Supporting Information

First radiosynthesis of 2-amino-5-[^{18}F]fluoropyridines via a "minimalist" radiofluorination/palladium-catalyzed amination sequence from anisyl(2-bromopyridinyl)iodonium triflate

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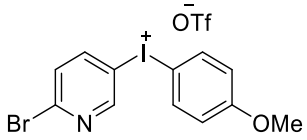
1. Chemistry

1.1. General materials and methods

Chemicals, reagents and solvents were purchased commercially and used as received. Previously described starting anisylpyridinyliodonium salts (such as anisyl(2-chloropyridinyl)iodonium triflate **4**, isomers and analogues bearing a cyano, methyl, methoxy, methylcarboxylate, *N*-methylcarboxamide) were prepared according to the literature procedures.[1,2] ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Brucker Avance 400 or 500 MHz spectrometer. Samples were dissolved in an appropriate deuterated solvent ($CDCl_3$ or CD_3OD). Chemical shifts (δ) are quoted in parts per million (ppm). Coupling constants (J) are given in Hz. Coupling patterns are abbreviated as follows: s (singlet), d (doublet), t (triplet), m (mutiplet), dd (doublet of doublet), ddd (doublet of doublet of doublet), dddd (doublet of doublet of doublet of doublet), td (triplet of doublet). High resolution mass spectra (HRMS) were recorded using a Shimazu IT-TOF. Melting points were determined with an Electrothermal IA900 series of digital melting point instrument. They are uncorrected and given in °C. IR spectra were recorded on a FT-IR spectrometer and are given in cm^{-1}.

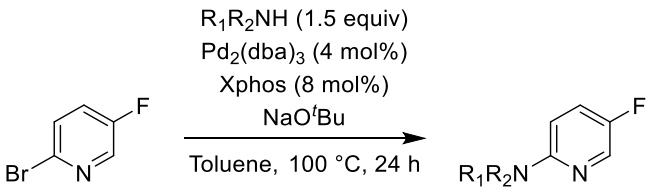
1.2. Preparation and characterization of anisyl(2-bromopyridinyl)iodonium triflate 5



To a solution of 2-bromo-5-iodopyridine (300 mg, 1.06 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) was added dropwise TfOH (373 µL, 4.23 mmol, 4.0 equiv) under argon. The reaction mixture was stirred for 10 min at rt and *m*-CPBA (77%, 414.5 mg, 1.85 mmol, 1.75 equiv) was added. The reaction mixture was stirred for 1.5 h at rt then cooled to 0 °C. Water (38 µL, 2.11 mmol, 2.0 equiv) and anisole (138 µL, 1.27 mmol, 1.2 equiv) were added. The reaction mixture was stirred for 30 min at 0 °C then concentrated under vacuum. Et_2O (2 mL) was added to the crude residue, and the mixture was stirred for 30 min at 0 °C. The resulting precipitate was filtered through a glass sintered funnel, washed with additional Et_2O (50 mL) and lyophilized to give the tittle product **5** as a grey solid (295 mg, 52% yield). Mp (°C): 143; R_f (CH_2Cl_2/MeOH 90:10): 0.7; ^{1}H NMR (600 MHz, CD_3OD) δ: 9.99 (d, J = 2.2 Hz, 1H), 8.39 (dd, J = 2.5, 8.6 Hz, 1H), 8.1 (d, J = 9.1 Hz, 2H), 7.74 (d, J = 8.5 Hz, 1H), 7.09 (d, J = 9.1 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (151 MHz, CD_3OD) δ: 164.8, 155.1, 146.8, 145.5, 138.8, 132.7, 121.8 (q, J = 316 Hz), 119.1, 114.6, 104.5, 56.4; ^{19}F NMR (376 MHz, CD_3OD) δ: -80.08; IR (cm^{-1}) ν_{max}: 3096, 1573, 1083, 514; HRMS (ESI): *m/z* calculated for $C_{12}H_{10}BrINO$ ($[M\text{-}OTf]$)$^{+}$: 389.8985, found: 389.8975.

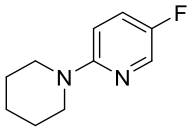
1.3. Preparation and characterization of 2-amino-5-fluoropyridines 1

1.3.1. General Procedure



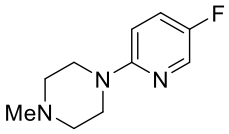
To 2-bromo-5-fluoropyridine **9** (100 mg, 0.57 mmol, 1.0 equiv), $Pd_2(dba)_3$ (10.4 mg, 0.011 mmol, 4 mol% Pd), Xphos (21.7 mg, 0.045 mmol, 8 mol%), NaO^tBu (163.8 mg, 1.70 mmol, 3.0 equiv) and amine (1.5 equiv) was added anhydrous toluene (2 mL) under argon. The reaction mixture was stirred at 100 °C for 24 h then cooled down to rt. The crude mixture was concentrated under vaccum. Purification by column chromatography on silica gel using CH_2Cl_2 or a 9:1 mixture of CH_2Cl_2/MeOH as eluent gave the desired 2-amino-5-fluoropyridines **1**.

1.3.2. 5-Fluoro-2-(piperidin-1-yl)pyridine 1a [1287218-71-6]



Fluoropyridine **1a** was obtained according to General Procedure from 2-bromo-5-fluoropyridine **9** (100 mg, 0.57 mmol, 1.0 equiv) and piperidine (84 µL, 0.85 mmol, 1.5 equiv) as a slightly yellow oil (102 mg, quantitative yield). R_f (CH_2Cl_2): 0.7; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.02 (d, *J* = 3.1 Hz, 1H), 7.23-7.19 (m, 1H), 6.59 (dd, *J* = 3.4, 9.3 Hz, 1H), 3.43 (m, 4H), 1.65-1.60 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 157.0, 153.2 (d, *J* = 243.4 Hz), 134.6 (d, *J* = 24.1 Hz), 125.0 (d, *J* = 20.1 Hz), 107.9 (d, *J* = 3.6 Hz), 47.2, 25.5, 24.6; ^{19}F NMR (471 MHz, $CDCl_3$) δ: -144.01; IR (cm^{-1}) ν_{max}: 2933, 1225, 1128.

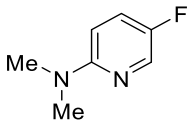
1.3.3. 5-Fluoro-2-(4-methylpyperazin-1-yl)-5-fluoropyridine 1b [1877101-49-9]



Fluoropyridine **1b** was obtained according to General Procedure from 2-bromo-5-fluoropyridine **9** (100 mg, 0.57 mmol, 1.0 equiv) and 1-methylpiperazine (95 µL, 0.85 mmol, 1.5 equiv) as a brown oil (111 mg, quantitative yield). R_f (CH_2Cl_2MeOH 90:10): 0.6; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.04 (d, *J* = 3.0 Hz, 1H), 7.26-7.22 (m, 1H), 6.60 (dd, *J* = 3.3, 9.2 Hz, 1H), 3.48 (t, *J* = 5.1 Hz, 4H), 2.53 (t, *J* = 5.2 Hz, 4H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 156.7,

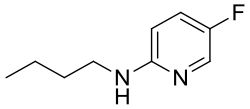
153.7 (d, *J* = 244.3 Hz), 134.8 (d, *J* = 23.9 Hz), 125.1 (d, *J* = 20.2 Hz), 107.8 (d, *J* = 3.8 Hz), 55.0, 46.3, 46.1; ^{19}F NMR (471 MHz, $CDCl_3$) δ: -142.84; IR (cm^{-1}) ν_{max}: 2938, 1336, 1245; HRMS (ESI): *m/z* calculated for $C_{10}H_{15}FN_3$ ($[M+H]$)$^+$: 196.1250, found: 196.1249.

1.3.4. 2-(*N*,*N*-Dimethylamino)-5-fluoropyridine 1c [1420961-53-0]



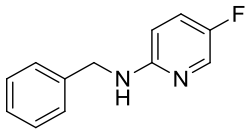
Fluoropyridine **1c** was obtained according to General Procedure from 2-bromo-5-fluoropyridine **9** (100 mg, 0.57 mmol, 1.0 equiv) and *N*,*N*-dimethylamine (57 µL, 0.85 mmol, 1.5 equiv) as a yellow oil (59 mg, 74% yield). R_f (CH_2Cl_2/MeOH 90:10): 0.5; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.03 (d, *J* = 3.0 Hz, 1H), 7.26-7.22 (m, 1H), 6.46 (dd, *J* = 3.3, 9.2 Hz, 1H), 3.06 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 155.2 (d, *J* = 249.5 Hz), 154.0, 135.4 (d, *J* = 25.2 Hz), 124.9 (d, *J* = 20.2 Hz), 115.3 (d, *J* = 3.8 Hz), 42.7; ^{19}F NMR (471 MHz, $CDCl_3$) δ: -145.88; IR (cm^{-1}) ν_{max}: 2896, 1372, 1226.

1.3.5. 2-(*n*-Butylamino)-5-fluoropyridine 1d [1248193-14-7]



Fluoropyridine **1d** was obtained according to General Procedure from 2-bromo-5-fluoropyridine **9** (100 mg, 0.57 mmol, 1.0 equiv) and *n*-butylamine (84 µL, 0.85 mmol, 1.5 equiv) as a yellow oil (95 mg, quantitative yield). R_f (CH_2Cl_2): 0.4; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.17 (d, *J* = 3.0 Hz, 1H), 7.30-7.28 (m, 1H), 7.00 (dd, *J* = 3.7, 9.1 Hz, 1H), 4.07 (t, *J* = 7.6 Hz, 1H), 1.67-1.61 (m, 1H), 1.39-1.31 (m, 1H), 0.91 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 155.3 (d, *J* = 249.5 Hz), 154.0, 135.4 (d, *J* = 25.2 Hz), 124.9 (d, *J* = 20.2 Hz), 115.3 (d, *J* = 3.8 Hz), 49.1, 30.4, 20.4, 14.1; ^{19}F NMR (471 MHz, $CDCl_3$) δ: -137.01; IR (cm^{-1}) ν_{max}: 3031, 1392, 1226.

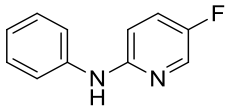
1.3.6. 2-Benzylamino-5-fluoropyridine 1e [1251026-62-6]



Fluoropyridine **1e** was obtained according to General Procedure from 2-bromo-5-fluoropyridine **9** (100 mg, 0.57 mmol, 1.0 equiv) and benzylamine (93 µL, 0.85 mmol, 1.5 equiv) as a yellow oil (17.1 mg, 15% yield). R_f (CH_2Cl_2): 0.6; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.97 (d, *J* = 2.9 Hz, 1H), 7.32-7.38 (m, 4H), 7.30-7.27 (m, 1H), 7.18 (m, 1H), 6.33 (dd, *J* = 3.4, 9.1 Hz, 1H), 4.87 (s, 1H) 4.47 (d, J = 5.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 155.5, 155.4, 152.6,

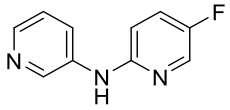
139.1, 134.8 (d, *J* = 24.6 Hz), 128.1, (d, J = 160.7 Hz), 127.4, 125.3 (d, J = 20.6 Hz), 107.1 (d, *J* = 3.9 Hz), 46.9; ^{19}F NMR (471 MHz, $CDCl_3$) δ: -143.45; IR (cm^{-1}) ν_{max}: 3029, 1467, 1218.

1.3.7. 2-Anilino-5-fluoropyridine 1f [51269-88-6]



Fluoropyridine **1f** was obtained according to General Procedure from 2-bromo-5-fluoropyridine **9** (100 mg, 0.57 mmol, 1.0 equiv) and aniline (78 µL, 0.85 mmol, 1.5 equiv) as a yellow solid (27 mg, 25% yield). Mp (°C): 87; R_f (CH_2Cl_2): 0.6; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.99 (d, *J* = 2.7 Hz, 1H), 7.27-7.17 (m, 5H), 6.97 (t, *J* = 7.2 Hz, 1H), 6.77 (dd, *J* = 3.4, 9.1 Hz, 1H), 6.49 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 155.4, 152.6, 140.8, 135.3 (d, *J* = 25.2 Hz), 129.5, 125.5 (d, *J* = 21.4 Hz), 123.0, 120.0, 109.1; ^{19}F NMR (471 MHz, $CDCl_3$) δ: -140.07; IR (cm^{-1}) ν_{max}: 3031, 1392, 1226.

1.3.8. 2-(3-Anilinoamino)-5-fluoropyridine 1g



Fluoropyridine **1g** was obtained according to General Procedure from 2-bromo-5-fluoropyridine **9** (100 mg, 0.57 mmol, 1.0 equiv) and 3-aminopyridine (80.2 mg, 0.85 mmol, 1.5 equiv) as a yellow solid (78 mg, 73% yield). Mp (°C): 146; R_f (CH_2Cl_2/MeOH 90:10): 0.6; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.60 (s, 1H), 8.22 (d, *J* = 4.4 Hz, 1H), 8.08 (d, *J* = 2.5 Hz, 1H), 8.00 (d, *J* = 7.9 Hz, 1H), 7.32-7.30 (m, 1H), 7.26-7.23 (m, 1H), 6.94 (s, 1H), 6.80 (dd, *J* = 3.1, 8.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 154.8 (d, *J* = 246.9 Hz), 151.7, 142.8, 140.8, 137.9, 135.0 (d, *J* = 25.5 Hz), 125.9 (d, *J* = 20.4 Hz), 125.6, 123.9, 110.5; ^{19}F NMR (471 MHz, $CDCl_3$) δ: -141.97; IR (cm^{-1}) ν_{max}: 3036, 1486, 1227 ; HRMS (ESI): *m/z* calculated for $C_{10}H_9FN_3$ $([M+H])^+$: 190.0781, found: 190.0785.

2. Radiochemistry

2.1. General procedures, materials

All experiments were carried behind a lead-wall or in a lead-shielded hot-cell to minimize the radiation exposure to personnel. No-carrier-added (nca) [^{18}F]fluoride anion was obtained through the ^{18}O(p, n)^{18}F nuclear reaction by irradiating ^{18}O-enriched water (97%, Eurisotop; 1.8 mL) with a beam of protons (18 MeV; 20–25 µA for 10-20 min) generated from a biomedical Cyclone 18/9 (IBA) cyclotron. Radioactivity measurements were performed using a calibrated ionizing chamber (Capintec R15C) and were corrected from background. Analytical High Performance Liquid Chromatography (HPLC) was carried out on a Waters e2695 (Separations module) coupled with a Waters 2998 (Photodiode Array Detector) and a MIP10 radioactive

detector (Nardeux). Semi-preparative HPLC was carried out using a Waters 515 HPLC pump coupled with a Waters 2487 UV detector set up at λ = 254 nm and a MIP10 radioactive detector (Nardeux). Pre-conditioned Light QMA carbonate anionic cartridges (Waters) were obtained from ABX. Silica Sep Pack cartridges were purchased from Waters.

2.2. Testing "minimalist" radiofluorination reaction from anisyl(2-chloropyridinyl)iodonium salts

2.2.1. Protocol

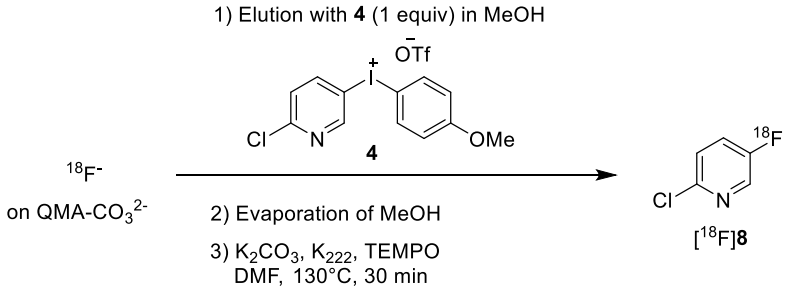
Minimalist radiofluorination of iodonium salts was conducted according to protocol based on works reported by Richarz et al.[3]

Method in DMF : [^{18}F]fluoride ion was fixed an a QMA carbonate anionic resin cartridge. The cartridge was washed with anhydrous MeOH (1 mL) and the radiofluoride was eluted was eluted with a solution of iodonium salt (0.02 mmol, 1 equiv) in anhydrous MeOH (500 µL). The elution yield was determined by comparing the radioactivity eluted into the reaction vial with the total radioactivity trapped on the anion exchange resin. MeOH was removed by heating at 70 °C for 3 min under nitrogen flow. TEMPO (1 equiv) in DMF (500 µL) was added to the residue, and the reaction mixture was stirred for 30 min at 130 °C then cooled to rt. After addition of mixture of ACN/H_2O (60:40 v/v; 500 µL), the mixture was injected onto a semi-preparative HPLC column (LUNA C18(2), 5 µm, 250 x 10 mm, flow rate at 3.5 mL/min, ACN/H_2O as eluent) for isolation of ^{18}F-products. The unreacted [^{18}F]fluoride and the desired [^{18}F]fluoropyridine were collected and measured for radioactivity. Isolated radiochemical yield was calculated as the ratio of the radioactivity of the desired [^{18}F]fluoropyridine compared to the total radioactivity injected onto the semi-preparative HPLC column.

Method in ACN : [^{18}F]fluoride ion was fixed an a QMA carbonate anionic resin cartridge. The cartridge was washed with anhydrous MeOH (1 mL) and the radiofluoride was eluted was eluted with a solution of iodonium salt (0.02 mmol, 1 equiv) in anhydrous MeOH (500 µL). The elution yield was determined by comparing the radioactivity eluted into the reaction vial with the total radioactivity trapped on the anion exchange resin. MeOH was removed by heating at 70 °C for 3 min under nitrogen flow. TEMPO (1 equiv) in ACN (500 µL) was added to the residue, and the reaction mixture was stirred for 15 min at 90 °C then cooled to rt. After addition of mixture of ACN/H_2O (60:40 v/v; 500 µL), the mixture was injected onto a semi-preparative HPLC column (LUNA C18(2), 5 µm, 250 x 10 mm, flow rate at 3.5 mL/min, ACN/H_2O as eluent) for isolation of ^{18}F-products. The unreacted [^{18}F]fluoride and the desired [^{18}F]fluoropyridine were collected and measured for radioactivity. Isolated radiochemical yield was calculated as the ratio of the radioactivity of the desired [^{18}F]fluoropyridine compared to the total radioactivity injected onto the semi-preparative HPLC column.

Results are presented in the following sections.

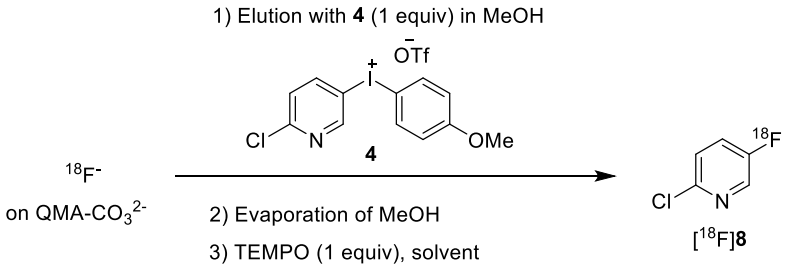
2.2.2. Table S1: Influence of additives (K_2CO_3, K_{222}, TEMPO) and of purification process for iodonium triflate **4**[a]



Entry	Isolation process for **4**	K_2CO_3		TEMPO		RCC±SEM[b]	Isolated RCY±SEM[c]
		equiv	mg	equiv	mg	(%, n = 3)	(%, n = 3)
1	Precipitation[d]	0	0	0	0	22±3	18±1
2	Precipitation[d]	0	0	1	3.2	54±4	43±3
3	Precipitation[d]	0	0	3	9.5	64±3	49±4
4	Precipitation[d]	0.2[f]	0.28	3	9.5	45±2	43±2
5	Precipitation[d]	3.6[f]	5	1	3.2	71±3	62±4
6	Al_2O_3[e]	0	0	1	3.2	60±5	49±2
7	Al_2O_3[e]	0	0	3	9.5	62±3	47±4
8	Al_2O_3[e]	0.2[f]	0.2	3	9.5	68±2	54±4
9	Al_2O_3[e]	3.6[f]	5	1	3.2	67±3	65±4

[a] Iodonium triflate **4** (10 mg, 0.02 mmol, 1 equiv).
[b] Radiochemical conversion of [^{18}F]fluoride ion, measured from HPLC chromatogram.
[c] Isolated decay corrected radiochemical yield calculated from [^{18}F]fluoride.
[d] Precipitation of the crude product as previously reported.[2]
[e] Basic alumina column after precipitation, then recrystallization as previously reported.[1,2]
[f] K_{222} (0.4 equiv or 7.2 equiv) was added when K_2CO_3 (0.2 equiv or 3.6 equiv) was present.

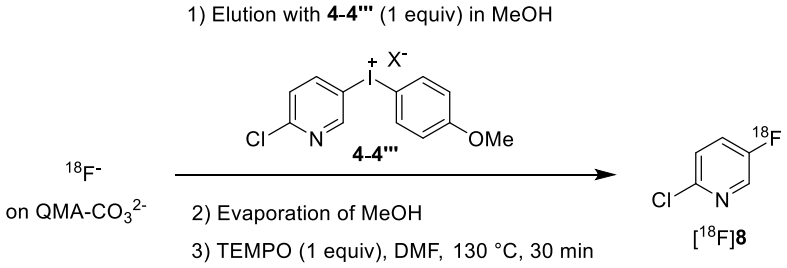
2.2.3. Table S2. Influence of the solvent in the minimalist radiofluorination of iodonium triflate **4** in the absence of K_2CO_3 and K_{222}[a]



Entry	Solvent	T (°C)	t (min)	RCC ± SEM[b] (%, n = 3)	Isolated RCY± SEM[c] (%, n = 3)
1	DMF	130	30	54±4	43±3
2	ACN	90	15	64±2	50±4
3	ACN	90	30	64±5	53±3

[a] Iodonium triflate **4** (10 mg, 0.02 mmol, 1 equiv) isolated by precipitation as previously reported,[2] TEMPO (3.2 mg, 0.02 mmol, 1 equiv).
[b] Radiochemical conversion of [^{18}F]fluoride ion, measured from HPLC chromatogram.
[c] Isolated decay corrected radiochemical yield calculated from [^{18}F]fluoride.

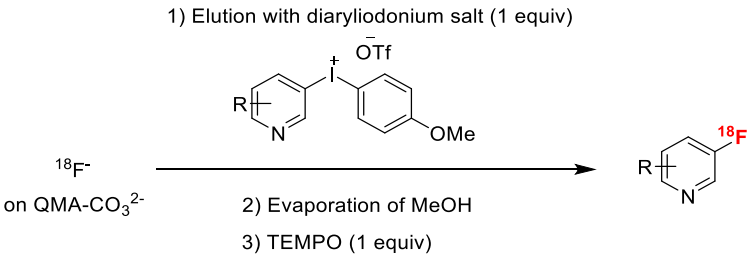
2.2.4. Table S3. Influence of the counter-ion of iodoniums **4** in its minimalist radiofluorination in the absence of K_2CO_3 and K_{222}[a]

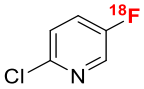
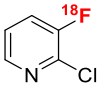
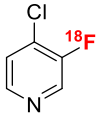
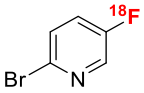
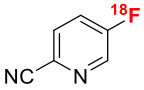
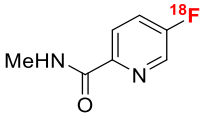
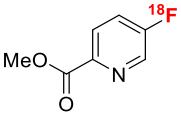
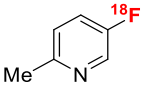


Entry	Iodonium	X	RCC ± SEM[b] (%, n = 3)	Isolated RCY ± SEM[c] (%, n = 3)
1	**4**[d]	OTf	54±4	43±3
2	**4'**	BF_4	39±2	44±2
3	**4''**	Br	2±2	2±1
4	**4'''**	OTs	40±3	32±1

[a] Iodonium salt **4**-**4'''** (0.02 mmol, 1 equiv), TEMPO (3.2 mg, 0.02 mmol, 1 equiv).
[b] Radiochemical conversion of [^{18}F]fluoride ion, measured from HPLC chromatogram.
[c] Isolated decay corrected radiochemical yield calculated from [^{18}F]fluoride.
[d] **4** isolated by precipitation as previously reported.[2]

2.2. Scope of "minimalist" radiofluorination reaction from functionalized anisyl(pyridinyl)iodonium triflates[a]

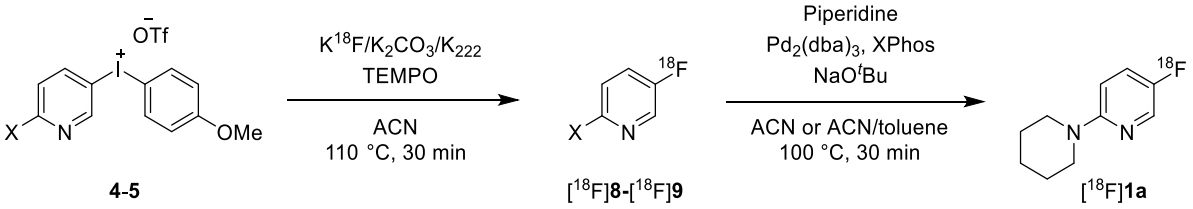


Entry	[^{18}F]Fluoropyridine	Isolated Yields ± SEM (%, n = 3) DMF, 130 °C, 30 min	MeCN, 90°C, 15 min
1		44±2	11±1
2		43±3	50±4
3		50±2	37±3
4		36±3	49±2
5		62±3	73±5
6		35±3	0
7		65±3	27±2
8		26±1	19±3
9		23±3	32±3
10		36±2	0

[a] Iodonium triflates isolated by precipitation as previously reported.[2]

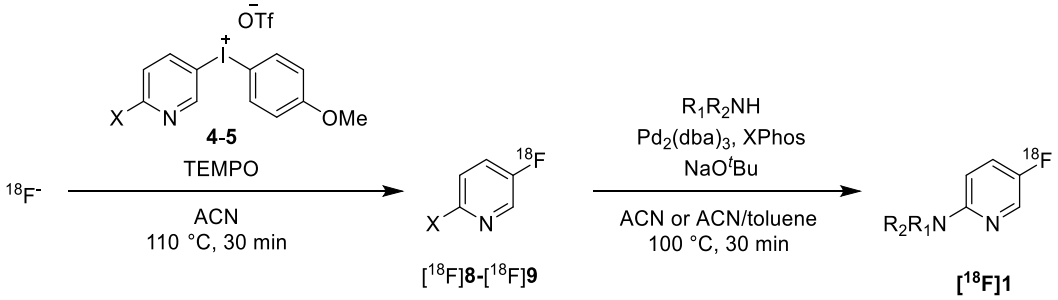
2.3 Radiosynthesis of 2-amino-5-[^{18}F]fluoropyridines [^{18}F]1

2.3.1 Route A (using classical radiofluorination procedure)



Aqueous cyclotron produced [^{18}F]fluoride was absorbed onto QMA carbonate anionic resin cartridge (from ABX) and then eluted in a V-vial with a solution of K_2CO_3 (5 mg, 36 µmol) and K_{222} (28 mg, 74 µmol) in MeCN/H_2O (50:50 v/v; 800 µL). Three successive cycles of azeotropic addition and evaporation of anhydrous MeCN (1 mL for each addition) were performed at 110 °C for 5 min under a nitrogen stream. Iodonium triflate precursor **4** or **5** (20 µmol) and TEMPO (3.1 mg, 20 µmol) in ACN (500 µL) were added to dried [^{18}F]fluoride. The reaction mixture was stirred for 30 min at 130 °C and then cooled to rt. An aliquot was taken off and injected to analytical HPLC (LUNA C18(2), 5 µm, 100 Å, 250 x 4.6, elution at 0.7 mL/min with a solution of MeCN/H_2O). Chromatograms revealed the formation of 2-halo-[^{18}F]fluoropyridines [^{18}F]**8** and [^{18}F]**9** in around 80±6% and 92±6% yields respectively. The crude mixture resulting from radiofluorination reaction was then passed through a silica Sep Pack cartridge (preconditioned with 1 mL toluene), then elution of the total radioactivity was carried out with toluene (1 mL) or a 1:1 mixture of ACN/toluene (1 mL). To the resulting solution were added $Pd_2(dba)_3$ (4.7 mg, 5 µmol), XPhos (4.6 mg, 10 µmol), NaO^{t}Bu (14.2 mg, 150 µmol) and piperidine (15 µL, 150 µmol). The mixture was stirred for 30 min at 100 °C, then cooled down to rt. Analytical HPLC (LUNA C18(2), 5 µm, 100 Å, 250 x 4.6 mm, elution at 0.7 mL/min with a solution of MeCN/H_2O) was performed for the identification of ^{18}F-products. Results are given in Table 2 of the manuscript.

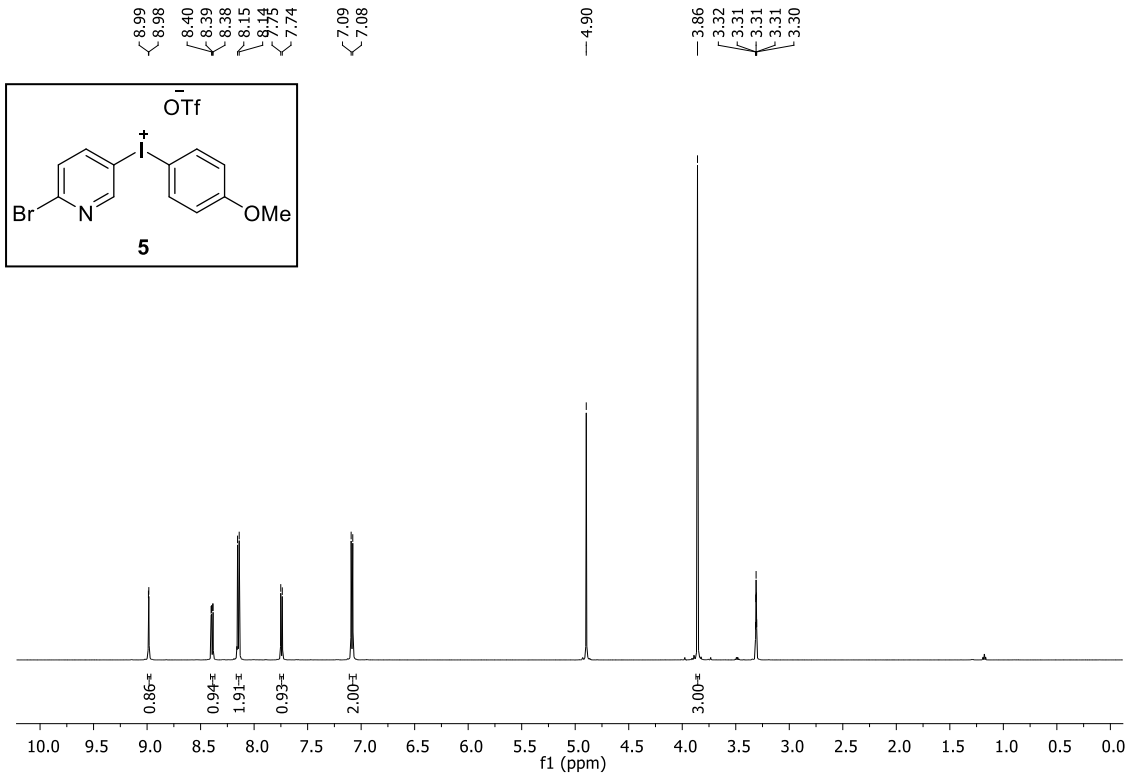
2.3.2 Route B (via minimalist radiofluorination)

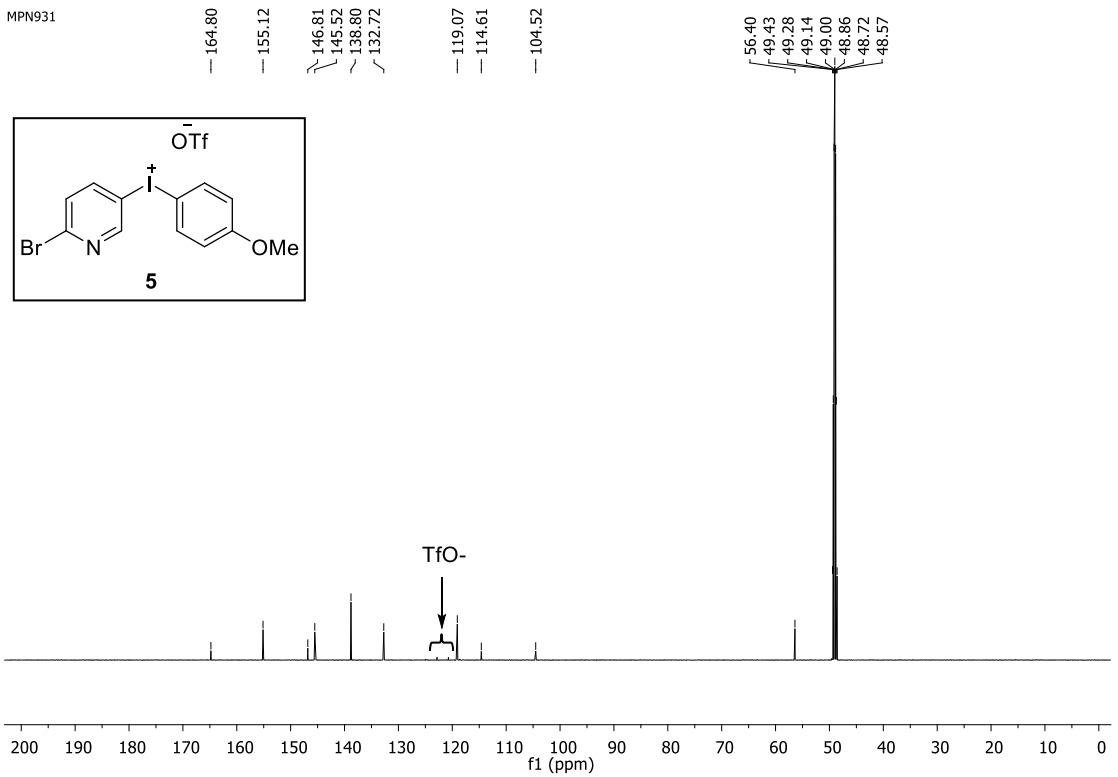


[^{18}F]Fluoride ion was fixed an a QMA carbonate anionic resin cartridge. The cartridge was washed with anhydrous MeOH (1 mL) and the radiofluoride was eluted was eluted with a solution of iodonium salt (0.02 mmol, 1 equiv) in anhydrous MeOH (500 µL). The elution yield

was determined by comparing the radioactivity eluted into the reaction vial with the total radioactivity trapped on the anion exchange resin. MeOH was removed by heating at 70 °C for 3 min under nitrogen flow. TEMPO (2.9 mg, 0.02 mmol, 1 equiv) in ACN (500 µL) were added to the residue and the reaction mixture was stirred for 30 min at 110 °C then cooled to rt. Toluene (500 µL) was added. An aliquot was taken off and injected to analytical HPLC (LUNA C18(2), 5 µm, 100 Å, 250 x 4.6, elution at 0.7 mL/min with a solution of MeCN/H_2O). Chromatograms revealed the formation of 2-halo-[^{18}F]fluoropyridines [^{18}F]**8** and [^{18}F]**9** in around 62±9% and 88±11% yields respectively. The crude mixture resulting from radiofluorination reaction was passed through a silica Sep Pack cartridge (preconditioned with 1 mL toluene) then elution of the total radioactivity was carried out with toluene (1 mL) or a 1:1 mixture of ACN/toluene (1 mL). To the resulting solution were added $Pd_2(dba)_3$ (4.7 mg, 5 µmol), XPhos (4.6 mg, 10 µmol), NaO^{t}Bu (14.2 mg, 150 µmol) and piperidine (15 µL, 150 µmol). The mixture was stirred for 30 min at 100 °C, then cooled down to rt. Analytical HPLC (LUNA C18(2), 5 µm, 100 Å, 250 x 4.6 mm, elution at 0.7 mL/min with a solution of MeCN/H_2O) was performed for the identification of ^{18}F-products. Results are given in Table 2 of the manuscript. Semi-preparative HPLC (LUNA C18(2), 5 µm, 100 Å, 250 x 10 mm, elution at 3.5 mL/min with a solution of MeCN/H_2O) was performed for the isolation of ^{18}F-products.

3. ^{1}H, ^{13}C and ^{19}F NMR Spectra

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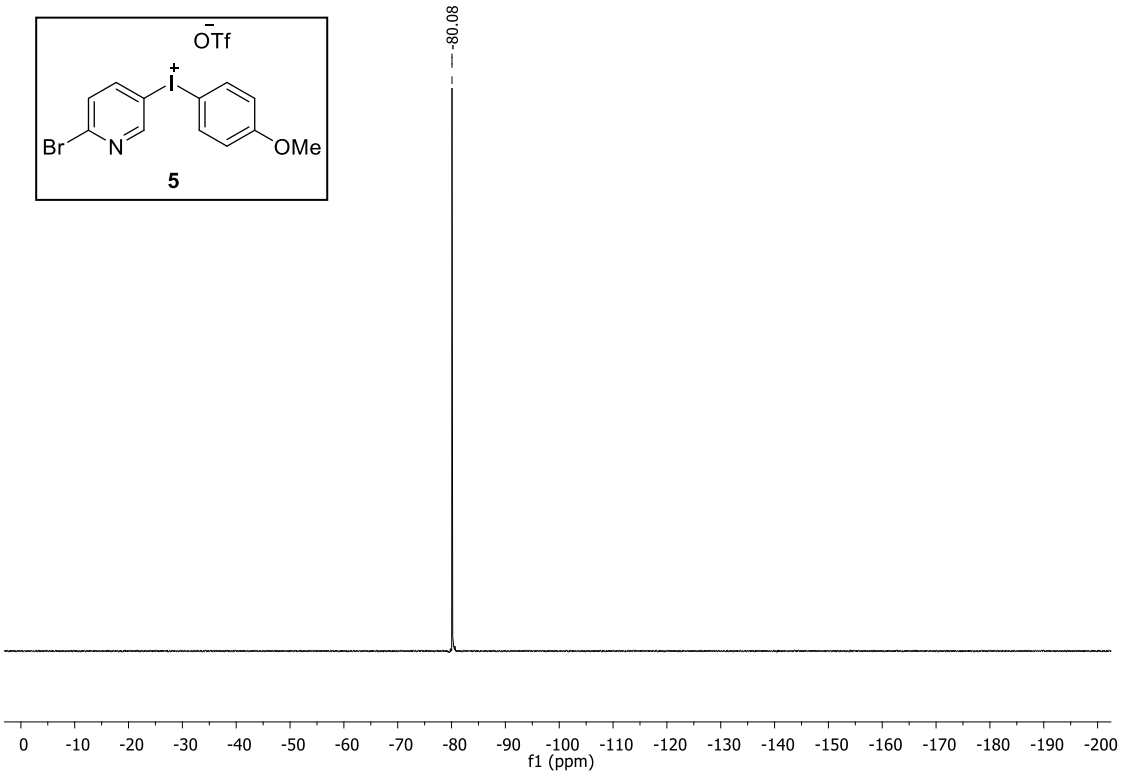
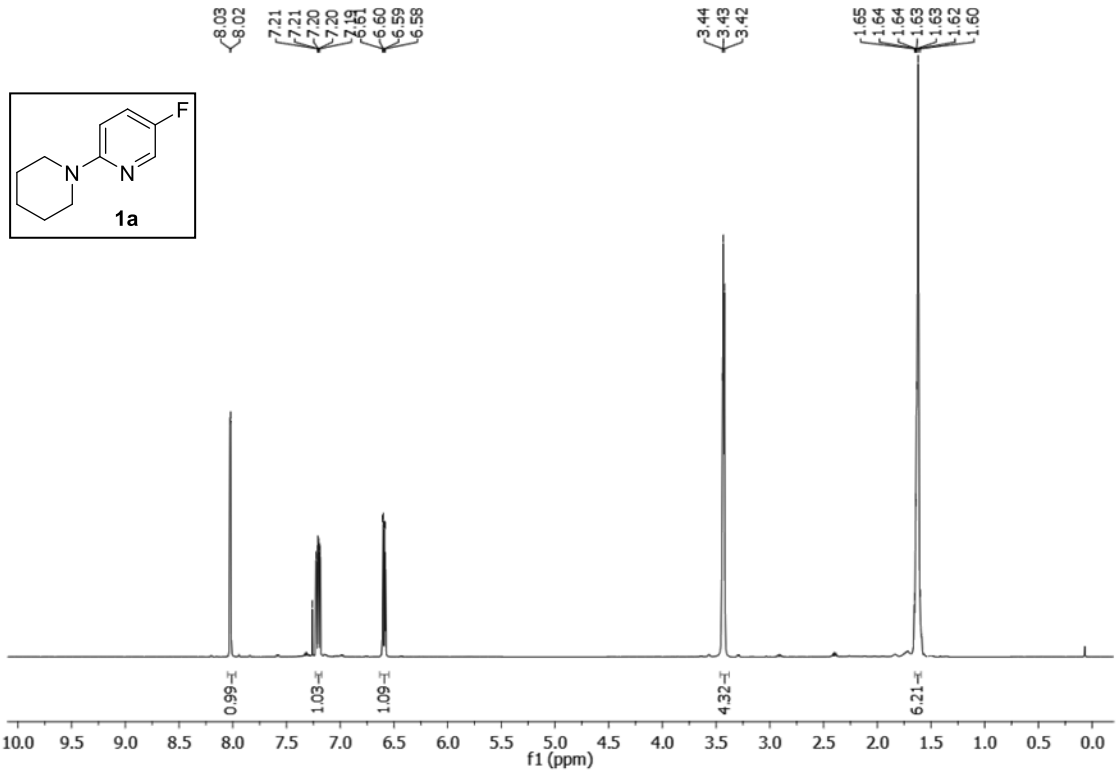
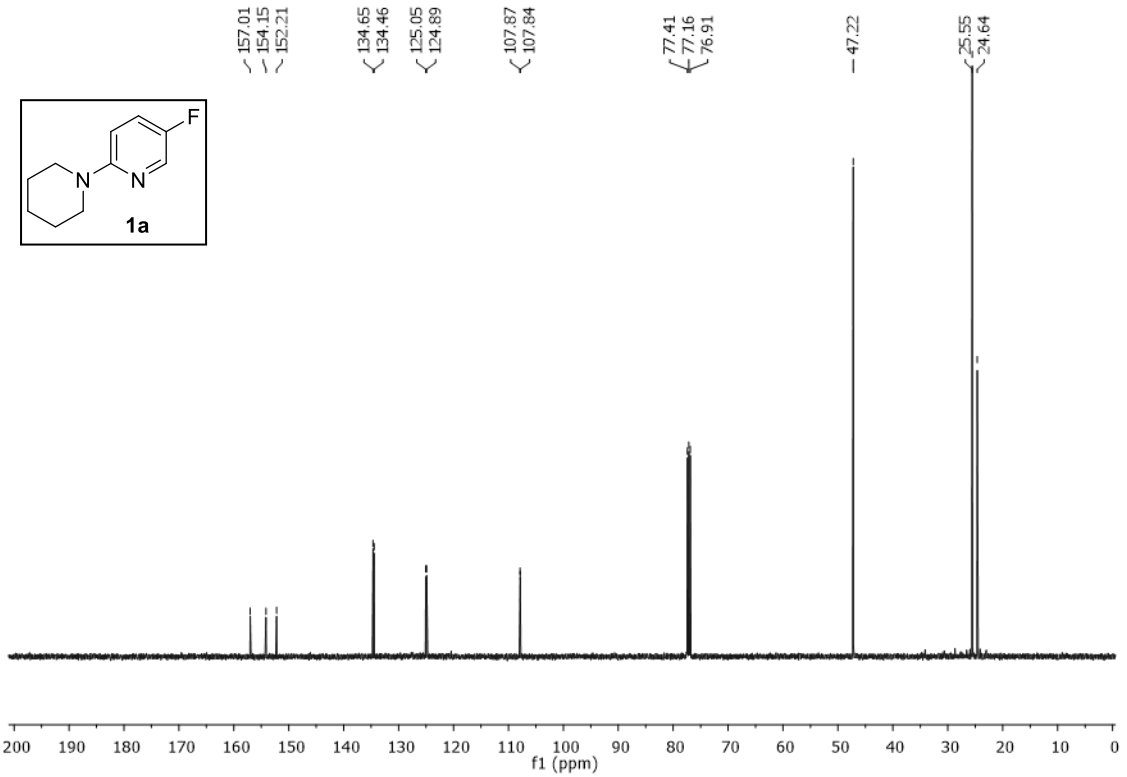
155.12
146.81
145.52
138.80
132.72
119.07
114.61
104.52
56.40
49.43
49.28
49.14
49.00
48.86
48.72
48.57
OTf
Br
N
OMe
5
TfO-
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OTf
Br
N
OMe
5
-80.08
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


8.03
8.02
7.21
7.21
7.20
7.20
7.19
6.61
6.60
6.59
6.58
3.44
3.43
3.42
1.65
1.64
1.64
1.63
1.63
1.62
1.60
F
N
N
1a
0.99
1.03
1.09
4.32
6.21
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


157.01
154.15
152.21
134.65
134.46
125.05
124.89
107.87
107.84
77.41
77.16
76.91
47.22
25.55
24.64
F
N
N
1a
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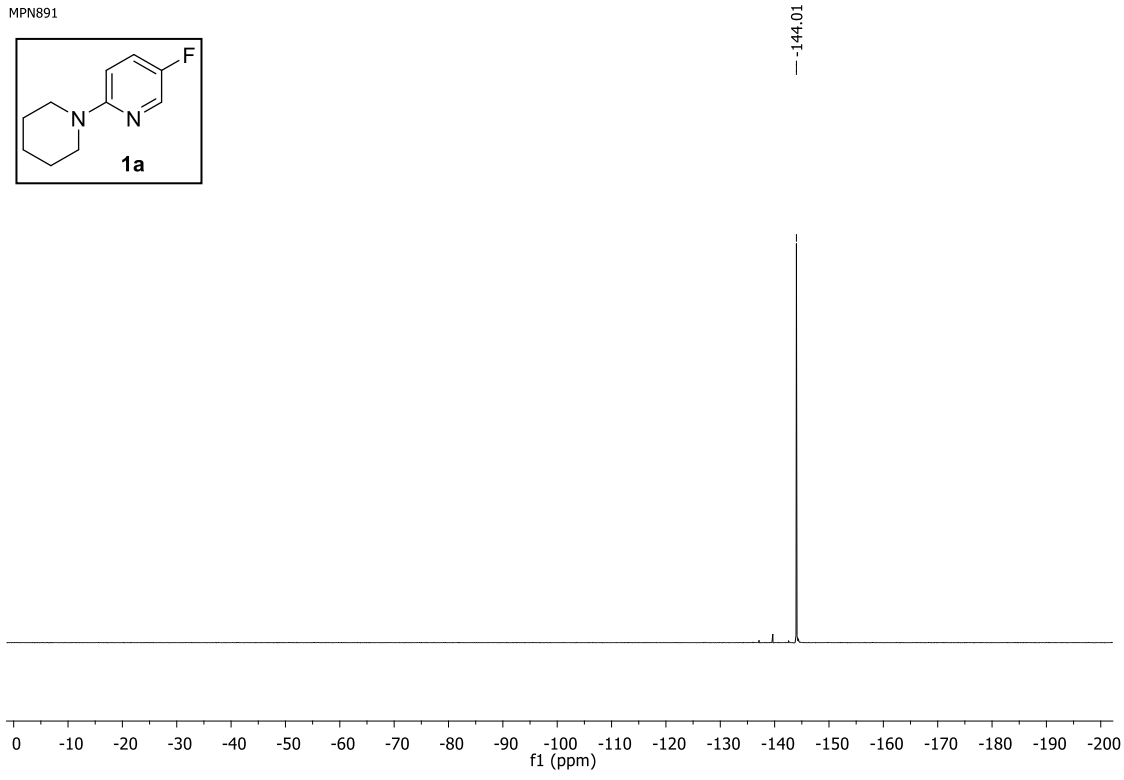
f1 (ppm)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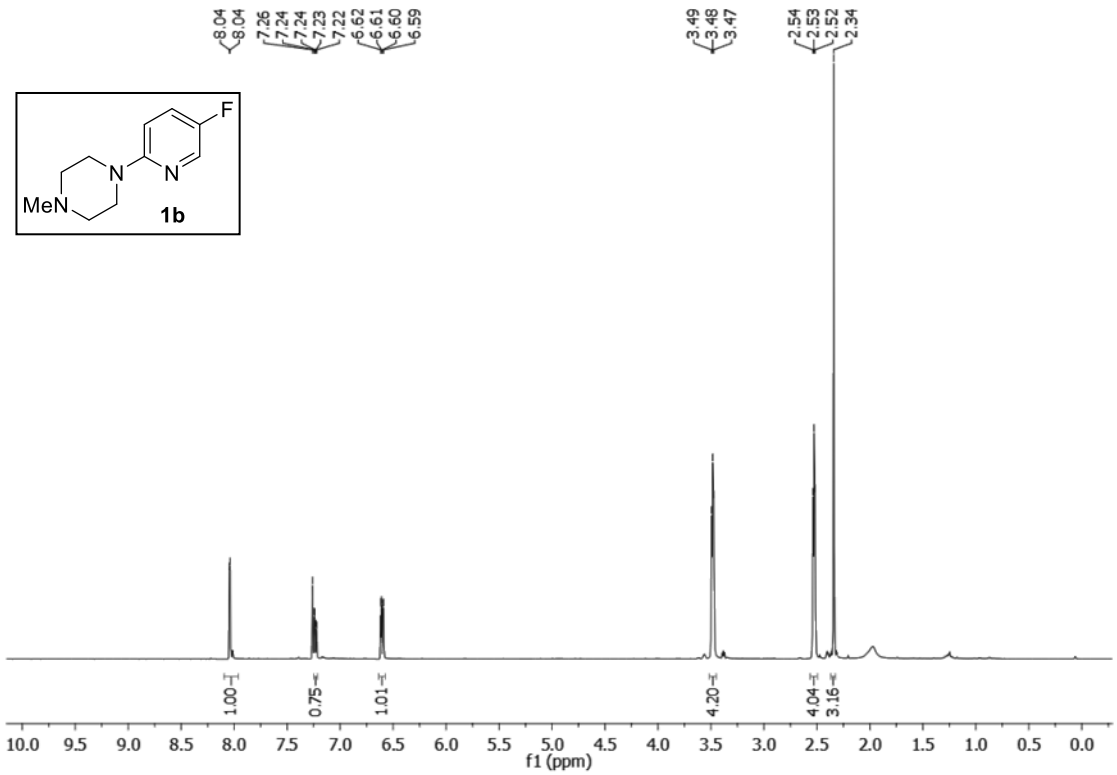
-144.01
F
N
N
1a
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)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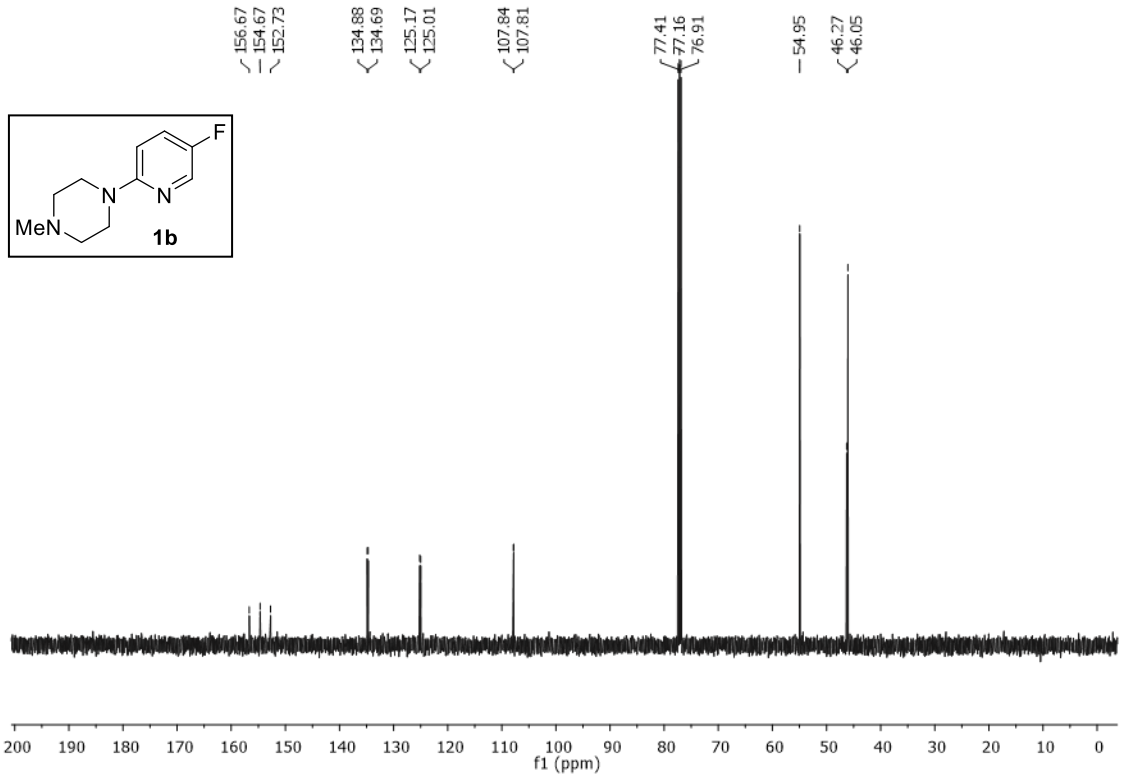
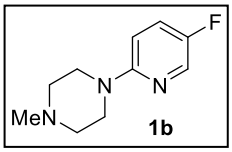
8.04
7.26
7.24
7.24
7.23
7.22
6.62
6.61
6.60
6.59
3.49
3.48
3.47
2.54
2.53
2.52
2.34
F
N
N
MeN
1b
1.00
0.75
1.01
4.20
4.04
3.16
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


156.67
154.67
152.73
134.88
134.69
125.17
125.01
107.84
107.81
77.41
77.16
76.91
54.95
46.27
46.05
F
N
N
MeN
1b
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


F
N
N
MeN

1b

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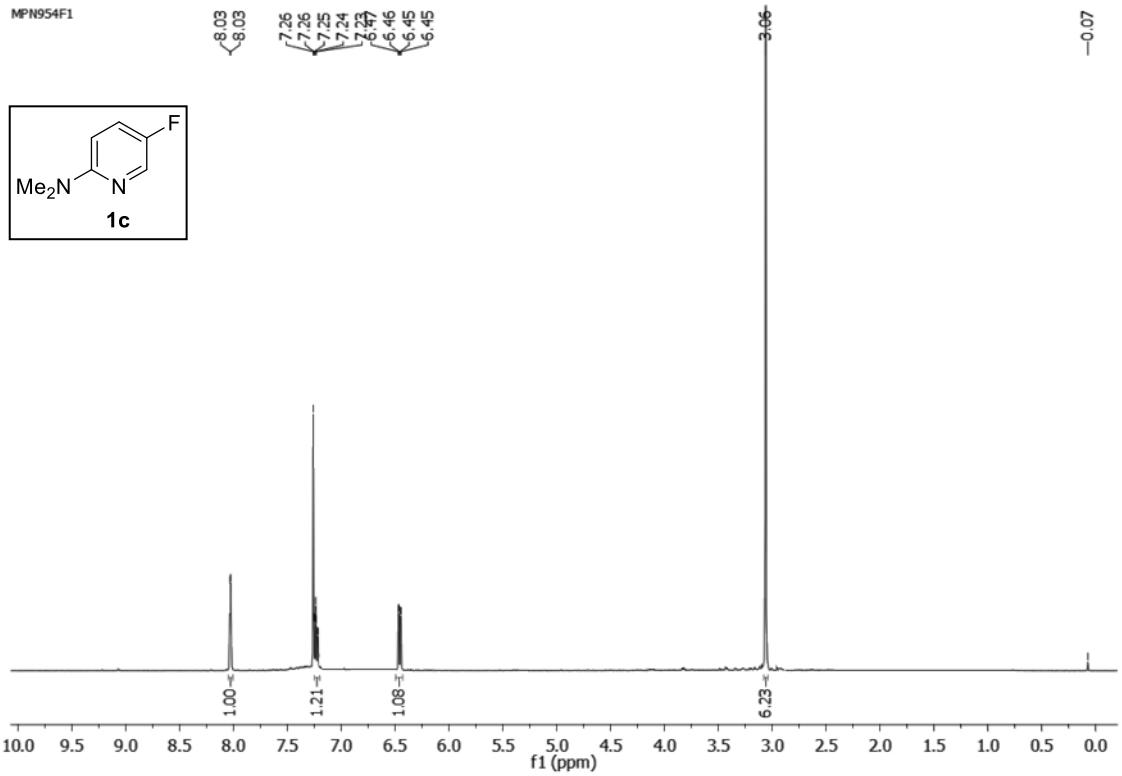
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)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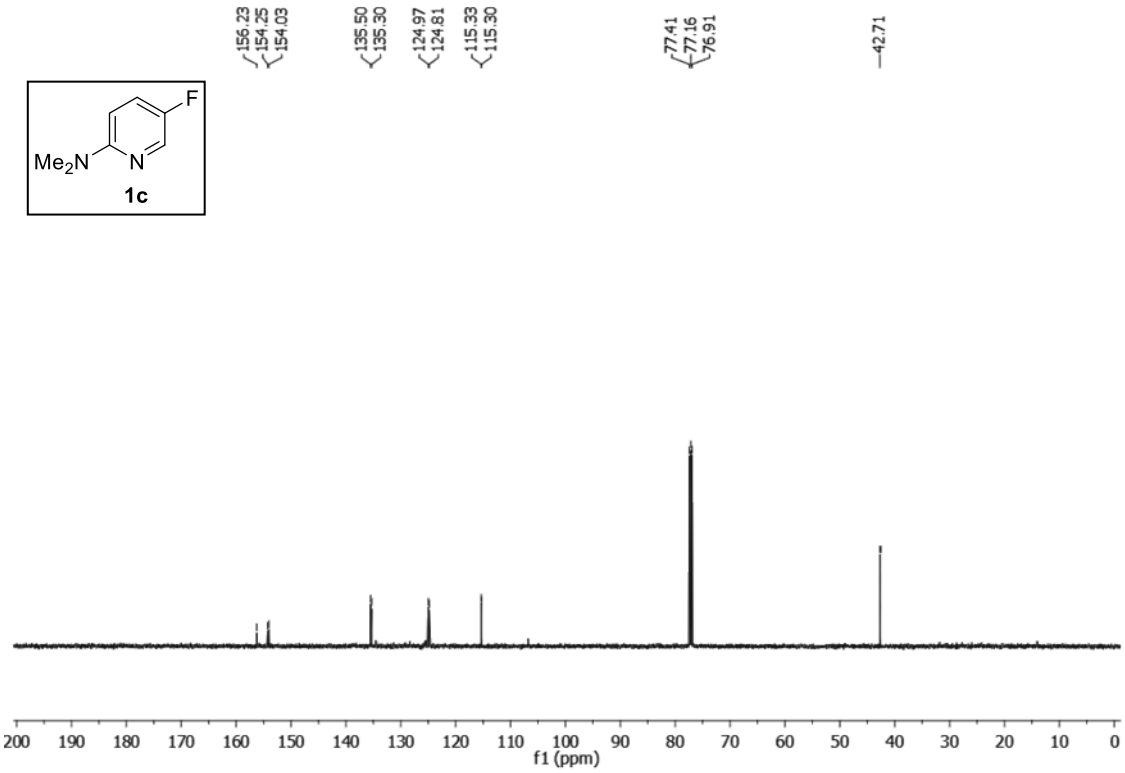
7.26
7.25
7.24
6.46
6.45
6.45
3.06
-0.07
F
Me2N
N
1c
1.00
1.21
1.08
6.23
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


156.23
154.25
154.03
135.50
135.30
124.97
124.81
115.33
115.30
77.41
77.16
76.91
42.71
F
Me2N
N
1c
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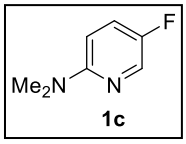
f1 (ppm)


F
Me2N
N

1c

-145.88
0
-10
-20
-30
-40
-50
-60
-70
-80
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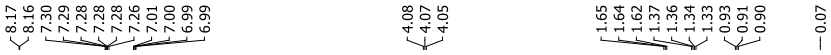
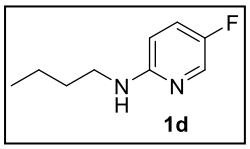
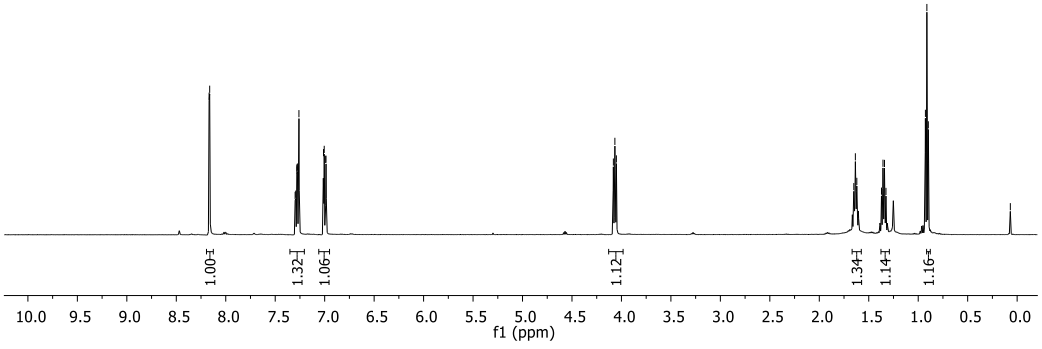
-160
-170
-180
-190
-200
f1 (ppm)


8.17
8.16
7.30
7.29
7.28
7.28
7.28
7.26
7.01
7.00
6.99
6.99
4.08
4.07
4.05
1.65
1.64
1.62
1.37
1.36
1.34
1.33
0.93
0.91
0.90
0.07


F
N
H
N

1d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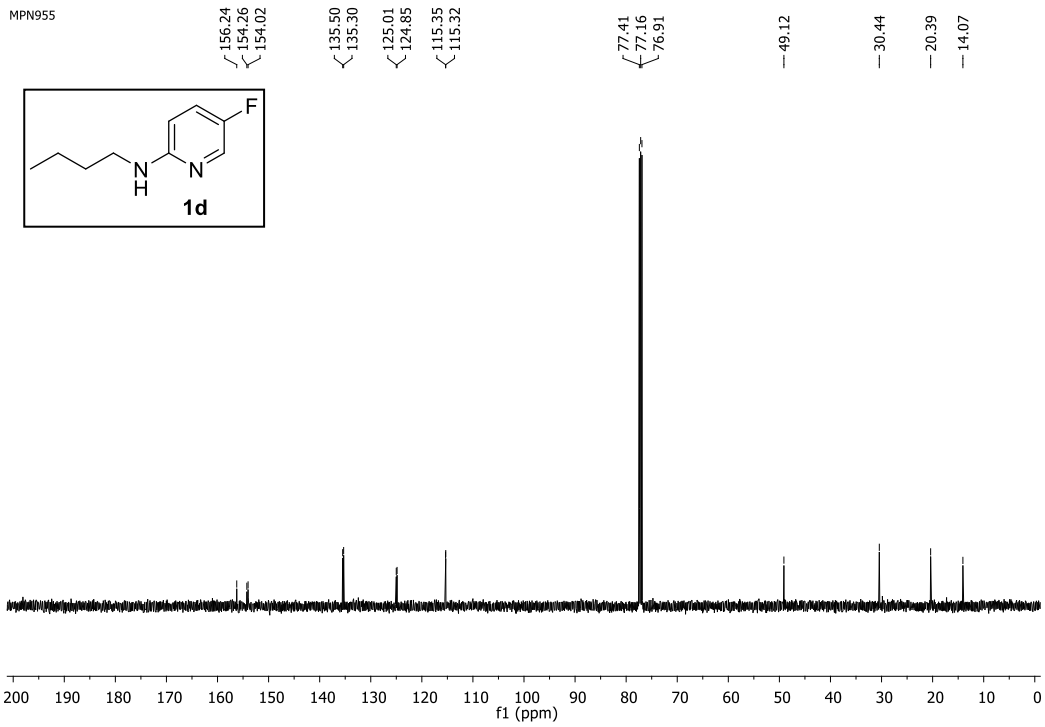
1.32
1.06
1.12
1.34
1.14
1.16
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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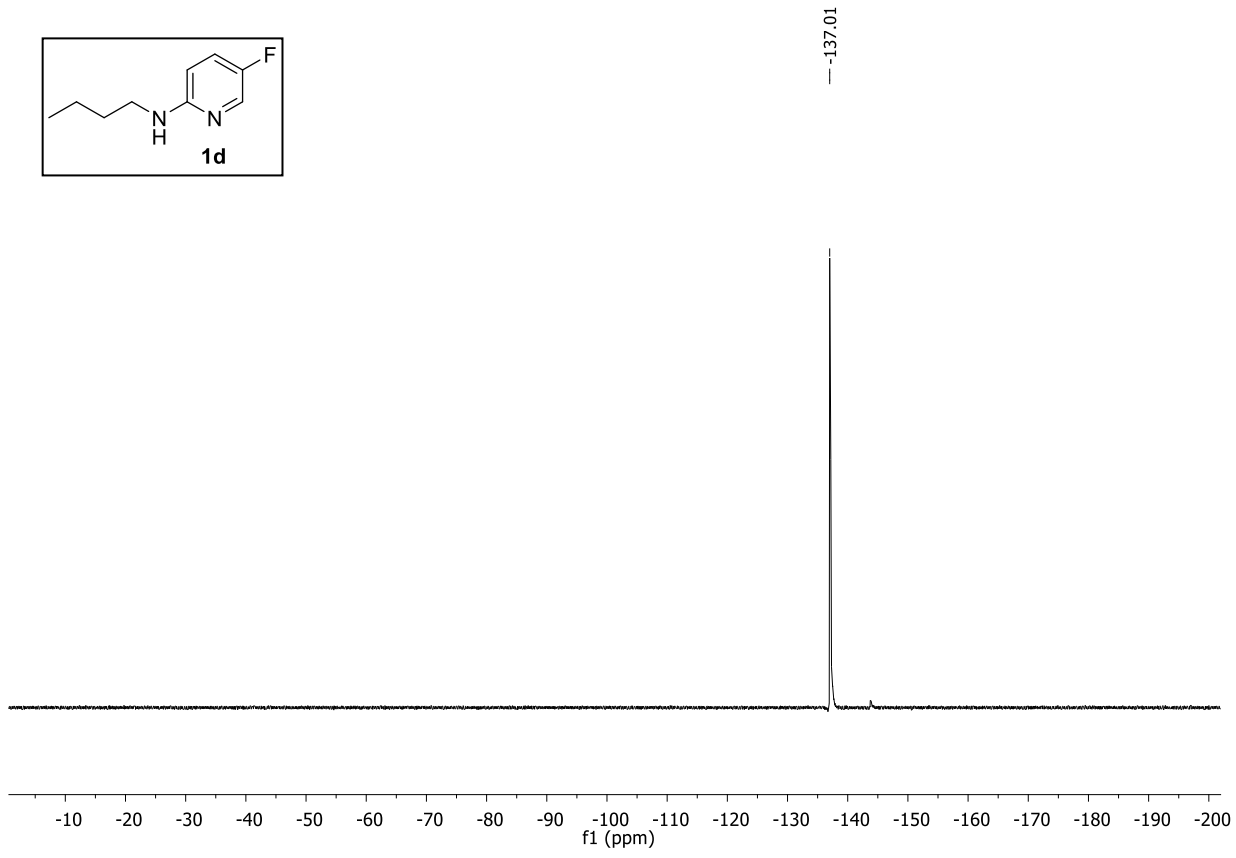
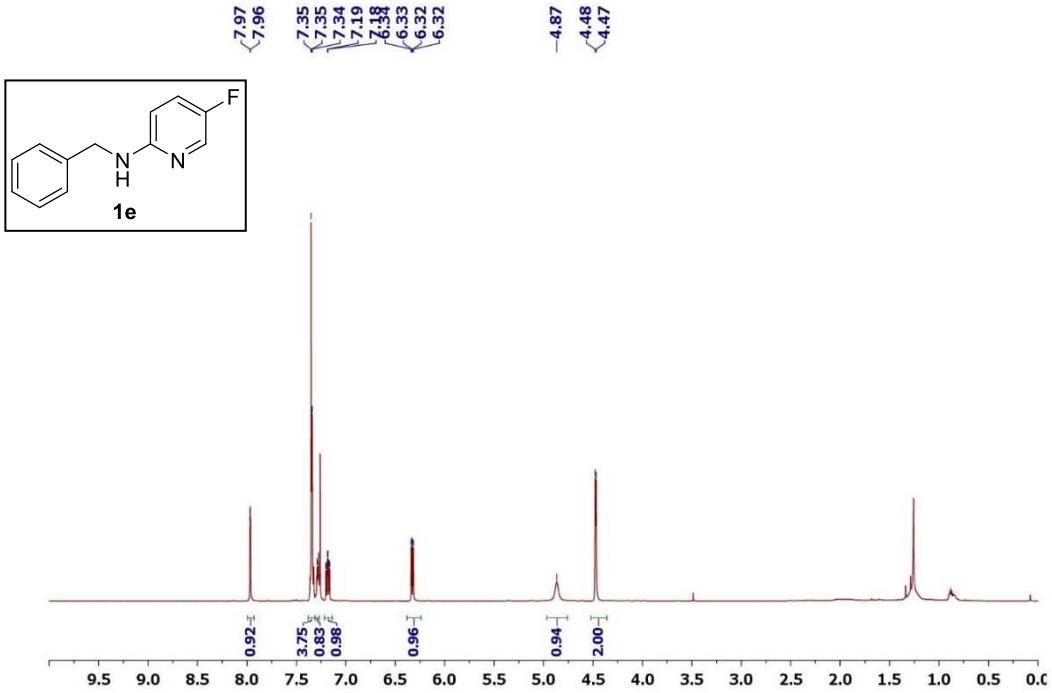
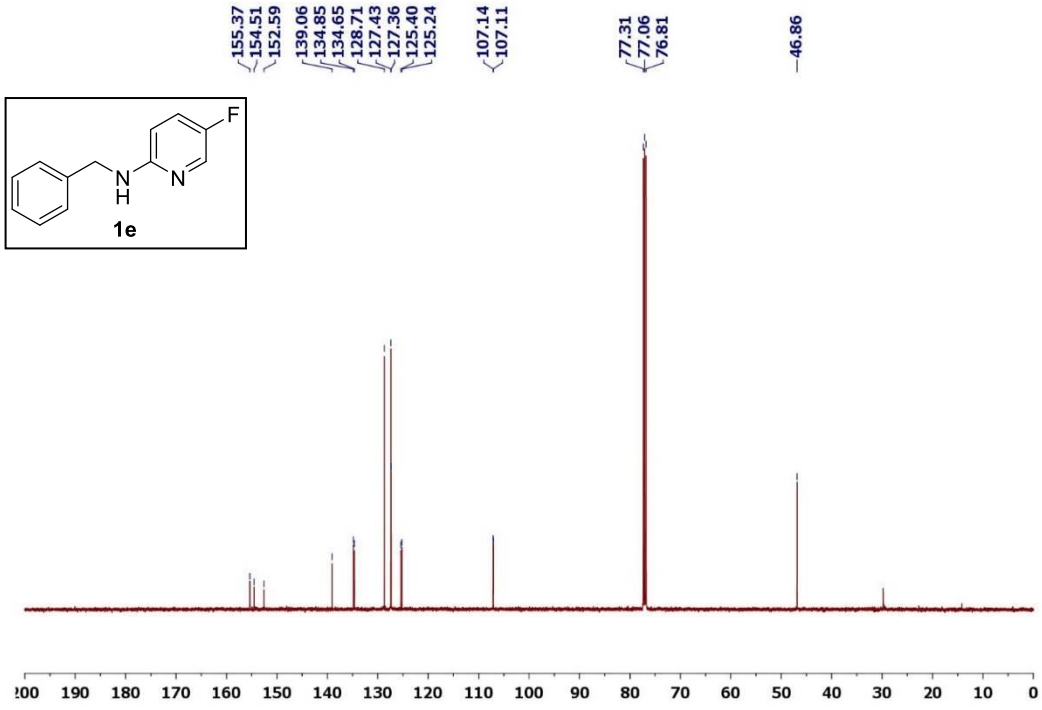
125.01
124.85
115.35
115.32
77.41
77.16
76.91
49.12
30.44
20.39
14.07
F
N
H
N
1d
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-137.01
F
N
H
N
1d
-10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


7.97
7.96
7.35
7.35
7.34
7.19
6.33
6.32
6.32
4.87
4.48
4.47
F
N
H
N
1e
0.92
3.75
0.83
0.98
0.96
0.94
2.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5


155.37
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139.06
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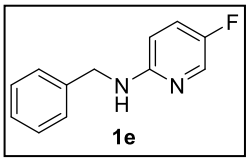
134.65
128.71
127.43
127.36
125.40
125.24
107.14
107.11
77.31
77.06
76.81
46.86
F
N
H
N
1e
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


F
N
H
N
1e

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-143.44
-143.45
-143.46
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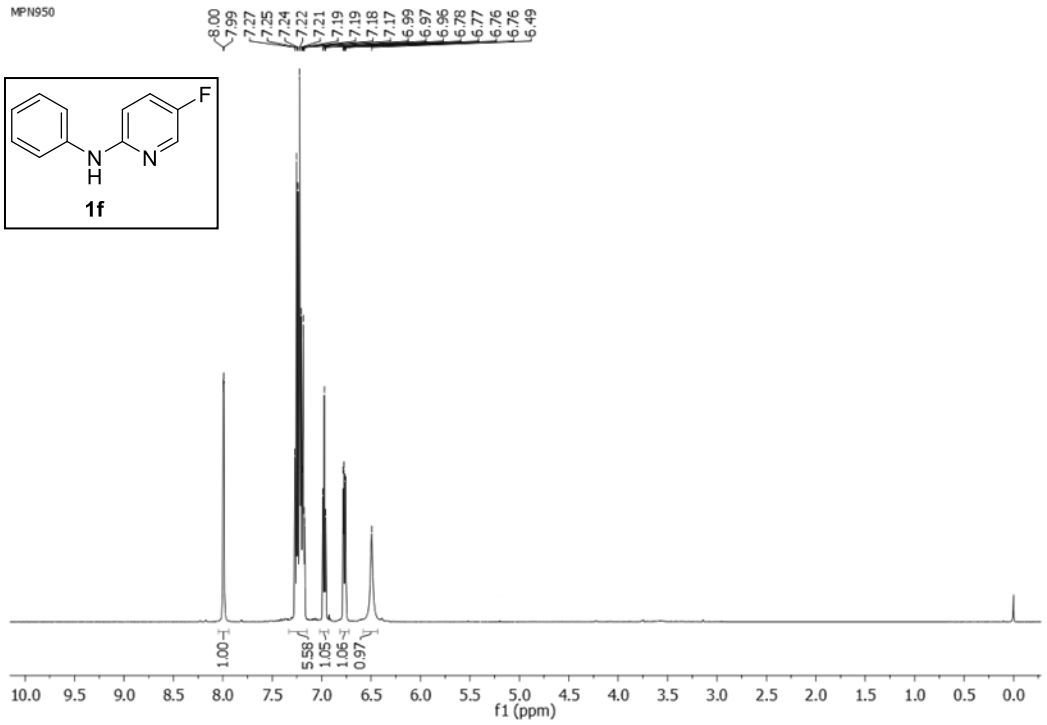
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7.25
7.24
7.22
7.21
7.19
7.19
7.18
7.17
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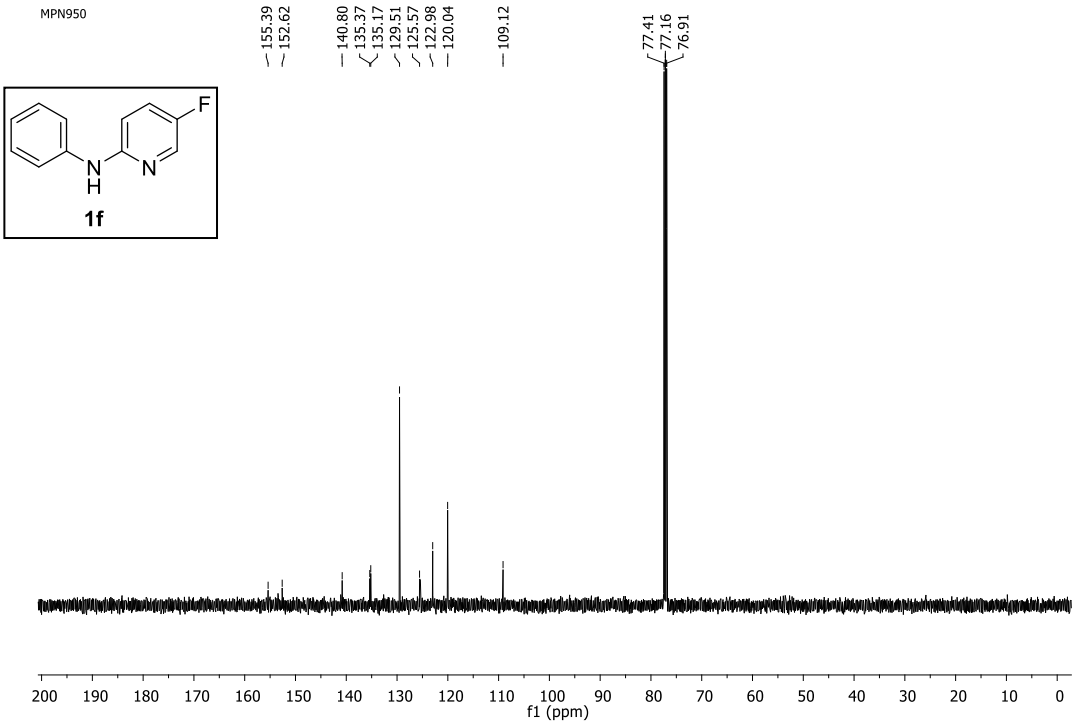
6.97
6.96
6.78
6.77
6.76
6.76
6.49
F
N
H
N
1f
1.00
5.58
1.05
1.06
0.97
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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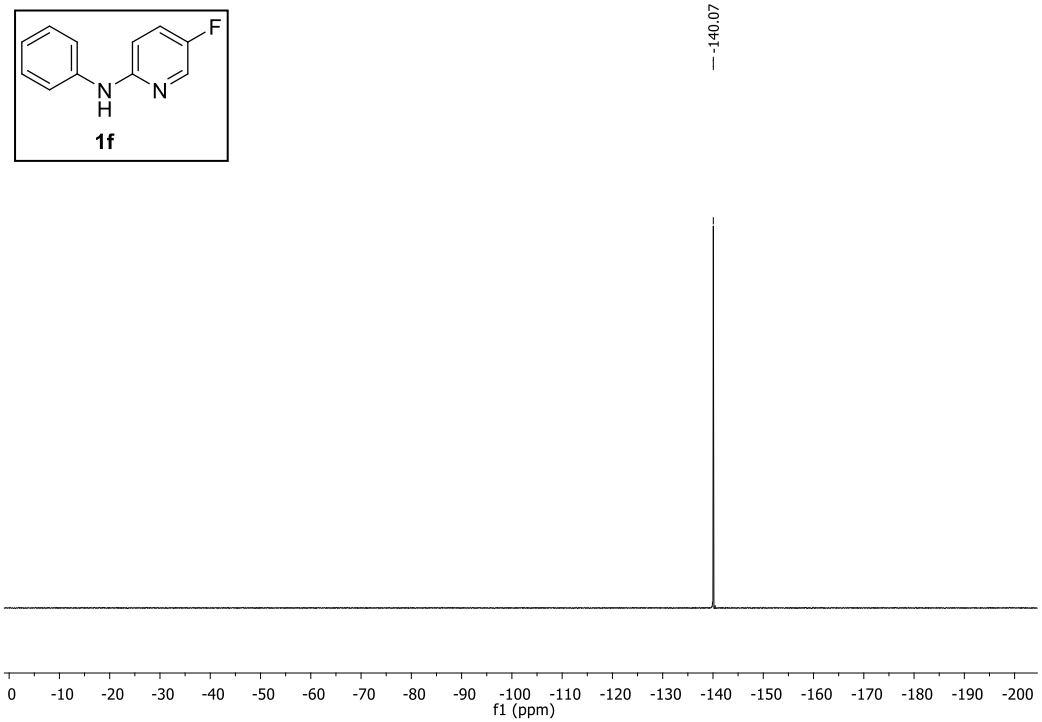
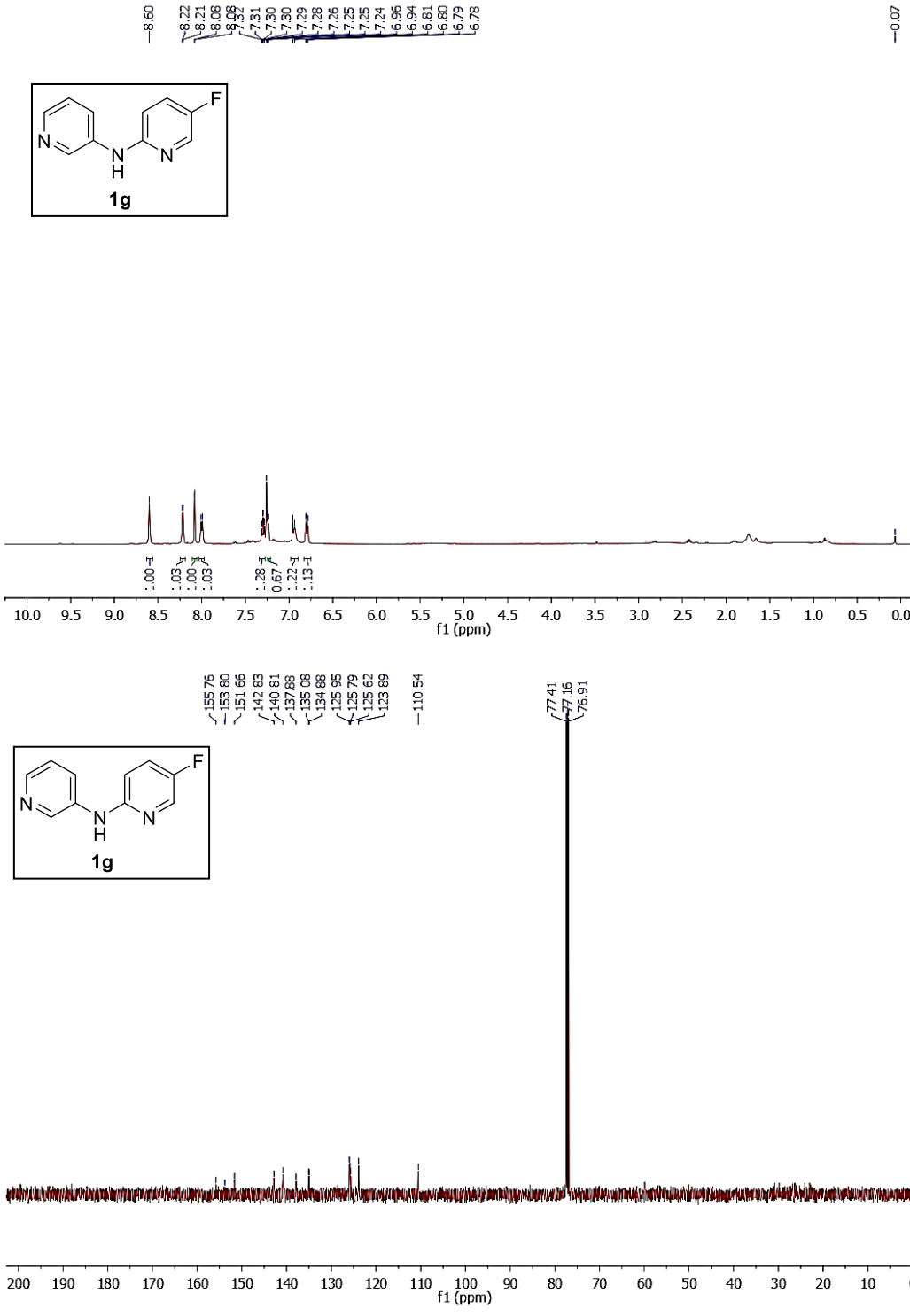
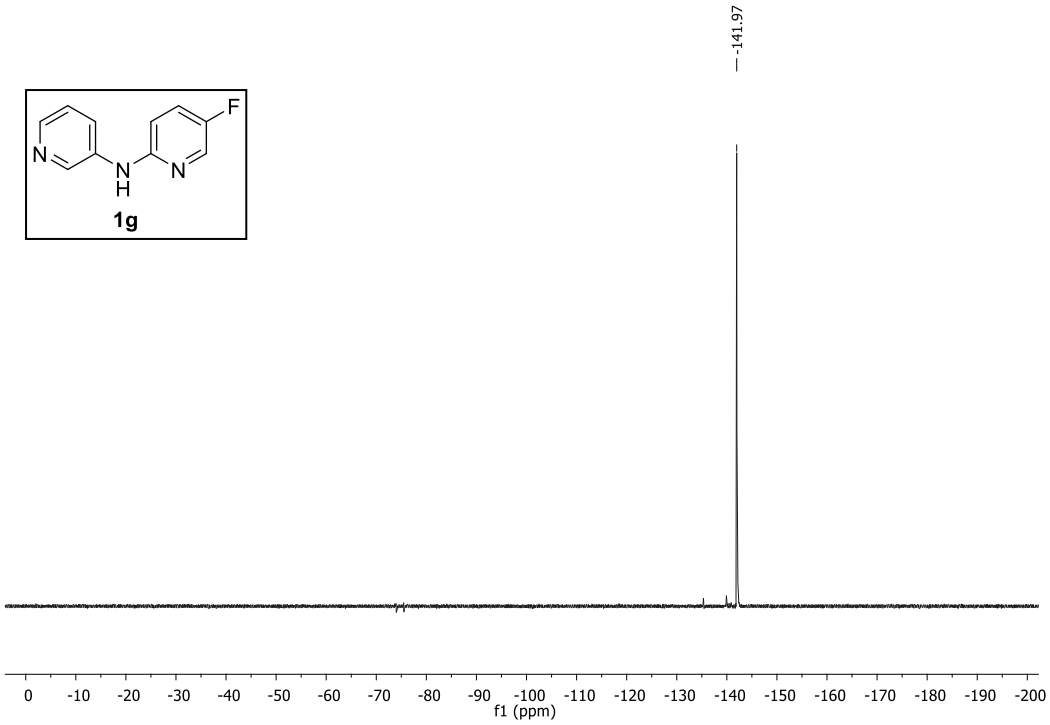
135.37
135.17
129.51
125.57
122.98
120.04
109.12
77.41
77.16
76.91
F
N
H
N
1f
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-140.07
F
N
H
N
1f
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


8.60
8.22
8.21
8.06
8.05
7.32
7.31
7.30
7.30
7.29
7.28
7.26
7.25
7.25
7.24
6.96
6.94
6.81
6.80
6.79
6.76
0.07
F
N
N
H
N
1g
1.00
1.03
1.00
1.03
1.28
0.67
1.22
1.13
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
155.76
153.80
151.66
142.83
140.81
137.88
135.08
134.88
125.95
125.79
125.62
123.89
110.54
77.41
77.16
76.91
F
N
N
H
N
1g
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

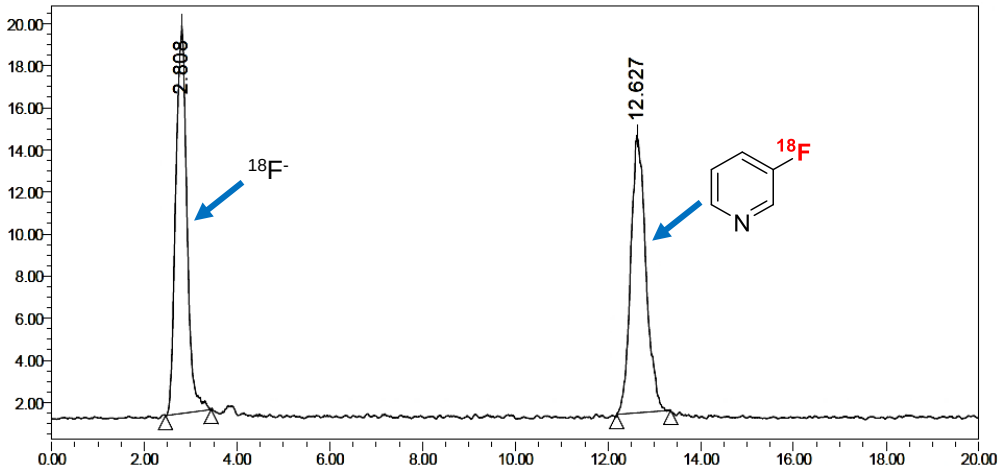

-141.97
F
N
N
H
N
1g
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

4. HPLC chromatograms

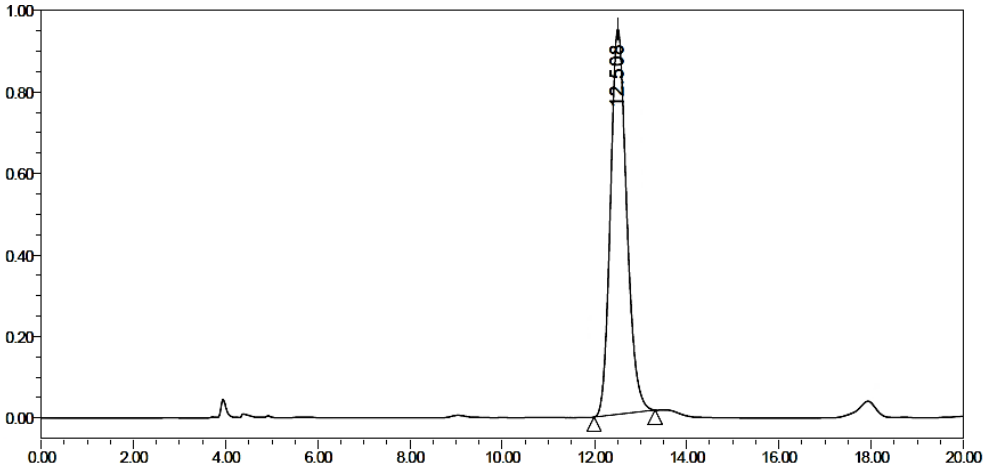
4.1 [^{18}F]Fluoropyridines obtained by minimalist radiofluorination of iodonium precursors

LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H_2O (20:80 to 50:50 over 10 min); flow rate: 0.7 mL/min; UV detection at λ = 254 nm.

Radioactive channel

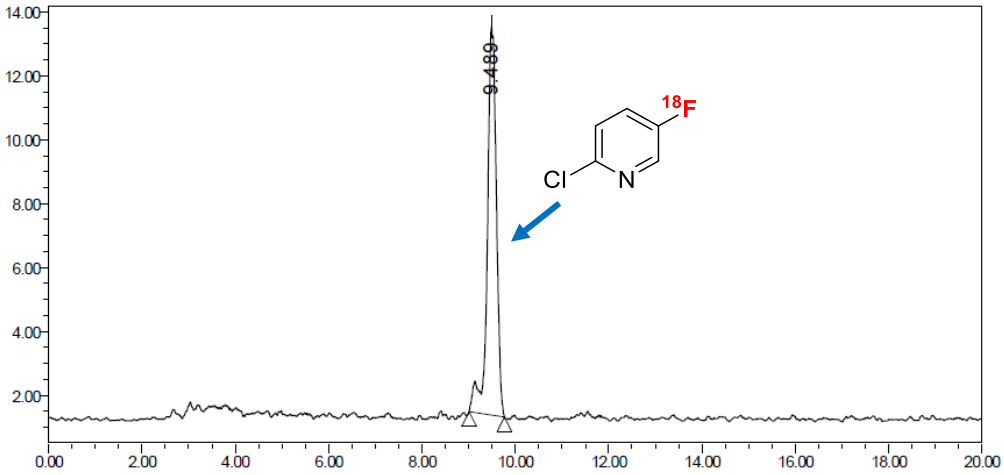


UV channel (crude product with added reference compound)

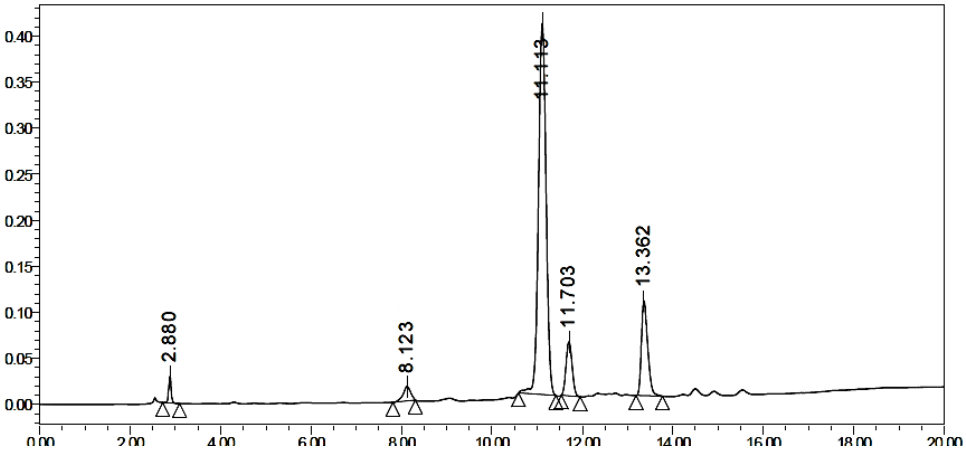


LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H_2O (40:60 to 90:10 over 8 min); flow rate: 0.7 mL/min; UV detection at λ = 254 nm.

Radioactive channel

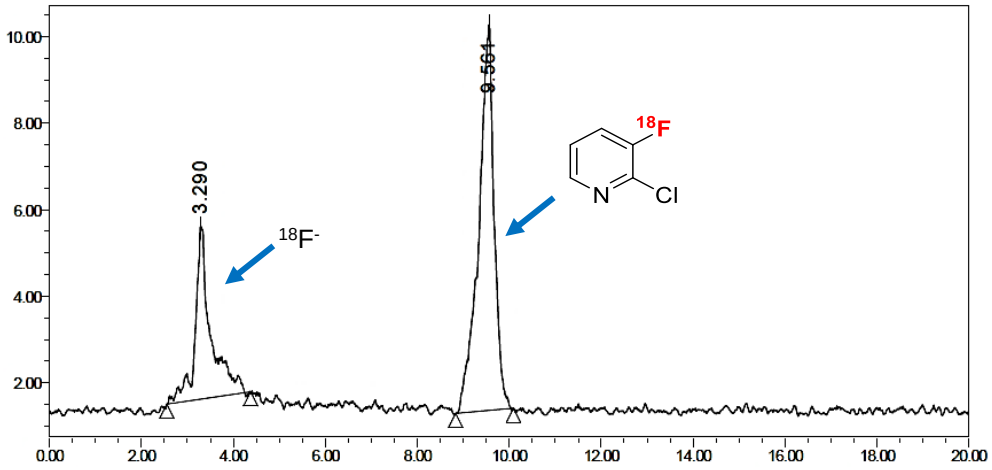


UV channel (crude product with no reference compound)

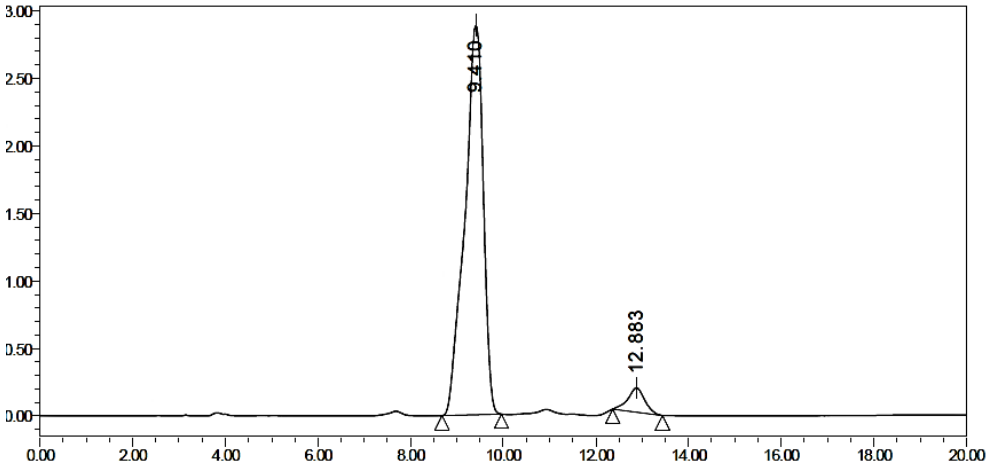


LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H_2O (50:50 to 60:40 over 8 min); flow rate: 1 mL/min; UV detection at λ = 254 nm.

Radioactive channel

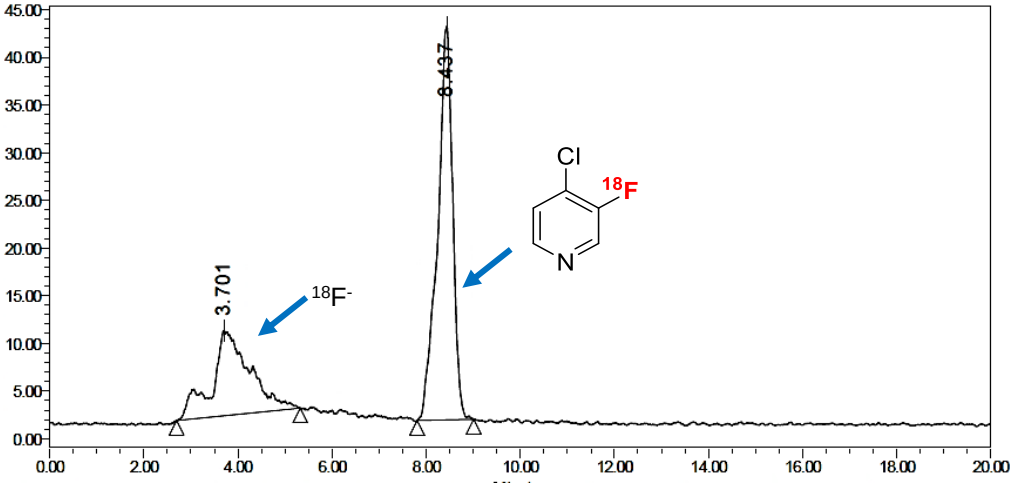


UV channel (crude product with added reference compound)

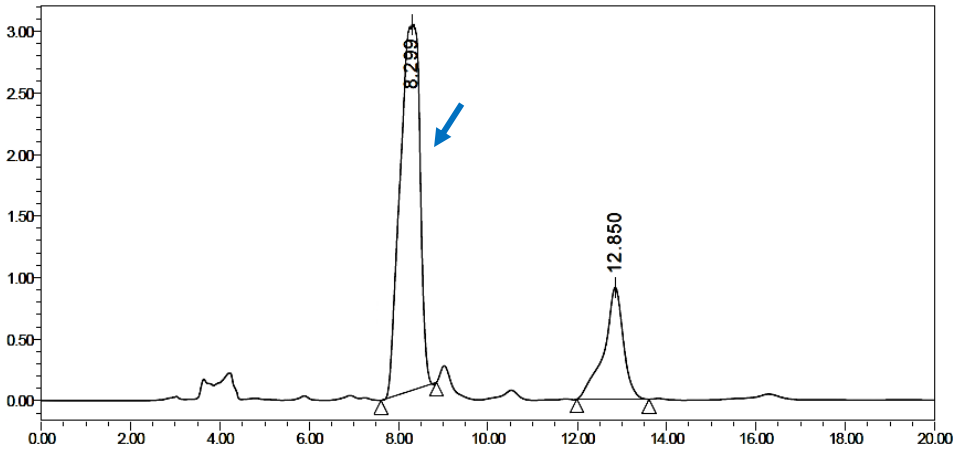


LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H_2O (50:50 to 60:40 over 8 min); flow rate: 1 mL/min; UV detection at λ = 254 nm.

Radioactive channel

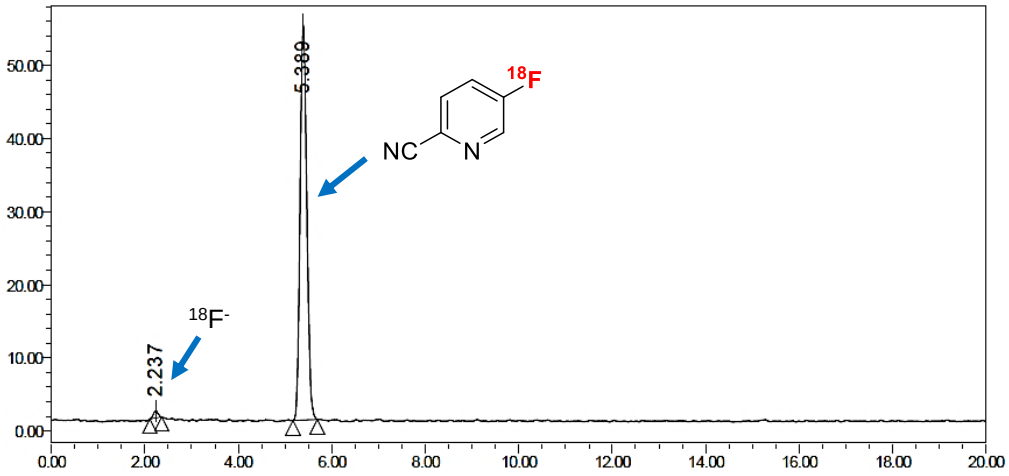


UV channel (crude product with added reference compound)

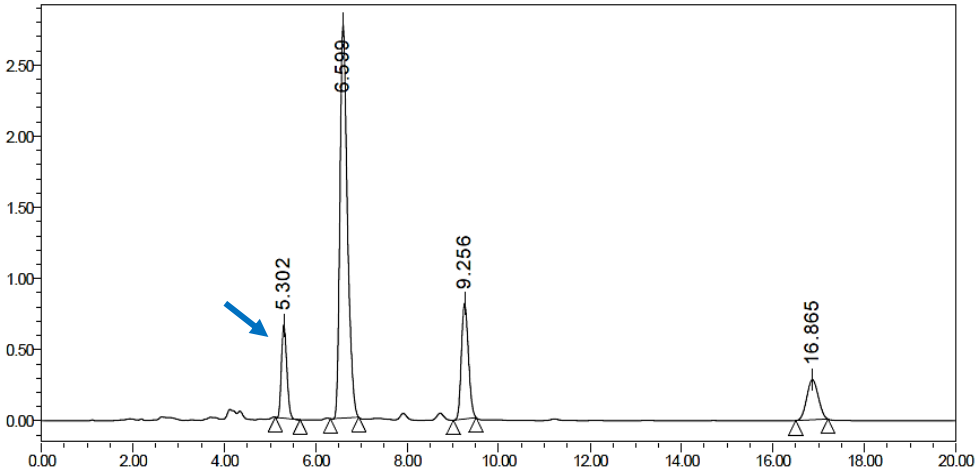


LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H_2O (50:50 to 60:40 over 8 min); flow rate: 1 mL/min; UV detection at λ = 254 nm.

Radioactive channel

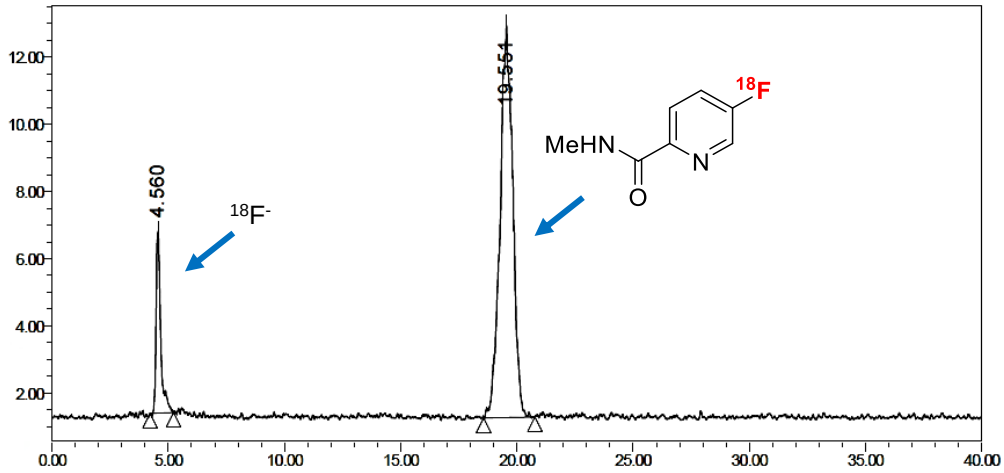


UV channel (crude product with added reference compound)

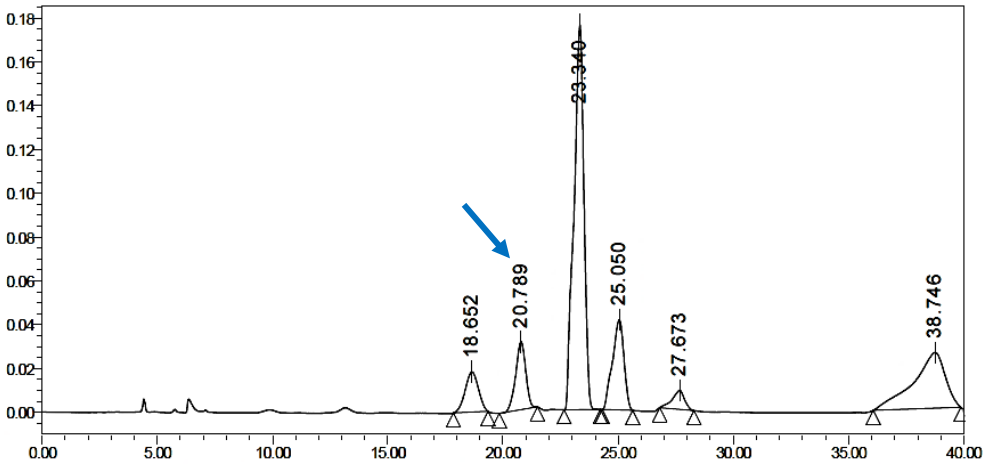


LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H_2O (20:80 to 50:50 over 10 min); flow rate: 0.7 mL/min; UV detection at λ = 254 nm.

Radioactive channel

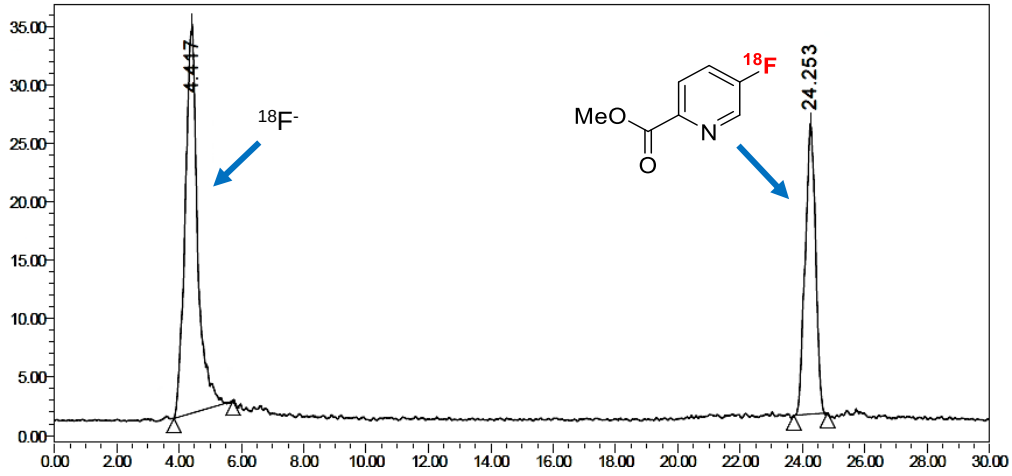


UV channel (crude product with added reference compound)

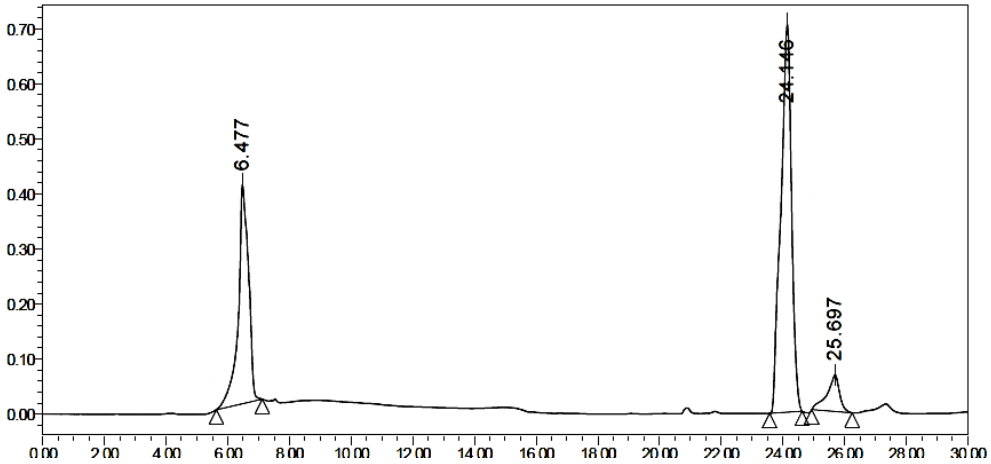


LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H_2O (5:95 to 50:50 over 10 min); flow rate: 0.5 mL/min; UV detection at λ = 254 nm.

Radioactive channel

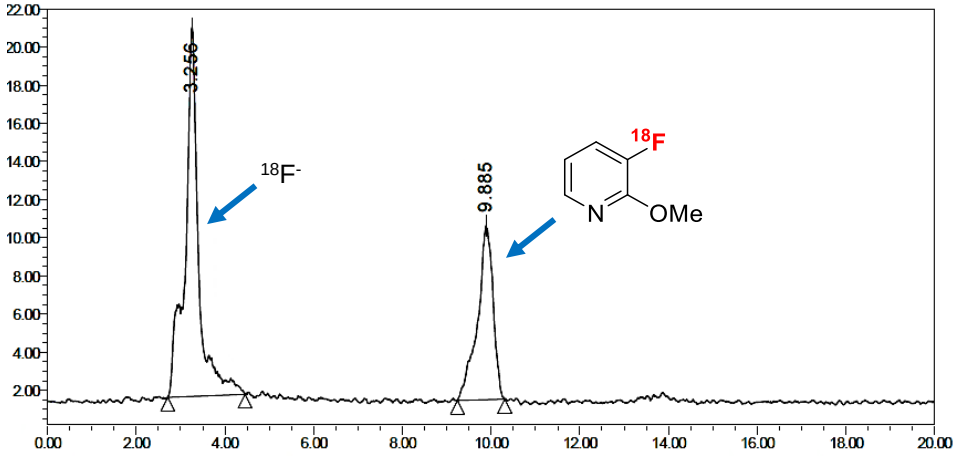


UV channel (crude product with added reference compound)

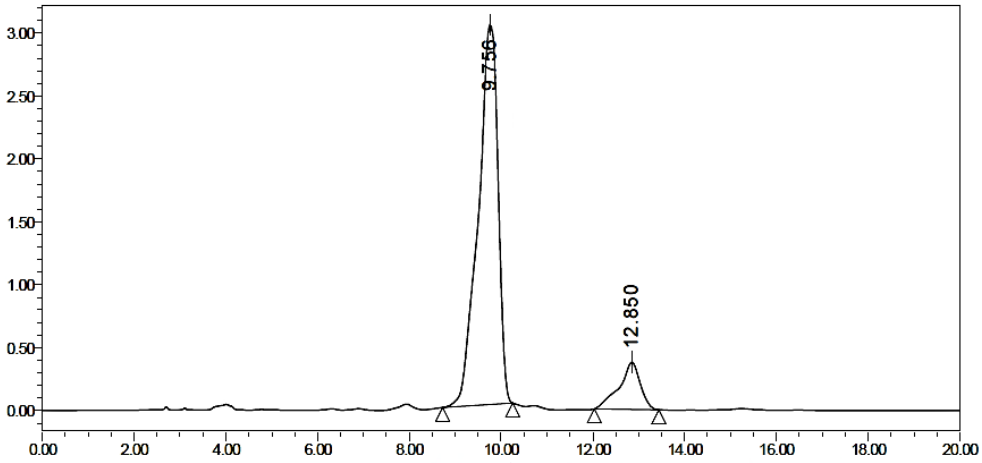


LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H_2O (50:50 to 60:40 over 8 min); flow rate: 0.7 mL/min; UV detection at λ = 254 nm.

Radioactive channel

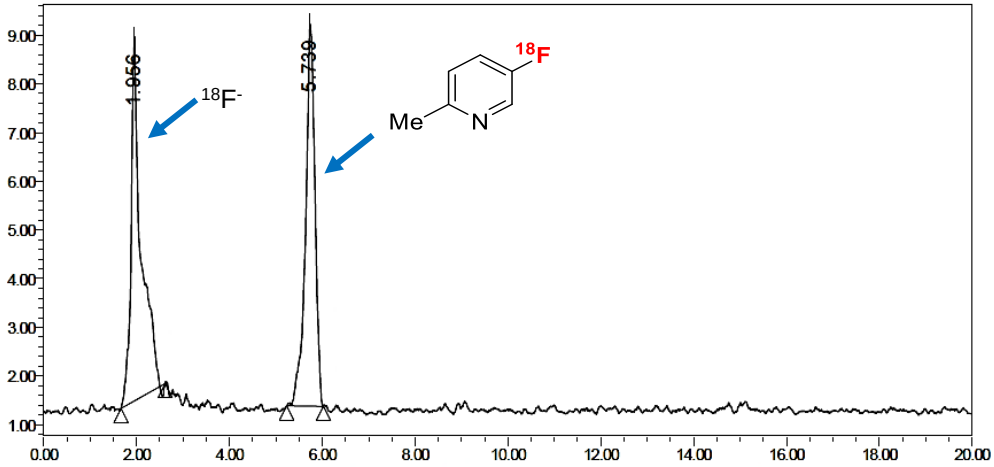


UV channel (crude product with added reference compound)

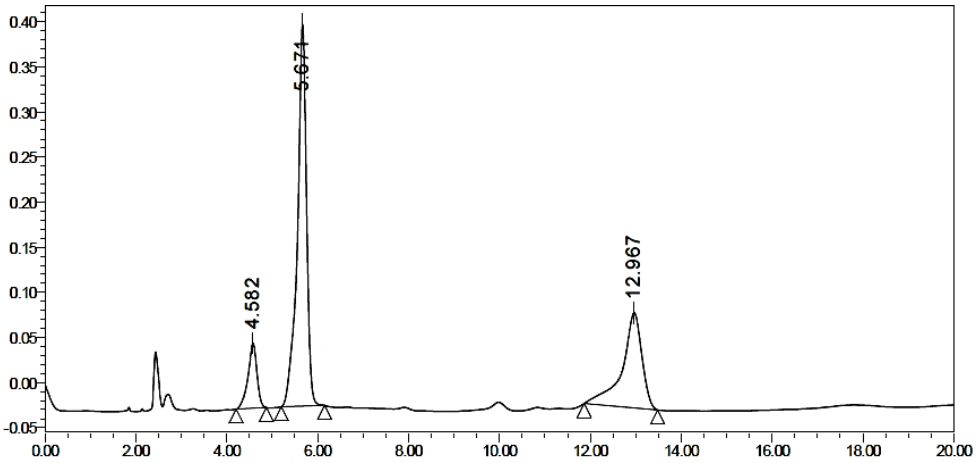


LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H_2O (50:50 to 60:40 over 8 min); flow rate: 0.7 mL/min; UV detection at λ = 254 nm.

Radioactive channel

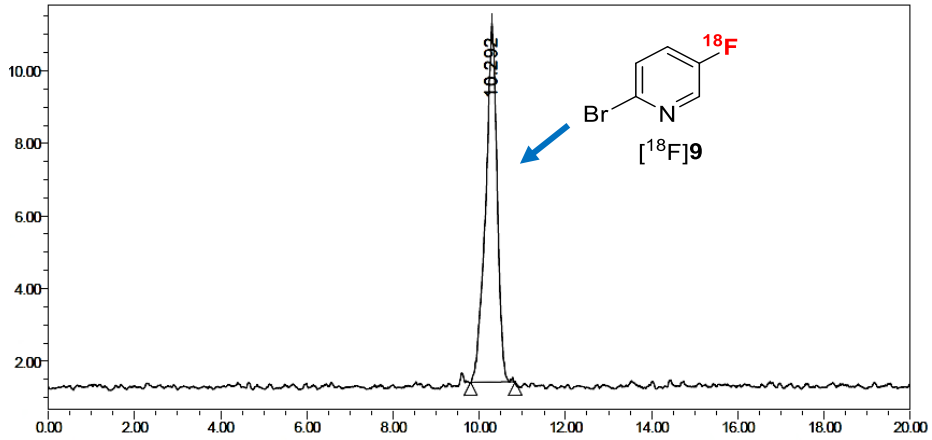


UV channel (crude product with added reference compound)

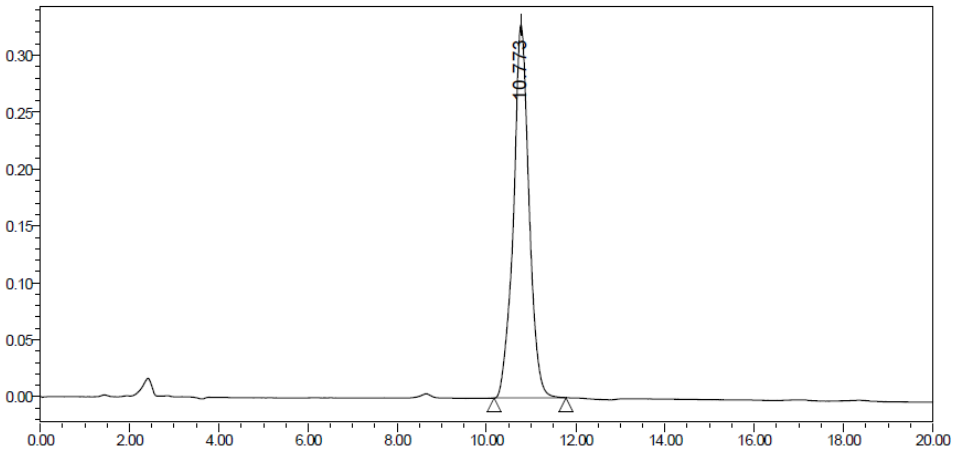


LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H_2O (50:50 to 60:40 over 8 min); flow rate: 0.7 mL/min; UV detection at λ = 254 nm.

Radioactive channel



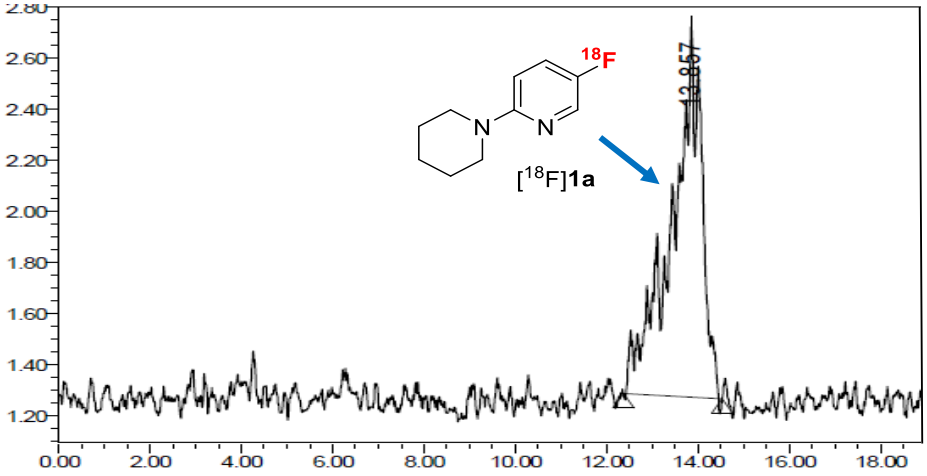
UV channel (reference compound)



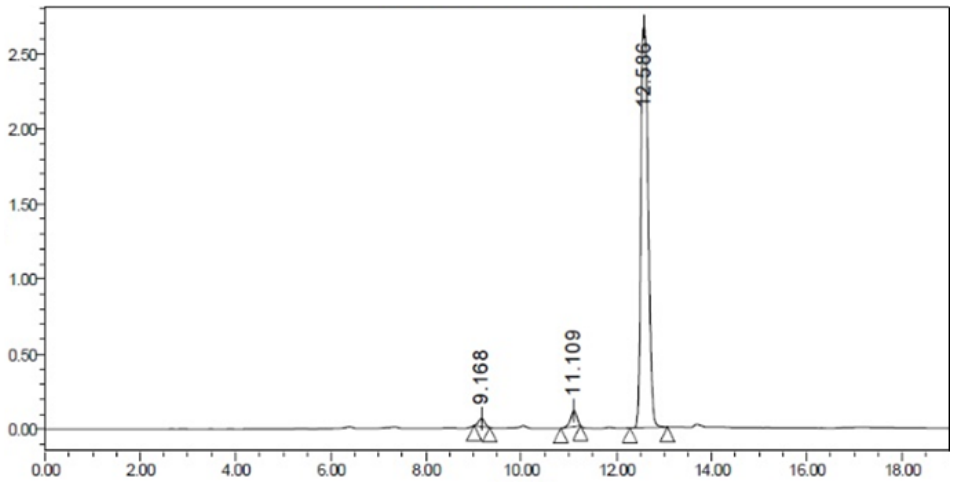
4.1 Amino-[^{18}F]-fluoropyridines 1

LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H_2O (40:60 to 50:50 over 8 min); flow rate: 0.7 mL/min; UV detection at λ = 254 nm.

Radioactive channel

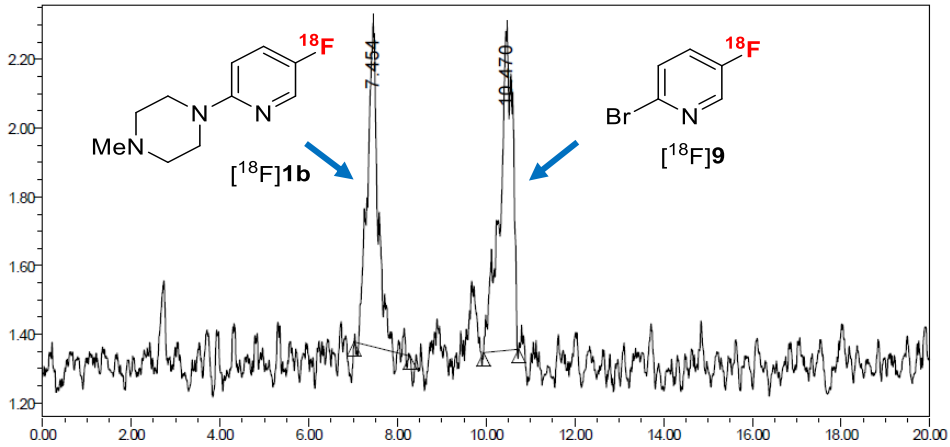


UV channel (reference aminofluoropyridine)

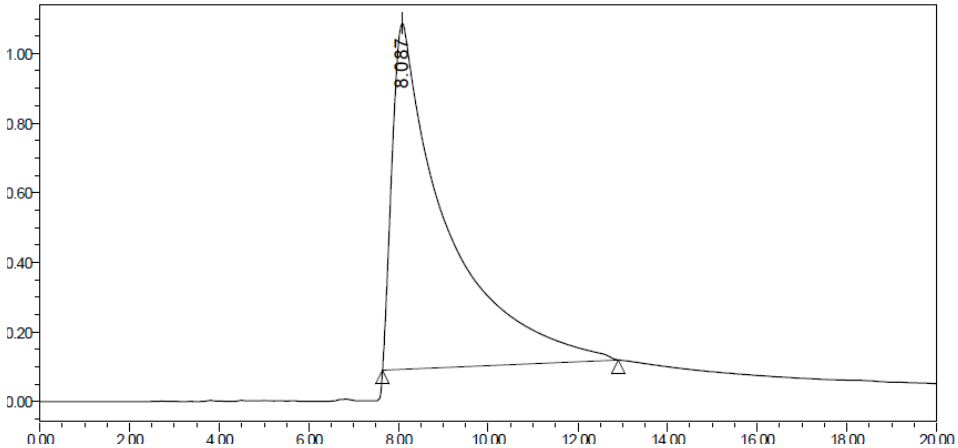


LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H_2O (50:50 to 60:40 over 8 min); flow rate: 0.7 mL/min; UV detection at λ = 254 nm.

Radioactive channel

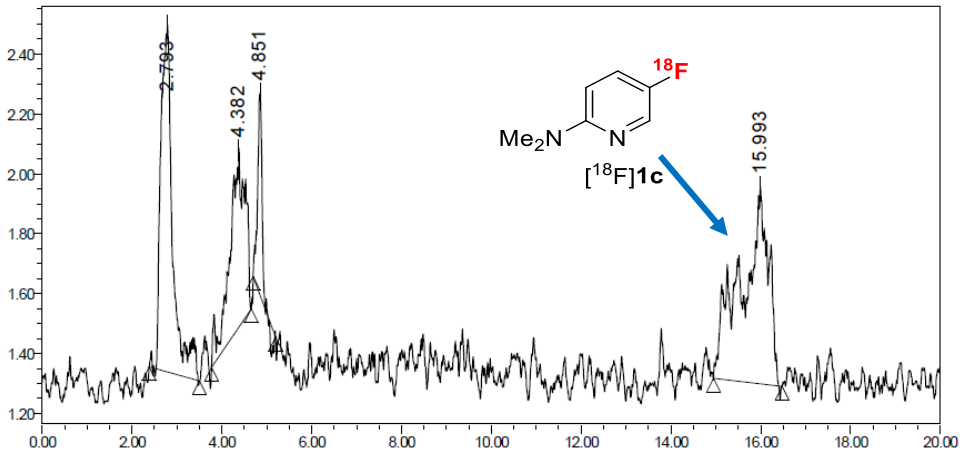


UV channel (reference aminofluoropyridine)

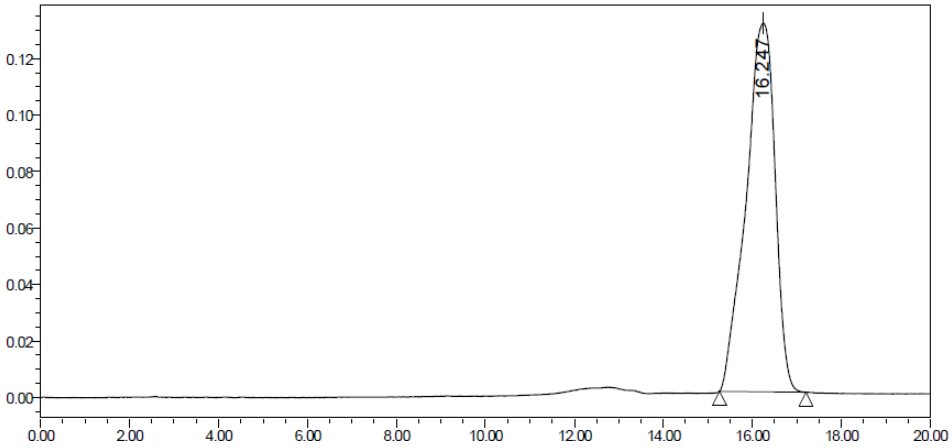


LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H_2O (30:70 to 50:50 over 8 min); flow rate: 0.7 mL/min; UV detection at λ = 254 nm.

Radioactive channel

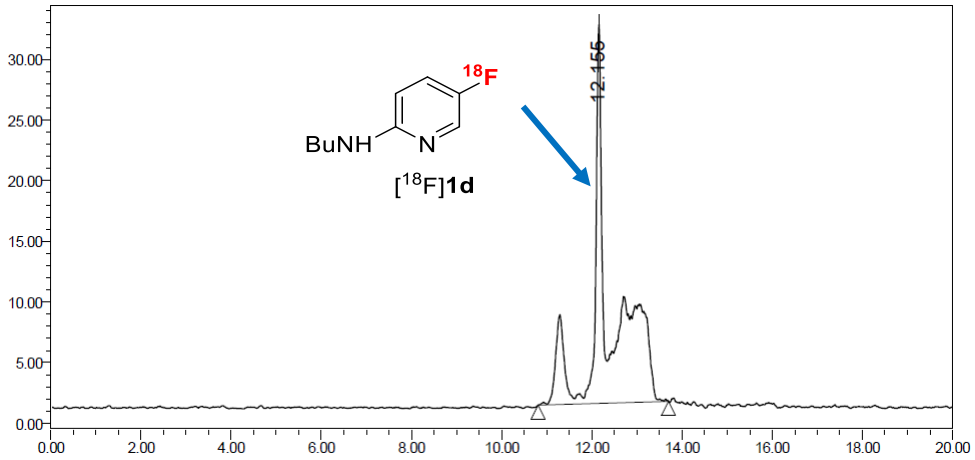


UV channel (reference aminofluoropyridine)

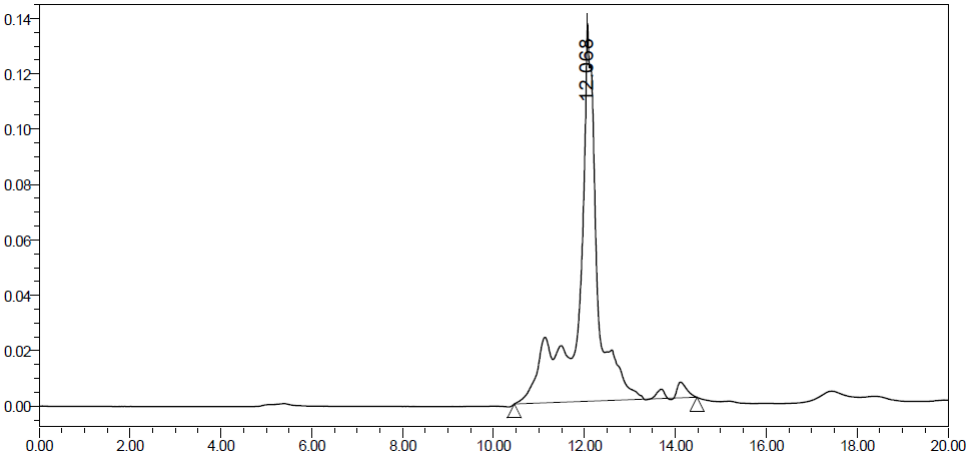


LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H_2O (30:70 to 50:50 over 8 min); flow rate: 0.7 mL/min; UV detection at λ = 254 nm.

Radioactive channel

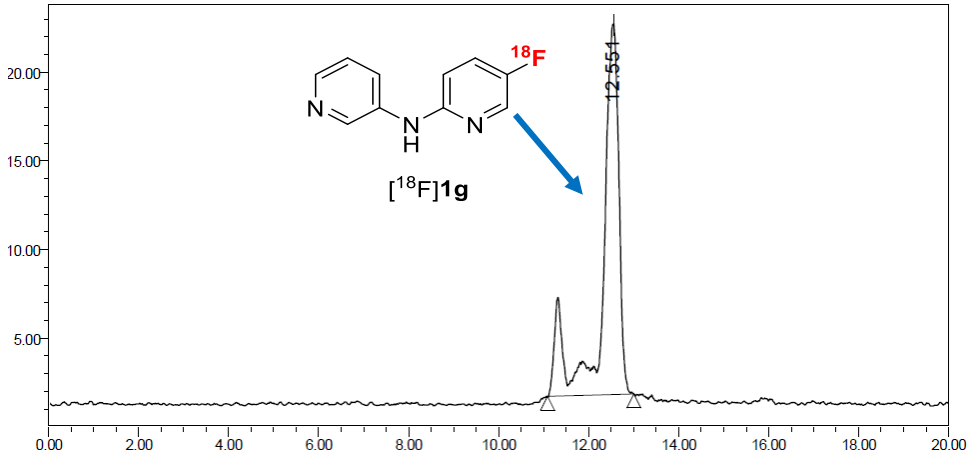


UV channel (reference aminofluoropyridine)

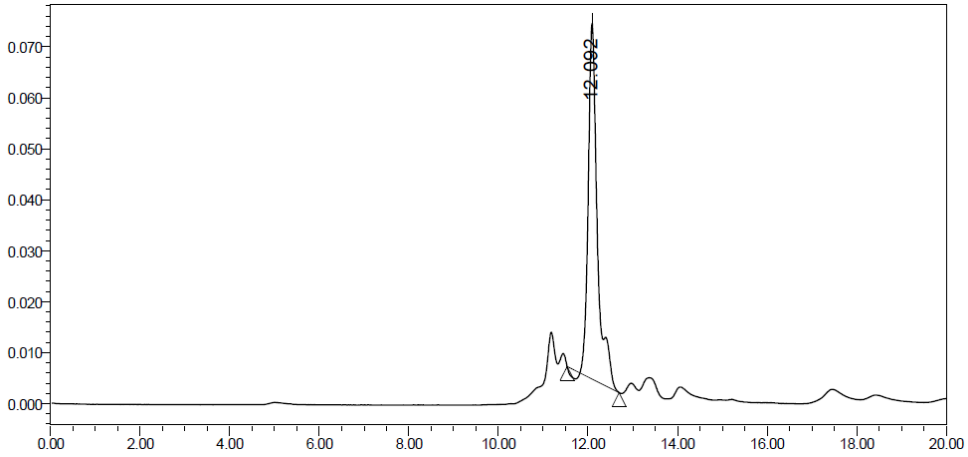


LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H_2O (30:70 to 50:50 over 8 min); flow rate: 0.7 mL/min; UV detection at λ = 254 nm.

Radioactive channel



UV channel (reference aminofluoropyridine)



5. References

1. M. Bielawski, J. Malmgren, L. M. Pardo, Y. Wikmark and B. Olofsson, *ChemistryOpen*, 2014, **3**, 19.

2. M. Pauton, C. Aubert, G. Bluet, F. Gruss-Leleu, S. Roy and C. Perrio, *Org. Process Res. Dev*., 2019; DOI:10.1021/acs.oprd.9b00021.

3. R. Richarz, P. Krapf, F. Zarrad, E. A. Urusova, B. Neumaier and B. D. Zlatopolskiy, *Org. Biomol. Chem*., 2014, **12**, 8094.