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Supporting Information

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Author Contributions

S.L. Investigation: Lead; Methodology: Lead; Writing – original draft: Lead
K.M. Investigation: Lead; Methodology: Lead; Writing – original draft: Lead
A.B. Investigation: Supporting; Methodology: Supporting; Writing – original draft: Supporting
P.S. Conceptualization: Lead; Funding acquisition: Lead; Supervision: Lead; Writing – original draft: Lead
M.S. Conceptualization: Lead; Funding acquisition: Lead; Supervision: Lead; Writing – original draft: Lead.

Supporting Information

Cu-Mediated Radiofluorination of (Hetero)Aromatic C–H Bonds with K^{18}F

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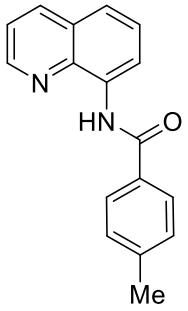
Table of Contents

1. Materials and Methods

All commercial products were used as received and reagents were stored under ambient conditions unless otherwise stated. 8-aminoquinonline was purchased from Synthonix. Acid chlorides and benzoic acid derivatives were purchased from Frontier Scientific, Oakwood Products, Acros Organics, Synthonix, Chem Impex, TCI America, Matrix Scientific, Alfa Aesar, Ark Pharm, and Sigma Aldrich. Oxalyl chloride was purchased from Acros Organics. Silver fluoride was purchased from Oakwood. 4-Methylmorpholine N-oxide (NMO), copper(I) iodide, and probenecid were purchased from Sigma Aldrich. Tamibarotene was purchased from AAChemPharm. Ataluren was purchased from ArkPharm. 4-[4-(2-butoxyethoxy)-5-methyl-1,3-thiazol-2-yl]benzoic acid (CAS 920269-72-3) and 4-[4-(2-butoxyethoxy)-5-methyl-1,3- thiazol-2-yl]benzoic acid (AC261066, CAS: 920269-72-3) were purchased from Atomax Chemicals Co., Ltd. The manipulation of solid reagents was conducted on the benchtop unless otherwise stated. Reactions were conducted under an ambient atmosphere unless otherwise stated. Reaction vessels were sealed with either a septum (flask) or a Teflon-lined cap (4 mL or 20 mL vial). Reactions conducted at elevated temperatures were heated on a hot plate using an aluminum block. Temperatures were regulated using an external thermocouple. For TLC analysis, R_F values are reported based on normal phase silica plates with fluorescent indicator.

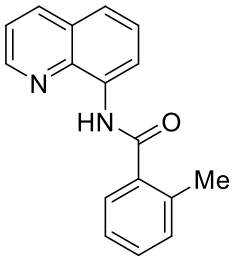
NMR spectra were obtained on a Varian vnmrs700 (699.76 MHz for ^{1}H; 175.95 MHz for ^{13}C), a Varian vnmr500 (500.09 MHz for ^{1}H; 470.56 MHz for ^{19}F; 125.75 MHz for ^{13}C), or a Varian MR400 (400.53 MHz for ^{1}H; 376.87 MHz for ^{19}F) spectrometer. All ^{13}C NMR data presented are proton-decoupled ^{13}C NMR spectra, unless noted otherwise. ^{1}H and ^{13}C NMR chemical shifts (δ) are reported in parts per million (ppm) relative to TMS with the residual solvent peak used as an internal reference. ^{1}H and ^{19}F NMR multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Melting point data (mp) were collected on an OptiMelt Automated Melting Point System and are uncorrected. High performance liquid chromatography (HPLC) was performed using a Shimadzu LC-2010A HT system equipped with a Bioscan B-FC-1000 radiation detector. Radio-TLC analyses were performed using a Bioscan AR 2000 Radio-TLC scanner with EMD Millipore TLC silica gel 60 plates (3.0 cm wide x 6.5 cm long).

2. Preparation and characterization of quinoline benzamide starting precursors



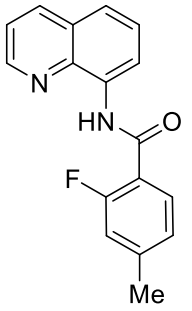
(**1H**)

***N*-(4-Methylbenzoyl)-8-aminoquinoline** (**1H**) was prepared according to the literature procedure.[1] 8-Aminoquinoline (290.1 mg, 2.0 mmol, 1 equiv) and NEt_3 (0.36 mL, 2.6 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (6.0 mL, 0.34 M) followed by a dropwise addition of 4-methylbenzoyl chloride (0.34 mL, 2.6 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**1H**) as a white solid (474.1 mg, 90% yield, R_f = 0.3 in 20% ethyl acetate in hexanes, mp = 119-120 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[2] HRMS (ESI^+) $[M + H]^+$ Calculated for $C_{17}H_{15}N_2O$: 263.1179; Found 263.1186.



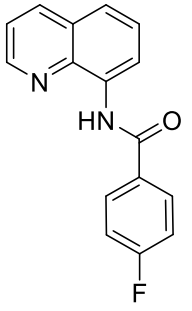
(**2H**)

***N*-(2-Methylbenzoyl)-8-aminoquinoline** (**2H**) was prepared according to the literature procedure.[3] 8-Aminoquinoline (434.4 mg, 3.0 mmol, 1 equiv) and NEt_3 (0.55 mL, 4.0 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (9.0 mL, 0.33 M) followed by a dropwise addition of 2-methylbenzoyl chloride (0.52 mL, 4.0 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**2H**) as a white solid (709.4 mg, 90% yield, R_f = 0.6 in 20% ethyl acetate in hexanes, mp = 94-95 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[2] HRMS (ESI^+) $[M + H]^+$ Calculated for $C_{17}H_{15}N_2O$: 263.1179; Found 262.1177.



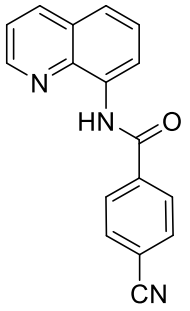
(**3H**/**1F**)

2-Fluoro-4-methyl-N-(quinolin-8-yl)benzamide (**3H**/**1F**) was prepared according to the literature procedure.[3] 8-Aminoquinoline (290.5 mg, 2.0 mmol, 1 equiv) and NEt_3 (0.35 mL, 2.5 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (7.0 mL, 0.29 M), followed by a dropwise addition of 2-fluoro-4-methylbenzoyl chloride (408.0 mg, 2.4 mmol, 1.2 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with water, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**3H**/**1F**) as a white solid (199.1 mg, 35% yield, R_f = 0.4 in 20% ethyl acetate in hexanes, mp = 131-132 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[1] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –112.8 (m, 1F). HRMS (ESI^+) $[M + H]^+$ Calculated for $C_{17}H_{14}FN_2O$: 281.1085; Found 281.1088.



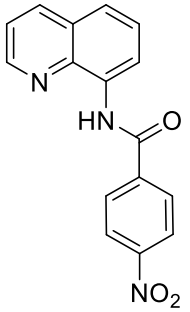
(**4H**)

***N*-(4-Fluorobenzoyl)-8-aminoquinoline (4H)** was prepared according to the literature procedure.[3] 8-Aminoquinoline (146.1 mg, 1.0 mmol, 1 equiv) and NEt_3 (0.18 mL, 1.3 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (3.0 mL, 0.34 M) followed by a dropwise addition of 4-fluorobenzoyl chloride (0.16 mL, 1.3 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (6% ethyl acetate in hexanes), affording the product (**4H**) as a white solid (257.6 mg, 96% yield, R_f = 0.54 in 30% ethyl acetate in hexanes, mp = 117-118 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[3] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –107.7 (m, 1F). HRMS (ESI^+) $[M + H]^+$ Calculated for $C_{16}H_{12}FN_2O$: 267.0928; Found 267.0930.



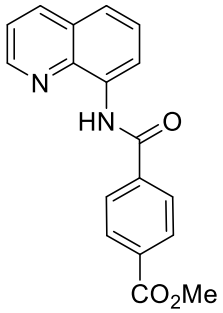
(**5H**)

***N*-(4-Cyanobenzoyl)-8-aminoquinoline** (**5H**) was prepared according to the literature procedure.[3] 8-Aminoquinoline (1.44 g, 10 mmol, 1 equiv) and NEt_3 (1.8 mL, 13 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (70 mL, 0.14 M) followed by a dropwise addition of 4-cyanobenzoyl chloride (2.4 g, 13 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl (2 x 15 mL), saturated aqueous $NaHCO_3$ (2 x 15 mL), and brine (25 mL). The organic layers were combined, dried over $NaSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (gradient of 100 % hexanes to 40% ethyl acetate in hexanes), affording the product (**5H**) as an off-white solid (2.49 g, 91% yield, R_f= 0.3 in 20% ethyl acetate in hexanes, mp = 182-183 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[1] HRMS (ESI^+) $[M + H]^+$ Calculated for $C_{17}H_{11}N_3O$: 274.0975; Found 274.0975.



(**6H**)

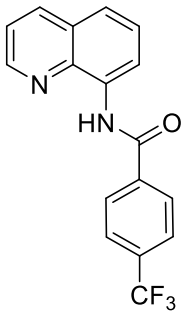
***N*-(4-Nitrobenzoyl)-8-aminoquinoline** (**6H**) was prepared according to the literature procedure.[3] 8-Aminoquinoline (1 g, 6.94 mmol, 1 equiv) and NEt_3 (1.26 mL, 9.02 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (50 mL, 0.14 M) followed by a dropwise addition of 4-nitrobenzoyl chloride (1.5 g, 9.02 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl (2 x 15 mL), saturated aqueous $NaHCO_3$ (2 x 15 mL), and brine (25 mL). The organic layers were combined, dried over $NaSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (gradient of 100 % hexanes to 40% ethyl acetate in hexanes), affording the product (**6H**) as a yellow solid (1.91 g, 94% yield, R_f= 0.4 in 20% ethyl acetate in hexanes, mp = 178-179 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[1] HRMS (ESI^+) $[M + H]^+$ Calculated for $C_{16}H_{11}N_3O_3$: 294.0873; Found 294.0873.



(**7H**)

Methyl 4-(quinolin-8-ylcarbamoyl)benzoate (**7H**) was prepared according to the literature procedure.[4] To an oven-dried vial, monomethyl terephthalate (359.9 mg, 2.0 mmol, 1 equiv) was placed under N_2. DMF (5 drops) and CH_2Cl_2 (4.0 mL, 0.5 M) were added, and the solution was cooled to 0 °C. Oxalyl chloride (0.2 mL, 2.4 mmol, 1.2 equiv) was added dropwise at 0 °C, resulting in vigorous bubbling. The mixture was allowed to warm to room temperature under N_2 and stirred for 4 h. The solvent was removed *in vacuo* and the resulting acid chloride was used immediately without further purification.

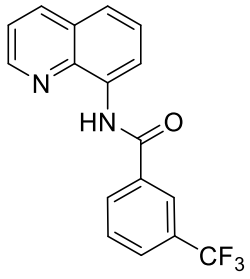
To another oven-dried vial, 8-aminoquinoline (384.2 mg, 2.7 mmol, 1.3 equiv) and NEt_3 (0.56 mL, 4.0 mmol, 2.0 equiv) were dissolved in anhydrous CH_2Cl_2 (4.0 mL, 0.67 M). A solution of acid chloride in CH_2Cl_2 (2.0 mL, 6.0 mL total, 0.44 M) was added dropwise at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (20% ethyl acetate in hexanes), affording the product (**7H**) as an off-white solid (421.6 mg, 69% yield, R_f = 0.4 in 20% ethyl acetate in hexanes, mp = 125-126 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[4] HRMS (ESI$^+$) $[M + H]^+$ Calculated for $C_{18}H_{14}N_2O_3$: 307.1077; Found 307.1084



(**8H**)

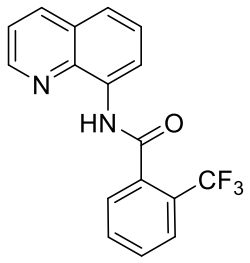
***N*-(4-Trifluorobenzoyl)-8-aminoquinoline** (**8H**) was prepared according to the literature procedure.[5] 8-Aminoquinoline (533 mg, 3.7 mmol, 1 equiv) and NEt_3 (0.67 mL, 4.8 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (11 mL, 0.33 M) followed by a dropwise addition of 4-trifluoromethylbenzoyl chloride (0.71 mL, 4.8 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. Recrystallization from hexanes/ethyl acetate (4:1) afforded the product (**8H**) as an off-white solid (995 mg, 85% yield, mp = 84-85 ºC). The ^1H and ^{13}C NMR spectra matched those

reported in the literature.[5] ^{19}F NMR (470 MHz, $CDCl_3$, ppm): δ –63.07 (s, 3F). HRMS (ESI^+) [M + H]$^+$ Calculated for $C_{17}H_{11}F_3N_2O$: 317.0896; Found 317.0899.



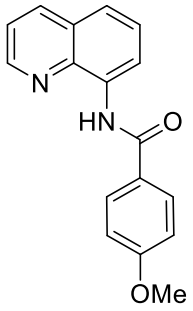
(**9H**)

***N*-(3-Trifluoromethylbenzoyl)-8-aminoquinoline** (**9H**) was prepared according to the literature procedure.[3] 8-Aminoquinoline (288.7 mg, 2.0 mmol, 1 equiv) and NEt_3 (0.36 mL, 2.6 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (6.0 mL, 0.33 M) followed by a dropwise addition of 3-(trifluoromethyl)benzoyl chloride (0.39 mL, 2.6 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**9H**) as a white solid (586.9 mg, 93% yield, R_f = 0.4 in 20% ethyl acetate in hexanes, mp = 80-81 °C). The ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[4] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –62.7 (s, 3F). HRMS (ESI^+) [M + H]$^+$ Calculated for $C_{17}H_{12}F_3N_2O$: 317.0896; Found 317.0899.



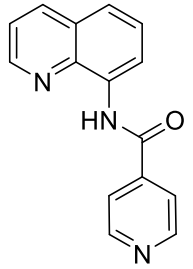
(**10H**)

***N*-(2-Trifluoromethylbenzoyl)-8-aminoquinoline** (**10H**) was prepared according to the literature procedure.[3] 8-Aminoquinoline (290.1 mg, 2.0 mmol, 1 equiv) and NEt_3 (0.36 mL, 2.6 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (6.0 mL, 0.34 M) followed by a dropwise addition of 2-(trifluoromethyl)benzoyl chloride (0.38 mL, 2.6 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**10H**) as a white solid (609.8 mg, 96% yield, R_f = 0.3 in 20% ethyl acetate in hexanes, mp = 105-106 °C). The ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[6] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –58.9 (d, J = 4 Hz, 3F). HRMS (ESI^+) [M + H]$^+$ Calculated for $C_{17}H_{12}F_3N_2O$: 317.0896; Found 317.0904.



(**11H**)

4-Methoxy-*N*-(quinolin-8-yl)benzamide (**11H**) was prepared according to the literature procedure.[1] 8-Aminoquinoline (286.6 mg, 2.0 mmol, 1 equiv) and NEt_3 (0.35 mL, 2.5 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (6.0 mL, 0.33 M) followed by a dropwise addition of 4-methyoxybenzoyl chloride (0.35 mL, 2.6 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (1% ethyl acetate in dichloromethane), affording the product (**11H**) as a white solid (370.9 mg, 67% yield, R_f = 0.31 in 20% ethyl acetate in hexanes, mp = 113-114 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[4] HRMS (ESI^+) $[M + H]^+$ Calculated for $C_{17}H_{15}N_2O_2$: 301.0947; Found 301.0950.

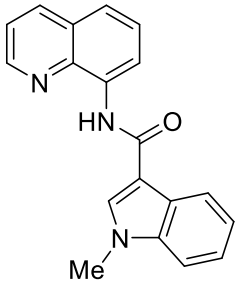


(**12H**)

***N*-(Quinolin-8-yl)isonicotinamide** (**12H**) was prepared according to the literature procedure.[7] To an oven dried vial, isonicotinic acid (245.0 mg, 2.0 mmol, 1 equiv) was placed under N_2. DMF (5 drops) and CH_2Cl_2 (4.4 mL, 0.45 M) were added, and the solution was cooled to 0 °C. Oxalyl chloride (0.2 mL, 2.4 mmol, 1.2 equiv) was added dropwise at 0 °C, resulting in vigorous bubbling. The mixture was allowed to warm to room temperature under N_2 and stirred for 3 h. The solvent was removed *in vacuo*, and the resulting acid chloride was used immediately without further purification.

To another oven-dried vial, 8-aminoquinoline (324.8 mg, 2.3 mmol, 1.1 equiv) and 4-dimethylaminopyridine (24.9 mg, 0.20 mmol, 0.1 equiv) were placed under N_2. Anhydrous CH_2Cl_2 (7.0 mL, 0.32 M) was added and the solution was cooled to 0 °C. NEt_3 (0.35 mL, 2.5 mmol, 1.3 equiv) was added at 0 °C. A solution of acid chloride in CH_2Cl_2 (4.0 mL, 11.0 mL total, 0.2 M) was added dropwise. The resulting mixture was allowed to warm to room temperature and left to stir overnight. The mixture was diluted with CH_2Cl_2 and washed with brine. Saturated aqueous $NaHCO_3$ was added to the brine layer to raise the pH from 5 to 7. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue

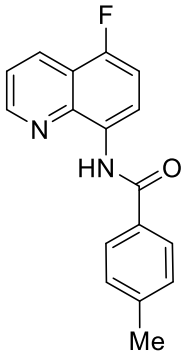
was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**12H**) as a peach solid (323.8 mg, 65% yield, R_f = 0.3 in 75% ethyl acetate in hexanes, mp = 122-123 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[7] HRMS (ESI^+) $[M + H]^+$ Calculated for $C_{15}H_{12}N_3O$: 250.0975; Found 250.0978.



(**13H**)

1-Methyl-*N*-(quinolin-8-yl)-1H-indole-3-carboxamide (13H) was prepared according to the literature procedure.[4] To an oven-dried vial, 1-methyl-1H-indole-3-carboxylic acid (351.5 mg, 2.0 mmol, 1 equiv) was placed under N_2. DMF (5 drops) and CH_2Cl_2 (4.0 mL, 0.5 M) were added, and the solution was cooled to 0 °C. Oxalyl chloride (0.2 mL, 2.4 mmol, 1.2 equiv) was added dropwise at 0 °C, resulting in vigorous bubbling. The mixture was allowed to warm to room temperature under N_2 and stirred for 6 h. The solvent was removed *in vacuo*, and the resulting acid chloride was used immediately without further purification.

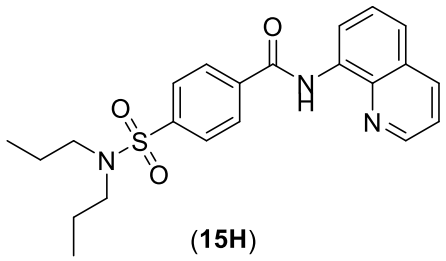
To another oven-dried vial, 8-aminoquinoline (376.7 mg, 2.6 mmol, 1.3 equiv) and NEt_3 (0.55 mL, 4.0 mmol, 2.0 equiv) were dissolved in anhydrous CH_2Cl_2 (4.0 mL, 0.65 M). A solution of acid chloride in CH_2Cl_2 (4.0 mL, 8.0 mL total, 0.33 M) was added dropwise at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was washed with saturated aqueous $NaHCO_3$, HCl (1 N), and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (30% ethyl acetate in hexanes), affording the product (**13H**) as an off-white solid (370.8 mg, 61% yield, R_f = 0.15 in 30% ethyl acetate in hexanes, mp = 182-183 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[1] HRMS (ESI^+) $[M + H]^+$ Calculated for $C_{19}H_{16}N_3O$: 302.1288; Found 302.1295



(**14H**)

***N*-(5-Fluoroquinolin-8-yl)-4-methylbenzamide** (**14H**) was prepared according to the literature procedure.[3] 5-Fluoro-8-aminoquinoline (193.9 mg, 1.2 mmol, 1 equiv) and NEt_3 (0.22 mL, 1.6

mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (3.6 mL, 0.33 M), followed by a dropwise addition of 4-methylbenzoyl chloride (0.2 mL, 1.5 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**14H**) as a white solid (243.4 mg, 73% yield, R_f = 0.5 in 20% ethyl acetate in hexanes, mp = 131-132 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[8] ^{19}F NMR (470 MHz, $CDCl_3$, ppm): δ –129.3 (m, 1F). HRMS (ESI$^+$) $[M + H]^+$ Calculated for $C_{17}H_{14}FN_2O$: 281.1085; Found 281.1090.

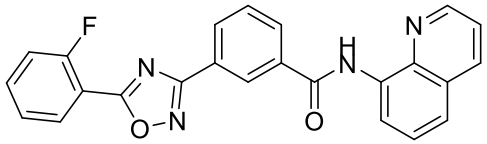


(**15H**)

4-(*N*,*N*-Dipropylsulfamoyl)-*N*-(quinolin-8-yl)benzamide (**15H**) was prepared according to the literature procedure.[4] To an oven-dried vial, probenecid (580.3 mg, 2.0 mmol, 1 equiv) was placed under N_2. DMF (5 drops) and CH_2Cl_2 (4.4 mL, 0.5 M) were added, and the solution was cooled to 0 °C. Oxalyl chloride (0.2 mL, 2.4 mmol, 1.2 equiv) was added dropwise at 0 °C, resulting in vigorous bubbling. The mixture was allowed to warm to room temperature under N_2 and stirred for 6 h. The solvent was removed *in vacuo*, and the resulting acid chloride was used immediately without further purification.

To another oven-dried vial, 8-aminoquinoline (324.1 mg, 2.3 mmol, 1.1 equiv) and NEt_3 (0.35 mL, 2.5 mmol, 1.2 equiv) were dissolved in anhydrous CH_2Cl_2 (4.0 mL, 0.56 M). A solution of acid chloride in CH_2Cl_2 (3.0 mL, 7.0 mL total, 0.32 M) was added dropwise at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was washed with brine, and the organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (15% ethyl acetate in hexanes), affording the product (**15H**) as a white solid (589.0 mg, 70% yield, R_f = 0.4 in 30% ethyl acetate in hexanes, mp = 125-126 °C).

^{1}H NMR (700 MHz, $CDCl_3$, ppm): δ 10.75 (s, 1H), 8.88 (dd, *J* = 7.7, 2.1 Hz, 1H), 8.83 (dd, *J* = 4.2, 2.1 Hz, 1H), 8.15-8.18 (multiple peaks, 3H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.54-7.58 (multiple peaks, 2H), 7.47 (dd, *J* = 7.7, 4.2 Hz, 1H), 3.11 (t, *J* = 7.7 Hz, 4H), 1.55 (m, *J* = 7.7 Hz, 4H), 0.87 (t, *J* = 7.7 Hz, 6H)
^{13}C NMR (176 MHz, $CDCl_3$, ppm): δ 163.73, 148.40, 143.15, 138.62, 138.40, 136.44, 134.03, 127.93, 127.941, 127.42, 127.33, 122.19, 121.81, 116.69, 50.00, 21.97, 11.13
HRMS (ESI+) $[M + H]^+$ Calculated for $C_{22}H_{26}N_3O_3S$: 412.1689; Found 412.1689.

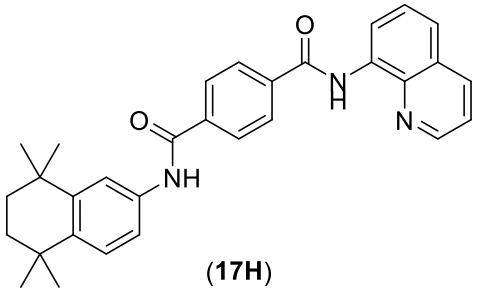


(**16H**)

3-(5-(2-Fluorophenyl)-1,2,4-oxadiazol-3-yl)-*N*-(quinolin-8-yl)benzamide (**16H**) was prepared according to the literature procedure.[4] To an oven-dried vial, ataluren (284.0 mg, 1.0 mmol, 1 equiv) was placed under N_2. DMF (5 drops) and CH_2Cl_2 (2.2 mL, 0.45 M) were added, and the solution was cooled to 0 °C. Oxalyl chloride (0.1 mL, 1.2 mmol, 1.2 equiv) was added dropwise at 0 °C, resulting in vigorous bubbling. The mixture was allowed to slowly warm to room temperature under N_2 and stirred for 4.5 h. The solvent was removed *in vacuo*, and the resulting acid chloride was used immediately without further purification.

To another oven-dried vial, 8-aminoquinoline (170.4 mg, 1.2 mmol, 1.2 equiv) and NEt_3 (0.20 mL, 1.4 mmol, 1.4 equiv) were dissolved in anhydrous CH_2Cl_2 (1.6 mL, 0.74 M). A solution of acid chloride in CH_2Cl_2 (4.0 mL, 5.6 mL total, 0.21 M) was added dropwise at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was washed with brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (5% ethyl acetate in dichloromethane), affording the product (**16H**) as a white solid (317.3 mg, 77% yield, R_f = 0.63 in 40% ethyl acetate in hexanes, mp = 170-171 °C).

^{1}H NMR (700 MHz, $CDCl_3$, ppm): δ 10.80 (s, 1H), 8.94 (d, *J* = 7.7 Hz, 1H), 8.88 (s, 1H), 8.86 (d, *J* = 4.2 Hz, 1H), 8.37 (d, *J* = 7.0 Hz, 1H), 8.24 (t, *J* = 7.0 Hz, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.69 (t, *J* = 7.7 Hz, 1H), 7.58-7.62 (multiple peaks, 2H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.47 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.34 (t, *J* = 7.7 Hz, 1H), 7.29 (t, *J* = 9.5 Hz, 1H)
^{13}C NMR (176 MHz, $CDCl_3$, ppm): δ 173.02 (d, *J* = 5.3 Hz), 168.14, 164.63, 160.81 (d, *J* = 261 Hz), 148.40, 138.77, 136.37, 136.07, 134.69 (d, *J* = 7.0 Hz), 134.41, 130.97, 130.68, 129.97, 129.44, 217.98, 217.56, 127.42, 126.46, 124.72 (d, *J* = 3.5 Hz), 121.82 (d, *J* = 31.7 Hz), 117.18 (d, *J* = 21.1 Hz), 116.72, 112.77, 112.70
^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –108.16 (m, 1F).
HRMS (ESI+) $[M + H]^+$ Calculated for $C_{24}H_{16}FN_4O_2$: 411.1252; Found 411.1259.



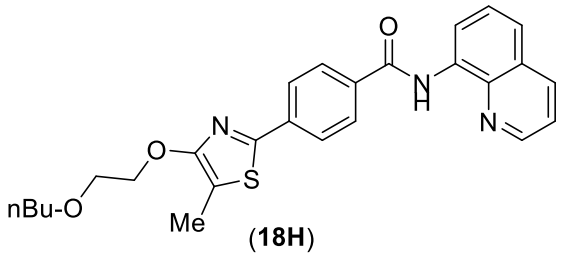
(**17H**)

***N*^{1}-(Quinolin-8-yl)-*N*^{4}-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)terephthalamide** (**17H**) was prepared according to the literature procedure.[4] To an oven-dried vial, tamibarotene (360.5 mg, 1.0 mmol, 1 equiv) were placed under N_2. DMF (5 drops) and CH_2Cl_2 (5.4 mL, 0.2 M) were added, and the solution was cooled to 0 °C. Oxalyl chloride (0.1 mL, 1.2 mmol, 1.2 equiv) was added dropwise at 0 °C, resulting in vigorous bubbling. The

mixture was allowed to warm to room temperature under N_2 and stirred for 4.5 h. The solvent was removed *in vacuo*, and the resulting acid chloride was used immediately without further purification.

To another oven-dried vial, 8-aminoquinoline (169.4 mg, 1.2 mmol, 1.2 equiv) and NEt_3 (0.20 mL, 1.4 mmol, 1.4 equiv) were dissolved in anhydrous CH_2Cl_2 (1.6 mL, 0.73 M). A solution of acid chloride in CH_2Cl_2 (4.0 mL, 5.6 mL total, 0.21 M) was added dropwise at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was washed with brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (20% ethyl acetate in hexanes), affording the product (**17H**) as an off-white solid (184.3 mg, 38% yield, R_f = 0.67 in 40% ethyl acetate in hexanes, mp = 155-156 °C).

^{1}H NMR (700 MHz, $CDCl_3$, ppm): δ 10.74 (s, 1H), 8.86 (dd, *J* = 6.3, 2.8 Hz, 1H), 8.80 (dd, *J* = 4.2, 1.4 Hz, 1H), 8.29 (s, 1H), 8.14 (dd, *J* = 7.7, 1.4 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 2H), 7.97 (d, *J* = 8.4 Hz, 2H), 7.62 (s, 1H), 7.49-7.54 (multiple peaks, 3H), 7.43 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 1.68 (s, 4H), 1.29 (s, 6H), 1.27 (s, 6H)
^{13}C NMR (176 MHz, $CDCl_3$, ppm): δ 164.92, 164.39, 148.36, 145.76, 141.59, 138.63, 138.24, 137.57, 136.35, 135.26, 134.13, 127.91, 127.55, 127.31, 127.21, 122.03, 121.74, 118.28, 118.22, 116.63, 35.03, 34.99, 34.41, 33.98, 31.83, 31.78
HRMS (ESI+) $[M + H]^+$ Calculated for $C_{31}H_{32}N_3O_2$: 478.2489; Found 478.2499.

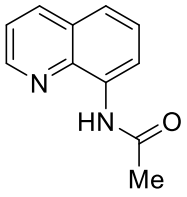


(**18H**)

4-(4-(2-Butoxyethoxy)-5-methylthiazol-2-yl)-*N*-(quinolin-8-yl)benzamide (**18H**) was prepared according to the literature procedure.[4] To an oven-dried vial, 4-[4-(2-butoxyethoxy)-5-methyl-1,3-thiazol-2-yl]benzoic acid (332.9 mg, 1.0 mmol, 1 equiv) was placed under N_2. DMF (5 drops) and CH_2Cl_2 (2.0 mL, 0.5 M) were added, and the solution was cooled to 0 °C. Oxalyl chloride (0.1 mL, 1.2 mmol, 1.2 equiv) was added dropwise at 0 °C, resulting in vigorous bubbling. The mixture was allowed to slowly warm to room temperature under N_2 and stirred for 6 h. The solvent was removed *in vacuo* and the resulting acid chloride was used immediately without further purification.

To another oven-dried vial, 8-aminoquinoline (200.9 mg, 1.4 mmol, 1.4 equiv) and NEt_3 (0.30 mL, 2.2 mmol, 2.2 equiv) were dissolved in anhydrous CH_2Cl_2 (2.0 mL, 0.70 M). A solution of acid chloride in CH_2Cl_2 (2.0 mL, 4.0 mL total, 0.35 M) was added dropwise at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (15% ethyl acetate in hexanes), affording the product (**18H**) as a yellow solid (366.5 mg, 80% yield, R_f = 0.4 in 20% ethyl acetate in hexanes, mp = 78-79 °C).

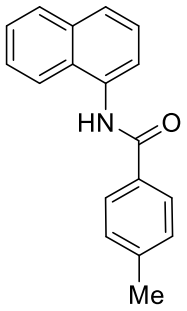
^{1}H NMR (700 MHz, $CDCl_3$, ppm): δ 10.75 (s, 1H), 8.91 (d, *J* = 7.7 Hz, 1H), 8.82 (d, *J* = 4.2 Hz, 1H), 8.15 (d, *J* = 7.7 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 2H), 7.97 (d, *J* = 8.4 Hz, 2H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.51 (d, *J* = 8.4, 1H), 7.44 (dd, *J* = 7.7, 4.2 Hz, 1H), 4.51 (t, *J* = 4.9 Hz, 2H), 3.77 (t, *J* = 4.9 Hz, 2H), 3.52 (t, *J* = 7.1 Hz, 2H), 2.31 (s, 3H), 1.58 (m, *J* = 7.1 Hz, 2H), 1.38 (m, *J* = 7.4 Hz, 2H), 0.91 (t, *J* = 7.4 Hz, 3H)
^{13}C NMR (176 MHz, $CDCl_3$, ppm): δ 164.60, 159.99, 157.68, 148.26, 138.67, 136.87, 136.31, 135.16, 134.41, 127.92, 137.80, 127.40, 125.41, 121.71, 121.67, 116.48, 108.63, 71.15, 69.74, 69.43, 31.72, 19.25, 13.91, 9.41
HRMS (ESI+) $[M + H]^+$ Calculated for $C_{26}H_{28}N_3O_3S$: 462.1846; Found 462.1848.



(**S1**)

***N*-(Quinolin-8-yl)acetamide** (**S1**) was prepared according to the literature procedure.[9] 8-Aminoquinoline (144.3 mg, 1.0 mmol, 1 equiv) was dissolved in acetic anhydride (5.0 mL, 0.2 M) and stirred overnight at room temperature. The mixture was concentrated and washed with brine and CH_2Cl_2 (2 x 20 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*, affording the product (**S1**) as a white solid (171.1 mg, 94% yield, R_f = 0.2 in 20% ethyl acetate in hexanes, mp = 94-96 °C).

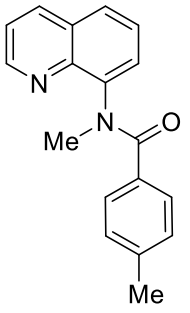
^{1}H NMR (700 MHz, $CDCl_3$, ppm): δ 9.75 (bs, 1H), 8.76 (dd, *J* = 4.2, 1.4 Hz, 1H), 8.73 (dd, *J* = 7.7, 1.4 Hz, 1H), 8.10 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.46 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.40 dd, *J* = 7.7, 4.2 Hz, 1H), 2.32 (s, 3H)
^{13}C NMR (175 MHz, $CDCl_3$, ppm): δ 168.67, 148.03, 137.17, 136.29, 134.47, 127.85, 127.33, 121.51, 121.37, 116.33, 25.07
HRMS (ESI^+) $[M + H]^+$ Calculated for $C_{11}H_{10}N_2O$: 187.0866; Found 187.0866.



(**S2**)

4-Methyl-*N*-(naphthalen-1-yl)benzamide (**S2**) was prepared according to the literature procedure.[3] 1-Aminonaphthalene (215.0 mg, 1.5 mmol, 1 equiv) and NEt_3 (0.3 mL, 2.2 mmol, 1.4 equiv) were dissolved in anhydrous CH_2Cl_2 (4.6 mL, 0.33 M), followed by a dropwise addition of 4-methylbenzoyl chloride (0.25 mL, 1.9 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous

$NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**S2**) as an off-white solid (266.0 mg, 67% yield, R_f = 0.3 in 20% ethyl acetate in hexanes, mp = 170-171 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[10] HRMS (ESI$^+$) $[M + H]^+$ Calculated for $C_{18}H_{16}NO$: 262.1226; Found 262.1231.

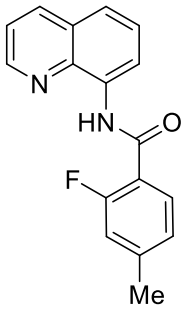


(**S3**)

***N*,4-Dimethyl-*N*-(quinolin-8-yl)benzamide** (**S3**) was prepared according to the modified literature procedure.[11] A suspension of sodium hydride (43.5 mg, 1.8 mmol, 3.0 equiv) in DMF (3.0 mL) was added to a solution of 4-methyl-*N*-(quinolin-8-yl)benzamide (154.0 mg, 0.60 mmol, 1 equiv) in DMF (3.0 mL, 6.0 mL total, 0.10 M) in an oven-dried vial at 0 °C under N_2. The reaction mixture was warmed to room temperature and stirred for 3 h. Methyl iodide (0.05 mL, 0.80 mmol, 1.4 equiv) was added, and the reaction was stirred an additional 1 h at room temperature under N_2. The reaction was diluted with CH_2Cl_2 (40 mL), washed with water (40 mL), dried over $MgSO_4$, and concentrated *in vacuo*, affording the product (**S3**) as a colorless oil (49.7 mg, 31% yield, R_f = 0.12 in 40% ethyl acetate in hexanes).

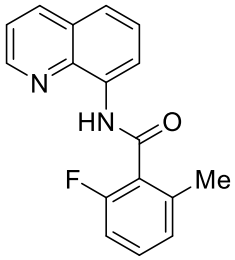
^{1}H NMR (700 MHz, $CDCl_3$, ppm): δ 8.96 (d, *J* = 4.2 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.64 (dd, *J* = 7.0, 2.1, 1H), 7.39 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.31-7.35 (multiple peaks, 2H), 7.15 (d, *J* = 7.7 Hz, 2H), 6.75 (d, *J* = 7.7 Hz, 2H), (s, 3H), 2.10 (s, 3H)
^{13}C NMR (175 MHz, $CDCl_3$, ppm): δ 172.09, 150.51, 143.87, 142.68, 139.34, 136.18, 133.66, 129.20, 129.12, 128.05, 128.01,127.39, 126.21, 121.62, 38.49, 21.17
HRMS (ESI$^+$) $[M + H]^+$ Calculated for $C_{18}H_{17}N_2O$: 277.1335; Found 277.1341

3. Preparation and characterization of fluorinated standards



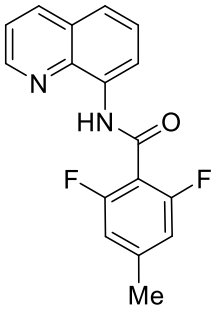
(**3H**/**1F**)

2-Fluoro-4-methyl-N-(quinolin-8-yl)benzamide (**3H**/**1F**) was prepared according to the literature procedure.[3] 8-Aminoquinoline (290.5 mg, 2.0 mmol, 1 equiv) and NEt_3 (0.35 mL, 2.5 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (7.0 mL, 0.29 M), followed by a dropwise addition of 2-fluoro-4-methylbenzoyl chloride (408.0 mg, 2.4 mmol, 1.2 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with water, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**3H**/**1F**) as a white solid (199.1 mg, 35% yield, R_f = 0.4 in 20% ethyl acetate in hexanes, mp = 131-132 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[1] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –112.8 (m, 1F). HRMS (ESI^+) $[M + H]^+$ Calculated for $C_{17}H_{14}FN_2O$: 281.1085; Found 281.1088.



(**2F**)

2-Fluoro-6-methyl-N-(quinolin-8-yl)benzamide (**2F**) was prepared according to the literature procedure.[1] In a glovebox, 2-methyl-*N*-(quinolin-8-yl)benzamide (129.0 mg, 0.5 mmol, 1 equiv), copper(I) iodide (24.0 mg, 0.13 mmol, 0.26 equiv), silver fluoride (245.2 mg, 1.9 mmol, 3.9 equiv), and *N*-methylmorpholine oxide (295.8 mg, 2.5 mmol, 5.1 equiv) were dissolved in DMF in the dark. The mixture was allowed to stir for 5 min. The reaction was then heated to 120 °C for 20 min. The solution was cooled to room temperature, diluted with ethyl acetate, filtered through a celite plug, and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**2F**) as a white solid (27.5 mg, 20% yield, R_f = 0.5 in 20% ethyl acetate in hexanes, mp = 122-123 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[1] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –115.9 (m, 1F). HRMS (ESI^+) $[M + H]^+$ Calculated for $C_{17}H_{15}N_2O$: 281.1085; Found 281.1087.

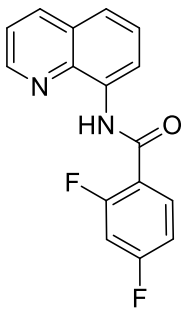


(**3F**)

2,6-Difluoro-*N*-(quinolin-8-yl)-4-methylbenzamide (**3F**) was prepared according to the literature procedure.[4] To an oven-dried vial, 2,6-difluoro-4-methylbenzoic acid (197.7 mg, 1.2 mmol, 1 equiv) was placed under N_2. DMF (5 drops) and CH_2Cl_2 (2.3 mL, 0.5 M) were added, and the solution was cooled to 0 °C. Oxalyl chloride (0.12 mL, 1.4 mmol, 1.2 equiv) was added dropwise at 0 °C. The mixture was allowed to warm to room temperature under N_2 and stirred for 4 h. The solvent was removed *in vacuo*, and the resulting acid chloride was used immediately without further purification.

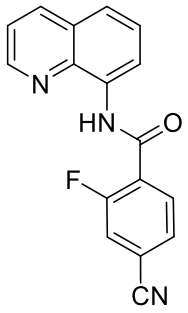
To another oven-dried vial, 8-aminoquinoline (232.1 mg, 1.6 mmol, 1.4 equiv) and NEt_3 (0.35 mL, 2.5 mmol, 2.20 equiv) were dissolved in anhydrous CH_2Cl_2 (2.0 mL, 0.80 M). A solution of acid chloride in CH_2Cl_2 (3.2 mL, 5.2 mL total, 0.31 M) was added dropwise at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**3F**) as a white solid (97.2 mg, 28% yield, R_f = 0.4 in 20% ethyl acetate in hexanes, mp = 136-137 °C).

^{1}H NMR (700 MHz, $CDCl_3$, ppm): δ 10.34 (s, 1H), 8.92 (dd, *J* = 7.0, 1.4 Hz, 1H), 8.77 (dd, *J* = 4.2, 1.4 Hz, 1H), 8.14 (dd, *J* = 8.0, 2.1 Hz, 1H), 7.57-7.52 (multiple peaks, 2H), 7.43 (dd, *J* = 8.4, 4.2 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 2H), 2.38 (s, 3H)
^{13}C NMR (175 MHz, $CDCl_3$, ppm): δ 160.80 (d, *J* = 7.0 Hz), 159.37 (d, *J* = 7.0 Hz), 158.75, 148.33, 143.71 (t, *J* = 10.6 Hz), 138.40, 136.28, 134.25, 127.89, 127.34, 122.16, 121.66, 116.95, 112.79 (d, *J* = 3.5 Hz), 112.67 (d, *J* = 3.5 Hz), 111.76 (t, *J* = 19.4 Hz),
21.52
^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –112.7 (d, *J* = 8 Hz, 2F).
HRMS (ESI+) $[M + H]^+$ Calculated for $C_{17}H_{13}F_2N_2O$: 299.0990; Found 299.0990.



(**4F**)

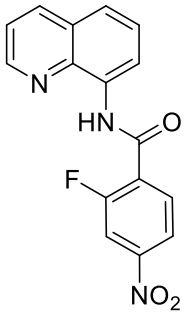
2,4-Difluoro-*N*-(quinolin-8-yl)benzamide (4F) was prepared according to the literature procedure.[1] 8-Aminoquinoline (145.2 mg, 1.0 mmol, 1 equiv) and NEt_3 (0.18 mL, 1.3 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (3.0 mL, 0.34 M) followed by a slow dropwise addition of 2,4-difluorobenzoyl chloride (0.15 mL, 1.2 mmol, 1.2 equiv). The resulting mixture was stirred at room temperature exposed to air overnight. The mixture was washed with 1 N HCl, sat. $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (8% ethyl acetate in hexane) affording the product (**4F**) as a white solid (261.4 mg, 49% yield, R_f = 0.58 in 20% ethyl acetate in hexanes, mp = 136–137 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[12] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –103.69 (m, 1F), –107.49 (m, 1F). HRMS (ESI+) $[M + H]^+$ Calculated for $C_{16}H_{11}F_2N_2O$: 285.0834; Found 285.0834.



(**5F**)

4-Cyano-2-fluoro-N-(quinolin-8-yl)benzamide (**5F**) was prepared according to the literature procedure.[4] To an oven-dried vial, 4-cyano-2-fluorobenzoic acid (165.5 mg, 1.0 mmol, 1 equiv) was placed under N_2. DMF (5 drops) and CH_2Cl_2 (2.0 mL, 0.50 M) were added, and the solution was cooled to 0 °C. Oxalyl chloride (0.1 mL, 1.2 mmol, 1.2 equiv) was added dropwise at 0 °C. The mixture was allowed to warm to room temperature under N_2 and stirred for 5 h. The solvent was removed *in vacuo*, and the resulting acid chloride was used immediately without further purification.

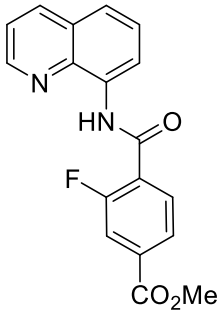
To another oven-dried vial, 8-aminoquinoline (209.8 mg, 1.5 mmol, 1.5 equiv) and NEt_3 (0.28 mL, 2.0 mmol, 2.0 equiv) were dissolved in anhydrous CH_2Cl_2 (2.0 mL, 0.73 M). A solution of acid chloride in CH_2Cl_2 (4.0 mL, 7.0 mL total, 0.21 M) was added dropwise at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**5F**) as an off-white solid (13.3 mg, 5% yield, R_f = 0.8 in 20% ethyl acetate in hexanes, mp = 205-206 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[1] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –109.59 (m, 1F). HRMS (ESI^+) $[M + H]^+$ Calculated for $C_{17}H_{11}FN_3O$: 292.0881; Found 292.0887.



(**6F**)

2-Fluoro-*N*-(quinolin-8-yl)-4-nitrobenzamide (**6F**) was prepared according to the literature procedure.[4] To an oven-dried vial, 2-fluoro-4-nitrobenzoic acid (191.5 mg, 1.0 mmol, 1 equiv) was placed under N_2. DMF (5 drops) and CH_2Cl_2 (2.0 mL, 0.52 M) were added, and the solution was cooled to 0 °C. Oxalyl chloride (0.1 mL, 1.2 mmol, 1.1 equiv) was added dropwise at 0 °C. The mixture was allowed to warm to room temperature under N_2 and stirred for 5 h. The solvent was removed *in vacuo*, and the resulting acid chloride was used immediately without further purification.

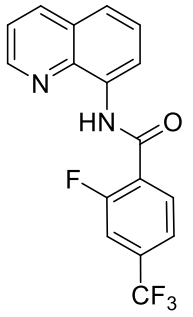
To another oven-dried vial, 8-aminoquinoline (196.3 mg, 1.4 mmol, 1.3 equiv) and NEt_3 (0.28 mL, 2.0 mmol, 1.9 equiv) were dissolved in anhydrous CH_2Cl_2 (2.0 mL, 0.68 M). A solution of acid chloride in CH_2Cl_2 (3.0 mL, 5.0 mL total, 0.27 M) was added dropwise at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**6F**) as a yellow solid (10.6 mg, 3% yield, R_f = 0.9 in 20% ethyl acetate in hexanes, mp = 200-201 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[1] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –108.04 (m, 1F). HRMS (ESI^+) $[M + H]^+$ Calculated for $C_{16}H_{11}FN_3O_3$: 312.0779; Found 312.0776.



(**7F**)

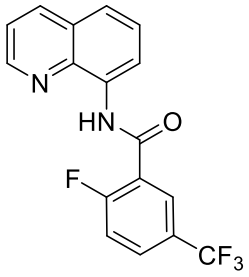
Methyl 3-fluoro-4-(quinolin-8-ylcarbamoyl)benzoate (**7F**) was prepared according to the literature procedure.[1] In a glovebox, methyl 4-(quinolin-8-ylcarbamoyl)benzoate (228.1 mg, 0.74 mmol, 1 equiv), copper(I) iodide (16.5 mg, 0.09 mmol, 0.12 equiv), silver fluoride (390.3 mg, 3.1 mmol, 4.1 equiv), and *N*-methylmorpholine oxide (441.3 mg, 3.8 mmol, 5.1 equiv) were dissolved in DMF in the dark. The mixture was allowed to stir for 5 min at room temperature. The reaction was heated to 90 °C for 1 h. The solution was cooled to room temperature, diluted with ethyl acetate, filtered through a celite plug, and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**7F**) as an off-

white solid (13.2 mg, 6% yield, R_f = 0.4 in 20% ethyl acetate in hexanes, mp = 142-143 °C). The ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[1] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –111.56 (s, 1F). HRMS (ESI$^+$) $[M + H]^+$ Calculated for $C_{18}H_{14}FN_2O_3$: 325.0983; Found 325.0985.



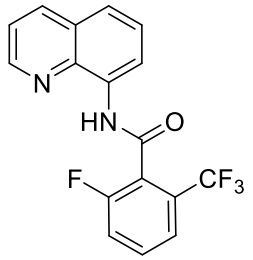
(**8F**)

2-Fluoro-*N*-(quinolin-8-yl)-4-trifluorobenzamide (**8F**) was prepared according to the literature procedure.[3] 8-Aminoquinoline (144 mg, 1.0 mmol, 1 equiv) and NEt_3 (0.18 mL, 1.3 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (3.0 mL, 0.33 M) followed by a dropwise addition of 2-fluoro-4-(trifluoromethyl)benzoyl chloride (0.2 mL, 1.3 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (8% ethyl acetate in hexanes), affording the product (**8F**) as an off-white solid (304 mg, 91% yield, R_f = 0.32 in 10% ethyl acetate in hexanes, mp = 82-84 °C). The ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[1] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –63.14 (s, 3F), –110.13 (m, 1F). HRMS (ESI$^+$) $[M + H]^+$ Calculated for $C_{17}H_{10}F_4N_2O$: 335.0802; Found 335.0805.



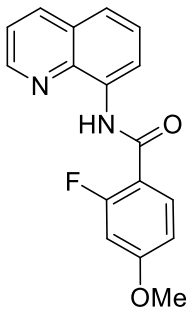
(**9F**)

2-Fluoro-*N*-(quinolin-8-yl)-5-(trifluoromethyl)benzamide (**9F**) was prepared according to the literature procedure.[3] 8-Aminoquinoline (145.3 mg, 1.0 mmol, 1 equiv) and NEt_3 (0.18 mL, 1.3 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (3 mL, 0.34 M), followed by a dropwise addition of 2-fluoro-5-(trifluoromethyl)benzoyl chloride (0.2 mL, 1.3 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**9F**) as a white solid (251.8 mg, 75% yield, R_f = 0.6 in 20% ethyl acetate in hexanes, mp = 143-140 °C). The ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[1] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –62.26 (s, 3F), –107.21 (m, 1F). HRMS (ESI$^+$) $[M + H]^+$ Calculated for $C_{17}H_{11}F_4N_2O$: 335.0802; Found 335.0811.



(**10F**)

2-Fluoro-N-(quinolin-8-yl)-6-(trifluoromethyl)benzamide (**10F**) was prepared according to the literature procedure.[1] In a glovebox, *N*-(quinolin-8-yl)-2-(trifluoromethyl)benzamide (155.0 mg, 0.49 mmol, 1 equiv), copper(I) iodide (19.3 mg, 0.10 mmol, 0.21 equiv), silver fluoride (254.4 mg, 2.0 mmol, 4.1 equiv), and *N*-methylmorpholine oxide (300.5 mg, 2.6 mmol, 5.2 equiv) were dissolved in DMF in the dark. The mixture was allowed to stir for 5 min at room temperature. The reaction was heated to 120 °C for 90 min. The solution was cooled to room temperature, diluted with ethyl acetate, filtered through a celite plug, and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**10F**) as a white solid (20.0 mg, 12% yield, R_f = 0.4 in 20% ethyl acetate in hexanes, mp = 173-174 °C). The ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[1] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –59.24 (s, 3F), –113.14 (m, 1F). HRMS (ESI^+) $[M + H]^+$ Calculated for $C_{17}H_{11}F_4N_2O$: 335.0802; Found 335.0806.

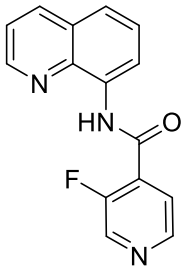


(**11F**)

2-Fluoro-*N*-(quinolin-8-yl)-4-methoxybenzamide (**11F**) was prepared according to the literature procedure.[4] To an oven-dried vial, 2-fluoro-4-methoxybenzoic acid (171.1 mg, 1.0 mmol, 1 equiv) was placed under N_2. DMF (5 drops) and CH_2Cl_2 (2.2 mL, 0.46 M) were added, and the solution was cooled to 0 °C. Oxalyl chloride (0.1 mL, 1.2 mmol, 1.2 equiv) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 1 h and then slowly warm to room temperature under N_2 and stirred for 6 h. The solvent was removed *in vacuo*, and the resulting acid chloride was used immediately without further purification.

To another oven-dried vial, 8-aminoquinoline (159.7 mg, 1.1 mmol, 1.1 equiv) and NEt_3 (0.20 mL, 1.4 mmol, 1.4 equiv) were dissolved in anhydrous CH_2Cl_2 (1.4 mL, 0.79 M). A solution of acid chloride in CH_2Cl_2 (2.0 mL, 3.4 mL total, 0.33 M) was added dropwise at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was washed with saturated aqueous $NaHCO_3$, 1 N HCl, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (100% dichloromethane), affording the product (**11F**) as a white solid (187.5 mg, 63% yield, R_f = 0.4 in 20% ethyl acetate in hexanes, mp = 147-148 °C). The ^{1}H and ^{13}C NMR spectra matched

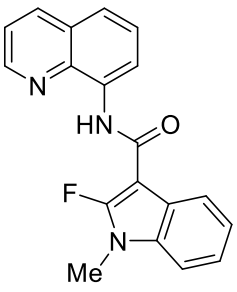
those reported in the literature.[13] ^{19}F NMR (377 MHz,s $CDCl_3$, ppm): δ –109.1 (m, 1F). HRMS (ESI^+) $[M + H]^+$ Calculated for $C_{17}H_{14}FN_2O_2$: 297.1034; Found 297.1037.



(**12F**)

3-Fluoro-*N*-(quinolin-8-yl)isonicotinamide (**12F**) was prepared according to the literature procedure.[4] To an oven-dried vial, 3-fluoroisonicotinic acid (140.7 mg, 1.0 mmol, 1 equiv) was placed under N_2. DMF (5 drops) and CH_2Cl_2 (2.0 mL, 0.50 M) were added, and the solution was cooled to 0 °C. Oxalyl chloride (0.1 mL, 1.2 mmol, 1.2 equiv) was added dropwise at 0 °C. The mixture was allowed to warm to room temperature under N_2 and stirred for 4 h. The solvent was removed *in vacuo*, and the resulting acid chloride was used immediately without further purification.

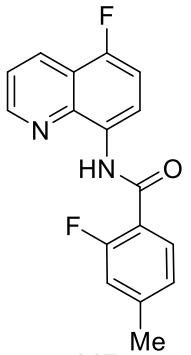
To another oven-dried vial, 8-aminoquinoline (206.3 mg, 1.4 mmol, 1.4 equiv) and NEt_3 (0.30 mL, 2.2 mmol, 2.2 equiv) were dissolved in anhydrous CH_2Cl_2 (2.0 mL, 0.72 M). A solution of acid chloride in CH_2Cl_2 (4.0 mL, 6.0 mL total, 0.24 M) was added dropwise at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**12F**) as an off-white solid (30.6 mg, 12% yield, R_f = 0.4 in 50% ethyl acetate in hexanes, mp = 155-156 °C). The ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[1] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –127.46 (m, 1F). HRMS (ESI^+) $[M + H]^+$ Calculated for $C_{15}H_{11}FN_3O$: 268.0881; Found 268.0887.



(**13F**)

2-Fluoro-1-methyl-N-(quinolin-8-yl)-1H-indole-3-carboxamide (13F) was prepared according to the literature procedure.[1] In a glovebox, a 1 dram vial was charged with 1-methyl-*N*-(quinolin-8-yl)-1H-indole-3-carboxamide **(13H)** (75.3 mg, 0.25 mmol, 1 equiv), copper(I) iodide (5.7 mg, 0.030 mmol, 0.12 equiv), *N*-methylmorpholine oxide (152.9 mg, 1.3 mmol, 5.2 equiv) and AgF (129.3 mg, 1.0 mmol, 4.1 equiv). The solids were dissolved in anhydrous DMF (1.0 mL, 0.25 M). The sealed vial was stirred at room temperature for 5 min, covered with aluminum foil, and then heated to 50 °C for 1 h. The reaction was cooled to room temperature,

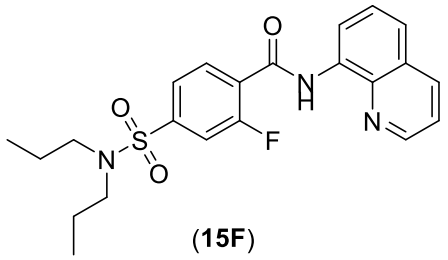
diluted with ethyl acetate (2 mL), filtered through a pad of celite, and then the solid phase was washed with ethyl acetate (2 x 10 mL). The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**13F**) as a yellow solid (11.5 mg, 14% yield, R_f = 0.38 in 30% ethyl acetate in hexanes, mp > 210 °C). The ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[1] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –124.0 (m, 1F). HRMS (ESI$^+$) $[M + H]^+$ Calculated for $C_{19}H_{15}FN_3O$: 320.1194; Found 320.1198.



(**14F**)

2-Fluoro-*N*-(5-fluoroquinolin-8-yl)-4-methylbenzamide (**14F**) was prepared according to the literature procedure.[3] 5-Fluoro-8-aminoquinoline (101.6 mg, 0.63 mmol, 1.4 equiv) and NEt_3 (0.11 mL, 0.79 mmol,1.7 equiv) were dissolved in anhydrous CH_2Cl_2 (2.2 mL, 0.78 M), followed by a dropwise addition of a solution of 2-fluoro-4-methylbenzoyl chloride (136.0 mg, 0.46 mmol, 1.0 equiv) in CH_2Cl_2 (1.4 mL, 2.2 mL total, 0.21 M). The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**14F**) as a white solid (113.7 mg, 48% yield, R_f = 0.6 in 20% ethyl acetate in hexanes, mp = 177-178 °C).

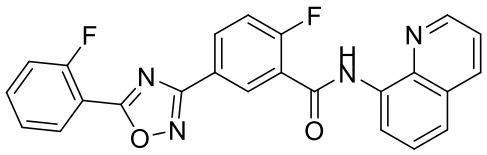
^{1}H NMR (700 MHz, $CDCl_3$, ppm): δ 10.97 (d, *J* = 14 Hz, 1H), 8.94 (d, *J* = 5.6 Hz, 1H), 8.92 (dd, *J* = 4.2, 1.4 Hz, 1H), 8.45 (dd, *J* = 8.4, 1.4 Hz, 1H), 8.11 (t, *J* = 8.4 Hz, 1H), 7.54 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.26 (t, *J* = 4.2 Hz, 1H), 7.13 (d, *J* = 5.6 Hz, 1H), 7.04 (d, *J* = 14 Hz, 1H), 2.44 (s, 3H)
^{13}C NMR (175 MHz, $CDCl_3$, ppm): δ 161.58 (d, *J* = 3.5 Hz), 160.49 (d, *J* = 248.2 Hz), 153.11 (d, *J* = 249.9 Hz), 149.27, 145.08 (d, *J* = 8.8 Hz), 139.05 (d, *J* = 1.8 Hz), 131.83 (d, *J* = 1.8 Hz), 131.48 (d, *J* = 3.5 Hz), 129.66 (d, *J* = 3.5 Hz), 125.73 (d, *J* = 3.5 Hz), 121.69 (d, *J* = 1.8 Hz), 118.88 (d, *J* = 12.3 Hz), 118.75 (d, *J* = 17.6 Hz), 116.70 (d, *J* = 3.5 Hz), 116.61 (d, *J* = 12.3 Hz), 110.42 (d, *J* = 19.4 Hz), 21.38
^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –112.97 (m, 1F), –128.97 (m, 1F).
HRMS (ESI$^+$) $[M + H]^+$ Calculated for $C_{17}H_{12}F_2N_2O$: 299.0990; Found 299.0992.



(**15F**)

4-(*N*,*N*-Dipropylsulfamoyl)-2-fluoro-*N*-(quinolin-8-yl)benzamide (**15F**) was prepared according to the literature procedure.[1] In a glovebox, a 1 dram vial was charged with *N*-(8-quinolinyl)benzamide **13H** (104.0 mg, 0.25 mmol, 1 equiv), copper(I) iodide (4.7 mg, 0.025 mmol, 0.10 equiv), *N*-methylmorpholine oxide (118.4 mg, 1.0 mmol, 4.0 equiv) and AgF (94.1 mg, 0.74 mmol, 2.9 equiv). The solids were dissolved in anhydrous DMF (1.0 mL, 0.25 M). The sealed vial was stirred at room temperature for 5 min, covered with aluminum foil, and then heated to 75 °C for 30 min. The reaction was cooled to room temperature, diluted with ethyl acetate (2 mL), filtered through a pad of celite, and then the solid phase was washed with ethyl acetate (2 x 1 mL). The crude residue was purified by column chromatography (8% ethyl acetate in hexanes), affording the product (**15F**) as a white solid (29.3 mg, 27% yield, R_f = 0.3 in 20% ethyl acetate in hexanes, mp = 176-177 °C).

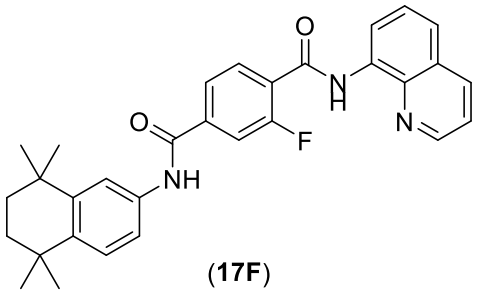
^{1}H NMR (700 MHz, $CDCl_3$, ppm): δ 11.15 (d, *J* = 12 Hz, 1H), 8.93 (dd, *J* = 6.3, 2.8 Hz, 1H), 8.87 (dd, *J* = 4.2, 2.1 Hz, 1H), 8.32 (t, *J* = 7.7 Hz, 1H), 8.19 (dd, *J* = 7.7, 2.1 Hz, 1H), 7.73 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.69 (dd, *J* = 10.5, 1.4 Hz, 1H), 7.57-7.60 (multiple peaks, 2H), 7.48 (dd, *J* = 8.4, 4.2 Hz, 1H), 3.13 (t, *J* = 7.7 Hz, 4H), 1.57 (m, *J* = 7.7 Hz, 4H), 0.88 (t, *J* = 7.7 Hz, 6H)
^{13}C NMR (176 MHz, $CDCl_3$, ppm): δ 160.36 (d, *J* = 100.3 Hz), 160.06, 159.20, 148.64, 145.09 (d, *J* = 7.0 Hz), 138.72, 136.37, 134.36, 133.10, 133.09, 127.99, 127.34, 125.49 (d, *J* = 10.6 Hz), 123.08 (d, *J* = 3.5 Hz), 122.58, 121.84, 117.45, 115.54, 115.38, 50.05, 21.99, 11.16
^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –109.41 (m, 1F)
HRMS (ESI+) $[M + H]^+$ Calculated for $C_{22}H_{25}FN_3O_3S$: 430.1595; Found 430.1591.



(**16F**)

2-Fluoro-5-(5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl)-*N*-(quinolin-8-yl)benzamide (**16F**) was prepared according to the literature procedure.[1] In a glovebox, a 1 dram vial was charged with *N*-(8-quinolinyl)benzamide **16H** (98.2 mg, 0.24 mmol, 1 equiv), copper(I) iodide (6.2 mg, 0.03 mmol, 0.14 equiv), *N*-methylmorpholine oxide (120.5 mg, 1.0 mmol, 4.3 equiv), and AgF (93.1 mg, 0.73 mmol, 3.1 equiv). The solids were dissolved in anhydrous DMF (1.0 mL, 0.24 M). The sealed vial was stirred at room temperature for 5 min, covered with aluminum foil, and then heated to 75 °C for 1 h. The reaction was cooled to room temperature, diluted with ethyl acetate (2 mL), filtered through a pad of celite, and then the solid phase was washed with ethyl acetate (2 x 20 mL). The crude residue was purified by column chromatography (4% ethyl acetate in dichloromethane), affording the product (**16F**) as a white solid (27.2 mg, 20% yield, R_f = 0.50 in 30% ethyl acetate in hexanes, mp = 201-202 °C).

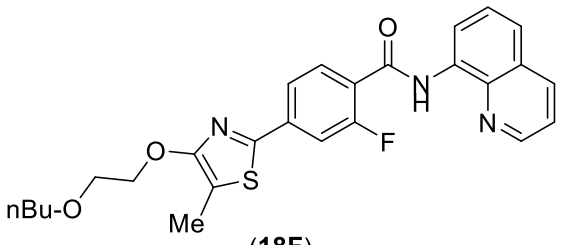
^{1}H NMR (700 MHz, $CDCl_3$, ppm): δ 11.15 (d, *J* = 4.9 Hz, 1H), 9.04 (d, *J* = 7.7 Hz, 1H), 8.99 (d, *J* = 7.7 Hz, 1H), 8.87 (d, *J* = 4.2, 1H), 8.35 (m, 1H), 8.24 (t, *J* = 7.7 Hz,1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.56-7.63 (multiple peaks, 3H), 7.48 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.39 (t, *J* = 9.8 Hz, 1H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.29 (t, *J* = 9.8 Hz, 1H)
^{13}C NMR (176 MHz, d_7-DMF, 75 °C, ppm): δ 173.54, 167.60, 161.59, 160.61, 160.12, 149.40, 138.85, 136.90, 135.87 (d, *J* = 10.6 Hz), 134.87, 132.99 (d, *J* = 10.6 Hz), 131.27, 131.04, 128.51, 127.28, 125.63 (d, *J* = 5.3 Hz),124.24, 123.44 (d, *J* = 12.3 Hz), 122.91, 122.53, 118.18 (d, *J* = 22.9 Hz), 117.46 (d, *J* = 22.9 Hz), 117.21, 112.48 (d, *J* = 12.3 Hz),
^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –108.15 (m, 1F), –108.41 (m, 1F)
HRMS (ESI+) $[M + H]^+$ Calculated for $C_{24}H_{15}F_2N_4O_2$: 429.1158; Found 429.1158.



(**17F**)

2-Fluoro-*N*^{1}-(quinolin-8-yl)-*N*^{4}-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)terephthalamide (**15F**) was prepared according to the literature procedure.[1] In a glovebox, a 1 dram vial was charged with *N*-(8-quinolinyl)benzamide **17H** (118.0 mg, 0.25 mmol, 1 equiv), copper(I) iodide (4.1 mg, 0.02 mmol, 0.09 equiv), *N*-methylmorpholine oxide (119.7 mg, 1.0 mmol, 4.1 equiv), and AgF (99.0 mg, 0.78 mmol, 3.2 equiv). The solids were dissolved in anhydrous DMF (1.0 mL, 0.25 M). The sealed vial was stirred at room temperature for 5 min, covered with aluminum foil, and then heated to 75 °C for 1 h. The reaction was cooled to room temperature, diluted with ethyl acetate (2 mL), filtered through a pad of celite, and then the solid phase was washed with ethyl acetate (2 x 20 mL). The crude residue was purified by column chromatography (18% ethyl acetate in hexanes), affording the product (**17F**) as a white solid (16.5 mg, 12% yield, R_f = 0.52 in 30% ethyl acetate in hexanes, mp = 190-191 °C).

^{1}H NMR (700 MHz, $CDCl_3$, ppm): δ 11.19 (d, *J* = 14.0 Hz, 1H), 8.94 (m, 1H), 8.86 (m, 1H), 8.28 (m, 1H), 8.17 (d, *J* = 7.7 Hz, 1H), 7.91 (m, 1H), 7.78 (d, *J* = 10.5 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.54–7.58 (multiple peaks, 3H), 7.44-7.48 (multiple peaks, 2H), 7.31 (d, *J* = 8.4 Hz, 1H), 1.68 (s, 4H), 1.29 (s, 6H), 1.27 (s, 6H)
^{13}C NMR (176 MHz, $CDCl_3$, ppm): δ 163.35, 161.11, 160.62, 159.68, 148.61, 145.91, 141.98, 140.27 (d, *J* = 7.0 Hz), 138.72, 136.28, 134.81, 134.46, 132.58, 127.95, 127.34, 127.30, 124.64 (d, *J* = 12.3 Hz), 122.60, 122.43, 121.79, 118.26 (d, *J* = 19.4 Hz), 117.36, 115.92 (d, *J* = 26.4 Hz), 34.99, 34.96, 34.44, 34.03, 31.83, 31.80
^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –110.5 (m, 1F).
HRMS (ESI+) $[M + H]^+$ Calculated for $C_{31}H_{31}FN_3O_2$: 496.2395; Found 496.2396.



(**18F**)

4-(4-(2-Butoxyethoxy)-5-methylthiazol-2-yl)-2-fluoro-*N*-(quinolin-8-yl)benzamide (**18F**) was prepared according to the literature procedure.[1] In a glovebox, a 1 dram vial was charged with *N*-(8-quinolinyl)benzamide **18H** (109.5 mg, 0.24 mmol, 1 equiv), copper(I) iodide (5.2 mg, 0.03 mmol, 0.12 equiv), *N*-methylmorpholine oxide (141.6 mg, 1.2 mmol, 5.1 equiv), and AgF (127.5 mg, 1.0 mmol, 4.2 equiv). The solids were dissolved in anhydrous DMF (1.0 mL, 0.24 M). The sealed vial was stirred at room temperature for 5 min, covered with aluminum foil, and then heated to 75 °C for 1 h. The reaction was cooled to room temperature, diluted with ethyl acetate (2 mL), filtered through a pad of celite, and then the solid phase was washed with ethyl acetate (2 x 1 mL). The crude residue was purified by column chromatography (9% ethyl acetate in hexanes), affording the product (**18F**) as a yellow solid (44.7 mg, 39% yield, R_f = 0.4 in 20% ethyl acetate in hexanes, mp = 96-97 °C).

^{1}H NMR (700 MHz, $CDCl_3$, ppm): δ 11.15 (d, *J* = 14 Hz, 1H), 8.96 (dd, *J* = 7.7, 1.4 Hz, 1H), 8.86 (dd, *J* = 4.2, 1.4 Hz, 1H), 8.22 (t, *J* = 8.4, 1H), 8.16 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.71-7.74 (multiple peaks, 2H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.54 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.45 (dd, *J* = 8.4, 4.2 Hz, 1H), 4.51 (t, *J* = 4.9 Hz, 2H), 3.77 (t, *J* = 4.9 Hz, 2H), 3.52 (t, *J* = 7.1 Hz, 2H), 2.32 (s, 3H), 1.58 (m, *J* = 7.1 Hz, 2H), 1.38 (m, *J* = 7.4 Hz, 2H), 0.91 (t, *J* = 7.4 Hz, 3H)
^{13}C NMR (176 MHz, $CDCl_3$, ppm): δ 161.3 (d, *J* = 74 Hz), 161.06, 160.26, 160.08, 156.14 (d, *J* = 3.5 Hz), 148.51, 139.00 (d, *J* = 10.6 Hz), 138.80, 136.26, 134.81, 132.66 (d, *J* = 1.8 Hz), 127.98, 127.38, 122.09, 121.89 (d, *J* = 10.6 Hz), 121.69, 121.32 (d, *J* = 1.8 Hz), 117.28, 112.67 (d, *J* = 28 Hz), 109.56, 71.20, 69.83, 69.44, 31.76, 19.28, 13.92, 9.47
^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –111.48 (m, 1F)
HRMS (ESI+) $[M + H]^+$ Calculated for $C_{26}H_{27}FN_3O_3S$: 480.1752; Found 480.1753.

4. Radiochemistry

4.1 General materials and methods

Materials and methods. HPLC grade acetonitrile, potassium trifluoromethanesulfonate, and anhydrous dimethylformamide were purchased from Fisher Scientific. Silver trifluoromethanesulfonate, sodium bicarbonate, Kryptofix® 2.2.2 ($K_{2.2.2}$), anhydrous acetonitrile, dimethylacetamine, *N*-methylmorpholine (NMM), *N*-methylmorpholine *N*-oxide (NMO), and 1,8-diazabicyclo[5.4.0]undec-7-ene were purchased from Sigma-Aldrich. Sterile product vials (10 mL) were purchased from Hollister-Stier. QMA-light Sep-Paks were purchased from Waters Corporation. QMA-light Sep-Paks were flushed with 10 mL of ethanol, followed by 90 mg/mL of an aqueous solution of potassium trifluoromethanesulfonate, and rinsed with 10 mL of MQ water prior to use for the generation of $Ag^{18}F$. QMA-light Sep-Paks were flushed with ethanol (10 mL), 0.5 M aqueous sodium bicarbonate (10 mL), and MQ water (10 mL) prior to use for the generation of $K^{18}F$.

Generation of $Ag^{18}F$. All loading operations were conducted under ambient atmosphere. Automated sample transfers utilized argon gas. Silver [^{18}F]fluoride was prepared with a TRACERLab FX_{FN} automated radiochemistry synthesis module (General Electronic, GE). [^{18}F]Fluoride was produced via the proton beam bombardment of ^{18}O-target water ($^{18}O(p,n)^{18}F$) using a GE PETTrace cyclotron (40 μA beam for 5-10 min generated ca. 315-620 mCi of [^{18}F]fluoride). The [^{18}F]fluoride was delivered to the automated synthesis module in a 1.5 mL bolus of [^{18}F]target water and trapped on the preconditioned QMA-light Sep-Pak to remove [^{18}O]target water and other aqueous impurities. [^{18}F]Fluoride was eluted into the reaction vessel using silver trifluoromethanesulfonate in MQ water (10 mg, 0.5 mL, 0.08 M) and $K_{2.2.2}$ in acetonitrile (15 mg, 1 mL, 0.04 M). Azeotropic drying was achieved by heating to 100 ºC and drawing vacuum for 6 min. The reaction vessel was then subjected to an argon stream and simultaneous vacuum draw for an additional 6 min to produce anhydrous $Ag^{18}F/K_{2.2.2}$. Overall 70% of radioactivity remained after azeotropic drying (66 ± 7%, n = 25; calculated from TRACERLab FX_{FN} reactor radiation detector by comparing radioactivity in the reaction vessel before and after azeotropic drying process). The reaction vessel was cooled to room temperature via an argon stream, and anhydrous dichloromethane (3.5 mL) was added to dissolve the dried reagents. The mixture was heated to 37 °C with stirring for 5 min to suspend the Ag[^{18}F]F/ $K_{2.2.2}$. The resulting solution was cooled to room temperature and transferred to a sterile vial.

Generation of $K^{18}F$. [^{18}F]Fluoride was produced by the same protocol described in generation of $Ag^{18}F$ (above). The [^{18}F]fluoride was delivered to the automated synthesis module (TRACERLab FX_{FN}, GE) in a 1.5 mL bolus of [^{18}F]target water and was trapped on the preconditioned QMA-light Sep-Pak to remove [^{18}O]target water and other aqueous impurities. [^{18}F]Fluoride was eluted into the reaction vessel using potassium trifluoromethanesulfonate (5 mg, 0.5 mL, 0.05 M) and $K_{2.2.2}$ in acetonitrile (15 mg, 1 mL, 0.04 M). Azeotropic drying/evaporation was achieved by heating the reaction vessel to 100 ºC and drawing vacuum for 6 min. Azeotropic drying was achieved by heating to 100 ºC and drawing vacuum for 6 min. The reaction vessel was then subjected to an argon stream and simultaneous vacuum draw for an additional 6 min to produce anhydrous $K^{18}F/K_{2.2.2}$. The reaction vessel was cooled to room temperature under an argon stream, and anhydrous DMF (6 mL) was added. The mixture was

heated to 50 °C with stirring for 5 min to suspend the K[^{18}F]F/ $K_{2.2.2}$. The resulting solution was cooled to room temperature and was transferred to a sterile vial.

4.2 Radiosynthesis of ^{18}F-labeled molecules

4.2.1. Manual synthesis general procedure. A stock solution of each of the following reagents, the quinoline benzamide precursor (0.2 M), $(MeCN)_4CuOTf$ (0.05 M), DBU (0.2 M), and *N*-methylmorpholine (NMM) (0.9 M), in DMF was prepared. To a 4 mL vial containing a stir bar were added 100 µL aliquots of each stock solution [quinoline benzamide precursors (20 µmol, 1 equiv), $(MeCN)_4CuOTf$ (5 µmol, 0.25 equiv), DBU (20 µmol, 1 equiv), and NMM (90 µmol, 4.5 equiv)]. K[^{18}F]F/$K_{2.2.2}$ in 200 µL of DMF (2500-3500 µCi of radioactivity) was used for each manual reaction, and additional DMF (400 µL) was also added to bring the total solution volume to 1 mL. The reaction vial was sealed and prestirred (1500 rpm) at room temperature for 5 min. The reaction vial was heated in an aluminum block with vigorous stirring (1500 rpm) at 90-110 °C for 30 min. After 30 min, the reaction was cooled to room temperature and the radiochemical conversion (RCC, %) was determined by radio-TLC analysis. The crude reaction mixture was spotted onto standard silica-coated glass plates and developed with hexanes:ethyl acetate (1:1) in a glass TLC chamber. The RCC was determined by dividing the integrated area of radiation under the fluorinated product spot by the total integrated area of radiation on the TLC plate. In reactions where the radio-HPLC traces show multiple peaks, the RCC (determined by radio-TLC) was corrected by dividing the integrated area of radiation under the desired F-18 labeled product peak by the total integrated area of radiation on the analytical radio-HPLC. To prepare samples for HPLC analysis, 80 µL of the reaction mixture was spiked with 20 µL of 2 mg/mL fluorinated standard solution in DMF. Eluent systems and columns used for HPLC analysis are described below in Section 4.6.

$$\text{RCC (\%)} = \frac{\text{Integration of the radioproduct peak}}{\text{Sum of integration of all peaks}}$$

4.2.2 Automated synthesis of 1^{18}F followed by semi-preparative HPLC purification
All loading operations were conducted under ambient atmosphere. Argon gas and vacuum were used for automated sample transfers. [^{18}F]Fluoride was produced via the ^{18}O(p, n)^{18}F nuclear reaction using a General Electronic (GE) PETTrace cyclotron (40 µA beam for 3 min generated ca. 200 mCi of [^{18}F]fluoride, and 30 min generated ca. 1.7 Ci of [^{18}F]fluoride). K^{18}F was produced as described in **Generation of K^{18}F** using a GE TRACERLab FX_{FN} automated synthesis module. DMF (0.5 mL) was added to the dried K^{18}F in the reactor, and the solution was stirred for 5 min at room temperature. A solution containing **1H** (5.3 mg, 20 µmol, 1 equiv), $(MeCN)_4CuOTf$ (2 mg, 5 µmol, 0.25 equiv), DBU (3 µL, 20 µmol, 1 equiv), and NMM (10 µL, 90 µmol, 4.5 equiv) in 0.8 mL of anhydrous DMF was added to the reactor containing 0.5 mL of a K^{18}F solution in DMF by applying Ar gas through the valve containing the reagent solution. The open valves leading out of the reactor were closed, and the reaction mixture was prestirred for 5 min at room temperature. The mixture was heated to 100 ºC and stirred for 30 min. The mixture was cooled to 30 ºC with compressed air cooling, and the resulting mixture was diluted by 3 mL of semi-preparative HPLC buffer (60 % acetonitrile in water, 0.1 % (v/v) trifluoroacetic acid) then loaded onto the HPLC injection loop by passing through a Sep-Pak alumina N plus light cartridge to remove unreacted residual [^{18}F]fluoride. The diluted mixture was injected onto the semi-prep HPLC for purification by HPLC conditions D described in Section 4.2.8. The peak for the desired ^{18}F-labeled organic product was collected for 2 min (t_R = 16.5 min, collected volume: 8 mL) in a

10 mL sterile product vial. The dose vial was transferred out of the synthesis module product identity were then determined using a Capintec dose calibrator and analytical HPLC (Table S1).

Entry	Starting activity (mCi)	Final Activity (mCi)	RCY, NDC (%)	Total time (min)	RCY, DC (%)
1	194	12	6	104	12
2	194	12	6	103	12
3	194	13	7	102	13
4	1,700	40	2	110	5
5	1,700	40	2	98	4
6	1,700	45	3	104	5

Table S1: Automated Syntheses of **1**^{18}**F**

4.2.3 Specific activity of 1^{18}F

A 20 µL aliquot was analyzed by HPLC, using HPLC Conditions A, and the area of the UV peak (280 nm) corresponding to the **1F** standard (t_R = 10.5 min) was determined. The molar concentration (µmol/µL) of **1F** in the sample was then determined by linear regression analysis against a standard curve generated from injection of identical volumes of solutions of known concentration of **1F**. The concentration of activity was determined by dividing the total activity ($4.0 – 4.5\times10^{-2}$ Ci) by the volume of the solution (8 mL). The end of synthesis (EOS) specific activity (Ci/µmol) is given by the division of the concentration of activity for **1**^{18}**F** (Ci/µL) by the molar concentration of the product ($7.3\text{-}9.2\times10^{-7}$ µmol/µL). EOS specific activity was found to be 6.4 ± 1 Ci/µmol for the high activity runs (n = 3, Table S1, entries 4 – 6).

4.2.4 Automated synthesis of 1^{18}F followed by manual hydrolysis to provide 19^{18}F

All loading operations were conducted under ambient atmosphere. Argon gas and vacuum was used for automated sample transfers. [^{18}F]Fluoride was produced via the ^{18}O(p, n)^{18}F nuclear reaction using a GE PETTrace cyclotron (40 µA beam for 30 min generated ca. 1.7 Ci of [^{18}F]fluoride). K^{18}F was produced as described in **Generation of K**^{18}**F** using an automated synthesis module, TRACERLab FX_{FN} (General Electronic, GE). DMF (0.2 mL) was added to the dried K^{18}F in the reactor, and the solution was stirred for 5 min at room temperature. A solution containing **1H** (5.3 mg, 3.8 µmol, 1 equiv), $(MeCN)_4CuOTf$ (2 mg, 0.1 µmol, 0.25 equiv), DBU (3 µL, 3.8 µmol, 1 equiv), and NMM (10 µL, 17 µmol, 4.5 equiv) in 0.8 mL of anhydrous DMF was added to the reactor containing 0.2 mL of a K^{18}F solution in DMF by applying Ar gas through the valve containing the reagent solution. The open valves leading out of the reactor were closed, and the reaction mixture was prestirred for 5 min at room temperature. The mixture was heated to 100 ºC and stirred for 30 min. The RCC of **1**^{18}**F** from **1H** was determined by radio-TLC (28 ± 6%, n=6), and product identity was determined using analytical HPLC. The mixture was cooled to 30 ºC with compressed air cooling, and for 3 runs the resulting mixture was transferred to the dilution flask containing 50 mM of EDTA solution (70 mL). The diluted mixture was slowly loaded onto the Sep-Pak C18 plus cartridge to trap ^{18}F-labeled organic products by removing unreacted residual [^{18}F]fluoride and copper. Radiochemical purity of **1**^{18}**F** following this purification was 83 ± 2%. The trapped **1**^{18}**F** was eluted with ethanol (2 mL) and collected in an 8 mL sterile product vial. An aliquot of the collected **1**^{18}**F** in ethanol (0.5 mL) was then added to 4 M NaOH (1 mL) in a 4 mL vial. The reaction vial was transferred to a hot plate and stirred for 30

min at 100 ºC. The resulting mixture was cooled to room temperature and neutralized by the addition of 6 N HCl (0.7 mL). Ethyl acetate (1 mL) was used to extract the organic portion from the mixture. The RCC of **19^{18}F** from **1^{18}F** was determined by radio-TLC (90 ± 2%, n=3) and the product identity was determined using analytical HPLC. The overall RCC to **19^{18}F** from [^{18}F]fluoride was 21 ± 2% (n=3).

4.2.5 Manual synthesis of 20^{18}F

[^{18}F]Fluorination of **18H** was carried out according to the procedure described in Section 4.2.1. The reaction was cooled to room temperature and a portion of the crude mixture (80 µL) was used for radio-TLC (hexanes:ethyl acetate = 1:1) and HPLC analysis. The crude reaction was then diluted with DI water (50 mL) and loaded onto a preconditioned QMA-C_{18} light Sep-Pak [EtOH (10 mL), D.I water (10 mL)]. The organic portions were eluted with EtOH (1 mL). The eluent quality was confirmed by radio-TLC analysis (hexanes:ethyl acetate = 1:1). To the eluent in EtOH (500 µL) was added 4 M NaOH (1 mL). The reaction was heated to 100 °C for 30 min with stirring at 1500 rpm. The reaction was cooled to room temperature, and the crude mixture was acidified with 1 N HCl (4 mL). The organic portion was extracted with ethyl acetate (1 mL). The RCC of the final product was determined by radio-TLC (hexanes:ethyl acetate = 1:1). A portion of the reaction mixture (80 µL) was spiked with 20 µL of 2 mg/mL AC 261066 standard in DMF. The eluent system and columns used for HPLC analysis (HPLC Conditions C) are described in Section 4.2.8.

4.2.6 Automated synthesis of 18^{18}F followed by manual hydrolysis to provide [^{18}F]AC 261066 (20^{18}F)

All loading operations were conducted under ambient atmosphere. Argon gas and vacuum was used for automated sample transfers. [^{18}F]Fluoride was produced via the ^{18}O(p, n)^{18}F nuclear reaction using a GE PETTrace cyclotron (40 µA beam for 30 min generated ca. 1.7 Ci of [^{18}F]fluoride). K^{18}F was produced as described in **Generation of K^{18}F** using an automated synthesis module, TRACERLab FX_{FN} (General Electronic, GE). DMF (0.5 mL) was added to the dried K^{18}F in the reactor, and the solution was stirred for 5 min at room temperature. A solution containing **18H** (3.5 mg, 7.8 µmol, 1 equiv), $(MeCN)_4CuOTf$ (0.76 mg, 2 µmol, 0.25 equiv), DBU (1.14 µL, 7.8 µmol, 1 equiv), and NMM (3.6 µL, 34 µmol, 4.5 equiv) in 1 mL of anhydrous DMF was added to the reactor containing 0.5 mL of a K^{18}F solution in DMF by applying Ar gas through the valve containing the reagent solution. The open valves leading out of the reactor were closed, and the reaction mixture was prestirred for 5 min at room temperature. The mixture was heated to 100 ºC and stirred for 30 min. The mixture was cooled to 30 ºC with compressed air cooling, and the resulting mixture was transferred to the dilution flask containing DI water (70 mL) by passing through a Sep-Pak alumina N plus light cartridge to remove unreacted residual [^{18}F]fluoride. DI water (3 mL) was added to the reactor and transferred by argon gas to the dilution flask to rinse the residue from the reactor. The diluted mixture was allowed to stir for approximately 1 min then slowly loaded onto the Sep-Pak C18 1cc vac cartridge. The trapped ^{18}F-labeled organic products were eluted with ethanol (1 mL) and collected in an 8 mL sterile product vial. The dose vial was transferred out of the synthesis module in a lead pig. Total activity of **18^{18}F** (36 ± 8 mCi, n=3), radiochemical yield (RCY, 3 ± 1%, n=3, decay-corrected) and product identity were then determined using a Capintec dose calibrator and analytical HPLC (Table S2). The automated synthesis time of **18^{18}F** was 100 min.

The collected **18^{18}F** in ethanol (1 mL) was then added to 4 M NaOH (2 mL) in a 4 mL vial. The reaction vial was transferred to a hot plate and stirred for 30 min at 100 ºC. The resulting mixture was cooled to room temperature and neutralized by the addition of 2 N HCl (2 mL). Ethyl acetate (1 mL) was used to extract the organic portion from the mixture. The RCC of **20^{18}F** from **18^{18}F** (98 ± 1%, n=5) was determined by radio-TLC. The isolated decay-corrected radiochemical yield (RCY, DC) of **20^{18}F** at EOS was also determined for several runs to be 2 ± 1% (n=3, Table S2) and RCP (>98%) was determined by analytical HPLC. Total synthesis time of **20^{18}F** from **18H** was 155-160 min.

Entry	Starting activity (mCi)	Collected 18^{18}F (mCi)	Final activity, 20^{18}F (mCi)	Total time (min)	RCY, DC (%)
1	1,700	30	5	155	1
2	1,700	32	5	160	1
3	1,700	45	17	155	3

Table S2: Automated Syntheses of **18^{18}F** and **20^{18}F**

4.2.7 Specific activity of 20^{18}F

A 15µL aliquot was analyzed by HPLC, using HPLC Conditions C, and the area of the UV peak (254 nm) corresponding to the **AC 261066** (**20F**) standard (t_R = 15.3 min) was determined. The molar concentration (µmol/µL) of **AC 261066** in the sample was then determined by linear regression analysis against a standard curve generated from injection of identical volumes of solutions of known concentration of **AC 261066**. The concentration of activity was determined by dividing the total activity (0.5-1.7×10^{-2} Ci) of **20^{18}F** by the volume of the solution (500 µL). The EOS specific activity (Ci/µmol) is obtained by the division of the concentration of activity for **20^{18}F** (0.7-3.5×10^{-5}Ci/µL) by the molar concentration of the product (1.3-3.2×10^{-5} µmol/µL). The EOS specific activity was found to be 0.80 ± 0.25 Ci/µmol (n = 3).

4.2.8 HPLC conditions

HPLC Conditions A.
Solvent: Isocratic 45 % acetonitrile in water, 0.1 % (v/v) trifluoroacetic acid
Flow rate: 2 mL/min, running time: 25 min
Column: Phenomenex® Kinetex PFP column 250 × 4.6 mm, 5 µm

HPLC Conditions B.
Solvent: Gradient

0-4 min	5 % acetonitrile in water, 0.1 % (v/v) trifluoroacetic acid
4-8 min	25 % acetonitrile in water, 0.1 % (v/v) trifluoroacetic acid
8-16 min	95 % acetonitrile in water, 0.1 % (v/v) trifluoroacetic acid
16-25 min	5 % acetonitrile in water, 0.1 % (v/v) trifluoroacetic acid

Flow rate: 2 mL/min, running time: 25 min
Column: Phenomenex® Kinetex PFP column 250 × 4.6 mm, 5 µm

HPLC Conditions C.
Solvent conditions: Gradient

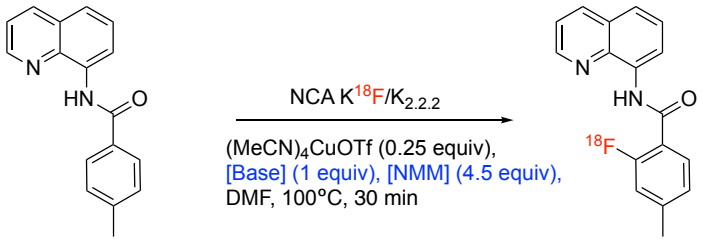
0-4 min	5 % acetonitrile in water, 0.1 % (v/v) trifluoroacetic acid
4-6 min	25 % acetonitrile in water, 0.1 % (v/v) trifluoroacetic acid
6-19 min	95 % acetonitrile in water, 0.1 % (v/v) trifluoroacetic acid
19-25 min	5 % acetonitrile in water, 0.1 % (v/v) trifluoroacetic acid

Flow rate: 2 mL/min, running time: 25 min
Column: Phenomenex® Kinetex PFP column 250 × 4.6 mm, 5 µm

HPLC Conditions D.
Solvent: Isocratic 60 % acetonitrile in water, 0.1 % (v/v) trifluoroacetic acid
Flow rate: 4 mL/min, running time: 30 min
Column: Phenomenex® Luna PFP(2) column 250 × 10.0 mm, 5 µm

4.3 Optimization Screens

4.3.1 Base screens

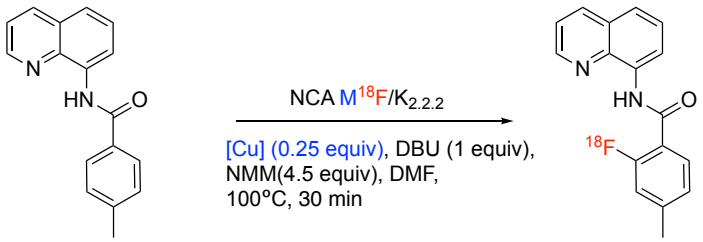


1H (20μmol, 1equiv)

Entry	Base	NMM	RCC[a, b] (%)
1	Pyridine	-	0
2	Pyridine	✓	0
3	DABCO	-	0
4	DABCO	✓	0
5	DMAP	-	6
6	DMAP	✓	10
7	Triethylamine	-	0
8	Triethylamine	✓	0
9	Proton sponge	-	0
10	Proton sponge	✓	0
11	DBN	-	42
12	DBN	✓	46
13	DBU	-	47
14	DBU	✓	52

[a]RCC was determined by radio-TLC (EtOAc/hex=1/1).
[b]The labeled product was identified by analytical HPLC.

4.3.2. Catalyst screens

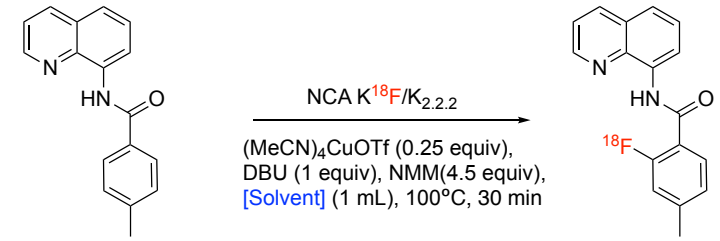


1H (20μmol, 1equiv)

Entry	[Cu]	Ag^{18}F, RCC[a, b] (%)	K^{18}F, RCC[a, b] (%)
1	CuI	35	24
2	$Cu(OAc)_2$	17	19
3	$(MeCN)_4Cu(PF_6)$	12	19
4	$(MeCN)_4Cu(BF_4)$	16	44
5	$(MeCN)_4Cu(OTf)$	40	50

[a]RCC was determined by radio-TLC (EtOAc/hex=1/1).
[b]The labeled product was identified by analytical HPLC.

4.3.3 Solvent screens

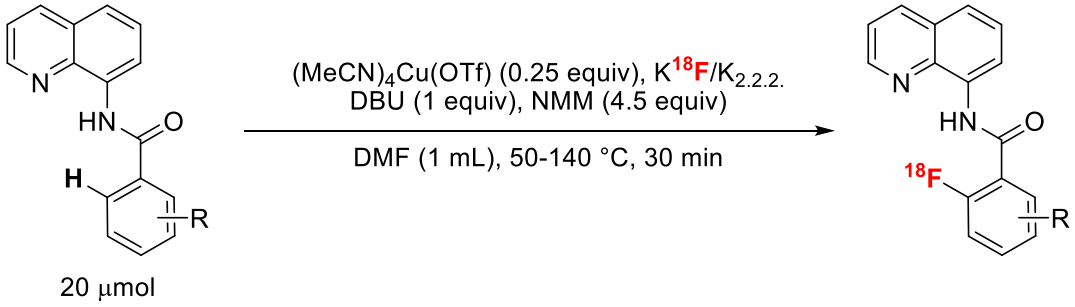


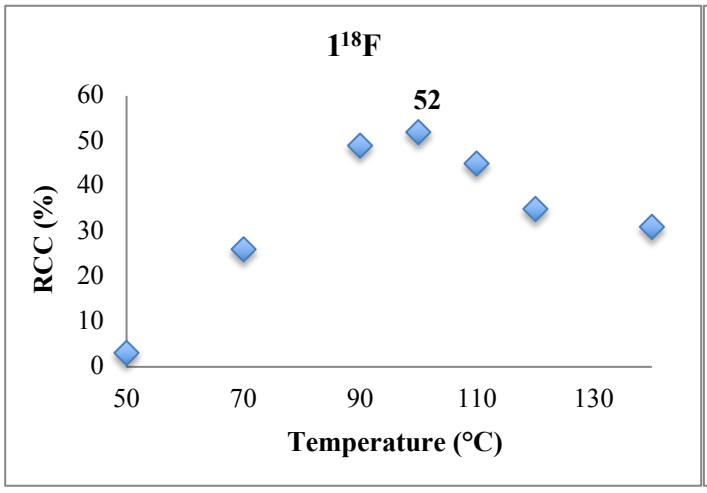
1H (20μmol, 1equiv)

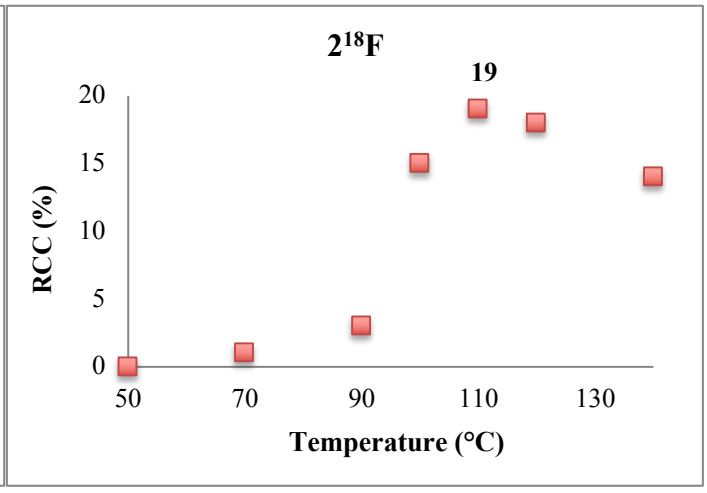
Entry	Solvent	RCC[a, b] (%)
1	DMPU	11
2	DMPU/DMF (1/2)	29
3	DMA	37
4	DMF	48

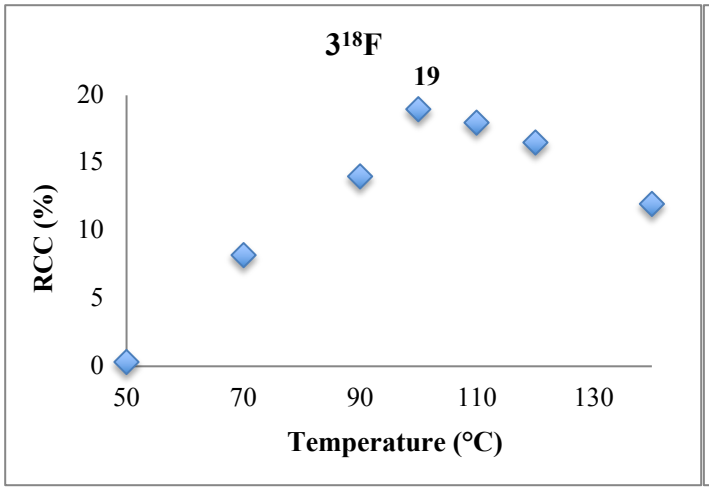
[a]RCC was determined by radio-TLC (EtOAc/hex=1/1).
[b]The labeled product was identified by analytical HPLC.

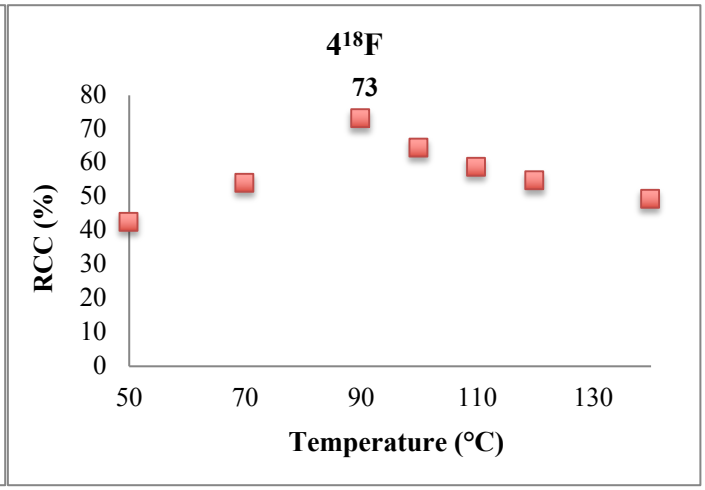
4.3.4 Investigation of reaction temperature

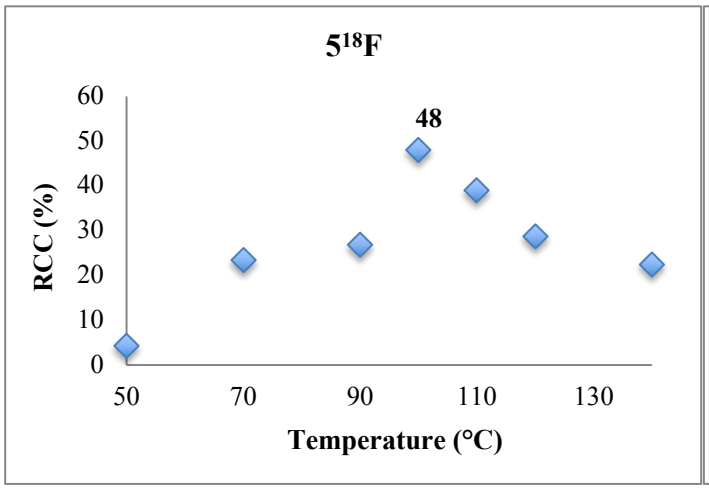


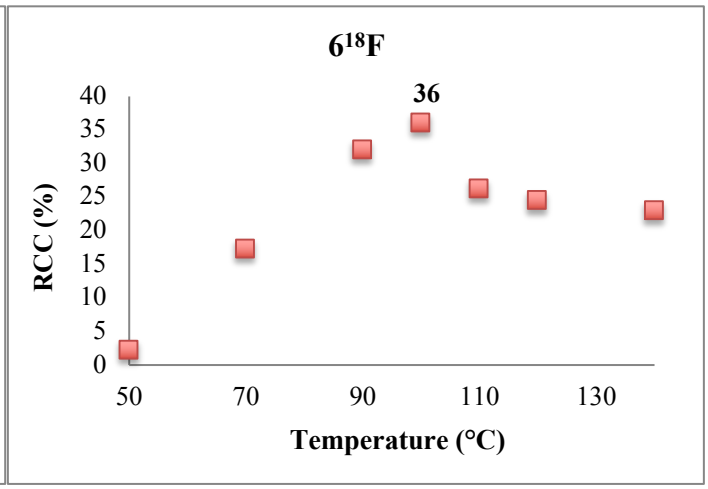


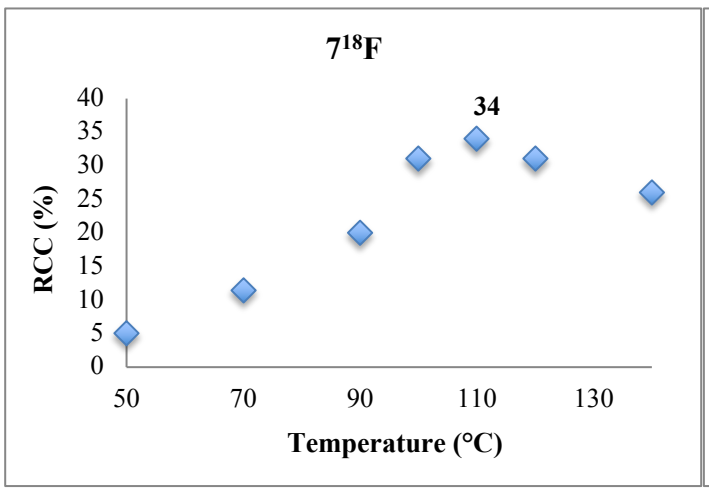


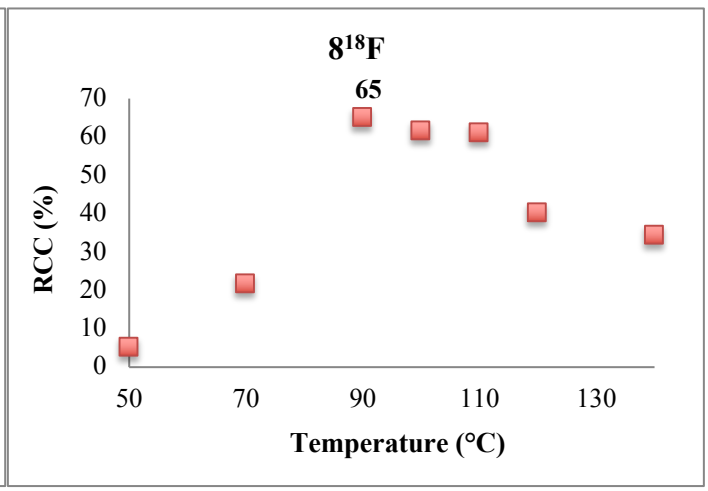

3 18F
19
RCC (%)
Temperature (°C)

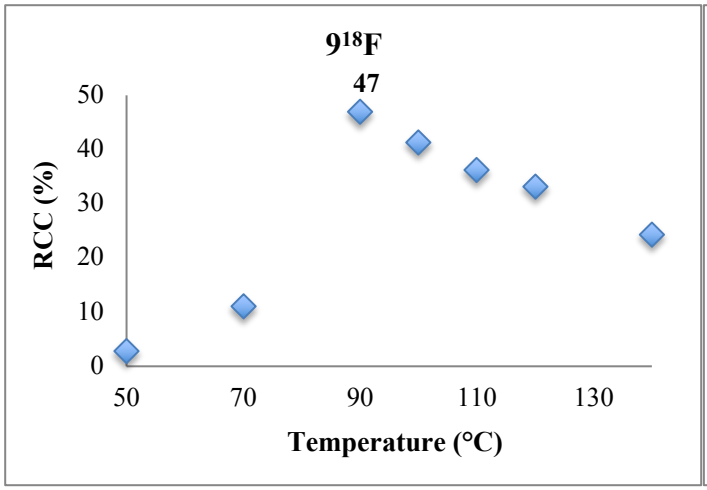

4 18F
73
RCC (%)
Temperature (°C)

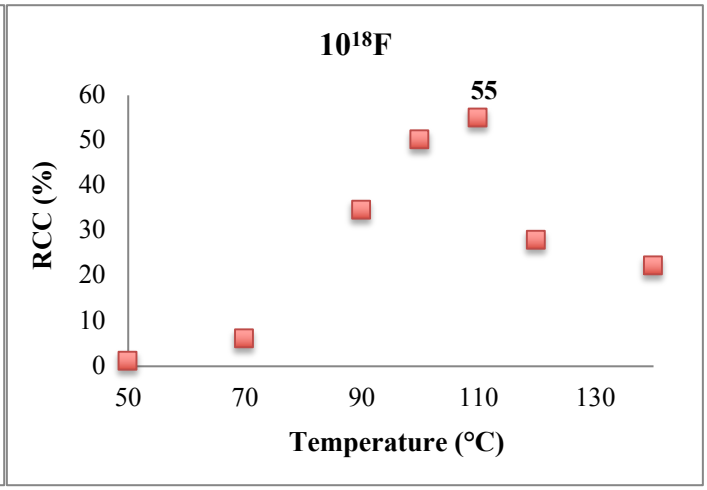

5 18F
48
RCC (%)
Temperature (°C)

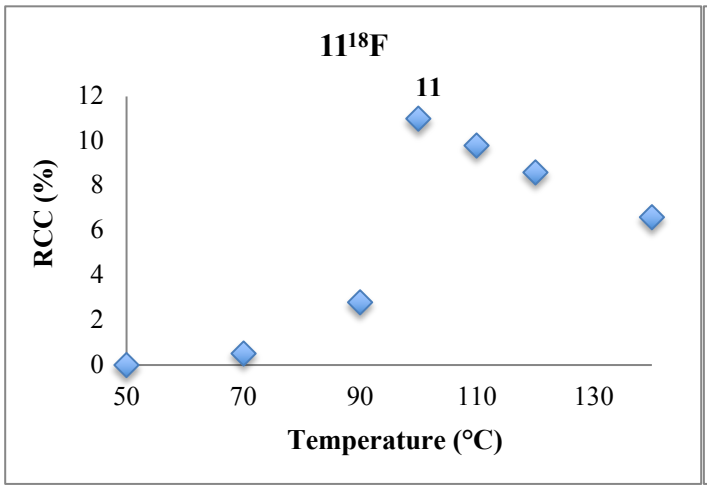

6 18F
36
RCC (%)
Temperature (°C)

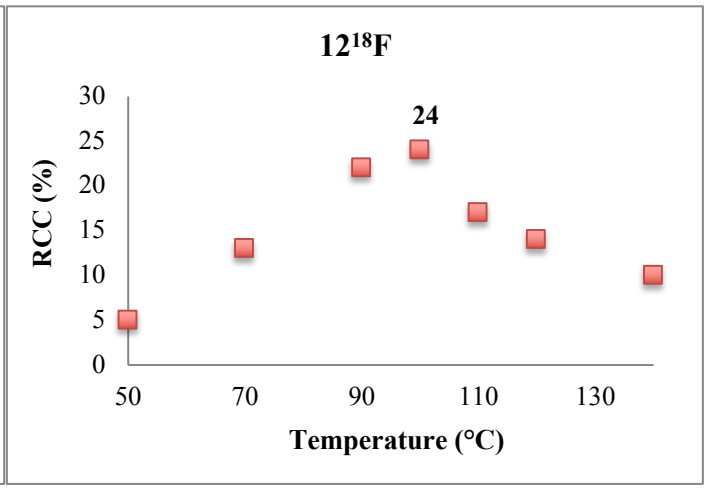

7 18F
34
RCC (%)
Temperature (°C)

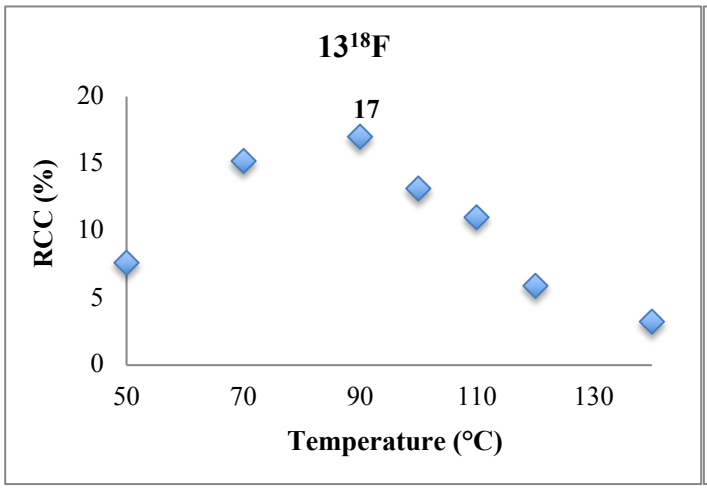

8 18F
65
RCC (%)
Temperature (°C)

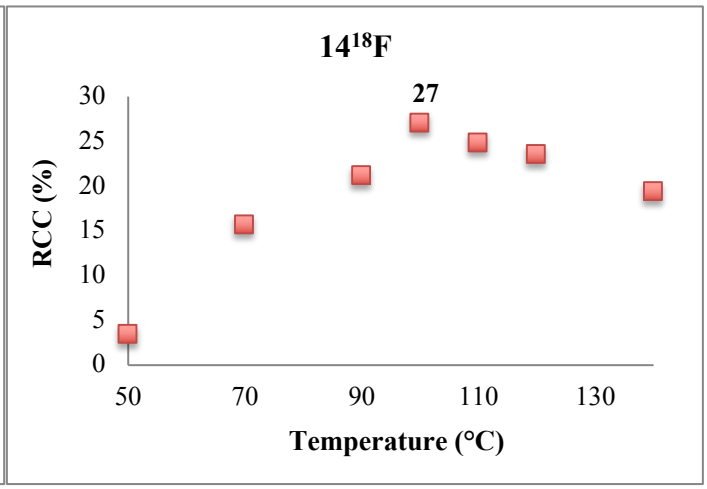

9[18]F
47
RCC (%)
50
40
30
20
10
0
50
70
90
110
130
Temperature (°C)


10[18]F
55
RCC (%)
60
50
40
30
20
10
0
50
70
90
110
130
Temperature (°C)

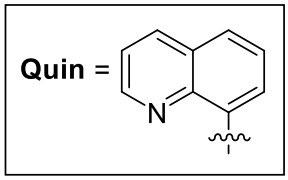

11[18]F
11
RCC (%)
12
10
8
6
4
2
0
50
70
90
110
130
Temperature (°C)

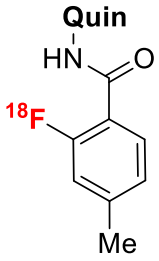

12[18]F
24
RCC (%)
30
25
20
15
10
5
0
50
70
90
110
130
Temperature (°C)


13[18]F
17
RCC (%)
20
15
10
5
0
50
70
90
110
130
Temperature (°C)


14[18]F
27
RCC (%)
30
25
20
15
10
5
0
50
70
90
110
130
Temperature (°C)

4.3.5 Substrate Scope with NMM and without NMM

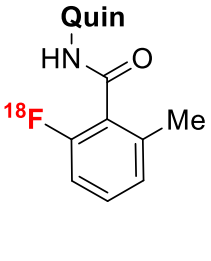




(**1**^{18}**F**)

52 ± 17% (n = 2)

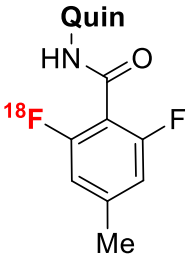
50 ± 2% (n = 5)



(**2**^{18}**F**)

10 ± 4% (n = 4)

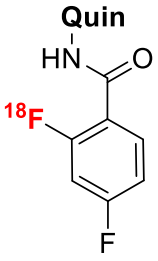
16 ± 2% (n = 5)



(**3**^{18}**F**)

35 ± 17% (n = 3)

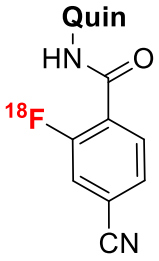
18 ± 1% (n = 5)



(**4**^{18}**F**)

70 ± 1% (n = 3)

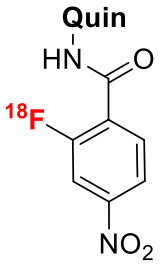
72 ± 0% (n = 5)



(**5**^{18}**F**)

40 ± 16% (n = 3)

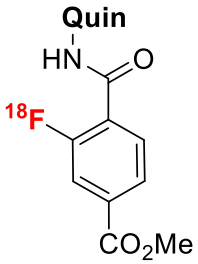
41 ± 5% (n = 4)



(**6**^{18}**F**)

13 ± 2% (n = 3)

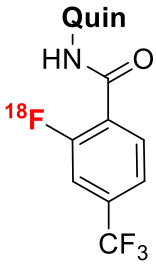
37 ± 1% (n = 4)



(**7**^{18}**F**)

22 ± 11% (n = 4)

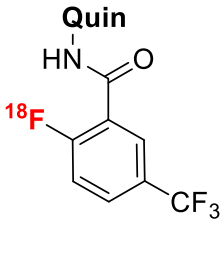
33 ± 1% (n = 5)



(**8**^{18}**F**)

63 ± 15% (n = 5)

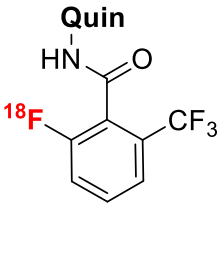
60 ± 4% (n = 5)



(**9**^{18}**F**)

28 ± 5% (n = 3)

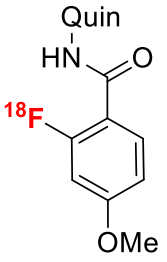
35 ± 3% (n = 4)



(**10**^{18}**F**)

57 ± 10% (n = 3)

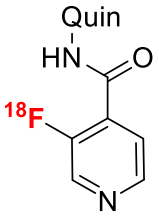
52 ± 2% (n = 4)



(**11**^{18}**F**)

17 ± 4% (n = 4)

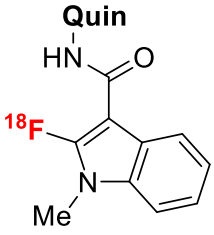
10 ± 1% (n = 5)



(**12**^{18}**F**)

16 ± 2% (n = 4)

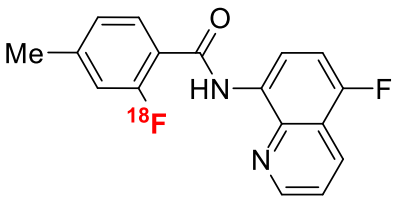
22 ± 2% (n = 5)



(**13**^{18}**F**)

15 ± 2% (n = 3)

16 ± 1% (n = 5)

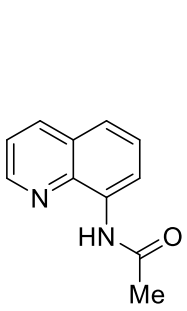


(**14**^{18}**F**)

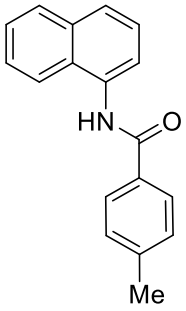
40 ± 14% (n = 3)

50 ± 1% (n = 5)

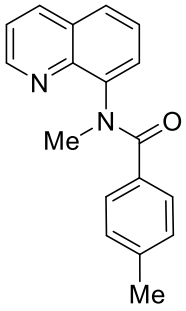
4.3.6 Control experiments



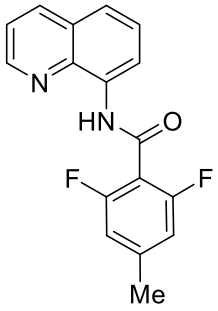
(**S1**)



(**S2**)



(**S3**)



(**3F**)

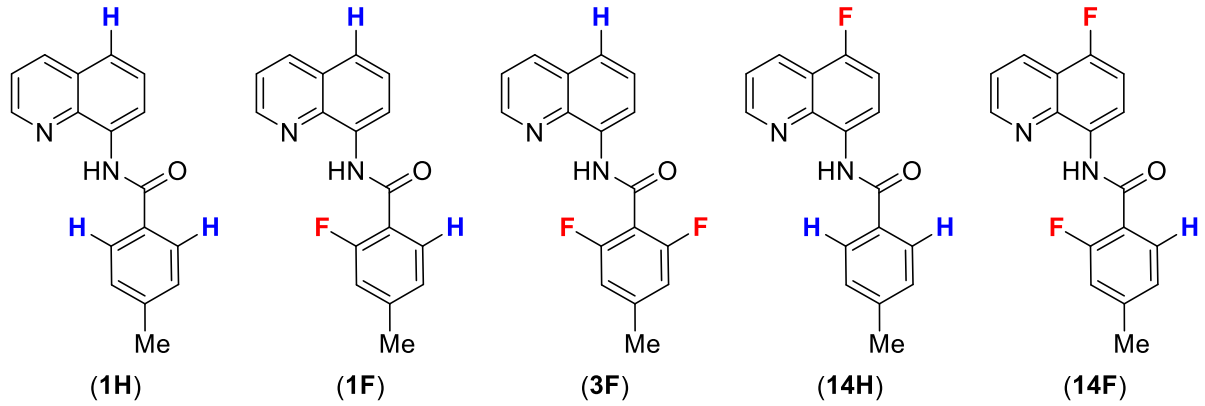
Optimized reaction conditions	RCC (%)
Substrate (S1, S2, S3, and 3F) (20 µmol, 1 equiv); $(MeCN)_4CuOTf$ (0.25 equiv); DBU (1 equiv); NMM (4.5 equiv); $K^{18}F/K_{2.2.2}$ (n.c.a); DMF (total volume 1mL), 70-140 ºC, 30 min	0

Literature reports suggest that one possible competing reaction would involve fluorination on the quinoline of the directing group rather than at the *ortho*-position of the arene substrate.[14–19] To test for this, we conducted a series of control reactions to see which components of the substrate are needed to achieve radiofluorination. We first examined substrate **S1**, which contains the amidoquinoline but not the arene. As expected (since there is no arene ring to undergo directed C–H radiofluorination), no radiofluorination was detected. We next examined **S2**, which eliminates the quinoline directing group. As expected (since there is no quinoline directing group), no radiofluorination was detected. We next examined **S3**, in which the N-H of the directing group is blocked with a methyl. As expected (since the directing group should be blocked from binding Cu), no radiofluorination was detected. Finally, we examined **S4** in which both the *ortho*-sites are contain ^{19}F atoms. As expected, no radiofluorination was detected. This indicates that isotopic exchange does not occur once an initial C–F bond is formed at these sites.

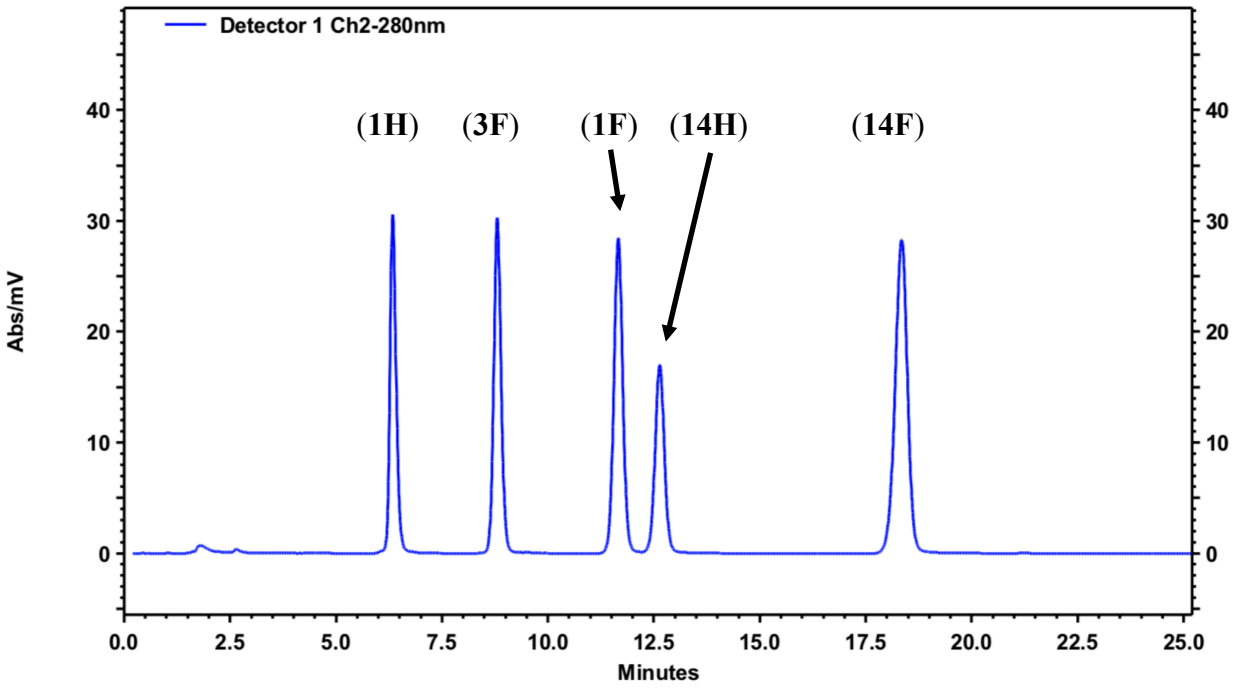
4.3.7 HPLC analysis of potential regioisomers

To further confirm that we were achieving the radiofluorination at the expected *ortho*-site rather than fluorination on the quinoline ring, we synthesized a series of possible isomeric products and demonstrated that they exhibit baseline separation by HPLC. This further confirms that the desired product **1F** is being formed.

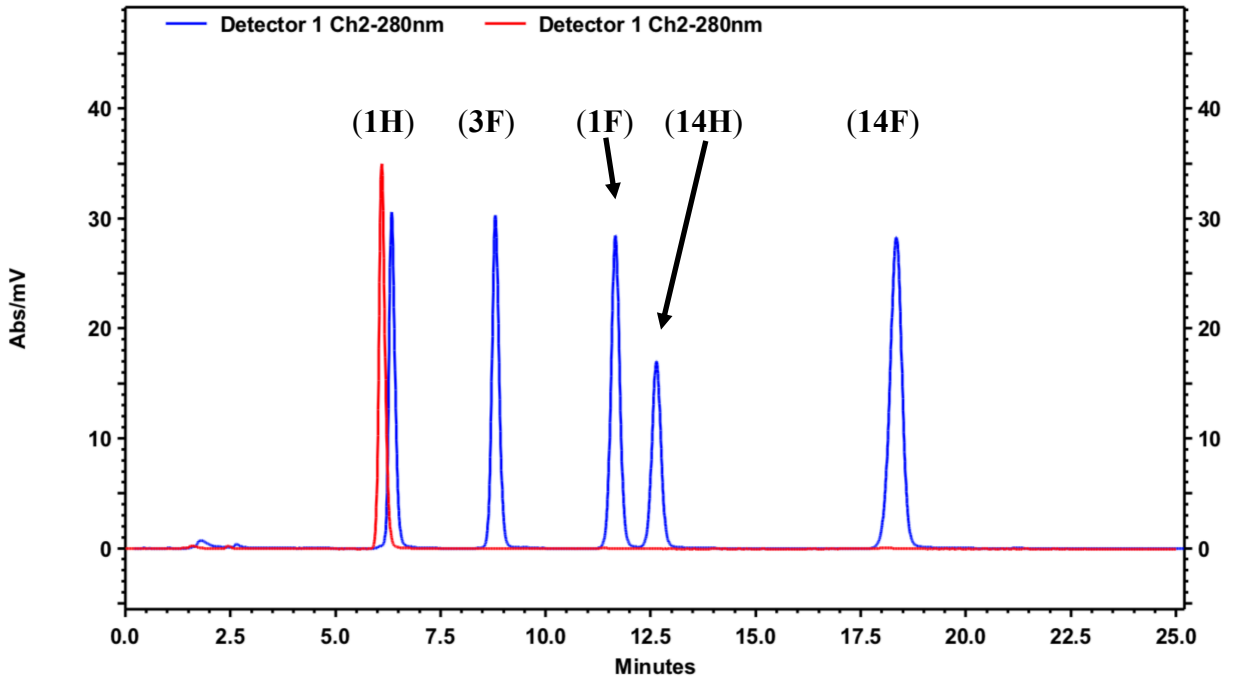
Isomers:
4-Methyl-*N*-(quinolin-8-yl)benzamide (**1H**)
2-Fluoro-4-methyl-*N*-(quinolin-8- yl)benzamide (**1F**)
2,6-Difluoro-4-methyl-*N*-(quinolin-8-yl)benzamide (**3F**)
N-(5-Fluoroquinolin-8-yl)-4-methylbenzamide (**14H**)
2-Fluoro-*N*-(5-fluoroquinolin-8-yl)-4-methylbenzamide (**14F**)



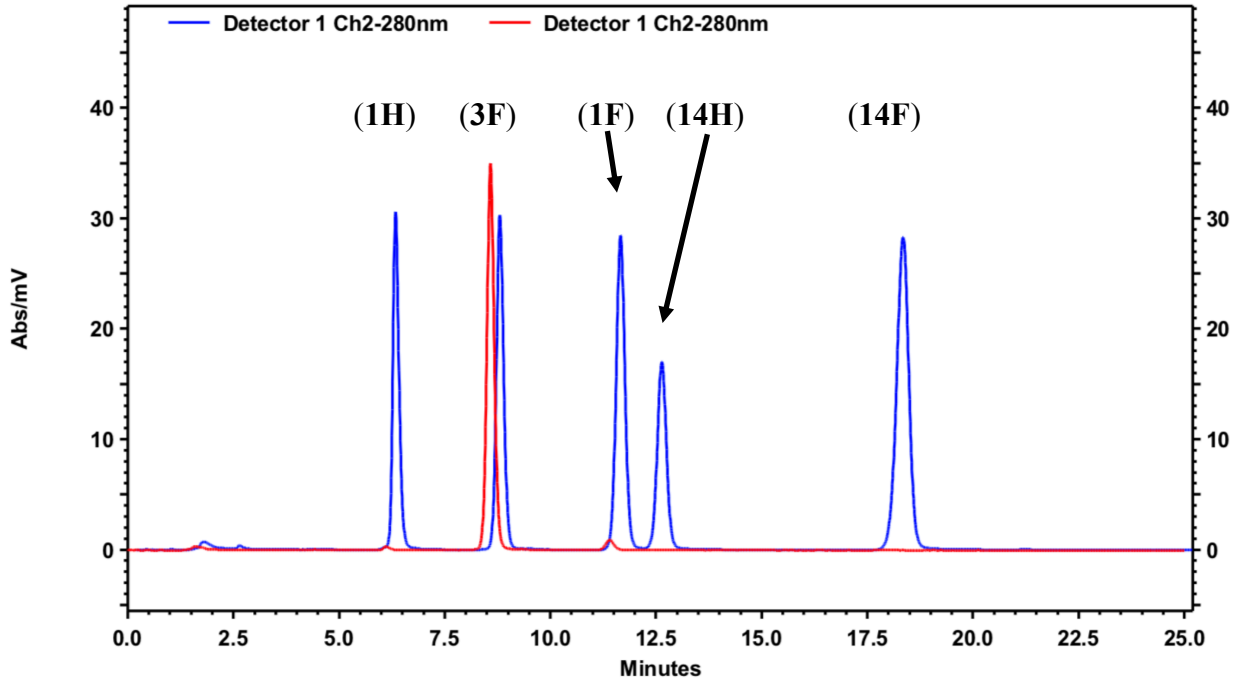
i. HPLC separation of co-injection of the five regiosomers, **1H, 1F, 3F, 14H,** and **14F**
HPLC Conditions A was used to separate the five regioisomers (blue line)



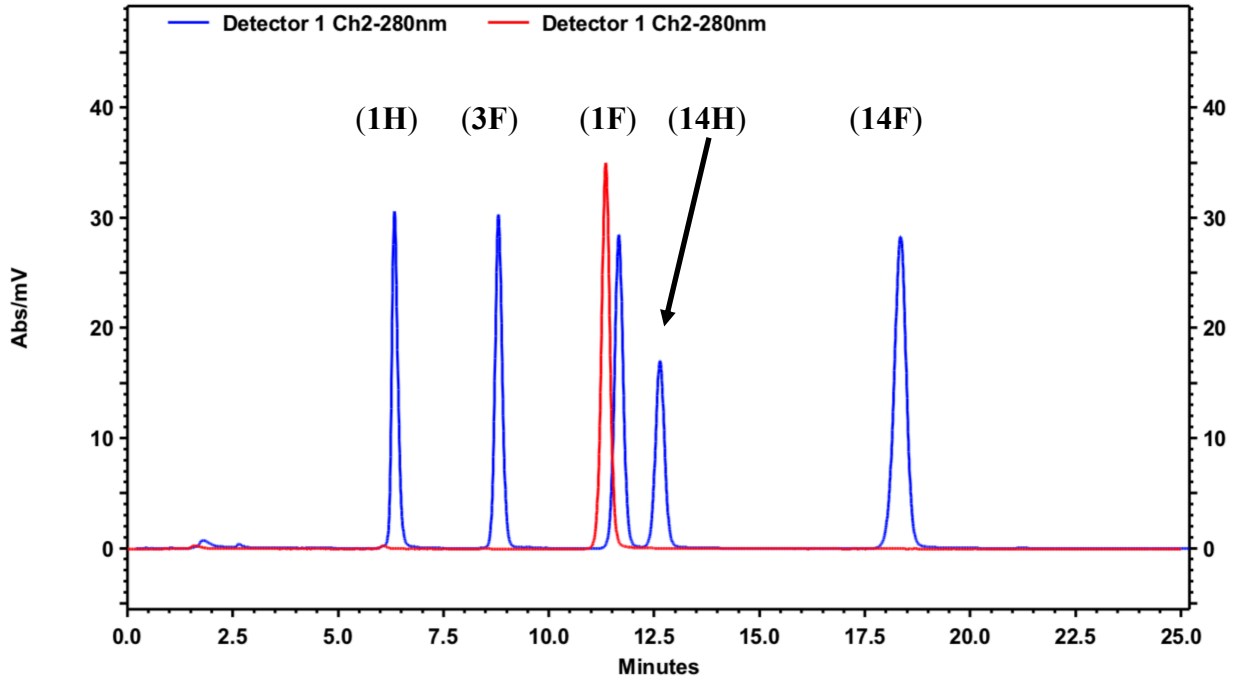
ii. Overlaid HPLC profile of separate single injection of **1H**



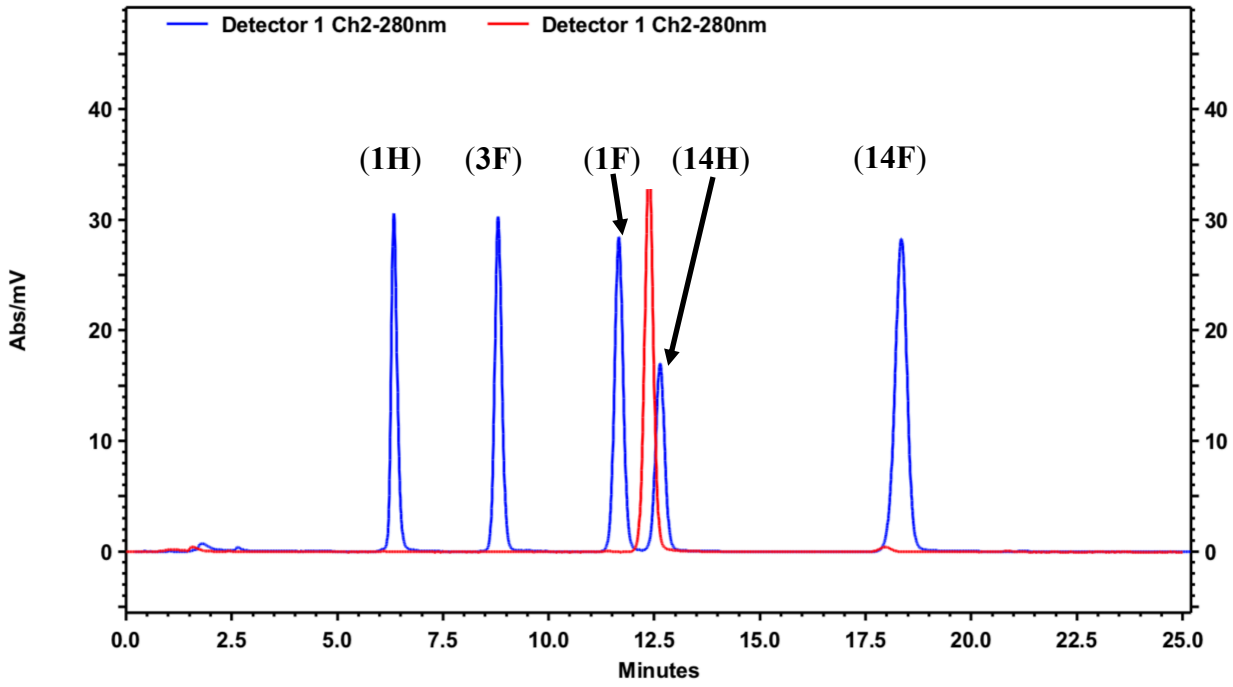
iii. Overlaid HPLC profile of separate single injection of **3F**



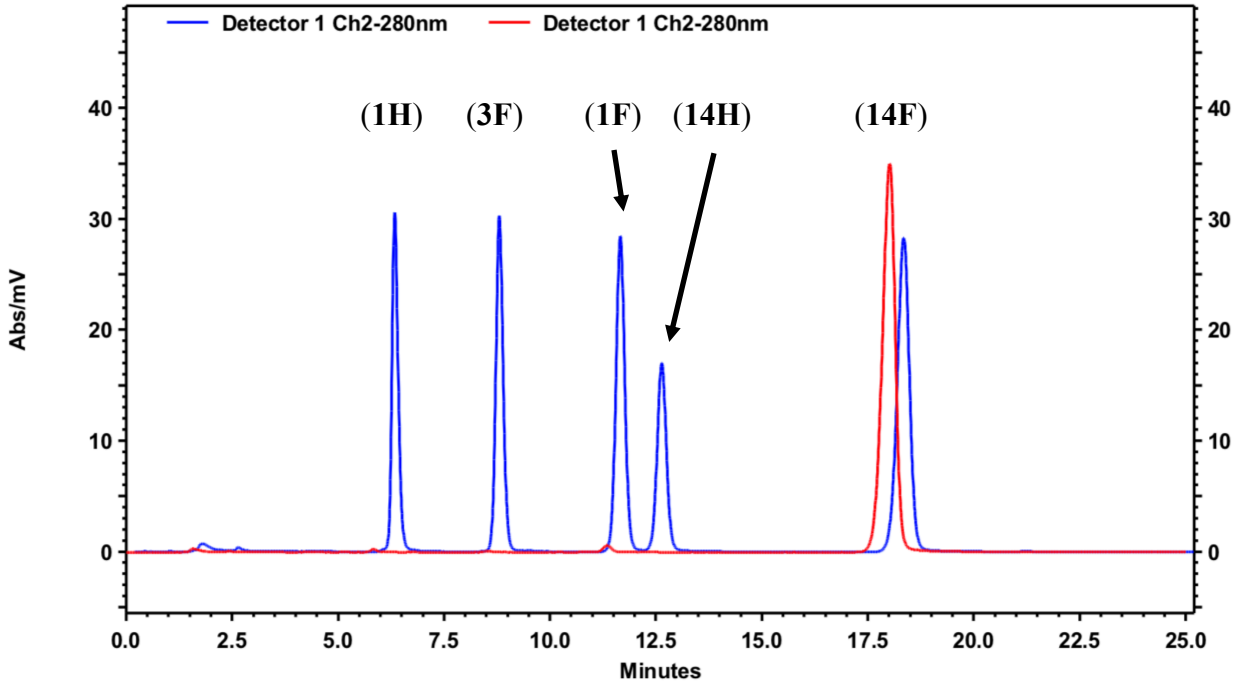
iv. Overlaid HPLC profile of separate single injection of **1F**



v. Overlaid HPLC profile of separate single injection of **14H**



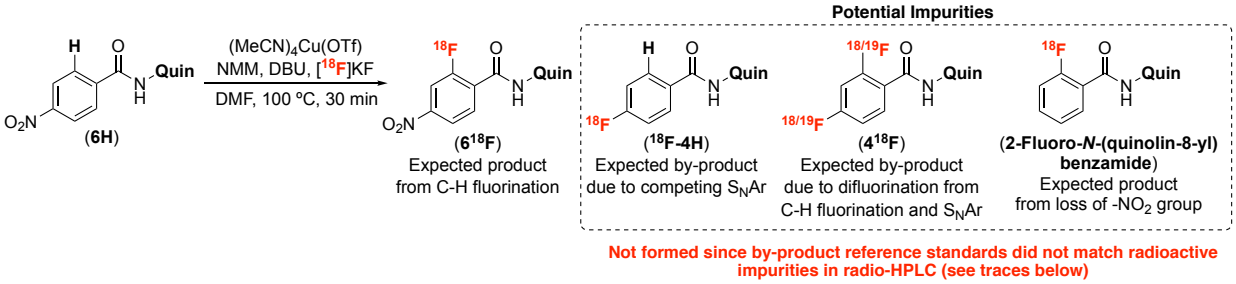
vi. Overlaid HPLC profile of separate single injection of **14F**



4.3.8 Investigation of potential side products

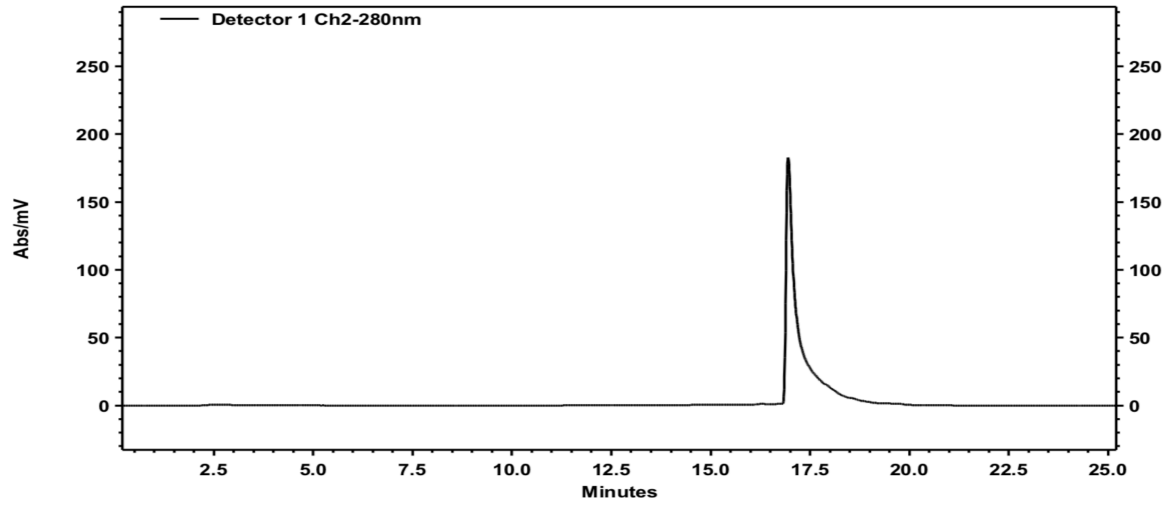
Arenes bearing electron-withdrawing substituents appeared to give rise to additional radioactive side products in some instances (e.g. **6H**, **7H** and **10H**). We attempted to identify these side products using radio-HPLC by co-injecting the crude reaction mixture with reference standards for side products that would result from potential side reactions such as competing S_NAr. However, none of the potential side products corresponded to the radioactive impurities (see below), and we have been unable to confirm the identity of any side products formed in the reaction to date.

Side-products associated with radiofluorination of 6H

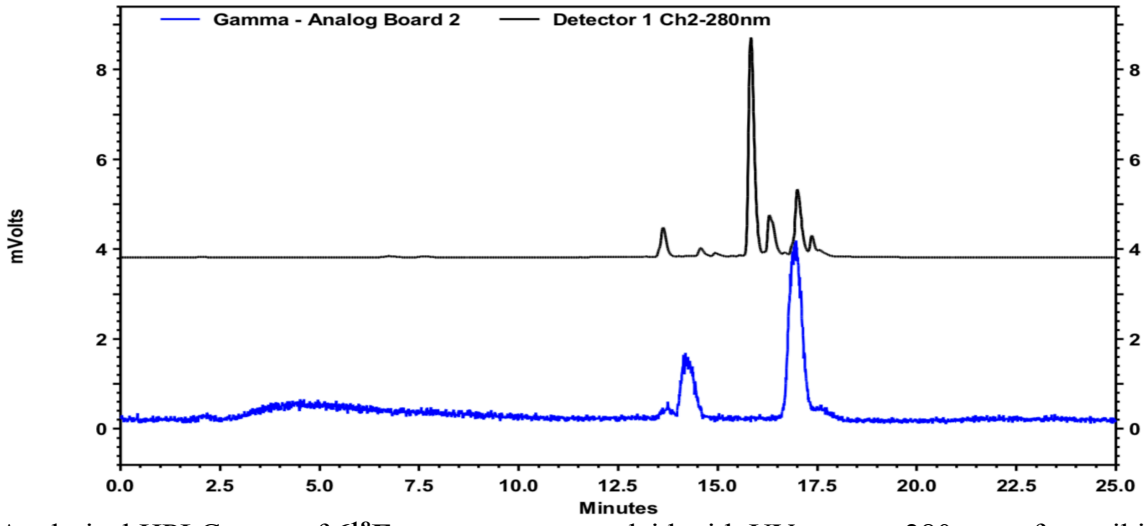


HPLC conditions: Condition B

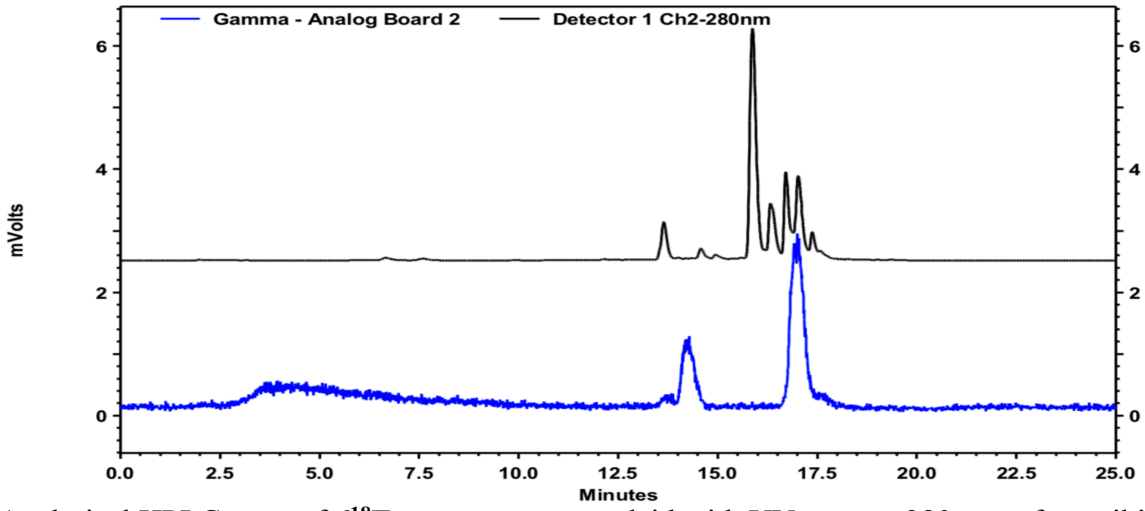
Analytical HPLC trace of **6F** standard (UV trace at 280 nm)



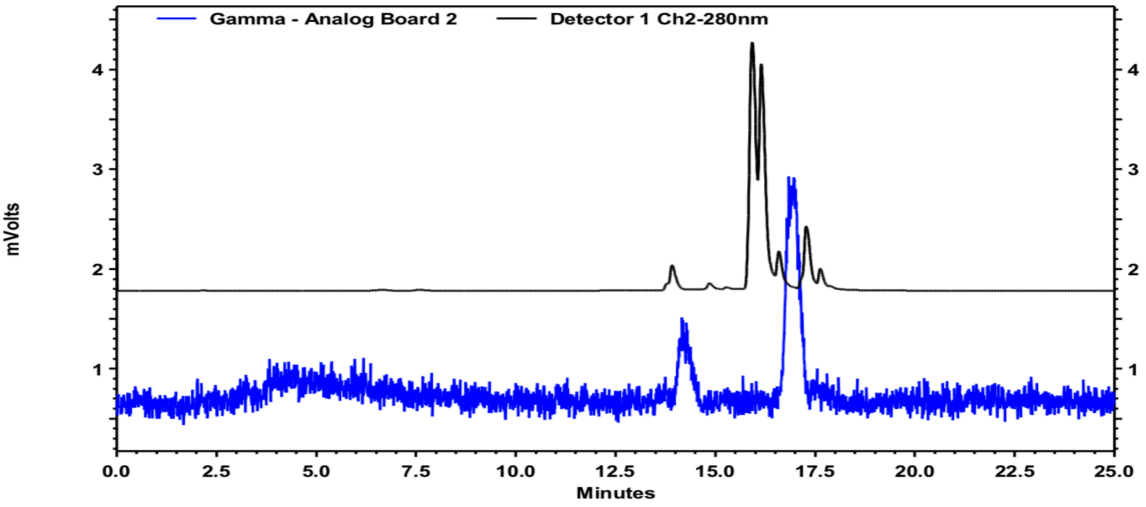
Analytical HPLC trace of **6**^{18}**F** gamma trace overlaid with UV trace at 280 nm



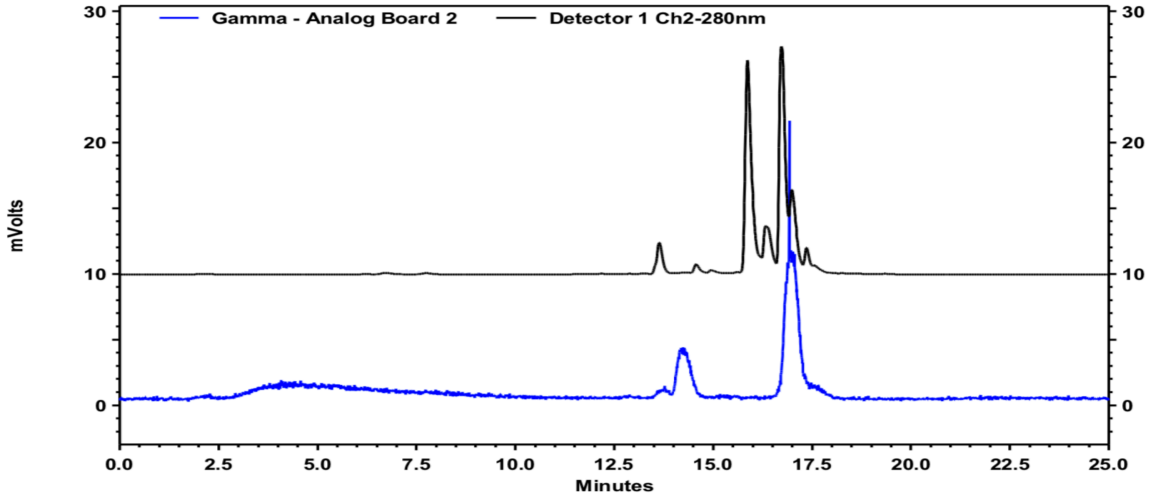
Analytical HPLC trace of **6**^{18}**F** gamma trace overlaid with UV trace at 280 nm, after spiking with **6F**



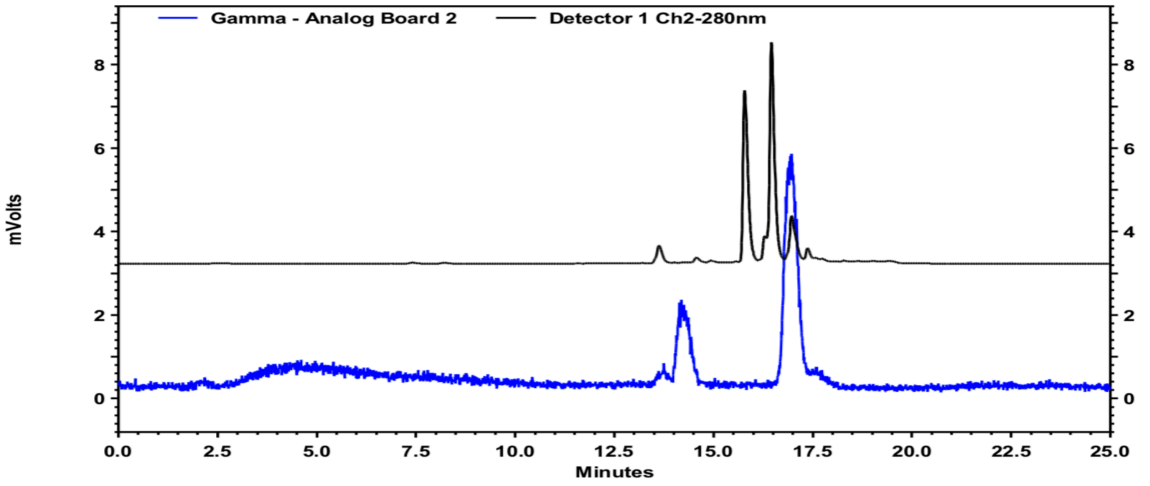
Analytical HPLC trace of **6**^{18}**F** gamma trace overlaid with UV trace at 280 nm, after spiking with **4H**



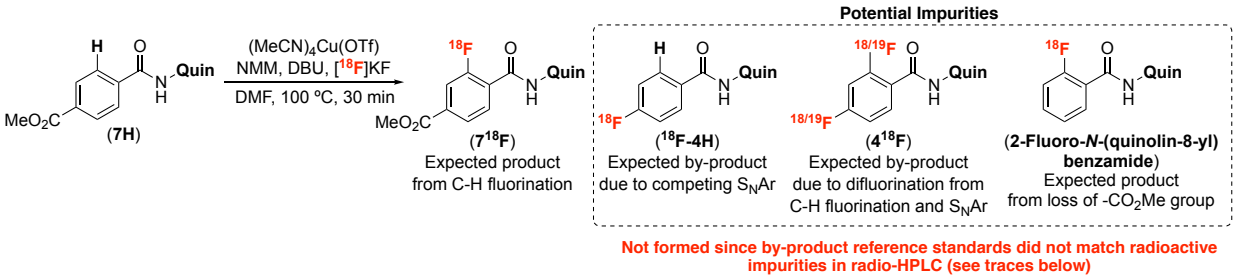
Analytical HPLC trace of **6^{18}F** gamma trace overlaid with UV trace at 280 nm, after spiking with **4F**



Analytical HPLC trace of **6^{18}F** gamma trace overlaid with UV trace at 280 nm, after spiking with 2-fluoro-*N*-(quinolin-8-yl)benzamide

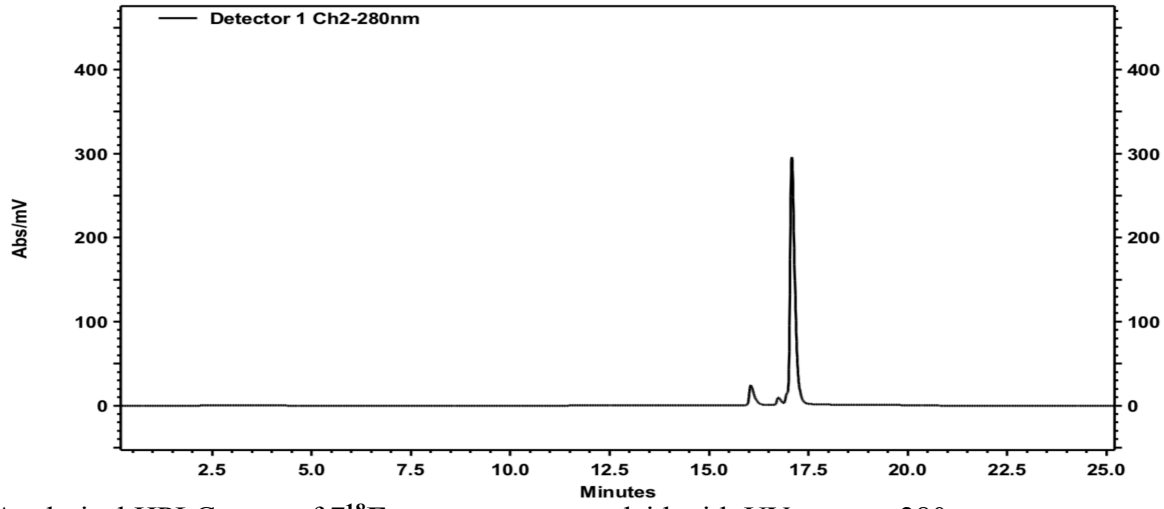


Side-products associated with radiofluorination of 7H

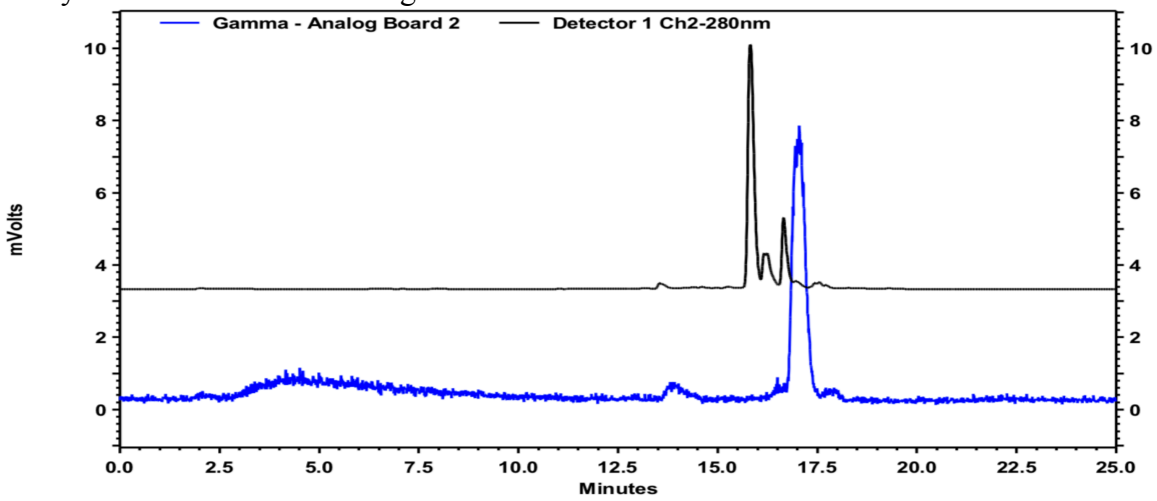


HPLC conditions: Condition B

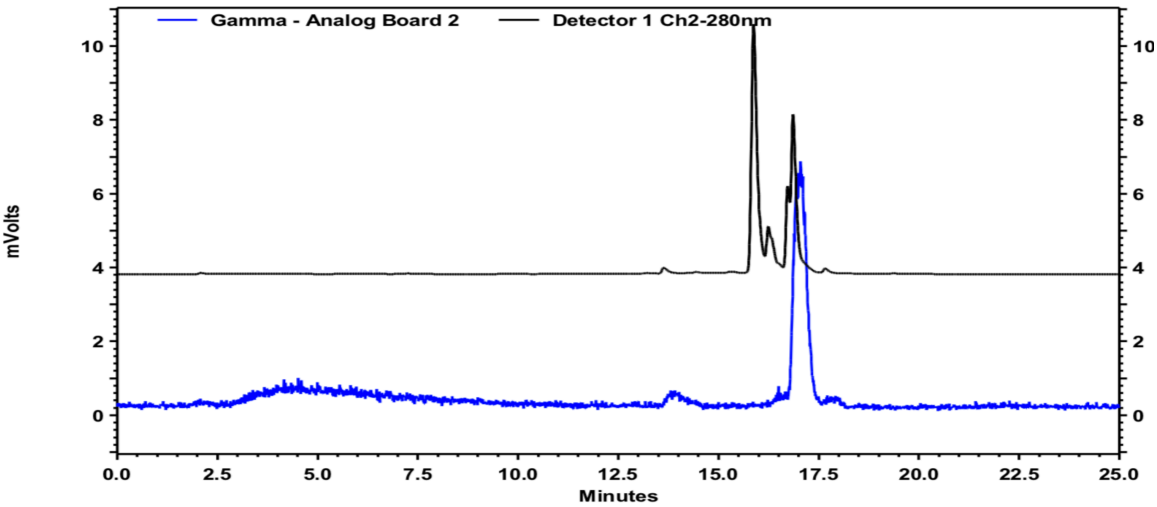
Analytical HPLC trace of **7F** standard (UV trace at 280 nm)



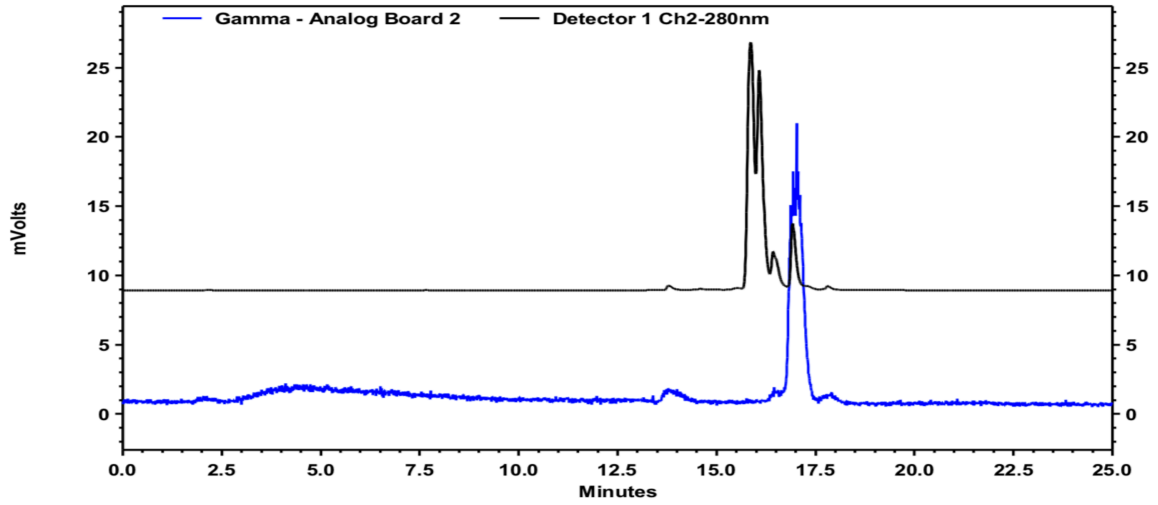
Analytical HPLC trace of **7^{18}F** gamma trace overlaid with UV trace at 280 nm



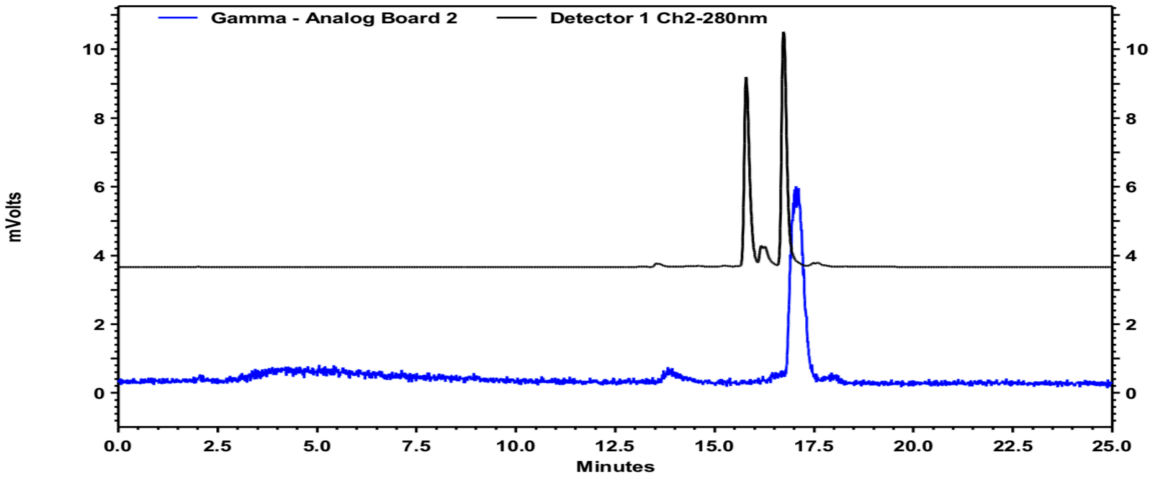
Analytical HPLC trace of **7^{18}F** gamma trace overlaid with UV trace at 280 nm, after spiking with **7F**



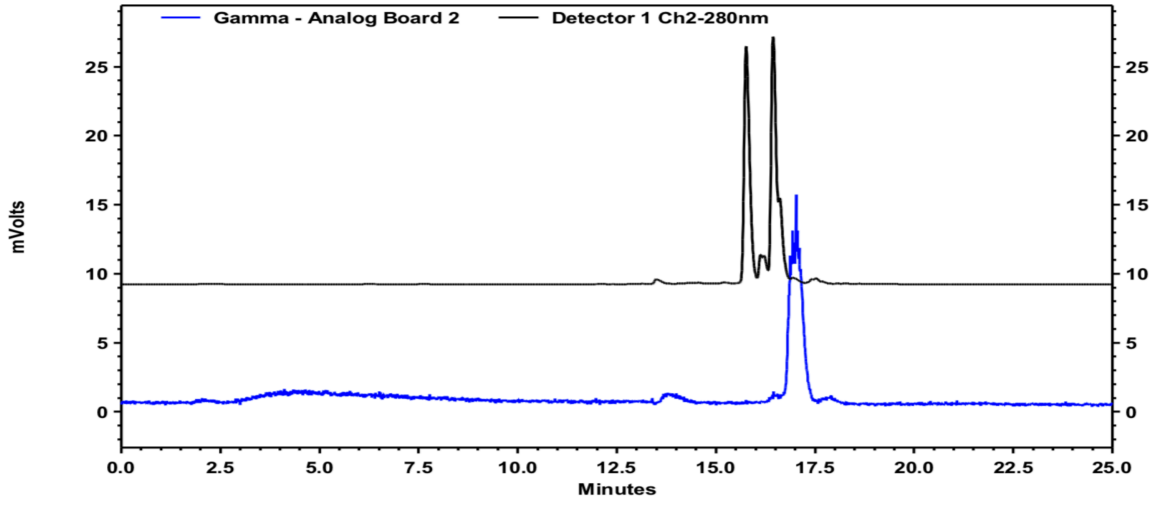
Analytical HPLC trace of **7**^{18}**F** gamma trace overlaid with UV trace at 280 nm, after spiking with **4H**



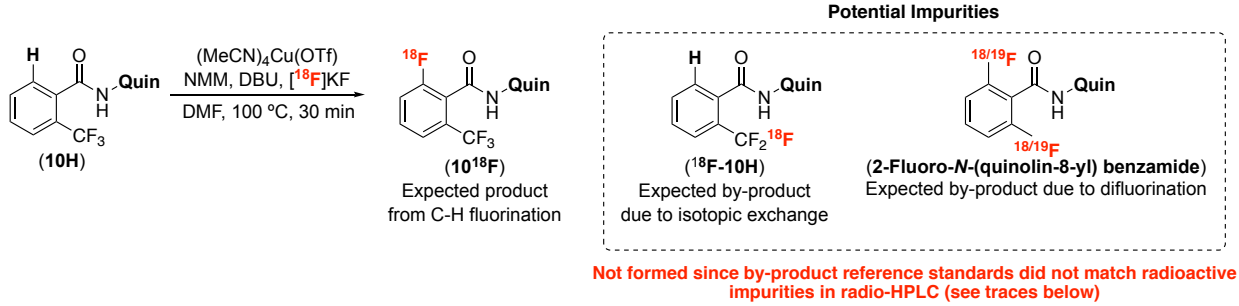
Analytical HPLC trace of **7**^{18}**F** gamma trace overlaid with UV trace at 280 nm, after spiking with **4F**



Analytical HPLC trace of **7**^{18}**F** gamma trace overlaid with UV trace at 280 nm, after spiking with 2-fluoro-*N*-(quinolin-8-yl)benzamide

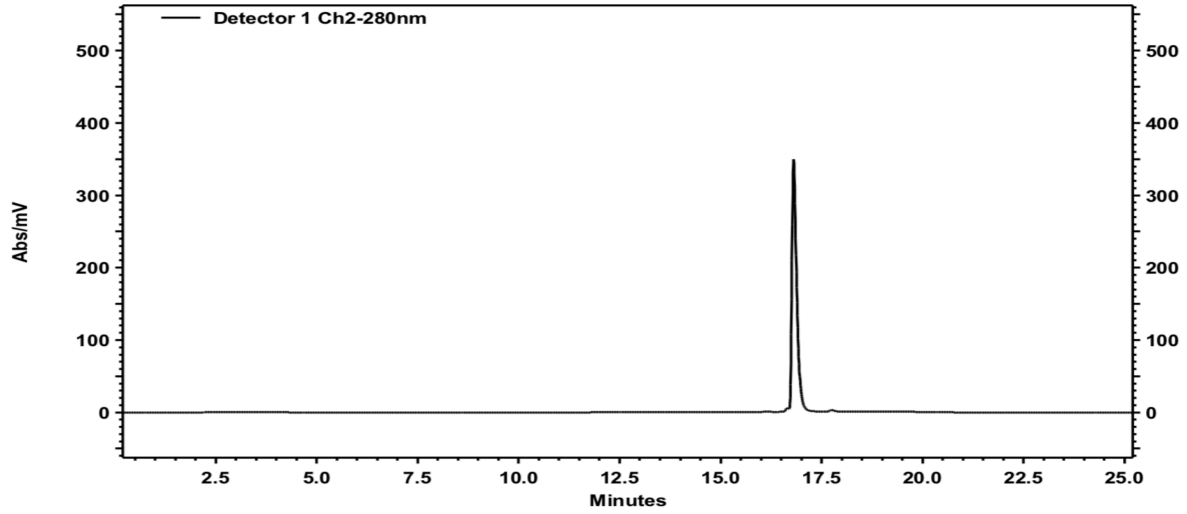


Side-products associated with radiofluorination of 10H

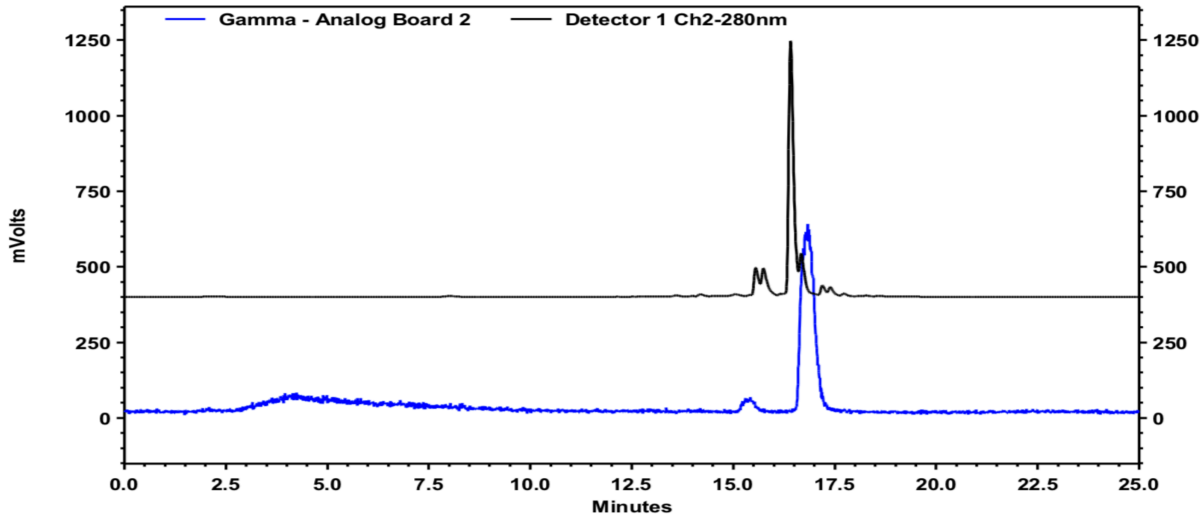


Not formed since by-product reference standards did not match radioactive impurities in radio-HPLC (see traces below)

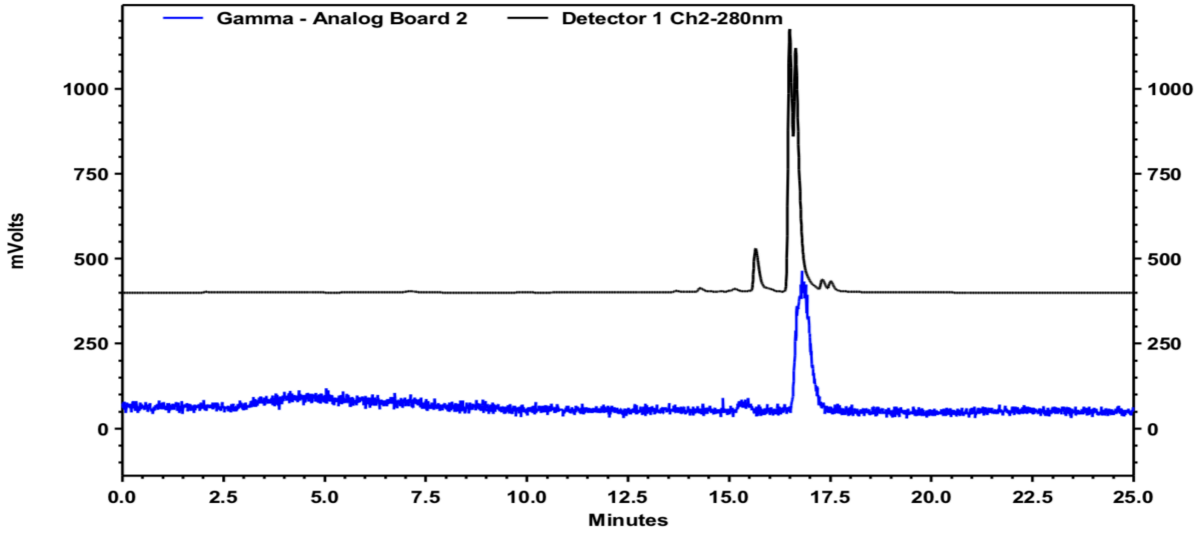
Analytical HPLC trace of **10F** standard (UV trace at 280 nm)



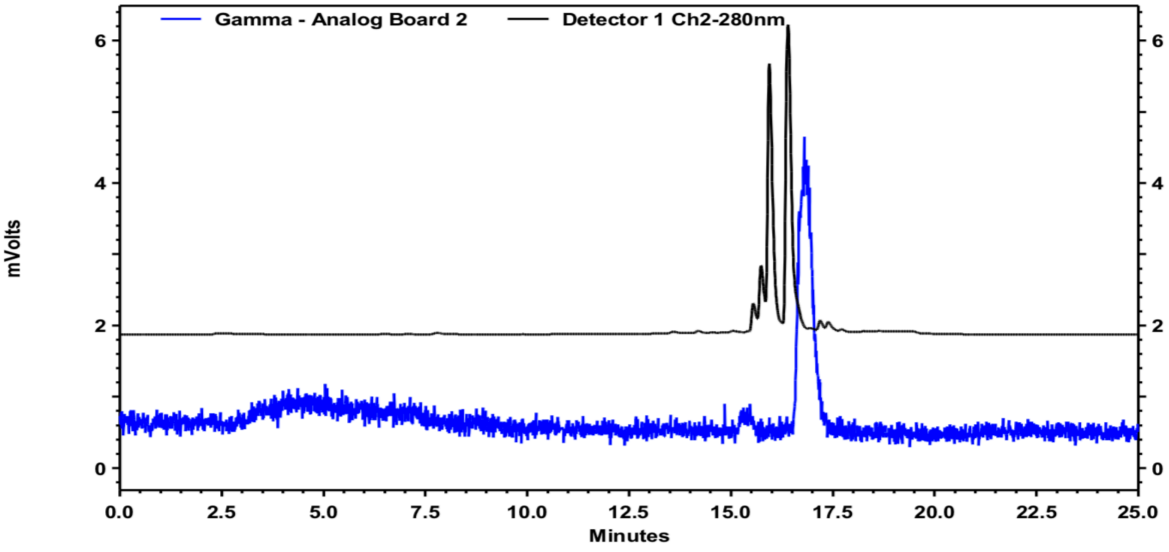
Analytical HPLC trace of **10^{18}F** gamma trace overlaid with UV trace at 280 nm



Analytical HPLC trace of **10**^{18}**F** gamma trace overlaid with UV trace at 280 nm, after spiking with **10F** (2nd UV peak corresponds to unreacted **10H** in reaction mixture)



Analytical HPLC trace of **10**^{18}**F** gamma trace overlaid with UV trace at 280 nm, after spiking with 2,6-difluoro-*N*-(quinolin-8-yl)benzamide



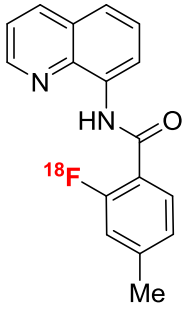
5. References:

(1) Truong, T.; Klimovica, K.; Daugulis, O. *J. Am. Chem. Soc.* **2013**, *135*, 9342–9345.
(2) Gou, F.-R.; Wang, X.-C.; Huo, P.-F.; Bi, H.-P.; Guan, Z.-H.; Liang, Y.-M. *Org. Lett.* **2009**, *11*, 5726–5729.
(3) Tran, L. D.; Popov, I.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 18237–18240.
(4) Ano, Y.; Tobisu, M.; Chatani, N. *Org. Lett.* **2012**, *14*, 354–357.
(5) Grigorjeva, L.; Daugulis, O. Org. Lett. **2014**, *16*, 4688-4690.
(6) Rouquet, G.; Chatani, N. *Chem. Sci.* **2013**, *4*, 2201–2208.
(7) Katayev, D.; Pfister, K. F.; Wendling, T.; Gooßen, L. J. *Chem. – Eur. J.* **2014**, *20*, 9902–9905.
(8) Ding, J.; Zhang, Y.; Li, J. *Org. Chem. Front.* **2017**, *4*, 1528–1532.
(9) Wang, Y.; Yu, F.; Han, X.; Li, M.; Tong, Y.; Ding, J.; Hou, H. *Inorg. Chem.* **2017**, *56*, 5953–5958.
(10) Al-Awadi, H.; Ibrahim, M. R.; Dib, H. H.; Al-Awadi, N. A.; Ibrahim, Y. A. *Tetrahedron* **2005**, *61*, 10507–10513.
(11) Arockiam, P. B.; Guillemard, L.; Wencel-Delord, J. Regiodivergent *Adv. Synth. Catal.* **2017**, *359*, 2571–2579.
(12) Zhong, F.; Geng, G.; Chen, B.; Pan, T.; Li, Q.; Zhang, H.; Bai, C. *Org. Biomol. Chem.* **2015**, *13*, 1792–1799.
(13) Shibata, K.; Chatani, N. *Org. Lett.* **2014**, *16*, 5148–5151.
(14) Chen, H.; Li, P.; Wang, M.; Wang, L. *Eur. J. Org. Chem.* **2018**, *2018*, 2091–2097.
(15) Wang, Y.; Yu, F.; Han, X.; Li, M.; Tong, Y.; Ding, J.; Hou, H. *Inorg. Chem.* **2017**, *56*, 5953–5958.
(16) Ding, J.; Zhang, Y.; Li, J. *Org. Chem. Front.* **2017**, *4*, 1528–1532.
(17) McCann, S. D.; Stahl, S. S. *Acc. Chem. Res.* **2015**, *48*, 1756–1766.
(18) Luo, S.; Su, L.; Jiang, Y.; Li, X.; Li, Z.; Sun, H.; Liu, J. *Synlett* **2018**, *29*, 1525–1529.
(19) Dou, Y.; Xie, Z.; Sun, Z.; Fang, H.; Shen, C.; Zhang, P.; Zhu, Q. *ChemCatChem* **2016**, *8*, 3570–3574.

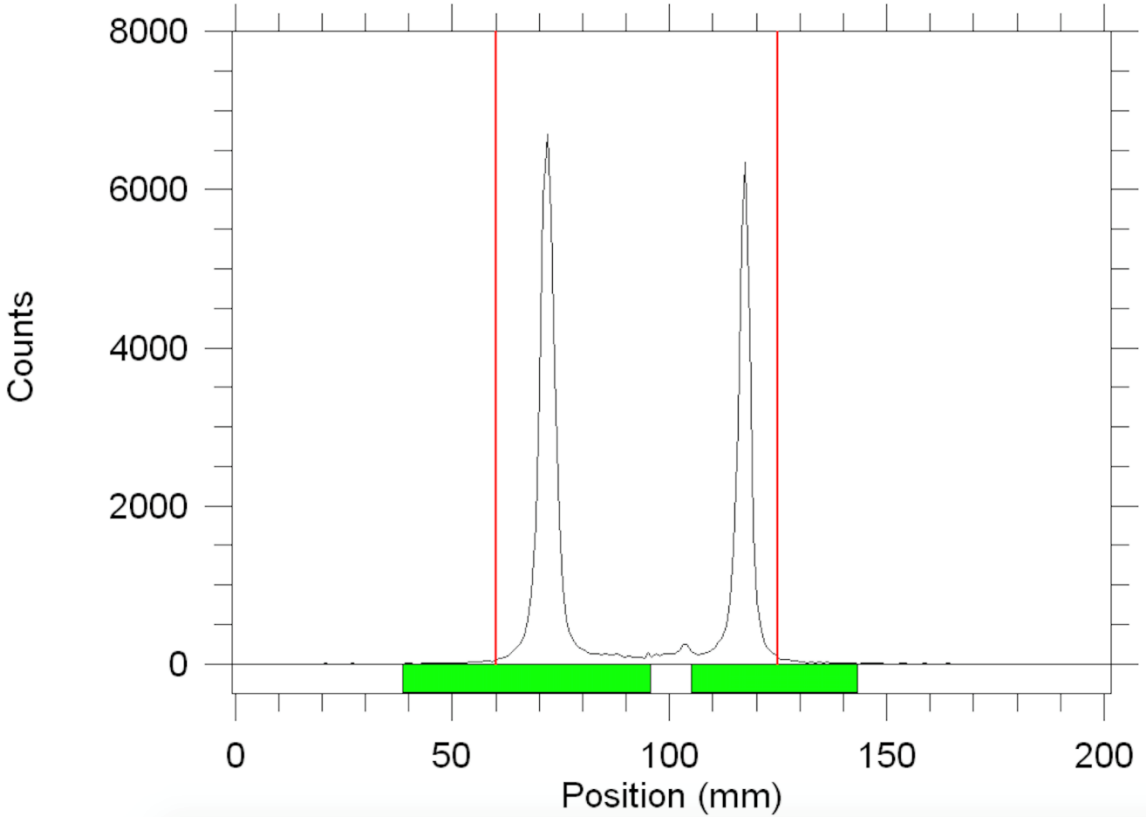
6. Radio-TLC/radio-HPLC analysis of $1^{18}F$ - $20^{18}F$

6.1 Manual syntheses of $1^{18}F$ - $18^{18}F$

2-(Fluoro-^{18}F)-4-methyl-*N*-(quinolin-8-yl)benzamide ($1^{18}F$)



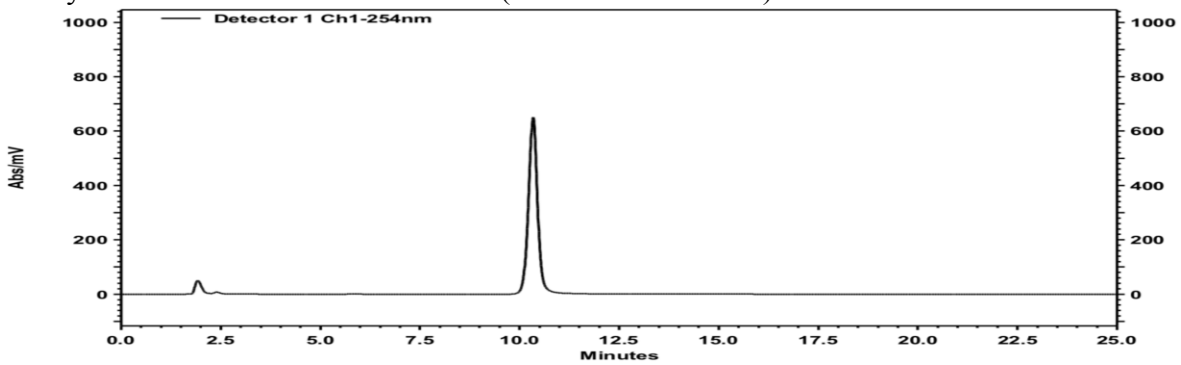
Radio-TLC conditions: Ethyl acetate/hexane = 1/1



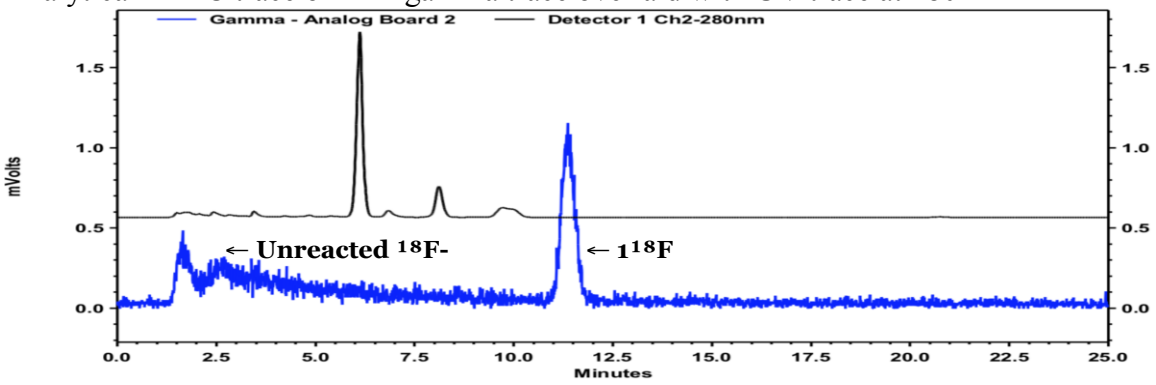
Replicate	Raw RCC (%)
1	52
2	49
3	48
4	51
5	54
Mean	50
Standard deviation	2

HPLC conditions: Condition A

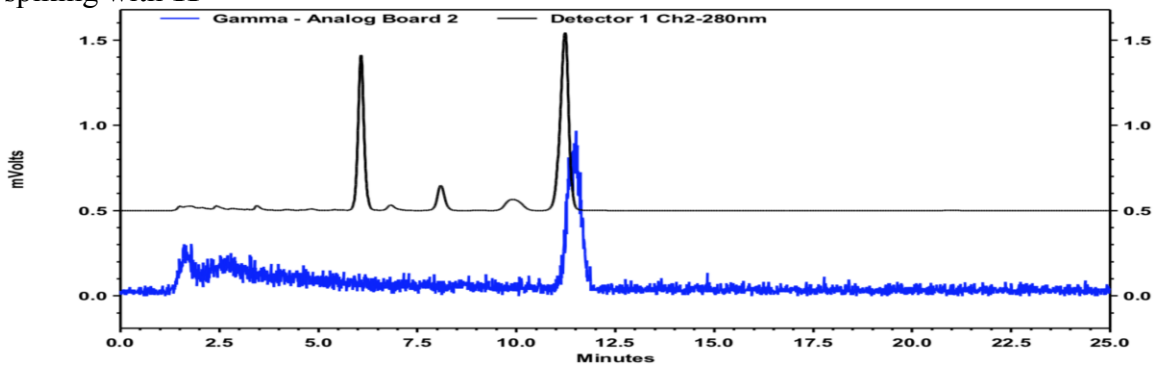
Analytical HPLC trace of **1F** standard (UV trace at 280 nm)



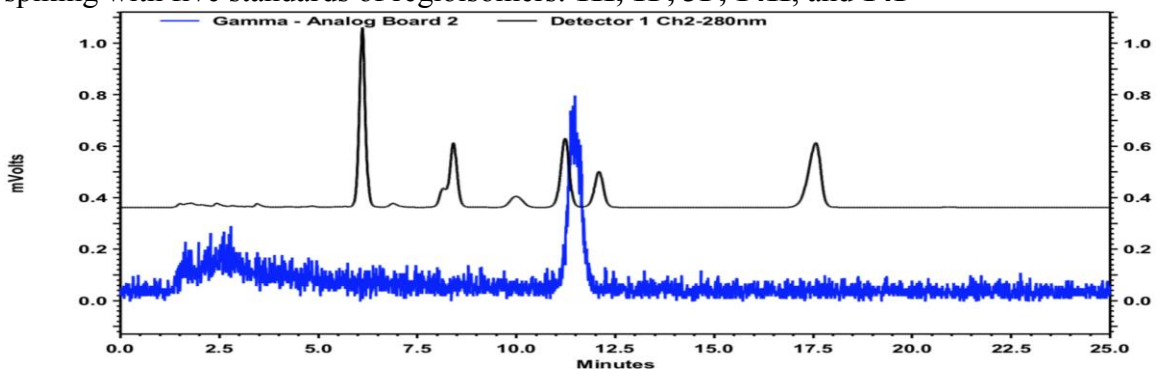
Analytical HPLC trace of **1^{18}F** gamma trace overlaid with UV trace at 280 nm



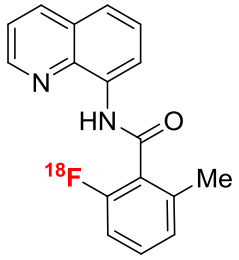
Analytical HPLC trace of **1^{18}F** gamma trace overlaid with UV trace at 280 nm, after spiking with **1F**



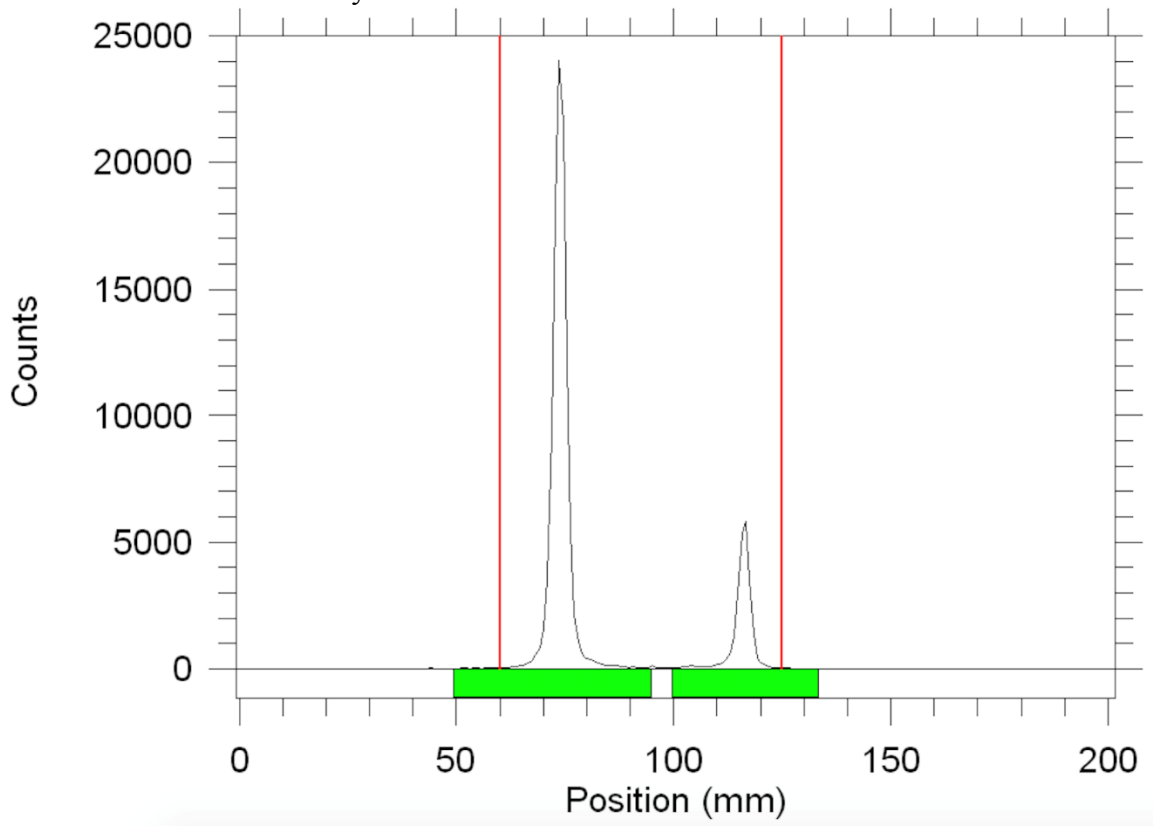
Analytical HPLC trace of **1^{18}F** gamma trace overlaid with UV trace at 280 nm, after spiking with five standards of regioisomers: **1H, 1F, 3F, 14H**, and **14F**



2-(Fluoro-^{18}F)-6-methyl-*N*-(quinolin-8-yl)benzamide ($2^{18}F$)



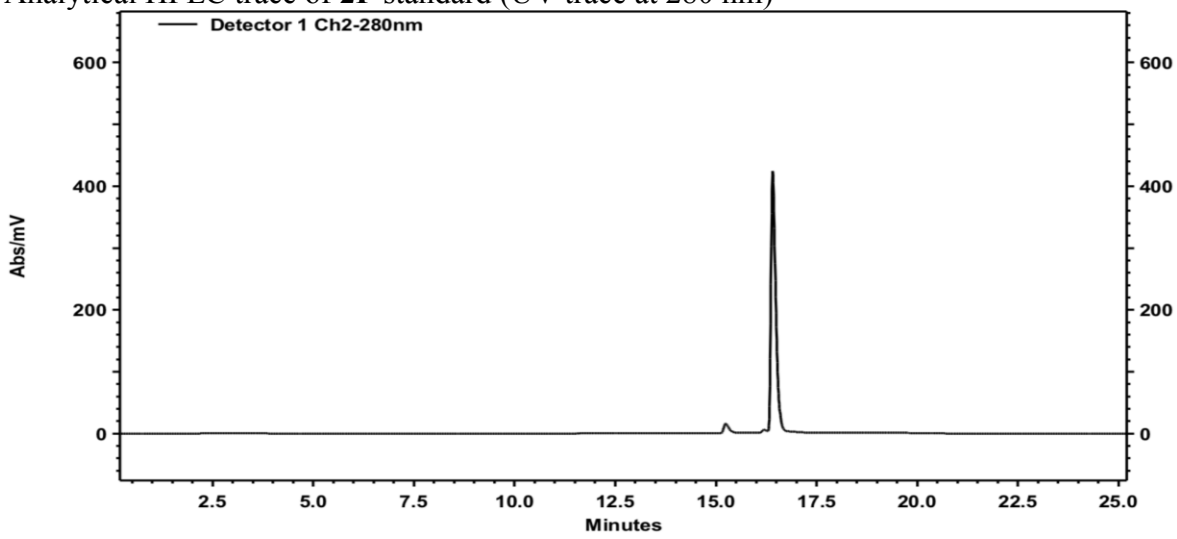
Radio-TLC conditions: Ethyl acetate/hexane = 1/1



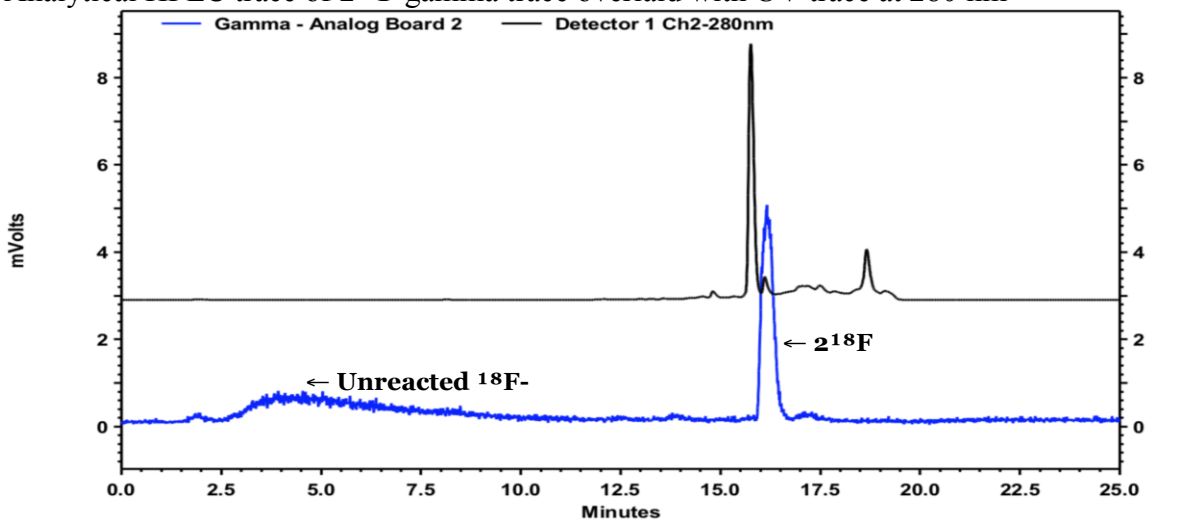
Replicate	Raw RCC (%)
1	19
2	18
3	16
4	16
5	14
Mean	16
Standard deviation	2

HPLC conditions: Condition B

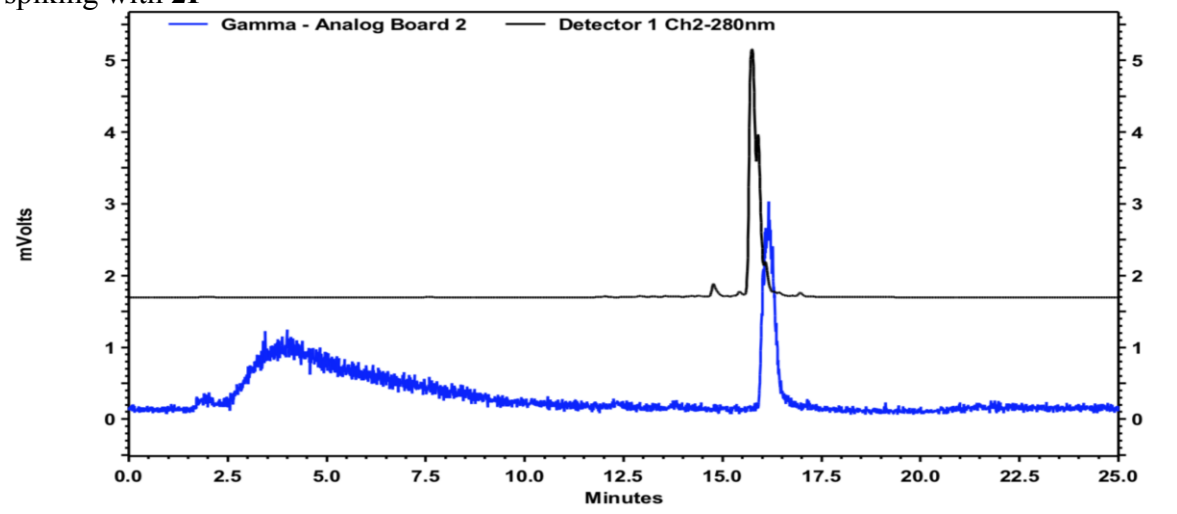
Analytical HPLC trace of **2F** standard (UV trace at 280 nm)



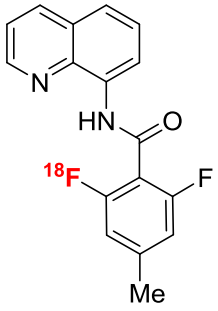
Analytical HPLC trace of **2^{18}F** gamma trace overlaid with UV trace at 280 nm



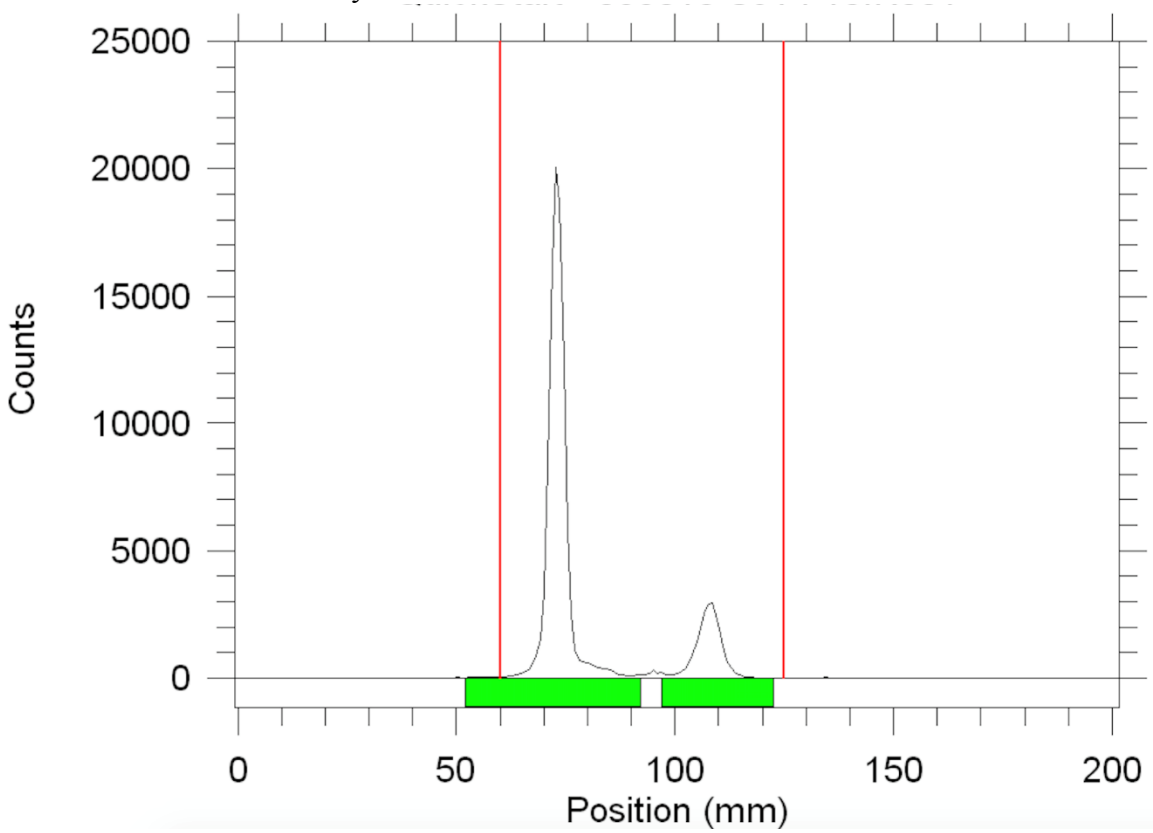
Analytical HPLC trace of **2^{18}F** gamma trace overlaid with UV trace at 280 nm, after spiking with **2F**



2-Fluoro-6-(fluoro-^{18}F)-4-methyl-*N*-(quinolin-8-yl)benzamide ($3^{18}F$)



Radio-TLC conditions: Ethyl acetate/hexane = 1/1

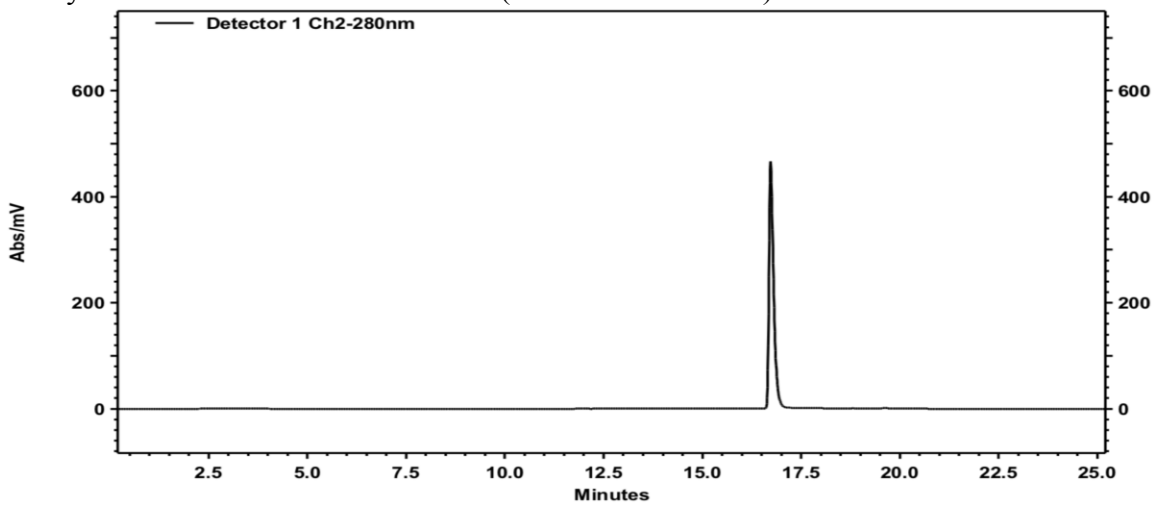


Replicate	Raw RCC (%)	Corrected RCC[a] (%)
1	19	16
2	17	14
3	17	14
4	18	15
5	18	15
Mean	18	15
Standard deviation	1	1

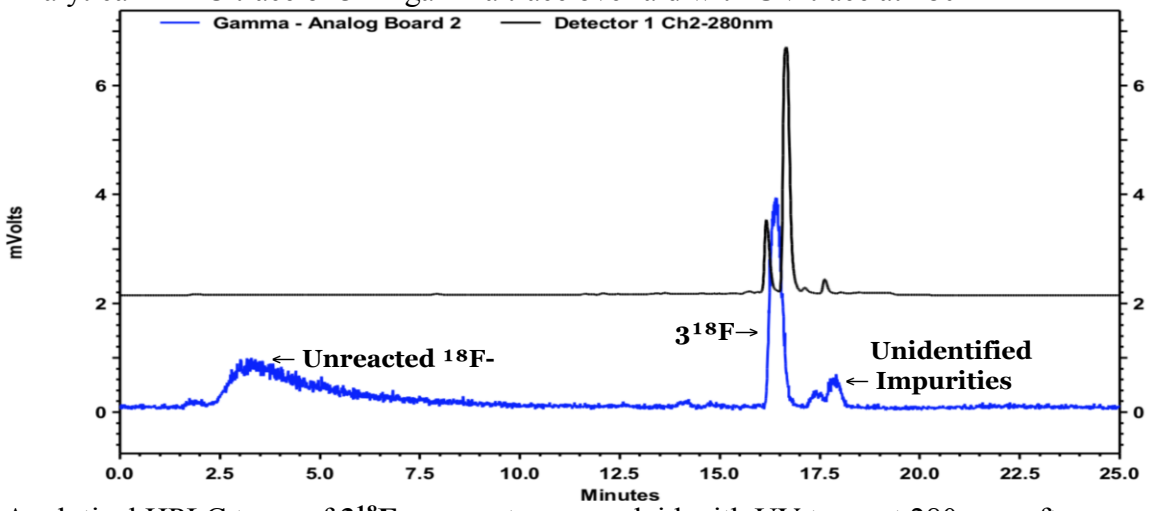
[a]Corrected RCC based on radio-analytical HPLC. The detailed procedure for corrected RCC is described in SI section 4.2.1 Manual synthesis general procedure.

HPLC conditions: Condition B

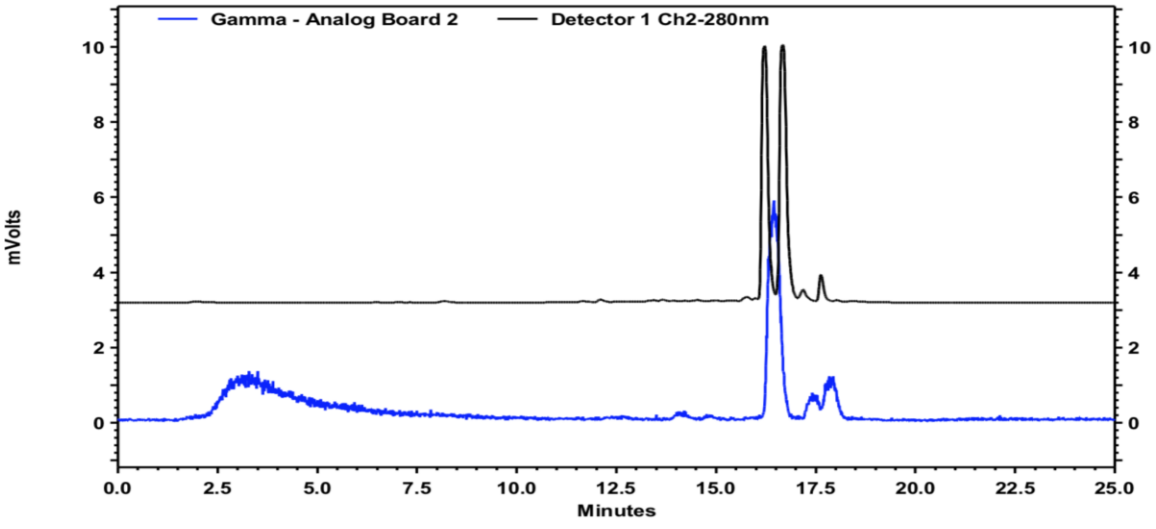
Analytical HPLC trace of **3F** standard (UV trace at 280 nm)



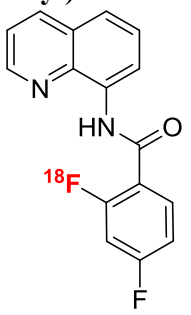
Analytical HPLC trace of **3^{18}F** gamma trace overlaid with UV trace at 280 nm



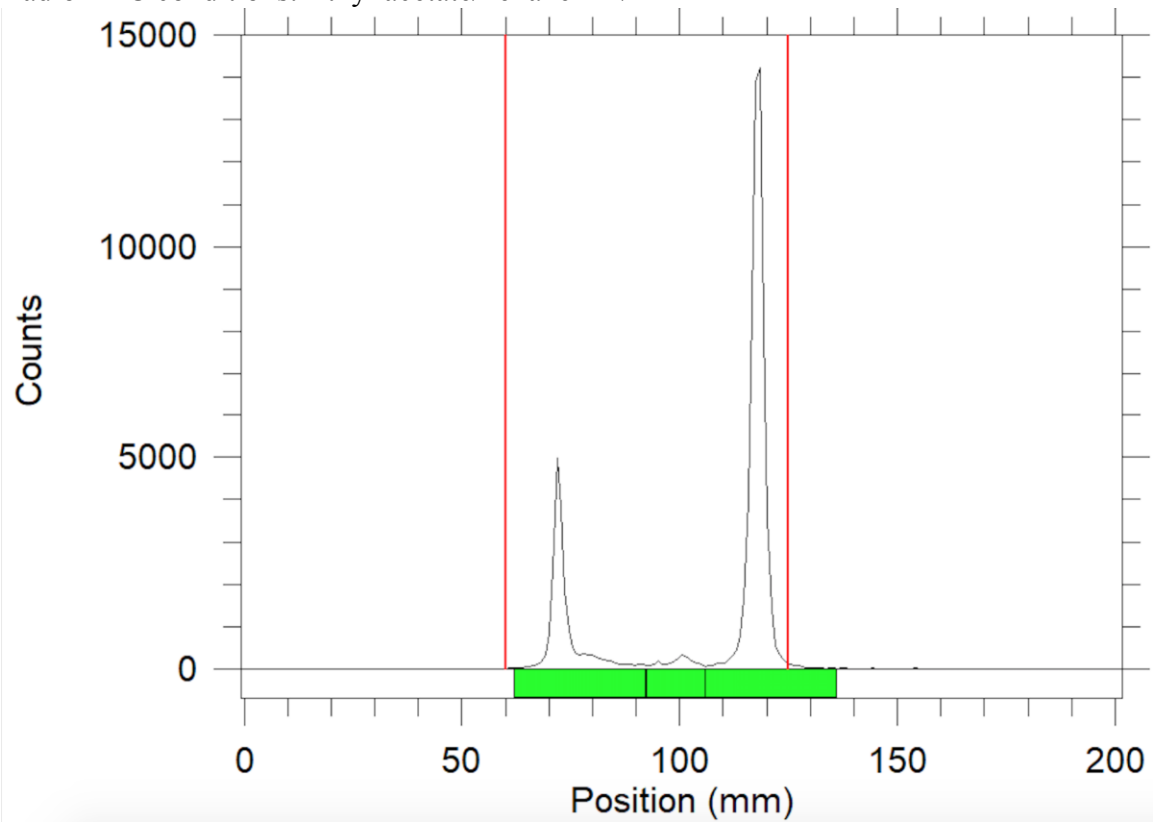
Analytical HPLC trace of **3^{18}F** gamma trace overlaid with UV trace at 280 nm, after spiking with **3F**



2-(Fluoro-^{18}F)-4-fluoro-*N*-(quinolin-8-yl)benzamide (4^{18}F)



Radio-TLC conditions: Ethyl acetate/hexane = 1/1

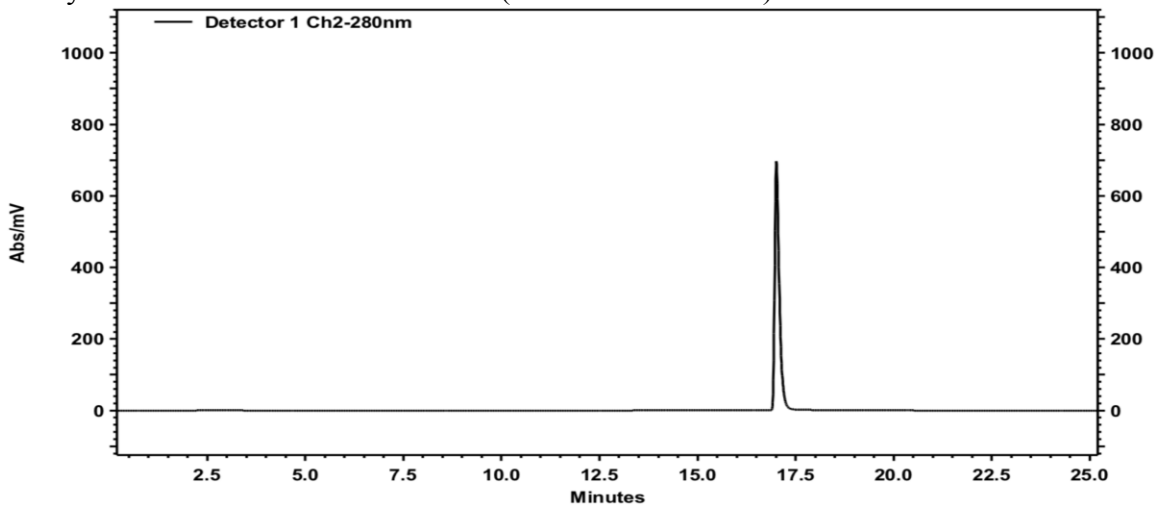


Replicate	Raw RCC (%)	Corrected RCC[a] (%)
1	72	62
2	72	62
3	72	62
4	71	61
5	73	62
Mean	72	62
Standard deviation	1	0

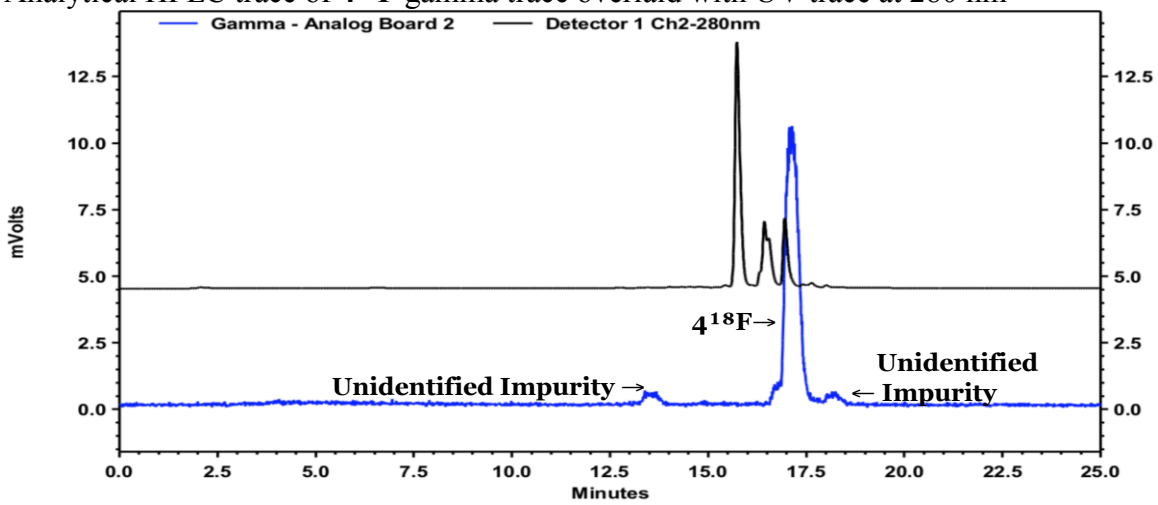
[a]Corrected RCC based on radio-analytical HPLC. The detailed procedure for corrected RCC is described in SI section 4.2.1 Manual synthesis general procedure.

HPLC conditions: Condition B

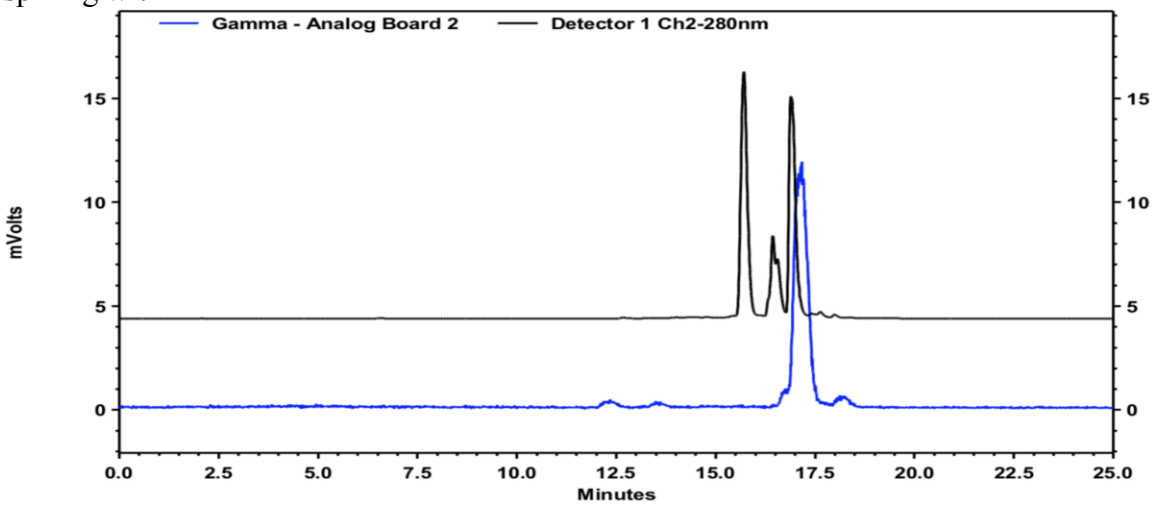
Analytical HPLC trace of **4F** standard (UV trace at 280 nm)



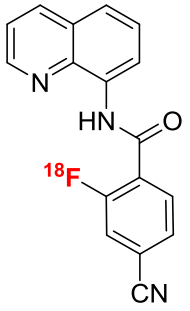
Analytical HPLC trace of **4^{18}F** gamma trace overlaid with UV trace at 280 nm



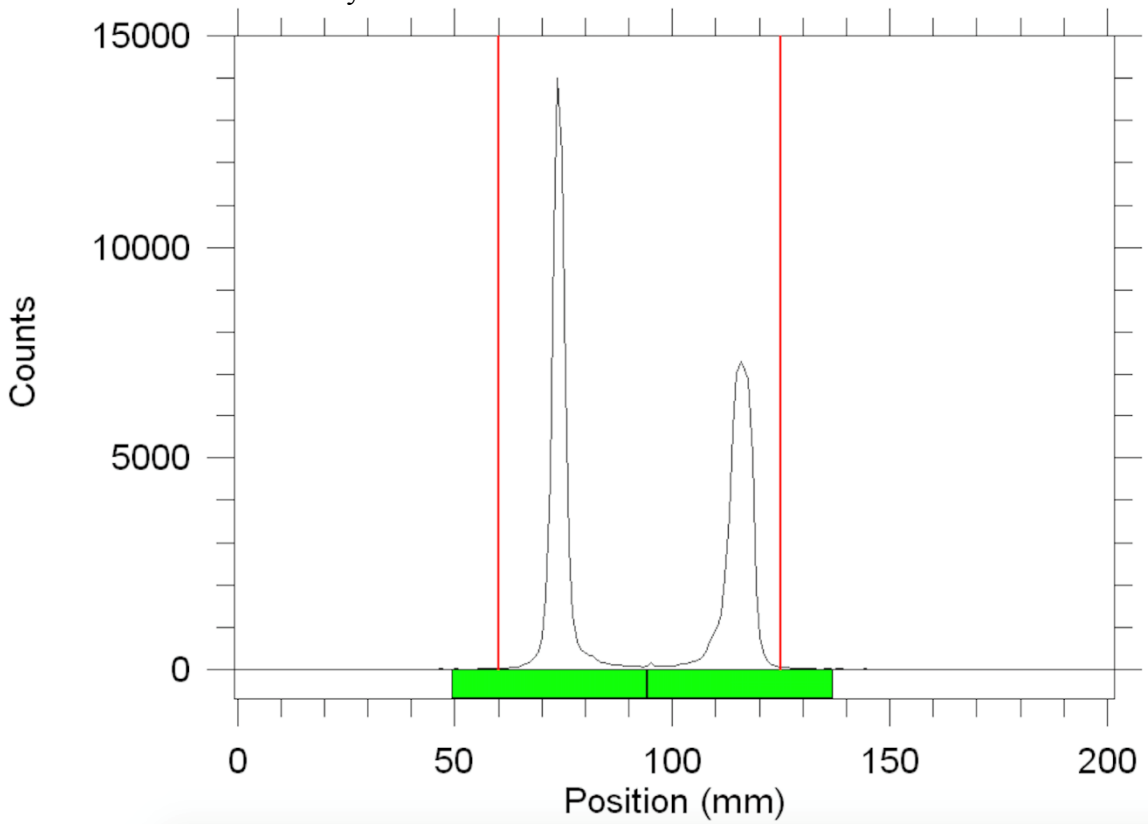
Analytical HPLC trace of **4^{18}F** gamma trace overlaid with UV trace at 280 nm, after spiking with **4F**



4-Cyano-2-(fluoro-^{18}*F*)-*N*-(quinolin-8-yl)benzamide (5^{18}F)



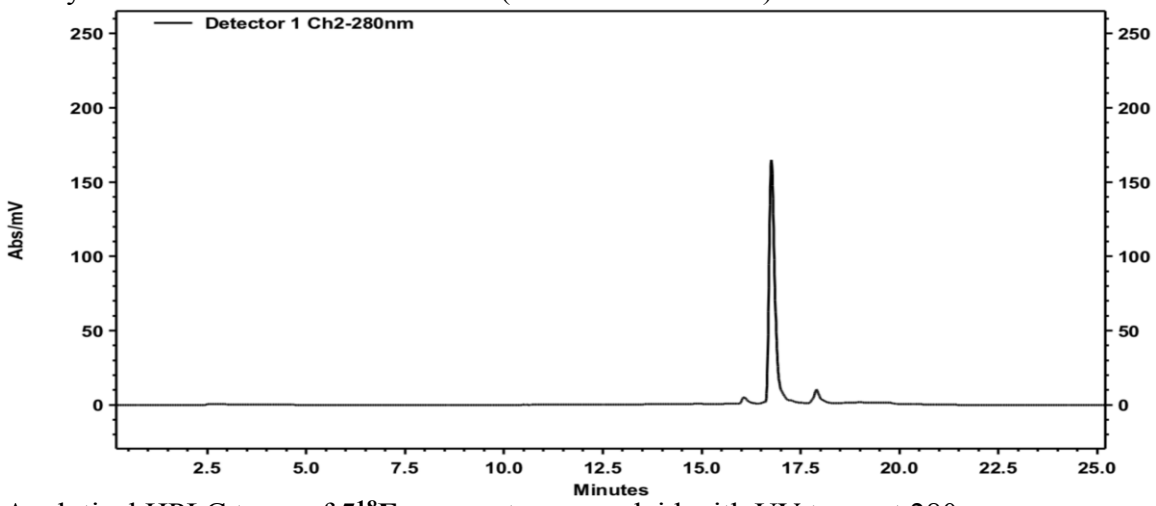
Radio-TLC conditions: Ethyl acetate/hexane = 1/1



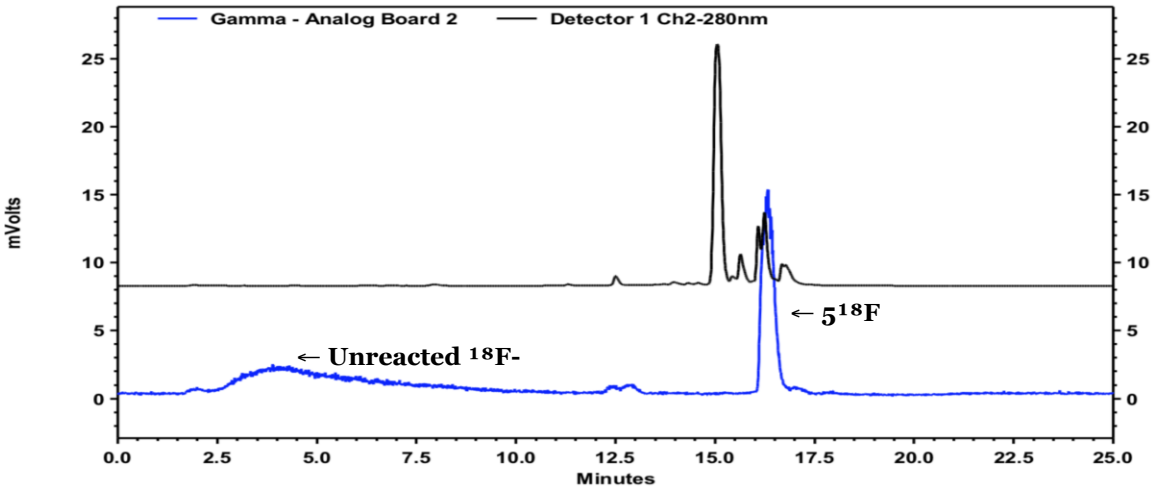
Replicate	Raw RCC (%)
1	36
2	38
3	39
4	43
5	48
Mean	41
Standard deviation	5

HPLC conditions: Condition B

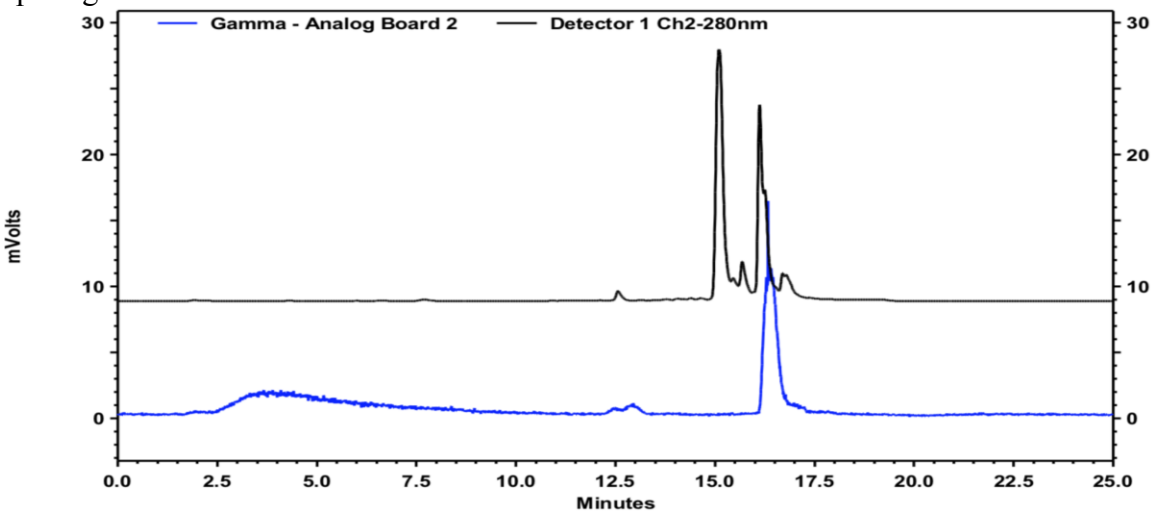
Analytical HPLC trace of **5F** standard (UV trace at 280 nm)



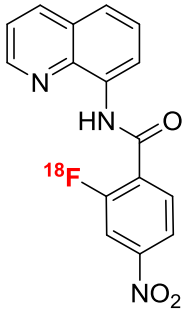
Analytical HPLC trace of **5^{18}F** gamma trace overlaid with UV trace at 280 nm



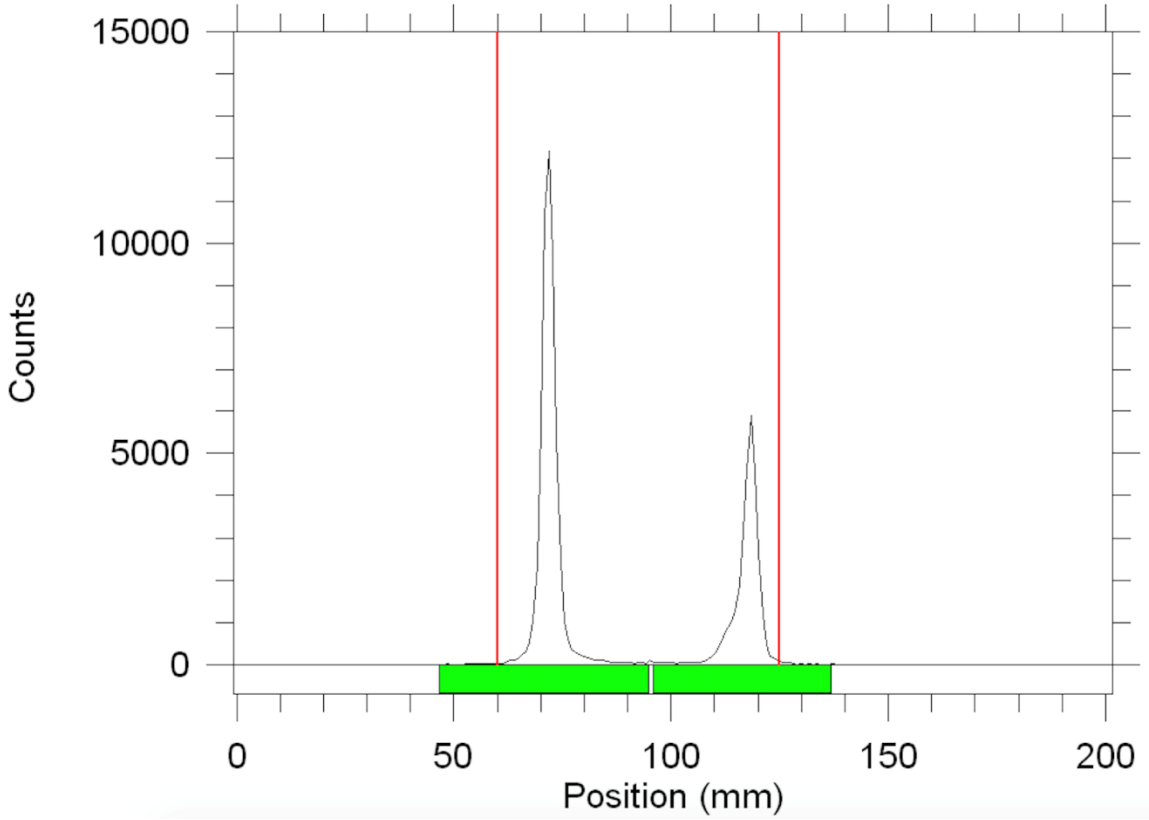
Analytical HPLC trace of **5^{18}F** gamma trace overlaid with UV trace at 280 nm, after spiking with **5F**



2-(Fluoro-^{18}F)-4-nitro-*N*-(quinolin-8-yl)benzamide ($6^{18}F$)



Radio-TLC conditions: Ethyl acetate/hexane = 1/1

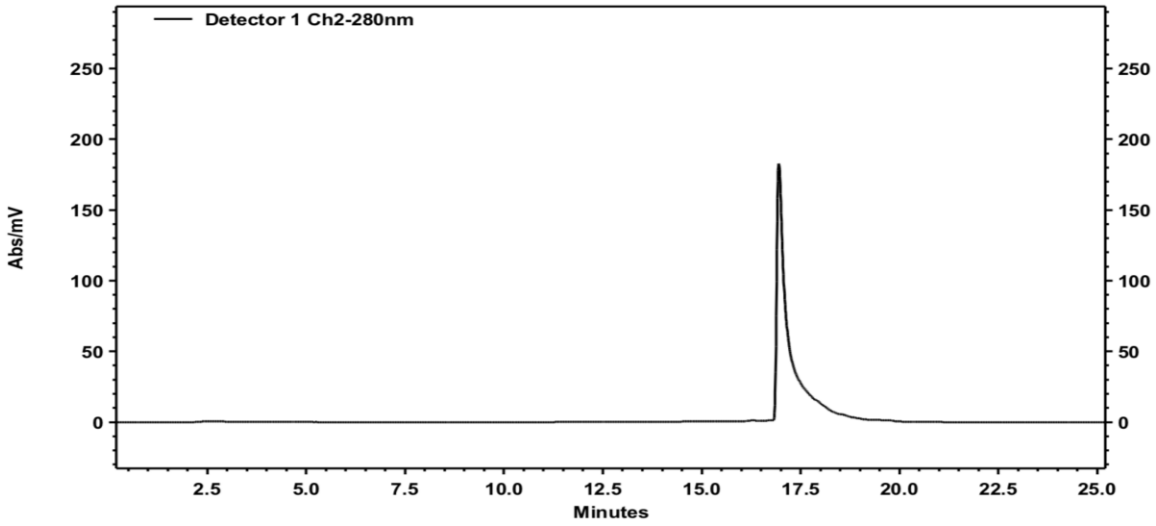


Replicate	Raw RCC (%)	Corrected RCC[a] (%)
1	37	24
2	40	26
3	36	23
4	38	24
5	37	24
Mean	37	24
Standard deviation	1	1

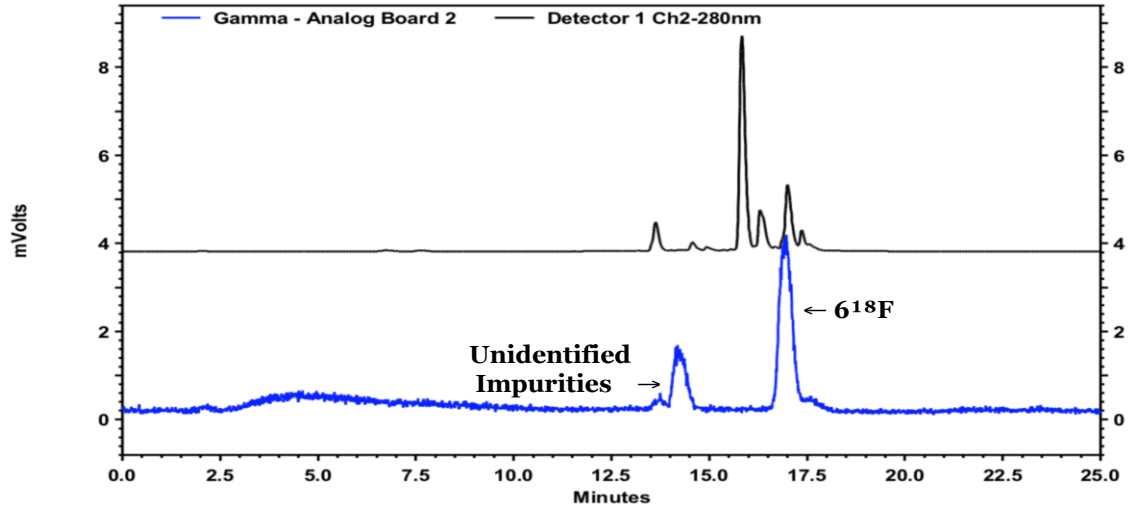
[a]Corrected RCC based on radio-analytical HPLC. The detailed procedure for corrected RCC is described in SI section 4.2.1 Manual synthesis general procedure.

HPLC conditions: Condition B

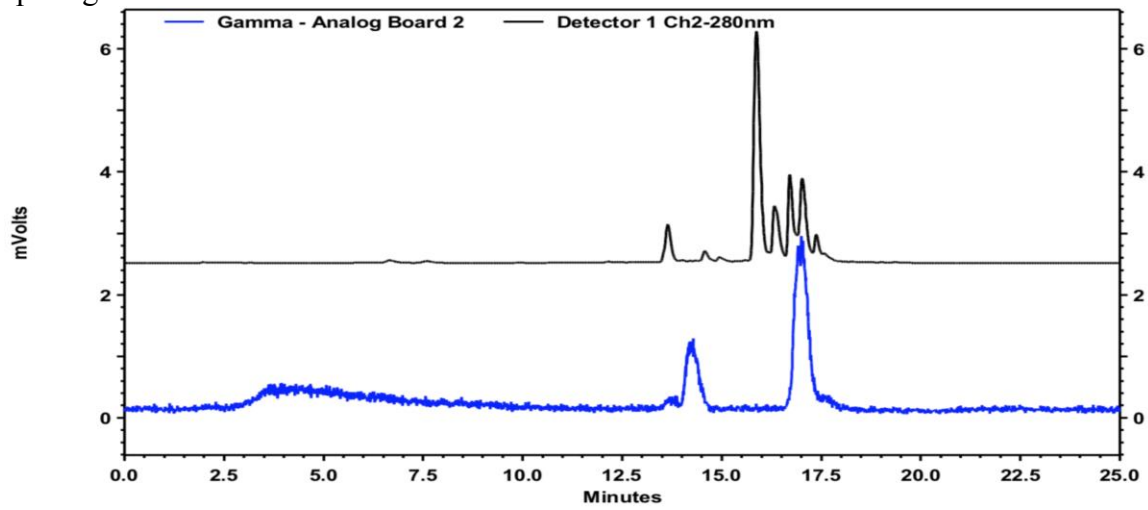
Analytical HPLC trace of **6F** standard (UV trace at 280 nm)



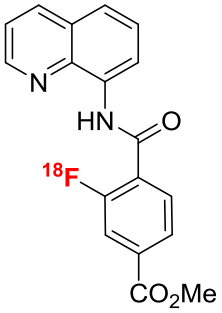
Analytical HPLC trace of **6^{18}F** gamma trace overlaid with UV trace at 280 nm



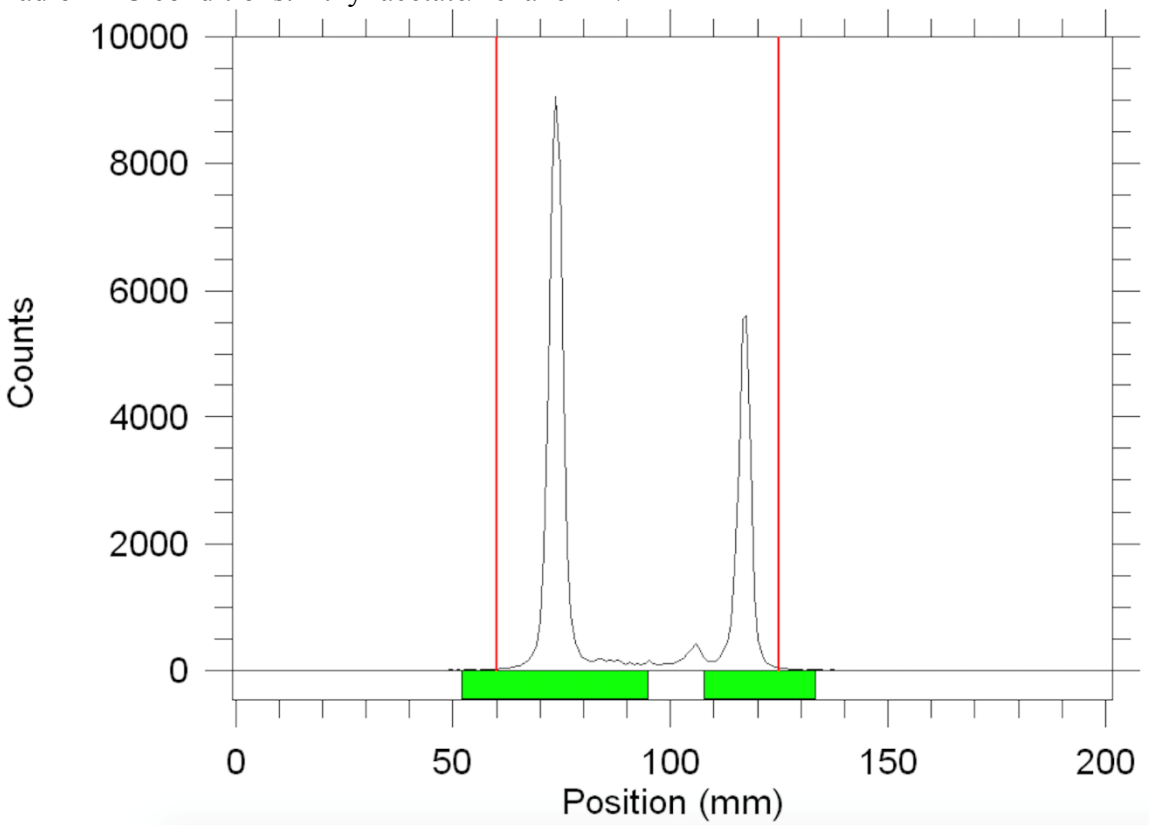
Analytical HPLC trace of **6^{18}F** gamma trace overlaid with UV trace at 280 nm, after spiking with **6F**



Methyl 3-(fluoro-^{18}F)-4-(quinolin-8-ylcarbamoyl)benzoate ($7^{18}F$)



Radio-TLC conditions: Ethyl acetate/hexane = 1/1

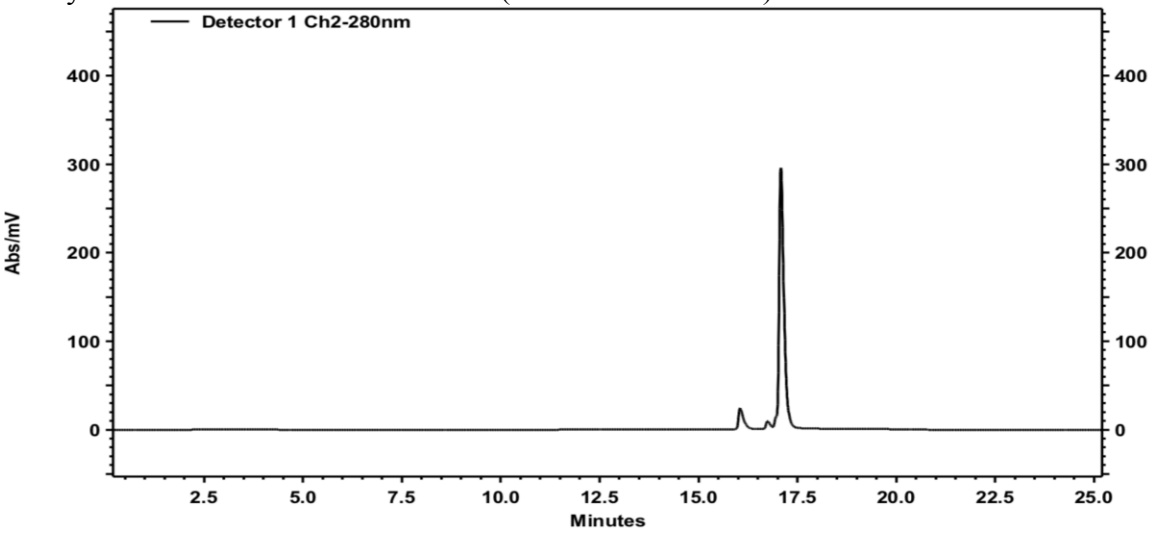


Replicate	Raw RCC (%)	Corrected RCC[a] (%)
1	32	28
2	33	29
3	33	29
4	34	30
5	33	29
Mean	33	29
Standard deviation	1	1

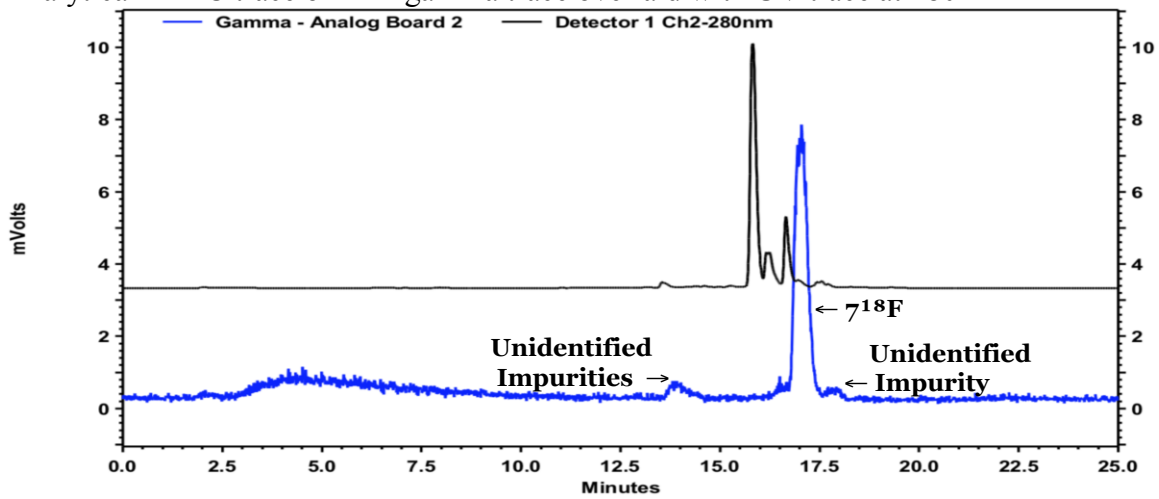
[a]Corrected RCC based on radio-analytical HPLC. The detailed procedure for corrected RCC is described in SI section 4.2.1 Manual synthesis general procedure.

HPLC conditions: Condition B

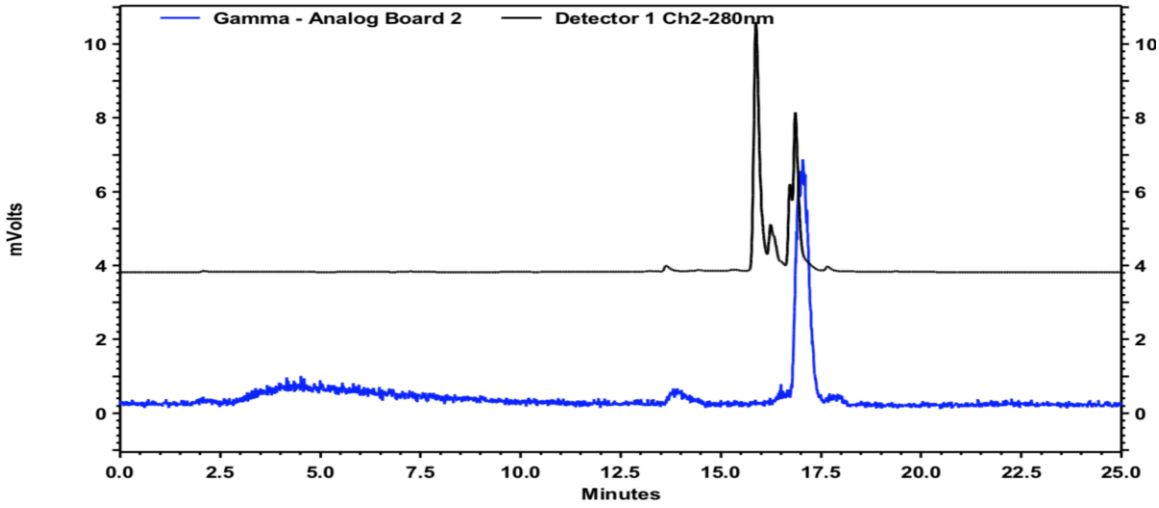
Analytical HPLC trace of **7F** standard (UV trace at 280 nm)



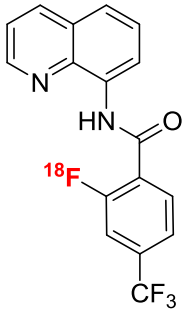
Analytical HPLC trace of **7^{18}F** gamma trace overlaid with UV trace at 280 nm



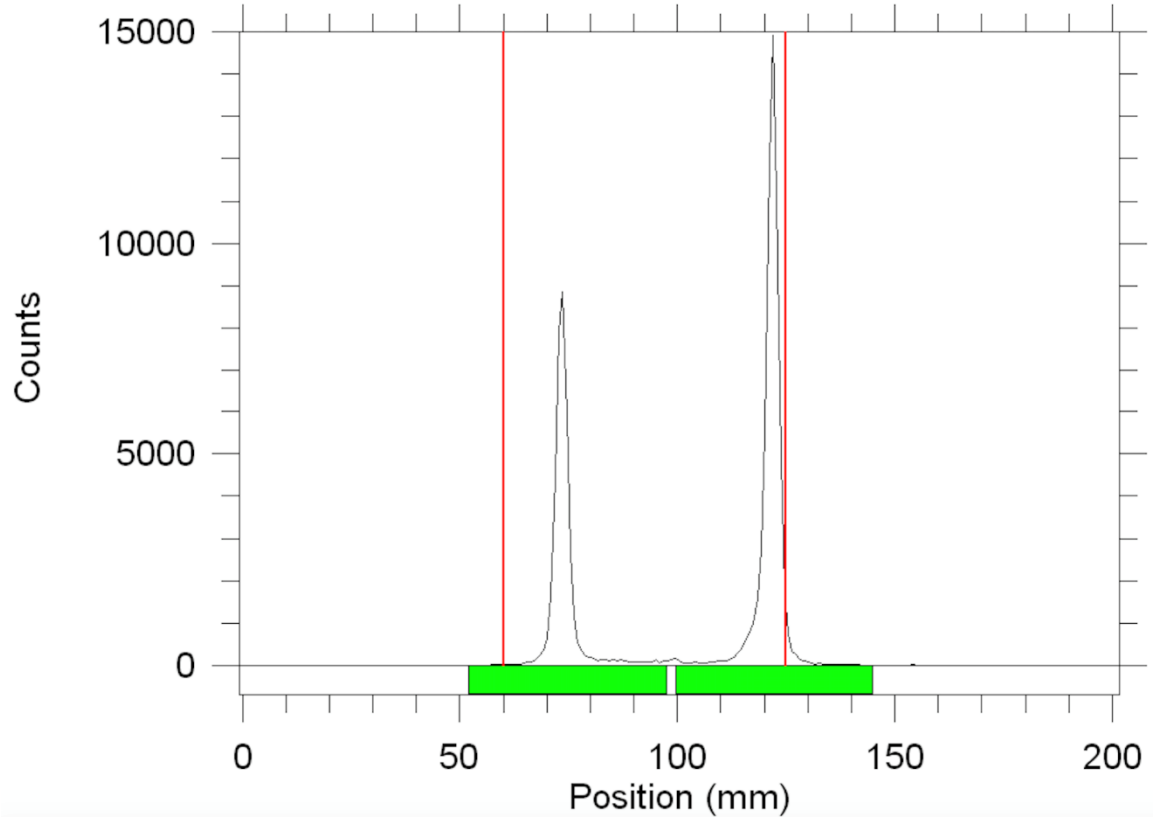
Analytical HPLC trace of **7^{18}F** gamma trace overlaid with UV trace at 280 nm, after spiking with **7F**



2-(Fluoro-^{18}F)-*N*-(quinolin-8-yl)-4-(trifluoromethyl)benzamide ($8^{18}F$)



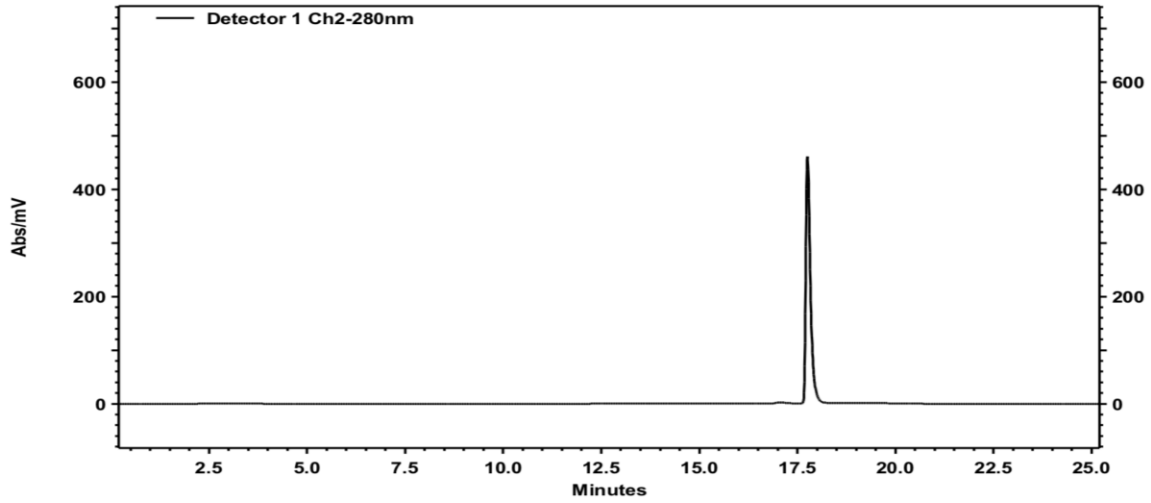
Radio-TLC conditions: Ethyl acetate/hexane = 1/1



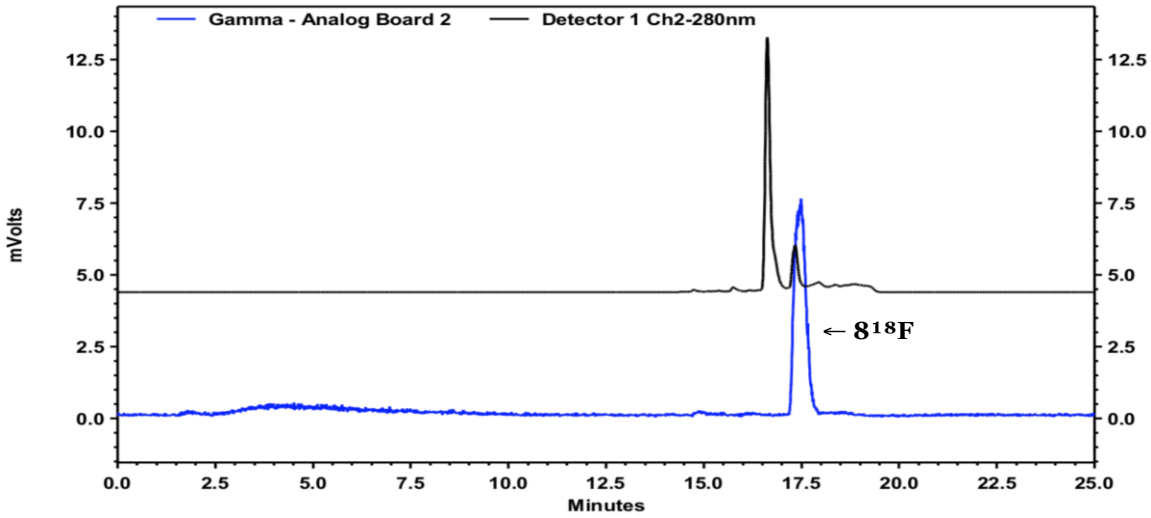
Replicate	Raw RCC (%)
1	65
2	61
3	62
4	59
5	56
Mean	60
Standard deviation	4

HPLC conditions: Condition B

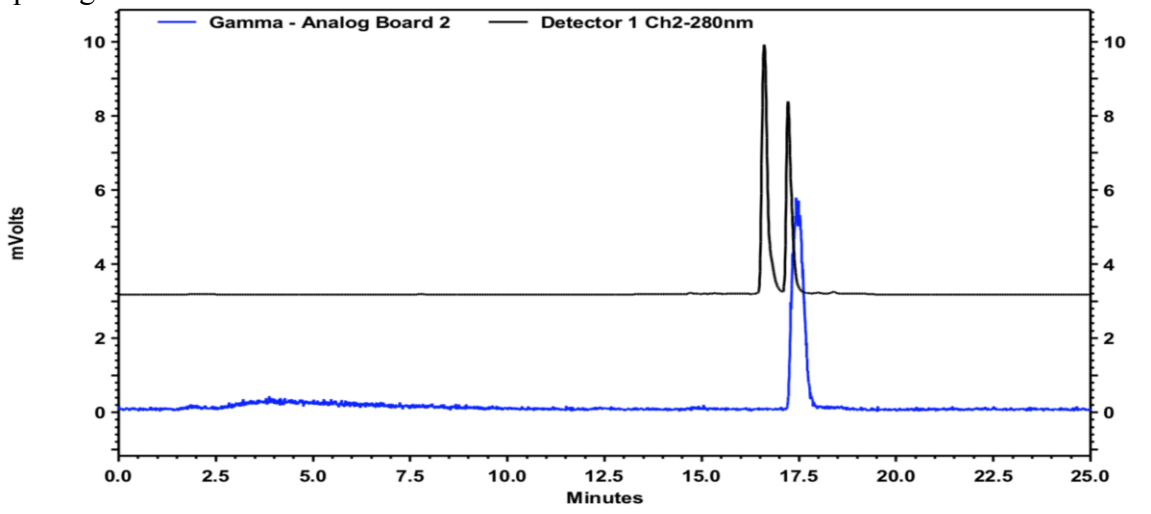
Analytical HPLC trace of **8F** standard (UV trace at 280 nm)



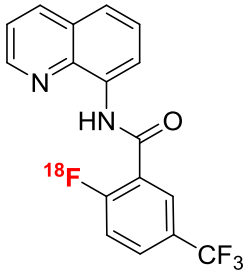
Analytical HPLC trace of **8^{18}F** gamma trace overlaid with UV trace at 280 nm



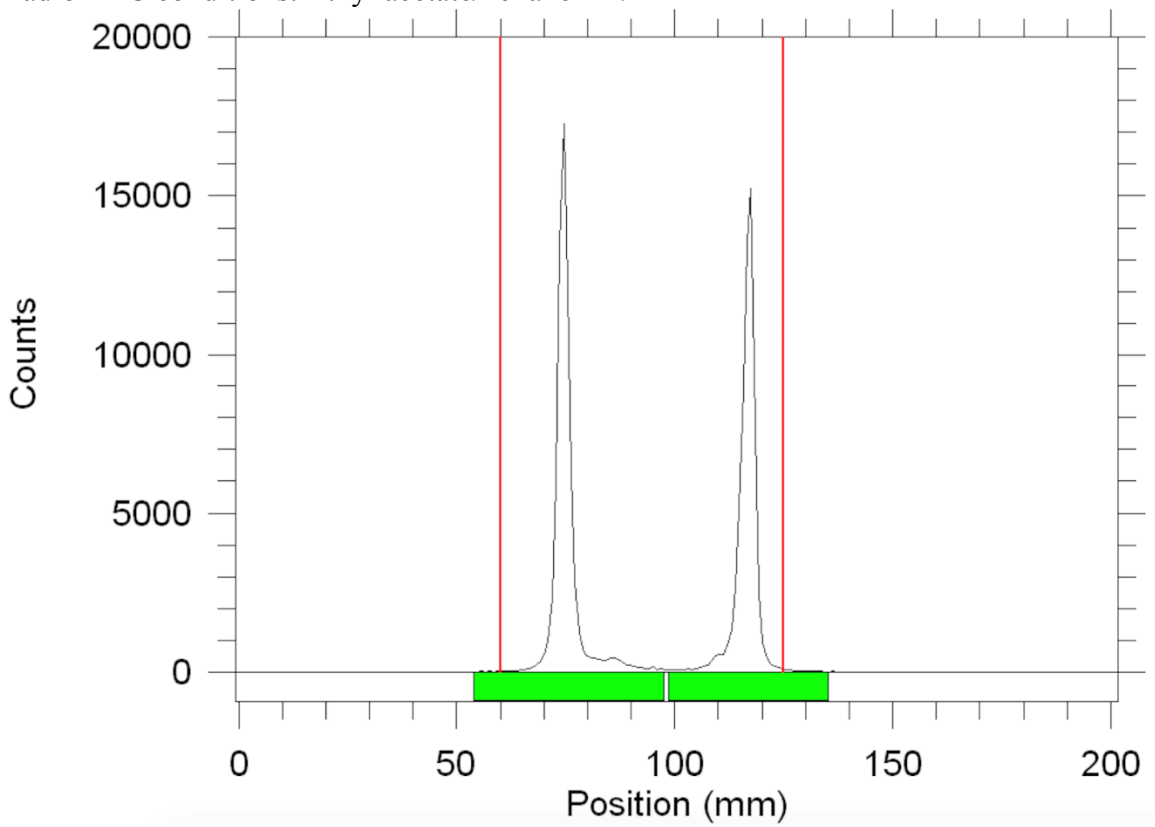
Analytical HPLC trace of **8^{18}F** gamma trace overlaid with UV trace at 280 nm, after spiking with **8F**



2-(Fluoro-^{18}F)-*N*-(quinolin-8-yl)-5-(trifluoromethyl)benzamide ($9^{18}F$)



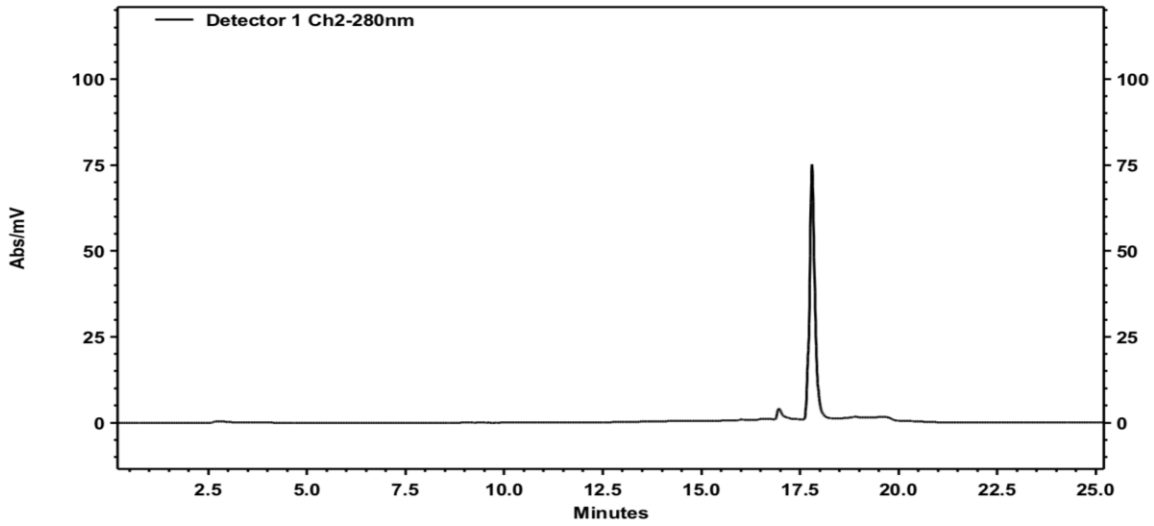
Radio-TLC conditions: Ethyl acetate/hexane = 1/1



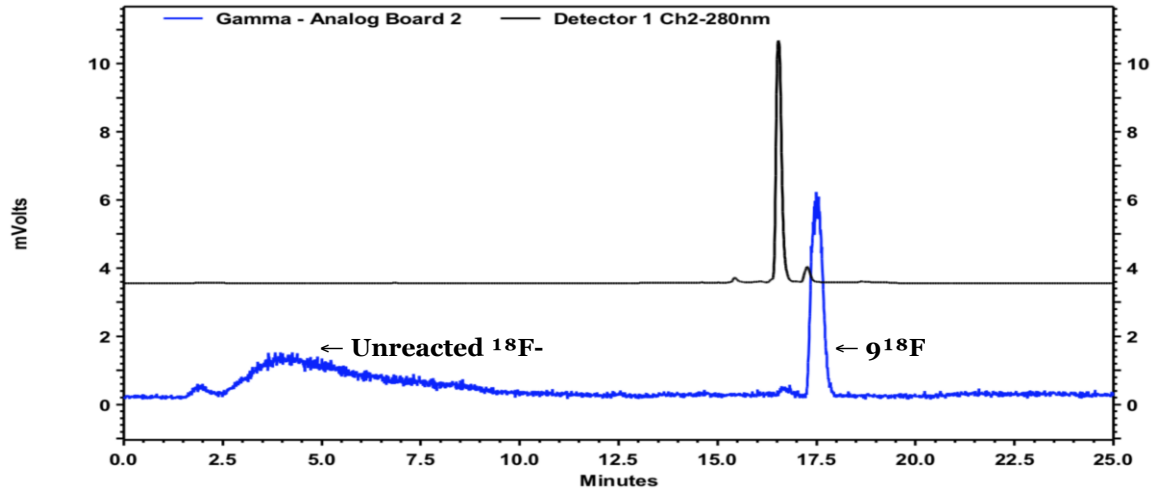
Replicate	Raw RCC (%)
1	36
2	40
3	34
4	32
5	37
Mean	35
Standard deviation	3

HPLC conditions: Condition B

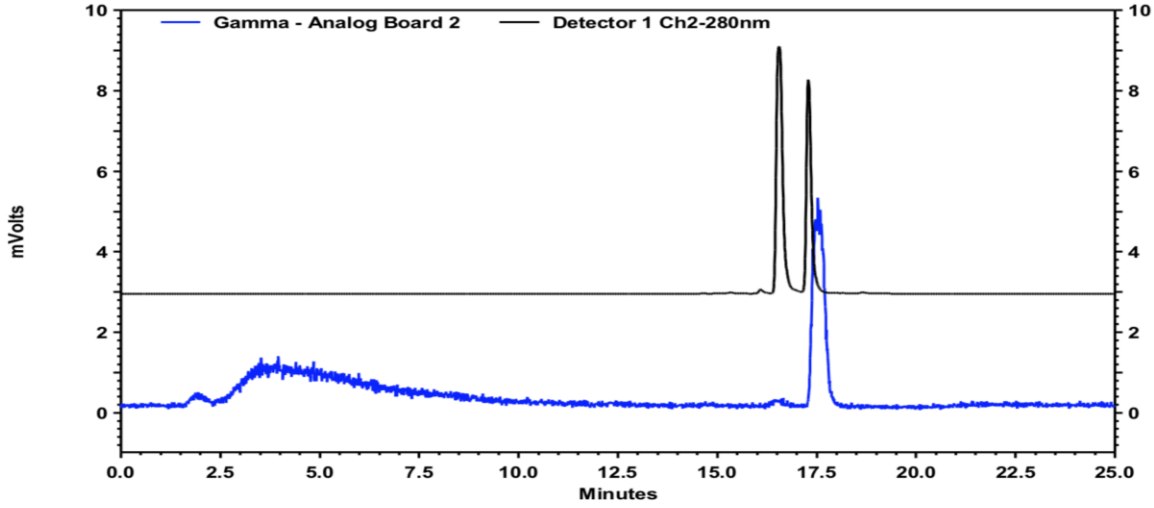
Analytical HPLC trace of **9F** standard (UV trace at 280 nm)



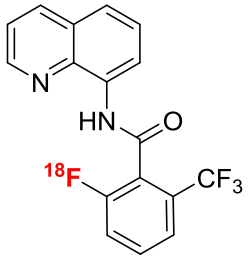
Analytical HPLC trace of **9^{18}F** gamma trace overlaid with UV trace at 280 nm



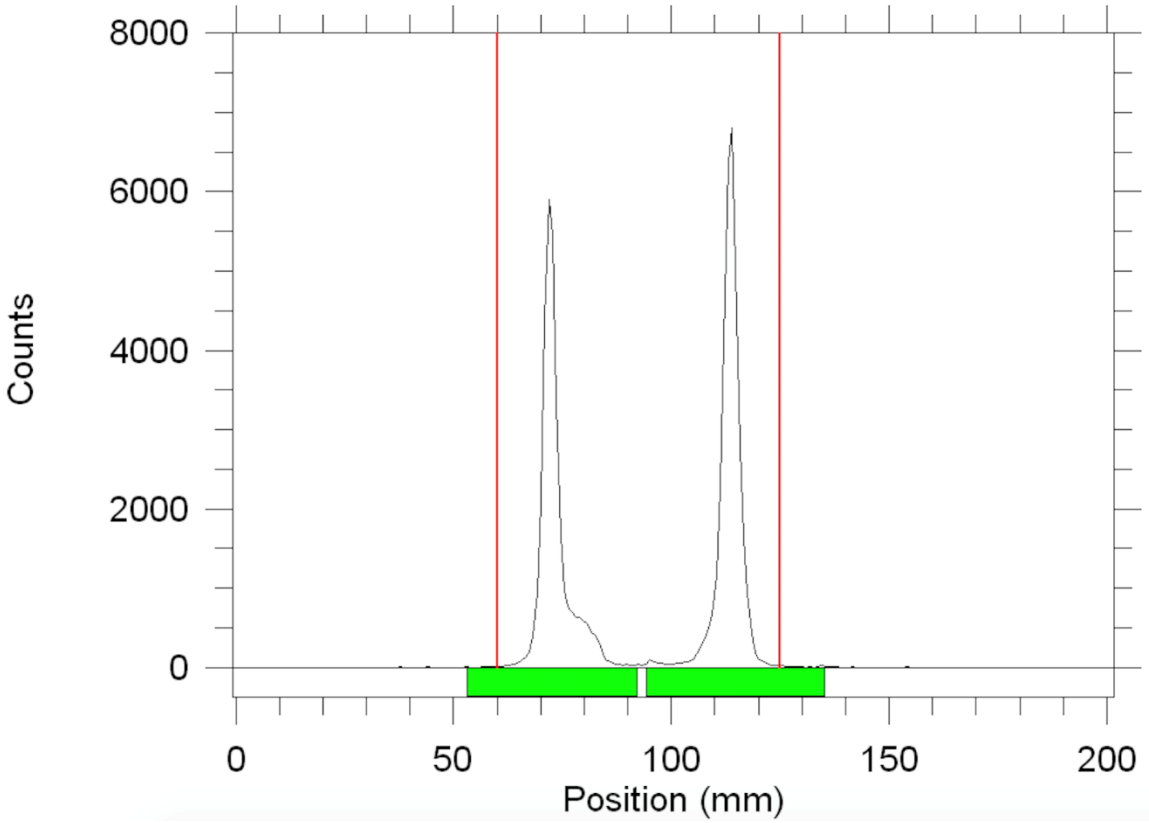
Analytical HPLC trace of **9^{18}F** gamma trace overlaid with UV trace at 280 nm, after spiking with **9F**



2-(Fluoro-^{18}F)-*N*-(quinolin-8-yl)-6-(trifluoromethyl)benzamide (10^{18}F)



Radio-TLC conditions: Ethyl acetate/hexane = 1/1

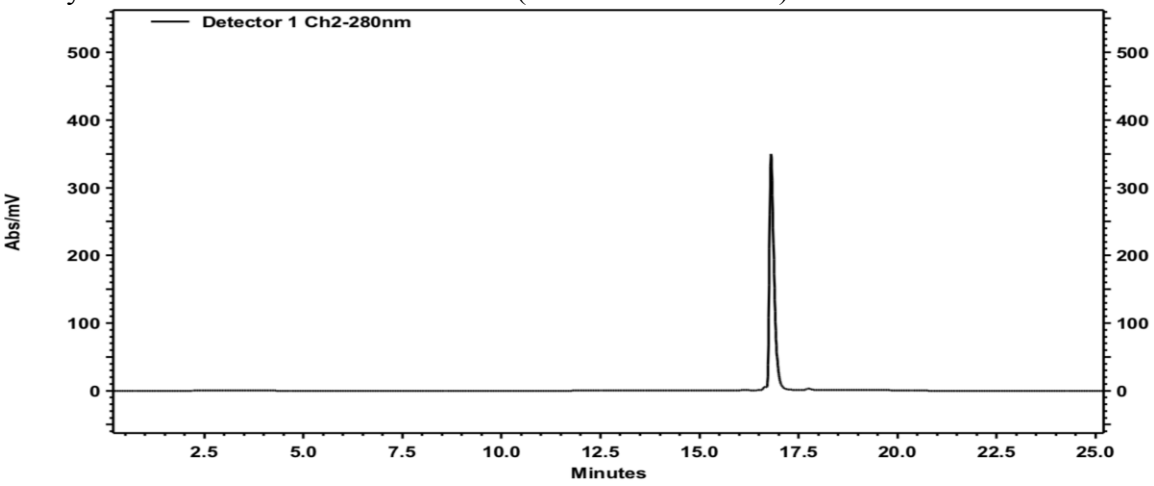


Replicate	Raw RCC (%)	Corrected RCC[a] (%)
1	55	43
2	52	41
3	52	41
4	49	38
5	51	40
Mean	52	41
Standard deviation	2	2

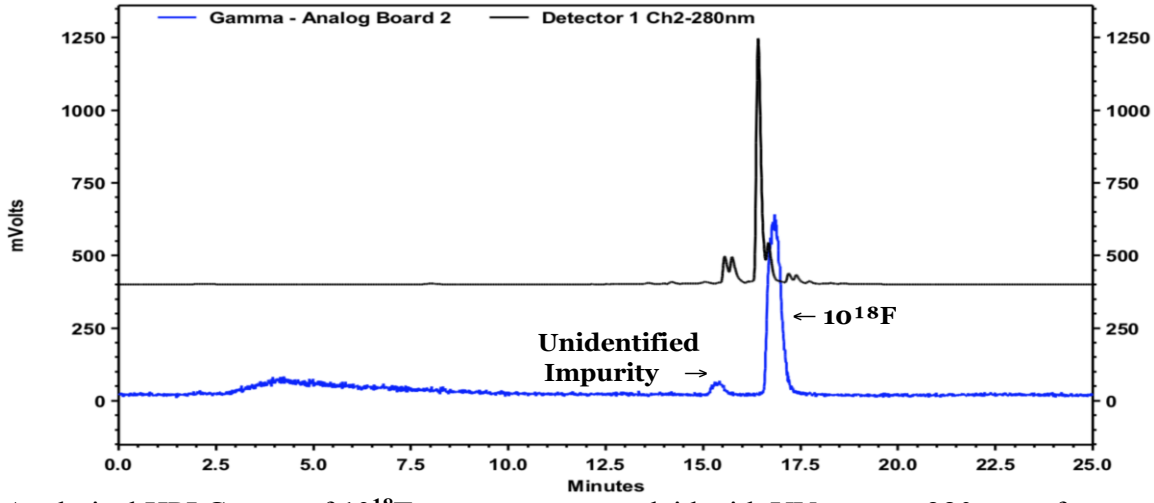
[a]Corrected RCC based on radio-analytical HPLC. The detailed procedure for corrected RCC is described in SI section 4.2.1 Manual synthesis general procedure.

HPLC conditions: Condition B

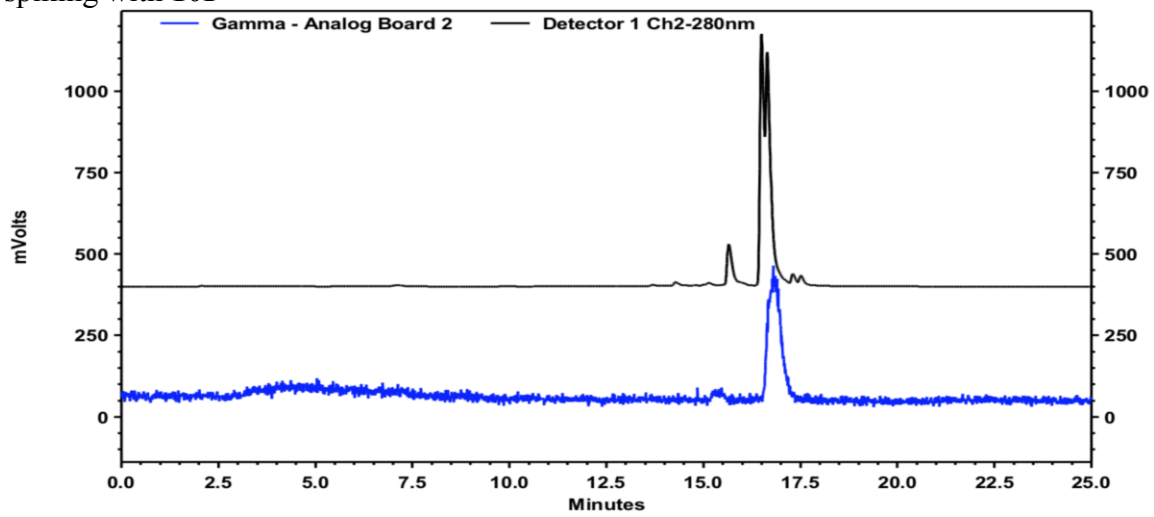
Analytical HPLC trace of **10F** standard (UV trace at 280 nm)



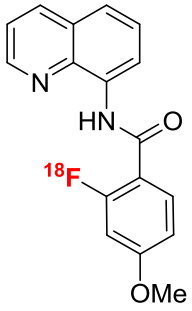
Analytical HPLC trace of **10^{18}F** gamma trace overlaid with UV trace at 280 nm



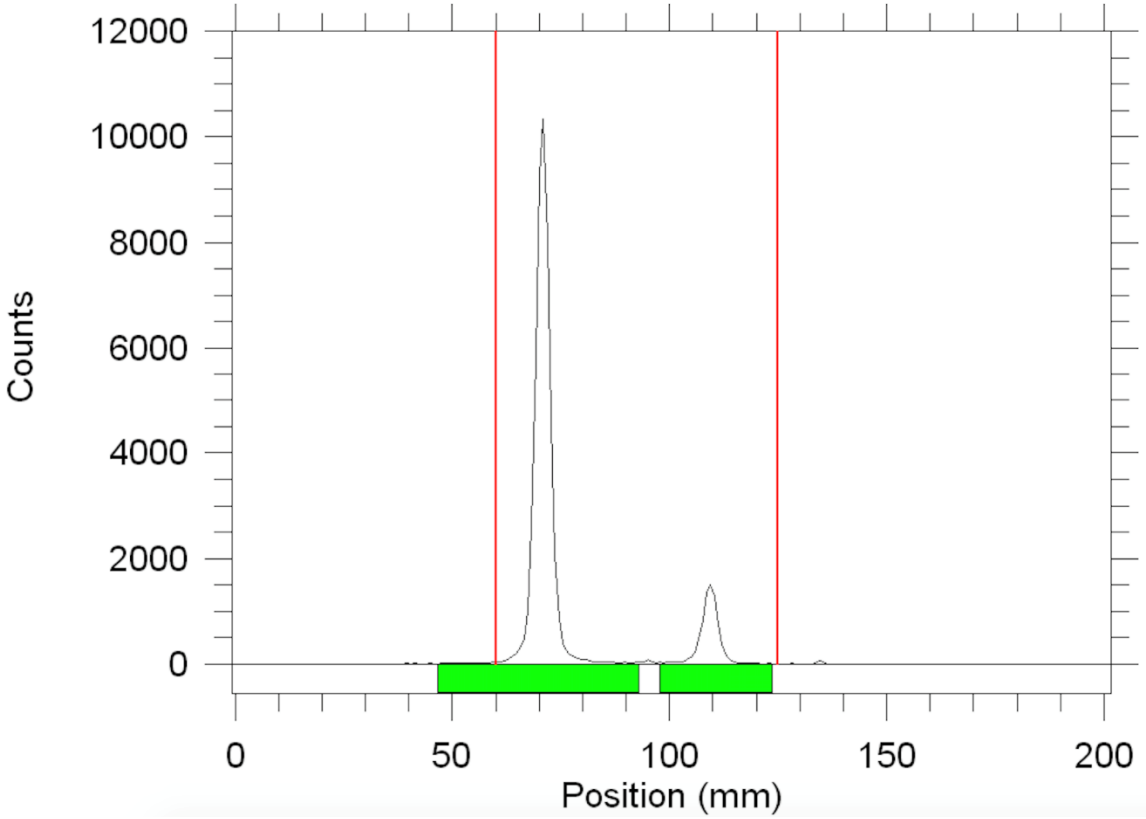
Analytical HPLC trace of **10^{18}F** gamma trace overlaid with UV trace at 280 nm, after spiking with **10F**



2-(Fluoro-^{18}F)-4-methoxy-*N*-(quinolin-8-yl)benzamide ($11^{18}F$)



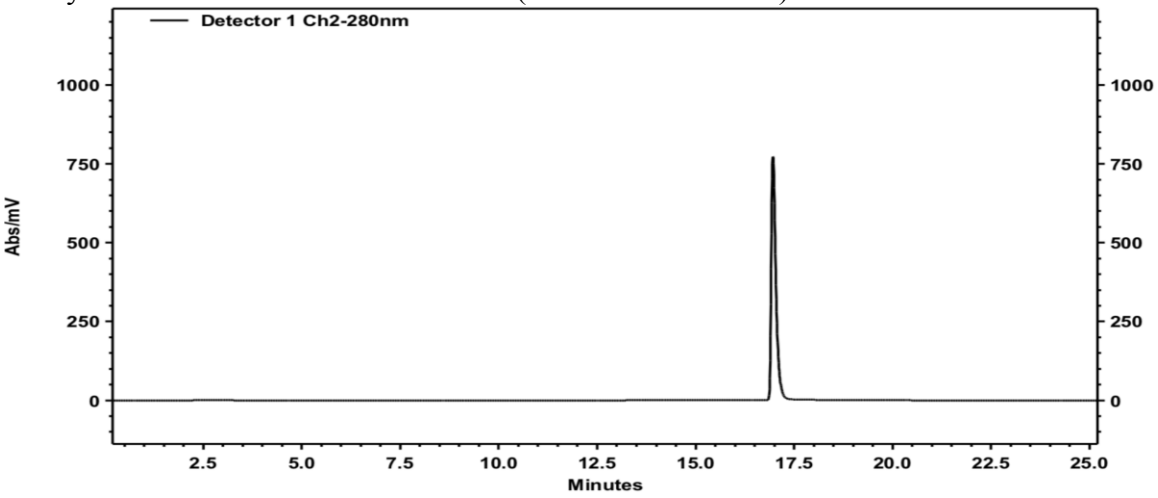
Radio-TLC conditions: Ethyl acetate/hexane = 1/1



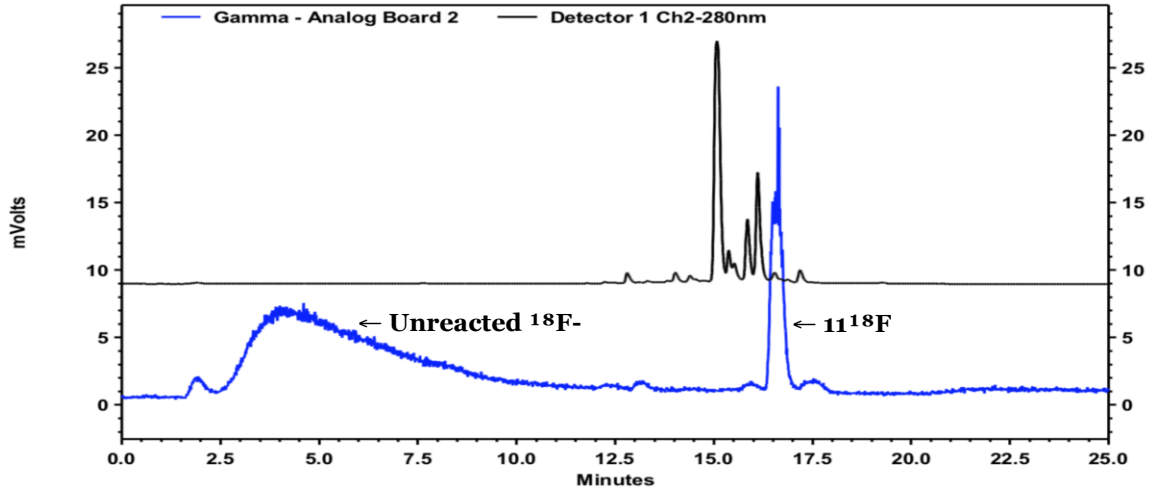
Replicate	Raw RCC (%)
1	11
2	10
3	10
4	11
5	11
Mean	10
Standard deviation	1

HPLC conditions: Condition B

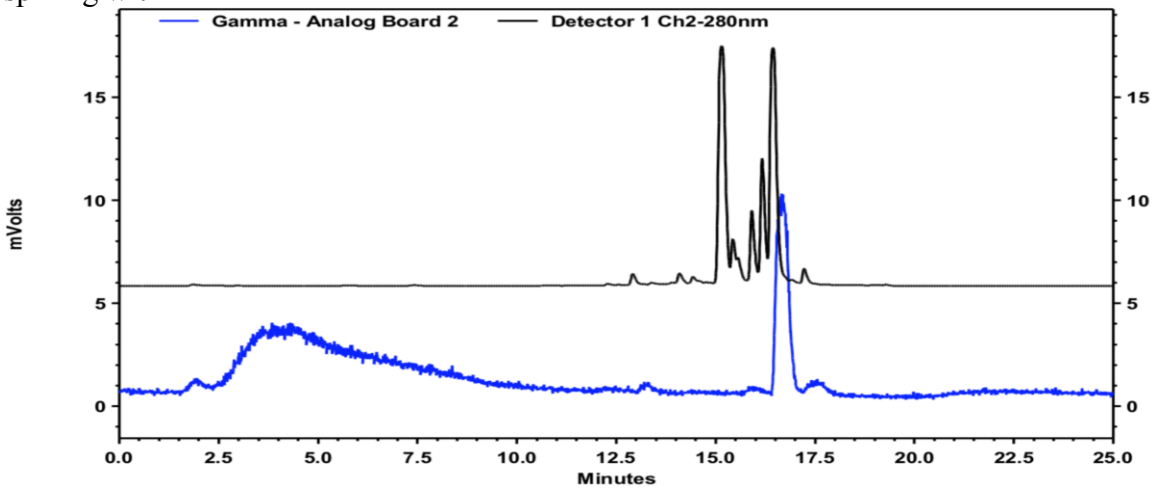
Analytical HPLC trace of **11F** standard (UV trace at 280 nm)



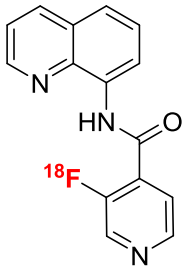
Analytical HPLC trace of **11^{18}F** gamma trace overlaid with UV trace at 280 nm



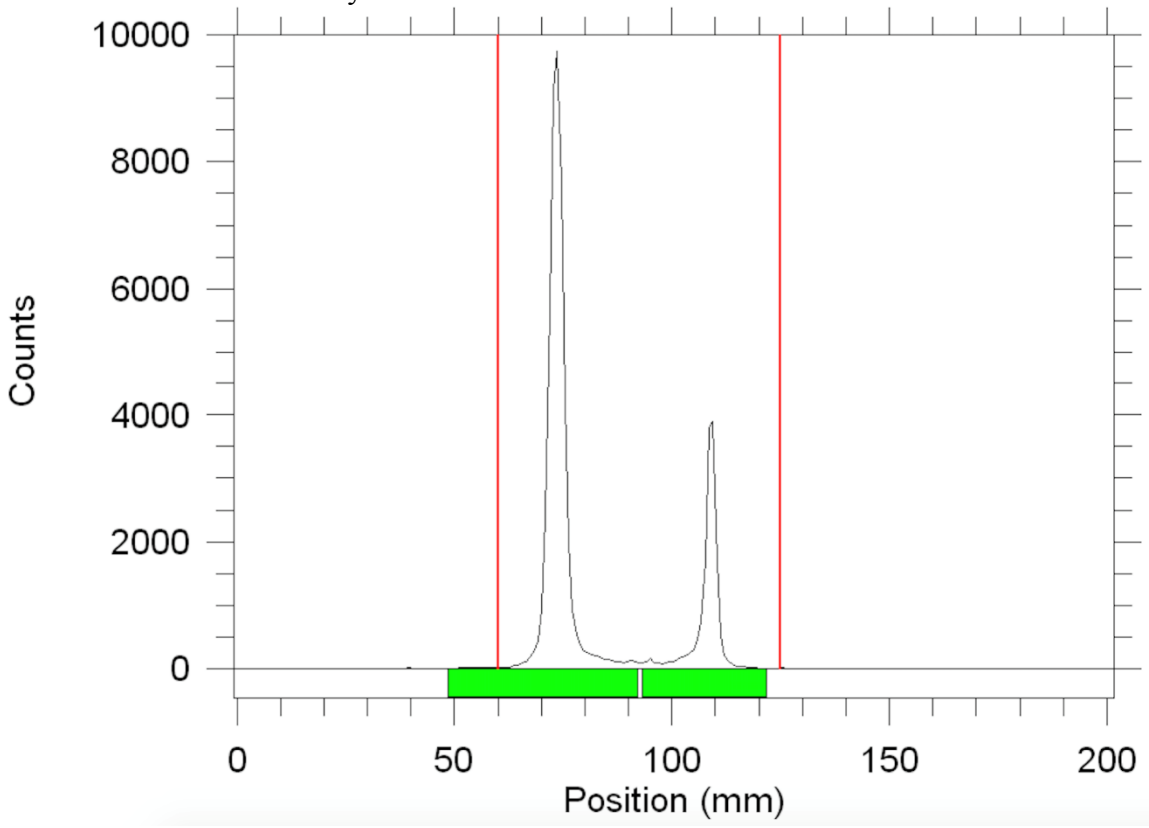
Analytical HPLC trace of **11^{18}F** gamma trace overlaid with UV trace at 280 nm, after spiking with **11F**



3-(Fluoro-^{18}F)-*N*-(quinolin-8-yl)isonicotinamide (12^{18}F)



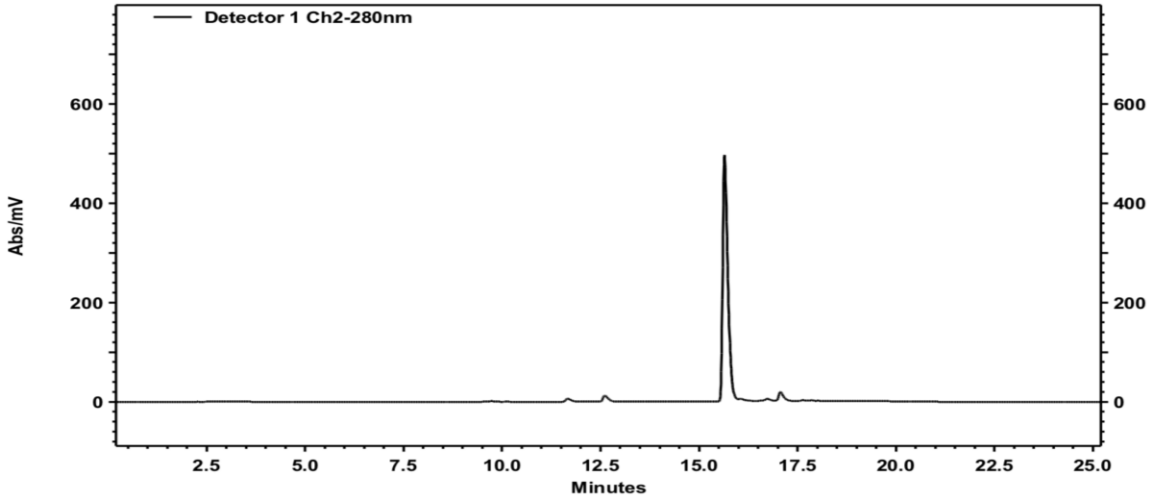
Radio-TLC conditions: Ethyl acetate/hexane = 1/1



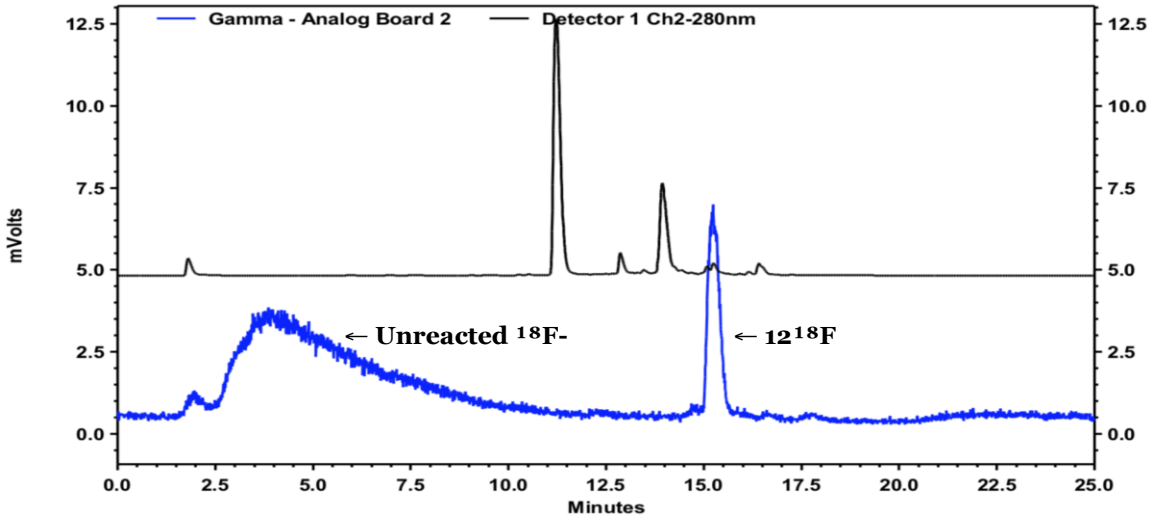
Replicate	Raw RCC (%)
1	22
2	24
3	21
4	18
5	24
Mean	22
Standard deviation	2

HPLC conditions: Condition B

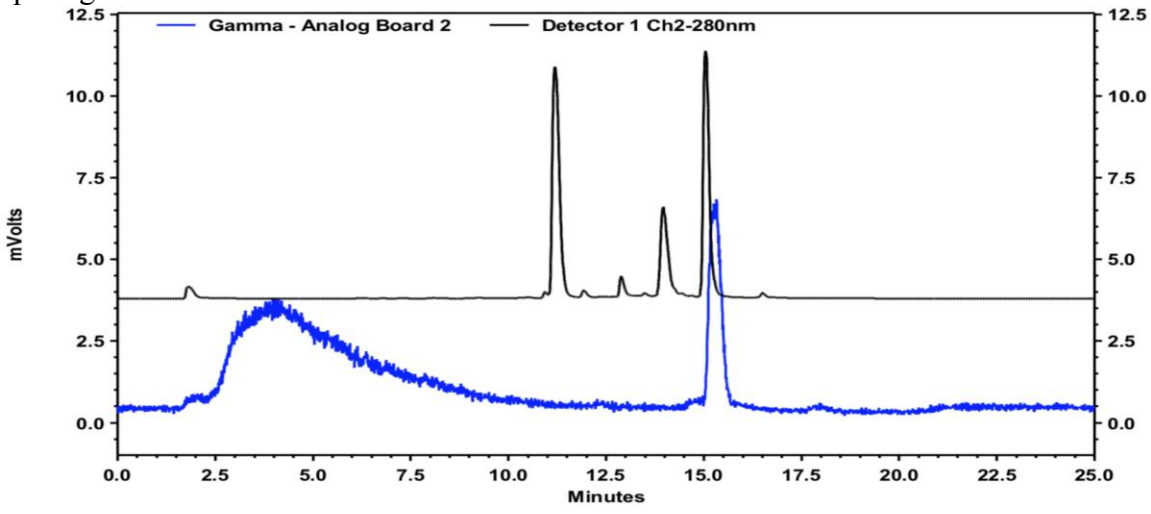
Analytical HPLC trace of **12F** standard (UV trace at 280 nm)



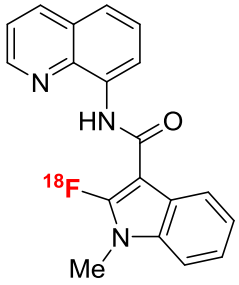
Analytical HPLC trace of **12^{18}F** gamma trace overlaid with UV trace at 280 nm



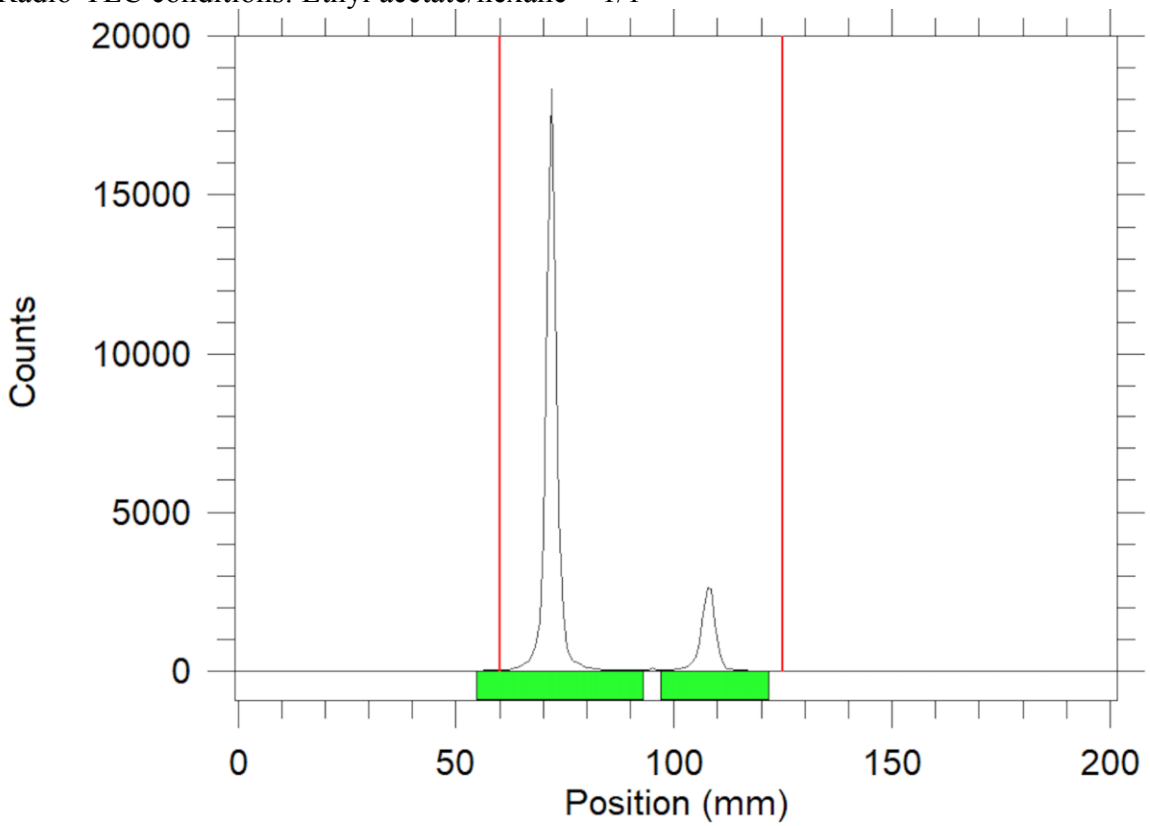
Analytical HPLC trace of **12^{18}F** gamma trace overlaid with UV trace at 280 nm, after spiking **12F**



2-(Fluoro-^{18}F)-1-methyl-*N*-(quinolin-8-yl)-1*H*-indole-3-carboxamide (13^{18}F)



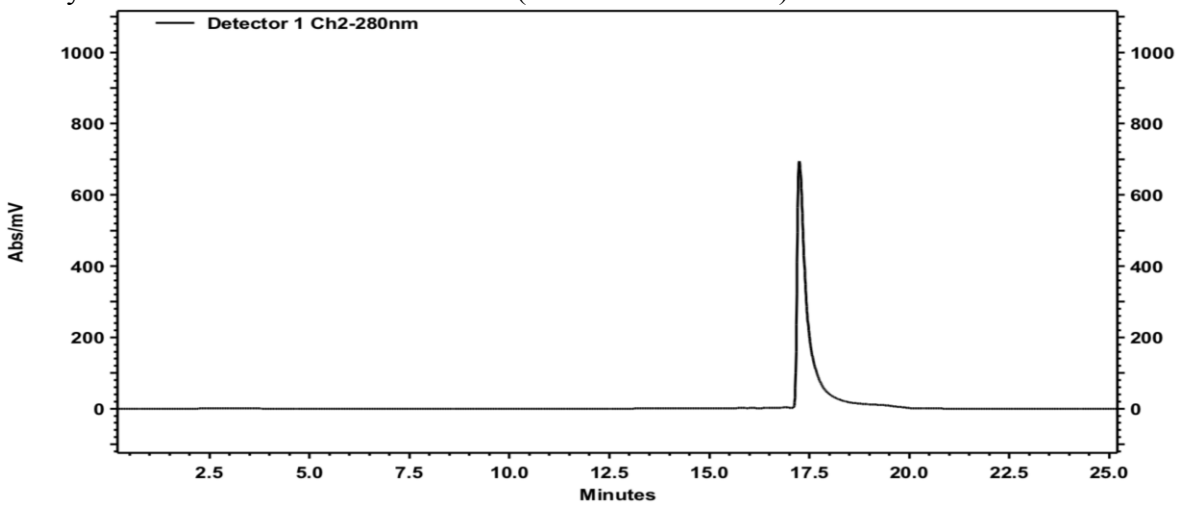
Radio-TLC conditions: Ethyl acetate/hexane = 1/1



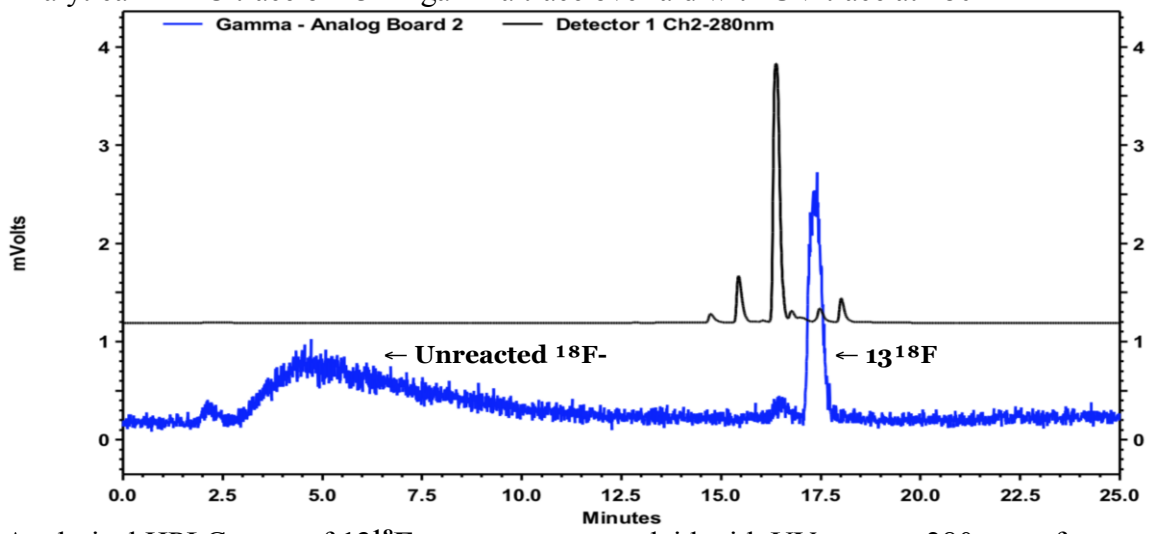
Replicate	Raw RCC (%)
1	17
2	15
3	16
4	14
Mean	16
Standard deviation	1

HPLC conditions: Condition B

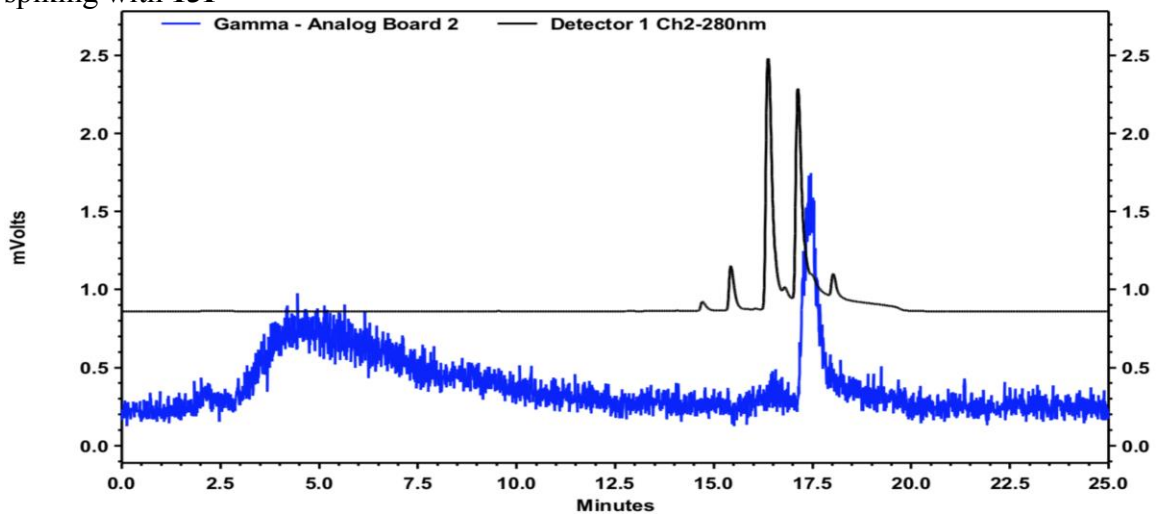
Analytical HPLC trace of **13F** standard (UV trace at 280 nm)



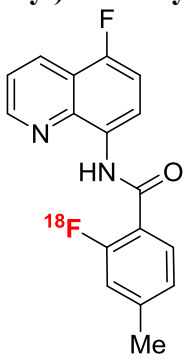
Analytical HPLC trace of **13^{18}F** gamma trace overlaid with UV trace at 280 nm



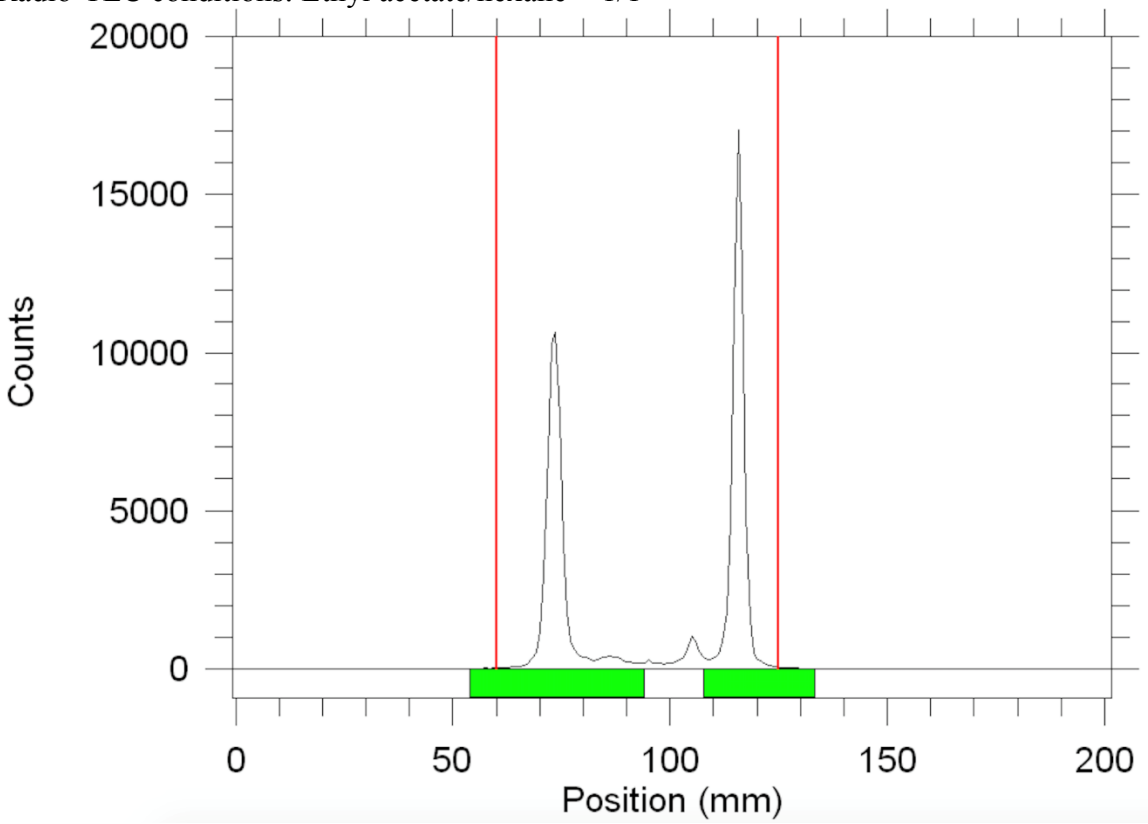
Analytical HPLC trace of **13^{18}F** gamma trace overlaid with UV trace at 280 nm, after spiking with **13F**



2-(Fluoro-^{18}F)-*N*-(5-fluoroquinolin-8-yl)-4-methylbenzamide ($14^{18}F$)



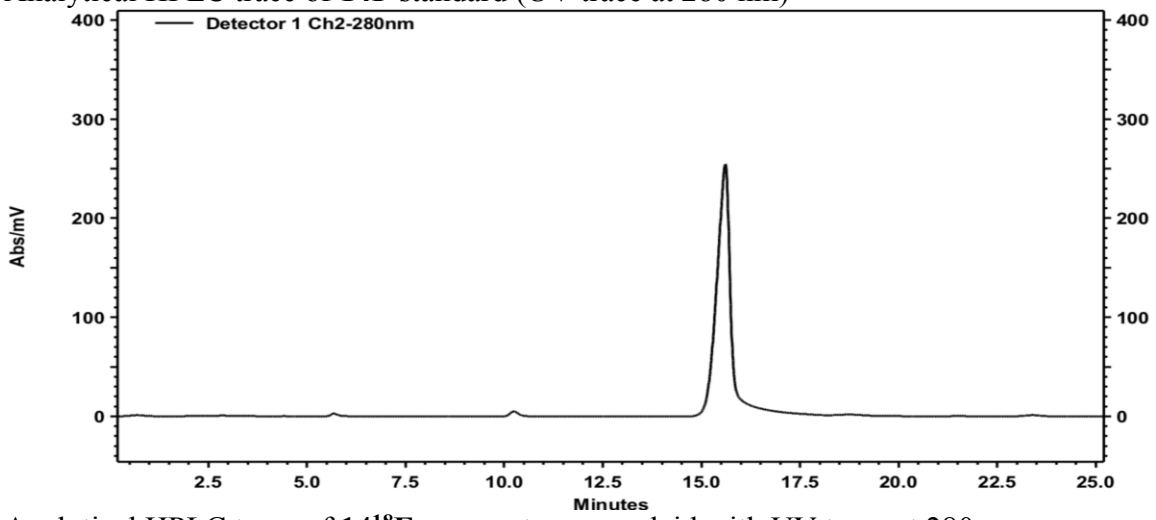
Radio-TLC conditions: Ethyl acetate/hexane = 1/1



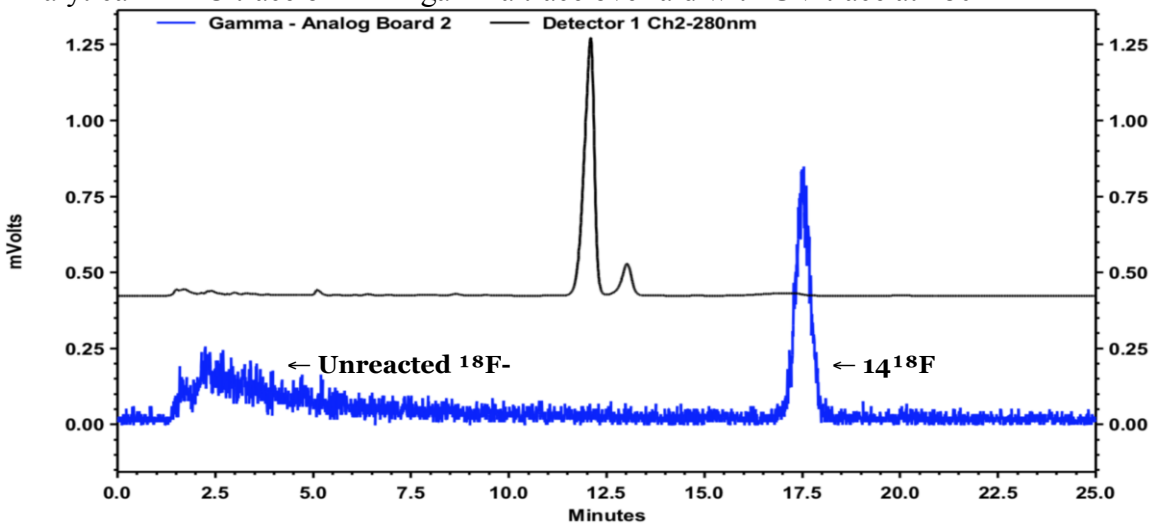
Replicate	Raw RCC (%)
1	49
2	51
3	50
4	49
5	50
Mean	50
Standard deviation	1

HPLC conditions: Condition A

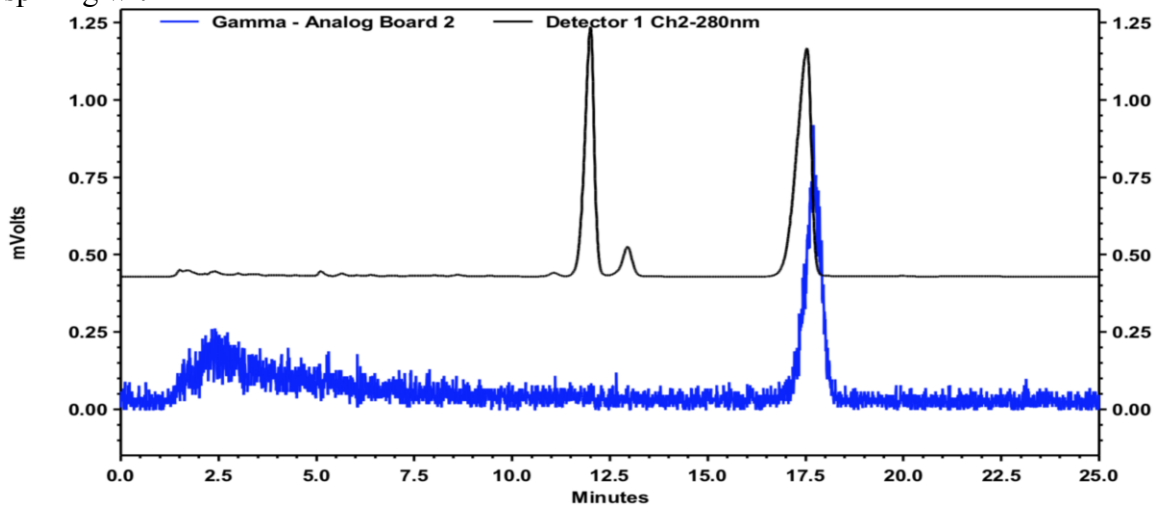
Analytical HPLC trace of **14F** standard (UV trace at 280 nm)



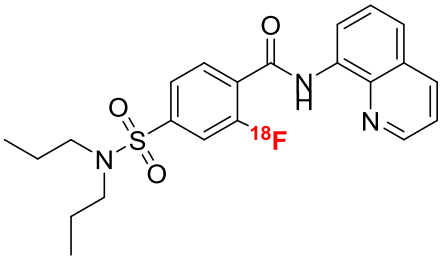
Analytical HPLC trace of **14^{18}F** gamma trace overlaid with UV trace at 280 nm



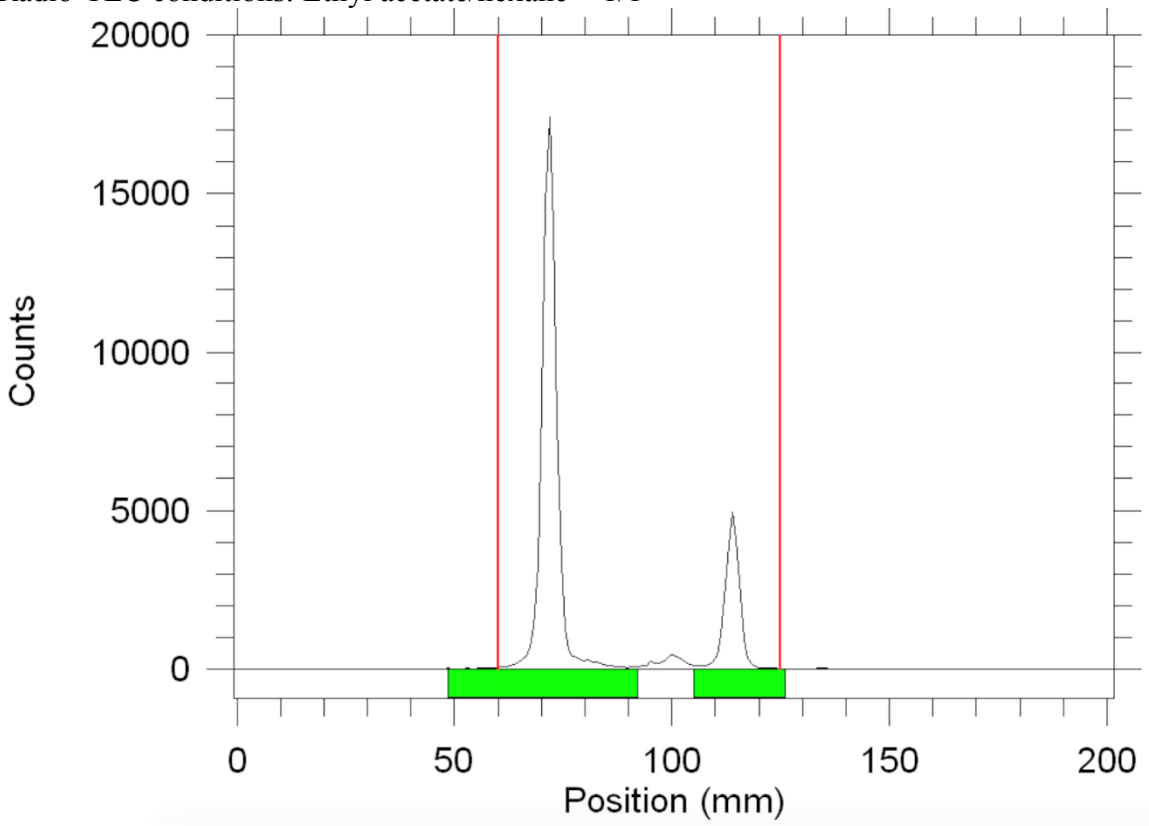
Analytical HPLC trace of **14^{18}F** gamma trace overlaid with UV trace at 280 nm, after spiking with **14F**



4-(*N*,*N*-Dipropylsulfamoyl)-2-(fluoro-^{18}*F*)-*N*-(quinolin-8-yl)benzamide (15^{18}F)



Radio-TLC conditions: Ethyl acetate/hexane = 1/1

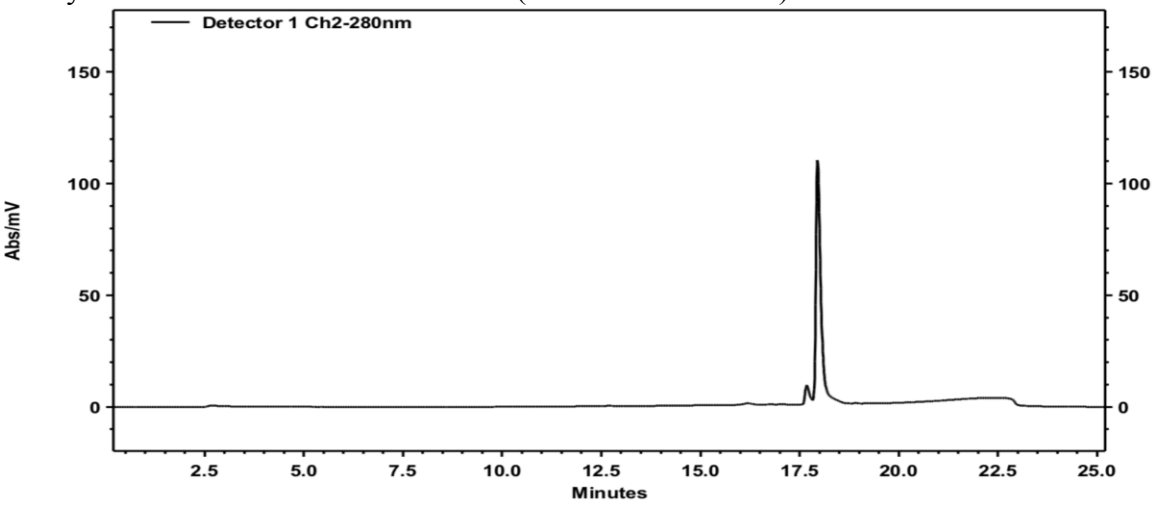


Replicate	Raw RCC (%)	Corrected RCC[a] (%)
1	22	21
2	18	17
3	23	22
4	22	21
5	19	18
Mean	21	20
Standard deviation	2	2

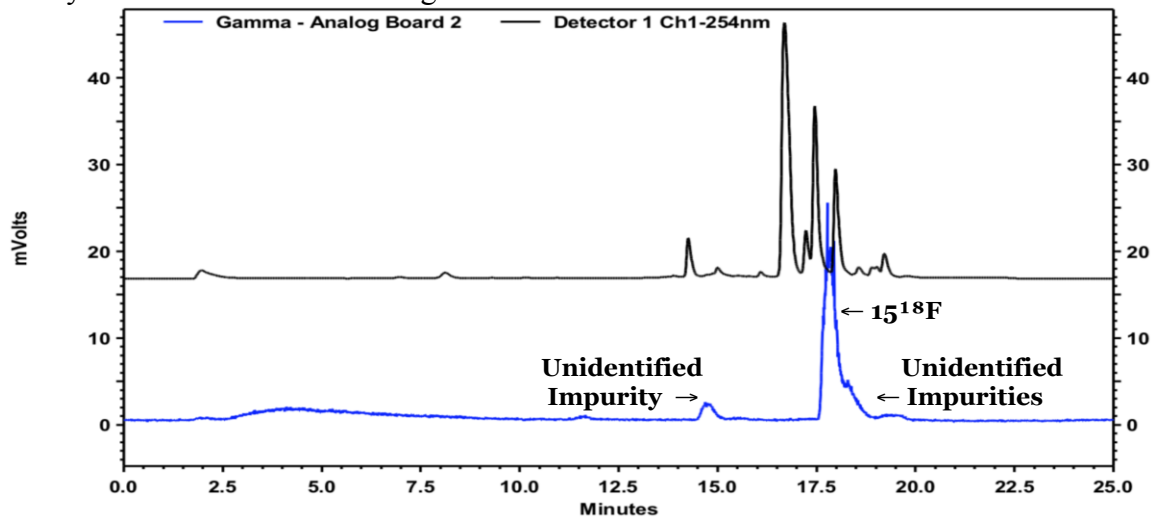
[a]Corrected RCC based on radio-analytical HPLC. The detailed procedure for corrected RCC is described in SI section 4.2.1 Manual synthesis general procedure.

HPLC conditions: Condition C

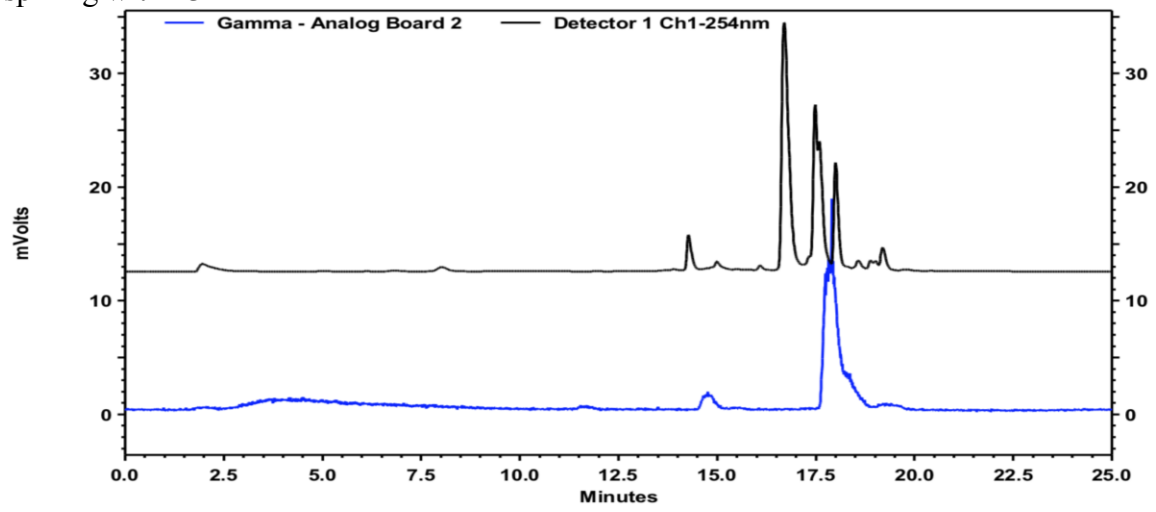
Analytical HPLC trace of **15F** standard (UV trace at 254 nm)



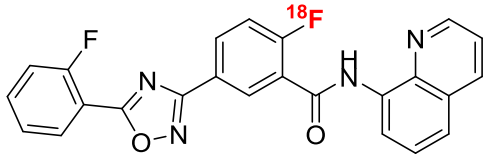
Analytical HPLC trace of **15^{18}F** gamma trace overlaid with UV trace at 254 nm



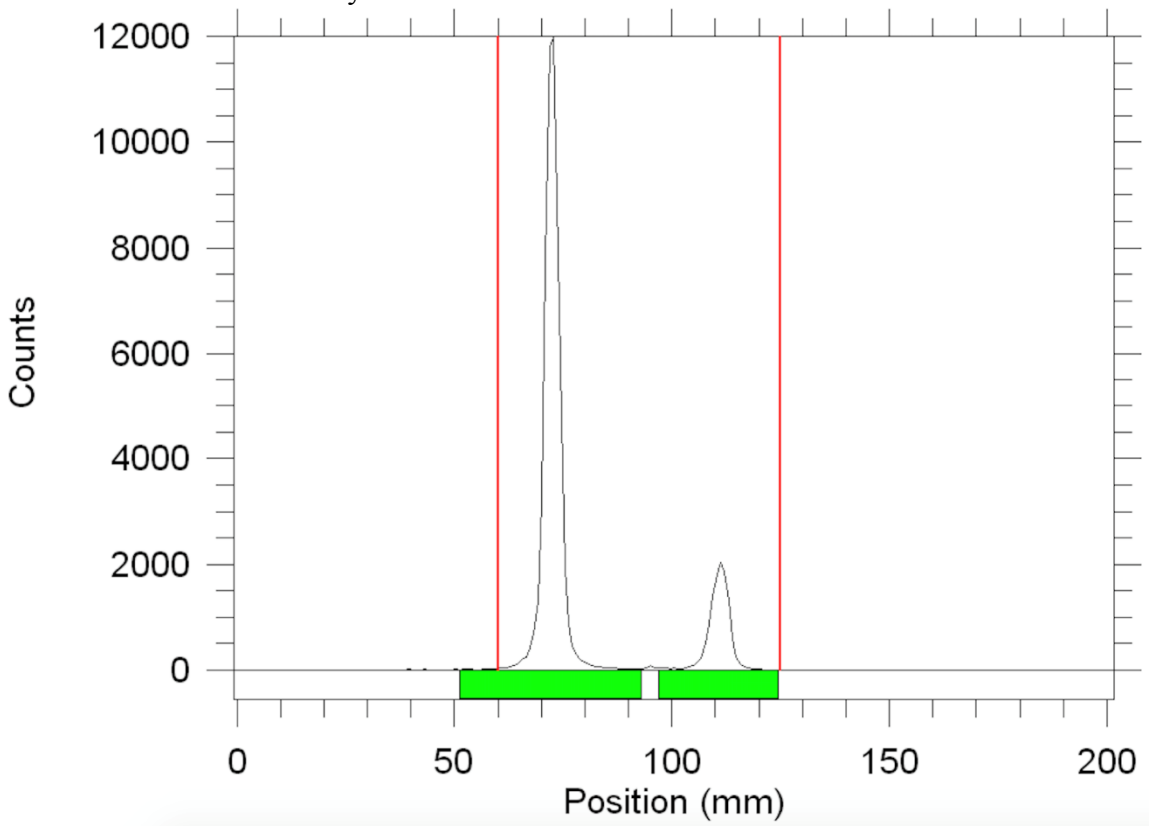
Analytical HPLC trace of **15^{18}F** gamma trace overlaid with UV trace at 254 nm, after spiking with **15F**



2-(Fluoro-^{18}*F*)-5-(5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl)-*N*-(quinolin-8-yl)benzamide (16^{18}F)



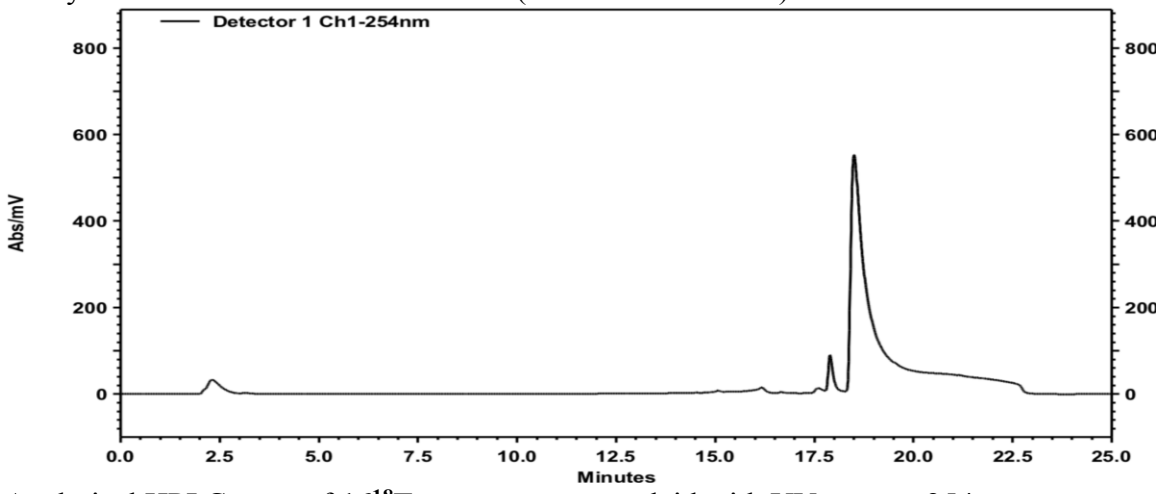
Radio-TLC conditions: Ethyl acetate/hexane = 1/1



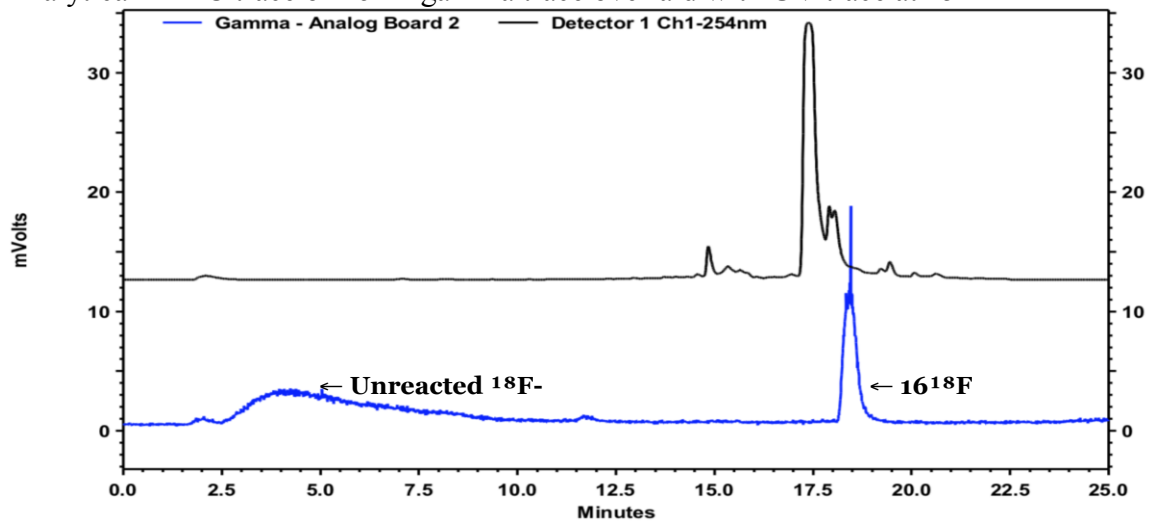
Replicate	Raw RCC (%)
1	17
2	11
3	11
4	12
5	12
Mean	13
Standard deviation	3

HPLC conditions: Condition C

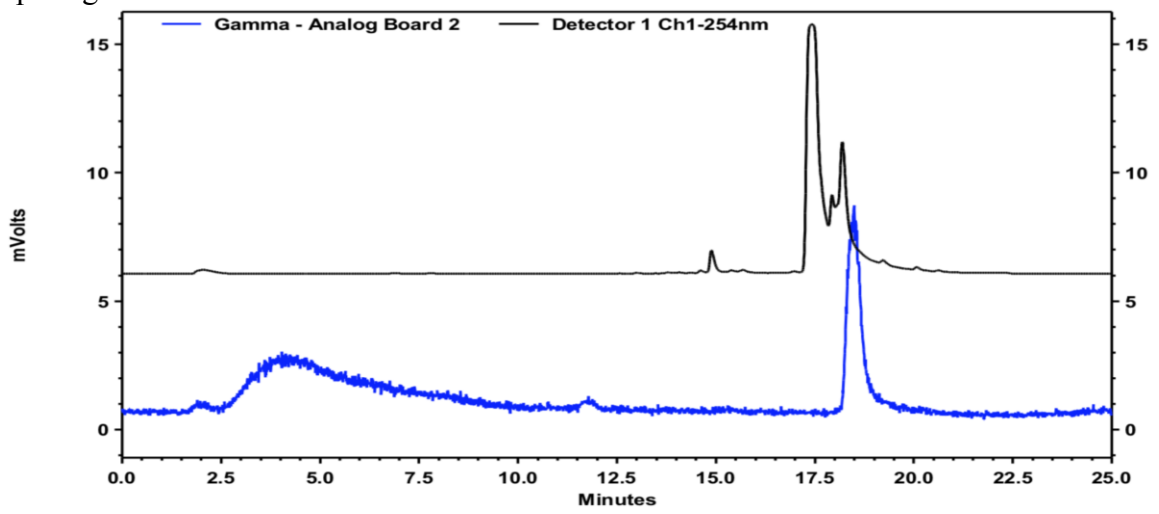
Analytical HPLC trace of **16F** standard (UV trace at 254 nm)



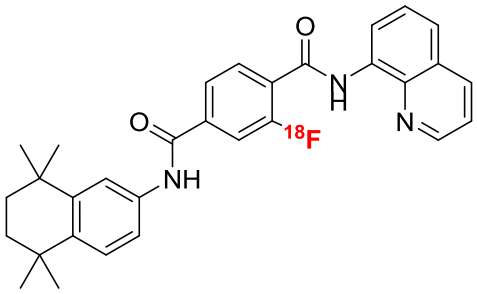
Analytical HPLC trace of **16^{18}F** gamma trace overlaid with UV trace at 254 nm



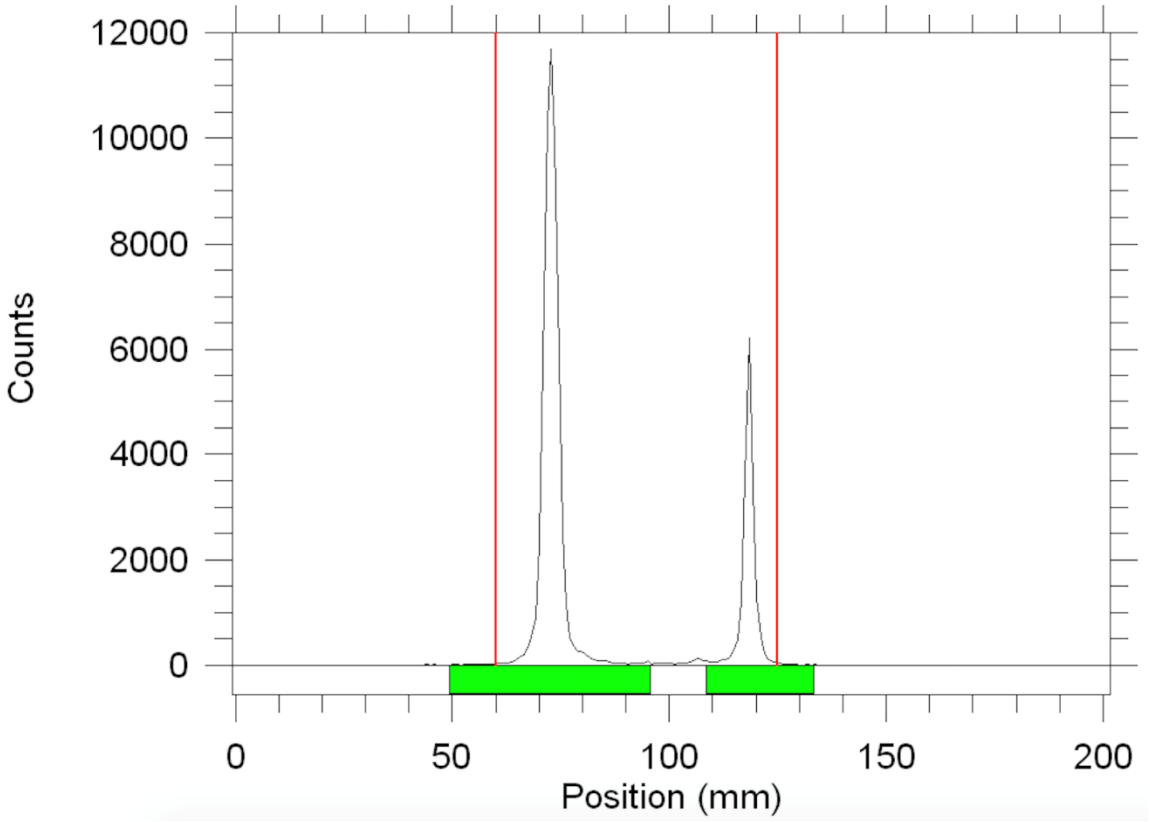
Analytical HPLC trace of **16^{18}F** gamma trace overlaid with UV trace at 254 nm, after spiking with **16F**



2-(Fluoro-^{18}F)-N^1-(quinolin-8-yl)-N^4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)terephthalamide (17^{18}F)



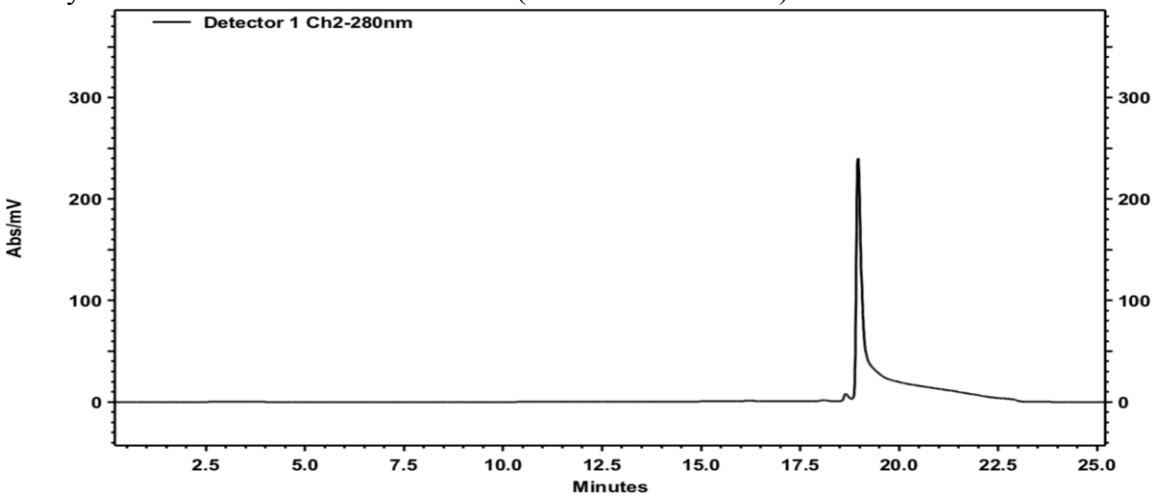
Radio-TLC conditions: Ethyl acetate/hexane = 1/1



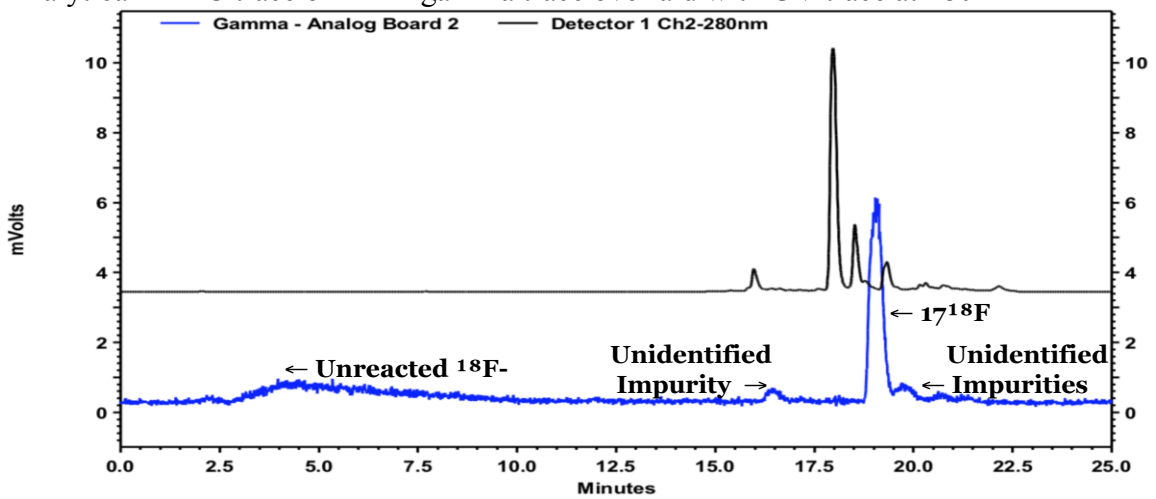
Replicate	Raw RCC (%)
1	21
2	22
3	22
4	22
5	26
Mean	22
Standard deviation	2

HPLC conditions: Condition C

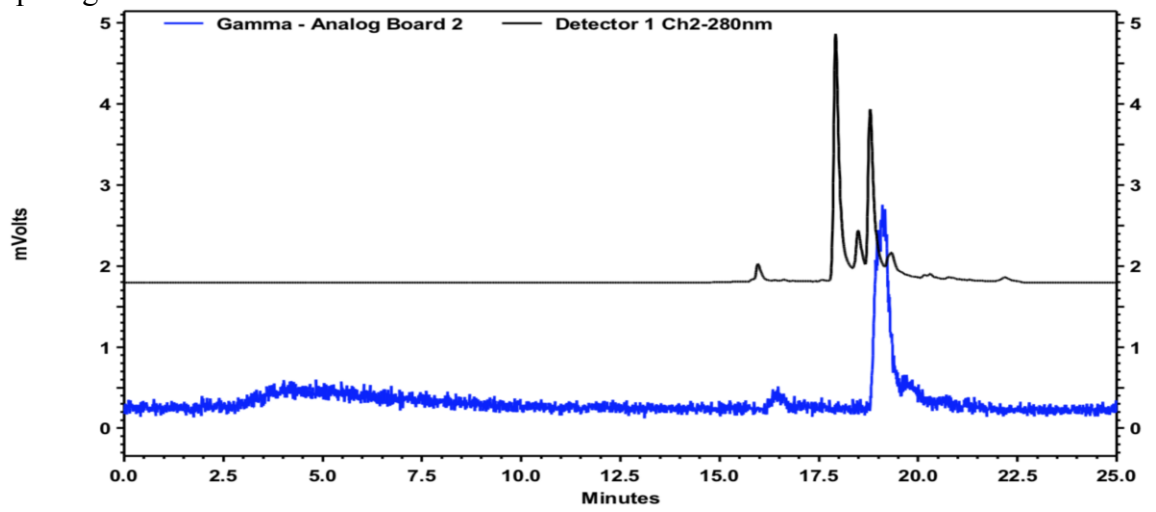
Analytical HPLC trace of **17F** standard (UV trace at 280 nm)



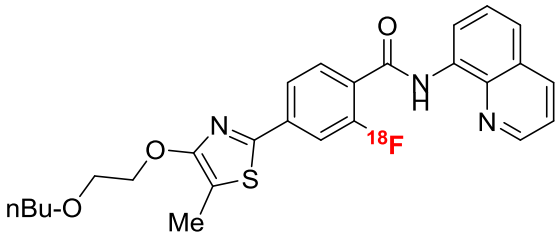
Analytical HPLC trace of **17^{18}F** gamma trace overlaid with UV trace at 280 nm



Analytical HPLC trace of **17^{18}F** gamma trace overlaid with UV trace at 280 nm, after spiking with **17F**

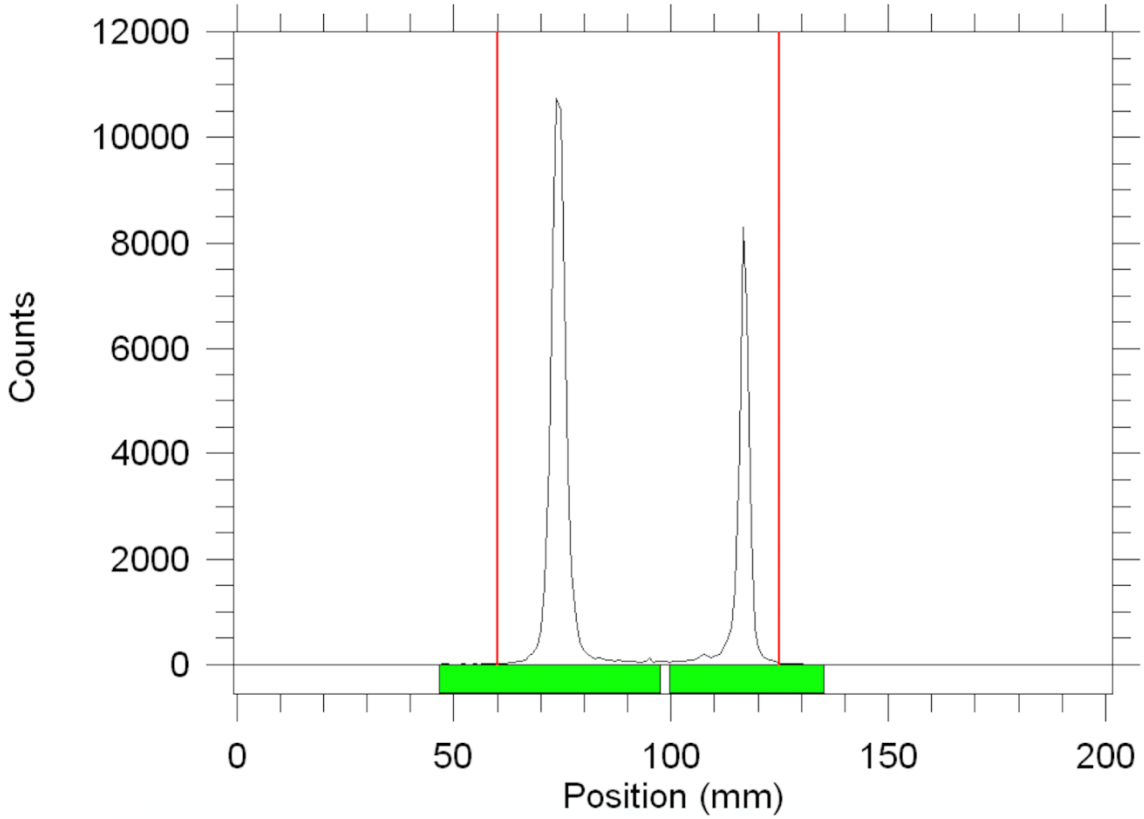


4-(4-(2-Butoxyethoxy)-5-methylthiazol-2-yl)-2-(fluoro-^{18}*F*)-*N*-(quinolin-8-yl)benzamide (18^{18}F)



18^{18}F from manual synthesis

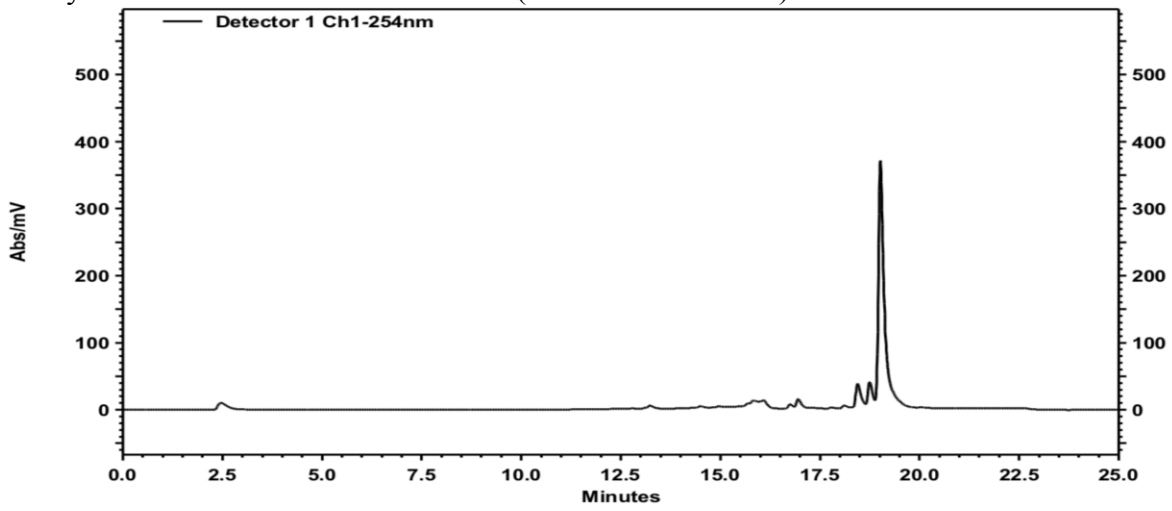
Radio-TLC conditions: Ethyl acetate/hexane = 1/1



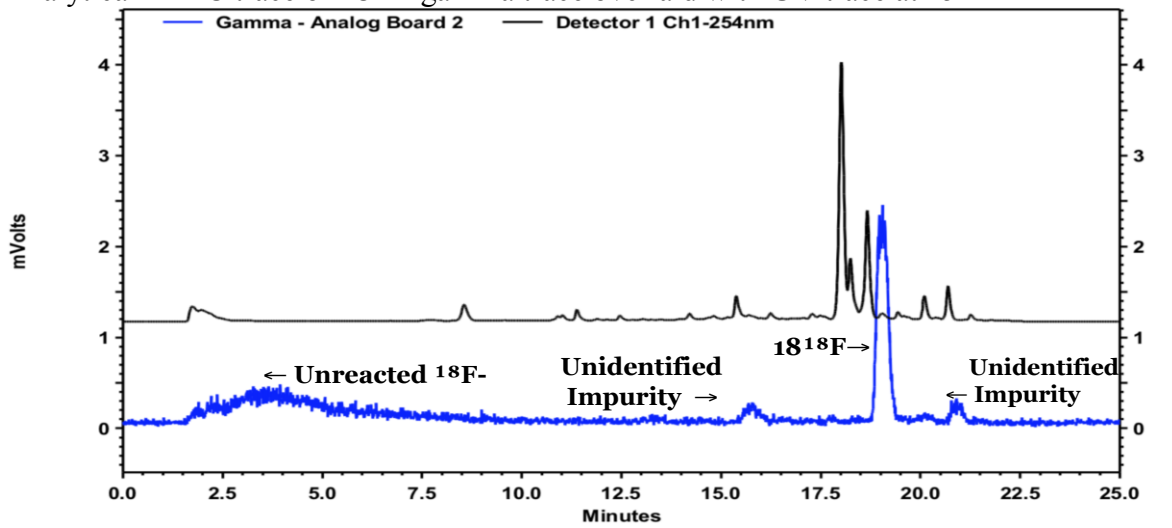
Replicate	Raw RCC (%)
1	38
2	39
3	35
4	39
5	37
6	38
7	35
Mean	37
Standard deviation	2

HPLC conditions: Condition C

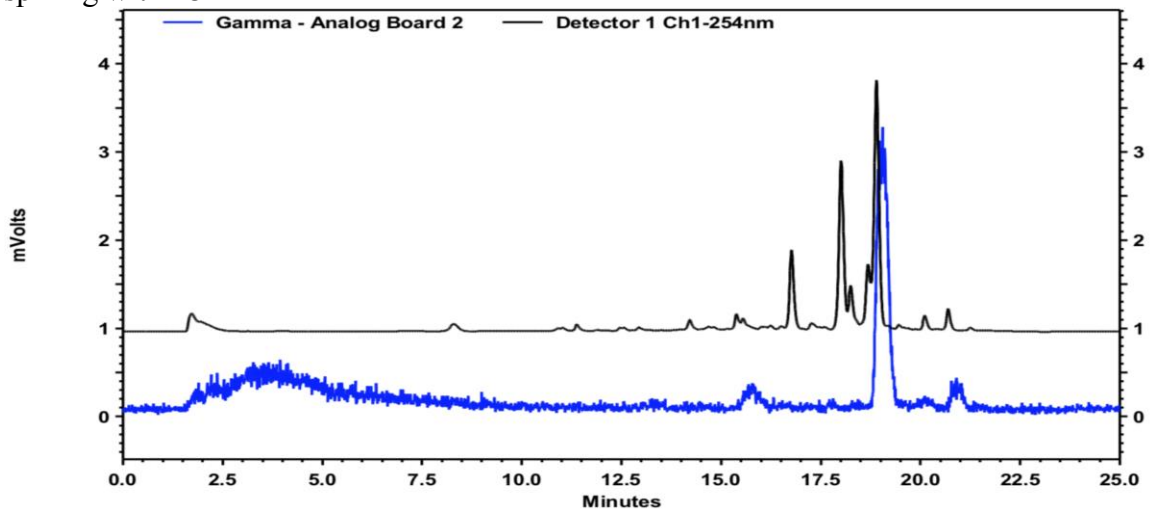
Analytical HPLC trace of **18F** standard (UV trace at 254 nm)



Analytical HPLC trace of **18^{18}F** gamma trace overlaid with UV trace at 254 nm

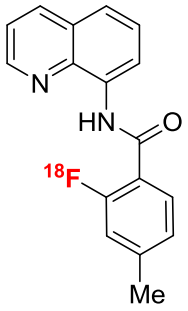


Analytical HPLC trace of **18^{18}F** gamma trace overlaid with UV trace at 254 nm, after spiking with **18F**



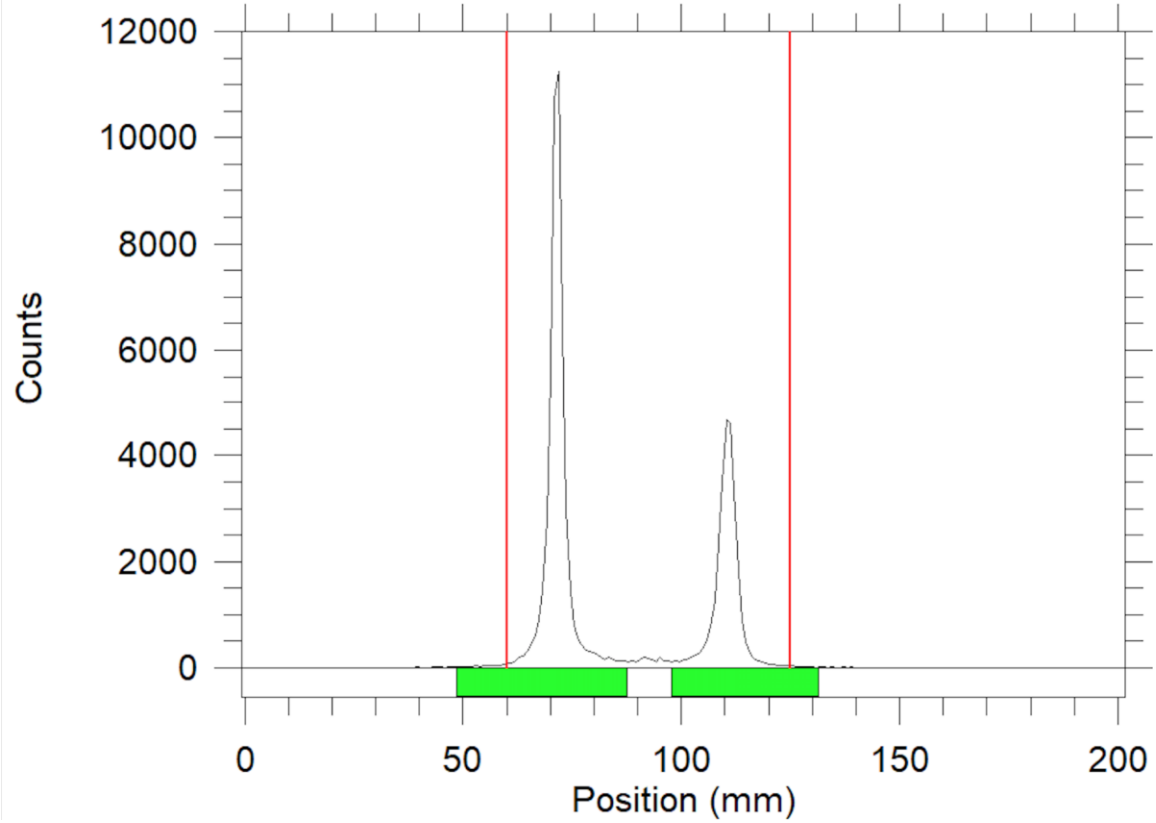
6.2 Automated syntheses of $1^{18}F$ and $18^{18}F$

2-(Fluoro-^{18}F)-4-methyl-*N*-(quinolin-8-yl)benzamide ($1^{18}F$)



Automated synthesis of $1^{18}F$ without purification

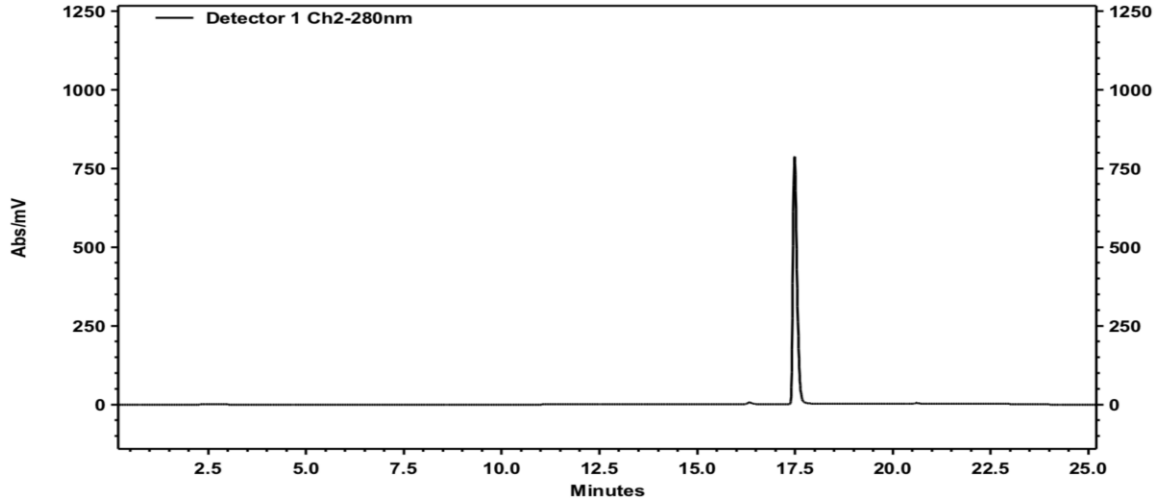
Radio-TLC conditions: Ethyl acetate/hexane = 1/1



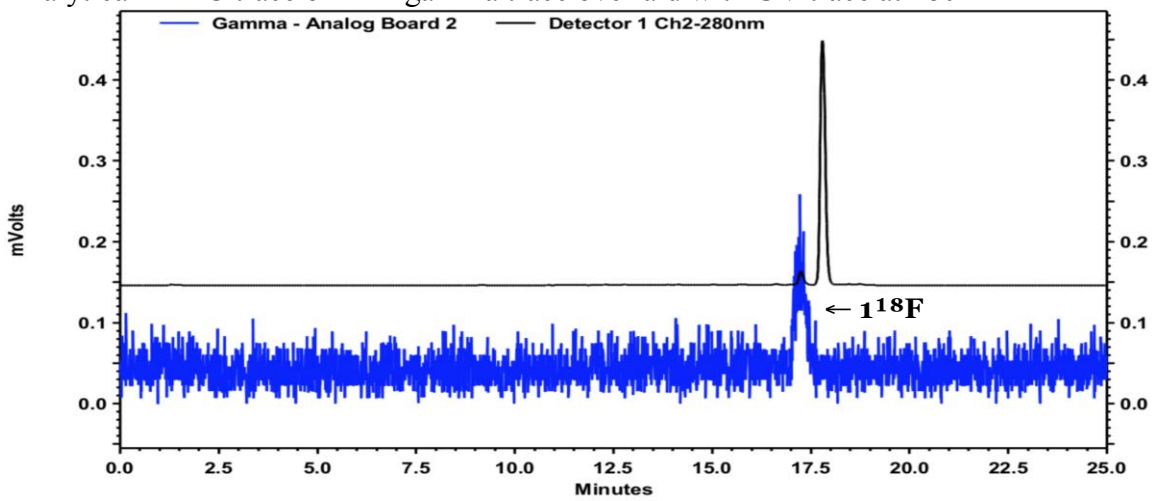
Replicate	Raw RCC (%)
1	36
2	30
3	31
4	25
5	24
6	20
Mean	28
Standard deviation	6

HPLC condition: Condition C

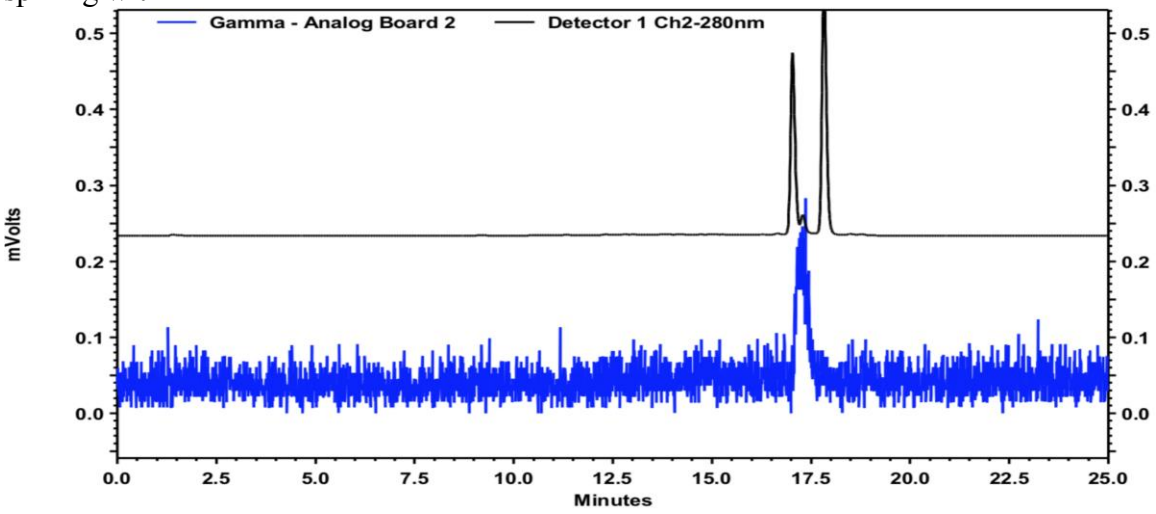
Analytical HPLC trace of **1F** standard (UV trace at 280 nm)



Analytical HPLC trace of **1^{18}F** gamma trace overlaid with UV trace at 280 nm

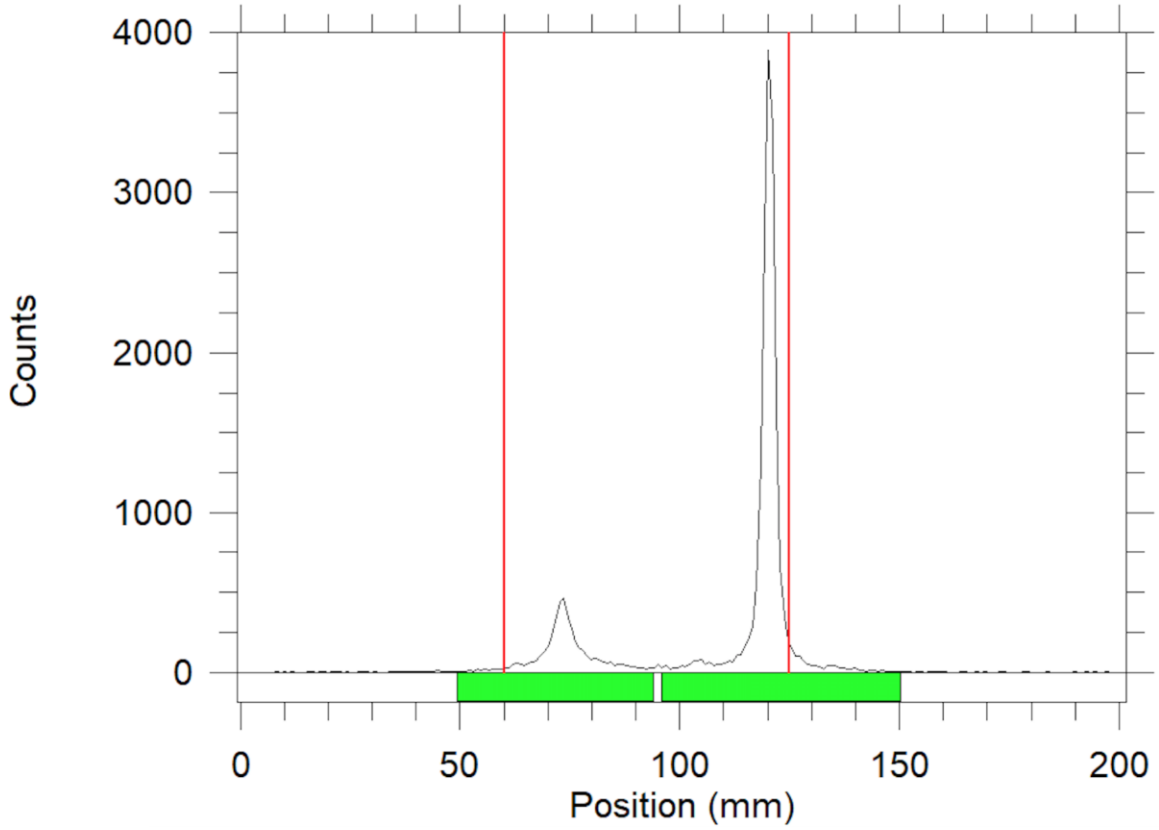


Analytical HPLC trace of **1^{18}F** gamma trace overlaid with UV trace at 280 nm, after spiking with **1F**



Automated synthesis of 1[18]F followed by SepPak purification

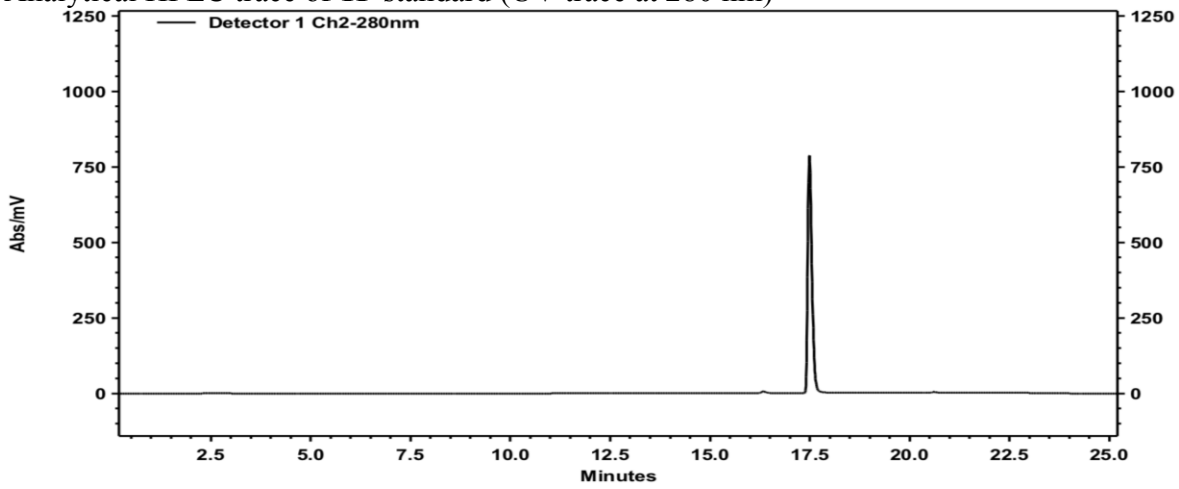
Radio-TLC conditions: Ethyl acetate/hexane = 1/1



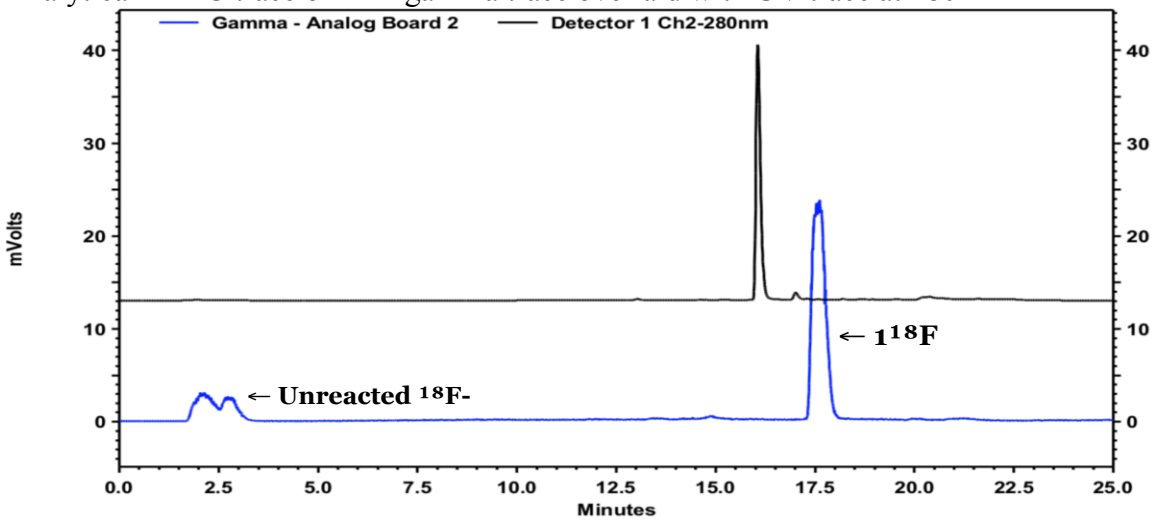
Replicate	Raw RCP (%)
1	84
2	85
3	81
Mean	83
Standard deviation	2

HPLC condition: Condition C

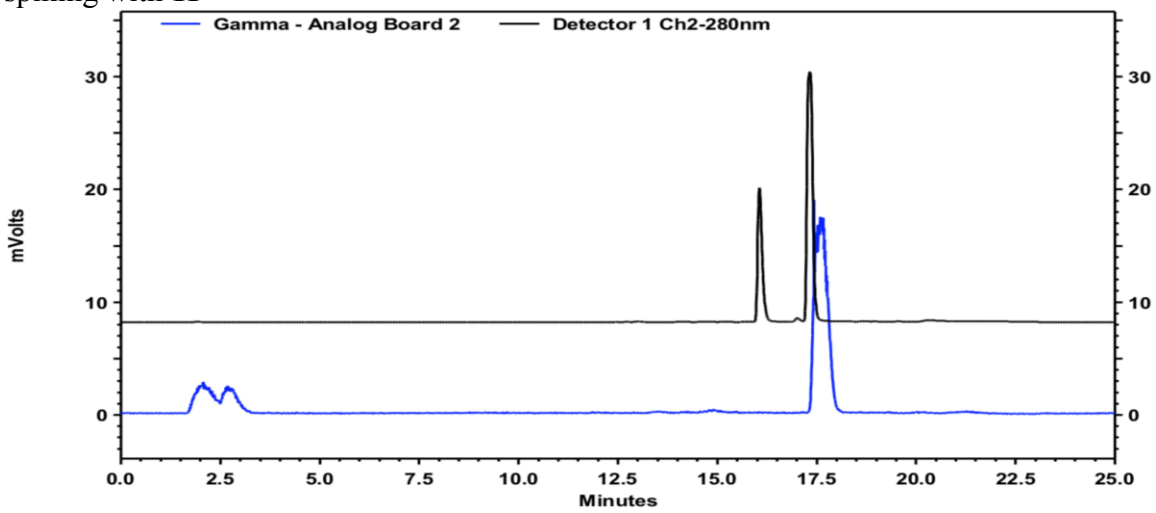
Analytical HPLC trace of **1F** standard (UV trace at 280 nm)



Analytical HPLC trace of **1^{18}F** gamma trace overlaid with UV trace at 280 nm

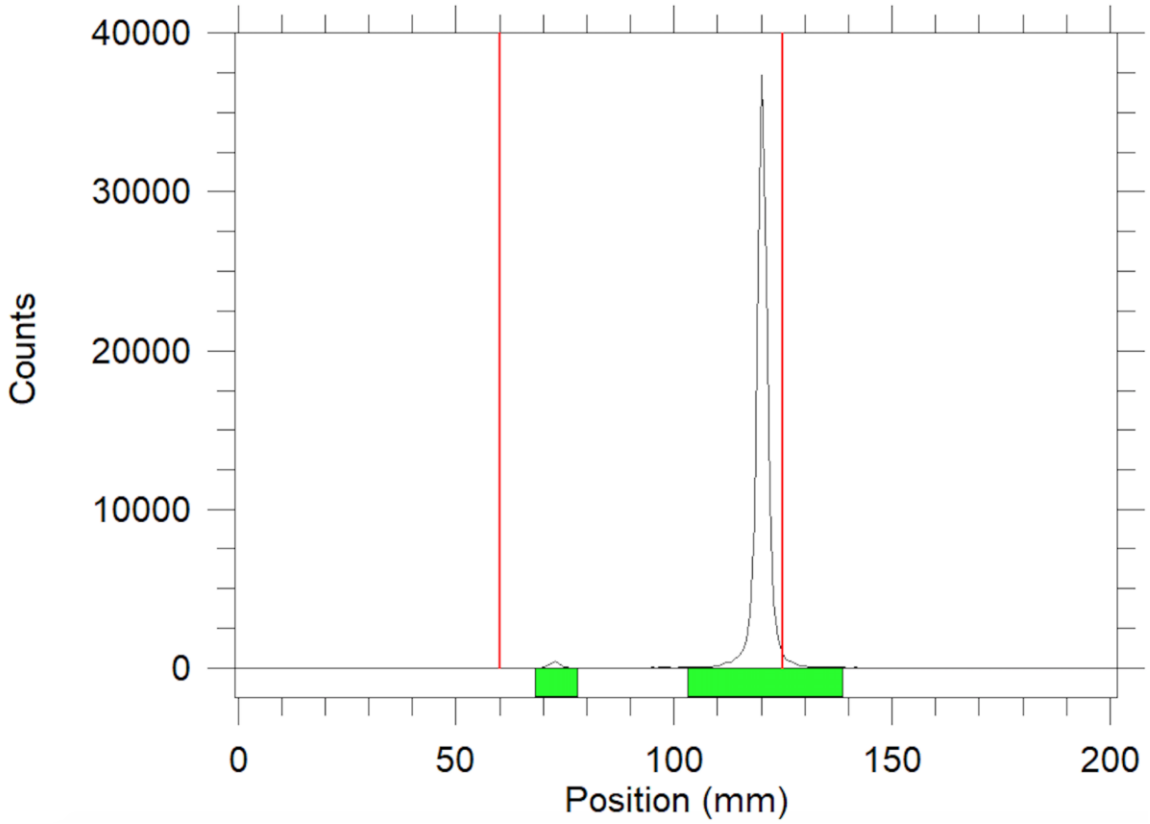


Analytical HPLC trace of **1^{18}F** gamma trace overlaid with UV trace at 280 nm, after spiking with **1F**



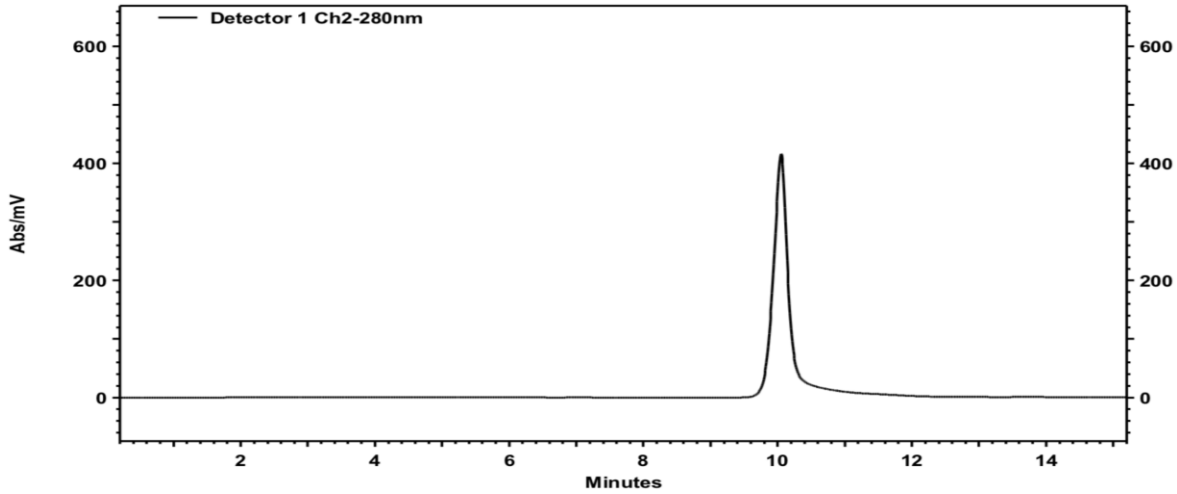
Automated synthesis of 1^{18}F followed by HPLC purification

Radio-TLC conditions: Ethyl acetate/hexane = 1/1

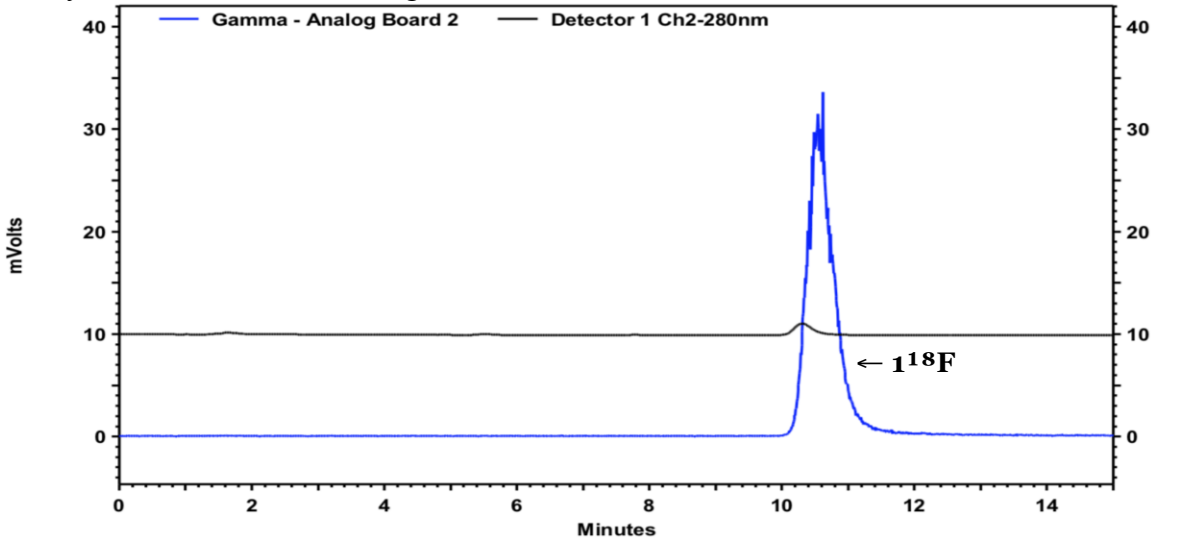


Replicate	Raw RCP (%)
1	99
2	97
3	98
Mean	98
Standard deviation	1

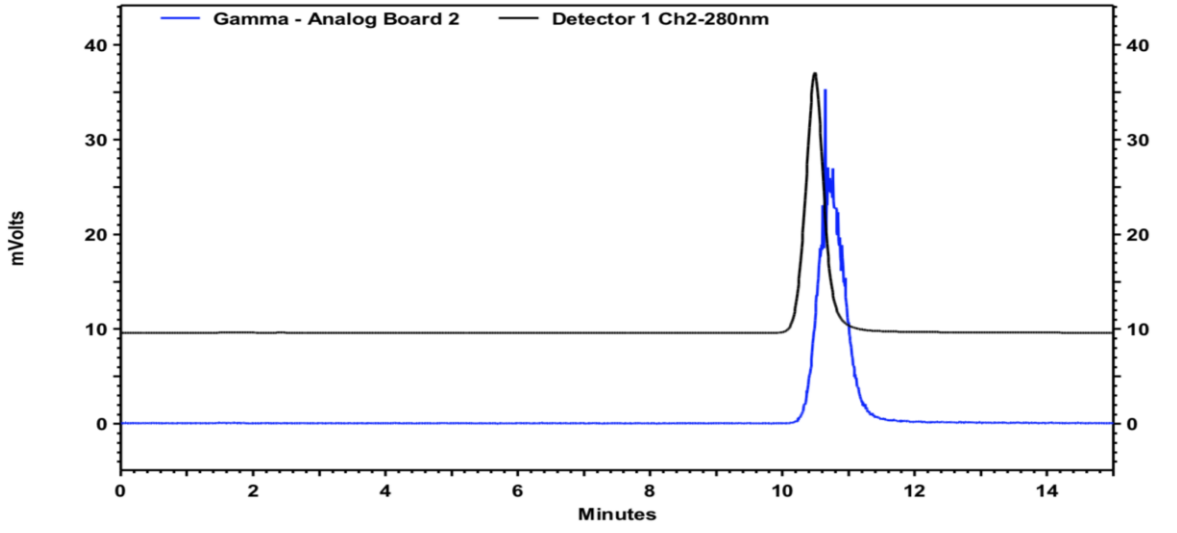
Analytical HPLC trace of **1F** standard (UV trace at 280 nm)



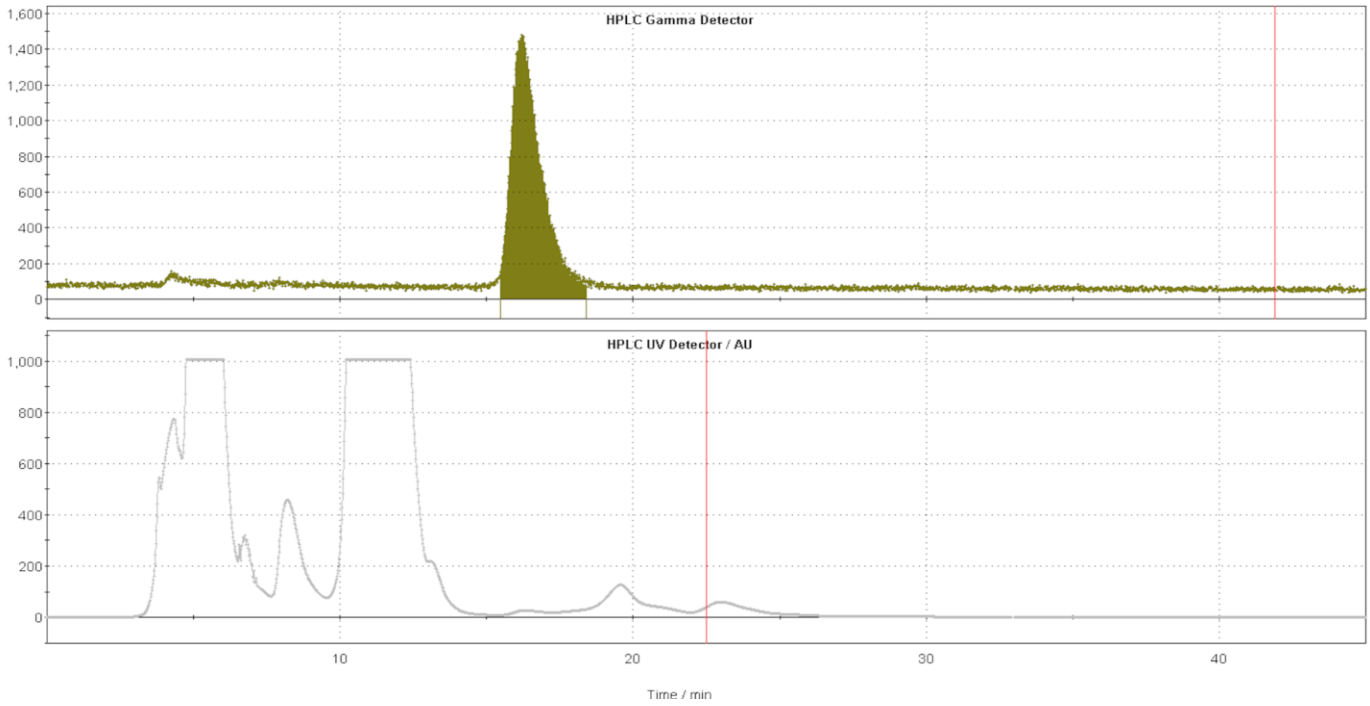
Analytical HPLC trace of **1**^{18}**F** gamma trace overlaid with UV trace at 280 nm



Analytical HPLC trace of **1**^{18}**F** gamma trace overlaid with UV trace at 280 nm, after spiking with **1F**

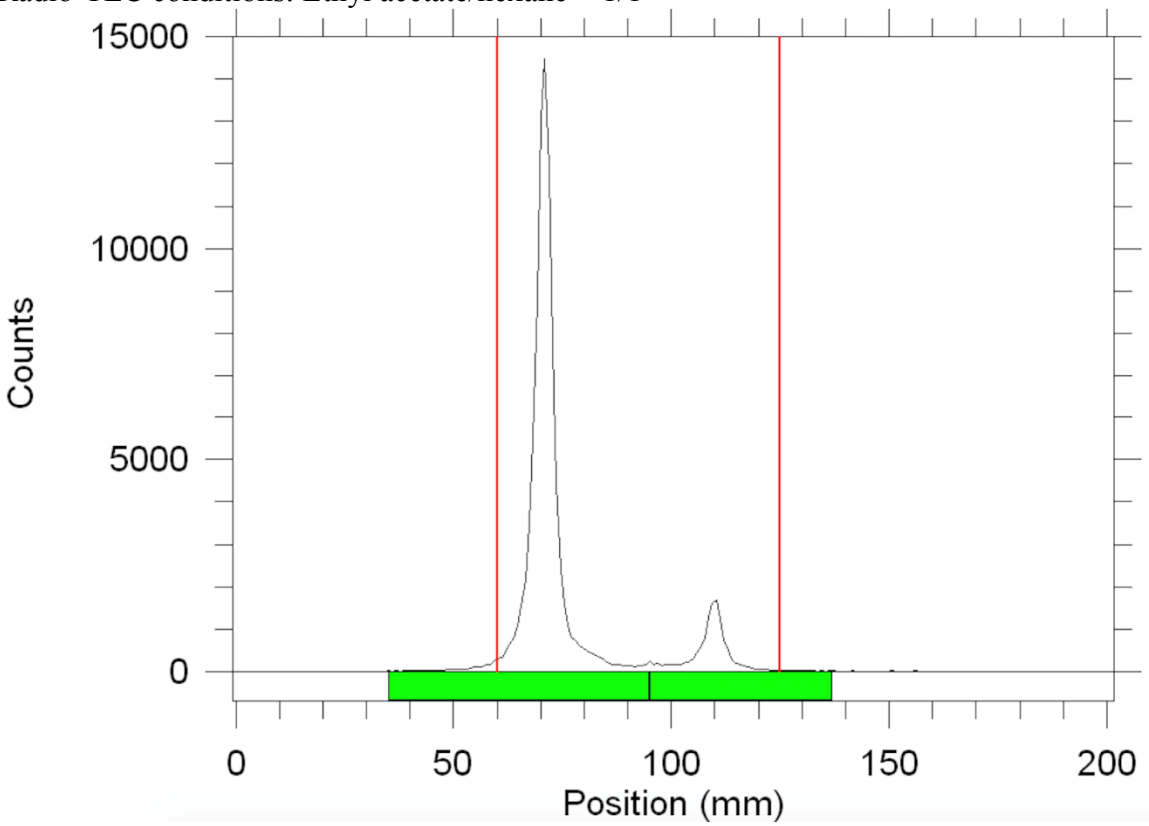


Semi-preparative HPLC trace of **1**^{18}**F**
HPLC conditions: Condition D
The peak including **1**^{18}**F** (R_T: 16 min, colored peak) was collected for analysis.



18^{18}F from automated synthesis without purification

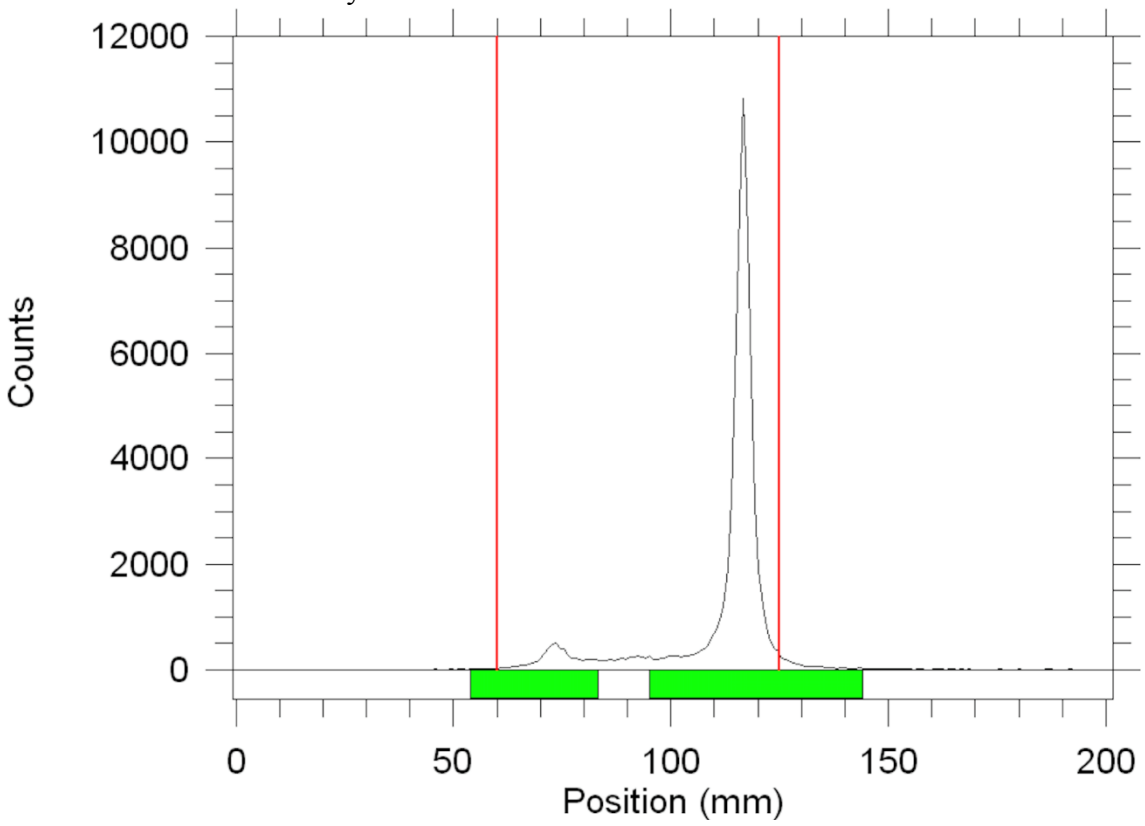
Radio-TLC conditions: Ethyl acetate/hexane = 1/1



Replicate	Raw RCC (%)
1	12
2	14
3	10
Mean	12
Standard deviation	2

18^{18}F from automated synthesis followed by Sep-Pak purification

Radio-TLC conditions: Ethyl acetate/hexane = 1/1

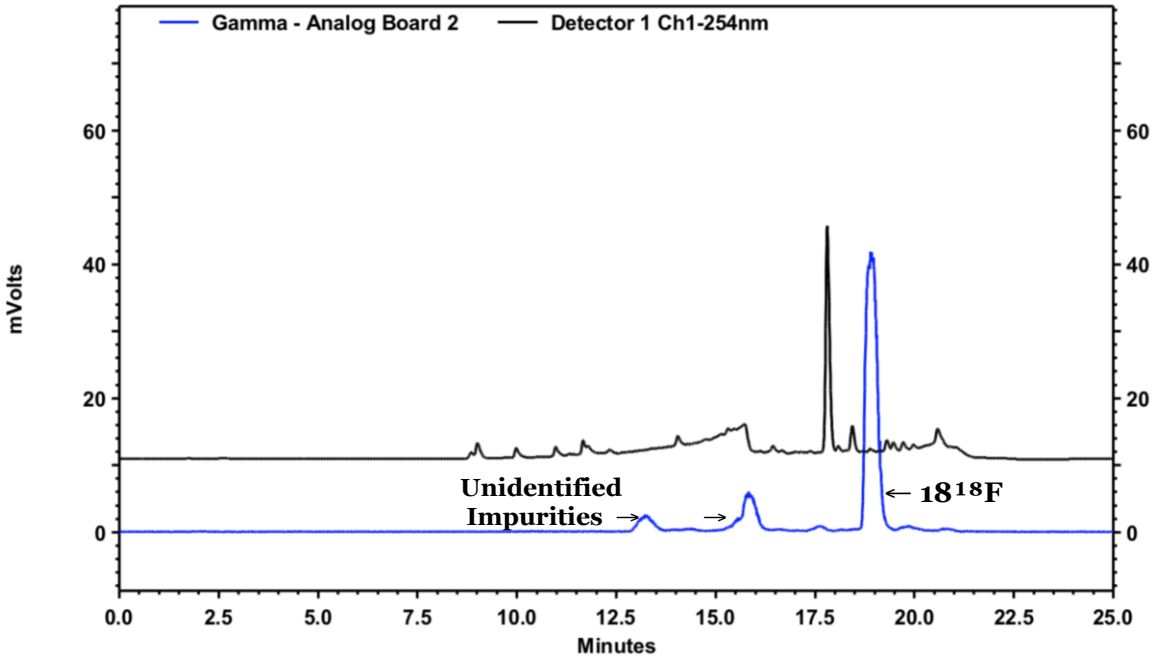


Replicate	Raw RCP (%)	Corrected RCP[a] (%)
1	100	74
2	97	72
3	97	72
4	96	71
5	99	73
Mean	98	72
Standard deviation	1	1

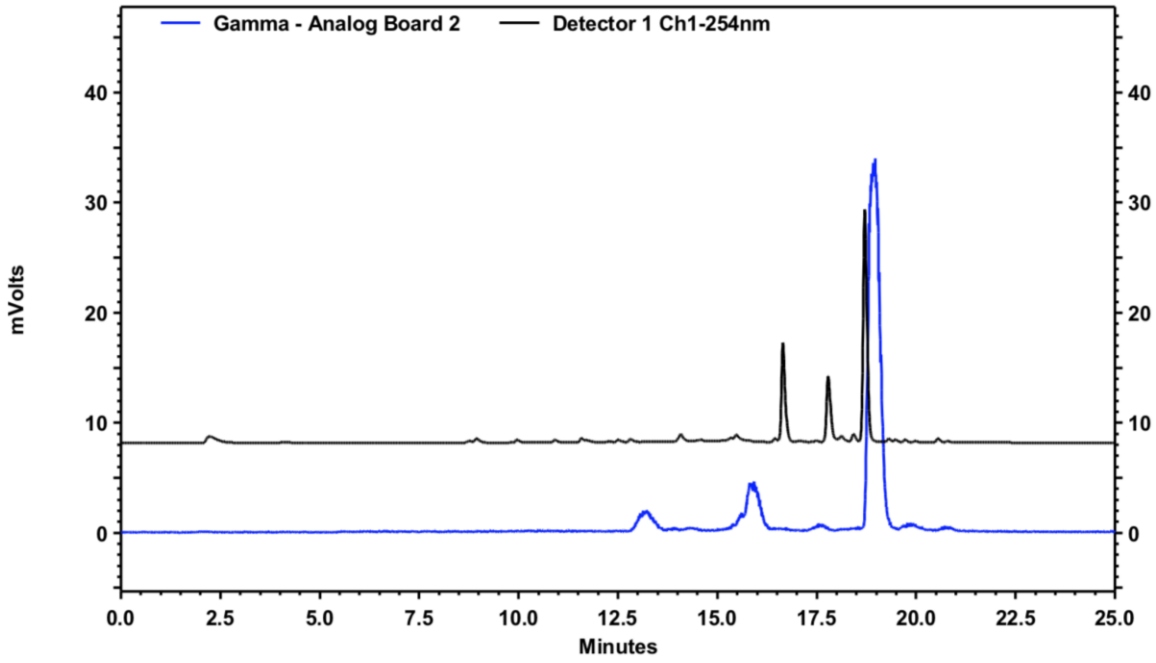
[a]Corrected RCC based on radio-analytical HPLC. The detailed procedure for corrected RCC is described in SI section 4.2.1 Manual synthesis general procedure.

HPLC conditions: Condition C

Analytical HPLC trace of **18^{18}F** gamma trace overlaid with UV trace at 254 nm

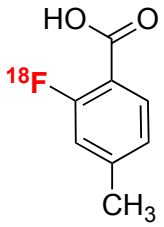


Analytical HPLC trace of **18^{18}F** gamma trace overlaid with UV trace at 254 nm, after spiking with **18F**



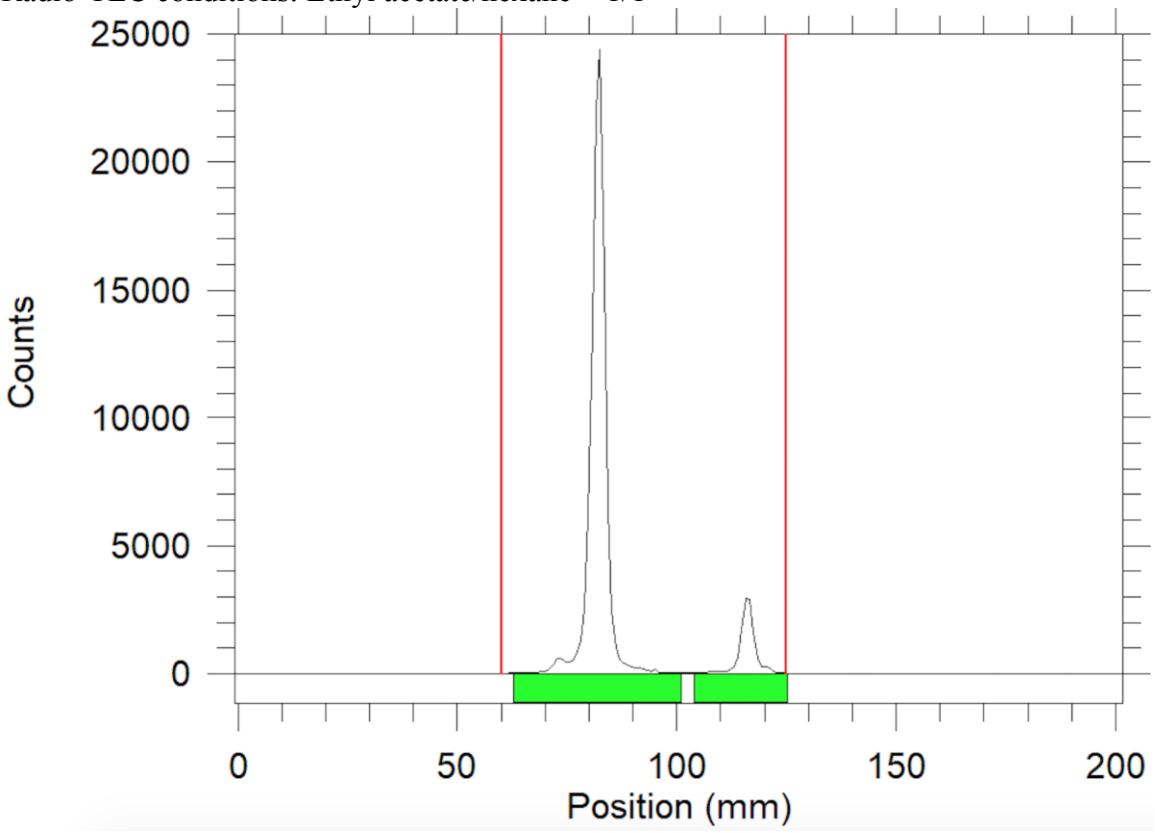
6.3 Hydrolysis studies to prepare $19^{18}F$ and $20^{18}F$

2-(fluoro-^{18}F)-4-methylbenzoic acid ($19^{18}F$)



$19^{18}F$ (from $1^{18}F$)

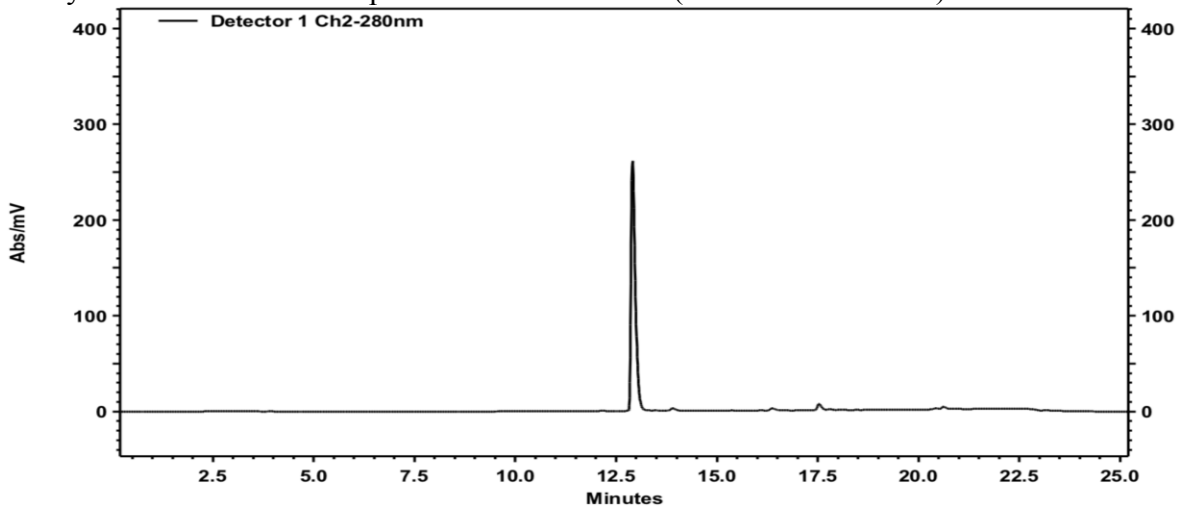
Radio-TLC conditions: Ethyl acetate/hexane = 1/1



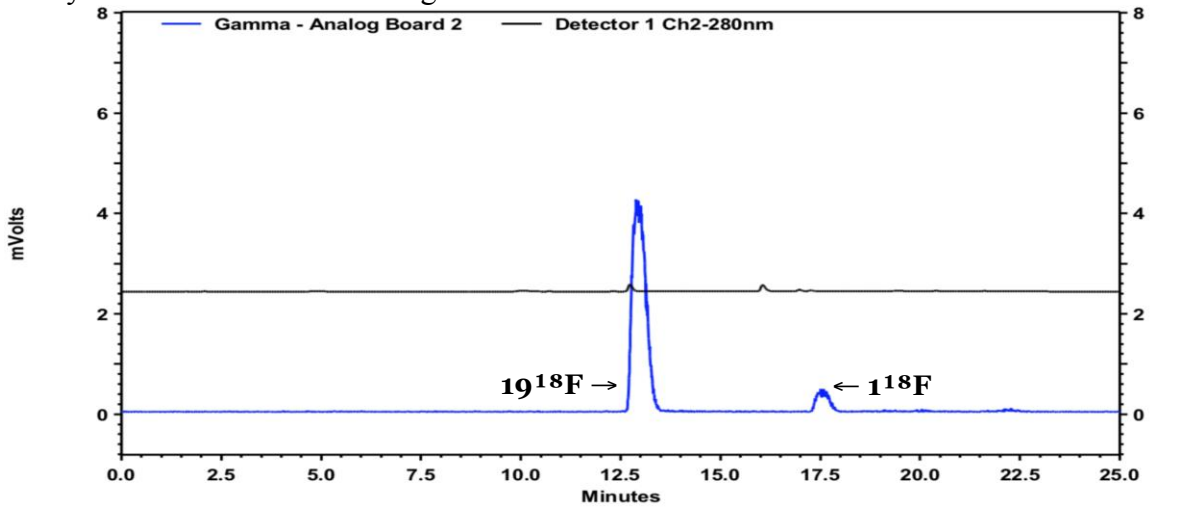
Replicate	Raw RCP (%)
1	90
2	89
3	91
Mean	90
Standard deviation	1

HPLC condition: Condition C

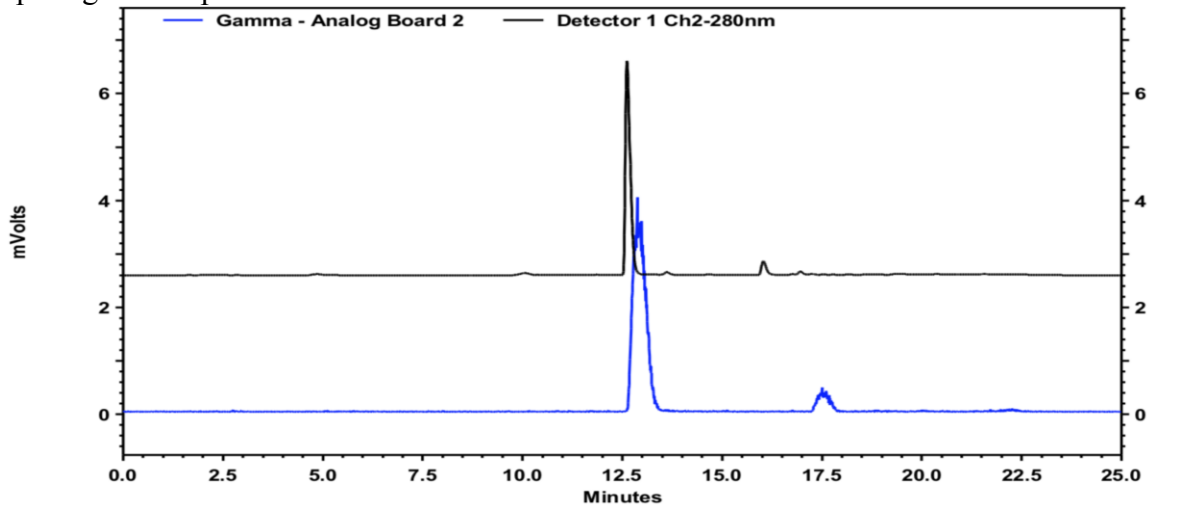
Analytical HPLC trace of deprotected **19F** standard (UV trace at 280 nm)



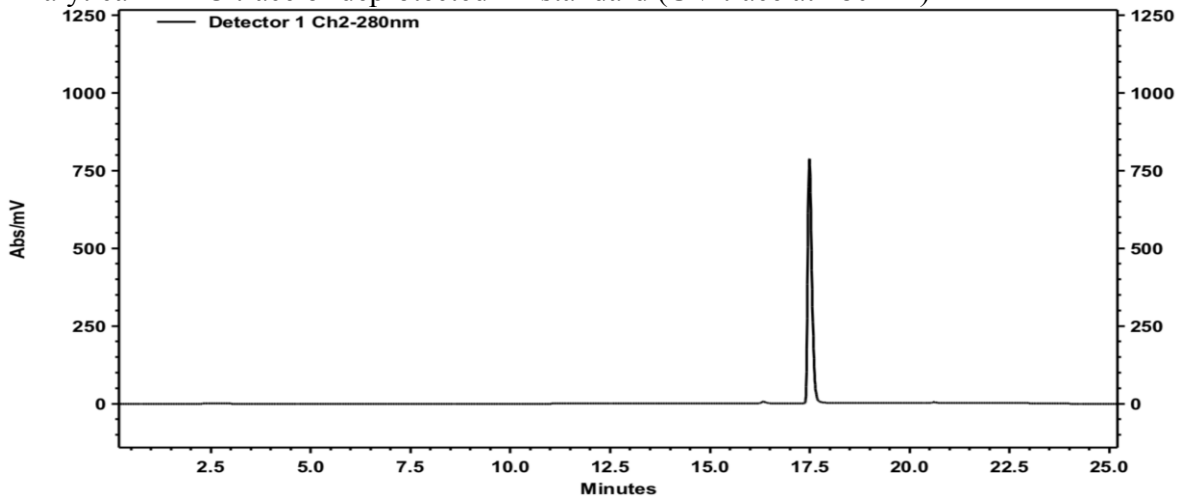
Analytical HPLC trace of **19^{18}F** gamma trace overlaid with UV trace at 280 nm



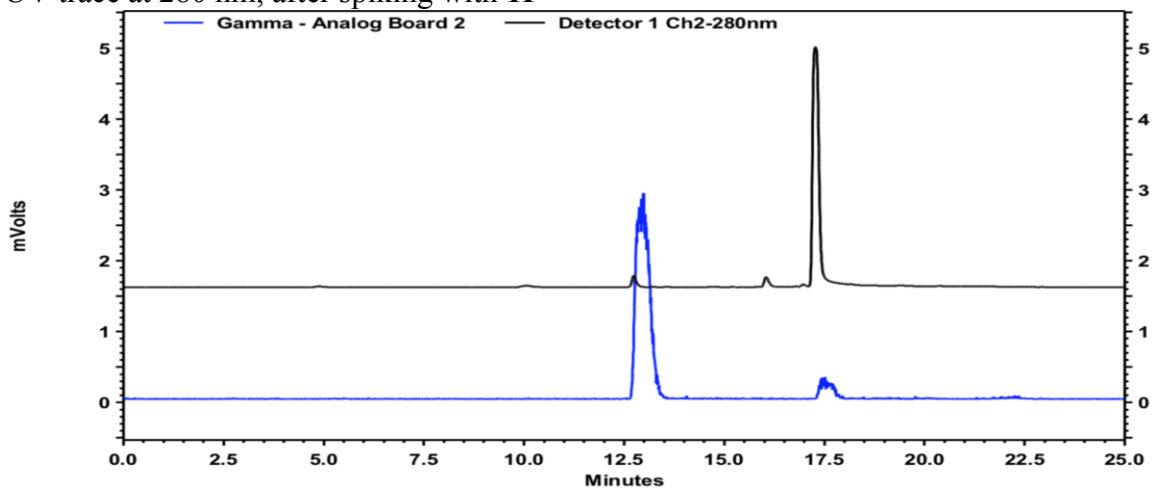
Analytical HPLC trace of **19^{18}F** gamma trace overlaid with UV trace at 280 nm, after spiking with deprotected **19F**



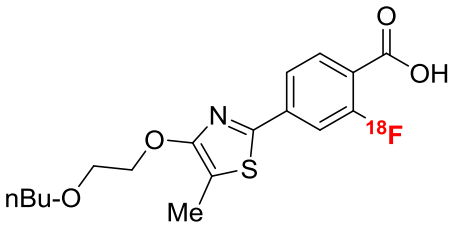
Analytical HPLC trace of deprotected **1F** standard (UV trace at 280 nm)



Analytical HPLC trace of **19^{18}F** containing unreacted **1^{18}F** gamma trace overlaid with UV trace at 280 nm, after spiking with **1F**

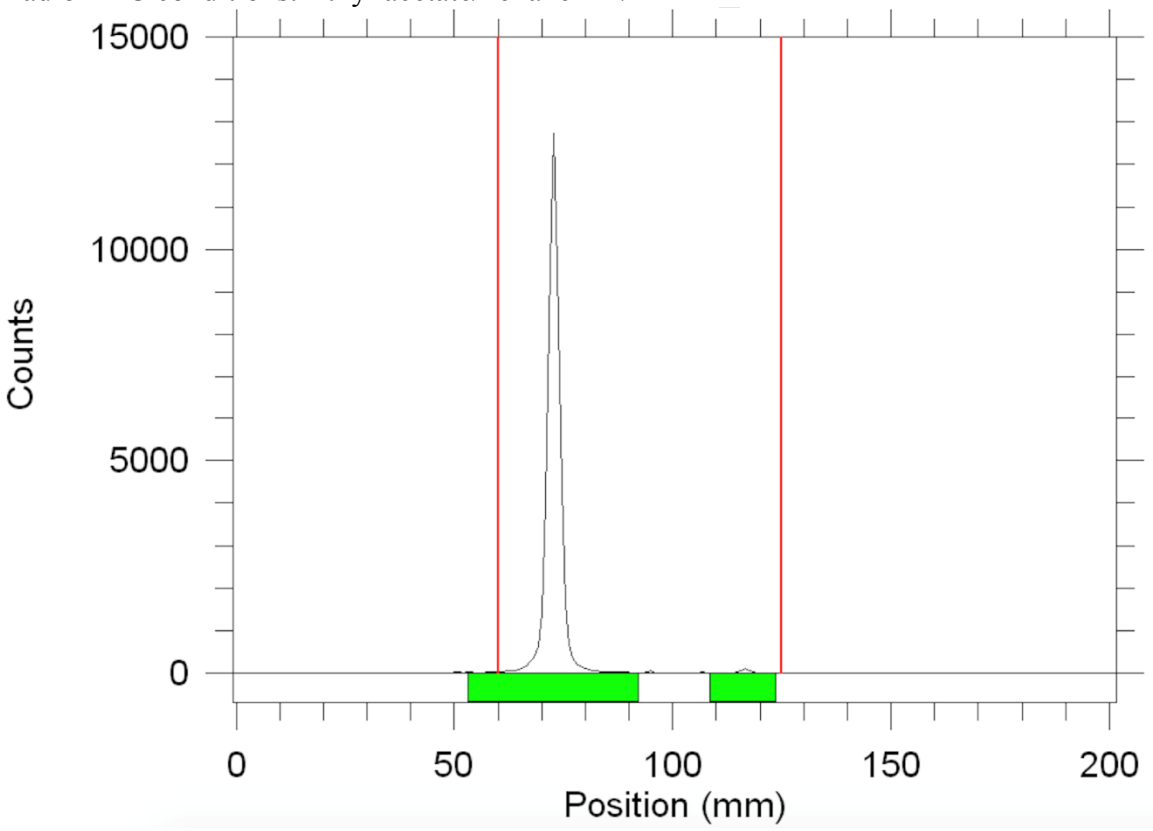


4-(4-(2-Butoxyethoxy)-5-methylthiazol-2-yl)-2-(fluoro-^{18}*F*)benzoic acid (20^{18}F)



20^{18}F (from 18^{18}F)

Radio-TLC conditions: Ethyl acetate/hexane = 1/1

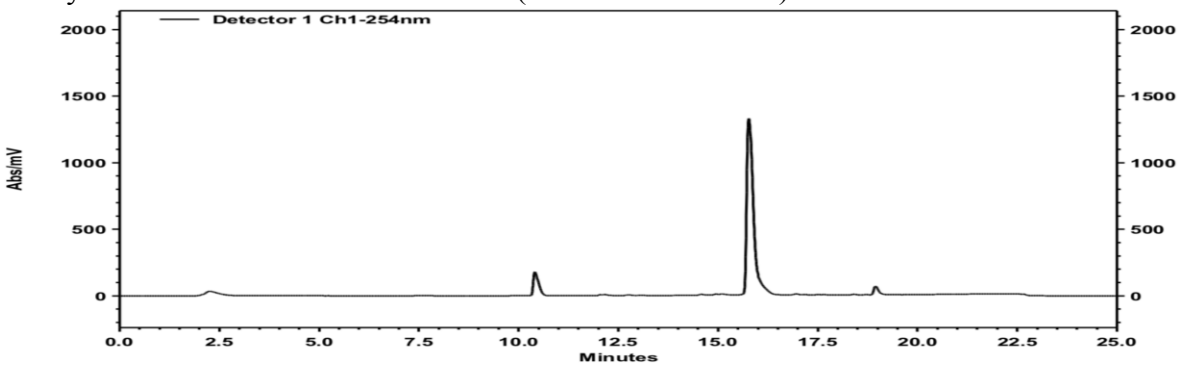


Replicate	Raw RCC[a] (%)
1	100
2	97
3	97
4	96
5	99
Mean	98
Standard deviation	1

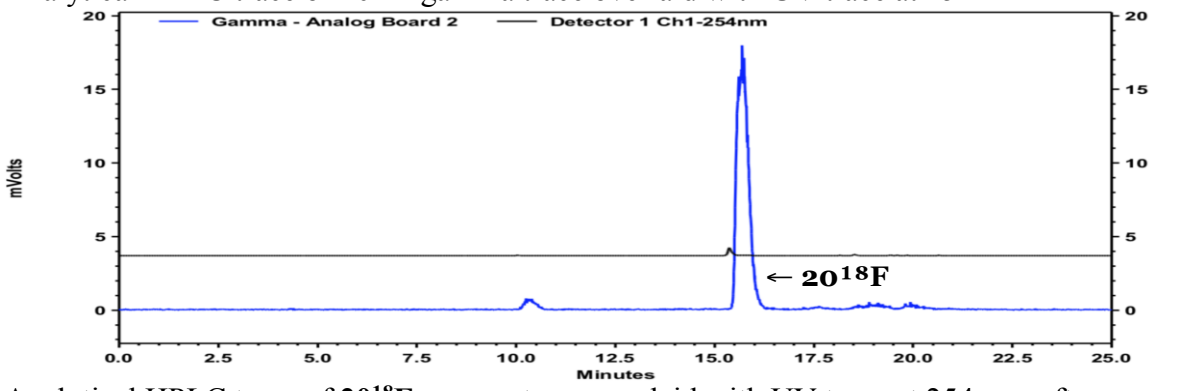
[a]RCC of **20^{18}F** from **18^{18}F**

HPLC conditions: Condition C

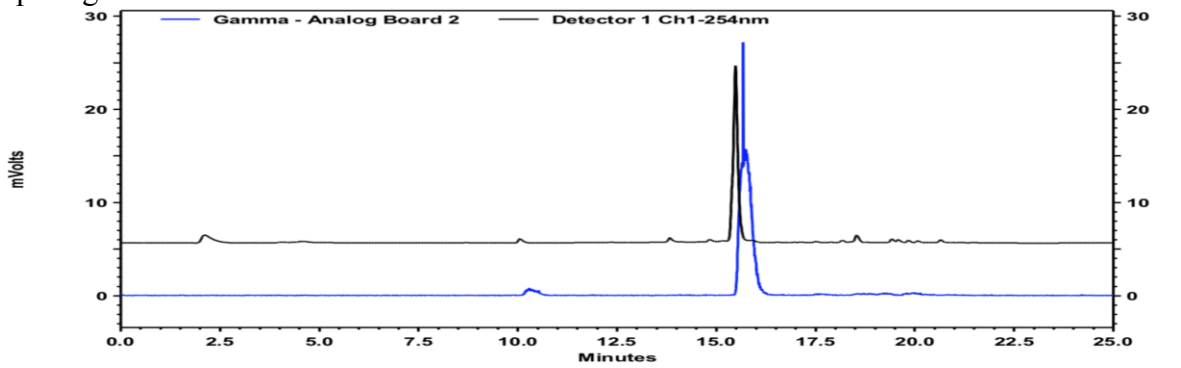
Analytical HPLC trace of **20F** standard (UV trace at 254 nm)



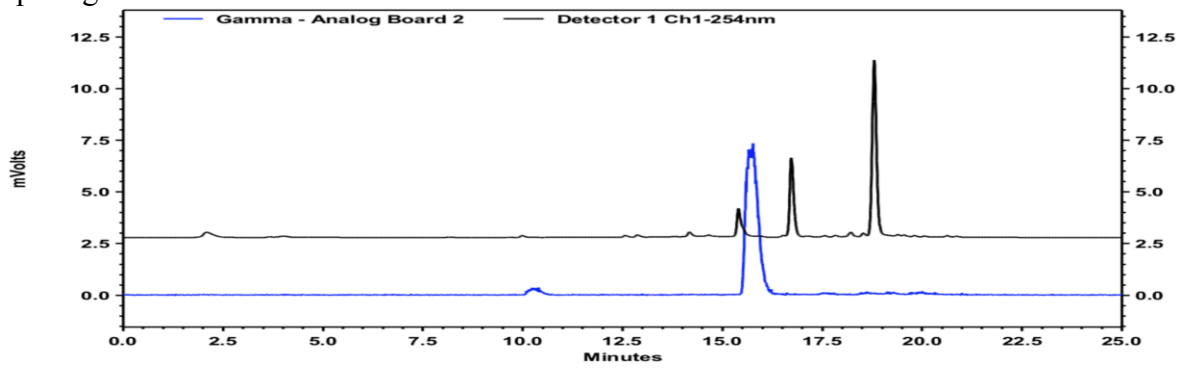
Analytical HPLC trace of **20^{18}F** gamma trace overlaid with UV trace at 254 nm



Analytical HPLC trace of **20^{18}F** gamma trace overlaid with UV trace at 254 nm, after spiking with **20F**

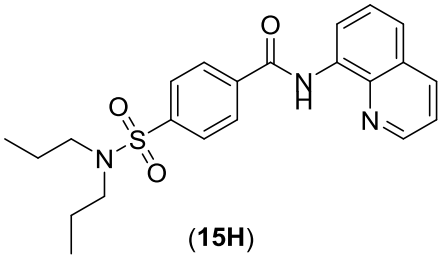


Analytical HPLC trace of **20^{18}F** gamma trace overlaid with UV trace at 254 nm, after spiking with **18F**



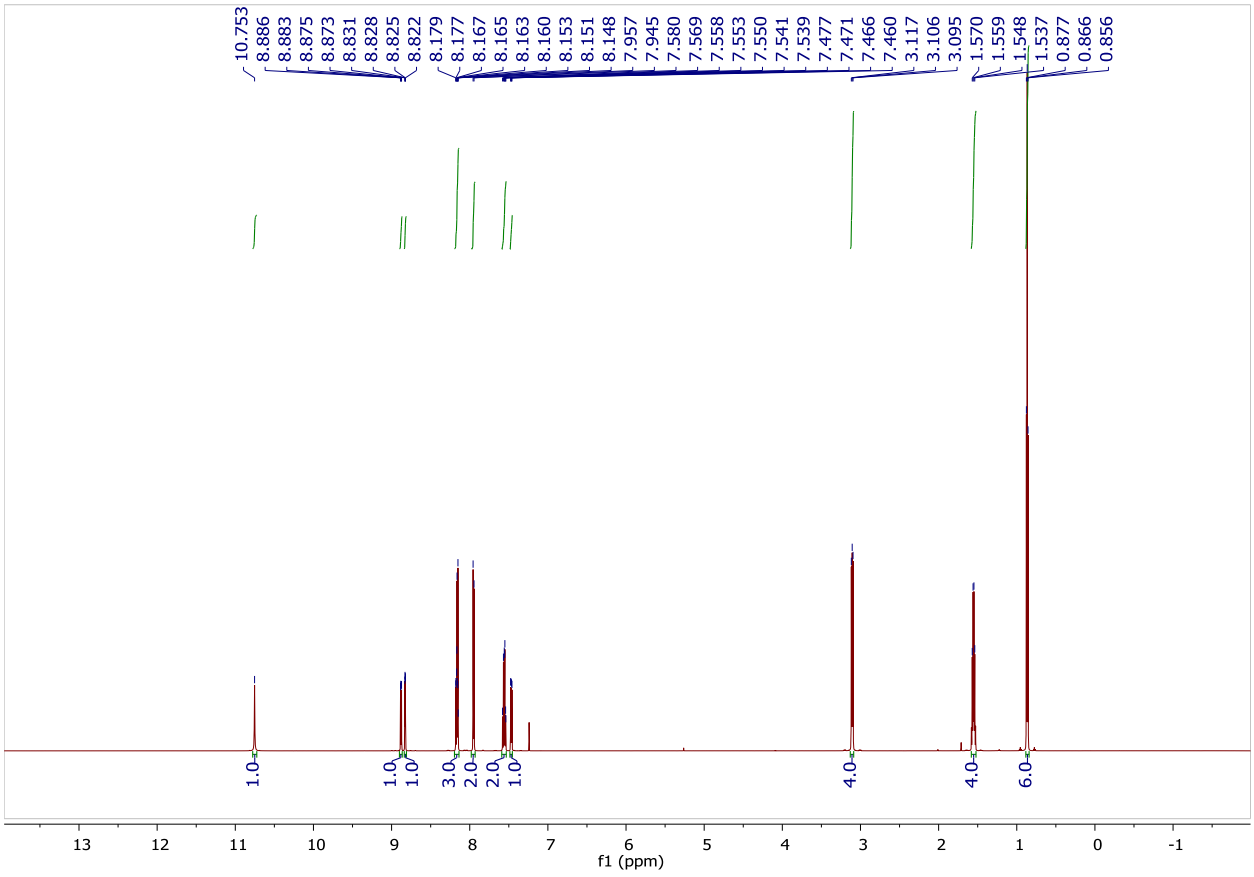
7. Spectral Data (^{1}H, ^{13}C, and ^{19}F NMR)

7.1 Precursors

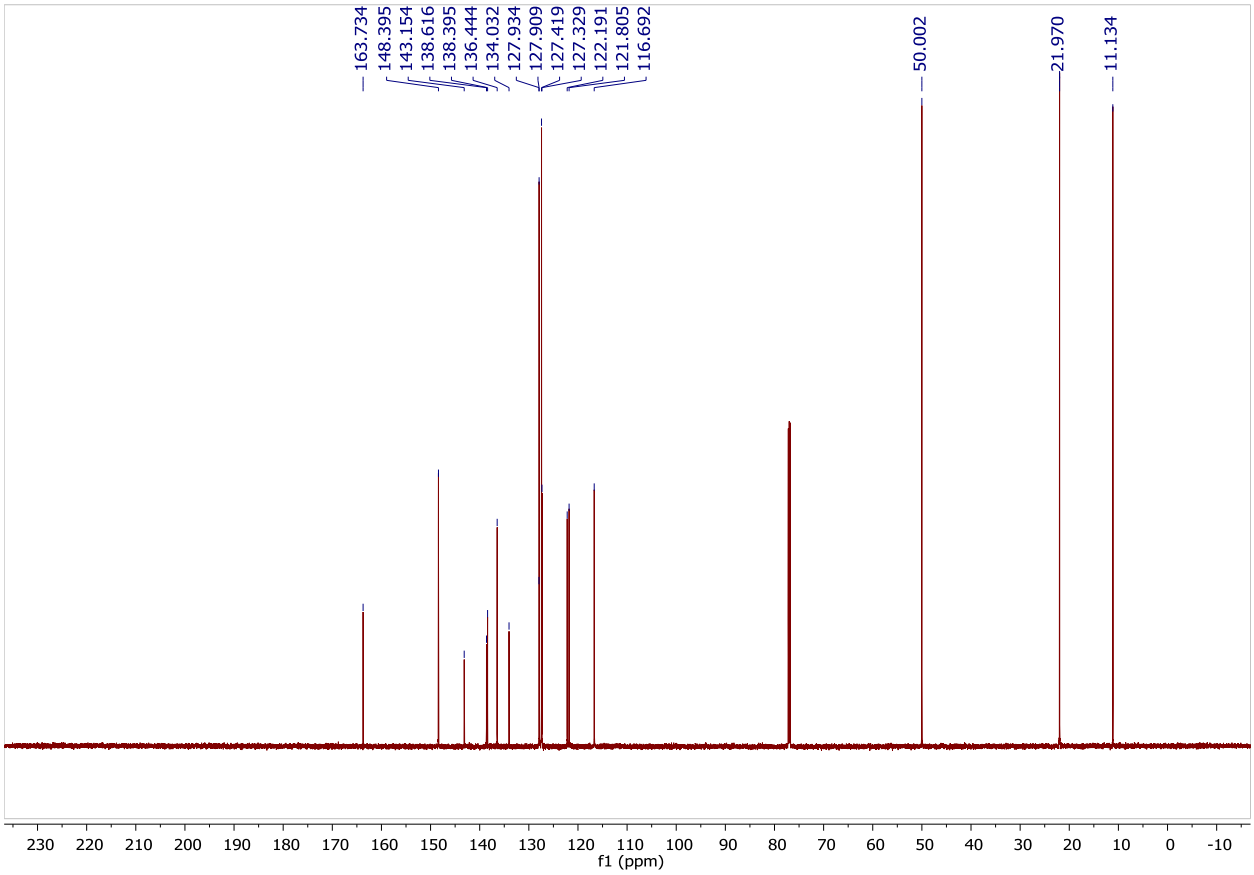


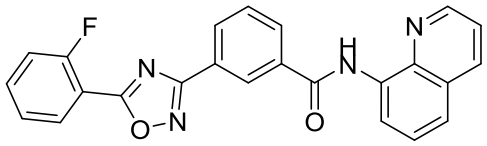
(**15H**)

^{1}H NMR of **15H**:



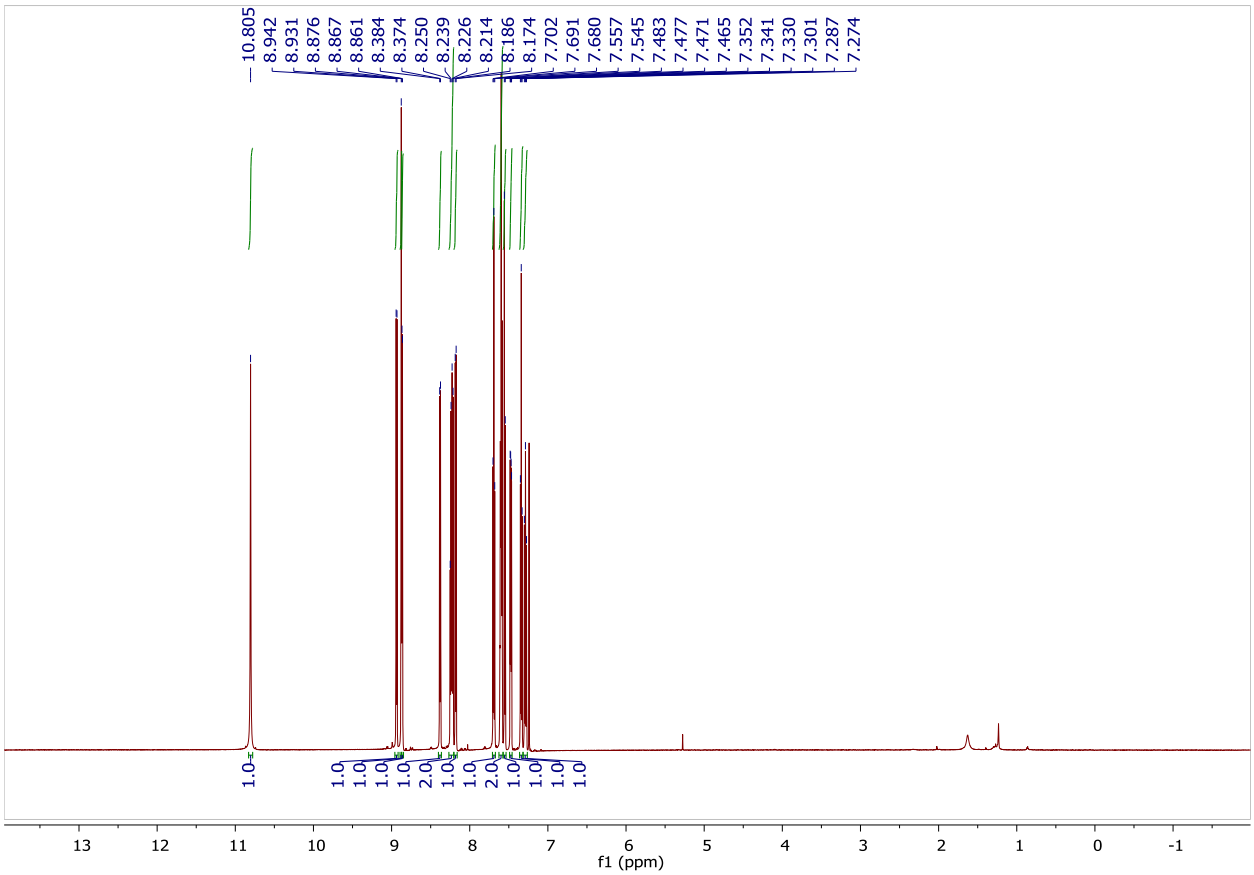
^{13}C NMR of **15H**:



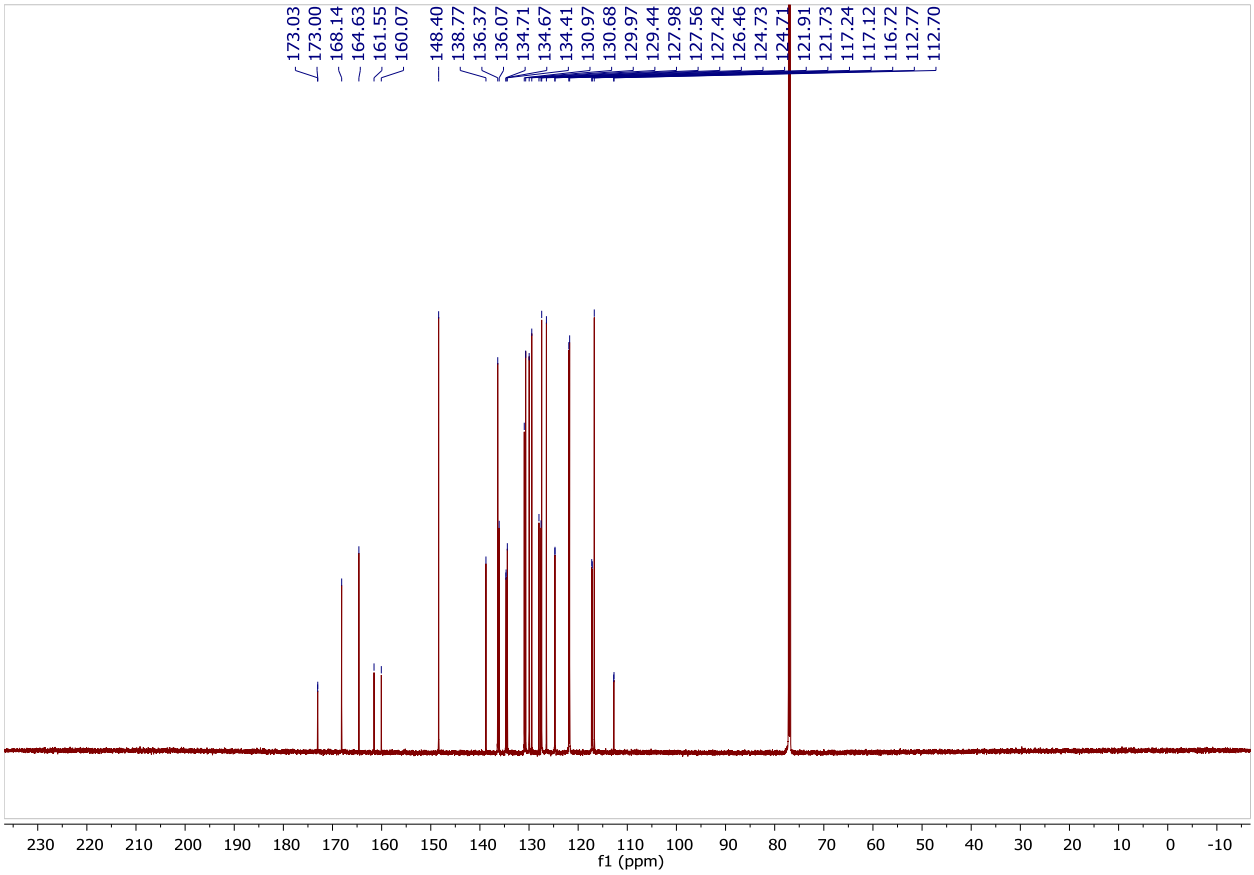


(**16H**)

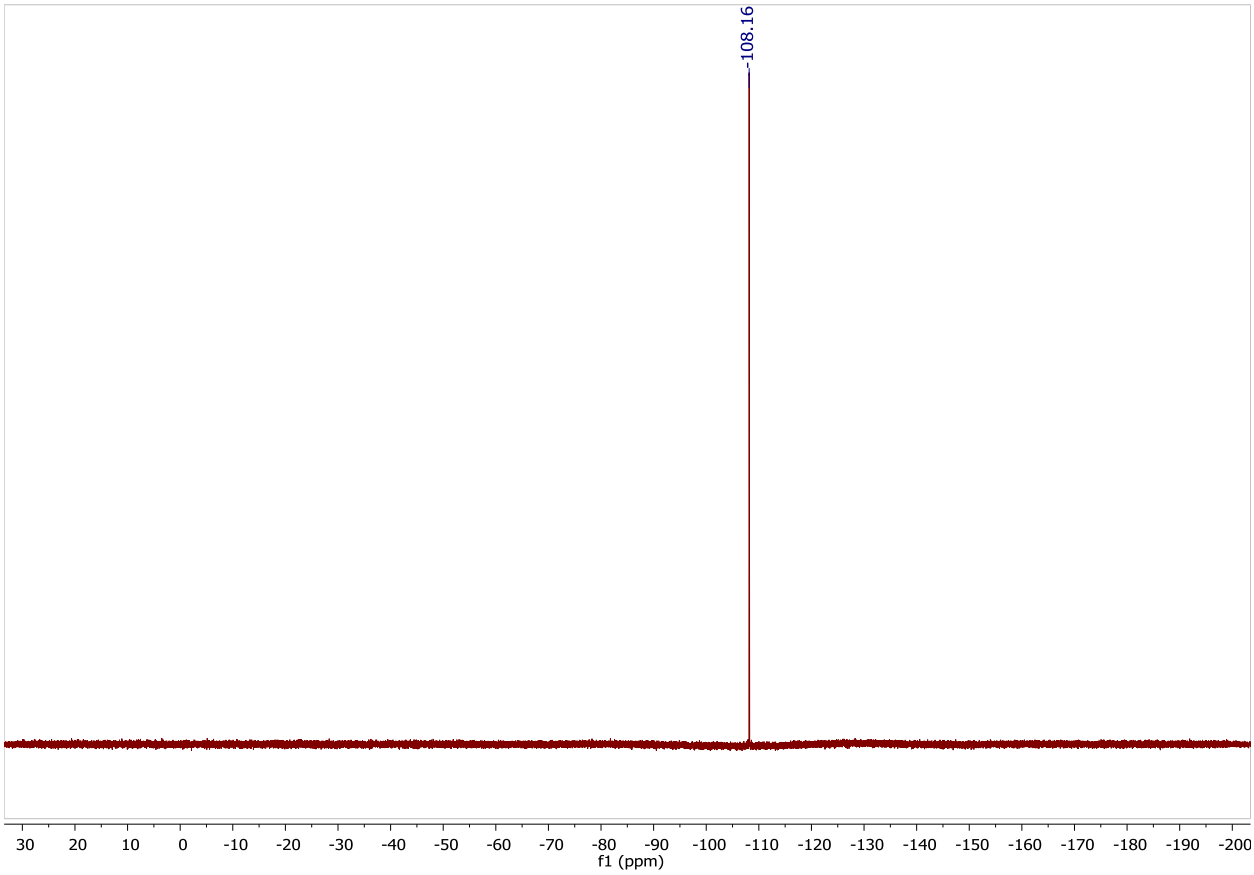
^{1}H NMR of **16H**:

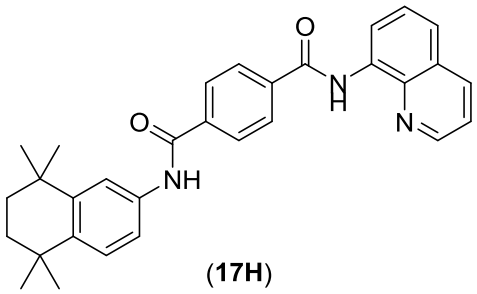


^{13}C NMR of **16H**:



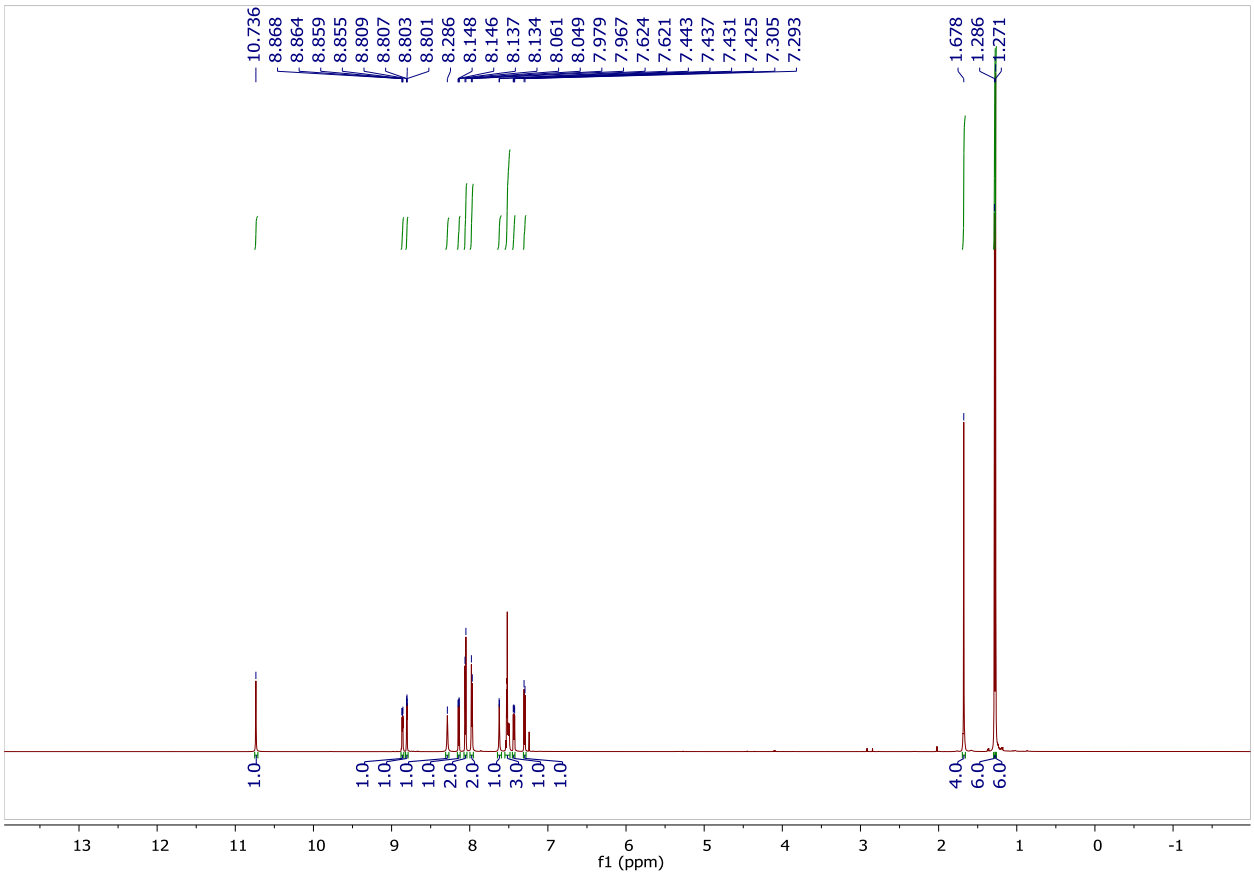
^{19}F NMR of **16H**:



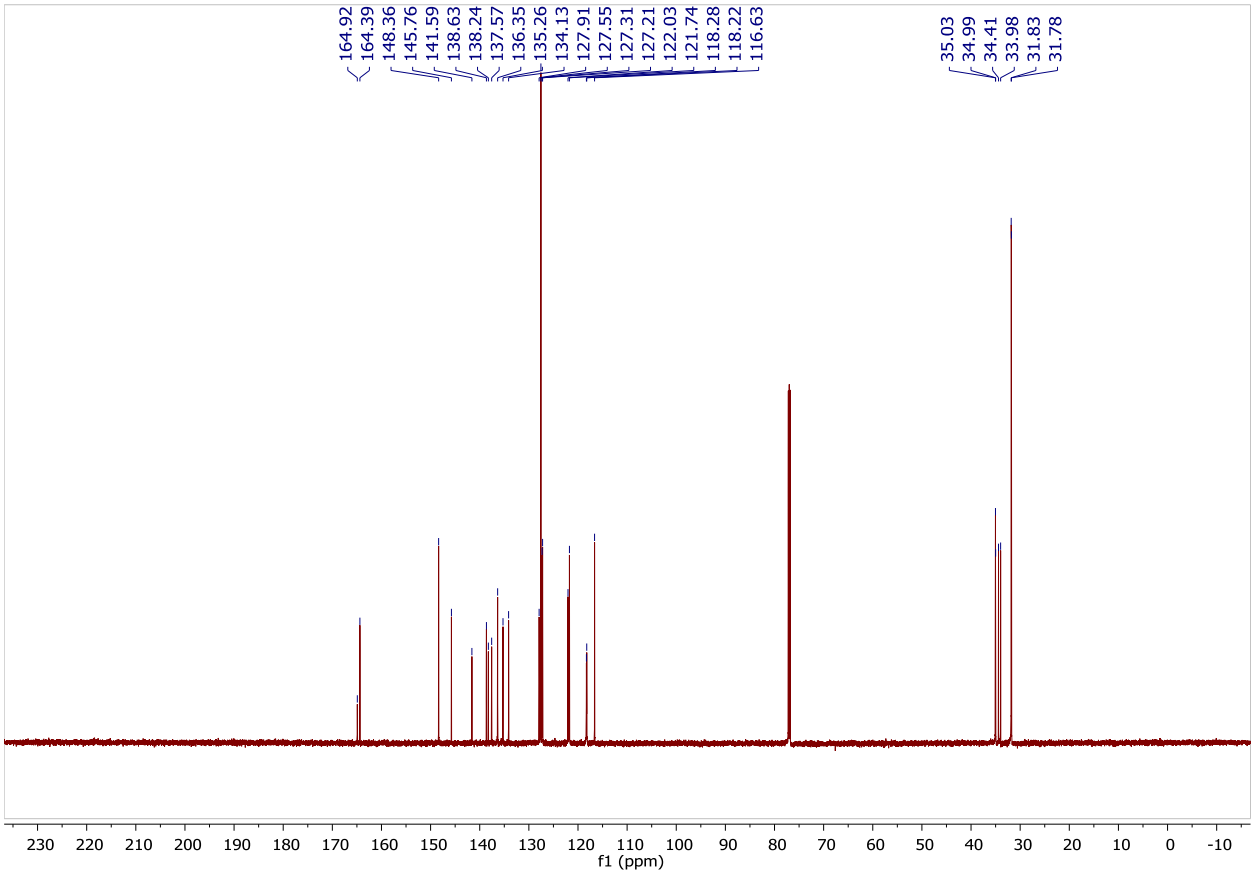


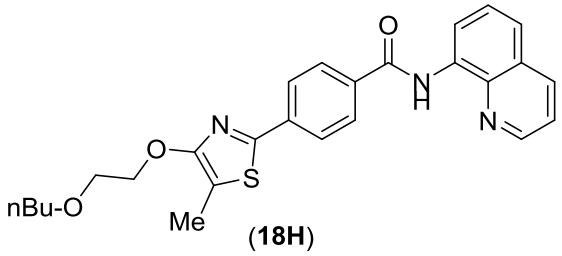
(**17H**)

^{1}H NMR of **17H**:



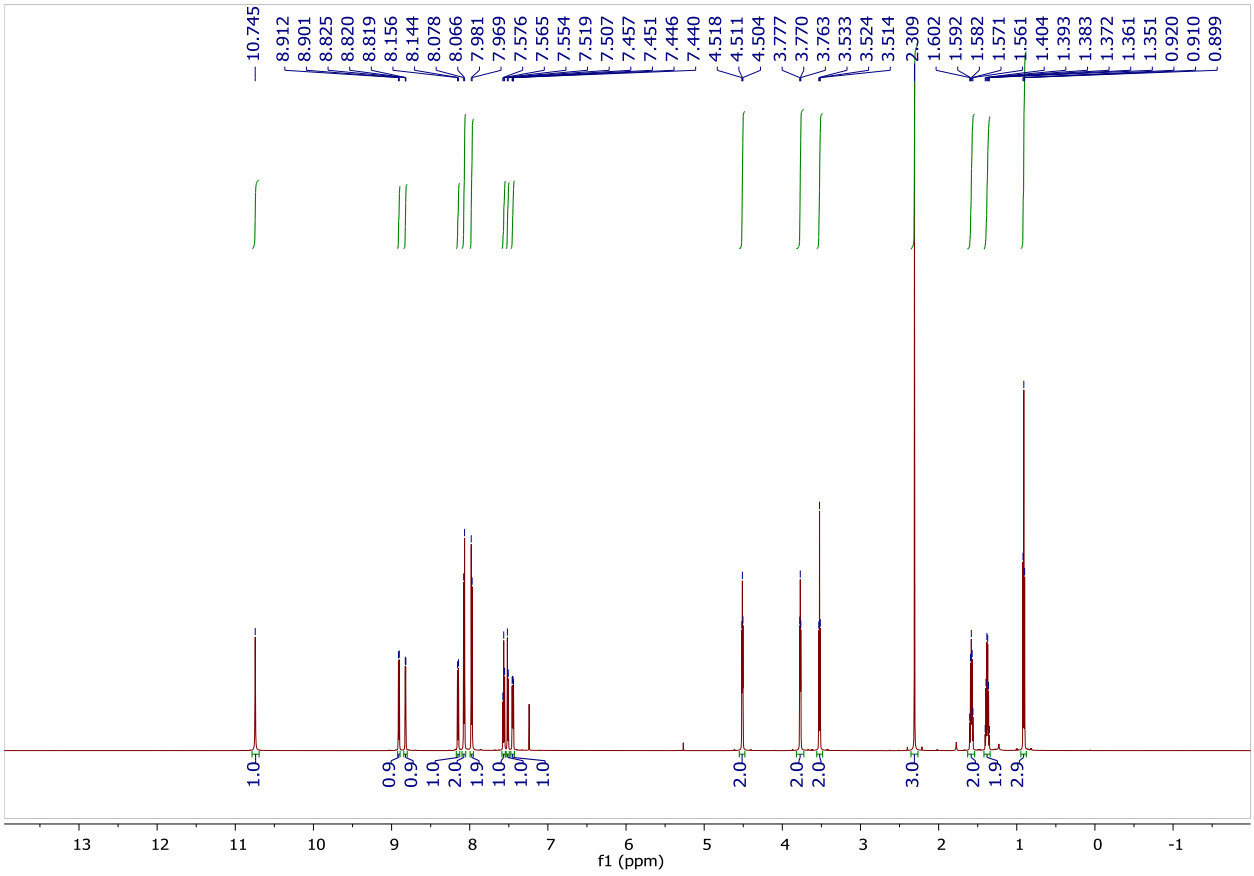
^{13}C NMR of **17H**:



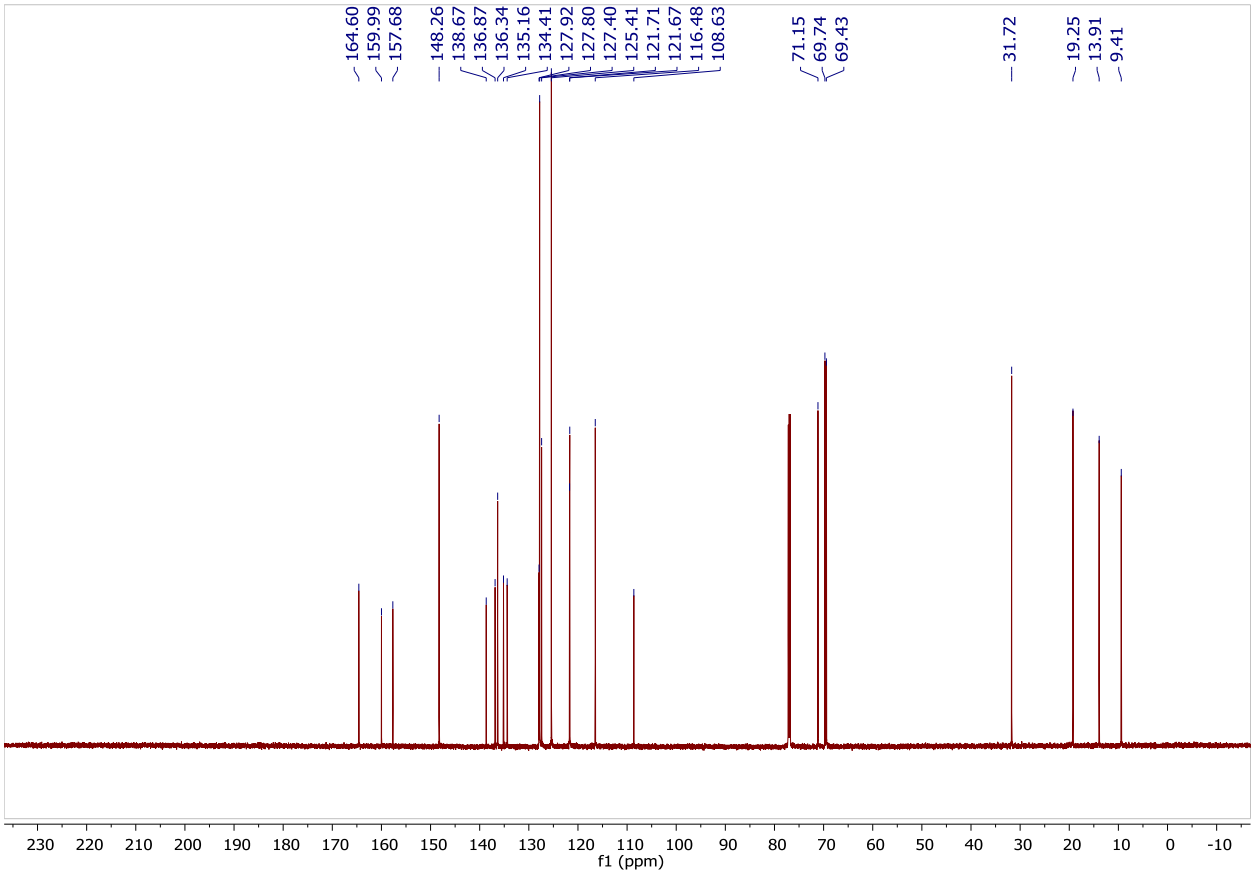


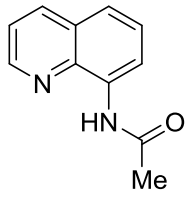
(**18H**)

^{1}H NMR of **18H**:



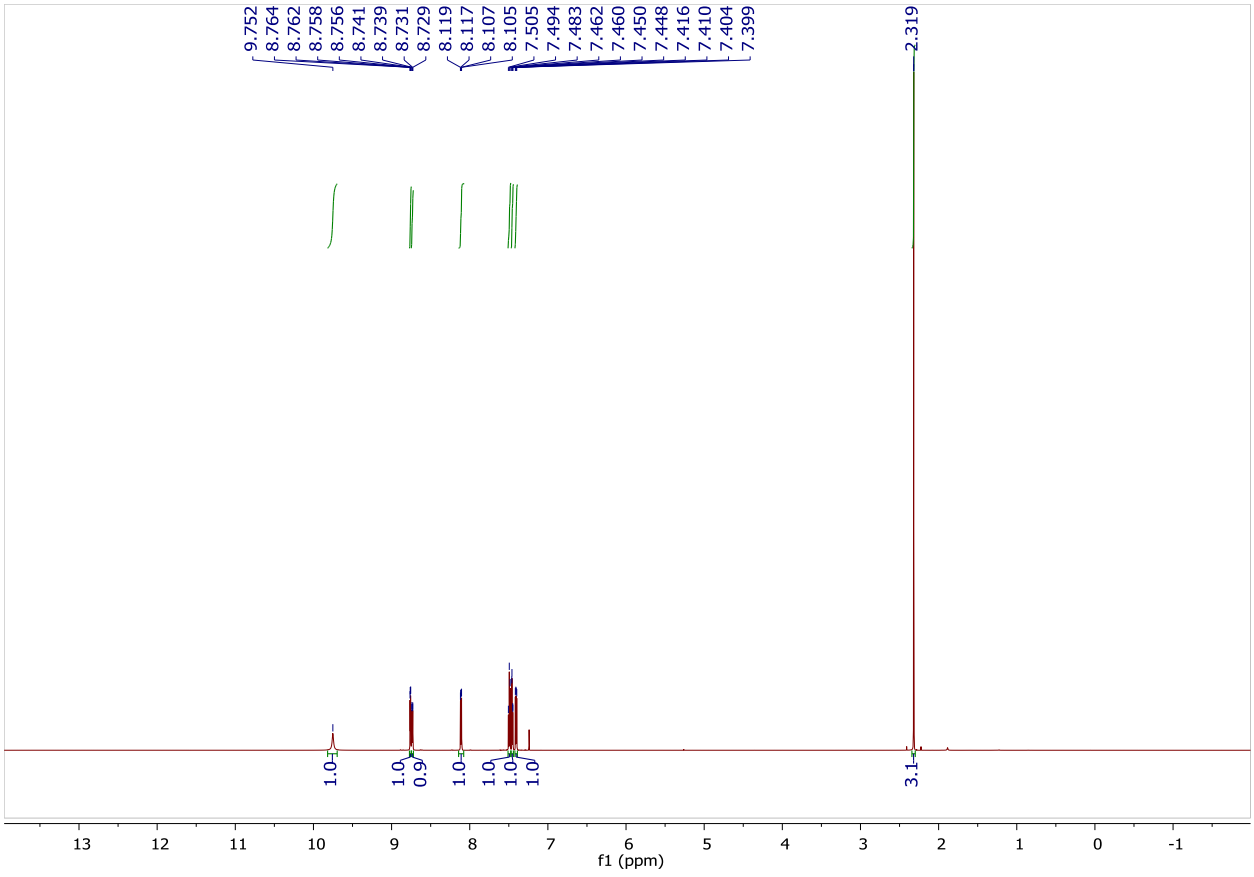
^{13}C NMR of **18H**:



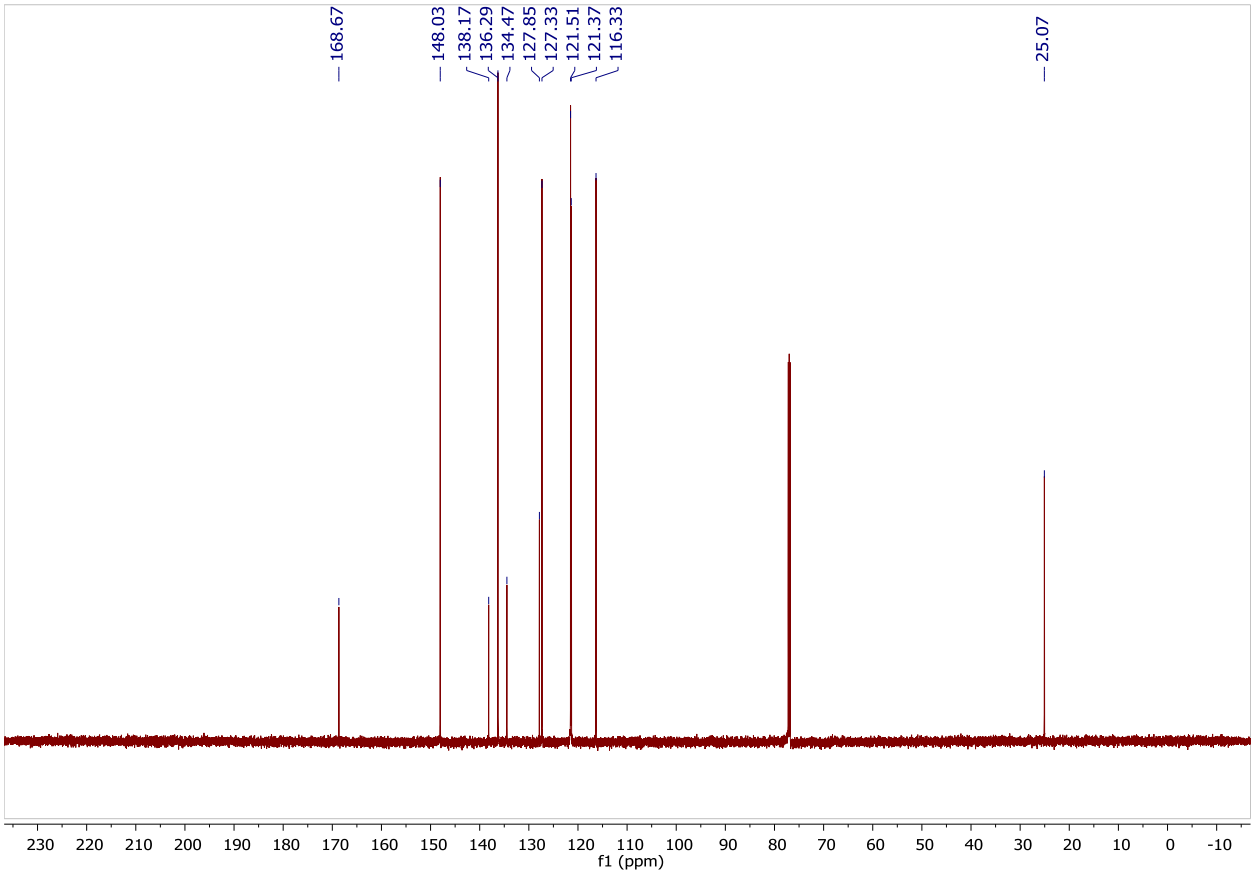


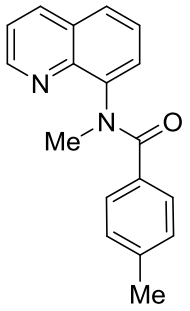
(**S1**)

^{1}H NMR of **S1**:



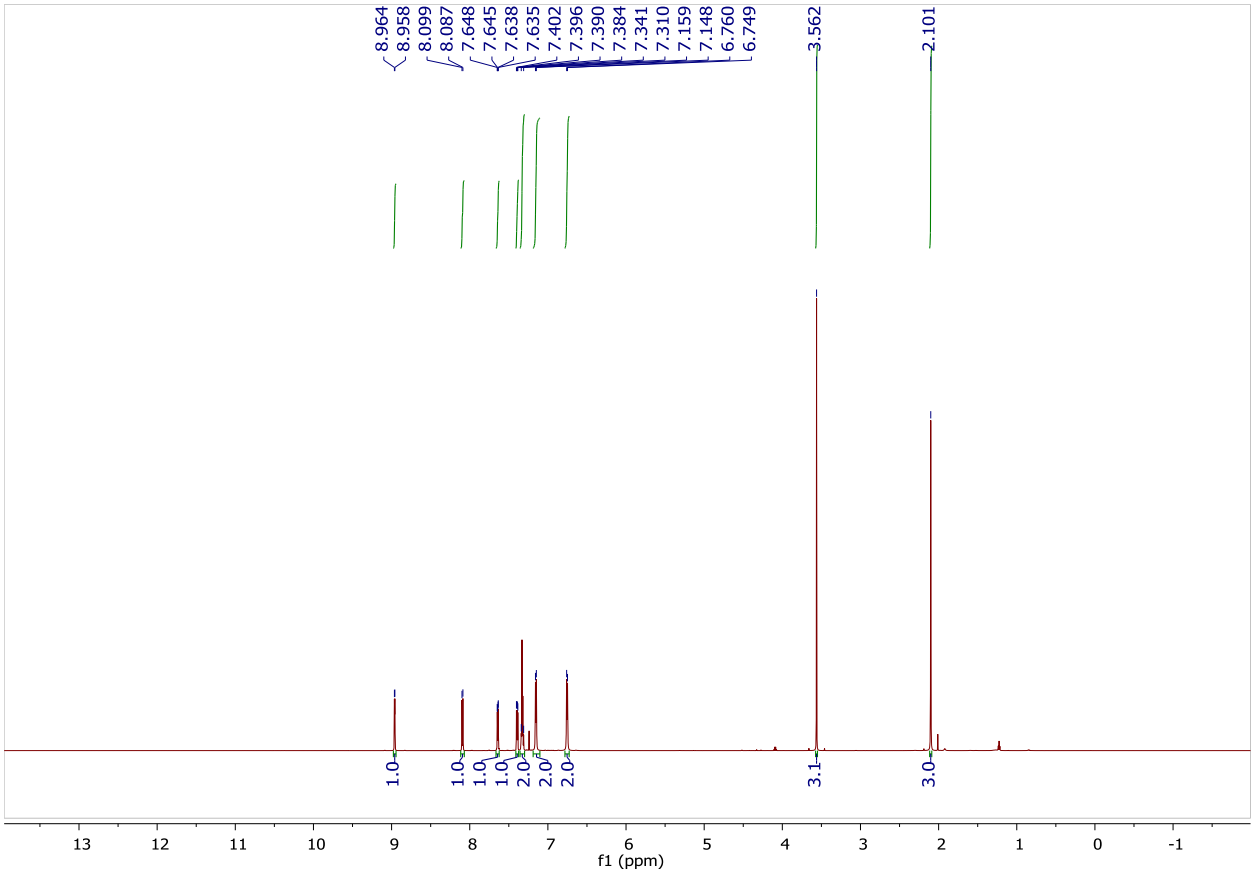
^{13}C NMR of **S1**:


168.67
148.03
138.17
136.29
134.47
127.85
127.33
121.51
121.37
116.33
25.07
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

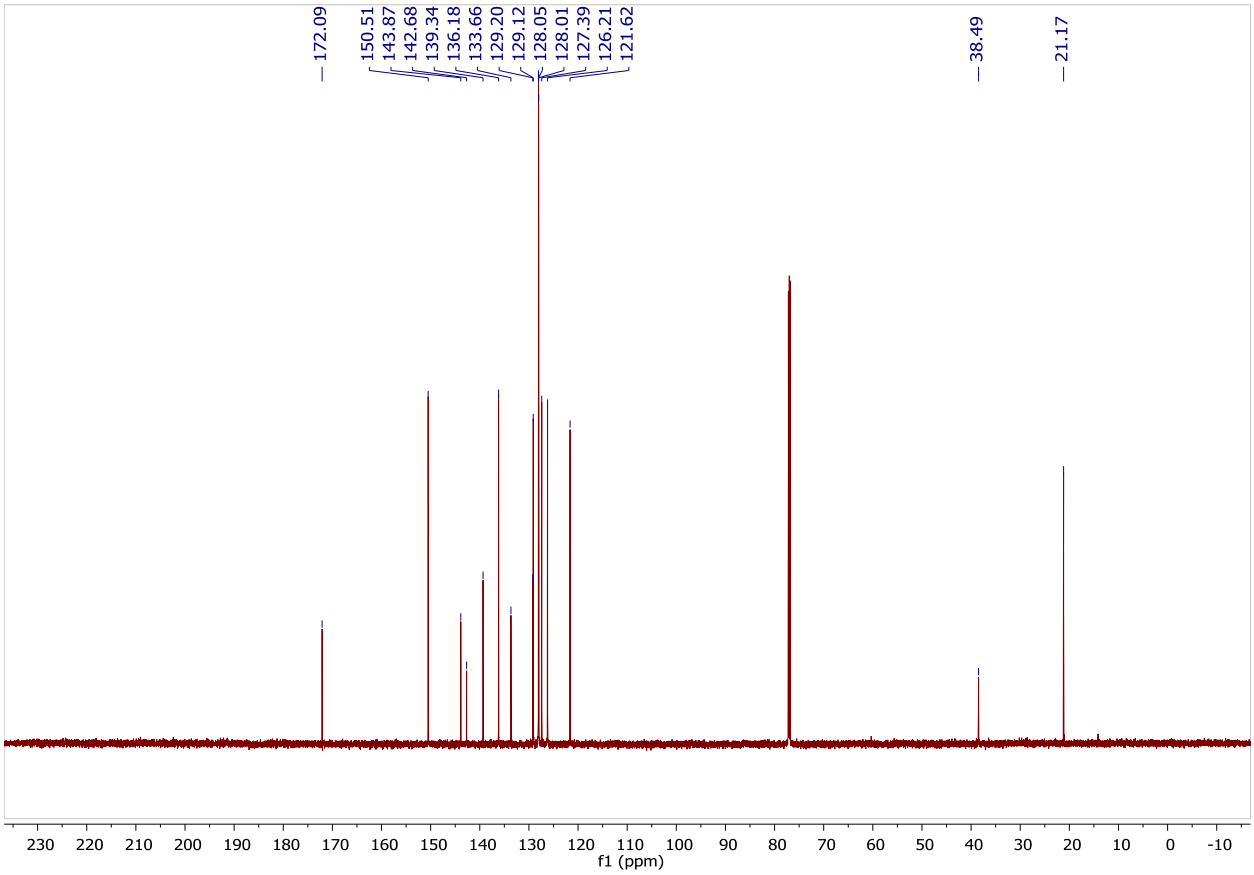


(**S3**)

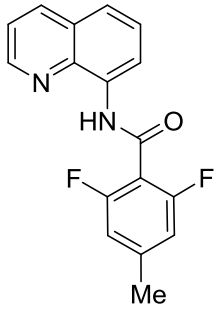
^{1}H NMR of **S3**:



^{13}C NMR of **S3**:

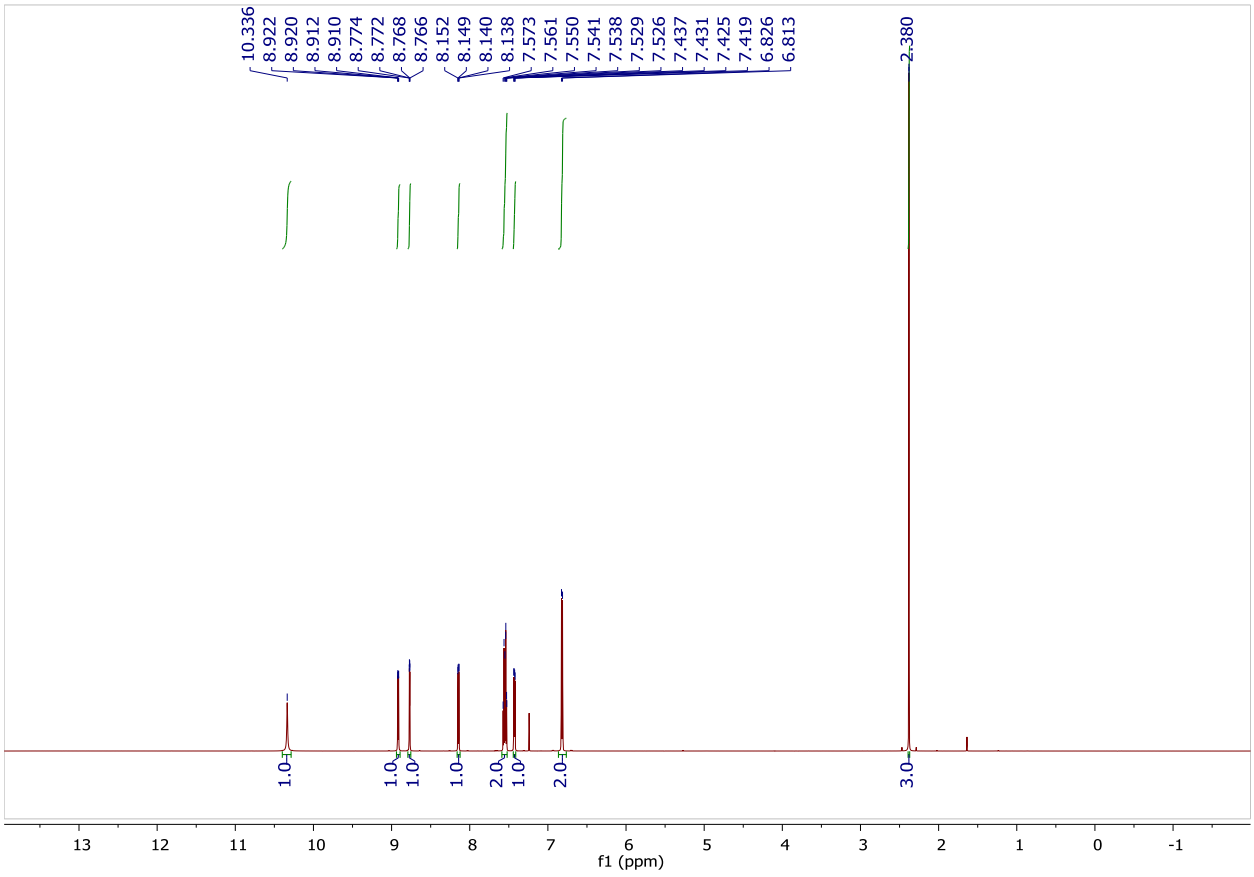

172.09
150.51
143.87
142.68
139.34
136.18
133.66
129.20
129.12
128.05
128.01
127.39
126.21
121.62
38.49
21.17
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

7.2 Fluorinated Reference Standards

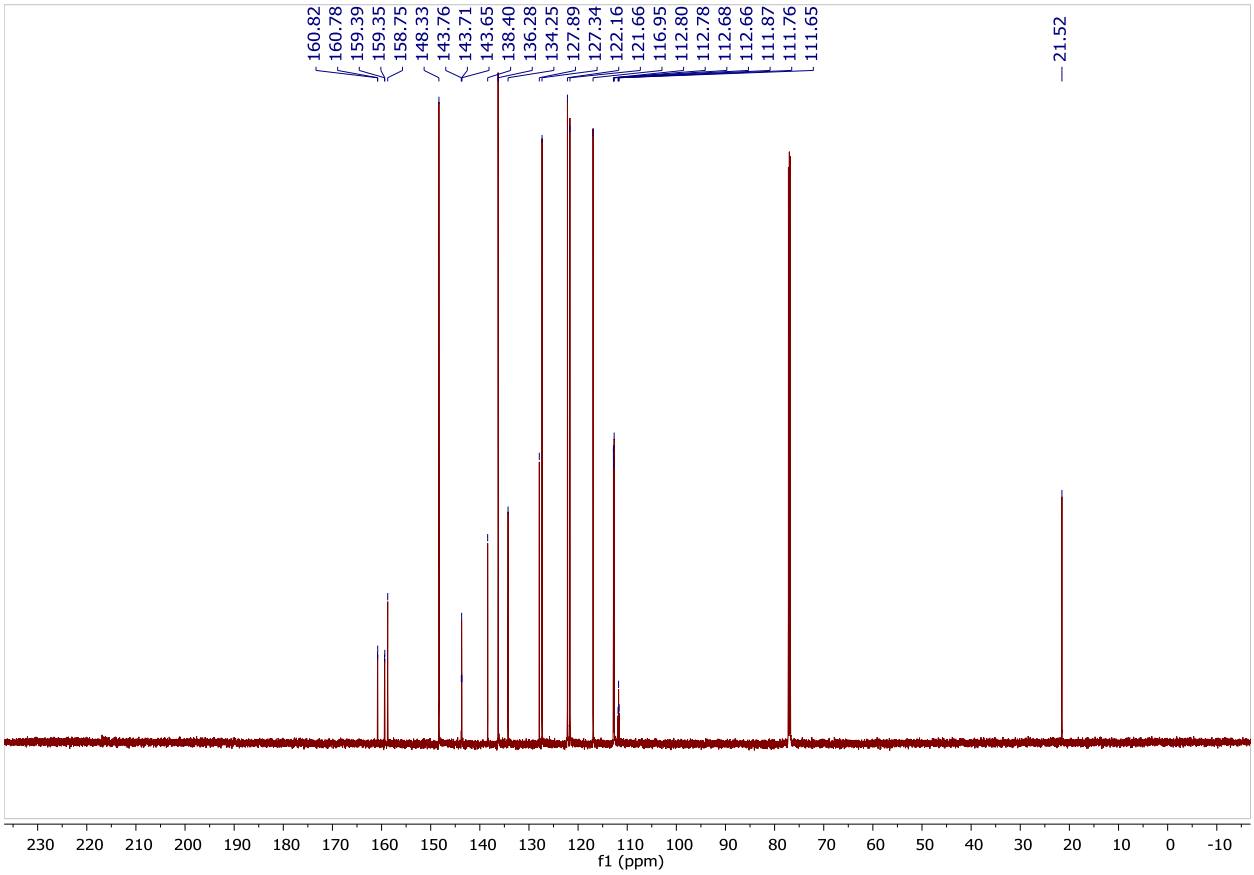


(**3F**)

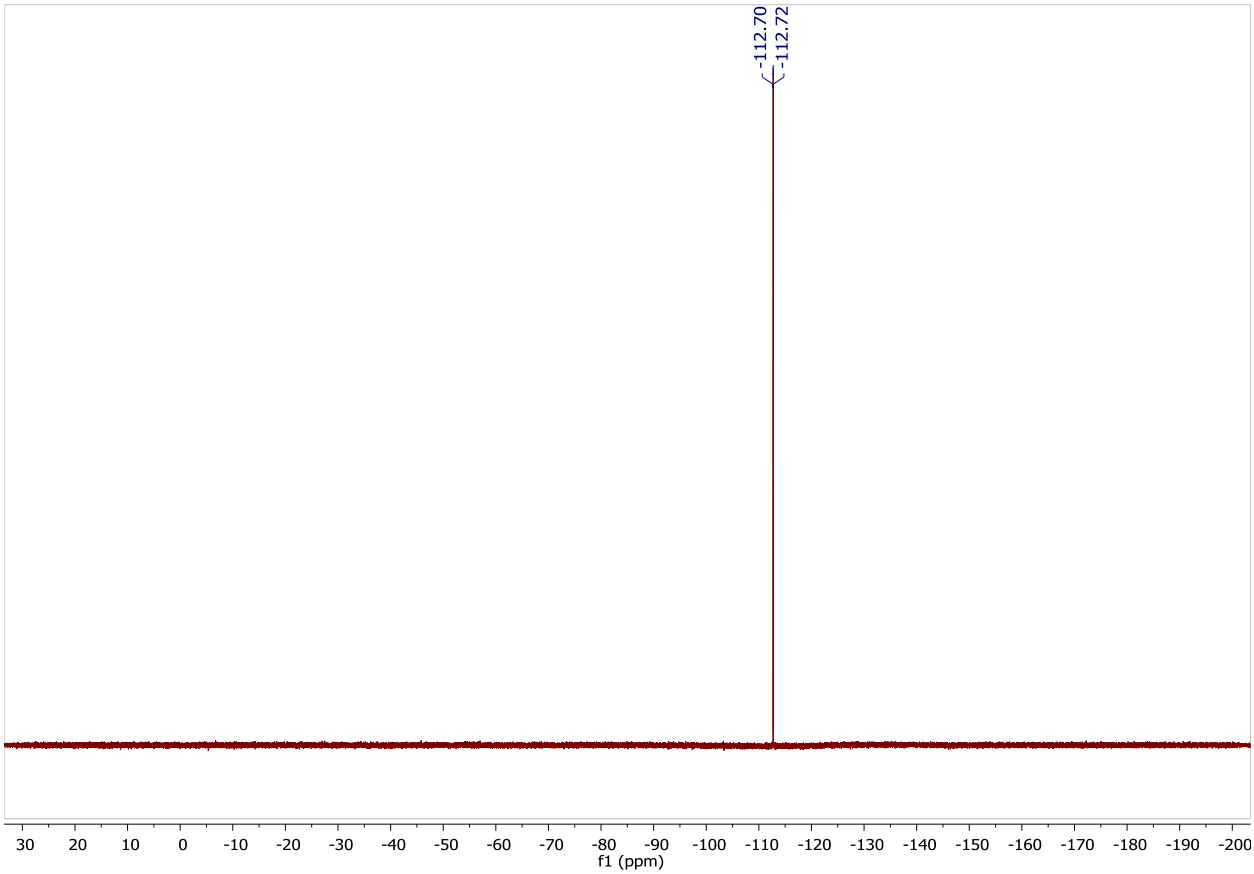
^{1}H NMR of **3F**:

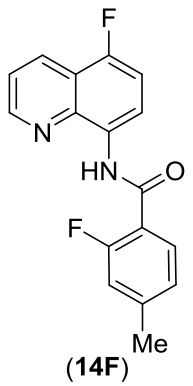


^{13}C NMR of **3F**:


160.82
160.78
159.39
159.35
158.75
148.33
143.76
143.71
143.65
138.40
136.28
134.25
127.89
127.34
122.16
121.66
116.95
112.80
112.78
112.68
112.66
111.87
111.76
111.65
21.52
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

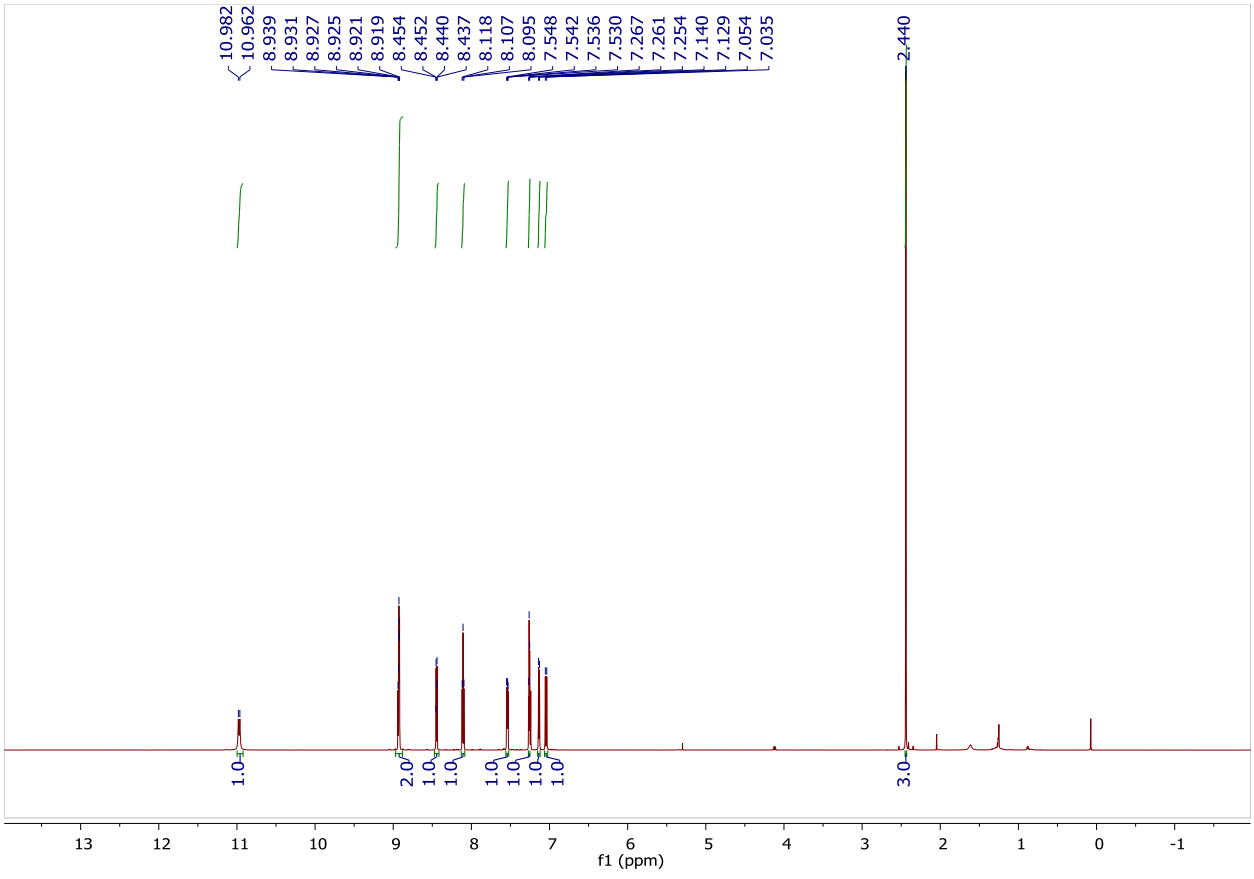
^{19}F NMR of **3F**:


-112.70
-112.72
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

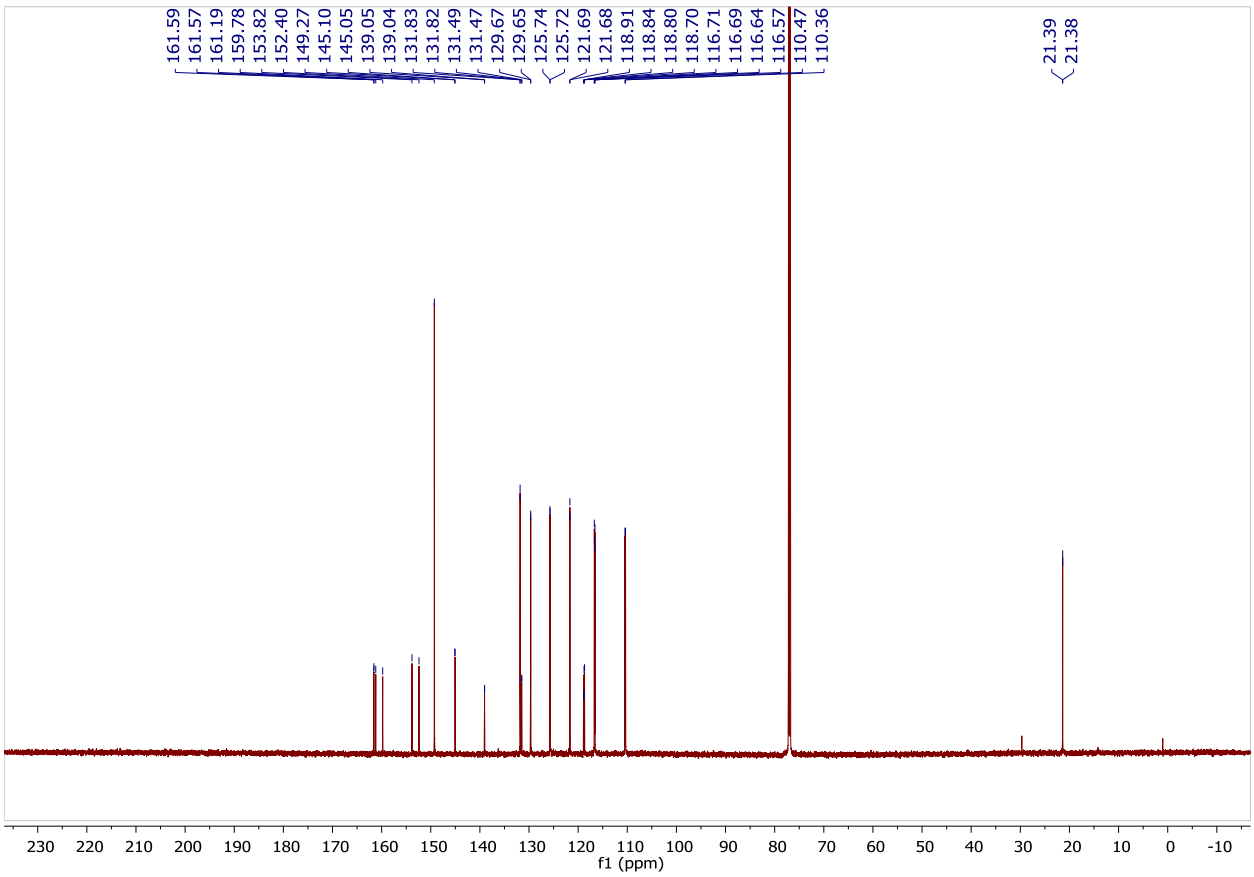


(**14F**)

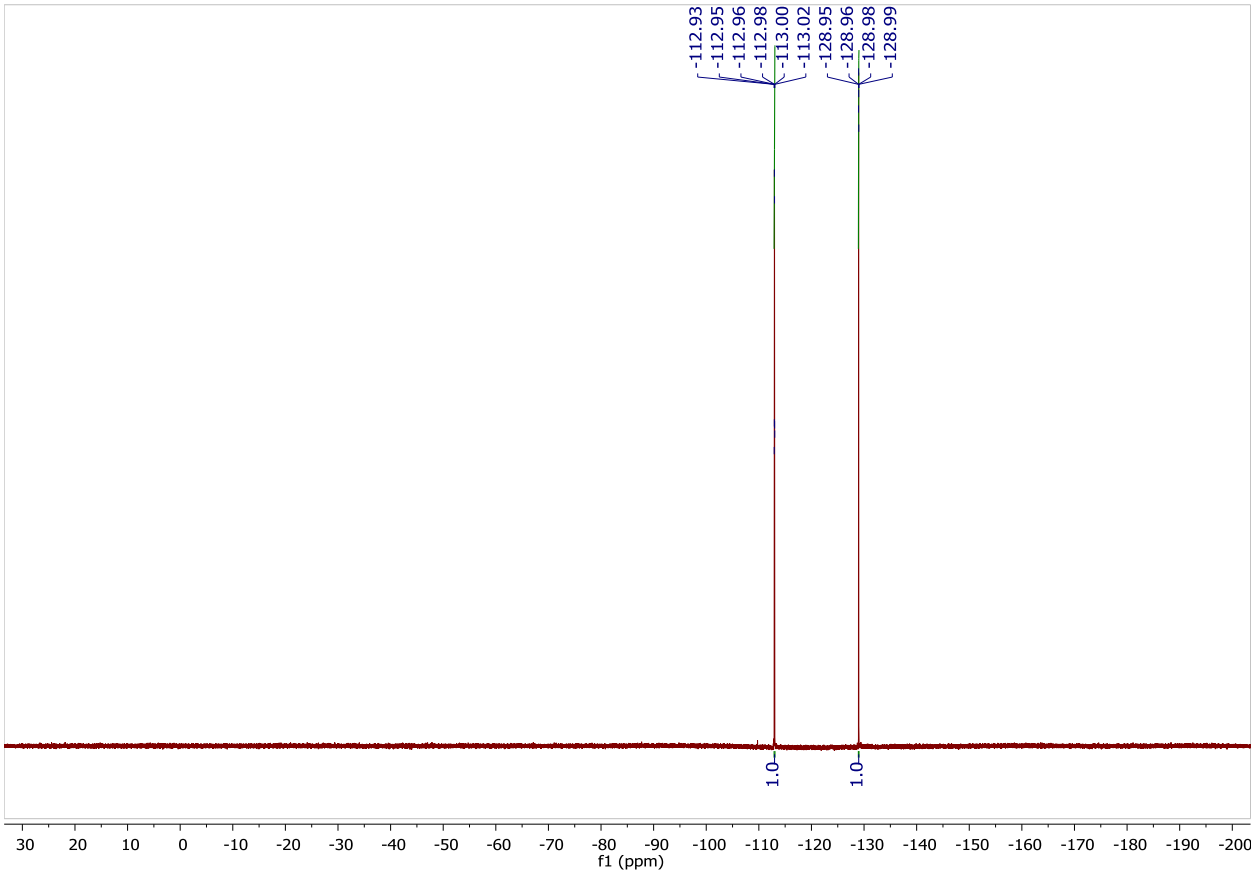
^{1}H NMR of **14F**:

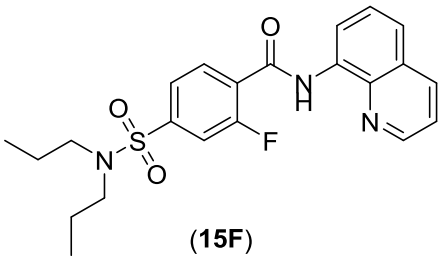


^{13}C NMR of **14F**:



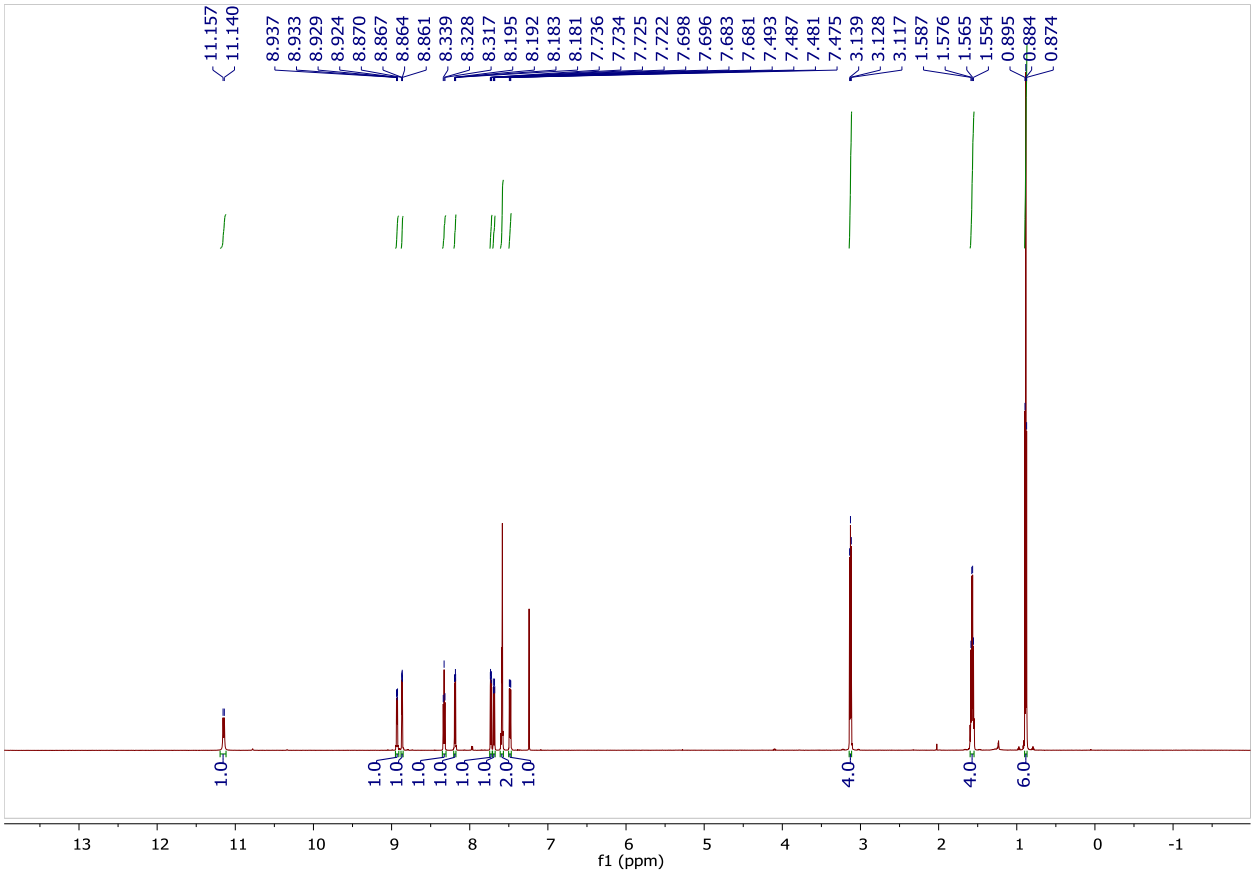
^{19}F NMR of **14F**:



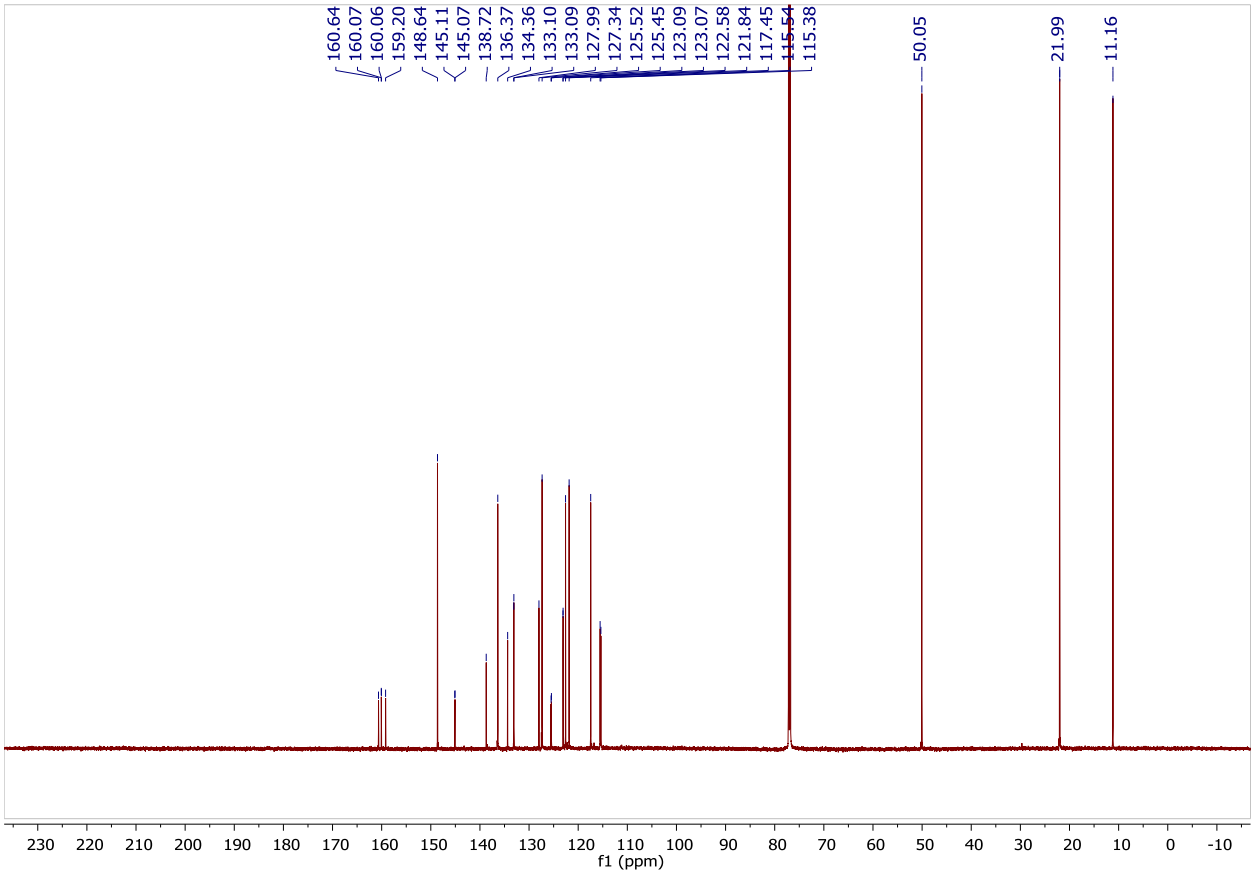


(**15F**)

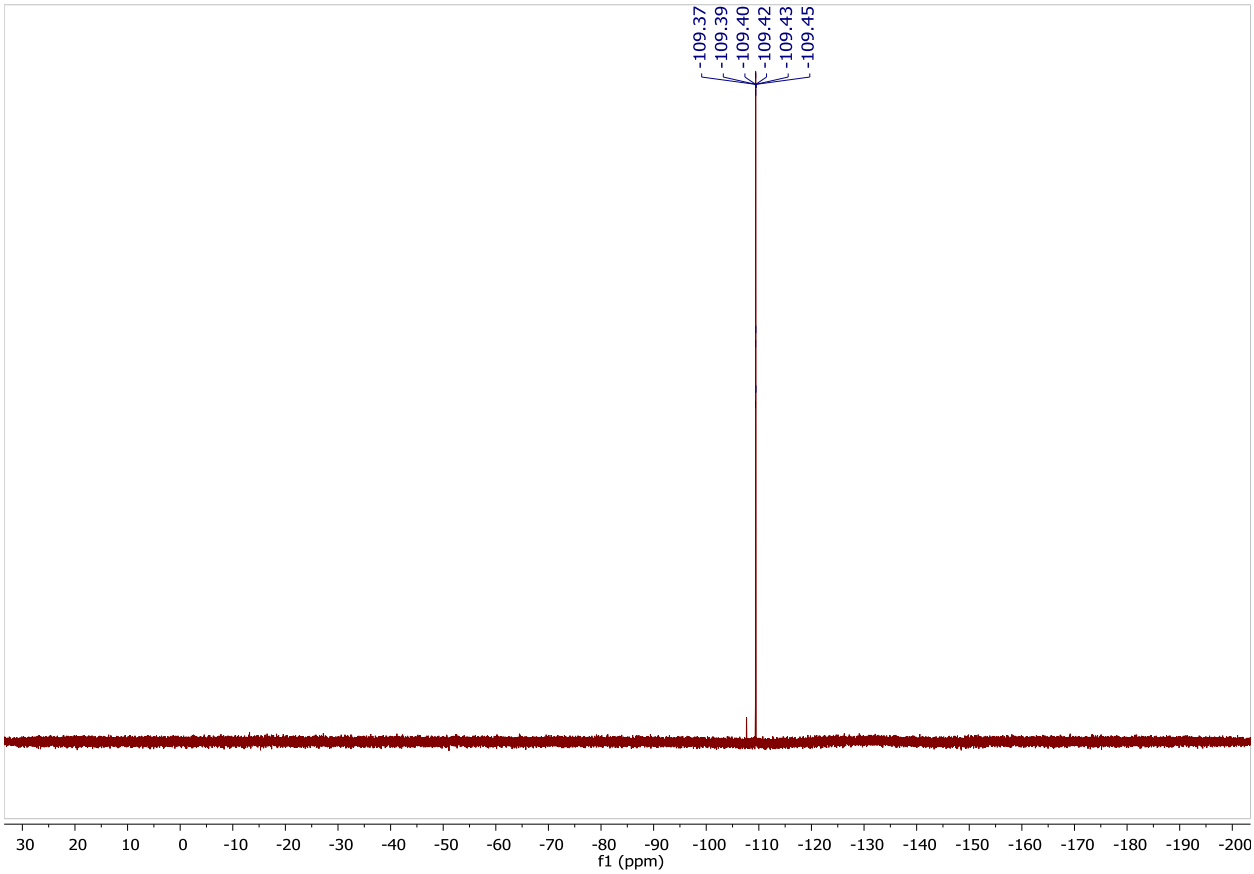
^{1}H NMR of **15F**:

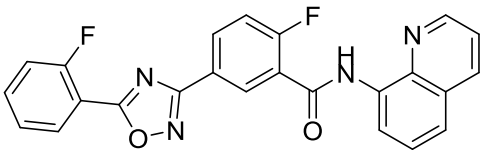


^{13}C NMR of **15F**:



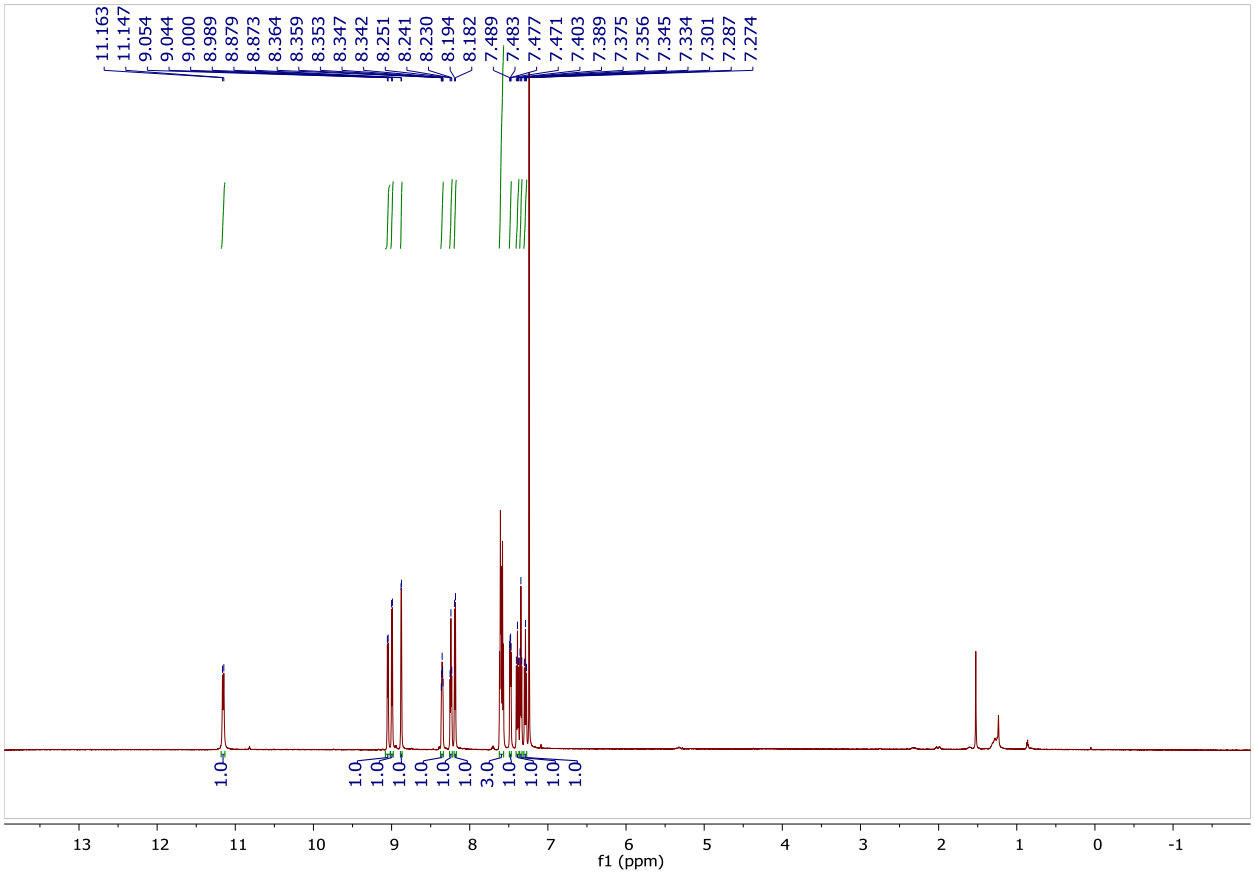
^{19}F NMR of **15F**:



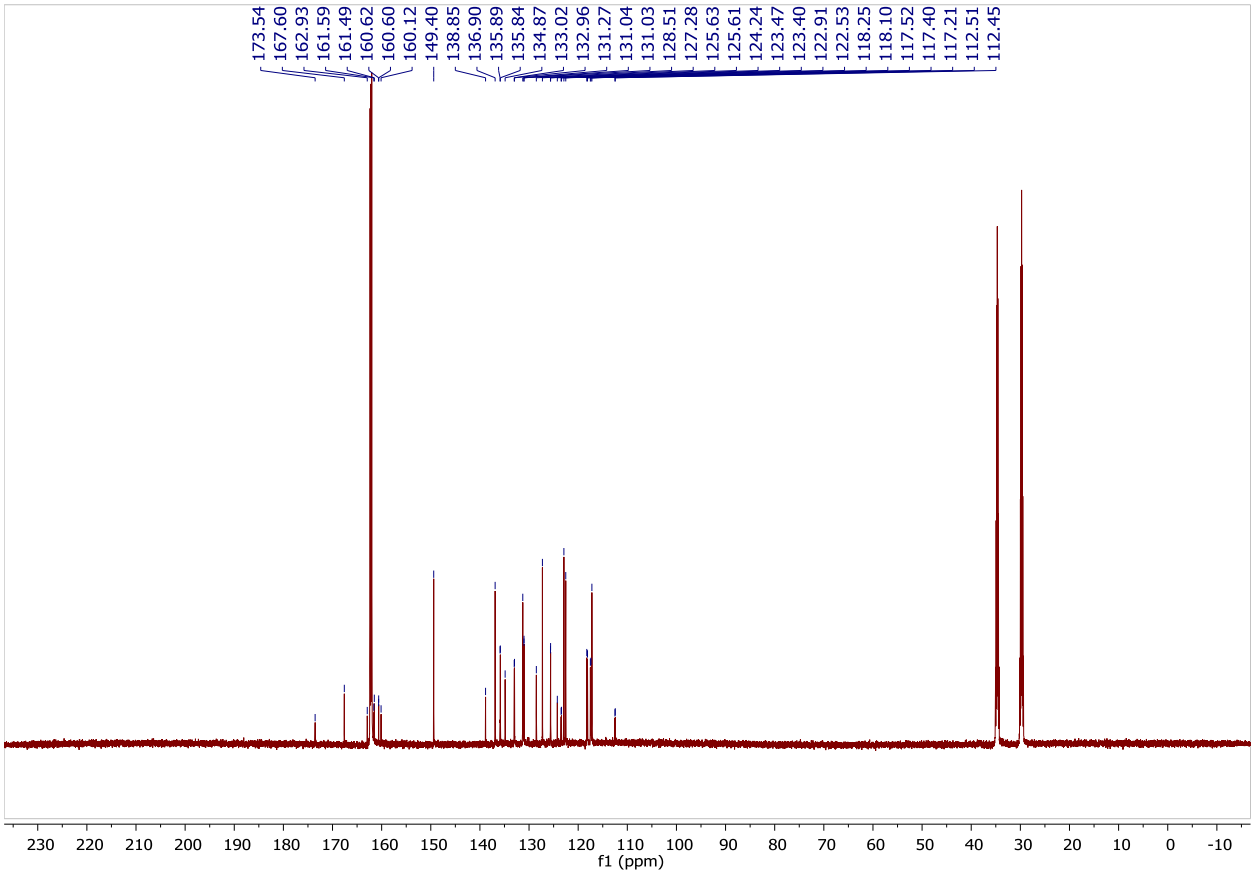


(**16F**)

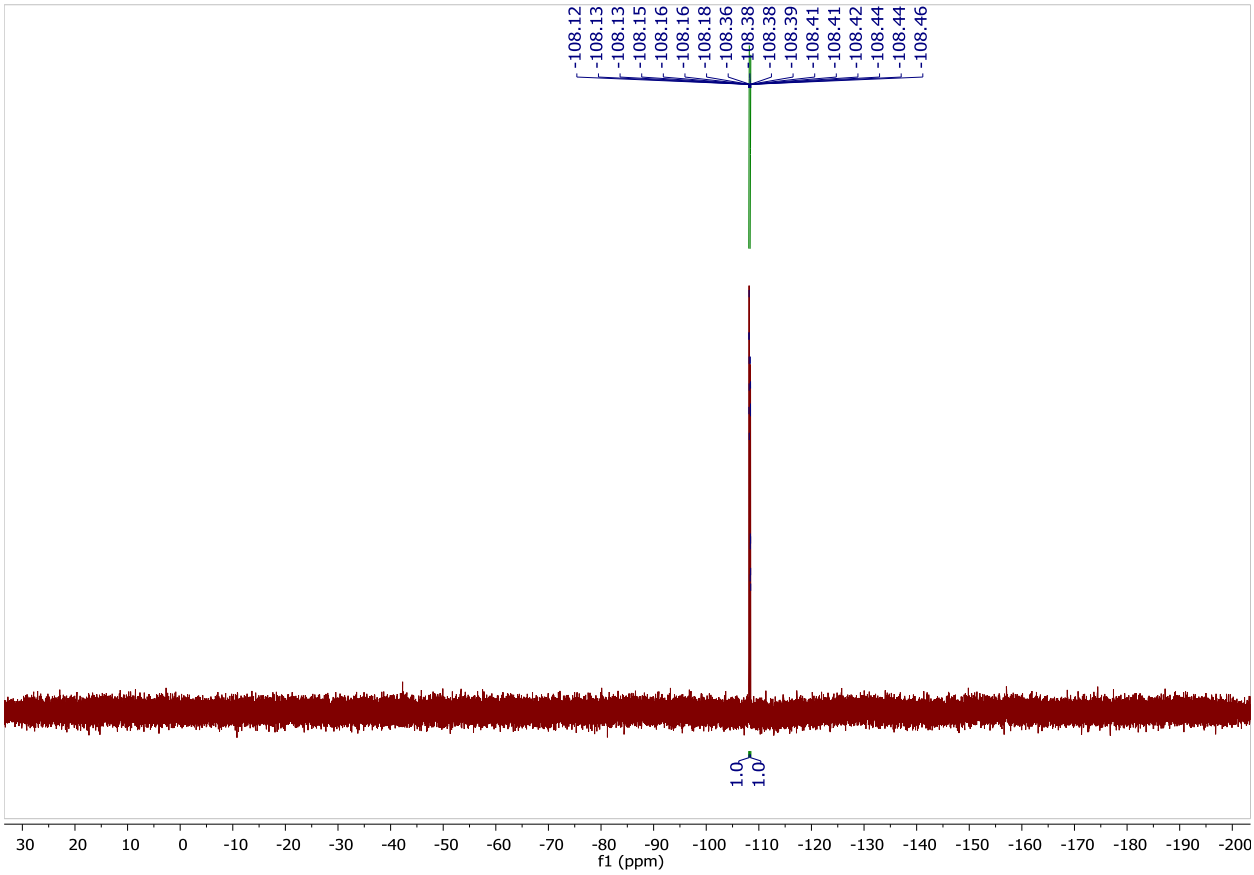
^{1}H NMR of **16F**:

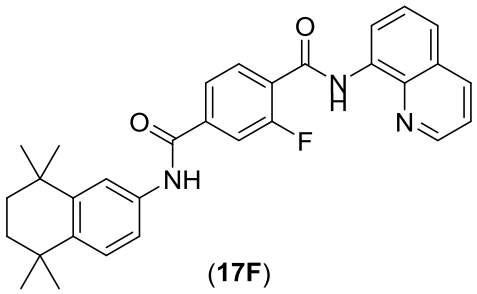


^{13}C NMR of **16F**:



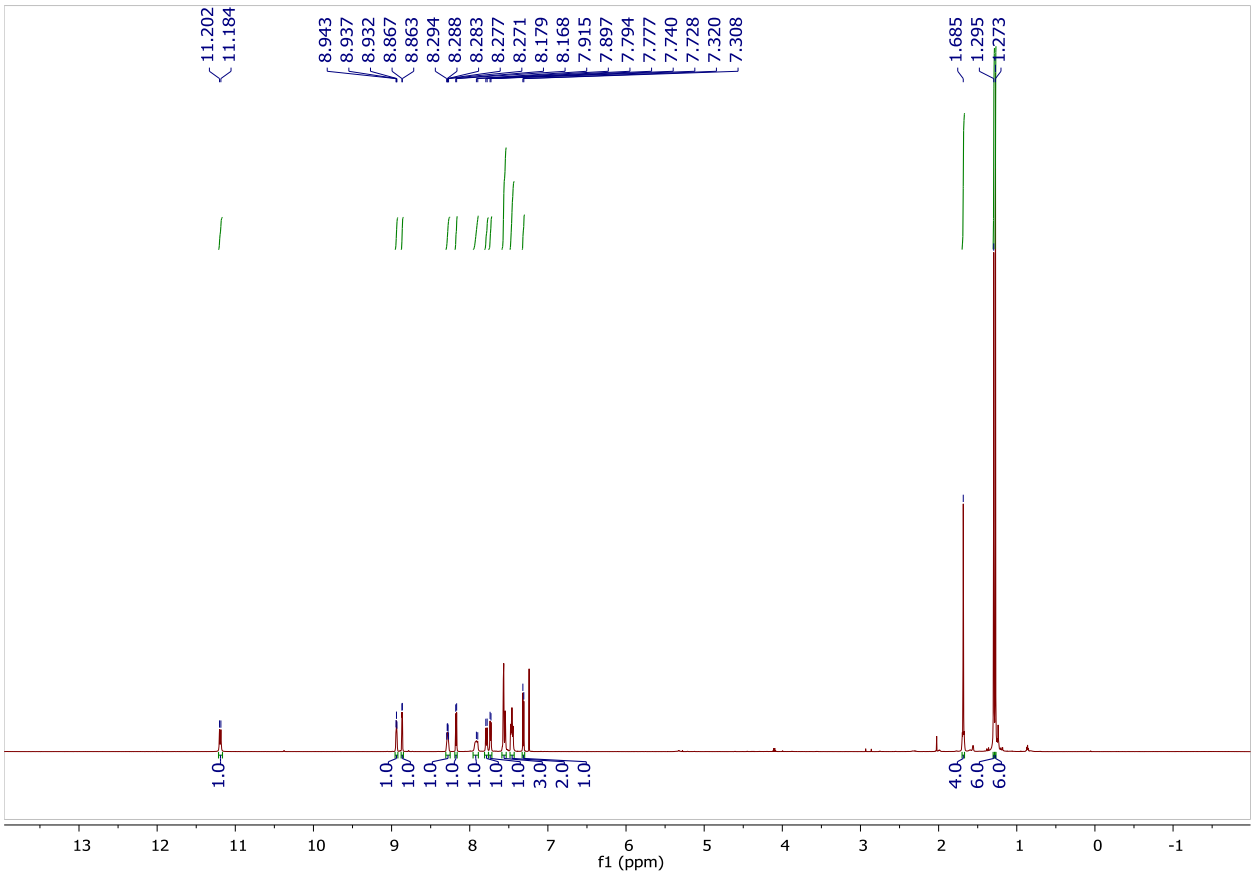
^{19}F NMR of **16F**:



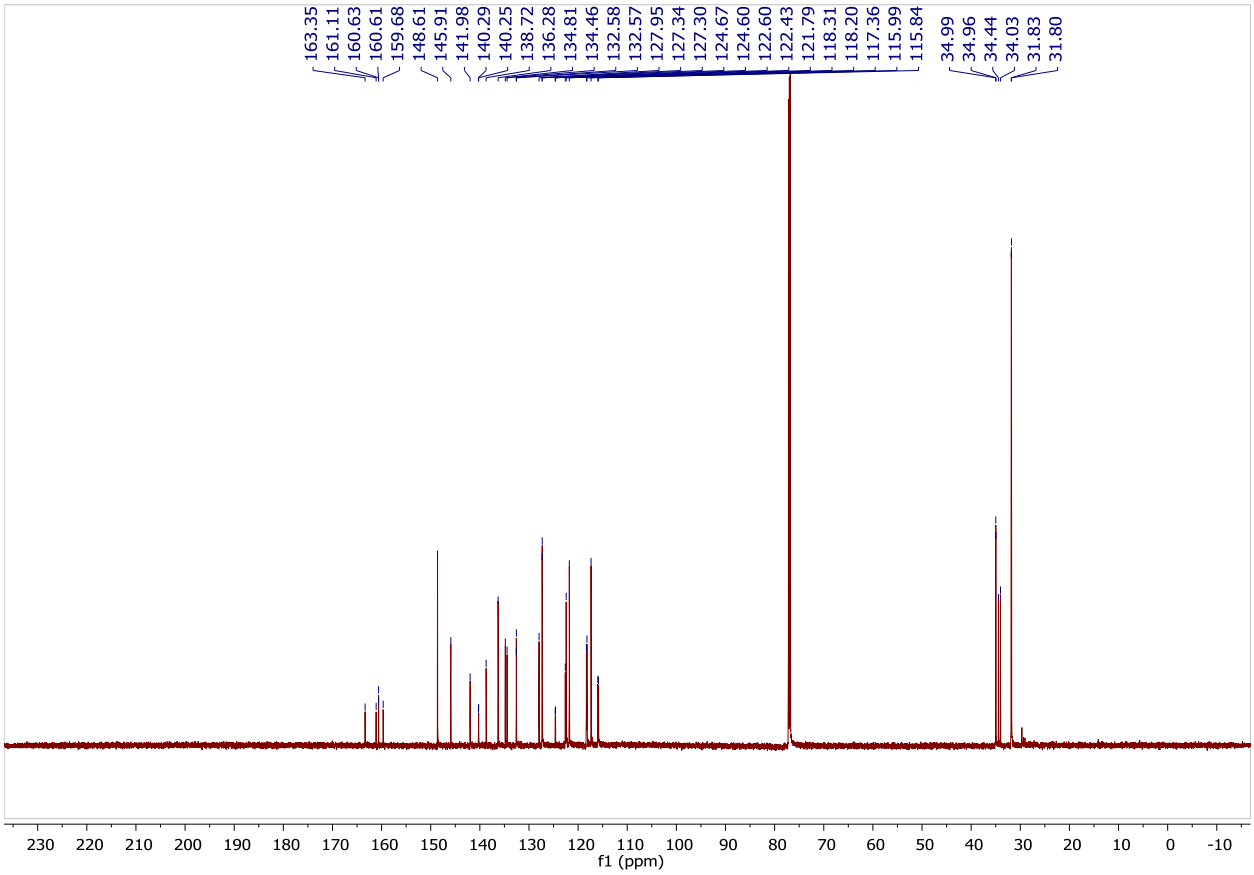


(**17F**)

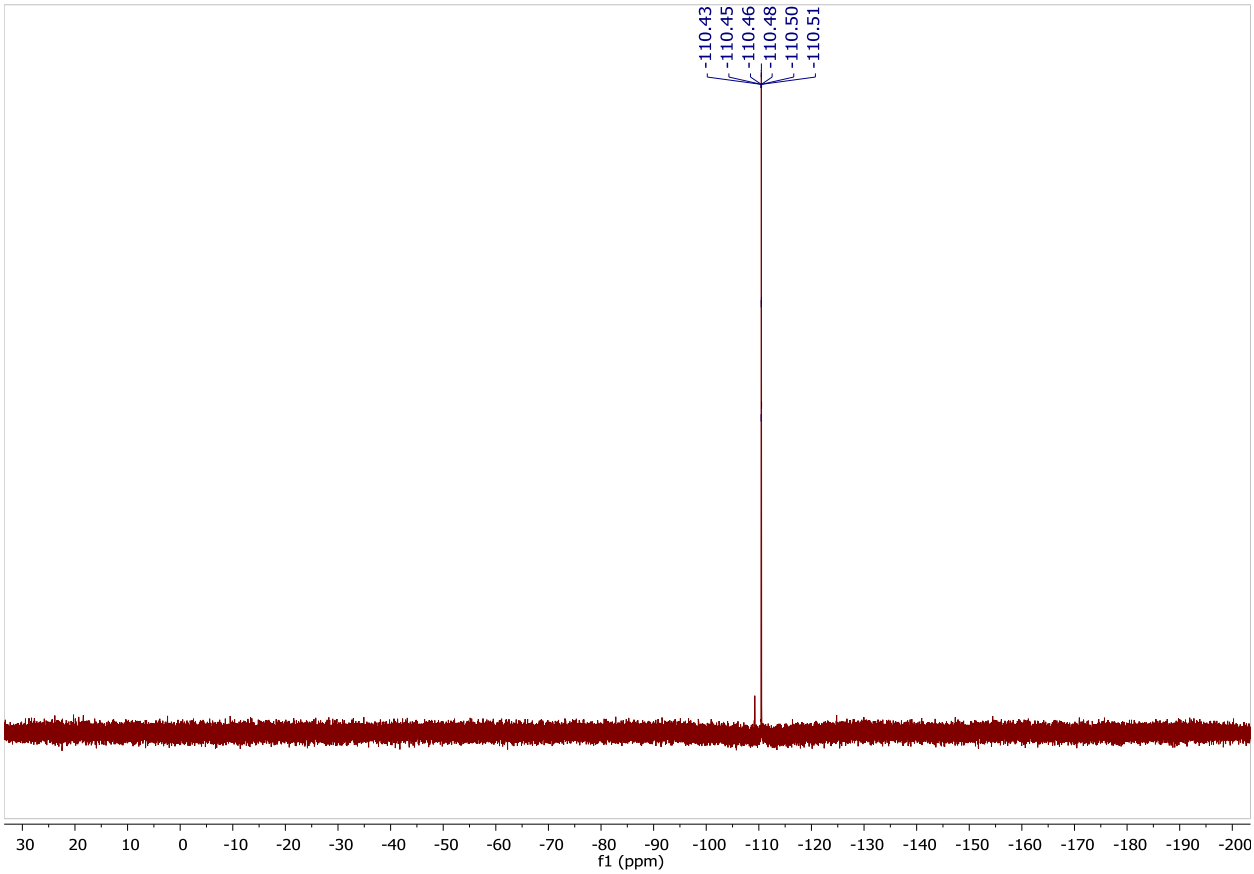
^{1}H NMR of **17F**:

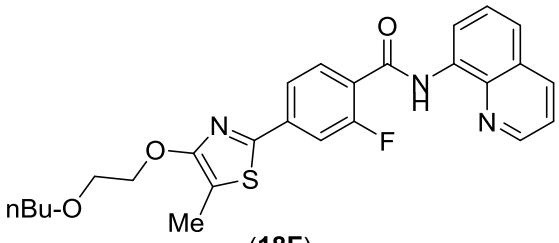


^{13}C NMR of **17F**:



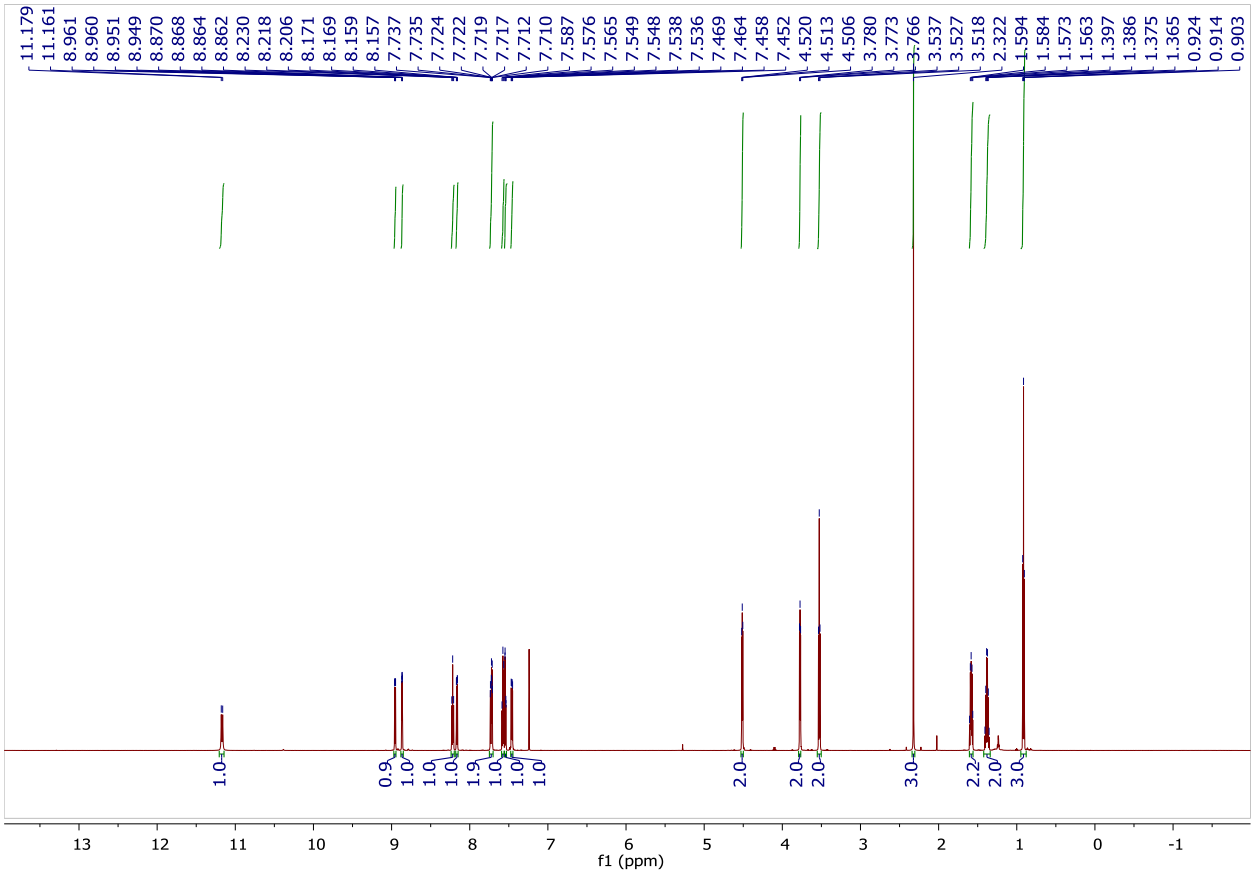
^{19}F NMR of **17F**:



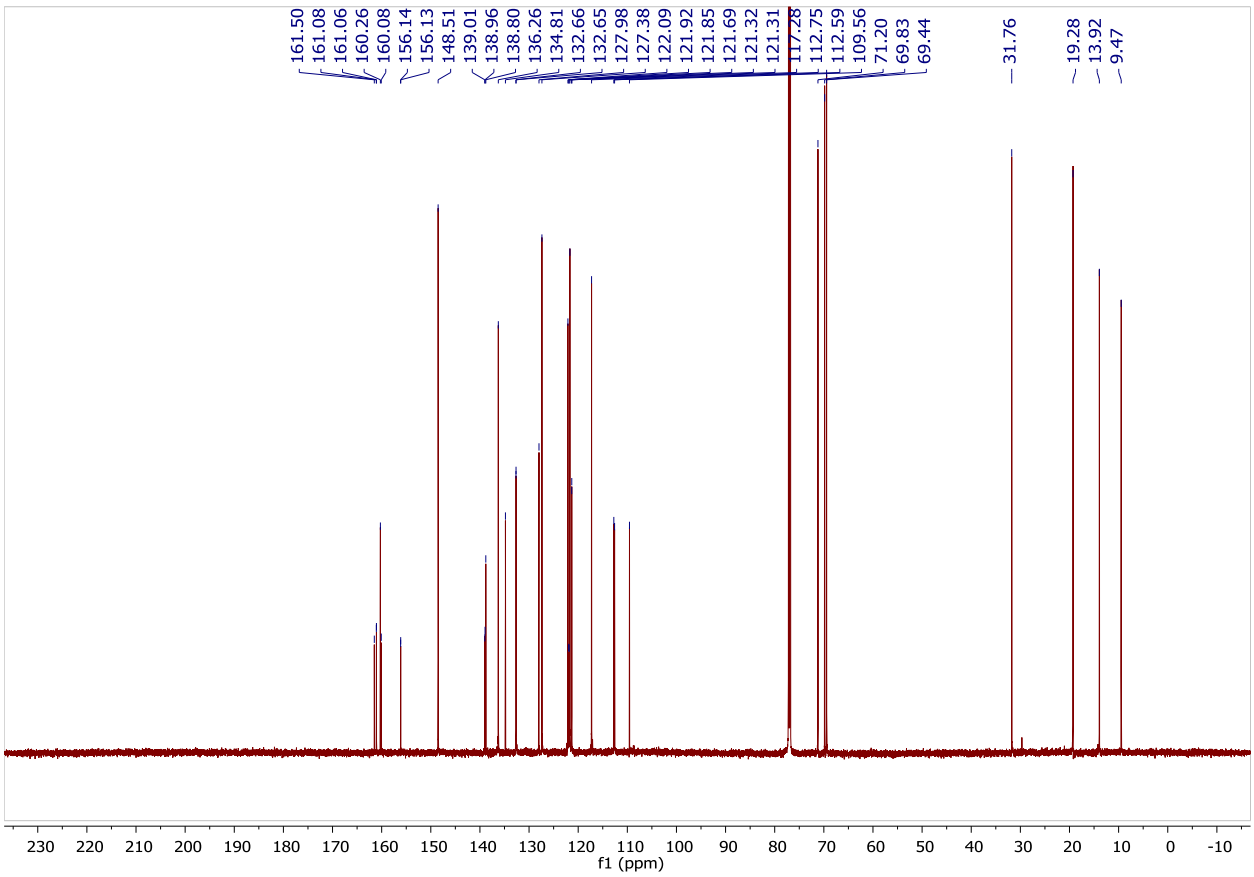


(**18F**)

^{1}H NMR of **18F**:



^{13}C NMR of **18F**:



^{19}F NMR of **18F**: