Electronic Supplementary Information

Selective syntheses of no-carrier-added 2- and 3-[^{18}F]fluorohalopyridines through the radiofluorination of halopyridinyl(4'-methoxyphenyl)iodonium tosylates

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Experimental Section

General

^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded at room temperature on a Bruker Avance-400 spectrometer (Billerica, MA). ^{1}H and ^{13}C chemical shifts are reported in δ units (ppm) downfield relative to the chemical shift for tetramethylsilane. Abbreviations s, d, t, and m denote singlet, doublet, triplet, and multiplet, respectively. High resolution mass spectra (HRMS) were acquired from the Mass Spectrometry Laboratory, University of Illinois at Urbana-Champaign (Urbana, IL) under electron ionization conditions using a double-focusing high-resolution mass spectrometer (Autospec; Micromass Inc., USA). Melting points were measured with a Mel-Temp manual melting point apparatus (Electrothermal; Fisher Scientific).

Materials

Anhydrous chloroform and acetonitrile were purchased in Sure/Seal^{TM} bottles (Sigma – Aldrich; Milwaukee, WI) and used without further treatment. Iodohalopyridines, *m*-CPBA (*m*-chloroperbenzoic acid), and *p*-TsOH·H_2O were also purchased from Sigma-Aldrich and used as received. 2-Bromo-6-iodopyridine was purchased from Ryan Scientific, Inc. (Mt. Pleasant, SC). All other reagents were purchased from either Sigma-Aldrich or Alfa Aesar (Ward Hill, MA) and used as received. Acetonitrile (high purity solvent, Burdick & Jackson, Morristown, NJ) for HPLC mobile phase was used without further treatment. NCA [^{18}F]fluoride ion was obtained through the ^{18}O(p,n)^{18}F nuclear reaction by irradiating [^{18}O]water (95 atom %) for 90–120 min with a proton beam (17 MeV; 20 μA) produced by a PETrace cyclotron (GE Medical Systems; Milwaukee, MI). QMA anionic resin cartridges were supplied by ORTG (Oakdale, TN).

Synthesis of halopyridinyl(4'-methoxyphenyl)iodonium tosylates

The synthesis of compound **1** is given in the main text, and this represents the general method applied to the preparation of the other halopyridinyl(4'-methoxyphenyl)iodonium tosylates described below.

(6-Bromopyridin-2-yl)(4'-methoxyphenyl)iodonium tosylate (**2**). White solid (0.65 g, 58%). mp = 122−124 °C; ^{1}H-NMR (MeOD-d_4) δ 8.11 (t, J = 6.4 Hz, 3H), 7.86-7.76 (m, 2H), 7.69 (d, J = 8 Hz, 2H), 7.22 (d, J = 8 Hz, 2H), 7.11 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H), 2.36 (s, 3H); ^{13}C-NMR (MeOD-d_4) δ 165.1, 144.1, 143.3, 141.8, 139.6, 136.3, 133.2, 131.4, 130.0, 127.1, 119.1, 117.6, 104.2, 56.6, 21.5; HRMS [M−OTs]$^{+}$ Calc'd. for $C_{12}H_{10}NOBrI$: 389.8991, Found: 389.9000.

(5-Bromopyridin-2-yl)(4'-methoxyphenyl)iodonium tosylate (**3**). White solid (0.59 g, 52%). mp = 156−158 °C; ^{1}H-NMR (DMF-d_7) δ 8.05 (dd, J = 0.8, 3.2 Hz, 1H), 8.37-8.24 (m, 4H), 7.66 (dd, J = 1.6, 6 Hz, 2H), 7.18-7.13 (m, 4H), 3.89 (s, 3H), 2.30 (s, 3H); ^{13}C-NMR (DMF-d_7) δ 162.8, 152.9, 148.6, 143.7, 138.5, 136.4, 133.2, 128.3, 126.0, 124.7, 117.8, 103.9, 56.0, 20.7; HRMS [M−OTs]$^{+}$ Calc'd. for $C_{12}H_{10}NOBrI$: 389.8991, Found: 389.9000.

(6-Chloropyridin-3-yl)(4'-methoxyphenyl)iodonium tosylate (**4**). White solid (0.32 g, 30%). mp = 181−183 °C; ^{1}H-NMR (DMF-d_7) δ 9.25 (dd, J = 0.4, 2.4 Hz, 1H), 8.80 (dd, J = 2.4, 8.4 Hz, 1H), 8.34 (d, J = 9.2 Hz, 2H), 7.75 (dd, J = 0.4, 8.4 Hz, 1H), 7.64 (dd, J = 2, 6.4 Hz, 2H), 7.14 (d, J = 8.8 Hz, 4H), 3.74 (s, 3H), 2.31 (s, 3H); ^{13}C-NMR (DMF-d_7) δ 163.0, 154.5, 153.9, 146.0, 145.8, 138.4, 138.0, 128.3, 127.8, 126.0, 117.9, 114.2, 105.155.8, 20.6; HRMS [M−OTs]$^{+}$ Calc'd. for $C_{12}H_{10}NOClI$: 345.9496, Found: 345.9501.

(6-Bromopyridin-3-yl)(4'-methoxyphenyl)iodonium tosylate (5). Beige solid (0.32 g, 28%). mp = 182−184 °C; ^{1}H-NMR (DMF-d_7) δ 9.22 (dd, J = 0.8, 2.4 Hz, 1H), 8.68 (dd, J = 2.4, 8.4 Hz, 1H), 8.34 (dd, J = 2.4, 7.2 Hz, 2H), 7.89 (dd, J = 0.8, 8.8 Hz, 1H), 7.65 (dd, J = 1.6, 6.4 Hz, 2H), 7.15 (dd, J = 1.2, 6.8 Hz, 4H), 3.88 (s, 3H), 2.31 (s, 3H); ^{13}C-NMR (DMF-d_7) δ 154.7, 145.9, 145.2, 145.1, 138.4, 138.0, 131.6, 128.3, 126.0, 117.9, 114.9, 104.9, 56.0, 20.7; HRMS [M−OTs]$^{+}$ Calc'd. for $C_{12}H_{10}NOBrI$: 389.8991, Found: 389.8993.

(2-Chloropyridin-3-yl)(4'-methoxyphenyl)iodonium tosylate (6). White solid (0.43 g, 41%). mp = 160−162 °C; ^{1}H-NMR (MeCN-d_3) δ 8.53 (dd, J = 1.6, 4.8 Hz, 1H), 8.47 (dd, J = 2, 8 Hz, 1H), 7.99 (dd, J = 2.4, 7.2 Hz, 2H), 7.40 (dd, J = 1.6, 6.4 Hz, 2H), 7.32 (q, J = 4.8 Hz, 1H), 7.10 (d, J = 8 Hz, 2H), 7.40 (dd, J = 2, 7.2 Hz, 2H), 3.81 (s, 3H), 2.32 (s, 3H); ^{13}C-NMR (MeCN-d_3) δ 164.0, 153.9, 152.8, 148.2, 144.5, 140.5, 138.9, 129.6,

126.4, 118.7, 116.7, 105.1, 56.7, 21.4; HRMS $[M-OTs]^+$ Calc'd. for $C_{12}H_{10}NOClI$: 345.9496, Found: 345.9494.

(2-Bromopyridin-3-yl)(4'-methoxyphenyl)iodonium tosylate (7). White solid (0.57 g, 51%). mp = 155−157 °C; ^{1}H-NMR (MeCN-d_3) δ 8.50 (dd, J = 1.6, 4.4 Hz, 1H), 8.36 (dd, J = 1.6, 8 Hz, 1H), 8.00 (dt, J = 2, 4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.36 (q, J = 4.8 Hz, 1H), 7.11 (d, J = 8 Hz, 2H), 6.98 (dd, J = 2, 7.2 Hz, 2H), 3.81 (s, 3H), 2.32 (s, 3H); ^{13}C-NMR (MeCN-d_3) δ 164.1, 153.9, 147.7, 145.5, 144.9, 140.5, 138.8, 129.6, 126.7, 126.6, 120.9, 118.8, 105.4, 56.7, 21.4; HRMS $[M-OTs]^+$ Calc'd. for $C_{12}H_{10}NOBrI$: 389.8991, Found: 389.8993.

Radiochemistry

Cyclotron-produced no-carrier-added (NCA) [^{18}F]fluoride ion (3.7−7.4 GBq) in [^{18}O]water (250–400 μL) was first adsorbed onto a QMA anionic resin cartridge within the CE module of a NanoTek apparatus (Advion; Louisville, TN), and then released with a solution of K_2CO_3 (0.8 mg; 5 nmol) plus K 2.2.2 (4.5 mg; 11 nmol) in MeCN-H_2O (9: 1 v/v; 450 μL) into a 2-mL V-vial. The solution was dried by two successive cycles of azeotropic evaporation with acetonitrile (0.6 mL) under nitrogen flow at 95 ºC.

Dried $^{18}F^-$-K 2.2.2-K^+ complex (3.7−5.6 GBq) was dissolved in DMF. A solution of halopyridinyl(4'-methoxyphenyl)iodonium salt (10 mM) was prepared separately in DMF. Each of the two solutions (280 μL) was loaded into a storage loop of the microfluidic apparatus. The detailed configuration of the microfluidic apparatus has been described earlier.[1] For radiofluorination, each solution (10–20 μL) was infused simultaneously into the micro-reactor (4-m coiled glass silica tube; internal diameter, 100 μm; internal volume, 31.4 μL) of the apparatus at a set flow rate in the range 4–10 μL/min and at a fixed temperature. The micro-reactor output was directly quenched with MeCN-H_2O (1: 1 v/v; 3 mL). Precursor amount, temperature and flow rates were varied to obtain high radiochemical yields (RCYs). Decay-corrected RCYs of [^{18}F]fluorohalopyridines were measured by reversed phase radio-HPLC on a Luna C18 column (250 × 4.6 mm i.d., 10 μm; Phenomenex; Torrance, CA). Two different chromatographic methods were applied for analyses of quenched reaction mixtures, as follows.

Method A: Column eluted at 1.5 mL/min with a gradient of MeCN-H_2O (50: 50, v/v) with the percentage of MeCN increased linearly from 50 to 80% over 7 min. This method was used for analyses of radioactive products from the reactions of **1**, **4**, and **7.**

Method B: Column eluted at 1.5 mL/min with a gradient of MeCN-H_2O (55: 45, v/v) with the percentage of MeCN increased linearly from 55 to 80% over 7 min. This method was used for analyses of radioactive products from the reactions of compounds **2**, **3**, **5**, and **6.**

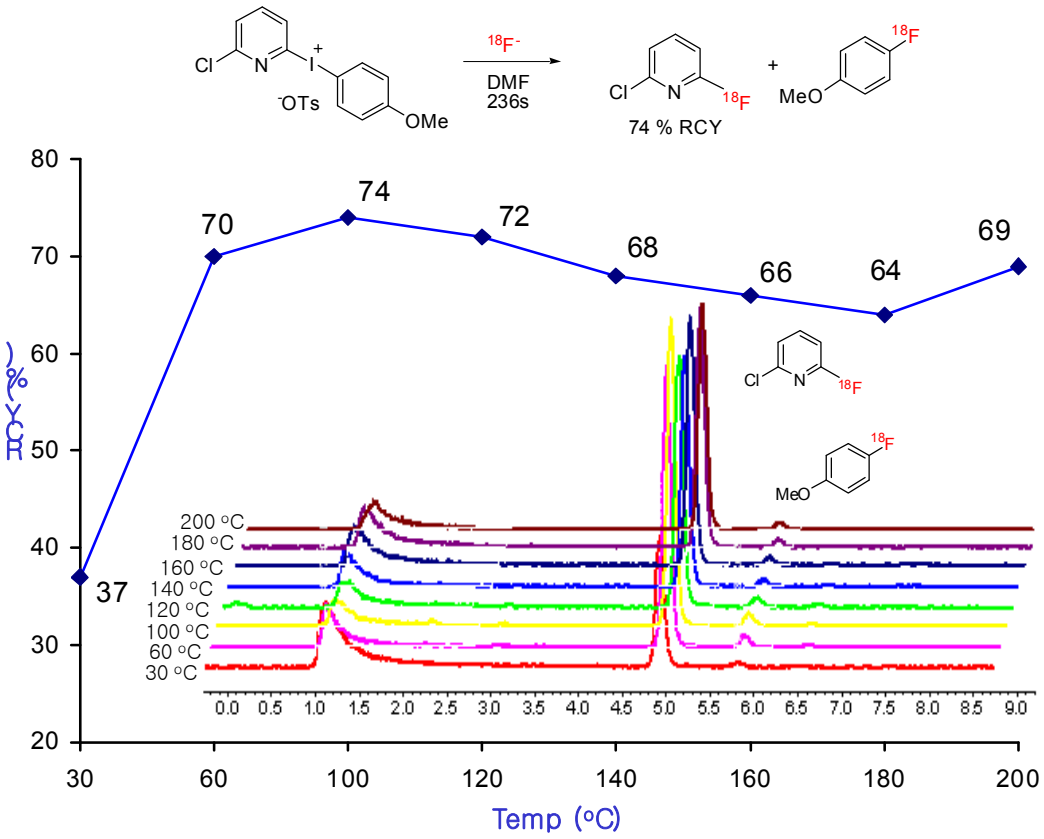


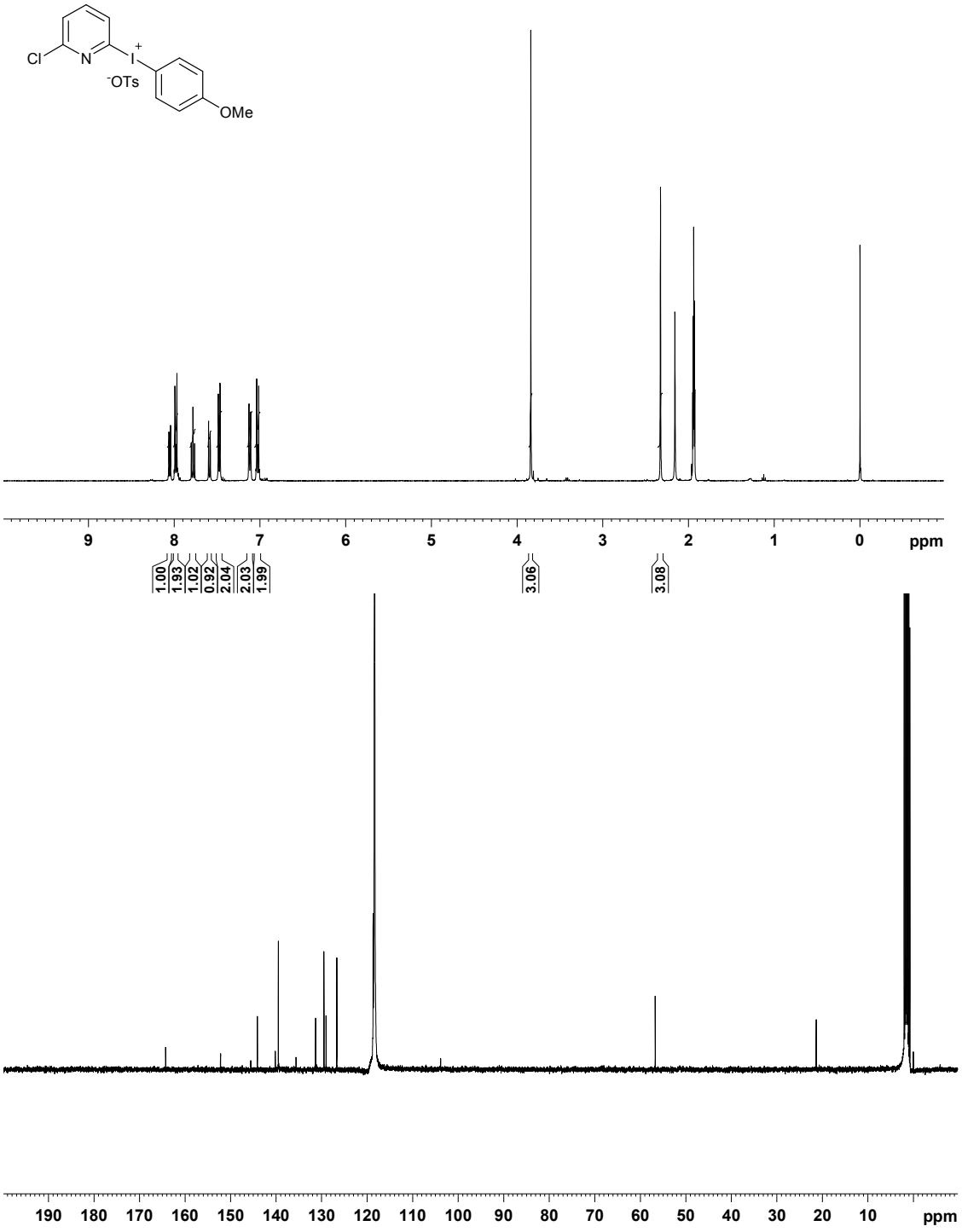
Figure S1. Radio-chromatograms from the HPLC analyses of quenched reaction mixtures from the radiofluorination of (6-chloropyridin-2-yl)(4'-methoxyphenyl)iodonium tosylate (**1**) in DMF at different temperatures. The plotted blue curve shows dependence of the RCY of [^{18}F]**8** on temperature (these RCYs are based on the radiochromatograms and are uncorrected for radioactivity adsorption in the apparatus).

References

1. a) J.-H. Chun, S. Lu, Y.-S. Lee and V. W. Pike, *J. Org. Chem.*, 2010, **75**, 3332−3338.
   b) S. Lu, A. M. Giamis and V. W. Pike, *Curr. Radiopharm.*, 2009, **2**, 49−55.

Appendix 1. ^{1}H and ^{13}C NMR spectra of halopyridinyliodonium tosylates

Compound **1**



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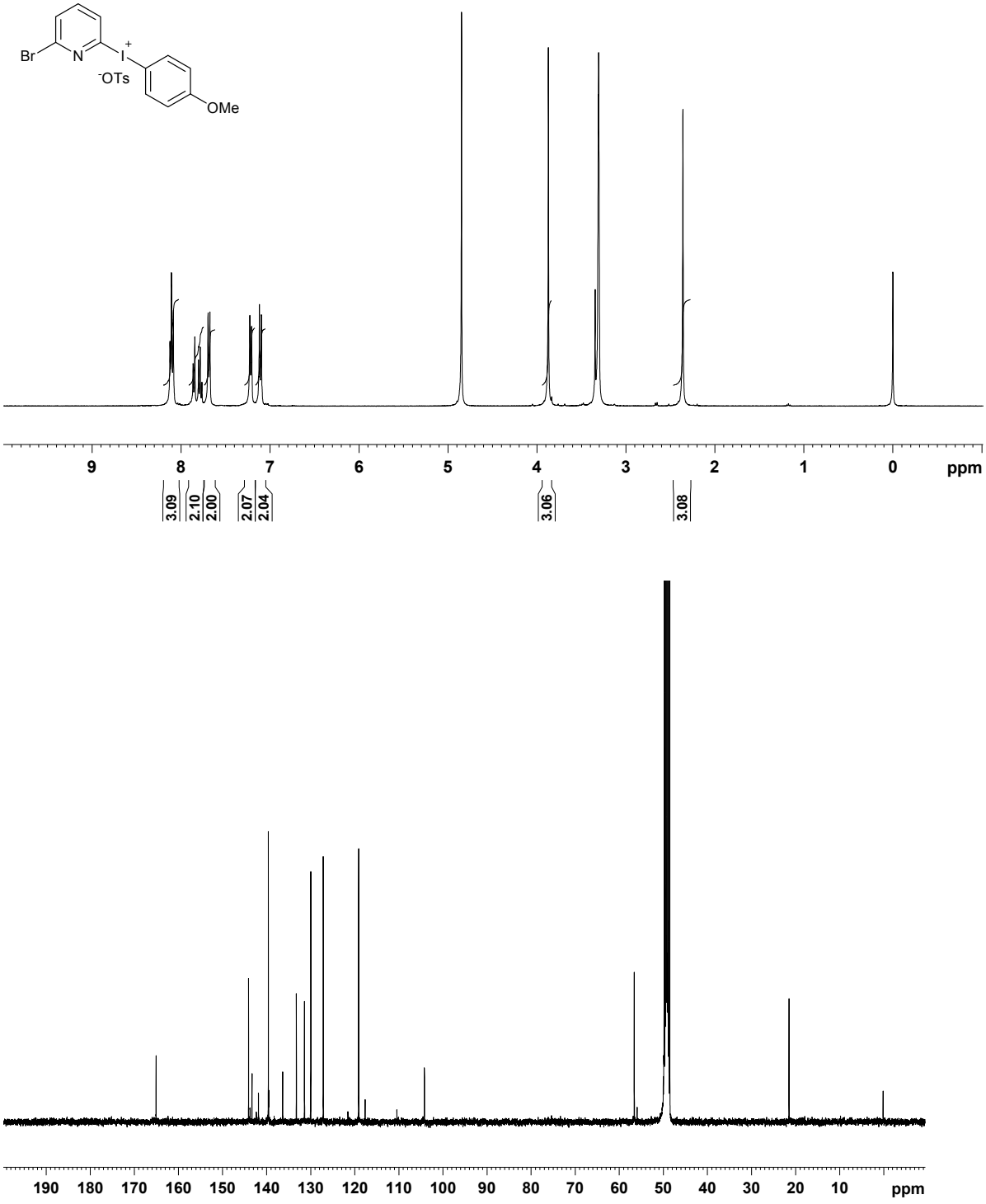
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2.00
2.07
2.04
3.06
3.08
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180
170
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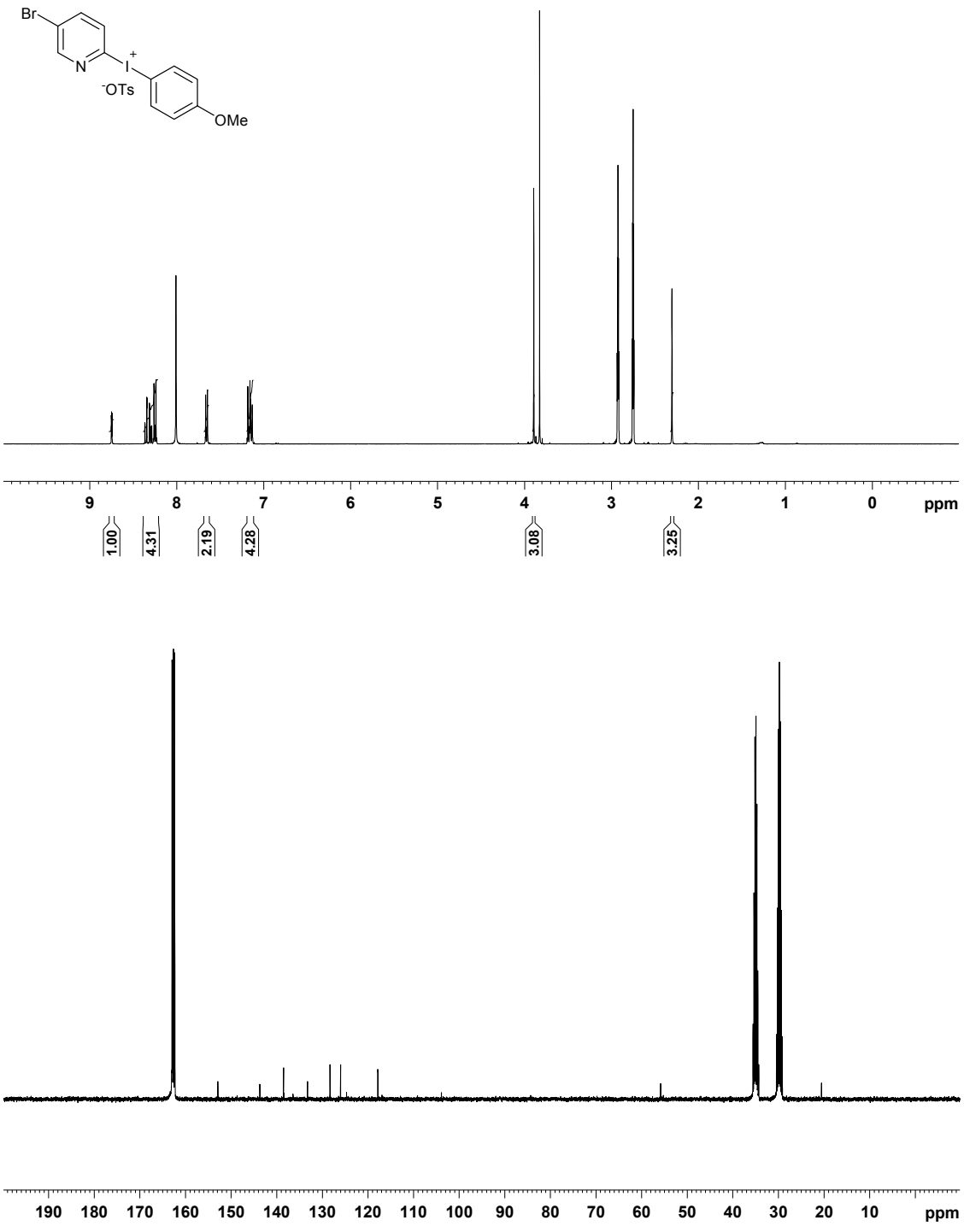
10
ppm

Compound **3**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3.25
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ppm

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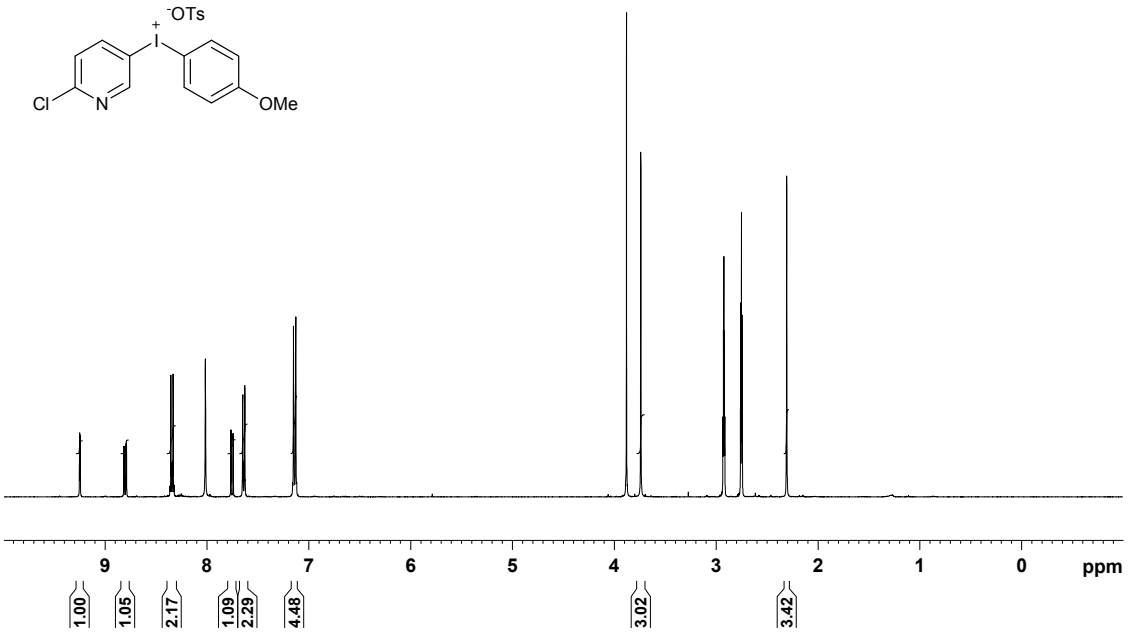
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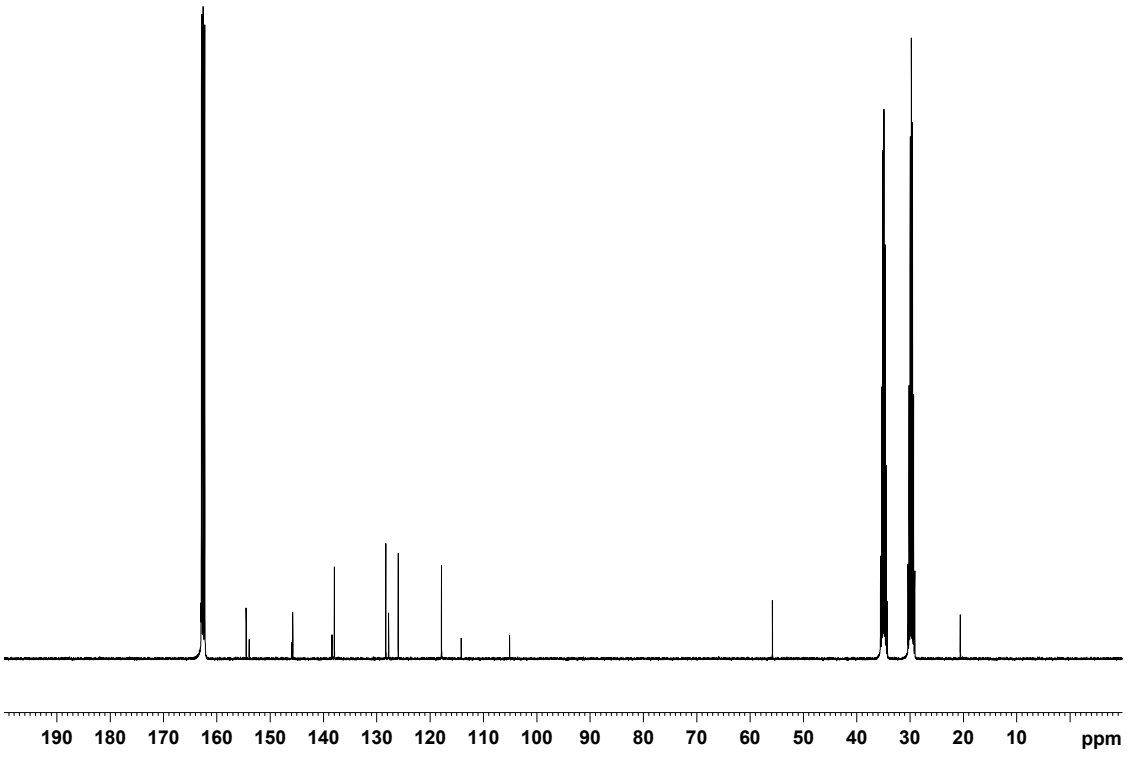
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30
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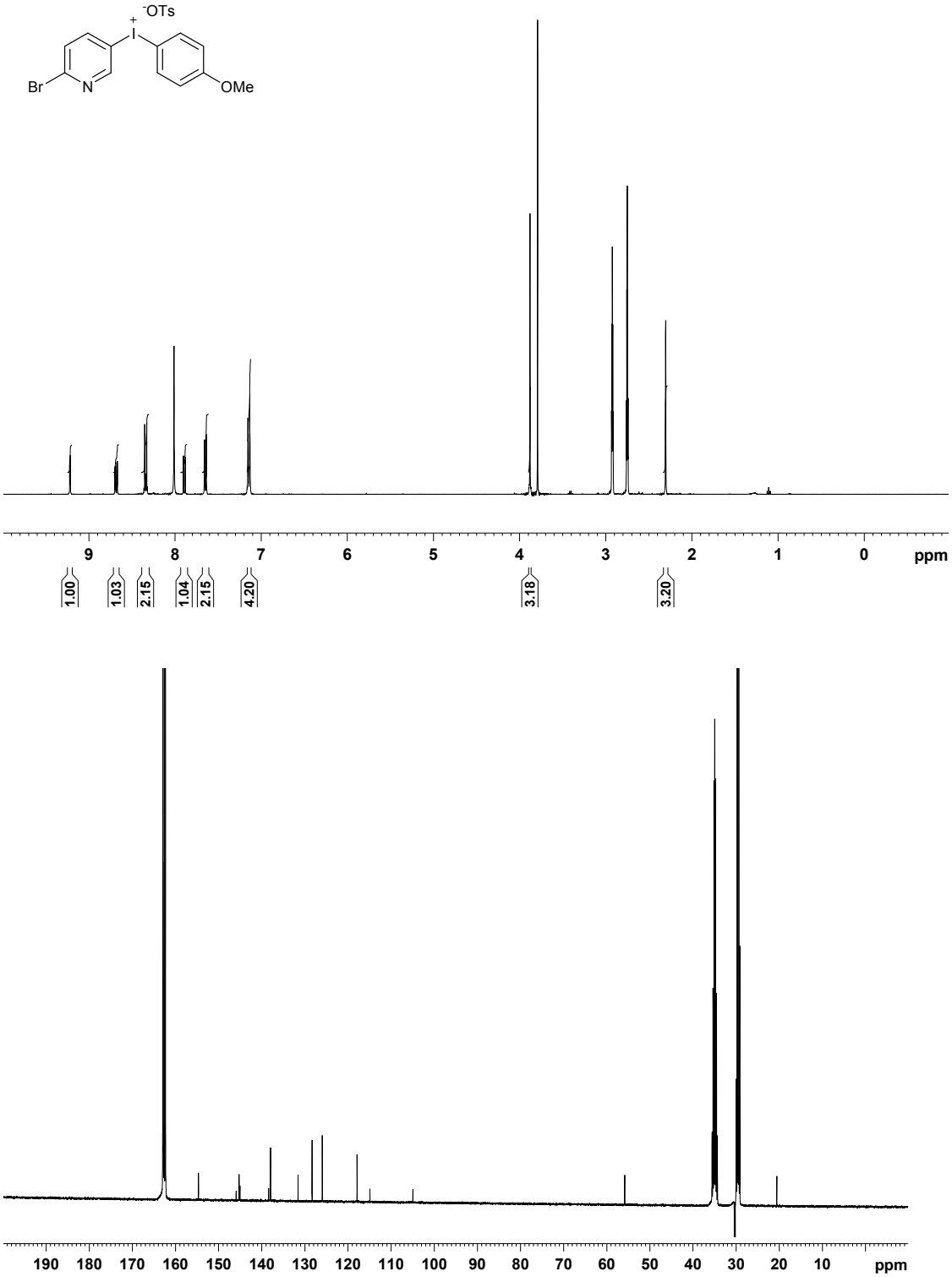
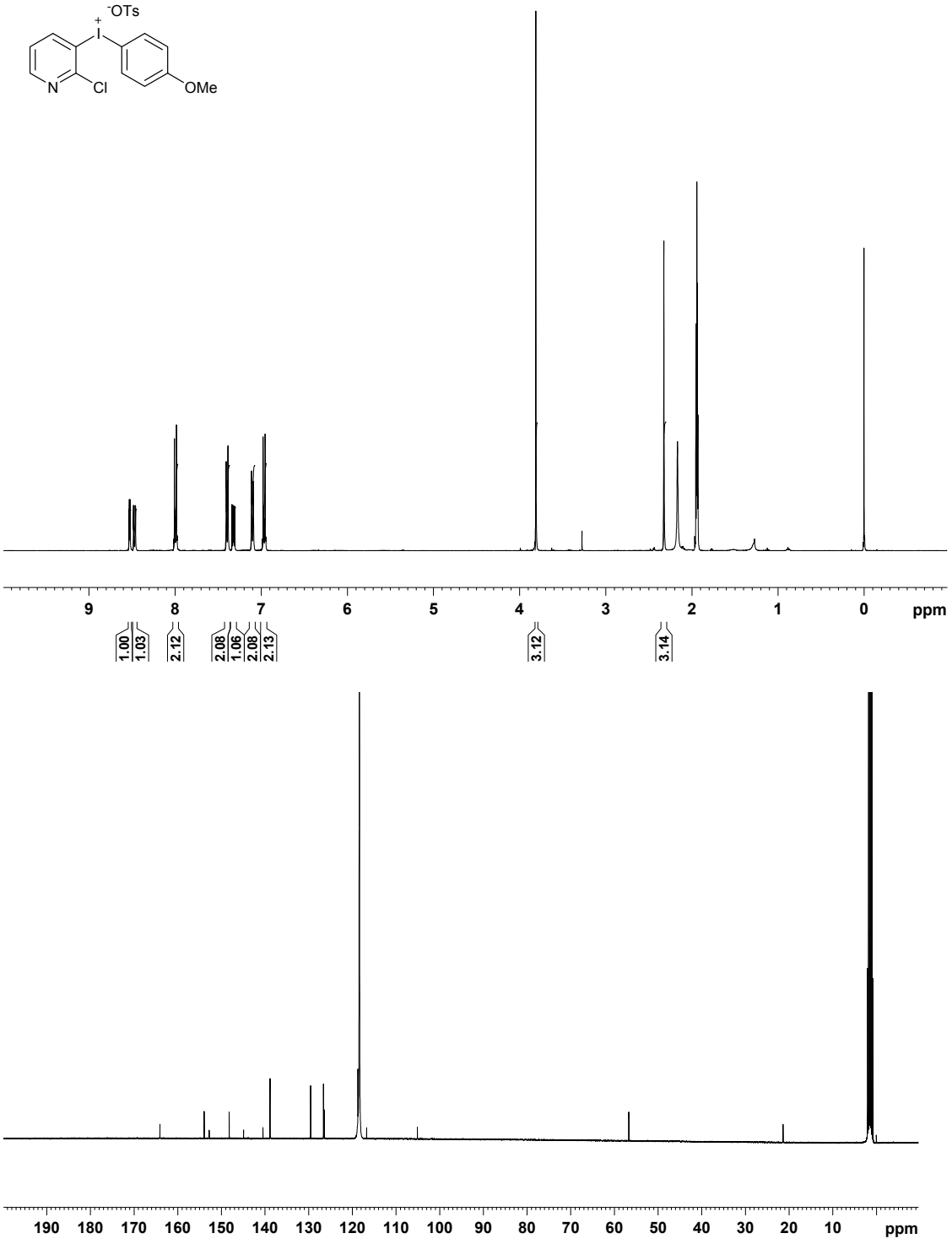
ppm

Compound **5**



Compound **6**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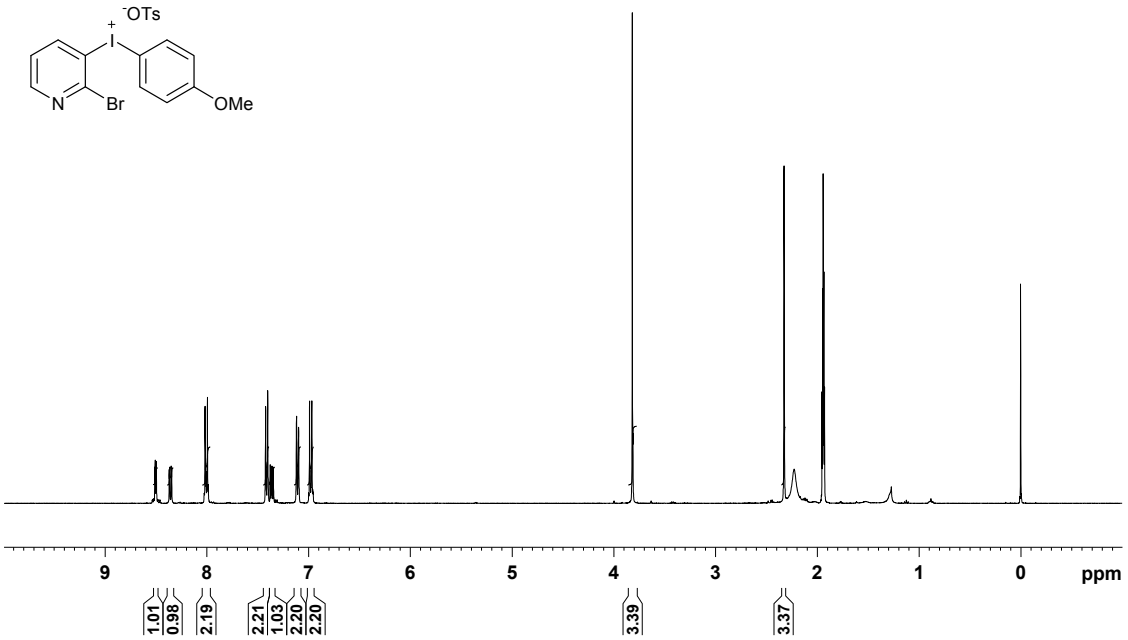
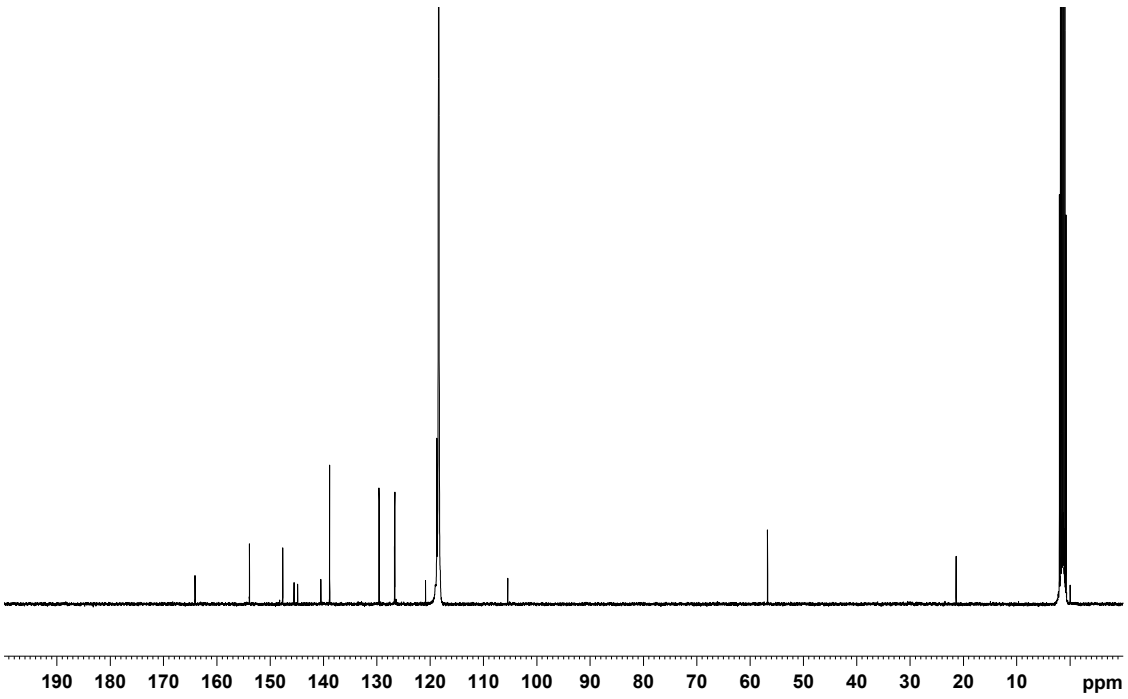
ppm

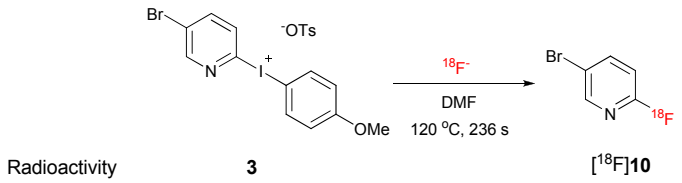
Compound **7**



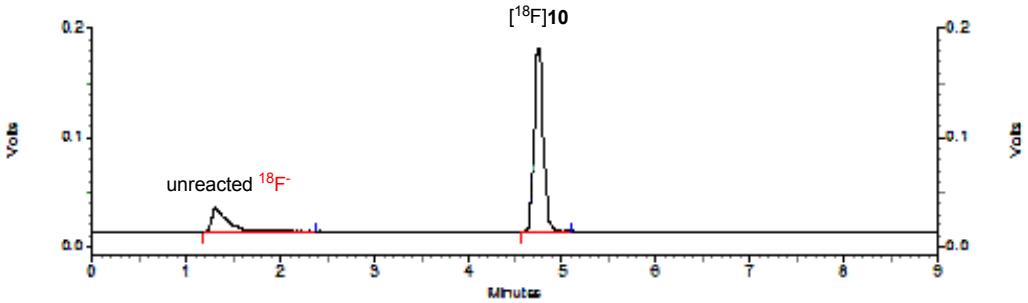


Appendix 2. Selected radio-HPLC chromatograms from the analyses of quenched reaction mixtures from the radiofluorination of halopyridinyl(4'-methoxypyridinyl)iodonium tosylates.

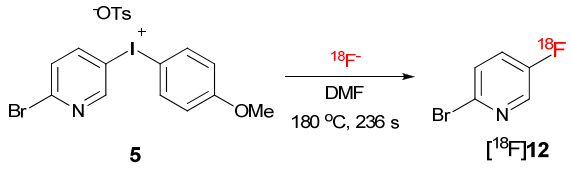
Radiofluorination of **3**



3 [18F]**10**



Radiofluorination of **5**



5 [18F]**12**