Original synthesis of radiolabelling precursors for the batch and on resin one-step/late stage radiofluorination of peptides

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I. Syntheses of precursors and cold references

1. Materials and methods

All commercially available reagents and solvents were used without further purification. Purifications of products were carried out by column chromatography using Merck silica gel (63-200 µm). ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were measured on a Brucker Avance 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm, δ) downfield from residual solvents peaks and coupling constants are reported in Hertz (Hz). Splitting patterns are designated as singlet (s), broad singlet (br. s), doublet (d), triplet (t), quartet (q) and quintet (quin). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m). Electrospray mass spectra were obtained using an ESI-Quadripole autopurify, Waters (pump: 2545, mass: ZQ2000) mass Spectrometer. Melting points (Mp) were measured on an electrothermal IA9200 and are reported in °C.

General procedure A: triflination reaction

Tf_2O (0.26 mL, 1.5 mmol, 1.5 eq.) was added dropwise to a solution of 6-hydroxypyridine derivative at 0 °C (1.0 mmol) in 5 mL of dry pyridine. The resulting solution was then stirred at room temperature until completion, diluted with water, and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography.

General procedure B: DABCO ammonium formation

To a solution of pyridine triflate derivative **1** (0.50 mmol) in THF (5.0 mL) at 0 °C was added dropwise a solution of DABCO (56 mg, 0.50 mmol, 1 eq.) in THF (5.0 mL). The reaction mixture was stirred at 0 °C until completion and monitored by LC-MS analysis. The reaction mixture was diluted with Et_2O (10 mL) and the resulting precipitate was filtered and washed with Et_2O to give the pure DABCO-pyridine **3**. The product was used without further purification.

General procedure C: trimethylammonium formation

To a solution of pyridine triflate derivative **1** (0.50 mmol) in THF (5.0 mL) at 0 °C was added dropwise a solution of NMe_3 (1M in THF, 0.50 mL, 0.50 mmol, 1 eq.). The reaction mixture was stirred at 0 °C until completion and monitored by LC-MS analysis. The reaction mixture was diluted with Et_2O (10 mL) and the resulting precipitate was filtered and washed with Et_2O to give the pure trimethylammonium-pyridine **2**. The product was used without further purification.

General procedure D: fluorination reaction

CsF (228 mg, 1.50 mmol, 3 eq.) was added to a solution of trialkyammonium derivative **2** or **3** (0.50 mmol) in DMF (2 mL) under argon and the reaction mixture was stirred at room temperature. After completion, EtOAc (20 mL) was added to the reaction mixture and the organic layer was washed with 5% LiCl (3 x 5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography.

General procedure E: fluorination reaction

CsF (61 mg, 0.40 mmol, 2 eq.) was added to a solution of trialkyammonium derivative **2** or **3** (0.20 mmol) in dry acetonitrile (1 mL) at 0 °C under argon and the reaction mixture was stirred at 0 °C until completion. EtOAc (15 mL) was then added to the reaction mixture and the organic layer was washed with 5% LiCl (3 x 5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography.

General procedure F: preparation of peptide conjugates

To a solution of NHS-containing pyridine **5** or **S18** (0.10 mmol, 1 eq.) in dry THF (1 mL) was added a solution of peptide (0.10 mmol, 1 eq.) in dry THF (0.5 mL) and the mixture was stirred at room temperature. After completion (30 min - 2hrs), the solvent was removed *in vacuo* and the crude was purified by flash chromatography (*n*-heptane/EtOAc).

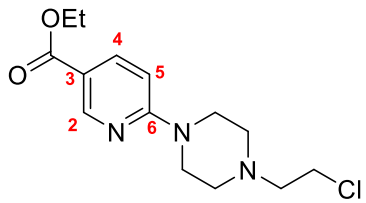
General procedure G: preparation of peptide conjugates

To a solution of NHS-containing pyridine **5** or **S18** (0.010 mmol, 1 eq.) in MeCN (0.1 mL) was added a solution of peptide (0.010 mmol, 1 eq.) in 0.1 M aq. $NaHCO_3$ pH 8.1 (0.2 mL) and the mixture was stirred at room temperature. pH was adjusted to ~8 with 0.1 M aq. $NaHCO_3$ pH 8.1 if needed. After completion, the solvent was removed *in vacuo* and the crude was purified by reverse phase chromatography (C-18, H_2O/MeCN/0.05% formic acid).

2. Syntheses and characterizations

a. Ethyl ester series

6-(4-(2-Chloroethyl)piperazin-1-yl)-nicotinic acid ethyl ester S1



To a solution of 6-chloronicotinic acid ethyl ester (30 mg, 0.13 mmol, 1 eq.) in DMF (3.0 mL) was added dropwise a solution of DABCO (18 mg, 0.16 mmol, 1.2 eq.) in DMF (1.0 mL). The reaction mixture was stirred at room temperature for 4 hours and at 50 °C for 2 hours. H_2O (5 mL) was then added and the product was extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-heptane/EtOAc = 90/10 to 50/50). Product **S1** was obtained as a yellow solid in 38 % yield (15 mg).

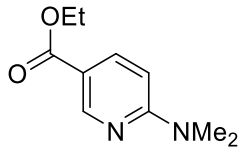
^{1}H ($CDCl_3$, 400 MHz): 8.79 (d, 1H, $J_{2,4}$ = 2.3 Hz, *H*-2), 8.01 (dd, 1H, $J_{4,5}$ = 9.0, $J_{2,4}$ = 2.3 Hz, *H*-4), 6.58 (d, 1H, $J_{4,5}$ = 9.0 Hz, *H*-5), 4.32 (q, 2H, *J* = 7.2 Hz, CH_2), 3.70 (t, 4H, *J* = 5.0 Hz, 2 CH_2), 3.62 (t, 2H, *J* = 6.8 Hz, CH_2), 2.78 (t, 2H, *J* = 6.8 Hz, CH_2), 2.61 (t, 4H, *J* = 5.0 Hz, 2 CH_2), 1.36 (t, 3H, *J* = 7.2 Hz, CH_3).

^{13}C ($CDCl_3$, 100 MHz): 165.9 (*C*=O), 160.5 (C_6), 150.9 (C_2), 138.4 (C_4), 115.0 (C_3), 105.0 (C_5), 60.4 (CH_2), 59.7 (CH_2), 52.8 (2 CH_2), 44.5 (2 CH_2), 40.8 (CH_2), 14.3 (CH_3).

HRMS (ESI): m/z calcd for $C_{14}H_{21}ClN_3O_2$ $[M+H]^+$: 298.1317; found: 298.1323.

Mp: 70-71 °C.

6-(Dimethylamino)-nicotinic acid ethyl ester S2



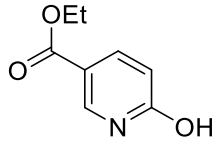
To a solution of 6-chloronicotinic acid ethyl ester (130 mg, 0.77 mmol, 1 eq.) in dry DMF (5.0 mL) was added $HNMe_2$·HCl (75 mg, 0.92 mmol, 1.2 eq.). The reaction mixture was stirred at 100 °C until completion. After cooling to room temperature, H_2O (10 mL) was added and the product was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (*n*-heptane/EtOAc = 90/10). Product **S2** was obtained as a yellow oil in 75 % yield (102 mg).

^{1}H ($CDCl_3$, 400 MHz): 8.80 (dd, 1H, $J_{2,4}$ = 2.4, $J_{2,5}$ = 0.6 Hz, *H*-2), 7.99 (dd, 1H, $J_{4,5}$ = 9.1, $J_{2,4}$ = 2.4 Hz, *H*-4), 6.45 (dd, 1H, $J_{4,5}$ = 9.1, $J_{2,5}$ = 0.6 Hz, *H*-5), 4.31 (q, 2H, *J* = 7.1 Hz, CH_2), 3.15 (s, 6H, 2 CH_3), 1.35 (t, 3H, *J* = 7.1 Hz, CH_3).

^{13}C ($CDCl_3$, 100 MHz): 166.3 (*C*=O), 160.8 (C_6), 151.1 (C_2), 138.0 (C_4), 113.8 (C_3), 104.4 (C_5), 60.3 (CH_2), 38.1 (2 CH_3), 14.4 (CH_3).

HRMS (ESI): m/z calcd for $C_{10}H_{15}N_2O_2$ $[M+H]^+$: 195.1128; found: 195.1130.

6-Hydroxynicotinic acid ethyl ester S3 [1]



Concentrated sulfuric acid (1 mL) was added to a mixture of 6-hydroxynicotinic acid (1.40 g, 10.0 mmol) in ethanol (10.0 mL) and the reaction mixture was refluxed for 3 h. After complete conversion, the mixture was cooled to 0 °C and pH was adjusted to 11–12 with a saturated solution of sodium carbonate. The product was then extracted with ethyl acetate (3x50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure to afford 2.95 g (87 %) of expected compound **S3** as a white crystalline solid. The product was used without further purification.

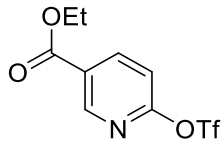
[1] G. Landelle *et al.*, *Journal of Fluorine Chemistry* **2017**, *203*, 155

^{1}H ($CDCl_3$, 400 MHz): 13.34 (br s, 1H, O*H*), 8.20 (d, 1H, $J_{2,4}$ = 2.5 Hz, *H*-2), 7.98 (dd, 1H, $J_{4,5}$ = 9.6, $J_{2,4}$ = 2.5 Hz, *H*-4), 6.54 (d, 1H, $J_{4,5}$ = 9.6 Hz, *H*-5), 4.29 (q, 2H, *J* = 7.2 Hz, CH_2), 1.32 (t, 3H, *J* = 7.2 Hz, CH_3).

^{13}C ($CDCl_3$, 100 MHz): 165.7 (*C*=O), 164.1 (C_6), 141.1 (C_2), 139.8 (C_4), 119.4 (C_5), 111.4 (C_3), 61.1 (*C*H_2), 14.3 (*C*H_3).

LC-MS (ESI): m/z calcd for $C_8H_{10}NO_3$ $[M+H]^+$: 168.1; found: 168.1.

6-(((Trifluoromethyl)sulfonyl)oxy)nicotinic acid ethyl ester 1a



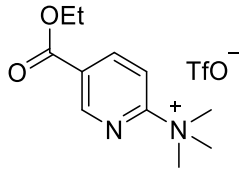
Prepared following procedure A starting from **S3**. Expected product **1a** was obtained as a colorless oil in 91 % yield (purification: silica gel, *n*-heptane/EtOAc: 80/20).

^{1}H ($CDCl_3$, 400 MHz): 9.01 (dd, 1H, $J_{2,4}$ = 2.3, $J_{2,5}$ = 0.5 Hz, *H*-2), 8.49 (dd, 1H, $J_{4,5}$ = 8.5, $J_{2,4}$ = 2.3 Hz, *H*-4), 7.24 (dd, 1H, $J_{4,5}$ = 8.5, $J_{2,5}$ = 0.6 Hz, *H*-5), 4.43 (q, 2H, *J* = 7.2 Hz, CH_2), 1.41 (t, 3H, *J* = 7.2 Hz, CH_3).

^{13}C ($CDCl_3$, 100 MHz): 163.7 (*C*=O), 158.1 (C_6), 150.5 (C_2), 142.3 (C_4), 127.1 (C_3), 118.5 (q, *J* = 320.1 Hz, *C*F_3), 114.7 (C_5), 62.1 (*C*H_2), 14.2 (*C*H_3).

HRMS (ESI): m/z calcd for $C_9H_9F_3NO_5S$ $[M+H]^+$: 300.0148; found: 300.0153.

***N*,*N*,*N*-Trimethyl-3-ethyloxycarbonylpyridin-2-aminium trifluoromethane sulfonate 2a**



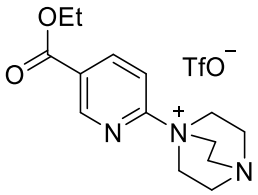
Prepared following procedure C starting from **1a**. Expected product **2a** was obtained as a white solid in 67 % yield.

^{1}H (DMSO-d_6, 400 MHz): 9.11 (dd, 1H, $J_{2,4}$ = 2.3, $J_{2,5}$ = 0.7 Hz, *H*-2), 8.68 (dd, 1H, $J_{4,5}$ = 8.7, $J_{2,4}$ = 2.3 Hz, *H*-4), 8.23 (dd, 1H, $J_{4,5}$ = 8.7, $J_{2,5}$ = 0.7 Hz, *H*-5), 4.41 (q, 2H, *J* = 7.1 Hz, CH_2), 3.62 (s, 9H, 3 CH_3), 1.35 (t, 3H, *J* = 7.1 Hz, CH_3).

^{13}C (DMSO-d_6, 100 MHz): 163.3 (*C*=O), 159.3 (C_6), 149.1 (C_2), 141.7 (C_4), 128.0 (C_3), 120.6 (q, *J* = 320.1 Hz, *C*F_3), 115.7 (C_5), 61.8 (*C*H_2), 54.6 (3 *C*H_3), 14.0 (*C*H_3).

HRMS (ESI): m/z calcd for $C_{11}H_{17}N_2O_2$ $[M]^+$: 209.1285; found: 209.1282.

3-Ethyloxycarbonylpyridin-6-(4-aza-1-azoniabicyclo[2.2.2]octane) trifluoromethanesulfonate 3a



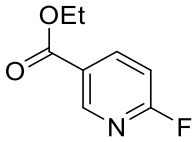
Prepared following procedure B starting from **1a**. Expected product **3a** was obtained as a white solid in 94 % yield.

^{1}H (DMSO-d$_6$, 400 MHz): 9.14 (dd, 1H, $J_{2,4}$ = 2.3, $J_{2,5}$ = 0.6 Hz, *H*-2), 8.70 (dd, 1H, $J_{4,5}$ = 8.7, $J_{2,4}$ = 2.3 Hz, *H*-4), 8.14 (dd, 1H, $J_{4,5}$ = 8.7, $J_{2,5}$ = 0.6 Hz, *H*-5), 4.41 (q, 2H, *J* = 7.1 Hz, CH_2), 3.90 (dd, 6H, *J* = 8.4, *J* = 6.6 Hz, 3 CH_2-DABCO), 3.23 (dd, 6H, *J* = 8.4, *J* = 6.6 Hz, 3 CH_2-DABCO), 1.35 (t, 3H, *J* = 7.1 Hz, CH_3).

^{13}C (DMSO-d$_6$, 100 MHz): 163.4 (*C*=O), 158.4 (C_6), 149.4 (C_2), 141.9 (C_4), 128.1 (C_3), 120.6 (q, *J* = 320.1 Hz, *C*F$_3$), 117.0 (C_5), 61.9 (*C*H$_2$), 53.9 (3 *C*H$_2$-DABCO), 45.1 (3 *C*H$_2$-DABCO), 14.1 (*C*H$_3$).

HRMS (ESI): m/z calcd for $C_{14}H_{20}N_3O_2$ $[M]^+$: 262.1550; found: 262.1550.

6-Fluoronicotinic acid ethyl ester 4a



Prepared following procedure D starting from **3a**. Expected product **4a** was obtained as a colourless oil in 91 % yield (purification: silica gel, *n*-heptane/EtOAc: 80/20).

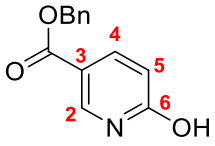
^{1}H (CDCl$_3$, 400 MHz): 8.88 (td, 1H, $J_{2,4}$ = 2.4, $J_{2,5}$ = 0.7, $J_{H\text{-}F}$ = 0.7 Hz, *H*-2), 8.40 (ddd, 1H, $J_{4,5}$ = 8.6, $J_{H\text{-}F}$ = 7.6, $J_{2,4}$ = 2.4 Hz, *H*-4), 6.99 (ddd, 1H, $J_{4,5}$ = 8.6, $J_{H\text{-}F}$ = 2.9, $J_{2,5}$ = 0.7 Hz, *H*-5), 4.40 (q, 2H, *J* = 7.2 Hz, CH_2), 1.40 (t, 3H, *J* = 7.2 Hz, CH_3).

^{13}C (CDCl$_3$, 100 MHz): 165.8 (d, $J_{C\text{-}F}$ = 245.1 Hz, C_6), 164.2 (*C*=O), 150.3 (d, $J_{C\text{-}F}$ = 16.2 Hz, C_2), 142.6 (d, $J_{C\text{-}F}$ = 9.4 Hz, C_4), 124.7 (d, $J_{C\text{-}F}$ = 4.4 Hz, C_3), 109.5 (d, $J_{C\text{-}F}$ = 38.0 Hz, C_5), 61.6 (*C*H$_2$), 14.3 (*C*H$_3$).

LCMS (ESI): m/z calcd for $C_8H_9FNO_2$ $[M+H]^+$: 170.1; found: 170.0.

b. Benzyl ester series

6-Hydroxynicotinic acid benzyl ester S4



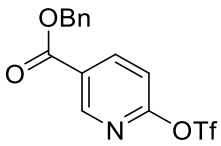
At 0 °C, EDC (2.30 g, 12.0 mmol, 1.2 eq.) and DMAP (122 mg, 1.0 mmol, 0.1 eq.) were added to a solution of 6-hydroxynicotinic acid (1.39 g, 10.0 mmol) and benzyl alcohol (1.56 mL, 15.0 mmol, 1.5 eq.) in 50 ml of dry CH_2Cl_2. The reaction mixture was stirred at room temperature for 16 h. After completion, the reaction mixture was washed with H_2O (15 mL), saturated aqueous $NaHCO_3$ solution (15 mL) and brine (15 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. The product was purified by column chromatography (CH_2Cl_2/MeOH = 95/5) to obtain 2.01 g (88%) of **S4** as white solid.

^{1}H (DMSO-d$_6$, 400 MHz): 12.14 (br s, 1H, O*H*), 8.07 (d, 1H, $J_{2,4}$ = 2.7 Hz, *H*-2), 7.82 (dd, 1H, $J_{4,5}$ = 9.7, $J_{2,4}$ = 2.7 Hz, *H*-4), 7.45-7.32 (m, 5H, 5 *H*-Ar), 6.38 (d, 1H, $J_{4,5}$ = 9.7 Hz, *H*-5), 5.27 (s, 2H, C*H*$_2$-Ph).

^{13}C (DMSO-d$_6$, 100 MHz): 163.8, 162.4 (*C*=O, C_6), 141.0 (C_2), 139.3 (C_4), 136.2 (*C*-Ar$_{quat}$), 128.5 (2 *C*-Ar), 128.1 (2 *C*-Ar), 128.0 (*C*-Ar), 119.6 (C_5), 108.0 (C_3), 65.8 (*C*H$_2$-Ph).

LC-MS (ESI): *m/z*: m/z calcd for $C_{13}H_{12}NO_3$ $[M+H]^+$: 230.1; found: 230.0.

6-(((Trifluoromethyl)sulfonyl)oxy)nicotinic acid benzyl ester 1b



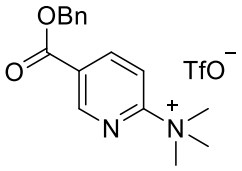
Prepared following procedure A starting from **S4**. Expected product **1b** was obtained as a colorless oil in 90 % yield (purification: silica gel, *n*-heptane/EtOAc: 70/30).

^{1}H (CDCl$_3$, 400 MHz): 8.97 (d, 1H, $J_{2,4}$ = 2.5 Hz, *H*-2), 8.43 (dd, 1H, $J_{4,5}$ = 8.5, $J_{2,4}$ = 2.5 Hz, *H*-4), 7.38-7.28 (m, 5H, 5 *H*-Ar), 7.16 (d, 1H, $J_{4,5}$ = 8.5 Hz, *H*-5), 5.33 (s, 2H, C*H*$_2$-Ph).

^{13}C (CDCl$_3$, 100 MHz): 163.5 (*C*=O), 158.2 (C_6), 150.6 (C_2), 142.4 (C_4), 135.0 (*C*-Ar$_{quat}$), 128.8 (2 *C*-Ar, C_3), 128.5 (2 *C*-Ar), 126.8 (*C*-Ar), 118.5 (q, J = 320.1 Hz, *C*F$_3$), 114.8 (C_5), 67.7 (*C*H$_2$-Ph).

HRMS (ESI): m/z calcd for $C_{14}H_{11}F_3NO_5S$ $[M+H]^+$: 362.0305; found: 362.0304.

***N*,*N*,*N*-Trimethyl-3-benzyloxycarbonylpyridin-2-aminium trifluoromethane sulfonate 2b**



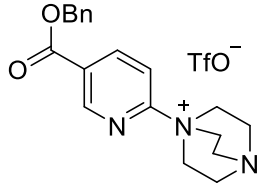
Prepared following procedure C starting from **1b**. Expected product **2b** was obtained as a white solid in 70 % yield.

^{1}H (DMSO-d$_6$, 400 MHz): 9.16 (dd, 1H, $J_{2,4}$ = 2.3, $J_{2,5}$ = 0.6 Hz, *H*-2), 8.72 (dd, 1H, $J_{4,5}$ = 8.7, $J_{2,4}$ = 2.3 Hz, *H*-4), 8.23 (dd, 1H, $J_{4,5}$ = 8.7, $J_{2,5}$ = 0.6 Hz, *H*-5), 7.52-7.49 (m, 2H, 2 *H*-Ar), 7.44-7.35 (m, 3H, 3 *H*-Ar), 5.45 (s, 2H, C*H*$_2$-Ph), 3.62 (s, 9H, 3 C*H*$_3$).

^{13}C (DMSO-d_6, 100 MHz): 163.2 (*C*=O), 159.4 (C_6), 149.2 (C_2), 141.9 (C_4), 135.5 (*C*-Ar_{quat}), 128.5 (2 *C*-Ar), 128.3 (*C*-Ar), 128.0 (2 *C*-Ar), 127.7 (C_3), 115.8 (C_5), 67.0 (*C*H_2-Ph), 54.6 (3 *C*H_3).
(CF_3 is not visible on the spectrum)

HRMS (ESI): m/z calcd for $C_{16}H_{19}N_2O_2$ $[M]^+$: 271.1441; found: 271.1442.

3-Benzyloxycarbonylpyridin-6-(4-aza-1-azoniabicyclo[2.2.2]octane) trifluoromethanesulfonate 3b



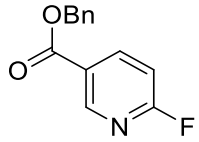
Prepared following procedure B starting from **1b**. Expected product **3b** was obtained as a white solid in 85 % yield.

^{1}H (DMSO-d_6, 400 MHz): 9.17 (d, 1H, $J_{2,4}$ = 2.3 Hz, *H*-2), 8.73 (dd, 1H, $J_{4,5}$ = 8.7, $J_{2,4}$ = 2.3 Hz, *H*-4), 8.14 (d, 1H, $J_{4,5}$ = 8.7 Hz, *H*-5), 7.52-7.49 (m, 2H, 2 *H*-Ar), 7.44-7.35 (m, 3H, 3 *H*-Ar), 5.44 (s, 2H, CH_2-Ph), 3.89 (t, 6H, *J* = 7.2 Hz, 3 CH_2-DABCO), 3.22 (t, 6H, *J* = 7.2 Hz, 3 CH_2-DABCO).

^{13}C (DMSO-d_6, 100 MHz): 163.2 (*C*=O), 158.5 (C_6), 149.4 (C_2), 142.0 (C_4), 135.5 (*C*-Ar_{quat}), 128.5 (2 *C*-Ar), 128.3 (*C*-Ar), 128.1 (2 *C*-Ar), 127.8 (C_3), 117.0 (C_5), 67.1 (*C*H_2-Ph), 53.8 (3 *C*H_2-DABCO), 45.0 (3 *C*H_2-DABCO).
(CF_3 is not visible on the spectrum)

HRMS (ESI): m/z calcd for $C_{19}H_{22}N_3O_2$ $[M]^+$: 324.1707; found: 324.1706.

6-Fluoronicotinic acid benzyl ester 4b



Prepared following procedure D starting from **3b**. Expected product **4b** was obtained as a white solid in 91 % yield (purification: silica gel, *n*-heptane/EtOAc: 80/20).

^{1}H ($CDCl_3$, 400 MHz): 8.92 (d, 1H, $J_{2,4}$ = 2.0 Hz, *H*-2), 8.42 (ddd, 1H, $J_{4,5}$ = 8.6, $J_{H\text{-}F}$ = 7.6, $J_{2,4}$ = 2.0 Hz, *H*-4), 7.46-7.34 (m, 5H, 5 *H*-Ar), 7.00 (dd, 1H, $J_{4,5}$ = 8.6, $J_{H\text{-}F}$ = 2.9 Hz, *H*-5), 5.39 (s, 2H, CH_2-Ph).

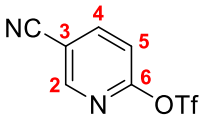
^{13}C ($CDCl_3$, 100 MHz): 165.9 (d, $J_{C\text{-}F}$ = 242.5 Hz, C_6), 164.1 (*C*=O), 150.5 (d, $J_{C\text{-}F}$ = 16.7 Hz, C_2), 142.7 (d, $J_{C\text{-}F}$ = 9.3 Hz, C_4), 135.3 (*C*-Ar_{quat}), 128.8 (2 *C*-Ar), 128.6 (*C*-Ar), 128.4 (2 *C*-Ar), 124.4 (d, $J_{C\text{-}F}$ = 4.2 Hz, C_3), 109.6 (d, $J_{C\text{-}F}$ = 37.3 Hz, C_5), 67.3 (*C*H_2-Ph).

HRMS (ESI): m/z calcd for $C_{13}H_{11}FNO_2$ $[M+H]^+$: 232.0768; found: 232.0768.

Mp: 39-40 °C.

c. Nitrile series

6-(((Trifluoromethyl)sulfonyl)oxy)nicotinonitrile 1c



Prepared following procedure A starting from 6-hydroxynicotinonitrile. Expected product **1c** was obtained as a pale yellow solid in 60 % yield (purification: silica gel, *n*-heptane/EtOAc: 70/30).

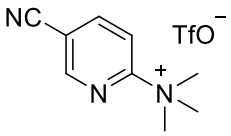
^{1}H (CDCl$_3$, 400 MHz): 8.72 (dd, 1H, $J_{2,4}$ = 2.3, $J_{2,5}$ = 0.6 Hz, *H*-2), 8.19 (dd, 1H, $J_{4,5}$ = 8.5, $J_{2,4}$ = 2.3 Hz, *H*-4), 7.33 (dd, 1H, $J_{4,5}$ = 8.5, $J_{2,5}$ = 0.6 Hz, *H*-5).

^{13}C (CDCl$_3$, 100 MHz): 157.4 (C_6), 152.2 (C_2), 144.3 (C_4), 118.5 (q, J = 321.3 Hz, CF_3), 115.7 (C_5), 114.9 (*C*N), 110.7 (C_3).

HRMS (ESI): m/z calcd for $C_7H_4F_3N_2O_3S$ $[M+H]^+$: 252.9889; found: 252.9889.

Mp: 59-60 °C.

***N,N,N*-Trimethyl-3-cyanopyridin-6-aminium trifluoromethane sulfonate 2c**



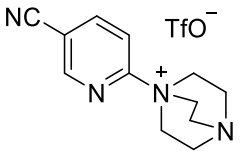
Prepared following procedure C starting from **1c**. Expected product **2c** was obtained as a white solid in 81 % yield.

^{1}H (DMSO-d$_6$, 400 MHz): 9.20 (dd, 1H, $J_{2,4}$ = 2.2, $J_{2,5}$ = 0.7 Hz, *H*-2), 8.82 (dd, 1H, $J_{4,5}$ = 8.8, $J_{2,4}$ = 2.2 Hz, *H*-4), 8.33 (dd, 1H, $J_{4,5}$ = 8.8, $J_{2,5}$ = 0.7 Hz, *H*-5), 3.60 (s, 9H, 3 CH_3).

^{13}C (DMSO-d$_6$, 100 MHz): 158.7 (C_6), 152.0 (C_2), 145.1 (C_4), 120.6 (q, J = 322.7 Hz, CF_3), 116.3 (C_5), 115.6 (*C*N), 111.3 (C_3), 54.6 (3 CH_3).

HRMS (ESI): m/z calcd for $C_9H_{12}N_3$ $[M]^+$: 162.1026; found: 162.1025.

3-Cyanopyridin-6-(4-aza-1-azoniabicyclo[2.2.2]octane) trifluoromethanesulfonate 3c



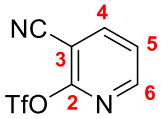
Prepared following procedure B starting from **1c**. Expected product **3c** was obtained as a white solid in 84 % yield.

^{1}H (DMSO-d_6, 400 MHz): 9.24 (dd, 1H, $J_{2,4}$ = 2.0, $J_{2,5}$ = 0.8 Hz, *H*-2), 8.83 (dd, 1H, $J_{4,5}$ = 8.7, $J_{2,4}$ = 2.0 Hz, *H*-4), 8.24 (dd, 1H, $J_{4,5}$ = 8.7, $J_{2,5}$ = 0.8 Hz, *H*-5), 3.88 (dd, 6H, *J* = 8.5, *J* = 6.7 Hz, 3 CH_2-DABCO), 3.22 (dd, 6H, *J* = 8.5, *J* = 6.7 Hz, 3 CH_2-DABCO).

^{13}C (DMSO-d_6, 100 MHz): 157.8 (C_6), 152.2 (C_2), 145.2 (C_4), 120.6 (q, *J* = 320.1 Hz, *C*F_3), 117.4 (C_5), 115.6, 111.5 (*C*N, C_3), 53.8 (3 *C*H_2-DABCO), 45.0 (3 *C*H_2-DABCO).

HRMS (ESI): m/z calcd for $C_{12}H_{15}N_4$ $[M]^+$: 215.1291; found: 215.1289.

2-(((Trifluoromethyl)sulfonyl)oxy)nicotinonitrile 1d



Prepared following procedure A starting from 3-cyano-2-pyridone. Expected product **1d** was obtained as a yellow solid in 60 % yield (purification: silica gel, *n*-heptane/EtOAc: 80/20 to 70/30).

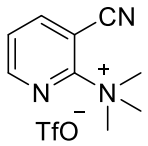
^{1}H ($CDCl_3$, 400 MHz): 8.64 (dd, 1H, $J_{5,6}$ = 4.9, $J_{4,6}$ = 1.9 Hz, *H*-6), 8.21 (dd, 1H, $J_{4,5}$ = 7.7, $J_{4,6}$ = 1.9 Hz, *H*-4), 7.56 (dd, 1H, $J_{4,5}$ = 7.7, $J_{5,6}$ = 4.9 Hz, *H*-5).

^{13}C ($CDCl_3$, 100 MHz): 155.4 (C_2), 152.1 (C_6), 144.5 (C_4), 123.9 (C_5), 118.5 (q, *J* = 321.3 Hz, *C*F_3), 112.1 (*C*N), 102.0 (C_3).

HRMS (ESI): m/z calcd for $C_7H_4F_3N_2O_3S$ $[M+H]^+$: 252.9889; found: 252.9886.

Mp: 32-33 °C.

***N*,*N*,*N*-Trimethyl-3-cyanopyridin-2-aminium trifluoromethane sulfonate 2d**



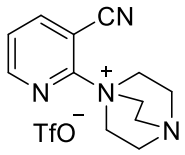
Prepared following procedure C starting from **1d**. Expected product **2d** was obtained as a pale pink solid in 50 % yield

^{1}H (DMSO-d_6, 400 MHz): 8.94 (dd, 1H, $J_{5,6}$ = 4.9, $J_{4,6}$ = 1.8 Hz, *H*-6), 8.81 (dd, 1H, $J_{4,5}$ = 7.8, $J_{4,6}$ = 1.8 Hz, *H*-4), 7.98 (dd, 1H, $J_{4,5}$ = 7.8, $J_{5,6}$ = 4.8 Hz, *H*-5), 3.77 (s, 9H, 3 CH_3).

^{13}C (DMSO-d_6, 100 MHz): 154.4 (C_2), 151.7 (C_6), 147.4 (C_4), 126.5 (C_5), 120.6 (q, *J* = 321.5 Hz, *C*F_3), 115.0 (*C*N), 102.0 (C_3), 55.2 (3 *C*H_3).

HRMS (ESI): m/z calcd for $C_9H_{12}N_3$ $[M]^+$: 162.1026; found: 162.1023.

3-Ethyloxycarbonylpyridin-2-(4-aza-1-azoniabicyclo[2.2.2]octane) trifluoromethanesulfonate 3d



Prepared following procedure B starting from **1d**. Expected product **3d** was obtained as a pale orange solid in 79 % yield.

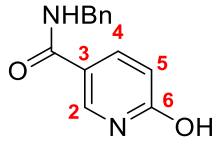
^{1}H (DMSO-d$_6$, 400 MHz): 8.98 (dd, 1H, $J_{5,6}$ = 4.9, $J_{4,6}$ = 1.8 Hz, *H*-6), 8.82 (dd, 1H, $J_{4,5}$ = 7.8, $J_{4,6}$ = 1.8 Hz, *H*-4), 7.98 (dd, 1H, $J_{4,5}$ = 7.8, $J_{5,6}$ = 4.9 Hz, *H*-5), 4.09 (dd, 6H, *J* = 8.3, *J* = 7.6 Hz, 3 C*H*$_2$-DABCO), 3.28 (dd, 6H, *J* = 8.3, *J* = 7.6 Hz, 3 C*H*$_2$-DABCO).

^{13}C (DMSO-d$_6$, 100 MHz): 153.6 (*C*$_2$), 152.1 (*C*$_6$), 147.7 (*C*$_4$), 126.4 (*C*$_5$), 120.7 (q, *J* = 322.3 Hz, *C*F$_3$), 114.9 (*C*N), 103.1 (*C*$_3$), 54.3 (3 *C*H$_2$-DABCO), 44.9 (3 *C*H$_2$-DABCO).

HRMS (ESI): m/z calcd for $C_{12}H_{15}N_4$ $[M]^+$: 212.1291; found: 215.1288.

d. Benzylamide series

***N*-Benzyl-6-hydroxynicotinamide S5**



At 0 °C, EDC (422 mg, 2.2 mmol, 1.1 eq.) was added to a solution of 6-hydroxynicotinic acid (278 mg, 2.0 mmol) and benzylamine (240 µL, 2.2 mmol, 1.1 eq.) in 10 ml of dry CH_2Cl_2. The reaction mixture was stirred at room temperature for 16 h. After reaction completion, the solvent was removed under reduced pressure and the product was purified by column chromatography (CH_2Cl_2/MeOH = 95/5 to 90/10) to obtain 300 mg (66 %) of **S5** as a white solid.

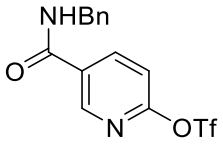
^{1}H (DMSO-d$_6$, 400 MHz): 11.89 (br s, 1H, O*H*), 8.80 (t, 1H, *J* = 5.9 Hz, N*H*), 8.05 (d, 1H, $J_{2,4}$ = 2.7 Hz, *H*-2), 7.91 (dd, 1H, $J_{4,5}$ = 9.6, $J_{2,4}$ = 2.7 Hz, *H*-4), 7.34-7.21 (m, 5H, 5 *H*-Ar), 6.37 (d, 1H, $J_{4,5}$ = 9.6 Hz, *H*-5), 4.43 (d, 2H, *J* = 5.9 Hz, C*H*$_2$-Ph).

^{13}C (DMSO-d$_6$, 100 MHz): 163.5, 162.3 (*C*=O, *C*$_6$), 139.6 (*C*-Ar$_{quat}$), 139.0 (*C*$_4$), 137.3 (*C*$_2$), 128.2 (2 *C*-Ar), 127.2 (2 *C*-Ar), 126.7 (*C*-Ar), 119.1 (*C*$_5$), 112.2 (*C*$_3$), 42.4 (*C*H$_2$-Ph).

LC-MS (ESI): m/z calcd for $C_{13}H_{13}N_2O_2$ $[M+H]^+$: 229.1; found: 229.1

Mp: 207-208 °C.

***N*-Benzyl-6-(((trifluoromethyl)sulfonyl)oxy)nicotinamide 1e**



Prepared following procedure A starting from **S5**. Expected product **1e** was obtained as a white solid in 92 % yield (purification: silica gel, *n*-heptane/EtOAc: 70/30).

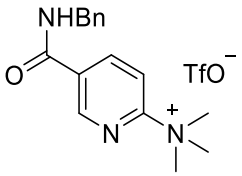
^{1}H (CDCl$_3$, 400 MHz): 8.66 (dd, 1H, $J_{2,4}$ = 2.4, $J_{2,5}$ = 0.6 Hz, *H*-2), 8.23 (dd, 1H, $J_{4,5}$ = 8.5, $J_{2,4}$ = 2.4 Hz, *H*-4), 7.31-7.22 (m, 5H, 5 *H*-Ar), 7.15 (dd, 1H, $J_{4,5}$ = 8.5, $J_{2,5}$ = 0.6 Hz, *H*-5), 6.55 (t, 1H, *J* = 5.7 Hz, N*H*), 4.56 (d, 2H, *J* = 5.7 Hz, CH_2-Ph).

^{13}C (CDCl$_3$, 100 MHz): 163.8 (*C*=O), 157.3 (C_6), 147.1 (C_2), 140.7 (C_4), 137.2 (*C*-Ar$_{quat}$), 130.9 (C_3), 129.0 (2 *C*-Ar), 128.0 (3 *C*-Ar), 118.5 (q, *J* = 321.3 Hz, *C*F$_3$), 115.1 (C_5), 44.4 (*C*H$_2$-Ph).

HRMS (ESI): m/z calcd for $C_{14}H_{12}F_3N_2O_4S$ $[M+H]^+$: 361.0464; found: 361.0463.

Mp: 84-85 °C.

***N*,*N*,*N*-Trimethyl-3-(*N*-benzylamide)pyridin-6-aminium trifluoromethane sulfonate 2e**



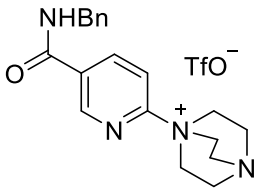
Prepared following procedure C starting from **1e**. Expected product **2e** was obtained as a white solid in 47 % yield.

^{1}H (DMSO-d$_6$, 400 MHz): 9.47 (t, 1H, *J* = 5.9 Hz, N*H*), 9.07 (dd, 1H, $J_{2,4}$ = 2.4, $J_{2,5}$ = 0.6 Hz, *H*-2), 8.62 (dd, 1H, $J_{4,5}$ = 8.7, $J_{2,4}$ = 2.4 Hz, *H*-4), 8.21 (dd, 1H, $J_{4,5}$ = 8.7, $J_{2,5}$ = 0.6 Hz, *H*-5), 7.37-7.24 (m, 5H, 5 *H*-Ar), 4.54 (d, 2H, *J* = 5.9 Hz, CH_2-Ph), 3.60 (s, 9H, 3 CH_3).

^{13}C (DMSO-d$_6$, 100 MHz): 163.1 (*C*=O), 158.1 (C_6), 147.6 (C_2), 139.8 (C_4), 138.8 (*C*-Ar$_{quat}$), 131.8 (C_3), 128.4 (2 *C*-Ar), 127.2 (2 *C*-Ar), 127.0 (*C*-Ar), 120.6 (q, *J* = 321.3 Hz, *C*F$_3$), 115.2 (C_5), 54.6 (3 *C*H$_3$), 42.7 (*C*H$_2$-Ph).

HRMS (ESI): m/z calcd for $C_{16}H_{20}N_3O$ $[M]^+$: 270.1601; found: 270.1601.

3-(*N*-Benzylamide)pyridin-6-(4-aza-1-azoniabicyclo[2.2.2]octane) trifluoromethanesulfonate 3e



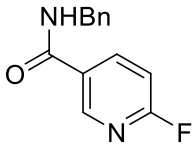
Prepared following procedure B starting from **1e**. Expected product **3e** was obtained as a white solid in 89 % yield.

^{1}H (DMSO-d_6, 400 MHz): 9.46 (t, 1H, *J* = 5.9 Hz, N*H*), 9.09 (d, 1H, $J_{2,4}$ = 2.1 Hz, *H*-2), 8.62 (dd, 1H, $J_{4,5}$ = 8.8, $J_{2,4}$ = 2.1 Hz, *H*-4), 8.11 (d, 1H, $J_{4,5}$ = 8.8 Hz, *H*-5), 7.34-7.24 (m, 5H, 5 *H*-Ar), 4.54 (d, 2H, *J* = 5.9 Hz, CH_2-Ph), 3.88 (dd, 6H, *J* = 8.6, *J* = 6.2 Hz, 3 CH_2-DABCO), 3.22 (dd, 6H, *J* = 8.6, *J* = 6.2 Hz, 3 CH_2-DABCO).

^{13}C (DMSO-d_6, 100 MHz): 163.1 (*C*=O), 157.2 (C_6), 147.7 (C_2), 140.0 (C_4), 138.8 (*C*-Ar_{quat}), 131.8 (C_3), 128.3 (2 *C*-Ar), 127.2 (2 *C*-Ar), 126.9 (*C*-Ar), 116.3 (C_5), 53.7 (3 CH_2-DABCO), 45.0 (3 CH_2-DABCO), 42.7 (CH_2-Ph).
(CF_3 is not visible on the spectrum)

HRMS (ESI): m/z calcd for $C_{19}H_{23}N_4O$ $[M]^+$: 323.1866; found: 323.1867.

***N*-Benzyl-6-fluoronicotinamide 4e**



Prepared following procedure D starting from **3e**. Expected product **4e** was obtained as a white solid in 79 % yield (purification: silica gel, *n*-heptane/EtOAc: 80/20 to 50/50).

^{1}H ($CDCl_3$, 400 MHz): 8.61 (s, 1H, *H*-2), 8.26 (ddd, 1H, $J_{4,5}$ = 8.6, $J_{H\text{-}F}$ = 7.5, $J_{2,4}$ = 2.5 Hz, *H*-4), 7.39-7.29 (m, 5H, 5 *H*-Ar), 7.00 (dd, 1H, $J_{4,5}$ = 8.6, $J_{H\text{-}F}$ = 2.8 Hz, *H*-5), 6.69 (t, 1H, *J* = 5.6 Hz, N*H*), 4.64 (d, 2H, *J* = 5.6 Hz, CH_2-Ph).

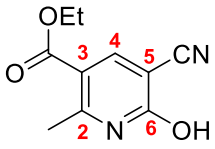
^{13}C ($CDCl_3$, 100 MHz): 165.0 (d, $J_{C\text{-}F}$ = 244.2 Hz, C_6), 164.4 (*C*=O), 146.7 (d, $J_{C\text{-}F}$ = 15.7 Hz, C_2), 140.9 (d, $J_{C\text{-}F}$ = 8.9 Hz, C_4), 137.6 (*C*-Ar_{quat}), 128.9 (2 *C*-Ar), 128.4 (d, $J_{C\text{-}F}$ = 4.1 Hz, C_3), 128.0 (2 *C*-Ar), 127.9 (*C*-Ar), 109.8 (d, $J_{C\text{-}F}$ = 37.4 Hz, C_5), 44.3 (CH_2-Ph).

HRMS (ESI): m/z calcd for $C_{13}H_{12}FN_2O$ $[M+H]^+$: 231.0928; found: 231.0927.

Mp: 103-104 °C.

e. Tetrasubstituted series

Ethyl 5-cyano-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate S6

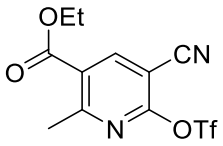


Prepared according to a previously reported procedure.[2]

^{1}H (DMF-d_7, 400 MHz): 12.63 (br s, 1H, O*H*), 8.88 (s, 1H, *H*-4), 4.33 (q, 2H, *J* = 7.1 Hz, CH_2), 2.76 (s, 3H, CH_3), 1.35 (t, 3H, *J* = 7.1 Hz, CH_3).

^{13}C (DMF-d_7, 100 MHz): 164.3 (*C*=O, *C*), 162.8 (*C*), 157.4 (*C*), 144.7 (C_4), 118.0 (*C*), 108.0 (*C*), 60.7 (*C*H_2), 18.8 (*C*H_3), 13.9 (*C*H_3).

5-Cyano-2-methyl-6-(((trifluoromethyl)sulfonyl)oxy)nicotinic acid ethyl ester 1f



Et_3N (140 µL, 1.00 mmol, 2.0 eq.) and Tf_2O (210 µL, 1.25 mmol, 2.5 eq.) were added to a cooled solution of **S6** (103 mg, 0.50 mmol, 1.0 eq.) in 3 mL of dry CH_2Cl_2. The resulting solution was stirred at 0 °C until completion. Water (2 mL) was added to the reaction mixture and the product was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (*n*-heptane/EtOAc = 70/30) to yield 95 mg (56 %) of **1f** as a white solid.

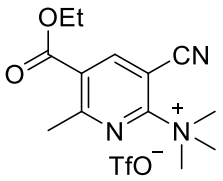
^{1}H ($CDCl_3$, 400 MHz): 8.65 (s, 1H, *H*-4), 4.44 (q, 2H, *J* = 7.2 Hz, CH_2), 2.92 (s, 3H, CH_3), 1.43 (t, 3H, *J* = 7.2 Hz, CH_3).

^{13}C ($CDCl_3$, 100 MHz): 165.5 (*C*=O), 163.0 (C_6), 154.9 (C_2), 146.5 (C_4), 125.8 (C_3), 118.3 (q, *J* = 320.8 Hz, *C*F_3), 111.5 (*C*N), 98.4 (C_5), 62.5 (*C*H_2), 25.0 (*C*H_3), 14.1 (*C*H_3).

HRMS (ESI): m/z calcd for $C_{11}H_{10}F_3N_2O_5S$ $[M+H]^+$: 339.0257; found: 339.0257.

Mp: 60-61 °C.

***N,N,N*-Trimethyl-2-methyl-3-ethyloxycarbonyl-5-cyanopyridin-6-aminium trifluoromethane sulfonate 2f**



Prepared following procedure C starting from **1f**. Expected product **2f** was obtained as a white solid in 88 % yield.

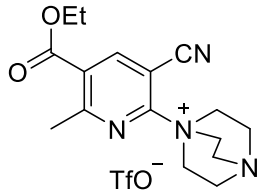
[2] S. M. Andersen, C.-J. Aurell, F. Zetterberg, M. Bollmark, R. Ehrl, P. Schuisky and A. Witt, *Org. Process Res. Dev*. **2013**, *17*, 1543

^{1}H (DMF-d_7, 400 MHz): 9.17 (s, 1H, *H*-4), 4.46 (q, 2H, *J* = 7.1 Hz, C*H*$_2$), 4.06 (s, 9H, 3 C*H*$_3$), 2.92 (s, 3H, C*H*$_3$), 1.41 (t, 3H, *J* = 7.1 Hz, C*H*$_3$).

^{13}C (DMF-d_7, 100 MHz): 163.5, 163.0 (*C*=O, *C*$_6$), 154.9 (*C*$_2$), 148.7 (*C*$_4$), 128.4 (*C*$_3$), 114.6 (*C*N), 100.2 (*C*$_5$), 62.6 (*C*H$_2$), 55.0 (3 *C*H$_3$), 24.0 (*C*H$_3$), 13.6 (*C*H$_3$).
(CF$_3$ is not visible on the spectrum)

HRMS (ESI): m/z calcd for $C_{13}H_{18}N_3O_2$ $[M]^+$: 248.1394; found: 248.1393.

2-Methyl-3-ethyloxycarbonyl-5-cyanopyridin-6-(4-aza-1-azoniabicyclo[2.2.2]octane) trifluoromethanesulfonate 3f



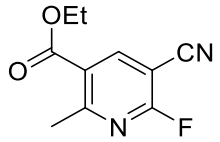
Prepared following procedure B starting from **1f**. Expected product **3f** was obtained as a white solid in 90 % yield.

^{1}H (DMF-d_7, 400 MHz): 9.15 (s, 1H, *H*-4), 4.46 (q, 2H, *J* = 7.1 Hz, C*H*$_2$), 4.36 (app t, 6H, *J* = 7.3 Hz, 3 C*H*$_2$-DABCO), 3.52 (app t, 6H, *J* = 7.3 Hz, 3 C*H*$_2$-DABCO), 2.92 (s, 3H, C*H*$_3$), 1.41 (t, 3H, *J* = 7.1 Hz, C*H*$_3$).

^{13}C (DMF-d_7, 100 MHz): 163.5, 163.2 (*C*=O, *C*$_6$), 153.9 (*C*$_2$), 148.9 (*C*$_4$), 128.2 (*C*$_3$), 121.5 (q, *J* = 322.1 Hz, *C*F$_3$), 114.4 (*C*N), 101.2 (*C*$_5$), 62.6 (*C*H$_2$), 54.8 (3 *C*H$_2$-DABCO), 45.4 (3 *C*H$_2$-DABCO), 24.0 (*C*H$_3$), 13.6 (*C*H$_3$).

HRMS (ESI): m/z calcd for $C_{16}H_{21}N_4O_2$ $[M]^+$: 301.1659; found: 301.1662.

5-Cyano-2-methyl-6-fluoronicotinic acid ethyl ester 4f



Prepared following procedure E starting from **3f**. Expected product **4f** was obtained as a white solid in 72 % yield (purification: silica gel, *n*-heptane/EtOAc: 85/15).

^{1}H (CDCl$_3$, 400 MHz): 8.54 (d, 1H, $J_{H\text{-}F}$ = 8.4 Hz, *H*-4), 4.35 (q, 2H, *J* = 7.2 Hz, C*H*$_2$), 2.81 (s, 3H, C*H*$_3$), 1.36 (t, 3H, *J* = 7.2 Hz, C*H*$_3$).

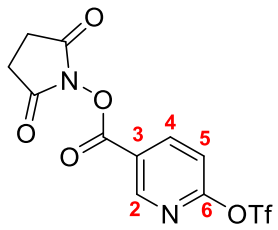
^{13}C (CDCl$_3$, 100 MHz): 166.0 (d, $J_{C\text{-}F}$ = 15.8 Hz, *C*$_2$), 163.4 (*C*=O), 162.1 (d, $J_{C\text{-}F}$ = 251.2 Hz, *C*$_6$), 147.1 (*C*$_4$), 124.2 (d, $J_{C\text{-}F}$ = 4.9 Hz, *C*$_3$), 112.0 (d, $J_{C\text{-}F}$ = 6.0 Hz, *C*N), 94.3 (d, $J_{C\text{-}F}$ = 32.4 Hz, *C*$_5$), 62.3 (*C*H$_2$), 25.1 (*C*H$_3$), 14.2 (*C*H$_3$).

HRMS (ESI): m/z calcd for $C_{10}H_{10}FN_2O_2$ $[M+H]^+$: 209.0721; found: 209.0718.

Mp: 51-52 °C.

f. *N*-hydroxysuccinimide ester series

6-(((Trifluoromethyl)sulfonyl)oxy)nicotinic acid (2,5-dioxo-1-pyrrolidinyl) ester 1g



10 % Pd/C (200 mg, 10 % w/w, 0.188 mmol, 0.050 eq) was added to a solution of **1b** (1.20 g, 3.3 mmol, 1.0 eq.) in EtOAc (20 mL) under argon. Hydrogen was bubbled through the reaction mixture and the suspension was stirred under hydrogen atmosphere until reaction completion. The suspension was then filtered through a Celite pad and the solvent was removed under reduced pressure. The residue was solubilized in 20 ml of dry CH_2Cl_2 and EDC (950 mg, 4.95 mmol, 1.5 eq.) and *N*-hydroxysuccinimide (456 mg, 3.96 mmol, 1.2 eq.) were added to the solution. The reaction mixture was stirred at room temperature for 2 hours. After reaction completion, water (10 mL) was added and the layers were separated. The product was further extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. The product was purified by column chromatography (*n*-heptane/EtOAc = 60/40 to 40/60) to yield 644 mg (53 %, 2 steps) of **1g** as a white solid.

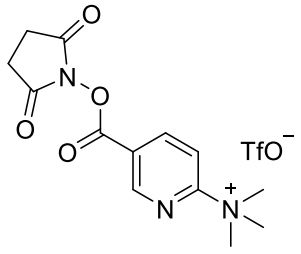
^{1}H (CDCl$_3$, 400 MHz): 9.14 (dd, 1H, $J_{2,4}$ = 2.4, $J_{2,5}$ = 0.5 Hz, *H*-2), 8.60 (dd, 1H, $J_{4,5}$ = 8.6, $J_{2,4}$ = 2.4 Hz, *H*-4), 7.35 (dd, 1H, $J_{4,5}$ = 8.6, $J_{2,5}$ = 0.5 Hz, *H*-5), 2.95 (s, 4H, 2 CH_2).

^{13}C (CDCl$_3$, 100 MHz): 168.6 (2 *C*=O), 159.4 (*C*=O or C_6), 159.2 (*C*=O or C_6), 151.3 (C_2), 143.1 (C_4), 122.4 (C_3), 118.5 (q, J = 320.8 Hz, *C*F$_3$), 115.3 (C_5), 25.7 (2 *C*H$_2$).

HRMS (ESI): m/z calcd for $C_{11}H_8F_3N_2O_7S$ $[M+H]^+$: 368.9999; found: 368.9997.

Mp: 134-135 °C.

***N,N,N*-Trimethyl-3-((2,5-dioxo-1-pyrrolidinyl)-carbonyl)pyridin-6-aminium trifluoromethane sulfonate 2g**



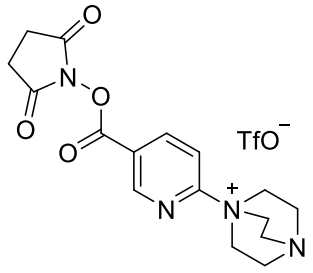
Prepared following procedure C starting from **1g**. Expected product **2g** was obtained as a white solid in 84 % yield.

^{1}H (DMSO-d_6, 400 MHz): 9.31 (dd, 1H, $J_{2,4}$ = 2.3, $J_{2,5}$ = 0.6 Hz, *H*-2), 8.91 (dd, 1H, $J_{4,5}$ = 8.8, $J_{2,4}$ = 2.3 Hz, *H*-4), 8.35 (dd, 1H, $J_{4,5}$ = 8.8, $J_{2,5}$ = 0.6 Hz, *H*-5), 3.64 (s, 9H, 3 CH_3), 2.93 (s, 4H, 2 CH_2).

^{13}C (DMSO-d_6, 100 MHz): 170.0 (2 *C*=O), 160.7 (*C*=O), 159.8 (C_6), 149.9 (C_2), 142.9 (C_4), 123.2 (C_3), 116.7 (C_5), 54.7 (3 *C*H_3), 25.6 (2 *C*H_2).
(CF_3 is not visible on the spectrum)

HRMS (ESI): m/z calcd for $C_9H_{13}N_2O_2$ $[M]^+$: 181.0972; found: 181.0969 (hydrolysis of NHS ester)

3-((2,5-Dioxo-1-pyrrolidinyl)-carbonyl)pyridin-6-(4-aza-1-azoniabicyclo[2.2.2]octane) trifluoromethanesulfonate 3g



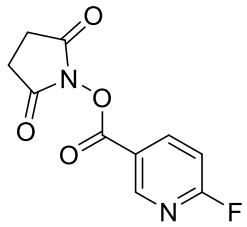
Prepared following procedure B starting from **1g**. Expected product **3g** was obtained as a white solid in 87 % yield.

^{1}H (DMSO-d_6, 400 MHz): 9.35 (d, 1H, $J_{2,4}$ = 2.4 Hz, *H*-2), 8.93 (dd, 1H, $J_{4,5}$ = 8.8, $J_{2,4}$ = 2.4 Hz, *H*-4), 8.26 (d, 1H, $J_{4,5}$ = 8.8 Hz, *H*-5), 3.93 (t, 6H, *J* = 7.3 Hz, 3 CH_2-DABCO), 3.25 (t, 6H, *J* = 7.3 Hz, 3 CH_2-DABCO), 2.94 (s, 4H, 2 CH_2).

^{13}C (DMSO-d_6, 100 MHz): 169.9 (2 *C*=O), 159.7 (*C*=O, C_6), 150.1 (C_2), 143.0 (C_4), 123.2 (C_3), 117.8 (C_5), 67.1 (*C*H_2-Ph), 53.9 (3 *C*H_2-DABCO), 45.0 (3 *C*H_2-DABCO), 25.6 (2 *C*H_2).
(CF_3 is not visible on the spectrum)

HRMS (ESI): m/z calcd for $C_{12}H_{16}N_3O_2$ $[M]^+$: 234.1237; found: 234.1237 (hydrolysis of NHS ester).

6-Fluoronicotinic acid (2,5-dioxo-1-pyrrolidinyl) ester 4g



EDC (210 mg, 1.10 mmol, 1.5 eq.) and *N*-hydroxysuccinimide (90 mg, 0.78 mmol, 1.1 eq.) were added to a solution of 6-fluoro-nicotinic acid (100 mg, 0.71 mmol) in 5 ml of dry CH_2Cl_2 and the reaction mixture was stirred at room temperature. After reaction completion, the solvent was removed under

reduced pressure and the product was purified by column chromatography (*n*-heptane/EtOAc = 50/50 to 100 % EtOAc) to obtain 115 mg (68 %) of **4g** as a white solid.

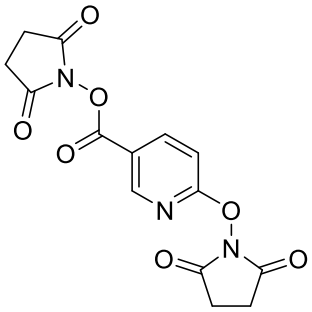
^{1}H (CDCl$_3$, 400 MHz): 9.00 (td, 1H, $J_{2,4}$ = 2.5, $J_{H\text{-}F}$ = 0.6, $J_{2,5}$ = 0.6 Hz, *H*-2), 8.49 (ddd, 1H, $J_{4,5}$ = 8.7, $J_{H\text{-}F}$ = 7.3, $J_{2,4}$ = 2.5 Hz, *H*-4), 7.10 (ddd, 1H, $J_{4,5}$ = 8.7, $J_{H\text{-}F}$ = 2.9, $J_{2,5}$ = 0.6 Hz, *H*-5), 2.92 (s, 4H, 2 CH_2).

^{13}C (CDCl$_3$, 100 MHz): 168.9 (2 *C*=O), 166.7 (d, $J_{C\text{-}F}$ = 249.4 Hz, C_6), 159.8 (*C*=O), 151.5 (d, $J_{C\text{-}F}$ = 17.3 Hz, C_2), 143.3 (d, $J_{C\text{-}F}$ = 9.9 Hz, C_4), 120.0 (C_3), 110.4 (d, $J_{C\text{-}F}$ = 37.5 Hz, C_5), 25.7 (2 *C*H$_2$).

HRMS (ESI): m/z calcd for $C_{10}H_8FN_2O_4$ $[M+H]^+$: 239.0463; found: 239.0462.

Mp: 172-173 °C.

6-((2,5-Dioxo-1-pyrrolidinyl)oxy)nicotinic acid (2,5-dioxo-1-pyrrolidinyl) ester S7



By-product obtained following procedure E starting from **3g**. Product **S7** was obtained as a white solid in 44 % yield (purification: silica gel, *n*-heptane/EtOAc: 40/60 to 100 % EtOAc).

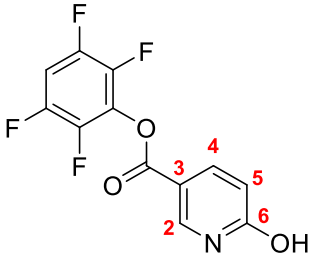
^{1}H (CDCl$_3$, 400 MHz): 8.80 (dd, 1H, $J_{2,4}$ = 2.3, $J_{2,5}$ = 0.6 Hz, *H*-2), 8.37 (dd, 1H, $J_{4,5}$ = 8.8, $J_{2,4}$ = 2.3 Hz, *H*-4), 7.16 (dd, 1H, $J_{4,5}$ = 8.8, $J_{2,5}$ = 0.6 Hz, *H*-5), 2.89-2.80 (m, 8H, 4 CH_2).

^{13}C (CDCl$_3$, 100 MHz): 169.5 (2 *C*=O), 168.8 (2 *C*=O), 164.2 (C_6), 160.0 (*C*=O), 150.7 (C_2), 141.9 (C_4), 119.2 (C_3), 109.4 (C_5), 25.7 (2 *C*H$_2$), 25.6 (2 *C*H$_2$).

LCMS (ESI): m/z calcd for $C_{14}H_{12}N_3O_7$ $[M+H]^+$: 334.07; found: 334.09.

g. Tetrafluorophenol ester series

6-Hydroxynicotinic acid 2,3,5,6-tetrafluorophenyl ester S8



At 0 °C, EDC (230 mg, 1.20 mmol, 1.2 eq.) and DMAP (12 mg, 0.10 mmol, 0.1 eq.) were added to a solution of 6-hydroxynicotinic acid (139 mg, 1.00 mmol) and tetrafluorophenol (200 mg, 1.20 mmol,

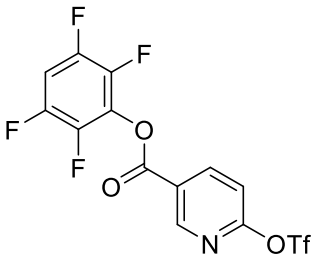
1.2 eq.) in 10 ml of dry CH_2Cl_2. The reaction mixture was stirred at room temperature for 16 h. After reaction completion, the reaction mixture was washed with H_2O (5 mL), saturated aqueous $NaHCO_3$ solution (5 mL) and brine (5 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. The product was purified by column chromatography (*n*-heptane/EtOAc = 50/50 to 20/80) to yield 230 mg (80%) of **S8** as a white solid.

^{1}H (DMSO-d_6, 400 MHz): 12.55 (br s, 1H, O*H*), 8.42 (d, 1H, $J_{2,4}$ = 2.7 Hz, *H*-2), 7.96 (tt, 1H, *J* = 10.8, *J* = 7.5 Hz, *H*-TFP), 7.90 (dd, 1H, $J_{4,5}$ = 9.7, $J_{2,4}$ = 2.7 Hz, *H*-4), 6.46 (d, 1H, $J_{4,5}$ = 9.7 Hz, *H*-5).

^{13}C (DMSO-d_6, 100 MHz): 162.2, 160.3 (*C*=O, C_6), 145.5 (dtd, *J* = 245.2, *J* = 12.4, *J* = 4.1 Hz, 2 F-*C*-TFP), 143.8 (C_2), 140.2 (ddd, *J* = 248.1, *J* = 14.3, *J* = 3.8 Hz, 2 F-*C*-TFP), 138.9 (C_4), 128.6 (m, *C*-O-TFP), 120.1 (C_5), 104.5 (t, *J* = 23.4 Hz, H*C*-TFP), 104.4 (C_3).

HRMS (ESI): m/z calcd for $C_{12}H_6F_4NO_3$ $[M+H]^+$: 288.0278; found: 288.0276.

6-(((Trifluoromethyl)sulfonyl)oxy)nicotinic acid 2,3,5,6-tetrafluorophenyl ester 1h



Prepared following procedure A starting from **S8**. Expected product **1h** was obtained as a white solid in 71 % yield (purification: silica gel, *n*-heptane/EtOAc: 70/30).

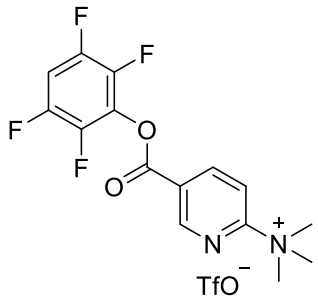
^{1}H ($CDCl_3$, 400 MHz): 9.14 (dd, 1H, $J_{2,4}$ = 2.3, $J_{2,5}$ = 0.5 Hz, *H*-2), 8.59 (dd, 1H, $J_{4,5}$ = 8.5, $J_{2,4}$ = 2.3 Hz, *H*-4), 7.30 (d, 1H, $J_{4,5}$ = 8.5, $J_{2,5}$ = 0.5 Hz, *H*-5), 7.04 (tt, 1H, *J* = 9.9, *J* = 7.1 Hz, *H*-TFP).

^{13}C ($CDCl_3$, 100 MHz): 159.9 (*C*=O), 159.1 (C_6), 151.5 (C_2), 146.1 (dtd, *J* = 249.5, *J* = 11.2, *J* = 5.0 Hz, 2 F-*C*-TFP), 143.3 (C_4), 140.6 (ddd, *J* = 253.1, *J* = 15.6, *J* = 4.7 Hz, 2 F-*C*-TFP), 124.2 (C_3), 118.5 (q, *J* = 322.4 Hz, *C*F_3), 115.3 (C_5), 104.1 (t, *J* = 22.8 Hz, H*C*-TFP).
(C-O from TFP is not visible)

HRMS (ESI): m/z calcd for $C_{13}H_5F_7NO_5S$ $[M+H]^+$: 419.9771; found: 419.9771.

Mp: 70-71 °C.

***N,N,N*-Trimethyl-3-((2,3,5,6-tetrafluorophenoxy)-carbonyl)pyridin-6-aminium trifluoromethane sulfonate 2h** [3]



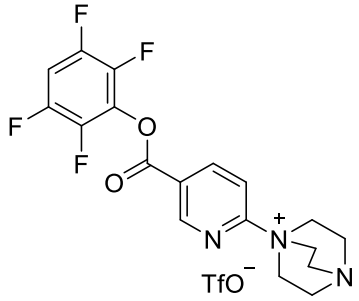
Prepared following procedure C starting from **1h**. Expected product **2h** was obtained as a white solid in 93 % yield.

^{1}H (DMF-d_7, 400 MHz): 9.49 (dd, 1H, $J_{2,4}$ = 2.4, $J_{2,5}$ = 0.6 Hz, *H*-2), 9.09 (dd, 1H, $J_{4,5}$ = 8.7, $J_{2,4}$ = 2.4 Hz, *H*-4), 8.63 (dd, 1H, $J_{4,5}$ = 8.7, $J_{2,5}$ = 0.6 Hz, *H*-5), 8.08 (tt, 1H, *J* = 11.1, *J* = 7.4 Hz, *H*-TFP), 3.96 (s, 9H, 3 CH_3).

^{13}C (DMF-d_7, 100 MHz): 161.7 (*C*=O), 160.9 (C_6), 151.3 (C_2), 146.9 (m, 2 F-*C*-TFP), 143.9 (C_4), 141.2 (m, 2 F-*C*-TFP), 126.0 (C_3), 117.3 (C_5), 105.9 (t, *J* = 24.3 Hz, H*C*-TFP), 55.6 (3 *C*H_3).
(C-O from TFP and CF_3 are not visible)

LC-MS (ESI): m/z calcd for $C_{15}H_{13}F_4N_2O_2$ $[M]^+$: 329.1; found: 329.1.

3-((2,3,5,6-Tetrafluorophenoxy)-carbonyl)pyridin-6-(4-aza-1-azoniabicyclo[2.2.2]octane) trifluoromethanesulfonate 3h



Prepared following procedure B starting from **1h**. Expected product **3h** was obtained as a white solid in 87 % yield.

^{1}H (DMSO-d_6, 400 MHz): 9.10 (dd, 1H, $J_{2,4}$ = 2.3, $J_{2,5}$ = 0.5 Hz, *H*-2), 8.66 (dd, 1H, $J_{4,5}$ = 8.7, $J_{2,4}$ = 2.3 Hz, *H*-4), 8.11 (dd, 1H, $J_{4,5}$ = 8.7, $J_{2,5}$ = 0.5 Hz, *H*-5), 7.20 (tt, 1H, *J* = 11.0, *J* = 7.2 Hz, *H*-TFP), 3.90 (dd, 6H, *J* = 8.4, *J* = 6.4 Hz, 3 CH_2-DABCO), 3.23 (dd, 6H, *J* = 8.4, *J* = 6.4 Hz, 3 CH_2-DABCO).

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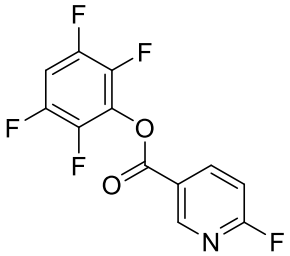
[3] D. E. Olberg, J. M. Arukwe, D. Grace, O. K. Hjelstuen, M. Solbakken, G. M. Kindberg and A. Cuthbertson, *J. Med. Chem*. **2010**, *53*, 1732

^{13}C (DMSO-d_6, 100 MHz): 164.9 (*C*=O), 158.1 (C_6), 149.5 (C_2), 141.9 (C_4), 129.4 (C_3), 116.7 (C_5), 95.1 (t, *J* = 23.9 Hz, H*C*-TFP), 53.8 (3 *C*H_2-DABCO), 45.0 (3 *C*H_2-DABCO*).*
(C-Ar from TFP and CF_3 are not visible)

HRMS (ESI): m/z calcd for $C_{18}H_{16}F_4N_3O_2$ $[M]^+$: 382.1173; found: 382.1173.

6-Fluoronicotinic acid 2,3,5,6-tetrafluorophenyl ester 4h [3]



Tetrafluorophenol (130 mg, 0.78 mmol, 1.1 eq.) and DCC (161 mg, 0.78 mmol, 1.1 eq.) were added to a solution of 6-fluoronicotinic acid (100 mg, 0.71 mmol, 1 eq.) in dioxane (5 mL) and the reaction mixture was stirred at room temperature until completion. DCCU was then filtered off and the solvent was removed *in vacuo*. The product was purified by column chromatography (*n*-heptane/EtOAc = 90/10 to 50/50) to yield 160 mg (78 %) of **4h** as a white solid.

^{1}H ($CDCl_3$, 400 MHz): 9.09 (d, 1H, $J_{2,4}$ = 2.5 Hz, *H*-2), 8.57 (ddd, 1H, $J_{4,5}$ = 8.6, $J_{H\text{-}F}$ = 8.0, $J_{2,4}$ = 2.5 Hz, *H*-4), 7.13 (dd, 1H, $J_{4,5}$ = 8.6, $J_{H\text{-}F}$ = 3.0 Hz, *H*-5), 7.09 (tt, 1H, *J* = 9.7, *J* = 7.0 Hz, *H*-TFP).

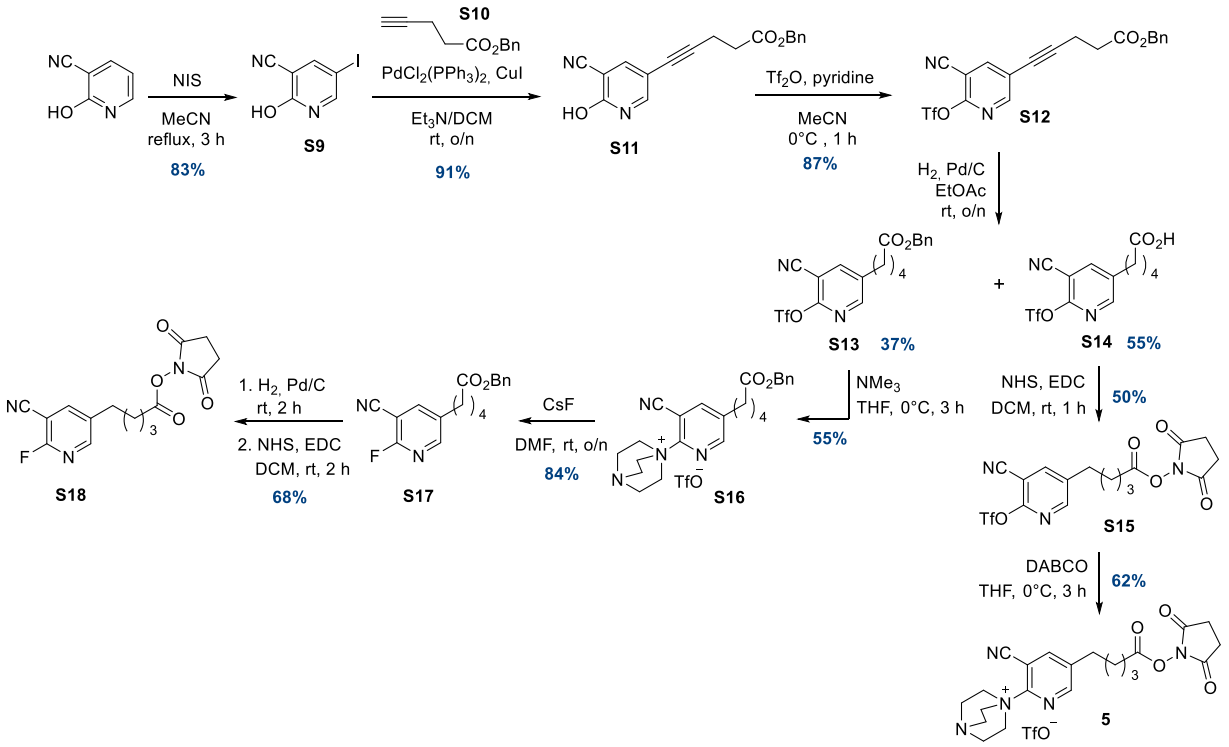
^{13}C ($CDCl_3$, 100 MHz): 166.6 (d, $J_{C\text{-}F}$ = 250.6 Hz, C_6), 160.3 (*C*=O), 151.6 (d, $J_{C\text{-}F}$ = 16.9 Hz, C_2), 146.0 (dtd, $J_{C\text{-}F}$ = 249.4, $J_{C\text{-}F}$ = 11.7, $J_{C\text{-}F}$ = 5.0 Hz, 2 F-*C*-TFP), 143.4 (d, $J_{C\text{-}F}$ = 9.7 Hz, C_4), 140.6 (ddd, $J_{C\text{-}F}$ = 252.1, $J_{C\text{-}F}$ = 15.4, $J_{C\text{-}F}$ = 4.5 Hz, 2 F-*C*-TFP), 129.1 (m, *C*-O-TFP), 121.8 (d, $J_{C\text{-}F}$ = 4.6 Hz, C_3), 110.2 (d, $J_{C\text{-}F}$ = 37.5 Hz, C_5), 103.8 (t, $J_{C\text{-}F}$ = 22.8 Hz, H*C*-TFP).

LC-MS (ESI): m/z calcd for $C_{12}H_5F_5NO_2$ $[M+H]^+$: 290.0; found: 290.0.

Mp: 68-69 °C.

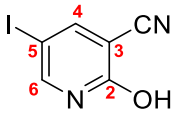
3. Pyridine tag for direct labelling of peptides

a. Synthesis of pyridine tag



Scheme S1. Preparation of pyridine tags **5** and **S18**

3-Cyano-2-hydroxy-5-iodopyridine S9 [4]



N-Iodosuccinimide (1.35 g, 6.0 mmol, 1.2 eq.) was added to a solution of 3-cyano-2-hydroxypyridine (600 mg, 5.0 mmol) in 10 ml of dry MeCN. The reaction mixture was then refluxed for 3 hours. A brown precipitate was formed during the reaction. The reaction mixture was cooled to room temperature and the precipitate was filtered and washed with Et_2O. The brown solid was dried under *vacuum* to give 1.02 g (83 %) of **S9**.

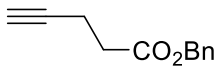
^{1}H (DMSO-d$_6$, 400 MHz): 12.79 (br s, 1H, O*H*), 8.36 (d, 1H, $J_{4,6}$ = 2.6 Hz, *H*-6), 8.04 (d, 1H, $J_{4,6}$ = 2.6 Hz, *H*-4).

^{13}C (DMSO-d$_6$, 100 MHz): 158.9 (C_2), 155.5 (C_6), 147.1 (C_4), 115.3 (*C*N), 105.5 (C_3), 63.6 (C_5).

LC-MS (ESI): m/z calcd for $C_6H_4IN_2O$ $[M+H]^+$: 246.9; found: 246.9.

[4] H. Sheng *et al. ChemPhysChem* **2018**, *19*, 2839

4-Pentynoic acid benzyl ester S10 [5]



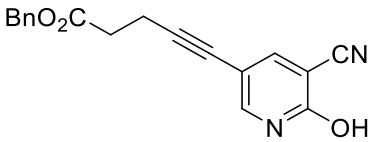
To a suspension of potassium carbonate (1.65 g, 12.0 mmol, 1.2 eq.) in DMF (5 mL) was added 4-pentynoic acid (1.18 g, 12.0 mmol, 1.2 eq.) in DMF (2.5 mL) at 0 °C and the reaction mixture was stirred for 10 minutes. Benzyl bromide (1.19 mL, 10.0 mmol, 1.0 eq.) was added and the mixture was warmed to 25 °C and stirred for 2 hours. Upon completion, water (5 mL) was added at 0 °C and the product was extracted with EtOAc·(3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. The product was purified by column chromatography (*n*-heptane/EtOAc = 90/10) to obtain 1.80 g (96%) of **S10** as a colorless oil.

^{1}H (CDCl$_3$, 400 MHz): 7.40-7.33 (m, 5H, 5 *H*-Ar), 5.17 (s, 2H, C*H*$_2$-Ph), 2.65-2.61 (m, 2H, C*H*$_2$), 2.65-2.61 (m, 2H, C*H*$_2$), 2.01 (t, 1H, *J* = 2.6 Hz, *H*C≡C-).

^{13}C (CDCl$_3$, 100 MHz): 171.6 (*C*=O), 135.8 (*C*-Ar), 128.6 (2 *C*-Ar), 128.3 (*C*-Ar), 128.3 (2 *C*-Ar), 82.5 (HC≡*C*-), 69.2 (H*C*≡C-), 66.5 (*C*H$_2$-Ph), 33.4 (*C*H$_2$), 14.4 (*C*H$_2$).

LC-MS (ESI): m/z calcd for $C_{12}H_{13}O_2$ $[M+H]^+$: 189.1; found: 189.1

5-(3-Cyano-2-hydroxy)pyridine-5-yl)pent-4-ynoic acid benzyl ester S11



To a suspension of **S9** (0.98 g, 4.00 mmol, 1.0 eq.), **S10** (1.13 g, 6.00 mmol, 1.5 eq.), CuI (77 mg, 0.40 mmol, 0.1 eq.) and $PdCl_2(PPh_3)_2$ (140 mg, 0.20 mmol, 0.05 eq.) in dry CH_2Cl_2 (40 mL) was added Et_3N (4.0 mL). The reaction mixture was stirred at room temperature until completion. 1N HCl (15 mL) was added and the layers were separated. The product was further extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. The product was purified by column chromatography (*n*-heptane/EtOAc = 50/50 to 100 % EtOAc) to obtain 1.11 g (91%) of **S11** as a beige solid.

^{1}H (CDCl$_3$, 400 MHz): 12.86 (s, 1H, O*H*), 8.06 (d, 1H, $J_{2,4}$ = 2.6 Hz, *H*-6), 7.89 (d, 1H, $J_{2,4}$ = 2.6 Hz, *H*-4), 7.40-7.30 (m, 5H, 5 *H*-Ar), 5.14 (s, 2H, C*H*$_2$-Ph), 2.65-2.64 (m, 4H, 2 *CH*$_2$).

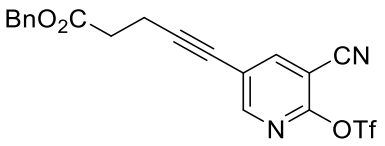
^{13}C (DMSO-d$_6$, 100 MHz): 171.2 (*C*=O), 158.7 (C_2), 150.7 (C_6), 144.7 (C_4), 136.1 (*C*-Ar), 128.4 (2 *C*-Ar), 128.0 (*C*-Ar), 127.9 (2 *C*-Ar), 115.5 (*C*N), 103.7 (C_3 or C_5), 101.1 (C_3 or C_5), 89.4 (-*C*≡C-Py), 75.1 (-C≡*C*-Py), 65.6 (*C*H$_2$-Ph), 32.7 (*C*H$_2$), 14.7 (*C*H$_2$).

[5] P. Nimnual *et al. Asian J. Org. Chem.* **2018**, *7*, 932

HRMS (ESI): m/z calcd for $C_{18}H_{15}N_2O_3$ $[M+H]^+$: 307.1077; found: 307.1076.

Mp: 149-150 °C.

5-(3-Cyano-2-((trifluoromethyl)sulfonyl)oxy)pyridine-5-yl)pent-4-ynoic acid benzyl ester S12



Pyridine (232 µL, 2.88 mmol, 1.15 eq.) and Tf_2O (462 µL, 2.75 mmol, 1.1 eq.) were added to a cooled solution of **S11** (765 mg, 2.50 mmol, 1.0 eq.) in 15 mL of dry MeCN. The resulting solution was stirred at 0 °C for 30 minutes. After completion, water (10 mL) was added to the reaction mixture and the product was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (*n*-heptane/EtOAc = 85/15 to 50/50) to obtain 0.95 g (87 %) of **S12** as a white solid.

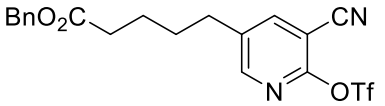
^{1}H (CDCl$_3$, 400 MHz): 8.43 (d, 1H, $J_{4,6}$ = 2.3 Hz, *H*-6), 7.93 (d, 1H, $J_{4,6}$ = 2.3 Hz, *H*-4), 7.39-7.33 (m, 5H, 5 *H*-Ar), 5.18 (s, 2H, CH_2-Ph), 2.80 (td, 2H, *J* = 7.1, *J* = 1.1 Hz, CH_2), 2.69 (td, 2H, *J* = 7.1, *J* = 1.1 Hz, CH_2).

^{13}C (CDCl$_3$, 100 MHz): 171.2 (*C*=O), 154.0 (C_6), 153.3 (C_2), 146.0 (C_4), 135.6 (*C*-Ar), 128.7 (2 *C*-Ar), 128.5 (*C*-Ar), 128.5 (2 *C*-Ar), 121.8 (C_5), 118.4 (q, *J* = 320.0 Hz, *C*F_3), 111.5 (*C*N), 101.7 (C_3), 96.6 (-*C*≡C-Py), 74.6 (-C≡*C*-Py), 66.8 (*C*H_2-Ph), 32.9 (*C*H_2), 15.5 (*C*H_2).

HRMS (ESI): m/z calcd for $C_{19}H_{14}F_3N_2O_5S$ $[M+H]^+$: 439.0570; found: 439.0570.

Mp: 78-79 °C.

5-(3-Cyano-2-((trifluoromethyl)sulfonyl)oxy)pyridine-5-yl)pentanoic acid benzyl ester S13



10 % Pd/C (180 mg, 20 % w/w, 0.340 mmol, 0.17 eq) was added to a solution of **S12** (876 mg, 2.00 mmol, 1.0 eq.) in EtOAc (10 mL) under argon. Hydrogen was bubbled through the reaction mixture and the solution was stirred under hydrogen atmosphere until disappearance of the starting material. The solution was filtered through a celite pad and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (*n*-heptane/EtOAc 80/20 to EtOAc/MeOH 90/10) to obtain 330 mg (37 %) of **S13** as a white solid and 390 mg (55 %) of **S14** as a white gum.

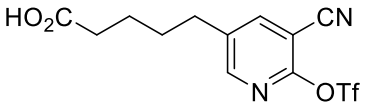
^{1}H (CDCl$_3$, 400 MHz): 8.36 (d, 1H, $J_{4,6}$ = 2.4 Hz, *H*-6), 7.90 (d, 1H, $J_{4,6}$ = 2.4 Hz, *H*-4), 7.41-7.31 (m, 5H, 5 *H*-Ar), 5.13 (s, 2H, CH_2-Ph), 2.71 (t, 2H, *J* = 7.5 Hz, CH_2), 2.42 (t, 2H, *J* = 6.9 Hz, CH_2), 1.76-1.64 (m, 4H, 2 CH_2).

^{13}C ($CDCl_3$, 100 MHz): 172.9 (*C*=O), 153.6 (C_2), 151.7 (C_6), 143.6 (C_4), 138.7 (C_5), 135.9 (*C*-Ar), 128.6 (2 *C*-Ar), 128.4 (3 *C*-Ar), 118.4 (q, *J* = 320.0 Hz, *C*F_3), 112.2 (*C*N), 101.6 (C_3), 66.4 (*C*H_2-Ph), 33.7 (*C*H_2), 31.6 (*C*H_2), 29.9 (*C*H_2), 24.3 (*C*H_2).

HRMS (ESI): m/z calcd for $C_{19}H_{18}F_3N_2O_5S$ $[M+H]^+$: 443.0883; found: 443.0881.

Mp: 69-70 °C.

5-(3-Cyano-2-((trifluoromethyl)sulfonyl)oxy)pyridine-5-yl)pentanoic acid S14

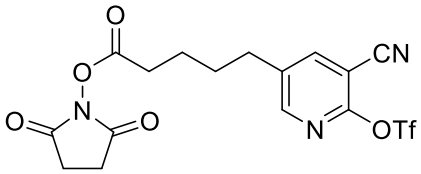


^{1}H (MeOH-d_4, 400 MHz): 8.51 (d, 1H, $J_{4,6}$ = 2.4 Hz, *H*-6), 8.35 (d, 1H, $J_{4,6}$ = 2.4 Hz, *H*-4), 2.79 (t, 2H, *J* = 7.4 Hz, C*H*$_2$), 2.36 (t, 2H, *J* = 7.0 Hz, C*H*$_2$), 1.76-1.62 (m, 4H, 2 C*H*$_2$).

^{13}C (MeOH-d_4, 100 MHz): 177.4 (*C*=O), 154.7 (C_2), 153.2 (C_6), 145.9 (C_4), 141.4 (C_5), 113.6 (*C*N), 103.0 (C_3), 34.5 (*C*H_2), 32.3 (*C*H_2), 31.2 (*C*H_2), 25.4 (*C*H_2).
(CF_3 is not visible on the spectrum)

HRMS (ESI): m/z calcd for $C_{12}H_{12}F_3N_2O_5S$ $[M+H]^+$: 353.0414; found: 353.0416.

5-(3-Cyano-2-((trifluoromethyl)sulfonyl)oxy)pyridine-5-yl)pentanoic acid (2,5-dioxo-1-pyrrolidinyl) ester S15



EDC (287 mg, 1.50 mmol, 1.5 eq.) and *N*-hydroxysuccinimide (127 mg, 1.10 mmol, 1.1 eq.) were added to a solution of **S14** (352 mg, 1.0 mmol) in 10 ml of dry CH_2Cl_2. The reaction mixture was stirred at room temperature for 1 hour. After completion, water (5 mL) was added and the layers were separated. The product was further extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. The product was purified by column chromatography (*n*-heptane/EtOAc = 50/50) to obtain 225 mg (50 %) of **S15** as a white solid.

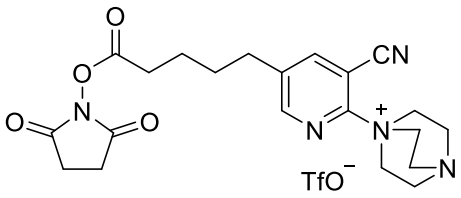
^{1}H ($CDCl_3$, 400 MHz): 8.41 (d, 1H, $J_{4,6}$ = 2.4 Hz, *H-6*), 8.03 (d, 1H, $J_{4,6}$ = 2.4 Hz, *H-4*), 2.85 (s, 4H, 2 C*H*$_2$), 2.77 (t, 2H, *J* = 7.5 Hz, C*H*$_2$), 2.68 (t, 2H, *J* = 6.9 Hz, C*H*$_2$), 1.87-1.77 (m, 4H, 2 C*H*$_2$).

^{13}C ($CDCl_3$, 100 MHz): 169.1 (2 *C*=O), 168.1 (*C*=O), 153.7 (C_2), 151.7 (C_6), 143.8 (C_4), 138.3 (C_5), 118.4 (q, *J* = 322.7 Hz, *C*F_3), 112.2 (*C*N), 101.6 (C_3), 31.3 (*C*H_2), 30.6 (*C*H_2), 29.2 (*C*H_2), 25.6 (2 *C*H_2), 24.0 (*C*H_2).

HRMS (ESI): m/z calcd for $C_{16}H_{15}F_3N_3O_7S$ $[M+H]^+$: 450.0577; found: 450.0577.

Mp: 123-124 °C.

Labelling pyridine tag 5



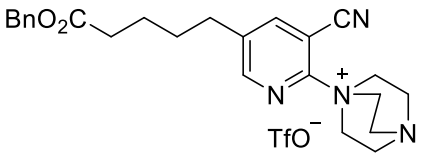
Prepared following procedure B starting from **S15**. Expected product **5** was obtained as a colorless oil in 62 % yield.

^{1}H (DMSO-d_6, 400 MHz): 8.85 (d, 1H, $J_{4,6}$ = 2.3 Hz, *H-6*), 8.71 (d, 1H, $J_{4,6}$ = 2.3 Hz, *H-4*), 4.06 (t, 6H, *J* = 7.3 Hz, 3 CH_2-DABCO), 3.27 (t, 6H, *J* = 7.3 Hz, 3 CH_2-DABCO), 2.84-2.80 (m, 6H, 3 CH_2), 2.75 (t, 2H, *J* = 7.0 Hz, CH_2), 1.79-1.71 (m, 2H, CH_2), 1.68-1.61 (m, 2H, CH_2).

^{13}C (DMSO-d_6, 100 MHz): 170.3 (2 *C*=O), 168.9 (*C*=O), 151.8 (C_2), 151.7 (C_6), 146.8 (C_4), 140.6 (C_5), 114.9 (*C*N), 102.5 (C_3), 54.2 (3 *C*H_2-DABCO), 44.9 (3 *C*H_2-DABCO), 29.9 (*C*H_2), 29.8 (*C*H_2), 28.6 (*C*H_2), 25.4 (2 *C*H_2), 23.4 (*C*H_2).
(CF_3 is not visible on the spectrum)

HRMS (ESI): m/z calcd for $C_{21}H_{26}N_5O_4$ $[M]^+$: 412.1979; found: 412.1978.

Compound S16



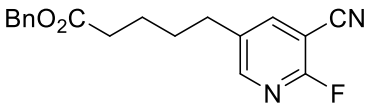
Prepared following procedure B starting from **S13**. Expected product **S16** was obtained as a colorless oil in 55 % yield.

^{1}H (DMSO-d_6, 400 MHz): 8.83 (d, 1H, $J_{4,6}$ = 2.2 Hz, *H-6*), 8.70 (d, 1H, $J_{4,6}$ = 2.2 Hz, *H-4*), 7.43-7.29 (m, 5H, 5 *H*-Ar), 5.09 (s, 2H, CH_2-Ph), 4.06 (t, 6H, *J* = 7.3 Hz, 3 CH_2-DABCO), 3.27 (t, 6H, *J* = 7.3 Hz, 3 CH_2-DABCO), 2.78 (t, 2H, *J* = 7.4 Hz, CH_2), 2.43 (t, 2H, *J* = 7.3 Hz, CH_2), 1.73-1.52 (m, 4H, 2 CH_2).

^{13}C (DMSO-d_6, 100 MHz): 172.6 (*C*=O), 151.7 (C_6, C_2), 146.8 (C_4), 140.8 (C_5), 136.2 (*C*-Ar), 128.4 (2 *C*-Ar), 128.0 (3 *C*-Ar), 114.9 (*C*N), 102.5 (C_3), 65.4 (*C*H_2-Ph), 54.2 (3 *C*H_2-DABCO), 44.9 (3 *C*H_2-DABCO), 33.0 (*C*H_2), 30.2 (*C*H_2), 29.1 (*C*H_2), 23.7 (*C*H_2).
(CF_3 is not visible on the spectrum)

HRMS (ESI): m/z calcd for $C_{24}H_{29}N_4O_2$ $[M]^+$: 405.2285; found: 405.2281.

5-(3-Cyano-2-fluoropyridine-5-yl)pentanoic acid benzyl ester S17



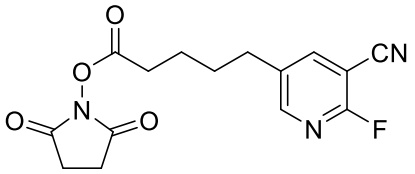
Prepared following procedure D starting from **S16**. Expected product **S17** was obtained as a colorless oil in 84 % yield (purification: silica gel, *n*-heptane/EtOAc: 90/10 to 70/30).

^{1}H (CDCl$_3$, 400 MHz): 8.15 (dd, 1H, $J_{4,6}$ = 2.4, $J_{6,F}$ = 0.7 Hz, *H*-6), 7.75 (dd, 1H, $J_{4,F}$ = 7.9, $J_{4,6}$ = 2.4 Hz, *H*-4), 7.33-7.24 (m, 5H, 5 *H*-Ar), 5.05 (s, 2H, CH_2-Ph), 2.59 (t, 2H, *J* = 7.7 Hz, CH_2), 2.34 (t, 2H, *J* = 6.9 Hz, CH_2), 1.67-1.53 (m, 4H, 2 CH_2).

^{13}C (CDCl$_3$, 100 MHz): 172.9 (*C*=O), 161.3 (d, $J_{C\text{-}F}$ = 245.4 Hz, C_2), 151.5 (d, $J_{C\text{-}F}$ = 14.1 Hz, C_6), 143.8 (C_4), 135.9 (*C*-Ar), 135.8 (d, $J_{C\text{-}F}$ = 3.5 Hz, C_5), 128.6 (2 *C*-Ar), 128.4 (3 *C*-Ar), 112.7 (d, $J_{C\text{-}F}$ = 5.6 Hz, *C*N), 96.7 (d, $J_{C\text{-}F}$ = 31.7 Hz, C_3), 66.4 (*C*H$_2$-Ph), 33.7 (*C*H$_2$), 31.4 (*C*H$_2$), 30.2 (*C*H$_2$), 24.3 (*C*H$_2$).

HRMS (ESI): m/z calcd for $C_{18}H_{18}FN_2O_2$ $[M+H]^+$: 313.1347; found: 313.1348.

5-(3-Cyano-2-fluoropyridine-5-yl)pentanoic acid (2,5-dioxo-1-pyrrolidinyl) ester S18



10 % Pd/C (40 mg, 20 % w/w, 75 µmol, 0.12 eq) was added to a solution of **S17** (200 mg, 0.64 mmol, 1.0 eq.) in EtOAc (5 mL) under argon. Hydrogen was bubbled through the reaction mixture and the solution was stirred under hydrogen atmosphere until completion. The solution was filtered through a celite pad and the solvent was removed under reduced pressure. The residue was solubilized in 10 ml of dry CH_2Cl_2 and EDC (184 mg, 0.96 mmol, 1.5 eq.) and *N*-hydroxysuccinimide (81 mg, 0.71 mmol, 1.1 eq.) were added to the solution. The reaction mixture was stirred at room temperature for 2 hours. After completion, water (5 mL) was added and the layers were separated. The product was further extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. The product was purified by column chromatography (*n*-heptane/EtOAc = 50/50) to obtain 139 mg (68 %, 2 steps) of **S18** as a white solid.

^{1}H (CDCl$_3$, 400 MHz): 8.27 (dd, 1H, $J_{4,6}$ = 2.5, $J_{6,F}$ = 0.9 Hz, *H*-6), 7.94 (dd, 1H, $J_{4,F}$ = 8.2, $J_{4,6}$ = 2.5 Hz, *H*-4), 2.86 (s, 4H, 2 CH_2), 2.72 (t, 2H, *J* = 7.1 Hz, CH_2), 2.67 (t, 2H, *J* = 6.6 Hz, CH_2), 1.86-1.75 (m, 4H, 2 CH_2).

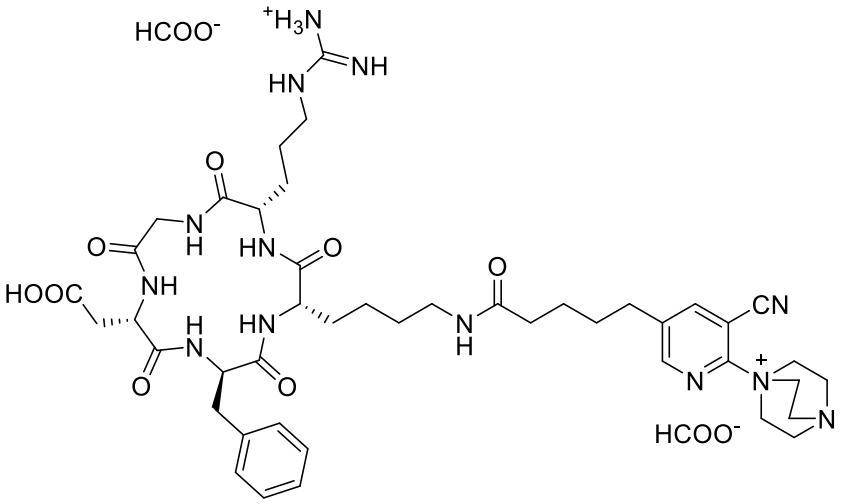
^{13}C (CDCl$_3$, 100 MHz): 169.2 (2 *C*=O), 168.2 (*C*=O), 161.4 (d, $J_{C\text{-}F}$ = 246.2 Hz, C_2), 151.6 (d, $J_{C\text{-}F}$ = 14.1 Hz, C_6), 144.0 (C_4), 135.5 (d, $J_{C\text{-}F}$ = 5.0 Hz, C_5), 112.8 (d, $J_{C\text{-}F}$ = 5.7 Hz, *C*N), 96.7 (d, $J_{C\text{-}F}$ = 31.9 Hz, C_3), 31.1 (*C*H$_2$), 30.6 (*C*H$_2$), 29.5 (*C*H$_2$), 25.6 (2 *C*H$_2$), 24.0 (*C*H$_2$).

HRMS (ESI): m/z calcd for $C_{15}H_{15}FN_3O_4$ $[M+H]^+$: 320.1041; found: 320.1042.

Mp: 96-97 °C.

b. Peptides precursors and cold references

RGDfK precursor 3i

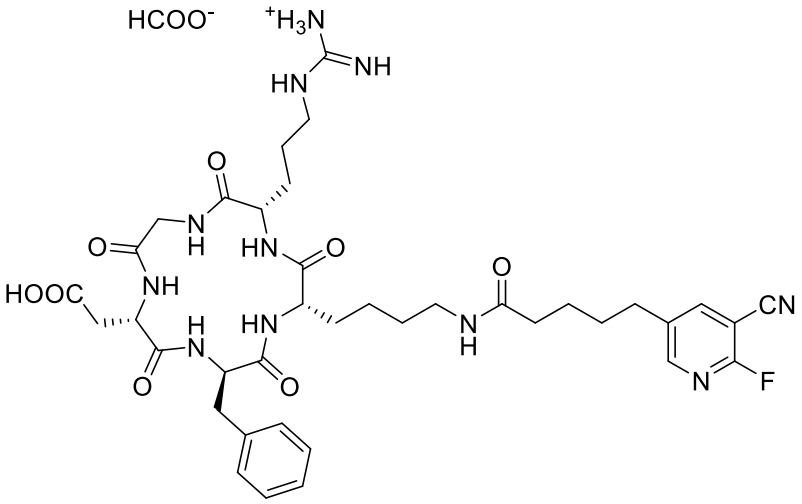


Prepared following procedure G starting from **5** and RGDfK. Expected product **3i** was obtained as a white fluffy solid in 70 % yield (purification: C-18, H_2O/MeCN/0.05% formic acid: 95/5 to 70/30).

^{1}H (D_2O, 400 MHz): 8.70 (d, 1H, $J_{4,6}$ = 2.4 Hz, *H*-6), 8.45 (d, 1H, $J_{4,6}$ = 2.4 Hz, *H*-4), 7.29-7.17 (m, 5H, *H*-Ar), 4.72 (m, 1H, *H*-α), 4.55 (dd, 1H, *J* = 10.4, *J* = 5.5 Hz, *H*-α), 4.37 (dd, 1H, *J* = 8.9, *J* = 6.0 Hz, *H*-α), 4.18 (d, 1H, *J* = 14.7 Hz, C*H*H-Ph), 4.12 (t, 6H, *J* = 7.4 Hz, 3 CH_2-DABCO), 3.77 (dd, 1H, *J* = 11.1, *J* = 4.3 Hz, *H*-α), 3.48 (d, 1H, *J* = 14.7 Hz, C*H*H-Ph), 3.41 (t, 6H, *J* = 7.4 Hz, 3 CH_2-DABCO), 3.21-3.13 (m, 2H, CH_2), 3.11-2.99 (m, 3H, CH_2, C*H*H), 2.92 (dd, 1H, *J* = 13.0, *J* = 10.5 Hz, C*H*H), 2.84 (t, 2H, *J* = 7.2 Hz, CH_2), 2.75 (dd, 1H, *J* = 15.9, *J* = 7.6 Hz, C*H*H), 2.59 (dd, 1H, *J* = 15.9, *J* = 7.0 Hz, C*H*H), 2.29 (t, 2H, *J* = 6.8 Hz, CH_2), 1.84 (m, 1H, C*H*H), 1.74-1.37 (m, 9H, 4 CH_2, C*H*H), 1.34-1.27 (m, 2H, CH_2), 0.90-0.78 (m, 2H, CH_2).

HRMS (ESI): m/z calcd for $C_{44}H_{63}N_{13}O_8$ $[M+H]^{2+}$: 450.7456; found: 450.7453.

RGDfK reference 4i

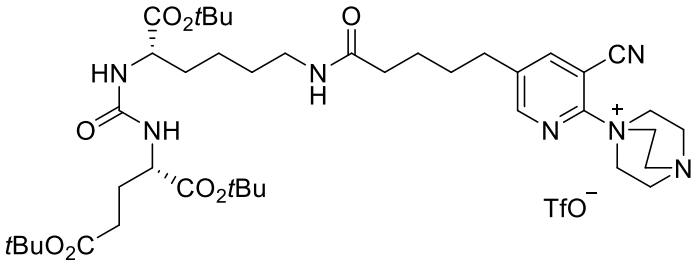


Prepared following procedure G starting from **S18** and RGDfK. Expected product **4i** was obtained as a white fluffy solid in 67 % yield (purification: C-18, H_2O/MeCN/0.05% formic acid: 95/5 to 70/30).

^{1}H (D_2O, 400 MHz): 8.29 (d, 1H, $J_{4,6}$ = 2.4 Hz, *H*-6), 8.20 (dd, 1H, $J_{4,F}$ = 8.2, $J_{4,6}$ = 2.4 Hz, *H*-4), 7.33-7.21 (m, 5H, *H*-Ar), 4.72 (m, 1H, *H*-α), 4.57 (dd, 1H, *J* = 10.6, *J* = 5.8 Hz, *H*-α), 4.37 (dd, 1H, *J* = 8.8, *J* = 5.9 Hz, *H*-α), 4.21 (d, 1H, *J* = 14.7 Hz, C*H*H-Ph), 3.81 (dd, 1H, *J* = 10.6, *J* = 4.3 Hz, *H*-α), 3.47 (d, 1H, *J* = 14.7 Hz, C*H*H-Ph), 3.23-3.13 (m, 2H, CH_2), 3.11-3.02 (m, 3H, CH_2, C*H*H), 2.94 (dd, 1H, *J* = 13.1, *J* = 10.4 Hz, C*H*H), 2.80-2.71 (m, 3H, CH_2, C*H*H), 2.61 (dd, 1H, *J* = 16.1, *J* = 7.2 Hz, C*H*H), 2.27 (t, 2H, *J* = 6.5 Hz, CH_2), 1.85 (m, 1H, C*H*H), 1.69-1.38 (m, 9H, 4 CH_2, C*H*H), 1.34-1.27 (m, 2H, CH_2), 0.92-0.80 (m, 2H, CH_2).

HRMS (ESI): m/z calcd for $C_{38}H_{51}FN_{11}O_8$ $[M+H]^+$: 808.3901; found: 808.3893.

PSMA precursor (protected) 3j



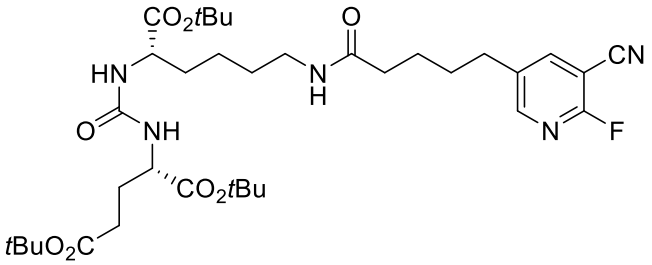
To a solution of **5** (28 mg, 0.050 mmol, 1 eq.) in dry MeCN (0.5 mL) was added a solution of protected PSMA (25 mg, 0.050 mmol, 1 eq.) in dry MeCN (0.5 mL) and the mixture was stirred at room temperature. After completion (2 hours), the solvent was removed *in vacuo* and the crude was purified by column chromatography (CH_2Cl_2/MeOH 95/5 to 85/15) to afford **3j** as a white solid (24 mg, 51 %).

^{1}H (MeOH-d_4, 400 MHz): 8.65 (d, 1H, $J_{4,6}$ = 2.2 Hz, *H*-6), 8.42 (d, 1H, $J_{4,6}$ = 2.2 Hz, *H*-4), 4.10-4.07 (m, 7H, 3 CH_2-DABCO, *H*-α), 3.98 (dd, 1H, *J* = 8.4, *J* = 5.1 Hz, *H*-α), 3.33 (t, 6H, *J* = 7.3 Hz, 3 CH_2-DABCO), 3.07 (t, 2H, *J* = 6.9 Hz, CH_2), 2.77-2.73 (m, 2H, CH_2), 2.24-2.19 (m, 2H, CH_2), 2.13 (d, 2H, *J* = 6.9 Hz, CH_2), 1.94 (m, 1H, C*H*H), 1.74-1.27 (m, 38H, 3 *t*Bu, 5 CH_2, C*H*H).

^{13}C (MeOH-d_4, 100 MHz): 175.6 (*C*=O), 173.9 (*C*=O), 173.8 (*C*=O), 173.5 (*C*=O), 159.9 (*C*$_2$), 157.8 (*C*=O), 153.1 (*C*$_6$), 148.0 (*C*$_4$), 143.2 (*C*$_5$), 115.7 (*C*N), 104.2 (*C*$_3$), 82.8 (*C*Me$_3$), 82.6 (*C*Me$_3$), 81.8 (*C*Me$_3$), 55.9 (3 *C*H_2-DABCO), 54.9 (*C*α), 54.2 (*C*α), 46.4 (3 *C*H_2-DABCO), 40.1 (*C*H_2), 36.5 (*C*H_2), 33.2 (*C*H_2), 32.5 (*C*H_2), 32.2 (*C*H_2), 30.9 (*C*H_2), 30.0 (*C*H_2), 29.1 (*C*H_2), 28.3 (9 *C*H_3), 26.2 (*C*H_2), 24.0 (*C*H_2).
(CF_3 *is not visible on the spectrum)*

HRMS (ESI): m/z calcd for $C_{41}H_{66}N_7O_8$ $[M]^+$: 784.4967; found: 784.4953.

PSMA reference (protected) 4j



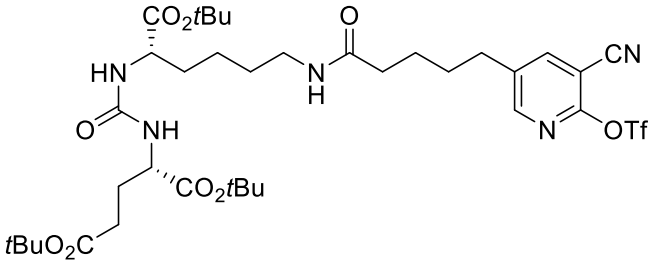
Prepared following procedure F starting from **S18** and protected PSMA. Expected product **4j** was obtained as a colorless gum in 87 % yield (purification: silica gel, *n*-heptane/EtOAc: 50/50 to 100 % EtOAc).

^{1}H (CDCl$_3$, 400 MHz): 8.25 (dd, 1H, $J_{4,6}$ = 2.2, $J_{6,F}$ = 0.8 Hz, *H*-6), 7.91 (dd, 1H, $J_{4,F}$ = 8.2, $J_{4,6}$ = 2.2 Hz, *H*-4), 6.56 (t, 1H, *J* = 5.6 Hz, N*H* amide), 5.62 (d, 1H, *J* = 8.5 Hz, N*H* urea), 5.38 (d, 1H, *J* = 8.0 Hz, N*H* urea), 4.31 (td, 1H, *J* = 8.5, *J* = 4.8 Hz, *H*-α), 4.19 (td, 1H, *J* = 8.0, *J* = 4.2 Hz, *H*-α), 3.29-3.13 (m, 4H, 2 CH_2), 2.68 (dd, 2H, *J* = 7.5, *J* = 6.6 Hz, CH_2), 2.38-2.21 (m, 4H, 2 CH_2), 2.06 (m, 1H, C*H*H), 1.83 (m, 1H, C*H*H), 1.76-1.61 (m, 6H, 3 CH_2), 1.58-1.24 (m, 29H, 3 *t*Bu, CH_2).

^{13}C (CDCl$_3$, 100 MHz): 173.3 (*C*=O), 172.8 (*C*=O), 172.3 (*C*=O), 172.2 (*C*=O), 161.3 (d, $J_{C\text{-}F}$ = 244.9 Hz, C_2), 157.3 (*C*=O), 151.6 (d, $J_{C\text{-}F}$ = 14.2 Hz, C_6), 144.0 (C_4), 136.2 (d, $J_{C\text{-}F}$ = 5.0 Hz, C_5), 112.8 (d, $J_{C\text{-}F}$ = 5.8 Hz, *C*N), 96.6 (d, $J_{C\text{-}F}$ = 31.9 Hz, C_3), 82.5 (*C*Me$_3$), 81.7 (*C*Me$_3$), 80.7 (*C*Me$_3$), 53.5 (*C*α), 53.1 (*C*α), 39.0 (*C*H$_2$), 35.8 (*C*H$_2$), 32.5 (*C*H$_2$), 31.6 (*C*H$_2$), 31.5 (*C*H$_2$), 30.5 (*C*H$_2$), 28.8 (*C*H$_2$), 28.0 (9 *C*H$_3$, *C*H$_2$), 25.0 (*C*H$_2$), 22.9 (*C*H$_2$).

HRMS (ESI): m/z calcd for $C_{35}H_{55}FN_5O_8$ $[M+H]^+$: 692.4029; found: 692.4024.

Compound 1j



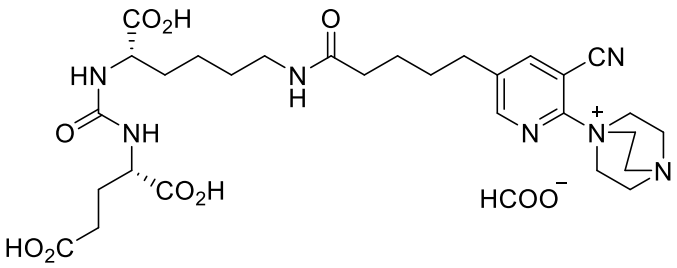
Prepared following procedure F starting from **S15** and protected PSMA. Expected product **1j** was obtained as a colorless gum in 89 % yield (purification: silica gel, EtOAc).

^{1}H (CDCl$_3$, 400 MHz): 8.40 (d, 1H, $J_{4,6}$ = 2.4 Hz, *H*-6), 8.01 (d, 1H, $J_{4,6}$ = 2.4 Hz, *H*-4), 6.58 (t, 1H, *J* = 5.6 Hz, N*H* amide), 5.60 (d, 1H, *J* = 8.2 Hz, N*H* urea), 5.36 (d, 1H, *J* = 7.6 Hz, N*H* urea), 4.31 (td, 1H, *J* = 8.5, *J* = 4.8 Hz, *H*-α), 4.19 (ddd, 1H, *J* = 8.6, *J* = 7.6, *J* = 4.0 Hz, *H*-α), 3.30-3.15 (m, 2H, CH_2), 2.74 (dd, 2H, *J* = 8.2, *J* = 6.0 Hz, CH_2), 2.39-2.23 (m, 4H, 2 CH_2), 2.07 (m, 1H, C*H*H), 1.88-1.79 (m, 2H, CH_2), 1.77-1.64 (m, 5H, 2 CH_2, C*H*H), 1.60-1.48 (m, 2H, CH_2), 1.45 (s, 9H, *t*Bu), 1.43 (s, 9H, *t*Bu), 1.42 (s, 9H, *t*Bu), 1.35-1.27 (m, 2H, CH_2).

^{13}C ($CDCl_3$, 100 MHz): 173.3 (*C*=O), 172.7 (*C*=O), 172.3 (*C*=O), 172.2 (*C*=O), 157.3 (*C*=O), 153.6 (C_2), 151.7 (C_6), 143.8 (C_4), 139.0 (C_5), 118.4 (q, *J* = 321.6 Hz, *C*F_3), 112.3 (*C*N), 101.5 (C_3), 82.5 (*C*Me_3), 81.7 (*C*Me_3), 80.7 (*C*Me_3), 53.5 (*C*α), 53.1 (*C*α), 39.0 (*C*H_2), 35.7 (*C*H_2), 32.5 (*C*H_2), 31.7 (*C*H_2), 31.5 (*C*H_2), 30.3 (*C*H_2), 28.8 (*C*H_2), 28.1 (3 *C*H_3), 28.0 (6 *C*H_3, *C*H_2), 25.0 (*C*H_2), 22.9 (*C*H_2).

HRMS (ESI): m/z calcd for $C_{36}H_{55}F_3N_5O_{11}S$ $[M+H]^+$: 822.3565; found: 822.3575.

PSMA labelling precursor S19

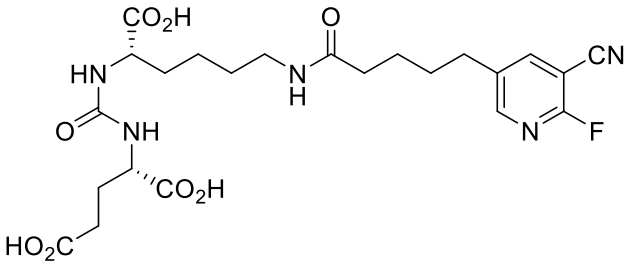


Prepared following procedure G starting from **5** and PSMA. Expected product **S19** was obtained as a white fluffy solid in 53 % yield (purification: C-18, H_2O/MeCN/0.05% formic acid: 95/5 to 80/20).

^{1}H (D_2O, 400 MHz): 8.60 (d, 1H, $J_{4,6}$ = 2.2 Hz, *H*-6), 8.35 (d, 1H, $J_{4,6}$ = 2.2 Hz, *H*-4), 4.13 (t, 6H, *J* = 7.4 Hz, 3 C*H*$_2$-DABCO), 4.03 (dd, 1H, *J* = 8.6, *J* = 5.0 Hz, *H*-α), 3.96 (dd, 1H, *J* = 8.6, *J* = 5.1 Hz, *H*-α), 3.36 (t, 6H, *J* = 7.4 Hz, 3 C*H*$_2$-DABCO), 3.15-3.03 (m, 2H, C*H*$_2$), 2.74 (t, 2H, *J* = 6.8 Hz, C*H*$_2$), 2.35 (t, 2H, *J* = 7.5 Hz, C*H*$_2$), 2.18 (t, 2H, *J* = 6.8 Hz, C*H*$_2$), 2.02 (m, 1H, C*H*H), 1.82 (m, 1H, C*H*H), 1.68 (m, 1H, C*H*H), 1.63-1.48 (m, 5H, 2 C*H*$_2$, C*H*H), 1.46-1.38 (m, 2H, C*H*$_2$), 1.33-1.21 (m, 2H, C*H*$_2$).

HRMS (ESI): m/z calcd for $C_{29}H_{42}N_7O_8$ $[M]^+$: 616.3089; found: 616.3084.

PSMA reference S20

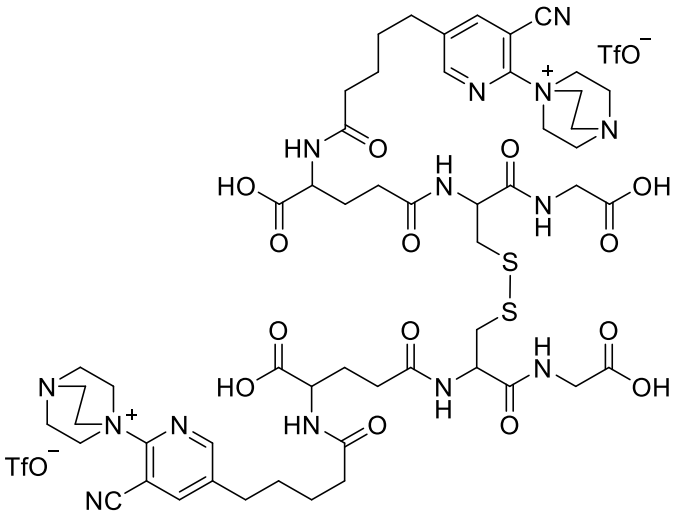


Prepared following procedure G starting from **S18** and PSMA. Expected product **S20** was obtained as a white fluffy solid in 50 % yield (purification: C-18, H_2O/MeCN/0.05% formic acid: 95/5 to 70/30).

^{1}H (DMSO-d_6, 400 MHz): 8.45 (dd, 1H, $J_{4,F}$ = 8.6, $J_{4,6}$ = 2.3 Hz, *H*-4), 8.42 (d, 1H, $J_{4,6}$ = 2.3 Hz, *H*-6), 7.77 (t, 1H, $J_{4,6}$ = 5.4 Hz, N*H*), 6.38 (br s, 1H, N*H*), 6.27 (br s, 1H, N*H*), 4.07-3.96 (m, 2H, 2 *H*-α), 3.02-2.97 (m, 2H, C*H*$_2$), 2.65 (t, 2H, *J* = 7.3 Hz, C*H*$_2$), 2.30-2.16 (m, 2H, C*H*$_2$), 2.07 (t, 2H, *J* = 7.0 Hz, C*H*$_2$), 1.83-1.69 (m, 2H, C*H*$_2$), 1.63-1.44 (m, 6H, 3 C*H*$_2$), 1.40-1.33 (m, 2H, C*H*$_2$), 1.30-1.24 (m, 2H, C*H*$_2$).

HRMS (ESI): m/z calcd for $C_{23}H_{31}FN_5O_8$ $[M+H]^+$: 524.2149; found: 524.2151.

Glutathione precursor 3k

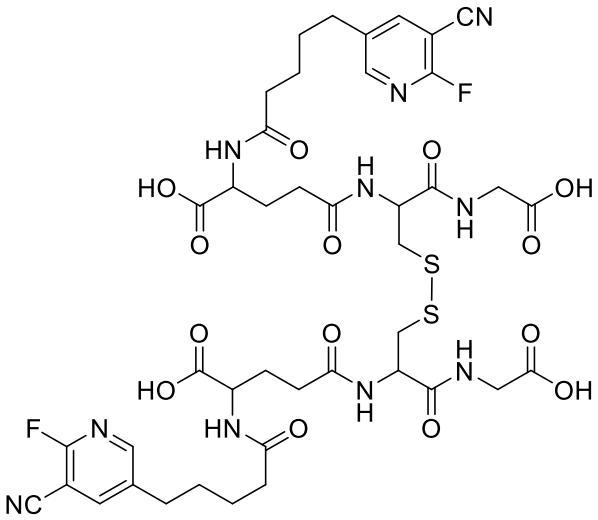


Prepared following procedure G starting from **5** and oxidized glutathione. Expected product **3k** was obtained as a white fluffy solid in 83 % yield (purification: Minitrap G-10).

^{1}H (D_2O, 400 MHz): 8.60 (d, 2H, $J_{4,6}$ = 2.2 Hz, 2 *H*-6), 8.36 (d, 2H, $J_{4,6}$ = 2.2 Hz, 2 *H*-4), 4.11 (t, 12H, *J* = 7.4 Hz, 6 CH_2-DABCO), 4.05 (dd, 2H, *J* = 8.4, *J* = 4.7 Hz, 2 *H*-α), 3.70-3.58 (m, 4H, 2 CH_2), 3.34 (t, 12H, *J* = 7.4 Hz, 6 CH_2-DABCO), 3.17 (dd, 2H, *J* = 14.3, *J* = 4.3 Hz, 2 C*H*H), 2.84 (dd, 2H, *J* = 14.3, *J* = 9.7 Hz, 2 C*H*H), 2.73 (t, 4H, *J* = 7.2 Hz, 2 CH_2), 2.30-2.19 (m, 8H, 4 CH_2), 2.01 (m, 2H, 2 C*H*H), 1.83 (m, 2H, 2 C*H*H), 1.63-1.44 (m, 8H, 4 CH_2). (two *H*-α are hidden by the solvent residual peak)

HRMS (ESI): m/z calcd for $C_{54}H_{74}N_{14}O_{14}S_2$ $[M]^{2+}$: 603.2470; found: 603.2476.

Glutathione reference (oxidized) S21



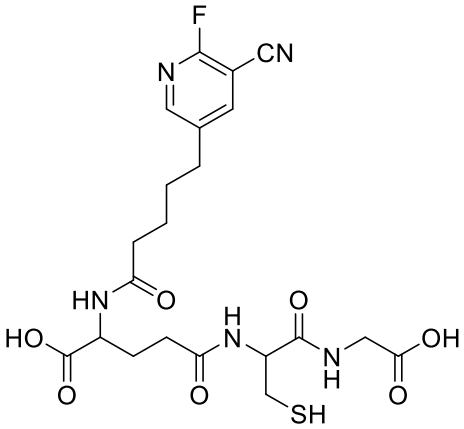
Prepared following procedure G starting from **S18** and oxidized glutathione. Expected product **S21** was obtained as a white fluffy solid in 82 % yield (purification: Minitrap G-10).

^{1}H (D_2O, 400 MHz): 8.18 (d, 2H, $J_{4,6}$ = 2.4 Hz, 2 *H*-6), 8.09 (dd, 2H, $J_{4,F}$ = 8.3, $J_{4,6}$ = 2.4 Hz, 2 *H*-4), 4.05 (dd, 2H, *J* = 8.3, *J* = 4.8 Hz, 2 *H*-α), 3.67 (d, 2H, *J* = 17.2 Hz, 2 C*H*H), 3.60 (d, 2H, *J* = 17.2 Hz, 2

C*H*H), 3.16 (dd, 2H, *J* = 14.4, *J* = 4.3 Hz, 2 C*H*H), 2.81 (dd, 2H, *J* = 14.4, *J* = 9.9 Hz, 2 C*H*H), 2.59 (t, 4H, *J* = 6.8 Hz, 2 CH_2), 2.27-2.23 (m, 4H, 2 CH_2), 2.19 (t, 4H, *J* = 6.8 Hz, 2 CH_2), 1.99 (m, 2H, 2 C*H*H), 1.81 (m, 2H, 2 C*H*H), 1.56-1.44 (m, 8H, 4 CH_2). (two *H*-α are hidden by the solvent residual peak)

HRMS (ESI): m/z calcd for $C_{42}H_{51}F_2N_{10}O_{14}S_2$ $[M+H]^+$: 1021.2990; found: 1021.2990.

Glutathione reference (reduced) 4k

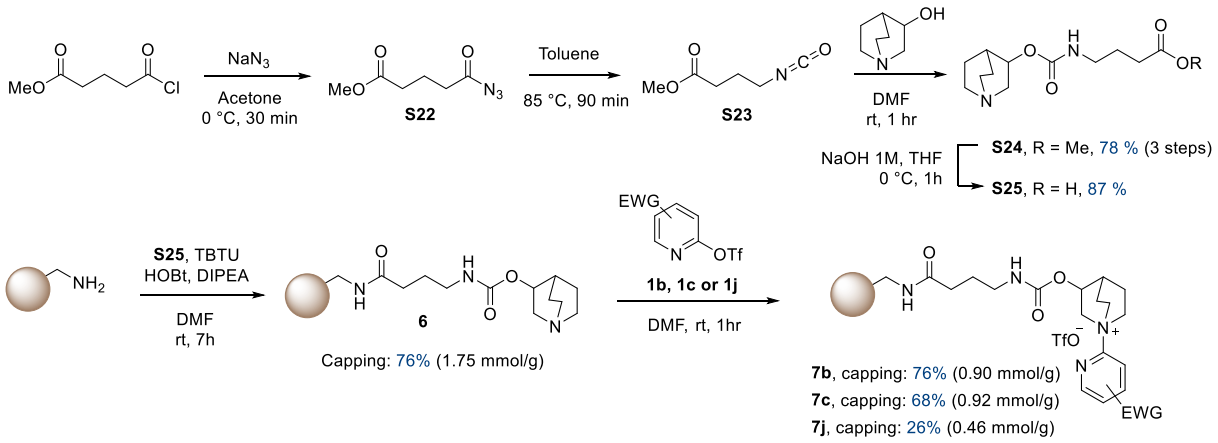


To a solution of **S21** (5.0 mg, 5.0 µmol, 1 eq.) in 500 µL H_2O/MeCN (60/40) was added TCEP (1.7 mg, 6.0 µmol, 1.2 eq.) and the mixture was stirred at room temperature for 1 hour. After completion, the solvent was removed *in vacuo* and the crude was purified by reverse phase chromatography (C-18, H_2O/MeCN/0.05% formic acid). **4k** was obtained as a white solid (3.7 mg, 74% yield).

^{1}H (D_2O, 400 MHz): 8.19 (d, 1H, $J_{4,6}$ = 2.4 Hz, *H*-6), 8.11 (dd, 1H, $J_{4,F}$ = 8.4, $J_{4,6}$ = 2.4 Hz, *H*-4), 4.44 (dd, 1H, *J* = 6.8, *J* = 5.4 Hz, *H*-α), 4.16 (m, 1H, *H*-α), 3.81 (s, 2H, CH_2), 2.85-2.74 (m, 2H, CH_2), 2.62 (t, 2H, *J* = 7.0 Hz, CH_2), 2.32 (t, 2H, *J* = 7.6 Hz, CH_2), 2.22 (t, 2H, *J* = 6.7 Hz, CH_2), 2.08 (m, 1H, C*H*H), 1.87 (m, 1H, C*H*H), 1.59-1.47 (m, 4H, 2 CH_2).

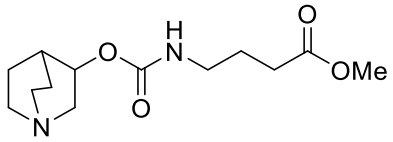
HRMS (ESI): m/z calcd for $C_{21}H_{27}FN_5O_7S$ $[M+H]^+$: 512.1610; found: 512.1614.

4. On-resin radiolabelling



Scheme S2. Preparation of precursors **7**

***N*-(Butanoic acid methyl ester)-carbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester S24**



To a stirred suspension of sodium azide (975 mg, 15.0 mmol, 1.5 equiv) in acetone (20 mL) at 0 °C was added glutaric acid monomethyl ester chloride (1.38 mL, 10.0 mmol, 1.0 equiv). The reaction mixture was stirred at 0 °C for 30 minutes. The reaction mixture was then filtered through celite and the solvent was evaporated *in vacuo* to give the corresponding azide **S22**, which was used in the next step without purification. Toluene (16 mL) was added to the crude azide and the mixture was stirred at 85 °C for 90 minutes to give the corresponding isocyanate **S23**. The reaction mixture was then added to a solution of 3-quinuclidinol (1.27 g, 10.0 mmol, 1 eq.) in DMF (10 mL). The resulting solution was stirred at room temperature for 1 hour. After completion, water (10 mL) was added and the product was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2/MeOH 90/10 + 0.1% NH_4OH) to give **S24** as a white solid (1.9 g, 78%).

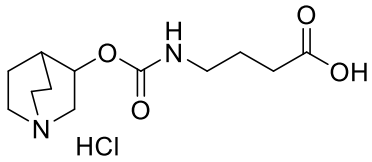
^{1}H (CDCl$_3$, 400 MHz): 4.99 (t, 1H, *J* = 5.5 Hz, N*H*), 4.68 (m, 1H, C*H*), 3.66 (s, 3H, CH_3), 3.23-3.17 (m, 3H, 3 C*H*), 2.91-2.66 (m, 5H, 5 C*H*), 2.35 (t, 2H, *J* = 7.3 Hz, CH_2), 1.99 (m, 1H, C*H*), 1.85-1.75 (m, 3H, 3 C*H*), 1.66 (m, 1H, C*H*), 1.54 (m, 1H, C*H*), 1.37 (m, 1H, C*H*).

^{13}C (CDCl$_3$, 100 MHz): 173.8 (*C*=O), 156.4 (*C*=O), 71.3 (*C*H), 55.7 (*C*H_2), 51.8 (*C*H_3), 47.5 (*C*H_2), 46.5 (*C*H_2), 40.4 (*C*H), 31.4 (*C*H_2), 25.5 (*C*H_2), 25.3 (*C*H_2), 24.6 (*C*H_2), 19.5 (*C*H_2).

HRMS (ESI): m/z calcd for $C_{13}H_{23}N_2O_4$ $[M+H]^+$: 271.1652; found: 271.1653.

Mp: 85-86 °C.

***N*-(Butanoic acid)carbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester hydrochloride S25**



To a solution of **S24** (540 mg, 2.0 mmol, 1 eq) in THF (5 ml) was added 2 M aq. NaOH (2.0 mL, 4.0 mmol, 2 eq.) and the solution was stirred until completion. The solution was acidified with 2 M aq. HCl until pH ~ 4 and the solvents were removed under reduced pressure. MeOH was then added to the crude and the insoluble NaCl salt was removed by centrifugation (wash step repeated 3 times). **S25** was obtained as a white solid (445 mg, 87 %) and used without further purification.

^{1}H (DMSO-d$_6$, 400 MHz): 7.24 (t, 1H, *J* = 5.7 Hz, N*H*), 4.62 (m, 1H, C*H*), 3.25 (m, 1H, C*H*), 2.99-2.94 (m, 2H, CH_2), 2.92-2.71 (m, 4H, 4 C*H*), 2.65 (m, 1H, C*H*), 2.18 (t, 2H, *J* = 7.2 Hz, CH_2), 1.98 (m, 1H, C*H*), 1.81 (m, 1H, C*H*), 1.68 (m, 1H, C*H*), 1.64-1.54 (m, 3H, 3 C*H*), 1.46 (m, 1H, C*H*).

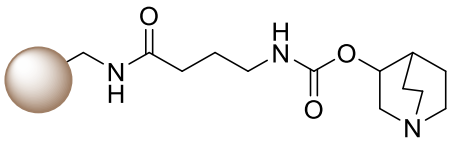
^{13}C (DMSO-d_6, 100 MHz): 174.4 (*C*=O), 155.8 (*C*=O), 68.7 (*C*H), 54.2 (CH_2), 46.1 (CH_2), 45.2 (*C*H), 39.8* (CH_2), 31.2 (CH_2), 24.9 (CH_2), 24.7 (CH_2), 22.5 (CH_2), 18.1 (CH_2).

HRMS (ESI): m/z calcd for $C_{12}H_{21}N_2O_4$ $[M+H]^+$: 257.1496; found: 257.1493.

* hidden by DMSO-d_6 peak

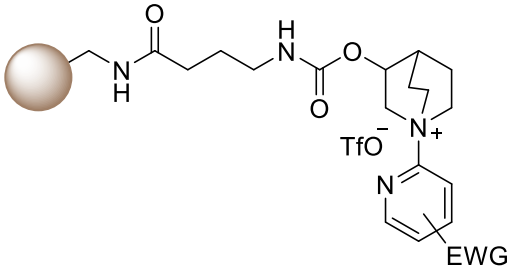
Mp: 164-165 °C.

Modified resin 6



At 0 °C, DIPEA (523 µL, 3.0 mmol, 6 eq.) and TBTU (321 mg, 1.0 mmol, 2 eq.) were added to a suspension of (aminomethyl)polystyrene resin (Sigma-Aldrich 473677, 125 mg, 0.50 mmol), **S25** (256 mg, 1.0 mmol, 2 eq.) and HOBt•H_2O (135 mg, 1.0 mmol, 2 eq.) in 4 ml of dry DMF. The mixture was stirred at room temperature for 7 hours. The resin was then filtered and washed with DMF (x 2), MeOH (x 3), CH_2Cl_2 (x3) and Et_2O (x 3) and dried under high vacuum for 2 hours.
The dried grafted resin was taken up in dry DMF (3 mL) and Ac_2O (240 µL, 2.5 mmol, 5 eq) and DIPEA (435 µL, 2.5 mmol, 5 eq.) were added. The suspension was stirred at room temperature for 2 hours. Resin was then filtered and washed with DMF (x 2), MeOH (x 3), CH_2Cl_2 (x3) and Et_2O (x 3) and dried under high vacuum for 2 hours. 215 mg of grafted resin **6** were obtained (76 % capping, final loading: 1.75 mmol/g).

Precursors 7



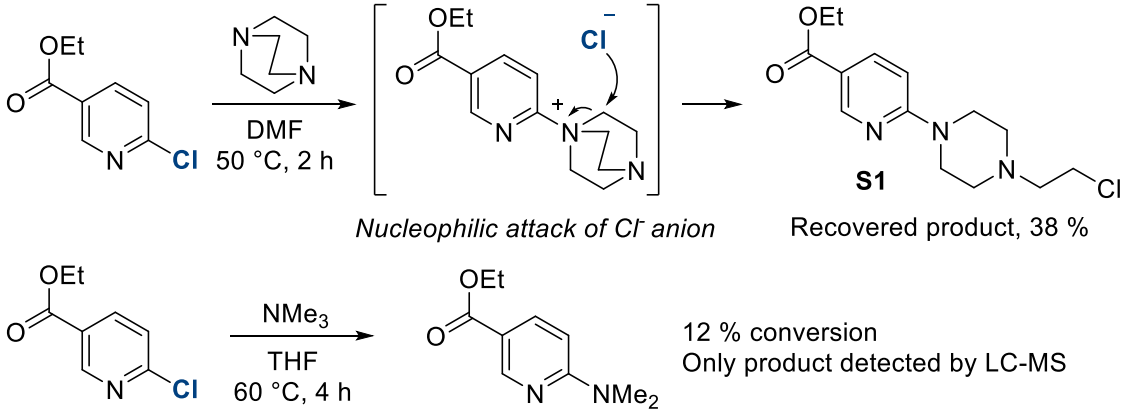
7b, capping: 76% (0.90 mmol/g)
7c, capping: 68% (0.92 mmol/g)
7j, capping: 26% (0.46 mmol/g)

Procedure i: A suspension of resin **6** (150 mg, 0.27 mmol, 1eq) in dry DMF (2 mL) was stirred at room temperature for 20 minutes and triflyl pyridine **1** (0.27 mmol, 1 eq.) was then added to the suspension. After 1 hour, the modified resin **7** was filtered and washed with DMF (x 2), CH_2Cl_2 (x3) and Et_2O (x 3) and dried under high vacuum for 2 hours.

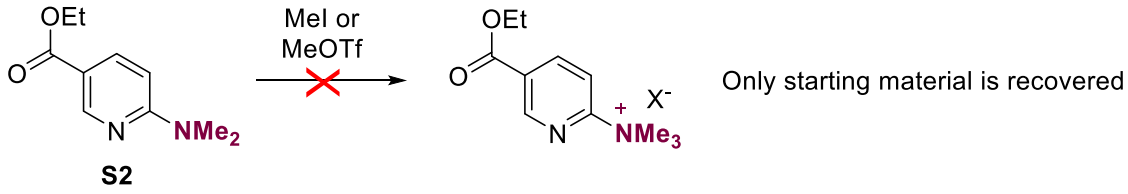
Procedure ii: Resin **6** (15 mg, 0.027 mmol, 1eq) was loaded into an empty cartridge (0.2 mL volume). The resin was incubated in a DMF solution (150 µL) of triflyl pyridine **1** (0.053 mmol, 2 eq.) at room temperature for 60 minutes. After 1 hour, the resin was washed with DMF (3 x 4 mL) and air dried.

5. Preliminary studies for the preparation of ammonium precursors

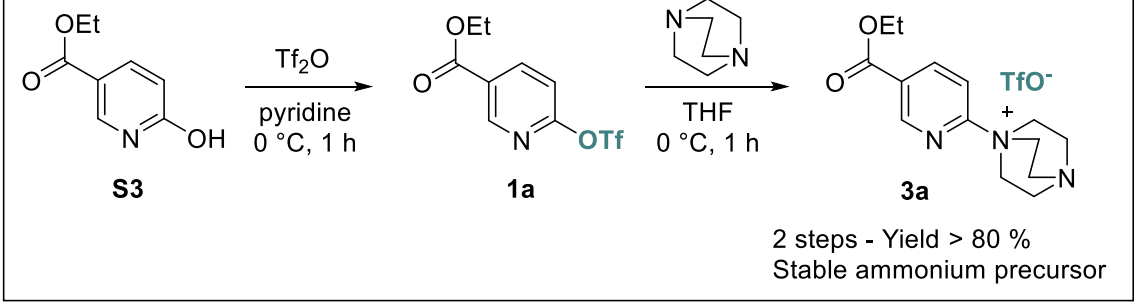
***Via* a chloropyridine intermediate:**



***Via* a dimethylaminopyridine intermediate:**



***Via* a triflylpyridine intermediate:**



Scheme S3. Envisaged strategies for the preparation of ammoniums precursors

II. Radiochemistry

No-carrier-added aqueous [^{18}F]fluoride ion was produced *via* the [^{18}O(p,n)^{18}F] nuclear reaction by irradiation of a 2 mL [^{18}O]water target (> 97%-enriched, CortecNet) on a Cyclone-18/9 cyclotron (18 MeV proton beam, IBA) and was transferred to the appropriate hot cell. Target hardware: commercial, 2-mL, two-port, stainless steel target holder equipped with a domed-end niobium cylinder insert. Target to hot cell liquid-transfer system: 60 m PTFE line (0.8 mm internal diameter ; 1/16 inch external diameter), 2.0 bar helium drive pressure, transfer time 3-6 min. Typical production of [^{18}F]fluoride ion at the end of bombardment for a 25 µA, 30 minutes irradiation: 27-30 GBq.

1. Analysis techniques

High Pressure Liquid Chromatography

High Pressure Liquid Chromatography (HPLC) was performed on the following systems:
Semi-preparative: integrated to the TRACERLab FXFN/FXNPro (GE Medical Systems): S1122 Solvent Delivery System (Sykam); U.V. Detector K-2501 (Knauer); radioactivity γ detector; column SymmetryPrep™ C18 7 µm 7.8x300 mm (Waters); H_2O/MeCN/TFA: 85/15/0.1 (v/v/v); flow rate: 5 mL/min; detection λ = 254 nm.

Analytic: Waters Alliance 2690 equipped with a UV spectrophotometer (Photodiode Array Detector, Waters 996 (Waters)) and a Berthold LB509 radioactivity detector; column: analytical Symmetry-M® C-18, 50 x 4.6 mm, 5 µm (Waters); solvent A : H_2O containing Low-UV PIC® B7 reagent (20 mL for 1000 mL), solvent B: H_2O / CH_3CN: 30:70 (v/v) containing Low-UV PIC® B7 reagent (20 mL for 1000 mL), flow rate: 2.0 mL/min; U.V. detection at λ = 254 nm.

Thin Layer Chromatography
Thin Layer Chromatography (TLC) was performed on pre-coated plates of silica gel 60F254 (Merck) and eluted with *n*-heptane/ethyl acetate (40/60). Radioactive compounds were detected using a Mini-Scan and Flow-Count radioactive detection system (Bioscan) and Chromeleon software (Thermo Scientific).

2. Kinetic studies

Preparation of K[^{18}F]F/K_{222} solution in DMSO
The aqueous solution containing [^{18}F]fluoride anions was automatically transferred to the TRACERLab FX-FN or FX N Pro after the end of irradiation. The irradiated water was then sucked through an anion exchange cartridge (Sep-Pak® Accell Plus QMA Plus Light cartridge, Waters) to fix [^{18}F]fluoride anions and remove the enriched water. The [^{18}F]fluoride anions were eluted from the resin and transferred to the reactor with a K_2CO_3/K_{222} solution (1 mL of water/acetonitrile 30/70 containing 4.5 mg of K_2CO_3 and 12 to 15 mg of Kryptofix® 222). Finally, the K[^{18}F]F-K_{222} complex was prepared by evaporation of the solution in two heating steps: (i) 60 °C for 7 min under reduced pressure along with a stream of helium and (ii) 120 °C for 5 min under vacuum. After cooling to 35 °C, the K[^{18}F]F-K_{222} complex was solubilized with DMSO (1.5 mL) and the solution was collected for kinetic studies in a 5-cm-lead shielded glove box.

Methodology

An aliquot of K[^{18}F]F-K_{222} solution in DMSO (250 to 400 MBq, 200 µL) was mixed with a solution of the appropriate precursor (3 to 4 mg) in DMSO (250 µL). Reactions were all performed at room temperature and 40 °C in triplicates. Aliquots were taken at 1, 2, 5, 15 and 30 minutes and analyzed by analytical HPLC and radioTLC. After 30 min reaction, the crude was diluted with 500 µL PBS pH 7.4 and an aliquot was taken again after 30 min additional reaction time to check stability of the radiofluorinated compound. Identifications of the radiofluorinated pyridines **4** were performed by comparison of the retention times with the non-radioactive fluorinated pyridines **4** (cold references). Conversions were determined by integration and comparison of the areas of the peaks of remaining $^{18}F^-$ and radiofluorinated pyridines from radioTLC chromatograms.

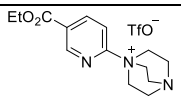
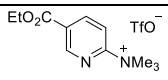
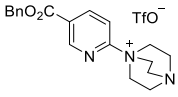
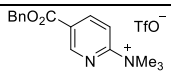
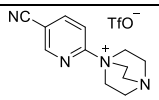
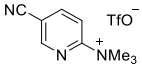
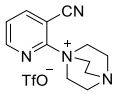
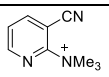
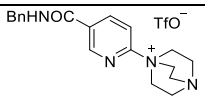
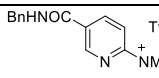
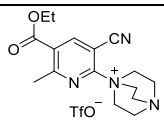
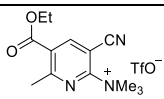
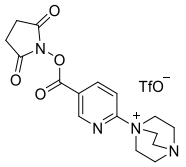
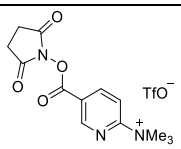
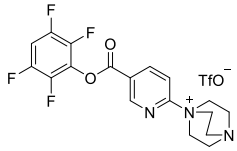
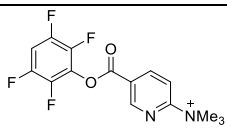
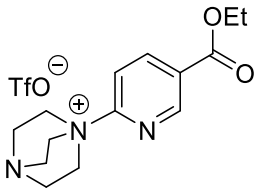
Precursor	Conversion (15 min, 25 °C)	Conversion (15 min, 40 °C)
 **3a**	76.0 ± 13.0 %	89.7 ± 1.1 %
 **2a**	72.7 ± 12.9 %	85.3 ± 1.5 %
 **3b**	81.7 ± 7.6 %	92.7 ± 0.6 %
 **2b**	70.0 ± 5.6 %	84.7 ± 3.1 %
 **3c**	68.3 ±8.5 %	83.7 ± 2.1 %
 **2c**	64.7 ± 15.8 %	94.0 ± 1.0 %
 **3d**	69.7 ± 6.4 %	82.0 ± 5.6 %
 **2d**	93.0 ± 2.6 %	95.7 ± 1.5 %
 **3e**	46.3 ± 9.9 %	68.7 ± 14.4 %
 **2e**	48.3 ± 2.5 %	85.0 ± 2.6 %
 **3f**	82.5 ± 4.9 %	93.0 ± 0.0 %
 **2f**	90.0 ± 1.0 %	94.3 ± 1.1 %
 **3g**	50.0 ± 2.6 %	57.0 ± 1.7 %
 **2g**	57.0 ± 2.0 %	66.0 ± 5.2 %
 **3h**	15.3 ± 0.6 %	19.3 ± 0.6 %
 **2h**	3.7 ± 0.6 %	4.3 ± 0.6 %

Table S1. Conversions after 15 min, reaction at 25 and 40 °C

3a

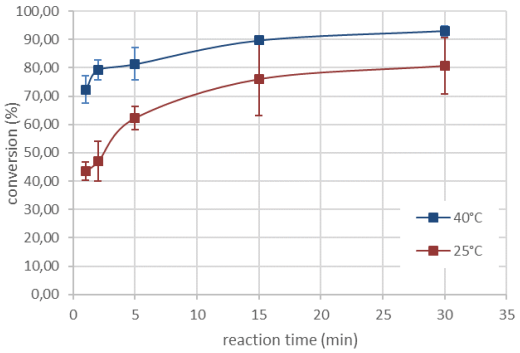


Conversion to **4a**, HPLC (eluent: A/B 50/50, R*t* = 1.82 min):

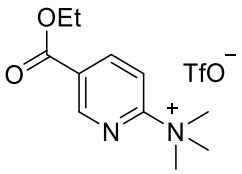
- 25 °C, 30 min, 76 % d.c.
- 40 °C, 30 min, 82 % d.c.

Conversion to **4a**, radioTLC:

time (min)	25 °C (%)	40 °C (%)
1	43.7 ± 3.2	72.3 ± 4.9
2	47.0 ± 7.0	79.3 ± 3.5
5	62.3 ± 4.0	81.3 ± 5.7
15	76.0 ± 13.0	89.7 ± 1.1
30	80.7 ± 10.0	93.0 ± 1.7



2a

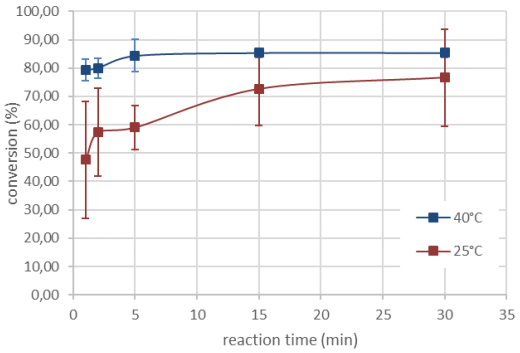


Conversion to **4a**, HPLC (eluent: A/B 50/50, R*t* = 1.82 min):

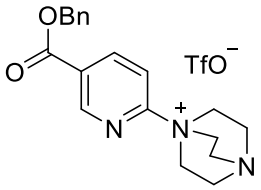
- 25 °C, 30 min, 87 % d.c.
- 40 °C, 30 min, 89 % d.c.

Conversion to **4a**, radioTLC:

time (min)	25 °C (%)	40 °C (%)
1	47.7 ± 20.6	79.3 ± 3.8
2	57.3 ± 15.5	80.0 ± 3.5
5	59.0 ± 7.8	84.3 ± 5.7
15	72.7 ± 12.9	85.3 ± 1.5
30	76.7 ± 17.1	85.3 ± 1.5



3b

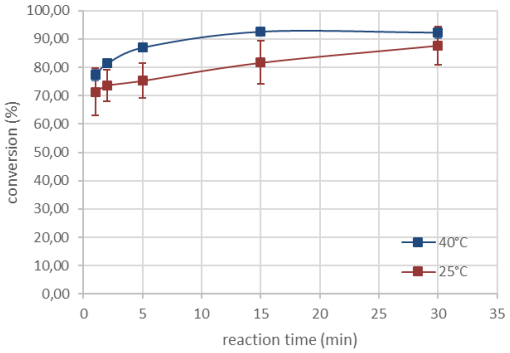


Conversion to **4b**, HPLC (eluent: A/B 30/70, R*t* = 2.21 min):

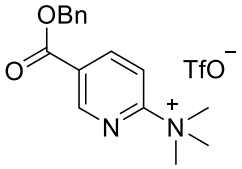
- 25 °C, 30 min, 81 % d.c.
- 40 °C, 30 min, 85 % d.c.

Conversion to **4b**, radioTLC:

time (min)	25 °C (%)	40 °C (%)
1	71.3 ± 8.3	77.3 ± 2.1
2	73.7 ± 5.5	81.3 ± 0.6
5	75.3 ± 6.0	87.0 ± 1.0
15	81.7 ± 7.6	92.7 ± 0.6
30	87.7 ± 6.8	92.3 ± 2.1



2b

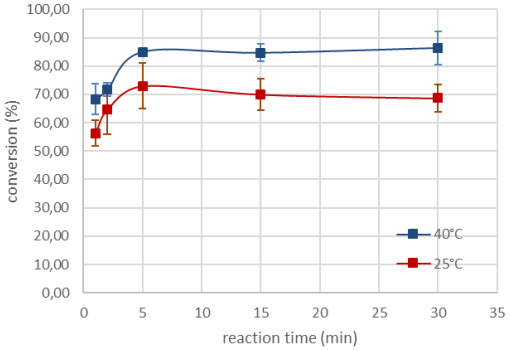


Conversion to **4b**, HPLC (eluent: A/B 30/70, R*t* = 2.21 min):

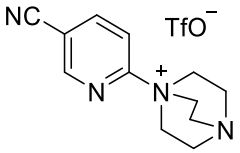
- 25 °C, 30 min, 61 % d.c.
- 40 °C, 30 min, 92 % d.c.

Conversion to **4b**, radioTLC:

time (min)	25 °C (%)	40 °C (%)
1	56.3 ± 4.5	68.3 ± 5.5
2	64.7 ± 8.6	71.7 ± 2.3
5	73.0 ± 7.9	85.0 ± 1.0
15	70.0 ± 5.6	84.7 ± 3.1
30	68.7 ± 4.9	86.3 ± 5.9



3c

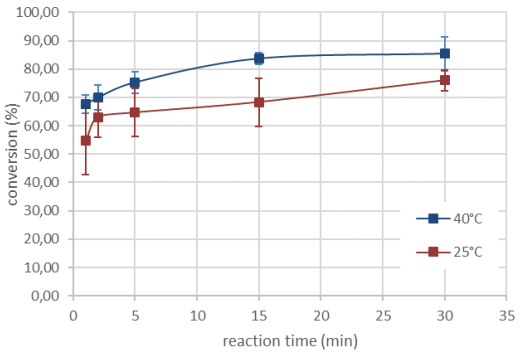


Conversion to **4c**, HPLC (eluent: A/B 80/20, R*t* = 1.37 min):

- 25 °C, 30 min, 76 % d.c.
- 40 °C, 30 min, 85 % d.c.

Conversion to **4c**, radioTLC:

time (min)	25 °C (%)	40 °C (%)
1	54.7 ± 11.8	67.7 ± 3.2
2	63.0 ± 7.2	70.0 ± 4.4
5	64.7 ± 8.4	75.3 ± 3.8
15	68.3 ± 8.5	83.7 ± 2.1
30	76.0 ± 3.6	85.3 ± 6.0



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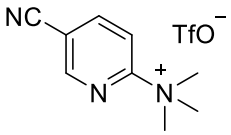
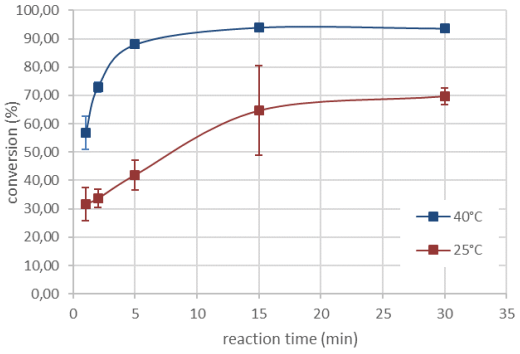


Conversion to **4c**, HPLC (eluent: A/B 80/20, R*t* = 1.37 min):

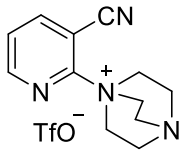
- 25 °C, 30 min, 87 % d.c.
- 40 °C, 30 min, 91 % d.c.

Conversion to **4c**, radioTLC:

time (min)	25 °C (%)	40 °C (%)
1	31.7 ± 5.9	56.7 ± 5.9
2	33.7 ± 3.2	73.0 ± 1.7
5	42.0 ± 5.3	88.0 ± 1.0
15	64.7 ± 15.8	94.0 ± 1.0
30	69.7 ± 3.1	93.7 ± 0.6



3d

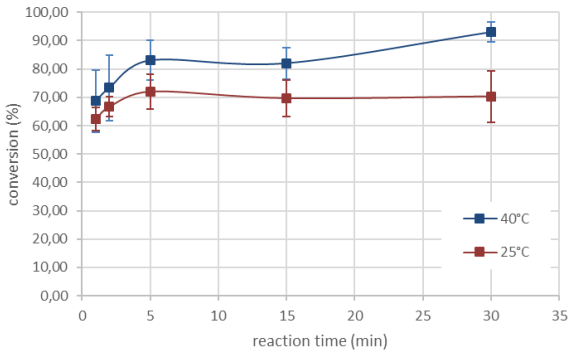


Conversion to **4d**, HPLC (eluent: A/B 80/20, R*t* = 2.06 min):

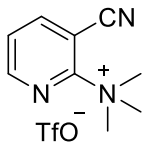
- 25 °C, 30 min, 84 % d.c.
- 40 °C, 30 min, 91 % d.c.

Conversion to **4d**, radioTLC:

time (min)	25 °C (%)	40 °C (%)
1	62.3 ± 4.2	68.7 ± 11.0
2	66.7 ± 3.5	73.3 ± 11.6
5	72.0 ± 6.2	83.0 ± 7.0
15	69.7 ± 6.4	82.0 ± 5.6
30	70.3 ± 9.0	93.0 ± 3.5



2d

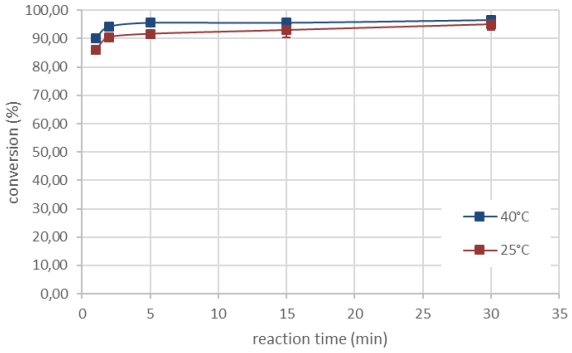


Conversion to **4d**, HPLC (eluent: A/B 80/20, R*t* = 2.06 min):

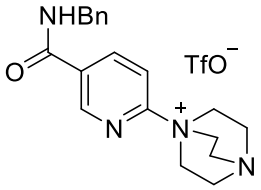
- 25 °C, 30 min, 85 % d.c.
- 40 °C, 30 min, 91 % d.c.

Conversion to **4d**, radioTLC:

time (min)	25 °C (%)	40 °C (%)
1	86.0 ± 0.0	90.0 ± 1.0
2	90.5 ± 0.7	94.3 ± 0.6
5	91.7 ± 1.1	95.7 ± 1.5
15	93.0 ± 2.6	95.7 ± 1.5
30	95.0 ± 2.0	96.7 ± 1.1



3e

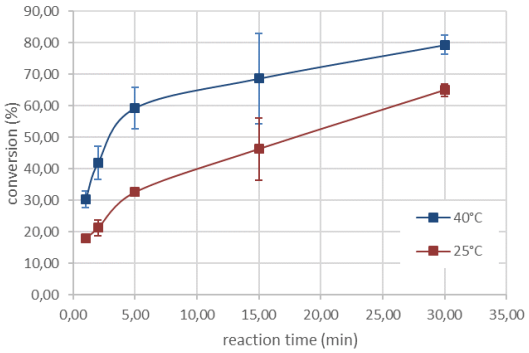


Conversion to **4e**, HPLC (eluent: A/B 60/40, R*t* = 2.16 min):

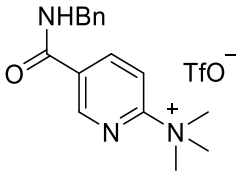
- 25 °C, 30 min, 63 % d.c.
- 40 °C, 30 min, 78 % d.c.

Conversion to **4e**, radioTLC:

time (min)	25 °C (%)	40 °C (%)
1,00	18.0 ± 1.0	30.3 ± 2.5
2,00	21.3 ± 2.5	42.0 ± 5.3
5,00	32.7 ± 1.1	59.3 ± 6.7
15,00	46.3 ± 9.9	68.7 ± 14.4
30,00	65.0 ± 2.0	79.3 ± 3.1



2e

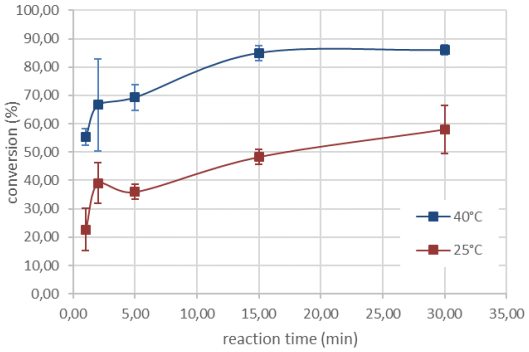


Conversion to **4e**, HPLC (eluent: A/B 60/40, R*t* = 2.16 min):

- 25 °C, 30 min, 67 % d.c.
- 40 °C, 30 min, 85 % d.c.

Conversion to **4e**, radioTLC:

time (min)	25 °C (%)	40 °C (%)
1,00	22.7 ± 7.5	55.3 ± 3.1
2,00	39.0 ± 7.2	66.7 ± 16.2
5,00	36.0 ± 2.6	69.3 ± 4.5
15,00	48.3 ± 2.5	85.0 ± 2.6
30,00	58.0 ± 8.5	86.0 ± 1.7



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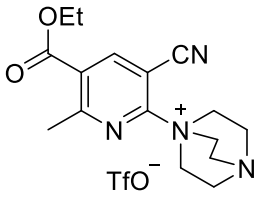
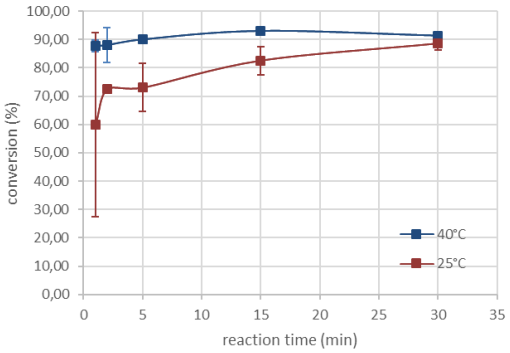


Conversion to **4f**, HPLC (eluent: A/B 30/70, R*t* = 1.54 min):

- 25 °C, 30 min, 81 % d.c.
- 40 °C, 30 min, 92 % d.c.

Conversion to **4f**, radioTLC:

time (min)	25 °C (%)	40 °C (%)
1	60.0 ± 32.5	87.7 ± 2.1
2	72.5 ± 0.7	88.0 ± 6.1
5	73.0 ± 8.5	90.0 ± 1.0
15	82.5 ± 4.9	93.0 ± 0.0
30	88.5 ± 2.1	91.3 ± 1.1



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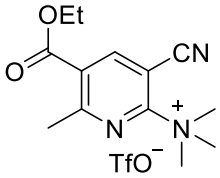
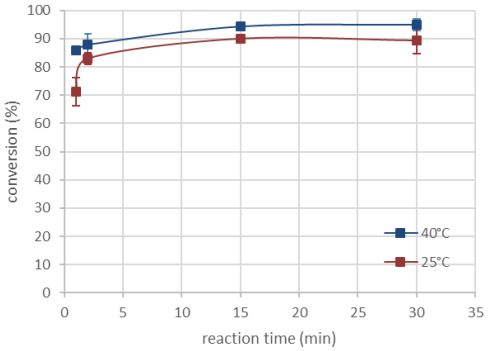


Conversion to **4f**, HPLC (eluent: A/B 30/70, R*t* = 1.54 min):

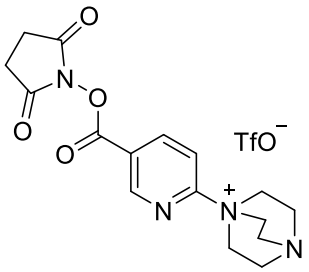
- 25 °C, 30 min, 89 % d.c.
- 40 °C, 30 min, 90 % d.c.

Conversion to **4f**, radioTLC:

time (min)	25 °C (%)	40 °C (%)
1	71.3 ± 4.9	86.0 ± 1.0
2	83.0 ± 2.0	88.0 ± 3.6
5	78.3 ± 7.8	87.7 ± 3.1
15	90.0 ± 1.0	94.3 ± 1.1
30	89.3 ± 4.7	95.0 ± 2.0



3g

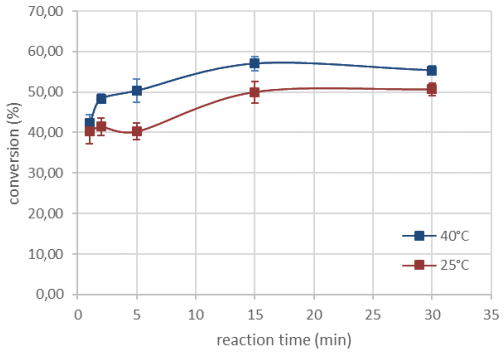


Conversion to **4g**, HPLC (eluent: A/B 70/30, R*t* = 1.98 min):

- 25 °C, 30 min, 57 % d.c.
- 40 °C, 30 min, 71 % d.c.

Conversion to **4g**, radioTLC:

time (min)	25 °C (%)	40 °C (%)
1	40.3 ± 3.1	42.3 ± 2.1
2	41.5 ± 2.1	48.3 ± 1.1
5	40.3 ± 2.1	50.3 ± 2.9
15	50.0 ± 2.6	57.0 ± 1.7
30	50.7 ± 1.5	55.3 ± 1.1



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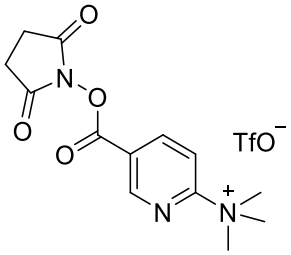
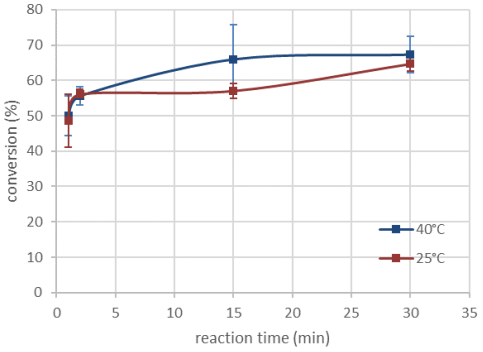


Conversion to **4g**, HPLC (eluent: A/B 70/30, R*t* = 1.98 min):

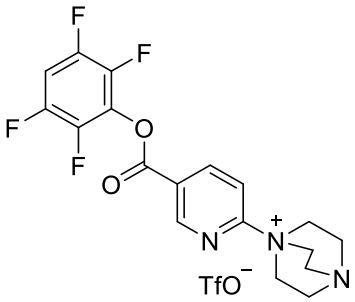
- 25 °C, 30 min, 68 % d.c.
- 40 °C, 30 min, 69 % d.c.

Conversion to **4g**, radioTLC:

time (min)	25 °C (%)	40 °C (%)
1	48.7 ± 7.5	50.0 ± 5.6
2	56.0 ± 1.4	55.7 ± 2.5
5	49.3 ± 2.1	50.0 ± 9.6
15	57.0 ± 2.0	66.0 ± 5.2
30	64.7 ± 4.9	67.3 ± 4.2



3h

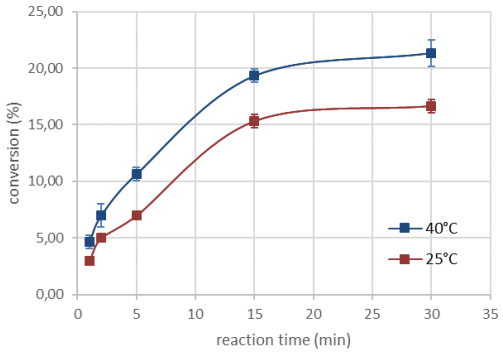


Conversion to **4h**, HPLC (eluent: A/B 50/50, R*t* = 1.70 min):

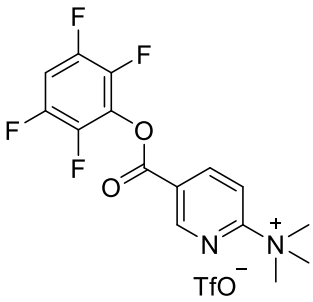
- 25 °C, 30 min, not detected
- 40 °C, 30 min, not detected

Conversion to **4h**, radioTLC:

time (min)	25 °C (%)	40 °C (%)
1	3.0 ± 0.0	4.7 ± 0.6
2	5.0 ± 0.0	7.0 ± 1.0
5	7.0 ± 0.0	10.7 ± 0.6
15	15.3 ± 0.6	19.3 ± 0.6
30	16.7 ± 0.6	21.3 ± 1.1



2h

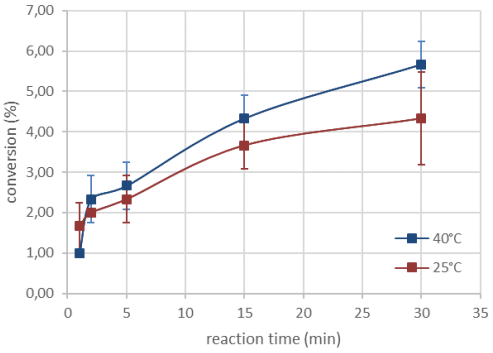


Conversion to **4h**, HPLC (eluent: A/B 50/50, R*t* = 1.70 min):

- 25 °C, 30 min, not detected
- 40 °C, 30 min, not detected

Conversion to **4h**, radioTLC:

time (min)	25 °C (%)	40 °C (%)
1	1.7 ± 0.6	1.0 ± 0.0
2	2.0 ± 0.0	2.3 ± 0.6
5	2.3 ± 0.6	2.7 ± 0.6
15	3.7 ± 0.6	4.3 ± 0.6
30	4.3 ± 1.1	5.7 ± 0.6



3. Example of automated radiosynthesis: 4c

The aqueous solution containing [^{18}F]fluoride anions was transferred to the TRACERLab FX-FN or FX N Pro after the end of irradiation. The irradiated water went through a QMA cartridge (Waters, France) to fix the [^{18}F]fluoride anions and remove the enriched water. [^{18}F]fluoride anions were then eluted from the resin and transferred to the reactor with a K_2CO_3/K_{222} solution (water/acetonitrile 30/70 (1 mL) containing 4.5 mg of K_2CO_3 and 12 to 15 mg of Kryptofix® 222). The K[^{18}F]F-K_{222} complex was then prepared by evaporation of the solution in two heating steps: (i) first at 60 °C for 7 minutes at a pressure ranging between 30 and 35 kPa and then (ii) at 120 °C for 5 minutes under vacuum. Temperature was then to 25 °C by compressed air flow. Radiofluorination was carried out by addition of **2c** (5 mg, 15.4 µmol) in solution in DMSO (1 mL) to the dried K[^{18}F]F-K_{222} complex and stirring at room temperature for 10 minutes. The crude was diluted with HPLC-solvent (3 mL) and transferred through an Alumina N cartridge (Waters, France) before HPLC purification on a SymmetryPrep™ C18 7 µm 7.8x300 mm column (Waters) (H_2O/MeCN/TFA: 85/15/0.1 (v/v/v); flow rate: 5 mL/min; detection λ = 254 nm). The fraction containing **4c** was collected and diluted with water (20 mL) for formulation on a Sep-Pak®Plus C18-based system (Waters, France). The purified tracer was finally recovered after elution of the C18 cartridge with DMSO (2 mL). Chemical and radiochemical purities were assessed on an aliquot by analytical HPLC, with an authentic sample of non-radioactive **4c** as standard (A/B 80/20, R*t* = 1.4 min). The expected **4c** was obtained with a 52% decay-corrected yield.

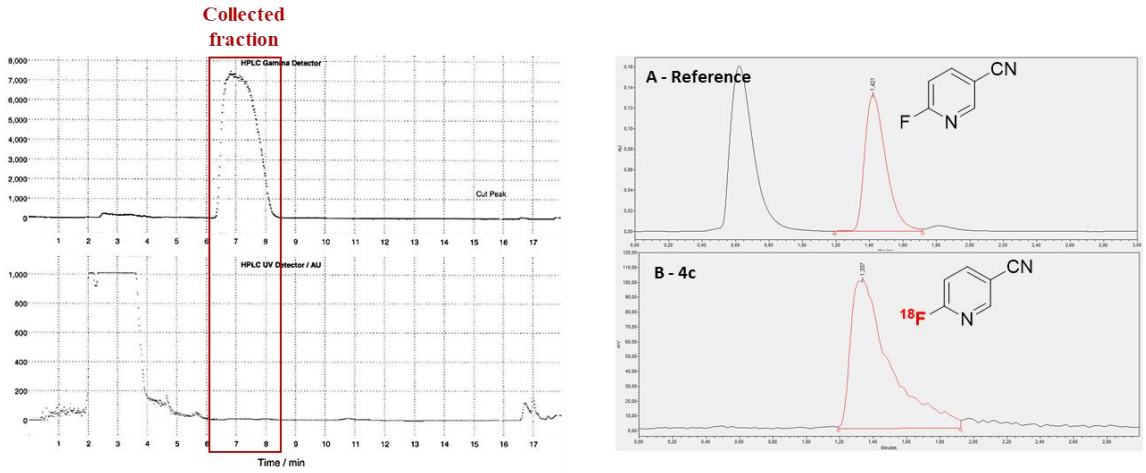


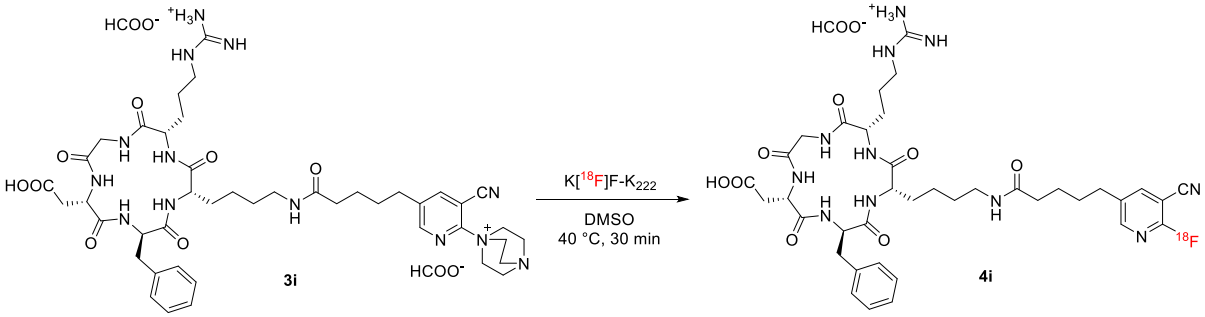
Figure S1. Semi-preparative HPLC chromatograms and analytic chromatograms after purification

4. Direct labelling of peptides

General protocol

An aliquot of K[^{18}F]F-K$_{222}$ solution in DMSO (250 to 400 MBq, 200 µL) was mixed with a solution of the appropriate precursor **3** in DMSO and the mixture was incubated at 40 °C for 30 minutes. Identification of the radiofluorinated compound **4** was performed by comparison of the retention time with the non-radioactive reference **4**. The reaction mixture was filtered on a short Alumina pad, washed with 200 µL DMSO and the radiochemical yield was obtained by measuring the activity in the eluate.

RGDfK



Scheme S4. Direct labelling of RGDfK

200 µL of K[^{18}F]F-K$_{222}$ in DMSO were added to a solution of **3i** (2 mg in 100 µL DMSO). After incubation for 30 minutes at 40 °C, mixture was analyzed by HPLC (A/B: 60/40). Similar retention times were observed for cold reference (t_r = 2.50 min) and for **4i** (t_r = 2.43 min). Alumina purification indicated a 42 % labelling yield.

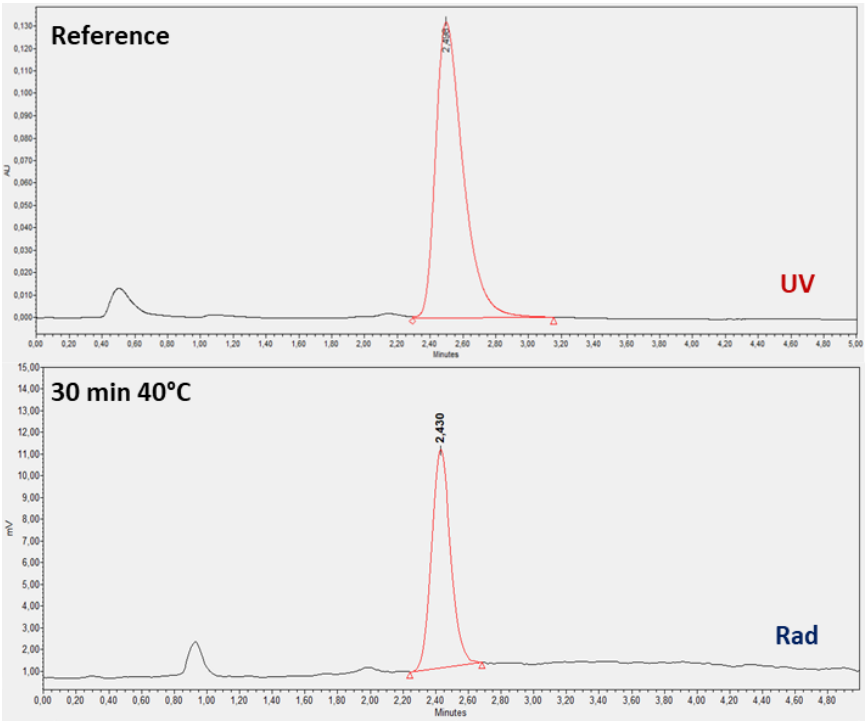
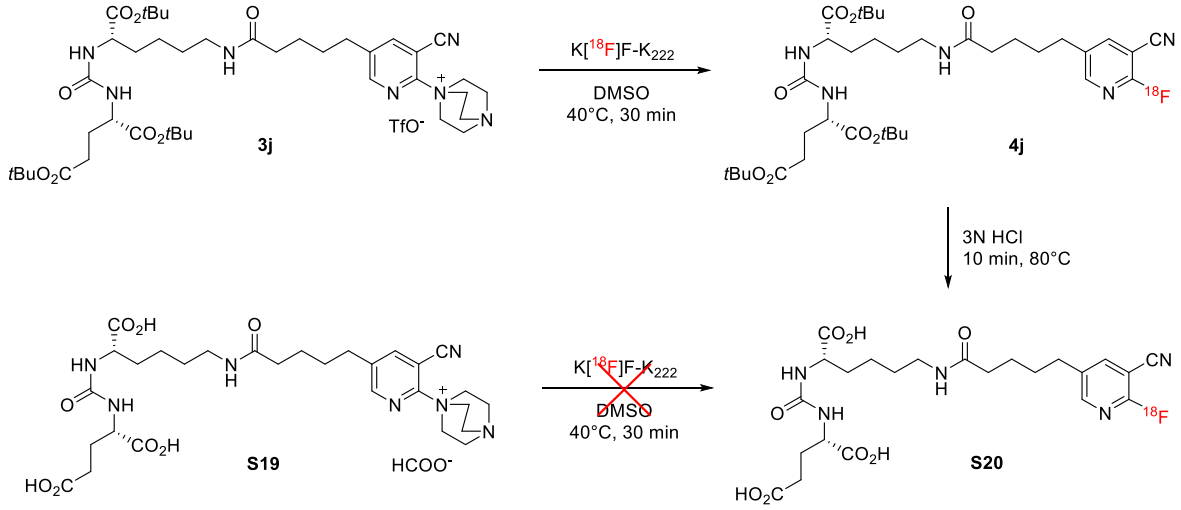


Figure S2. Analytic chromatogram of radiofluorination of cyclic RGDfK

PSMA



Scheme S5. Direct labelling of PSMA

Direct radiolabelling of **S19** following general protocol was not efficient and **S20** was not detected by HPLC. Direct radiolabelling was next attempted on protected precursor **3j**. 200 µL of K[^{18}F]F-K$_{222}$ in DMSO were added to a solution of **3j** (2 mg in 100 µL DMSO). After incubation for 30 minutes at 40 °C, HPLC (A/B: 15/85) showed a similar retention time for cold reference (t_r = 2.07 min) and for **4j** (t_r = 2.07 min). Alumina purification gave a 47 % labelling yield. 200 µL 3N HCl were then added to the purified fraction and the solution was incubated at 80 °C for 10 minutes. The solution was analyzed by HPLC (A/B: 75/25) and similar retention times for cold reference (t_r = 2.26 min) and for **S20** (t_r = 2.15 min) were observed.

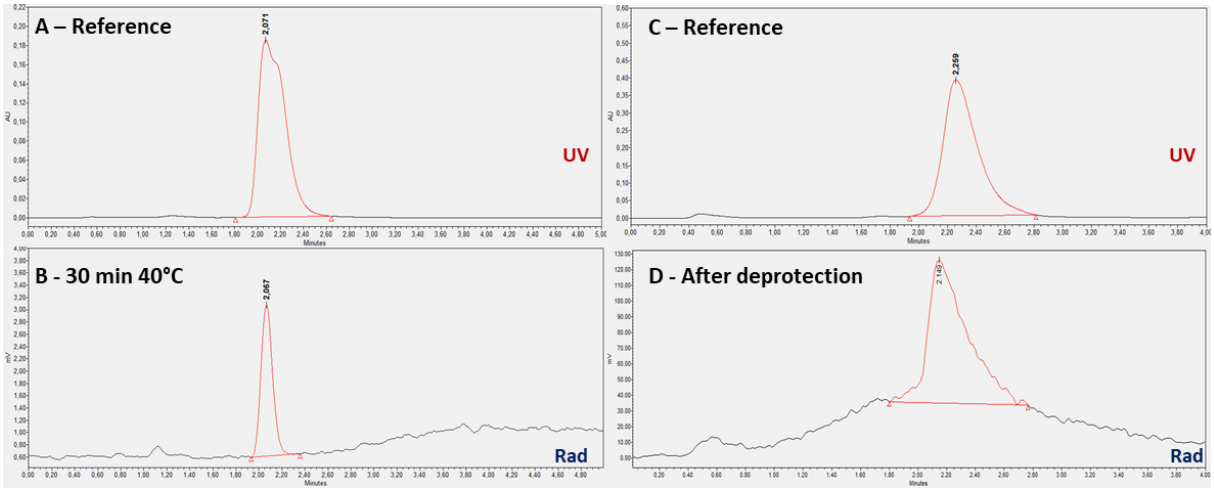
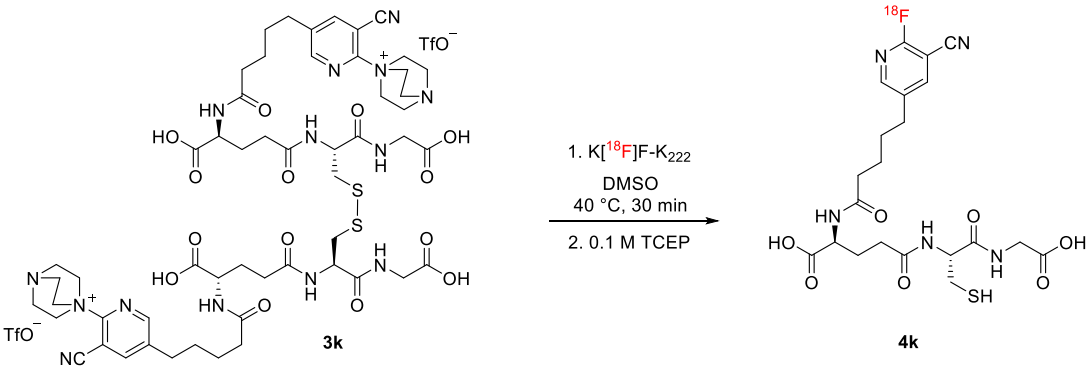


Figure S3. Analytic chromatograms of radiofluorination of PSMA. A - UV trace of **4j** coinjected with cold reference **4j**; B - Radioactive trace of **4j**; C - UV trace - coinjection with cold reference **S20**; D - Radioactive trace of **S20**.

Glutathione



Scheme S6. Direct labelling of Glutathione

200 µL of K[^{18}F]F-K$_{222}$ in DMSO were added to a solution of **3k** (2 mg in 100 µL DMSO). After incubation for 30 minutes at 40 °C, 0.1 M TCEP solution (20 µL) was added to an aliquot of the reaction mixture (40 µL) and HPLC analysis (A/B: 80/20) showed a similar retention time for cold reference (t_r = 2.75 min) and for **4k** (t_r = 2.62 min). Alumina purification indicated a 55 % labelling yield.

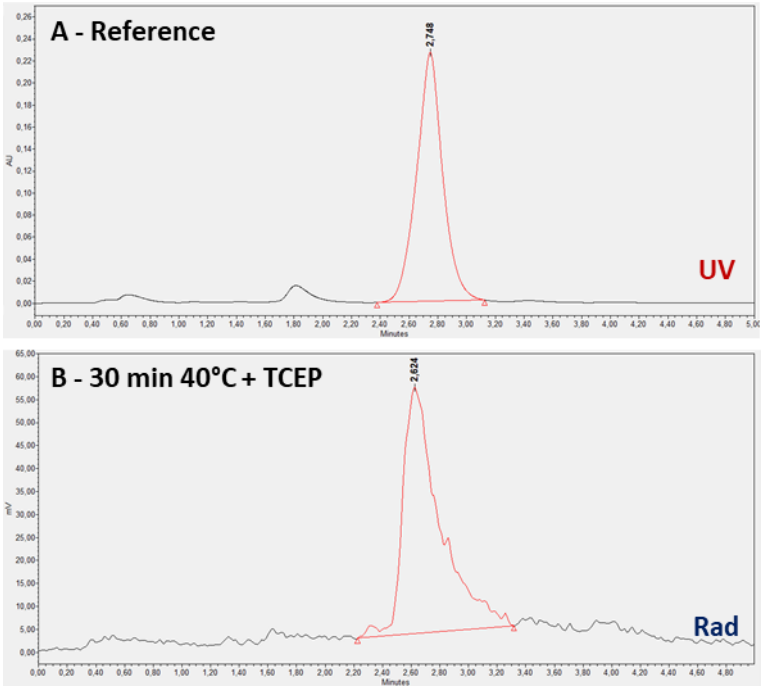


Figure S4. Analytic chromatograms of radiofluorination of glutathione. A - UV trace of reference **4k**; B - Radioactive trace of **4k**

5. On-resin labelling

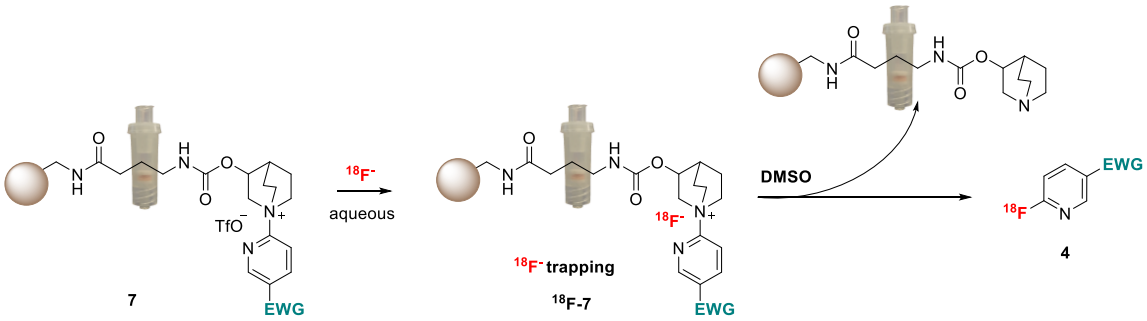


Figure S5. Principle of our on-resin radiofluorination process

The aqueous solution containing [^{18}F]fluoride anions (5.55 to 9.25 GBq) was transferred to the TRACERLab FX-FN or FX N Pro after the end of irradiation. The irradiated water went through a cartridge (placed where the QMA cartridge is usually connected) filled with pyridine-modified resin **7** (15 mg) to fix the [^{18}F]fluoride anions and remove the enriched water. [^{18}F]F$^-$ trapping efficiency was determined based on the activity recovered in the flow-through. Water was then flushed from the resin for 5 minutes and **4** was slowly eluted from the resin with 4 mL DMSO over ~15 minutes *via* a moderate pressure. To remove unreacted [^{18}F]F$^-$, the crude was diluted with water (40 mL) for formulation on a Sep-Pak®Plus C18-based system (Waters, France) (**Figure S6**). The purified tracer was finally recovered after elution of the C18 cartridge with DMSO (2 mL). Alternatively, the crude was passed through an Alumina N cartridge (Waters, France) (**Figure S7**). Chemical and radiochemical purities were assessed on an aliquot by radioTLC and analytical HPLC (**Figures S8-S10**), with a sample of cold references **4** as standards. Radiochemical yields are decay corrected and calculated based on the starting activity.

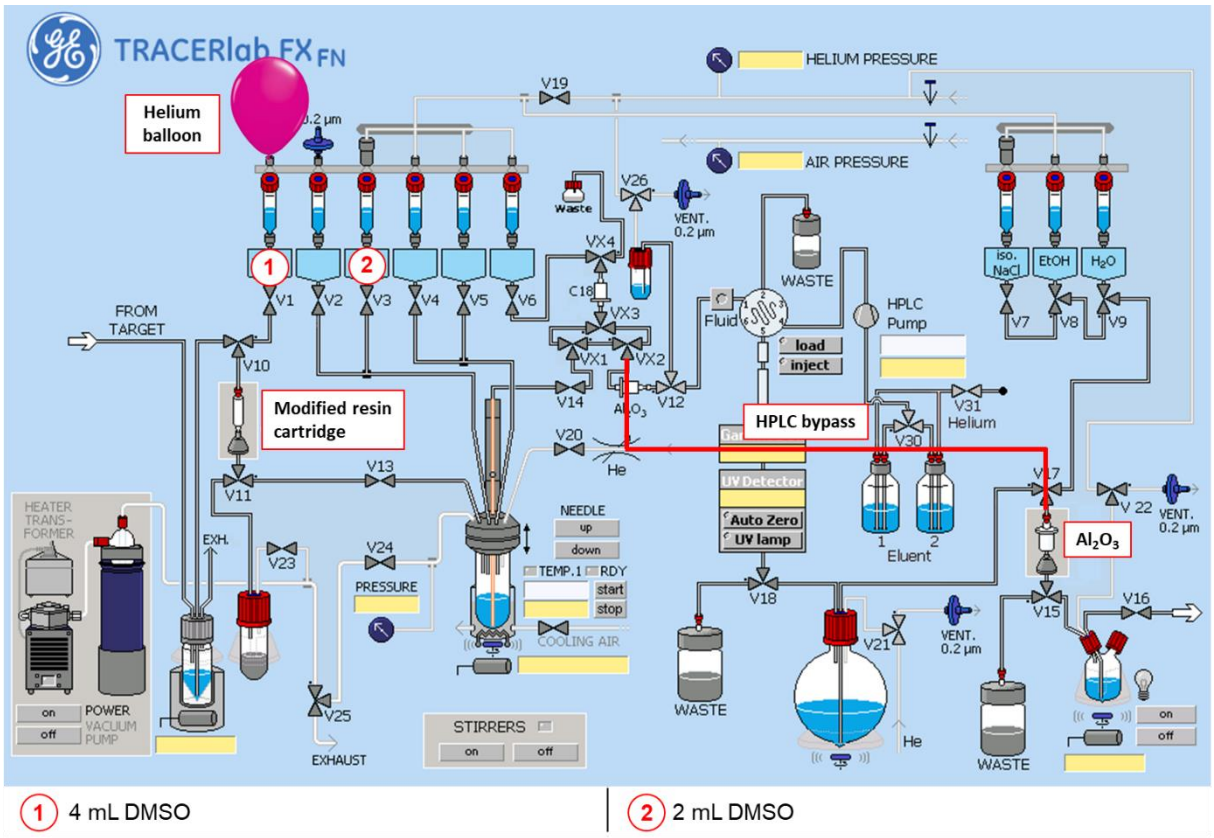


Figure S6. Synoptic of FXFn automate, formulation on Alumina N cartridge

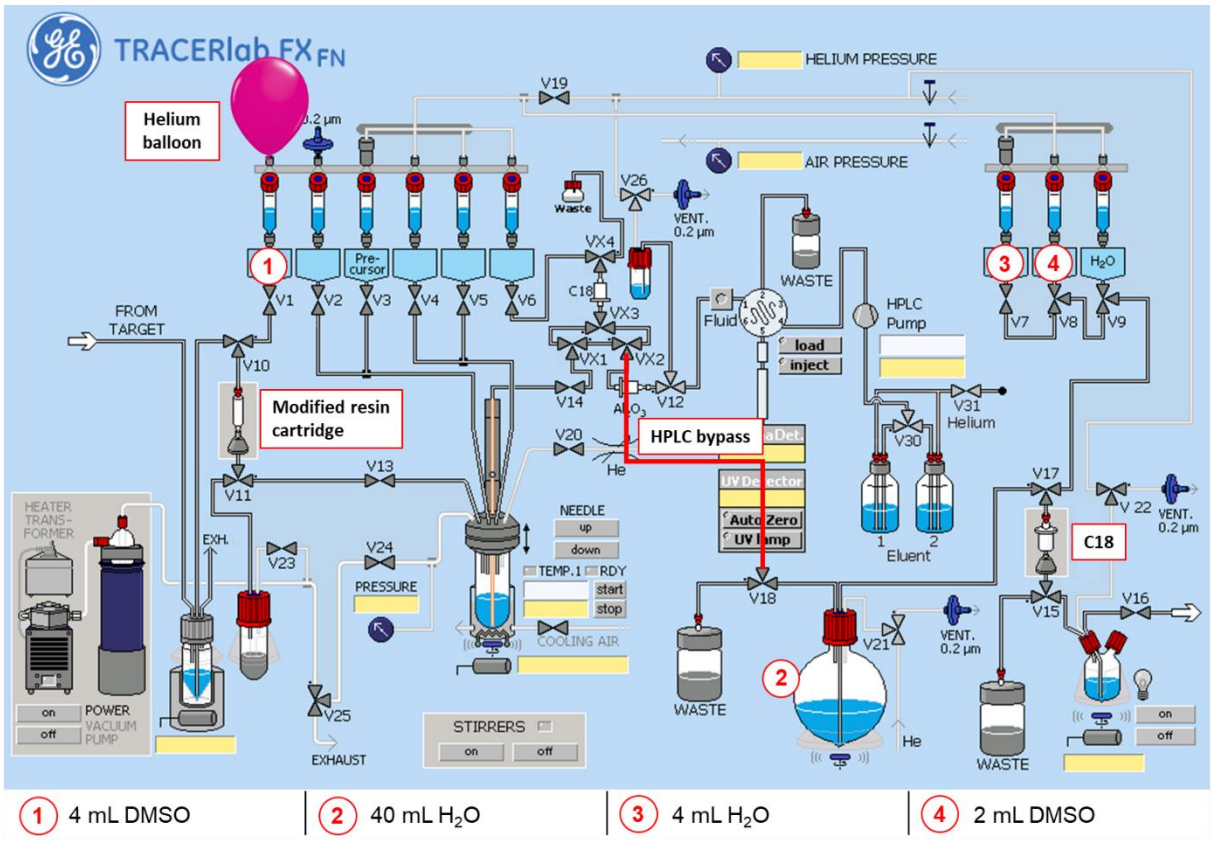


Figure S7. Synoptic of FXFn automate, formulation on Sep-Pak® Plus C18

Resin 7b

[^{18}F]F$^-$ trapping efficiency: 35 %
Radiochemical yield (formulation on Sep-Pak®Plus C18 cartridge) = **8.1 ± 2.4 % d.c. (n = 3)**

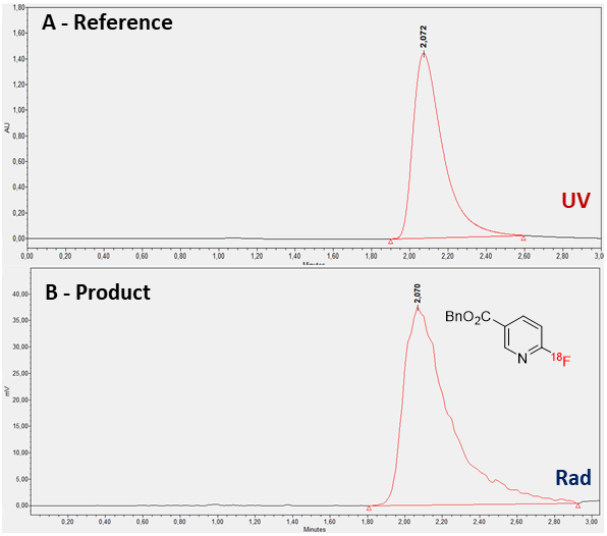


Figure S8. Analytic chromatograms of on-resin radiofluorination of **7b**. A - UV trace of reference **4b**; B - Radioactive trace of **4b**; HPLC Eluent: A/B: 30/70

Resin 7c

[^{18}F]F$^-$ trapping efficiency: 23 %
Radiochemical yield: Sep-Pak®Plus C18 cartridge, **0.4 % d.c.;** Alumina N cartridge, **3.1 % d.c.**

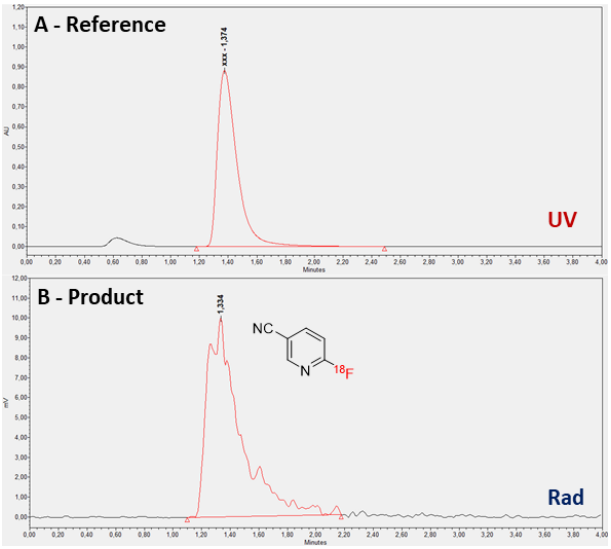


Figure S9. Analytic chromatograms of on-resin radiofluorination of **7c**. A - UV trace of reference **4c**; B - Radioactive trace of **4c**; HPLC Eluent: A/B: 70/30

Resin 7j

[^{18}F]F^{-} trapping efficiency: 31 %
Radiochemical yield: Sep-Pak®Plus C18 cartridge, **0.4 % d.c.;** Alumina N cartridge, **0.9 % d.c.**

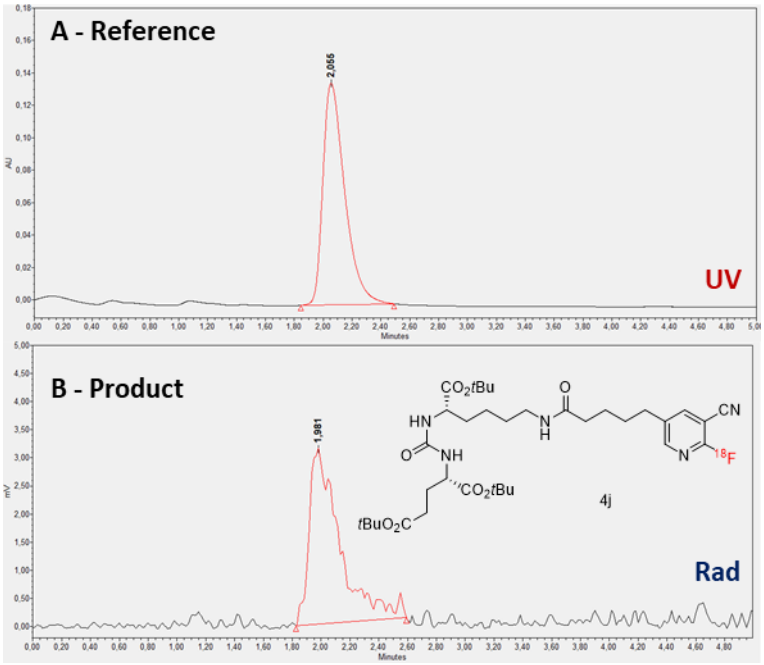


Figure S10. Analytic chromatograms of on-resin radiofluorination of **7j**. A - UV trace of reference **4j**; B - Radioactive trace of **4j**; HPLC Eluent: A/B: 15/85

6. Stability studies

The stability of **4** was tested on the model compound **4c** in Fetal Bovine Serum (FBS). **4c** solution (100 µL in DMSO, 9.25 MBq) was mixed with FBS (900 µl) and incubated at 40 °C. Aliquots (300 µl) were taken at 30 min and 60 min for HPLC analysis. 300 µL MeCN was added to the aliquot for protein precipitation and the sample was centrifuged to pellet the precipitated proteins. Activities in both fractions (supernatant & pelleted proteins) were measured to ensure that radioactivity was mainly recovered in the soluble fraction. As seen in **Table S2**, 82 % of radioactivity is recovered in the supernatant. HPLC of the supernatant was then performed using the analytical HPLC method described in the analysis techniques section (eluent: A/B 72/28). No degradation was observed in serum after 60 min at 40 °C (**Figure S11**, A-D). RadioTLC analyses (**Figure S11**, E&F) confirmed these observations.

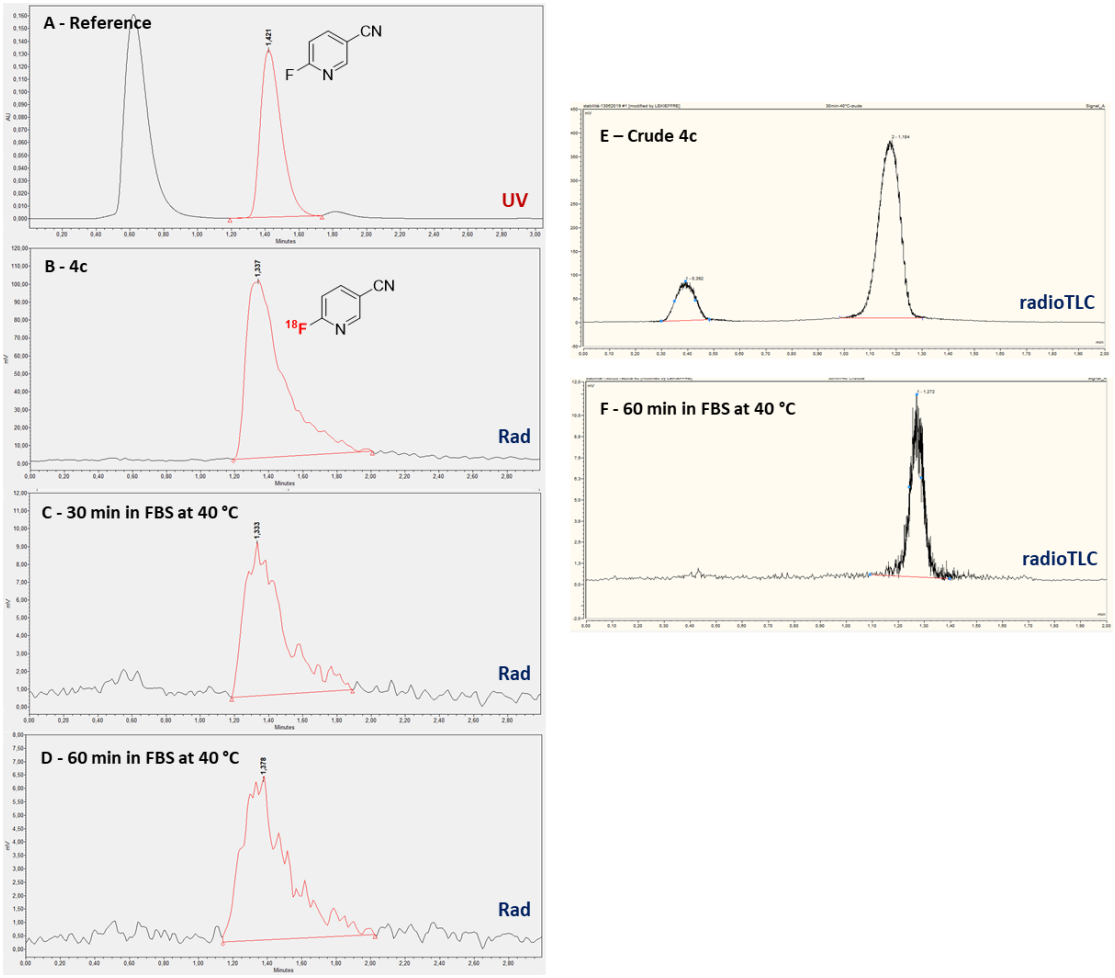
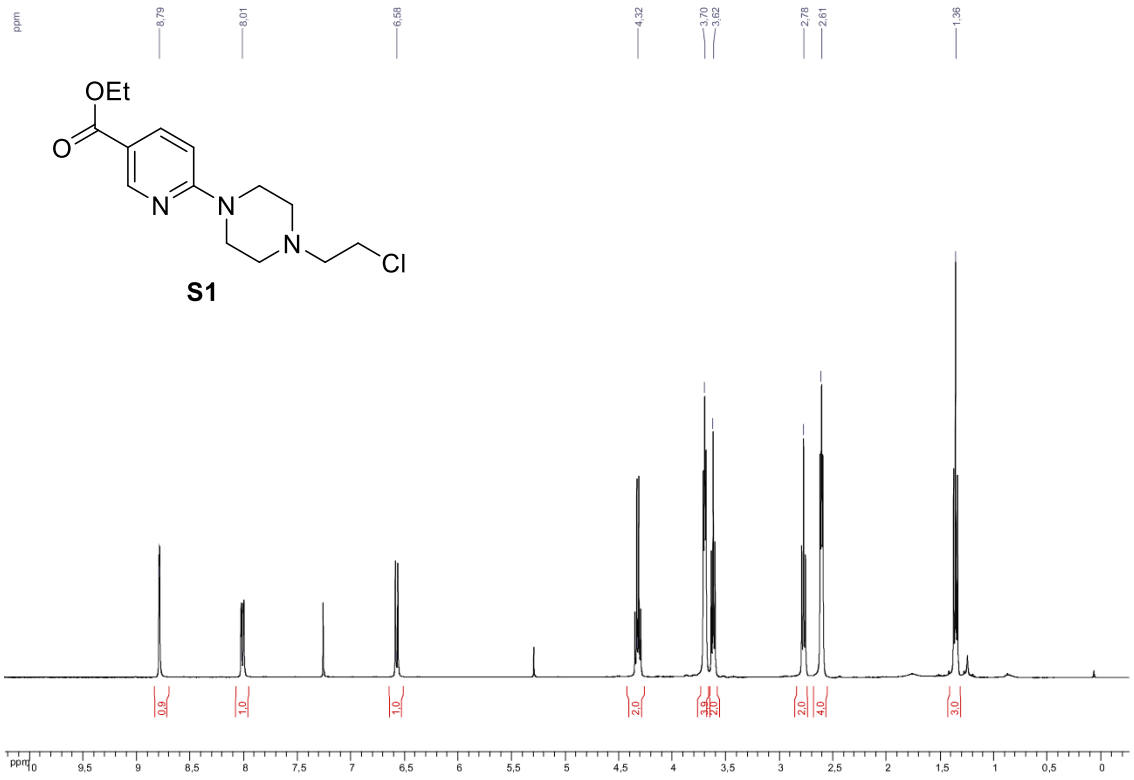


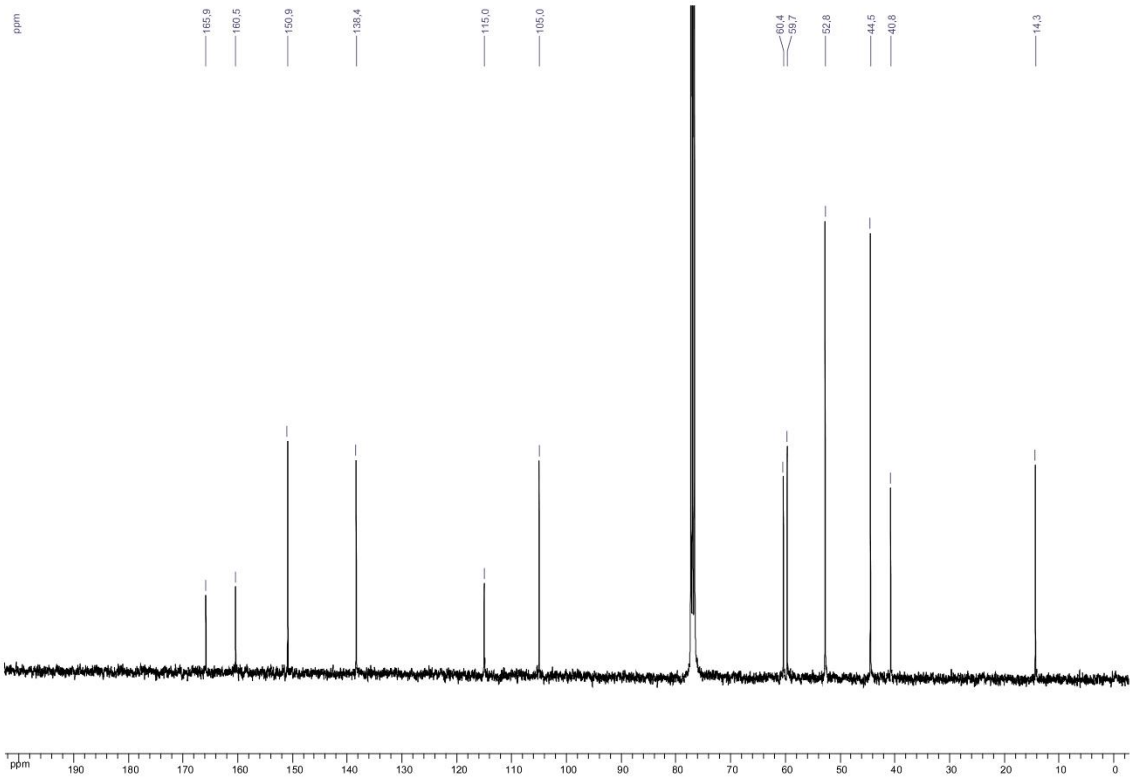
Figure S11. Stability study of **4c**. A-D - HPLC traces: A – UV trace of reference **4c**; B – radioactive trace of **4c**; C - 30 min at 40 °C in FBS; D - 60 min at 40 °C in FBS; E & F - radioTLC: E - Crude **4c**; F – After 60 min at 40 °C in FBS (supernatant)

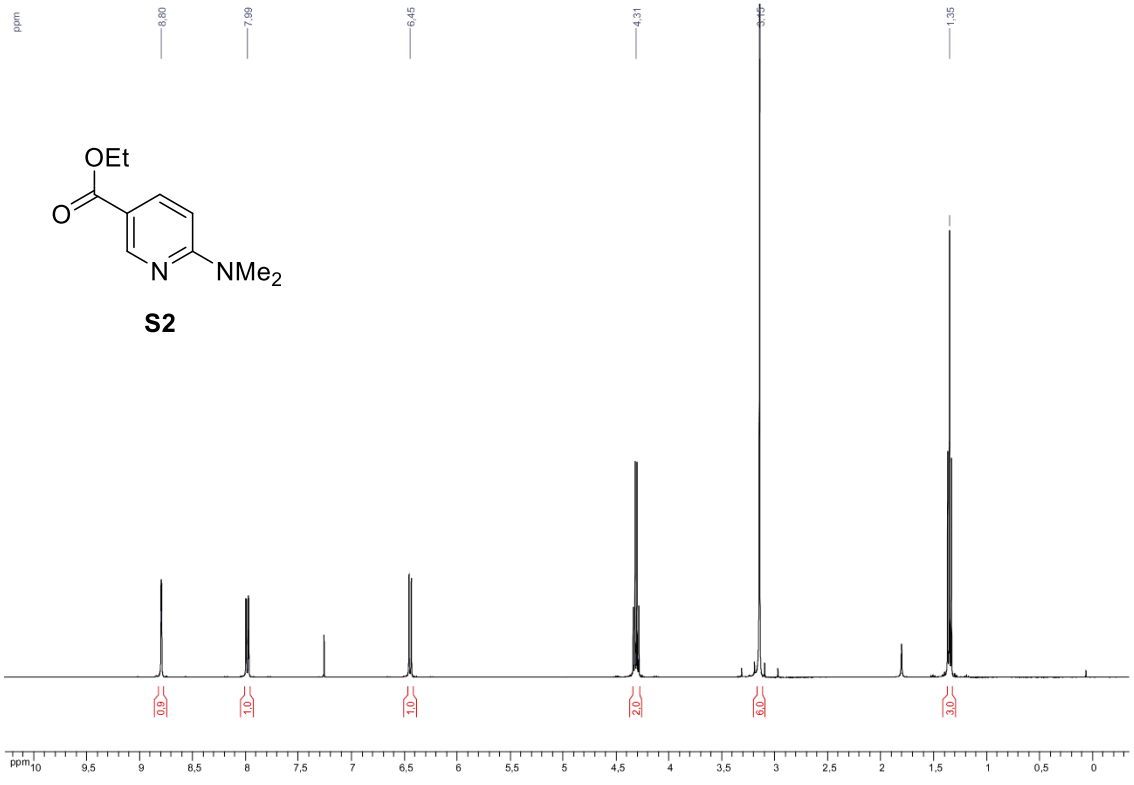
Incubation time	Radioactivity		
	Before centrifugation (MBq)	Supernatant (MBq)	Precipitated proteins (MBq)
30 min	9.25	7.60 (82 %)	1.65 (18 %)
60 min	7.45	6.11 (82 %)	1.34 (18 %)

Table S2. Repartition of activity in supernatant (soluble fraction) and pelleted proteins.

III. ^{1}H and ^{13}C NMR spectra



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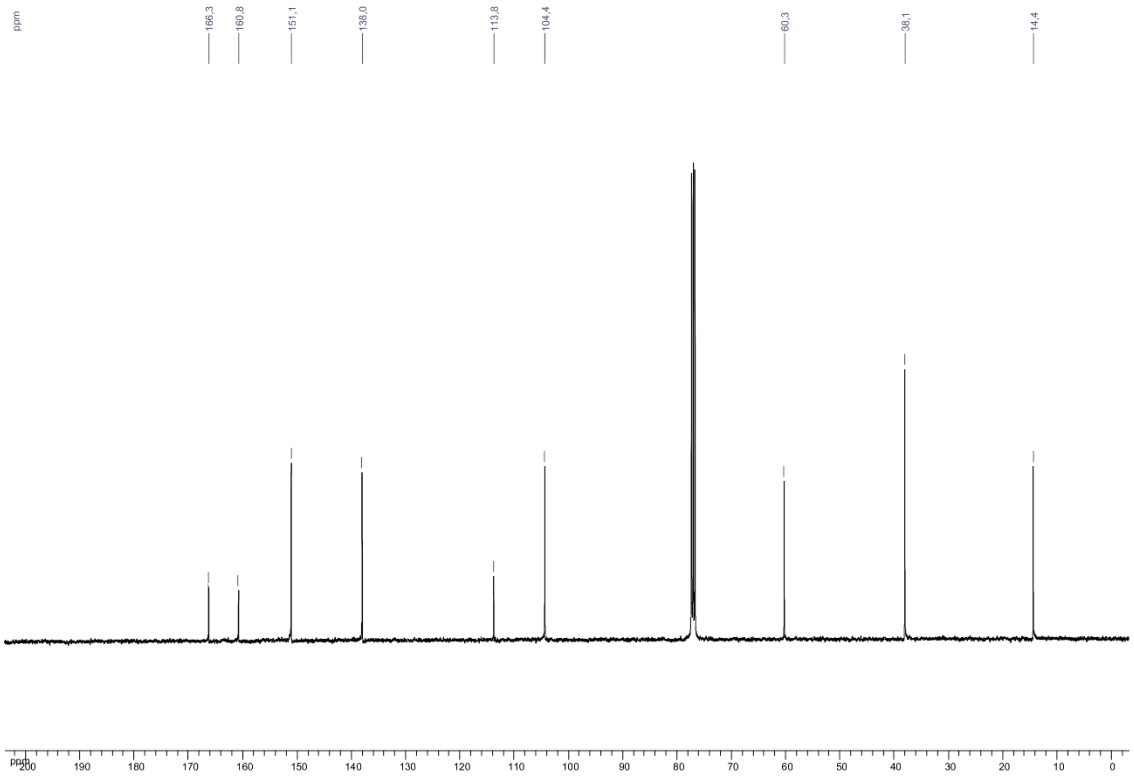
S2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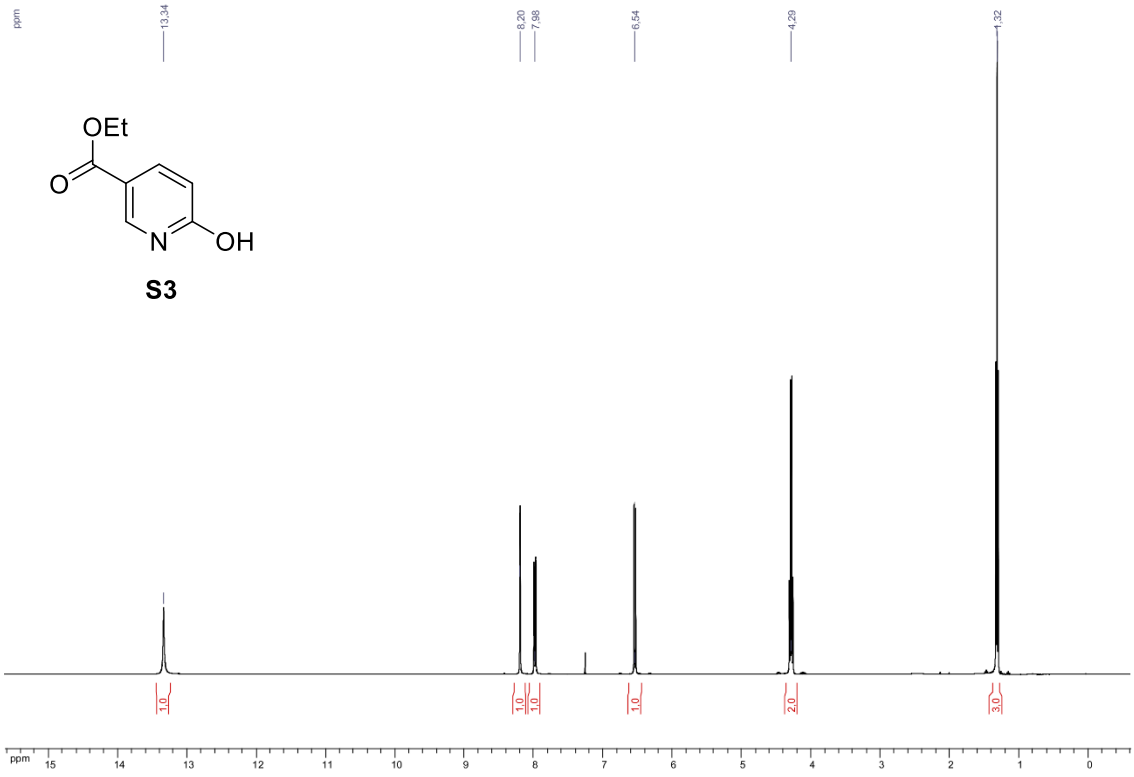
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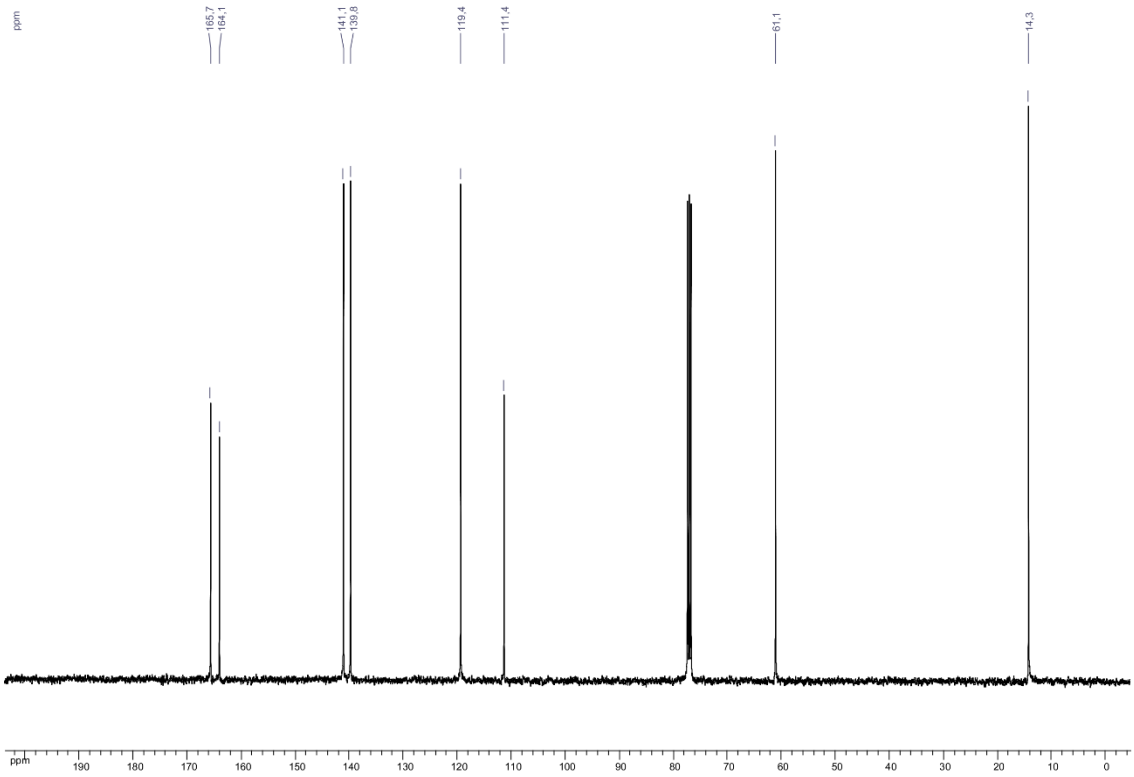
S3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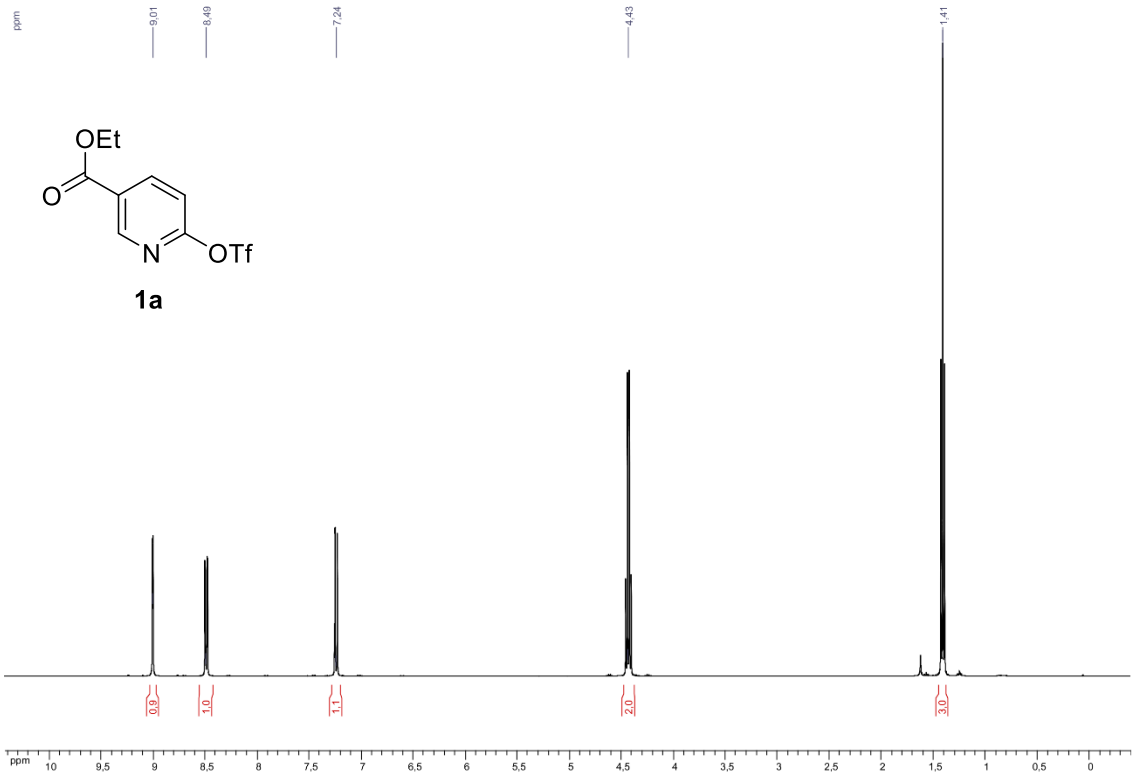
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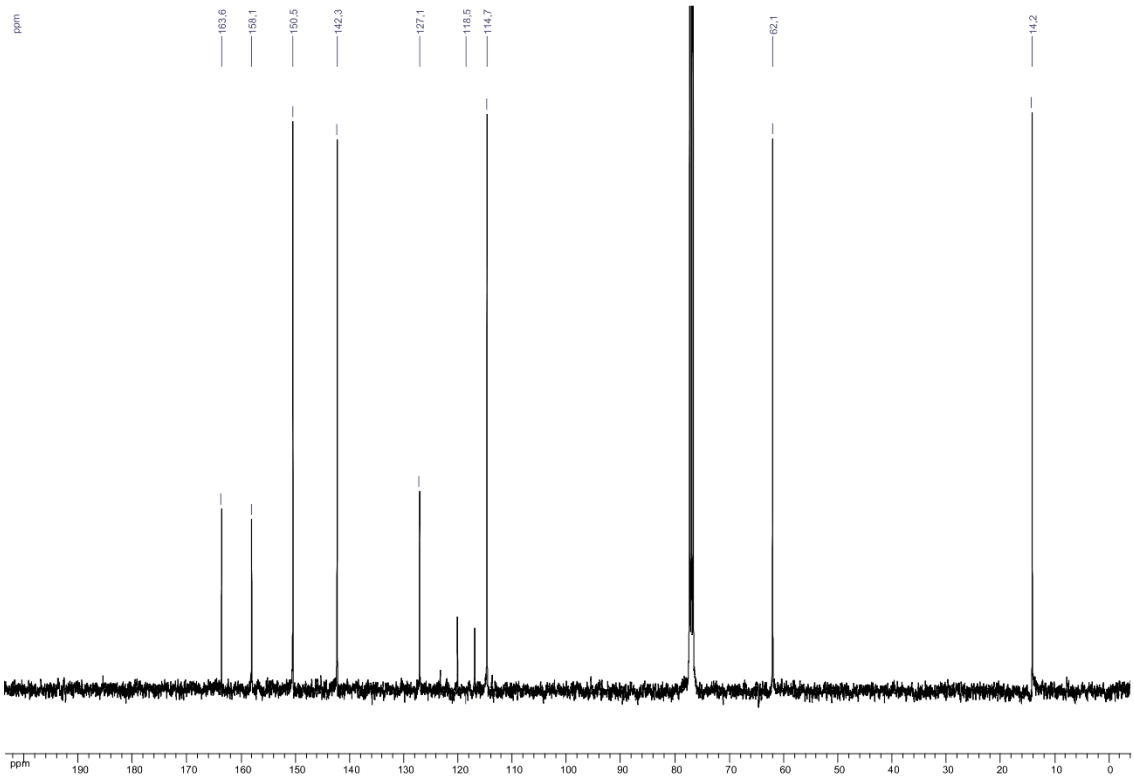
1a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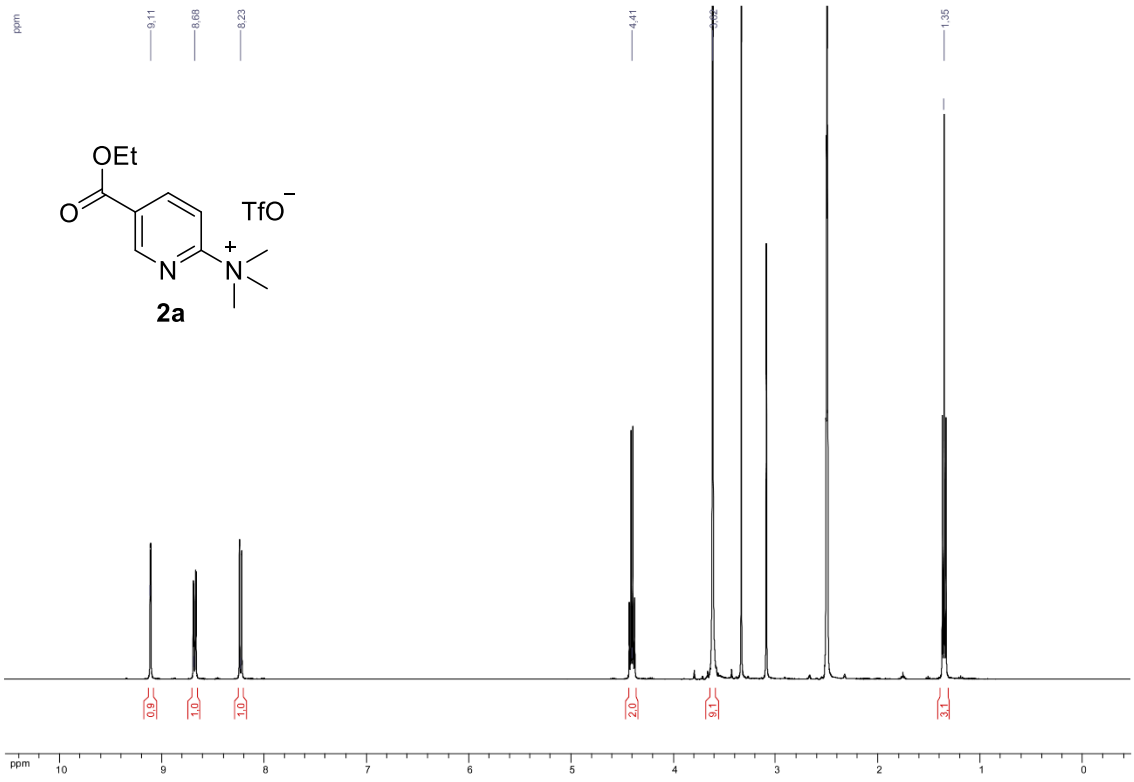
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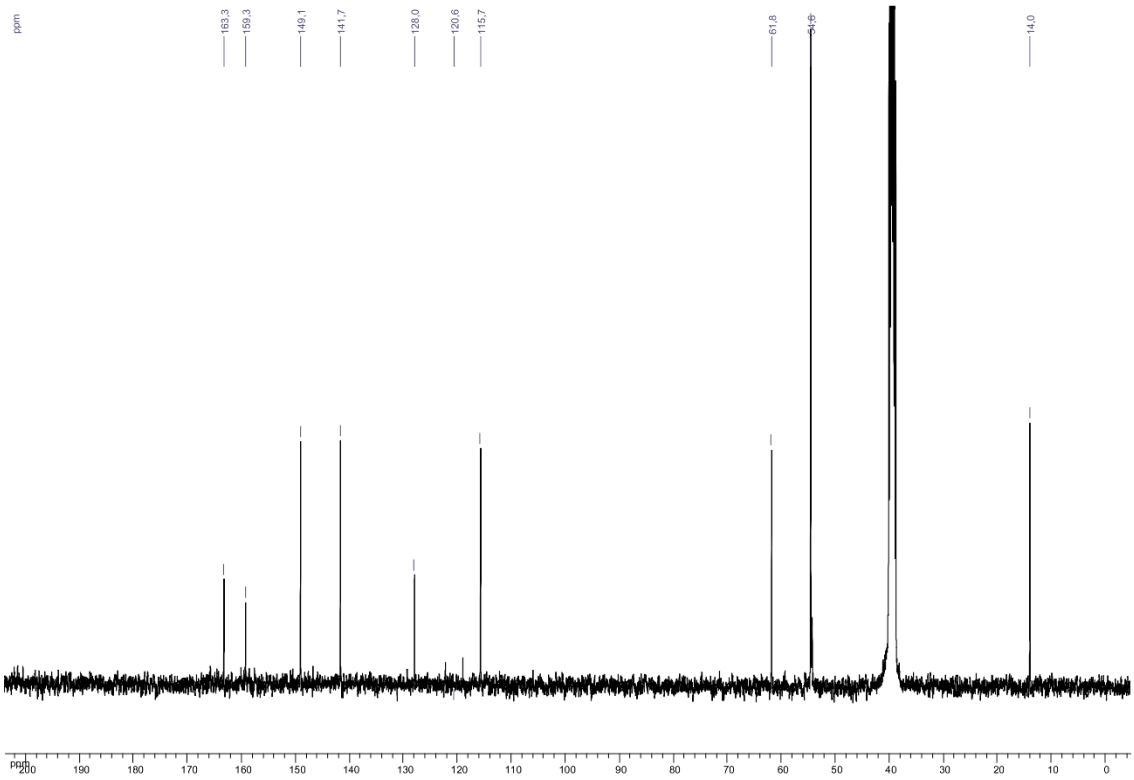
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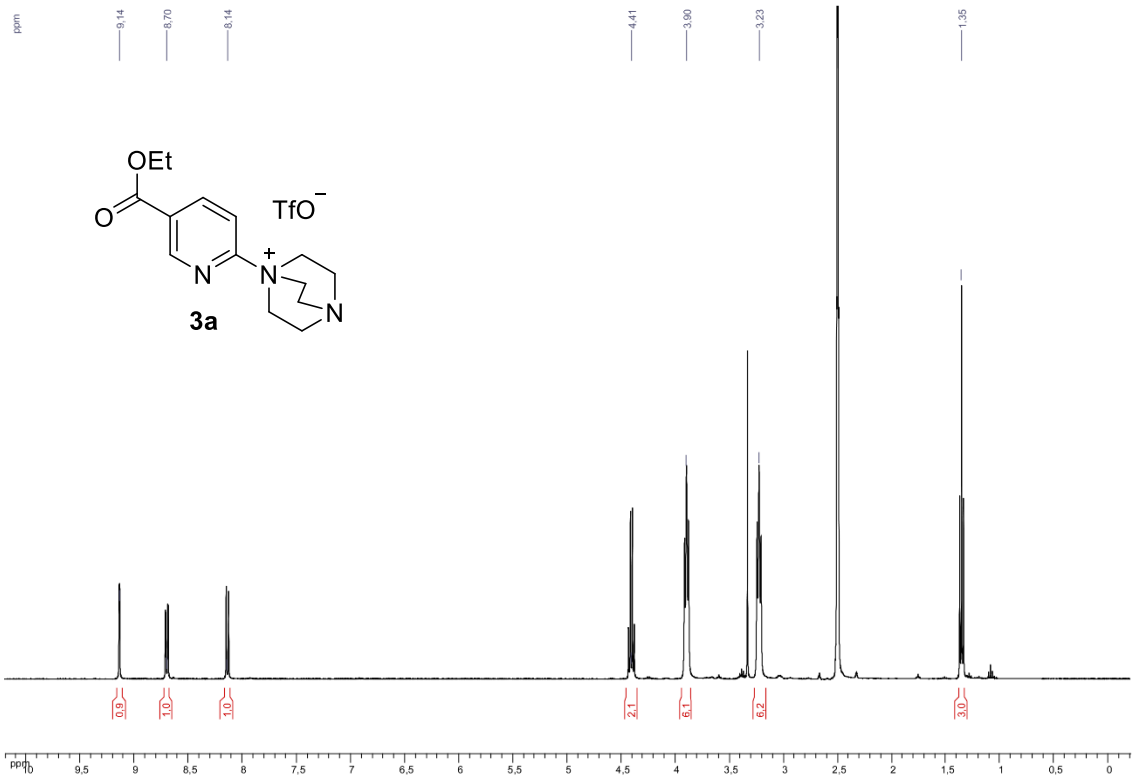
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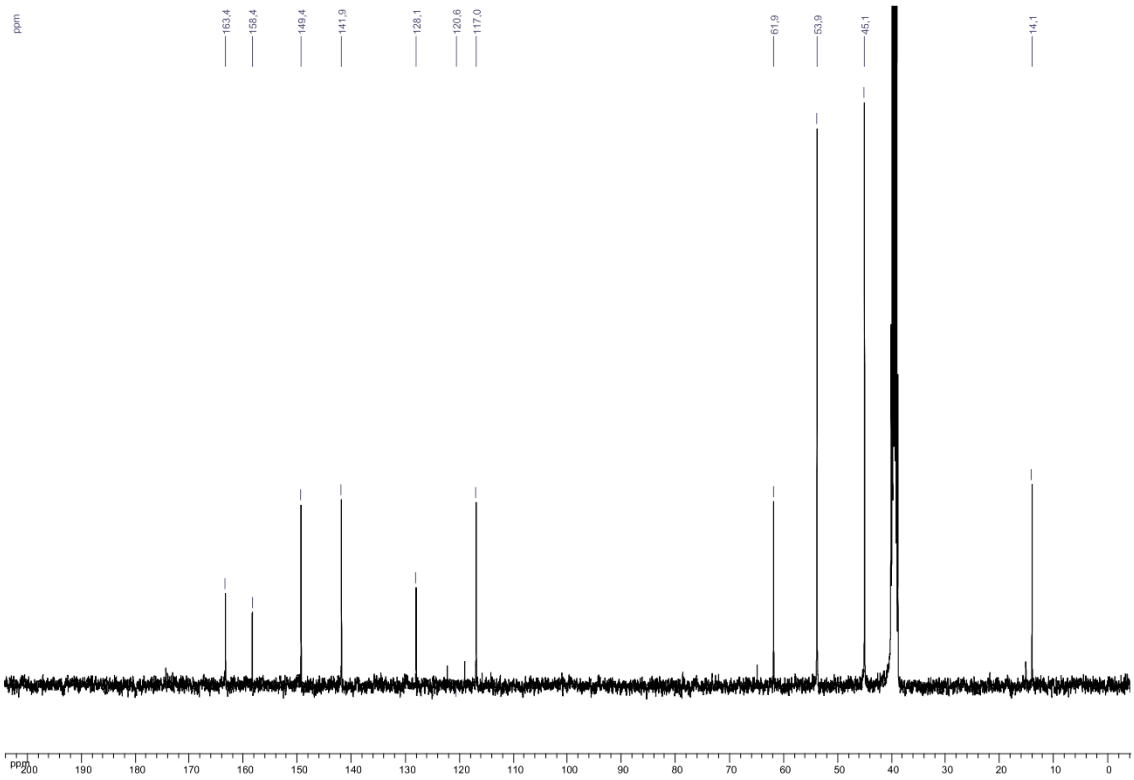
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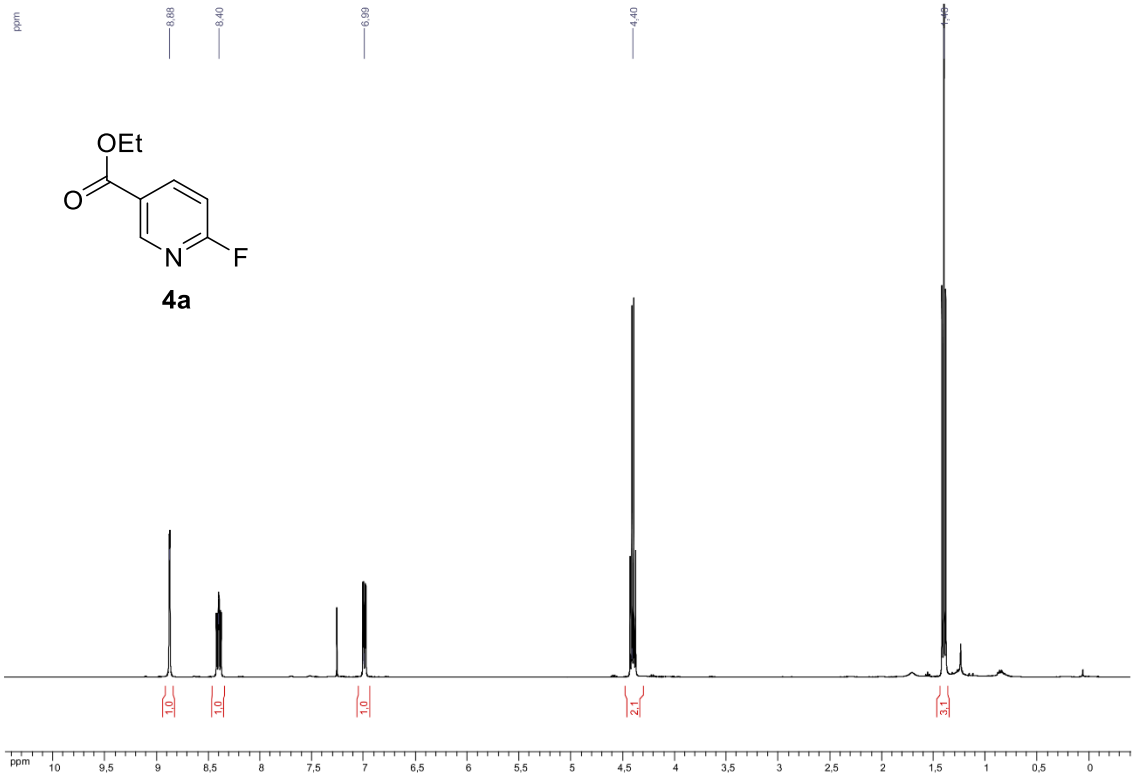
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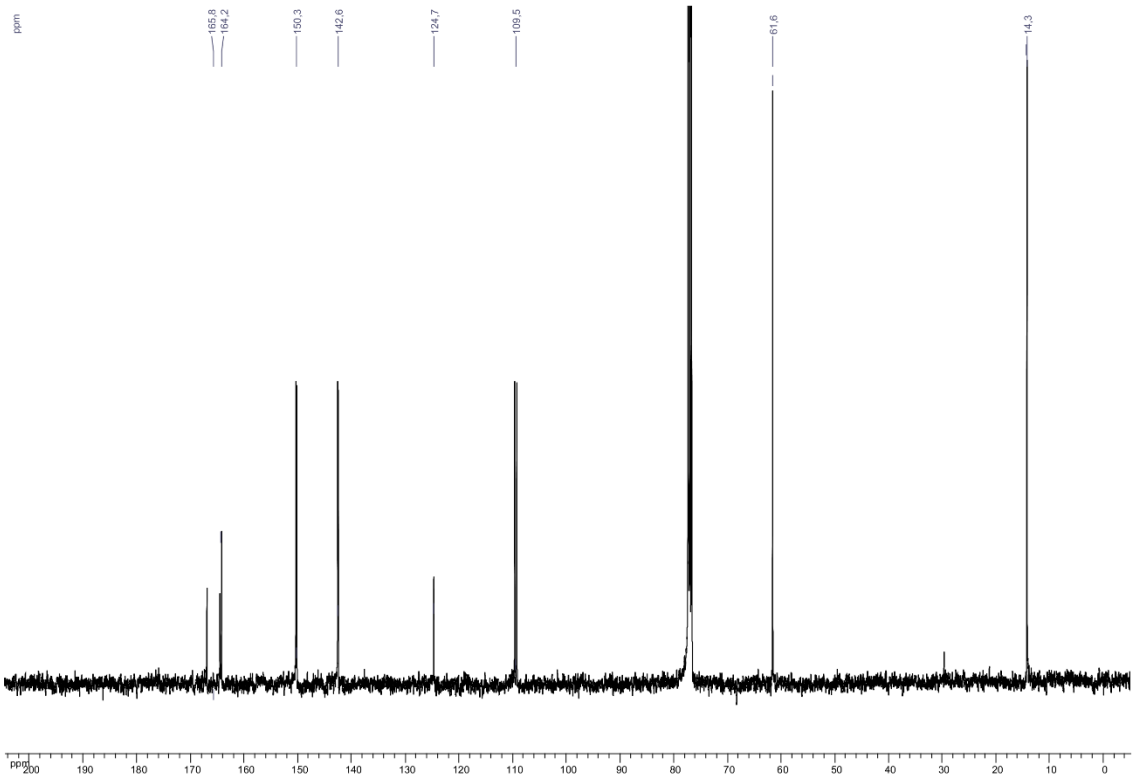
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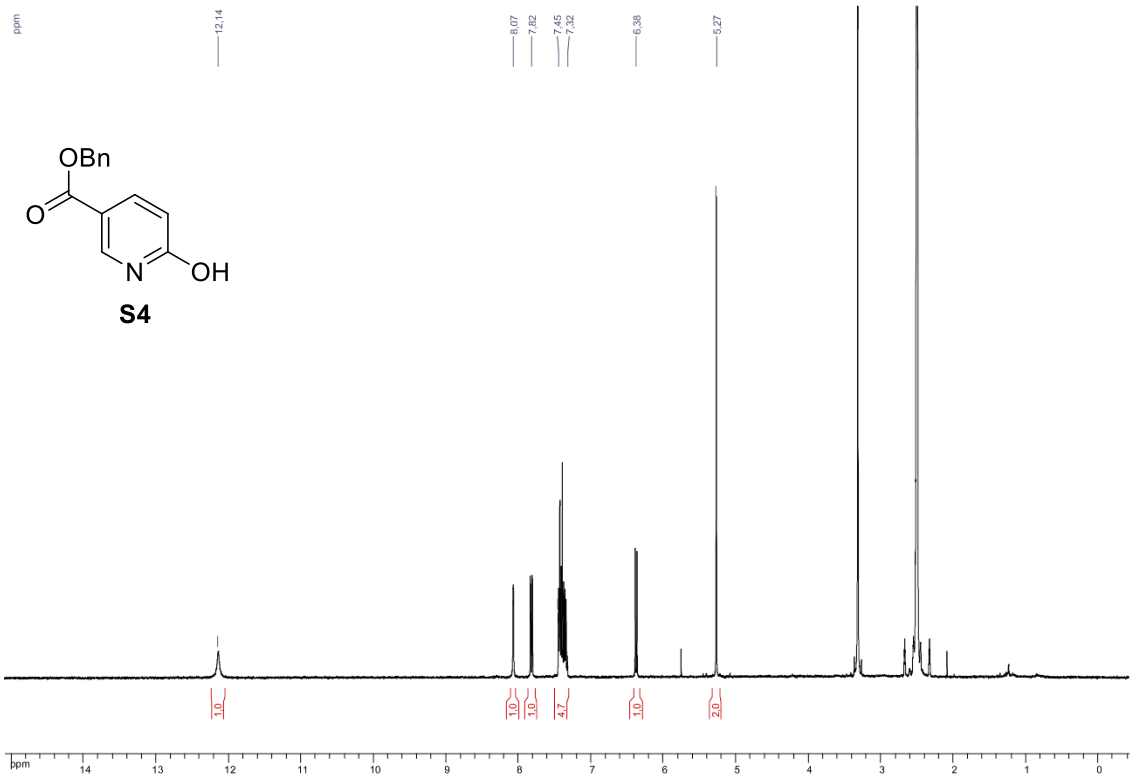
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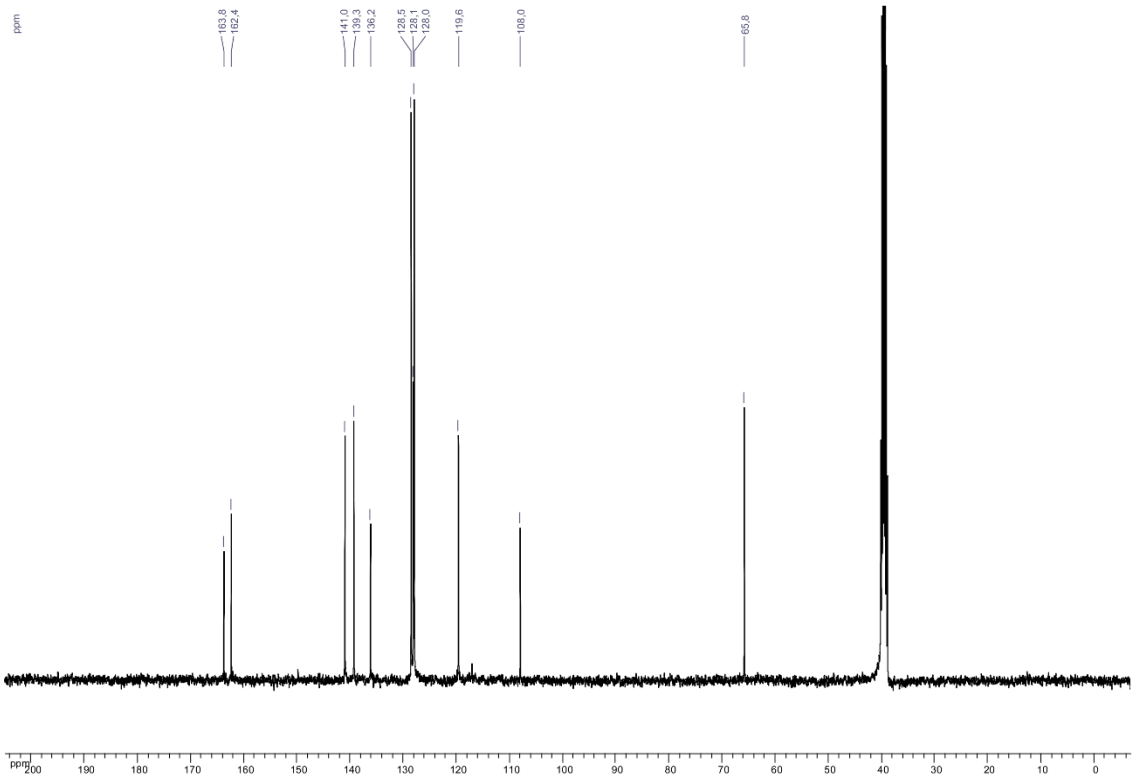
S4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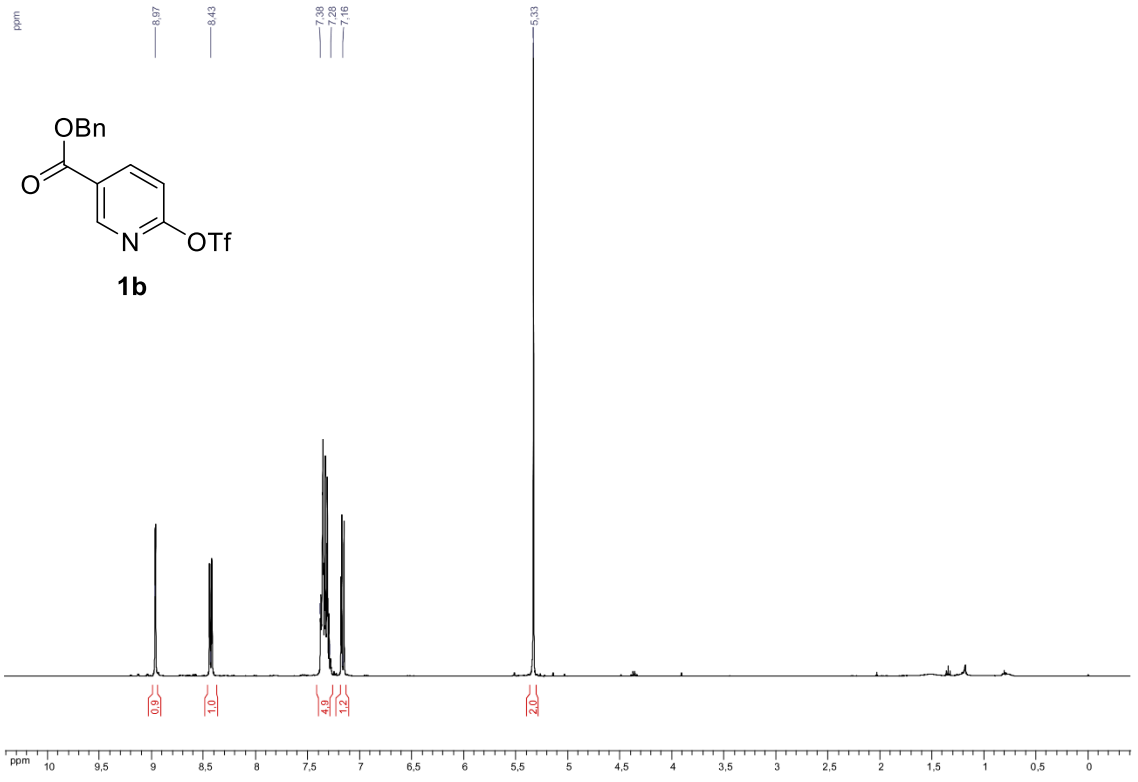
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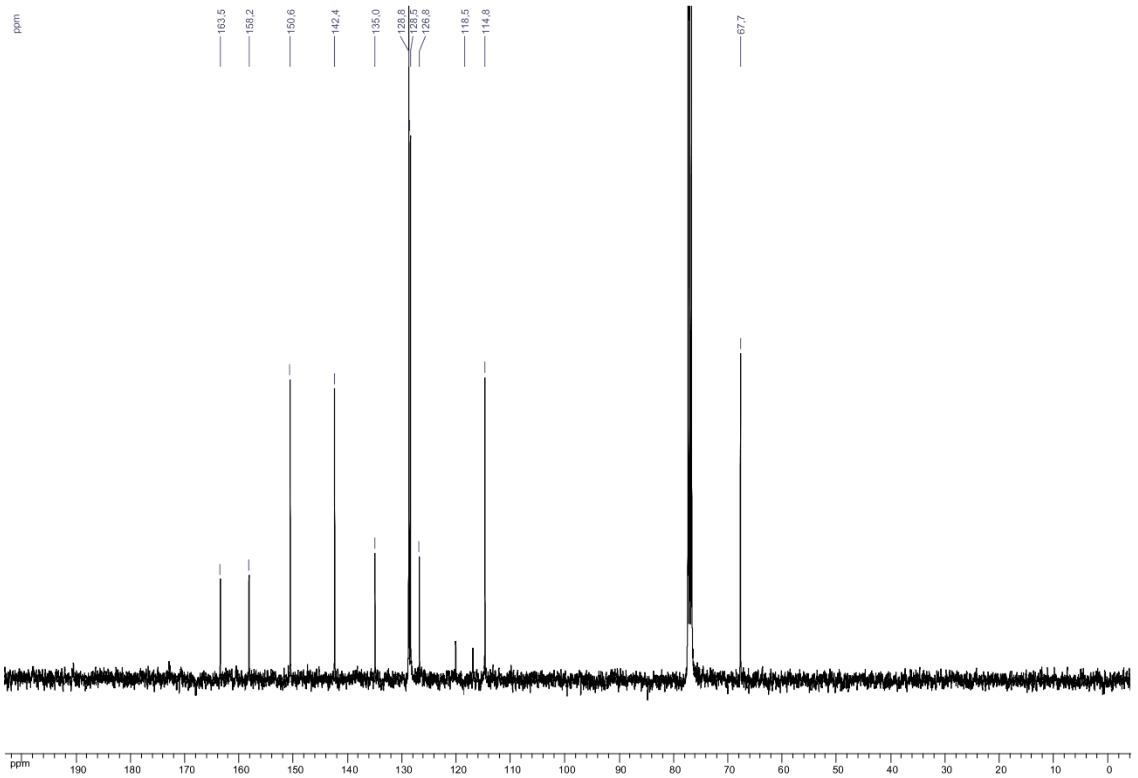
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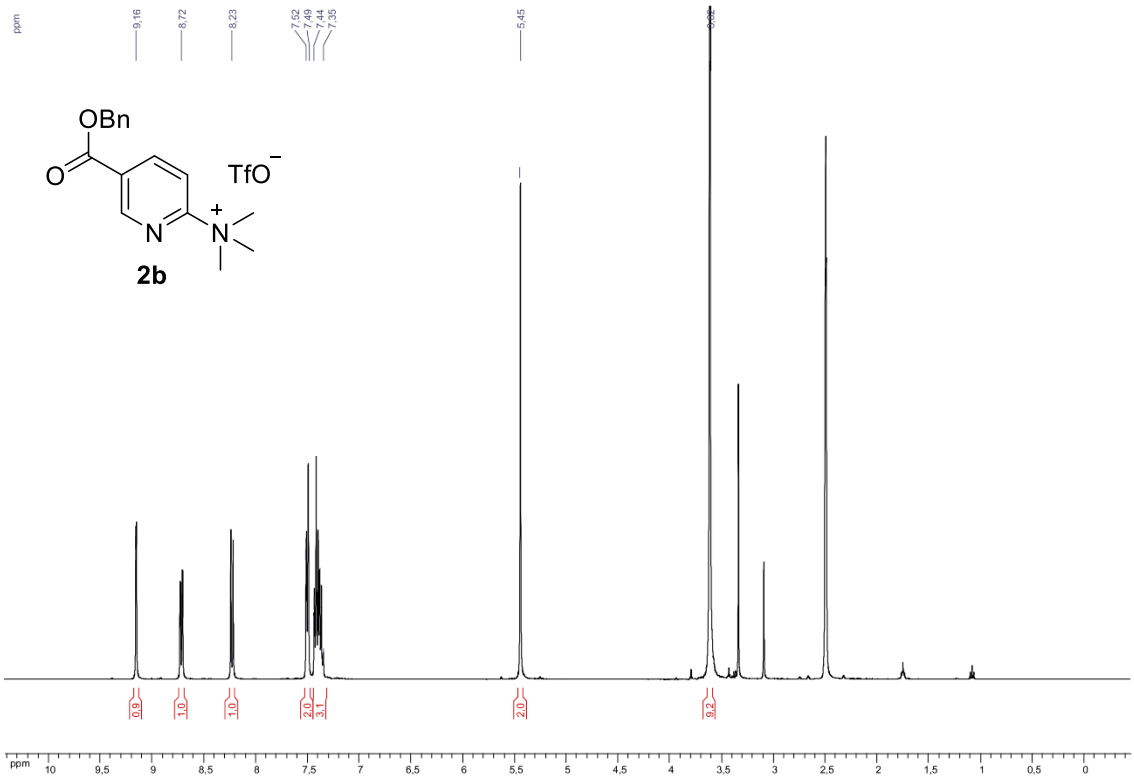
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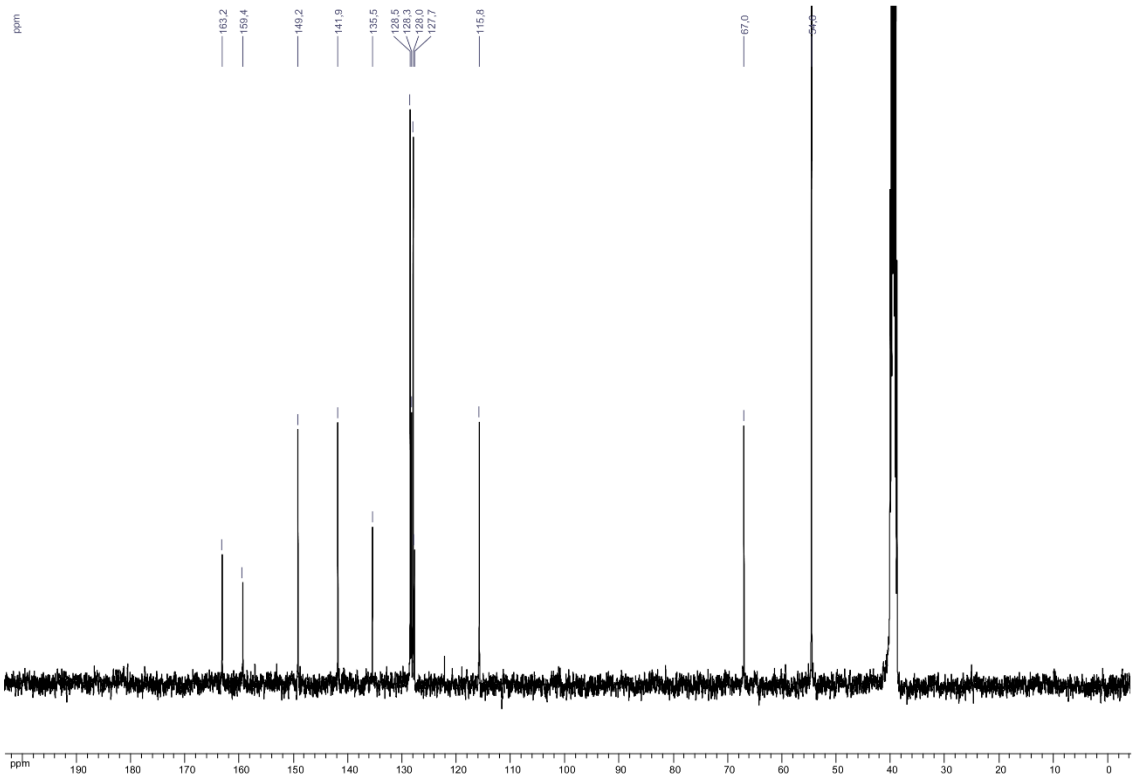
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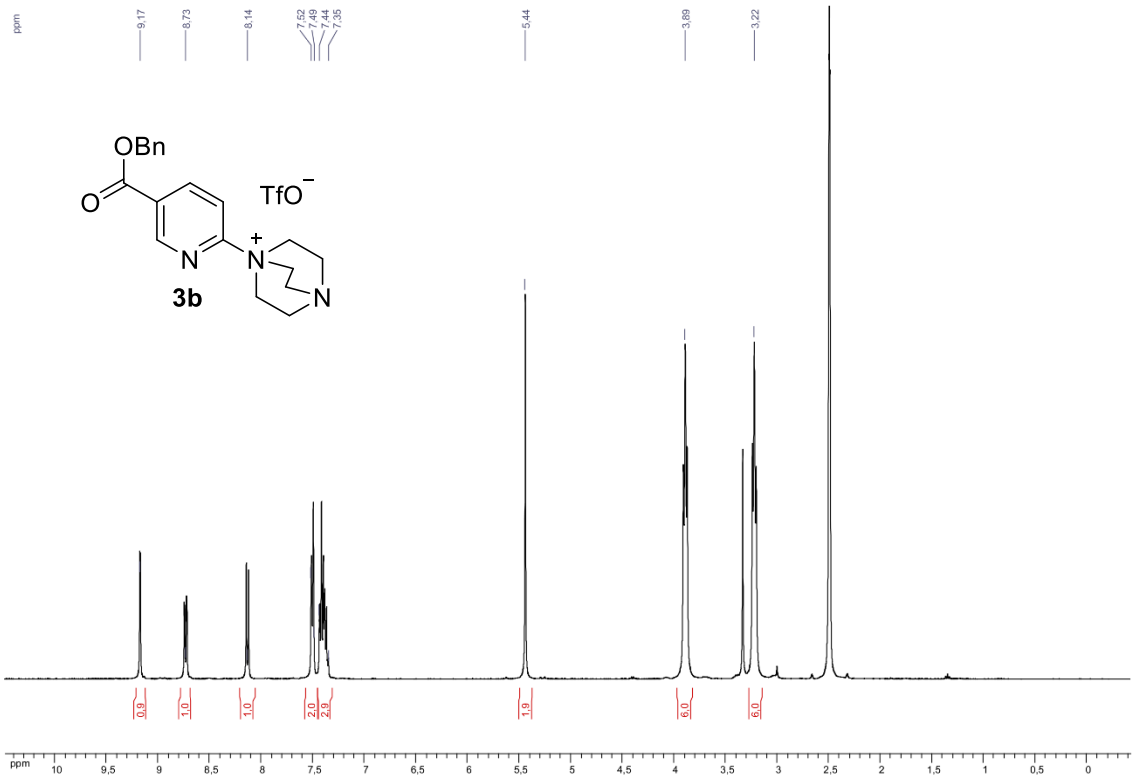
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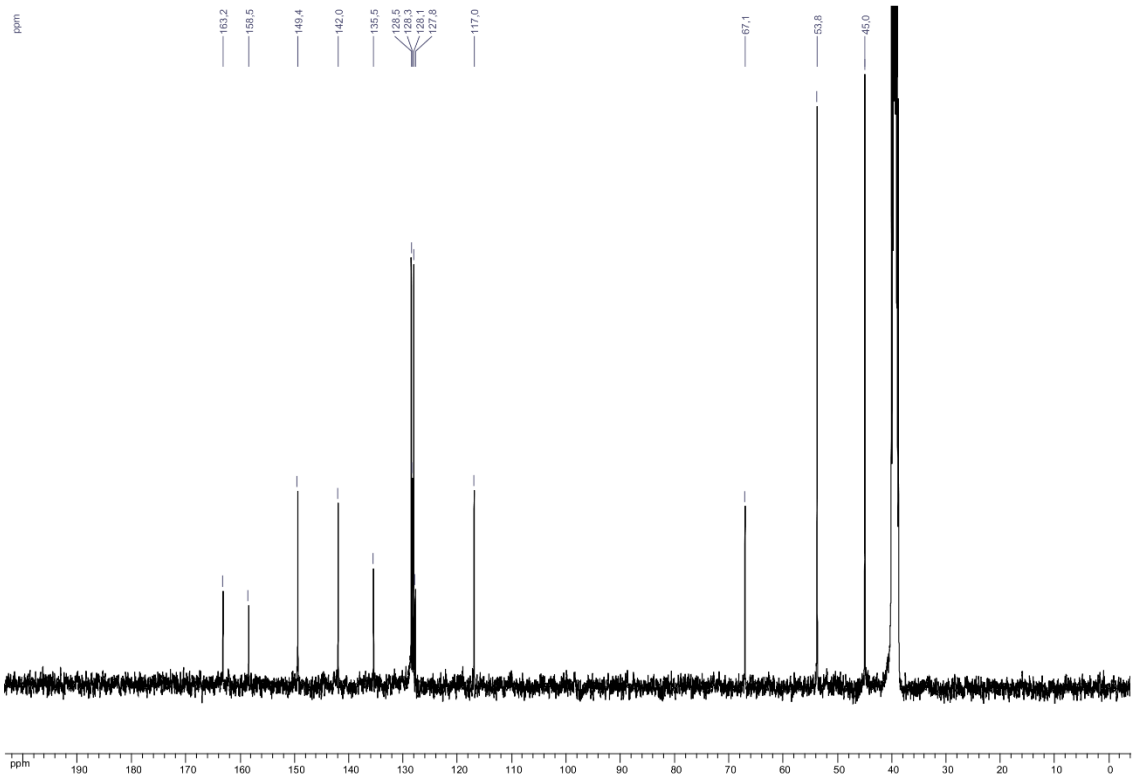
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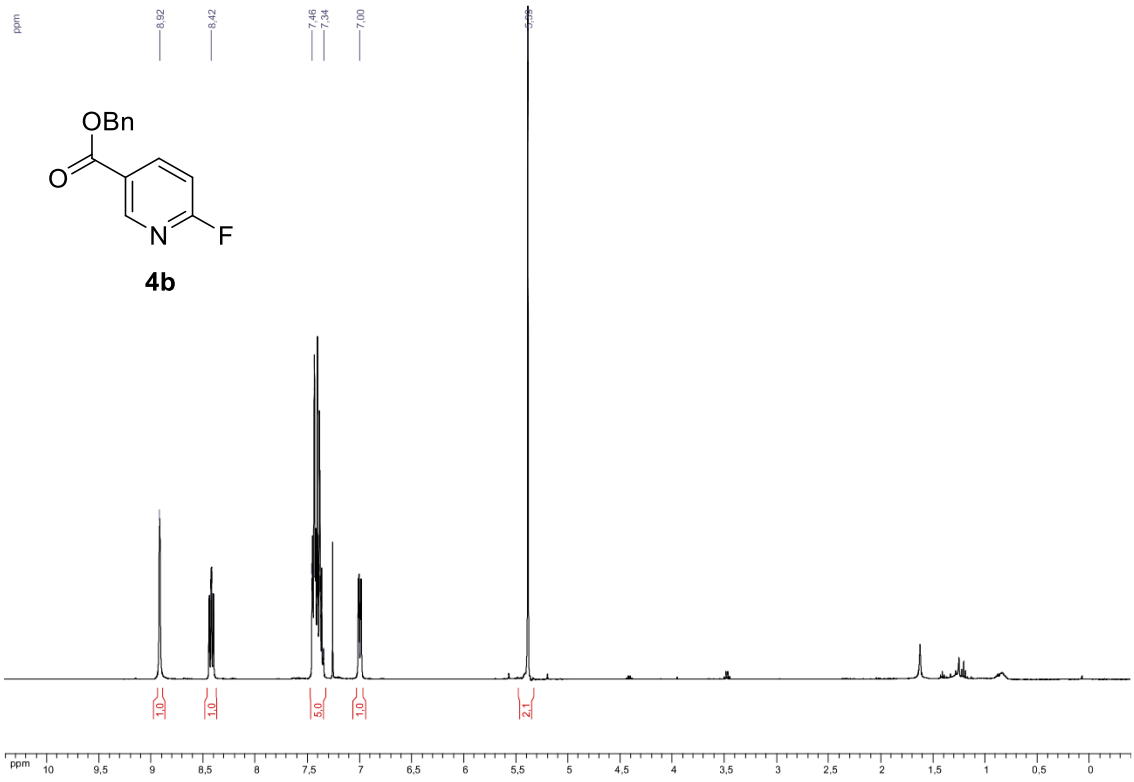
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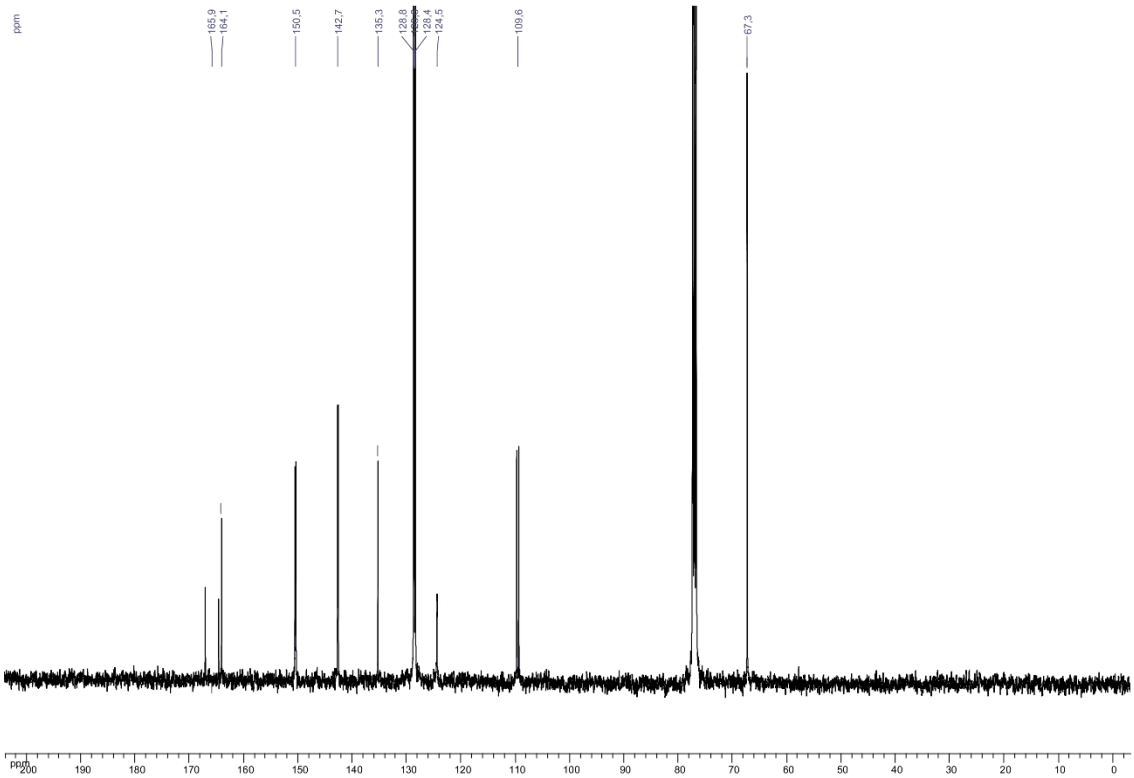
4b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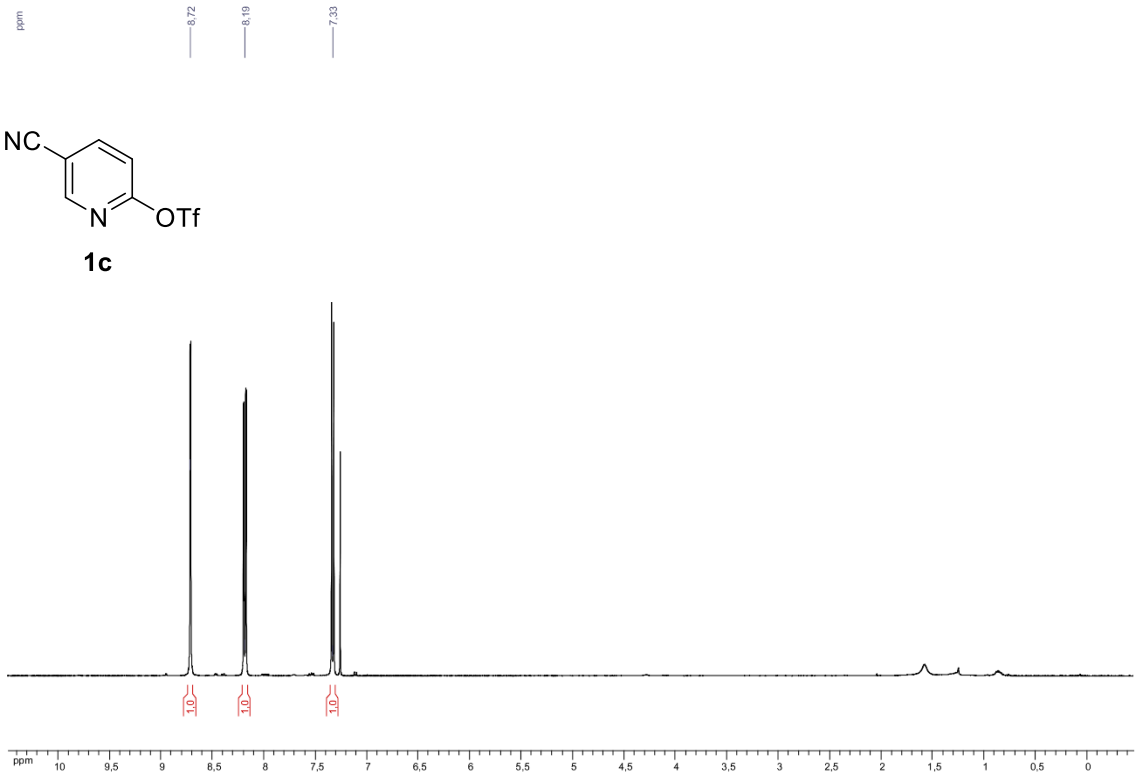
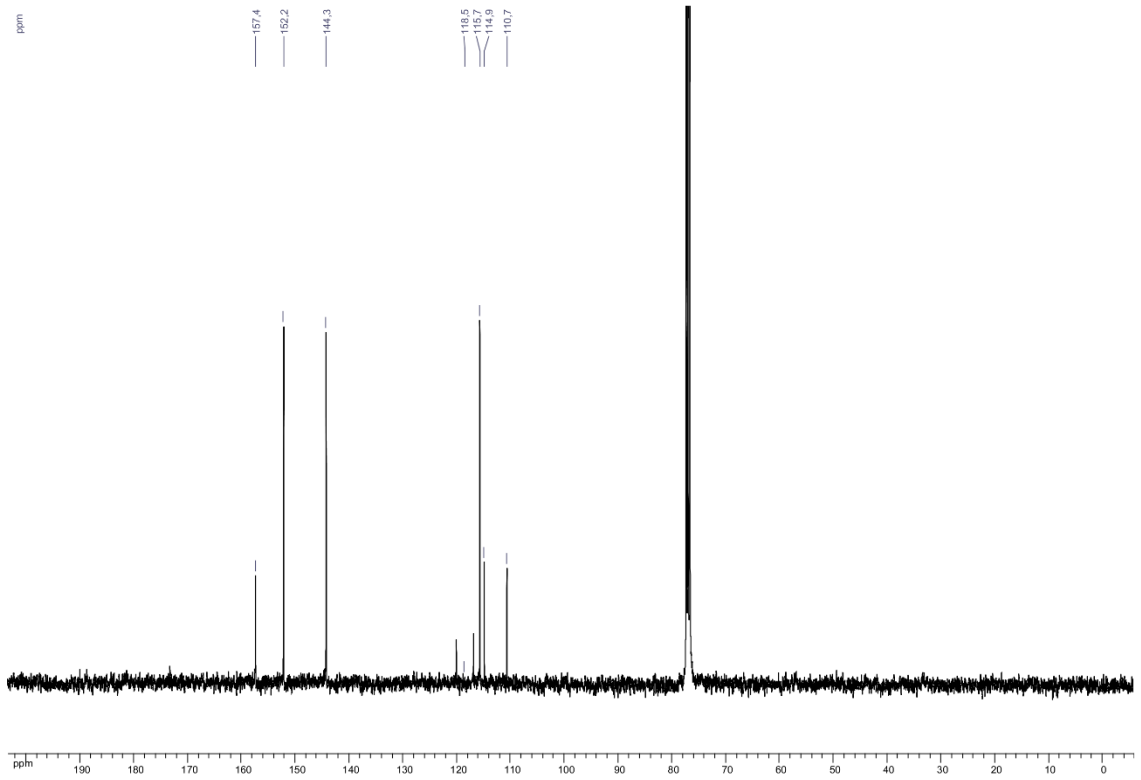
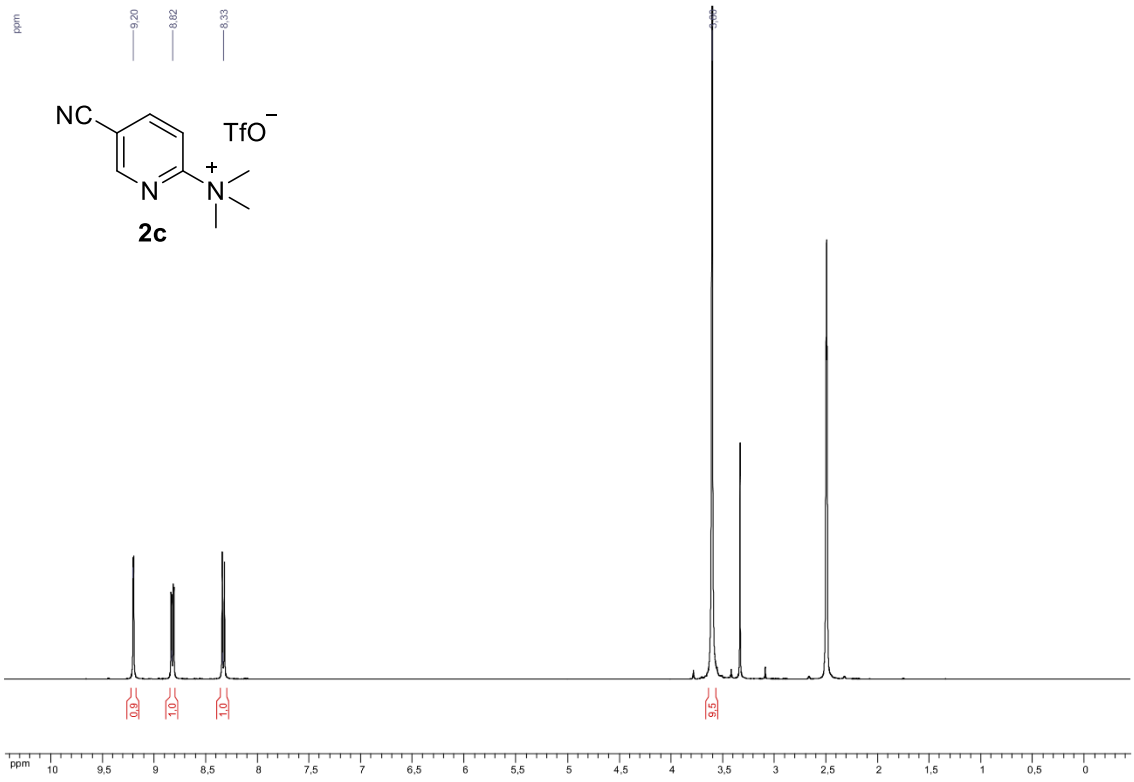
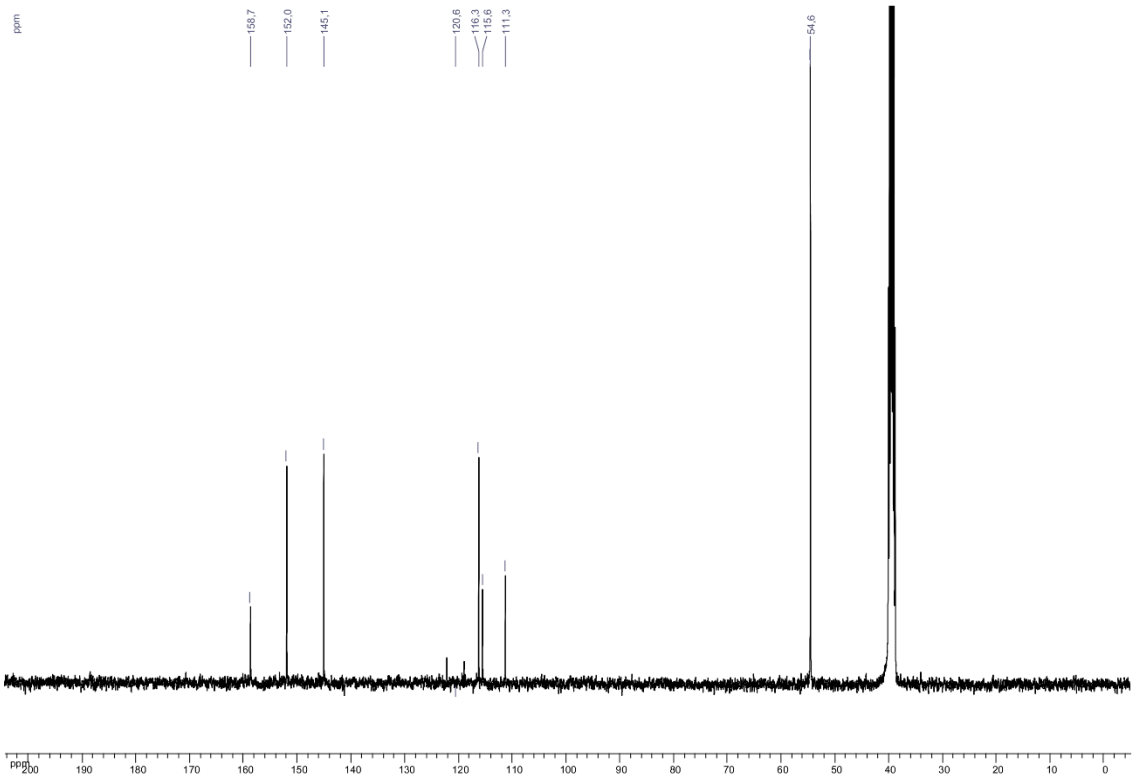
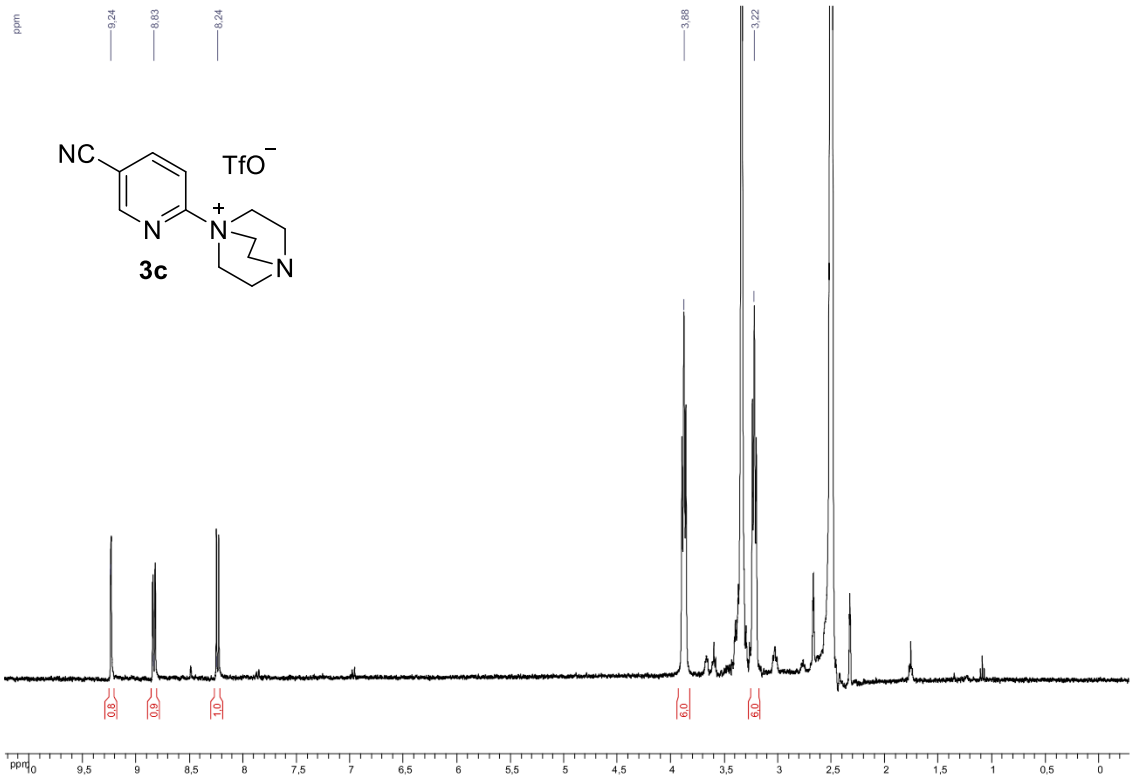
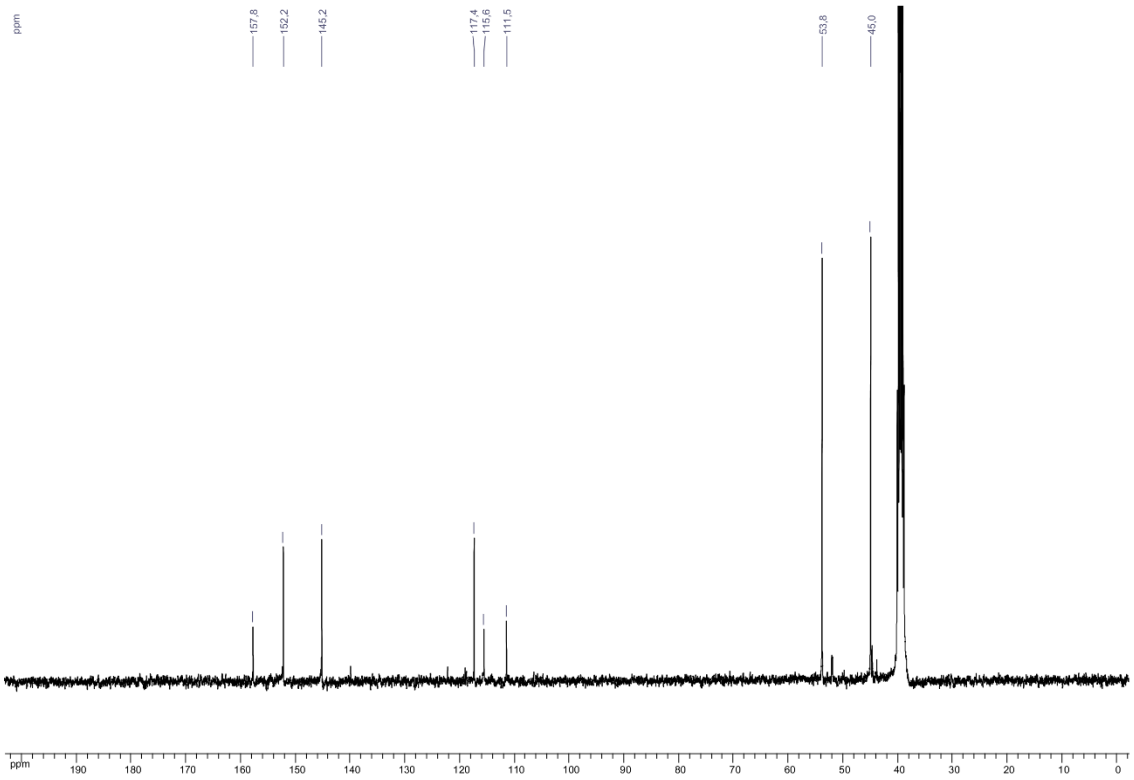

ppm
8,72
8,19
7,33
NC
N
OTf
1c
1,0
1,0
1,0
ppm
10
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0

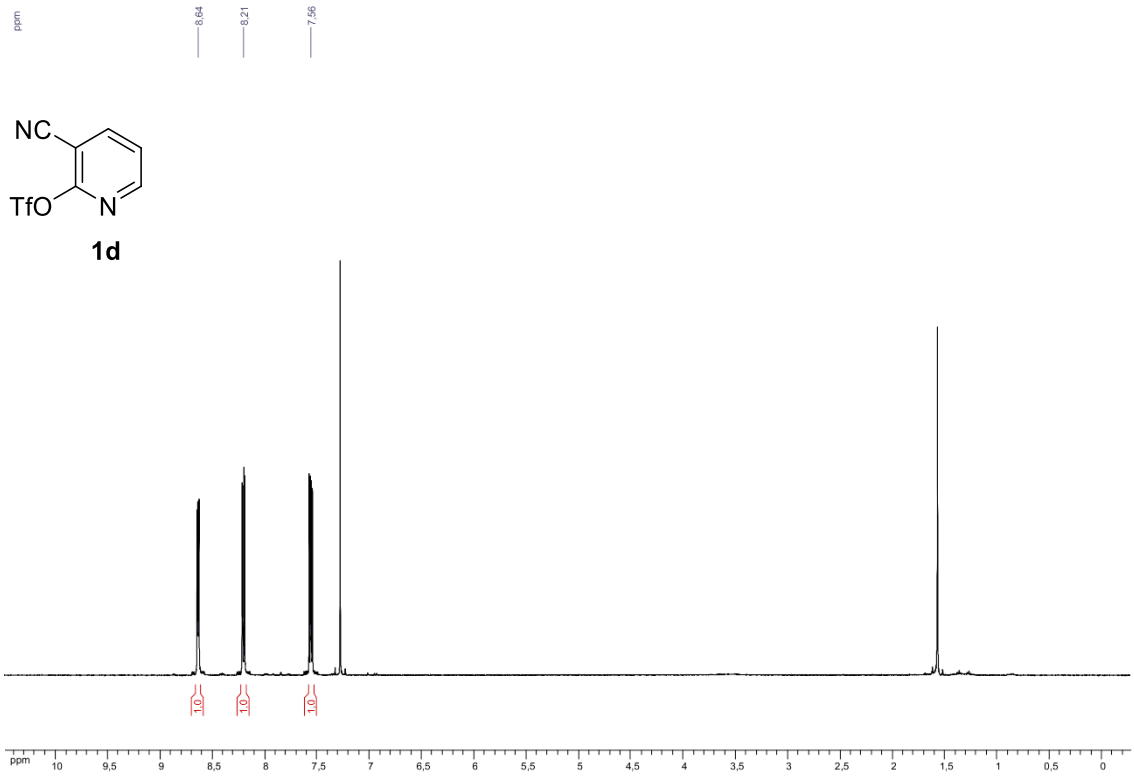

ppm
157,4
152,2
144,3
118,5
115,7
114,9
110,7
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

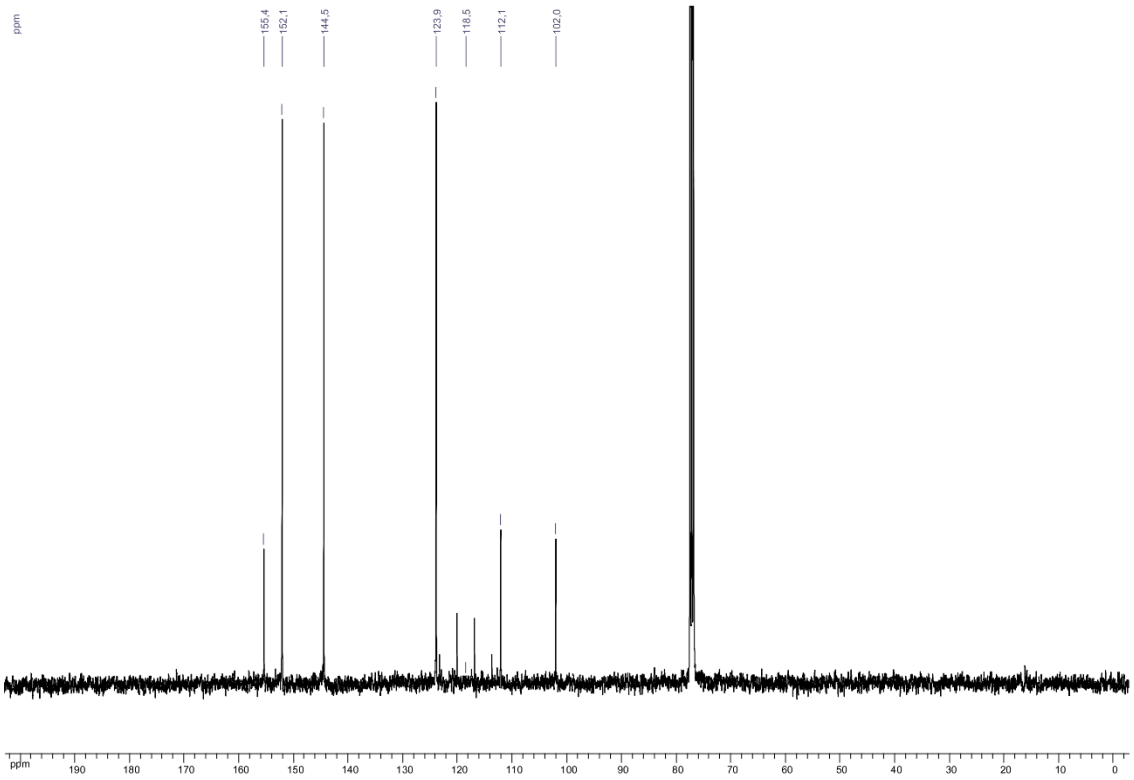

ppm
9,20
8,82
8,33
NC
TfO⁻
N
N⁺
2c
0,9
1,0
1,0
9,5
ppm 10 9,5 9 8,5 8 7,5 7 6,5 6 5,5 5 4,5 4 3,5 3 2,5 2 1,5 1 0,5 0

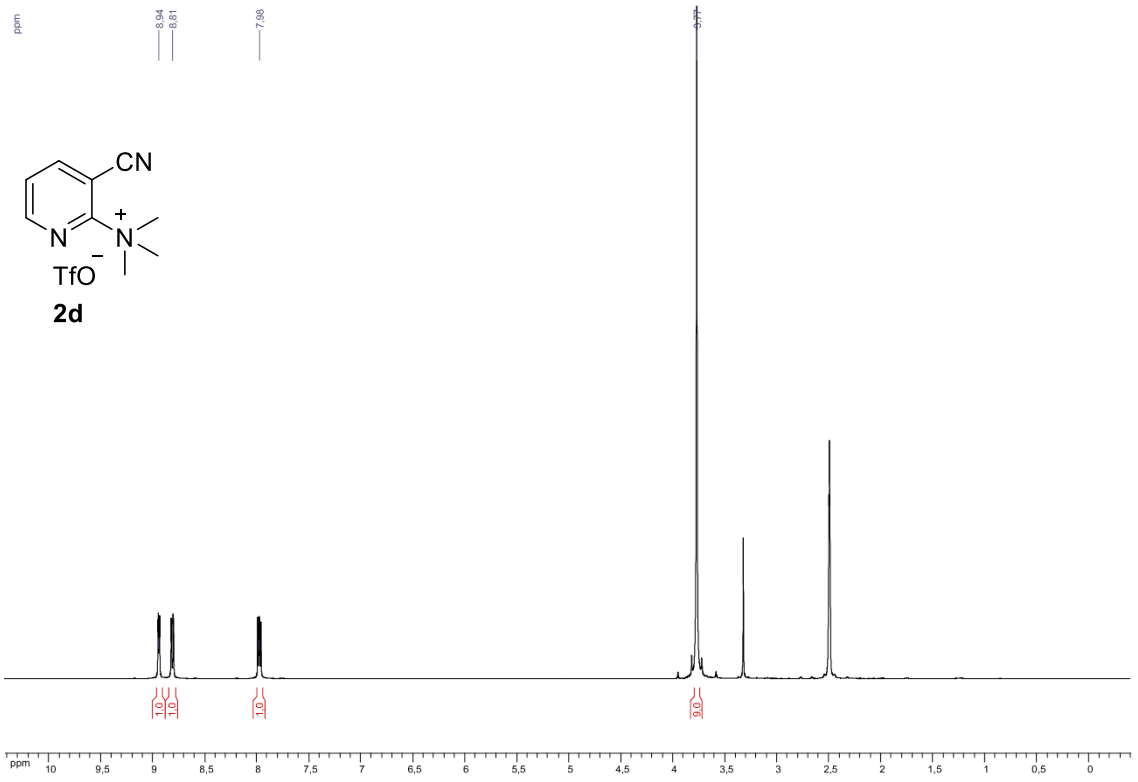

ppm
158,7
152,0
145,1
120,6
116,3
115,6
111,3
54,6
ppm 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


ppm
9,24
8,83
8,24
3,88
3,22
NC
TfO
N
N
N
3c
0,8
0,9
1,0
6,0
6,0
ppm
10
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0

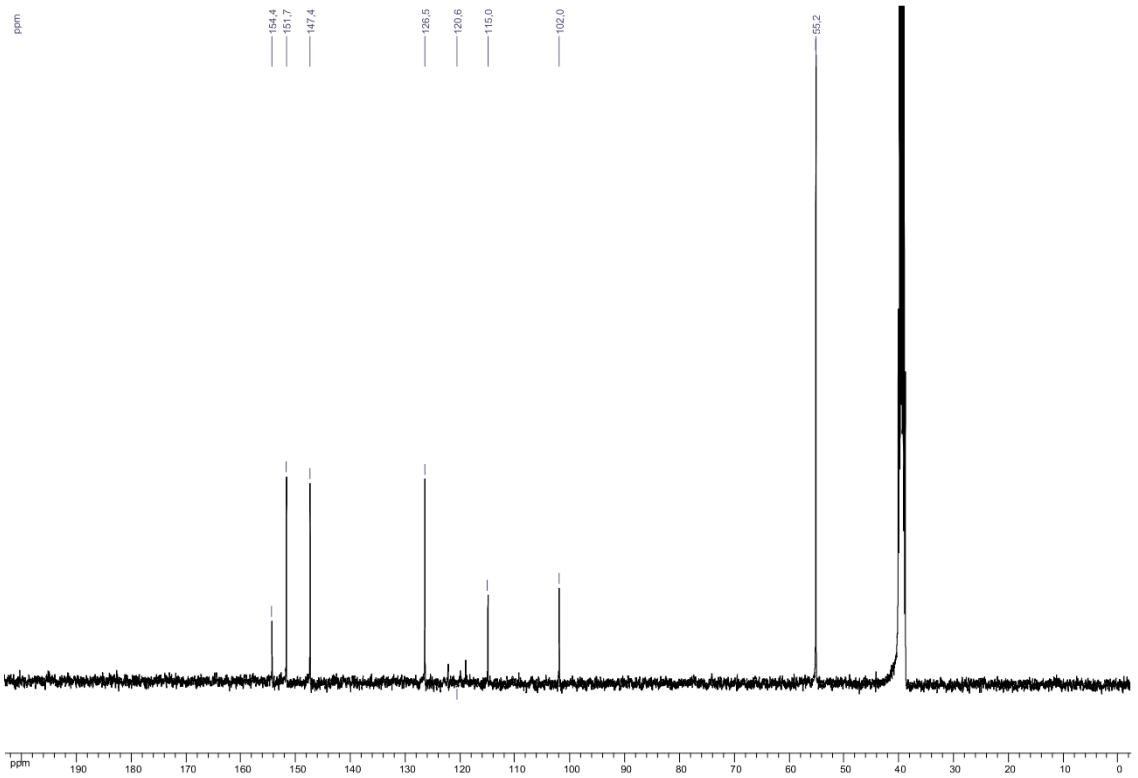

ppm
157,8
152,2
145,2
117,4
115,6
111,5
53,8
45,0
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

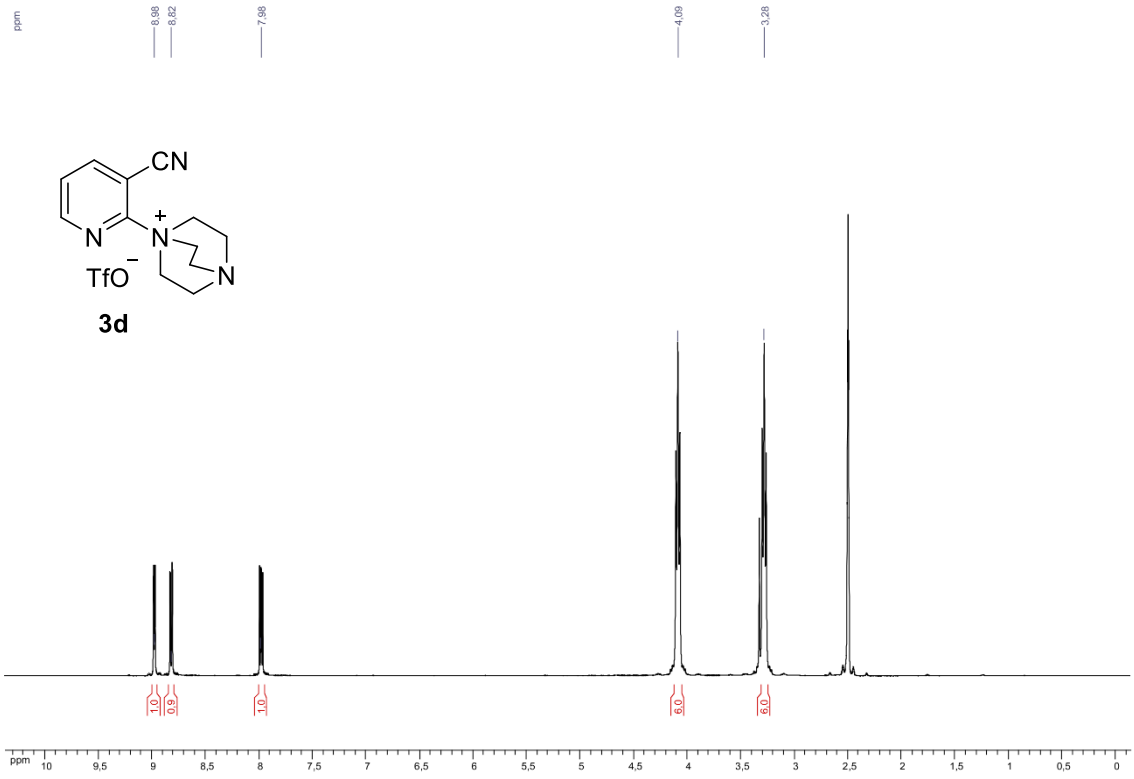

ppm
8.64
8.21
7.56
NC
TfO
N
1d
1.0
1.0
1.0
ppm
10
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0


ppm
155.4
152.1
144.5
123.9
118.5
112.1
102.0
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

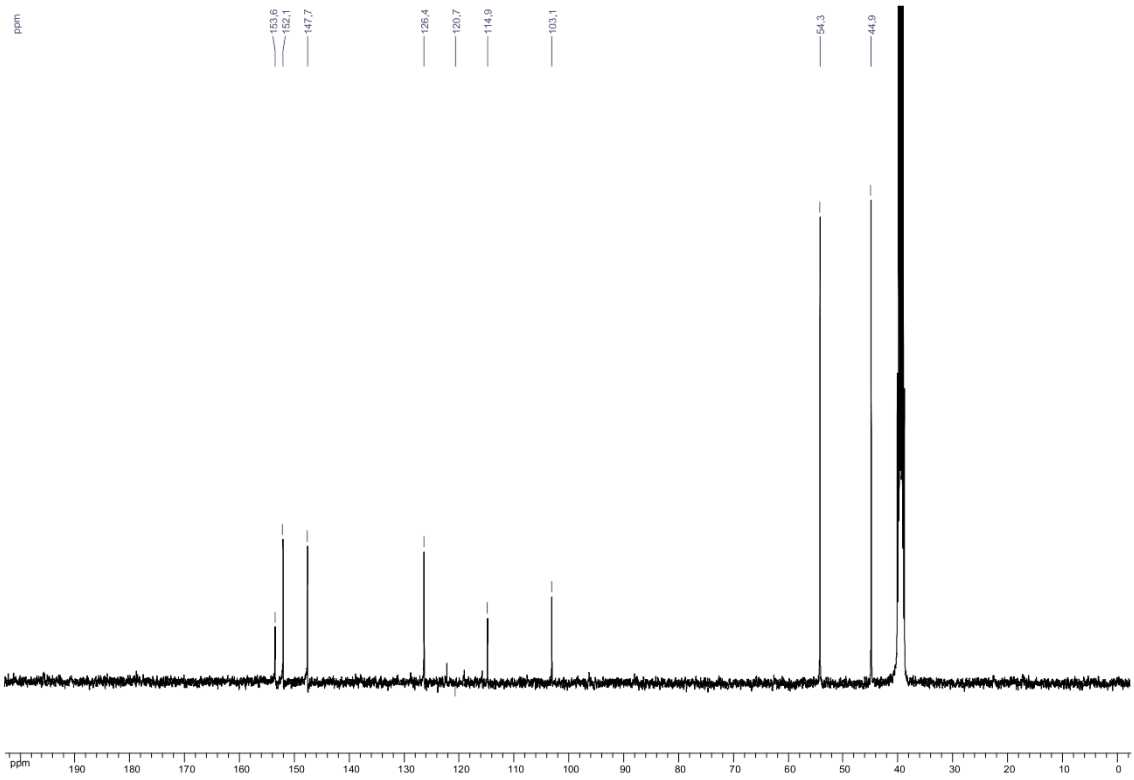

ppm
8,94
8,81
7,98
3,77
CN
N
+
N
TfO
−
1,0
1,0
1,0
3,0
10
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0

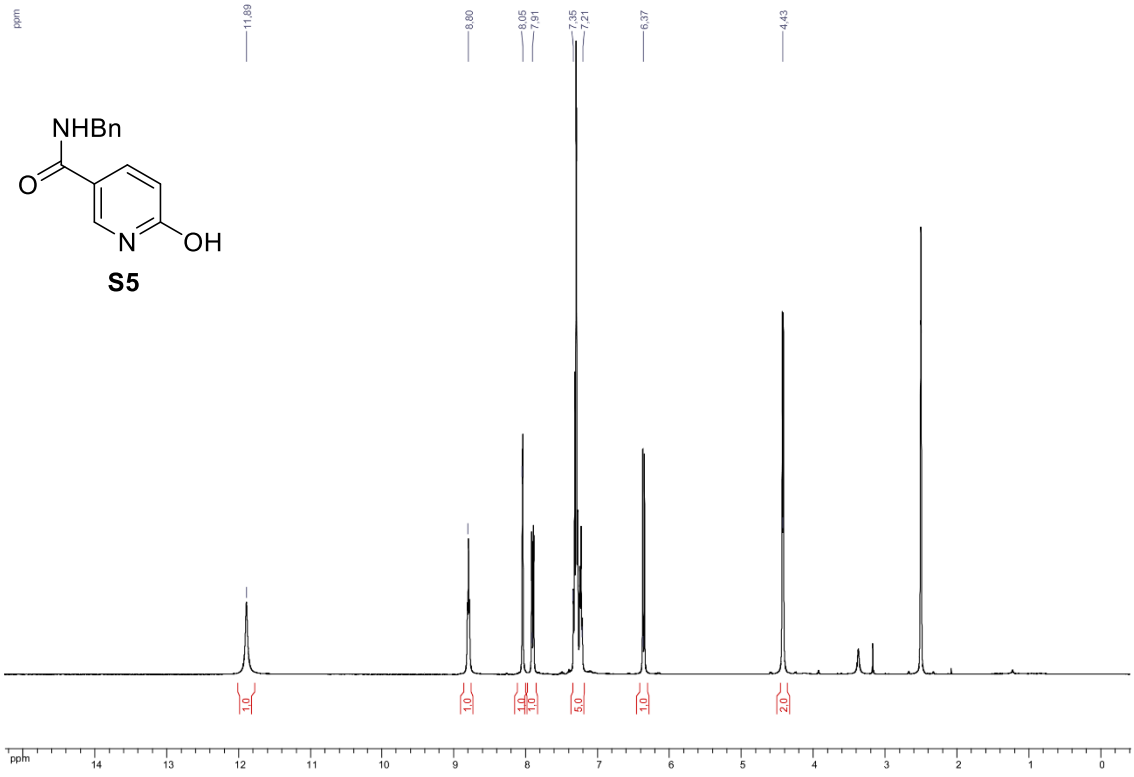
2d

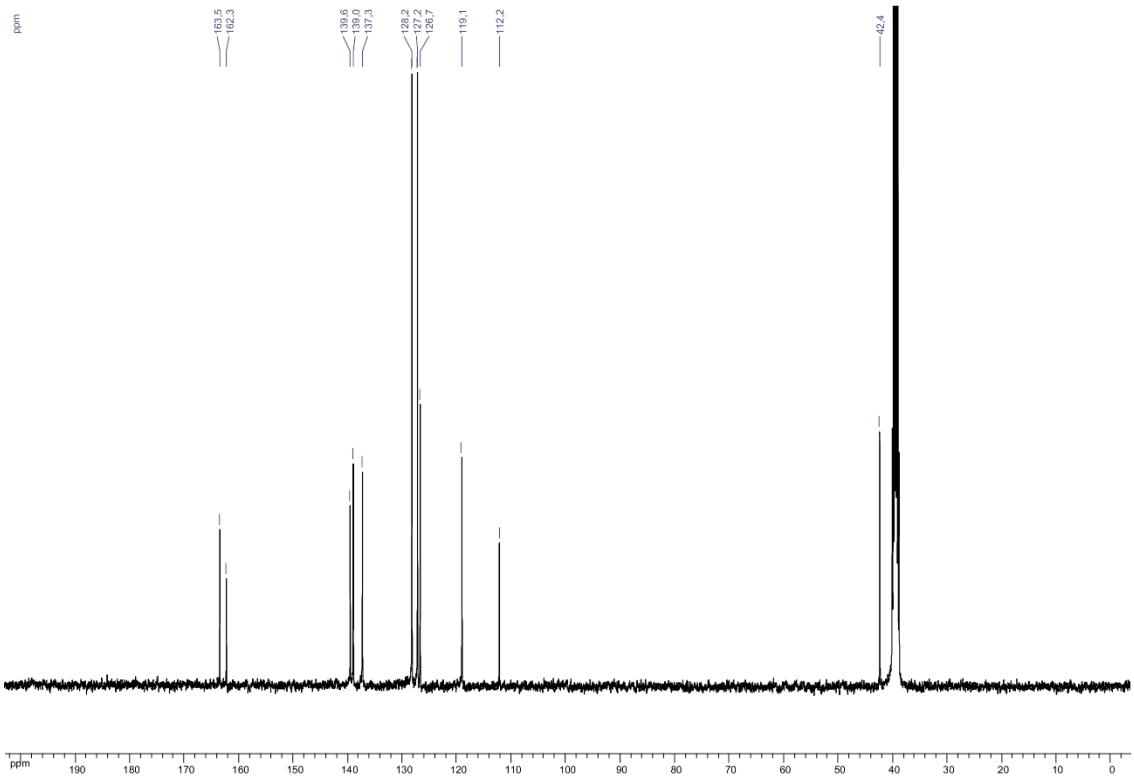

ppm
154,4
151,7
147,4
126,5
120,6
115,0
102,0
55,2
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

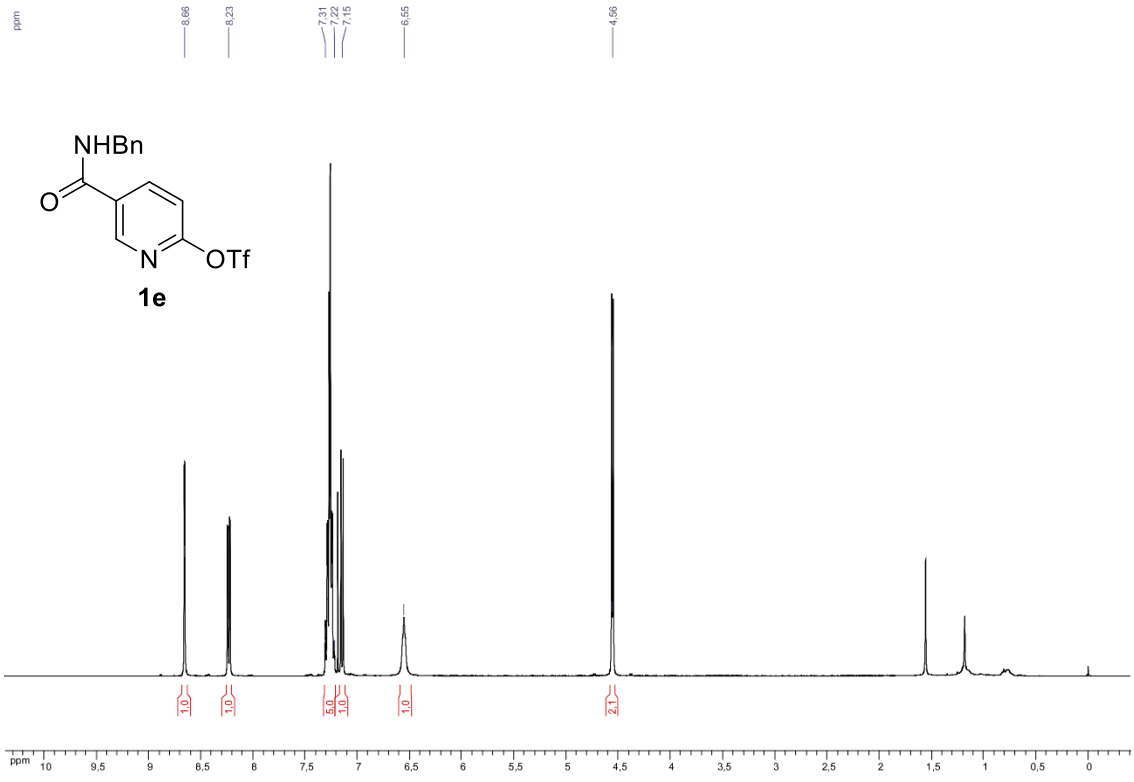

ppm
8,98
8,82
7,98
4,09
3,28
CN
N
N
+
TfO
−
N
1,0
0,9
1,0
6,0
6,0
ppm
10
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0

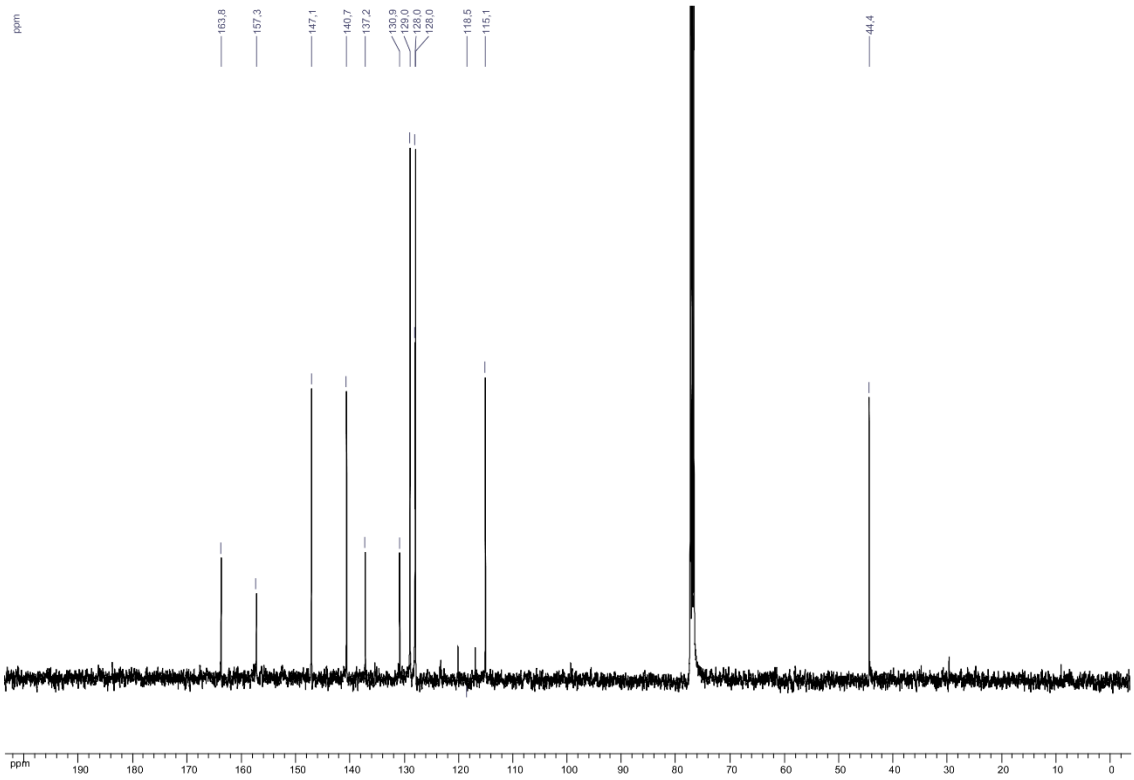
3d

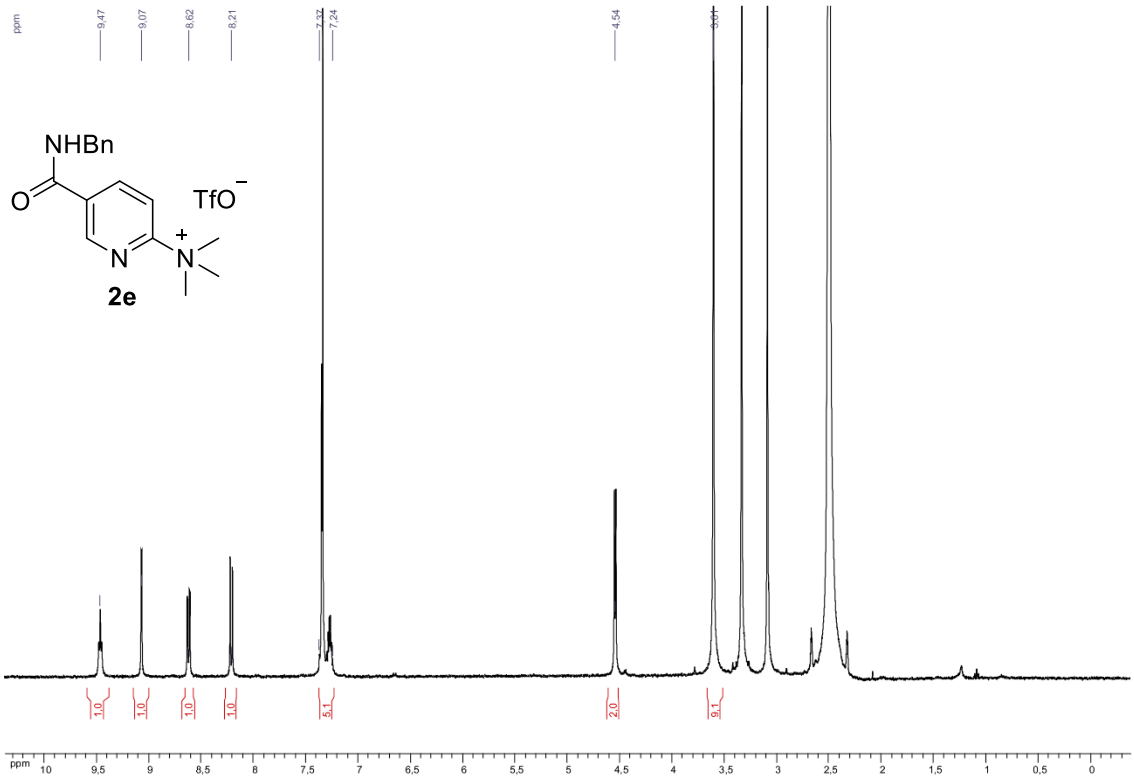

ppm
153,6
152,1
147,7
126,4
120,7
114,9
103,1
54,3
44,9
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

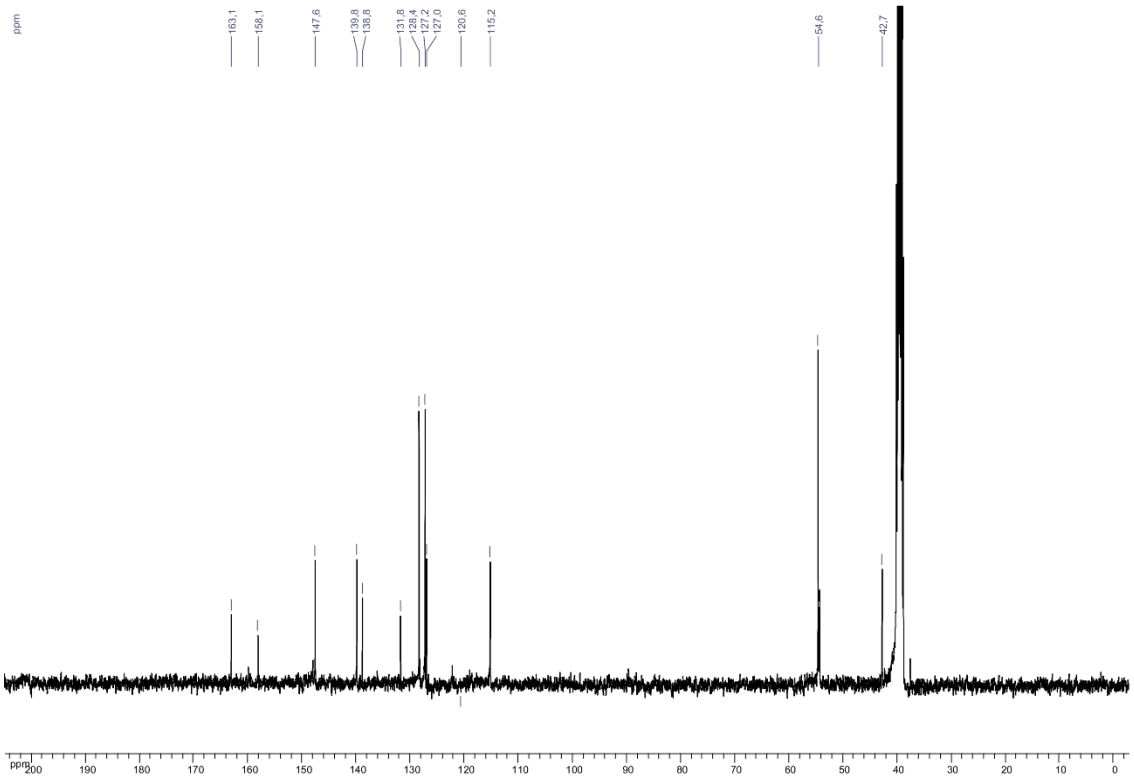

ppm
11.89
8.80
8.05
7.91
7.35
7.21
6.37
4.43
NHBn
O
N
OH
S5
1.0
1.0
1.0
1.0
5.0
1.0
2.0
ppm
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0

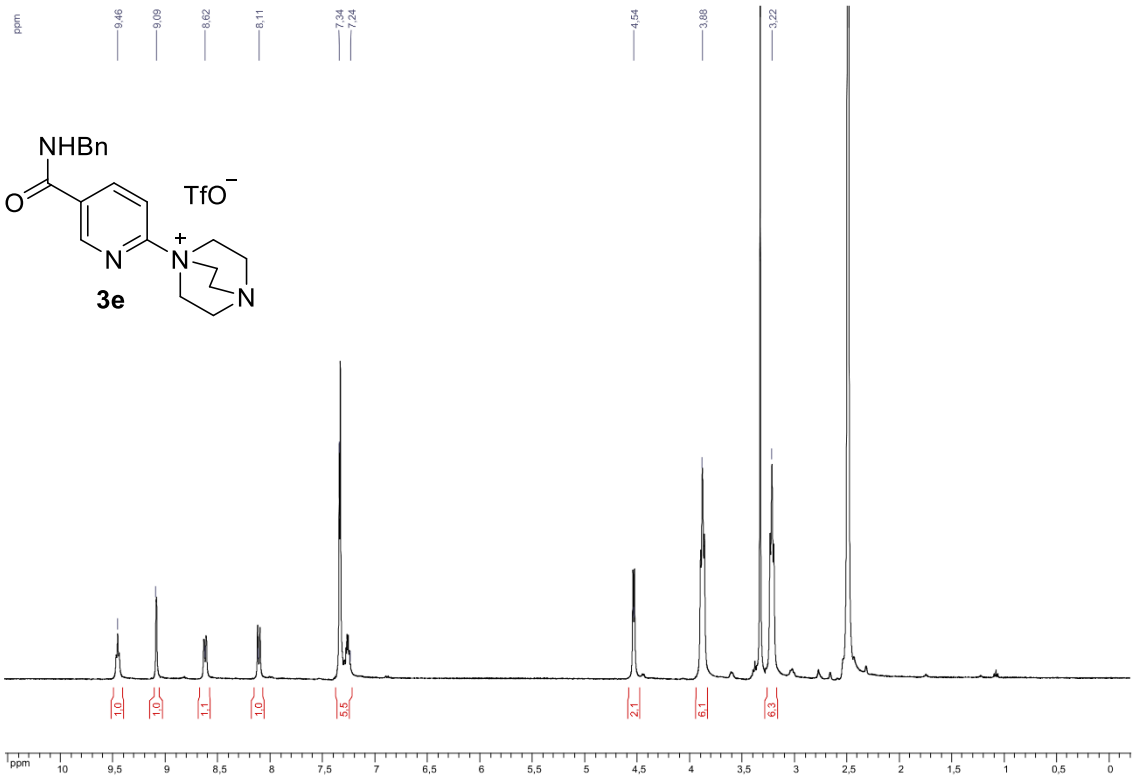

ppm
163.5
162.3
139.6
139.0
137.3
128.2
127.2
126.7
119.1
112.2
42.4
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

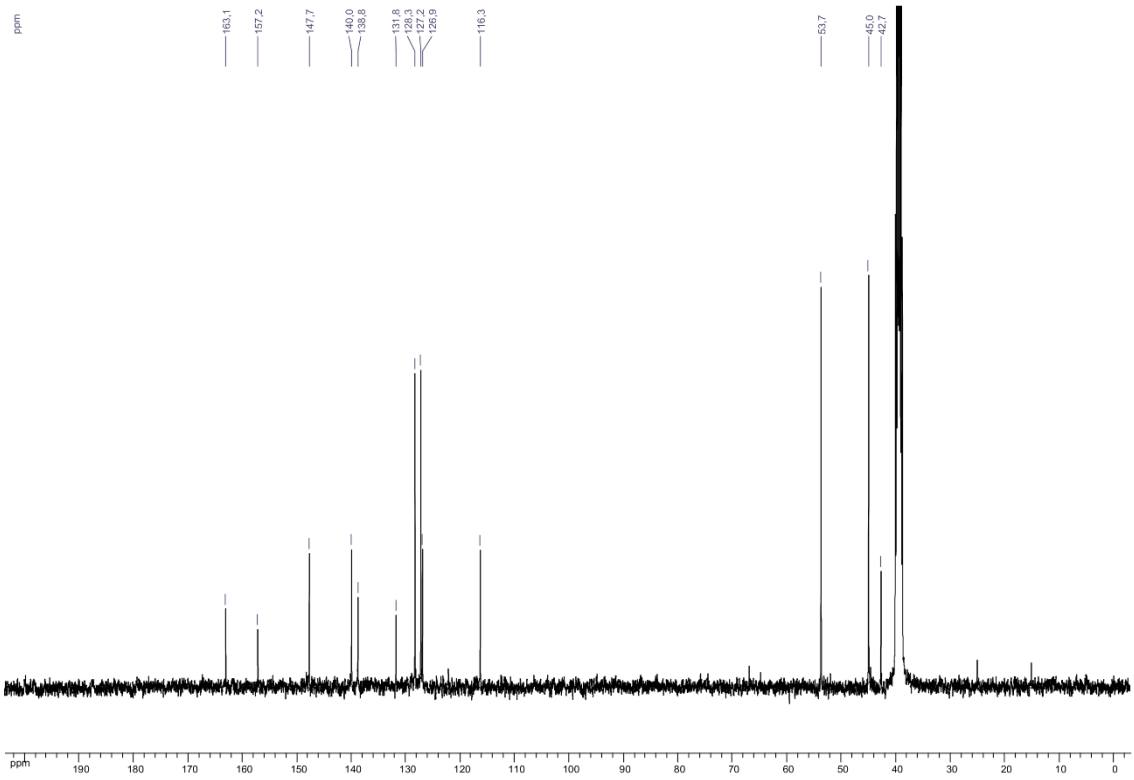

ppm
8,66
8,23
7,31
7,22
7,15
6,55
4,56
NHBn
O
N
OTf
1e
1,0
1,0
5,0
1,0
1,0
2,1
ppm
10
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0

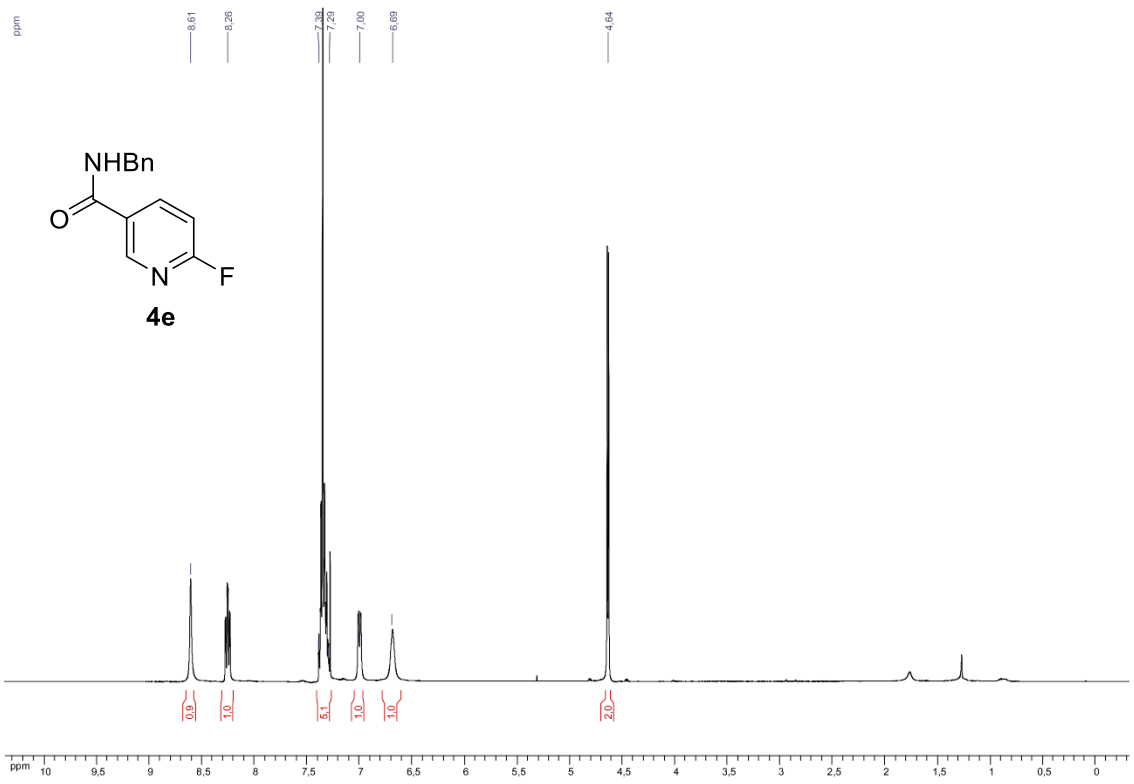

ppm
163,8
157,3
147,1
140,7
137,2
130,9
129,0
128,0
128,0
118,5
115,1
44,4
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

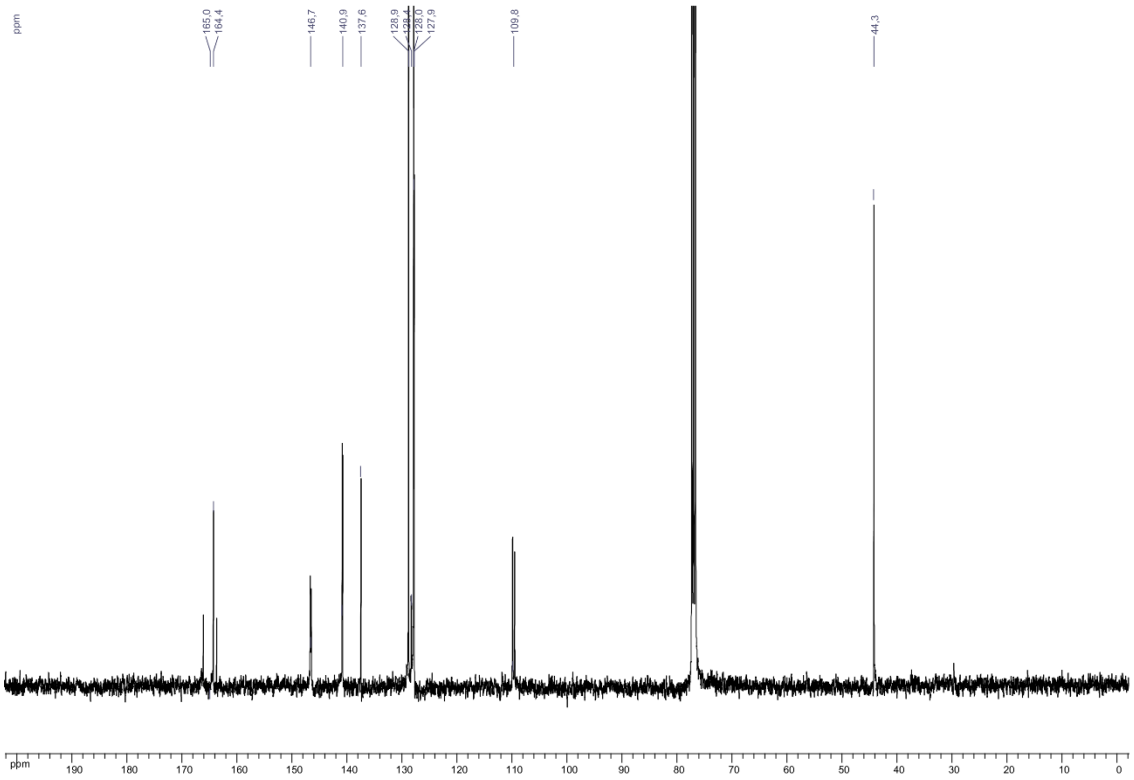

ppm
9.47
9.07
8.62
8.21
7.32
7.24
4.54
3.01
NHBn
O
TfO⁻
N
N⁺
2e
1.0
1.0
1.0
1.0
5.1
2.0
9.1
ppm 10 9.5 9 8.5 8 7.5 7 6.5 6 5.5 5 4.5 4 3.5 3 2.5 2 1.5 1 0.5 0

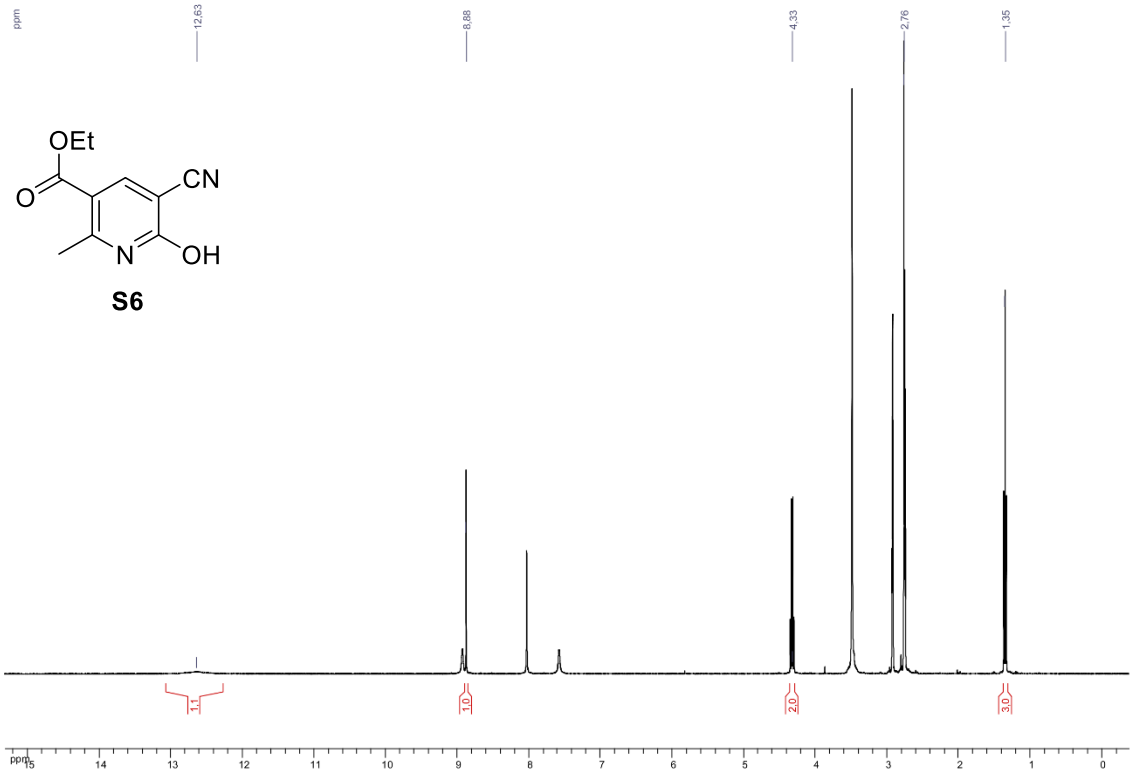

ppm
163.1
158.1
147.6
139.8
138.8
131.8
128.4
127.2
127.0
120.6
115.2
54.6
42.7
ppm 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


NHBn
O
TfO⁻
N
N
N
3e
ppm
9.46
9.09
8.62
8.11
7.34
7.24
4.54
3.88
3.22
1.0
1.0
1.1
1.0
5.5
2.1
6.1
6.3

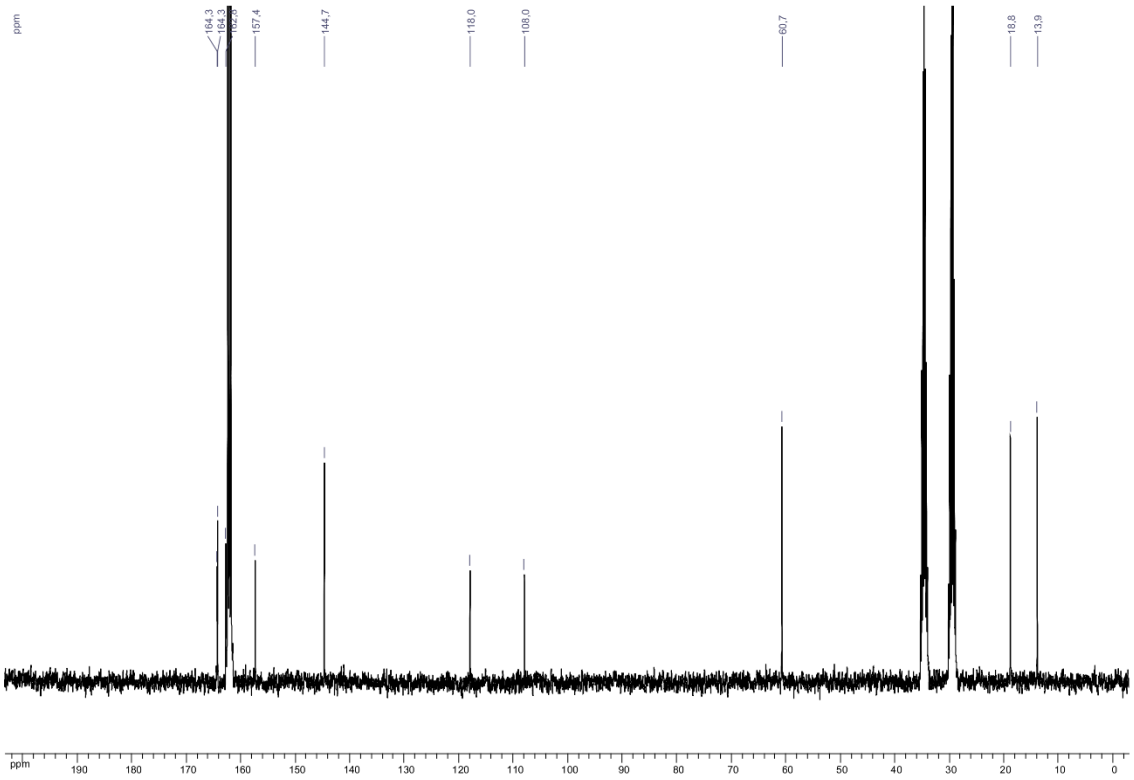

ppm
163.1
157.2
147.7
140.0
138.8
131.8
128.3
127.2
126.9
116.3
53.7
45.0
42.7

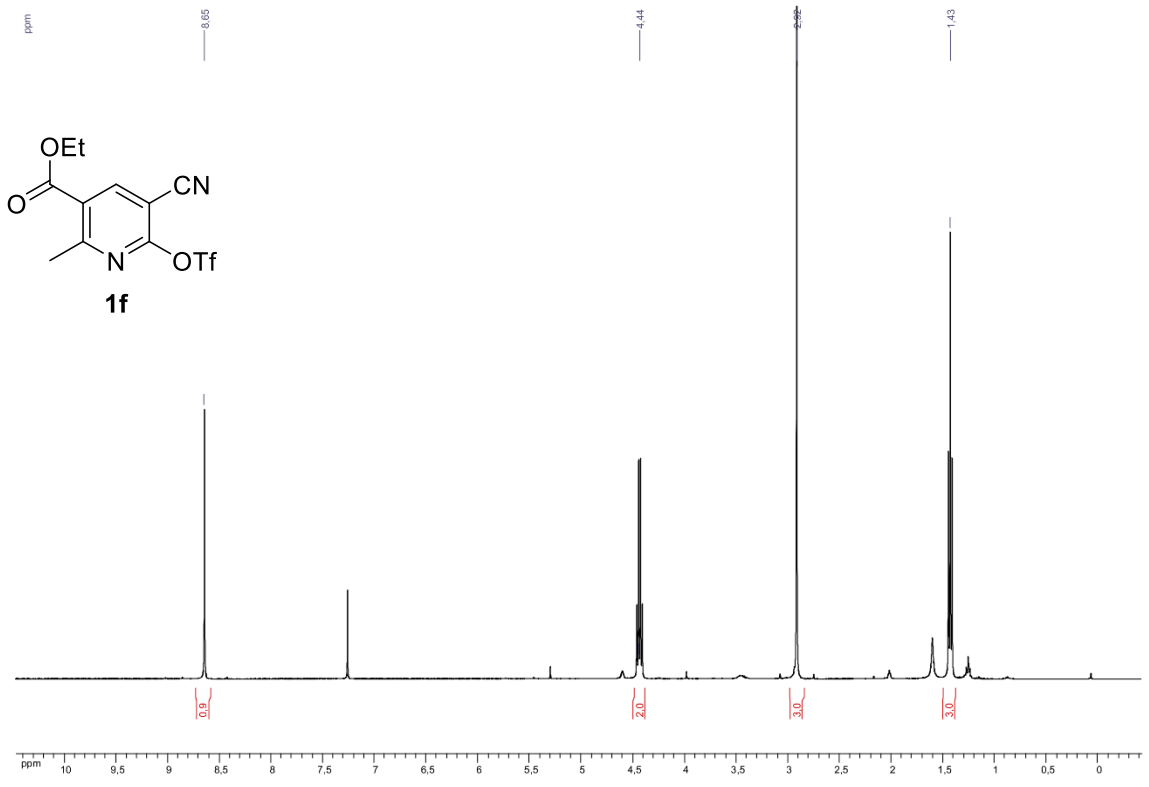

ppm
8,61
8,26
7,39
7,29
7,00
6,69
4,64
NHBn
O
N
F
4e
0,9
1,0
5,1
1,0
1,0
2,0
ppm
10
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0

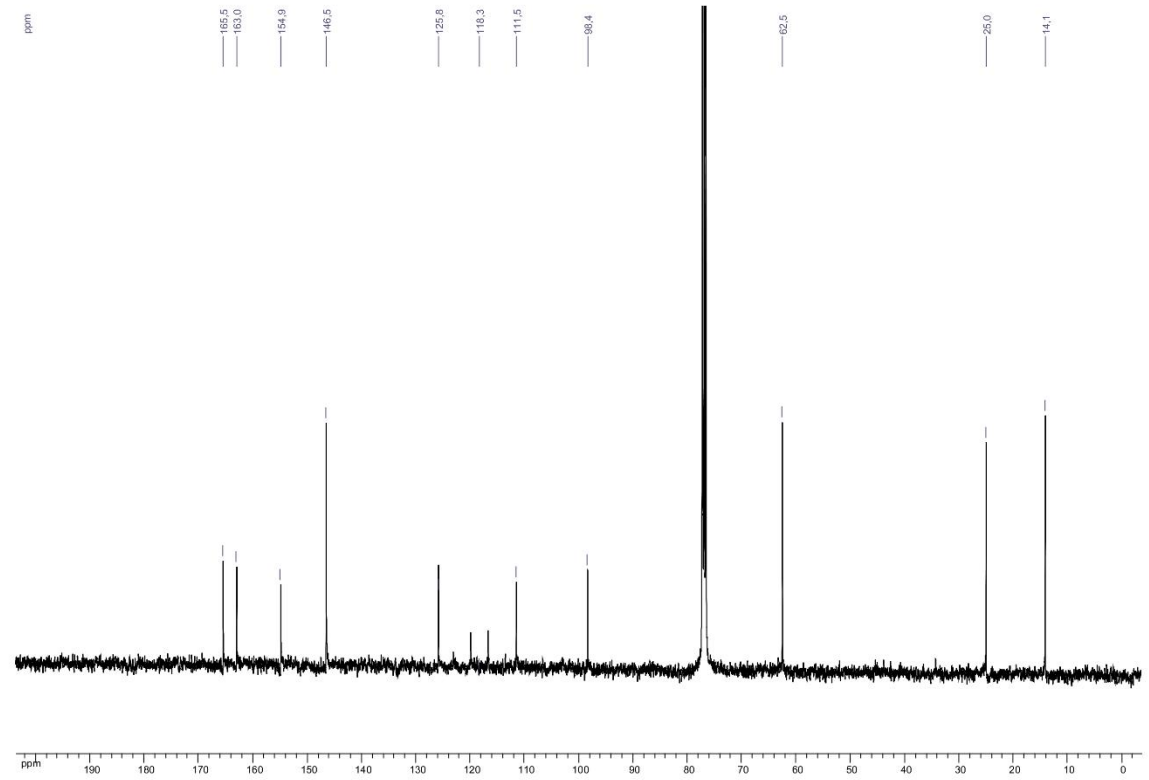

ppm
165,0
164,4
146,7
140,9
137,6
128,9
128,4
128,0
127,9
109,8
44,3
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

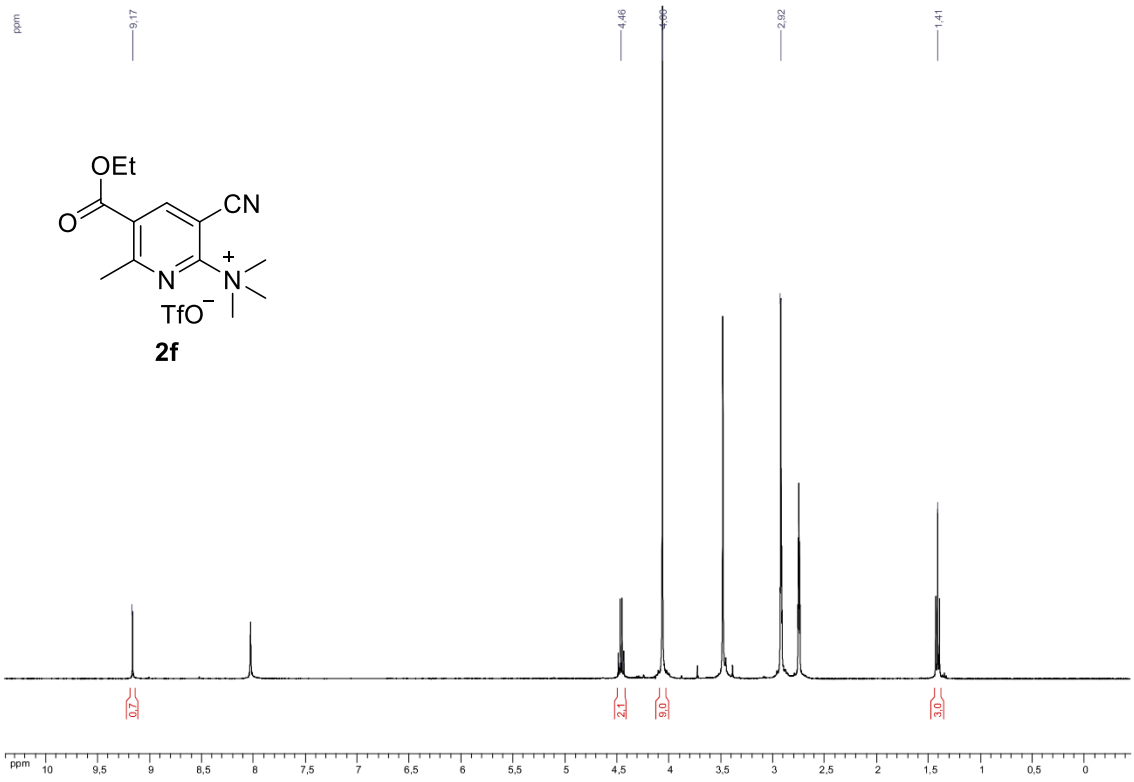

ppm
12.63
8.88
4.33
2.76
1.35
OEt
O
CN
N
OH
1.1
1.0
2.0
3.0
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0

S6

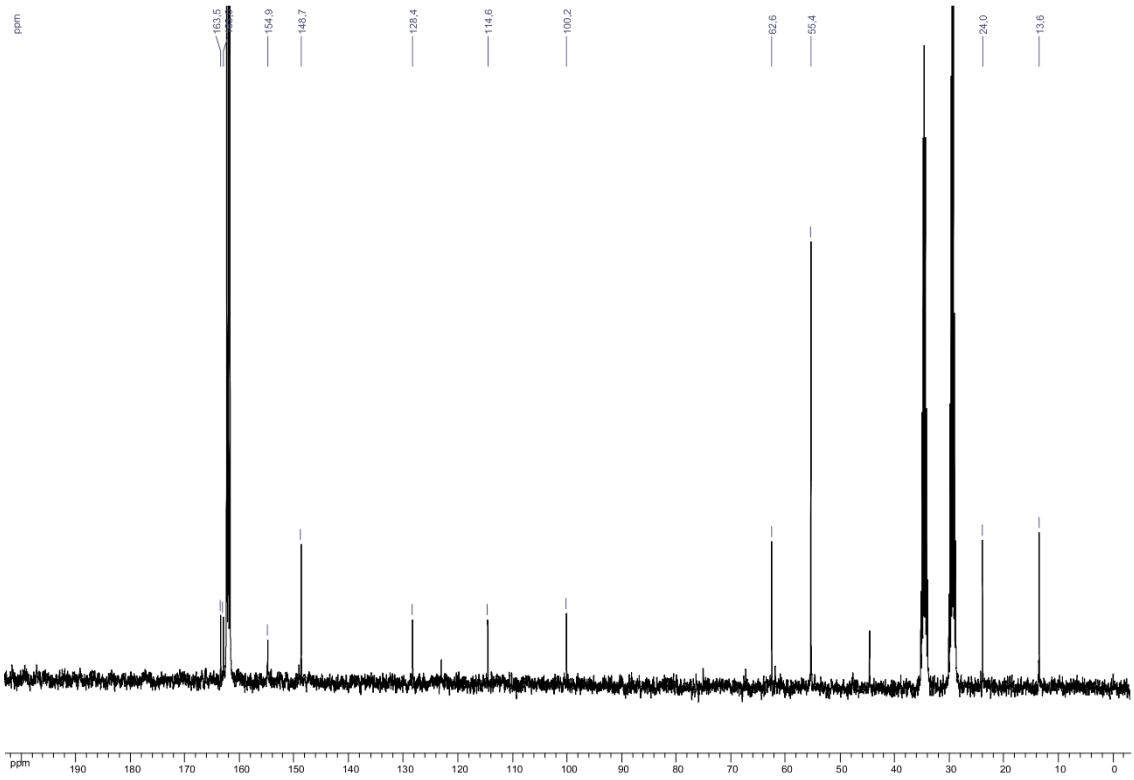

ppm
164.3
164.3
157.4
144.7
118.0
108.0
60.7
18.8
13.9
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

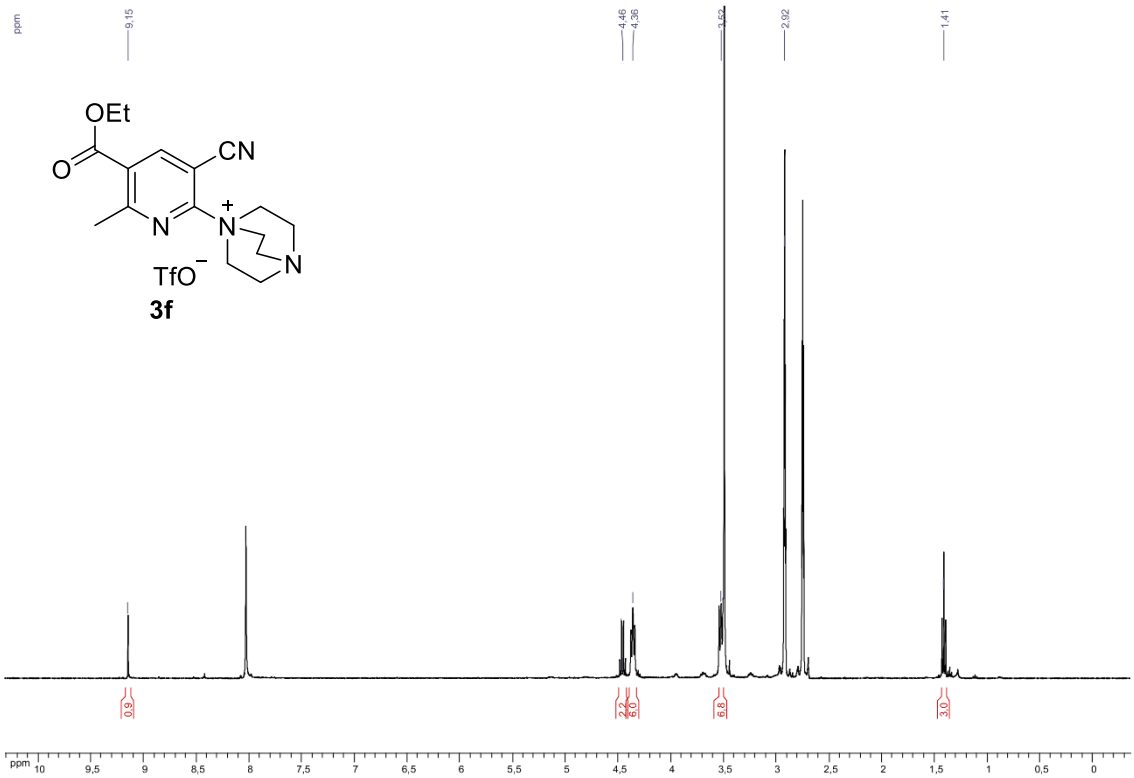

OEt
O
CN
N
OTf
1f
8,65
4,44
2,98
1,43
0,9
2,0
3,0
3,0


165,5
163,0
154,9
146,5
125,8
118,3
111,5
98,4
62,5
25,0
14,1

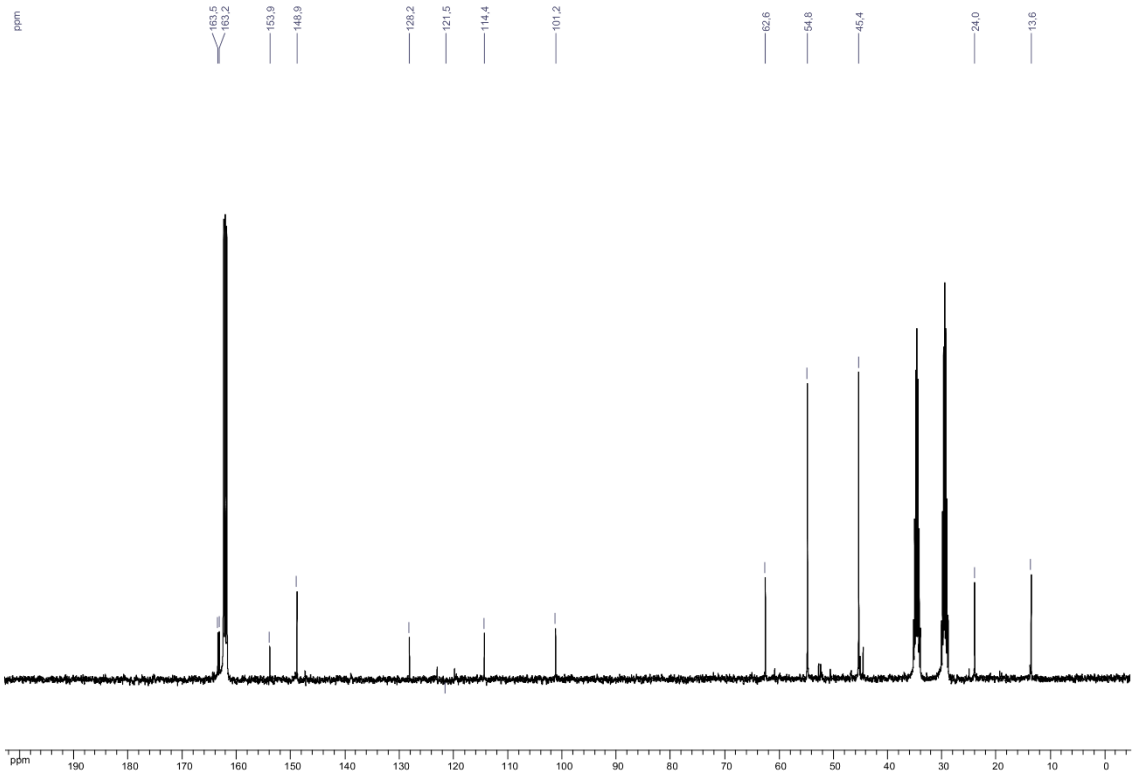

ppm
9,17
4,46
4,00
2,92
1,41
OEt
O
CN
N
+
N
TfO⁻
0,7
2,1
9,0
3,0
ppm
10
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0

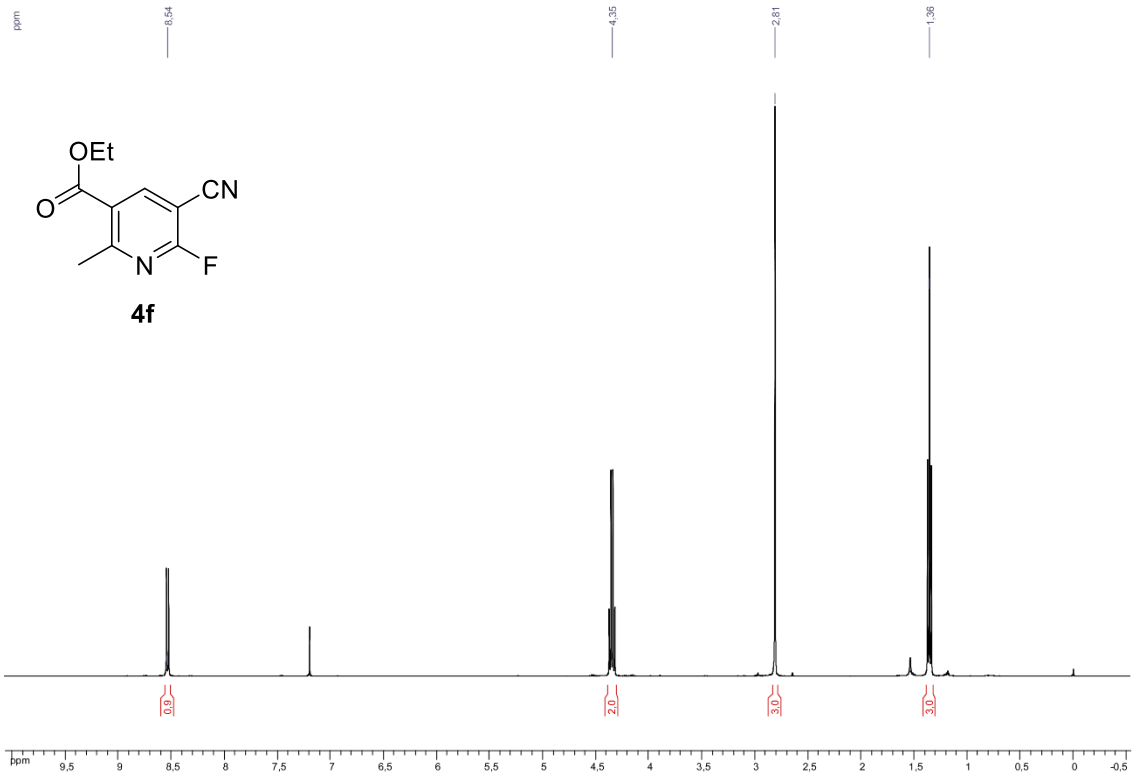
2f


ppm
163,5
154,9
148,7
128,4
114,6
100,2
62,6
55,4
24,0
13,6
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

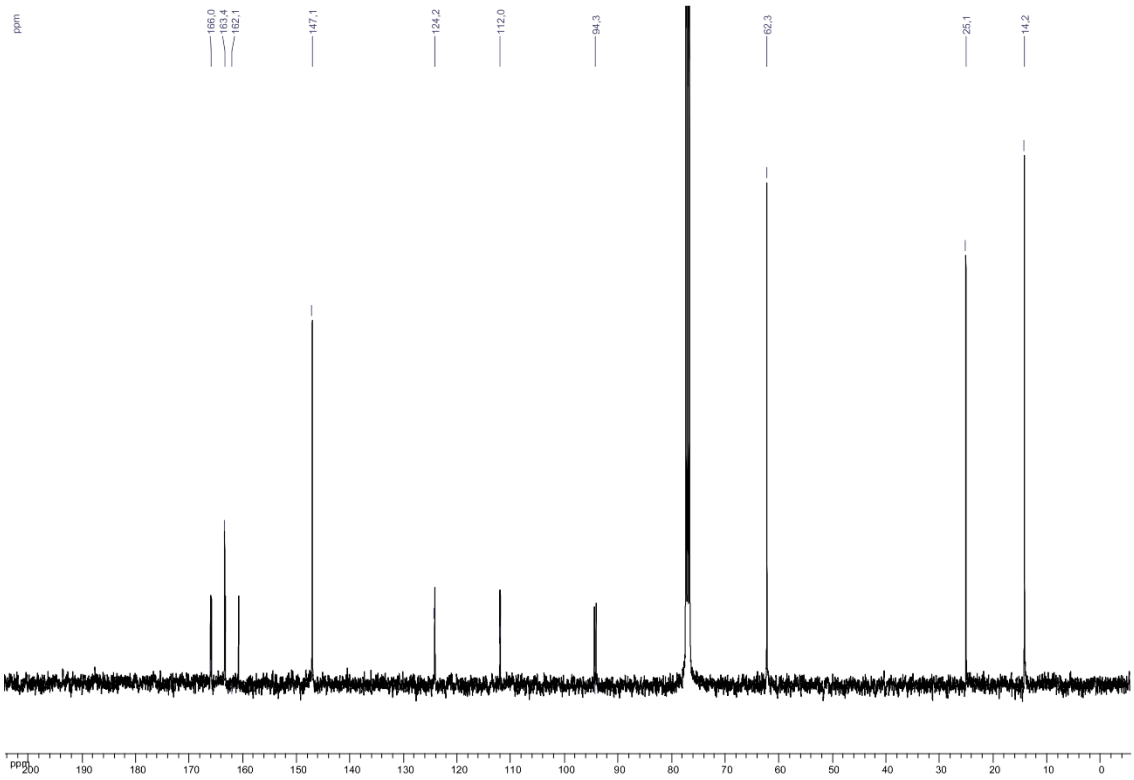

ppm
9.15
4.46
4.36
3.52
2.92
1.41
OEt
O
CN
N
N
N
TfO
0.9
2.2
6.0
6.8
3.0
10
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0

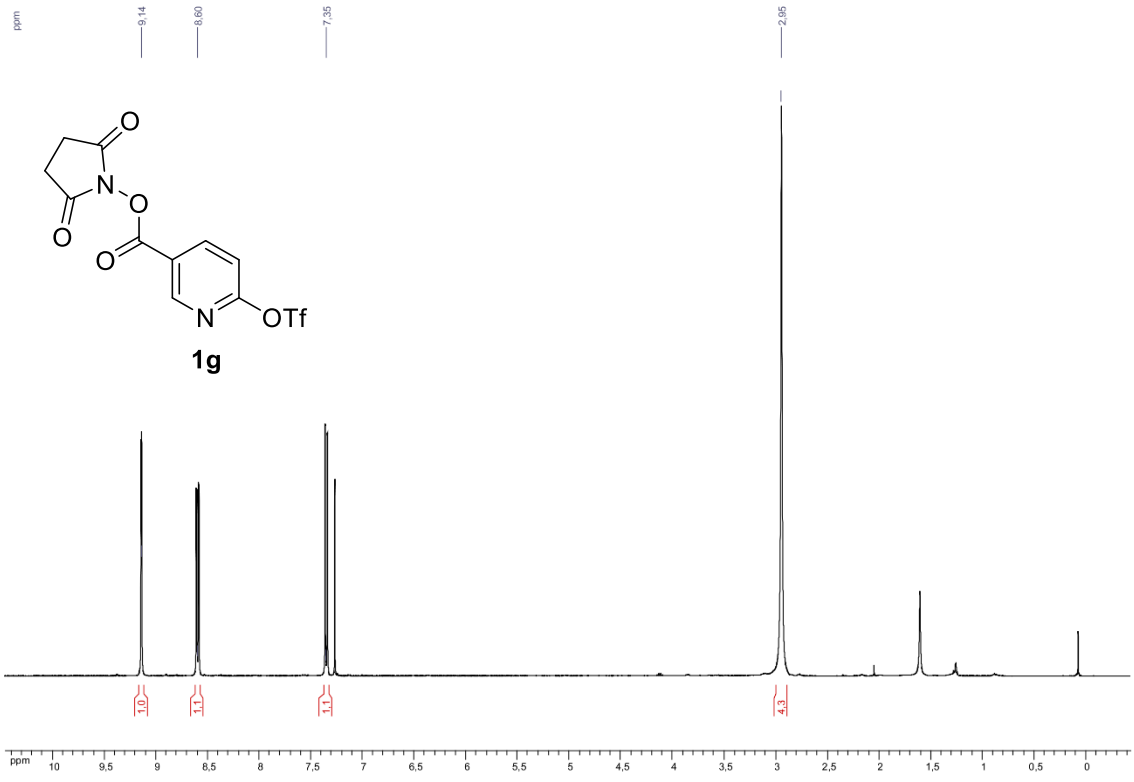
3f

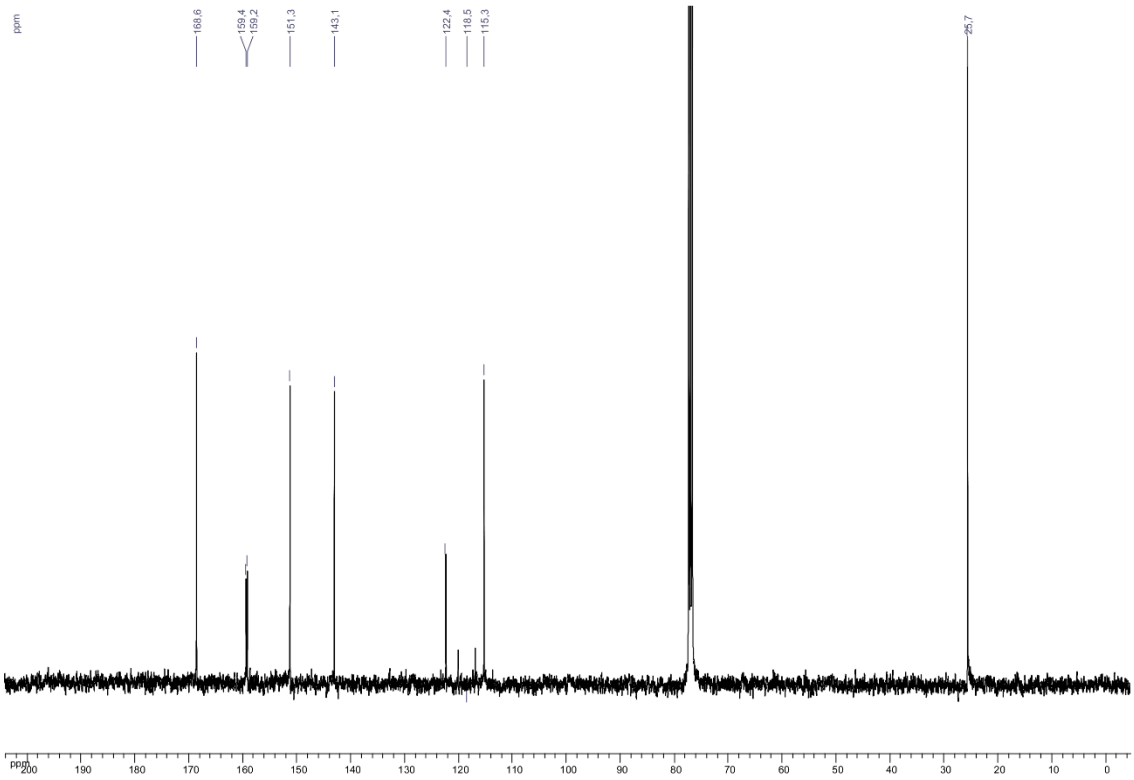

ppm
163.5
163.2
153.9
148.9
128.2
121.5
114.4
101.2
62.6
54.8
45.4
24.0
13.6
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

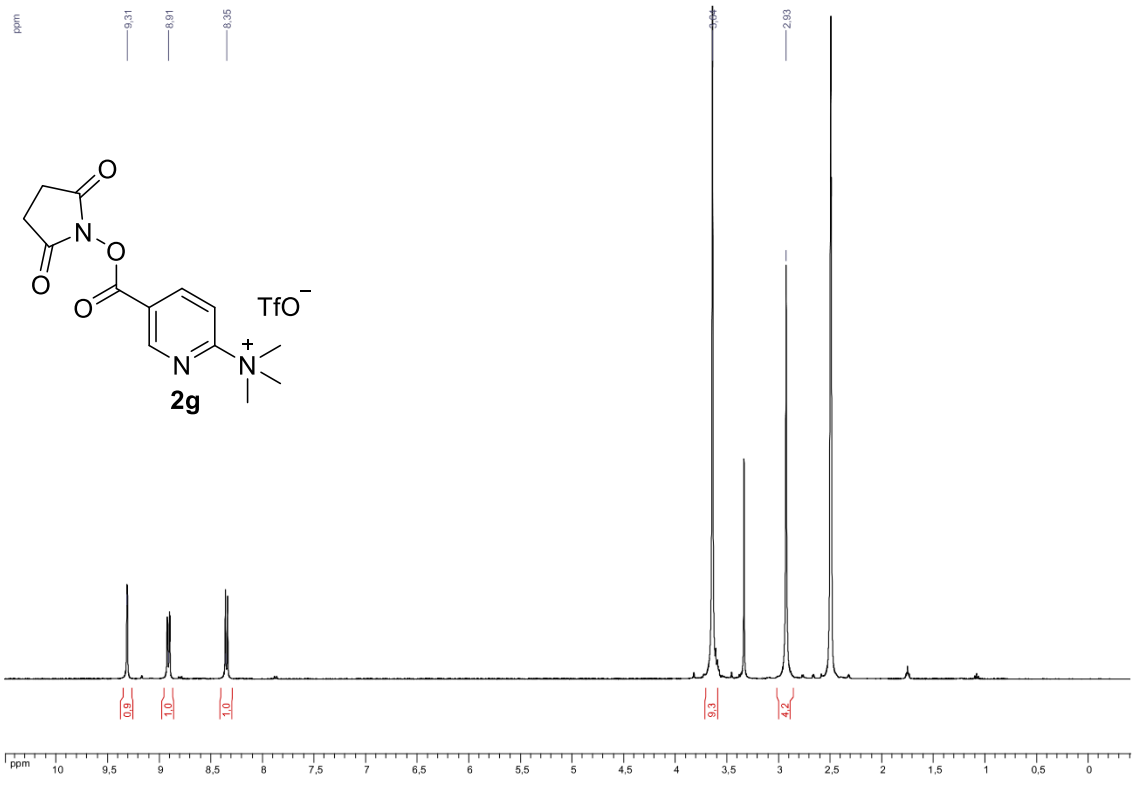

ppm
8,54
4,35
2,81
1,36
OEt
O
CN
N
F
0,9
2,0
3,0
3,0
ppm
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0
-0,5

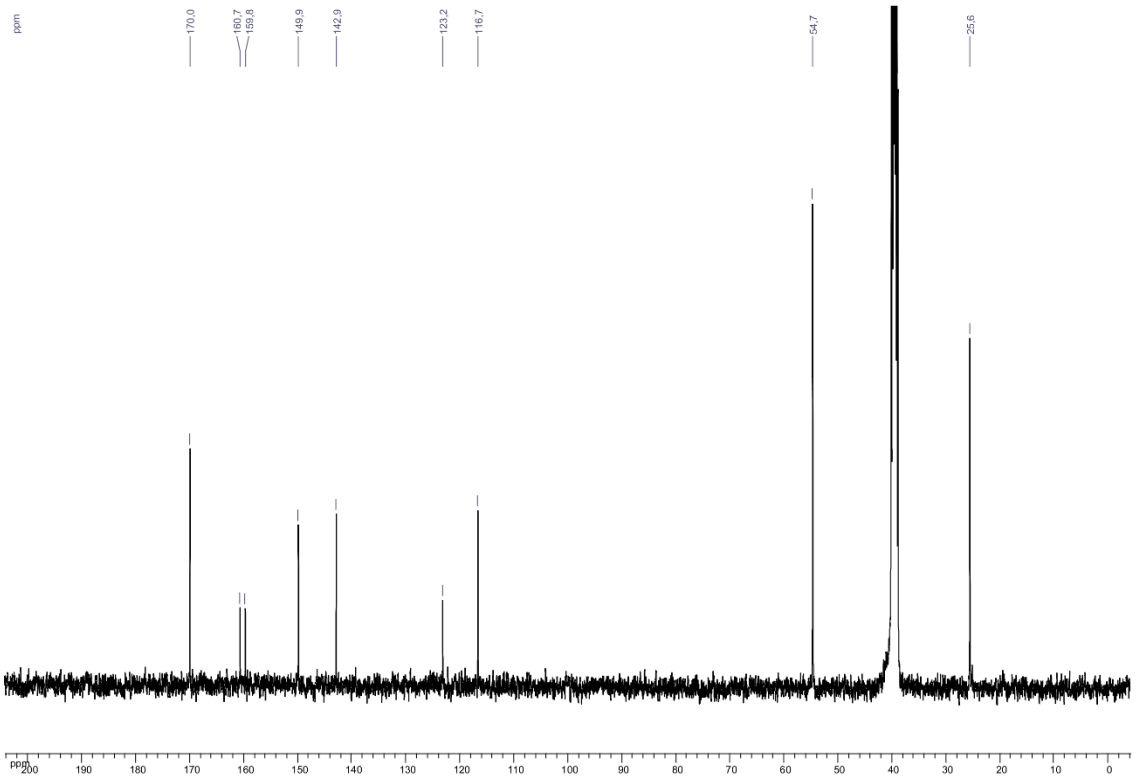
4f

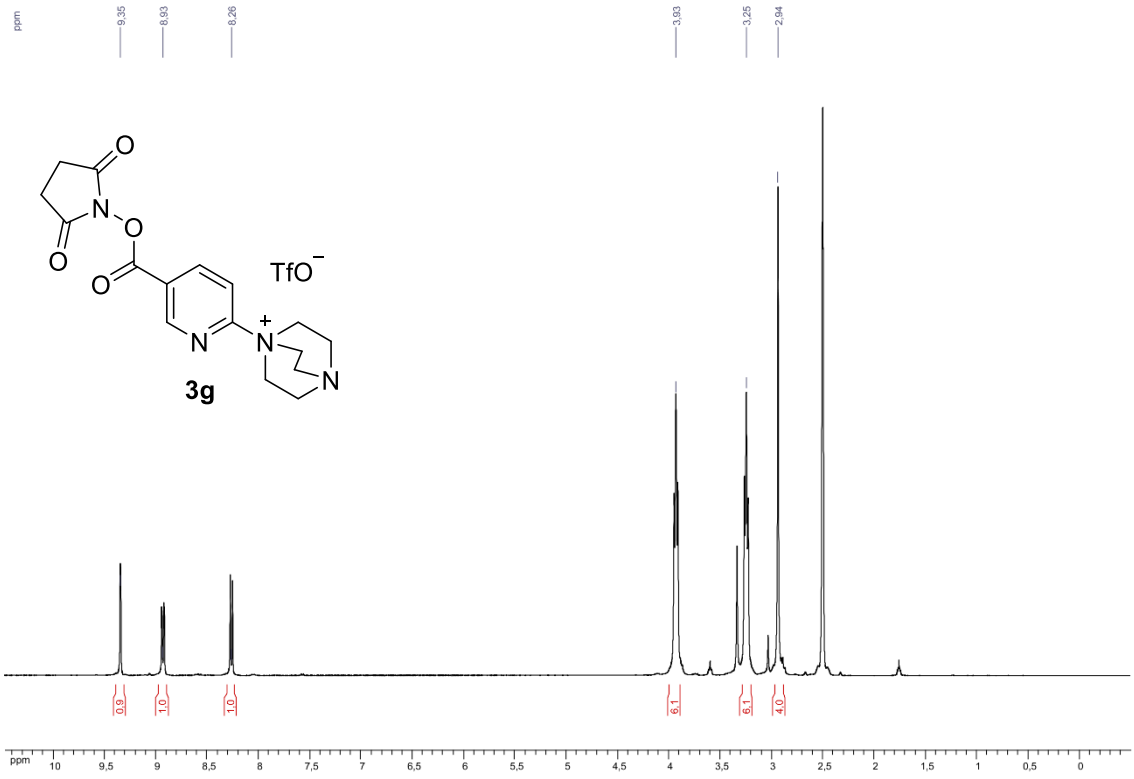

ppm
166,0
163,4
162,1
147,1
124,2
112,0
94,3
62,3
25,1
14,2
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

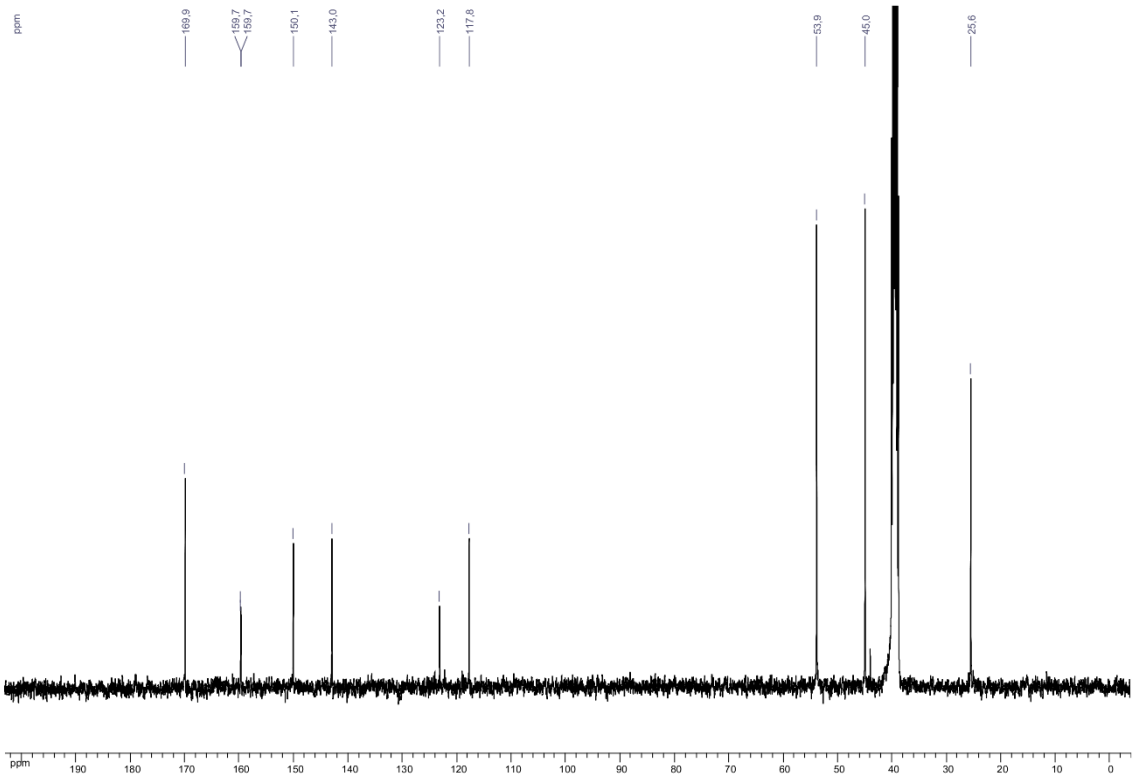

ppm
9.14
8.60
7.35
2.95
O
N
O
O
O
N
OTf
1g
1.0
1.1
1.1
4.3
ppm
10
9.5
9
8.5
8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0

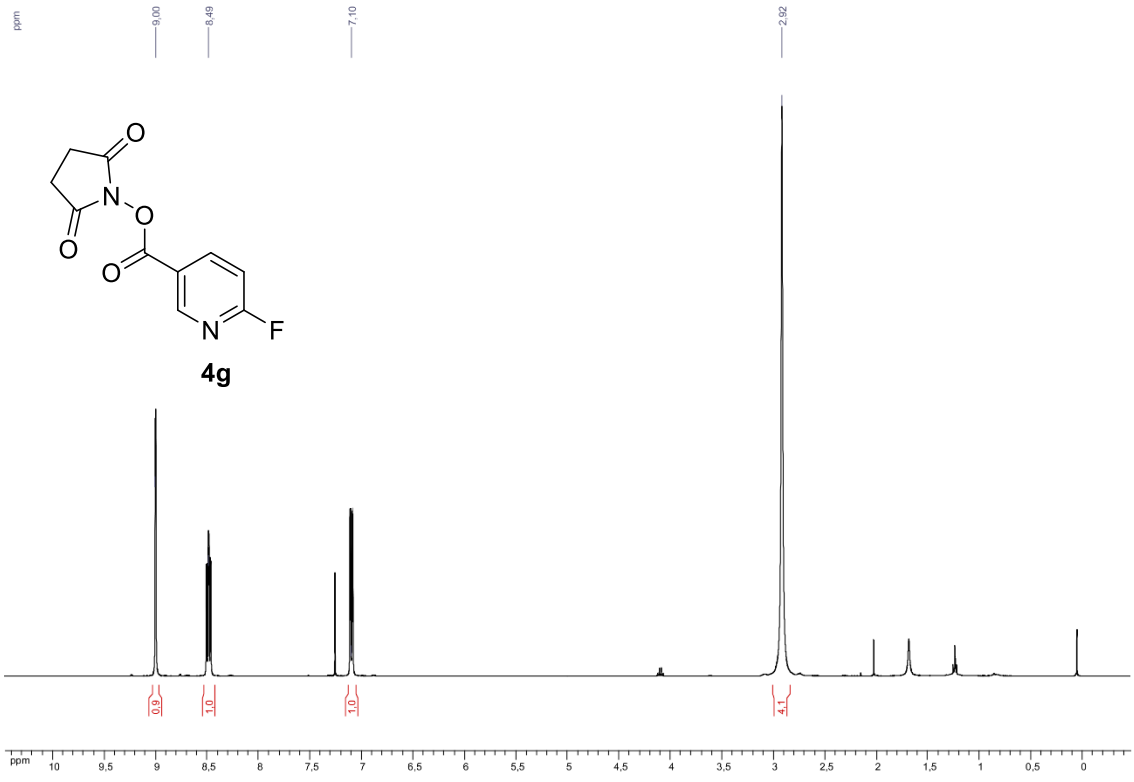

ppm
168.6
159.4
159.2
151.3
143.1
122.4
118.5
115.3
25.7
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


ppm
9,31
8,91
8,35
2,93
TfO⁻
2g
0,9
1,0
1,0
9,3
4,2

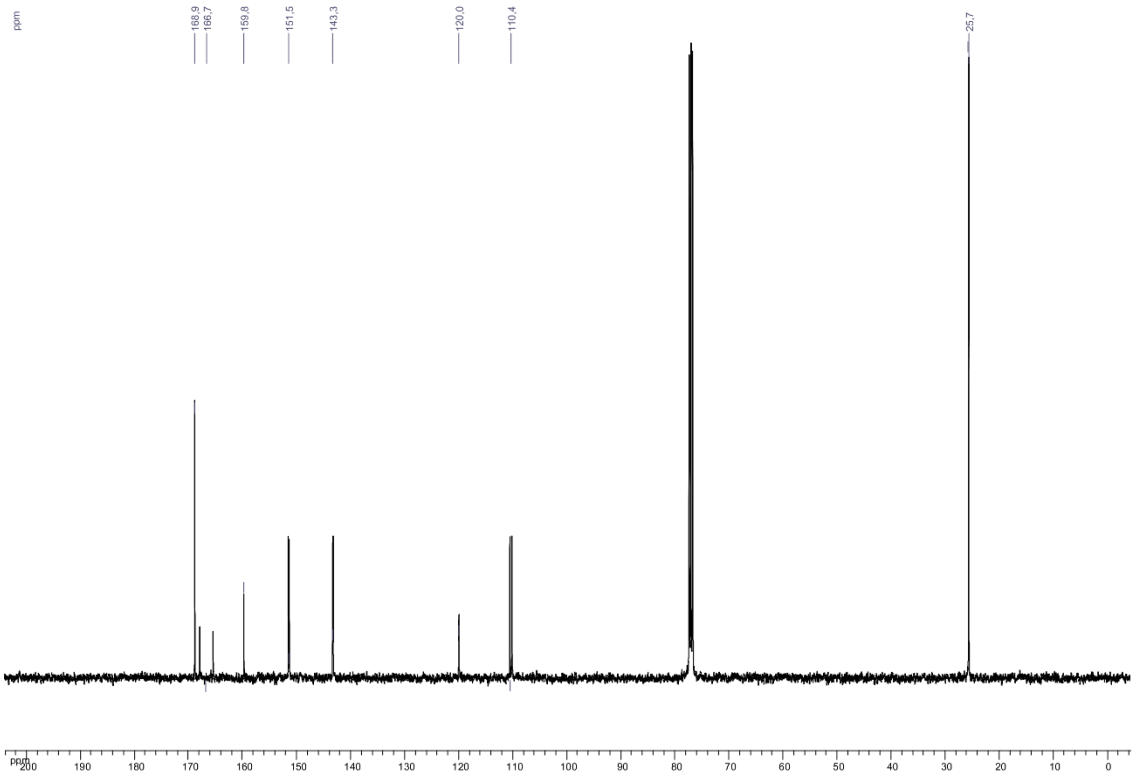

ppm
170,0
160,7
159,8
149,9
142,9
123,2
116,7
54,7
25,6

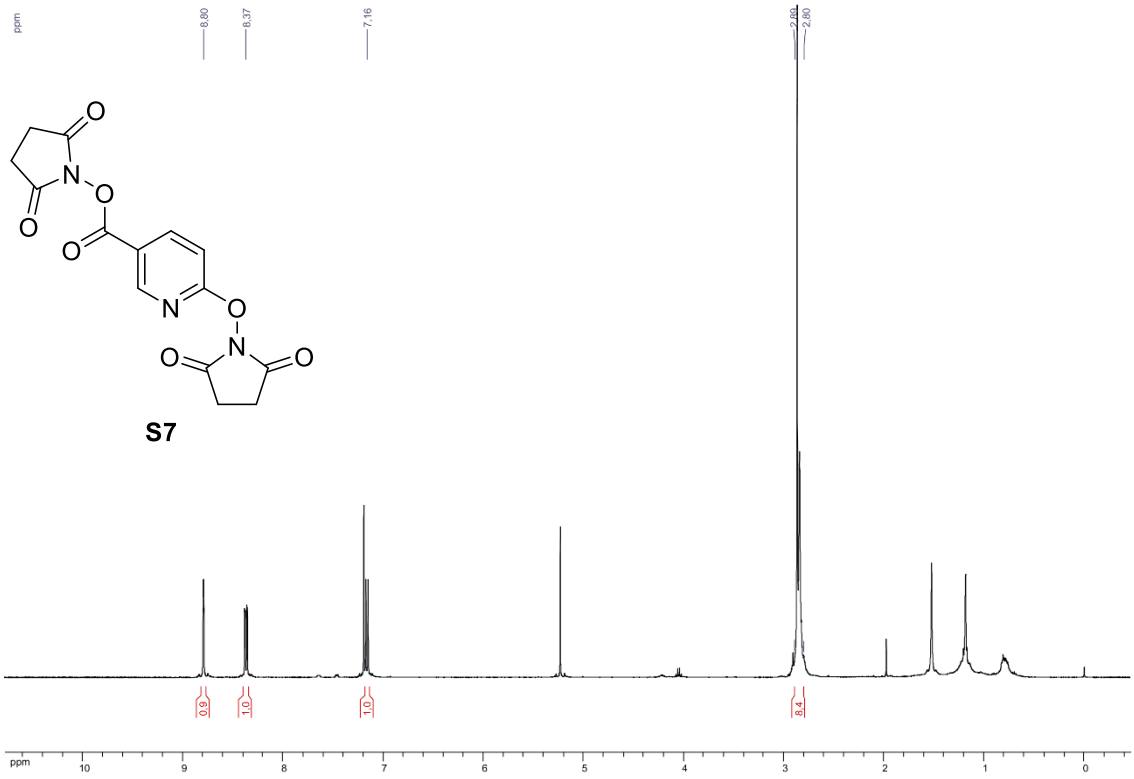

ppm
9,35
8,93
8,26
3,93
3,25
2,94
TfO⁻
3g
0,9
1,0
1,0
6,1
6,1
4,0


ppm
169,9
159,7
159,7
150,1
143,0
123,2
117,8
53,9
45,0
25,6

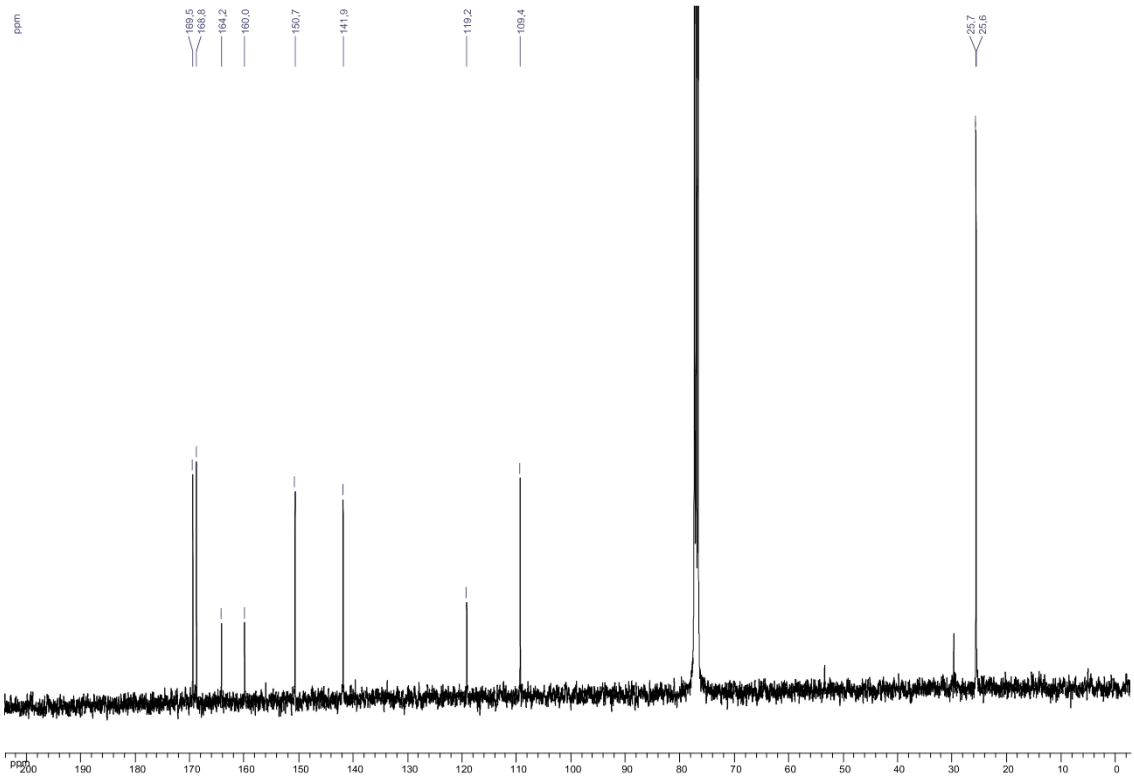

ppm
9,00
8,49
7,10
2,92
O
N
O
O
O
N
F
0,9
1,0
1,0
4,1
ppm
10
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0

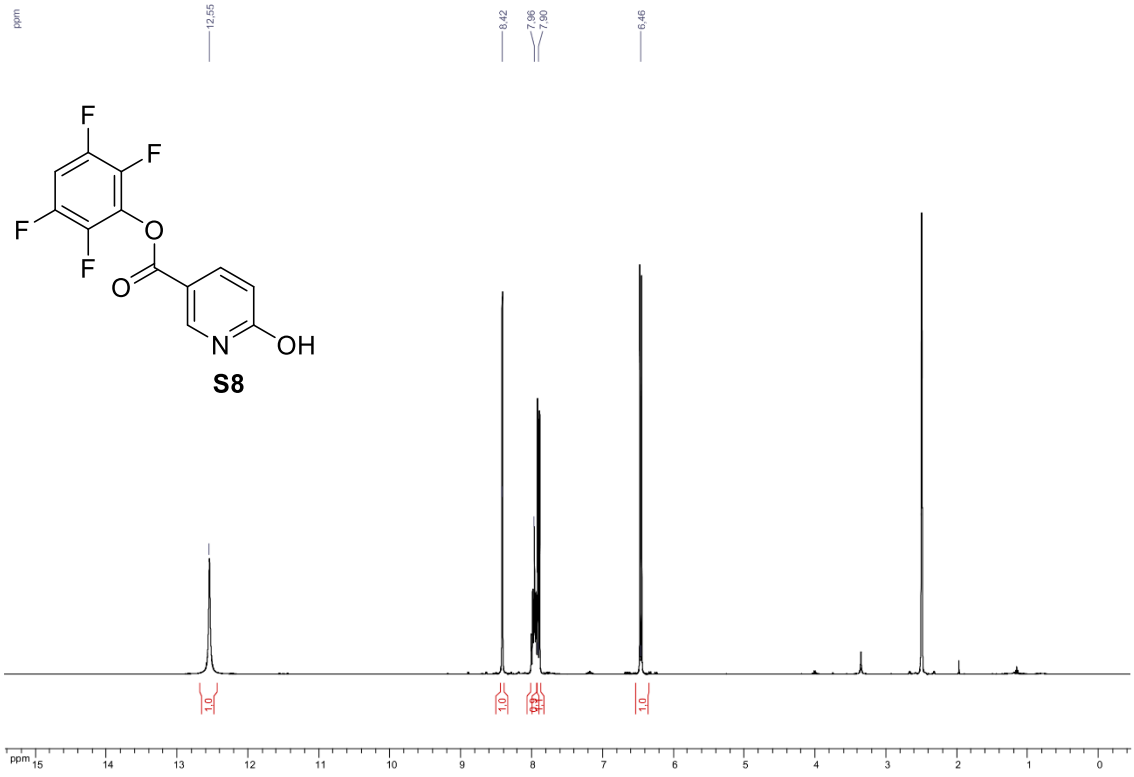
4g


ppm
168,9
166,7
159,8
151,5
143,3
120,0
110,4
25,7
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

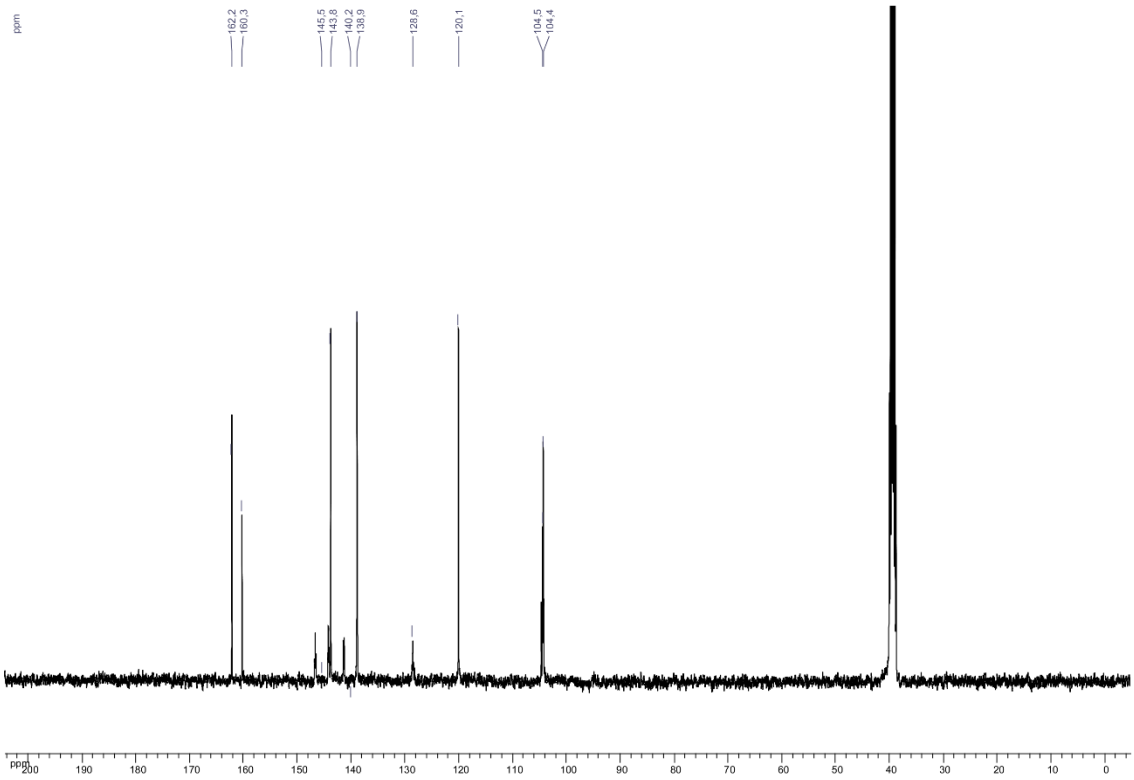

ppm
8.80
8.37
7.16
2.69
2.80
0.9
1.0
1.0
8.4
ppm
10
9
8
7
6
5
4
3
2
1
0

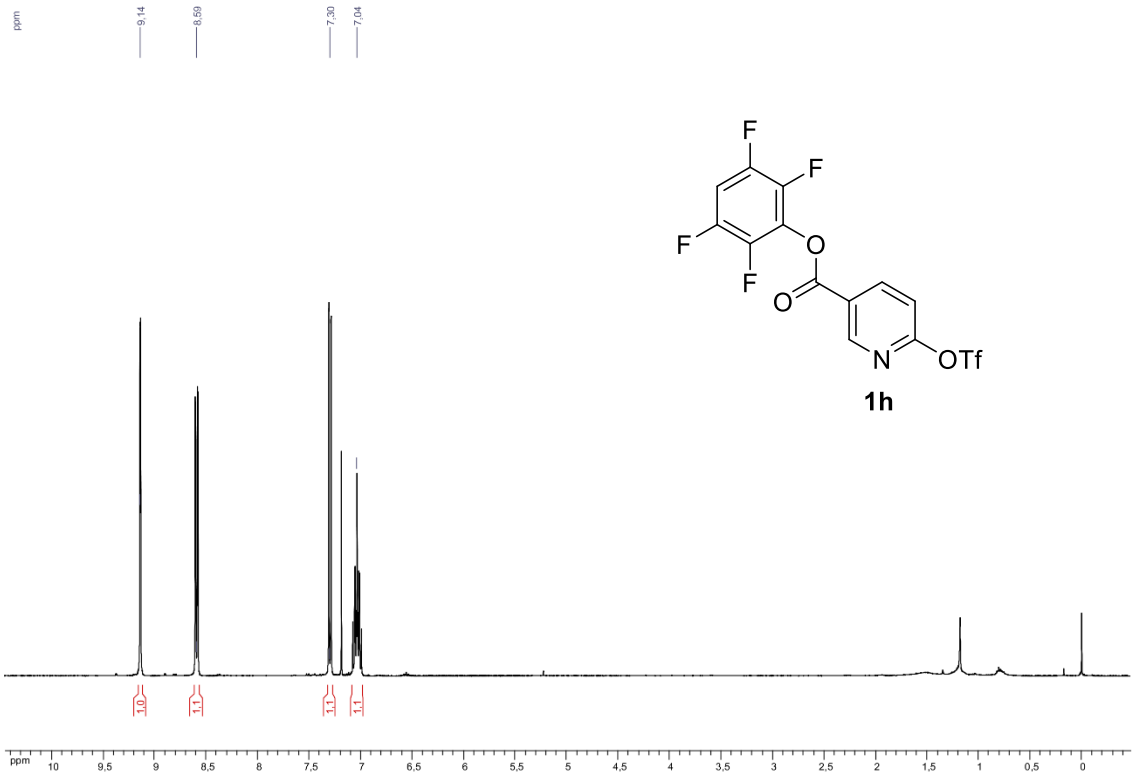
S7

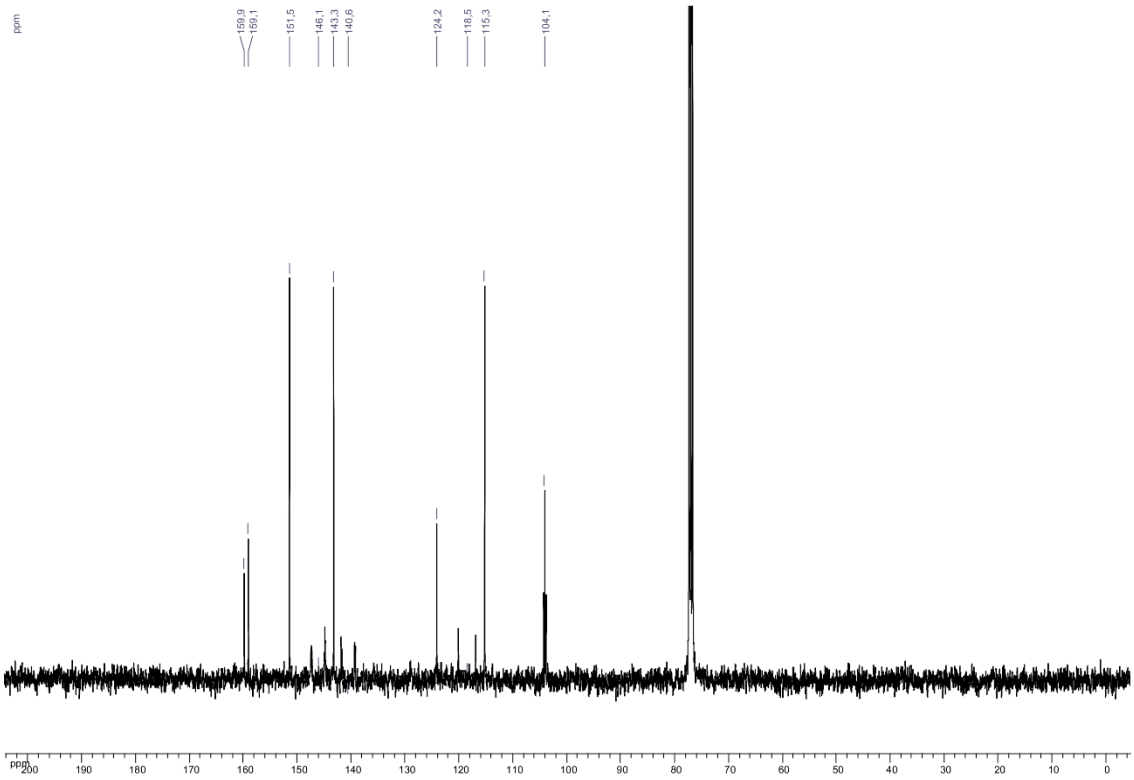

ppm
169.5
168.8
164.2
160.0
150.7
141.9
119.2
109.4
25.7
25.6
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

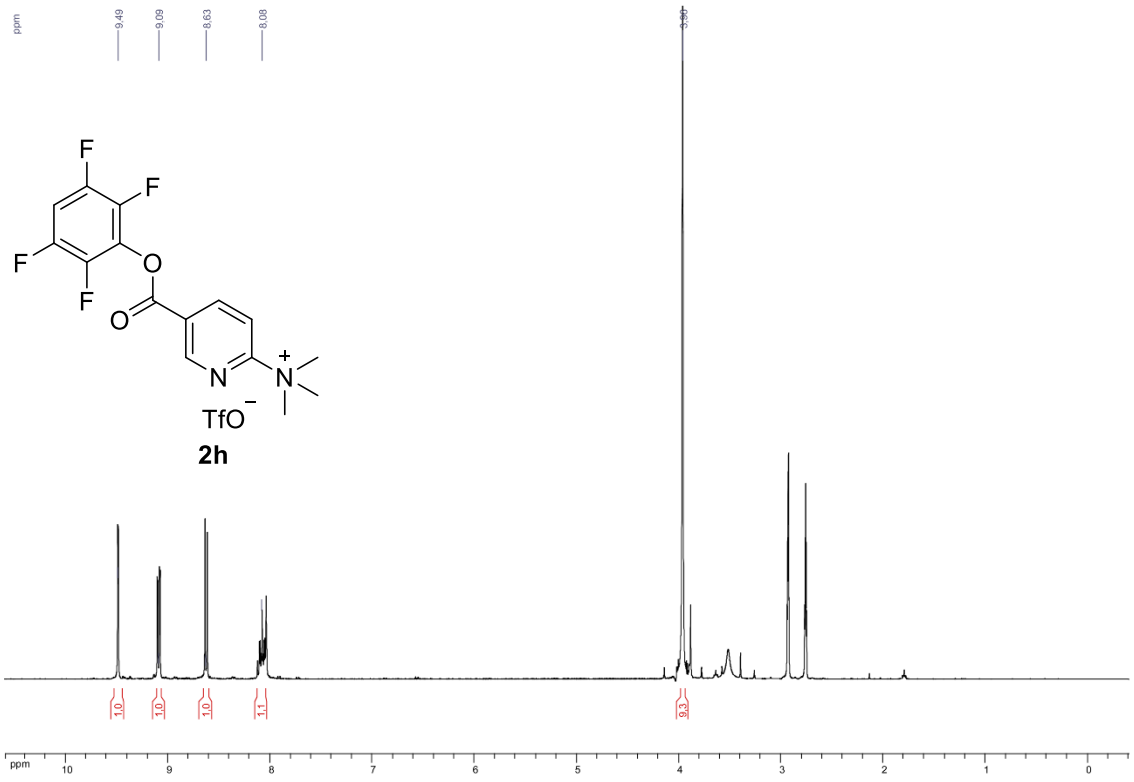

ppm
12,55
8,42
7,96
7,90
6,46
F
F
F
F
O
O
N
OH
1,0
1,0
4,2
1,0
ppm
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0

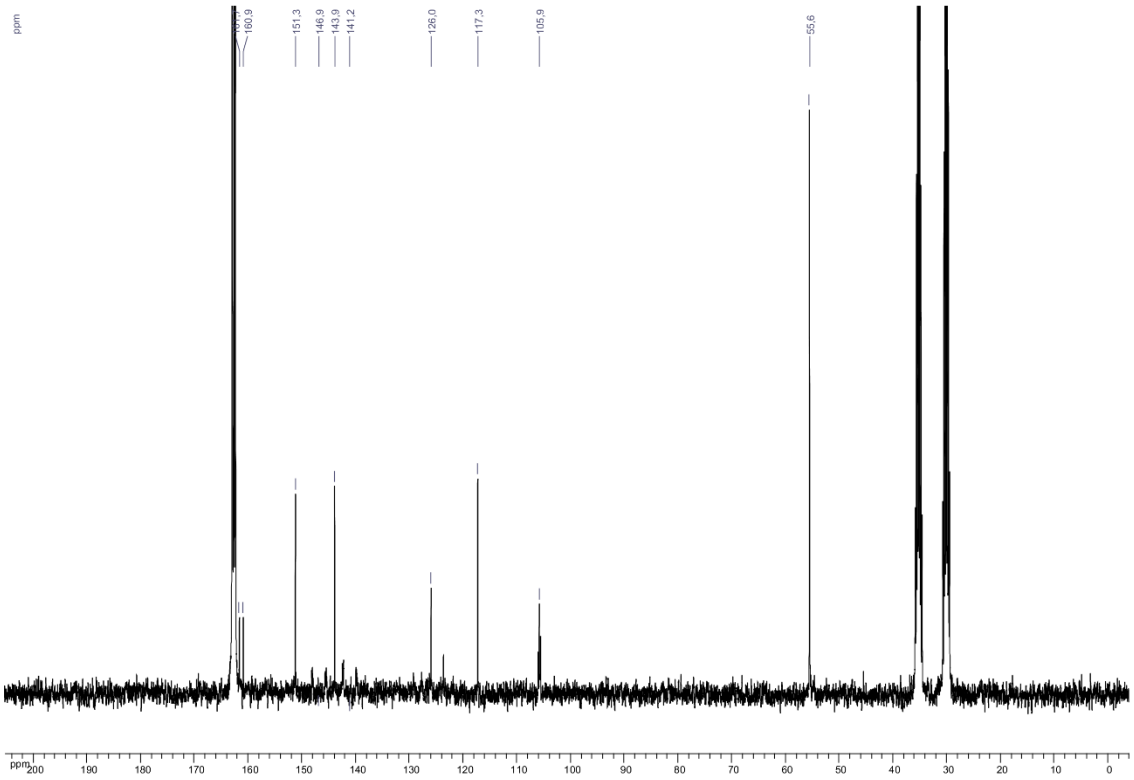
S8

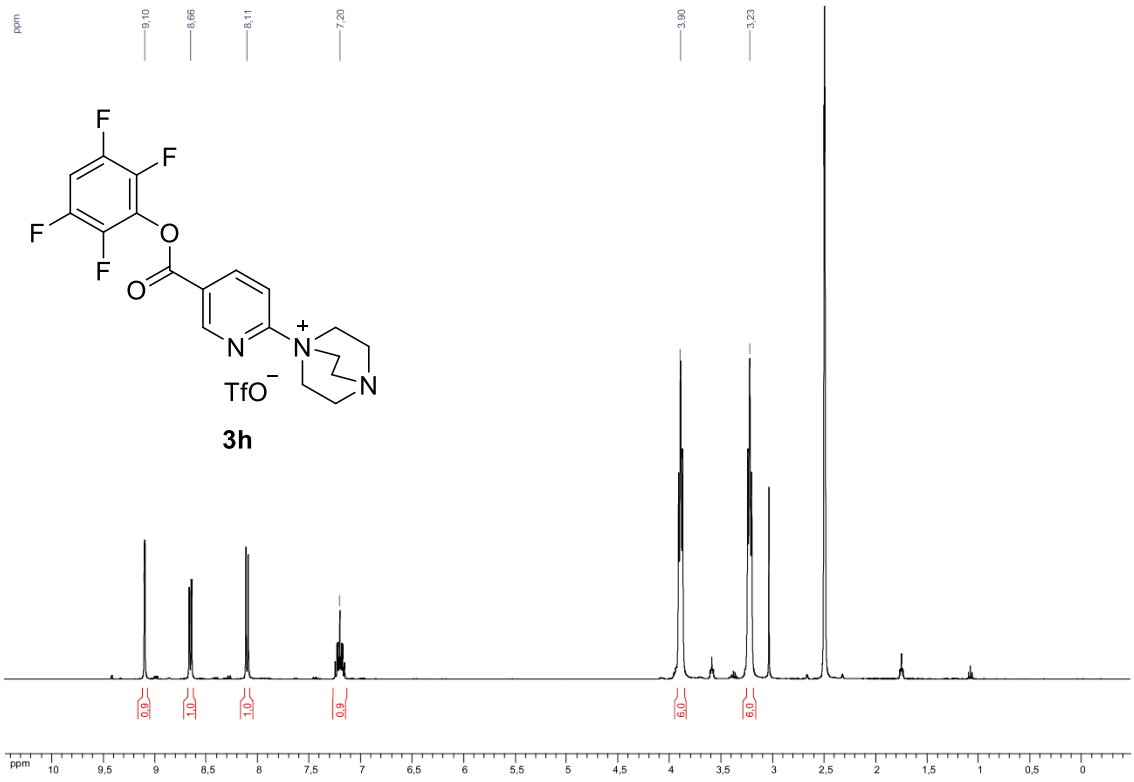

ppm
162,2
160,3
145,5
143,8
140,2
138,9
128,6
120,1
104,5
104,4
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


ppm
9,14
8,59
7,30
7,04
F
F
F
F
O
O
N
OTf
1h
1,0
1,1
1,1
1,1
ppm
10
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0

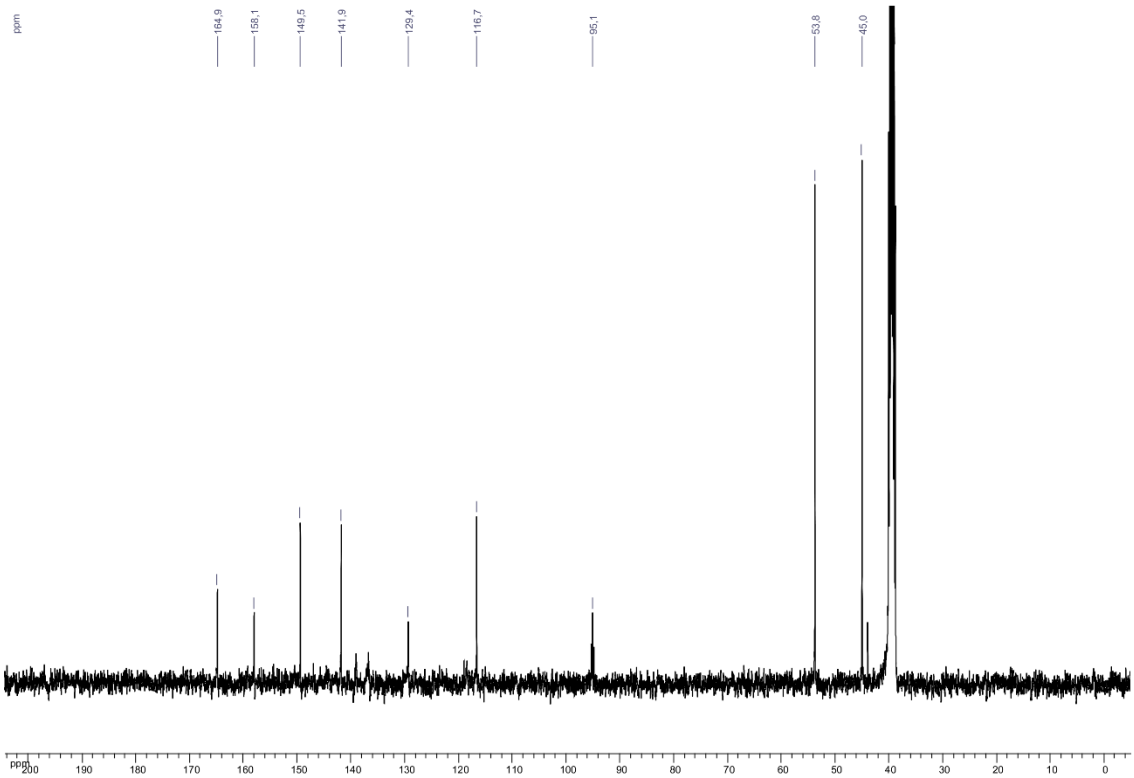

ppm
159,9
159,1
151,5
146,1
143,3
140,6
124,2
118,5
115,3
104,1
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

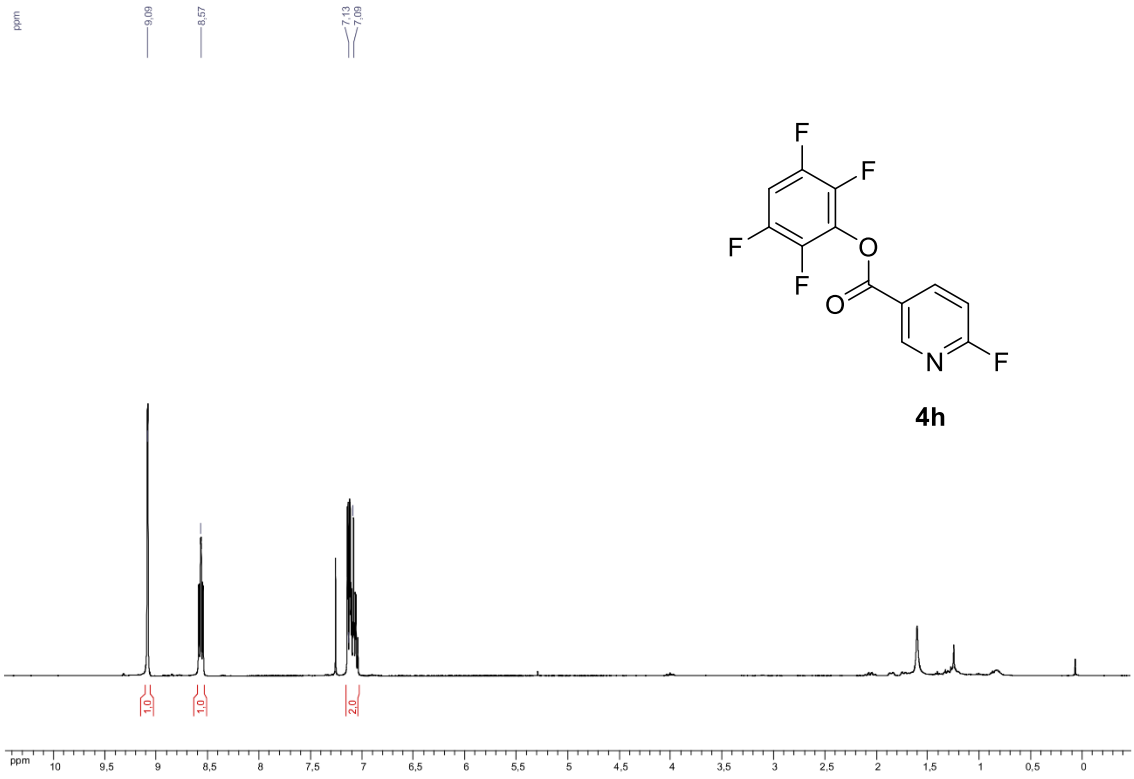

ppm
9.49
9.09
8.63
8.08
3.97
F
F
F
F
O
O
N
+
N
TfO
−
2h
1.0
1.0
1.0
1.1
9.3
ppm
10
9
8
7
6
5
4
3
2
1
0


ppm
160.9
151.3
146.9
143.9
141.2
126.0
117.3
105.9
55.6
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

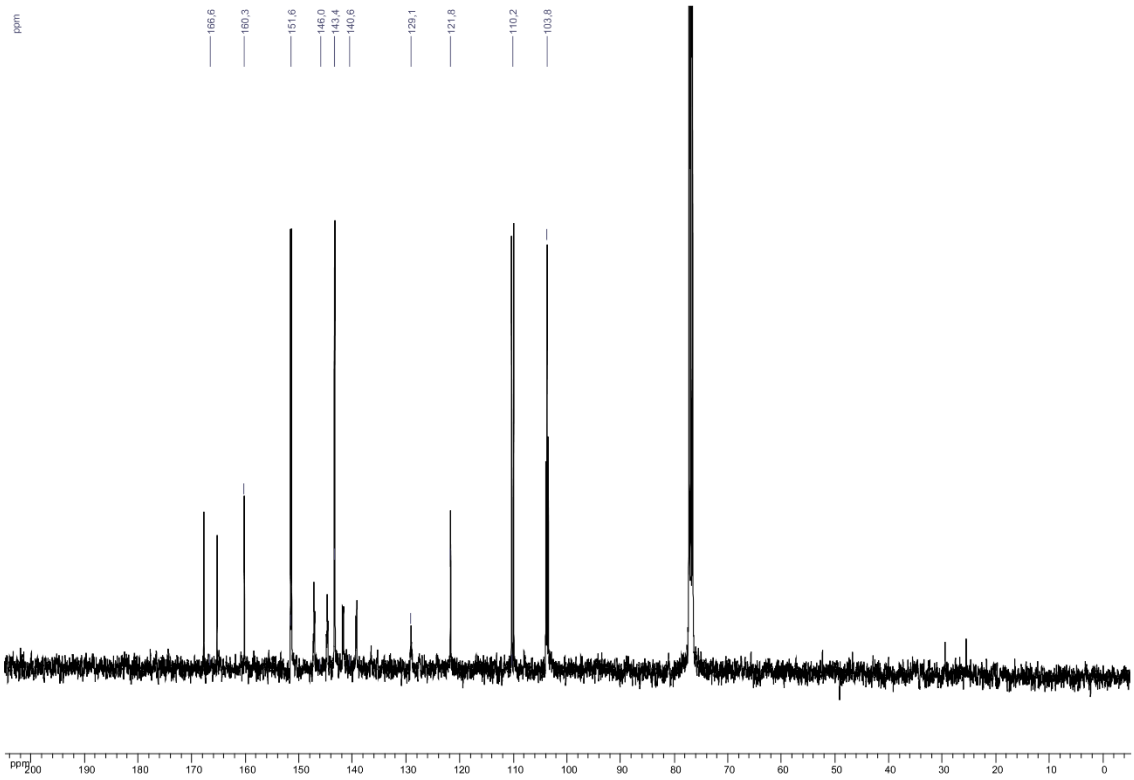

ppm
9,10
8,66
8,11
7,20
3,90
3,23
F
F
F
F
O
O
N
N
N
TfO⁻
0,9
1,0
1,0
0,9
6,0
6,0
ppm
10
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0

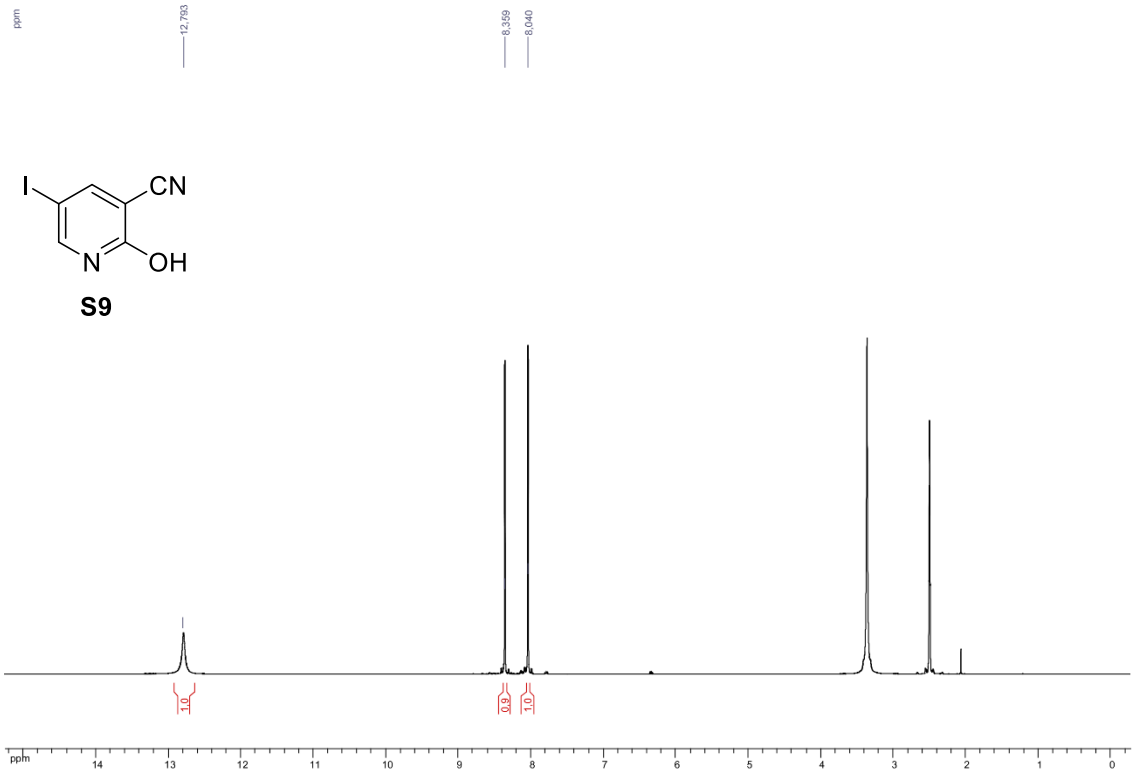
3h


ppm
164,9
158,1
149,5
141,9
129,4
116,7
95,1
53,8
45,0
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

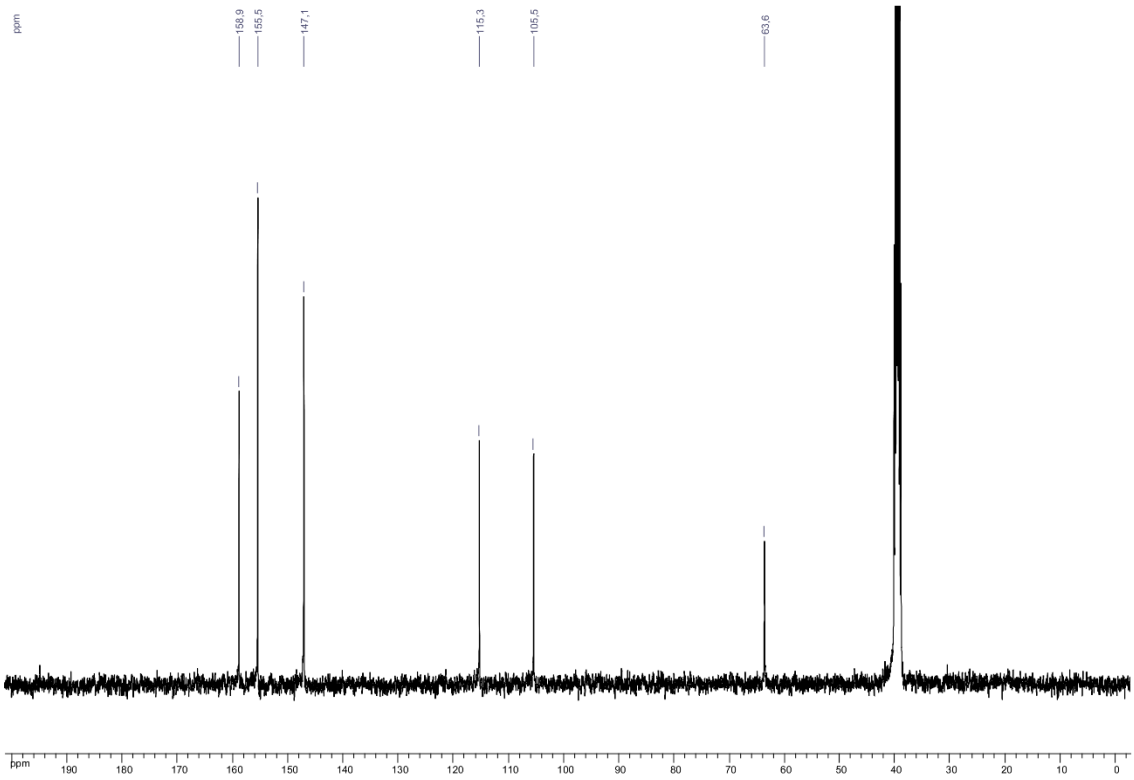

ppm
9,09
8,57
7,13
7,09
F
F
F
F
O
O
N
F
1,0
1,0
2,0
ppm
10
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0

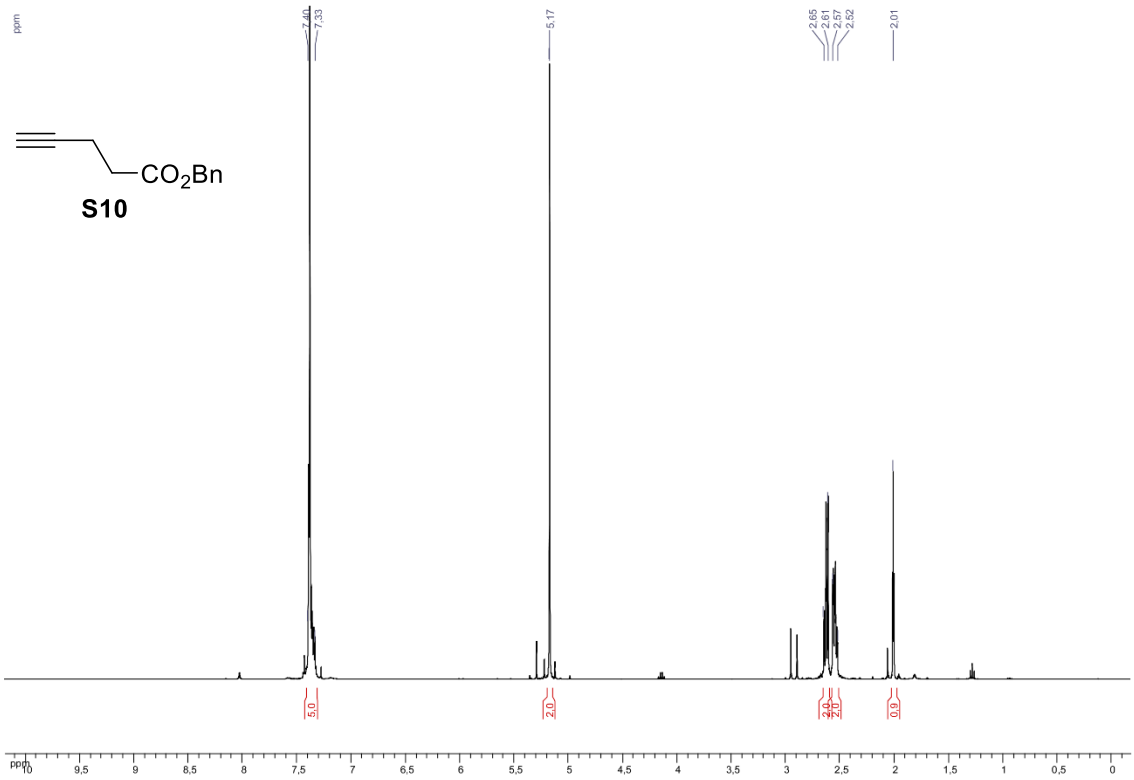
4h


ppm
166,6
160,3
151,6
146,0
143,4
140,6
129,1
121,8
110,2
103,8
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


ppm
12,793
8,359
8,040
I
CN
N
OH
1,0
0,9
1,0
ppm
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0

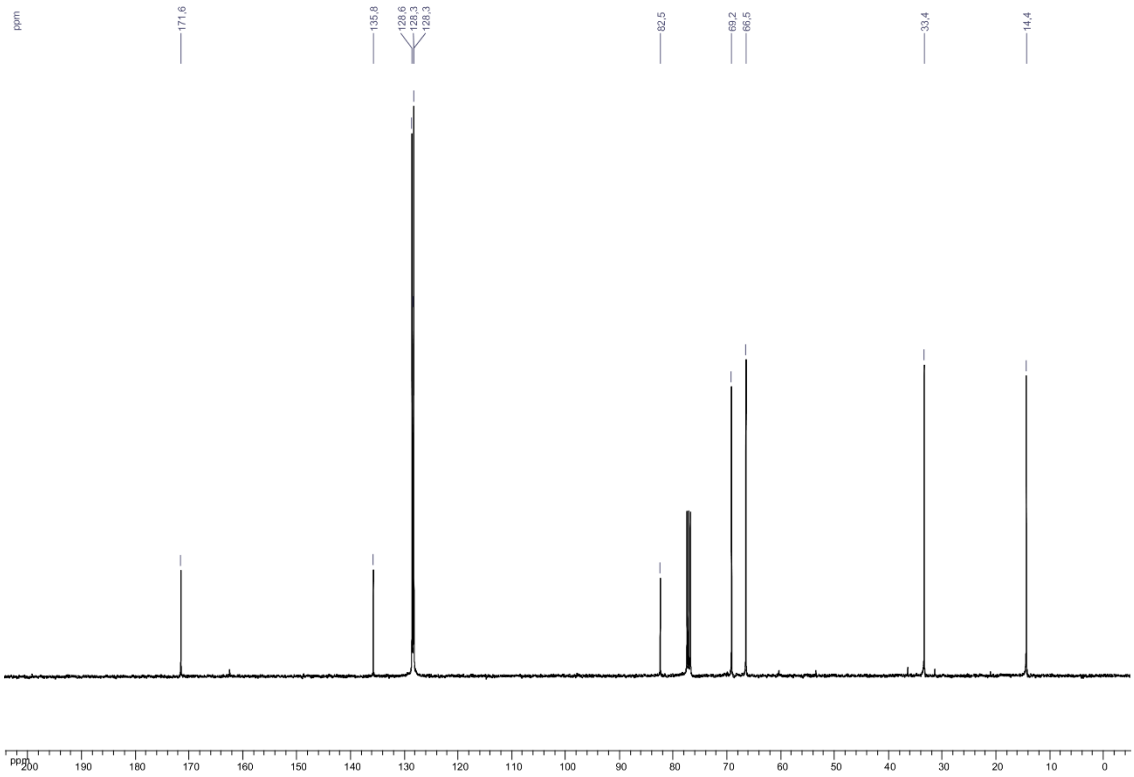
S9

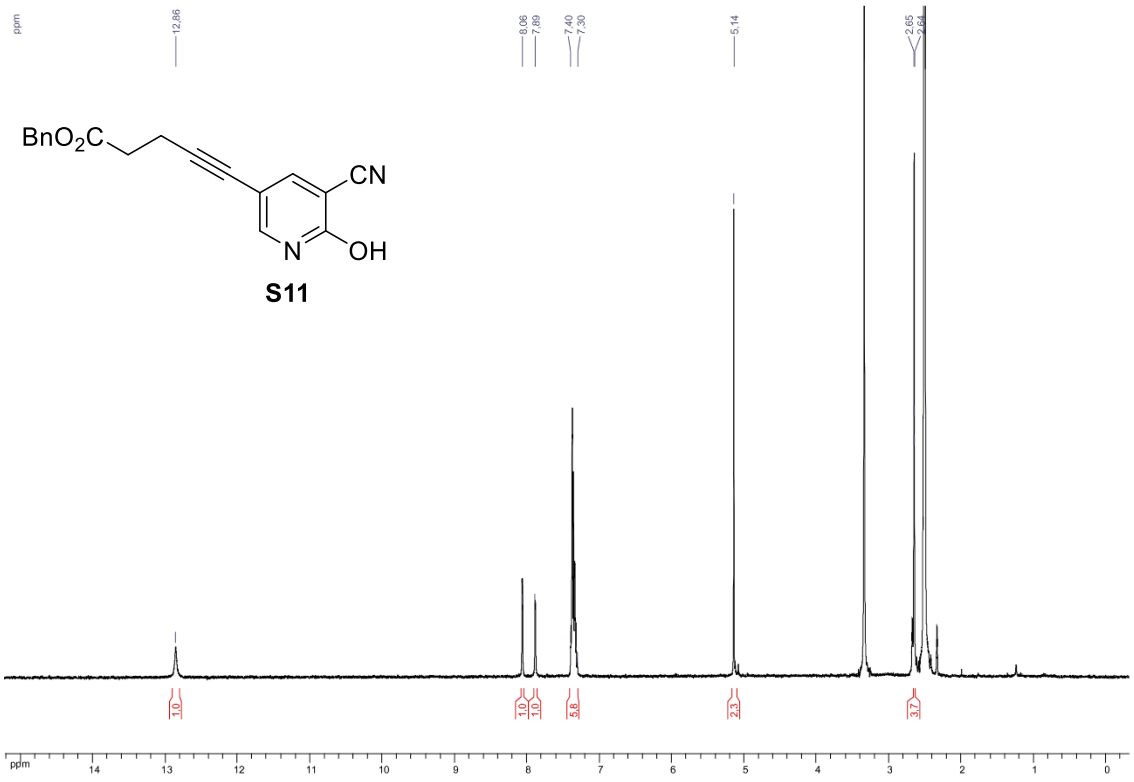

ppm
158,9
155,5
147,1
115,3
105,5
63,6
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

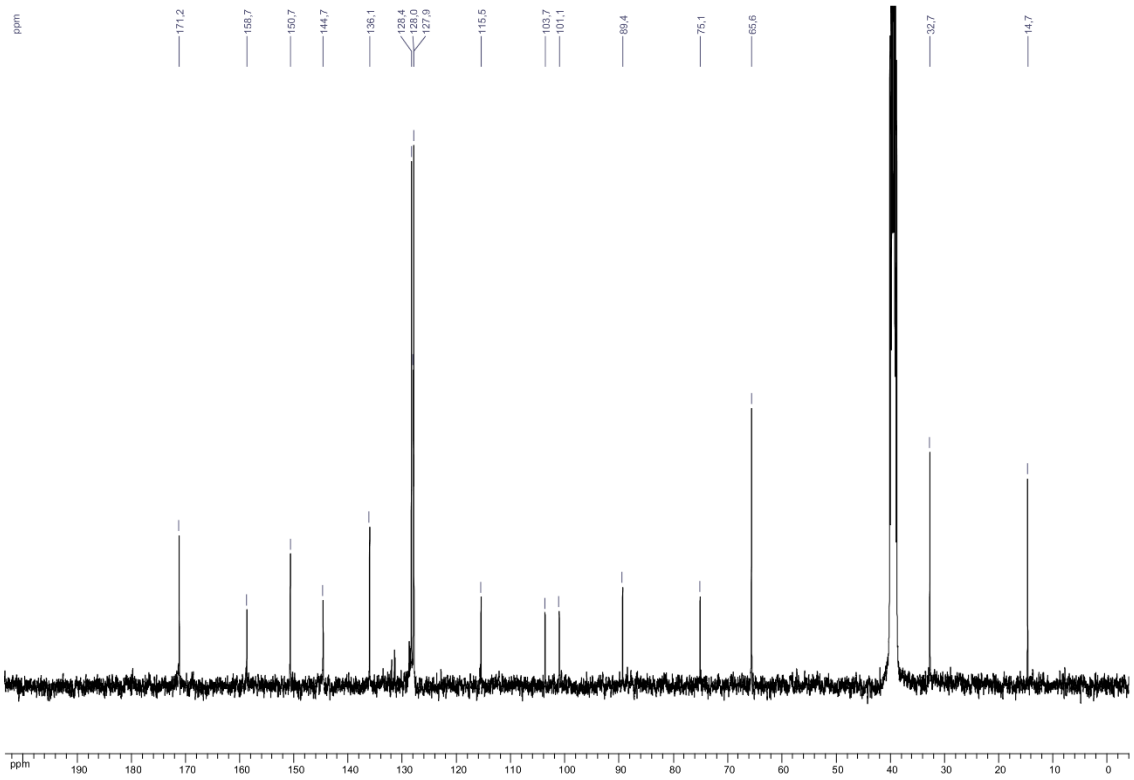

ppm
7.40
7.33
5.17
2.65
2.61
2.57
2.52
2.01
5.0
2.0
2.0
2.0
0.9
ppm
10
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0

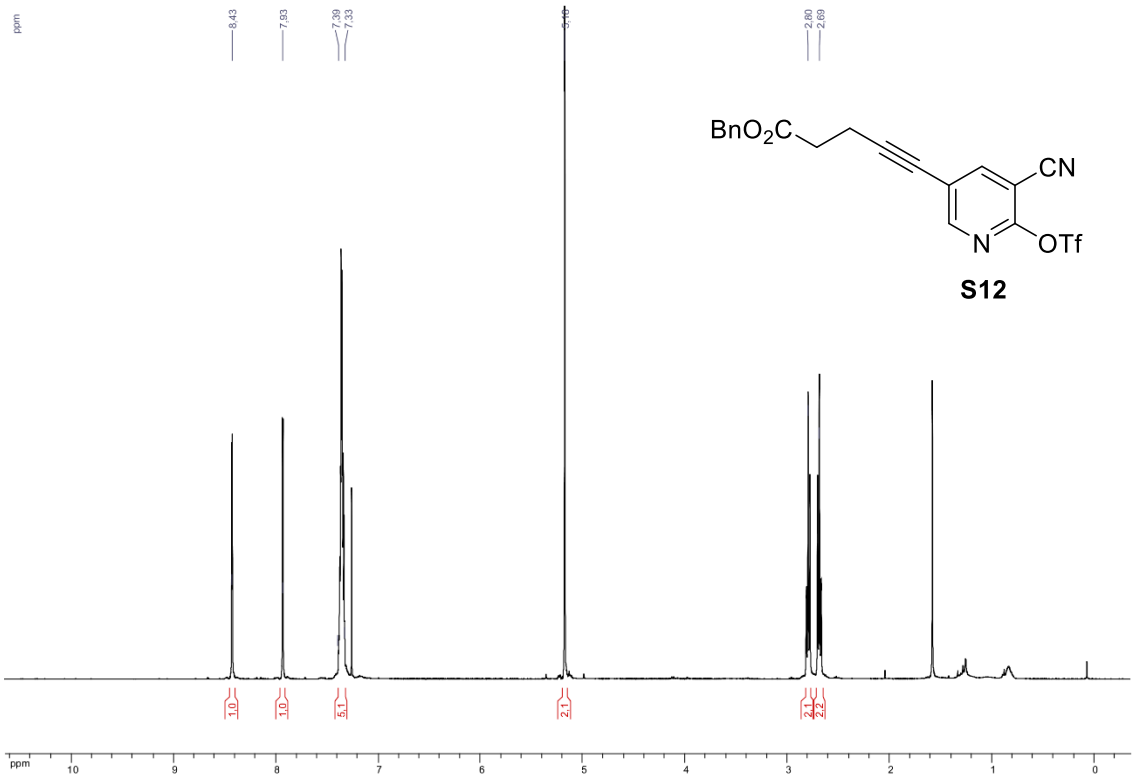
CO_2Bn

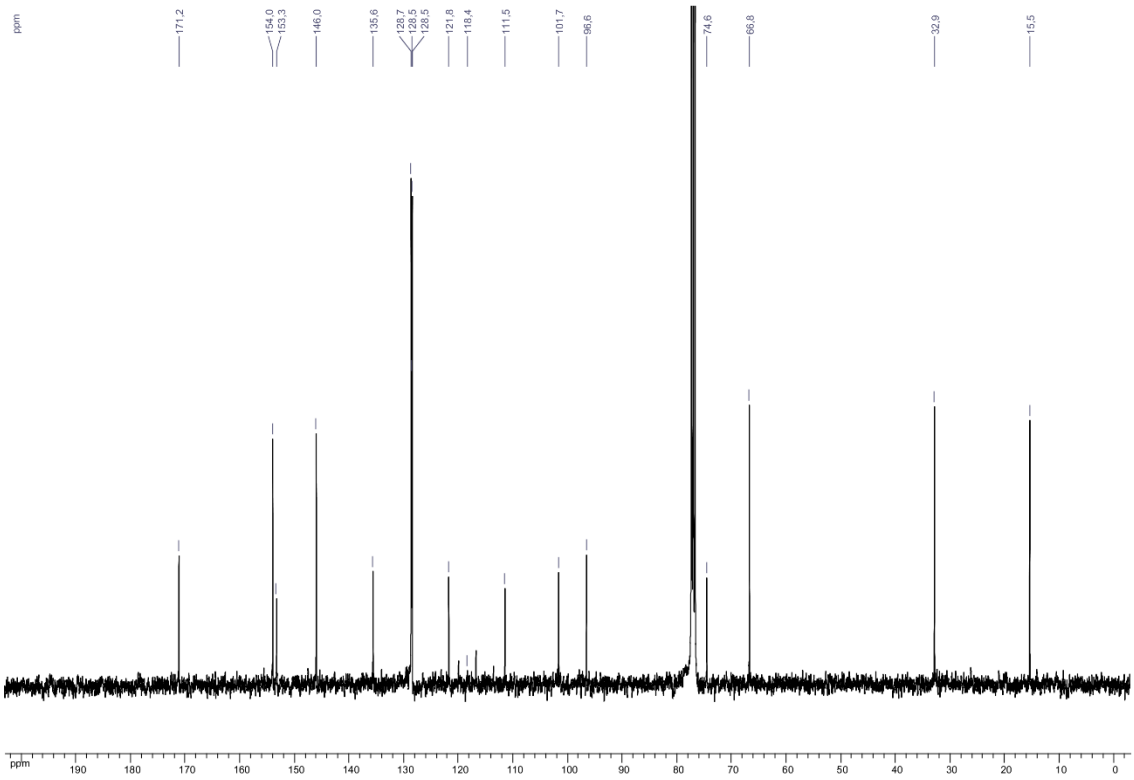
S10

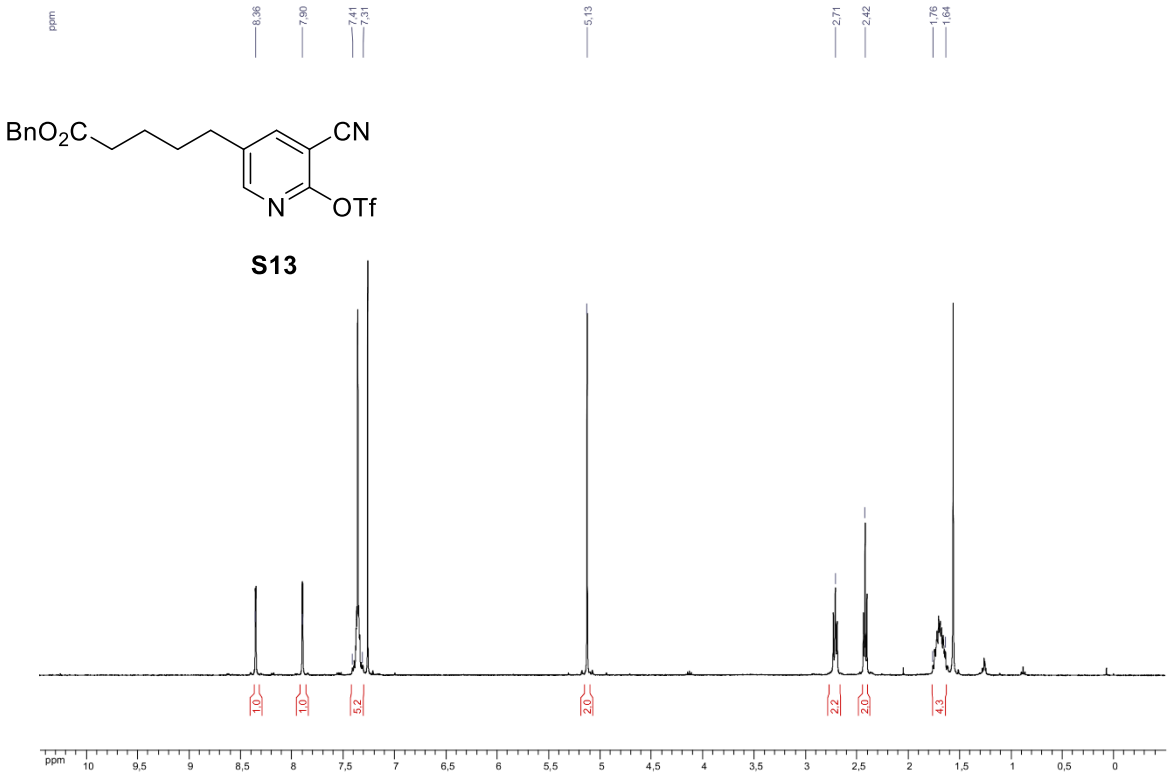

ppm
171,6
135,8
128,6
128,3
128,3
82,5
69,2
66,5
33,4
14,4
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


ppm
12.86
8.06
7.89
7.40
7.30
5.14
2.65
2.64
BnO2C
CN
N
OH
S11
1.0
1.0
1.0
5.8
2.3
3.7
ppm
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0

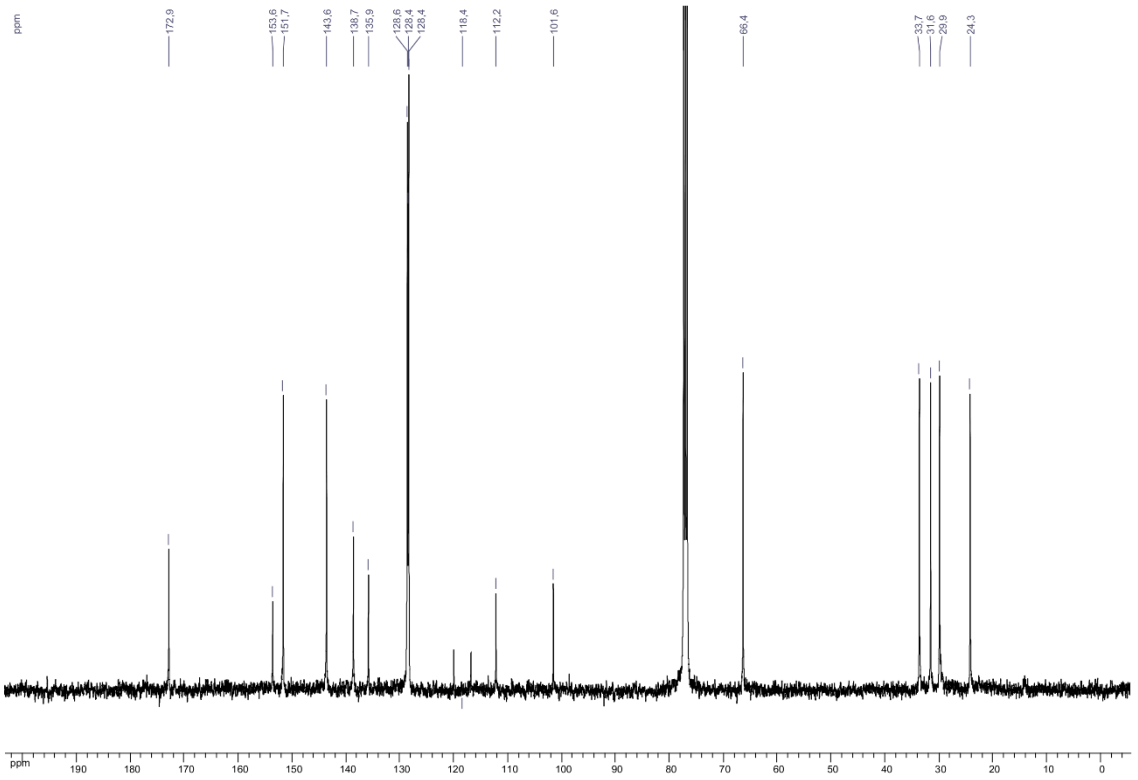

ppm
171.2
158.7
150.7
144.7
136.1
128.4
128.0
127.9
115.5
103.7
101.1
89.4
76.1
65.6
32.7
14.7
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

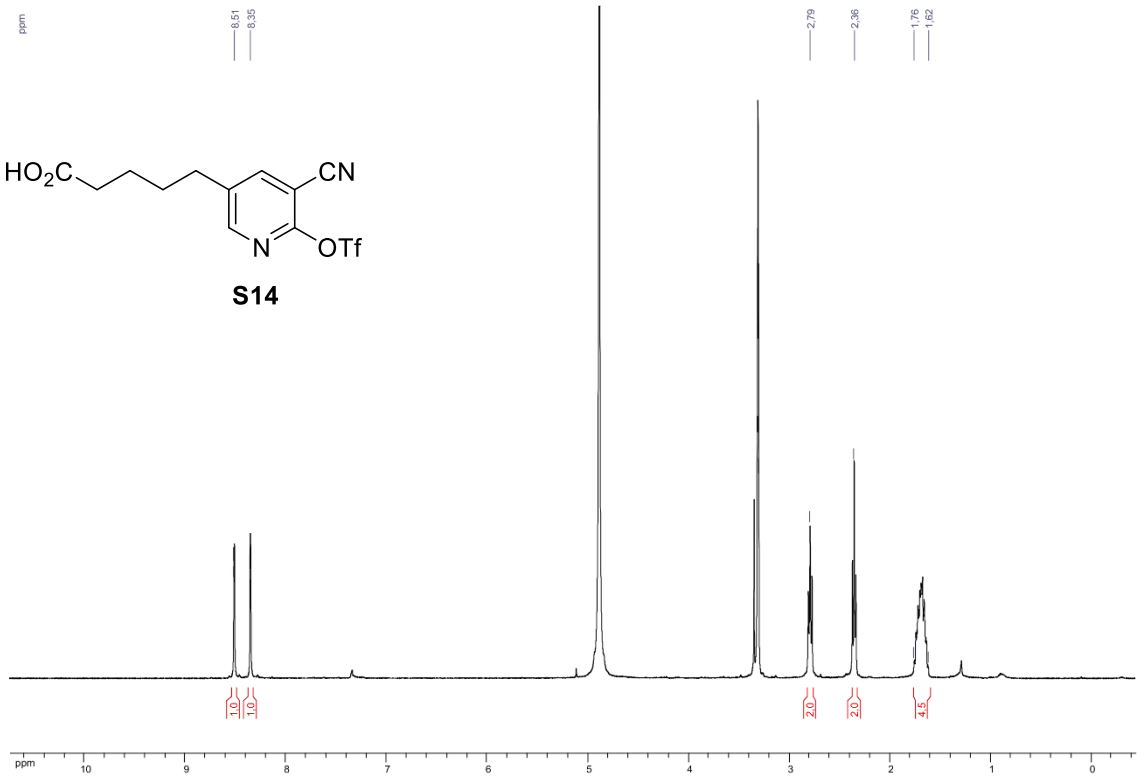

ppm
8.43
7.93
7.39
7.33
5.16
2.80
2.69
BnO2C
CN
N
OTf
S12
1.0
1.0
5.1
2.1
2.1
2.2
ppm
10
9
8
7
6
5
4
3
2
1
0


ppm
171.2
154.0
153.3
146.0
135.6
128.7
128.5
128.5
121.8
118.4
111.5
101.7
96.6
74.6
66.8
32.9
15.5
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

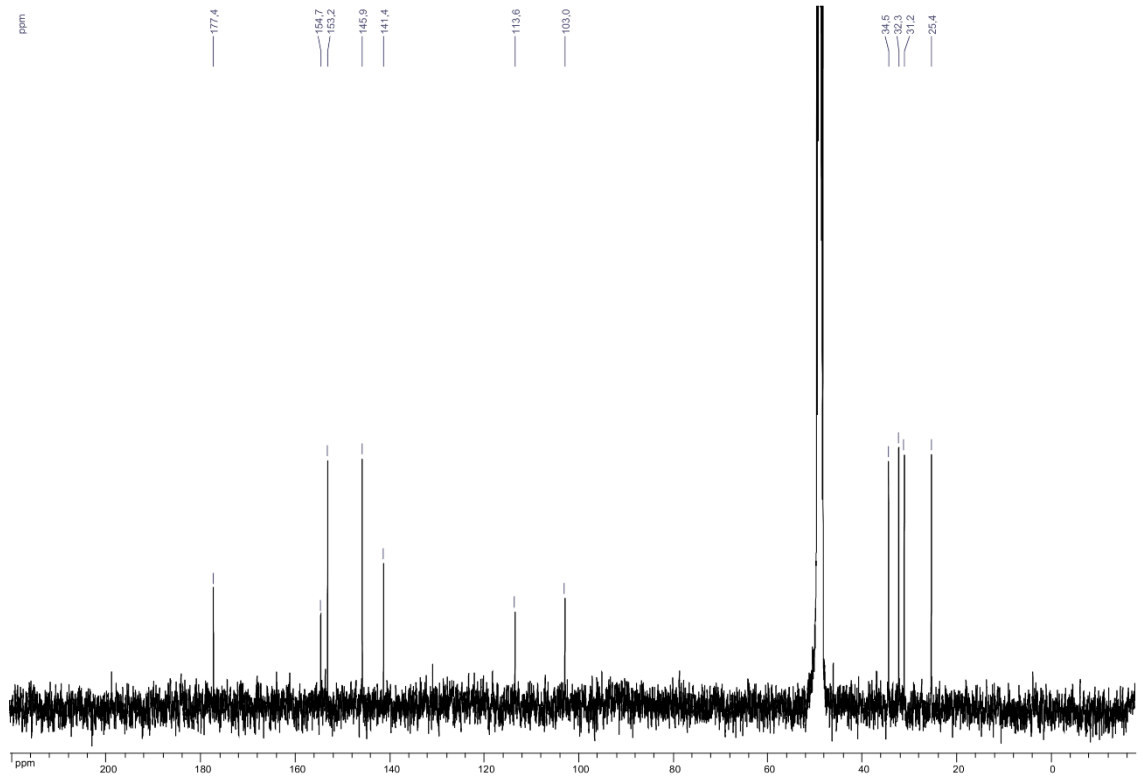

ppm
8,36
7,90
7,41
7,31
5,13
2,71
2,42
1,76
1,64
BnO2C
CN
N
OTf
1,0
1,0
5,2
2,0
2,2
2,0
4,3
ppm
10
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0

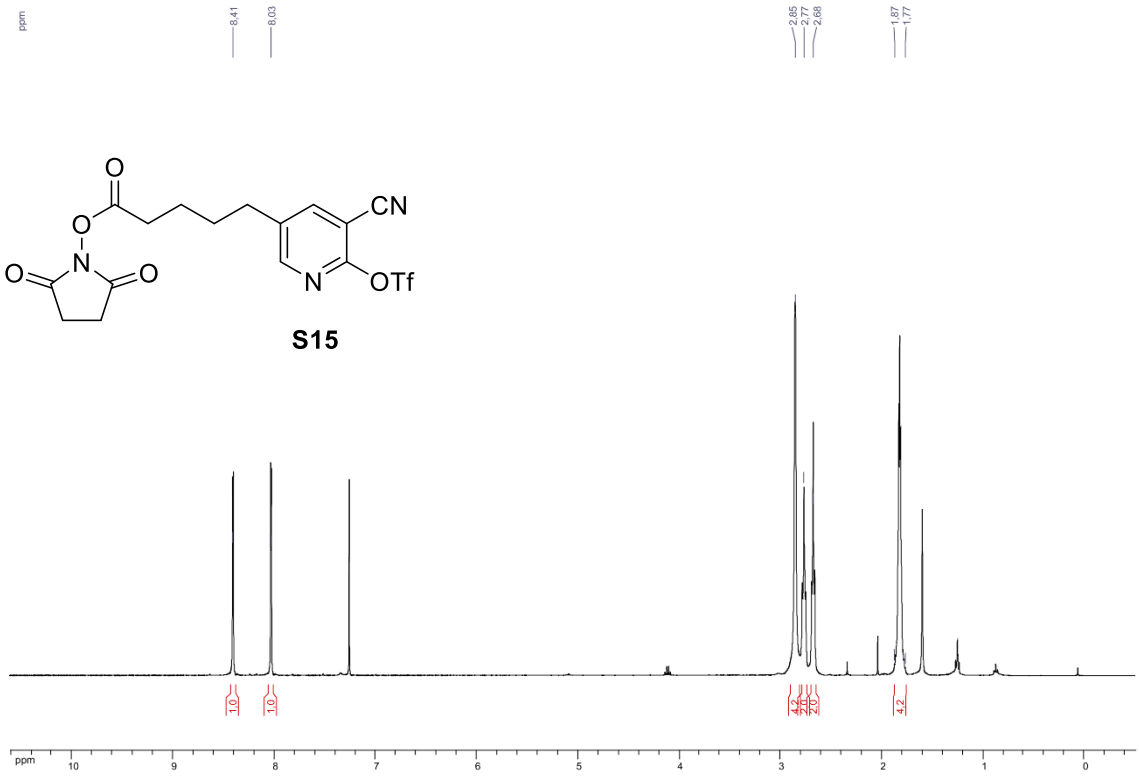
S13


ppm
172,9
153,6
151,7
143,6
138,7
135,9
128,6
128,4
128,4
118,4
112,2
101,6
66,4
33,7
31,6
29,9
24,3
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

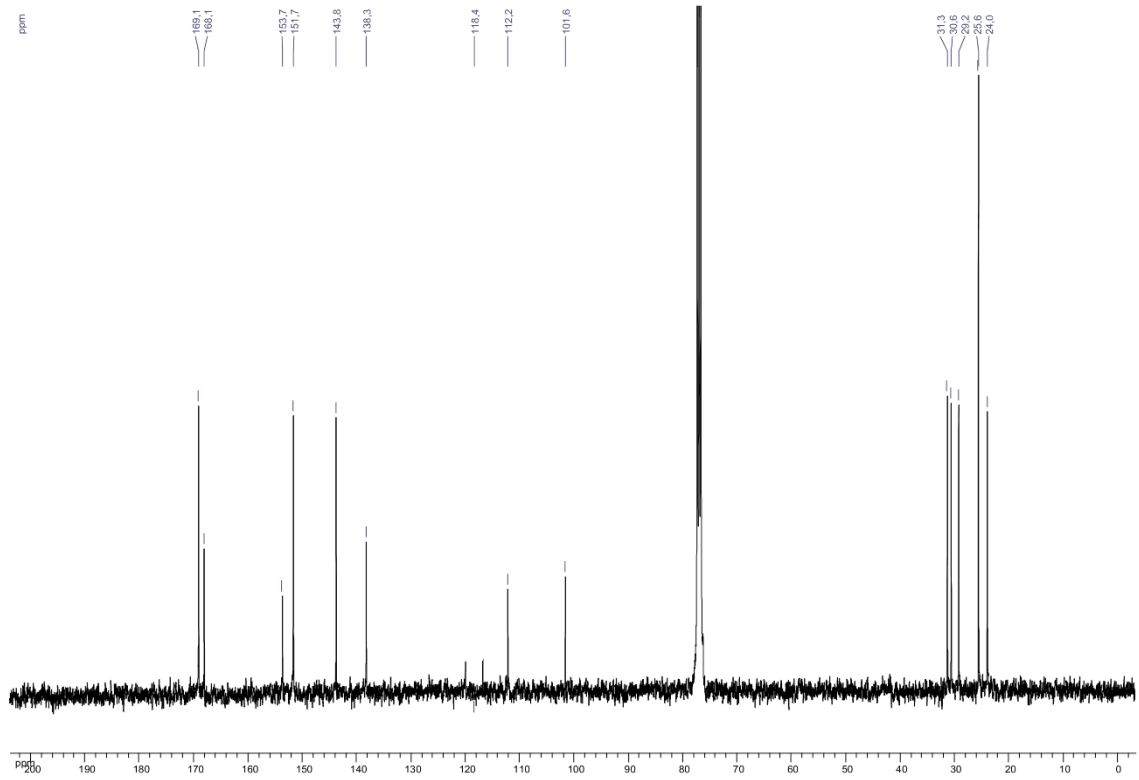

ppm
8.51
8.35
2.79
2.36
1.76
1.62
HO2C
CN
N
OTf
1.0
1.0
2.0
2.0
4.5
10
9
8
7
6
5
4
3
2
1
0

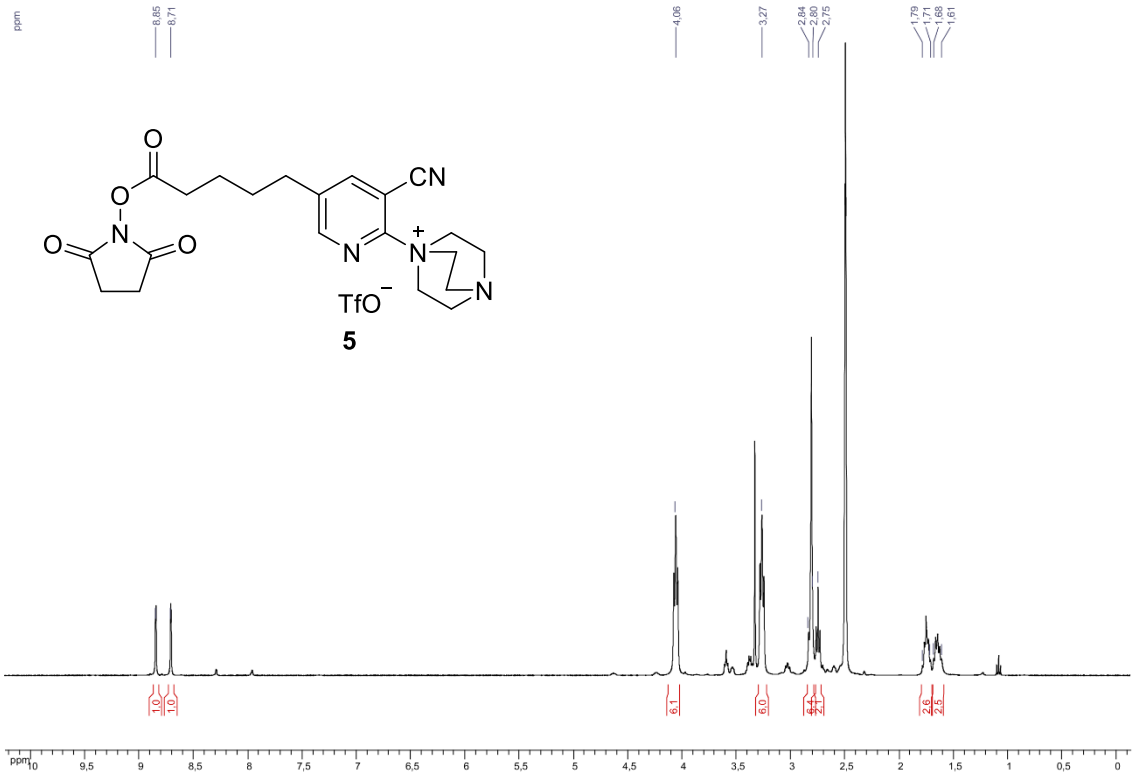
S14


ppm
177.4
154.7
153.2
145.9
141.4
113.6
103.0
34.5
32.3
31.2
25.4
200
180
160
140
120
100
80
60
40
20
0

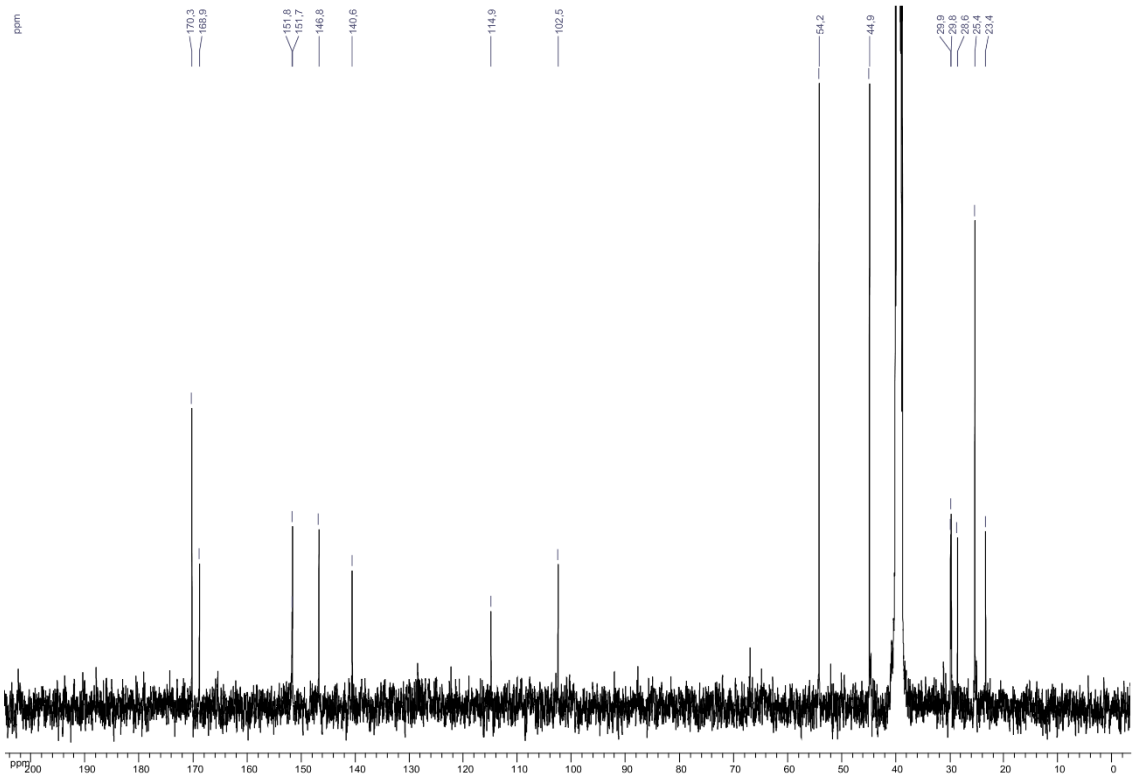

ppm
8.41
8.03
2.85
2.77
2.68
1.87
1.77
O
O
N
O
O
CN
N
OTf
1.0
1.0
4.2
4.2
ppm
10
9
8
7
6
5
4
3
2
1
0

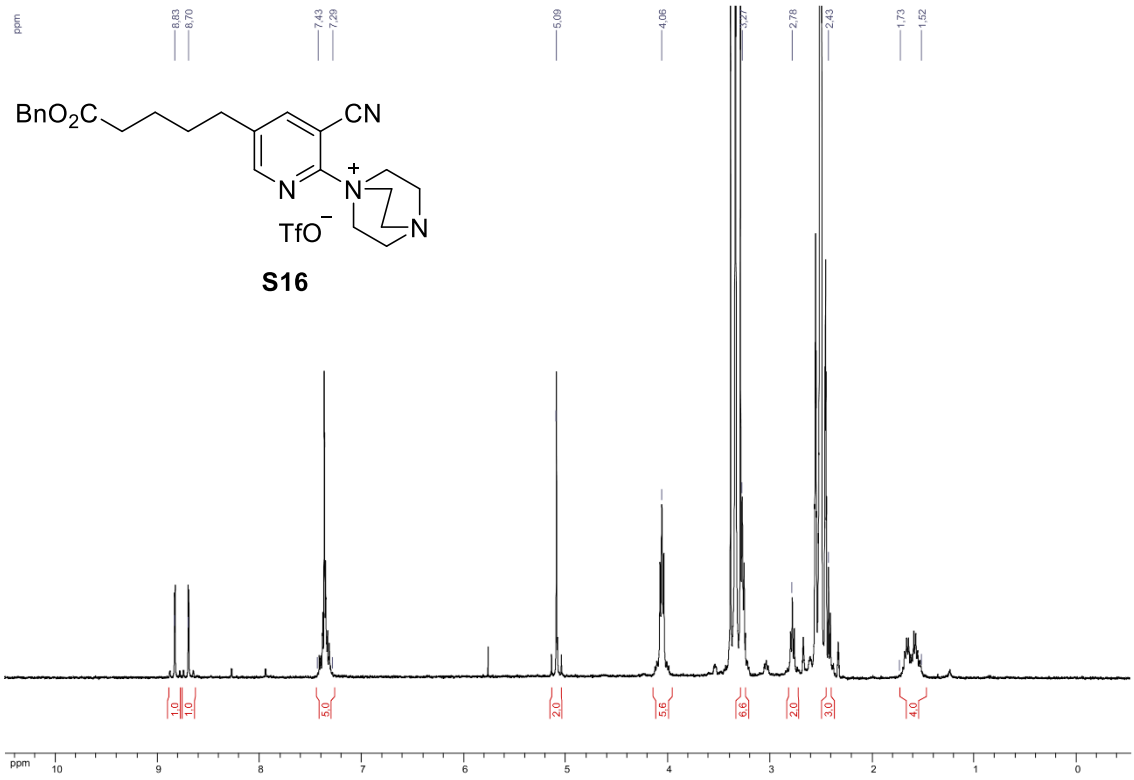
S15


ppm
169.1
168.1
153.7
151.7
143.8
138.3
118.4
112.2
101.6
31.3
30.6
29.2
25.6
24.0
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

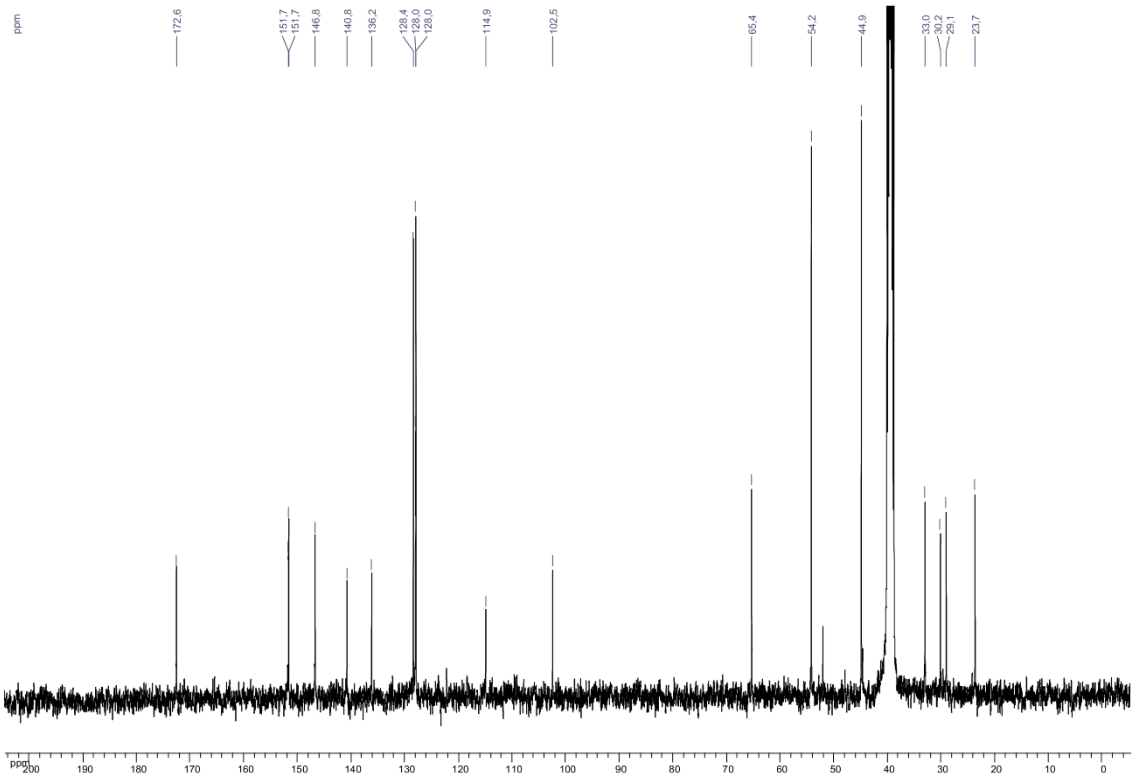

ppm
8,85
8,71
4,06
3,27
2,84
2,80
2,75
1,79
1,71
1,68
1,61
O
O
N
O
O
CN
N
N
N
TfO⁻
1,0
1,0
6,1
6,0
4,4
2,1
2,6
2,5
ppm
10
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0

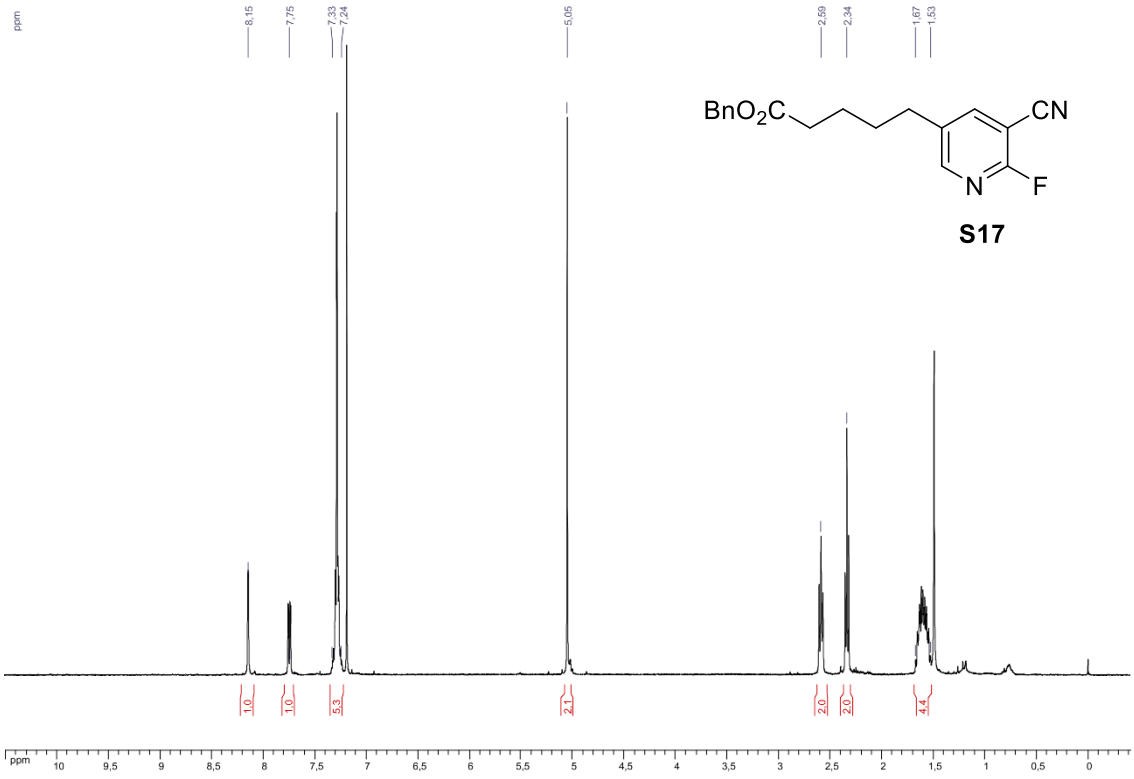
5

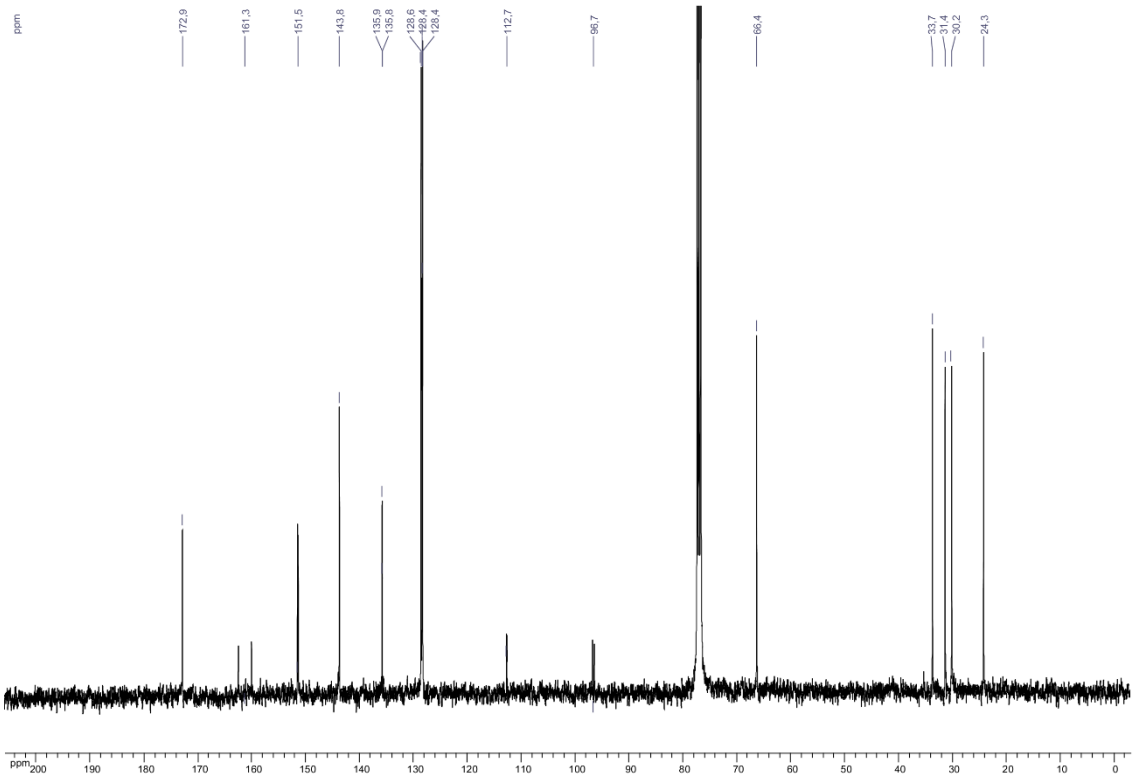

ppm
170,3
168,9
151,8
151,7
146,8
140,6
114,9
102,5
54,2
44,9
29,9
29,8
29,6
25,5
25,4
23,4
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


ppm
8.83
8.70
7.43
7.29
5.09
4.06
3.27
2.78
2.43
1.73
1.52
BnO2C
CN
N
N
TfO
N
1.0
1.0
1.0
5.0
2.0
5.6
6.6
2.0
3.0
4.0
ppm
10
9
8
7
6
5
4
3
2
1
0

S16

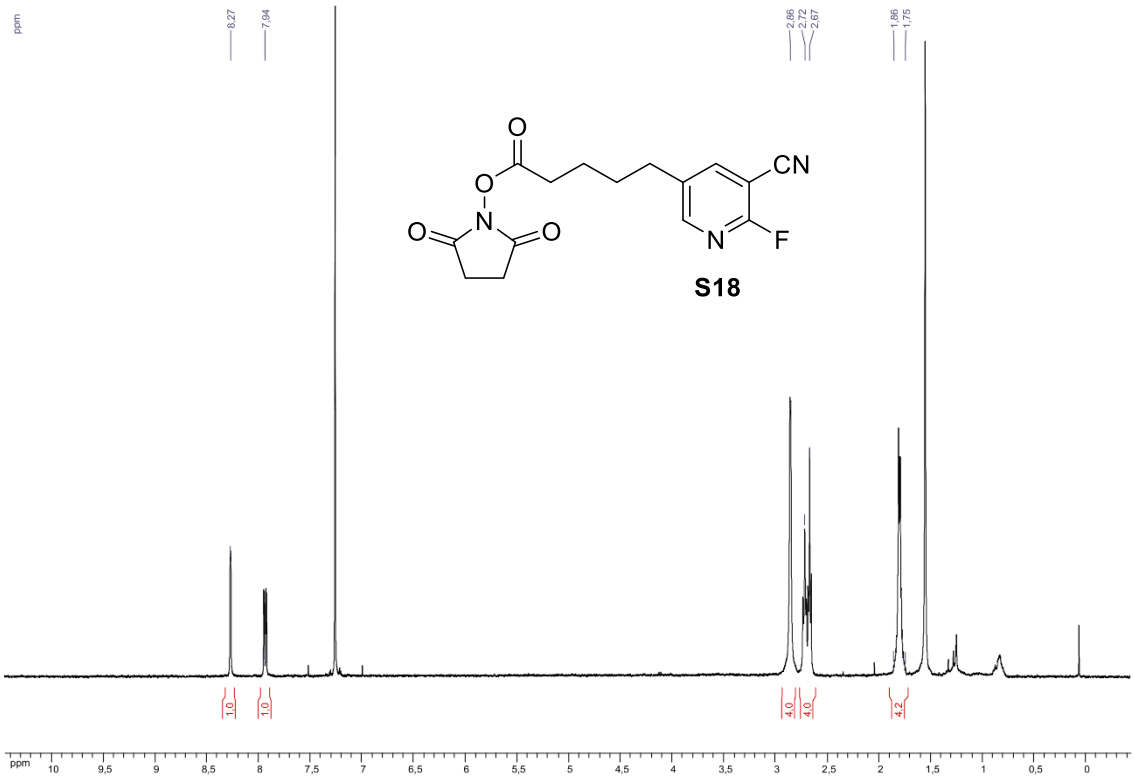

ppm
172.6
151.7
151.7
146.8
140.8
136.2
128.4
128.0
128.0
114.9
102.5
65.4
54.2
44.9
33.0
30.2
29.1
23.7
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

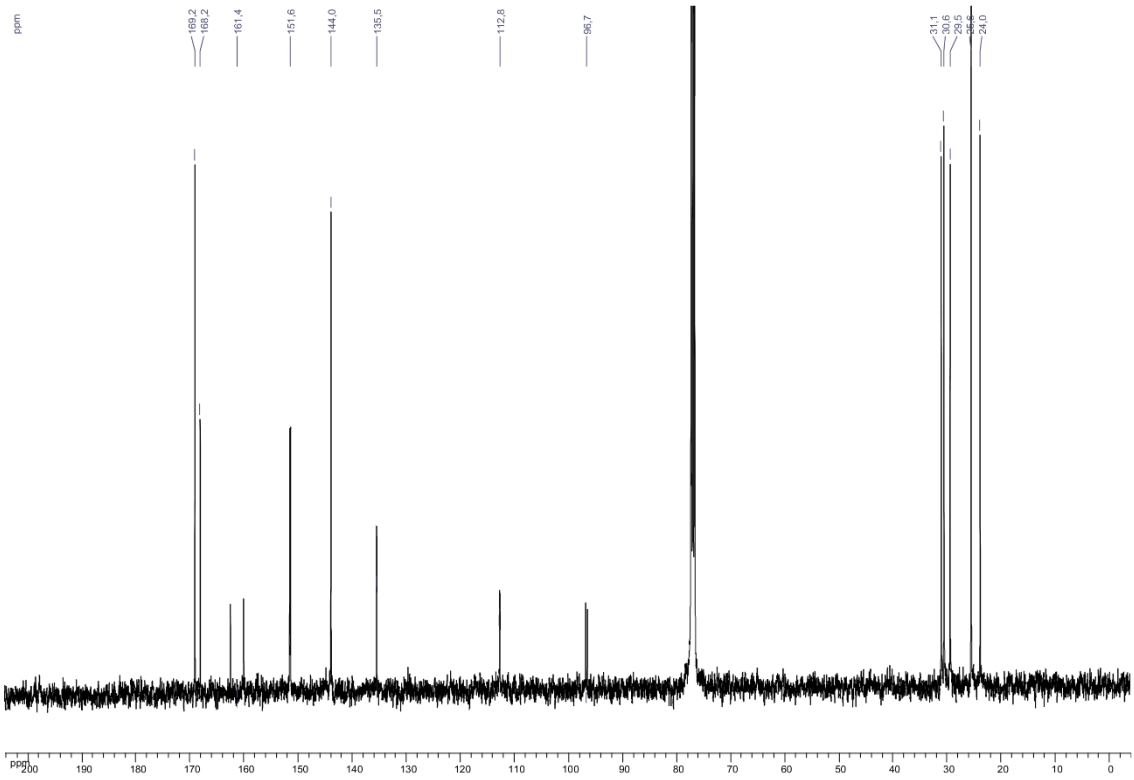

ppm
8,15
7,75
7,33
7,24
5,05
2,59
2,34
1,67
1,53
1,0
1,0
5,3
2,1
2,0
2,0
4,4
ppm
10
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0

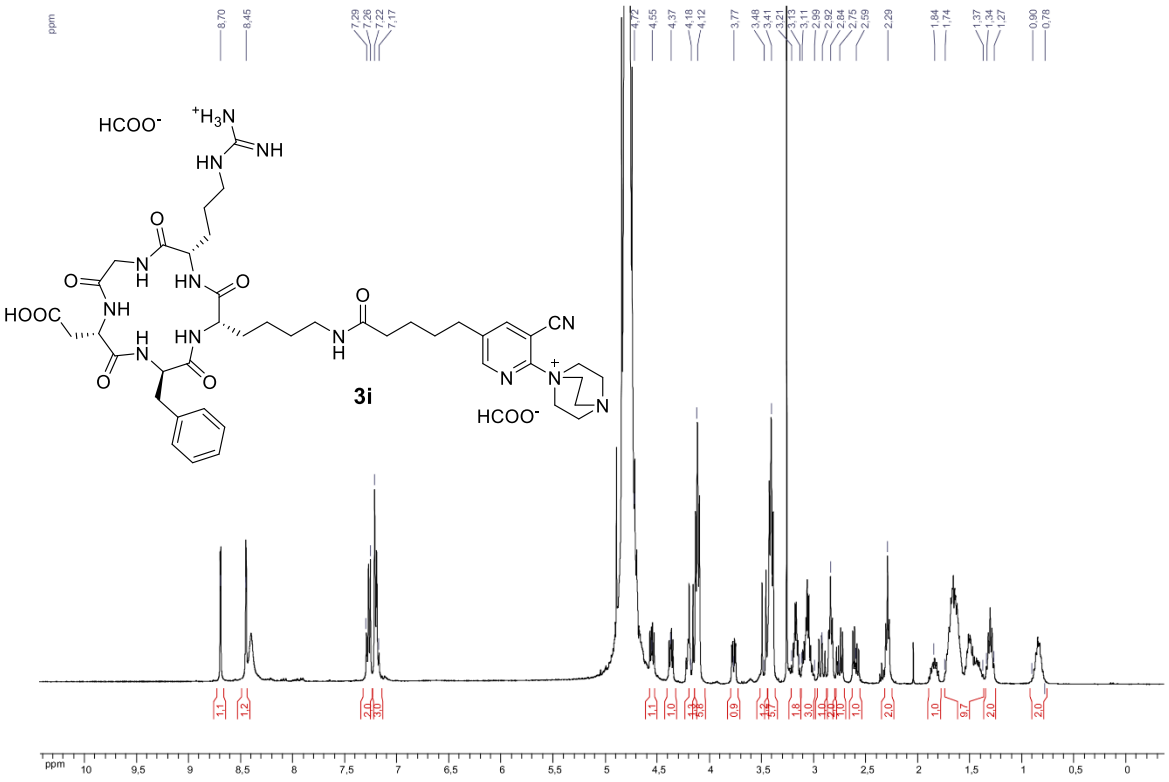

ppm
172,9
161,3
151,5
143,8
135,9
135,8
128,6
128,4
128,4
112,7
96,7
66,4
33,7
31,4
30,2
24,3
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

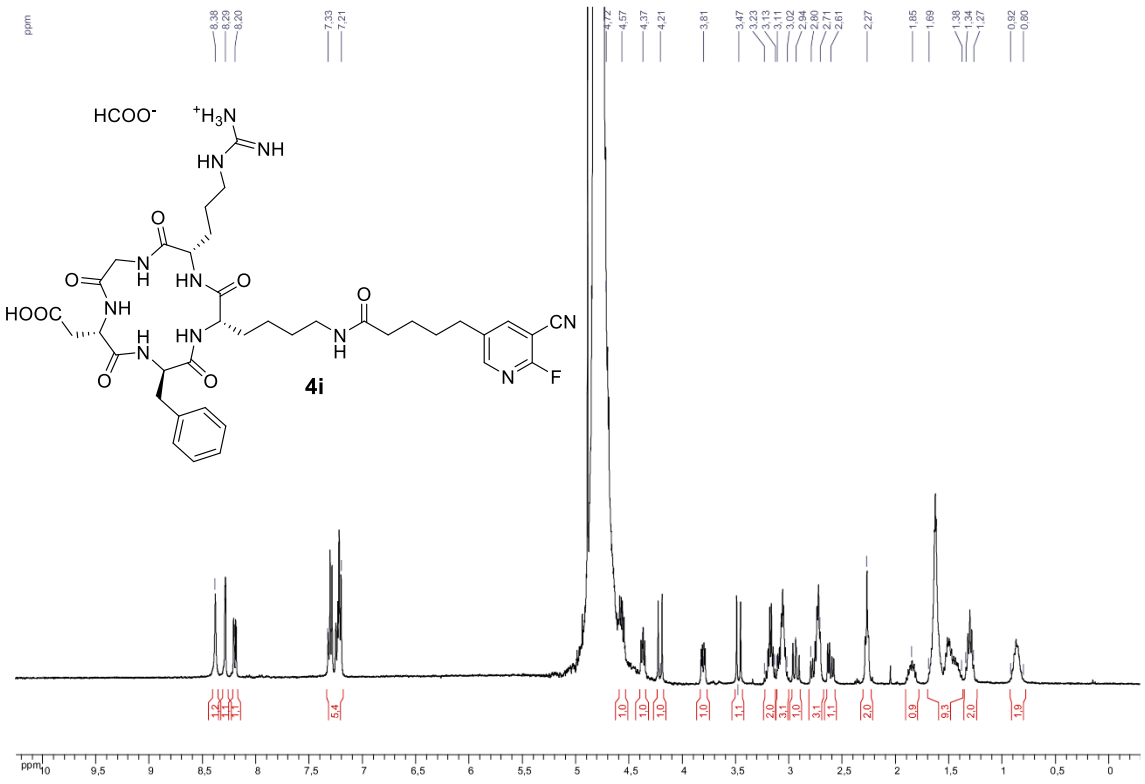
BnO2C
CN
N
F

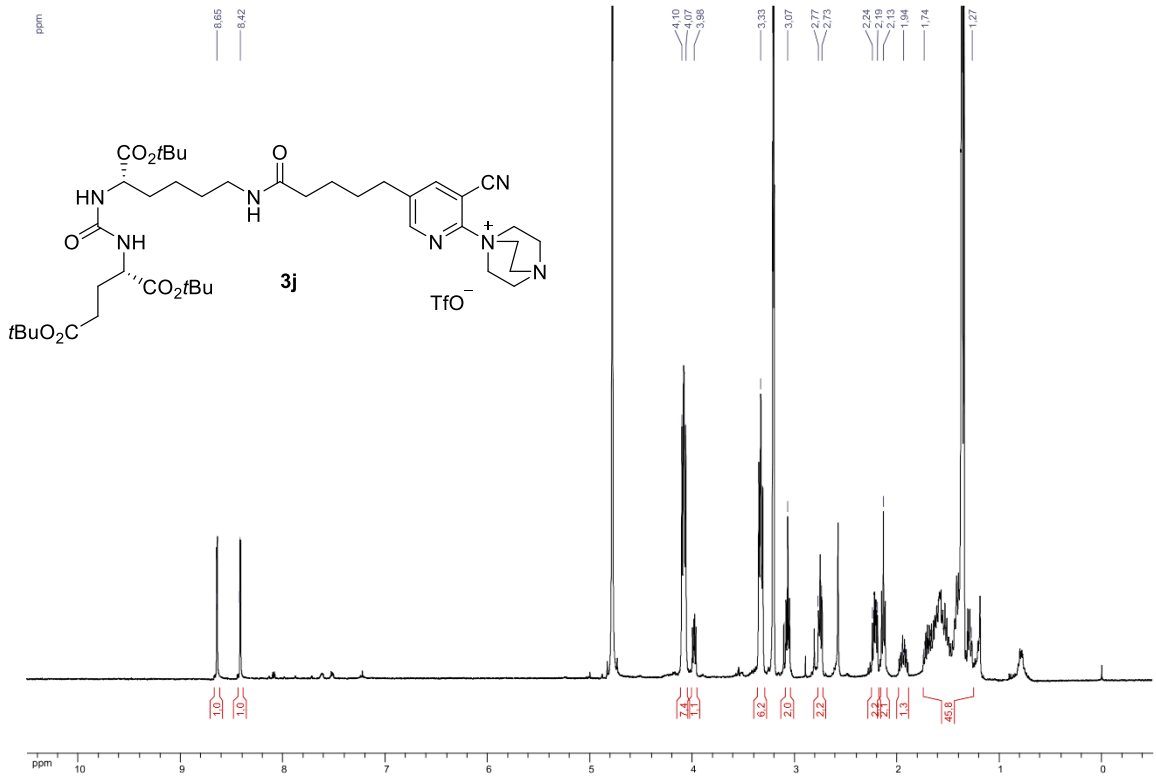
S17

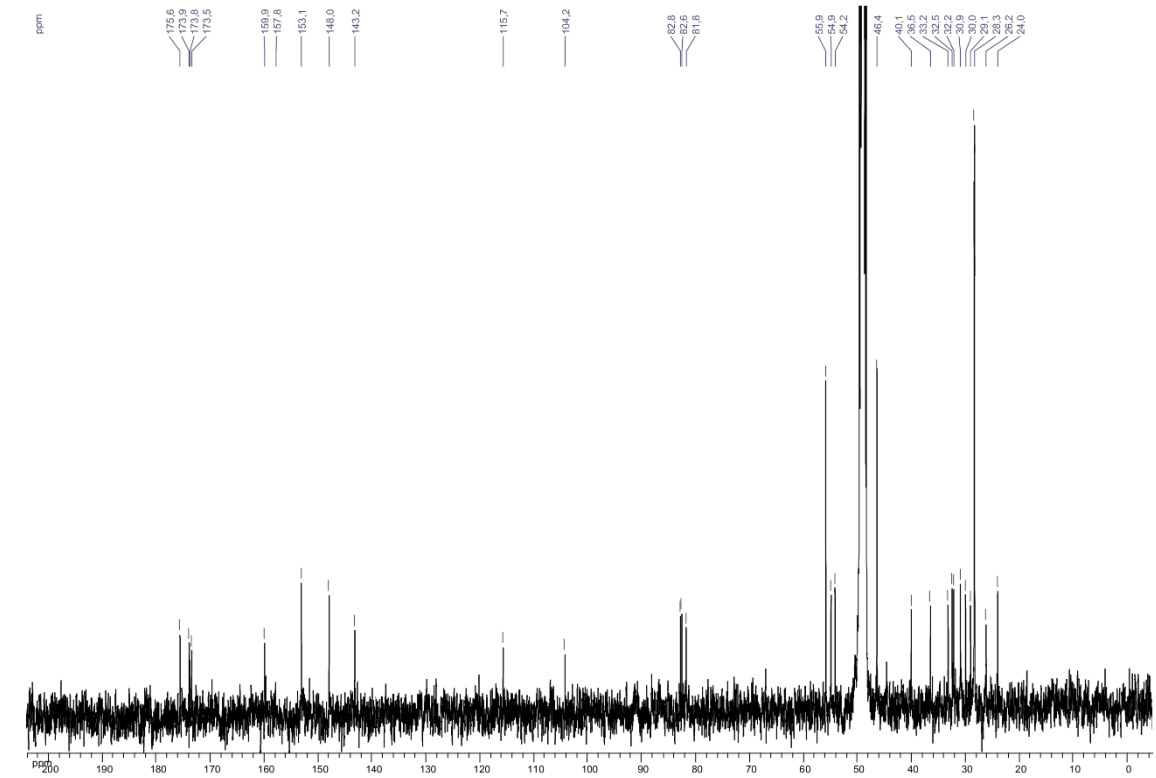

ppm
8,27
7,94
2,86
2,72
2,67
1,86
1,75
O
O
N
O
O
CN
N
F
S18
1,0
1,0
4,0
4,0
4,2
ppm
10
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0

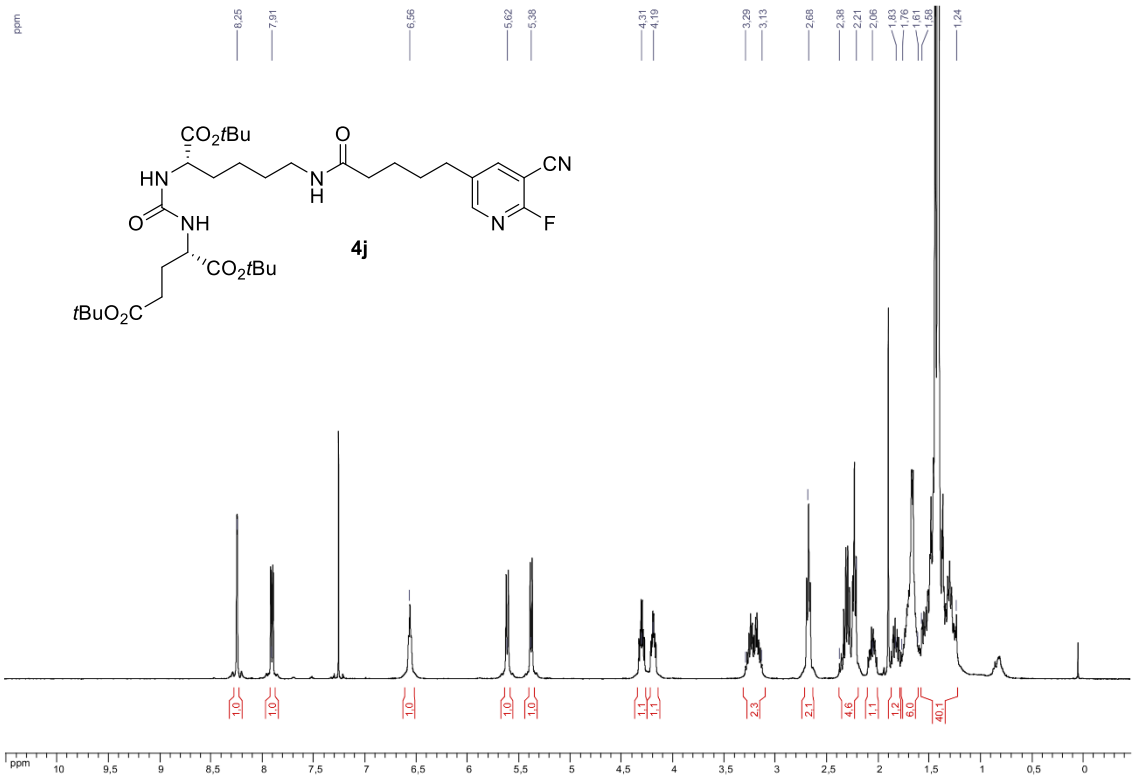

ppm
169,2
168,2
161,4
151,6
144,0
135,5
112,8
96,7
31,1
30,6
29,5
25,8
24,0
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

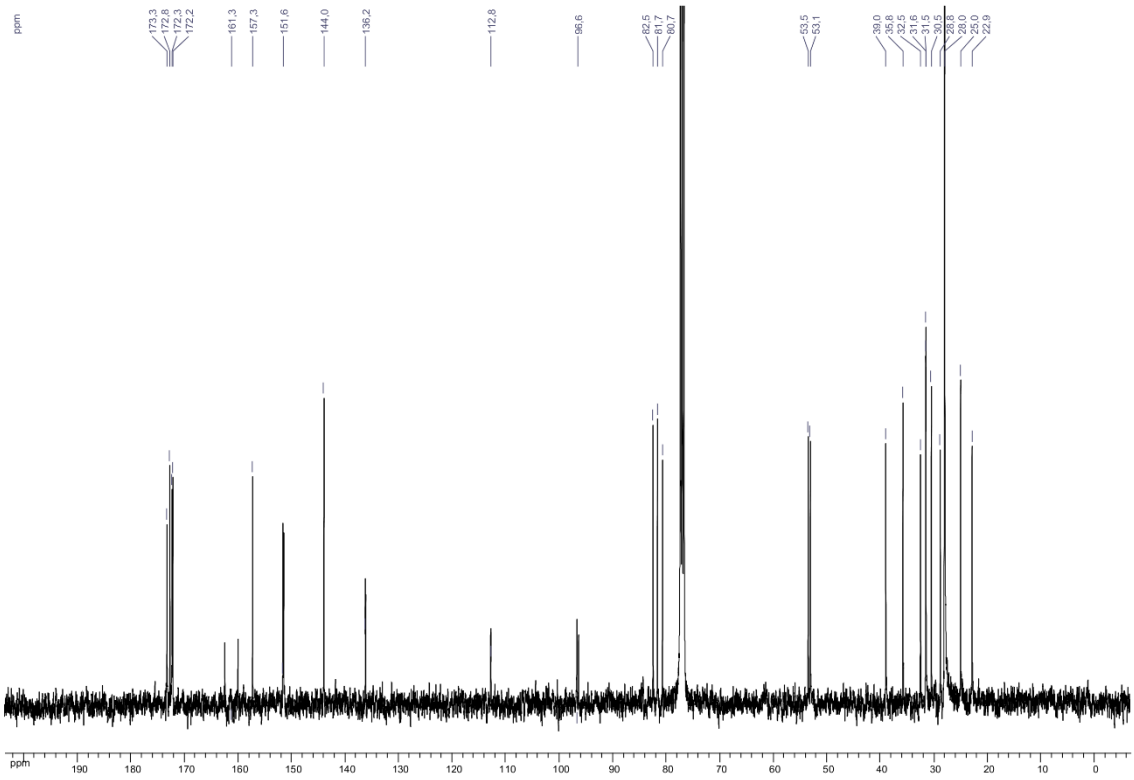

HCOO-
+H3N
NH
HN
HOOC
NH
HN
CN
N
+
HCOO-
3i

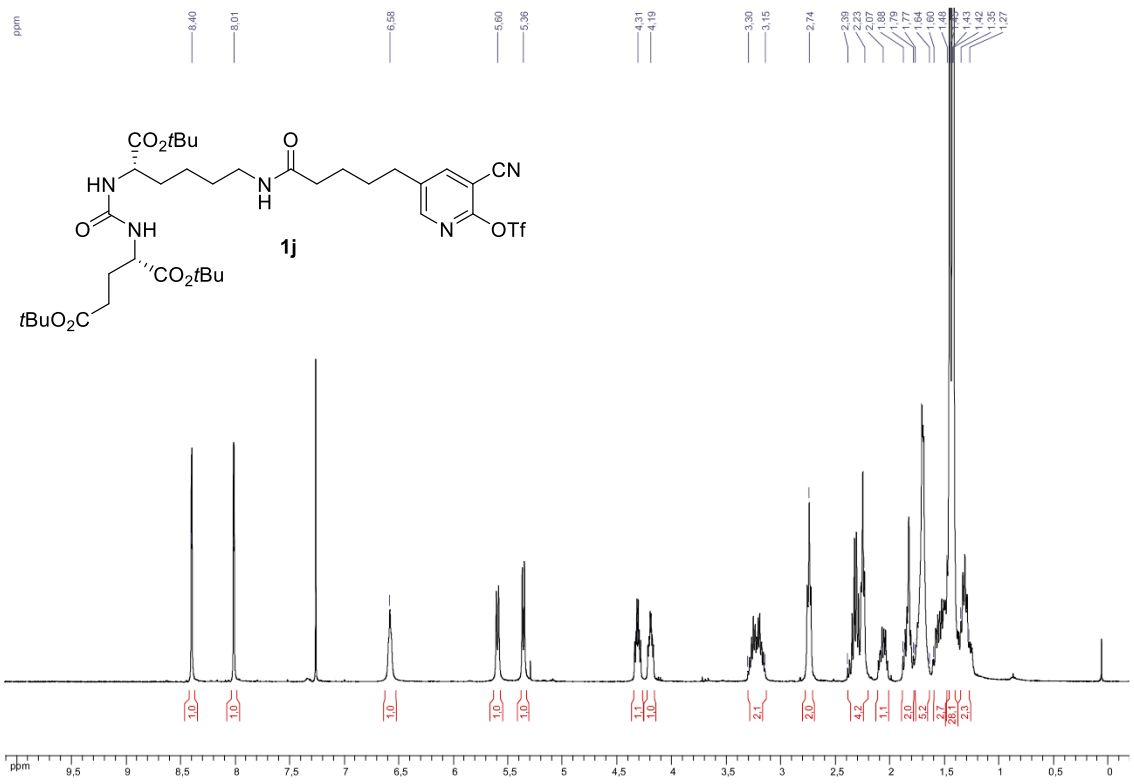

HCOO-
+H3N
NH
HN
HOOC
NH
HN
CN
F
4i

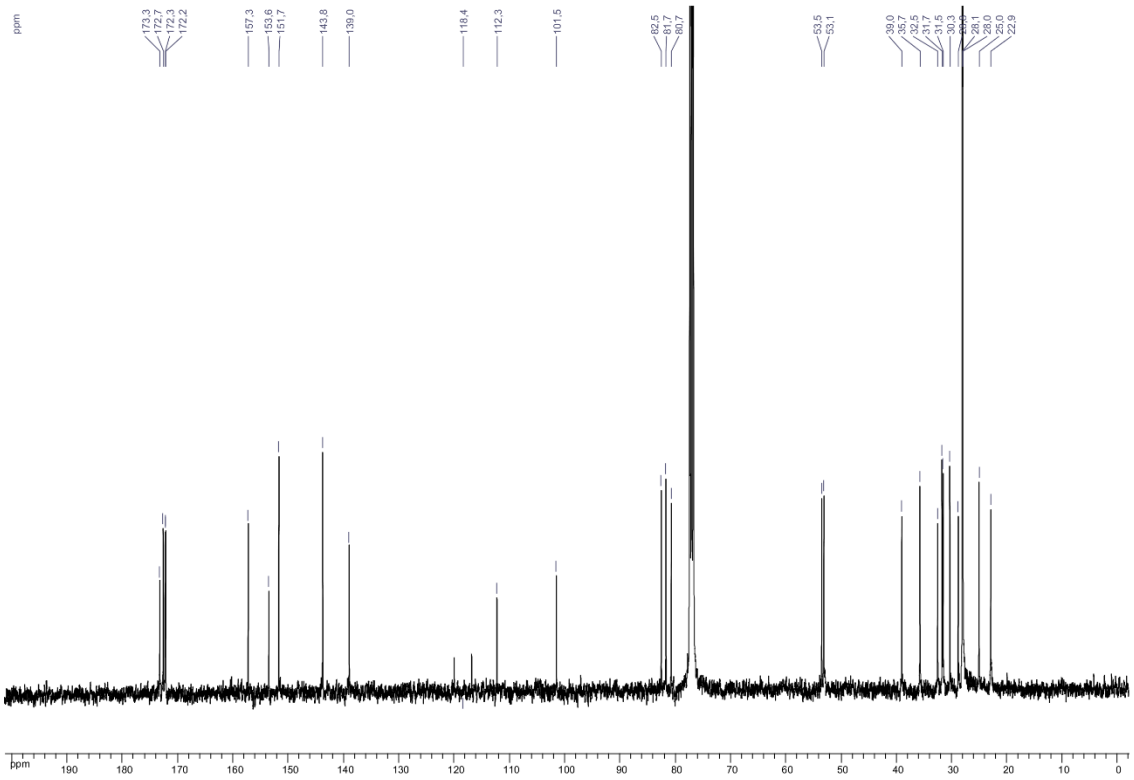

8,65
8,42
4,10
4,07
3,98
3,33
3,07
2,77
2,73
2,24
2,19
2,13
1,94
1,74
1,27
CO2tBu
HN
O
NH
CO2tBu
tBuO2C
O
N
H
CN
N
N
N
TfO−
3j
1,0
1,0
7,4
1,1
6,2
2,0
2,2
2,2
2,1
1,3
45,8
ppm
10
9
8
7
6
5
4
3
2
1
0

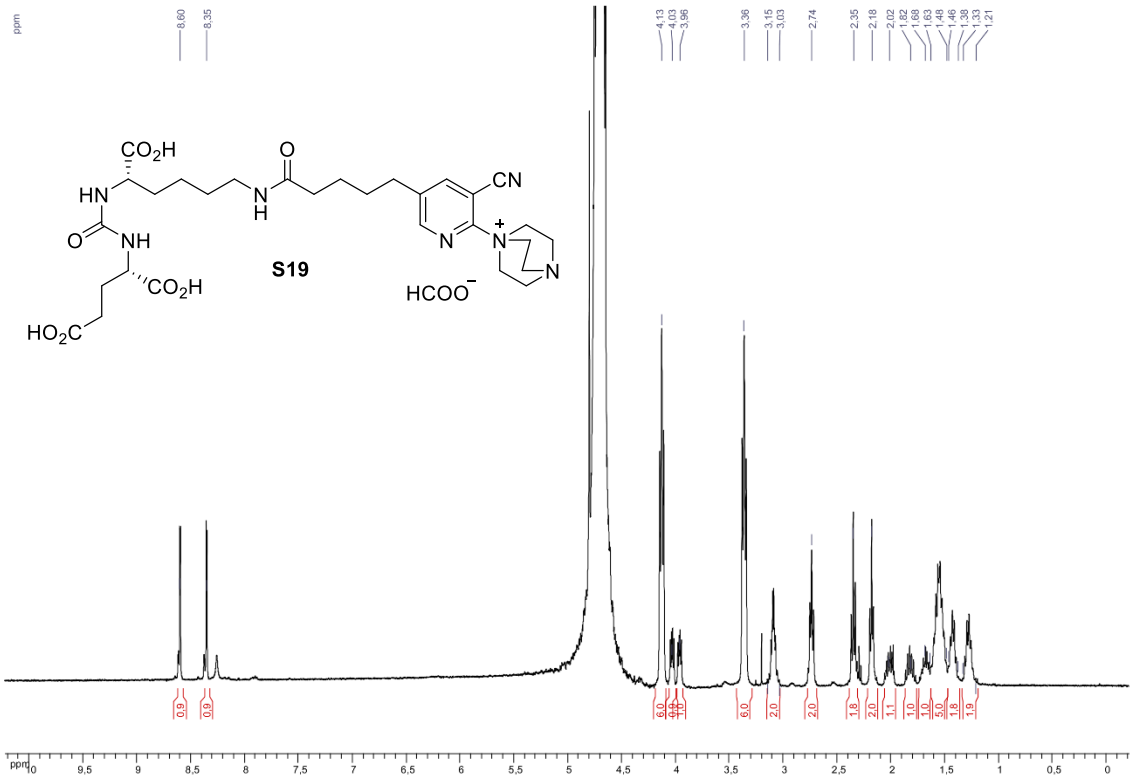

175,6
173,9
173,8
173,5
159,9
157,8
153,1
148,0
143,2
115,7
104,2
82,8
82,6
81,8
55,9
54,9
54,2
46,4
40,1
36,5
33,2
32,5
32,2
30,9
30,0
29,1
28,3
26,2
24,0
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

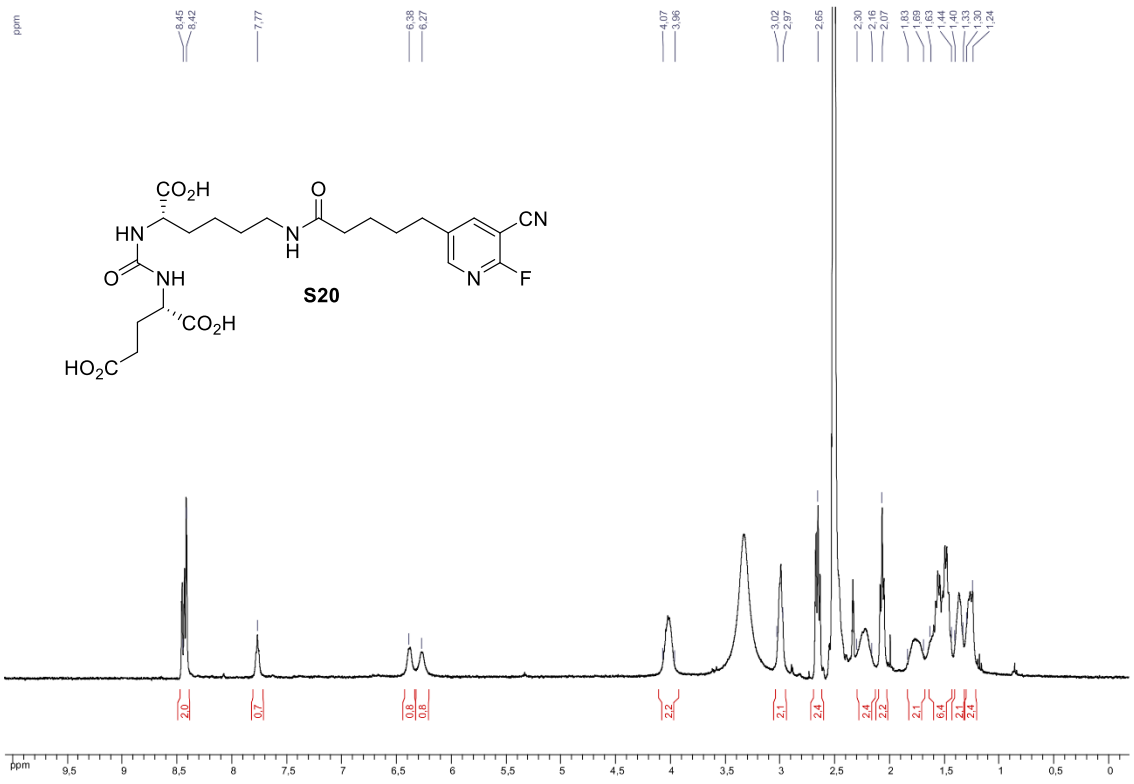

ppm
8,25
7,91
6,56
5,62
5,38
4,31
4,19
3,29
3,13
2,68
2,38
2,21
2,06
1,83
1,76
1,61
1,58
1,24
CO2tBu
HN
O
NH
CO2tBu
tBuO2C
O
N
H
CN
N
F
4j
1,0
1,0
1,0
1,0
1,0
1,1
1,1
2,3
2,1
4,6
1,1
1,2
6,0
40,1
ppm
10
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0

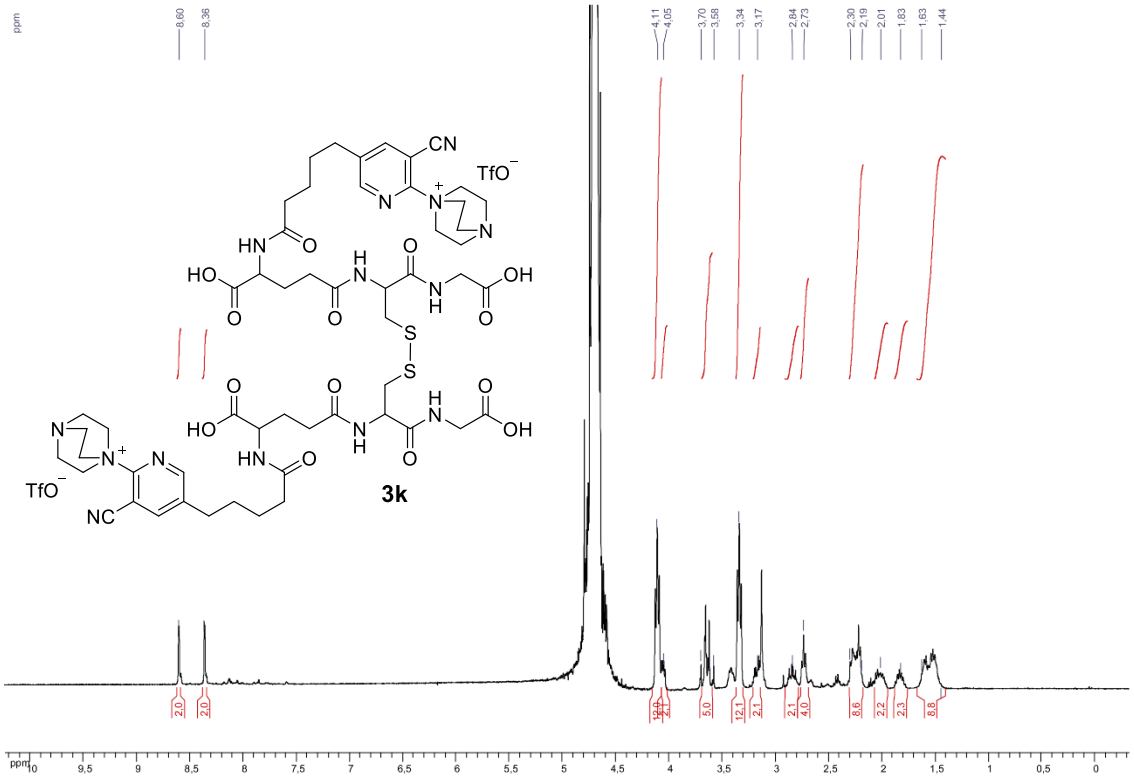

ppm
173,3
172,8
172,3
172,2
161,3
157,3
151,6
144,0
136,2
112,8
96,6
82,5
81,7
80,7
53,5
53,1
39,0
35,8
32,5
31,6
31,5
30,5
28,8
28,0
25,0
22,9
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

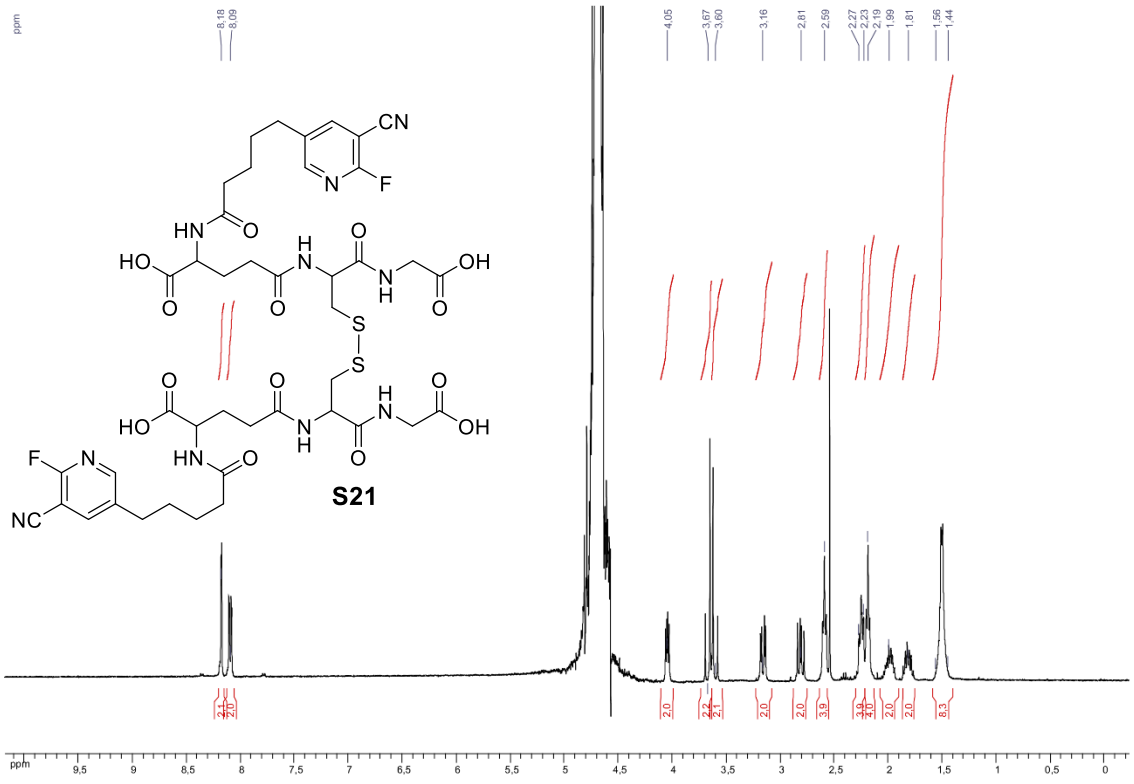

8,40
8,01
6,58
5,60
5,36
4,31
4,19
3,30
3,15
2,74
2,39
2,23
2,07
1,88
1,79
1,77
1,64
1,60
1,48
1,43
1,42
1,35
1,27
CO2tBu
HN
O
NH
O
N
H
CN
N
OTf
CO2tBu
tBuO2C
1j

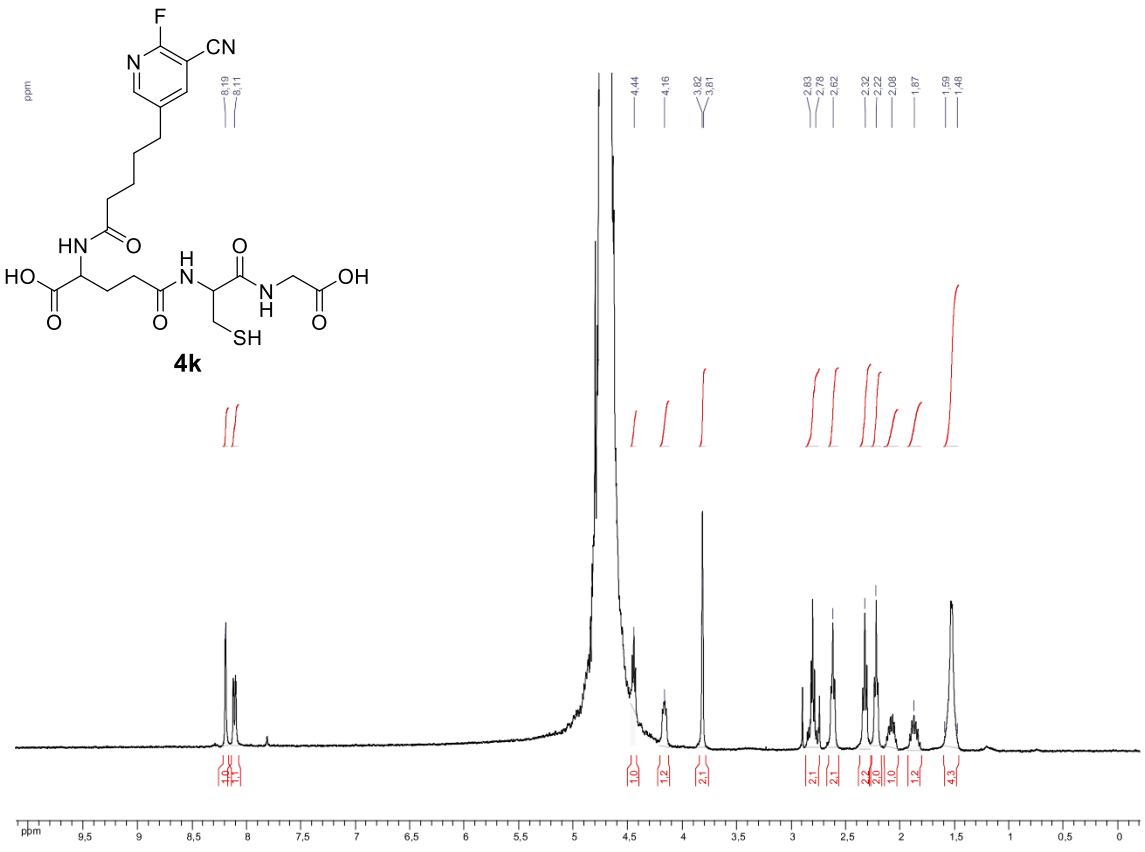

173,3
172,7
172,3
172,2
157,3
153,6
151,7
143,8
139,0
118,4
112,3
101,5
82,5
81,7
80,7
53,5
53,1
39,0
35,7
32,5
31,7
31,5
29,3
28,1
28,0
25,0
22,9

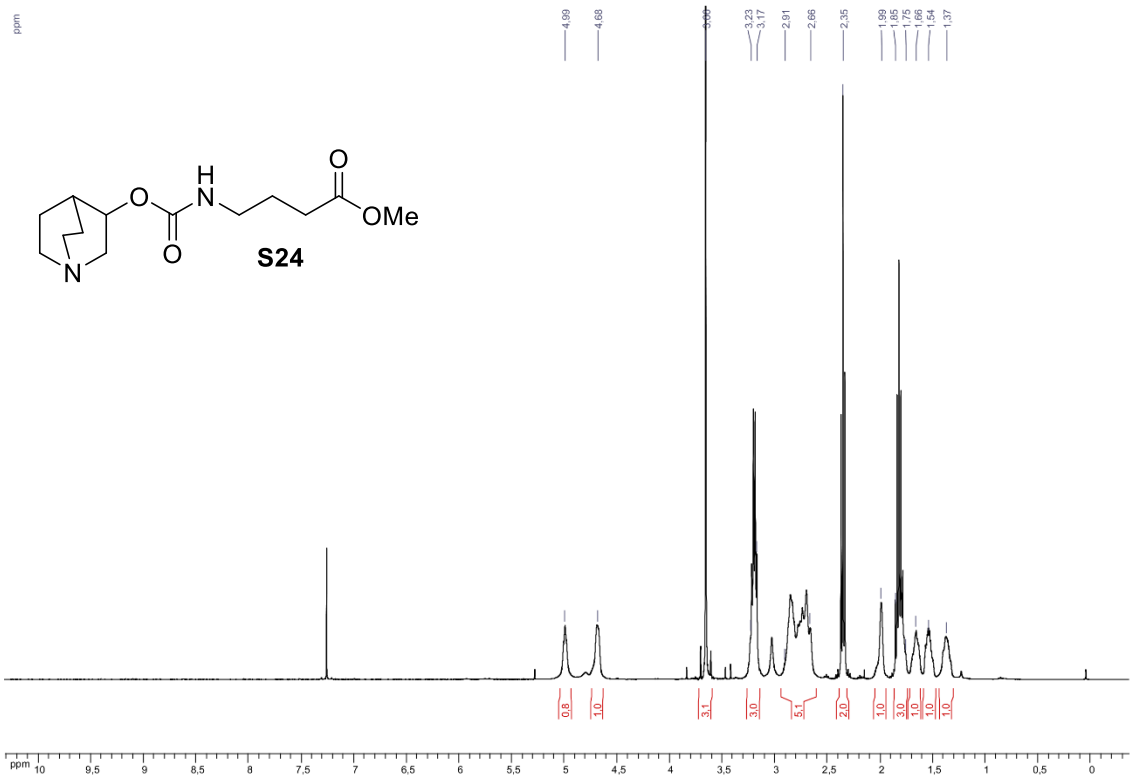

S19
HCOO⁻

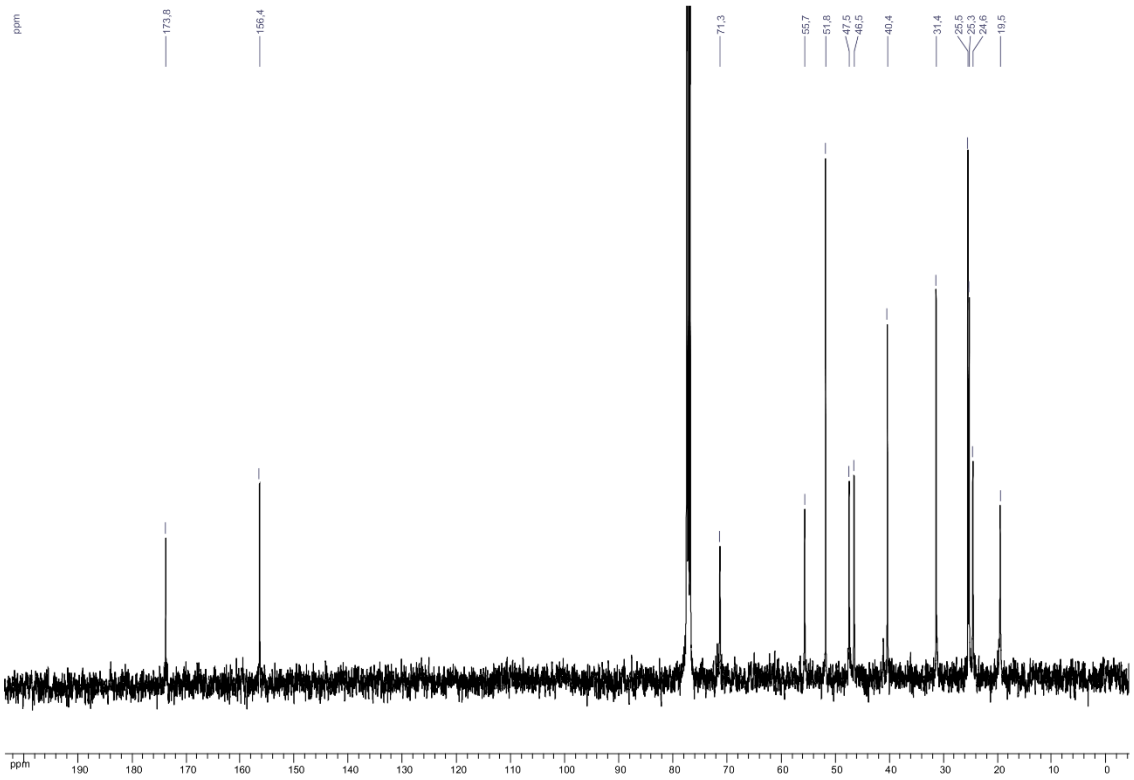

S20

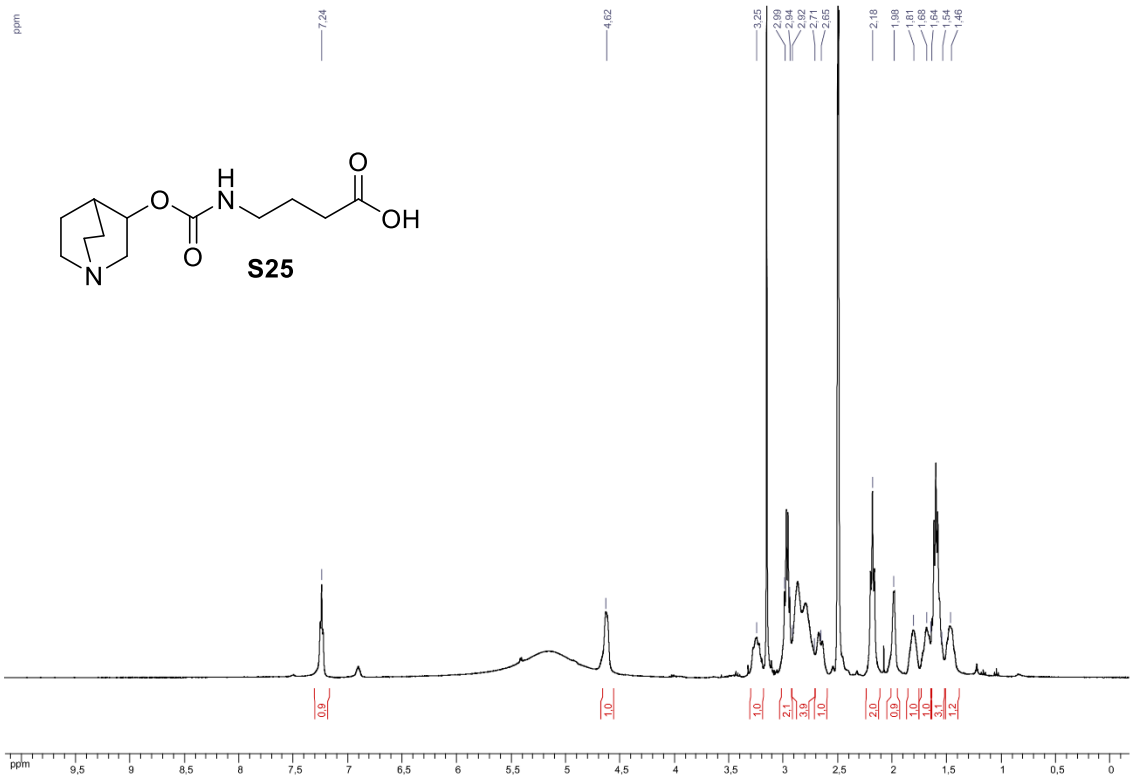

3k

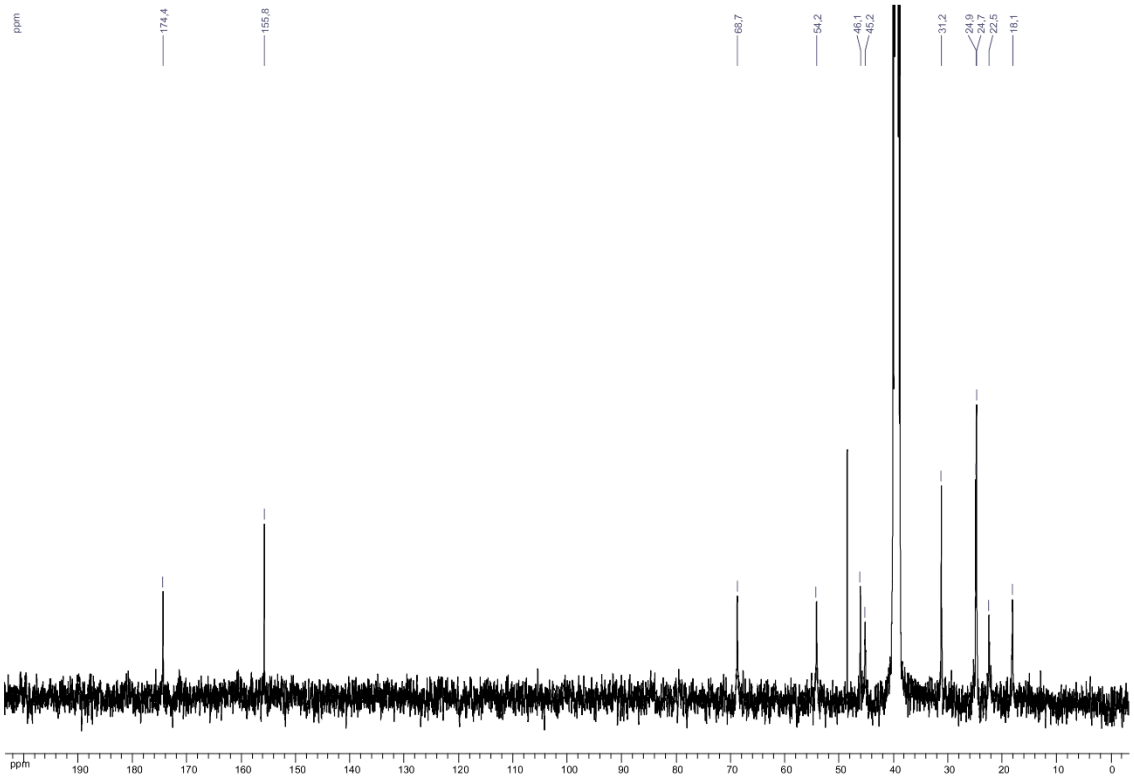

S21


F
CN
N
HN
O
HO
O
O
H
N
O
N
H
OH
O
SH
4k
ppm
8,19
8,11
4,44
4,16
3,82
3,81
2,83
2,78
2,62
2,32
2,22
2,08
1,87
1,59
1,48
1,0
1,1
1,0
1,2
2,1
2,1
2,1
2,2
2,0
1,0
1,2
4,3
ppm
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0


ppm
4,99
4,68
3,23
3,17
2,91
2,66
2,35
1,99
1,85
1,75
1,66
1,54
1,37
0,8
1,0
3,1
3,0
5,1
2,0
1,0
3,0
1,0
1,0
1,0
ppm
10
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0


ppm
173,8
156,4
71,3
55,7
51,8
47,5
46,5
40,4
31,4
25,5
25,3
24,6
19,5
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


ppm
7,24
4,62
3,25
2,99
2,94
2,92
2,71
2,65
2,18
1,98
1,81
1,68
1,64
1,54
1,46
O
H
N
O
O
OH
N
S25
0,9
1,0
1,0
2,1
3,9
1,0
2,0
0,9
1,0
1,0
3,1
1,2
ppm
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0


ppm
174,4
155,8
68,7
54,2
46,1
45,2
31,2
24,9
24,7
22,5
18,1
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0