Electronic Supplementary Material (ESI) for RSC Advances.

Supporting Information

Alkali halides as nucleophilic reagent source for *N*-directed palladium-catalysed *ortho*-C–H halogenation of *s*-tetrazines and other heteroaromatics

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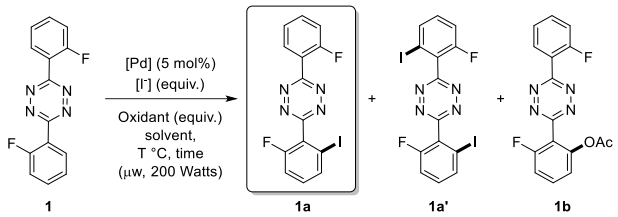
General Conditions

All reagents were purchased from commercial suppliers and used without purifications. All experiments were carried out under air using a microwave reaction vessel. Microwave heating was carried out using a CEM Discover microwave reactor. The microwave reactions were run in closed reaction vessels with magnetic stirring and with the temperature controlled via IR detection. Flash chromatography was performed on silica gel (40-63 µm). The identity and purity of the products were established at the "Chemical Analysis Platform and Molecular Synthesis University of Burgundy" (PACSMUB Platform – SATT SAYENS) using high-resolution mass spectrometry, elemental analysis and multinuclear NMR. ^{1}H (500, 400 or 300 MHz), ^{13}C (125 or 101 MHz), ^{19}F (470 or 282 MHz) spectra were recorded on Bruker AVANCE III instruments in $CDCl_3$ or CD_2Cl_2 solution. Chemical shifts are reported in ppm relative to $CDCl_3$ (^{1}H: 7.26 and ^{13}C: 77.16) or CD_2Cl_2 (^{1}H: 5.32 and ^{13}C: 54.00) and coupling constants *J* are given in Hz. High resolution mass spectra (HRMS) were obtained on a Thermo LTQ-Orbitrap XL with ESI source.

Optimization studies

Optimization studies for* ortho-*selective C–H iodination

Table S1: Screening reaction conditions for mono-iodination of 3,6-bis(2-fluorophenyl)-1,2,4,5-tetrazine (**1**).[a]

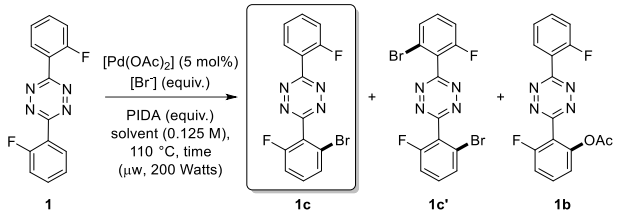


Entry	[Pd] (5 mol%)	Oxidant (equiv.)	[I⁻] (equiv.)	Solvent [0.125 M]	T (°C)	Time (min)	Conv. (%)	1a (%)	1a' (%)	1b (%)
1	-	PIDA (1.2)	NaI (1.2)	HOAc	110	30	0	0	0	0
2	$Pd(OAc)_2$	-	NaI (1.2)	HOAc	110	30	0	0	0	0
3	$Pd(OAc)_2$	PIDA (1.2)	-	HOAc	110	30	57	0	0	50[b]
4	$Pd(OAc)_2$	**PIDA (2.0)**	NaI (2.0)	HOAc	110	30	98	63	35	0
5	$Pd(OAc)_2$	**PIFA (1.2)**	NaI (1.2)	HOAc	110	30	38	26	12	0
6	$Pd(OAc)_2$	**$K_2S_2O_8$ (1.2)**	NaI (1.2)	HOAc	110	30	0	0	0	0
7	$Pd(OAc)_2$	PIDA (1.2)	NaI (1.2)	**CH_3NO_2**	110	30	0	0	0	0
8	$Pd(OAc)_2$	PIDA (1.2)	NaI (1.2)	**DCE**	90	30	0	0	0	0
9	$Pd(OAc)_2$	PIDA (1.2)	NaI (1.2)	**$PhCF_3$**	110	30	0	0	0	0
10	**$Pd(dba)_2$**	PIDA (1.2)	NaI (1.2)	HOAc	110	30	46	43	3	0
11	**$Pd(OPiv)_2$**	PIDA (1.2)	NaI (1.2)	HOAc	110	30	79	68	11	0
12	$Pd(OAc)_2$	PIDA (1.2)	**NaI (1.2)**	HOAc	110	30	86	67 (55)	19 (9)	0
13	$Pd(OAc)_2$	PIDA (1.2)	**LiI (1.2)**	HOAc	110	30	82	70	12	0
14	$Pd(OAc)_2$	PIDA (1.2)	**KI (1.2)**	HOAc	110	30	84	72 (68)	12	0
15	$Pd(OAc)_2$	PIDA (1.2)	**N(*t*Bu)I (1.2)**	HOAc	110	30	79	70	9	0

[a] Conditions: 3,6-bis(2-fluorophenyl)-1,2,4,5-tetrazine (**1**, 0.25 mmol, 1 equiv.), [Pd] (5 mol%), [I⁻] (1.2-2.0 equiv.), oxidant (1.2-2.0 equiv.), solvent [0.125 M], 90-110 °C, 30 min, microwave irradiations (200 Watts), under air. Conversion and selectivity based on **1** by ^{1}H and ^{19}F NMR analysis. Isolated yield are given under bracket. PIDA: Phenyliodine diacetate [$PhI(OAc)_2$]. PIFA: Bis(trifluoroacetoxy)iodobenzene [$PhI(OCOCF_3)_2$]. DCE: Dichloroethane. [b] 7% of diacetoxylated product was observed.

Optimization studies for* ortho-*selective C–H bromination

Table S2: Screening reaction conditions for mono-bromination of 3,6-bis(2-fluorophenyl)-1,2,4,5-tetrazine (**1**).[a]

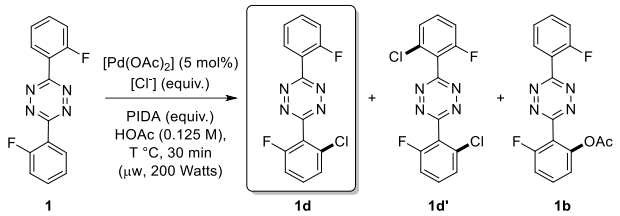


Entry	Oxidant (equiv.)	[Br⁻] (equiv.)	Solvent [0.125 M]	T (°C)	Time (min)	Conv. (%)	1c (%)	1c' (%)	1b (%)
1	PIDA (3.2)	NaBr (3.2)	CH_3NO_2	110	45	5	0	0	0
2	PIDA (1.2)	NaBr (3.2)	HOAc	110	45	47	47	0	0
3	PIDA (1.2)	NaBr (1.2)	HOAc	110	30	88	71 (60)	11	3[b]
4	PIDA (1.2)	KBr (1.2)	HOAc	110	30	86	73 (60)	13 (9)	0

[a] Conditions: 3,6-bis(2-fluorophenyl)-1,2,4,5-tetrazine (**1**, 0.25 mmol, 1 equiv.), $[Pd(OAc)_2]$ (5 mol%), $[Br^-]$ (1.2-3.2 equiv.), PIDA (1.2-3.2 equiv.), solvent [0.125 M], 110 °C, 30-45 min, microwave irradiations (200 Watts), under air. Conversion and selectivity based on **1** by ^1H and ^{19}F NMR analysis. Isolated yield are given under bracket. PIDA: Phenyliodine diacetate $[PhI(OAc)_2]$. [b] 3% of diacetoxylated product was observed.

Optimization studies for* ortho-*selective C–H chlorination

Table S3: Screening reaction conditions for mono-chlorination of 3,6-bis(2-fluorophenyl)-1,2,4,5-tetrazine (**1**).[a]

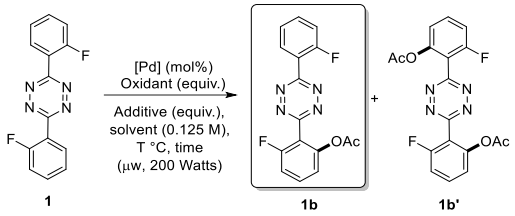


Entry	[Cl⁻] (equiv.)	Solvent [0.125 M]	T (°C)	Time (min)	Conv. (%)	1d (%)	1d' (%)	1b (%)
1	NaCl (1.2)	HOAc	110	30	87	61	12	10[b]
2	KCl (1.2)	HOAc	120	30	83	67	12	6[c]
3	KCl (1.2)	HOAc	110	30	89	62 (55%)	17 (11%)	8[c]

[a] Conditions: 3,6-bis(2-fluorophenyl)-1,2,4,5-tetrazine (**1**, 0.25 mmol, 1 equiv.), $[Pd(OAc)_2]$ (5 mol%), $[Cl^-]$ (1.2 equiv.), PIDA (1.2 equiv.), HOAc [0.125 M], 110 °C, 30 min, microwave irradiations (200 Watts), under air. Conversion and selectivity based on **1** by ^1H and ^{19}F NMR analysis. PIDA: Phenyliodine diacetate $[PhI(OAc)_2]$. [b] 4% of diacetoxylated product was observed. [c] 2% of diacetoxylated product was observed.

Optimization studies for* ortho*-selective C–H acetoxylation

Table S4: Screening reaction conditions for mono-acetoxylation of 3,6-bis(2-fluorophenyl)-1,2,4,5-tetrazine (**1**).[a]



Entry	$[Pd(OAc)_2]$ (mol%)	Oxidant (equiv.)	Additive (equiv.)	Solvent [0.125 M]	T (°C)	Time (min)	Conv. (%)	1b (%)	1b' (%)
1	(10)	PIDA (1.2)	-	HOAc	110	10	59	52	7
2	**(5)**	PIDA (1.2)	-	HOAc	110	10	57	52	5
3	(5)	PIDA (1.2)	-	HOAc	110	**30**	57	50	7
4	(5)	PIDA (1.2)	**KOAc (1.2)**	HOAc	110	30	50	50	Trace
5	(10)	PIDA (1.2)	-	HOAc	**120**	30	65	56	9
6	(10)	PIDA (1.2)	-	HOAc	110	30	60	54 (40)	6
7	(10)	PIDA (3.0)	-	HOAc	110	10	77	53	24
8	(10)	$K_2S_2O_8$ (3.0)	-	HOAc	110	10	21	21	0
9	(10)	PIDA (6.0)	-	HOAc	110	30	56	51	5
10	(10)	PIDA (3.0)	-	HOAc	120	10	100	50 (40)	50 (40)

[a] Conditions: 3,6-bis(2-fluorophenyl)-1,2,4,5-tetrazine (**1**, 0.25 mmol, 1 equiv.), $[Pd(OAc)_2]$ (5-10 mol%), oxidant (1.2-6.0 equiv.), additive (0-1.2 equiv.), HOAc [0.125 M], 110-120 °C, 10-30 min, microwave irradiations (200 Watts), under air. Conversion and selectivity based on **1** by ^1H and ^{19}F NMR analysis. PIDA: Phenyliodine diacetate $[PhI(OAc)_2]$.

General procedures

General procedure for the halogenation of heteroaryl derivatives

As a typical experiment, in a microwave reaction vessel equipped with a magnetic stirring bar was charged with heteroaryls (1 equiv., 0.25 mmol), $[Pd(OAc)_2]$ (5 mol%), PIDA (1.2 equiv., 0.3 mmol) and KX (1.2 equiv., 0.3 mmol) in acetic acid [0.125 M] under air. The mixture was heated at 110 °C during the corresponding time under microwaves irradiations (200 Watts). After cooling down to room temperature, the solvent was removed under vacuum and the residue was analysed by ^1H and ^{19}F NMR spectroscopy to determine the conversion and selectivity of the halogenation reaction. The crude mixture was purified by silica gel column chromatography using an appropriate ratio of eluent (Dichloromethane or Ethyl Acetate/Heptane or Pentane) to afford the targeted product.

3-(2-Fluoro-6-iodophenyl)-6-(2-fluorophenyl)-1,2,4,5-tetrazine (1a)[1]

Isolated yield: 68% (67 mg, as a purple solid). Rf = 0.51 (Dichloromethane/Heptane: 7/3).

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.46–8.40 (m, 1H), 7.88–7.84 (m, 1H), 7.71–7.63 (m, 1H), 7.46–7.30 (m, 4H).

$^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$): δ (ppm) = –108.8 (1F), –111.0 (1F).

3-(2-Bromo-6-fluorophenyl)-6-(2-fluorophenyl)-1,2,4,5-tetrazine (1c)[1]

Isolated yield: 60% (52 mg, as a purple solid). Rf = 0.52 (Dichloromethane/Heptane: 7/3).

^1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.42 (td, *J* = 7.6 and 1.8 Hz, 1H), 7.69–7.65 (m, 1H), 7.62 (dt, *J* = 8.2 and 1.0 Hz, 1H), 7.48 (td, *J* = 8.3 and 5.8 Hz, 1H), 7.43 (td, *J* = 7.6 and 1.1 Hz, 1H), 7.36 (ddd, *J* = 10.9, 8.4 and 1.1 Hz, 1H), 7.30 (td, *J* = 8.9 and 1.0 Hz, 1H).

$^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$): δ (ppm) = –110.0 (1F), –111.0 (1F).

3-(2-Chloro-6-fluorophenyl)-6-(2-fluorophenyl)-1,2,4,5-tetrazine (1d)[1]

Isolated yield: 55% (42 mg, as a purple solid). Rf = 0.55 (Dichloromethane/Heptane: 7/3).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.42 (td, *J* = 7.6 and 1.8 Hz, 1H), 7.70–7.63 (m, 1H), 7.55 (td, *J* = 8.3 and 5.8 Hz, 1H), 7.46–7.43 (m, 2H), 7.41–7.33 (m, 1H), 7.29–7.23 (m, 1H).

^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$): δ (ppm) = –111.1 (1F), –111.1 (1F).

3-(2-Iodophenyl)-6-phenyl-1,2,4,5-tetrazine (2a)[1]

Isolated yield: 61% (55 mg, as a purple solid). Rf = 0.44 (Dichloromethane/Heptane: 1/1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.73–8.71 (m, 2H), 8.12 (dd, *J* = 8.0 and 1.0 Hz, 1H), 7.99 (dd, *J* = 7.7 and 1.6 Hz, 1H), 7.70–7.58 (m, 4H), 7.31–7.26 (m, 1H).

3-(2-Bromophenyl)-6-phenyl-1,2,4,5-tetrazine (2c)[2]

Isolated yield: 48% (37 mg, as a purple solid). Rf = 0.34 (Dichloromethane/Heptane: 1/1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.72–8.70 (m, 2H), 8.02 (dd, *J* = 7.7 and 1.7 Hz, 1H), 7.83 (dd, *J* = 8.0 and 1.1 Hz, 1H), 7.69–7.62 (m, 3H), 7.57 (td, *J* = 7.6 and 1.2 Hz, 1H), 7.49 (td, *J* = 7.8 and 1.7 Hz, 1H).

3-(2-Chlorophenyl)-6-phenyl-1,2,4,5-tetrazine (2d)[2]

Isolated yield: 35% (23 mg, as a purple solid). Rf = 0.45 (Dichloromethane/Heptane: 1/1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) = 8.69–8.67 (m, 2H), 8.05 (dd, *J* = 7.4 and 2.0 Hz, 1H), 7.71–7.64 (m, 4H), 7.61–7.54 (m, 2H).

3-(4-Fluoro-6-Iodophenyl)-6-(4-fluorophenyl)-1,2,4,5-tetrazine (3a)

Isolated yield: 51% (50 mg, as a purple solid). Rf = 0.36 (Dichloromethane/Heptane: 1/1).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.74–8.71 (m, 2H), 8.03 (dd, *J* = 8.7 and 5.7 Hz, 1H), 7.85 (dd, *J* = 8.0 and 2.6 Hz, 1H), 7.35–7.30 (m, 3H).

^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$): δ (ppm) = –105.3 (1F), –107.3 (1F).

^{13}C NMR (125 MHz, CD_2Cl_2): δ (ppm) = 167.6 (d, *J* = 254.1 Hz), 167.1, 164.9 (d, *J* = 256.7 Hz), 163.0, 134.0 (d, *J* = 3.5 Hz), 133.4 (d, *J* = 9.1 Hz), 131.3 (d, *J* = 9.2 Hz), 128.9 (d, *J* = 24.3 Hz), 128.4 (d, *J* = 3.2 Hz), 117.2 (d, *J* = 22.3 Hz), 116.7 (d, *J* = 21.5 Hz), 95.8 (d, *J* = 8.4 Hz).

HRMS + p ESI (m/z) $[M+H]^+$ calcd for $C_{14}H_8F_2IN_4$: 396.97562; Found: 396.97519.

3-(4-Fluoro-6-bromophenyl)-6-(4-fluorophenyl)-1,2,4,5-tetrazine (3c)

Isolated yield: 50% (43 mg, as a purple solid). Rf = 0.36 (Dichloromethane/Heptane: 2/3).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.74–8.71 (m, 2H), 8.06 (dd, *J* = 8.7 and 5.9 Hz, 1H), 7.58 (dd, *J* = 8.2 and 2.5 Hz, 1H), 7.35–7.27 (m, 3H).

^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$): δ (ppm) = –105.3 (1F), –106.3 (1F).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 167.2 (d, *J* = 255.2 Hz), 165.8, 165.1 (d, *J* = 256.9 Hz), 162.5, 133.7 (d, *J* = 9.2 Hz), 130.9 (d, *J* = 9.0 Hz), 130.0 (d, *J* = 3.5 Hz), 127.7 (d, *J* = 3.0 Hz), 123.3 (d, *J* = 9.9 Hz), 122.2 (d, *J* = 24.8 Hz), 116.9 (d, *J* = 22.1 Hz), 115.7 (d, *J* = 21.5 Hz).

HRMS + p ESI (m/z) $[M+H]^+$ calcd for $C_{14}H_8BrF_2N_4$: 348.98949; Found: 348.98915.

3-(4-Fluoro-6-chlorophenyl)-6-(4-fluorophenyl)-1,2,4,5-tetrazine (3d)

Isolated yield: 45% (34 mg, as a purple solid). Rf = 0.33 (Dichloromethane/Heptane: 2/3).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.74–8.70 (m, 2H), 8.10 (dd, *J* = 8.7 and 5.9 Hz, 1H), 7.39 (dd, *J* = 8.4 and 2.5 Hz, 1H), 7.34–7.30 (m, 2H), 7.28–7.23 (m, 1H).

^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$): δ (ppm) = –105.3 (1F), –106.0 (1F).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 167.2 (d, *J* = 255.0 Hz), 165.3 (d, *J* = 256.2 Hz), 165.1, 162.5, 135.3 (d, *J* = 10.7 Hz), 133.8 (d, *J* = 9.6 Hz), 130.9 (d, *J* = 9.2 Hz), 128.1 (d, *J* = 3.7 Hz), 127.7 (d, *J* = 3.2 Hz), 119.0 (d, *J* = 25.0 Hz), 116.9 (d, *J* = 22.2 Hz), 115.2 (d, *J* = 21.6 Hz).

HRMS + p ESI (m/z) $[M+H]^+$ calcd for $C_{14}H_8ClF_2N_4$: 305.04001; Found: 305.03974.

3-(3-Fluoro-6-iodophenyl)-6-(3-fluorophenyl)-1,2,4,5-tetrazine (4a)

Isolated yield: 35% (35 mg, as a purple solid). Rf = 0.2 (Dichloromethane/Pentane: 3/7).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.52 (ddd, *J* = 7.8, 1.6 and 1.0 Hz, 1H), 8.41 (ddd, *J* = 9.7, 2.6 and 1.5 Hz, 1H), 8.08 (dd, *J* = 8.8 and 5.3 Hz, 1H), 7.78 (dd, *J* = 8.9 and 3.0 Hz, 1H), 7.62 (td, *J* = 8.1 and 5.7 Hz, 1H), 7.38 (tdd, *J* = 8.3, 2.7 and 1.0 Hz, 1H), 7.07 (ddd, *J* = 8.7, 7.8 and 3.0 Hz, 1H).

^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$): δ (ppm) = –110.7 (1F), –112.4 (1F).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 166.8 (d, *J* = 2.4 Hz), 164.7 (d, *J* = 247.7 Hz), 164.3 (d, *J* = 250.1 Hz), 162.7 (d, *J* = 3.2 Hz), 142.8 (d, *J* = 7.6 Hz), 138.5 (d, *J* = 7.7 Hz), 133.7 (d, *J* = 8.2 Hz), 131.2 (d, *J* = 8.0 Hz), 124.4 (d, *J* = 3.1 Hz), 120.5 (d, *J* = 21.3 Hz), 120.2 (d, *J* = 21.6 Hz), 119.2 (d, *J* = 24.3 Hz), 115.6 (d, *J* = 24.0 Hz), 88.7 (d, *J* = 3.7 Hz).

HRMS + p ESI (m/z) $[M+H]^+$ calcd for $C_{14}H_8F_2IN_4$: 396.97562; Found: 396.97516.

3-(3-Fluoro-6-bromophenyl)-6-(3-fluorophenyl)-1,2,4,5-tetrazine (4c)

Isolated yield: 35% (30 mg, as a purple solid). Rf = 0.35 (Dichloromethane/Pentane: 3/7).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.52 (d, *J* = 7.8 Hz, 1H), 8.41 (d, *J* = 9.5 Hz, 1H), 7.81–7.78 (m, 2H), 7.62 (td, *J* = 8.0 and 5.6 Hz, 1H), 7.38 (td, *J* = 8.3 and 2.7 Hz, 1H), 7.22 (td, *J* = 8.2 and 3.1 Hz, 1H).

^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$): δ (ppm) = –110.7 (1F), –113.1 (1F).

^{13}C NMR (125 MHz, CD_2Cl_2): δ (ppm) = 166.5 (d, *J* = 2.3 Hz), 164.9 (d, *J* = 246.8 Hz), 163.5 (d, *J* = 248.6 Hz), 163.2 (d, *J* = 3.2 Hz), 136.6 (d, *J* = 7.8 Hz), 135.6 (d, *J* = 8.2 Hz), 134.2 (d, *J* = 8.3 Hz), 131.8 (d, *J* = 7.9 Hz), 124.7 (d, *J* = 3.0 Hz), 120.7 (d, *J* = 21.5 Hz), 120.5 (d, *J* = 22.2 Hz), 119.8 (d, *J* = 25.1 Hz), 117.2 (d, *J* = 3.4 Hz), 115.7 (d, *J* = 24.0 Hz).

HRMS + p ESI (m/z) $[M+H]^+$ calcd for $C_{14}H_8BrF_2N_4$: 348.98949; Found: 348.98911.

3-(3-Fluoro-6-chlorophenyl)-6-(3-fluorophenyl)-1,2,4,5-tetrazine (4d)

Isolated yield: 28% (21 mg, as a purple solid). Rf = 0.4 (Dichloromethane/Pentane: 3/7).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.51 (d, *J* = 7.9 Hz, 1H), 8.40 (dt, *J* = 9.6 and 2.0 Hz, 1H), 7.83 (dd, *J* = 8.5 and 3.1 Hz, 1H), 7.65–7.59 (m, 2H), 7.38 (td, *J* = 8.0 and 2.5 Hz, 1H), 7.31–7.26 (m, 1H).

^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$): δ (ppm) = –110.7 (1F), –113.6 (1F).

^{13}C NMR (125 MHz, CD_2Cl_2): δ (ppm) = 165.8 (d, *J* = 2.2 Hz), 164.9 (d, *J* = 254.4 Hz), 163.2 (d, *J* = 3.2 Hz), 162.9 (d, *J* = 255.6 Hz), 134.2 (d, *J* = 8.3 Hz), 133.6 (d, *J* = 8.2 Hz), 133.4 (d, *J* = 8.2 Hz), 131.8 (d, *J* = 8.1 Hz), 129.3 (d, *J* = 3.5 Hz), 124.7 (d, *J* = 3.0 Hz), 120.7 (d, *J* = 21.4 Hz), 120.4 (d, *J* = 22.8 Hz), 119.5 (d, *J* = 25.3 Hz), 115.7 (d, *J* = 24.1 Hz).

HRMS + p ESI (m/z) $[M+H]^+$ calcd for $C_{14}H_8ClF_2N_4$: 305.04001; Found: 305.03989.

1-(2-Iodophenyl)-2-phenyl-diazene (5a)[3]

Isolated yield: 39% (46 mg, as an orange solid). Rf = 0.4 (Dichloromethane/Heptane: 2/3).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.04 (dd, *J* = 7.9 and 1.3 Hz, 1H), 8.02–7.99 (m, 2H), 7.64 (dd, *J* = 8.0 and 1.6 Hz, 1H), 7.57–7.50 (m, 3H), 7.45–7.41 (m, 1H), 7.19–7.15 (m, 1H).

1-(2-Bromophenyl)-2-phenyl-diazene (5c)[3]

Isolated yield: 60% (39 mg, as an orange solid). Rf = 0.4 (Dichloromethane/Heptane: 2/3).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.99 (dd, *J* = 8.1 and 1.7 Hz, 2H), 7.76 (dd, *J* = 7.9 and 1.4 Hz, 1H), 7.68 (dd, *J* = 8.0 and 1.7 Hz, 1H), 7.56-7.50 (m, 3H), 7.40 (td, *J* = 7.6 and 1.4 Hz, 1H), 7.32 (td, *J* = 7.5 and 1.7 Hz, 1H).

2-(2-Iodo-6-methylphenyl)-pyrimidine (6a)[4]

Isolated yield: 65% (48 mg, as a colourless oil). Rf = 0.3 (Dichloromethane/Heptane: 3/7).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.90 (d, *J* = 4.9 Hz, 2H), 7.76 (dd, *J* = 7.9 and 0.4 Hz, 1H), 7.32 (t, *J* = 4.9 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.01 (t, *J* = 7.8 Hz, 1H), 2.12 (s, 3H).

2-(2-Bromo-6-methylphenyl)-pyrimidine (6c)[5]

Isolated yield: 61% (38 mg, as a colourless oil). Rf = 0.3 (Dichloromethane/Heptane: 1/1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.90 (d, *J* = 4.9 Hz, 2H), 7.49 (d, *J* = 7.7 and 0.6 Hz, 1H), 7.32 (t, *J* = 4.9 Hz, 1H), 7.24–7.21 (m, 1H), 7.17 (t, *J* = 7.7 Hz, 1H), 2.11 (s, 3H).

9-Iodo-2-methyl-napthtol[1,2-*d*]thiazole (7a)

Isolated yield: 56% (45 mg, as a white solid). Rf = 0.33 (Ethyl acetate/Heptane: 1.5/8.5).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.40 (d, *J* = 7.4 Hz, 1H), 7.92 (dd, *J* = 8.3 and 5.6 Hz, 2H), 7.75 (d, *J* = 8.7 Hz, 1H), 7.16 (t, *J* = 7.7 Hz, 1H), 2.97 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 163.0, 147.0, 141.9, 134.9, 133.3, 129.4, 128.6, 126.5, 126.1, 119.7, 88.7, 20.5.

HRMS + p ESI (m/z) $[M+H]^+$ calcd for $C_{12}H_9INS$: 325.94949; Found: 325.94913.

9-Chloro-2-methyl-napthtol[1,2-*d*]thiazole (7d)

Isolated yield: 53% (31 mg, as a yellow solid). Rf = 0.37 (Ethyl acetate/Heptane: 1.5/8.5).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.93 (d, *J* = 8.7 Hz, 1H), 7.86 (dd, *J* = 8.1 and 1.0 Hz, 1H), 7.79 (d, *J* = 8.7 Hz, 1H), 7.74 (dd, *J* = 7.5 and 1.2 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 2.99 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 164.3, 147.6, 135.5, 134.4, 130.3, 129.7, 127.8, 126.1, 125.8, 125.7, 120.0, 20.7.

HRMS + p ESI (m/z) $[M+H]^+$ calcd for $C_{12}H_9ClNS$: 234.01387; Found: 234.01377.

1-(2-Iodophenyl)-4-nitro-*1H*-pyrazole (8a)

Isolated yield: 62% (49 mg, as a white solid). Rf = 0.25 (Dichloromethane/Heptane: 3/7).

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 8.45 (d, *J* = 0.5 Hz, 1H), 8.27 (s, 1H), 8.03 (dd, *J* = 8.0 and 1.3 Hz, 1H), 7.54 (td, *J* = 7.6 and 1.4 Hz, 1H), 7.46 (dd, *J* = 7.9 and 1.7 Hz, 1H), 7.28 (t, *J* = 8.0 and 1.7 Hz, 1H).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 142.4, 140.9, 140.5, 136.9, 132.1, 131.0, 130.0, 128.4, 94.3.

HRMS + p ESI (m/z) $[M+H]^+$ calcd for $C_9H_7IN_3O_2$: 315.95775; Found: 315.95757.

1-(2-Iodophenyl)-4-bromo-*1H*-pyrazole (9a)

Isolated yield: 80% (76 mg, as a white solid). Rf = 0.25 (Ethyl acetate/Heptane: 1/9).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.86 (dd, *J* = 8.0 and 1.3 Hz, 1H), 7.75 (s, 1H), 7.55 (s, 1H), 7.51 (dd, *J* = 8.1 and 1.3 Hz, 1H), 7.13 (t, *J* = 8.0 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 141.8, 140.5, 138.3, 133.6, 132.1, 131.2, 130.4, 98.5, 95.0.

HRMS + p ESI (m/z) $[M+H]^+$ calcd for $C_9H_6BrClIN_2$: 382.84421; Found: 382.84384.

1-(2-bromo-6-iodophenyl)-4-bromo-*1H*-pyrazole (10a)

Isolated yield: 70% (75 mg, as a white solid). Rf = 0.4 (Dichloromethane/Heptane: 1/9).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.90 (dd, *J* = 8.0 and 1.3 Hz, 1H), 7.75 (s, 1H), 7.68 (dd, *J* = 8.1 and 1.3 Hz, 1H), 7.55 (d, *J* = 0.5 Hz, 1H), 7.05 (t, *J* = 8.0 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 141.8, 141.7, 139.0, 133.6, 132.4, 131.0, 122.9, 98.4, 95.0.

HRMS + p ESI (m/z) $[M+H]^+$ calcd for $C_9H_6Br_2IN_2$: 426.79369. Found 426.79311.

4-Bromo-1-[(2-iodo-6-methylphenyl)methyl]-*1H*-pyrazole (11a)

Isolated yield: 51% (48 mg, as a white solid). Rf = 0.37 (Ethyl acetate/Heptane: 1.5/8.5).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.78 (d, *J* = 7.6 Hz, 1H), 7.47 (s, 1H), 7.25 (s, 1H), 7.20 (d, *J* = 7.7 Hz, 1H), 6.97 (t, *J* = 7.7 Hz, 1H), 5.5 (s, 2H), 2.37 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 140.4, 139.8, 138.2, 135.6, 131.4, 130.8, 129.0, 103.0, 93.2, 59.0, 20.9.

HRMS + p ESI (m/z) $[M+H]^+$ calcd for $C_{11}H_{11}BrIN_2$: 376.91448. Found: 376.91405.

3-(2-Bromophenylmethyl)-6-(phenylmethyl)-1,2,4,5-tetrazine (12c)

Isolated yield: 54% (46 mg, as a purple solid). Rf = 0.35 (Ethyl acetate/Heptane: 1/9).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.58 (dd, *J* = 8.0 and 1.2 Hz, 1H), 7.42–7.38 (m, 3H), 7.34–7.29 (m, 3H), 7.28–7.25 (m, 1H), 7.16 (td, *J* = 7.7 and 1.7 Hz, 1H), 4.79 (s, 2H), 4.62 (s, 2H).
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 169.2, 168.7, 135.9, 135.6, 133.2, 132.0, 129.4, 129.3, 129.0, 127.9, 127.5, 125.1, 41.4, 41.3.
HRMS + p ESI (m/z) $[M+H]^+$ calcd for $C_{16}H_{14}BrN_4$: 341.03964; Found: 341.03923.

2-(2,4-Difluorophenyl)-6-bromo-pyridine (13c)
Isolated yield: 51% (34 mg, as a colourless oil). Rf = 0.35 (Ethyl acetate/Heptane: 3/7).
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.75 (dd, *J* = 4.8 and 0.6 Hz, 1H), 7.80 (td, *J* = 7.7 and 1.8 Hz, 1H), 7.38–7.33 (m, 2H), 7.26 (dt, *J* = 8.0 and 2.2 Hz, 1H), 6.92 (td, *J* = 8.9 and 2.5 Hz, 1H).
^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$): δ (ppm) = –107.7 (d, *J* = 7.3 Hz, 1F), –108.6 (d, *J* = 7.3 Hz, 1F).
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 163.4 (dd, *J* = 252.9 and 13.4 Hz), 161.7 (dd, *J* = 252.5 and 13.1 Hz), 152.9, 149.8, 136.5, 126.8 (dd, *J* = 18.7 and 4.4 Hz), 125.8, 124.1 (dd, *J* = 11.7 and 5.4 Hz), 123.3, 116.6 (dd, *J* = 24.3 and 3.9 Hz), 104.1 (dd, *J* = 26.8 and 25.1 Hz).
HRMS + p ESI (m/z) $[M+H]^+$ calcd for $C_{11}H_7BrF_2N$: 269.97244; Found: 269.97211.

2-(2,4-Difluorophenyl)-6-chloro-pyridine (13d)
Isolated yield: 70% (39 mg, as a colourless oil). Rf = 0.3 (Ethyl acetate/Heptane: 3/7).
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.75 (d, *J* = 4.4 Hz, 1H), 7.80 (td, *J* = 7.7 and 1.8 Hz, 1H), 7.39 (dd, *J* = 7.8 and 1.0 Hz, 1H), 7.34 (ddd, *J* = 7.6, 4.9 and 1.2 Hz, 1H), 7.08 (dt, *J* = 8.3, 2.4, 1H), 6.87 (td, *J* = 8.9 and 2.5 Hz, 1H).
^{19}F{^{1}H} NMR (470 MHz, CD_2Cl_2): δ (ppm) = –109.4 (d, *J* = 7.0 Hz, 1F), –109.5 (d, *J* = 7.0 Hz, 1F).
^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) = 163.5 (dd, *J* = 252.1 and 14.4 Hz), 162.2 (dd, *J* = 249.2 and 11.17 Hz), 151.5, 149.8, 136.5, 135.3 (dd, *J* = 12.7 and 6.6 Hz), 125.9, 125.0 (dd, *J* = 19.0 and 4.2 Hz), 123.3, 113.6 (dd, *J* = 24.7 and 4.0 Hz), 103.6 (dd, *J* = 26.8 and 25.2 Hz).
HRMS + p ESI (m/z) $[M+H]^+$ calcd for $C_{11}H_7F_2NCl$: 226.02296. Found: 226.02279.

1-(2-Bromophenyl)-4-chloro-*1H*-pyrazole (15)
Isolated yield: 46% (29 mg, as a white solid). Rf = 0.35 (Ethyl acetate/Heptane: 1.5/8.5).
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.82 (s, 1H), 7.71 (dd, *J* = 8.0 and 1.4 Hz, 1H), 7.67 (s, 1H), 7.49 (dd, *J* = 7.9 and 1.8 Hz, 1H), 7.43 (td, *J* = 7.6 and 1.4 Hz, 1H), 7.30 (td, *J* = 7.8 and 1.8 Hz, 1H).

1-(2-Bromo-5-iodophenyl)-4-chloro-*1H*-pyrazole (16)
Isolated yield: 90% (86 mg, as a white solid). Rf = 0.37 (Ethyl acetate/Heptane: 1.5/8.5).
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.86 (dd, *J* = 8.0 and 1.3 Hz, 1H), 7.75 (s, 1H), 7.55 (s, 1H), 7.51 (dd, *J* = 8.1 and 1.3 Hz, 1H), 7.13 (t, *J* = 8.1 Hz, 1H).
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 141.8, 140.5, 138.3, 133.6, 132.1, 131.2, 130.4, 98.5, 95.0.
HRMS + p ESI (m/z) $[M+H]^+$ calcd for $C_9H_6BrClIN_2$: 382.84421; Found: 382.84380.

General procedure for the acetoxylation

As a typical experiment, in a microwave reaction vessel equipped with a magnetic stirring bar was charged with 3,6-bis(2-fluorophenyl)-1,2,4,5-tetrazine (1 equiv., 0.25 mmol), $[Pd(OAc)_2]$ (5 mol%), and PIDA (1,2 equiv., 0.3 mmol) in acetic acid [0.125 M] under air. The mixture was heated at 110 °C during 30 min under microwaves irradiations (200 Watts). After cooling down at room temperature, the solvent was removed in vacuum and the residue was analysed by ^{1}H and ^{19}F NMR to determine the conversion and the selectivity of the acetoxylation reaction. The crude mixture was purified by silica gel column chromatography using an appropriate ratio of eluent (Dichloromethane/Heptane) to afford the desired product.

3-(2-Fluoro-6-acetylphenyl)-6-(2-fluorophenyl)-1,2,4,5-tetrazine (1b)

Isolated yield: 40% (33 mg, as a purple solid). Rf = 0.3 (Dichloromethane/Heptane: 3/1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) = 8.36 (td, *J* = 7.7 and 1.7 Hz, 1H), 7.72–7.63 (m, 2H), 7.46 (td, *J* = 7.8 and 0.9 Hz, 1H), 7.37 (dd, *J* = 11.0 and 8.4 Hz, 1H), 7.28 (t, *J* = 8.7 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 1H), 2.18 (s, 3H).

^{19}F{^{1}H} NMR (470 MHz, CD_2Cl_2): δ (ppm) = –112.7 (1F), –113.8 (1F).

^{13}C NMR (125 MHz, CD_2Cl_2): δ (ppm) = 169.5, 164.0 (d, *J* = 5.7 Hz), 162.2 (d, *J* = 259.3 Hz), 162.8 (d, *J* = 255.7 Hz), 162.2 (d, *J* = 3.9 Hz), 150.7 (d, *J* = 4.3 Hz), 135.1 (d, *J* = 8.8 Hz), 133.7 (d, *J* = 10.2 Hz), 132.2 (d, *J* = 0.7 Hz), 125.6 (d, *J* = 3.9 Hz), 121.0 (d, *J* = 9.9 Hz), 120,5 (d, *J* = 23.6 Hz), 118.0 (d, *J* = 21.6 Hz), 116.4 (d, *J* = 14.9 Hz), 114.8 (d, *J* = 21.5 Hz), 21.0.

HRMS + p ESI (m/z) $[M+Na]^+$ calcd for $C_{16}H_{10}F_2N_4O_2Na$: 351.06640; Found: 351.06613.

3-(2-Fluoro-6-acetylphenyl)-6-(2-fluorophenyl)-1,2,4,5-tetrazine (1b')

Isolated yield: 40% (39 mg, as a purple solid). Rf = 0.20 (Dichloromethane/Heptane: 3/1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) = 7.70–7.65 (m, 2H), 7.29 (t, *J* = 9.0 Hz, 2H), 7.21 (d, *J* = 8.3 Hz, 2H), 2.17 (s, 6H).

^{19}F{^{1}H} NMR (470 MHz, CD_2Cl_2): δ (ppm) = –113.8 (2F).

^{13}C NMR (125 MHz, CD_2Cl_2): δ (ppm) = 169.4, 162.8 (d, *J* = 255.9 Hz), 162.4 (d, *J* = 3.1 Hz), 150.7 (d, *J* = 4.3 Hz), 133.9 (d, *J* = 10.3 Hz), 120.5 (d, *J* = 3.5 Hz), 116.2 (d, *J* = 14.8 Hz), 114.8 (d, *J* = 21.4 Hz), 21.0.

HRMS + p ESI (m/z) $[M+Na]^+$ calcd for $C_{18}H_{12}F_2N_4O_4Na$: 409.07188; Found: 409.07130.

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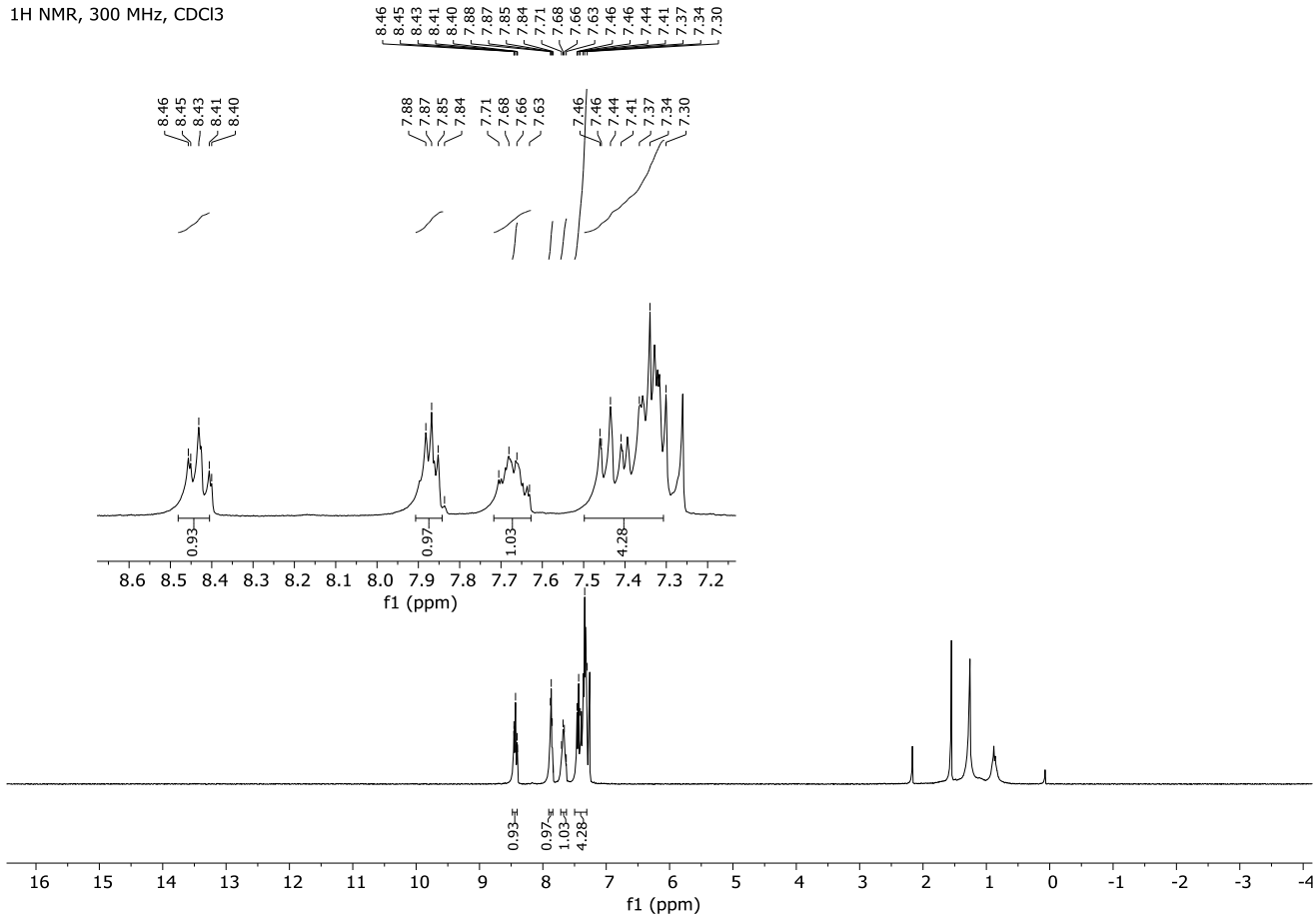
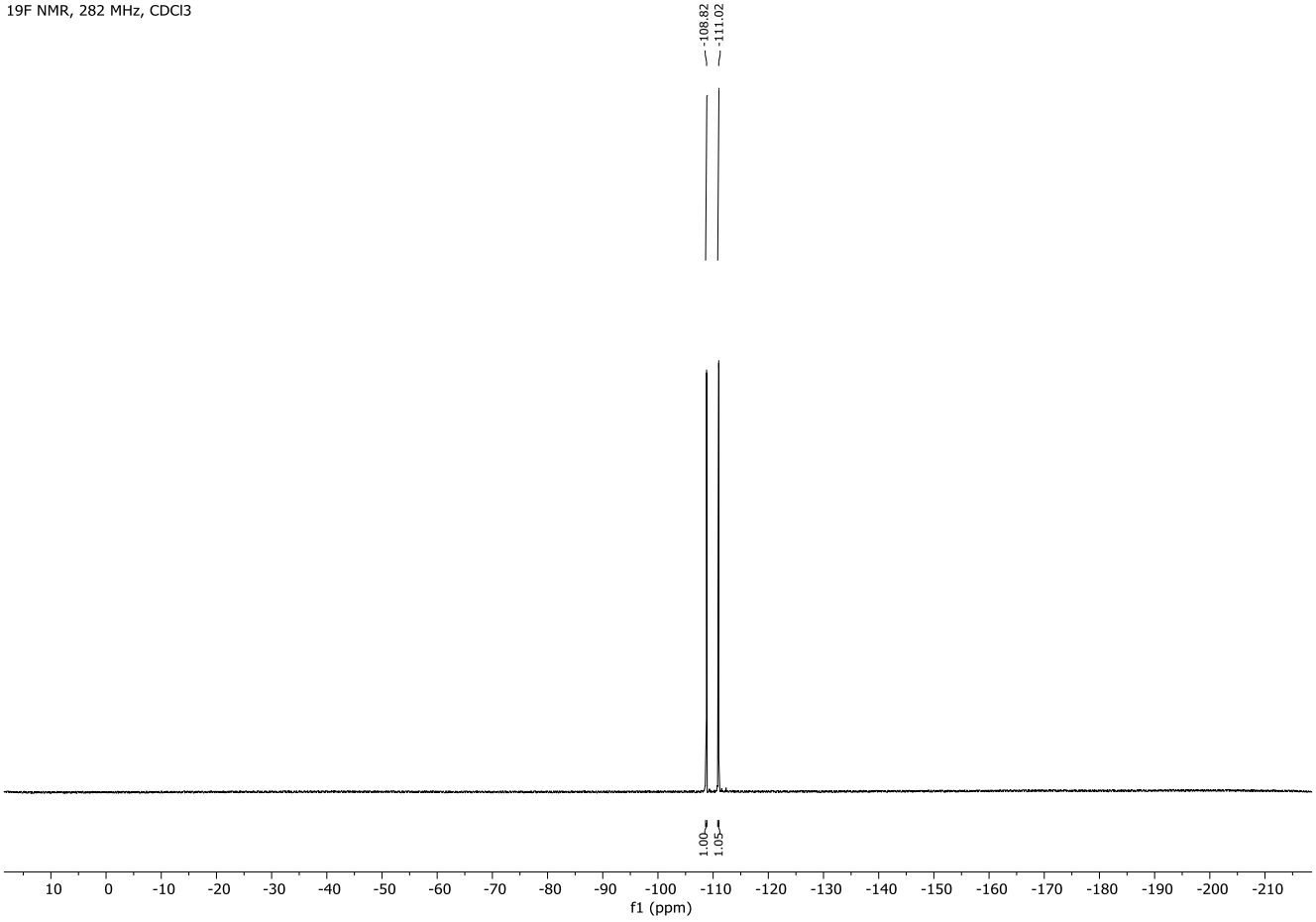
Copy of NMR spectrum

3-(2-Fluoro-6-iodophenyl)-6-(2-fluorophenyl)-1,2,4,5-tetrazine (1a)

1H NMR, 300 MHz, CDCl3

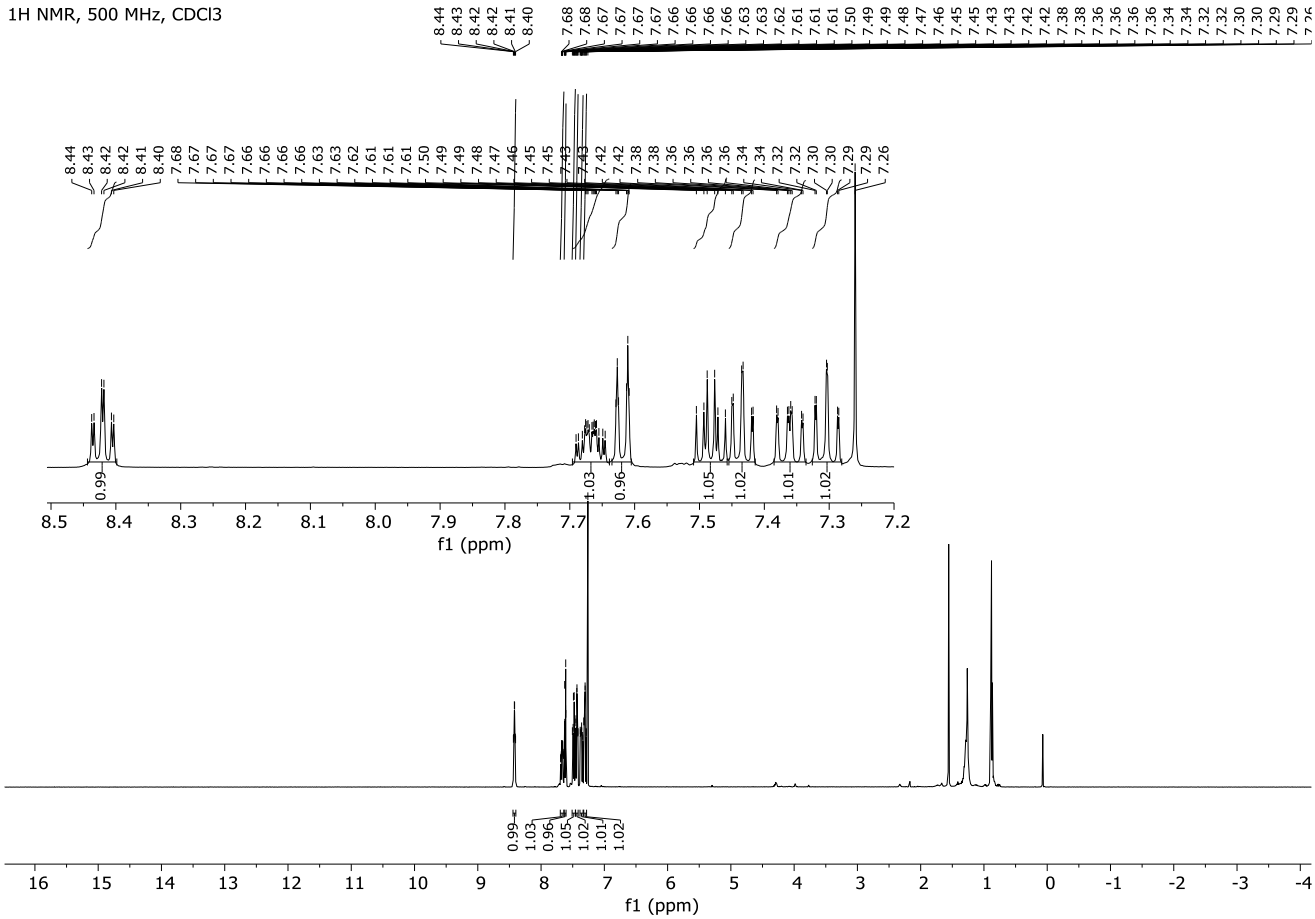


19F NMR, 282 MHz, CDCl3

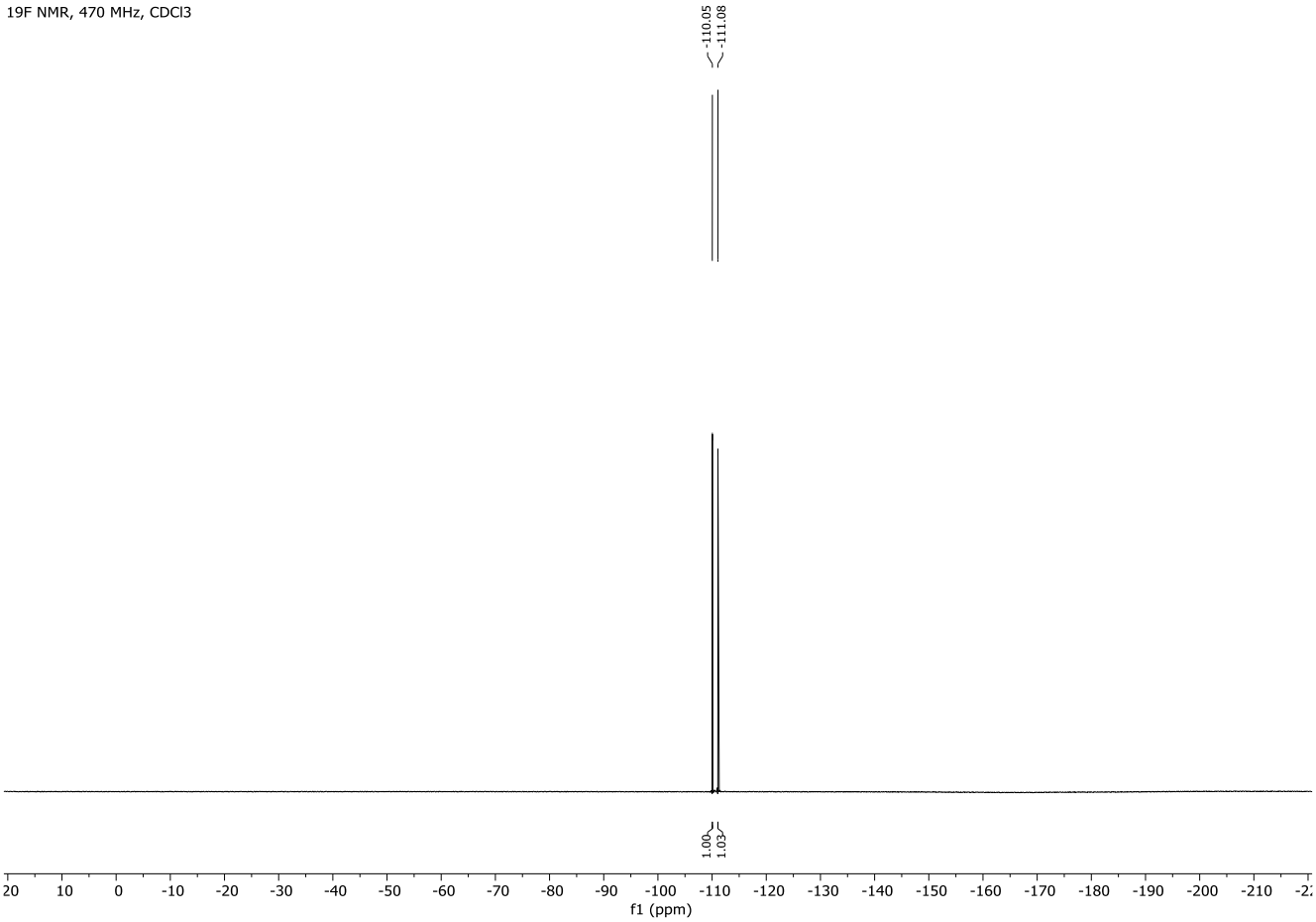


3-(2-Bromo-6-fluorophenyl)-6-(2-fluorophenyl)-1,2,4,5-tetrazine (1c)

1H NMR, 500 MHz, CDCl3

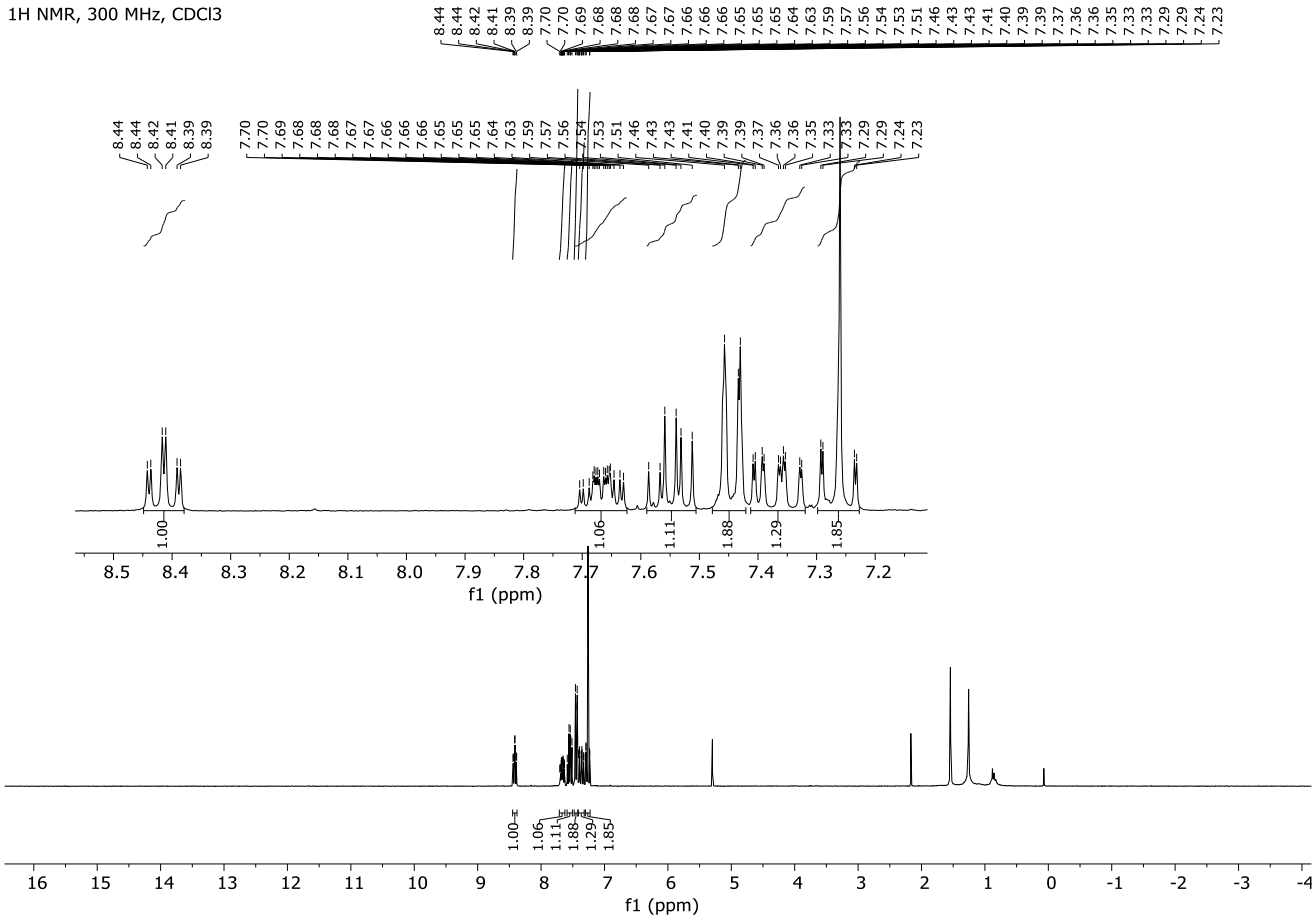


19F NMR, 470 MHz, CDCl3

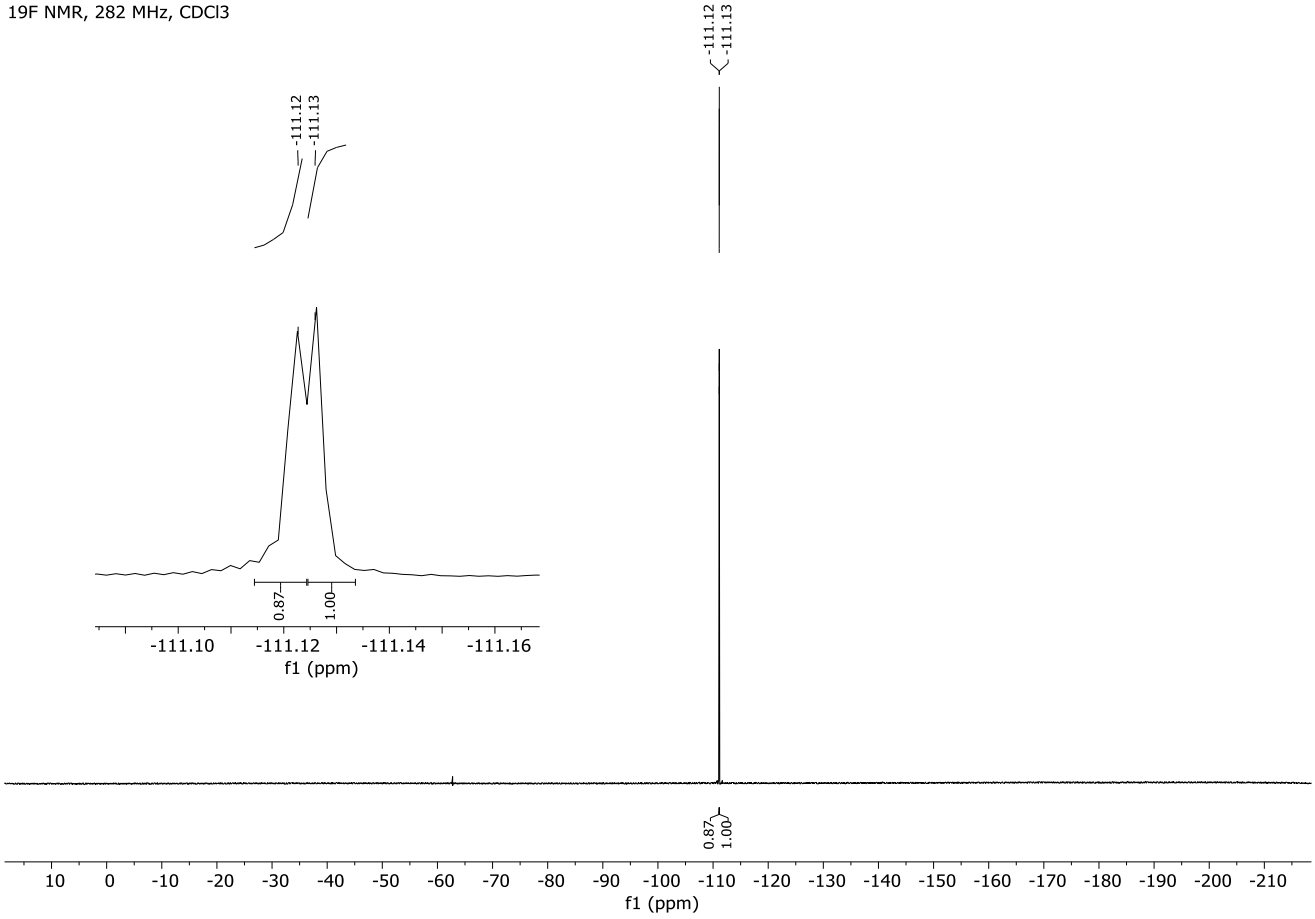


3-(2-Chloro-6-fluorophenyl)-6-(2-fluorophenyl)-1,2,4,5-tetrazine (1d)

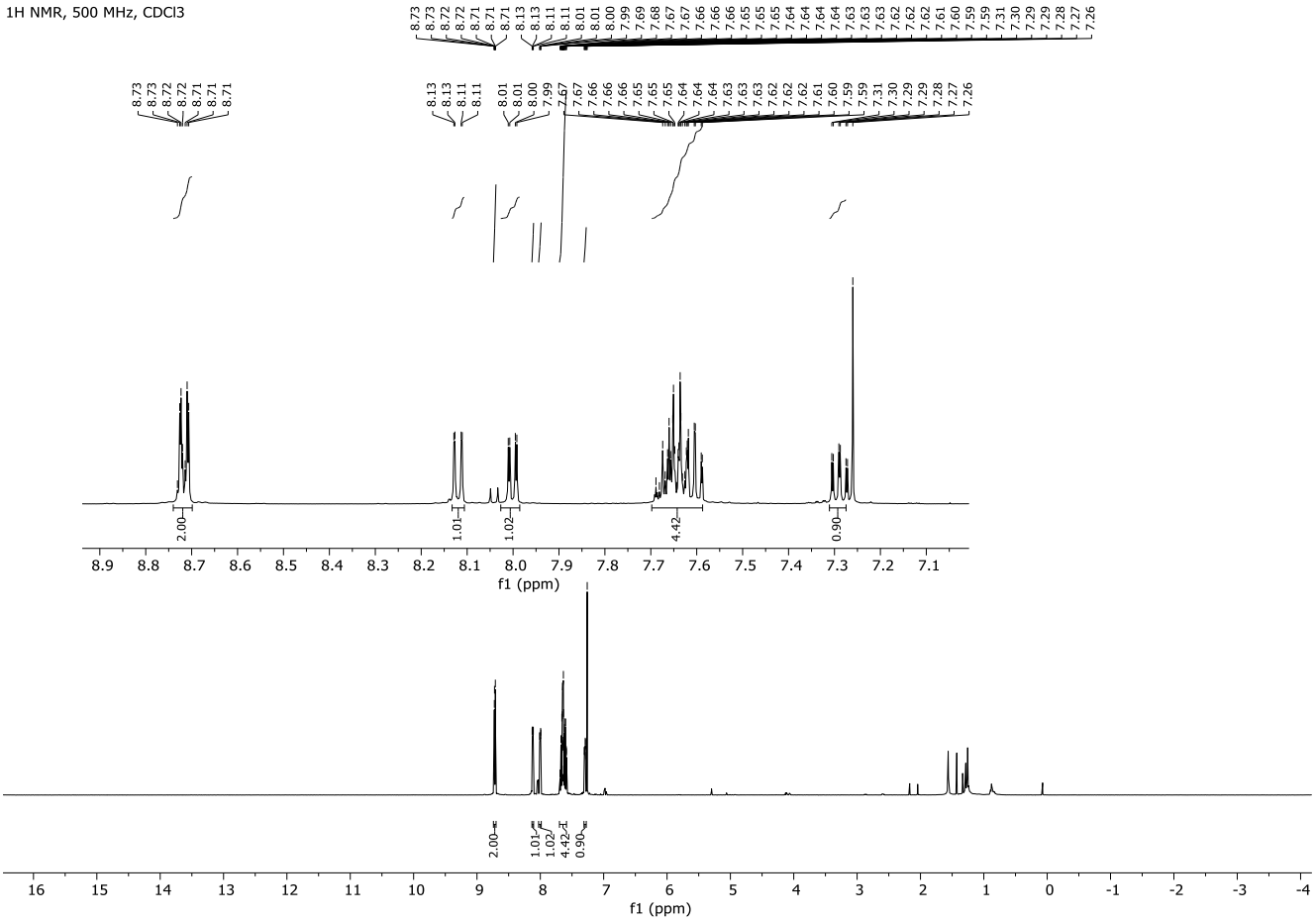
1H NMR, 300 MHz, CDCl3



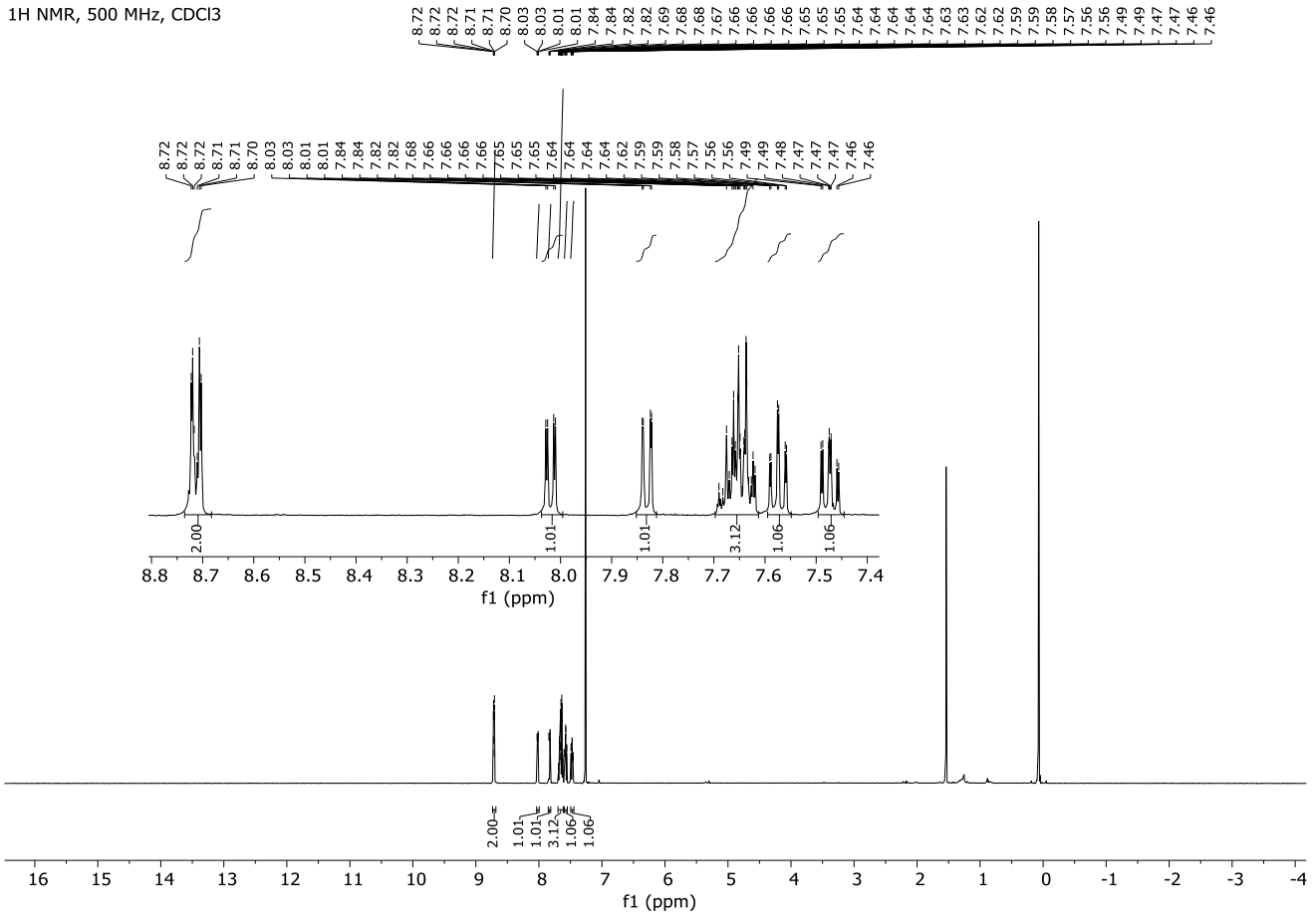
19F NMR, 282 MHz, CDCl3



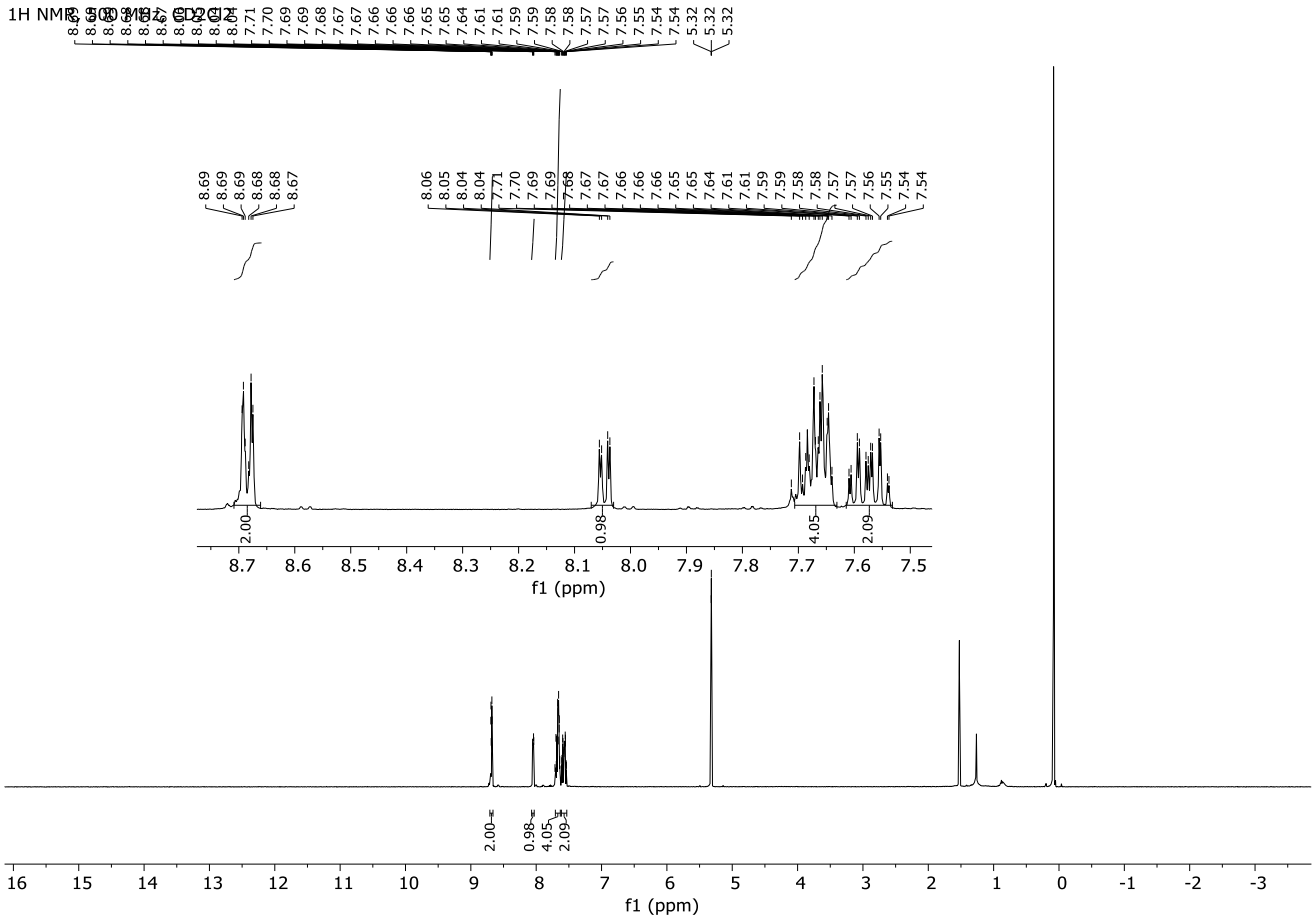
3-(2-Iodophenyl)-6-phenyl-1,2,4,5-tetrazine (2a)



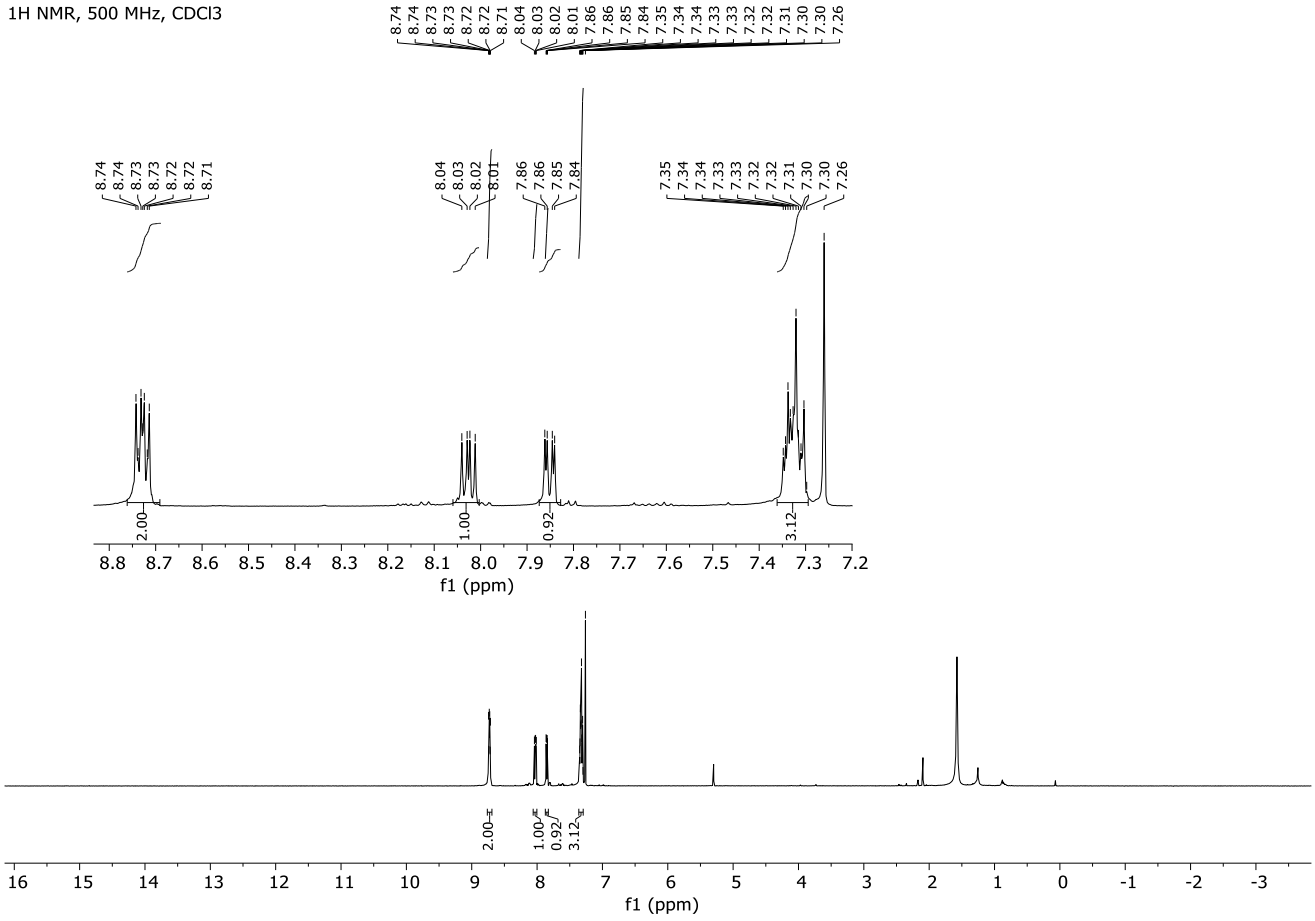
3-(2-Bromophenyl)-6-phenyl-1,2,4,5-tetrazine (2c)



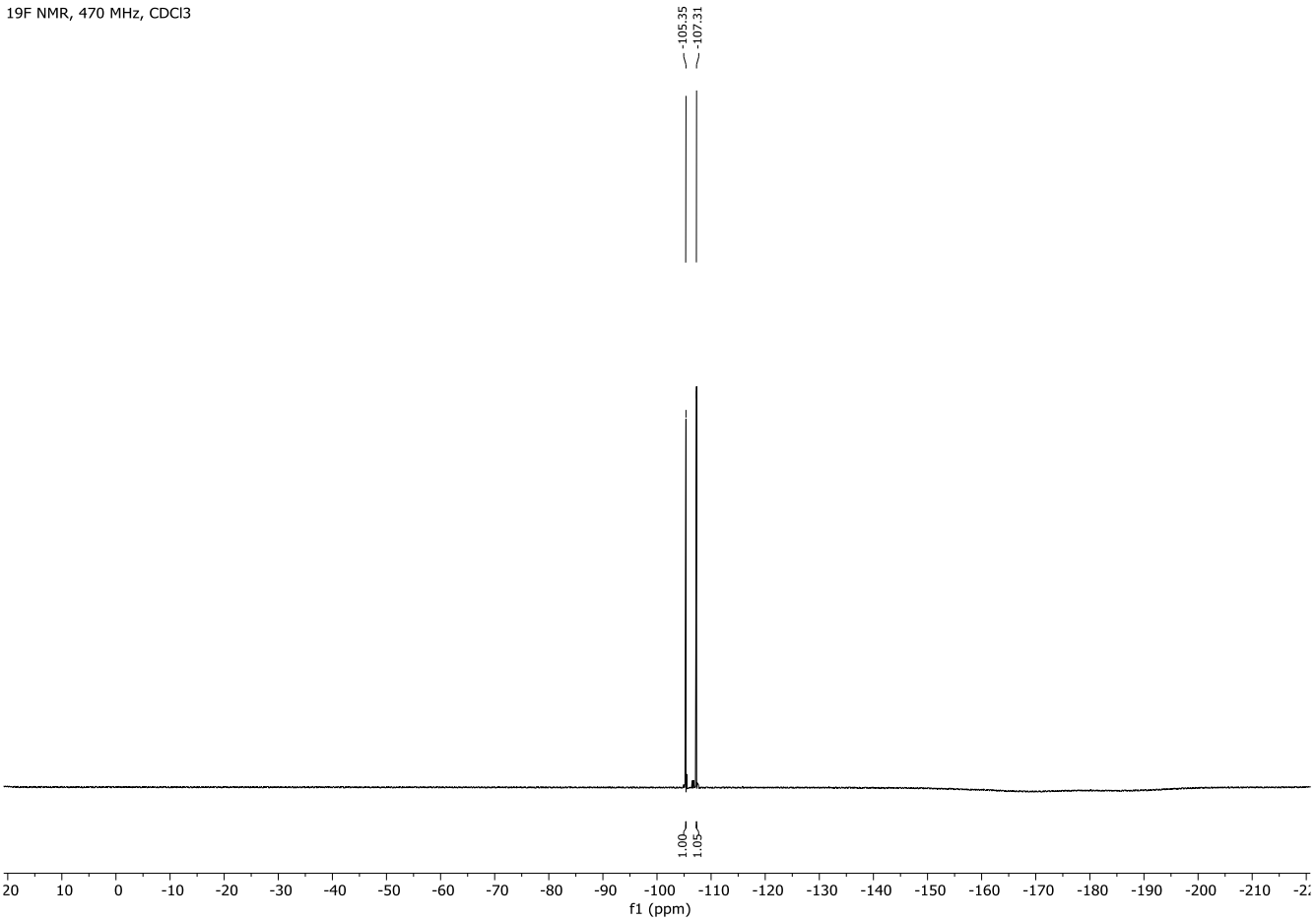
3-(2-Chlorophenyl)-6-phenyl-1,2,4,5-tetrazine (2d)



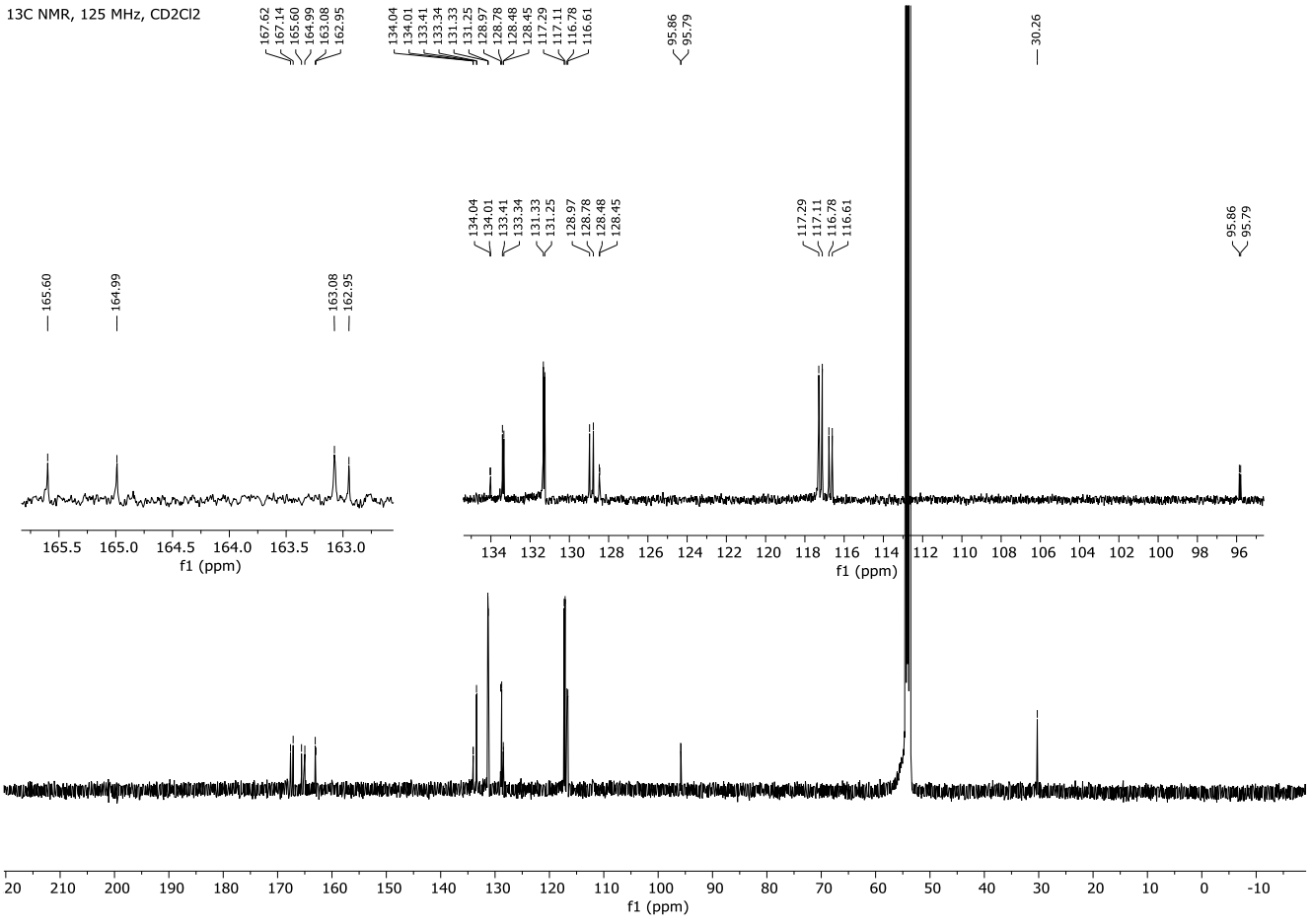
3-(4-Fluoro-6-Iodophenyl)-6-(4-fluorophenyl)-1,2,4,5-tetrazine (3a)



19F NMR, 470 MHz, CDCl3

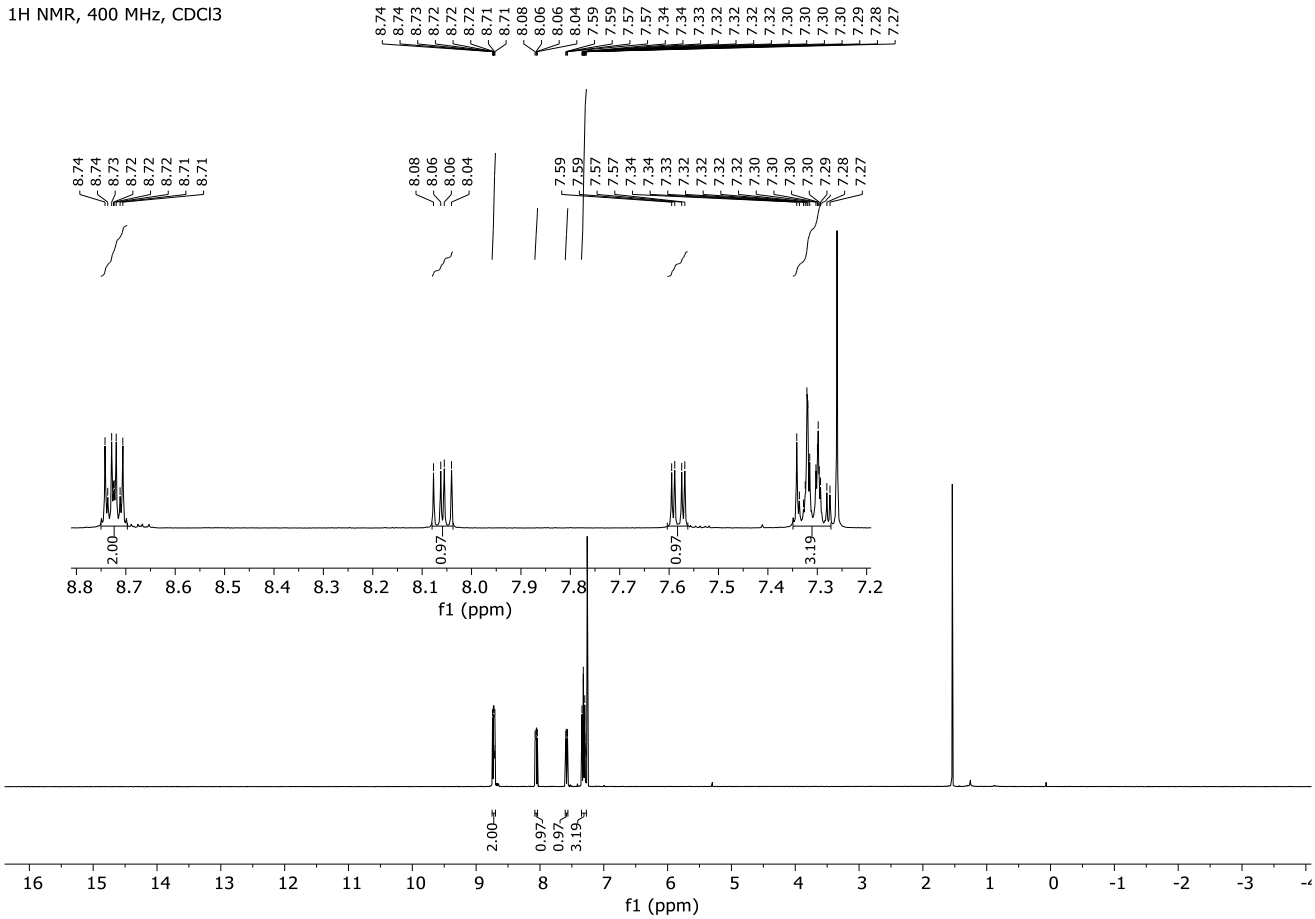


13C NMR, 125 MHz, CD2Cl2

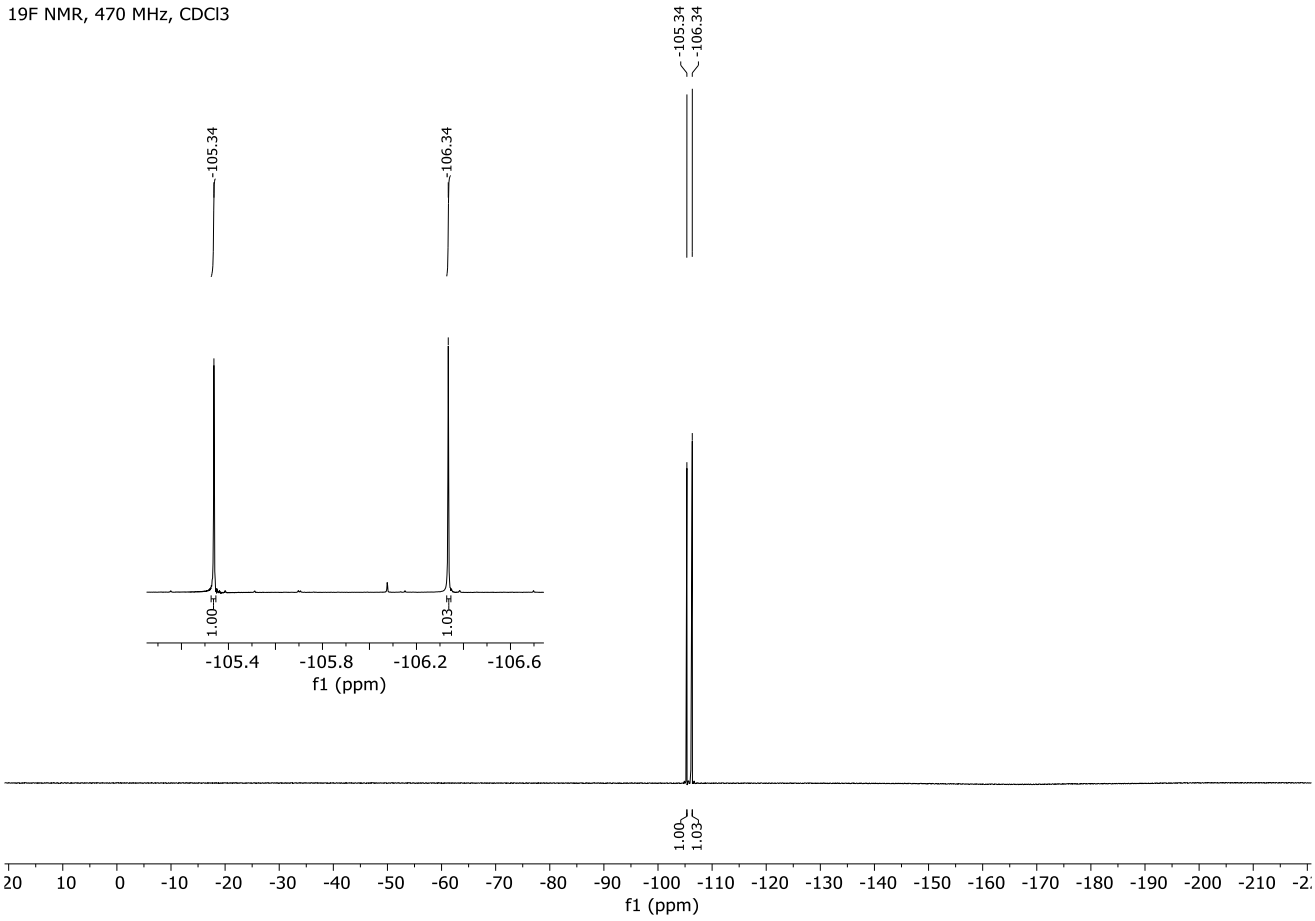


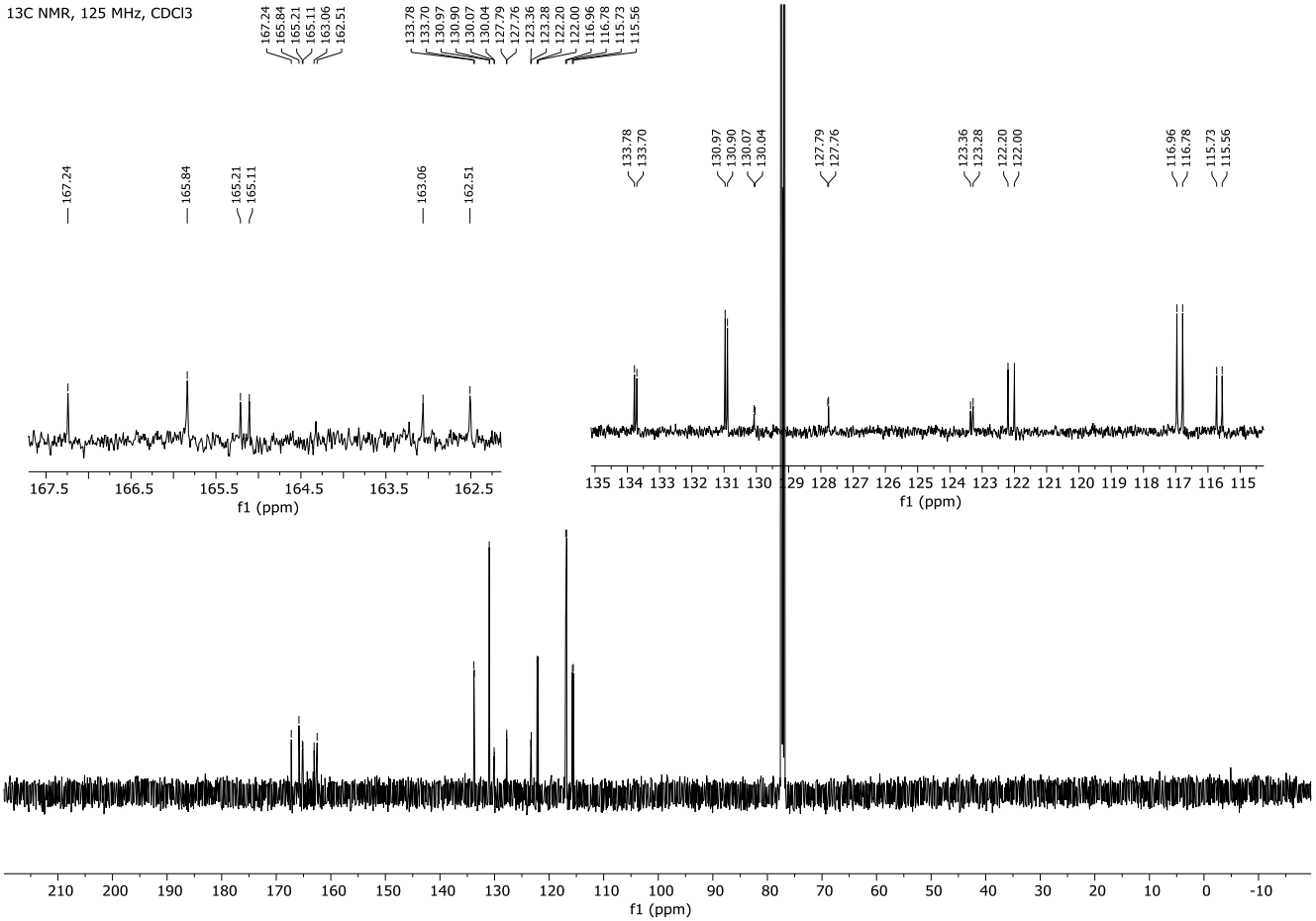
3-(4-Fluoro-6-bromophenyl)-6-(4-fluorophenyl)-1,2,4,5-tetrazine (3c)

1H NMR, 400 MHz, CDCl3

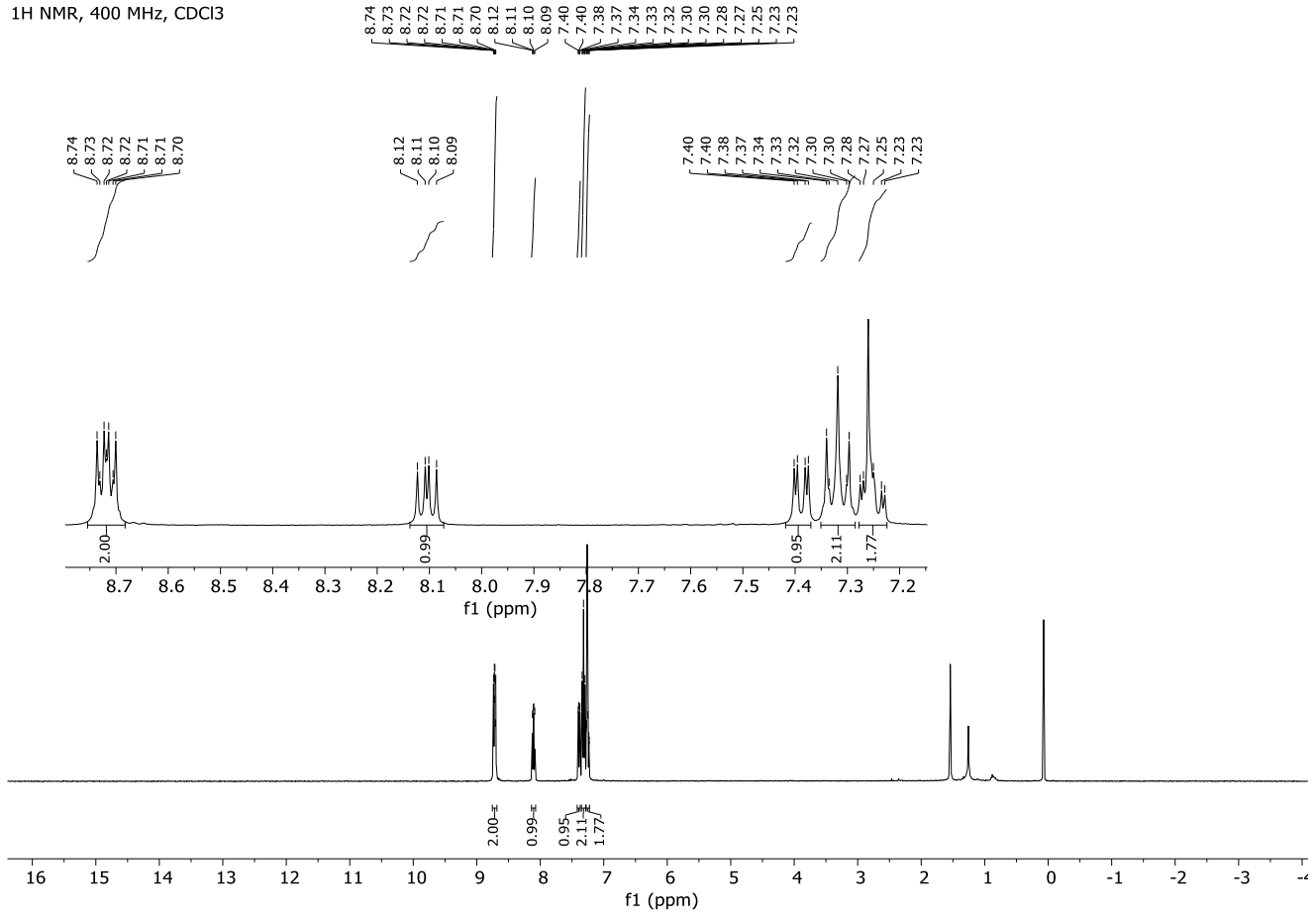


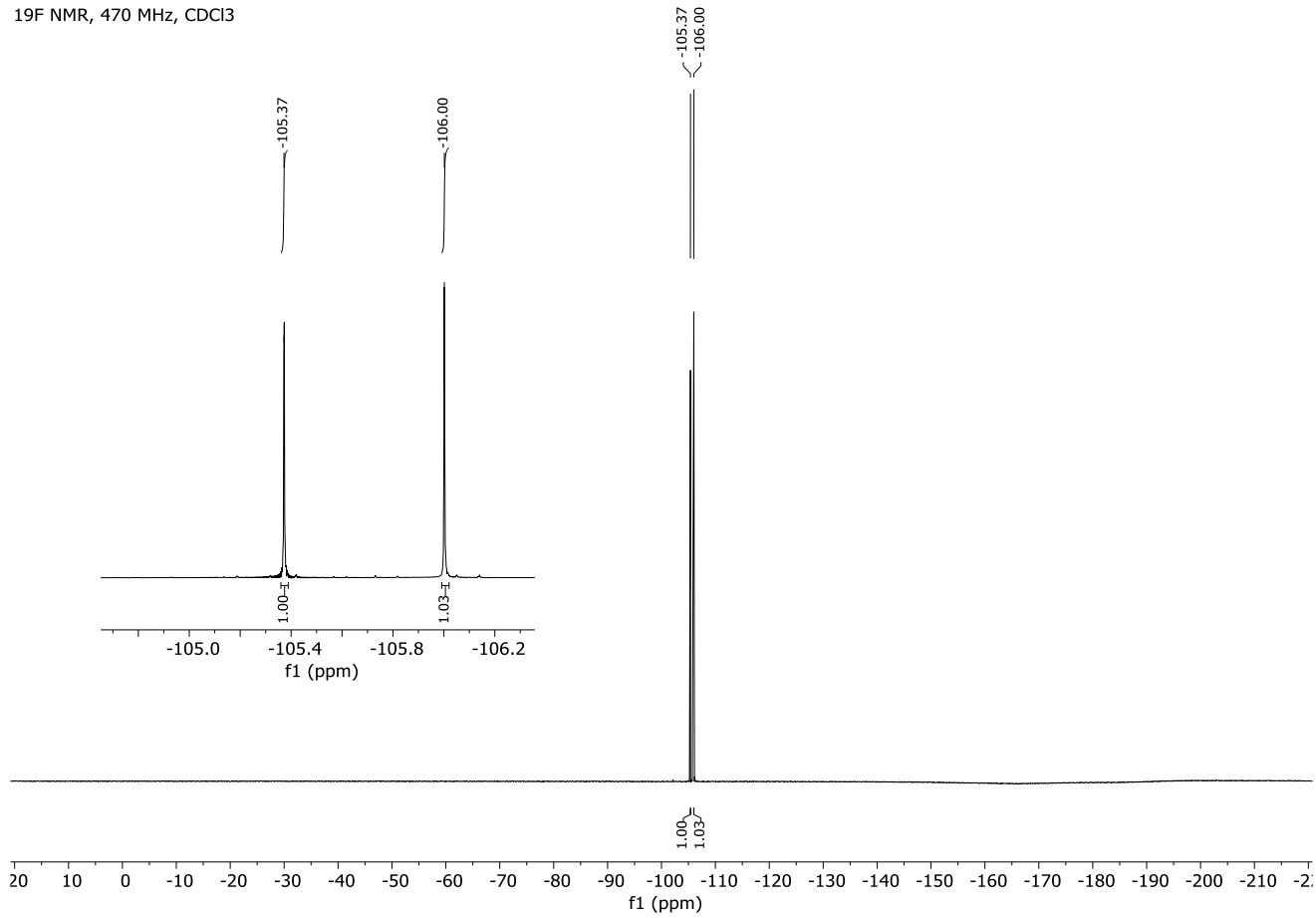
19F NMR, 470 MHz, CDCl3

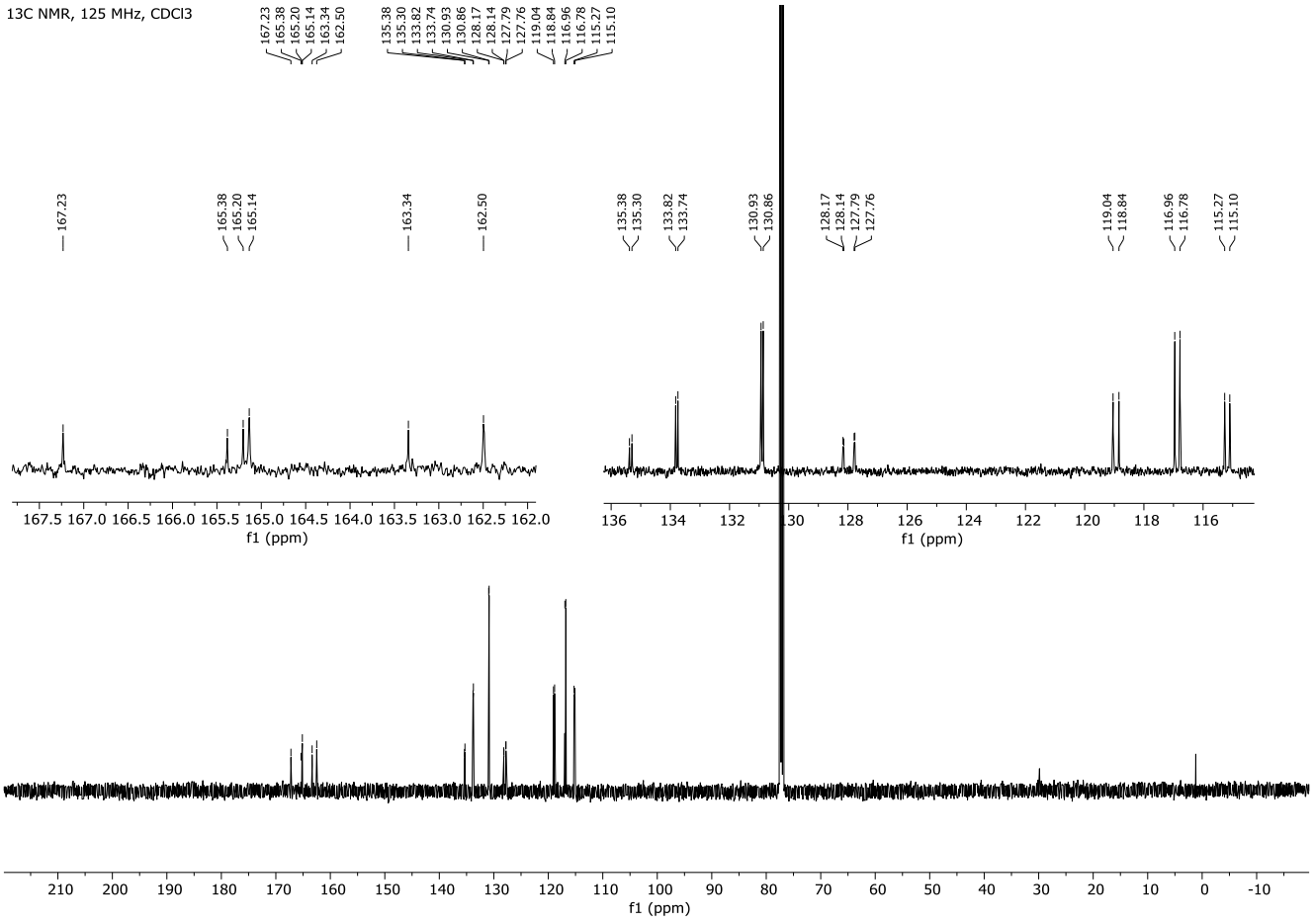




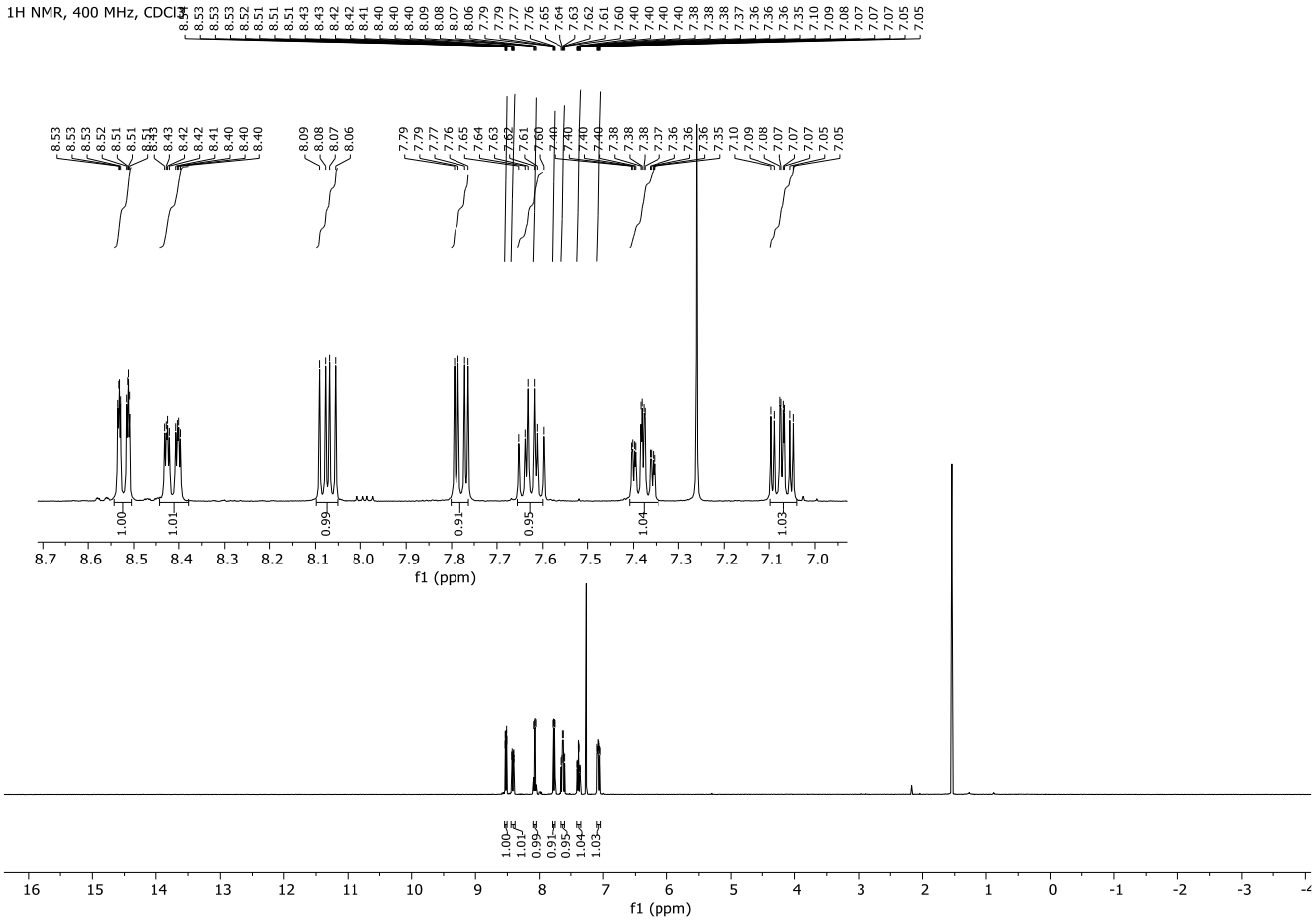
3-(4-Fluoro-6-chlorophenyl)-6-(4-fluorophenyl)-1,2,4,5-tetrazine (3d)

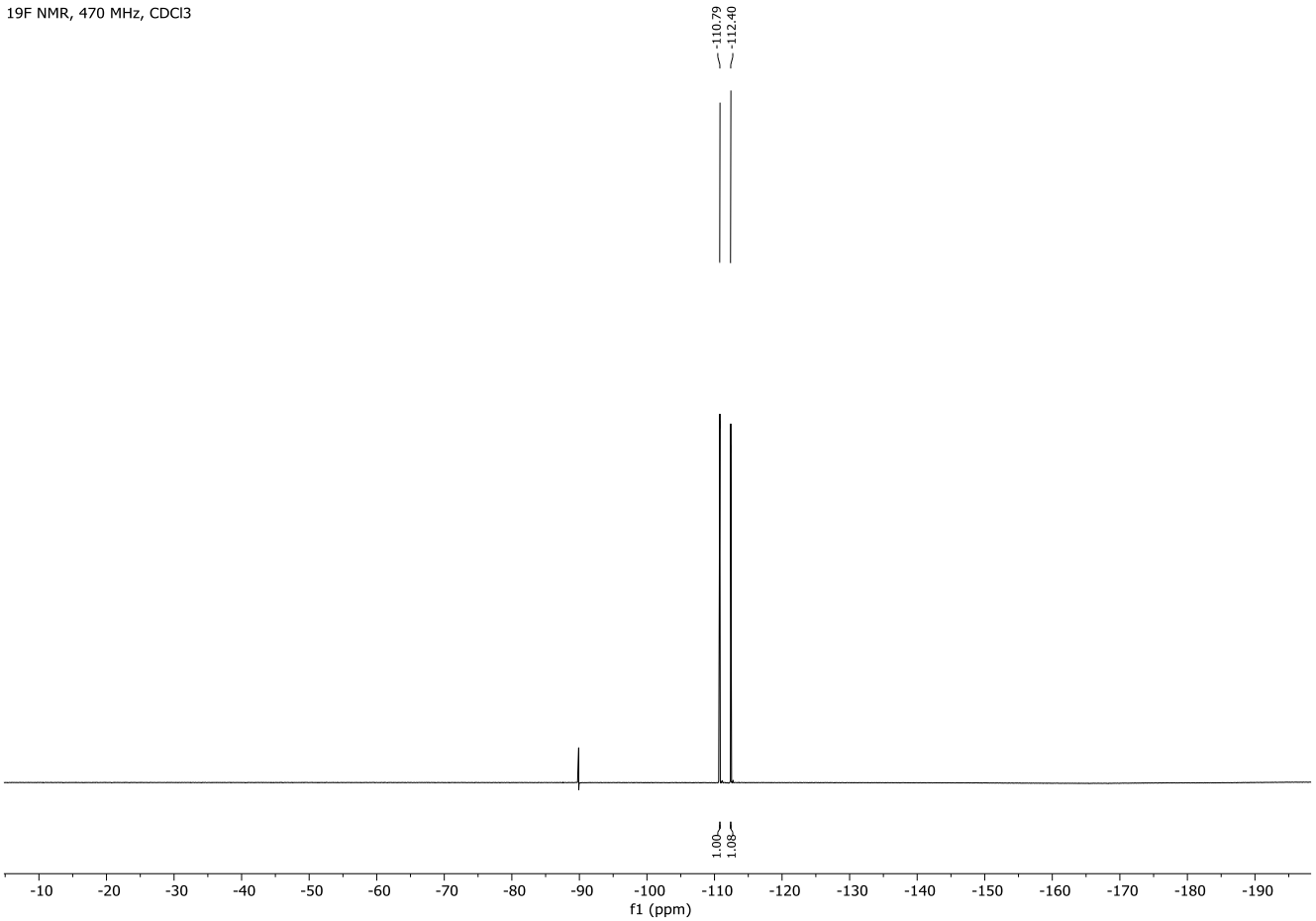


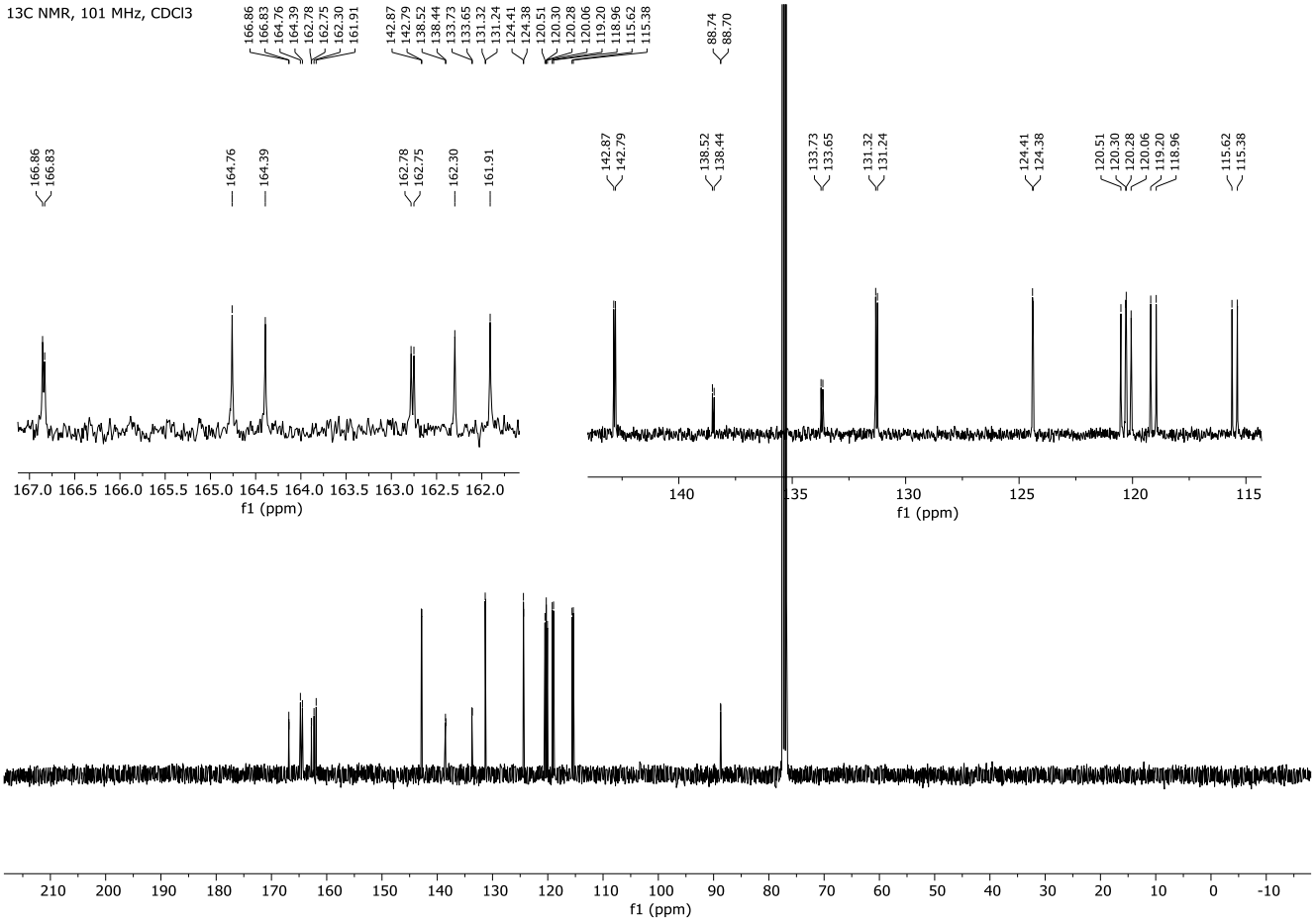

19F NMR, 470 MHz, CDCl3
-105.37
-106.00
1.00
1.03
f1 (ppm)


13C NMR, 125 MHz, CDCl3
167.23
165.38
165.20
165.14
163.34
162.50
135.38
135.30
133.82
133.74
130.93
130.86
128.17
128.14
127.79
127.76
119.04
118.84
116.96
116.78
115.27
115.10
f1 (ppm)

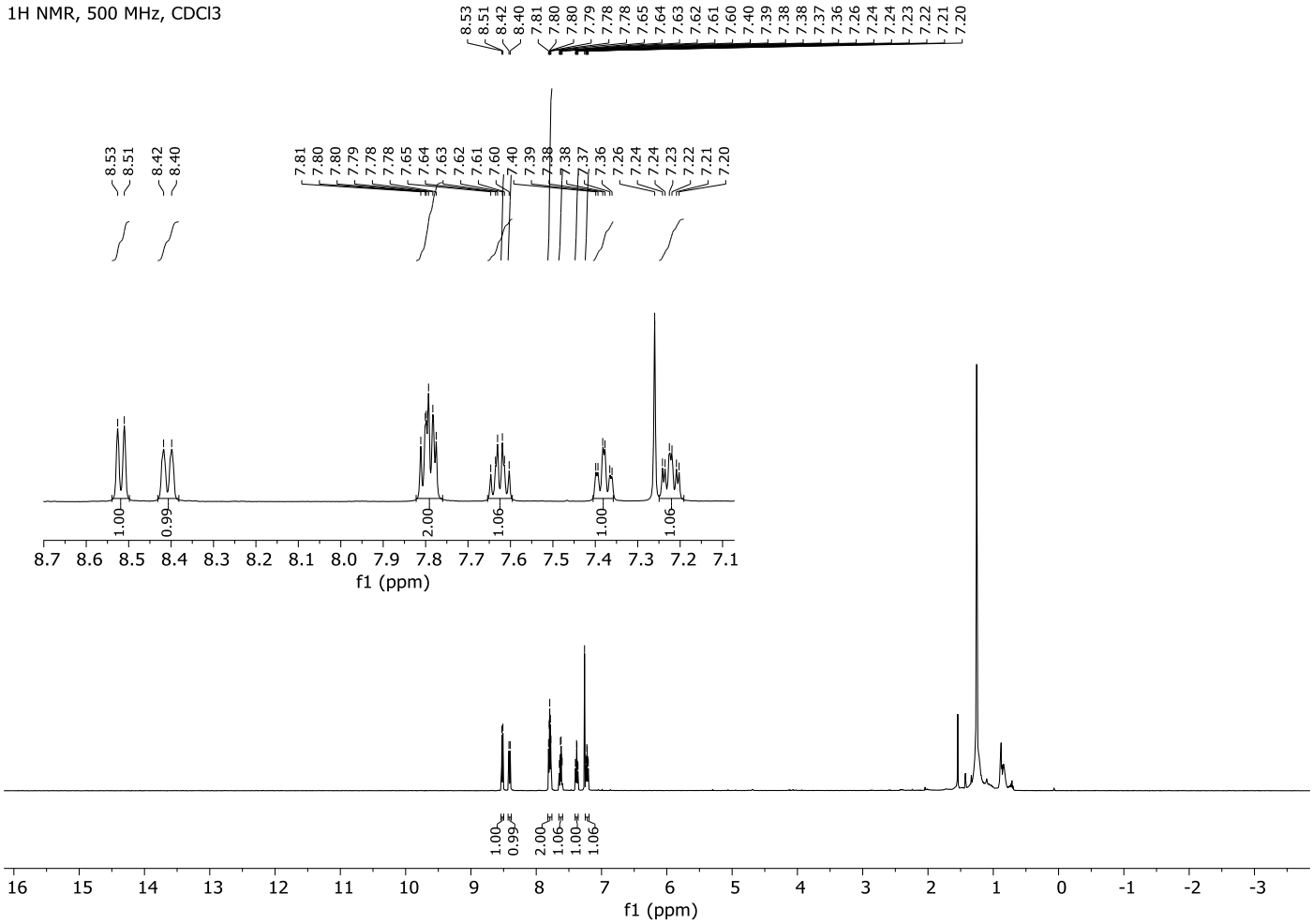
3-(3-Fluoro-6-iodophenyl)-6-(3-fluorophenyl)-1,2,4,5-tetrazine (4a)



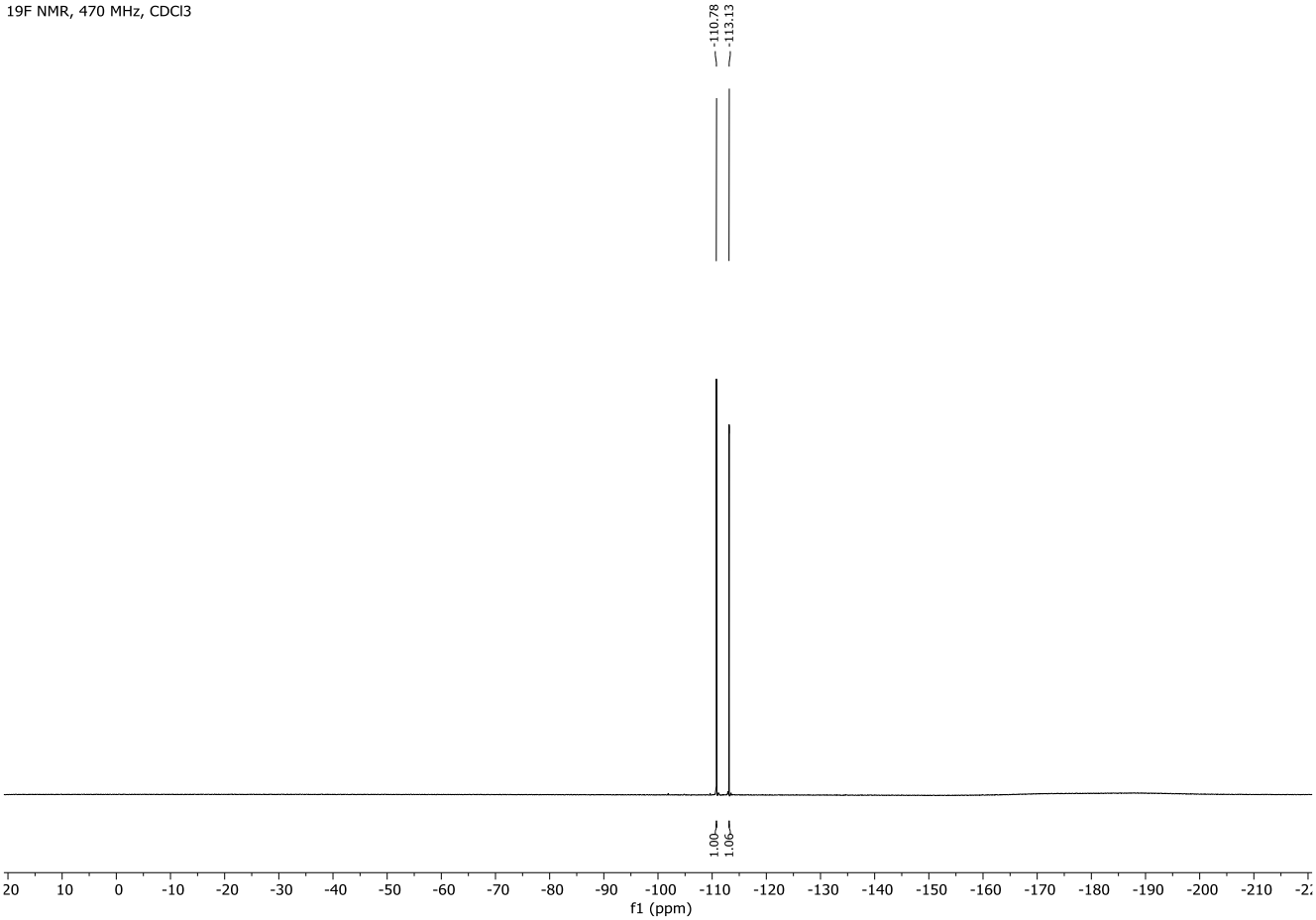




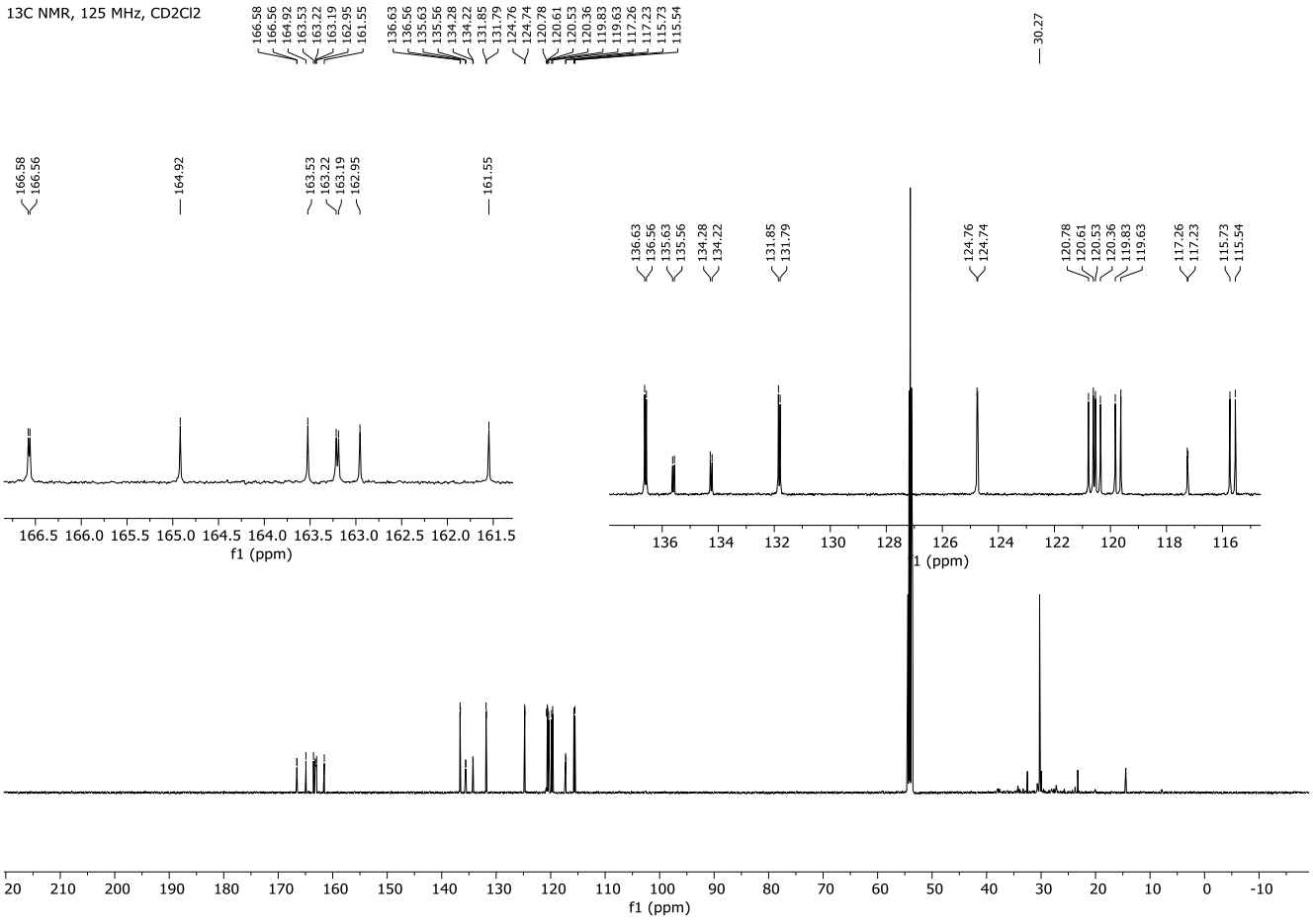
3-(3-Fluoro-6-bromophenyl)-6-(3-fluorophenyl)-1,2,4,5-tetrazine (4c)



19F NMR, 470 MHz, CDCl3

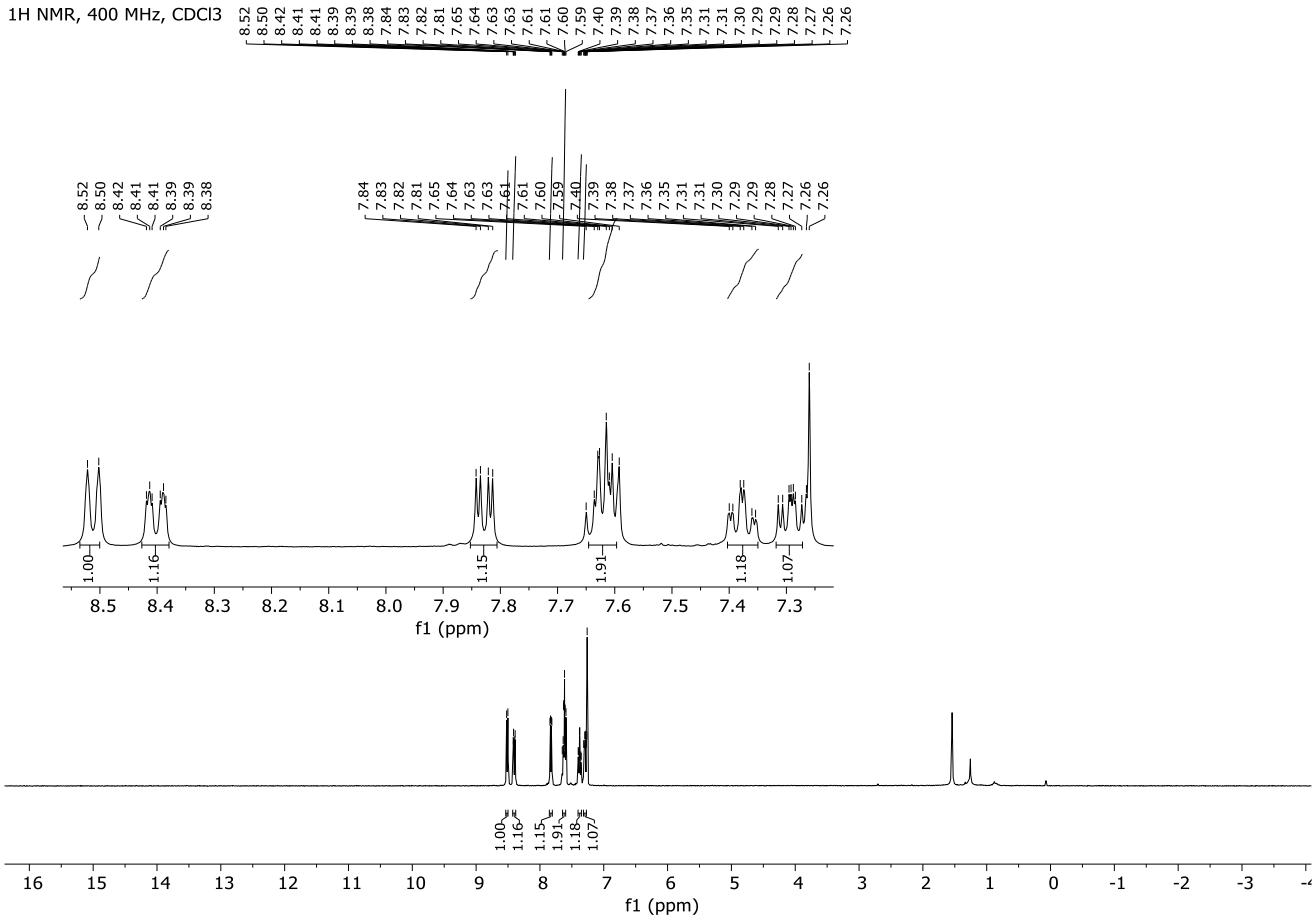


13C NMR, 125 MHz, CD2Cl2

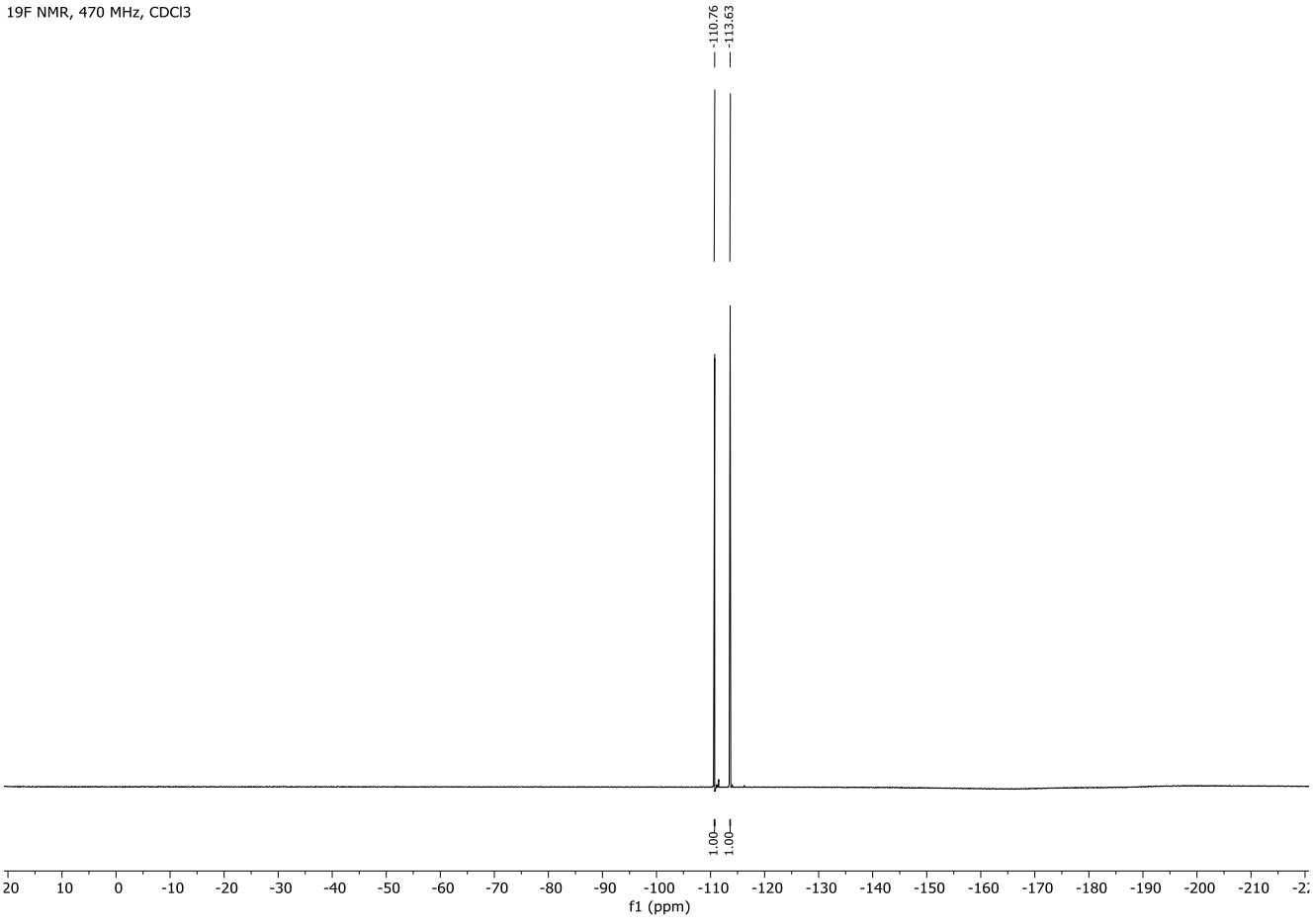


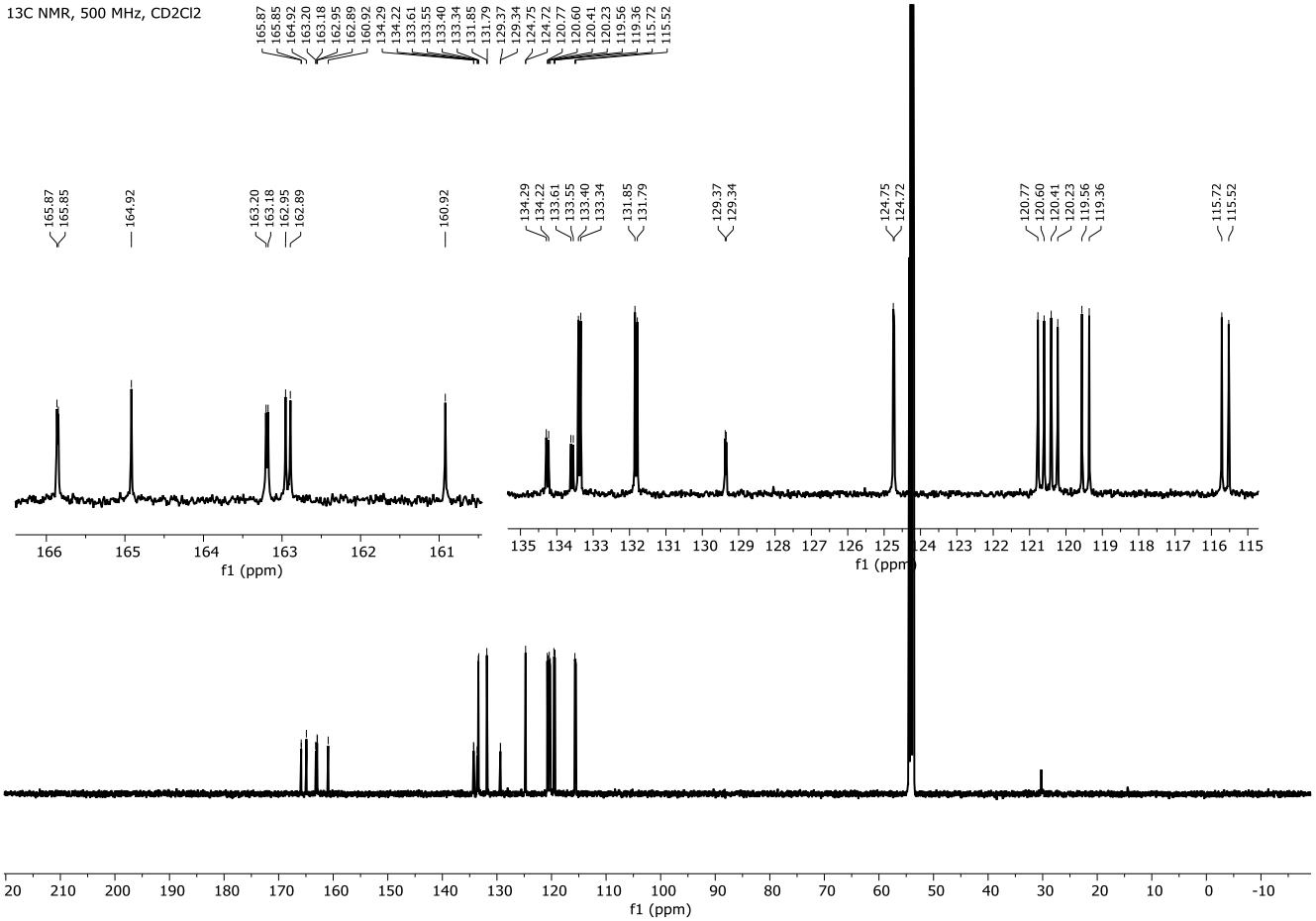
3-(3-Fluoro-6-chlorophenyl)-6-(3-fluorophenyl)-1,2,4,5-tetrazine (4d)

1H NMR, 400 MHz, CDCl3

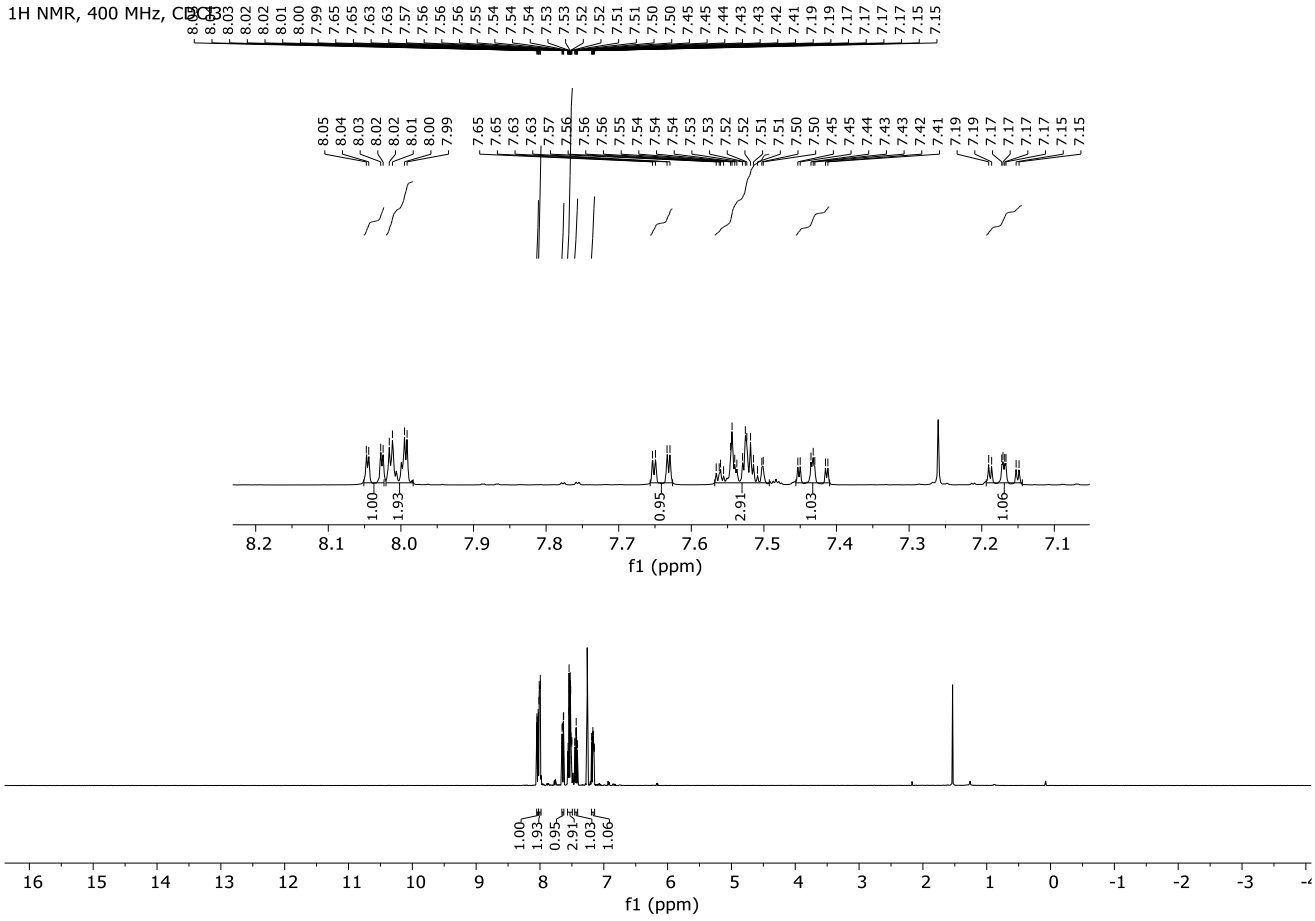


19F NMR, 470 MHz, CDCl3

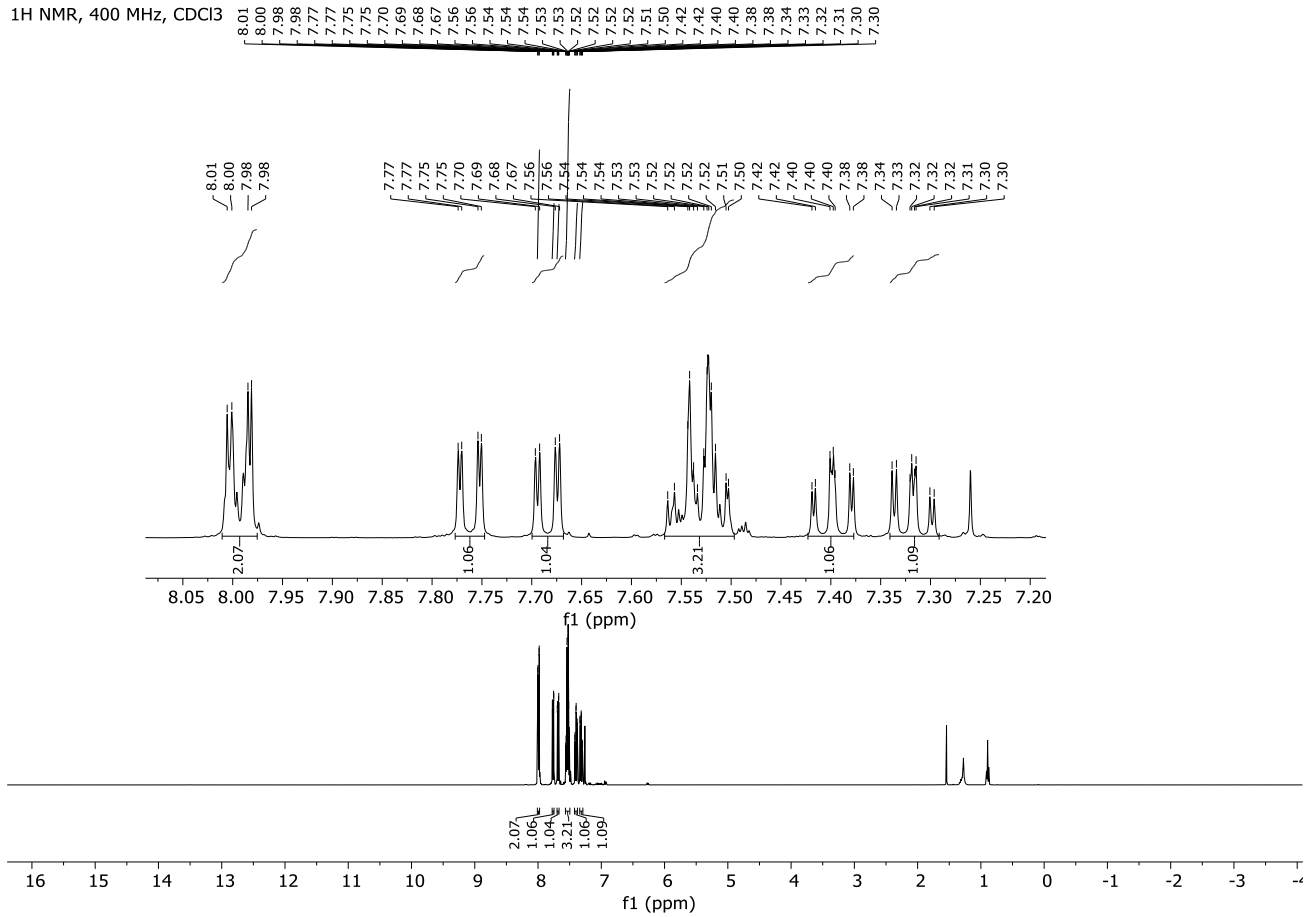




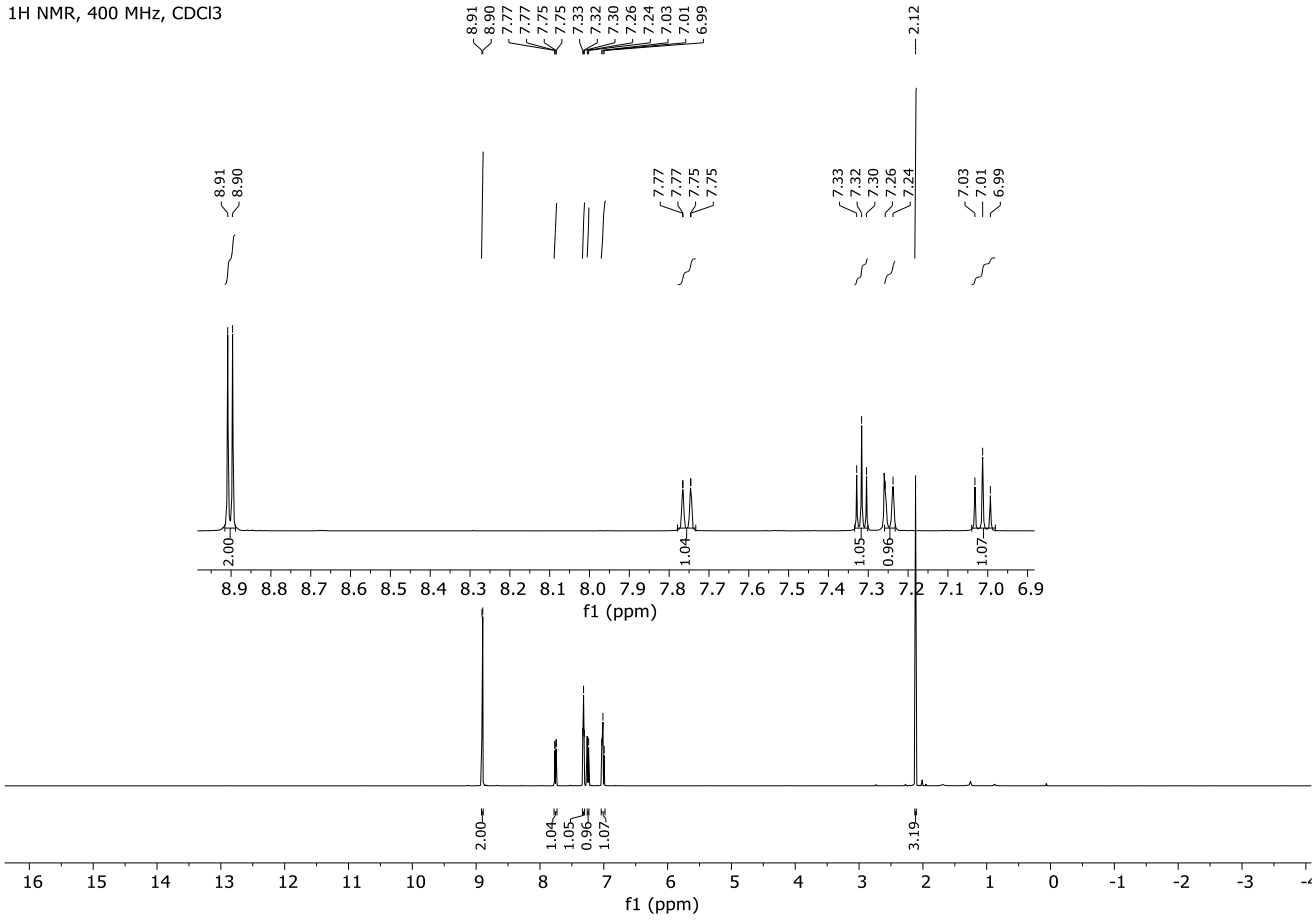
1-(2-Iodophenyl)-2-phenyl-diazene (5a)



1-(2-Bromophenyl)-2-phenyl-diazene (5c)

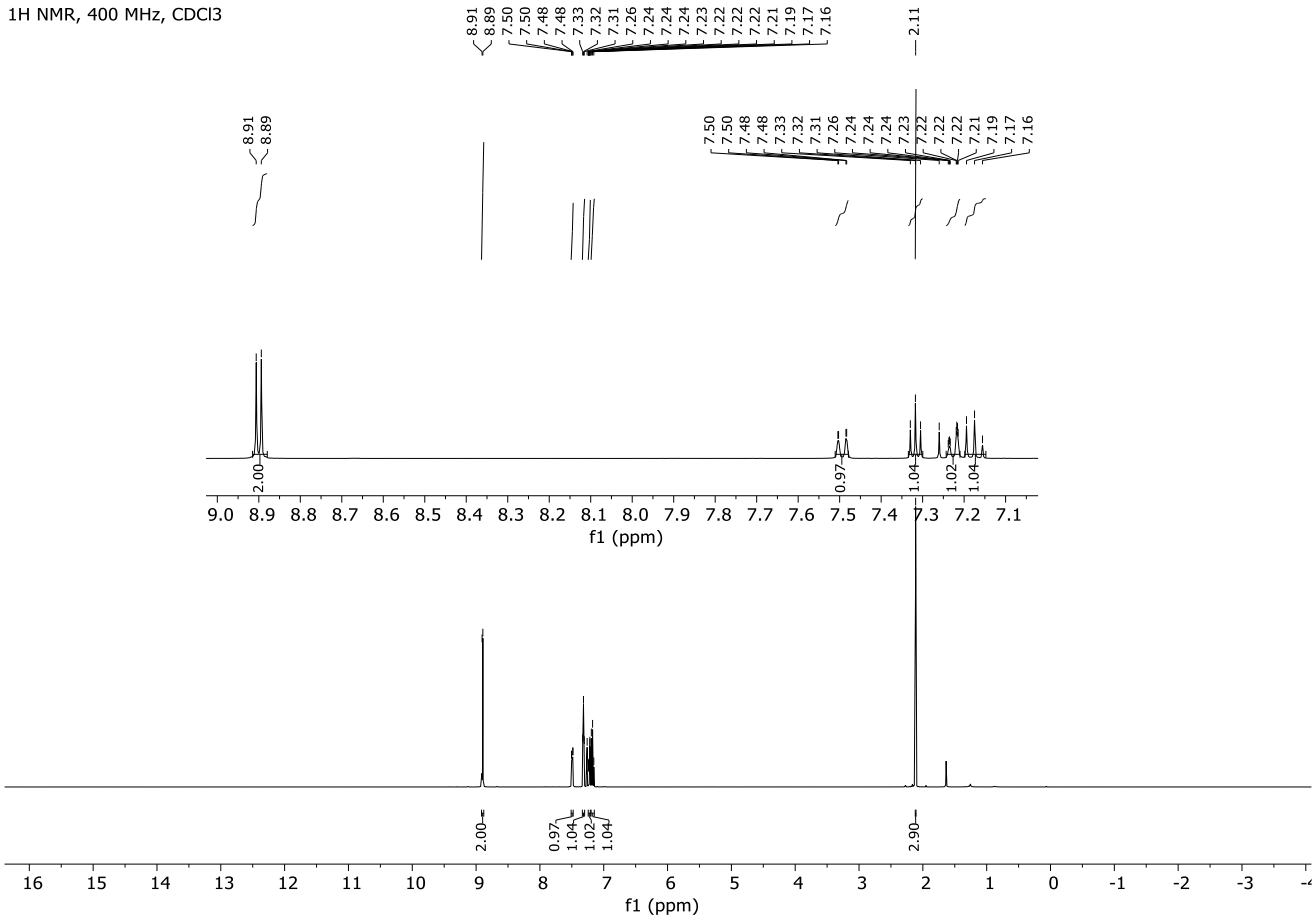


2-(2-Iodo-6-methylphenyl)-pyrimidine (6a)



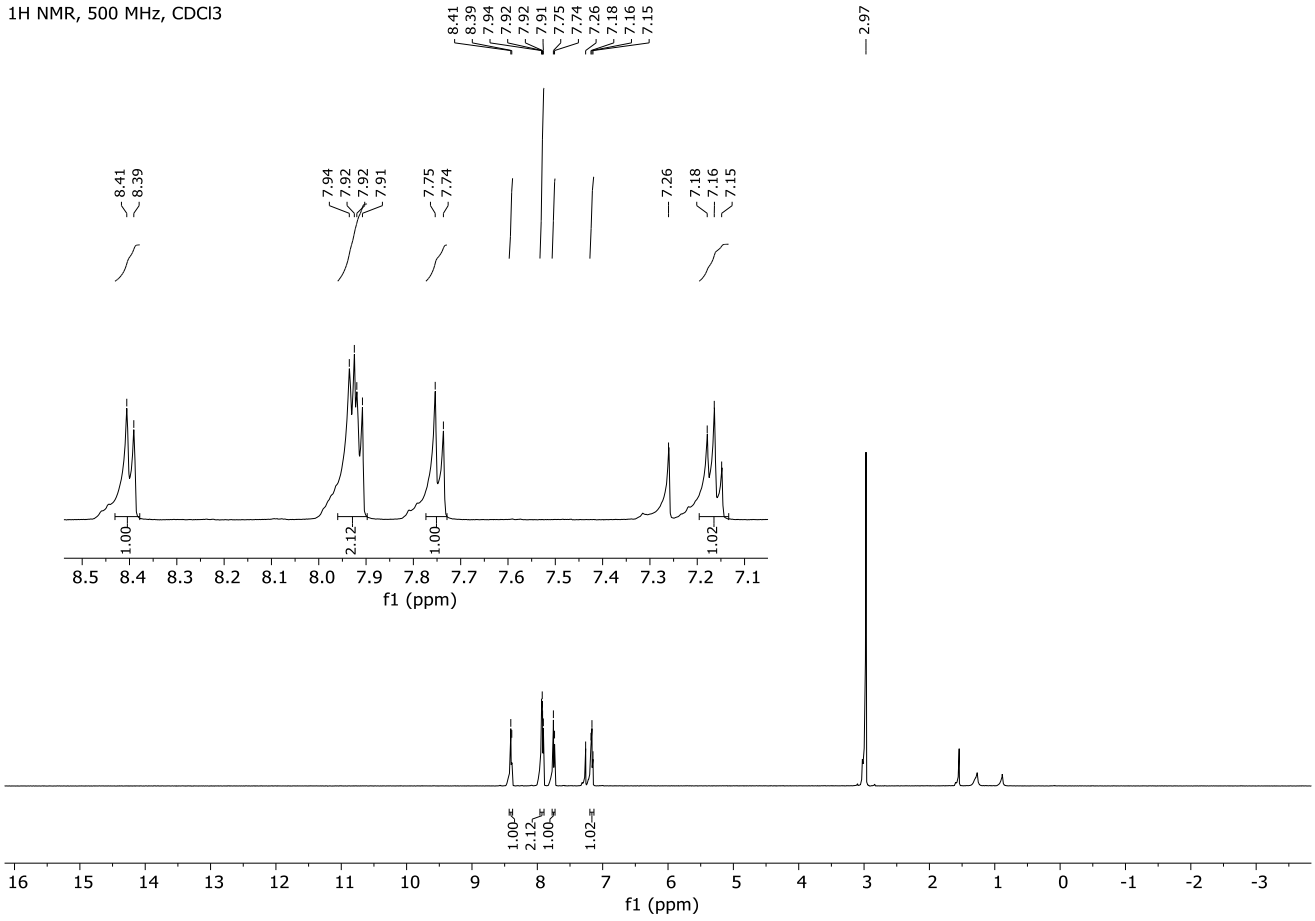
2-(2-Bromo-6-methylphenyl)-pyrimidine (6c)

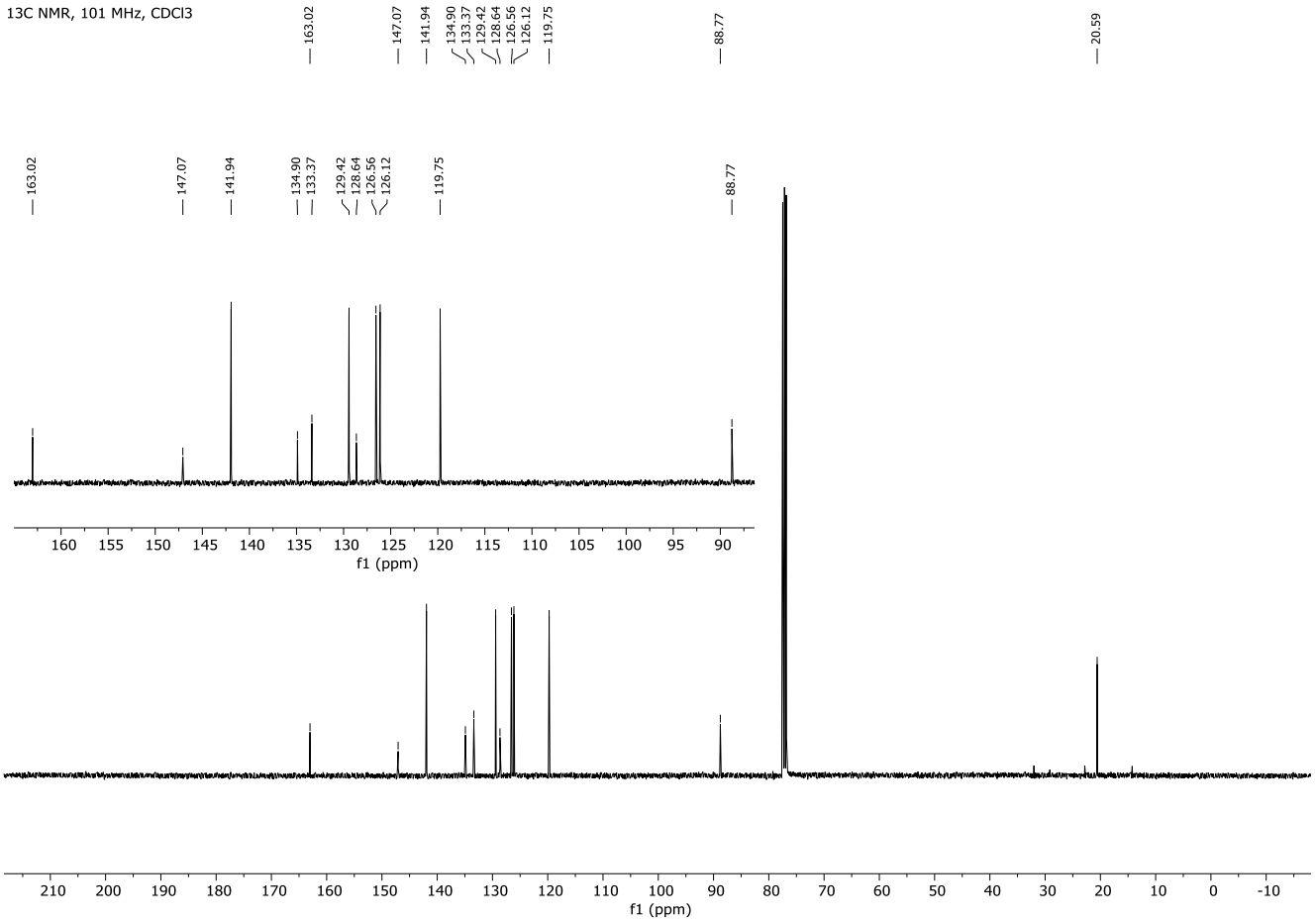
1H NMR, 400 MHz, CDCl3



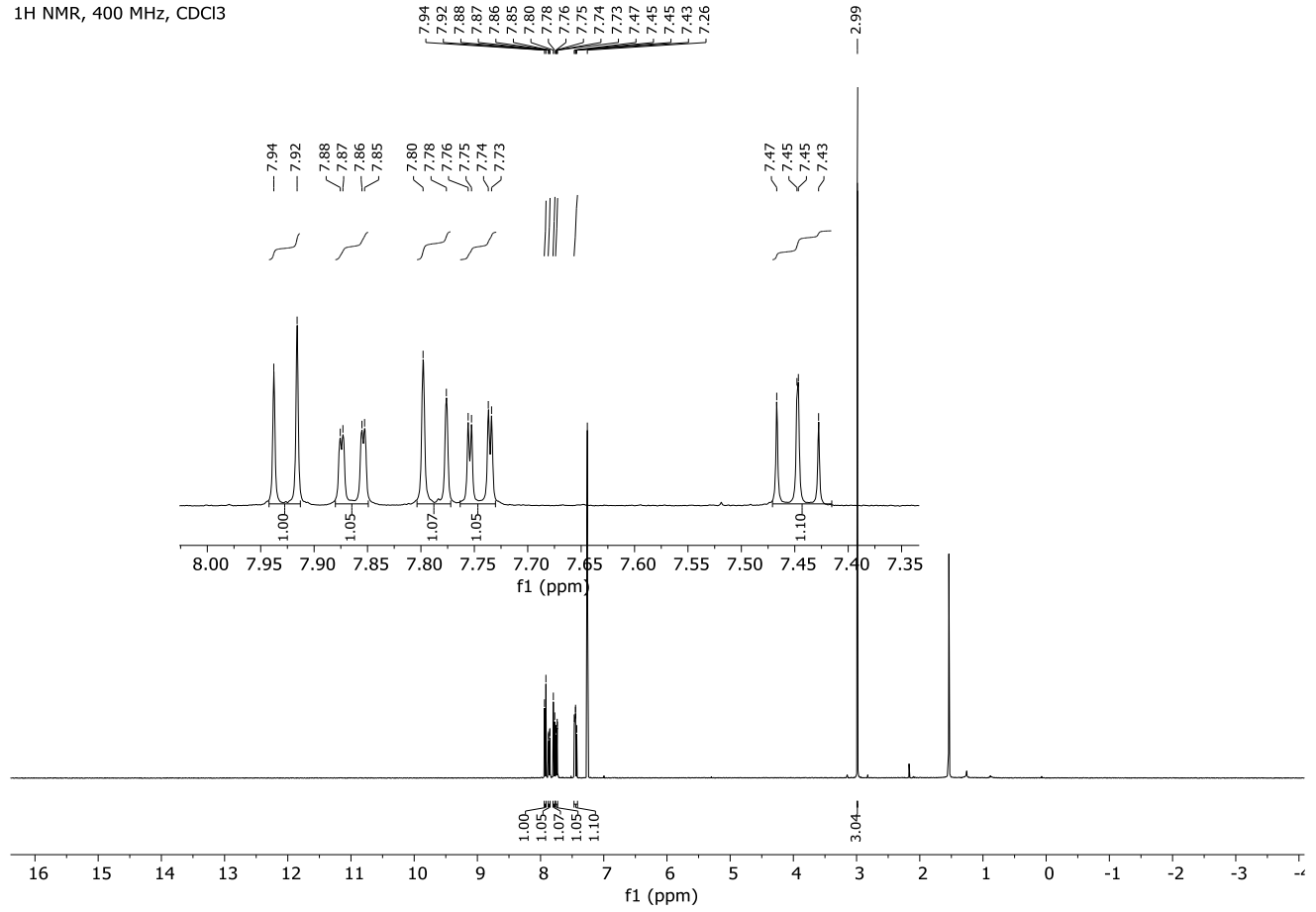
9-Iodo-2-methyl-napthtol[1,2-*d*]thiazole (7a)

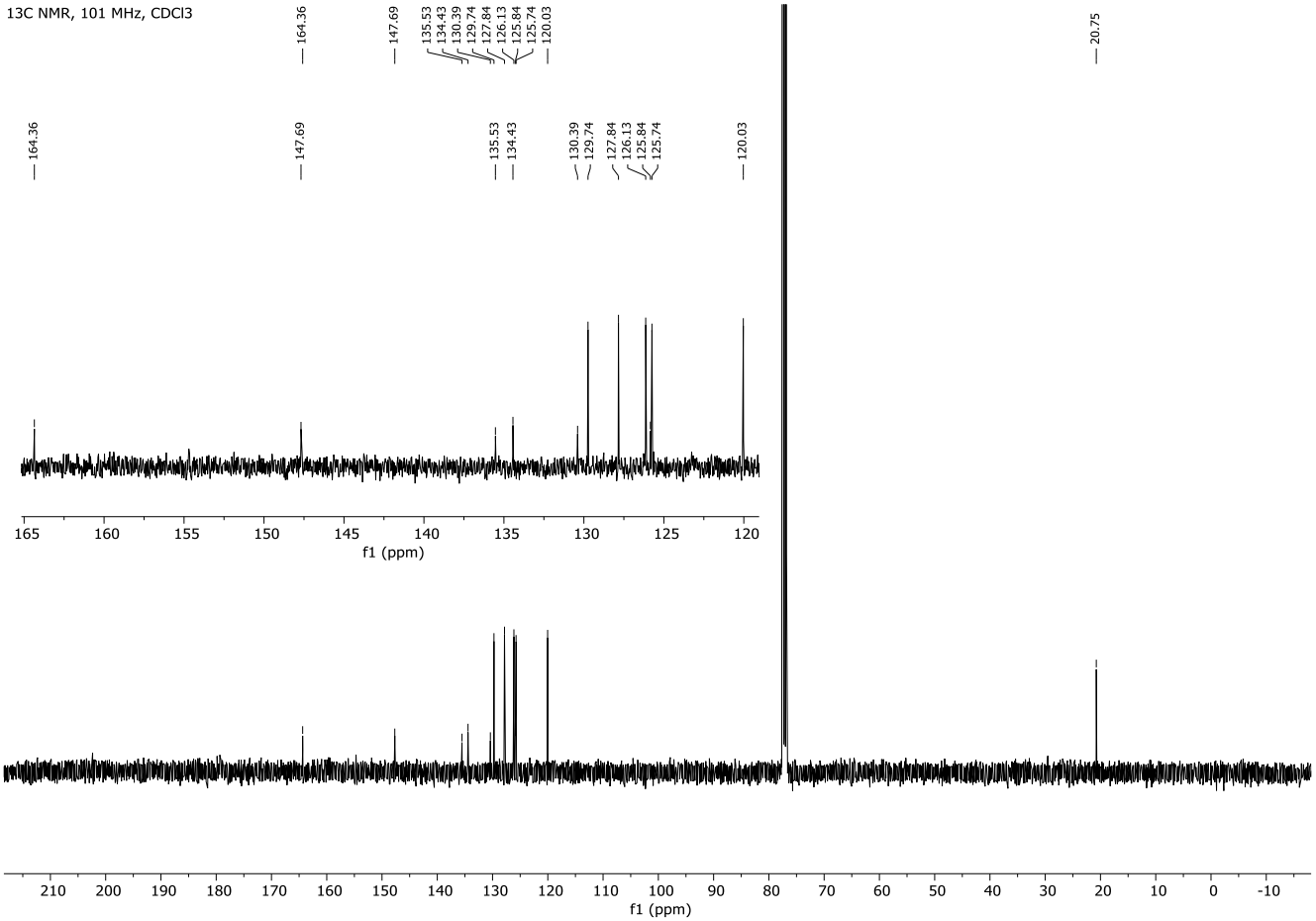
1H NMR, 500 MHz, CDCl3



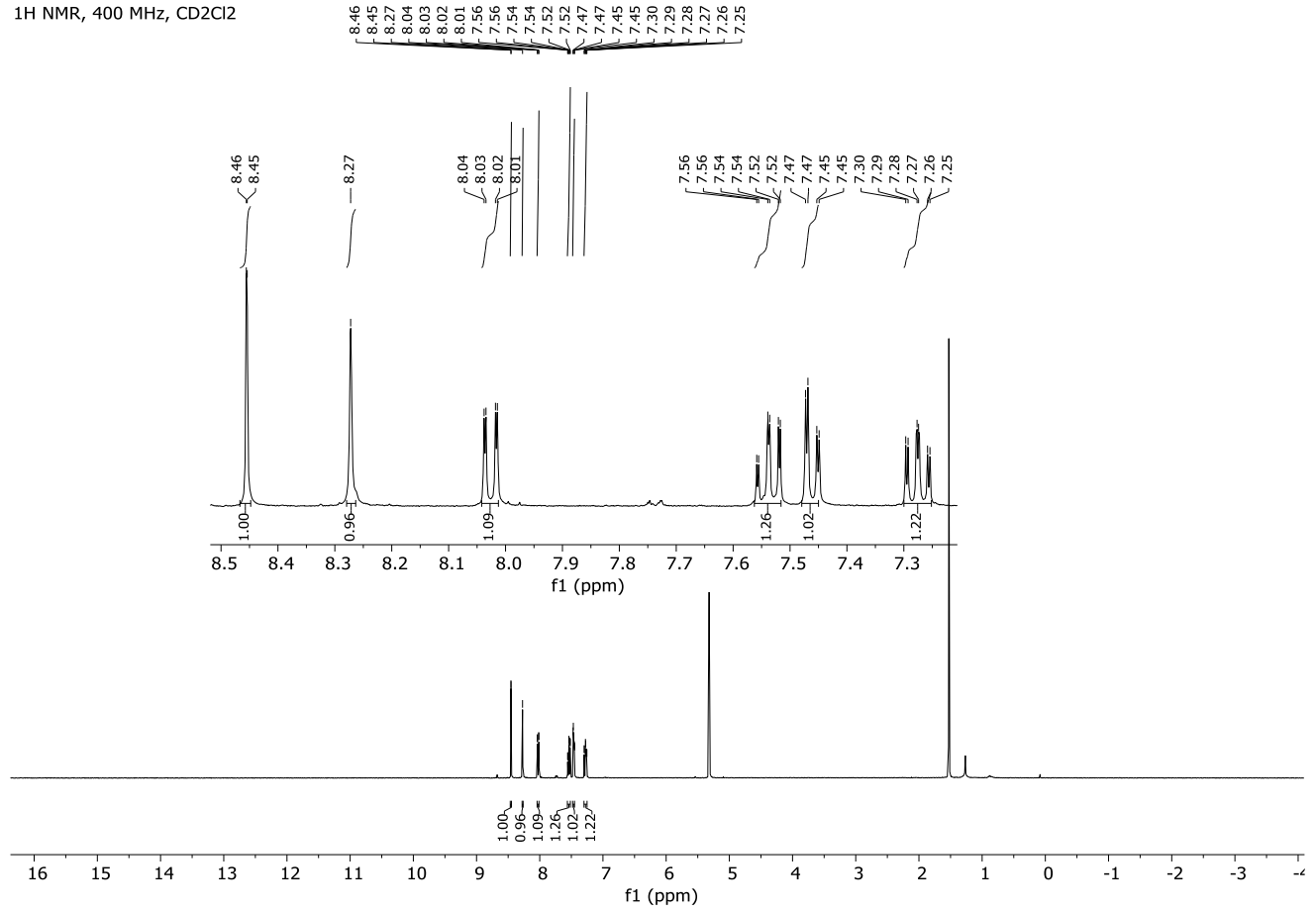


9-Chloro-2-methyl-napthtol[1,2-*d*]thiazole (7d)

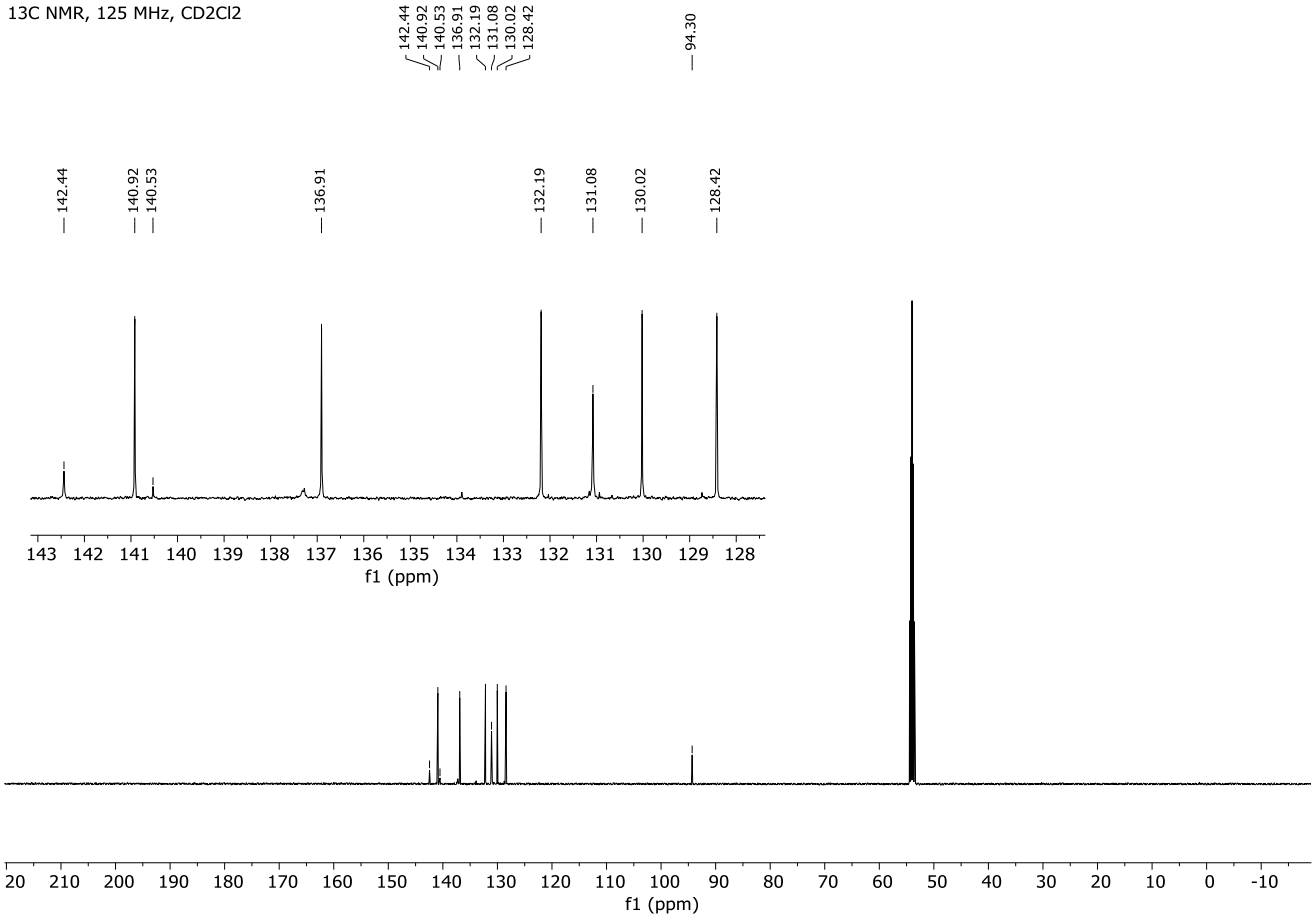




1-(2-Iodophenyl)-4-nitro-*1H*-pyrazole (8a)

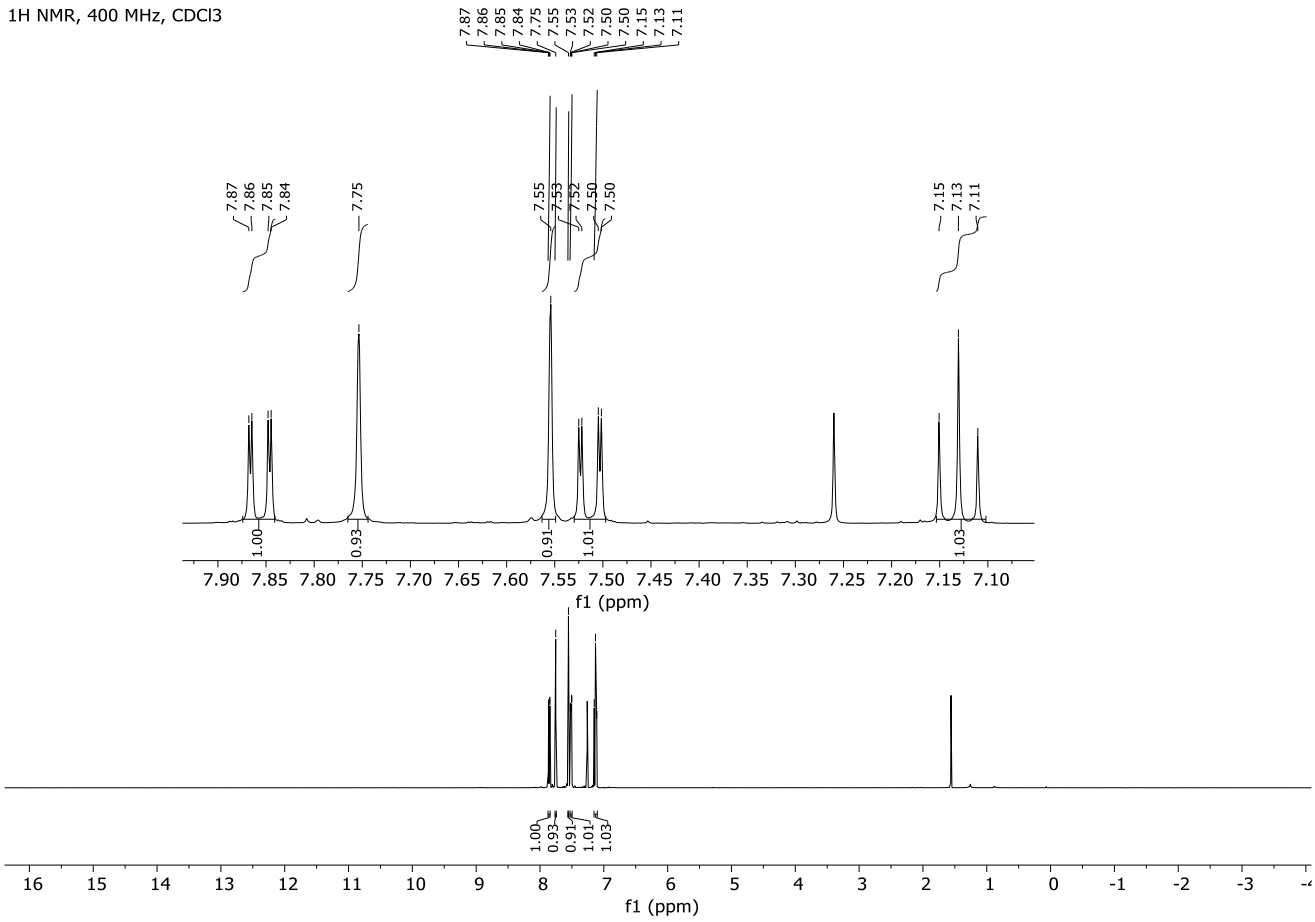


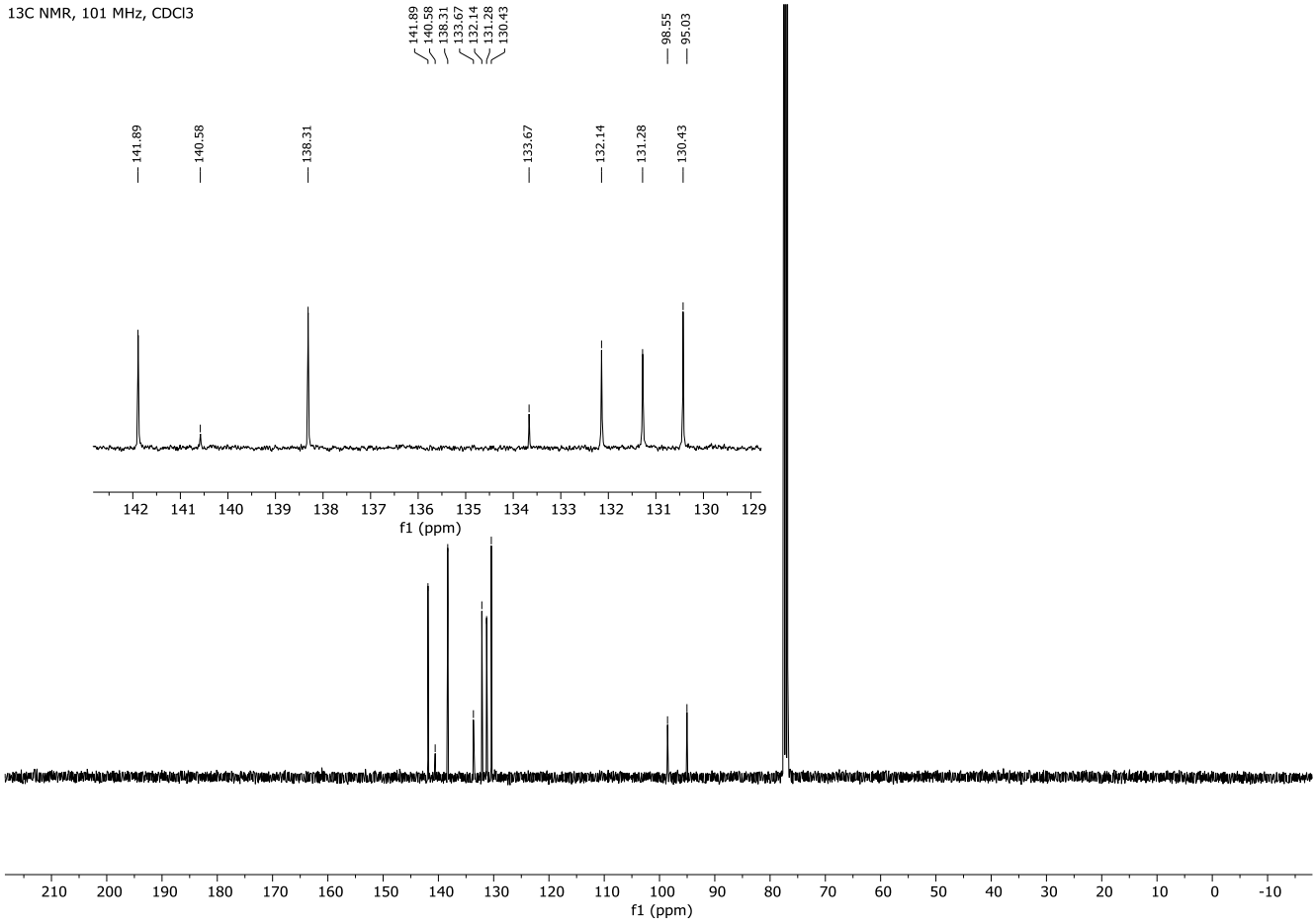
13C NMR, 125 MHz, CD2Cl2



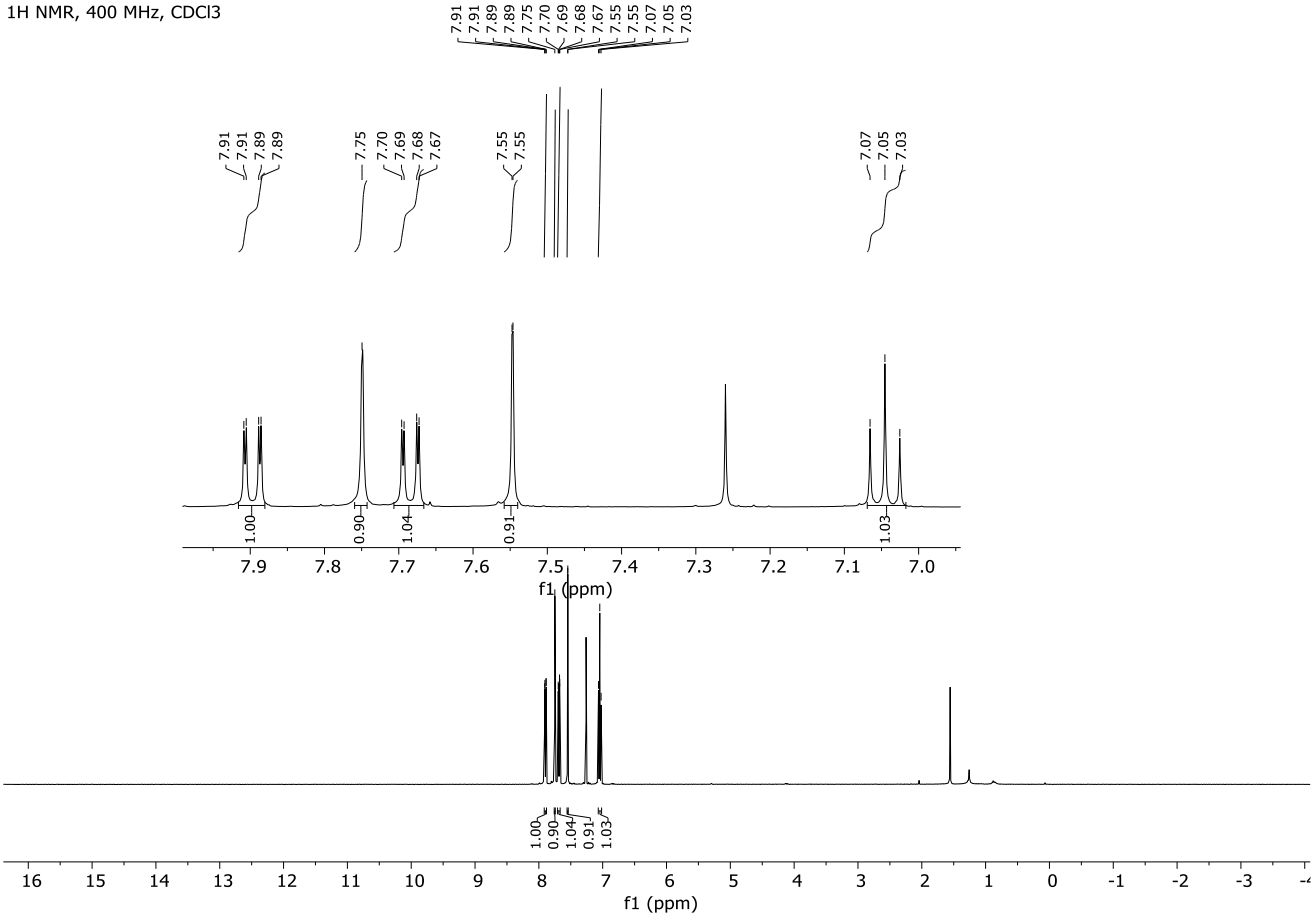
1-(2-chloro-6-Iodophenyl)-4-bromo-*1H*-pyrazole (9a)

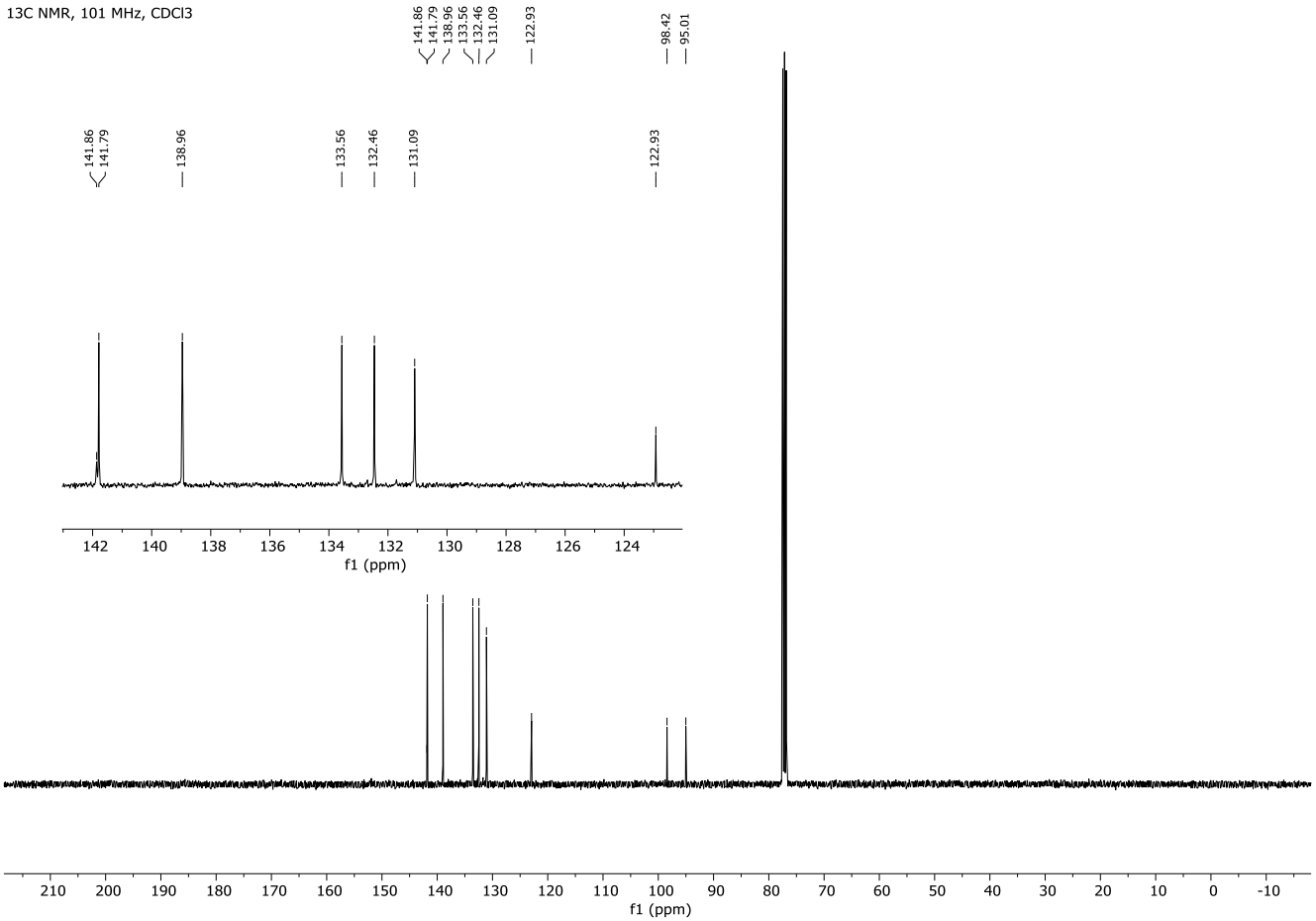
1H NMR, 400 MHz, CDCl3



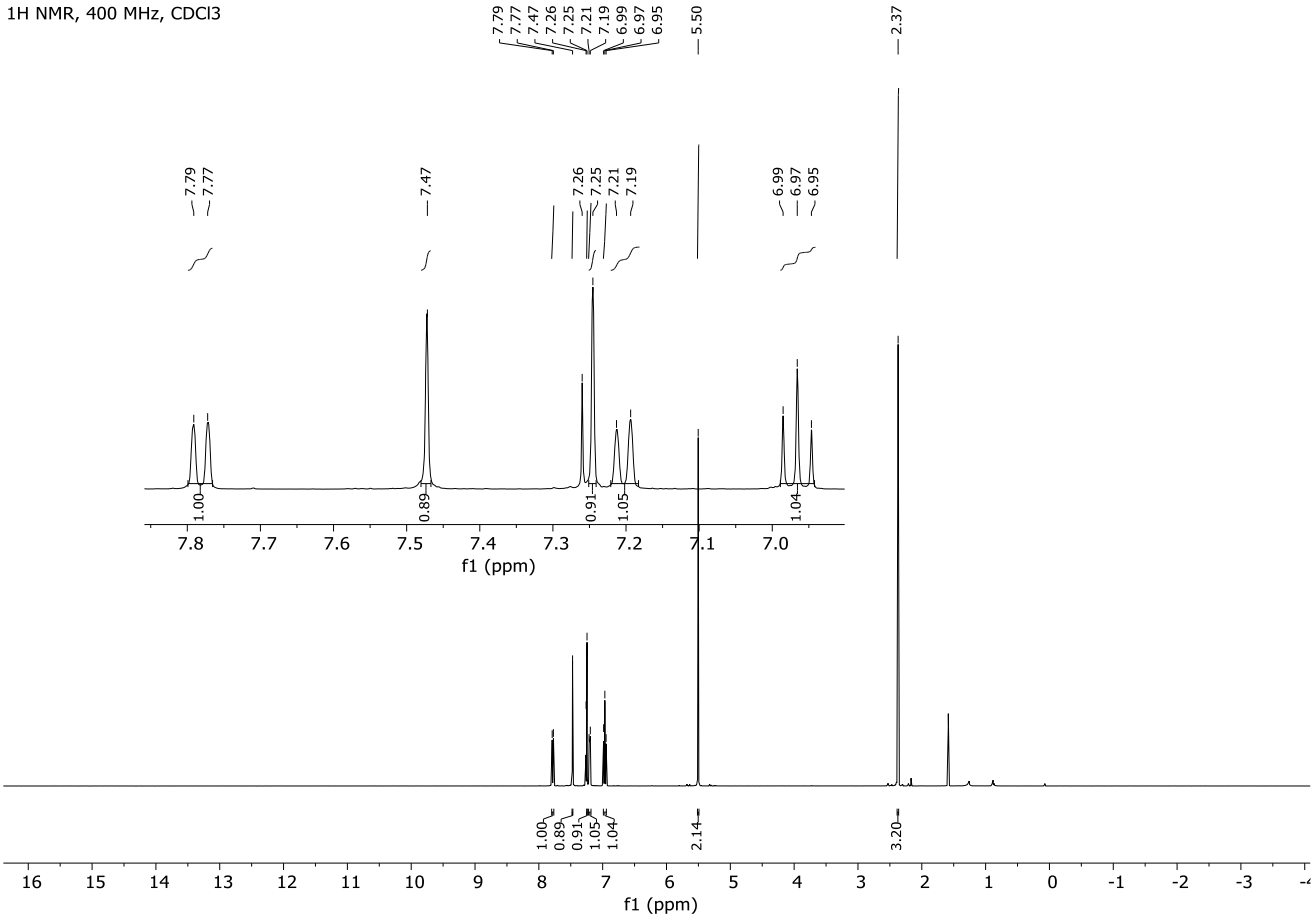


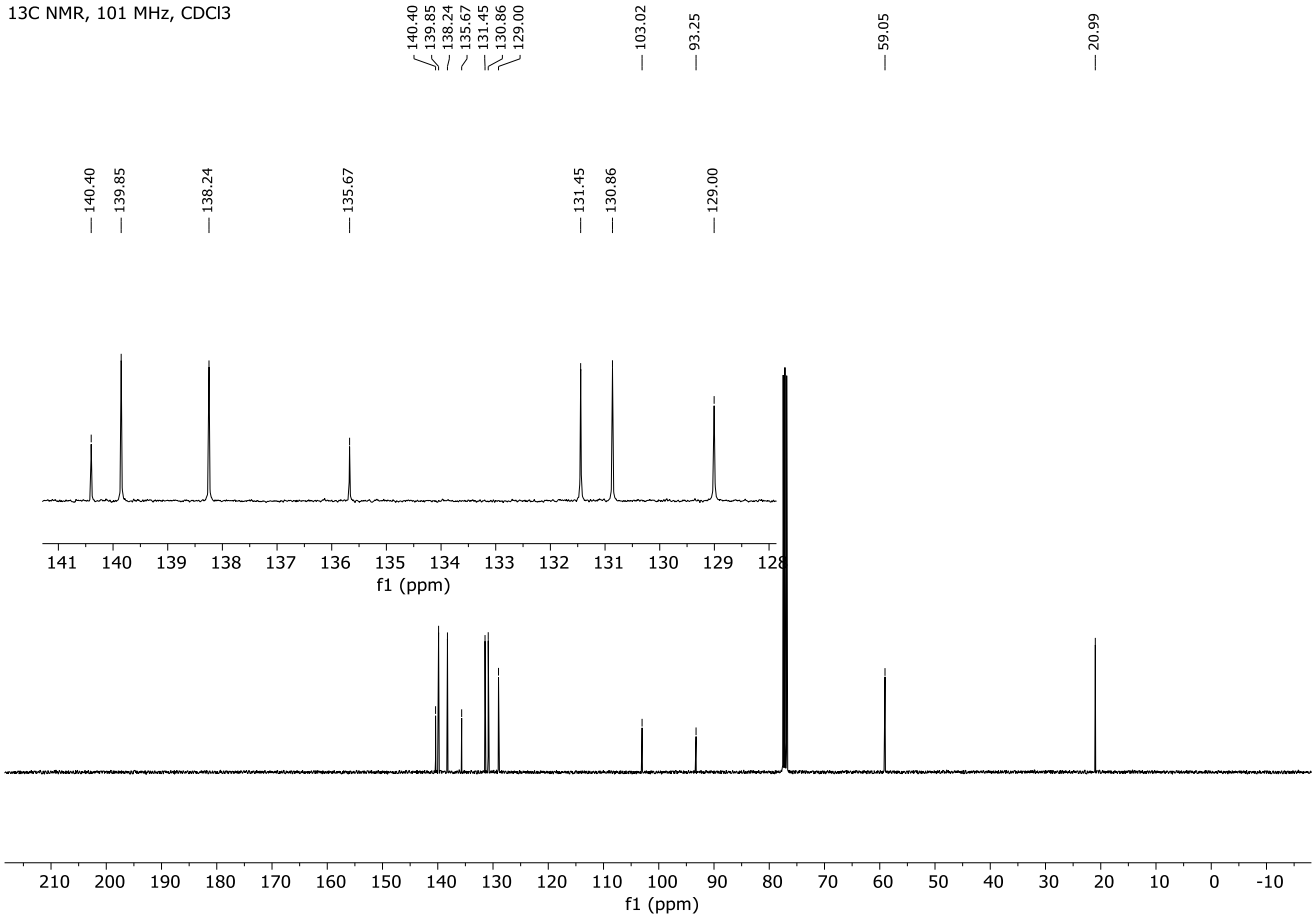
1-(2-Bromo-6-iodophenyl)-4-bromo-*1H*-pyrazole (10a)



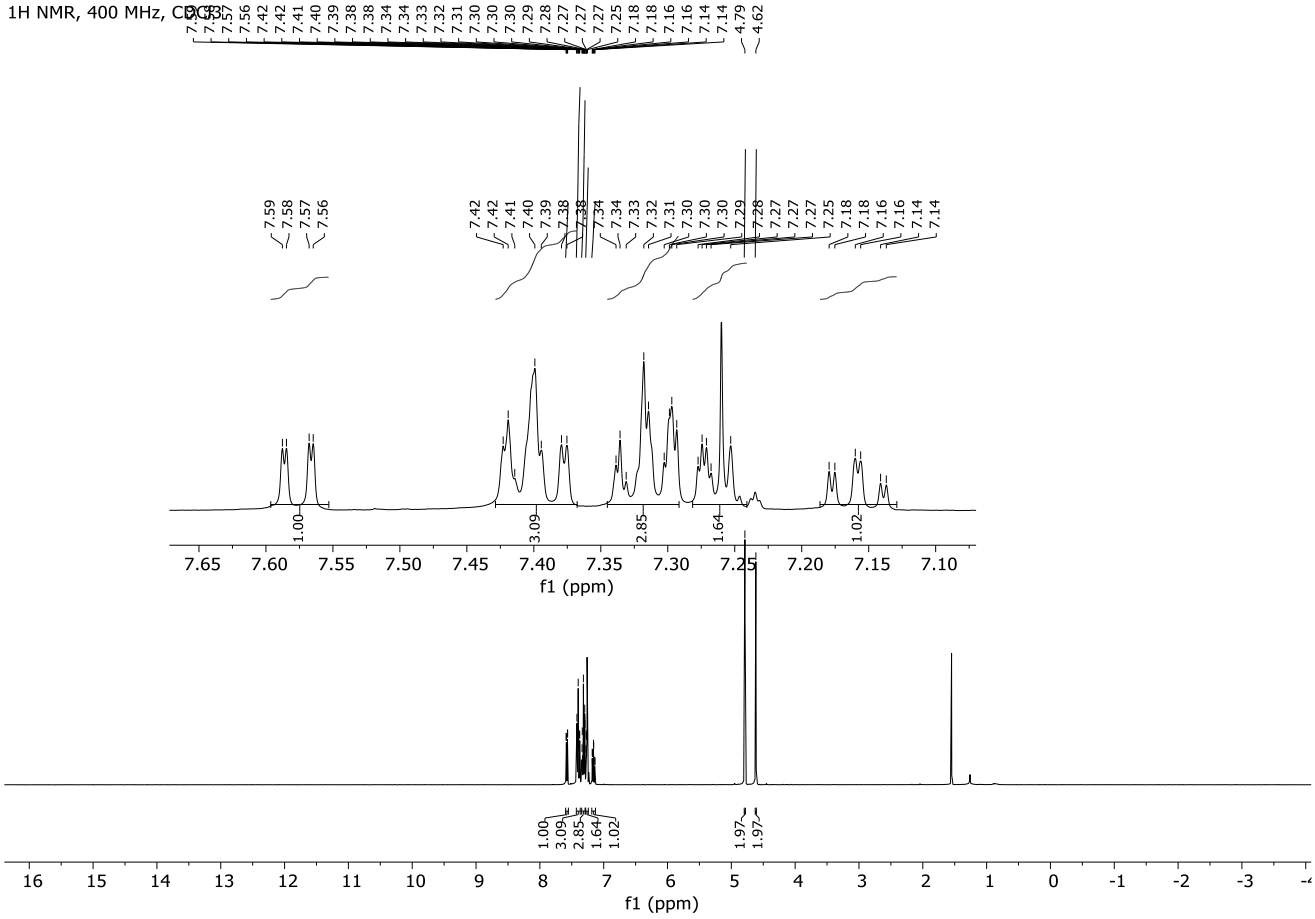


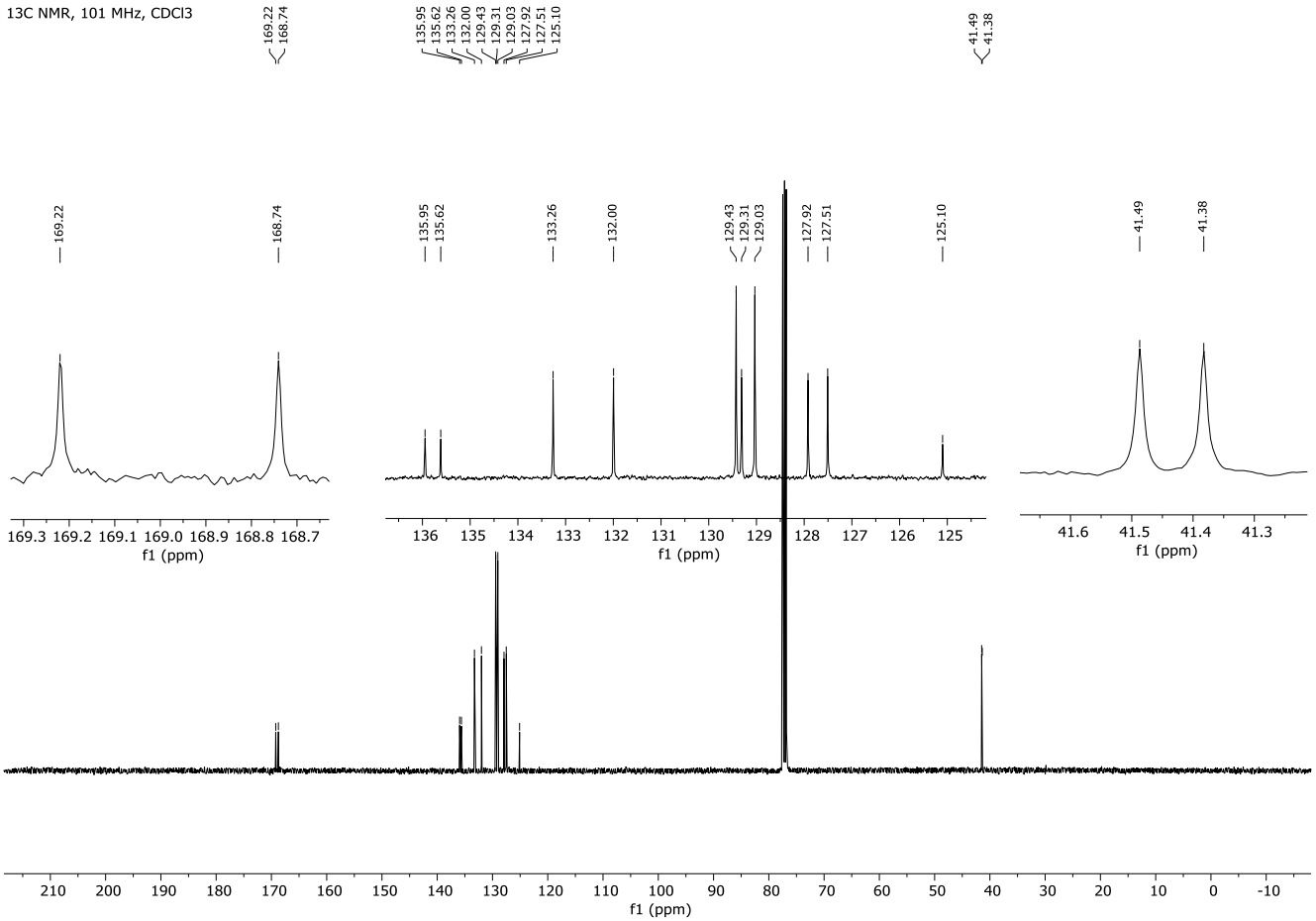
4-Bromo-1-[(2-methyl-6-iodophenyl)methyl]-*1H*-pyrazole (11a)



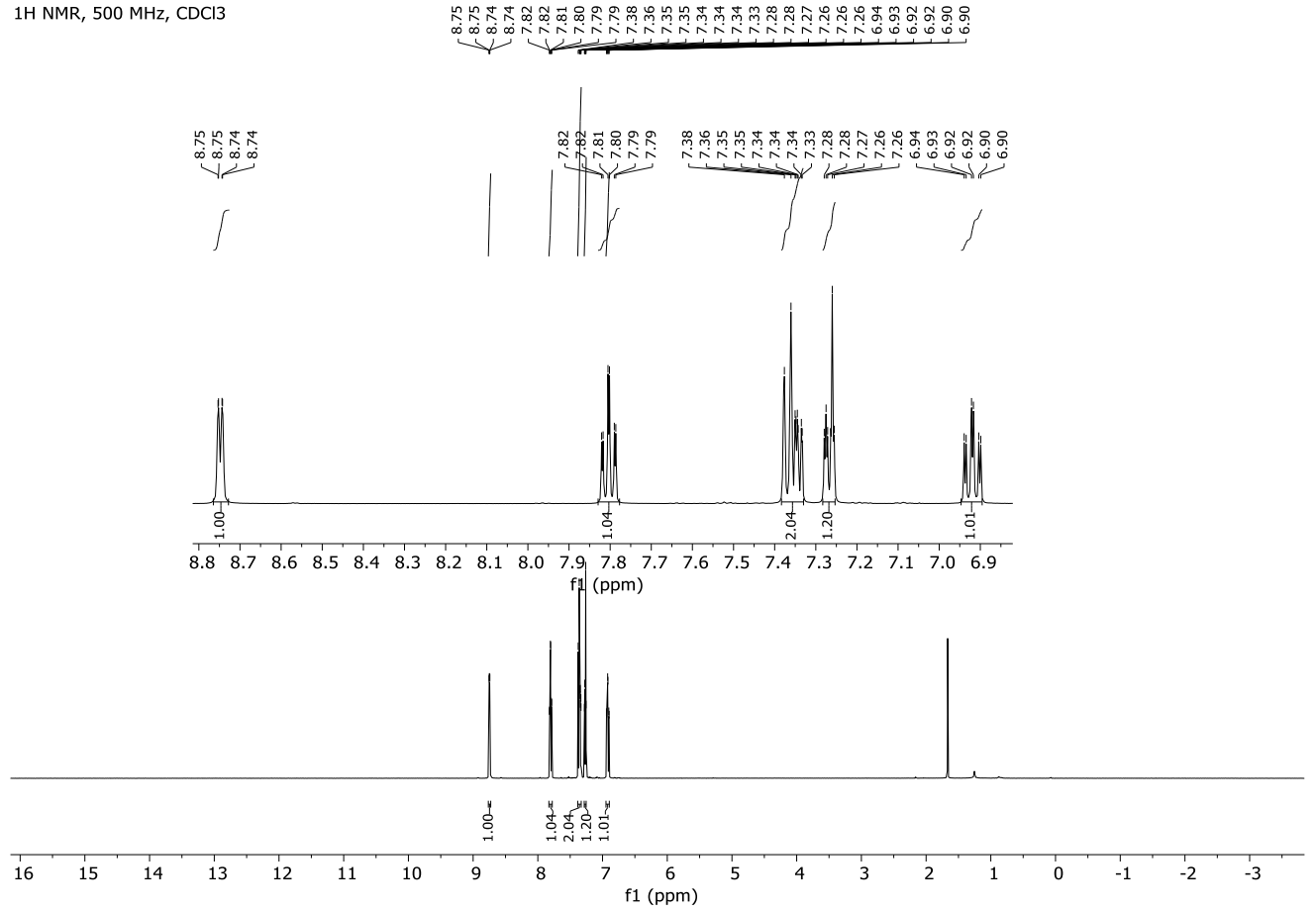


3-(2-Bromophenylmethyl)-6-(phenylmethyl)-1,2,4,5-tetrazine (12c)

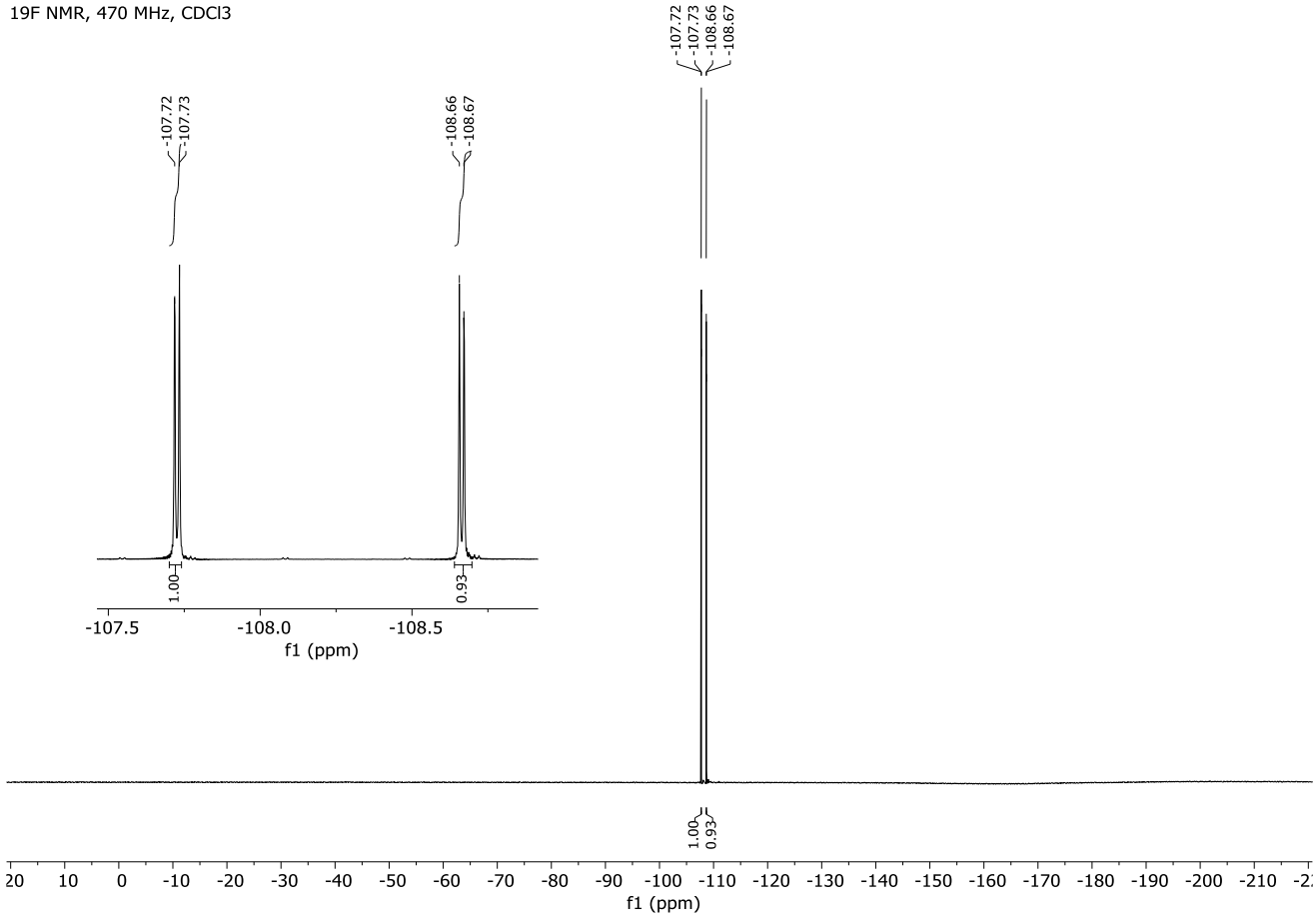




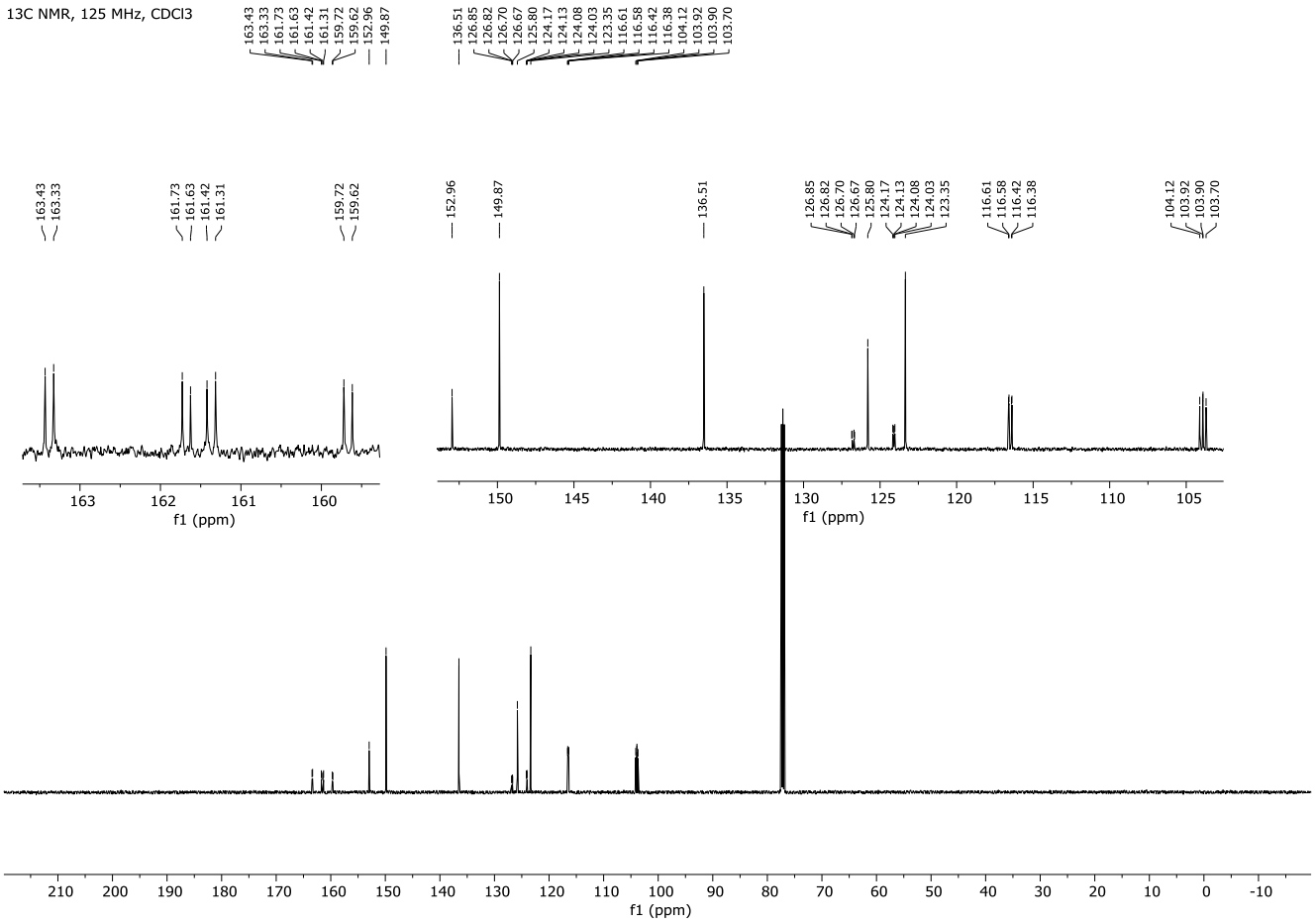
2-(2,4-Difluorophenyl)-6-bromo-pyridine (13c)



19F NMR, 470 MHz, CDCl3

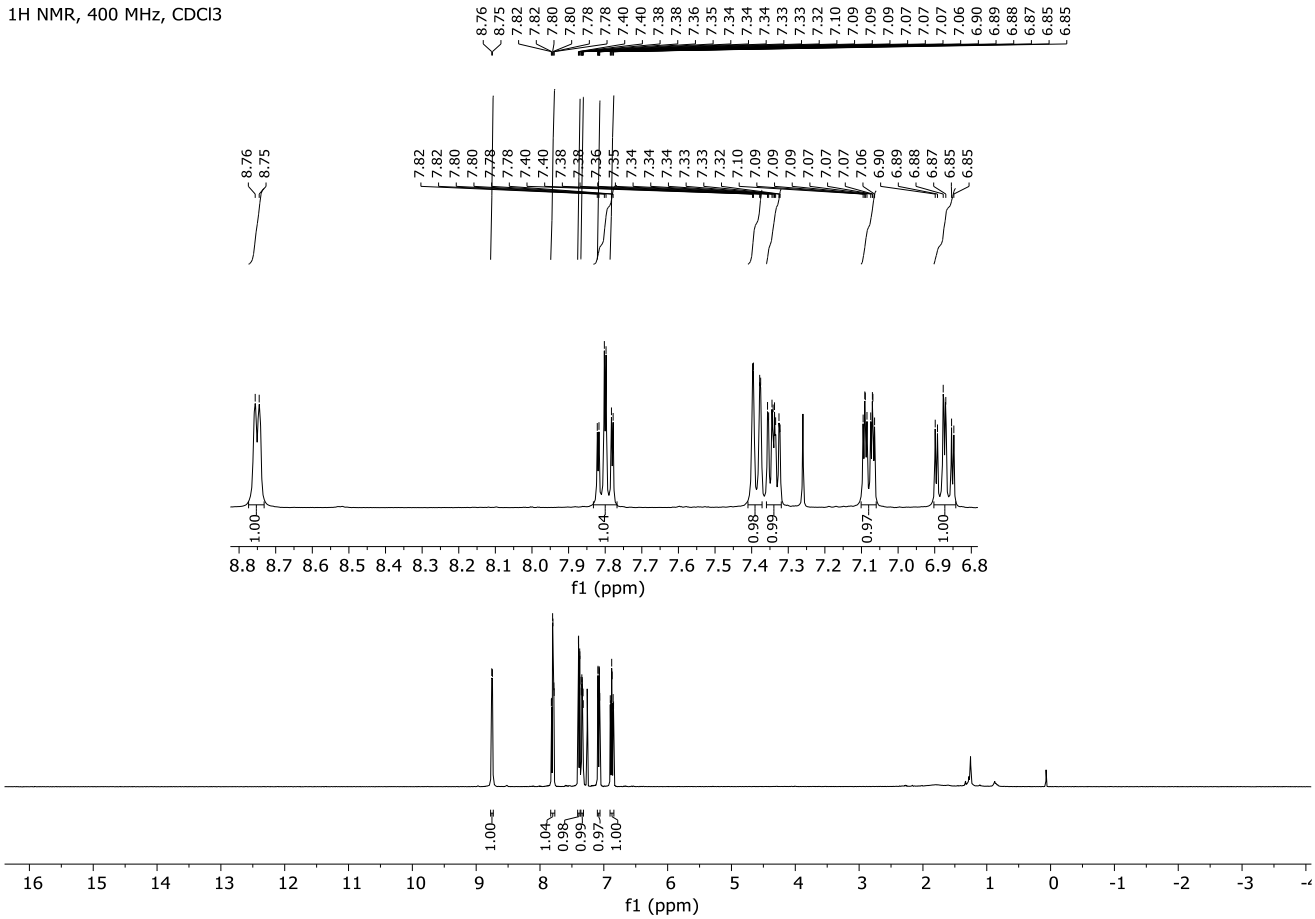


13C NMR, 125 MHz, CDCl3

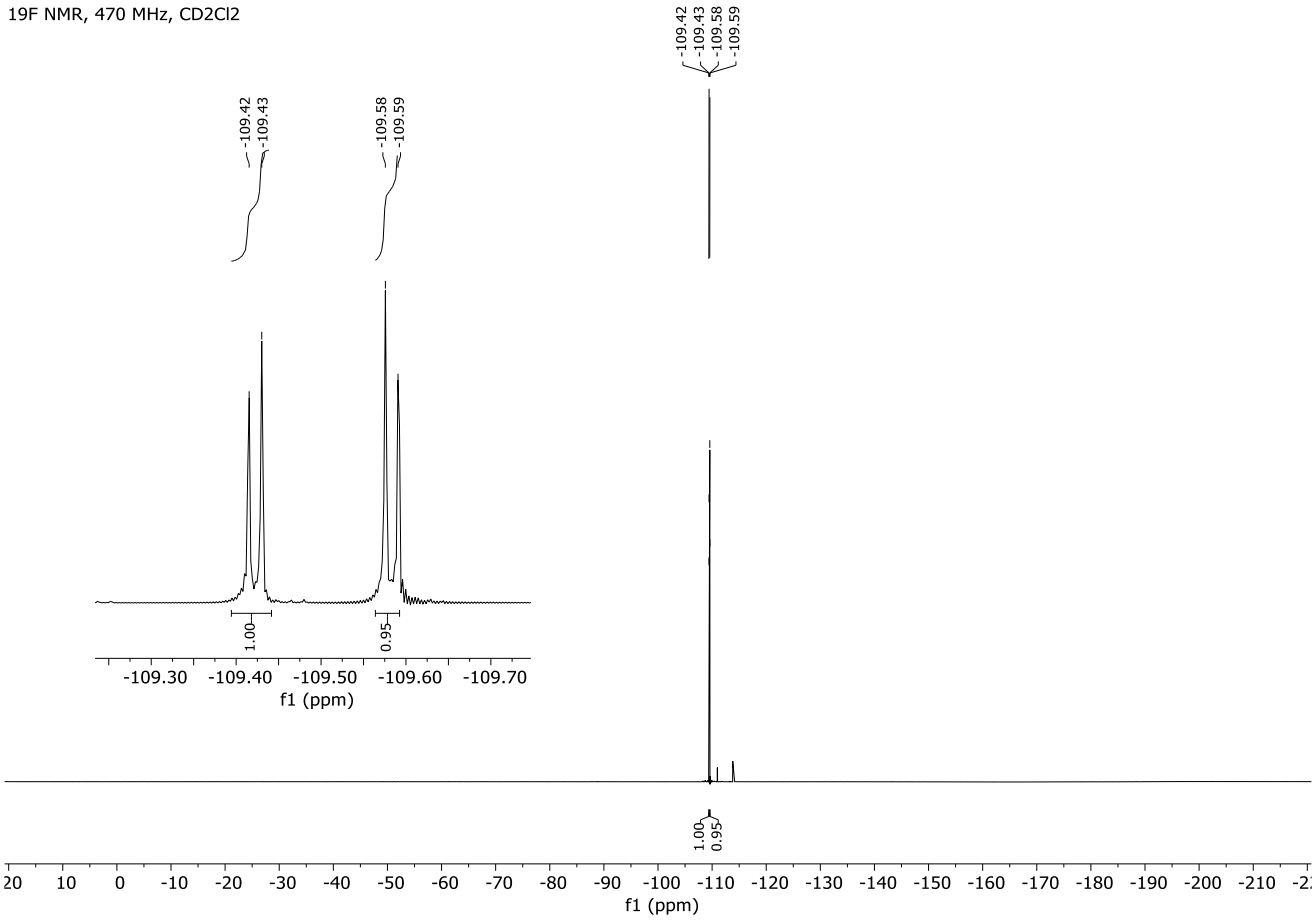


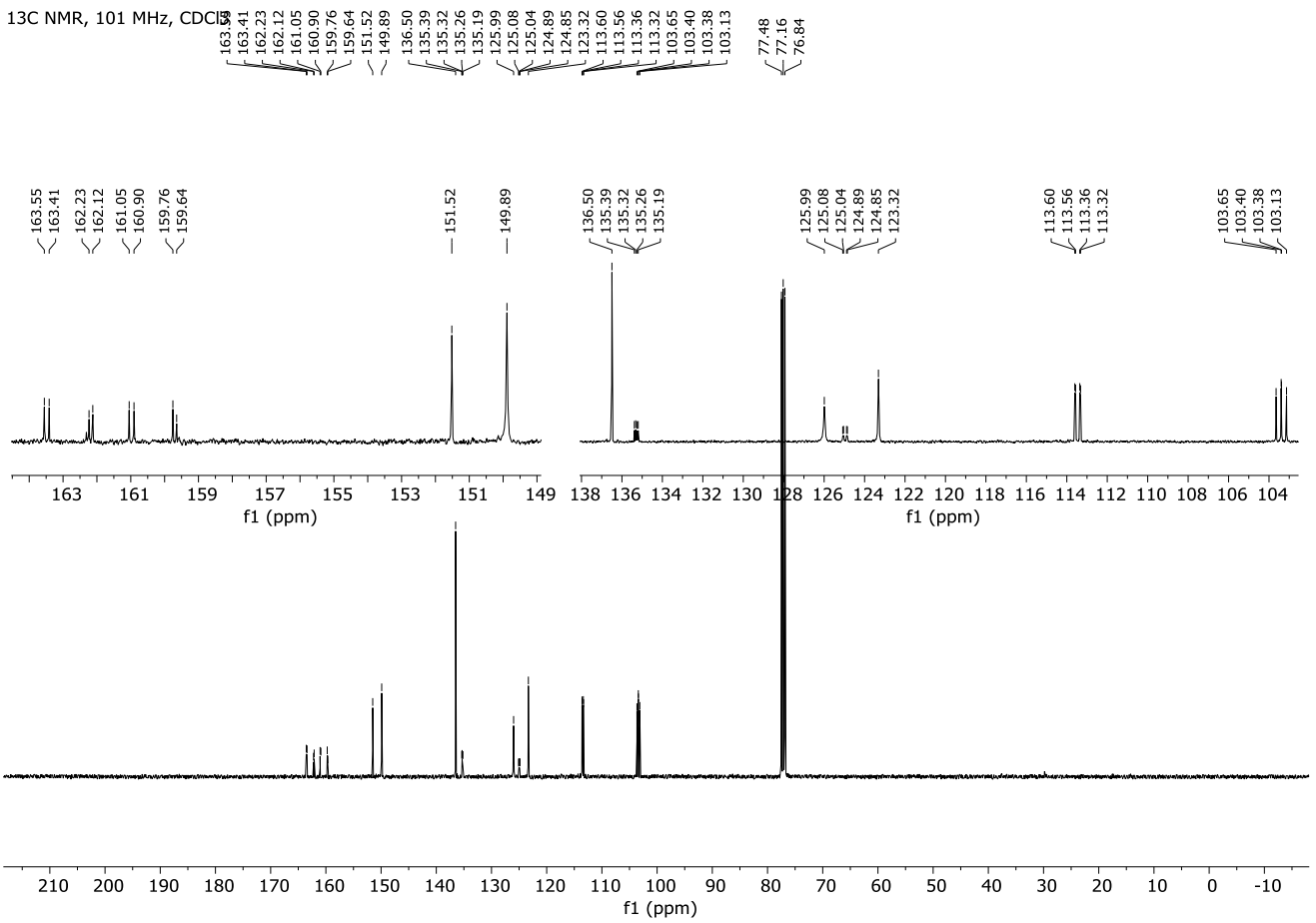
2-(2,4-Difluorophenyl)-6-chloro-pyridine (13d)

1H NMR, 400 MHz, CDCl3

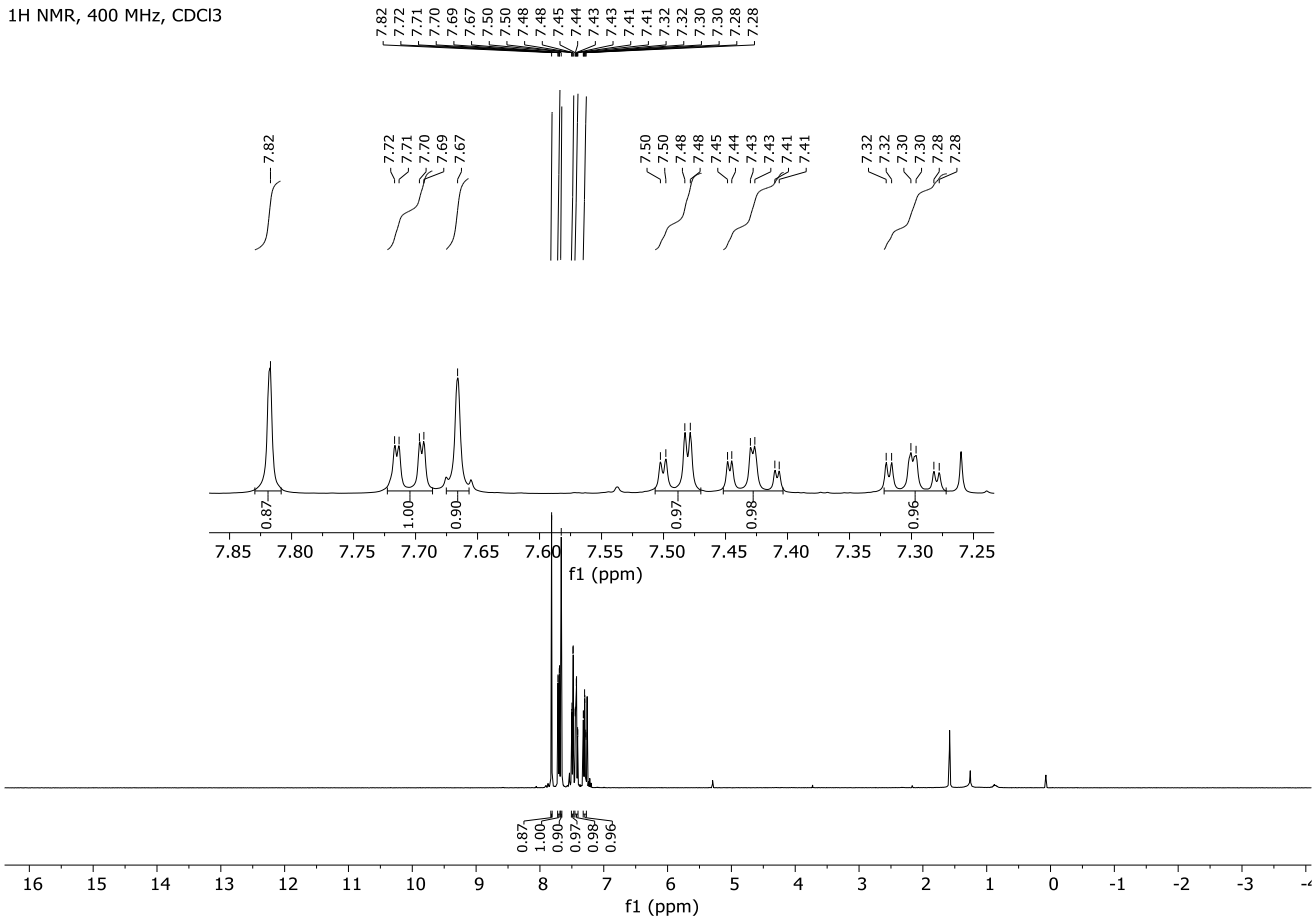


19F NMR, 470 MHz, CD2Cl2



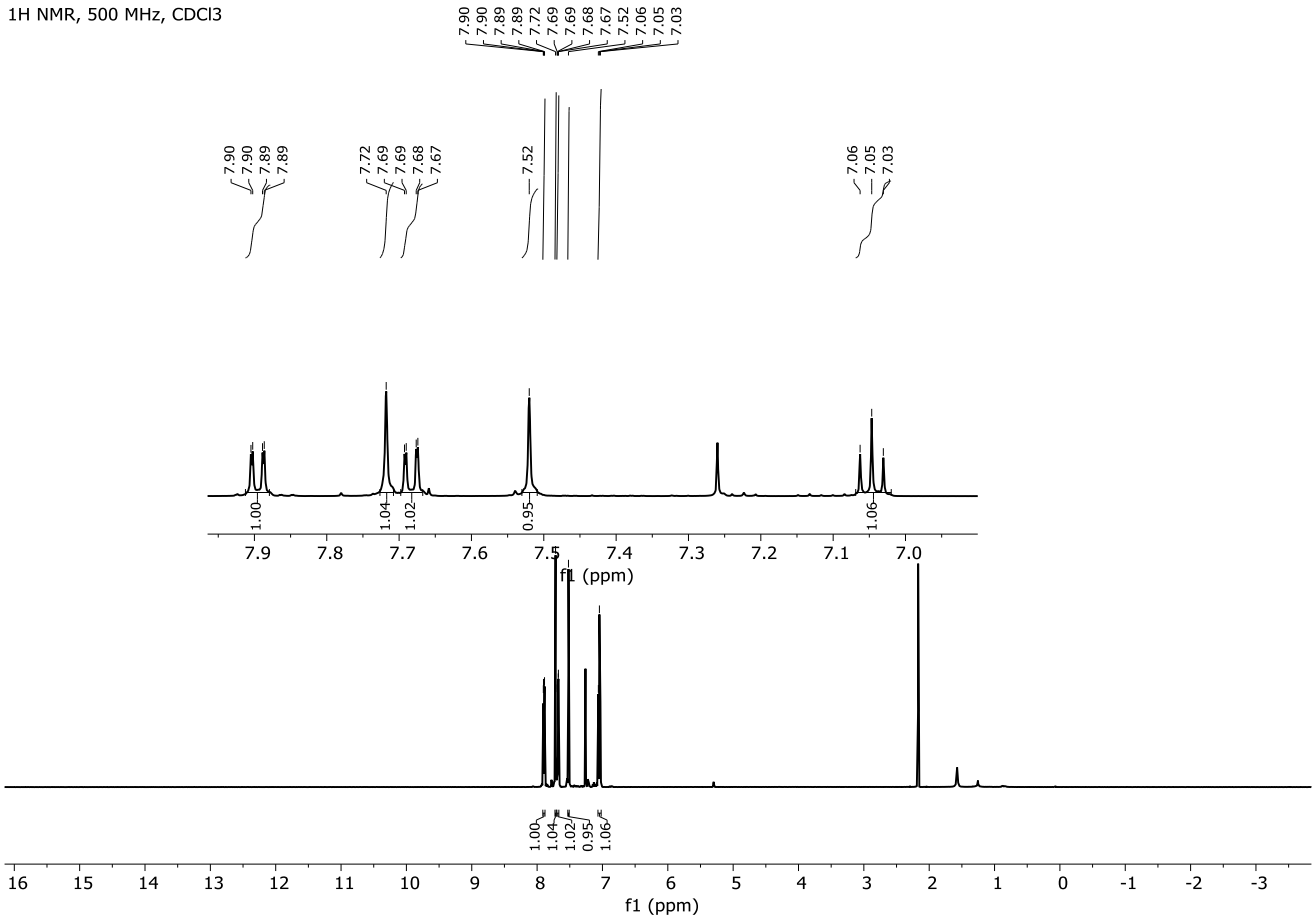


1-(2-Bromophenyl)-4-chloro-*1H*-pyrazole (15)

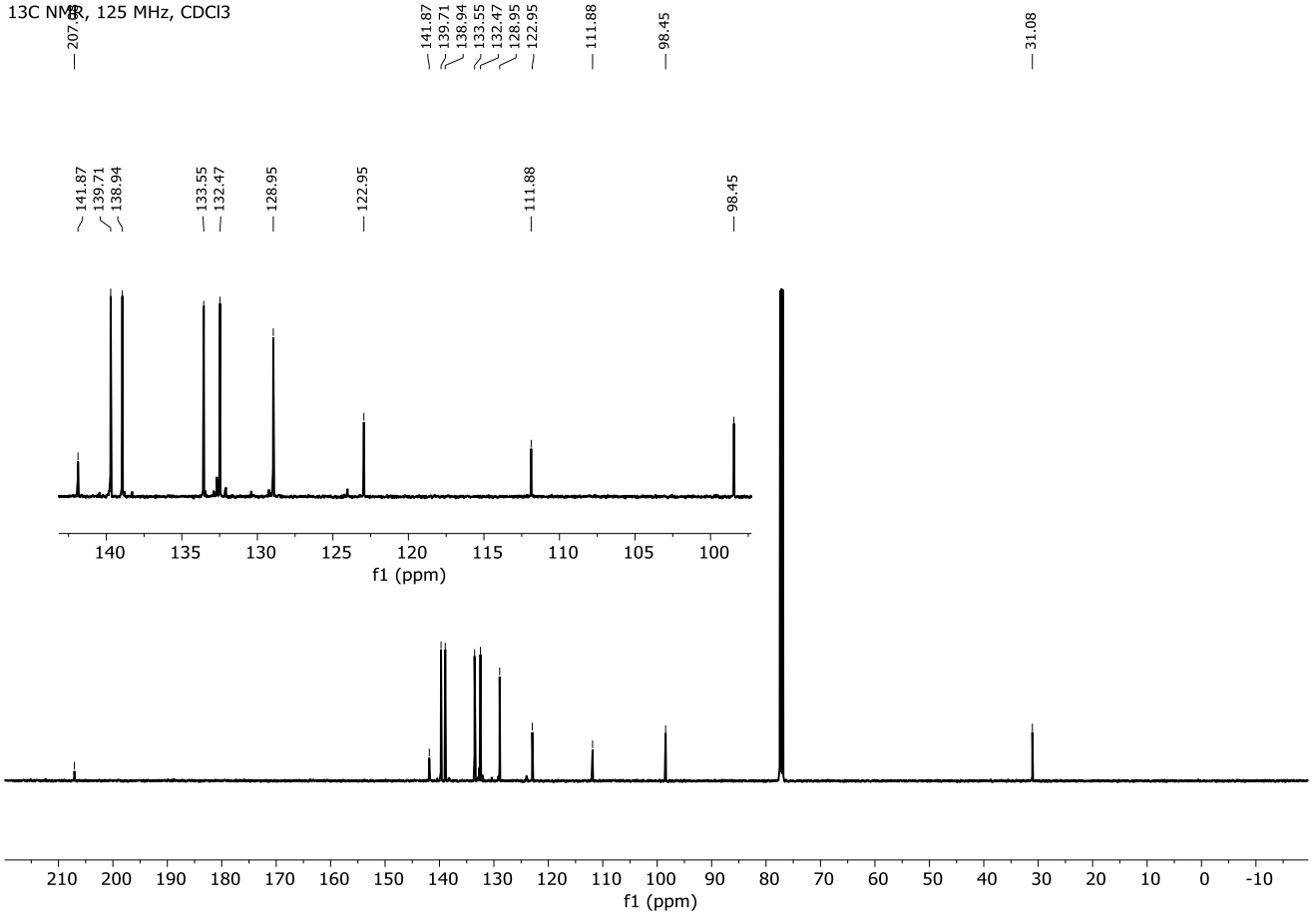


1-(2-Bromo-5-iodophenyl)-4-chloro-*1H*-pyrazole (16)

1H NMR, 500 MHz, CDCl3

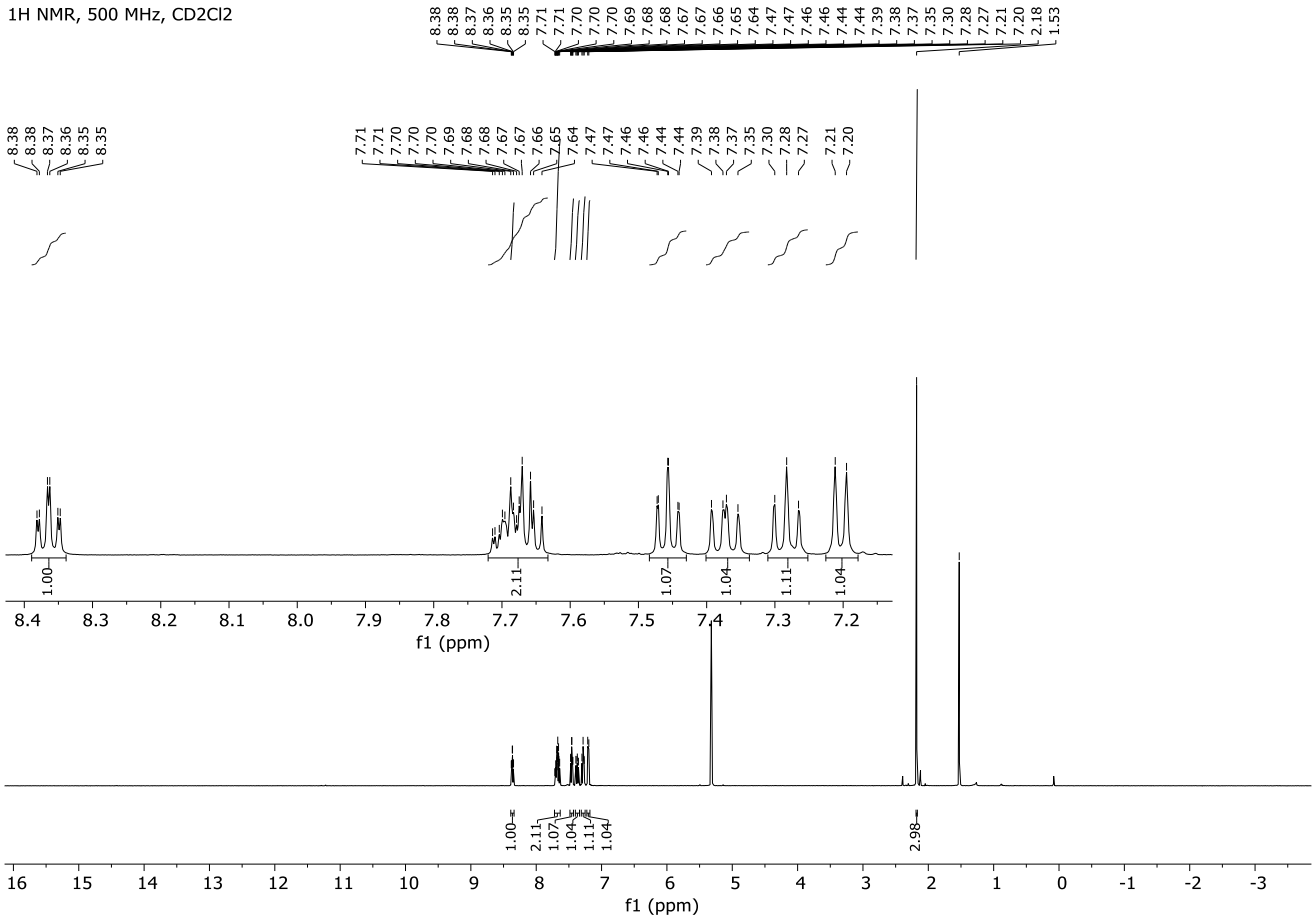


13C NMR, 125 MHz, CDCl3

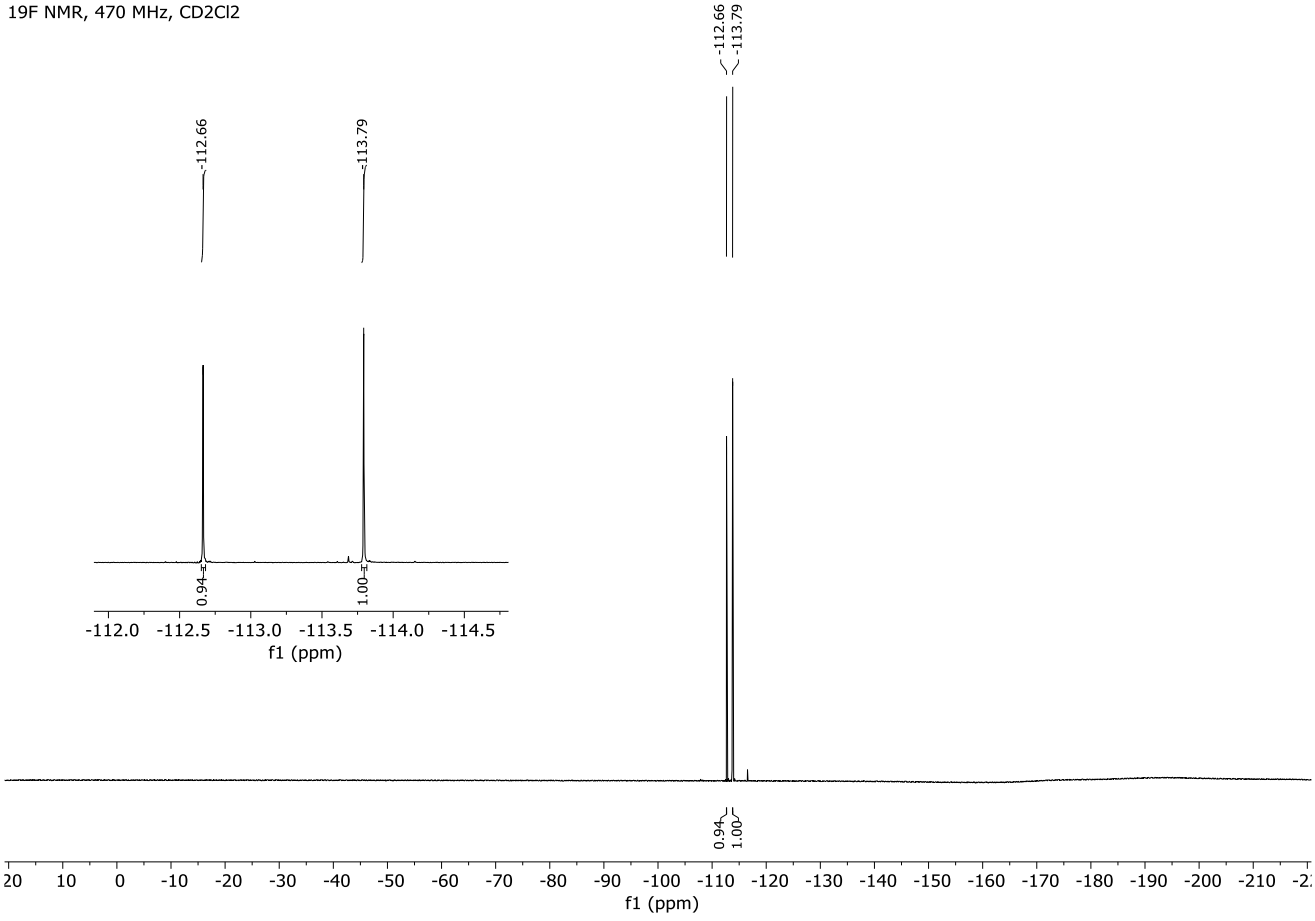


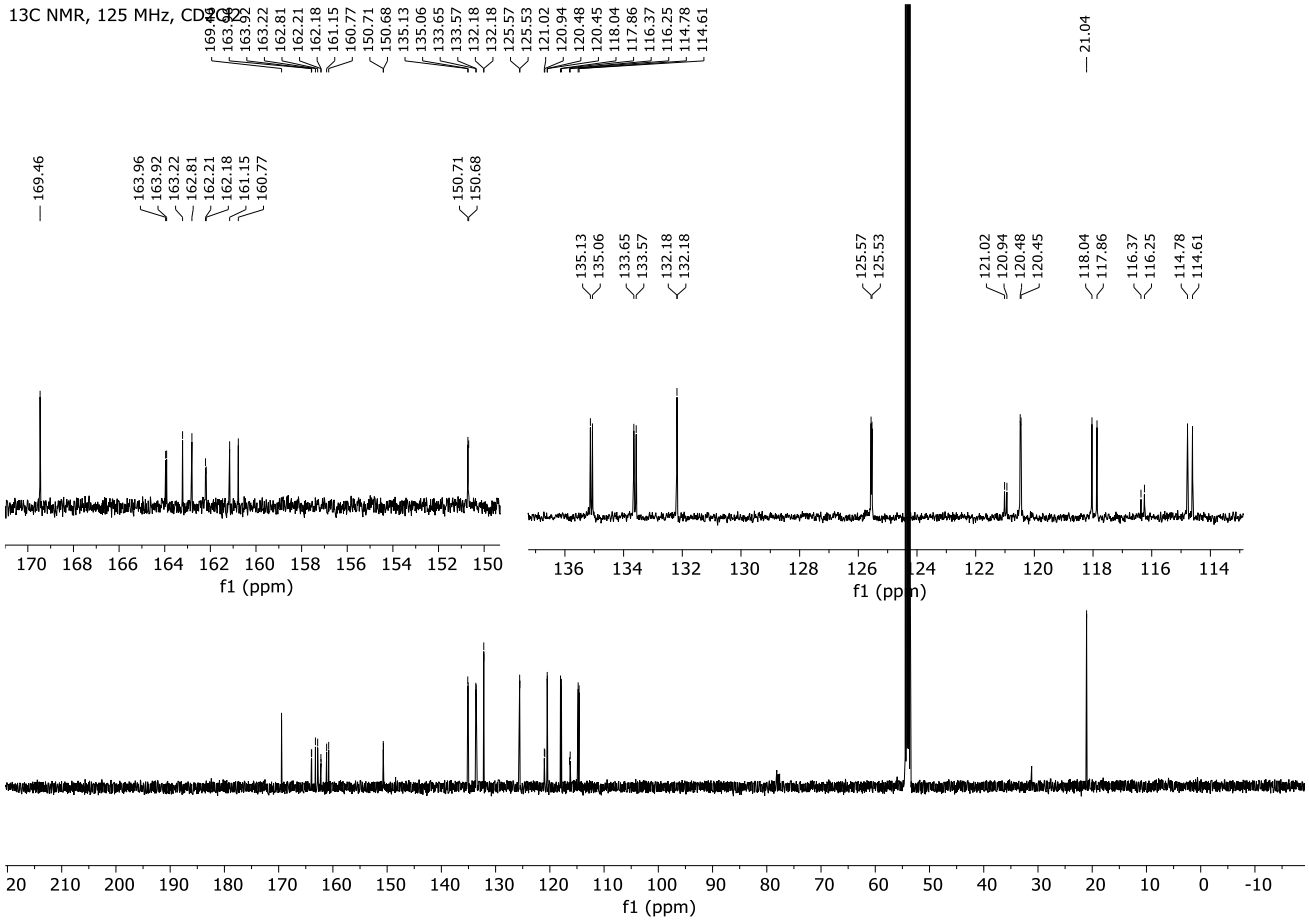
3-(2-Fluoro-6-acetylphenyl)-6-(2-fluorophenyl)-1,2,4,5-tetrazine (1b)

1H NMR, 500 MHz, CD2Cl2

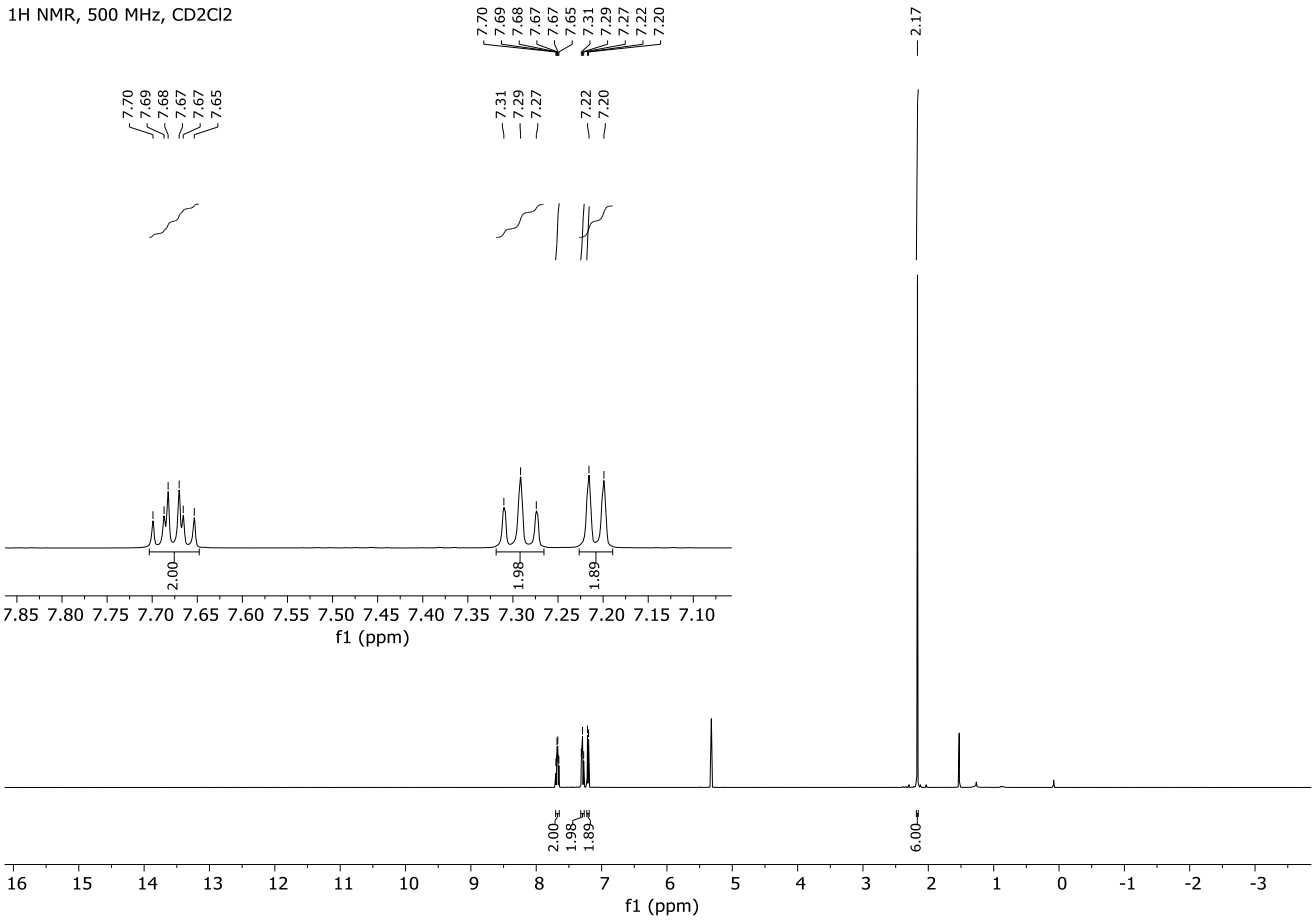


19F NMR, 470 MHz, CD2Cl2

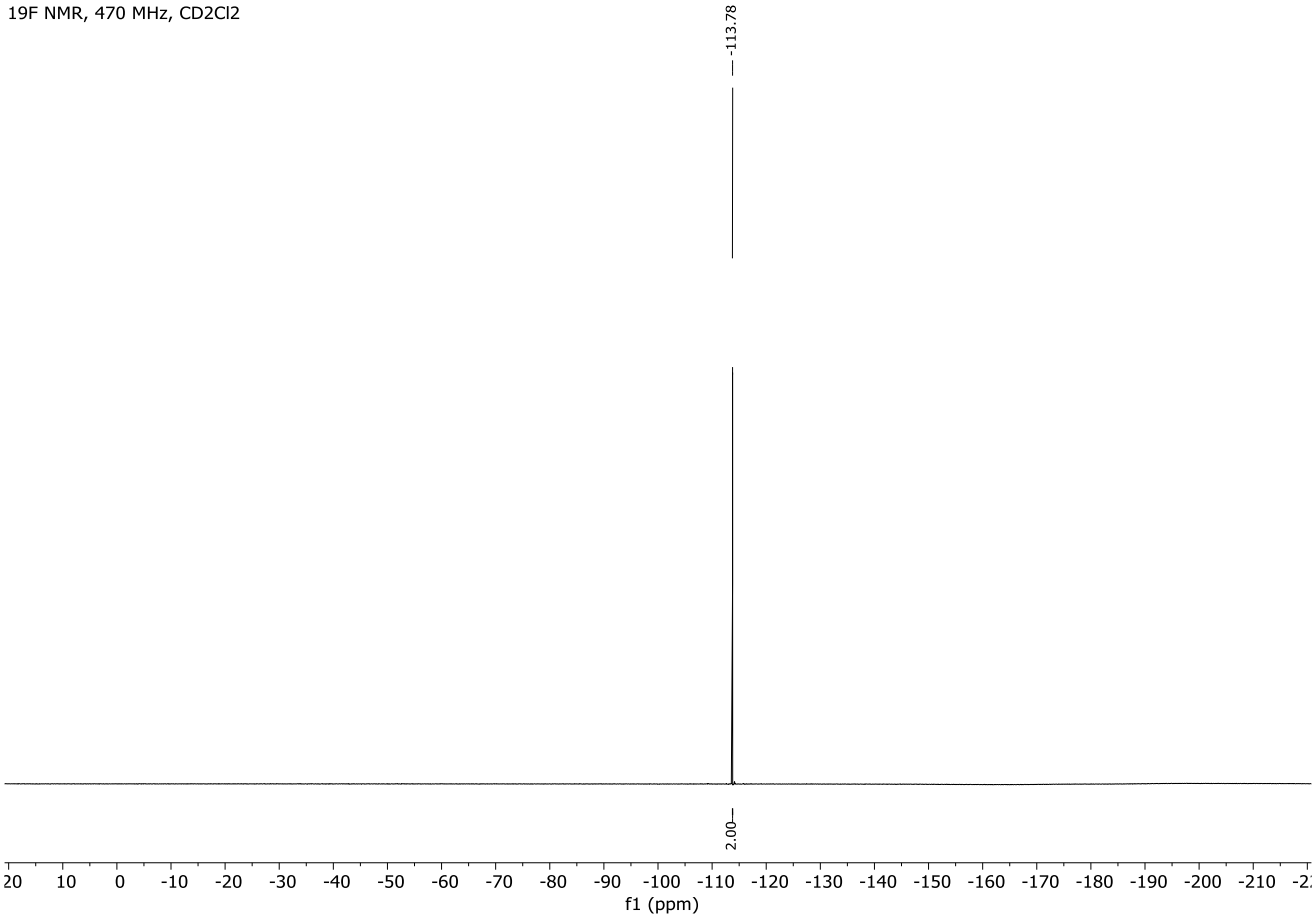




3,6-bis(2-Fluoro-6-acetylphenyl)-1,2,4,5-tetrazine (1b')



19F NMR, 470 MHz, CD2Cl2



13C NMR, 125 MHz, CD2Cl2