CuCl-Catalyzed *Ortho* Trifluoromethylation of Arenes and Heteroarenes with Pivalamido Directing Group

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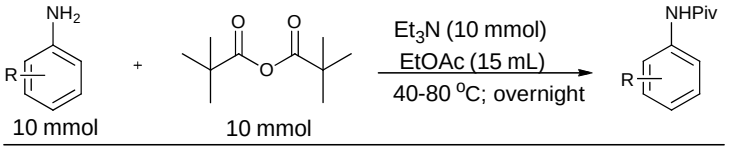
1. General Comments

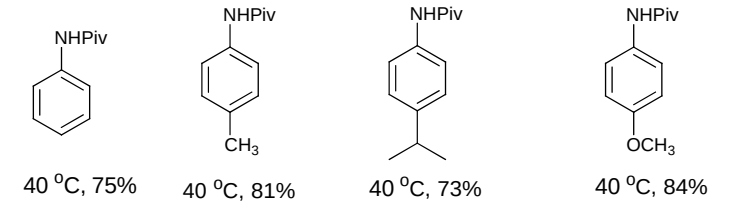
All the reactions were carried out in pre-dried a screwcapped tube with a Teflon-lined septum under N_2 atmosphere. Togni reagent was prepared according to the literatues[1]. All of the solvents were fresh distilled. Column chromatography was performed on silica gel (particle size 10-40 μm, Ocean Chemical Factory of Qingdao, China). ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL AL-400MHz spectrometer at ambient temperature with $CDCl_3$ as the solvent. Chemical shifts (δ) were given in ppm, referenced to the residual proton resonance of $CDCl_3$ (7.26), to the carbon resonance of $CDCl_3$ (77.16). Coupling constants (*J*) were given in Hertz (Hz). The term m, dq, q, t, d, s referred to multiplet, doublet quartet, quartet, triplet, doublet, singlet. Mass spectra were obtained using Bruker Esquire ion trap mass spectrometer in positive mode. The reaction progress was monitored by ^{19}F NMR. ^{19}F NMR yields, using fluorobenzene as internal standard, were obtained in proportion to the integral area of fluorobenzene signal.

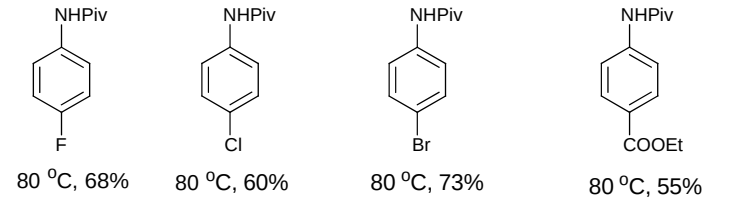
2. Preparation for Starting Materials

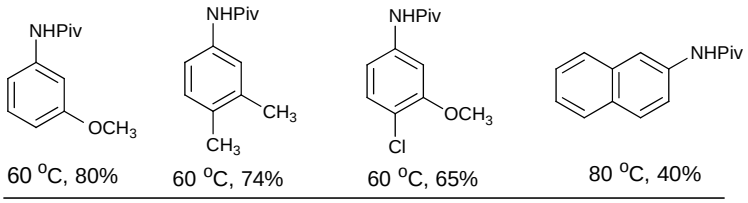
1) Preparation for N-Arylpivalamides

A sealed tube was charged with the mixture of Anilines (10 mmol), Et_3N (10 mmol), and stirred in EtOAc (15 mL) at room temperature, then Pivaloyl anhydride (10 mmol) was added. The tube was sealed and the mixture was allowed to stir at 40-80 °C overnight. After completion, the mixture was cooled to room temperature, then water (15 mL) was added and the mixture was extracted with EtOAc (15 mL x 2), dried by anhydrous Na_2SO_4. Evaporation of the solvent followed by recrystallization (petroleum ether and methanol as the solvents) provided the corresponding product.



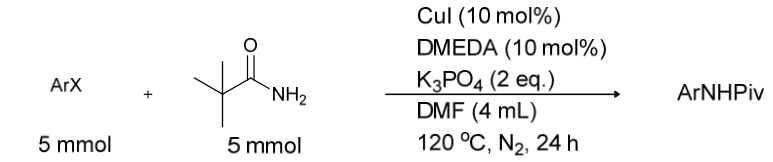


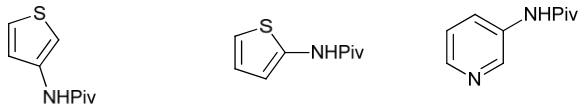




2) Preparation for NHPiv-substituted heterocyclic compounds

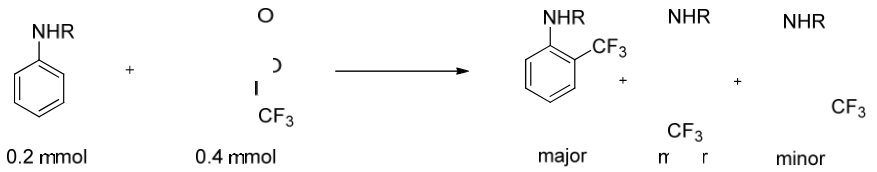
A sealed tube was charged with the mixture of Halogenated heterocyclic compounds (5 mmol), Pivalamide (5 mmol), CuI (0.5 mmol, 100 mg) and K_3PO_4 (10 mmol, 2.12 g), then DMEDA (0.5 mmol, 54 μL) and DMF (4 mL) were added under nitrogen atmosphere. The tube was sealed and the mixture was allowed to stir at 120 °C for 24 h. After completion, the mixture was cooled to room temperature, then water (30 mL) was added and the mixture was extracted with EtOAc (30 mL x 3), dried by anhydrous Na_2SO_4. Evaporation of the solvent followed by purification on silica gel (petroleum ether/ethyl acetate = 5/1) provided the corresponding product.





3. Reaction Condition Optimization

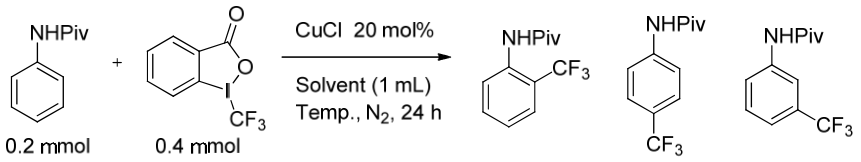
Screening the protecting-group:



No.	R	Catalyst	ent(1 mL)	Base	T(°C)	Time(h)	ld [a]
1	Piv	% CuCl	EtOAc		60	24	%
2	Piv	% CuCl	Ac		30	24	%
3	Piv	% CuCl	OH	(2 eq.) 1,2,2,6,6-methylpiperidine	30	24	n.r.
4	Piv	% CuCl	OH	O_4	30	24	%
5	Piv	% CuCl	OH	(0.5 eq.) CsF	30	24	%
6	Boc	% CuCl	OH		30	24	%
7		% CuCl	*t*-BuOH		30	24	20%
8	Ac	20% CuCl	*t*-BuOH		30	24	17%

[a] GC- yield of r oduct.

Screening the reaction conditions for producing **3a**:

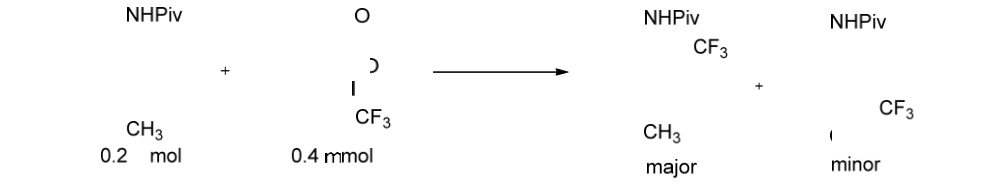


1 **2** **3a** **4a** **5a**

No.	Solvent	Temp.	Conversion	ratio of 3a: 4a: 5a
1	CH_3OH	30 °C	54%	32% :15% :7%
2	EtOAc	30 °C	87%	58% :23% :6%
3	CH_3CN	30 °C	83%	50% :22% :11%
4	1,4-dioxane	30 °C	43%	28% :10% :5%
5	$CHCl_3$	30 °C	82%	47% :23% :12%
6	*t*-BuOH	30 °C	93%	67% :17% :9%
7	CH_2OHCH_2OH	30 °C	trace	
8	Toluene	30 °C	trace	
9	THF	30 °C	trace	
10	*t*-BuOH	60 °C	94%	62% :24% :8%
11[a]	*t*-BuOH	30 °C	88%	55% :23% :10%
12[b]	*t*-BuOH	30 °C	56%	40% :11% :5%
13[c]	*t*-BuOH	30 °C	69%	48% :13% :8%

[a] 0.04 mmol of glycol was added as ligand. [b] 0.04 mmol of 1,10-phen was added as ligand. [c] 0.04 mmol of DMEDA was added as ligand.

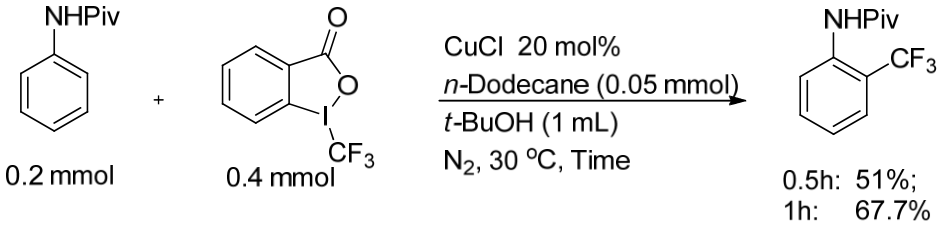
Screening the reaction conditions for producing **3b**:



No.	Catalyst	Solven mL)	Ligand	)	Time(h)	MS Yield [a]
1[b]	2 % CuCl	CH_2 OH	% PPh_3	60	12	%
2[b]	% CuI	CH_2 OH	% PPh_3	60	24	%
3[b]	20 Ac)$_2$	CH_2 OH	% PPh_3	60	24	%
4	% CuCl	CH_2 OH	20% PPh_3	60	24	%
5	% CuCl	CH_2 OH		80	24	%
6	% CuCl	CH_3CN		80	24	%
7	% CuCl	THF		80	24	%
8	% CuCl	EtOAc		80	24	%
9	% CuCl	MF		80	24	%
10	% CuCl	DCE		80	24	%
11	% CuCl	OH		80	24	%
12	% CuCl	DCM		80	24	%
13	% CuCl	EtOAc		80	24	%
14	% CuCl	EtOAc		80	24	%
15	1 eq. CuCl	EtOAc		80	24	%
16	% CuCl	EtOAc	2 % 1,10-Phen	80	24	%
17	%CuCl	EtOAc	MEDA	80	24	%
18	Ac		20%TMEDA	80	24	%
19	20% CuCl	*t*-BuOH		30	24	40%
20				60	24	

[a] GC-MS y major product. mmol togni reagent.

GC yield of the major product **3a** after different periods:

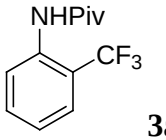


0.5h: 51%;
1h: 67.7%
3h: 70.5%
6h: 71.7%
9h: 72.5%
18h: 74.5%
24h: 75%

4. Experimental Section

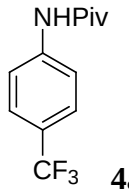
General procedure for the synthesis of N-(2-(trifluoromethyl)aryl)pivalamide

A sealed tube was charged with the mixture of N-Arylpivalamide **1** (0.4 mmol), togni reagent **2** (0.8 mmol, 252.8 mg), CuCl (0.08 mmol, 8 mg), then stirred in *t*-BuOH (1 mL) at room temperature under nitrogen atmosphere. Half an hour later, the tube was sealed and the mixture was allowed to stir at 30-120 °C for indicated time. After completion, the mixture was cooled to room temperature, then $NaHCO_3$ aq. (5 mL) was added and the mixture was extracted with EtOAc (5 mL x 3), dried by anhydrous Na_2SO_4. Evaporation of the solvent followed by purification on silica gel chromatography (petroleum ether/dichloromethane/ethyl acetate = 40/3/1) provided the corresponding product **3**.



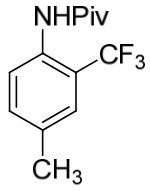
3a

N-(2-(trifluoromethyl)phenyl)pivalamide[2]: White Solid, 63 mg (65% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.32 (s, 9H), 7.20 (t, J_{H-H} = 7.6 Hz, 1H), 7.54 (t, J_{H-H} = 7.9 Hz, 1H), 7.59 (d, J_{H-H} = 7.9 Hz, 1H), 7.79 (s, 1H), 8.24 (d, J_{H-H} = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 27.5, 40.0, 120.0 (q, J_{F-C} = 29.5 Hz), 124.2, 124.3, 124.4 (q, J_{F-C} = 272.8 Hz), 126.1 (q, J_{F-C} = 5.4 Hz), 133.0, 135.8, 176.8; ^{19}F NMR ($CDCl_3$, 376 MHz): δ -60.69 (s); ESI-MS: $[M+ Na]^+$ *m*/*z* 268.1; HRMS: calculated for $C_{12}H_{14}F_3NO[M+H^+]$: 246.1100; found, 246.1101.



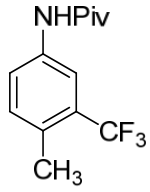
4a

N-(4-(trifluoromethyl)phenyl)pivalamide[3]: White Solid, 15 mg (15% yield), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.32 (s, 9H), 7.49 (s, 1H), 7.55 (d, J_{H-H} = 8.6 Hz, 2H), 7.65 (d, J_{H-H} = 8.6 Hz, 2H); ^{19}F NMR ($CDCl_3$, 376 MHz): δ -61.98 (s); ESI-MS: $[M+Na]^+$ *m/z* 268.2.



3b

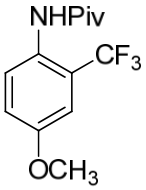
N-(4-methyl-2-(trifluoromethyl)phenyl)pivalamide: White Solid, 71 mg (69% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.31 (s, 9H), 2.35 (s, 3H), 7.34 (d, J_{H-H} = 8.5 Hz, 1H), 7.39 (s, 1H), 7.70 (s, 1H), 8.05 (d, J_{H-H} = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 20.9, 27.5, 39.8, 120.2 (q, J_{F-C} = 29.0 Hz), 124.4 (q, J_{F-C} = 273.0 Hz), 124.7, 126.4 (q, J_{F-C} = 5.3 Hz), 133.1, 133.4, 134.3, 176.8; ^{19}F NMR ($CDCl_3$, 376 MHz): δ -60.66 (s); ESI-MS: $[M+Na]^+$ *m/z* 282.1; HRMS: calculated for $C_{13}H_{16}F_3NO[M+Na^+]$: 260.1257; found, 260.1258.



5b

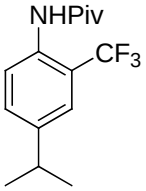
N-(4-methyl-3-(trifluoromethyl)phenyl)pivalamide: White Solid, 13 mg (13% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.31 (s, 9H), 2.43 (s, 3H), 7.22 (d, J_{H-H} = 8.3 Hz, 1H), 7.39 (s, 1H), 7.65 (d, J_{H-H} = 8.3 Hz, 1H), 7.73 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 18.8, 27.6, 39.7, 117.6 (q, J_{F-C} = 5.8 Hz), 123.1, 124.3 (q, J_{F-C} = 273.9

Hz), 129.3 (q, J_{F-C} = 29.9 Hz), 132.2, 132.5, 136.0, 176.9; ^{19}F NMR ($CDCl_3$, 376 MHz): δ -61.77 (s); ESI-MS: $[M+ Na]^+$ *m*/*z* 282.1.



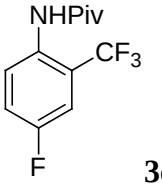
3c

N-(4-methoxy-2-(trifluoromethyl)phenyl)pivalamide: White Solid, 68 mg (63% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.30 (s, 9H), 3.82 (s, 3H), 7.06 (d, J_{H-H} = 9.0 Hz, 1H), 7.11 (s, 1H), 7.56 (s, 1H), 7.95 (d, J_{H-H} = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 27.5, 39.7, 55.8, 111.7 (q, J_{F-C} = 5.4 Hz), 117.7, 122.4 (q, J_{F-C} = 28.8 Hz), 123.9 (q, J_{F-C} = 272.1 Hz), 127.3, 128.3, 156.4, 176.9; ^{19}F NMR ($CDCl_3$, 376 MHz): δ -61.95 (s); ESI-MS: $[M+ Na]^+$ *m*/*z* 298.1.



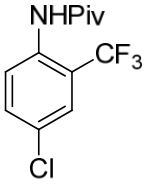
3d

N-(4-isopropyl-2-(trifluoromethyl)phenyl)pivalamide: White Solid, 63 mg (55% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.24 (d, J_{H-H} = 6.9 Hz, 6H), 1.31 (s, 9H), 2.92 (sept, J_{H-H} = 6.9 Hz, 1H), 7.40 (d, J_{H-H} = 8.6 Hz, 1H), 7.43 (s, 1H), 7.71 (s, 1H), 8.08 (d, J_{H-H} = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 23.9, 27.5, 33.7, 39.9, 120.2 (q, J_{F-C} = 29.0 Hz), 123.9 (q, J_{F-C} = 5.2 Hz), 124.5 (q, J_{F-C} = 273.1 Hz), 124.8, 130.9, 133.4, 145.3, 176.8; ^{19}F NMR ($CDCl_3$, 376 MHz): δ -60.54 (s); ESI-MS: $[M+ Na]^+$ *m*/*z* 310.1.



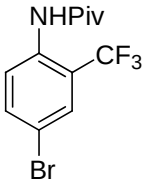
3e

N-(4-fluoro-2-(trifluoromethyl)phenyl)pivalamide: White Solid, 44 mg (42% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.31 (s, 9H), 7.21-7.28 (m, 1H), 7.31 (dd, J = 8.5, 2.9 Hz, 1H), 7.67 (s, 1H), 8.14 (dd, J = 9.1, 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 27.4, 39.9, 113.4 (dq, J_{F-C} = 26.0, 5.4 Hz), 119.7 (d, J_{F-C} = 21.8 Hz), 122.1 (dq, J_{F-C} = 30.5, 7.6 Hz), 123.4 (q, J_{F-C} = 273.2 Hz), 127.1 (d, J_{F-C} = 7.7 Hz), 131.9, 158.7 (d, J_{F-C} = 246.4 Hz), 176.9; ^{19}F NMR ($CDCl_3$, 376 MHz): δ -115.85 (s), -61.28 (s); ESI-MS: $[M+ Na]^+$ *m/z* 286.1.



3f

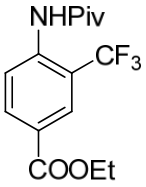
N-(4-chloro-2-(trifluoromethyl)phenyl)pivalamide: White Solid, 36 mg (32% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.31 (s, 9H), 7.50 (d, J_{H-H} = 9.0 Hz, 1H), 7.57 (s, 1H), 7.75 (s, 1H), 8.23 (d, J_{H-H} = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 27.4, 40.0, 121.2 (q, J_{F-C} = 30.5 Hz), 123.5 (q, J_{F-C} = 273.3 Hz), 125.6, 126.2 (q, J_{F-C} = 5.5 Hz), 129.6, 132.9, 134.5, 176.8; ^{19}F NMR ($CDCl_3$, 376 MHz): δ -61.12 (s); ESI-MS: $[M+ Na]^+$ *m/z* 302.1, 304.2.



3g

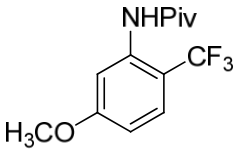
N-(4-bromo-2-(trifluoromethyl)phenyl)pivalamide: Light Yellow Solid, 63 mg (49% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.31 (s, 9H), 7.65 (dd, J_{H-H} = 8.9, 1.9 Hz,

1H), 7.72 (d, J_{H-H} = 1.9 Hz, 1H), 7.75 (s, 1H), 8.19 (d, J_{H-H} = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 27.4, 40.1, 116.8, 121.3 (q, J_{F-C} = 30.0 Hz), 123.4 (q, J_{F-C} = 273.7 Hz), 125.7, 129.1 (q, J_{F-C} = 5.5 Hz), 135.0, 135.9, 176.8; ^{19}F NMR ($CDCl_3$, 376 MHz): δ -61.06 (s); ESI-MS: $[M+ Na]^+$ *m*/*z* 346.1, 348.0.



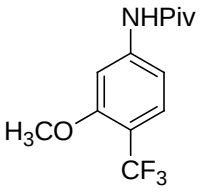
3h

ethyl 4-pivalamido-3-(trifluoromethyl)benzoate: Oil, 38 mg (30% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.32 (s, 9H), 1.40 (t, J_{H-H} = 7.2 Hz, 3H), 4.38 (q, J_{H-H} = 7.2 Hz, 2H), 7.98 (s, 1H), 8.19 (d, J_{H-H} = 8.7 Hz, 1H), 8.28 (s, 1H), 8.50 (d, J_{H-H} = 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 14.4, 27.4, 40.3, 61.5, 118.7 (q, J_{F-C} = 30.1 Hz), 122.6, 124.0 (q, J_{F-C} = 272.4 Hz), 125.8, 127.8 (q, J_{F-C} = 5.3 Hz), 134.3, 139.8, 165.1, 176.8; ^{19}F NMR ($CDCl_3$, 376 MHz): δ -60.88 (s); ESI-MS: $[M+ Na]^+$ *m*/*z* 340.1.



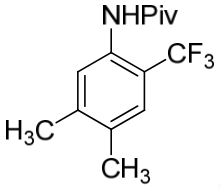
3i

N-(5-methoxy-2-(trifluoromethyl)phenyl)pivalamide: Oil, 44 mg (40% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.31 (s, 9H), 3.85 (s, 3H), 6.69 (d, J_{H-H} = 8.6 Hz, 1H), 7.47 (d, J_{H-H} = 8.8 Hz, 1H), 7.85 (s, 1H), 7.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 27.4, 40.1, 55.7, 108.0, 110.4, 111.4 (q, J_{F-C} = 29.8 Hz), 124.8 (q, J_{F-C} = 271.8 Hz), 127.3 (q, J_{F-C} = 5.0 Hz), 137.6, 163.0, 176.9; ^{19}F NMR ($CDCl_3$, 376 MHz): δ -59.25 (s); ESI-MS: $[M+ Na]^+$ *m*/*z* 298.1.



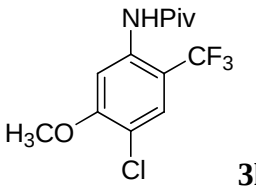
4i

N-(3-methoxy-4-(trifluoromethyl)phenyl)pivalamide: White Solid, 17 mg (16% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.33 (s, 9H), 3.90 (s, 3H), 6.80 (d, J_{H-H} = 8.3 Hz, 1H), 7.45 (d, J_{H-H} = 8.3 Hz, 1H), 7.46 (s, 1H), 7.76 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 27.7, 40.0, 56.1, 103.6, 110.1, 114.2 (q, J_{F-C} = 31.2 Hz), 123.8 (q, J_{F-C} = 271.6 Hz), 127.6 (q, J_{F-C} = 5.0 Hz), 142.9, 158.5, 177.2; ^{19}F NMR ($CDCl_3$, 376 MHz): δ -61.77 (s); ESI-MS: $[M+ Na]^+$ *m*/*z* 298.4.



3j

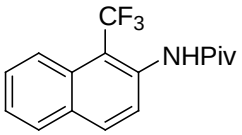
N-(4,5-dimethyl-2-(trifluoromethyl)phenyl)pivalamide: Oil, 52 mg (48% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.31 (s, 9H), 2.25 (s, 3H), 2.29 (s, 3H), 7.33 (s, 1H), 7.67 (s, 1H), 7.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 19.4, 20.1, 27.5, 39.9, 117.8 (q, J_{F-C} = 29.2 Hz), 124.6 (q, J_{F-C} = 272.5 Hz), 125.7, 126.8 (q, J_{F-C} = 5.2 Hz), 133.0, 133.2, 142.0, 176.8; ^{19}F NMR ($CDCl_3$, 376 MHz): δ -60.05 (s); ESI-MS: $[M+ Na]^+$ *m*/*z* 296.1.



3k

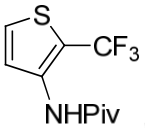
N-(4-chloro-5-methoxy-2-(trifluoromethyl)phenyl)pivalamide: White Solid, 49 mg (40% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.32 (s, 9H), 3.96 (s, 3H), 7.56 (s, 1H), 7.87 (s, 1H), 8.17 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 27.4, 40.3, 56.6, 106.7,

111.6 (q, J_{F-C} = 30.7 Hz), 117.2, 124.0 (q, J_{F-C} = 272.1 Hz), 127.5 (q, J_{F-C} = 5.4 Hz), 136.2, 158.1, 177.1; ^{19}F NMR ($CDCl_3$, 376 MHz): δ -59.46 (s); ESI-MS: $[M+ Na]^+$ *m*/*z* 332.0, 334.1.



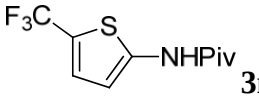
3l

N-(1-(trifluoromethyl)naphthalen-2-yl)pivalamide: Light Yellow Solid, 63 mg (54% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.36 (s, 9H), 7.50 (t, J_{H-H} = 7.8 Hz, 1H), 7.58 (t, J_{H-H} = 6.9 Hz, 1H), 7.84 (d, J_{H-H} = 8.0 Hz, 1H), 7.95 (d, J_{H-H} = 9.1 Hz, 1H), 8.10 (d, J_{H-H} = 9.1 Hz, 1H), 8.18 (d, J_{H-H} = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 27.5, 40.0, 114.3 (q, J_{F-C} = 27.4 Hz), 123.8, 124.5 (q, J_{F-C} = 4.7 Hz), 125.9, 128.0, 128.7, 125.9 (q, J_{F-C} = 275.3 Hz), 130.1, 131.4, 133.0, 135.6, 177.1; ^{19}F NMR ($CDCl_3$, 376 MHz): δ -50.98 (s); ESI-MS: $[M+ Na]^+$ *m*/*z* 318.1.



3m

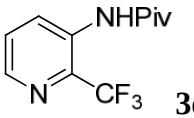
N-(2-(trifluoromethyl)thiophen-3-yl)pivalamide: White Solid, 86 mg (86% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.30 (s, 9H), 7.41 (d, J_{H-H} = 5.5 Hz, 1H), 7.93 (d, J_{H-H} = 5.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 27.5, 39.7, 111.5 (q, J_{F-C} = 36.3 Hz), 123.3 (q, J_{F-C} = 268.3 Hz), 123.8, 127.5, 137.6, 175.8; ^{19}F NMR ($CDCl_3$, 376 MHz): δ -53.50 (s); ESI-MS: $[M+ Na]^+$ *m*/*z* 274.1.



3n

N-(5-(trifluoromethyl)thiophen-2-yl)pivalamide: White Solid, 52 mg (52% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.33 (s, 9H), 6.57 (d, J_{H-H} = 3.8 Hz, 1H), 7.19 (d, J_{H-H}

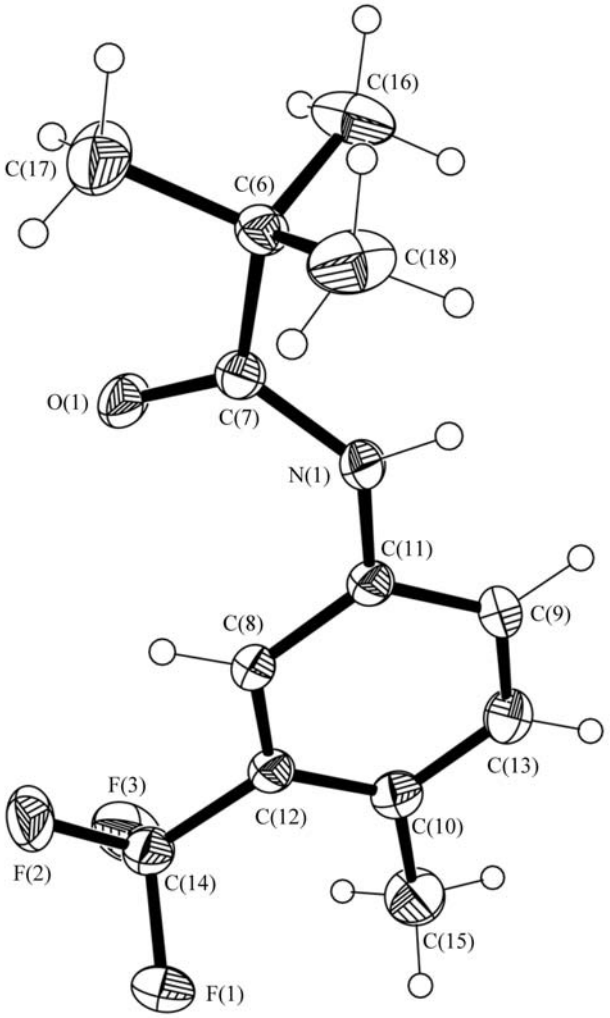
= 3.8 Hz, 1H), 8.23 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 27.5, 39.1, 109.9, 122.9 (q, J_{F-C} = 38.0 Hz), 123.2 (q, J_{F-C} = 268.1 Hz), 125.6 (q, J_{F-C} = 4.0 Hz), 142.4, 175.4; ^{19}F NMR ($CDCl_3$, 376 MHz): δ -54.67 (s); ESI-MS: $[M+ Na]^+$ *m*/*z* 274.1.



3o

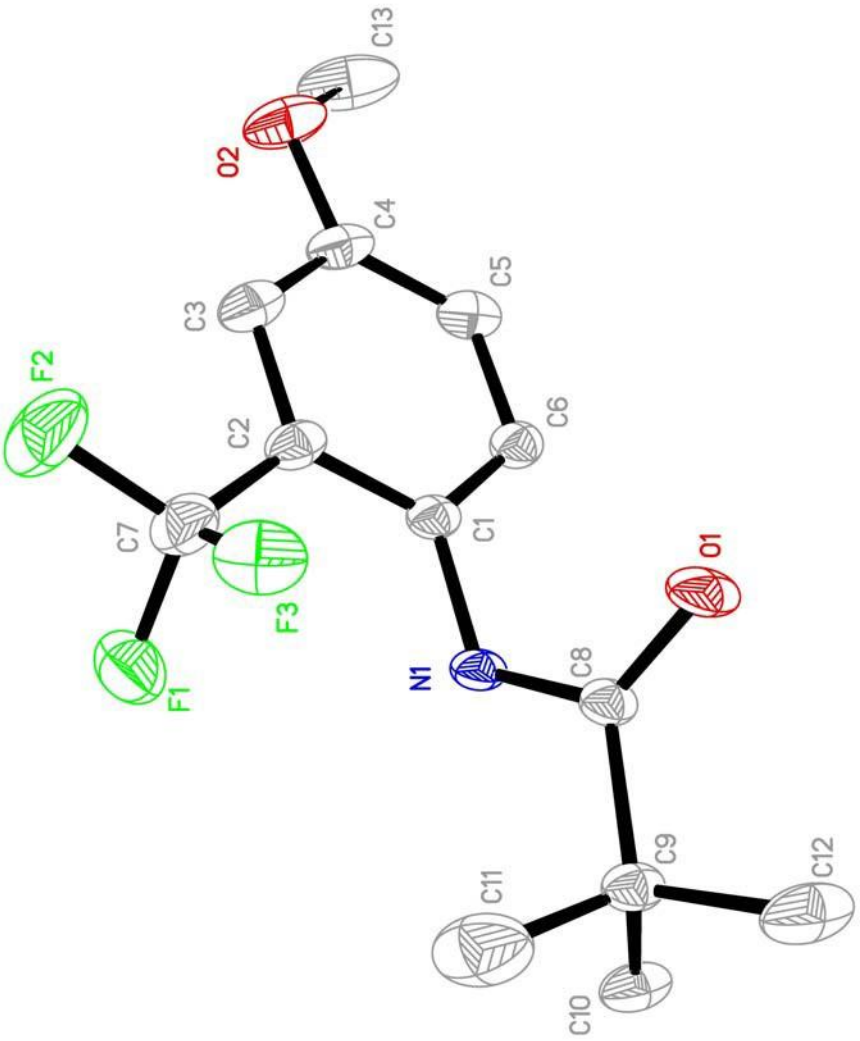
N-(2-(trifluoromethyl)pyridin-3-yl)pivalamide: Light Yellow Solid, 50 mg (51% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.36 (s, 9H), 7.50 (dd, J_{H-H} = 8.4, 4.5 Hz, 1H), 7.88 (s, 1H), 8.41 (d, J_{H-H} = 4.5 Hz, 1H), 8.71 (d, J_{H-H} = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 27.4, 40.2, 122.4 (q, J_{F-C} = 274.9 Hz), 127.2, 131.6, 133.4, 136.3 (q, J_{F-C} = 32.4 Hz), 144.3, 177.2; ^{19}F NMR ($CDCl_3$, 376 MHz): δ -64.35 (s); ESI-MS: $[M+ Na]^+$ *m*/*z* 269.3.

5. Crystal Structure of 5b



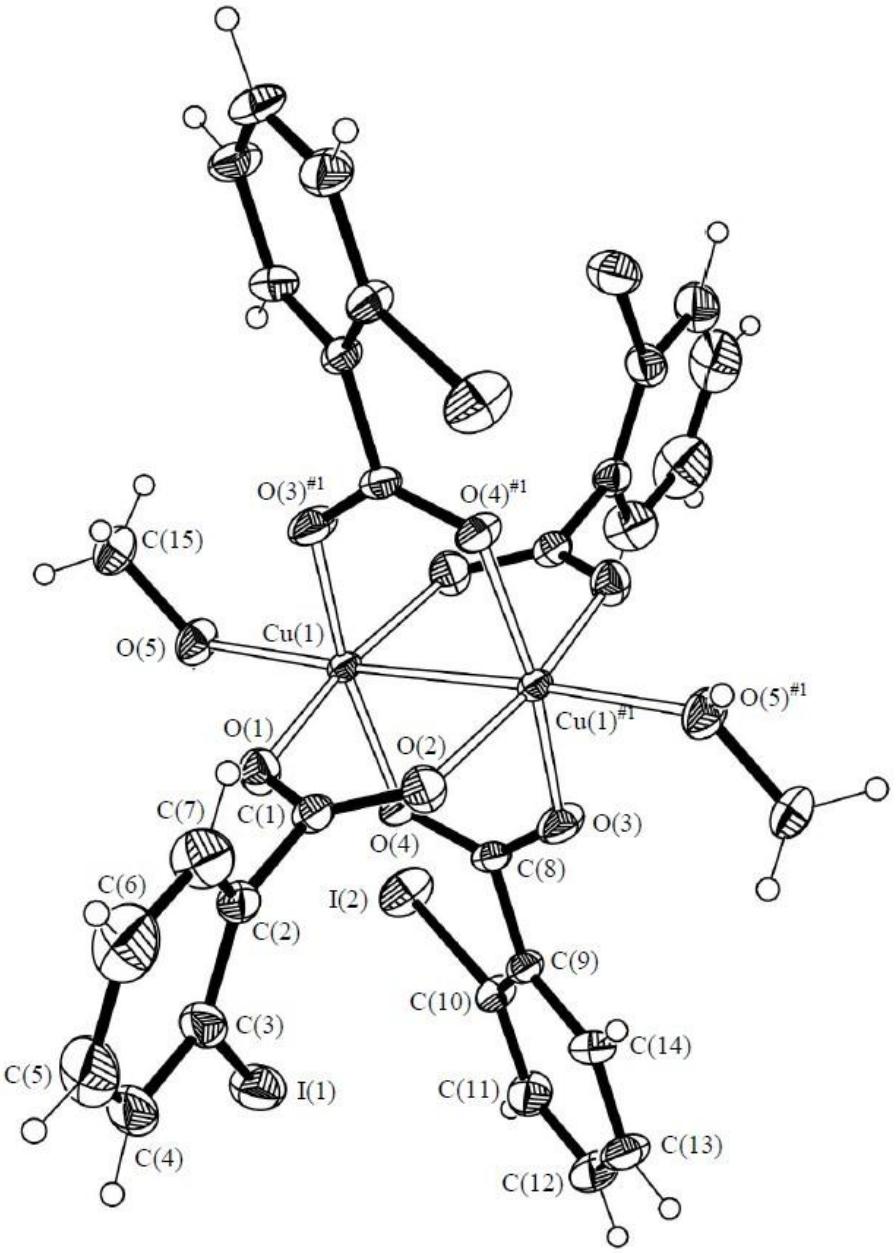
Ortep drawing of $C_{13}H_{16}NOF_3$ with 35% probability ellipsoids, showing the atomic numbering scheme.

6. Crystal Structure of 3c



Ortep drawing of $C_{13}H_{16}F_3NO_2$ with 30% probability ellipsoids, showing the atomic numbering scheme.

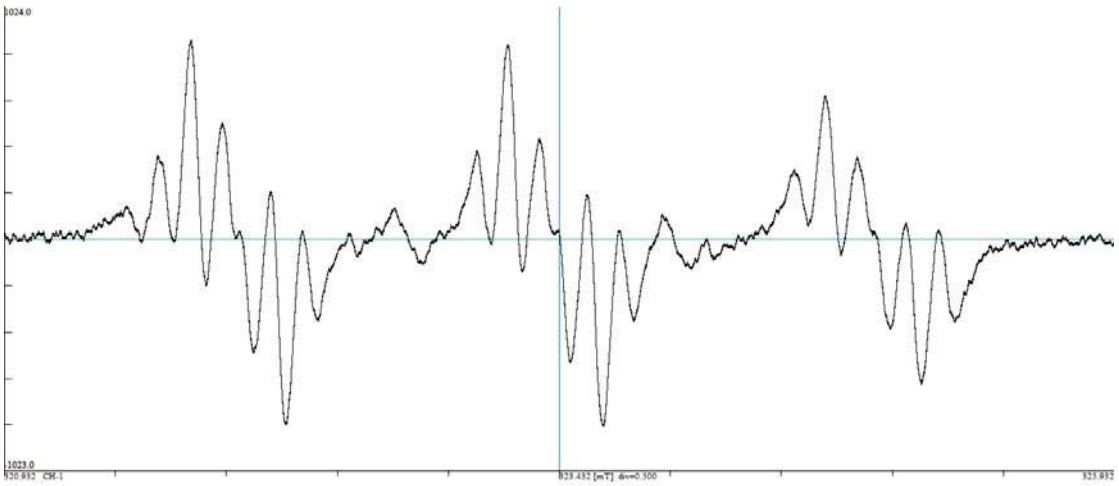
7. Crystal Structure of Cupric Iodobenzoate 6

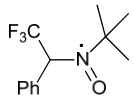


Ortep drawing of $[Cu(C_7H_4IO_2)_2(CH_3OH)]_2$ with 50% probability ellipsoids, showing the atomic numbering scheme.

8. Capture of Trifluoromethyl Radical by EPR

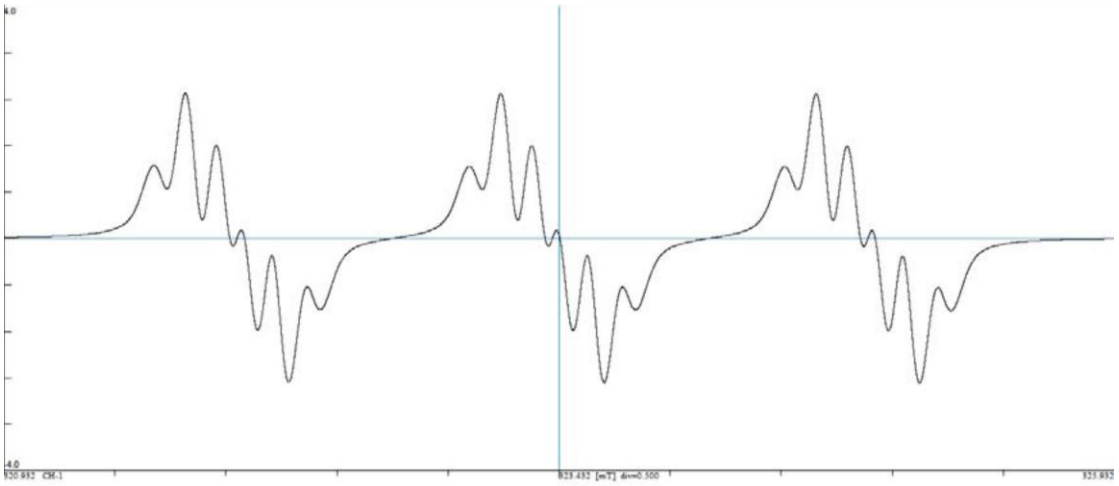
A sealed tube was charged with the mixture of N-Phenylpivalamide **1a** (0.1 mmol), Togni reagent **2** (0.2 mmol, 63.2 mg), CuCl (0.02 mmol, 2 mg), PBN (4.7 mg), then *t*-BuOH (1 mL) was added under nitrogen atmosphere, the reaction was proceeded under 40 ^{o}C, and 5 minutes later, the reaction was detected by EPR.

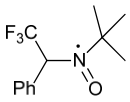




Spectrum Detected by EPR (at 5 min)

7



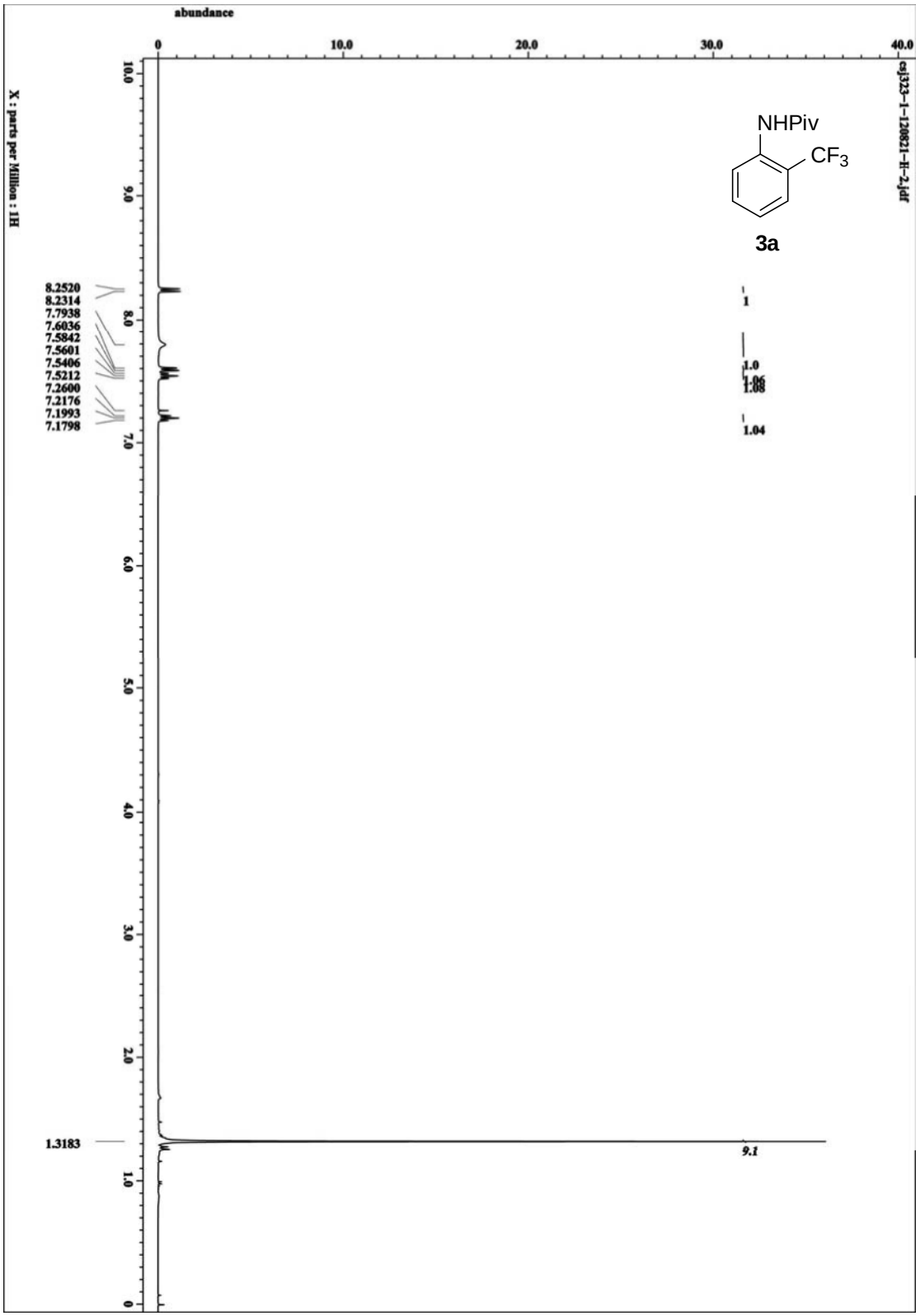


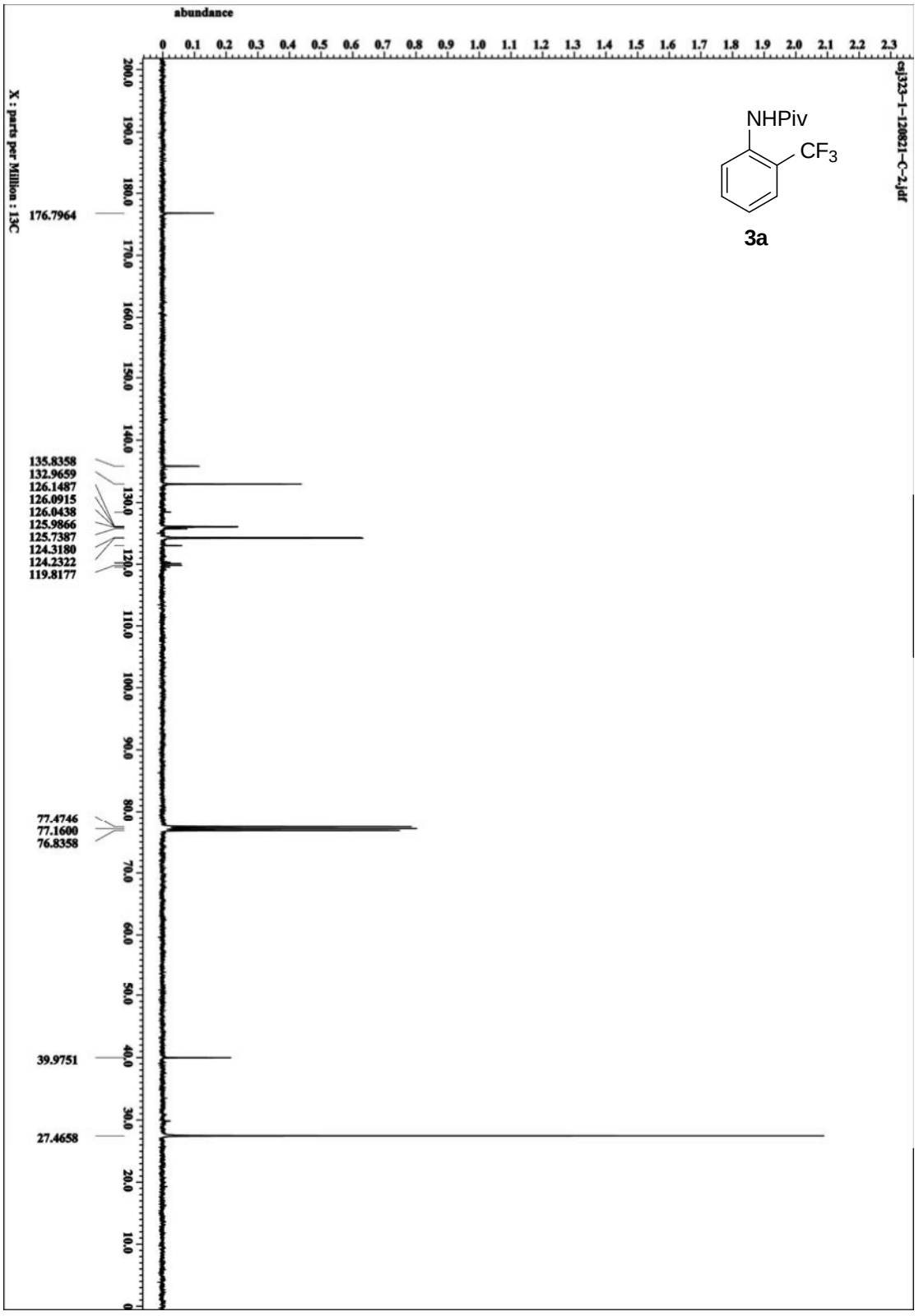
Simulation: A_N=1.42 mT, A_H=0.24 mT, A_F=0.14 mT

7

The experimental results are consistent with the simulatio.

9. Copies of ^{1}H, ^{13}C and ^{19}F NMR Spectra

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126.0915
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124.2322
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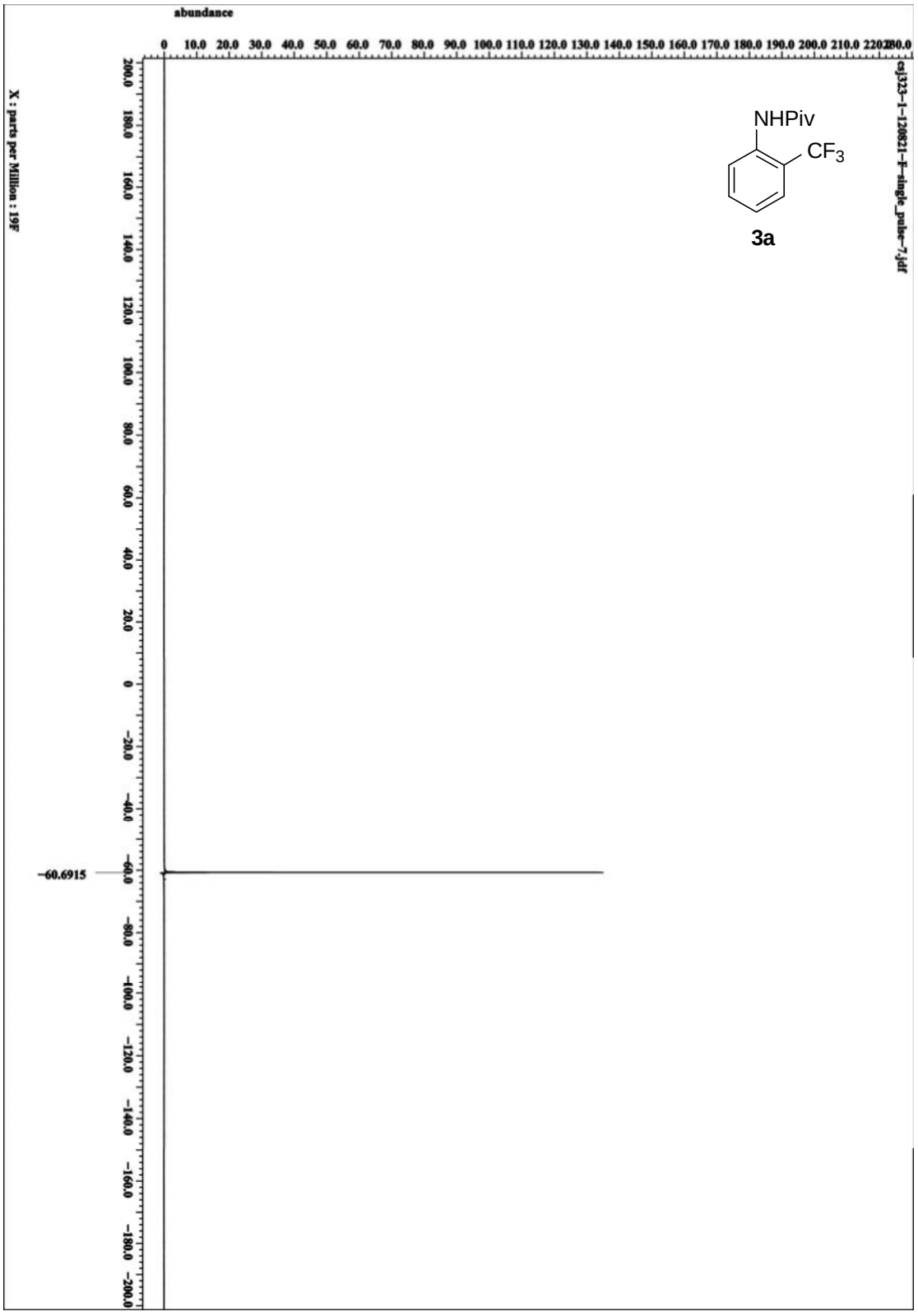
27.4658


abundance
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3a
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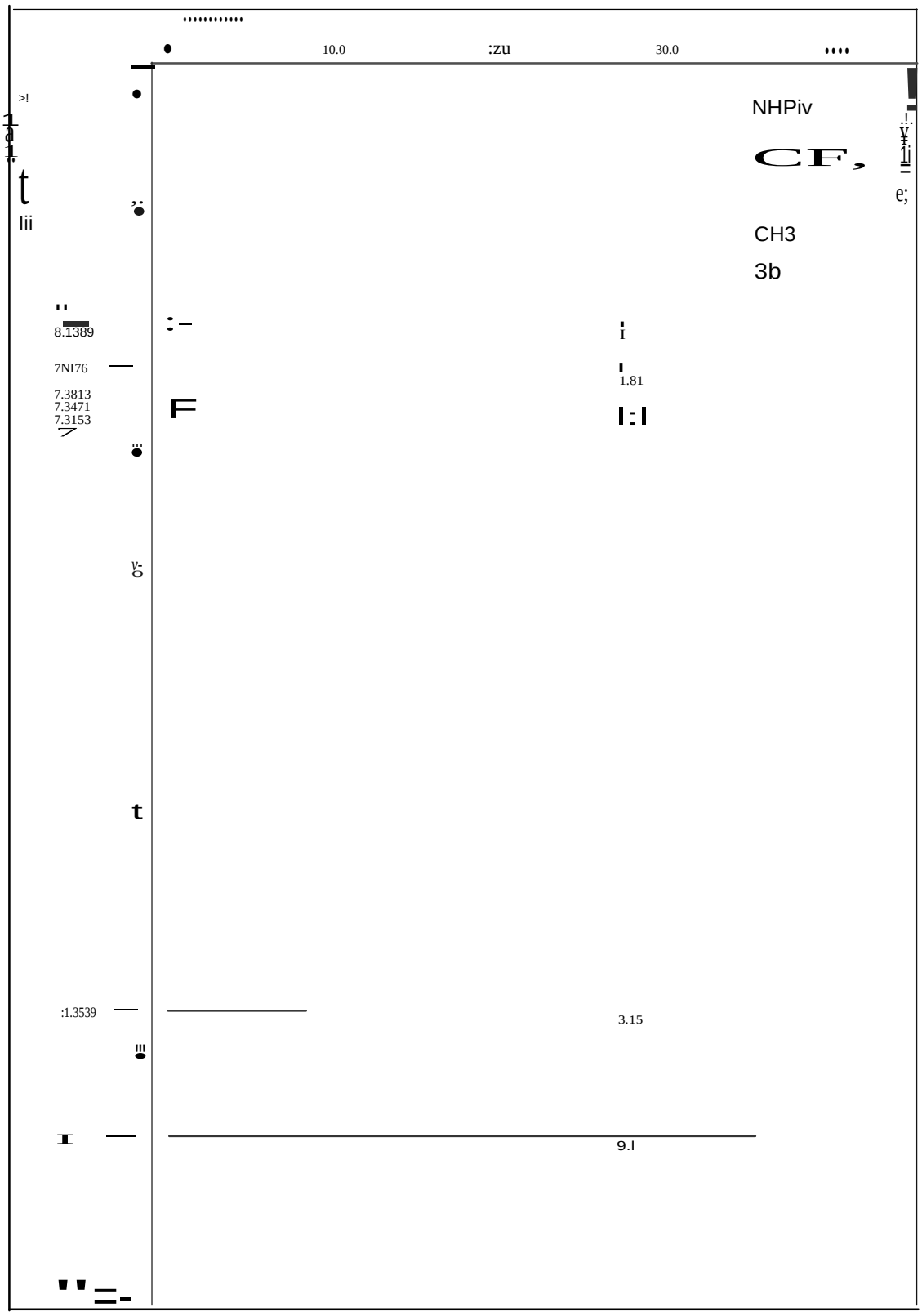
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CF,
CH3
3b
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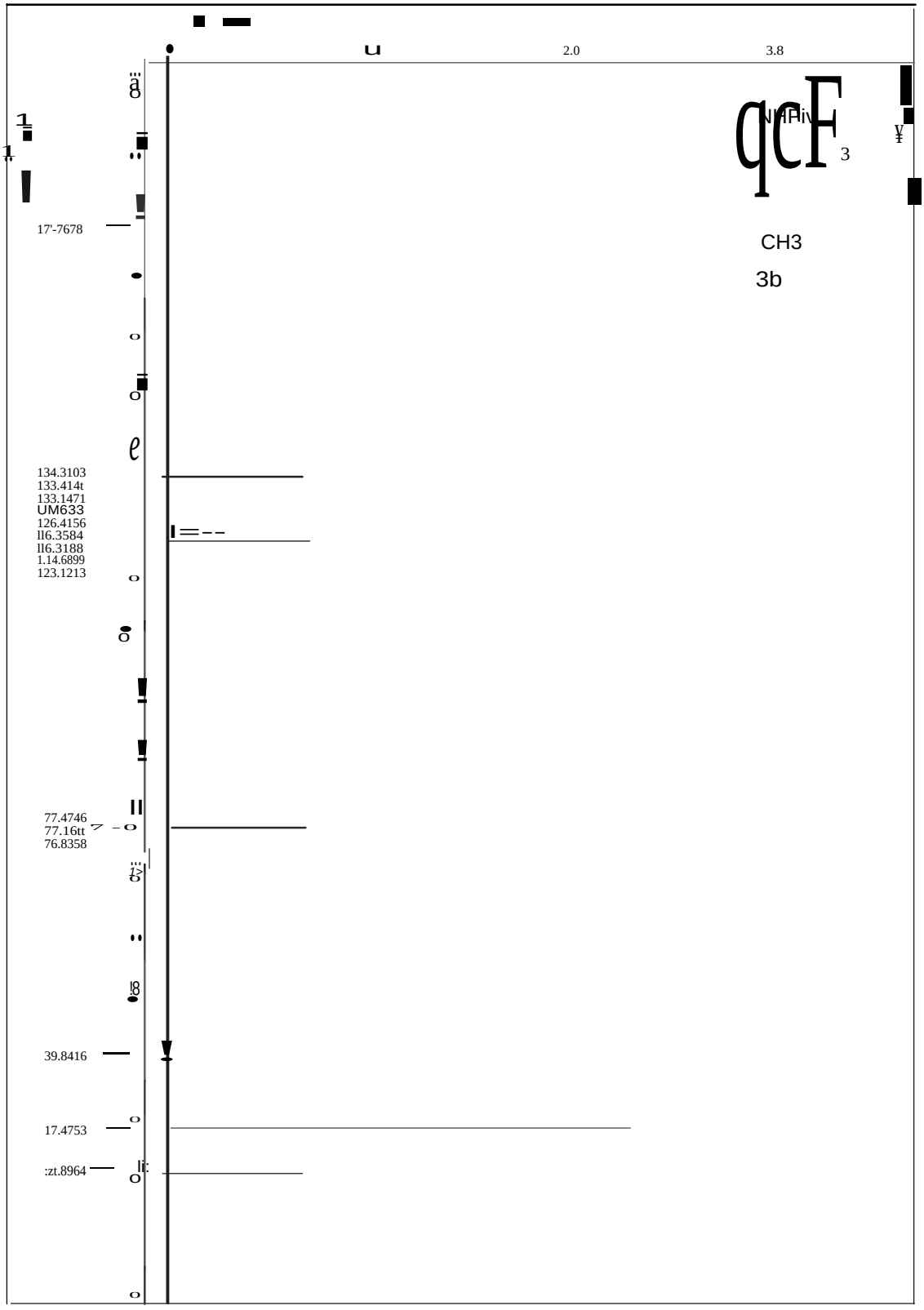
7.3471
7.3153
1.81
3.15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CH3
3b
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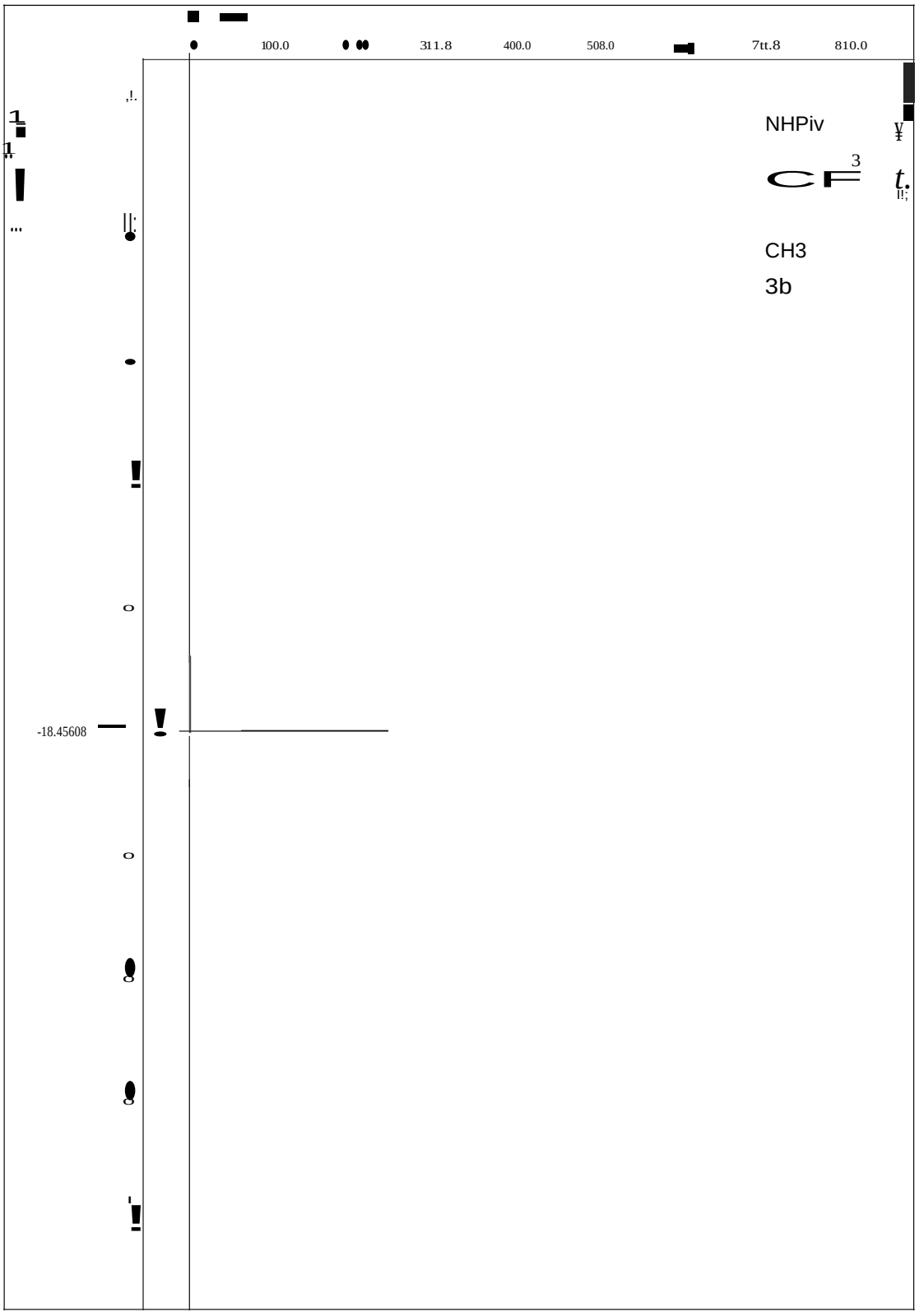
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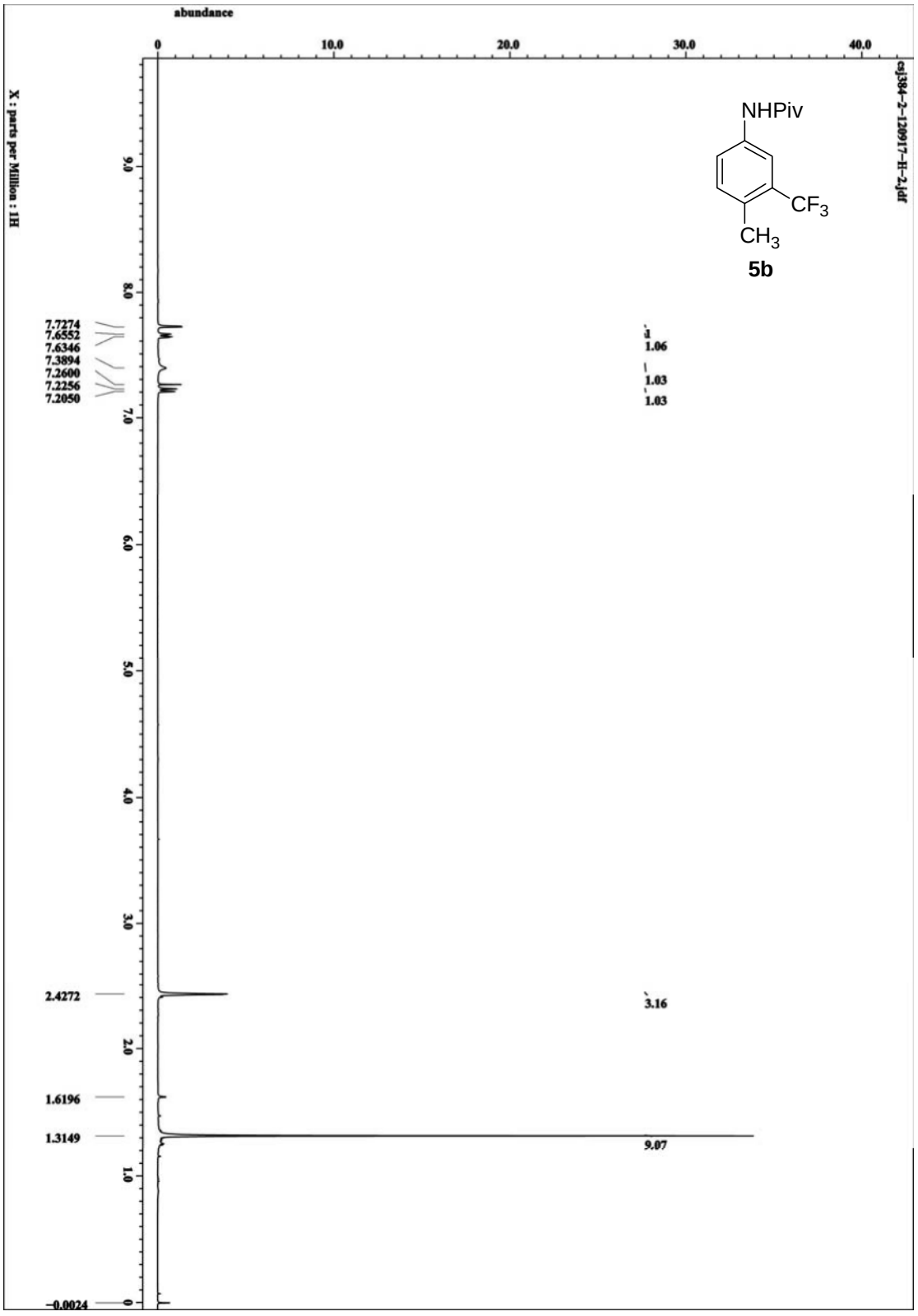
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CH3
5b
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7.3894
7.2600
7.2256
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9.07
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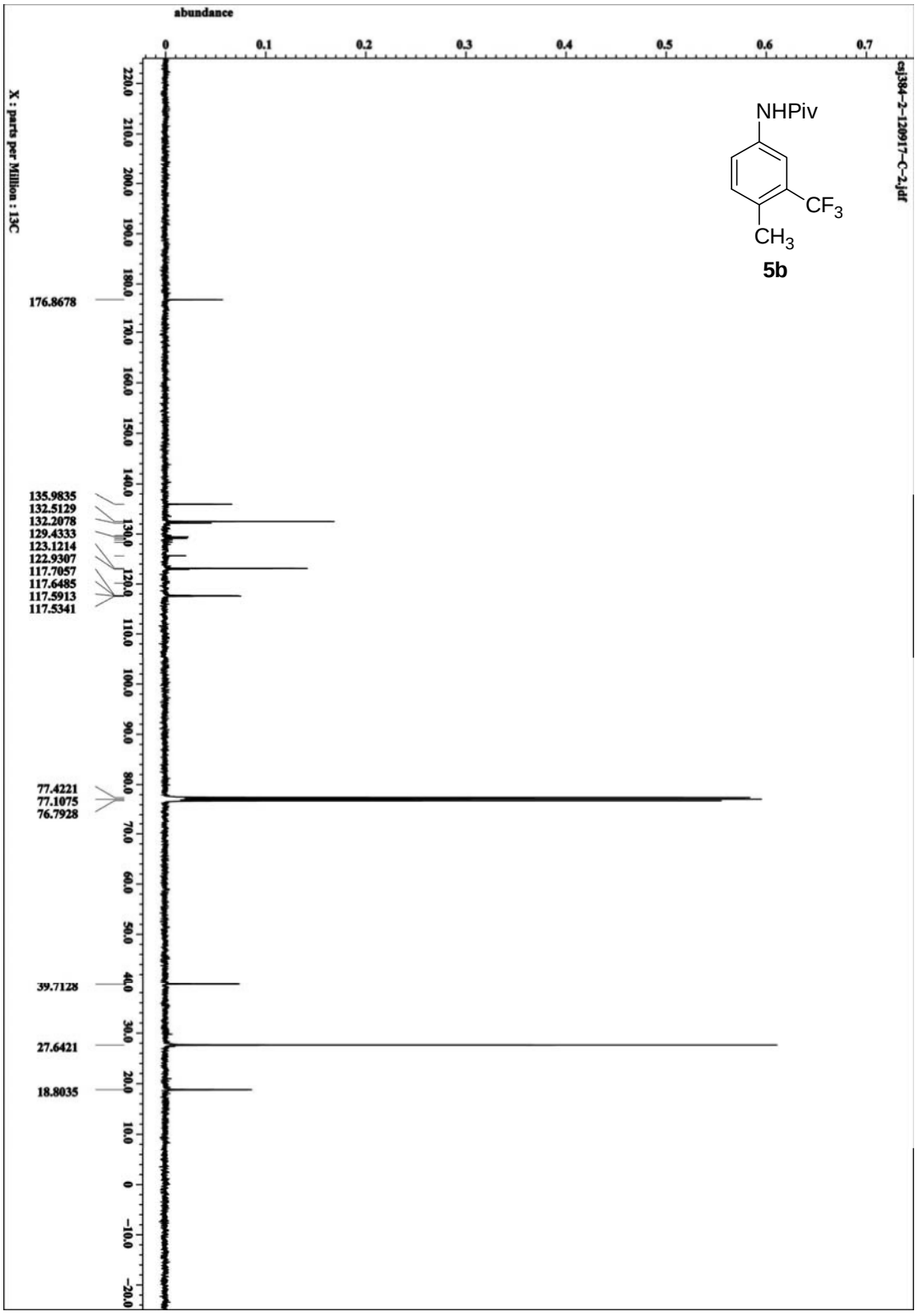
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CH3
5b
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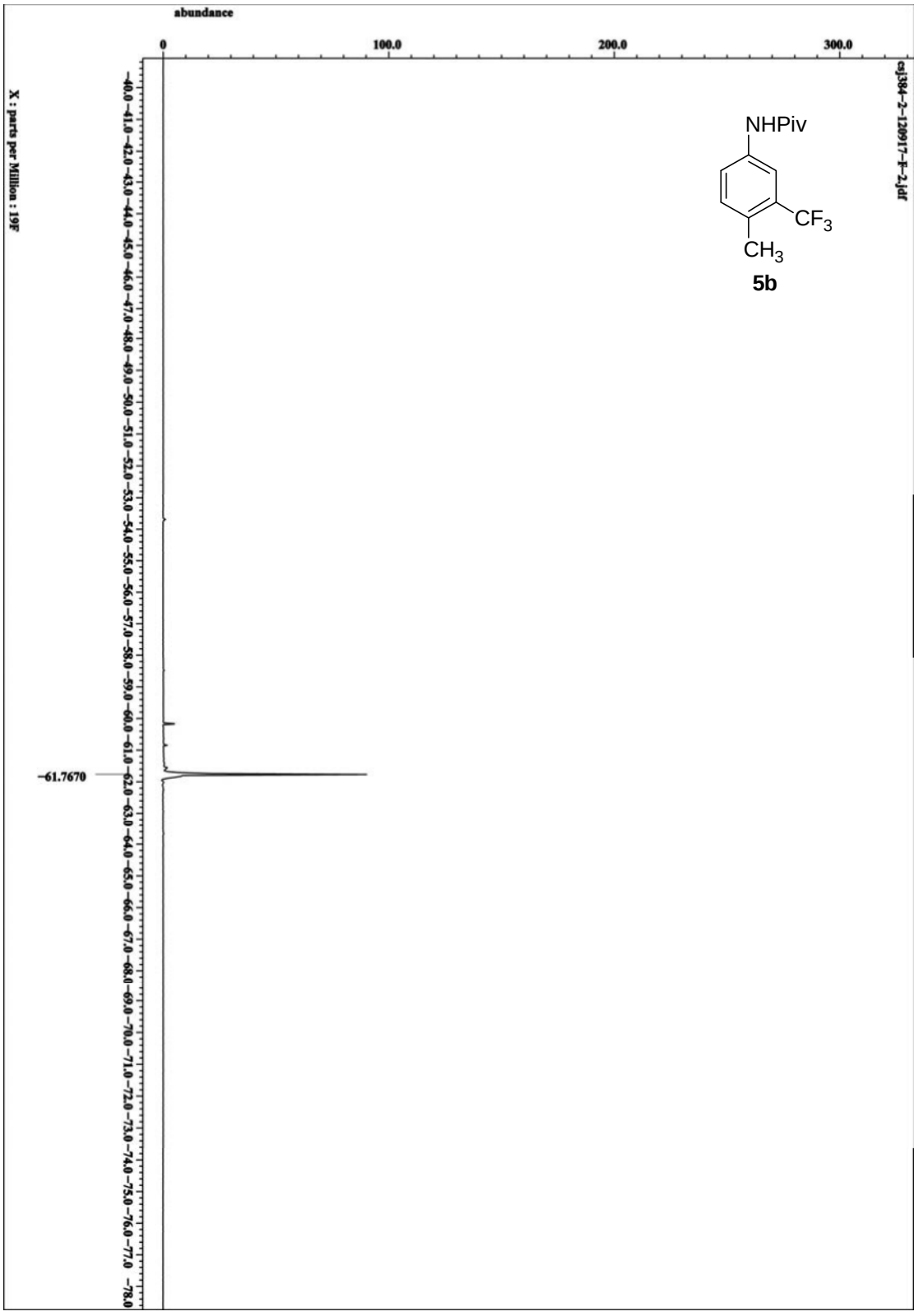
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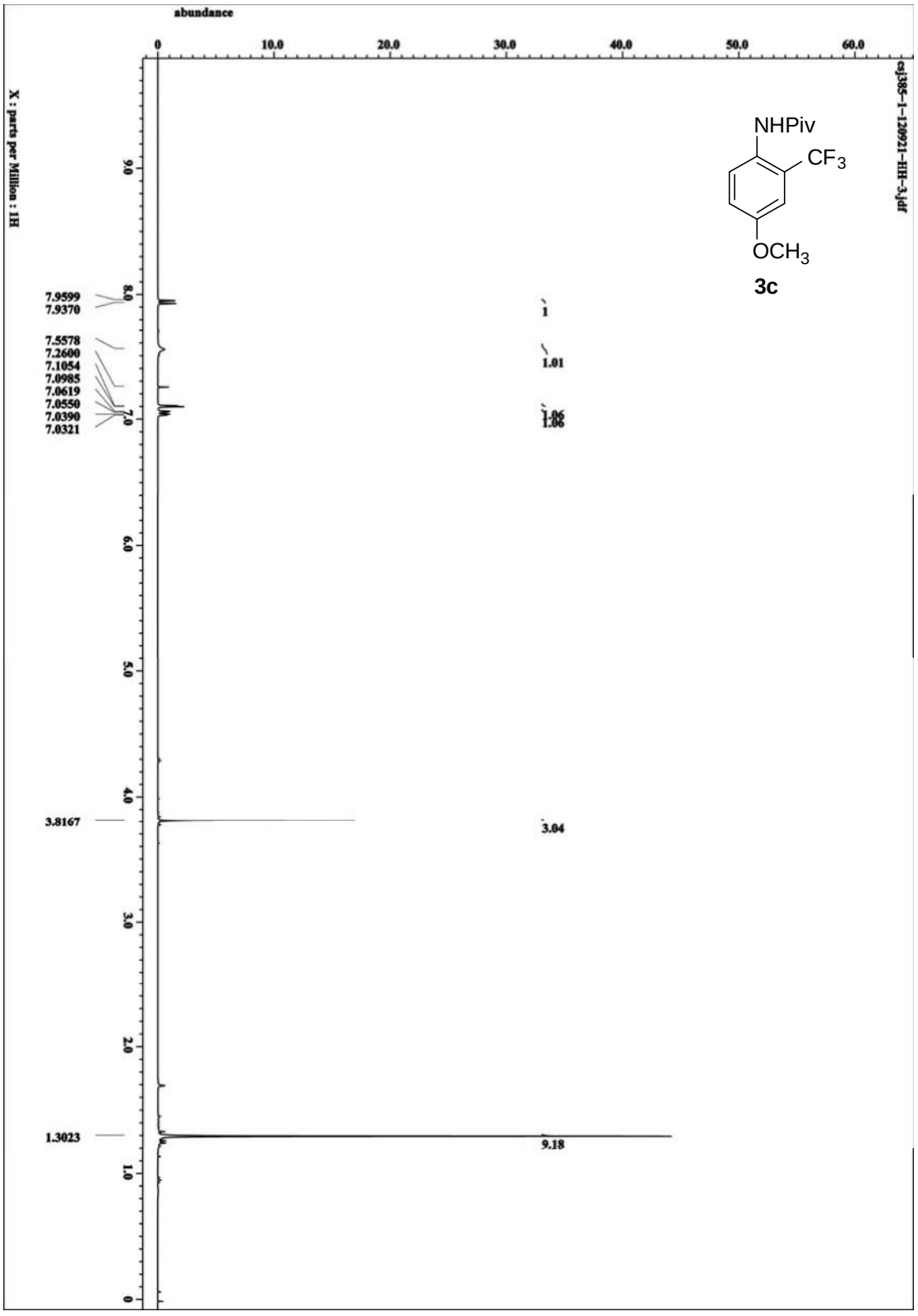
NHPiv
CF3
CH3
5b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X : parts per Million : 1H
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CF3
OCH3
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1.01
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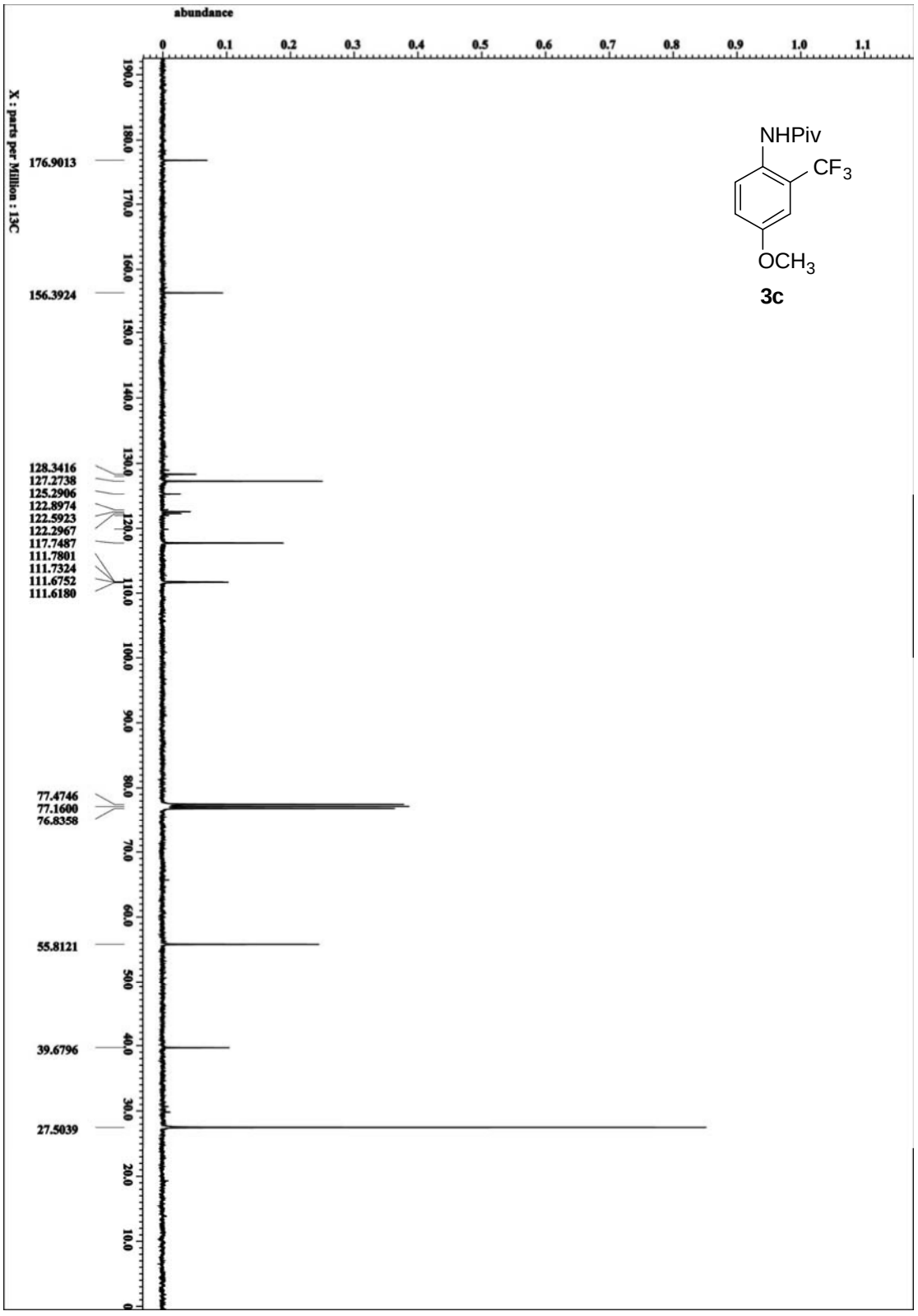
9.18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111.7801
111.7324
111.6752
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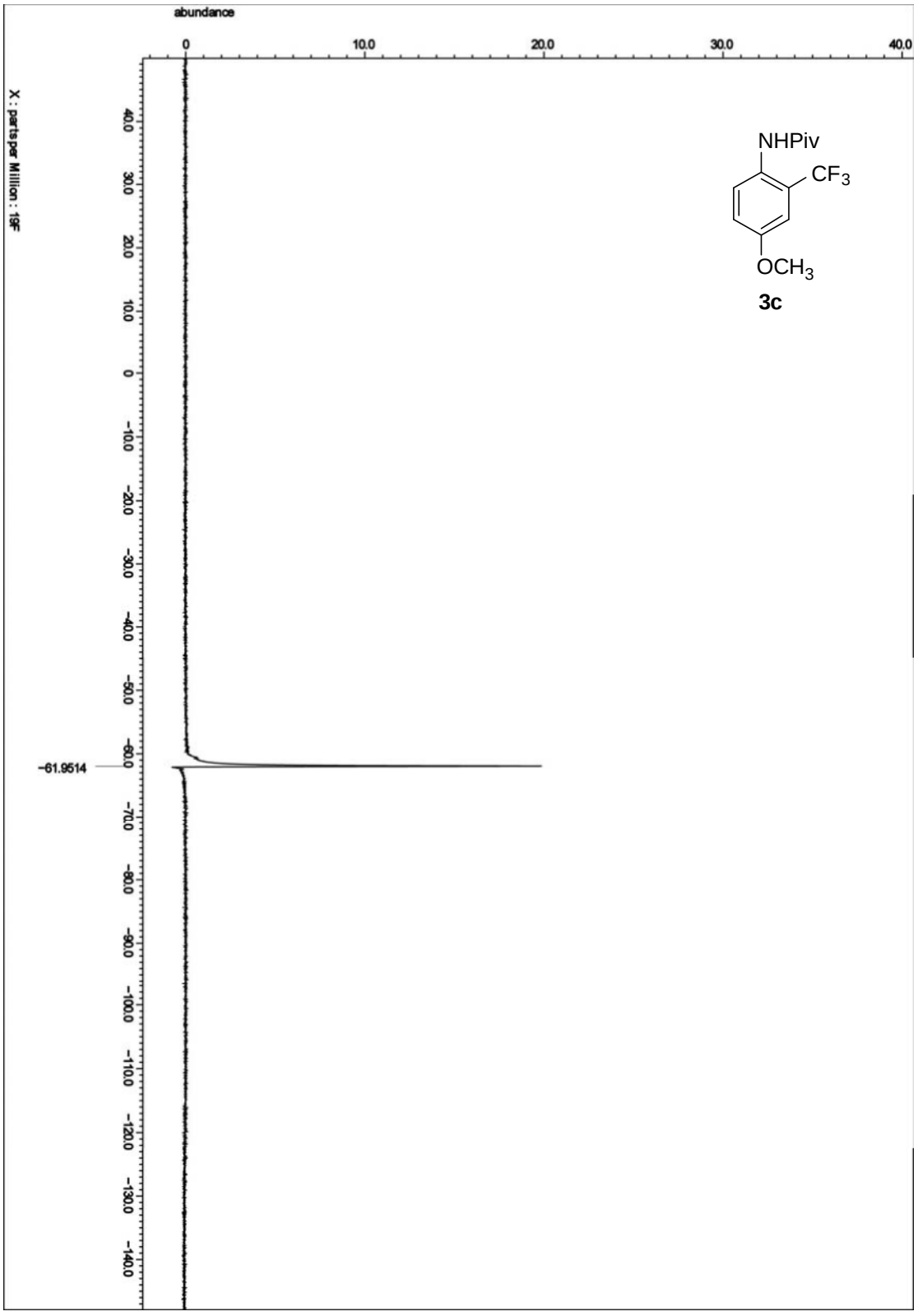
CF3
OCH3
3c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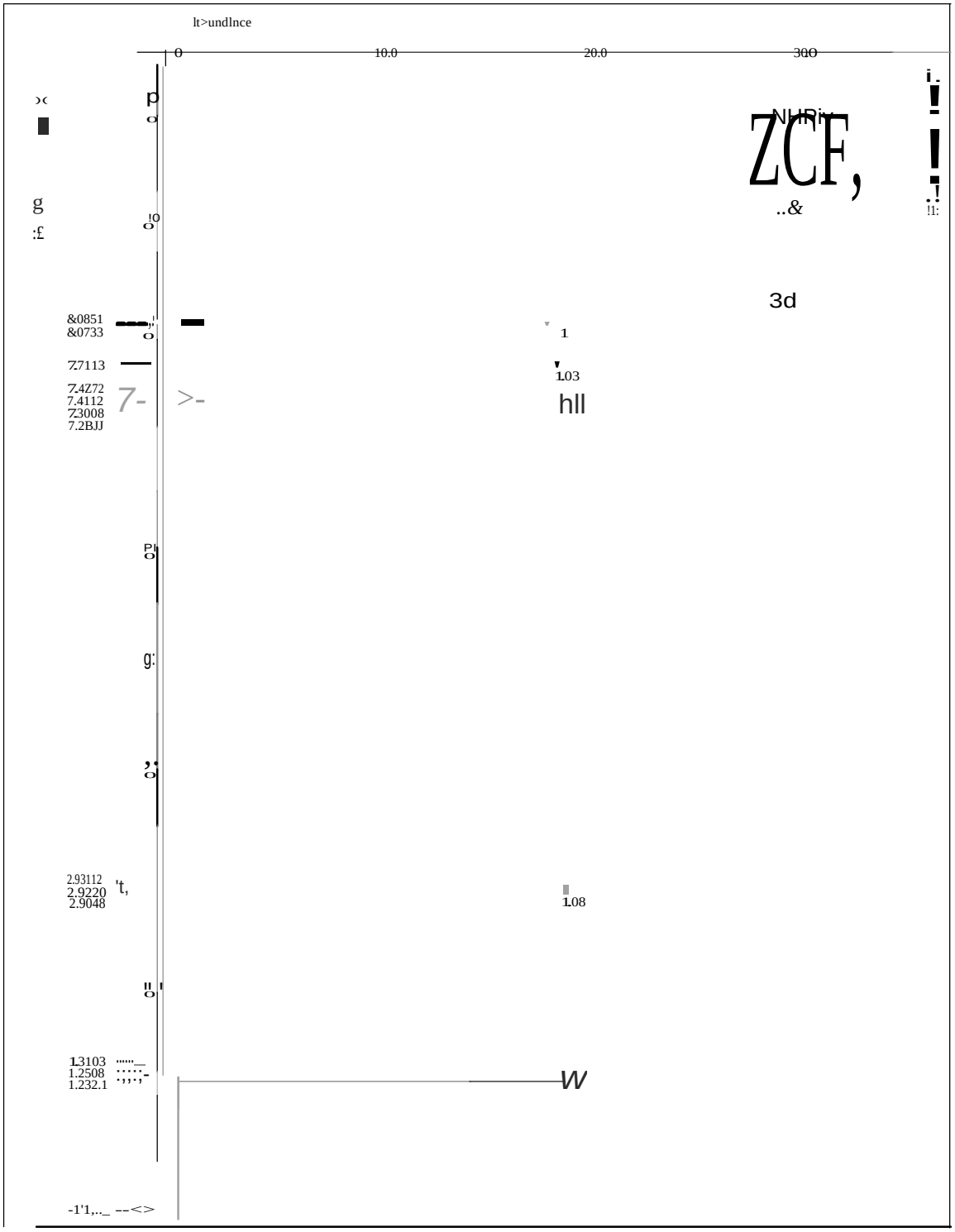
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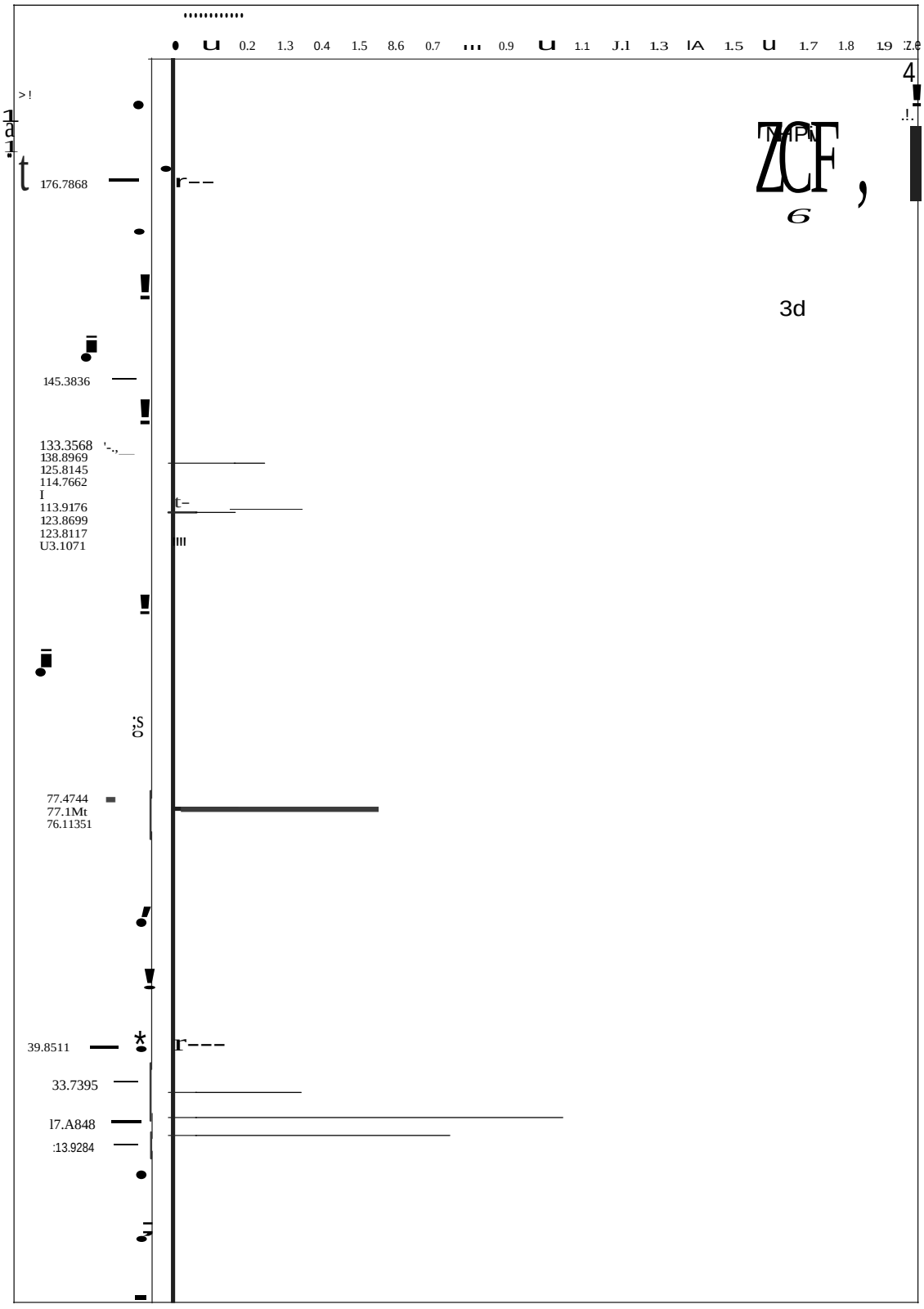
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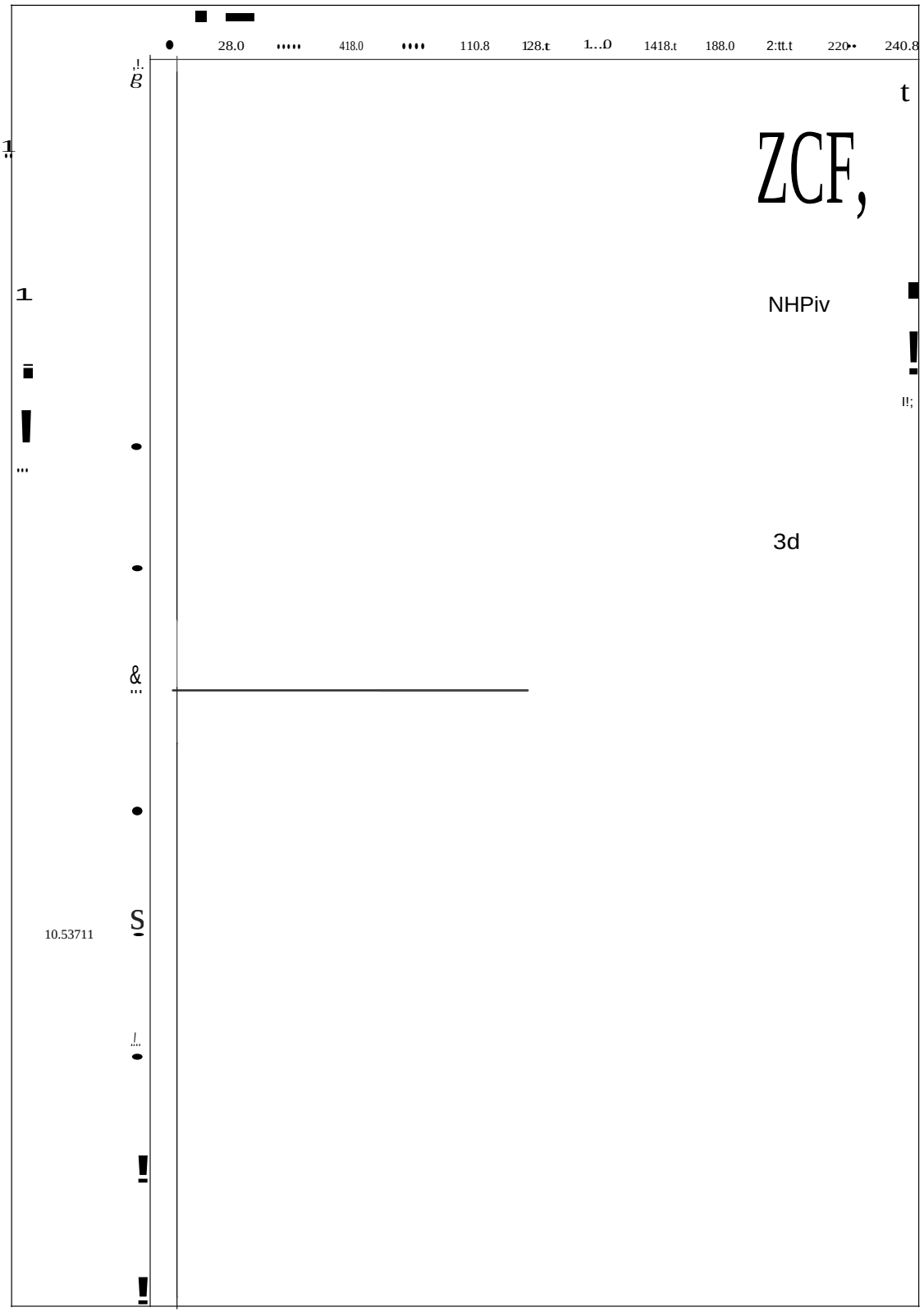
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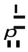

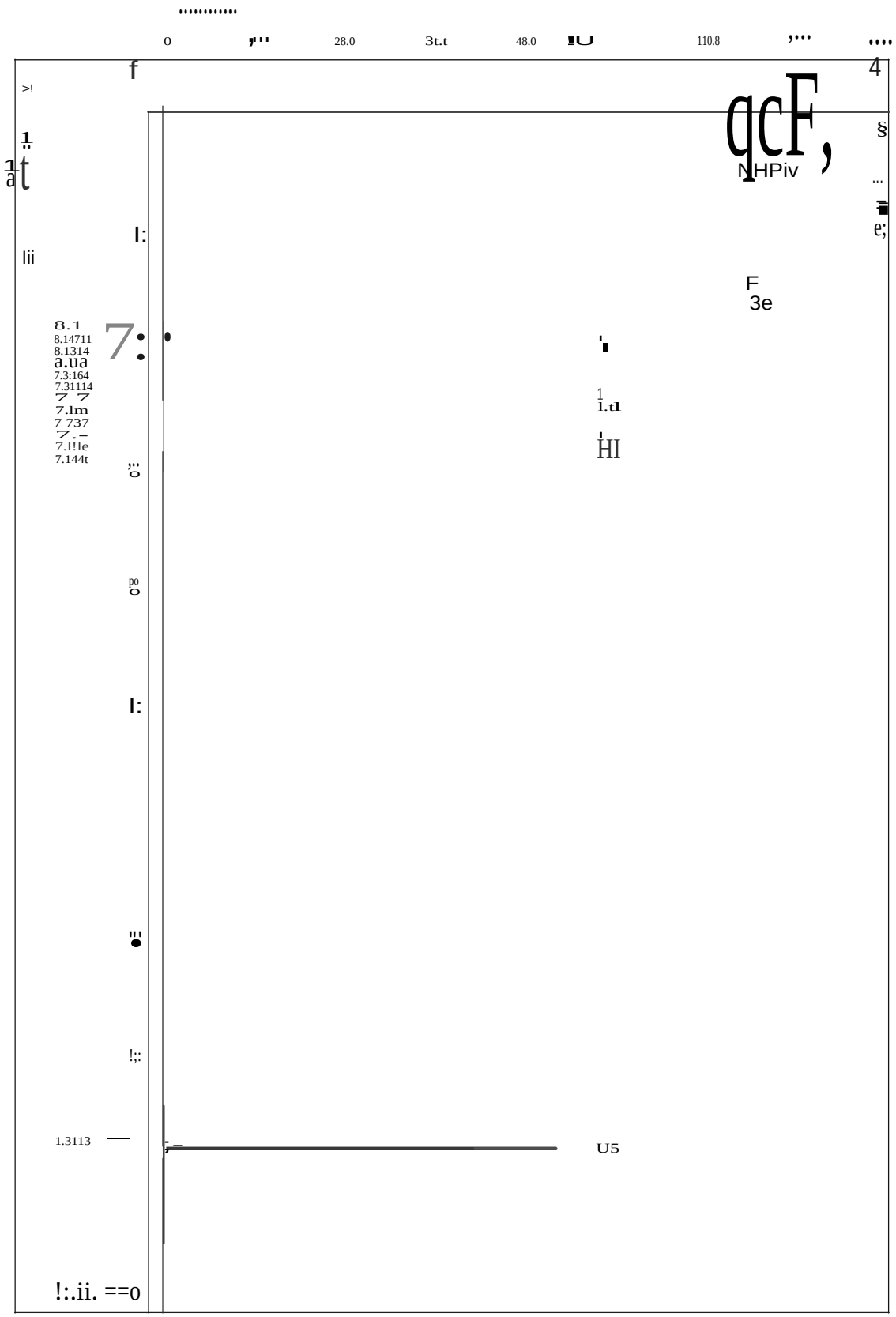
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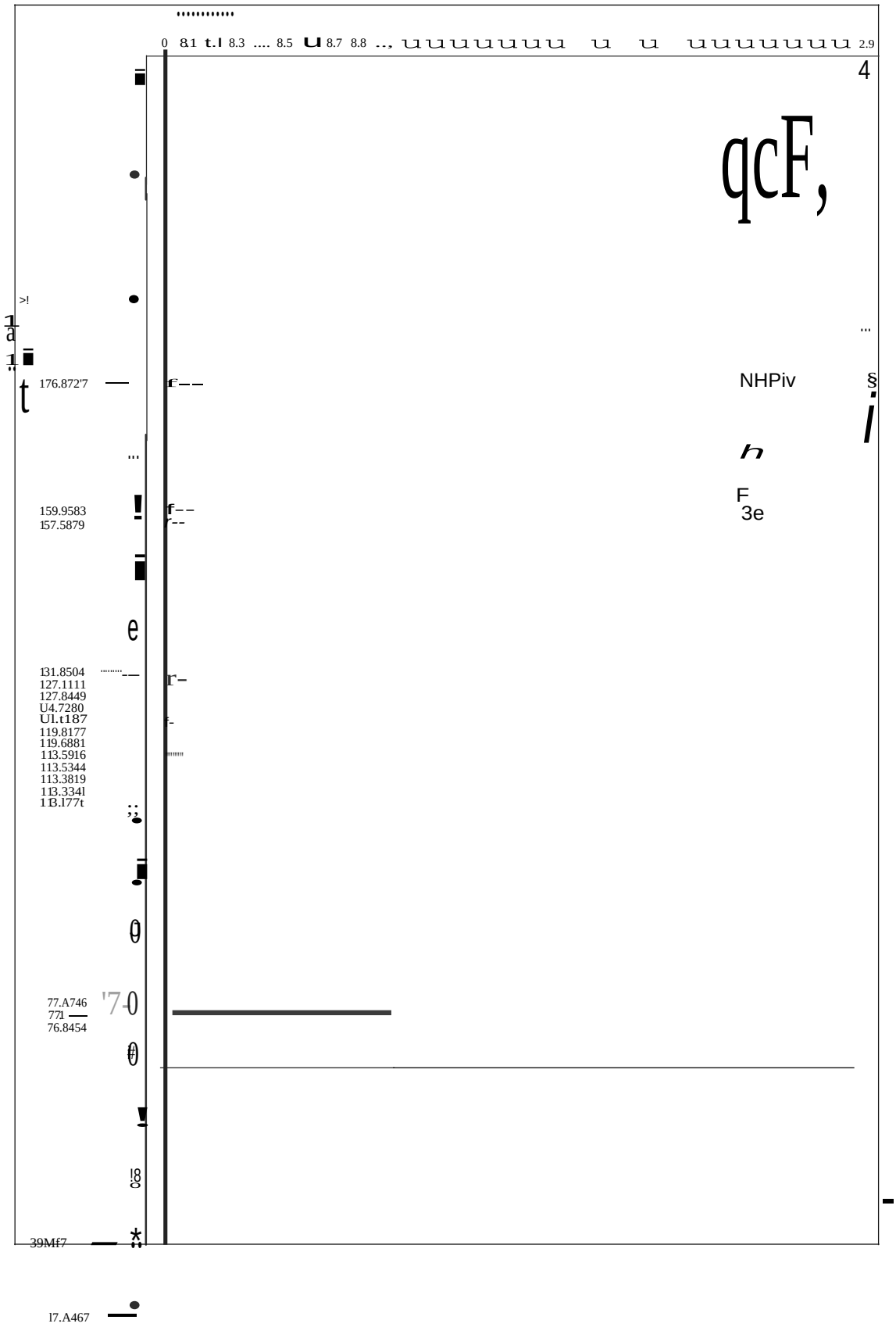
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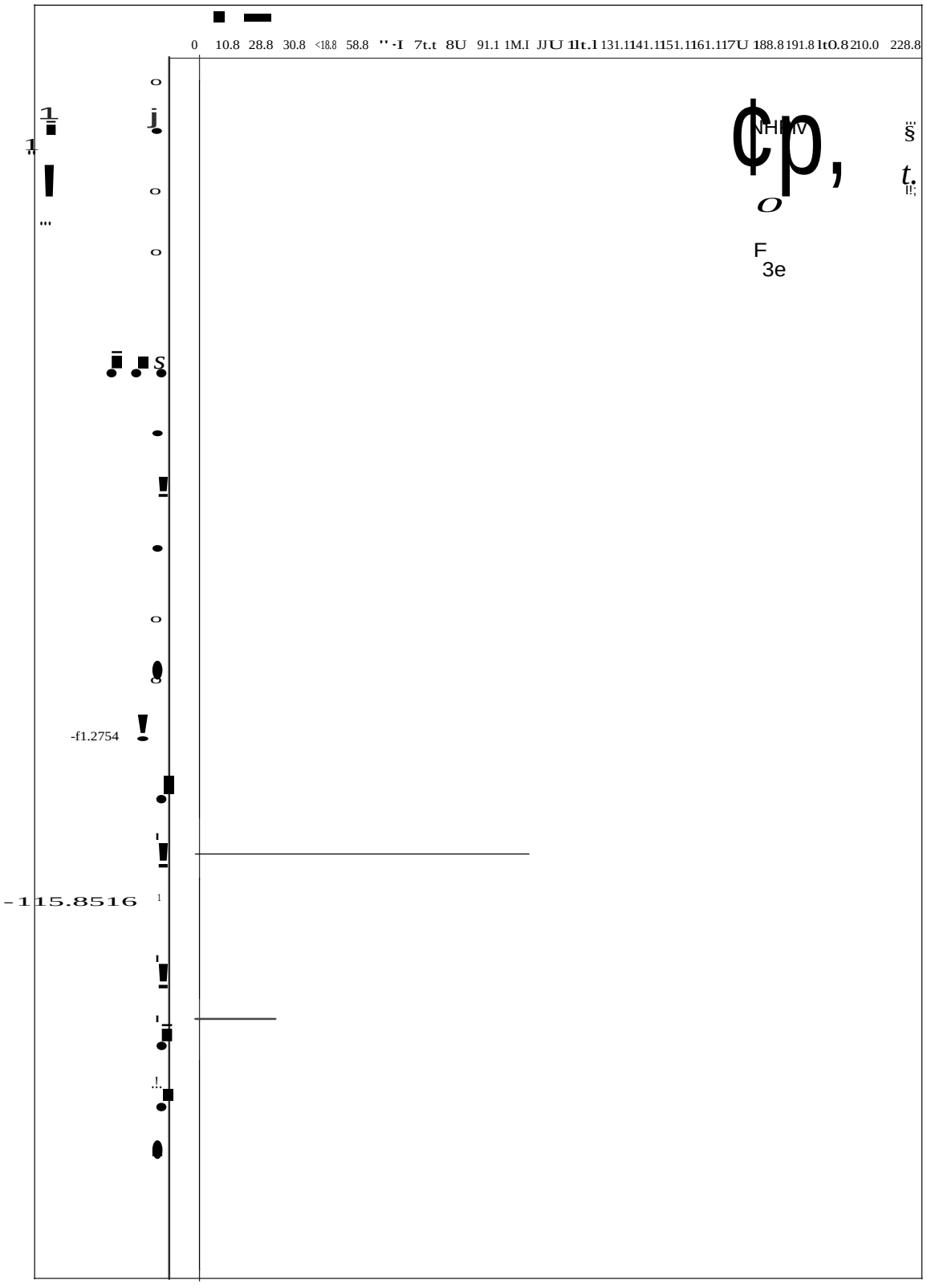
0 10.8 28.8 30.8 58.8 91.1 131.1 141.1 151.1 161.1 188.8 191.8 210.0 228.8
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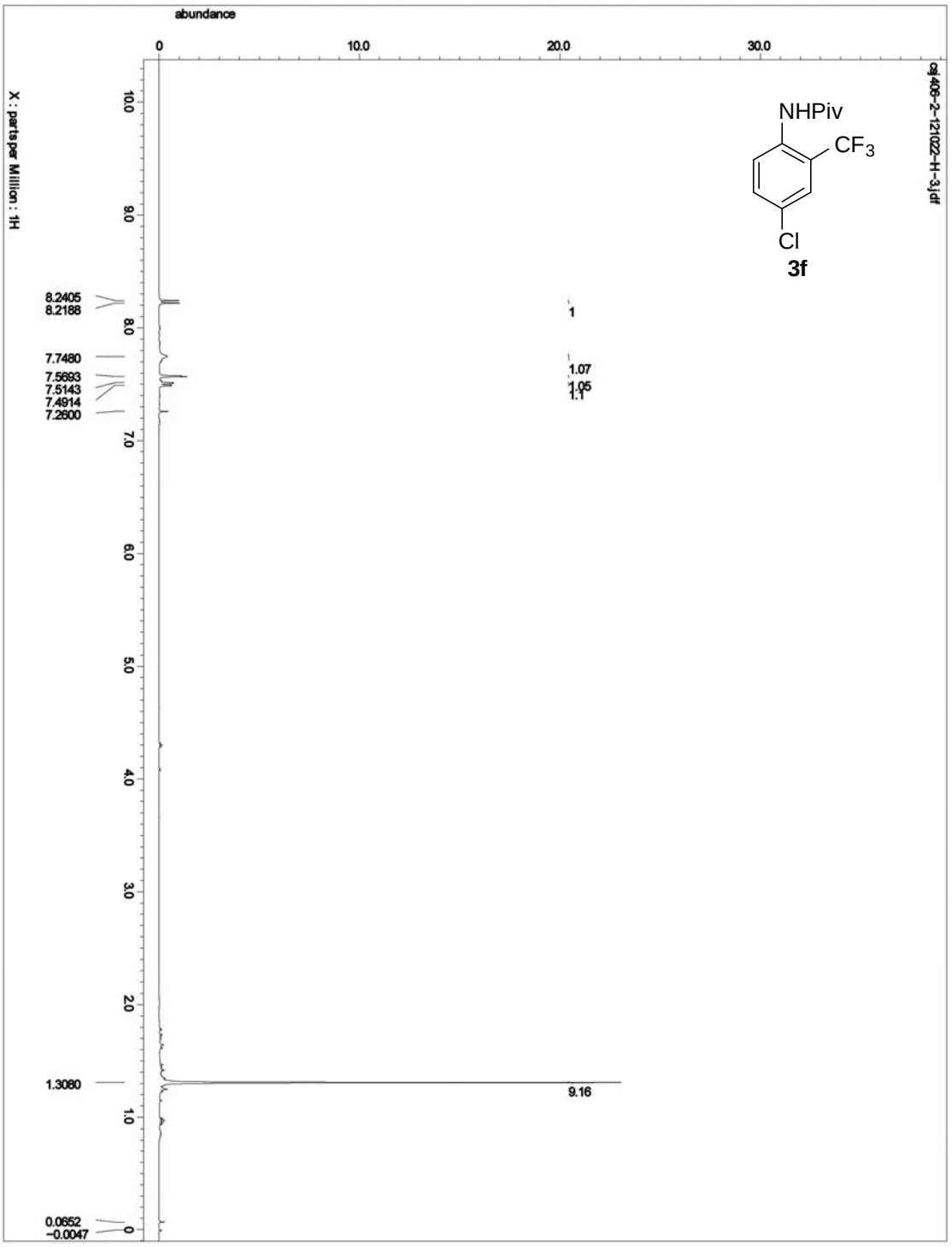
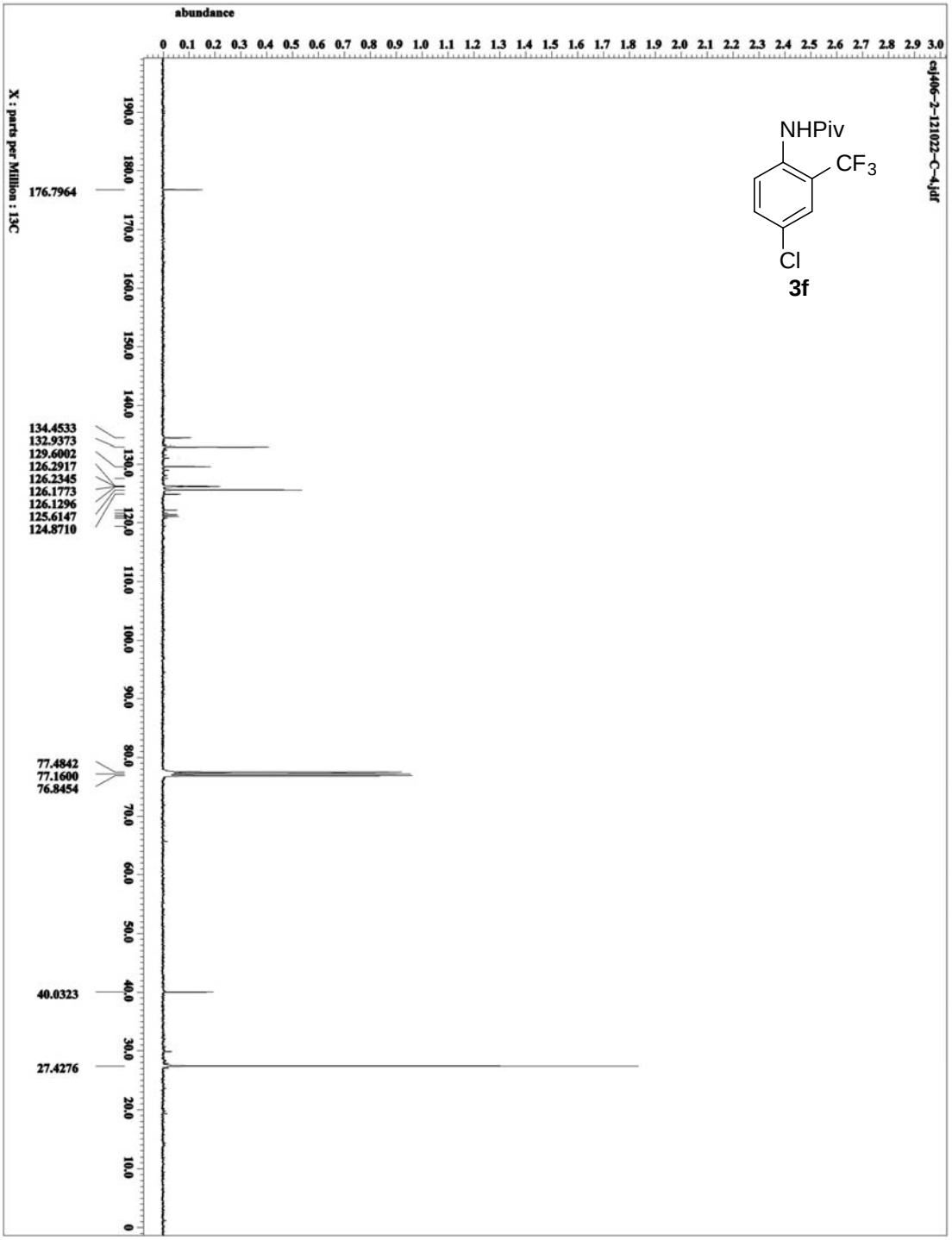
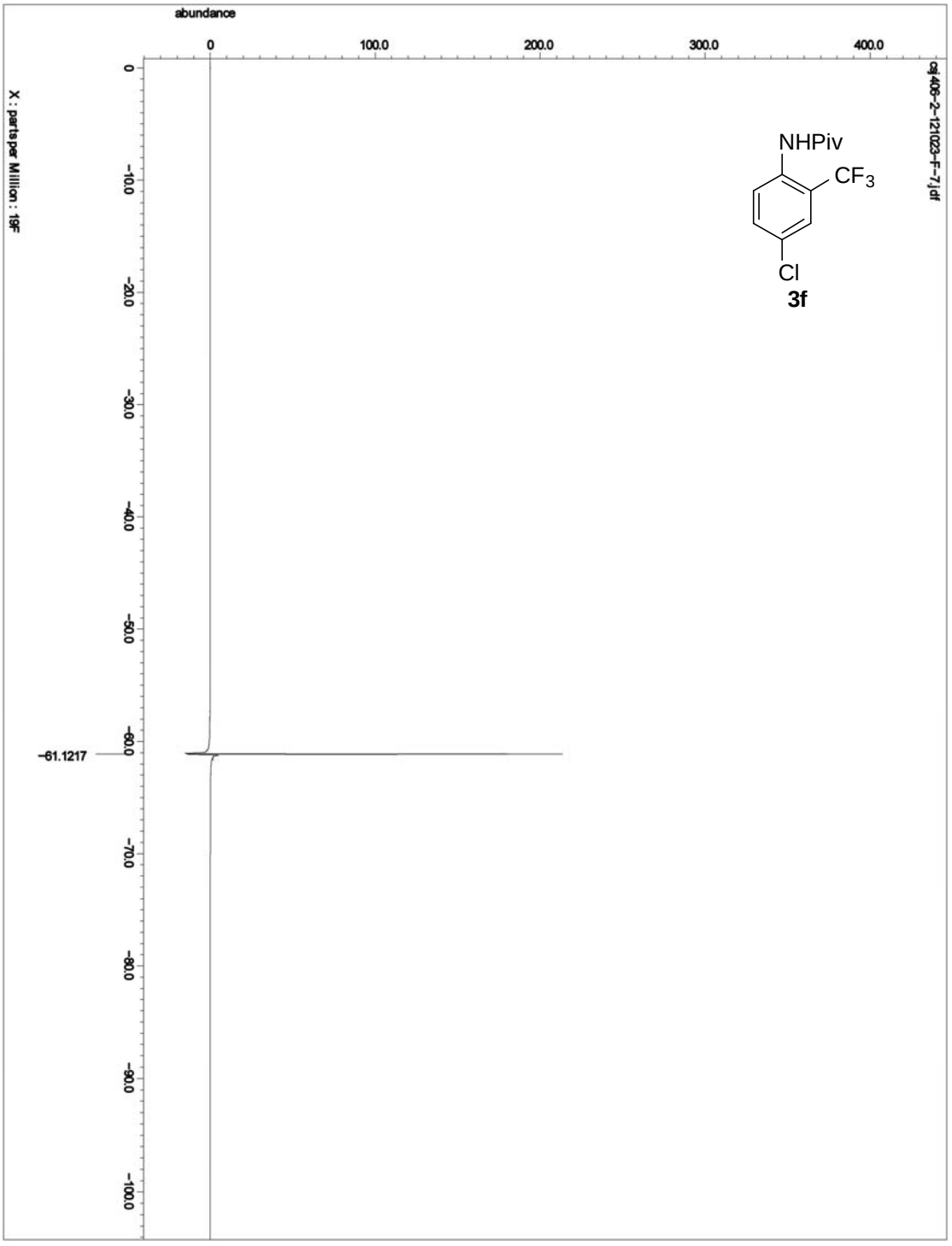
-115.8516
F
3e


abundance
X : parts per Million : 1H
sq406-2-121022-H-3.jdf
NHPiv
CF3
Cl
3f
8.2405
8.2188
7.7480
7.5693
7.5143
7.4914
7.2600
1.3080
0.0652
-0.0047
1
1.07
1.05
1.1
9.16


abundance
X : parts per Million : 13C
cuj406-2-121022-C-4.jdf
176.7964
134.4533
132.9373
129.6002
126.2917
126.2345
126.1773
126.1296
125.6147
124.8710
77.4842
77.1600
76.8454
40.0323
27.4276
NHPiv
CF3
Cl
3f


abundance
0
100.0
200.0
300.0
400.0
X : parts per Million : 19F
0
-10.0
-20.0
-30.0
-40.0
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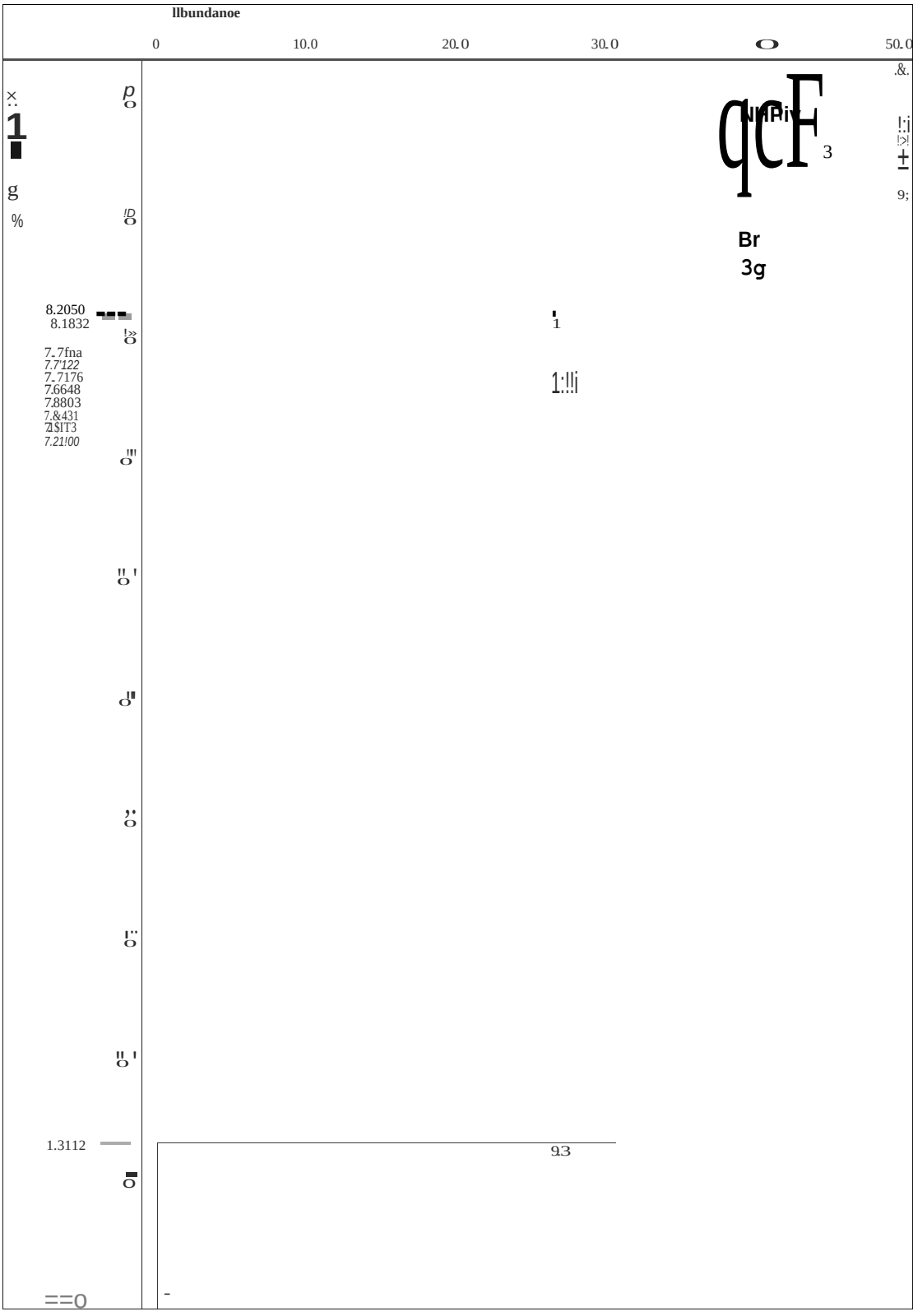
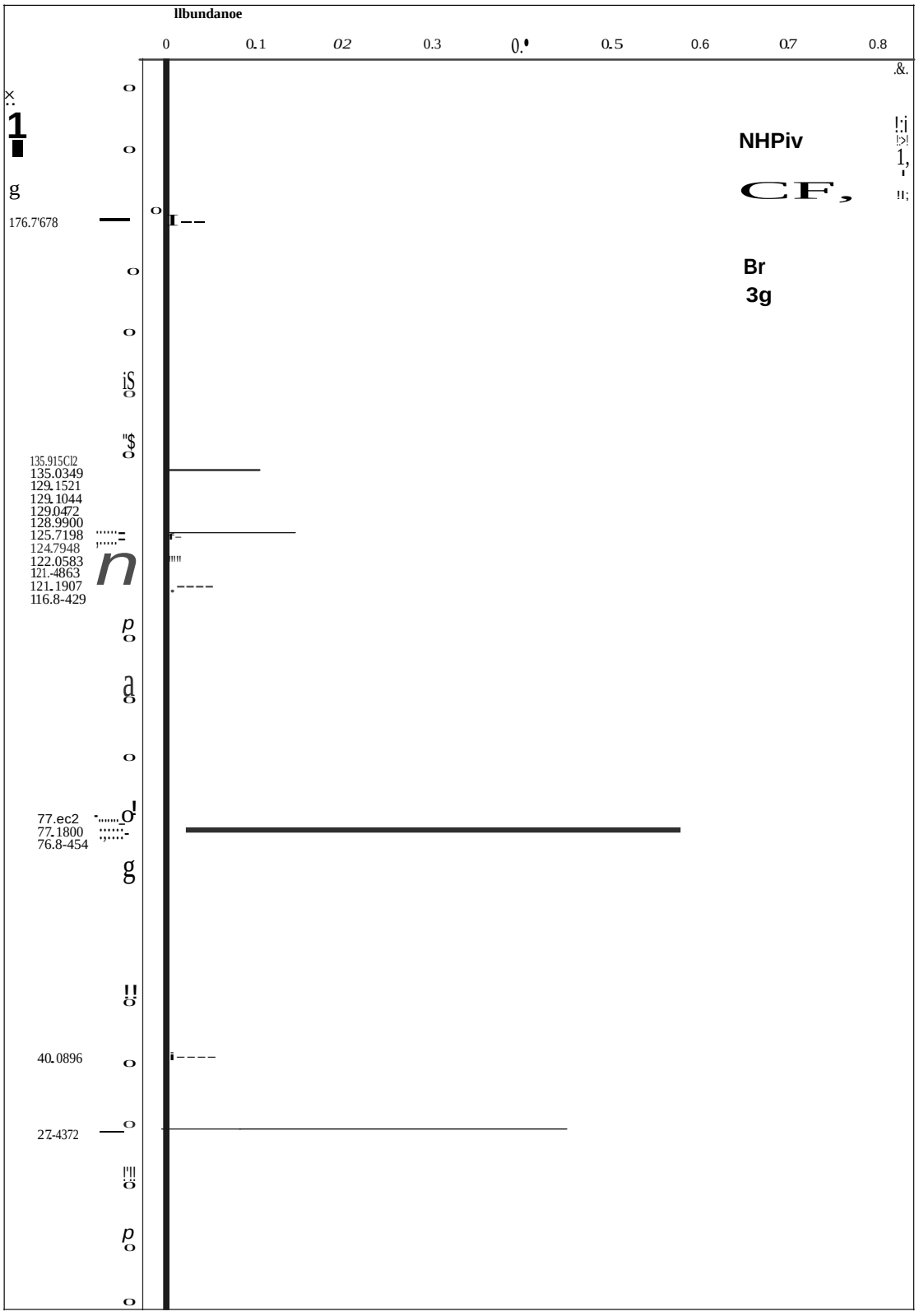
-100.0
-61.1217
NHPiv
CF3
Cl
3f


llbundanoe
0
10.0
20.0
30.0
50.0
qcF 3
Br
3g
8.2050
8.1832
7.7fna
7.7122
7.7176
7.6648
7.8803
7.&431
7.21!00
1.3112
==0


Ilbundanoe
0
0.1
02
0.3
0.5
0.6
0.7
0.8
NHPiv
CF,
Br
3g
176.7'678
135.915Cl2
135.0349
129.1521
129.1044
129.0472
128.9900
125.7198
124.7948
122.0583
121.-4863
121.1907
116.8-429
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77.1800
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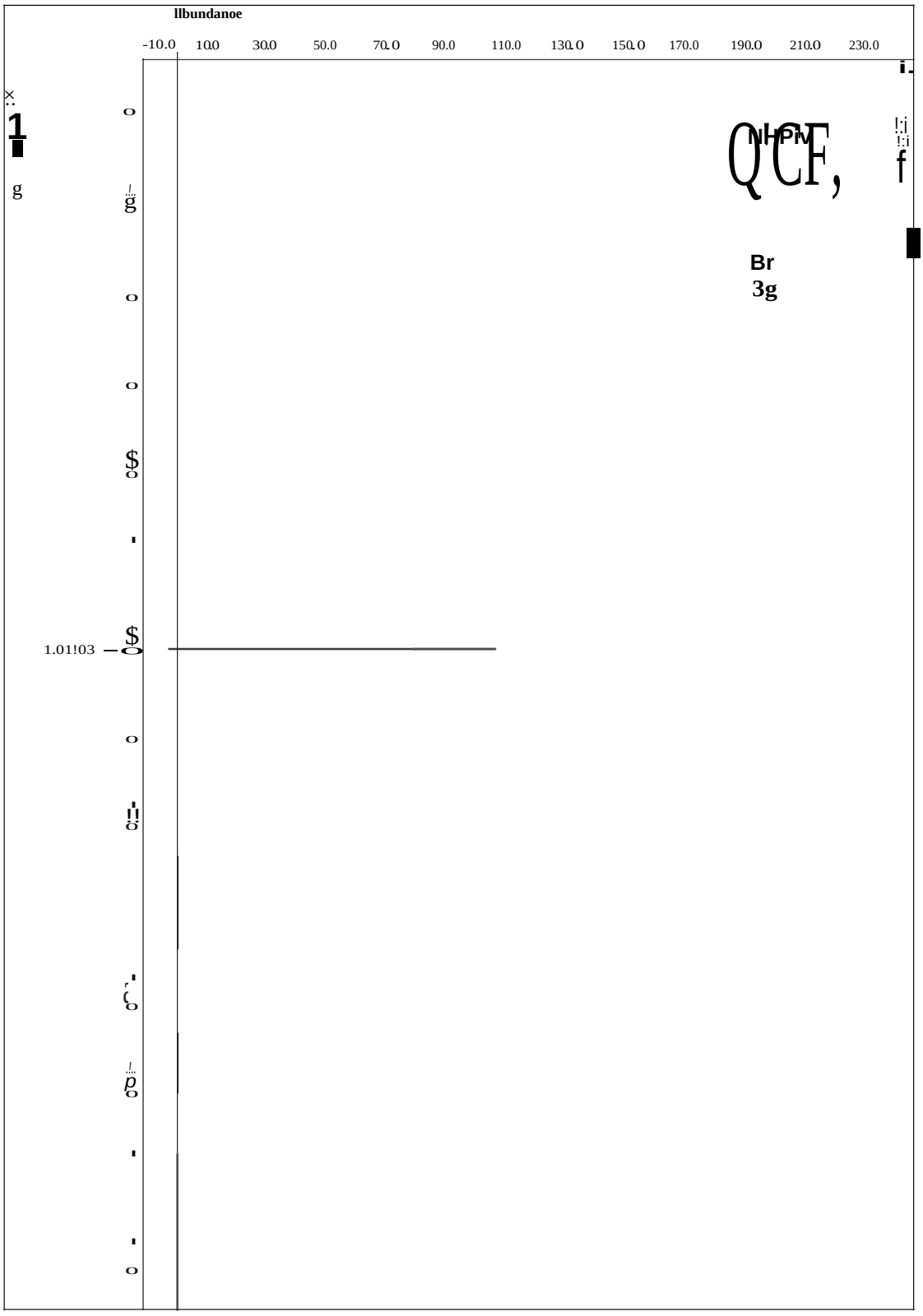
40.0896
27-4372


llbundanoe
-10.0
10.0
30.0
50.0
70.0
90.0
110.0
130.0
150.0
170.0
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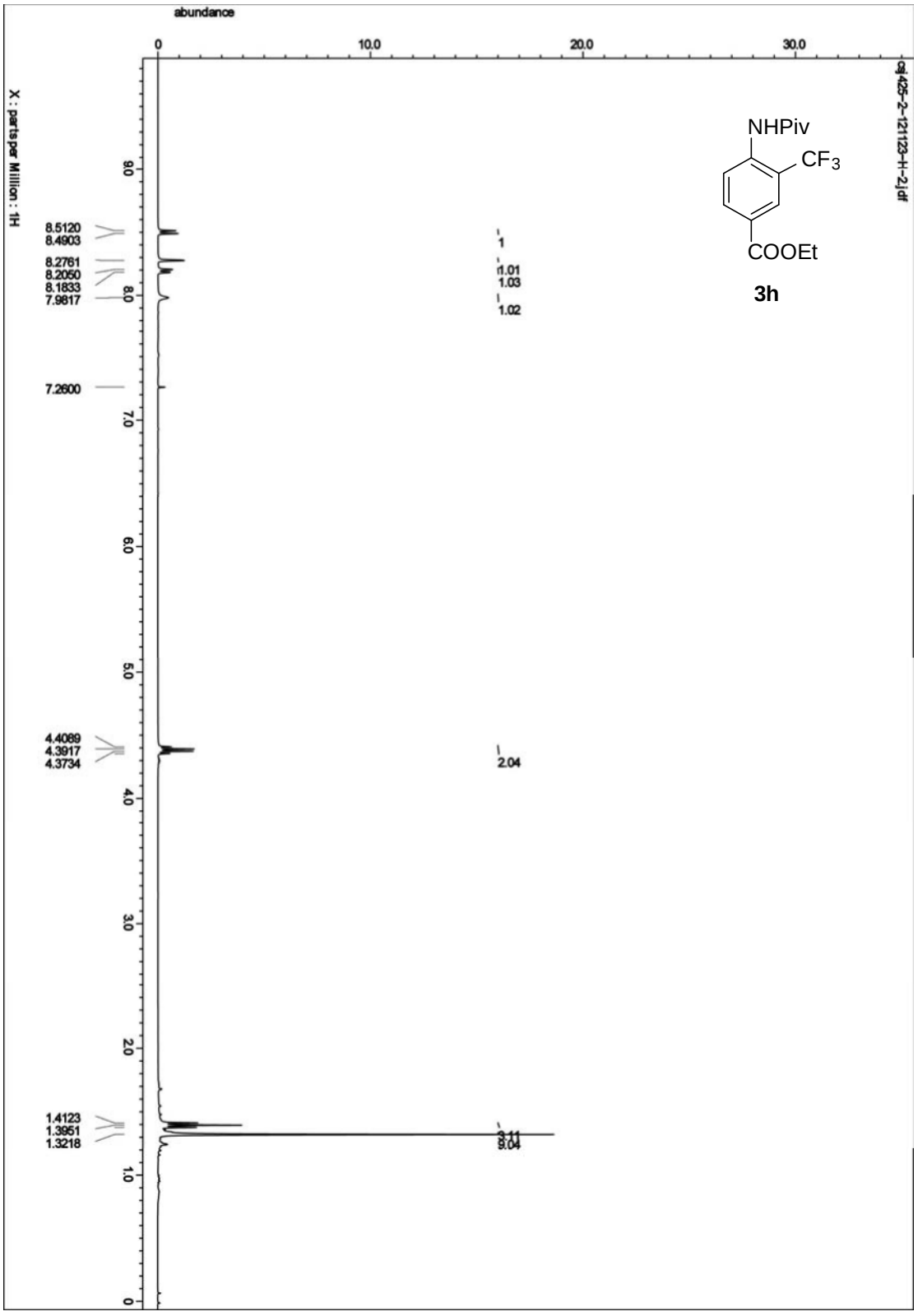
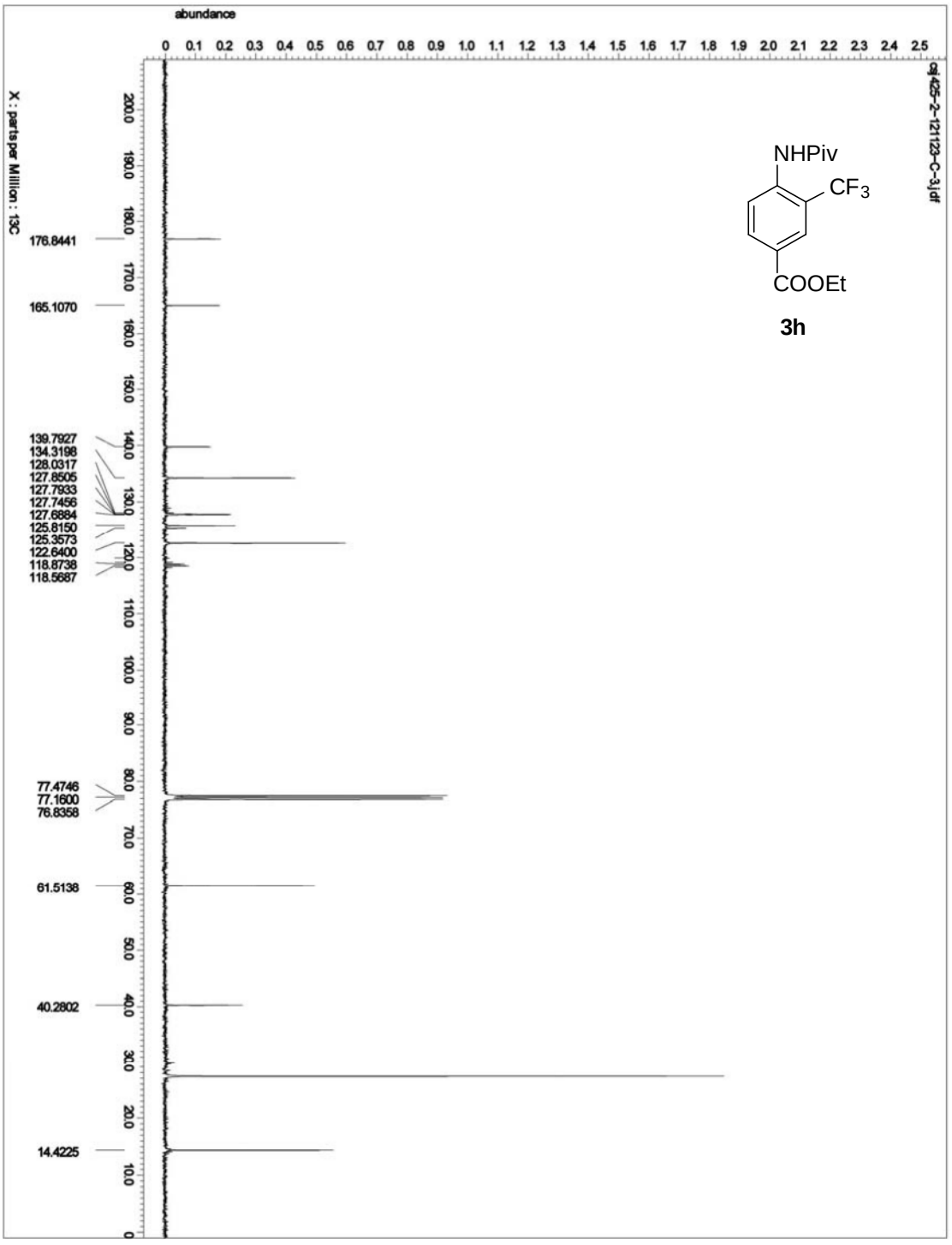
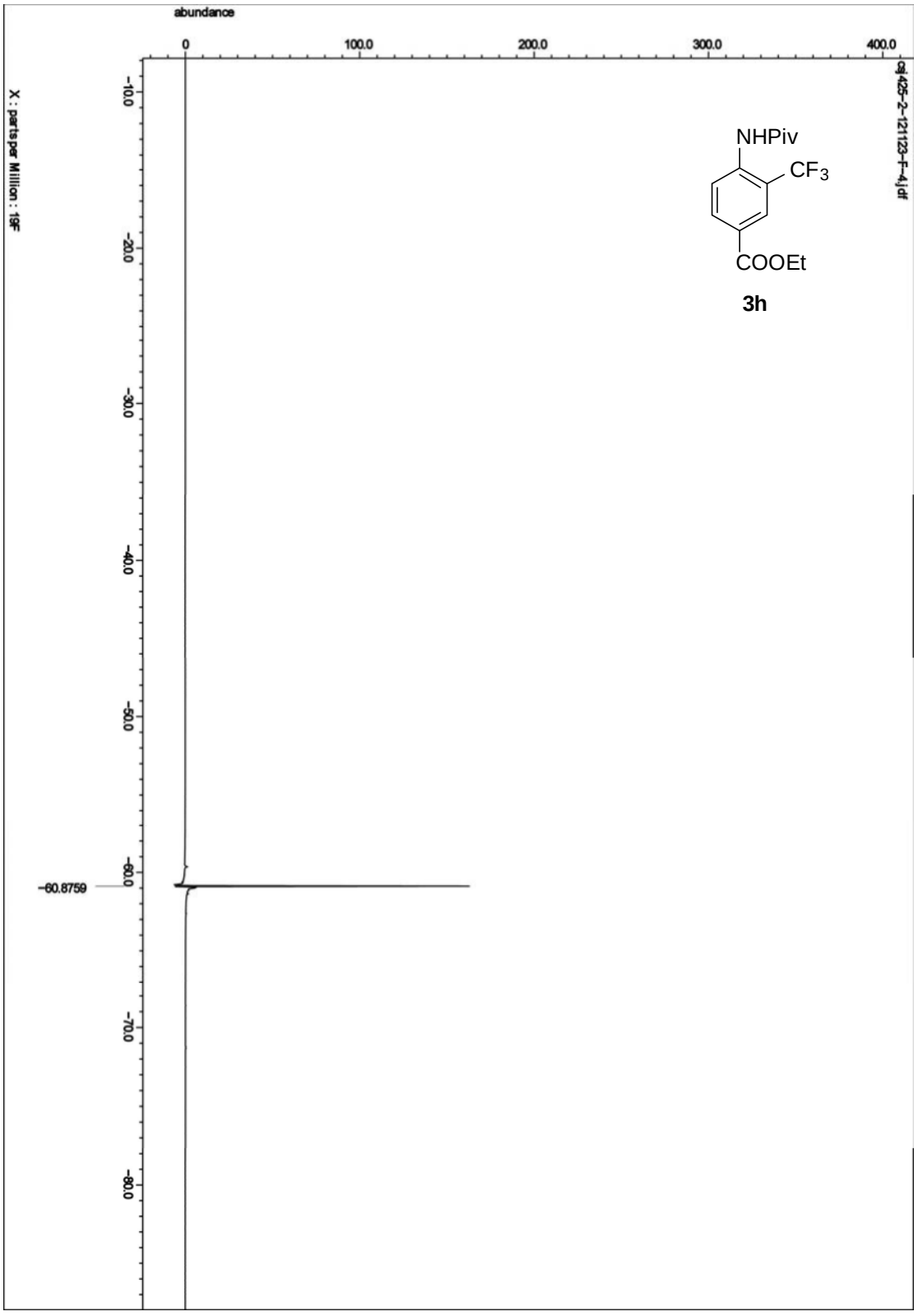
230.0
1.01!03
QCF,
NHPM
Br
3g


abundance
X : parts per Million : 1H
NHPiv
CF3
COOEt
3h
8.5120
8.4903
8.2761
8.2050
8.1833
7.9817
7.2600
4.4089
4.3917
4.3734
1.4123
1.3951
1.3218
1
1.01
1.03
1.02
2.04
2.11
9.04


abundance
X : parts per Million : 13C
cq425-2-121123-C-3.jdf
176.8441
165.1070
139.7927
134.3198
128.0317
127.8505
127.7933
127.7456
127.6884
125.8150
125.3573
122.6400
118.8738
118.5687
77.4746
77.1600
76.8358
61.5138
40.2802
14.4225
NHPiv
CF3
COOEt
3h


abundance
0
100.0
200.0
300.0
400.0
X : parts per Million : 19F
-10.0
-20.0
-30.0
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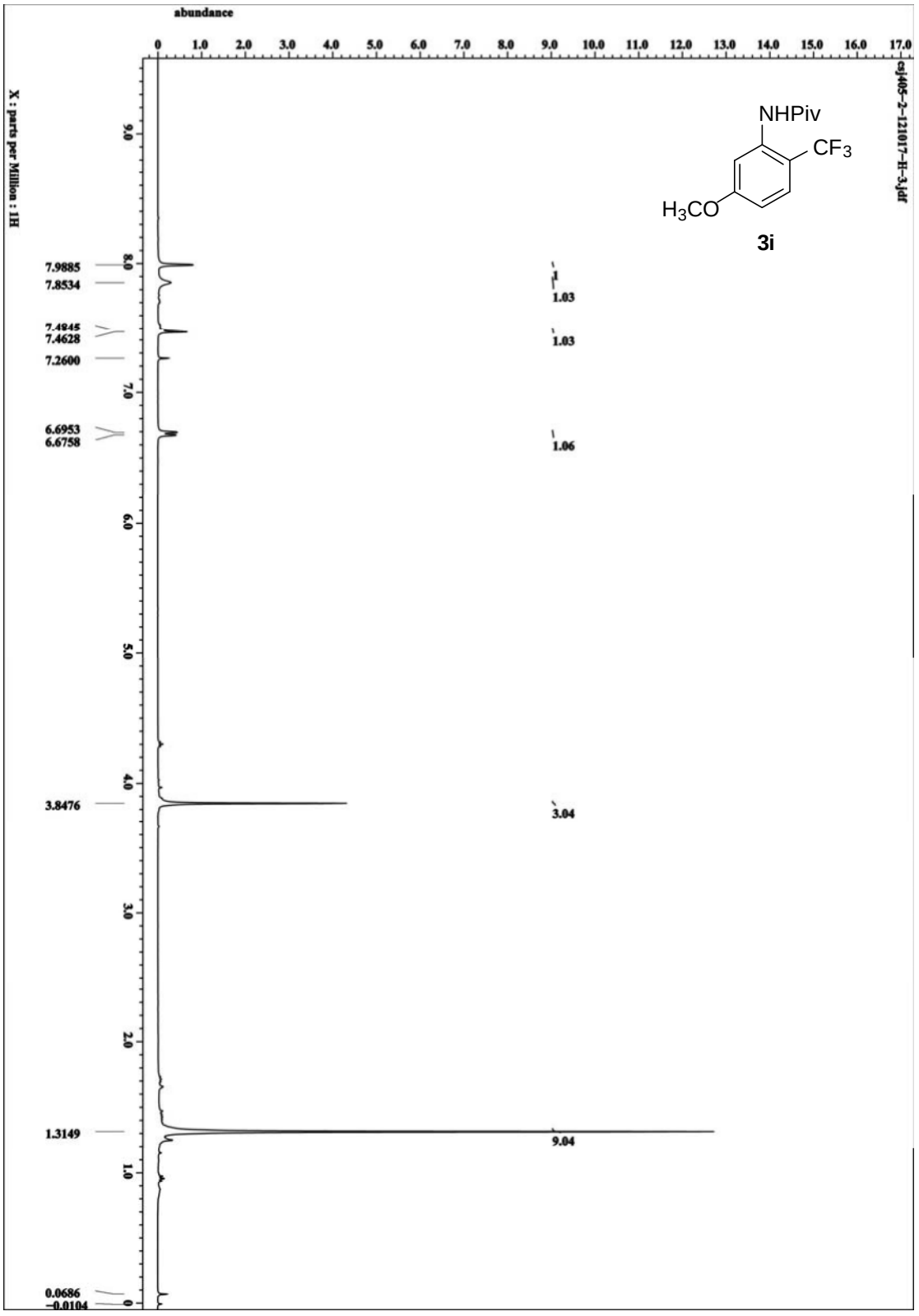
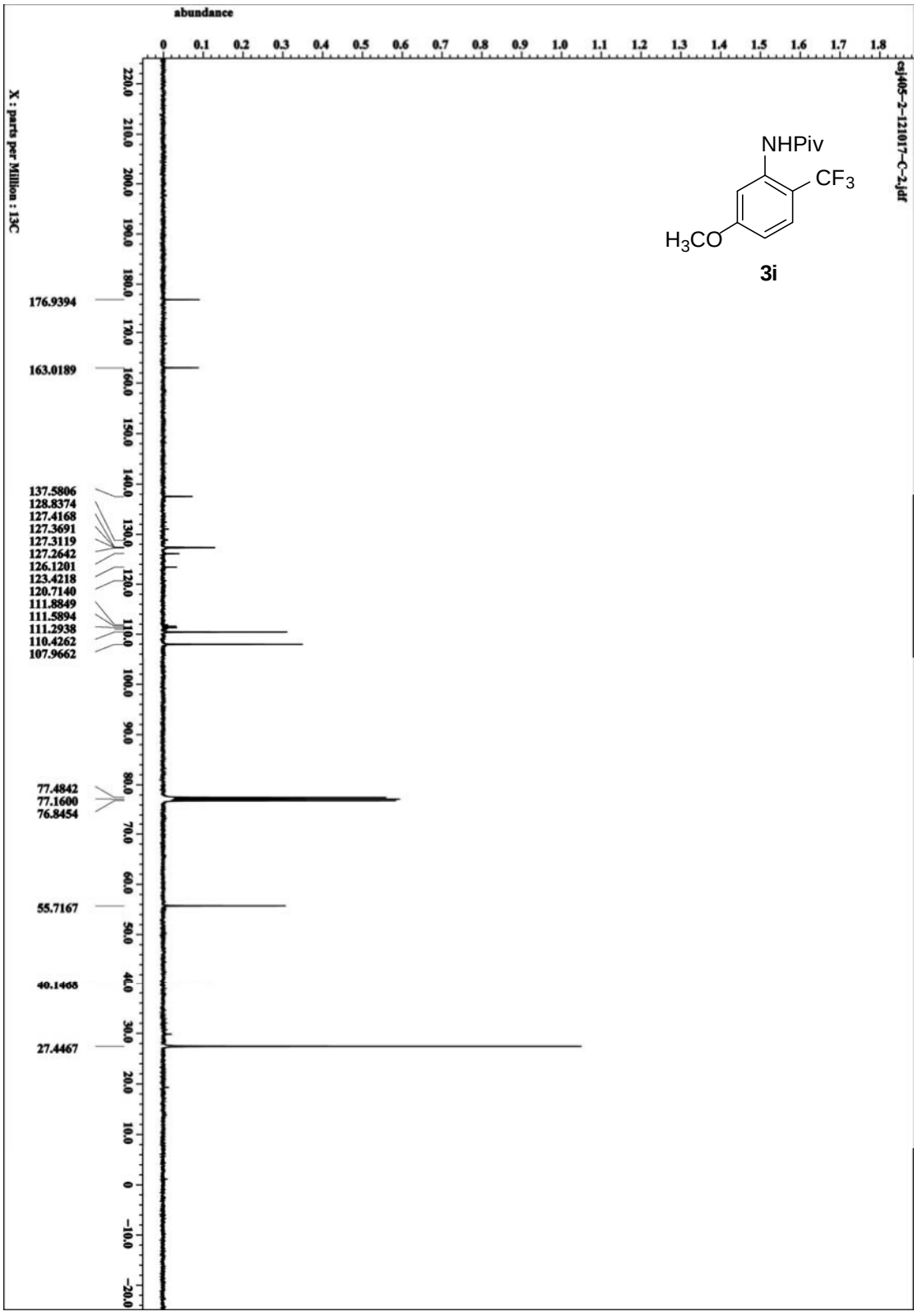
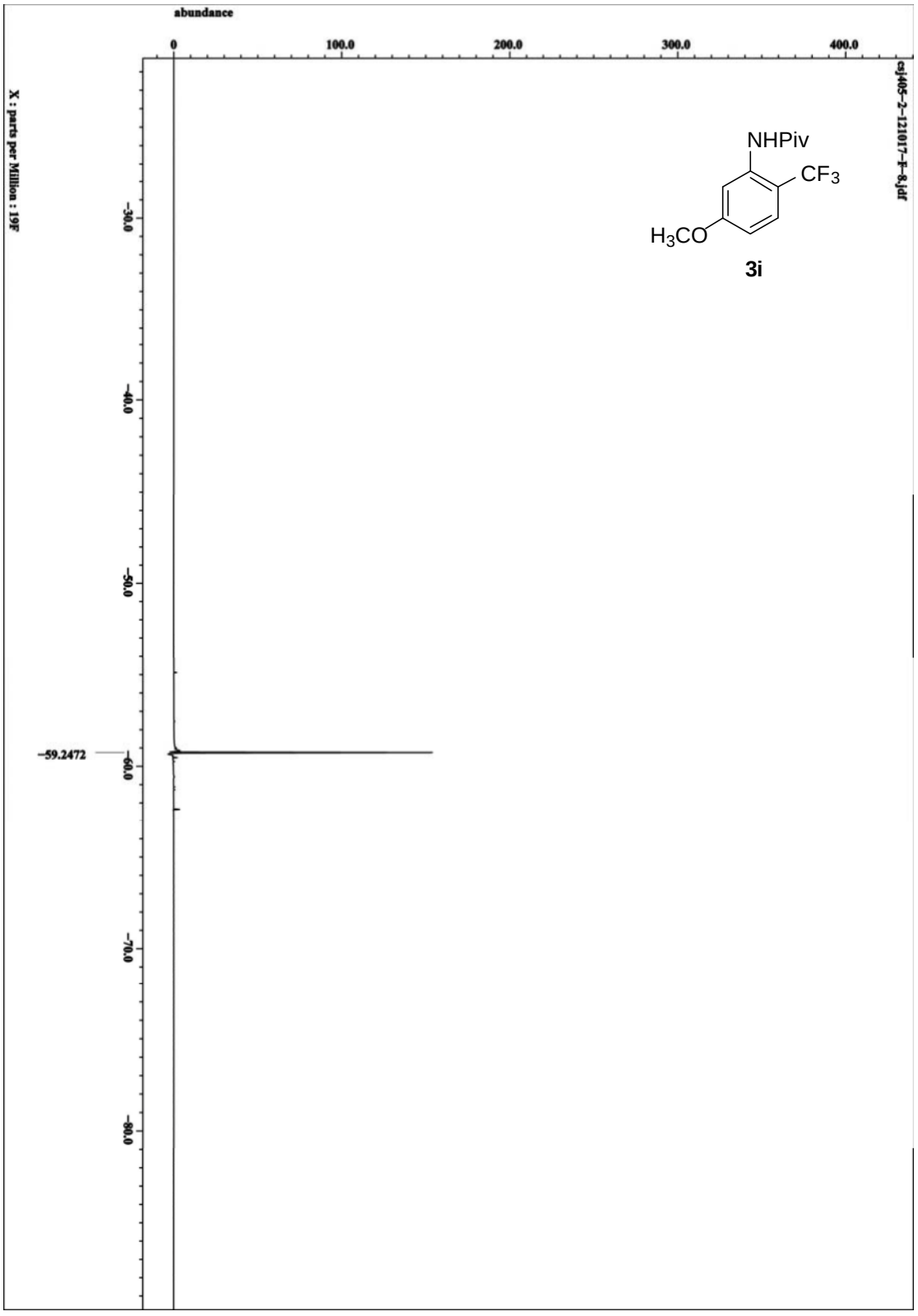
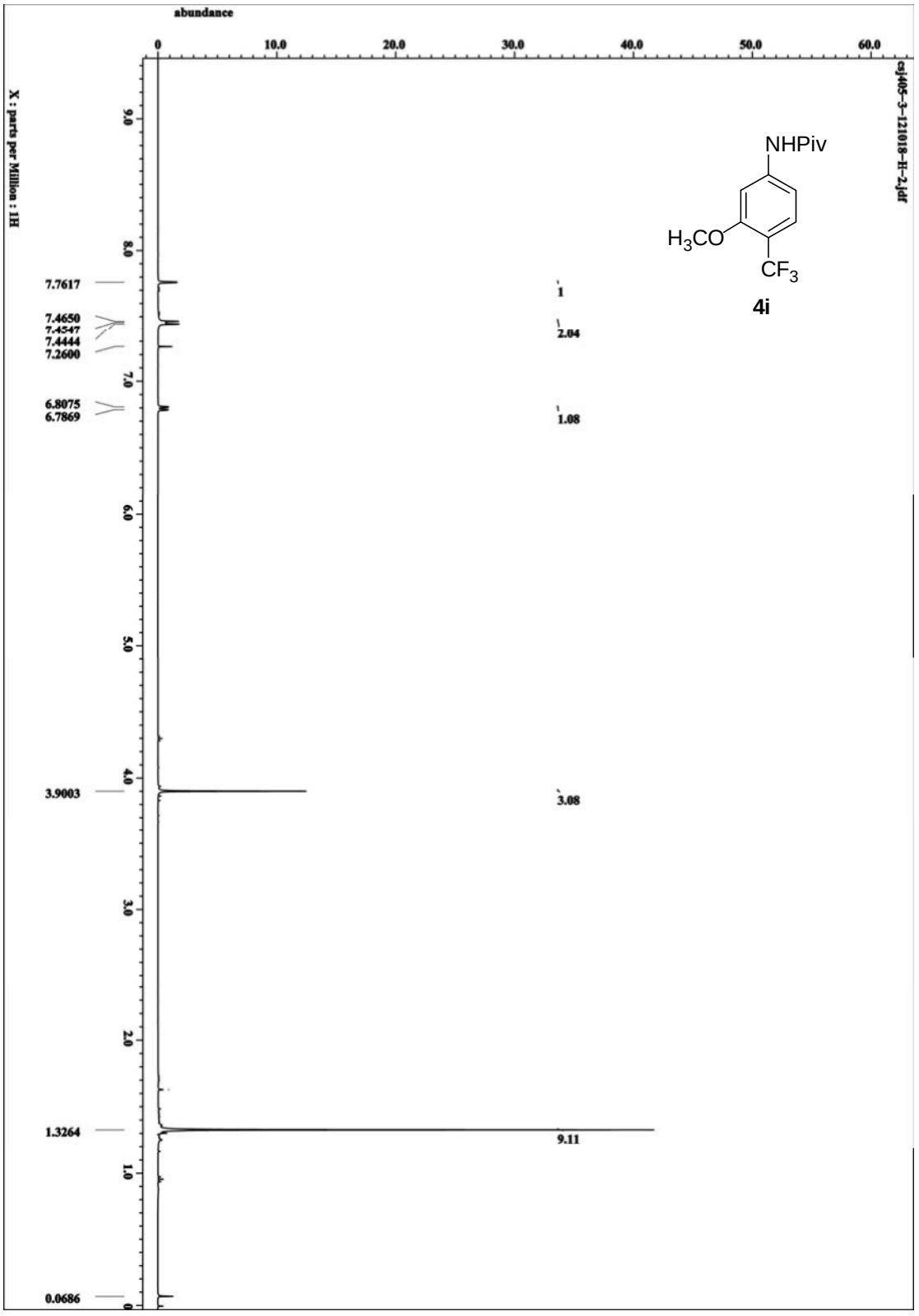
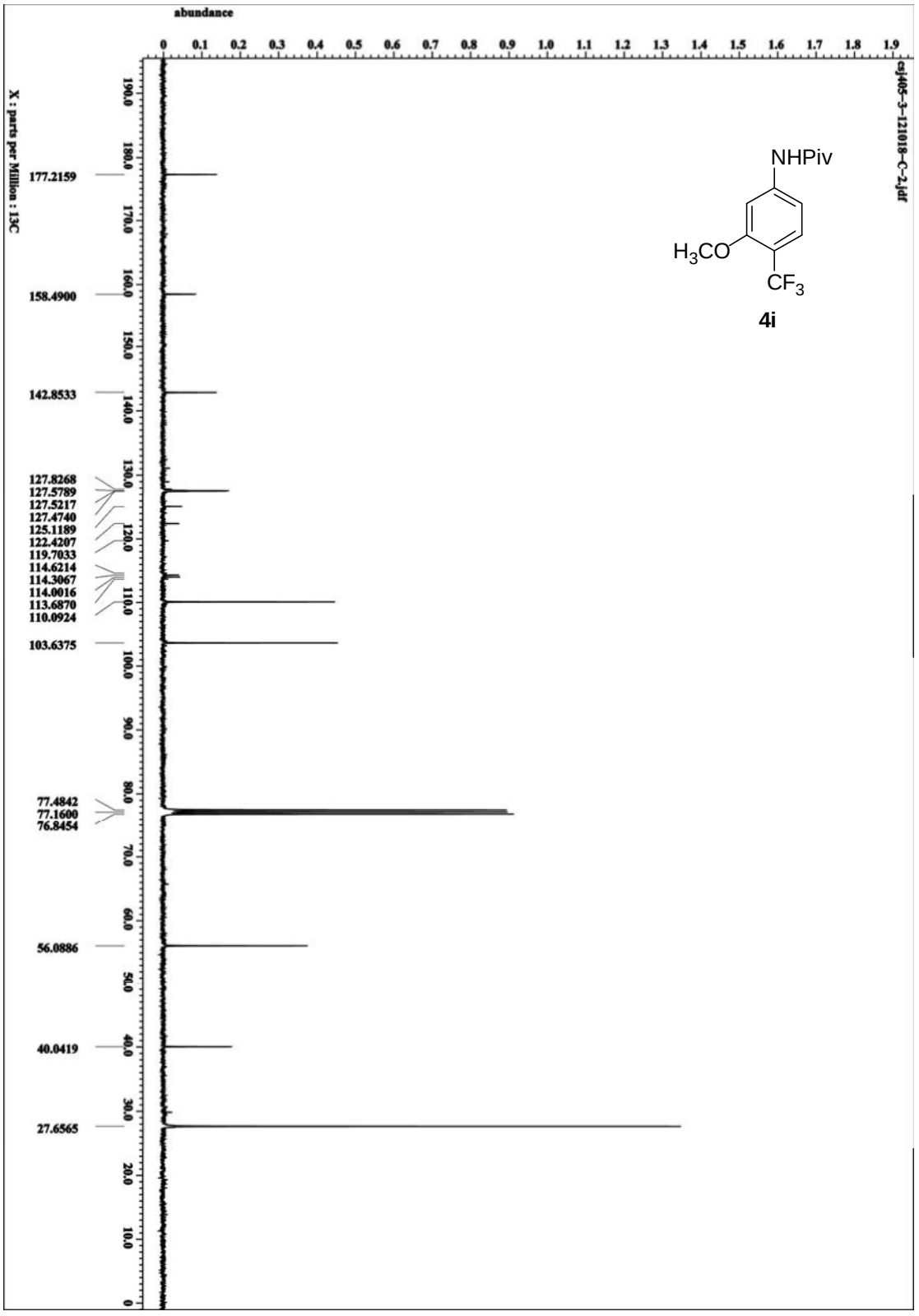
-60.8759
NHPiv
CF3
COOEt
3h


abundance
csj405-2-121017-H-3.jdf
X : parts per Million : 1H
NHPiv
CF3
H3CO
3i
7.9885
7.8534
7.4845
7.4628
7.2600
6.6953
6.6758
3.8476
1.3149
0.0686
-0.0104
1.03
1.03
1.06
3.04
9.04


abundance
csj405-2-121017-C-2.jdf
X : parts per Million : 13C
NHPiv
CF3
H3CO
3i
176.9394
163.0189
137.5806
128.8374
127.4168
127.3691
127.3119
127.2642
126.1201
123.4218
120.7140
111.8849
111.5894
111.2938
110.4262
107.9662
77.4842
77.1600
76.8454
55.7167
40.1468
27.4467


abundance
0
100.0
200.0
300.0
400.0
csj405-2-121017-F-8.jdf
X : parts per Million : 19F
-30.0
-40.0
-50.0
-59.2472
-60.0
-70.0
-80.0
NHPiv
CF3
H3CO
3i


abundance
0
10.0
20.0
30.0
40.0
50.0
60.0
csj405-3-121018-H-2.jdf
X : parts per Million : 1H
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
7.7617
7.4650
7.4547
7.4444
7.2600
6.8075
6.7869
3.9003
1.3264
0.0686
1
2.04
1.08
3.08
9.11
NHPiv
H3CO
CF3
4i


abundance
X : parts per Million : 13C
csj405-3-121018-C-2.jdf
177.2159
158.4900
142.8533
127.8268
127.5789
127.5217
127.4740
125.1189
122.4207
119.7033
114.6214
114.3067
114.0016
113.6870
110.0924
103.6375
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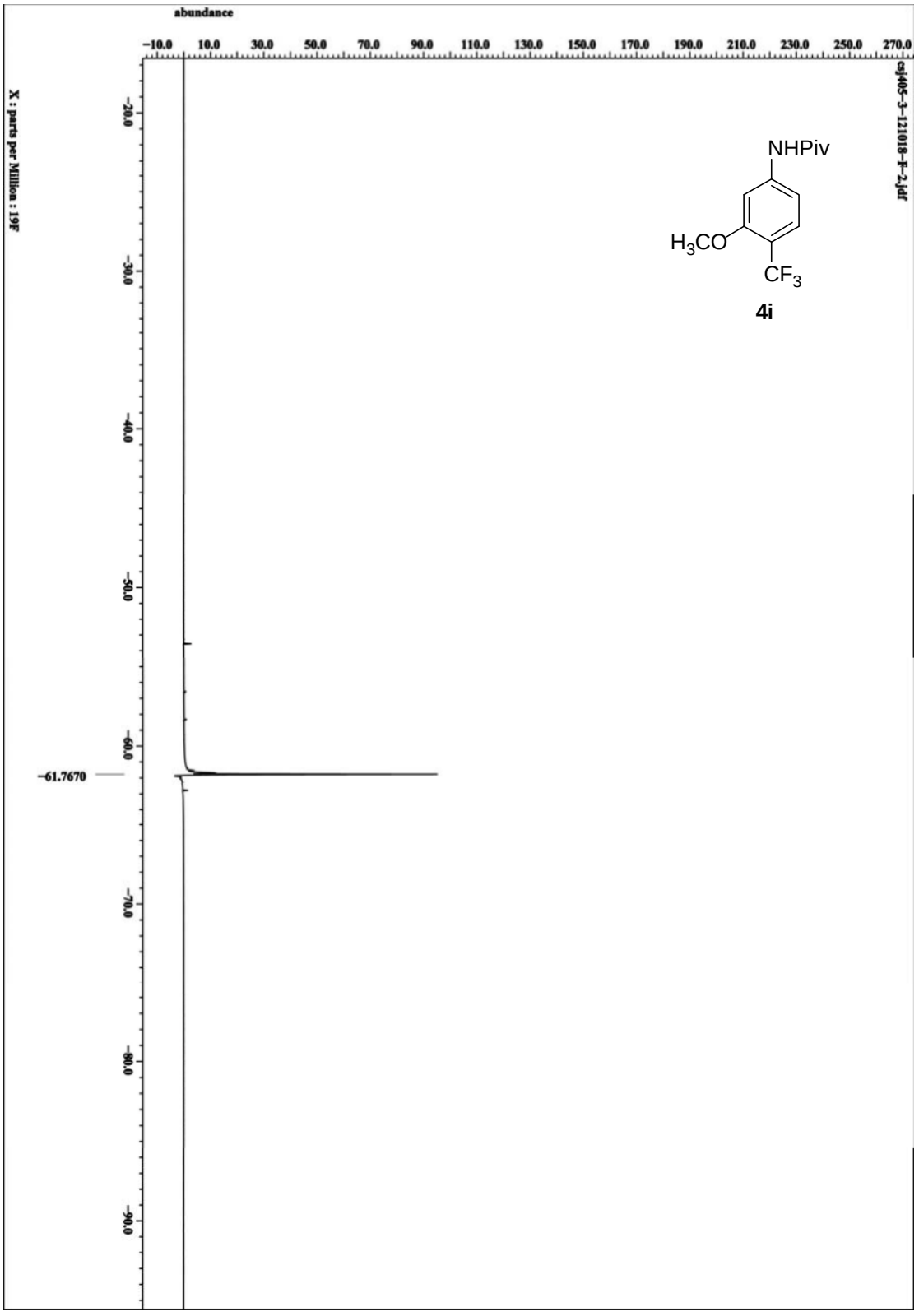
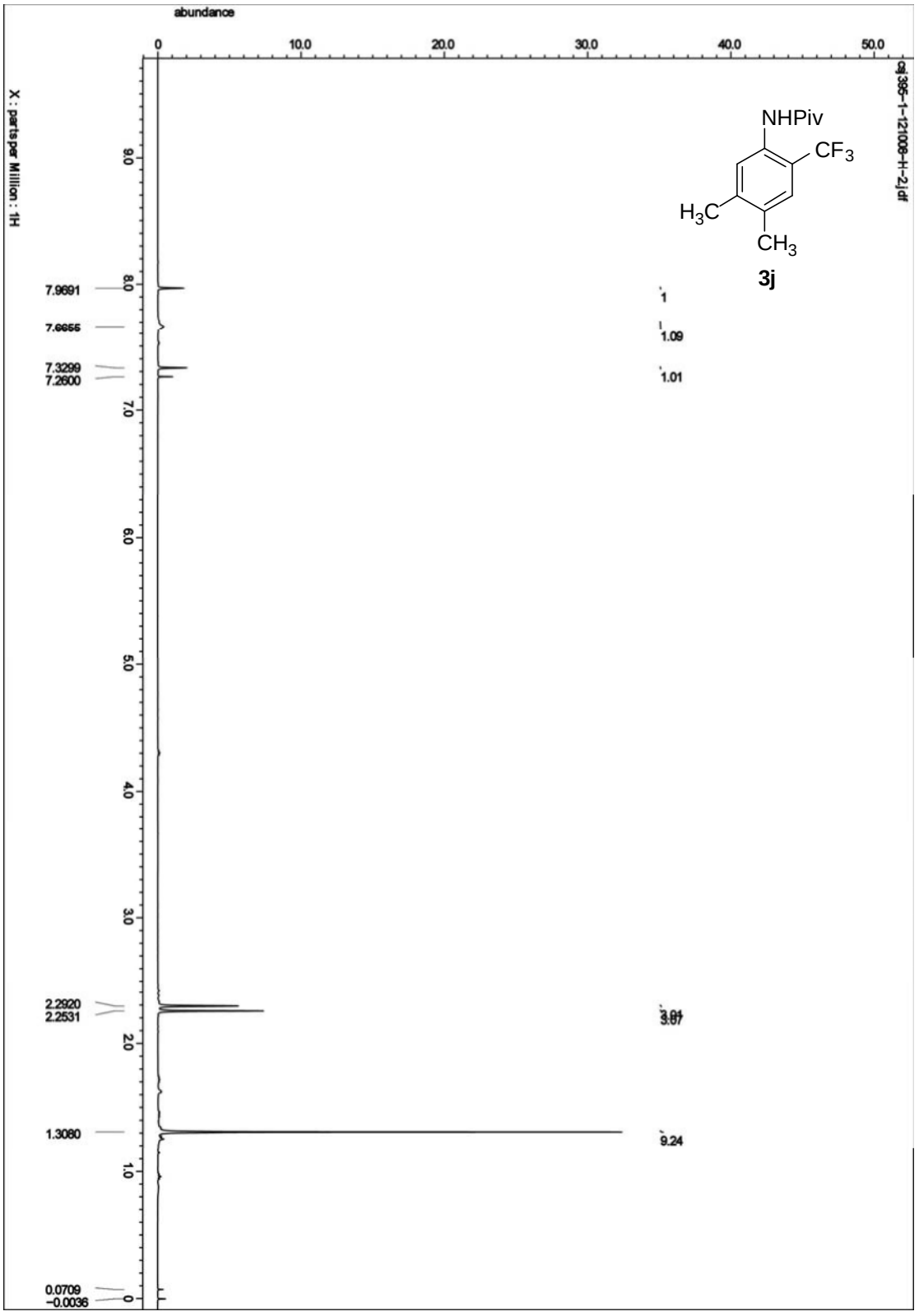
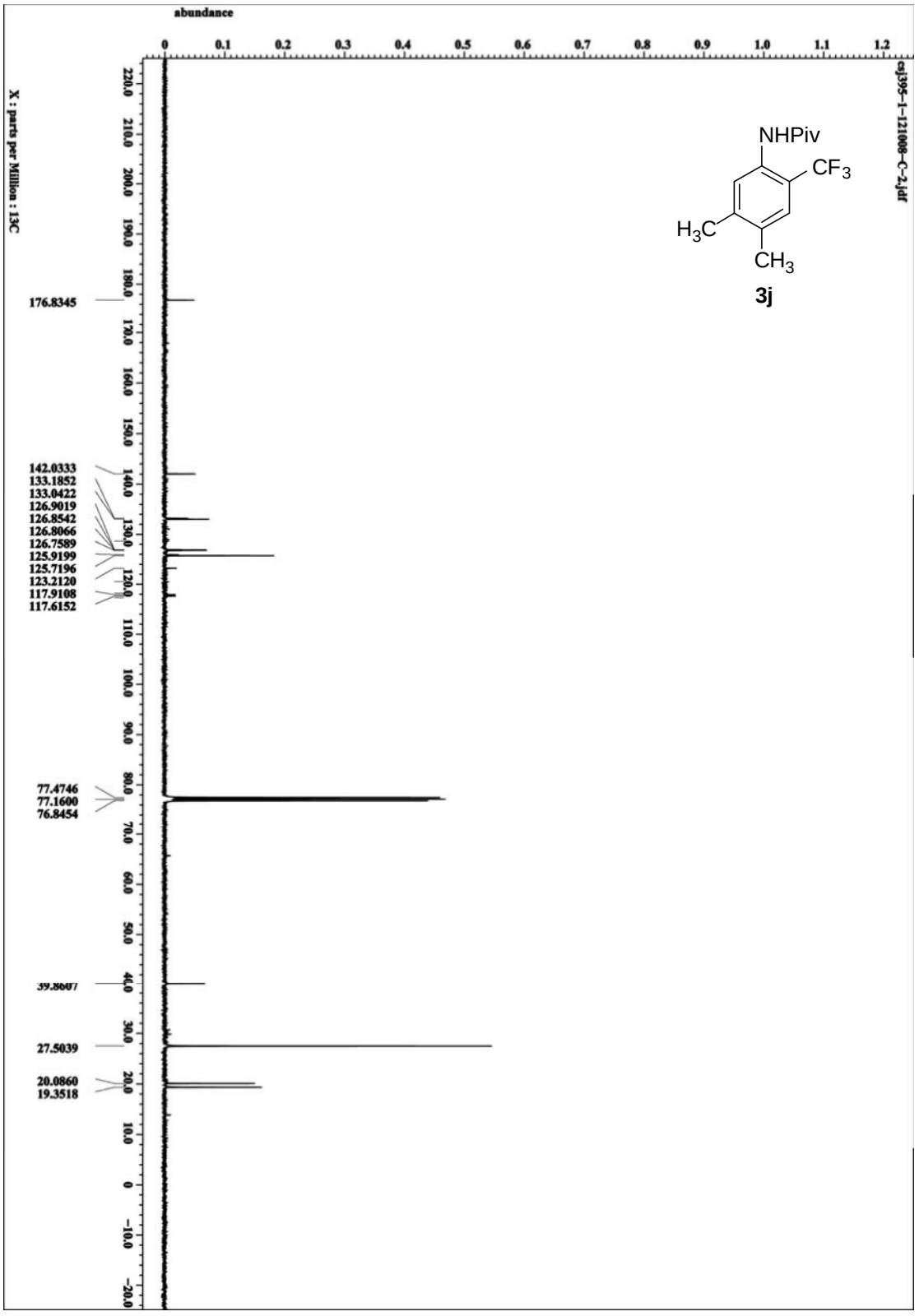
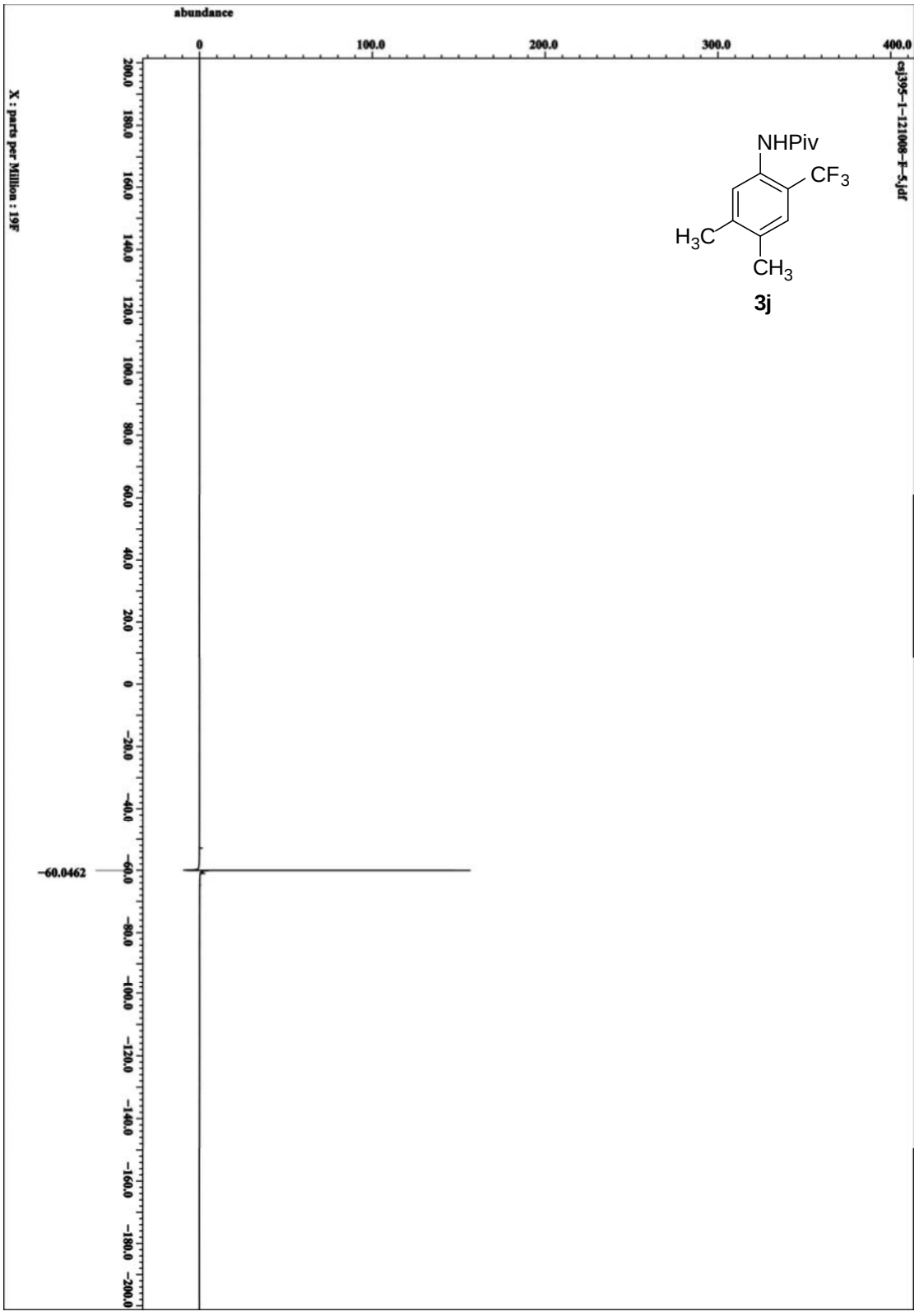
40.0419
27.6565
NHPiv
H3CO
CF3
4i


abundance
X : parts per Million : 19F
csj405-3-121018-F-2.jdf
−61.7670
NHPiv
H3CO
CF3
4i


abundance
X : parts per Million : 1H
NHPiv
CF3
H3C
CH3
3j
7.9691
7.6655
7.3299
7.2600
2.2920
2.2531
1.3080
0.0709
−0.0036
1
1.09
1.01
9.24


abundance
X : parts per Million : 13C
csj395-1-121008-C-2.jdf
NHPiv
CF3
H3C
CH3
3j
176.8345
142.0333
133.1852
133.0422
126.9019
126.8542
126.8066
126.7589
125.9199
125.7196
123.2120
117.9108
117.6152
77.4746
77.1600
76.8454
39.8607
27.5039
20.0860
19.3518


abundance
0
100.0
200.0
300.0
400.0
csj395-1-121008-F-5.jdf
X : parts per Million : 19F
200.0
180.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0
-20.0
-40.0
-60.0
-80.0
-100.0
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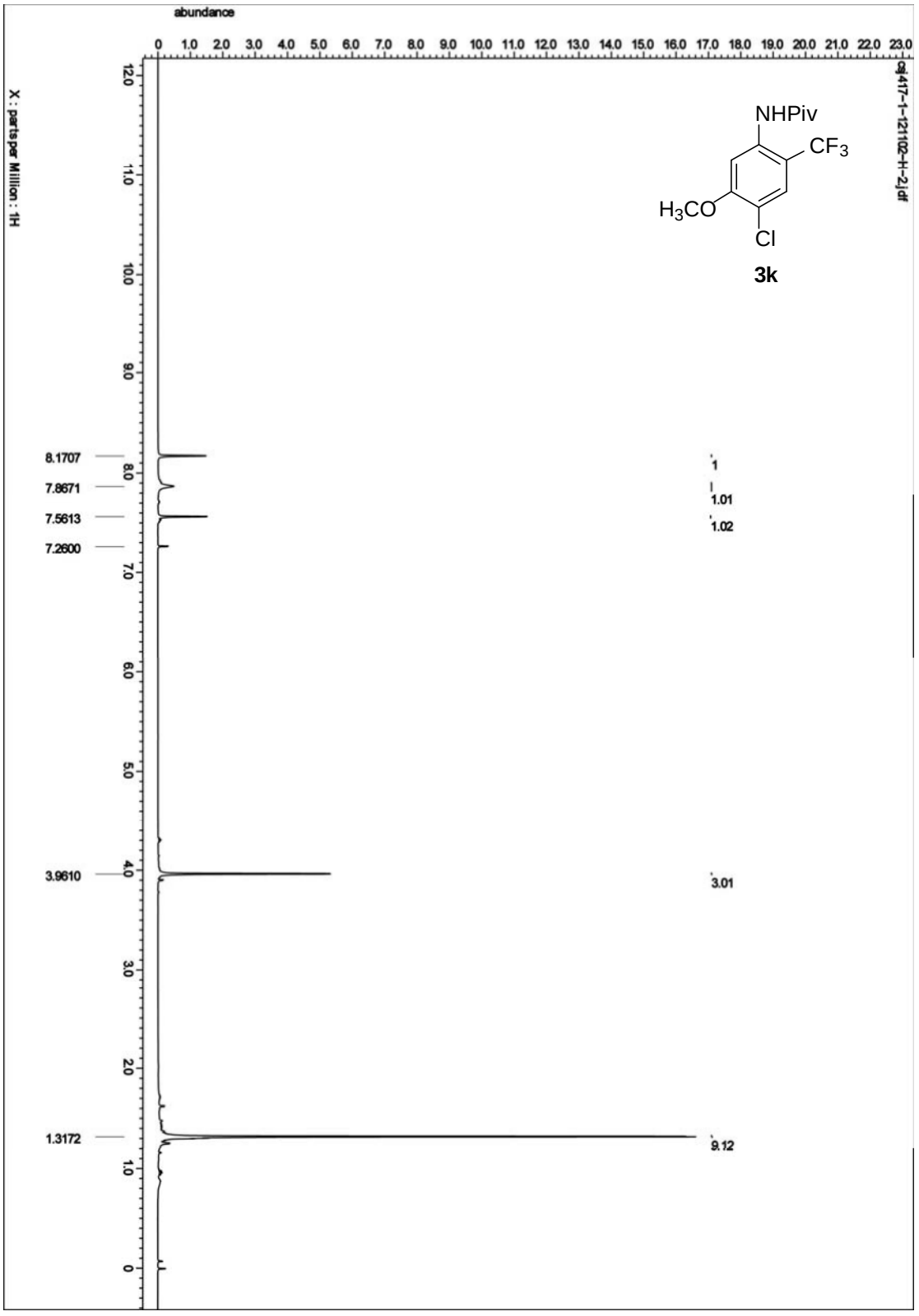
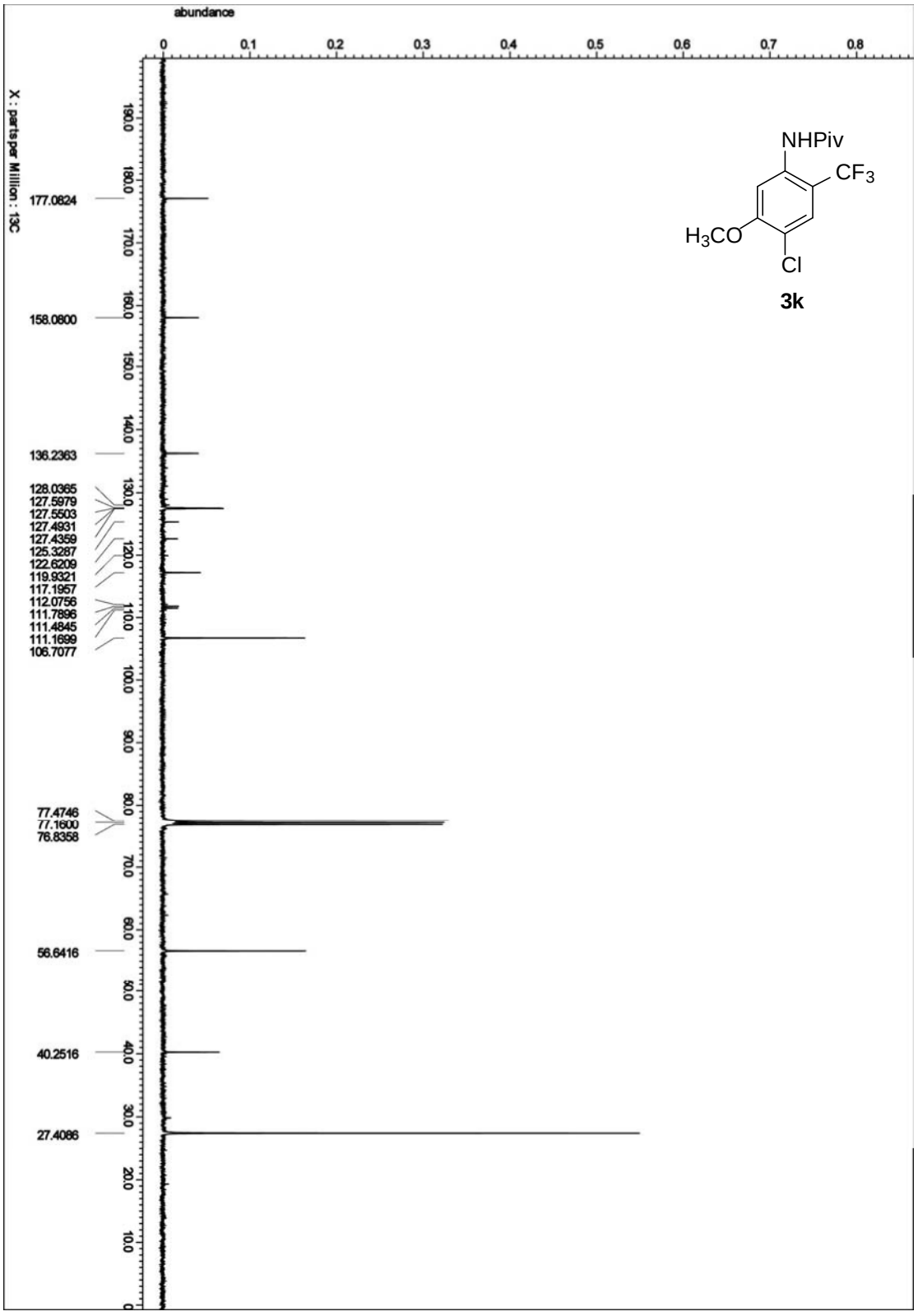
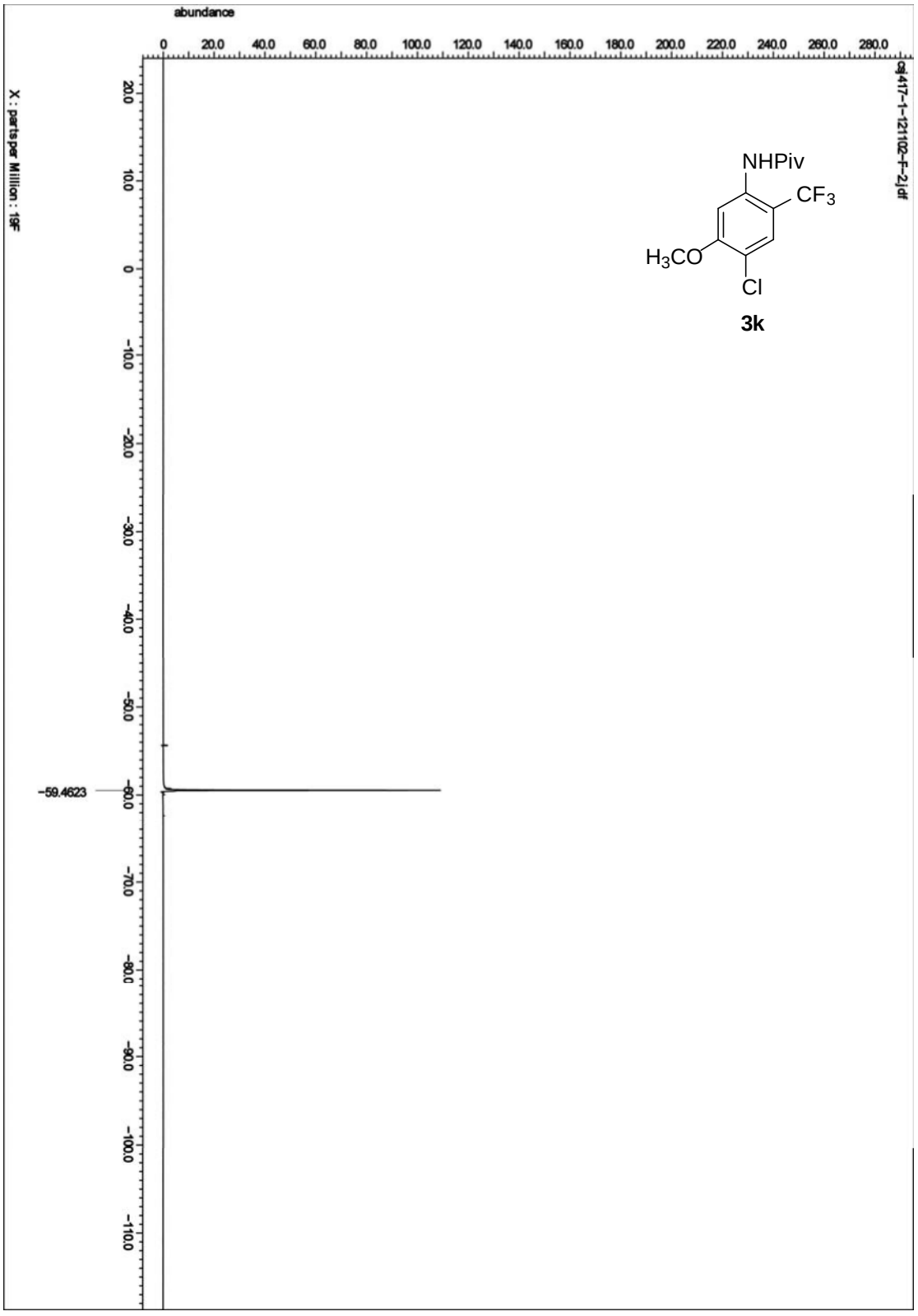
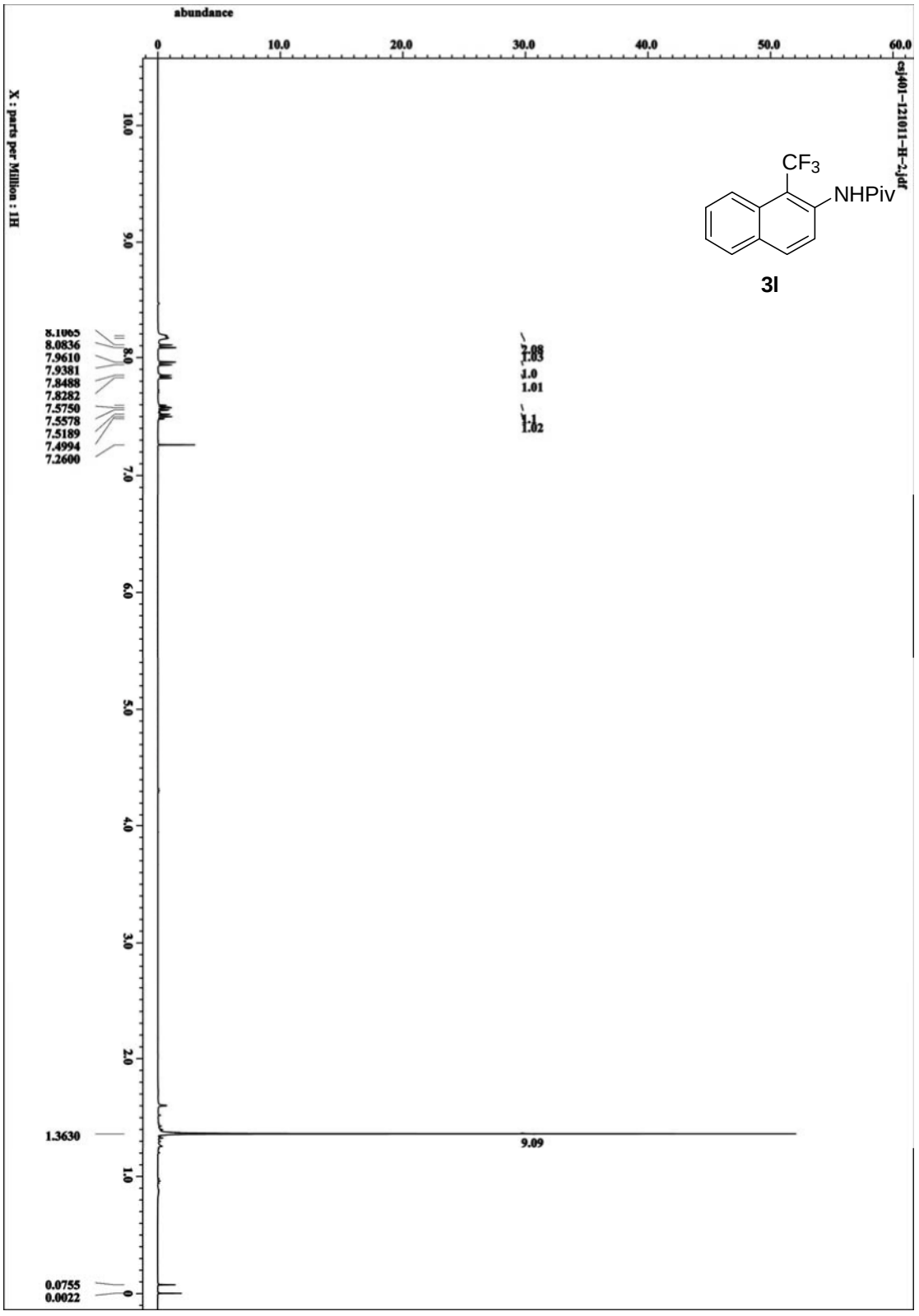
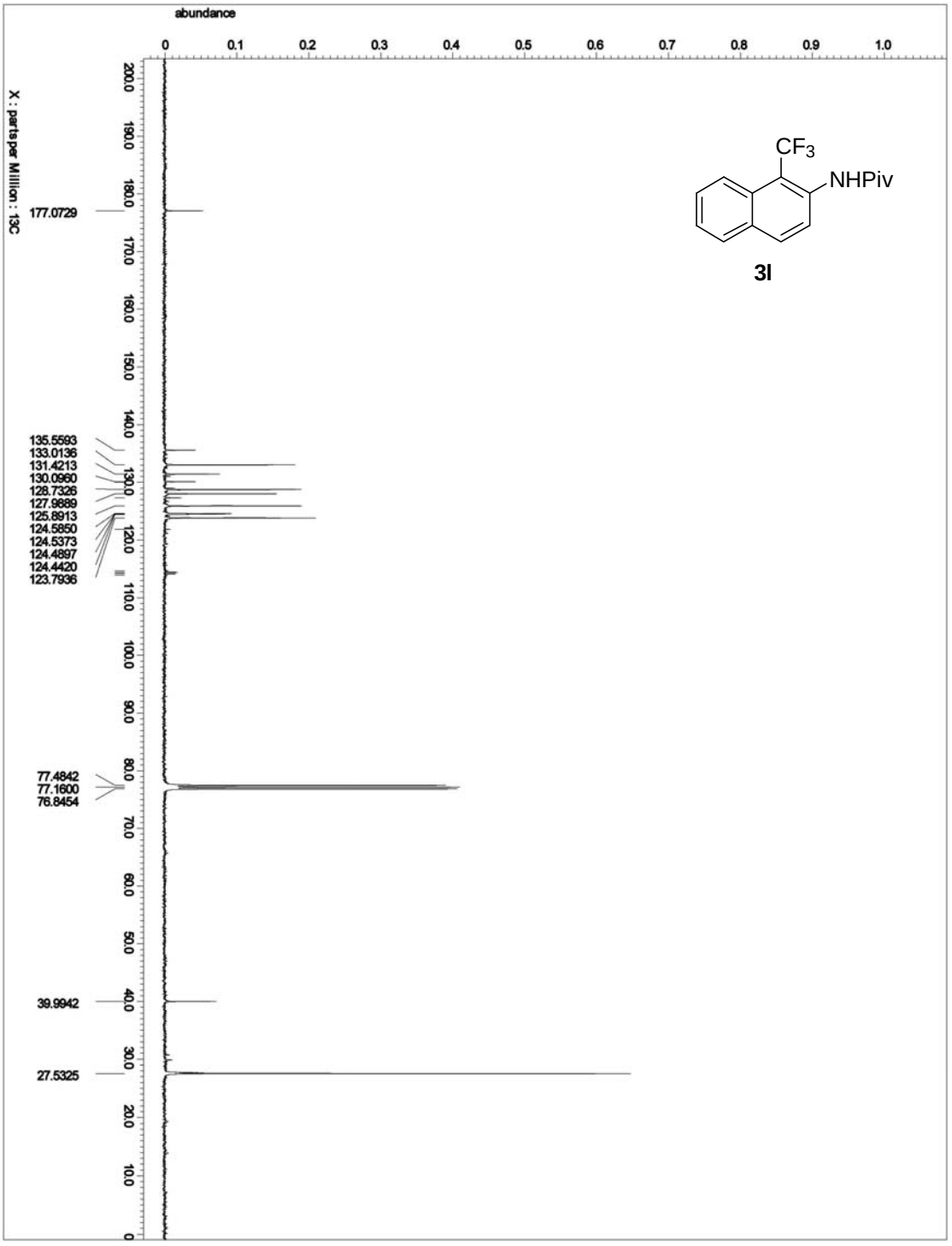
-60.0462
NHPiv
CF3
H3C
CH3
3j


abundance
X : parts per Million : 1H
cj417-1-121102-H-2.jdf
NHPiv
CF3
H3CO
Cl
3k
8.1707
7.8671
7.5613
7.2600
3.9610
1.3172
1
1.01
1.02
3.01
9.12

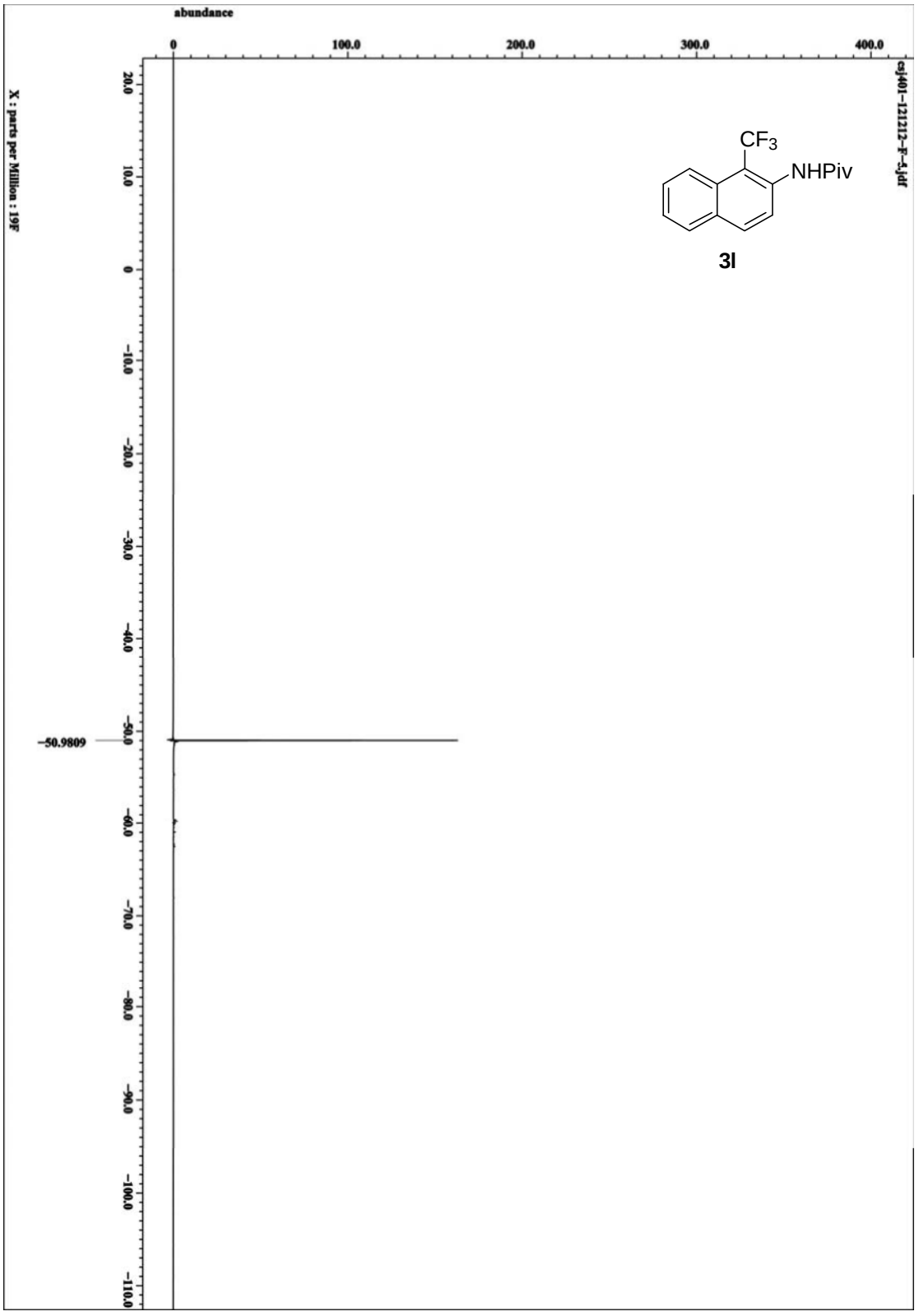

abundance
X : parts per Million : 13C
177.0824
158.0800
136.2363
128.0365
127.5979
127.5503
127.4931
127.4359
125.3287
122.6209
119.9321
117.1957
112.0756
111.7896
111.4845
111.1699
106.7077
77.4746
77.1600
76.8358
56.6416
40.2516
27.4086
NHPiv
CF3
H3CO
Cl
3k

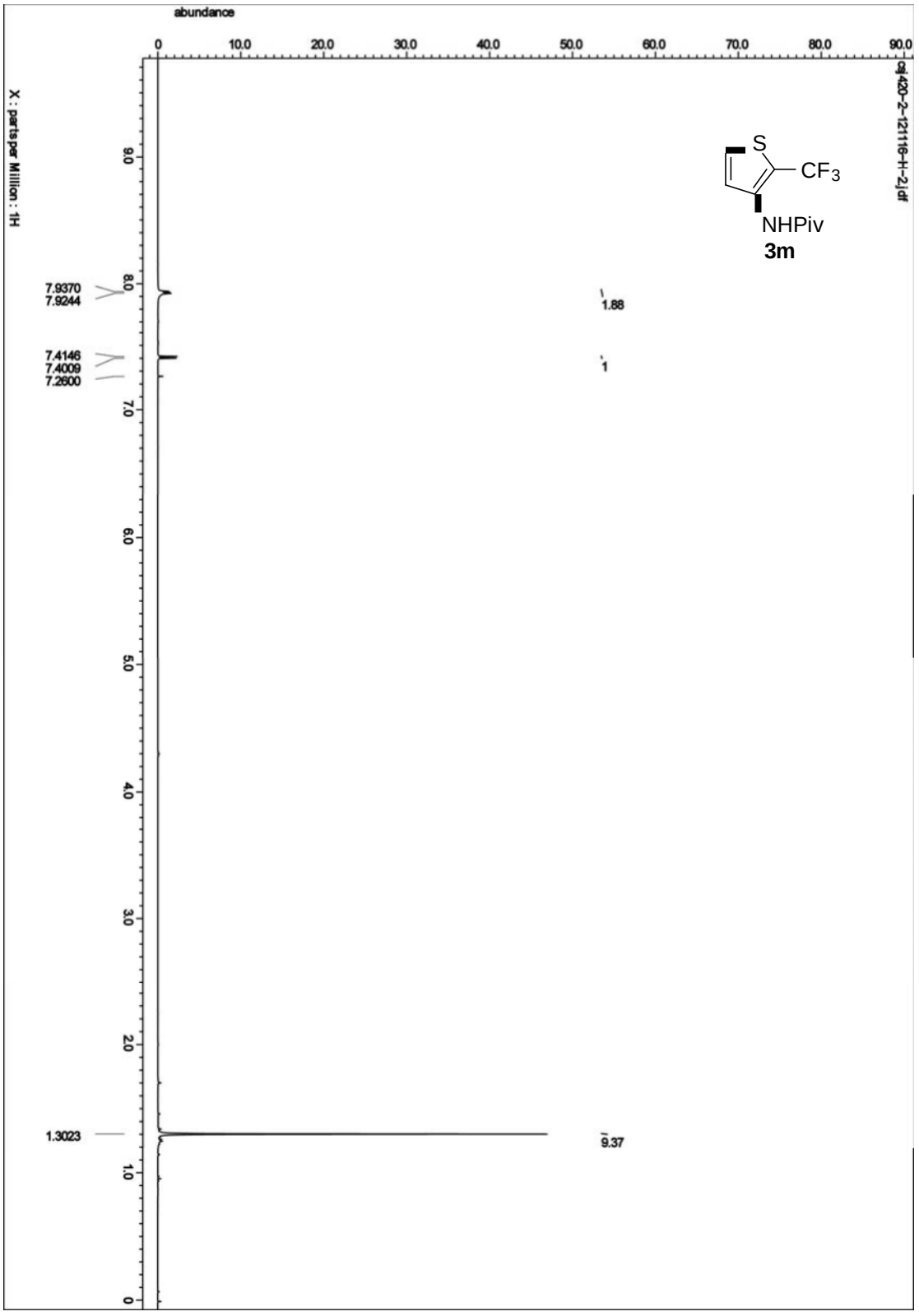

abundance
X : parts per Million : 19F
-59.4623
NHPiv
CF3
H3CO
Cl
3k

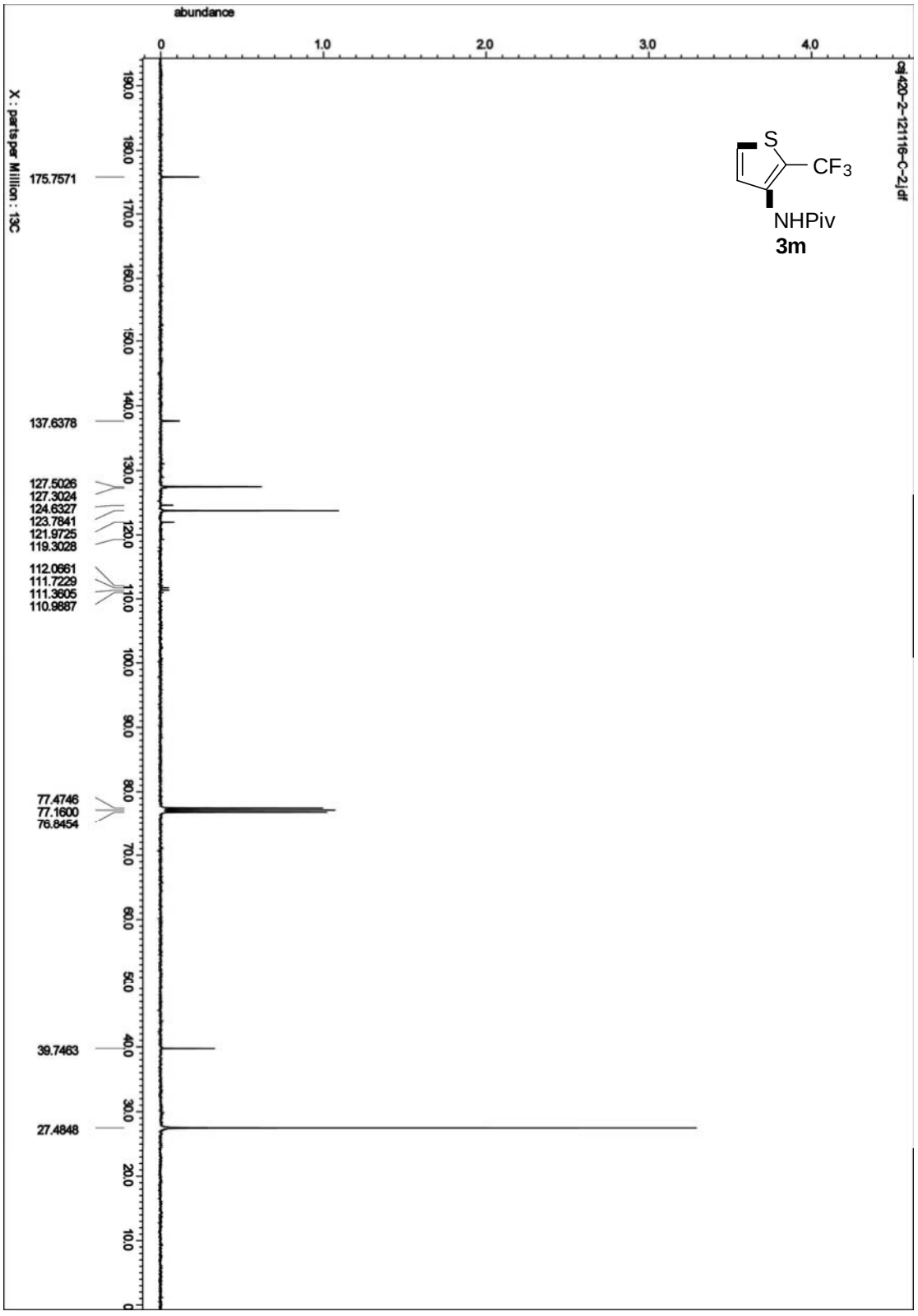

abundance
X : parts per Million : 1H
csj401-121011-H-2.jdf
CF3
NHPiv
3l
8.1065
8.0836
7.9610
7.9381
7.8488
7.8282
7.5750
7.5578
7.5189
7.4994
7.2600
2.08
1.03
1.0
1.01
1.1
1.02
1.3630
9.09
0.0755
0.0022

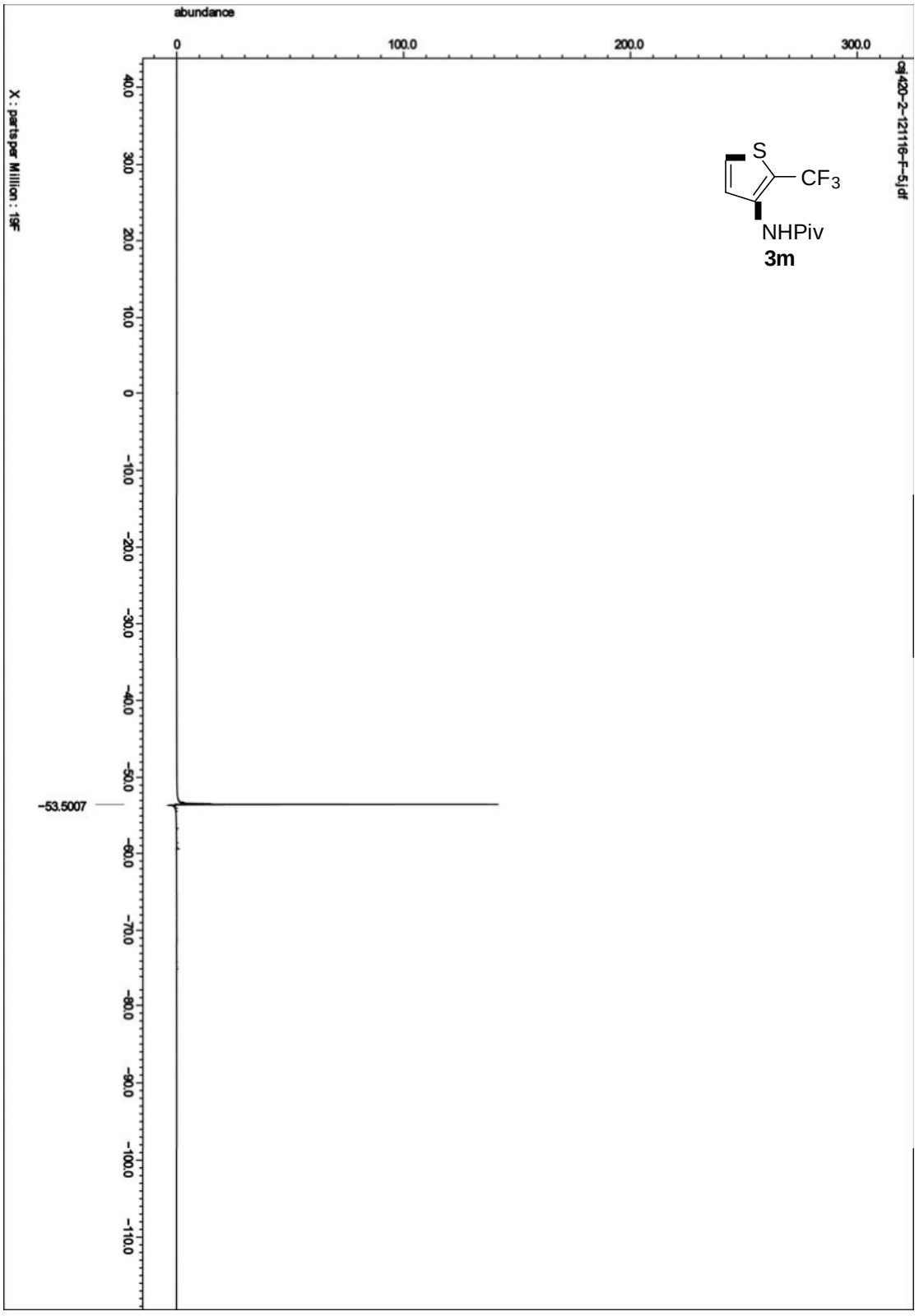

abundance
X : parts per Million : 13C
177.0729
135.5593
133.0136
131.4213
130.0960
128.7326
127.9889
125.8913
124.5850
124.5373
124.4897
124.4420
123.7936
77.4842
77.1600
76.8454
39.9942
27.5325
CF3
NHPiv

3l


abundance
0
100.0
200.0
300.0
400.0
csj401-121212-F-5.jdf
X : parts per Million : 19F
20.0
10.0
0
-10.0
-20.0
-30.0
-40.0
-50.0
-60.0
-70.0
-80.0
-90.0
-100.0
-110.0
-50.9809
CF3
NHPiv
3l


abundance
X : parts per Million : 1H
7.9370
7.9244
7.4146
7.4009
7.2600
1.3023
1.88
1
9.37
S
CF3
NHPiv
3m


abundance
X : parts per Million : 13C
175.7571
137.6378
127.5026
127.3024
124.6327
123.7841
121.9725
119.3028
112.0661
111.7229
111.3605
110.9887
77.4746
77.1600
76.8454
39.7463
27.4848
S
CF3
NHPiv
3m


abundance
0
100.0
200.0
300.0
X : parts per Million : 19F
40.0
30.0
20.0
10.0
0
-10.0
-20.0
-30.0
-40.0
-50.0
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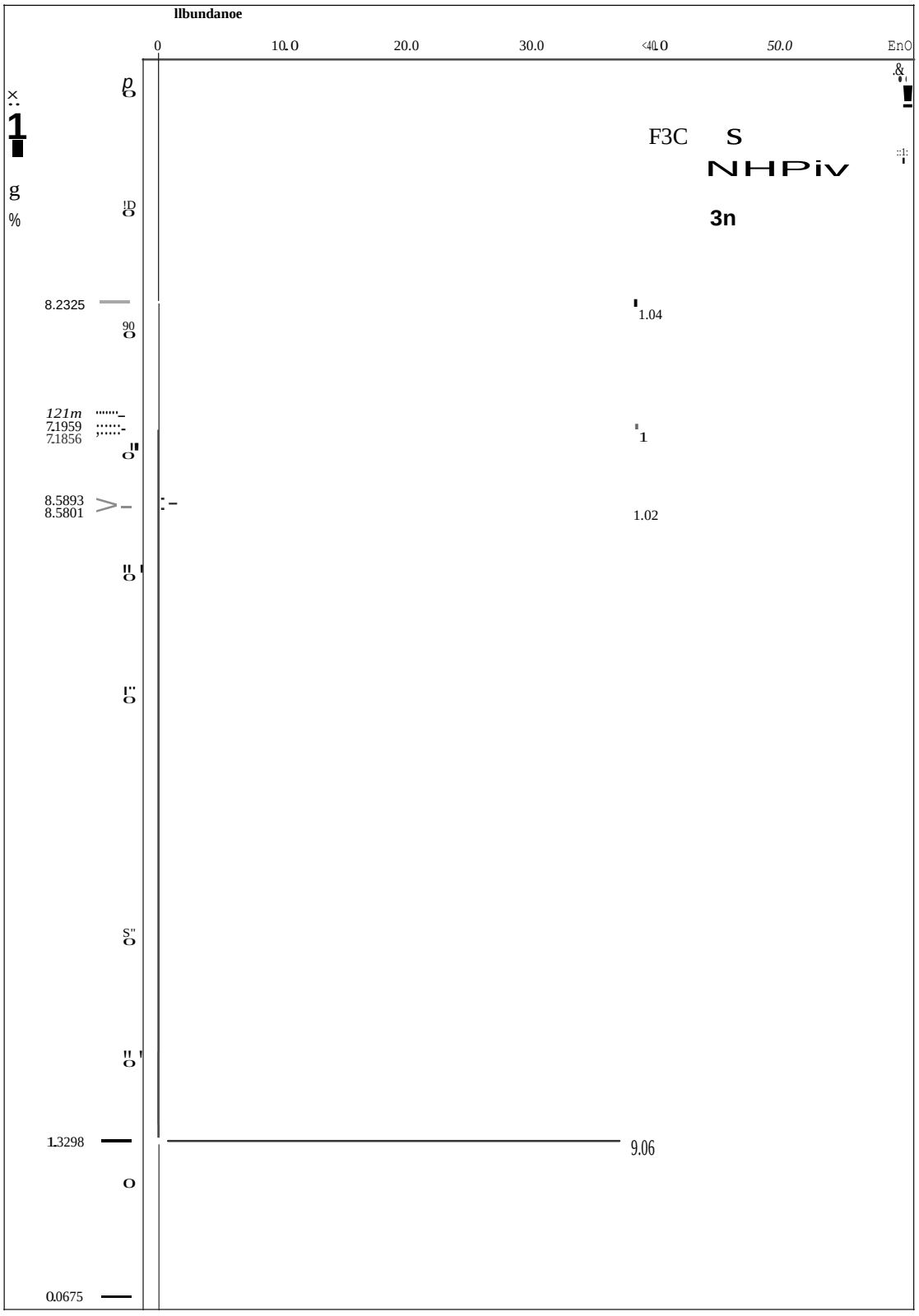
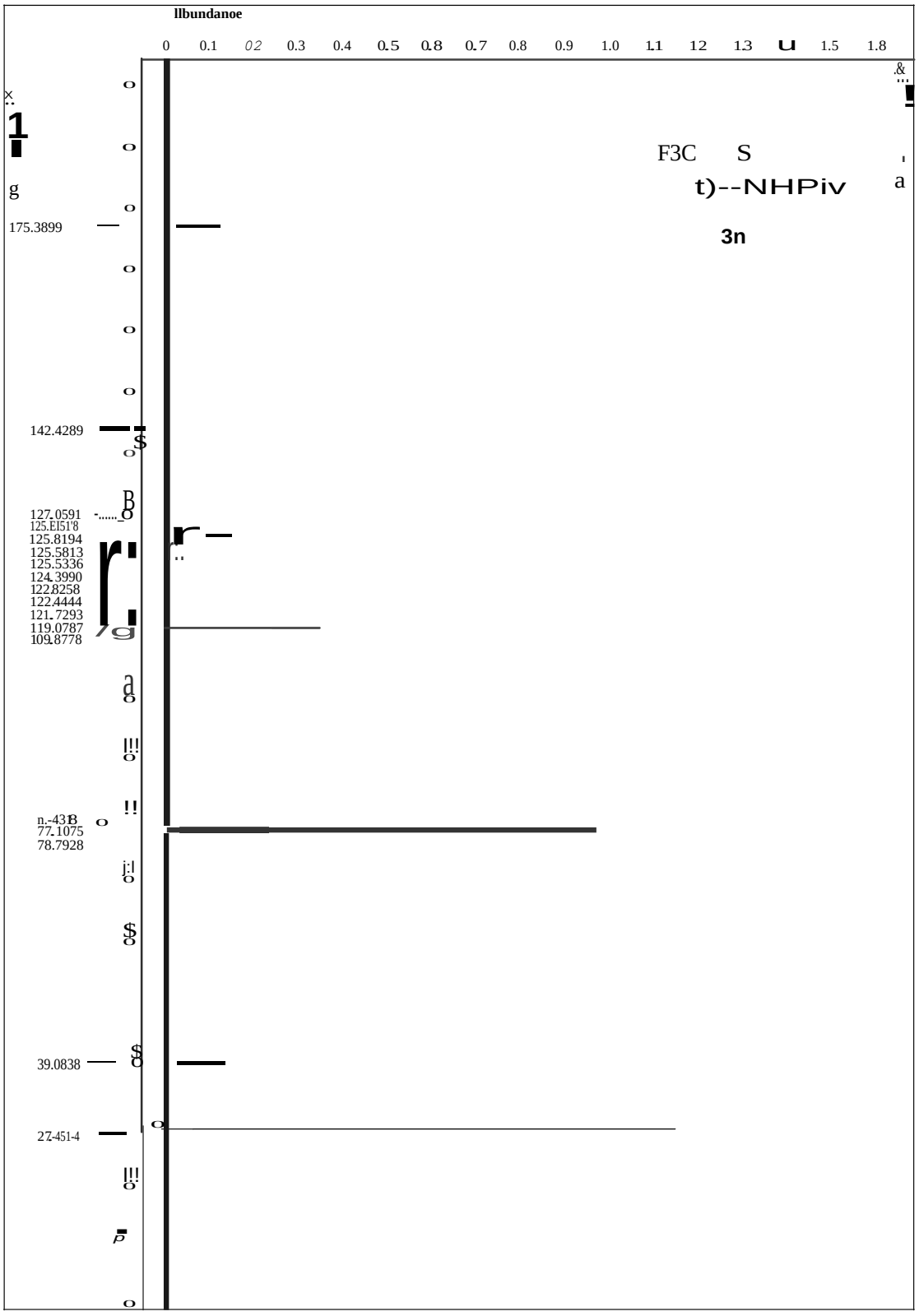
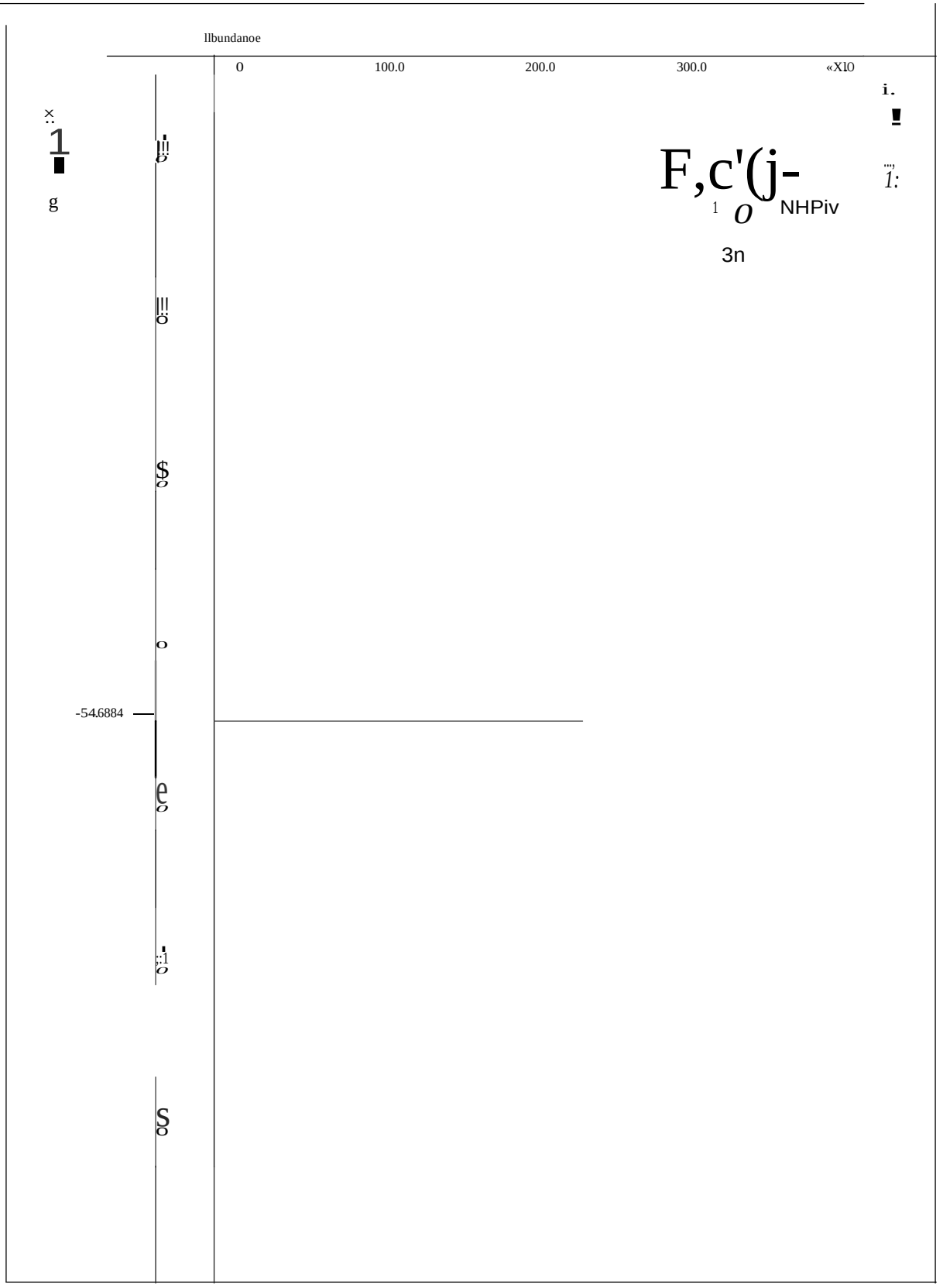
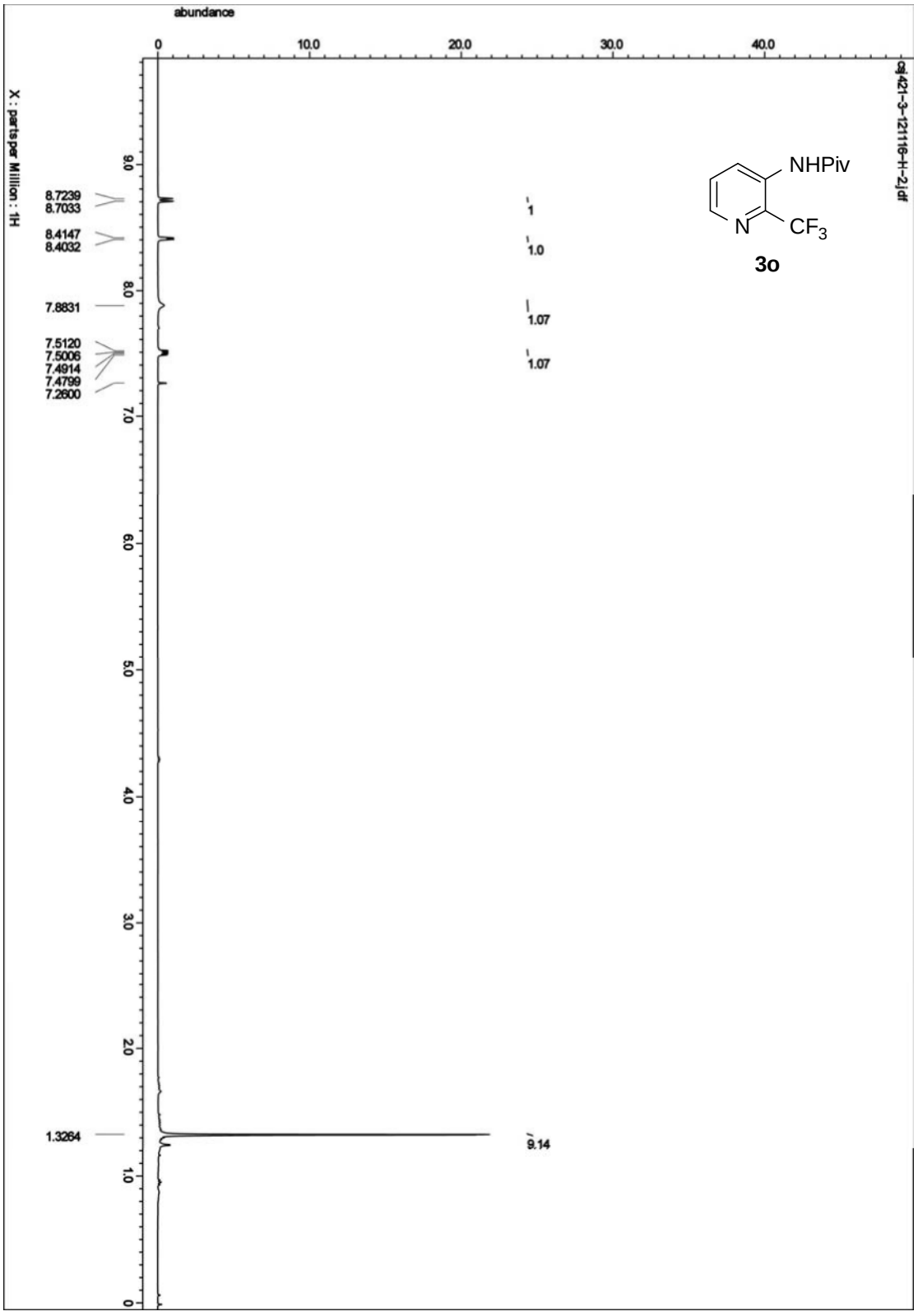
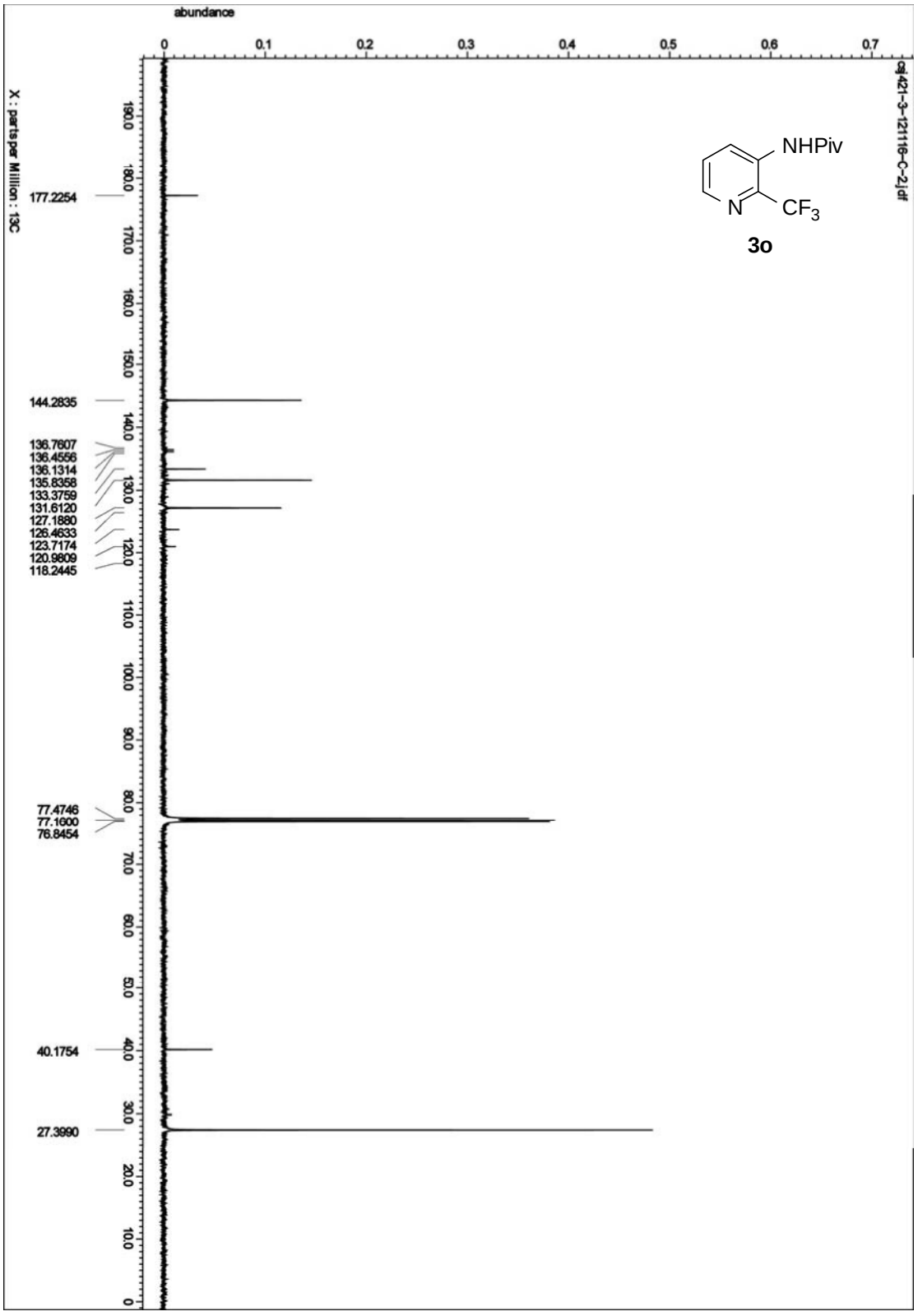
-110.0
-53.5007
S
CF3
NHPiv
3m

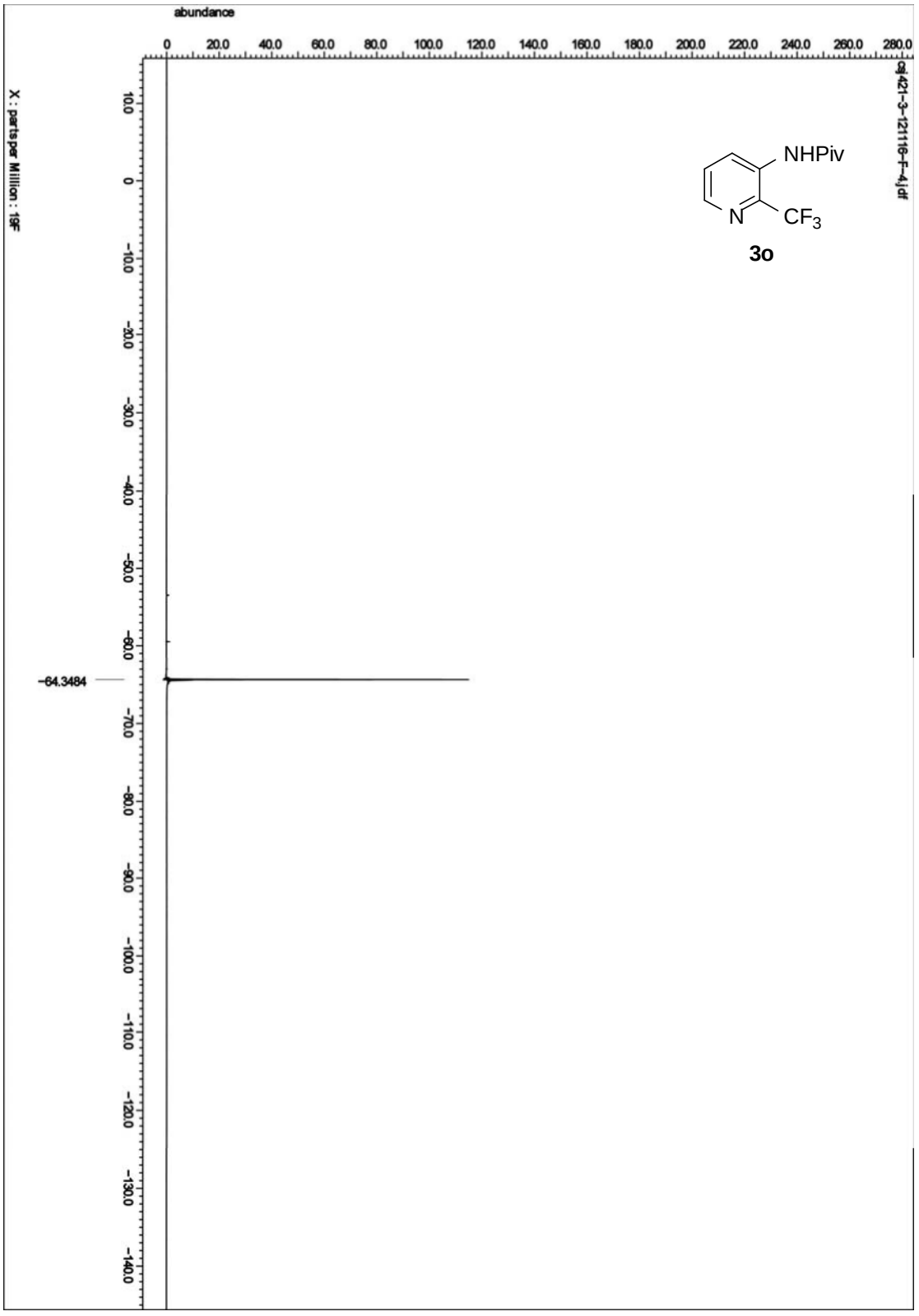

llbundanoe
0
10.0
20.0
30.0
40.0
50.0
F3C
S
NHPiv
3n
8.2325
1.04
121m
7.1959
7.1856
1
8.5893
8.5801
1.02
1.3298
9.06
0.0675


llbundanoe
0 0.1 02 0.3 0.4 0.5 0.8 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.5 1.8
F3C S
t)--NHPiv
3n
175.3899
142.4289
127.0591
125.EI51'8
125.8194
125.5813
125.5336
124.3990
122.8258
122.4444
121.7293
119.0787
109.8778
77.1075
78.7928
39.0838
27-451-4


llbundanoe
0
100.0
200.0
300.0
«X10
NHPiv
3n
-54.6884


abundance
0
10.0
20.0
30.0
40.0
X : parts per Million : 1H
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
8.7239
8.7033
8.4147
8.4032
7.8831
7.5120
7.5006
7.4914
7.4799
7.2600
1.3264
1
1.0
1.07
1.07
9.14
NHPiv
N
CF3
3o


abundance
X : parts per Million : 13C
177.2254
144.2835
136.7607
136.4556
136.1314
135.8358
133.3759
131.6120
127.1880
126.4633
123.7174
120.9809
118.2445
77.4746
77.1600
76.8454
40.1754
27.3990
NHPiv
N
CF3
3o


abundance
X : parts per Million : 19F
-64.3484
NHPiv
N
CF3
3o

10. References:

1. A. T. Parsons and S. L. Buchwald, *Angew. Chem. Int. Ed.*, 2011, **123**, 9286.

2. K. Smith, G. A. El-Hiti, P. J. Gareth and H. Anna, *J. Chem. Soc., Perk. Trans. 1*, 1999, **16**, 2299.

3. S. Kaname and C. David, *Org. Lett.*, 2011, **13**, 2256.