Supporting Information

A domino reaction strategy for facile and modular construction of synthetically challenging functionalized *ortho*-fluoroanilines

Benedikt W. Grau,[a] Sascha Kohlbauer,[a] Yungyeong Gu,[a] Friedrich Hahn,[b] Josephine Lösing,[b] Maximilian Stangier,[c] Lutz Ackermann,[c] Manfred Marschall,[b] and Svetlana B. Tsogoeva*[a]

Correspondence to: svetlana.tsogoeva@fau.de

[a] Dr. B. W. Grau, S. Kohlbauer, Y. Gu, Prof. Dr. S. B. Tsogoeva
Organic Chemistry Chair I and Interdisciplinary Center for Molecular Materials (ICMM)
Friedrich-Alexander-Universität Erlangen-Nürnberg
Nikolaus Fiebiger-Straße 10, 91058 Erlangen, Germany
E-mail: svetlana.tsogoeva@fau.de
[b] Dr. F. Hahn, J. Lösing, Prof. Dr. M. Marschall
Institute for Clinical and Molecular Virology
Friedrich-Alexander University of Erlangen-Nürnberg (FAU)
Schlossgarten 4, 91054 Erlangen, Germany
[c] Dr. M. Stangier, Prof. Dr. L. Ackermann
Institut für Organische und Biomolekulare Chemie
Georg-August-Universität Göttingen
Tammannstraße 2, 37077 Göttingen, Germany

Table of content

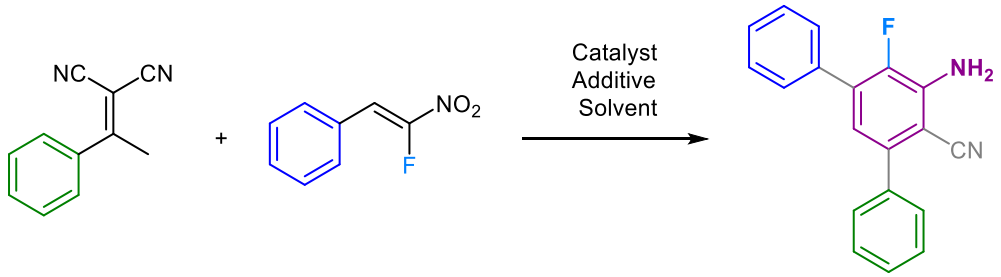
General information....3
Optimization of a new domino reaction....4
Procedures for the synthesis of the starting materials....5
General procedure towards diaryl-substituted fluoroanilines 3a-3j....6
General procedure towards triaryl-substituted fluoroanilines 5a-n....7
Characterization of diaryl-substituted fluoroanilines 3a-3j....8
Characterization of triaryl-substituted fluoroanilines 5a-n....12
Synthesis of quinazolines 9 and 10....65
X-ray crystallography of 5n....95
Biological Methodology....97
UV/Vis Spectra....98
Cyclic voltammetry....101
References....102

General information

All chemicals used for synthesis were purchased from commercial sources and were used without further purification. All solvents were purified by distillation under aerobic conditions or were purchased in HPLC-grade-quality. All products were dried in high vacuum (up to 10^{-3} mbar). Thin layer chromatography (TLC) was performed on pre-coated aluminum sheets ALUGRAM® SIL G/UV254 (0.2 mm silica gel with fluorescent indicator, MachereyNagel & Co).^{1}H-NMR (^{13}C-NMR) spectra were recorded at room temperature on a Bruker Avance 300, 400, 500 or 600 spectrometers operating at 300 MHz, 400 MHz, 500MHz or 600MHz. All chemical shifts are given in the ppm-scale and refer to the non-deuterized proportion of the solvent. ^{13}C-NMRs were measured with ^{1}H and ^{19}F decoupling to increase the visibility of the signals if they were measured with 126 MHz. In the case of 151 MHz measurements, the multiplicity of ^{13}C signals is given, indicating coupling with fluorine. The title on the right side can identify decoupled spectra. ESI, APPI, and MALDI mass spectra were recorded on a Bruker Daltonik maXis 4G, a Bruker Daltonik micrOTOF II focus, and a Bruker Daltonik ultraflexTOF/TOF. IR spectra were recorded on a Varian IR-660 apparatus. The absorption is indicated in wave numbers [cm^{-1}]. X-ray crystallography was performed on a SuperNova, Dual, Cu at zero, Atlas diffractometer.

Optimization of a new domino reaction

Table S1: Optimization of *m*-terphenyl domino reaction.



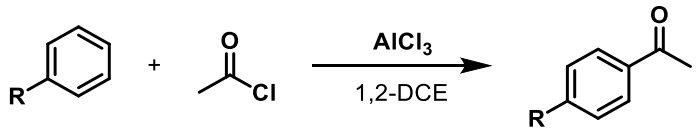
Entry	Cat	Amount Cat [mol%]	Solvent	Temperature [°C]	Time	Yield
1	DABCO	100	CH_3CN	50	o.n.	32%
2	$Cu(OTf)_2$/TEA	5	CH_3CN	50 → 70	2d	n.c.[a]
3	DABCO	100	DMSO	50	3d	12%
4	DABCO	100	THF	50	4d	>10%
5	DABCO	100	EtOH	50	3d	20%
6	DABCO	100	H_2O	50	1d	15%
7	DABCO	100	CH_2Cl_2	50	3d	27%
8	DABCO	100	Toluene	50	4d	16%
9	DABCO	100	CH_3CN	r.t.	1d	18%
10	DABCO	100	CH_3CN	70	1d	18%
11	DBU	100	CH_3CN	50	1d	48%
12	DIPEA	100	CH_3CN	50	2d	22%
13	DMAP	100	CH_3CN	50	2d	28%
14	Pyridine	100	CH_3CN	50	1d	n.c.[a]
15	TEA	100	CH_3CN	50	2d	37%
16	DBU	20	CH_3CN	50	5d	>5%
17	DBU	50	CH_3CN	50	2d	43%
18	DBU	200	CH_3CN	50	1d	43%
19	DBU/ Schreiner's Catalyst	100 / 25	CH_3CN	50	1d	69%
20	$DBU/CuBr_2$	1.00 / 25	CH_3CN	50	1d	13%
21	$DBU/FeCl_3$	100 / 25	CH_3CN	50	1d	6%
22	$DBU/TiCl_4$	100 / 25	CH_3CN	50	1d	n.c.[a]
23	DBU/ Schreiner's Catalyst	100 / 25	CH_3CN	50	1d	59%
24[b]	DBU/ Schreiner's Catalyst	100 / 25	CH_3CN	50	1d	57%
25[c]	DBU/ Schreiner's Catalyst	100 / 25	CH_3CN	50	1d	64%
26	DBU/ Schreiner's Catalyst	100 / 25	CH_3CN	50	1d	62%
27	DBU/PPh_3	100 / 25	CH_3CN	50	1d	40%
28	DBU/Thiourea	100 / 25	CH_3CN	50	1d	61%

Starting material in 2 mL solvent and heated to given T, °C.
[a] n.c.: no conversion observed.
[b] 1.2 equivalents of nitrostyrene were used.
[c] 1.2 equivalents of α,α-dicyanoolefin were used.

Procedures for the synthesis of the starting materials

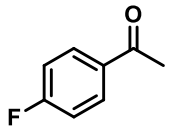
Fluoronitrostyrenes **2a-e** were synthesized according to literature procedure.[4d]

Benzophenones were either bought with >95% purity or synthesized *via* Friedel-Craft acylation:



In a two-neck flask, 1,2-DCE (c[1,2-DCE] = 0.50 ml/mmol) was mixed with finely powdered $AlCl_3$ (1.20 equiv.) and acetyl chloride (1.05 equiv.) was added while stirring and cooling with ice water. The benzene derivative (1.00 equiv.) was added dropwise, and the mixture was stirred for 1 h. After removing the ice bath, the flask kept stirring overnight. To decompose the ketone-aluminium chloride complex, the mixture was carefully poured into chilled water (c[water] = 5.00 ml/mmol) and aluminium hydroxide that may have precipitated was brought into the solution with few drops of conc. HCl. The organic layer was separated, and the aqueous phase was extracted twice with DCM. The combined extracts were carefully washed with water, 2 % NaOH solution and again with water. After drying over K_2CO_3, the solvent was evaporated under reduced pressure to obtain the desired product in sufficient purity.

1-(4-fluorophenyl)ethan-1-one

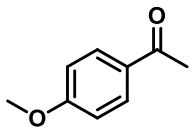


^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 8.01–7.96 (m, 2H), 7.16–7.10 (m, 2H), 2.59 (s, 3H) ppm.

^{19}F-NMR (282MHz, Chloroform-*d*): δ = -105.33 ppm.

The recorded NMR data was consistent with the literature.[34a]

1-(4-methoxyphenyl)ethan-1-one



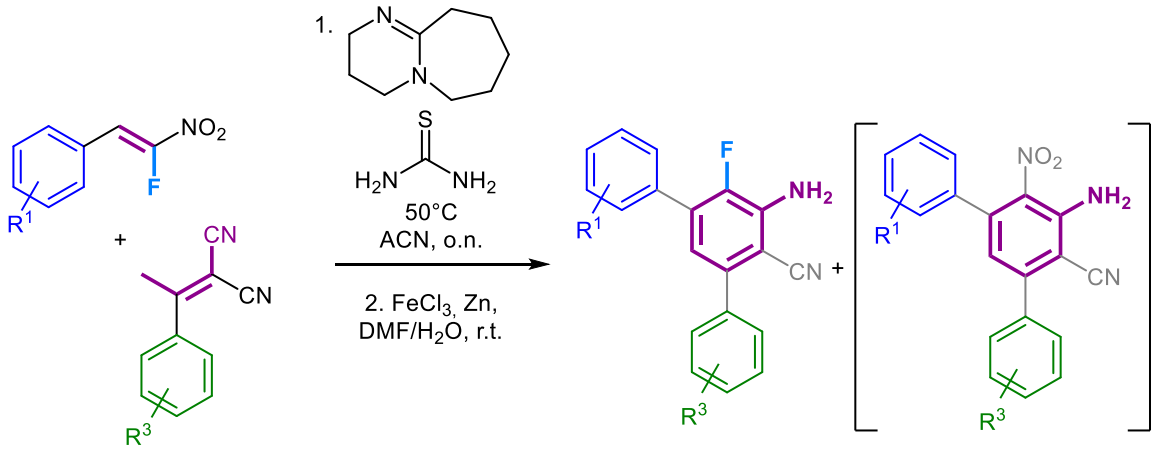
^{1}H-NMR (300 MHz, Chloroform-*d*): δ = 7.99 – 7.87 (m, 2H), 6.98 – 6.87 (m, 2H), 3.87 (s, 3H), 2.55 (s, 3H) ppm.

The recorded NMR data was consistent with the literature.[34a]

Knoevenagel condensation of benzophenones towards **1a-e** was adapted from literature procedure.[34b]

Synthesis of deoxy-benzoins and α,α-dicyanoolefins **4a-i** were adapted from literature procedure.[23c]

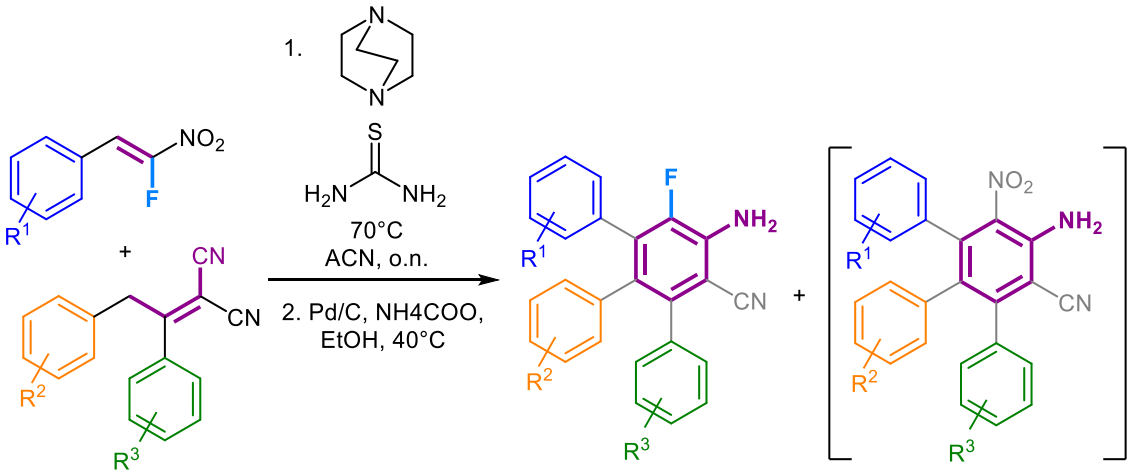
General procedure towards diaryl-substituted fluoroanilines 3a-3j.



To a solution of *α*,*α*-dicyanoolefin (200 µmol), fluoro-nitrostyrene (200 µmol) and thiourea (50 µmol) in 2 ml acetonitrile DBU (200 µmol) was added. The yellowish reaction mixture was heated to 50 °C and was allowed to stir overnight. The resulting brownish solution was concentrated under reduced pressure and purified by column chromatography (*iso*-Hexane : DCM : Et_2O = 8 : 3 : 1) to obtain the desired *m*-terphenyl (10 : 1.2 mixture with nitro-derivative). The product can be identified as a strong blueish fluorescent spot (R_f = 0.5), with the yellow spot of the nitro-derivative at the same position.

To a suspension of domino-mixture (1 equiv.) in DMF/H_2O (7 ml/ 2 ml), $FeCl_3$ (0.8 equiv.) and Zn (20.0 equiv.) were added. After stirring at room temperature for 3.5 h, complete conversion of the nitro-derivatives to amine-derivatives was indicated by TLC as evanishment of the yellow spot. The mixture was filtered. The filter cake was washed with DCM and 20 ml of water was added to the filtrate. The filtrate was extracted with 8 ml DCM four times. The combined organic phases were washed with saturated ammonium chloride solution and water. After drying over $MgSO_4$ and evaporation of the solvent under reduced pressure, column chromatography (Hexane : DCM : Et_2O = 8 : 3 : 1, blue fluorescent spot) gave the pure fluoro-substituted *m*-terphenyls.

General procedure towards triaryl-substituted fluoroanilines 5a-n.

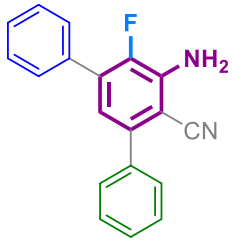


To a mixture of *α,α*-dicyanoolefin (200 µmol), nitrostyrene (200 µmol) and thiourea (100 µmol) in 2.5 ml acetonitrile DABCO (200 µmol) was added in one portion and the reaction was heated to 70 °C overnight. The yellowish reaction mixture turned brown. After 18 h the reaction was checked to see if TLC indicated the complete consumption of the starting material. The reaction mixture was allowed to cool down to room temperature, concentrated under reduced pressure and purified *via* a short plug (Hexane : EtOAc = 10 : 1 or Hexane : DCM : Et_2O = 8 : 3 : 1) to yield the product and the corresponding nitro derivate as an inseparable mixture (yellow fluorescent spot, R_f = 0.40). The dry mixture was dissolved in 15 ml degassed EtOH, Pd/C (15 mg) and ammoniumformate (150 mg) was added, and the reaction was heated to 40 °C. After TLC indicated the consumption of the nitro derivative (0.5-24 h, absence of yellow spot, new fluorescent spot around R_f = 0.15) the solvent was evaporated, dissolved in DCM, filtered, and adsorbed on silica. The crude mixture was purified *via* column chromatography, using the same eluent as above, to obtain the pure fluor-derivatives.

Characterization of diaryl-substituted fluoroanilines 3a-3j

5'-amino-6'-fluoro-[1,1':3',1''-terphenyl]-4'-carbonitrile **3a**

29.2 mg, 101 µmol, 51% yield



$C_{19}H_{13}FN_2$
MW: 288.33

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.63 – 7.53 (m, 4H), 7.53 – 7.37 (m, 6H), 6.84 (d, *J* = 6.8 Hz, 1H), 4.69 (s, 2H).

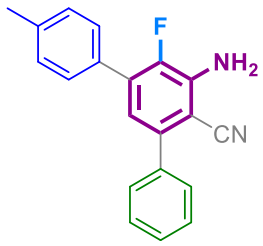
^{13}C NMR (126 MHz, Chloroform-*d*) δ = 146.93, 141.15, 140.22, 138.27, 134.51, 132.83, 129.03, 128.86, 128.80, 128.77, 128.72, 128.69, 119.77, 116.59, 95.98.

^{19}F NMR (283 MHz, Chloroform-*d*) δ = -140.61 (d, *J* = 7.0 Hz).

HR-MS (APPI positive mode): *m/z* = calc. for ($[M]^+$): 288.1057, found: 288.1061.

5'-amino-6'-fluoro-4-methyl-[1,1':3',1''-terphenyl]-4'-carbonitrile **3b**

26.9 mg, 89.0 µmol, 44% yield



$C_{20}H_{15}FN_2$
MW: 302.35

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.62 – 7.54 (m, 2H), 7.53 – 7.39 (m, 5H), 7.28 (d, *J* = 7.7 Hz, 2H), 6.83 (d, *J* = 6.8 Hz, 1H), 4.67 (s, 2H), 2.42 (s, 3H).

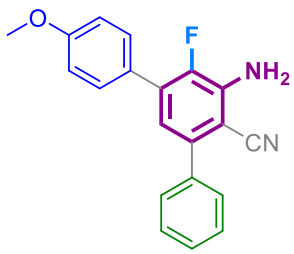
^{13}C NMR (126 MHz, Chloroform-*d*) δ = 146.97, 141.10, 140.20, 138.95, 138.36, 132.84, 131.57, 129.51, 128.91, 128.80, 128.70, 128.69, 119.72, 116.66, 95.73, 21.42.

^{19}F NMR (283 MHz, Chloroform-*d*) δ = -140.66 (d, *J* = 6.5 Hz).

HR-MS (APPI positive mode): *m/z* = calc. for ($[M]^+$): 302.1214, found: 302.1215.

5'-amino-6'-fluoro-4-methoxy-[1,1':3',1''-terphenyl]-4'-carbonitrile **3c**

17.4 mg, 54.7 µmol, 27% yield



$C_{20}H_{15}FN_2O$
MW: 318.35

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.61 – 7.50 (m, 4H), 7.51 – 7.38 (m, 3H), 7.08 – 6.94 (m, 2H), 6.81 (d, *J* = 6.9 Hz, 1H), 4.66 (s, 2H), 3.86 (s, 3H).

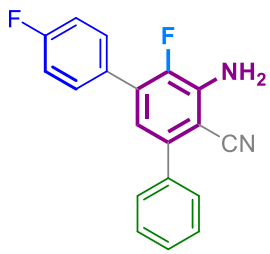
^{13}C NMR (126 MHz, Chloroform-*d*) δ = 160.17, 146.90, 141.08, 140.20, 138.39, 132.48, 130.32, 128.79, 128.69, 128.68, 126.75, 119.55, 116.70, 114.25, 95.43, 55.50.

^{19}F NMR (471 MHz, Chloroform-*d*) δ = -140.89.

HR-MS (APPI positive mode): *m/z* = calc. for ($[M]^+$): 318.1163, found: 318.1163.

5'-amino-4,6'-difluoro-[1,1':3',1"-terphenyl]-4'-carbonitrile **3d**

21.5 mg, 70.2 µmol, 35% yield



$C_{19}H_{12}F_2N_2$
MW: 306.32

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.59 – 7.52 (m, 4H), 7.51 – 7.40 (m, 3H), 7.20 – 7.12 (m, 2H), 6.79 (d, *J* = 6.8 Hz, 1H), 4.69 (s, 2H).

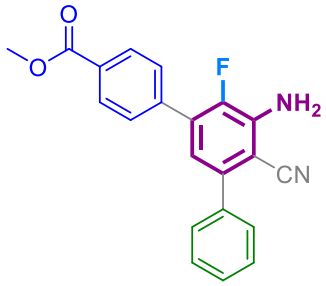
^{13}C NMR (126 MHz, Chloroform-*d*) δ = 163.14, 146.86, 141.30, 140.23, 138.19, 131.83, 130.87, 130.49, 128.85, 128.82, 128.69, 119.56, 116.49, 115.88, 96.12.

^{19}F NMR (471 MHz, Chloroform-*d*) δ = -112.49, -140.79.

HR-MS (APPI positive mode): *m/z* = calc. for ($[M]^+$): 306.0963, found: 306.0970.

methyl 5'-amino-4'-cyano-6'-fluoro-[1,1':3',1"-terphenyl]-4-carboxylate **3e**

36.9 mg, 107 µmol, 53% yield



$C_{21}H_{15}FN_2O_2$
MW: 346.36

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.13 (d, *J* = 8.5 Hz, 2H), 7.64 (dd, *J* = 8.4, 1.7 Hz, 2H), 7.60 – 7.52 (m, 2H), 7.52 – 7.36 (m, 3H), 6.83 (d, *J* = 6.7 Hz, 1H), 4.72 (s, 2H), 3.95 (s, 3H).

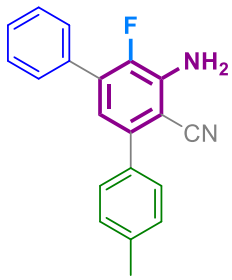
^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.75, 146.90, 141.42, 140.27, 138.98, 138.06, 131.74, 130.40, 129.99, 129.10, 128.88, 128.87, 128.69, 119.44, 116.36, 96.69, 52.44.

^{19}F NMR (471 MHz, Chloroform-*d*) δ = -140.10.

HR-MS (APPI positive mode): *m/z* = calc. for ($[M]^+$): 346.1112, found: 346.1119.

5'-amino-6'-fluoro-4"-methyl-[1,1':3',1"-terphenyl]-4'-carbonitrile **3f**

11.6 mg, 38.4 µmol, 19% yield



$C_{20}H_{15}FN_2$
MW: 302.35

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.59 – 7.53 (m, 2H), 7.51 – 7.40 (m, 5H), 7.28 (d, *J* = 7.9 Hz, 2H), 6.82 (d, *J* = 6.8 Hz, 1H), 4.66 (s, 2H), 2.41 (s, 3H).

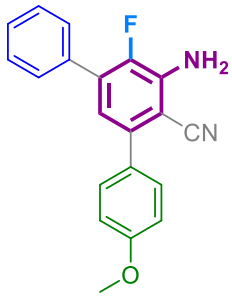
^{13}C NMR (126 MHz, Chloroform-*d*) δ = 146.83, 141.22, 140.14, 138.71, 135.42, 134.61, 132.85, 129.53, 129.05, 128.84, 128.77, 128.56, 119.68, 116.73, 96.02, 21.39.

^{19}F NMR (471 MHz, Chloroform-*d*) δ = -140.99.

HR-MS (APPI positive mode): *m/z* = calc. for ($[M]^+$): 302,1214, found: 302.1217.

5'-amino-6'-fluoro-4''-methoxy-[1,1':3',1''-terphenyl]-4'-carbonitrile **3g**

40.8 mg, 128 µmol, 64% yield



$C_{20}H_{15}FN_2O$
MW: 318.35

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.65 – 7.53 (m, 2H), 7.55 – 7.37 (m, 5H), 7.00 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 6.7 Hz, 1H), 4.65 (s, 2H), 3.86 (s, 3H).

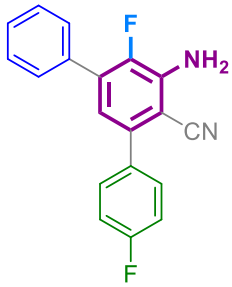
^{13}C NMR (126 MHz Chloroform-*d*) δ = 160.10, 146.69, 140.90, 140.12, 134.62, 132.86, 130.69, 129.92, 129.04, 128.83, 128.77, 119.58, 116.85, 114.26, 95.94, 55.51.

^{19}F NMR (471 MHz, Chloroform-*d*) δ = -141.28.

HR-MS (APPI positive mode): *m/z* = calc. for ([M]$^+$): 319.1241, found: 319.1247.

5'-amino-4'',6'-difluoro-[1,1':3',1''-terphenyl]-4'-carbonitrile **3h**

19.9 mg, 65.0 µmol, 32% yield



$C_{19}H_{12}F_2N_2$
MW: 306.32

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.61 – 7.41 (m, 7H), 7.24 – 7.06 (m, 2H), 6.79 (d, *J* = 6.7 Hz, 1H), 4.69 (s, 2H).

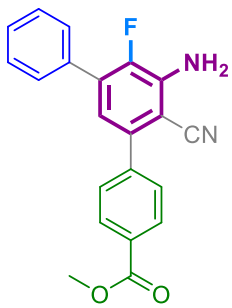
^{13}C NMR (126 MHz, Chloroform-*d*) δ = 163.14, 146.96, 140.28, 140.11, 134.39, 134.33, 132.93, 130.50, 129.02, 128.96, 128.81, 119.70, 116.49, 115.85, 95.93.

^{19}F NMR (471 MHz, Chloroform-*d*) δ = -113.08, -140.38.

HR-MS (APPI positive mode): *m/z* = calc. for ([M]$^+$): 306.0963, found: 306.0966.

methyl 5'-amino-6'-cyano-4'-fluoro-[1,1':3',1''-terphenyl]-4-carboxylate **3i**

17.4 mg, 50.2 µmol, 25% yield



$C_{21}H_{15}FN_2O_2$
MW: 346.36

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.23 – 8.01 (m, 2H), 7.69 – 7.60 (m, 2H), 7.60 – 7.53 (m, 2H), 7.53 – 7.34 (m, 3H), 6.84 (d, *J* = 6.6 Hz, 1H), 4.73 (s, 2H), 3.95 (s, 3H).

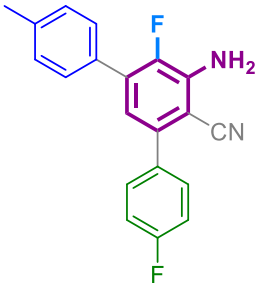
^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.78, 147.26, 142.66, 140.48, 139.94, 134.26, 132.99, 130.33, 130.09, 129.02, 128.83, 128.79, 119.76, 116.27, 95.69, 52.40.

^{19}F NMR (283 MHz, Chloroform-*d*) δ = -139.45 (d, *J* = 6.9 Hz).

HR-MS (APPI positive mode): *m/z* = calc. for ([M]$^+$): 346.1112, found: 346.1115.

5'-amino-4'',6'-difluoro-4-methyl-[1,1':3',1''-terphenyl]-4'-carbonitrile **3j**

Bigscale: 182.8 mg, 570 µmol, 34% yield



$C_{20}H_{14}F_2N_2$
MW: 320.34

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.55 – 7.49 (m, 2H), 7.49 – 7.43 (m, 2H), 7.32 – 7.26 (m, 2H), 7.20 – 7.12 (m, 2H), 6.78 (d, *J* = 6.8 Hz, 1H), 4.67 (s, 2H), 2.42 (s, 3H) ppm.

^{13}C NMR (126 MHz, Chloroform-*d*) δ = 163.15, 147.00, 140.26, 140.06, 139.07, 134.42, 132.94, 131.46, 130.50, 129.55, 128.91, 119.66, 116.57, 115.85, 95.68, 21.43 ppm.

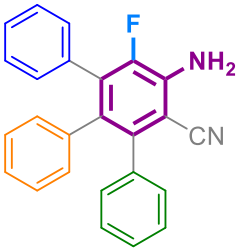
^{19}F NMR (471 MHz, Chloroform-*d*) δ = -113.17 (tt, *J* = 8.6, 5.3 Hz), -140.41 (dt, *J* = 6.9, 1.7 Hz) ppm.

HR-MS (APPI positive mode): *m/z* = calc. for ($[M]^+$): 320.1120, found: 320.1123.

Characterization of triaryl-substituted fluoroanilines 5a-n

4'-amino-5'-fluoro-6'-phenyl-[1,1':2',1''-terphenyl]-3'-carbonitrile **5a**

37.7 mg, 95.2 µmol, 48% yield



$C_{25}H_{17}FN_2$
MW: 364.42

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.22 – 7.17 (m, 6H), 7.12 – 7.07 (m, 2H), 7.07 – 7.03 (m, 2H), 6.95 – 6.84 (m, 3H), 6.74 – 6.64 (m, 2H), 4.65 (s, 2H) ppm.

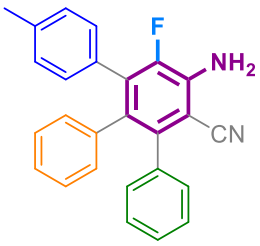
^{13}C NMR (126 MHz, Chloroform-*d*) δ = 147.11, 140.42, 138.44, 137.83, 137.46, 133.61, 133.54, 131.68, 131.43, 130.35, 130.23, 127.96, 127.84, 127.79, 127.70, 127.27, 126.27, 116.35, 98.31 ppm.

^{19}F NMR (283 MHz, Chloroform-*d*) δ = -135.13 ppm.

HR-MS (APPI positive mode): *m/z* = calc. for ($[M]^+$): 364.1370, found: 364.1370.

4'-amino-5'-fluoro-6'-(*p*-tolyl)-[1,1':2',1''-terphenyl]-3'-carbonitrile **5b**

46.3 mg, 122 µmol, 61 % yield



$C_{26}H_{19}FN_2$
MW: 378.45

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.21 – 7.16 (m, 3H), 7.11 – 7.05 (m, 2H), 7.00 (d, *J* = 7.9 Hz, 2H), 6.97 – 6.85 (m, 5H), 6.72 – 6.66 (m, 2H), 4.63 (s, 2H), 2.27 (s, 3H) ppm.

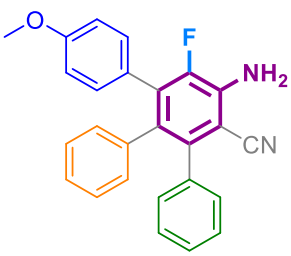
^{13}C NMR (126 MHz, Chloroform-*d*) δ = 147.19, 140.39, 138.42, 137.92, 137.60, 137.47, 133.64, 131.70, 131.48, 130.43, 130.22, 130.22, 128.60, 127.93, 127.74, 127.27, 126.19, 116.40, 98.13, 21.37 ppm.

^{19}F NMR (283 MHz, Chloroform-*d*) δ = -135.15 ppm.

HR-MS (APPI positive mode): *m/z* = calc. for ($[M]^+$): 378.1527, found: 378.1524.

4'-amino-5'-fluoro-6'-(4-methoxyphenyl)-[1,1':2',1''-terphenyl]-3'-carbonitrile **5c**

12.6 mg, 31.9 µmol, 16% yield



$C_{26}H_{19}FN_2O$
MW: 394.45

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 7.24 – 7.14 (m, 3H), 7.12 – 7.05 (m, 2H), 7.01 – 6.94 (m, 2H), 6.95 – 6.85 (m, 3H), 6.79 – 6.61 (m, 4H), 4.63 (s, 2H), 3.74 (s, 3H) ppm.

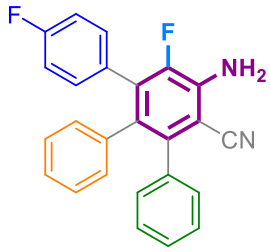
^{13}C NMR (126 MHz, Chloroform-*d*) δ = 159.02, 147.27, 140.40, 138.42, 137.94, 137.64, 133.32, 131.72, 131.62, 131.55, 130.22, 127.93, 127.73, 127.34, 126.20, 125.61, 116.42, 113.37, 98.04, 55.26 ppm.

^{19}F NMR (283 MHz, Chloroform-*d*) δ = -135.27 ppm.

HR-MS (APPI positive mode): *m/z* = calc. for ($[M]^+$): 395.1554, found: 395.1557.

4'-amino-5'-fluoro-6'-(4-methoxyphenyl)-[1,1':2',1''-terphenyl]-3'-carbonitrile **5d**

31.4 mg, 82.1 µmol, 41% yield



$C_{25}H_{16}F_2N_2$
MW: 382.41

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.23 – 7.16 (m, 3H), 7.14 – 7.06 (m, 2H), 7.07 – 6.99 (m, 2H), 6.96 – 6.84 (m, 5H), 6.74 – 6.62 (m, 2H), 4.67 (s, 2H) ppm.

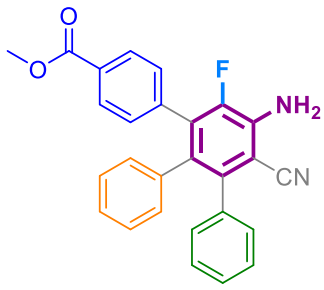
^{13}C NMR (101 MHz, Chloroform-*d*) δ = 162.08 (d, *J* = 247.7 Hz), 147.00 (d, *J* = 239.9 Hz), 140.42 (d, *J* = 3.9 Hz), 138.46, 138.30, 137.61, 137.20 (d, *J* = 2.1 Hz), 132.43 (d, *J* = 12.4 Hz), 131.99 (dd, *J* = 8.0, 1.0 Hz), 131.53, 131.25, 130.07, 129.30 (d, *J* = 3.7 Hz), 127.87, 127.73, 127.32, 126.29, 116.14 (d, *J* = 4.3 Hz), 114.90 (d, *J* = 21.8 Hz), 98.34 (d, *J* = 5.7 Hz) ppm.

^{19}F NMR (377 MHz, Chloroform-*d*) δ = -113.85, -135.15 ppm.

HR-MS (APPI positive mode): *m/z* = calc. for ([M]$^+$): 382.1276, found: 382.1282.

4'-amino-5'-fluoro-6'-(4-methoxyphenyl)-[1,1':2',1''-terphenyl]-3'-carbonitrile **5e**

32.4 mg, 72.1 µmol, 36% yield



$C_{27}H_{19}FN_2O_2$
MW: 422.46

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 7.86 (d, *J* = 8.5 Hz, 2H), 7.24 – 7.15 (m, 4H), 7.17 – 7.04 (m, 5H), 6.97 – 6.82 (m, 3H), 6.71 – 6.63 (m, 2H), 4.68 (s, 2H), 3.87 (s, 3H) ppm.

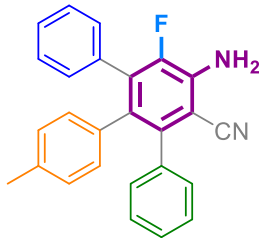
^{13}C NMR (151 MHz, Chloroform-*d*) δ = 166.87, 146.89 (d, *J* = 241.0 Hz), 140.65 (d, *J* = 3.9 Hz), 138.51, 138.47, 138.40, 137.56, 137.02 (d, *J* = 1.9 Hz), 131.58, 130.49 (d, *J* = 1.1 Hz), 130.18, 129.35, 129.11, 128.02, 127.92, 127.47, 126.58, 116.15 (d, *J* = 4.3 Hz), 98.82 (d, *J* = 5.7 Hz), 74.63, 52.29 ppm.

^{19}F NMR (283 MHz, Chloroform-*d*) δ = -135.06 ppm.

HR-MS (APPI positive mode): *m/z* = calc. for ([M]$^+$): 422.1425, found: 422.1432.

4'-amino-5'-fluoro-4-methyl-6'-phenyl-[1,1':2',1''-terphenyl]-3'-carbonitrile **5f**

19.5 mg, 51.5 µmol, 26% yield



$C_{26}H_{19}FN_2$
MW: 378.45

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.22 – 7.17 (m, 2H), 7.11 – 7.07 (m, 3H), 7.07 – 7.02 (m, 4H), 6.68 (d, *J* = 7.7 Hz, 3H), 6.54 (d, *J* = 8.1 Hz, 2H), 4.62 (s, 2H), 2.10 (s, 3H) ppm.

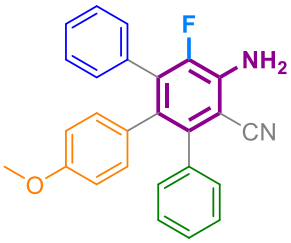
^{13}C NMR (126 MHz, Chloroform-*d*) δ = 147.13, 140.47, 138.27, 138.01, 135.73, 135.65, 134.32, 133.69, 131.48, 131.47, 130.36, 130.23, 128.00, 127.95, 127.83, 127.69, 127.61, 116.41, 98.35, 21.16 ppm.

^{19}F NMR (471 MHz, Chloroform-*d*) δ = -135.09 ppm.

HR-MS (ESI positive mode): *m/z* = calc. for ([M+H]$^+$): 379.160503, found: 379.159303.

4'-amino-5'-fluoro-4-methoxy-6'-phenyl-[1,1':2',1''-terphenyl]-3'-carbonitrile **5g**

21.6 mg, 54.8 µmol, 27% yield



$C_{26}H_{19}FN_2O$
MW: 394.45

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 7.25 – 7.16 (m, 6H), 7.14 – 7.01 (m, 4H), 6.57 (d, *J* = 8.9 Hz, 2H), 6.42 (d, *J* = 8.8 Hz, 2H), 4.62 (s, 2H), 3.62 (s, 3H) ppm.

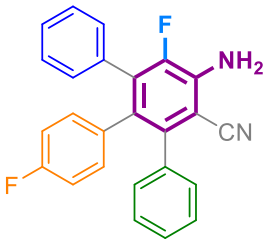
^{13}C NMR (126 MHz, Chloroform-*d*) δ = 157.81, 147.13, 140.58, 138.27, 138.02, 133.80, 133.70, 132.69, 131.09, 130.36, 130.23, 129.73, 128.01, 127.90, 127.71, 127.63, 116.41, 112.76, 98.32, 55.07 ppm.

^{19}F NMR (283 MHz, Chloroform-*d*) δ = -135.02 ppm.

HR-MS (ESI positive mode): *m/z* = calc. for ($[M+H]^+$): 395.155418, found: 395.155716.

4'-amino-4,5'-difluoro-6'-phenyl-[1,1':2',1''-terphenyl]-3'-carbonitrile **5h**

61.5 mg, 161 µmol, 80% yield



$C_{25}H_{16}F_2N_2$
MW: 382.41

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 7.27 – 7.16 (m, 6H), 7.12 – 7.00 (m, 4H), 6.69 – 6.54 (m, 4H), 4.67 (s, 2H) ppm.

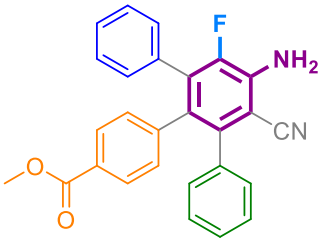
^{13}C NMR (126 MHz, Chloroform-*d*) δ = 161.23, 147.08, 140.56, 138.61, 137.66, 133.66, 133.45, 133.38, 133.16, 130.29, 130.22, 130.16, 128.11, 128.00, 127.92, 127.83, 116.22, 114.37, 98.32 ppm.

^{19}F NMR (283 MHz, Chloroform-*d*) δ = -115.72, -134.89 ppm.

HR-MS (ESI positive mode): *m/z* = calc. for ($[M+H]^+$): 383.135431, found: 383.135499.

methyl 4'-amino-3'-cyano-5'-fluoro-6'-phenyl-[1,1':2',1''-terphenyl]-4-carboxylate **5i**

40.9 mg, 96.8 µmol, 48% yield



$C_{27}H_{19}FN_2O_2$
MW: 422.46

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 7.57 (d, *J* = 8.4 Hz, 2H), 7.24 – 7.15 (m, 6H), 7.11 – 6.99 (m, 4H), 6.76 (d, *J* = 8.5 Hz, 2H), 4.72 (s, 2H), 3.80 (s, 3H) ppm.

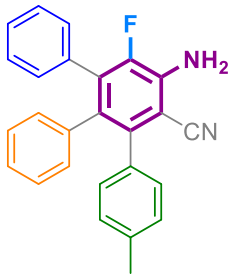
^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.95, 147.05, 142.67, 140.35, 138.88, 137.35, 133.35, 133.08, 131.73, 130.23, 130.12, 130.11, 128.55, 128.13, 128.07, 128.02, 127.97, 127.84, 116.11, 98.36, 52.09 ppm.

^{19}F NMR (283 MHz, Chloroform-*d*) δ = -134.97 ppm.

HR-MS (ESI positive mode): *m/z* = calc. for ($[M+H]^+$): 423.150333, found: 423.150016.

4'-amino-5'-fluoro-4''-methyl-6'-phenyl-[1,1':2',1''-terphenyl]-3'-carbonitrile **5j**

34.4 mg, 90.9 µmol, 45% yield



$C_{26}H_{19}FN_2$
MW: 378.45

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 7.24 – 7.12 (m, 3H), 7.09 – 7.02 (m, 2H), 6.99 (s, 4H), 6.95 – 6.82 (m, 3H), 6.82 – 6.59 (m, 2H), 4.63 (s, 2H), 2.27 (s, 3H) ppm.

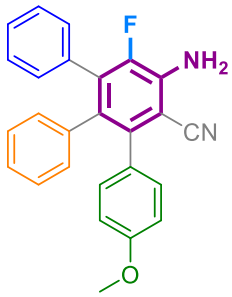
^{13}C NMR (126 MHz, Chloroform-*d*) δ = 147.00, 140.48, 138.40, 137.58, 137.42, 134.81, 133.62, 133.56, 131.68, 131.37, 130.33, 130.05, 128.68, 127.80, 127.63, 127.24, 126.17, 116.50, 98.44, 21.35 ppm.

^{19}F NMR (283 MHz, Chloroform-*d*) δ = -135.36 ppm.

HR-MS (APPI positive mode): *m/z* = calc. for ($[M]^+$): 379.1605, found: 379.1607.

4'-amino-5'-fluoro-4''-methoxy-6'-phenyl-[1,1':2',1''-terphenyl]-3'-carbonitrile **5k**

32.9 mg, 83.4 µmol, 42% yield



$C_{26}H_{19}FN_2O$
MW: 394.45

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 7.21 – 7.13 (m, 3H), 7.10 – 6.95 (m, 4H), 6.95 – 6.82 (m, 3H), 6.82 – 6.57 (m, 4H), 4.63 (s, 2H), 3.74 (s, 3H) ppm.

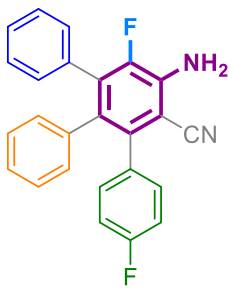
^{13}C NMR (126 MHz, Chloroform-*d*) δ = 159.03, 146.98, 140.15, 138.40, 137.61, 133.64, 133.58, 131.69, 131.53, 131.43, 130.33, 130.09, 127.81, 127.64, 127.32, 126.18, 116.55, 113.43, 98.53, 55.22 ppm.

^{19}F NMR (283 MHz, Chloroform-*d*) δ = -135.42 ppm.

HR-MS (APPI positive mode): *m/z* = calc. for ($[M]^+$): 394.1476, found: 394.1474.

4'-amino-4'',5'-difluoro-6'-phenyl-[1,1':2',1''-terphenyl]-3'-carbonitrile **5l**

39.3 mg, 103 µmol, 51% yield



$C_{25}H_{16}F_2N_2$
MW: 382.41

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 7.23 – 7.14 (m, 3H), 7.14 – 6.98 (m, 4H), 6.98 – 6.82 (m, 5H), 6.79 – 6.51 (m, 2H), 4.67 (s, 2H) ppm.

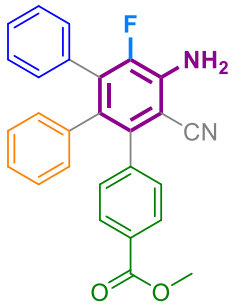
^{13}C NMR (126 MHz, Chloroform-*d*) δ = 162.26, 147.18, 139.29, 138.56, 137.30, 133.79, 133.70, 133.40, 131.97, 131.61, 131.58, 130.29, 127.87, 127.77, 127.42, 126.41, 116.27, 115.10, 98.23 ppm.

^{19}F NMR (283 MHz, Chloroform-*d*) δ = -113.87, -113.90 ppm.

HR-MS (APPI positive mode): *m/z* = calc. for ($[M]^+$): 382.1276, found: 382.1281.

methyl 5'-amino-6'-cyano-4'-fluoro-3'-phenyl-[1,1':2',1''-terphenyl]-4-carboxylate **5m**

34.1 mg, 80.7 µmol, 40% yield



$C_{27}H_{19}FN_2O_2$
MW: 422.46

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 7.99 – 7.77 (m, 2H), 7.24 – 7.12 (m, 5H), 7.12 – 6.95 (m, 2H), 6.96 – 6.80 (m, 3H), 6.75 – 6.50 (m, 2H), 4.69 (s, 2H), 3.87 (s, 3H) ppm.

^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.85, 147.34, 142.63, 139.24, 138.71, 137.02, 133.76, 133.24, 131.56, 131.34, 130.39, 130.29, 129.40, 129.29, 127.90, 127.83, 127.46, 126.57, 116.05, 97.75, 52.24 ppm.

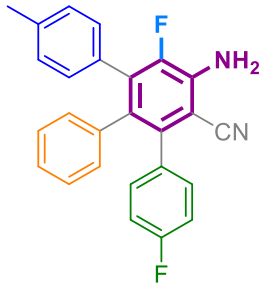
^{19}F NMR (283 MHz, Chloroform-*d*) δ = -134.22 ppm.

HR-MS (APPI positive mode): *m/z* = calc. for ($[M]^+$): 423.1503, found: 423.1499.

4'-amino-4'',5'-difluoro-6'-(*p*-tolyl)-[1,1':2',1''-terphenyl]-3'-carbonitrile **5n**

50.2 mg, 127 µmol, 63% yield

Bigscale: 1.05 g, 2.66 mmol, 33% yield



$C_{26}H_{18}F_2N_2$
MW: 396.44

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 7.14 – 6.96 (m, 5H), 6.96 – 6.84 (m, 7H), 6.74 – 6.62 (m, 2H), 4.64 (s, 2H), 2.27 (s, 3H) ppm.

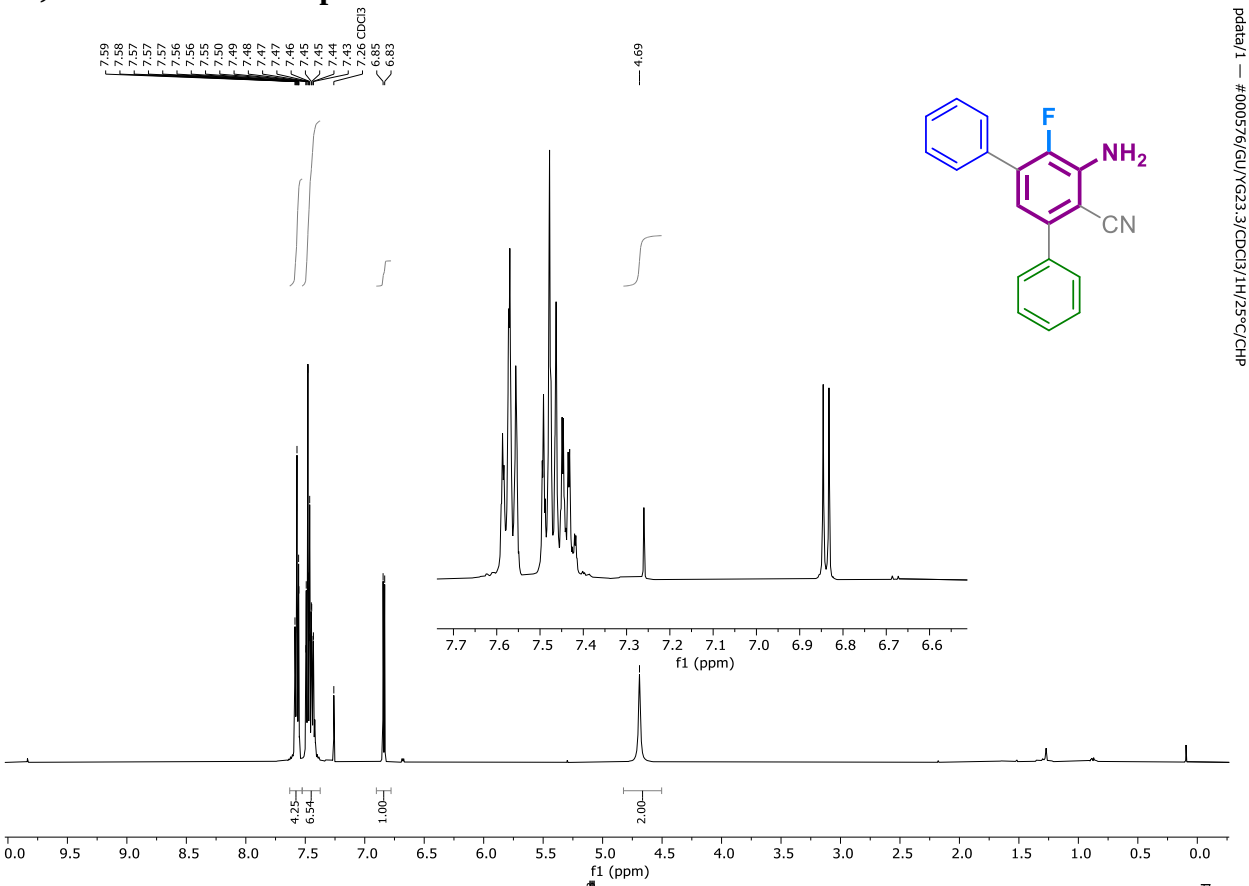
^{13}C NMR (126 MHz, Chloroform-*d*) δ = 162.24, 147.27, 139.27, 138.52, 137.56, 137.45, 133.88, 133.74, 131.97, 131.64, 131.63, 130.29, 130.17, 128.63, 127.43, 126.34, 116.33, 115.08, 98.06, 21.36 ppm.

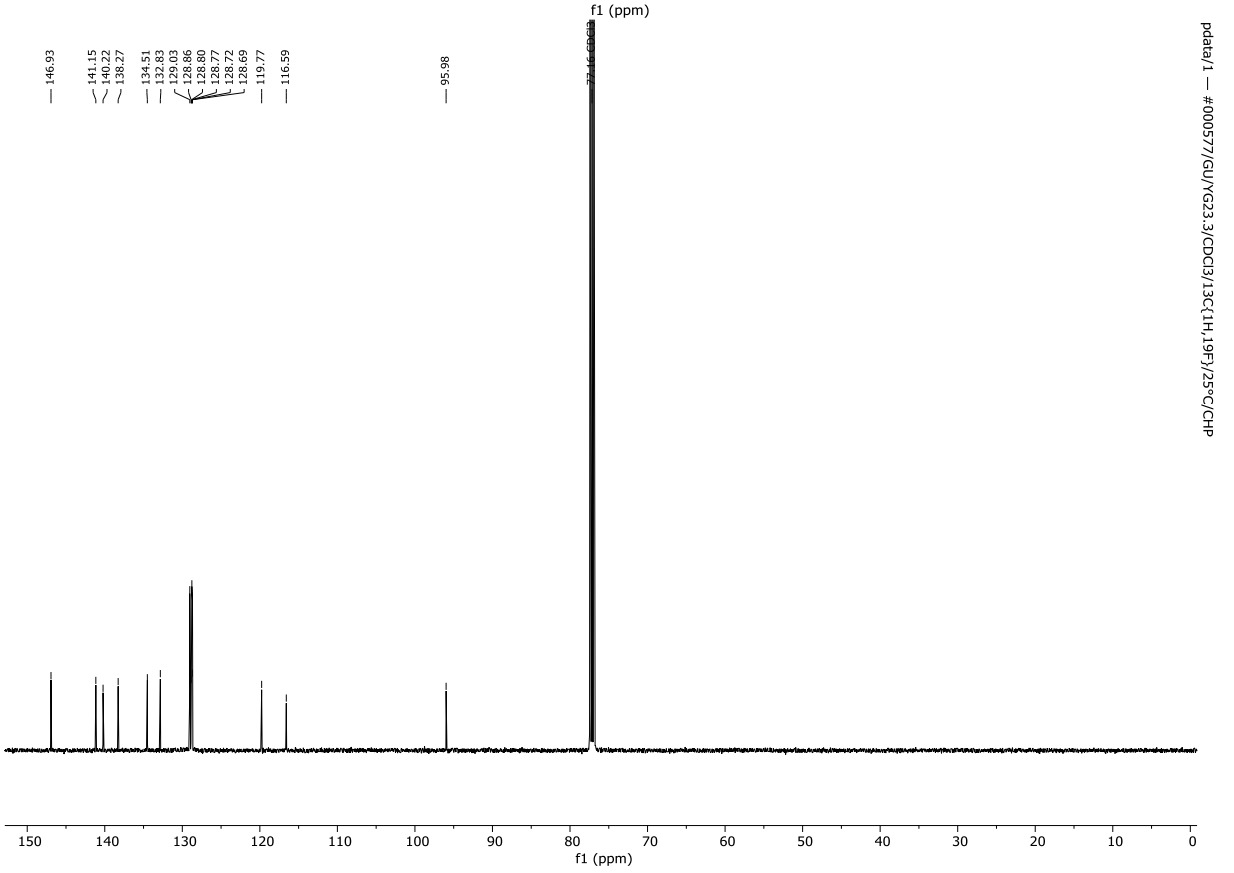
^{19}F NMR (471 MHz, Chloroform-*d*) δ = -113.99, -134.78 ppm.

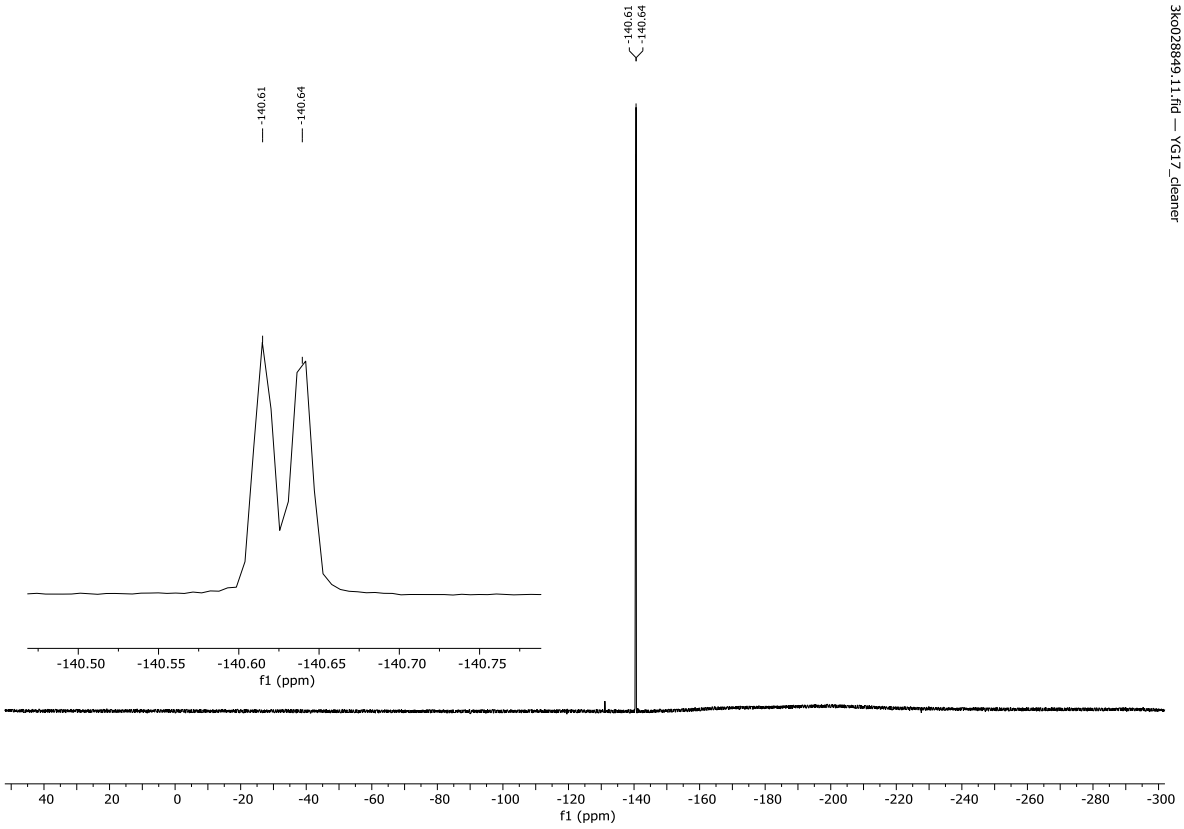
HR-MS (APPI positive mode): *m/z* = calc. for ($[M]^+$): 396.1433, found: 396.1443.

Elemental Analysis: calc. (%): N (7.07), C (78.8), H (4.58); found: N (7.03), C (78.4), H (4.68).

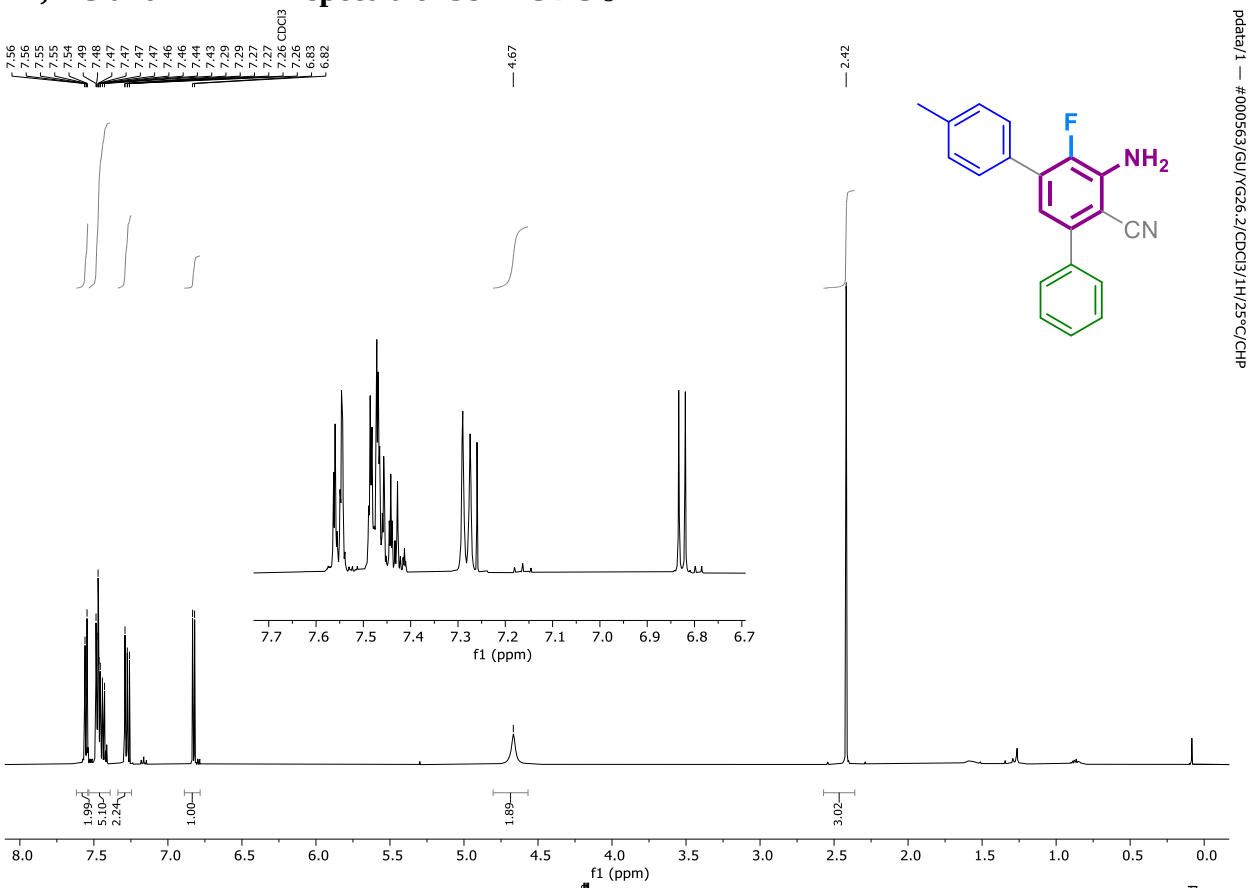
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 3a in $CDCl_3$

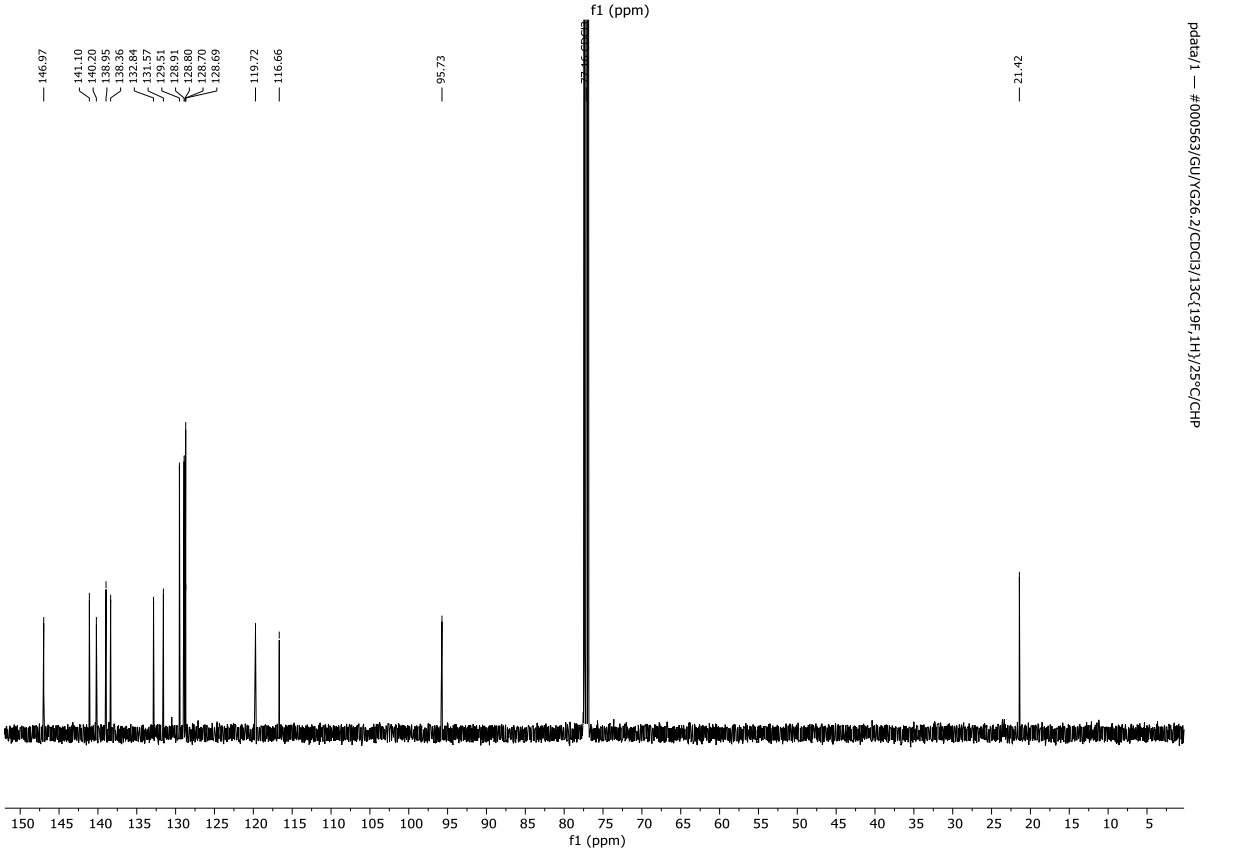


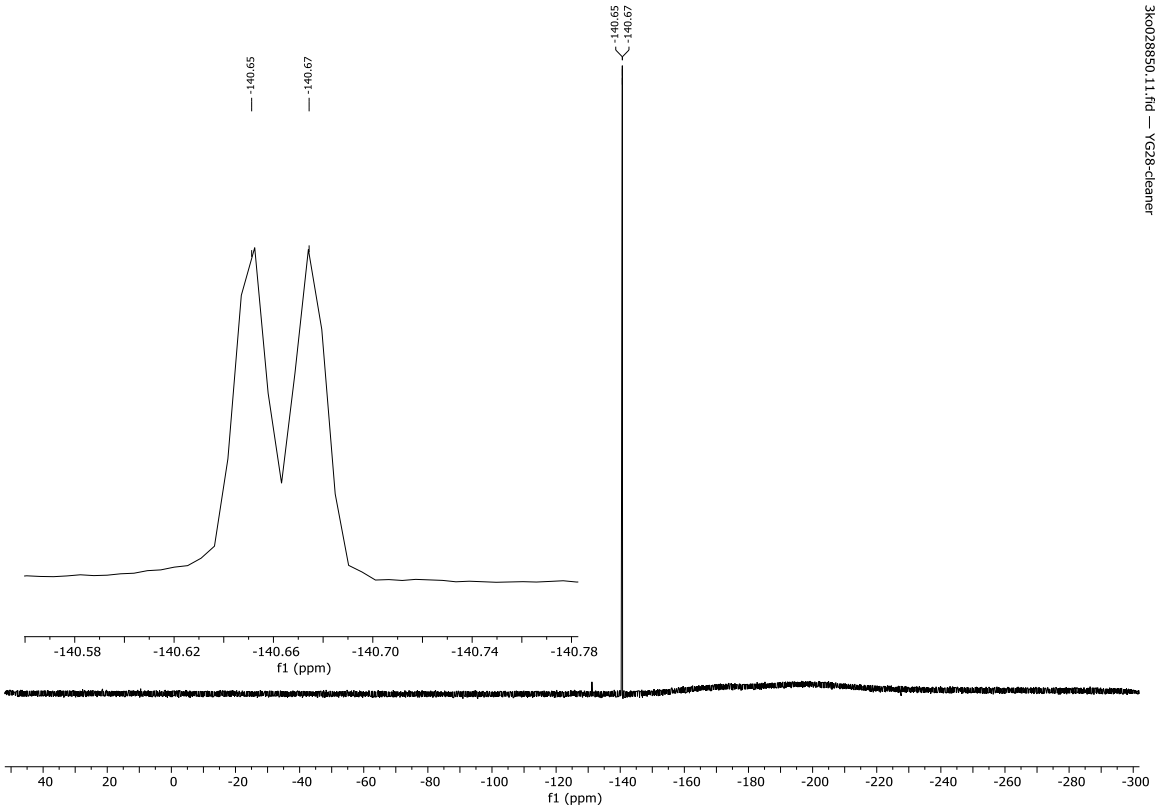



-140.61
-140.64
3ko028849.11.fid — YG17_cleaner
-140.61
-140.64
-140.50
-140.55
-140.60
-140.65
-140.70
-140.75
f1 (ppm)
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280
-300
f1 (ppm)

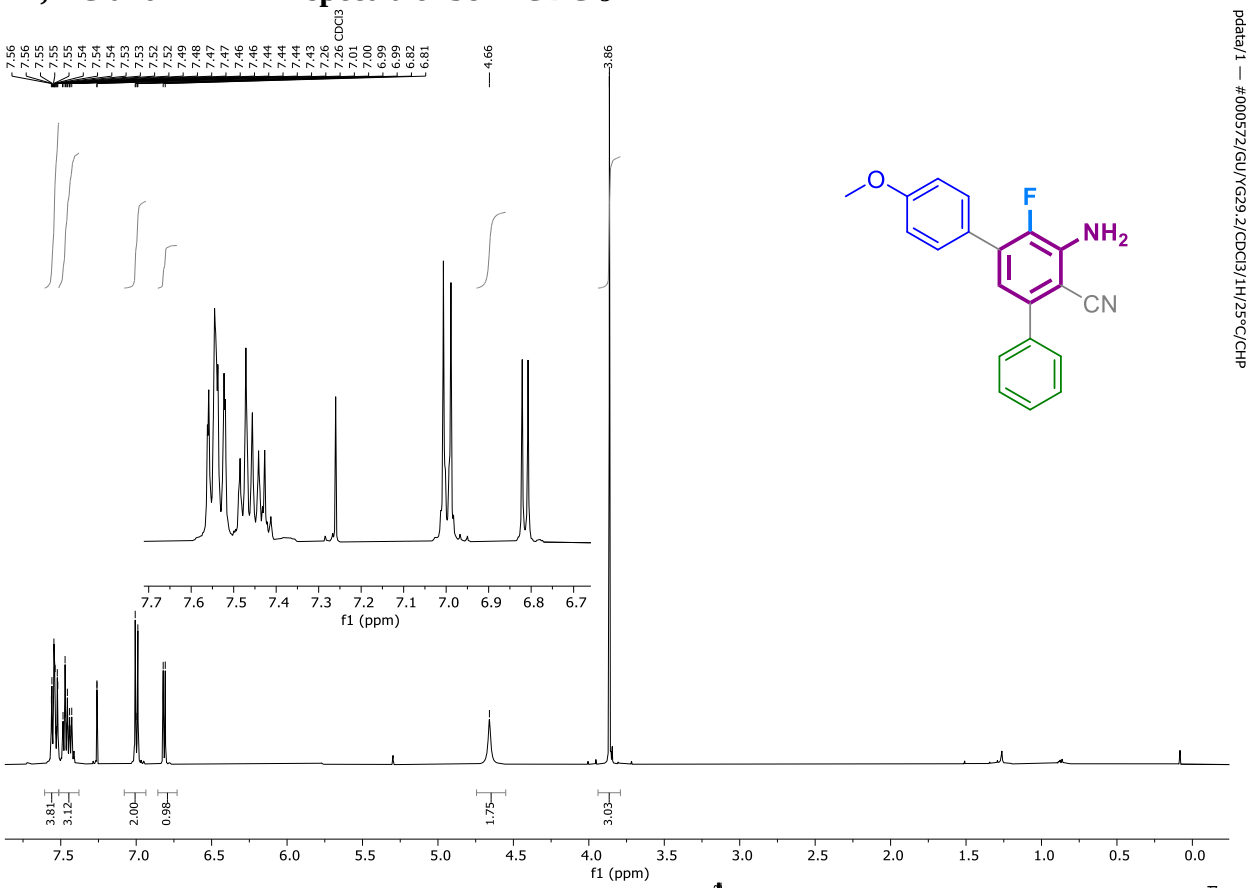
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 3b in $CDCl_3$

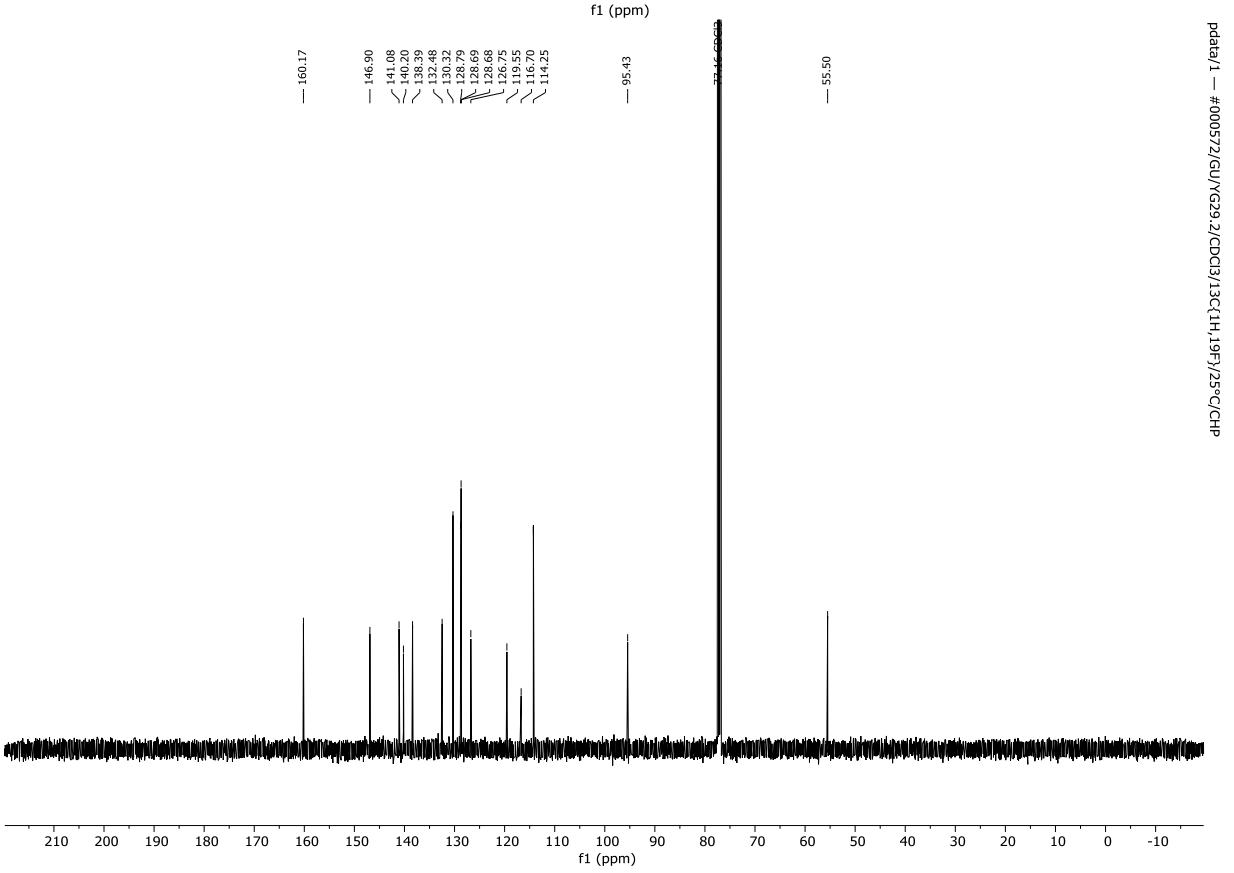


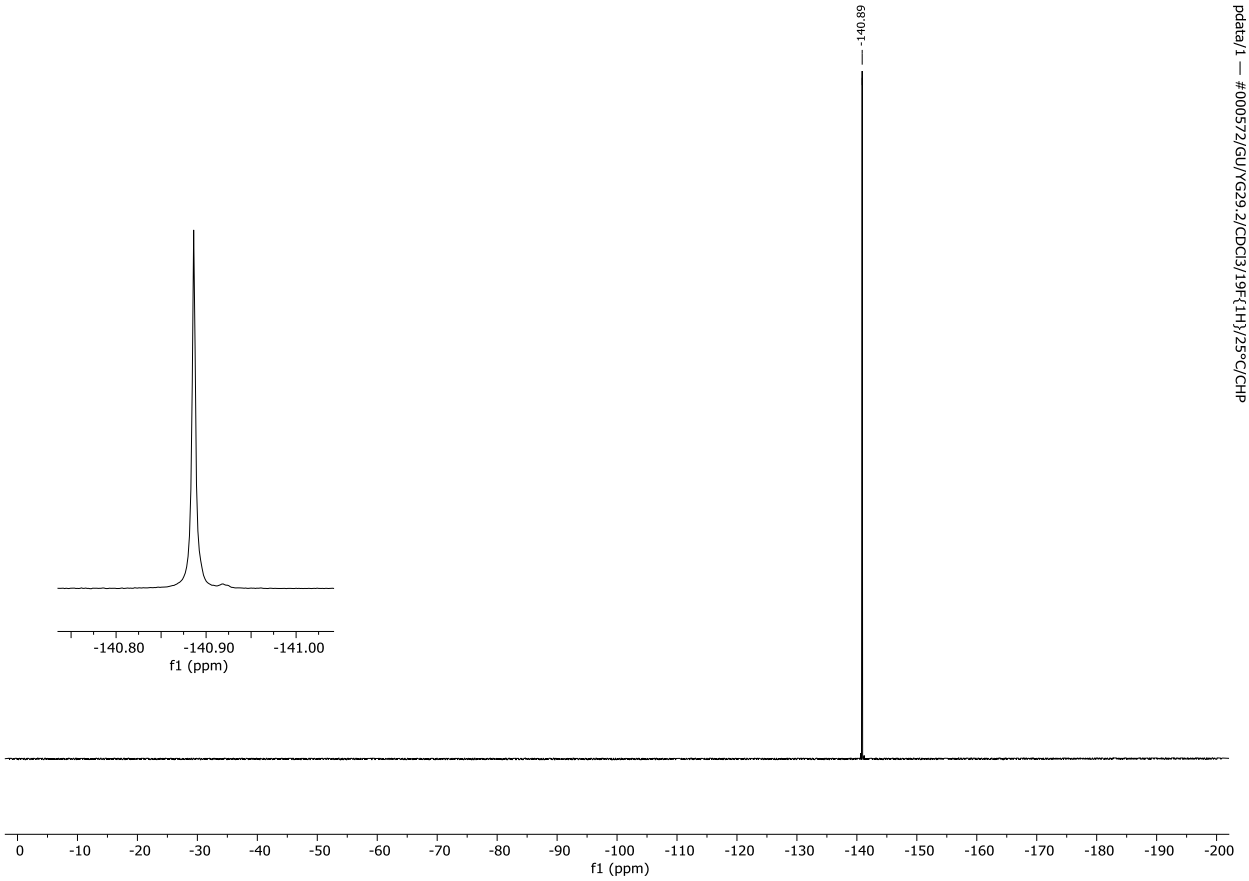



3ko028850.11.fid — YG28-cleaner
-140.65
-140.67
-140.65
-140.67
-140.58
-140.62
-140.66
-140.70
-140.74
-140.78
f1 (ppm)
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280
-300
f1 (ppm)

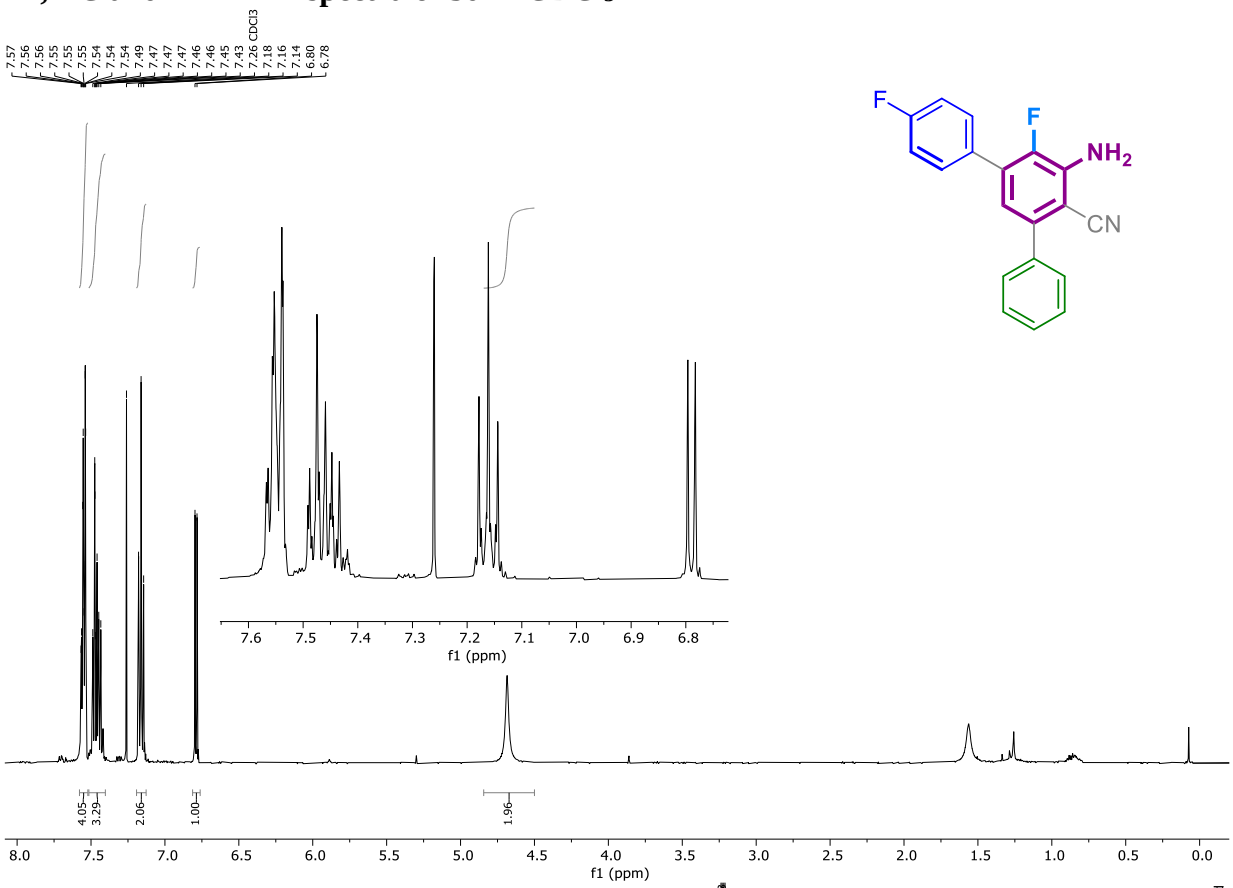
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 3c in $CDCl_3$

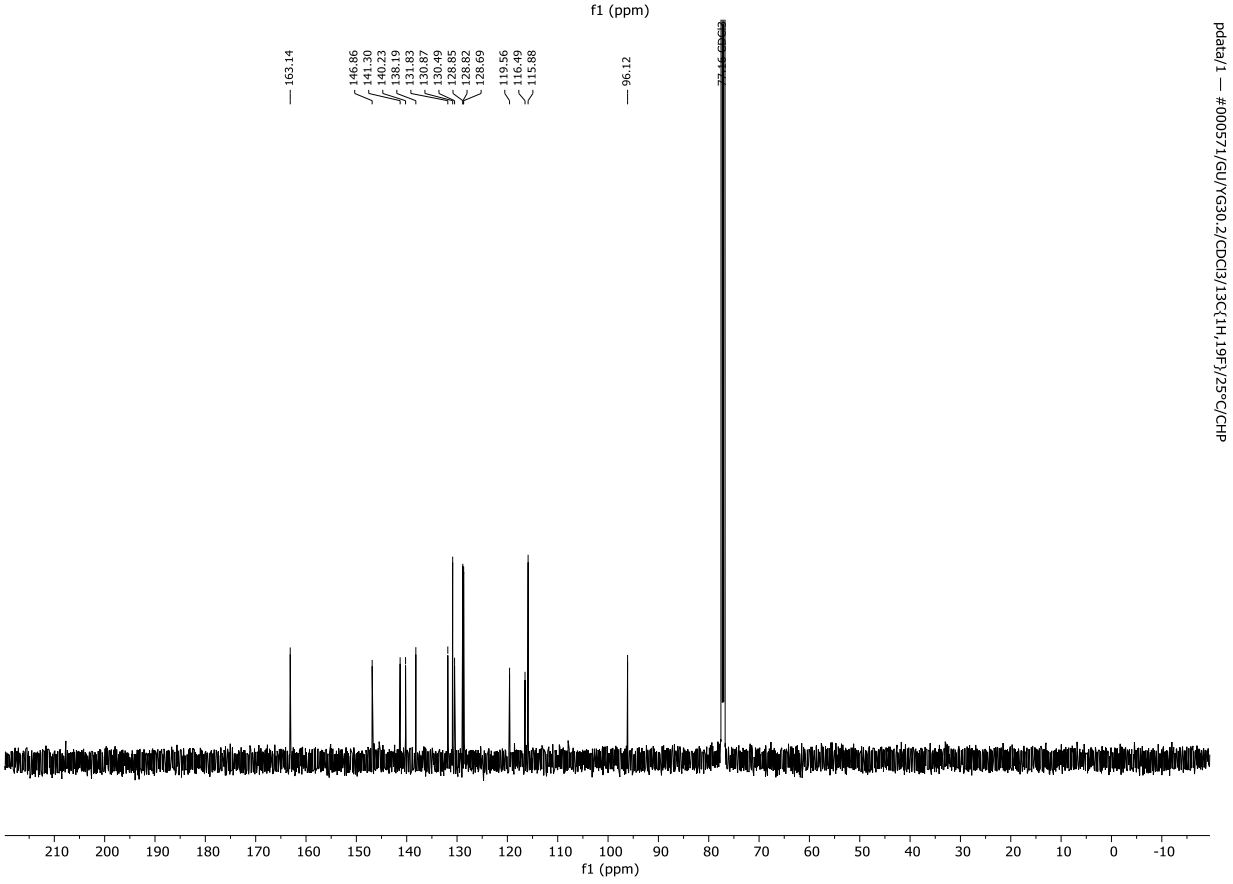


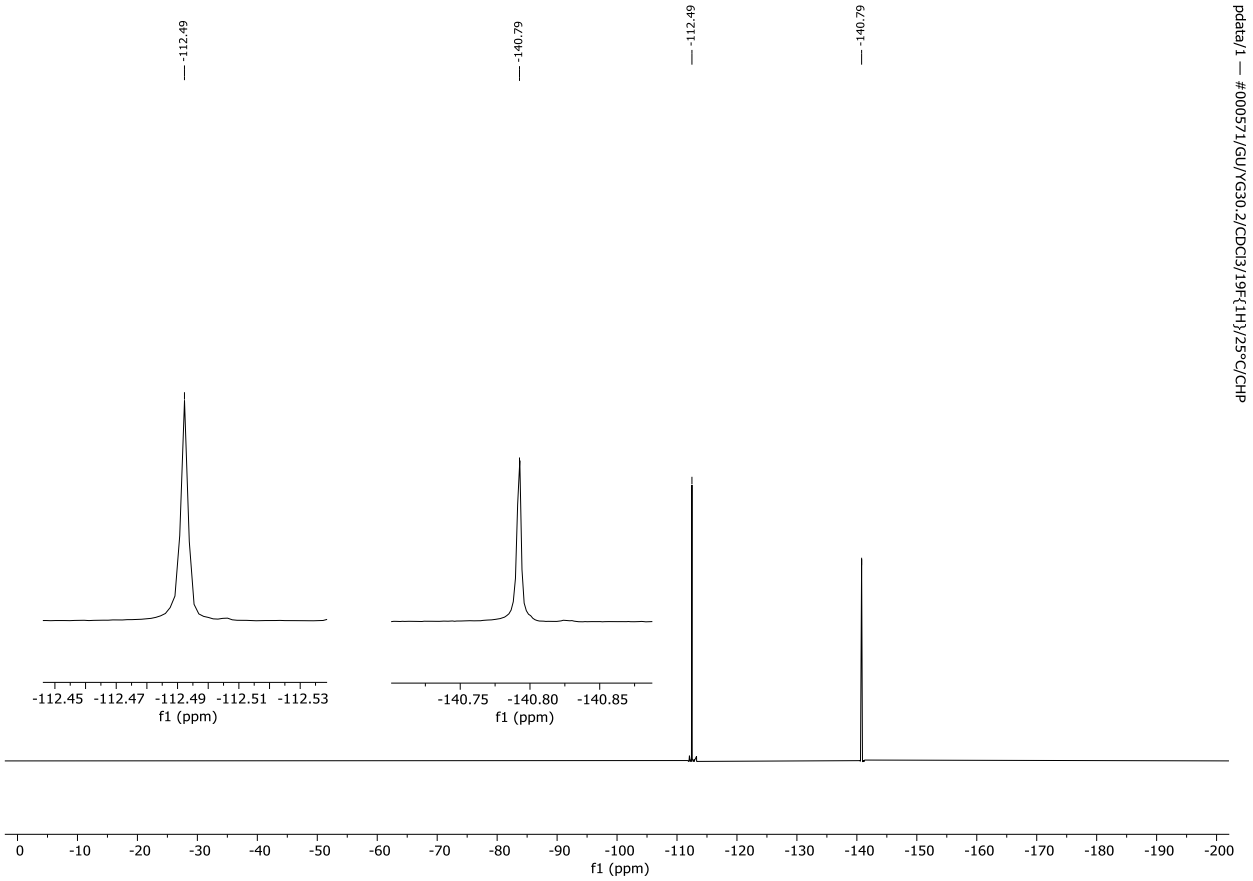



-140.89
pdata/1 — #000572/GU/YG29.2/CDCl3/19F{1H}/25°C/CHP
-140.80
-140.90
-141.00
f1 (ppm)
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

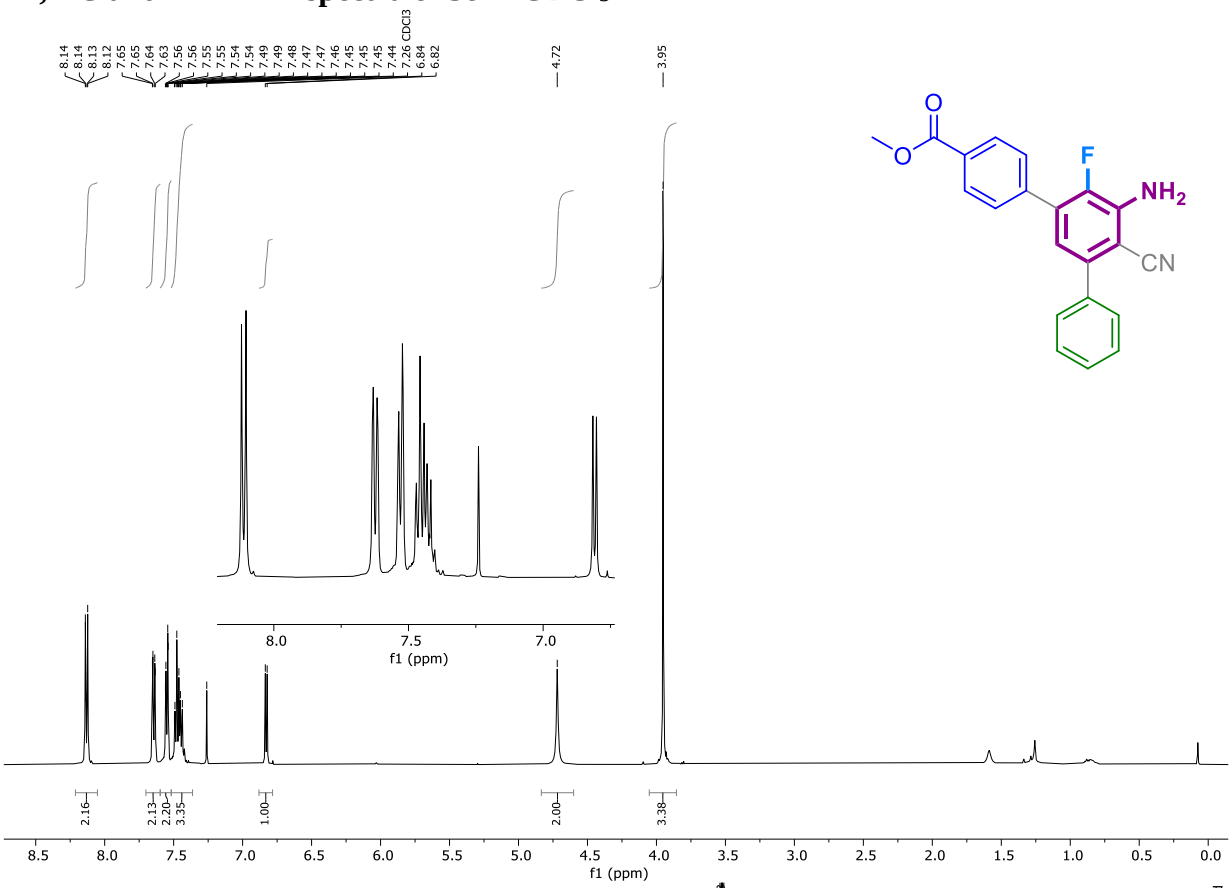
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 3d in $CDCl_3$

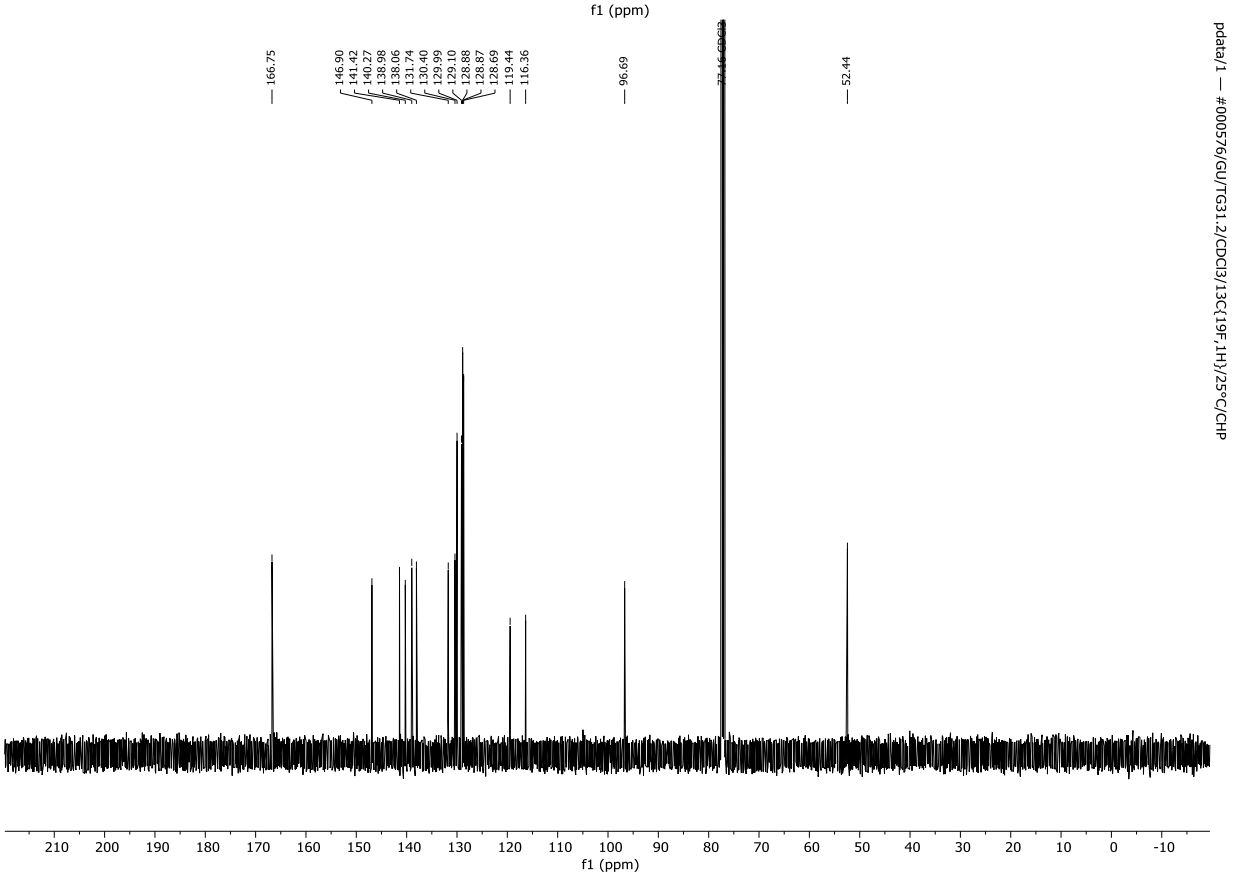


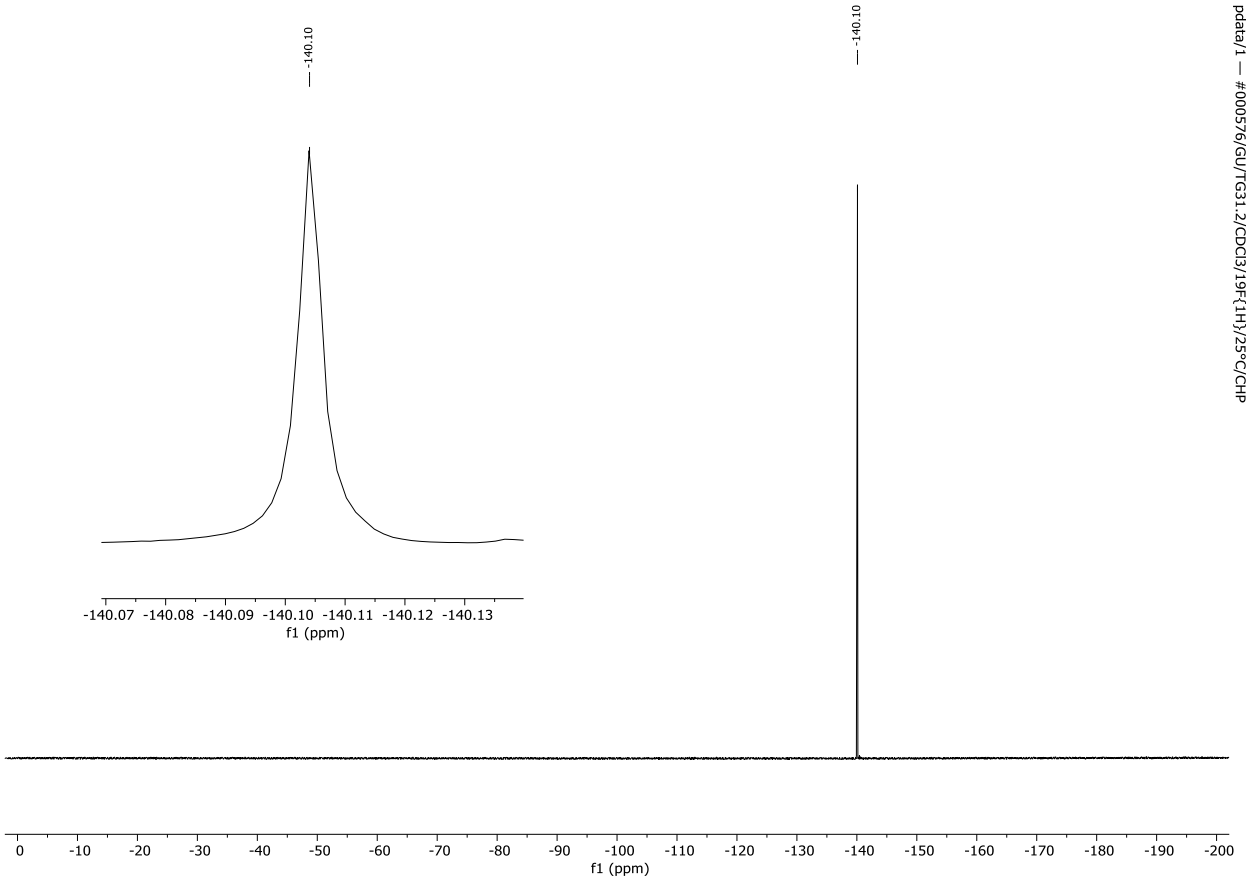



-112.49
-140.79
-112.49
-140.79
pdata/1 — #000571/GU/YG30.2/CDCl3/19F{1H}/25°C/CHP
-112.45 -112.47 -112.49 -112.51 -112.53
f1 (ppm)
-140.75 -140.80 -140.85
f1 (ppm)
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

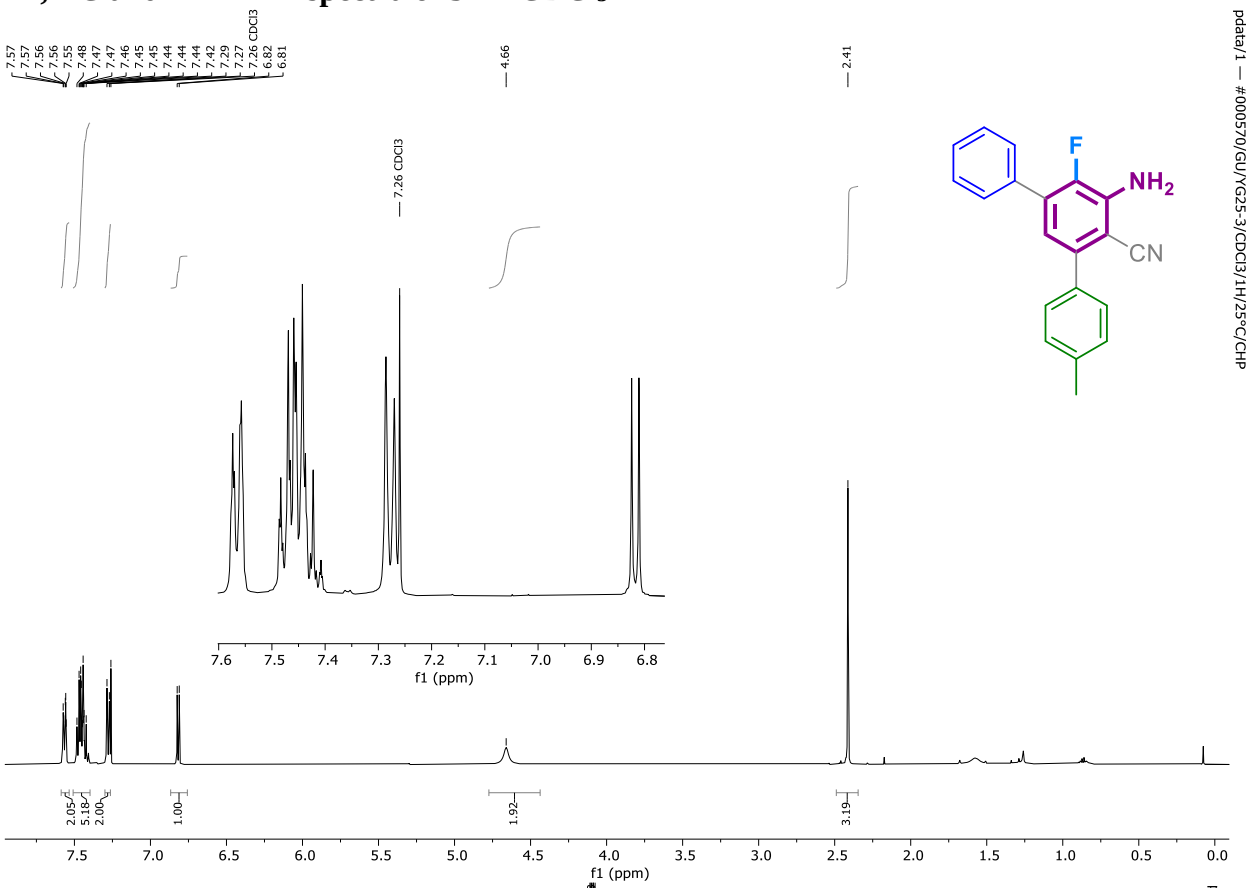
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 3e in $CDCl_3$

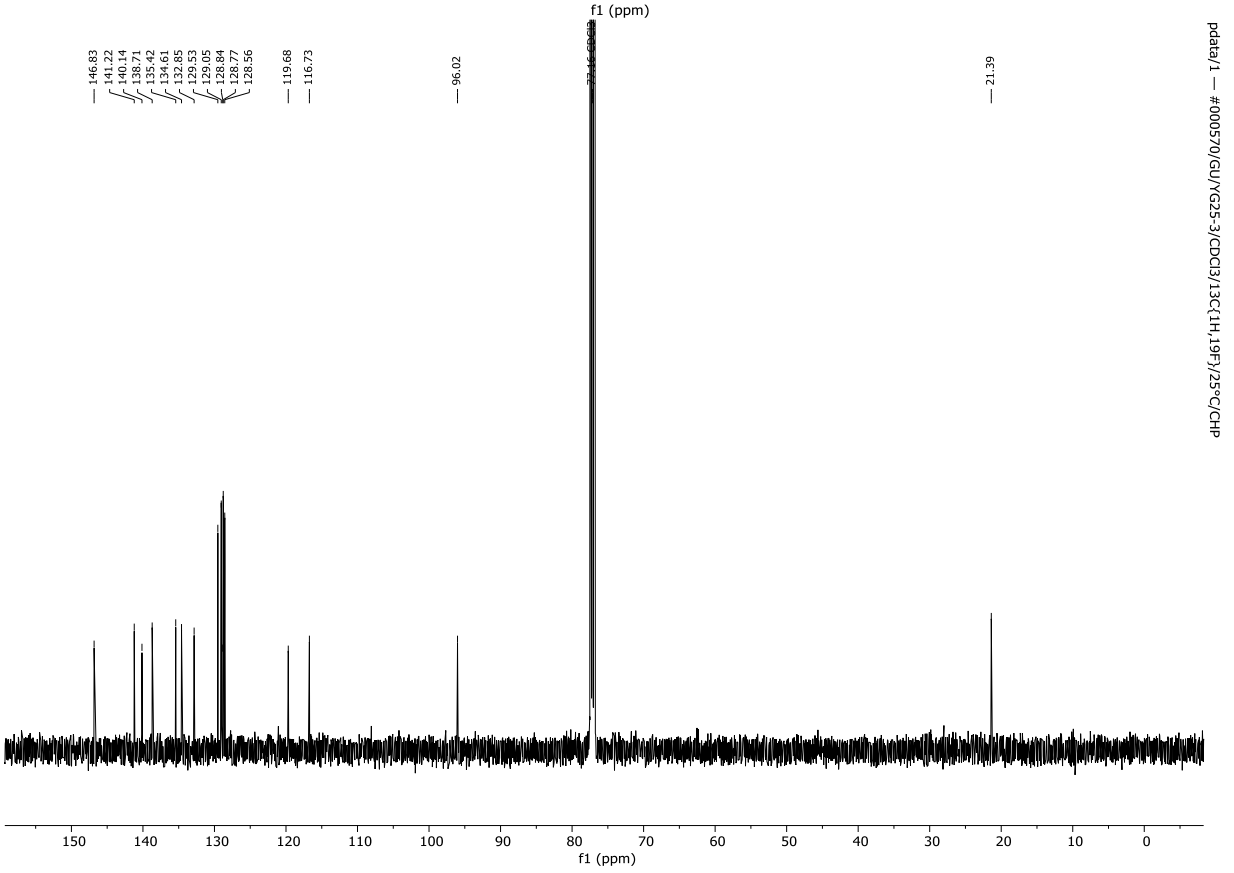


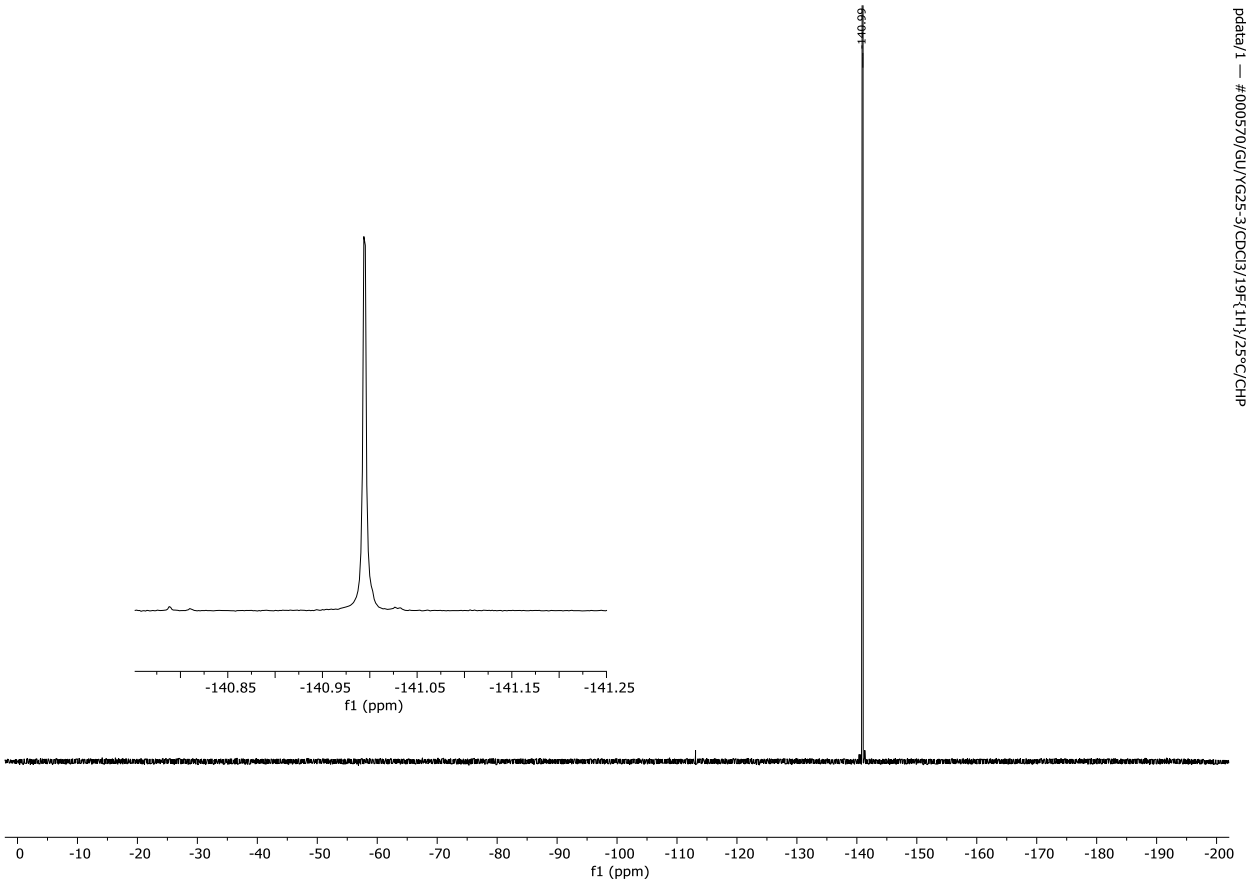



-140.10
-140.10
pdata/1 — #000576/GU/TG31.2/CDCl3/19F{1H}/25°C/CHP
-140.07 -140.08 -140.09 -140.10 -140.11 -140.12 -140.13
f1 (ppm)
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

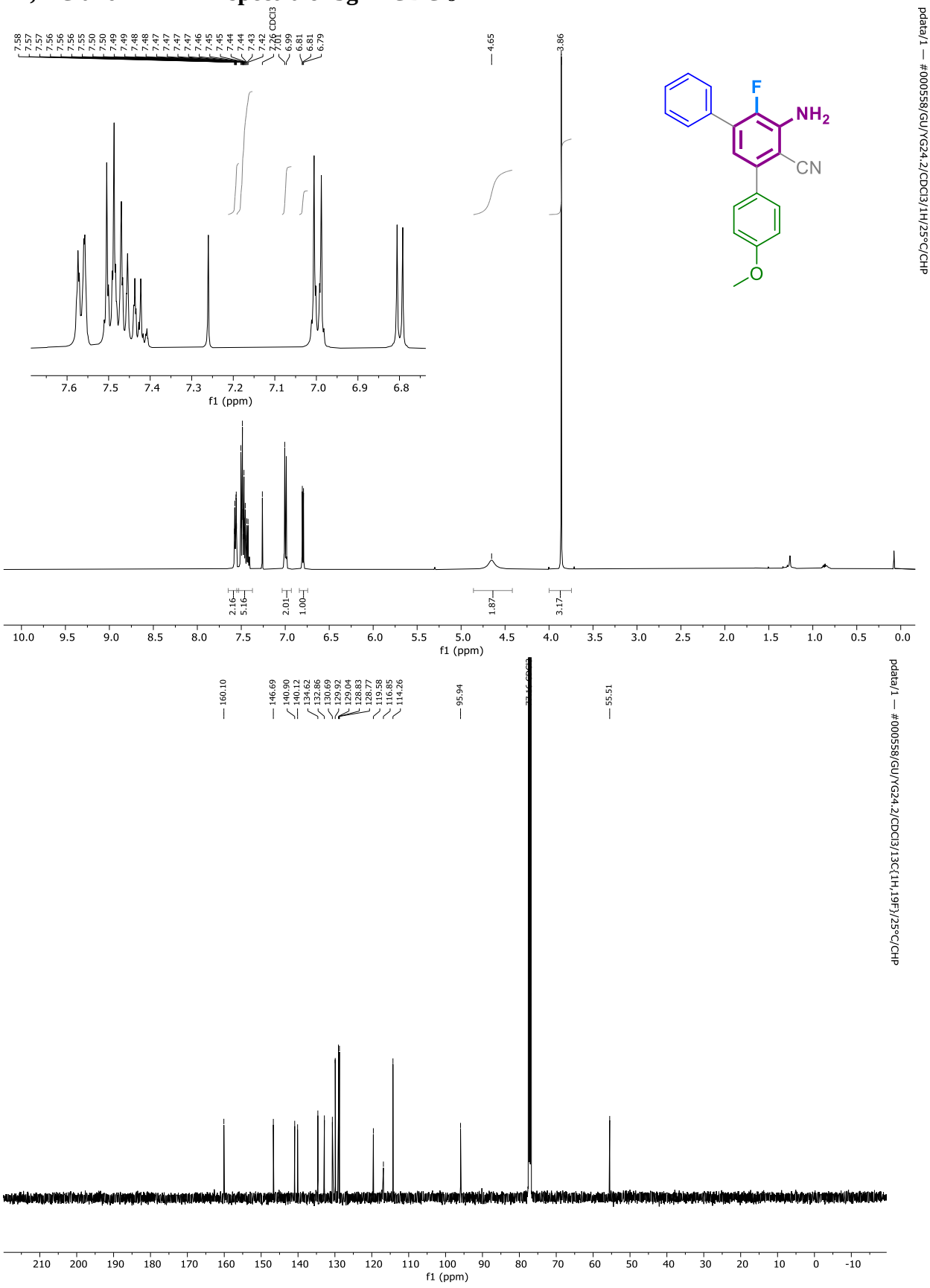
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 3f in $CDCl_3$

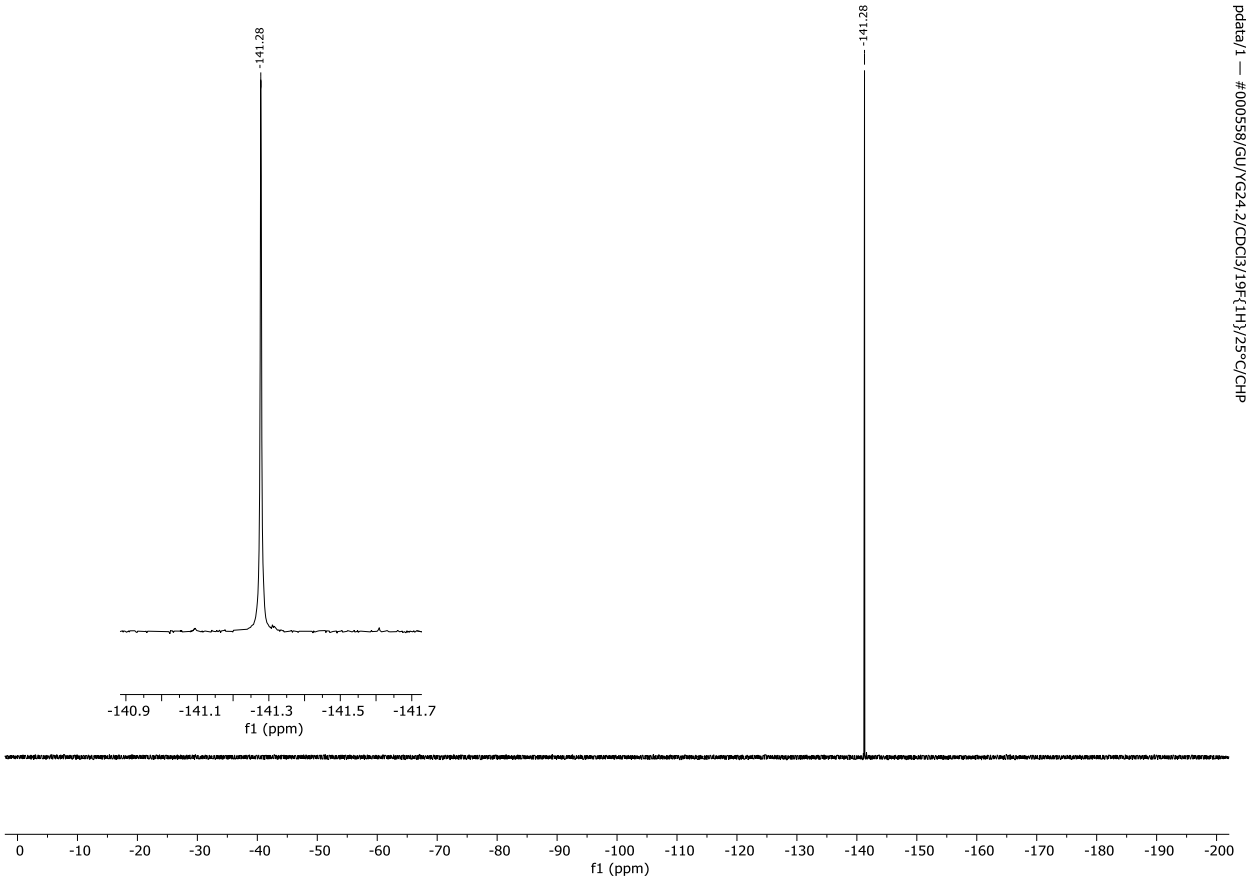




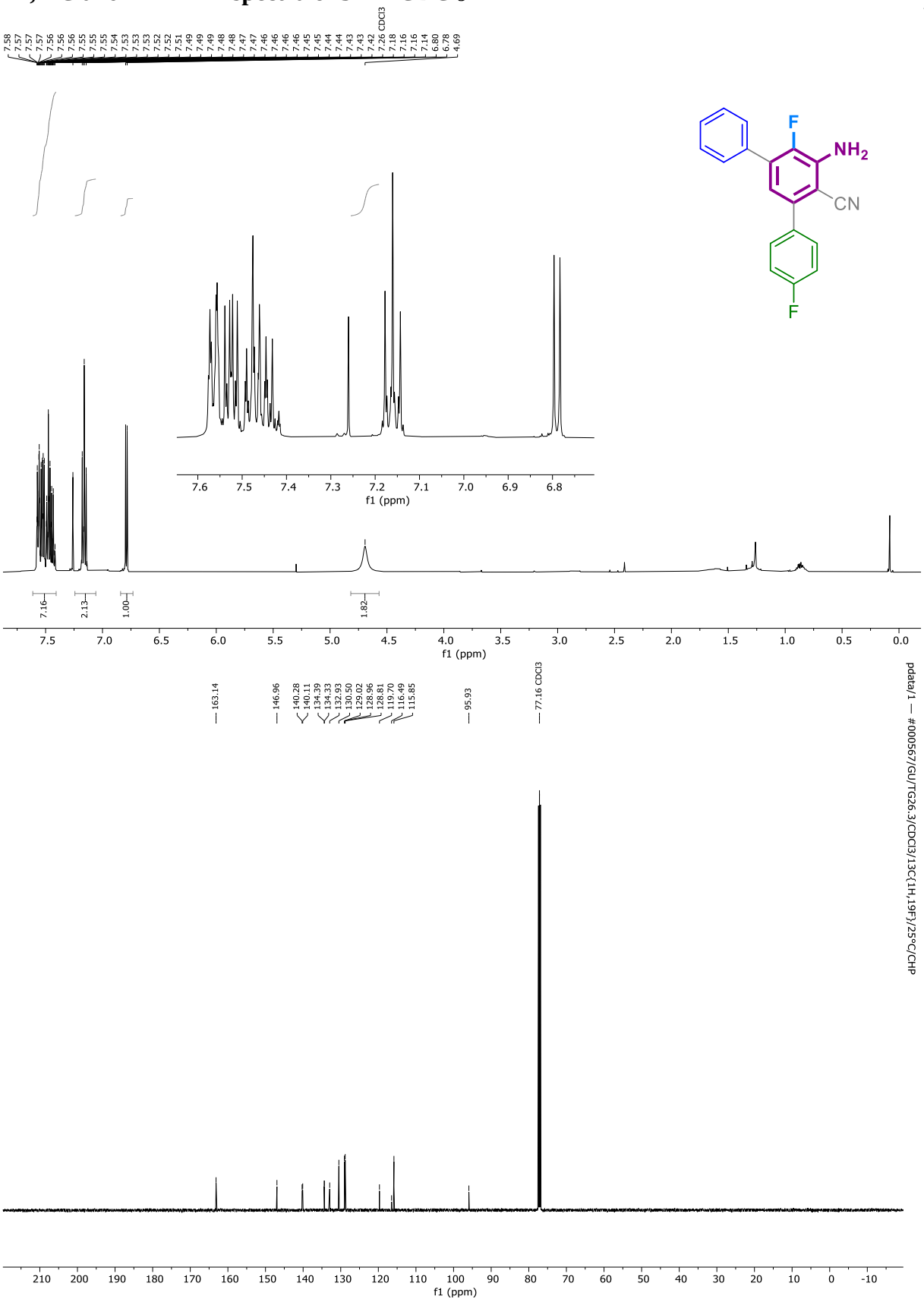

pdata/1 — #000570/GU/YG25-3/CDCl3/19F{1H}/25°C/CHP
-140.91
-140.85
-140.95
-141.05
-141.15
-141.25
f1 (ppm)
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

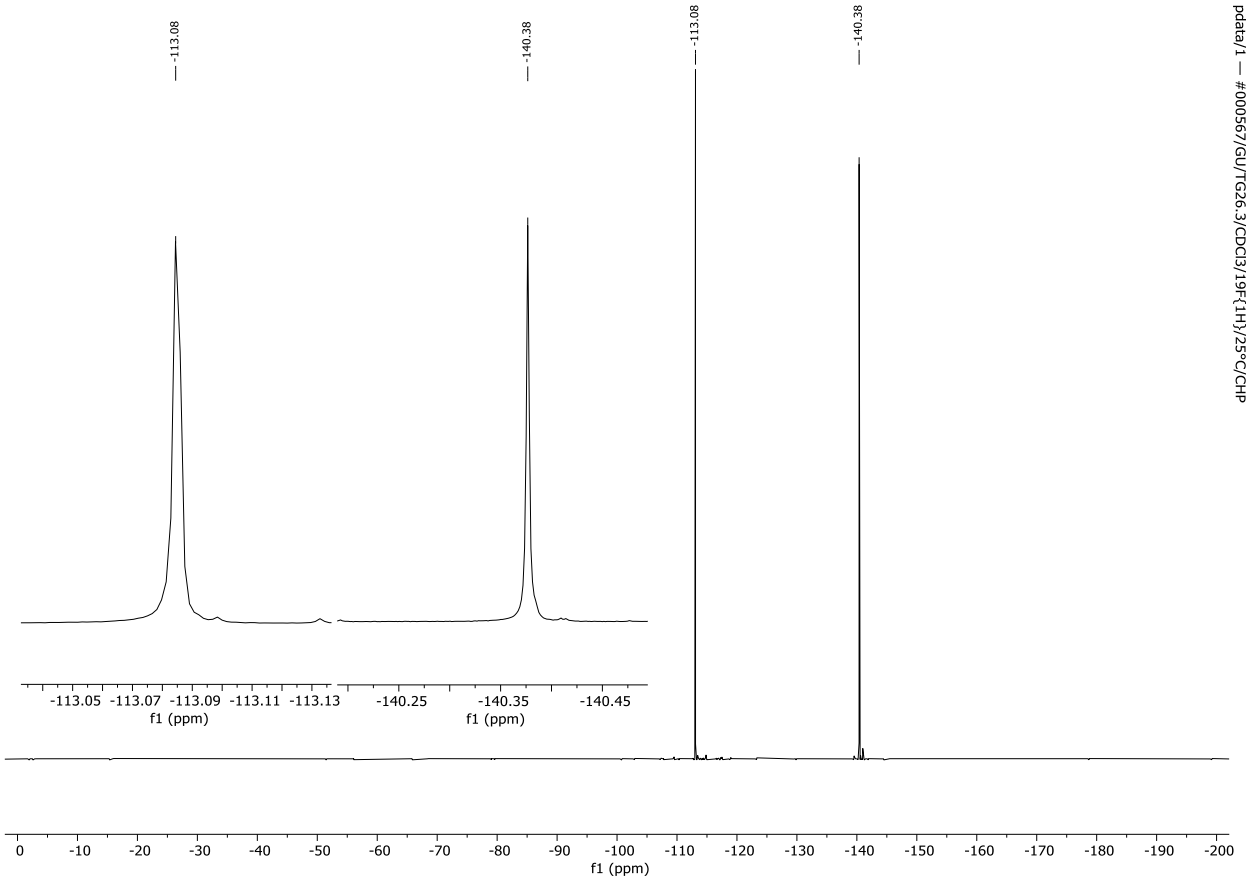
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 3g in $CDCl_3$



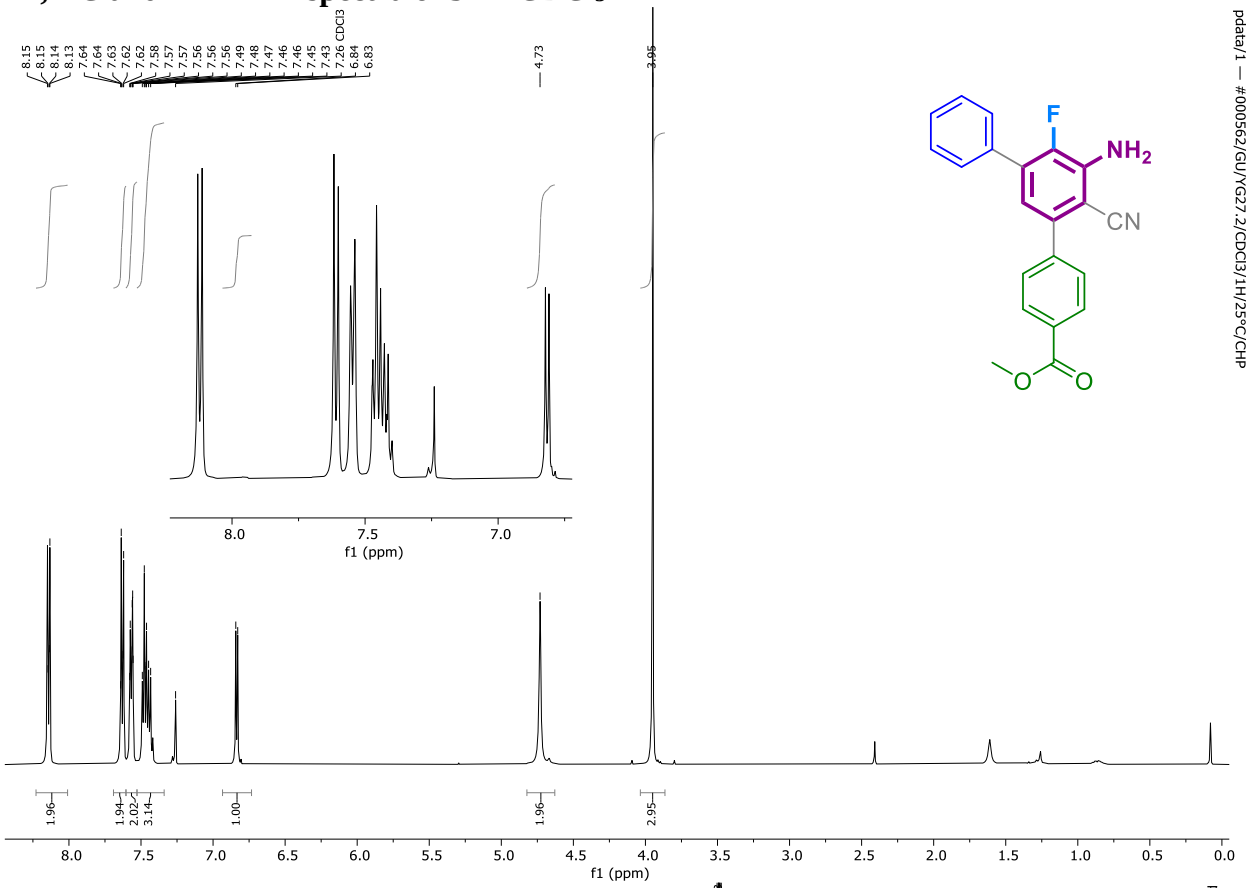

-141.28
-141.28
pdata/1 — #000558/GU/YG24-2/CDCl3/19F{1H}/25°C/CHP
-140.9
-141.1
-141.3
-141.5
-141.7
f1 (ppm)
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

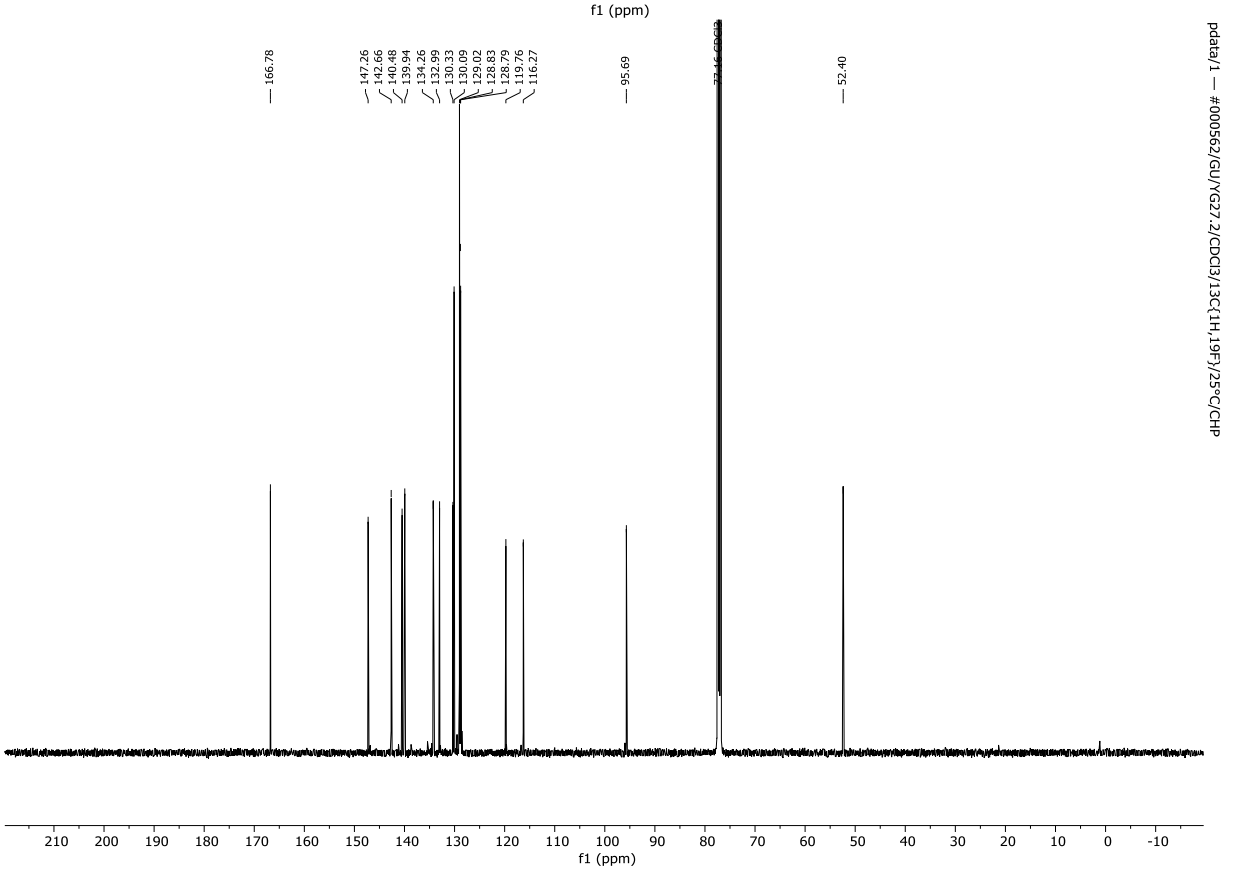
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 3h in $CDCl_3$

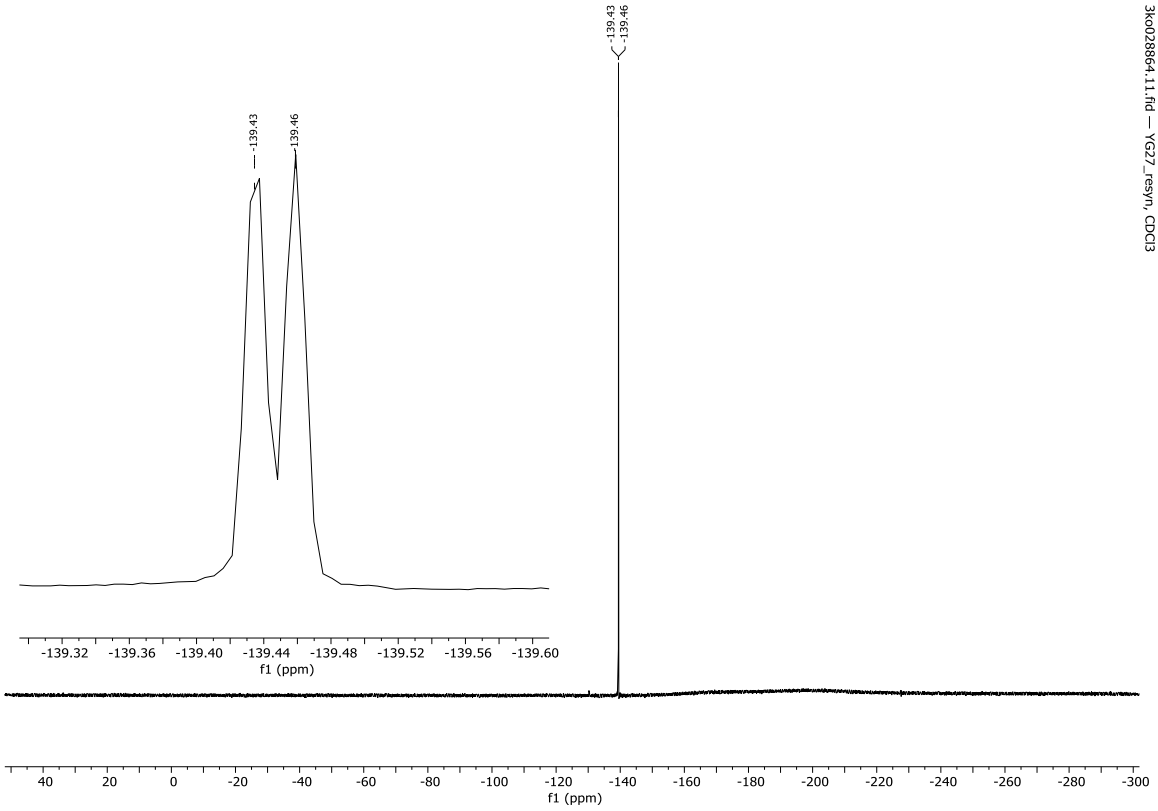



— -113.08
— -140.38
— -113.08
— -140.38
pdata/1 — #000567/GU/TG26.3/CDCl3/19F{1H}/25°C/CHP
-113.05 -113.07 -113.09 -113.11 -113.13
f1 (ppm)
-140.25 -140.35 -140.45
f1 (ppm)
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

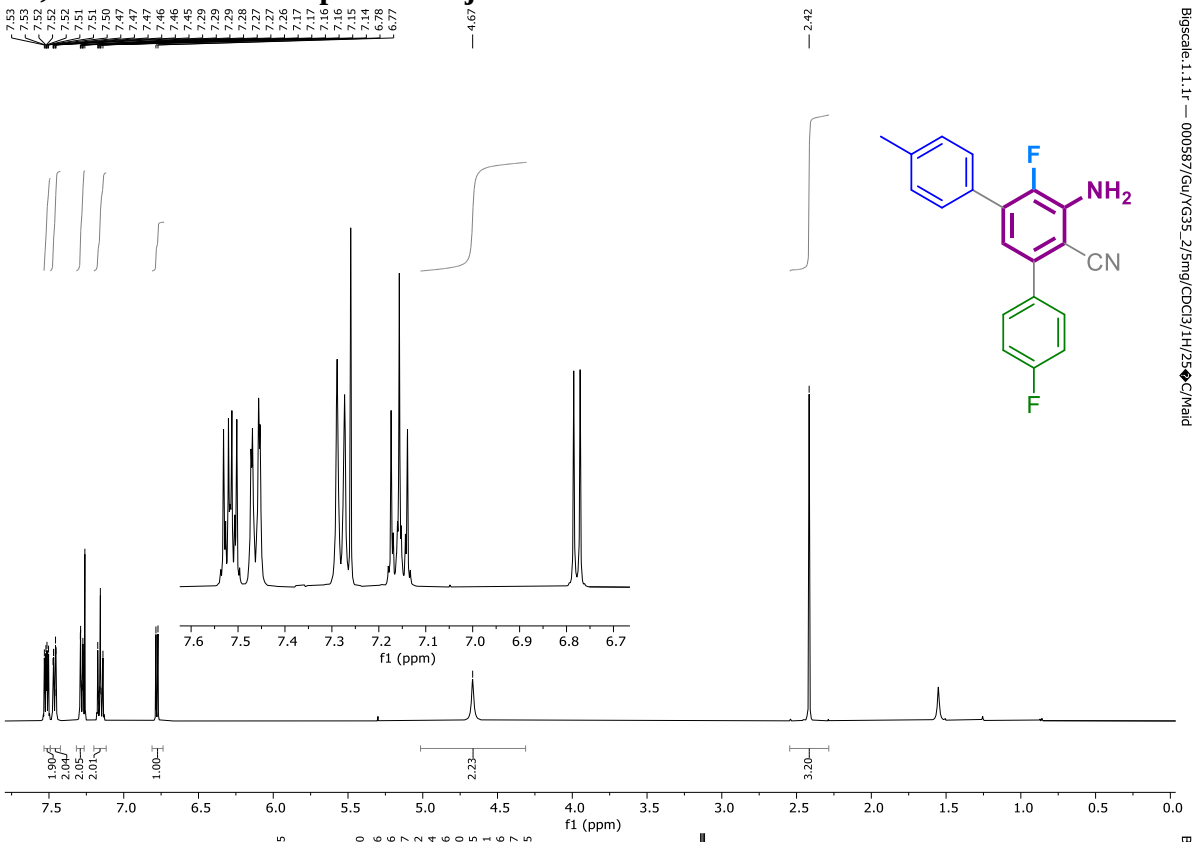
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 3i in $CDCl_3$

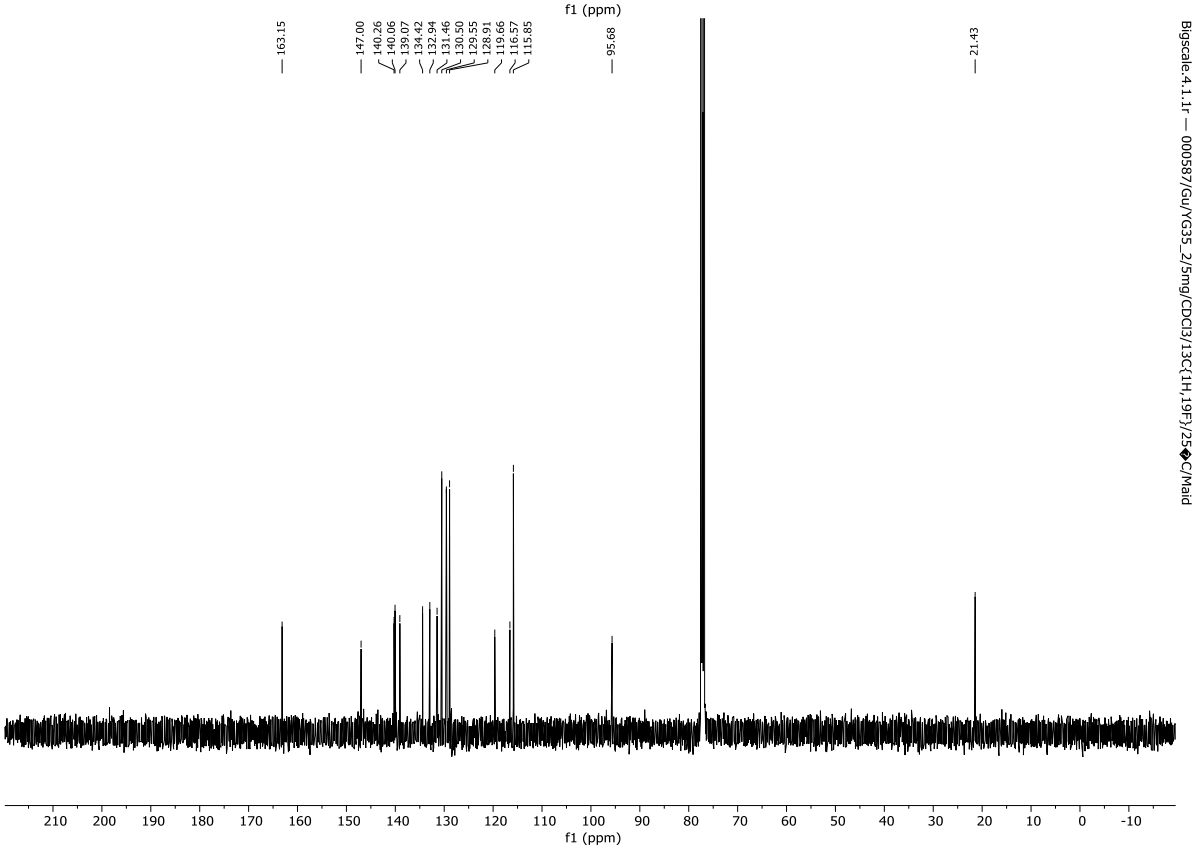


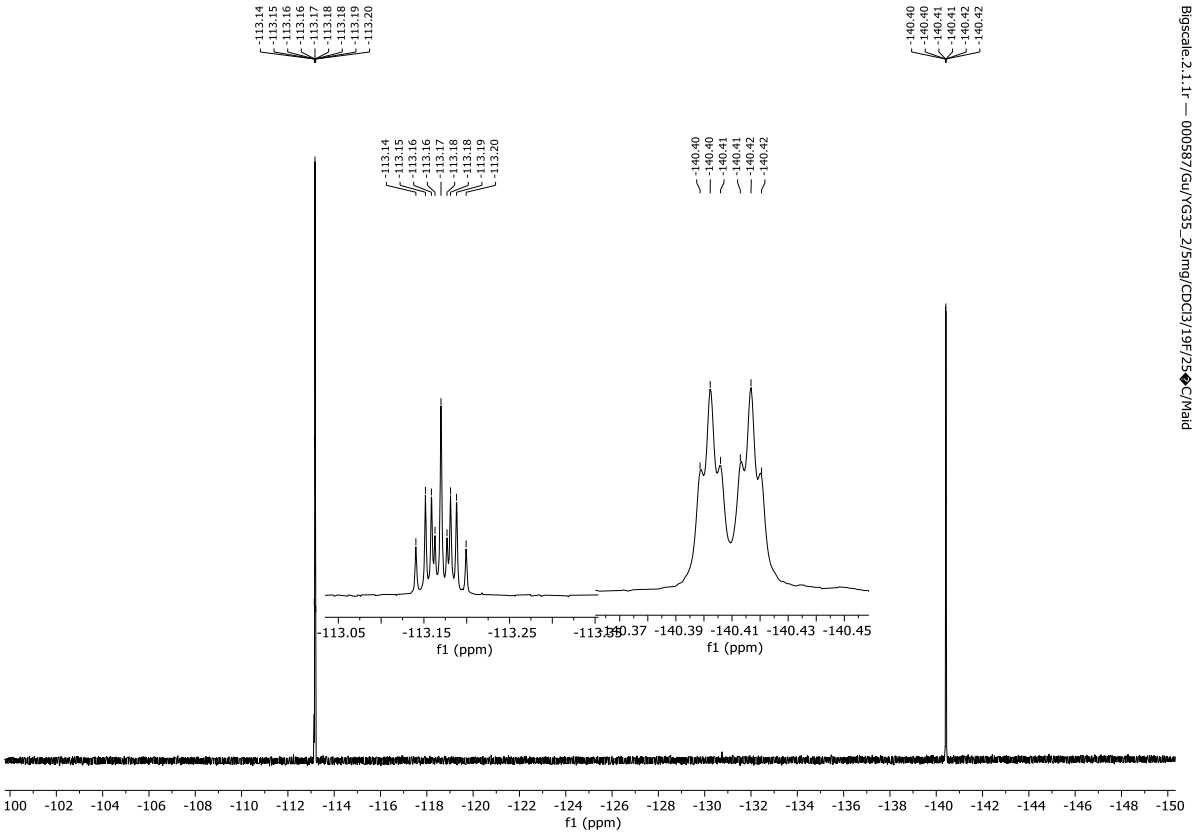



-139.43
-139.46
3ko028864.11.fid — YG27_resyn, CDCl3
-139.43
-139.46
-139.32
-139.36
-139.40
-139.44
-139.48
-139.52
-139.56
-139.60
f1 (ppm)
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280
-300
f1 (ppm)

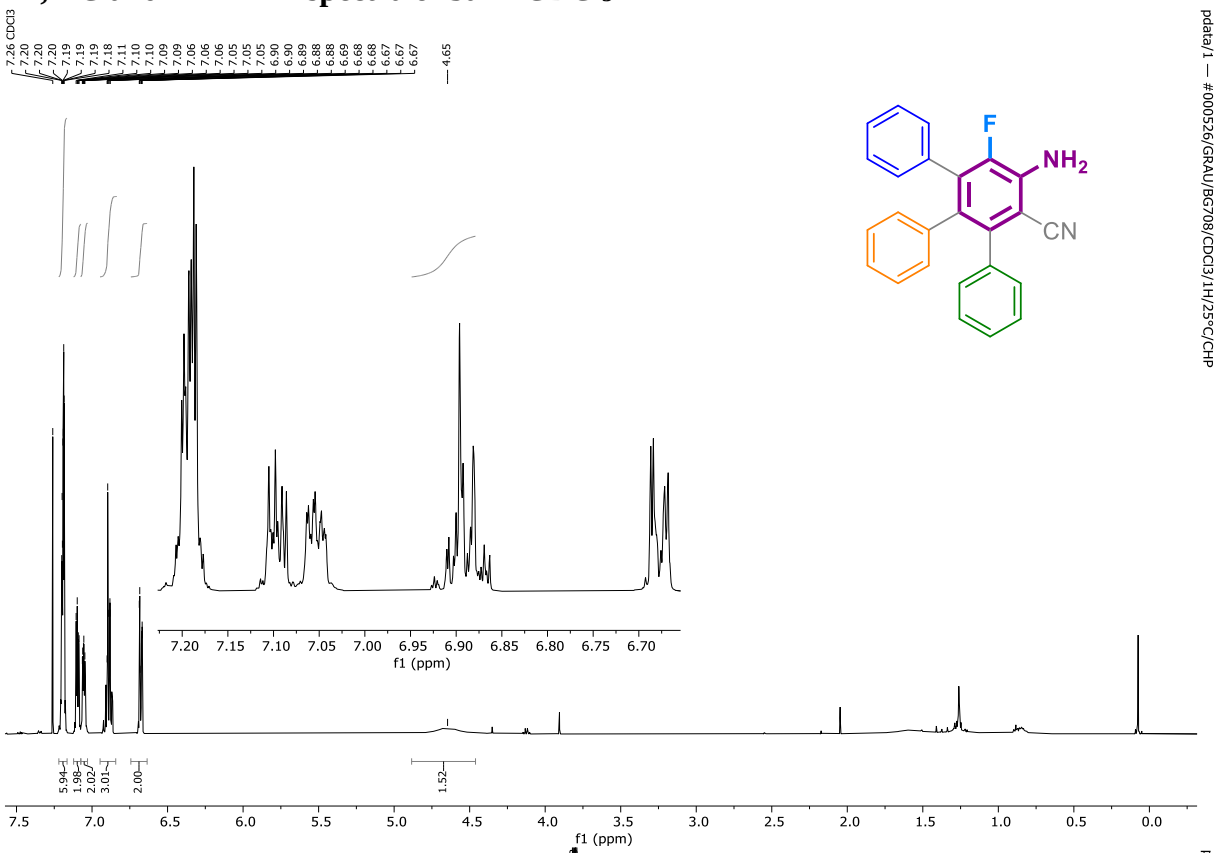
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 3j in $CDCl_3$

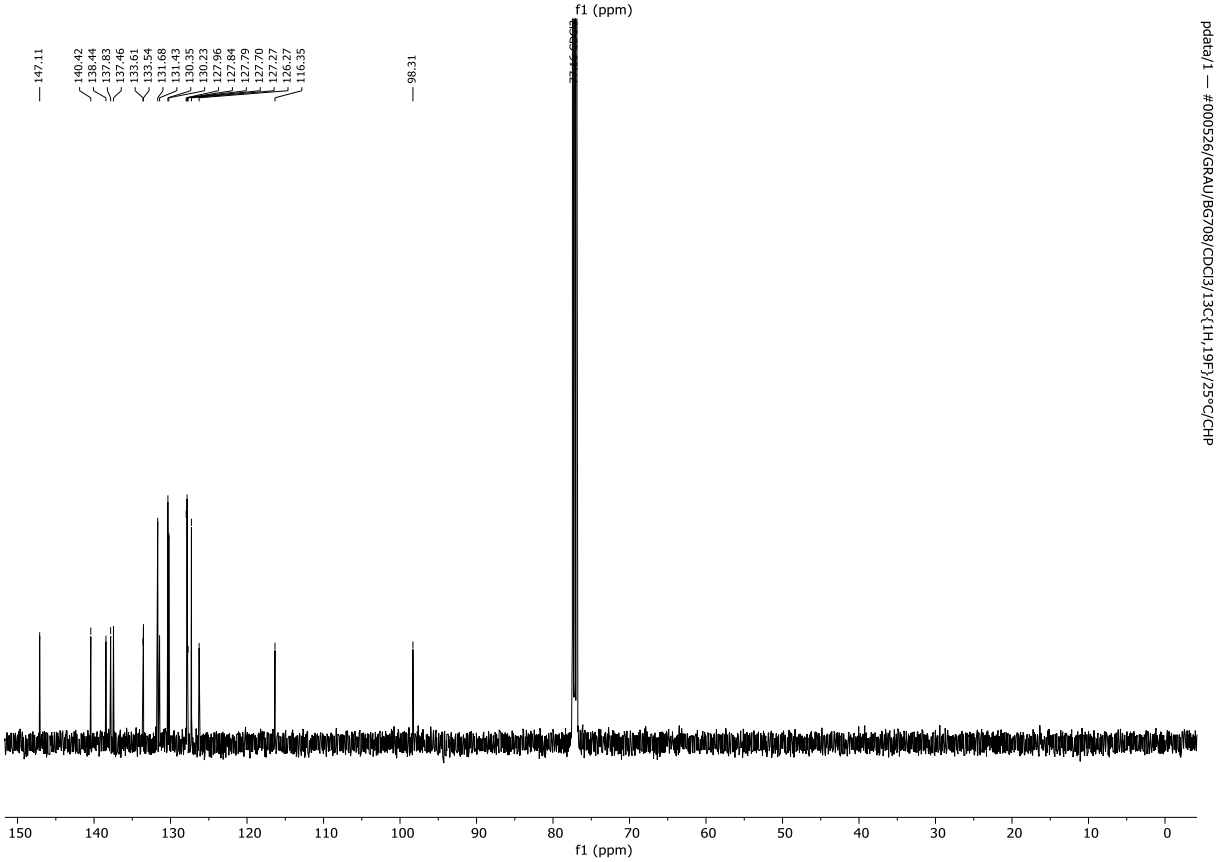


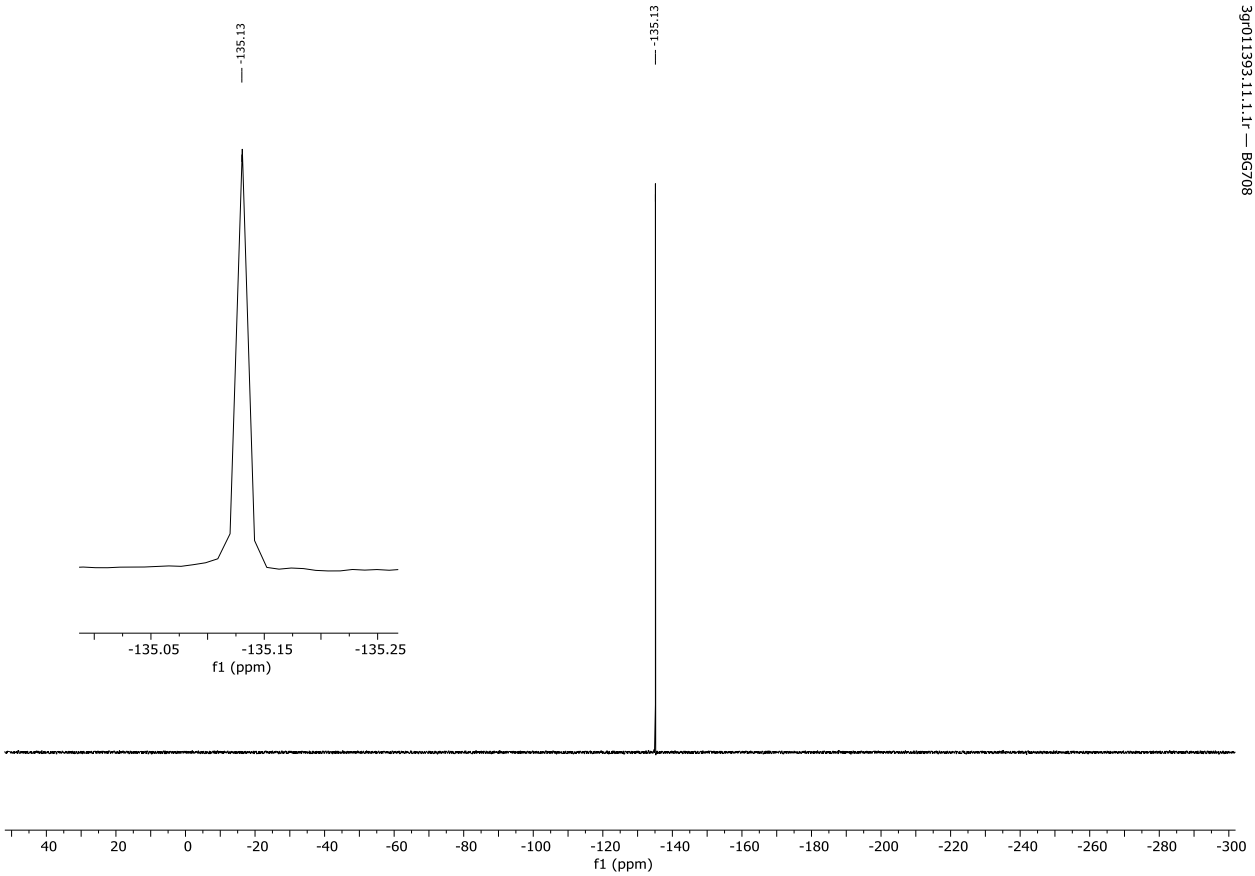




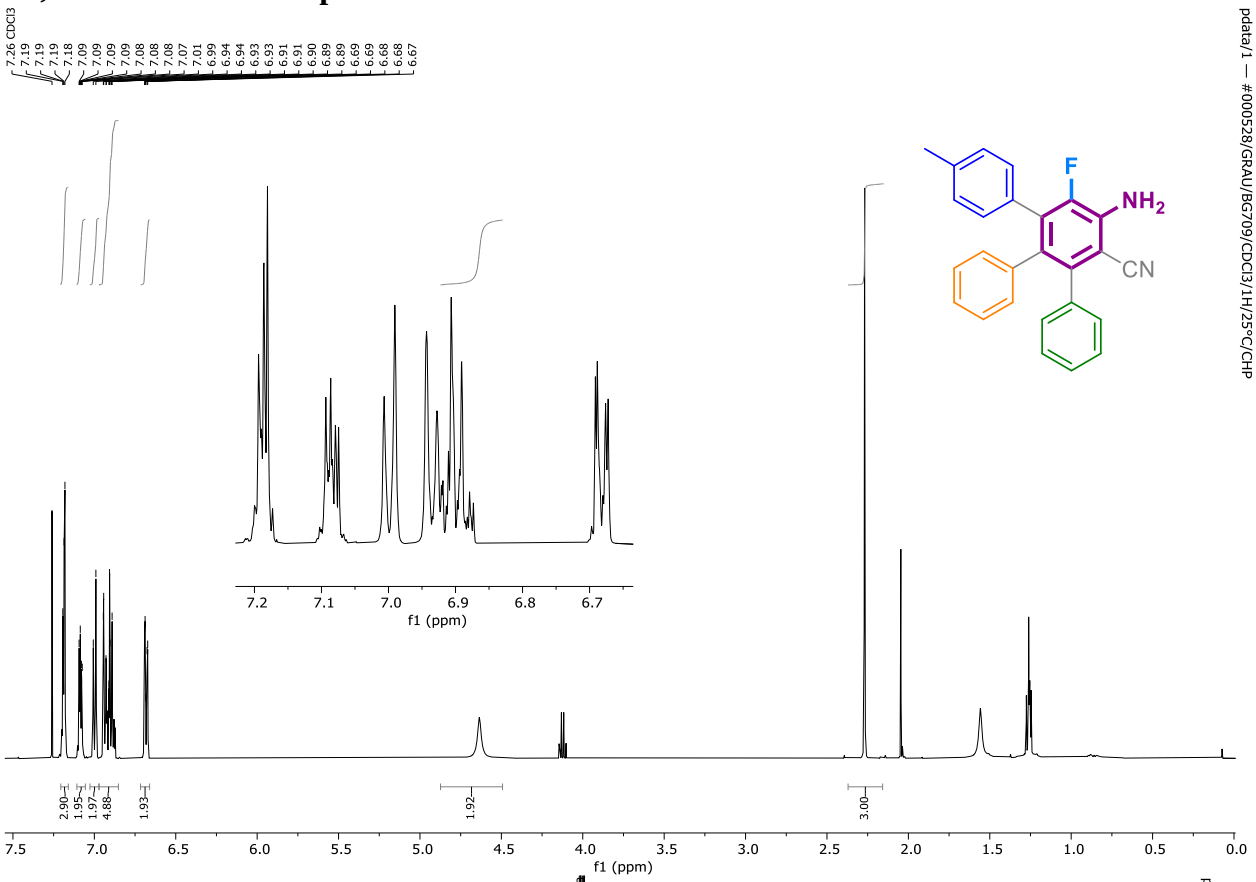
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 5a in $CDCl_3$

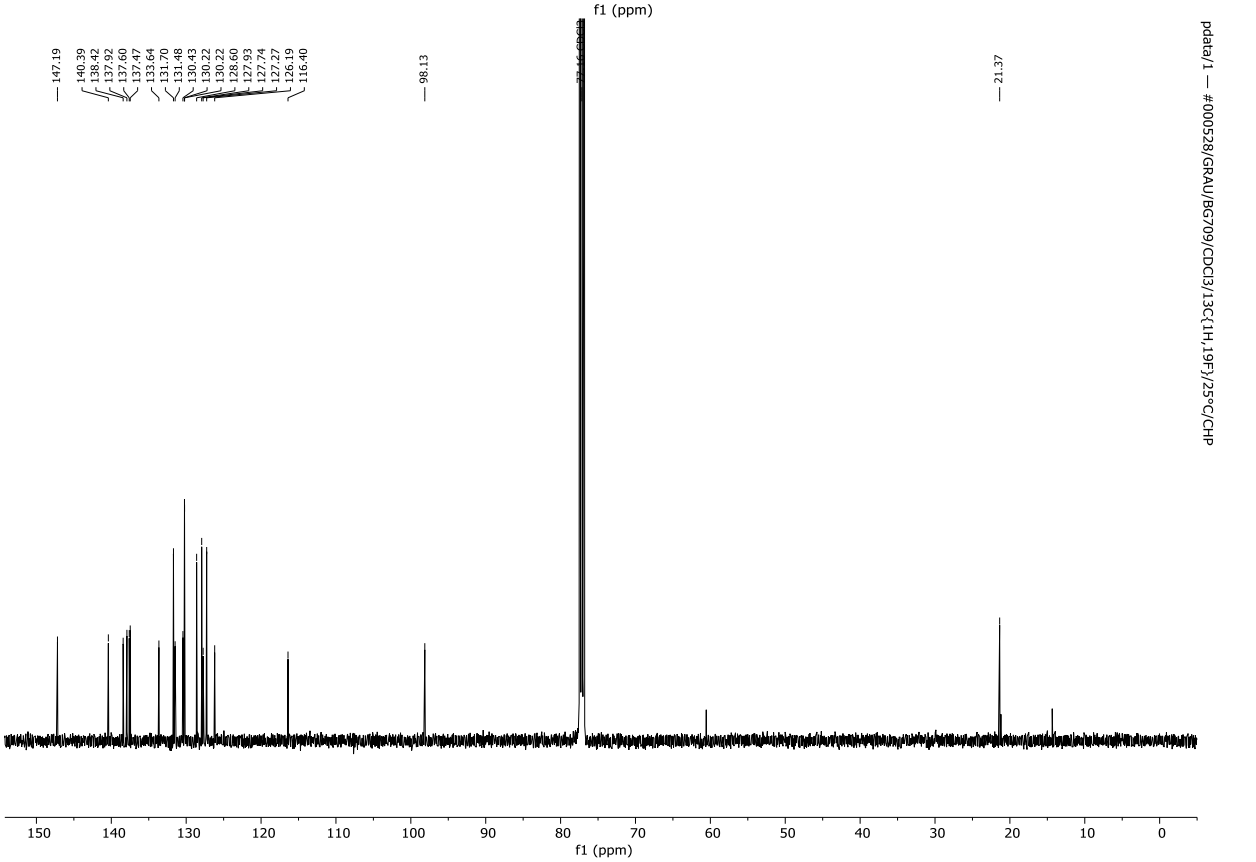


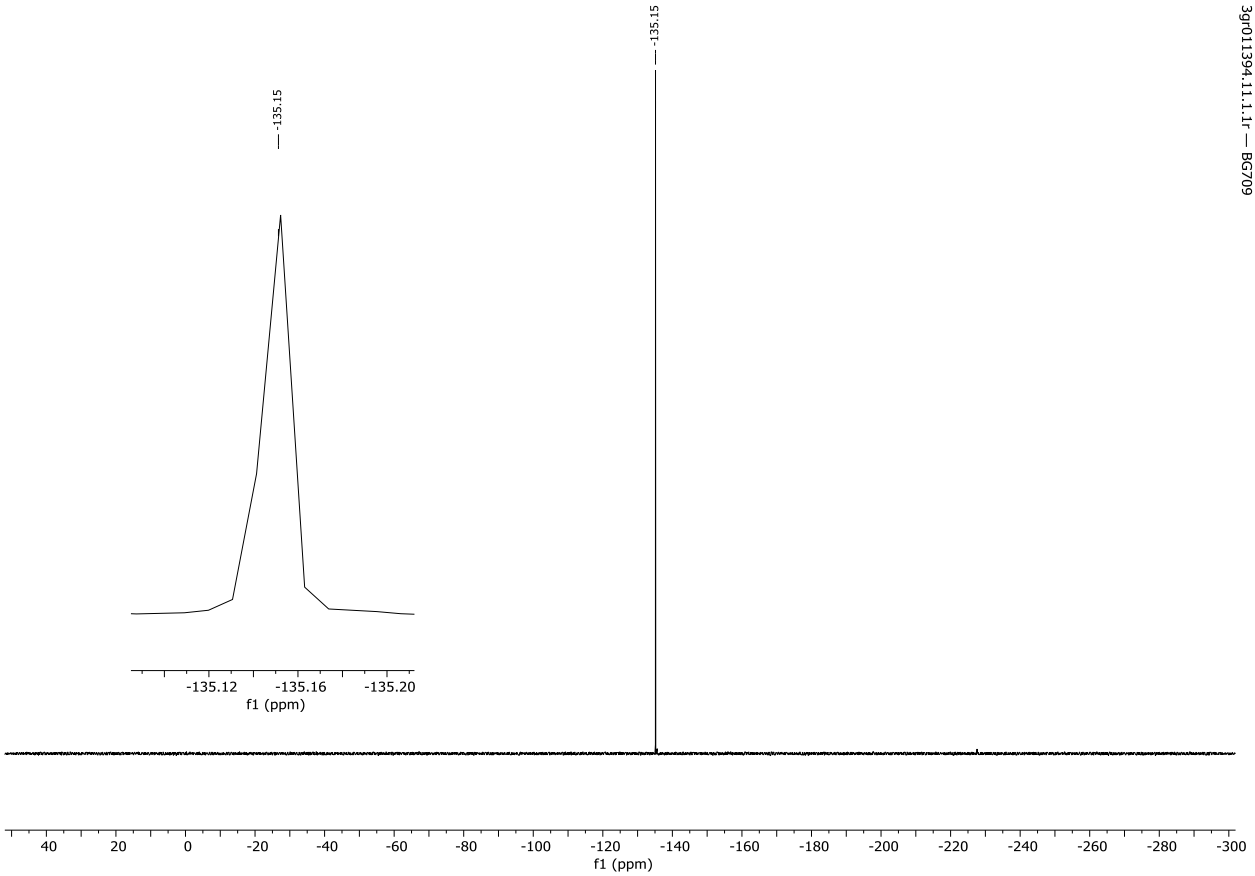



-135.13
-135.13
3gr011393.11.1.1r — BG708
-135.05
-135.15
-135.25
f1 (ppm)
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280
-300
f1 (ppm)

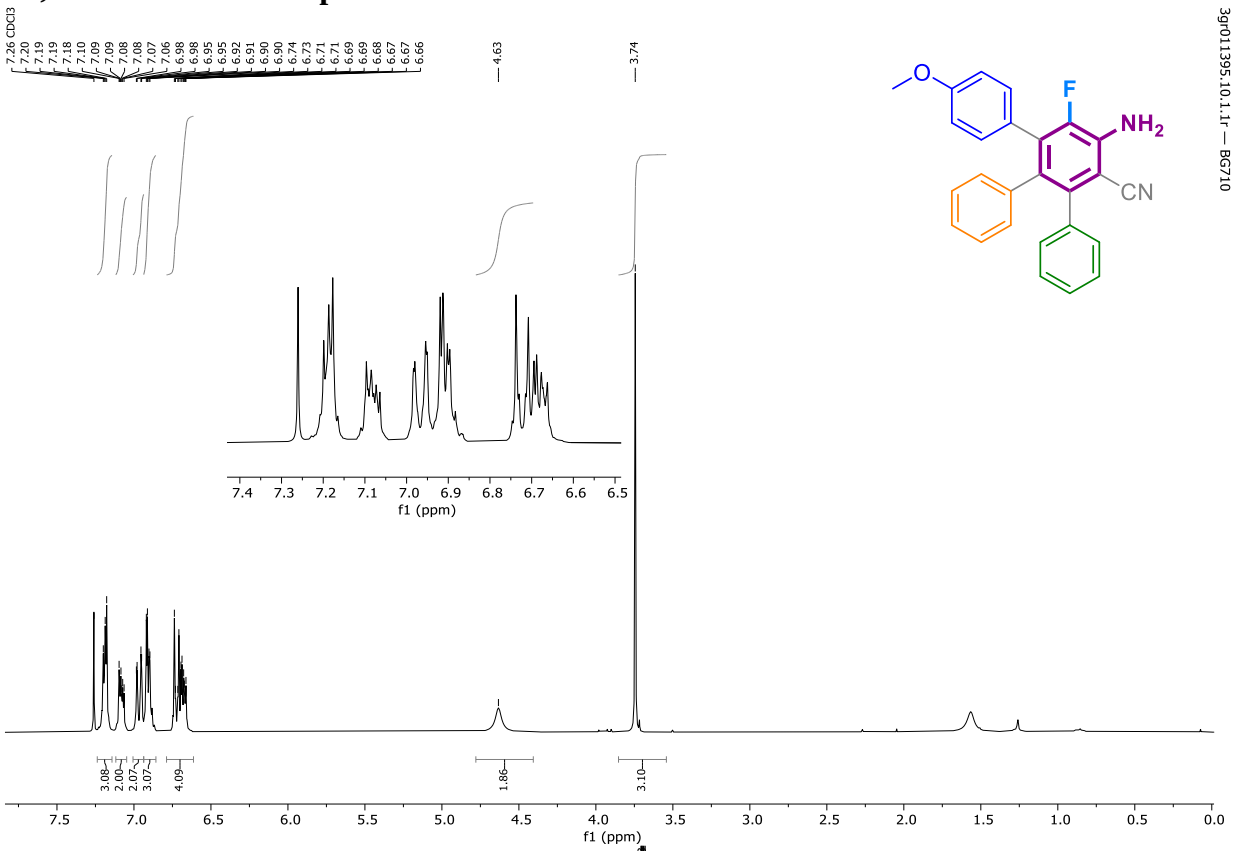
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 5b in $CDCl_3$

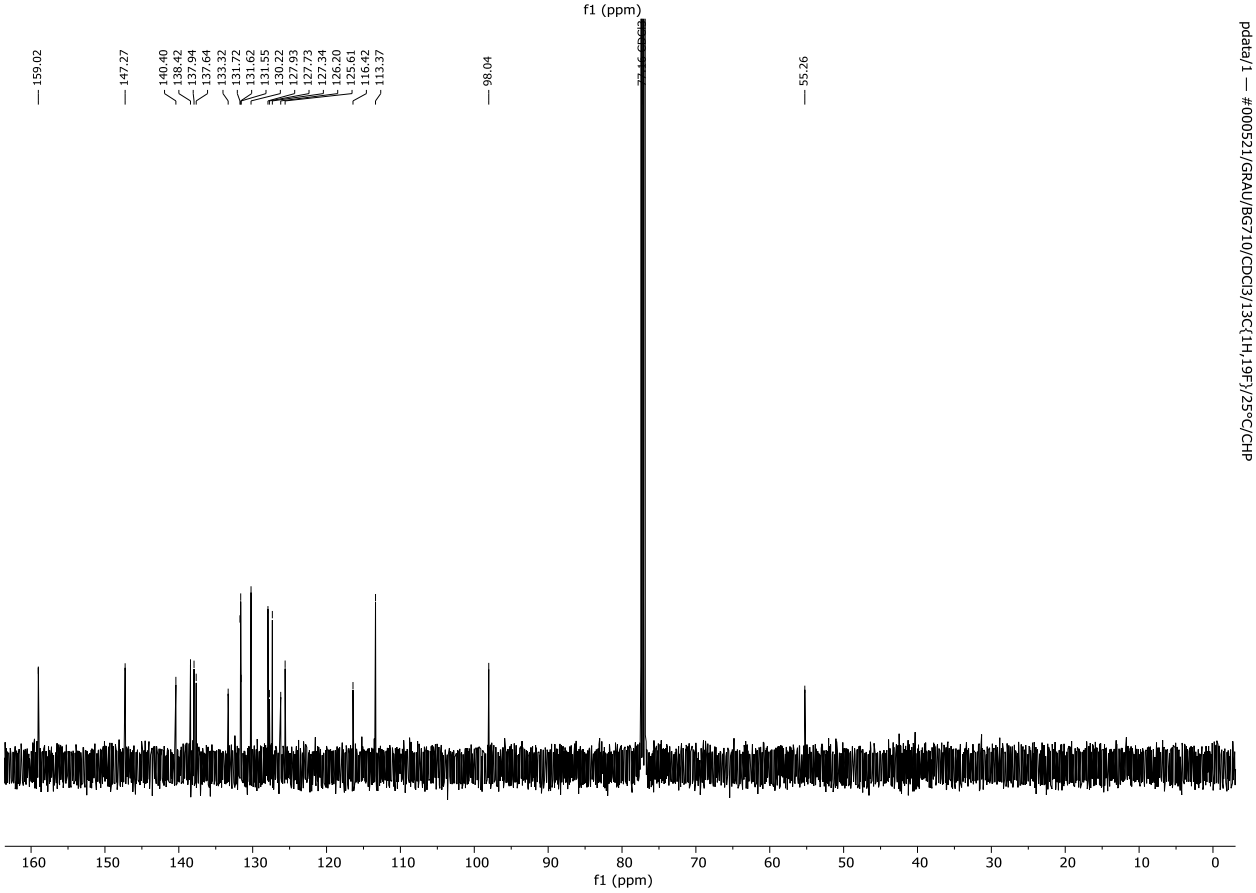


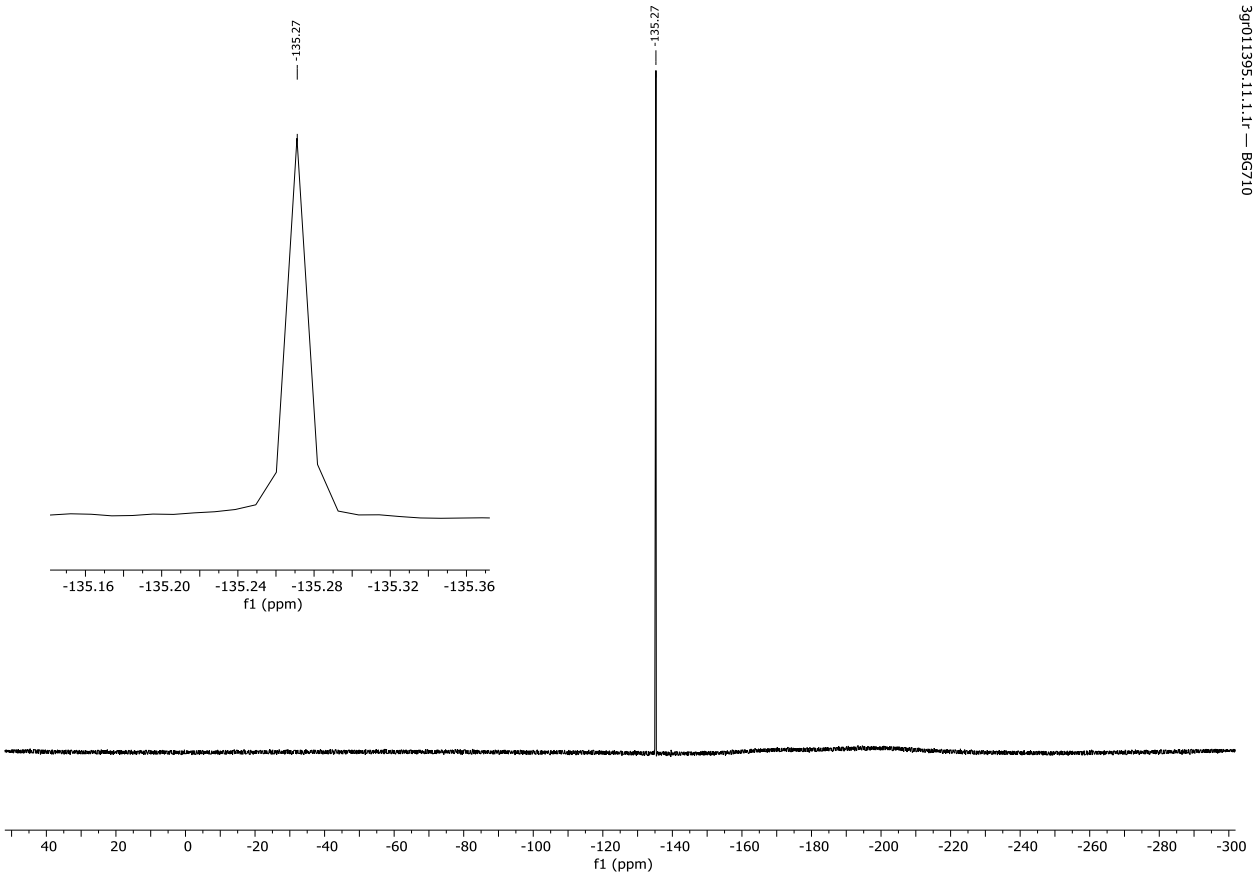



-135.15
-135.15
3gr011394.11.1.1r — BG709
-135.12
-135.16
-135.20
f1 (ppm)
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280
-300
f1 (ppm)

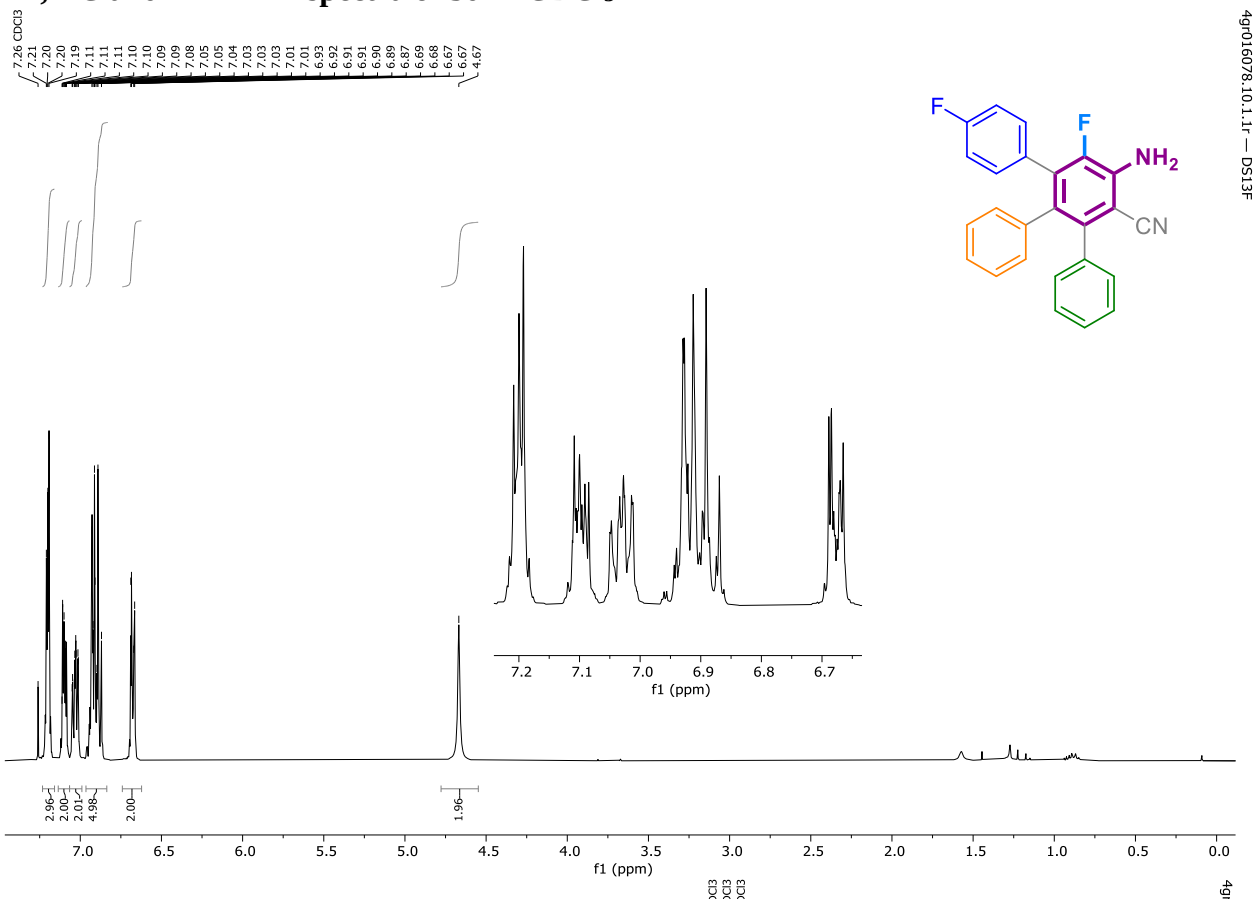
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 5c in $CDCl_3$

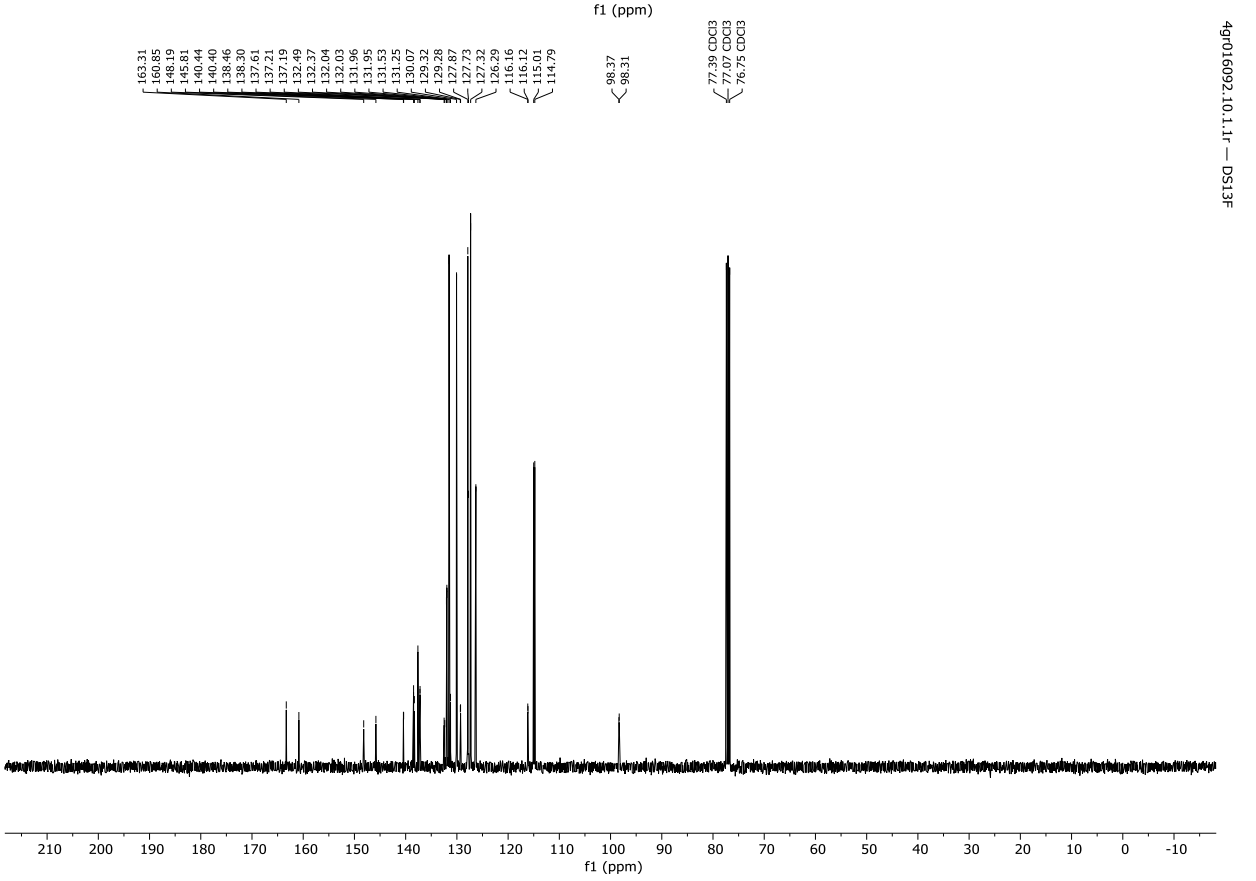


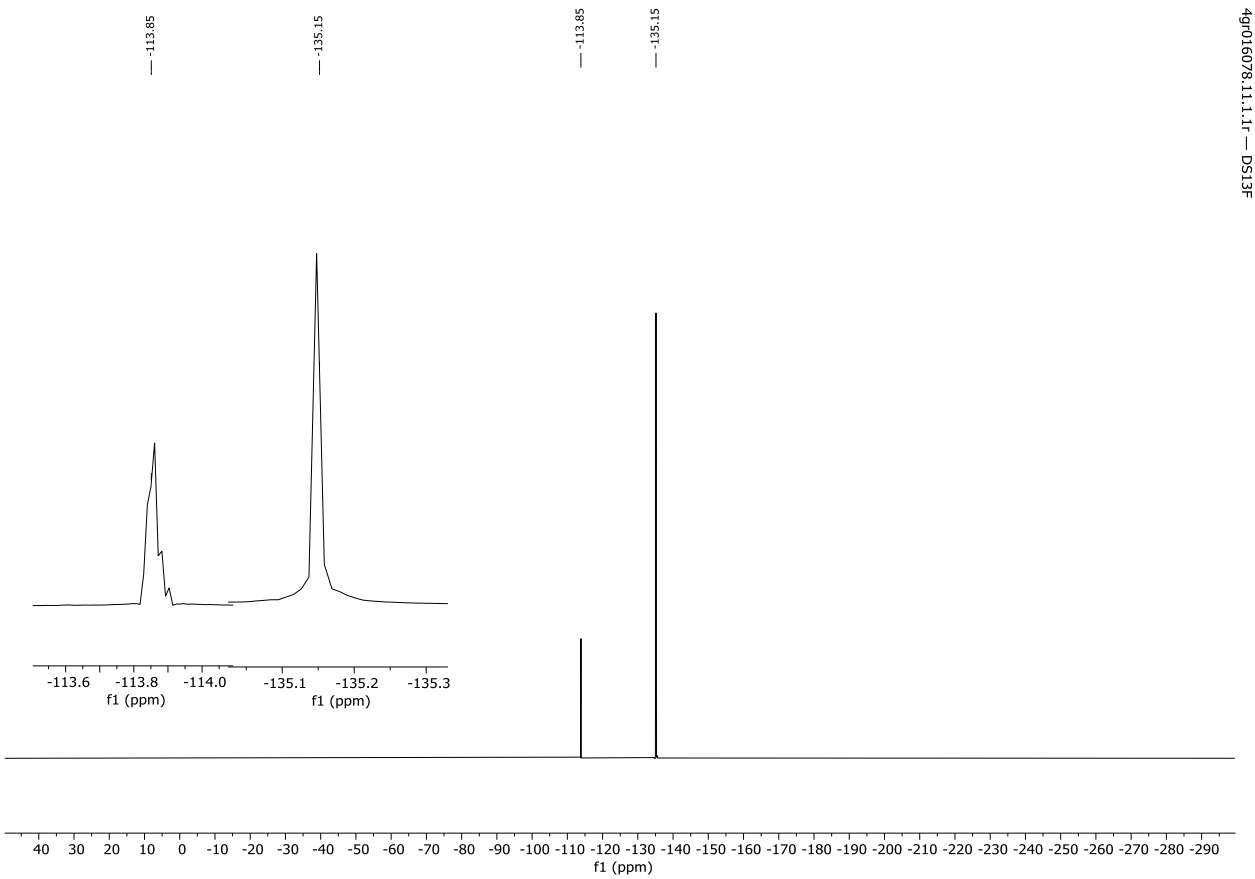



-135.27
-135.27
3gr011395.11.1.1r — BG710
-135.16
-135.20
-135.24
-135.28
-135.32
-135.36
f1 (ppm)
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280
-300
f1 (ppm)

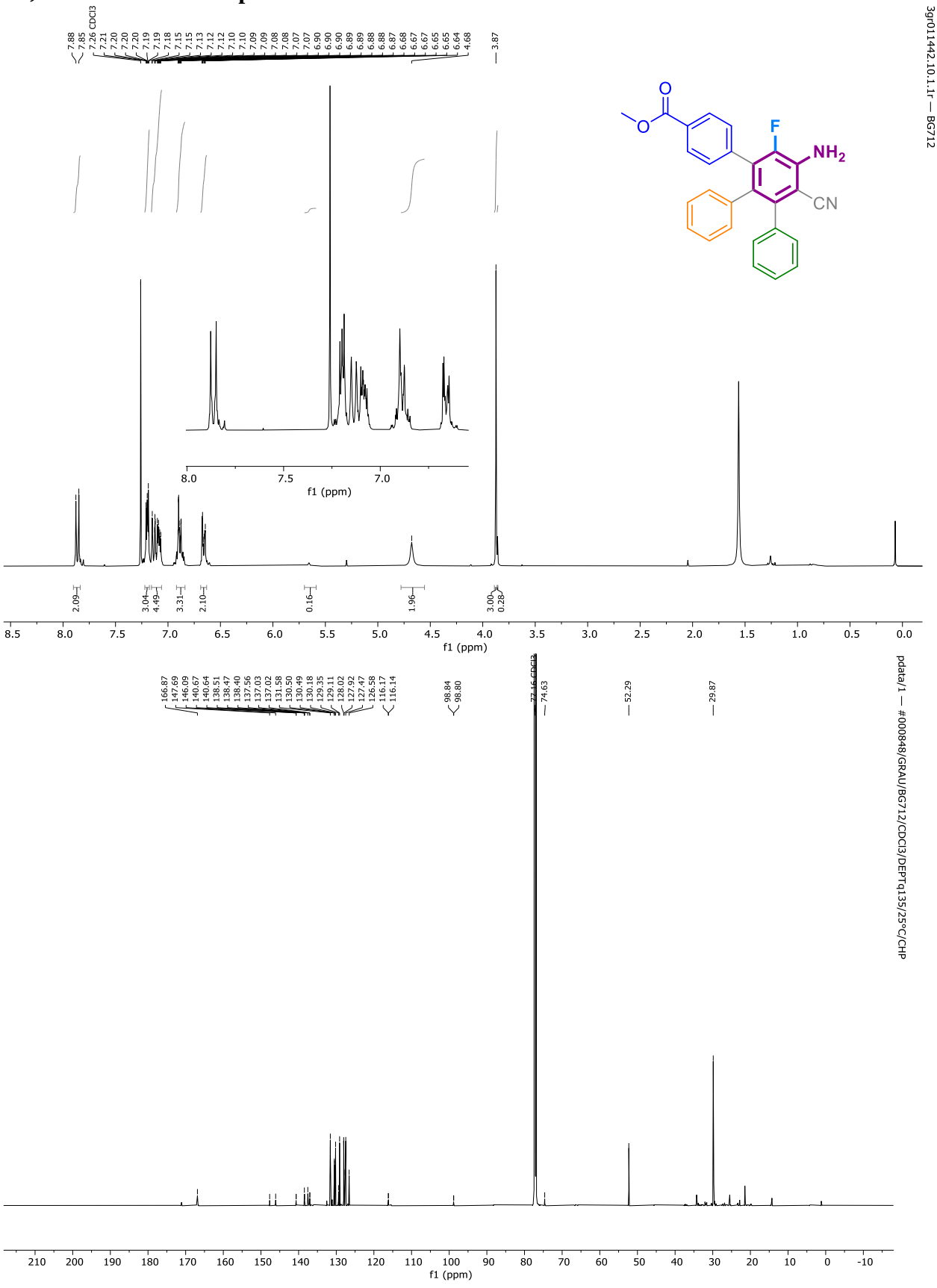
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 5d in $CDCl_3$

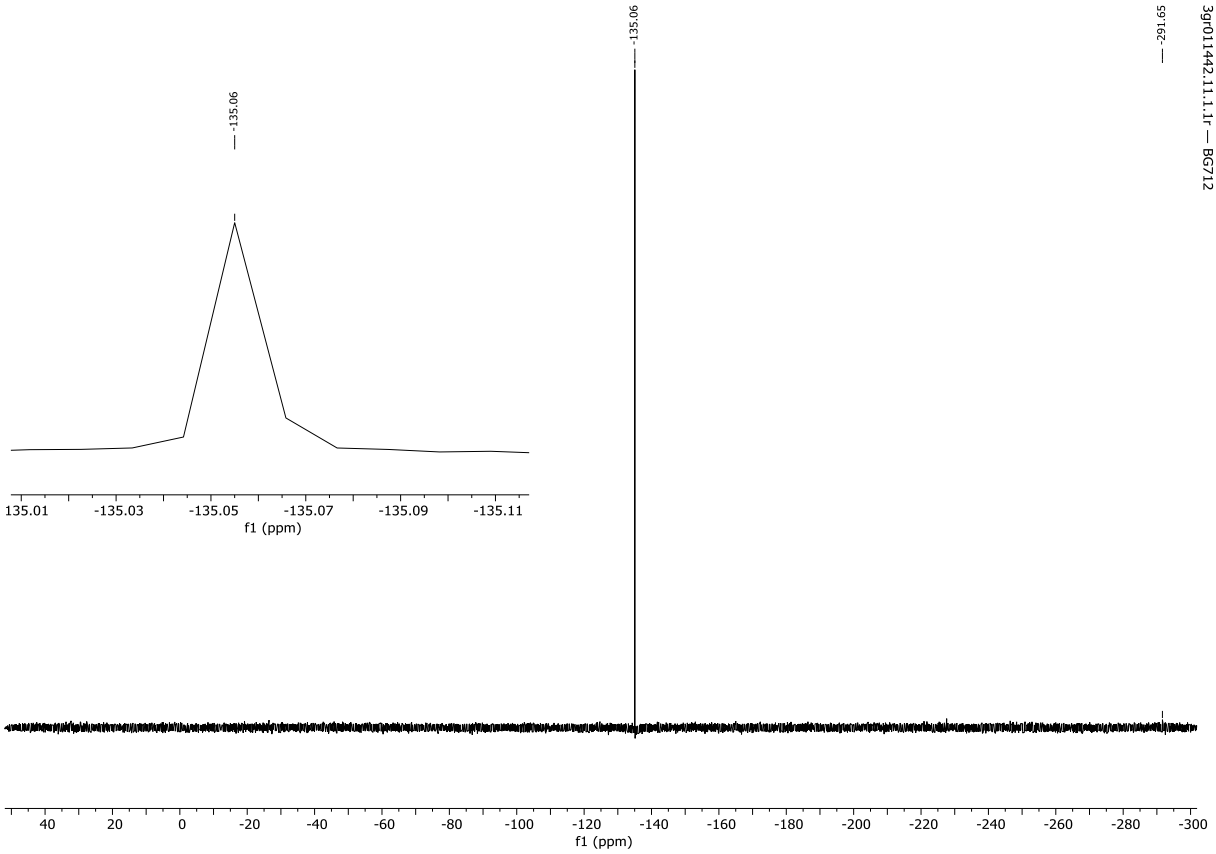




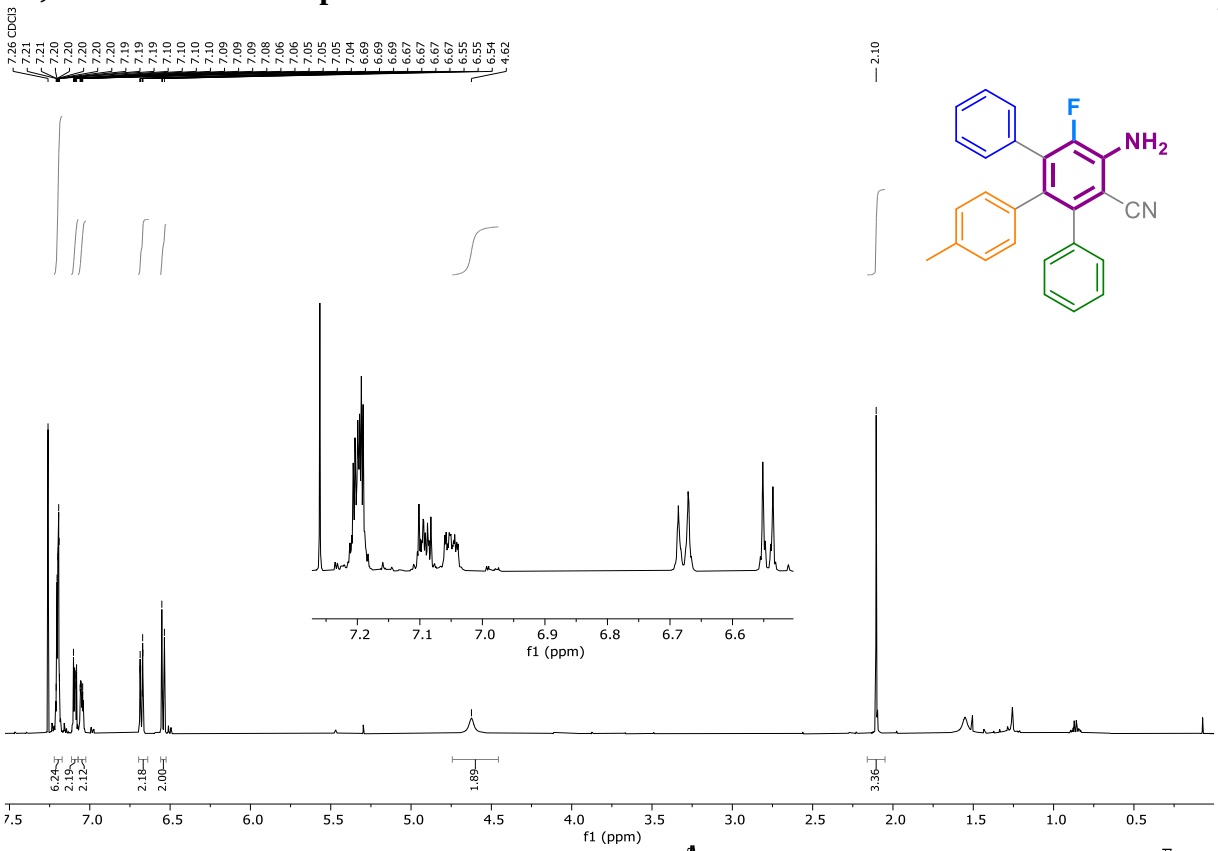

-113.85
-135.15
-113.85
-135.15
4gr016078.11.1.1r — DS13F
-113.6
-113.8
-114.0
f1 (ppm)
-135.1
-135.2
-135.3
f1 (ppm)
40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250 -260 -270 -280 -290
f1 (ppm)

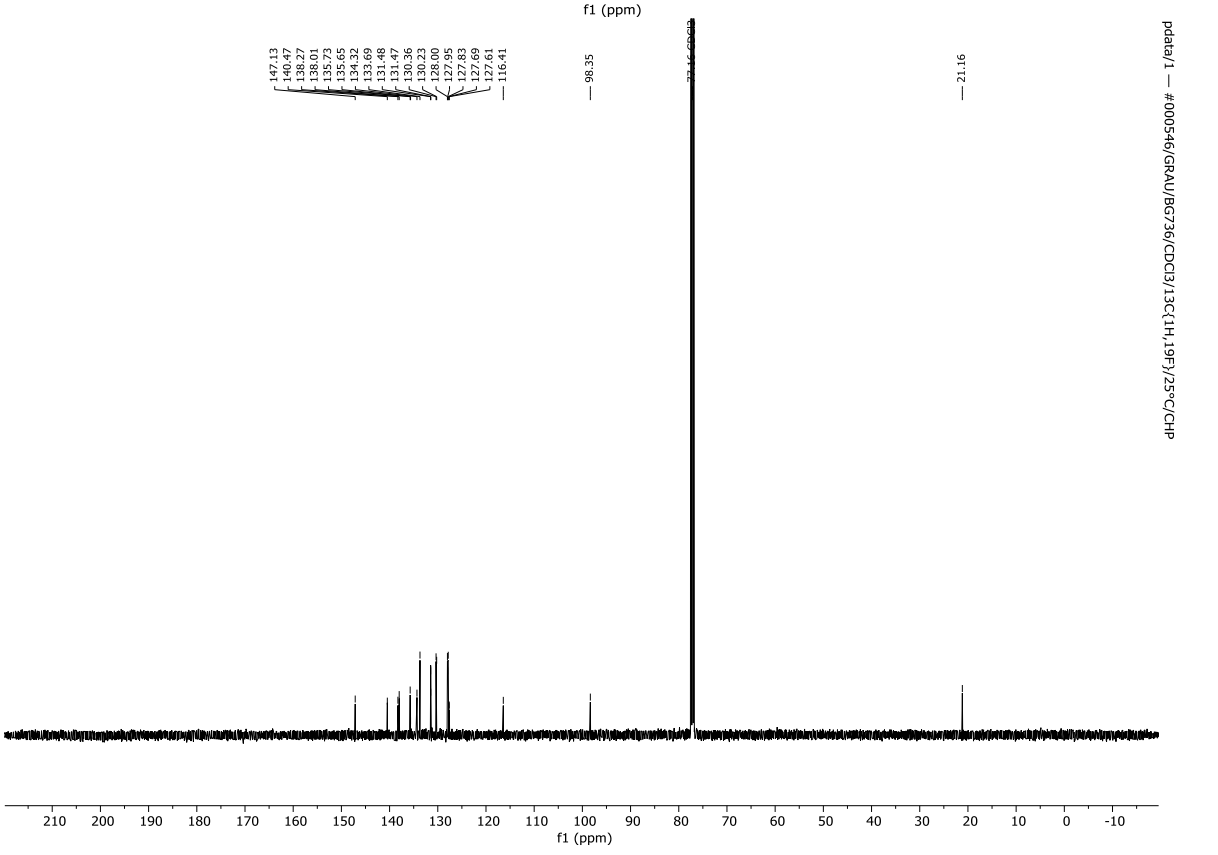
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 5e in $CDCl_3$

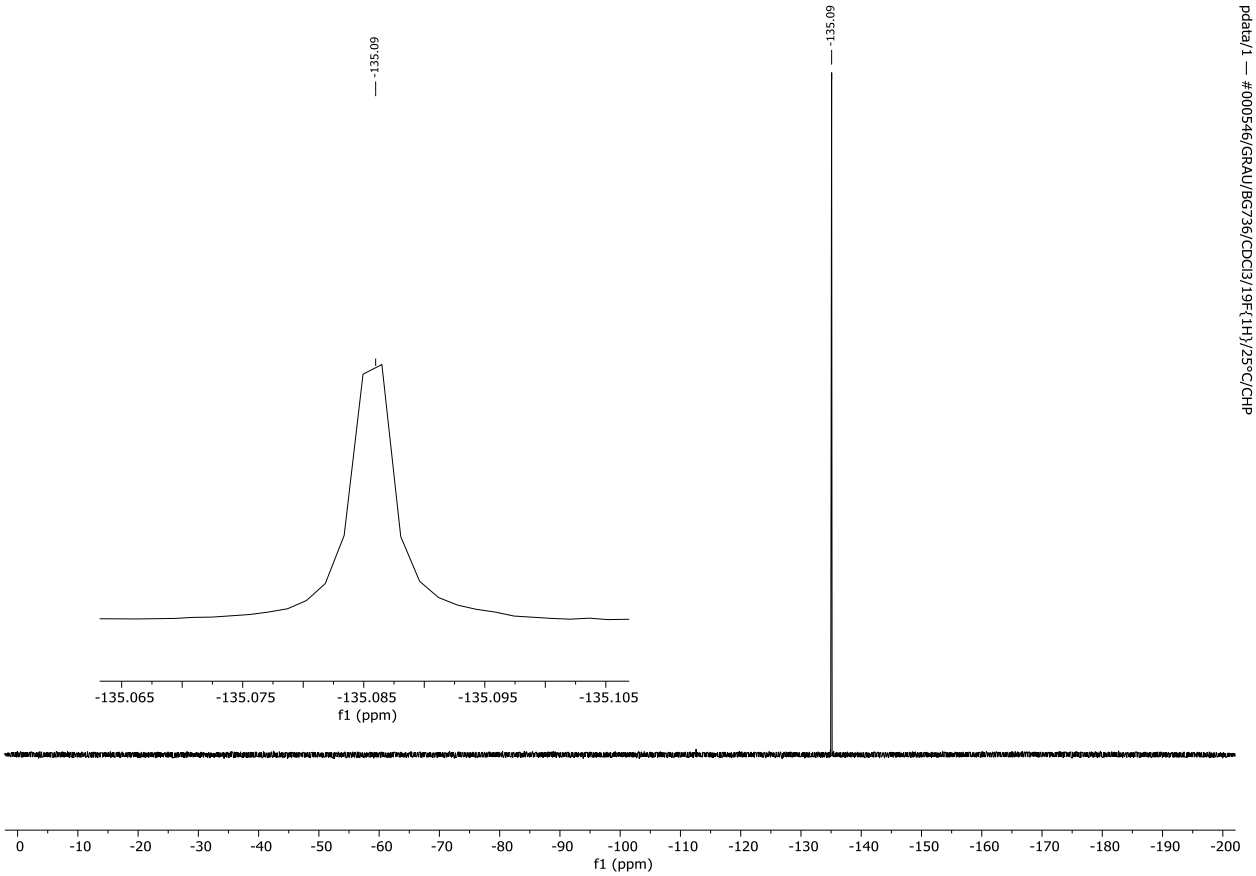



3gr011442.11.1.1r — BG712
-135.06
-291.69
-135.06
135.01
-135.03
-135.05
-135.07
-135.09
-135.11
f1 (ppm)
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280
-300
f1 (ppm)

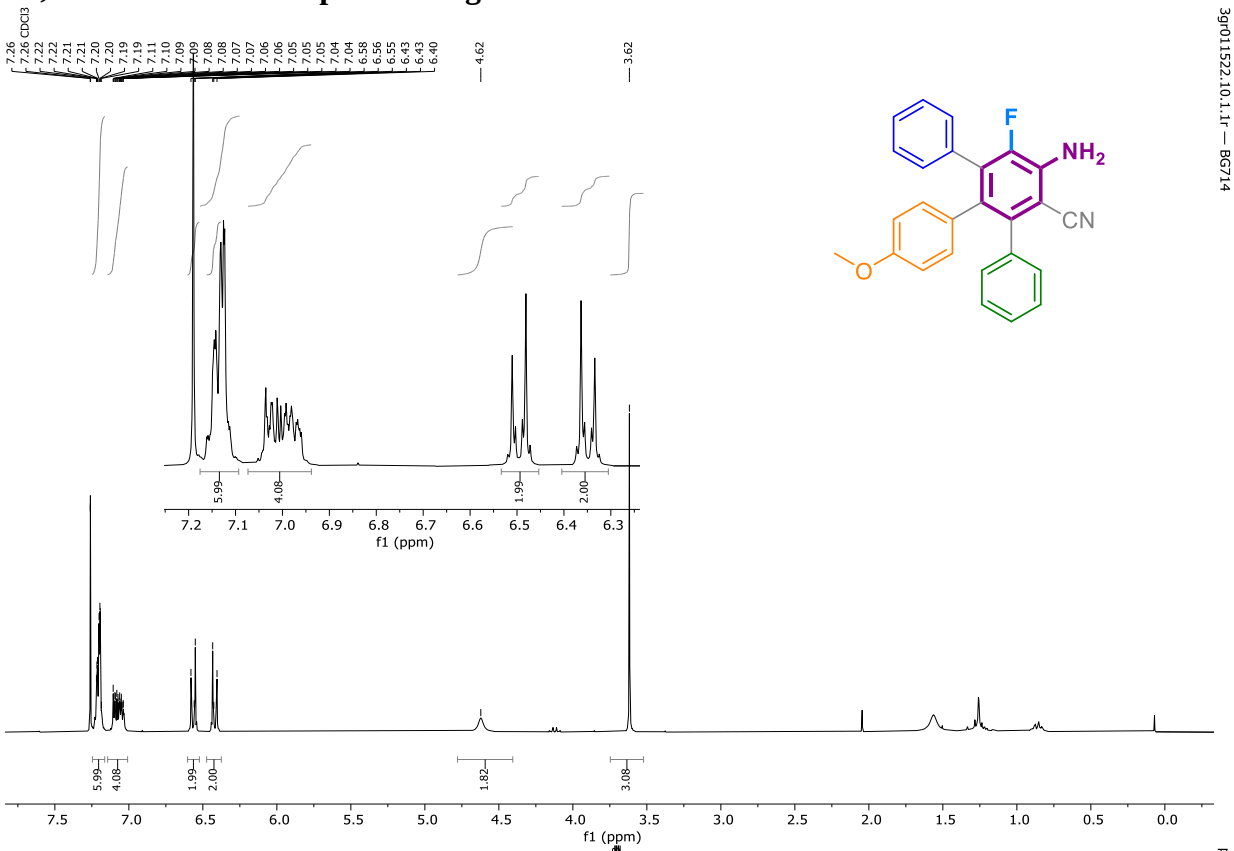
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 5f in $CDCl_3$

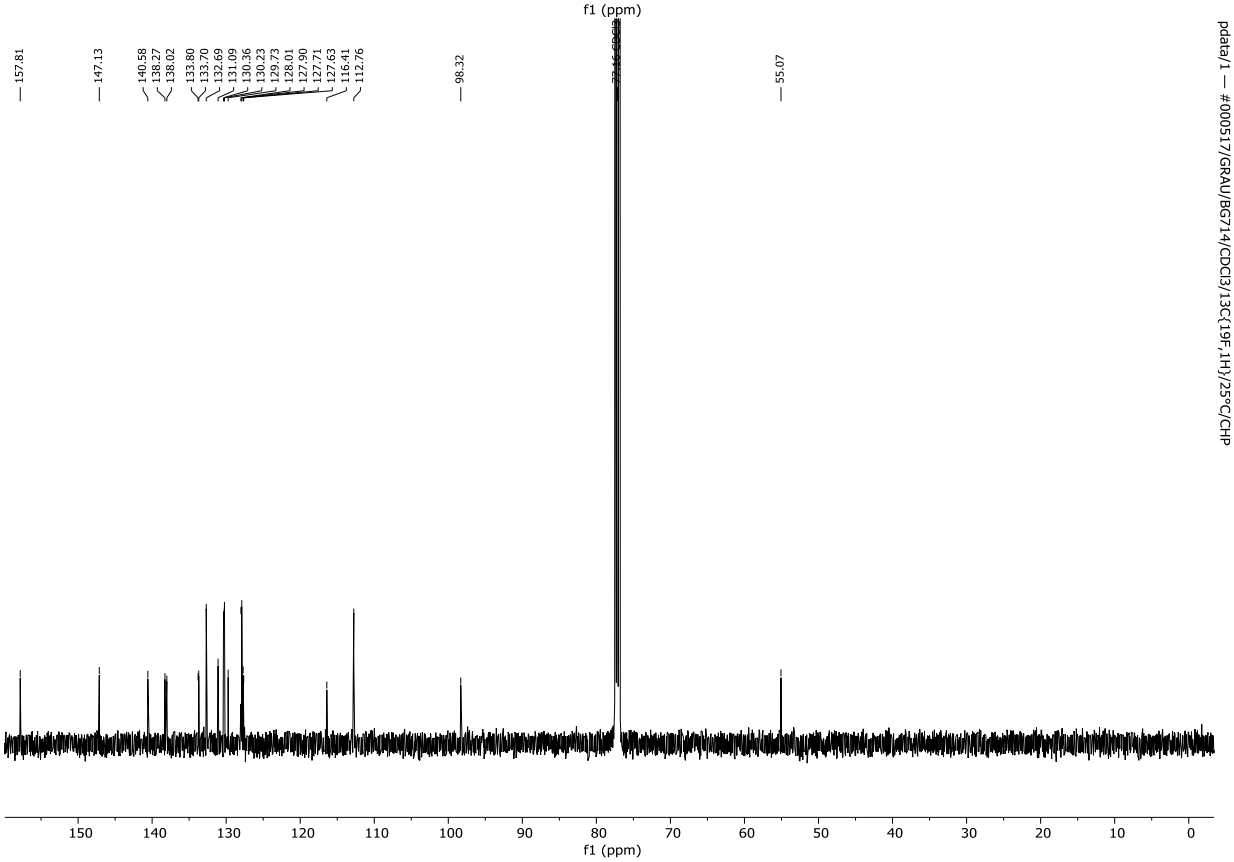


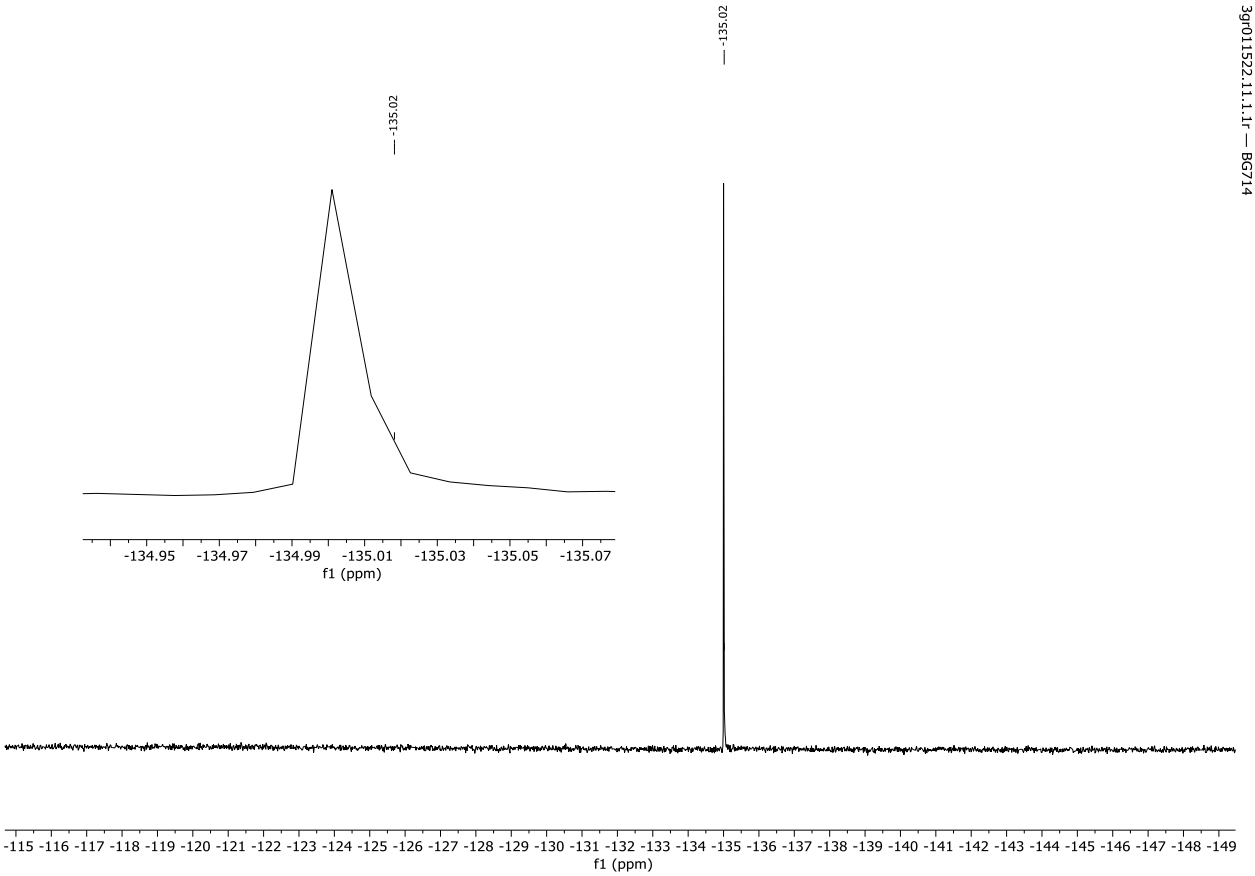



— -135.09
— -135.09
-135.065
-135.075
-135.085
-135.095
-135.105
f1 (ppm)
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)
pdata/1 — #000546/GRAU/BG736/CDCl3/19F{1H}/25°C/CHP

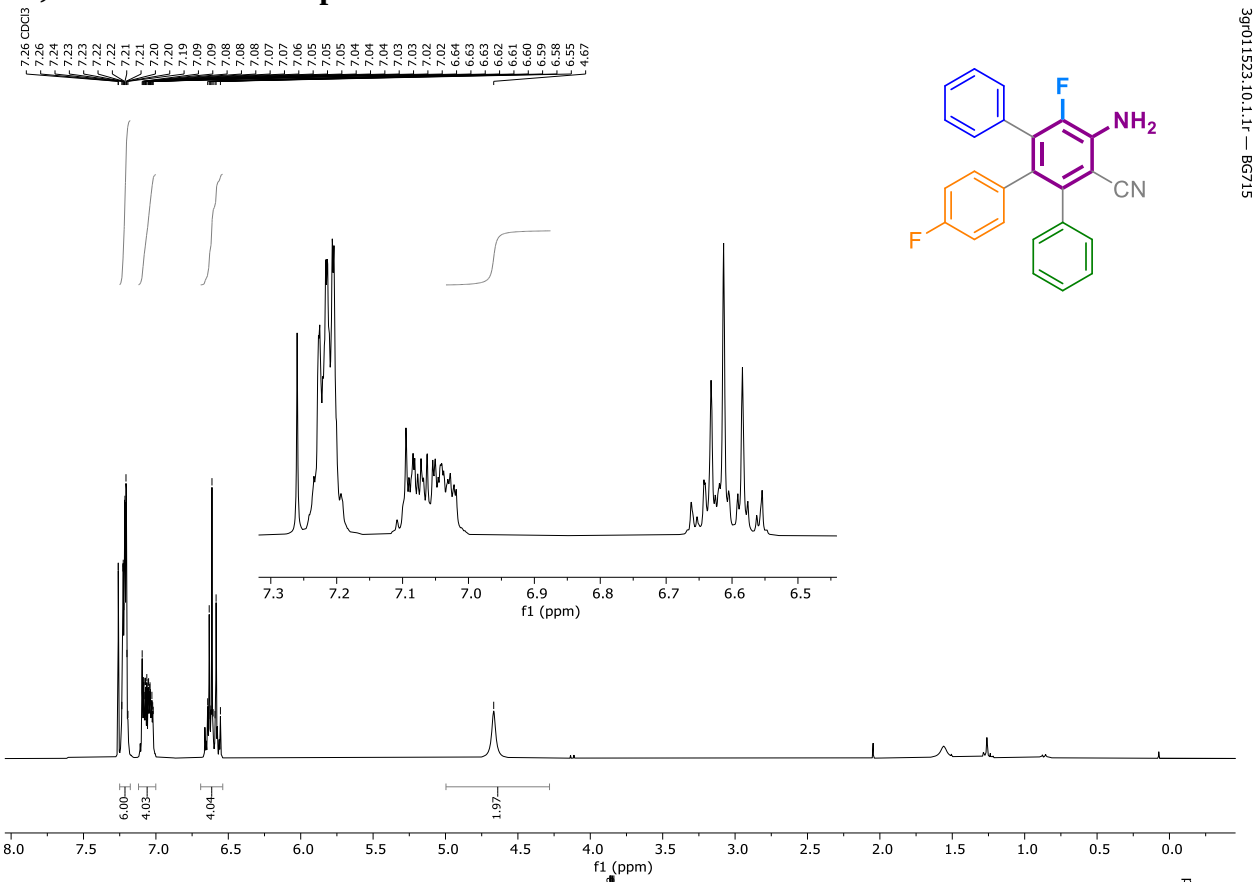
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 5g in $CDCl_3$

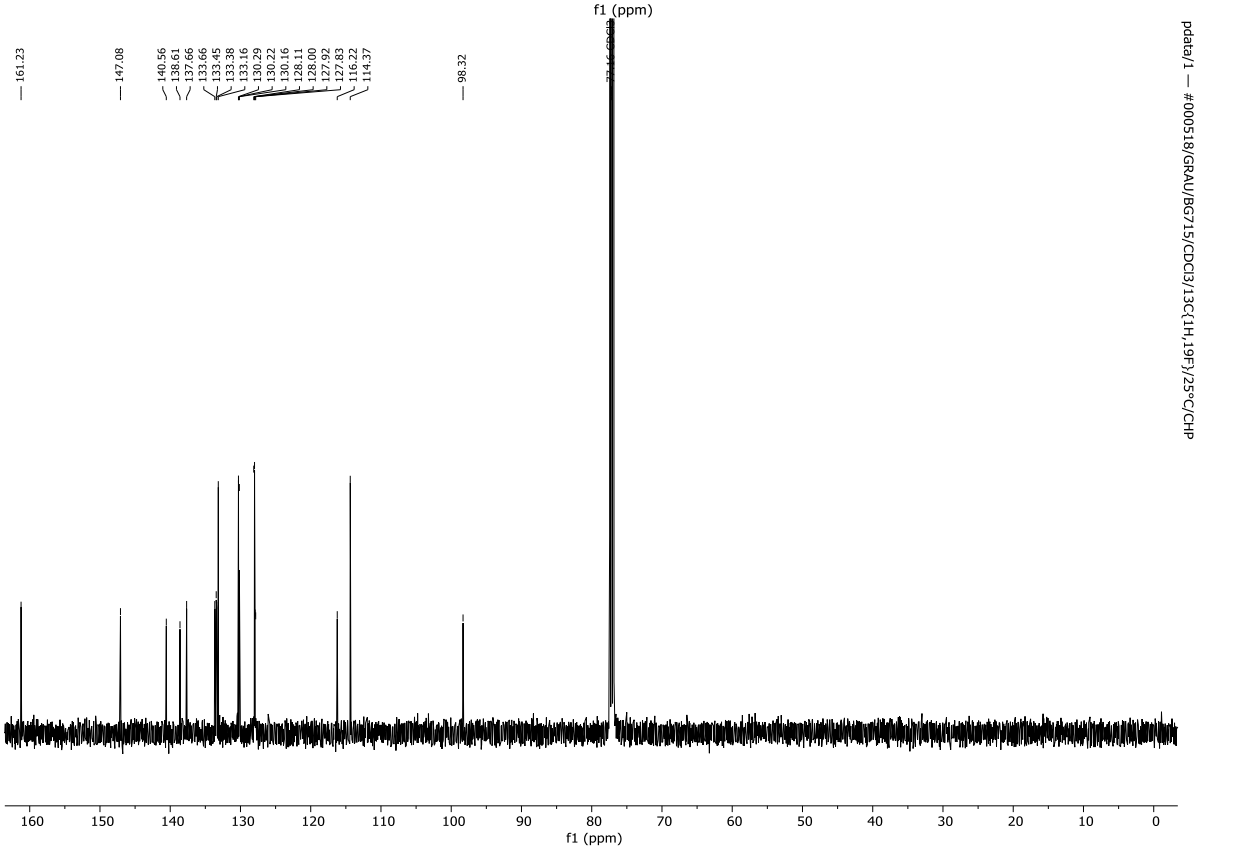


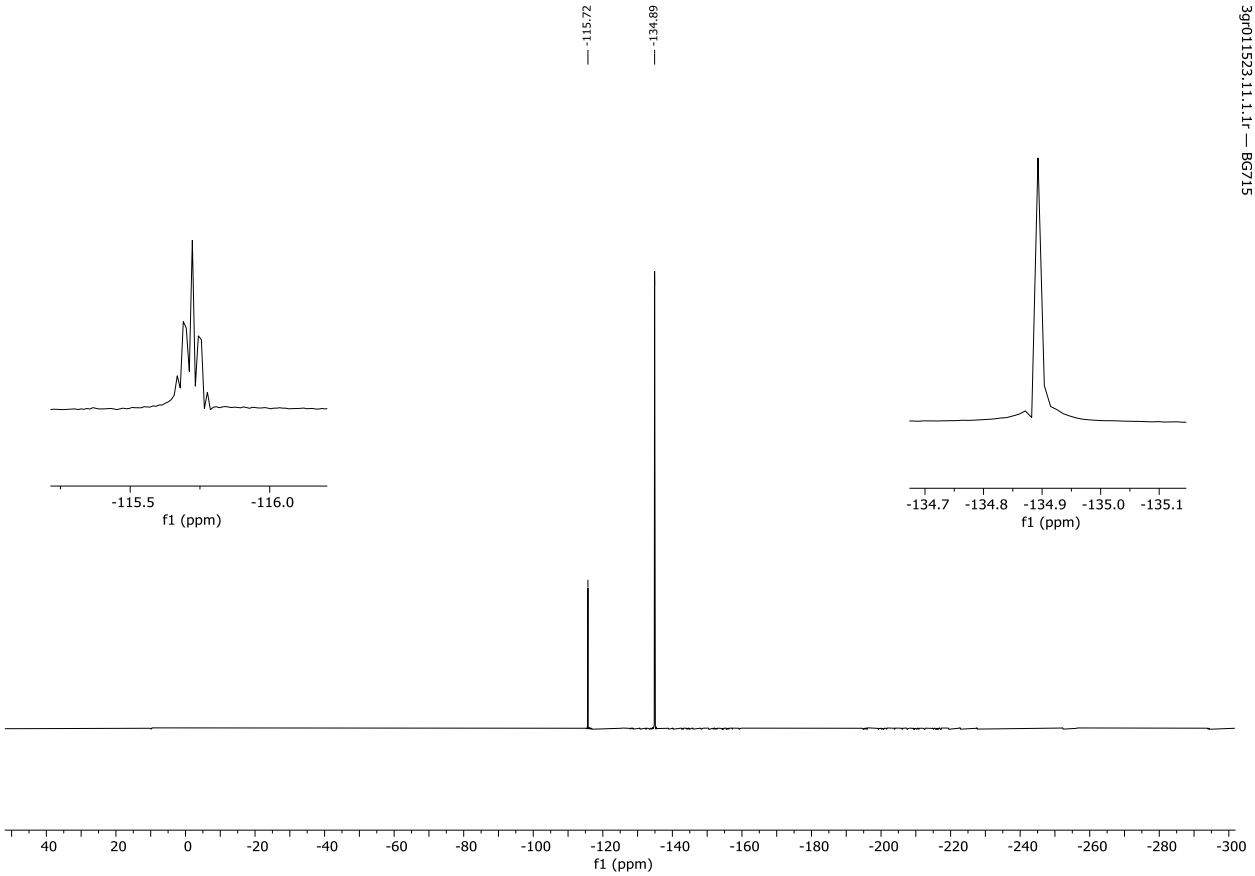



-135.02
-135.02
3gr011522.11.1.1r — BG714
-134.95 -134.97 -134.99 -135.01 -135.03 -135.05 -135.07
f1 (ppm)
-115 -116 -117 -118 -119 -120 -121 -122 -123 -124 -125 -126 -127 -128 -129 -130 -131 -132 -133 -134 -135 -136 -137 -138 -139 -140 -141 -142 -143 -144 -145 -146 -147 -148 -149
f1 (ppm)

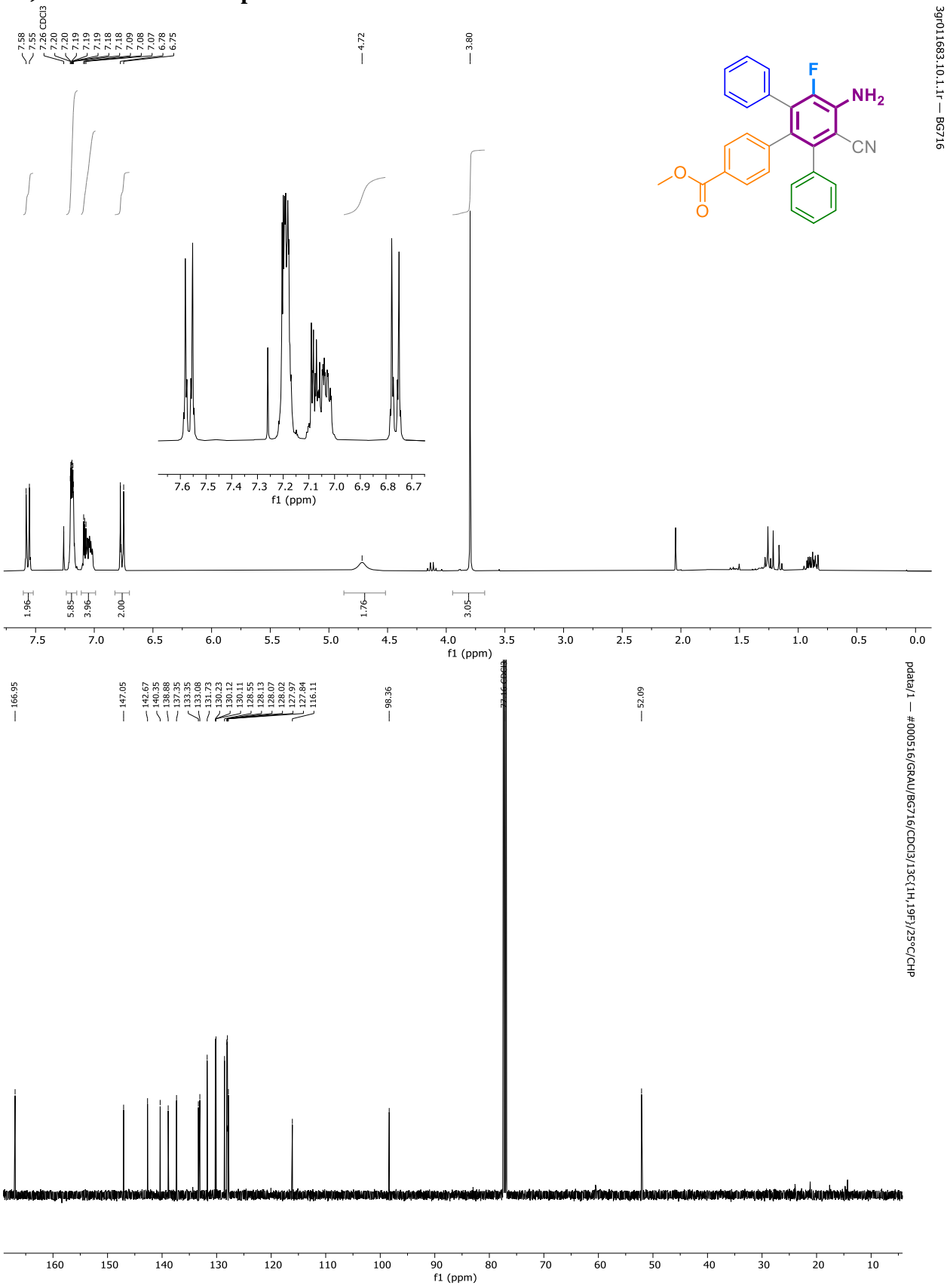
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 5h in $CDCl_3$

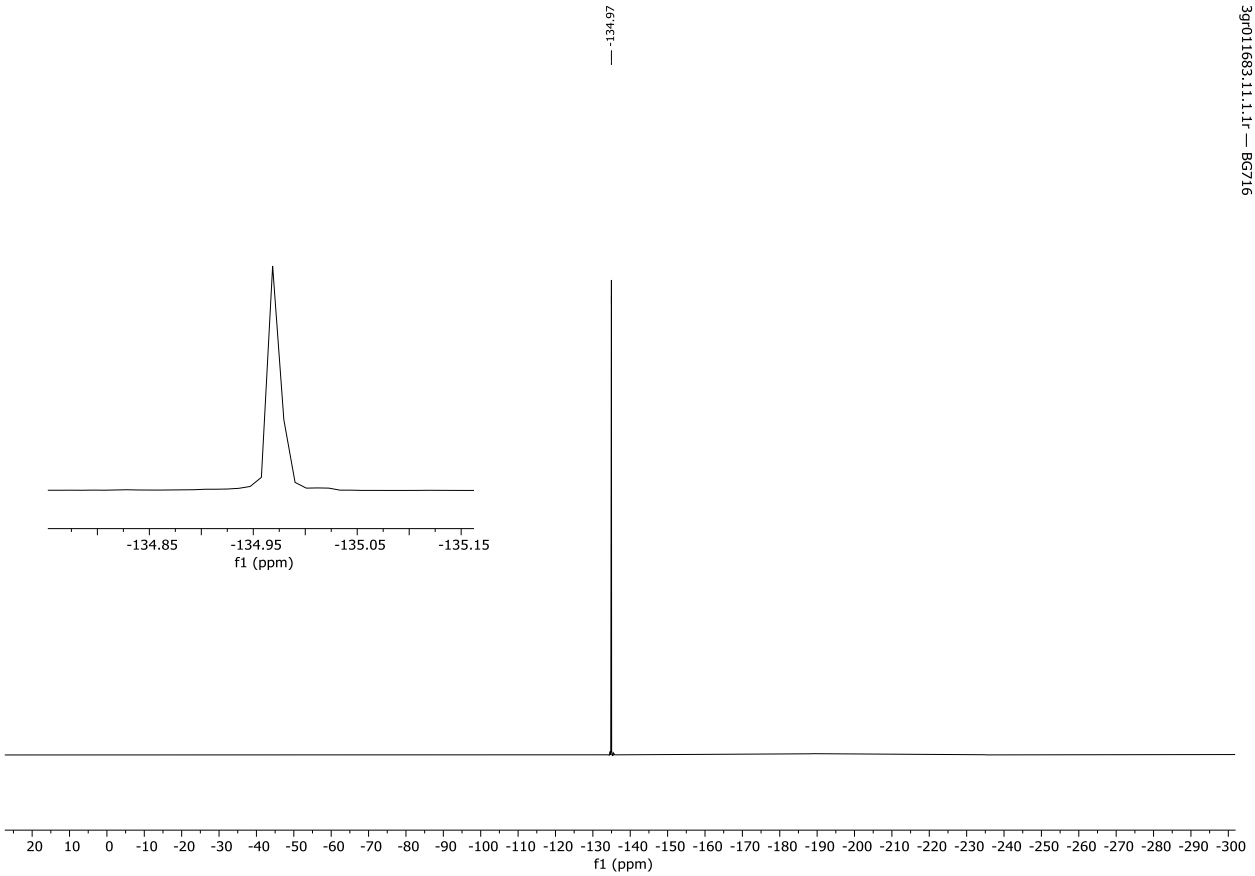




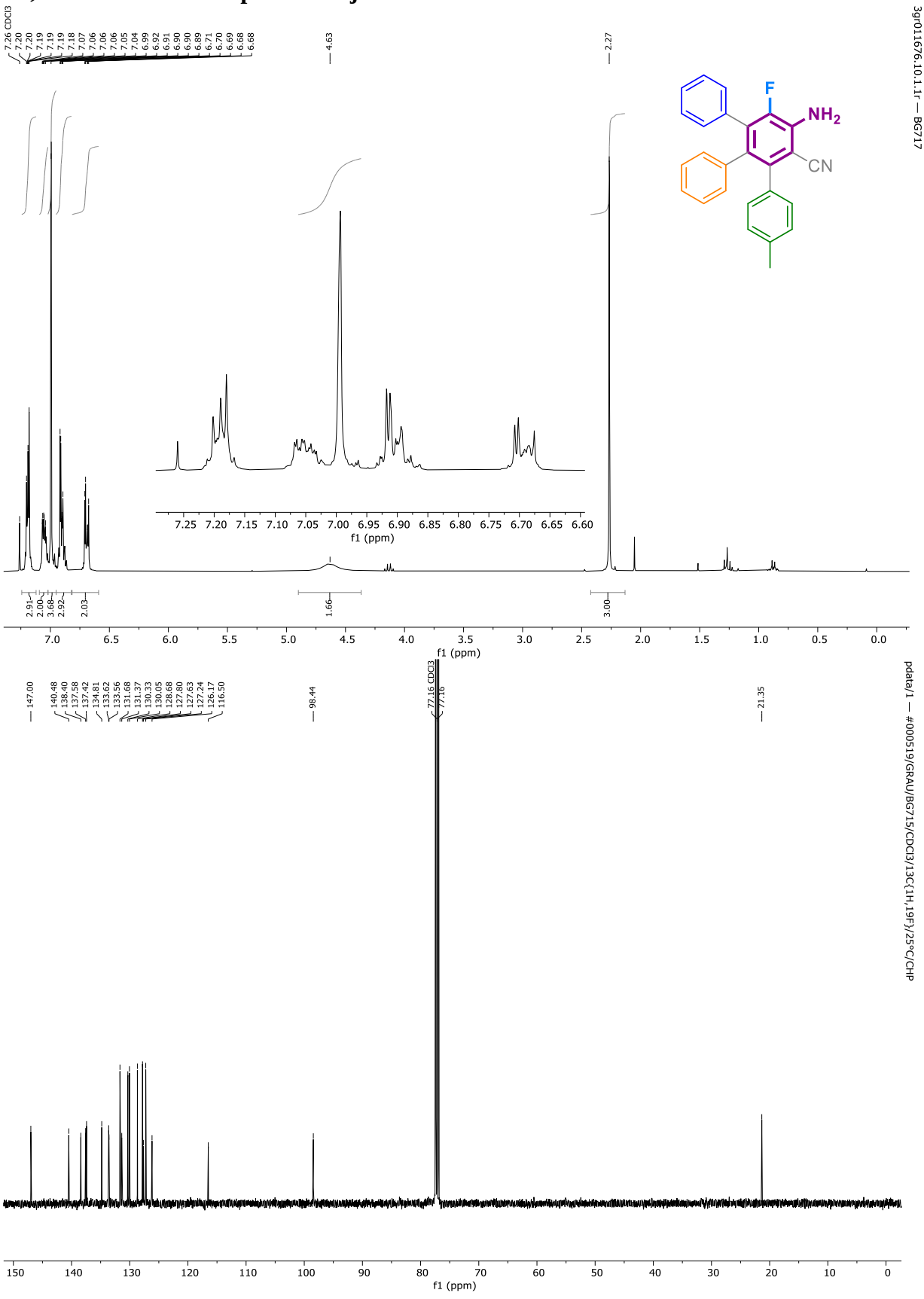

-115.72
-134.89
3gr011523.11.1.1r — BG715
-115.5
-116.0
f1 (ppm)
-134.7
-134.8
-134.9
-135.0
-135.1
f1 (ppm)
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280
-300
f1 (ppm)

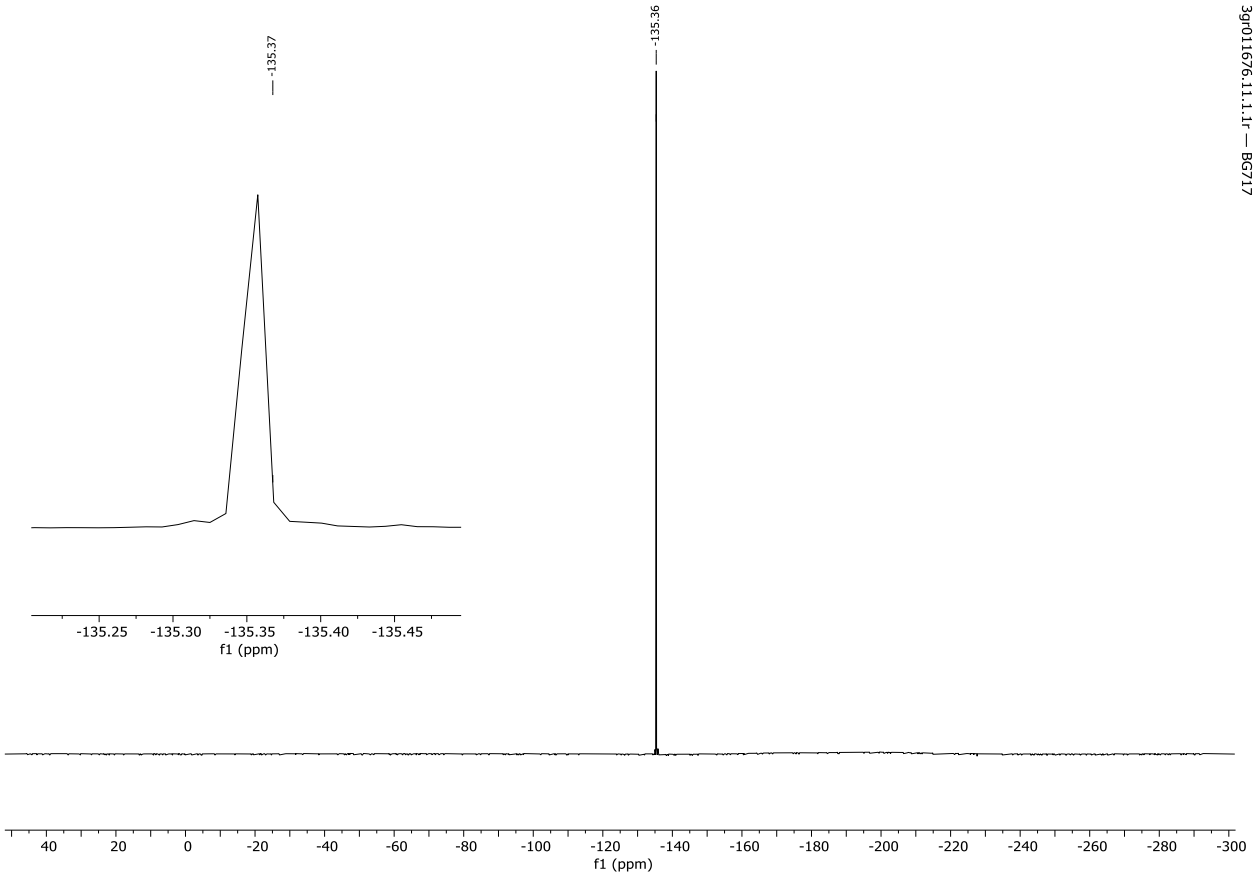
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 5i in $CDCl_3$



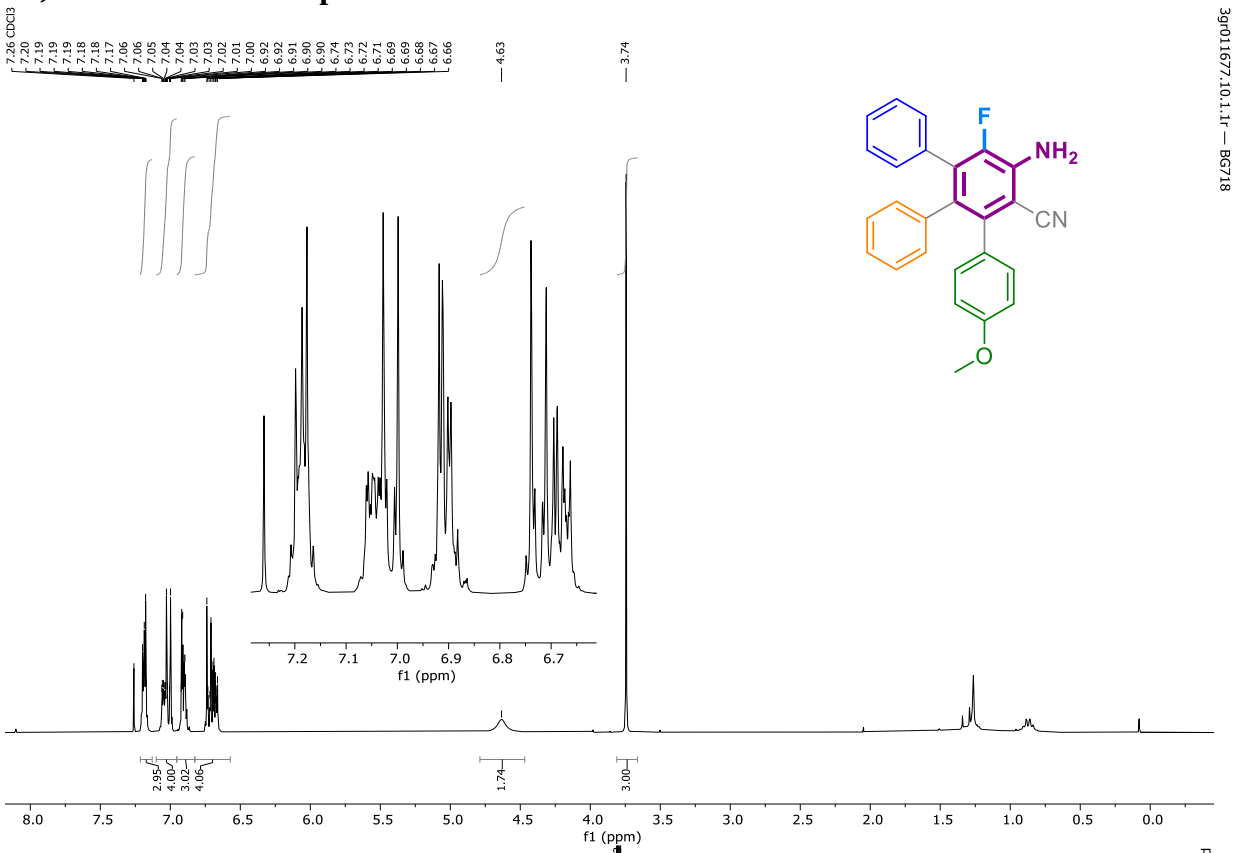

— -134.97
3gr011683.11.1.1r — BG716
-134.85
-134.95
-135.05
-135.15
f1 (ppm)
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250 -260 -270 -280 -290 -300
f1 (ppm)

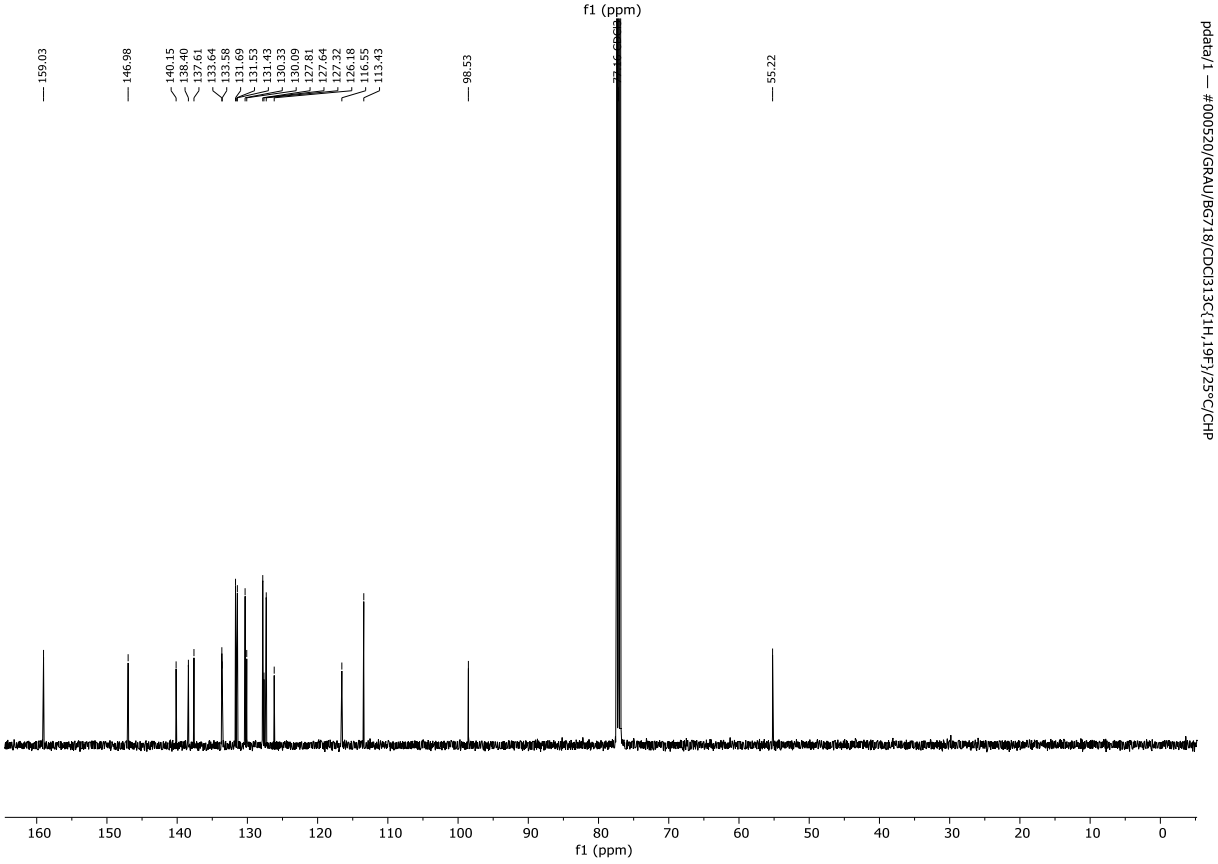
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 5j in $CDCl_3$

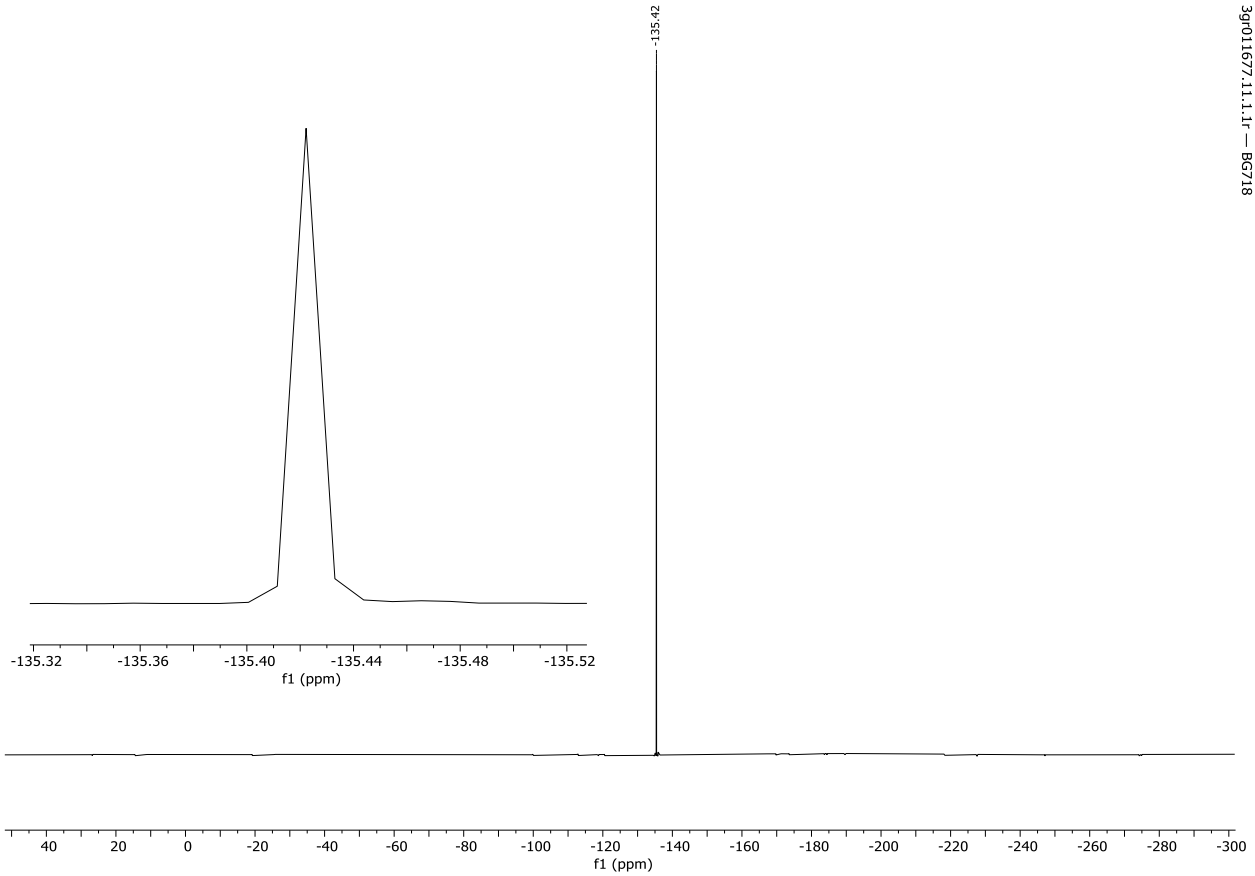



-135.37
-135.36
3gr011676.11.1.1r — BG717
-135.25
-135.30
-135.35
-135.40
-135.45
f1 (ppm)
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280
-300
f1 (ppm)

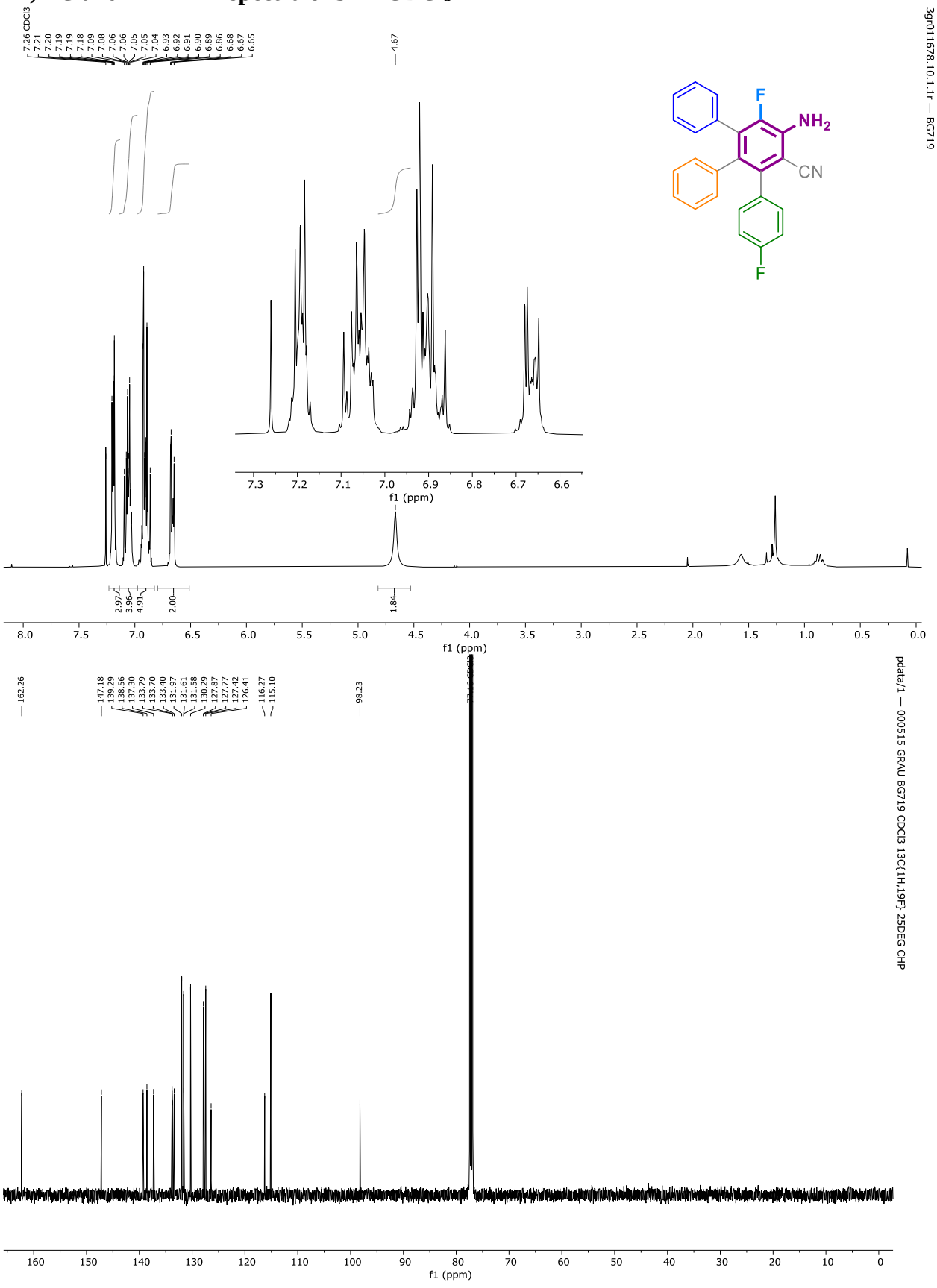
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 5k in $CDCl_3$

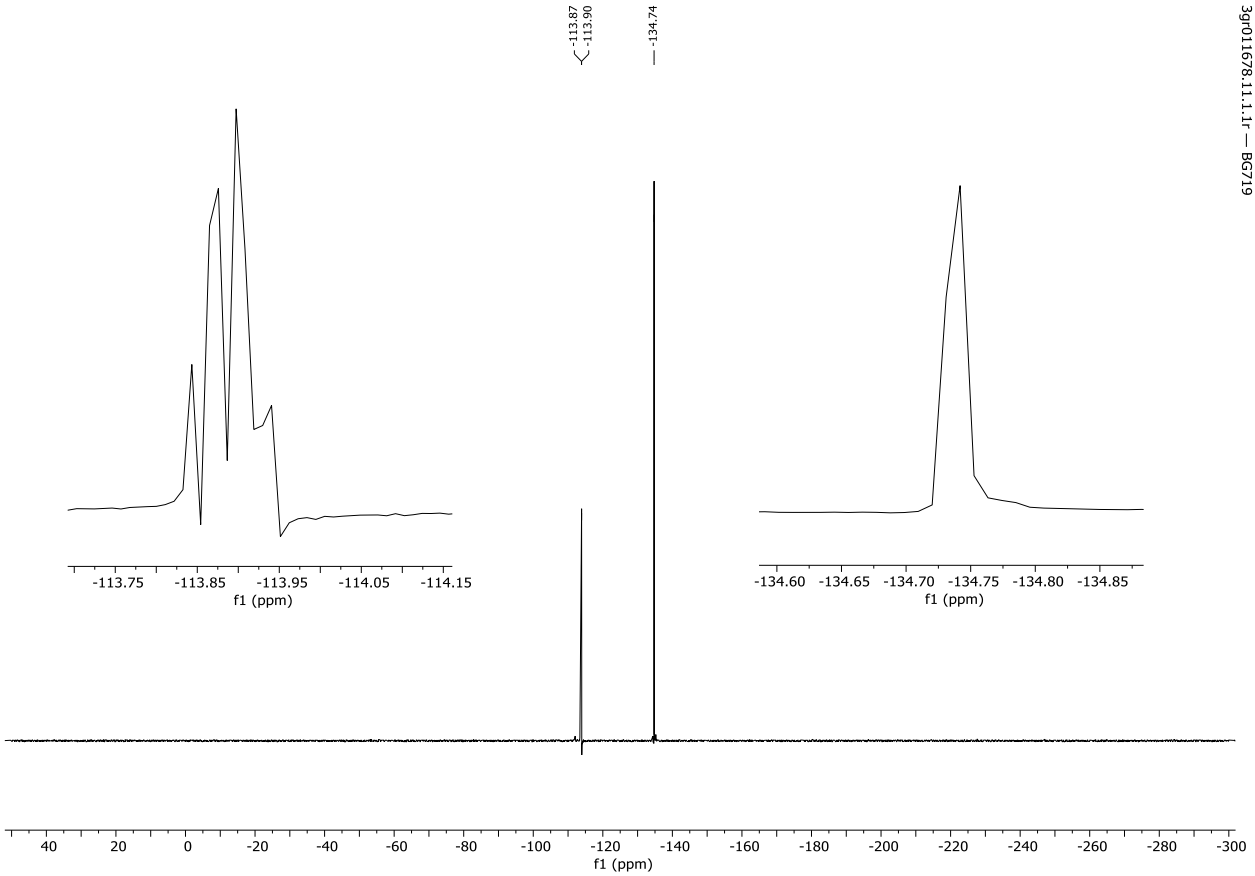




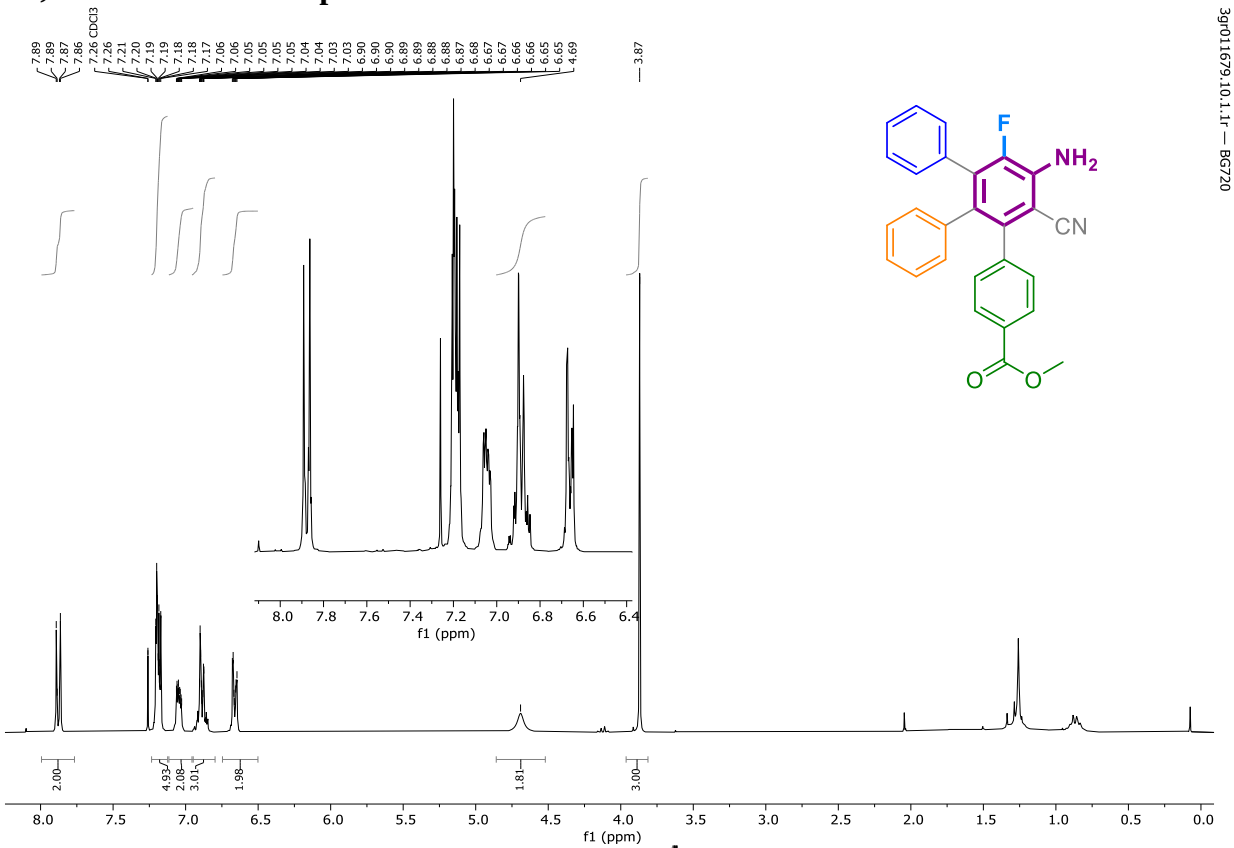

-135.42
3gr01677.11.1.1r — BG718
-135.32
-135.36
-135.40
-135.44
-135.48
-135.52
f1 (ppm)
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280
-300
f1 (ppm)

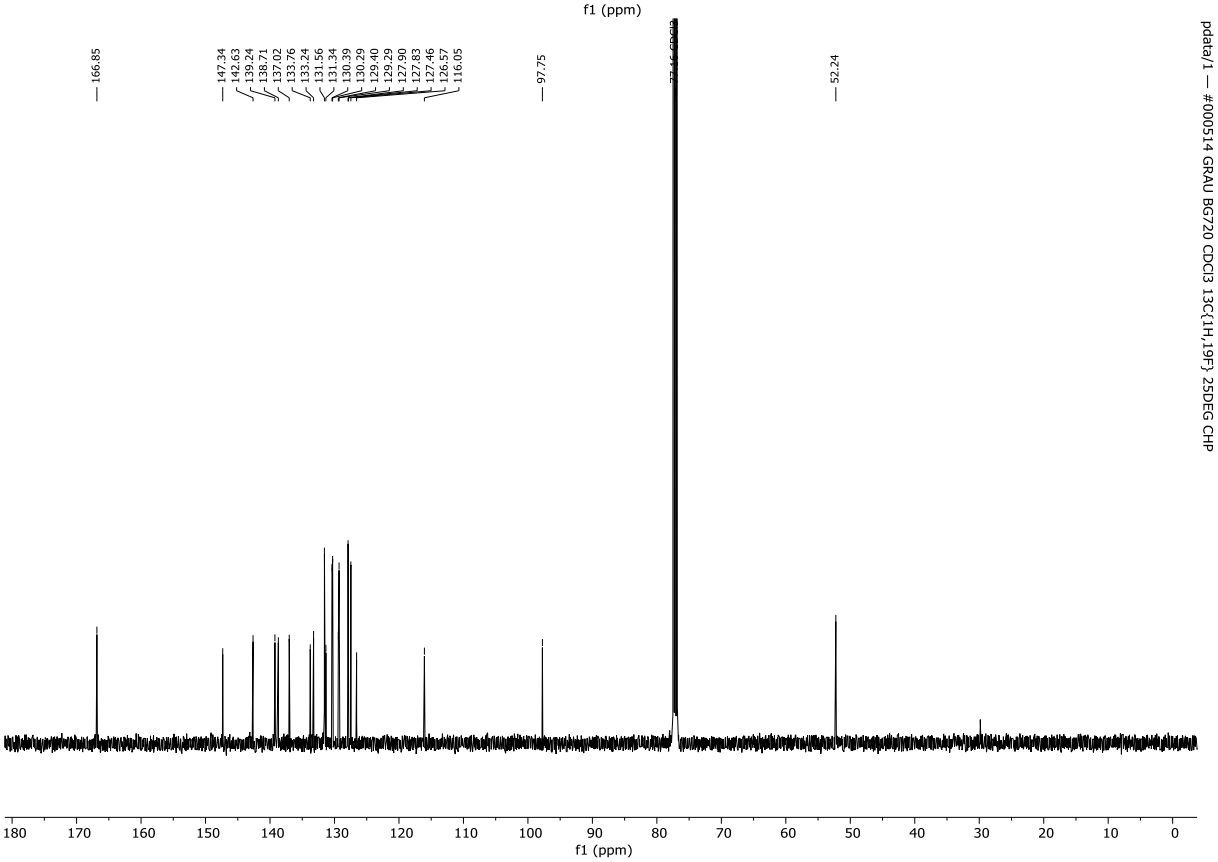
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 5l in $CDCl_3$

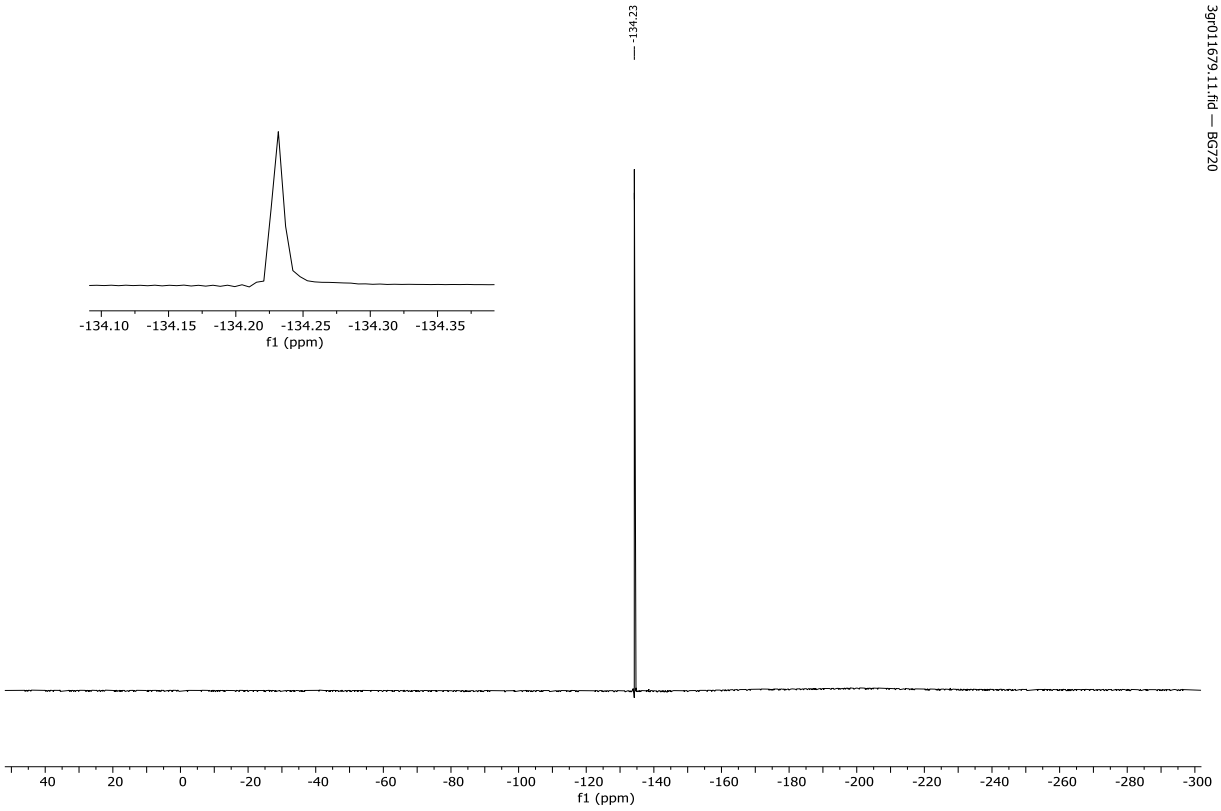



-113.87
-113.90
-134.74
3gr011678.11.1.1r — BG719
-113.75
-113.85
-113.95
-114.05
-114.15
f1 (ppm)
-134.60
-134.65
-134.70
-134.75
-134.80
-134.85
f1 (ppm)
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280
-300
f1 (ppm)

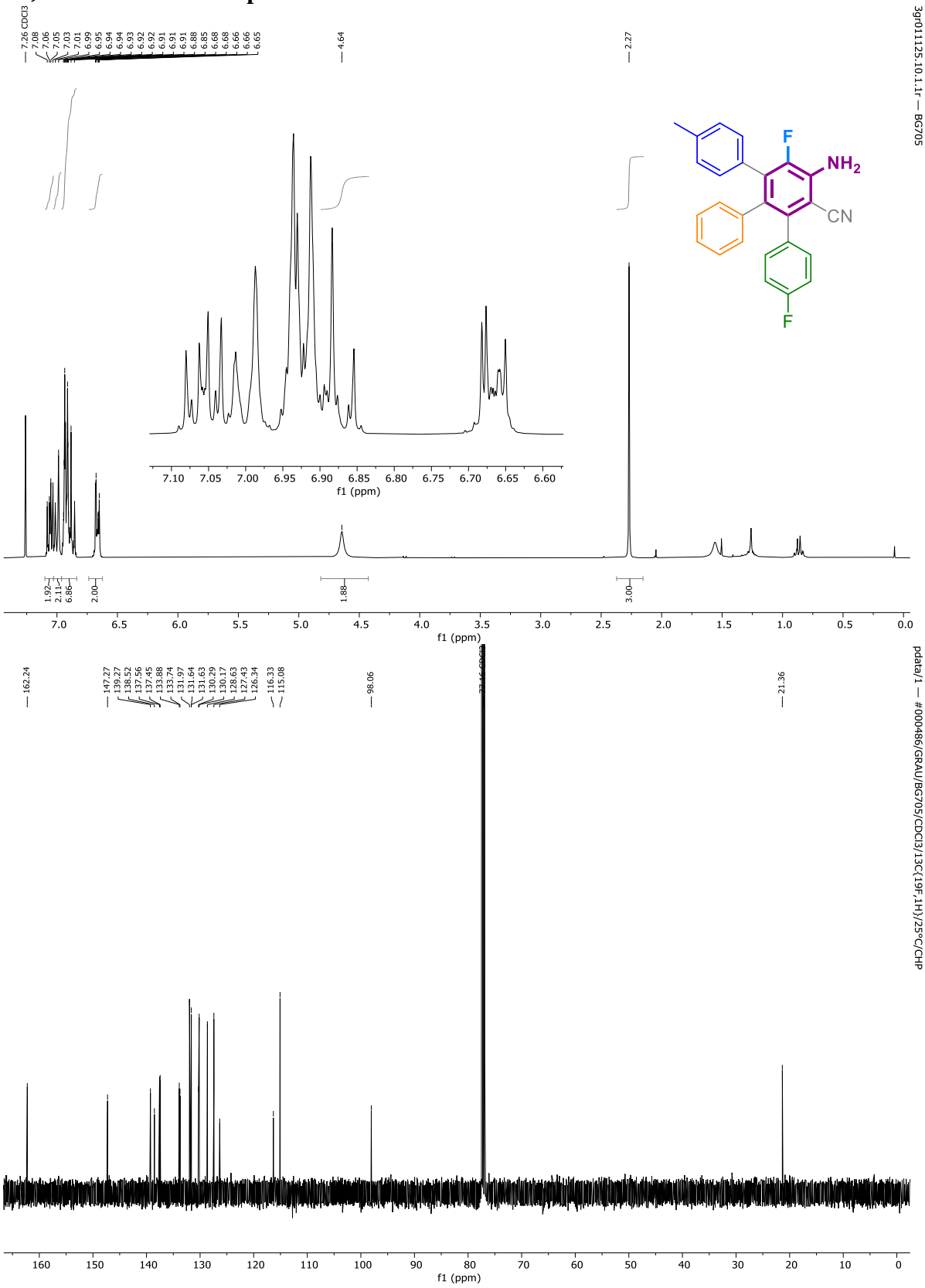
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 5m in $CDCl_3$

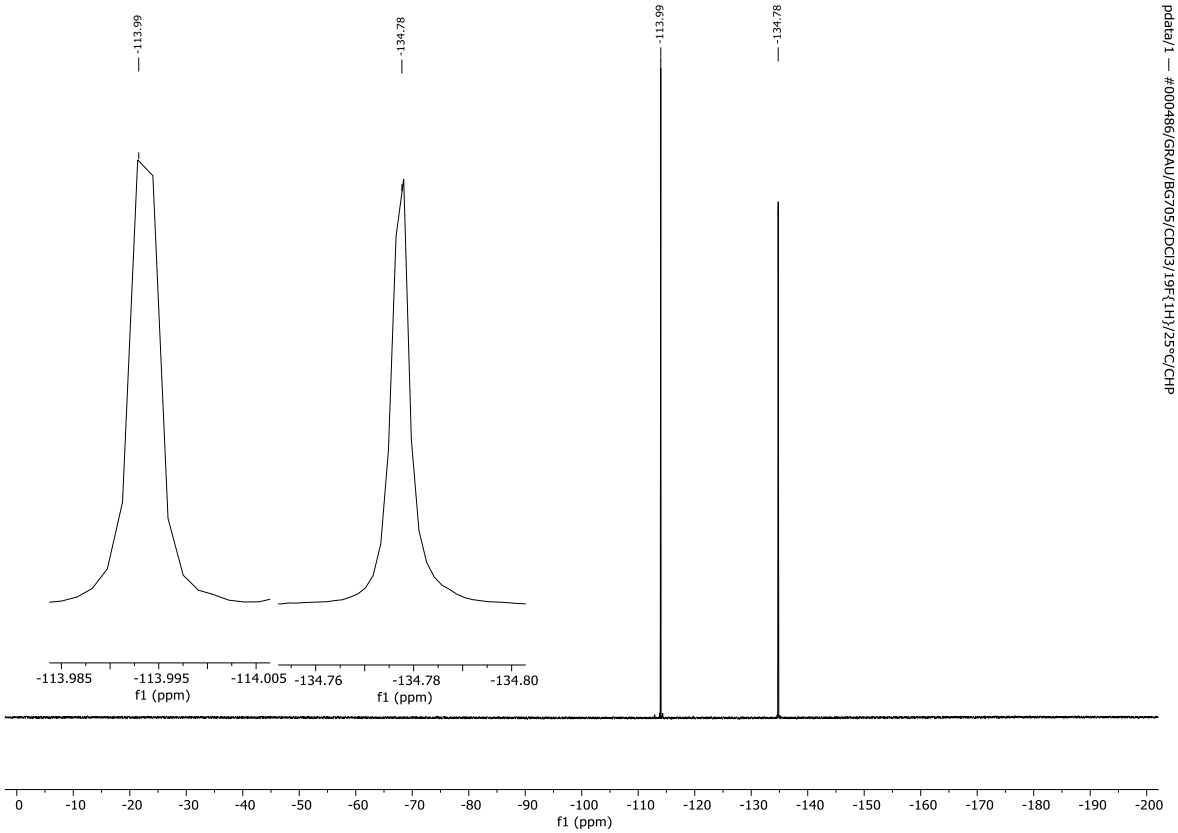




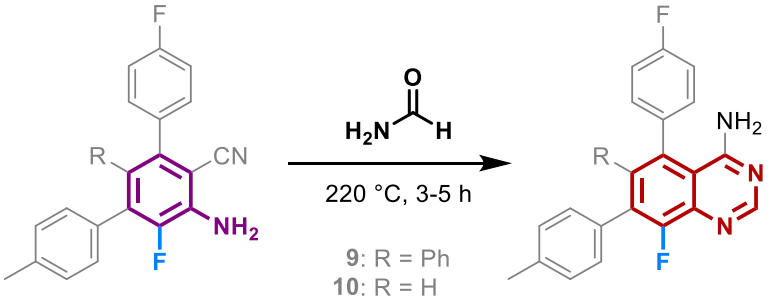

-134.23
3gr01679.11.fid — BG720
-134.10
-134.15
-134.20
-134.25
-134.30
-134.35
f1 (ppm)
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280
-300
f1 (ppm)

^{1}H, ^{13}C and ^{19}F-NMR-spectra of 5n in $CDCl_3$




-113.99
-134.78
-113.99
-134.78
pdata/1 — #000486/GRAU/BG705/CDCl3/19F{1H}/25°C/CHP
-113.985
-113.995
-114.005
f1 (ppm)
-134.76
-134.78
-134.80
f1 (ppm)
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

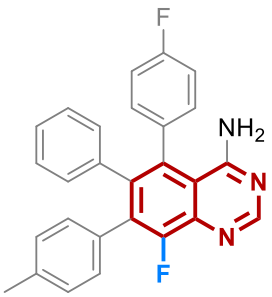
Synthesis of quinazolines 9 and 10



In a one neck flask equipped with reflux condenser, fluoro-derivative **3j** or **5n** (1.00 equiv.) was suspended in formamide (83.0 equiv.) and the resulting mixture was heated to 220°C for 3 – 5 h. The suspension turned clear and dark over time. After TLC indicated complete consumption of starting material, the mixture was allowed to cool down, and poured into ice water. The resulting precipitate was incorporated with DCM. After extracting the aqueous phase four additional times with DCM, the organic phases were collected, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified *via* column chromatography (DCM : acetone = 5 : 1) to yield the desired quinazoline derivative as off-white crystalline solids in 77-85% yield.

8-fluoro-5-(4-fluorophenyl)-6-phenyl-7-(*p*-tolyl)quinazolin-4-amine **9**

Off-white, crystalline solid, 181 mg, 427 µmol, 85% yield.



$C_{27}H_{19}F_2N_3$
MW: 423.47

^{1}H NMR (500 MHz, Methylene Chloride-d_2) δ = 8.58 (d, J = 0.4 Hz, 1H), 7.20 – 7.13 (m, 2H), 7.03 (d, J = 0.8 Hz, 4H), 6.99 – 6.91 (m, 5H), 6.82 – 6.72 (m, 2H), 2.27 (s, 3H).

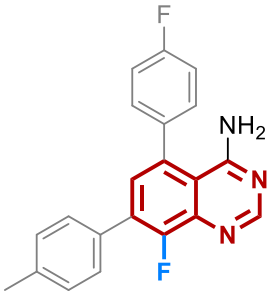
^{13}C NMR (126 MHz, Methylene Chloride-d_2) δ = 162.77, 161.68, 155.99, 154.35, 141.59, 141.01, 138.55, 137.92, 135.47, 132.93, 132.39, 132.03, 131.60, 131.33, 130.69, 128.95, 127.53, 126.73, 116.00, 113.65, 21.46.

^{19}F NMR (471 MHz, Methylene Chloride-d_2) δ = -113.53, -125.93.

HR-MS (APPI positive mode): *m/z* = calc. for ($[M]^+$): 424.1620, found: 424.1629.

8-fluoro-5-(4-fluorophenyl)-7-(*p*-tolyl)quinazolin-4-amine **10**

Off-white, crystalline solid, 57.2 mg, 165 µmol, 77% yield.



$C_{21}H_{15}F_2N_3$
MW: 347.37

^{1}H NMR (500 MHz, Methylene Chloride-d_2) δ = 8.58 (s, 1H), 7.61 – 7.55 (m, 3H), 7.50 – 7.43 (m, 2H), 7.34 – 7.30 (m, 2H), 7.29 – 7.19 (m, 2H), 2.42 (d, J = 0.7 Hz, 3H).

^{13}C NMR (126 MHz, Methylene Chloride-d_2) δ = 163.53, 161.40, 156.13, 154.03, 142.78, 139.40, 136.68, 133.95, 132.09, 131.79, 130.11, 129.97, 129.94, 129.61, 116.51, 112.80, 21.55.

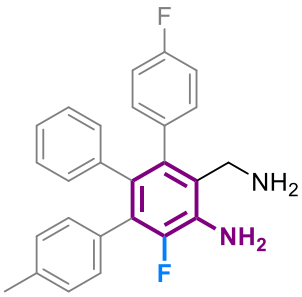
^{19}F NMR (471 MHz, Methylene Chloride-d_2) δ = -113.28, -130.99.

HR-MS (APPI): *m/z* = calc. for ($[M]^+$): 348.1307, found: 348.1307.

Synthesis of compounds 11-18

3'-(aminomethyl)-4",5'-difluoro-6'-(*p*-tolyl)-[1,1':2',1"-terphenyl]-4'-amine **11**

Off-white solid, 241 mg, 602 µmol, 95% yield.



$C_{26}H_{22}F_2N_2$
MW: 400.47

In a two-neck flask equipped with a septum and a reflux condenser, fluorine derivate **5n** (250 mg, 631 µmol, 1.00 equiv.) was dissolved in 4 ml dry THF, and dimethylsulfate-borane-diethyl ether complex (192 mg, 239 µl, 2.52 mmol, 4.00 equiv.) was added carefully. The resulting mixture was heated to 70 °C for 3 h. After cooling to 0 °C with an ice bath, a mixture of water (6.5 ml) and HCl (6 M, 1.5 ml) was added carefully (strong bubbling observed!) under N_2-atmosphere. As soon as the bubbling abated, the reaction mixture was heated to 95 °C for 1 h, and after cooling to room temperature, poured onto NaOH solution (1 M, 55 ml). A voluminous precipitate formed, additionally the pH was checked to confirm a basic solution. The suspension was extracted 3x with DCM (400 ml, the product is very insoluble), the organic phases were combined, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to obtain the desired product as an off-white powder in satisfying purity (241 mg, 602 µmol, 95% yield).

Very bad solubility! Decent solubility in DCM/MeOH mixture or DMSO

^{1}H NMR (600 MHz, Acetonitrile-d_3) δ = 7.08 – 6.94 (m, 6H), 6.91 – 6.83 (m, 5H), 6.82 – 6.74 (m, 2H), 5.00 (s, 2H), 3.54 (s, 2H), 2.23 (s, 3H) ppm.

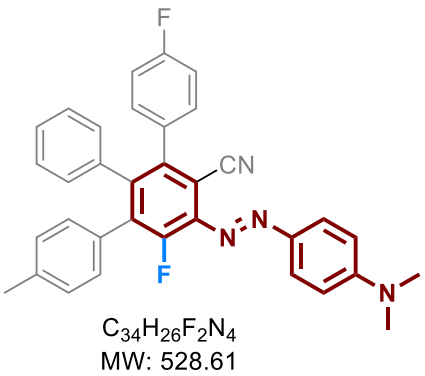
^{13}C NMR (151 MHz, Acetonitrile-d_3) δ = 162.18 (d, J = 243.2 Hz), 149.77, 148.22, 140.78 (d, J = 2.4 Hz), 137.49 (d, J = 3.2 Hz), 137.39, 137.06 (d, J = 3.3 Hz), 135.51 (d, J = 14.5 Hz), 133.22 (d, J = 8.0 Hz), 132.78, 131.51 (d=1.0 Hz), 131.44, 129.09, 128.13 (d, J = 13.8 Hz), 127.61, 127.05 (d, J = 3.9 Hz), 126.37, 114.81 (d, J = 21.4 Hz), 41.88 (d, J = 2.8 Hz), 21.08 ppm.

^{19}F NMR (471 MHz, Acetonitrile-d_3) δ = -118.37, -139.74 ppm.

HR-MS (ESI positive mode): m/z = calc. for ($[M+H]^+$): 401.182382, found: 401.182219.

(*E*)-4'-((4-(dimethylamino)phenyl)diazenyl)-4'',5'-difluoro-6'-(*p*-tolyl)-[1,1':2',1''-terphenyl]-3'-carbonitrile **12**

Red solid, 12.9 mg, 24.4 µmol 27% yield.



$C_{34}H_{26}F_2N_4$
MW: 528.61

To a solution of **5n** (36.4 mg, 92 µmol) in 3.5 ml MeCN *tert*-butyl nitrite (17.8 µl, 0.15 mmol) and *N,N*-dimethylaniline (15.1 µl, 0.12 mmol) was added successively while cooling to 0°C. After removing the ice bath, the red solution was stirred at rt overnight. The solvent was removed, and the raw mixture was purified by column chromatography (SiO_2, Hexane : EtOAc = 8 : 1) and precipitation from chloroform and hexane. The product was obtained as a red solid (12.9 mg, 24.4 µmol, 27%).

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.03 – 7.92 (m, 2H), 7.18 – 7.05 (m, 2H), 7.03 – 6.95 (m, 7H), 6.94 – 6.86 (m, 2H), 6.79 – 6.70 (m, 4H), 3.13 (s, 6H), 2.27 (s, 3H) ppm.

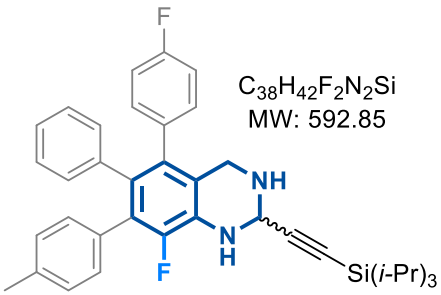
^{13}C NMR (126 MHz, Chloroform-*d*) *δ* = 162.4, 153.5, 151.8, 144.5, 143.6, 142.4, 141.6, 137.7, 137.3, 135.3, 133.3, 132.2, 131.0, 130.3, 130.1, 128.7, 127.5, 126.8, 126.4, 116.2, 115.2, 112.0, 107.1, 40.7, 21.4 ppm.

^{19}F NMR (471 MHz, Chloroform-*d*) *δ* -113.74 (m), -124.34 (s) ppm.

HR-MS (APPI positive mode): *m/z* = calc. for ($[M+H]^+$): 529.2198, found: 529.2205.

8-fluoro-5-(4-fluorophenyl)-6-phenyl-7-(*p*-tolyl)-2-((triisopropylsilyl)ethynyl)-1,2,3,4-tetrahydroquinazoline **13**

Sticky colorless oil, 11.9 mg, 20.2 µmol, 16% yield.



Diamine **11** (50.0 mg, 125 µmol, 1.00 equiv.) and 3- (triisopropylsilyl)propiolaldehyde (26.3 mg, 125 µmol 1.00 equiv.) were dissolved in 4 ml chloroform and SiO_2 (37.5 mg, 634 µmol, 5.00 equiv.) was added. The resulting suspension was stirred for 24 h, until TLC indicated full consumption of the starting material. The yellowish suspension was filtered, and the filter cake was washed with chloroform. After evaporation of the organic solvent, the crude mixture was purified *via* column chromatography (Hexane : EtOAc = 16 : 1) to yield **13** as sticky colorless oil in 16% yield (11.9 mg, 20.2 µmol).
^{1}H NMR (300 MHz, Acetone-d_6) δ = 7.14 – 6.58 (m, 13H), 5.66 (s, 1H), 5.21 – 5.08 (m, 1H), 3.99 (d, J = 17.0 Hz, 1H), 3.56 (d, J = 17.0 Hz, 1H), 2.21 (s, 3H), 1.07 (s, 21H) ppm.

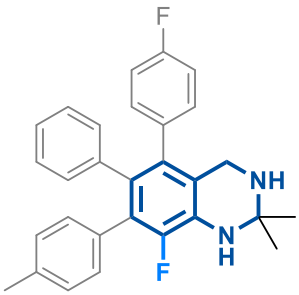
^{13}C NMR (126 MHz, Acetone-d_6) δ = 162.17, 148.49, 140.22, 136.79, 136.34, 134.71, 133.07, 132.85, 132.78, 132.57, 131.43, 128.92, 127.56, 127.23, 126.20, 121.47, 115.28, 115.09, 108.44, 101.46, 83.82, 21.30, 18.92, 18.90, 11.89 ppm.

^{19}F NMR (471 MHz, Acetone-d_6) δ = -117.79, -141.23 ppm.

HR-MS (APPI positive mode): *m/z* = calc. for ($[M+H]^+$): 593.3158, found: 593.3161.

8-fluoro-5-(4-fluorophenyl)-2,2-dimethyl-6-phenyl-7-(*p*-tolyl)-1,2,3,4-tetrahydroquinazoline **14**

Off-white solid, 24.4 mg, 55.4 µmol, 74% yield.



$C_{29}H_{26}F_2N_2$
MW: 440.54

Diamine **11** (30 mg, 74.9 µmol, 1.00 equiv.) was mixed with acetone (21 ml) and SiO_2 (45.0 mg, 749 µmol, 10.0 equiv.), the resulting mixture was heated to 50 °C for 3 d, till TLC indicated the complete conversion of the starting material. The silica was filtered off, washed three times with acetone and the solvent removed under reduced pressure. The off-white residue could be identified as desired product, which was obtained in 74% yield (24.4 mg, 55.4 µmol).

VERY BAD SOLUABILITY!

^{1}H NMR (300 MHz, Acetone-d_6) δ = 7.07 – 6.99 (m, 2H), 6.97 – 6.82 (m, 9H), 6.78 – 6.73 (m, 2H), 5.25 (s, 1H), 3.62 (s, 2H), 2.21 (s, 3H), 1.41 (s, 6H) ppm.

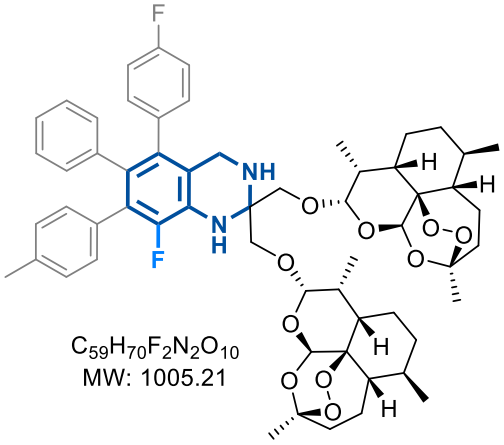
^{13}C NMR (126 MHz, Acetone-d_6) δ = 162.13, 147.87, 140.42, 136.68, 136.66, 134.60, 133.32, 132.94, 132.77, 132.25, 131.49, 129.36, 128.90, 127.54, 127.10, 126.05, 119.97, 115.11, 64.54, 42.57, 28.50, 21.08 ppm.

^{19}F NMR (283 MHz, Acetone-d_6) δ = -117.79 – -117.95 (m), -142.02 ppm.

HR-MS (APPI positive mode): *m/z* = calc. for ($[M]^+$): 441.2137, found: 441.2134.

8-fluoro-5-(4-fluorophenyl)-6-phenyl-7-(*p*-tolyl)-2,2-bis((((3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-3,6,9-trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromen-10-yl)oxy)methyl)-1,2,3,4-tetrahydroquinazoline **15**

White solid, 14.0 mg, 13.9 µmol, 16% yield.



Diamine **11** (35.0 mg, 87.4 µmol, 1.00 equiv.) and 1,3-bis(((3R,5aS,6R,8aS,9R,10S,12R,12aR)-3,6,9 -trimethyldecahydro 12H-3,12-epoxy[1,2] dioxepino[4,3-i]isochromen-10-yl)oxy)propan-2-one (54.4 mg, 87.4 µmol, 1.00 equiv.) were dissolved in 4 ml $CHCl_3$ and SiO_2 (26.3 mg, 437 µmol, 5.00 equiv.) was added. The resulting suspension was stirred overnight until TLC indicated the consumption of the diamine, afterwards the solvent was evaporated under reduced pressure and the resulting mixture adsorbed on silica was purified *via* column chromatography to obtain the desired product in 16% yield (14.0 mg, 13.9 µmol).

^{1}H NMR (500 MHz, Methylene Chloride-d_2) δ 7.01 – 6.94 (m, 6H), 6.92 – 6.87 (m, 3H), 6.87 – 6.81 (m, 2H), 6.79 – 6.69 (m, 2H), 5.41 (s, 1H), 5.37 (s, 1H), 4.85 (d, *J* = 3.5 Hz, 1H), 4.79 (d, *J* = 3.5 Hz, 1H), 4.65 (s, 1H), 4.04 (d, *J* = 9.6 Hz, 1H), 3.82 (d, *J* = 10.1 Hz, 1H), 3.64 (d, *J* = 3.7 Hz, 2H), 3.59 (d, *J* = 10.1 Hz, 1H), 3.35 (d, *J* = 9.6 Hz, 1H), 2.66 – 2.53 (m, 2H), 2.40 – 2.28 (m, 2H), 2.25 (s, 3H), 2.05 – 1.97 (m, 2H), 1.92 – 1.82 (m, 2H), 1.84 – 1.42 (m, 10H), 1.39 – 1.21 (m, 10H), 0.99 – 0.88 (m, 14H).

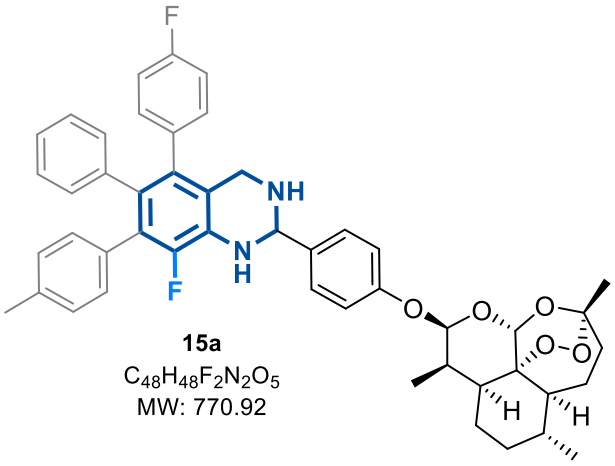
^{13}C NMR (126 MHz, CD_2Cl_2) δ 161.93, 147.65, 139.81, 136.98, 135.69, 134.24, 132.50, 132.45, 131.12, 130.43, 130.32, 128.68, 127.30, 127.21, 125.88, 120.53, 114.95, 104.54, 104.50, 103.41, 103.09, 88.53, 88.49, 83.11, 81.44, 81.43, 71.02, 70.11, 68.59, 44.85, 44.83, 41.44, 41.37, 37.99, 37.00, 35.17, 34.41, 31.56, 28.96, 26.42, 25.38, 25.17, 25.14, 24.15, 21.40, 21.12, 20.74, 20.72, 17.83, 17.77, 14.97, 13.47, 13.41, 8.23.

^{19}F NMR (471 MHz, CD_2Cl2) δ -116.93, -142.41.

HR-MS (APPI): *m/z* = calc. for ($[M]^+$): 1005.5071, found: 1005.5070.

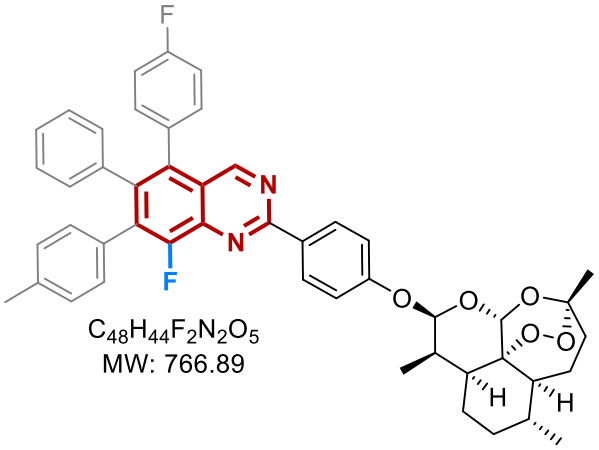
8-fluoro-5-(4-fluorophenyl)-6-phenyl-7-(*p*-tolyl)-2-(4-(((3*S*,5a*R*,6*S*,8a*R*,9*S*,10*R*,12*S*,12a*S*)-3,6,9-trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromen-10-yl)oxy)phenyl)quinazoline **16**

White solid, 15.6 mg, 20.3 µmol, 63% yield.



15a
$C_{48}H_{48}F_2N_2O_5$
MW: 770.92

Diamine **11** (50.0 mg, 125 µmol, 1.00 equiv.), (10S)-10-(4-formylphenyl)-dihydroartemisinin (48.5 mg, 125 µmol, 1.00 equiv.) and SiO_2 (37.5 mg, 624 µmol, 5.00 equiv.) were suspended in 4 ml DCM and heated to 40 °C for two days, till TLC indicated the complete consumption of the starting material. The solvent was evaporated under reduced pressure and the resulting mixture adsorbed on silica was purified *via* column chromatography (Hexane : EtOAc = 10 : 1). To obtain the tetrahydro-quinazoline intermediate **15a** in 52% yield (50.1 mg, 65.0 µmol).



$C_{48}H_{44}F_2N_2O_5$
MW: 766.89

Intermediate **15a** (25.0 mg, 32.4 µmol, 1.00 equiv.) and Rose Bengal (3.16 mg, 1.62 µmol, 0.10 equiv.) were dissolved in 2 ml DMF under oxygen atmosphere and stirred overnight irradiated with white light at room temperature. The pink reaction mixture was poured onto a mixture of saturated NH_4Cl and water (1:1, 10 ml) and the aqueous phase was extracted 3 times with Et_2O (50 ml). The organic phases were combined, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The pure product was obtained *via* column chromatography (Hexane : EtOAc = 10 : 1) in 63% yield (15.6 mg, 20.3 µmol).

Modified after procedure.[25]

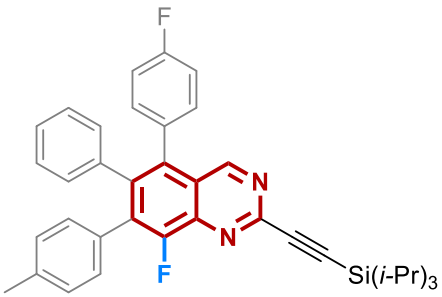
^{1}H NMR (500 MHz, Methylene Chloride-d_2) δ = 9.14 (d, J = 1.4 Hz, 1H), 8.65 – 8.59 (m, 2H), 7.28 – 7.20 (m, 2H), 7.17 – 7.13 (m, 2H), 7.08 (s, 4H), 7.04 – 6.96 (m, 5H), 6.90 – 6.83 (m, 2H), 5.62 (d, J = 3.5 Hz, 1H), 5.49 (s, 1H), 2.82 – 2.76 (m, 1H), 2.40 – 2.32 (m, 1H), 2.31 (s, 3H), 2.06 – 1.95 (m, 2H), 1.93 – 1.86 (m, 1H), 1.76 – 1.70 (m, 1H), 1.64 – 1.58 (m, 1H), 1.52 – 1.42 (m, 2H), 1.41 – 1.29 (m, 5H), 1.06 (d, J = 7.3 Hz, 3H), 1.03 (d, J = 7.4 Hz, 1H), 0.97 (d, J = 6.3 Hz, 3H) ppm.

^{13}C NMR (126 MHz, Methylene Chloride-d_2) δ = 162.60, 161.13, 160.62, 160.10, 153.98, 141.14, 140.88, 138.43, 138.09, 134.53, 133.54, 133.35, 132.62, 131.88, 131.72, 131.33, 130.85, 130.83, 129.02, 127.75, 126.99, 123.37, 117.09, 115.40, 104.70, 100.59, 88.90, 81.41, 53.17, 44.95, 38.00, 36.91, 35.22, 31.55, 26.32, 25.21, 25.04, 21.51, 20.64, 13.27 ppm.

^{19}F NMR (471 MHz, Methylene Chloride-d_2) δ = -115.40, -129.12 ppm.
HR-MS (ESI positive mode): *m/z* = calc. for ($[M+H]^+$): 767.329105, found: 767.329733.

8-fluoro-5-(4-fluorophenyl)-6-phenyl-7-(*p*-tolyl)-2-((triisopropylsilyl)ethynyl)quinazoline **17**

Off-yellow solid, 22.2 mg, 37.7 µmol, 30% yield.



$C_{38}H_{38}F_2N_2Si$
MW: 588.82

Diamine **11** (50.0 mg, 125 µmol, 1.00 equiv.) and 3-(triisopropylsilyl)propiolaldehyde (26.3 mg, 125 µmol, 1.00 equiv.) were dissolved in 1.5 ml DMF and Rose Bengal (6.08 mg, 6.24 µmol, 0.05 equiv.) was added, and the resulting mixture irradiated with white light source under oxygen atmosphere overnight. After TLC showed the consumption of the diamine, the pink reaction mixture was poured onto a mixture of saturated NH_4Cl and water (1:1, 15 ml) and the aqueous phase was extracted three times with Et_2O (70 ml). The organic phases were combined, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The pure product was obtained *via* column chromatography (Hexane : EtOAc = 16 : 1) in 30% yield (22.2 mg, 37.7 µmol).

^{1}H NMR (500 MHz, Acetone-d_6) δ = 9.04 (d, J = 1.5 Hz, 1H), 7.34 – 7.25 (m, 2H), 7.14 – 7.05 (m, 6H), 7.05 – 6.99 (m, 3H), 6.99 – 6.94 (m, 2H), 2.26 (s, 3H), 1.27 – 1.14 (m, 21H) ppm.

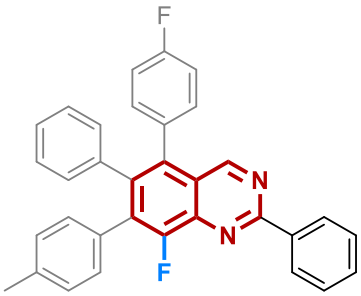
^{13}C NMR (126 MHz, Acetone-d_6) δ = 163.01, 160.27, 153.57, 149.37, 143.30, 140.77, 138.58, 138.30, 135.13, 134.37, 134.16, 132.72, 131.91, 131.44, 131.14, 129.35, 128.10, 127.58, 123.91, 115.71, 107.09, 90.95, 21.16, 18.96, 11.99 ppm.

^{19}F NMR (471 MHz, Acetone-d_6) δ = -115.75, -127.88 ppm.

HR-MS (APPI positive mode): *m/z* = calc. for ($[M+H]^+$): 589.2845, found: 589.2862.

8-fluoro-5-(4-fluorophenyl)-2,6-diphenyl-7-(*p*-tolyl)quinazoline **18**

White solid, 23.5 mg, 48.0 µmol, 65% yield.



$C_{33}H_{22}F_2N_2$
MW: 484.55

Diamine **11** (30.0 mg, 74.9 µmol, 1.00 equiv.) and benzaldehyde (7.95 mg, 7.64 µl, 74.9 µmol, 1.00 equiv.) were dissolved in 1 ml DMF and Rose Bengal (3.65 mg, 3.75 µmol, 0.05 equiv.) was added, and the resulting mixture irradiated with white light source under oxygen atmosphere overnight. After TLC showed the consumption of the diamine, the pink reaction mixture was poured onto a mixture of saturated NH_4Cl and water (1:1, 7 ml) and the aqueous phase was extracted 3 times with Et_2O (30 ml). The organic phases were combined, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The pure product was obtained *via* column chromatography (Hexane : EtOAc = 10 : 1) in 65% yield (23.5 mg, 48.0 µmol).

Modified after procedure.[25]

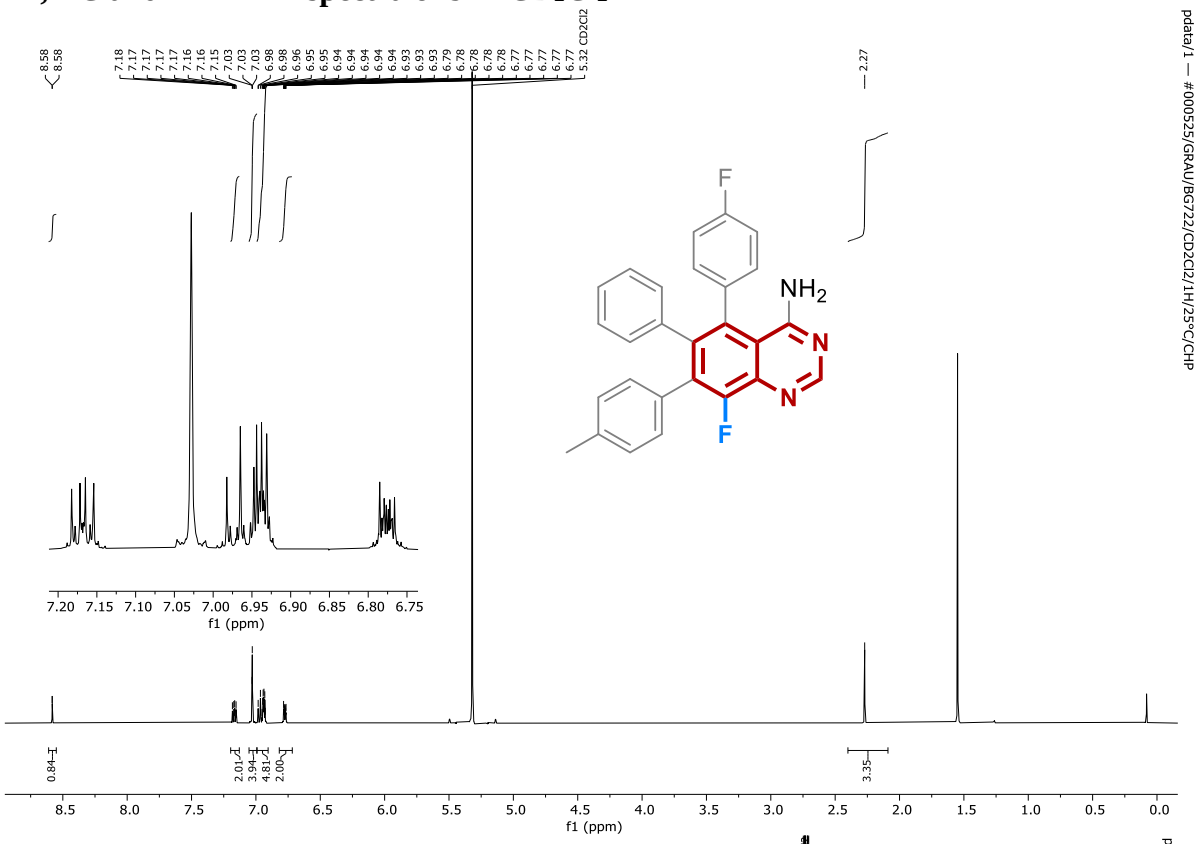
^{1}H NMR (500 MHz, Methylene Chloride-d_2) δ = 9.18 (d, J = 1.5 Hz, 1H), 8.70 – 8.62 (m, 2H), 7.59 – 7.50 (m, 3H), 7.21 – 7.13 (m, 2H), 7.08 (s, 4H), 7.04 – 6.95 (m, 5H), 6.90 – 6.84 (m, 2H), 2.31 (s, 3H) ppm.

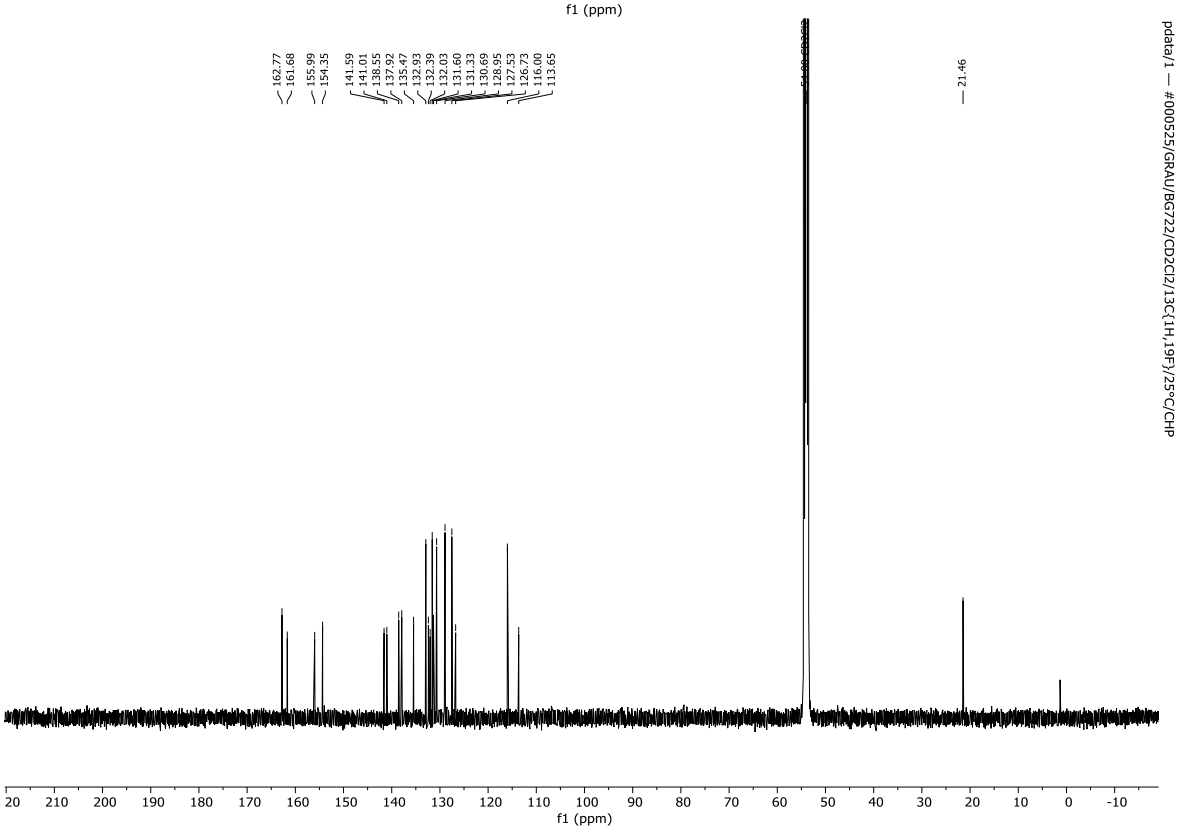
^{13}C NMR (126 MHz, Methylene Chloride-d_2) δ = 162.63, 161.39, 160.21, 154.08, 141.37, 141.10, 138.36, 138.19, 138.15, 134.55, 133.54, 133.47, 132.54, 131.69, 131.55, 131.25, 130.84, 129.23, 129.20, 129.05, 127.78, 127.04, 123.64, 115.44, 21.51 ppm.

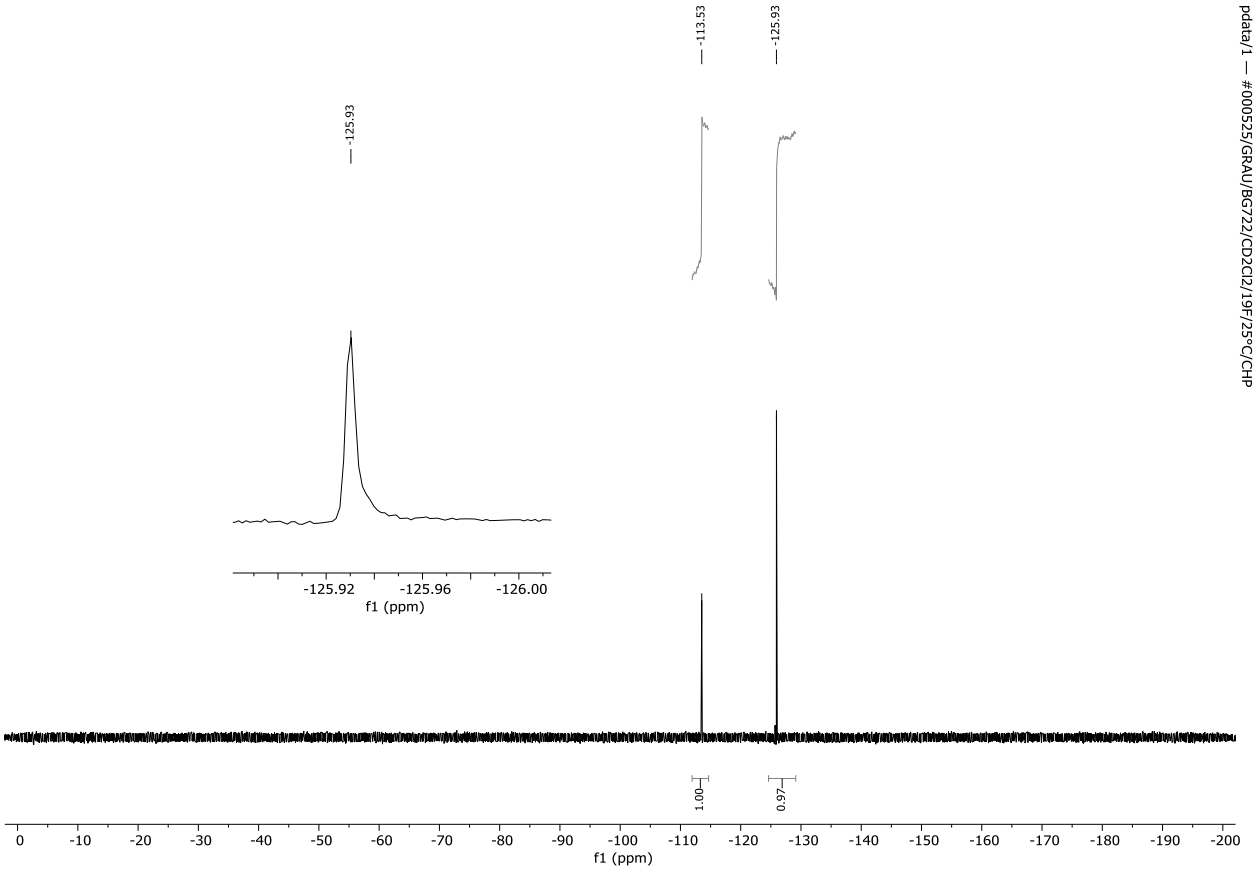
^{19}F NMR (471 MHz, Methylene Chloride-d_2) δ = -115.32, -128.85 ppm.

HR-MS (ESI positive mode): *m/z* = calc. for ($[M+H]^+$): 485.182382, found: 485.182350.

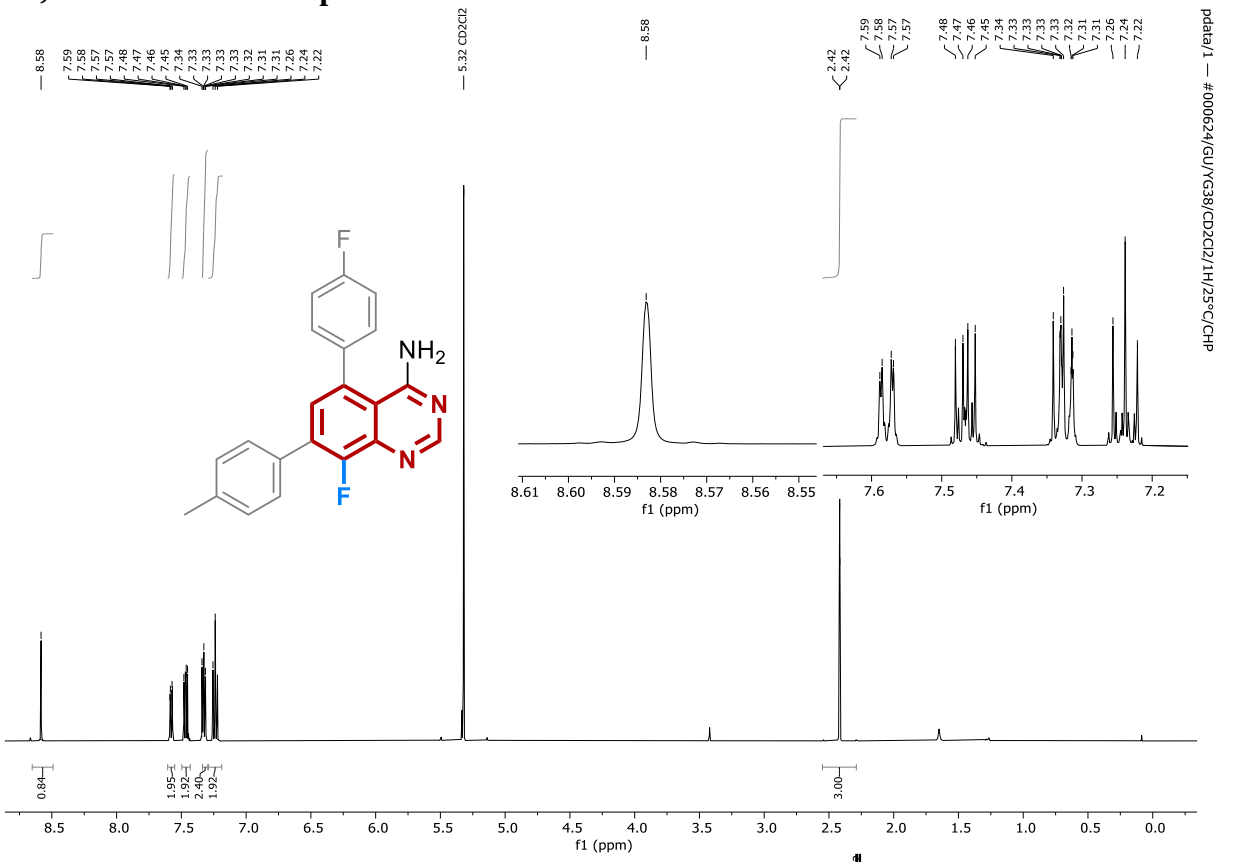
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 9 in CD_2Cl_2

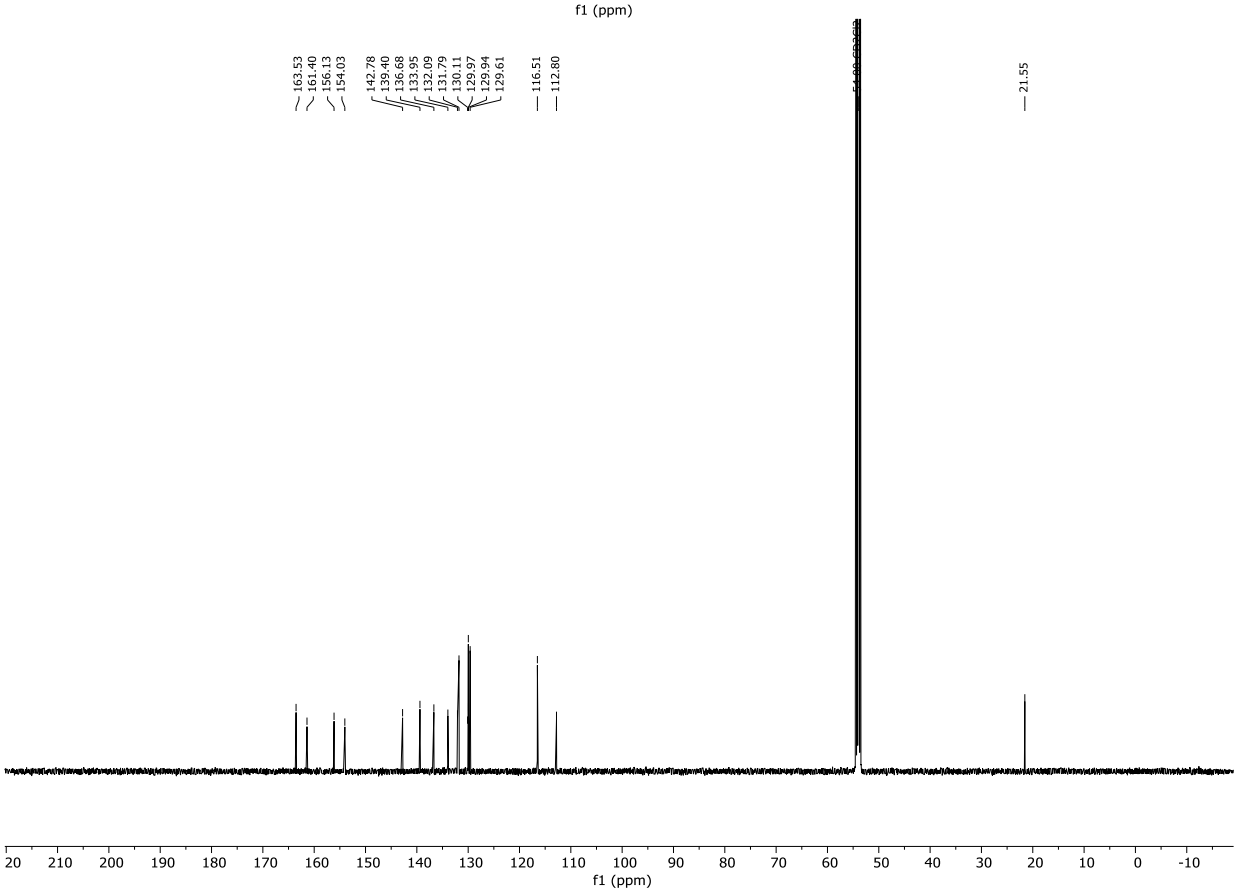


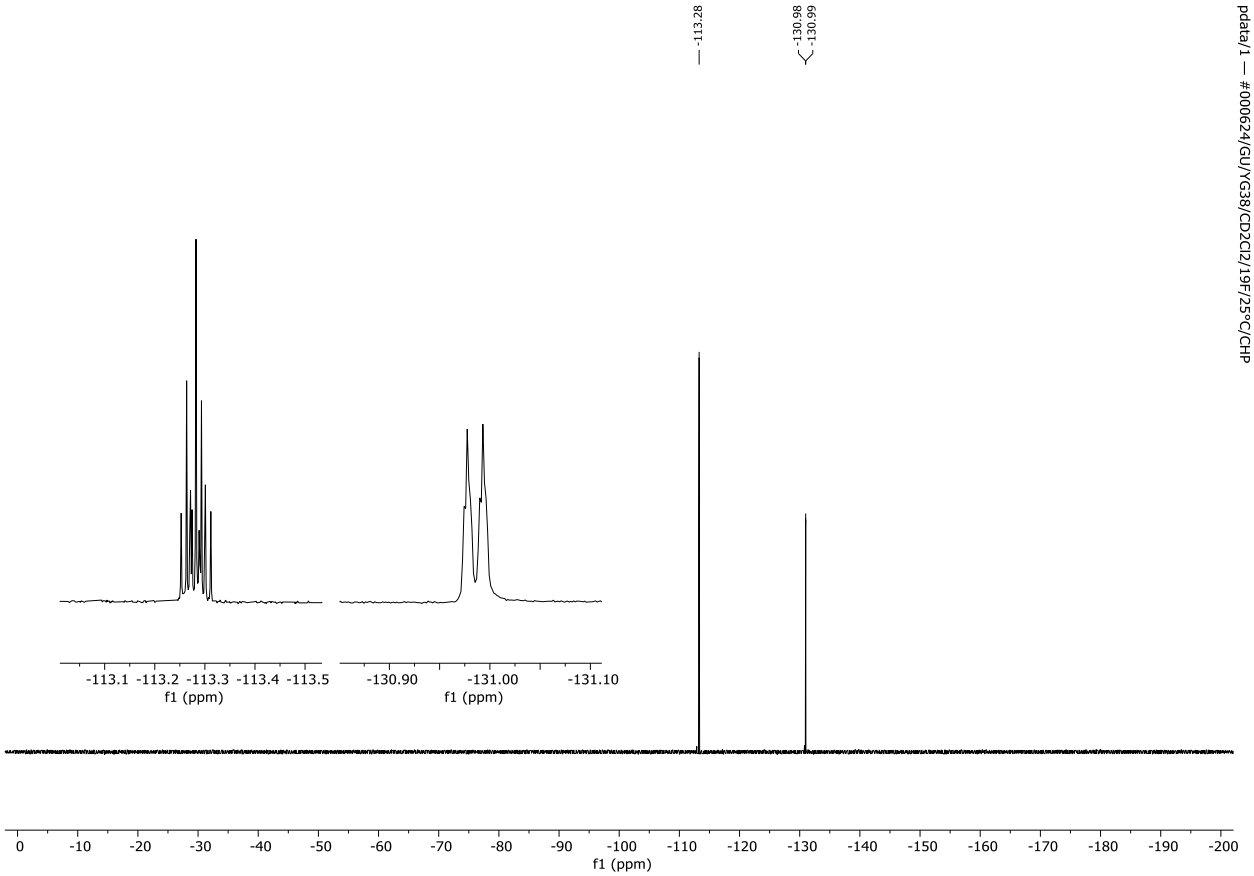



pdata/1 — #000525/GRAU/BG722/CD2Cl2/19F/25°C/CHP
-113.53
-125.93
-125.93
-125.92
-125.96
-126.00
f1 (ppm)
1.00
0.97
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

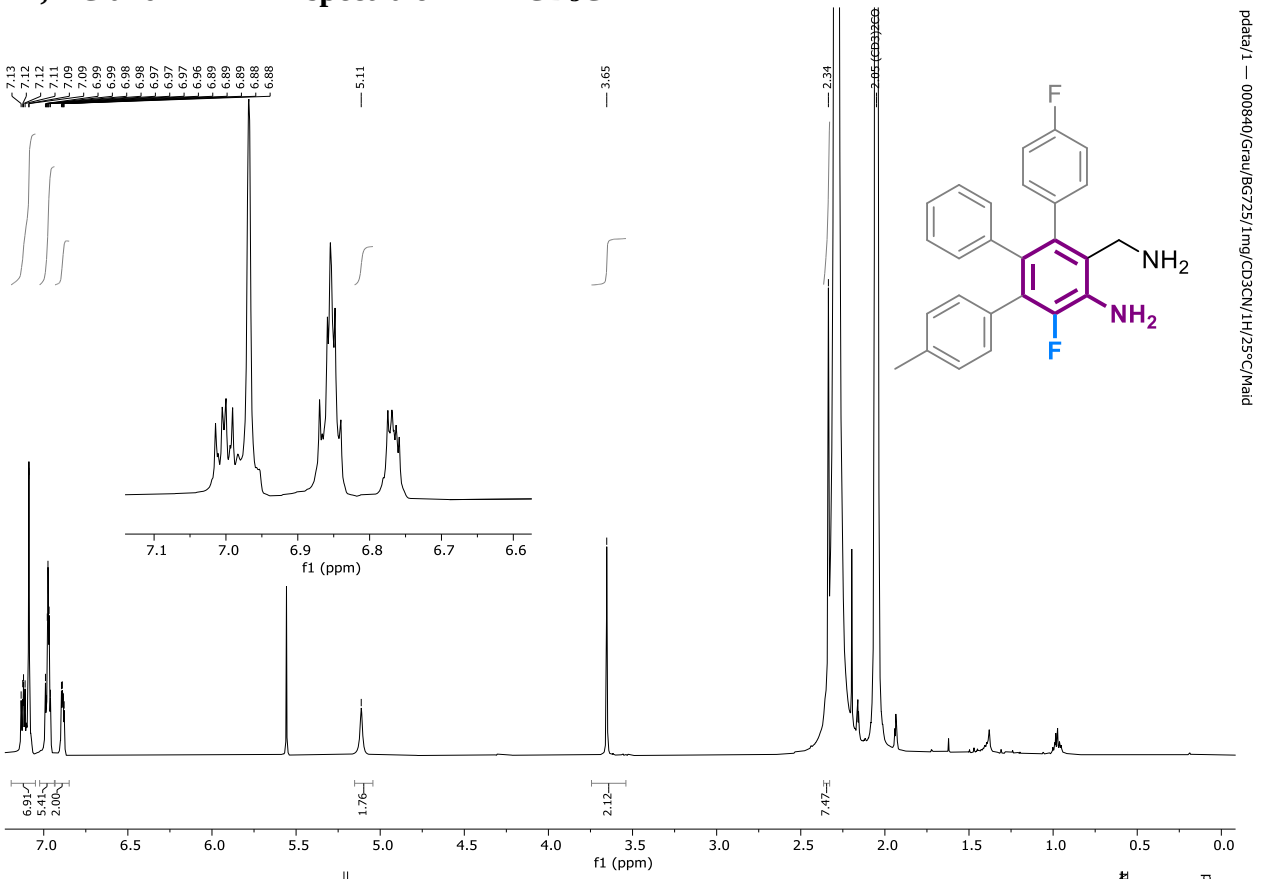
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 10 in CD_2Cl_2

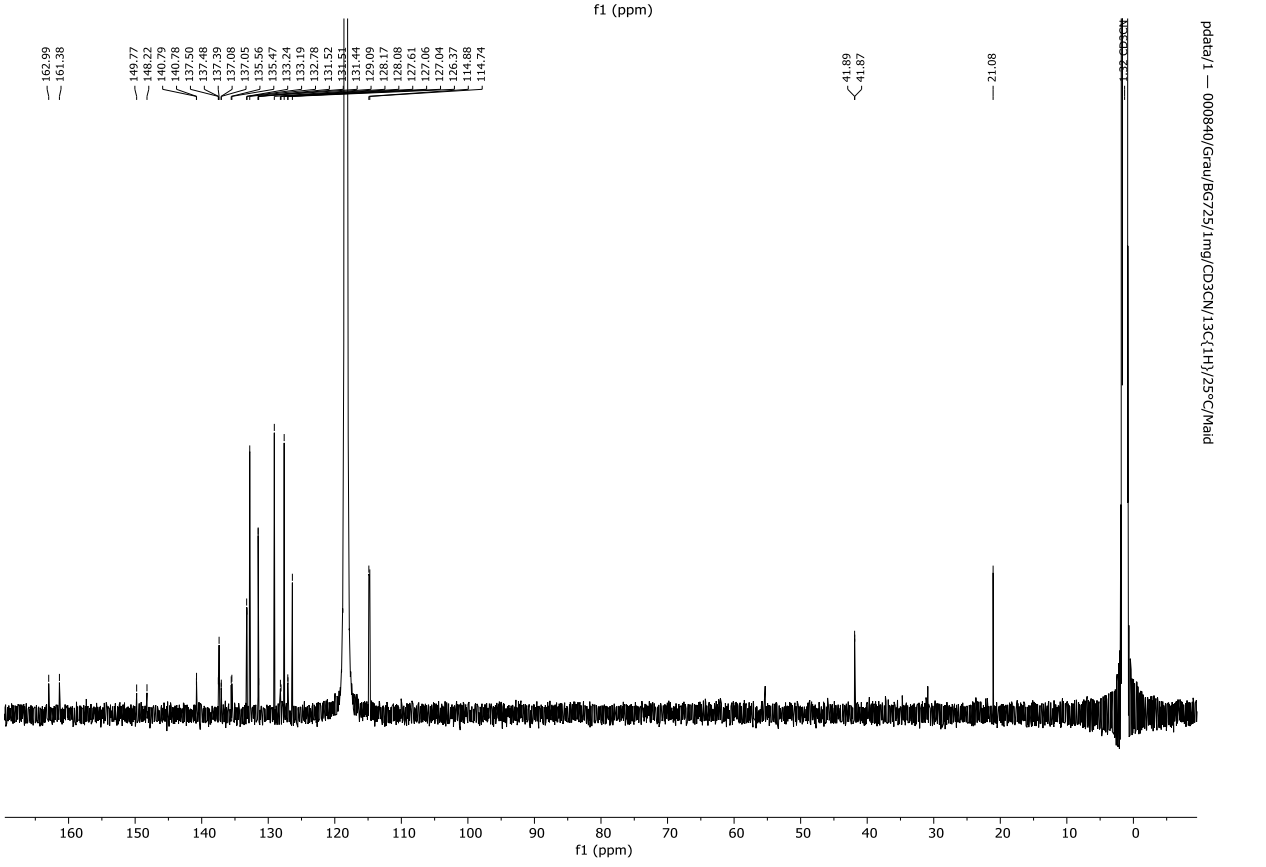


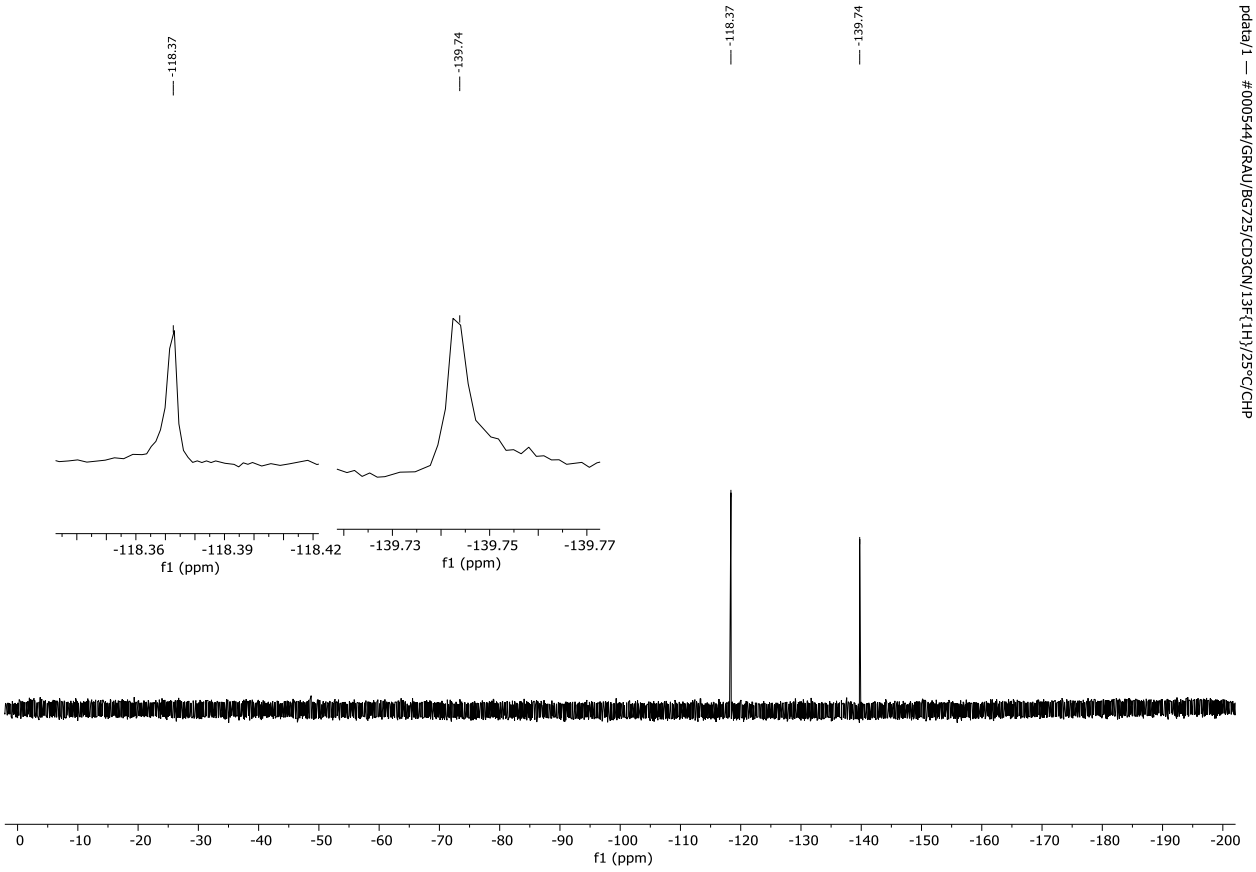



-113.28
-130.98
-130.99
pdata/1 — #000624/GU/YG38/CD2Cl2/19F/25°C/CHP
-113.1 -113.2 -113.3 -113.4 -113.5
f1 (ppm)
-130.90 -131.00 -131.10
f1 (ppm)
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

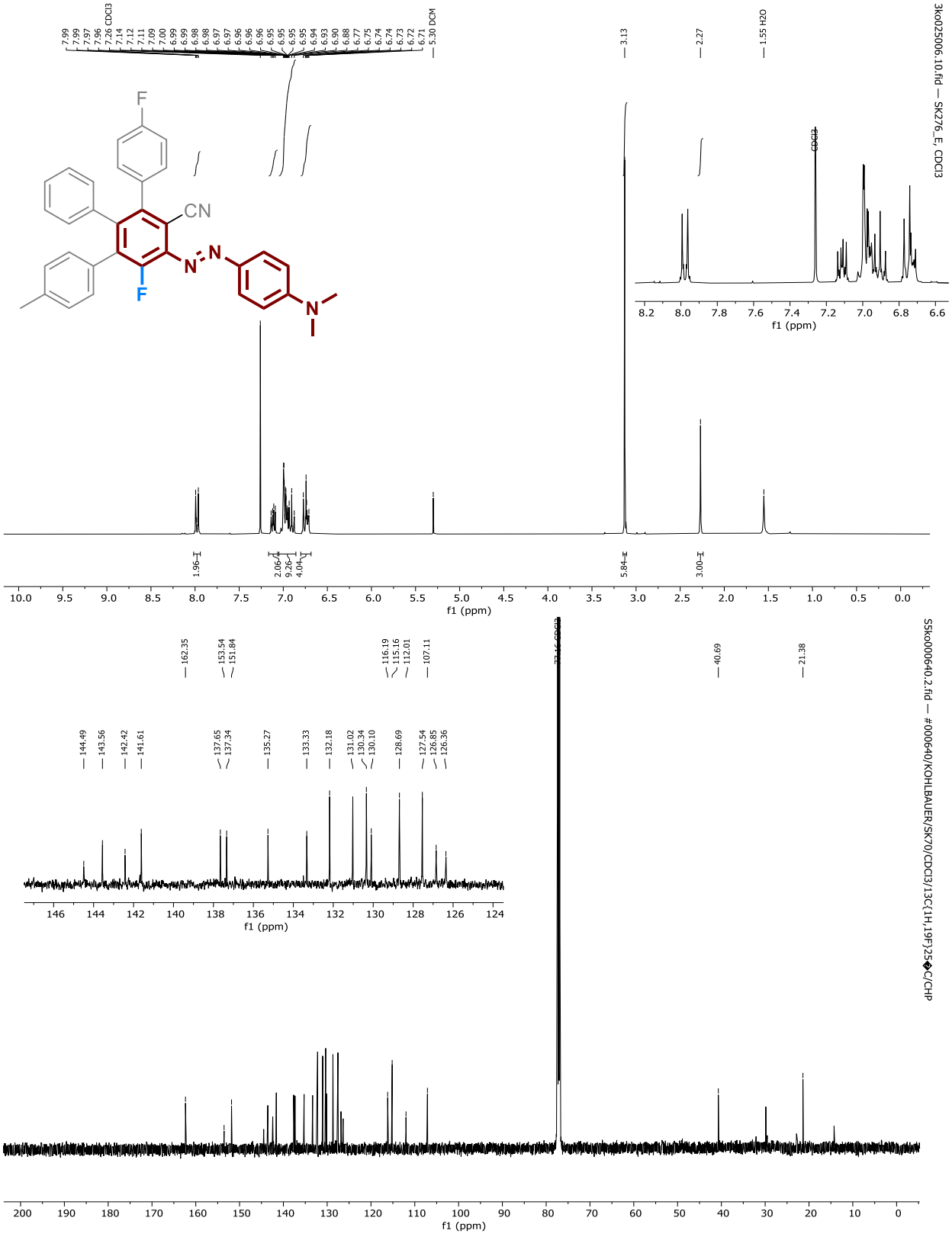
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 11 in CD_3CN

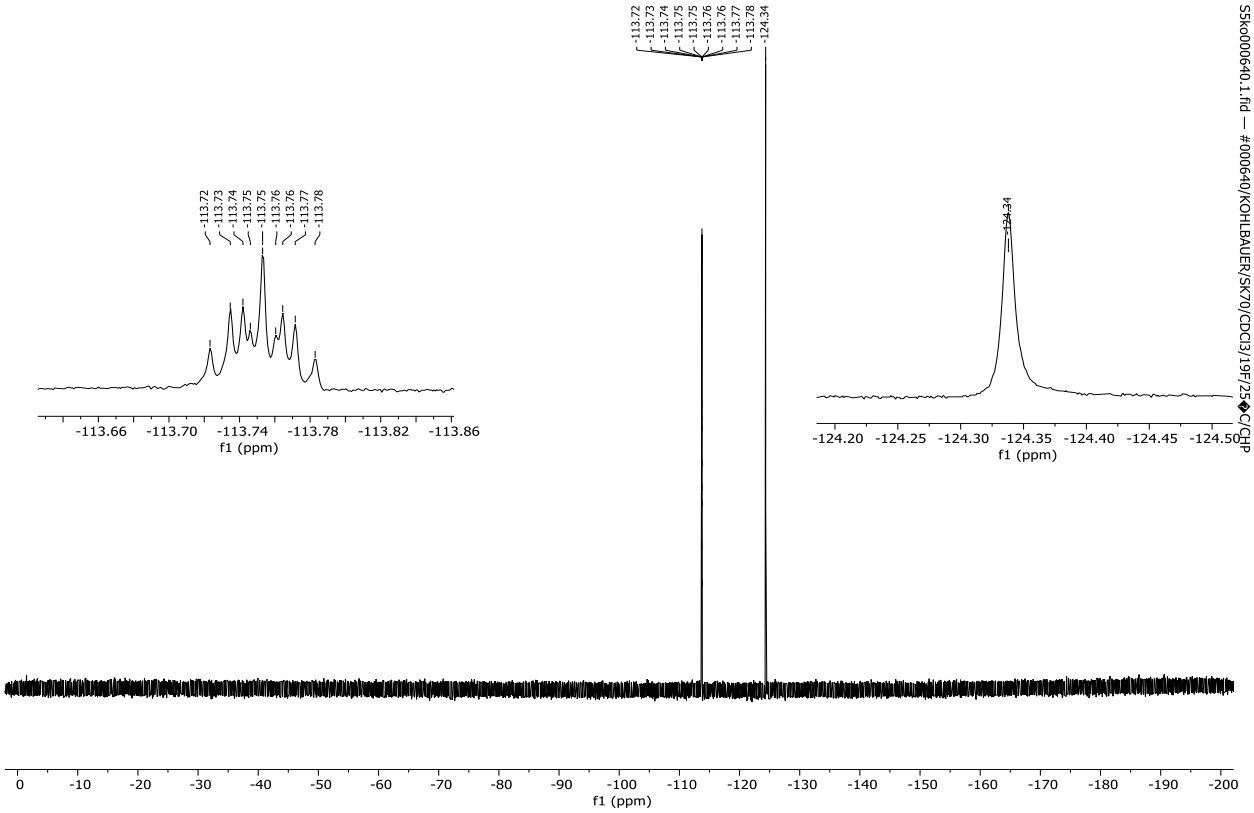




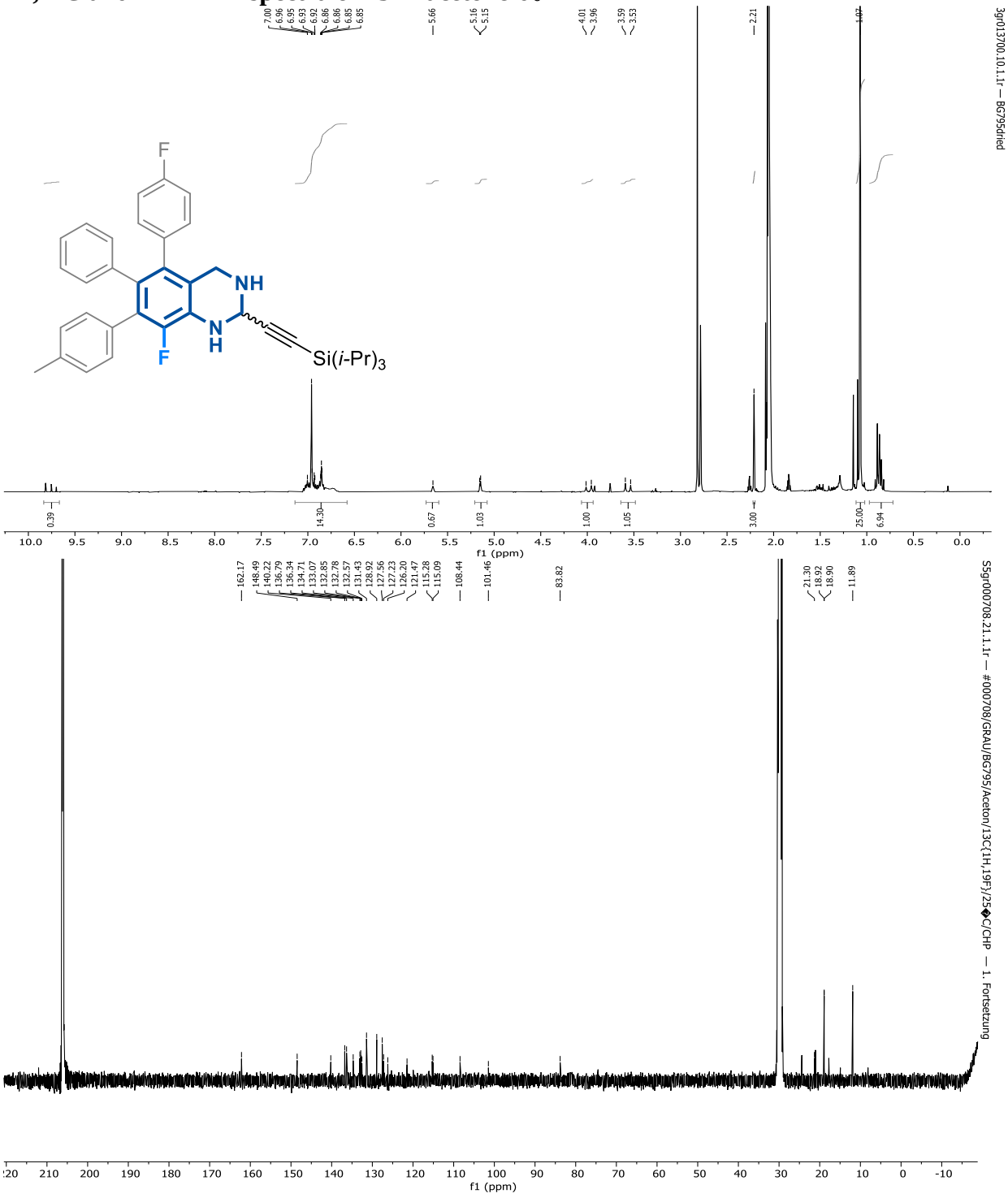

— -118.37
— -139.74
— -118.37
— -139.74
pdata/1 — #000544/GRAU/BG725/CD3CN/13F{1H}/25°C/CHP
-118.36
-118.39
-118.42
f1 (ppm)
-139.73
-139.75
-139.77
f1 (ppm)
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

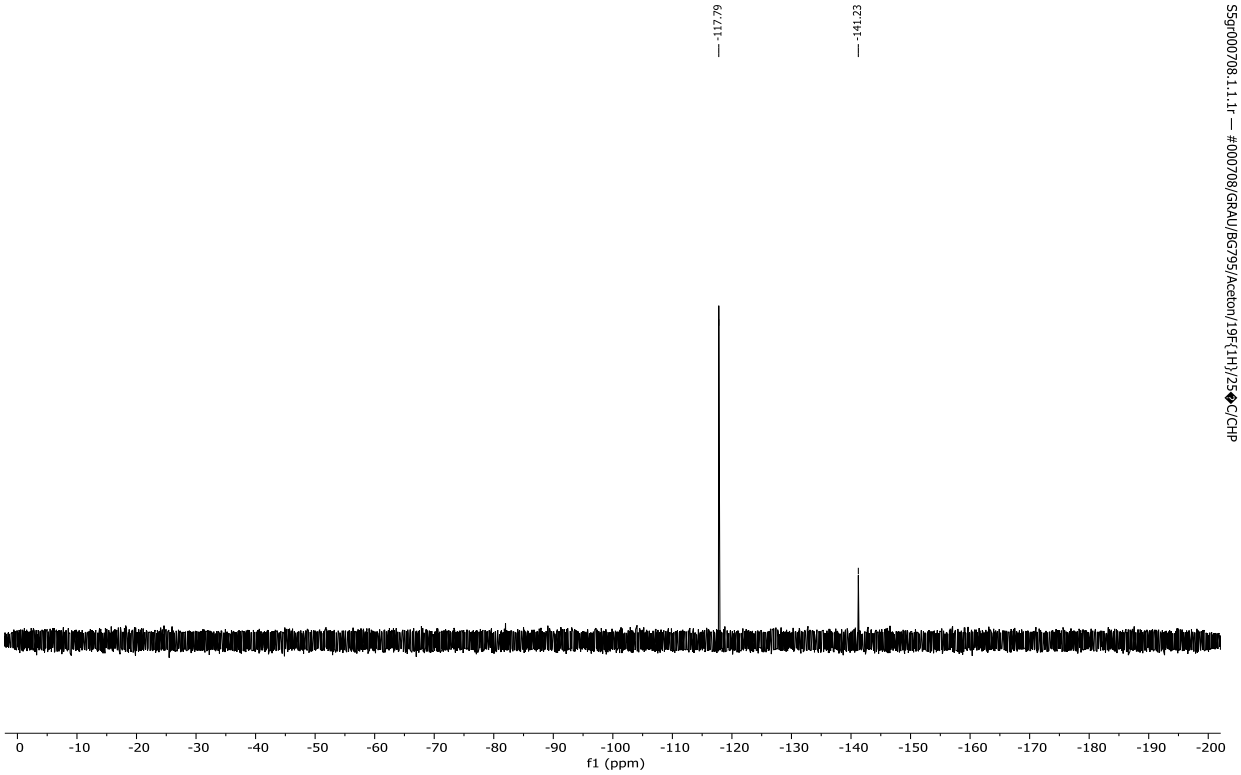
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 12 in $CDCl_3$



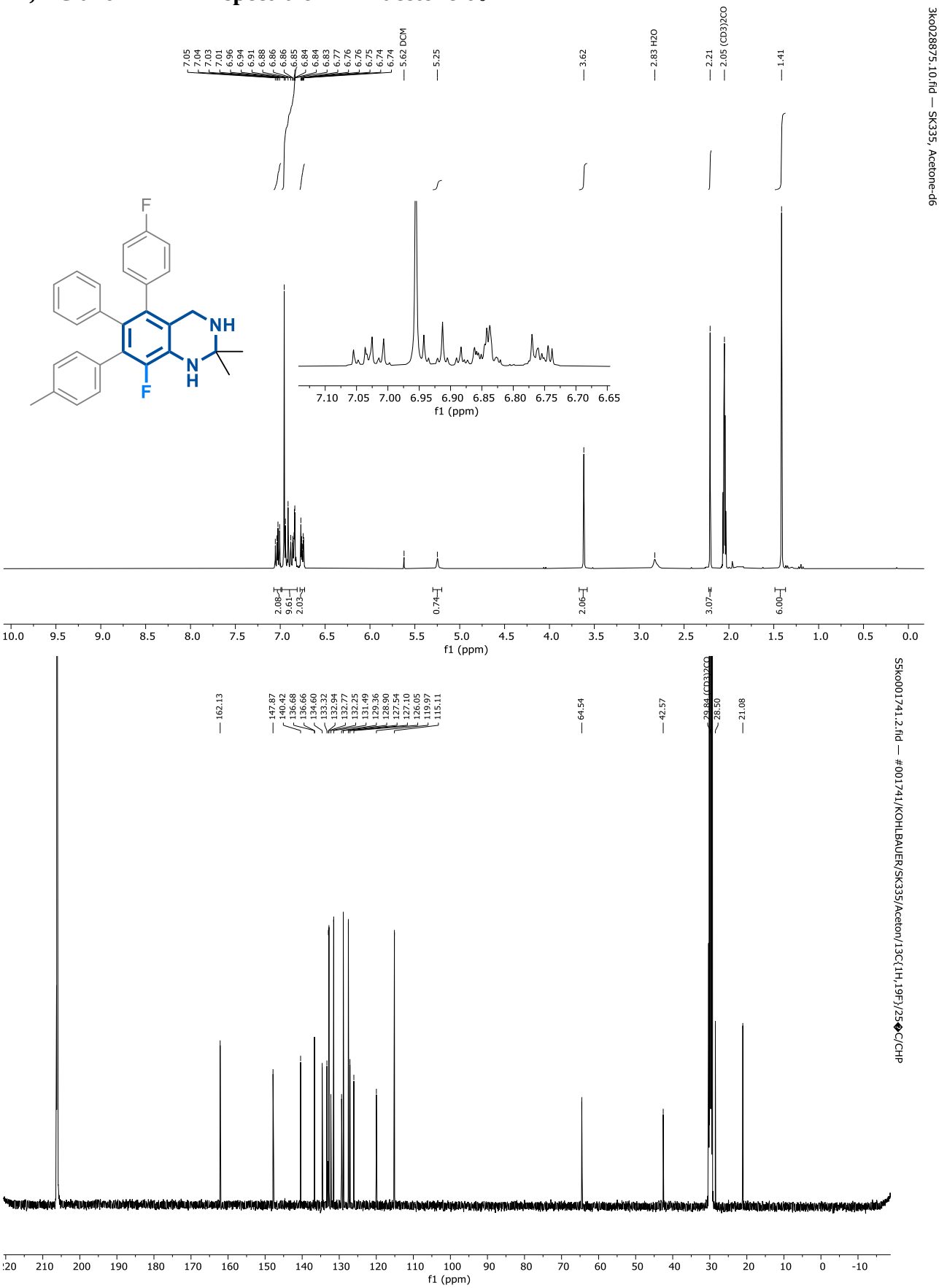

-113.72
-113.73
-113.74
-113.75
-113.75
-113.76
-113.76
-113.77
-113.78
-124.34
-113.66 -113.70 -113.74 -113.78 -113.82 -113.86
f1 (ppm)
-124.20 -124.25 -124.30 -124.35 -124.40 -124.45 -124.50
f1 (ppm)
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)
S5ko000640.1.fid — #000640/KOHLBAUER/SK70/CDCl3/19F/25␀C/CUP

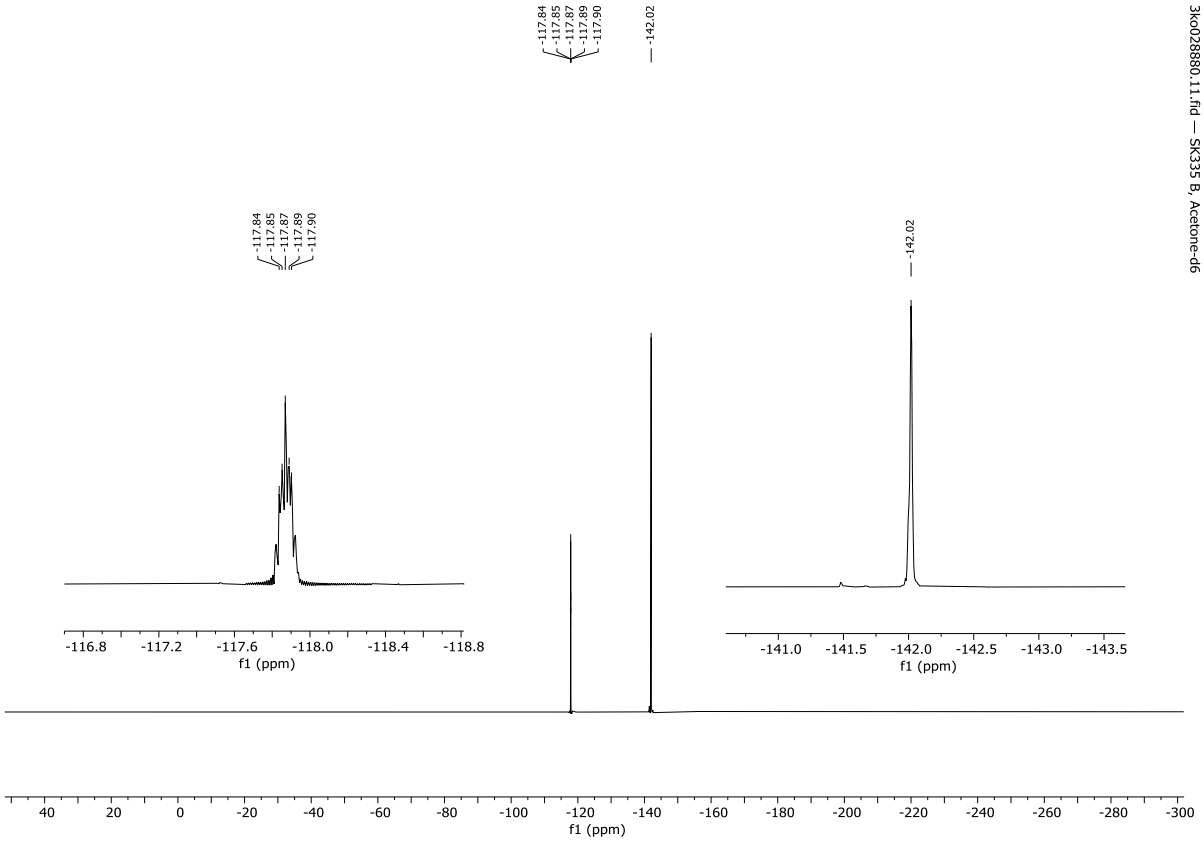
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 13 in acetone-d$_6$



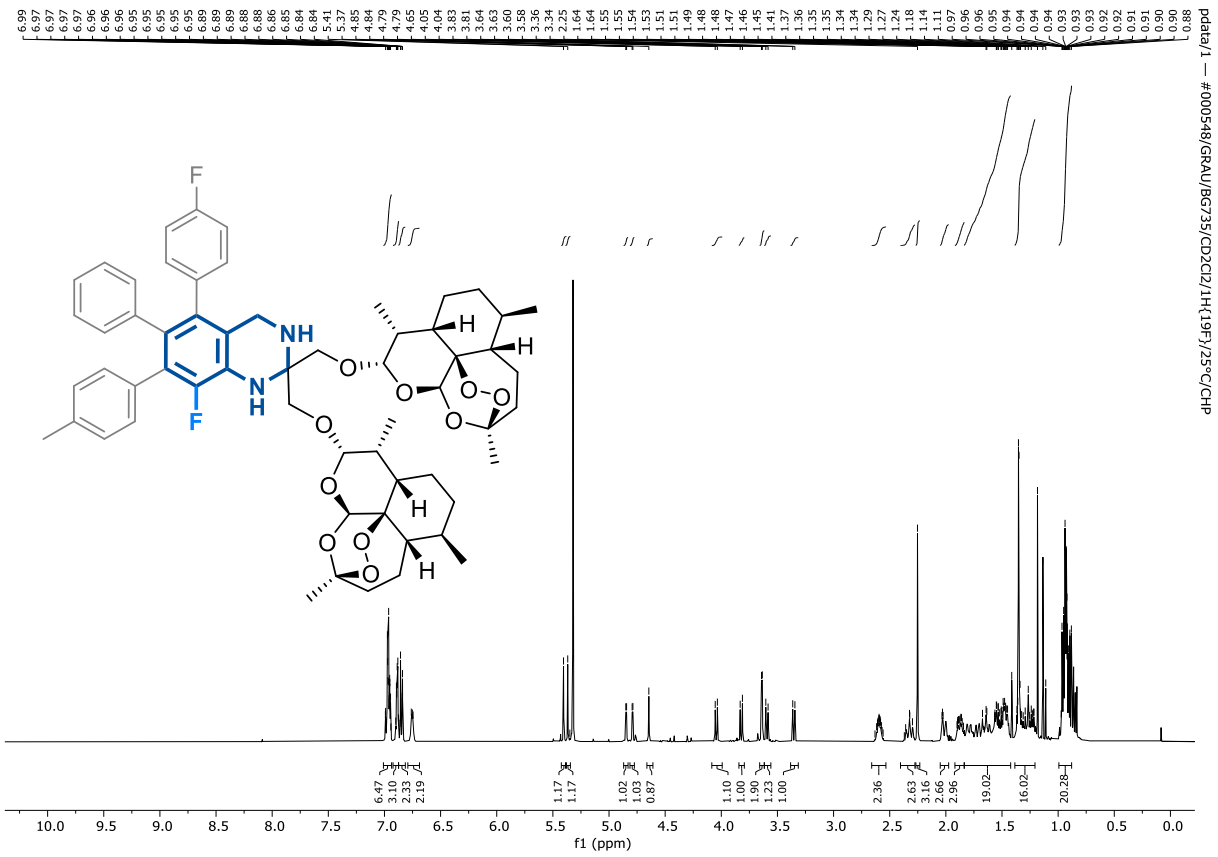

-117.79
-141.23
S5gf000708.1.1.1r — #000708/GRAU/BG795/Aceton/19F{1H}/25◆C/CHP
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

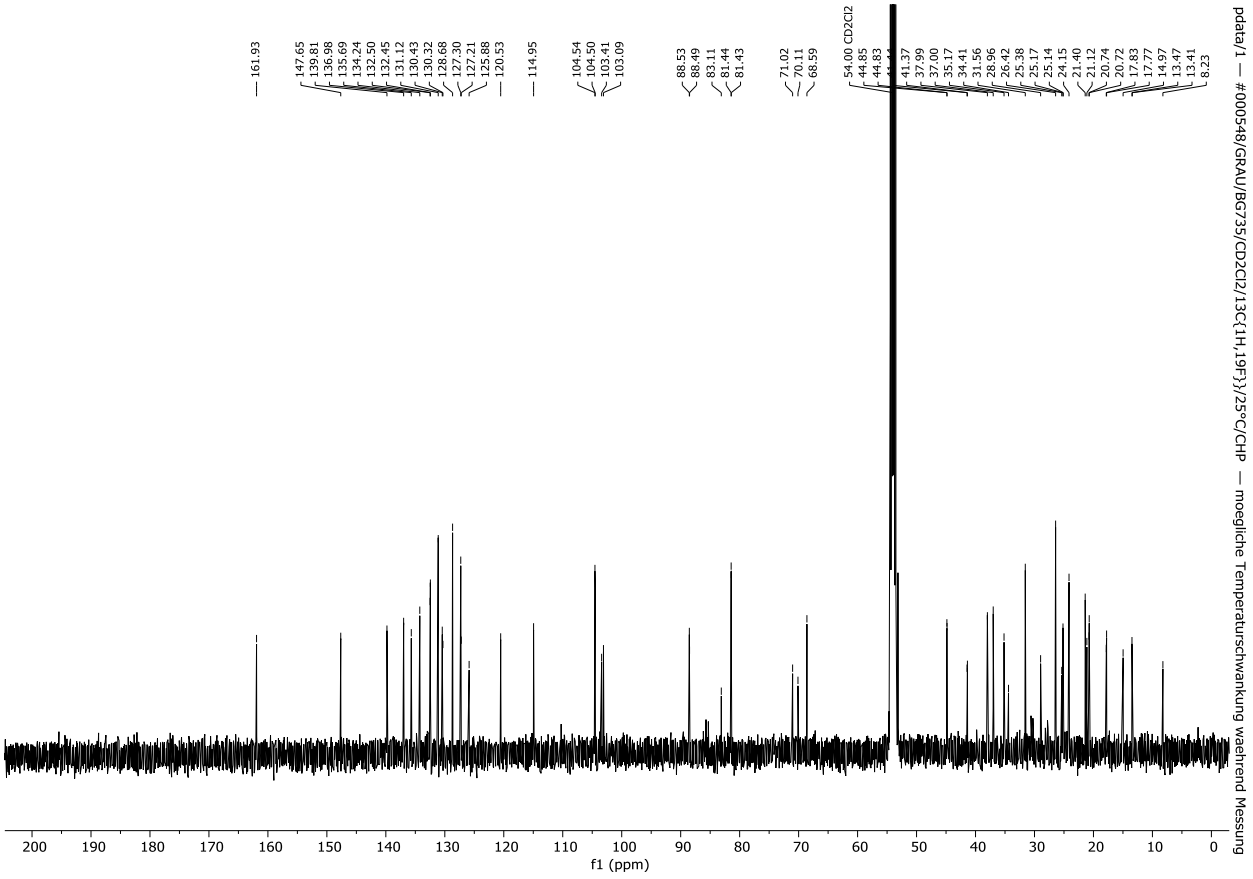
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 14 in acetone-d_6

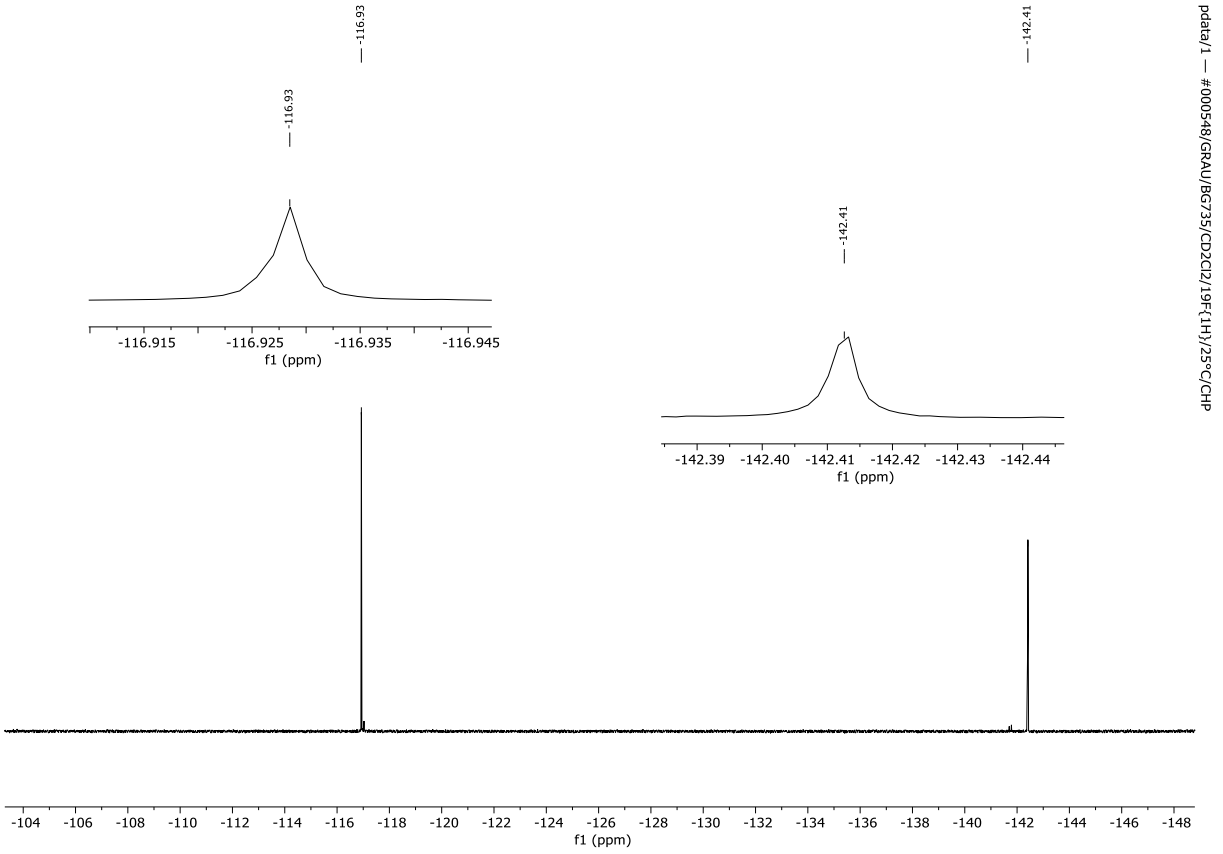



3ko028880.11.fid — SK335 B, Acetone-d6
-117.84
-117.85
-117.87
-117.89
-117.90
-142.02
-116.8
-117.2
-117.6
-118.0
-118.4
-118.8
f1 (ppm)
-141.0
-141.5
-142.0
-142.5
-143.0
-143.5
f1 (ppm)
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280
-300
f1 (ppm)

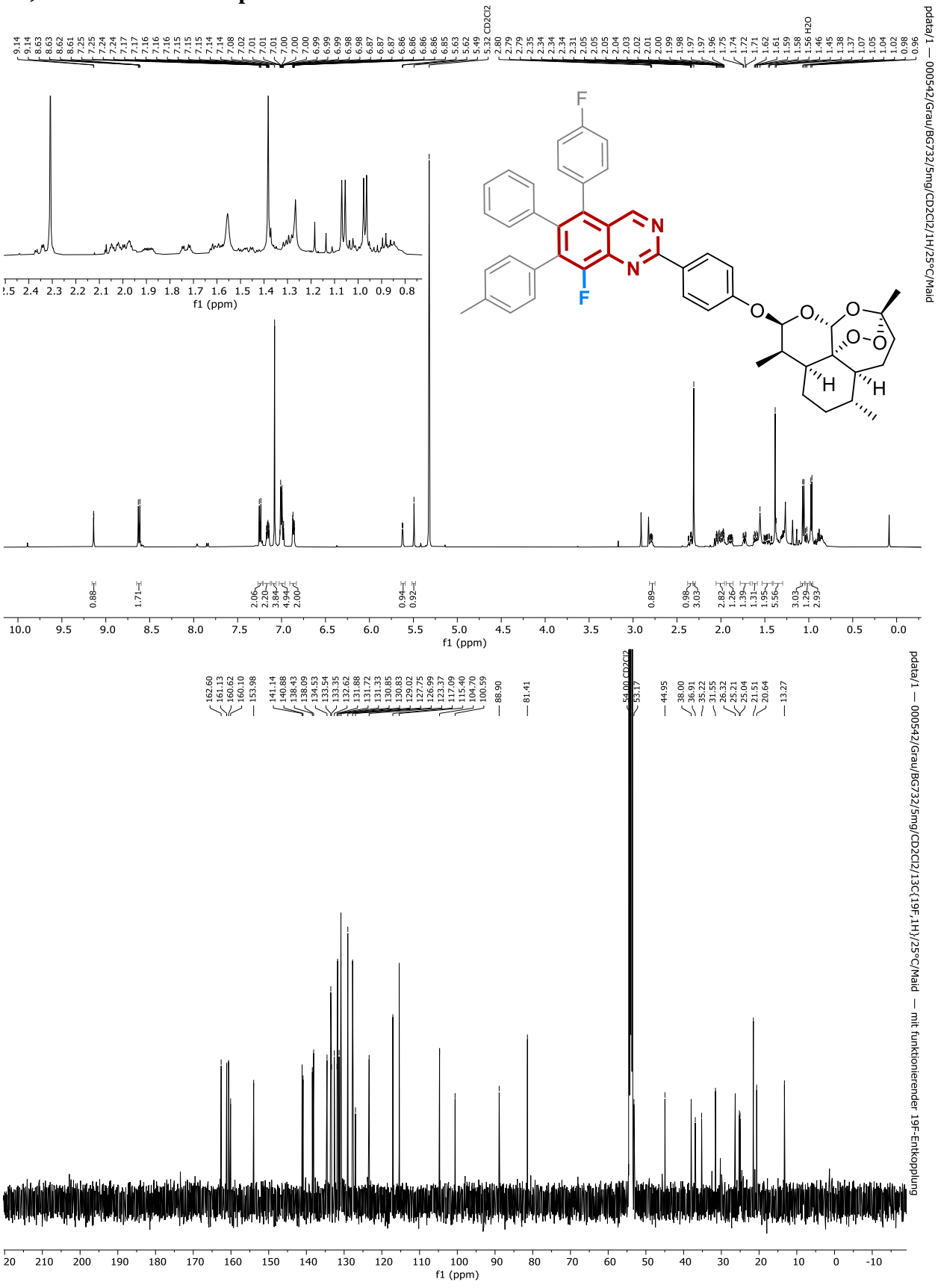
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 15 in CD_2Cl_2

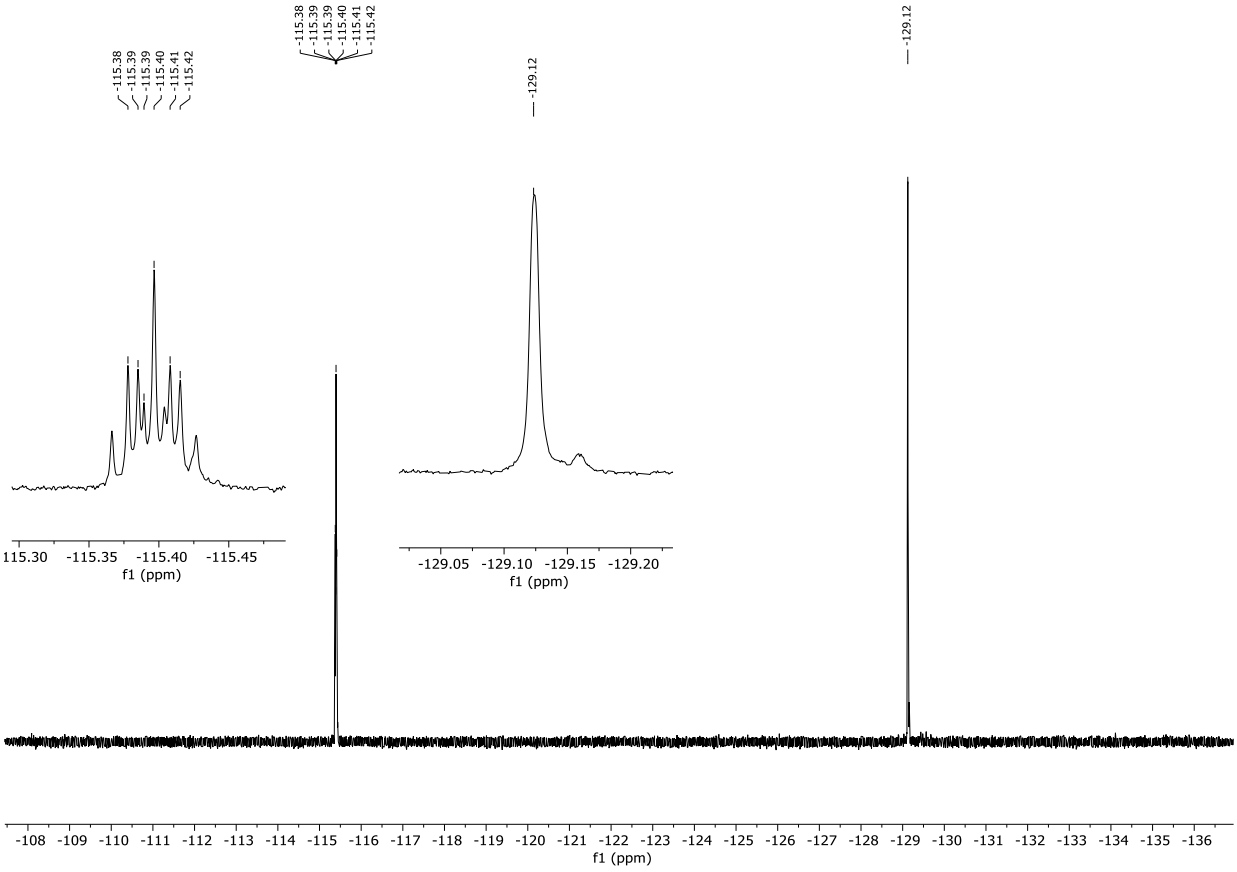




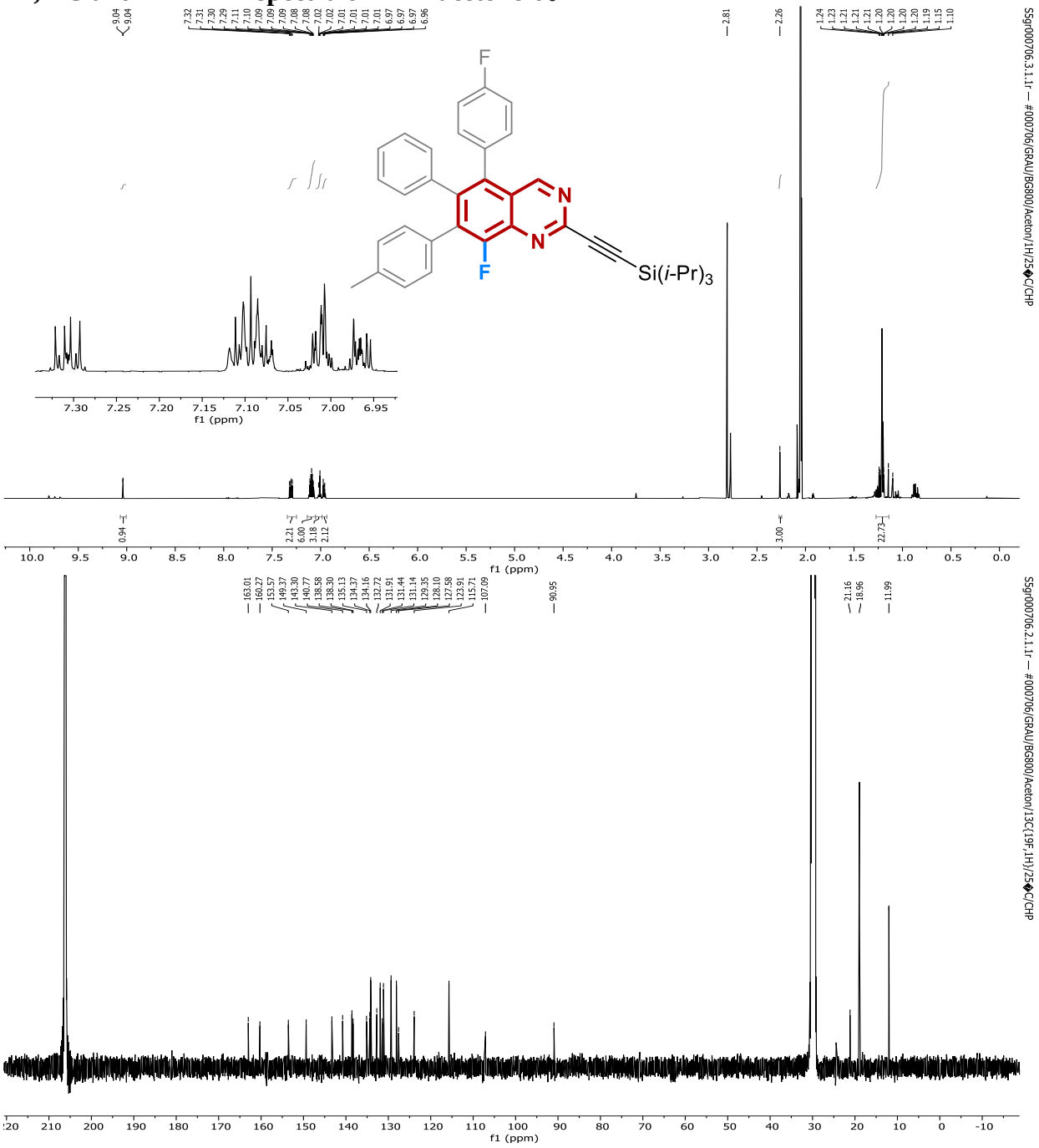

-116.93
-116.93
-142.41
-142.41
-116.915
-116.925
-116.935
-116.945
f1 (ppm)
-142.39
-142.40
-142.41
-142.42
-142.43
-142.44
f1 (ppm)
-104
-106
-108
-110
-112
-114
-116
-118
-120
-122
-124
-126
-128
-130
-132
-134
-136
-138
-140
-142
-144
-146
-148
f1 (ppm)
pdata/1 — #000548/GRAU/BG735/CD2Cl2/19F{1H}/25°C/CHP

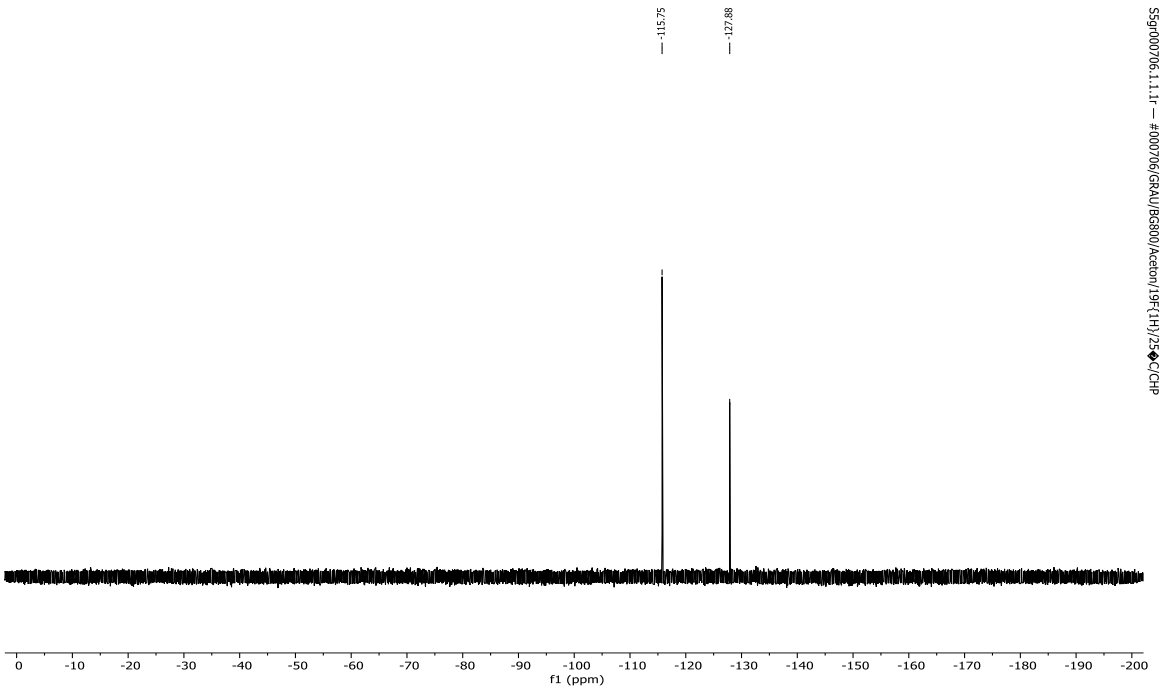
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 16 in CD_2Cl_2



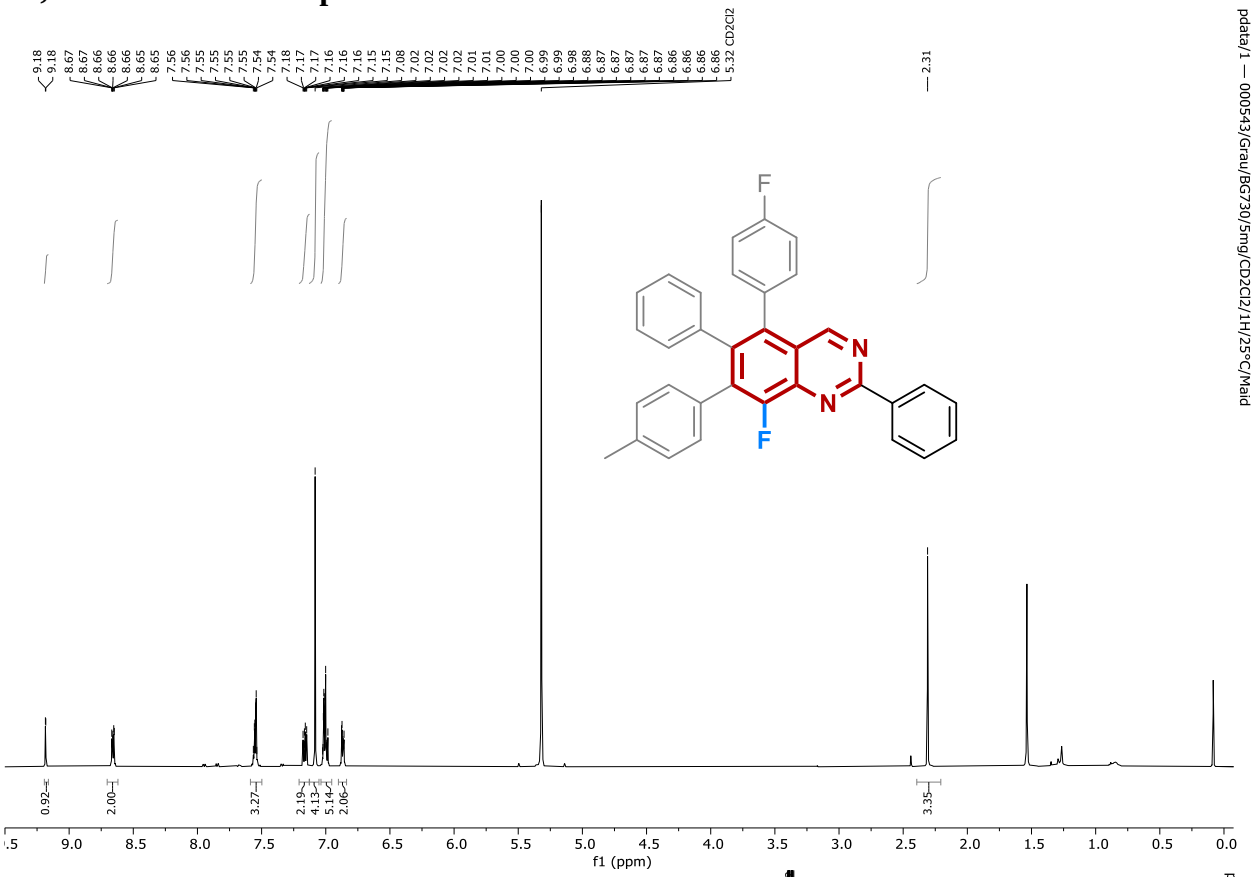

-115.38
-115.39
-115.39
-115.40
-115.41
-115.42
-129.12
115.30 -115.35 -115.40 -115.45
f1 (ppm)
-129.05 -129.10 -129.15 -129.20
f1 (ppm)
-108 -109 -110 -111 -112 -113 -114 -115 -116 -117 -118 -119 -120 -121 -122 -123 -124 -125 -126 -127 -128 -129 -130 -131 -132 -133 -134 -135 -136
f1 (ppm)
pdata/1 — 000542/Grau/BG732/5mg/CD2Cl2/19F/25°C/Maid

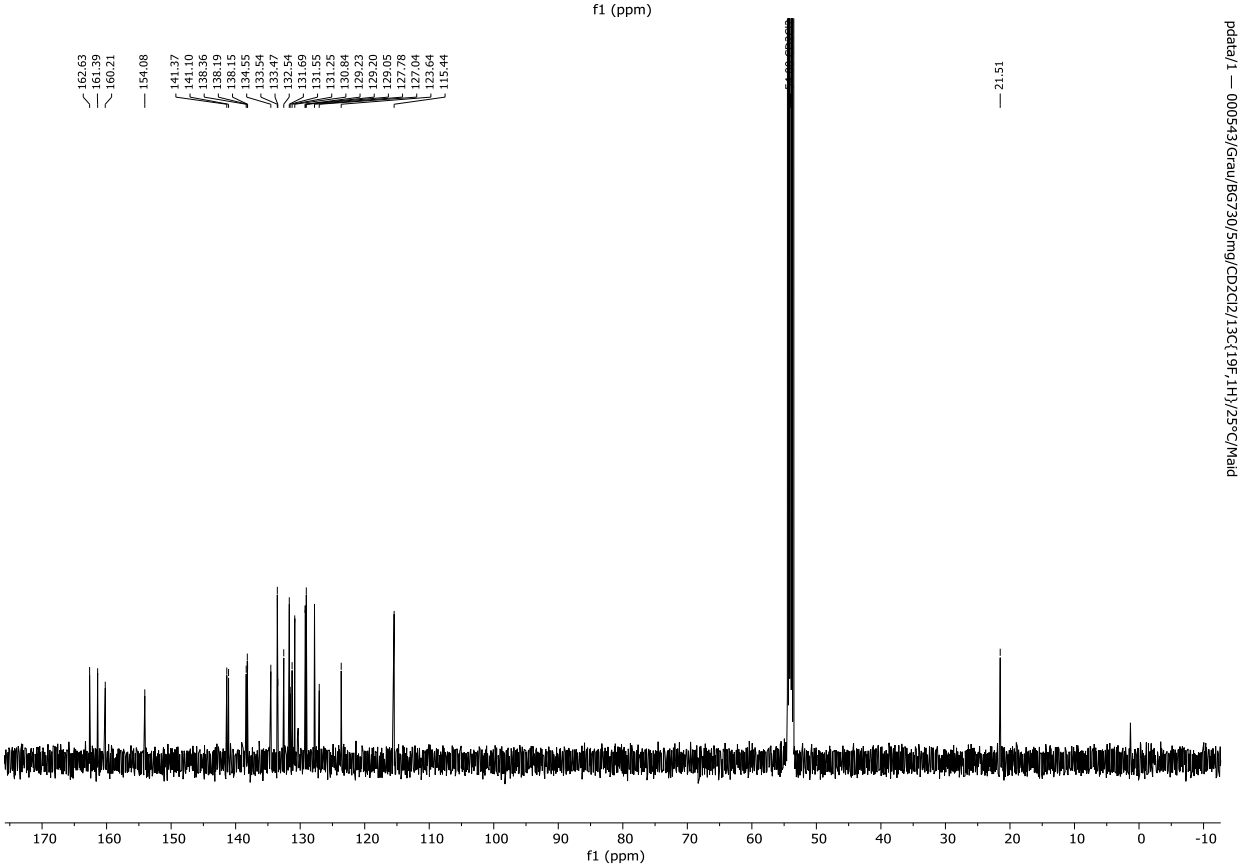
^{1}H, ^{13}C and ^{19}F-NMR-spectra of 17 in acetone-d_6

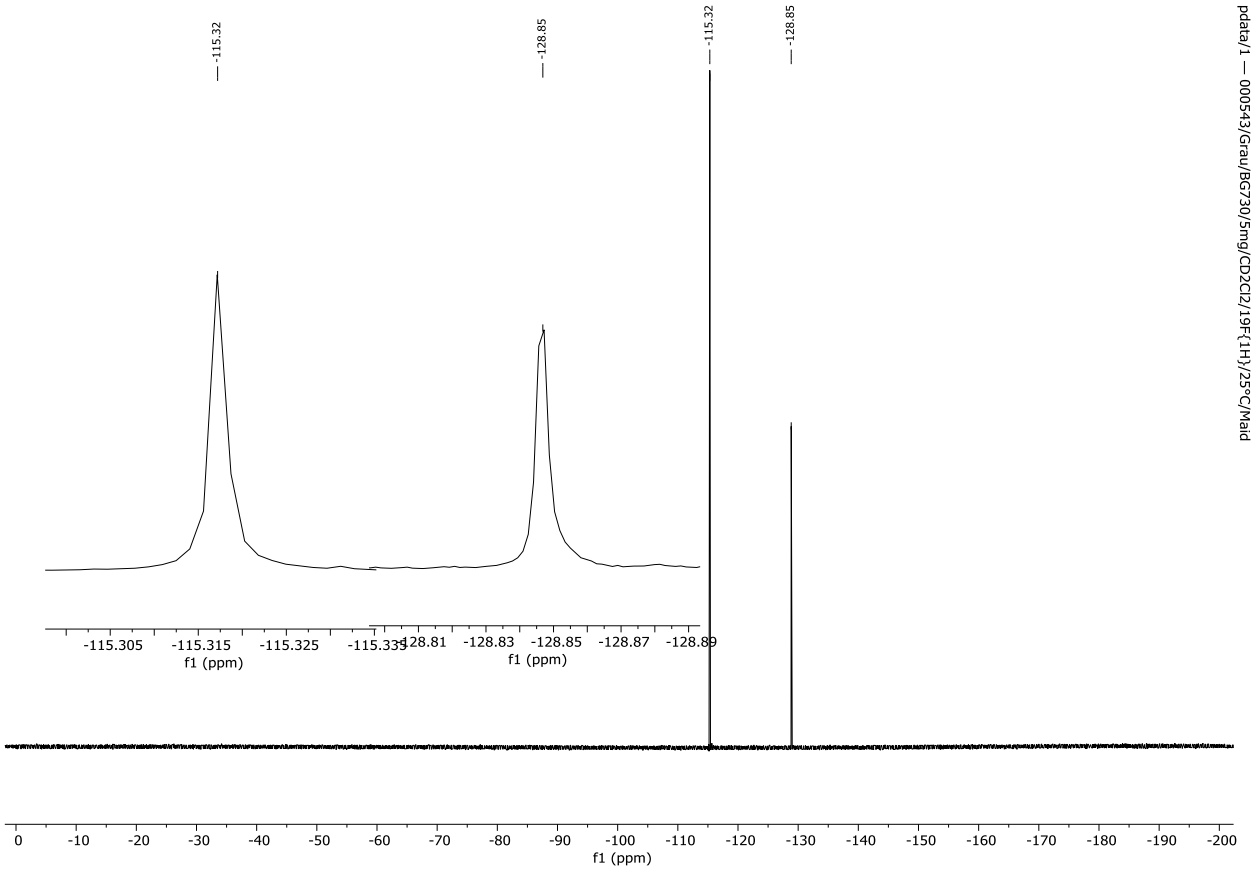



-115.75
-127.88
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)
S5gr000706.1.1.1r — #000706/GRAU/BG800/Aceton/19F{1H}/25◆C/CHP

^{1}H, ^{13}C and ^{19}F-NMR-spectra of 18 in CD_2Cl_2

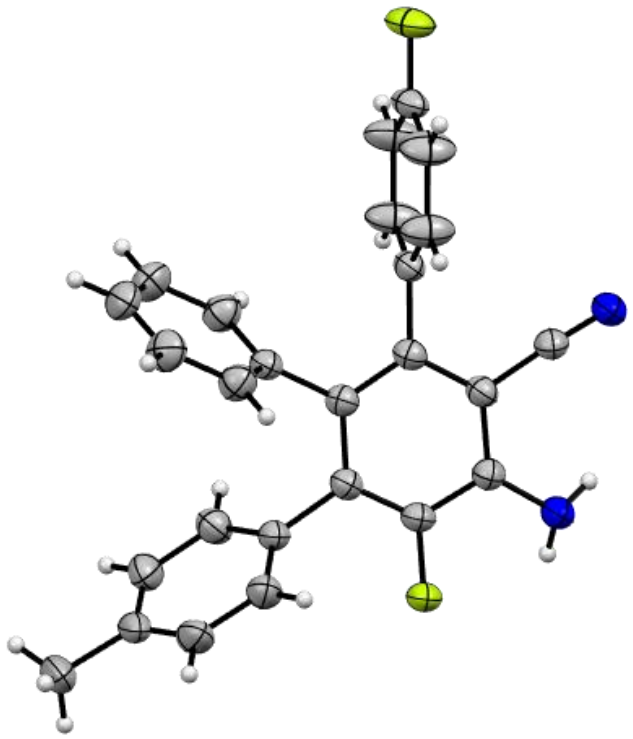





-115.32
-128.85
-115.32
-128.85
pdata/1 — 000543/Grau/BG730/5mg/CD2Cl2/19F{1H}/25°C/Maid
-115.305
-115.315
-115.325
-115.335
f1 (ppm)
-128.81
-128.83
-128.85
-128.87
-128.89
f1 (ppm)
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

X-ray crystallography of 5n

Crystal Data and Experimental



Compound	**20Tso_BG04**
Formula	$C_{26}H_{18}F_2N_2$
$D_{calc.}$/ g cm^{-3}	1.286
m/mm^{-1}	0.721
Formula Weight	396.42
Colour	clear light colourless
Shape	needle
Size/mm^3	0.47×0.12×0.09
T/K	152.8(9)
Crystal System	monoclinic
Space Group	$C2/c$
a/Å	26.4195(6)
b/Å	6.4278(2)
c/Å	24.1425(6)
a/°	90
b/°	92.372(2)
g/°	90
V/Å^3	4096.35(19)
Z	8
Z'	1
Wavelength/Å	1.54184
Radiation type	Cu K$_a$
Q_{min}/°	3.349
Q_{max}/°	69.363
Measured Refl's.	19202
Indep't Refl's	3792
Refl's I≥2 s(I)	3288
R_{int}	0.0280
Parameters	274
Restraints	0
Largest Peak	0.422
Deepest Hole	-0.378
GooF	1.054
wR_2 (all data)	0.1284
wR_2	0.1219
R_1 (all data)	0.0507
R_1	0.0439

Experimental. Single clear light colourless needle crystals of **20Tso_BG04** recrystallised from a mixture of MeOH and DCM by solvent layering. A suitable crystal with dimensions 0.47 × 0.12 × 0.09 mm^3 was selected and mounted on a mylar loop in perfluoroether oil on a SuperNova, Dual, Cu at home/near, Atlas diffractometer. The crystal was kept at a steady T = 152.8(9) K during data collection. The structure was solved with the ShelXT (Sheldrick, 2015) solution program using dual methods and by using Olex2 (Dolomanov et al., 2009) as the graphical interface. The model was refined with ShelXL 2018/3 (Sheldrick, 2015) using full matrix least squares minimisation on $\boldsymbol{F^2}$.

CCDC 2109016 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Crystal Data. $C_{26}H_{18}F_2N_2$, M_r = 396.42, monoclinic, $C2/c$ (No. 15), a = 26.4195(6) Å, b = 6.4278(2) Å, c = 24.1425(6) Å, b = 92.372(2)°, a = g = 90°, V = 4096.35(19) Å^3, T = 152.8(9) K, Z = 8, Z' = 1, m(Cu K$_a$) = 0.721, 19202 reflections measured, 3792 unique (R_{int} = 0.0280) which were used in all calculations. The final wR_2 was 0.1284 (all data) and R_1 was 0.0439 (I≥2 s(I)).

A clear light colourless needle-shaped crystal with dimensions 0.47 × 0.12 × 0.09 mm^3 was mounted on a mylar loop in perfluoroether oil. Data were collected using a SuperNova, Dual, Cu at home/near, Atlas diffractometer equipped with a Cryojet - Oxford Instruments low-temperature device operating at T = 152.8(9) K.

Data were measured using *w* scans using Cu K_a radiation. The diffraction pattern was indexed and the total number of runs and images was based on the strategy calculation from the program CrysAlisPro (Rigaku, V1.171.40.67a, 2019). The maximum resolution that was achieved was Q = 69.363° (0.82 Å).

The diffraction pattern was indexed and the total number of runs and images was based on the strategy calculation from the program CrysAlisPro (Rigaku, V1.171.40.67a, 2019). The unit cell was refined using CrysAlisPro (Rigaku, V1.171.40.67a, 2019) on 8748 reflections, 46% of the observed reflections.

Data reduction, scaling and absorption corrections were performed using CrysAlisPro (Rigaku, V1.171.40.67a, 2019). The final completeness is 99.70 % out to 69.363° in Q. A gaussian absorption correction was performed using CrysAlisPro 1.171.40.67a (Rigaku Oxford Diffraction, 2019) Numerical absorption correction based on gaussian integration over a multifaceted crystal model Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm. The absorption coefficient m of this material is 0.721 mm^{-1} at this wavelength (l = 1.54184Å) and the minimum and maximum transmissions are 0.604 and 1.000.

The structure was solved, and the space group $C2/c$ (# 15) determined by the ShelXT (Sheldrick, 2015) structure solution program using dual methods and refined by full matrix least squares minimisation on $\boldsymbol{F^2}$ using version 2018/3 of ShelXL 2018/3 (Sheldrick, 2015). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model. Hydrogen atom positions were calculated geometrically and refined using the riding model.

_exptl_absorpt_process_details: CrysAlisPro 1.171.40.67a (Rigaku Oxford Diffraction, 2019) Numerical absorption correction based on gaussian integration over a multifaceted crystal modelEmpirical absorption correction using spherical harmonicsas implemented in SCALE3 ABSPACK.

There is a single molecule in the asymmetric unit, which is represented by the reported sum formula. In other words: Z is 8 and Z' is 1.

Biological Methodology

HCMV GFP-based replication model in primary fibroblasts and antiviral drug analysis

HCMV replication was analyzed in 96-well cell culture plates using quadruplicate determinations as described earlier[34c]. To this end, 13.500 primary human fibroblasts (HFFs) were seeded per well, infected with HCMV AD169-GFP[34d] at MOI of 0.001 (referring to a maximum 25% GFP-positive cells at 7 days) and treated with serial dilutions of antiviral compounds. At 7 days post infection (d p.i.), HFFs were fixed with 10% formalin for 20 min at 4 °C and replication was quantified by measurement of the intracellular GFP fluorescence in a Victor X4 Plate Reader (PerkinElmer, Waltham. MA, USA). Antiviral activity was defined as the compound-induced reduction of viral replication relative to the solvent control. To assess putative drug-induced cytotoxicity, HFFs were cultivated in 96-well plates and treated with serial dilutions of antiviral compounds for 7 d. At the time point of measurement, cells were incubated with a final concentration of 40 µg/ml Neutral Red (NR) solution (Sigma-Aldrich) at 37 °C for 4 h to allow uptake of NR. Subsequently, cells were washed with PBS and the incorporated NR was released by destain solution (50% ethanol, 1% acetic acid and 49% H_2O) for subsequent quantitation of the NR fluorescence (560/630 nm) in a Victor X4 Plate Reader as indicator of cell viability[34e]. The 50% effective antiviral (EC_{50}) and 50% cytotoxic concentrations (CC_{50}) were determined by fitting two parameter logistic dose-response curves to the experimentally determined values.

UV/Vis Spectra

UV/Vis measurements were carried out on an Agilent Technologies Cary 60 UV/Vis-NIR spectrophotometer at rt. Fluorescence measurements were carried out on an Agilent Technologies Cary Eclipse Fluorescence Spectrometer. All measurements were performed in precision cells SUPRASIL made of quartz from HELLMA Analytics with a layer thickness of d = 1 cm and maximum filling volume of 3500 µL. Before each measurement a baseline correction with the corresponding solvent filled cuvettes was performed.

Spectra of Quinazolines

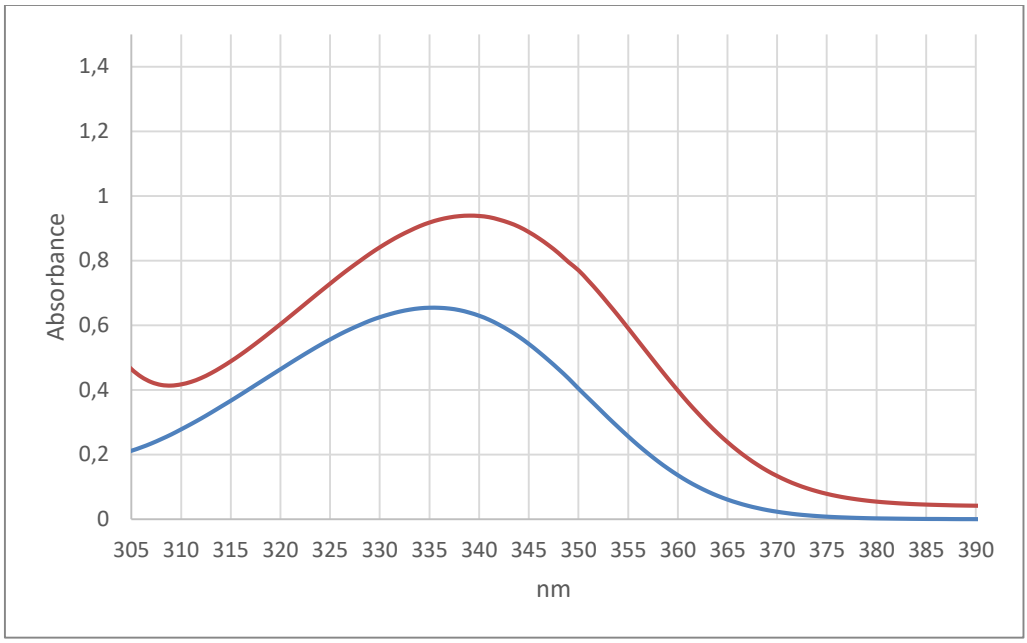


Figure S1. UV/Vis spectra of **3j** (red) and **5n** (blue)

The UV/Vis measurements show absorption maxima of **5n** at 335 nm and that of **3j** at 340 nm. *Meta*-terphenyl **3j** shows the greatest absorbance at similar concentrations.

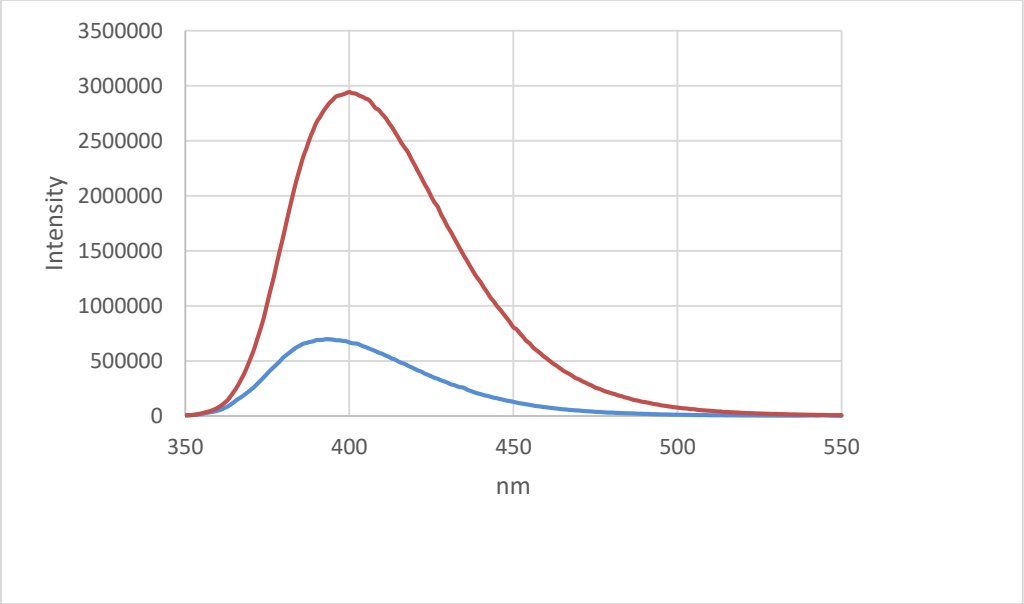


Figure S2. Fluorescence spectra of **3j** (red) and **5n** (blue)

Meta-terphenyl **3j** shows a fluorescence maximum at 400 nm, whereas **5n** shows a maximum at 395 nm. The absorption maxima from *meta*-terphenyl **3j** is greater than that of **5n** at similar concentrations. This can also be observed by looking at samples of the compounds in solution under an UV lamp. No notable solvatochromatic effect could be observed by changing the solvent from DCM to toluene or MeCN.

*Spectra of azo dye **12***

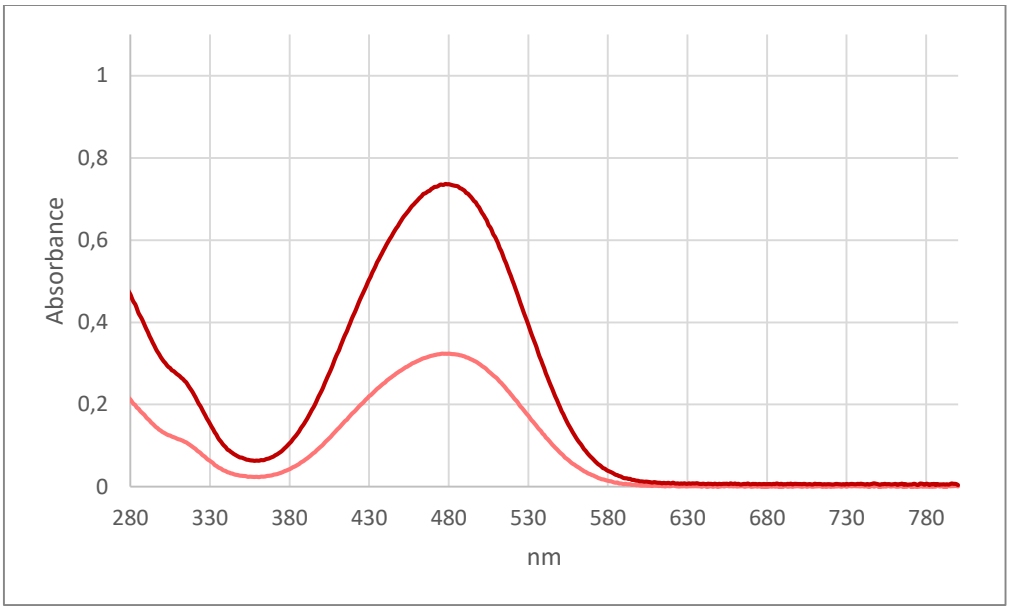


Figure S3. UV/Vis spectra of **12** with the concentration of $6 \cdot 10^{-5}$ M (dark red) and $3 \cdot 10^{-5}$ M (light red)

UV/Vis spectra of azo dye **12** in spectral grade DMSO are shown above. It exhibits absorption in the blue & green light range, explaining the red color of the compound. The maximum absorption was measured to be at a wavelength of 478 nm.

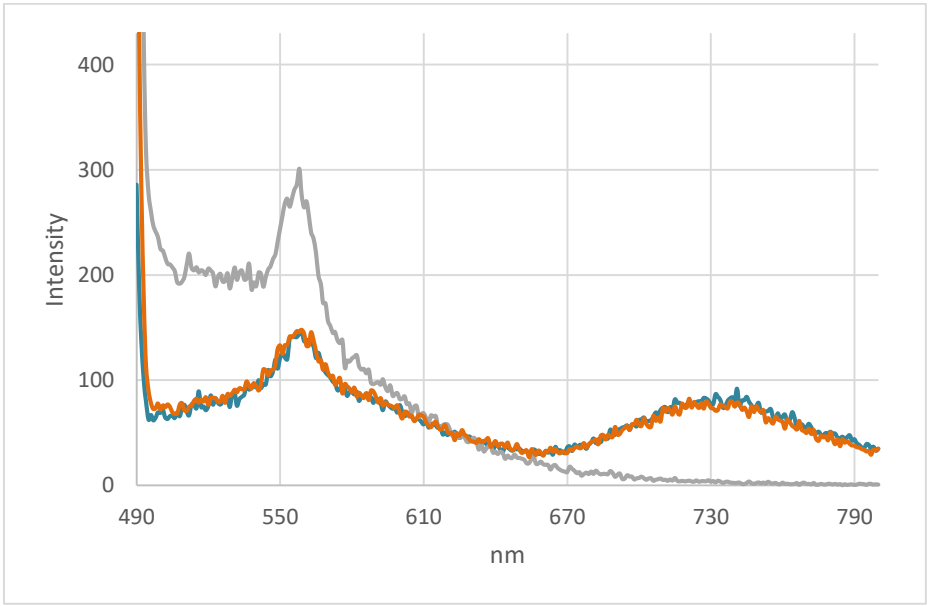


Figure S3. Fluorescence spectra of **12** with conc. of $6 \cdot 10^{-5}$ M (orange & blue) versus pure DMSO (grey)

The measurement was conducted in spectral grade DMSO at a concentration of $6 \cdot 10^{-5}$ M. Measurements with a standard slit width of 5 showed no signal, hence the measurement was performed at a slit width of 10. The chosen excitation wavelength was 478 nm. Two peaks are visible in the spectrum. The left peak is strongest in the blank measurement, indicating it not being emission of **12**, but from a solvent effect, which diminishes with addition of **12**. The right peak with a maximum at around 730 nm is only seen with **12**. We cannot be sure, if this is fluorescence or another effect. There could be conglomeration of our molecules or heat radiation from **12**. Overall the signal strength is very weak, indicating no significant fluorescence of azo dye **12**.

Cyclic voltammetry

Cyclic voltammetry measurements were conducted with a Metrohm Autolab PGSTAT204 potentiostat and Nova 2.1 software. For all experiments a glassy carbon or a platinum working electrode (disk, diameter: 3 mm), a platinum wire counter electrode and a SCE-electrode was used as the reference electrode. Dichloromethane with 0.1 mol/L n-Bu_4NPF_6 as conducting salt served as electrolyte for the measurements. The voltammograms were recorded at a scan rate of 100 mV/s, if not indicated otherwise.

References

[4d] A. S. Aldoshin, A. A. Tabolin, S. L. Ioffe, V. G. Nenajdenko, *Eur. J. Org. Chem.,* **2018**, *2018*, 3816-3825.

[23c] B. W. Grau, M. Dill, F. Hampel, A. Kahnt, N. Jux, S. B. Tsogoeva, *Angew. Chem. Int. Ed.,* **2021**, *60*, 22307-22314.

[25] T. Yamaguchi, Y. Sugiura, E. Yamaguchi, N. Tada, A. Itoh, *Asian J. Org. Chem.,* **2017**, *6*, 432-435.

[34] a) Y.-X. Chen, J.-T. He, M.-C. Wu, Z.-L. Liu, K. Tang, P.-J. Xia, K. Chen, H.-Y. Xiang, X.-Q. Chen, H. Yang, *Org. Lett.,* **2022**, *24*, 3920-3925; b) D. M. Barnes, A. R. Haight, T. Hameury, M. A. McLaughlin, J. Mei, J. S. Tedrow, J. D. Riva Toma, *Tetrahedron,* **2006**, *62*, 11311-11319; c) C. Wangen, A. Raithel, J. Tillmanns, C. Gege, A. Herrmann, D. Vitt, H. Kohlhof, M. Marschall, F. Hahn, *Antivir. Res.,* **2024**, *221*, 105769; d) M. Marschall, M. Freitag, S. Weiler, G. Sorg, T. Stamminger, *Antimicrob. Agents Chemother.,* **2000**, *44*, 1588-1597; e) G. Repetto, A. del Peso, J. L. Zurita, *Nat. Protoc.,* **2008**, *3*, 1125-1131.