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SYNTHESIS OF *N*-[4-(2'-[^{18}F]FLUOROALKOXYBENZOYL)]- AND *N*-(3-[^{123}I]IODO-4-METHOXYBENZOYL)PYRROLIDIN-2-ONES AS POTENTIAL BRAIN IMAGING AGENTS

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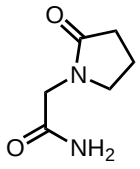
Abstract – The microfluidic synthesis of promising brain imaging PET agents *N*-[4-(2'-[^{18}F]fluoroalkyloxybenzoyl)]pyrrolidin-2-ones **13a-c** was accomplished by nucleophilic radiofluorination of the corresponding tosylate precursors **9a-c** with Kryptofix-potassium carbonate-[^{18}F]fluoride. Decay corrected radiochemical yields of 35±5% (**13a**), 38±8% (**13b**) and 40±5% (**13c**) were obtained with radiochemical purities of ≥ 93%. The total reaction time, including HPLC purification was 40 min. *N*-(3-[^{123}I]Iodo-4-methoxybenzoyl)pyrrolidin-2-one, **18**, was prepared by radioiododestannylation of tin precursor **17** using Na^{123}I and 0.3% peracetic acid in 84% radiochemical yield in 20 min.

Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) are non-invasive imaging modalities that provide *in vivo* physicochemical pharmacokinetic information as well as measurement and quantification of biochemical processes.[1-4] These imaging techniques are valuable tools to identify the neuronal networks in cognitive processes, evaluate disease pathways and predict the early onset of the diseases. The early detection of a disease often determines how effectively any treatment or therapy works.[5,6] In the neuronal network, neurotransmitters such as dopamine, GABA, serotonin etc. bind to specific brain cell receptors that receive messages.[7-9] This targeted binding further helps to evaluate whether abnormally high or low levels of neurotransmitters are associated with specific brain conditions.[10] Racetams such as piracetam (**1**) and aniracetam (**2**) are drugs that are nootropic and known to be effective for cognitive disorders, dementia, vertigo and dyslexia.[11] These are low-molecular-weight derivatives of γ-aminobutyric acid (GABA) and have been demonstrated to have

neuroprotective and anticonvulsant properties.[12,13]



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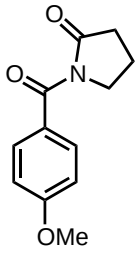
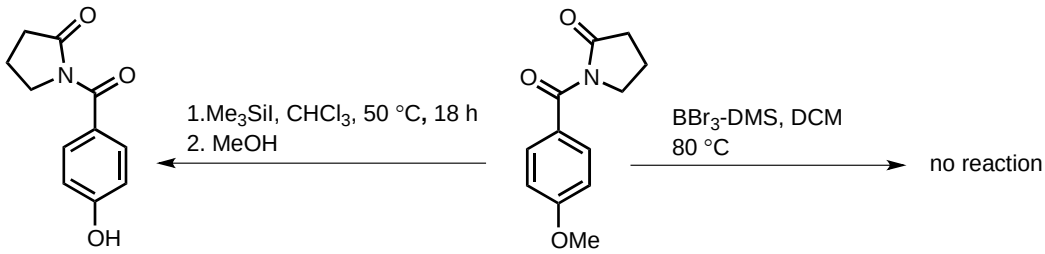


2

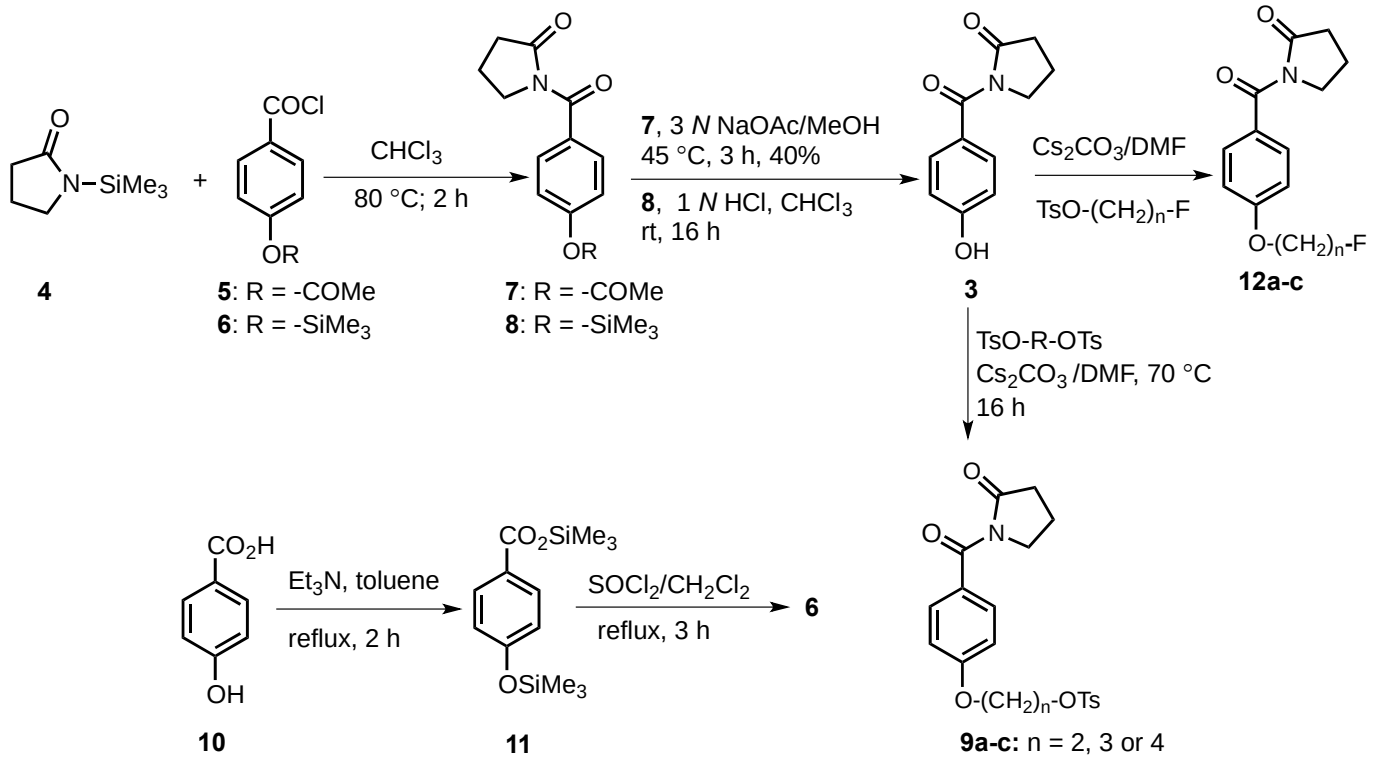
Piracetam has a variety of physiological properties that effect the restoration of cell membrane fluidity.[14] Recently, ^{99m}Tc-piracetam was reported as a brain imaging agent.[15] Aniracetam (**2**), having the core pyrrolidinone structure of piracetam, is more lipophilic and exhibits similar physiological properties. Aniracetam and piracetam were shown to be positive allosteric modulators of AMPA receptor.[16,17] It is known that aniracetam, when orally ingested, quickly breaks down into *N*-anisoyl-GABA which is a pharmacologically active metabolite.[18] We wish to report the syntheses of *N*-[4-(2'-[^{18}F]fluoroalkyloxy-benzoyl)]pyrrolidin-2-ones **13a-c** and *N*-(3-[^{123}I]iodo-4-methoxybenzoyl)pyrrolidin-2-one, **18**, as potential PET and SPECT brain imaging agents respectively.

The preparations of crucial tosylate precusors **9a-c** used in the radiofluorination reactions are described in **Scheme 1**. Attempts to demethylate the commercially available aniracetam using BBr_3-DMS to obtain the key intermediate **3** failed. Trimethylsilyl iodide demethylation of **2** in chloroform at 50 °C provided a yield of phenol **3** of less than 5%. However, *N*-[4-hydroxybenzoyl]pyrrolidin-2-one, **3**, was successfully prepared by two routes starting from *N*-trimethylsilylpyrrolidin-2-one, **4**. *N*-Benzoylation of pyrrolidinone **4** with either 4-acetoxybenzoyl chloride, **5**, or 4-trimethylsilyloxybenzoyl chloride, **6**, in



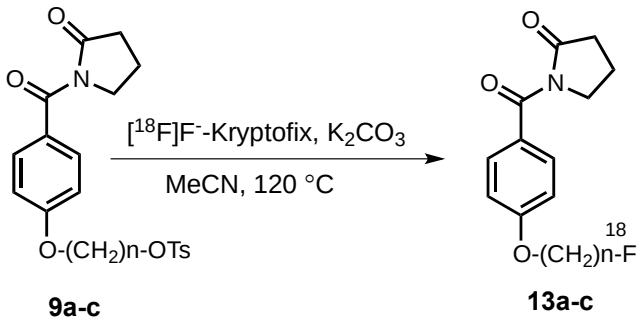
3 **2**

chloroform at 80 °C for 2 h provided acetoxy compound **7** and trimethylsilyl compound, **8**, in 84% and 78% respectively. Benzoyl chloride **6** was prepared, following the literature procedure,[19] starting from 4-hydroxybenzoic acid, **10**, by refluxing it with trimethylsilyl chloride in toluene for 2 h in the presence of triethylamine to obtain trimethylsilyl benzoate **11** which was converted to benzoyl chloride **6** by treating it with thionyl chloride in dichloromethane under reflux for 3 h. Deacetylation of **7** with 3 *N* sodium acetate in methanol at 45 °C for 3 h and desilylation of **8** with 1 *N* HCl in chloroform for 16 h at rt provided phenol **3**.



Scheme 1

Alkylation of **3** with 1,2-ditosylethane, 1,3-ditosylpropane or 1,4-ditosylbutane in DMF using cesium carbonate as base and heating at 70 °C for 16 h furnished the tosylate precursors **9a-c** in 36-42% yield. Similarly 2-fluoroethyloxy-, 3-fluoropropyloxy- and 4-fluorobutyloxybenzoylpyrrolidin-2-ones, **12a-c**, were prepared by the alkylation of phenol **3** with 2-fluoroethyl-, 3-fluoropropyl- and 4-fluorobutyl tosylate. Nucleophilic radiofluorination of tosylate precursors **9a-c** was carried out in an Advion NanoTek LF Microfluidic Synthesis System using [^{18}F]F$^-$-Kryptofix-K_2CO_3 complex in acetonitrile at 120 °C to obtain *N*-(4-[^{18}F]fluoroalkyloxy)benzoylpyrrolidin-2-ones **13a-c** in ≥30 % radiochemical yield [**Scheme 2**]. The crude radiochemical yields were determined by radio-TLC and pure products were



Scheme 2

isolated by semi-preparative HPLC purification on a PerkinElmer 200 Quartenary System. Appropriate

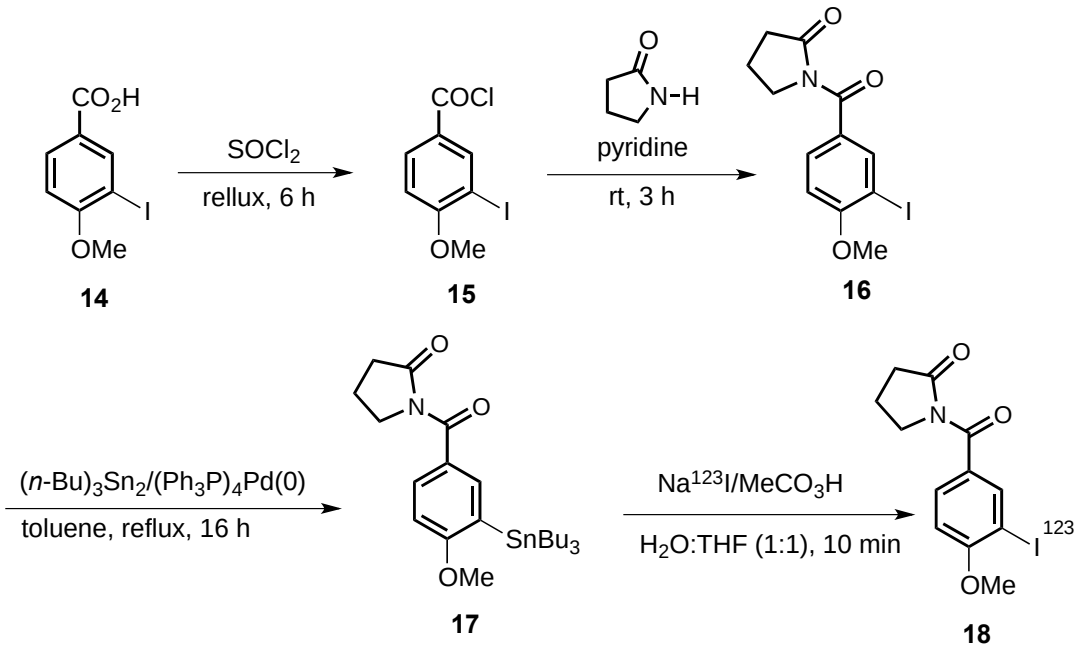
radioactive peaks were collected, diluted with water and then passed through a C_{18} Sep-Pak cartridge to trap the desired products and eliminate the unreacted radioactive fluoride. Finally, the desired products were released from the solid phase using diethyl ether (2 mL). The radiochemical purity of the products was determined using Agilent 1200 Binary Analytical radio-HPLC System (**Table 1**) and the identity of the products was confirmed by the co-elution of **13a-c** with their corresponding cold standard compounds **12a-c**.

Table 1

Tracer	%RCY (n=3)	RCP	RT	R_f
13a	35±5	≥97	3.63	4.28
13b	38±8	≥95	4.04	4.36
13c	40±5	≥93	4.24	4.42

RCY = radiochemical yield; RCP = radiochemical purity;
RT = retention time; R_f = retention factor from radio-TLC of Bioscan

The SPECT agent *N*-(3-[^{123}I]iodo-4-methoxybenzoyl)pyrrolidin-2-one, **18**, was synthesized in four steps starting from 3-iodo-4-methoxybenzoic acid, **14**, in 84% radiochemical yield. Benzoic acid **14** was converted to benzoyl chloride **15** in quantitative yield by refluxing it in excess thionyl chloride. The crude benzoyl chloride **15** was used for *N*-benzoylation of pyrrolidin-2-one using pyridine as base to afford



Scheme 3

iodoaniracetam **16**. Palladium catalyzed deiodostannylation of **16** was carried out using hexabutylditin, tetrakis(triphenylphosphine)palladium(0) in refluxing toluene to afford the tin precursor **17**.

Radioiodination of the tin precursor **17** with $Na^{123}I$ and 0.3% peracetic acid produced *N*-(3-[^{123}I]iodo-4-methoxybenzoyl)pyrrolidin-2-one, **18**. The formation of the labeled compound monitored by radio-TLC and the product was purified using a C_{18} Sep-Pak cartridge. The radiochemical purity (≥98%) was determined using an Agilent Binary 1200 analytical radio-HPLC system [**Figure 1**] and the product identity was confirmed by the co-elution of the radioactive peak with the non-radioactive standard **16.**

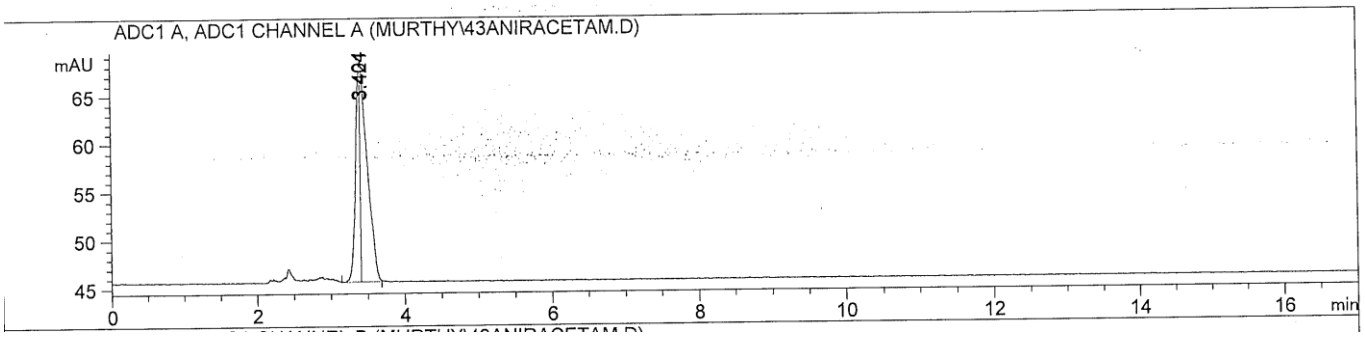


Figure 1. Radioanalytical HPLC of SPECT agent **18**; retentiom time = 3.40

CONCLUSIONS

We successfully synthesized radiofluorinated aniracetam analogues **13a-c** as potential PET agents for brain imaging starting from 4-hydroxybenzoic acid in six steps. The nucleophilic radiofluorination of tosylate precursors **9a-c** consistently provided the radiolabeled products **13a-c** in high radiochemical yield (30-46% non-decay-corrected) and purity (≥93%). Also *N*-(3-[^{123}I]iodo-4-methoxybenzoyl)pyrrolidin-2-one was prepared as a SPECT agent in 84% radiochemical yield starting from 3-iodo-4-methoxybenzoic acid in four steps. Preliminary imaging studies indicate that there is a brain uptake and more detailed studies are currently underway.

EXPERIMENTAL

All reagents and solvents were purchased from Acros Chemicals or Sigma-Aldrich and were used as received. Column chromatography was performed using silica gel (60 Å, 230–400 mesh, Sorbent Technologies, USA). Analytical thin-layer chromatography was performed using 250 μm silica plates (Analtech, Inc., Newark, DE). ^{1}H-NMR and ^{13}C-NMR spectra were recorded at (300 MHz or 500 MHz) and 125 MHz, respectively. Chemical shifts for ^{1}H-NMR and ^{13}C-NMR spectra were referenced to the residual protons of the deuterated solvents or to TMS. High Resolution Mass Spectrometry was performed using a JEOL AccuTOF™ DART Mass Spectrometer. No-carrier-added [^{18}F]F^-, produced from recycled [^{18}O] water, was obtained from PETNet (Knoxville, TN). Thin-layer chromatography

visualization was performed with radiation detectors using a BioScan AR-2500 radio-TLC reader and Win Scan 1.3 software. All radio-TLC plates were developed using EtOAc/hexane mixture. Analytical radio-HPLC analyses were performed on an Agilent 1200 series instrument employing a 254 nm UV detector and a Phenomenex Luna C_{18} column, 5µ, 4.6 x 250 mm, using 5% EtOH/95% water as the eluent at a flow rate of 1mL/min. F-18 Labelling was performed in 100 µm x 2m reactor using Advion NanoTek Microfluidic Synthesis System controlled by NanoTek LF 1.4 Software. Semipreparative HPLC was performed using PerkinElmer 200 series.

***N*-[4-Acetoxybenzoyl]pyrrolidin-2-one (7):** A 50 mL round bottomed flask was charged with a mixture of *N*-trimethylsilylpyrrolidin-2-one (0.56 g, 3.6 mmol) and 4-acetoxybenzoyl chloride (0.71 g, 3.6 mmol) in $CHCl_3$ (25 mL) and was refluxed for 2 h under argon. The solvent was removed under vacuum, the residue was dissolved in Et_2O (30 mL) and ethereal layer was washed sequentially with saturated solution of $NaHCO_3$ (10 mL), water (10 mL) and brine (10 mL). The Et_2O solution was dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo* to obtain *N*-[4-acetoxybenzoyl]pyrrolidin- 2-one, **8**, as a light yellow solid, 0.75 g (84%, crude).

Trimethylsilyl 4-trimethylsilyloxybenzoate (11): To a mixture of 4-hydroxybenzoic acid (1.38 g, 10.0 mmol) and trimethylsilyl chloride (3.21g; 3.74 mL, 30.0 mmol) in 50 mL round bottomed flask in dry toluene (20.0 mL) was added triethylamine (4.40 g, 44 mmol) dropwise and the reaction mixture was refluxed for 2 h under argon. The reaction solution was vacuum filtered to remove the precipitated triethylamine hydrochloride, the toluene was evaporated *in vacuo*, and the product was isolated by distillation under high vacuum to obtain 2.54 g of benzoate **10** (90%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.6 Hz, 2H), 6.98 (d, *J* = 7.6 Hz, 2H), 0.45 (s, 9H) and 0.23 (s, 9H).

4-Trimethylsilyloxybenzoyl Chloride (6): A mixture of trimethylsilyl 4-trimethylsilyloxybenzoate (2.52 g, 9.00 mmol) and thionyl chloride (2.24 g; 10.8 mmol) dissolved in CH_2Cl_2 (5 mL) in 25 mL round bottomed flask was refluxed under argon for 2 h. The solvent was removed under vacuum and the light yellow liquid was distilled by short-path distillation apparatus to obtain 1.24 g of 4-trimethylsilyloxy-benzoyl chloride (60%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.6 Hz, 2H), 6.98 (d, *J* = 7.6 Hz, 2H) and 0.25 (s, 9H).

***N*-[4-Trimethysilyloxybenzoyl]pyrrolidin-2-one (8):** A 50 mL round bottomed flask was charged with a mixture of *N*-trimethylsilylpyrrolidin-2-one (0.56 g, 3.6 mmol) and 4-trimethlsilyloxybenzoyl chloride (0.82 g, 3.6 mmol) in $CHCl_3$ (25 mL) and was refluxed for 2 h under argon. The solvent was removed under vacuum, the residue dissolved in Et_2O (30 mL), and the ethereal layer was washed sequentially with a saturated aqueous solution of $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL). The solutions was dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo* to yield a gummy solid. The product

was purified by silica gel column chromatorgraphy using EtOAc:petroleum ether = 1:4 to obtain 0.72 g of *N*-[4-trimethylsilyloxybenzoyl]pyrrolidin-2-one, **8** (72%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.35 (d, *J* = 7.6 Hz, 2H) 7.18 (d, *J* = 7.6 Hz, 2H), 3.91 (t, *J* = 2.4 Hz, 2H), 2.62 (t, *J* = 2.4, 2H), 2.13-2.20 (m, 2H) and 0.23 (s, 9H).

***N*-[4-Hydroxybenzoyl]pyrrolidin-2-one (3):**

From *N*-[4-acetoxybenzoyl]pyrrolidin-2-one: A mixture of acetoxy compound **7** (0.30 g, 1.2 mmol), 3 *M* sodium acetate in MeOH (3 mL) was stirred at 45 °C for 3 h. The reaction mixture was then neutralized with dil. hydrochloric acid to pH 7 and the solvent was removed *in vacuo*. The gummy residue was purified by silica gel column chromatography using EtOAc:petroleum ether = 45:55 to obtain 98.0 mg of phenol **3** (40%).

From *N*-[4-trimethylsilyloxybenzoyl]pyrrolidin-2-one: A mixture of silyloxy compound **8** (0.70 g, 2.5 mmol) and 1 N hydrochloric acid (5 mL) in $CHCl_3$ (20 mL) was stirred at room temperature for 16 h. The solvent was removed *in vacuo* and the crude product was purified as mentioned before to obtain 0.13 g of phenol **3** (25%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.60 (d, *J* = 7.6 Hz, 2H) 6.95 (d, *J* = 7.6 Hz, 2H), 3.95 (t, *J* = 2.4 Hz, 2H), 2.65 (t, *J* = 2.4, 2H) and 2.19-2.27 (m, 2H).

General procedure for alkylation of *N*-[4-hydroxybenzoyl]pyrrolidin-2-one, 3, with ditosylates: A mixture of phenol **3** (0.5 mmol) and 1,2-ditosylethane, or 1,3-ditosylpropane, or 1,4-ditosylbutane (1.25 mmol) was dissolved in anhydrous DMF (10 mL) in a 25 mL round bottomed flask. Cesium carbonate was then added and the mixture heated at 70 °C for 16 h under argon. The reaction mixture then was poured into ice and then extracted with Et_2O (2 x 50 mL) and the combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the gummy solid was purified by silica gel flash chromatography using EtOAc;hexane = 1:1 to obtain tosylate precursors **9a-c**.

***N*-[4-(2'-Tosyloxyethyloxy)benzoyl]pyrrolidn-2-one (9a):** Yield = 38%, ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 4.37-4.40 (m, 2H), 4.17-4.20 (m, 2H), 3.93 (t, *J* = 5.4 Hz, 2H), 2.60 (t, *J* = 5.4 Hz, 2H), 2.45 (s, 3H) and 2.08-2.18 (m, 2H), ^{13}C-NMR (300 MHz, $CDCl_3$): δ 17.69, 21.64, 33.39, 46.77, 65.37, 67.76, 113.49, 126.90, 127.97, 129.86, 131.61, 132.79, 145.01, 161.11, 169.82 and 174.59. HRMS (ES) calculated for (M + H) $C_{20}H_{21}NO_6S$: 404.11678. observed: 404.11617.

***N*-[4-(3'-Tosyloxypropyloxy)benzoyl]pyrrolidn-2-one (9b):** Yield = 41%, ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.73 (d, *J* = 8.4 Hz, 2H), 4.24 (t, *J* = 5.4 Hz, 2H), 3.91-4.00 (m, 4H) 3.93 (t, *J* = 5.4 Hz, 2H), 2.60 (t, *J* = 5.4 Hz, 2H), 2.35 (s, 3H) and

2.08-2.19 (m, 2H), ^{13}C-NMR (300 MHz, $CDCl_3$): δ 17.02, 21.54, 28.67, 33.38, 46.77, 63.08, 66.71, 113.32, 126.39, 127.74, 129.82, 131.59, 132.58, 144.88, 161.65, 169.91, and 174.58. HRMS (ES) calculated for (M + H) $C_{21}H_{23}NO_6S$: 418.13243.11678. Observed: 418.13307.

***N*-[4-(4'-Tosyloxybutyloxy)benzoyl]pyrrolidn-2-one (9c):** Yield = 28%, ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.89 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.75 (d, *J* = 8.4 Hz, 2H), 4.34-4.38 (m, 2H), 4.15-4.18 (m, 4H), 3.91 (t, *J* = 5.4 Hz, 2H), 2.64 (t, *J* = 5.4 Hz, 2H), 2.49 (s, 3H) and 2.08-2.18 (m, 2H), ^{13}C-NMR (300 MHz, $CDCl_3$): δ 17.04, 21.58, 24.62, 28.63, 33.38, 46.74, 63.28, 66.68, 113.46, 126.42, 127.47, 129.72, 131.49, 132.85, 144.68, 161.35, 169.61, and 174.28. HRMS (ES) calculated for (M + H) $C_{22}H_{25}NO_6S$: 432.14016. Observed: 432.14382.

General procedure for alkylation of *N*-[4-hydroxybenzoyl]pyrrolidin-2-one, 3, with fluoroalkyl tosylates: A mixture of phenol **3** (0.5 mmol) and 2-fluoroethyl tosylate, 3-fluoropropyl tosylate, or 4-fluorobutyl tosylate (1.25 mmol) was dissolved in anhydrous DMF (10 mL) in 25 mL round bottomed flask. Cesium carbonate was then added and the reaction was heated at 70 °C for 16 h under argon. The reaction mixture was poured into ice and then extracted with Et_2O (2 x 50 mL) and the combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the gummy solid was purified by silica gel flash chromatography using EtOAc:hexane = 1:1 to obtain cold standard fluoro compounds **12a-c**.

***N*-[4-(2-Fluoroethyloxy)benzoyl]pyrrolidn-2-one (12a):** Yield = 40%, ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 4.84 (t, *J* = 4.8, Hz, 1H), 4.60 (t, *J* = 4.8, Hz, 1H), 4.30 (t, *J* = 4.8, Hz, 1H), 4.28 (t, *J* = 4.8, Hz, 1H), 3.93 (t, *J* = 7.5 Hz, 2H), 2.61 (t, *J* = 7.5 Hz, 2H), 2.08-2.18 (m, 2H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ 17.86, 33.54, 46.93, 67.38, 82.90, 113.76, 124.94, 131.88, 161.74, 170.05 and 174.76. HRMS (ES) calculated for (M + H) $C_{13}H_{14}FNO_3$: 252.10361 Observed: 252.10356.

***N*-[4-(2-Fluoropropyloxy)benzoyl]pyrrolidn-2-one (12b):** Yield = 42%, ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.52 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 4.78 (t, *J* = 4.8, Hz, 1H), 4.56 (t, *J* = 4.8, Hz, 1H), 4.26 (t, *J* = 4.8, Hz, 1H), 4.22 (t, *J* = 4.8, Hz, 1H), 3.92 (t, *J* = 7.5 Hz, 2H), 2.58 (t, *J* = 7.5 Hz, 2H), 1.91-2.35 (m, 4H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ 17.26, 33.37, 33.39, 46.78, 63.60, 79.40, 81.58, 113.49, 126.30, 131.69, 162.02, 169.96 and 174.59. HRMS (ES) calculated for (M + H) $C_{14}H_{16}FNO_3$: 266.10361 Observed: 266.11925.

***N*-[4-(2-Fluorobutyloxy)benzoyl]pyrrolidn-2-one (12c):** Yield = 38%, ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 4.82 (t, *J* = 4.8, Hz, 1H), 4.58 (t, *J* = 4.8, Hz, 1H), 4.27 (t, *J* = 4.8, Hz, 1H), 4.25 (t, *J* = 4.8, Hz, 1H), 3.92 (t, *J* = 7.5 Hz, 2H), 2.58 (t, *J* = 7.5 Hz, 2H), 2.13-2.44 (m, 6H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ 17.86, 30.37, 33.74, 33.79, 46.91, 67.60, 78.40, 82.38, 113.94, 125.12,

131.67, 161.02, 169.99 and 174.93. HRMS (ES) calculated for (M + H) $C_{15}H_{18}FNO_3$: 280.10561 Observed: 280.10342.

General procedure for radiofluorination of tosylate precursors 9a-c: The details of operation of the NanoTek Microfluidic System have been described previously.[20] Cyclotron-produced, no-carrier-added [^{18}F]fluoride ion (100 mCi) in [^{18}O]water (225 - 350 μL) was first adsorbed onto an anion exchange resin ORTG cartridge within the concentrator module of a NanoTek apparatus (Advion Biosciences), and then released with a solution of K_2CO_3 (1.8 mg) plus $K_{2.2.2}$ (12.0 mg) in MeCN/H_2O (9.5:0.5 v/v; 400 μL) into a 5 mL V-vial. The solution was dried by three cycles of azeotropic evaporation using MeCN (0.45 mL) at 100 ºC. The dry $^{18}F^-$-K2.2.2-K^+ complex was dissolved in MeCN (0.5 mL). The isotope solution was then loaded into the loop of the reactor module (431 μL), and the tosylate precursor **9a-c** (10 mg in 0.5 mL of MeCN) solution was loaded into the other loop on the reagent module (431 μL). These solutions were concurrently infused into a 2 m long micro reactor coil (100 μm) at a combined flow rate of 200 μL/min at 120 ºC. The radiofluorinated product was collected and purified by Semipreparative HPLC column (Phenomenex Luna reverse phase column, 250 × 10 mm, 10μ, using gradient elution (A: MeCN, B: water; 0.5 min 40% A and 60% B; 5 - 15 min 40% A - 70% A and 15 - 30 min 70% A, flow rate 3mL/min). A fraction (12-14 min) was collected, diluted with water (10 mL), and passed through a C_{18} Sep-Pak cartridge to trap the desired product. The cartridge was then washed with Et_2O (2 mL) and the solvent evaporated under a stream of argon to afford 30-35 mCi of radiofluorinated pyrrolidinones **13a-c**.

3-Iodo-4-methoxybenzoyl chloride (15): A mixture of 3-iodo-4-methoxybenzoic acid (0.50 g, 1.8 mmol) and thionyl chloride (10 mL) in 50 mL RB flask was refluxed for 6 h. Excess thionyl chloride was removed *in vacuo* and the residue was further connected to high vacuum until mass of the crude product remained constant. The crude product 3-iodo-4-methoxybenzoyl chloride, **15**, was used in the next reaction without further purification.

***N*-[3-Iodo-4-methoxybenzoyl]pyrrolidin-2-one (16):** A mixture of 3-iodo-4-methoxybenzoyl chloride, 15 (0.53 g, 1.8 mmol), pyrrolidin-2-one (0.16 g, 1.9 mmol) in pyridine (10 mL) was stirred at room temperature for 3 h. The reaction mixture was poured into EtOAc (100 mL) and was washed sequentially with 1 N hydrochloric acid (25 mL), water (2 x 50 mL), saturated aqueous $NaHCO_3$ (2 x 25 mL), and then with brine (20 mL). The organic layer was dried over anhydrous Na_2SO_a and the solvent removed *in vacuo*. The crude product was isolated by silica gel column flash chromatography using EtOAc:hexane = 4:6 to afford 0.22 g of white solid (35%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.07 (s, 1H), 7.61 (dd, *J* = 2.4 Hz, *J* = 8.4 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 3.93 (t, *J* = 7.2 Hz, 2H), 3.91 (s, 3H), 3.91 (t, *J* = 7.2 Hz, 2H), 2.62 (t, *J* = 7.2 Hz, 2H), 2.08-2.20 (m, 2H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ 17.81, 33.45, 46.86, 56.64, 84.90,

109.52, 128.08, 131.74, 140.96, 161.17, 168.60 and 171.72. HRMS (ES) calculated for (M + H) $C_{12}H_{12}INO_3$: 345.99401 Observed: 345.99307.

***N*-[4-Methoxy-3-tributylstannylbenzoyl]pyrrolidin-2-one (17):** To *N*-[3-iodo-4-methoxybenzoyl]-pyrrolidin-2-one, **16**, (250.0 mg; 0.72 mmol in 25 mL round bottomed flask was added hexamethylditin (0.46 g, 0.79 mmol), tetrakis(triphenylphosphine)palladium(0) (50.0 mg, 6 mol%), and toluene (5 mL). The resulting reaction mixture was refluxed under argon for 16 h. Precipitated palladium was filtered out using celite and the solvent was removed *in vacuo*. The residue was purified by silica gel flash column chromatography using EtOAc:haxne = 15:85 to obtain 160.0 mg of *N*-[4-methoxy-3-tributylstannyl-benzoyl]pyrrolidin-2-one (44%) as a color less oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.61 (d, *J* = 8.4 Hz, 1H) 5.76 (d, *J* = 8.4 Hz, 1H), 3.93 (t, *J* = 7.2 Hz, 2H), 3.91 (s, 3H), 2.59 (t, *J* = 7.2 Hz, 2H), 2.00-2.17 (m, 2H), 1.45-1.56 (m, 6H), 1.25-1.37 (m, 6H), 1.03 (t, 7.8 Hz, 6H) and 0.93 (t, 7.4 Hz, 9H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ 13.67, 17.78, 27.29, 29.06, 33.42, 46.87, 55.21, 79.75, 107.55, 126.21, 130.00, 132.51, 138.67, 167.09, 170.56 and 174.42. HRMS (ES) calculated for (M + H) $C_{24}H_{39}NO_3Sn$: 510.20302 Observed: 510.20358.

***N*-(3-[^{123}I]Iodo-4-methoxybenzoyl)pyrrolidin-2-one (18):** To a no-carrier-added $Na^{123}I$ (0.5 mCi in 0.1% aqueous NaOH) in a 2 mL Wheaton vial was added tin precursor **17** (100 mL of 4.8 x 10^{-2} M solution in water:THF = 1:1). Peracetic acid (100 mL, 0.3% solution) was added and the resulting reaction mixture was stirred for 10 min at rt. The reaction was monitored by Bioscan radio-TLC and the final product was purified by trapping it on a C_{18} Sep-Pak and eluting it with Et_2O (2 mL) to obtain 0.42 mCi of *N*-(3-[^{123}I]iodo-4-methoxybenzoyl]pyrrolidin-2-one, **18** (84%). The solvent was removed under a stream of argon and the product was formulated in 0.9% saline. The radiochemical purity was assessed by analytical radio-HPLC and the identity of the product was confirmed by co-elution of the radioactive peak with the cold standard.

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