$Pd(OAc)_2$-Catalyzed Regioselective Aromatic C-H Bond Fluorination

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Supporting Information

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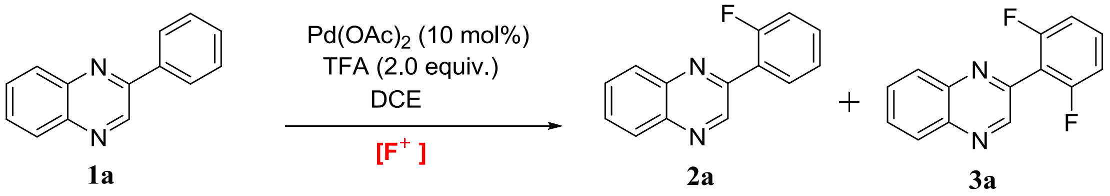
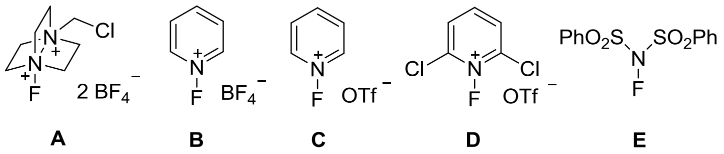
General

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without purifications. All solvents for reactions were dried and distilled prior to use according to standard methods. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker AVANCE III 500 instrument in $CDCl_3$ using TMS as internal standard, operating at 500 MHz and 125 MHz, respectively. ^{19}F NMR were recorded on a Varian Inova 400 instrument in $CDCl_3$ at 376 MHz with CF_3COOH as external standard, Chemical shifts (δ) are expressed in ppm and coupling constants J are given in Hz. GC-MS experiments were performed with an Agilent 6890N GC system equipped with a 5973N mass-selective detector, high resolution mass spectra (HRMS) were obtained on a Waters GCT Premier TOF MS with EI or CI source. Electrospray ionization (ESI) mass experiments were performed on a Thermo LCQ fleet. Starting materials 2-arylquinoxalines (**1a**-**1t**),[1,2] 2-phenylbenzo[d]oxazole (**3b**)[3] and 2-phenylpyrazine (**3c**)[4] were synthesized according to the literature procedures.

Screening of the fluorination condition

Table 1. Screening of fluorination agents [a]

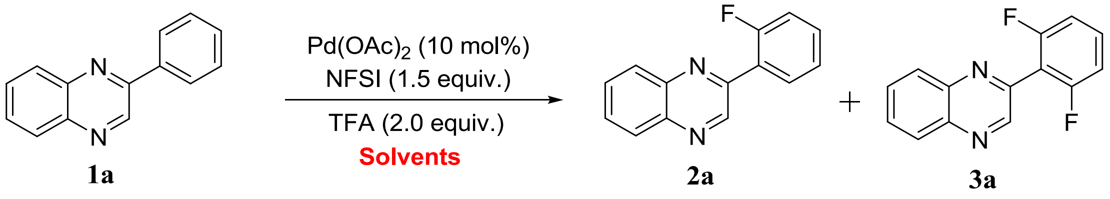




Entry	[F$^+$]	Conv. of 1a (%) [b]	Yield of 2a / 3a (%) [b]
1	**A** (1.5 equiv.)	12	trace / 0
2	**B** (1.5 equiv.)	7	5 / 0
3	**C** (1.5 equiv.)	5	3 / 0
4	**D** (1.5 equiv.)	6	5 / trace
5	**E (1.5 equiv.)**	**95**	**68 / 25**
6	**E** (1.0 equiv.)	65	45 / 19
7	**E** (2.0 equiv.)	96	60 / 31

[a] Reaction condition : **1a** (0.1 mmol), Pd (OAc)$_2$ (2.2 mg), TFA = Trifluoroacetic acid (23 mg), DCE = 1, 2-chloroethane (1.0 mL), 110 °C, under air, 24 h. [b] GC-MS yield.

Table 2. Screening of solvents [a]

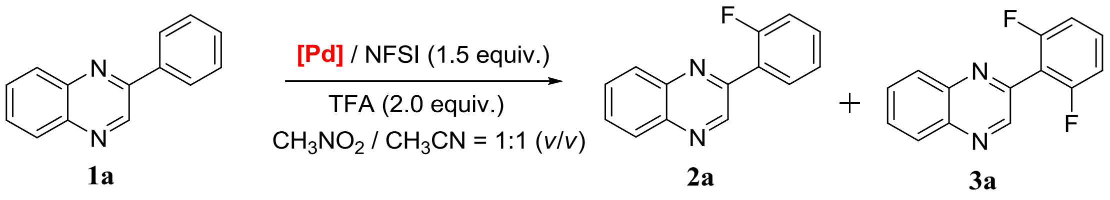


Entry	Solvents	T (°C)	Time (hr)	Conv. of 1a (%) [b]	Yield of 2a / 3a (%) [b]
1	DCE	r.t.	24	0	0
2	DCE	80	24	15	13 / 1
3	DCE	95	24	48	42 / 4
4	DCE	110	24	95	68 / 25
5	DCE	125	24	96	67 / 28
6	DCE	110	12	94	68 / 24
7	CH_3CN	110	12	62	53 / 1.5
8	Toulene	110	12	49	38 / 2

9	$CF_3C_6H_5$	110	12	trace	0 / 0
10	1,4-dioxane	110	12	37	12 / trace
11	DMF	110	12	8	trace / 0
12	DMA	110	12	16	15 / trace
13	NMP	110	12	trace	trace / trace
14	$CHCl_3$	110	12	28	15 / trace
15	EtOAc	110	12	28	22 / trace
16	THF	110	12	14	12 / trace
17	CH_3NO_2	110	12	91	54 / 33
18	n-Hexane	110	12	34	9 / trace
19	DCE / CH_3CN = 1:1	110	12	65	60 / 2
20	DCE / CH_3CN = 1:2	110	12	65	60 / 2
21	DCE / CH_3CN = 2:1	110	12	65	59 / 2
22	DCE / CH_3CN = 10:1	110	12	68	62 / 3
23	DCE / CH_3CN = 1:10	110	12	64	58 / 2
24	**CH_3NO_2 / CH_3CN = 1:1**	**110**	**12**	**82**	**78 / 3**
25	CH_3NO_2 / CH_3CN = 10:1	110	12	91	76 / 13
26	CH_3NO_2 / CH_3CN = 1:10	110	12	65	61 / 2

[a] Reaction condition : **1a** (0.1 mmol), $Pd(OAc)_2$ (2.2 mg), NFSI = N-Fluorobenzenesulfoonimide (47 mg), TFA = Trifluoroacetic acid (23 mg), solvents (1.0 mL), under air. [b] GC-MS yield.

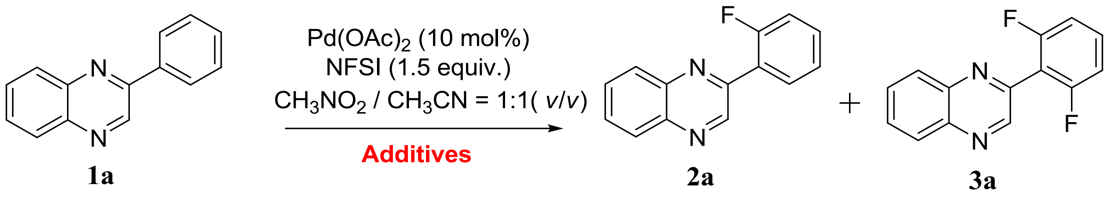
Table 3. Screening of catalysts [a]



Entry	[Pd]	Conv. of 1a (%) [b]	Yield of 2a / 3a (%) [b]
1	**$Pd(OAc)_2$ (10 mol%)**	**82**	**78 / 3**
2	$Pd(OAc)_2$ (5 mol%)	66	63 / 2
3	$Pd(OAc)_2$ (10 mol%)	65	62 / 1.5 [c]
4	$Pd(OAc)_2$ (10 mol%)	83	78 / 4 [d]
5	$Pd(OOCCF_3)_2$ (10 mol%)	79	73 / 2
6	$PdCl_2$ (10 mol%)	trace	trace / 0
7	$Pd(PPh_3)_2Cl_2$ (10 mol%)	62	58 / 2
8	$Pd_2(dba)_3$ (10 mol%)	40	32 / trace
9	$Pd(PPh_3)_4$ (10 mol%)	68	65 / 2
10	——	trace	0 / 0

[a] Reaction condition : **1a** (0.1 mmol), NFSI = N-Fluorobenzenesulfoonimide (47 mg), TFA = Trifluoroacetic acid (23 mg), CH_3NO_2 / CH_3CN = 1:1 (*v*/*v*) (1.0 mL), 110 °C, under air, 12 h. [b] GC-MS yield. [c] Under Ar atmosphere. [d] Under O_2 atmosphere.

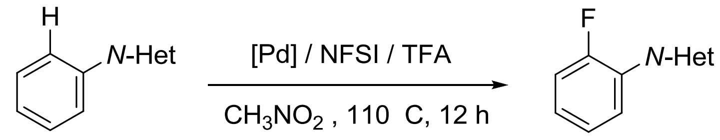
Table 4. Screening of additives [a]



Entry	Additives	Conv. of 1a (%) [b]	Yield of 2a / 3a (%) [b]
1	——	15	10 / 2
2	——	61	55 / 3 [c]
3	TFA (1.0 equiv)	75	69 / 3
4	**TFA (2.0 equiv)**	**82**	**78 / 3**
5	TFA (3.0 equiv)	82	78 / 3
6	TFA (10.0 equiv)	83	74 / 3
7	HOAc (2.0 equiv)	22	19 / trace
8	CH_3CSOH (2.0 equiv)	trace	0 / 0
9	$ClCH_2COOH$ (2.0 equiv)	18	16 / trace
10	$BrCH_2COOH$ (2.0 equiv)	2	2 / trace
11	$Cl_2CHCOOH$ (2.0 equiv)	50	48 / 2
12	$Cl_3CHCOOH$ (2.0 equiv)	0	0
13 [d]	$Cl_3CHCOOH$ (2.0 equiv)	87	46 / 36
14	CH_3CH_2COOH	14	13 / trace
15	PivOH (2.0 equiv)	20	18 / trace
16	HOTf (2.0 equiv)	91	48 / trace [d]
17	MSA (2.0 equiv)	96	64 / 15 [d]
18	PTSA (2.0 equiv)	69	56 / 5 [d]
19	NH_2SO_2OH	9	5 / trace
20	TFAA (2.0equiv)	75	70 / 3
21	p-Nitrobenzoic acid (2.0 equiv)	41	38 / trace
22	Cinnamic acid	18	13 /4
23	NMP (2.0 equiv)	8	7 / trace

[a] Reaction condition : **1a** (0.1 mmol), $Pd(OAc)_2$ (2.2 mg), NFSI = N-Fluorobenzenesulfoonimide (47 mg), CH_3NO_2 / CH_3CN = 1:1 (*v*/*v*) (1.0 mL), 110 °C, under air, 12 h. TFA = Trifluoroacetic acid, HOAc = Acetic acid, HOTf = Trifluoromethanesulfonic acid, MSA = Methanesulfonic acid, PTSA = p-toluenesulfonic acid, NMP = N-Methyl pyrrolidone, TFAA = Trifluoroacetic anhydride, PivOH = Pivalic acid. [b] GC-MS yield. [c] $Pd(OOCCF_3)_2$ (10 mol %) was used in place of $Pd(OAc)_2$ (10 mol %). [d] C-H bond oxidation to form corresponding esters were occurred as the main side reaction led to the poor selectivity. [d] CH_3NO_2 (1.0 mL) was used as the solvent.

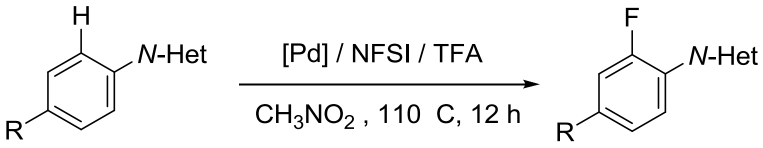
Table 5. Fluronination of other N-heteroaromatics



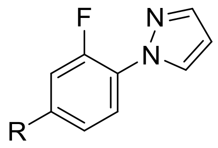
N-Het :	
quinoxaline (**1a**);	74 %[a]
pyrazole (**3a**);	75 %[b]
oxazole (**3b**);	64 %[c]
pyrazine (**3c**);	76 %[d]
pyridine (**3d**);	trace[e]
quinoline (**3e**);	4 %[e]

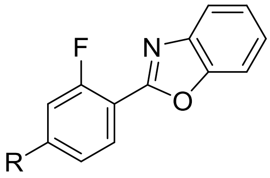
Reaction conditions : [a] **1a** (0.1 mmol), $Pd(OAc)_2$ (2.2 mg), NFSI = (47 mg), CH_3NO_2 / CH_3CN = 1:1 (*v*/*v*) (1.0 mL), TFA (23 mg), 110 °C, under air, 12 h, isolated yield. [b] **3a** (0.1 mmol), $Pd(OAc)_2$ (2.2 mg), NFSI (47 mg), CH_3NO_2 (1.0 mL), TFA (23 mg), 110 °C, under air, 12 h., GC-MS yield, for product **4a** can not be separated from the starting material **3a**. [c] **3b** (0.1 mmol), $Pd(OOCCF_3)_2$ (3.3 mg), NFSI = (63 mg), CH_3NO_2 (1.0 mL), TFA (23 mg), 110 °C, under air, 12 h, isolated yield. [d] **3c** (0.1 mmol), $Pd(OAc)_2$ (2.2 mg), NFSI = (95 mg), CH_3NO_2 (1.0 mL), TFA (35 mg), 110 °C, under air, 12 h, isolated yield. [e] **3d** or **3e** (0.1 mmol), $Pd(OAc)_2$ (2.2 mg), NFSI = (47 mg), CH_3NO_2 (1.0 mL), TFA (23 mg), 110 °C, under air, 12 h, GC-MS yields.

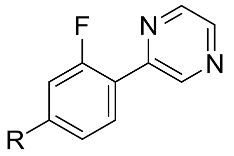
Table 6. *Ortho*-monofluorination using other aryl-*N*-heterocyclic directing groups



3 **4**







4a-1: R= H	75%[a]	**4b-1**: R= H	64%[c]	**4c-1**: R= H	76%[e]
4a-2: R= Cl	62%[b]	**4b-2**: R= Cl	35%[d]	**4c-2**: R= Cl	38%[f]
4a-3: R= Me	74%[a]	**4b-3**: R= OMe	53%[c]	**4c-3**: R= OMe	62%[e]

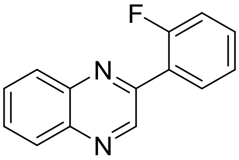
Reaction conditions : [a] **3a-1** or **3a-3** (0.2 mmol), $Pd(OAc)_2$ (4.4 mg), NFSI (94 mg), CH_3NO_2 (2.0 mL), TFA (46 mg), 110 °C, under air, 12 h, GC-MS yield, for product **4a-1** or **4a-3** can not be separated from the starting material **3a-1** or **3a-3**. [b] $Pd_2(dba)_3$ (13.5 mg) was used instead of $Pd(OAc)_2$ based on condition a, isolated yield. [c] **3b** (0.2 mmol), $Pd(OOCCF_3)_2$ (6.6 mg), NFSI = (126 mg), CH_3NO_2 (2.0 mL), TFA (46 mg), 110 °C, under air, 12 h, isolated yield. [d] GC-MS yield, for product **4b-2** can not be separated from the starting material **3b-2**.[e] **3c-1** or **3c-3** (0.2 mmol), $Pd(OAc)_2$ (4.4 mg), NFSI = (190 mg), CH_3NO_2 (2.0 mL), TFA (70 mg), 110 °C, under air, 12 h, isolated yields. [f] **3c-2** (0.3 mmol), $Pd(OAc)_2$ (6.6 mg), NFSI = (280 mg), CH_3NO_2 (2.5 mL), TFA (105 mg), 110 °C, under air, 12 h, isolated yields.

Typical experimental procedure for synthesis of 2 and 4

1 or **3** (0.2 mmol), NFSI (94.5 mg, 0.3 mmol), Pd(OAc)$_2$ (4.5 mg, 0.02 mmol), TFA (45.6 mg, 0.4 mmol) and a mixed solvent (CH_3NO_2 / CH_3CN, 2.0 mL) were sequentially added to a 25-mL tube under air. Then the tube was sealed and stirred at 110 ºC until the completion of the reaction (monitored by TLC). After the evaporation of the solvent, the residue was purified by column chromatography on silica gel (100-200 mesh) directly using petroleum ether-EtOAc as eluent to give desired product **2** or **4**.

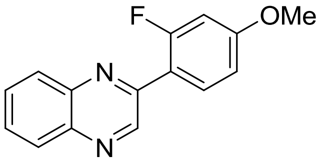
Characterization of all Products

2-(2-fluorophenyl)quinoxaline (2a)



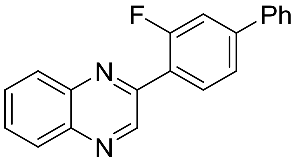
Isolated as yellow solid (33.2 mg, 74%); R_f =0.60 (petroleum ether-EtOAc= 6:1); mp 60-61 ℃; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.34 (d, J = 3.0 Hz, 1H), 8.20-8.11 (m, 3H), 7.83-7.78 (m, 2H), 7.53-7.49 (m, 1H), 7.39-7.36 (m, 1H), 7.29-7.25 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.8 (d, J = 250.0 Hz), 149.2 (d, J = 3.8 Hz), 145.9 (d, J = 11.3 Hz), 142.6, 141.4, 131.9 (d, J = 8.8 Hz), 131.5 (d, J = 2.5 Hz), 130.3, 130.0, 129.6, 129.2, 125.0 (d, J = 2.5 Hz), 124.9 (d, J = 12.5 Hz), 116.5 (d, J = 23.8 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -115.2 (d, J = 3.7 Hz); MS (EI, 70eV): m/z (%) = 224 (100) [M$^+$], 197 (39); HRMS (EI): [M$^+$] calcd. for $C_{14}H_9N_2F$, 224.0750; found 224.0752.

2-(2-fluoro-4-methoxyphenyl)quinoxaline (2b)



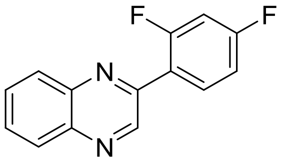
Isolated as pale yellow solid (39.6 mg, 78%); R_f =0.41 (petroleum ether-EtOAc= 6:1); mp 98-99 ℃; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 9.31 (d, J = 3.0 Hz, 1H), 8.15-8.11 (m, 3H), 7.81-7.74 (m, 2H), 6.92 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1H), 6.79 (dd, J_1 = 8.0 Hz, J_2 = 2.5 Hz, 1H), 3.90 (s, 3H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$): δ = 162.7 (d, J = 11.7 Hz), 161.8 (d, J = 248.6 Hz), 149.2 (d, J = 3.5 Hz), 145.7 (d, J = 12.5 Hz), 142.6, 141.0, 132.1 (d, J = 5.0 Hz), 130.2, 129.6, 129.4, 129.1, 117.3 (d, J = 13.0 Hz), 111.4 (d, J = 2.9 Hz), 102.0 (d, J = 26.4 Hz), 55.8 ppm; ^{19}F NMR (376 MHz, CDCl$_3$): δ -112.1- -112.0 (m); MS (EI, 70eV): m/z (%) = 254 (100) [M$^+$], 239 (28), 227 (19); HRMS (EI): [M$^+$] calcd. for $C_{15}H_{11}N_2OF$, 254.0855; found 254.0845.

2-(3-fluorobiphenyl-4-yl)quinoxaline (2c)



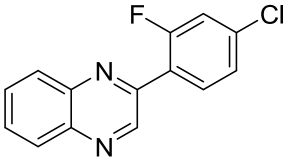
Isolated as white solid (45.6 mg, 76%); R_f =0.52 (petroleum ether-EtOAc= 6:1); mp 162-163 ℃; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 9.40 (s, 1H), 8.26-8.17 (m, 3H), 7.85-7.79 (m, 2H), 7.69-7.68 (m, 2H), 7.62 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 7.53-7.49 (m, 3H), 7.44 (t, J = 7.3 Hz, 1H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$): δ = 161.2 (d, J = 249.2 Hz), 149.0, 145.9 (d, J = 11.8 Hz), 145.3 (d, J = 8.2 Hz), 142.7, 141.5, 139.1, 131.8 (d, J = 3.4 Hz), 130.3, 129.9, 129.6, 129.2, 129.0, 128.4, 127.1, 123.6 (d, J = 3.0 Hz), 123.5 (d, J = 12.3 Hz), 114.9 (d, J = 23.2 Hz) ppm; ^{19}F NMR (376 MHz, CDCl$_3$): δ -114.7- -114.6 (m); MS (EI, 70eV): m/z (%) = 300 (100) [M$^+$], 273 (17); HRMS (EI): [M$^+$] calcd. for $C_{20}H_{13}N_2F$, 300.1063; found 300.1075.

2-(2,4-difluorophenyl)quinoxaline (2d) [5]



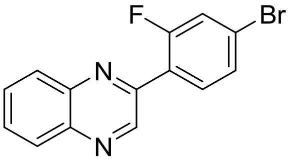
Isolated as white solid (32.4 mg, 67%); R_f =0.53 (petroleum ether-EtOAc= 6:1); mp 143-144℃ (lit. 148℃); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.31 (d, J = 3.0 Hz, 1H), 8.19-8.15 (m, 3H), 7.84-7.79 (m, 2H), 7.14-7.10 (m, 1H), 7.05-7.00 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.2 (dd, J_1 = 251.9 Hz, J_2 = 12.1 Hz), 161.1 (dd, J_1 = 252.2 Hz, J_2 = 12.1 Hz), 148.3 (d, J = 3.5 Hz), 145.6 (d, J = 11.5 Hz), 142.5, 141.4, 132.7 (dd, J_1 = 9.6 Hz, J_2 = 4.5 Hz), 130.4, 130.0, 129.5, 129.2, 121.3 (dd, J_1 = 12.7 Hz, J_2 = 3.6 Hz), 112.6 (dd, J_1 = 20.9 Hz, J_2 = 3.4 Hz), 104.7 (t, J = 26.0 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -111.6 - -111.5 (m), -105.8 - -105.7 (m); MS (EI, 70eV): m/z (%) = 242 (100) [M^+], 215 (42).

2-(4-chloro-2-fluorophenyl)quinoxaline (2e)



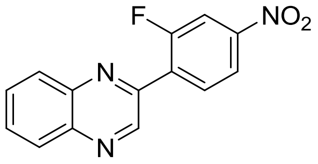
Isolated as pale yellow solid (35.1 mg, 68%); R_f =0.63 (petroleum ether-EtOAc= 6:1); mp 127-128 ℃; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.32 (d, J = 3.0 Hz, 1H), 8.17-8.14 (m, 3H), 7.83-7.81 (m, 2H), 7.37 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.31 (dd, J_1 = 10.5 Hz, J_2 = 2.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.6 (d, J = 253.0 Hz), 148.1 (d, J = 3.4 Hz), 145.5 (d, J = 11.7 Hz), 142.5, 141.6, 137.1 (d, J = 10.4 Hz), 132.3 (d, J = 4.2 Hz), 130.4, 130.2, 129.6, 129.2, 125.6 (d, J = 3.4 Hz), 123.6 (d, J = 12.7 Hz), 117.2 (d, J = 26.0 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -112.4 - -112.3 (m); MS (EI, 70eV): m/z (%) = 258 (100) [M^+], 223 (29); HRMS (EI): [M^+] calcd. for $C_{14}H_8N_2FCl$, 258.0360; found 258.0374.

2-(4-bromo-2-fluorophenyl)quinoxaline (2f)



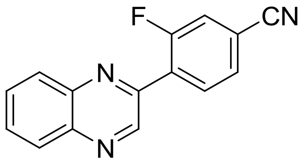
Isolated as white solid (39.2 mg, 65%); R_f =0.58 (petroleum ether-EtOAc= 6:1); mp 142-143 ℃; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.32 (d, J = 3.0 Hz, 1H), 8.18-8.15 (m, 2H), 8.07 (t, J = 8.3 Hz, 1H), 7.83-7.81 (m, 2H), 7.53 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1H), 7.47 (dd, J_1 = 10.5 Hz, J_2 = 1.5 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.5 (d, J = 253.8 Hz), 148.1, 145.6 (d, J = 11.7 Hz), 142.5, 141.6, 132.5 (d, J = 3.5 Hz), 130.4, 130.2, 129.6, 129.3, 128.5 (d, J = 3.6 Hz), 124.8 (d, J = 9.9 Hz), 124.0 (d, J = 12.6 Hz), 120.1 (d, J = 26.2 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -112.3- -112.2 (m); MS (EI, 70eV): m/z (%) = 302 (100) [M^+], 275 (23), 223 (43); HRMS (EI): [M^+] calcd. for $C_{14}H_8N_2FBr$, 301.9855; found 301.9824.

2-(2-fluoro-4-nitrophenyl)quinoxaline (2g)



Isolated as white solid (31.2 mg, 58%); R_f =0.46 (petroleum ether-EtOAc= 6:1); mp 202-203 ℃; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.40 (d, J = 2.0 Hz, 1H), 8.42 (t, J = 8.0 Hz, 1H), 8.25 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1H), 8.22 (dd, J_1 = 6.5 Hz, J_2 = 3.5 Hz, 2H), 7.59 (dd, J_1 = 10.5 Hz, J_2 = 2.0 Hz, 1H), 7.88 (dd, J_1 = 6.3 Hz, J_2 = 3.8 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.2 (d, J = 253.9 Hz), 149.5 (d, J = 8.9 Hz), 146.8, 145.1 (d, J = 12.6 Hz), 142.6, 141.8, 132.6 (d, J = 3.2 Hz), 131.2, 130.9, 130.9, 129.9, 129.2, 119.9 (d, J = 3.2 Hz), 112.5 (d, J = 27.8 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -110.5 - -110.4 (m); MS (EI, 70eV): m/z (%) = 269 (100) [M^+], 223 (44); HRMS (CI): $[M+H]^+$ calcd. for $C_{14}H_9N_3O_2F$, 270.0679; found 270.0688.

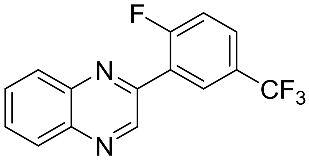
3-fluoro-4-(quinoxalin-2-yl)benzonitrile (2h)



Isolated as white solid (31.4 mg, 63%); R_f =0.37 (petroleum ether-EtOAc= 6:1); mp 183-184 ℃; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.37 (s, 1H), 8.34 (t, J = 7.8 Hz, 1H), 8.19 (dd, J_1 = 6.3 Hz, J_2 =

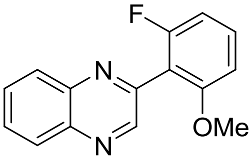
3.8 Hz, 2H), 7.86 (dd, J_1 = 6.5 Hz, J_2 = 3.5 Hz, 2H), 7.68 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.59 (dd, J_1 = 10.3 Hz, J_2 = 1.3 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.2 (d, J = 253.0 Hz), 147.0, 145.3 (d, J = 11.4 Hz), 142.5, 142.0, 132.7 (d, J = 3.5 Hz), 130.9, 130.8, 129.8, 129.7 (d, J = 12.5 Hz), 129.4, 128.7 (d, J = 3.9 Hz), 120.4 (d, J = 26.4 Hz), 117.2 (d, J = 3.8 Hz), 115.0 (d, J = 9.3 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -111.9 - -111.8 (m); MS (EI, 70eV): *m/z* (%) = 249 (100) [M^+], 222 (27); HRMS (CI): $[M+H]^+$ calcd. for $C_{15}H_9N_3F$, 250.0781; found 250.0780.

2-(2-fluoro-5-(trifluoromethyl)phenyl)quinoxaline (2i)



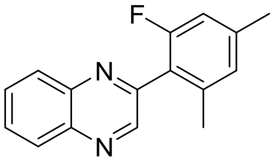
Isolated as pale yellow solid (33.9 mg, 58%); R_f =0.58 (petroleum ether-EtOAc= 6:1); mp 64-65 ℃; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.36 (d, J = 3.5 Hz, 1H), 8.51 (dd, J_1 = 7.0 Hz, J_2 = 2.0 Hz, 1H), 8.22-8.17 (m, 2H), 7.86-7.82 (m, 2H), 7.80-7.77 (m, 1H), 7.39 (t, J = 9.5 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.5 (d, J = 254.3 Hz), 147.4 (d, J = 3.3 Hz), 145.4, 145.3, 142.5, 141.8, 130.5 (d, J = 7.4 Hz), 129.7, 129.3 (d, J = 3.7 Hz), 129.3, 128.8 (dq, J_1 = 9.3 Hz, J_2 = 3.4 Hz), 127.8 (qd, J_1 = 33.2 Hz, J_2 = 3.2 Hz), 125.7 (d, J = 13.8 Hz), 123.6 (q, J = 270.5 Hz), 117.3 (d, J = 24.1 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -109.7 (s), -69.3 (s); MS (EI, 70eV): *m/z* (%) = 292 (100) [M^+], 265 (32); HRMS (EI): [M^+] calcd. for $C_{15}H_8N_2F_4$, 292.0624; found 292.0629.

2-(2-fluoro-6-methoxyphenyl)quinoxaline (2j)



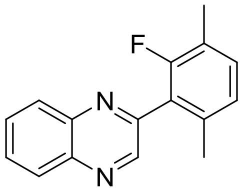
Isolated as pale yellow oil (44.2 mg, 87%); R_f =0.27 (petroleum ether-EtOAc= 6:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.95 (s, 1H), 8.21-8.17 (m, 2H), 7.81 (td, J_1 = 7.0 Hz, J_2 = 3.5 Hz, 2H), 7.44 (td, J_1 = 8.4 Hz, J_2 = 6.5 Hz, 1H), 6.90 (t, J = 9.0 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 3.83 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.2 (d, J = 247.5 Hz), 158.6 (d, J = 6.3 Hz), 148.0, 147.3, 142.5, 141.2, 131.3 (d, J = 10.5 Hz), 130.1 (2C), 129.6, 129.2, 115.4 (d, J = 16.9 Hz), 108.8 (d, J = 22.2 Hz), 106.9 (d, J = 3.2 Hz), 56.2 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -114.6- -114.5 (m); MS (EI, 70eV): *m/z* (%) = 253 (100) $[M-H]^+$, 237 (34), 225 (28); HRMS (EI): $[M^+]$ calcd. for $C_{15}H_{11}N_2OF$, 254.0855; found 254.0849.

2-(2-fluoro-4,6-dimethylphenyl)quinoxaline (2k)



Isolated as white solid (43.8 mg, 87%); R_f =0.58 (petroleum ether-EtOAc= 6:1); mp 85-86 ℃; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.93 (d, J = 2.5 Hz, 1H), 8.19-8.15 (m, 2H), 7.83-7.81 (m, 2H), 7.00 (s, 1H), 6.91 (d, J = 10.5Hz, 1H), 2.41 (s, 3H), 2.31 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.6 (d, J = 244.7 Hz), 150.4, 147.0 (d, J = 3.2 Hz), 142.3, 141.2 (d, J = 9.0 Hz), 141.2, 139.3 (d, J = 2.8 Hz), 130.1, 130.0, 129.5, 129.3, 127.4 (d, J = 2.4 Hz), 122.2 (d, J = 15.0 Hz), 113.8 (d, J = 22.0 Hz), 21.3 (d, J = 1.6 Hz), 19.8 (d, J = 2.3 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -116.9 (d, J = 8.3 Hz); MS (EI, 70eV): *m/z* (%) = 251 (100) $[M-H]^+$; HRMS (EI): $[M^+]$ calcd. for $C_{16}H_{13}N_2F$, 252.1063; found 252.1047.

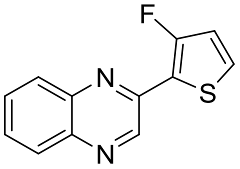
2-(2-fluoro-3,6-dimethylphenyl)quinoxaline (2l)



Isolated as pale yellow solid (43.3 mg, 86%); R_f =0.63 (petroleum ether-EtOAc= 6:1); mp 53-54 ℃; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.94 (s, 1H), 8.20-8.17 (m, 2H), 7.83 (dd, J_1 = 6.3 Hz, J_2 = 3.8 Hz, 2H), 7.22 (t, J = 8.0 Hz, 1H), 7.06 (d, J = 7.5 Hz, 1H), 2.64 (s, 3H), 2.33 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.9 (d, J = 243.9 Hz), 149.6, 145.8, 141.3, 140.2, 135.7, 131.0 (d, J = 5.8 Hz),, 129.1, 129.0, 128.5, 128.3, 124.9 (d, J = 3.5 Hz), 123.8 (d, J = 15.6 Hz), 121.6 (d, J = 18.2 Hz), 18.5 (d, J = 2.1 Hz), 13.3 (d, J = 4.1 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -119.8 (d, J = 7.5 Hz); MS (EI, 70eV): *m/z* (%) = 251 (100) $[M-H]^+$; HRMS (CI):

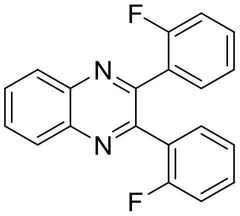
$[M+H]^+$ calcd. for $C_{16}H_{14}N_2F$, 253.1141; found 253.1151.

2-(3-fluorothiophen-2-yl)quinoxaline (2m)



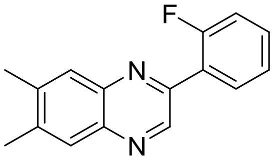
Isolated as yellow solid (25.8 mg, 56%); R_f =0.59 (petroleum ether-EtOAc= 6:1); mp 61-62 ℃; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 9.39 (s,1H), 8.16 (dd, J_1 = 8.5 Hz, J_2 = 1.0 Hz, 1H), 8.09 (dd, J_1 = 8.3 Hz, J_2 = 1.3 Hz, 1H), 7.81-7.74 (m, 2H), 7.44 (dd, J_1 = 5.5 Hz, J_2 = 3.5 Hz, 1H), 6.98 (d, J = 5.5 Hz, 1H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$): δ = 155.8 (d, J = 265.8 Hz), 145.1, 141.3 (d, J = 11.6 Hz), 139.4, 132.7, 129.6, 128.7, 128.0, 127.8, 127.3 (d, J = 10.2 Hz), 119.8 (d, J = 13.4 Hz), 117.9 (d, J = 27.2 Hz) ppm; ^{19}F NMR (376 MHz, CDCl$_3$): δ -121.0 (s); MS (EI, 70eV): *m/z* (%) = 230 (100) [M$^+$], 203 (34); HRMS (CI): $[M+H]^+$ calcd. for $C_{12}H_8N_2FS$, 231.0392; found 231.0401.

2,3-bis(2-fluorophenyl)quinoxaline (2n)



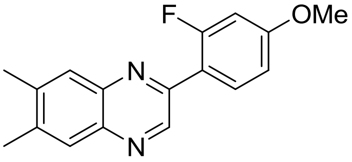
Isolated as white solid (35.0 mg, 55%); R_f =0.52 (petroleum ether-EtOAc= 6:1); mp 118-119 ℃; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 8.24 (dd, J_1 = 6.0 Hz, J_2 = 3.5 Hz, 2H), 7.86 (dd, J_1 = 6.3 Hz, J_2 = 3.3 Hz, 2H), 7.60 (td, J_1 = 7.5 Hz, J_2 = 1.5 Hz, 2H), 7.39-7.35 (m, 2H), 7.23 (td, J_1 = 7.8 Hz, J_2 = 0.67 Hz, 2H), 6.95 (t, J = 9.3 Hz, 2H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$): δ = 159.6 (d, J = 252.4 Hz), 150.5, 141.4, 131.6, 131.0 (d, J = 8.6 Hz), 130.4, 129.4, 126.8 (d, J = 11.3 Hz), 124.2, 115.5 (d, J = 20.8 Hz) ppm; ^{19}F NMR (376 MHz, CDCl$_3$): δ -114.2 (s); MS (EI, 70eV): *m/z* (%) = 318 (100) [M$^+$], 299 (15), 197 (62); HRMS (CI): $[M+H]^+$ calcd. for $C_{20}H_{13}N_2F_2$, 319.1047; found 319.1047.

2-(2-fluorophenyl)-6,7-dimethylquinoxaline (2o)



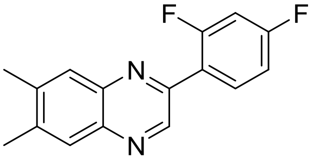
Isolated as white solid (38.8 mg, 77%); R_f =0.57 (petroleum ether-EtOAc= 6:1); mp 86-87 ℃; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.23 (d, J = 3.0 Hz, 1H), 8.10 (td, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H), 7.92 (s, 1H), 7.89 (s, 1H), 7.51-7.46 (m, 1H), 7.36 (td, J_1 = 7.7 Hz, J_2 = 1.1 Hz, 1H), 7.27-7.23 (m, 1H), 2.53 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.8 (d, J = 249.3 Hz), 148.3 (d, J = 2.6 Hz), 145.0 (d, J = 11.0 Hz), 141.6, 140.8, 140.7, 140.4, 131.5 (d, J = 8.2 Hz), 131.4 (d, J = 2.4 Hz), 128.6, 128.2, 125.3 (d, J = 12.7 Hz), 124.9 (d, J = 3.4 Hz), 116.4 (d, J = 22.8 Hz), 20.4 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -115.3 (s); MS (EI, 70eV): *m/z* (%) = 252 (100) [M^+], 237 (13), 225 (10); HRMS (EI): [M^+] calcd. for $C_{16}H_{13}N_2F$, 252.1063; found 252.1054.

2-(2-fluoro-4-methoxyphenyl)-6,7-dimethylquinoxaline (2p)



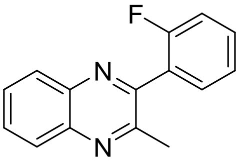
Isolated as white solid (42.8 mg, 76%); R_f =0.42 (petroleum ether-EtOAc= 6:1); mp 144-145 ℃; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.20 (d, J = 2.5 Hz, 1H), 8.08 (t, J = 8.8 Hz, 1H), 7.89 (s, 1H), 7.86 (s, 1H), 6.90 (dd, J_1 = 9.0 Hz, J_2 = 2.5 Hz, 1H), 6.77 (dd, J_1 = 13.3 Hz, J_2 = 2.3 Hz, 1H), 3.89 (s, 3H), 2.52 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.4 (d, J = 11.2 Hz), 161.7 (d, J = 249.1 Hz), 148.2, 144.8 (d, J = 11.9 Hz), 141.5, 140.7, 140.1, 140.1 (d, J = 10.7 Hz), 132.0 (d, J = 4.7 Hz), 128.5, 128.1, 117.6 (d, J = 12.8 Hz), 111.3 (d, J = 2.3 Hz), 102.0 (d, J = 26.4 Hz), 55.8, 20.4, 20.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -112.3- -112.2 (m); MS (EI, 70eV): *m/z* (%) = 282 (100) [M^+], 267 (23); HRMS (EI): [M^+] calcd. for $C_{17}H_{15}N_2OF$, 282.1168; found 282.1185.

2-(2,4-difluorophenyl)-6,7-dimethylquinoxaline (2q)[5]



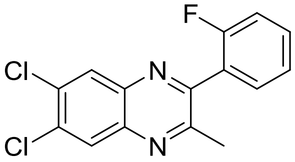
Isolated as white solid (35.5 mg, 66%); R_f =0.53 (petroleum ether-EtOAc= 6:1); mp 146-147℃ (lit. 140℃); ^{1}H NMR (500 MHz, CDCl$_3$): δ = 9.18 (d, J = 3.0 Hz, 1H), 8.13 (td, J_1 = 8.8 Hz, J_2 = 6.5 Hz, 1H), 7.90 (s, 2H), 7.09 (td, J_1 = 8.3 Hz, J_2 = 2.5 Hz, 1H), 7.02-6.98 (m, 1H), 2.53 (s, 6H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$): δ = 164.0 (dd, J_1 = 251.3 Hz, J_2 = 11.9 Hz), 161.0 (dd, J_1 = 251.7 Hz, J_2 = 12.3 Hz), 147.3, 144.4 (d, J = 11.4 Hz), 141.5, 141.1, 140.9, 140.2, 132.6 (dd, J_1 = 9.5 Hz, J_2 = 4.6 Hz), 128.5, 128.0, 121.6 (dd, J_1 = 12.6 Hz, J_2 = 3.4 Hz), 112.5 (dd, J_1 = 21.0 Hz, J_2 = 3.4 Hz), 104.6 (t, J = 25.9 Hz), 20.4 ppm; ^{19}F NMR (376 MHz, CDCl$_3$): δ -110.7 (d, J = 7.5 Hz), -106.4 - -106.3 (m); MS (EI, 70eV): *m/z* (%) = 269 (100) [M-H]$^+$, 239 (14), 223 (43) .

2-(2-fluorophenyl)-3-methylquinoxaline (2r)



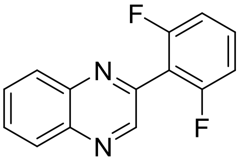
Isolated as pale yellow solid (36.2 mg, 76%); R_f =0.48 (petroleum ether-EtOAc= 6:1); mp 91-92 ℃; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 8.19-8.15 (m, 2H), 7.83-7.76 (m, 2H), 7.57-7.51 (m, 2H), 7.36 (d, J = 7.3 Hz, 1H), 7.25 (d, J = 9.0 Hz, 1H), 2.75 (d, J = 1.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$): δ = 158.9 (d, J = 246.4 Hz), 151.7, 150.2, 140.2, 138.6, 130.5 (d, J = 8.0 Hz), 130.3 (d, J = 3.0 Hz), 130.0, 128.9, 128.3, 126.3, 125.3 (d, J = 15.4 Hz), 123.9 (d, J = 3.2 Hz), 115.0 (d, J = 21.0 Hz), 21.2 (d, J = 4.5 Hz) ppm; ^{19}F NMR (376 MHz, CDCl$_3$): δ -113.7 (s); MS (EI, 70eV): *m/z* (%) = 237 (100) [M-H]$^+$; HRMS (CI): [M+H]$^+$ calcd. for $C_{15}H_{12}N_2F$, 239.0985; found 239.0991.

6,7-dichloro-2-(2-fluorophenyl)-3-methylquinoxaline (2s)



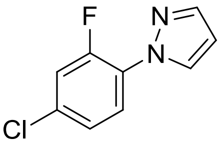
Isolated as yellow solid (43.9 mg, 72%); R_f =0.74 (petroleum ether-EtOAc= 6:1); mp 112-113 ℃; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 8.25 (s, 2H), 7.56-7.51 (m, 2H), 7.36 (dd, J_1 = 7.8 Hz, J_2 = 7.3 Hz, 1H), 7.25 (t, J = 9.3 Hz, 1H), 2.70 (d, J = 2.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$): δ = 159.8 (d, J = 246.6 Hz), 154.4, 152.2, 139.9, 139.0, 135.3, 134.4, 131.8 (d, J = 8.1 Hz), 131.2 (d, J = 3.0 Hz), 129.9, 128.5, 126.0 (d, J = 15.4 Hz), 124.9 (d, J = 3.3 Hz), 116.1 (d, J = 21.3 Hz), 22.5 (d, J = 4.8 Hz) ppm; ^{19}F NMR (376 MHz, CDCl$_3$): δ -113.6 (s); MS (EI, 70eV): *m/z* (%) = 305 (100) [M-H]$^+$; HRMS (CI): [M+H]$^+$ calcd. for $C_{15}H_{10}N_2FCl_2$, 307.0205; found 307.1210.

2-(2,6-difluorophenyl)quinoxaline (2aa)



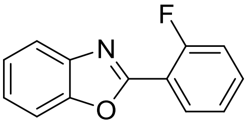
Isolated as yellow solid (40.6 mg, 84%); R_f =0.51 (petroleum ether-EtOAc= 6:1); mp 70-71 ℃; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 9.03 (s, 1H), 8.21 (td, J_1 = 5.0 Hz, J_2 = 2.4 Hz, 2H), 7.86-7.84 (m, 2H), 7.51-7.46 (m, 1H), 7.12 (t, J = 8.0 Hz, 2H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$): δ = 160.8 (dd, J_1 = 250.9 Hz, J_2 = 6.5 Hz), 146.1, 145.5, 142.5, 141.3, 131.5 (t, J = 10.2 Hz), 130.6, 130.5, 129.7, 129.2, 115.3 (d, J = 18.8 Hz), 112.2 (dd, J_1 = 20.2 Hz, J_2 = 5.2 Hz) ppm; ^{19}F NMR (376 MHz, CDCl$_3$): δ -113.4- -113.3 (m); MS (EI, 70eV): *m/z* (%) = 242 (100) [M$^+$], 215 (76); HRMS (CI): [M+H]$^+$ calcd. for $C_{14}H_9N_2F_2$, 243.0734; found 243.0750.

1-(4-chloro-2-fluorophenyl)-1H-pyrazole (4a-2)



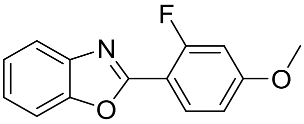
Isolated as pale yellow oil (24.3 mg, 62%); R_f =0.60 (petroleum ether-EtOAc= 10:1); ^{1}H NMR (500 MHz, CDCl$_3$): δ = 8.00 (t, J = 2.8 Hz, 1H), 7.89 (t, J = 8.8 Hz, 1H), 7.76 (s, 1H), 7.29-7.26 (m, 2H), 6.50 (t, J = 2.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$): δ = 153.1 (d, J = 251.3 Hz), 141.1, 132.4 (d, J = 10.0 Hz), 130.6 (d, J = 11.3 Hz), 127.3 (d, J = 7.5 Hz), 125.3 (d, J = 3.8 Hz), 125.1, 117.5 (d, J = 25.0 Hz), 107.8 ppm; ^{19}F NMR (376 MHz, CDCl$_3$): δ -112.5 (s); MS (EI, 70eV): m/z (%) = 196 (100) [M$^+$]. HRMS (CI): [M]$^+$ calcd. for $C_9H_6N_2FCl$, 196.0204; found 196.0201.

2-(2-fluorophenyl)benzo[d]oxazole (4b-1) [6]



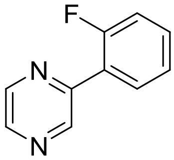
Isolated as white solid (27.3 mg, 64%); R_f =0.59 (petroleum ether-EtOAc= 6:1); mp 87-88 ℃; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 8.26 (td, J_1 = 7.5 Hz, J_2 = 2.0 Hz, 1H), 7.87-7.84 (m, 1H), 7.65-7.62 (m, 1H), 7.56-7.52 (m, 1H), 7.42-7.38 (m, 2H), 7.33 (td, J_1 = 7.5 Hz, J_2 = 0.9 Hz, 1H), 7.44 (ddd, J_1 = 11.0 Hz, J_2 = 8.5 Hz, J_3 = 0.5 Hz, 1H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$): δ = 160.9 (d, J = 257.4 Hz), 159.5 (d, J = 5.8 Hz), 150.6, 141.7, 133.2 (d, J = 8.9 Hz), 130.6, 125.6, 124.8, 124.6 (d, J = 4.1 Hz), 120.4, 117.2 (d, J = 21.0 Hz), 115.6 (d, J = 10.4 Hz), 110.8 ppm; ^{19}F NMR (376 MHz, CDCl$_3$): δ -109.4 (s); MS (EI, 70eV): m/z (%) = 213 (100) [M$^+$].

2-(2-fluoro-4-methoxyphenyl)benzo[d]oxazole (4b-3)



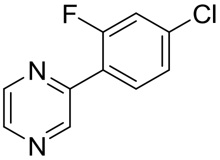
Isolated as white solid (25.7 mg, 53%); R_f =0.32 (petroleum ether-EtOAc= 6:1); mp 94-95 °C; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 8.16 (t, J = 8.5 Hz, 1H), 7.81 (t, J = 3.5 Hz, 1H), 7.59 (t, J = 3.5 Hz, 1H), 7.37-7.35 (m, 2H), 6.85 (dd, J_1 = 9.0 Hz, J_2 = 2.0 Hz, 1H), 6.79 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 3.89 (s, 3H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$): δ = 163.5 (d, J = 11.3 Hz), 162.0 (d, J = 256.3 Hz), 159.7 (d, J = 5.0 Hz), 150.3, 141.9, 131.4 (d, J = 3.8 Hz), 129.4, 125.0, 124.5, 120.0, 110.9 (d, J = 2.5 Hz), 110.5, 102.6 (d, J = 23.8 Hz), 55.8 ppm; ^{19}F NMR (376 MHz, CDCl$_3$): δ -107.3 (s); MS (EI, 70eV): m/z (%) = 243 (100) [M$^+$]. HRMS (CI): [M]$^+$ calcd. for $C_{14}H_{10}NO_2F$, 243.0696; found 243.0694.

2-(2-fluorophenyl)pyrazine (4c-1)



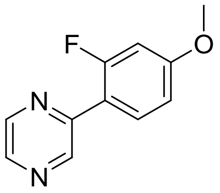
Isolated as pale yellow oil (26.4 mg, 76%); R_f =0.49 (petroleum ether-EtOAc= 6:1); ^{1}H NMR (500 MHz, CDCl$_3$): δ = 9.11 (d, J = 7.0 Hz, 1H), 8.71 (s, 1H), 8.56 (s, 1H), 8.01 (td, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1H), 7.49-7.44 (m, 1H), 7.32 (t, J = 7.8 Hz, 1H), 7.23 (dd, J_1 = 11.0 Hz, J_2 = 8.5 Hz, 1H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$): δ = 160.5 (d, J = 248.8 Hz), 149.5, 145.5 (d, J = 12.3 Hz), 144.5, 143.1, 131.6 (d, J = 8.3 Hz), 131.0 (d, J = 2.1 Hz), 124.9 (d, J = 3.0 Hz), 124.4 (d, J = 12.2 Hz), 116.4 (d, J = 22.4 Hz), ppm; ^{19}F NMR (376 MHz, CDCl$_3$): δ -115.1 (s); MS (EI, 70eV): m/z (%) = 174 (100) [M$^+$]; HRMS (CI): [M+H]$^+$ calcd. for $C_{10}H_8N_2F$, 175.0672; found 175.0668.

2-(4-chloro-2-fluorophenyl)pyrazine (4c-2)



Isolated as yellow solid (23.7 mg, 38%); R_f =0.43 (petroleum ether-EtOAc= 6:1); mp 52-53 °C; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 9.08 (d, J = 1.8 Hz, 1H), 8.69 (t, J = 1.8 Hz, 1H), 8.56 (d, J = 2.4 Hz, 1H), 8.01 (t, J = 8.5 Hz, 1H), 7.31 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1H), 7.26 (dd, J_1 = 11.0 Hz, J_2 = 2.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$): δ = 160.2 (d, J = 253.8 Hz), 148.4, 145.3 (d, J = 13.8 Hz), 144.5, 143.4, 136.7 (d, J = 11.3 Hz), 131.7 (d, J = 3.8 Hz), 125.4 (d, J = 3.8 Hz), 123.0 (d, J = 11.3 Hz), 117.2 (d, J = 26.3 Hz) ppm; ^{19}F NMR (376 MHz, CDCl$_3$): δ -112.9 (s); MS (EI, 70eV): m/z (%) = 208 (100) [M$^+$]; HRMS (CI): [M]$^+$ calcd. for $C_{10}H_6N_2FCl$, 208.0204; found 208.0206.

2-(2-fluoro-4-methoxyphenyl)pyrazine (4c-3)



Isolated as pale yellow solid (25.3 mg, 62%); R_f =0.38 (petroleum ether-EtOAc= 6:1); mp 62-63 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.07 (s, 1H), 8.65 (s, 1H), 8.49 (s, 1H), 7.98 (t, J = 8.9 Hz, 1H), 6.87 (dd, J_1 = 8.8 Hz, J_2 = 2.5 Hz, 1H), 6.75 (dd, J_1 = 13.0 Hz, J_2 = 2.5 Hz, 1H), 3.88 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.3 (d, J = 10.8 Hz), 161.4 (d, J = 250.0 Hz), 149.5, 145.1 (d, J = 12.5 Hz), 144.3, 142.3, 131.5 (d, J = 5.0 Hz), 116.7 (d, J = 11.3 Hz), 111.1 (d, J = 2.5 Hz), 102.0 (d, J = 26.3 Hz), 55.8 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -112.8 (s); MS (EI, 70eV): m/z (%) = 204 (100) [M^+]; HRMS (CI): $[M]^+$ calcd. for $C_{11}H_9N_2OF$, 204.0699; found 204.0706.

Preliminary mechanistic studies

Kinetic studies

1a (0.2 mmol), NFSI (94.5 mg, 0.3 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), TFA (45.6 mg, 0.4 mmol), dodecane (23 μL, standard) and a mixed solvent [CH_3NO_2 / CH_3CN= 1:1 (v/v), 2.0 mL] were sequentially added to a 25-mL tube under air. Then the tube was sealed and stirred at 110 ºC. An aliquot of the mixture was taken and analyzed by GC-MS at the time of 1h, 2h, 3h, 4h, 6h, 8h, 10h and 12h.

Time (h)	1	2	3	4	6	8	10	12
Conv. of **1a** (%)	24	40	58	66	73	77	80	82
Yield of **2a** (%)	23	38	56	63	70	74	76	78
Yield of **2aa** (%)	0.6	1.1	1.6	2	2.5	2.8	3	3

Difluorination occurred as soon as the monofluorinated azaarene was formed. according to the preliminary kinetic studies.

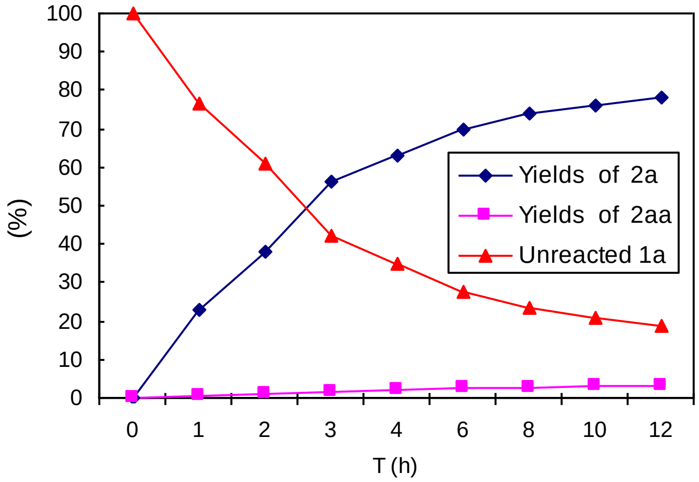
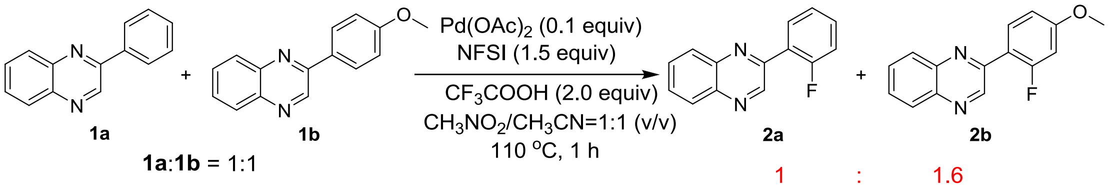


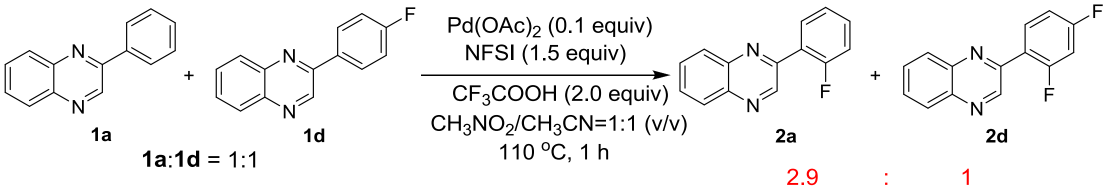
Figure 1. *Plots of the unreacted **1a** and the yields of **2a**, **2aa** against reaction time (h) for the Pd(II)-catalyzed ortho-fluorination of **1a***

Intermolecular competition experiments

*(a) Substrates **1a** and **1b***



*(b) Substrates **1a** and **1d***

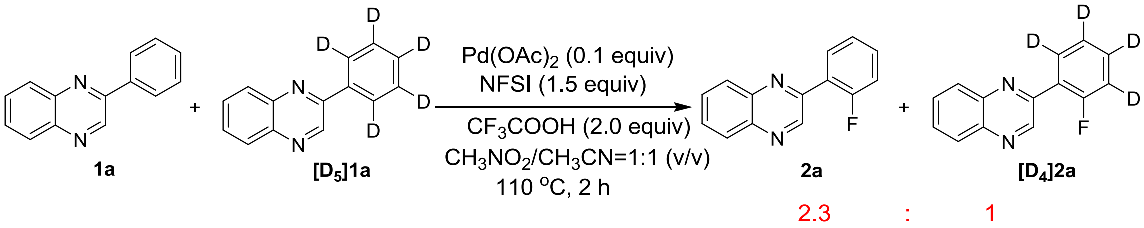


The series of competition experiments above disclosed that substrates bearing electron-rich aryl rings were faster fluorinated than the electron-deficient ones under the standard condition.

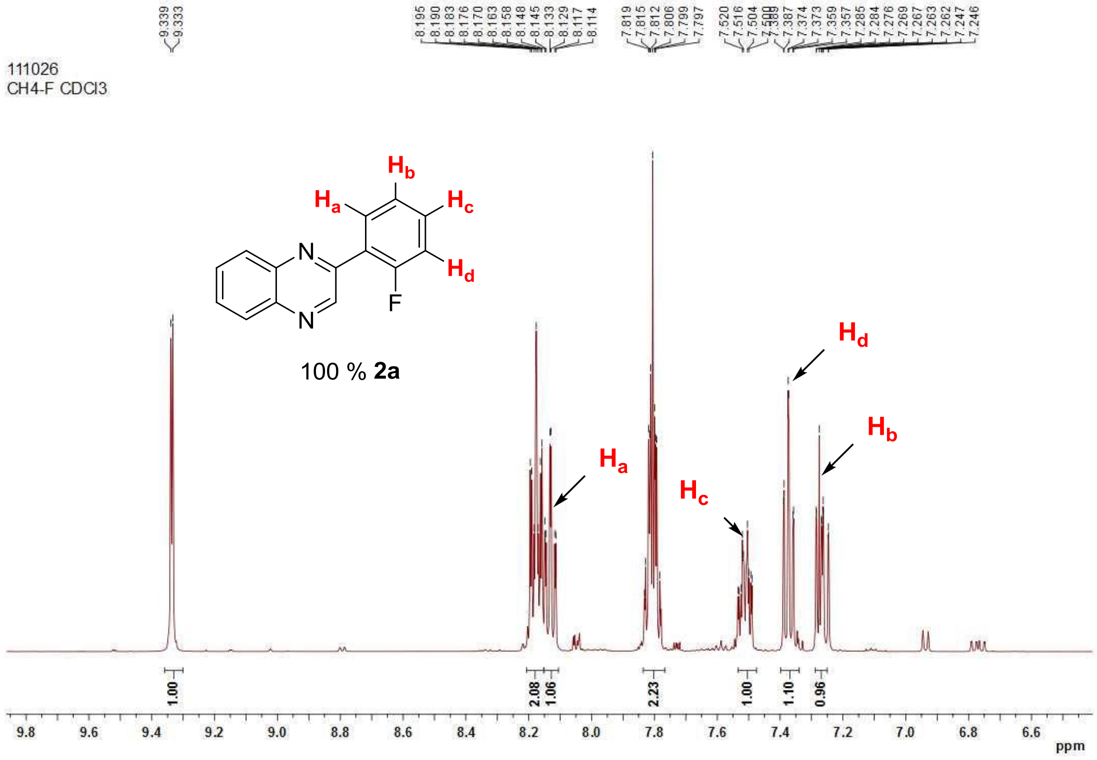
KIE Studies

See our previous publication[7] for the synthesis of **$[D_5]$1a** and **$[D_4]$1a**.

Determination of intermolecular kinetic isotope effect



To a 25-mL tube was sequentially added 2-phenyl-*d5*-quinoxaline (**[D$_5$]1a**) (31.7 mg, 0.15 mmol), 2-phenyl quinoxaline (**1a**) (30.1 mg, 0.15 mmol), Pd(OAc)$_2$ (6.7 mg, 0.03 mmol), NFSI (141.8 mg, 0.45 mmol), TFA (68.4 mg, 0.6 mmol) and a mixed solvent [CH_3NO_2 / CH_3CN = 1:1 (v/v)] (3.0 mL) under air. The tube was sealed and heated to 110 °C for 2 h. The resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on silica gel (100-200 mesh) using petroleum ether-EtOAc (10:1, v/v) as eluent. A mixture of **2a** and **[D$_4$]2a** was determined on the basis of ^{1}H NMR analysis. Based on the integrations related to different hydrogen resonances, the kinetic isotope effect is calculated to be $k_H / k_D \approx$ 2.3 (Figure 2).



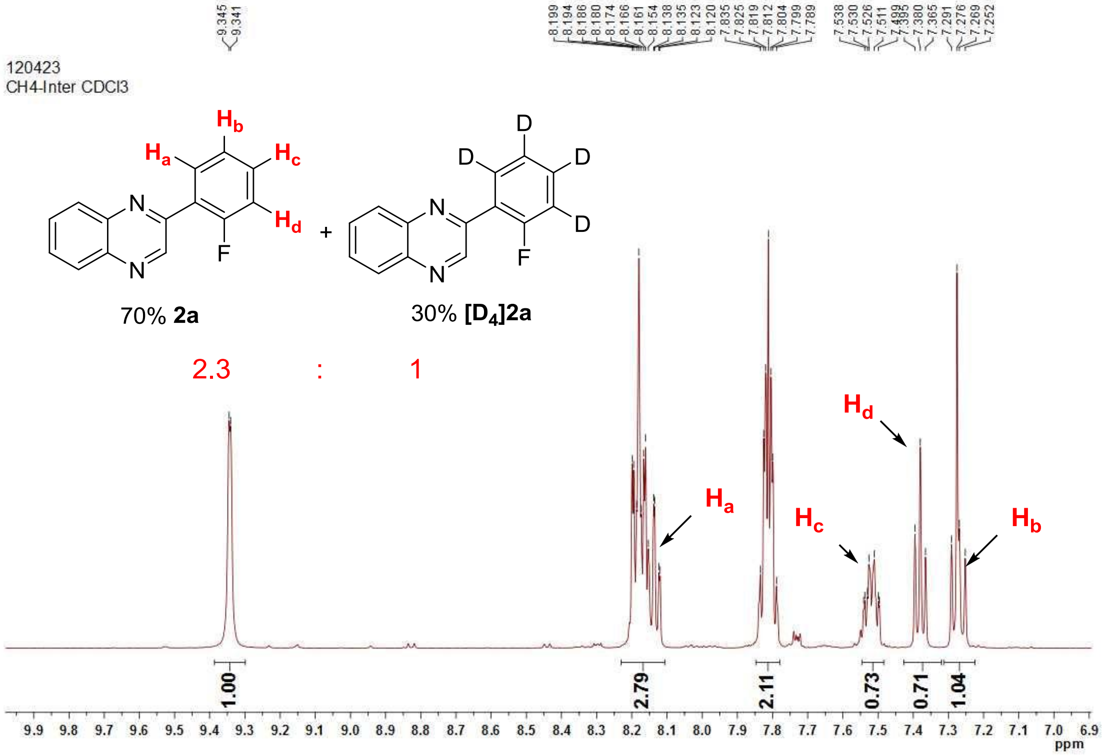
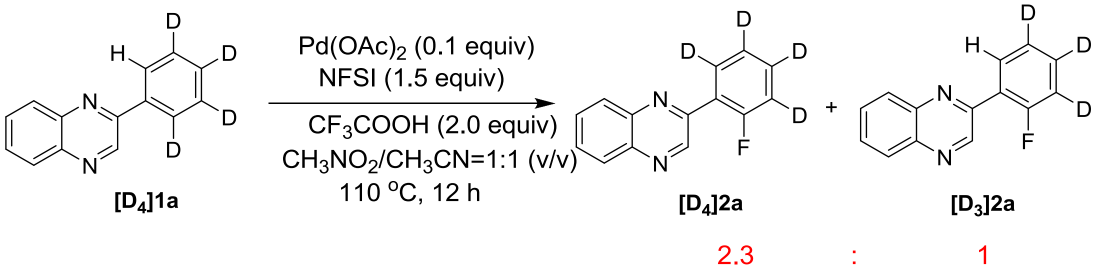


Figure 2. *^{1}H NMR spectra of* ***2a*** *and* ***[D$_4$]2a***

Determination of Intramolecular Kinetic Isotope Effect



To a 25-mL tube was sequentially added 2-phenyl-2,3,4,5-*d4*-quinoxaline (**[D$_4$]1a**) (42.0 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), NFSI (94.5 mg, 0.3 mmol), TFA (45.6 mg, 0.4 mmol) and a mixed solvent [CH_3NO_2 / CH_3CN = 1:1 (v/v)] (2.0 mL) under air. The tube was sealed and heated to 110 ^{o}C for 12 h. The resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on silica gel (100-200 mesh) using petroleum ether-EtOAc (10:1, v/v) as eluent. ^{1}H NMR analysis of the isolated mixture of **[D$_4$]2a** and **[D$_3$]2a** showed about 30.0 % hydrogen content (8.14 ppm). Based on this intergration, the kinetic isotope effect is caculated to be $k_H / k_D \approx 2.3$ (Figure 3).

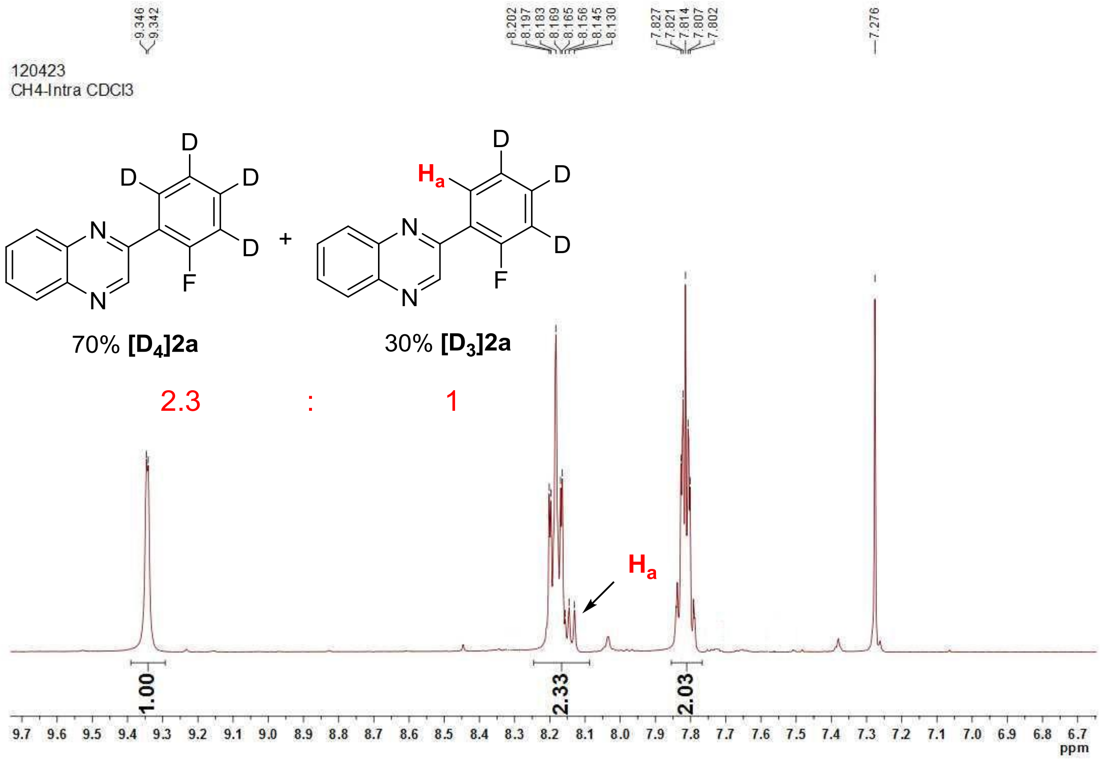


Figure 3. ^{1}*H NMR spectra of* ***[D$_4$]2a*** *and* ***[D$_3$]2a***

The series of experiments above disclosed that the kinetic isotope effect was observed both in the intramolecular (k_H / k_D ≈ 2.3) and intermolecular (k_H/k_D ≈ 2.3) competition experiments, suggesting that the aromatic C-H activation is involved in the rate-limiting step.

ESI-MS studies

To a 25-mL tube was sequentially added 2-phenyl quinoxaline (**1a**) (10.6 mg, 0.05 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), NFSI (19.0 mg, 0.06 mmol), TFA (11.4 mg, 0.1 mmol) and a mixed solvent [CH_3NO_2 / CH_3CN = 1:1 (v/v)] (1.0 mL). The suspension was allowed to stir at 110 °C for 1 hour under air, then diluted by methanol and subjected directly to ESI-MS analysis. The spectrum was shown in Figure 4. Cyclopalladation (II) intermediates were detected at *m/z* = 466 ([**I** + H]$^+$), *m/z* = 311 (**I-1**), m/z = 329 (**I-2**), *m/z* = 517 ([**II** + H]$^+$), *m/z* = 535 ([**II-1** + H]$^+$), and at *m/z* = 553 ([**II-2** + H]$^+$, the coordination complex between the monofluorinated product **2a** and Pd(II)). The reductive eliminated Pd(II) intermediates differed only in the type of ligands coordinated to the central Pd atom were also observed at *m/z* = 608 ([**IV** + H]$^+$), *m/z* = 626 ([**IV-1** + H]$^+$), *m/z* = 649 ([**IV-2** + H]$^+$), *m/z* = 667 ([**IV-3** +

H]$^+$), *m/z* = 814 ([**IV-4** + H]$^+$), *m/z* = 832 ([**IV-5** + H]$^+$), and at *m/z* = 850 ([**IV-6** + H]$^+$). (Scheme 1)

A tadem mass spectrometric (MS/MS) experments were took place to assign the structures of corresponding Pd(II) intermediates.(Figure 5)

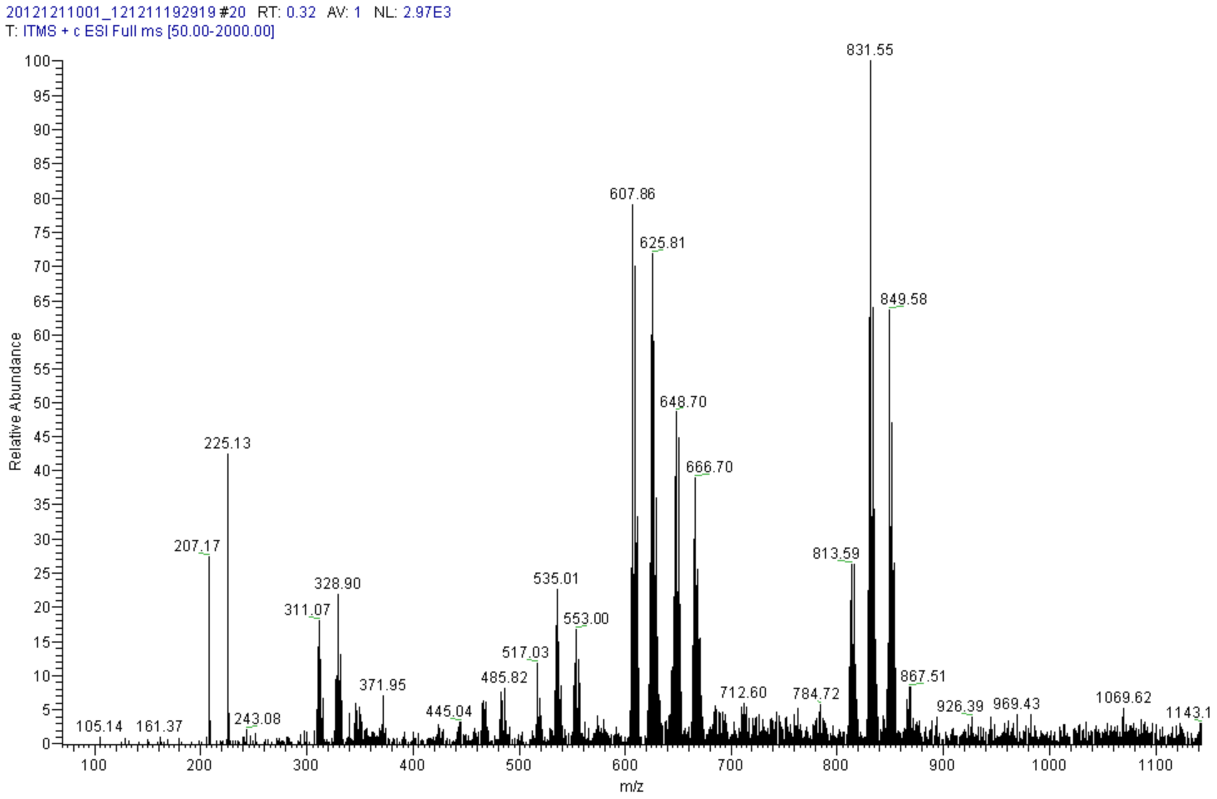
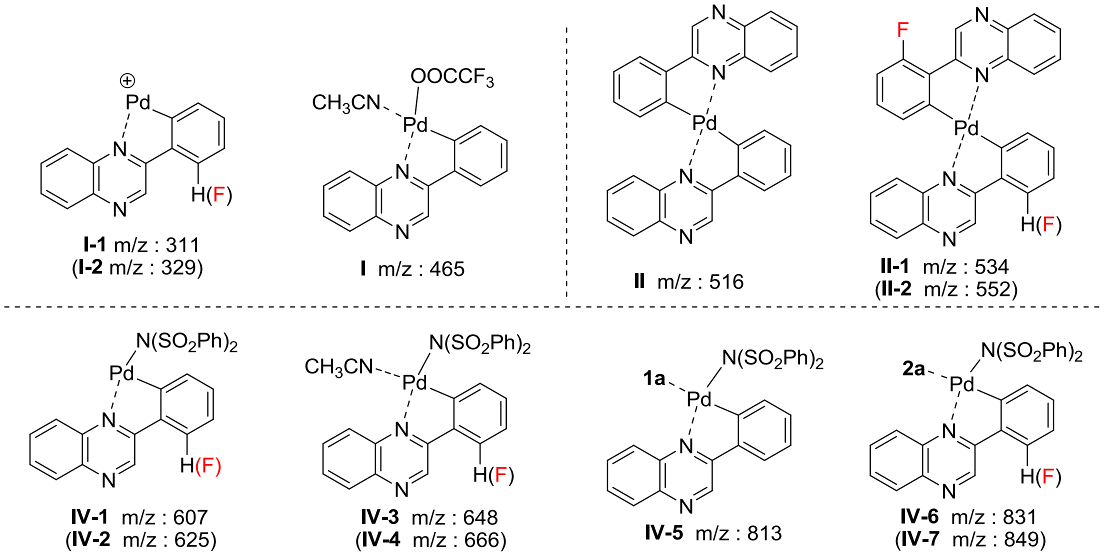
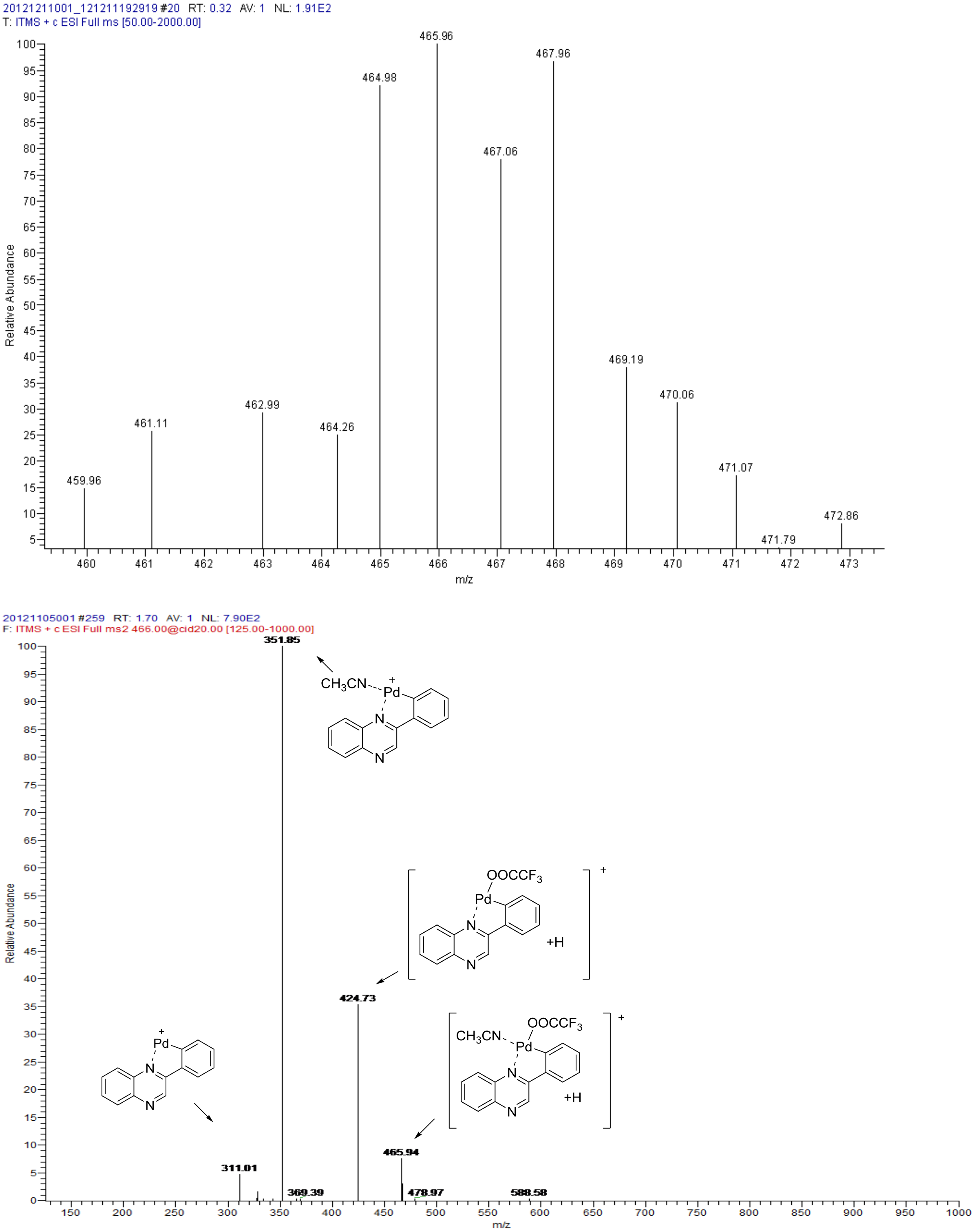


Figure 4. *ESI-MS spectrum of reductive eliminated Pd(II) complex*



Scheme 1. *The analysis of Pd(II) intermediates*

a)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Relative Abundance
m/z
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461.11
462.99
464.26
464.98
465.96
467.06
467.96
469.19
470.06
471.07
471.79
472.86
20121105001 #259 RT: 1.70 AV: 1 NL: 7.90E2
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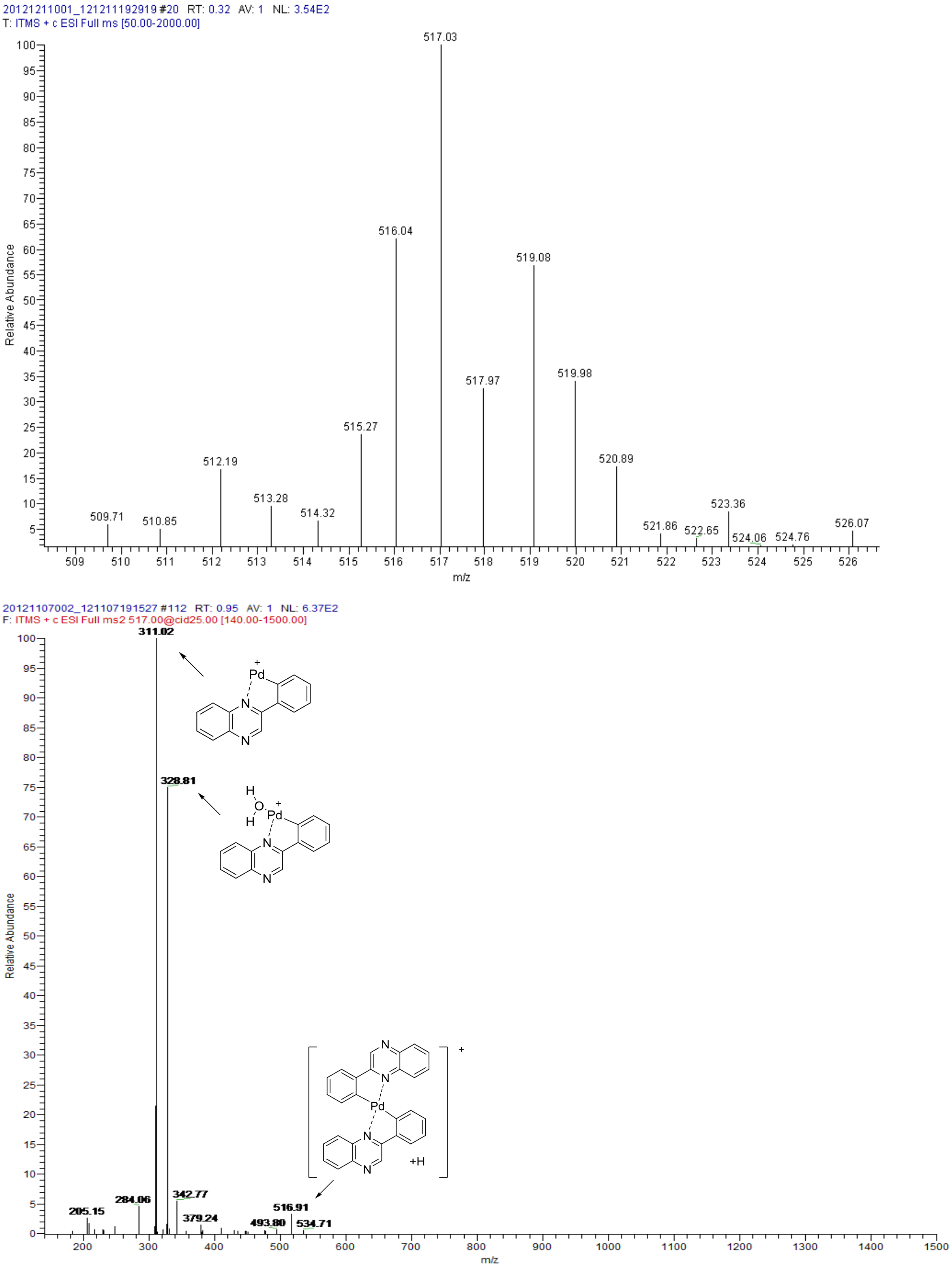
351.85
424.73
311.01
369.39
465.94
478.97
588.58
CH3CN
Pd
N
OOCCF3
+H
+

m/z: 466

b)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Relative Abundance
m/z
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516.04
519.08
517.97
519.98
515.27
512.19
520.89
513.28
523.36
514.32
509.71
510.85
526.07
521.86
522.65
524.06
524.76
20121107002_121107191527 #112 RT: 0.95 AV: 1 NL: 6.37E2
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311.02
328.81
342.77
284.06
205.15
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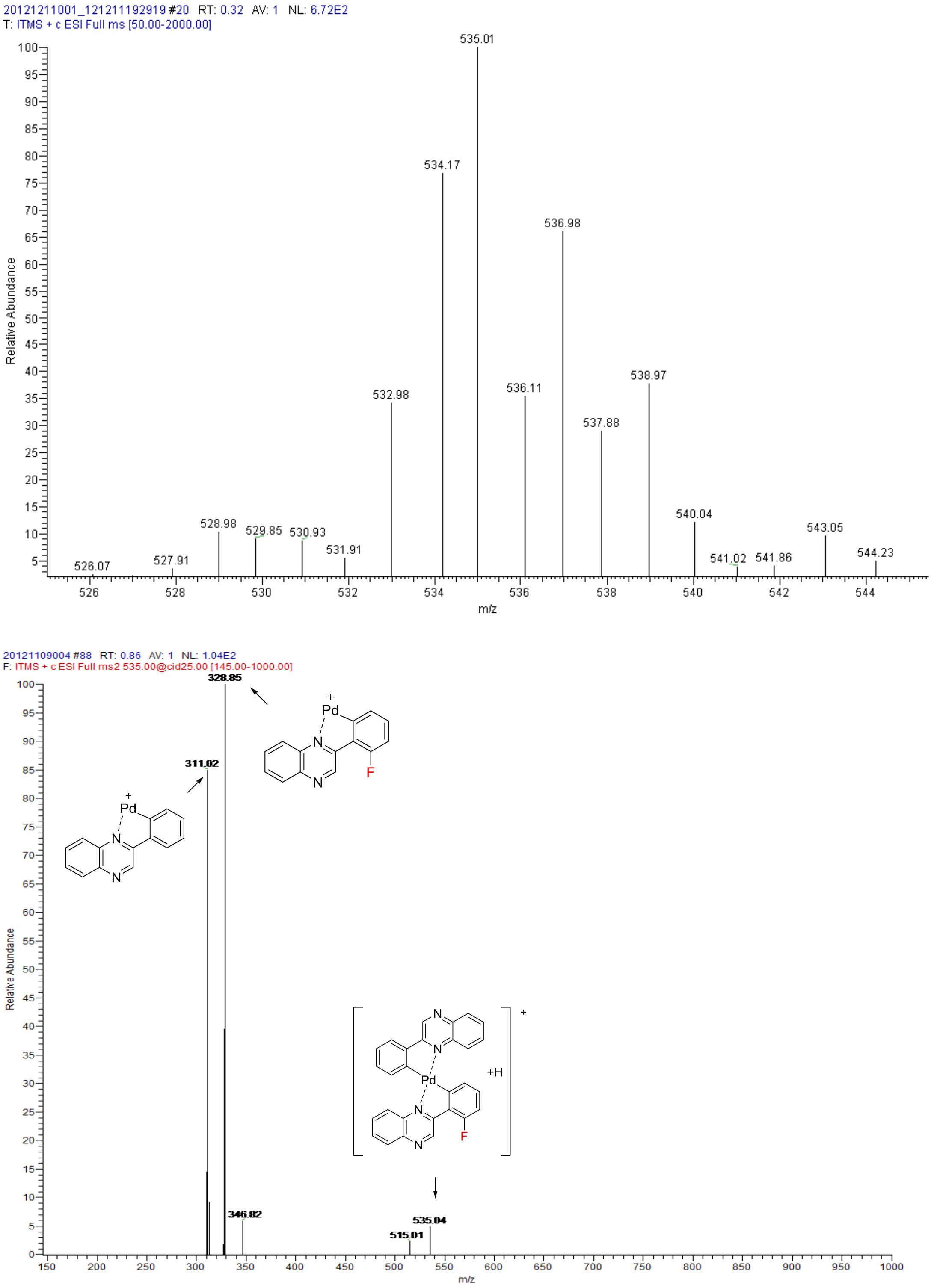
516.91
493.80
534.71
Pd
N
H
O
+H
+

m/z: 517

c)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Relative Abundance
m/z
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534.17
536.98
538.97
536.11
532.98
537.88
540.04
528.98
529.85
530.93
543.05
531.91
527.91
526.07
541.02
541.86
544.23
20121109004 #88 RT: 0.86 AV: 1 NL: 1.04E2
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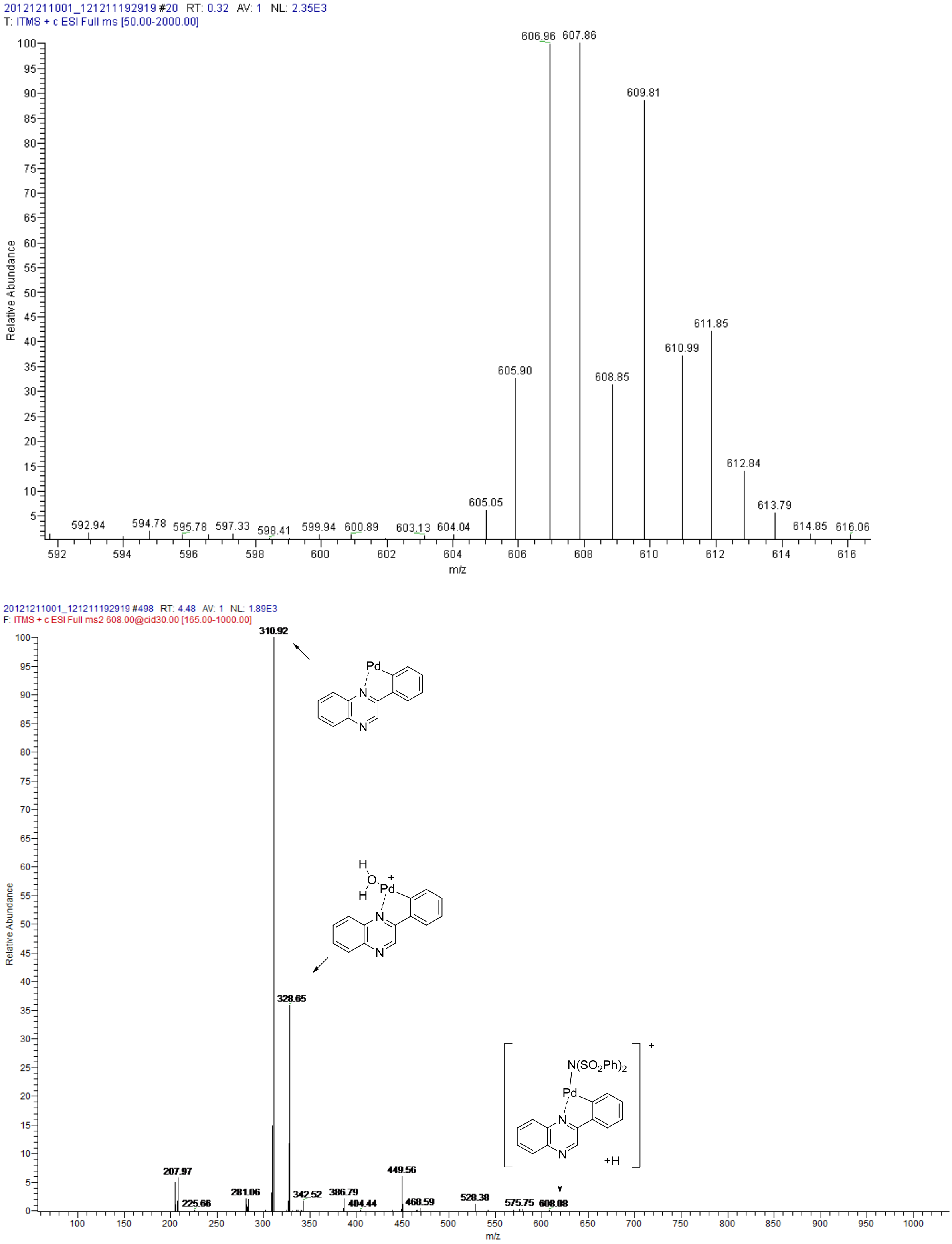
311.02
346.82
535.04
515.01
Pd
N
F
+
+H

m/z: 535

d)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605.05
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592.94
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598.41
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600.89
603.13
604.04
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616.06
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Relative Abundance
m/z
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328.65
207.97
225.66
281.06
342.52
386.79
404.44
449.56
468.59
528.38
575.75
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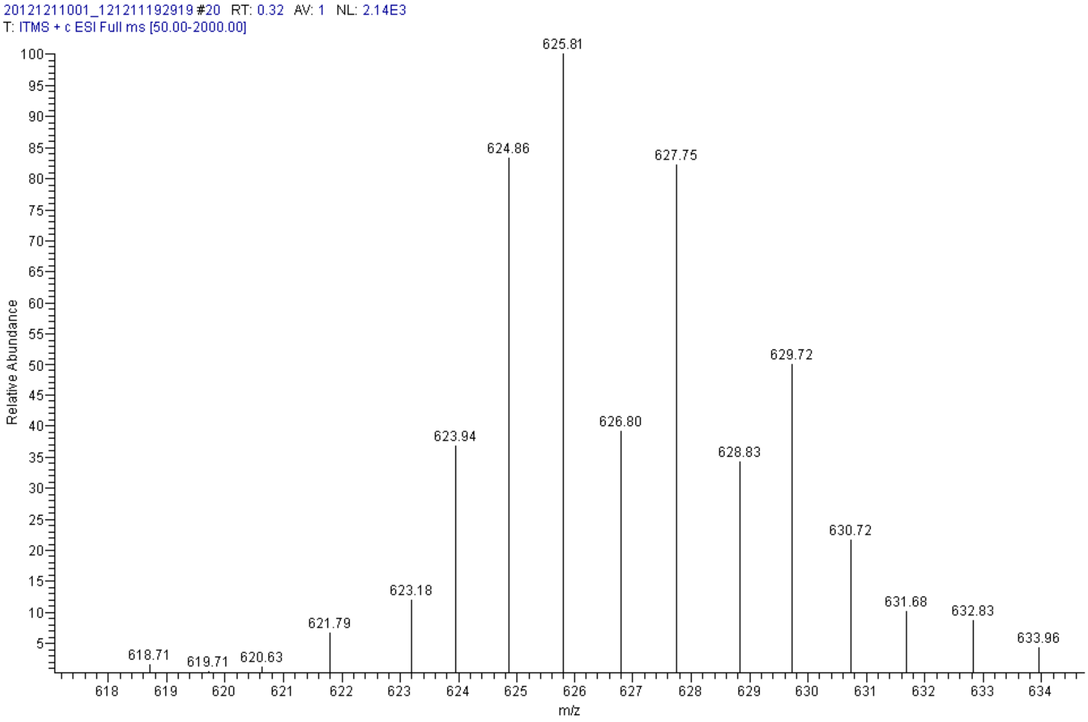
Pd
N
N
H
O
H
N(SO2Ph)2
+H
+

m/z: 608

e)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628.83
630.72
623.18
631.68
632.83
621.79
633.96
618.71
619.71
620.63
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
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630
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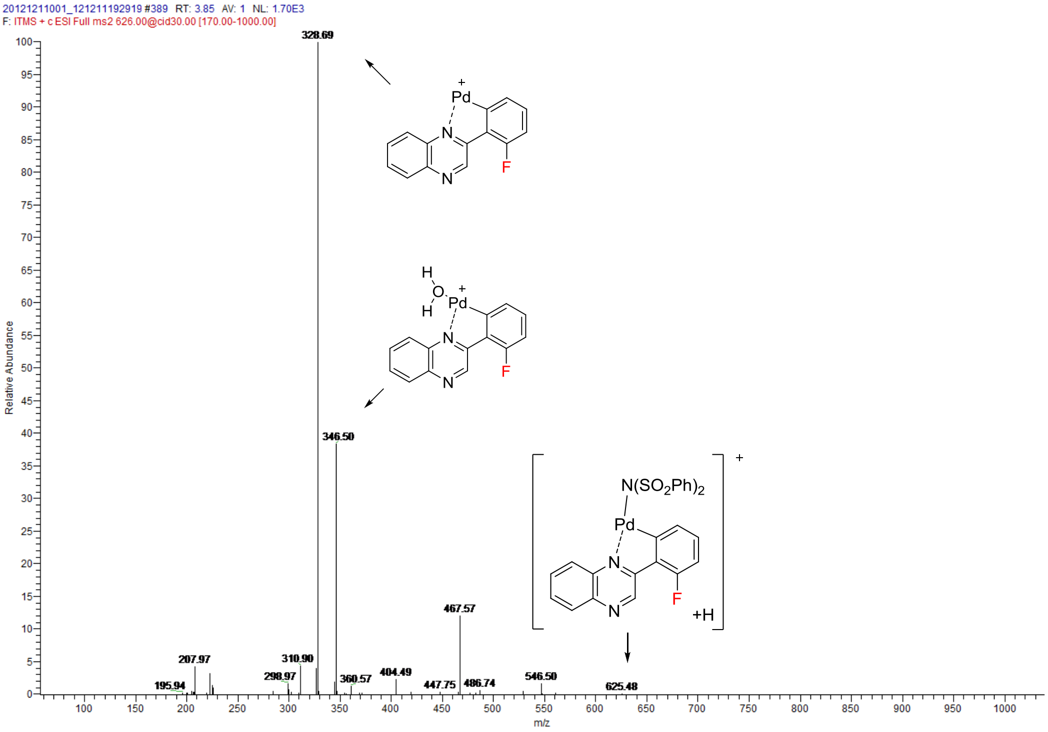
632
633
634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m/z
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404.49
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546.50
625.48
Pd
+
N
N
F
H
O
H
N(SO2Ph)2
+H
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
100
150
200
250
300
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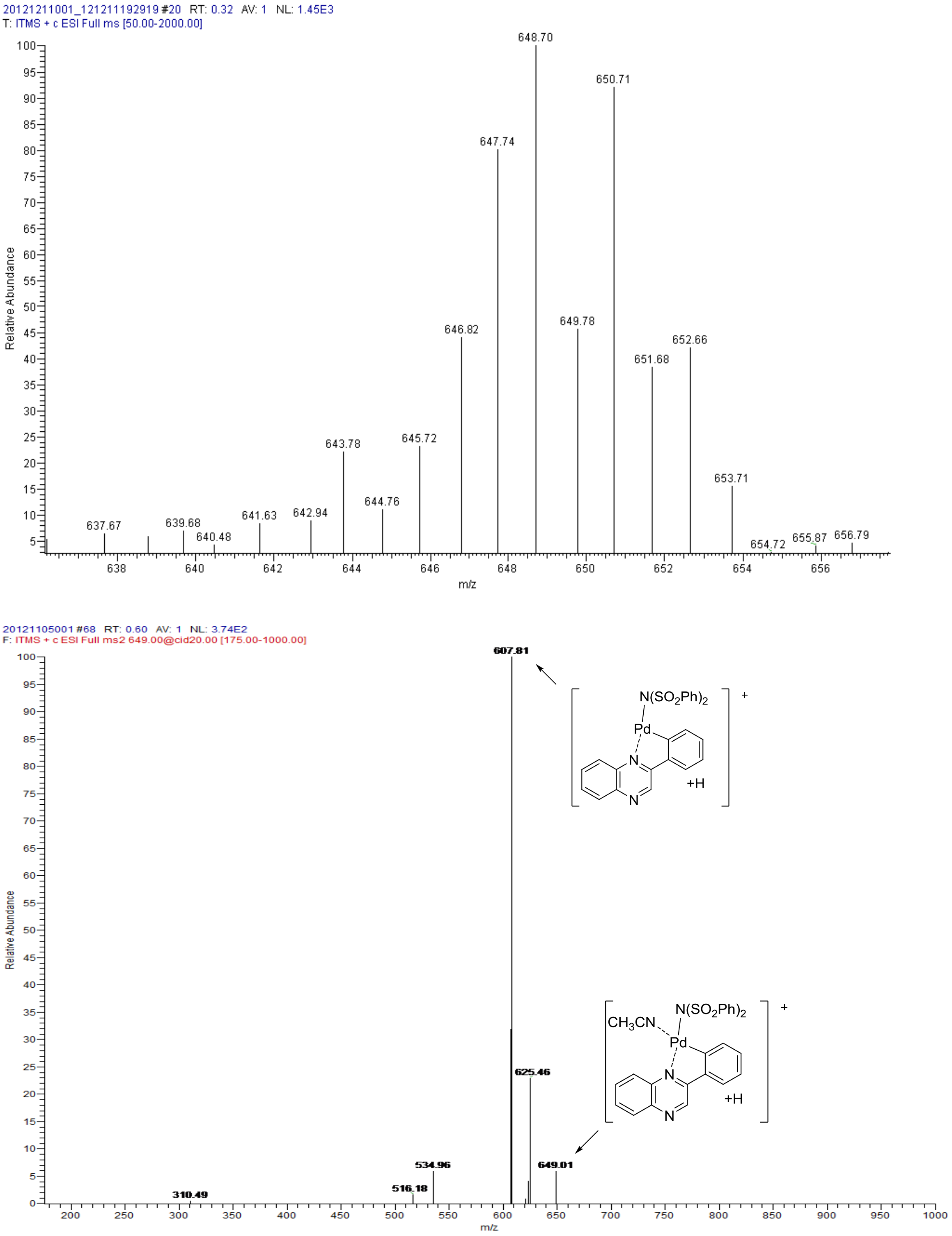
450
500
550
600
650
700
750
800
850
900
950
1000

m/z: 626

f)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644.76
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+H
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CH3CN
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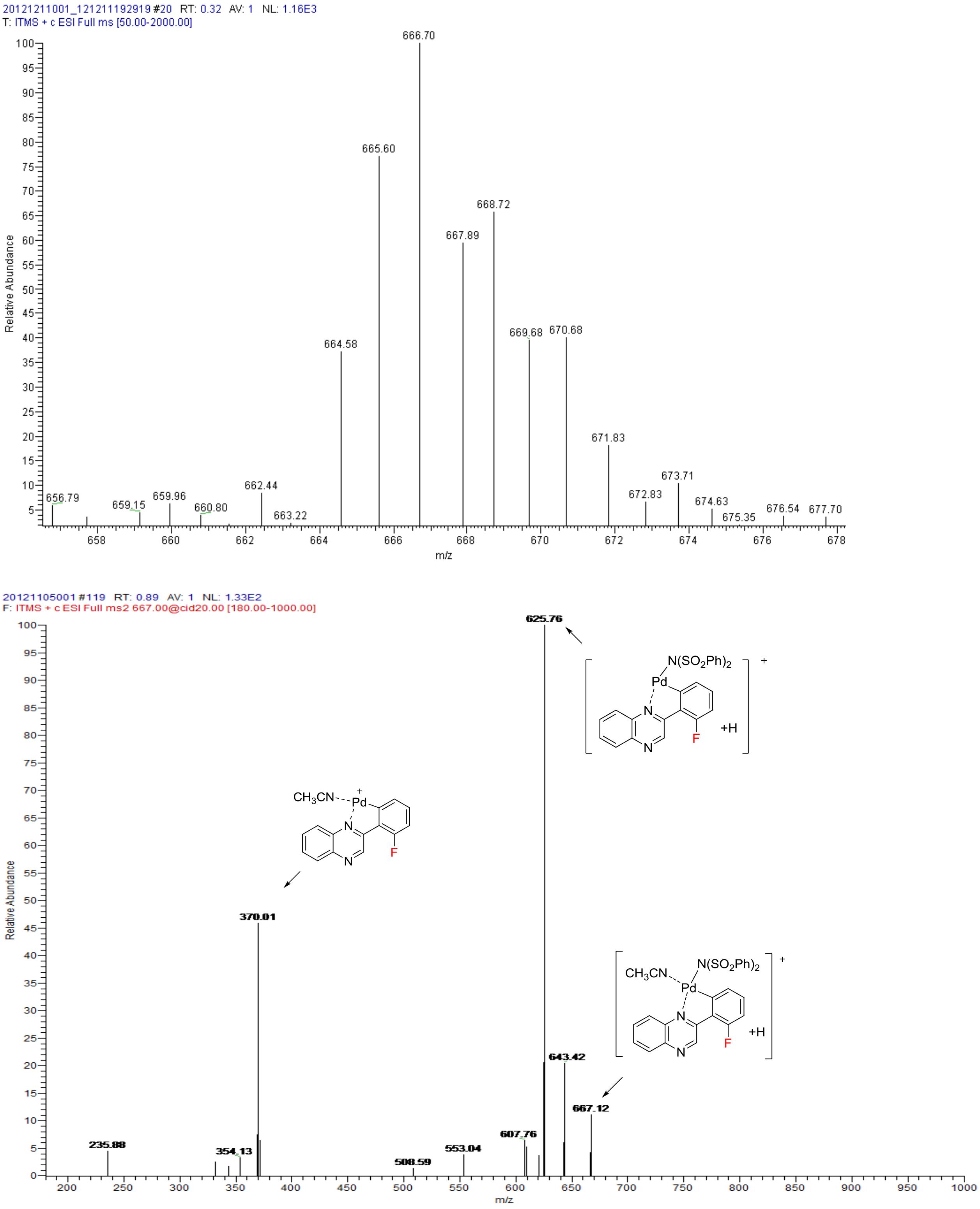
Pd
N
N
+H
+

m/z: 649

g)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T: ITMS + c ESI Full ms [50.00-2000.00]
Relative Abundance
m/z
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665.60
668.72
667.89
669.68
670.68
664.58
671.83
673.71
672.83
674.63
675.35
676.54
677.70
662.44
663.22
656.79
659.15
659.96
660.80
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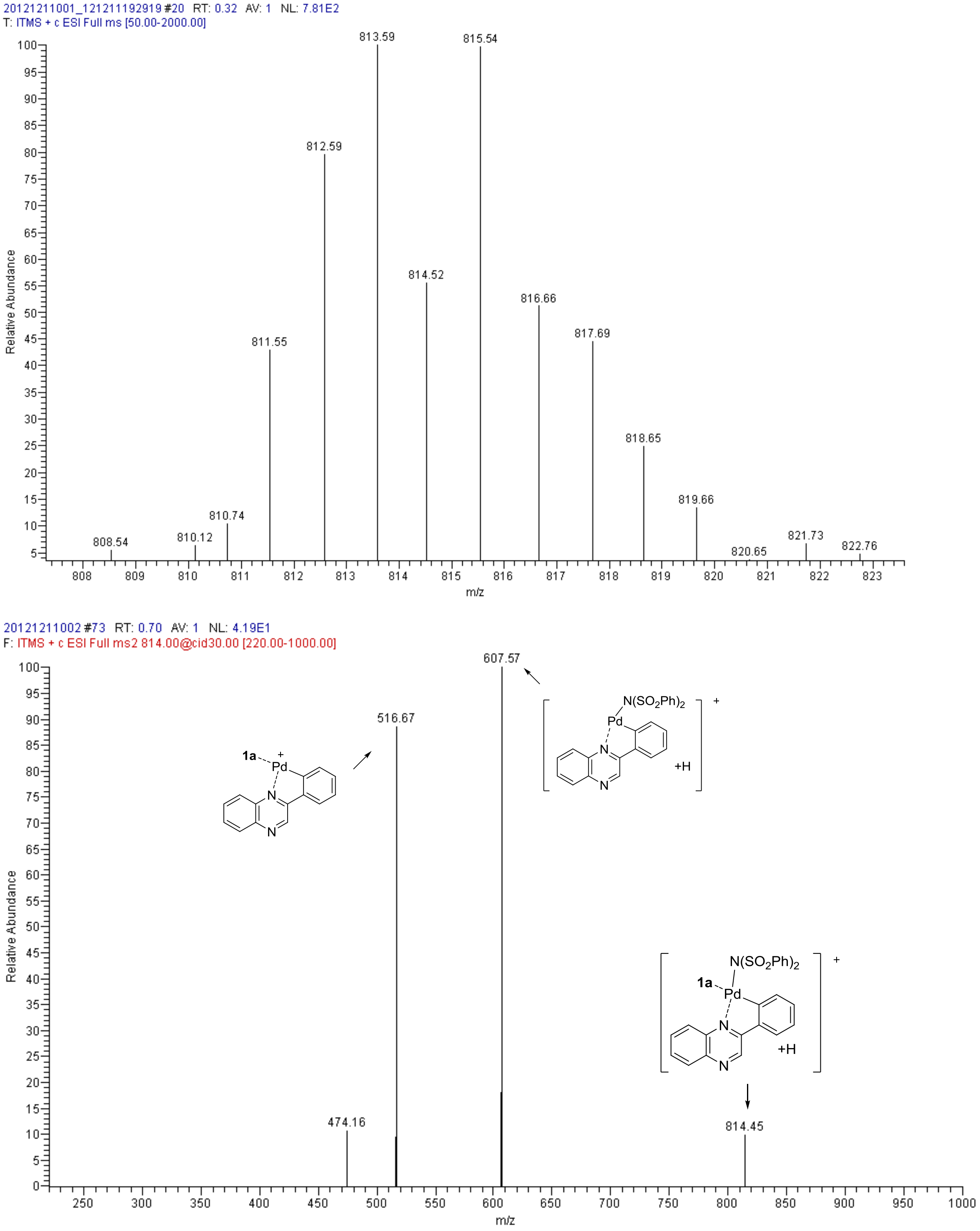
F: ITMS + c ESI Full ms2 667.00@cid20.00 [180.00-1000.00]
Relative Abundance
m/z
625.76
370.01
643.42
667.12
607.76
553.04
508.59
354.13
235.88
N(SO2Ph)2
Pd
N
N
F
+H
+
CH3CN
Pd
+
N
N
F
CH3CN
N(SO2Ph)2
Pd
N
N
F
+H
+

m/z: 667

h)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810.74
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815.54
816.66
817.69
818.65
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820.65
821.73
822.76
20121211002 #73 RT: 0.70 AV: 1 NL: 4.19E1
F: ITMS + c ESI Full ms2 814.00@cid30.00 [220.00-1000.00]
474.16
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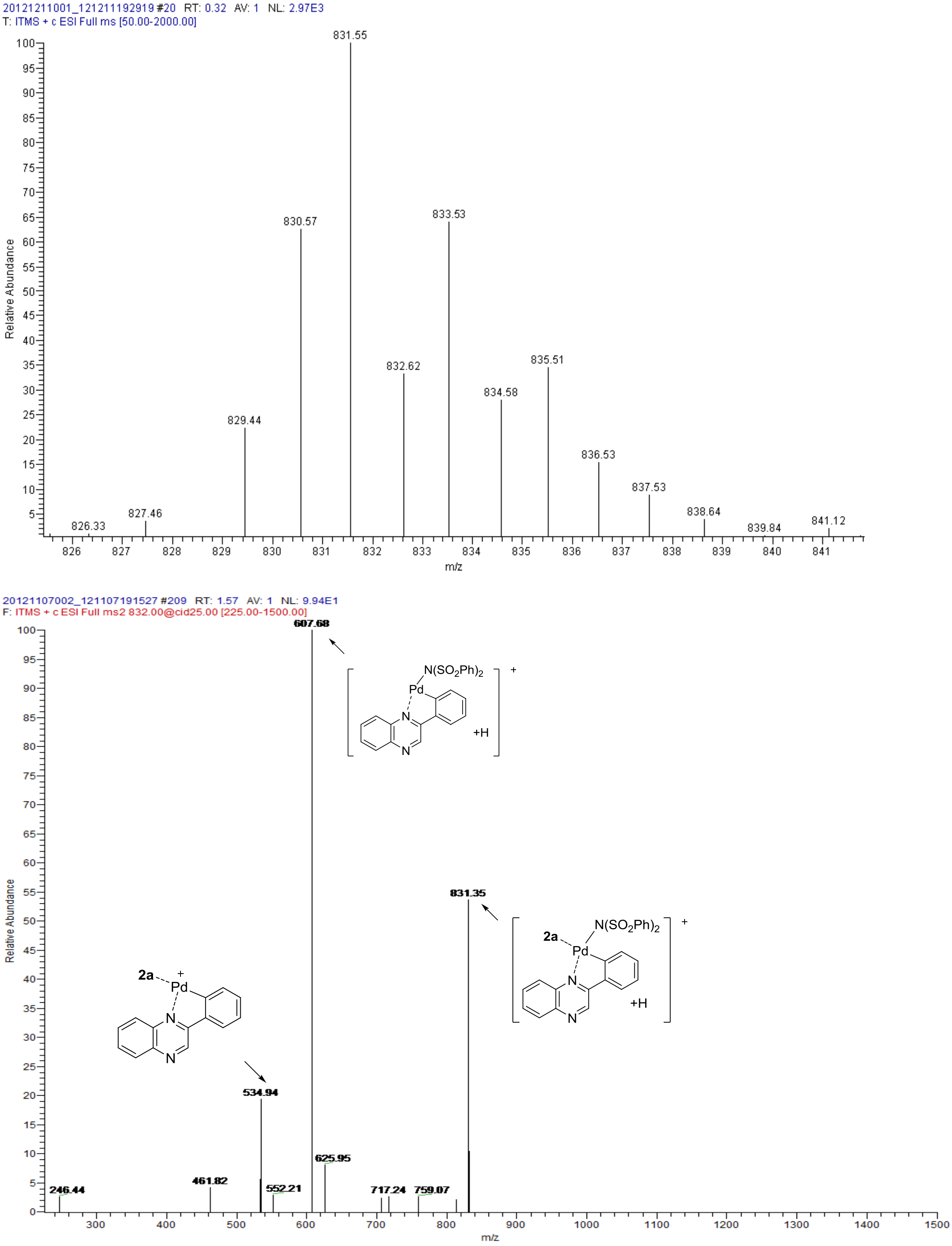
607.57
814.45
1a
Pd
N
+
N(SO2Ph)2
+H

m/z: 814

i)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832.62
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836.53
837.53
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838.64
826.33
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831.35
534.94
625.95
461.82
552.21
717.24
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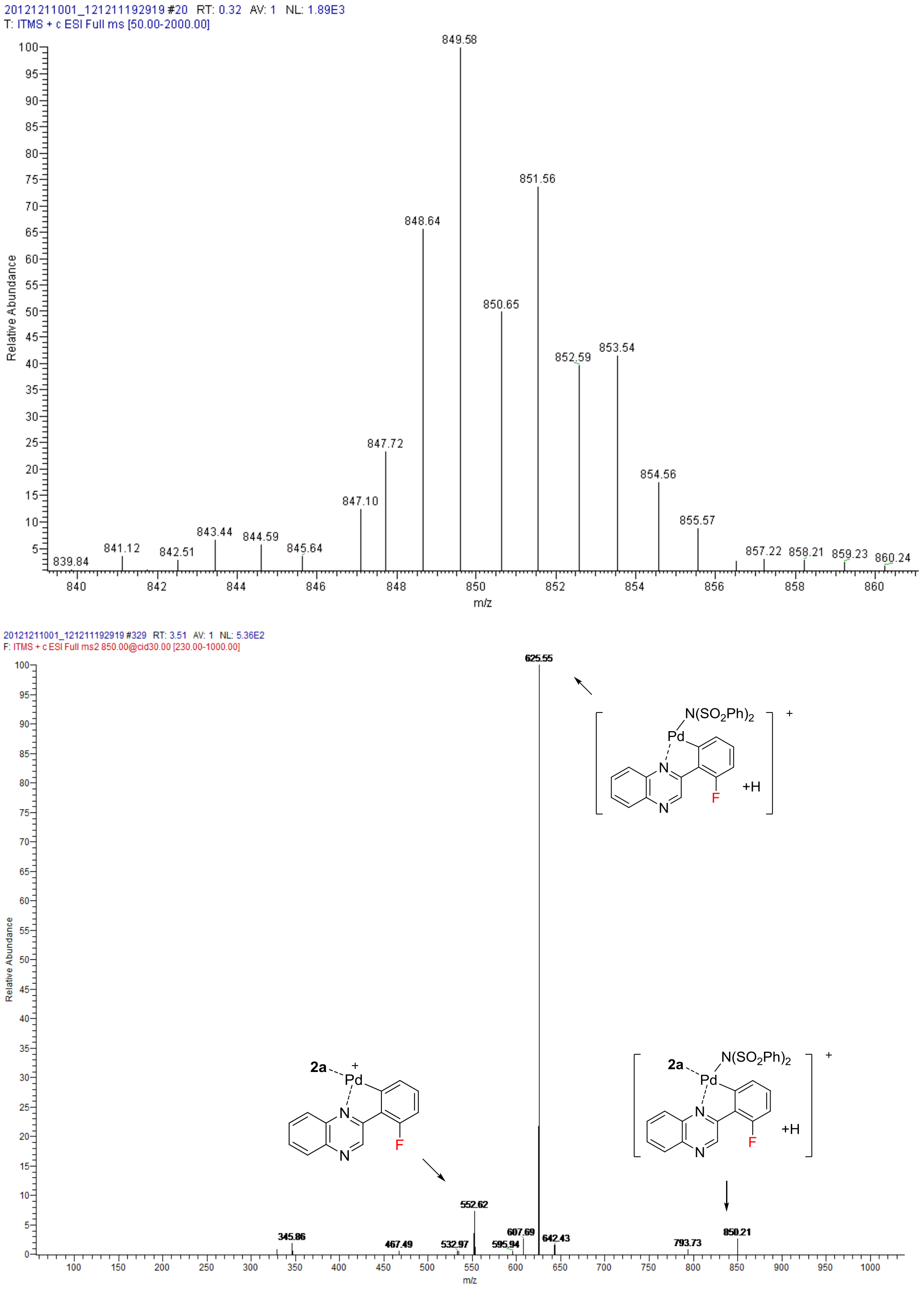
246.44
N(SO2Ph)2
Pd
N
N
+H
+
2a
2a
Pd
+

m/z: 832

j)

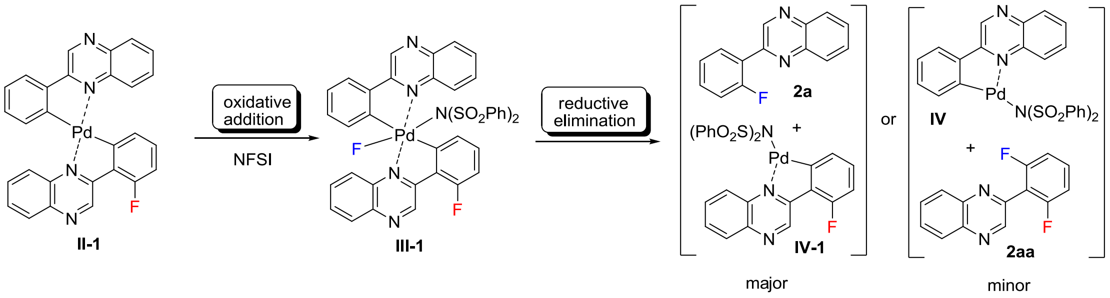


m/z: 850

Figure 5. *ESI-MS/MS spectra for Pd(II) complexes: a) Pd(II) intermediate* ***I*** *(m/z 466); b) Pd(II) intermediate* ***II*** *(m/z 517); c) Pd(II) intermediate* ***II-1*** *(m/z 535);d) reductive eliminated Pd(II) intermediate* ***IV-1*** *(m/z 608); e) reductive eliminated Pd(II) intermediate* ***IV-2*** *(m/z 626); f) reductive eliminated Pd(II) intermediate* ***IV-3*** *(m/z 649);g) reductive eliminated Pd(II)*

*intermediate **IV-4** (m/z 667); h) reductive eliminated Pd(II) intermediate **IV-5** (m/z 814); i) reductive eliminated Pd(II) intermediate **IV-6** (m/z 832); j) reductive eliminated Pd(II) intermediate **IV-7** (m/z 850).*

Notably, the formation of the intermediates **II** and **II-1** revealed that the competing coordination with **I** was occurred between **1a** and monofluorinated product **2a** which resulted in the minor difluorinated product **2aa** (the fluorination of **1a** is faster than **2a**). In addition, the observation disclosed the reason why the difluorination occurred as soon as the monofluorinated azaarene was formed (Scheme 2).



Scheme 2. *Reductive elimination of Pd (IV) intermediate **III-1***

Proposed mechanism

Based on the above mechanistic experiments and previous literatures, a proposed mechanism involving Pd(II/IV) catalytic cycles is depicted in Figure 6. The coordination between **1a** and Pd(II) to form palladacyclic intermediate **I** (***determined by ESI-MS***), which could further coordinated with another **1a** to give **II** (***determined by ESI-MS***). Then the intermediate **II** was fast oxidated by NFSI to generate Pd(IV) intermediate **III** which fast underwent reductive elimination to produce **2a** and the Pd(II) intermediates **IV** (***determined by ESI-MS***).

A competing coordination with intermediate **I** between **1a** and monofluorinated product **2a** was observed by the ESI-MS studies, which led to the generation of the difluorinted product **2aa**. However the coordination between intermediate **I** and **2a** was minor in the present of CH_3CN, which serves as a spectator ligand that can displace the relatively weakly coordinated product **2a** from the Pd(II) center[8]. Even if **2a** coordinated with **I**, the relatively slow C-F bond elimination of **2a** (determined by the aforementioned "**Intermolecular competition experiments**") made the second fluorination sluggish. Thus, a selective aromatic monofluorination was developed.

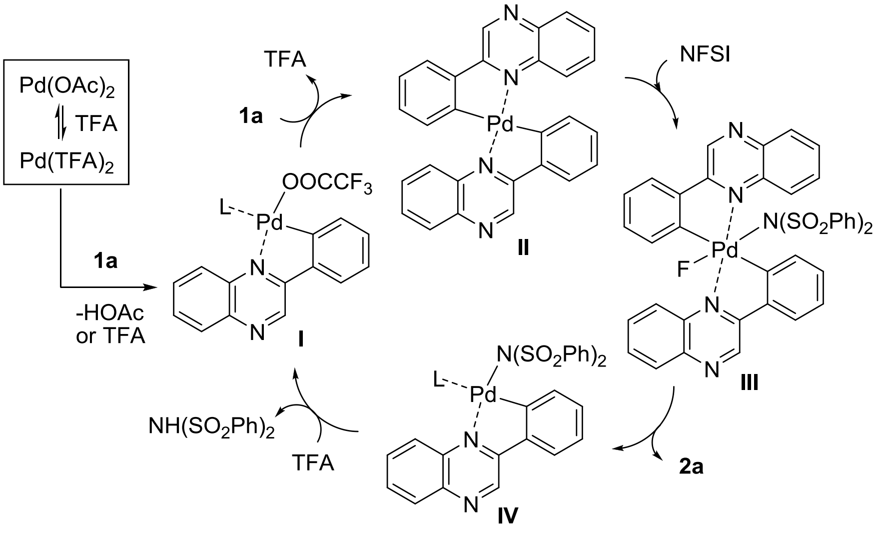
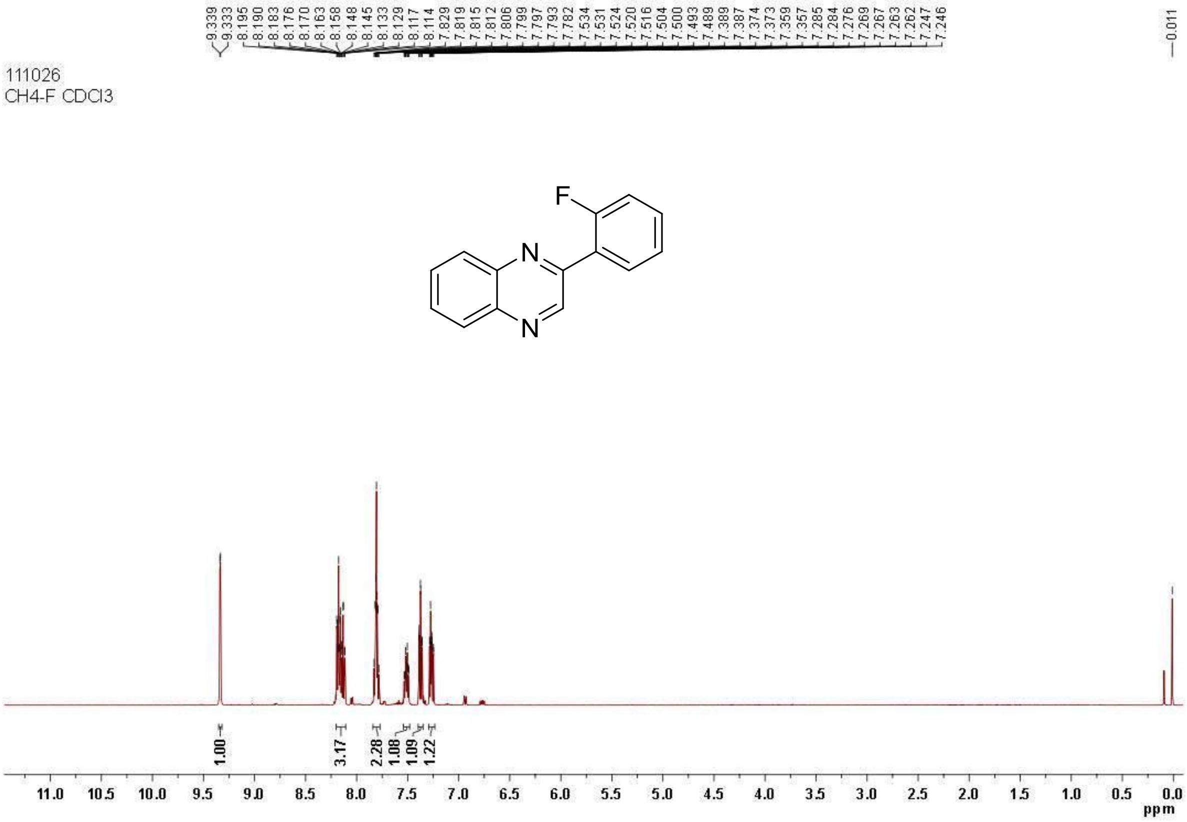


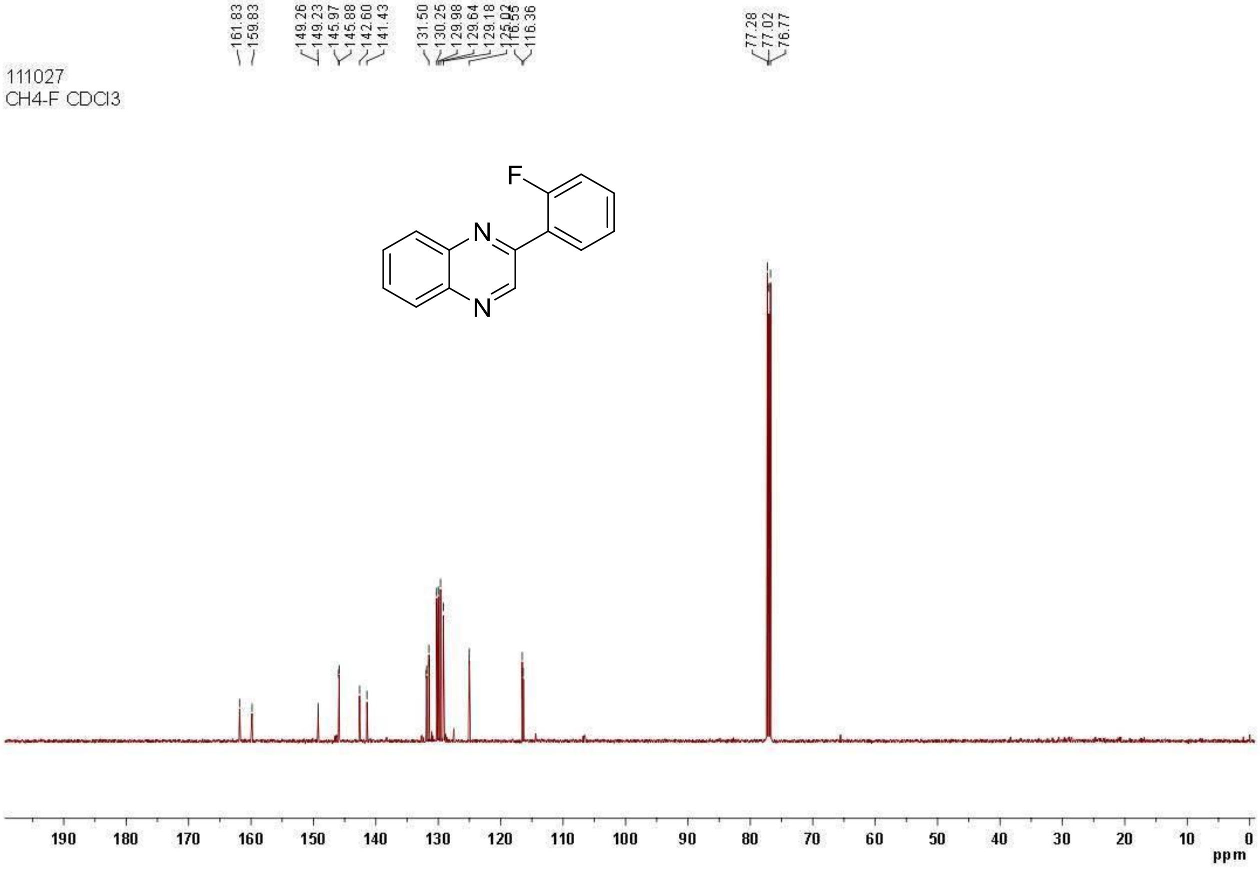
Figure 6. *Proposed mechanism*

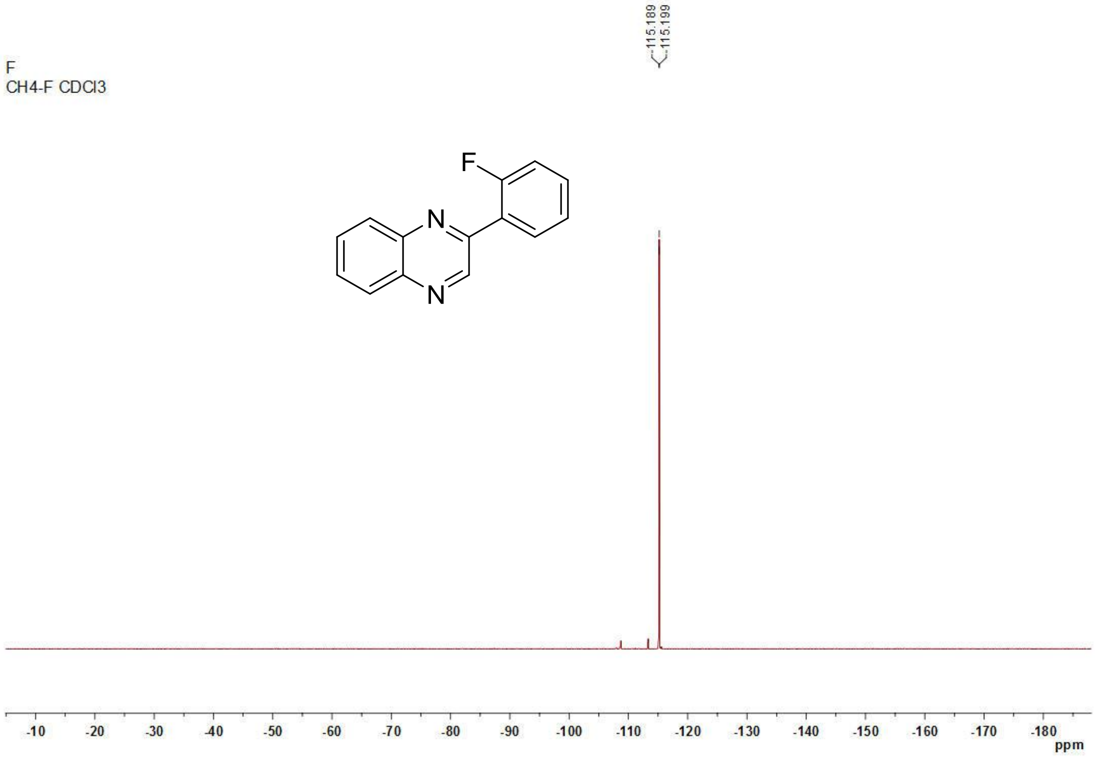
References

1. B. Das, K. Venkateswarlu, K. Suneel, A. Majh, *Tetrahedron Lett.* **2007**, *48*, 5371.
2. J. S.Yadav, B. V. S. Reddy, K. Premalatha, K. S. Shankar, *Synthesis* **2008**, 3787.
3. D. Kumar, S. Rudrawar, A. K. Chakraborti, *Aust. J. Chem.* **2008**, 881.
4. C. Liu, Q. Ni, F.-Y. Bao, J.-S. Qiu, *Green Chem.* **2011**, 1260.
5. S. A. Kotharkar. D. B. Shinde, *Bull. Korean Chem. Soc.* **2006**, 1466.
6. J. Bonnamour, C. Bolm, *Org. Lett.* **2008**, 2665.
7. Y.-K. Liu, S.-J. Lou, D.-Q. Xu and Z.-Y. Xu, *Chem. Eur. J.* **2010**, 13590.
8. K. S. L. Chan, M. Wasa, X. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2011**, 9081.

^{1}H, ^{13}C and ^{19}F NMR spectra of all products



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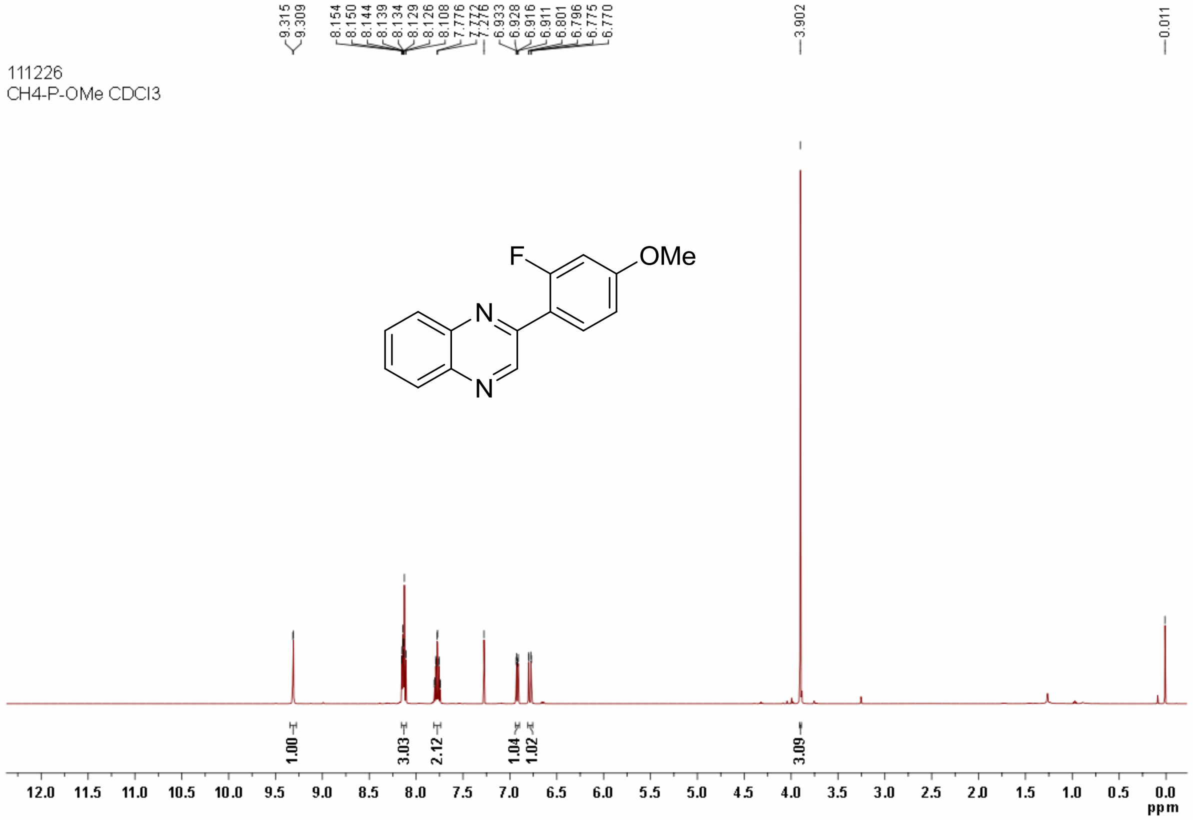
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6.801
6.796
6.775
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111226
CH4-P-OMe CDCl3
F
OMe
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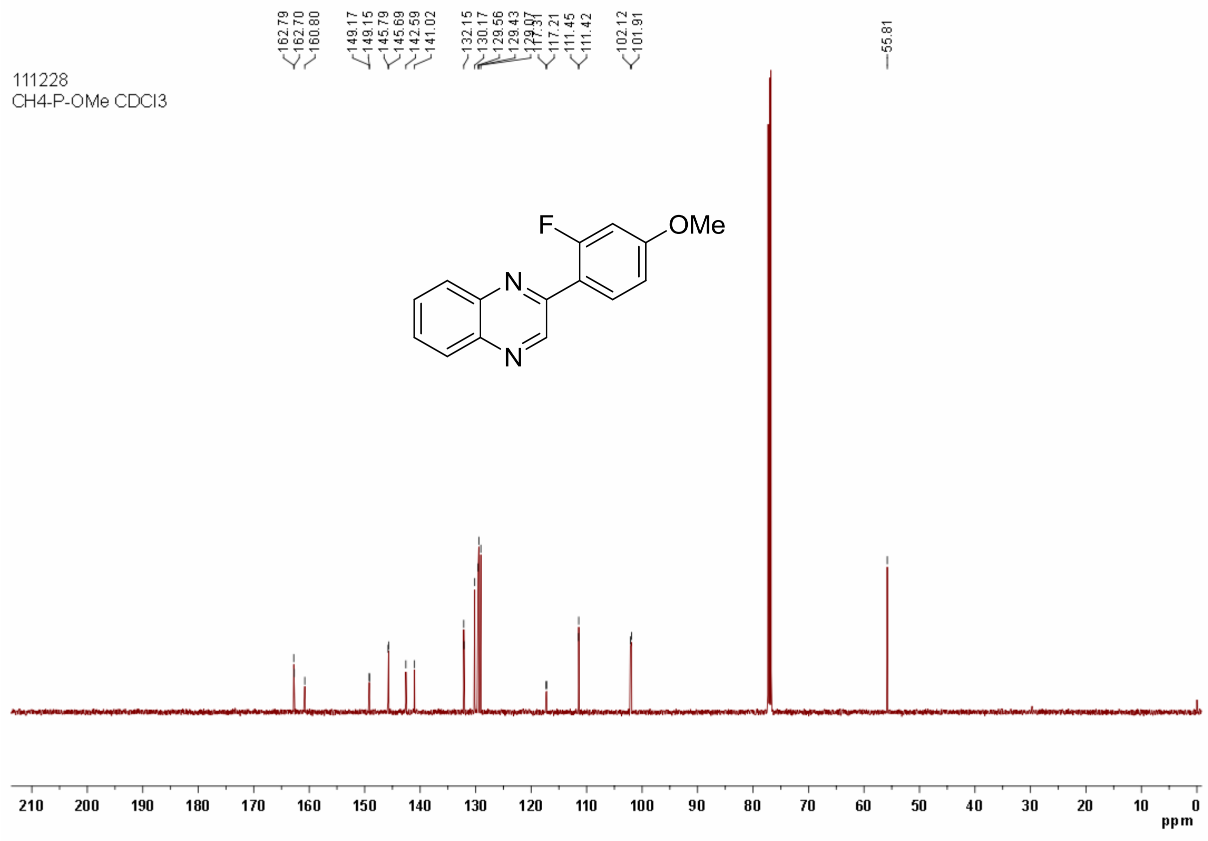
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117.21
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CH4-P-OMe CDCl3
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OMe
N
N
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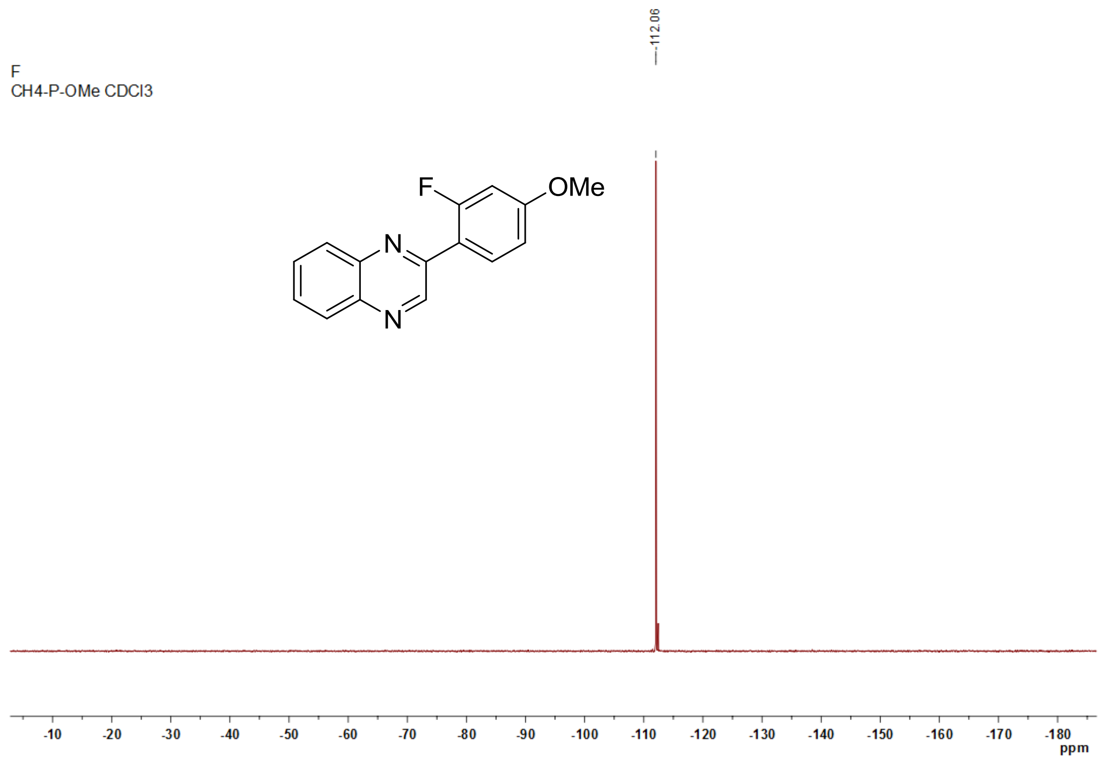
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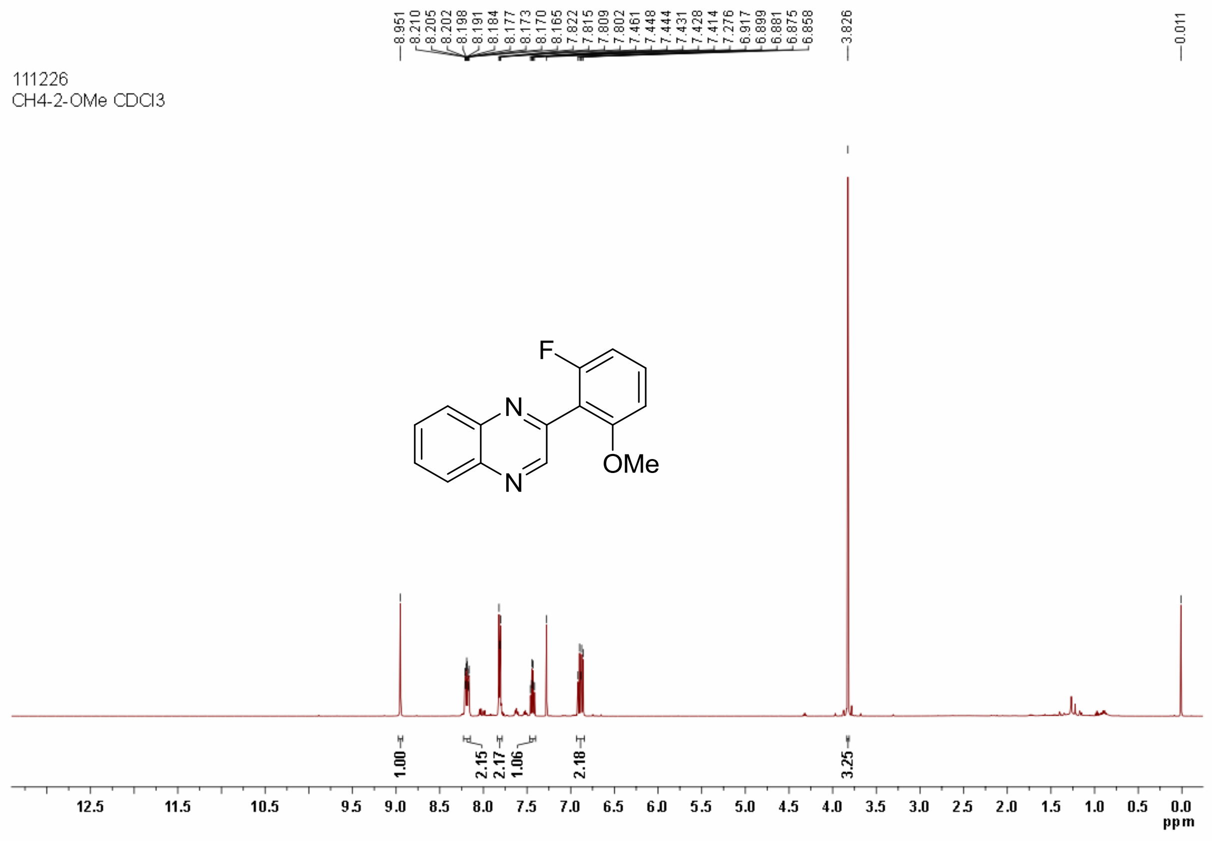
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3.25
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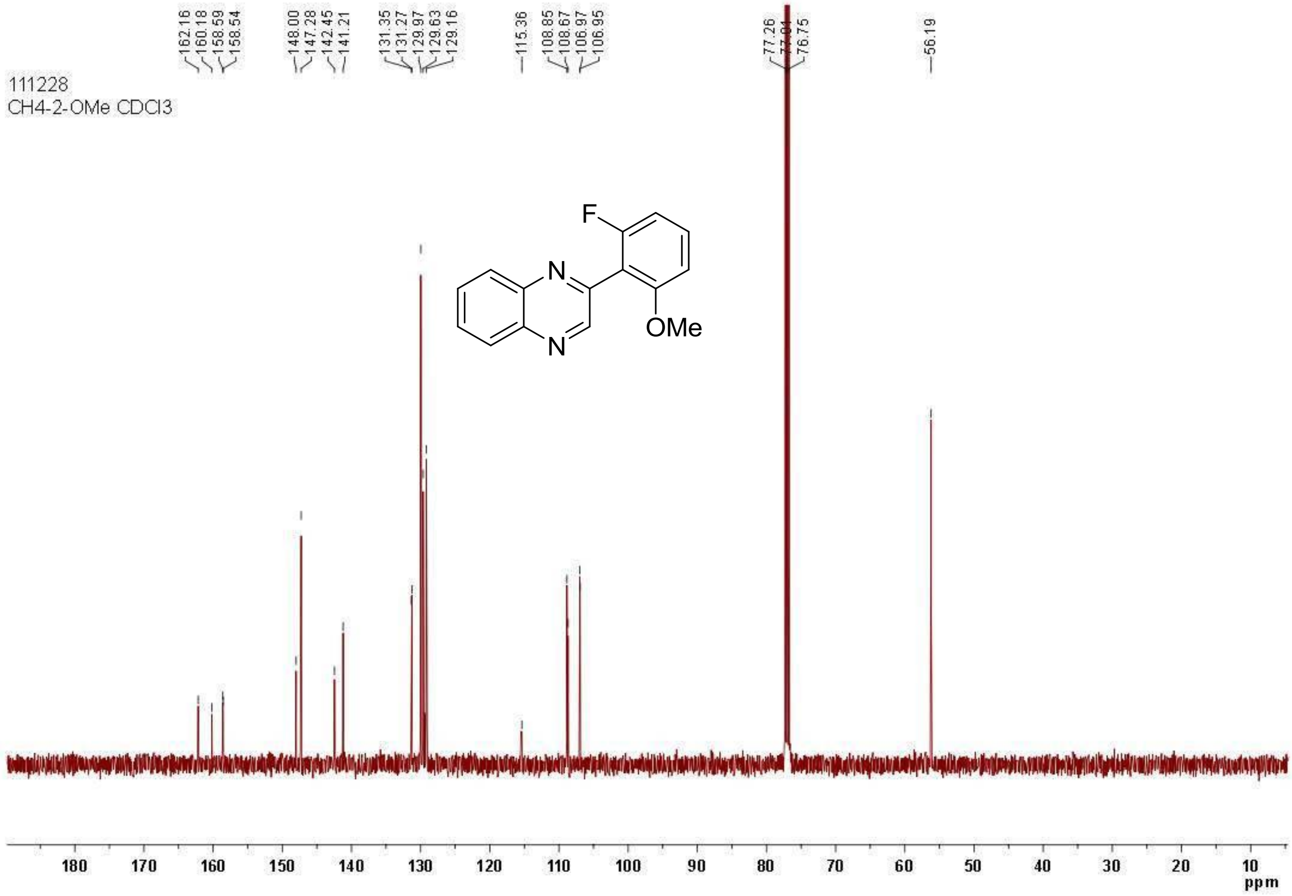
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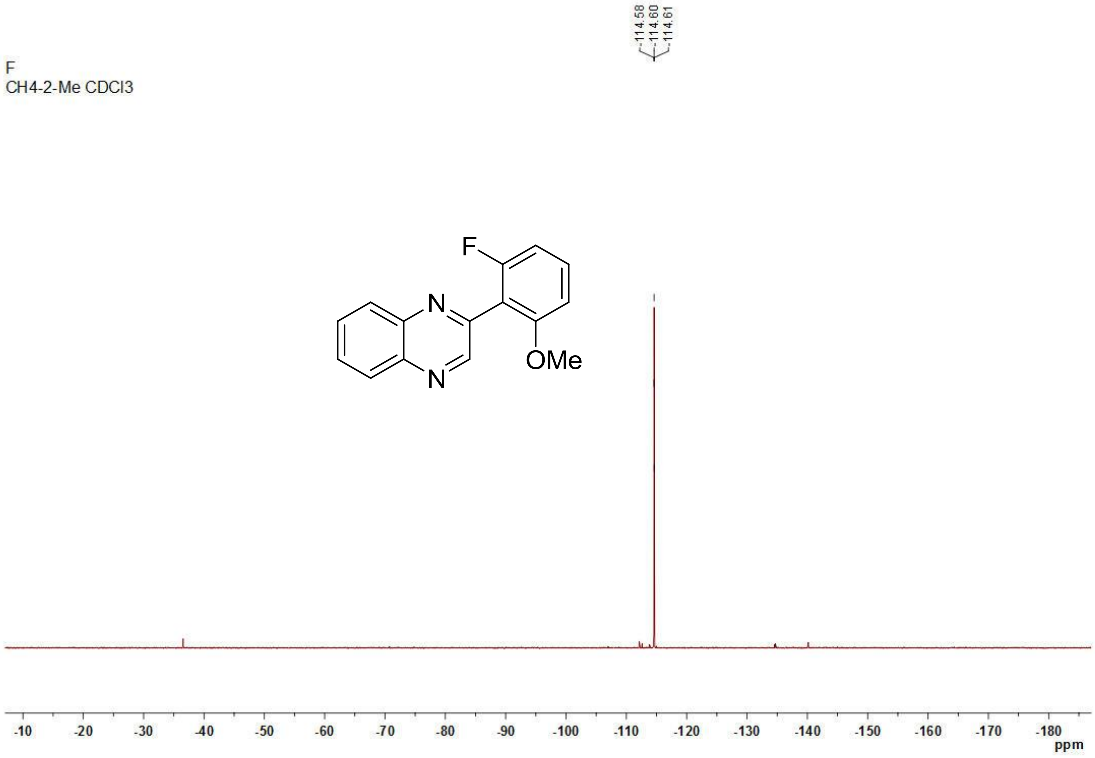
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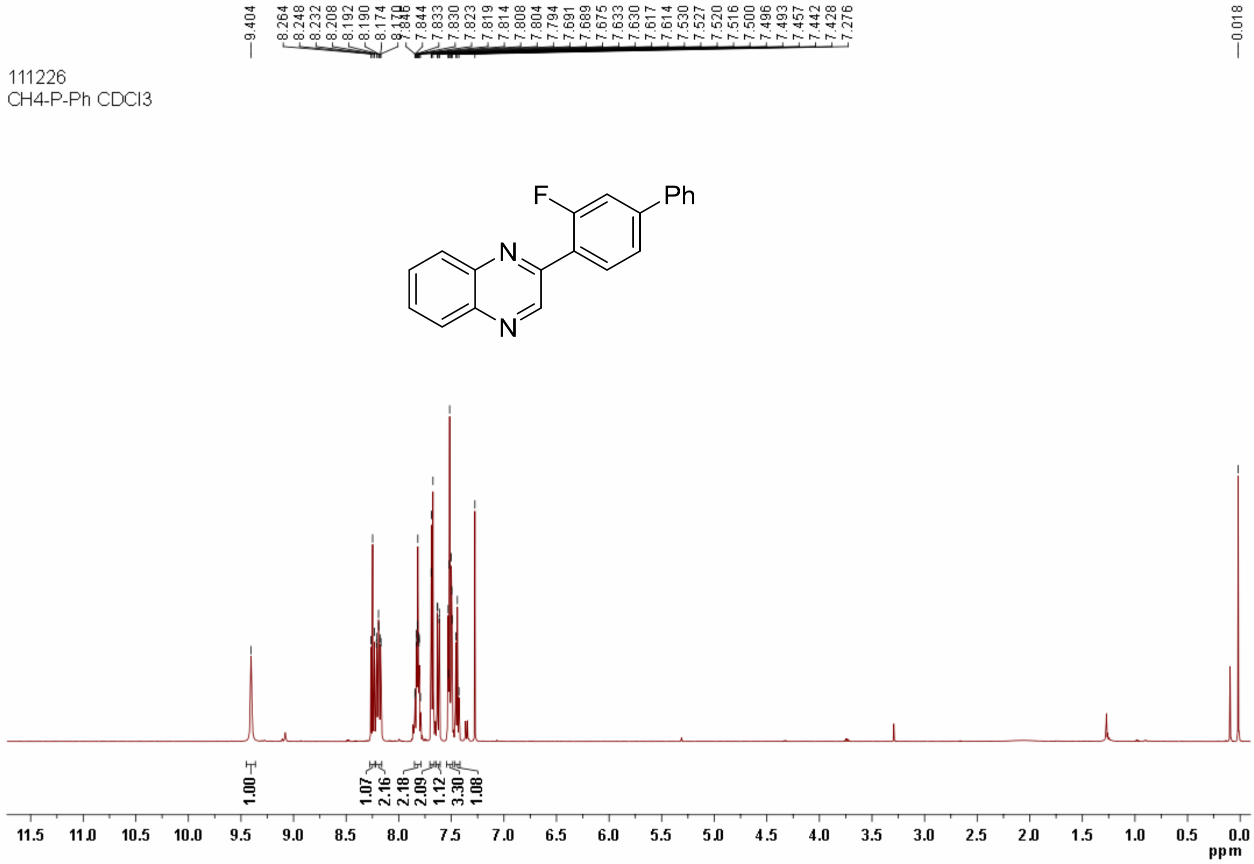
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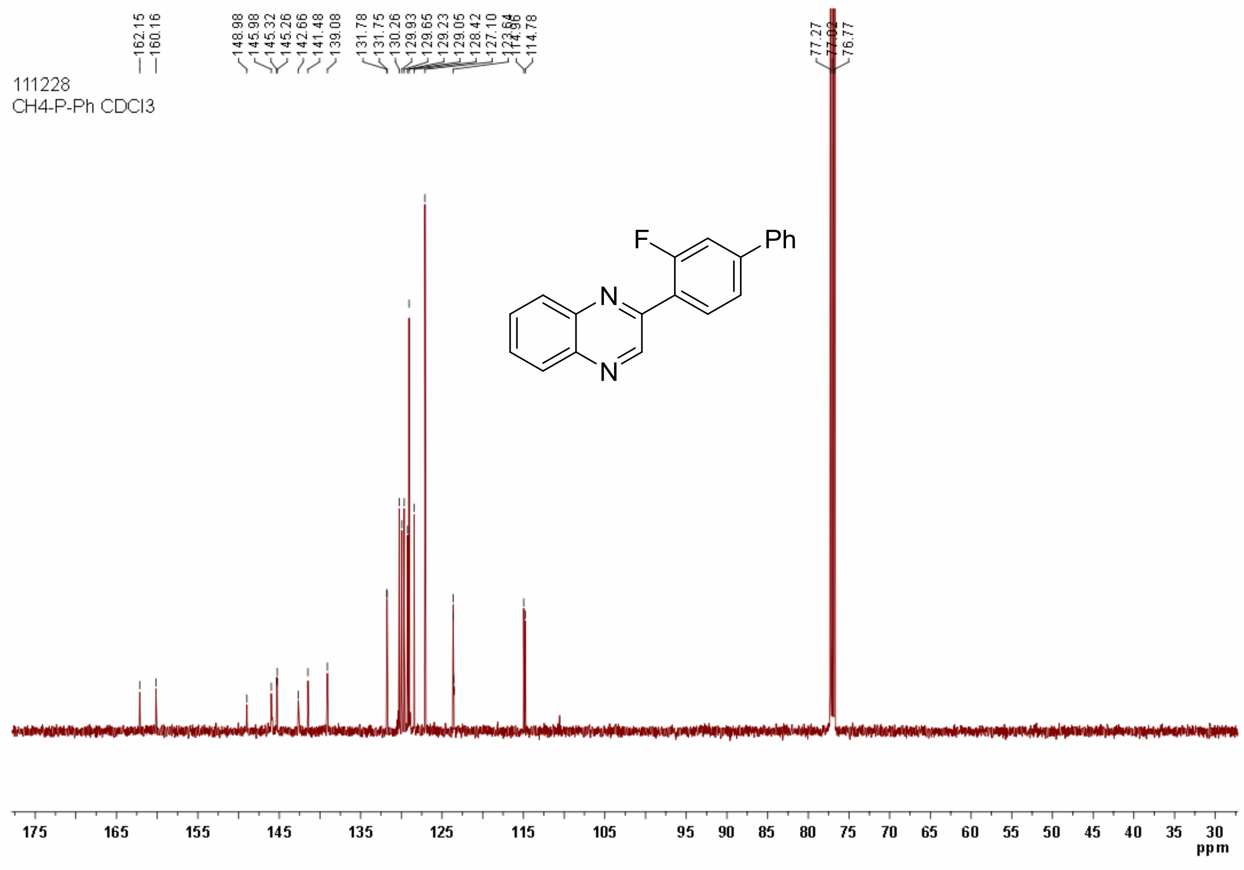
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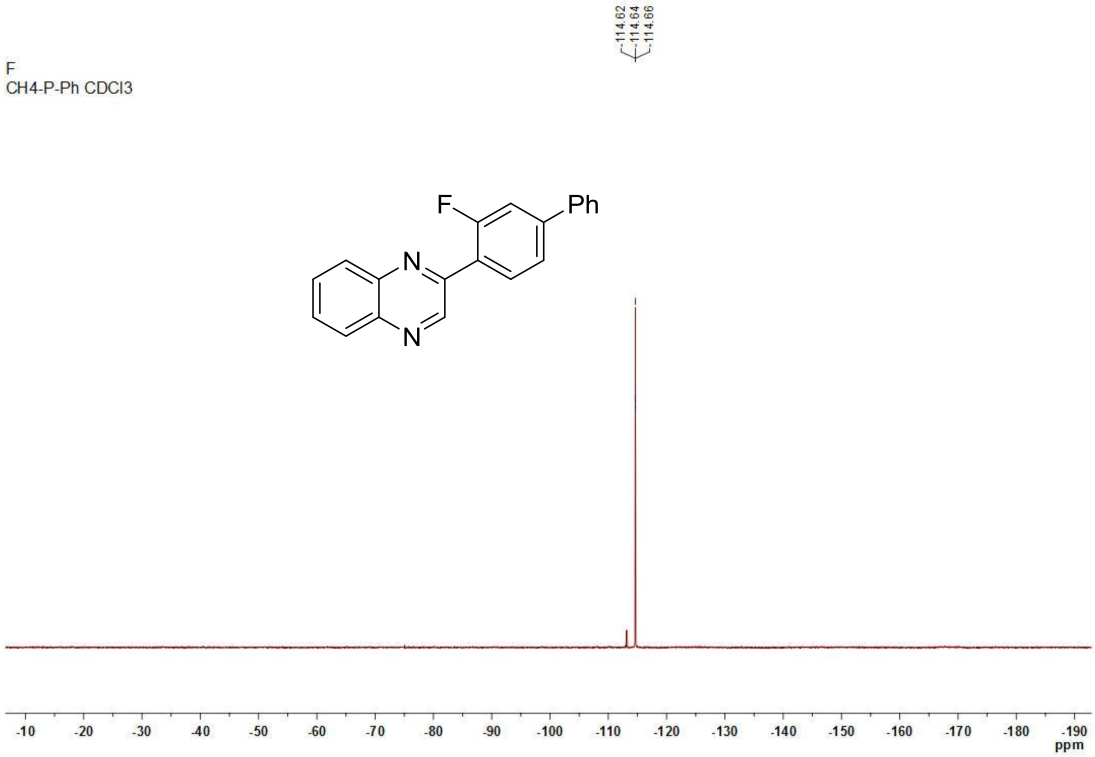
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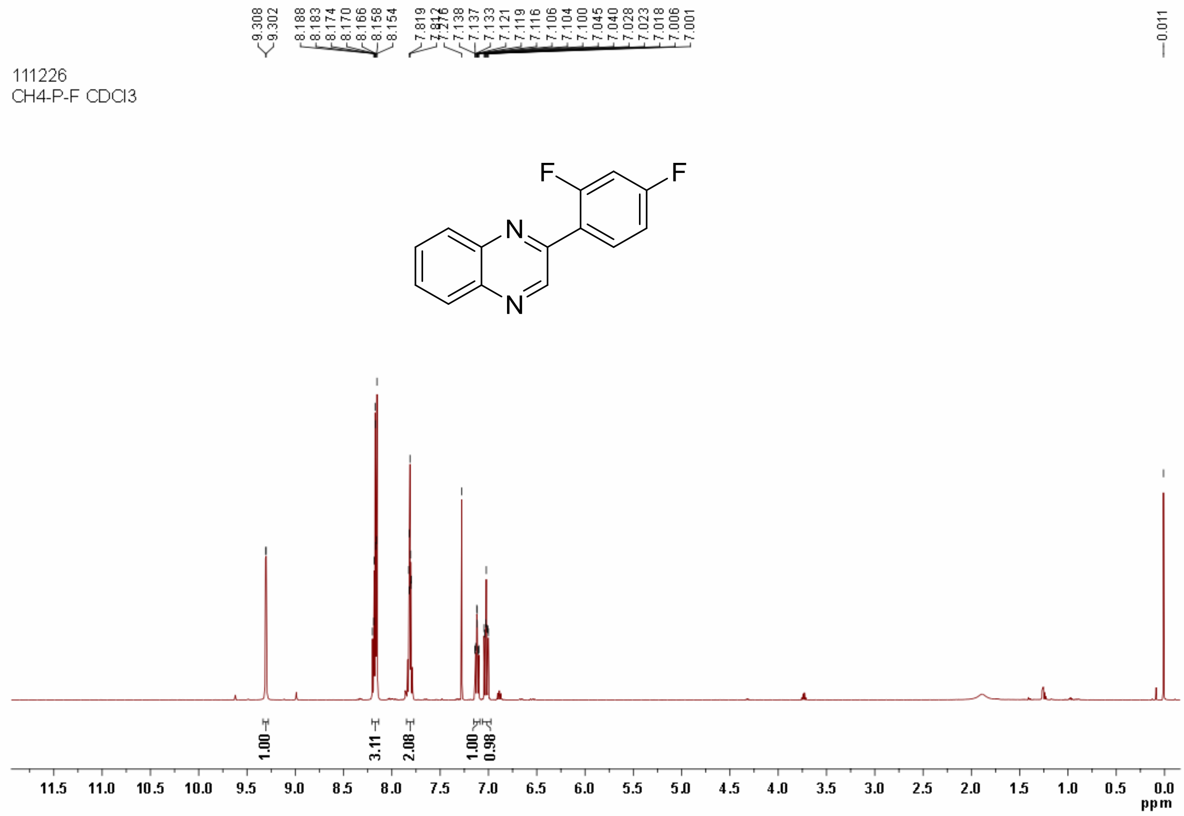
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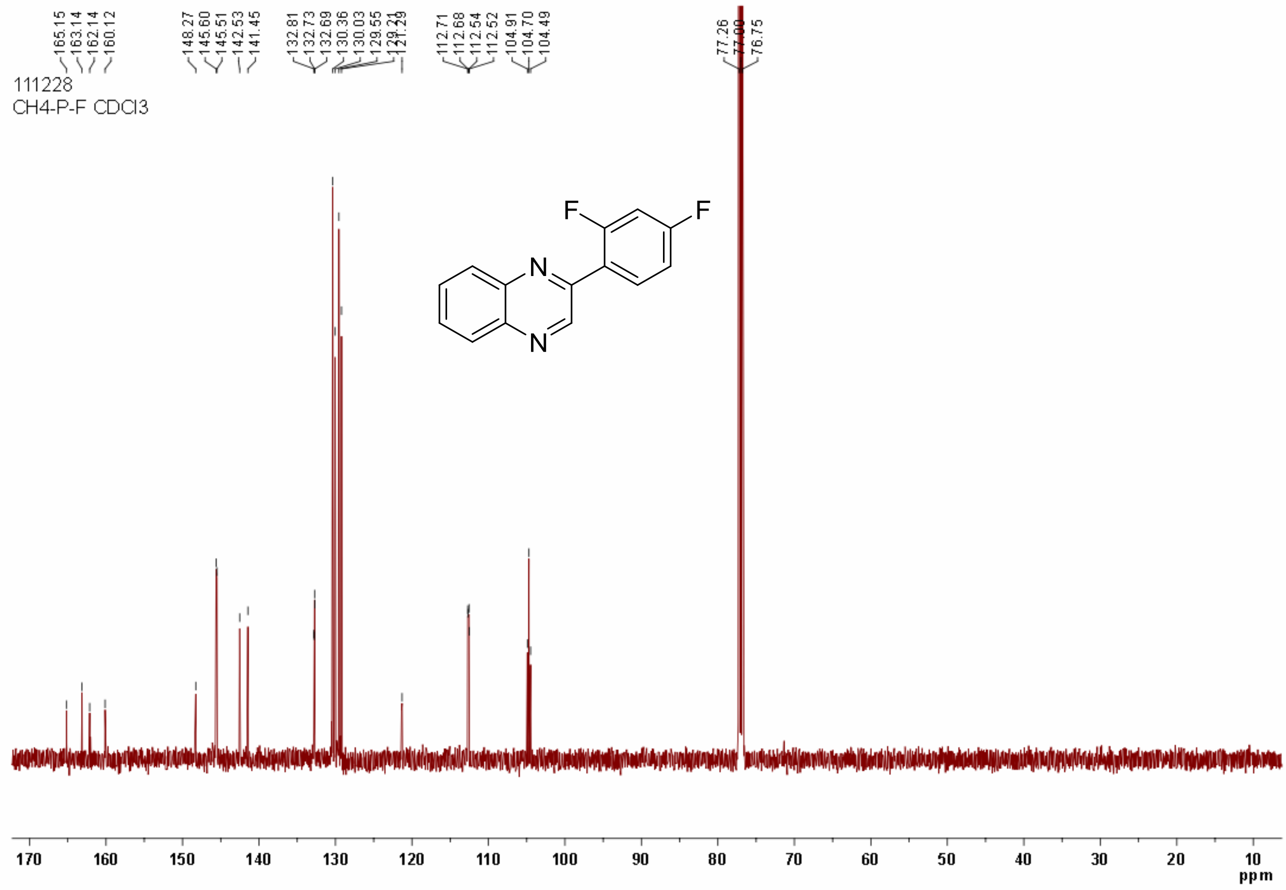
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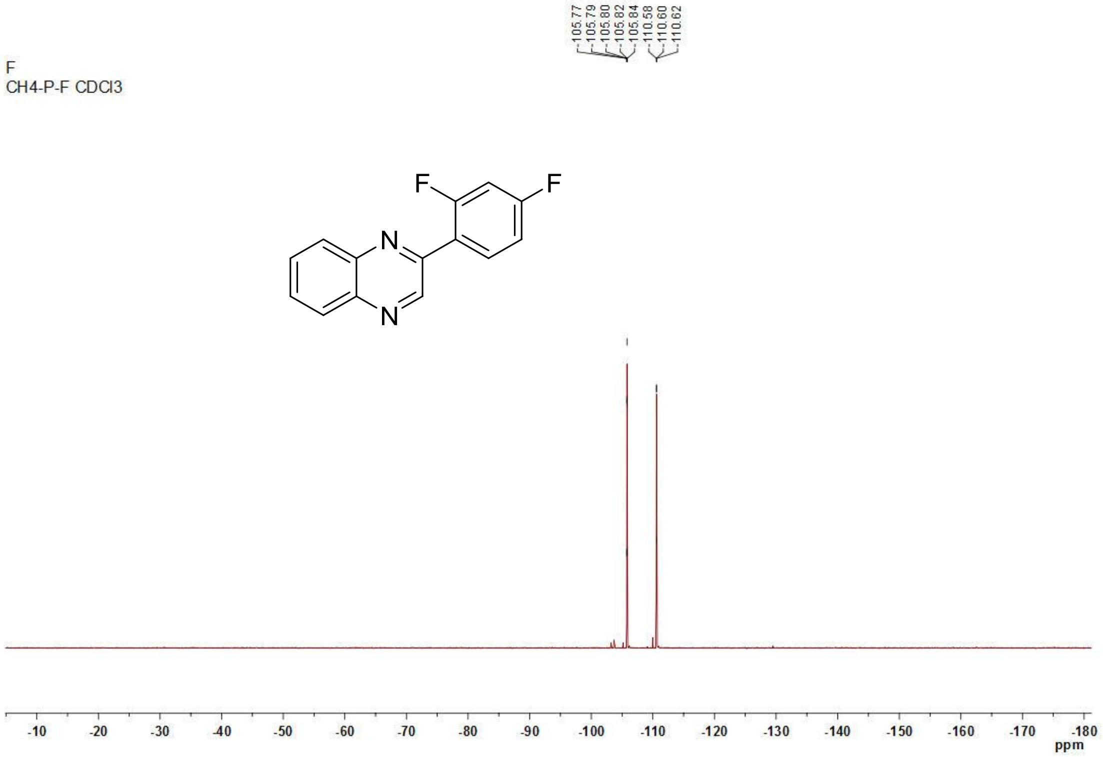
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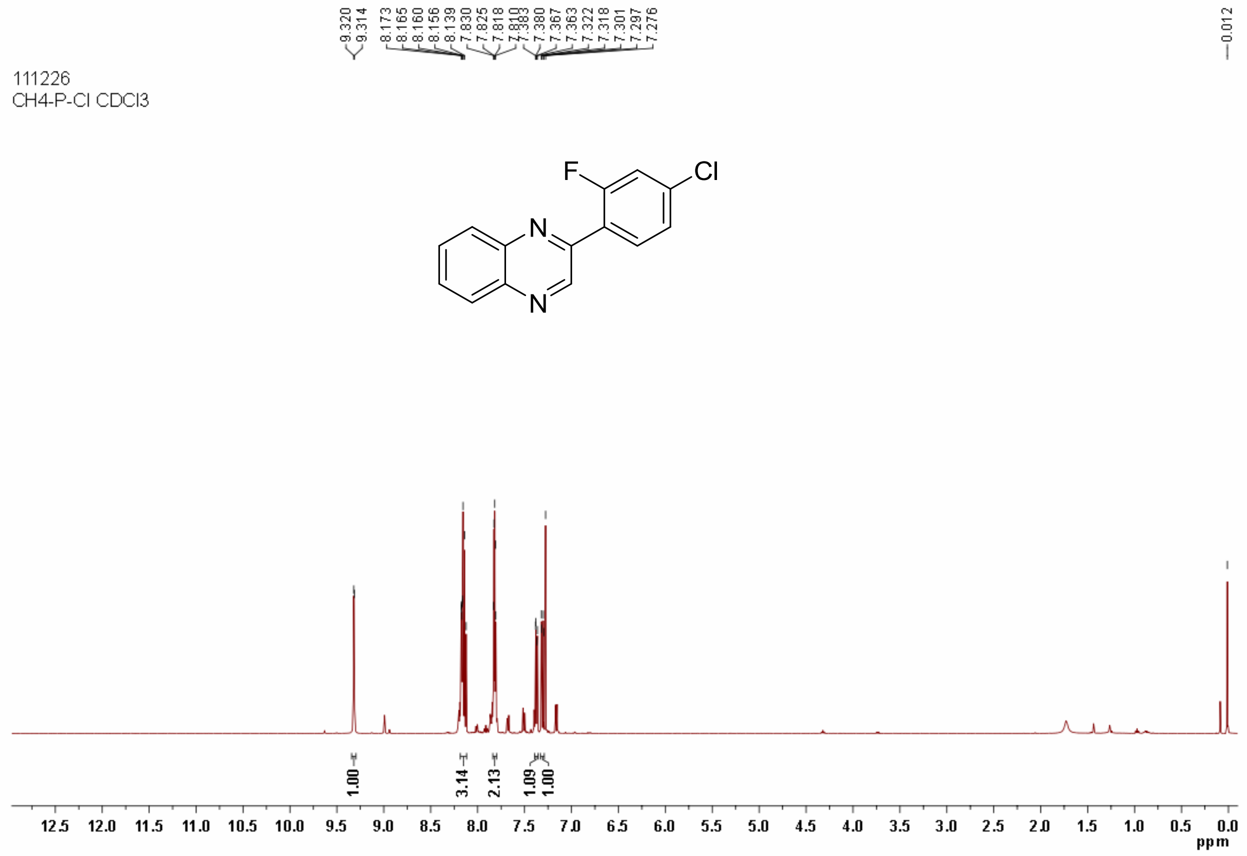
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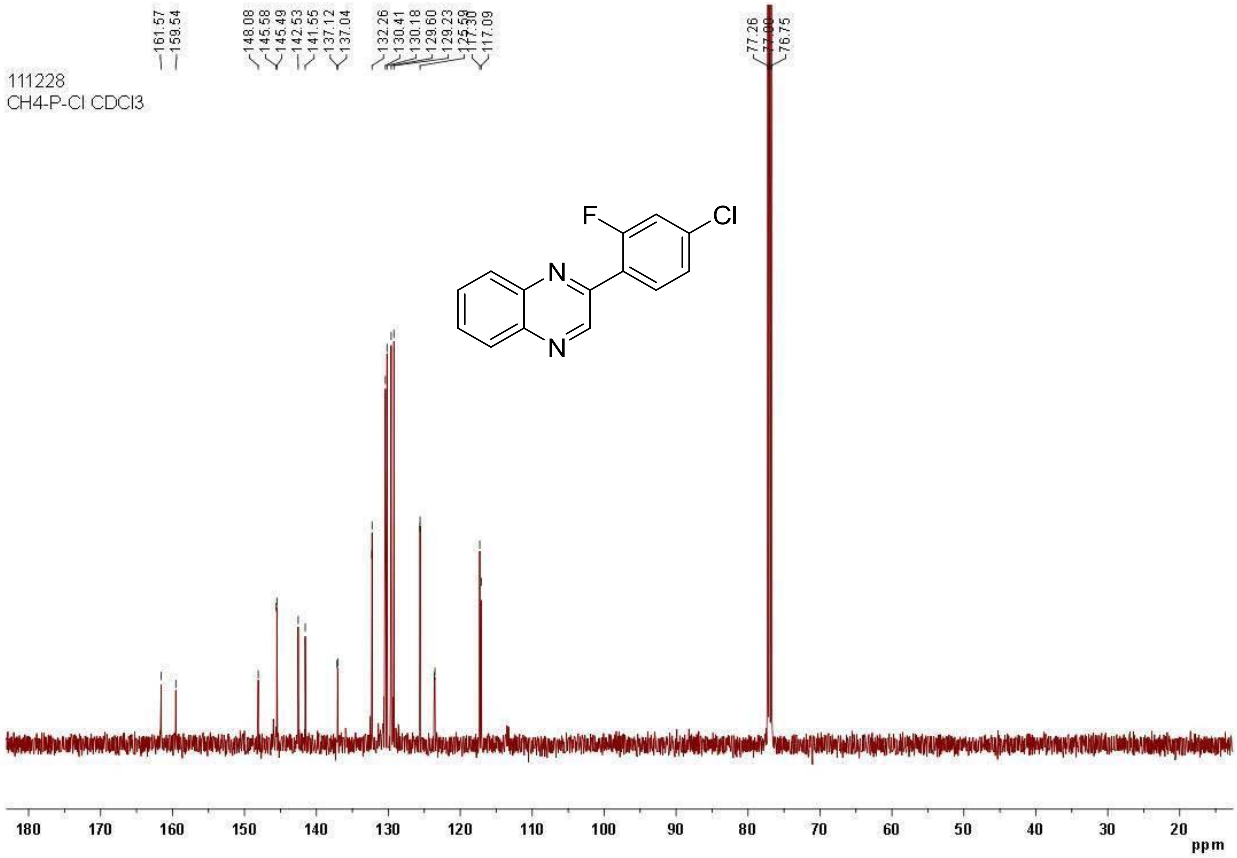
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111228
CH4-P-Cl CDCl3
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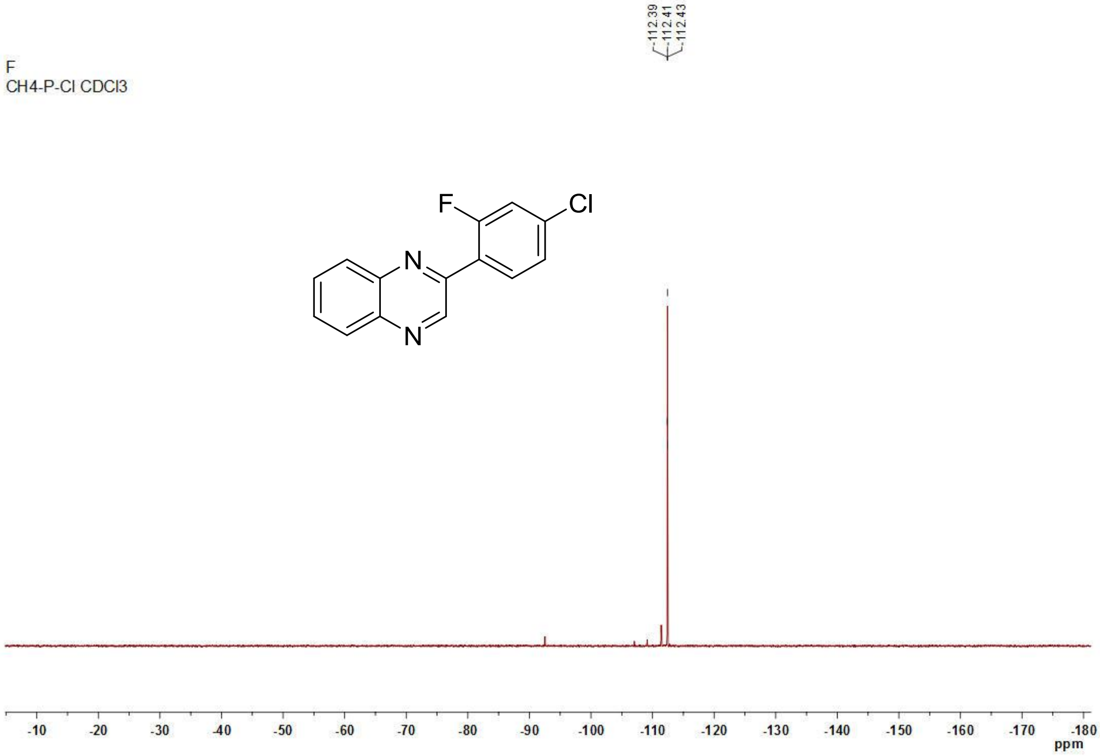
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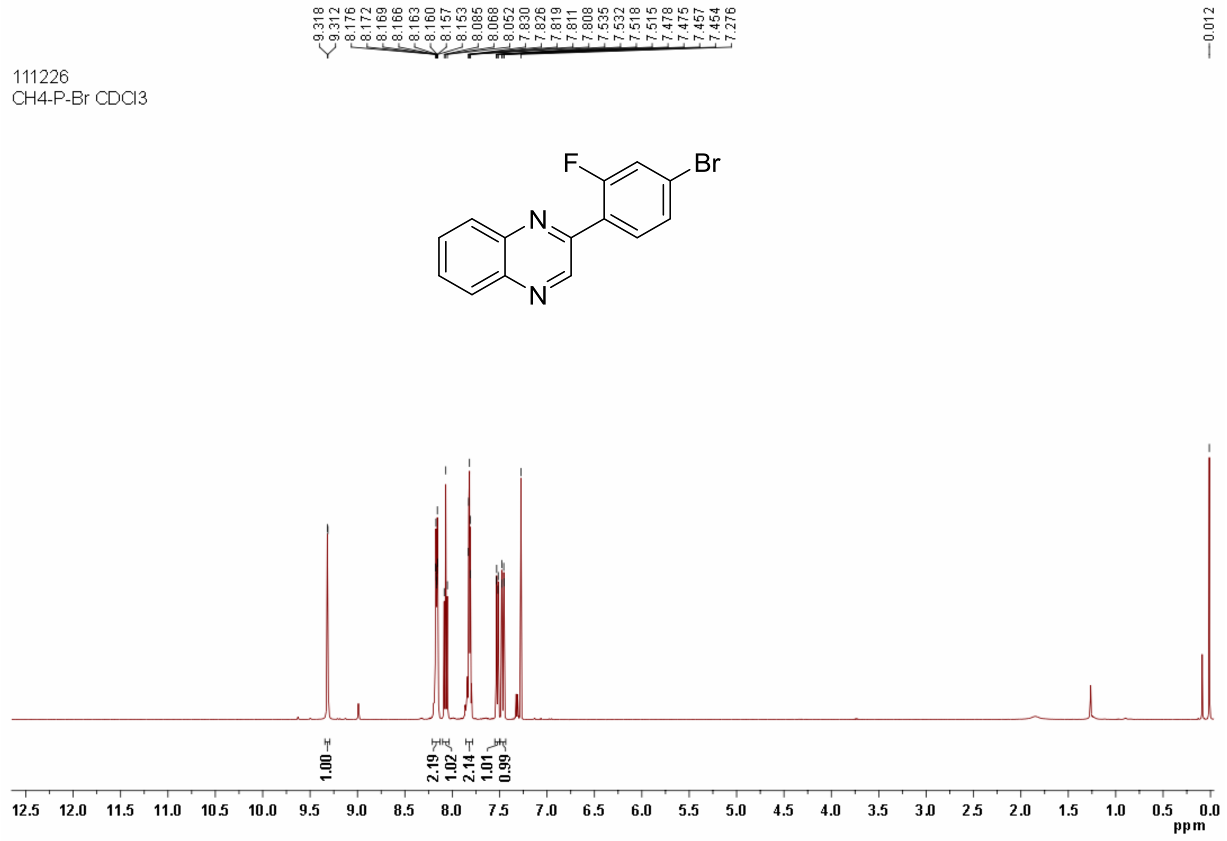
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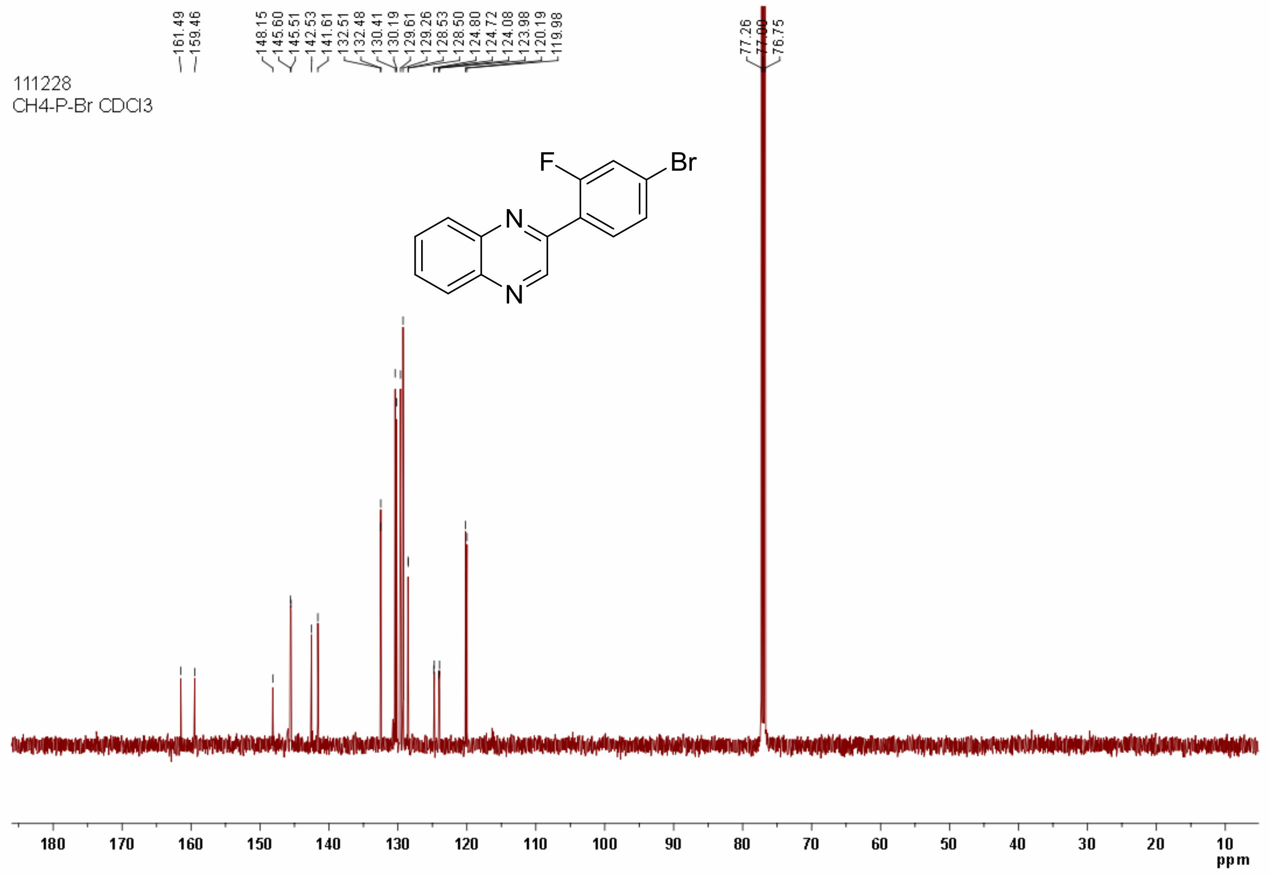
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124.08
123.98
120.19
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77.00
76.75
111228
CH4-P-Br CDCl3
F
Br
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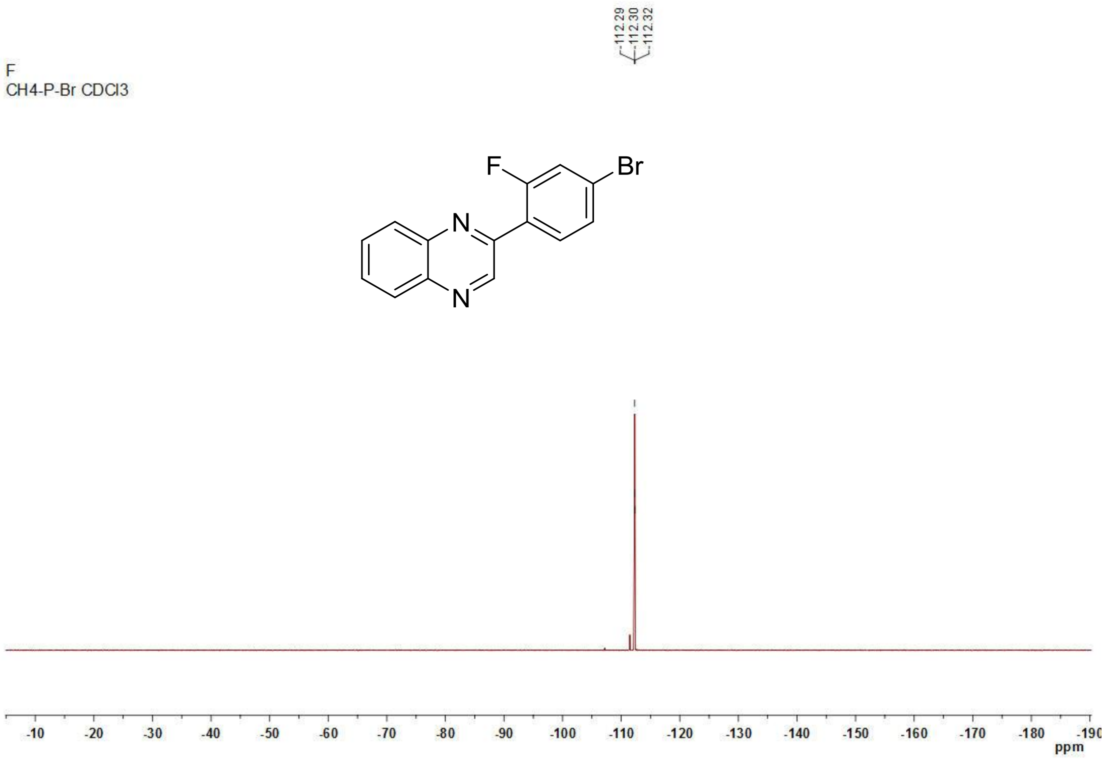
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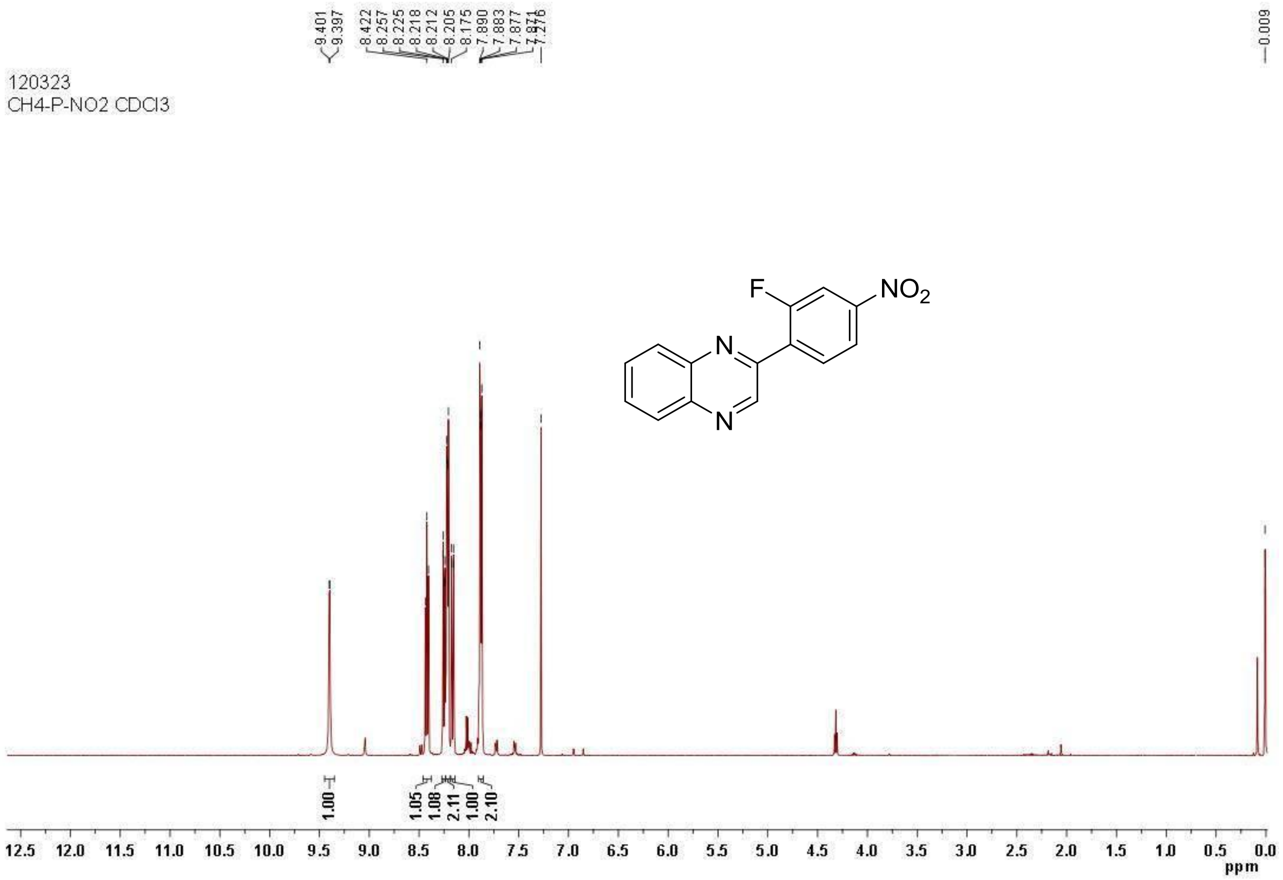
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7.871
7.276
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F
NO2
N
N
1.00
1.05
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2.11
1.00
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12.5
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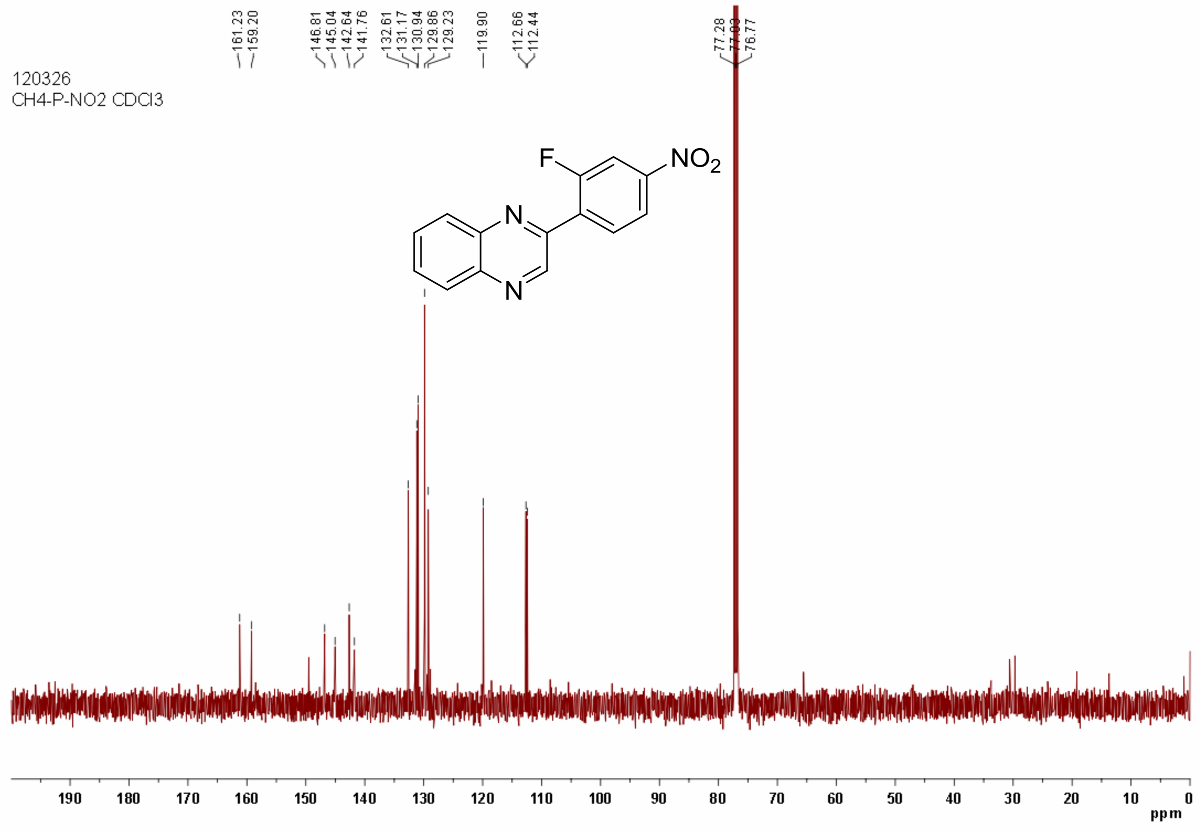
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112.44
77.28
77.03
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N
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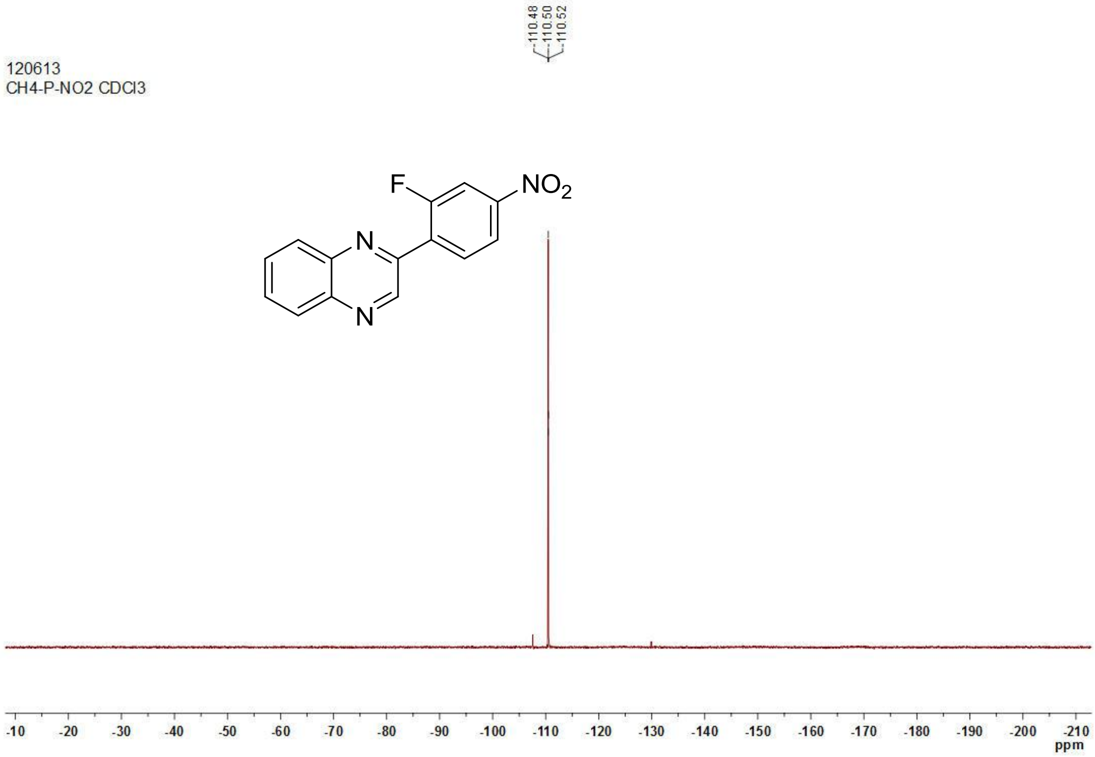
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NO2
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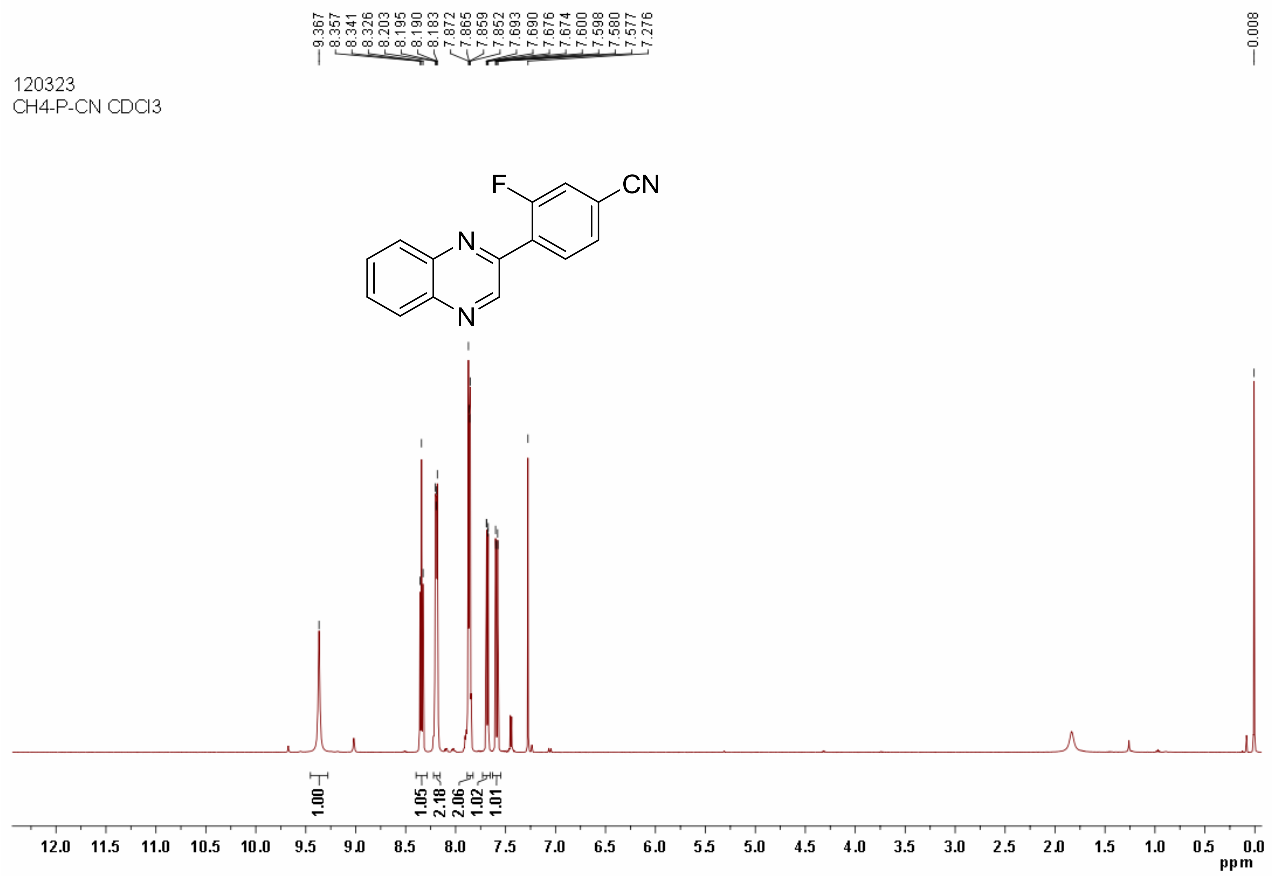
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7.693
7.690
7.676
7.674
7.600
7.598
7.580
7.577
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CN
N
N
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1.05
2.18
2.06
1.02
1.01
12.0
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11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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4.0
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3.0
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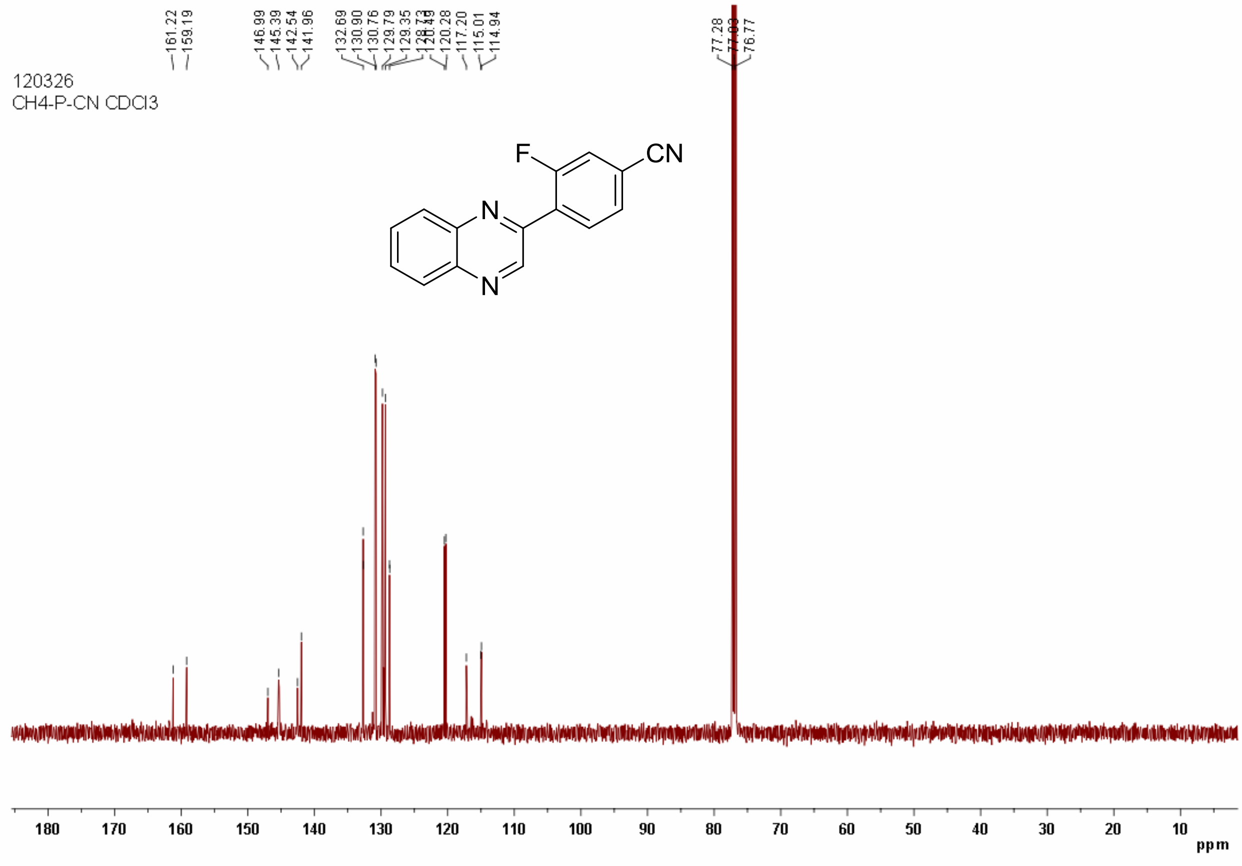
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117.20
115.01
114.94
77.28
77.03
76.77
120326
CH4-P-CN CDCl3
F
CN
N
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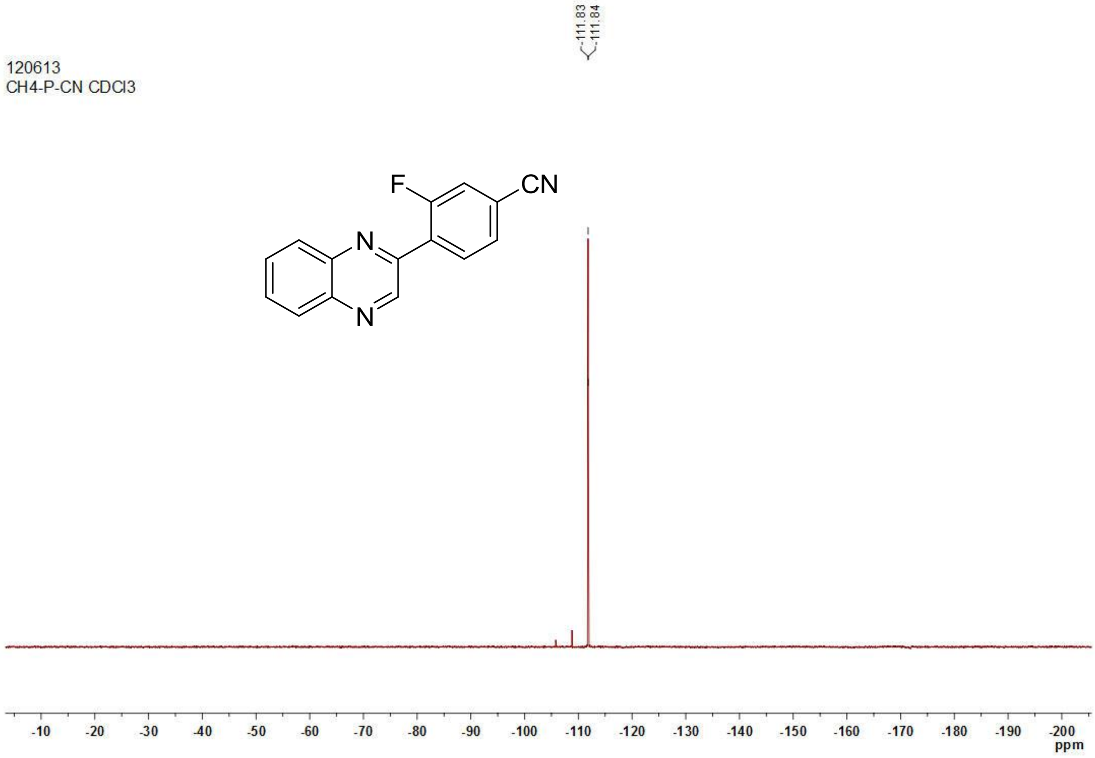
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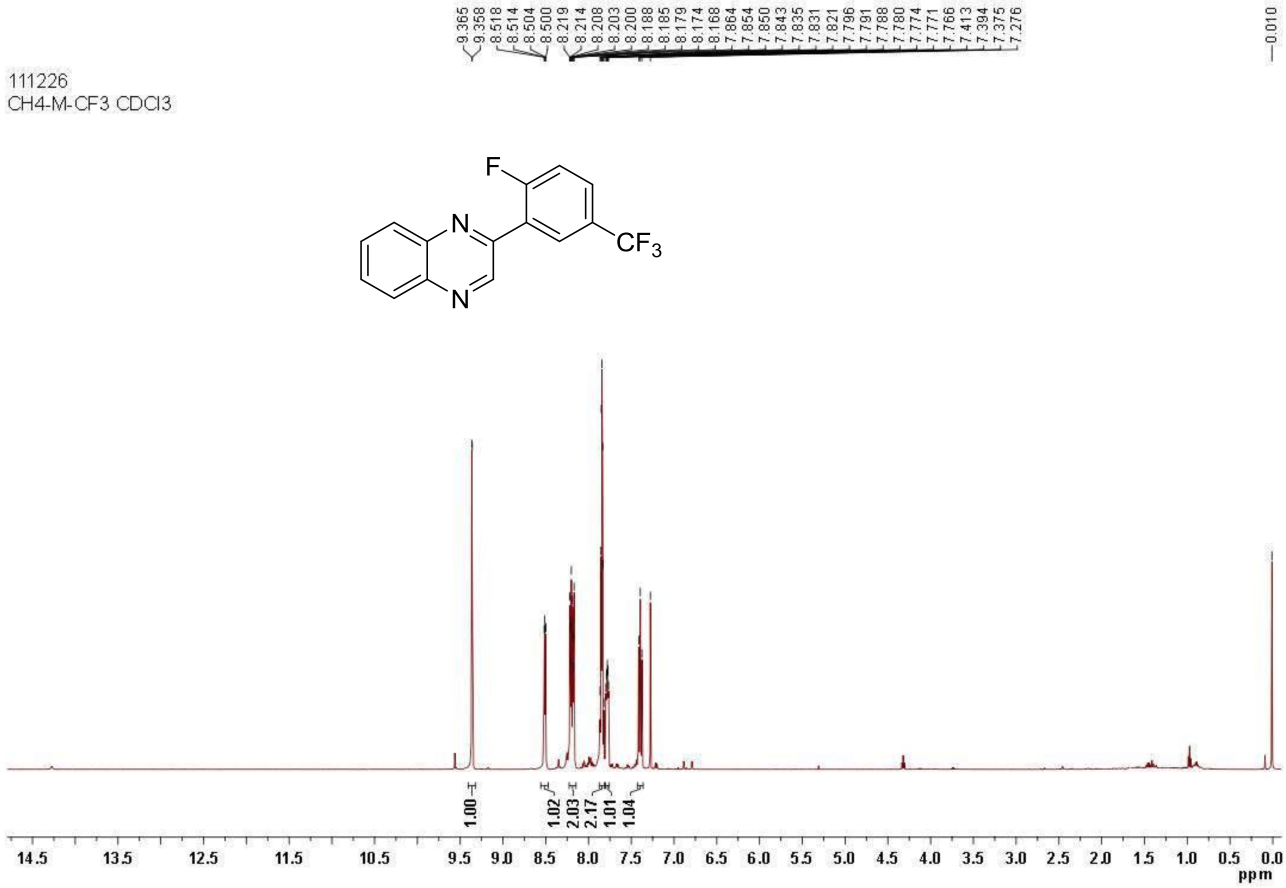
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8.185
8.179
8.174
8.168
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7.854
7.850
7.843
7.835
7.831
7.821
7.796
7.791
7.788
7.780
7.774
7.771
7.766
7.413
7.394
7.375
7.276
-0.010
111226
CH4-M-CF3 CDCl3
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N
N
CF3
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1.02
2.03
2.17
1.01
1.04
14.5
13.5
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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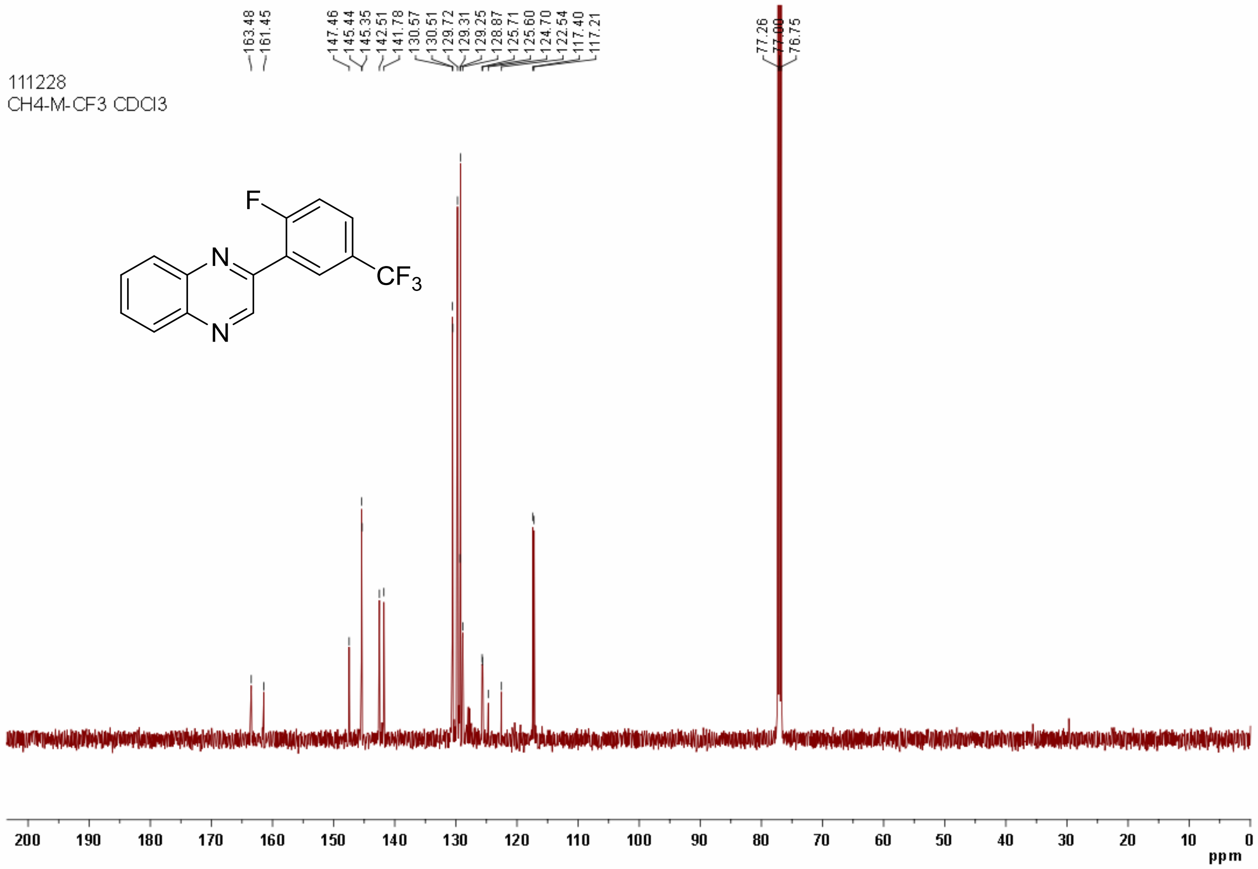
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129.25
128.87
125.71
125.60
124.70
122.54
117.40
117.21
77.26
77.00
76.75
111228
CH4-M-CF3 CDCl3
F
N
N
CF3
200
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140
130
120
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20
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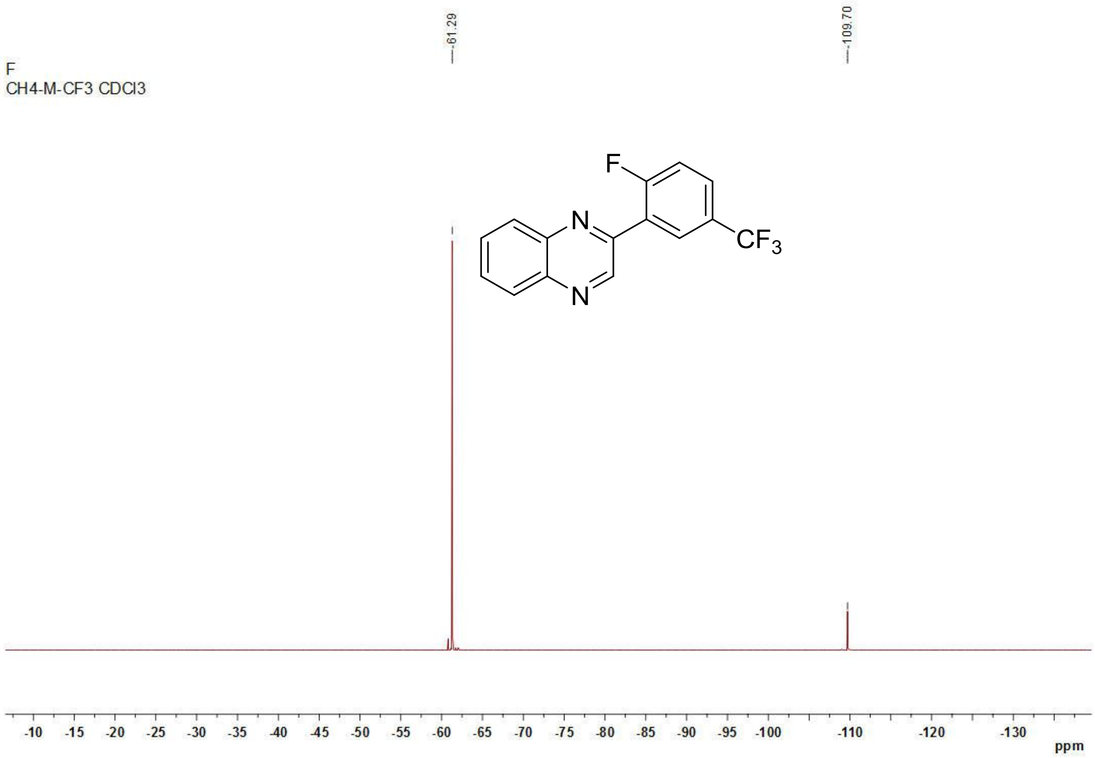
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N
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-40
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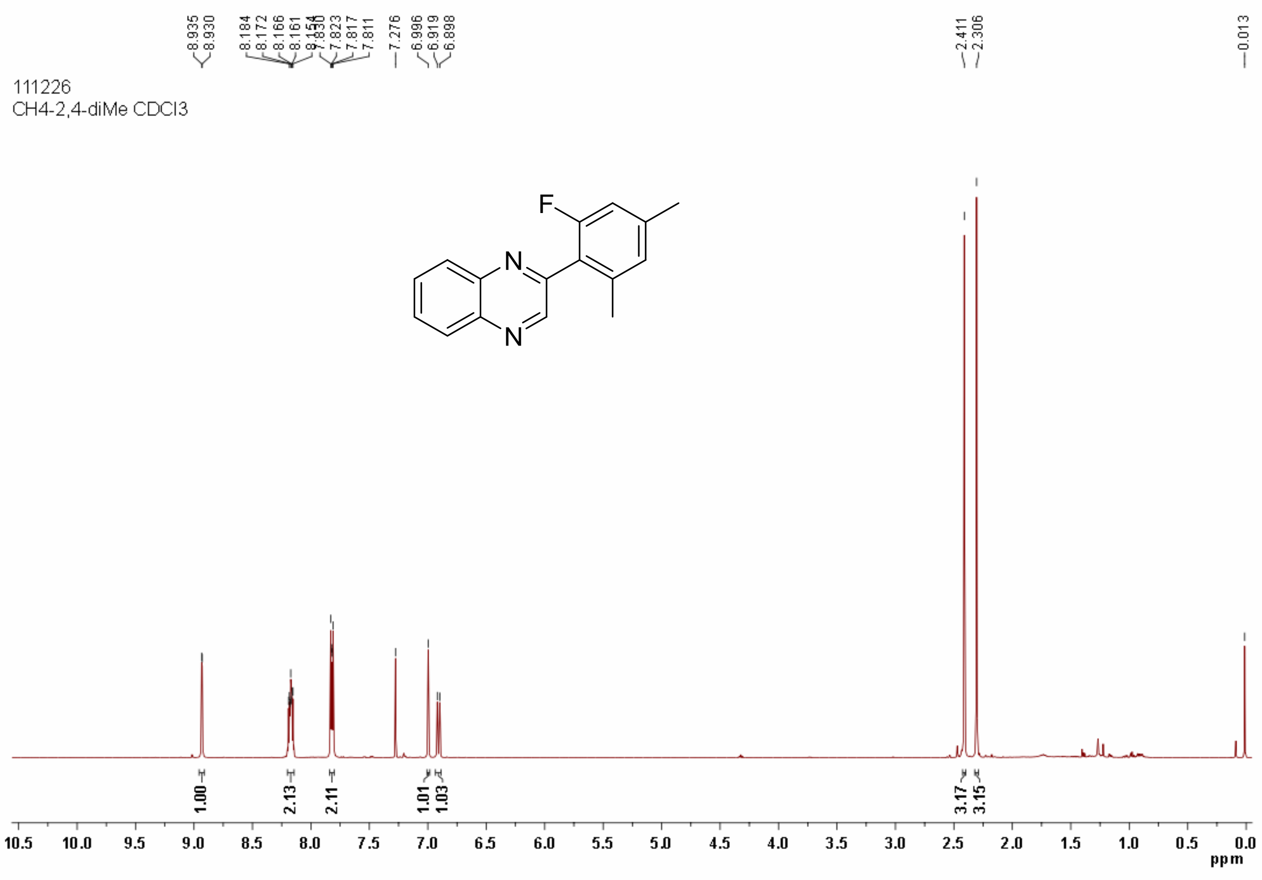
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8.161
8.154
7.830
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7.817
7.811
7.276
6.996
6.919
6.898
2.411
2.306
-0.013
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CH4-2,4-diMe CDCl3
F
N
N
1.00
2.13
2.11
1.01
1.03
3.17
3.15
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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4.0
3.5
3.0
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1.5
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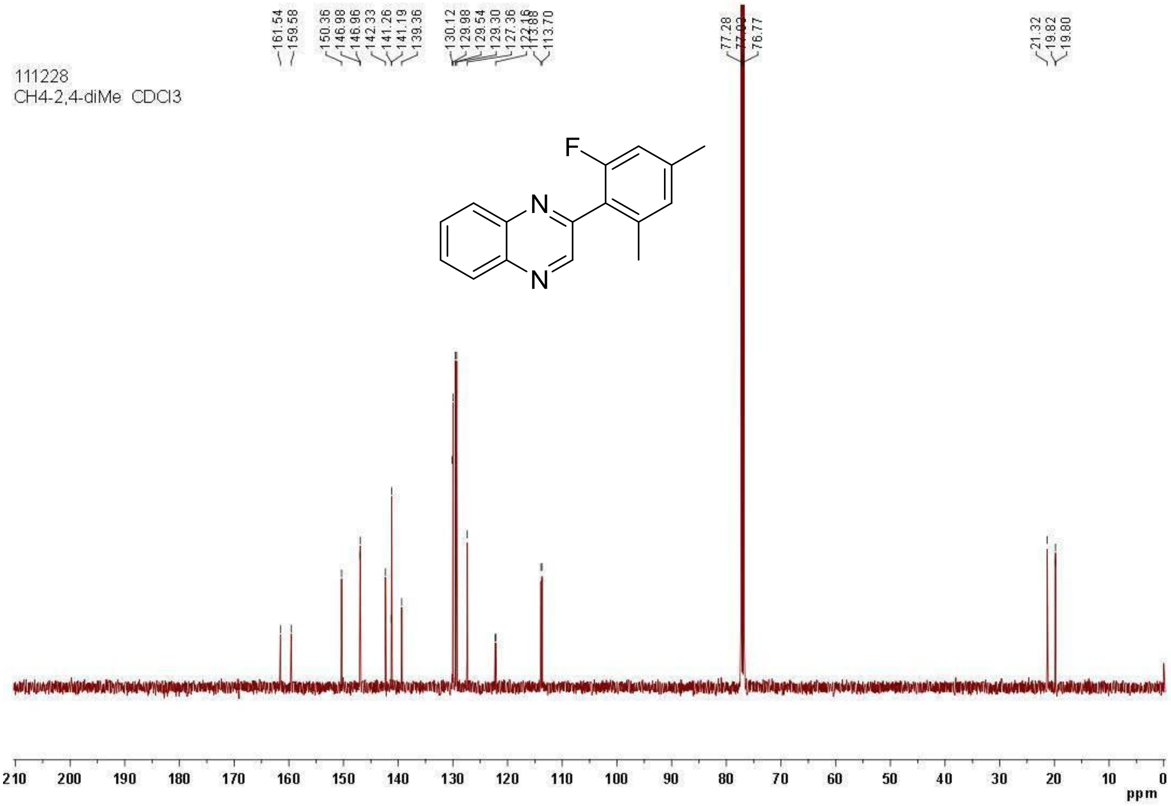
0.5
0.0
ppm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127.36
122.16
113.88
113.70
77.28
77.02
76.77
21.32
19.82
19.80
111228
CH4-2,4-diMe CDCl3
F
N
N
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200
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140
130
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100
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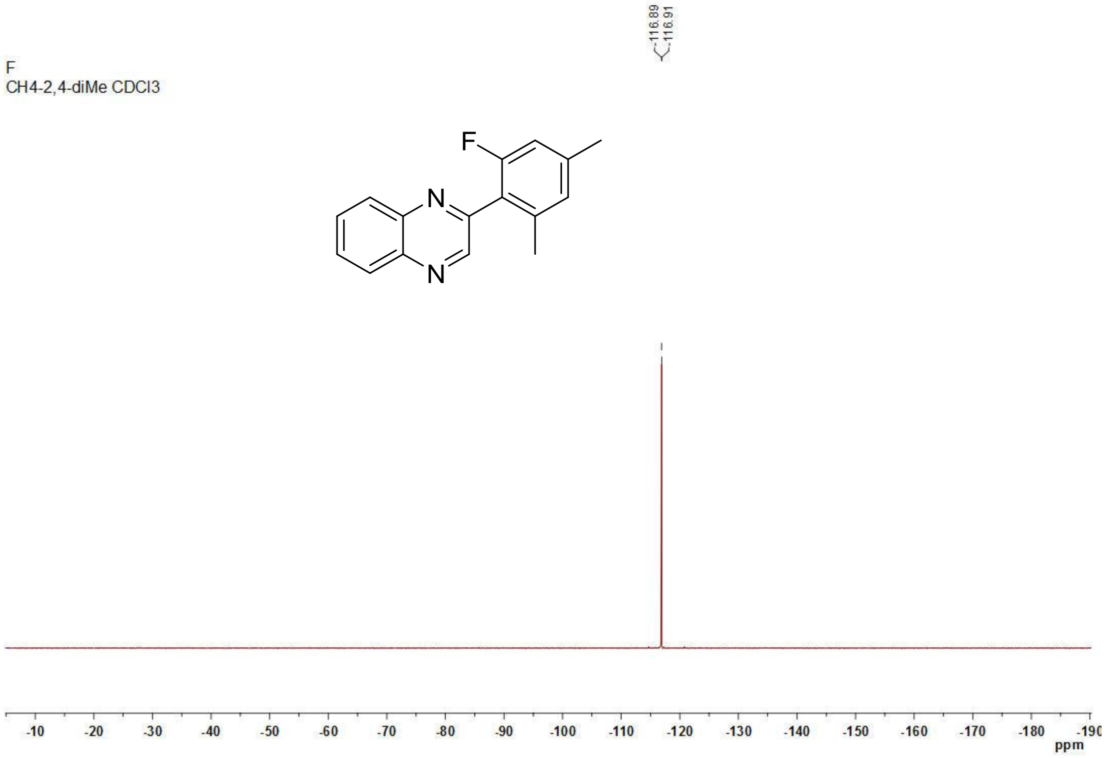
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N
-10
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-30
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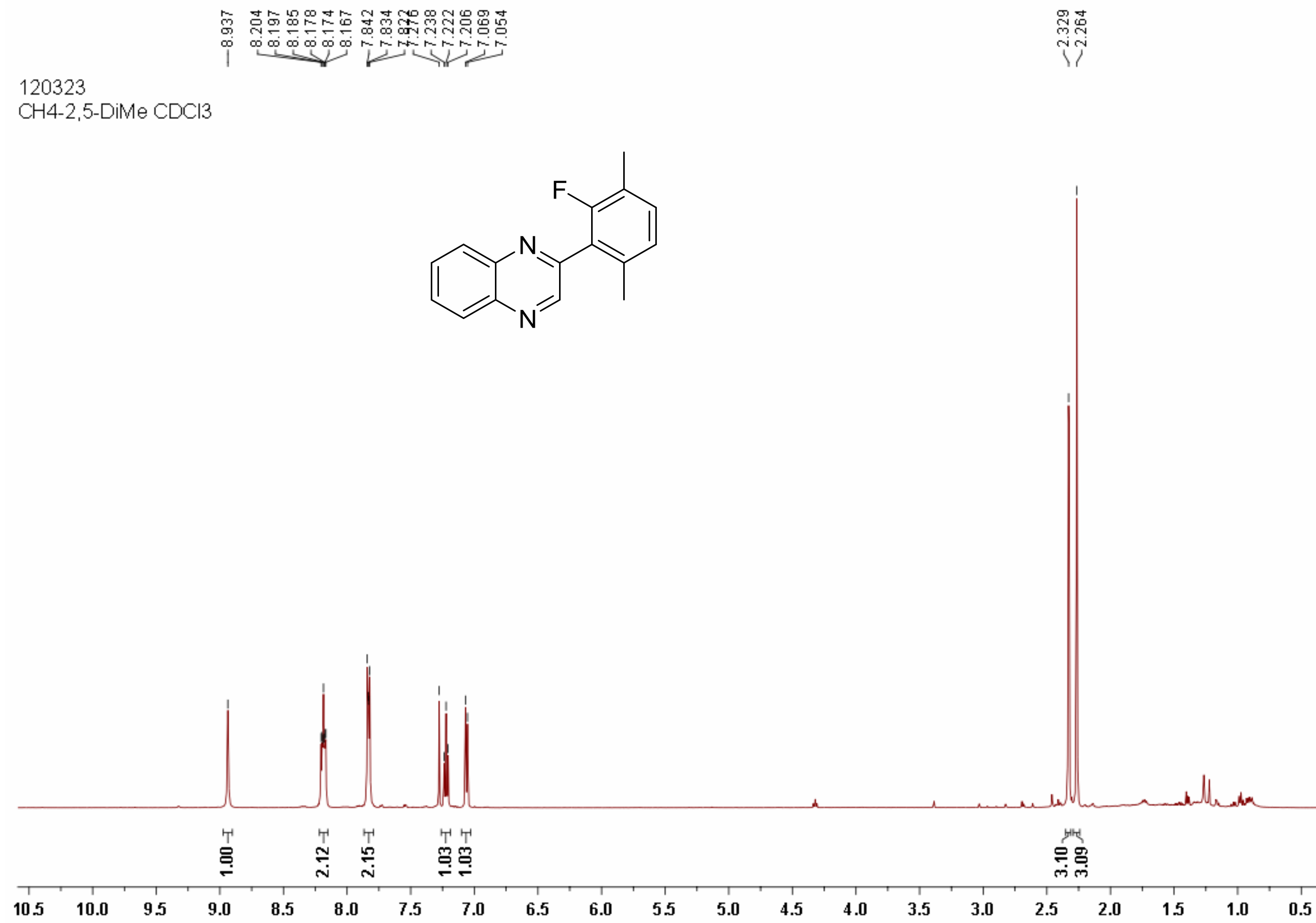
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7.822
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7.222
7.206
7.069
7.054
2.329
2.264
120323
CH4-2,5-DiMe CDCl3
F
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2.12
2.15
1.03
1.03
3.10
3.09
10.5
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8.0
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7.0
6.5
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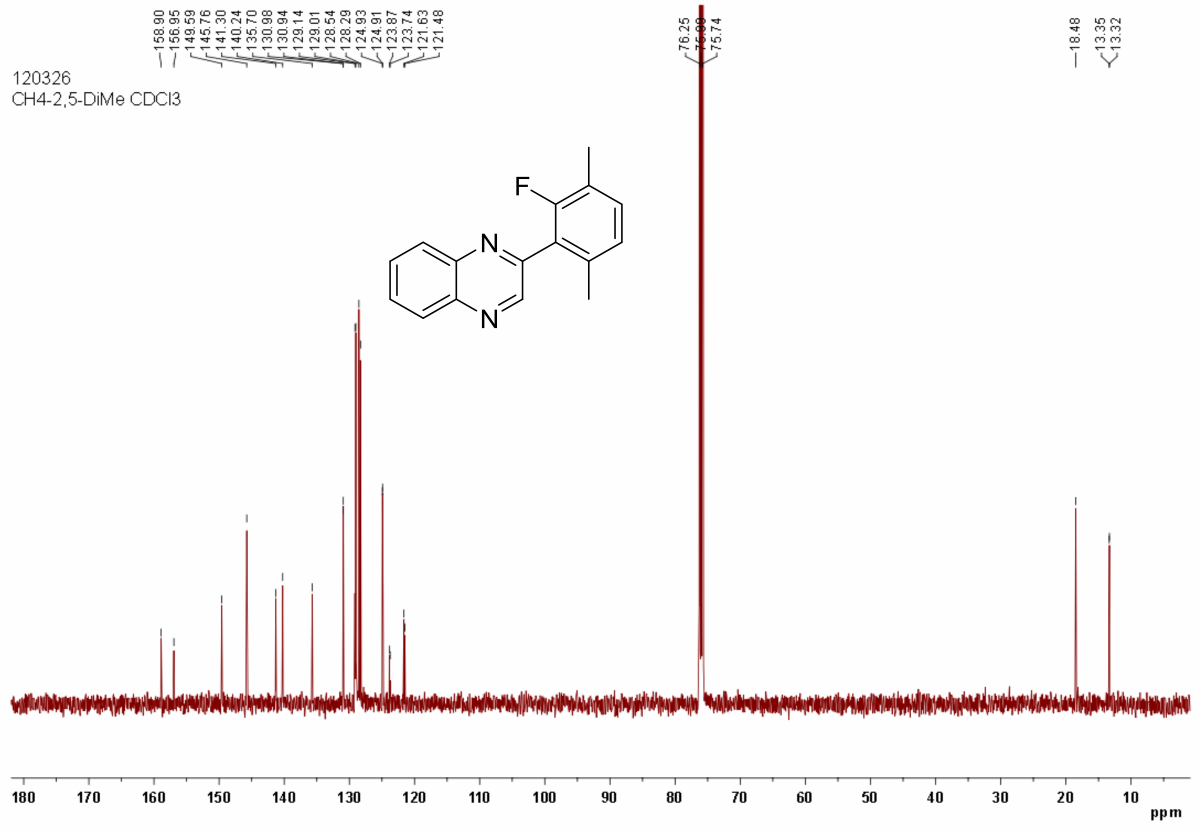
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124.91
123.87
123.74
121.63
121.48
76.25
75.99
75.74
18.48
13.35
13.32
120326
CH4-2,5-DiMe CDCl3
F
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150
140
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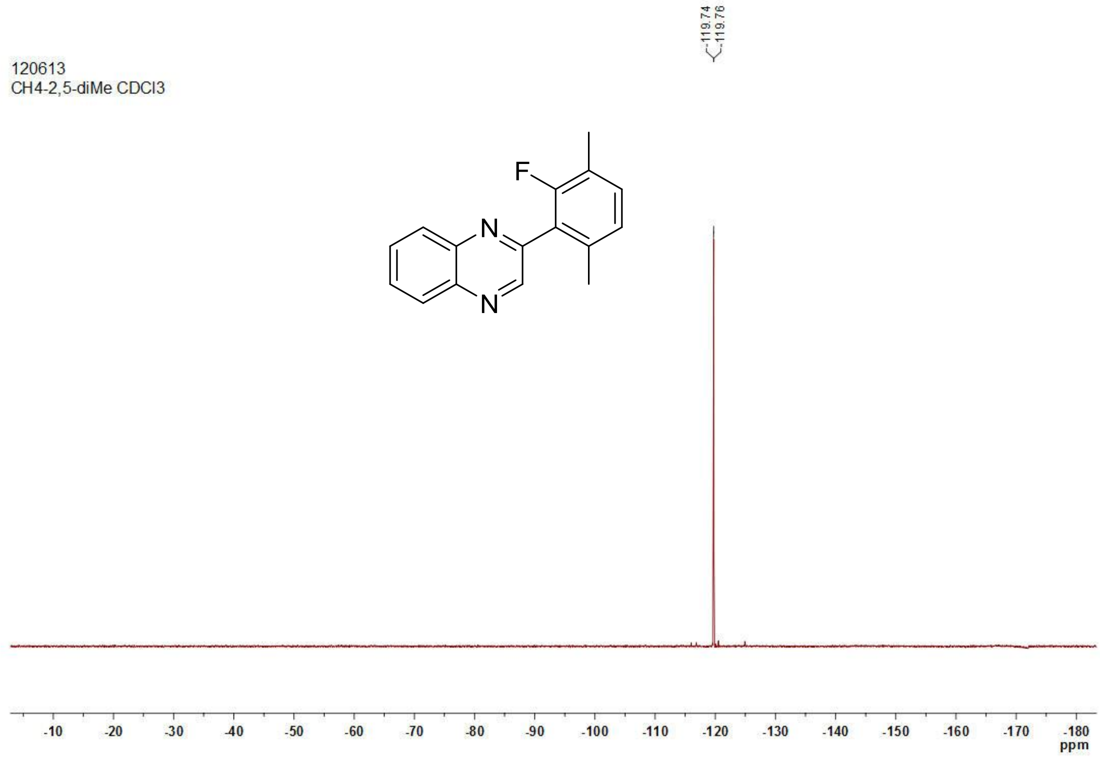
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N
N
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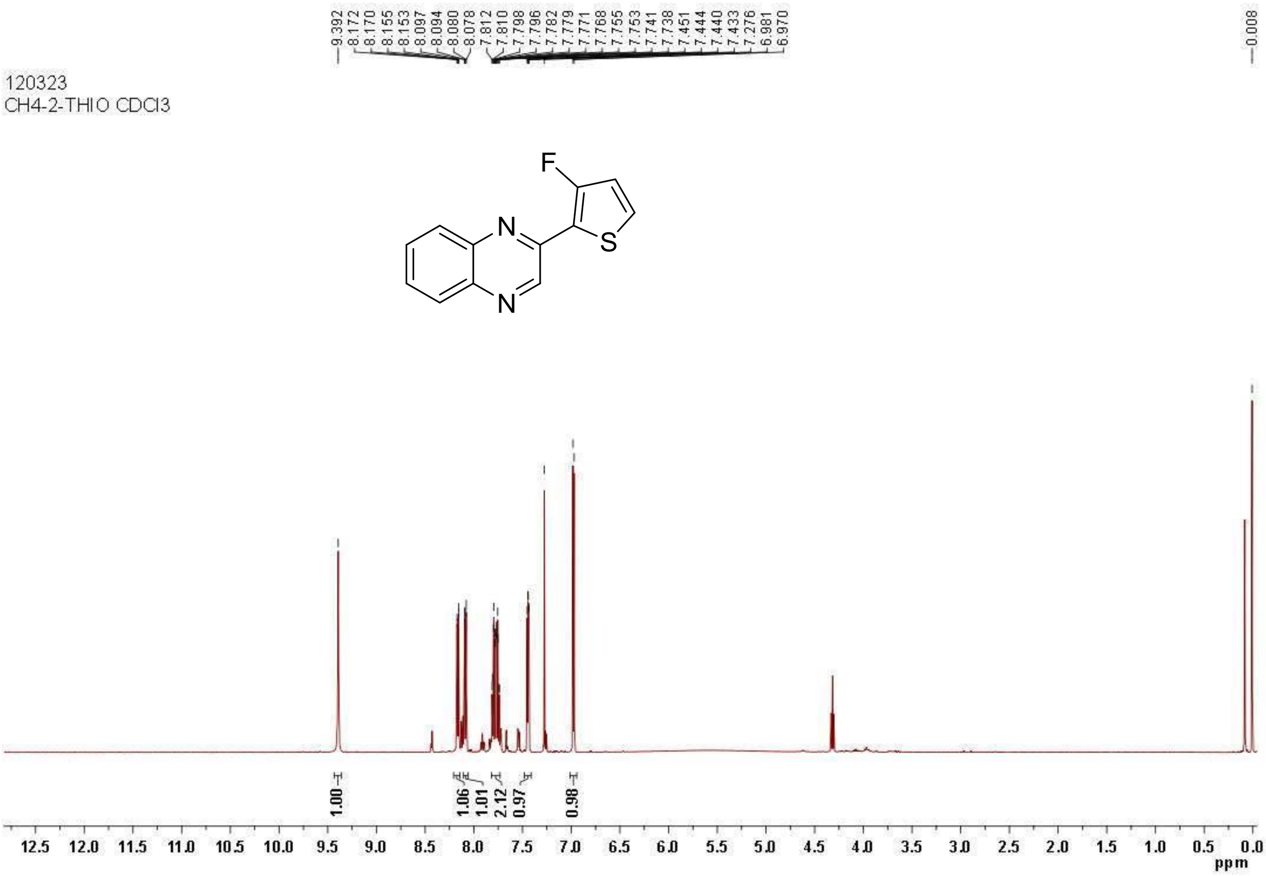
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7.782
7.779
7.771
7.768
7.755
7.753
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7.440
7.433
7.276
6.981
6.970
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CH4-2-THIO CDCl3
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N
N
S
1.00
1.06
1.01
2.12
0.97
0.98
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
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8.0
7.5
7.0
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6.0
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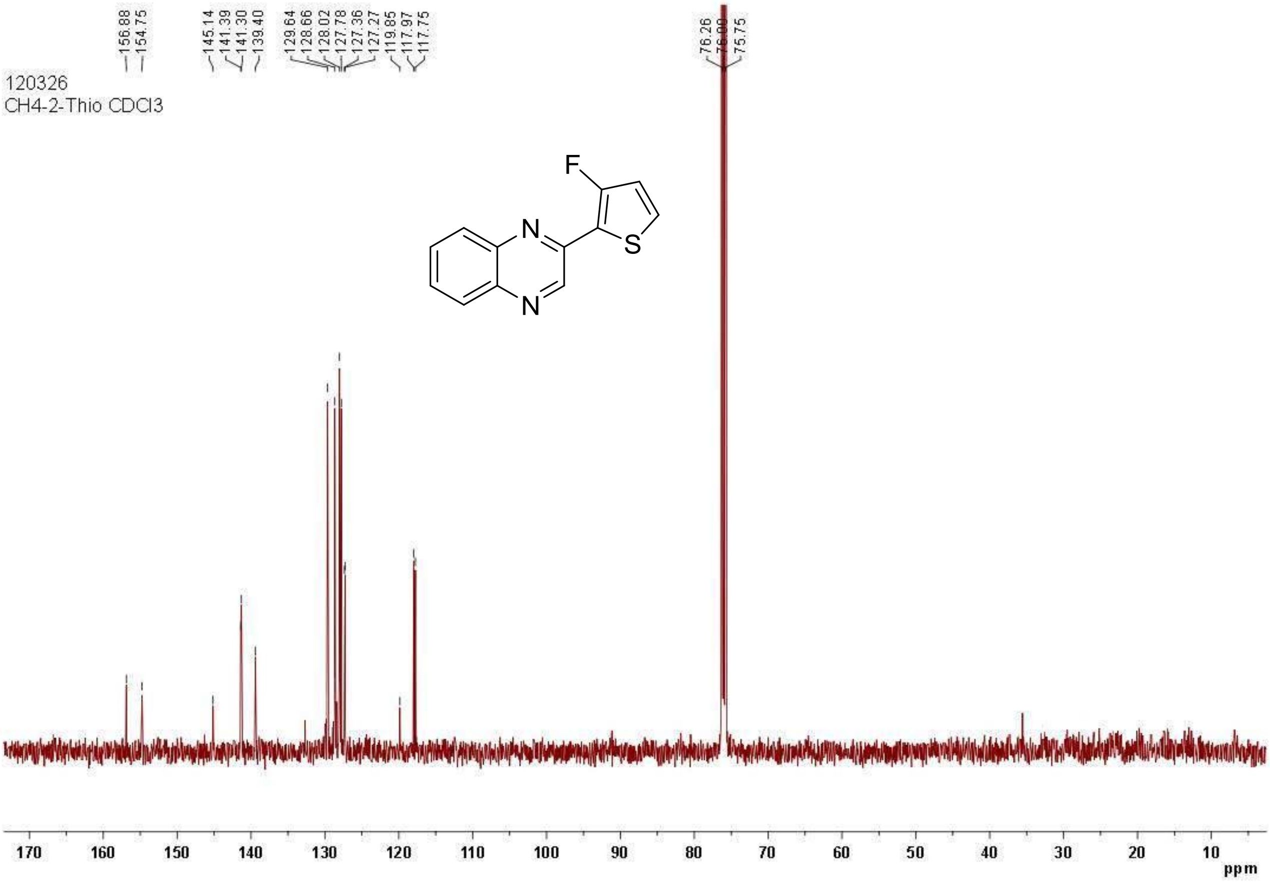
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117.97
117.75
76.26
76.00
75.75
120326
CH4-2-Thio CDCl3
F
N
N
S
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150
140
130
120
110
100
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70
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10
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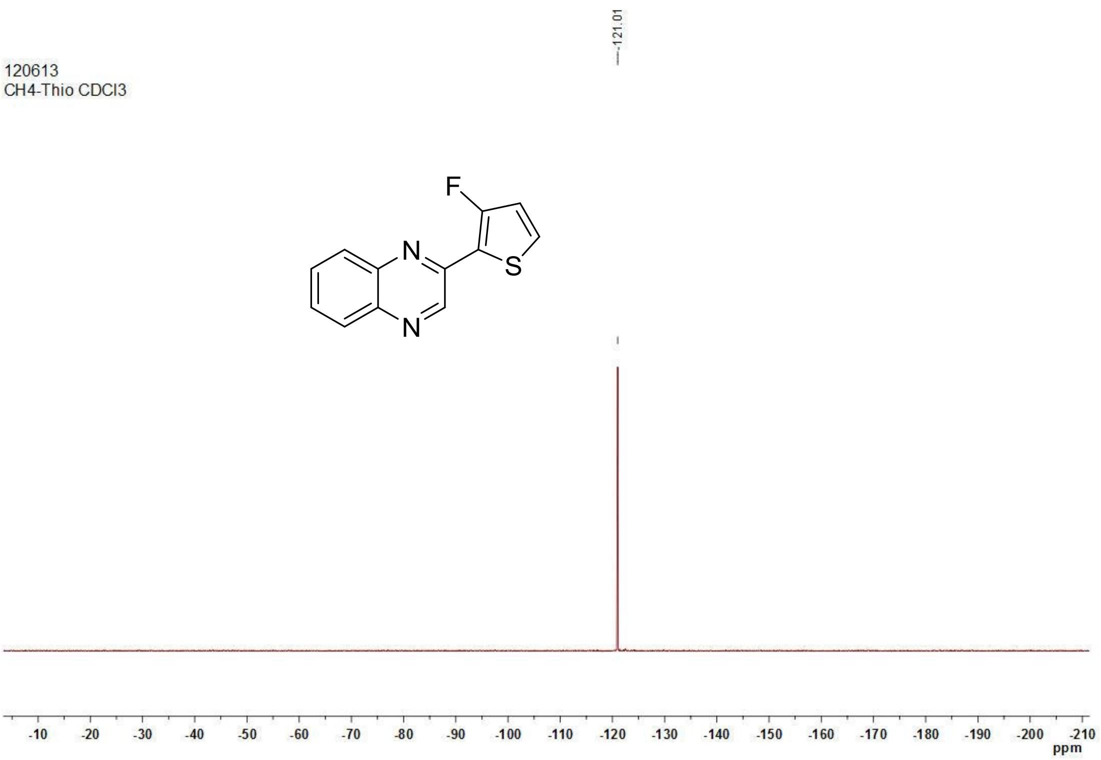
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S
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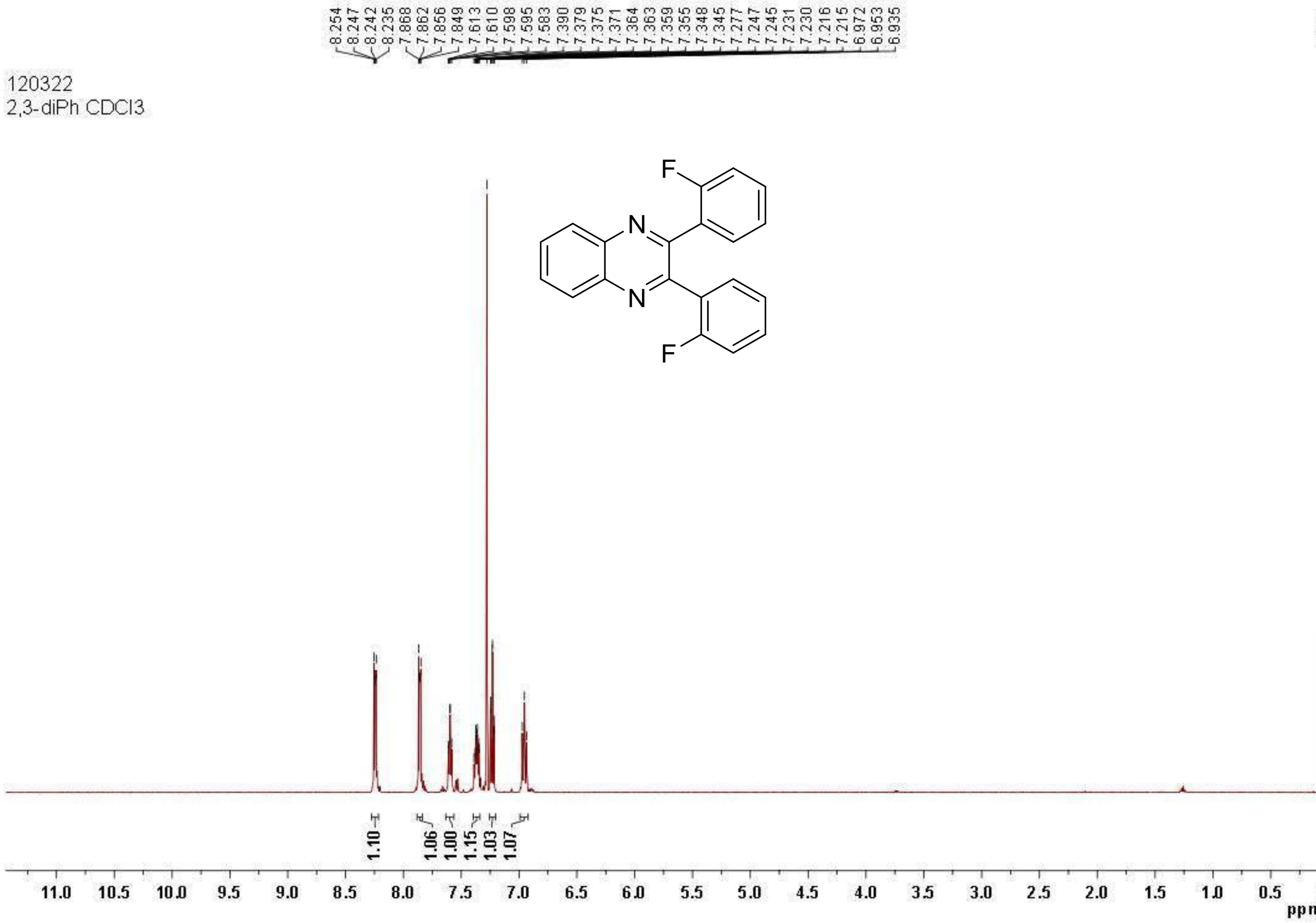
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7.610
7.598
7.595
7.583
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7.379
7.375
7.371
7.364
7.363
7.359
7.355
7.348
7.345
7.277
7.247
7.245
7.231
7.230
7.216
7.215
6.972
6.953
6.935
120322
2,3-diPh CDCl3
F
N
N
F
1.10
1.06
1.00
1.15
1.03
1.07
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
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1.0
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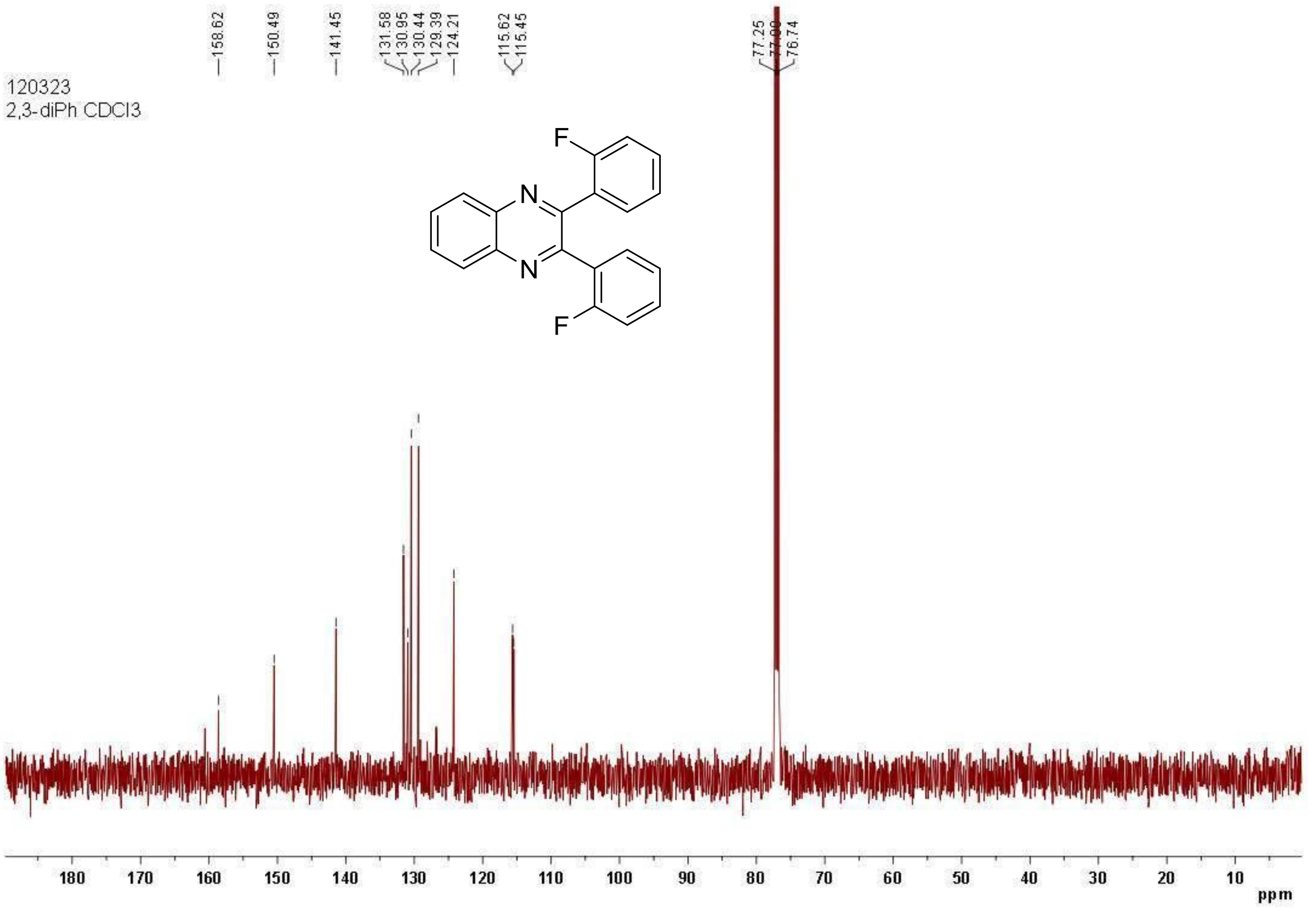
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124.21
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115.45
77.25
77.00
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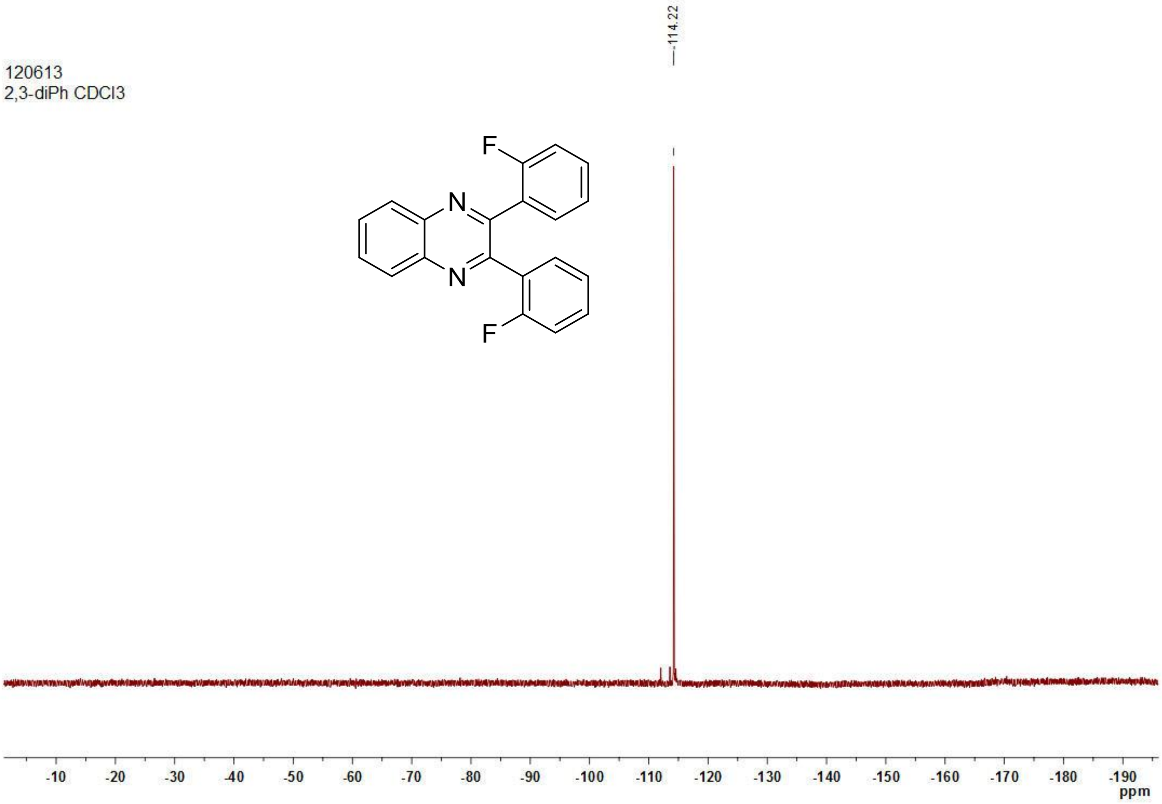
10
ppm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N
N
F
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-120
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-150
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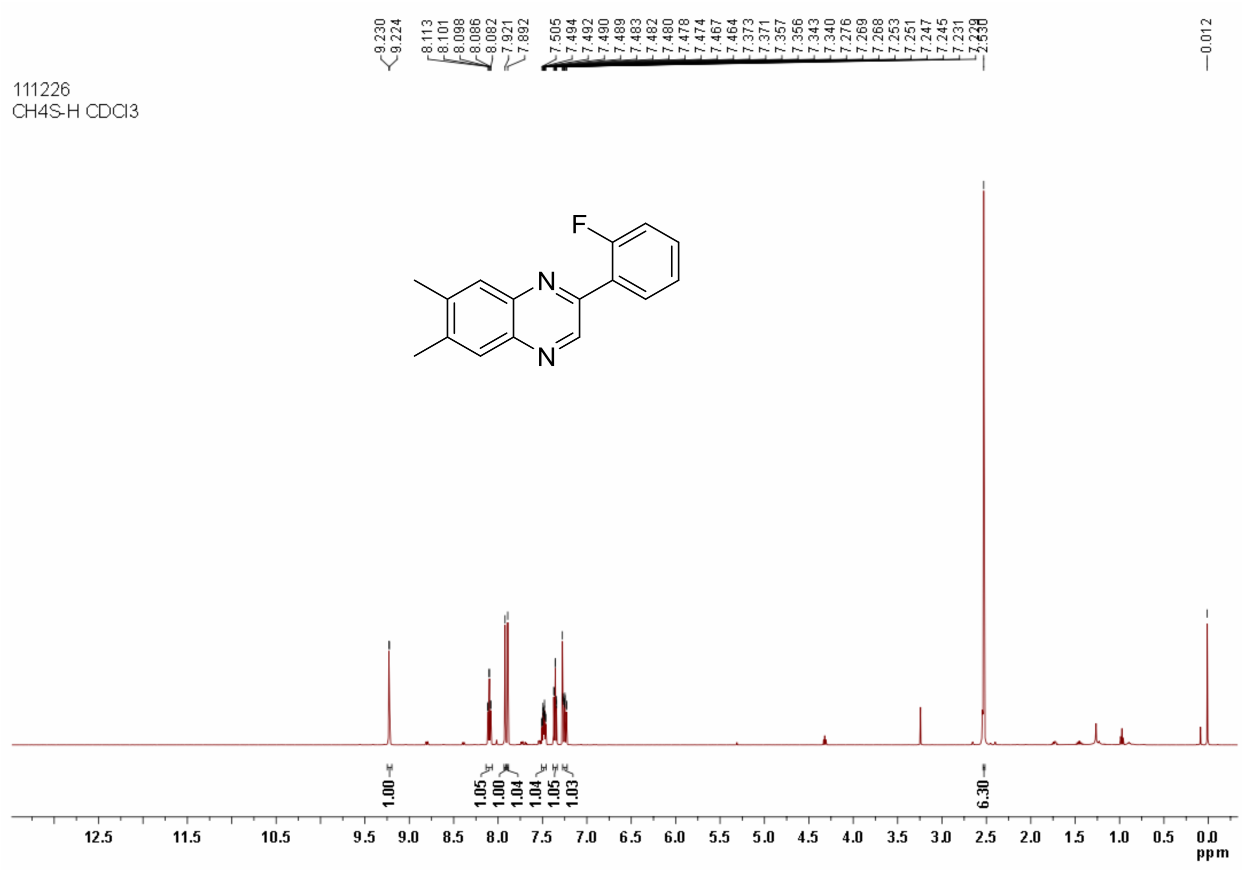
ppm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7.480
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7.474
7.467
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7.371
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7.343
7.340
7.276
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7.268
7.253
7.251
7.247
7.245
7.231
7.229
2.530
-0.012
111226
CH4S-H CDCl3
F
N
N
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1.05
1.00
1.04
1.04
1.05
1.03
6.30
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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4.0
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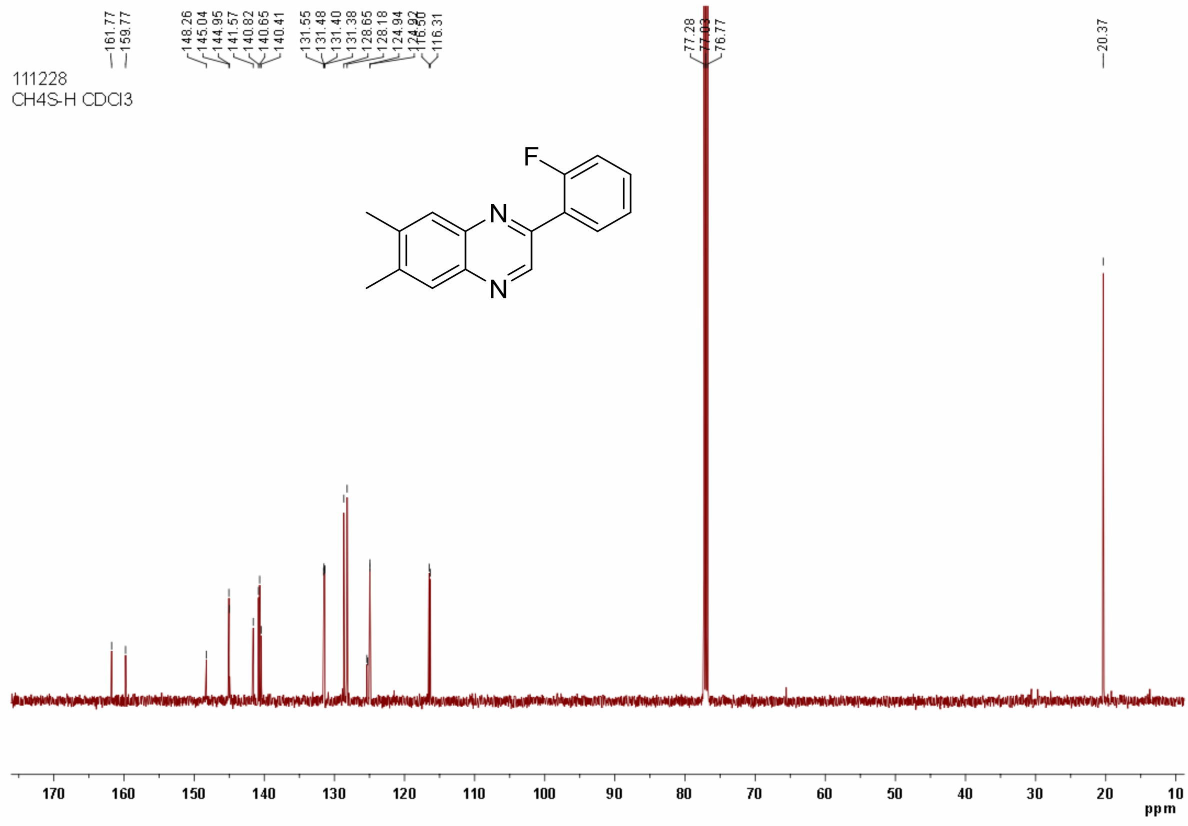
0.5
0.0
ppm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128.18
124.94
124.92
116.50
116.31
77.28
77.03
76.77
20.37
111228
CH4S-H CDCl3
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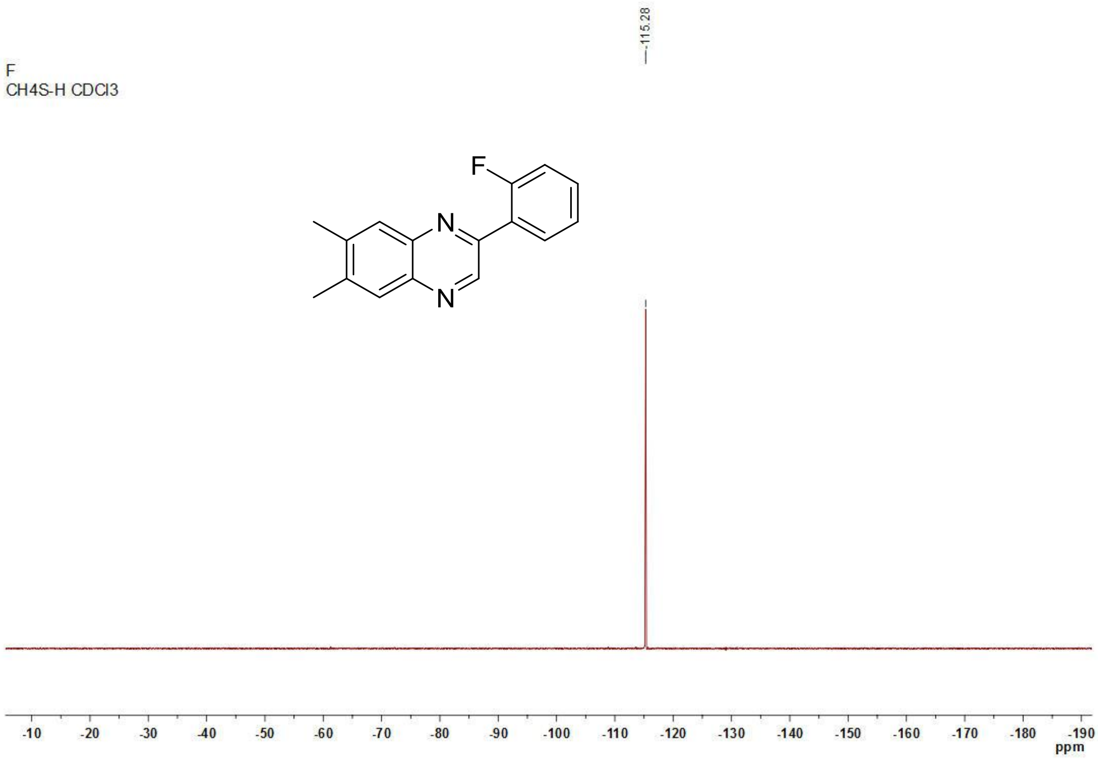
10
ppm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-120
-130
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-150
-160
-170
-180
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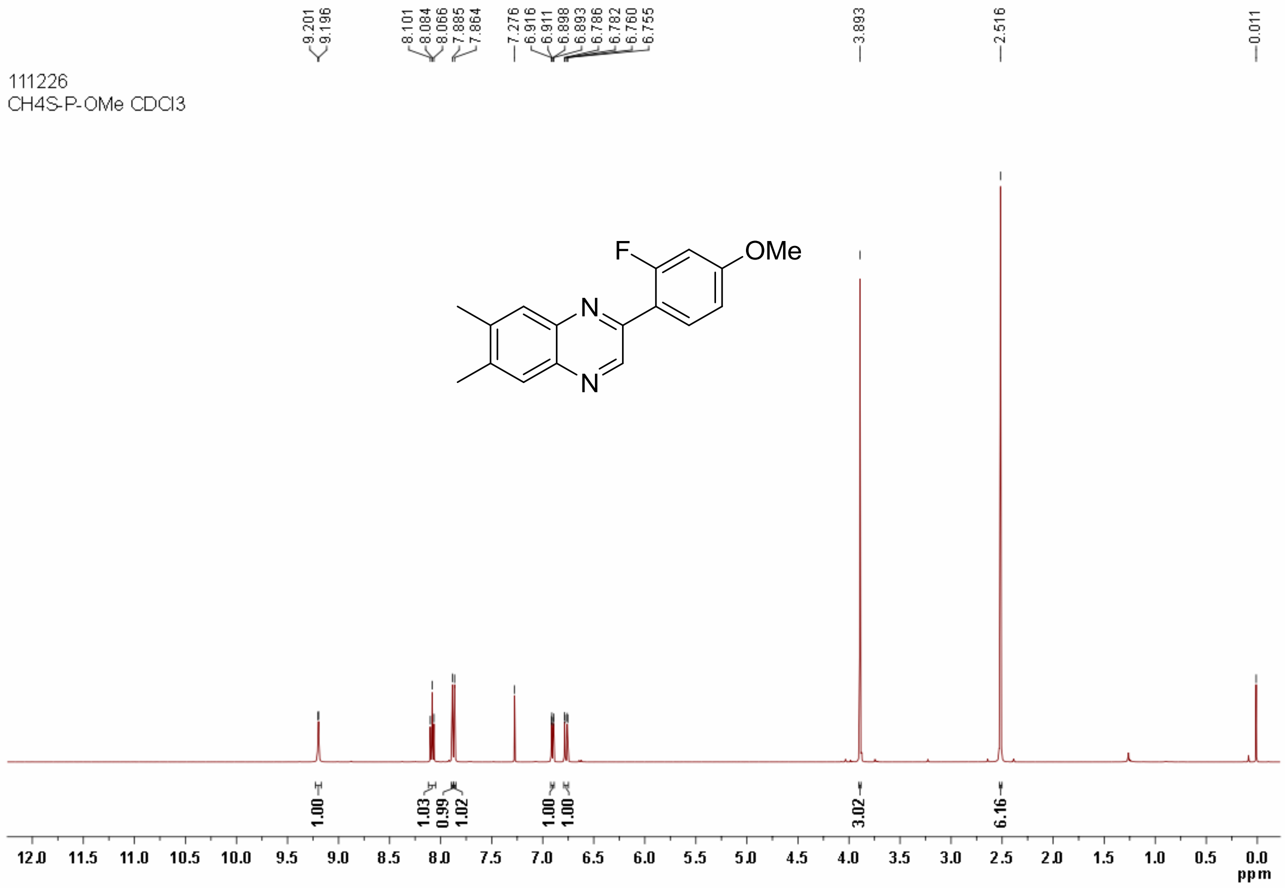
ppm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6.786
6.782
6.760
6.755
3.893
2.516
0.011
111226
CH4S-P-OMe CDCl3
F
OMe
N
N
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1.03
0.99
1.02
1.00
1.00
3.02
6.16
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
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6.5
6.0
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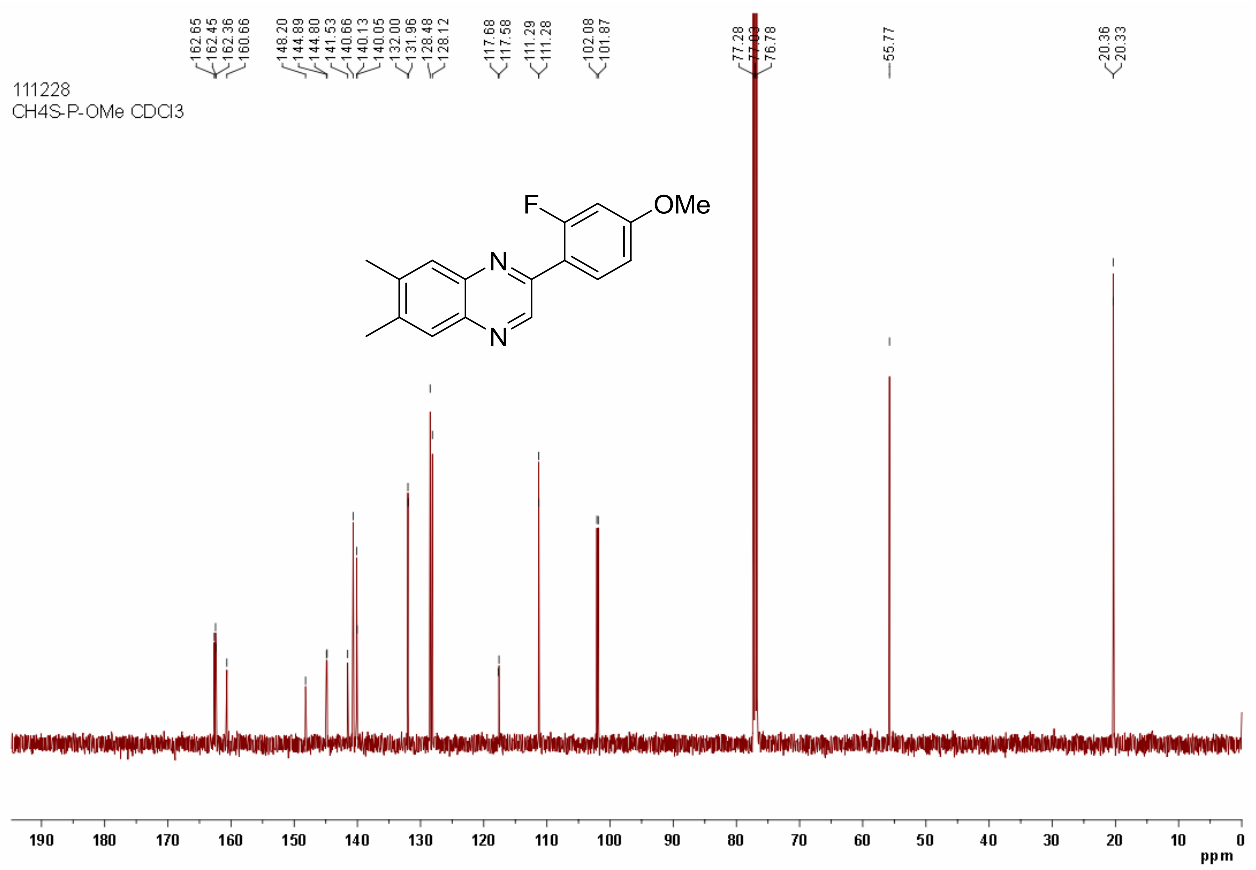
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128.12
117.68
117.58
111.29
111.28
102.08
101.87
77.28
77.03
76.78
55.77
20.36
20.33
111228
CH4S-P-OMe CDCl3
F
OMe
N
N
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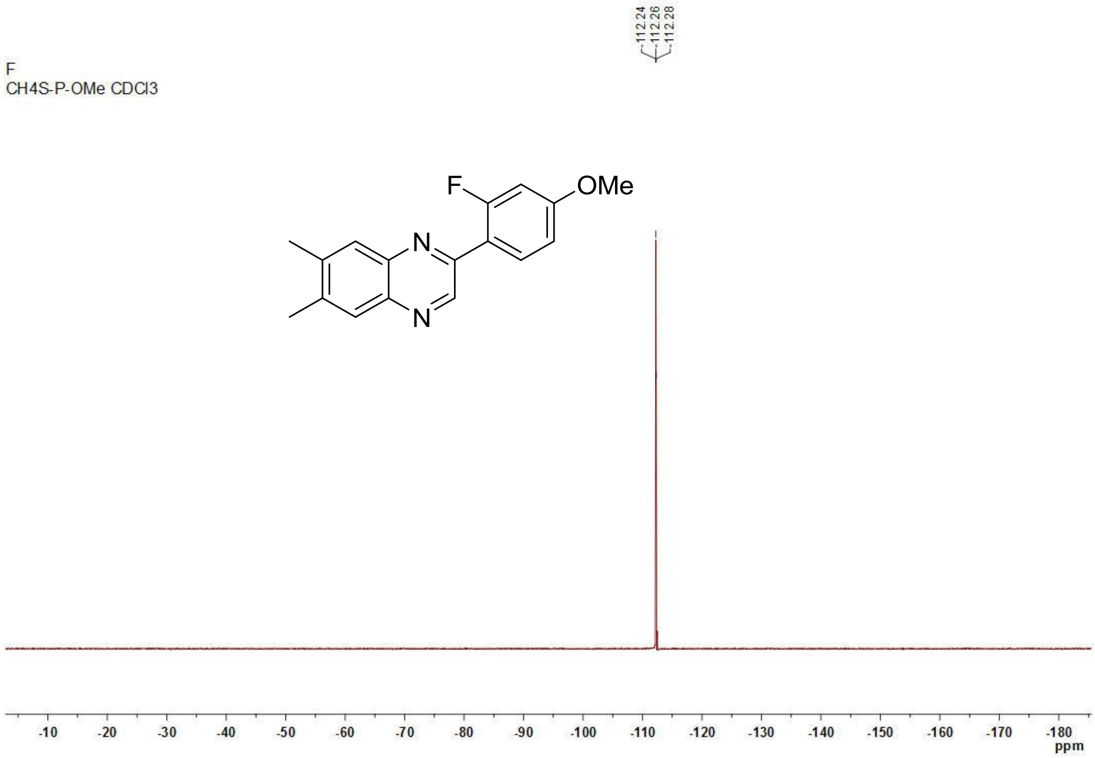
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OMe
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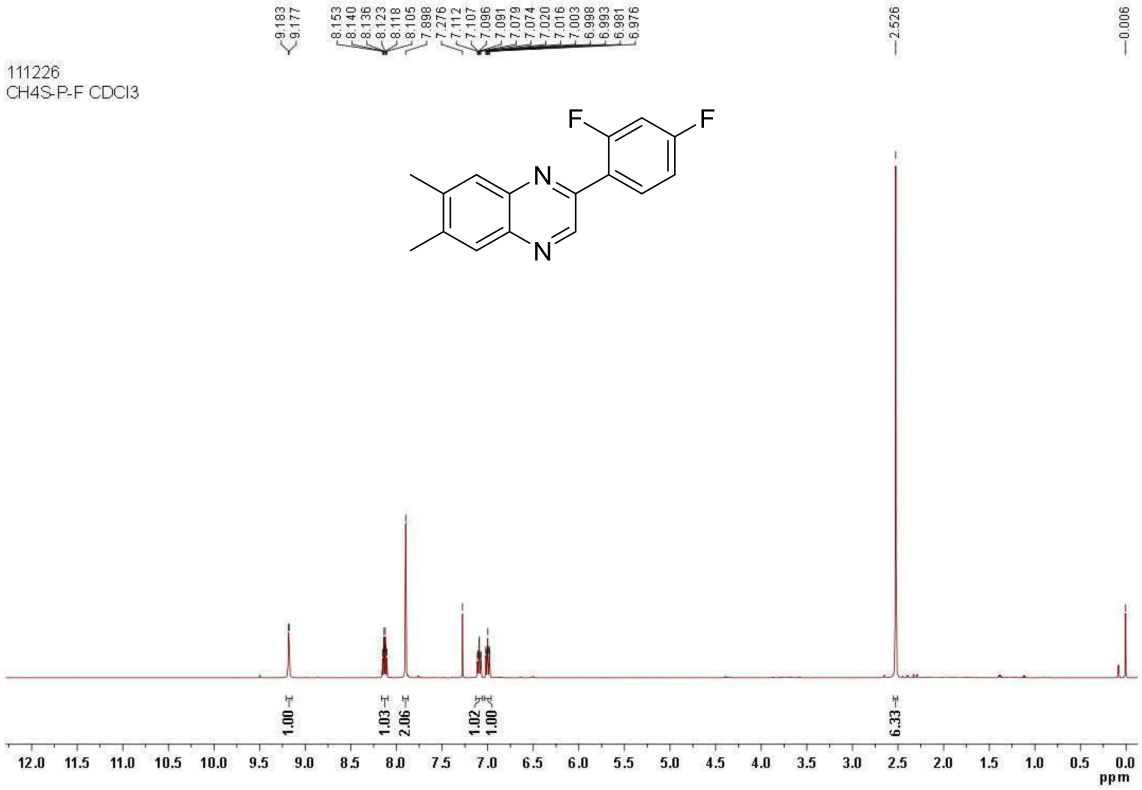
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7.112
7.107
7.096
7.091
7.079
7.074
7.020
7.016
7.003
6.998
6.993
6.981
6.976
2.526
0.006
111226
CH4S-P-F CDCl3
F
F
N
N
1.00
1.03
2.06
1.02
1.00
6.33
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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3.0
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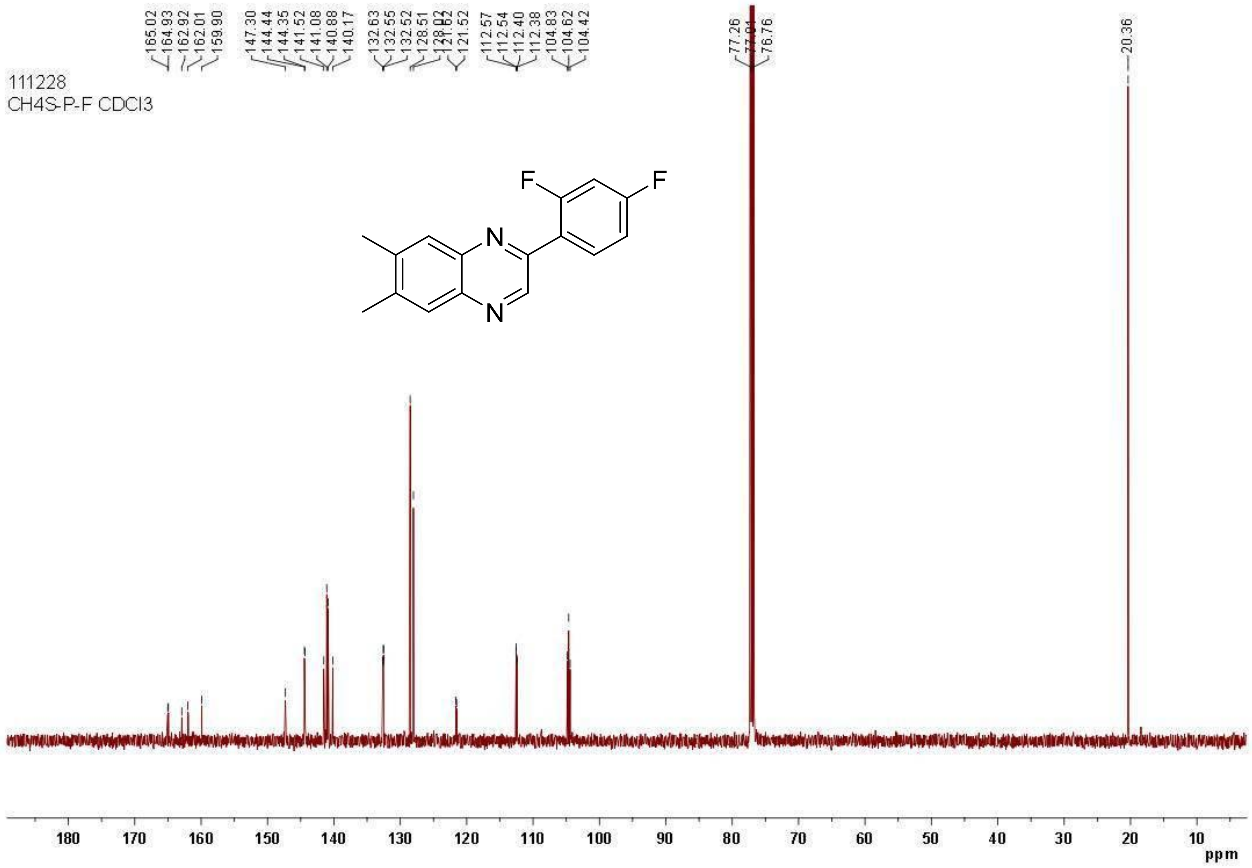
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144.35
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141.08
140.88
140.17
132.63
132.55
132.52
128.51
128.02
121.62
121.52
112.57
112.54
112.40
112.38
104.83
104.62
104.42
77.26
77.01
76.76
20.36
111228
CH4S-P-F CDCl3
F
F
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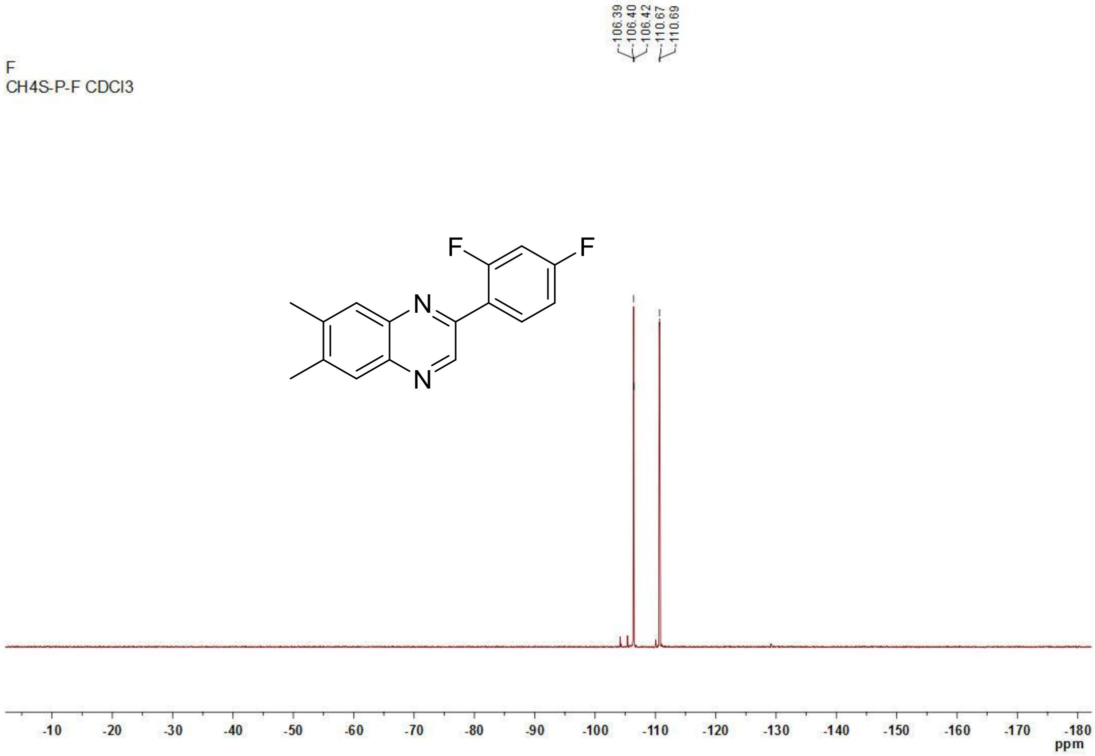
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-30
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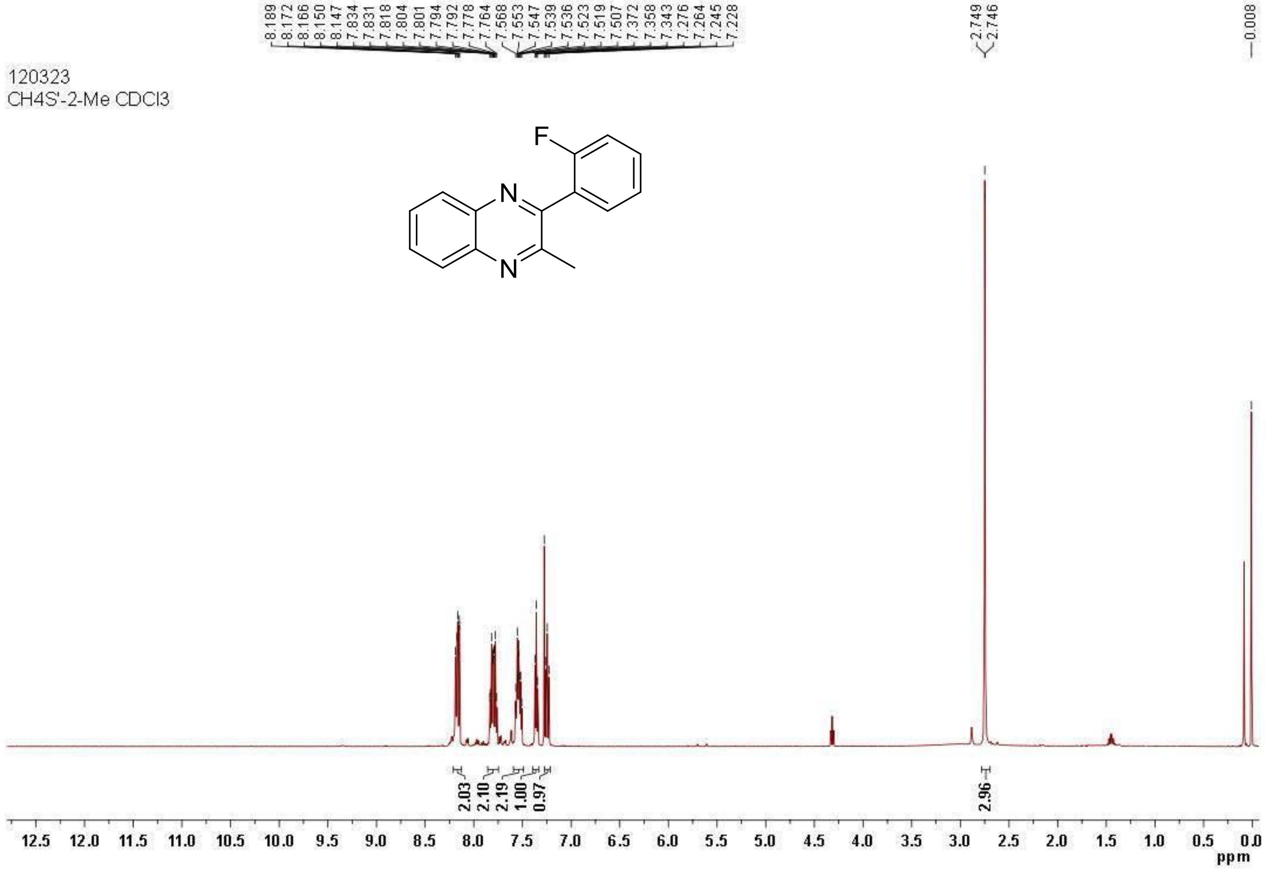
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7.804
7.801
7.794
7.792
7.778
7.764
7.568
7.553
7.547
7.539
7.536
7.523
7.519
7.507
7.372
7.358
7.343
7.276
7.264
7.245
7.228
2.749
2.746
0.008
120323
CH4S'-2-Me CDCl3
F
N
N
2.03
2.10
2.19
1.00
0.97
2.96
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.0
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1.5
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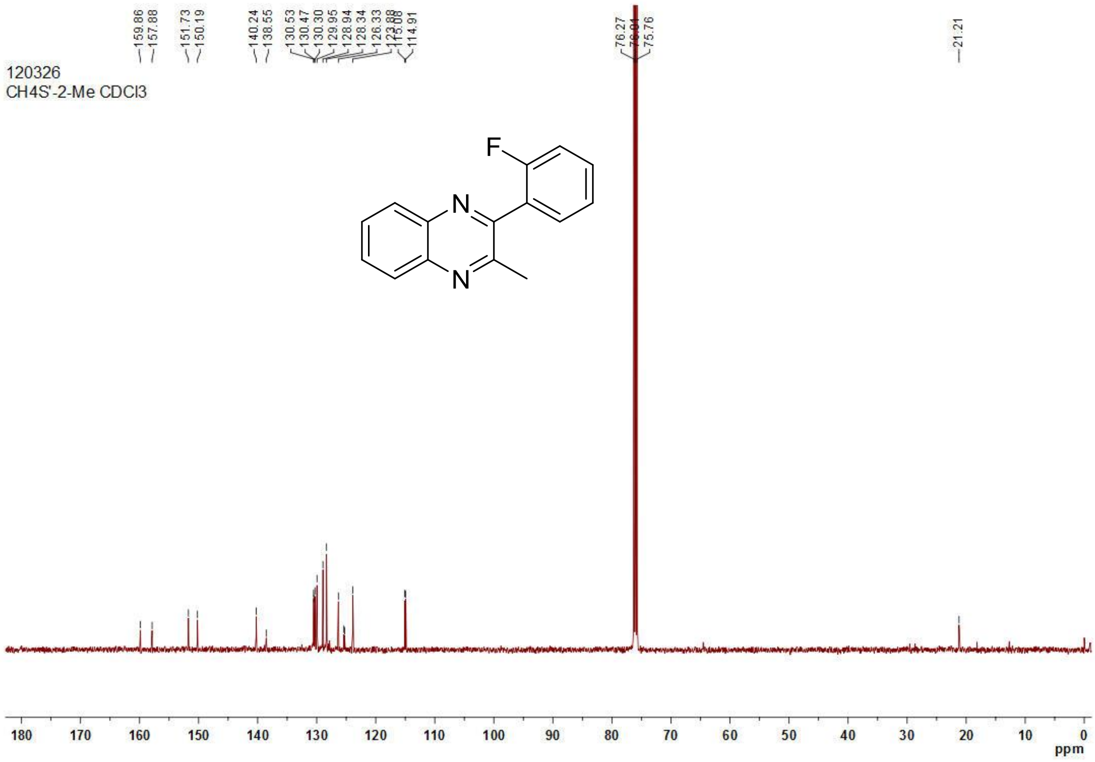
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130.47
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129.95
128.94
128.34
126.33
123.88
115.08
114.91
76.27
76.01
75.76
21.21
120326
CH4S'-2-Me CDCl3
F
N
N
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
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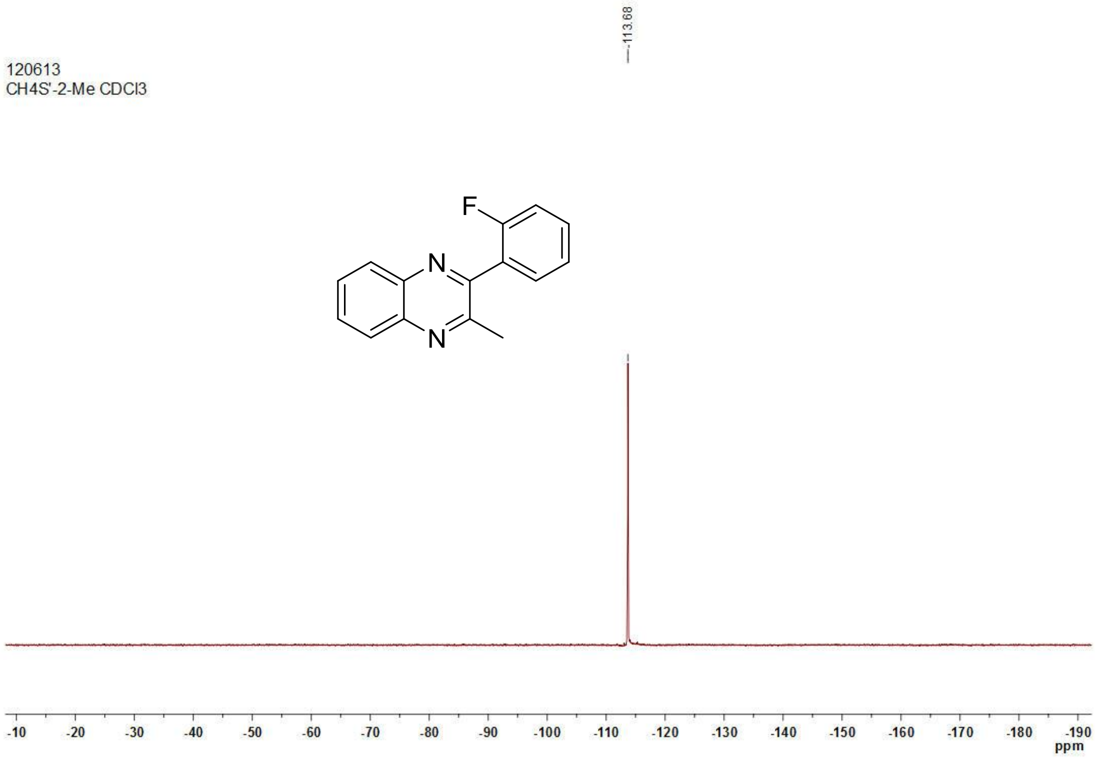
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CH4S'-2-Me CDCl3
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N
N
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-20
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-40
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-90
-100
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-130
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-150
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-170
-180
-190
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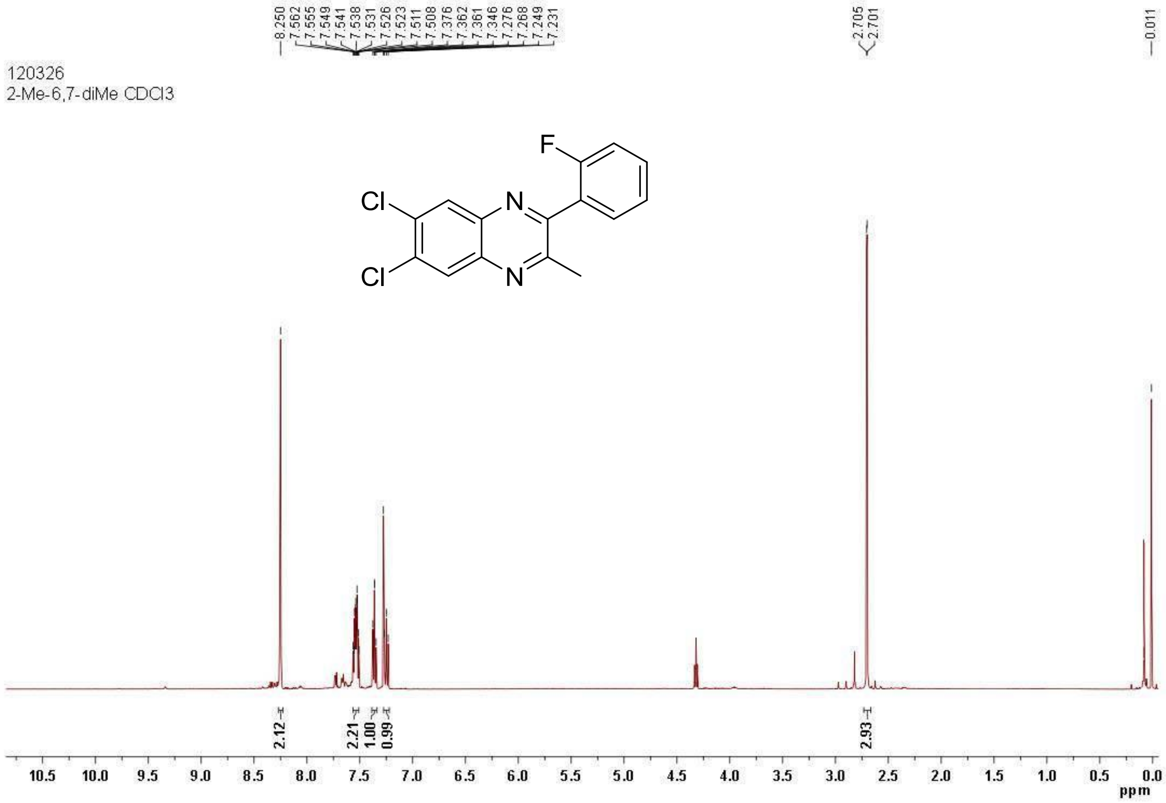
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7.538
7.531
7.526
7.523
7.511
7.508
7.376
7.362
7.361
7.346
7.276
7.268
7.249
7.231
2.705
2.701
0.011
120326
2-Me-6,7-diMe CDCl3
F
Cl
Cl
N
N
2.12
2.21
1.00
0.99
2.93
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
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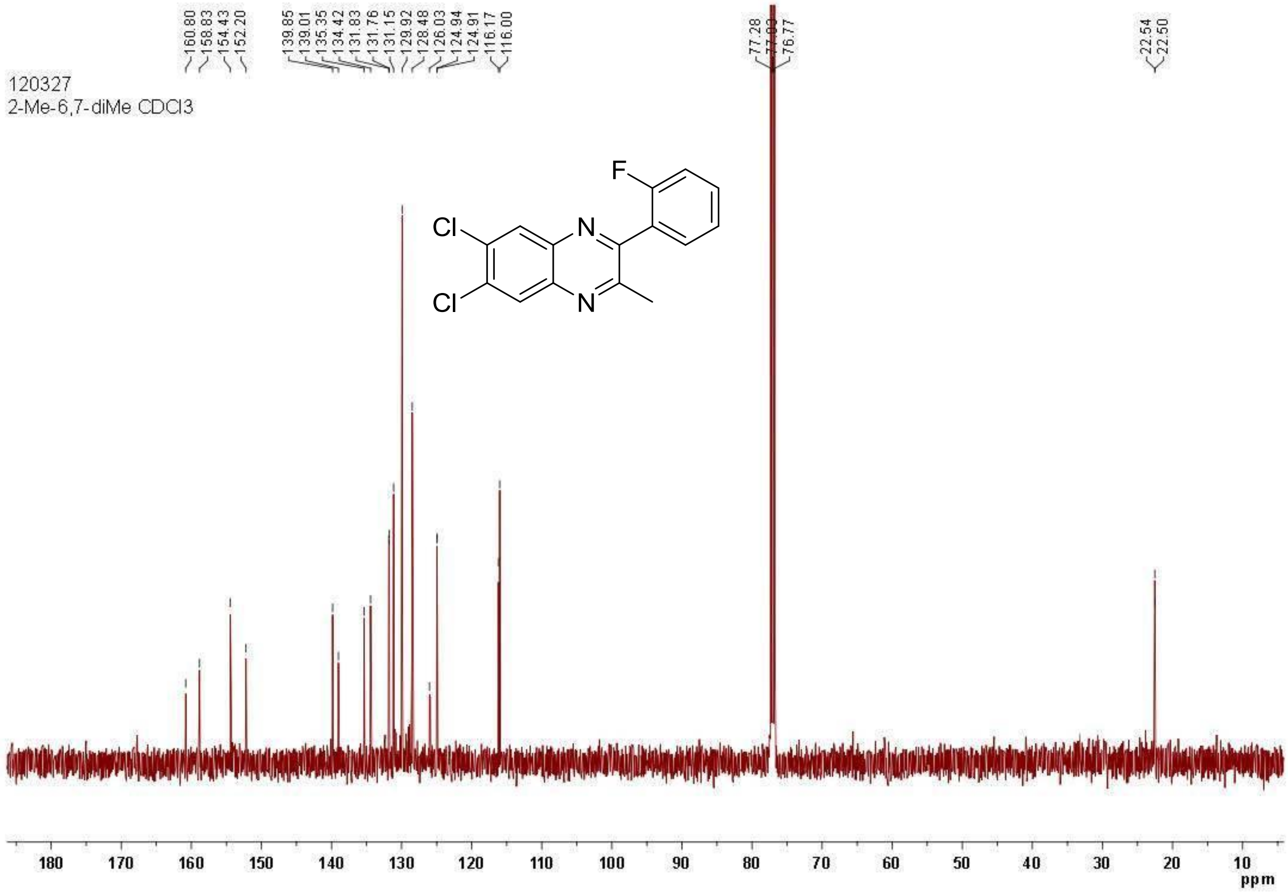
1.5
1.0
0.5
0.0
ppm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131.15
129.92
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126.03
124.94
124.91
116.17
116.00
77.28
77.03
76.77
22.54
22.50
120327
2-Me-6,7-diMe CDCl3
F
Cl
Cl
N
N
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170
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150
140
130
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110
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70
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30
20
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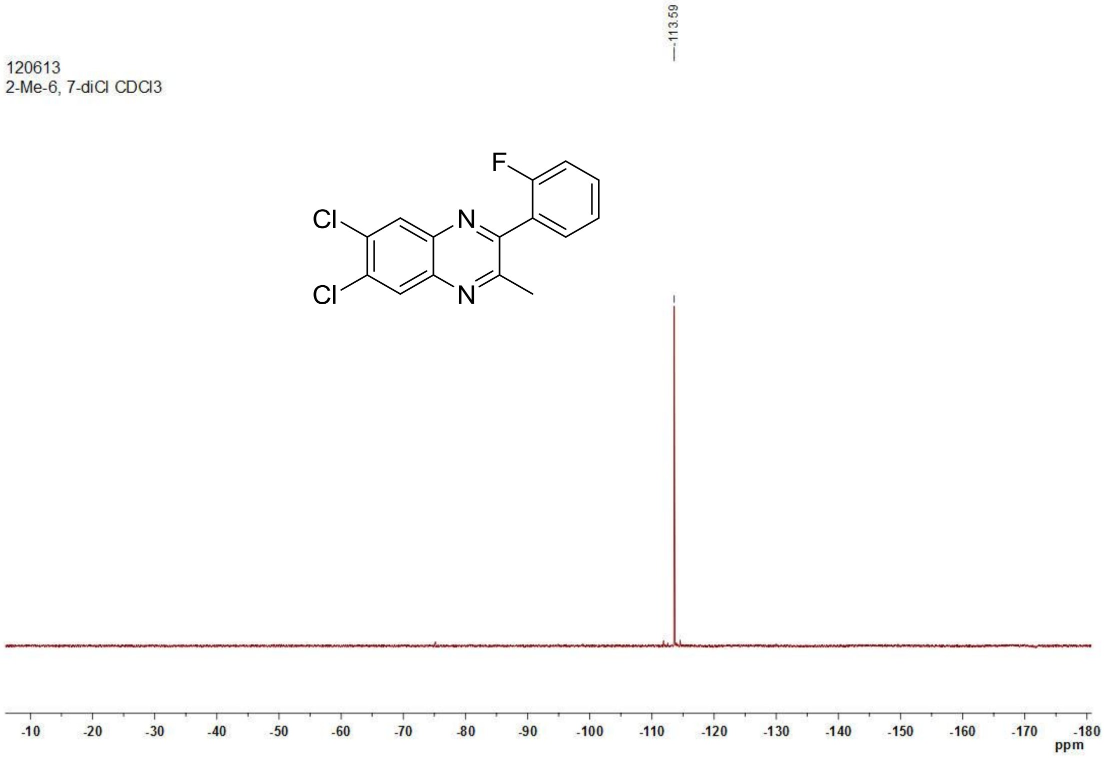
ppm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Cl
N
Cl
N
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-20
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-80
-90
-100
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-120
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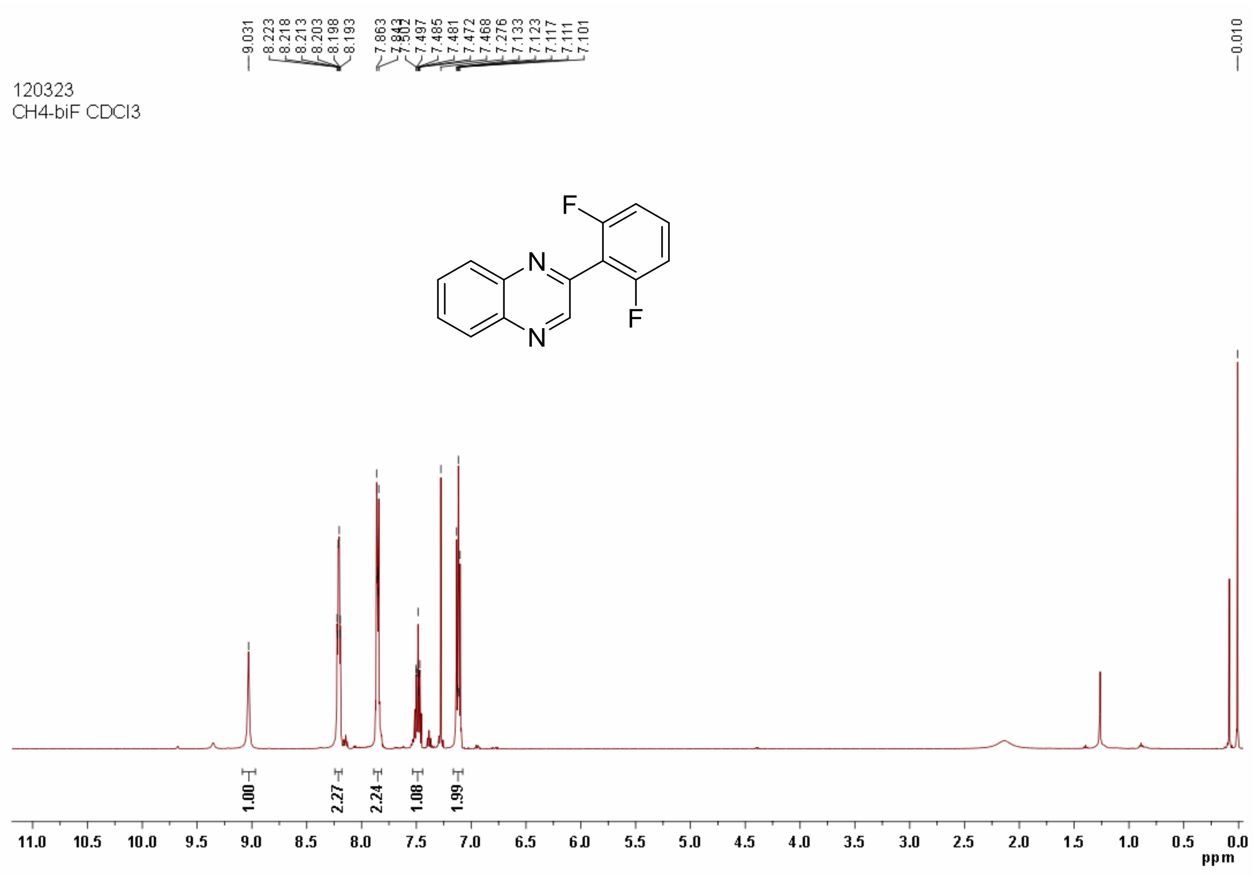
-140
-150
-160
-170
-180
ppm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7.843
7.502
7.497
7.485
7.481
7.472
7.468
7.276
7.133
7.123
7.117
7.111
7.101
0.010
120323
CH4-biF CDCl3
F
N
N
F
1.00
2.27
2.24
1.08
1.99
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.0
3.5
3.0
2.5
2.0
1.5
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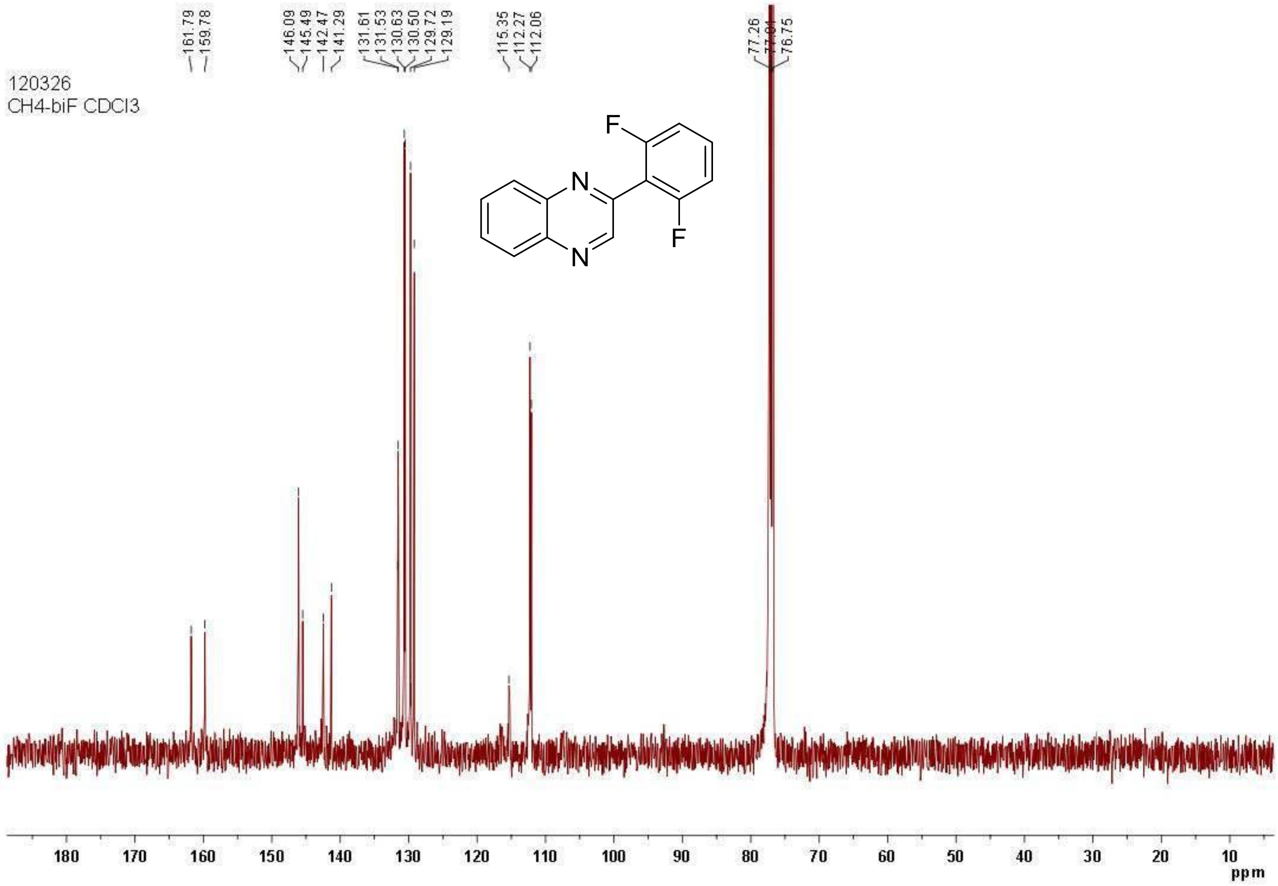
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130.50
129.72
129.19
115.35
112.27
112.06
77.26
77.01
76.75
120326
CH4-biF CDCl3
F
N
N
F
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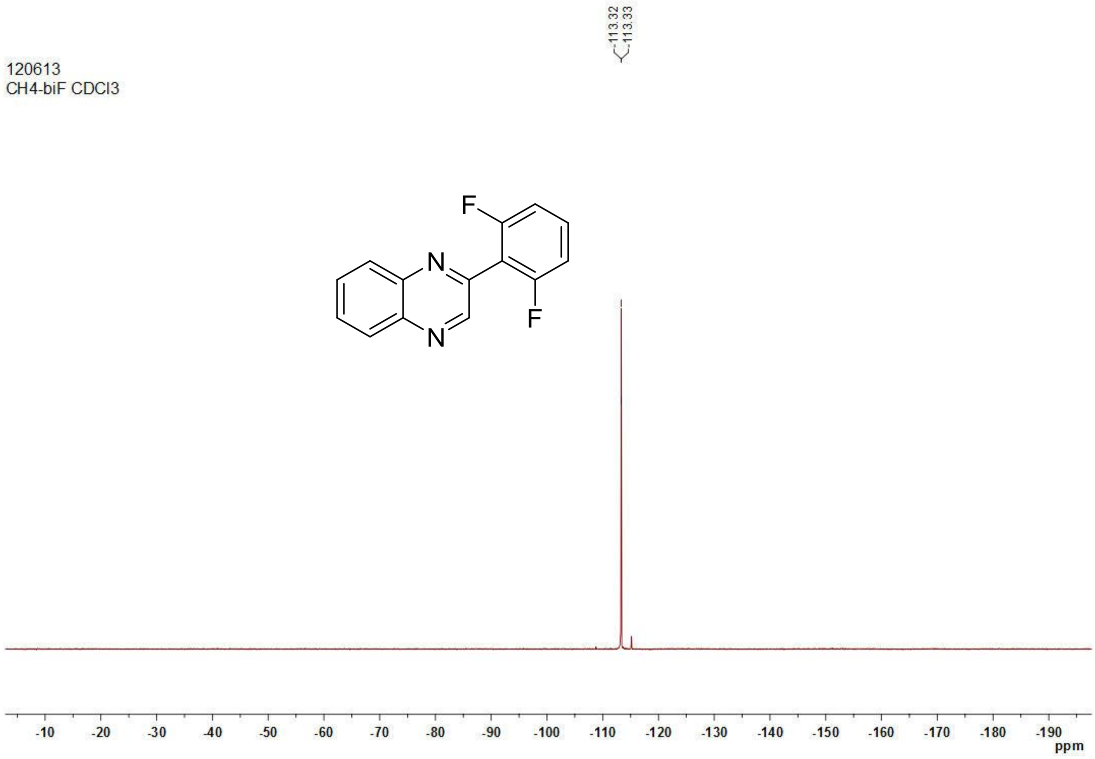
50
40
30
20
10
ppm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N
N
F
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-30
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-170
-180
-190
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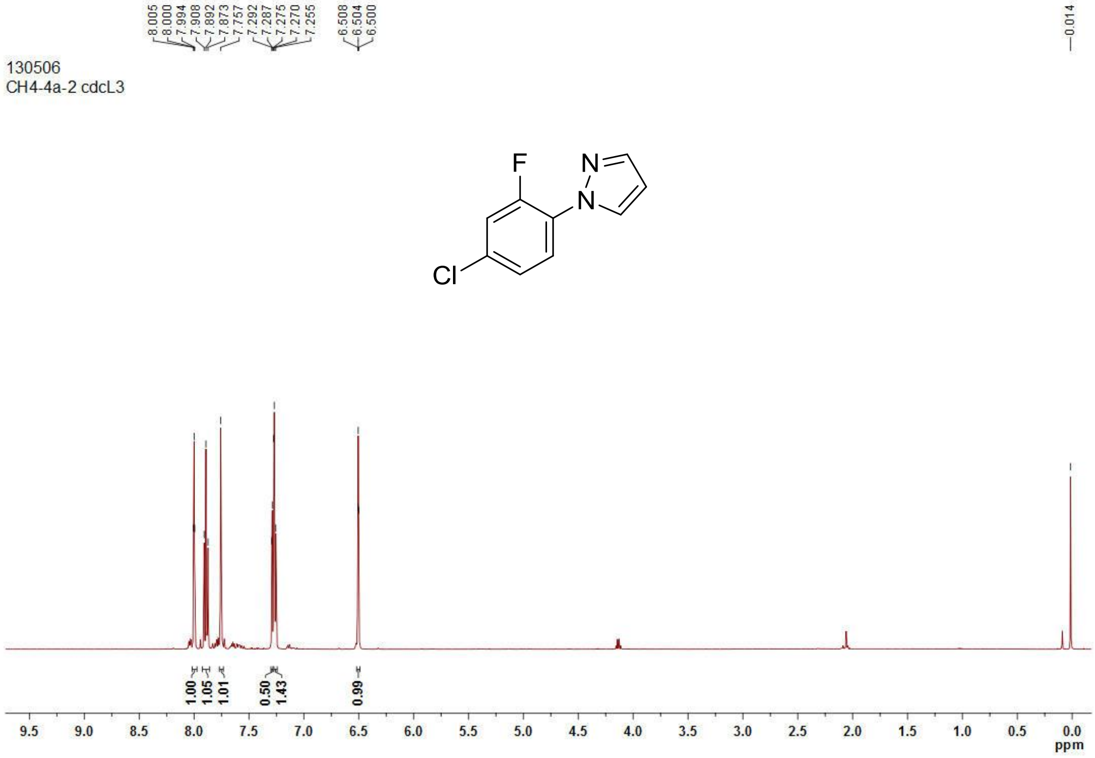
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7.275
7.270
7.255
6.508
6.504
6.500
0.014
130506
CH4-4a-2 cdcL3
F
N
N
Cl
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1.05
1.01
0.50
1.43
0.99
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.0
3.5
3.0
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1.5
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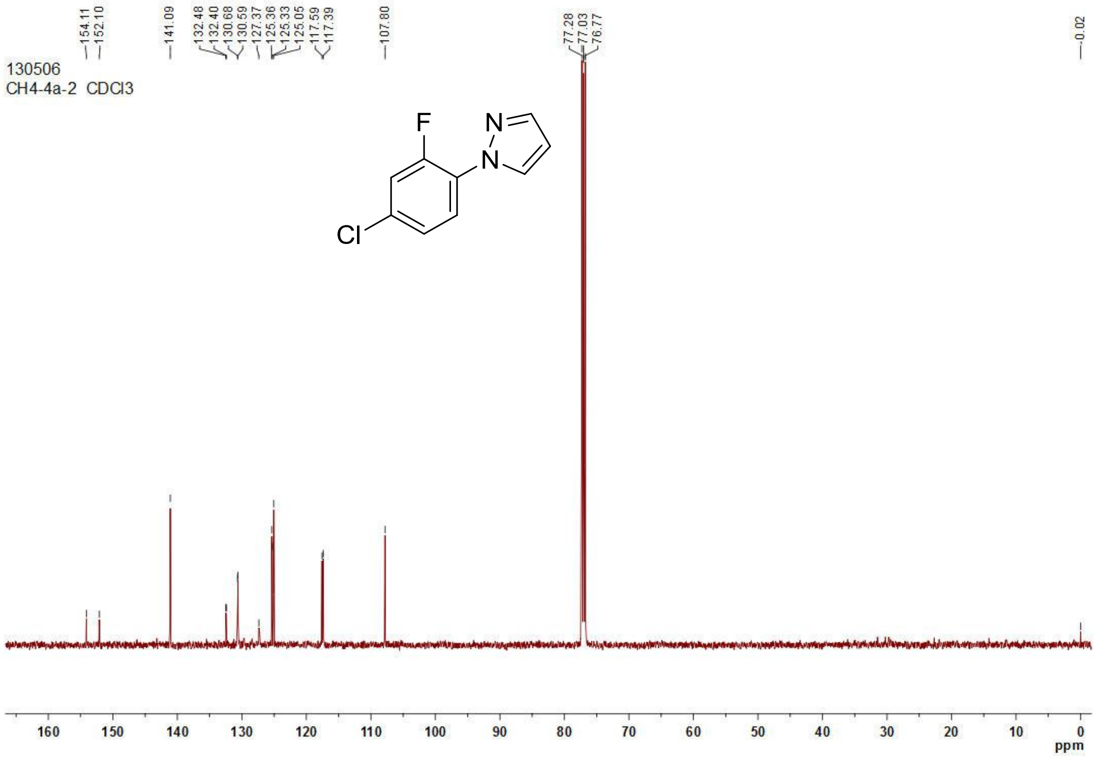
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125.33
125.05
117.59
117.39
107.80
77.28
77.03
76.77
0.02
130506
CH4-4a-2 CDCl3
F
N
N
Cl
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140
130
120
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100
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60
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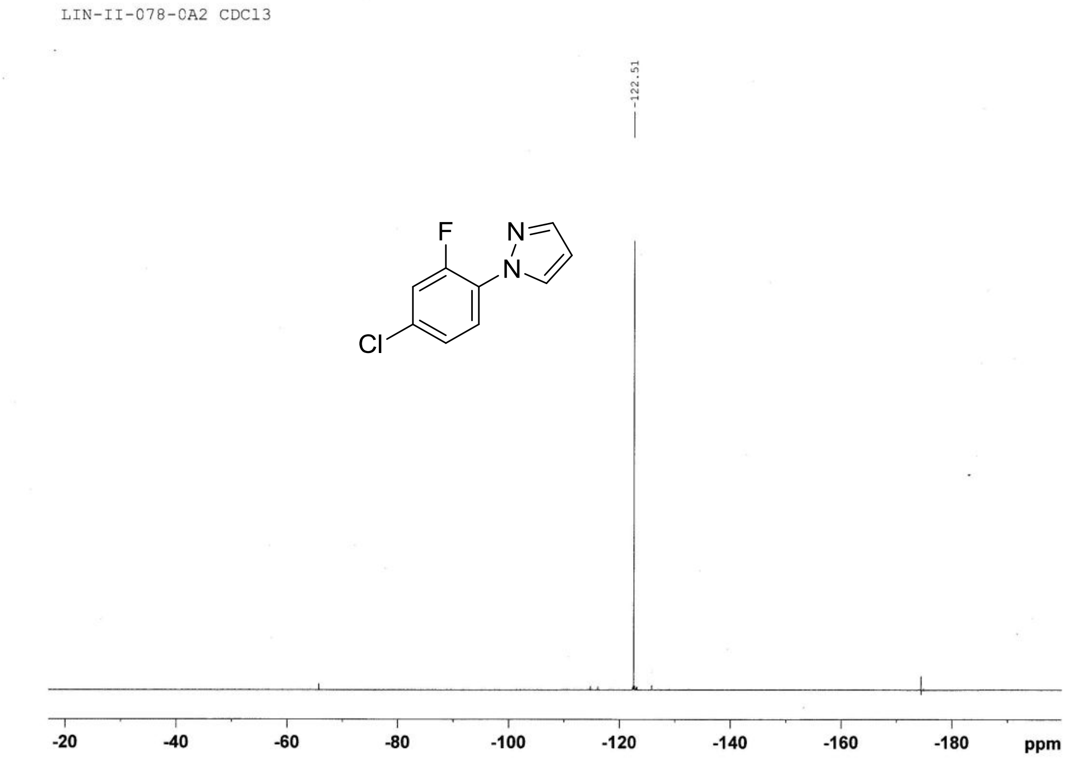
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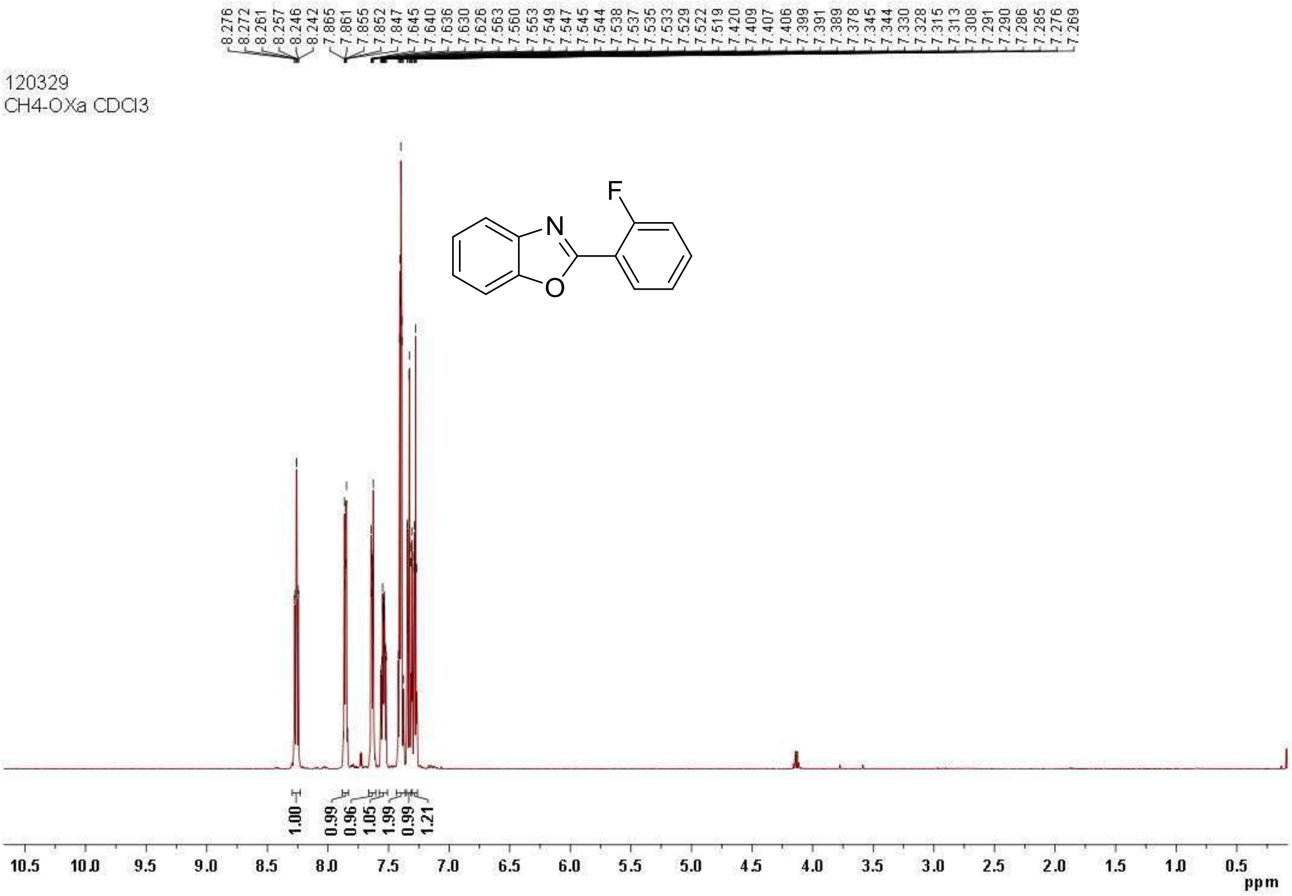
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7.640
7.636
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7.626
7.563
7.560
7.553
7.549
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7.545
7.544
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7.537
7.535
7.533
7.529
7.522
7.519
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7.409
7.407
7.406
7.399
7.391
7.389
7.378
7.345
7.344
7.330
7.328
7.315
7.313
7.308
7.291
7.290
7.286
7.285
7.276
7.269
120329
CH4-OXa CDCl3
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N
O
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1.05
1.99
0.99
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10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
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1.0
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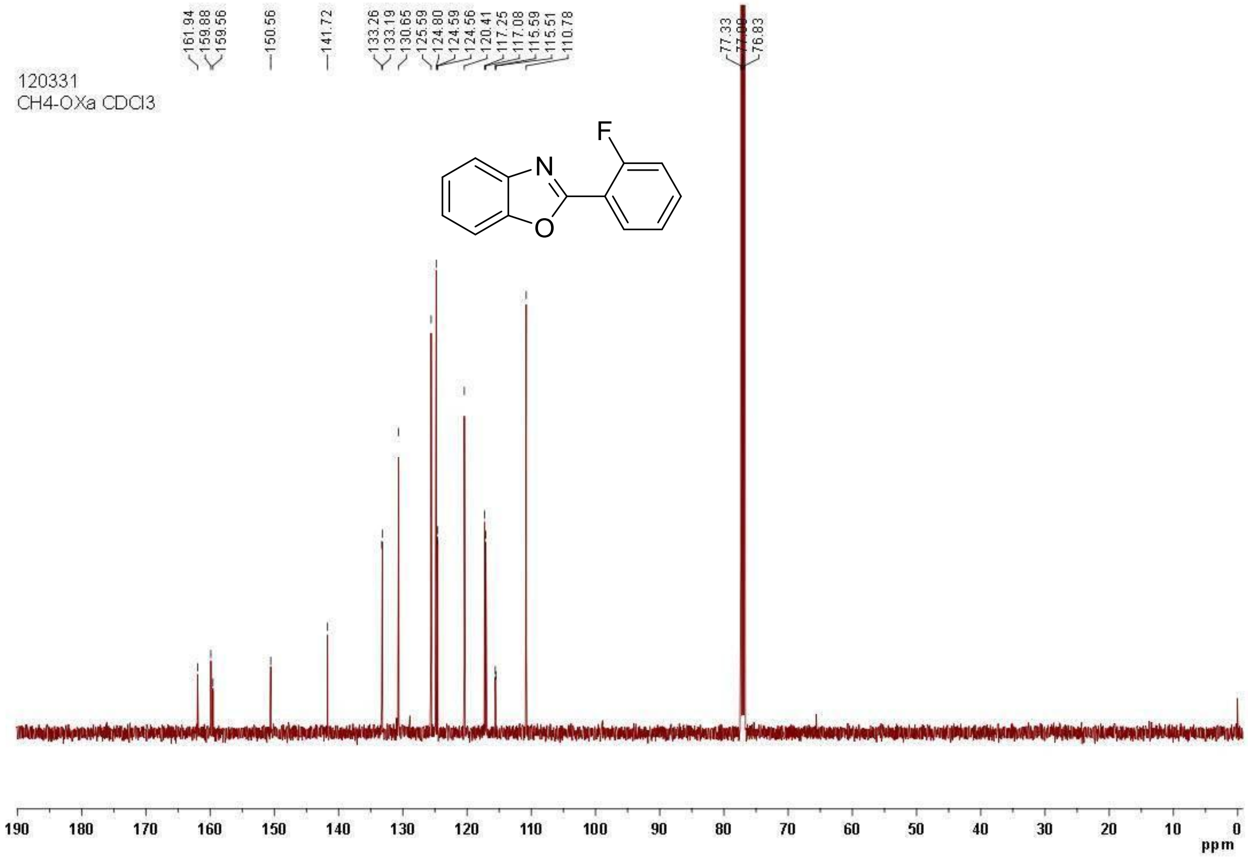
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117.25
117.08
115.59
115.51
110.78
77.33
77.08
76.83
120331
CH4-OXa CDCl3
F
N
O
190
180
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160
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140
130
120
110
100
90
80
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60
50
40
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20
10
0
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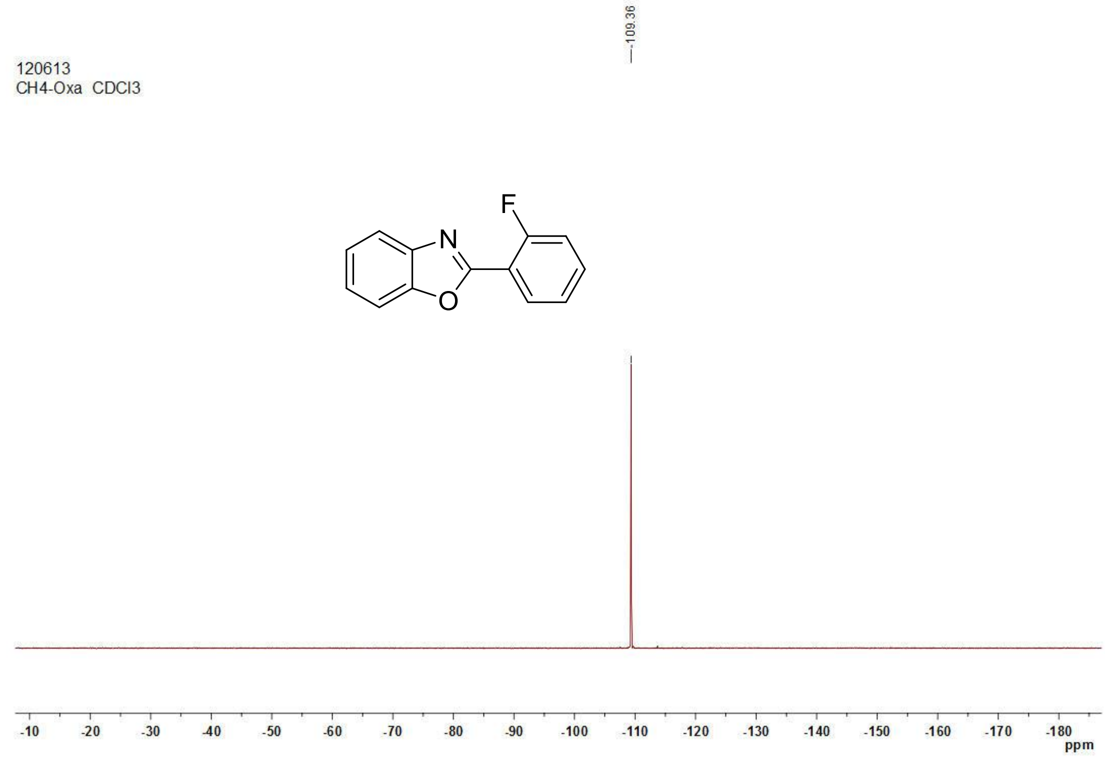
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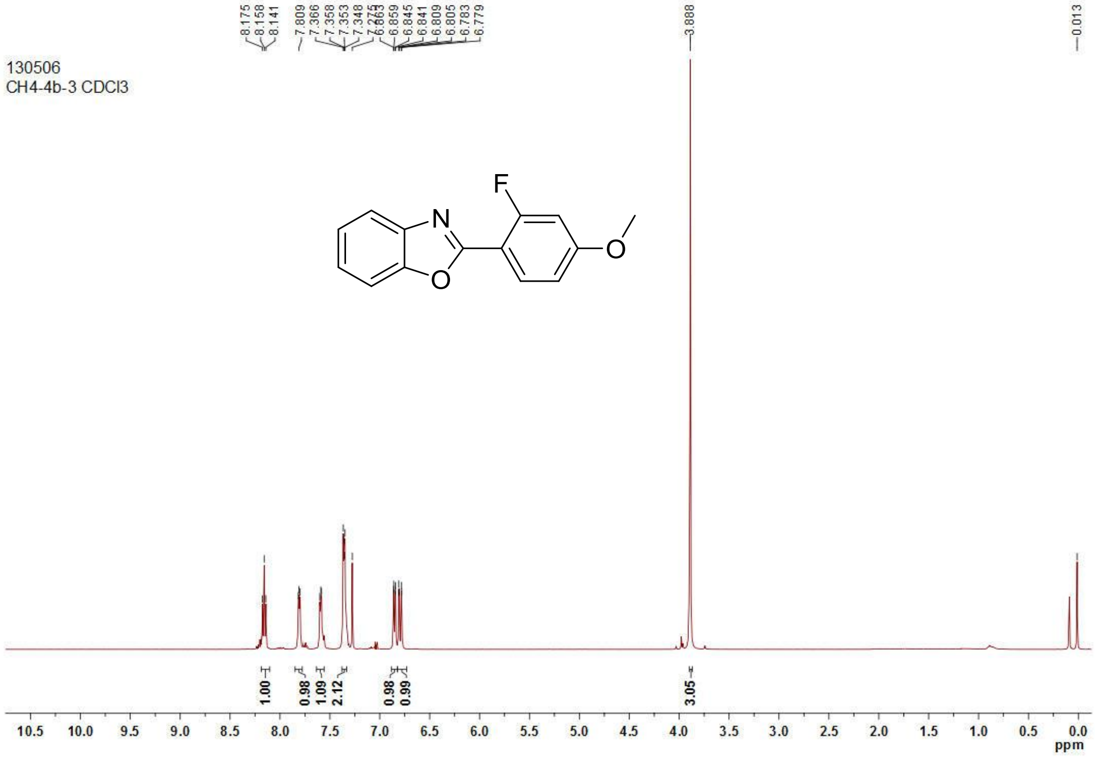
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6.859
6.845
6.841
6.809
6.805
6.783
6.779
3.888
0.013
130506
CH4-4b-3 CDCl3
F
N
O
O
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0.98
1.09
2.12
0.98
0.99
3.05
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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4.0
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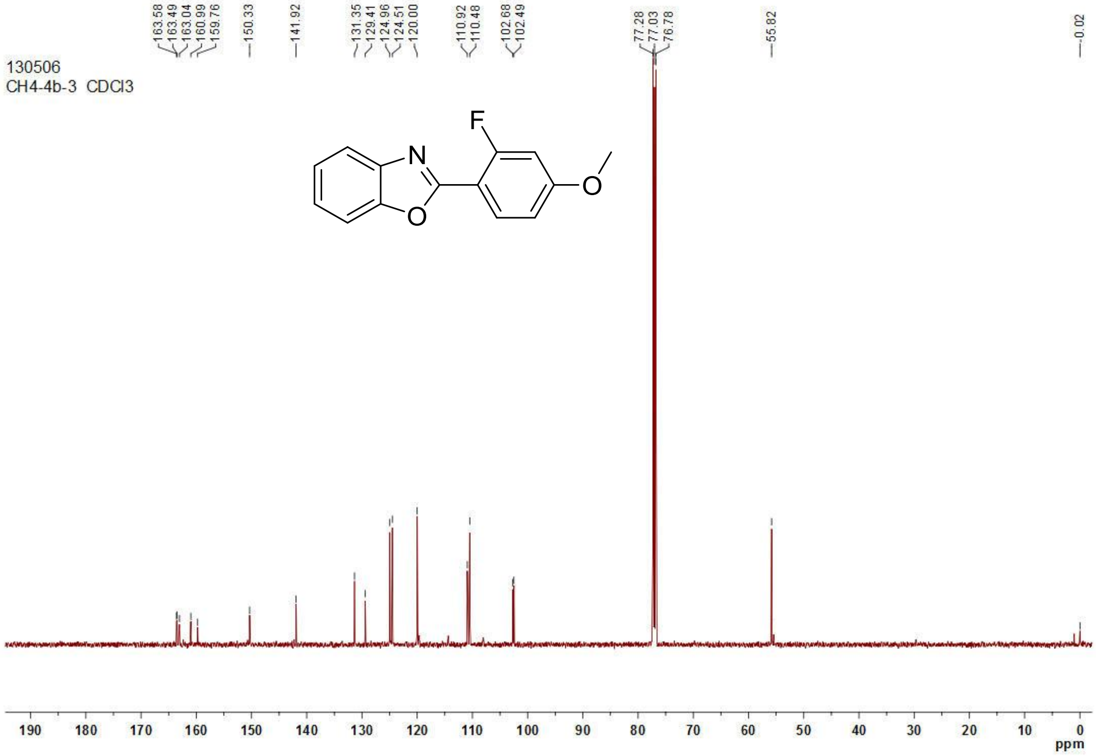
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124.51
120.00
110.92
110.48
102.68
102.49
77.28
77.03
76.78
55.82
0.02
130506
CH4-4b-3 CDCl3
F
N
O
O
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180
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140
130
120
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100
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80
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60
50
40
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20
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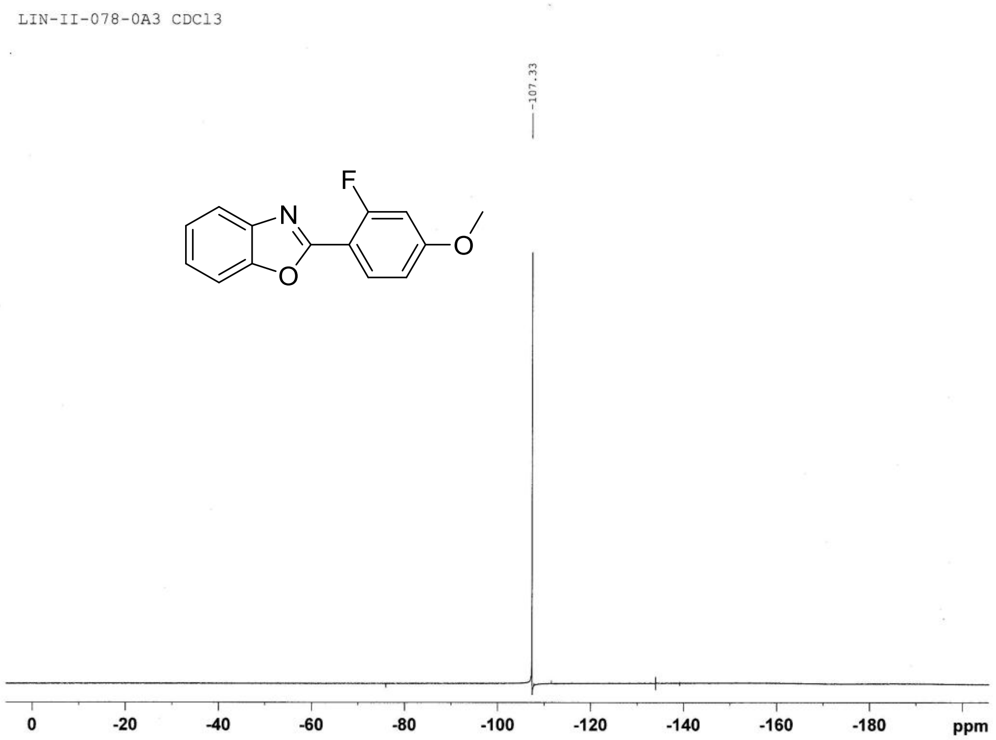
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-140
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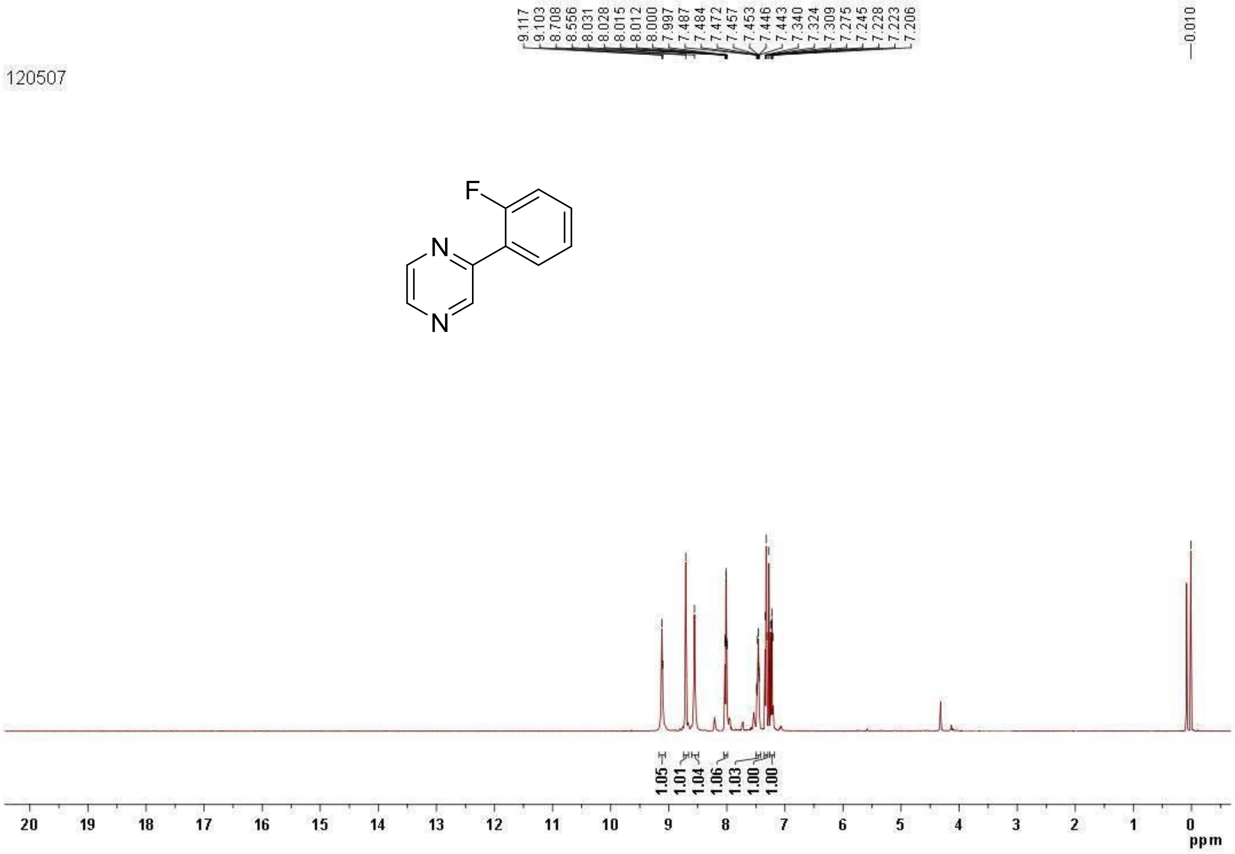
-180
ppm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8.000
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7.472
7.457
7.453
7.446
7.443
7.340
7.324
7.309
7.275
7.245
7.228
7.223
7.206
0.010
F
N
N
1.05
1.01
1.04
1.06
1.03
1.00
1.00
20
19
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13
12
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7
6
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2
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0
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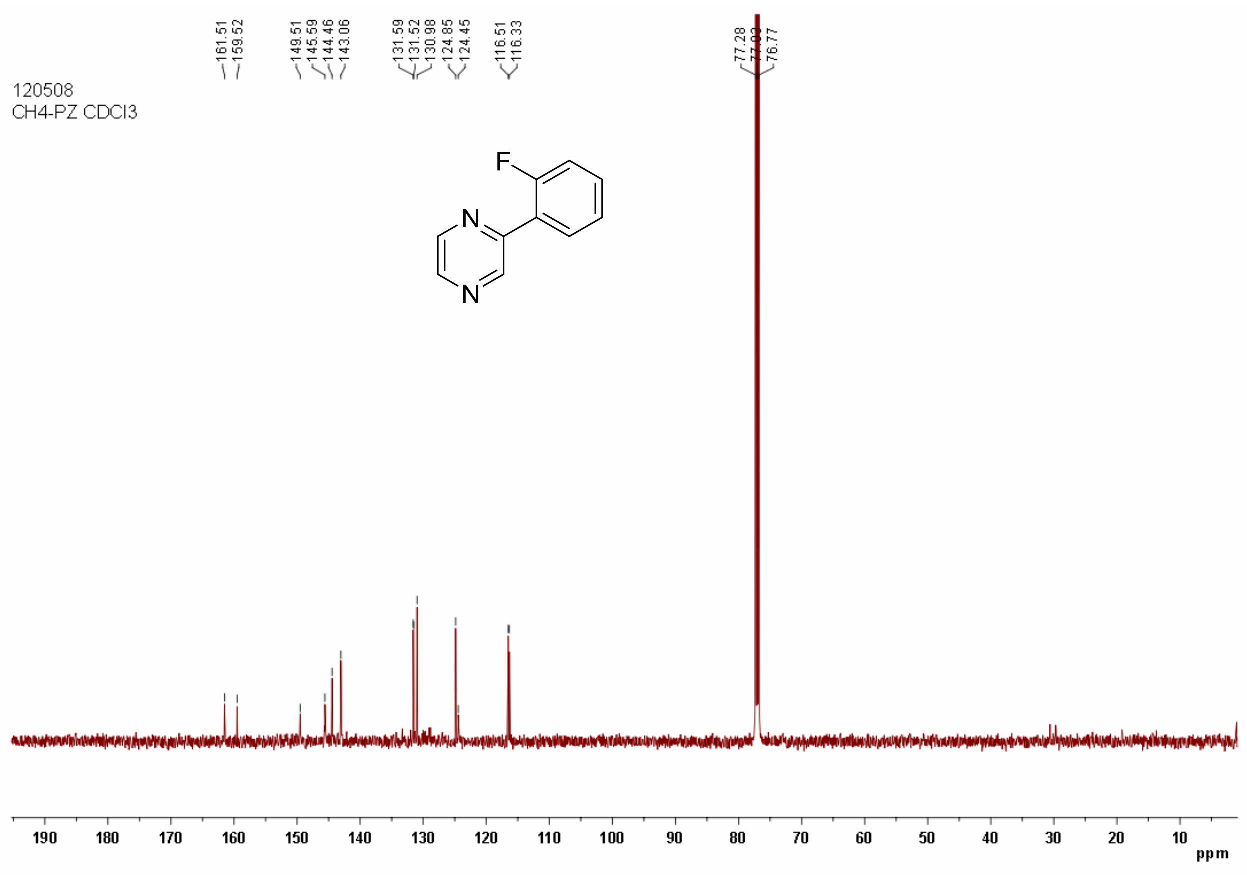
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116.33
77.28
77.03
76.77
120508
CH4-PZ CDCl3
F
N
N
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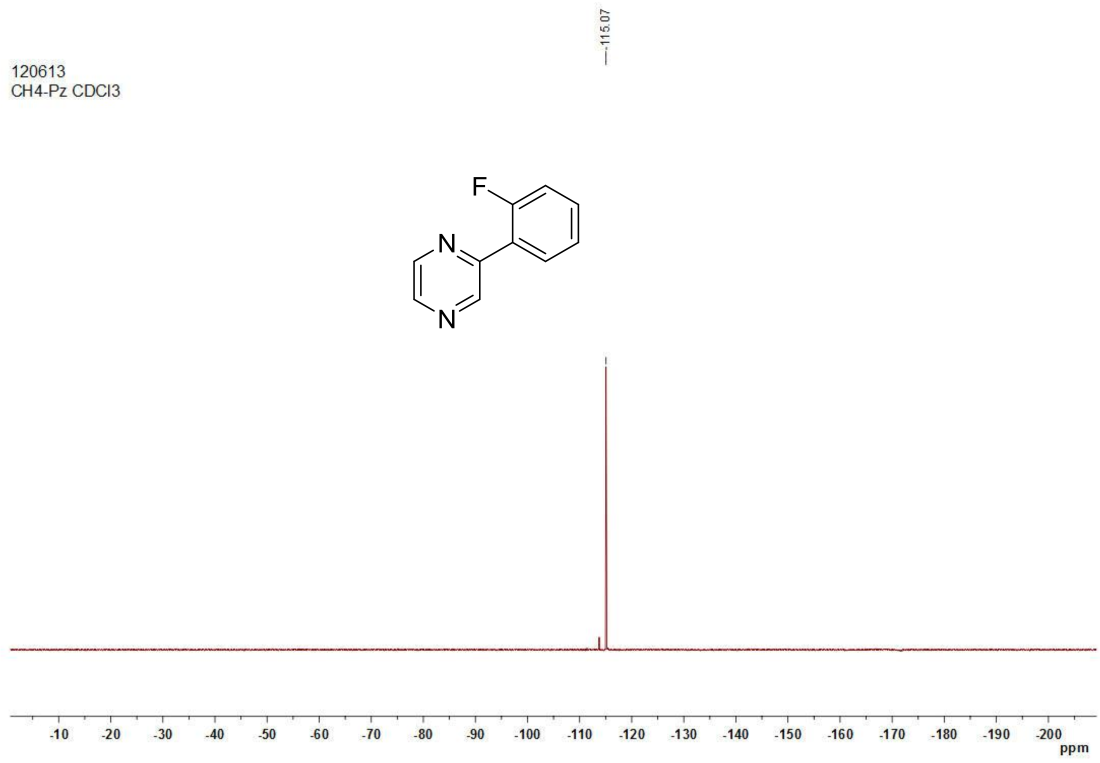
ppm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120613
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N
-10
-20
-30
-40
-50
-60
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-140
-150
-160
-170
-180
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-200
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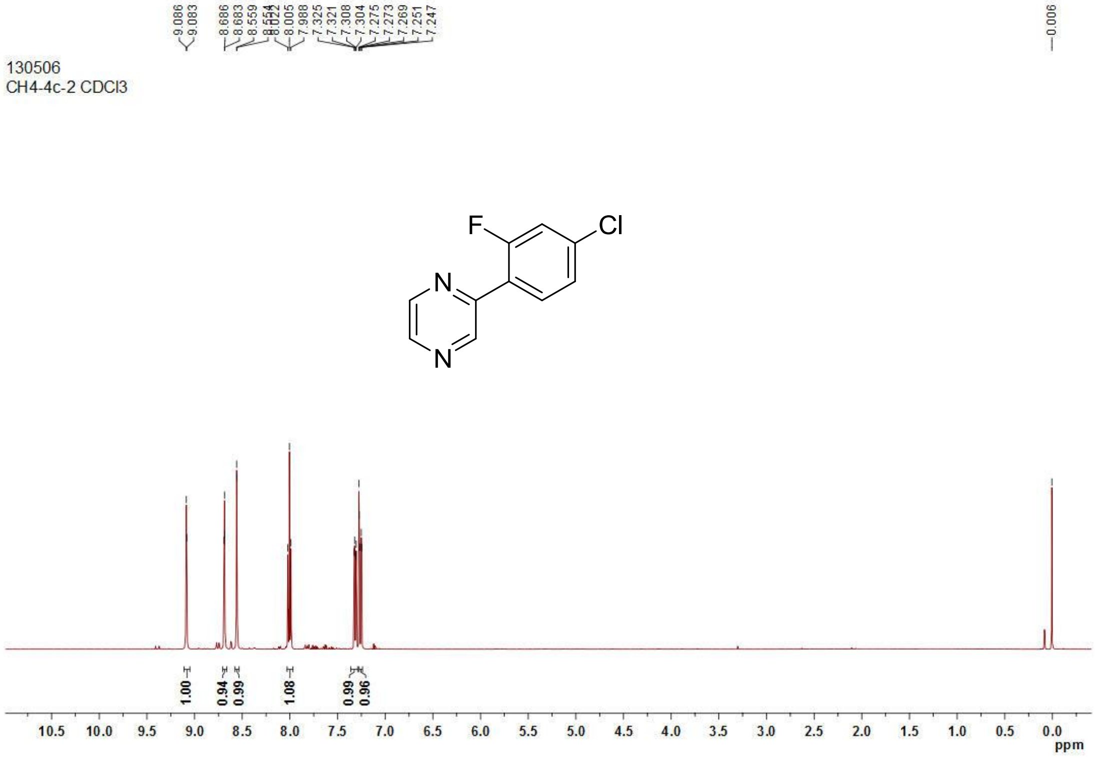
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8.686
8.683
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8.554
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8.005
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7.308
7.304
7.275
7.273
7.269
7.251
7.247
0.006
130506
CH4-4c-2 CDCl3
F
Cl
N
N
1.00
0.94
0.99
1.08
0.99
0.96
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.0
3.5
3.0
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1.5
1.0
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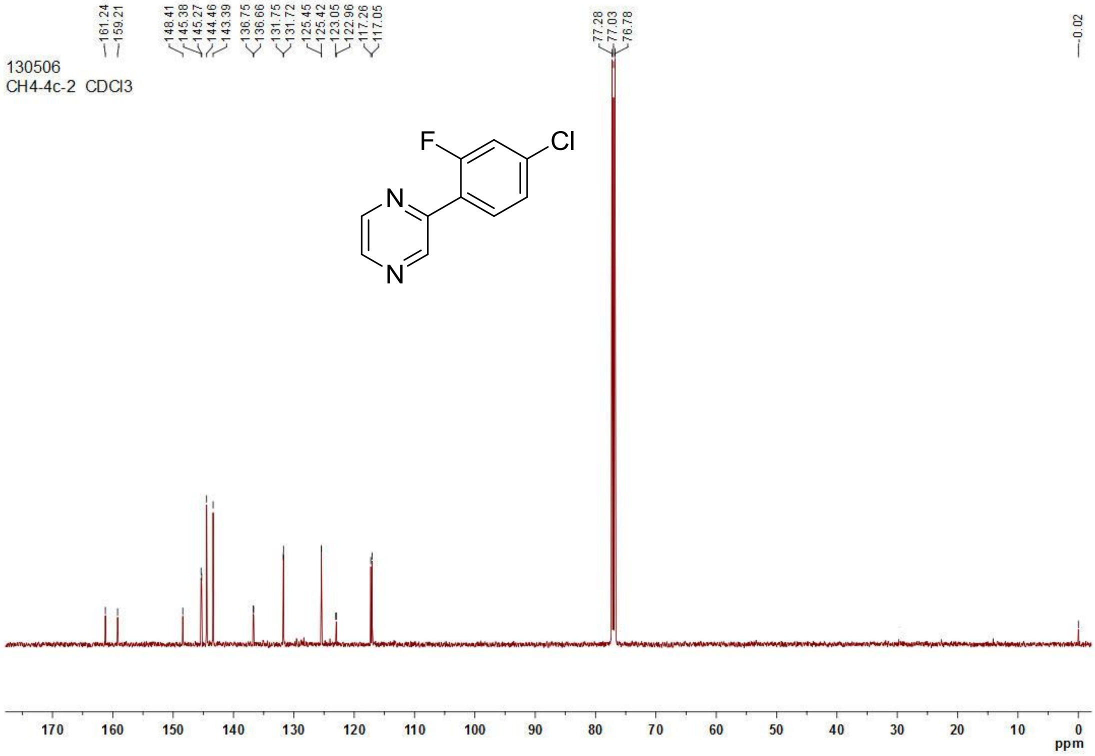
0.0
ppm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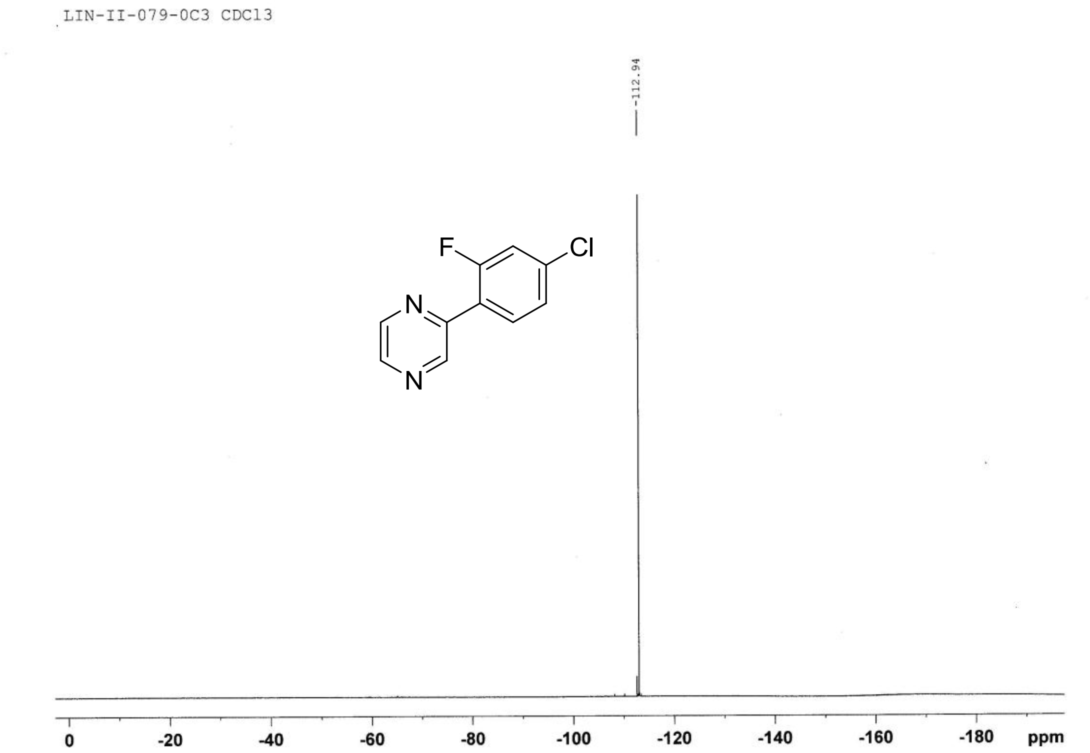
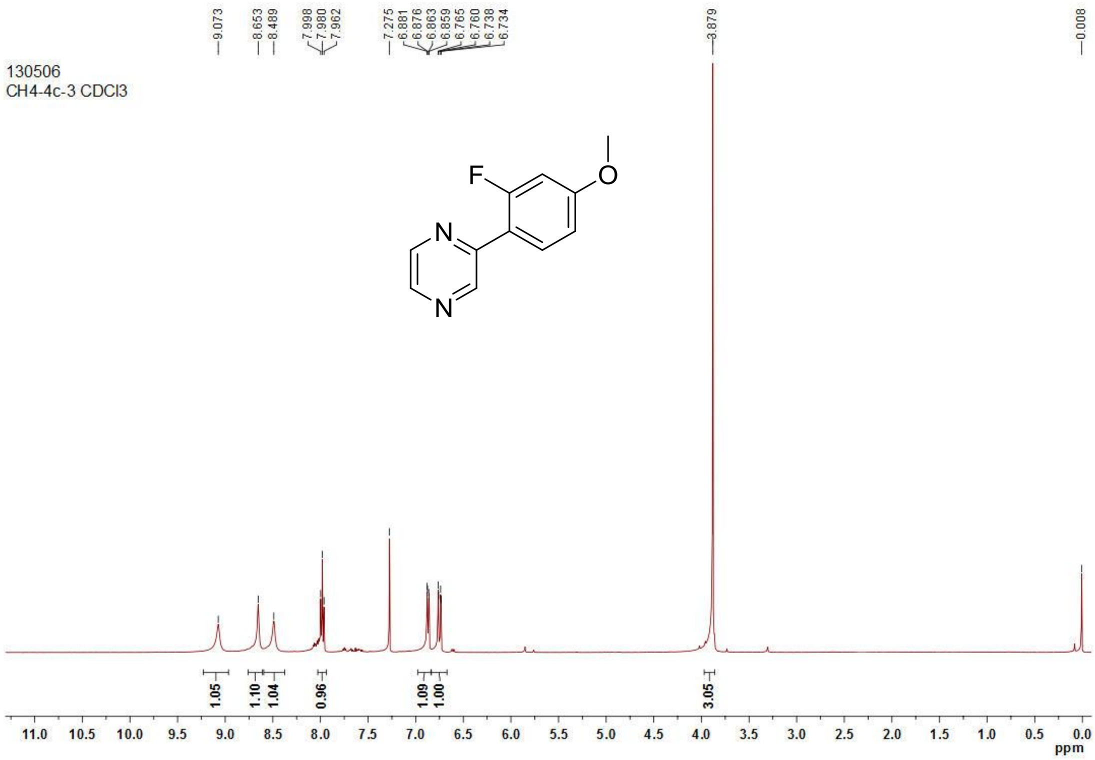
145.27
144.46
143.39
136.75
136.66
131.75
131.72
125.45
125.42
123.05
122.96
117.26
117.05
77.28
77.03
76.78
-0.02
130506
CH4-4c-2 CDCl3
F
Cl
N
N
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


LIN-II-079-OC3 CDCl3
-112.94
F
Cl
N
N
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
ppm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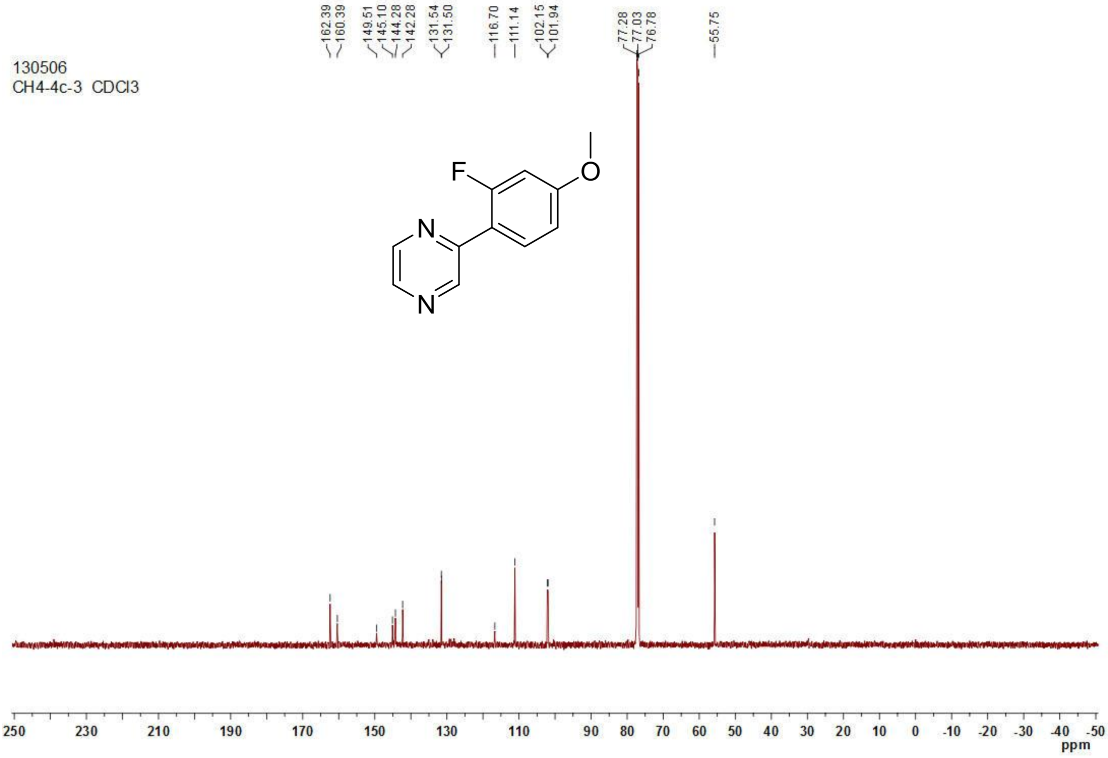
8.653
8.489
7.998
7.980
7.962
7.275
6.881
6.876
6.863
6.859
6.765
6.760
6.738
6.734
3.879
0.008
130506
CH4-4c-3 CDCl3
F
O
N
N
1.05
1.10
1.04
0.96
1.09
1.00
3.05
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


130506
CH4-4c-3 CDCl3
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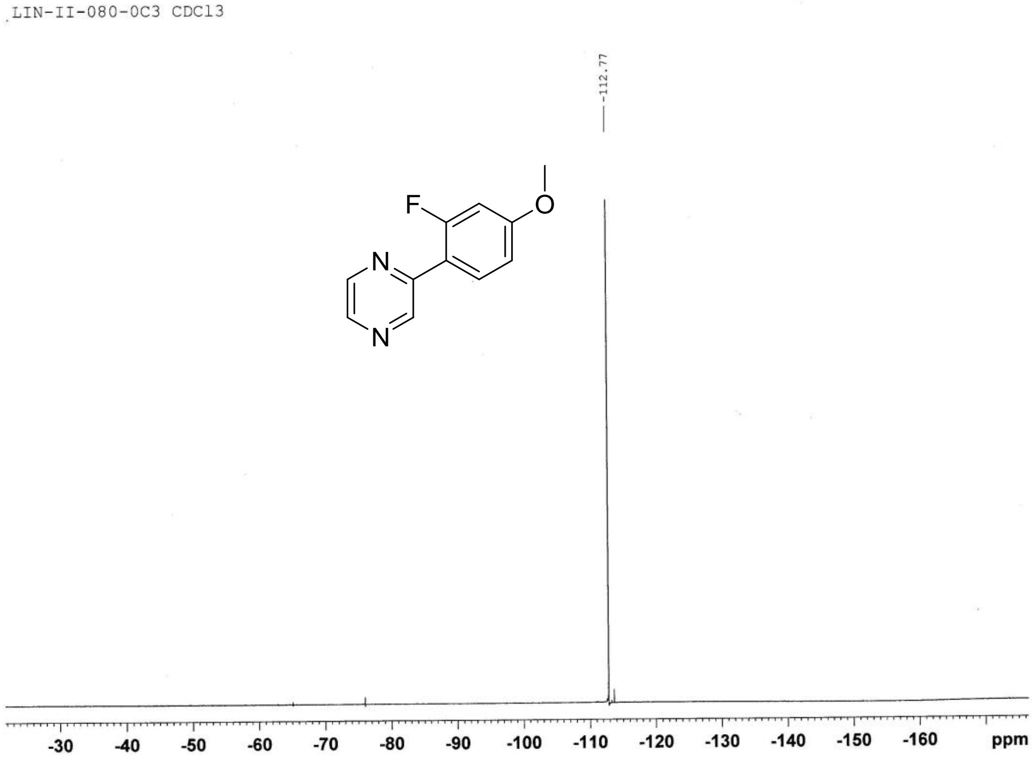
160.39
149.51
145.10
144.28
142.28
131.54
131.50
116.70
111.14
102.15
101.94
77.28
77.03
76.78
55.75
F
O
N
N
250 230 210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50
ppm


LIN-II-080-0C3 CDCl3
-112.77
F
O
N
N
-30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160
ppm