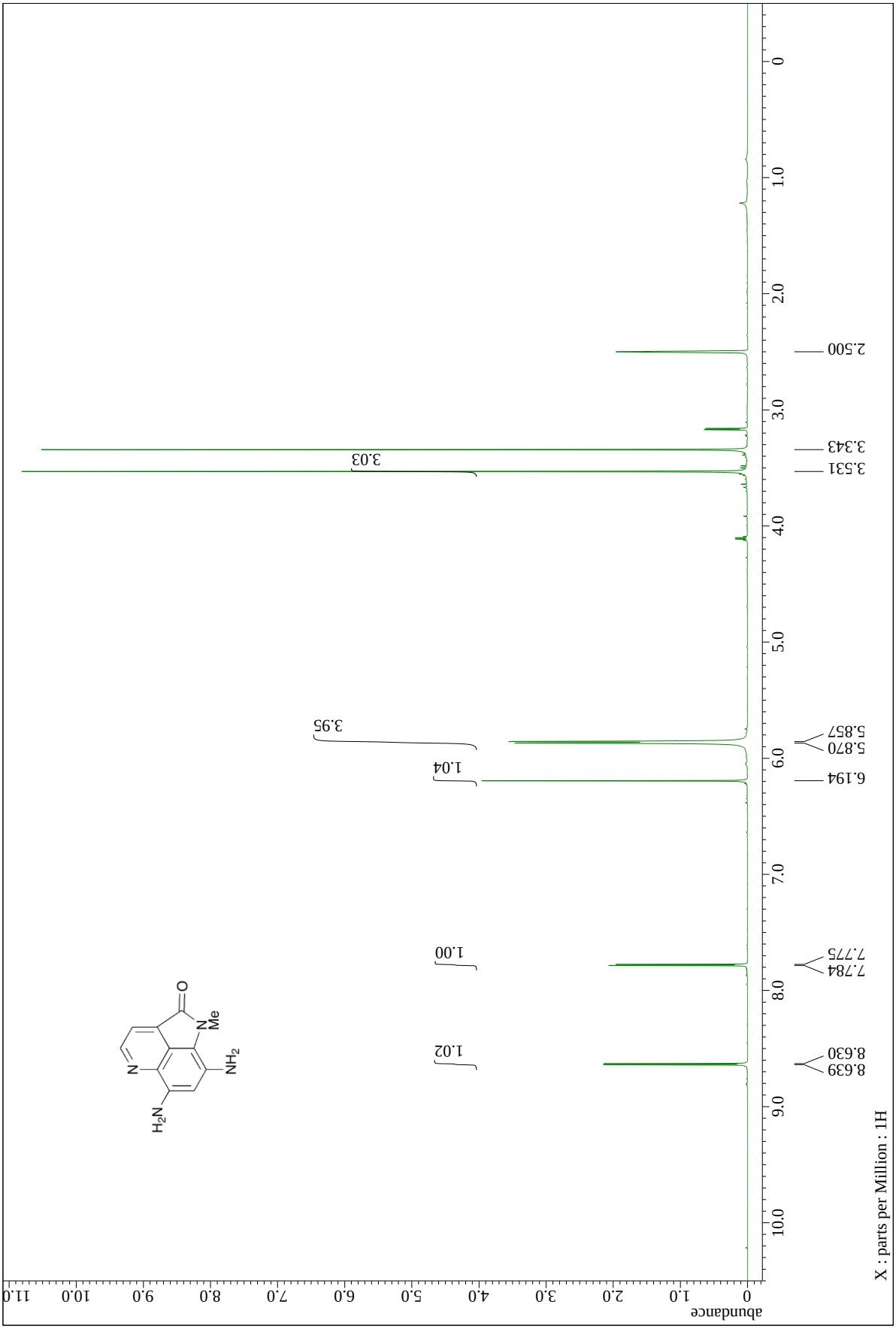
N-methyl oxyindole **11** □

^{13}C-NMR (125 MHz DMSO-d6)□



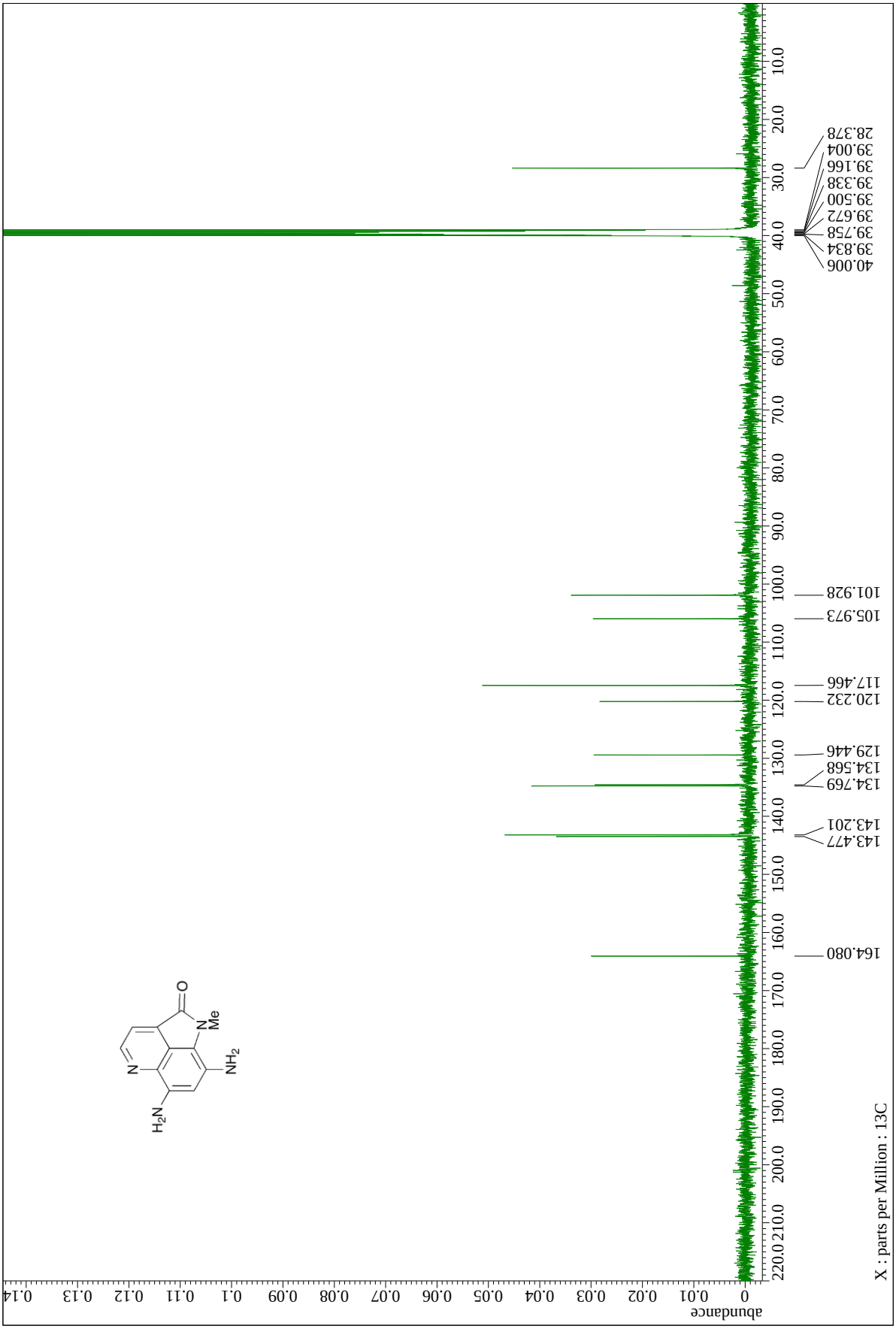
Aniline **12** □

^{1}H-NMR (500 MHz DMSO-d6)□



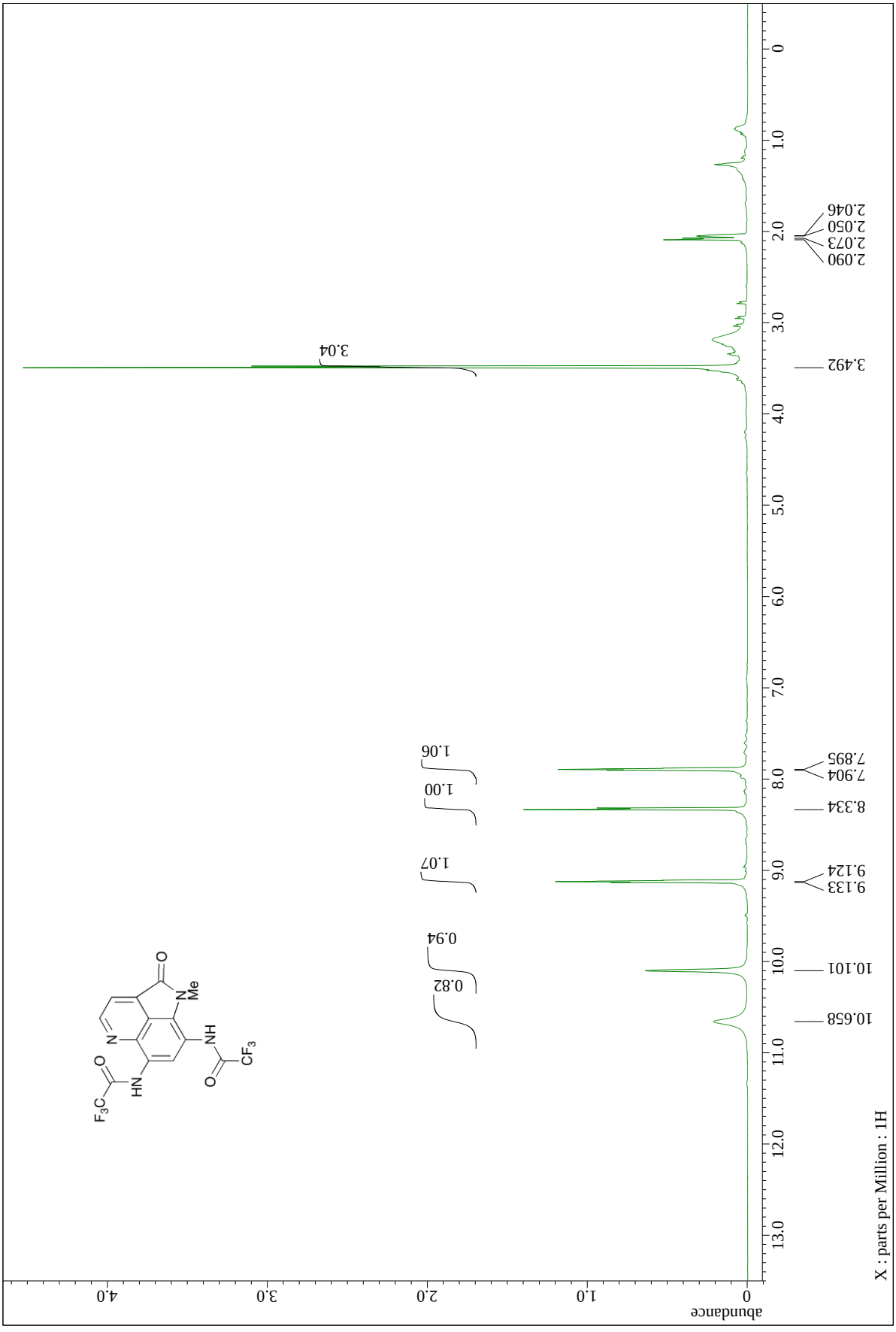
Aniline **12** □

^{13}C-NMR (125 MHz DMSO-d6)□



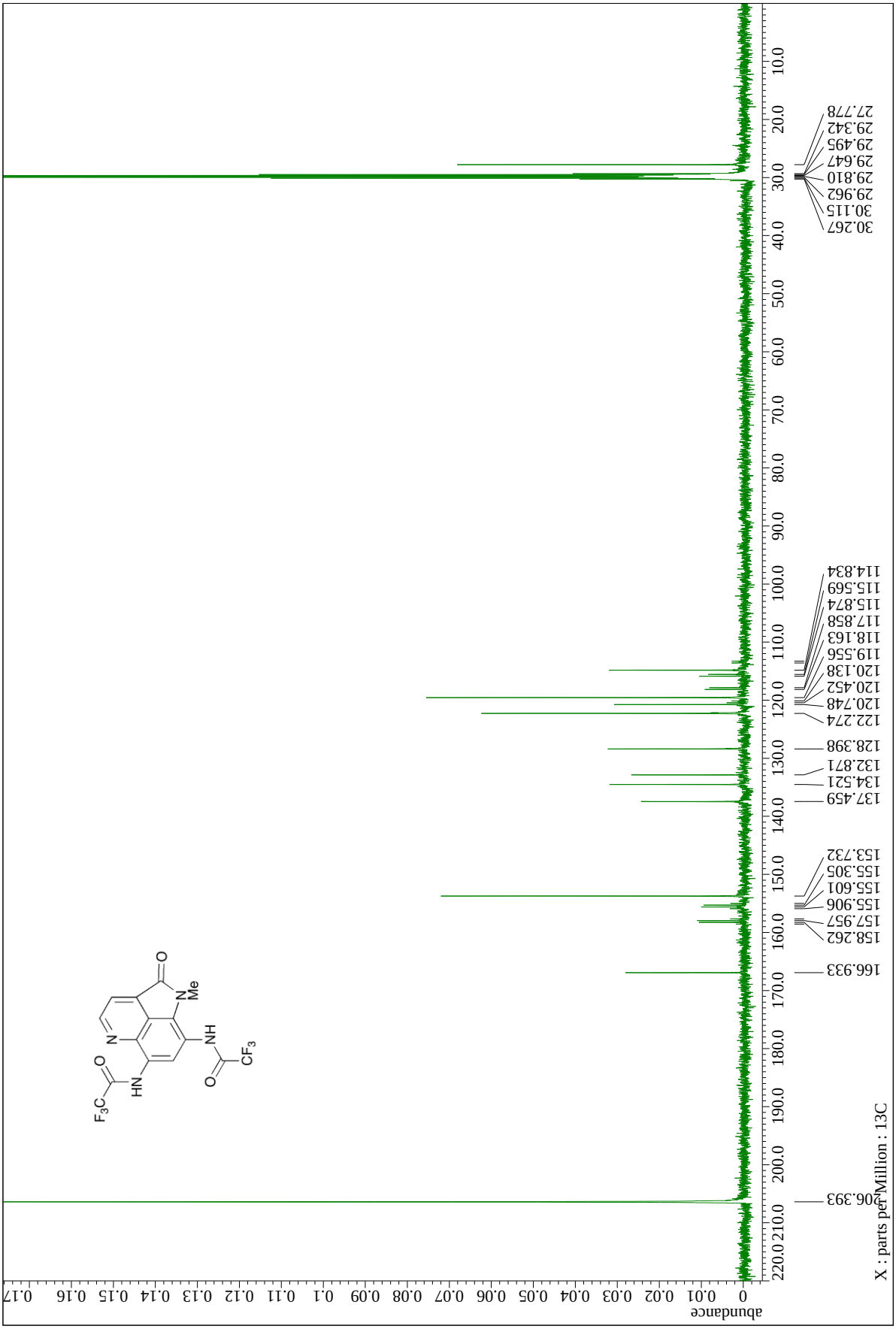
TFA amide **13** □

^{1}H-NMR (500 MHz acetone-d6)□



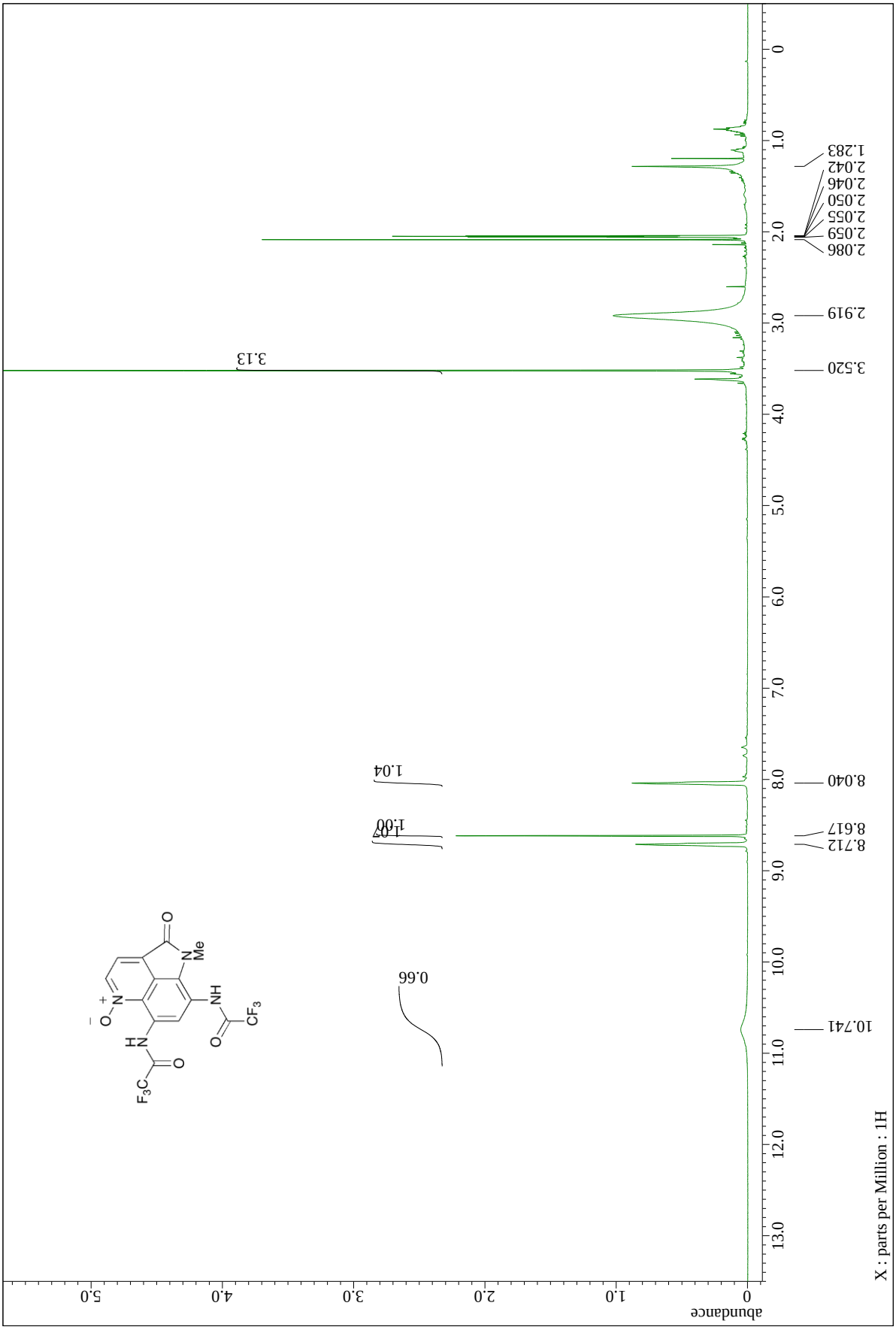
TFA amide **13** □

^{13}C-NMR (125 MHz acetone-d6)□

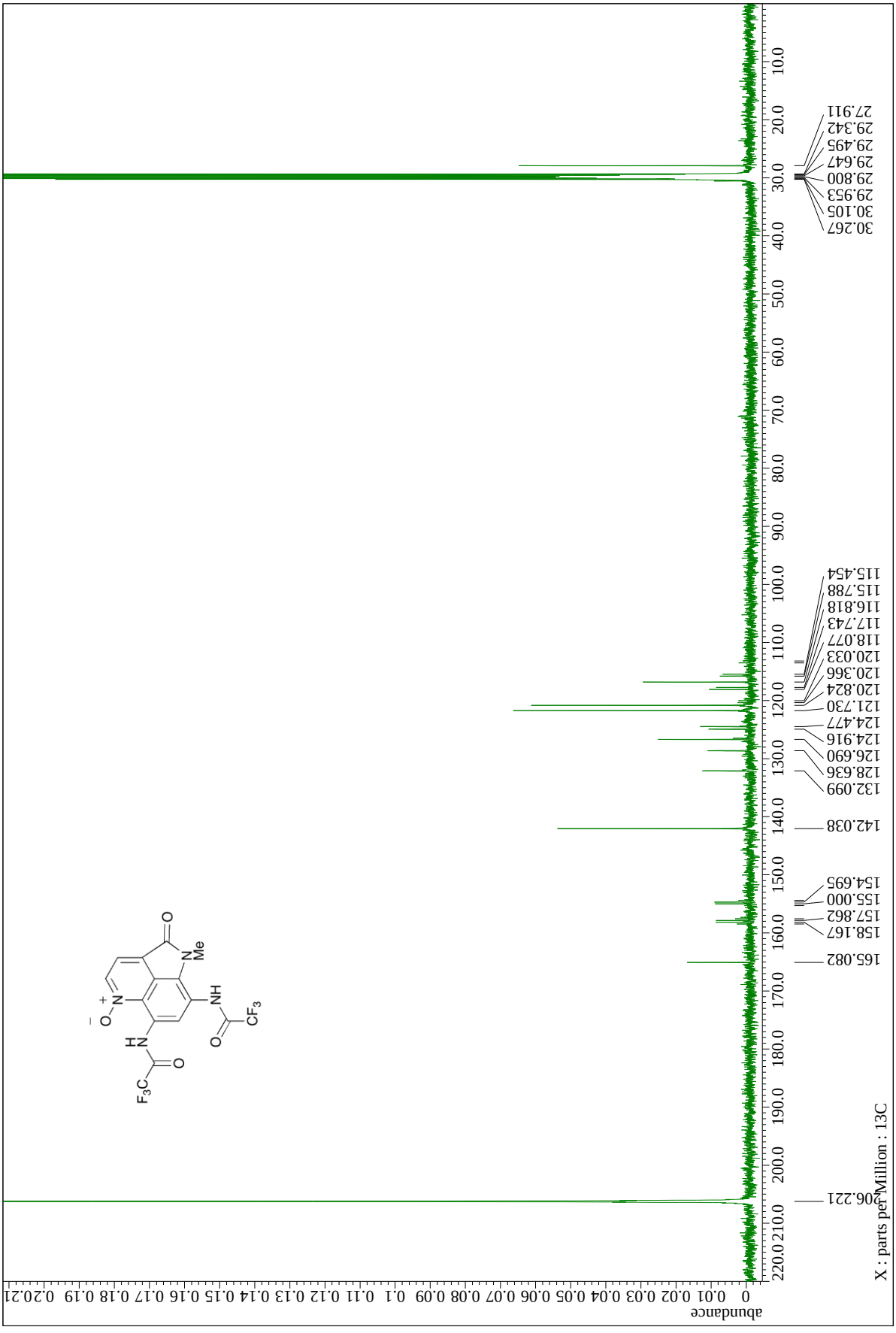


^{1}H-NMR (500 MHz acetone-d6)

N-oxide **14**

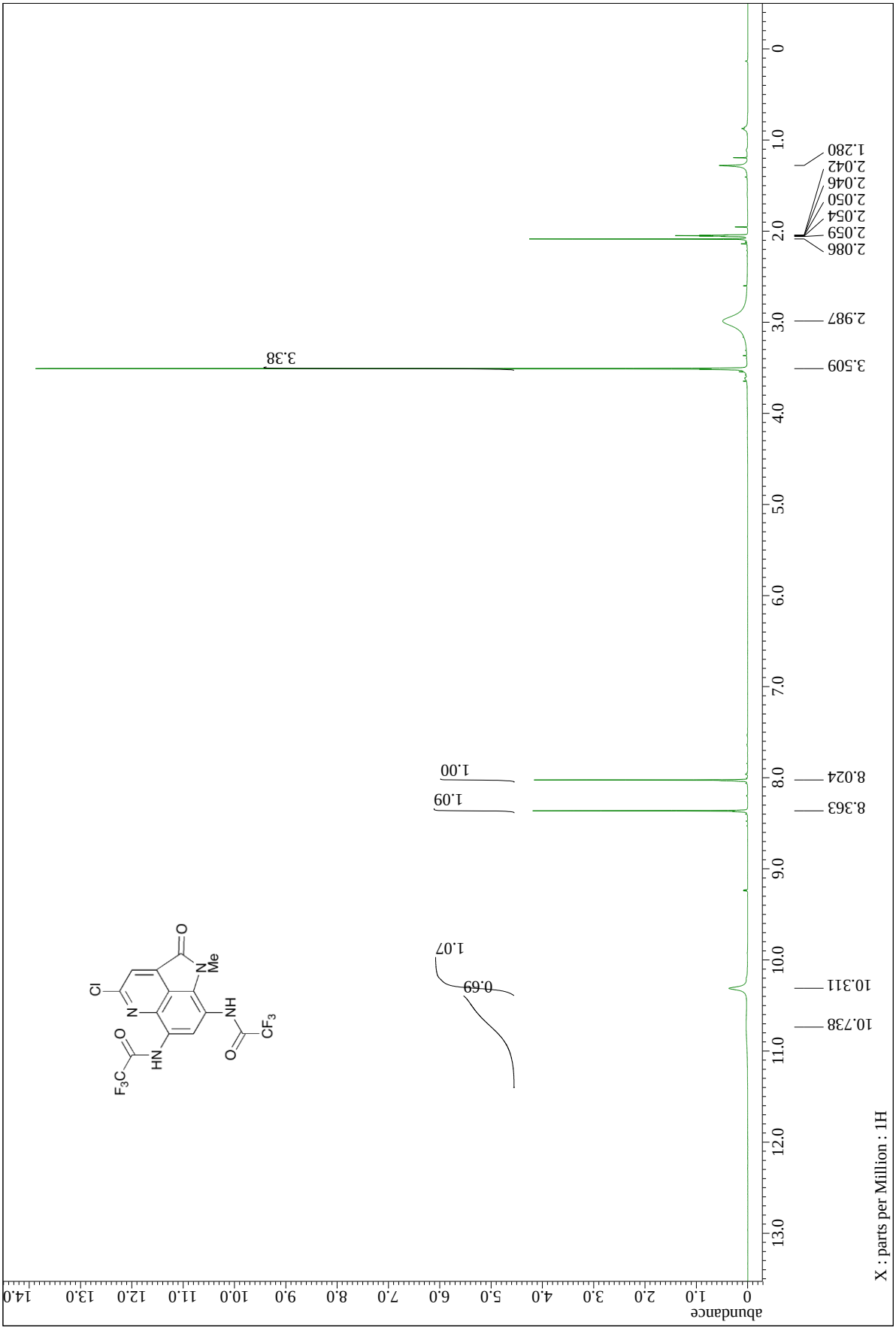


N-oxide **14** □ ^{13}C-NMR (125 MHz acetone-d6)□

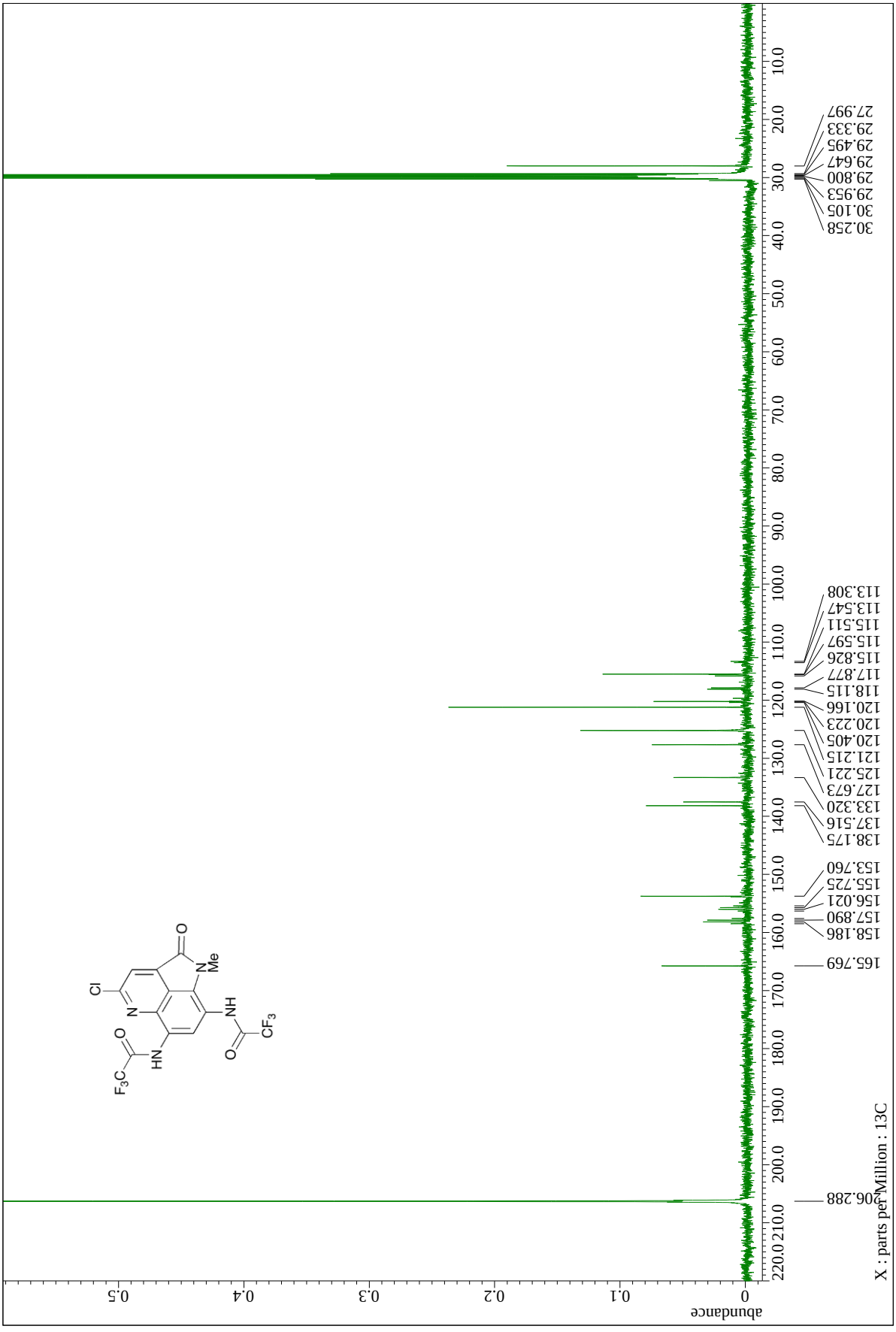


C4 chlorine compound **15** □

^{1}H-NMR (500 MHz acetone-d6)

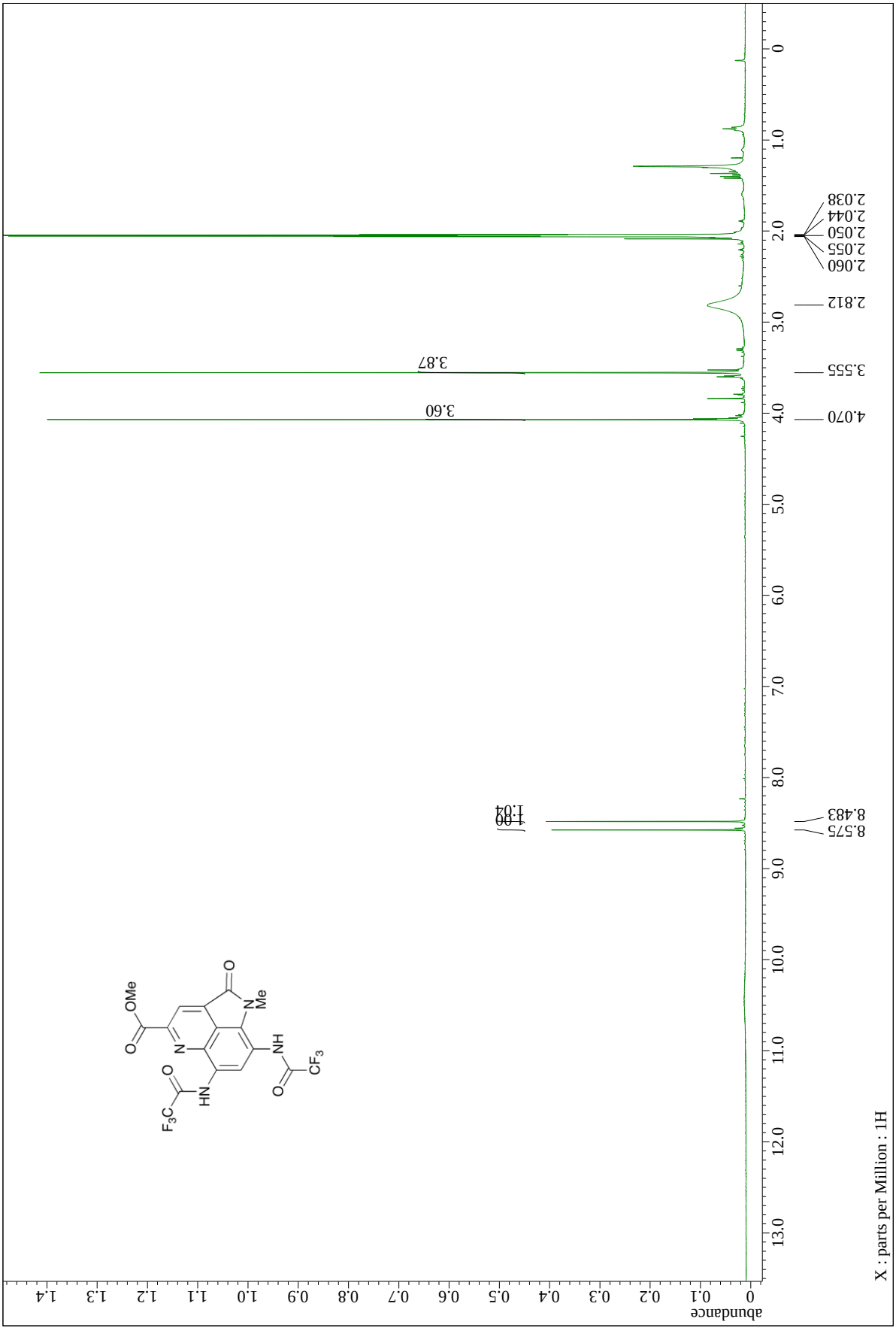


C4 chlorine compound **15** □ ^{13}C-NMR (125 MHz acetone-d6)□



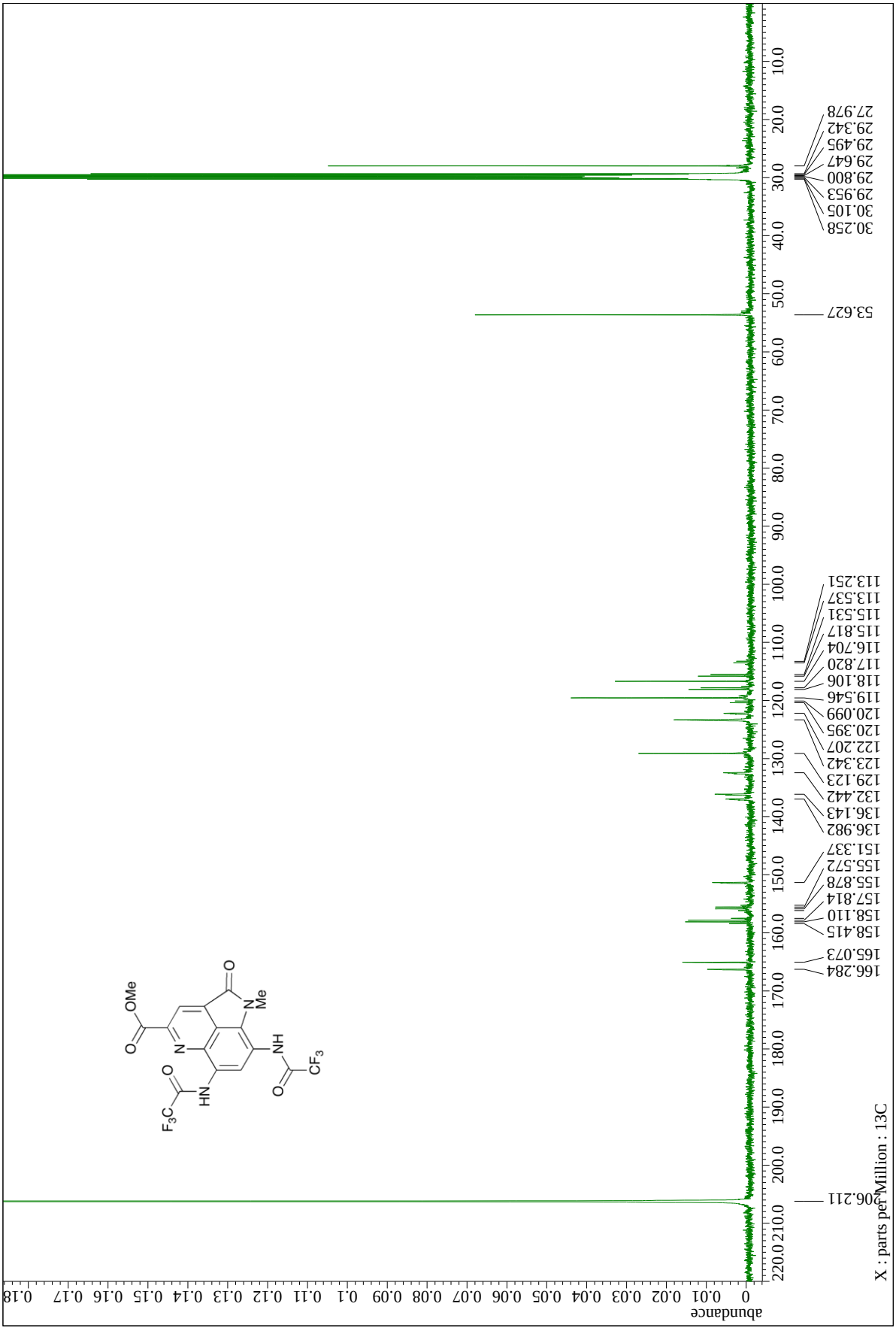
Methyl ester **16** □

^{1}H-NMR (400 MHz acetone-d6)□



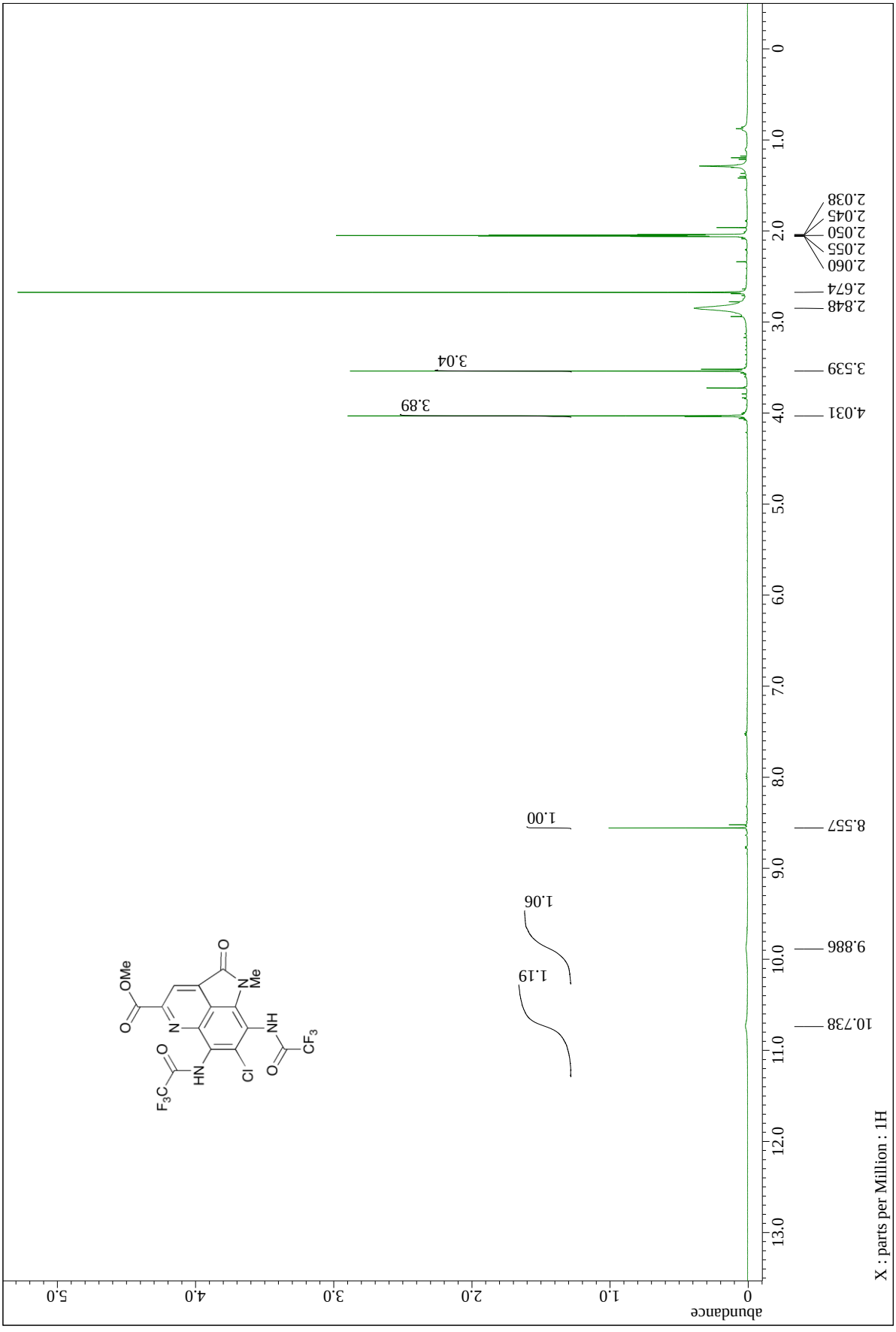
Methyl ester **16** □

^{13}C-NMR (125 MHz acetone-d6)□



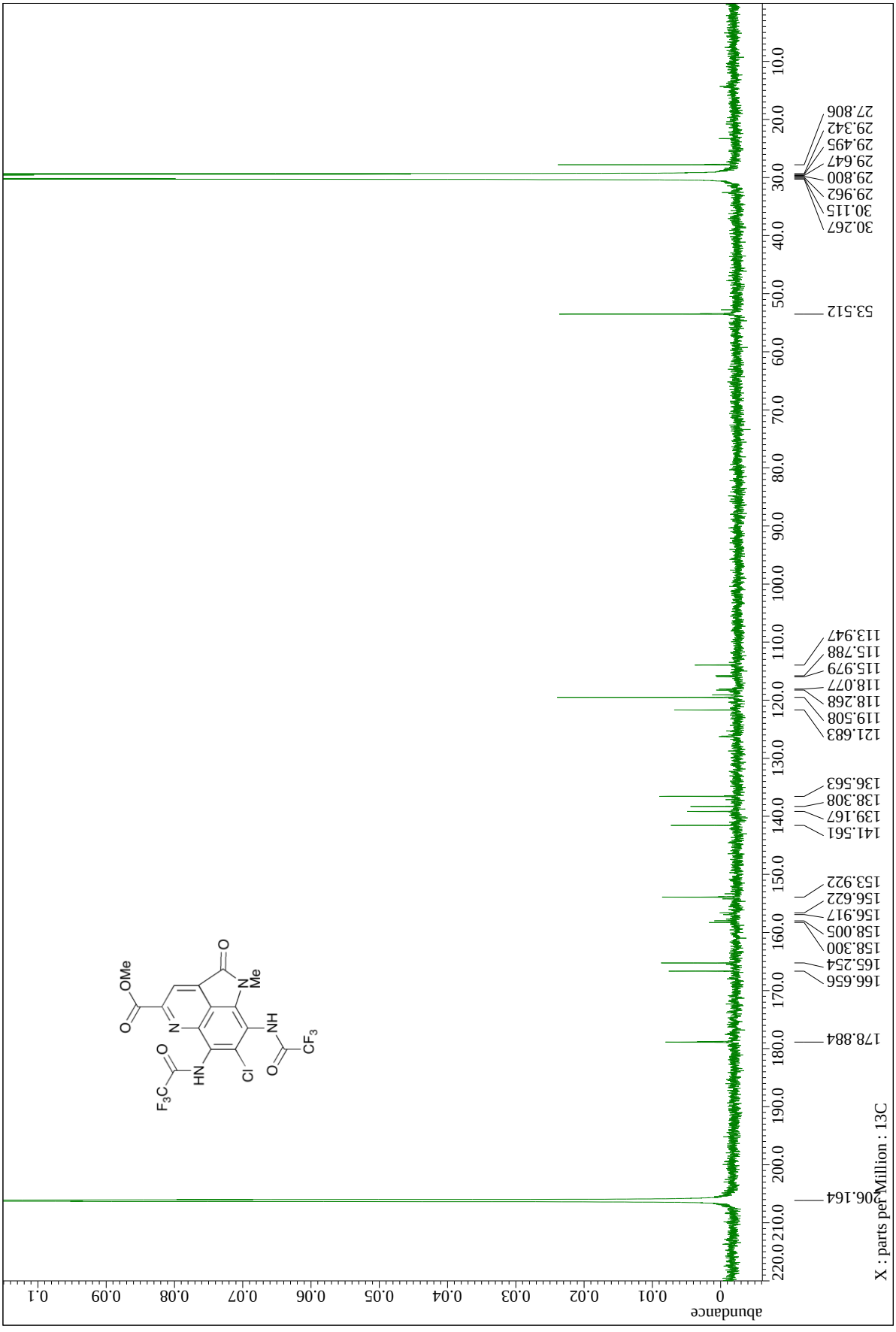
C7 chlorine compound **17** □

^{1}H-NMR (400 MHz acetone-d6)□



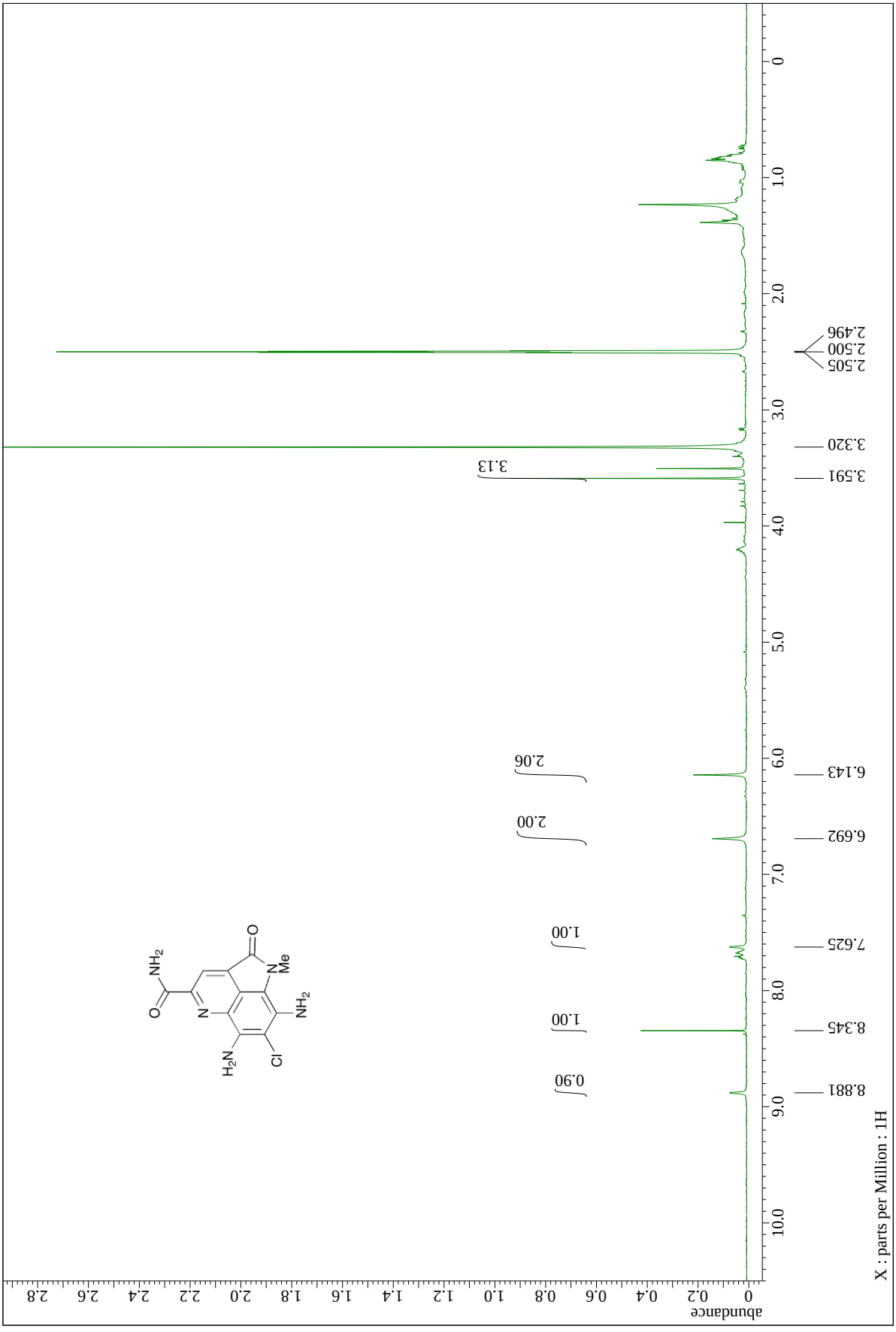
C7 chlorine compound **17** □

^{13}C-NMR (125 MHz acetone-d6)□



Ammosamide B (2) □

^{1}H-NMR (400 MHz DMSO-d6)□



Ammosamide B (2) □

^{13}C-NMR (100 MHz DMSO-d6)□