Supporting Information

Slicing and Splicing of Bromodifluoro-*N*-arylacetamides: Dearomatization and Difunctionalization of Pyridines

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1. General Information

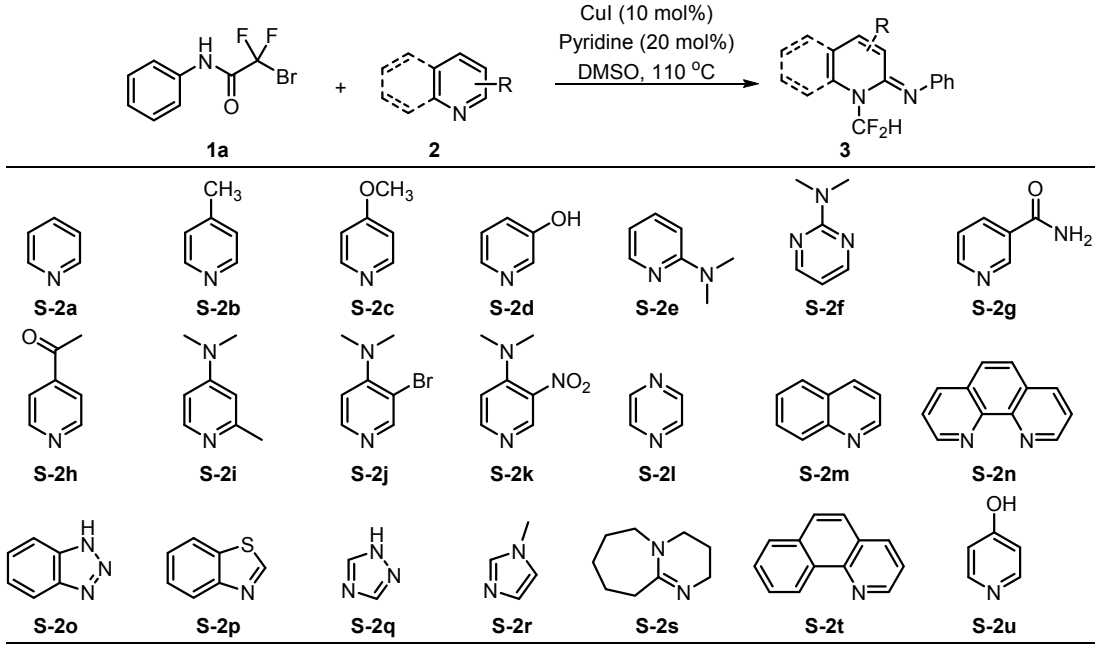
All reactions were carried out under argon atmosphere with dry solvents in flame-dried glassware unless otherwise noted. Dimethyl sulfoxide, 4-(dimethylamino)pyridine, and CuI were purchased from commercial sources and used as received. Flash chromatographic separations were carried out on 200-300 mesh silica gel. Reactions were monitored by TLC or GC analysis of reaction aliquots. GC analyses were performed on an Agilent 7890 Gas Chromatography using a HP-5 capillary column (30 m × 0.32 mm, 0.5 μm film) and Shimadzu 2010 Plus Gas Chromatograph with a barrier discharge ionization detector (BID) using helium as a carrier gas. ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded in deuterated solvents on a Bruker AVANCE III or JNM-ECZ600R spectrometer and calibrated using residual undeuterated solvent ($CDCl_3$ at 7.26 ppm ^{1}H NMR, 77.16 ppm ^{13}C NMR). Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High resolution mass spectrometry (HRMS) was recorded on a QTOF mass analyzer with electrospray ionization (ESI) through a Bruker Daltonics - micrOTOF-QII or Waters G2-XS QTOF mass spectrometer.

Bromodifluoroacetamides **1a**-**1q** were synthesized from ethyl bromodifluoroacetate and the corresponding aniline according to the reported procedure.[1] 4-Aminopyridines **2b**-**2i** were synthesized from 4-halopyridines and the corresponding amines according to the reported procedure.[2]

2. Screening of aromatic nitrogen heteroarenes for *N*-difluoromethylation /*β*-imidization

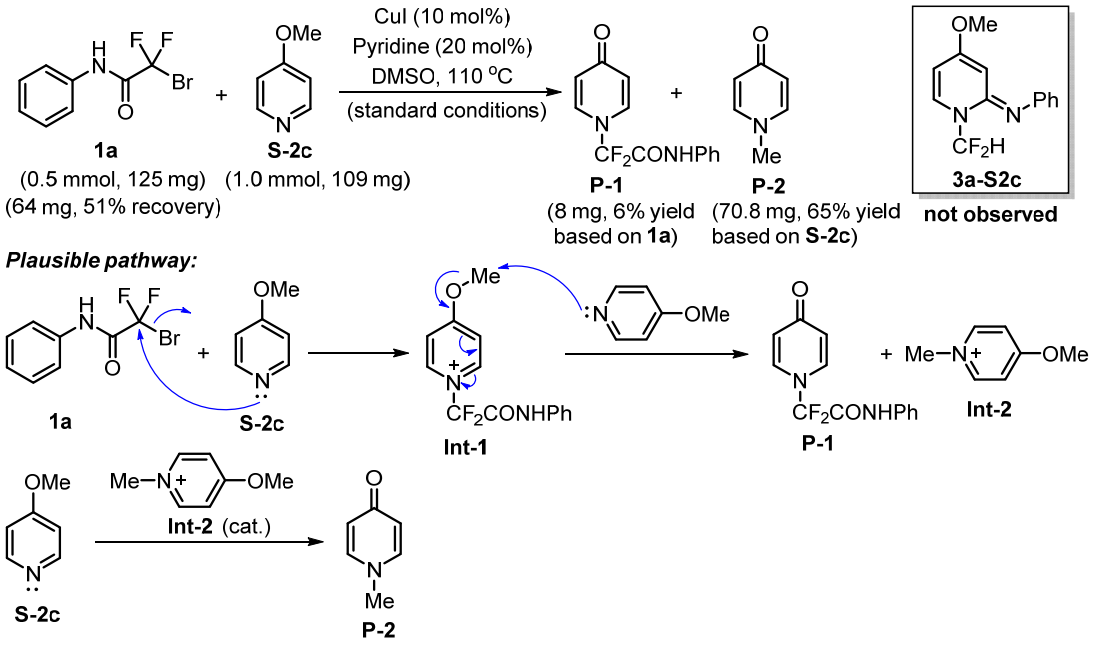
A series of nitrogen containing heterocyclic substrates have been subjected with 2-bromo-2,2-difluoro-*N*-phenylacetamide **1a**, catalytic amount of CuI and pyridine in DMSO (1.0 mL) at 110 ^{o}C. Unfortunately, some of which did not work and starting materials were partially recovered (**S-2a** - **S-2s**), while the others were messy resulting complicated inseparable mixture (**S-2t** and **S-2u**).

Scheme S1. Screening of aromatic nitrogen heterocycles



Reaction conditions: unless otherwise noted, all reactions were performed with **1a** (0.2 mmol), **2** (0.3 mmol), CuI (10 mol%), and pyridine (20 mol%) in DMSO (0.5 mL) at 110 °C under Ar for 12 h.

For the reaction of substrate 4-methoxy pyridine (**S-2c**), instead of desired product (**3a-S2c**), compounds 2,2-difluoro-2-(4-oxopyridin-1(4*H*)-yl)-*N*-phenylacetamide (**P-1**) and 1-methylpyridin-4(1*H*)-one (**P-2**) were isolated, and a large amount of **1a** was also recovered. For the formation of these two compounds, we proposed a preliminary mechanism as followed (Scheme S2). First, an *N*-difluoroacetamide-4-methoxy-pyridium salt (**Int-1**) was formed from nucleophilic substitution of **1a** by **S-2c**. Then, the nucleophilic attack of **S-2c** toward the methoxy carbon of **Int-1** could lead to **P-1** and *N*-methyl-4-methoxy-pyridium salt (**Int-2**). Next, the nucleophilic attack of **S-2c** toward the methoxy carbon of **Int-2** could lead to **P-2** and regenerate **Int-2**. Therefore, the major formation of **P-2** could be viewed as an *N*-methyl-4-methoxy-pyridium salt (**Int-2**) catalyzed hydrolysis of **S-2c**.



Scheme S2. Possible mechanism for *N*-methyl and *N*-$CF_2CONHPh$ pyridinone

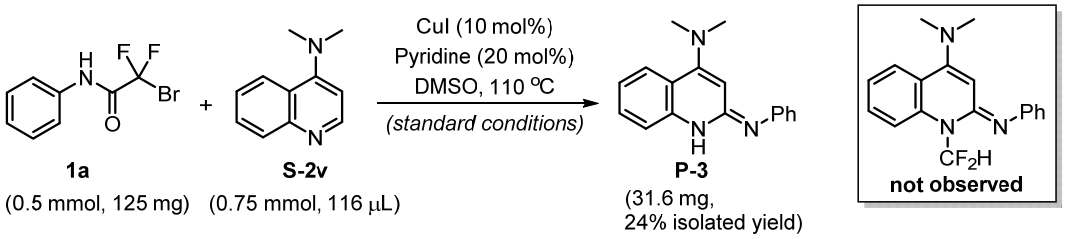
Preparation and characterization of compounds P-1 and P-2:

To a mixture of 2-bromo-2,2-difluoro-*N*-phenylacetamide (**1a**) (125 mg, 0.5 mmol), CuI (10.0 mg, 0.05 mmol), 4-methoxypyridine (**S-2c**) (102 μL, 109 mg, 1.0 mmol) in DMSO (1.0 mL) were added pyridine (8 μL, 0.10 mmol). The resultant mixture was stirred at 110 °C (oil bath) for 12 hrs and monitored by TLC. The reaction was quenched with ethyl acetate and water, and then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated in vacuum and the residue was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give compound **P-1** as pale yellow solid (8 mg, 6% yield based on **1a**), compound **P-2** as as white solid (70.8 mg, 65% yield based on **S-2c**), and **1a** (64 mg, 51% recovery yield).

2,2-Difluoro-2-(4-oxopyridin-1(4*H*)-yl)-*N*-phenylacetamide (**P-1**). Pale yellow solid, mp 64-65 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.30 (s, 1H), 7.98 (d, J = 8.1 Hz, 2H), 7.70 (d, J = 7.3 Hz, 2H), 7.42 (t, J = 8.0 Hz, 2H), 7.23 (t, J = 7.5 Hz, 1H), 6.28 (d, J = 8.1 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 178.6, 157.1 (t, J = 34.2 Hz), 137.0, 135.5 (2C), 129.5 (2C), 126.3, 121.7 (2C), 118.7 (2C), 112.5 (t, J = 270.8 Hz); ^{19}F NMR (565 MHz, DMSO-d_6) δ -87.36. HRMS (ESI): m/z calcd. for $C_{13}H_{11}F_2N_2O_2^+$ [M+H$^+$]: 265.0783, found: 265.0790.

1-Methylpyridin-4(1*H*)-one (**P-2**).[3] White solid, mp 91-92 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.66 (d, J = 7.6 Hz, 2H), 6.12 (d, J = 7.6 Hz, 2H), 3.66 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 177.5, 142.2 (2C), 117.8 (2C), 43.2.

For the reaction of substrate *N*,*N*-dimethylquinolin-4-amine (**S-2v**) under the standard conditions, the de-difluoromethylated product (**P-3**) was isolated with large amounts of both starting materials being recovered.

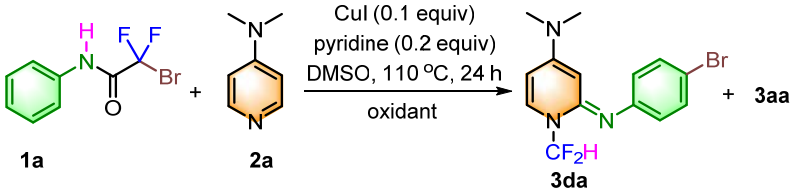


Preparation and characterization of compound P-3:

(*E*)-*N*,*N*-Dimethyl-2-(phenylimino)-1,2-dihydroquinolin-4-amine (P-3). To a mixture of 2-bromo-2,2-difluoro-*N*-phenylacetamide (**1a**) (125 mg, 0.5 mmol), CuI (10.0 mg, 0.05 mmol), 4-(dimethylamino)quinolin (**S-2v**) (116 μL, 0.75 mmol) in DMSO (1.0 mL) were added pyridine (8 μL, 0.10 mmol). The resultant mixture was stirred at 110 °C (oil bath) for 12 hrs and monitored by TLC. The reaction was quenched with ethyl acetate and water, and then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated in vacuum and the residue was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the title compound as pale yellow oil (31.6 mg, 24% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.3 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.48 – 7.40 (m, 3H), 7.28 (t, J = 7.9 Hz, 2H), 7.18 – 7.13 (m, 1H), 7.00 (t, J = 7.4 Hz, 1H), 6.33 (s, 1H), 2.89 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.3, 155.0, 149.0, 140.6, 129.5, 129.4 (2C), 127.1, 124.5, 123.0, 122.0, 120.6 (2C), 119.9, 96.9, 44.0 (2C). HRMS (ESI): m/z [M+H$^+$] calcd for $C_{17}H_{18}N_3^+$: 264.1495, found: 264.1502.

3. Screening of oxidants for in situ preparation of an active bromination species.

Table S1. Optimization of bromination reaction conditions.[a]

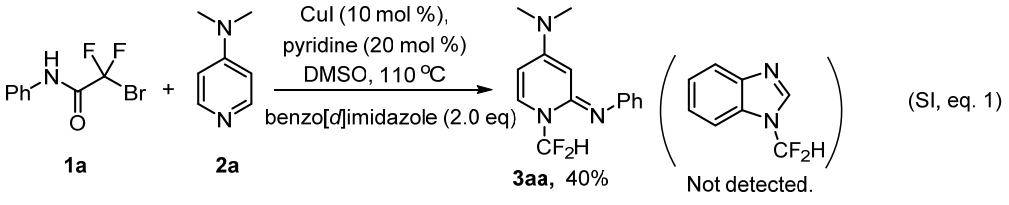


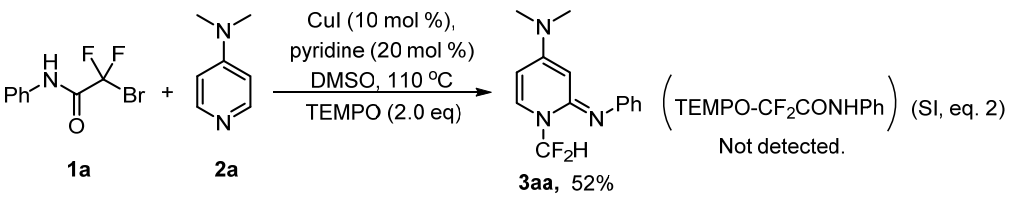
entry	oxidant	yield of **3da**[b] (%)	yield of **3aa**[b] (%)
1	$K_2S_2O_8$	n.d.	n.d.
2	DDQ	n.d.	n.d.
3	TBHP	n.d.	28
4	Ag_2O	n.d.	n.d.
5	*m*-CPBA	n.d.	n.d.
6	$PhI(OAc)_2$	4	55
7	Dess-Martin periodinane	n.d.	n.d.
8	H_2O_2	44	18
9[c]	O_2	59(50)	n.d.

[a]Reaction conditions: unless otherwise noted, all reactions were performed with **1a** (0.2 mmol), **2a** (0.3 mmol), CuI (0.02 mmol, 0.1 equiv), pyridine (0.04 mmol, 0.2 equiv), DMSO (0.5 mL), under Ar at 110 °C for 24 h. The value in parentheses is the isolated yield. [b]GC yield. n.d. = not detected. [c]O_2 (balloon).

4. Mechanistic studies

(a) Radical and carbene trap experiments.

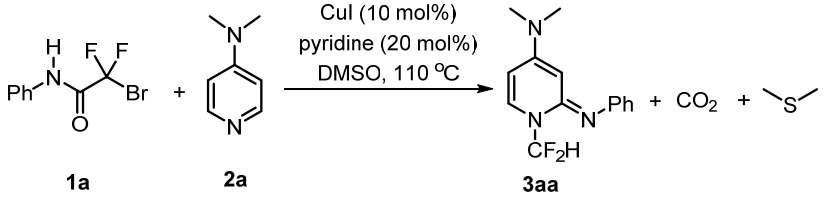




Benzo[*d*]imidazole, which can trap difluorocarbene as literature reported,[4] was added under the standard reaction. But 1-(difluoromethyl)-1*H*-benzo[*d*]imidazole was not formed and the desired product **3aa** was formed in 40% yield (SI, eq. 1), which indicate the reaction might bypass difluorocarbene intermediate and proceed through other ways. When the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added to the reaction mixture, the desired product **3aa** was observed with 54% yield and the TEMPO-$CF_2CONHPh$ was not detected, which suggested that a radical intermediate may not be involved in this transformation (SI, eq. 2).

(b) Capturing CO_2 and Me_2S

After completing the reaction, we used GC system to analyze the ingredient of gas phase and liquid phase of this reaction tub respectively. The CO_2 and dimethyl sulfide was detected, which indicated that the rearrangement of **B** affording **C** may be reasonable.



1a **2a** **3aa**

SHIMADZU LabSolutions 分析报告

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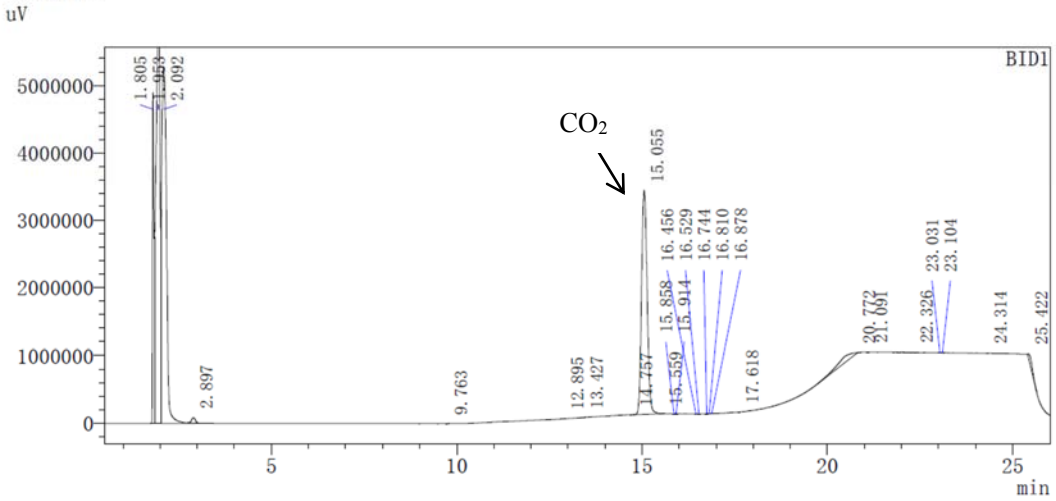
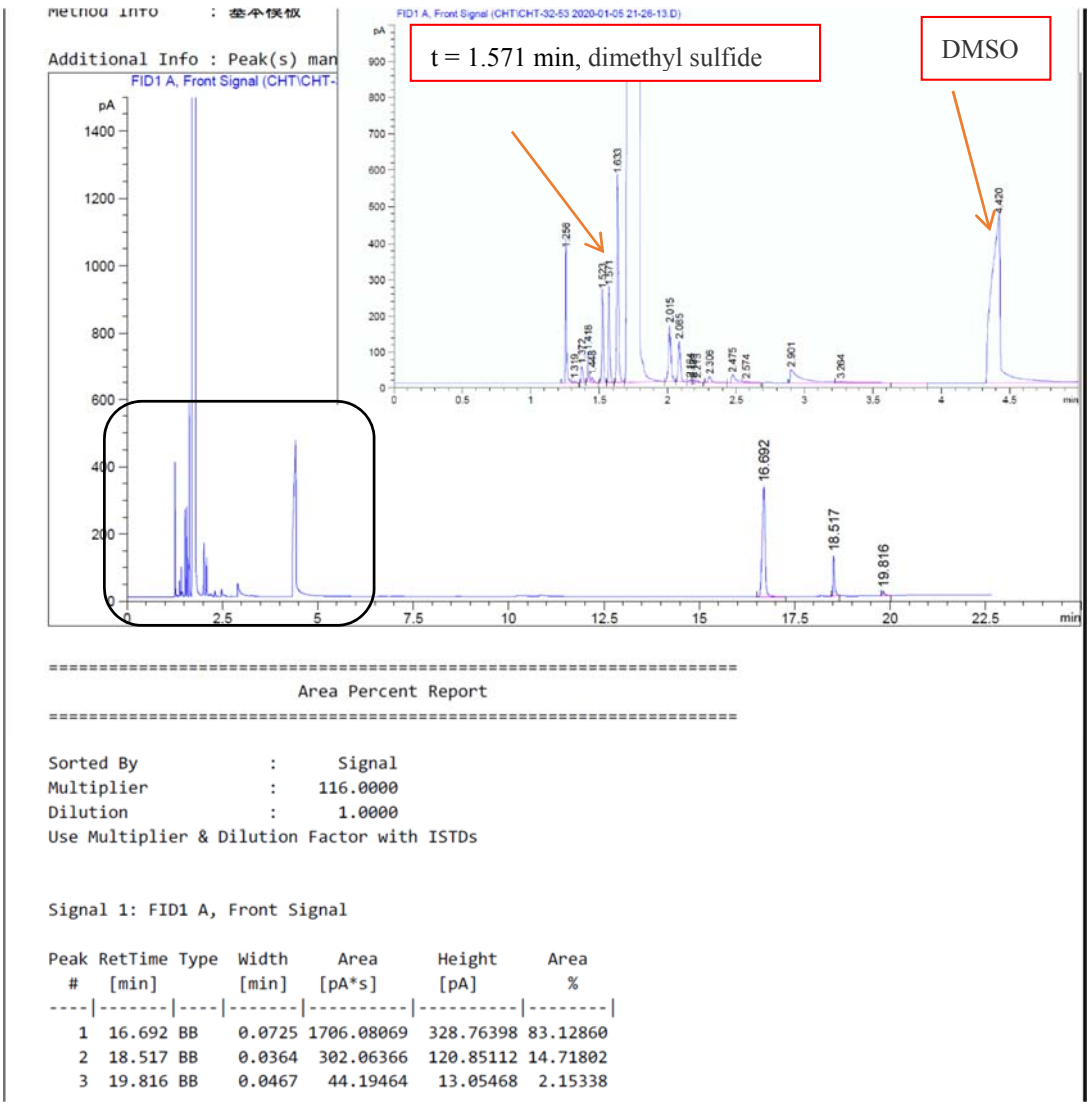


Figure S1. GC Analysis Report for capturing of CO_2. The ingredient of gas phase were analyzed by on-line Shimadzu 2010 Plus Gas Chromatograph with a barrier discharge ionization detector (BID) using He as a carrier gas.

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Area Percent Report

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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
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   2  18.517 BB    0.0364  302.06366  120.85112 14.71802
   3  19.816 BB    0.0467   44.19464   13.05468  2.15338
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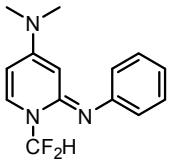
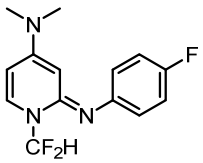
Figure S2. GC Analysis Report for capturing of Me_2S. GC analysis was performed on an Agilent 7890 Gas Chromatography using a HP-5 capillary column (30 m × 0.32 mm, 0.5 μm film).

5. Representative procedure I and characterization of 3aa-3qa, 3ab-3ai

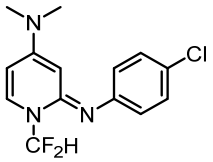


Synthesis of (*E*)-1-(difluoromethyl)-4-(*N*,*N*-dimethylamino)-2-(phenylimino)-1,2-dihydropyridine (3aa). ***Representative Procedure I.*** To a mixture of 2-bromo-2,2-difluoro-*N*-phenylacetamide (**1a**) (250 mg, 1.0 mmol), CuI (19.0 mg, 0.10 mmol), 4-(*N*,*N*-dimethylamino)pyridine (**2a**) (183 mg, 1.50 mmol) in DMSO

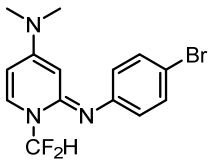
(1.0 mL) were added pyridine (16 μL, 0.20 mmol). The resultant mixture was stirred at 110 °C (oil bath) for 12 hrs and monitored by TLC. The reaction was quenched with ethyl acetate and water, and then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated in vacuum and the residue was purified by silica gel column chromatography (DCM/EtOAc = 10/1) to give the desired product **3aa** as yellow oil (181 mg, 69% yield) (The isolated yield is 72% when the reaction was run in a 0.2 mmol scale). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (t, *J* = 61.3 Hz, 1H), 7.31 – 7.24 (m, 2H), 7.16 (d, *J* = 8.2 Hz, 1H), 6.97 – 6.88 (m, 3H), 5.77 (dd, *J* = 8.2, 2.3 Hz, 1H), 5.17 (d, *J* = 2.3 Hz, 1H), 2.85 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.1, 152.0, 151.1, 129.4 (3C), 122.6 (2C), 121.5, 108.3 (t, *J* = 249.6 Hz), 97.5, 85.6, 39.5 (2C); ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.15 (d, *J* = 61.3 Hz, 2F). HRMS (ESI): m/z [M+H$^+$] calcd for $C_{14}H_{16}F_2N_3^+$: 264.1307, found: 264.1310.



(*E*)-1-(Difluoromethyl)-2-((4-fluorophenyl)imino)-4-(*N*,*N*-dimethylamino)-1,2-dihydropyridine (3ba). The title compound was prepared according to *Representative Procedure I* except that 2-bromo-2,2-difluoro-*N*-(4-fluorophenyl)acetamide was used instead of 2-bromo-2,2-difluoro-*N*-phenylacetamide. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the title compound as yellow oil (87 mg, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (t, *J* = 61.3 Hz, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 7.01 – 6.92 (m, 2H), 6.87 – 6.79 (m, 2H), 5.77 (dd, *J* = 8.2, 2.2 Hz, 1H), 5.07 (d, *J* = 2.2 Hz, 1H), 2.86 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.3 (d, *J* = 239.4 Hz), 153.2, 152.6, 147.1 (d, *J* = 2.3 Hz), 129.4 (t, *J* = 3.5 Hz), 123.6 (d, *J* = 7.8 Hz, 2C), 115.9 (d, *J* = 22.0 Hz, 2C), 108.2 (t, *J* = 249.5 Hz), 97.5, 85.4, 39.5 (2C). ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.19 (d, *J* = 61.3 Hz, 2F), -123.35 – -123.47 (m, 1F); HRMS (ESI): m/z [M+H$^+$] calcd for $C_{14}H_{15}F_3N_3^+$: 282.1213, found: 282.1217.

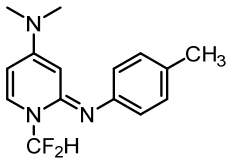


(*E*)-1-(Difluoromethyl)-2-((4-chlorophenyl)imino)-4-(*N*,*N*-dimethylamino)-1,2-dihydropyridine (3ca). The title compound was prepared according to *Representative Procedure I* except that 2-bromo-*N*-(4-chlorophenyl)-2,2-difluoroacetamide was used instead of 2-bromo-2,2-difluoro-*N*-phenylacetamide. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (102 mg, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (t, *J* = 61.0 Hz, 1H), 7.21 – 7.09 (m, 3H), 6.80 (d, *J* = 7.7 Hz, 2H), 5.77 (d, *J* = 8.0 Hz, 1H), 5.09 (s, 1H), 2.81 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.7, 152.2, 148.8, 129.7, 129.4 (2C), 126.6, 124.1 (2C), 108.3 (t, *J* = 249.6 Hz), 98.1, 85.6, 39.6 (2C); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -102.83 (s, 2F). HRMS (ESI): m/z [M+H^{+}] calcd for $C_{14}H_{15}ClF_2N_3^{+}$: 298.0917, found: 298.0914.

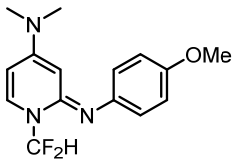


(*E*)-1-(Difluoromethyl)-2-((4-bromophenyl)imino)-4-(*N*,*N*-dimethylamino)-1,2-dihydropyridine (3da). The title compound was prepared according to *Representative Procedure I* except that 2-bromo-*N*-(4-bromophenyl)-2,2-difluoroacetamide was used instead of 2-bromo-2,2-difluoro-*N*-phenylacetamide. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (124 mg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (t, *J* = 61.3 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 8.2 Hz, 1H), 6.79 (d, *J* = 8.5 Hz, 2H), 5.78 (dd, *J* = 8.2 Hz, 2.0 Hz, 1H), 5.12 (d, *J* = 2.0 Hz, 1H), 2.87 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.4, 152.2, 150.3, 132.3 (2C), 129.5, 124.5 (2C), 113.8, 108.2 (t, *J* = 249.9 Hz), 97.7, 85.3, 39.6 (2C); ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.15

(d, J = 61.3 Hz, 2F). HRMS (ESI): m/z [M+H$^+$] calcd for $C_{14}H_{15}BrF_2N_3^+$: 342.0412, found: 342.0408.

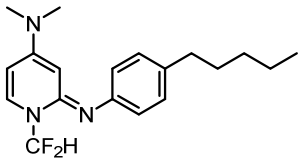


(*E*)-1-(Difluoromethyl)-2-(*p*-tolylimino)-4-(*N*,*N*-dimethylamino)-1,2-dihydropyridine (3ea). The title compound was prepared according to *Representative Procedure I* except that 2-bromo-2,2-difluoro-*N*-(*p*-tolyl)acetamide was used instead of 2-bromo-2,2-difluoro-*N*-phenylacetamide. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (91 mg, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (t, J = 61.3 Hz, 1H), 7.14 (d, J = 8.2 Hz, 1H), 7.07 (d, J = 8.0 Hz, 2H), 6.81 (d, J = 8.0 Hz, 2H), 5.75 (dd, J = 8.2 Hz, 2.1 Hz, 1H), 5.19 (d, J = 2.1 Hz, 1H), 2.85 (s, 6H), 2.30 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.0, 152.1, 148.1, 130.6, 130.0 (2C), 129.3, 122.3 (2C), 108.3 (t, J = 249.5 Hz), 97.5, 85.7, 39.5 (2C), 21.0; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -102.80 (s, 2F). HRMS (ESI): m/z [M+H$^+$] calcd for $C_{15}H_{18}F_2N_3^+$: 278.1463, found: 278.1460.

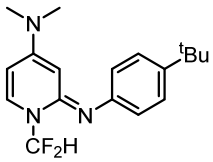


(*E*)-1-(Difluoromethyl)-2-((4-methoxyphenyl)imino)-4-(*N*,*N*-dimethylamino)-1,2-dihydropyridine (3fa). The title compound was prepared according to *Representative Procedure I* except that 2-bromo-2,2-difluoro-*N*-(4-methoxyphenyl)acetamide was used instead of 2-bromo-2,2-difluoro-*N*-phenylacetamide. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (82 mg, 56% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (t, J = 61.4 Hz, 1H), 7.14 (d, J = 8.2 Hz, 1H), 6.86 – 6.80 (m, 4H), 5.75 (d, J = 8.2 Hz, 1H), 5.14 (s, 1H), 3.79 (s, 3H), 2.85 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.6, 153.0, 152.4, 144.1, 129.4, 123.3 (2C), 114.8 (2C), 108.3 (t, J = 249.3 Hz),

97.4, 85.8, 55.6, 39.5 (2C); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -103.07 (s, 2F). HRMS (ESI): m/z [M+H$^+$] calcd for $C_{15}H_{18}F_2N_3O^+$: 294.1412, found: 294.1416.

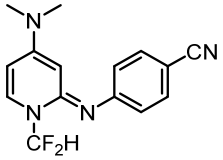


(*E*)-1-(Difluoromethyl)-2-((4-pentylphenyl)imino)-4-(*N*,*N*-dimethylamino)-1,2-dihydropyridine (3ga). The title compound was prepared according to *Representative Procedure I* except that 2-bromo-2,2-difluoro-*N*-(*p*-pentylphenyl)acetamide was used instead of 2-bromo-2,2-difluoro-*N*-phenylacetamide. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (125 mg, 75% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (t, *J* = 60.0 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.11 (d, *J* = 7.4 Hz, 2H), 6.97 (d, *J* = 7.4 Hz, 2H), 6.06 (d, *J* = 8.1 Hz, 1H), 5.41 (s, 1H), 2.93 (s, 6H), 2.55 (t, *J* = 7.5 Hz, 2H), 1.66 – 1.53 (m, 2H), 1.38 – 1.21 (m, 4H), 0.87 (t, *J* = 6.3 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 154.5, 151.6, 143.5, 138.0, 130.7, 129.5 (2C), 123.0 (2C), 108.8 (t, *J* = 253.3 Hz), 99.8, 87.0, 39.9 (2C), 35.5, 31.6, 31.3, 22.6, 14.2; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -101.14 (s, 2F). HRMS (ESI): m/z [M+H$^+$] calcd for $C_{19}H_{26}F_2N_3^+$: 334.2089, found: 334.2084.

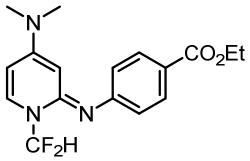


(*E*)-1-(Difluoromethyl)-2-((4-(*tert*-butyl)phenyl)imino)-4-(*N*,*N*-dimethylamino)-1,2-dihydropyridine (3ha). The title compound was prepared according to *Representative Procedure I* except that 2-bromo-*N*-(4-(*tert*-butyl)phenyl)-2,2-difluoroacetamide was used instead of 2-bromo-2,2-difluoro-*N*-phenylacetamide. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (107 mg, 67% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (t, *J* = 60.7 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 1H), 6.85 (d, *J* = 7.9 Hz, 2H), 5.81

(d, J = 8.0 Hz, 1H), 5.31 (s, 1H), 2.82 (s, 6H), 1.23 (s, 9H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 153.7, 151.7, 145.7, 144.9, 129.9, 126.2 (2C), 122.2 (2C), 108.5 (t, J = 250.9 Hz), 98.5, 86.3, 39.7 (2C), 34.3, 31.6 (3C); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -102.23 (s, 2F). HRMS (ESI): m/z [M+H$^+$] calcd for $C_{18}H_{24}F_2N_3^+$: 320.1933, found: 320.1923.

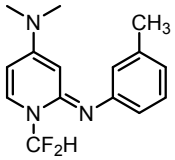


(*E*)-1-(Difluoromethyl)-2-((4-cyanophenyl)imino)-4-(*N*,*N*-dimethylamino)-1,2-dihydropyridine (3ia). The title compound was prepared according to *Representative Procedure I* except that 2-bromo-*N*-(4-cyanophenyl)-2,2-difluoroacetamide was used instead of 2-bromo-2,2-difluoro-*N*-phenylacetamide. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (102 mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (t, J = 61.1 Hz, 1H), 7.52 (d, J = 8.2 Hz, 2H), 7.23 (d, J = 8.2 Hz, 1H), 6.98 (d, J = 8.2 Hz, 2H), 5.86 (d, J = 8.2 Hz, 1H), 5.22 (s, 1H), 2.91 (s, 6H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 156.0, 154.1, 152.2, 133.6 (2C), 129.8, 123.2 (2C), 120.4, 108.2 (t, J = 250.7 Hz), 103.3, 98.2, 85.0, 39.7 (2C); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -103.03 (s, 2F). HRMS (ESI): m/z [M+H$^+$] calcd for $C_{15}H_{15}F_2N_4^+$: 289.1259, found: 289.1257.

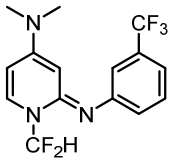


(*E*)-1-(Difluoromethyl)-2-((4-ethoxycarbonylphenyl)imino)-4-(*N*,*N*-dimethylamino)-1,2-dihydropyridine (3ja). The title compound was prepared according to *Representative Procedure I* except that 2-bromo-2,2-difluoro-*N*-(4-ethoxycarbonylphenyl)acetamide was used instead of 2-bromo-2,2-difluoro-*N*-phenylacetamide. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as

yellow oil (109 mg, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 7.77 (m, 3H), 7.19 (d, *J* = 8.2 Hz, 1H), 6.95 (d, *J* = 7.9 Hz, 2H), 5.81 (d, *J* = 8.2 Hz, 1H), 5.22 (s, 1H), 4.33 (q, *J* = 7.0 Hz, 2H), 2.86 (s, 6H), 1.37 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.1, 156.2, 153.6, 152.0, 131.2 (2C), 129.5, 122.9, 122.3 (2C), 108.2 (t, *J* = 250.0 Hz), 97.9, 85.3, 60.5, 39.6 (2C), 14.5; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -103.02 (s, 2F). HRMS (ESI): m/z [M+H$^+$] calcd for $C_{17}H_{20}F_2N_3O_2^+$: 336.1518, found: 336.1518.

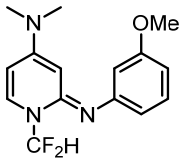


(*E*)-1-(Difluoromethyl)-2-(*m*-tolylimino)-4-(*N*,*N*-dimethylamino)-1,2-dihydropyridine (3ka). The title compound was prepared according to *Representative Procedure I* except that 2-bromo-2,2-difluoro-*N*-(*m*-tolylphenyl)acetamide was used instead of 2-bromo-2,2-difluoro-*N*-phenylacetamide. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (88 mg, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (t, *J* = 59.9 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 6.91 (s, 1H), 6.89 – 6.83 (m, 2H), 6.09 (d, *J* = 8.0 Hz, 1H), 5.45 (s, 1H), 2.95 (s, 6H), 2.31 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.7, 151.6, 145.9, 139.5, 130.7, 129.4, 124.3, 124.0, 120.1, 108.8 (t, *J* = 250.3 Hz), 100.0, 87.3, 40.0 (2C), 21.5; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -101.07 (s, 2F). HRMS (ESI): m/z [M+H$^+$] calcd for $C_{15}H_{18}F_2N_3^+$: 278.1463, found: 278.1459.

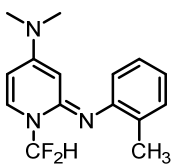


(*E*)-1-(Difluoromethyl)-2-((3-(trifluoromethyl)phenyl)imino)-4-(*N*,*N*-dimethylamino)-1,2-dihydropyridine (3la). The title compound was prepared according to *Representative Procedure I* except that

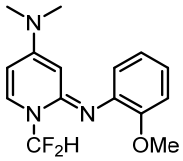
2-bromo-2,2-difluoro-*N*-(3-(trifluoromethyl)phenyl)acetamide was used instead of 2-bromo-2,2-difluoro-*N*-phenylacetamide. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (121 mg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (t, *J* = 61.3 Hz, 1H), 7.27 (t, *J* = 7.8 Hz, 1H), 7.15 – 7.05 (m, 3H), 7.01 (d, *J* = 7.9 Hz, 1H), 5.73 (d, *J* = 8.2 Hz, 1H), 5.08 (s, 1H), 2.78 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.7, 152.5, 151.7, 131.5 (q, *J* = 31.6 Hz), 129.8, 129.5 (t, *J* = 3.50 Hz), 126.2, 124.6 (q, *J* = 273.45 Hz), 119.5 (q, *J* = 3.6 Hz), 117.8 (q, *J* = 3.9 Hz), 108.2 (t, *J* = 249.2 Hz), 97.9, 85.0, 39.6 (2C); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -62.55 (s, 3F), -103.11 (s, 2F). HRMS (ESI): m/z [M+H$^+$] calcd for $C_{15}H_{15}F_5N_3^+$: 332.1181, found: 332.1186.



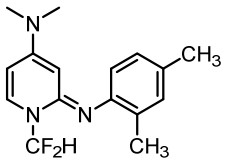
(*E*)-1-(Difluoromethyl)-2-((3-methoxyphenyl)imino)-4-(*N*,*N*-dimethylamino)-1,2-dihydropyridine (3ma). The title compound was prepared according to *Representative Procedure I* except that 2-bromo-2,2-difluoro-*N*-(*m*-methoxyphenyl)acetamide was used instead of 2-bromo-2,2-difluoro-*N*-phenylacetamide. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (90.6 mg, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (t, *J* = 61.3 Hz, 1H), 7.22 – 7.11 (m, 2H), 6.56 – 6.46 (m, 3H), 5.77 (d, *J* = 8.1 Hz, 1H), 5.21 (s, 1H), 3.78 (s, 3H), 2.86 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.9, 153.2, 152.5, 152.0, 130.0, 129.4, 115.0, 108.3 (t, *J* = 249.7 Hz), 107.8, 107.7, 97.6, 85.8, 55.3, 39.6 (2C); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -102.67 (s, 2F). HRMS (ESI): m/z [M+H$^+$] calcd for $C_{15}H_{18}F_2N_3O^+$: 294.1412, found: 294.1417.



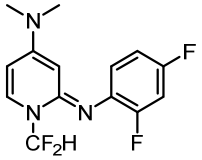
(*E*)-1-(Difluoromethyl)-2-(*o*-tolylimino)-4-(*N*,*N*-dimethylamino)-1,2-dihydropyridine (3na). The title compound was prepared according to *Representative Procedure I* except that 2-bromo-2,2-difluoro-*N*-(*o*-tolylphenyl)acetamide was used instead of 2-bromo-2,2-difluoro-*N*-phenylacetamide. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (94 mg, 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (t, *J* = 61.1 Hz, 1H), 7.24 – 7.15 (m, 2H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.96 – 6.86 (m, 2H), 5.73 (d, *J* = 8.0 Hz, 1H), 4.84 (s, 1H), 2.84 (s, 6H), 2.14 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.4, 150.8, 147.7, 131.2, 130.7, 129.5, 126.8, 122.4, 122.4, 108.5 (t, *J* = 249.6 Hz), 97.8, 85.7, 39.5 (2C), 18.0; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -102.88 (s, 2F). HRMS (ESI): m/z [M+H$^+$] calcd for $C_{15}H_{18}F_2N_3^+$: 278.1463, found: 278.1461.



(*E*)-1-(Difluoromethyl)-2-((2-methoxyphenyl)imino)-4-(*N*,*N*-dimethylamino)-1,2-dihydropyridine (3oa). The title compound was prepared according to *Representative Procedure I* except that 2-bromo-2,2-difluoro-*N*-(2-methoxyphenyl)acetamide was used instead of 2-bromo-2,2-difluoro-*N*-phenylacetamide. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (83.6 mg, 57% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (t, *J* = 61.4 Hz, 1H), 7.14 (d, *J* = 8.2 Hz, 1H), 7.04 – 6.94 (m, 4H), 5.76 (d, *J* = 8.2 Hz, 1H), 4.96 (s, 1H), 3.78 (s, 3H), 2.82 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 152.8, 152.1, 152.0, 139.9, 129.0, 123.6, 122.3, 121.4, 112.2, 108.3 (t, *J* = 248.6 Hz), 97.5, 86.2, 55.9, 39.4 (2C); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -103.01 (s, 2F). HRMS (ESI): m/z [M+H$^+$] calcd for $C_{15}H_{18}F_2N_3O^+$: 294.1412, found: 294.1408.

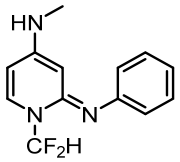


(*E*)-1-(Difluoromethyl)-2-((2,4-dimethylphenyl)imino)-4-(*N*,*N*-dimethylamino)-1, 2-dihydropyridine (3pa). The title compound was prepared according to *Representative Procedure I* except that 2-bromo-*N*-(2,4-dimethylphenyl)-2,2-difluoroacetamide was used instead of 2-bromo-2,2-difluoro-*N*-phenylacetamide. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (85 mg, 58% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (t, *J* = 61.5 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 1H), 6.99 (s, 1H), 6.91 (d, *J* = 7.7 Hz, 1H), 6.73 (d, *J* = 7.7 Hz, 1H), 5.74 (dd, *J* = 8.2 Hz, 1.84 Hz, 1H), 4.93 (s, 1H), 2.83 (s, 6H), 2.28 (s, 3H), 2.10 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 152.9, 150.9, 146.1, 131.4, 130.9, 130.5, 129.3, 127.3, 121.7, 108.4 (t, *J* = 248.5 Hz), 97.3, 85.8, 39.5 (2C), 20.9, 18.0; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -103.31 (s, 2F). HRMS (ESI): m/z [M+H^{+}] calcd for $C_{16}H_{20}F_2N_3^{+}$: 292.1620, found: 292.1617.

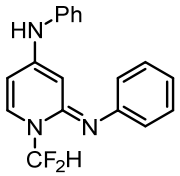


(*E*)-1-(Difluoromethyl)-2-((2,4-difluorophenyl)imino)-4-(*N*,*N*-dimethylamino)-1,2 -dihydropyridine (3qa). The title compound was prepared according to *Representative Procedure I* except that 2-bromo-*N*-(2,4-fluorophenyl)-2,2-difluoroacetamide was used instead of 2-bromo-2,2-difluoro-*N*-phenylacetamide. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (110 mg, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (t, *J* = 61.2 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 1H), 6.93 (dd, *J* = 15.2, 8.6 Hz, 1H), 6.86 – 6.73 (m, 2H), 5.83 (d, *J* = 8.2 Hz, 1H), 4.92 (s, 1H), 2.88 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.9 (dd, *J* = 242.24 Hz, 10.9 Hz), 154.9 (dd, *J* = 247.51 Hz, 11.9 Hz), 153.6, 153.0, 134.2 (dd, *J* = 127.76 Hz, 3.35 Hz), 129.4 (t, *J* = 3.6 Hz), 125.5 (dd, *J* = 9.0,

4.3 Hz), 111.3 (dd, *J* = 21.4, 3.7 Hz), 108.3 (t, *J* = 249.6 Hz), 104.4 (t, *J* = 25.2 Hz), 97.9, 85.72, 39.5 (2C); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -102.96 (s, 2F), -119.86 (s, 1F), -120.89 (s, 1F). HRMS (ESI): m/z [M+H$^+$] calcd for $C_{14}H_{14}F_4N_3^+$: 300.1118, found: 300.1106.

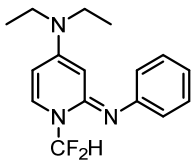


(*E*)-1-(Difluoromethyl)-2-(phenylimino)-4-(methylamino)-1,2-dihydropyridine (3ab). The title compound was prepared according to *Representative Procedure I* except that 4-(methylamino)pyridine was used instead of 4-(dimethylamino)pyridine. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (83 mg, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (t, *J* = 61.2 Hz, 1H), 7.26 – 7.17 (m, 2H), 7.04 (d, *J* = 7.8 Hz, 1H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.85 (d, *J* = 7.7 Hz, 2H), 5.40 (d, *J* = 7.8 Hz, 1H), 5.10 (s, 1H), 4.18 (s, 1H), 2.56 (d, *J* = 4.9 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 152.6, 152.1, 150.2, 129.4 (2C), 129.3, 122.7 (2C), 121.9, 108.4 (t, J = 249.8 Hz), 100.5, 84.1, 29.6; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -102.77 (s, 2F). HRMS (ESI): m/z [M+H$^+$] calcd for $C_{13}H_{14}F_2N_3^+$: 250.1150, found: 250.1156.

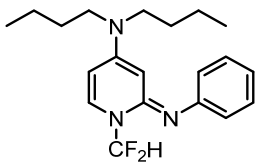


(*E*)-1-(Difluoromethyl)-2-(phenylimino)-4-(phenylamino)-1,2-dihydropyridine (3ac). The title compound was prepared according to *Representative Procedure I* except that 4-(phenylamino)pyridine was used instead of 4-(dimethylamino)pyridine. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (98 mg, 63% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (t, *J* = 61.1 Hz, 1H), 7.24 – 7.14 (m, 4H), 7.11 (d, *J* = 7.8 Hz, 1H), 6.99 (t, *J* = 7.4 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 2H), 6.87 (t, *J* = 7.4 Hz, 1H), 6.79

(d, J = 7.7 Hz, 2H), 5.90 (s, 1H), 5.69 – 5.59 (m, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 151.8, 150.1, 148.9, 138.8, 130.1, 129.5 (2C), 129.3 (2C), 124.6, 122.5 (2C), 122.1 (3C), 108.2 (t, J = 249.3 Hz), 100.0, 89.5; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -103.07 (s, 2F). HRMS (ESI): m/z [M+H$^+$] calcd for $C_{18}H_{16}F_2N_3^+$: 312.1307, found: 312.1311.

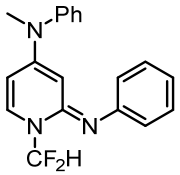


(*E*)-1-(Difluoromethyl)-2-(phenylimino)-4-(diethylamino)-1,2-dihydropyridine (3ad). The title compound was prepared according to *Representative Procedure I* except that 4-(diethylamino)pyridine was used instead of 4-(dimethylamino)pyridine. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (102 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (t, J = 60.7 Hz, 1H), 7.25 – 7.16 (m, 3H), 6.95 – 6.87 (m, 3H), 5.79 (d, J = 7.8 Hz, 1H), 5.21 (s, 1H), 3.12 (q, J = 6.7 Hz, 4H), 1.00 (t, J = 6.7 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 152.0, 151.8, 148.8, 130.2, 129.4 (2C), 123.0 (2C), 122.2, 108.5 (t, J = 251.6 Hz), 98.6, 85.8, 44.6 (2C), 12.9 (2C); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -102.15 (s, 2F). HRMS (ESI): m/z [M+H$^+$] calcd for $C_{16}H_{20}F_2N_3^+$: 292.1620, found: 292.1625.

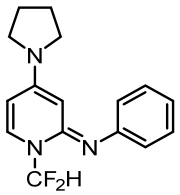


(*E*)-1-(Difluoromethyl)-2-(phenylimino)-4-(dibutylamino)-1,2-dihydropyridine (3ae). The title compound was prepared according to *Representative Procedure I* except that 4-(dibutylamino)pyridine was used instead of 4-(dimethylamino)pyridine. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (104 mg, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (t, J = 60.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.28 – 7.16 (m, 2H), 7.06 – 6.92 (m, 3H), 5.96 (d, J = 8.0 Hz, 1H), 5.28 (s, 1H), 3.08 (t, J = 7.1 Hz,

4H), 1.45 – 1.32 (m, 4H), 1.22 – 1.08 (m, 4H), 0.79 (t, J = 7.1 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 153.0, 151.9, 146.1, 130.8, 129.5 (2C), 123.5 (2C), 123.5, 108.8 (t, J = 253.3 Hz), 100.0, 87.0, 50.9 (2C), 29.6 (2C), 20.0 (2C), 13.8 (2C); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -101.03 (s, 2F). HRMS (ESI): m/z [M+H^+] calcd for $C_{20}H_{28}F_2N_3^+$: 348.2246, found: 348.2240.

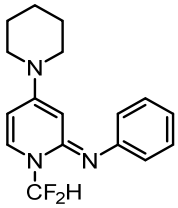


(*E*)-1-(Difluoromethyl)-2-(phenylimino)-4-(methylphenylamino)-1,2-dihydropyridine (3af). The title compound was prepared according to *Representative Procedure I* except that 4-(methylphenylamino)pyridine was used instead of 4-(dimethylamino)pyridine. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (83 mg, 51% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (t, J = 61.3 Hz, 1H), 7.28 (t, J = 7.4 Hz, 2H), 7.24 – 7.12 (m, 3H), 7.01 (d, J = 7.7 Hz, 2H), 6.93 – 6.83 (m, 4H), 5.36 – 5.30 (m, 2H), 2.97 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 152.1, 151.9, 150.7, 145.5, 129.7 (2C), 129.4 (2C), 128.5, 126.9, 126.7, 122.5 (3C), 121.8, 108.2 (t, J = 249.5 Hz), 99.7, 88.0, 40.1; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -103.17 (s, 2F). HRMS (ESI): m/z [M+H^+] calcd for $C_{19}H_{18}F_2N_3^+$: 326.1463, found: 326.1463.

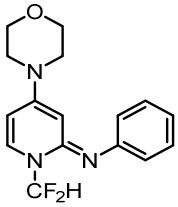


(*E*)-1-(Difluoromethyl)-2-(phenylimino)-4-(pyrrolidin-1-yl)-1,2-dihydropyridine (3ag). The title compound was prepared according to *Representative Procedure I* except that 4-(pyrrolidin-1-yl)pyridine was used instead of 4-(dimethylamino)pyridine. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (81 mg, 56% yield). ^{1}H NMR (400

MHz, $CDCl_3$) δ 8.00 (t, *J* = 61.1 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 1H), 6.90 – 6.83 (m, 3H), 5.66 (d, *J* = 8.0 Hz, 1H), 5.04 (s, 1H), 3.25 – 2.97 (m, 4H), 1.90 – 1.76 (m, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 152.1, 150.8, 150.4, 129.6, 129.3 (2C), 122.7 (2C), 121.6, 108.4 (t, *J* = 249.1 Hz), 98.9, 85.1, 47.5 (2C), 25.2 (2C); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -102.58 (s, 2F). HRMS (ESI): m/z [$M+H^+$] calcd for $C_{16}H_{18}F_2N_3^+$: 290.1463, found: 290.1465.



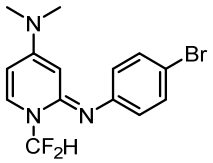
(*E*)-1-(Difluoromethyl)-2-(phenylimino)-4-(piperidin-1-yl)-1,2-dihydropyridine (3ah). The title compound was prepared according to *Representative Procedure I* except that 4-(piperidin-1-yl)pyridine was used instead of 4-(dimethylamino)pyridine. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (89 mg, 58% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (t, *J* = 61.2 Hz, 1H), 7.21 (t, *J* = 7.9 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 1H), 6.93 – 6.79 (m, 3H), 5.75 (d, *J* = 8.0 Hz, 1H), 5.34 (s, 1H), 3.12 – 2.96 (m, 4H), 1.56 – 1.41 (m, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 153.7, 152.1, 129.4 (3C), 122.6 (2C), 121.8, 108.3 (t, *J* = 249.0 Hz), 98.8, 88.2, 47.7 (2C), 25.4 (2C), 24.3; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -101.60 (s, 2F). HRMS (ESI): m/z [$M+H^+$] calcd for $C_{17}H_{20}F_2N_3^+$: 304.1620, found: 304.1625.



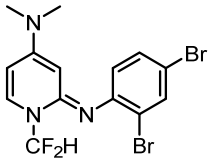
(*E*)-1-(Difluoromethyl)-2-(phenylimino)-4-(4-morpholinyl)-1,2-dihydropyridine (3ai). The title compound was prepared according to *Representative Procedure I* except that 4-(4-morpholinyl)pyridine was used instead of 4-(dimethylamino)pyridine. The crude product was purified by silica gel column chromatography (DCM/EtOAc =

10:1) to give the desired product as yellow oil (68 mg, 45% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (t, *J* = 61.1 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.90 (t, *J* = 7.3 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 2H), 5.70 (d, *J* = 8.0 Hz, 1H), 5.33 (s, 1H), 3.67 – 3.58 (m, 4H), 3.04 – 2.95 (m, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.9, 151.6, 150.1, 129.7, 129.5 (2C), 122.4 (2C), 122.0, 108.2 (t, *J* = 249.2 Hz), 98.0, 89.2, 66.3 (2C), 46.5 (2C); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -103.27 (s, 2F). HRMS (ESI): m/z [M+H$^+$] calcd for $C_{16}H_{18}F_2N_3O^+$: 306.1412, found: 306.1413.

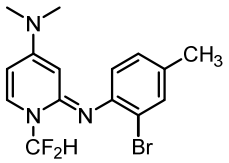
6. Representative procedure II and characterization of 4b-4l



(*E*)-2-((4-Bromophenyl)imino)-1-(difluoromethyl)-4-(*N*,*N*-dimethylamino)-1,2-dihydropyridine (3da). ***Representative Procedure II.*** A mixture of 2-bromo-2,2-difluoro-*N*-phenylacetamide (**1a**) (125 mg, 0.5 mmol), CuI (10.0 mg, 0.05 mmol), pyridine (8 μL, 0.1 mmol), and 4-dimethylaminopyridine (**2a**) (93 mg, 0.75 mmol) in DMSO (1.0 mL) was stirred at 110 ^{o}C (oil bath) for 20 hrs under O_2 atmosphere. The reaction was quenched with ethyl acetate and water, and then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated in vacuum and the residue was purified by silica gel column chromatography (DCM/EtOAc = 10/1) to give the desired product as yellow oil (85 mg, 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (t, *J* = 61.3 Hz, 1H), 7.35 (d, *J* = 8.6 Hz, 2H), 7.16 (d, *J* = 8.2 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 2H), 5.78 (dd, *J* = 8.2, 2.6 Hz, 1H), 5.12 (d, *J* = 2.6 Hz, 1H), 2.87 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.4, 152.2, 150.4, 132.3 (2C), 129.5, 124.5 (2C), 113.8, 108.2 (t, *J* = 249.0 Hz), 97.6, 85.3, 39.56 (2C). The NMR data of **3da** by this strategy are the same as those prepared by using 2-bromo-N-(4-bromophenyl)-2,2-difluoroacetamide according to *Representative Procedure I* and its structure was further confirmed by X-ray single crystal analysis.

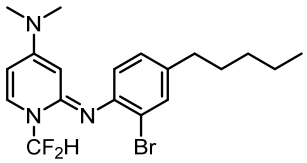


(*E*)-1-(Difluoromethyl)-2-((2,4-dibromophenyl)imino)-4-(dimethylamino)-1,2-dihydropyridine (4b). The title compound was prepared according to *Representative Procedure II* except that 2-bromo-*N*-(4-bromophenyl)-2,2-difluoroacetamide was used instead of 2-bromo-2,2-difluoro-*N*-phenylacetamide. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (92 mg, 44% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (t, *J* = 61.3 Hz, 1H), 7.69 (s, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 5.83 (d, *J* = 8.1 Hz, 1H), 4.88 (s, 1H), 2.89 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.7, 151.8, 148.4, 135.4, 131.2, 129.5, 125.0, 119.4, 113.8, 108.3 (t, *J* = 249.6 Hz), 97.9, 85.4, 39.7 (2C); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -103.01 (s, 2F). HRMS (ESI): m/z [M+H^+] calcd for $C_{14}H_{14}Br_2F_2N_3^+$: 419.9517, found: 419.9525.

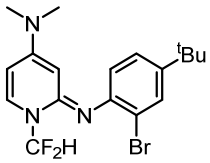


(*E*)-1-(Difluoromethyl)-2-((2-bromo-4-methylphenyl)imino)-4-(dimethylamino)-1,2-dihydropyridine (4c). The title compound was prepared according to *Representative Procedure II* except that 2-bromo-2,2-difluoro-*N*-(*p*-tolyl)acetamide was used instead of 2-bromo-2,2-difluoro-*N*-phenylacetamide. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (76 mg, 43% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (t, *J* = 61.4 Hz, 1H), 7.39 (s, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 6.85 (d, *J* = 7.9 Hz, 1H), 5.79 (d, *J* = 8.0 Hz, 1H), 4.91 (s, 1H), 2.85 (s, 6H), 2.28 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.2, 151.9, 146.2, 133.5, 132.4, 129.2, 129.0, 123.4, 118.1, 108.4 (t, *J* = 250.1 Hz), 97.6, 85.6, 39.5 (2C), 20.5; ^{19}F{^{1}H}

NMR (376 MHz, $CDCl_3$) δ -102.99 (s, 2F). HRMS (ESI): m/z [M+H^+] calcd for $C_{15}H_{17}BrF_2N_3^+$: 356.0568, found: 356.0568.

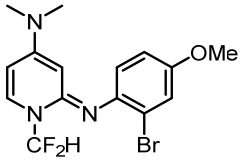


(*E*)-1-(Difluoromethyl)-2-((2-bromo-4-pentylphenyl)imino)-4-(dimethylamino)-1, 2-dihydropyridine (4d). The title compound was prepared according to *Representative Procedure II* except that 2-bromo-2,2-difluoro-*N*-(*p*-pentylphenyl)acetamide was used instead of 2-bromo-2,2-difluoro-*N*-phenylacetamide. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (86 mg, 42% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (t, *J* = 61.4 Hz, 1H), 7.38 (s, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 5.77 (d, *J* = 8.2 Hz, 1H), 4.93 (s, 1H), 2.86 (s, 6H), 2.52 (t, *J* = 7.6 Hz, 2H), 1.64 – 1.53 (m, 2H), 1.37 – 1.24 (m, 4H), 0.87 (t, *J* = 6.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.2, 151.8, 146.4, 137.6, 132.9, 129.3, 128.4, 123.3, 118.1, 108.4 (t, *J* = 249.0 Hz), 97.6, 85.7, 39.5 (2C), 35.1, 31.5, 31.2, 22.7, 14.2; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -103.06 (s, 2F). HRMS (ESI): m/z [M+H^+] calcd for $C_{19}H_{25}BrF_2N_3^+$: 412.1194, found: 412.1190.

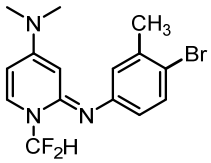


(*E*)-1-(Difluoromethyl)-2-((2-bromo-4-(*tert*-butyl)phenyl)imino)-4-(dimethylamino)-1,2-dihydropyridine (4e). The title compound was prepared according to *Representative Procedure II* except that 2-bromo-*N*-(4-(*tert*-butyl)phenyl)-2,2-difluoroacetamide was used instead of 2-bromo-2,2-difluoro-*N*-phenylacetamide. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (115 mg, 58% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (t, *J* = 61.4 Hz,

1H), 7.56 (s, 1H), 7.24 – 7.14 (m, 2H), 6.90 (d, J = 8.2 Hz, 1H), 5.79 (d, J = 8.0 Hz, 1H), 4.99 (s, 1H), 2.86 (s, 6H), 1.30 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 153.3, 151.6, 146.0, 145.8, 130.0, 129.2, 125.3, 122.8, 118.1, 108.4 (t, J = 250.0 Hz), 97.6, 85.6, 39.5 (2C), 34.3, 31.5 (3C); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -103.02 (s, 2F). HRMS (ESI): m/z [M+H^+] calcd for $C_{18}H_{23}BrF_2N_3^+$: 398.1038, found: 398.1041.

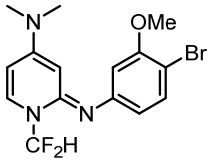


(*E*)-1-(Difluoromethyl)-2-((2-bromo-4-methoxyphenyl)imino)-4-(dimethylamino) -1,2-dihydropyridine (4f). The title compound was prepared according to *Representative Procedure II* except that 2-bromo-2,2-difluoro-*N*-(4-methoxyphenyl)acetamide was used instead of 2-bromo-2,2-difluoro-*N*-phenylacetamide. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (74 mg, 40% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (t, J = 61.4 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.14 (s, 1H), 6.91 – 6.75 (m, 2H), 5.71 (d, J = 8.1 Hz, 1H), 4.80 (s, 1H), 3.706 (s, 3H), 2.85 (s, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 154.9, 153.2, 152.3, 142.4, 129.3, 124.0, 118.3, 118.1, 114.7, 108.3 (t, J = 249.2 Hz), 97.5, 85.7, 55.8, 39.5 (2C); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -103.04 (s, 2F). HRMS (ESI): m/z [M+H^+] calcd for $C_{15}H_{17}BrF_2N_3O^+$: 372.0518, found: 372.0517.

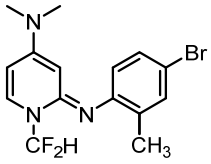


(*E*)-1-(Difluoromethyl)-2-((4-bromo-3-methylphenyl)imino)-4-(dimethylamino)-1 ,2-dihydropyridine (4g). The title compound was prepared according to *Representative Procedure II* except that 2-bromo-2,2-difluoro-*N*-(*m*-methylphenyl)acetamide was used instead of 2-bromo-2,2-difluoro-*N*-phenylacetamide. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (81 mg, 46% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (t, J = 61.3 Hz,

1H), 7.37 (d, *J* = 8.3 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 6.81 (s, 1H), 6.63 (d, *J* = 8.3 Hz, 1H), 5.77 (d, *J* = 8.0 Hz, 1H), 5.14 (s, 1H), 2.86 (s, 6H), 2.33 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 153.3, 152.1, 150.4, 138.5, 132.9, 129.4, 125.3, 121.6, 116.4, 108.2 (t, *J* = 248.9 Hz), 97.6, 85.3, 39.5 (2C), 23.0; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -103.07 (s, 2F). HRMS (ESI): m/z [$M+H^+$] calcd for $C_{15}H_{17}BrF_2N_3^+$: 356.0568, found: 356.0568.

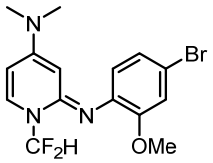


(*E*)-1-(Difluoromethyl)-2-((4-bromo-3-methoxyphenyl)imino)-4-(dimethylamino) -1,2-dihydropyridine (4h). The title compound was prepared according to *Representative Procedure II* except that 2-bromo-2,2-difluoro-*N*-(*m*-methoxyphenyl)acetamide was used instead of 2-bromo-2,2-difluoro-*N*-phenylacetamide. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (66 mg, 36% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (t, *J* = 61.2 Hz, 1H), 7.42 (d, *J* = 8.7 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 1H), 6.57 (s, 1H), 6.43 (d, *J* = 8.7 Hz, 1H), 5.83 (d, *J* = 8.1 Hz, 1H), 4.94 (s, 1H), 3.75 (s, 3H), 2.88 (s, 6H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 156.6, 153.9, 152.2, 139.5, 133.5, 129.9, 116.8, 115.9, 108.3 (t, *J* = 250.3 Hz), 107.3, 98.4, 85.9, 56.2, 39.7 (2C); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -102.50 (s, 2F). HRMS (ESI): m/z [$M+H^+$] calcd for $C_{15}H_{17}BrF_2N_3O^+$: 372.0518, found: 372.0517.

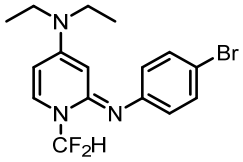


(*E*)-1-(Difluoromethyl)-2-((4-bromo-2-methylphenyl)imino)-4-(dimethylamino)-1 ,2-dihydropyridine (4i). The title compound was prepared according to *Representative Procedure II* except that

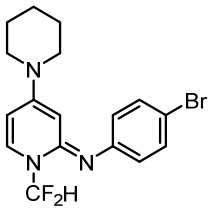
2-bromo-2,2-difluoro-*N*-(*o*-methylphenyl)acetamide was used instead of 2-bromo-2,2-difluoro-*N*-phenylacetamide. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (122 mg, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (t, *J* = 61.4 Hz, 1H), 7.29 (s, 1H), 7.22 – 7.13 (m, 2H), 6.71 (d, *J* = 8.3 Hz, 1H), 5.76 (d, *J* = 8.1 Hz, 1H), 4.84 (s, 1H), 2.85 (s, 6H), 2.09 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.2, 151.0, 148.5, 133.3, 133.2, 129.5, 129.3, 123.6, 113.9, 108.3 (t, *J* = 248.9 Hz), 97.4, 85.2, 39.6 (2C), 17.9; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -103.43 (s, 2F). HRMS (ESI): m/z [M+H$^+$] calcd for $C_{15}H_{17}BrF_2N_3^+$: 356.0568, found: 356.0568.



(*E*)-1-(Difluoromethyl)-2-((4-bromo-2-methoxyphenyl)imino)-4-(dimethylamino) -1,2-dihydropyridine (4j). The title compound was prepared according to *Representative Procedure II* except that 2-bromo-2,2-difluoro-*N*-(*o*-methoxyphenyl)acetamide was used instead of 2-bromo-2,2-difluoro-*N*-phenylacetamide. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (96 mg, 52% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (t, *J* = 61.2 Hz, 1H), 7.17 (d, *J* = 8.2 Hz, 1H), 7.04 – 6.94 (m, 2H), 6.78 (d, *J* = 8.0 Hz, 1H), 5.79 (d, *J* = 8.2 Hz, 1H), 4.90 (s, 1H), 3.76 (s, 3H), 2.85 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.2, 153.0, 152.2, 138.9, 129.2, 124.8, 124.2, 115.4, 114.2, 108.3 (t, *J* = 249.2 Hz), 97.7, 86.0, 56.1, 39.6 (2C); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -102.83 (s, 2F). HRMS (ESI): m/z [M+H$^+$] calcd for $C_{15}H_{17}BrF_2N_3O^+$: 372.0518, found: 372.0517.



(*E*)-1-(Difluoromethyl)-2-((4-bromophenyl)imino)-4-(diethylamino)-1,2-dihydropyridine (4k). The title compound was prepared according to *Representative Procedure II* except that 4-(diethylamino)pyridine was used instead of 4-(dimethylamino)pyridine. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (108 mg, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (t, *J* = 61.3 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 2H), 5.74 (d, *J* = 8.0 Hz, 1H), 5.14 (s, 1H), 3.19 (q, *J* = 7.2 Hz, 4H), 1.08 (t, *J* = 7.2 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 152.4, 151.3, 150.4, 132.2 (2C), 129.7, 124.6 (2C), 113.6, 108.2 (t, *J* = 248.8 Hz), 97.6, 84.5, 44.4 (2C), 13.0 (2C); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -103.06 (s, 2F). HRMS (ESI): m/z [M+H$^+$] calcd for $C_{16}H_{19}BrF_2N_3^+$: 370.0725, found: 370.0727.



(*E*)-1-(difluoromethyl)-2-((4-bromophenyl)imino)-4-(piperidin-1-yl)-1,2-dihydropyridine (4l). The title compound was prepared according to *Representative Procedure II* except that 4-(piperidin-1-yl)pyridine was used instead of 4-(dimethylamino)pyridine. The crude product was purified by silica gel column chromatography (DCM/EtOAc = 10:1) to give the desired product as yellow oil (91 mg, 48% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (t, *J* = 61.2 Hz, 1H), 7.36 (d, *J* = 7.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 2H), 5.83 (d, *J* = 8.0 Hz, 1H), 5.34 (s, 1H), 3.17 – 3.12 (m, 4H), 1.58 – 1.49 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.8, 152.3, 138.2, 132.3 (2C), 129.5, 124.5 (2C), 113.9, 108.1 (t, *J* = 249.2 Hz), 98.8, 87.4, 47.6 (2C), 25.3 (2C), 24.2; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -103.15 (s, 2F). HRMS (ESI): m/z [M+H$^+$] calcd for $C_{17}H_{19}BrF_2N_3^+$: 382.0725, found: 382.0723.

7. X-Ray crystal structure of 3aa and 3da

(1) X-Ray crystal structure of **3aa** (CCDC 1877511) (50% thermal ellipsoids)

Procedure for the recrystallization of **3aa**: To a 0.5 mL glass tube containing **3aa** (10 mg) was added CH_2Cl_2 (0.4 mL) and a clear solution was formed. The above tube was placed in a 10 mL glass sample bottle that contains 5 mL petroleum ether. The sample bottle was sealed with a plastic cap and kept in refrigerator (4 ^oC). After two days, colorless crystals were produced in the glass tube. These crystals were measured on a Rigaku XtaLAB mini for single crystal XRD to determine the absolute configuration of **3aa**. CCDC 1877511 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.

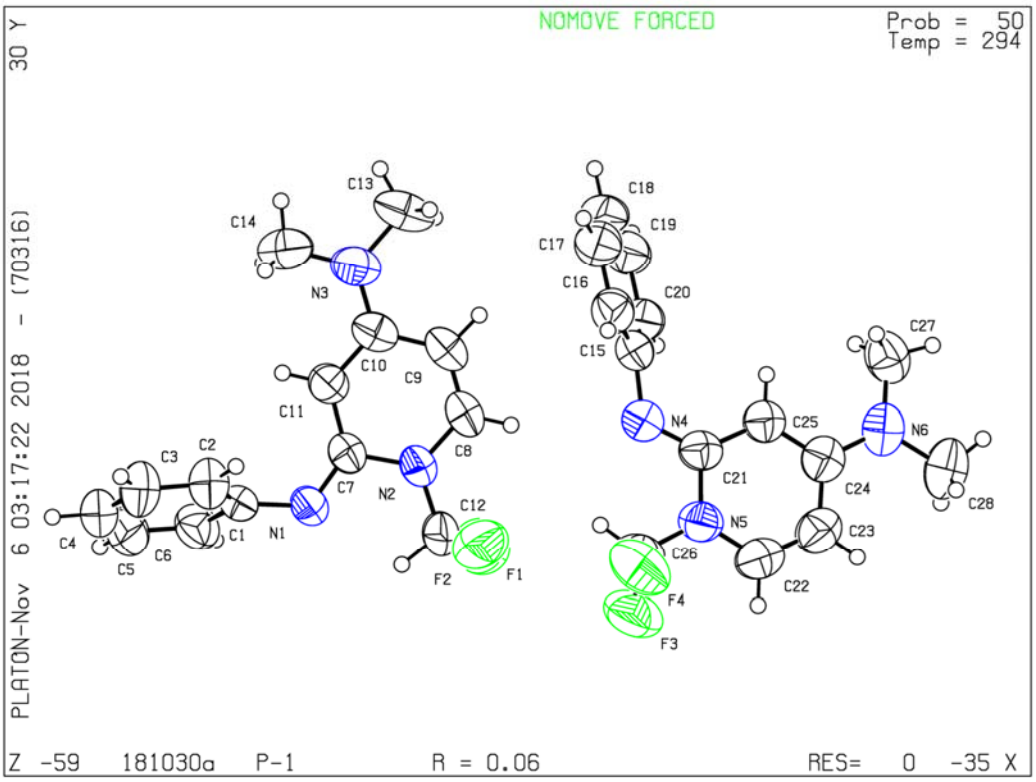


Table 1. Crystal data and structure refinement for 181030A.

Identification code	181030a
Empirical formula	C28 H30 F4 N6
Formula weight	526.58
Temperature	294(2) K

Wavelength	0.71073 A
Crystal system, space group	TRICLINIC, P-1
Unit cell dimensions	a = 9.999(10) A alpha = 95.251(9) deg. b = 10.196(9) A beta = 108.338(6) deg. c = 14.409(15) A gamma = 99.802(12) deg.
Volume	1357(2) A^3
Z, Calculated density	2, 1.288 Mg/m^3
Absorption coefficient	0.098 mm^-1
F(000)	552
Crystal size	0.41 x 0.24 x 0.22 mm
Theta range for data collection	3.02 to 27.55 deg
Limiting indices	-13<=h<=13, -13<=k<=13, -18<=l<=18
Reflections collected / unique	14384 / 6206 [R(int) = 0.0537]
Completeness to theta = 27.55	99.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000 and 0.920
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6206 / 0 / 347
Goodness-of-fit on F^2	1.043
Final R indices [I>2sigma(I)]	R1 = 0.0611, wR2 = 0.1734
R indices (all data)	R1 = 0.0953, wR2 = 0.2055
Largest diff. peak and hole	0.191 and -0.272 e.A^-3

X-Ray crystal structure of **3da** (CCDC 1880644) (50% thermal ellipsoids)

Procedure for the recrystallization of **3da**: To a 0.5 mL glass tube containing **3da** (10 mg) was added CH_2Cl_2 (0.4 mL) and a clear solution was formed. The above tube was placed in a 10 mL glass sample bottle that contains 5 mL petroleum ether. The sample bottle was sealed with a plastic cap and kept in refrigerator (4 ^oC). After two days, colorless crystals were produced in the glass tube. These crystals were measured on a Rigaku XtaLAB for single crystal XRD to determine the absolute configuration of **3da**. CCDC 1880644 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.

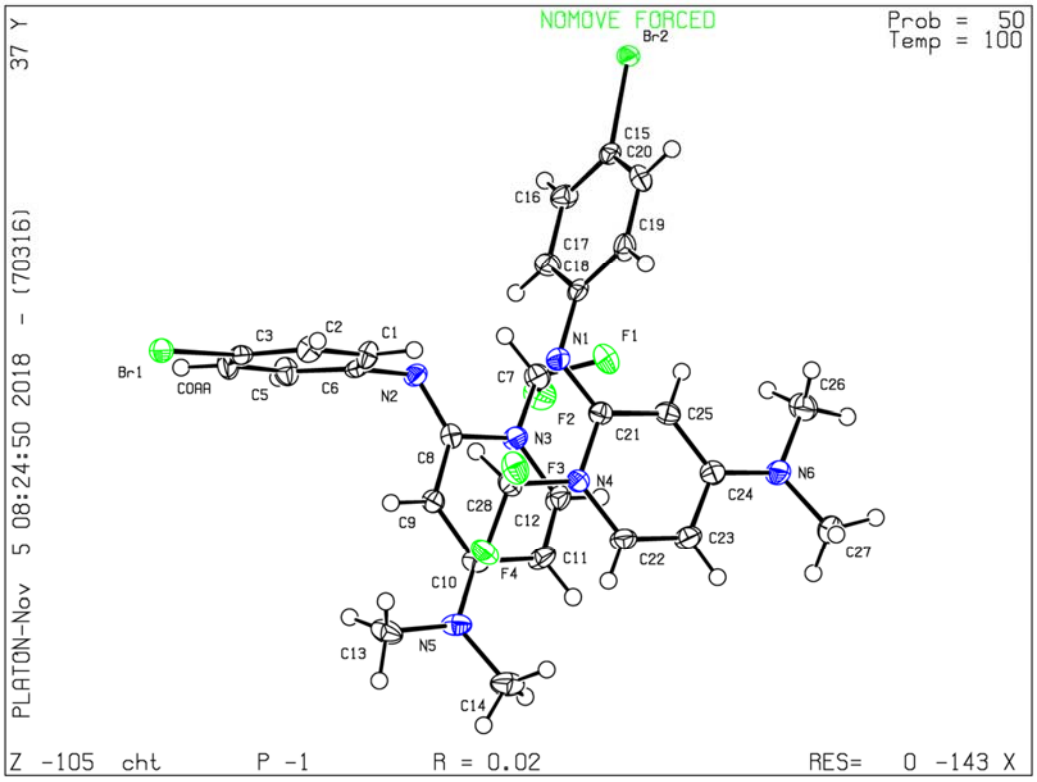


Table 1 Crystal data and structure refinement for CHT.

Identification code	CHT
Empirical formula	$C_{28}H_{28}Br_2F_4N_6$
Formula weight	684.38
Temperature/K	100.00(10)
Crystal system	triclinic
Space group	P-1
a/Å	8.32014(16)
b/Å	9.66755(20)
c/Å	17.7512(4)
α/°	81.8858(17)
β/°	88.0313(16)
γ/°	83.4840(16)
Volume/Å^3	1404.16(5)
Z	2
ρ_{calc}g/cm^3	1.619
μ/mm^{-1}	2.943
F(000)	688.0
Crystal size/mm^3	0.25 × 0.15 × 0.05
Radiation	MoKα (λ = 0.71073)

2Θ range for data collection/°	4.282 to 52.736
Index ranges	-10 ⩽ h ⩽ 10, -12 ⩽ k ⩽ 12, -22 ⩽ l ⩽ 22
Reflections collected	26735
Independent reflections	5637 [R_{int} = 0.0341, R_{sigma} = 0.0308]
Data/restraints/parameters	5637/0/365
Goodness-of-fit on F^2	1.050
Final R indexes [I>=2σ (I)]	R_1 = 0.0249, wR_2 = 0.0541
Final R indexes [all data]	R_1 = 0.0333, wR_2 = 0.0562
Largest diff. peak/hole / e $Å^{-3}$	0.39/-0.32

8. References:

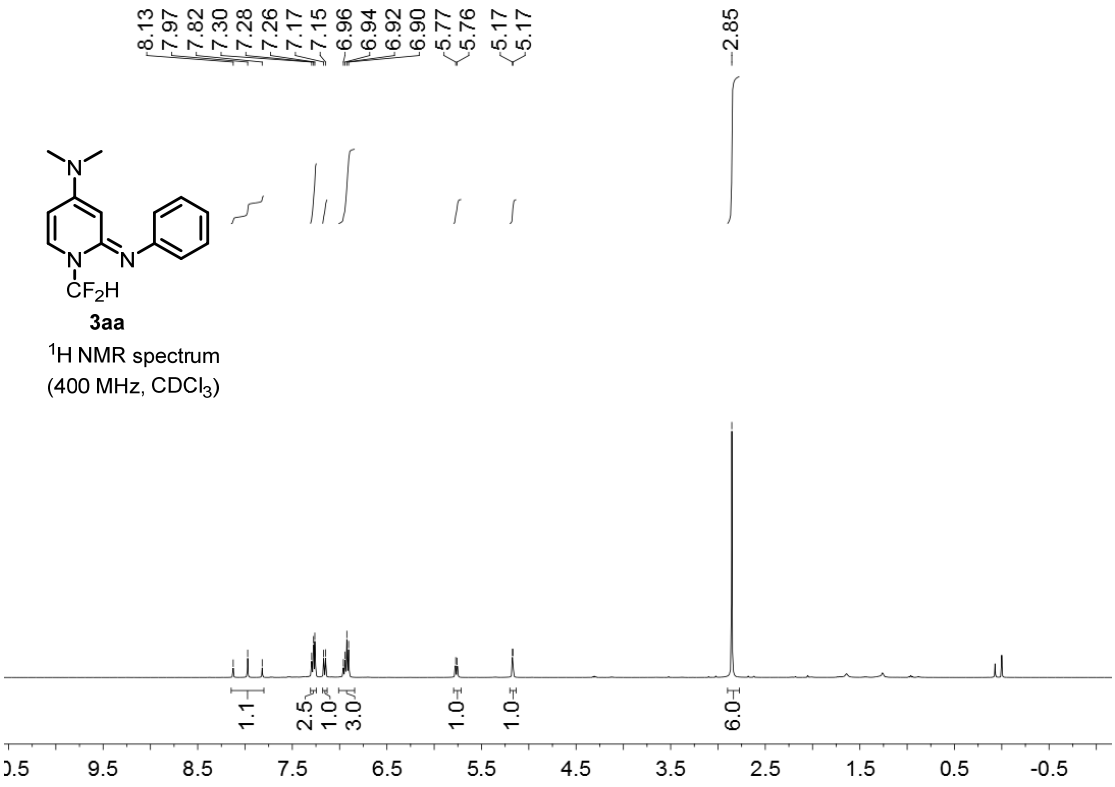
1. Li, Y.; Liu, J.; Zhao, S.; Du, X.; Guo, M.; Zhao, W.; Tang, X.; Wang, G. Copper-Catalyzed Fluoroolefination of Silyl Enol Ethers and Ketones toward the Synthesis of β-Fluoroenones. *Org. Lett*. **2018**, *20*, 917-920.

2. Kinens, A.; Balkaitis, S.; Suna, E. Preparative-Scale Synthesis of Vedejs Chiral DMAP Catalysts. *J. Org. Chem*. **2018**, *83*, 12449-12459.

3. (a) Beak, P.; Bonham, J. The Deuteration of Some *N*-Methyl-4-pyridones. *J. Am. Chem. Soc*. **1965**, *87*, 3365-3371. (b) Yi, X.; Chen, J.; Xu, X.; Ma, Y. Solvent and Substituent Effects on the Conversion of 4-Methoxypyridines to *N*-Methyl-4-pyridones. *Synth. Commun*. **2017**, *47*, 872-877.

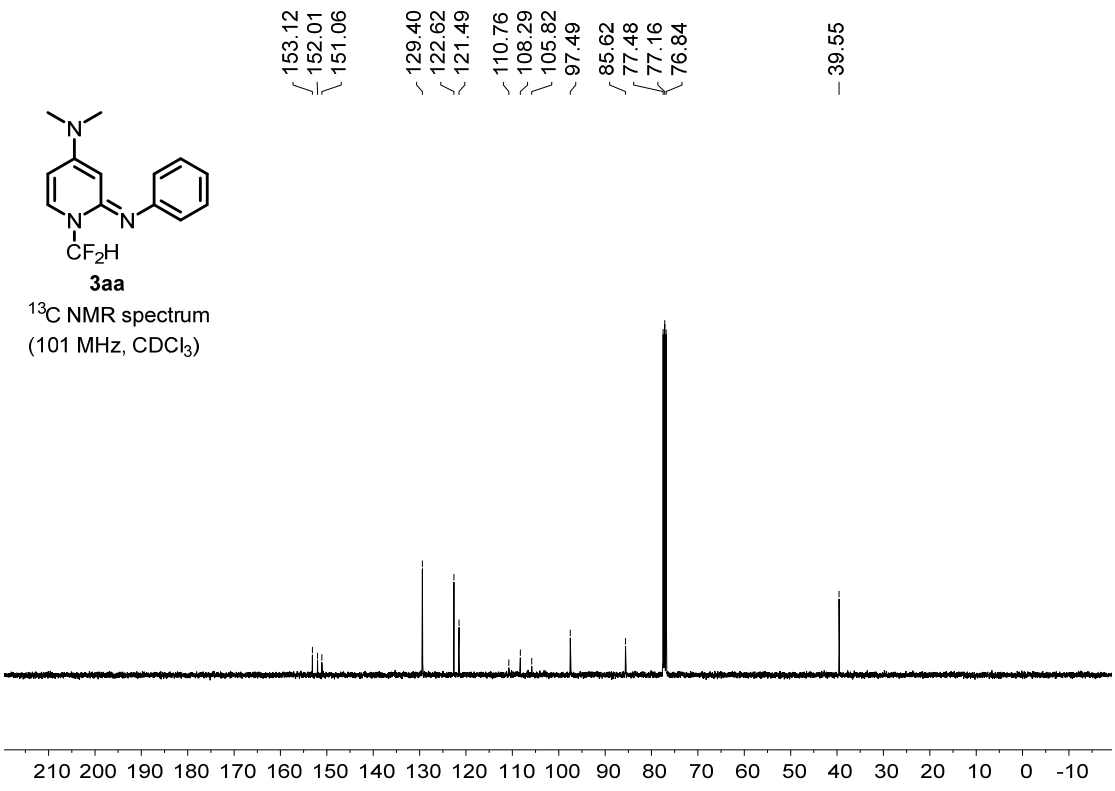
4. Ma, X.; Zhou, Y.; Song, Q. Synthesis of *β*-Aminoenones *via* Cross-Coupling of In-Situ Generated Isocyanides with 1,3-Dicarbonyl Compounds. *Org. Lett*. **2018**, *20*, 4777−4781.

9. ^{1}H NMR, ^{19}F NMR, ^{13}C NMR, and HRMS spectra.



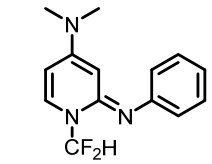
3aa

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



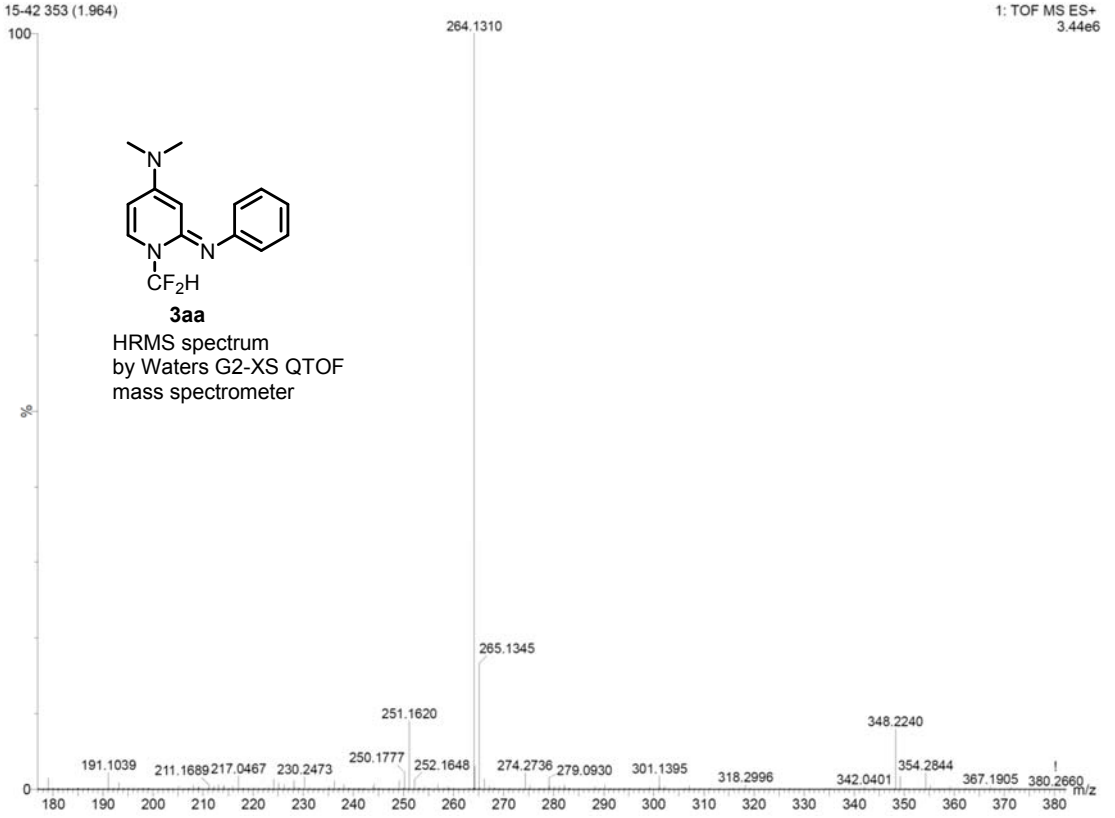
3aa

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



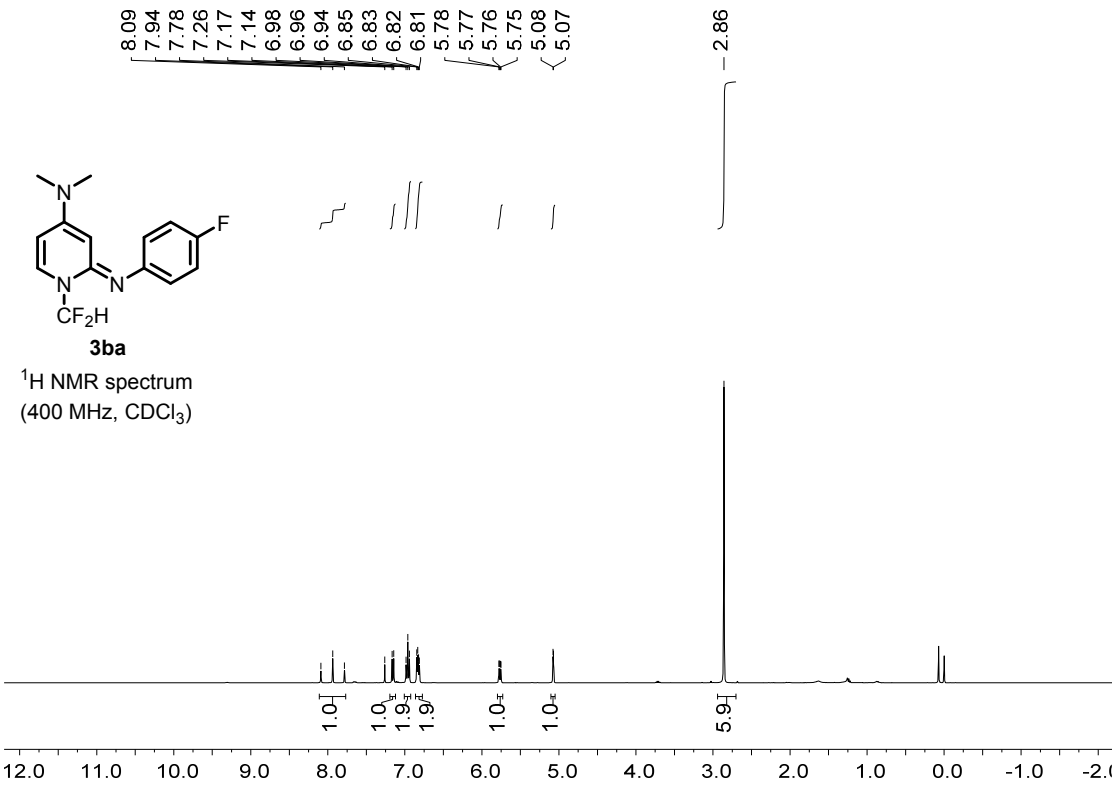
3aa

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



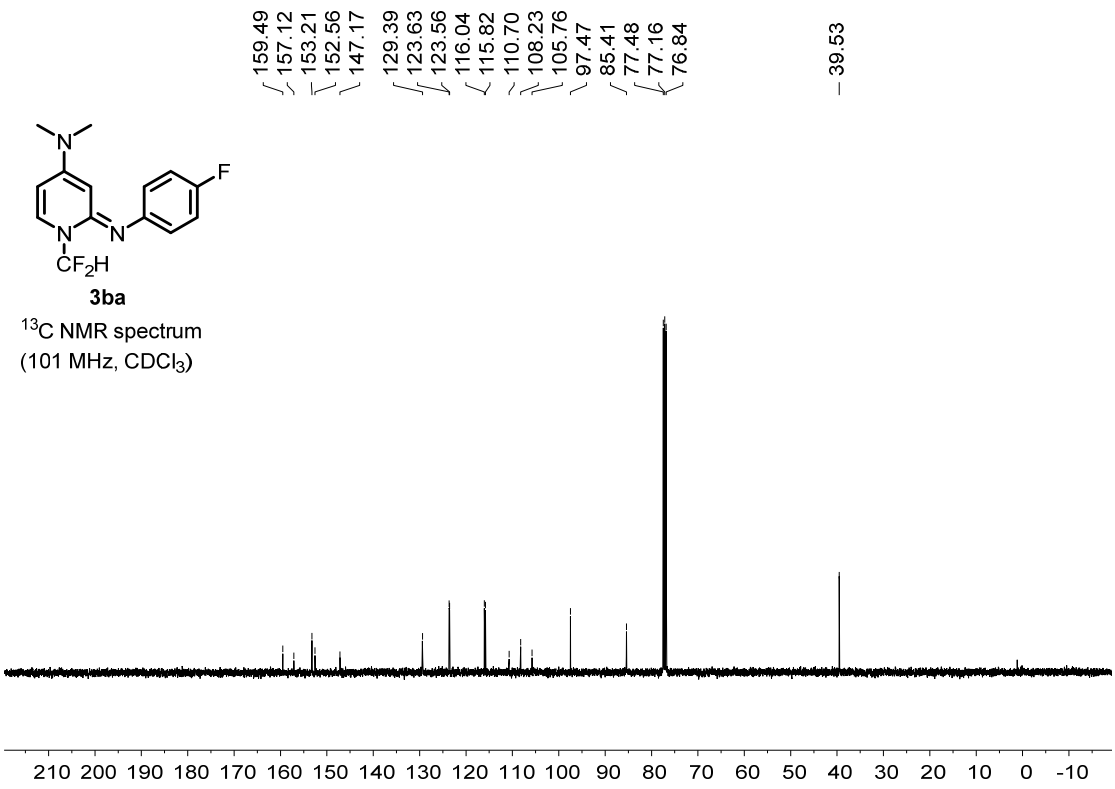
3aa

HRMS spectrum
by Waters G2-XS QTOF
mass spectrometer



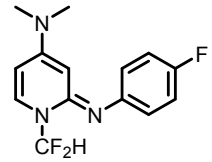
3ba

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



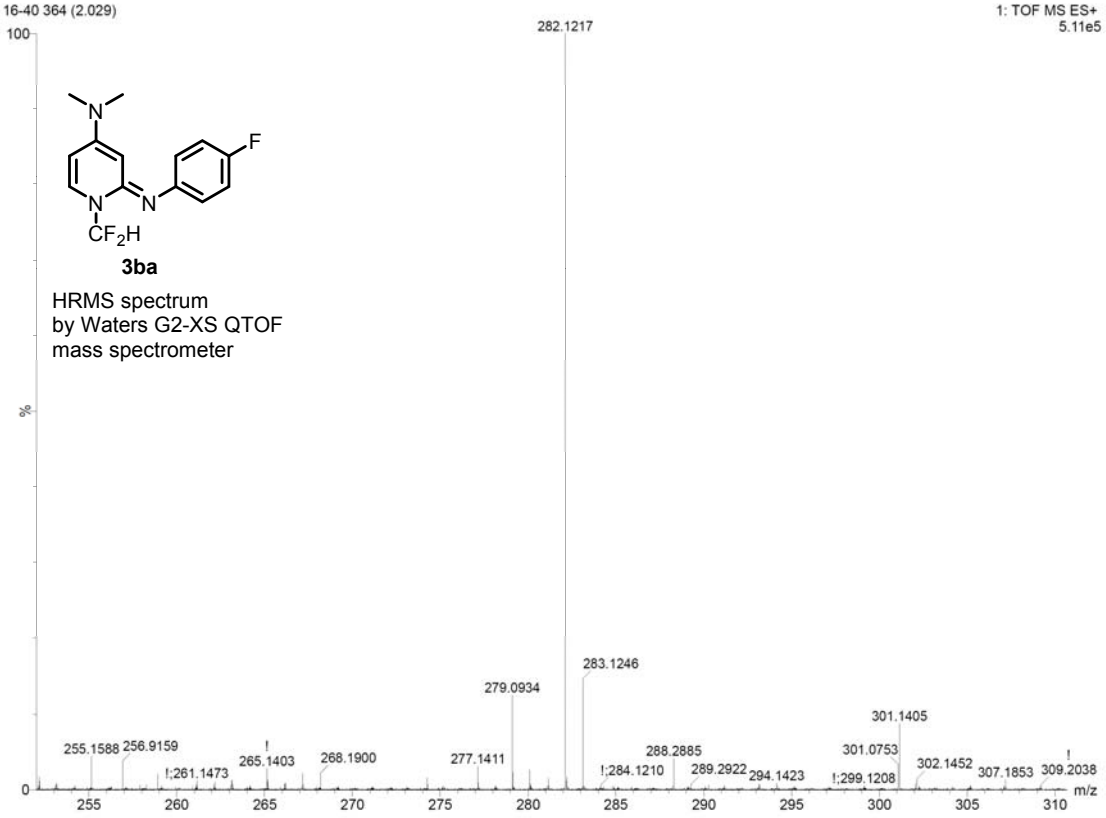
3ba

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



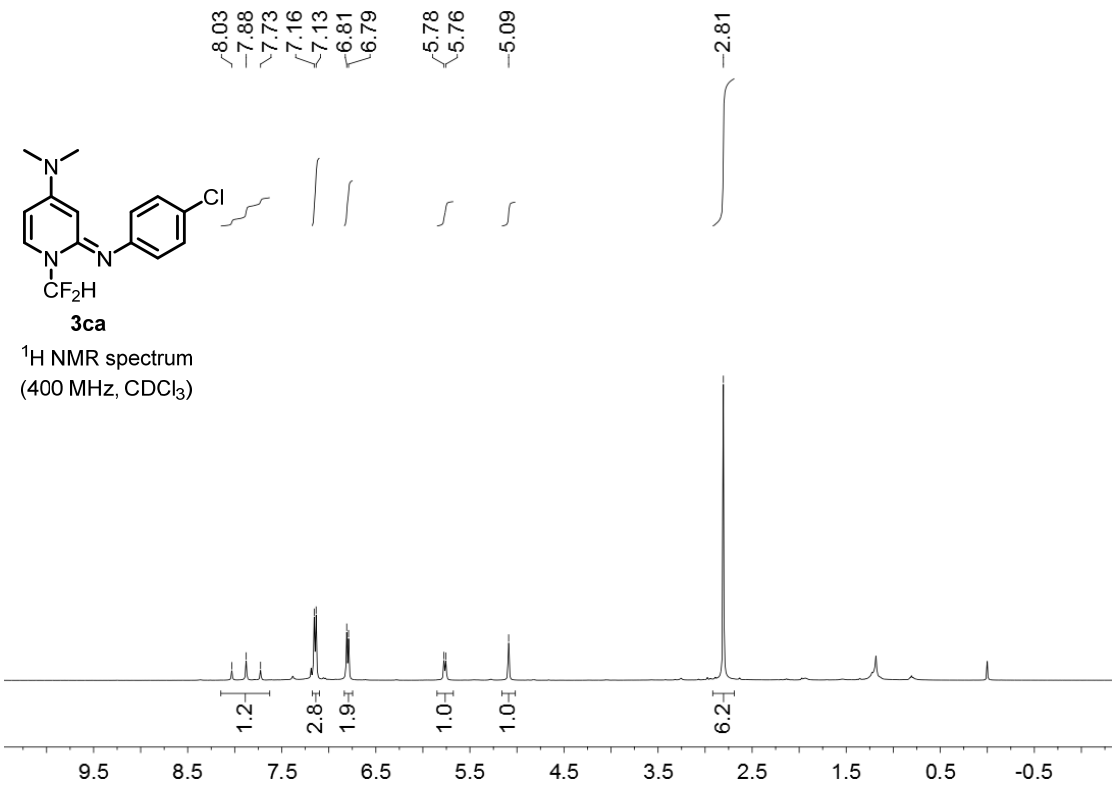
3ba

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



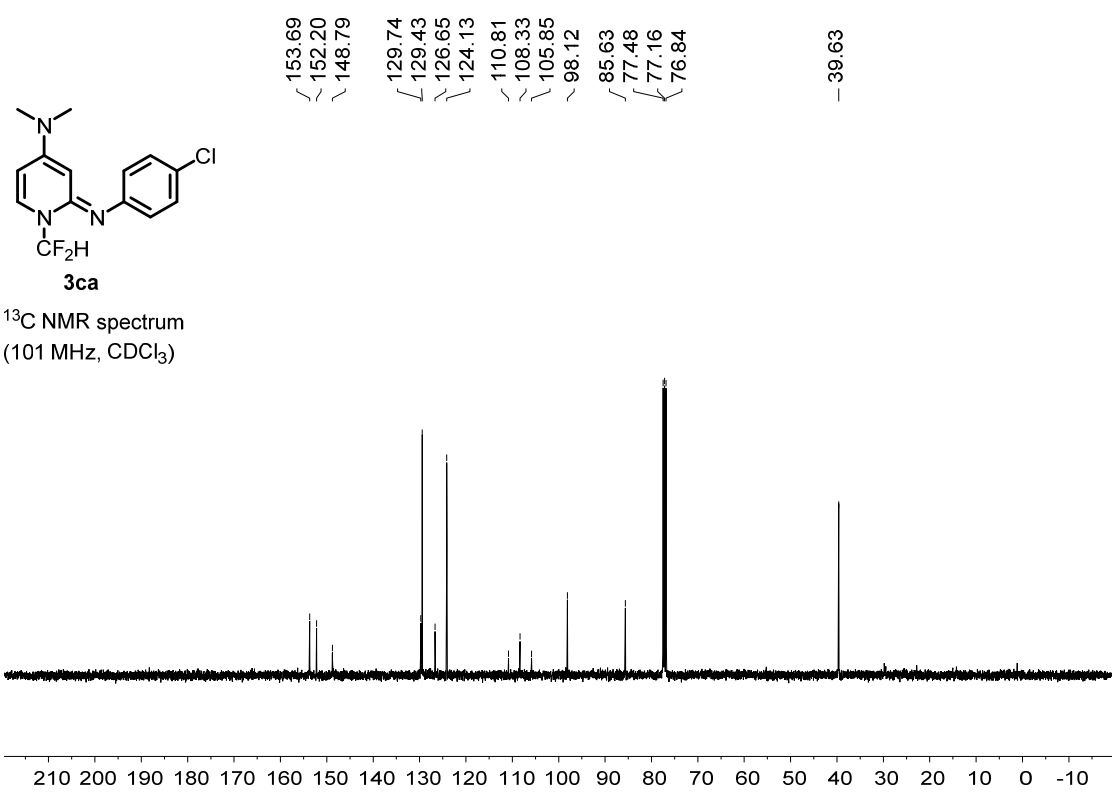
3ba

HRMS spectrum
by Waters G2-XS QTOF
mass spectrometer



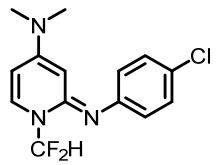
3ca

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



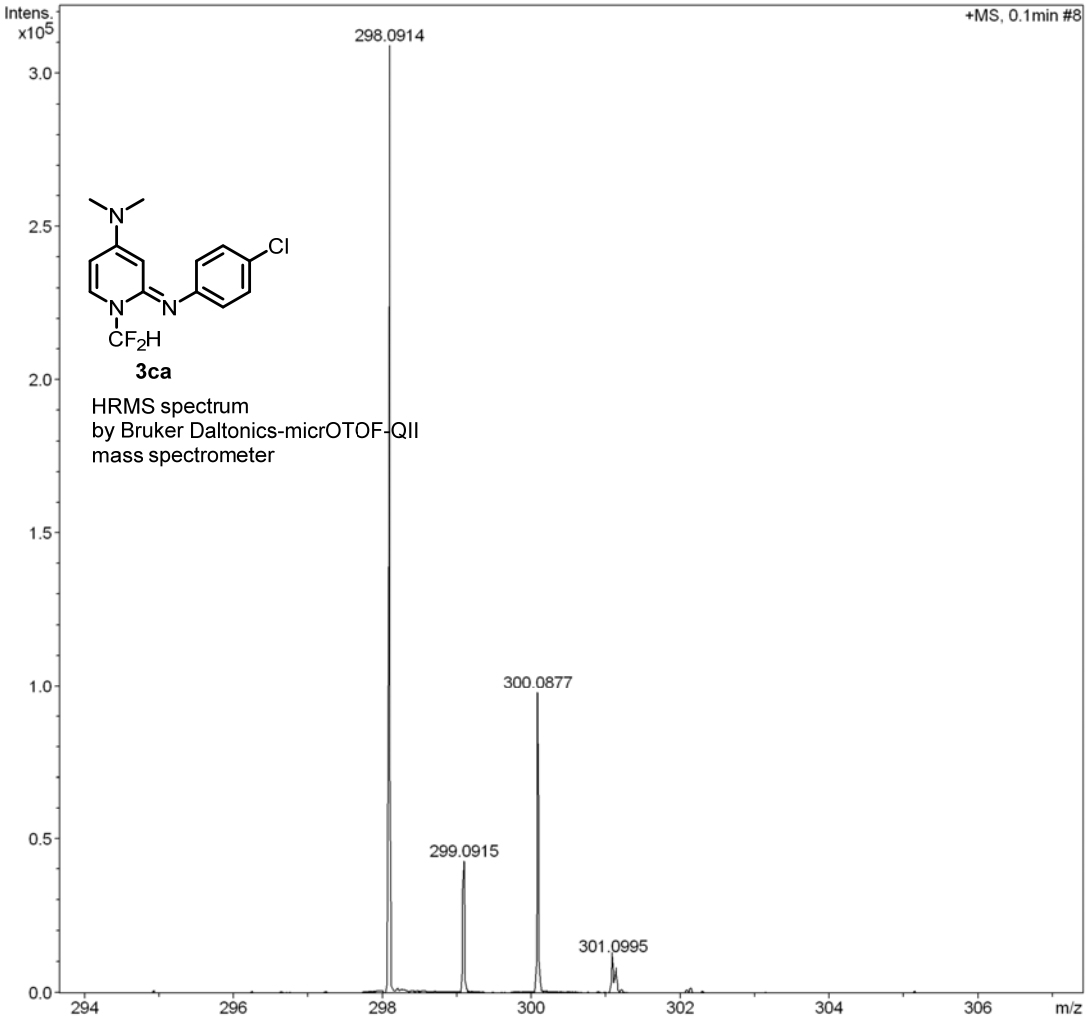
3ca

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



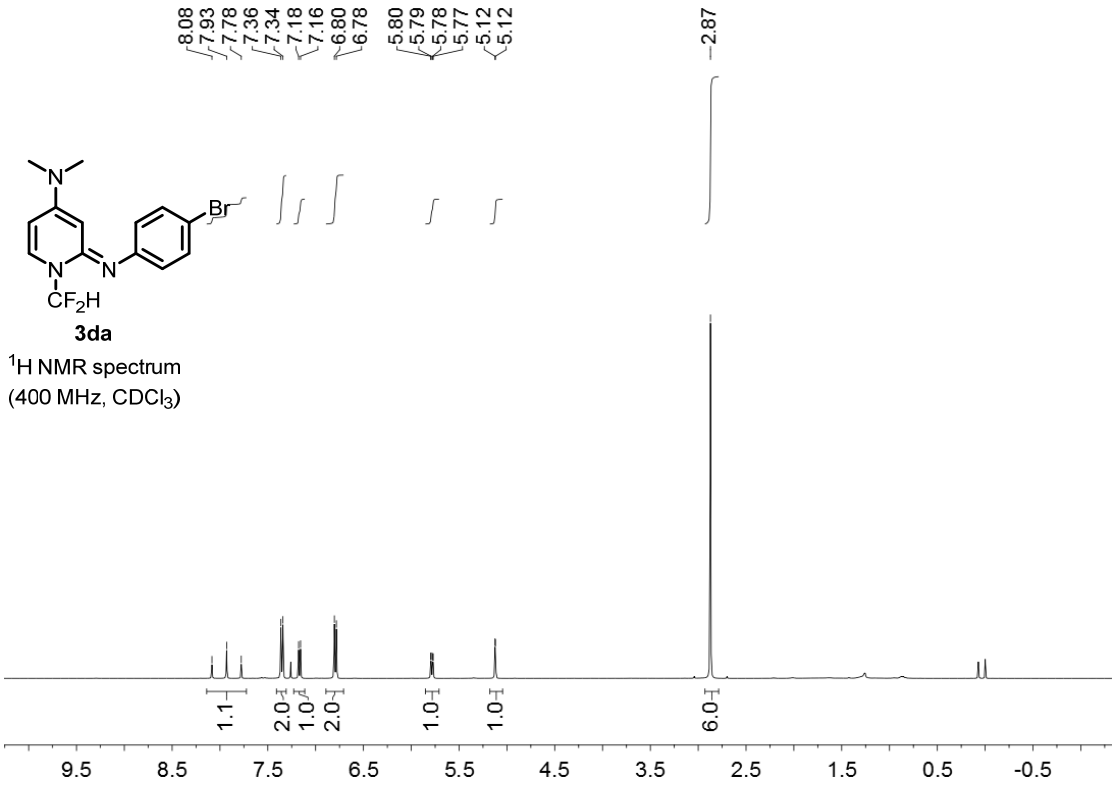
3ca

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



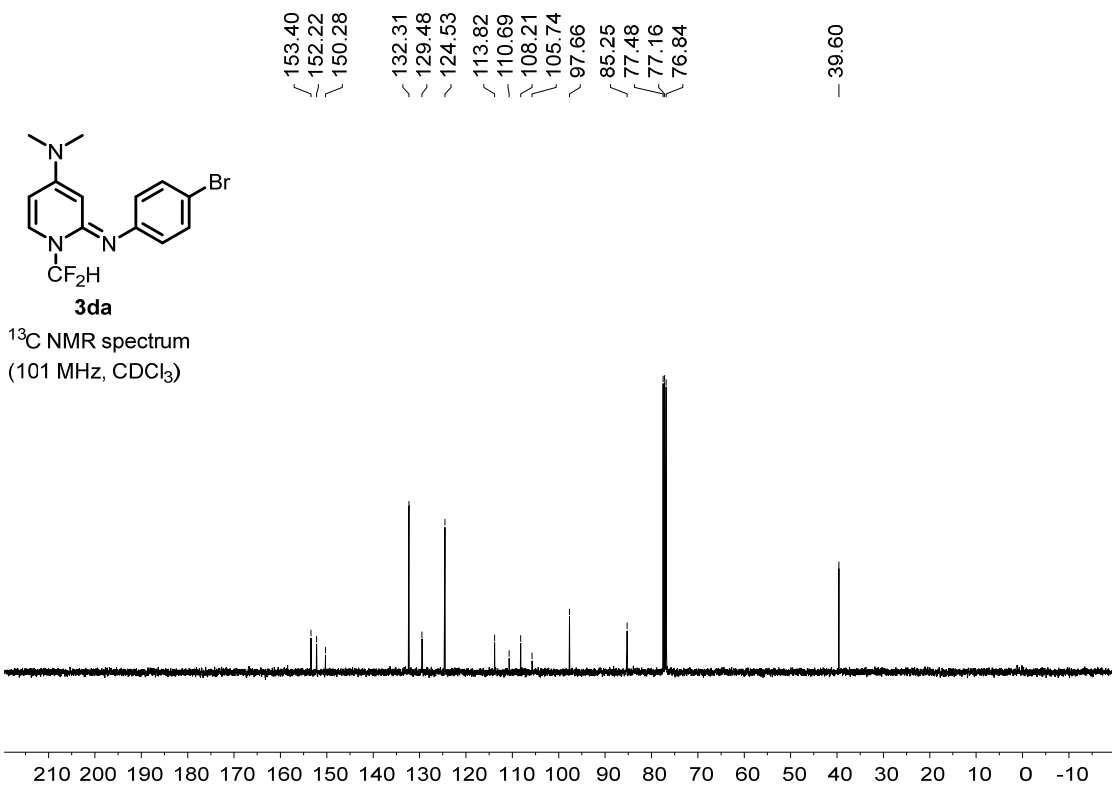
3ca

HRMS spectrum
by Bruker Daltonics-micrOTOF-QII
mass spectrometer



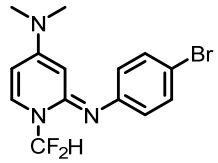
3da

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



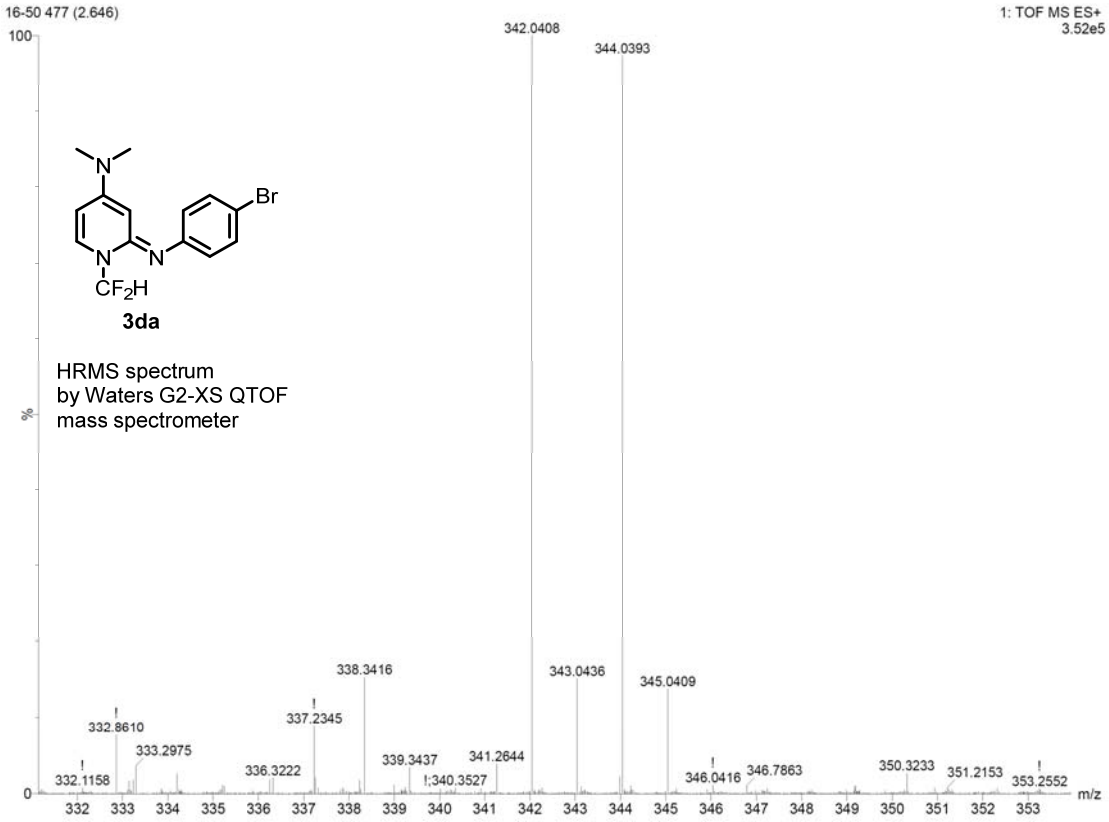
3da

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



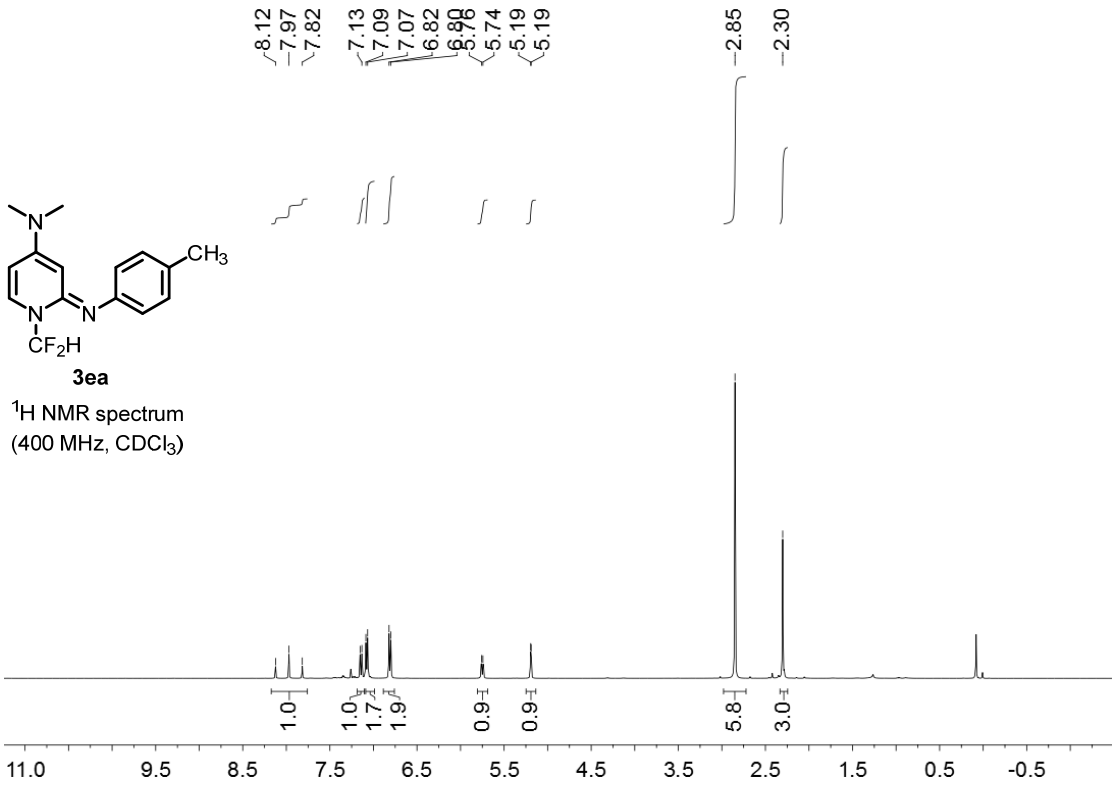
3da

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



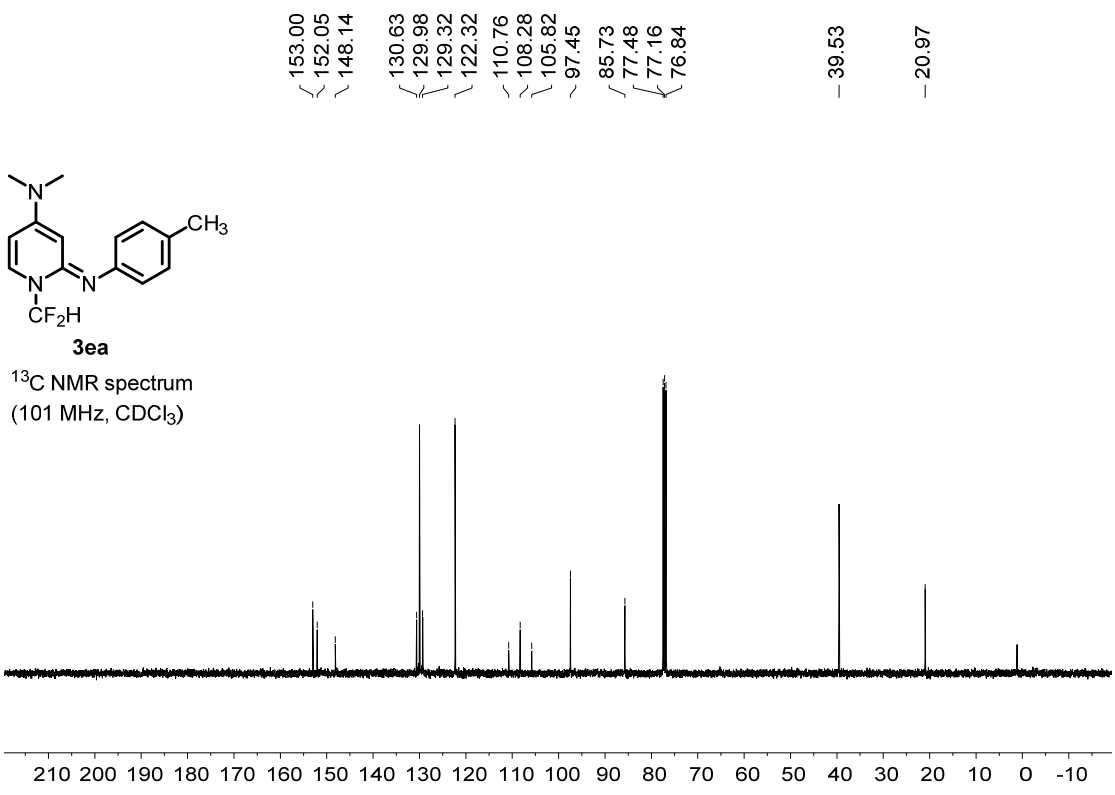
3da

HRMS spectrum
by Waters G2-XS QTOF
mass spectrometer



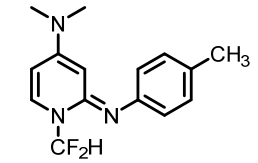
3ea

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



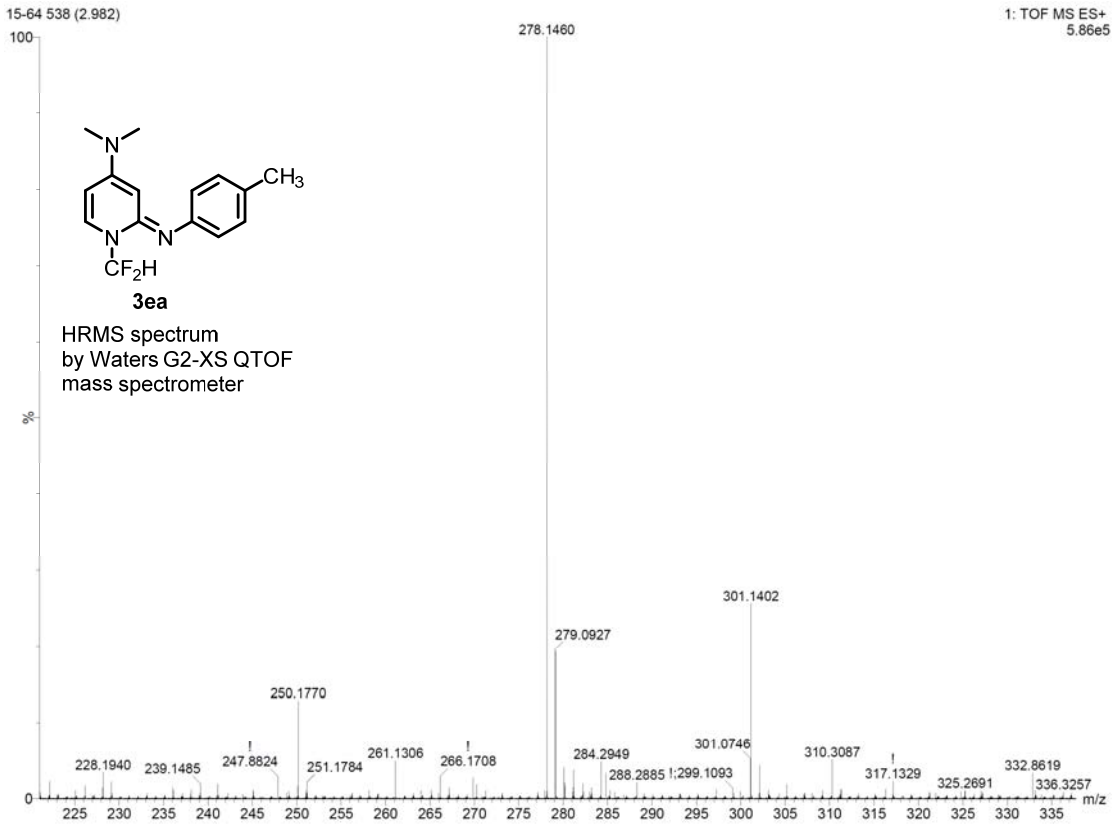
3ea

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



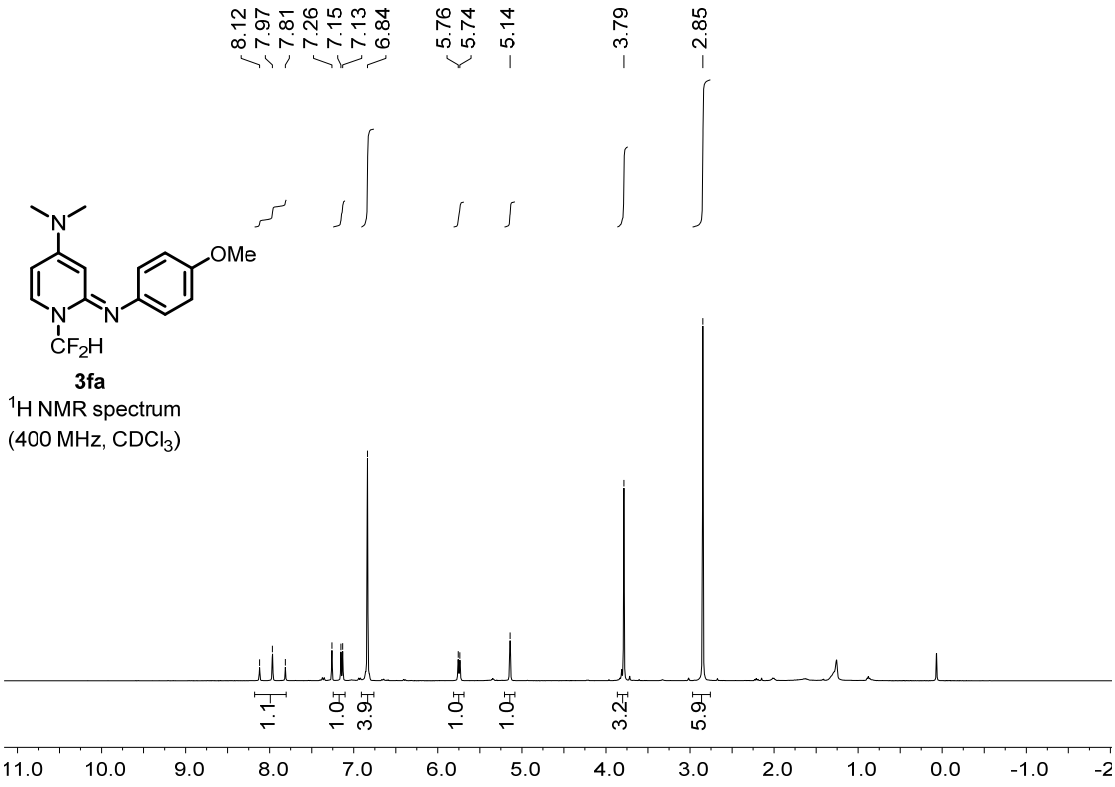
3ea

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



3ea

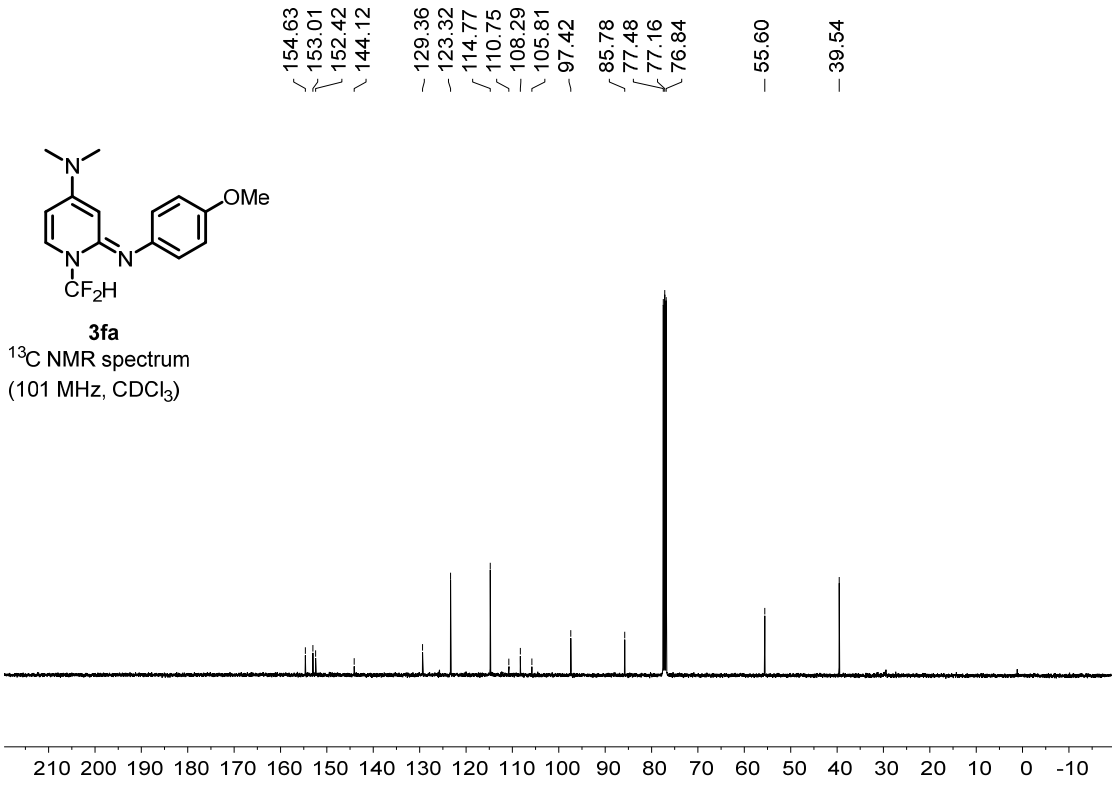
HRMS spectrum
by Waters G2-XS QTOF
mass spectrometer



3fa

^{1}H NMR spectrum

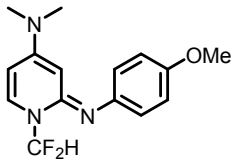
(400 MHz, $CDCl_3$)



3fa

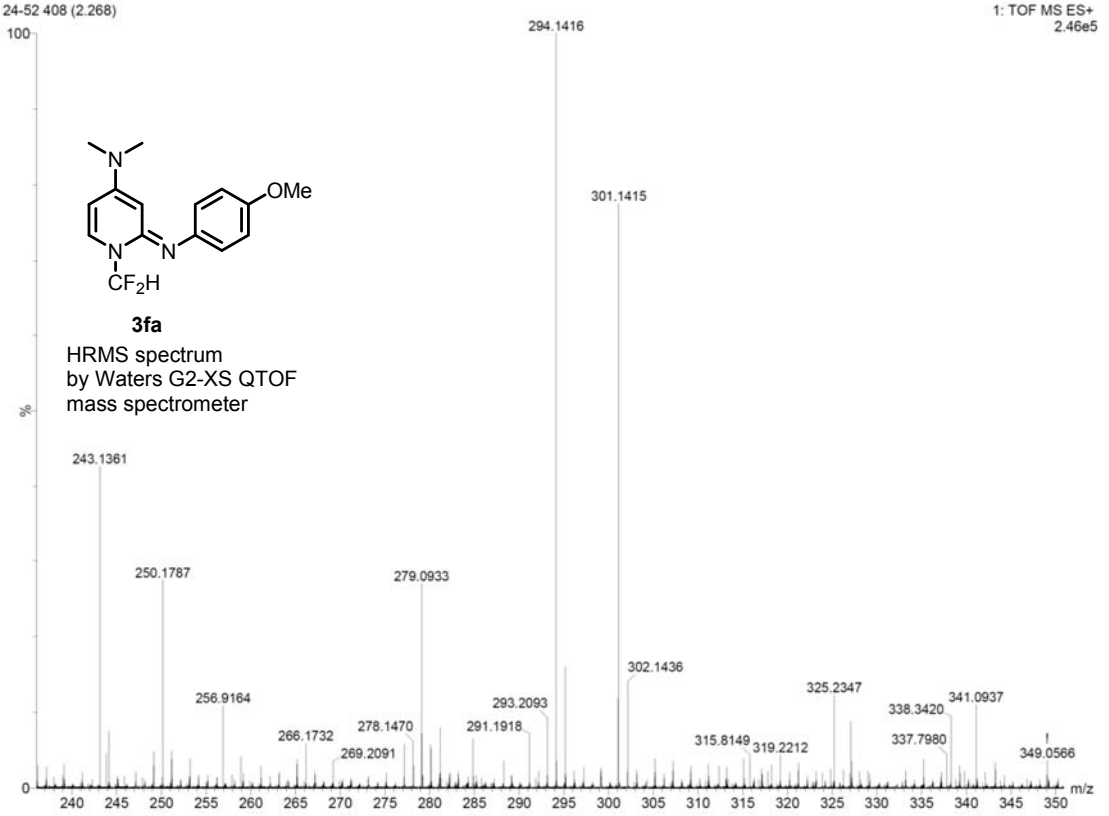
^{13}C NMR spectrum

(101 MHz, $CDCl_3$)



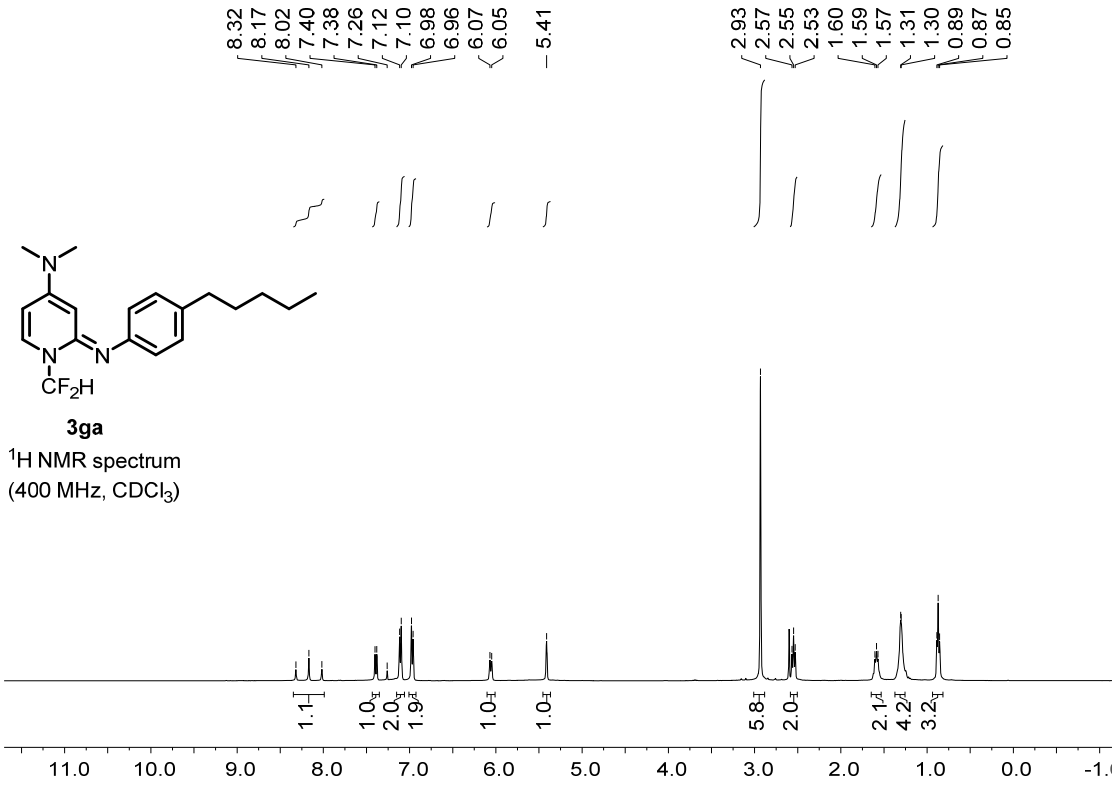
3fa

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



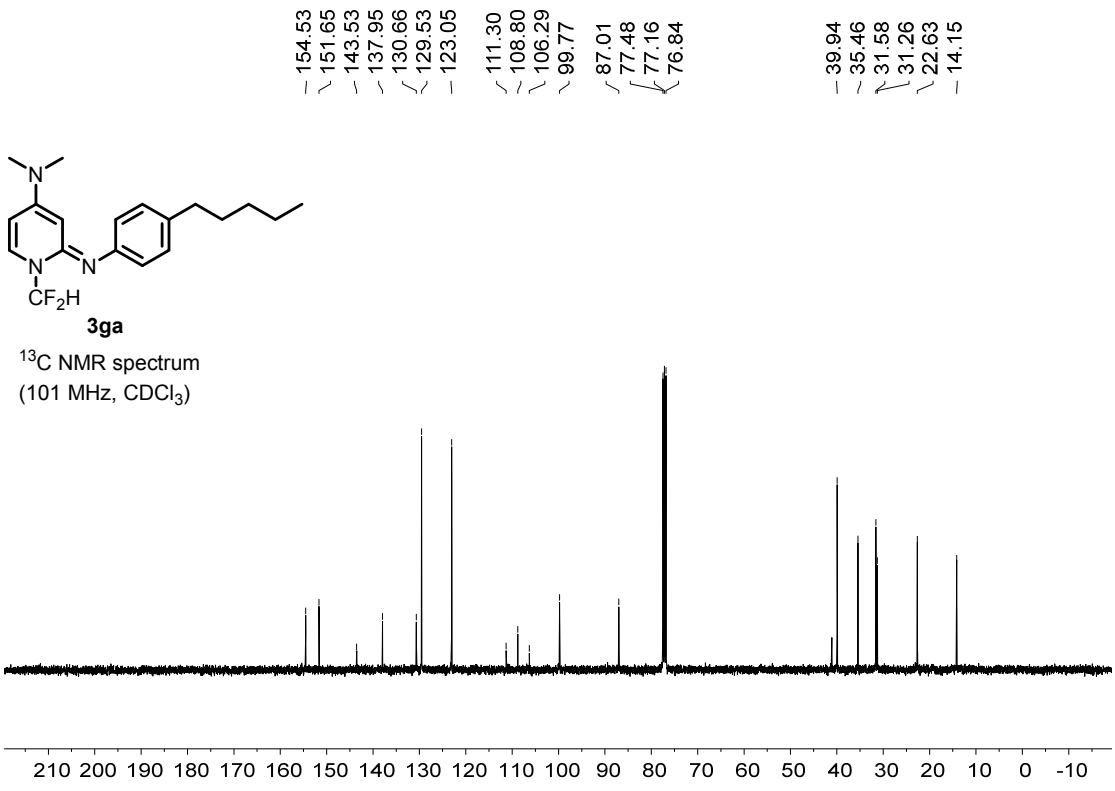
3fa

HRMS spectrum
by Waters G2-XS QTOF
mass spectrometer



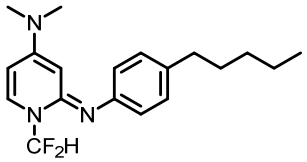
3ga

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



3ga

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

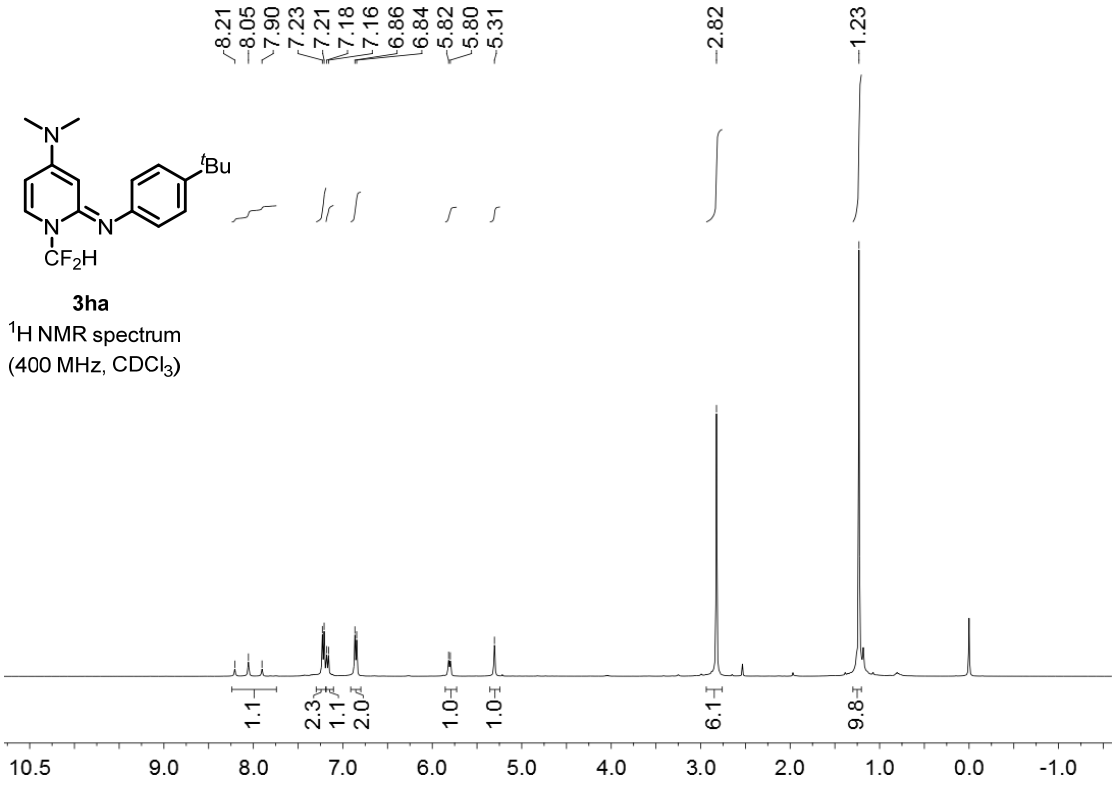


3ga

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

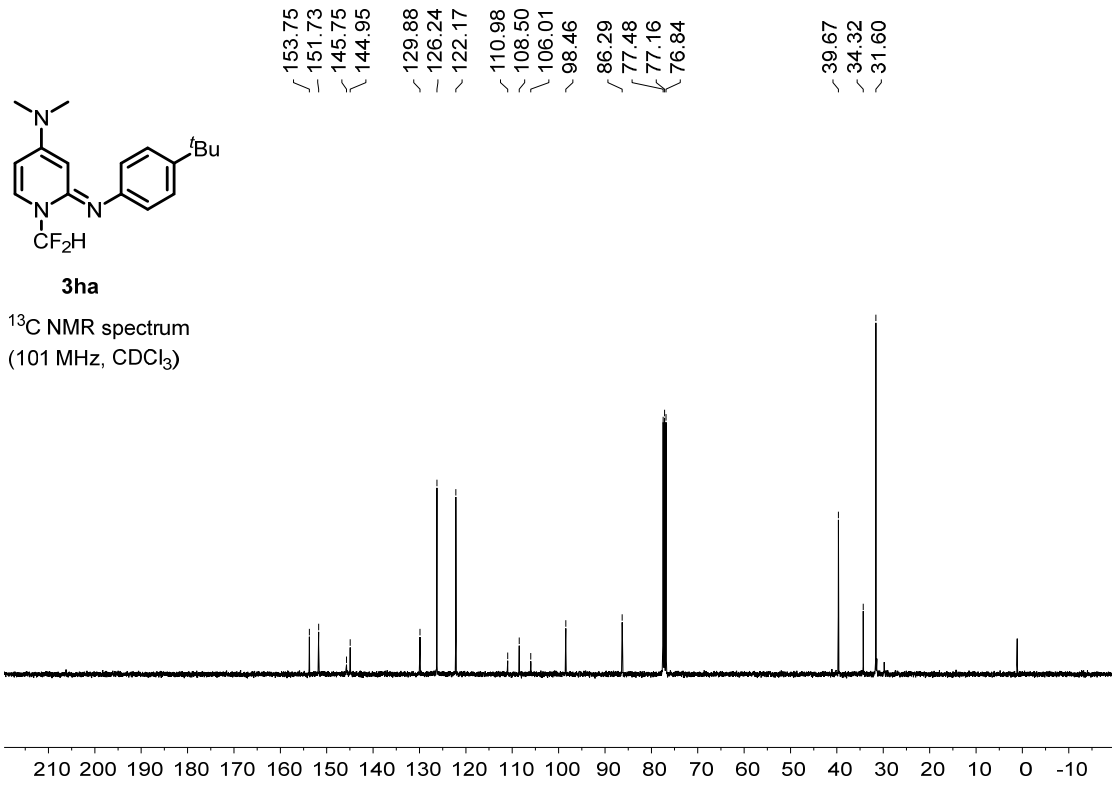
3ga

HRMS spectrum
by Waters G2-XS QTOF
mass spectrometer



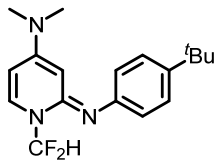
3ha

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



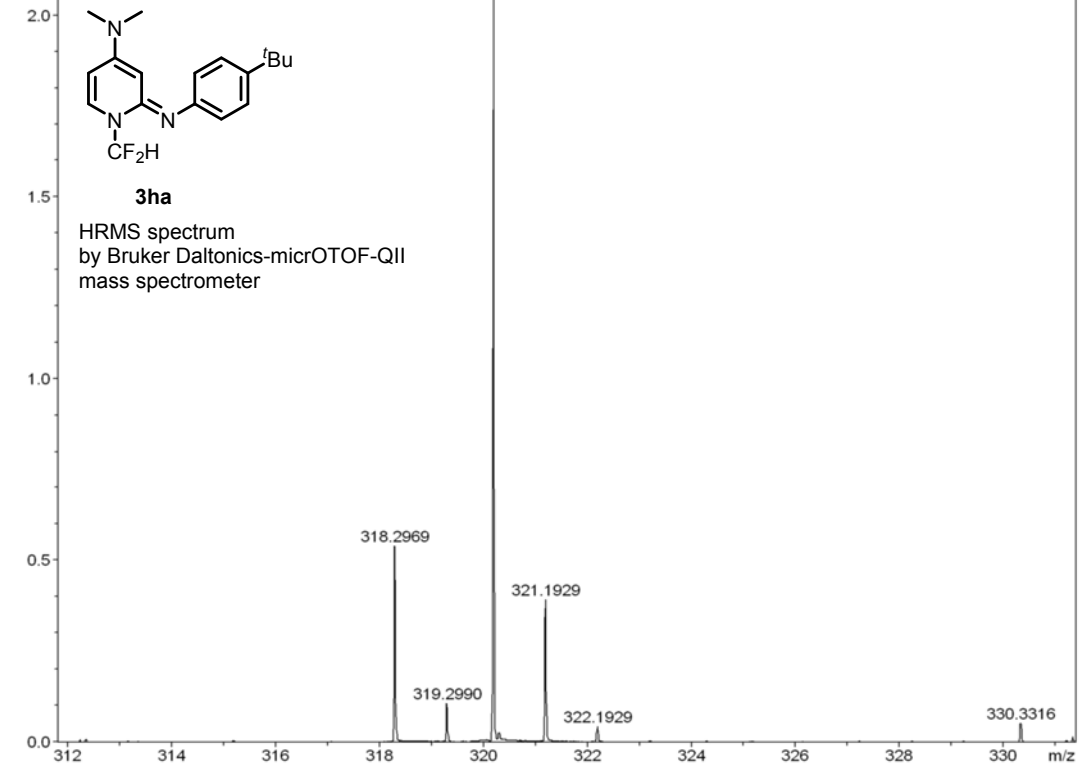
3ha

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



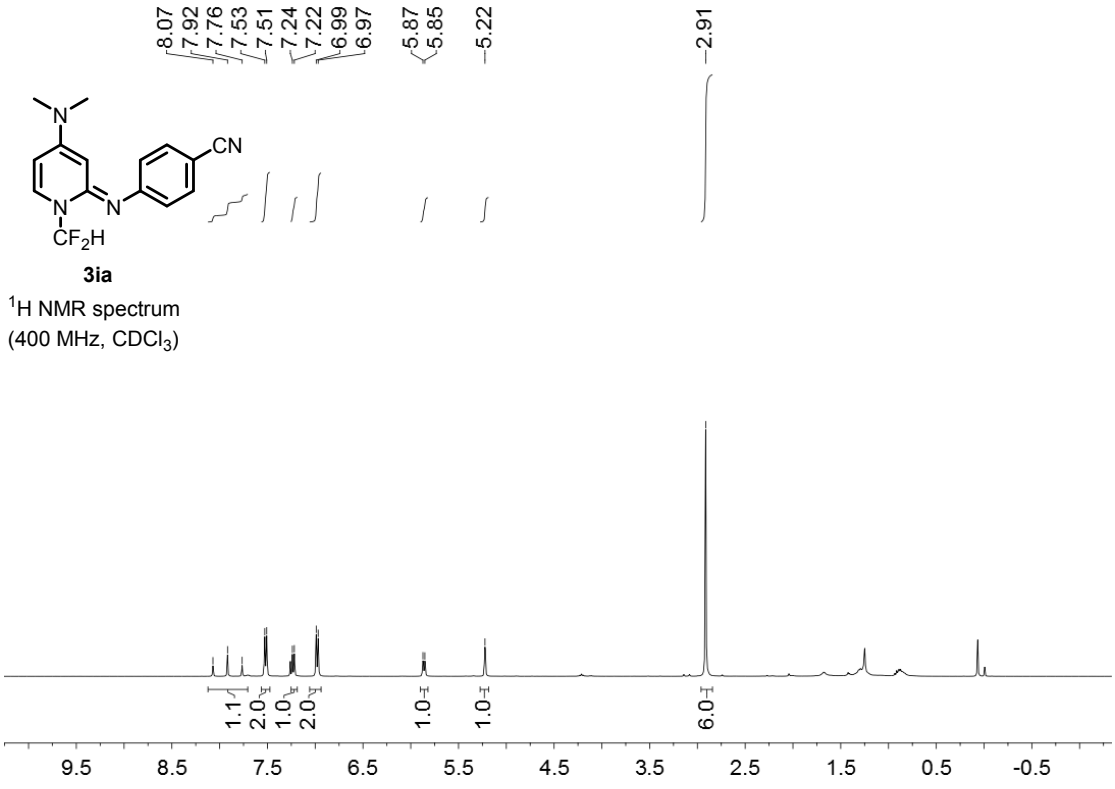
3ha

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



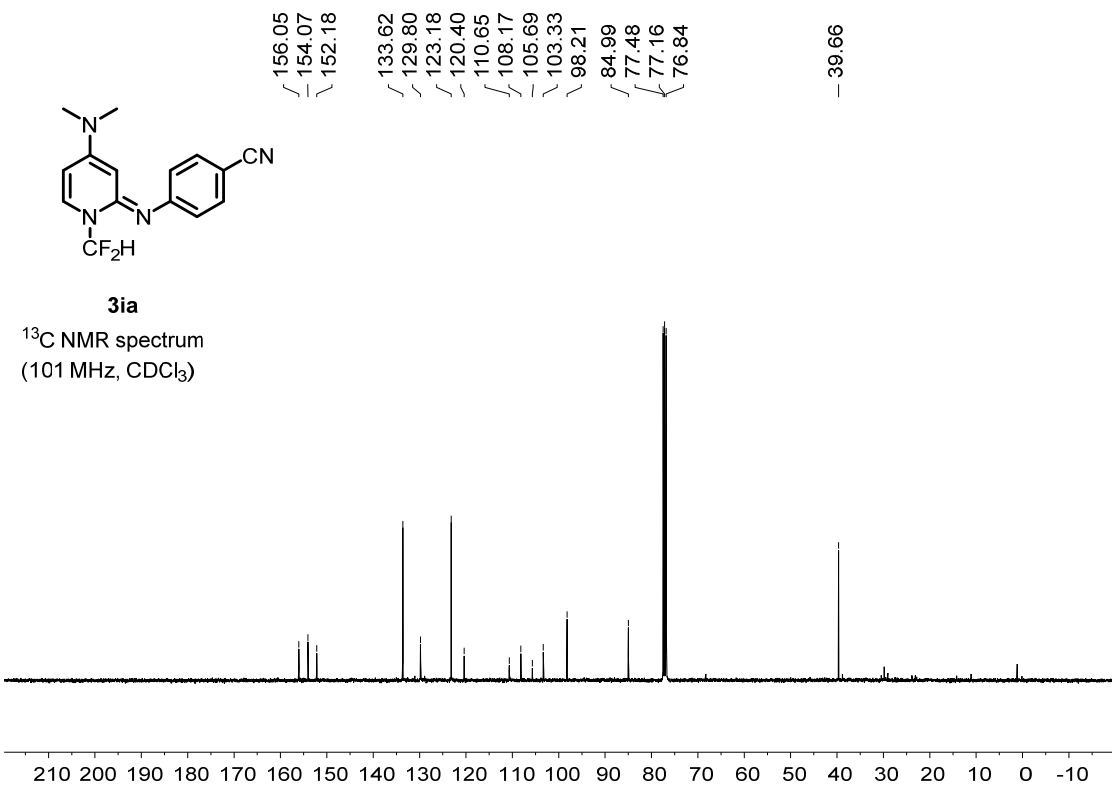
3ha

HRMS spectrum
by Bruker Daltonics-micrOTOF-QII
mass spectrometer



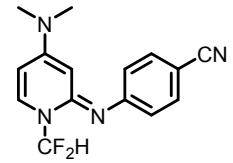
3ia

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



3ia

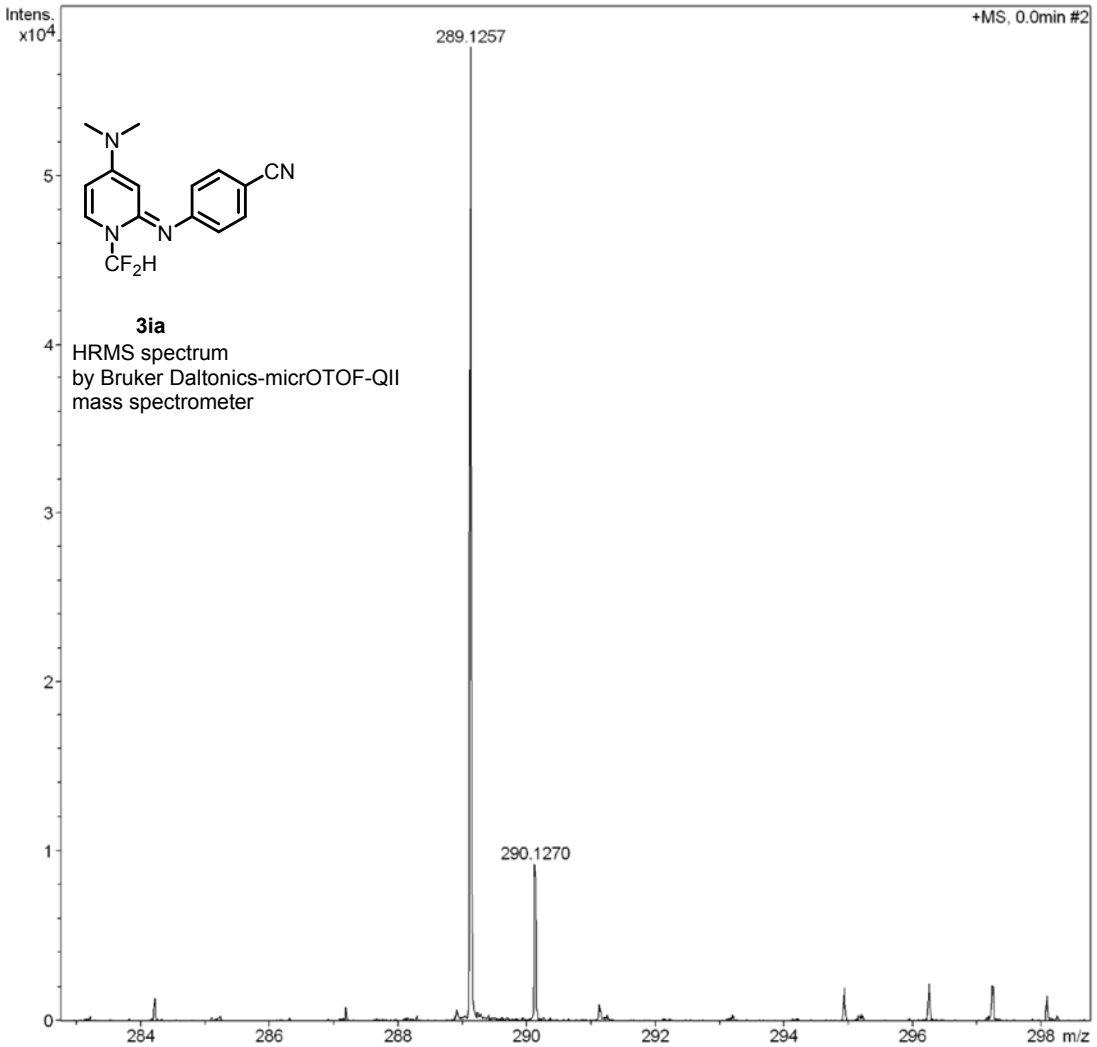
^{13}C NMR spectrum
(101 MHz, $CDCl_3$)



3ia

^{19}F NMR spectrum

(376 MHz, $CDCl_3$)

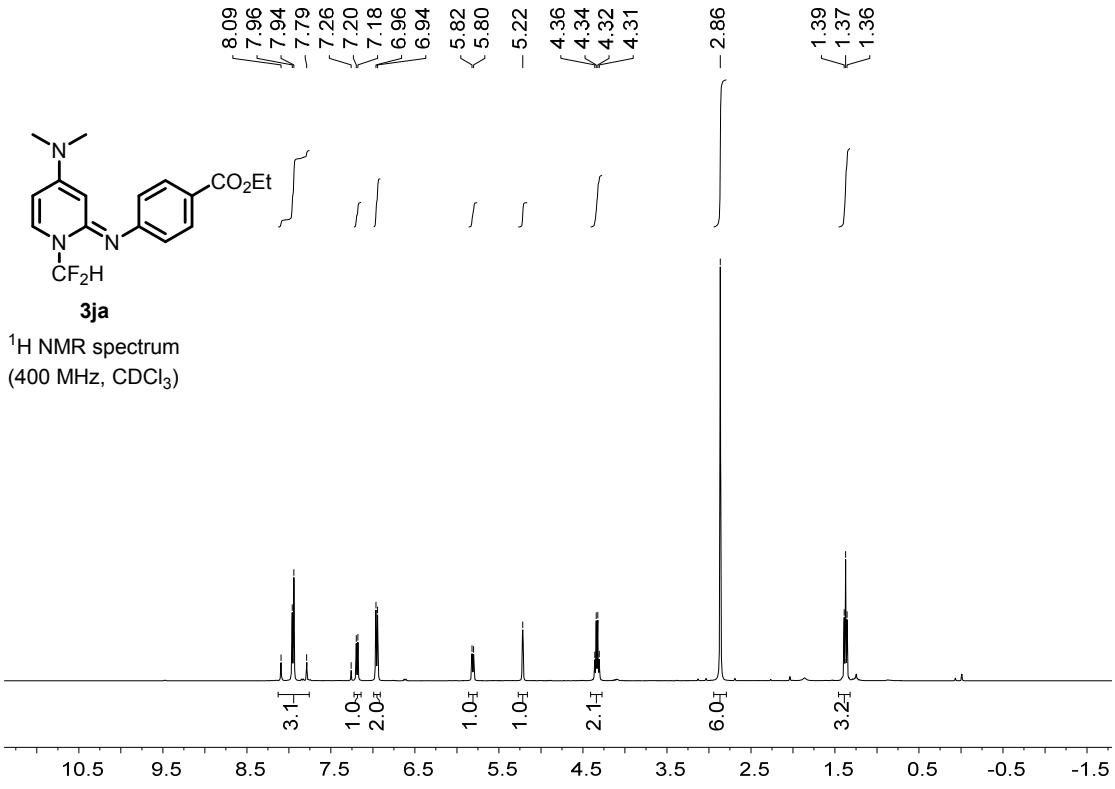


3ia

HRMS spectrum

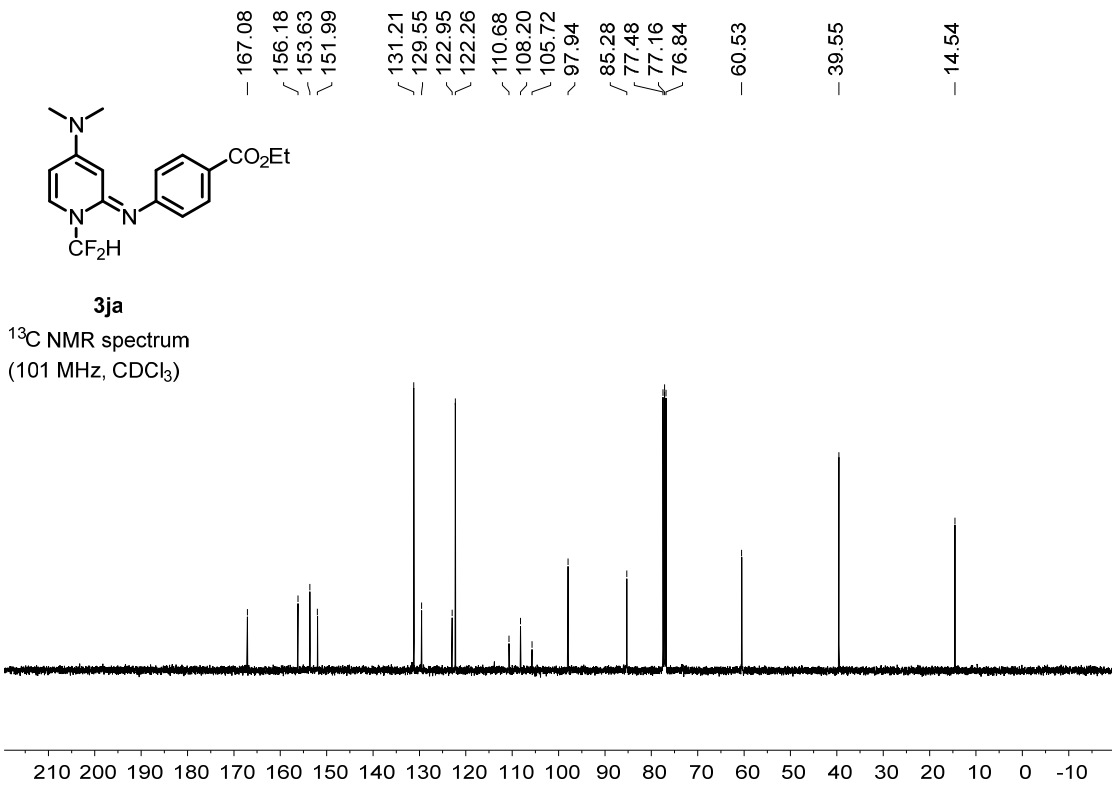
by Bruker Daltonics-micrOTOF-QII

mass spectrometer



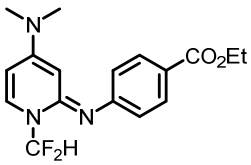
3ja

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



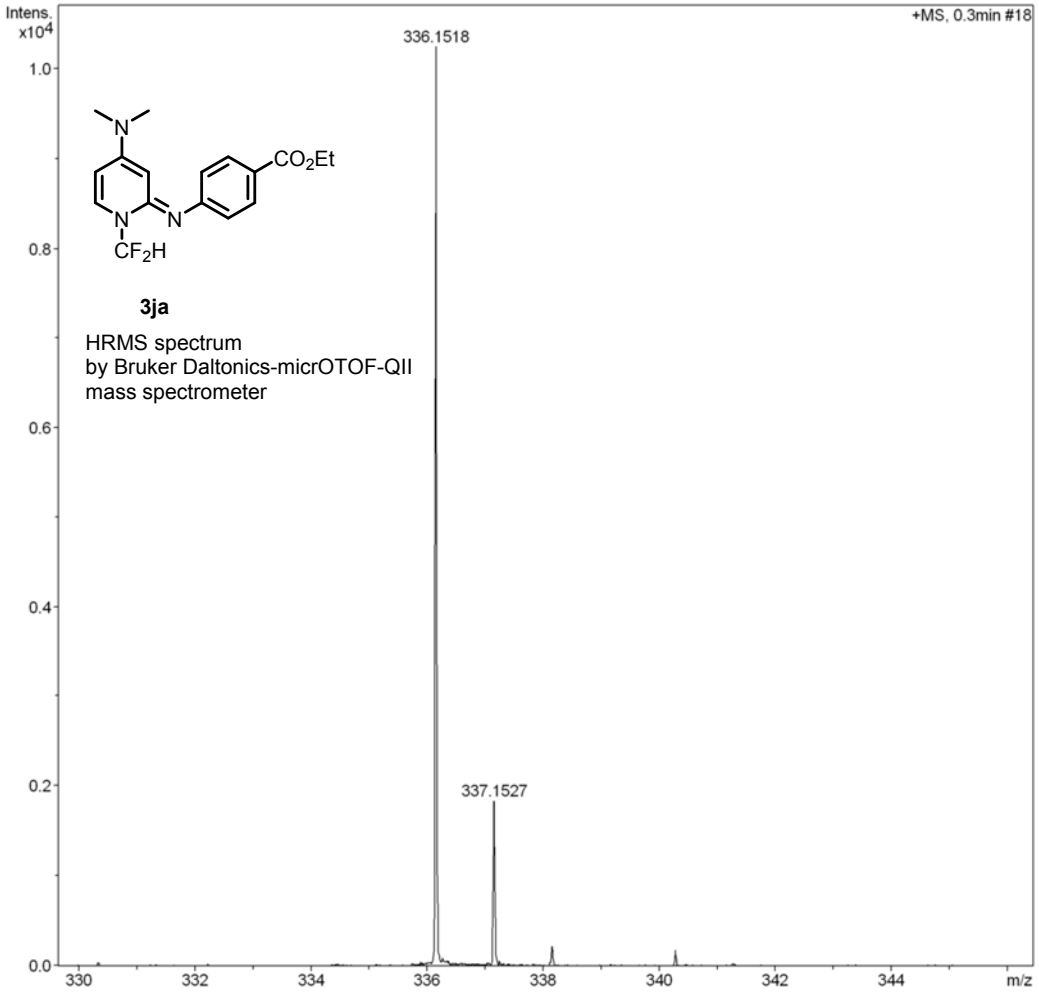
3ja

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



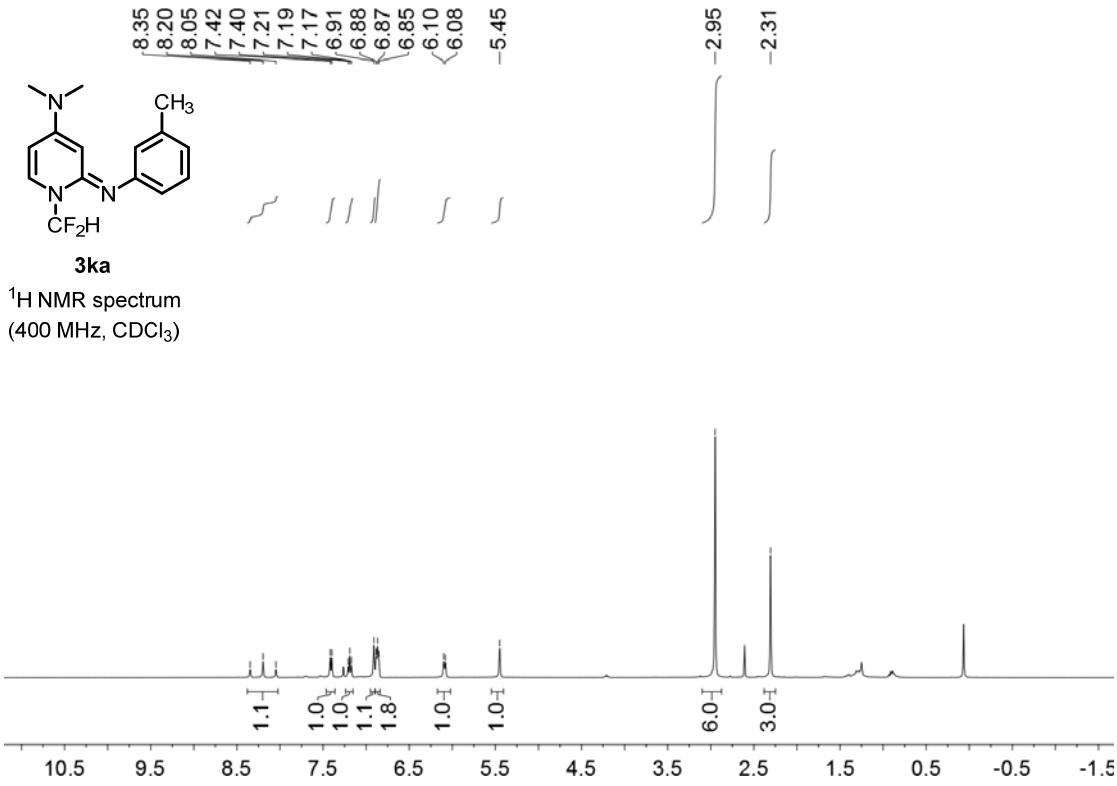
3ja

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



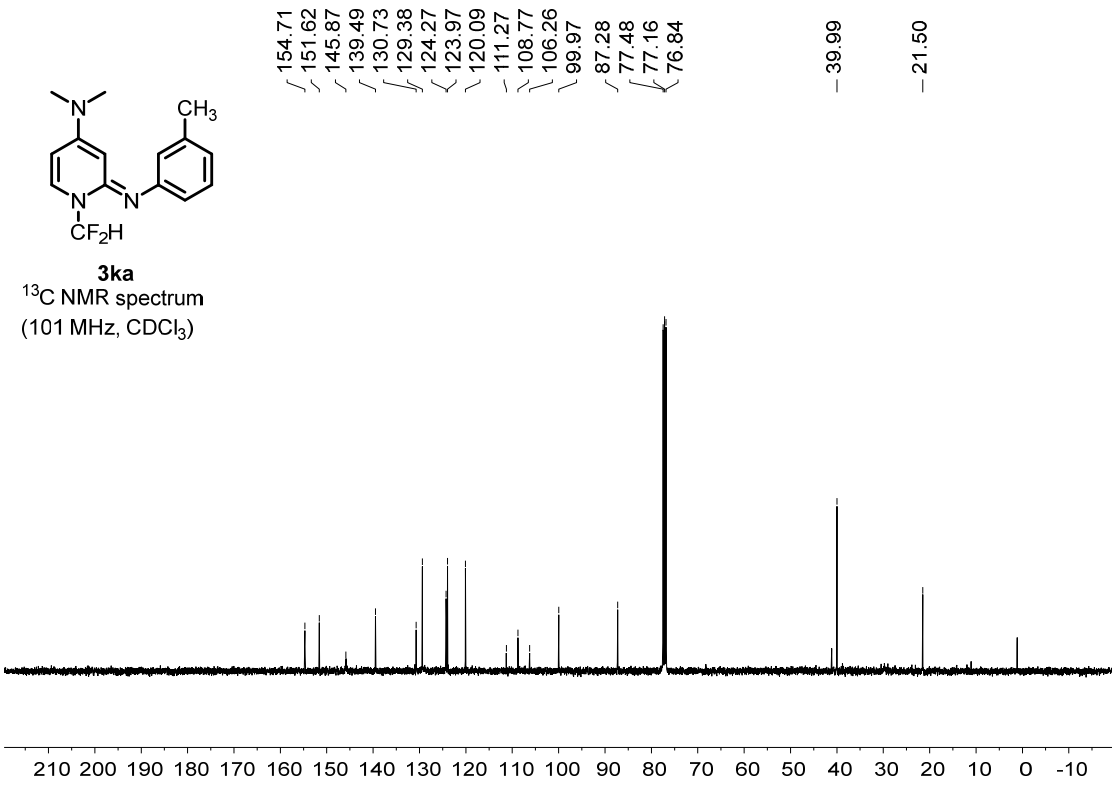
3ja

HRMS spectrum
by Bruker Daltonics-micrOTOF-QII
mass spectrometer



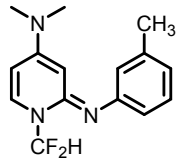
3ka

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



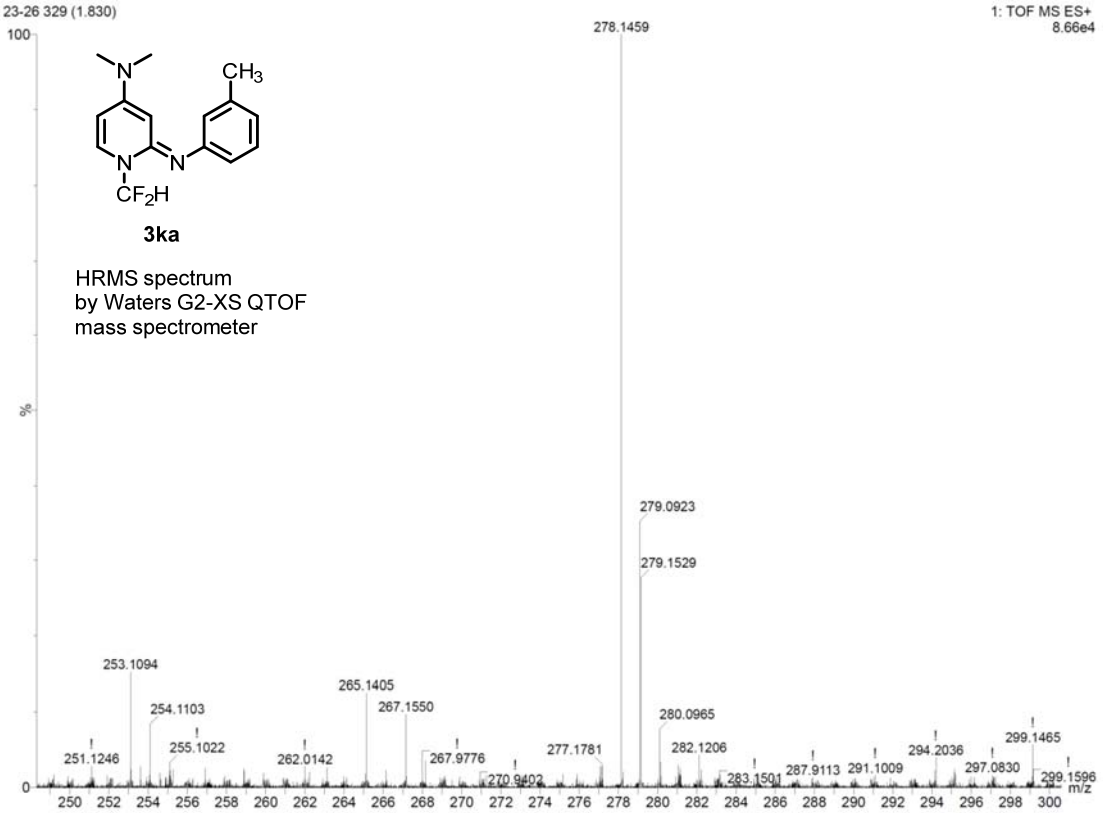
3ka

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



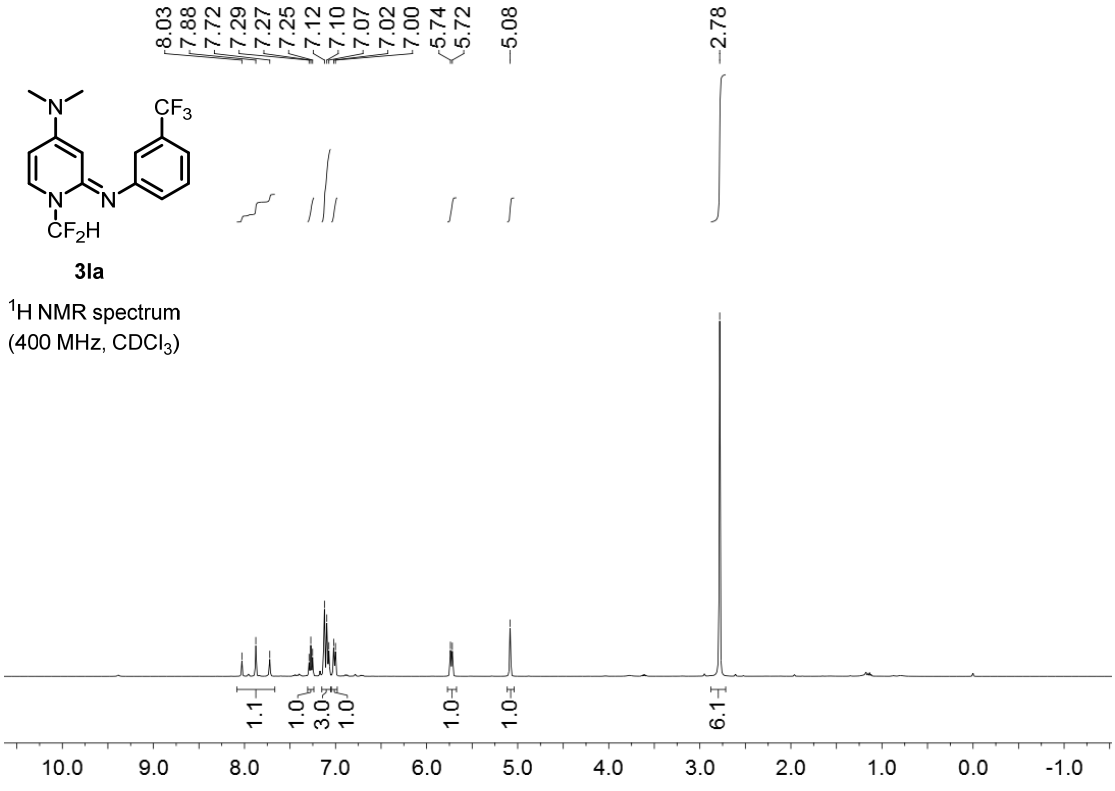
3ka

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



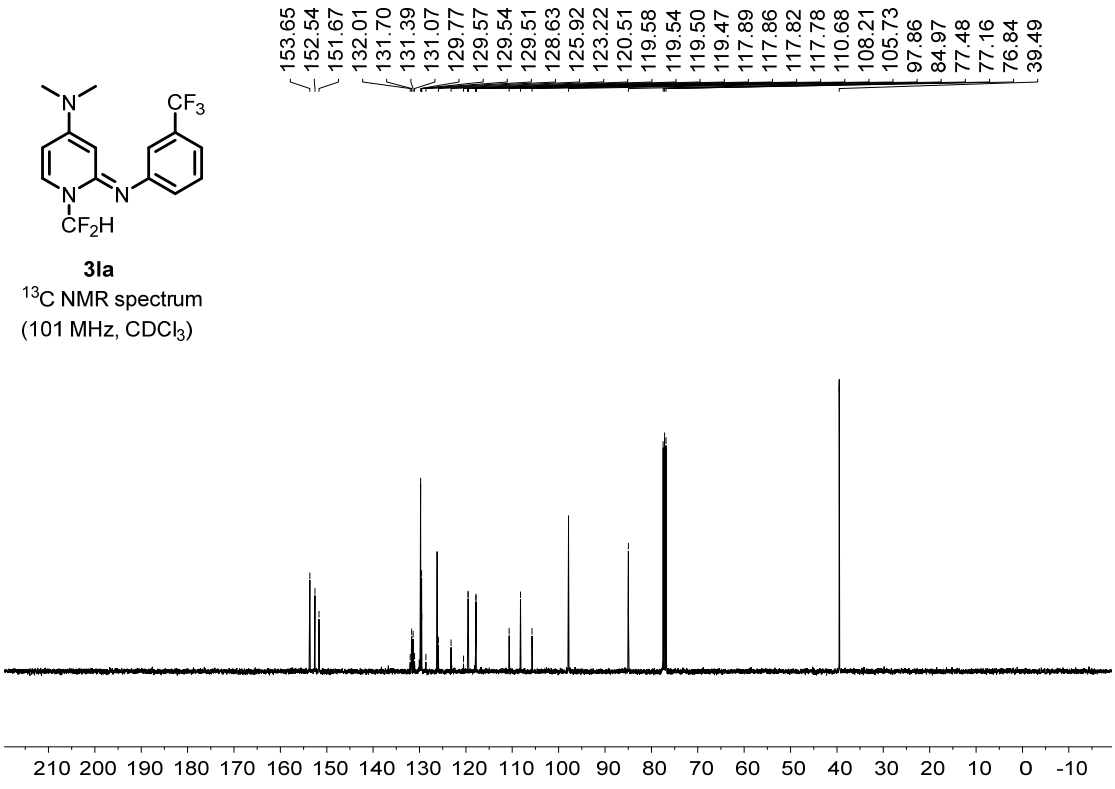
3ka

HRMS spectrum
by Waters G2-XS QTOF
mass spectrometer



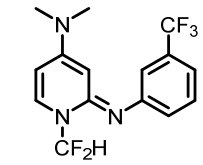
3la

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



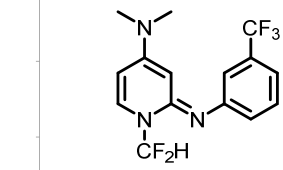
3la

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



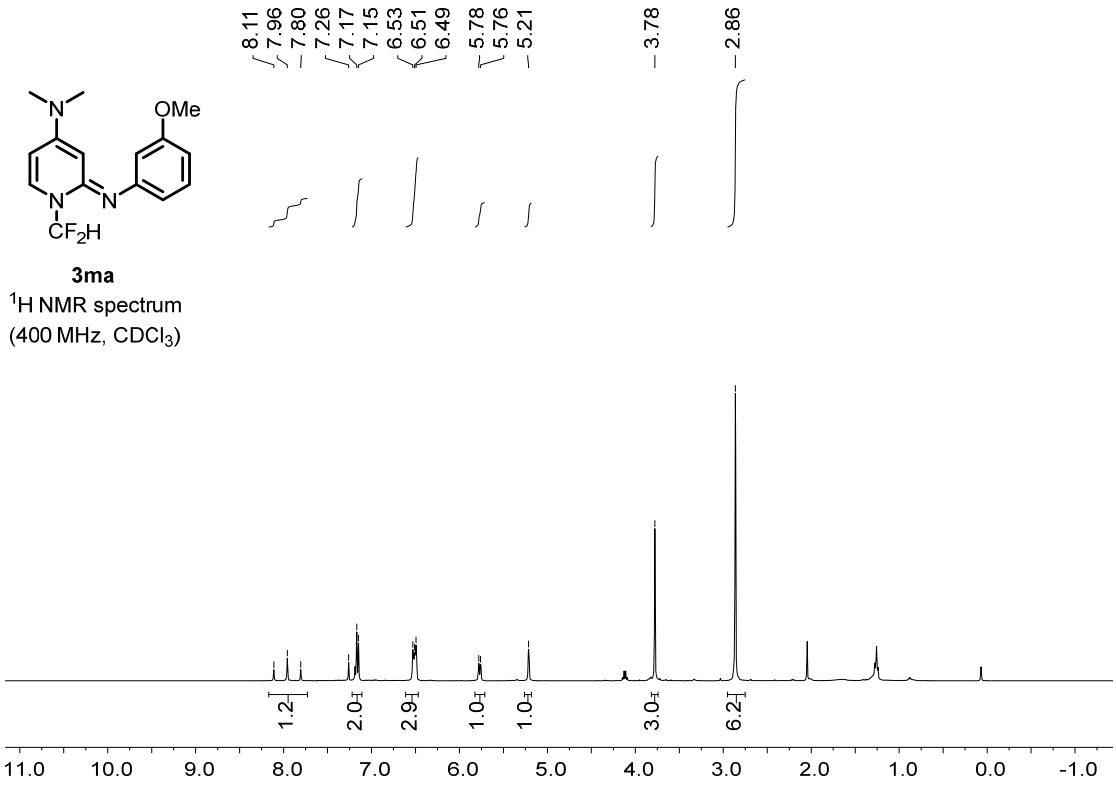
3la

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



3la

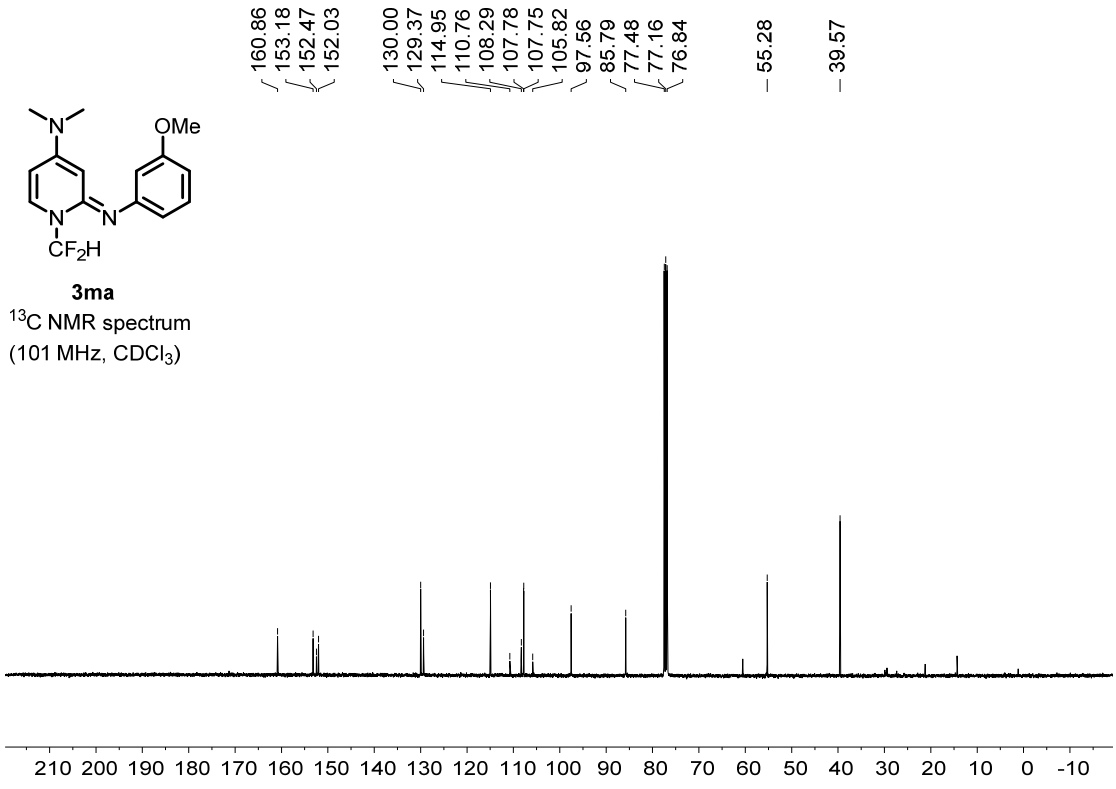
HRMS spectrum
by Waters G2-XS QTOF
mass spectrometer



3ma

^{1}H NMR spectrum

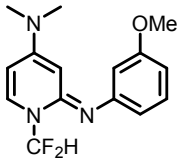
(400 MHz, $CDCl_3$)



3ma

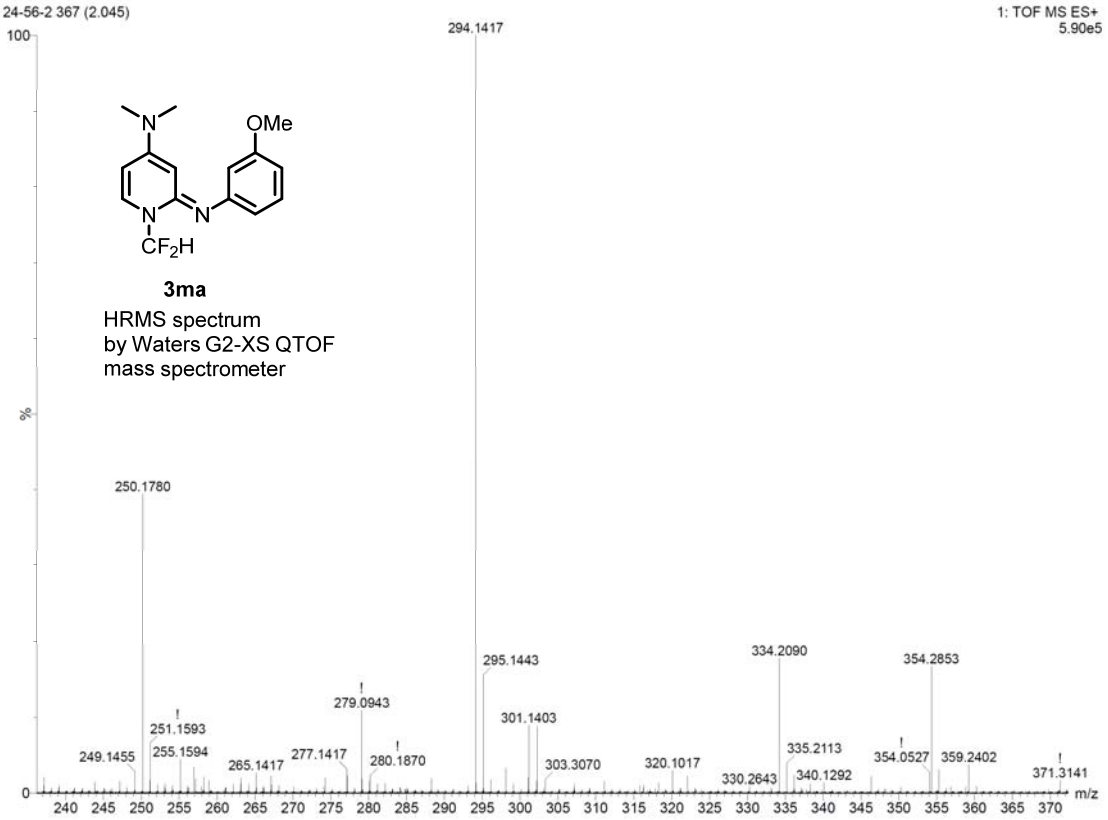
^{13}C NMR spectrum

(101 MHz, $CDCl_3$)



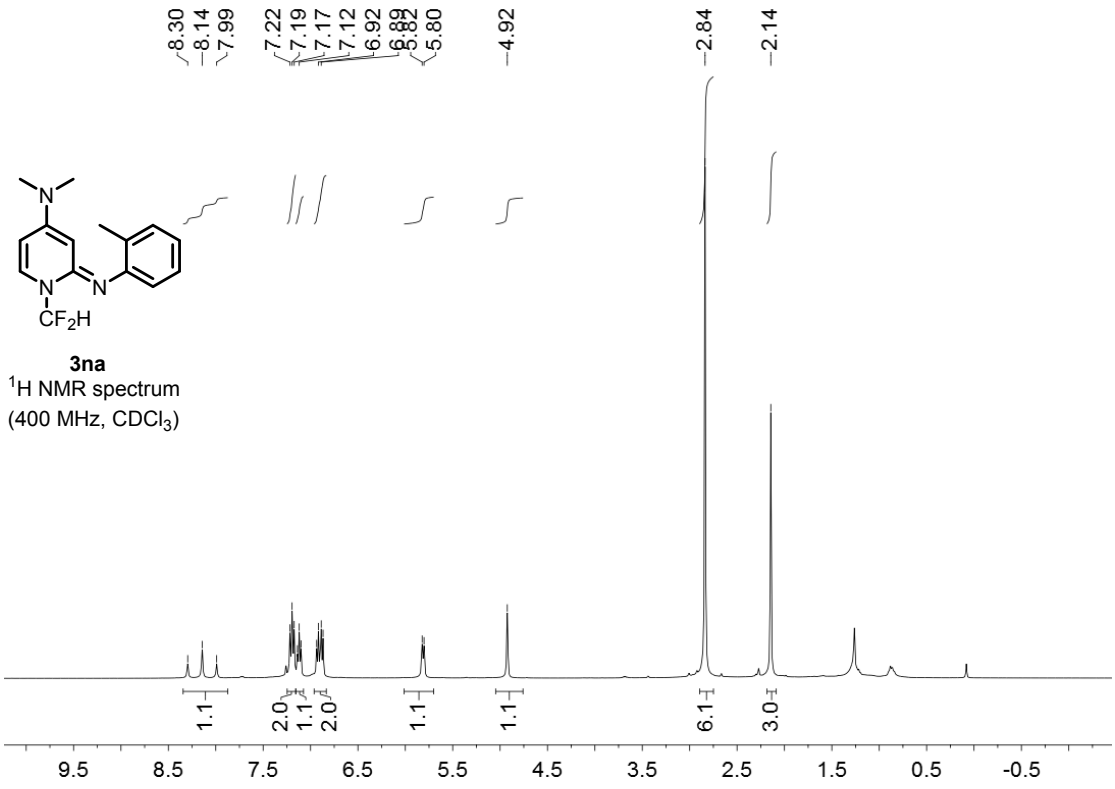
3ma

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



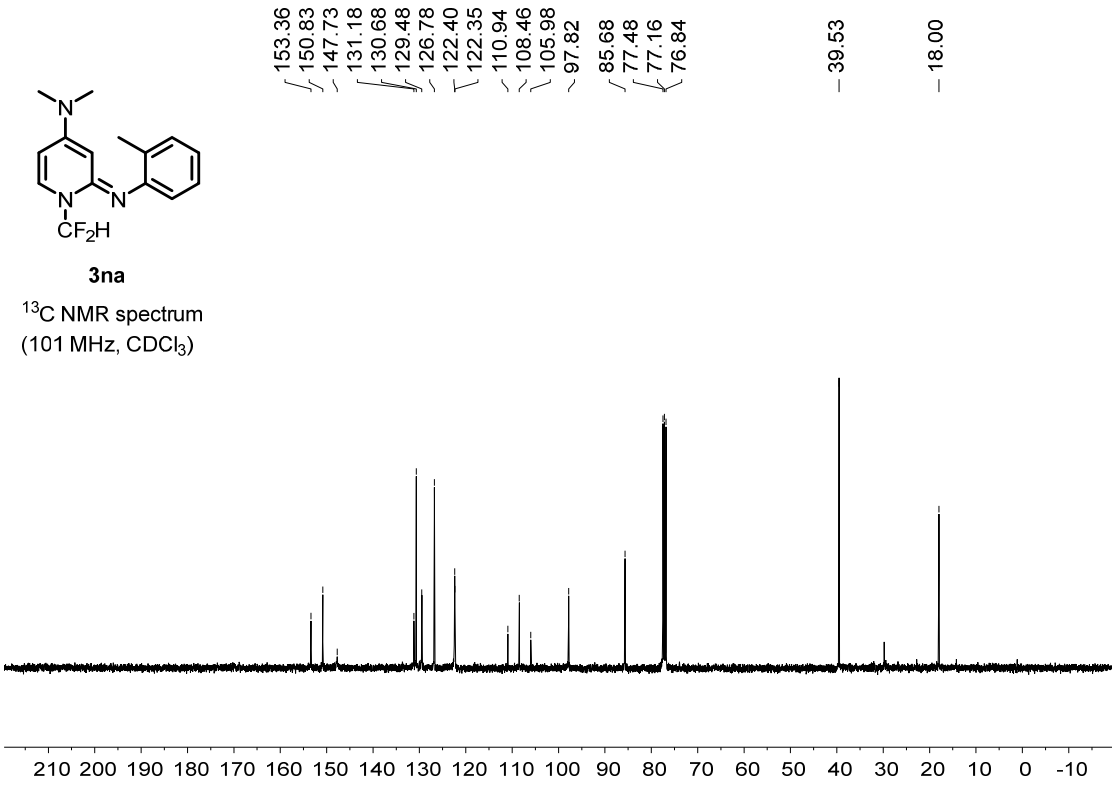
3ma

HRMS spectrum
by Waters G2-XS QTOF
mass spectrometer



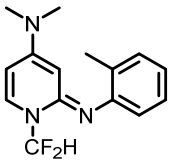
3na

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



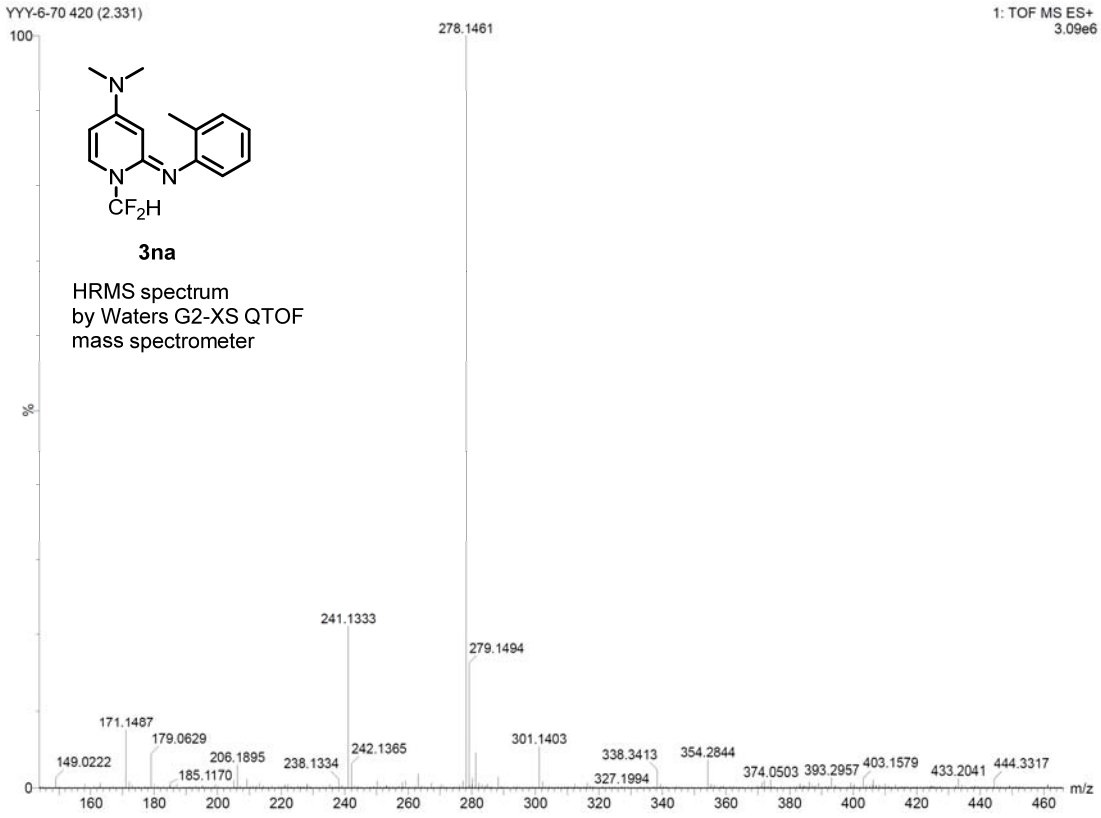
3na

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



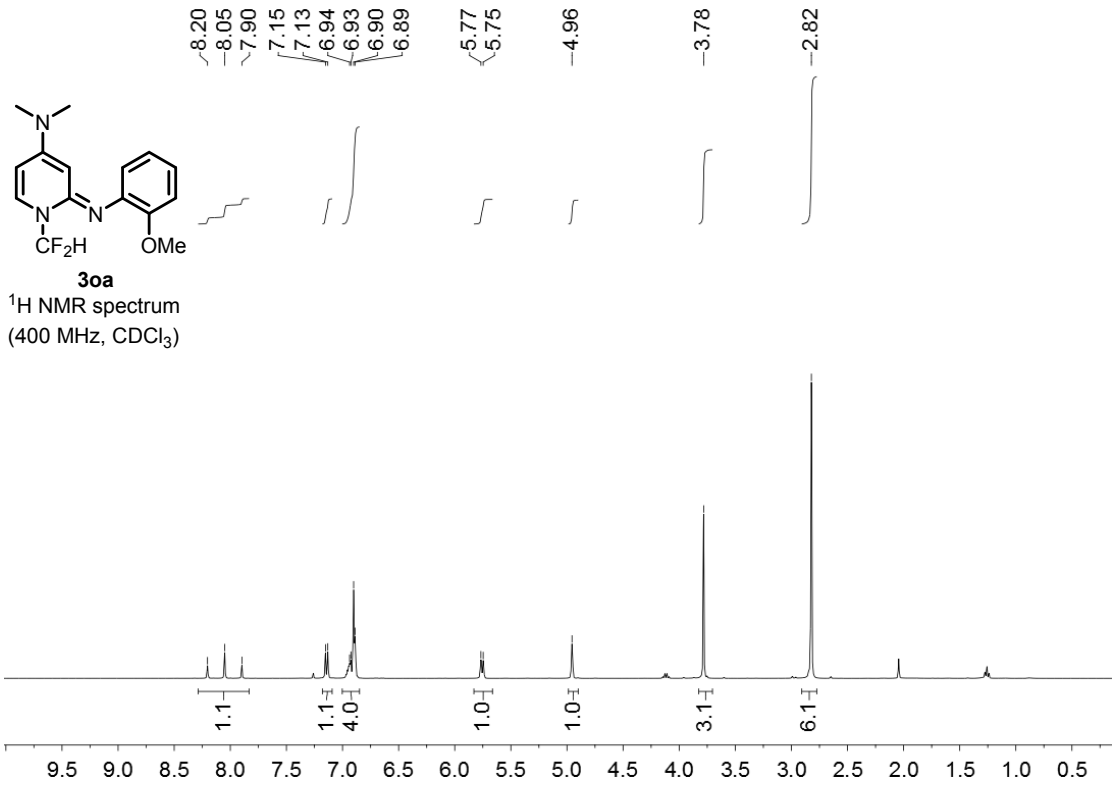
3na

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



3na

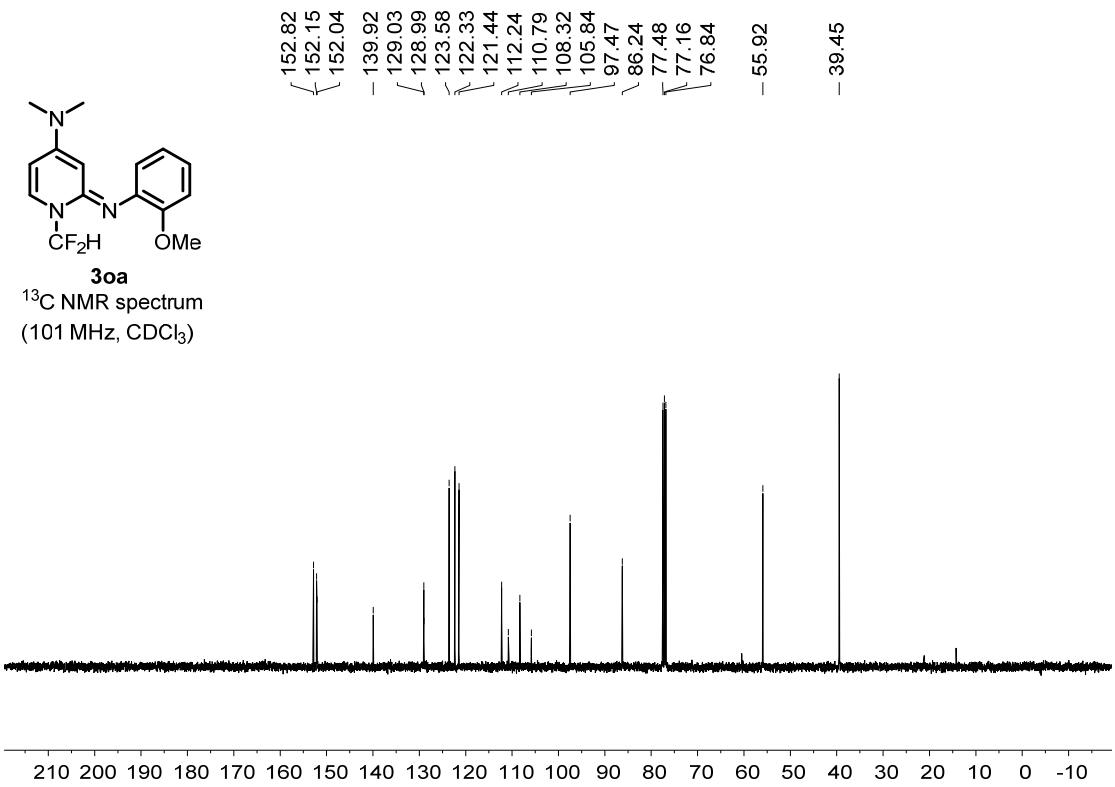
HRMS spectrum
by Waters G2-XS QTOF
mass spectrometer



3oa

^{1}H NMR spectrum

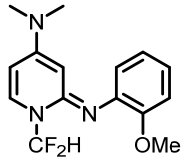
(400 MHz, $CDCl_3$)



3oa

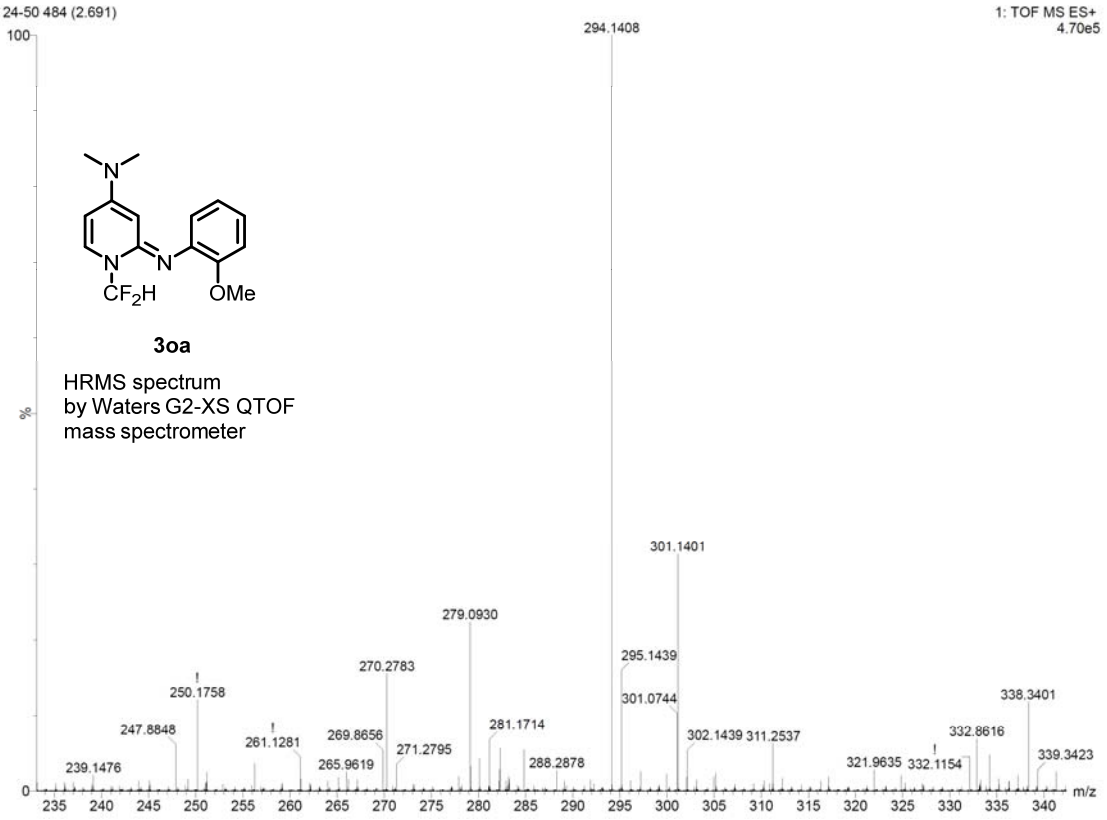
^{13}C NMR spectrum

(101 MHz, $CDCl_3$)



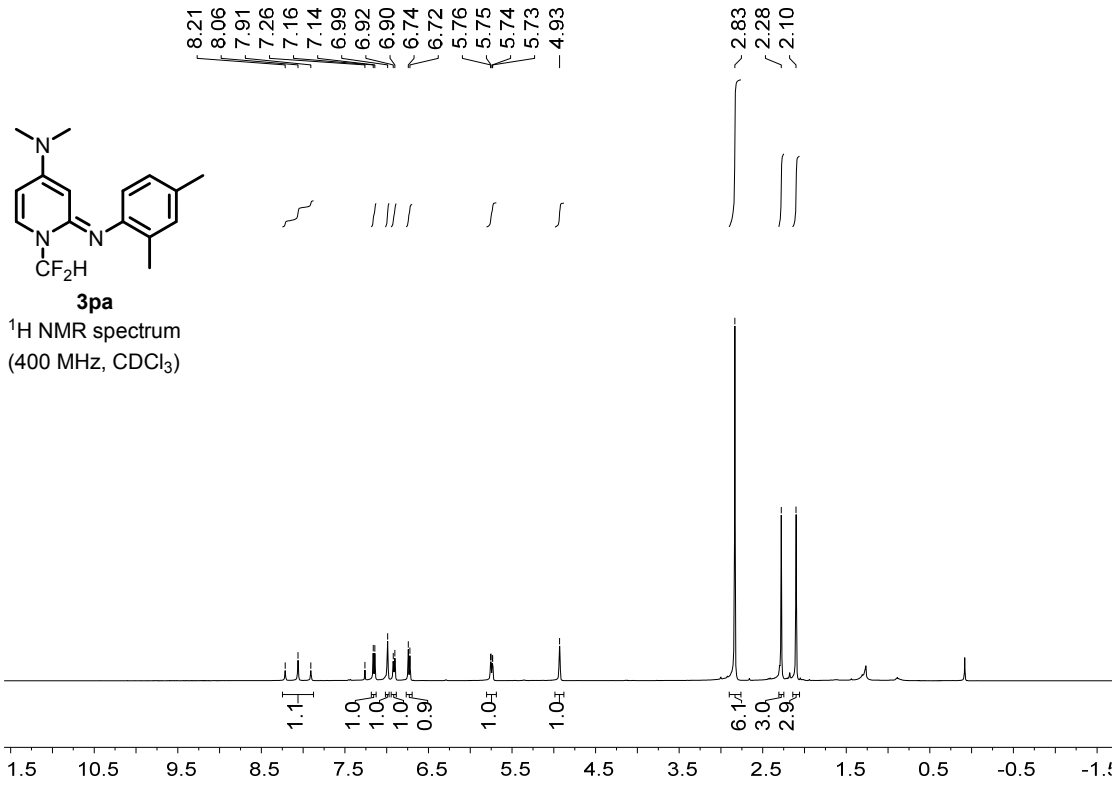
3oa

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



3oa

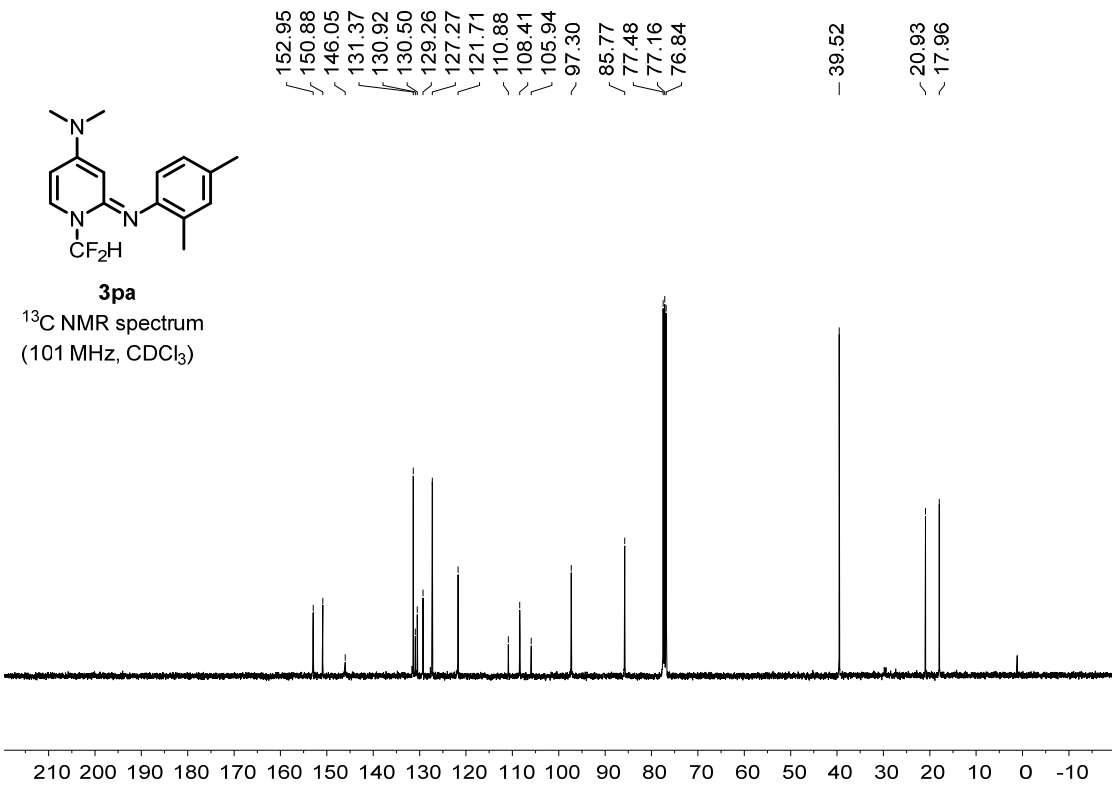
HRMS spectrum
by Waters G2-XS QTOF
mass spectrometer



3pa

^{1}H NMR spectrum

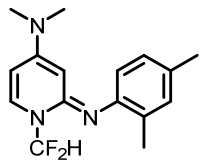
(400 MHz, $CDCl_3$)



3pa

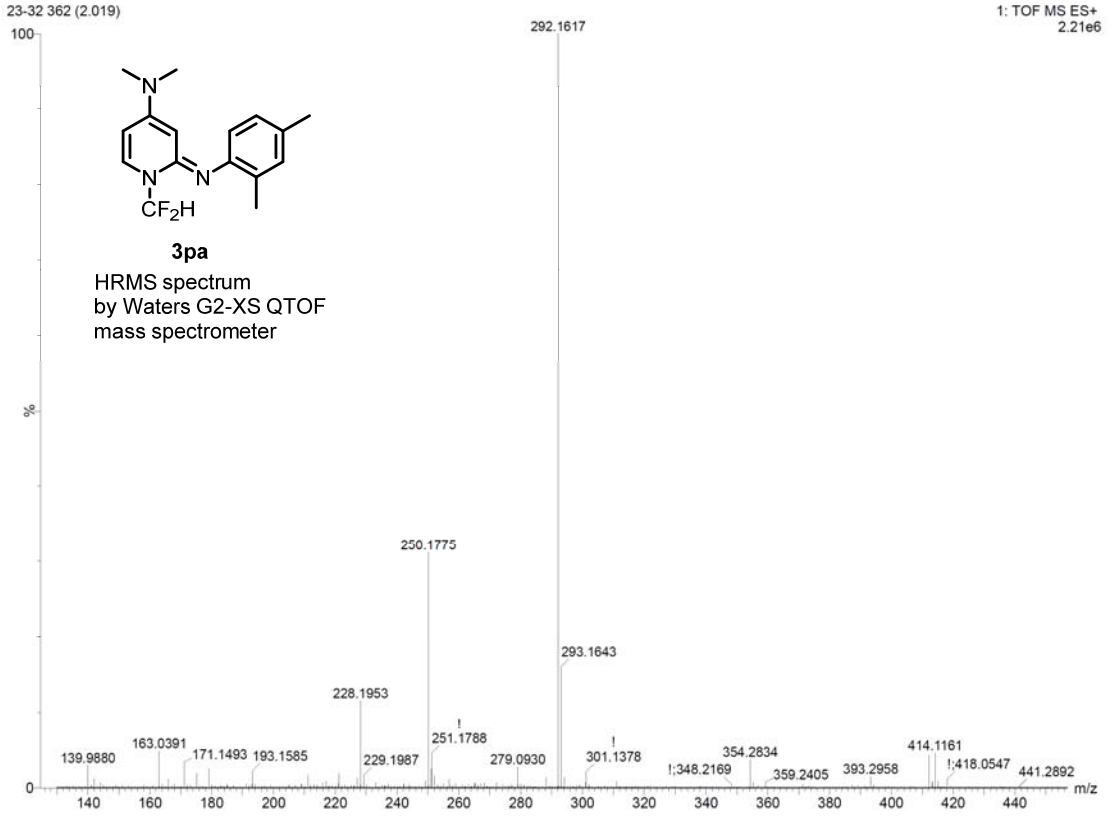
^{13}C NMR spectrum

(101 MHz, $CDCl_3$)



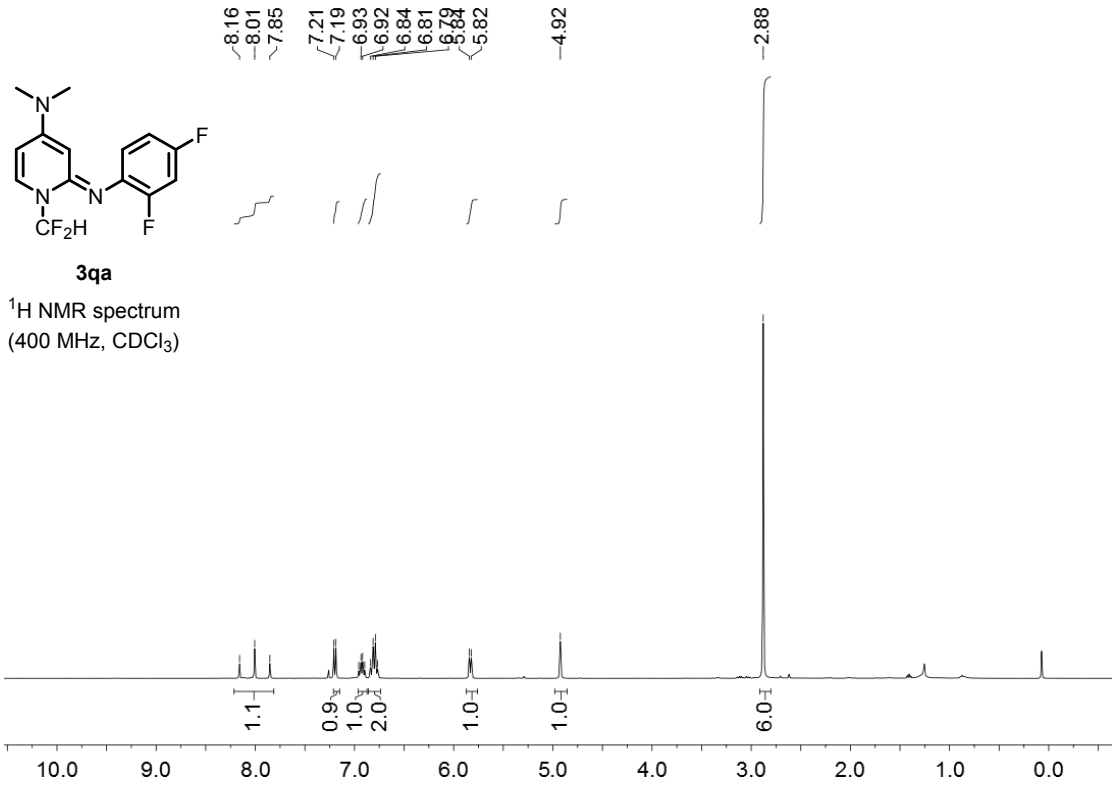
3pa

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



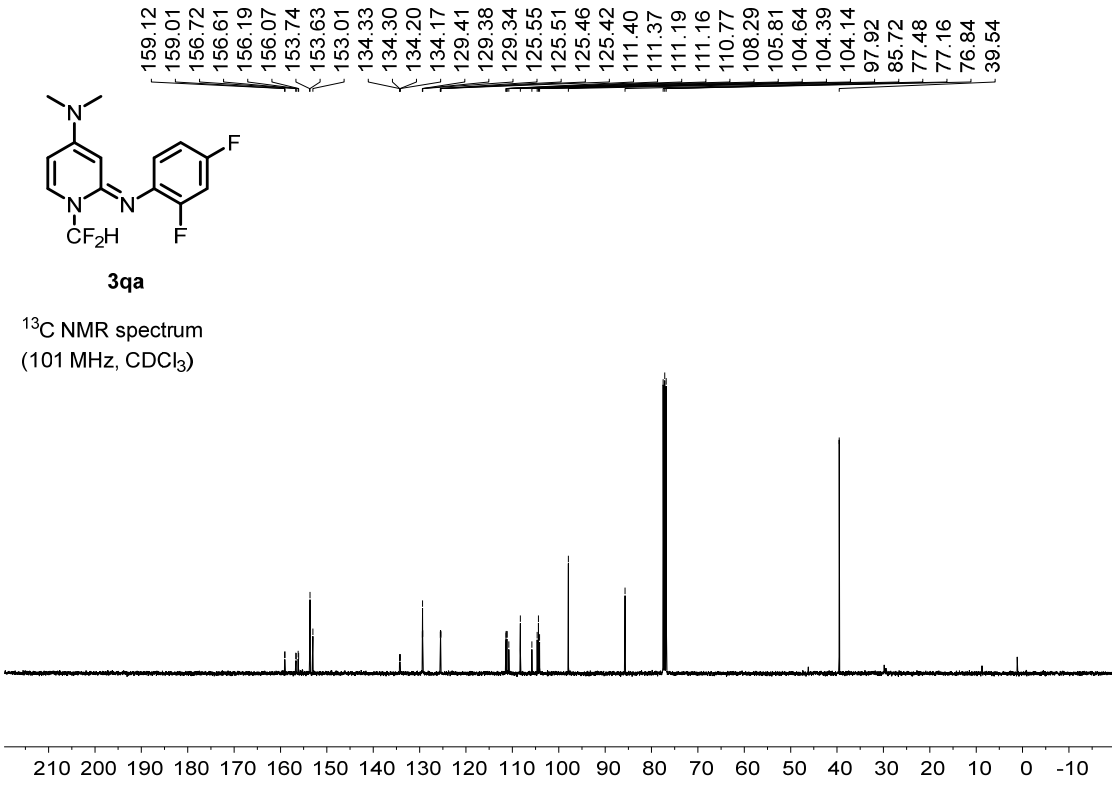
3pa

HRMS spectrum
by Waters G2-XS QTOF
mass spectrometer



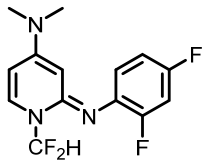
3qa

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



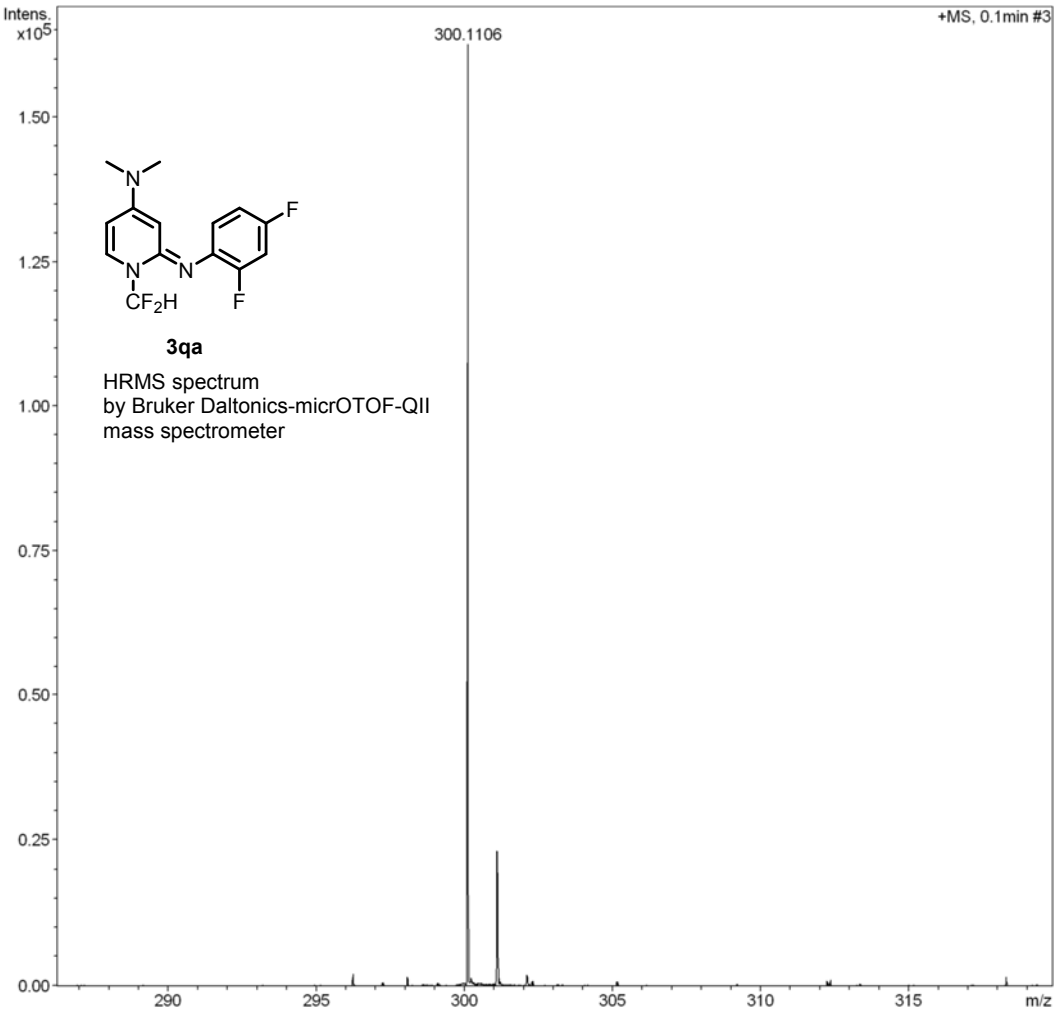
3qa

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



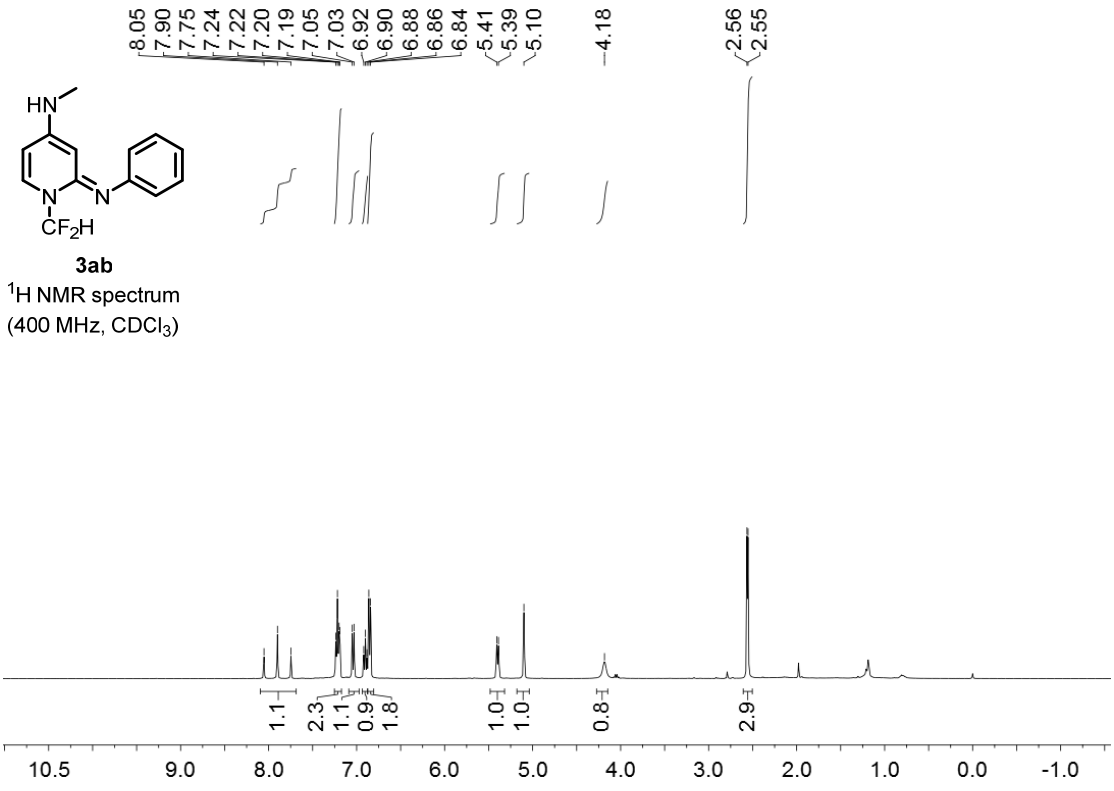
3qa

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



3qa

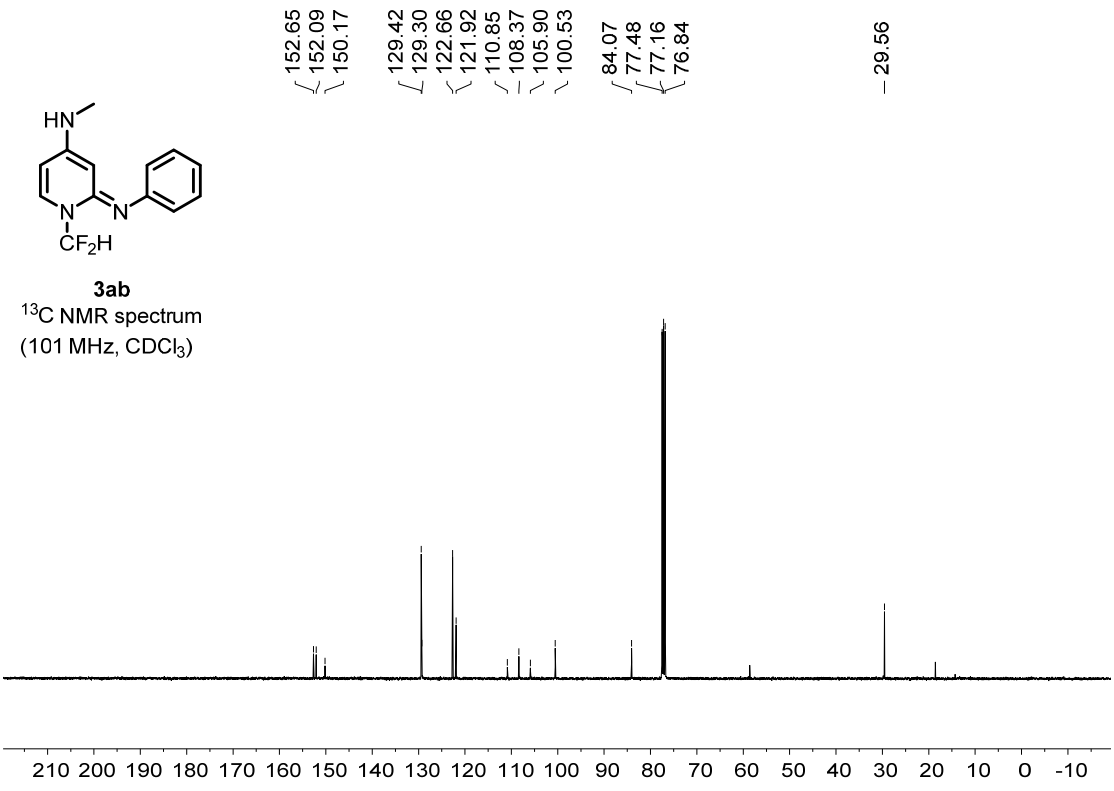
HRMS spectrum
by Bruker Daltonics-micrOTOF-QII
mass spectrometer



3ab

^{1}H NMR spectrum

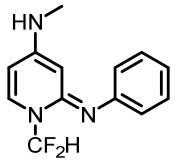
(400 MHz, $CDCl_3$)



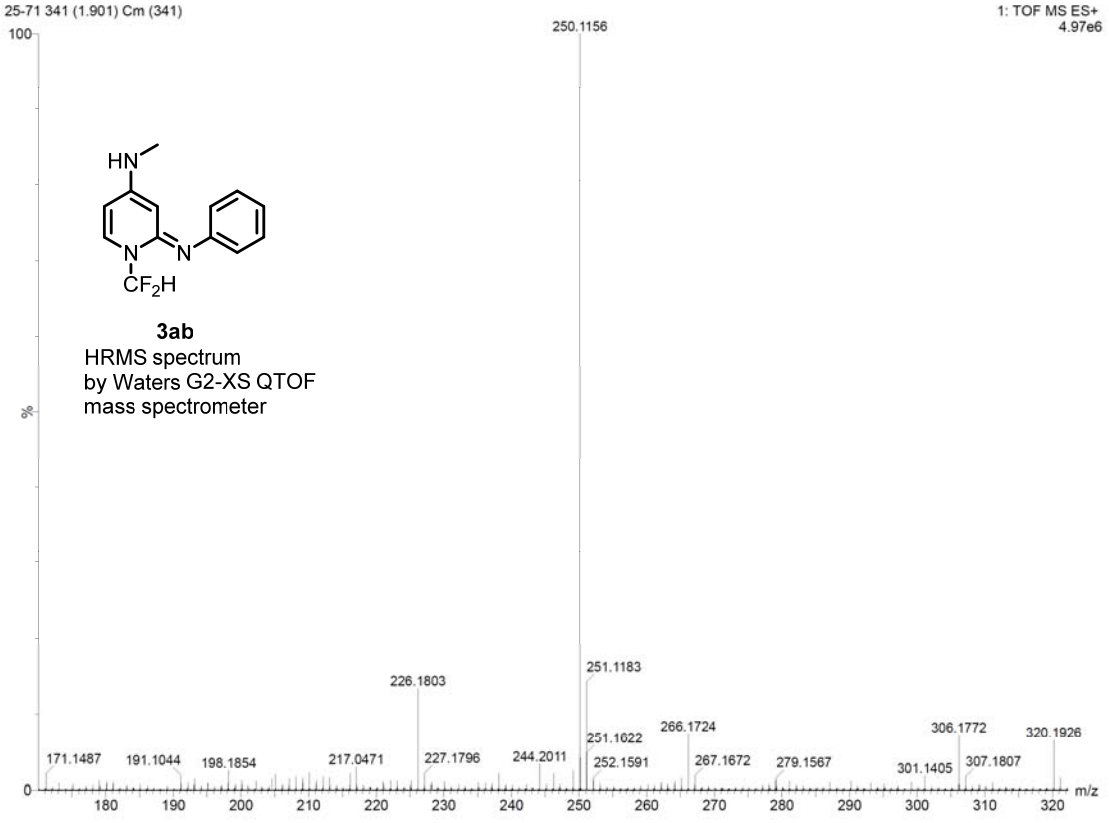
3ab

^{13}C NMR spectrum

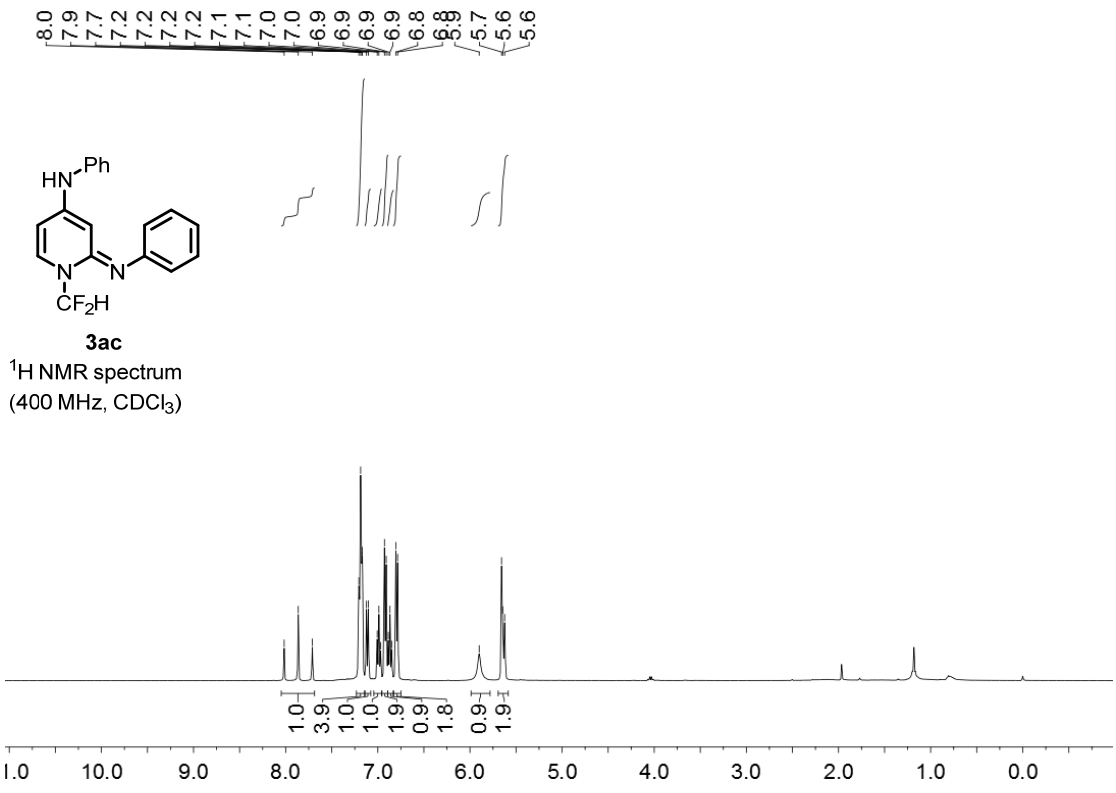
(101 MHz, $CDCl_3$)



3ab
^{19}F NMR spectrum
(376 MHz, $CDCl_3$)



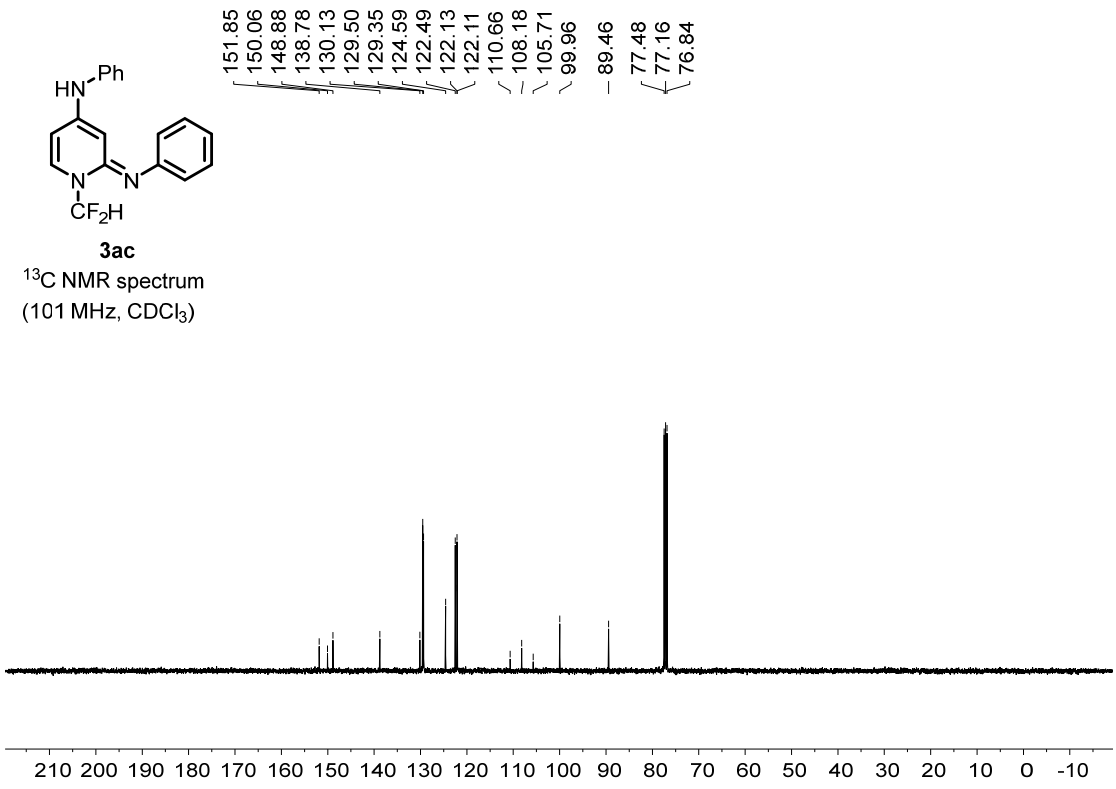
3ab
HRMS spectrum
by Waters G2-XS QTOF
mass spectrometer



3ac

^{1}H NMR spectrum

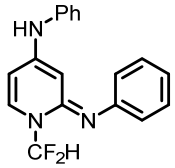
(400 MHz, $CDCl_3$)



3ac

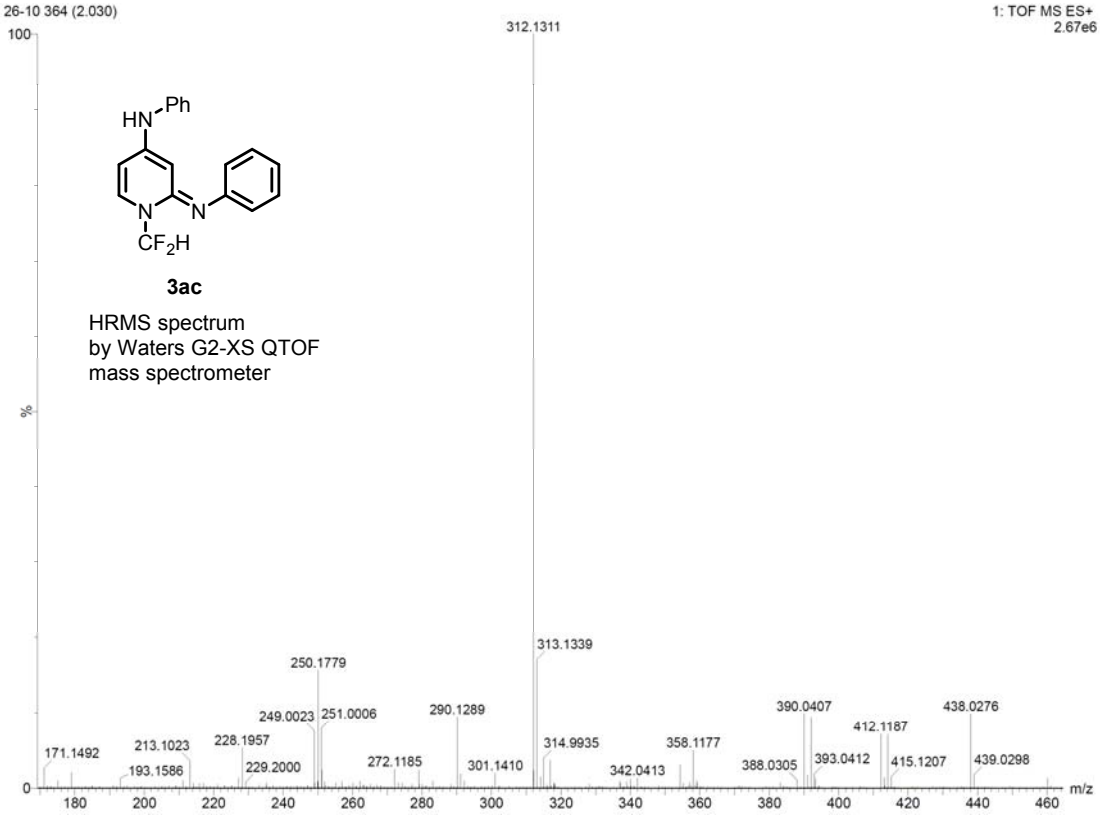
^{13}C NMR spectrum

(101 MHz, $CDCl_3$)



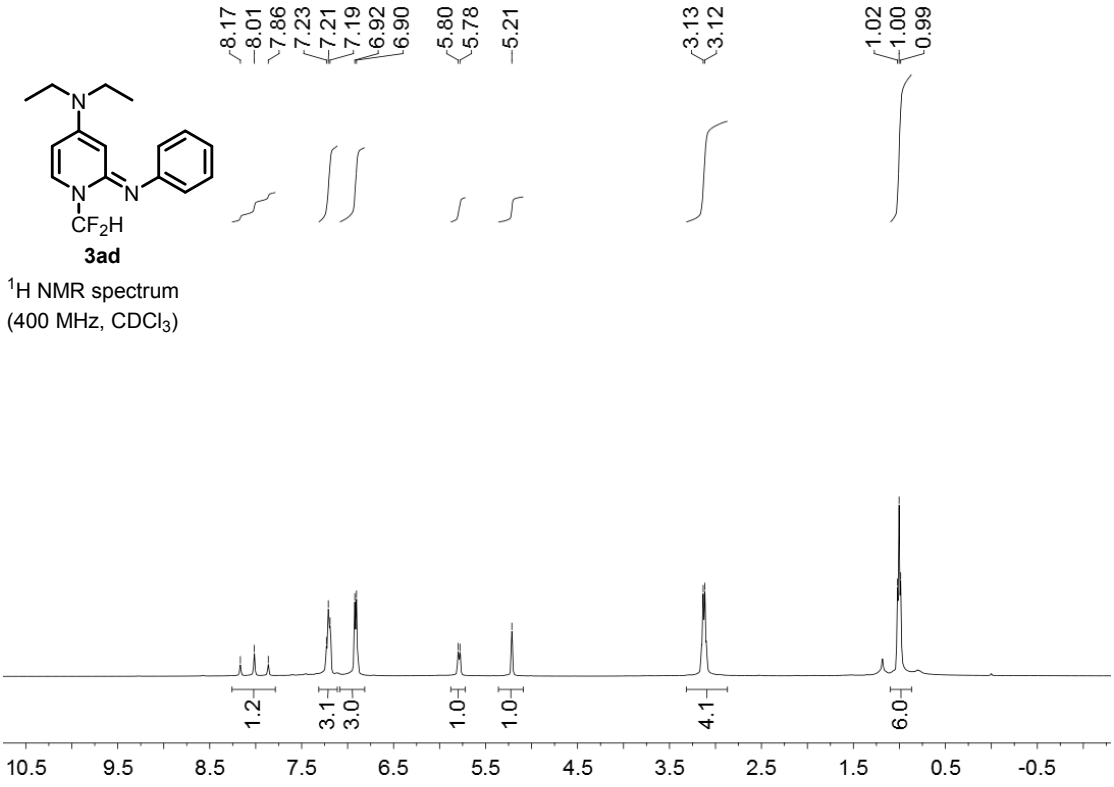
3ac

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



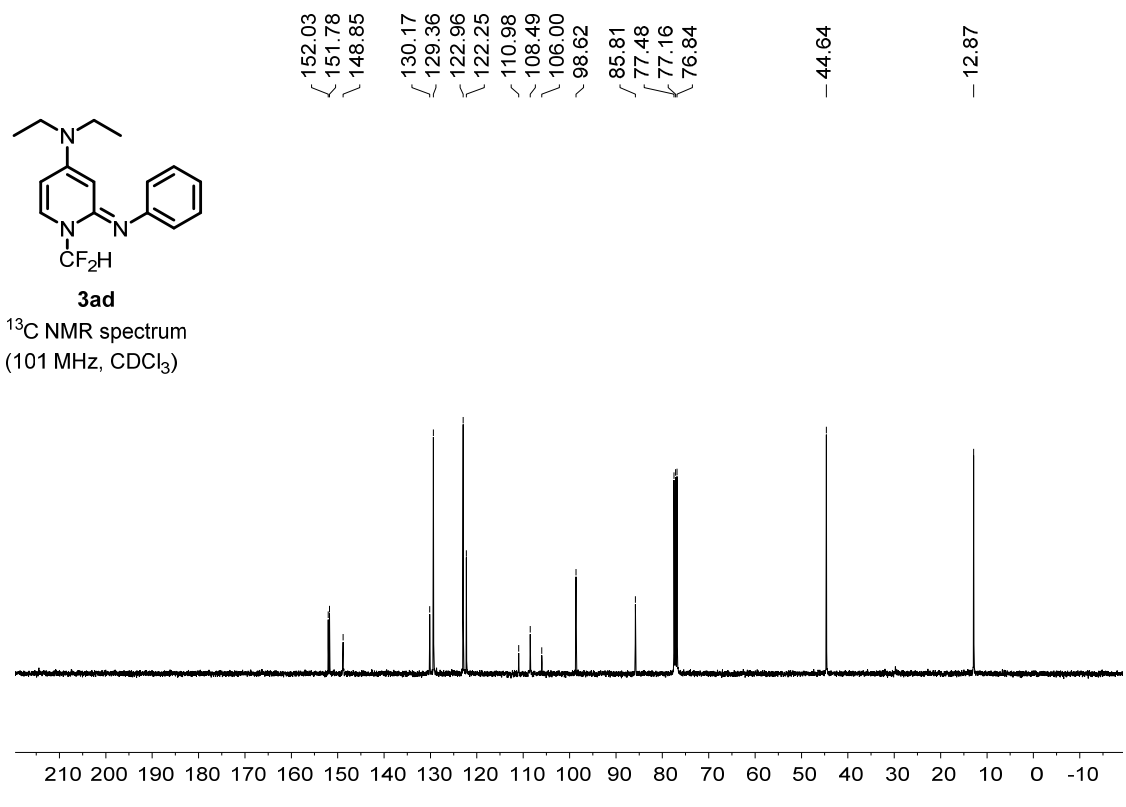
3ac

HRMS spectrum
by Waters G2-XS QTOF
mass spectrometer



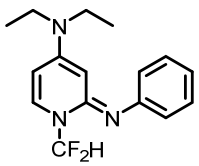
3ad

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



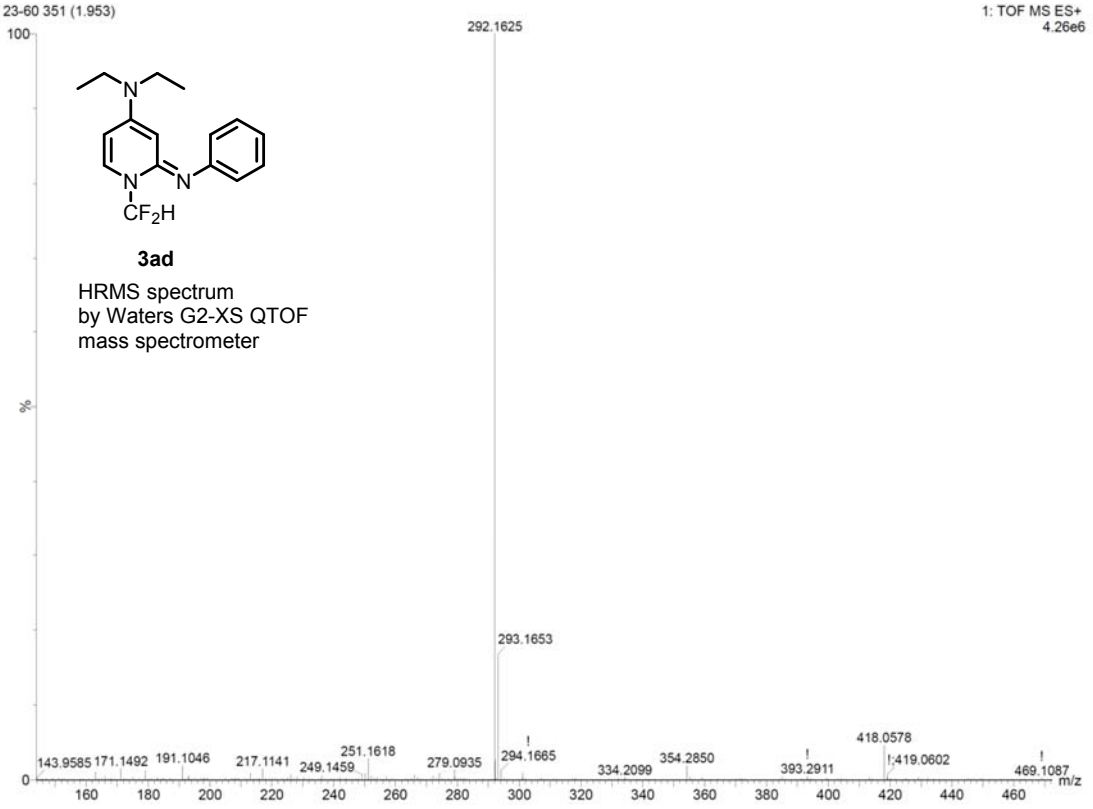
3ad

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



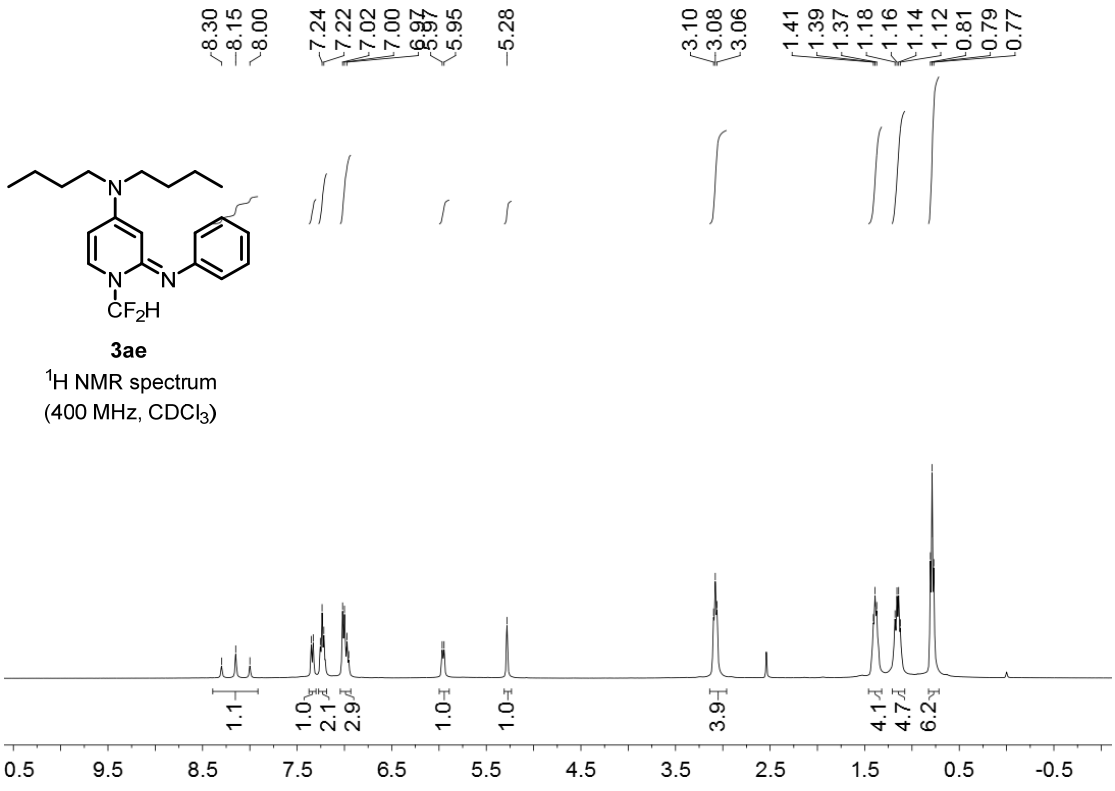
3ad

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



3ad

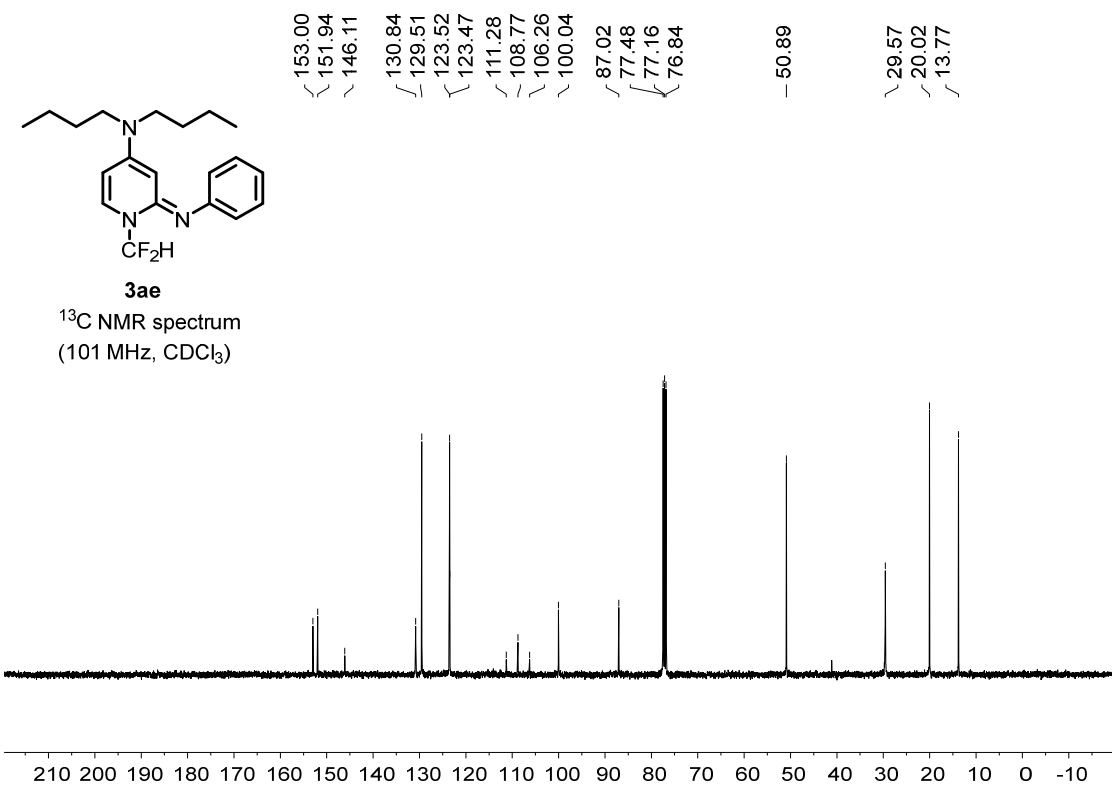
HRMS spectrum
by Waters G2-XS QTOF
mass spectrometer



3ae

^{1}H NMR spectrum

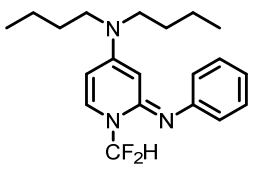
(400 MHz, $CDCl_3$)



3ae

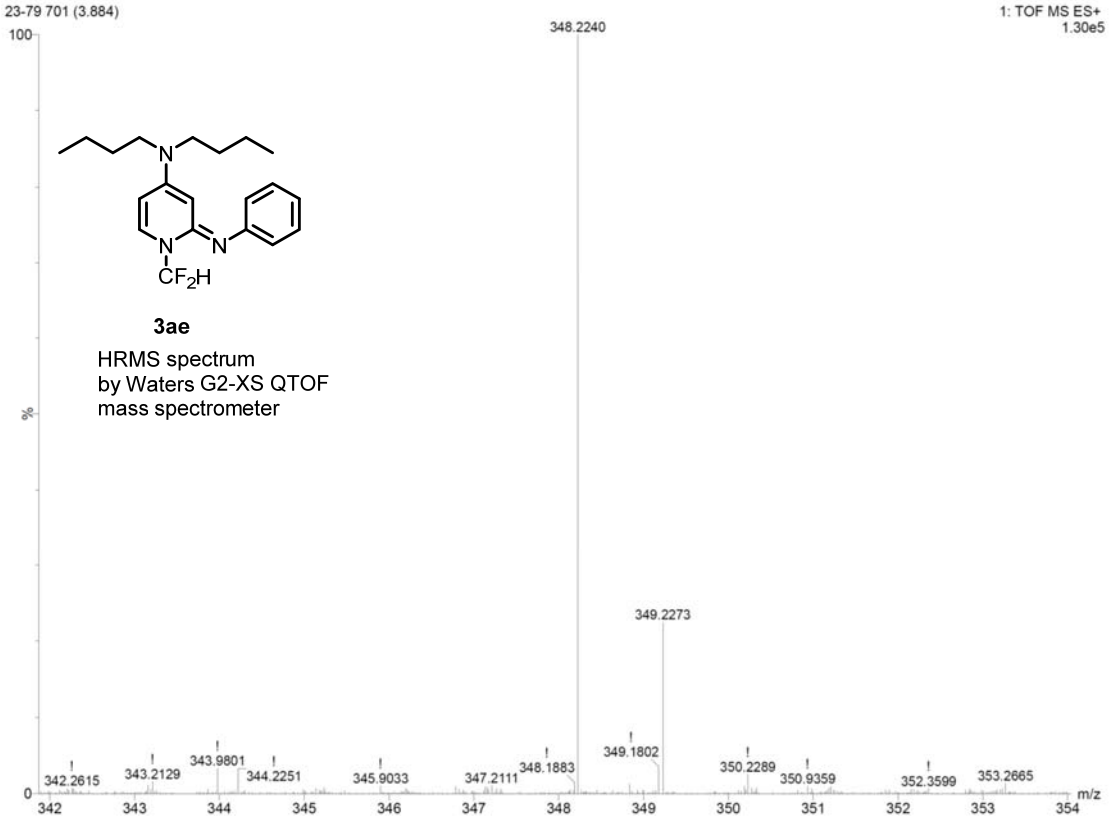
^{13}C NMR spectrum

(101 MHz, $CDCl_3$)



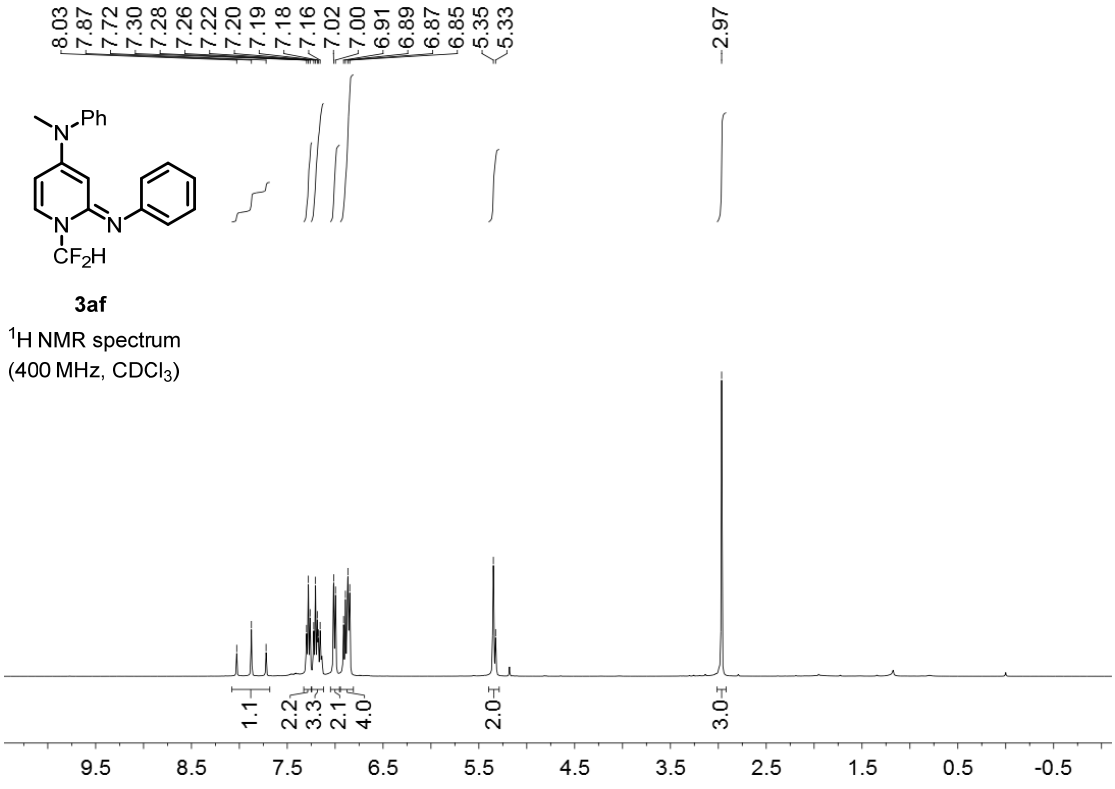
3ae

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



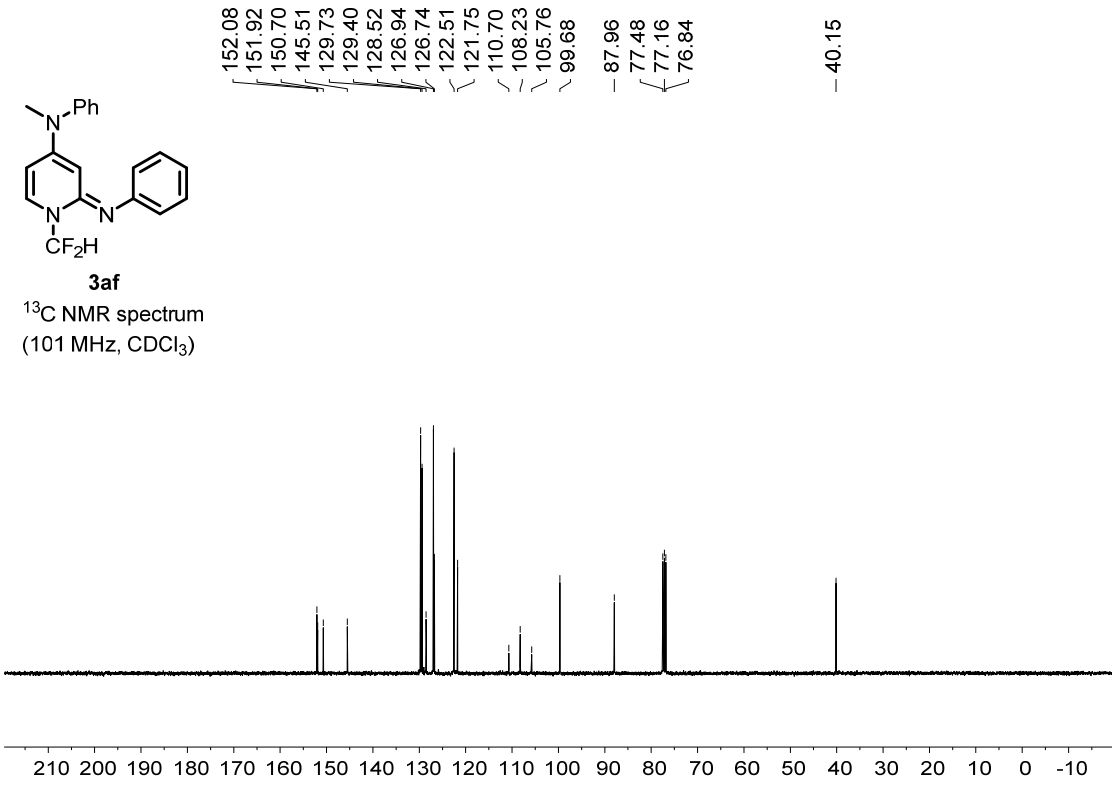
3ae

HRMS spectrum
by Waters G2-XS QTOF
mass spectrometer



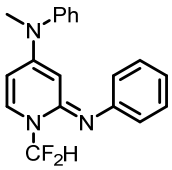
3af

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



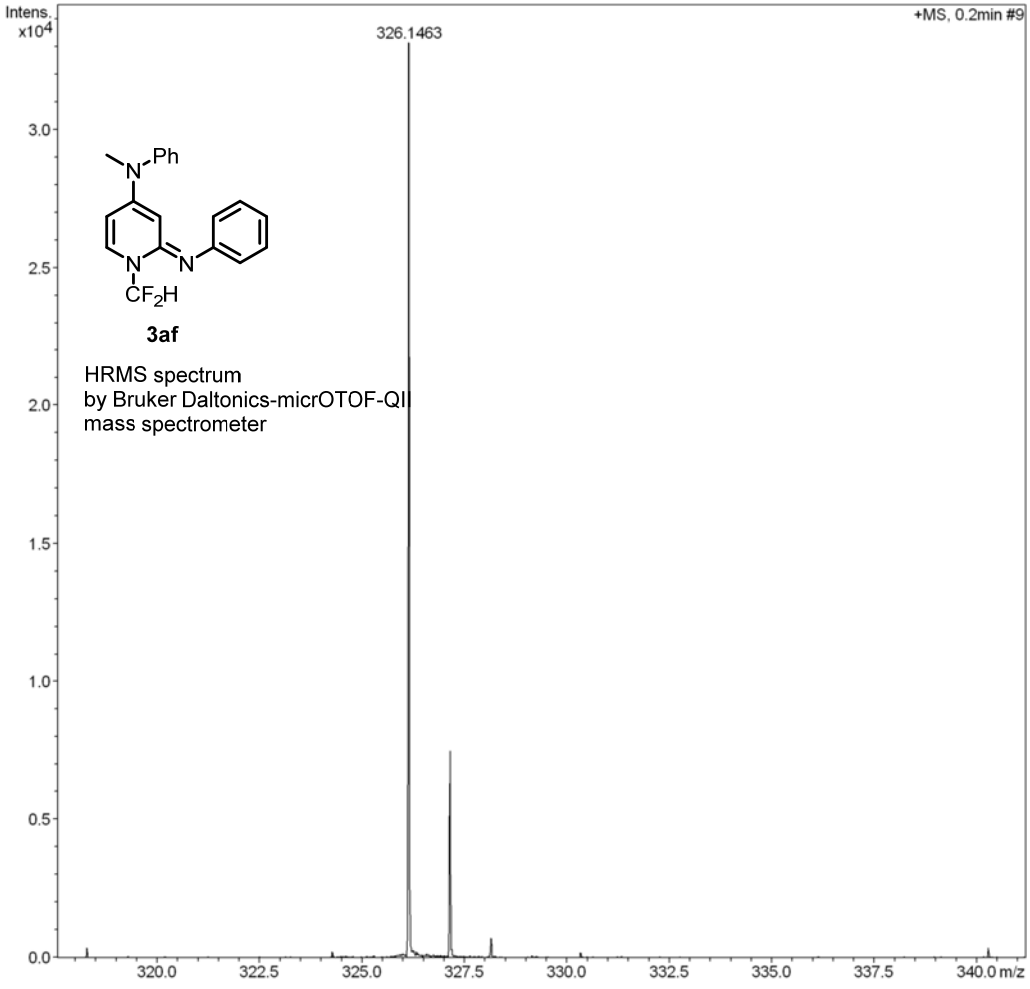
3af

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



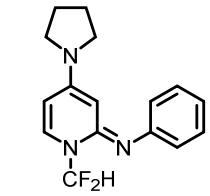
3af

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



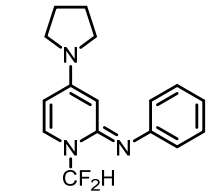
3af

HRMS spectrum
by Bruker Daltonics-micrOTOF-QII
mass spectrometer



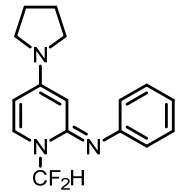
3ag

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



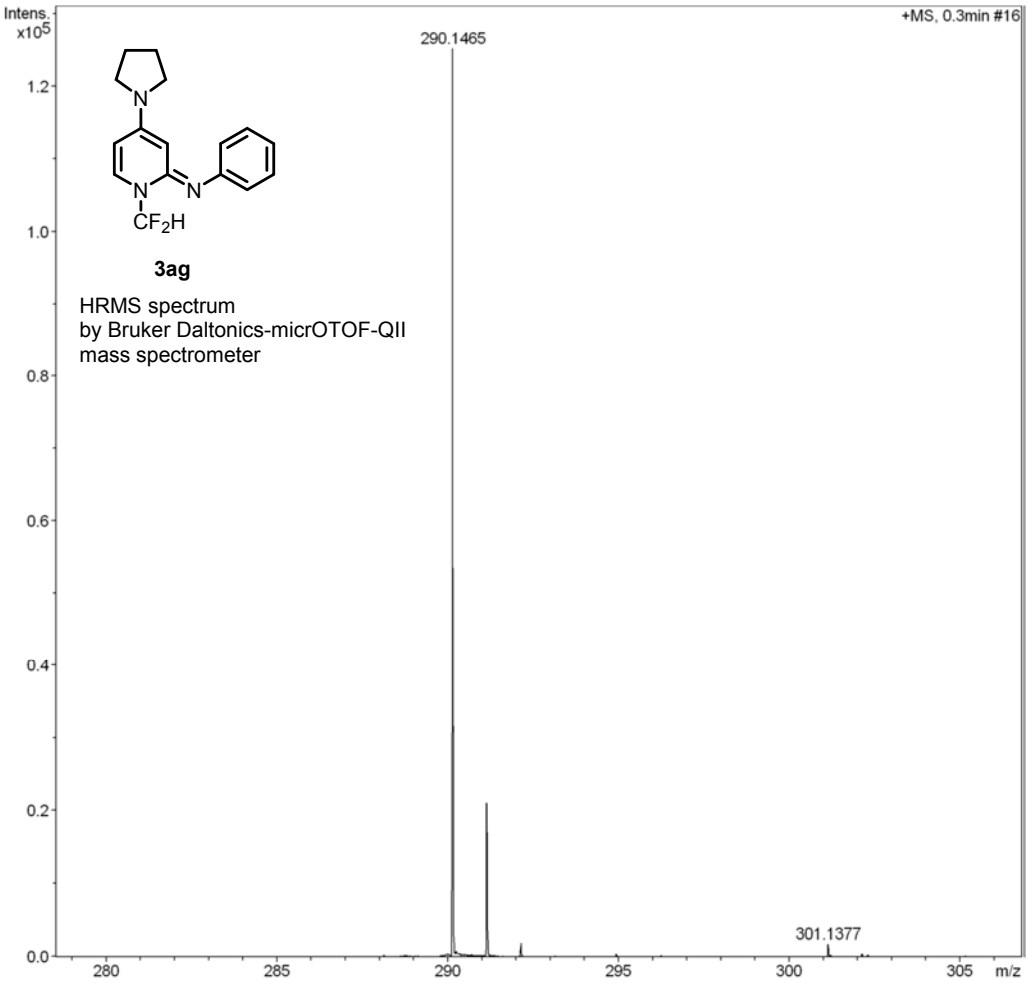
3ag

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



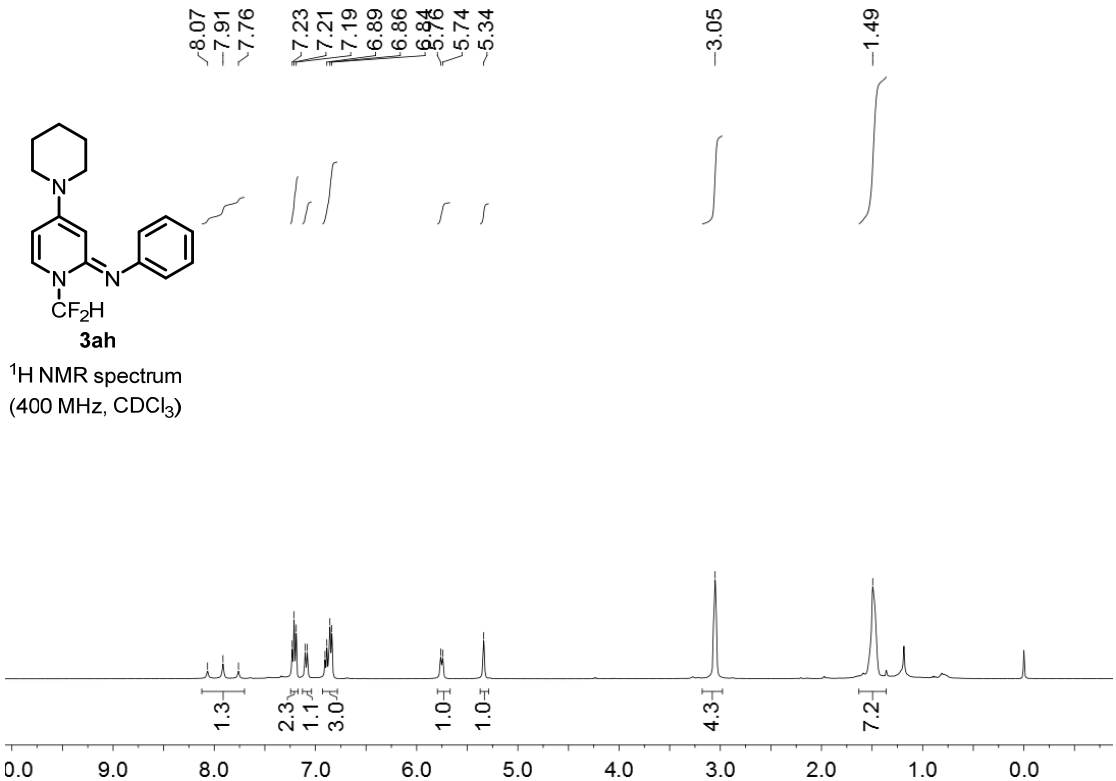
3ag

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



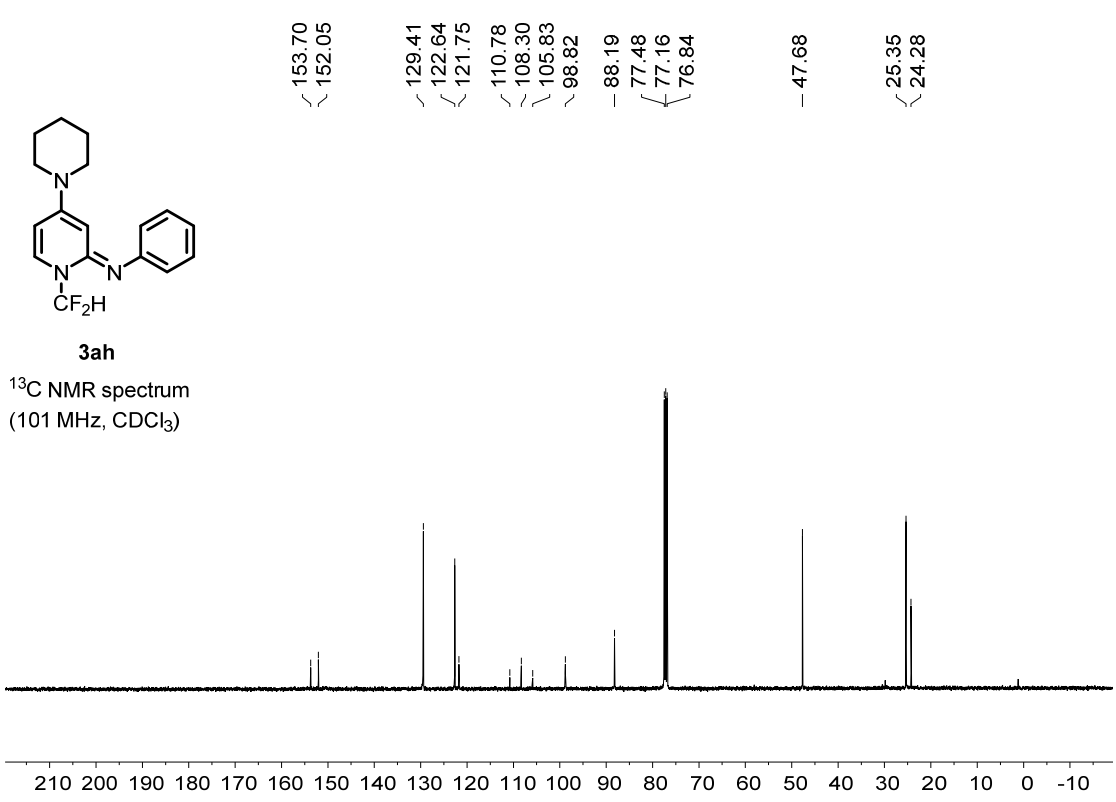
3ag

HRMS spectrum
by Bruker Daltonics-micrOTOF-QII
mass spectrometer



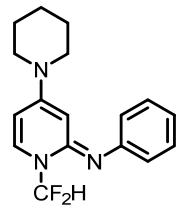
3ah

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



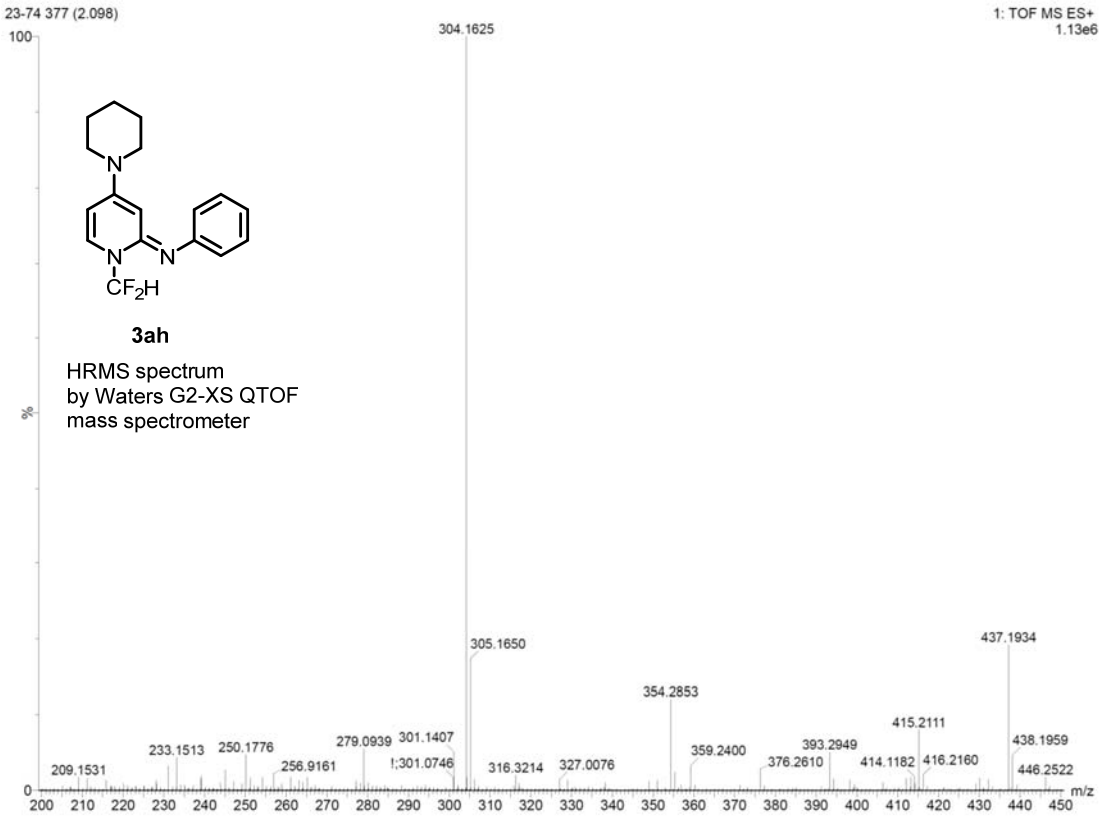
3ah

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



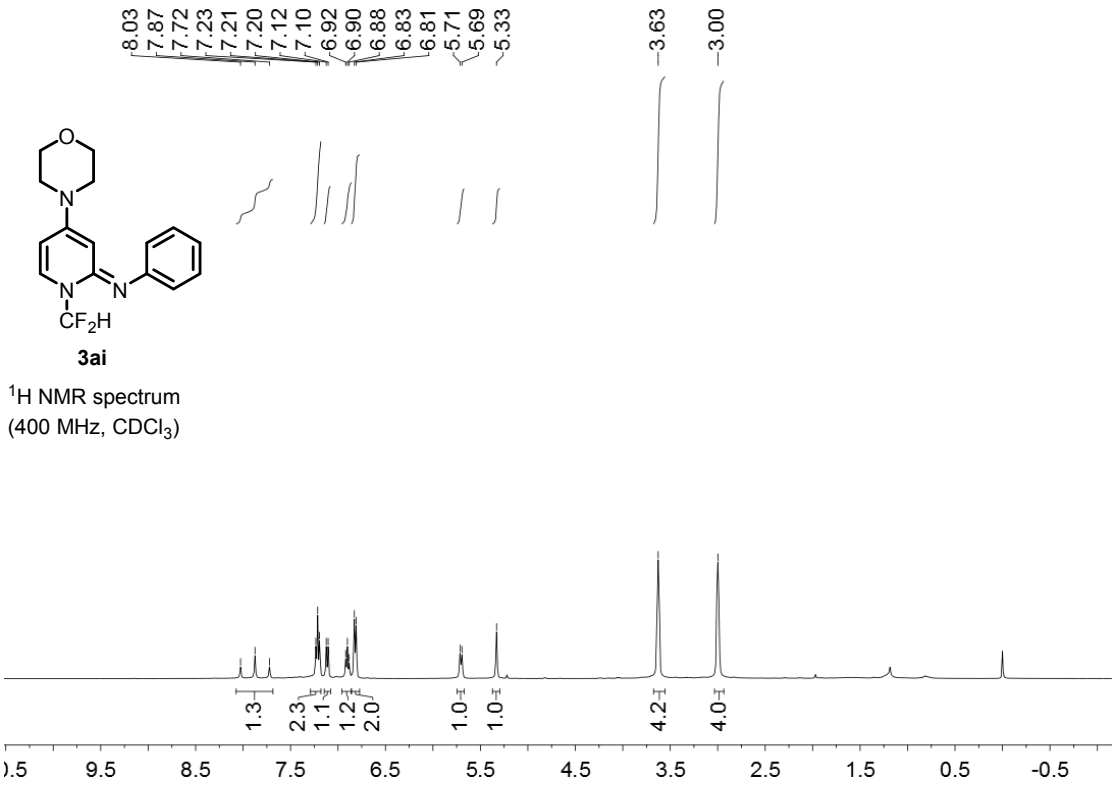
3ah

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



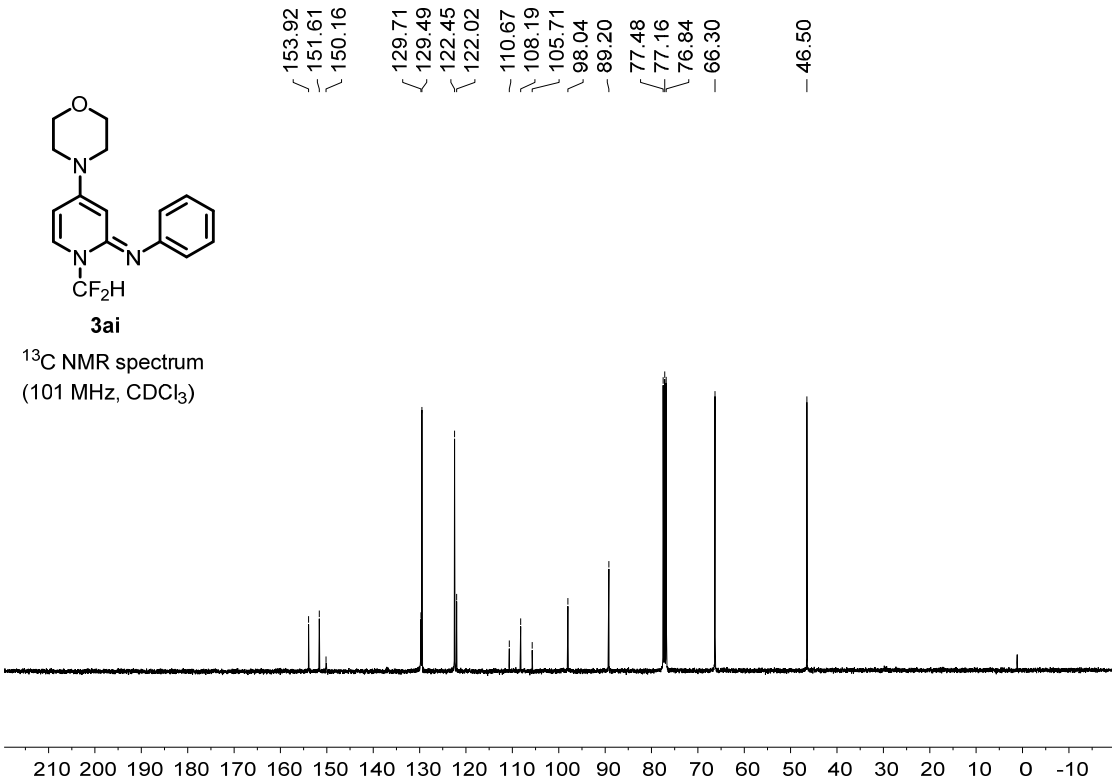
3ah

HRMS spectrum
by Waters G2-XS QTOF
mass spectrometer



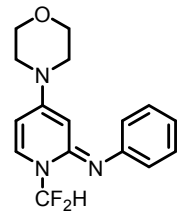
3ai

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



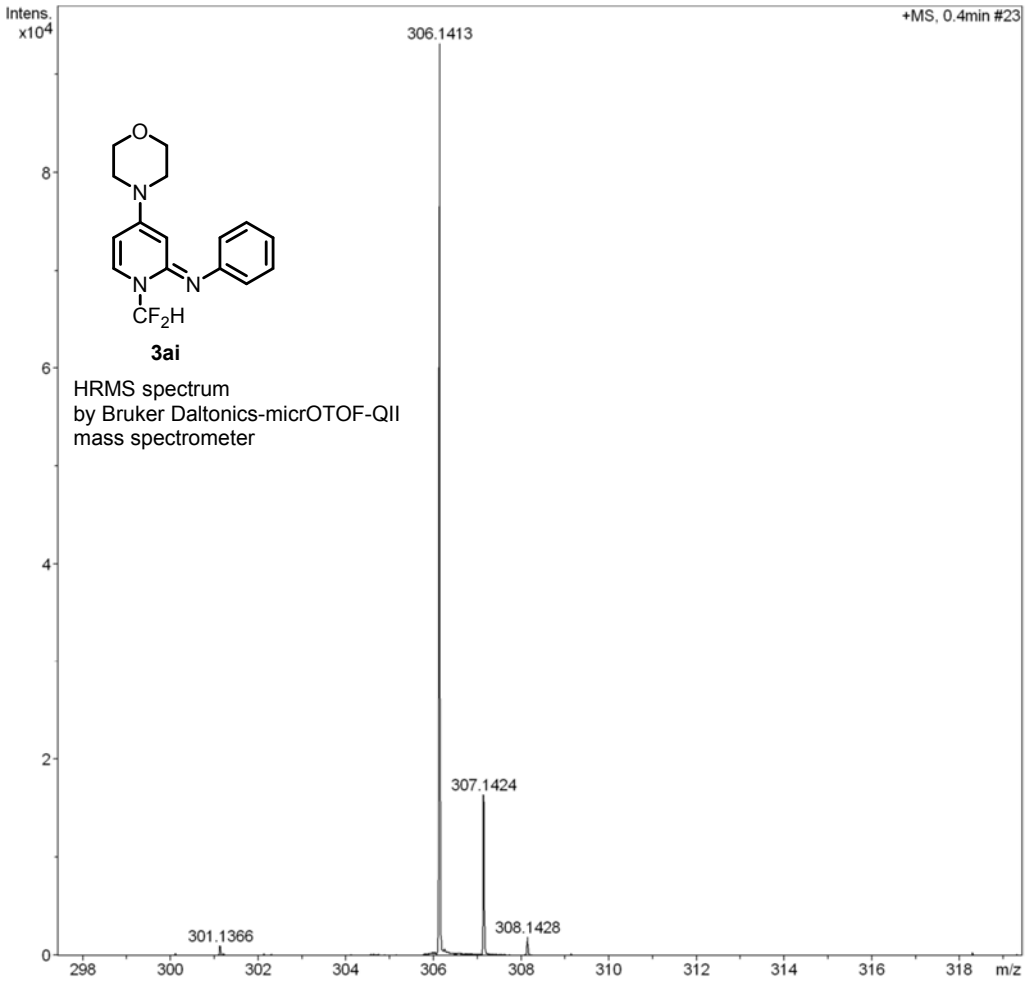
3ai

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



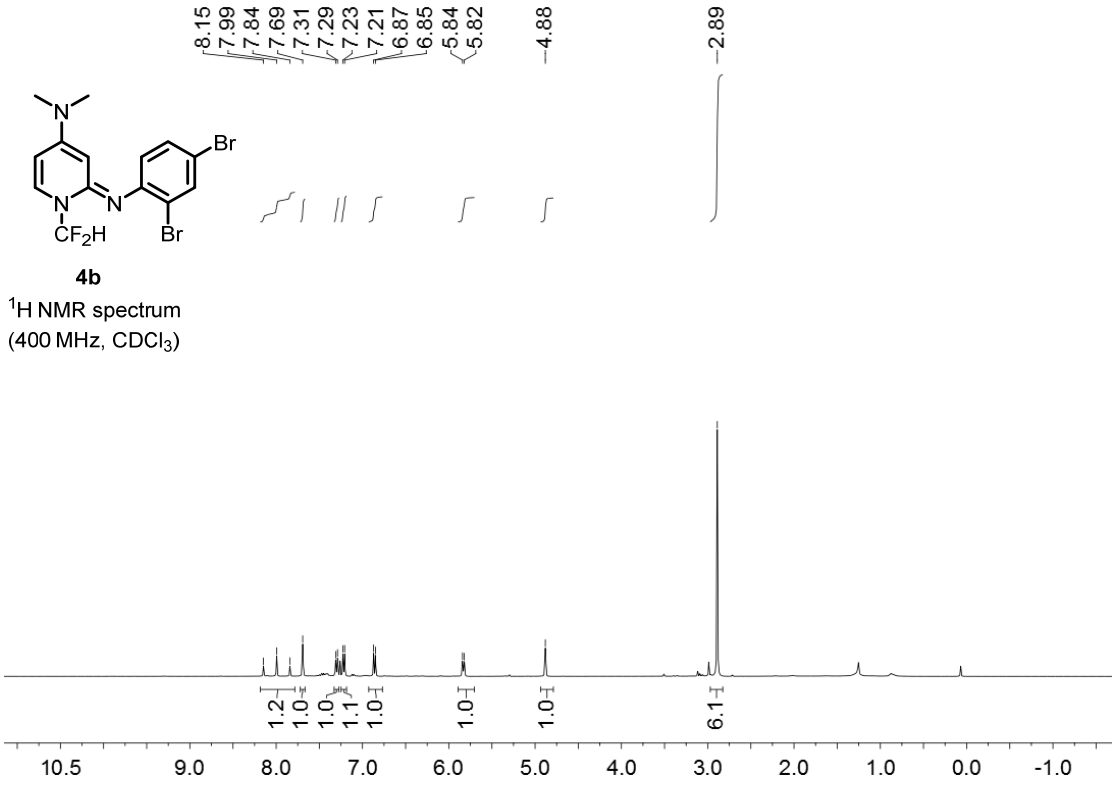
3ai

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



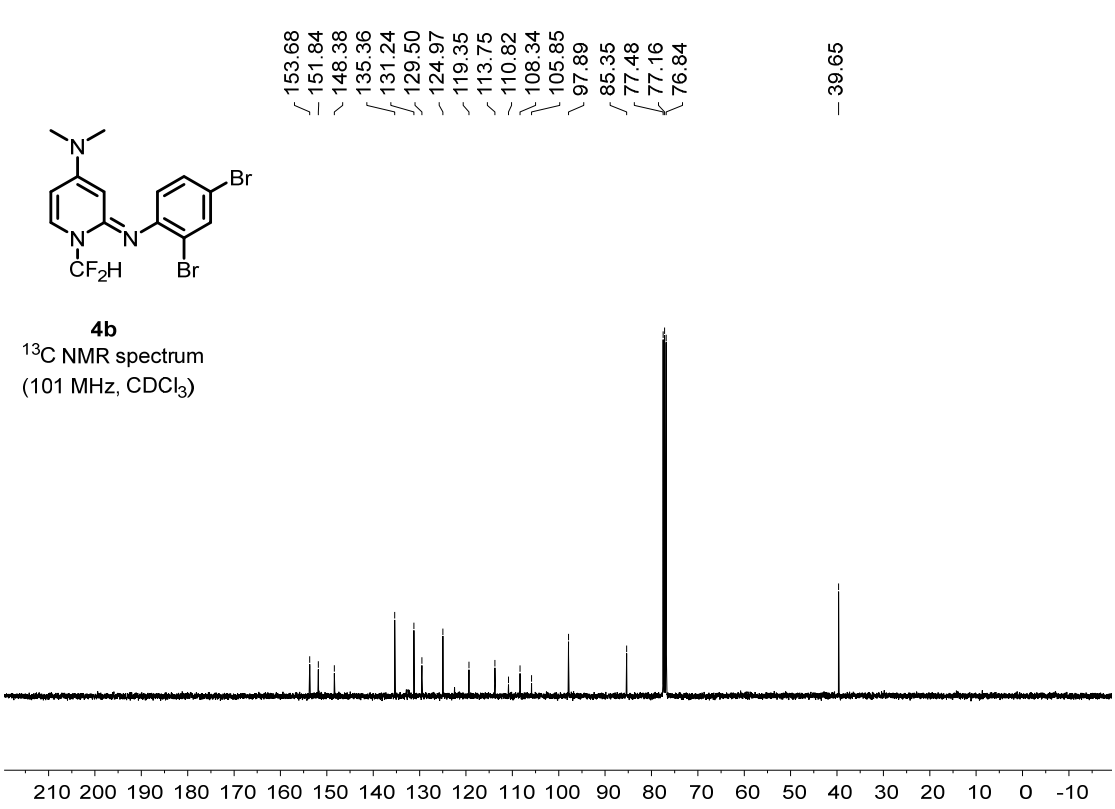
3ai

HRMS spectrum
by Bruker Daltonics-micrOTOF-QII
mass spectrometer



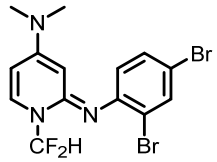
4b

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



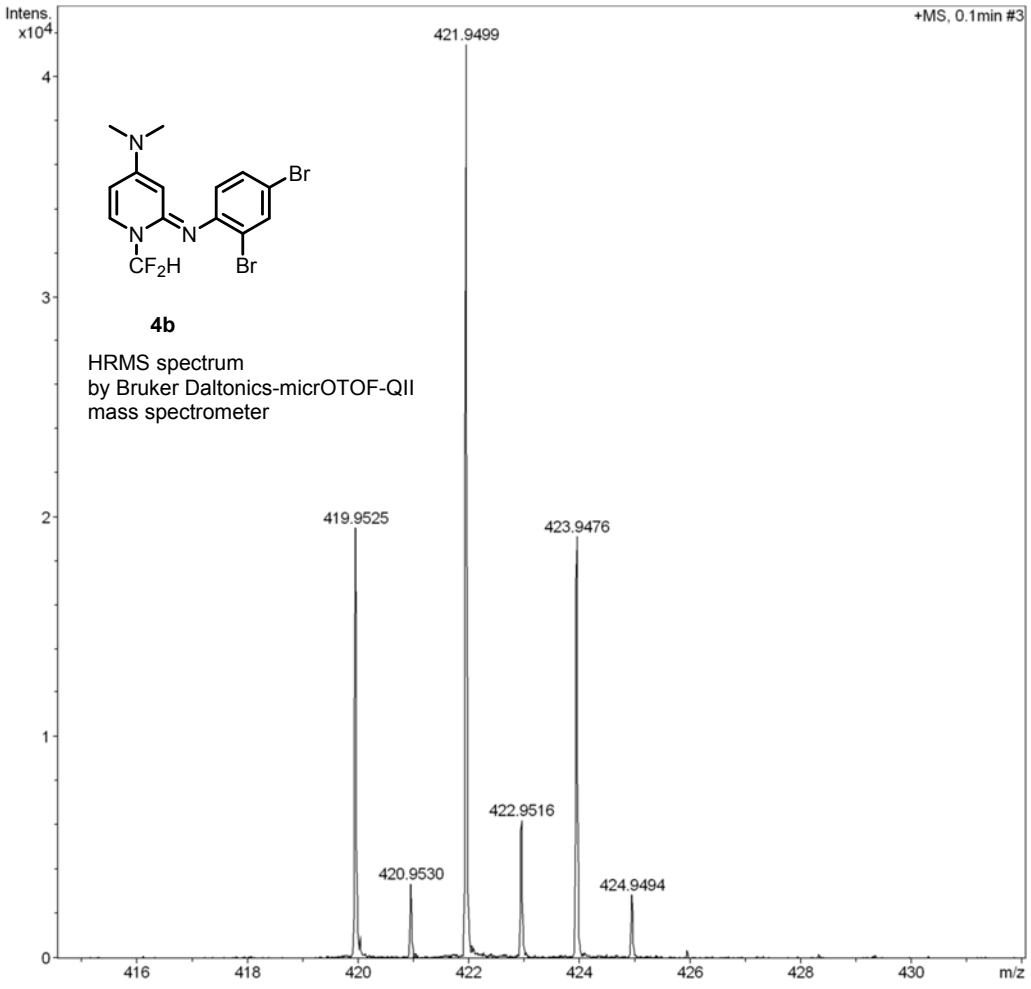
4b

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



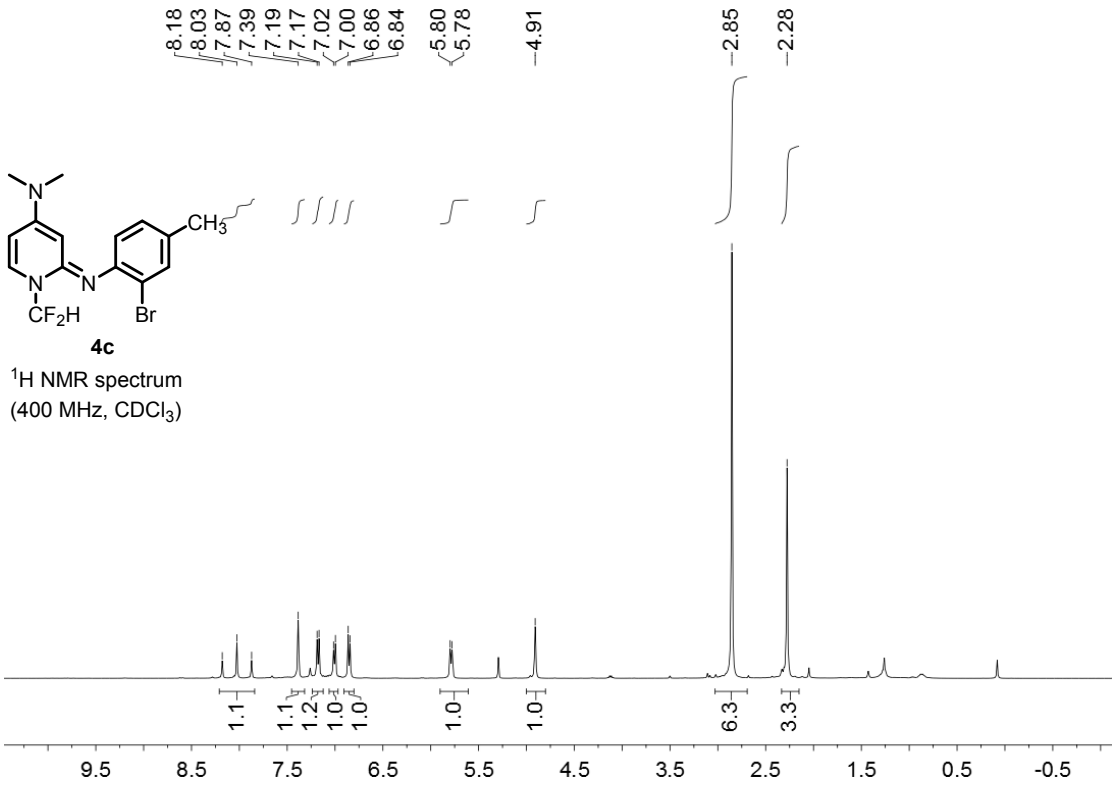
4b

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



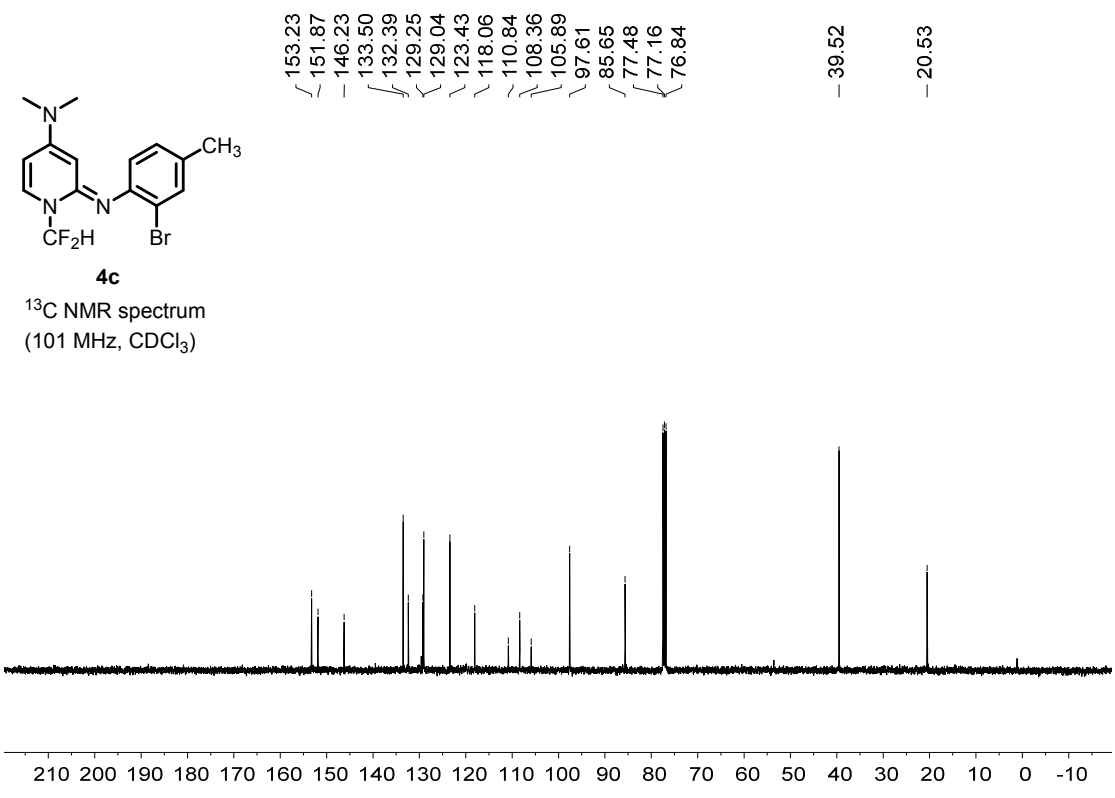
4b

HRMS spectrum
by Bruker Daltonics-micrOTOF-QII
mass spectrometer



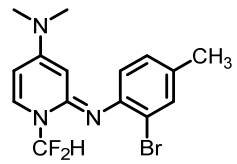
4c

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



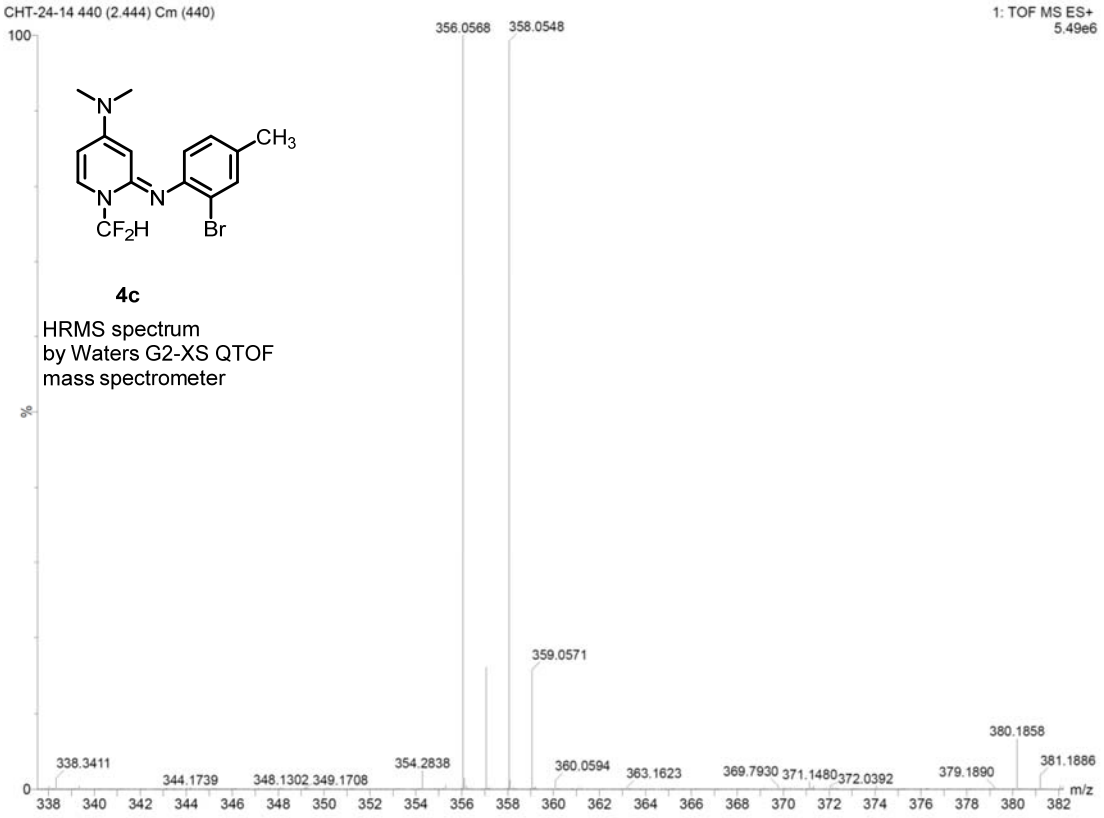
4c

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



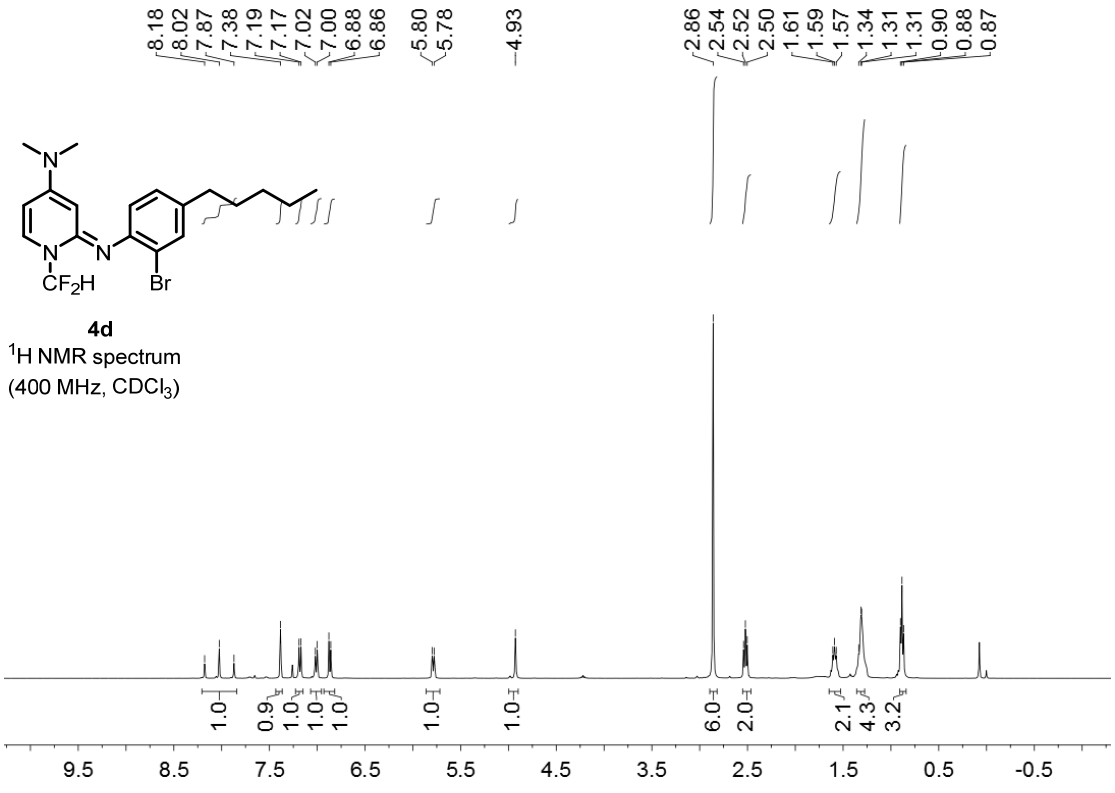
4c

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



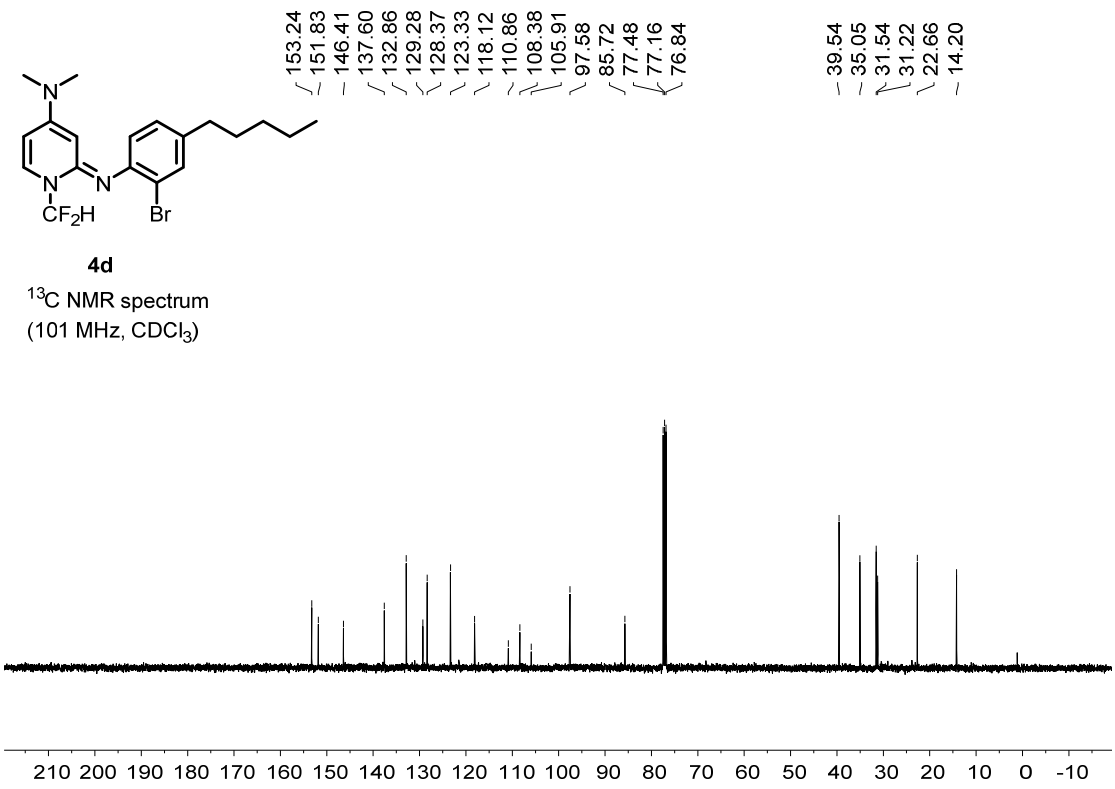
4c

HRMS spectrum
by Waters G2-XS QTOF
mass spectrometer



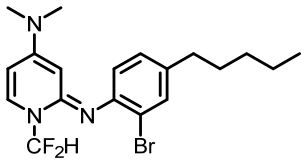
4d

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



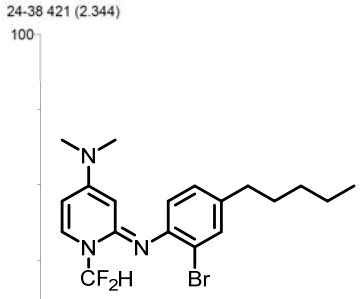
4d

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



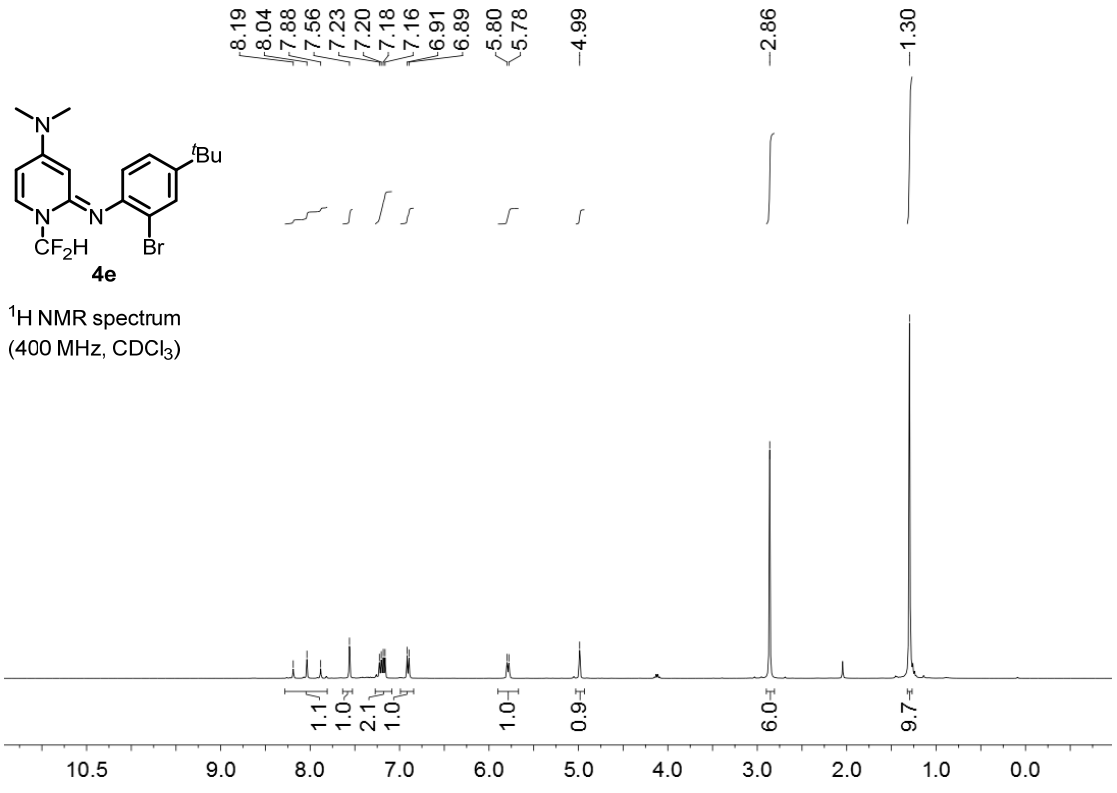
4d

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



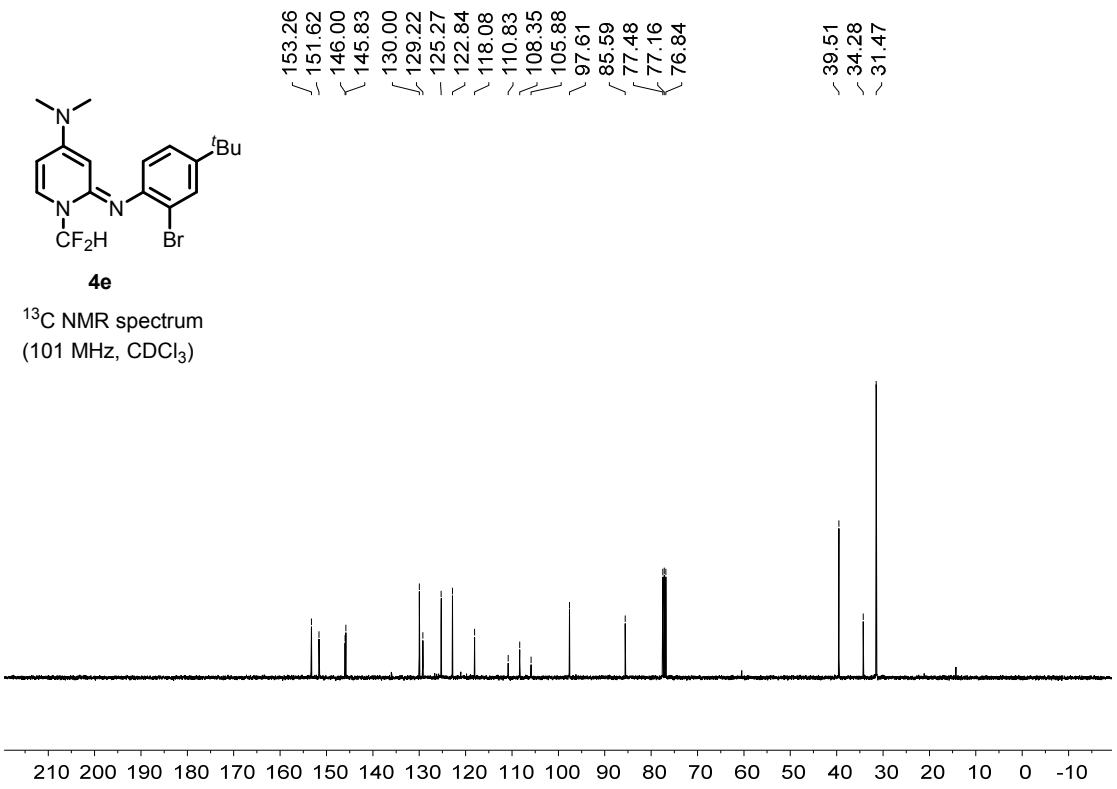
4d

HRMS spectrum
by Waters G2-XS QTOF
mass spectrometer



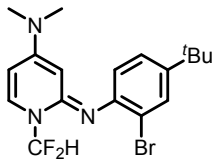
4e

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



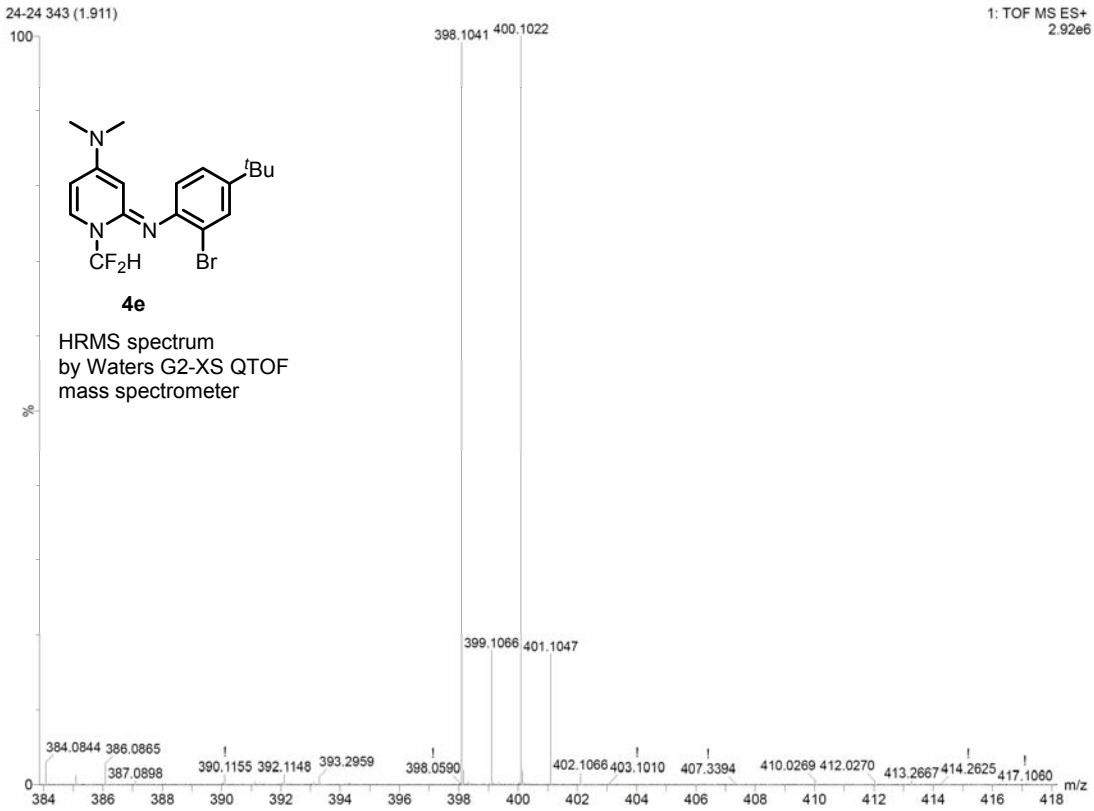
4e

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



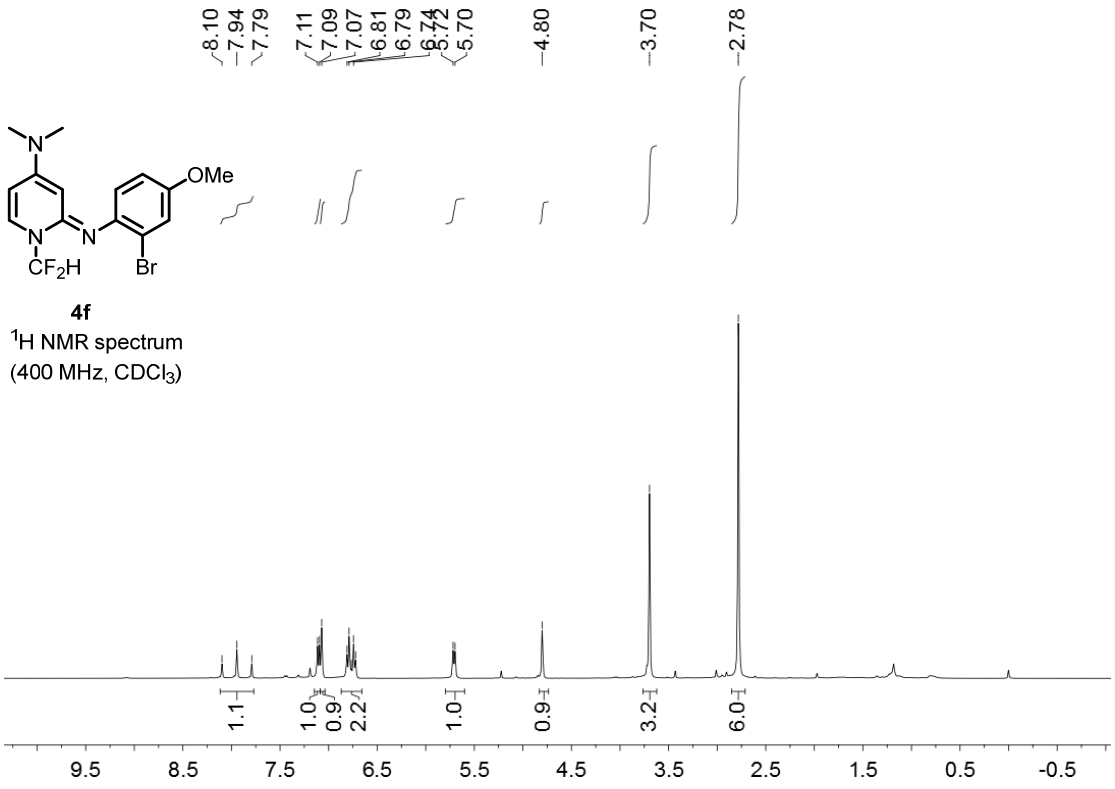
4e

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



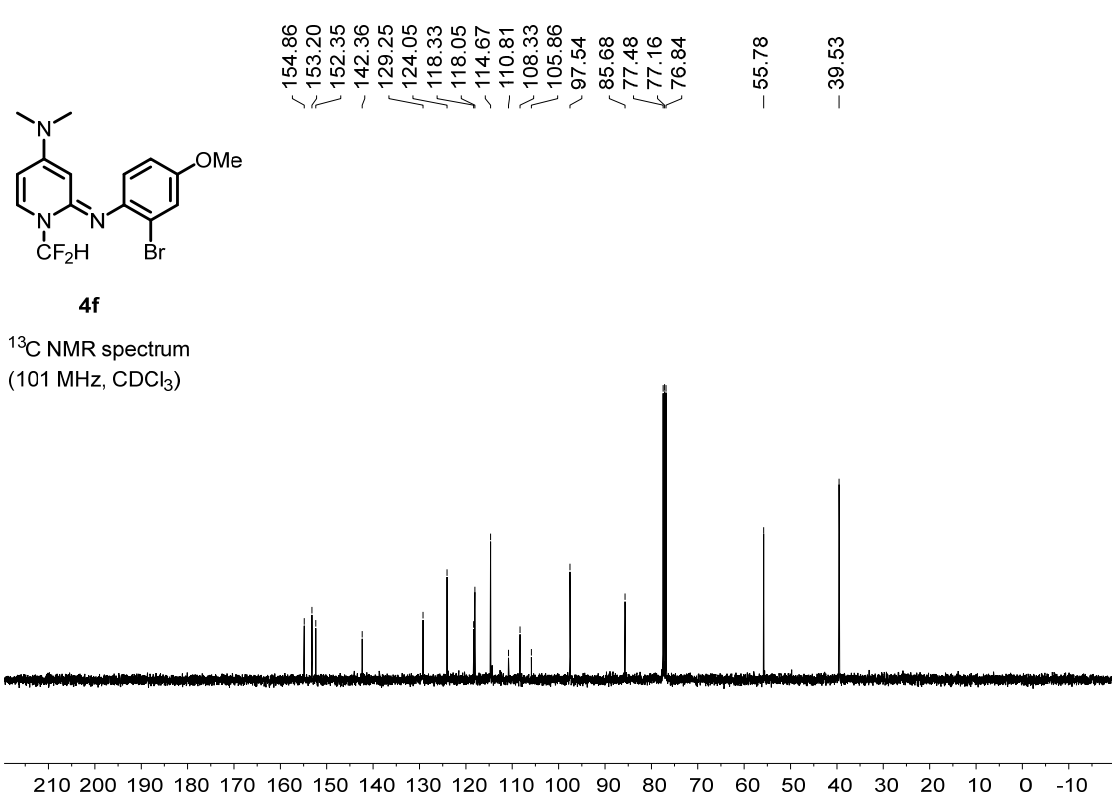
4e

HRMS spectrum
by Waters G2-XS QTOF
mass spectrometer



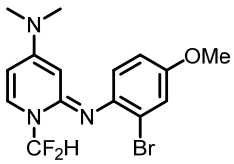
4f

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



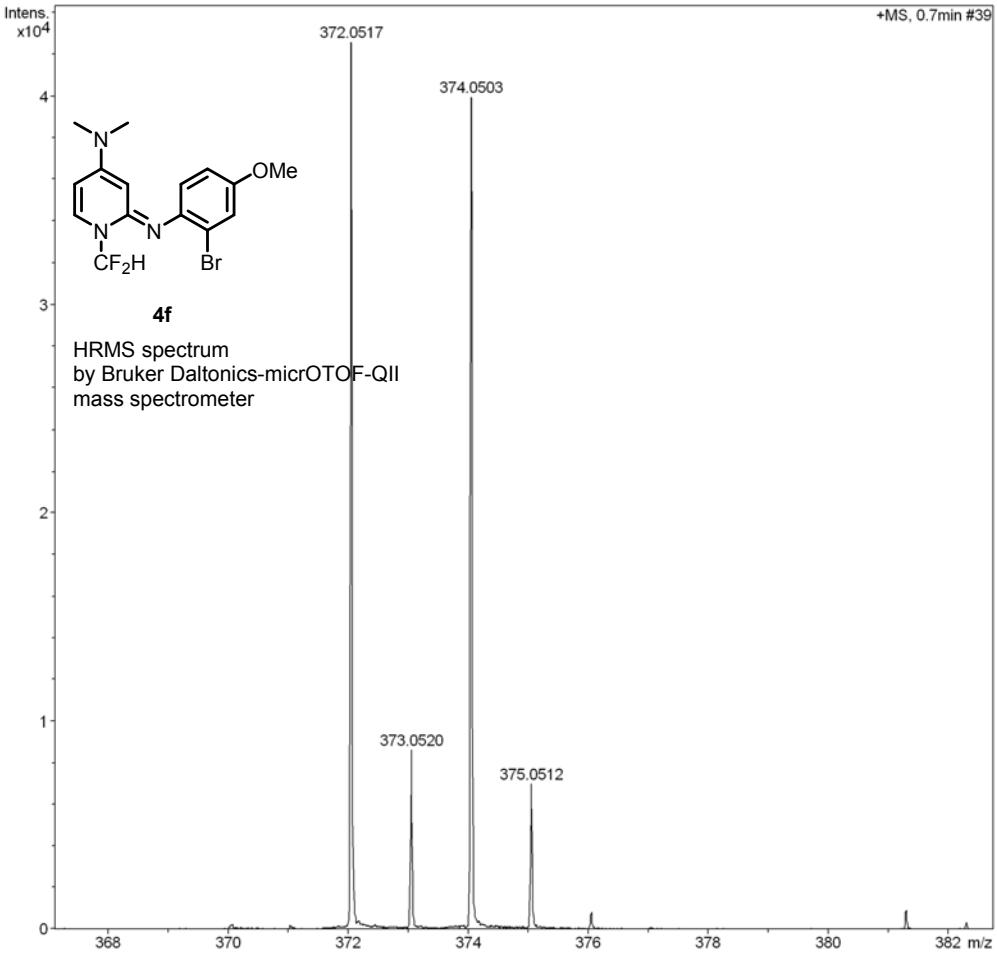
4f

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



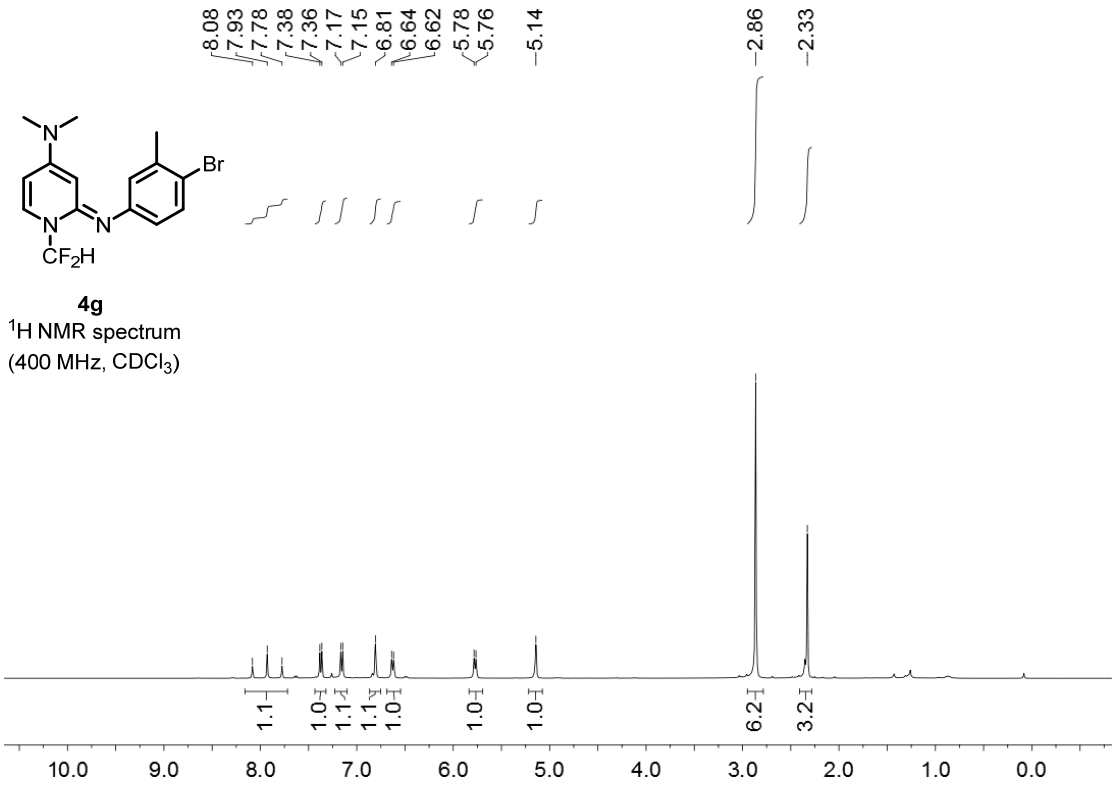
4f

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



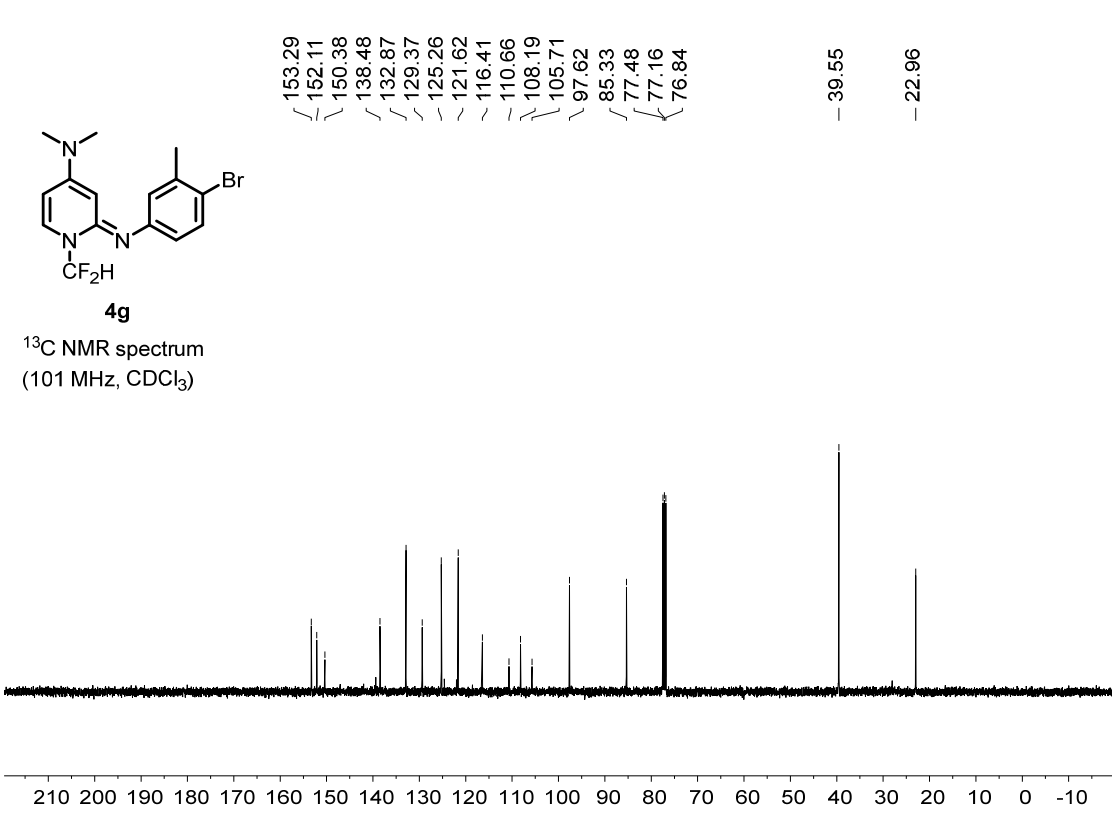
4f

HRMS spectrum
by Bruker Daltonics-micrOTOF-QII
mass spectrometer



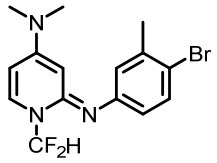
4g

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



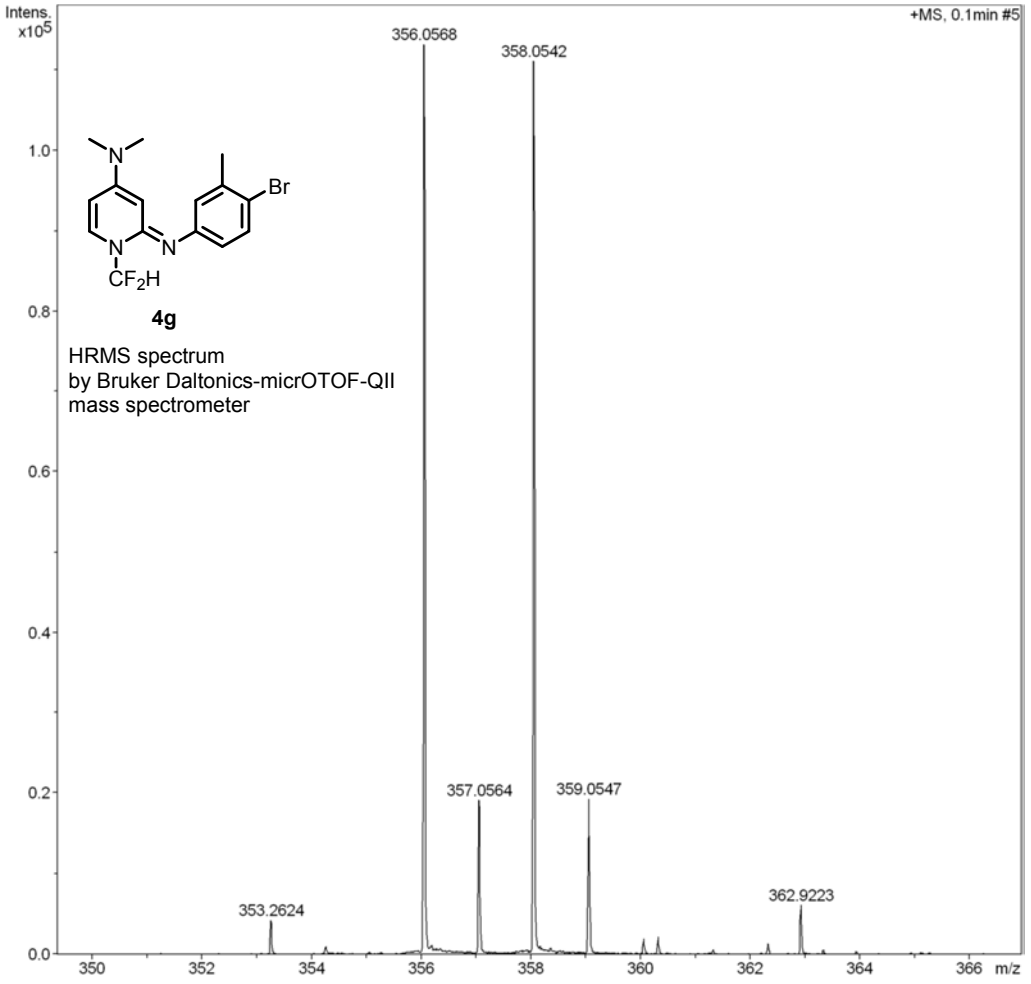
4g

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



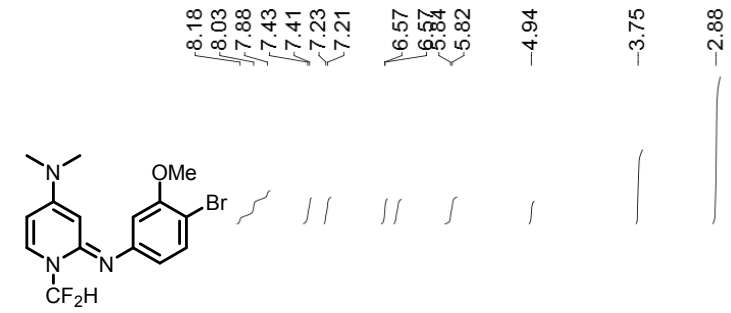
4g

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



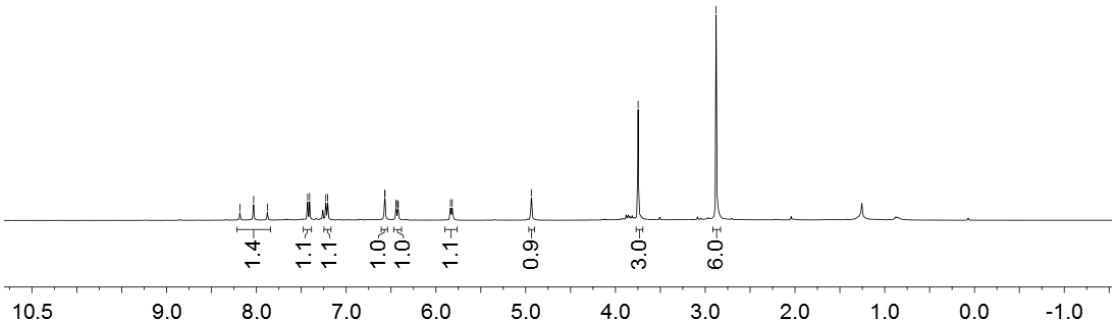
4g

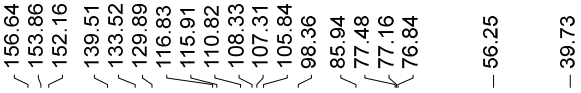
HRMS spectrum
by Bruker Daltonics-micrOTOF-QII
mass spectrometer

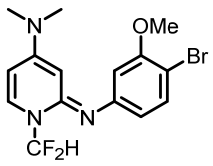


4h

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

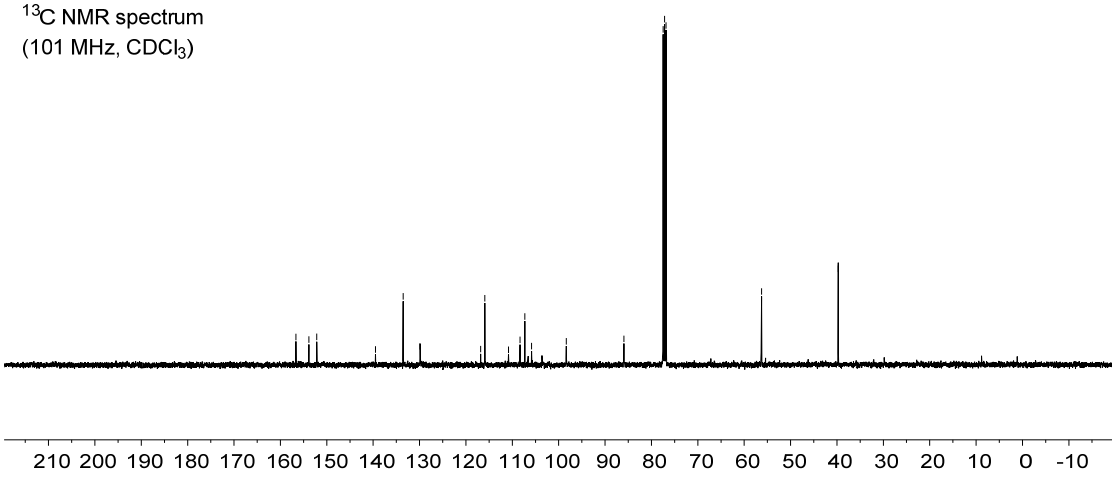


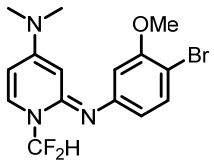




4h

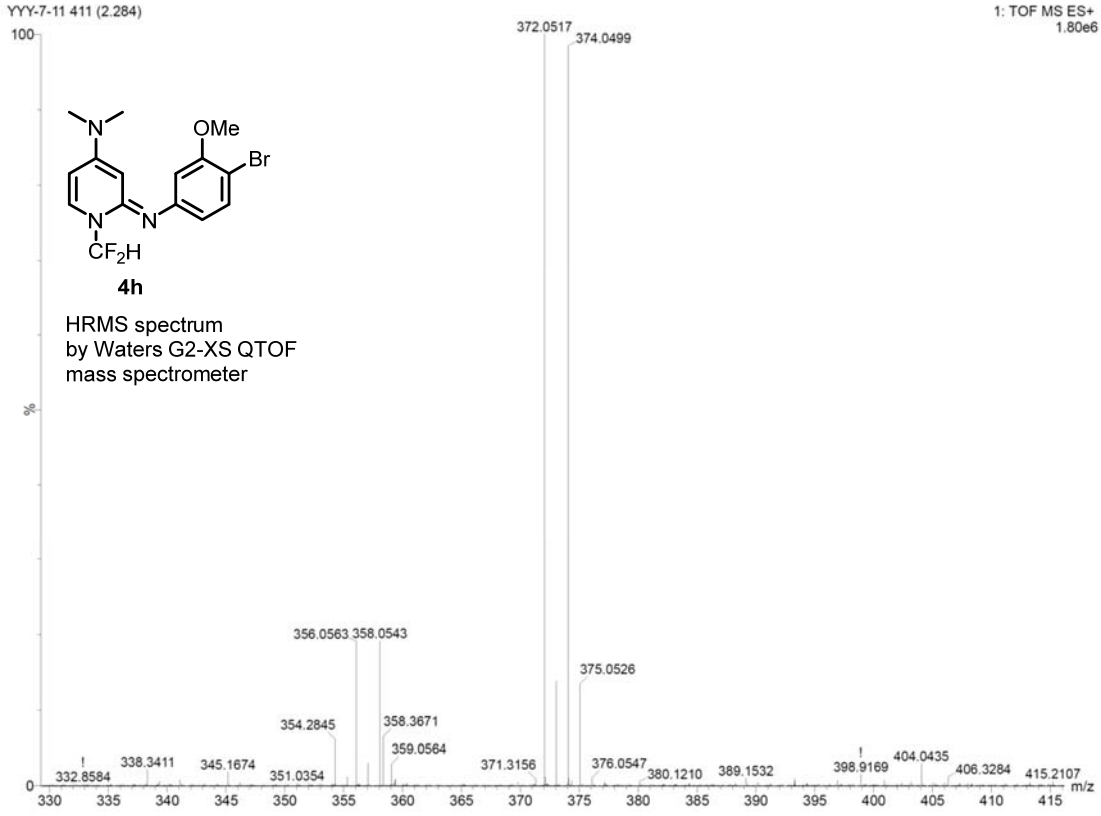
^{13}C NMR spectrum
(101 MHz, $CDCl_3$)





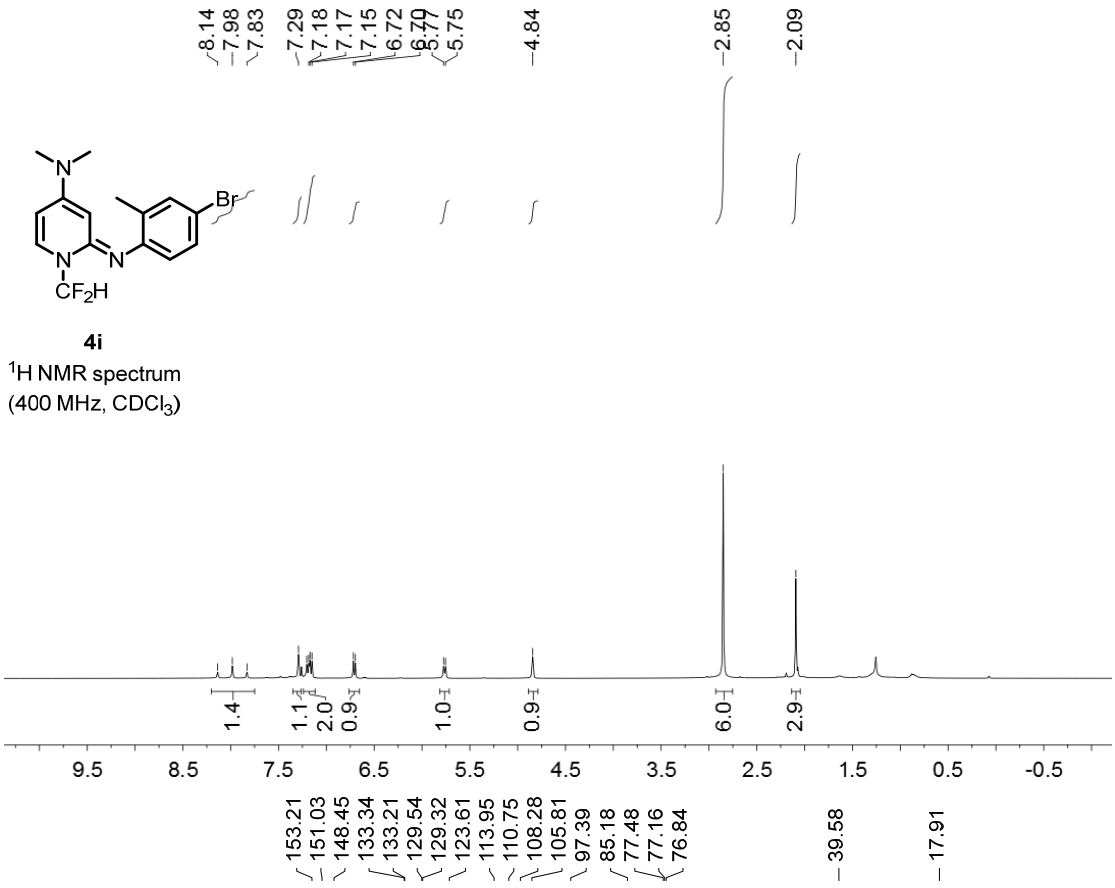
4h

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



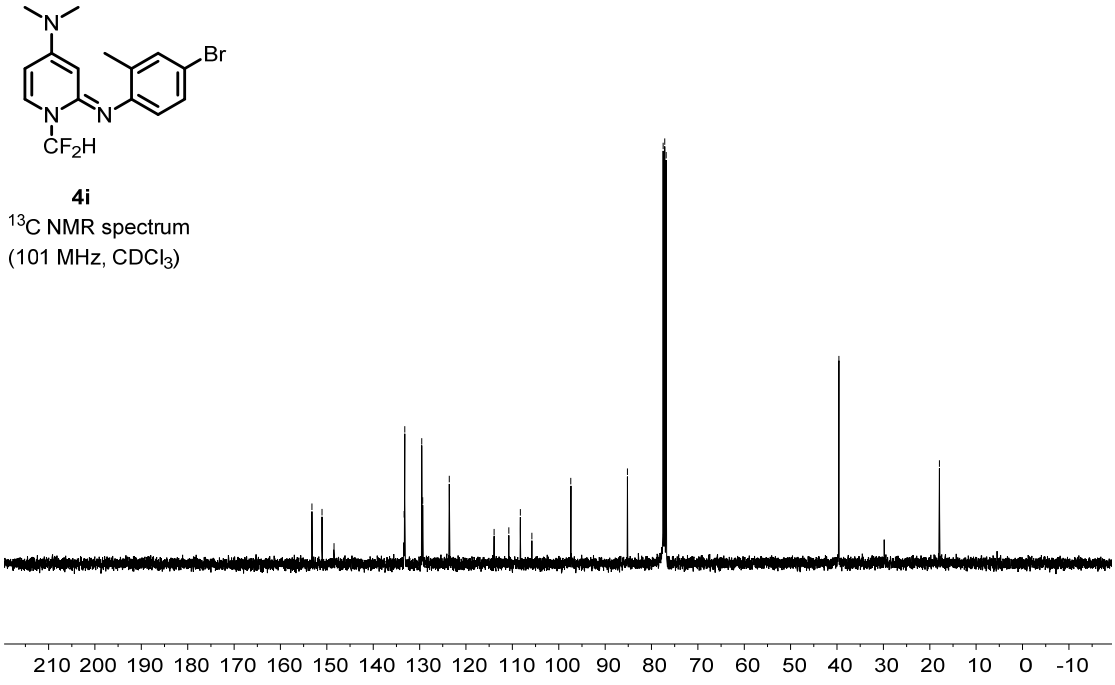
4h

HRMS spectrum
by Waters G2-XS QTOF
mass spectrometer



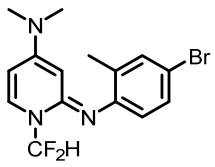
4i

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



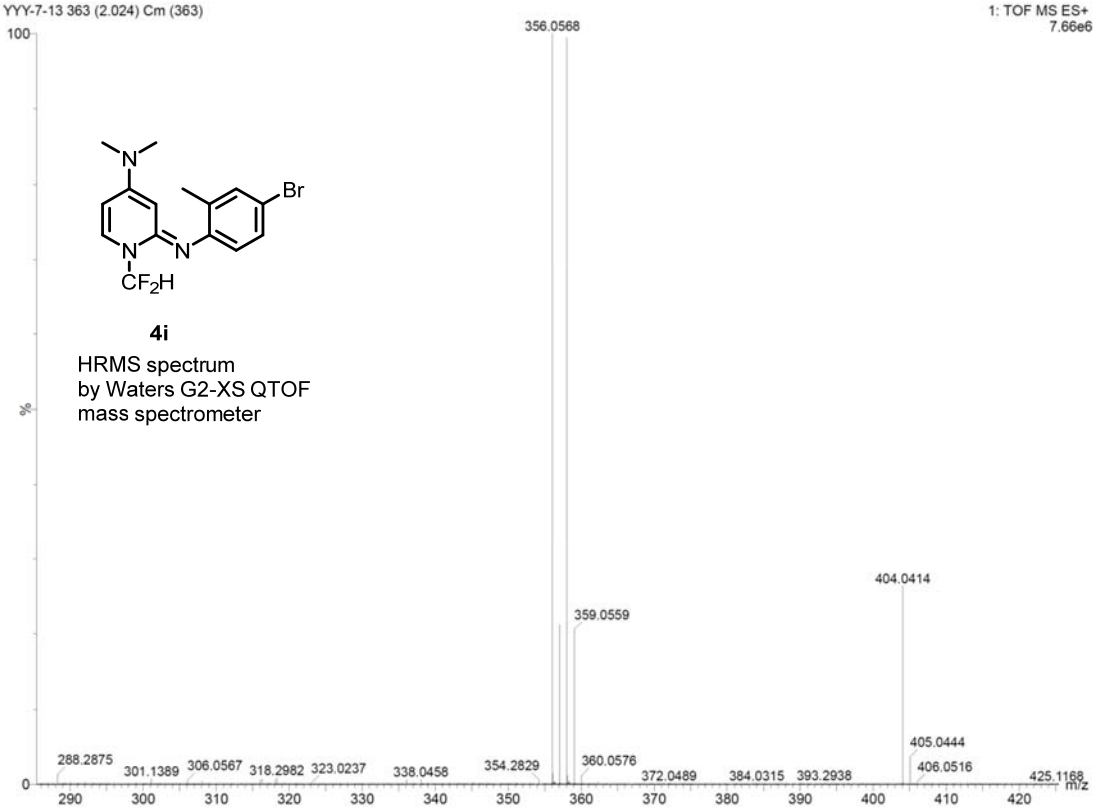
4i

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



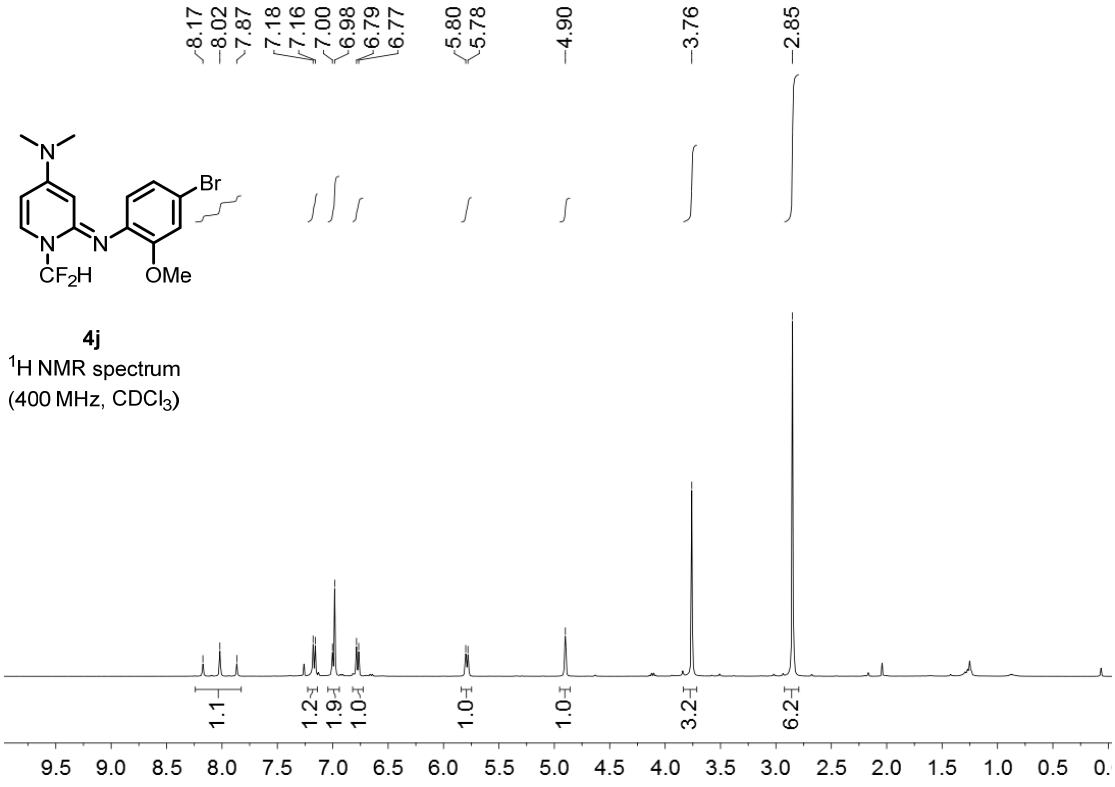
4i

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



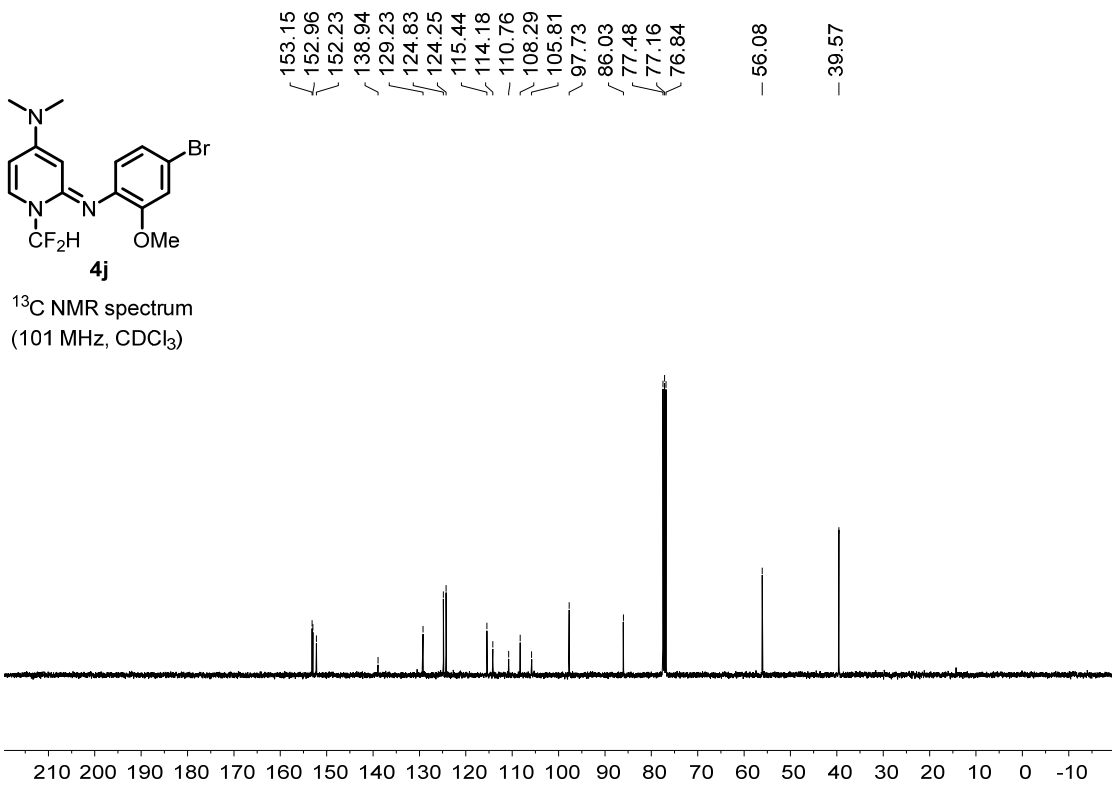
4i

HRMS spectrum
by Waters G2-XS QTOF
mass spectrometer



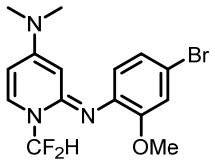
4j

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



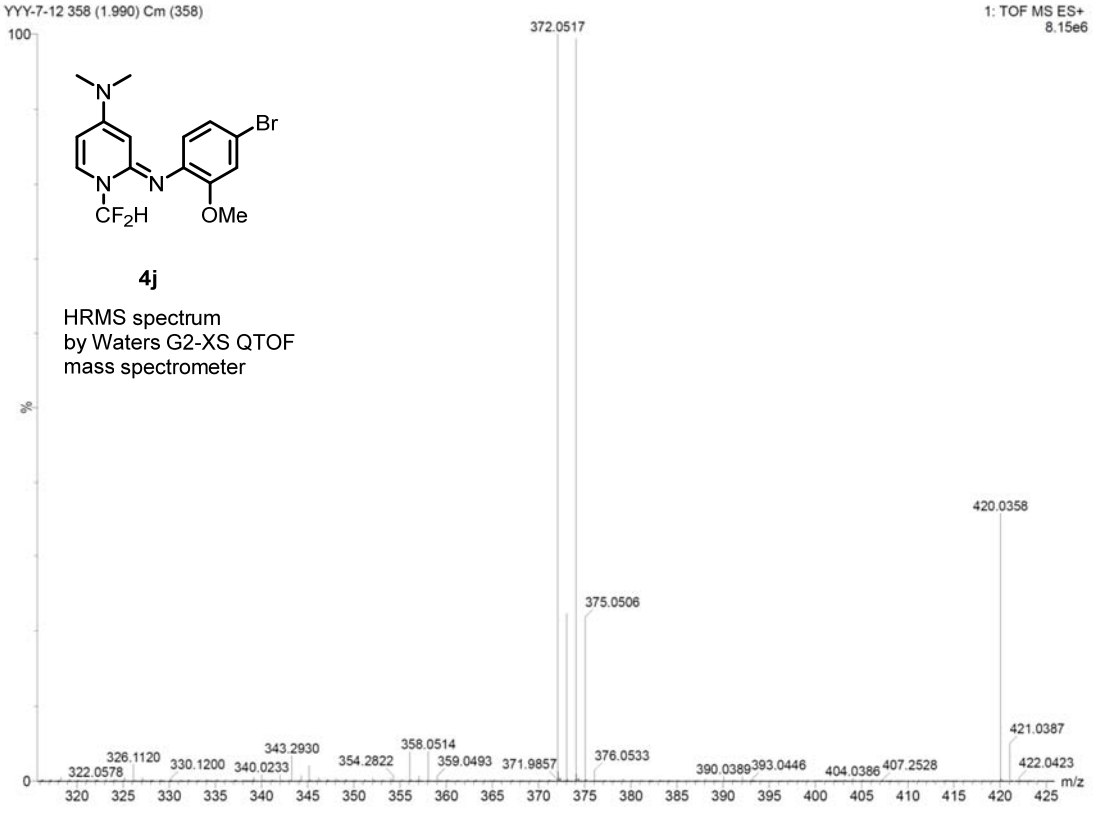
4j

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



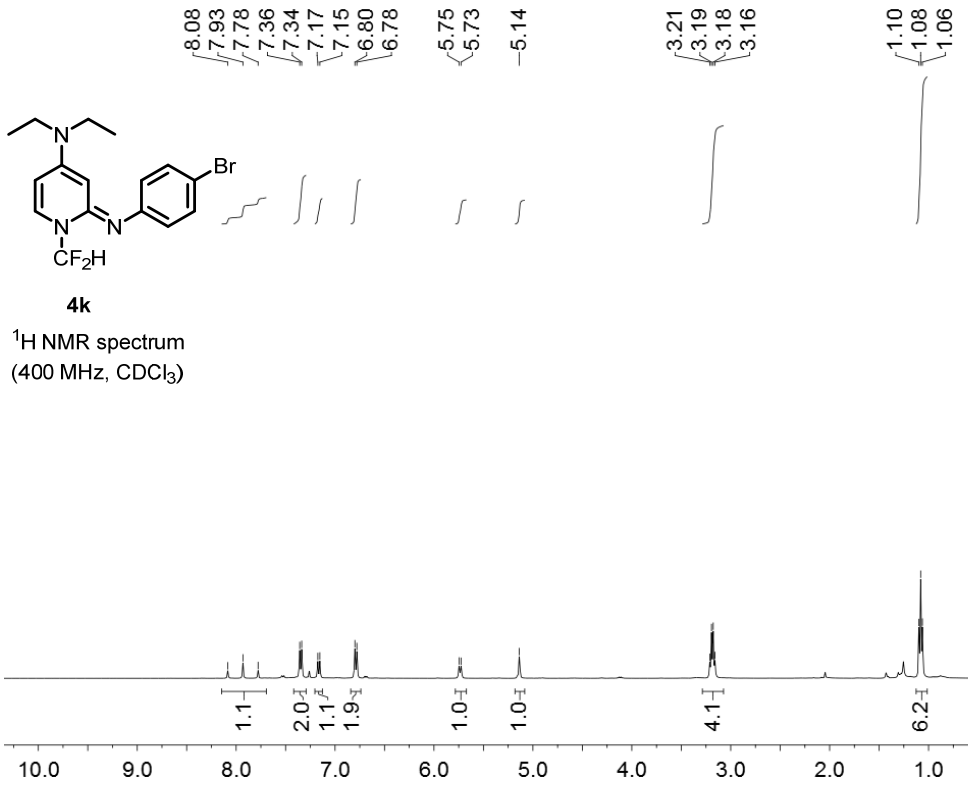
4j

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



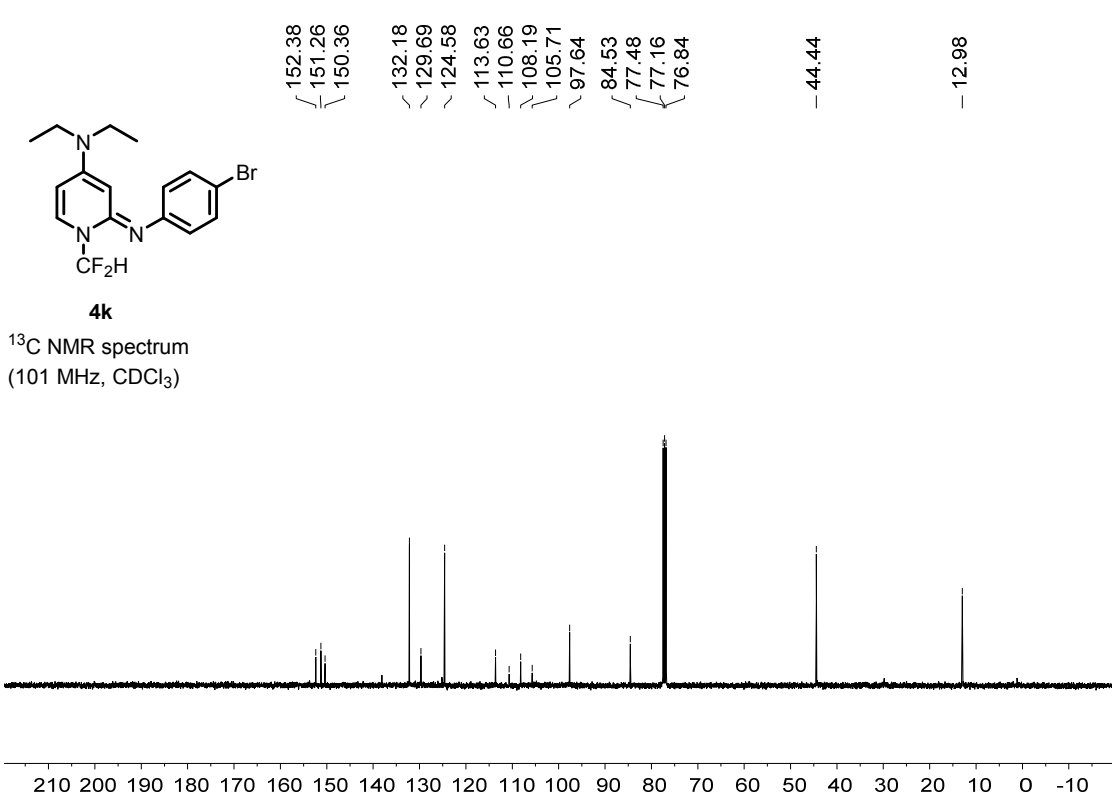
4j

HRMS spectrum
by Waters G2-XS QTOF
mass spectrometer



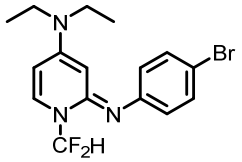
4k

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



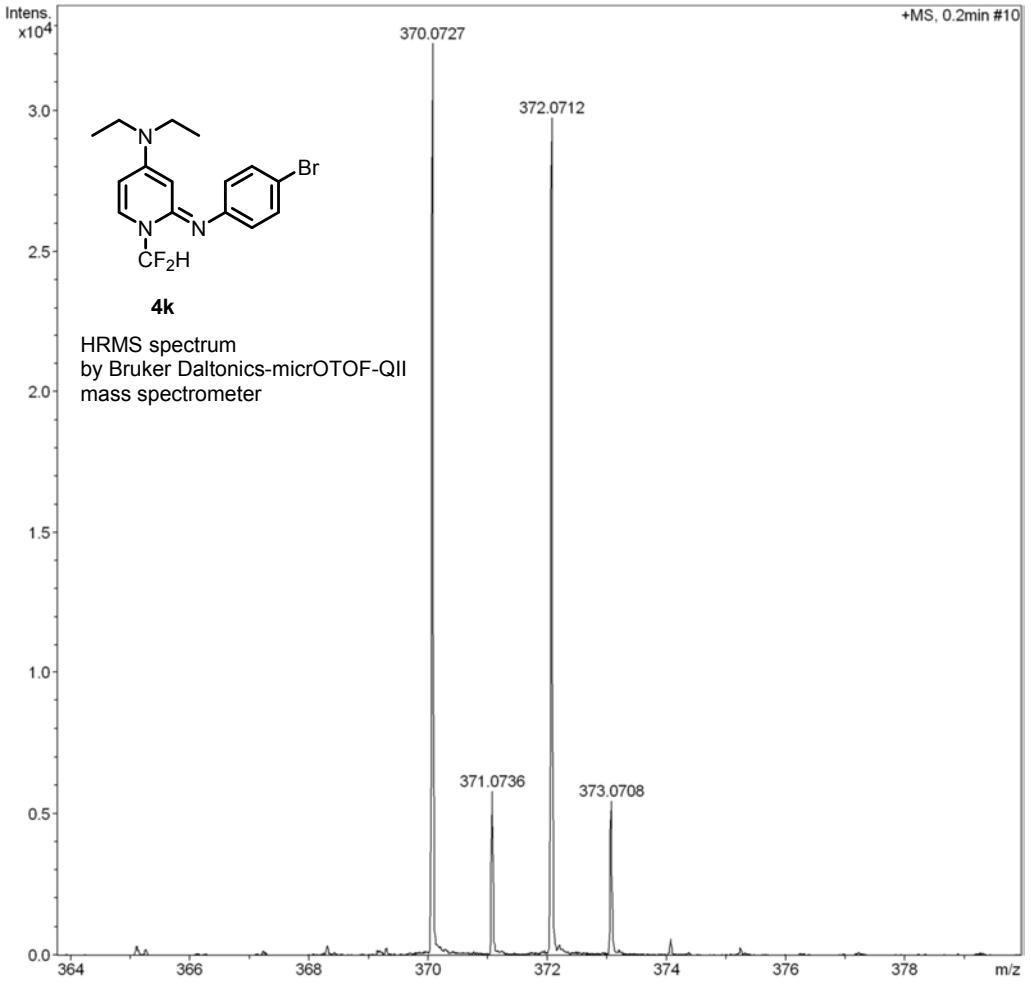
4k

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



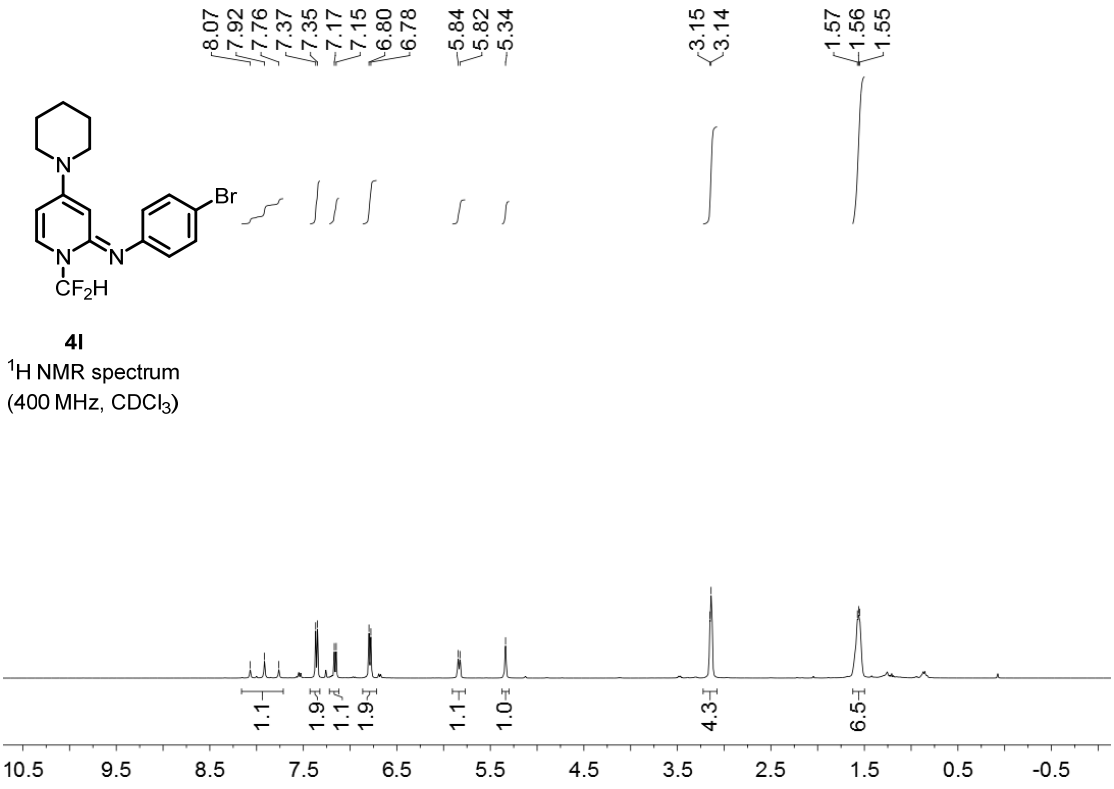
4k

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



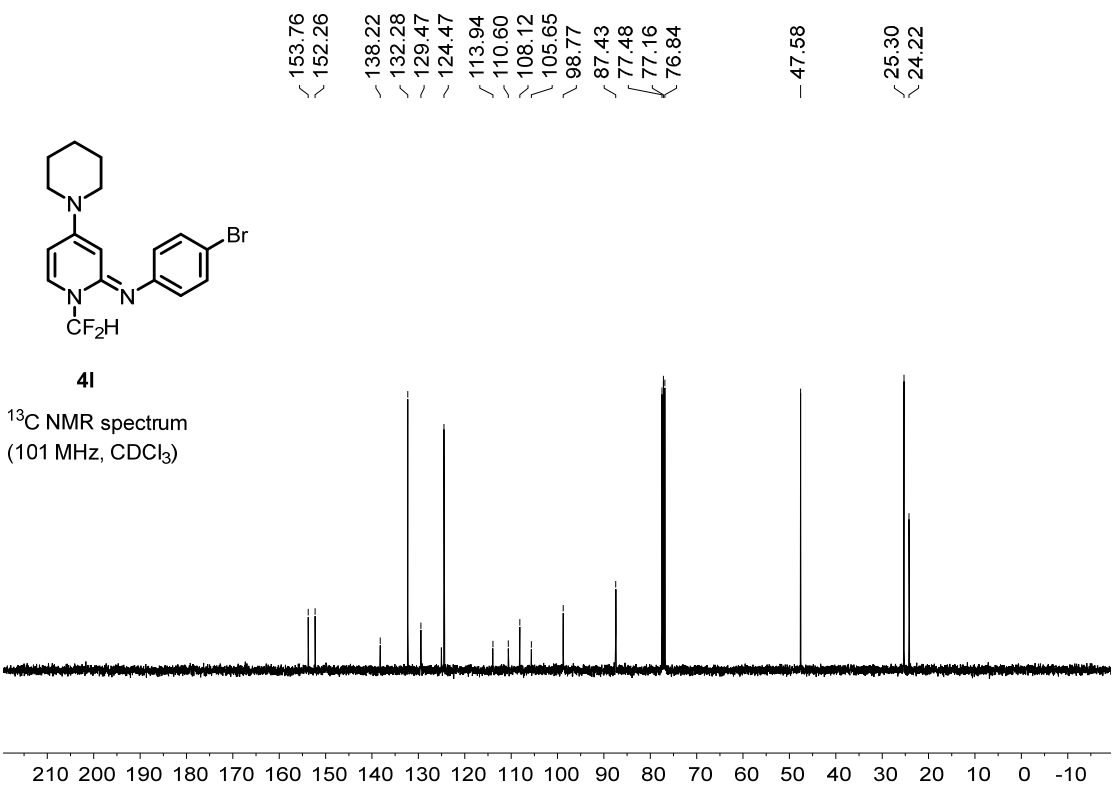
4k

HRMS spectrum
by Bruker Daltonics-micrOTOF-QII
mass spectrometer



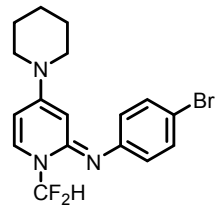
4l

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



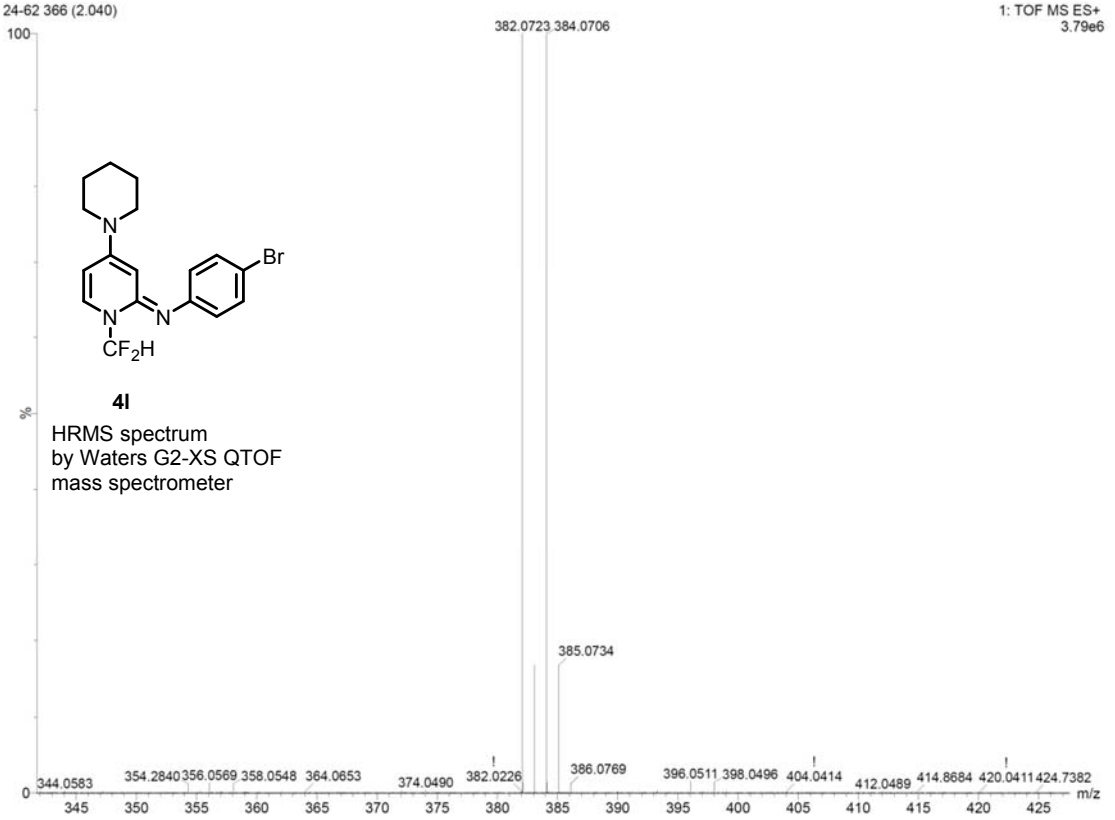
4l

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



4l

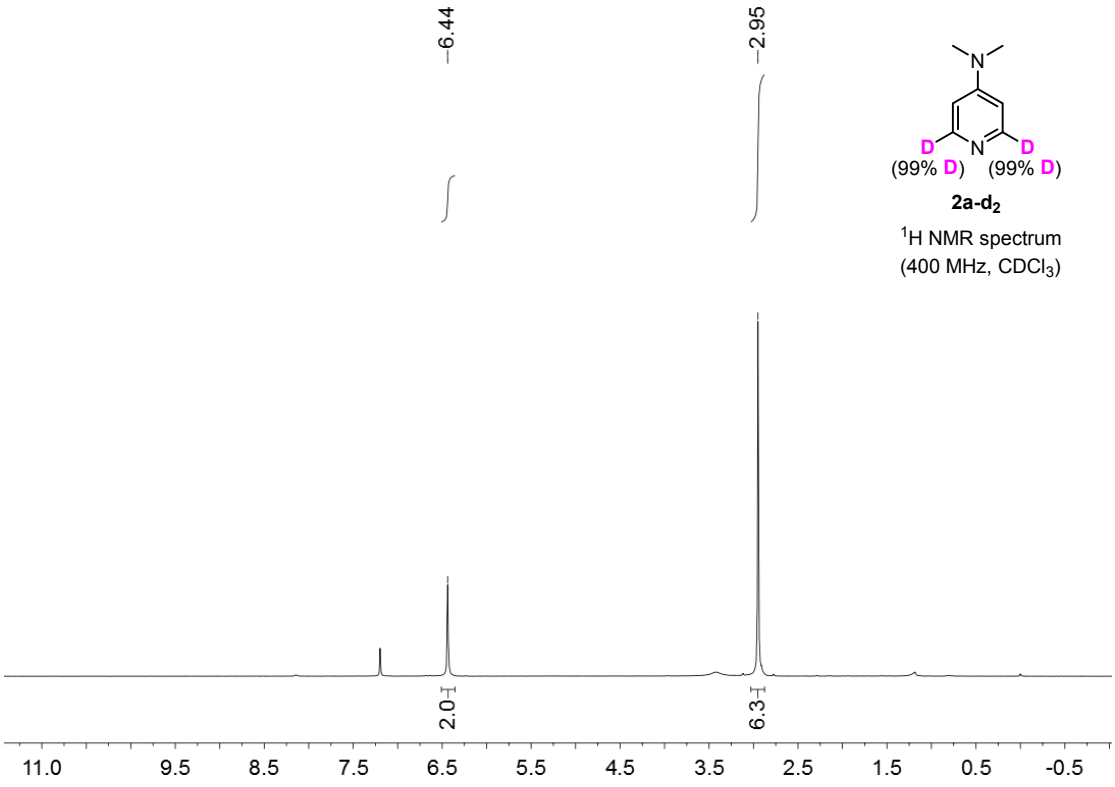
^{19}F NMR spectrum
(376 MHz, $CDCl_3$)



4l

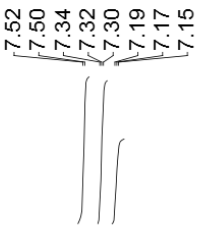
HRMS spectrum
by Waters G2-XS QTOF
mass spectrometer

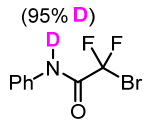
10. ^{1}H NMR spectra of deuterated compounds.



2a-d$_2$

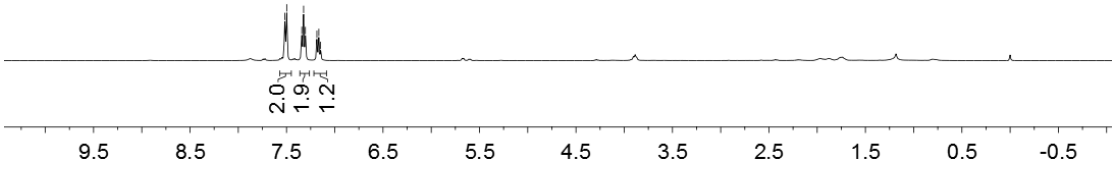
^{1}H NMR spectrum
(400 MHz, $CDCl_3$)

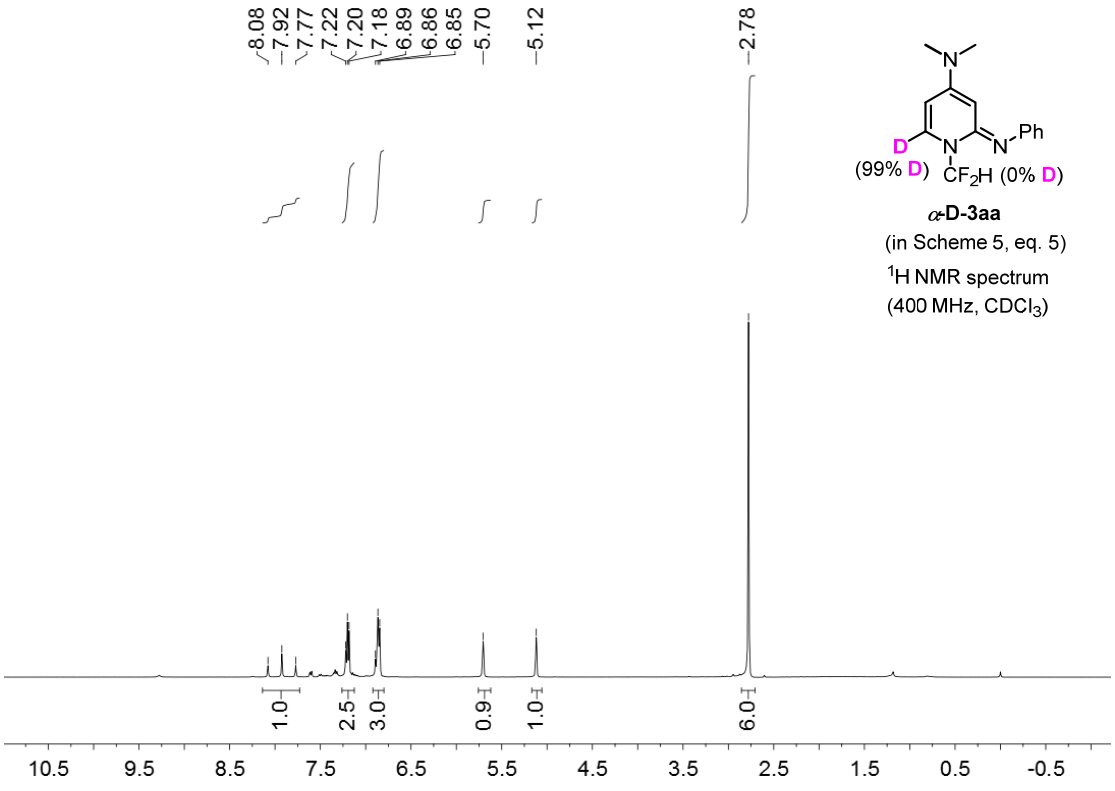




1a-d$_1$

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



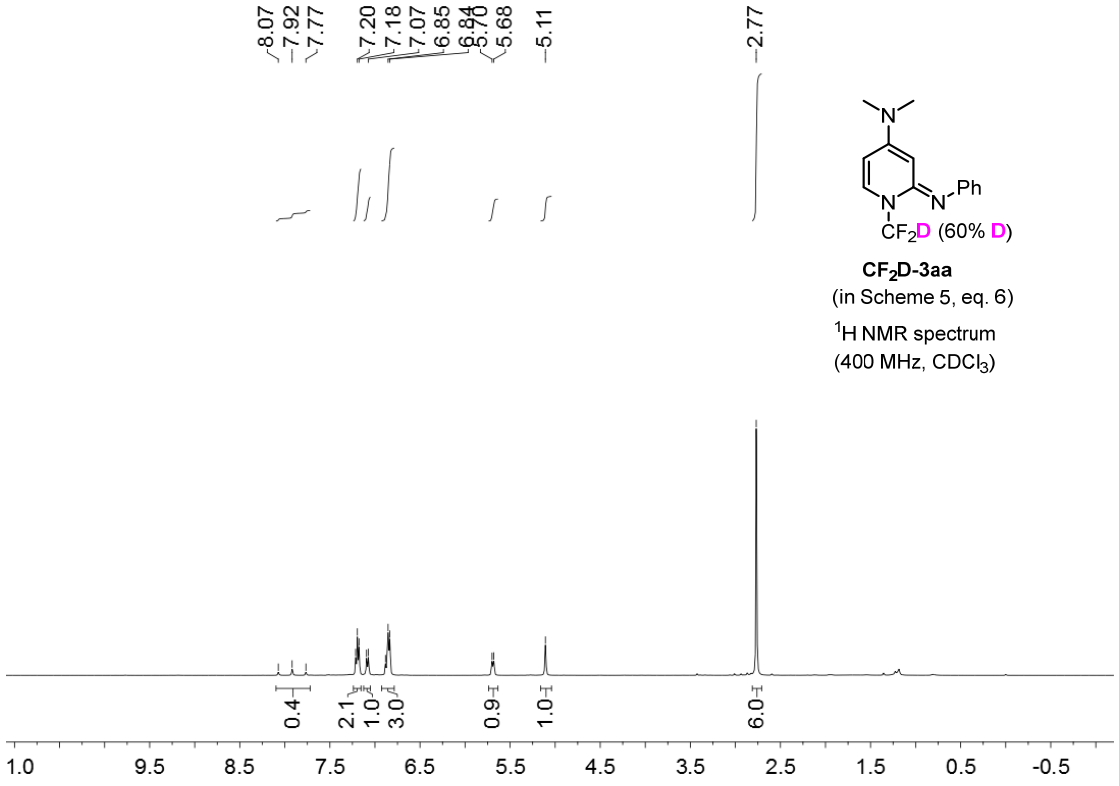


α-D-3aa

(in Scheme 5, eq. 5)

^{1}H NMR spectrum

(400 MHz, $CDCl_3$)

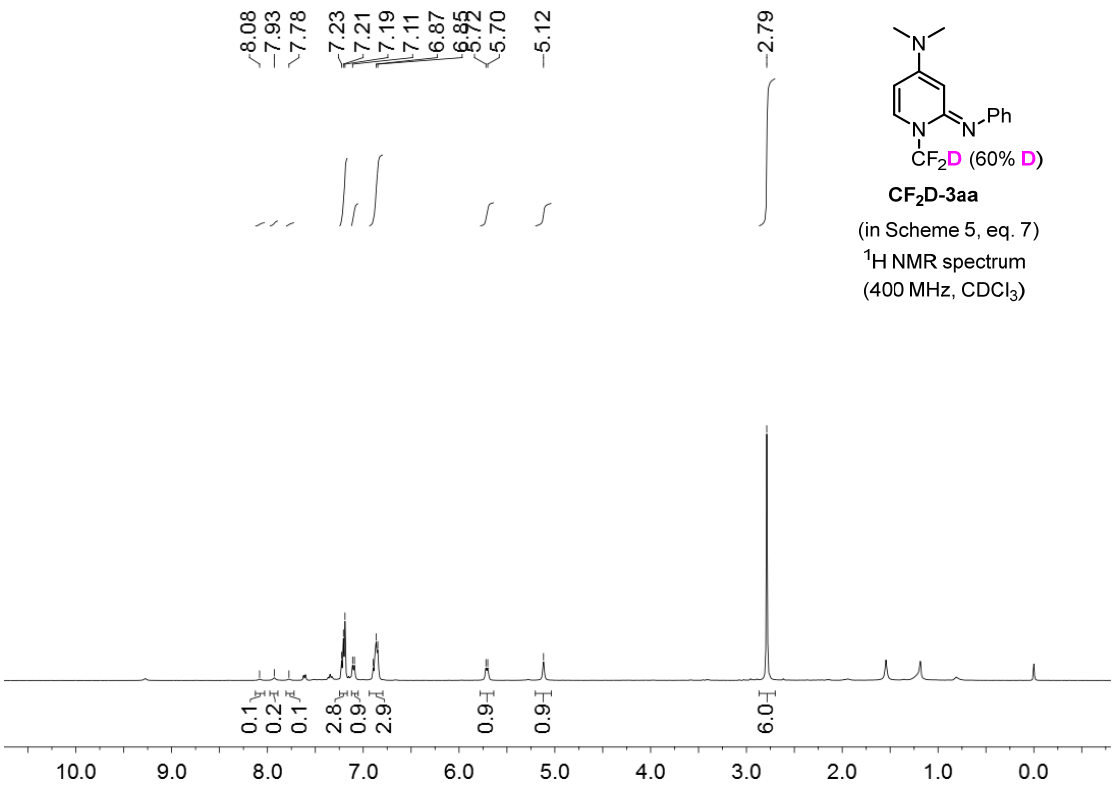


CF_2D-3aa

(in Scheme 5, eq. 6)

^{1}H NMR spectrum

(400 MHz, $CDCl_3$)



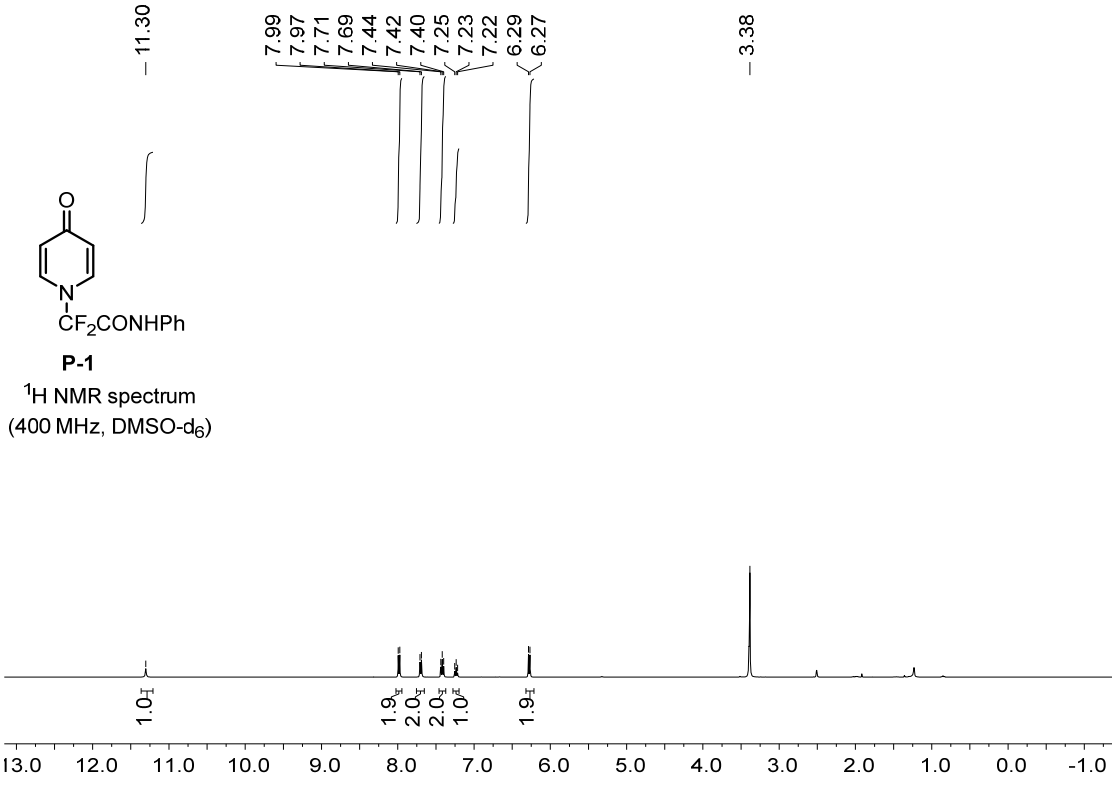
CF_2D-3aa

(in Scheme 5, eq. 7)

^{1}H NMR spectrum

(400 MHz, $CDCl_3$)

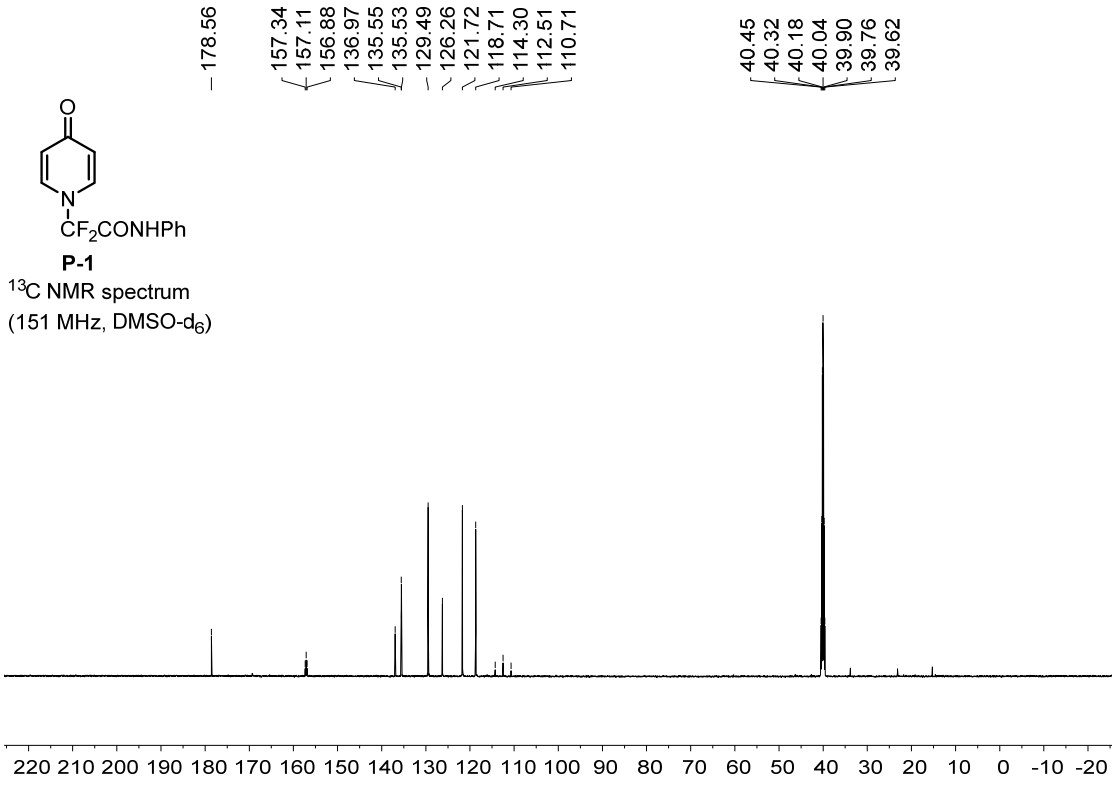
11. NMR and HRMS spectra of compounds P-1, P-2, and P-3.



P-1

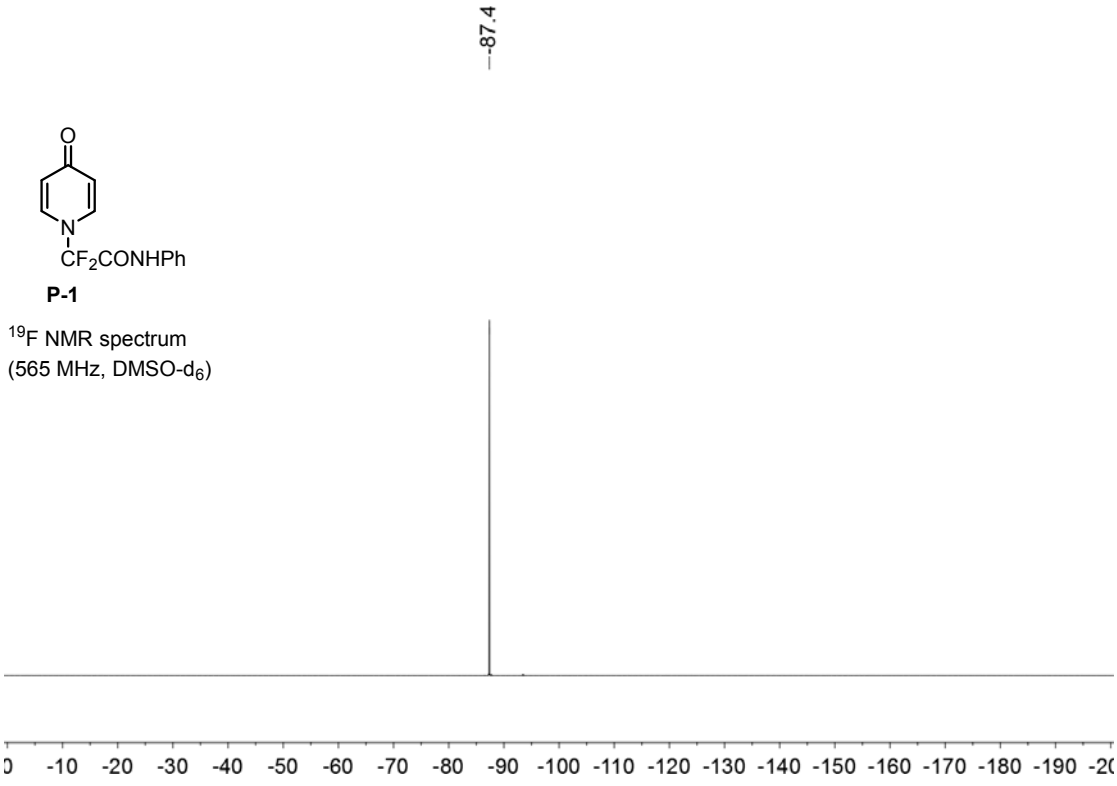
^{1}H NMR spectrum

(400 MHz, DMSO-d_6)



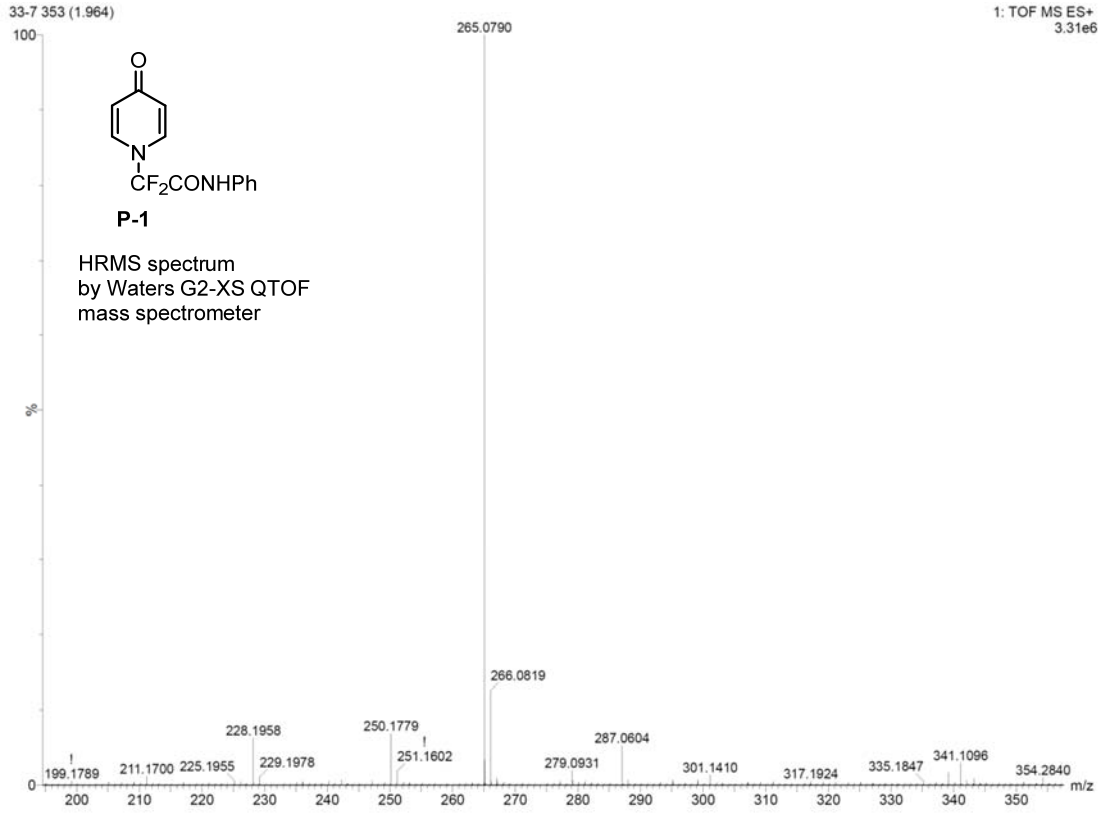
P-1

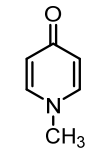
^{13}C NMR spectrum
(151 MHz, DMSO-d_6)



P-1

^{19}F NMR spectrum
(565 MHz, DMSO-d_6)



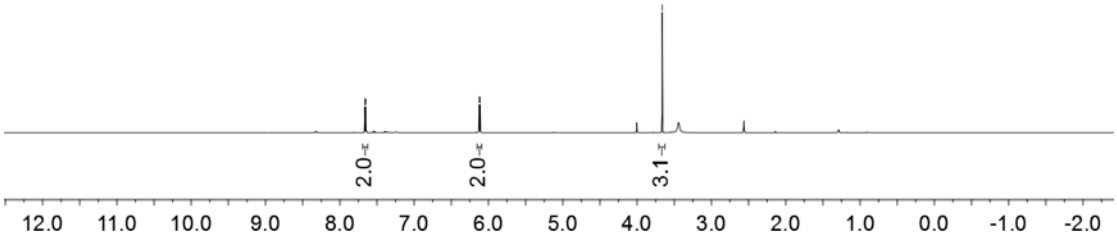


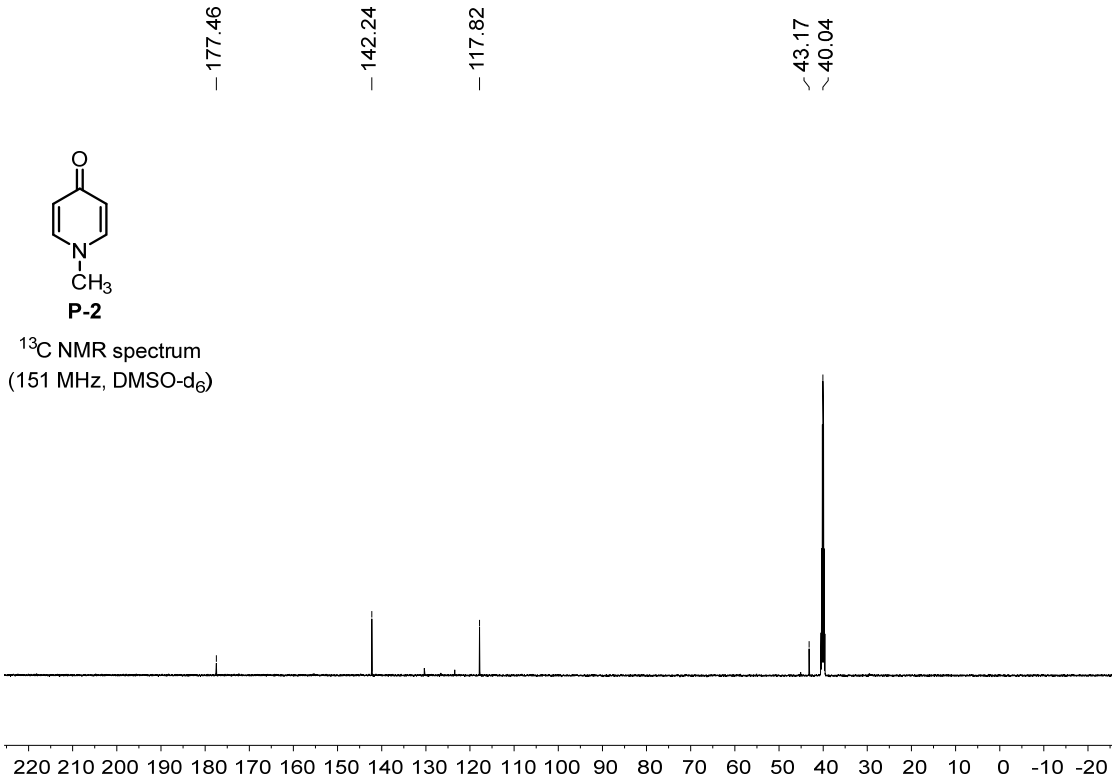
P-1

HRMS spectrum
by Waters G2-XS QTOF
mass spectrometer

P-2

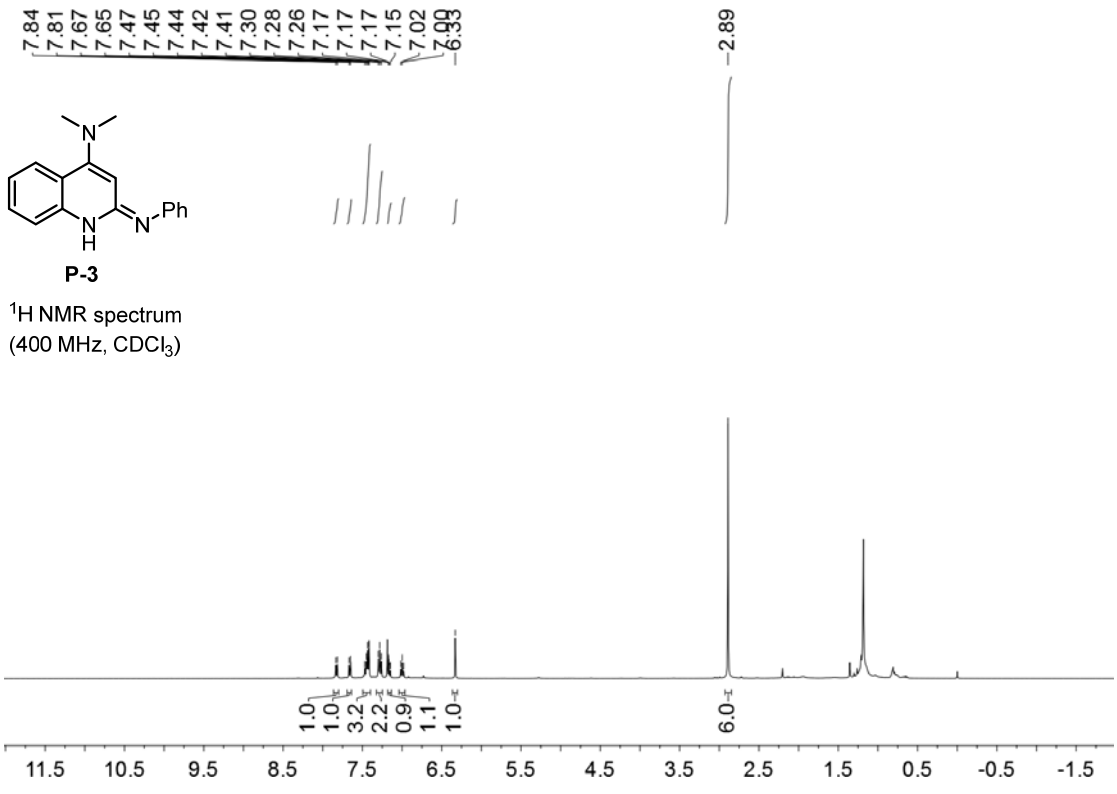
^{1}H NMR spectrum
(600 MHz, DMSO-d_6)





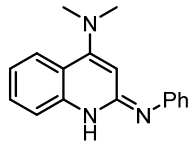
P-2

^{13}C NMR spectrum
(151 MHz, DMSO-d_6)



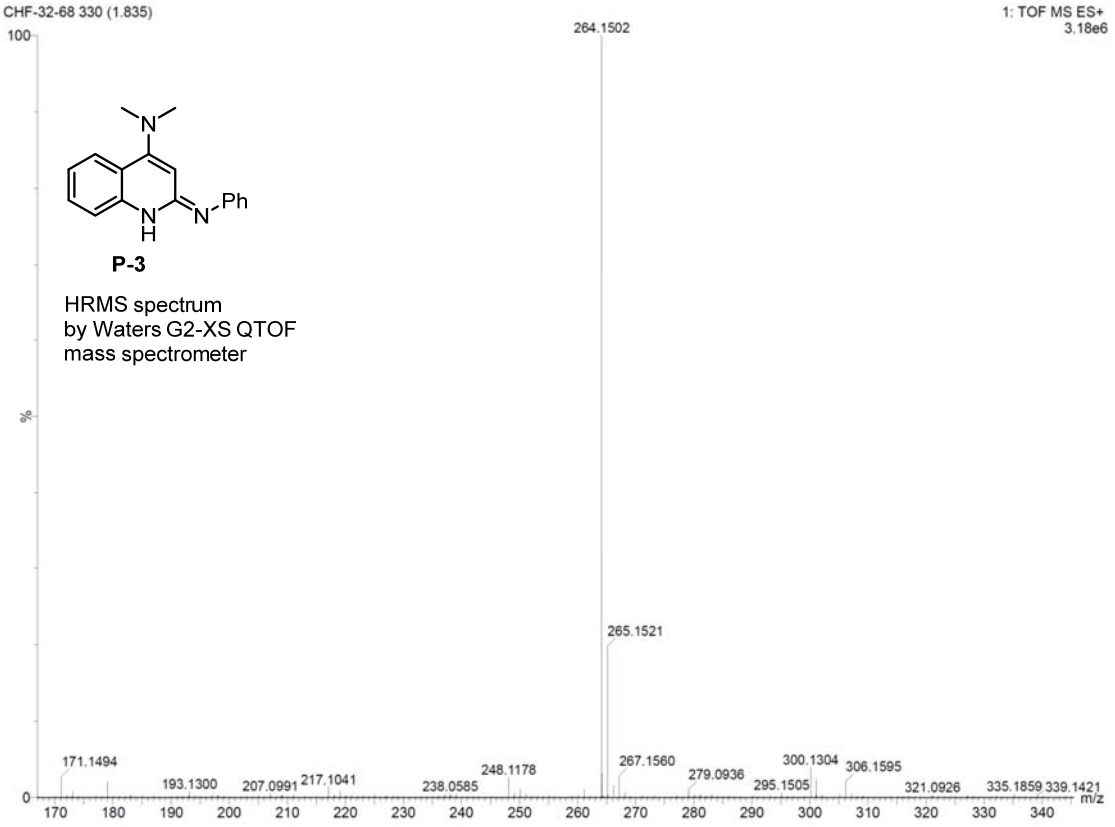
P-3

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



P-3

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



P-3

HRMS spectrum
by Waters G2-XS QTOF
mass spectrometer