

SUPPORTING INFORMATION – PART 1

for

New Synthesis of Fluorinated Pyrazoles

Riccardo Surmont, Guido Verniest, and Norbert De Kimpe*

*Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering,**Ghent University, Coupure Links 653, 9000 Ghent, Belgium*

TABLE OF CONTENTS:

I. General methods	(S2)
II. Experimental procedures and spectroscopic data (¹ H NMR, ¹³ C NMR, ¹⁹ F NMR, IR, MS and/or elemental analysis) of compounds 2 , 3 , 7 , 9 , 10 , 12a-f , 14a-d , 16 , 17a , 18a-d .	
1. Synthesis of 5-aminopyrazole 2 and 3-aminopyrazole 3	(S2)
2. Synthesis of 3-amino-4-fluoro-5-phenyl-1 <i>H</i> -pyrazole 9 ..	(S3)
3. Synthesis of 4,4-difluoro-2,4-dihydro-3 <i>H</i> -pyrazol-3-ones 12a-f	(S3)
4. Synthesis of 4-fluoro-3-hydroxy-5-phenyl-1 <i>H</i> -pyrazole 10	(S5)
5. Synthesis of fluorinated β-ketonitriles 14a-d	(S6)
6. Synthesis of 4-substituted pyrazoles 18a-d	(S7)
7. Synthesis of intermediates 16 and 17a	(S8)
III. Reaction of 2-fluoro-2-methyl-3-oxo-3-phenylpropanenitrile 23 and 2,2-dichloro-3-oxo-3-phenylpropanenitrile 25 with hydrazine	(S9)
IV. Copies of NMR spectra of 2 , 3 , 7 , 9 , 10 , 12a-f , 14b-c	(S10)
[Copies of NMR spectra of 16 , 17a , 18a-d , 22-24 are included in Supp. Info PART 2]	
V. References	(S49)

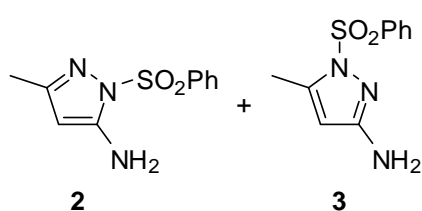
* Corresponding author. Tel.: +32 (0)9 264 59 51; fax: +32 (0)9 264 62 43; e-mail: norbert.dekimpe@UGent.be.

I. General methods

^1H NMR (300 MHz), ^{13}C NMR (75 MHz) and ^{19}F NMR (282 MHz) spectra were recorded using a FT 300 MHz NMR spectrometer. The compounds were diluted in CDCl_3 using tetramethylsilane (TMS, $\delta=0$ ppm) as internal reference for proton spectra. Carbon spectra were referenced on the solvent. ^{19}F NMR spectra were recorded using CDCl_3 as a lock solvent. Peak assignments were performed with the use of ^1H - ^{13}C HSQC 2D-NMR. IR spectra were obtained from a ATR infrared spectrometer. Mass spectra were recorded (70eV) using either GC-MS coupling or a direct inlet system. LC-MS data were obtained via an electrospray (ES, 4000V) mass spectrometer. Elemental analysis of selected new compounds was performed using a CHN-elemental analyser.

II. Experimental procedures and spectroscopic data (^1H NMR, ^{13}C NMR, ^{19}F NMR, IR, MS and/or elemental analysis) of compounds **2**, **3**, **7**, **9**, **10**, **12a-f**, **14a-d**, **16**, **17a**, **18a-d**.

1. Synthesis of 5-aminopyrazole **2**¹ and 3-aminopyrazole **3**



To a solution of 1.00 g (10.31 mmol, 1 equiv) of 3-amino-5-methyl-1*H*-pyrazole **1** in 50 mL of acetonitrile was added 3.25 g (10.31 mmol, 1 equiv) of NFSI and 4.27 g (30.93 mmol, 3 equiv) of K_2CO_3 and the mixture was stirred at room temperature for 1 hour. After addition of 2 mL of triethylamine, the mixture was filtered over Celite® and the filtrate was poured into 50 mL of water and 100 mL of EtOAc. The organic phase was separated and the aqueous phase was extracted twice with 50 mL of EtOAc. The combined organic phases were dried over MgSO_4 and after evaporation of the solvents in vacuo, the crude crystals were recrystallized in hexane and diethyl ether (1:1) to afford 2.20 g of a 9:1 mixture of 5-amino-3-methyl-1-phenylsulfonyl-1*H*-pyrazole **2** and 3-amino-5-methyl-1-phenylsulfonyl-1*H*-pyrazole **3** (9.28 mmol, 90% yield, ratio **2**:**3** 9:1). M.p. = 187.5°C (hexane/Et₂O 1:1). White crystals. ^1H NMR (CDCl_3): δ 2.09 (3H, s, CH_3 , **2**); 2.46 (3H, s, CH_3 , **3**); 3.90 (2H, s, NH_2 , **2**); 4.91 (2H, s, NH_2 , **3**); 5.20 (1H, s, CH, **2**); 5.58 (1H, s, CH, **3**); 7.52 (2H, t, $J = 7.5$ Hz, $2 \times \text{CH}_{\text{ar}}$, **2** and **3**); 7.63 (1H, t, $J = 7.5$ Hz, CH_{ar} , **2** and **3**); 7.91 (2H, d, $J = 7.5$ Hz, $2 \times \text{CH}_{\text{ar}}$, **3**); 7.98 (2H, d, $J = 7.5$ Hz, $2 \times \text{CH}_{\text{ar}}$, **2**). ^{13}C NMR (acetone- d_6): δ 13.3 (CH_3); 89.1 (CH); 127.5 ($2 \times \text{CH}_{\text{ar}}$); 129.4 ($2 \times \text{CH}_{\text{ar}}$); 134.3 (CH_{ar}); 138.3 (C_{ar}); 151.7 (NC_q); 155.1 (NC_qN). IR (ATR, cm^{-1}): ν 3470; 3289; 3222; 3179; 1628; 1585; 1497; 1445; 1361; 1333; 1197; 1171; 1124; 995; 794; 750; 742; 724; 678. MS (ES+) m/z (%): 238 ($\text{M}+\text{H}^+$, 100). Anal. Calcd for $\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}_2\text{S}$: C 50.62; H 4.67; N 17.71. Found: C 50.34; H 4.34; N 17.46. Spectral data (^1H NMR) of **2** were in accordance with those reported in the literature.¹

2. Synthesis of 3-amino-4-fluoro-5-phenyl-1H-pyrazole 9

2-Fluoro-3-oxo-3-phenylpropanenitrile 7.² Fluoroacetonitrile **4** (1.00 g, 16.94 mmol, 1 equiv) and Ph₂P(O)Cl **5** (4.01 g, 16.94 mmol, 1 equiv) were dissolved in 150 mL of THF in an inert atmosphere. At -78°C, 34 mL of LiHMDS (33.9 mmol, 1 M in THF, 2 equiv) was slowly added, leading to a yellow solution of phosphine oxide anion **6**. After stirring for 15 min at -78°C, 2.62 g (18.63 mmol, 1.1 equiv) of benzoyl chloride was added dropwise and the temperature was allowed to rise to room temperature. After 1 h, saturated brine (100 mL) was added to the reaction mixture, and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried with MgSO₄. After filtration and evaporation of the solvents in vacuo, the crude product was purified by flash chromatography (hexane/EtOAc 7:3, R_f = 0.30) to yield 0.90 g of 2-fluoro-3-oxo-3-phenylpropanenitrile **4** (5.52 mmol, 33% yield). Colourless oil. Flash chromatography (hexane/EtOAc 7:3, R_f = 0.30). ¹H NMR (CDCl₃): δ 6.16 (1H, d, J = 46.8 Hz, CH); 7.58 (2H, t, J = 7.7 Hz, 2 × CH_{ar}); 7.73 (1H, tt, J = 7.7 Hz, 1.1 Hz, CH_{ar}); 8.01 (2H, dd, J = 7.7 Hz, 1.1 Hz, 2 × CH_{ar}). ¹⁹F NMR (CDCl₃): δ -192.2 (1F, d, J = 46.8 Hz, CF). ¹³C NMR (CDCl₃): δ 79.5 (d, J = 196.1 Hz, CF); 112.2 (d, J = 30.0 Hz, CN); 129.2 (2 × CH_{ar}); 129.3 (2 × CH_{ar}); 131.5 (C_{ar}); 135.6 (CH_{ar}); 184.7 (d, J = 19.6 Hz, C=O). Spectral data (¹H NMR, ¹⁹F NMR) of **7** were in accordance with those reported in the literature.²

3-Amino-4-fluoro-5-phenyl-1H-pyrazole 9. In a 50 mL flask, 0.90 g (5.52 mmol, 1 equiv) of 2-fluoro-3-oxo-3-phenylpropanenitrile **7** was dissolved in 20 mL of isopropanol. To this solution, 0.22 g (80% in water, 5.52 mmol, 1 equiv) of hydrazine was added and the mixture was heated at reflux temperature during 2.5 hours. After completion of the reaction, the solvents were evaporated in vacuo and the crude oil was purified by flash chromatography (EtOAc, R_f = 0.33) yielding 0.70 g of 3-amino-4-fluoro-5-phenyl-1H-pyrazole **9** (3.97 mmol, 72% yield). M.p. = 96.8°C (hexane/Et₂O 1:1). Red crystals. ¹H NMR (CDCl₃): δ 7.36 (1H, t, J = 7.4 Hz, CH_{ar}); 7.44 (2H, t, J = 7.4 Hz, 2 × CH_{ar}); 7.60 (2H, d, J = 7.4 Hz, 2 × CH_{ar}); NH and NH₂ invisible. ¹⁹F NMR (CDCl₃): δ -186.0 (1F, s, CF). ¹³C NMR (CDCl₃): δ 125.2 and 125.3 (2 × CH_{ar}); 127.8 (d, J = 4.6 Hz, NC_q); 128.4 (CH_{ar}); 128.6 (C_{ar}); 129.0 (2 × CH_{ar}); 135.3 (d, J = 243.5 Hz, CF); 141.9 (d, J = 11.5 Hz, NC_qN). IR (ATR, cm⁻¹): ν 3404; 3381; 3368; 3170; 3111 (NH); 2951; 2923; 1662; 1600; 1550; 1515; 1445; 1386; 1327; 1286; 1243; 1098; 965; 912; 758; 689. MS (ES+) m/z (%): 178 (M+H⁺, 100). Anal. Calcd. for C₉H₈FN₃: C, 61.01; H, 4.55; N, 23.72. Found: C, 60.87; H, 4.61; N, 23.61.

3. Synthesis of 4,4-difluoro-2,4-dihydro-3H-pyrazol-3-ones 12a-f

4,4-Difluoro-5-phenyl-2,4-dihydro-3H-pyrazol-3-one 12a. In a 25 mL flask, 0.50 g (2.19 mmol, 1 equiv) of ethyl 2,2-difluoro-3-oxo-3-phenylpropanoate **11a**³ was dissolved in 20 mL of isopropanol. To this solution, 0.09 g (80% in water, 2.19 mmol, 1 equiv) of hydrazine was added and the mixture was heated at reflux temperature during 2 hours. After completion of the reaction the solvents were evaporated in vacuo and the crude oil was purified by flash chromatography (hexane/EtOAc 3:2, R_f = 0.49) yielding 0.22 g of 4,4-difluoro-5-phenyl-2,4-dihydro-3H-pyrazol-3-one **310a** (1.14 mmol, 52% yield). M.p. = 79°C (hexane/Et₂O 1:1).

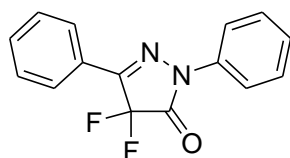
White crystals. ^1H NMR (CDCl_3): δ 7.45-7.57 (3H, m, $3 \times \text{CH}_{\text{ar}}$); 7.84-7.90 (2H, m, $2 \times \text{CH}_{\text{ar}}$); 8.88 (1H, s(broad), NH). ^{19}F NMR (CDCl_3): δ -118.7 (2F, s, CF_2). ^{13}C NMR (CDCl_3): δ 107.7 (t, $J = 259.0$ Hz, CF_2); 126.3 ($2 \times \text{CH}_{\text{ar}}$); 126.6 (C_{ar}); 129.1 ($2 \times \text{CH}_{\text{ar}}$); 131.9 (CH_{ar}); 150.3 (t, $J = 20.8$ Hz, $\text{C}=\text{N}$); 162.8 (t, $J = 28.8$ Hz, $\text{C}=\text{O}$). IR (ATR, cm^{-1}): ν 3229 (NH); 3139; 1744 ($\text{C}=\text{O}$); 1212; 1112; 746. MS (ES-) m/z (%): 195 ($\text{M}-\text{H}^+$, 100). Anal. Calcd. for $\text{C}_9\text{H}_6\text{F}_2\text{N}_2\text{O}$: C, 55.11; H, 3.08; N, 14.28. Found: C, 55.64; H, 2.77; N, 13.91.

4,4-Difluoro-5-phenyl-2-propyl-2,4-dihydro-3H-pyrazol-3-one 12b. In a dry flask of 25 mL, 0.06 g of NaH (60% in mineral oil, 1.41 mmol, 1.1 equiv) was suspended in 10 mL of dry DMF under N_2 atmosphere. After cooling to 0°C , 0.25 g (1.28 mmol, 1 equiv) of 4,4-difluoro-5-phenyl-2,4-dihydro-3H-pyrazol-3-one **12a** in 4 mL of dry DMF was added. The mixture was stirred for 45 min. at 0°C and 0.17 g (1.41 mmol, 1.1 equiv) of propyl bromide was added at 0°C . The reaction was monitored by ^{19}F NMR. After stirring 15 hours at 60°C , the reaction mixture was cooled and poured in 30 mL of water and extracted three times with 30 mL of diethyl ether. The combined organic phases were washed twice with 30 mL of saturated aq. NaCl and dried over MgSO_4 . After evaporation of the solvent in vacuo the crude oil was purified via flash chromatography (hexane/EtOAc 4:1, $R_f = 0.48$) to yield 0.26 g of 4,4-difluoro-5-phenyl-2-propyl-2,4-dihydro-3H-pyrazol-3-one **12b** (1.09 mmol, 87% yield) as a yellow oil. ^1H NMR (CDCl_3): δ 0.98 (3H, t, $J = 7.4$ Hz, CH_3); 1.81 (2H, sext, $J = 7.4$ Hz, CH_2); 3.74 (2H, t, $J = 7.4$ Hz, NCH_2); 7.43-7.56 (3H, m, $3 \times \text{CH}_{\text{ar}}$); 7.84-7.90 (2H, m, $2 \times \text{CH}_{\text{ar}}$). ^{19}F NMR (CDCl_3): δ -118.1 (2F, s, CF_2). ^{13}C NMR (CDCl_3): δ 10.9 (CH_3); 21.0 (CH_2); 46.6 (NCH_2); 109.1 (t, $J = 258.5$ Hz, CF_2); 126.2 ($2 \times \text{CH}_{\text{ar}}$); 126.6 (C_{ar}); 129.0 ($2 \times \text{CH}_{\text{ar}}$); 131.6 (CH_{ar}); 148.9 (t, $J = 20.8$ Hz, $\text{C}=\text{N}$); 160.9 (t, $J = 29.4$ Hz, $\text{C}=\text{O}$). IR (ATR, cm^{-1}): ν 2968; 1747 ($\text{C}=\text{O}$); 1419; 1242; 1108; 744. MS (ES+) m/z (%): 256 ($\text{M}+\text{NH}_4^+$, 100). Anal. Calcd. for $\text{C}_{12}\text{H}_{12}\text{F}_2\text{N}_2\text{O}$: C, 60.50; H, 5.08; N, 11.76. Found: C, 63.01; H, 5.35; N, 12.16.

5-Ethyl-4,4-difluoro-2,4-dihydro-3H-pyrazol-3-one 12c. Compound **12c** was prepared starting from ethyl 2,2-difluoro-3-oxopentanoate **11b** using an analogous procedure as for the synthesis of compound **12a**. Flash chromatography (hexane/EtOAc 7:3, $R_f = 0.41$). Yield = 87%. Yellow oil. ^1H NMR (CDCl_3): δ 1.26 (3H, t, $J = 7.4$ Hz, CH_3); 2.55 (2H, tt, $J = 7.4$ Hz, 1.5 Hz, CH_2); 9.62 (1H, s(broad), NH). ^{19}F NMR (CDCl_3): δ -124.7 (2F, s, CF_2). ^{13}C NMR (CDCl_3): δ 8.7 (CH_3); 19.8 (CH_2); 107.3 (t, $J = 257.9$ Hz, CF_2); 155.9 (t, $J = 21.9$ Hz, $\text{C}=\text{N}$); 163.5 (t, $J = 28.8$ Hz, $\text{C}=\text{O}$). IR (ATR, cm^{-1}): ν 3292 (NH); 2987; 2948; 1753 ($\text{C}=\text{O}$); 1464; 1409; 1290; 1185; 1112; 1049; 995; 934; 793; 744; 715; 658. MS (ES-) m/z (%): 147 ($\text{M}-\text{H}^+$, 100).

4-Fluoro-4-methyl-5-phenyl-2,4-dihydro-3H-pyrazol-3-one 12d. Compound **12d** was prepared starting from ethyl 2-fluoro-2-methyl-3-oxo-3-phenylpropanoate **11c**⁴ using an analogous procedure as for the synthesis of compound **12a**. Yield = 72%. M.p. = 117°C (hexane/Et₂O 1:1). Yellow crystals. ^1H NMR (CDCl_3): δ 1.80 (3H, d, $J = 22.6$ Hz, CH_3); 7.46 (1H, d, $J = 1.7$ Hz, CH_{ar}); 7.48 (2H, d, $J = 2.2$ Hz, $2 \times \text{CH}_{\text{ar}}$); 7.82-7.87 (2H, m, $2 \times \text{CH}_{\text{ar}}$); 9.17 (1H, s(broad), NH). ^{19}F NMR (CDCl_3): δ -168.0 (1F, q, $J = 22.6$ Hz, CF). ^{13}C NMR (CDCl_3): δ 20.8 (d, $J = 26.5$ Hz, CH_3); 91.1 (d, $J = 195.0$ Hz, CF); 126.2 ($2 \times \text{CH}_{\text{ar}}$); 128.8 (C_{ar}); 128.9 ($2 \times \text{CH}_{\text{ar}}$); 130.8 (CH_{ar}); 156.3 (d, $J = 15.0$ Hz, $\text{C}=\text{N}$); 173.2 (d, $J = 20.8$ Hz, $\text{C}=\text{O}$). IR (ATR, cm^{-1}): ν 3203 (NH); 3125; 1725 ($\text{C}=\text{O}$); 1196; 1114; 738; 691. MS (ES-) m/z (%): 191 ($\text{M}-\text{H}^+$, 100).

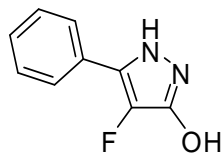
4,4-Difluoro-2-methyl-5-phenyl-2,4-dihydro-3H-pyrazol-3-one 12e. To a solution of 0.40 g (1.76 mmol, 1 equiv) of ethyl 2,2-difluoro-3-oxo-3-phenylpropanoate **11a** in 10 mL of isopropanol was added 0.08 g (1.76 mmol, 1 equiv) of methylhydrazine and the mixture was heated at reflux temperature for 3 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography (hexane/EtOAc 9:1, R_f = 0.23) to yield 0.30 g of 4,4-difluoro-2-methyl-5-phenyl-2,4-dihydro-3H-pyrazol-3-one **12eb** (1.43 mmol, 81% yield). M.p. = 98.7°C (hexane/Et₂O 1:1). Yellow crystals. ¹H NMR (CDCl₃): δ 3.44 (3H, s, NCH₃); 7.44-7.56 (3H, m, 3 × CH_{ar}); 7.86 (2H, d, J = 7.7 Hz, 2 × CH_{ar}). ¹⁹F NMR (CDCl₃): δ -118.2 (2F, s, CF₂). ¹³C NMR (CDCl₃): δ 32.0 (NCH₃); 108.7 (t, J = 258.5 Hz, CF₂); 126.2 (2 × CH_{ar}); 126.4 (C_{ar}); 129.1 (2 × CH_{ar}); 131.7 (CH_{ar}); 149.0 (t, J = 20.8 Hz, C=N); 160.9 (t, J = 28.8 Hz, C=O). IR (ATR, cm⁻¹): ν 3074; 3004; 2951; 1740 (C=O); 1455; 1358; 1246; 1229; 1133; 1107; 1038; 1025; 958; 868; 742; 691. MS (ES⁺) *m/z* (%): 211 (M+H⁺, 10); 228 (M+NH₄⁺, 60); 242 (100). Anal. Calcd. for C₁₀H₈F₂N₂O: C, 57.14; H, 3.84; N, 13.33. Found: C, 57.21; H, 3.58; N, 13.33.



4,4-Difluoro-2,5-diphenyl-2,4-dihydro-3H-pyrazol-3-one 12f. Compound **311c** was prepared analogously to compound **12e**, using phenylhydrazine and a catalytic amount of acetic acid. The reaction time was extended to 48 hours. Flash chromatography (hexane/EtOAc 7:3, R_f = 0.58). Yield = 74%. M.p. = 79.6°C (hexane/Et₂O 1:1). Yellow crystals. ¹H NMR (CDCl₃): δ 7.31 (1H, t, J = 7.5 Hz, CH_{ar}); 7.45-7.61 (5H, m, 5 × CH_{ar}); 7.93-8.02 (4H, m, 4 × CH_{ar}). ¹⁹F NMR (CDCl₃): δ -115.5 (2F, s, CF₂). ¹³C NMR (CDCl₃): δ 109.0 (t, J = 258.5 Hz, CF₂); 118.6 (2 × CH_{ar}); 126.2 (C_{ar}); 126.3 (CH_{ar}); 126.6 (2 × CH_{ar}); 129.1 (2 × CH_{ar}); 129.2 (2 × CH_{ar}); 132.2 (CH_{ar}); 136.6 (C_{ar}); 149.6 (t, J = 21.3 Hz, C=N); 159.1 (t, J = 29.4 Hz, C=O). IR (ATR, cm⁻¹): ν 3058; 2923; 2851; 1765 (C=O); 1599 (C=N); 1506; 1446; 1372; 1337; 1310; 1283; 1250; 1120; 1106; 1016; 951; 752; 693. MS (ES⁺) *m/z* (%): 242 (100); 273 (M+H⁺); 290 (M+NH₄⁺, 100). Anal. Calcd. for C₁₅H₁₀F₂N₂O: C, 66.17; H, 3.70; N, 10.29. Found: C, 66.13; H, 3.53; N, 10.26.

4. Synthesis of 4-fluoro-3-hydroxy-5-phenyl-1H-pyrazole 10⁵

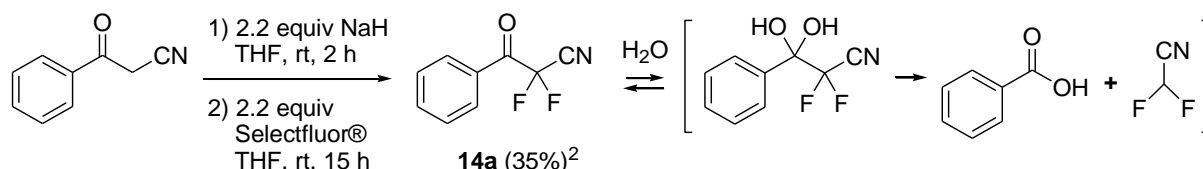
Method A: In a 25 mL flask, 0.46 g (2.19 mmol, 1 equiv) of 2-fluoro-3-oxo-3-phenylpropanoate **8**³ was dissolved in 20 mL of isopropanol. To this solution, 0.09 g (80% in water, 2.19 mmol, 1 equiv) of hydrazine was added and the mixture was heated at reflux temperature during 3 hours. After completion of the reaction the solvents were evaporated in vacuo affording 0.32 g of 4-fluoro-3-hydroxy-5-phenyl-1H-pyrazole **10** (1.82 mmol, 83% yield) as red crystals. M.p. = 218°C (Et₂O). Red crystals. ¹H NMR (CD₃OD): δ 7.27 (1H, t, J = 7.5 Hz, CH_{ar}); 7.39 (2H, t, J = 7.5 Hz, 2 × CH_{ar}); 7.67 (1H, d, J = 7.5 Hz, 2 × CH_{ar}); NH and OH invisible. ¹⁹F NMR (CD₃OD): δ -190.5 (1F, s, CF). ¹³C NMR (CD₃OD): δ 125.1 (2 × CH_{ar}); 128.2 (CH_{ar}); 128.6 (2 × CH_{ar}); 129.5 (d, J = 16.2 Hz, NC_q); 130.3 (C_{ar}); 132.7 (d, J = 240.0 Hz, CF); 149.2 (d, J = 12.7 Hz, NC_qO). IR (ATR, cm⁻¹): ν 3062; 2624; 1616; 1591; 1557; 1527; 1503; 1255; 1154; 1073; 1032; 936; 842; 787; 755; 717; 690; 664. MS (ES⁺) *m/z* (%): 179 (M+H⁺, 100). Spectral data (¹⁹F NMR) of **10** were in accordance with those reported in the literature.⁵



Method B: To a solution of 1.00 g (5.10 mmol, 1 equiv) of 4,4-difluoro-5-phenyl-2,4-dihydro-3H-pyrazol-3-one **12a** in 20 mL of EtOAc was added 0.10 g of Pd/C (10 wt%) and the mixture was stirred at room temperature under H₂ at 5 bar for 24 hours. The mixture was filtered through Celite® and the solvent was evaporated to afford 0.36 g (2.04 mmol, 40% yield) of 4-fluoro-3-hydroxy-5-phenyl-1H-pyrazole **10** as red crystals after recrystallization from Et₂O.

5. Synthesis of fluorinated β -ketonitriles **14a-d**

Difluorinated β -ketonitriles **14** were synthesized via difluorination of the corresponding β -ketonitriles using 2.2 equiv of sodium hydride and 2.2 equiv of Selectfluor® in acetonitrile at room temperature during 15 hours according to literature procedures.^{2b} However, after aqueous workup, a 1:1 mixture of difluorinated benzoylacetone and benzoic acid was obtained. The formation of benzoic acid can be explained by a haloform-type reaction of the difluorinated β -ketonitrile **14a** with water. Benzoic acid was removed by washing the mixture with a saturated sodium bicarbonate solution. The labile 2,2-difluoro-3-oxopropanenitrile **14a** was isolated in 35% yield. During flash chromatography on silica gel, pure 2,2-difluoro-3-oxopropanenitrile **14a** was converted into a 3:1 mixture of the keto-form and the corresponding hydrate (determined by ¹⁹F NMR). The ¹³C NMR spectral data (CDCl₃) of the hydrate showed a typical signal of the hydrate at 94.6 ppm (t, J = 25.4 Hz, C(OH)₂) and the ¹⁹F NMR signal was shifted upfield compared to the keto form (-105.4 ppm (hydrate) vs. -91.9 ppm (keto)). Spectroscopic data of **14a** were in agreement with literature data.^{2b} An analogous procedure was followed for the preparation of **14d**, which was unstable and used directly without purification in further reactions.



3-(4-Chlorophenyl)-2,2-difluoro-3-oxopropanenitrile 14b. Flash chromatography (hexane/EtOAc 87:13, R_f = 0.08). Yield = 33%. Yellow oil. ¹H NMR (CDCl₃): δ 7.57 (2H, d, J = 8.8 Hz, 2 \times CH_{ar}); 8.04 (2H, d, J = 8.8 Hz, 2 \times CH_{ar}). ¹⁹F NMR (CDCl₃): δ -91.9 (2F, s). ¹³C NMR (CDCl₃): δ 105.9 (t, J = 260.2 Hz, CF₂); 109.8 (t, J = 42.1 Hz, CN); 127.2 (C_{ar}); 129.8 (2 \times CH_{ar}); 131.5 (2 \times CH_{ar}); 143.2 (C_{ar}); 179.9 (t, J = 27.7 Hz, C=O). IR (NaCl, cm⁻¹): ν 2925; 2260 (CN); 1710 (C=O); 1590; 1492; 1405; 1178; 1095; 889. MS (ES-) *m/z* (%): 155/157 (M+OH-CHF₂CN, 100).

2,2-Difluoro-3-oxo-3-tolylpropanenitrile 14c. Flash chromatography (hexane/EtOAc 9:1, R_f = 0.17). Yield = 26%. Yellow oil. ¹H NMR (CDCl₃): δ 2.48 (3H, s, CH₃); 7.37 (2H, d, J = 8.5 Hz, 2 \times CH_{ar}); 7.99 (2H, d, J = 8.5 Hz, 2 \times CH_{ar}). ¹⁹F NMR (CDCl₃): δ -91.9 (2F, s). ¹³C NMR (CDCl₃): δ 22.0 (CH₃); 106.1 (t, J = 260.8 Hz, CF₂); 110.2 (t, J = 42.1 Hz, CN); 126.5 (C_{ar}); 130.0 (2 \times CH_{ar}); 130.3 (2 \times CH_{ar}); 147.9 (C_{ar}); 180.4 (t, J = 27.1 Hz, C=O). IR (NaCl, cm⁻¹): ν 2925; 2263 (CN); 1781; 1699 (C=O); 1606; 1300; 1172; 1095; 890; 749. MS (ES-) *m/z* (%): 135 (M+OH-CHF₂CN, 100).

6. Synthesis of 4-substituted pyrazoles 18a-d

4-Fluoro-5-phenyl-1H-pyrazole 18a.⁶ In a 50 mL flask, 1.00 g (5.52 mmol, 1 equiv) of 2,2-difluoro-3-oxo-3-phenylpropanenitrile **14a** was dissolved in 20 mL of isopropanol. To this solution, 0.14 g (80% in water, 5.52 mmol, 1 equiv) of hydrazine was added and the mixture was heated at reflux temperature during two hours. After completion of the reaction, the solvents were evaporated in vacuo and the crude oil was purified by flash chromatography (hexane/EtOAc 3:1, R_f = 0.19) yielding 0.40 g of 4-fluoro-5-phenyl-1H-pyrazole **18a** (2.49 mmol, 45% yield). M.p. = 96.8°C (hexane/Et₂O 1:1). White crystals. ¹H NMR (CDCl₃): δ 7.31-7.46 (3H, m, 3 × CH_{ar}); 7.48 (1H, d, J = 4.4 Hz, CH); 7.75 (2H, d, J = 7.4 Hz, 2 × CH_{ar}); 11.04 (1H, s(broad), NH). ¹⁹F NMR (CDCl₃): δ -177.0 (1F, s). ¹³C NMR (CDCl₃): δ 121.0 (d, J = 19.6 Hz, CH); 125.9 (d, J = 3.5 Hz, 2 × CH_{ar}); 128.3 (CH_{ar}); 128.9 (2 × CH_{ar}); 129.1 (d, J = 3.5 Hz, C_{ar}); 133.5 (d, J = 12.7 Hz, NC_q); 147.1 (d, J = 255.0 Hz, CF). IR (KBr, cm⁻¹): ν 3167; 3140; 2917; 1601; 1533; 1447; 1364; 1187; 1098; 941; 759; 690. MS (ES+) m/z (%): 163 (M+H⁺, 100). Anal. Calcd. for C₉H₇FN₂: C, 66.66; H, 4.35; N, 17.27. Found: C, 66.31; H, 4.31; N, 17.31. Spectral data (¹H NMR, ¹⁹F NMR, ¹³C NMR) of **18a** were in accordance with those reported in the literature.

5-(4-Chlorophenyl)-4-fluoro-1H-pyrazole 18b. Compound **18b** was prepared using an analogous procedure as for the synthesis of compound **18a**. Flash chromatography (hexane/EtOAc 3:1, R_f = 0.15). Yield = 42%. M.p. = 131.8°C (hexane/Et₂O 1:1). White crystals. ¹H NMR (CDCl₃): δ 7.40 (2H, d, J = 8.7 Hz, 2 × CH_{ar}); 7.51 (1H, d, J = 4.7 Hz, CH); 7.73 (2H, d, J = 8.7 Hz, 2 × CH_{ar}). ¹⁹F NMR (CDCl₃): δ -176.3 (1F, d, J = 4.7 Hz, CF). ¹³C NMR (CDCl₃): δ 119.6 (d, J = 24.2 Hz, CH); 127.1 (d, J = 4.6 Hz, 2 × CH_{ar}); 127.9 (d, J = 4.6 Hz, C_{ar}); 129.0 (2 × CH_{ar}); 133.8 (d, J = 11.5 Hz, NC_q); 134.2 (C_{ar}Cl); 147.2 (d, J = 249.2 Hz, CF). IR (KBr, cm⁻¹): ν 3167; 3133; 2929; 1592; 1533; 1408; 1186; 1094; 938; 832. MS (ES+) m/z (%): 197/199 (M+H⁺, 100). Anal. Calcd. for C₉H₆ClFN₂: C, 54.98; H, 3.08; N, 14.25. Found: C, 54.80; H, 3.32; N, 13.90.

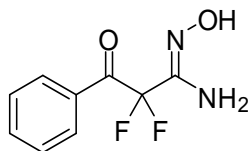
4-Fluoro-5-tolyl-1H-pyrazole 18c. Compound **18c** was prepared using an analogous procedure as for the synthesis of compound **18a**. Flash chromatography (hexane/EtOAc 3:1, R_f = 0.15). Yield = 48%. M.p. = 103.5°C (hexane/Et₂O 1:1). White crystals. ¹H NMR (CDCl₃): δ 2.37 (3H, s, CH₃); 7.21 (2H, d, J = 8.0 Hz, 2 × CH_{ar}); 7.44 (1H, d, J = 4.4 Hz, CH); 7.61 (2H, d, J = 8.0 Hz, 2 × CH_{ar}); 11.16 (1H, s(broad), NH). ¹⁹F NMR (CDCl₃): δ -177.6 (1F, d, J = 4.4 Hz, CF). ¹³C NMR (CDCl₃): δ 21.3 (CH₃); 121.5 (d, J = 21.9 Hz, CH); 125.8 (d, J = 3.5 Hz, 2 × CH_{ar}); 126.1 (d, J = 3.5 Hz, C_{ar}); 129.5 (2 × CH_{ar}); 133.0 (d, J = 13.9 Hz, NC_q); 138.2 (C_{ar}Me); 146.9 (d, J = 246.9 Hz, CF). IR (KBr, cm⁻¹): ν 3166; 2930; 1591; 1529; 1362; 1182; 1097; 937; 820. MS (ES+) m/z (%): 176 (M+H⁺, 100). Anal. Calcd. for C₁₀H₉FN₂: C, 68.17; H, 5.15; N, 15.90. Found: C, 68.26; H, 4.96; N, 15.74.

5-tert-Butyl-4-fluoro-1H-pyrazole 18d. Compound **18d** was prepared using an analogous procedure as for the synthesis of compound **18a**. Flash chromatography (hexane/EtOAc 3:1, R_f = 0.12). Yield = 24%. Orange oil. ¹H NMR (CDCl₃): δ 1.37 (9H, d, J = 0.8 Hz, 3 × CH₃); 7.34 (1H, d, J = 4.4 Hz, CH). ¹⁹F NMR (CDCl₃): δ -177.4 (1F, d, J = 4.4 Hz, CF). ¹³C NMR (CDCl₃): δ 29.0 (3 × CH₃); 31.3 (d, J = 3.4 Hz, C(CH₃)₃); 122.7 (d, J = 20.4 Hz, CH); 139.8 (d, J = 16.2 Hz, NC_q); 146.5

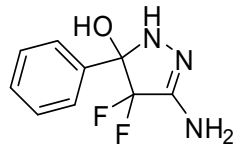
(d, $J = 242.5$ Hz, CF). IR (NaCl, cm^{-1}): ν 3157; 3090; 2968; 1594; 1523; 1462; 1363; 1301; 1109; 1094; 945; 835; 684. MS (ES+) m/z (%): 143 ($\text{M}+\text{H}^+$, 100).

7. Synthesis of intermediates 16 and 17a

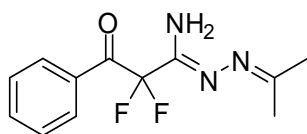
2,2-Difluoro- N' -hydroxy-3-oxo-3-phenylpropanehydroxamic amide 16. To a solution of 0.50 g (2.76 mmol, 1 equiv) of 2,2-difluoro-3-oxo-3-phenylpropanenitrile **14a** in 15 mL of isopropanol was added 166 mg (2.76 mmol, 1 equiv) of NH_2OH (50% in H_2O) and the mixture was stirred at reflux temperature during 15 hours. After evaporation of the solvent, the crude material was purified by flash chromatography (hexane/EtOAc 7:3, $R_f = 0.20$) to yield 0.47 g of 2,2-difluoro- N' -hydroxy-3-oxo-3-phenylpropane hydroxamic amide **16** (2.21 mmol, 80% yield). M.p. = 114.6°C (Et_2O). Yellow crystals. ^1H NMR (acetone- d_6): δ 5.96 (2H, s(broad), NH_2); 7.54 (2H, t, $J = 7.7$ Hz, $2 \times \text{CH}_{\text{ar}}$); 7.68 (1H, t, $J = 7.7$ Hz, CH_{ar}); 7.97 (2H, d, $J = 7.7$ Hz, $2 \times \text{CH}_{\text{ar}}$); 9.49 (1H, s, OH). ^{19}F NMR (acetone- d_6): δ -104.4 (2F, s, CF_2). ^{13}C NMR (acetone- d_6): δ 113.1 (t, $J = 249.8$ Hz, CF_2); 128.2 (C_{ar}); 128.7 ($2 \times \text{CH}_{\text{ar}}$); 130.0 ($2 \times \text{CH}_{\text{ar}}$); 134.2 (CH_{ar}); 147.6 (t, $J = 28.8$ Hz, $\text{NC}=\text{N}$); 186.1 (t, $J = 26.5$ Hz, $\text{C}=\text{O}$). IR (ATR, cm^{-1}): ν 3480; 3386; 3267; 3182; 2918; 1703; 1693; 1597; 1448; 1409; 1284; 1155; 1101; 946; 918; 800; 770; 715; 680; 668. MS (ES+) m/z (%): 215 ($\text{M}+\text{H}^+$, 100). MS (ES-) m/z (%): 193 ($\text{M}-\text{HF}-\text{H}^+$, 100).



3-Amino-4,4-difluoro-5-hydroxy-5-phenyl-4,5-dihydro-1H-pyrazole 17a. To a solution of 0.50 g (2.76 mmol, 1 equiv) of 2,2-difluoro-3-oxo-3-phenylpropanenitrile **14a** in 20 mL of isopropanol was added 138 mg (2.76 mmol, 1 equiv) of $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ and the mixture was stirred at room temperature for 1 hour. After evaporation of the solvent, the compound was crystallized in diethyl ether to yield 0.58 g of 3-amino-4,4-difluoro-5-hydroxy-5-phenyl-4,5-dihydro-1H-pyrazole **17a** (2.73 mmol, 99% yield) as white crystals. M.p. = 130.9°C (Et_2O). ^1H NMR (dms- d_6): δ 5.87 (2H, s(broad), NH_2); 6.00 (1H, s(broad), NH); 6.73 (1H, s(broad), OH); 7.33-7.40 (3H, m, $3 \times \text{CH}_{\text{ar}}$); 7.56-7.61 (2H, m, $2 \times \text{CH}_{\text{ar}}$). ^{19}F NMR (dms- d_6): δ -109.3 (1F, d, $J = 251.2$ Hz, CF_2); -127.9 (1F, d, $J = 251.2$ Hz, CF_2). ^{13}C NMR (dms- d_6): δ 90.3 (dd, $J = 31.2$ Hz, 19.6 Hz, NCO); 122.5 (dd, $J = 266.5$ Hz, 253.8 Hz, CF_2); 128.1 ($2 \times \text{CH}_{\text{ar}}$); 128.3 ($2 \times \text{CH}_{\text{ar}}$); 129.1 (CH_{ar}); 137.9 (C_{ar}); 148.7 (t, $J = 23.7$ Hz, $\text{NC}=\text{N}$). IR (ATR, cm^{-1}): ν 3452; 3321; 3244; 3196; 3146; 2774; 1664; 1461; 1384; 1271; 1220; 1171; 1106; 1014; 911; 889; 774; 743; 702. MS (ES+) m/z (%): 196 ($\text{M}-\text{OH}^-$, 100); 214 ($\text{M}+\text{H}^+$, 92). It should be noted that 5-hydroxypyrazole **17a** reacted rapidly with acetone and underwent subsequent ring opening toward N' -(isopropylidene)hydrazonamide **22**, which represents in fact the trapped hydrazone intermediate.

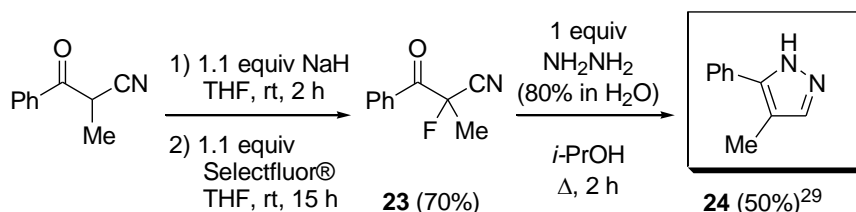


2,2-Difluoro-3-oxo-3-phenyl- N' -(isopropylidene)propanehydrazonamide 22. A solution of 0.58 g (2.73 mmol, 1 equiv) of 3-amino-4,4-difluoro-5-hydroxy-5-phenyl-4,5-dihydro-1H-pyrazole **17a** in acetone was stirred for 15 hours at room temperature. After evaporation of the solvent the compound was purified by flash chromatography (hexane/EtOAc 3:7, $R_f = 0.50$) to afford 0.51 g of pure 2,2-difluoro-3-oxo-3-phenyl- N' -(isopropylidene)propanehydrazonamide **22** (2.02 mmol, 74% yield) as a yellow oil. ^1H NMR (CDCl_3): δ 1.62 (3H, s, CH_3); 1.91 (3H, s, CH_3); 5.73 (2H, s(broad), NH_2); 7.42 (2H, t, $J = 7.2$ Hz, $2 \times \text{CH}_{\text{ar}}$); 7.55 (1H, t, $J = 7.2$ Hz, CH_{ar}); 8.05 (2H, d, $J = 7.2$ Hz, $2 \times$

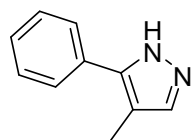


CH_{ar}). ¹⁹F NMR (CDCl₃): δ -105.3 (2F, s, CF₂). ¹³C NMR (CDCl₃): δ 17.8 (CH₃); 24.5 (CH₃); 112.2 (t, J = 253.8 Hz, CF₂); 128.1 (2 × CH_{ar}); 129.8 (2 × CH_{ar}); 132.2 (C_{ar}); 133.7 (CH_{ar}); 149.6 (t, J = 28.3 Hz, NC=N); 166.3 (C=N); 186.4 (t, J = 26.5 Hz, C=O). IR (ATR, cm⁻¹): ν 3470; 3361; 2920; 1709; 1649; 1598; 1450; 1400; 1280; 1159; 1091; 917; 766; 710; 686; 671. MS (ES+) *m/z* (%): 254 (M+H⁺, 100).

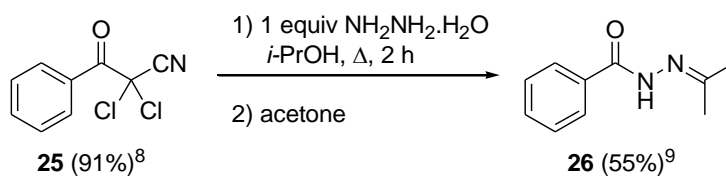
III. Reaction of 2-fluoro-2-methyl-3-oxo-3-phenylpropanenitrile **23** and 2,2-dichloro-3-oxo-3-phenylpropanenitrile **25** with hydrazine



2-Fluoro-2-methyl-3-oxo-3-phenylpropanenitrile 23. To a solution of 1.00 g (6.29 mmol, 1 equiv) of 2-methyl-3-oxo-3-phenylpropanenitrile^{2a} in 50 mL of acetonitrile under N₂ atmosphere was added 0.28 g (60% in mineral oil, 6.92 mmol, 1.1 equiv) of sodium hydride at 0°C and the mixture was stirred for two hours at room temperature. Then, 2.45 g (6.92 mmol, 1.1 equiv) of Selectfluor® was added and the mixture was stirred for 15 hours at room temperature. The reaction mixture was poured into 70 mL of water and extracted three times with 100 mL of EtOAc. After drying the organic phase over MgSO₄, the solvents were evaporated in vacuo and the crude oil was purified by flash chromatography (hexane/EtOAc 4:1, R_f = 0.45) yielding 0.78 g of 2-fluoro-2-methyl-3-oxo-3-phenylpropanenitrile **23** (4.40 mmol, 70% yield) as a colourless oil. ¹H NMR (CDCl₃): δ 2.08 (3H, d, J = 22.3 Hz, CH₃); 7.52-7.56 (2H, m, 2 × CH_{ar}); 7.67-7.71 (1H, m, CH_{ar}); 8.10-8.14 (2H, m, 2 × CH_{ar}). ¹⁹F NMR (CDCl₃): δ -146.3 (1F, q, J = 22.3 Hz, CF). ¹³C NMR (CDCl₃): δ 23.7 (d, J = 24.2 Hz, CH₃); 89.3 (d, J = 195.0 Hz, CF); 115.6 (d, J = 32.2 Hz, CN); 128.9 (2 × CH_{ar}); 130.0 (d, J = 4.6 Hz, 2 × CH_{ar}); 131.3 (d, J = 3.5 Hz, C_{ar}); 134.9 (CH_{ar}); 188.3 (d, J = 24.2 Hz, C=O). IR (ATR, cm⁻¹): ν 3064; 1699 (C=O); 1597; 1450; 1379; 1263; 1172; 979; 936; 836; 712; 686. MS (ES-) *m/z* (%): 121 (PhCOO⁻, 100). MS (ES+) *m/z* (%): 228 (100).

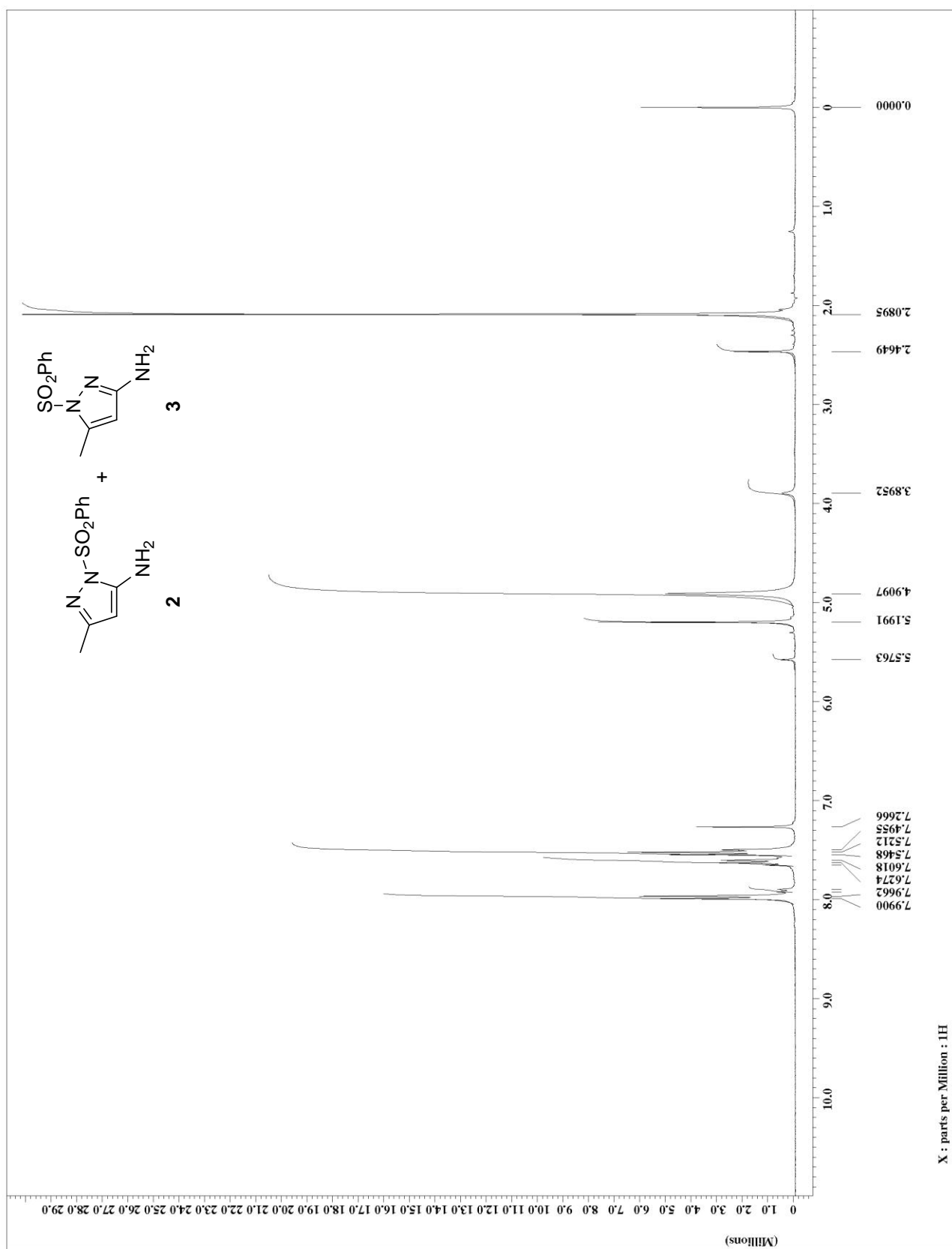


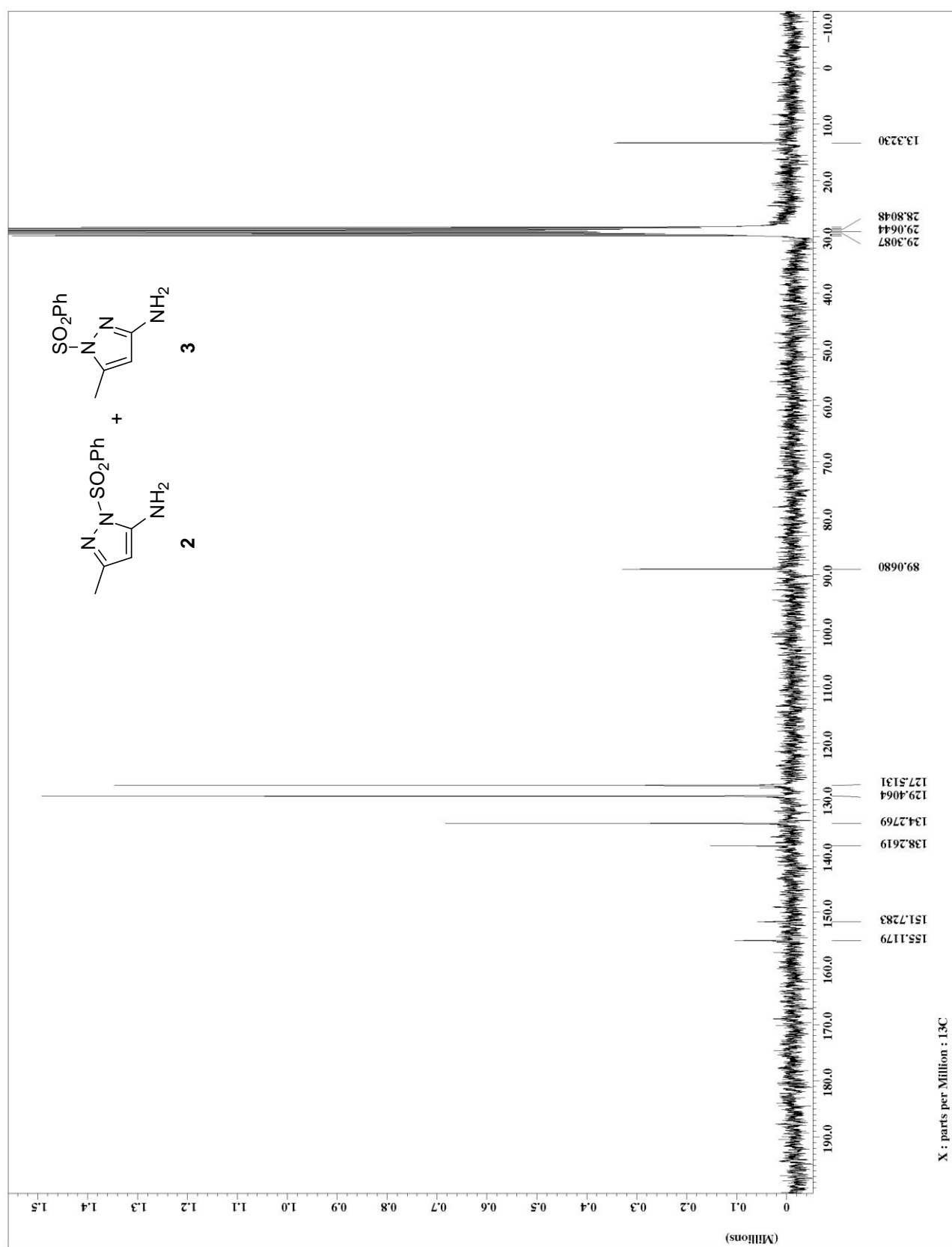
4-Methyl-5-phenyl-1H-pyrazole 24.⁷ Compound **24** was prepared using an analogous procedure as for the synthesis of compound **18a**. Flash chromatography (hexane/EtOAc 65:35, R_f = 0.22). Yield = 50%. M.p. = 118°C (hexane/Et₂O 1:1). White crystals. ¹H NMR (CDCl₃): δ 2.21 (3H, s, CH₃); 7.31 (1H, t, J = 7.2 Hz, CH_{ar}); 7.34 (1H, s, CH); 7.39 (2H, t, J = 7.2 Hz, 2 × CH_{ar}); 7.58 (2H, t, J = 7.2 Hz, 2 × CH_{ar}); 11.33 (1H, s(broad), NH). ¹³C NMR (CDCl₃): δ 9.6 (CH₃); 112.8 (C_qMe); 127.4 (2 × CH_{ar}); 127.6 (CH_{ar}); 128.5 (2 × CH_{ar}); 132.1 (C_{ar}); 134.9 (NCH); 144.9 (NC_q). MS (ES+) *m/z* (%): 159 (M+H⁺, 100). GC-MS (EI): *m/z* (%): 158 (M⁺, 100); 157 (M⁺-H, 70); 130 (M⁺-N₂, 31); 128 (10); 115 (4); 104 (8); 103 (8); 81 (5); 78 (10); 77 (C₆H₅⁺, 16); 55 (17); 51(9). Spectral data (¹H NMR, ¹³C NMR) of **24** were in accordance with those reported in the literature.⁷

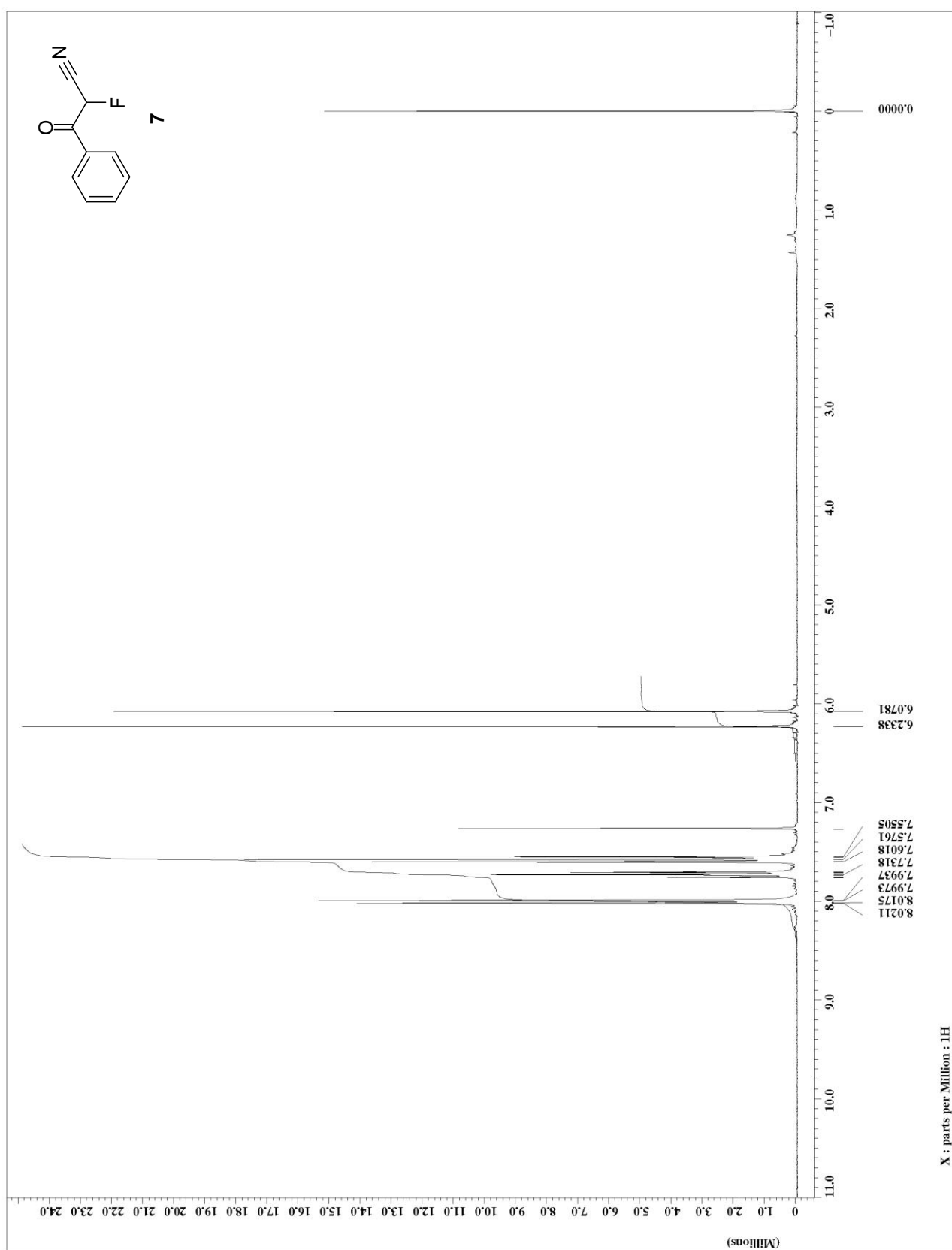


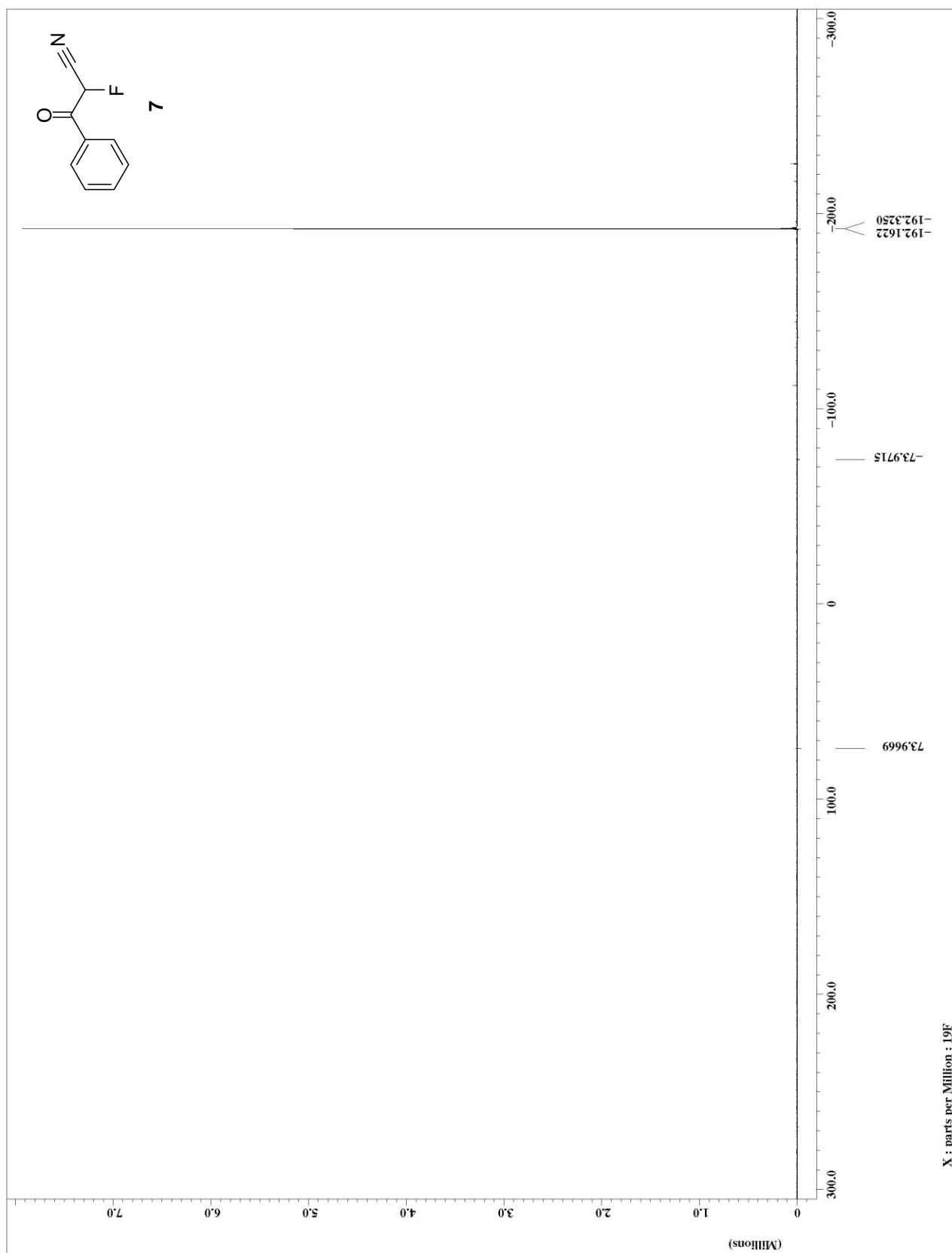
With the aim to establish a similar new entry toward 3-chloropyrazoles, 2,2-dichloro-2-oxopropanenitrile **25**,⁸ prepared from benzoylacetonitrile and sulfuryl chloride in 91% yield according to literature procedures, was reacted with hydrazine. However, in this case only benzoic hydrazide crystals were formed, which were converted into the known benzoic acid isopropylidene hydrazide **26**,⁹ upon dissolving in acetone.

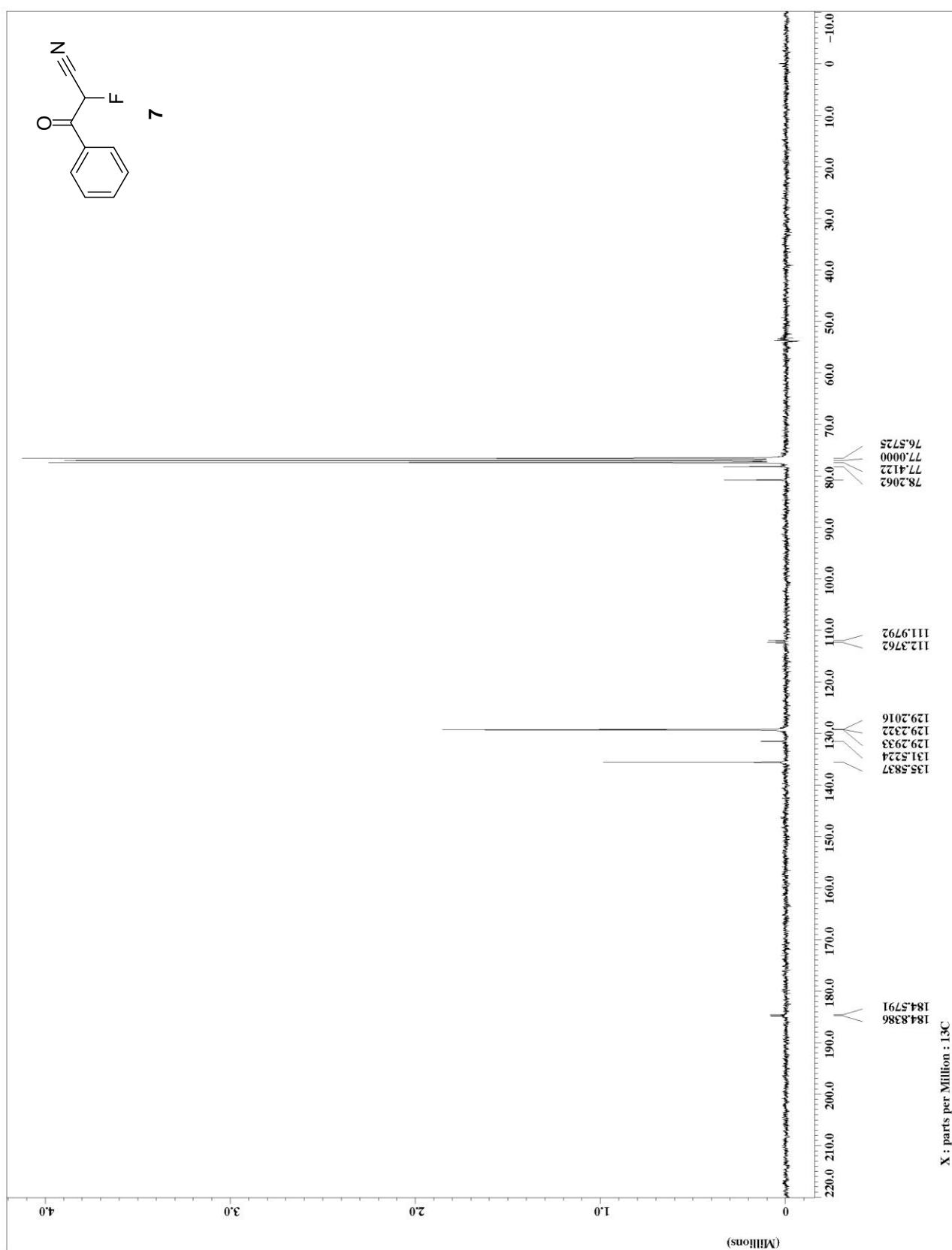
IV. Copies of NMR spectra of **2**, **3**, **7**, **9**, **10**, **12a-f**, **14b-c**.

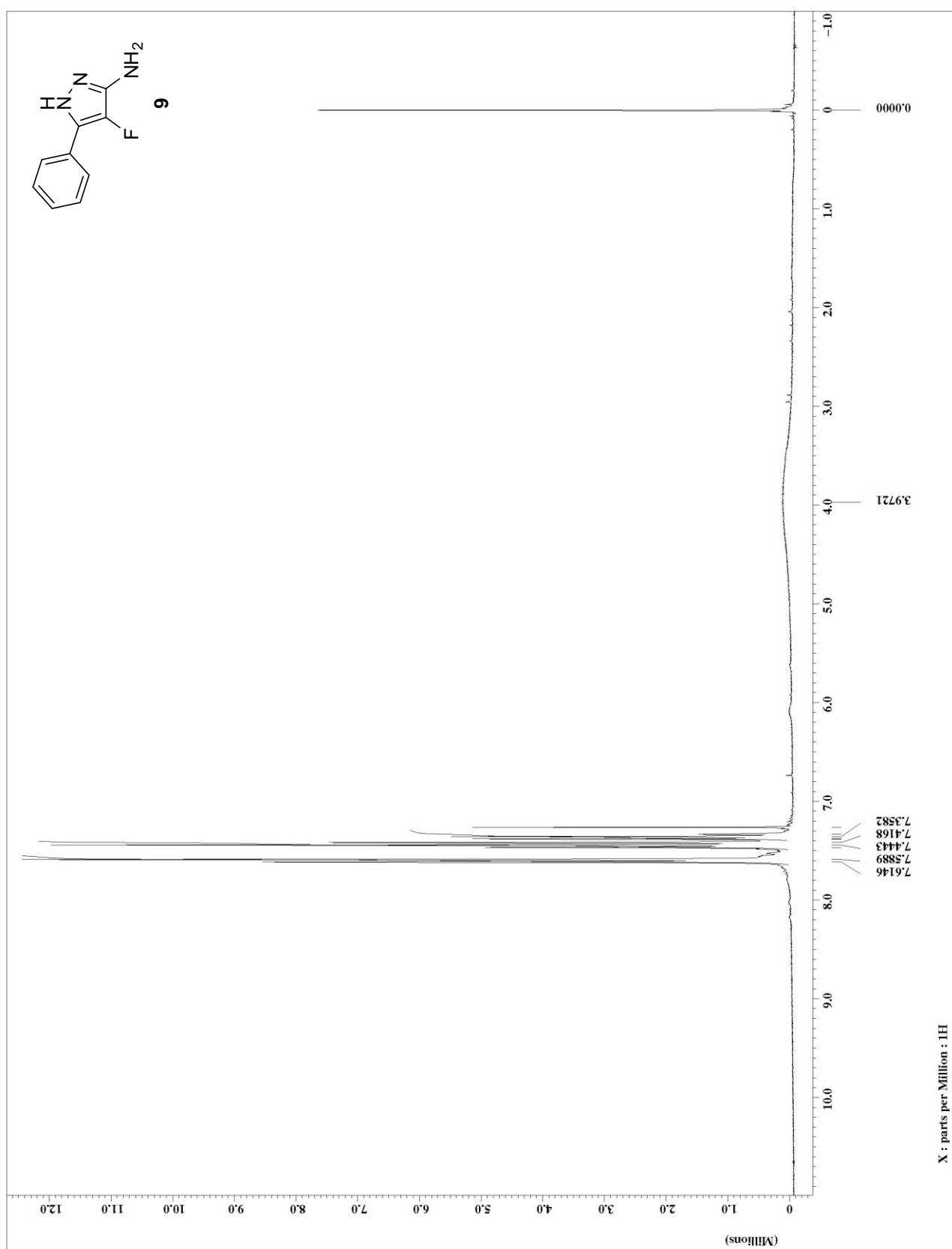


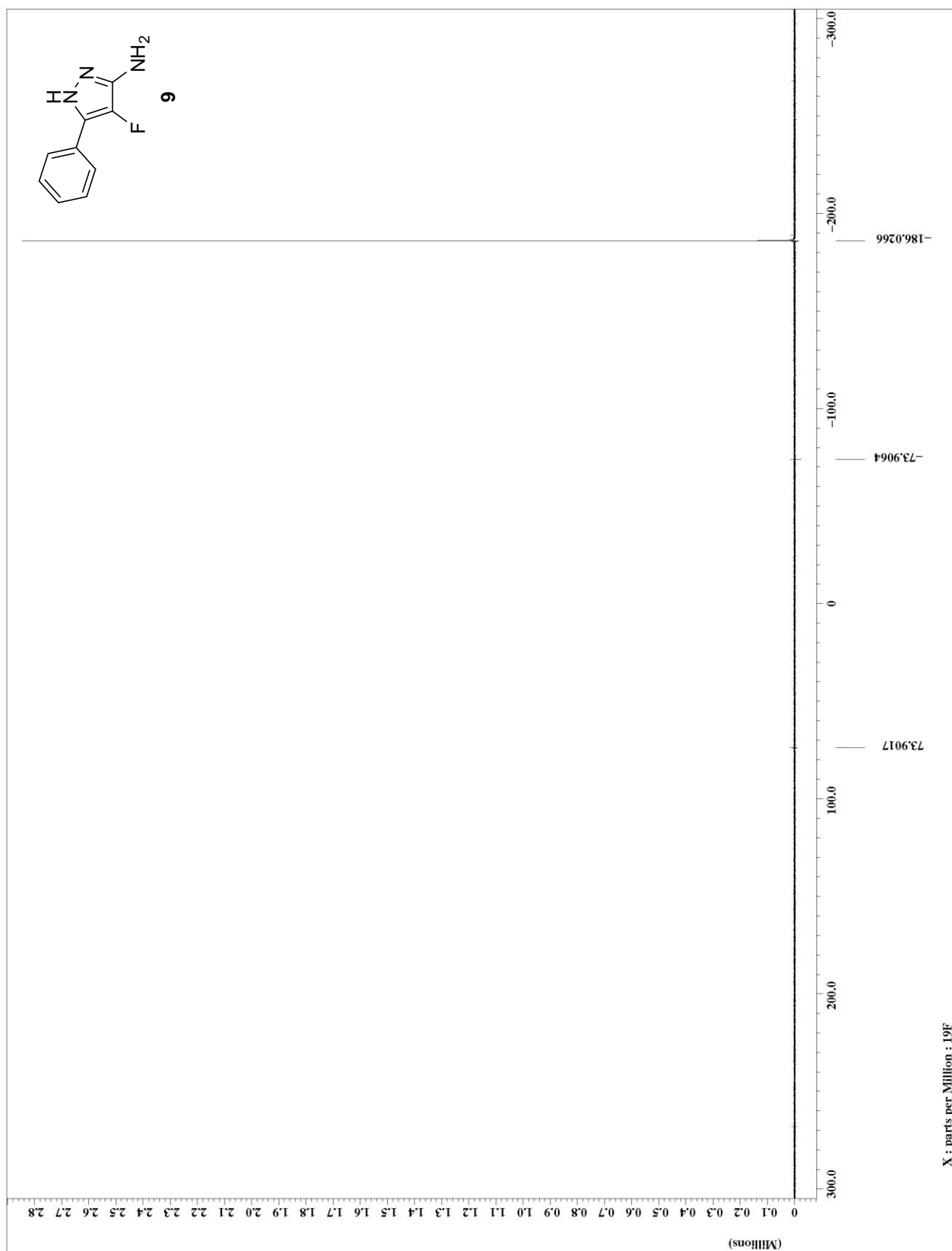


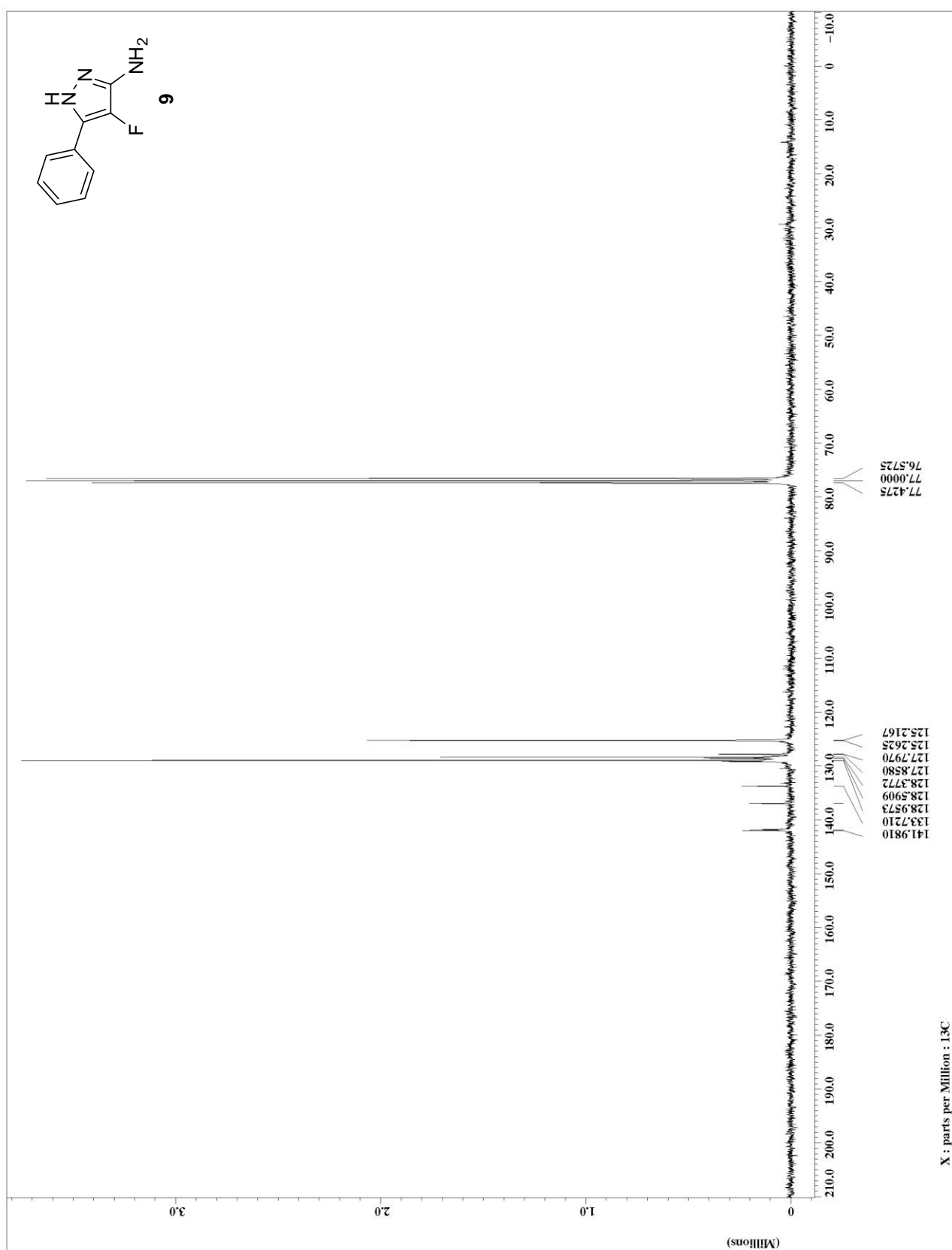


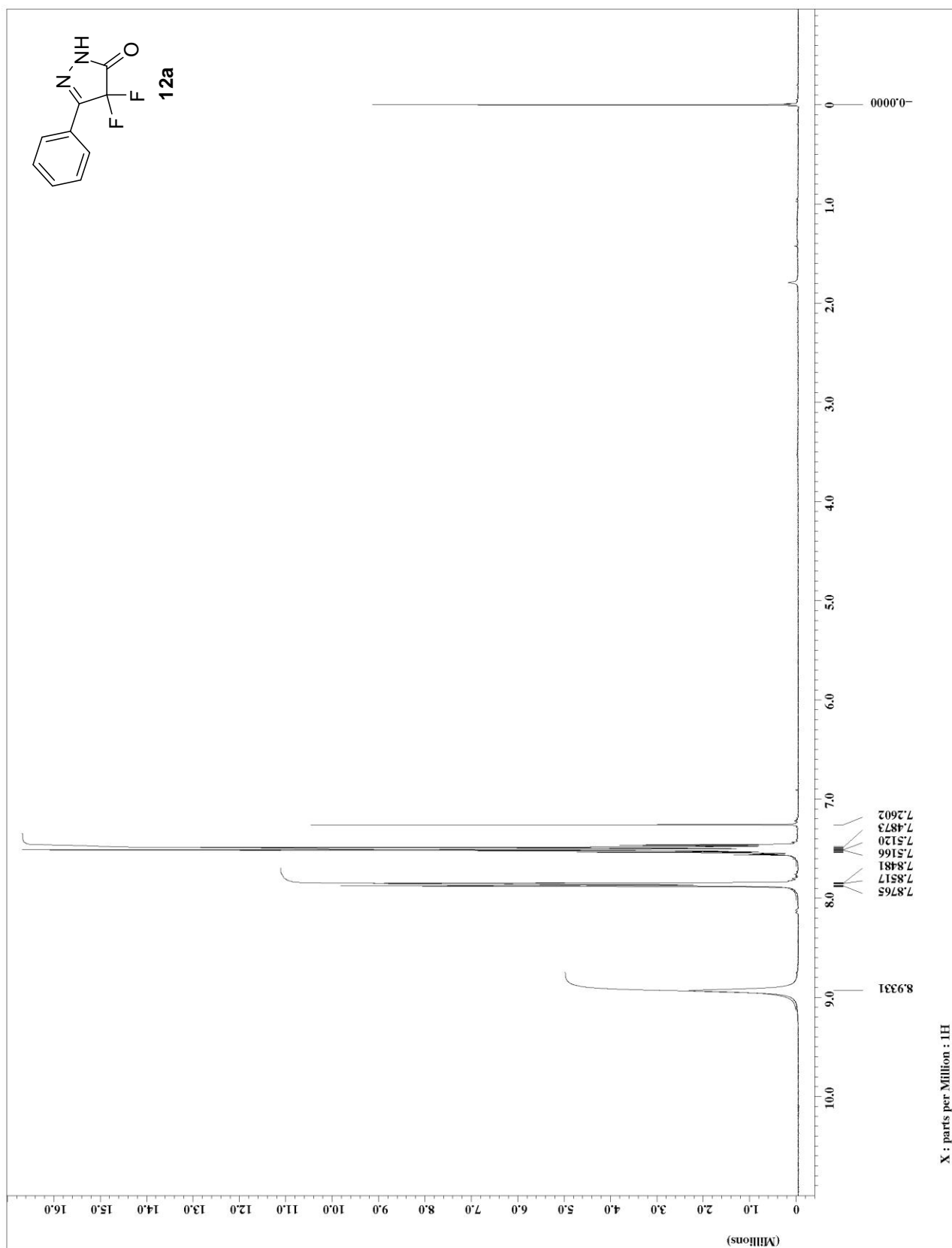


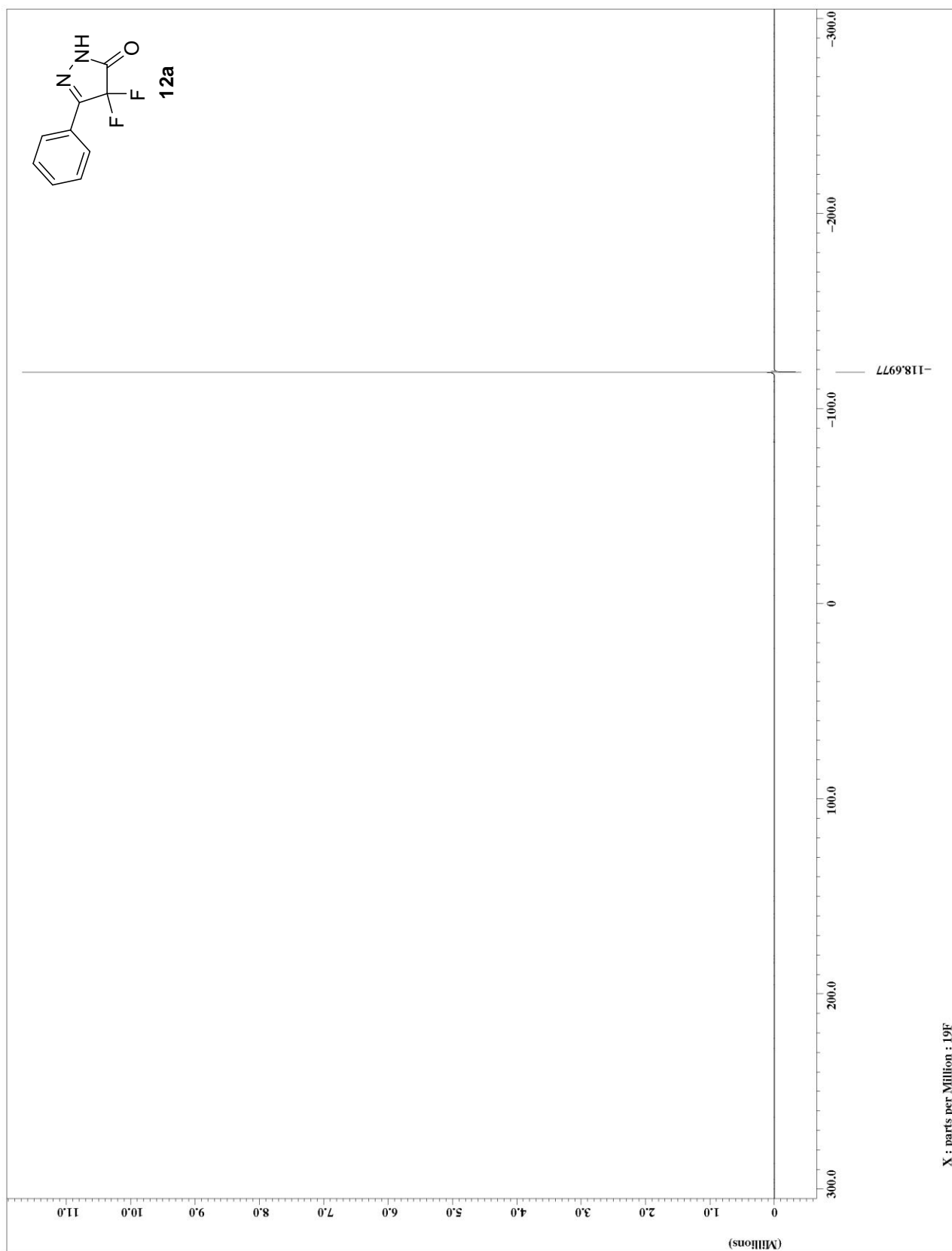


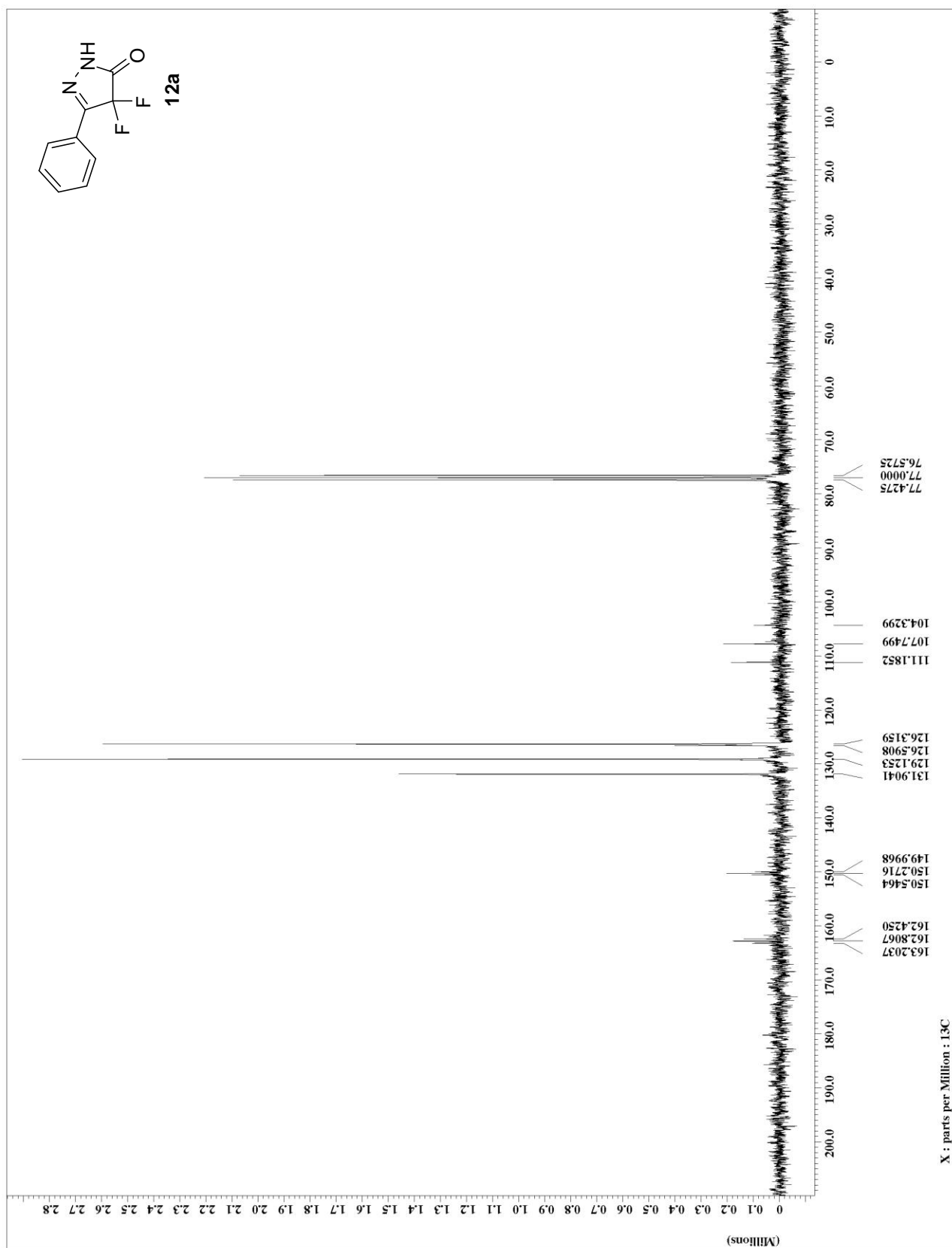


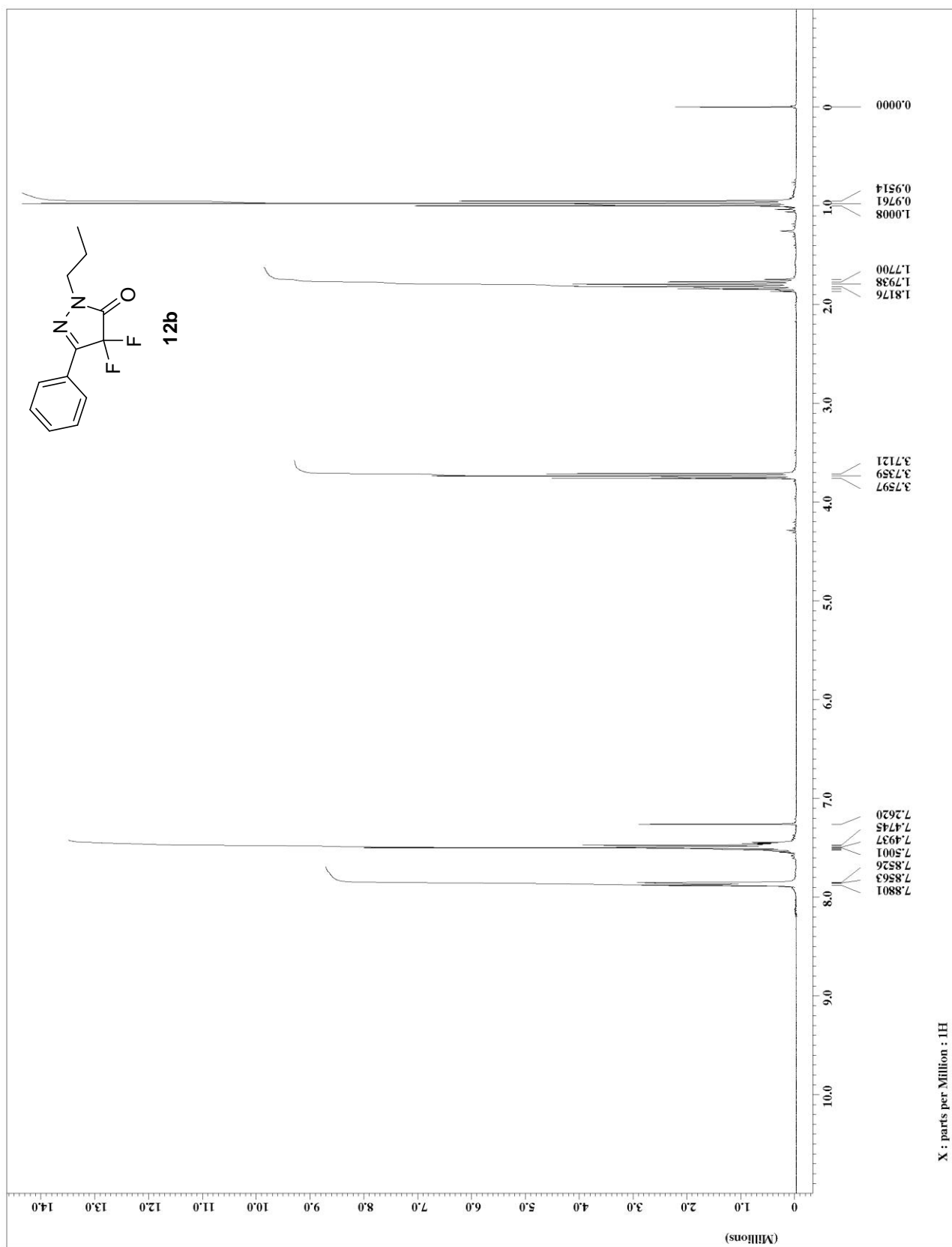


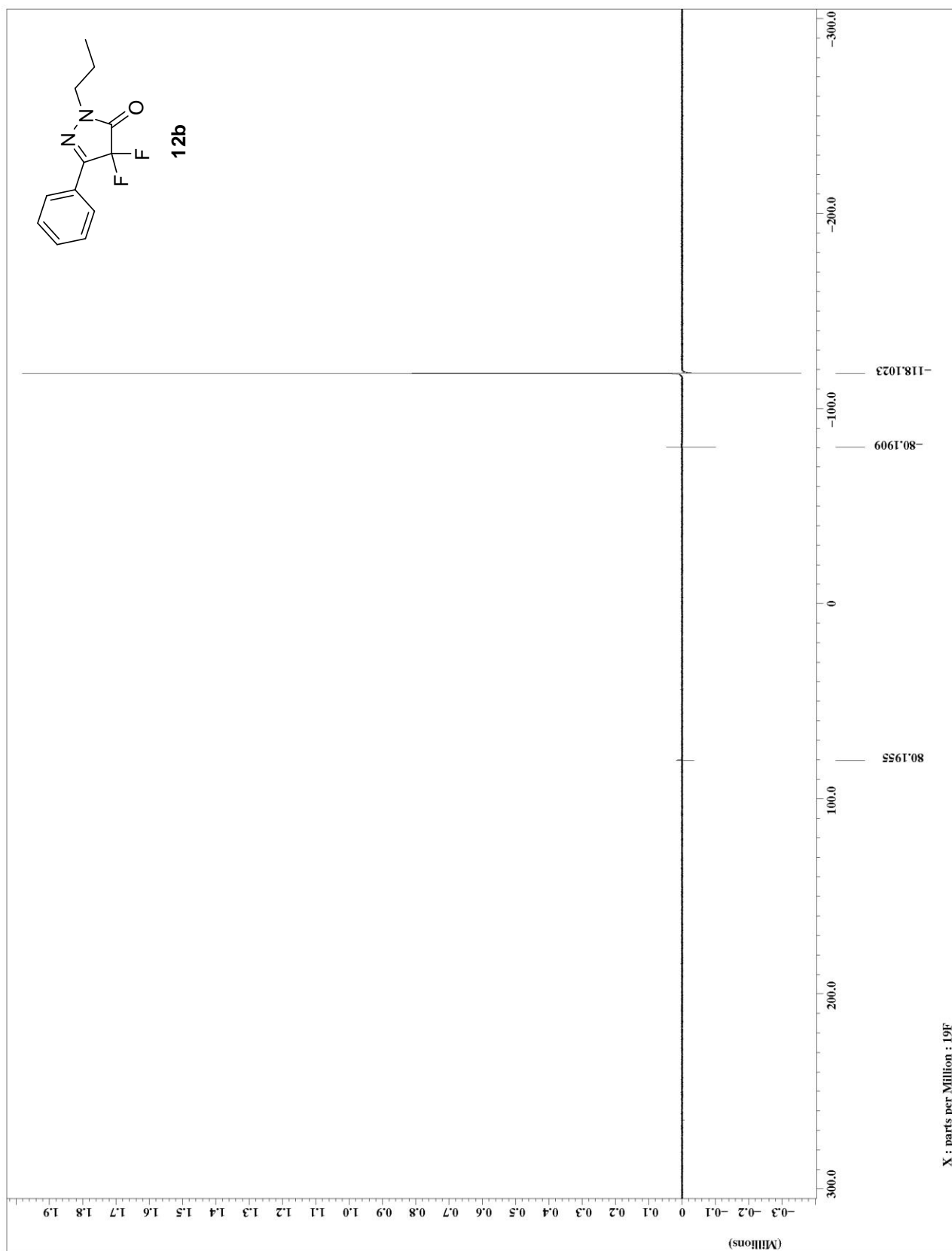


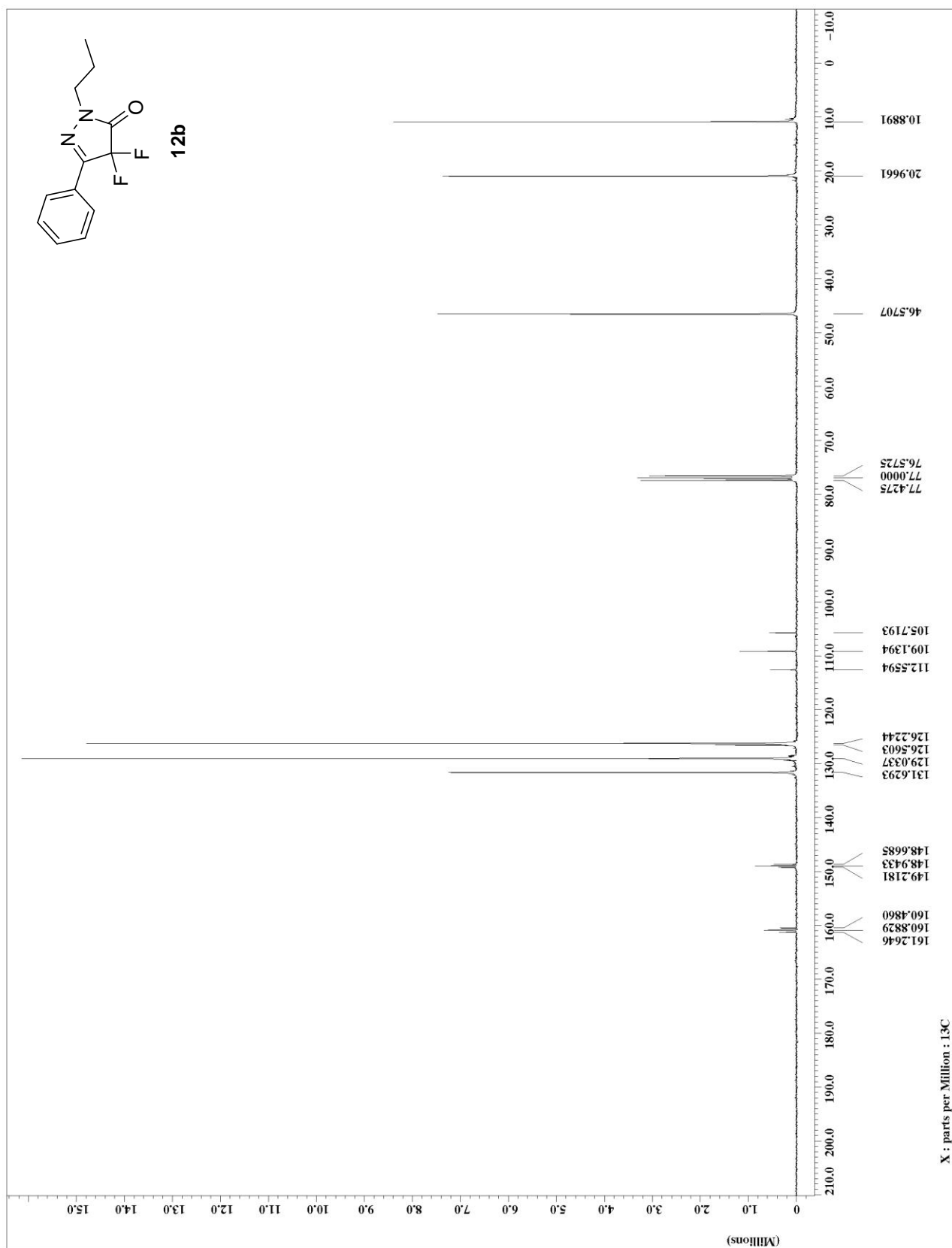


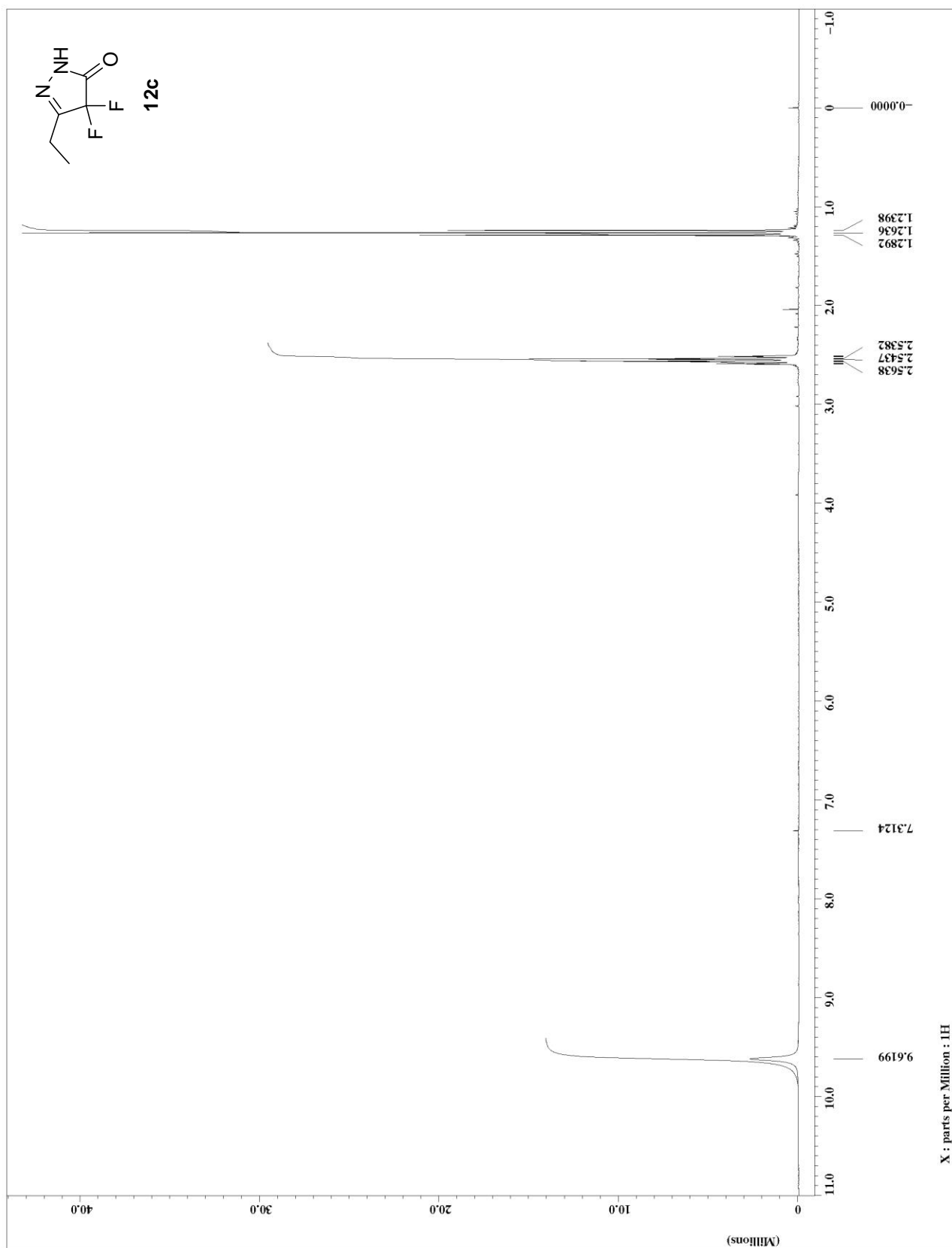


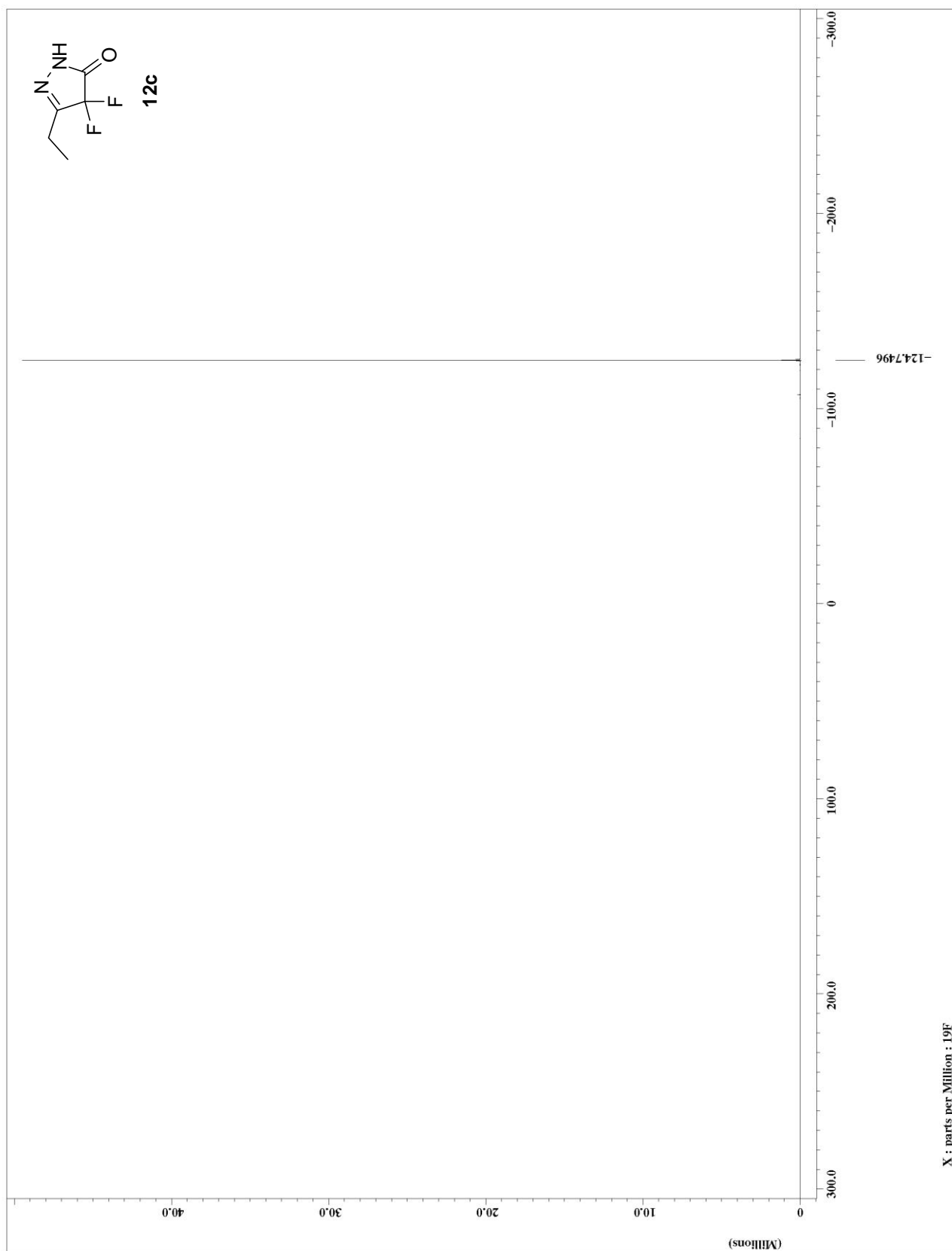


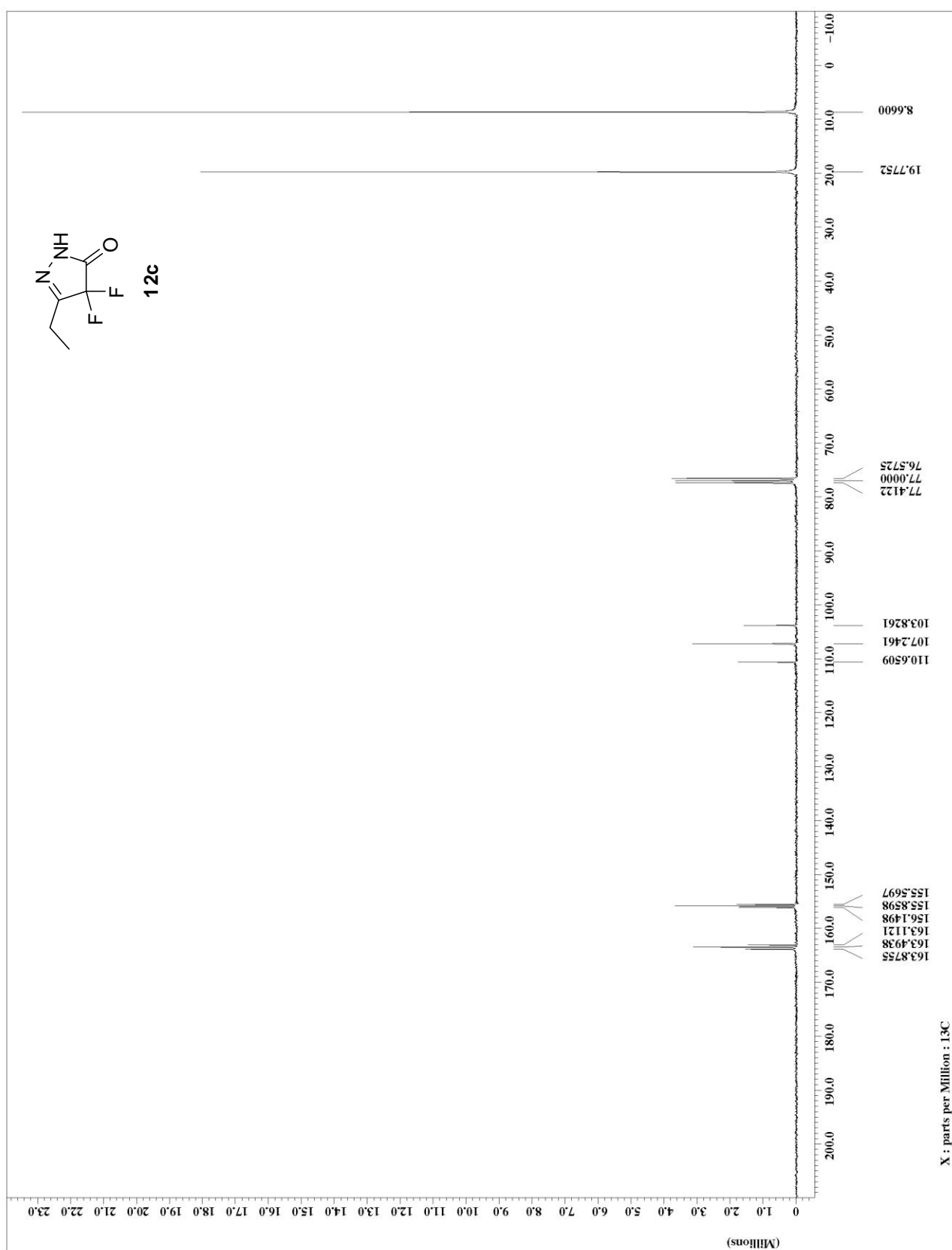


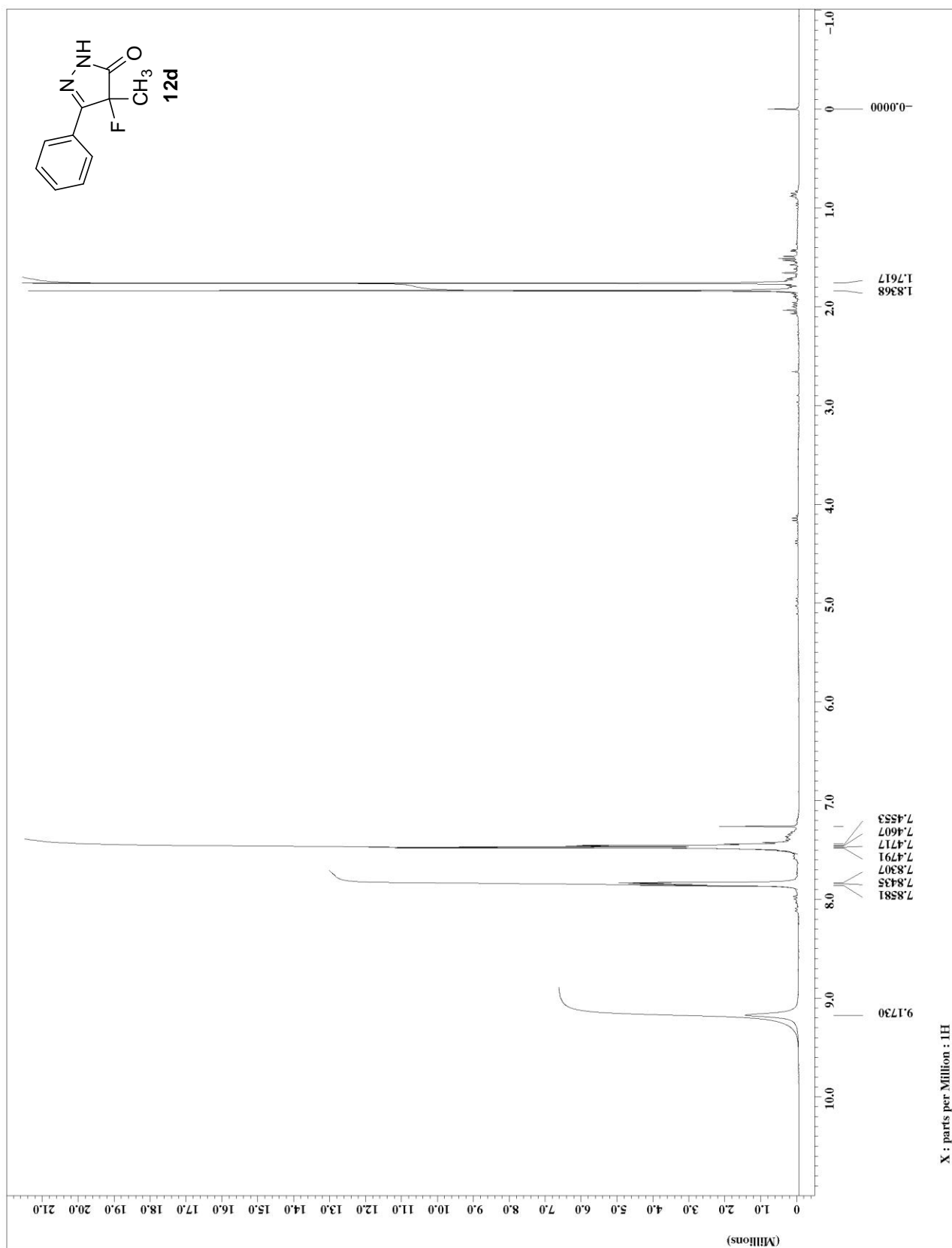


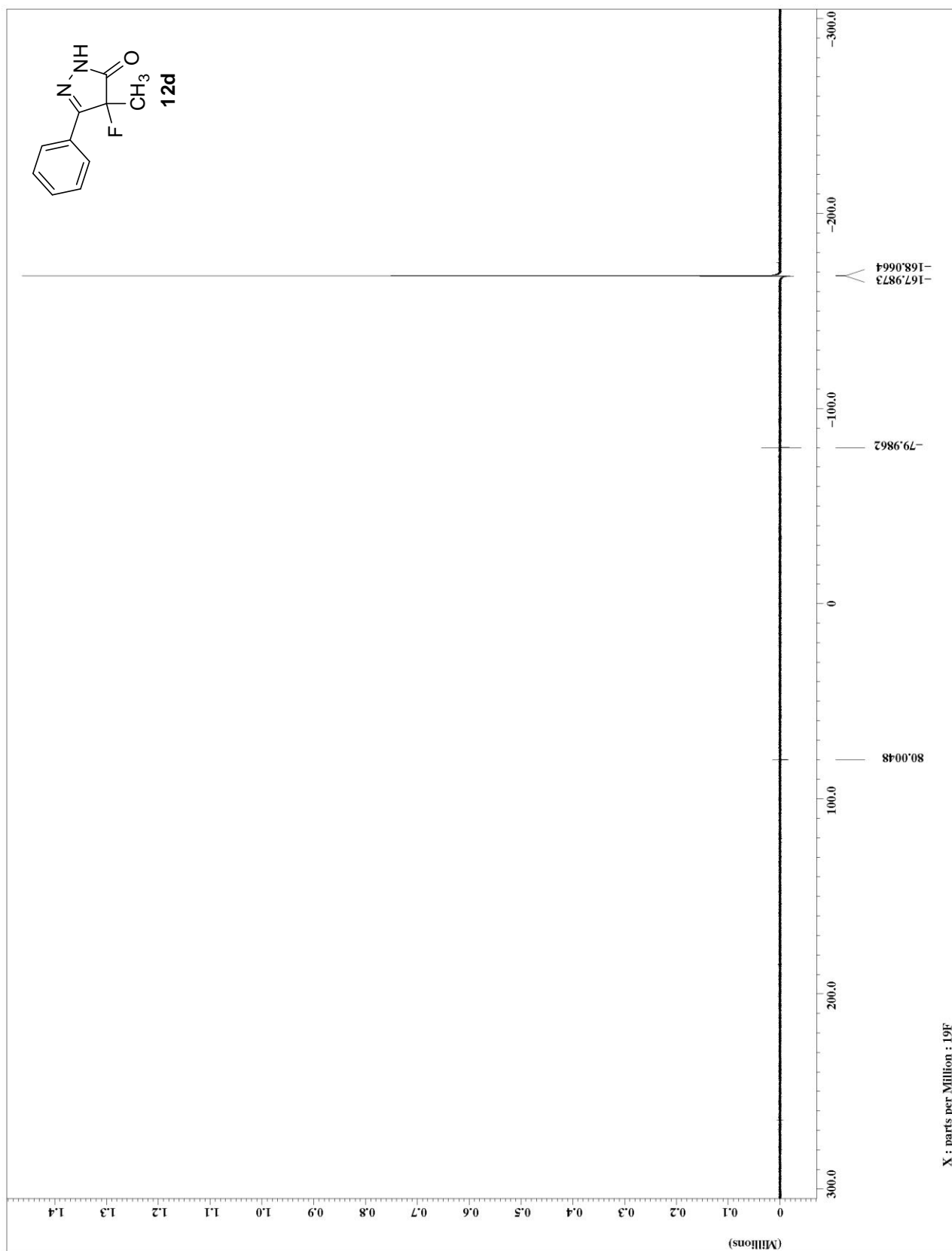


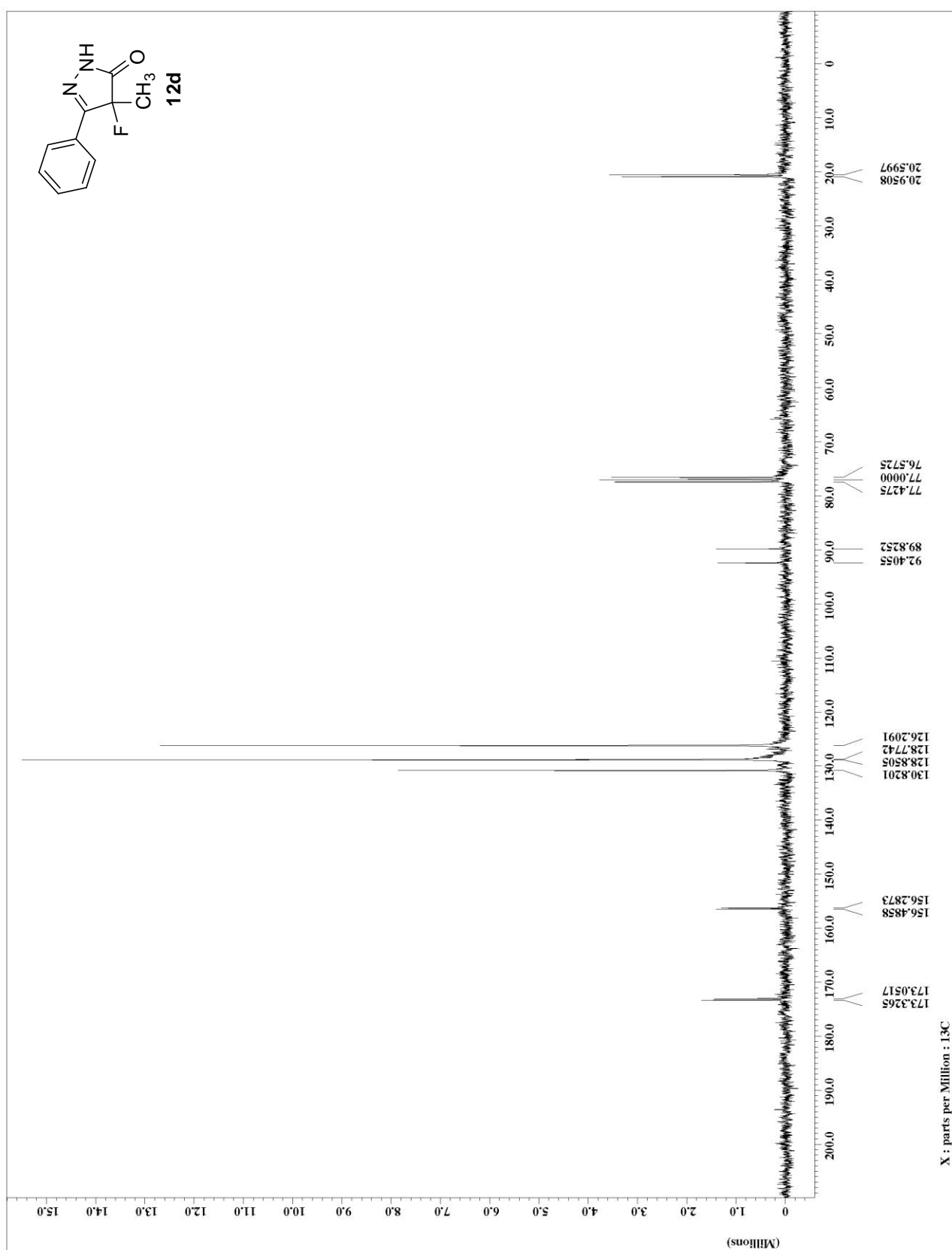


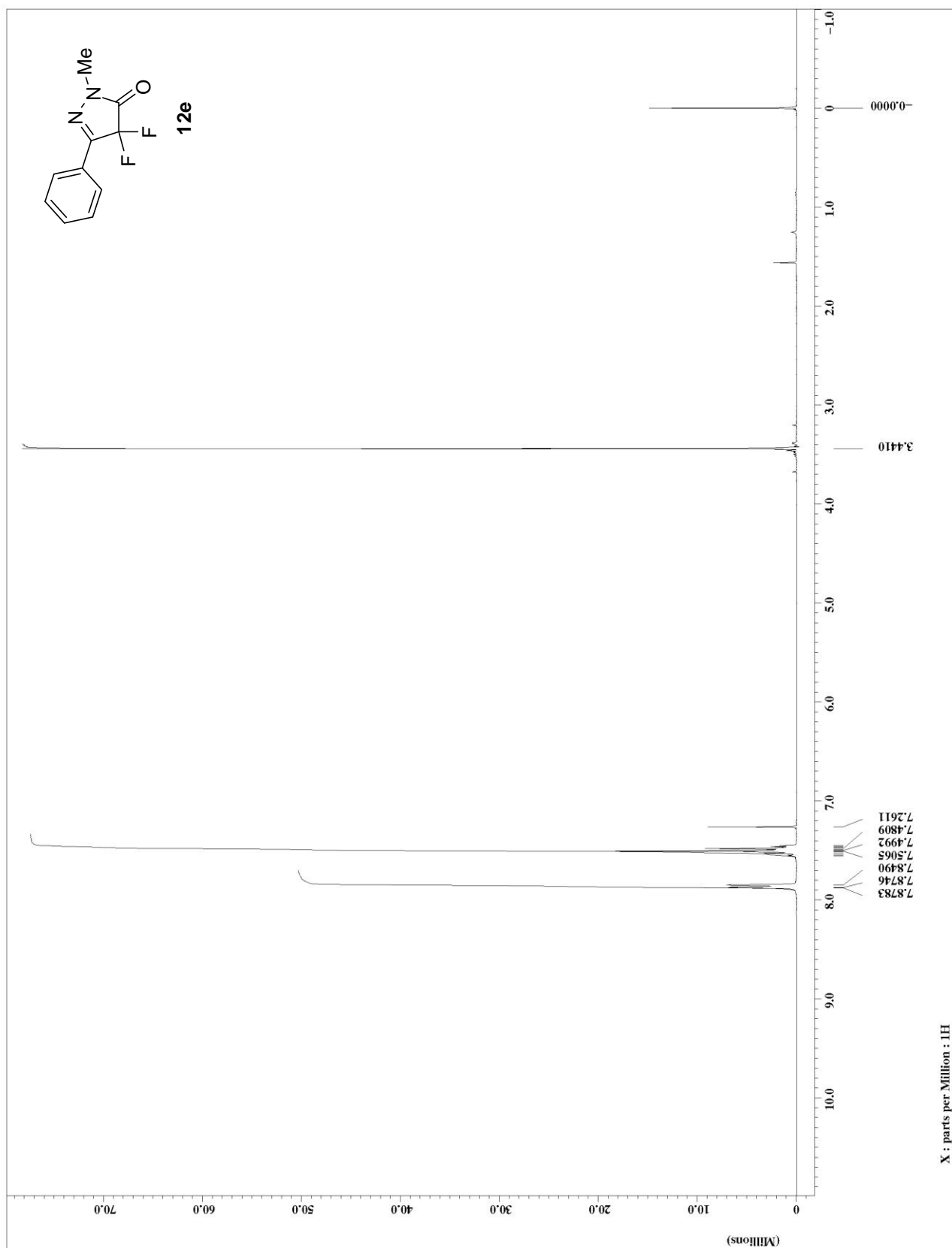


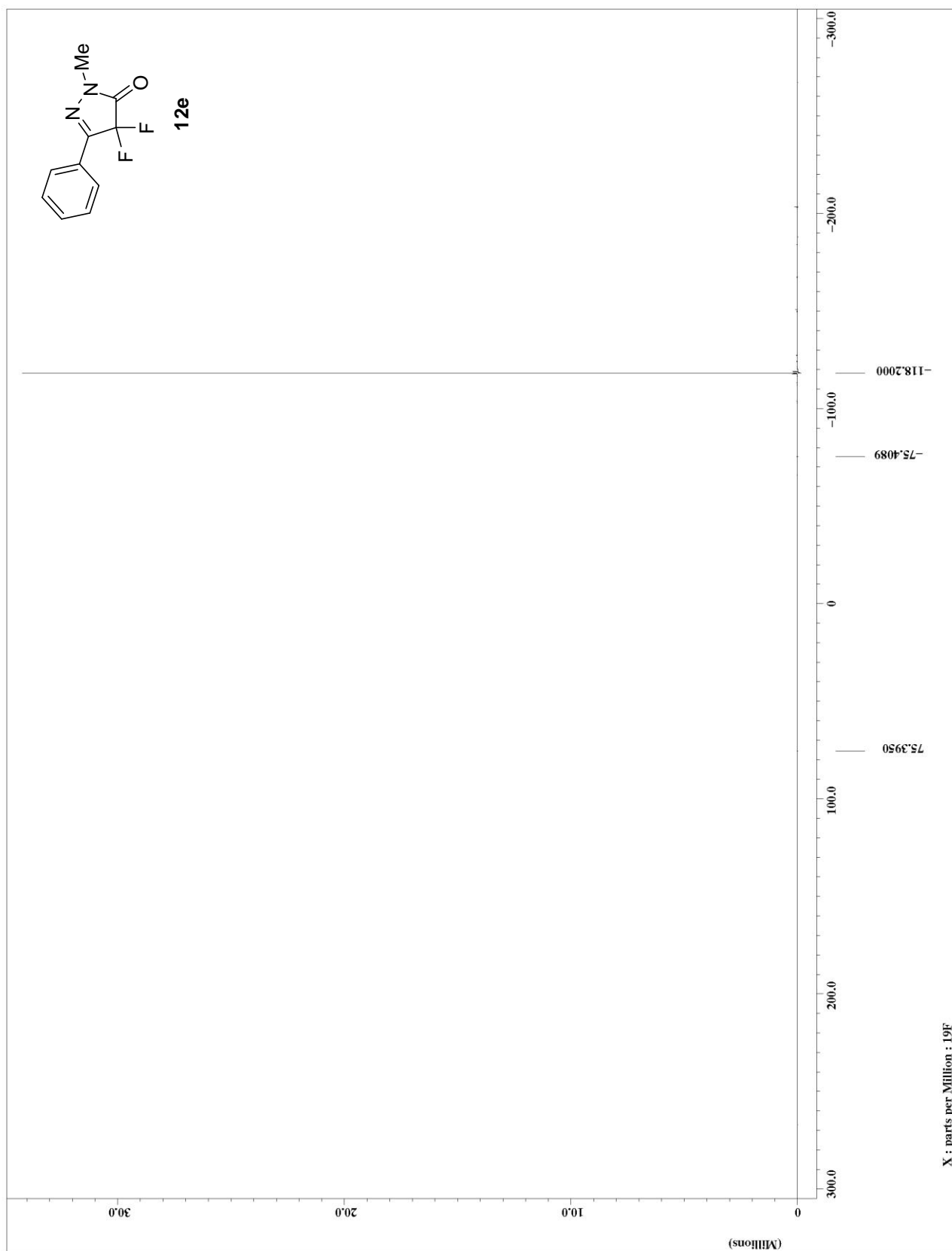


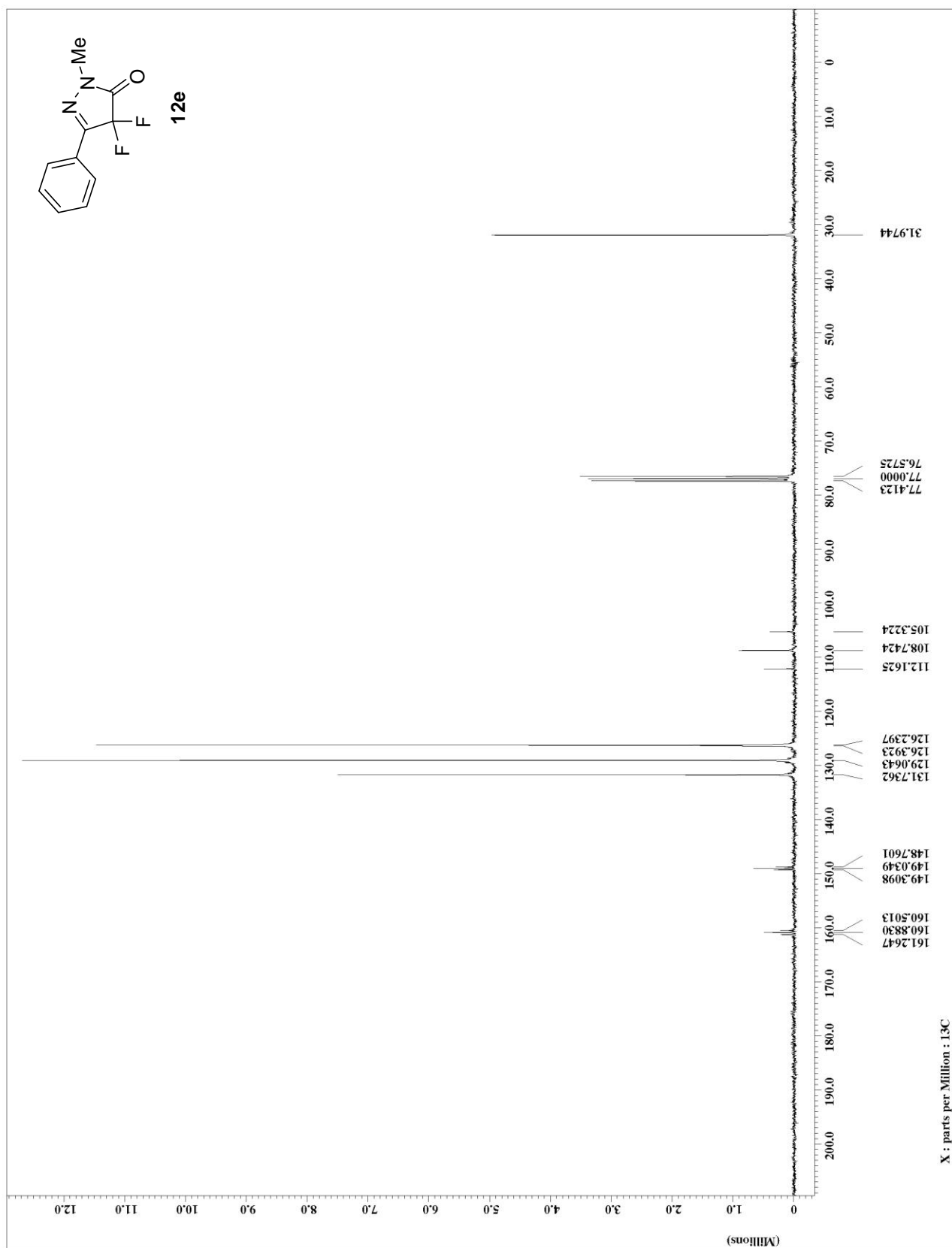


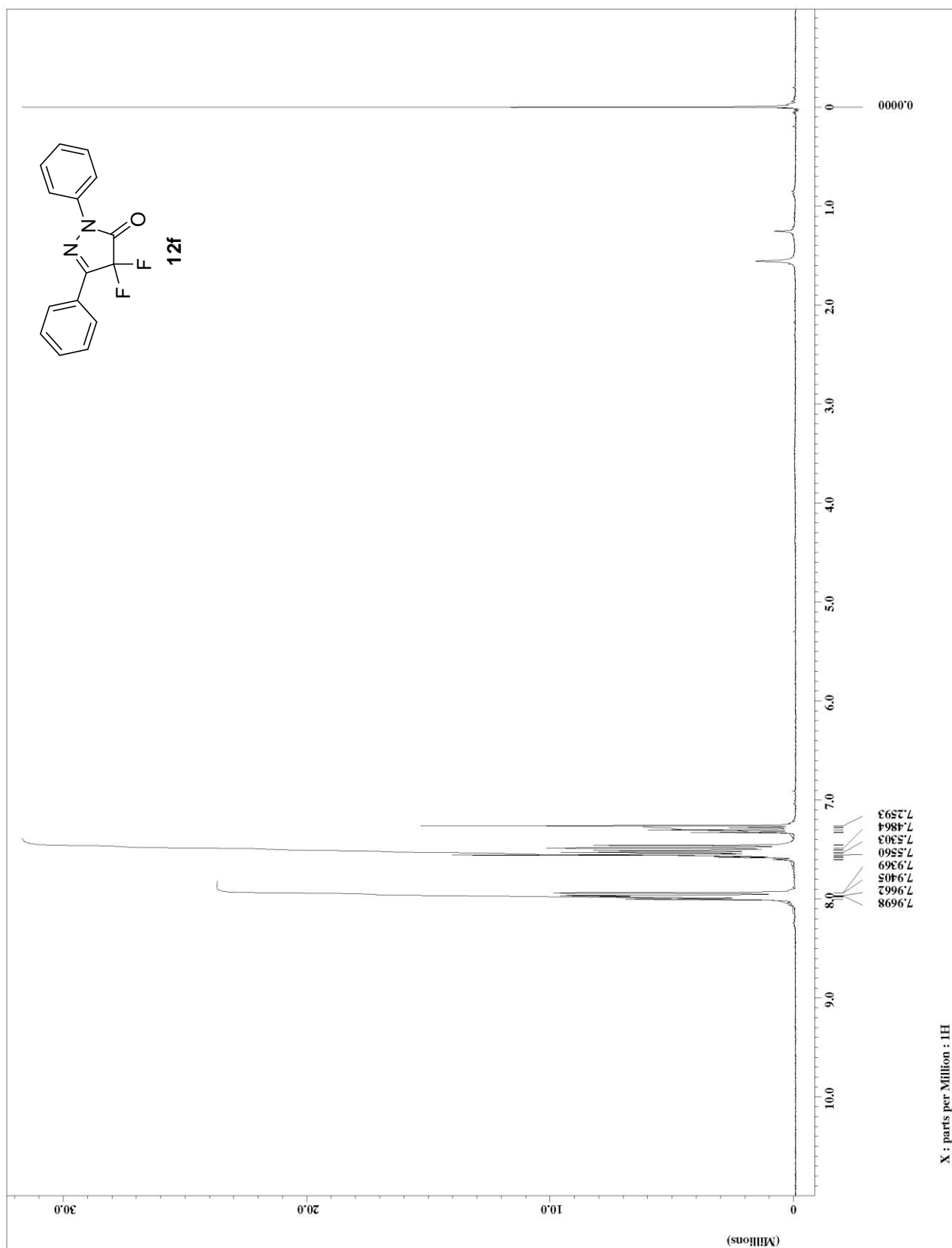


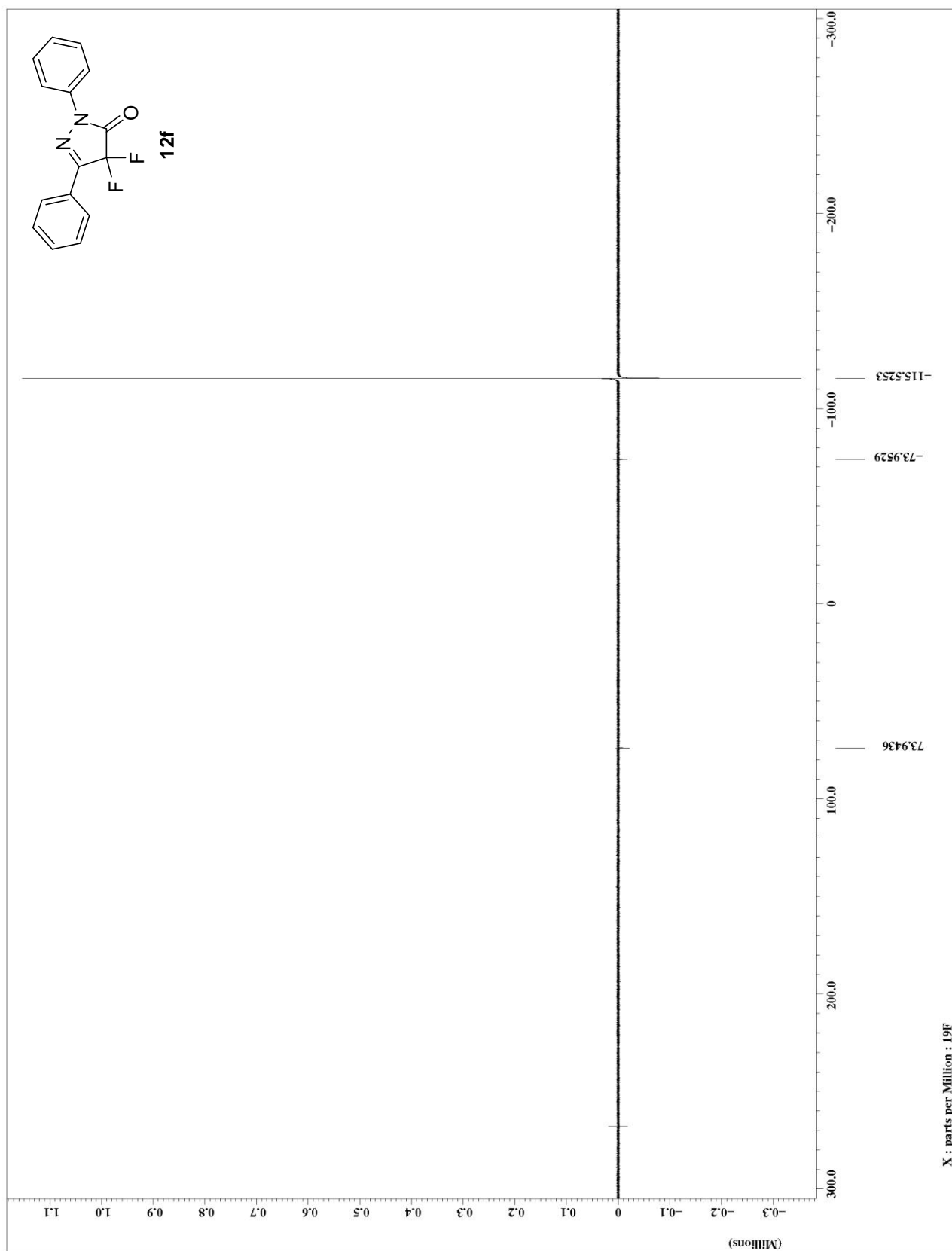


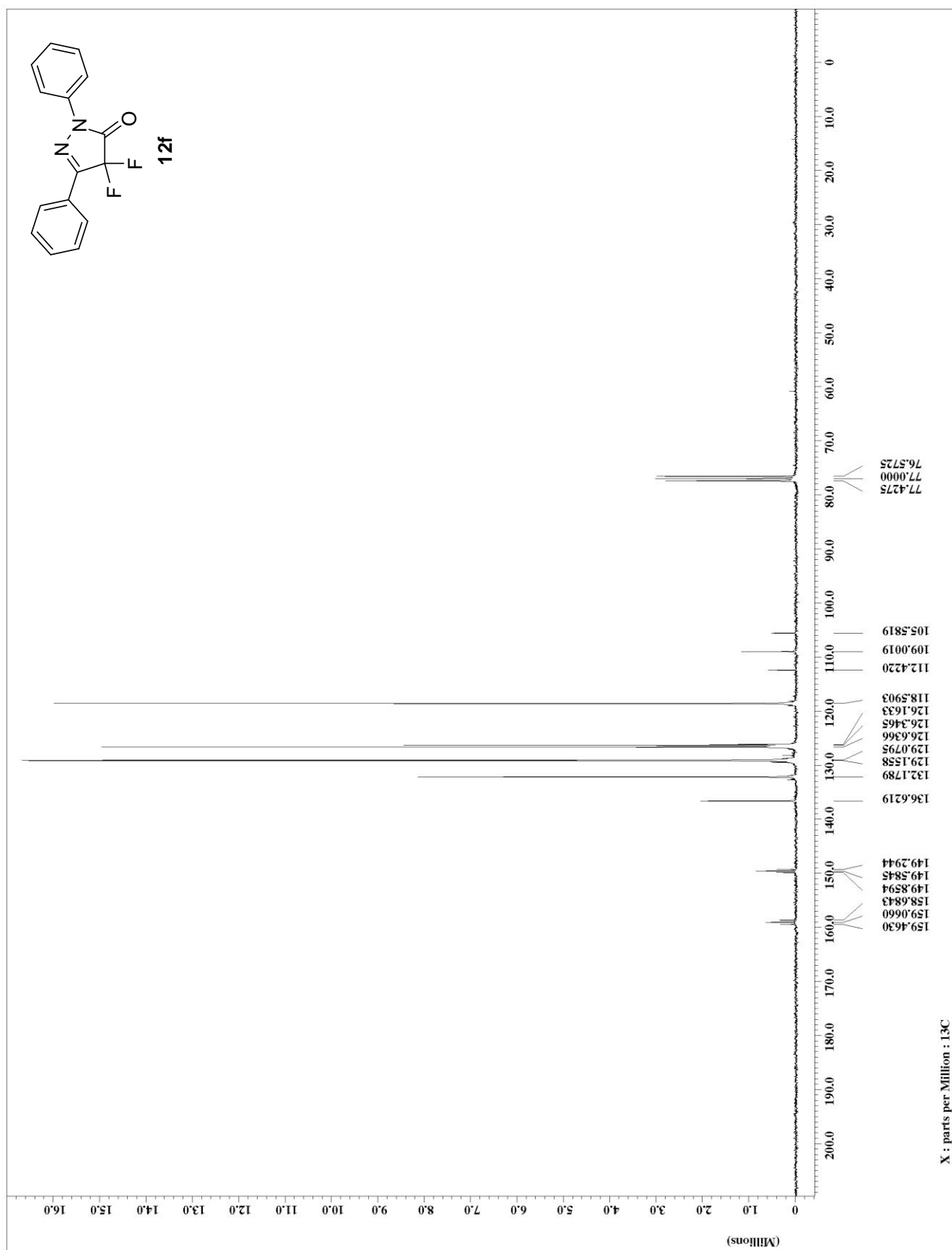


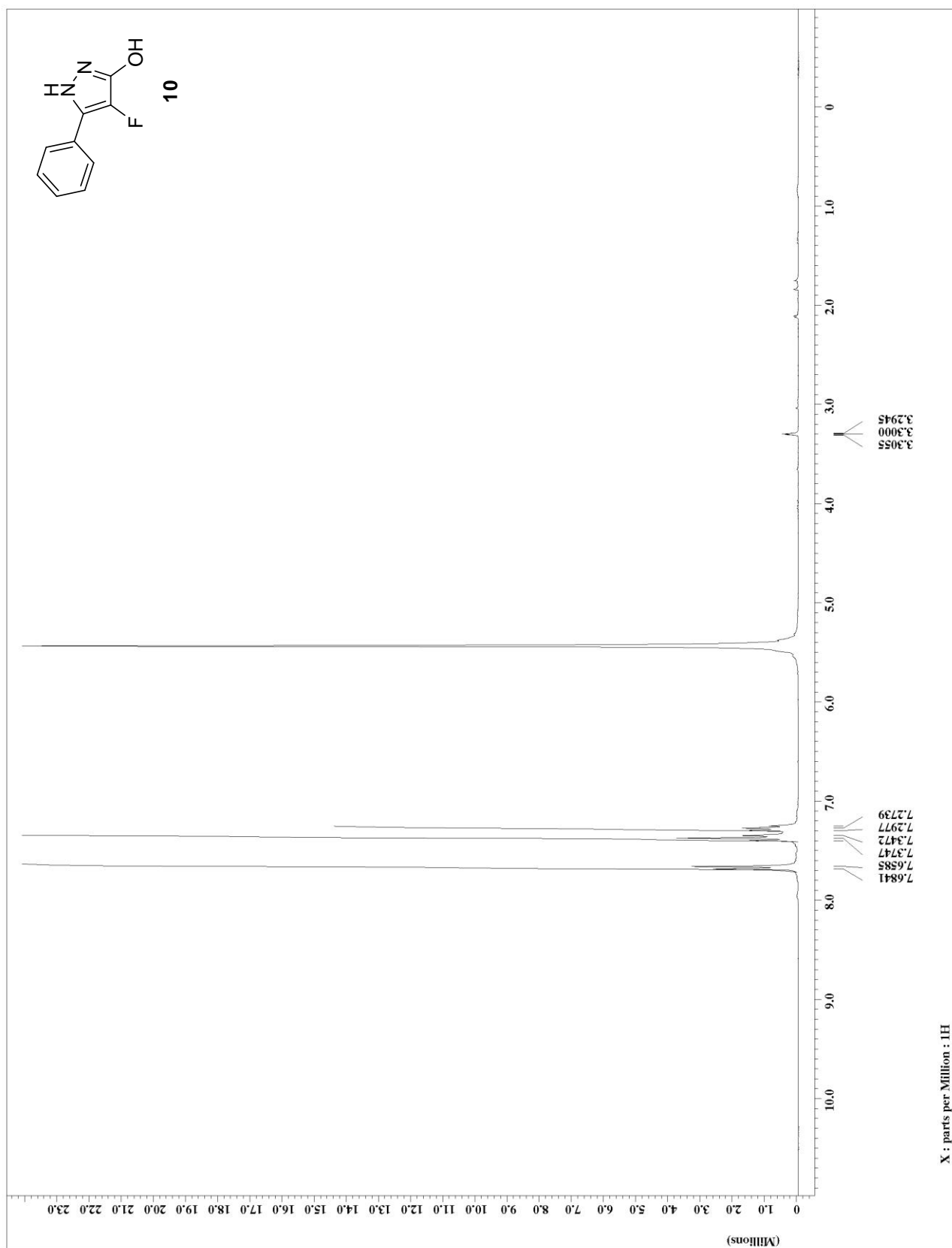


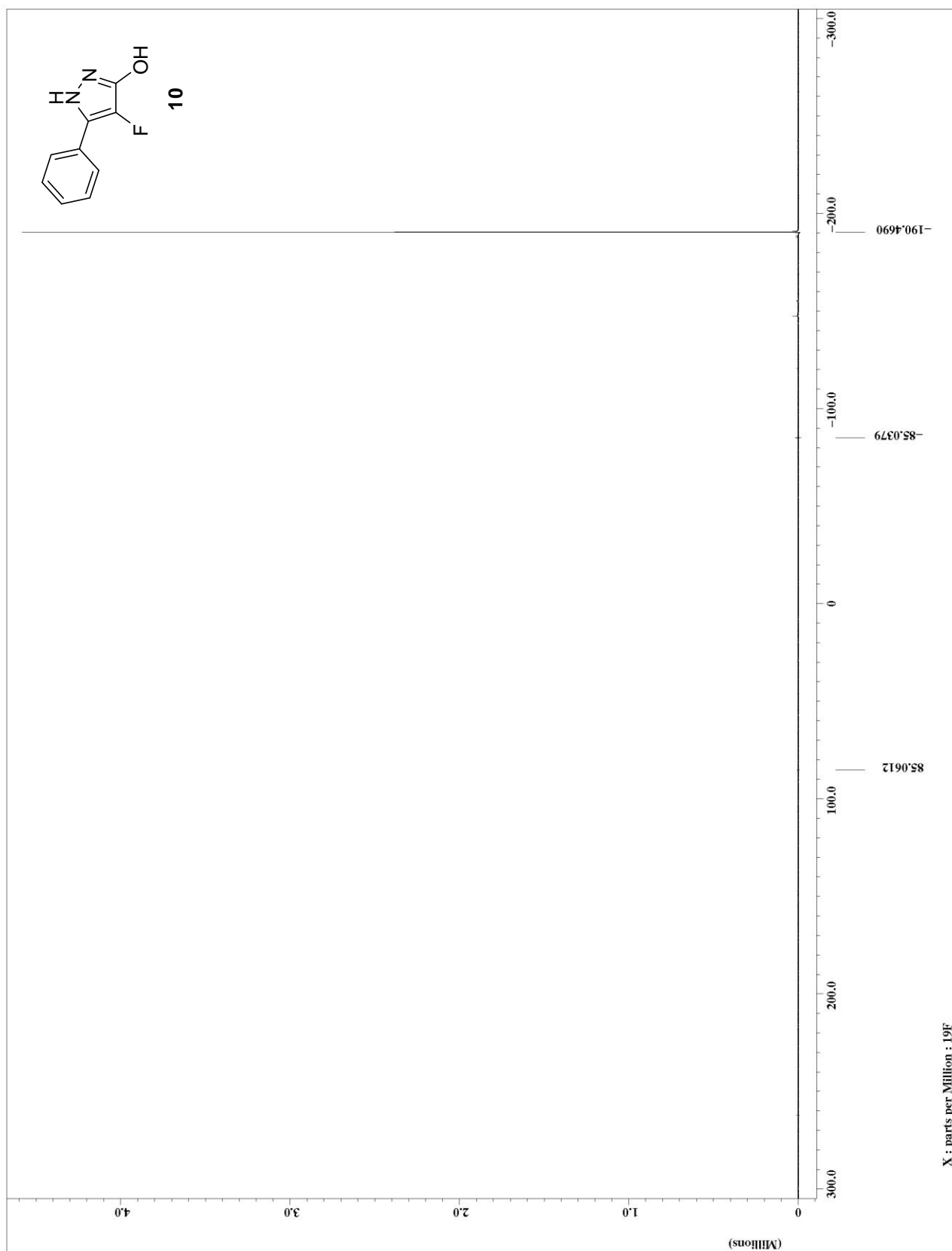


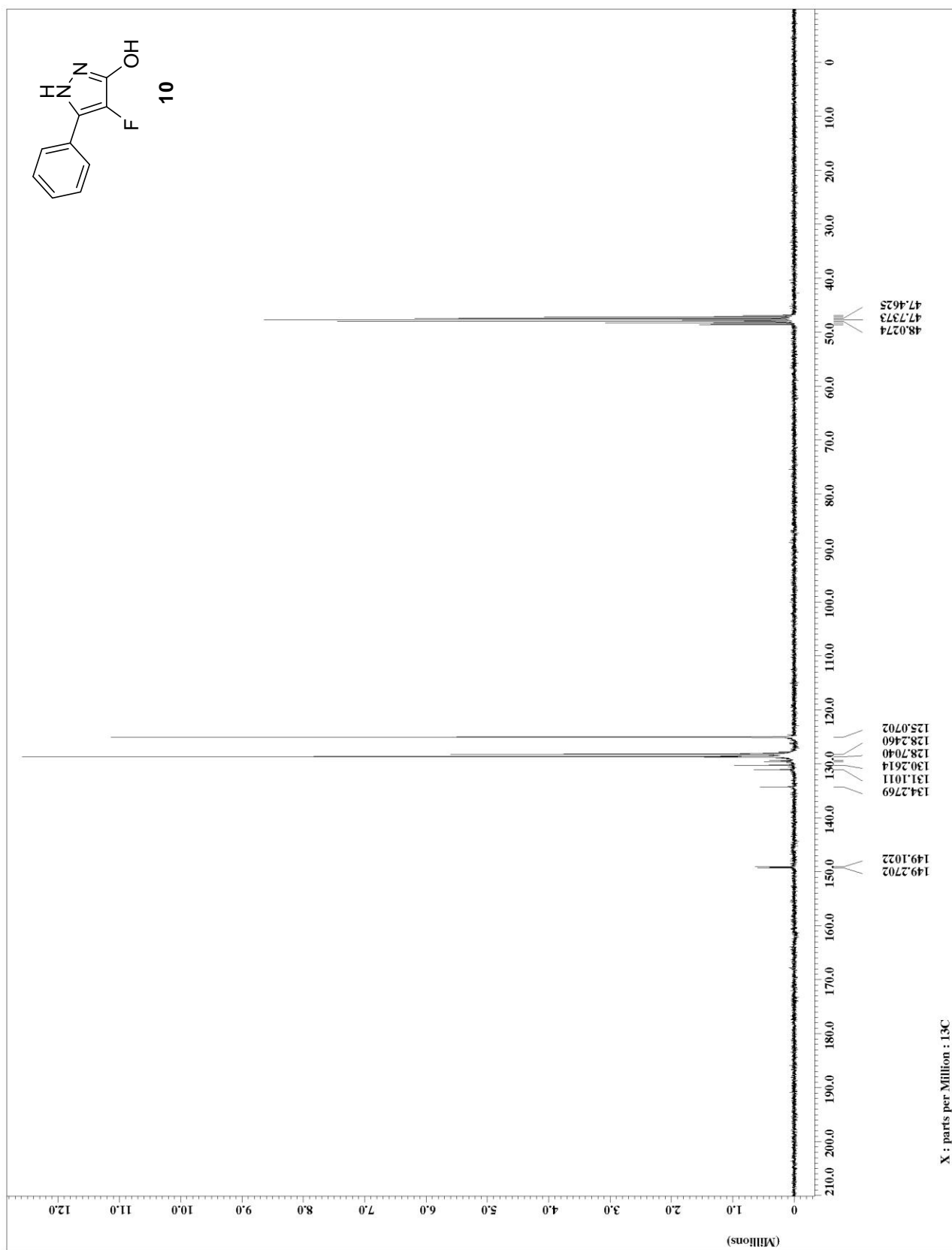


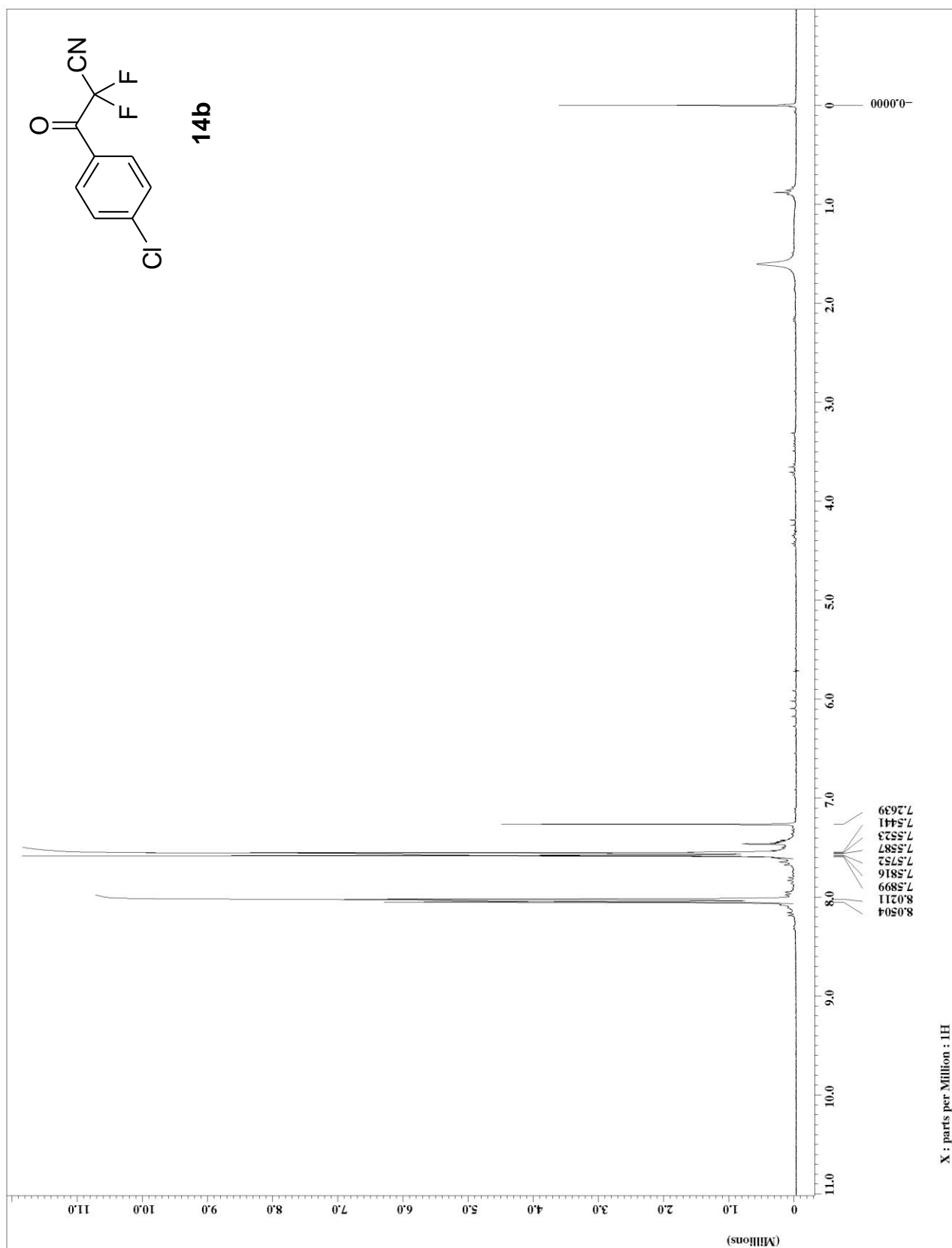


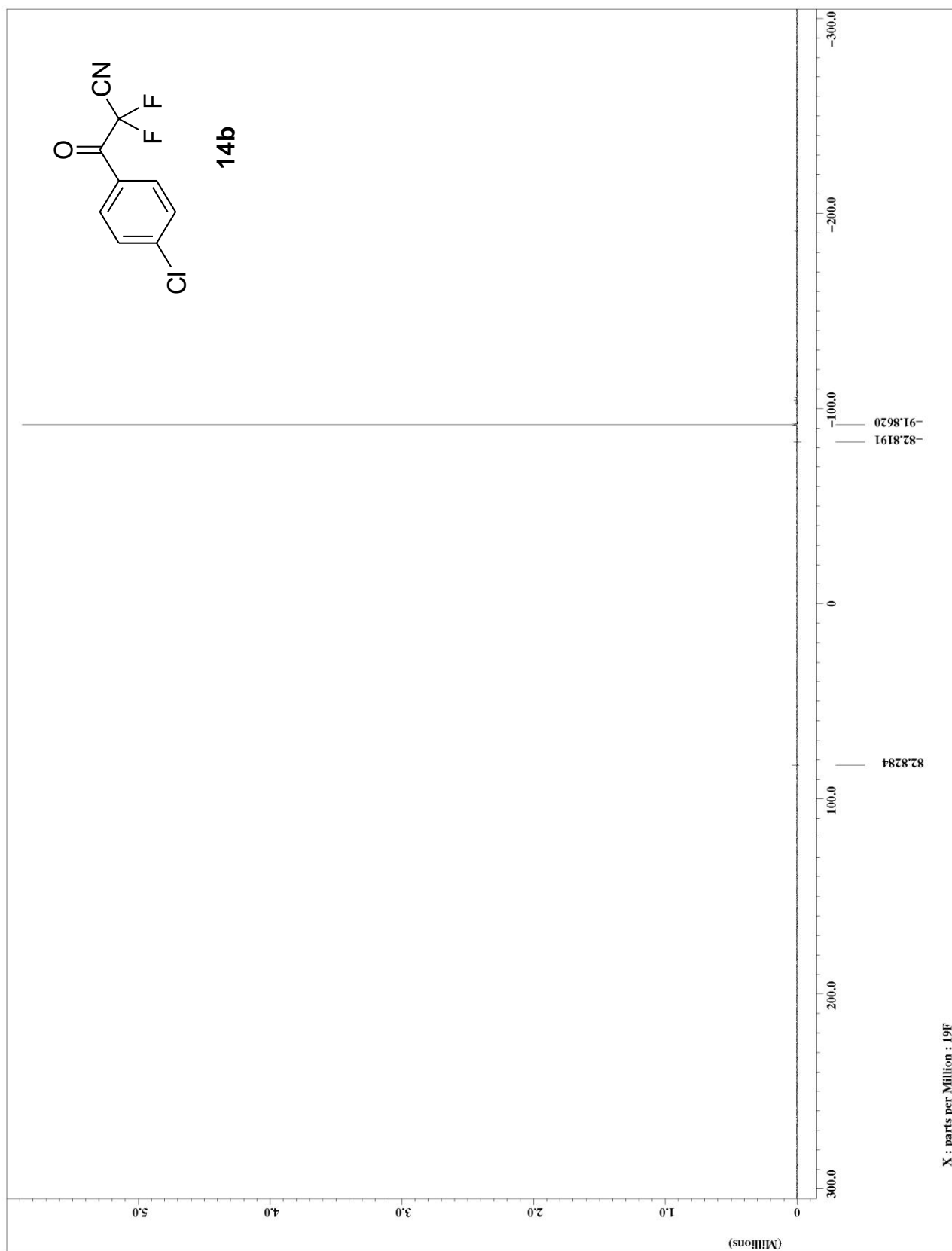


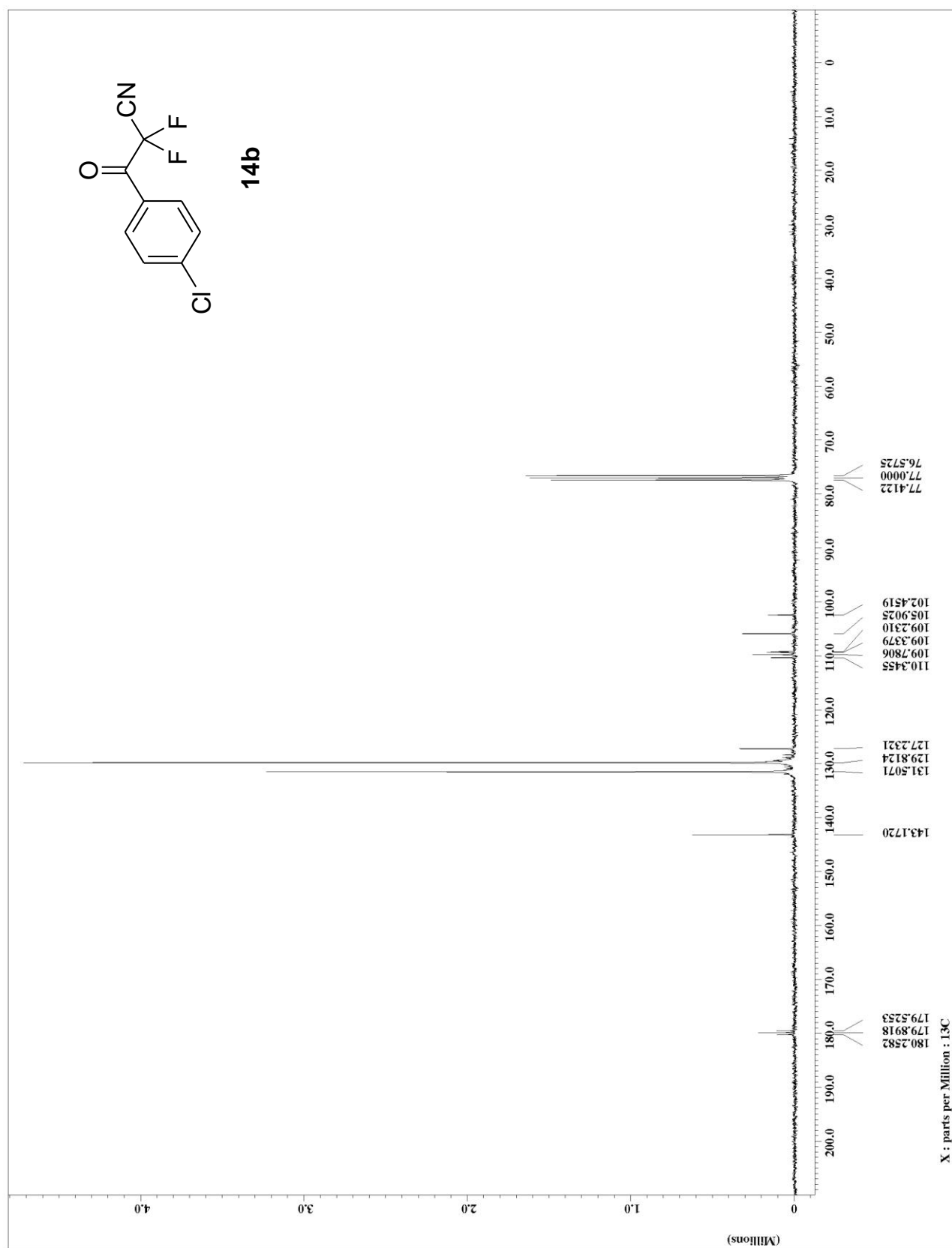


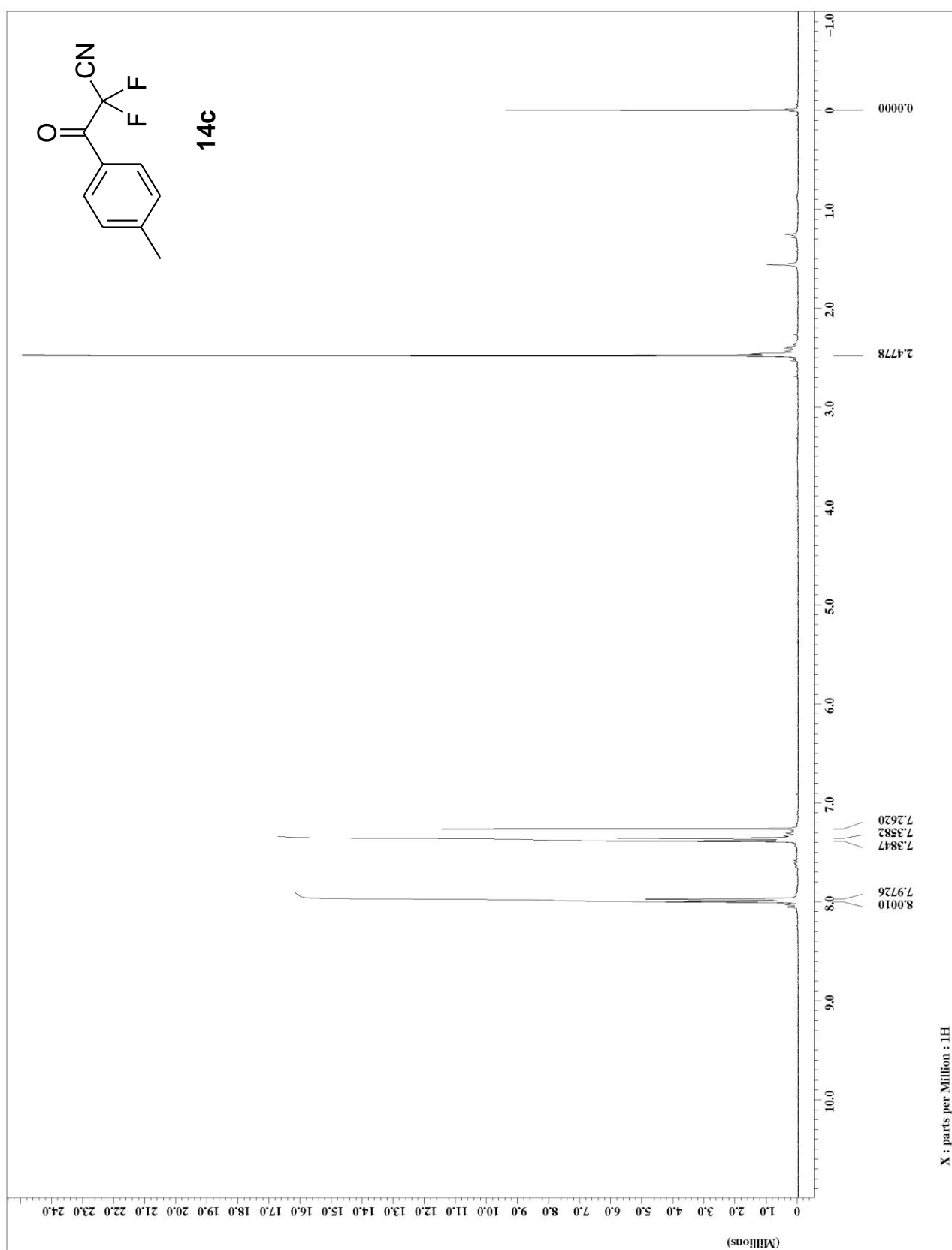


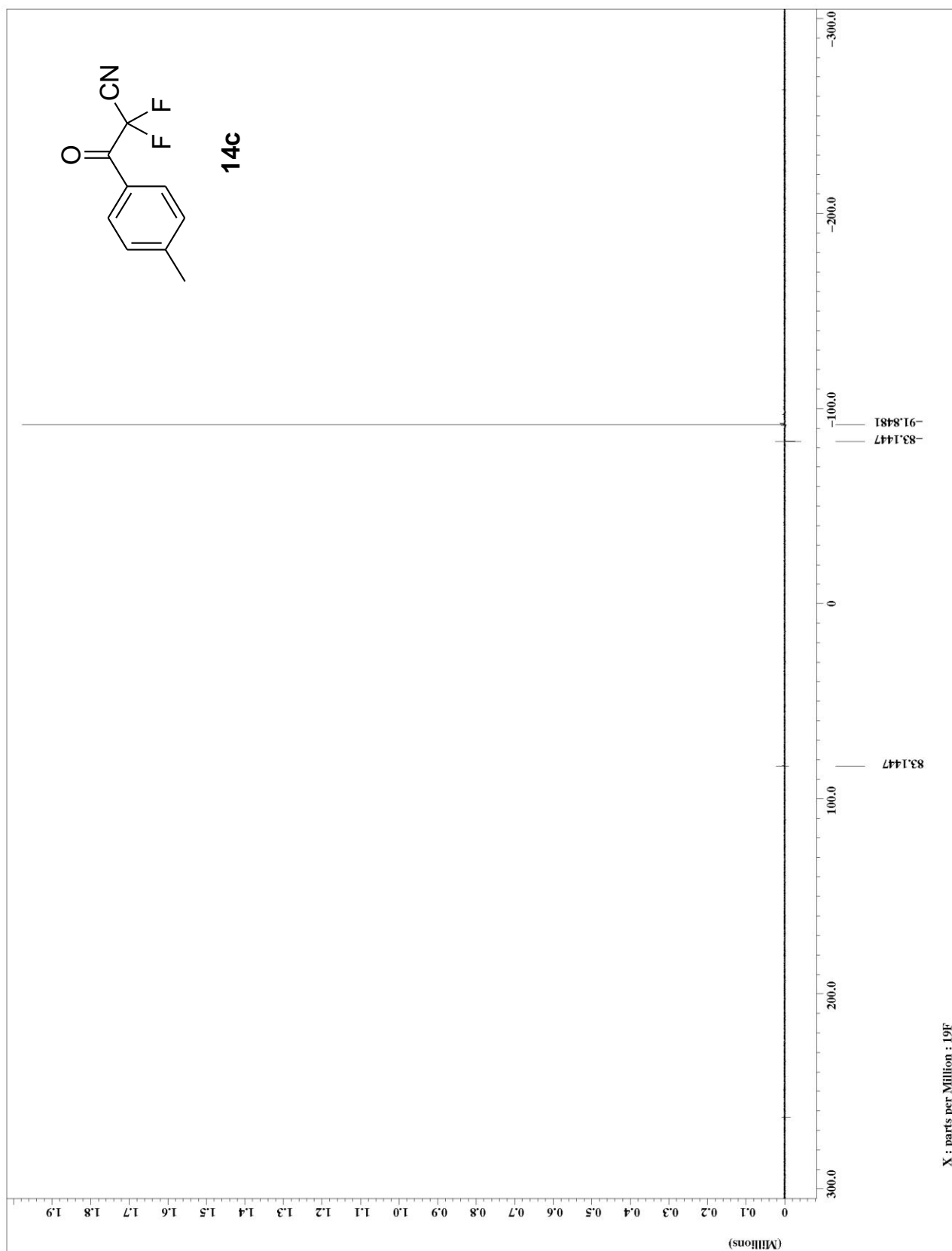


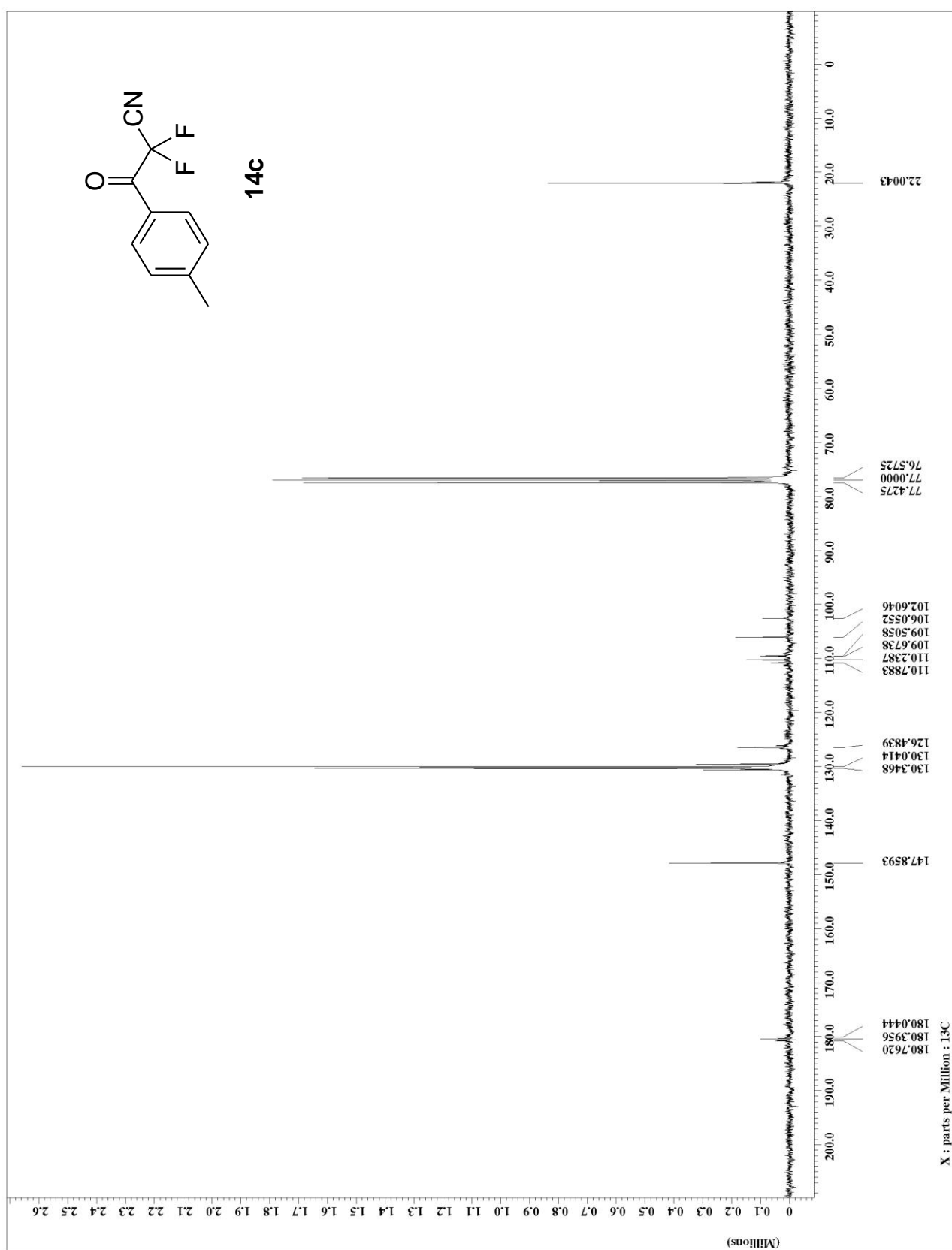












V. REFERENCES

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- ¹ Ramiz, M. M. M.; Elghandour, A. H. H.; Ibrahim, M. K. A.; Mansour, O. A. E. R. *Arch. Pharm.* **1989**, 322, 557.
- ² (a) Ridge, D. N.; William Hanifin, J.; Harten, L. A.; Johnson, B. D.; Menschik, J.; Nicolau, G.; Sloboda, A. E.; Watts, D. E. *J. Med. Chem.* **1979**, 22, 1385. (b) Peng, W.; Shreeve, J. M. *Tetrahedron Lett.* **2005**, 46, 4905.
- ³ Xiao, J.-C.; Shreeve, J. M. *J. Fluorine Chem.* **2005**, 126, 475.
- ⁴ Kitazume, T.; Kobayashi, T. *J. Fluorine Chem.* **1986**, 31, 357.
- ⁵ Kagaruki, S. R. F.; Kitazume, T.; Ishikawa, N. *Bull. Chem. Soc. Jpn.* **1981**, 54, 3221.
- ⁶ Hanamoto, T.; Suetake, T.; Koga, Y.; Kawanami, T.; Furuno, H.; Inanaga, J. *Tetrahedron* **2007**, 63, 5062.
- ⁷ Padwa, A.; Eisenbarth, P. *Tetrahedron* **1985**, 41, 283.
- ⁸ Riebel, H. J.; Hammann, I.; Unterstenhoefer, G. Ger. Offen. DE 2053713, 1972; *Chem. Abstr.* **1972**, 77, 75003.
- ⁹ Cavill, J. L.; Elliott, R. L.; Evans, G.; Jones, I. L.; Platts, J. A.; Ruda, A. M.; Tomkinson, N. C. O. *Tetrahedron* **2006**, 62, 410.