Supporting information

Late-Stage Functionalization of the 4-amino-2-Pyridone Chemotype Using Electrochemical and MCR approaches

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1. General considerations

All solvents and commercially available reagents were purchased from Fisher Scientifics and Fluorochem and used without further purification unless otherwise stated. Solvents used for work-up and purification procedures were of technical grade. TLC was carried out using Sigma-Aldrich TLC plates (silica gel on Al foils, SUPELCO Analytical, Merck 60 F254 silica plates). Visualization was accomplished by irradiation with a UV lamp and/or staining with either $KMnO_4$ or ninhydrin. Column chromatography was performed over Silica gel 60 Å (40-63µ mesh). Residual solvent was removed using a static oil pump (< 10 mbar).

All reactions were carried out under aerobic conditions unless otherwise stated. Electrolyses were performed using an IKA Electrasyn 2.0, using carbon graphite working electrode and graphite counter electrode, and using a variable stirring rate between 400- 1500 rpm. Microwave assisted reaction were performed using a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC). The machine consists of a continuous focused microwave power delivery system with an operator-selectable power output from 0 to 300 W. The temperature inside the reaction vessel was monitored using a calibrated infrared temperature control mounted under the reaction vessel. All experiments were performed using a stirring option whereby the reaction mixtures were stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel.

NMR spectra were obtained using a Bruker AV-400 MHz NMR and Jeol 600 MHz ECZ600R NMR spectrometers and are reported in parts per million (ppm) relative to TMS. All heteronuclear NMR spectra were ^{1}H- decoupled and recorded at room temperature unless otherwise stated. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ, ppm), integration, multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet; br, broad), and coupling constant (Hz). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). Data for ^{19}F NMR spectra are reported as follows: chemical shift (δ, ppm), integration, and multiplicity (s, singlet).
Elemental analyses were performed by using a FlashSmart CHNS analyzer (Thermo Fisher) with gas-chromatographic separation. All final compounds were >95% pure as determined by elemental analysis (within 0.4% of the theoretical values). Low resolution mass spectrometry measurements were performed on an Agilent 6100 Series InfinityLab LC/MSD iQ, Single Quadropole analyzer and are reported in the form of (m/z). Melting points were taken using a Gallenkamp melting point apparatus and were uncorrected.

2. Electrochemistry experiments

GENERAL POLISHING PROCEDURE: Graphite and platinum electrodes were washed after each experiment by sonication in acetone (5 minutes x2) and methanol (5 minutes).
When the platinum electrode surface resulted passivated, the surface layer was removed by alumina scrub, then washed with water, methanol and acetone.
Ag wire electrode was washed using water and acetone.

CYCLIC VOLTAMMETRY EXPERIMENTS:

Figure S1. Electrasyn 2.0 and cyclic voltammetry set of electrodes used for collecting the voltammograms.

1. All CV Experiments were performed with Electrasyn 2.0.
2. Data were elaborated with Excel.
3. Experimental conditions: Methanol as solvent (4.0 mL); $TBAClO_4$ as supporting electrolyte (100 mM), cyclic voltammetry kit as electrodes: 1) Working electrode: 3 mm diameter glassy carbon disc electrode, 2) Counter electrode: platinum plate electrode, 3) Reference electrode: Ag wire (Ag/AgCl); $TBAClO_4$ 0.1 M as supporting electrolyte.
   Experimental parameters: Segments: 3. Initial voltage: 0.0 V. Upper voltage: 2.0 V. Lower voltage: -1.0 V. Final voltage: 0.0 V. Sweep: 100mV/s.

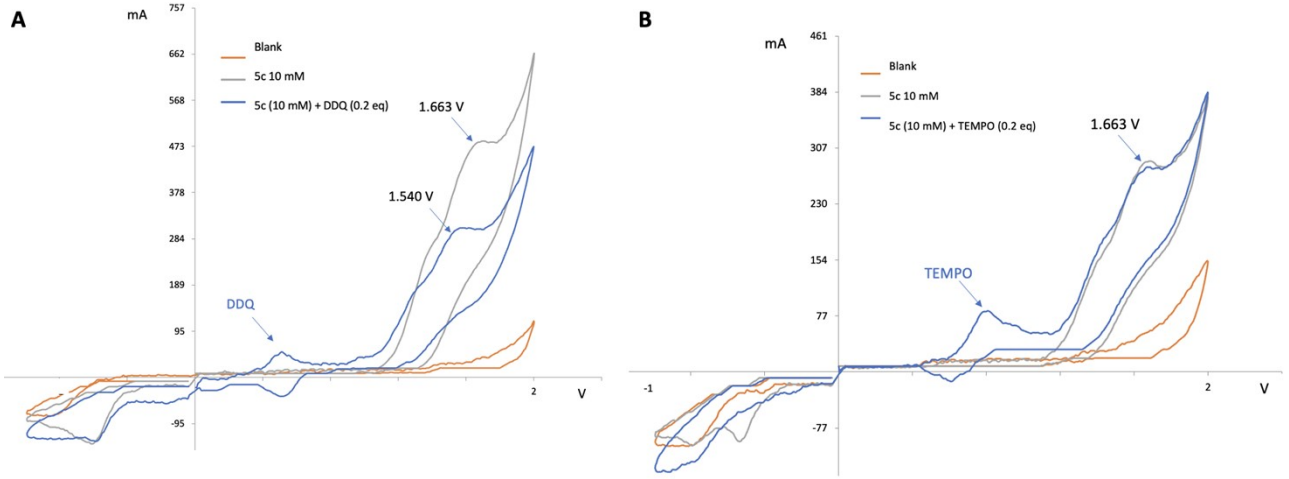


Figure S2. Voltammograms of **5c** in combination with different electrocatalyst (DDQ an TEMPO, 0.2 eq). Graphs: A) In orange: blank (only $TBAClO_4$ 100 mM); In grey: $TBAClO_4$ 100 mM, **5c** 10 mM; In blue: $TBAClO_4$ 100 mM, **5c** 10 mM and DDQ 2 mM. B) In orange: blank (only $TBAClO_4$ 100 mM); In grey: $TBAClO_4$ 100 mM, **5c** 10 mM; In blue: $TBAClO_4$ 100 mM, **5c** 10 mM and TEMPO 2 mM.

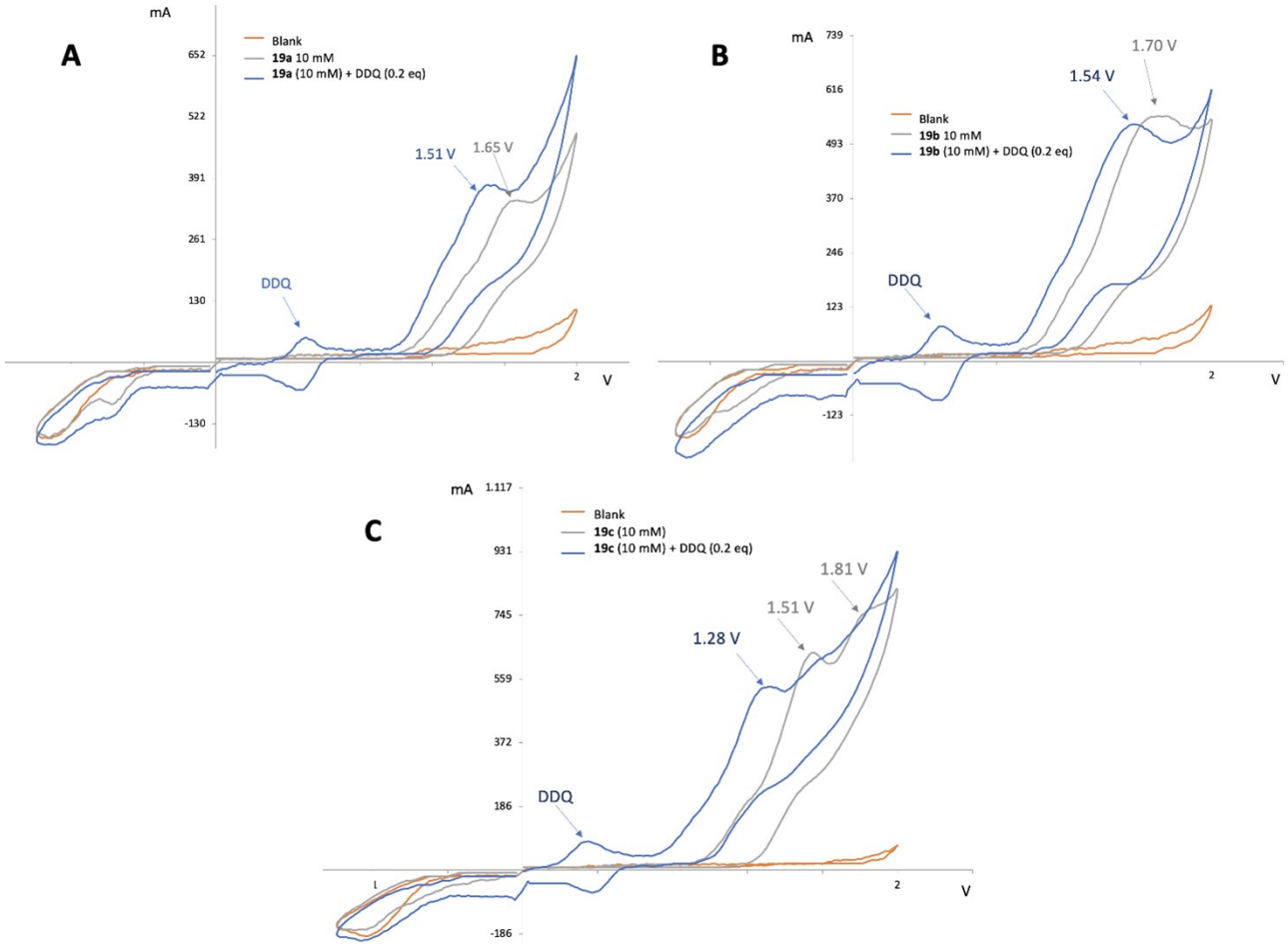
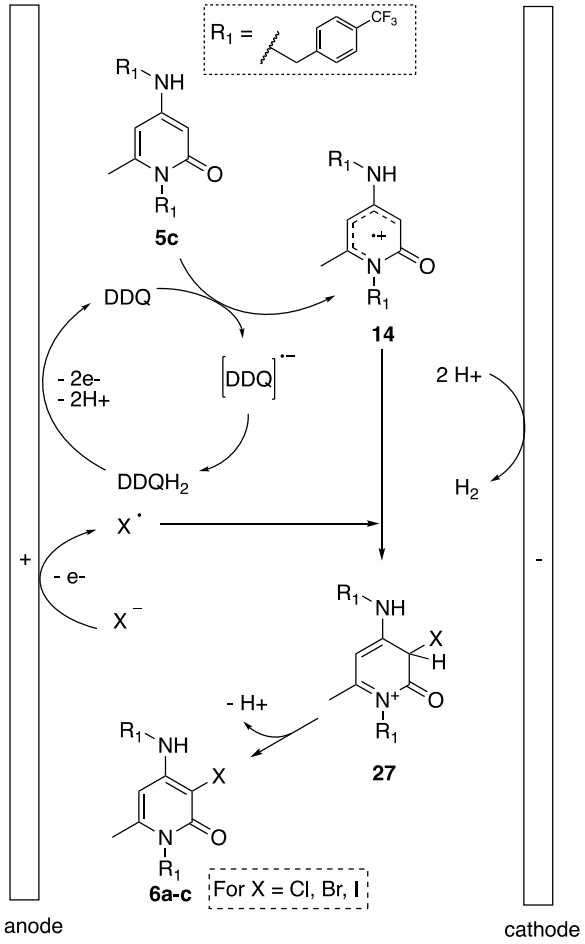
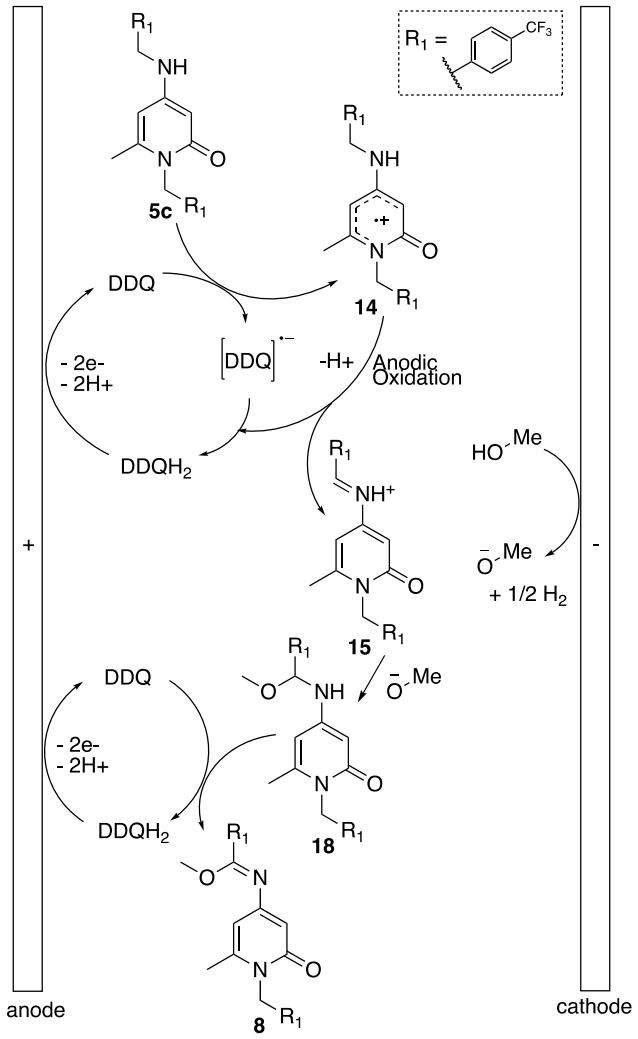


Figure S3. Voltammograms of **19a-c** in the reaction conditions. Graphs: A) In orange: blank (only $TBAClO_4$ 100 mM); In grey: $TBAClO_4$ 100 mM, **19a** 10 mM; In blue: $TBAClO_4$ 100 mM, **19a** 10 mM and DDQ 2 mM. B) In orange: blank (only $TBAClO_4$ 100 mM); In grey: $TBAClO_4$ 100 mM, **19b** 10 mM; In blue: $TBAClO_4$ 100 mM, **19b** 10 mM and DDQ 2 mM. C) In orange: blank (only $TBAClO_4$ 100 mM); In grey: $TBAClO_4$ 100 mM, **19c** 10 mM; In blue: $TBAClO_4$ 100 mM, **19c** 10 mM and DDQ 2 mM.

3. Proposed reaction mechanisms

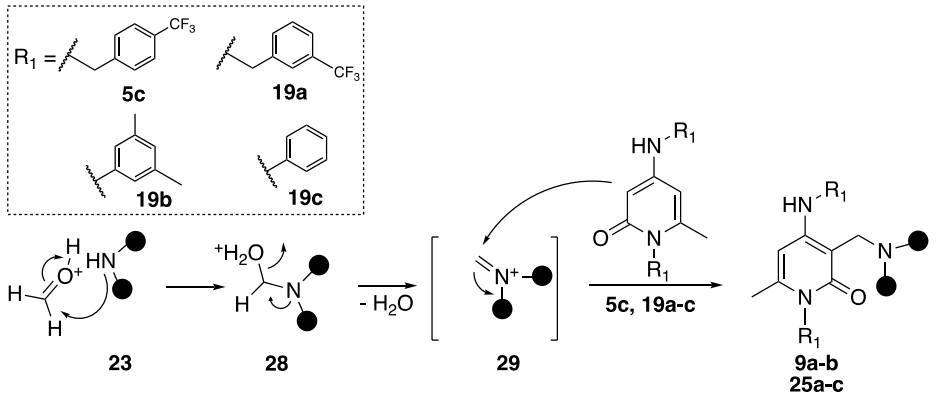


Scheme S1. Synthesis of compounds of type **6**.
After the DDQ mediated anodic oxidation of **5c** to radical cation **14**, this intermediate reacts with the radical X·, anodically generated starting from the corresponding supporting electrolyte, giving rise to the tetrameric intermediate of type **27** which, by losing a proton, yields the desired product of type **6**.

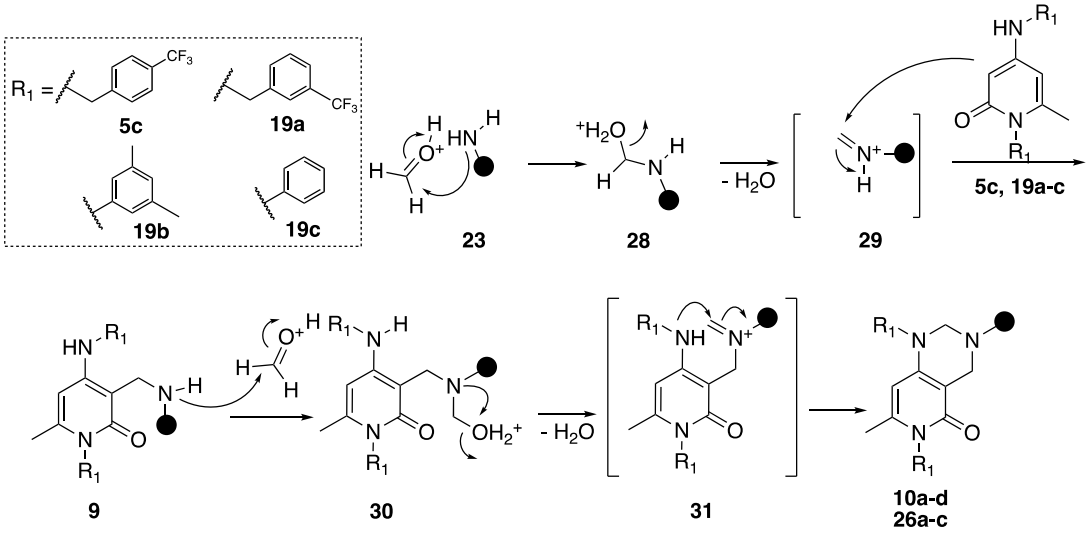


Scheme S2. Synthesis of compound **8**.

After the DDQ mediated anodic oxidation of **5c** to radical cation **14**, this intermediate is further oxidized to iminium cation **15**, which then reacts with methoxide (cathodically generated *in situ* from the solvent, MeOH). The resulting amine **18** is further oxidized (DDQ catalyzed reaction), giving rise to the corresponding enamine **8**.



Scheme S3. MCR using secondary amine as nucleophiles: Mannich reaction.
The iminium cation **28**, formed through condensation reaction between amine **23** and formaldehyde, reacts with the 4-amino-2-pyridone **5c** or **19a-c**, giving rise to the corresponding product **9a-b or 25a-c**.



Scheme S4. MCR using primary amine as nucleophiles.
The iminium cation **28**, formed through condensation reaction between amine **23** and formaldehyde, reacts with the 4-amino-2-pyridone **5c** or **19a-c**, giving rise to the corresponding intermediate of type **9**. The highly reactive intermediate is not isolable, and reacts with another equivalent of formaldehyde, affording the iminium cation **31**, which then gives rise to the corresponding products **10a-d** or **26a-c** through intramolecular cyclization due to the nucleophilic attack of the N4.

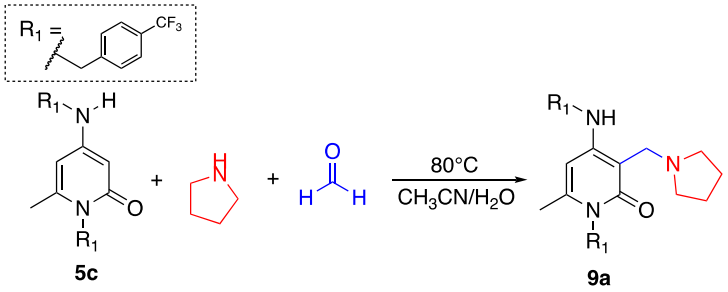
4. Tables for the optimization of reaction conditions

Table S1. Optimization conditions for the synthesis of compound **8**.[a]

Entry	Supporting electrolyte	TFA (cat.)	Yield (%)[b]	I (mA)	Total charge (F/mol)
1	NaCN	no	0	10	2
2	**NaCN**	**no**	**20**	**1.5**	**8**
3	nBu$_4$ClO$_4$	yes	0	1.5	2
4	nBu$_4$ClO$_4$	no	0	1.5	2
5	nBu$_4$F	yes	0	1.5	2
6	nBu$_4$F	yes	0	1.5	2
7	NaClO$_4$	yes	0	1.5	2
8	NaClO$_4$	no	0	1.5	2
9	MeONa	yes	0	1.5	2
10	MeONa	no	0	1.5	2
11	KBr	yes	0	1.5	2
12	Et$_4$NTs	yes	0	1.5	2
13	nBu$_4$PF$_6$	yes	0	1.5	2
14	nBu$_4$PF$_6$	no	0	1.5	2
15[c]	/	yes	0	1.5	Not started

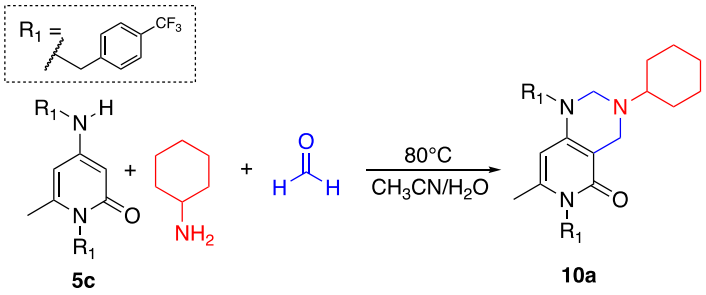
[a]Reaction Conditions: graphite anode (8 x 52.5 x 2 mm), graphite electrode (8 x 52.5 x 2 mm), **5c** (0.1 mmol), DDQ (0.02 mmol), electrolyte (0.2 mmol), methanol (4 mL), electrolysis at a constant current for 2-8 F/mol in an undivided cell at room temperature.
[b]Isolated yields.
[c]Resistance too high.

Table S2. Optimization conditions for the synthesis of **9a**.



Entry	heating	time	yield (%)
1	conventional	overnight	70
2	Microwave, sealed tube	40 minutes	73
3	Microwave, open vessel	40 minutes	72

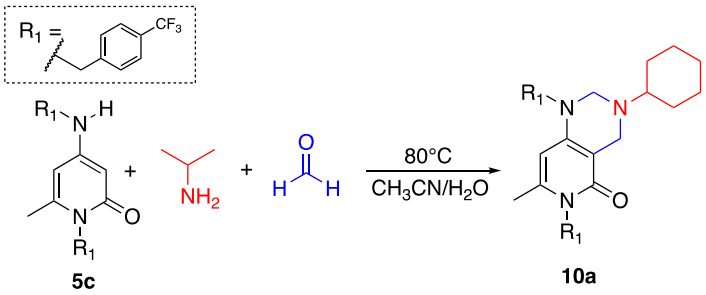
Table S3. Optimization conditions for the synthesis of **10a**.



5c 10a

Entry	heating	time	yield (%)
1	conventional	overnight	47
2	microwave, sealed tube	40 minutes	43
3	microwave, open vessel	overnight	63

Table S4. Optimization conditions for the synthesis of **10b**.



5c 10a

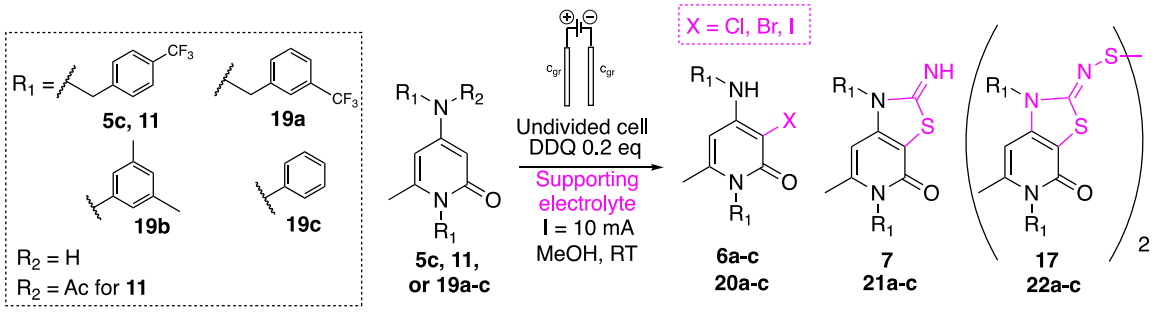
Entry	heating	time	yield (%)
1	conventional	overnight	40
2	microwave, sealed tube	40 minutes	40
3	microwave, open vessel	overnight	40

5. General procedures

GENERAL PROCEDURE 1 (GP1)

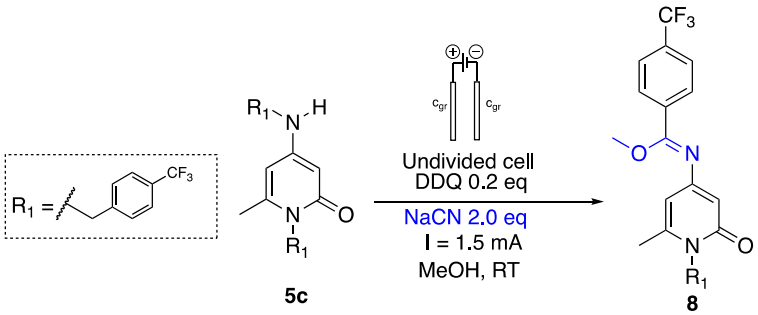
In a 10 mL microwave tube, equipped with magnetic stir bar and septum, a mixture 4-hydroxy-6-methyl-2-pyrone (100 mg, 1 equivalent, 0.79 mmol) and the proper amine (2 equivalents) was heated at 100°C for 6 minutes in the microwave apparatus (maximum power input: 300 W; maximum pressure: 250 psi; power max: OFF; stirring: ON). After cooling to room temperature, the solid was solubilized in AcOEt, washed with distilled H_2O, and the organic phase extracted 3 times, then the collected organic layers were washed with BRINE, and finally dried over Na_2SO_4. Once removed the solvent under reduced pressure, the resulting crude was purified by flash chromatography, affording the desired product.

GENERAL PROCEDURE 2 (GP2)



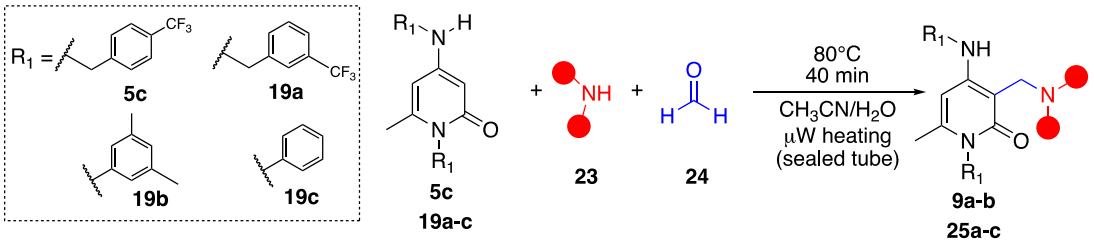
A 10 mL IKA Electrasyn electrochemical vial was charged with compound **5c, 11** or **19a-c** (0.10 mmol, 1 eq), DDQ (4.54 mg, 0.02 mmol, 0.2 eq), the appropriate supporting electrolyte (0.2 mmol, 2 eq), TFA (depending on the case, catalytic amount, 1 drop), and MeOH (4 mL). The resulting mixture was then electrolysed at a constant current of 10 mA until complete conversion of the starting material, as monitored by TLC analysis (2-4 F/mol). Upon completion, the crude reaction mixture was poured into water and extracted with ethyl acetate. The combined organic extracts were washed with BRINE, dried over Na_2SO4, filtered, and the solvent was removed under vacuum. The desired product was then obtained pure after flash chromatography purification.

GENERAL PROCEDURE 3 (GP3)



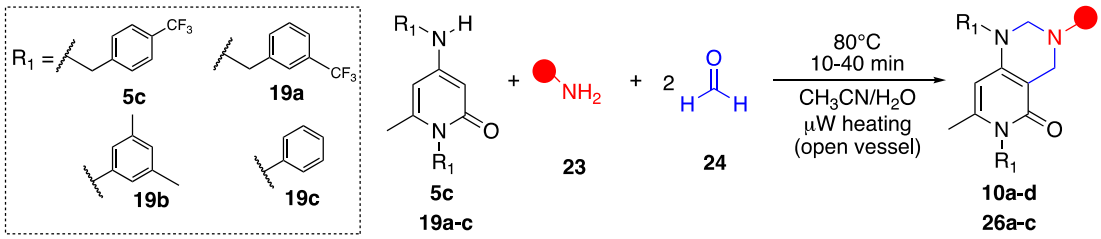
A 10 mL IKA Electrasyn electrochemical vial was charged with compound **5c** (0.10 mmol, 1 eq), DDQ (5.45 mg, 0.02 mmol, 0.2 eq), NaCN (9.8 mg, 0.20 mmol, 2 eq), and MeOH (4.0 mL). The resulting mixture was then electrolysed at a constant current of 1.5 mA until complete conversion of the starting material, as monitored by TLC analysis (8 F/mol). Upon completion, the crude reaction mixture was purified by flash chromatography (DCM/MeOH 98:2), affording the desired product (20%).

GENERAL PROCEDURE 4 (GP4)



A microwave tube was charged with compound **5c** or **19a-c** (0.1 mmol, 1 eq), the appropriate amine **23** (0.2 mmol, 2 eq), formaldehyde (0.15 mmol, 1.5 eq) acetic acid (20 mol%), and acetonitrile/distilled water (1:1, 2 mL). The resulting mixture was heated at 80°C in the microwave apparatus in sealed tube (maximum power input: 300 W; maximum pressure: 250 psi; power max: OFF; stirring: ON) for 40 minutes, verifying the complete conversion of the starting material by TLC monitoring. Then saturated aqueous $NaHCO_3$ was added, and the aqueous phase was extracted three times with dichloromethane, the combined organic layers dried over Na_2SO_4, and the solvent evaporated under reduced pressure. The obtained crude of the reaction was purified by flash chromatography, affording the desired product as yellowish solid.

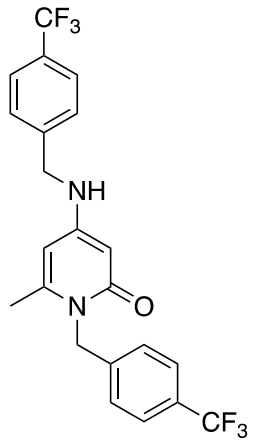
GENERAL PROCEDURE 5 (GP5)



A 10 mL round-bottomed flask was charged with compound **5c** or **19a-b** (0.1 mmol, 1 eq), the appropriate amine **23** (0.2 mmol, 2 eq), formaldehyde (0.4 mmol, 4 eq), acetic acid (20 mol%), and acetonitrile/distilled water (1:1, 2 mL). The resulting mixture was heated at 80°C in the microwave apparatus (maximum power input: 300 W; maximum pressure: 250 psi; power max: OFF; stirring: ON) for 10-40 minutes, verifying the complete conversion of the starting material by TLC monitoring. Then saturated aqueous $NaHCO_3$ was added, and the aqueous phase was extracted three times with dichloromethane, the combined organic layers dried over Na_2SO_4, and the solvent evaporated under reduced pressure. The obtained crude of the reaction was purified by flash chromatography, affording the desired product as white solid.

6. Characterization of the compounds

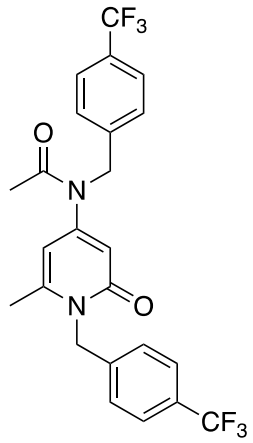
4-Amino-2-pyridones starting materials:



Compound 5c

6-methyl-1-(4-(trifluoromethyl)benzyl)-4-((4-(trifluoromethyl)benzyl)amino)pyridin-2(1*H*)-one

According to GP1, using 4-(trifluoromethyl)benzylamine as proper amine (2 equivalents, 1.58 mmol, 138μL) the desired product was obtained after flash chromatography purification ($CHCl_3$/MeOH 99/1-98/2), in 55% yield (180.40 mg). White solid, m.p. 171-173 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.505 (2H, d, J = 7.83 Hz), 7.46 (2H, d, J = 7.83 Hz), 7.33 (2H, d, J = 7.83 Hz), 7.16 (2H, d, J = 7.83 Hz), 5.53 (1H, d, J = 1.89 Hz), 5.46 (1H, d, J = 1.89 Hz), 5.18 (2H, bs), 4.79 (1H, bs), 4.26 (2H, d, J = 4.60 Hz), 2.04 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.5, 153.9, 144.5, 140.7, 140.5, 128.8 (q, $J_{C\text{-}F}$ = 32.51 Hz), 128.5 (q, $J_{C\text{-}F}$ = 32.51 Hz), 126.4, 125.6, 124.7, 124.7, 123.0 (2C, q, $J_{C\text{-}F}$ = 271.69 Hz), 99.0, 89.9, 45.3, 44.9, 19.4. ^{19}F NMR (564 MHz, $CDCl_3$) δ - 62.43 (3F, s), - 62.45 (3F, s). MS (ESI) m/z 441.2 $[M+H]^+$; 463.3 $[M+Na]^+$.

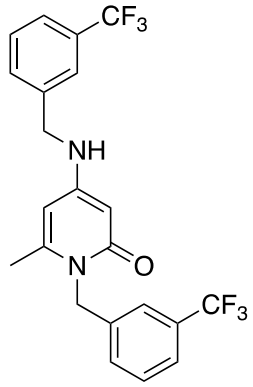


Compound 11

***N*-(6-methyl-2-oxo-1-(4-(trifluoromethyl)benzyl)-1,2-dihydropyridin-4-yl)-*N*-(4-(trifluoromethyl)benzyl)acetamide**

In a 10 mL microwave tube, equipped with magnetic stir bar and septum, a mixture of compound **5c** (0.10 mmol, 44-04 mg), acetyl chloride (2.5 eq, 0.25 mmol, 17.77 μL), and pyridine (2.5 eq, 0.25 mmol, 20.14 μL) in anhydrous DCM (1.5 mL) was heated at 45 °C for 30 min in the microwave apparatus (maximum power input: 300 W; maximum pressure: 250 psi; power max: OFF; stirring: ON). After cooling to room temperature, the solution was diluted with Ethyl Acetate and washed with $NaHCO_3$ sat. sol. The aqueous phase was then extracted with Ethyl Acetate (3 times), and the

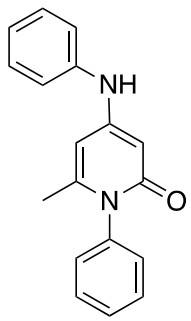
collected organic layers washed with BRINE, dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The crude of the reaction was then purified by flash chromatography (DCM/MeOH 98/2), affording in 51% yield (46.00 mg) the desired product as yellowish solids. m.p. 82-84 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.49 (m, 4H), 7.28 (2H, d, J = 8.37 Hz), 7.17 (2H, d, J = 8.37 Hz), 6.19 (1H, d, J = 2.30 Hz), 5.84 (1H, s), 5.26 (2H, s), 4.85 (2H, s), 2.18 (3H, s), 2.09 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.6, 162.7, 151.7, 146.5, 139.6, 138.7, 128.9 (q, $J_{C\text{-}F}$ = 32.83 Hz), 128.8 (q, $J_{C\text{-}F}$ = 32.51 Hz), 126.9, 125.7, 124.8, 124.8, 124.6, 124.5, 122.9 (q, $J_{C\text{-}F}$ = 272.08 Hz), 121.8 (q, $J_{C\text{-}F}$ = 272.08 Hz), 113.1, 105.4, 50.3, 45.8, 21.7, 19.7. ^{19}F NMR (564 MHz, $CDCl_3$) δ -62.47 (3F, s), -62.57 (3F, s). MS (ESI) m/z 483.1 $[M+H]^+$**.**



Compound 19a

6-methyl-1-(3-(trifluoromethyl)benzyl)-4-((3-(trifluoromethyl)benzyl)amino)pyridin-2(1*H*)-one

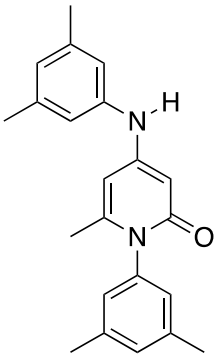
According to GP1, using 3-(trifluoromethyl)benzylamine as proper amine (2 equivalents, 1.58 mmol, 138μL) the desired product was obtained after flash chromatography purification ($CHCl_3$/MeOH 99/1-98/2), in 55% yield (180.40 mg). White solid, m.p. 190-194 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.28 (6H, m), 7.20 (1H, d, J = 7.50 Hz), 5.52 (1H, d, J = 1.87 Hz), 5.37 (1H, d, J = 2.41 Hz), 5.22 (1H, t, J = 5.35 Hz), 5.14 (2H, bs), 4.20 (2H, d, J = 5.62 Hz), 2.00 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.7, 155.0, 145.3, 138.9, 138.6, 131.1 (q, $J_{C\text{-}F}$ = 32.21 Hz), 131.0 (q, $J_{C\text{-}F}$ = 33.28 Hz), 130.6, 129.6, 129.3, 129.2, 124.4, 124.3, 124.0 (2C), 124.0 (q, $J_{C\text{-}F}$ = 272.26 Hz), 124.0 (q, $J_{C\text{-}F}$ = 272.97 Hz), 123.9, 123.8, 123.0, (2C), 100.1, 90.7, 46.3, 45.8, 20.4. ^{19}F NMR (564 MHz, $CDCl_3$) δ -62.49 (6F, bs). MS (ESI) m/z 441.2 $[M+H]^+$.



Compound 19b

6-methyl-1-phenyl-4-(phenylamino)pyridin-2(1*H*)-one

According to GP1, using aniline as proper amine (2 equivalents, 1.58 mmol, 156 μL) the desired product was obtained after flash chromatography purification (hexane/ethyl actetate 6/4), in 50% yield (109.2 mg). White solid, m.p. 190-195 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.35 (2H, m), 7.32-7.20 (1H, m), 7.25-7.21 (2H, m), 7.11-7.06 (4H, m), 7.03-7.00 (1H, t, J = 7.43 Hz), 6.55 (1H, s), 5.92 (1H, d, J = 2.48 Hz), 5.75 (1H, d, J = 1.73 Hz), 1.77 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 165.1, 130.1, 145.9, 139.3, 138.9, 129.5, 129.3, 128.5, 124.2, 122.6, 99.7, 93.6, 21.6. MS (ESI) m/z 277.1 $[M+H]^+$.

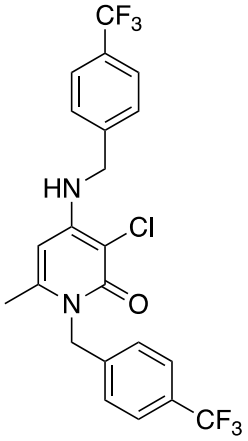


Compound 19c

1-(3,5-dimethylphenyl)-4-((3,5-dimethylphenyl)amino)-6-methylpyridin-2(1*H*)-one

According to GP1, using 3,5-dimethylaniline as proper amine (2 equivalents, 1.58 mmol, 197.2 μL) the desired product was obtained after flash chromatography purification (Dichloromethane/Methanol 98/2), in 40% yield (105.0 mg). White solid, m.p. 210-215 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (1H, s), 6.80 (2H, s), 6.78 (2H, s), 6.74 (1H, s), 6.59 (1H, s), 6.02 (1H, d, J = 2.34 Hz), 5.74 (1H, d, J = 1.69 Hz), 2.32 (6H, s), 2.29 (6H, s), 1.87 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 165.3, 153.0, 145.7, 139.3, 139.2, \38.9, 138.8, 130.1, 126.0, 125.8, 120.1, 99.8, 93.5, 21.5, 21.4, 21.2. MS (ESI) *m/z* 355.2 $[M+Na]^+$.

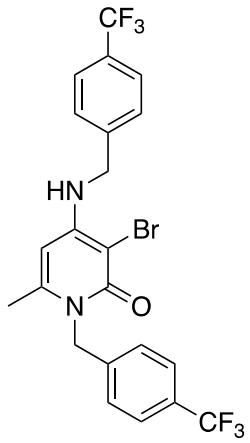
e-LSF:



Compound 6a

3-chloro-6-methyl-1-(4-(trifluoromethyl)benzyl)-4-((4-(trifluoromethyl)benzyl)amino)pyridin-2(1*H*)-one

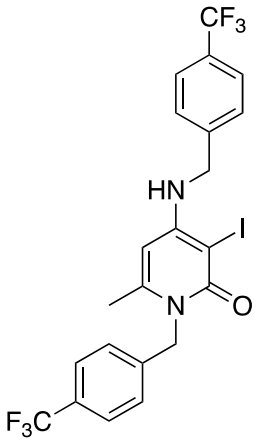
According to GP2, with compound **5c** as staring material (44.0 mg), using KCl (14.91 mg) as supporting electrolyte, and in the presence of TFA, after electrolyzing the reaction mixture for 4 F/mol, the title compound (19.00 mg) was isolated by flash chromatography (dichloromethane/methanol 98/2) in 40% yield. White solid. m.p. 72-75 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (2H, d, *J* = 8.55 Hz), 7.48 (2H, d, *J* = 8.55 Hz), 7.35 (2H, d, *J* = 7.60 Hz), 7.21 (2H, d, *J* = 7.60 Hz), 5.56, (1H, s), 5.33 (1H, t, *J* = 5.70 Hz), 5.27 (2H, s), 4.48 (2H, d, *J* = 5.70 Hz), 2.10 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.5, 149.3, 143.6, 140.7, 139.8, 129.1 (q, $J_{C\text{-}F}$ = 33.88 Hz), 128.8 (q, $J_{C\text{-}F}$ = 31.88 Hz), 126.0, 125.9, 125.0, 124.9, 124.8, 124.7, 123.0 (2C, q, $J_{C\text{-}F}$ = 271.78 Hz), 98.7, 94.0, 46.3, 45.3, 19.9. ^{19}F NMR (564 MHz, $CDCl_3$) δ -62.46 (3F, s), -62.48 (3F, s). MS (ESI) *m/z* 475.3, 477.1 $[M+H]^+$**.**



Compound 6b

3-bromo-6-methyl-1-(4-(trifluoromethyl)benzyl)-4-((4-(trifluoromethyl)benzyl)amino)pyridin-2(1H)-one

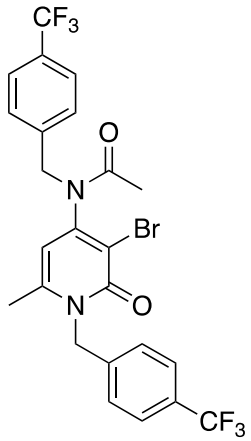
According to GP2, with compound **5c** as staring material (44.0 mg), using KBr (23.80 mg) as supporting electrolyte, and in the presence of TFA, after electrolyzing the reaction mixture for 4 F/mol, the title compound (29.60 mg) was isolated by flash chromatography (dichloromethane/methanol 98/2) in 57 % yield. White solid. m.p. 74-76 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (2H, d, J = 8.48 Hz), 7.47 (2H, d, J = 8.48 Hz), 7.34 (2H, d, J = 7.63 Hz), 7.19 (2H, d, J = 8.48 Hz), 5.52 (1H, s), 5.37 (1H, t, J = 5.85 Hz), 5.27 (2H, s), 4.47 (2H, d, J = 5.85 Hz), 2.08 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.8, 151.8, 145.4, 141.8, 141.0, 130.0 (m), 127.0, 126.9, 126.0, 125.9, 125.7, 125.7, 124.0 (2C, q, $J_{C\text{-}F}$ = 272.1 Hz), 95.2, 91.2, 47.6, 46.5, 20.9. ^{19}F NMR (564 MHz, $CDCl_3$) δ -62.45 (3F, s), -62.48 (3F, s). MS (ESI) m/z 519.2, 521.2 $[M+H]^+$**.**



Compound 6c

3-iodo-6-methyl-1-(4-(trifluoromethyl)benzyl)-4-((4-(trifluoromethyl)benzyl)amino)pyridin-2(1*H*)-one

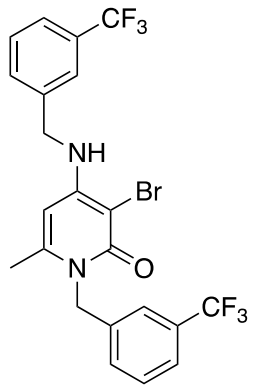
According to GP2, with compound **5c** as staring material (44.0 mg), using I_2 (50.76 mg) as supporting electrolyte, after electrolyzing the reaction mixture for 2 F/mol, the title compound (40.80 mg) was isolated by flash chromatography (dichloromethane/methanol 98/2) in 72 % yield. Yellowish solid. m.p. 135-138 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (2H, d, J = 8.18 Hz), 7.47 (2H, d, J = 8.18 Hz), 7.34 (2H, d, J = 8.18 Hz), 7.19 (2H, d, J = 8.18 Hz), 5.33 (1H, t, J = 6.00 Hz), 5.29 (2H, s), 4.48 (2H, d, J = 6.00 Hz), 2.09 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.7, 163.8, 152.8, 147.6, 140.7, 139.8, 129.9 (2C, q, $J_{C\text{-}F}$ = 33.25 Hz), 128.1, 126.8, 126.0 (2C), 125.7 (2C), 124.0 (2C, q, $J_{C\text{-}F}$ = 272.15 Hz), 114.3, 106.5, 51.5, 46.9, 22.8, 20.8. ^{19}F NMR (564 MHz, $CDCl_3$) δ -62.45 (3F, s), -62.48 (3F, s). MS (ESI) m/z 567.2 $[M+H]^+$**.**



Compound 13

***N*-(3-bromo-6-methyl-2-oxo-1-(4-(trifluoromethyl)benzyl)-1,2-dihydropyridin-4-yl)-*N*-(4-(trifluoromethyl)benzyl)acetamide**

According to GP2, with compound **11** as staring material (48.2 mg), using KBr (23.80 mg) as supporting electrolyte, and in the presence of TFA, after electrolyzing the reaction mixture for 4 F/mol, the title compound (9.0 mg) was isolated by flash chromatography (dichlorometane 100% – dichloromethane/acetone 95/5) in 16 % yield. White solid. m.p. 73-75 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (2H, d, J = 8.16 Hz), 7.48 (2H, d, J = 7.70 Hz), 7.33 (2H, d, J = 8.16 Hz), 7.20 (2H, d, J = 7.70 Hz), 5.62 (1H, s), 5.32 (2H, d, J = 5.22 Hz), 5.26 (1H, d, J = 14.70 Hz), 4.35 (1H, d, J = 14.70 Hz), 2.14 (3H, s), 1.95 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.7, 159.6, 150.0, 144.9, 139.3, 137.9, 129.1 (2C, q, $J_{C\text{-}F}$ = 32.51 Hz), 128.1, 125.9, 124.9, 124.8, 124.2, 122.8 (q, $J_{C\text{-}F}$ = 273.5 Hz), 122.6 (q, $J_{C\text{-}F}$ = 270.1 Hz), 113.5, 107.0, 49.1, 47.6, 21.0, 19.4. ^{19}F NMR (564 MHz, $CDCl_3$) δ -62.47 (3F, s), -62.63 (3F, s). MS (ESI) m/z 561.3, 563.3 $[M+H]^+$**.**

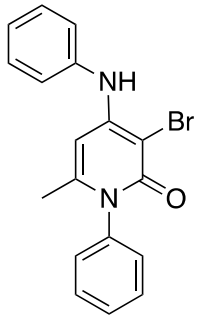


Compound 20a

3-bromo-6-methyl-1-(3-(trifluoromethyl)benzyl)-4-((3-(trifluoromethyl)benzyl)amino)pyridin-2(1*H*)-one

According to GP2, with compound **19a** as staring material (44.0 mg), using KBr (23.80 mg) as supporting electrolyte, and in the presence of TFA, after electrolyzing the reaction mixture for 4 F/mol, the title compound (27.40 mg) was isolated by flash chromatography (dichloromethane/methanol 98/2) in 53 % yield. Yellow solid. m.p. 100-105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.48 (2H, m), 7.43-7.41 (3H, m), 7.35-7.31 (2H, m), 7.27-7.25 (1H, m), 5.56 (1H, s), 5.35 (1H, t, J = 6.00 Hz), 5.27 (2H, s), 4.46 (2H, d, J = 6.00 Hz), 2.09 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.8, 151.8, 146.0, 145.3, 138.7, 137.9, 131.4 (q, $J_{C\text{-}F}$ = 31.52 Hz), 131.0 (q, $J_{C\text{-}F}$ = 31.52 Hz), 130.1

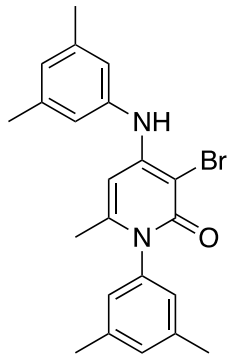
(2C), 129.6, 129.4, 124.7 (2C), 124.3 (2C), 124.0 (2C, q, J_{C-F} = 273.0 Hz), 123.7, 123.6, 123.3 (2C), 95.3, 91.2, 47.6, 46.6, 20.9. ^{19}F NMR (564 MHz, $CDCl_3$) δ -62.47 (3F, s), -62.56 (3F, s). MS (ESI) *m/z* 519.1, 521.1 $[M+H]^+$, 541.1, 543.1 $[M+Na]^+$**.**



Compound 20b

3-bromo-6-methyl-1-phenyl-4-(phenylamino)pyridin-2(1*H*)-one

According to GP2, with compound **19b** as staring material (27.3 mg), using KBr (23.80 mg) as supporting electrolyte, and in the presence of TFA, after electrolyzing the reaction mixture for 4 F/mol, the title compound (17.10 mg) was isolated by flash chromatography (petroleum ether/ethyl acetate 6/4- 5/5) in 48 % yield. Yellow solid. m.p. 186-189 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.42 (2H, m), 7.37-7.33 (3H, m), 7.20-7.16 (3H, m), 7.13-7.11 (2H, m), 6.63 (1H, s), 5.91 (1H, s), 1.78 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 160.2, 150.3, 144.9, 138.9, 138.4, 129.6, 129.5, 128.7, 128.3, 125.8, 124.6, 95.8, 92.7, 21.7. MS (ESI) *m/z* 355.1, 357.1 $[M+H]^+$ 377.0, 379.0 $[M+Na]^+$.

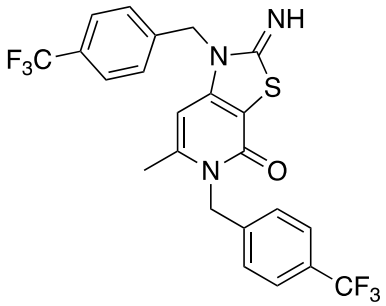


Compound 20c

3-bromo-1-(3,5-dimethylphenyl)-4-((3,5-dimethylphenyl)amino)-6-methylpyridin-2(1*H*)-one

According to GP2, with compound **19c** as staring material (33.2 mg), using KBr (23.80 mg) as supporting electrolyte, and in the presence of TFA, after electrolyzing the reaction mixture for 4 F/mol, the title compound (20.2 mg) was isolated by flash chromatography (petroleum ether/ethyl acetate 7/3) in mixture with a second bromination product in 48 % yield (yield of the mixture of product), which cannot by separated.* Yellow solid. m.p. 115-120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (2H, s), 6.77 (1H, s), 6.72 (2H, s), 6.46 ((1H, s), 5.83 (1H, s), 2.36 (6H, s), 2.26 (6H, s), 1.81 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 160.3, 150.0, 145.2, 139.7, 139.4, 138.7, 138.3, 137.0, 125.8, 125.7, 124.2, 122.3, 95.6, 92.9, 24.0, 21.7, 21.3. MS (ESI) *m/z* 411.1, 413.1 $[M+H]^+$.

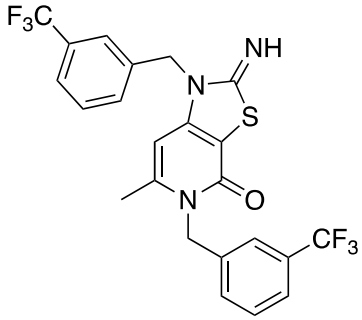
***N.B.** Compound **20c** could not be isolated as a pure product, but in mixture with a second bromination product. The loss of complete chemoselectivity might be due to a higher reactivity of the more electron-rich starting material **19c**, as shown in the voltammograms reported in Figure S3.*



Compound 7

2-imino-6-methyl-1,5-bis(4-(trifluoromethyl)benzyl)-1,2-dihydrothiazolo[5,4-*c*]pyridin-4(5*H*)-one

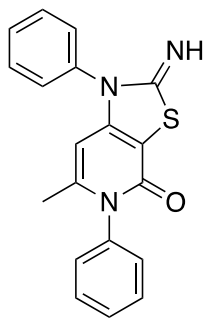
According to GP2, with compound **5c** as staring material (44.0 mg), using KSCN (19.44 mg) as supporting electrolyte, after electrolyzing the reaction mixture for 4 F/mol, the title compound (13.43 mg) was isolated by flash chromatography (Petroleum ether/AcOEt 9/1- 8-2) in 27 % yield. Yellow solid. m.p. 155-160 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (2H, d, J = 8.28 Hz), 7.49 (2H, d, J = 8.28 Hz), 7.32 (2H, d, J = 8.28 Hz), 7.20 (2H, d, J = 8.28 Hz), 7.57 (1H, s), 5.30 (2H, s), 5.08 (2H, s), 2.18 (3H, s). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (1H, bs), 7.74-7.70 (4H, m), 7.53 (2H, d, J = 7.97 Hz), 7.35 (2H, d, J = 7.97 Hz), 6.47 (1H, s), 5.37 (2H, s), 5.18 (2H, s), 2.26 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.0, 156.9, 146.7, 146.0, 140.3, 139.5, 130.1 (2C, q, $J_{C\text{-}F}$ = 32.39 Hz), 127.03, 126.9, 126.0 (2C), 125.9, 122.4 (2C, q, $J_{C\text{-}F}$ = 272.1 Hz), 103.9, 94.4, 46.8, 45.8, 21.3. ^{19}F NMR (564 MHz, $CDCl_3$) δ -62.53 (3F, s), -62.54 (3F, s). MS (ESI) m/z 498.1 $[M+H]^+$**.**



Compound 21a

2-imino-6-methyl-1,5-bis(3-(trifluoromethyl)benzyl)-1,2-dihydrothiazolo[5,4-*c*]pyridin-4(5*H*)-one

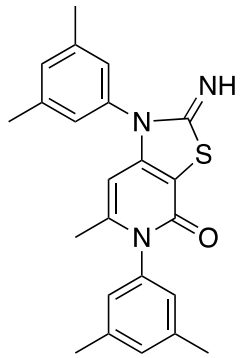
According to GP2, with compound **19a** as staring material (44.0 mg), using KSCN (19.44 mg) as supporting electrolyte, after electrolyzing the reaction mixture for 4 F/mol, the title compound (14.00 mg) was isolated by flash chromatography (dichloromethane/methanol 98/2) in 28 % yield. White solid. m.p. 155-158 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.35 (7H, m), 7.27-7.25 (1H, m), 5.77 (1H, s), 5.30 (2H, bs), 5.08 (2H, s), 2.20 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.1, 156.9, 146.7, 145.9, 137.3, 136.6, 131.3 (q, $J_{C\text{-}F}$ = 32.79 Hz), 131.2 (q, $J_{C\text{-}F}$ = 32.46 Hz), 130.0, 129.9, 129.5, 124.8 (2C), 124.6 (2C), 123.8 (2C, q, $J_{C\text{-}F}$ = 273.0 Hz), 123.7, 123.6, 123.4 (2C), 104.0, 94.4, 46.8, 45.9, 21.3. ^{19}F NMR (564 MHz, $CDCl_3$) δ -62.52 (3F, s), -62.55 (3F, s). MS (ESI) m/z 498.2 $[M+H]^+$**.**



Compound 21b

2-imino-6-methyl-1,5-diphenyl-1,2-dihydrothiazolo[5,4-*c*]pyridin-4(5*H*)-one

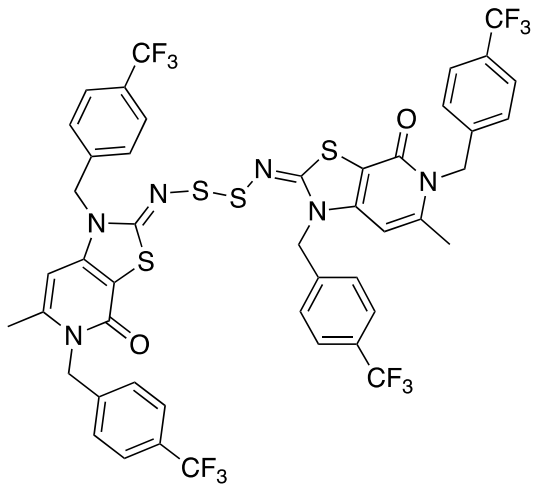
According to GP2, with compound **19b** as staring material (27.3 mg), using KSCN (19.44 mg) as supporting electrolyte, after electrolyzing the reaction mixture for 4 F/mol, the title compound (9.00 mg) was isolated by flash chromatography (petroleum ether/AcOEt/Et_3N 40/60/1) in 27 % yield. White solid. m.p. 160-163 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.51 (2H, m), 7.47-7.38 (4H, m), 7.35-7.32 (2H, m), 7.14-7.12 (2H, m), 5.56 (1H, s), 1.82 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.6, 157.3, 147.5, 145.8, 138.1, 130.3, 129.8, 129.5, 129.0, 128.5, 128.1, 104.3, 94.5, 22.0. MS (ESI) *m*/*z* 334.1 $[M+H]^+$**.**



Compound 21c

1,5-bis(3,5-dimethylphenyl)-2-imino-6-methyl-1,2-dihydrothiazolo[5,4-*c*]pyridin-4(5*H*)-one

According to GP2, with compound **19c** as staring material (33.2 mg), using KSCN (19.44 mg) as supporting electrolyte, after electrolyzing the reaction mixture for 4 F/mol, the title compound (8.00 mg) was isolated by flash chromatography (petroleum ether/AcOEt/Et_3N 50/50/1) in 21 % yield. Yellow solid. m.p. 103-108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (1H, s), 6.99 (1H, s), 6.91 (2H, s), 6.73 (2H, s), 5.51 (1H, s), 2.33 (6H, s), 2.27 (6H, s), 1.84, 3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.4, 147.6, 145.8, 140.3, 139.5, 138.0, 131.3, 130.7, 126.0, 125.6, 104.1, 94.4, 21.9, 21.3 (2C). MS (ESI) *m*/*z* 390.2 $[M+H]^+$**.**

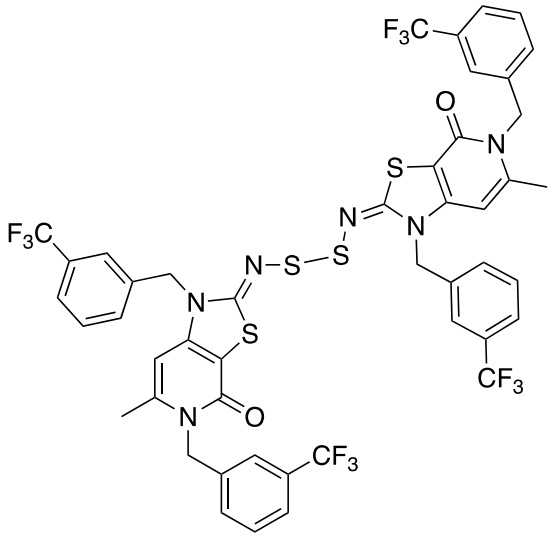


Compound 17

(2*Z*,2'*E*)-2,2'-(disulfanediylbis(azaneylylidene))bis(6-methyl-1,5-bis(4-(trifluoromethyl)benzyl)-1,2-dihydrothiazolo[5,4-*c*]pyridin-4(5*H*)-one)

According to GP2, with compound **5c** as staring material (44.0 mg), using KSCN (19.44 mg) as supporting electrolyte, after electrolyzing the reaction mixture for 4 F/mol, the title compound (14.26 mg) was isolated by flash chromatography (Petroleum ether/Acetone 9/1- 8-2) in 27 % yield. Yellow solid. m.p. 156-159 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (4H, d, *J* = 8.71 Hz), 7.42 (4H, d, *J* =

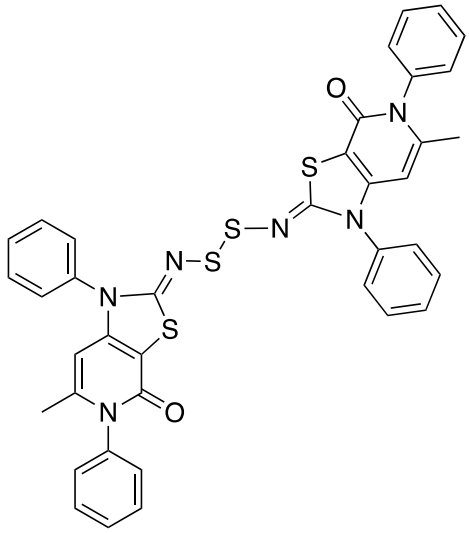
7.66 Hz), 7.27 (4H, d, *J* = 7.66 Hz), 7.20 (4H, d, *J* = 8.71 Hz), 5.82 (2H, s), 5.32 (4H, s), 5.17 (4H, s), 2.20 (6H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 171.2, 157.3, 146.3 (2C), 140.1, 138.9, 130.1 (2C, q, J_{C-F} = 32.39 Hz), 127.2, 126.8, 125.9 (2C), 125.3-122.5 (2C, q, J_{C-F} = 271.49 Hz), 106.5, 94.2, 47.2, 46.9, 21.4. ^{19}F NMR (564 MHz, $CDCl_3$) *δ* -62.56 (6F, s), -62.58 (6F, s). MS (ESI) *m/z* 1079.0 $[M+Na]^+$**.**



Compound 22a

(2*Z*,2'*E*)-2,2'-(disulfanediylbis(azaneylylidene))bis(6-methyl-1,5-bis(3-(trifluoromethyl)benzyl)-1,2-dihydrothiazolo[5,4-*c*]pyridin-4(5*H*)-one)

According to GP2, with compound **19a** as staring material (44.0 mg), using KSCN (19.44 mg) as supporting electrolyte, after electrolyzing the reaction mixture for 4 F/mol, the title compound (8.9 mg) was isolated by flash chromatography (Petroleum ether/Acetone 9/1- 8-2) in 17 % yield. Yellow solid. m.p. 110-115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.46-7-42 (8H, m), 7.39-7.36 (6H, m), 7.24 (2H, d, *J* = 7.93 Hz), 5.84 (2H, s), 5.32 (4H, s), 5.18 (4H, s), 2.21 (6H, s).^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 171.4, 157.3, 146.3, 146.2, 137.2, 136.0, 130.3, 129.8, 129.7, 129.6, 125.2, 124.9 (2C), 124.6, 123.8 (2C), 123.4 (2C), 122.5, 106.6, 94.3, 47.9, 46.9, 21.4. ^{19}F NMR (564 MHz, $CDCl_3$) *δ* -62.53 (12F, s). MS (ESI) *m/z* 1079.0 $[M+Na]^+$**.**

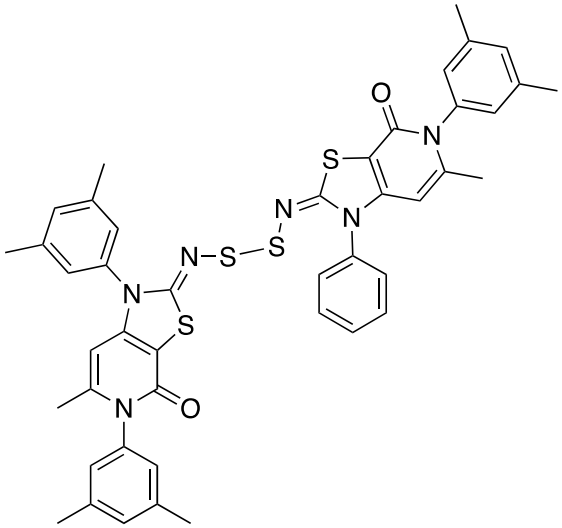


Compound 22b

(2*Z*,2'*Z*)-2,2'-(disulfanediylbis(azaneylylidene))bis(6-methyl-1,5-diphenyl-1,2-dihydrothiazolo[5,4-*c*]pyridin-4(5*H*)-one)

According to GP2, with compound **19b** as staring material (27.3 mg), using KSCN (19.44 mg) as supporting electrolyte, after electrolyzing the reaction mixture for 4 F/mol, the title compound (3.5 mg) was isolated by flash chromatography (Petroleum ether/AcOEt 5/5) in 10 % yield. Yellow solid.

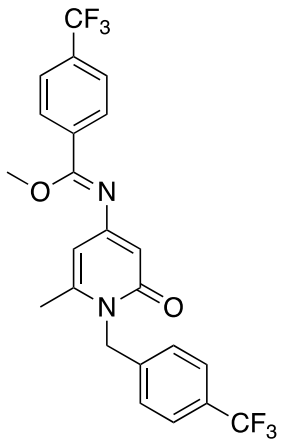
m.p. 164-166 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.44 (8H, m), 7.41-7.37 (4H, m), 7.36-7.34 (4H, m), 7.15-7.13 (4H, m), 5.59 (2H, s), 1.81 (6H, s).^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.6, 157.6, 147.5, 145.8, 138.2, 135.1, 130.2, 129.9, 129.5, 129.1, 128.4, 128.1, 106.7, 94.6, 22.1. MS (ESI) *m*/*z* 729.2 $[M+H]^+$, 751.2 $[M+Na]^+$**.**



Compound 22c

(*E*)-2-(((((*Z*)-1,5-bis(3,5-dimethylphenyl)-6-methyl-4-oxo-4,5-dihydrothiazolo[5,4-*c*]pyridin-2(1*H*)-ylidene)amino)disulfaneyl)imino)-5-(3,5-dimethylphenyl)-6-methyl-1-phenyl-1,2-dihydrothiazolo[5,4-*c*]pyridin-4(5*H*)-one

According to GP2, with compound **19c** as staring material (33.2 mg), using KSCN (19.44 mg) as supporting electrolyte, after electrolyzing the reaction mixture for 4 F/mol, the title compound (4.0 mg) was isolated by flash chromatography (Petroleum ether/AcOEt 6/4) in 10 % yield. Yellow solid. m.p. 179-183 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (4H, s), 6.74 (4H, s), 6.72 (4H, s), 5.52 (2H, s), 2.28 (12H, s), 2.27 (12H, s), 1.83 (6H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.8, 157.6, 147.7, 145.8, 139.9, 139.5, 138.0, 134.9, 131.4, 130.7, 125.9, 125.6, 106.6, 94.5, 29.7, 22.0, 21.3. MS (ESI) *m*/*z* 813.2 $[M+H]^+$**.**



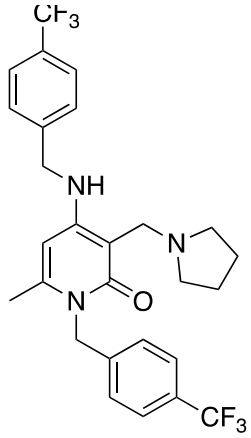
Compound 8

methyl (*Z*)-*N*-(6-methyl-2-oxo-1-(4-(trifluoromethyl)benzyl)-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzimidate

According to GP3, with compound **5c** as staring material (44.0 mg), using NaCN (9.80 mg) as supporting electrolyte, after electrolyzing the reaction mixture for 8 F/mol, the title compound (10.0 mg) was isolated by flash chromatography (petroleum ether/ethyl acetate 60/40 – 50/50) in 20 %

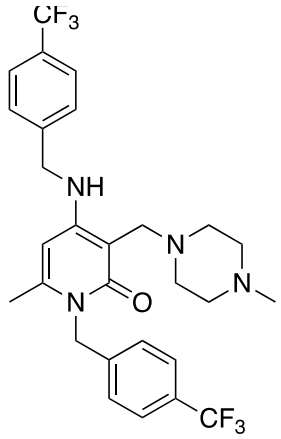
yield. Yellowish solid. m.p. 80-90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.5 (4H, s), 7.48 (2H, J = 8.00 Hz, s), 7.13 (2H, d, J = 8.00 Hz), 5.71 (1H, d, J = 2.00 Hz), 5.62 (1H, s), 5.25 (2H, s), 3.89 (3H, s), 2.11 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.0, 156.6, 156.5, 145.1, 139.5, 132.4, 131.5, 128.4 (2C, q, $J_{C\text{-}F}$ = 33.34 Hz), 128.0, 125.3, 124.49, 124.46, 124.0 (2C, q, $J_{C\text{-}F}$ = 270.1 Hz), 103.7, 103.3, 53.4, 45.0, 28.4, 19.3. ^{19}F NMR (564 MHz, $CDCl_3$) δ -62.53 (3F, s), -62.54 (3F, s). MS (ESI) m/z 469.2 $[M+H]^+$**.**

MCR-LSF:



Compound 9a
6-methyl-3-(pyrrolidin-1-ylmethyl)-1-(4-(trifluoromethyl)benzyl)-4-((4-(trifluoromethyl)benzyl)amino)pyridin-2(1*H*)-one

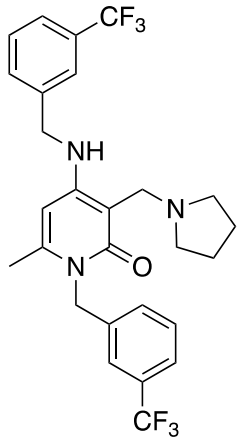
According to GP4, using pyrrolidine (14.22 mg, 16.42 μL) as amine and **5c** as substrate (44.04 mg), the title compound (38.3 mg) was isolated by flash chromatography (dichloromethane/methanol 90/10) in 73% yield after 40 minutes of reaction. White solid. m.p. 120-123 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (1H, s), 7.62 (2H, d, J = 7.79 Hz), 7.56 (2H, d, J = 7.79 Hz), 7.45 (2H, d, J = 8.12 Hz), 7.25 (2H, d, J = 8.12 Hz), 5.60 (1H, s), 5.30 (2H, s), 4.52 (2H, d, J = 5.91 Hz), 4.03 (2H, s), 2.87 (4H, s), 2.15 (3H, s), 1.88 (4H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.4, 154.6, 146.7, 141.8, 140.0, 128.7, (q, $J_{C\text{-}F}$ = 30.79 Hz), 128.4 (q, $J_{C\text{-}F}$ = 32.02 Hz), 126.1, 125.3, 124.8 (2C), 124.6 (2C), 123.11 (q, $J_{C\text{-}F}$ = 272.1 Hz), 122.9 (q, $J_{C\text{-}F}$ = 272.1 Hz), 95.5, 92.0, 51.5, 48.8, 45.7, 45.0, 22.1, 20.2. ^{19}F NMR (564 MHz, $CDCl_3$) δ -62.33 (3F, s), -62.50 (3F, s). MS (ESI) m/z 524.2 $[M+H]^+$**.**



Compound 9b
6-methyl-3-((4-methylpiperazin-1-yl)methyl)-1-(4-(trifluoromethyl)benzyl)-4-((4-(trifluoromethyl)benzyl)amino)pyridin-2(1*H*)-one

According to GP4, using 1-methylpiperazine as amine (20.03 mg, 22.26 μL) and **5c** as substrate (44.04 mg), the title compound (36.0 mg) was isolated by flash chromatography

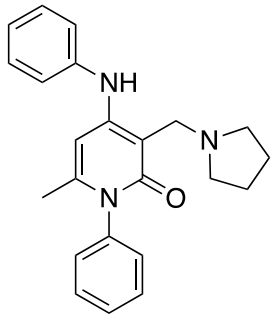
(dichloromethane/methanol 90:10) in 65% yield after 40 minutes. White solid. m.p. 134-136 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (1H, t, J = 5.67 Hz), 7.55 (2H, d, J = 8.09 Hz), 7.46 (2H, d, J = 8.09 Hz), 7.37 (2H, d, J = 8.09), 7.16 (2H, d, J = 8.09), 5.52 (1H, s), 5.21 (2H, s), 4.39 (2H, d, J = 5.67 Hz), 3.70 (2H, s), 2.49-2.11 (8H, m), 2.15 (3H, s), 2.07 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.2, 154.9, 145,3, 143.1, 141.8, 129.7 (q, $J_{C\text{-}F}$ = 32.06 Hz), 129.4 (q, $J_{C\text{-}F}$ = 32.06 Hz), 127.2, 126.7, 125.7, 124.1 (2C, q, $J_{C\text{-}F}$ = 271.4 Hz), 95.6, 55.1, 54.2, 52.1, 46.5, 46.1, 45.9, 21.1. ^{19}F NMR (564 MHz, $CDCl_3$) δ -62.36 (3F, s), -62.42 (3F, s). MS (ESI) m/z 553.2 $[M+H]^+$**.**



Compound 25a

6-methyl-3-(pyrrolidin-1-ylmethyl)-1-(3-(trifluoromethyl)benzyl)-4-((3-(trifluoromethyl)benzyl)amino)pyridin-2(1*H*)-one

According to GP4, using pyrrolidine (14.22 mg, 16.42 μL) as amine and compound **19a** as substrate (44.04 mg), the title compound (29.0 mg) was isolated by flash chromatography (dichloromethane/methanol 95/5) in 55% yield after 40 minutes of reaction. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (1H, s), 7.48-7.37 (5H, m), 7.33 (1H, t, J = 7.80 Hz), 7.28 (1H, s), 7.21 (1H, d, J = 7.80 Hz), 5.53 (1H, s), 5.22 (2H, s), 4.42 (2H, d, J = 6.32 Hz), 3.93 (2H, s), 2.75 (4H, bs), 2.06 (3H, s), 1.77 (4H, bs). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.3, 155.0, 145.7, 140.1, 138.6, 131.1 (q, $J_{C\text{-}F}$ = 31.14 Hz), 130.1, 129.7, 129.3, 129.2, 124.1, 124.1 (q, $J_{C\text{-}F}$ = 271.16 Hz), 124.0 (q, $J_{C\text{-}F}$ = 271.16 Hz), 123.4, 123.0, 96.0,53.0, 46.5, 46.0, 29.7, 23.5, 21.1. ^{19}F NMR (564 MHz, $CDCl_3$) δ -62.43 (3F, s), -62.50 (3F, s). MS (ESI) m/z 524.3 $[M+H]^+$**.**

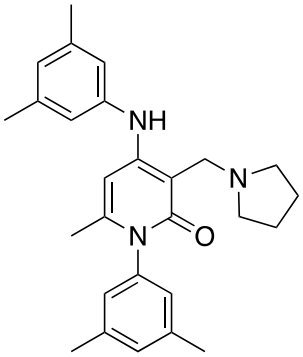


Compound 25b

6-methyl-1-phenyl-4-(phenylamino)-3-(pyrrolidin-1-ylmethyl)pyridin-2(1*H*)-one

According to GP4, using pyrrolidine (14.22 mg, 16.42 μL) as amine and compound **19b** as substrate (27.30 mg), the title compound (21.5 mg) was isolated by flash chromatography (dichloromethane/methanol 96/4 – 90/10) in 60% yield after 40 minutes of reaction. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (1H, bs), 7.42-7.38 (2H, m), 7.33 (1H, d, J = 7.35 Hz), 7.30-7.25 (2H, m), 7.21-7.08 (4H, m), 7.02 (1H, t, J = 7.35 Hz), 6.05 (1H, s), 3.87 (2H, s), 2.72 (4H, bs), 1.81 (4H, bs), 1.78

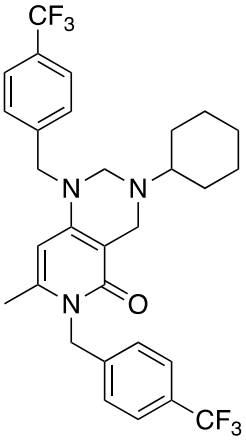
(3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.1, 153.3, 145.1, 140.5, 139.3, 129.5, 129.3, 128.4, 128.3, 123.5, 122.5, 96.8, 53.1, 51.1, 23.7, 21.8. MS (ESI) *m/z* 360.2 $[M+H]^+$**.**



Compound 25c

1-(3,5-dimethylphenyl)-4-((3,5-dimethylphenyl)amino)-6-methyl-3-(pyrrolidin-1-ylmethyl)pyridin-2(1*H*)-one

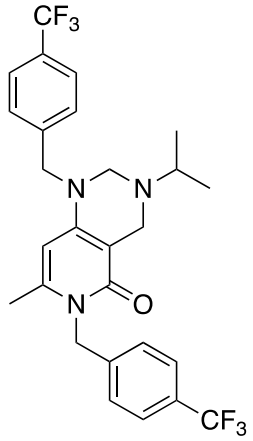
According to GP4, using pyrrolidine (14.22 mg, 16.42 μL) as amine and **19c** as substrate (32.24 mg), the title compound (27.8 mg) was isolated by flash chromatography (dichloromethane/methanol 96/4 – 90/10) in 67% yield after 40 minutes of reaction. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (1H, s), 7.03 (1H, s), 6.83 (2H, s), 6.77 (3H, s), 6.11 (1H, s), 3.90 (2H, s), 2.73 (4H, bs), 2.36 (6H, s), 2.34 (6H, s), 1.89 (3H, s), 1.88 (4H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.0, 152.9, 144.7, 140.5, 139.3, 139.1, 139.0, 129.9, 125.9, 125.2, 120.2, 96.8, 53.1, 51.2, 23.8, 21.8, 21.4, 21.2. MS (ESI) *m/z* 416.3 $[M+H]^+$**.**



Compound 10a

3-cyclohexyl-7-methyl-1,6-bis(4-(trifluoromethyl)benzyl)-2,3,4,6-tetrahydropyrido[4,3-*d*]pyrimidin-5(1*H*)-one

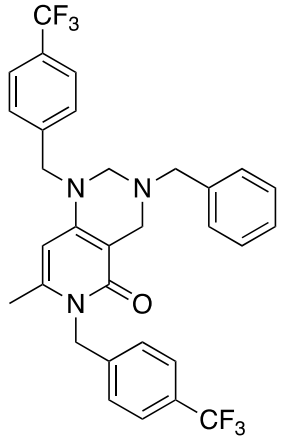
According to GP5, using cyclohexylamine as amine (19.83 mg, 22.93 μL) and **5c** as substrate (44.04 mg, 0.1mmol), the title compound (24.0 mg) was isolated by flash chromatography (ethyl acetate/methanol 98/2 – 95/5) in 63% yield after 40 minutes of reaction. White solid. m.p. 155-158 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (2H, d, J = 7.95 Hz), 7.57 (2H, d, J = 7.95 Hz), 7.40 (2H, d, J = 7.95 Hz), 7,28 (2H, d, J = 7.95 Hz), 5.62 (1H, s), 5.33 (2H, s), 4.53 (2H, s), 4.16 (2H, s), 3.90 (2H, s), 2.55-2.51 (1H, m), 2.15 (3H, s), 1.95 (2H, m), 1.79 (2H, m), 1.63 (1H, m), 1.33-1.13 (5H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.6, 150.7, 143.8, 142.0, 141.7, 129.8 (q, $J_{C\text{-}F}$ = 39.65 Hz), 129.5 (q, $J_{C\text{-}F}$ = 39.65 Hz), 129.3, 126.8, 125.9, 125.8, 125.7 (2C), 124.1 (2C, q, $J_{C\text{-}F}$ = 271.6 Hz), 99.7, 96.2, 66.8, 59.4, 52.3, 46.0, 30.3, 26.0, 25.5, 20.9. ^{19}F NMR (564 MHz, $CDCl_3$) δ -62.40 (3F, s), -62.42 (3F, s). MS (ESI) *m/z* 564.2 $[M+H]^+$**.**



Compound 10b

3-isopropyl-7-methyl-1,6-bis(4-(trifluoromethyl)benzyl)-2,3,4,6-tetrahydropyrido[4,3-*d*]pyrimidin-5(1*H*)-one

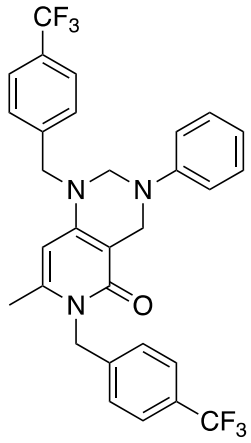
According to GP5, using isopropylamine as amine (11.82 mg, 17.03 μL) and **5c** as substrate (44.04 mg), the title compound (20.5 mg) was isolated by flash chromatography (ethyl acetate/methanol 100/0 – 97/3) in 40% yield after 20 minutes of reaction. White solid. m.p. 83-87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (2H, d, J = 8.11 Hz), 7.57 (2H, d, J = 8.11 Hz), 7.41 (2H, d, J = 8.11 Hz) 7.28 (2H, d, J = 8.11 Hz), 5.63 (1H, s), 5.34 (2H, s), 4.57 (2H, s), 4.10 (2H, s), 3.85 (2H, s), 3.00-2.95 (1H, m), 2.15 (3H, s), 1.18 (3H, s), 1.16 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.6, 150.5, 143.8, 141.9, 141.6, 129.8 (q, $J_{C\text{-}F}$ = 39.83 Hz), 129.5 (q, $J_{C\text{-}F}$ = 40.06 Hz), 126.8, 125.9 (2C), 125.7 (2C), 124.1 (2C, q, $J_{C\text{-}F}$ = 277.54 Hz), 99.9, 96.2, 67.1, 52.5, 51.4, 46.1 29.7, 20.9, 19.9. ^{19}F NMR (564 MHz, $CDCl_3$) δ -62.40 (3F, s), -62.41 (3F, s). MS (ESI) *m/z* 524.2 $[M+H]^+$**.**



Compound 10c

3-benzyl-7-methyl-1,6-bis(4-(trifluoromethyl)benzyl)-2,3,4,6-tetrahydropyrido[4,3-*d*]pyrimidin-5(1*H*)-one

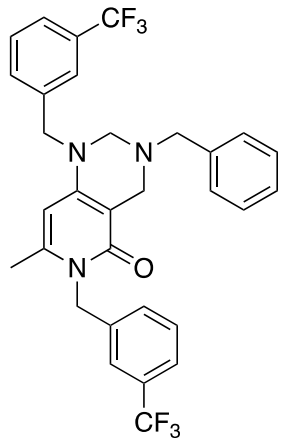
According to GP5, using benzylamine as amine (21.43 mg, 21.85 μL) and **5c** as substrate (44.04 mg), the title compound (42.0 mg) was isolated by flash chromatography (ethyl acetate 100%) in 73% yield after 10 minutes of reaction. White solid. m.p. 145-148 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (2H, d, J = 8.23 Hz), 7.59 (2H, d, J = 8.23 Hz), 7.36 (2H, d, J = 7.99 Hz), 7.31-7.26 (7H, m), 5.67 (1H, s), 5.34 (2H, s), 4.46 (2H, s), 4.03 (2H, s), 3.92 (2H, s), 3.77 (2H, s), 2.18 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.8, 150.3, 144.04, 141.9, 141.7, 137.8, 130.0 (2C, q, $J_{C\text{-}F}$ = 32.06 Hz), 129.0, 128.4, 127.7, 127.4, 126.8, 125.8 (3C), 125.7 (2C), 124.2 (q, $J_{C\text{-}F}$ = 272.03 Hz), 124.1 (q, $J_{C\text{-}F}$ = 271.36 Hz), 98.4, 96.0, 68.1, 57.8, 52.1, 49.7, 46.2, 21.0. ^{19}F NMR (564 MHz, $CDCl_3$) δ -62.39 (3F, s), -62.40 (3F, s). MS (ESI) *m/z* 572.2 $[M+H]^+$**.**



Compound 10d

7-methyl-3-phenyl-1,6-bis(4-(trifluoromethyl)benzyl)-2,3,4,6-tetrahydropyrido[4,3-*d*]pyrimidin-5(1*H*)-one

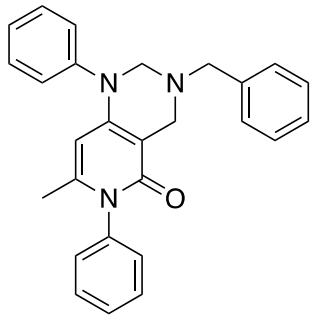
According to GP5, using aniline as amine (8.63 mg, 18.26 μL) and **5c** as substrate (44.04 mg), the title compound (32.4mg) was isolated by flash chromatography (petroleum ether/ethyl acetate 40/60) in 58% yield after 10 minutes of reaction. White solid. m.p. 160-165 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (2H, d, J = 8.09 Hz), 7.54 (2H, d, J = 8.09 Hz), 7.31 (2H, d, J = 8.09 Hz), 7,26 (2H, m), 7.22 (2H, d, J = 8.09 Hz), 6.98 (2H, d, J = 8.09 Hz), 6.94 (2H, t, J = 7.74 Hz), 5.58 (1H, s), 5.36 (2H, s), 4.76 (2H, s), 4.54 (2H, s), 4.50 (2H, s), 2.14 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.5, 151.0, 148.7, 144.3, 141.5, 129.9 (2C, q, $J_{C\text{-}F}$ = 32.09 Hz), 126.8, 125.8 (3C) 124.1 (2C, q, $J_{C\text{-}F}$ = 272.2 Hz), 121.0, 117.8, 99.0, 96.2, 67.8, 51.8, 46.5, 46.2, 29.7, 20.9. ^{19}F NMR (564 MHz, $CDCl_3$) δ -62.41 (6F, bs). MS (ESI) m/z 558.2 $[M+H]^+$**.**



Compound 26a

3-benzyl-7-methyl-1,6-bis(3-(trifluoromethyl)benzyl)-2,3,4,6-tetrahydropyrido[4,3-*d*]pyrimidin-5(1*H*)-one

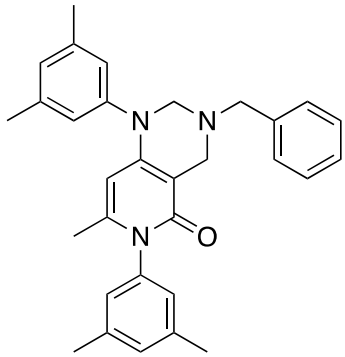
According to GP5, using benzylamine as amine (21.43 mg, 21.85 μL) and **19a** as substrate (44.04 mg), the title compound (45.9 mg) was isolated by flash chromatography (dichloromethane/ethyl acetate 1/1) in 80% yield after 10 minutes of reaction. Yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (1H, d, J = 8.10 Hz), 7.49 (1H, d, J = 7.26 Hz), 7.46 (2H, t, J = 7.74 Hz), 7,44-7,40 (3H, m), 7.34 (1H, d, J = 8.04 Hz), 7.29-7.25 (4H, m), 7.23-7.20 (1H, m), 5.65 (1H, s), 5.30 (2H, s), 4.43 (2H, s), 4.00 (2H, s), 3.88 (2H, s), 3.74 (2H, s), 2.15 (3H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.9, 150.4, 144.1, 139.0, 138.7, 137.9, 131.1 (q, $J_{C\text{-}F}$ = 32,66 Hz), 131.1 (q, $J_{C\text{-}F}$ = 31.98 Hz), 130.0, 129.9, 129.5, 129.4, 129.0, 128.5, 127.4, 124.1 (q, $J_{C\text{-}F}$ = 272.03 Hz), 124.1 (q, $J_{C\text{-}F}$ = 272.23 Hz), 124.5, 124.2, 123.4, 123.3, 98.6, 96.1, 68.2, 57.8, 52.1, 49.6, 46.2, 21.0.^{19}F NMR (564 MHz, $CDCl_3$) δ -62.55 (6F, s). MS (ESI) m/z 572.3 $[M+H]^+$**.**



Compound 26b

3-benzyl-7-methyl-1,6-diphenyl-2,3,4,6-tetrahydropyrido[4,3-*d*]pyrimidin-5(1*H*)-one

According to GP5, using benzylamine as amine (21.43 mg, 21.85 μL) and **19b** as substrate (27.30 mg), the title compound (31.0 mg) was isolated by flash chromatography (dichloromethane/methanol 98/2) in 76% yield after 10 minutes of reaction. White solid. m.p. 110-115 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 (2H, t, J = 7.80 Hz), 7.39 (3H, t, J = 7.38 Hz), 7.29 (2H, m), 7.26-7.23 (3H, m), 7.22-7.18 (5H, m), 7.67 (1H, s), 4.36 (2H, s), 3.97 (2H, s), 3.86 (2H, s), 1.80 (3H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.7, 149.7, 144.0, 143.1, 139.1, 138.3, 129.7, 129.5, 129.1, 128.6, 128.4 (2C), 127.3, 126.3, 126.1, 99.6, 97.4, 69.6, 57.2, 49.4, 21.7. MS (ESI) m/z 408.2 $[M+H]^+$**.**



Compound 26c

3-benzyl-1,6-bis(3,5-dimethylphenyl)-7-methyl-2,3,4,6-tetrahydropyrido[4,3-*d*]pyrimidin-5(1*H*)-one

According to GP5, using benzylamine as amine (21.43 mg, 21.85 μL) and **19c** as substrate (33.24 mg), the title compound (42.4 mg) was isolated by flash chromatography (DCM/Methanol 98/2) in 91% yield after 20 minutes of reaction. White solid. m.p. 115-120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7-34 (2H, m), 7.32-7.28 (2H, m), 7.26-7.24 (1H, m), 7.04 (1H, s), 6.91 (1H, s), 6.85 (2H, s), 6.84 (2H, s), 5.67 (1H, s), 3.90 (2H, s) 2.36 (6H, s), 2.35 (6H, s), 1.86 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.7, 149.7, 143.7, 143.1, 139.3, 139.0, 138.4, 130.0, 129.1, 128.3, 127.8, 127.2, 126.0, 124.1, 98.9, 97.2, 69.7, 57.1, 49.1, 21.6, 21.3 (2C). MS (ESI) m/z 464.3 $[M+H]^+$; 468.3 $[M+Na]^+$.

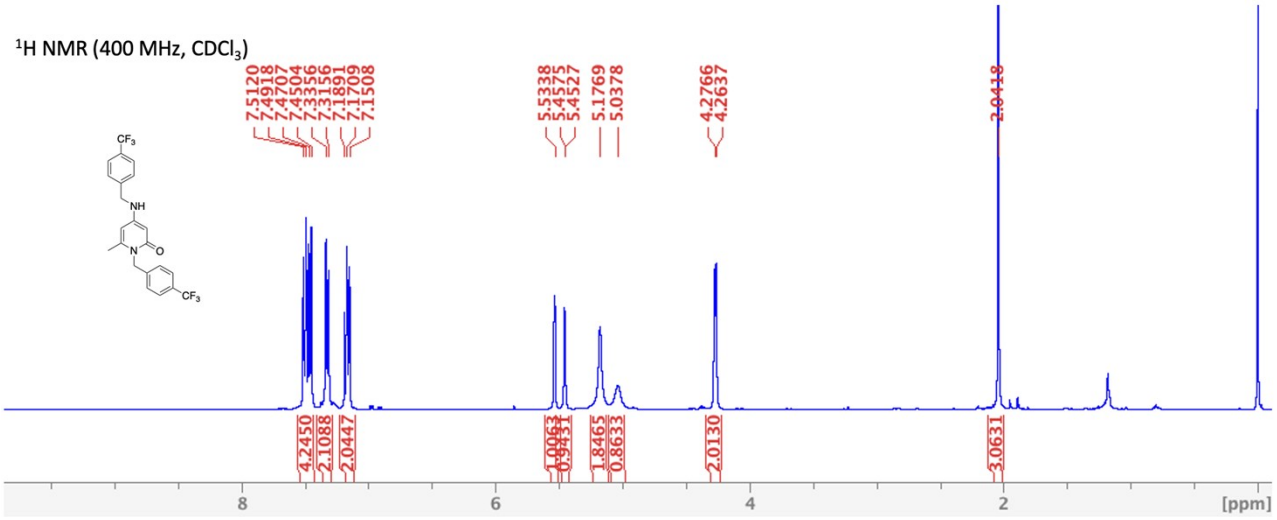
Table S5. Elemental Analysis

Cmpd.	Elemental analysis (%)					
	Calculated			Found		
	C	H	N	C	H	N
5c	60.00	4.12	6.36	60.10	4.02	6.38
11	59.75	4.18	5.81	59.95	4.11	5.76
19a	60.00	4.12	6.36	60.05	4.10	6.40
19b	78.24	5.84	10.14	78.20	5.88	10.05
19c	79.48	7.28	8.43	79.42	7.26	8.40
6a	55.65	3.61	5.90	55.48	3.67	5.86
6b	50.89	3.30	5.39	50.95	3.34	5.27
6c	46.66	3.03	4.95	46.63	3.12	4.90
13	51.35	3.41	4.99	51.43	3.45	4.92
20a	50.89	3.30	5.39	50.86	3.25	5.42
20b	60.86	4.26	7.89	60.80	4.21	7.92
20c	64.24	5.64	6.81	64.22	5.61	6.78
7	55.53	3.44	8.45	55.48	3.40	8.65
21a	55.53	3.44	8.45	55.50	3.41	8.50
21b	68.45	4.53	12.60	68.41	4.57	12.60
21c	70.92	5.95	10.79	70.90	5.95	10.75
17	52.27	3.05	7.95	52.35	3.01	7.78
22a	52.27	3.05	7.95	52.25	3.01	7.91
22b	62.62	3.87	11.53	62.60	3.85	11.49
22c	65.69	5.27	9.99	65.64	5.29	9.95
8	58.98	3.87	5.98	58.96	3.81	5.77
9a	61.95	5.20	8.03	61.91	5.15	8.22
9b	60.86	5.47	10.14	60.88	5.43	10.24
25a	61.95	5.20	8.03	61.91	5.15	8.06
25b	76.85	7.01	11.69	76.80	6.99	11.73
25c	78.03	8.00	10.11	78.00	7.95	10.06
10a	63.93	3.41	4.99	63.98	3.45	4.86
10b	61.95	5.20	8.03	61.84	5.23	8.00
10c	65.14	4.76	7.35	65.12	4.73	7.39
10d	64.63	4.52	7.54	64.57	4.49	7.59
26a	65.14	4.76	7.35	65.10	4.71	7.32
26b	79.58	6.18	10.31	79.57	8.16	10.29
26c	80.31	7.17	9.06	80.32	7.19	9.04

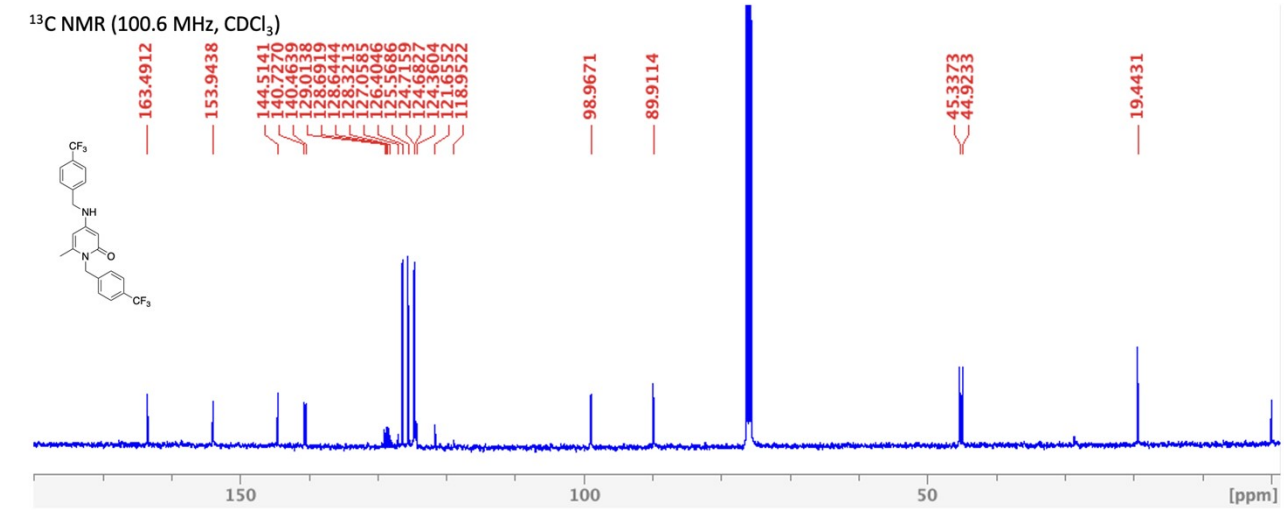
7. NMR Spectra

Starting materials:
Compound 5c

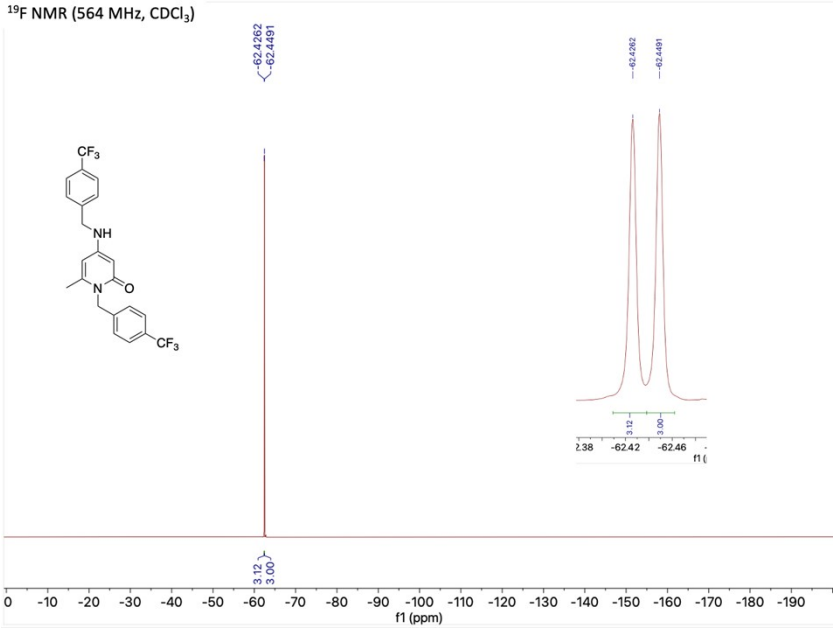
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100.6 MHz, $CDCl_3$)

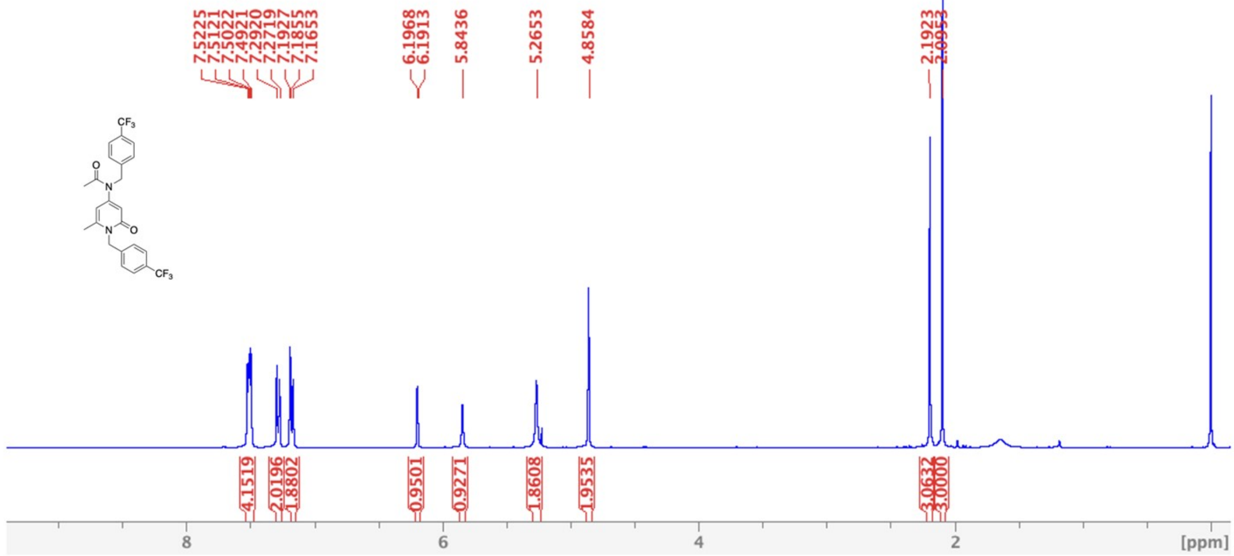


^{19}F NMR (564 MHz, $CDCl_3$)

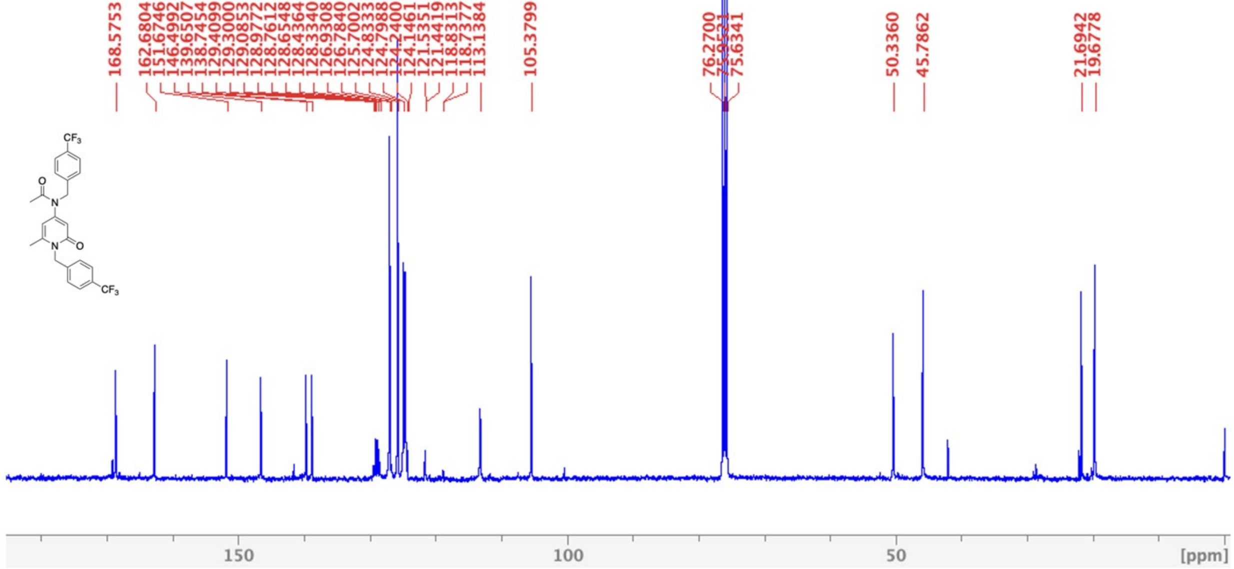


Compound 11

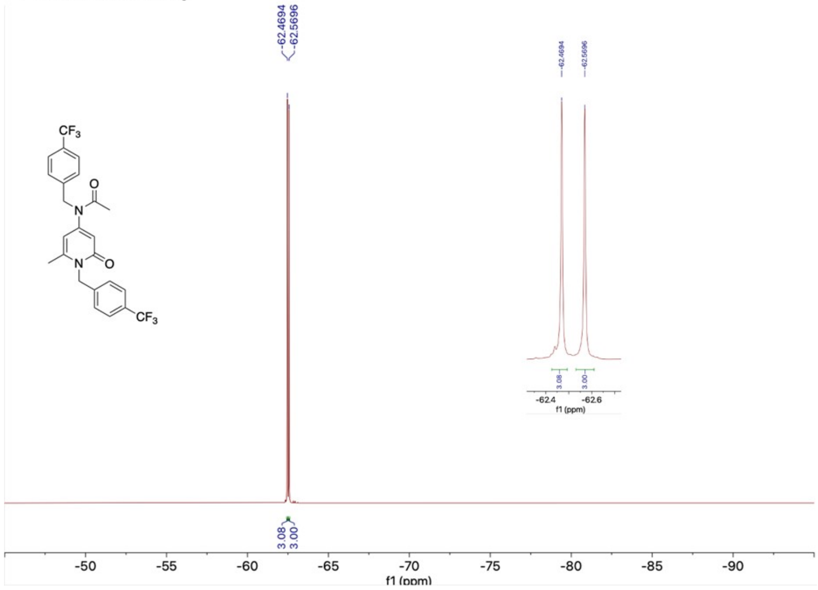
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100.6 MHz, $CDCl_3$)

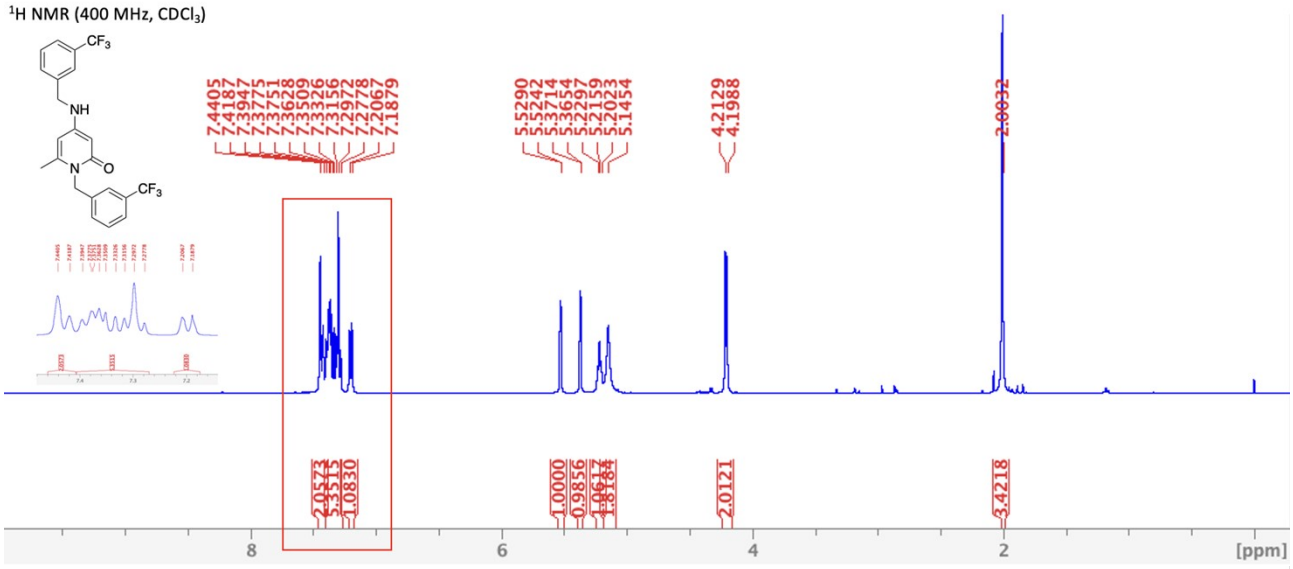


^{19}F NMR (564 MHz, $CDCl_3$)

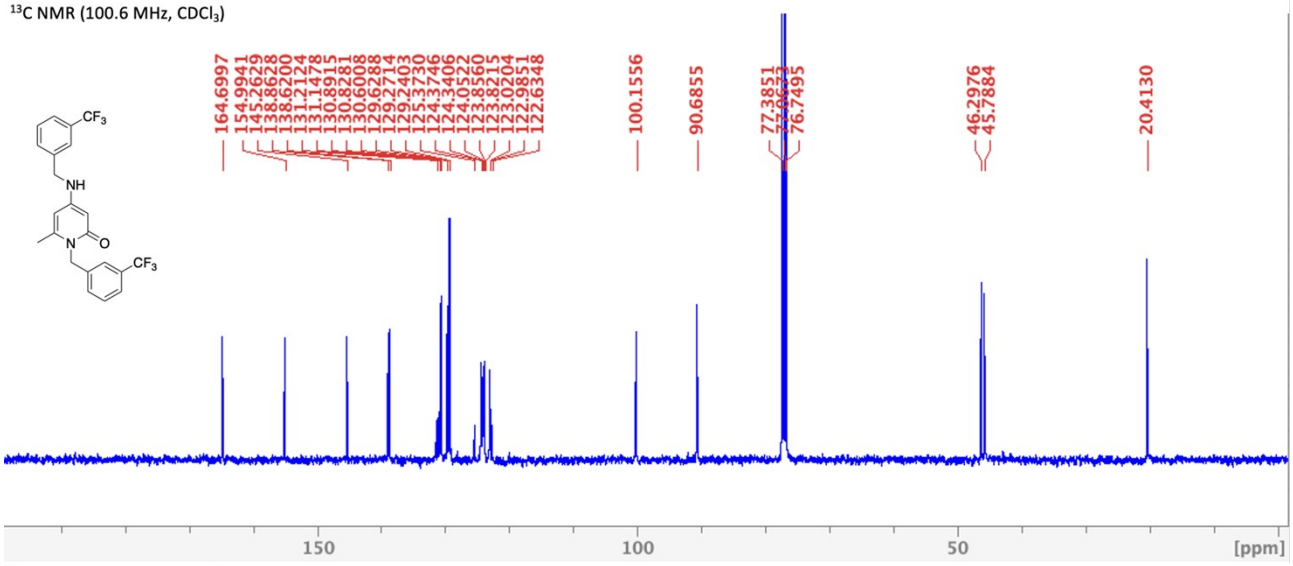


Compound 19a

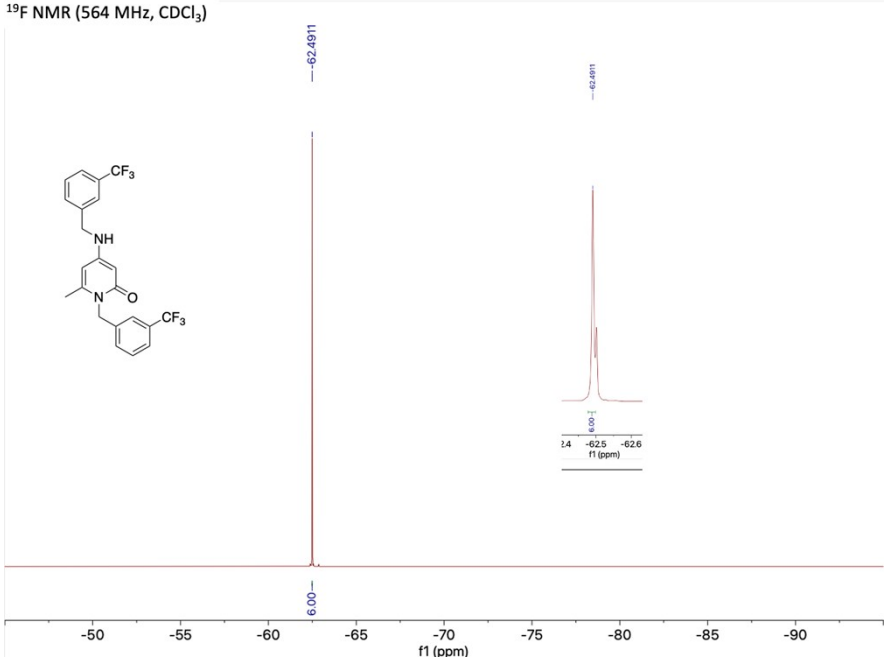
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100.6 MHz, $CDCl_3$)

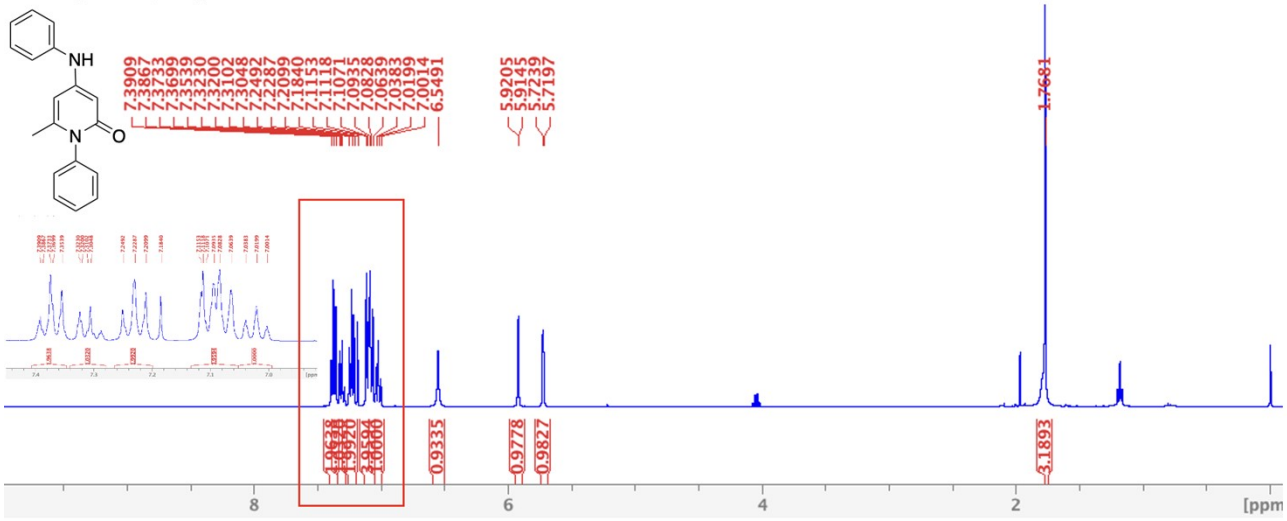


^{19}F NMR (564 MHz, $CDCl_3$)

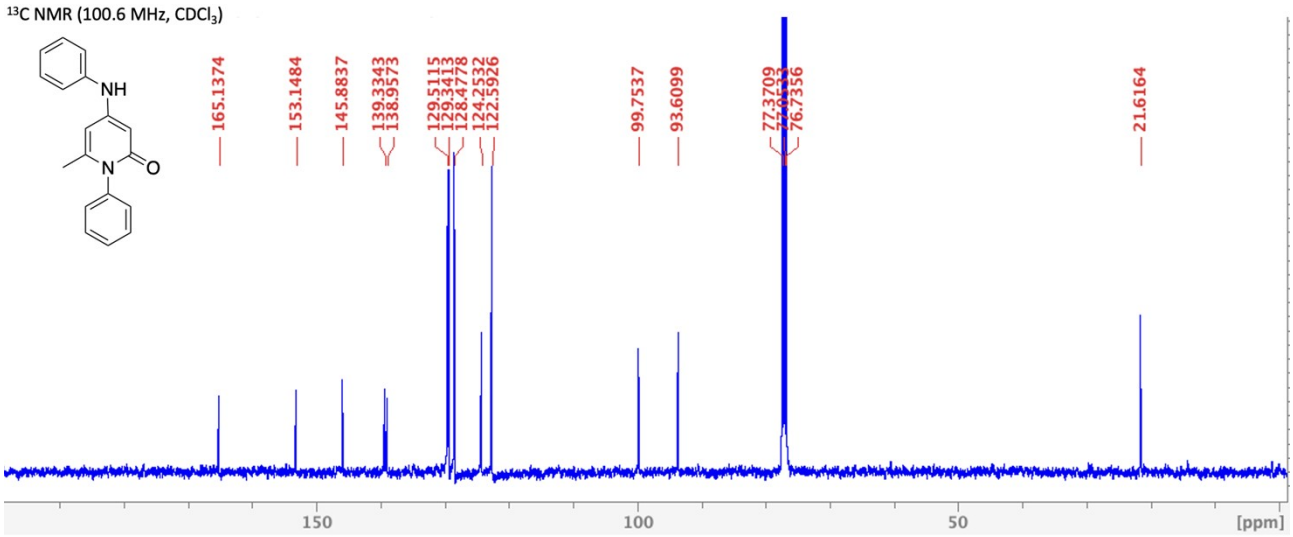


Compound 19b

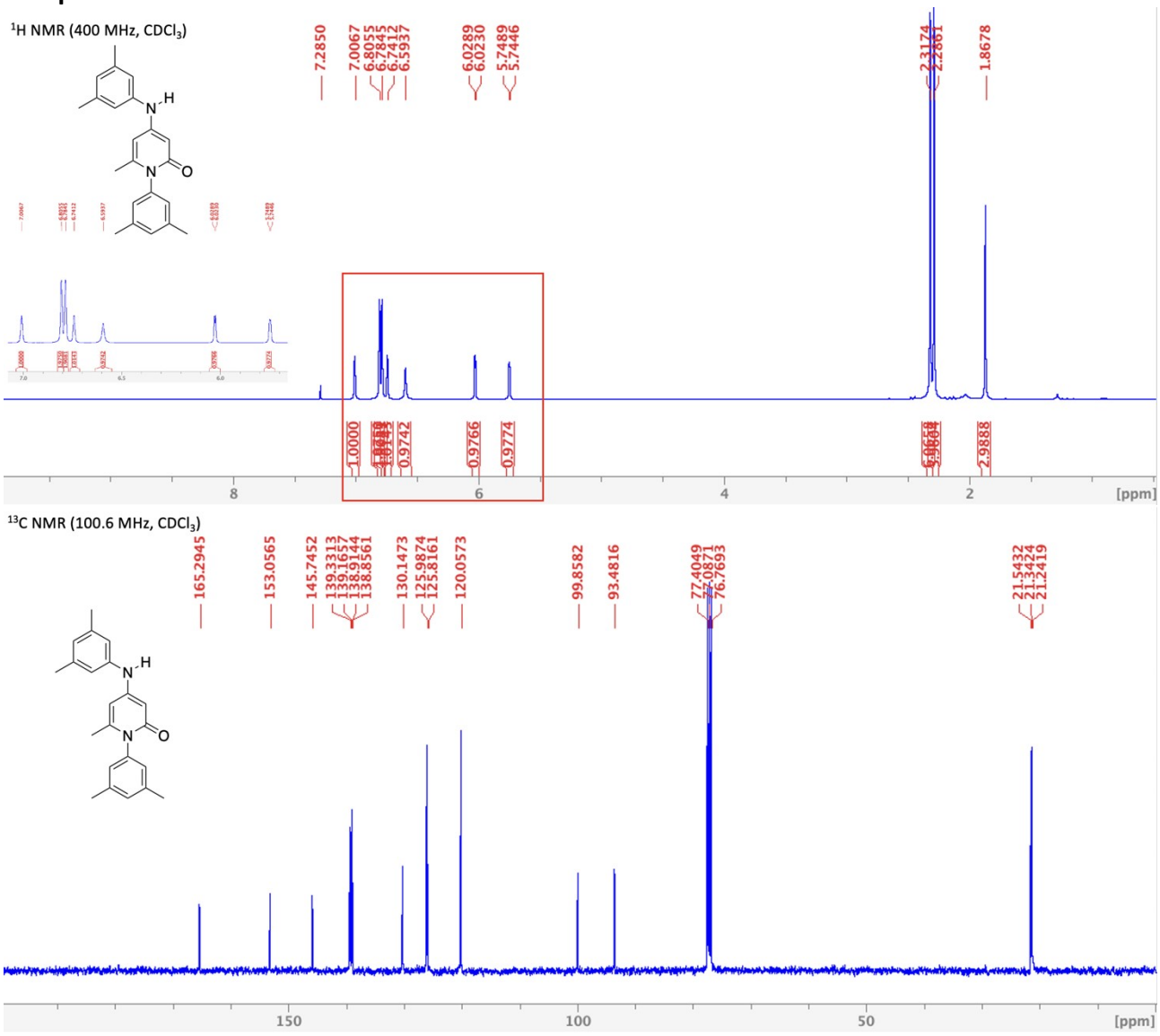
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100.6 MHz, $CDCl_3$)



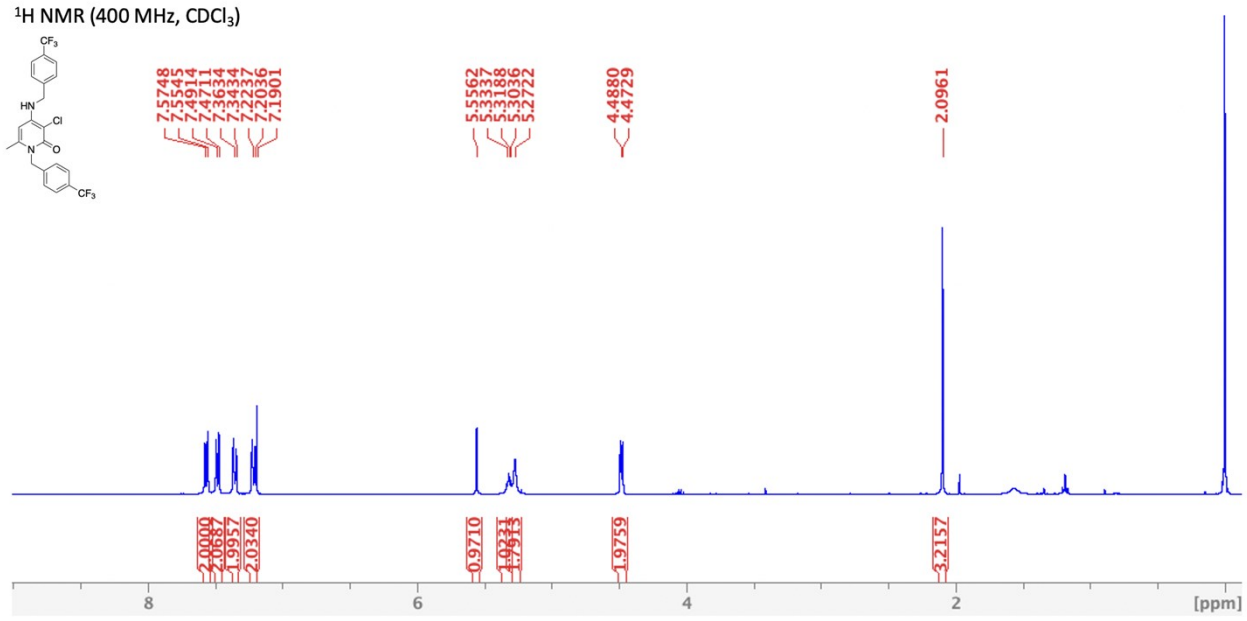
Compound 19c



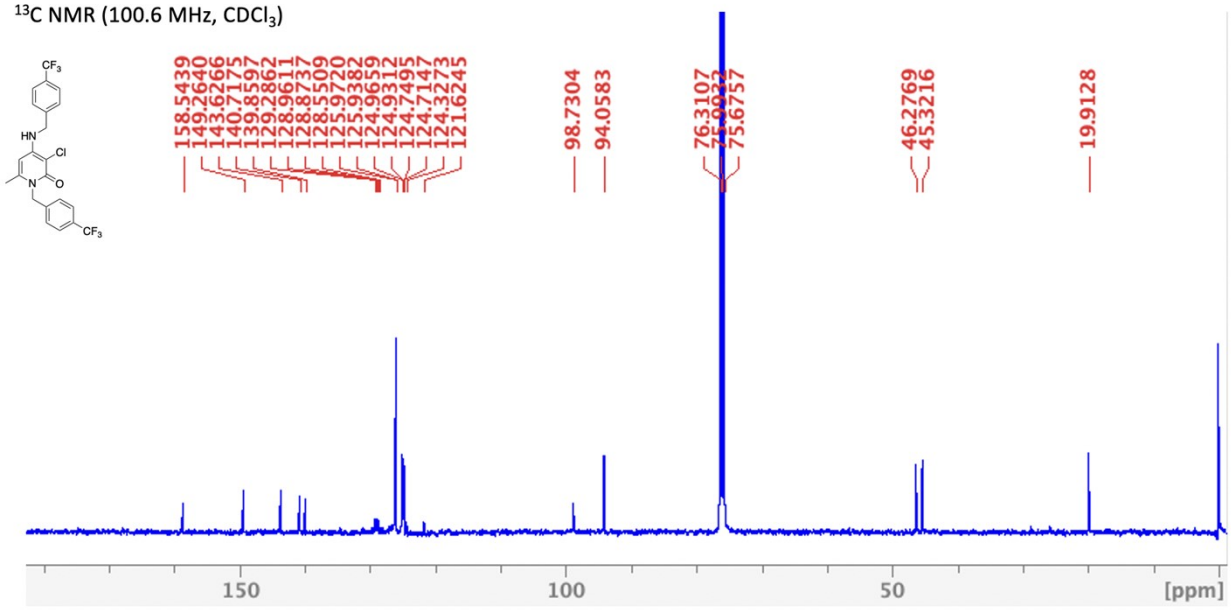
e-LSF:

Compound 6a

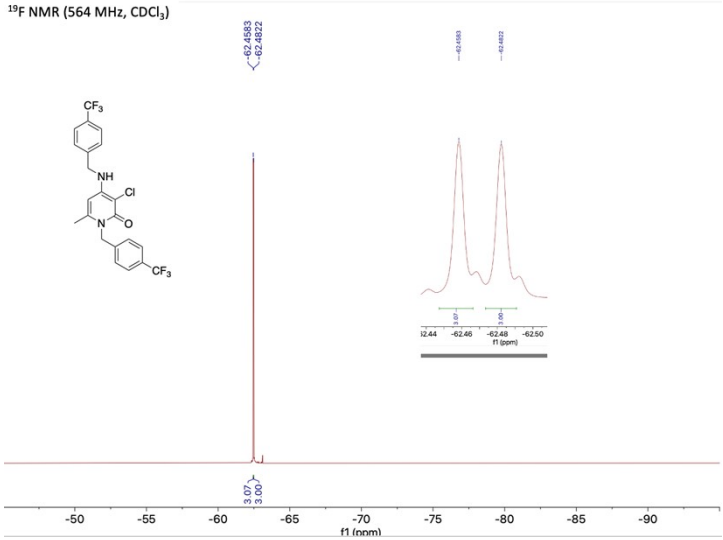
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100.6 MHz, $CDCl_3$)

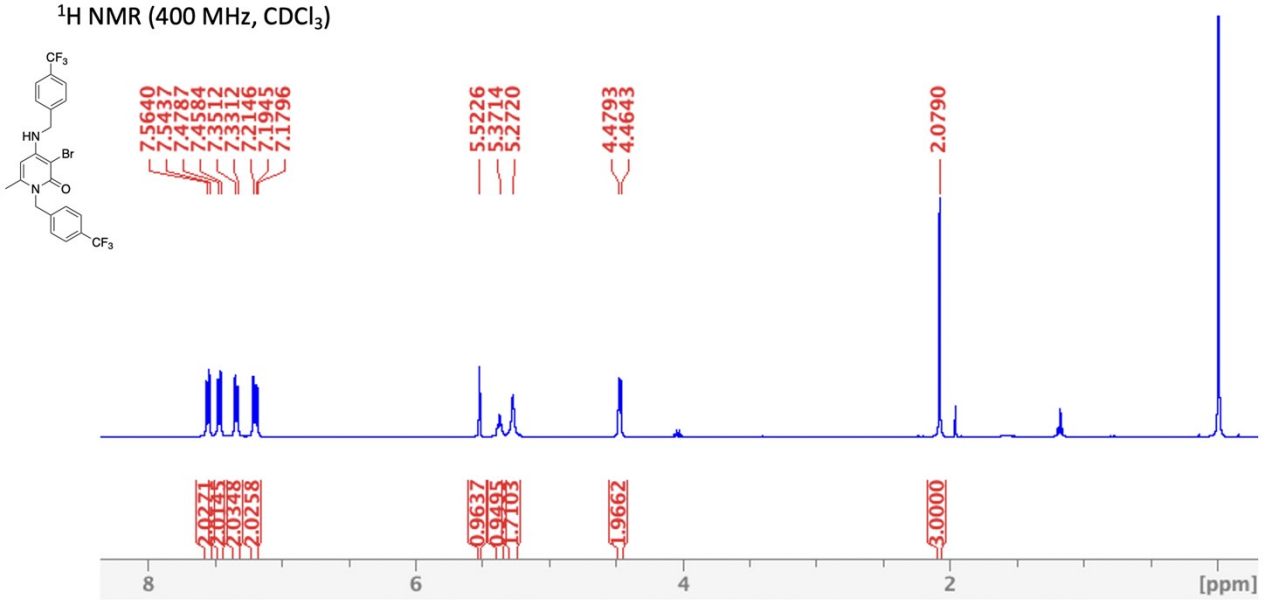


^{19}F NMR (564 MHz, $CDCl_3$)

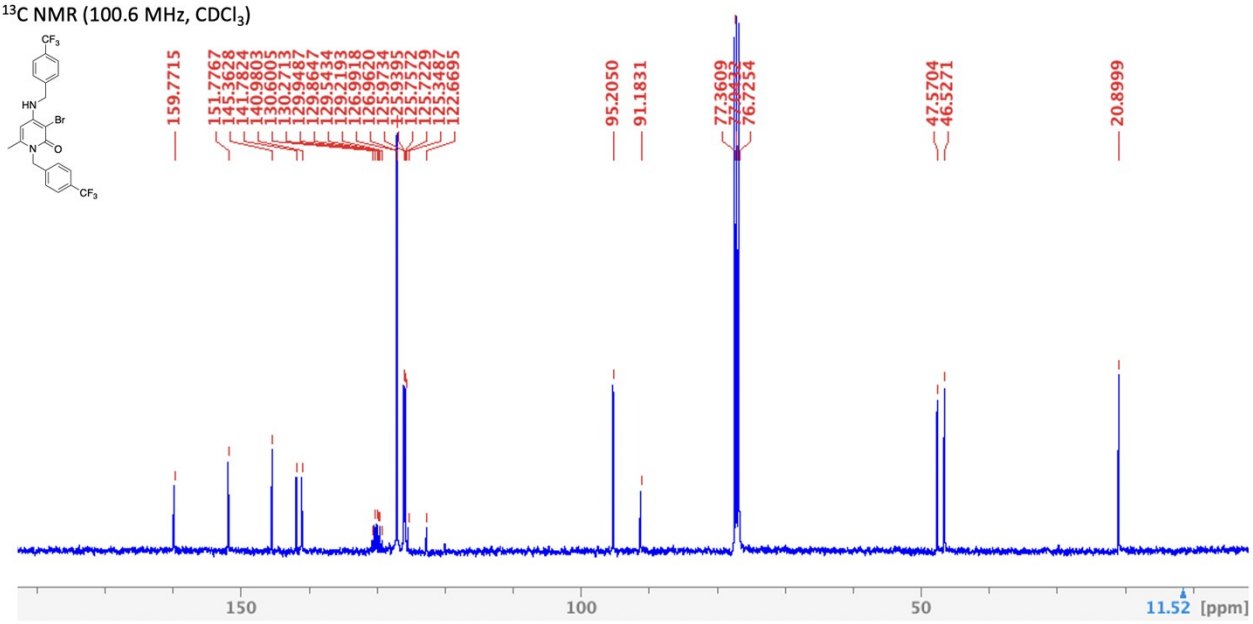


Compound 6b

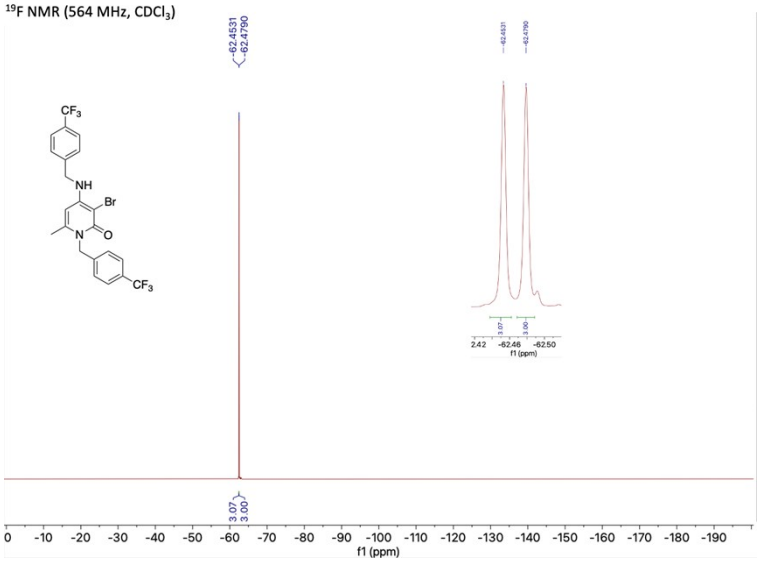
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100.6 MHz, $CDCl_3$)

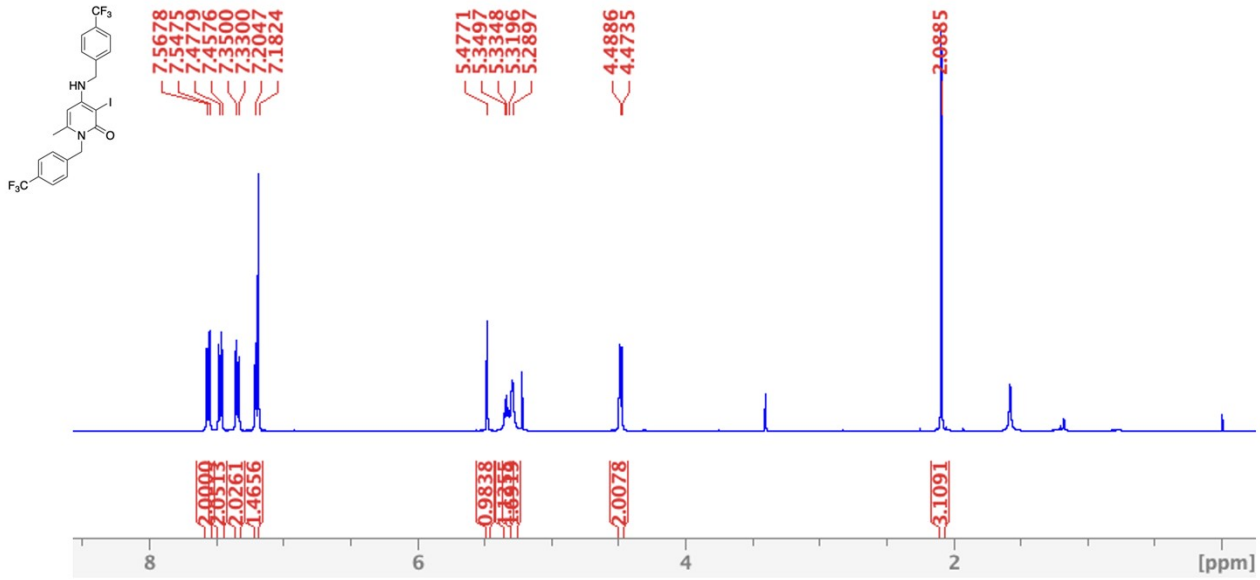


^{19}F NMR (564 MHz, $CDCl_3$)

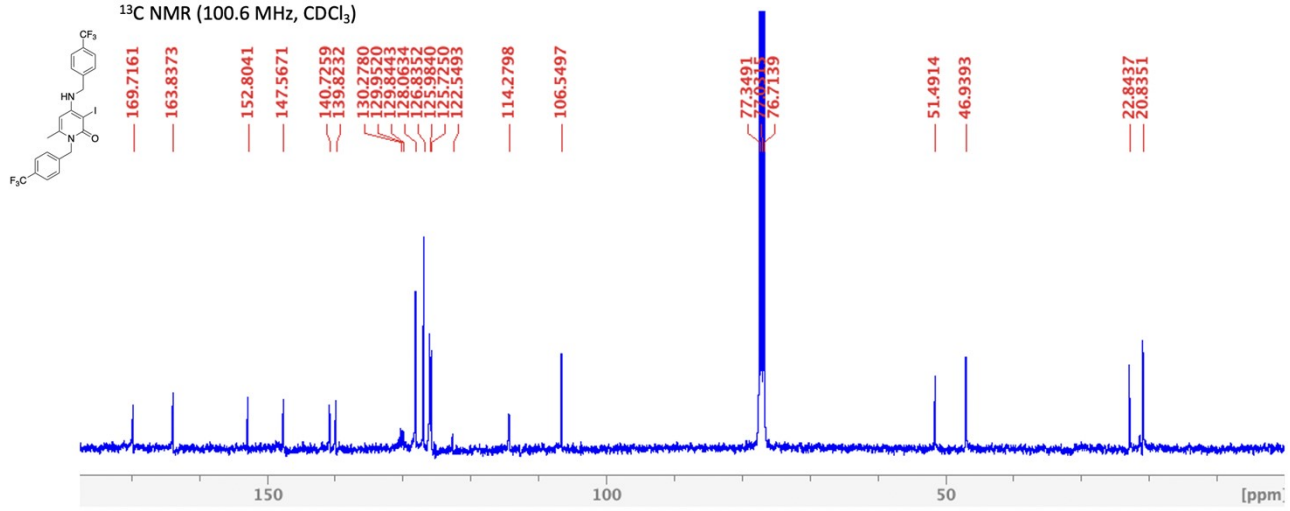


Compound 6c

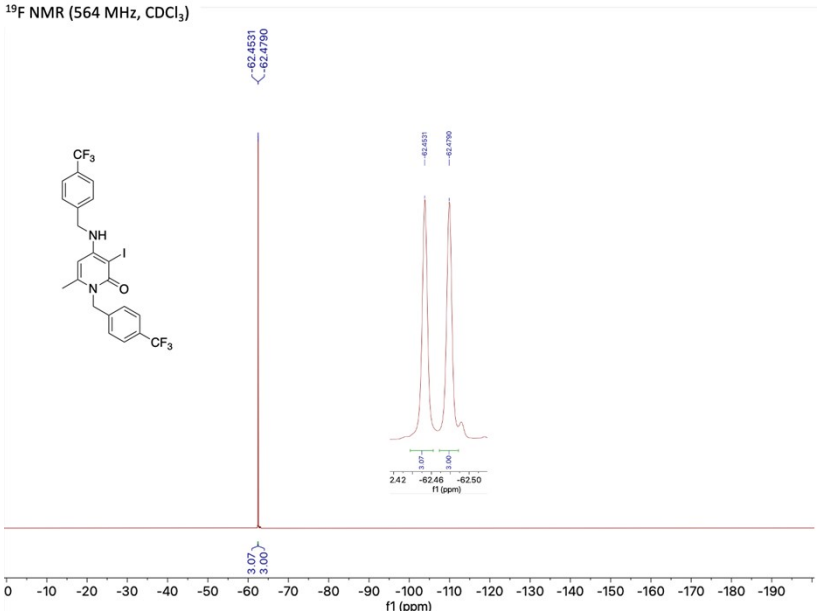
^{1}H NMR (400 MHz, $CDCl_3$)



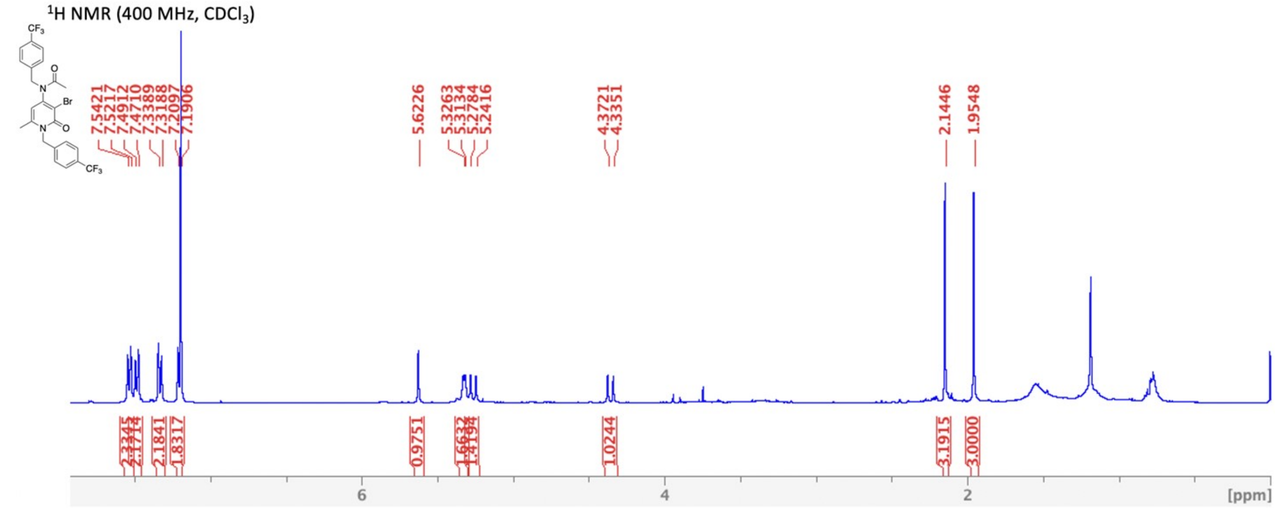
^{13}C NMR (100.6 MHz, $CDCl_3$)



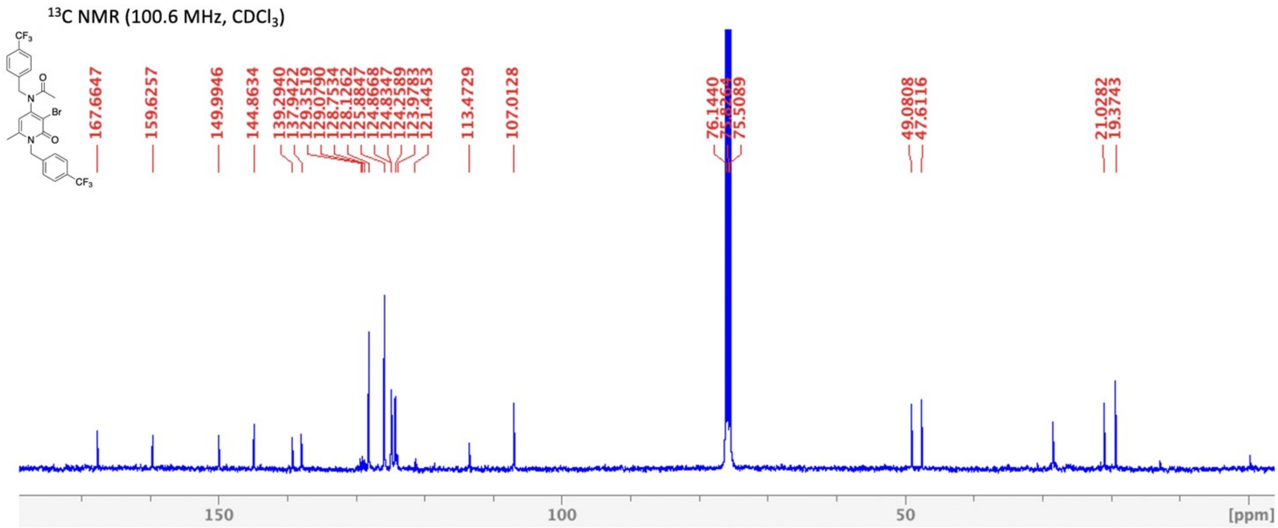
^{19}F NMR (564 MHz, $CDCl_3$)



Compound 13



^{1}H NMR (400 MHz, CDCl$_3$)
7.5421
7.5217
7.4912
7.4710
7.3389
7.3188
7.2097
7.1906
5.6226
5.3263
5.3134
5.2784
5.2416
4.3721
4.3351
2.1446
1.9548
2.3345
2.1714
2.1841
1.8317
0.9751
1.6632
1.4194
1.0244
3.1915
3.0000
6
4
2
[ppm]



^{13}C NMR (100.6 MHz, CDCl$_3$)
167.6647
159.6257
149.9946
144.8634
139.2940
137.9422
129.3519
129.0790
128.7534
128.1262
125.8847
124.8668
124.8347
124.2589
123.9783
121.4453
113.4729
107.0128
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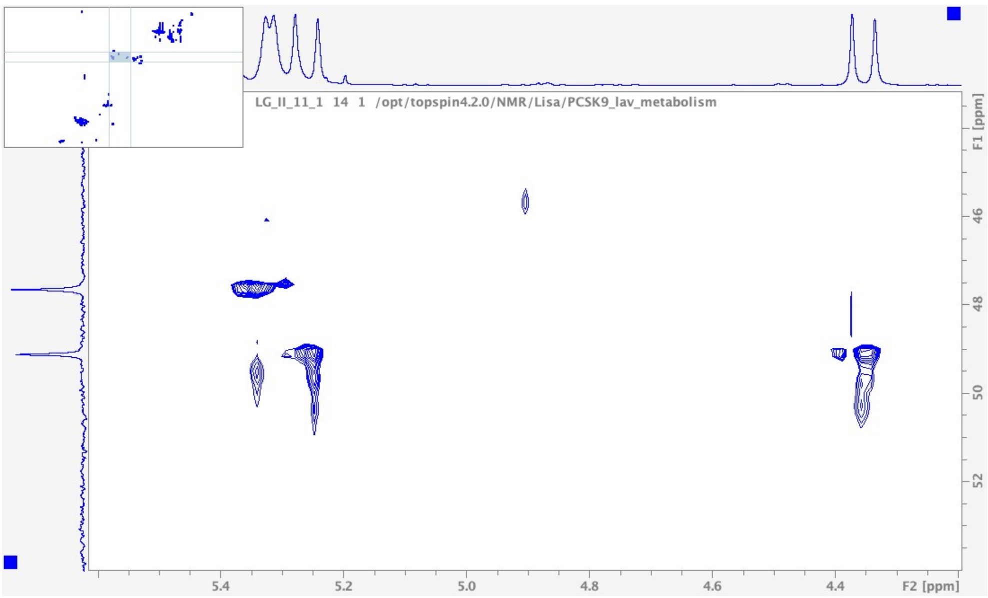
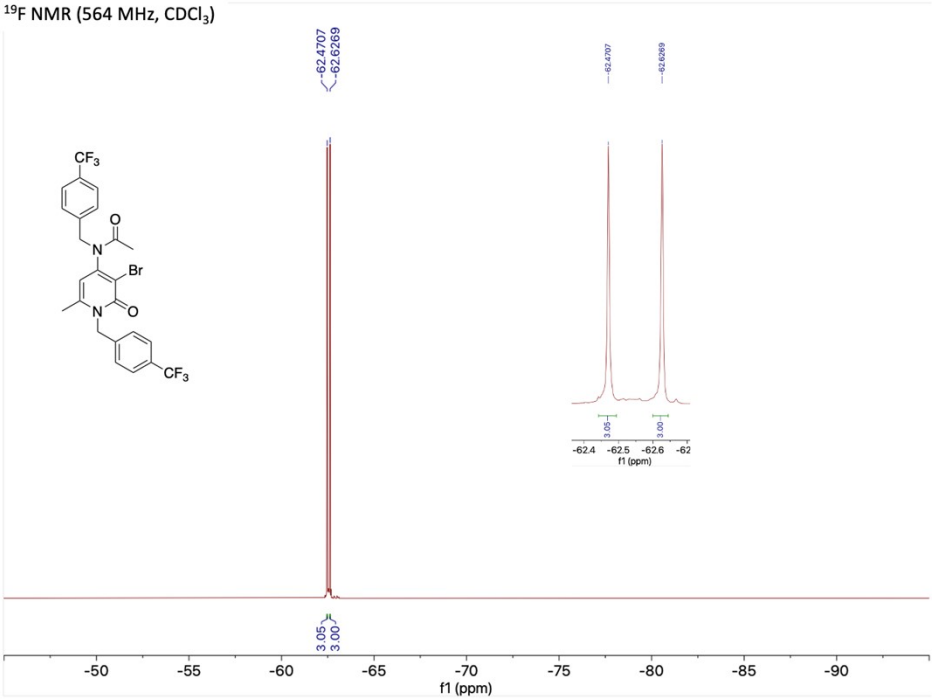
49.0808
47.6116
21.0282
19.3743
150
100
50
[ppm]



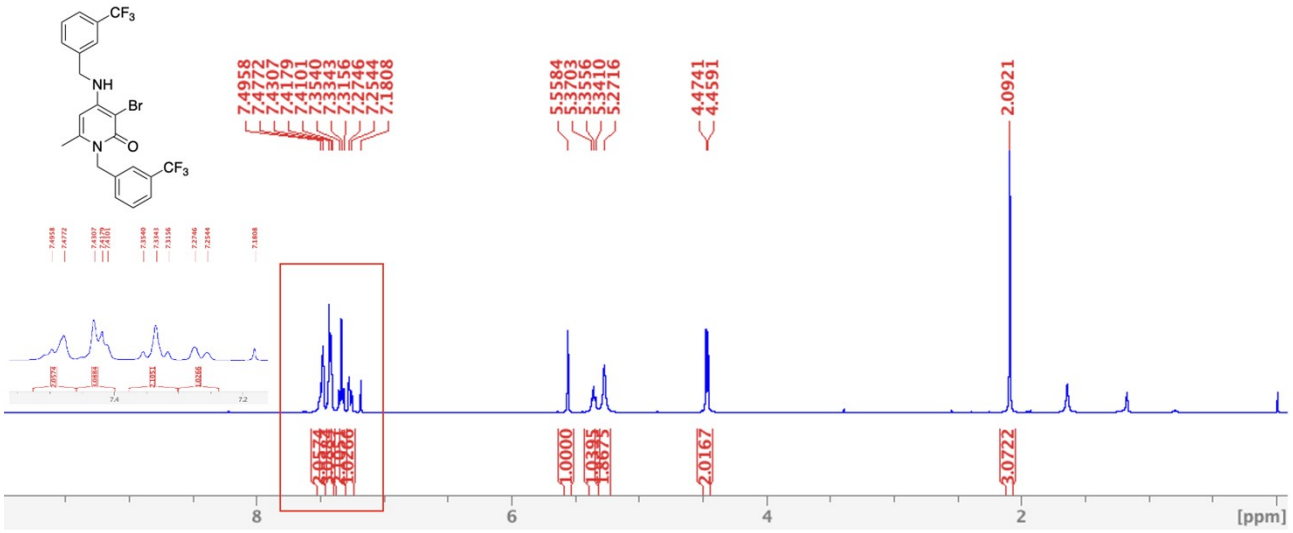
LG_II_11_1 14 1 /opt/topspin4.2.0/NMR/Lisa/PCSK9_lav_metabolism
F1 [ppm]
46
48
50
52
5.4
5.2
5.0
4.8
4.6
4.4
F2 [ppm]

^{19}F NMR (564 MHz, $CDCl_3$)

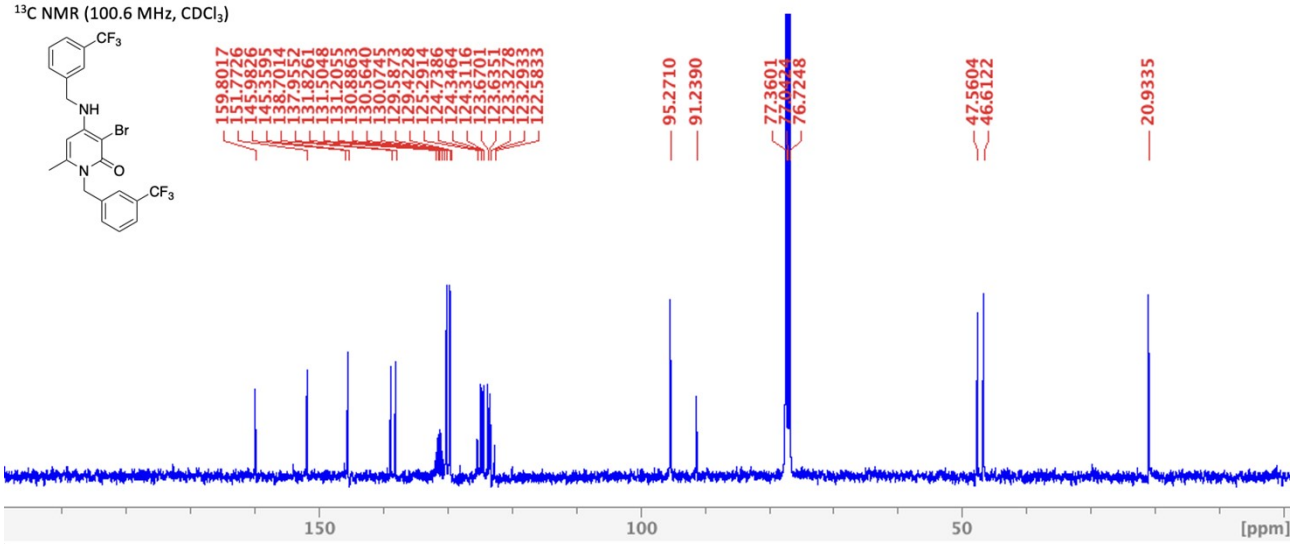


Compound 20a

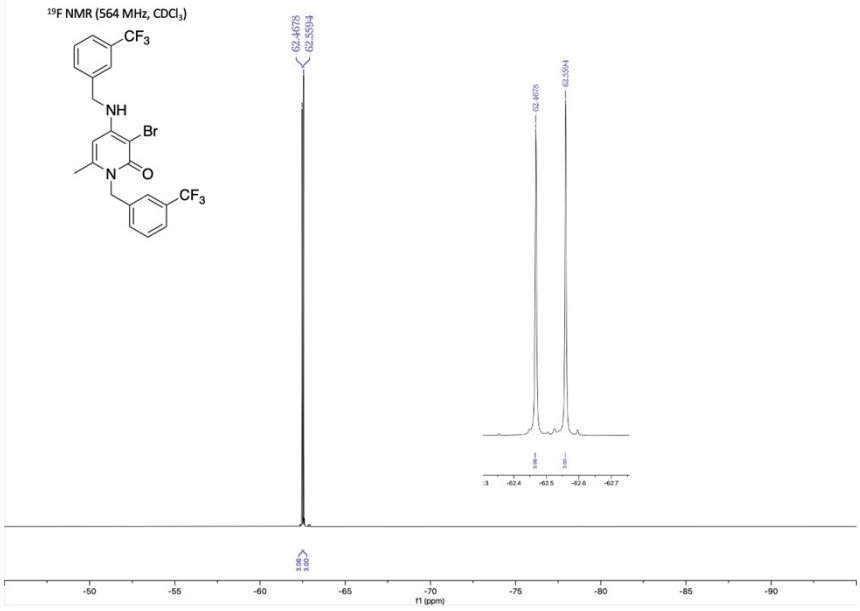
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100.6 MHz, $CDCl_3$)

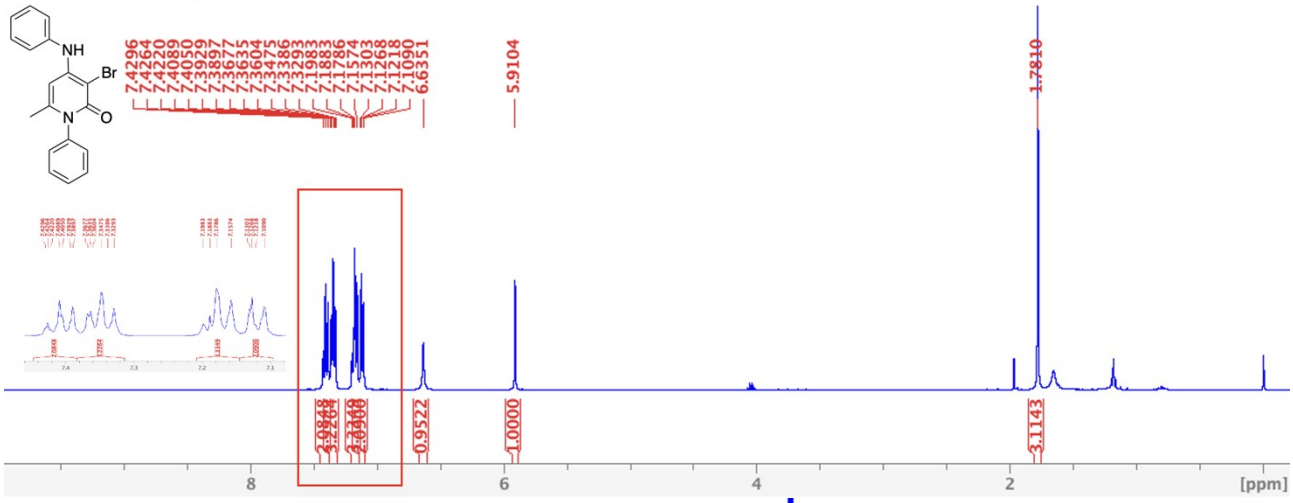


^{19}F NMR (564 MHz, $CDCl_3$)

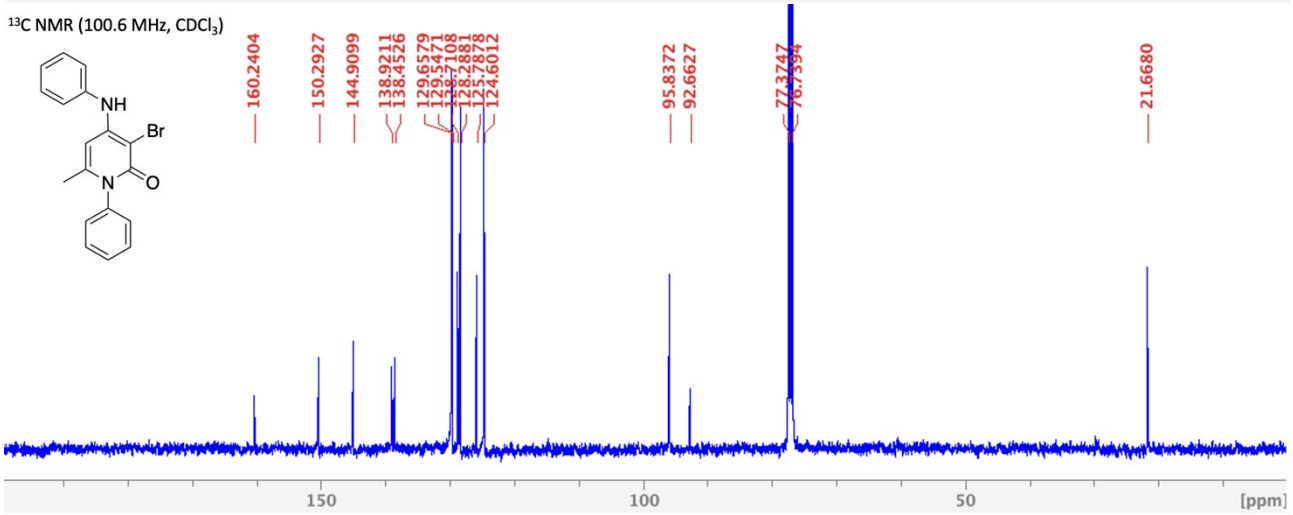


Compound 20b

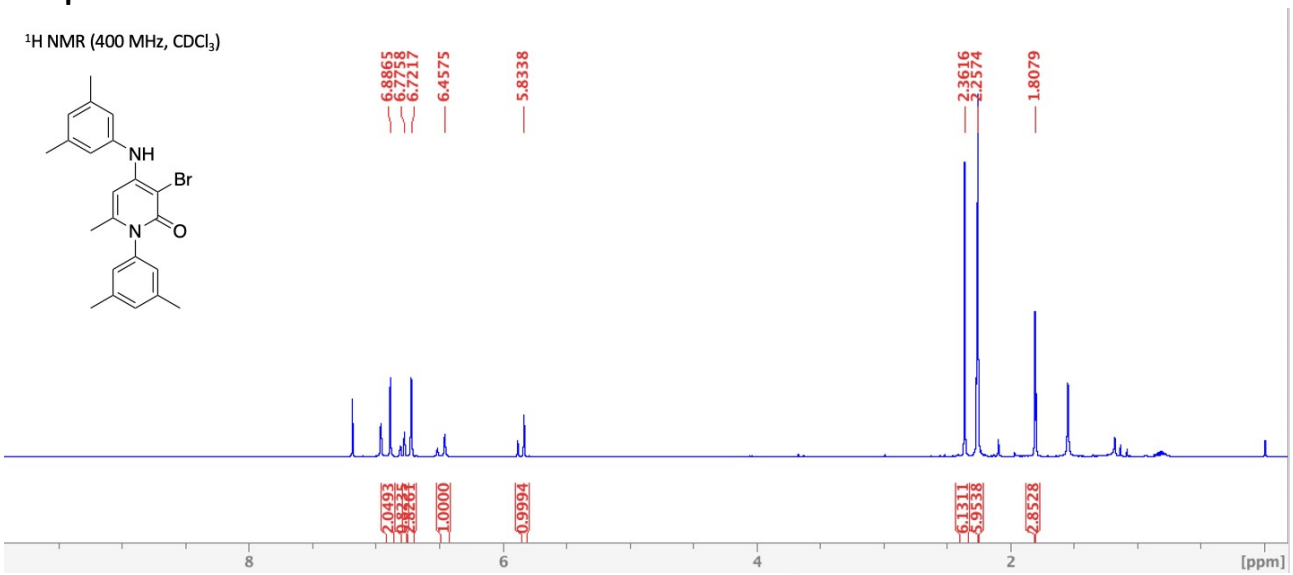
^{1}H NMR (400 MHz, $CDCl_3$)

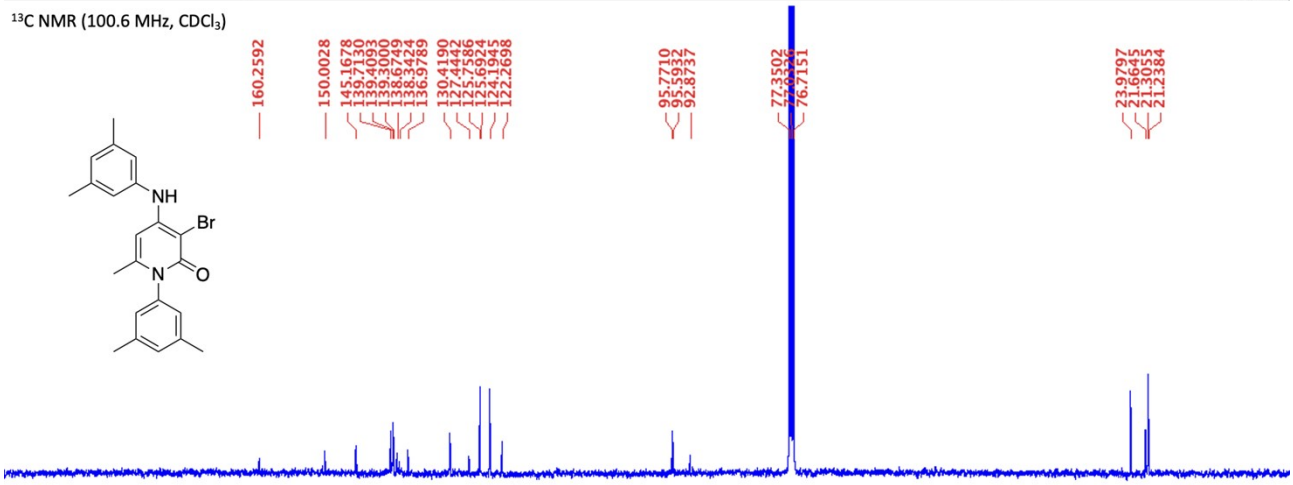


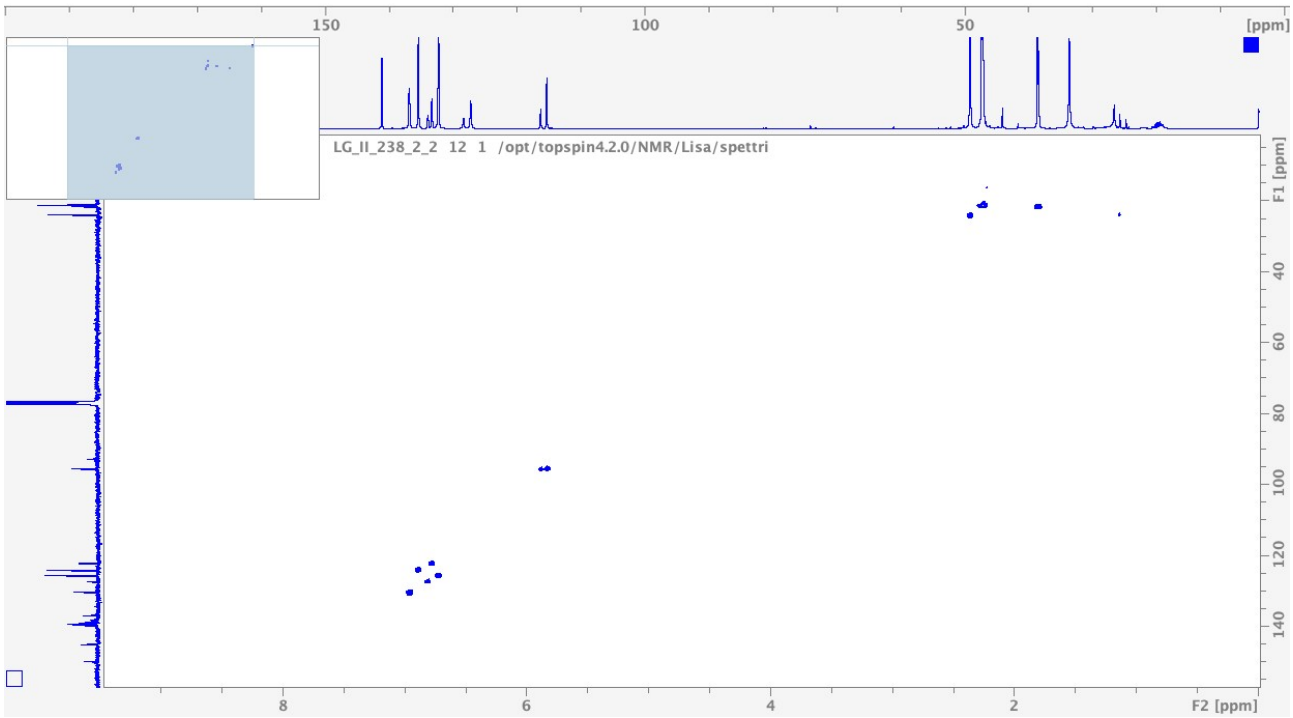
^{13}C NMR (100.6 MHz, $CDCl_3$)



Compound 20c

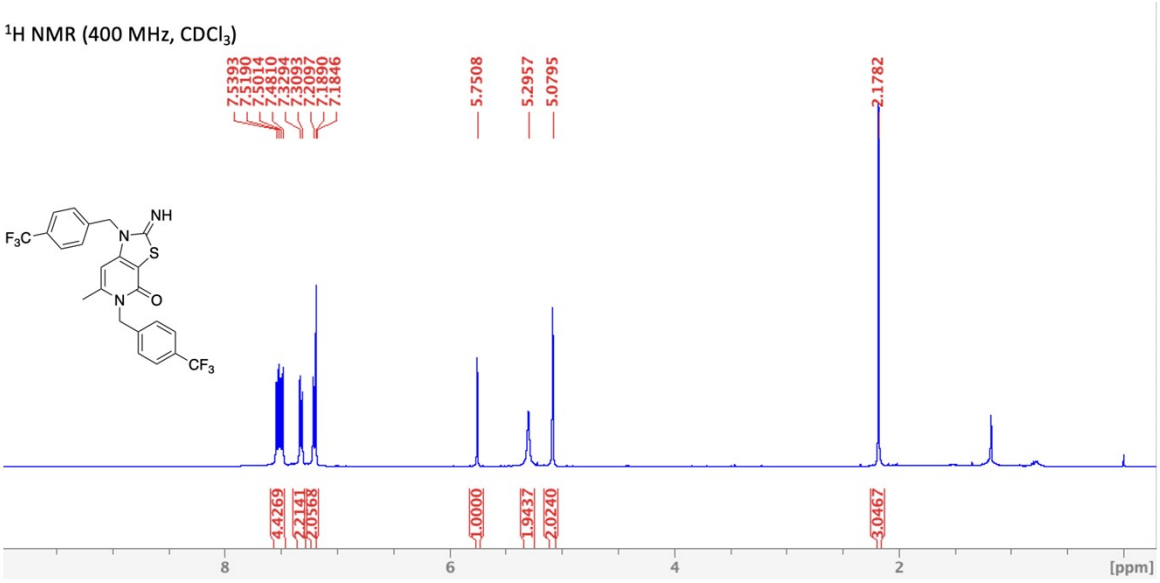




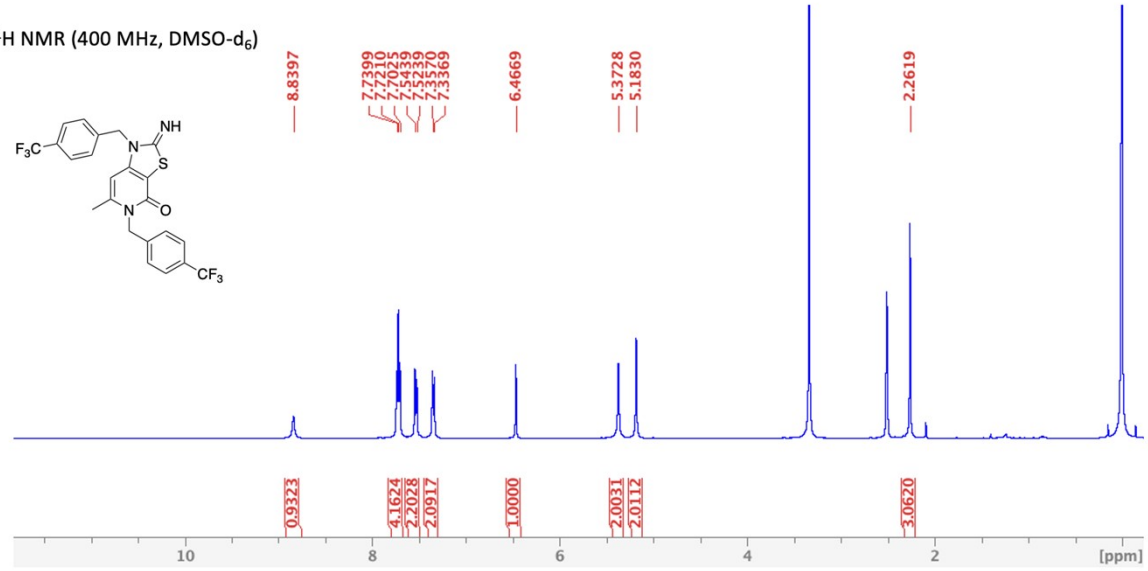


Compound 7

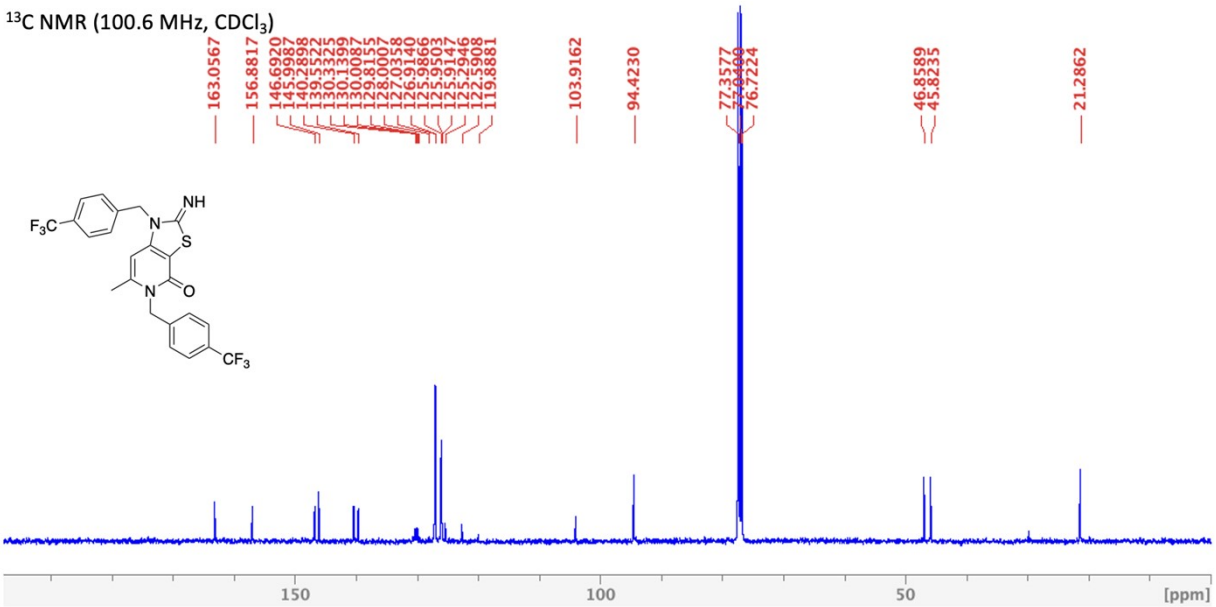
^{1}H NMR (400 MHz, $CDCl_3$)



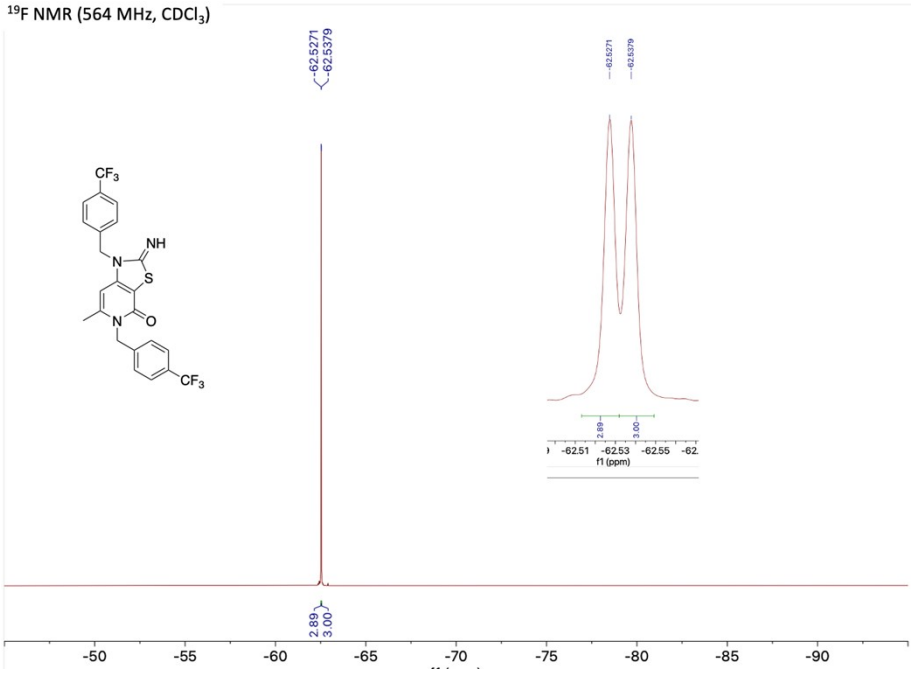
^{1}H NMR (400 MHz, DMSO-d_6)



^{13}C NMR (100.6 MHz, $CDCl_3$)

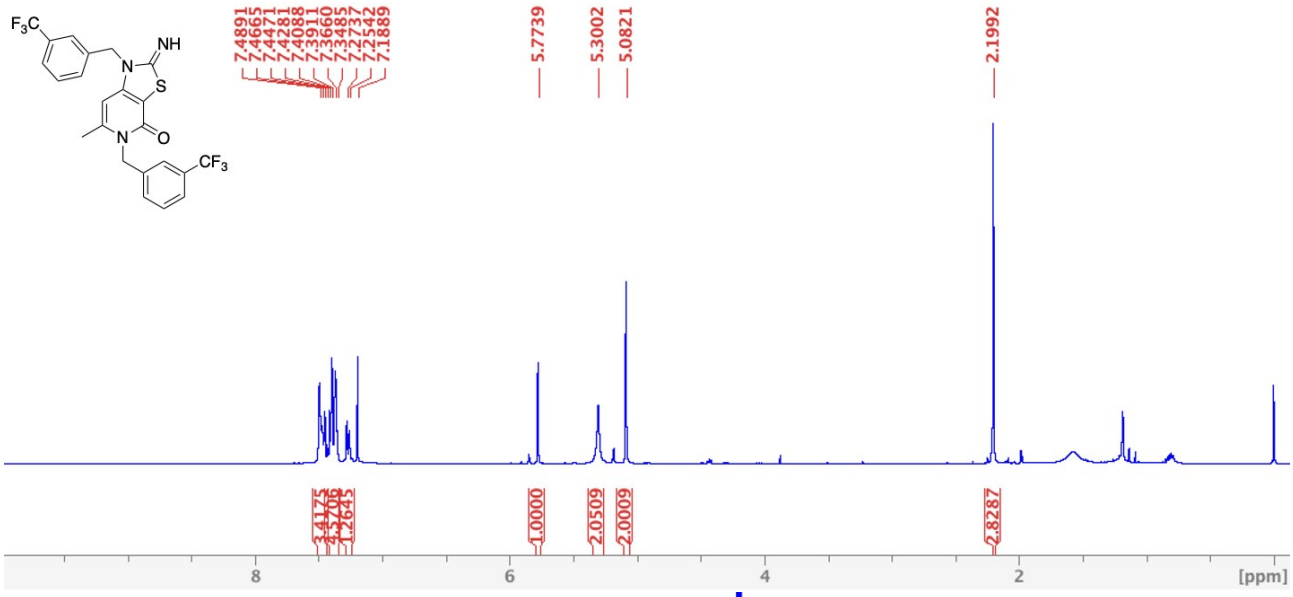


^{19}F NMR (564 MHz, $CDCl_3$)

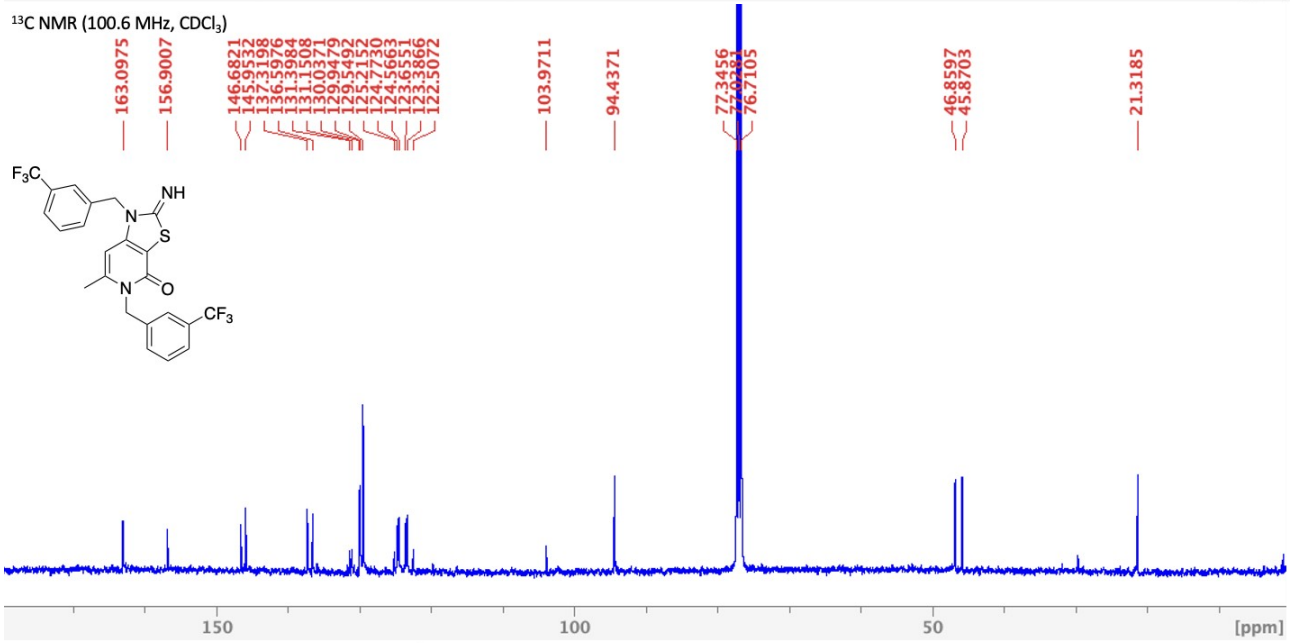


Compound 21a

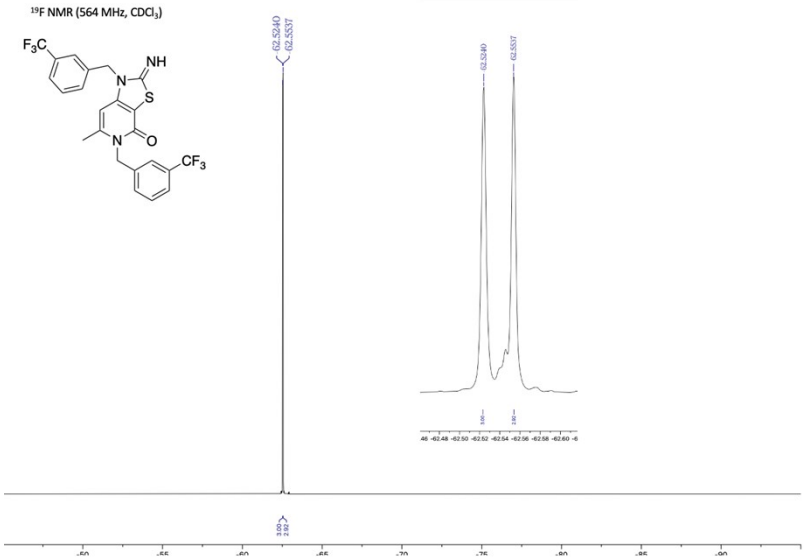
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100.6 MHz, $CDCl_3$)

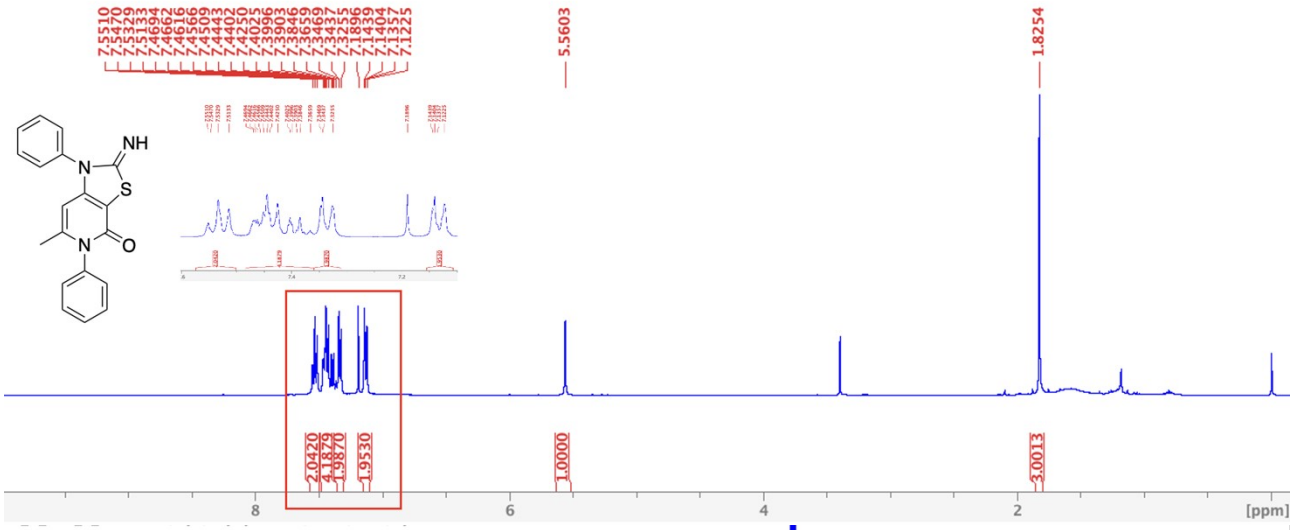


^{19}F NMR (564 MHz, $CDCl_3$)

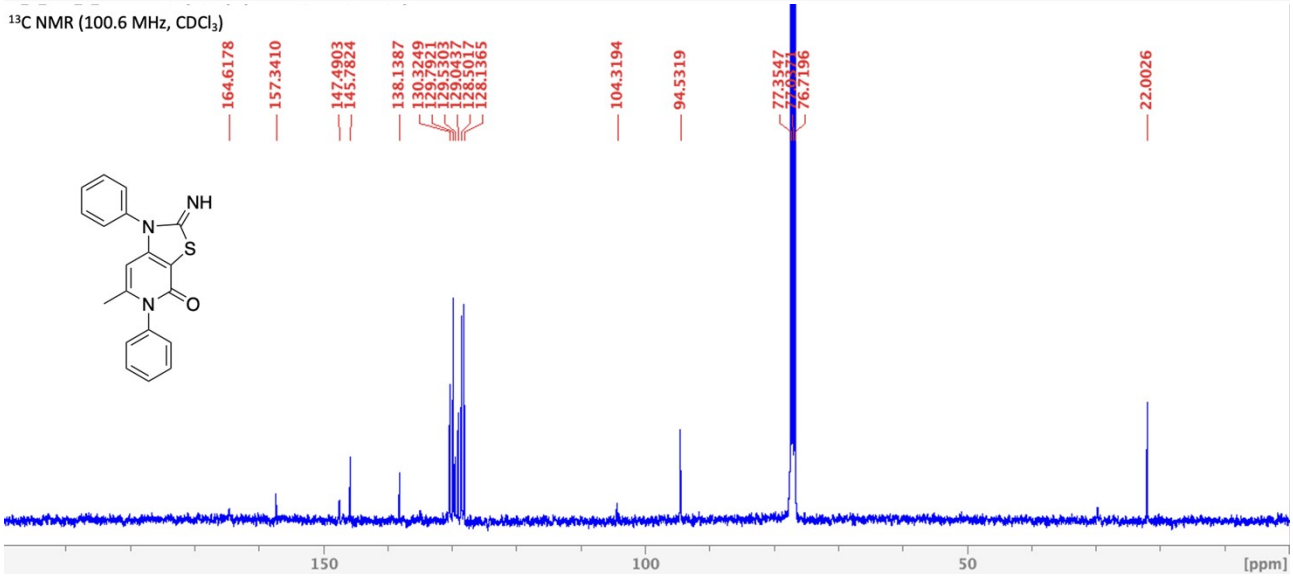


Compound 21b

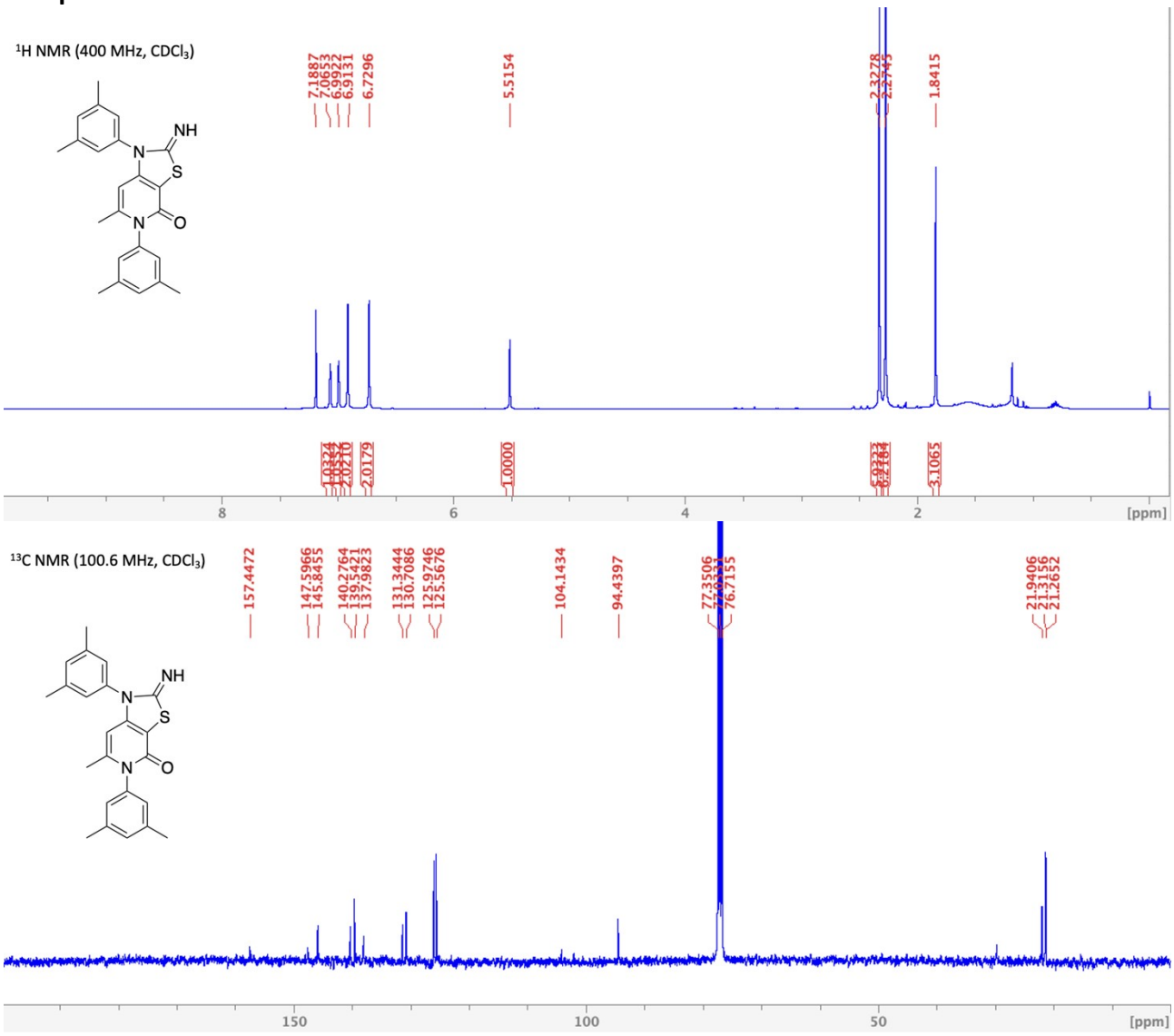
^{1}H NMR (400 MHz, $CDCl_3$)



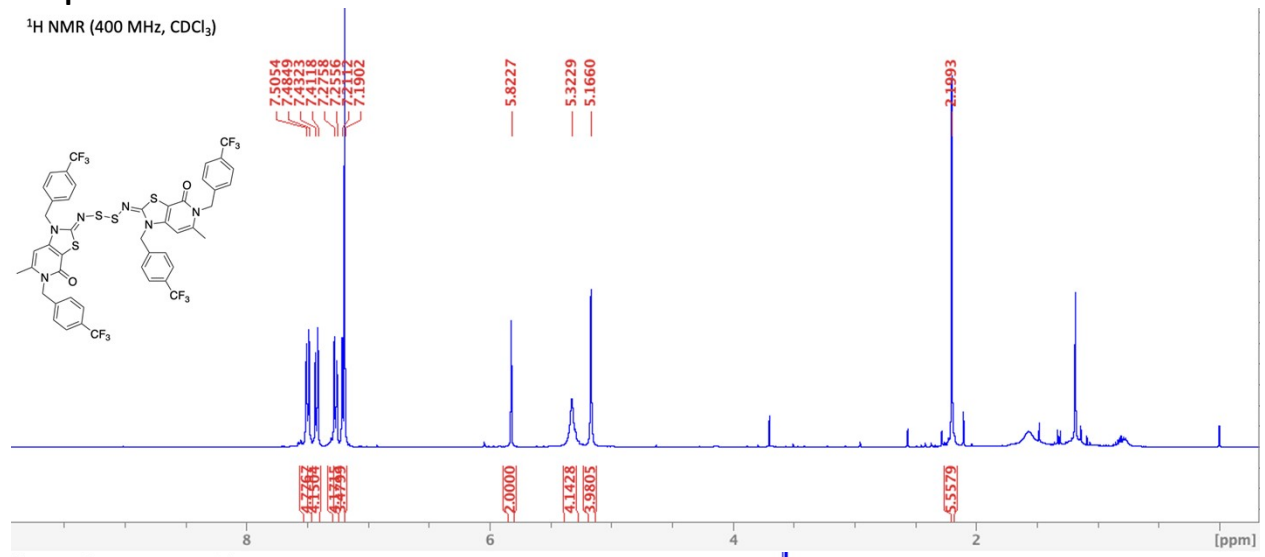
^{13}C NMR (100.6 MHz, $CDCl_3$)

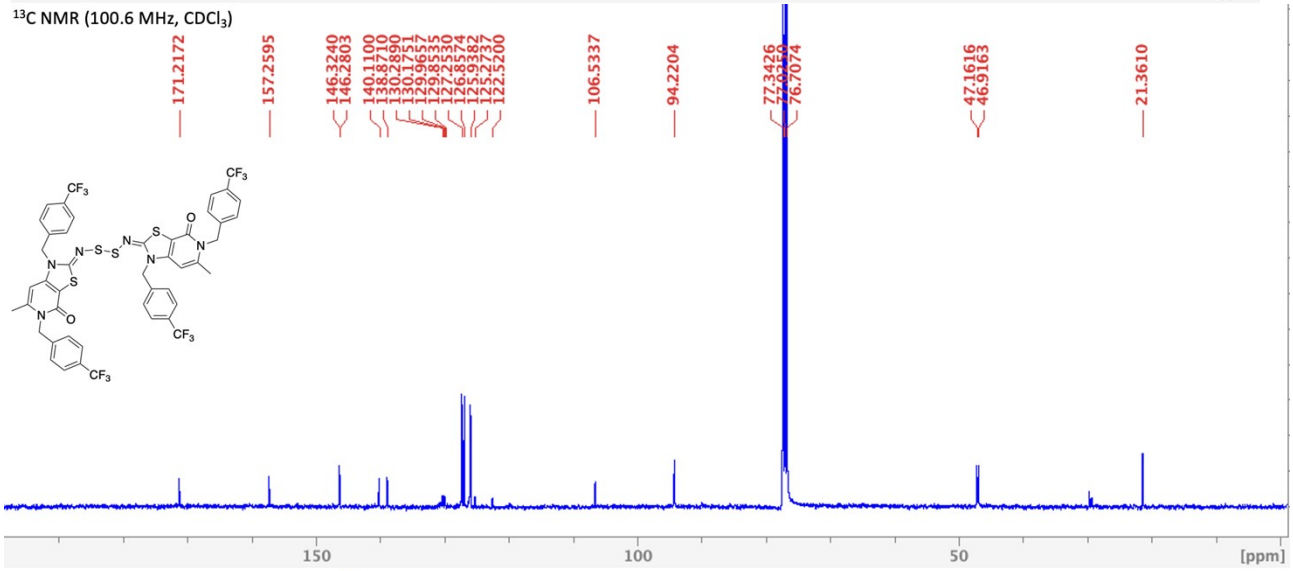


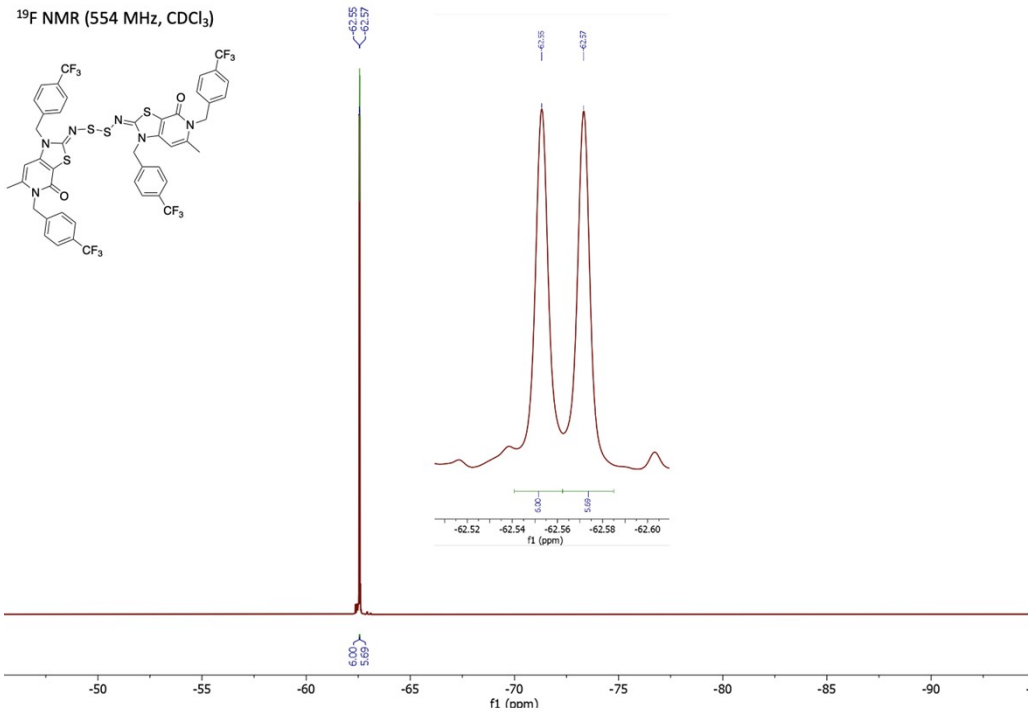
Compound 21c



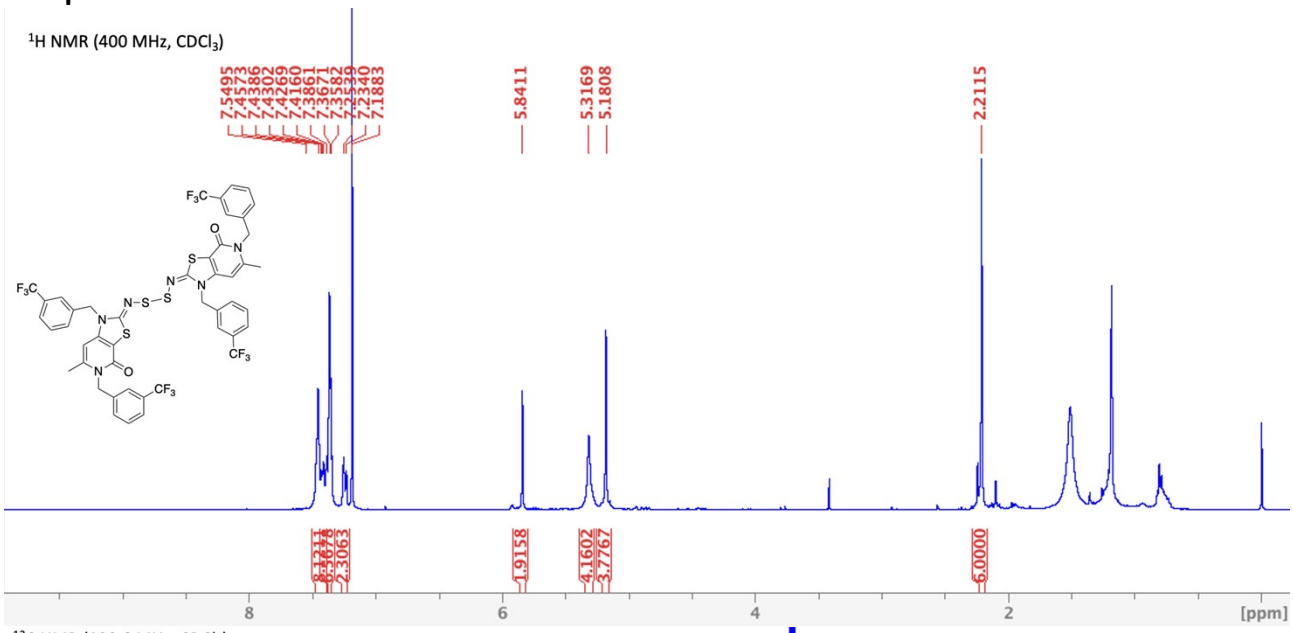
Compound 17

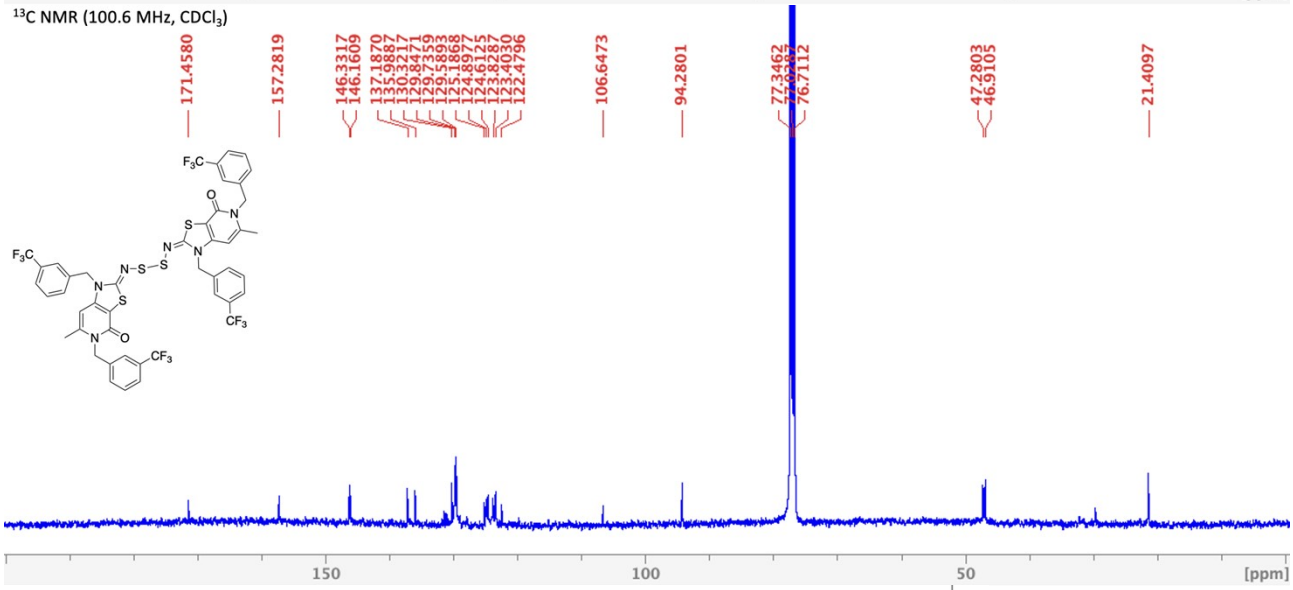

^{1}H NMR (400 MHz, $CDCl_3$)
7.5054
7.4839
7.4333
7.4118
7.2758
7.2556
7.2112
7.1902
5.8227
5.3229
5.1660
2.1993
2.0000
4.1428
3.9805
5.5579
8
6
4
2
[ppm]

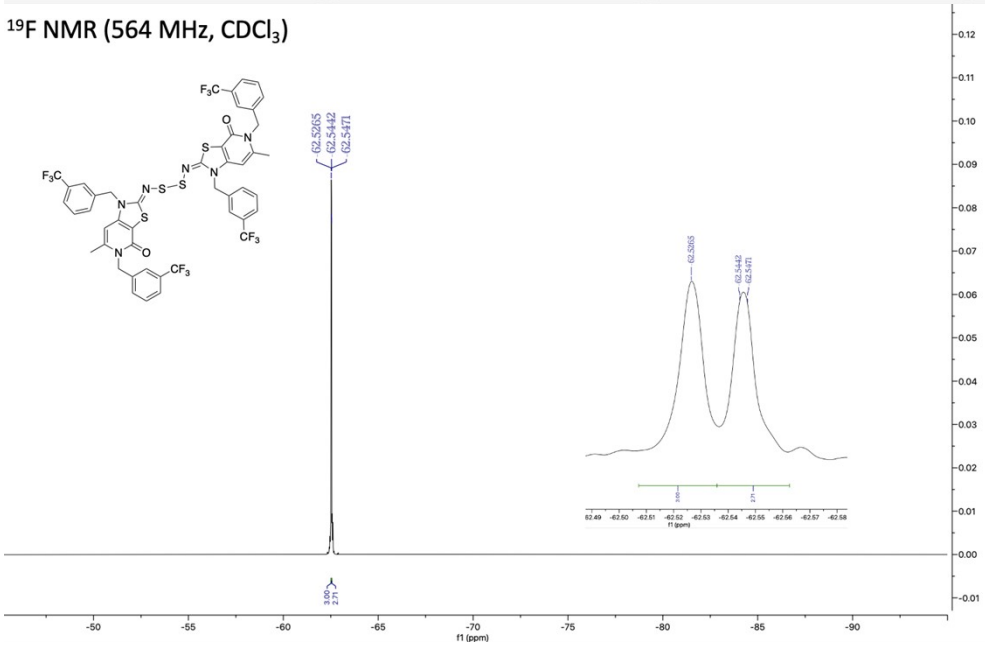

^{13}C NMR (100.6 MHz, $CDCl_3$)
171.2172
157.2595
146.3240
146.2803
140.1100
138.8710
130.2890
130.1751
129.9657
129.8535
127.2530
126.8574
125.9382
125.2737
122.5200
106.5337
94.2204
77.3426
77.0250
76.7074
47.1616
46.9163
21.3610
150
100
50
[ppm]


^{19}F NMR (554 MHz, $CDCl_3$)
-62.55
-62.57
6.00
5.69
-62.52
-62.54
-62.56
-62.58
-62.60
f1 (ppm)
-50
-55
-60
-65
-70
-75
-80
-85
-90
f1 (ppm)

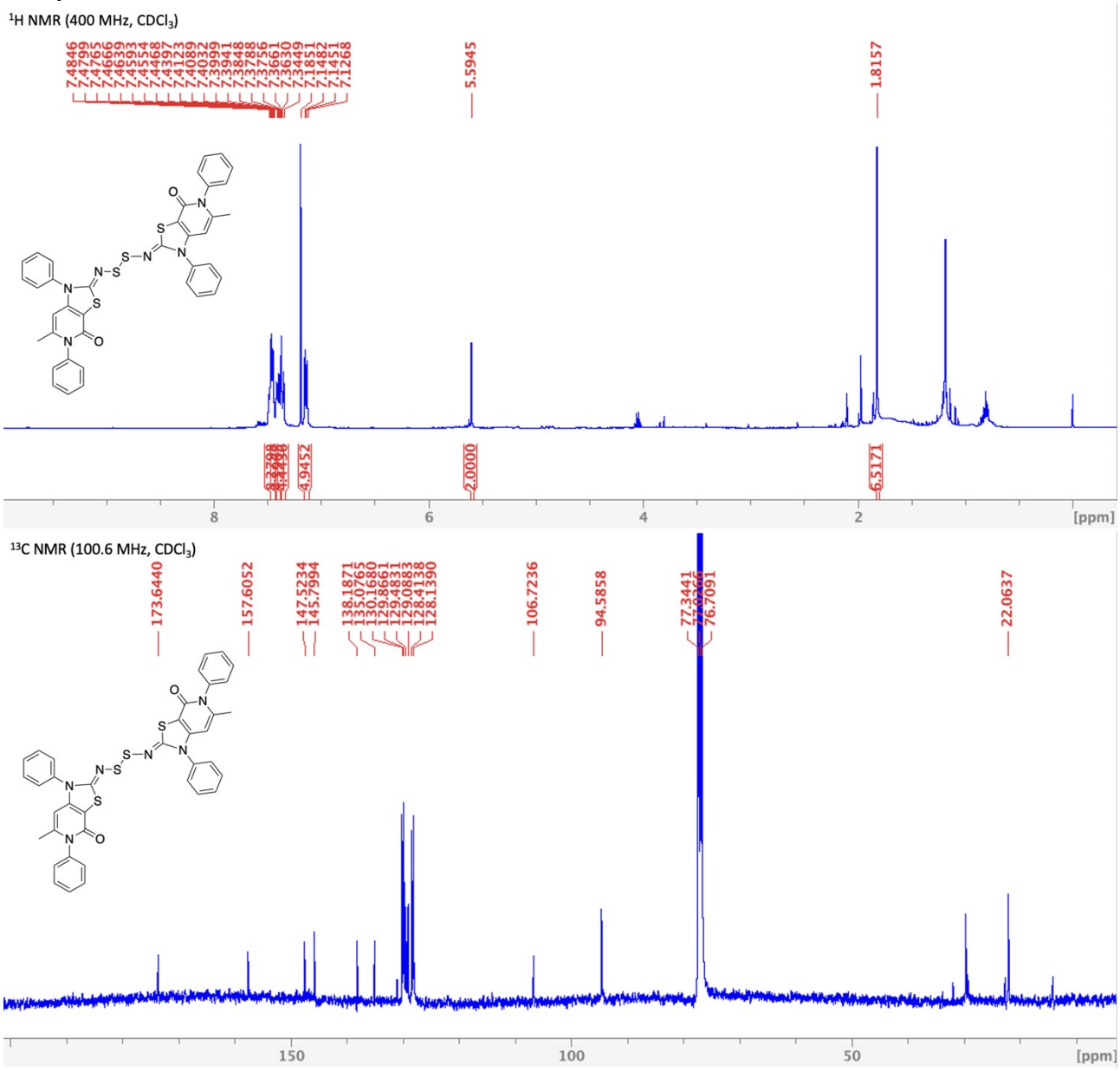
Compound 22a



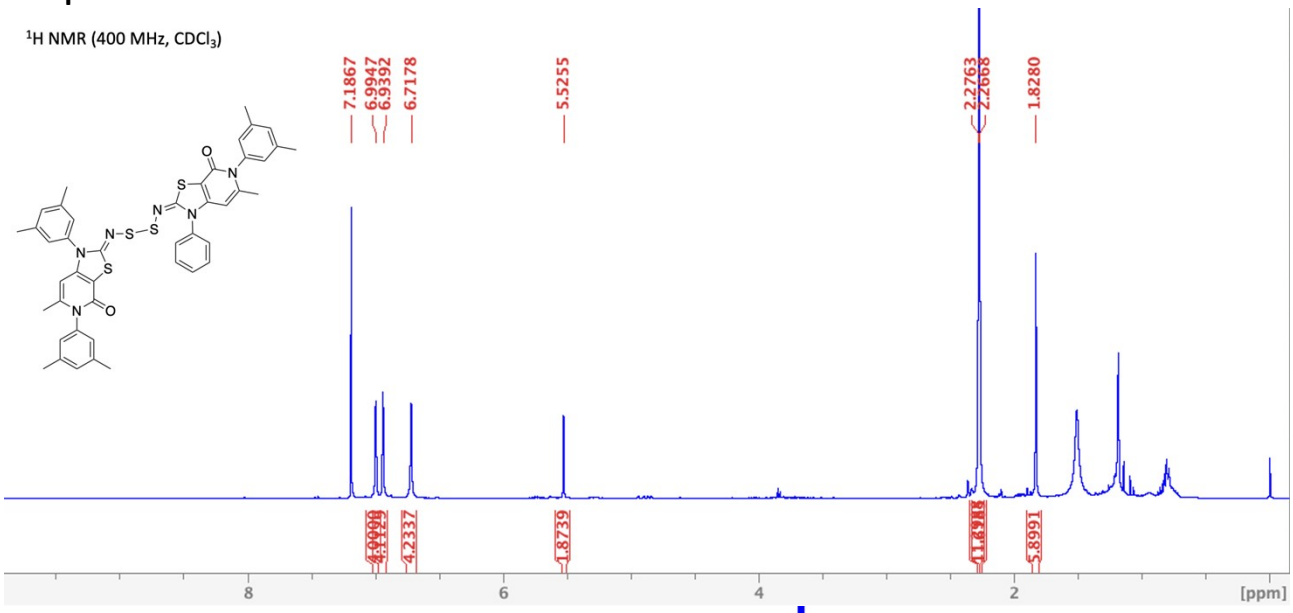


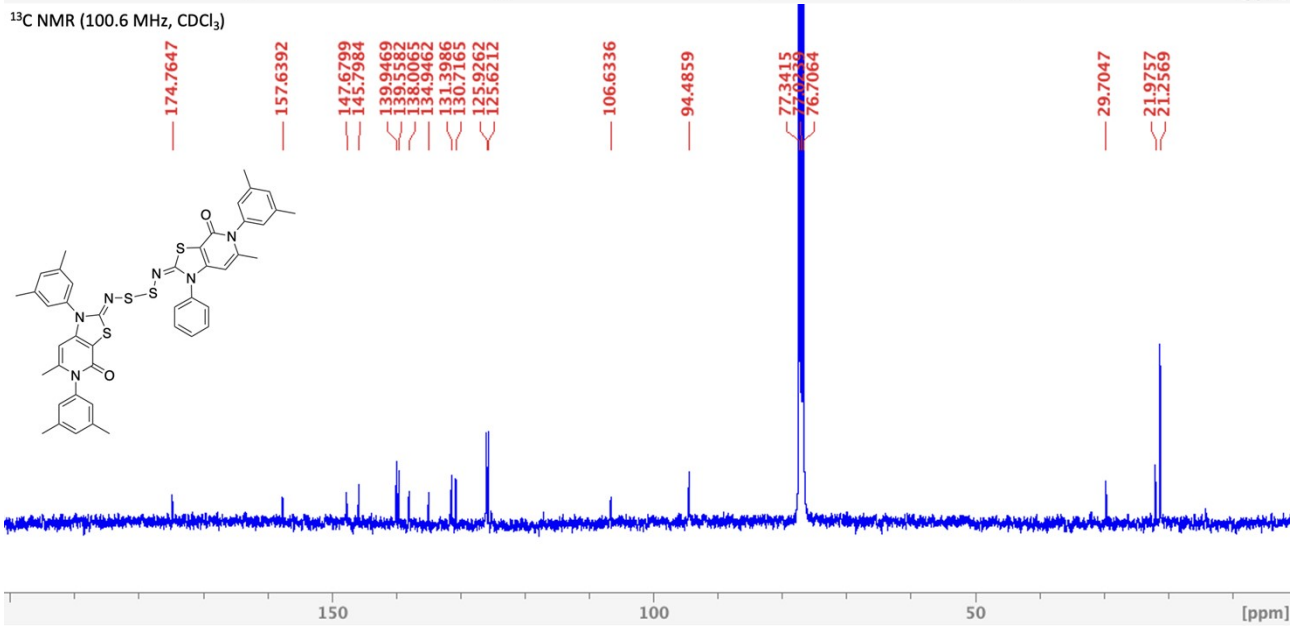


Compound 22b

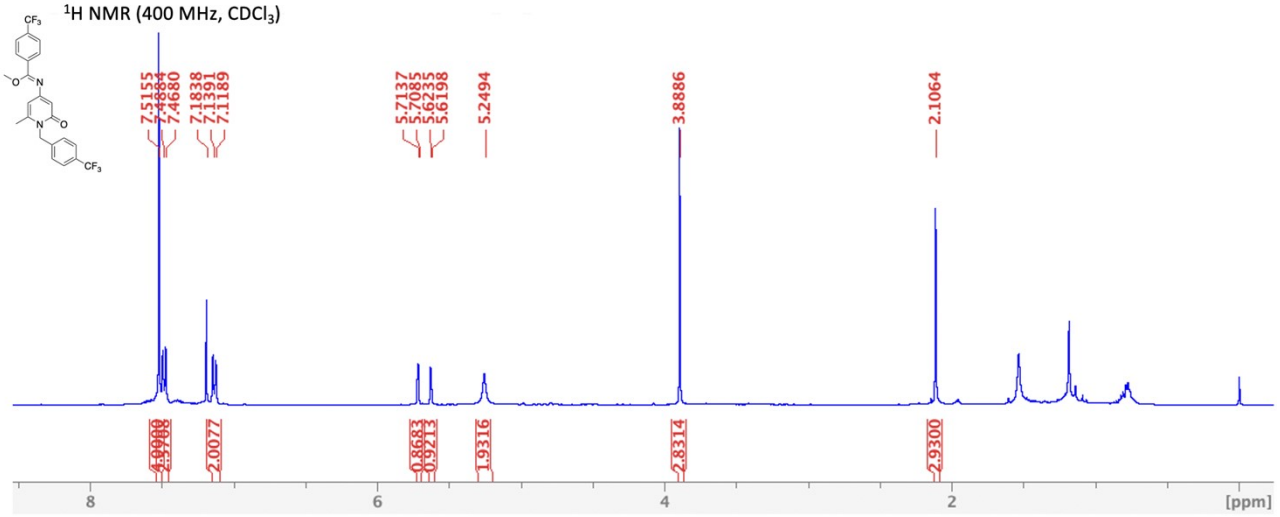


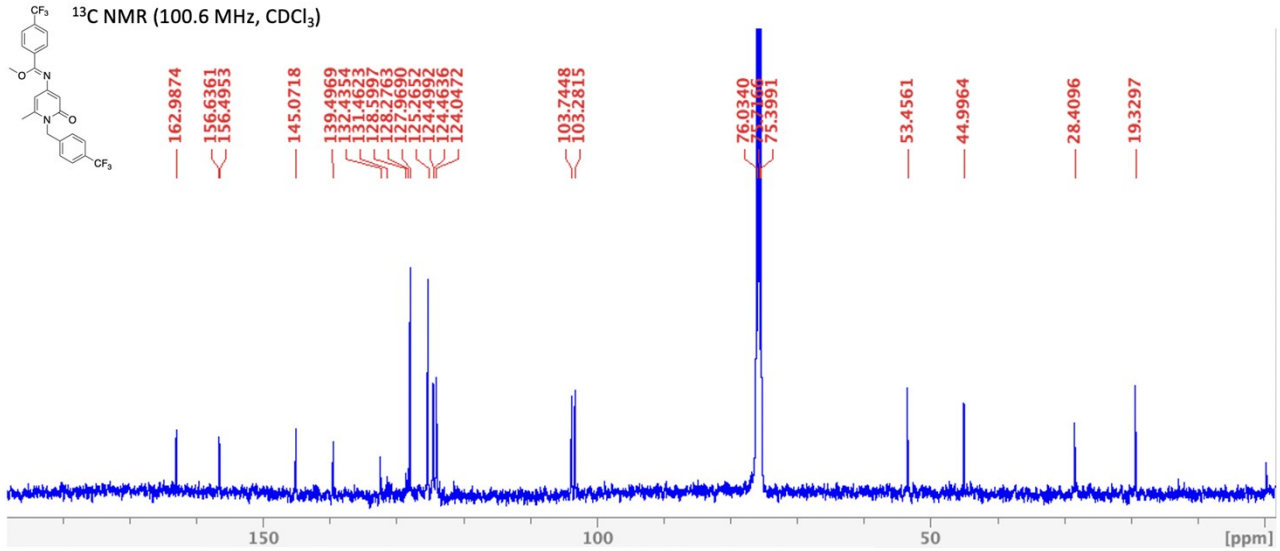
Compound 22c

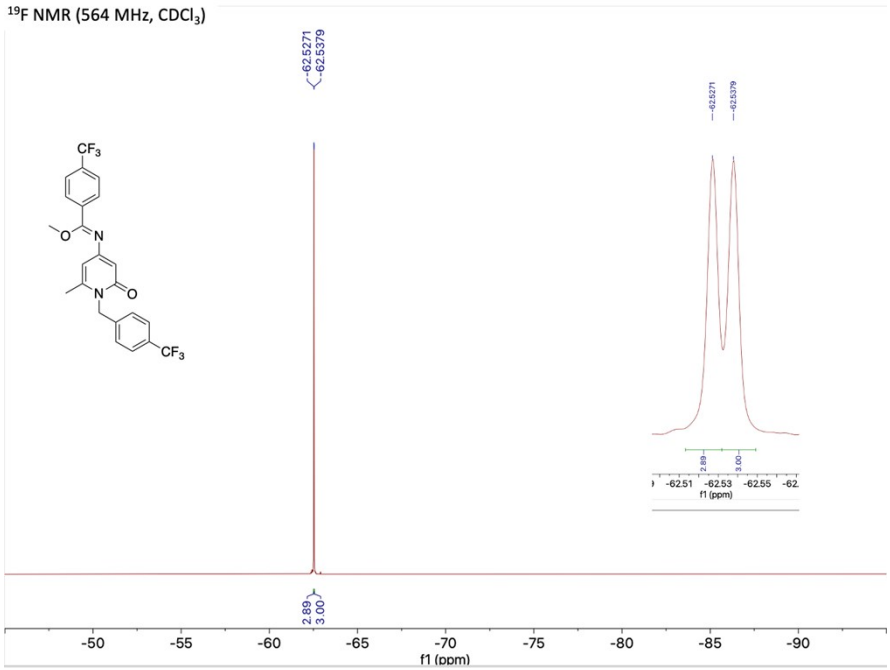




Compound 8


^{1}H NMR (400 MHz, $CDCl_3$)
7.5155
7.4680
7.1838
7.1391
7.1189
5.7137
5.7085
5.6235
5.6198
5.2494
3.8886
2.1064
4.0000
2.9700
2.0077
0.8683
0.9213
1.9316
2.8314
2.9300
8
6
4
2
[ppm]

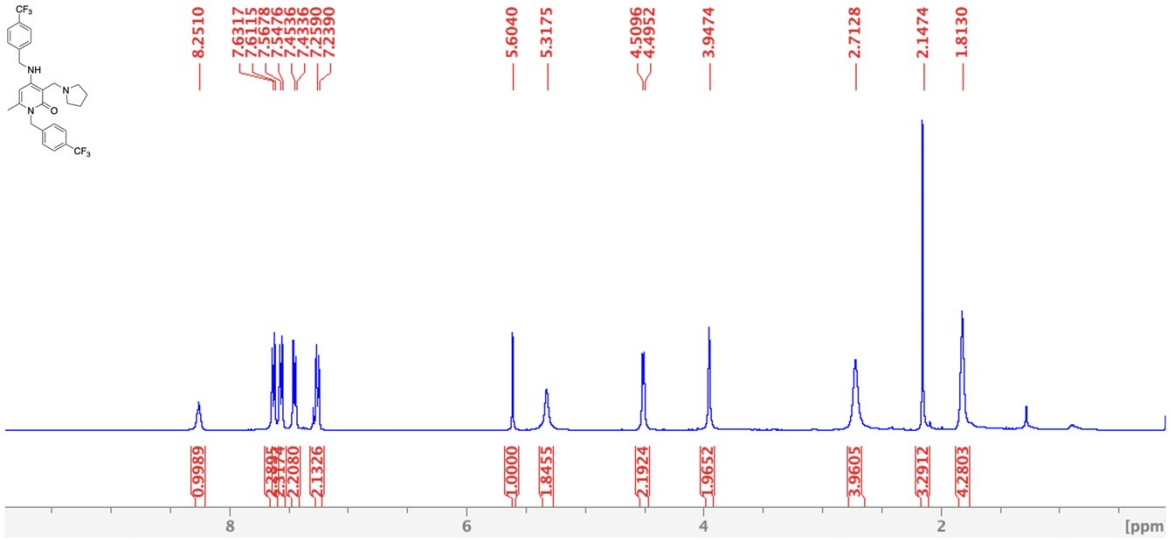

^{13}C NMR (100.6 MHz, $CDCl_3$)
162.9874
156.6361
156.4953
145.0718
139.4969
132.4354
131.4623
128.5997
128.2763
127.9690
125.2652
124.4992
124.4636
124.0472
103.7448
103.2815
76.0340
75.7166
75.3991
53.4561
44.9964
28.4096
19.3297
150
100
50
[ppm]


^{19}F NMR (564 MHz, $CDCl_3$)
-62.5271
-62.5379
2.89
3.00
-50
-55
-60
-65
-70
-75
-80
-85
-90
f1 (ppm)

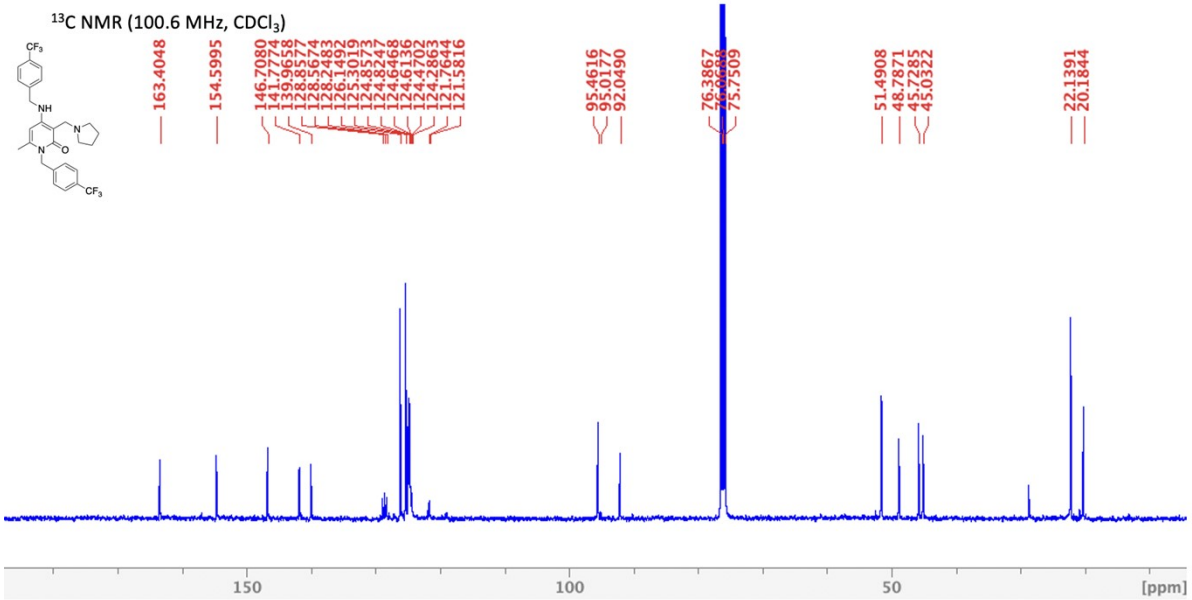
MCR-LSF:

Compound 9a

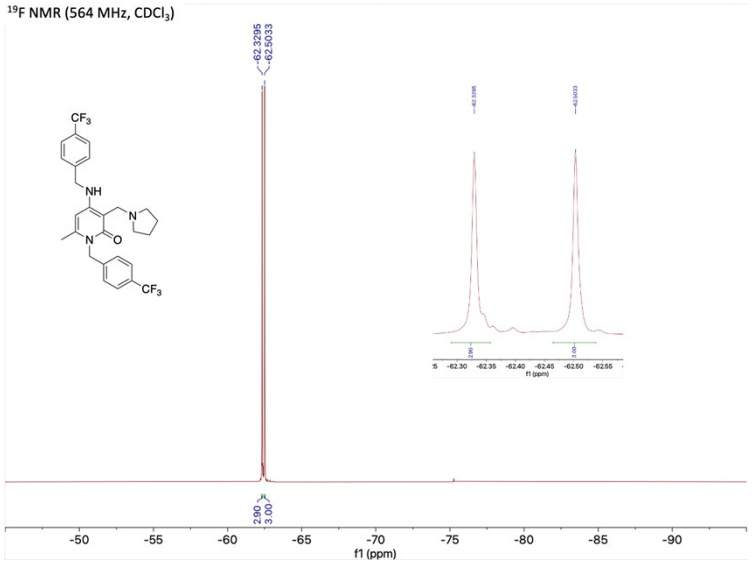
^{1}H NMR (400 MHz, $CDCl_3$)



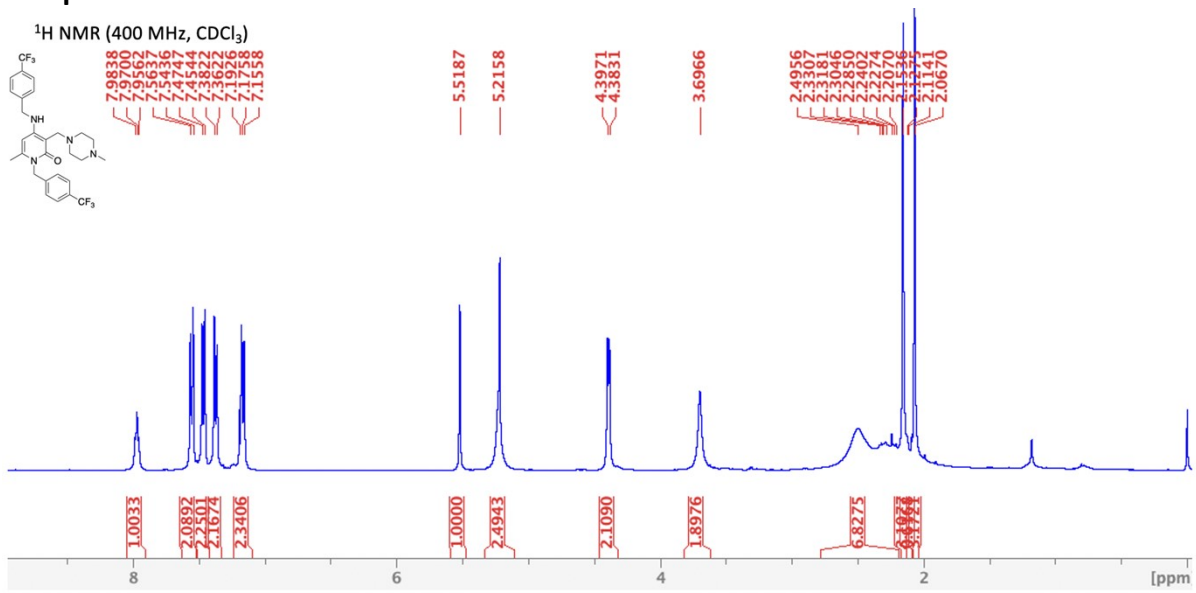
^{13}C NMR (100.6 MHz, $CDCl_3$)

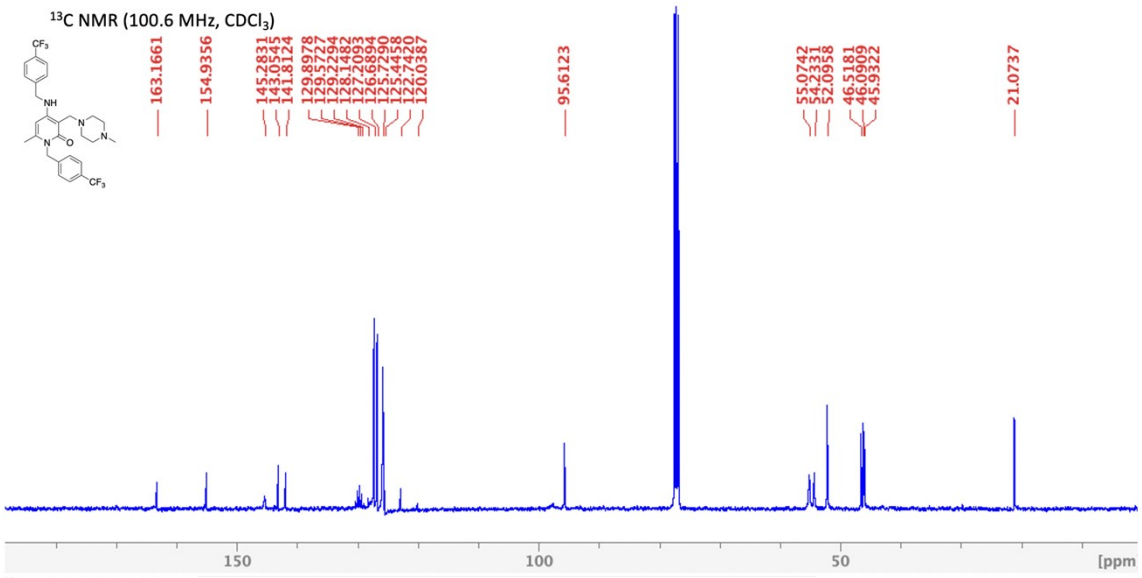


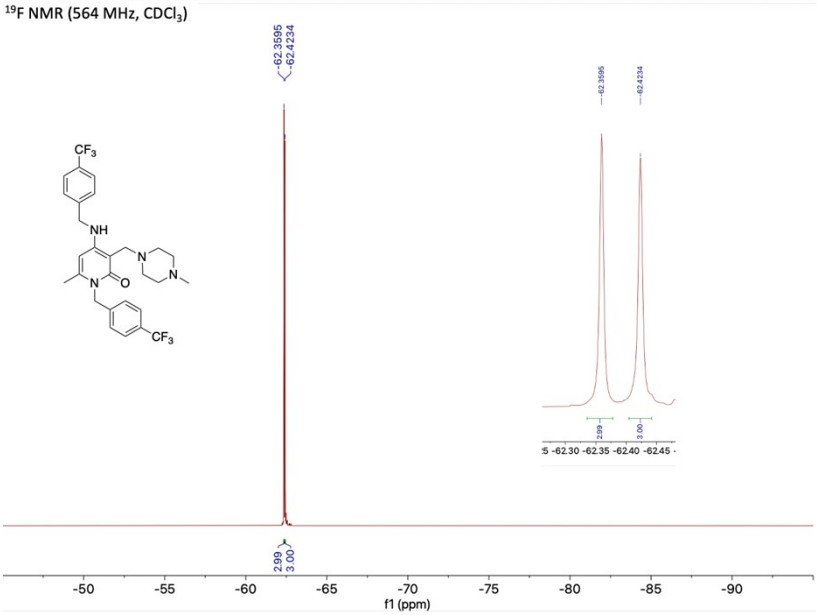
^{19}F NMR (564 MHz, $CDCl_3$)



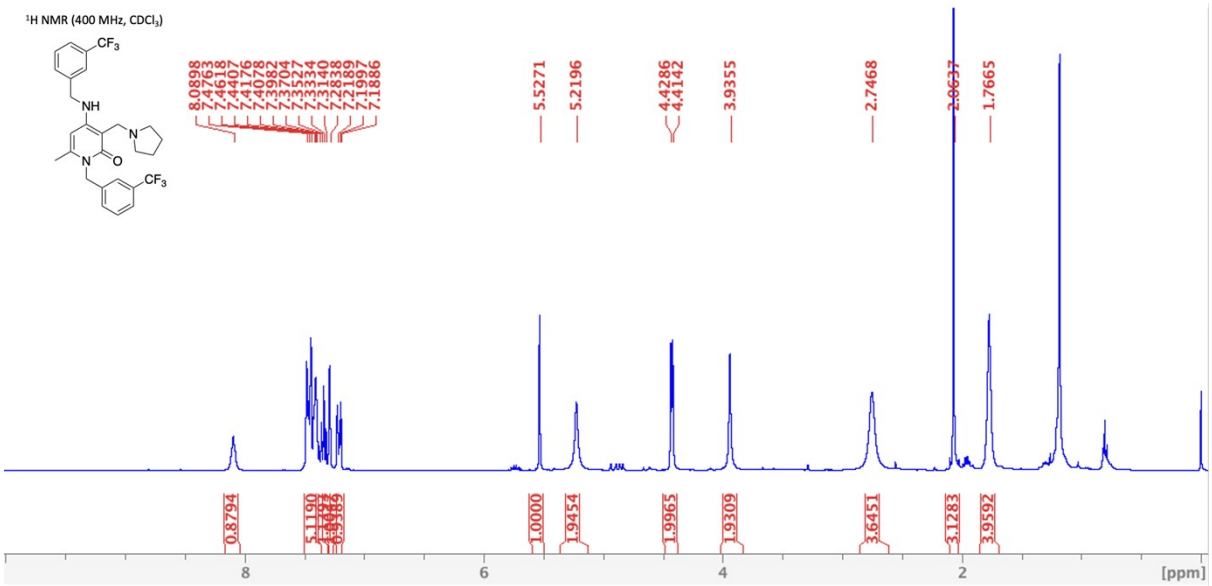
Compound 9b

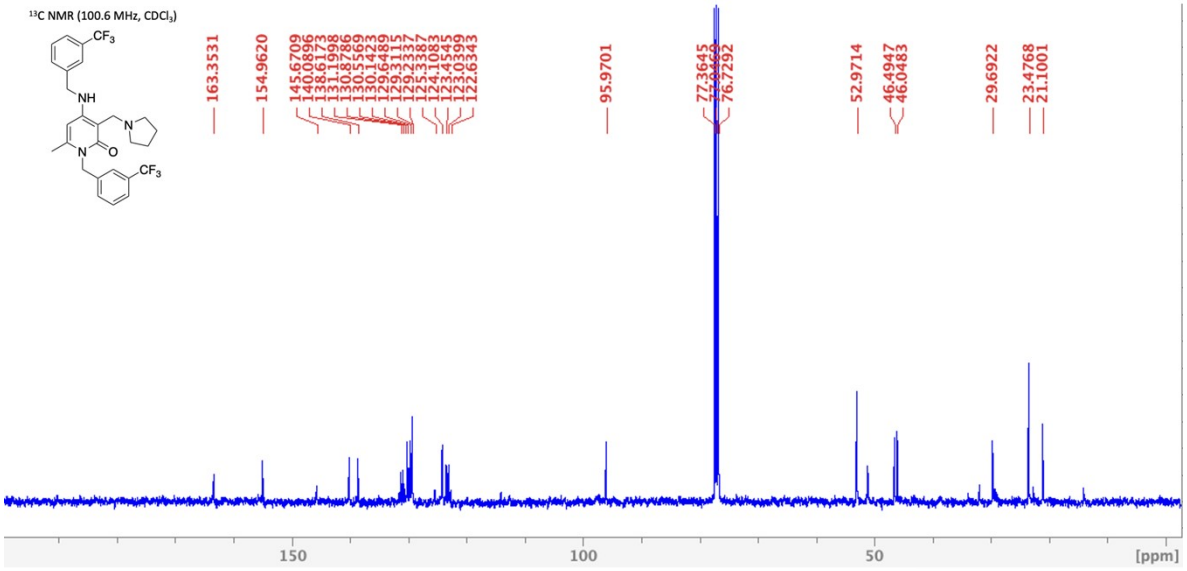

^{1}H NMR (400 MHz, $CDCl_3$)
7.9838
7.9700
7.9562
7.5637
7.5436
7.4747
7.4544
7.3822
7.3622
7.1926
7.1558
5.5187
5.2158
4.3971
4.3831
3.6966
2.4956
2.3307
2.3181
2.3046
2.2850
2.2402
2.2274
2.2070
2.1141
2.0670
1.0033
2.0892
2.0801
2.1074
2.3406
1.0000
2.4943
2.1090
1.8976
6.8275
8
6
4
2
[ppm

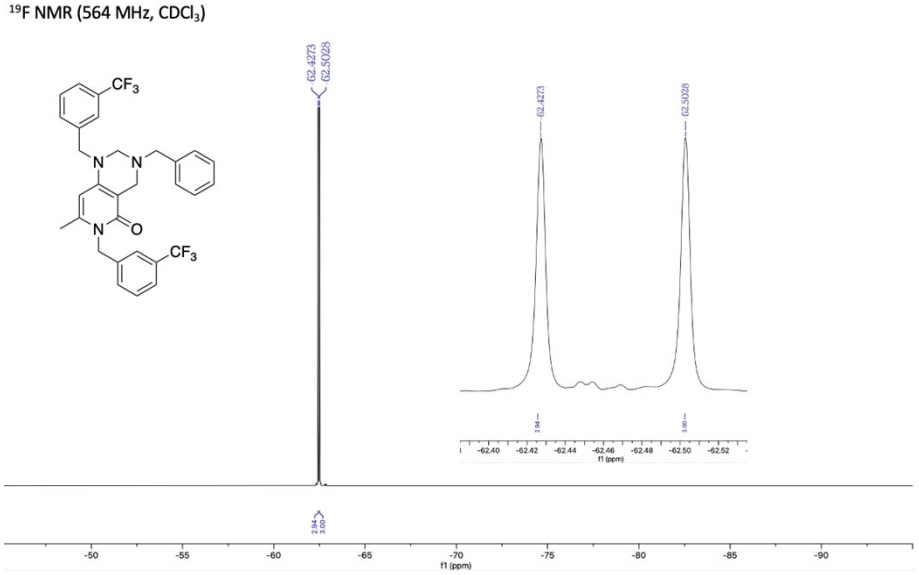

^{13}C NMR (100.6 MHz, $CDCl_3$)
163.1661
154.9356
145.2831
143.0545
141.8124
129.8978
129.5727
129.2294
128.1482
127.2093
126.6894
125.7450
122.7420
120.0387
95.6123
55.0742
54.2331
52.0958
46.5181
46.0909
45.9322
21.0737
150
100
50
[ppm


^{19}F NMR (564 MHz, $CDCl_3$)
-62.3595
-62.4234
2.99
3.00
-50
-55
-60
-65
-70
-75
-80
-85
-90
f1 (ppm)

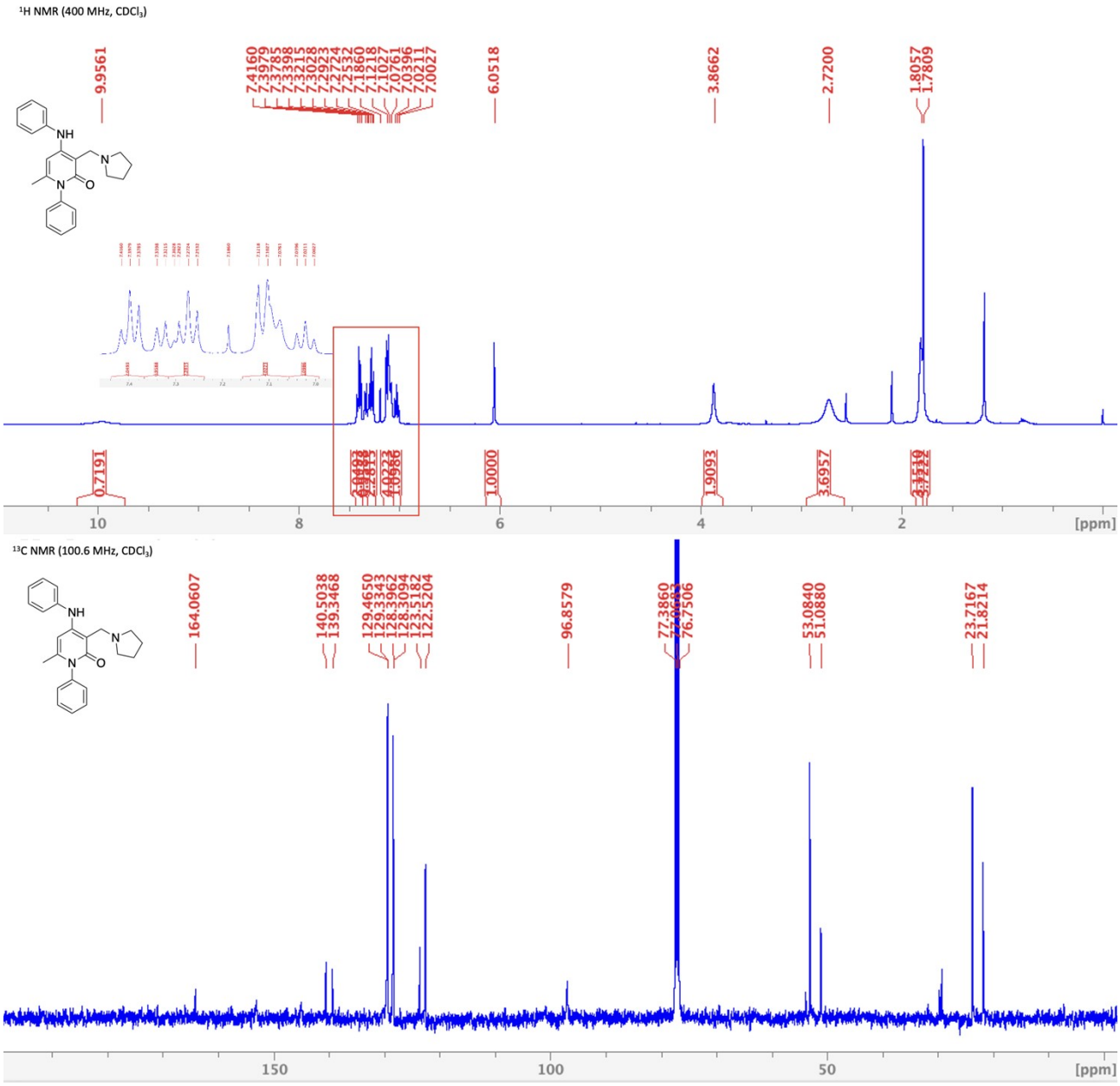
Compound 25a





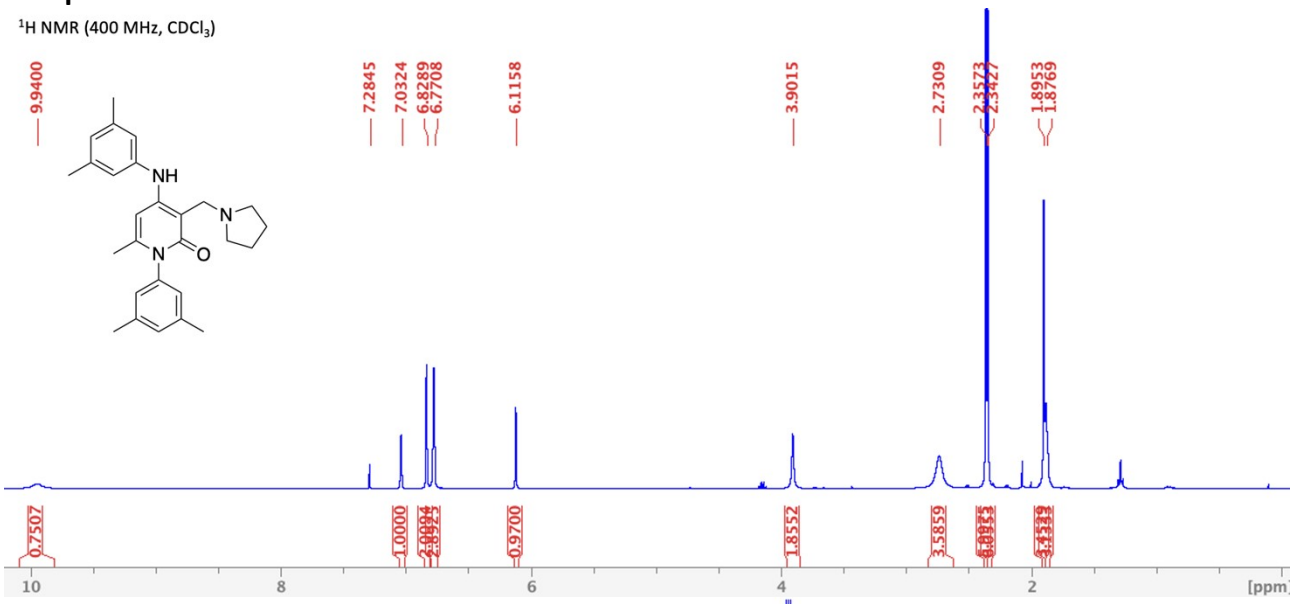


Compound 25b

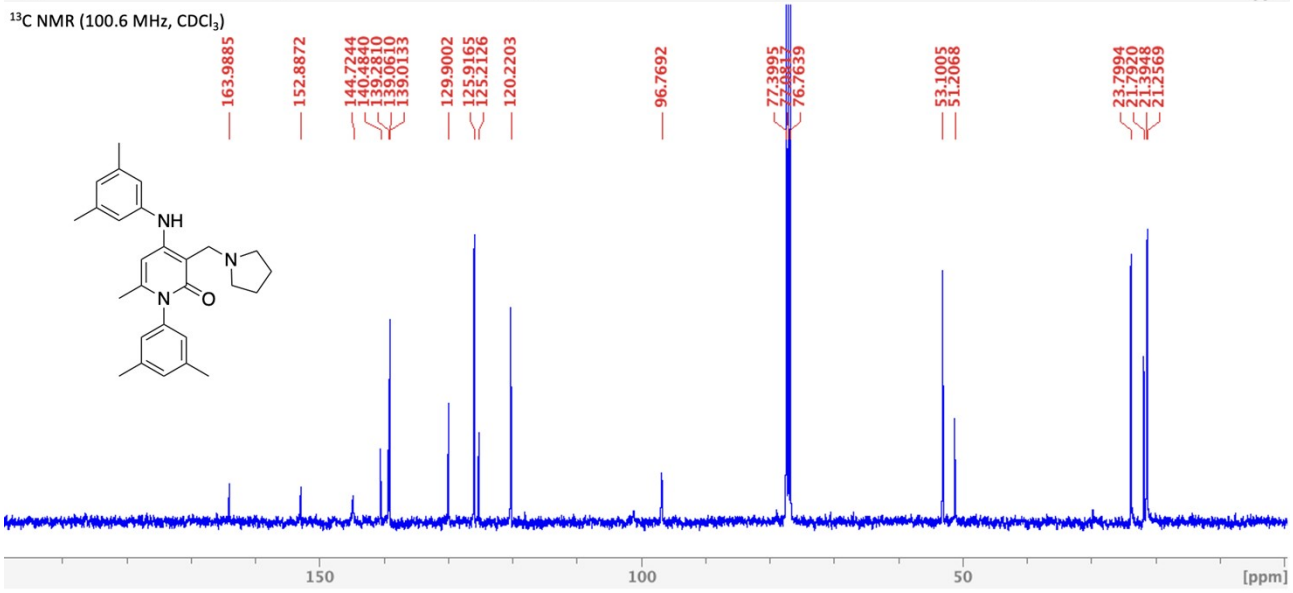


Compound 25c

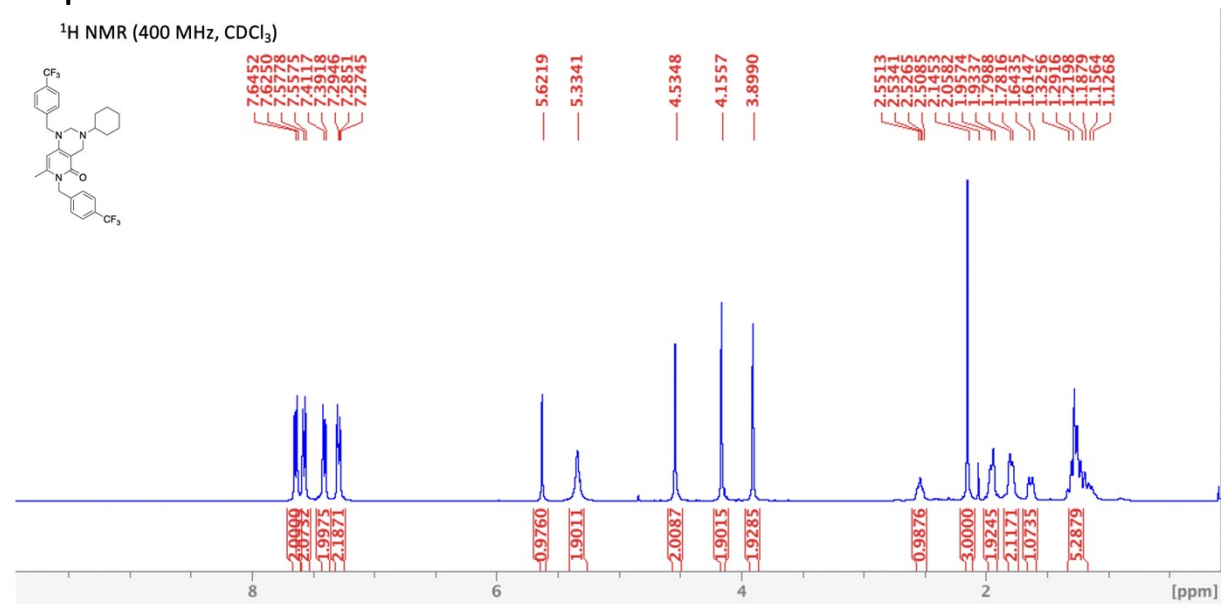
^{1}H NMR (400 MHz, $CDCl_3$)

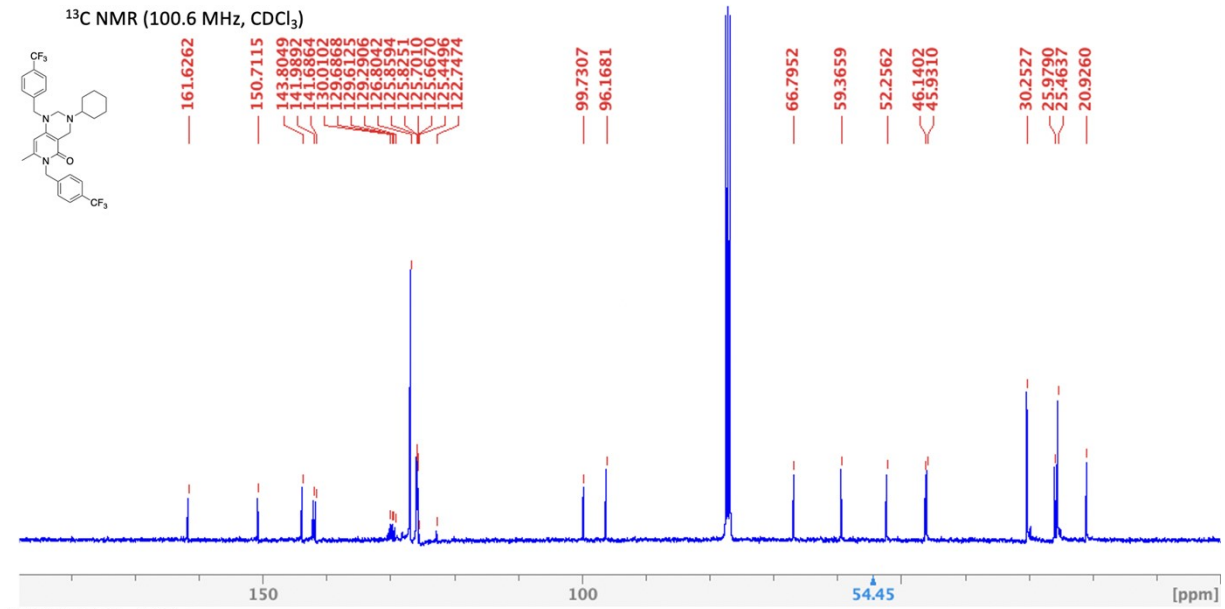


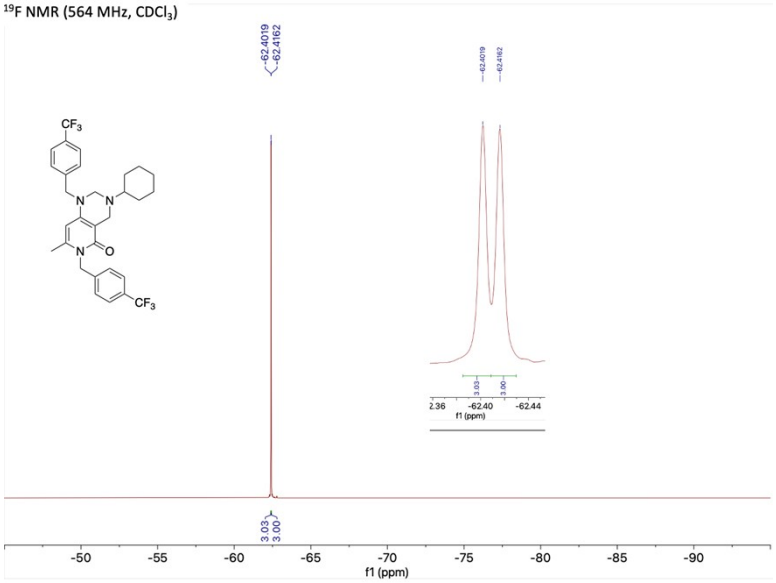
^{13}C NMR (100.6 MHz, $CDCl_3$)



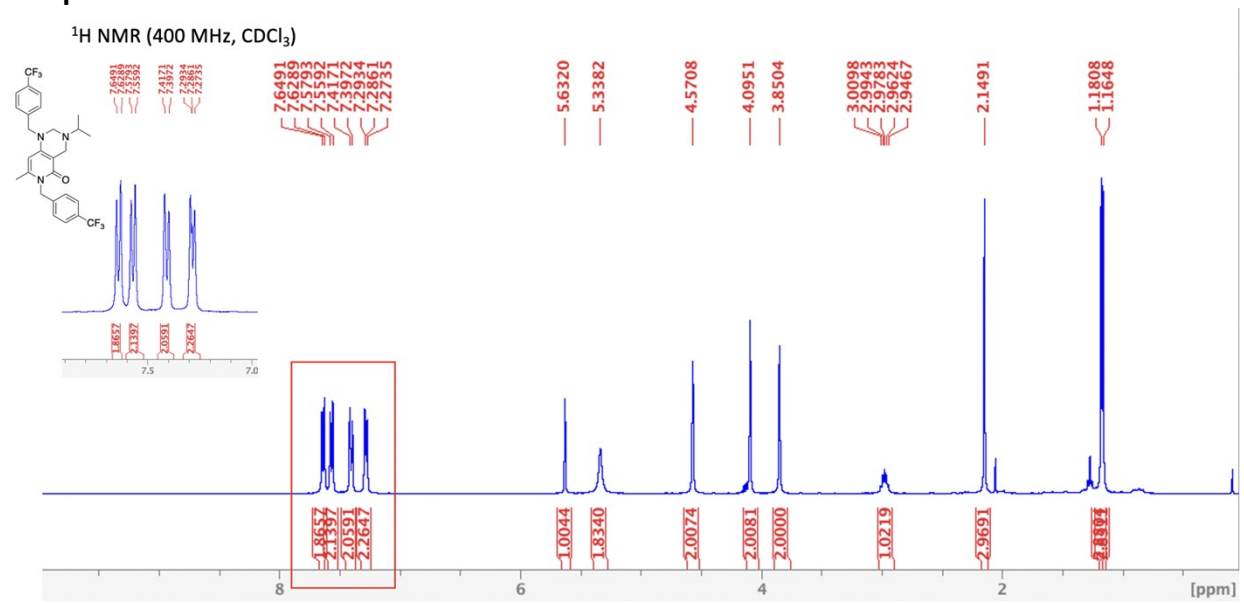
Compound 10a

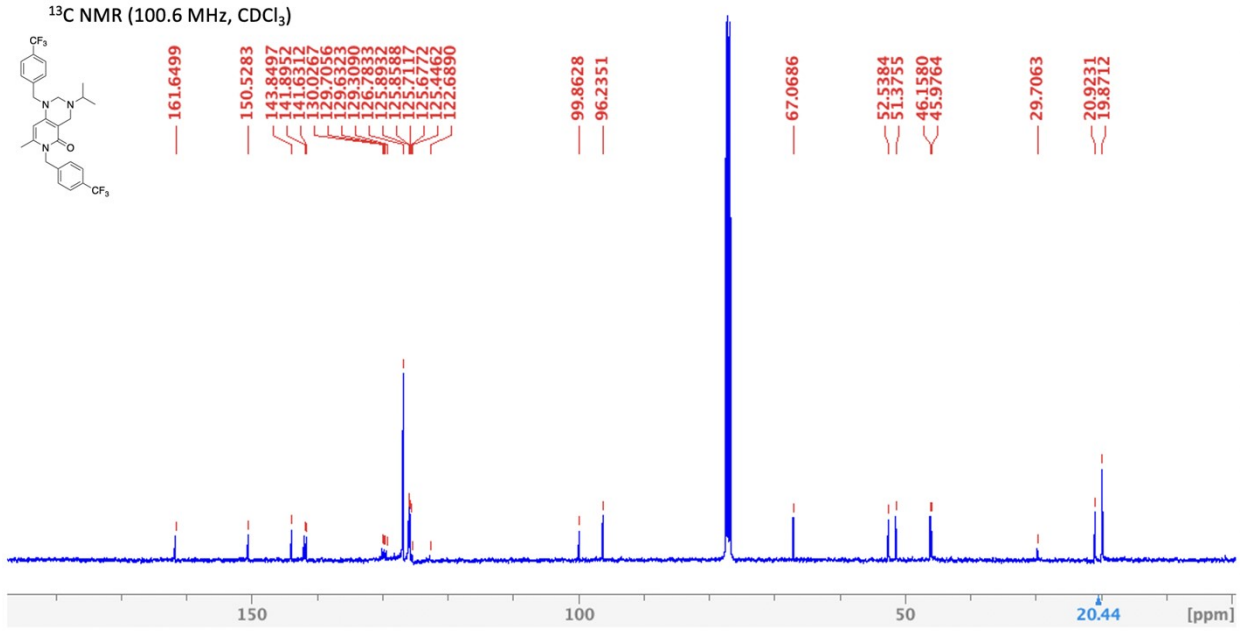


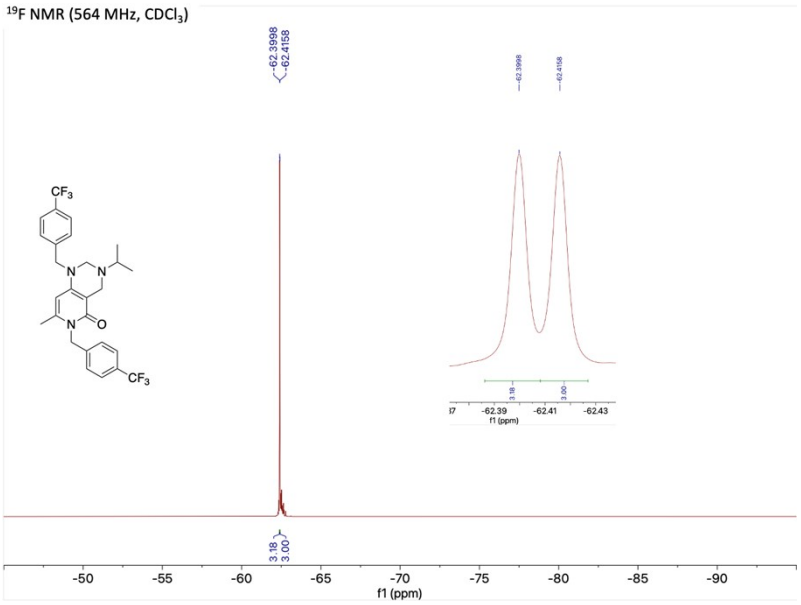




Compound 10b

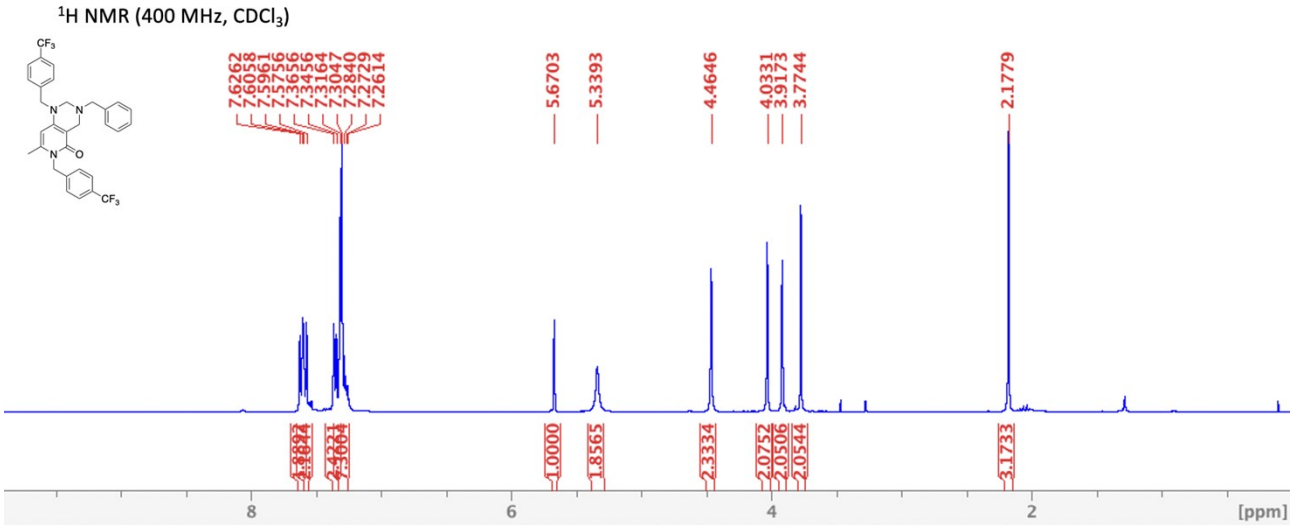




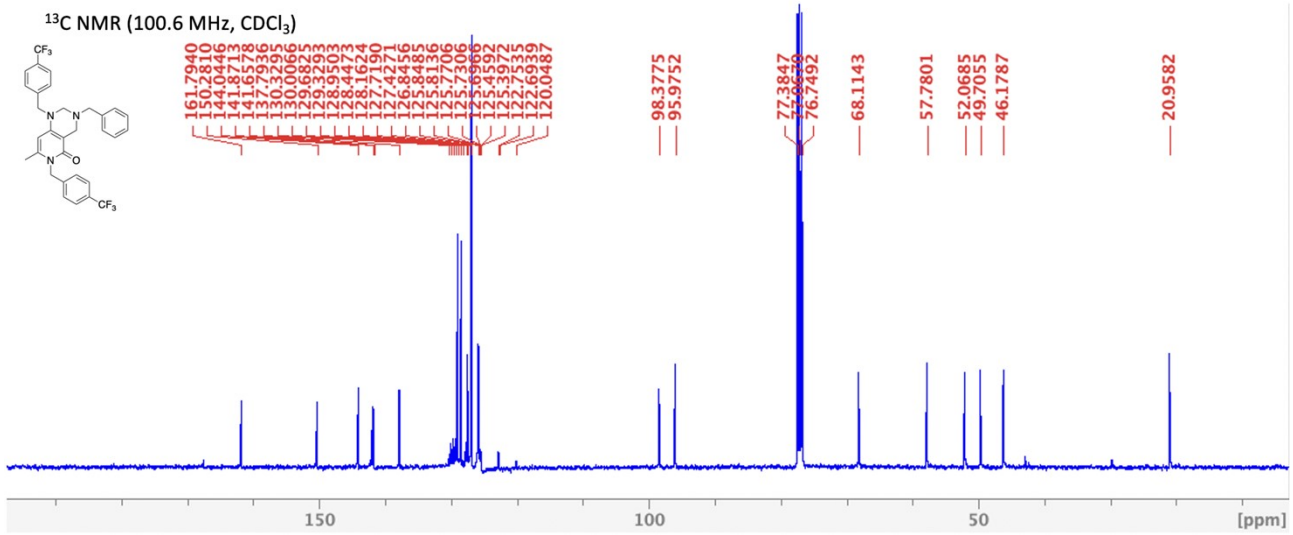


Compound 10c

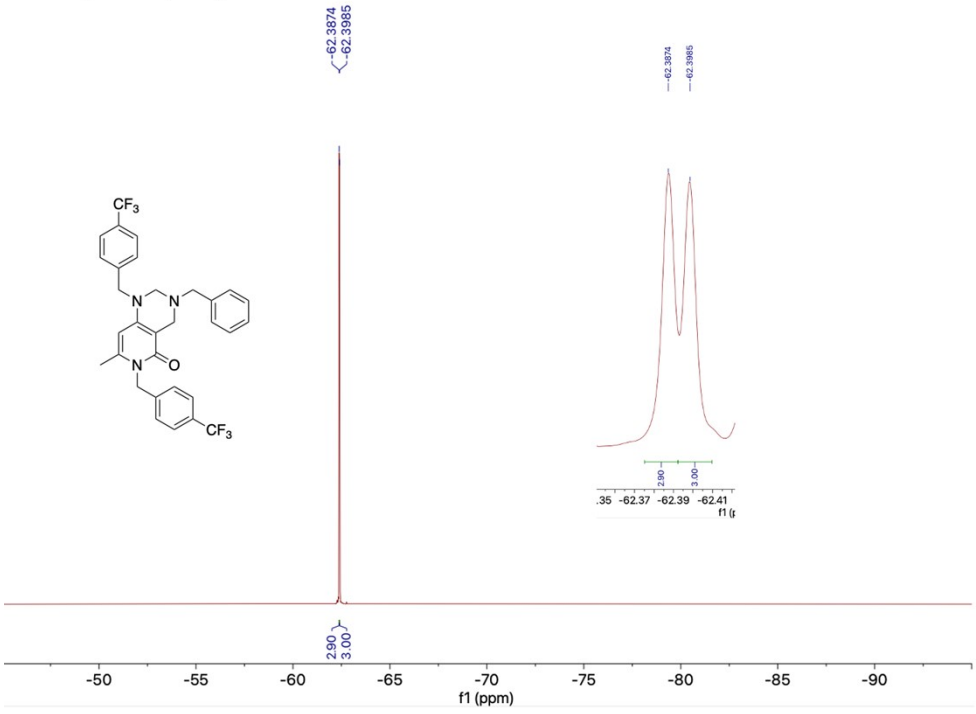
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100.6 MHz, $CDCl_3$)

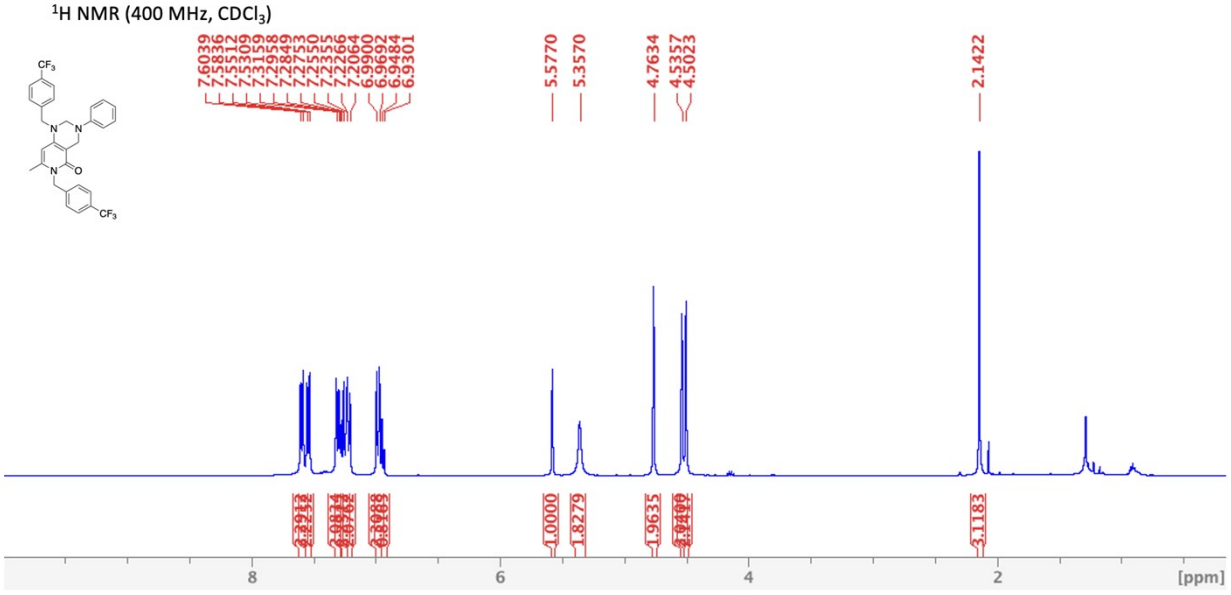


^{19}F NMR (564 MHz, $CDCl_3$)

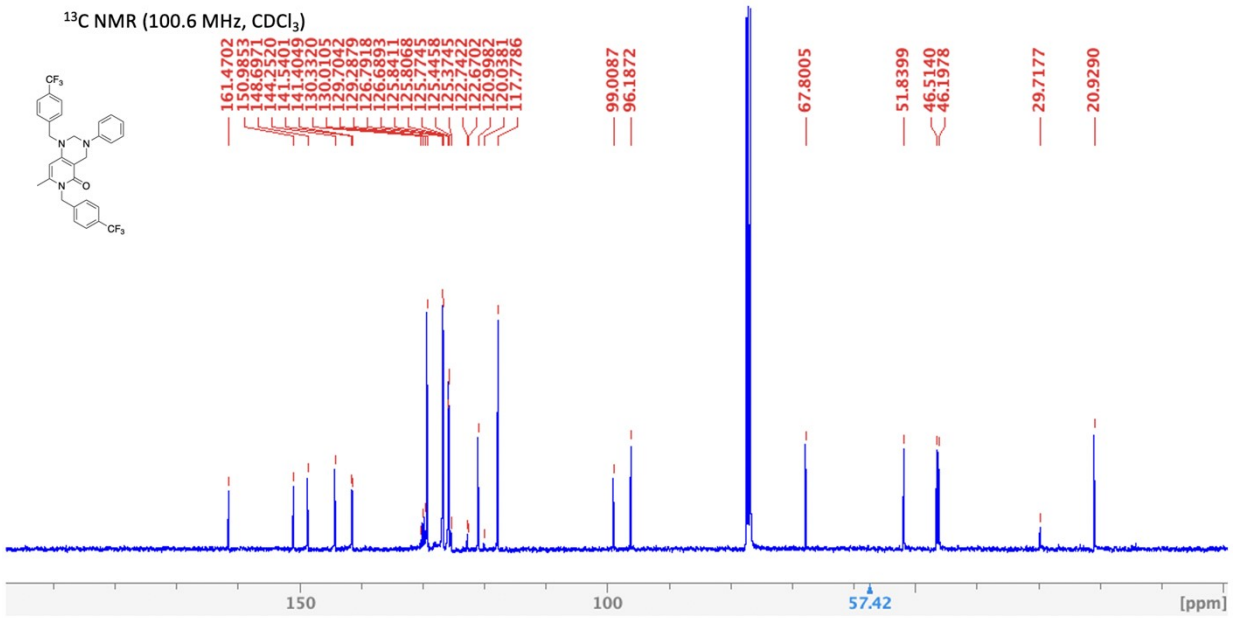


Compound 10d

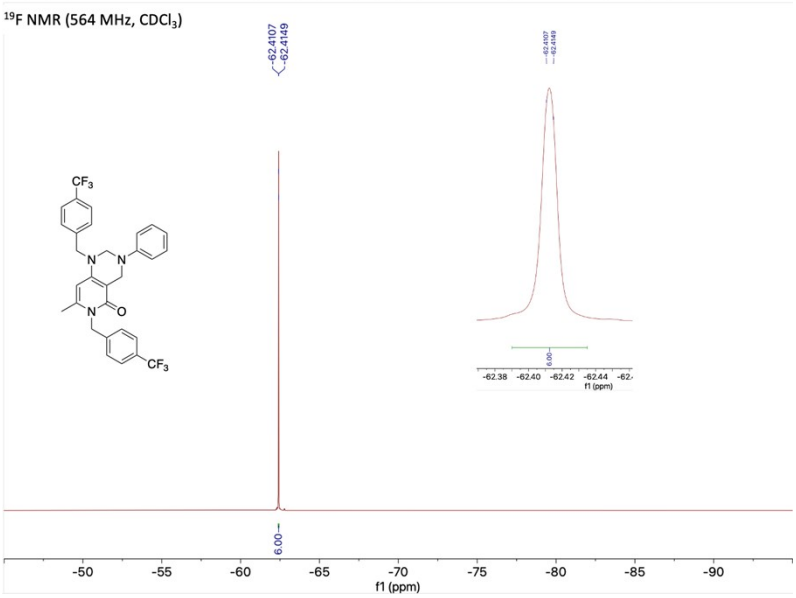
^{1}H NMR (400 MHz, $CDCl_3$)



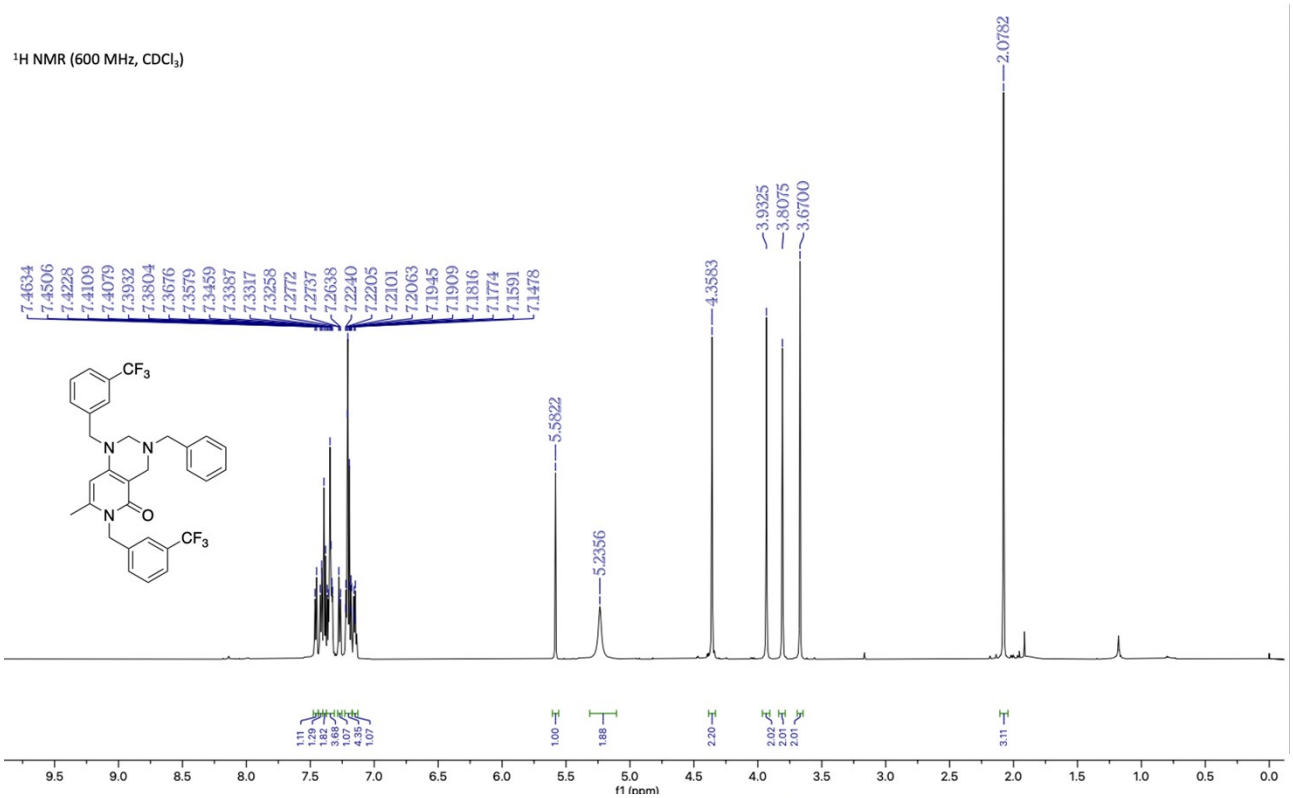
^{13}C NMR (100.6 MHz, $CDCl_3$)

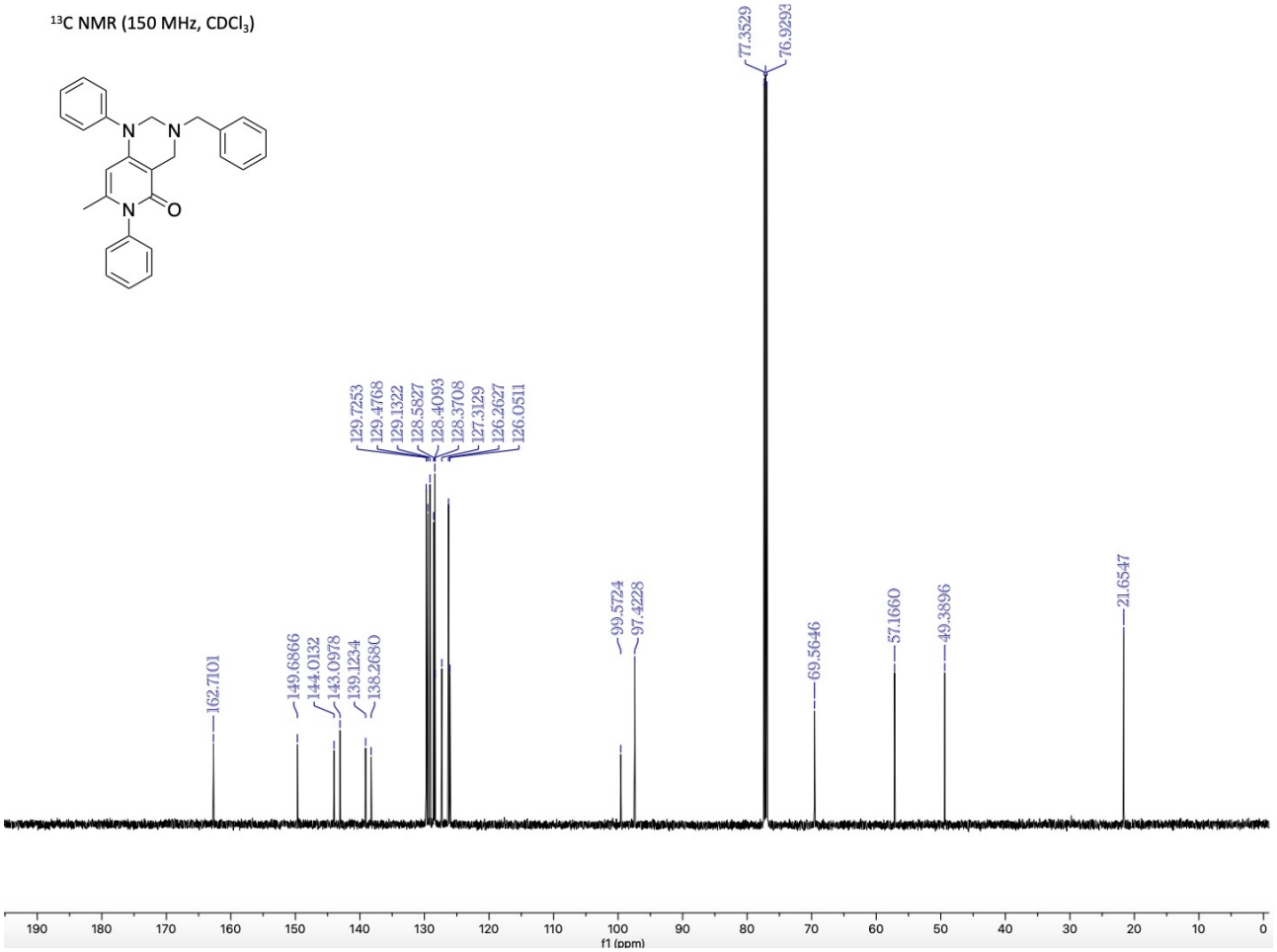


^{19}F NMR (564 MHz, $CDCl_3$)

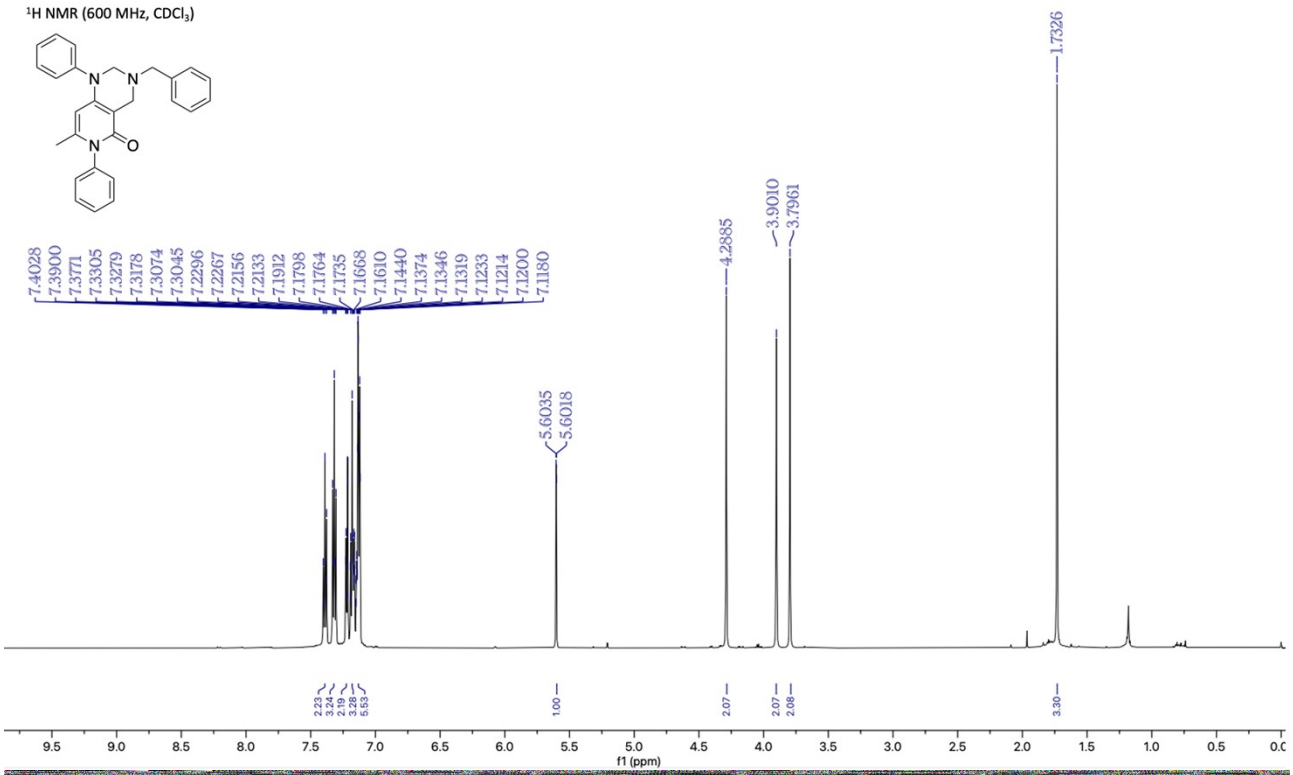


Compound 26a

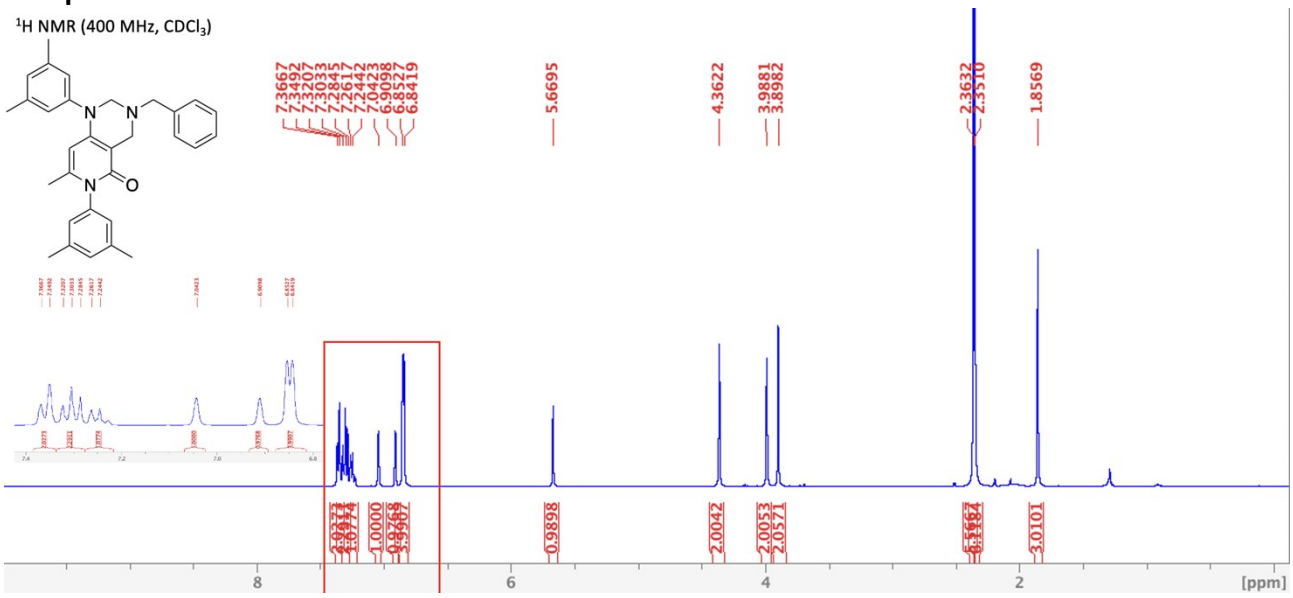


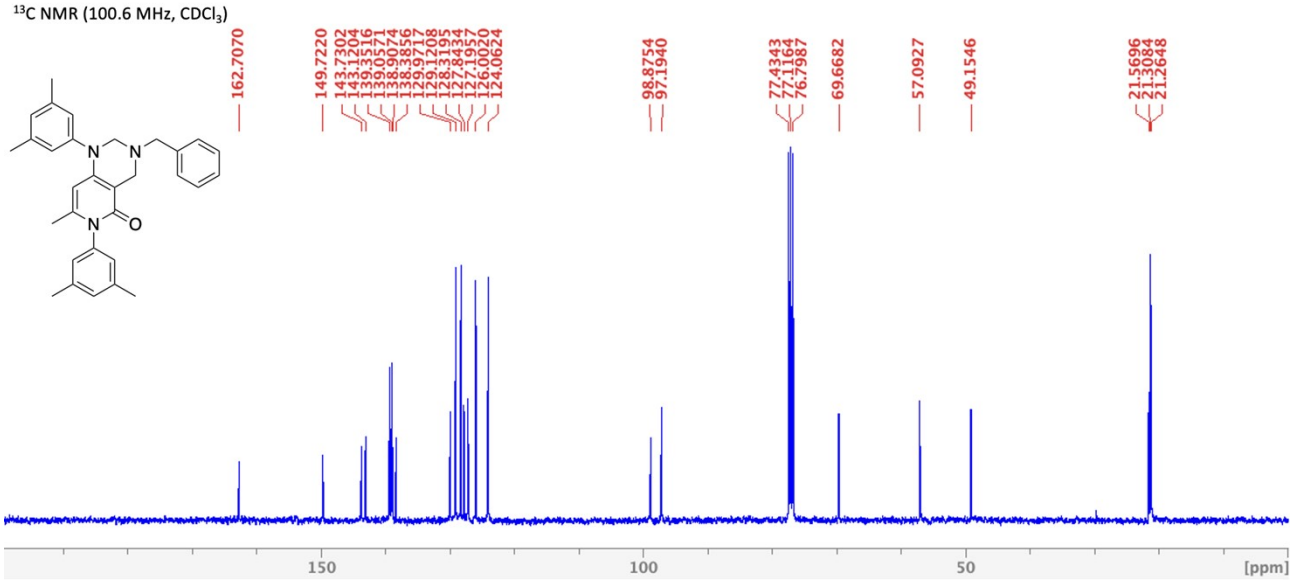


Compound 26b



Compound 26c





8. X-ray diffraction analysis

The crystal structures of compounds **7** and **17** were determined by X-ray diffraction on single crystals grown by slow evaporation of a solution of chloroform and hexane. Crystal data and experimental details for data collection and structure refinement are reported in Table 5. Intensity data and cell parameters were recorded at 200(2) K on a Bruker D8 Venture PhotonII diffractometer (CuK radiation = 1.54178 Å). The raw frame data were processed using SAINT and SADABS to yield the reflection data files.[A] The structures were solved by Direct Methods using the SHELXT program[B] and refined on F_o^2 by full-matrix least-squares procedures, using SHELXL-2018[C] in the WinGX suite v.2021.2.[D] All non-hydrogen atoms were refined with anisotropic atomic displacements. The hydrogen atoms were included in the refinement at idealized geometry and refined "riding" on the corresponding parent atoms. In view of the presence of disordered electron density which could not be properly modelled, the structures were subJected to the program SQUEEZE.[E] In both cases, the solvent contribution to the diffraction pattern (water for **7** and chloroform for **17**) was removed and modified F_o^2 written to a new HKL file. The number of electrons corresponding to the solvent molecules were included in the formula, formula weight, calculated density, m and F(000). The weighting schemes used in the last cycle of refinement were $w = 1/ [\sigma^2 F_o^2 + (0.0538P)^2 + 2.2826P]$ (**7**) and $w = 1/ [\sigma^2 F_o^2 + (0.3806P)^2]$ (**17**), where $P = (F_o^2 + 2F_c^2)/3$. The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. 2351138-2351139 and can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge, CB2 IEZ, UK (e-mail deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

A. SADABS 2016/2, Krause, L.; Herbst-Irmer, R.; Sheldrick, G. M.; Stalke, D. Comparison of silver and molybdenum microfocus X-ray sources for single-crystal structure determination. *J. Appl. Cryst*. **2015**, *48*, 3-10.

B. Sheldrick, G. M. SHELXT – Integrated space-group and crystal-structure determination. *Acta Cryst.* **2015**, *A71*, 3-8.

C. Sheldrick, G. M. Crystal structure refinement with SHELXL. *Acta Cryst*. **2008**, *A64*, 112-122.

D. Farrugia. L. J. WinGX suite for small-molecule single-crystal crystallography. *J. Appl. Crystallogr*. **1999**, *32*, 837-838.

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Table 6. Crystal data and structure refinement information for compounds **7** and **17**.

Compound	**7**	**17**
empirical formula	$C_{23}H_{17}F_6N_3OS$ 0.5(H_2O)	$C_{46}H_{32}F_{12}N_6O_2S_4$ 2.5($CHCl_3$)
M	506.46	1355.43
crys syst	Orthorhombic	Triclinic
space group	*Fdd*2	*P*-1
a/Å	13.8237(7)	10.9640(7)
b/Å	50.8400(10)	14.7925(9)
c/Å	12.4078(5)	19.0470(9)
a/°	90	79.382(2)
□/°	90	87.727(2)
g/°	90	73.299(2)
V/Å^3	8720.2(6)	2907.9(3)
Z	16	2
ρ /g cm^{-3}	1.543	1.548
□□/mm^{-1}	2.021	5.412
F(000)	4144	1366
total reflections	35778	106552
unique reflections (R_{int})	4157 (0.0834)	11517 (0.0685)
observed reflections *[F_o>4σ(F_o)]*	3509	10602
GOF on F^{2a}	1.014	1.017
R_{indices} *[F_o>4σ(F_o)]*^{b} R_1, wR_2	0.0371, 0.927	0.0989, 11517
largest diff. peak and hole (eÅ^{-3})	0.156, -0.139	1.213, -1.000

[a]Goodness-of-fit S = [Σw(F_o^2-F_c^2)^2/ (n-p)]1/2, where n is the number of reflections and p the number of parameters. [b]R_1 = Σ ‖F_o|-|F_c‖/Σ|F_o|, wR_2 = [Σ[w(F_o^2-F_c^2)^2]/Σ[w(F_o^2)^2]]$^{1/2}$.

Compound **7** crystallizes in the space group *Fdd*2 with one independent molecule in the unit cell (Figure Sx). It consists of a planar bicyclic fragment comprising the atoms C1-C8/C16/N1-N3/S1/O1, and two trifluorotoluene moieties bonded to C8 and C16, that protrude in the same direction from the mean plane of the core, forming an angle of 70.05(3)° and 87.43(2)°, respectively. The molecules form a supramolecular ribbon along the direction of the crystallographic axis *c* through N-H···O hydrogen bonds [N3-H3N···O1(-*x*+3/2, -*y*+1, *z*+1/2). N3···O1=2.9876(2) Å; N3-H3N···O1=166.9(3)°].

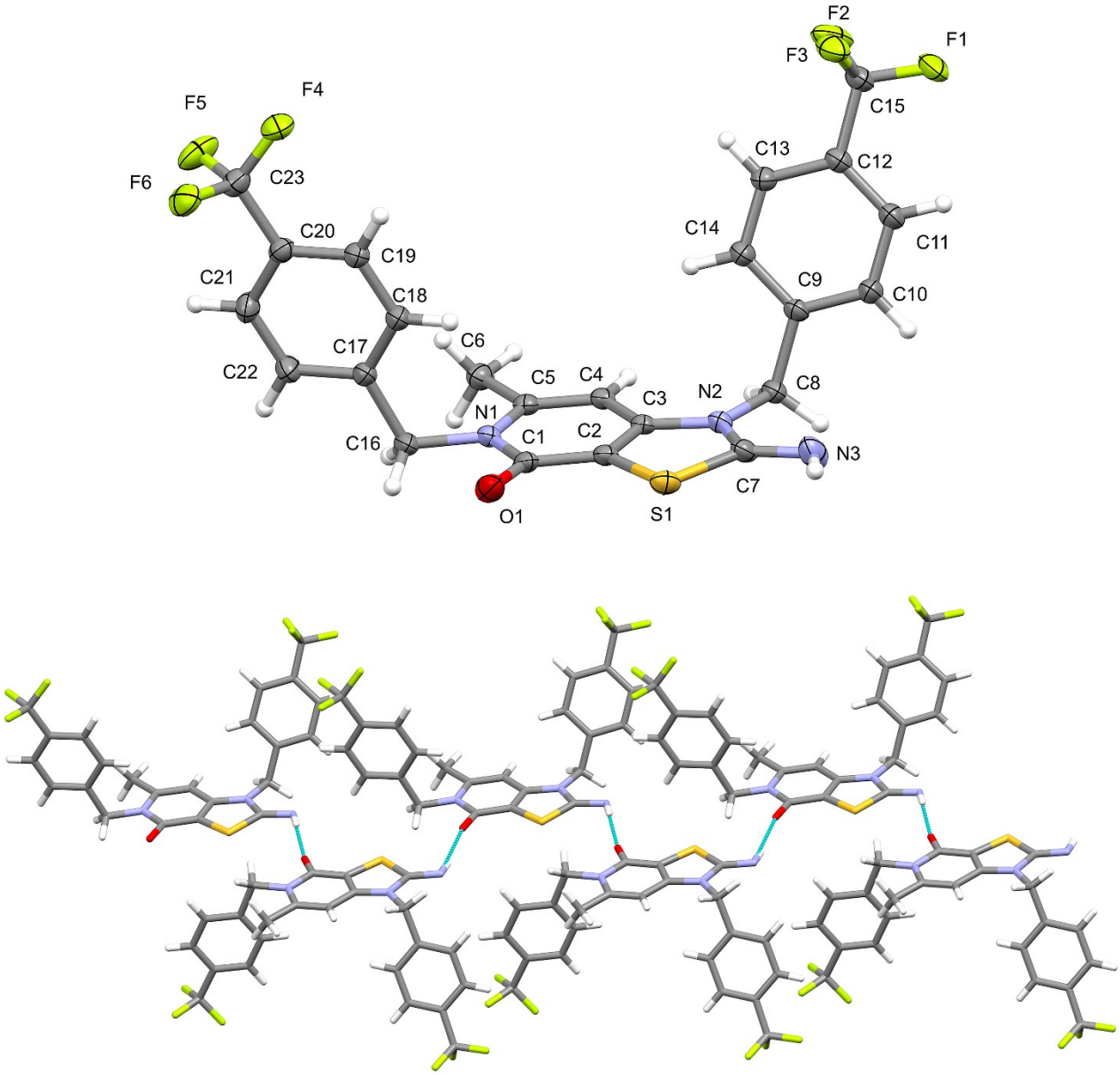

Figure S4. Top: ortep view of **7** with labelling scheme and ellipsoids at the 20% probability level. Bottom: supramolecular ribbon along the *c*-axis direction of the unit cell. H bonds are represented as cyan dotted lines.

Compound **17** crystallizes in the space group *P*-1 with one independent molecule in the unit cell (Figure Sy and Figure 2 in the main text). It can be described as a dimeric form of **7**, in which the -C=NH fragment (-C7=N3-H3N) is replaced by a -C=N-S- moiety that generates a dimer through a -C=N-S-S-N=C- bridge. Also in this case, the bicyclic moieties are planar and the trifluorotoluene fragments protrude from the main planes passing through the planar core forming angles of

83.04(3)°, 80.77(3)°, 82.63(2)° and 80.99(4)°. Since the -C=NH fragment is not present in the molecule, no classic N-H···O hydrogen bonds are formed, and the crystal packing is mainly consolidated by dispersion interactions.

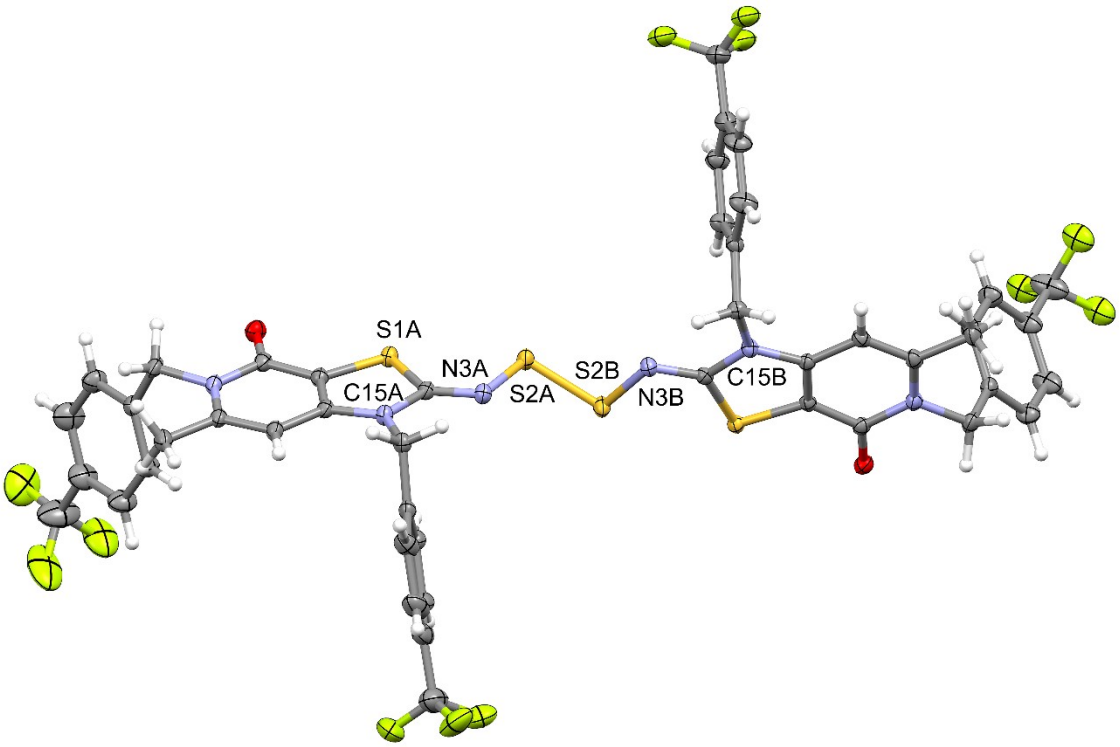

Figure S5. Top: ortep view of **17** with partial labelling scheme and ellipsoids at the 20% probability level. Solvent molecules have been omitted for clarity. The fluorine atoms in the trifluorotoluene rings are disordered over two geometrical positions, but only the maJor component is shown in the figure.