Convenient Entry to $^{18}$F-Labeled Amines through the Staudinger Reduction

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1. Synthesis of reference compounds and precursors

**General information**

All reagents and solvents were purchased from ABX, Sigma Aldrich, Fluorochem and VWR and used as received, without further purification, unless stated otherwise. Dry THF and DCM were obtained from a SG Water solvent purification system and dry dimethyl sulfoxide (DMSO), MeCN, pyridine and methanol (MeOH) were purchased from commercial suppliers. Room temperature corresponds to a temperature interval from 18–21 °C. Reactions requiring anhydrous conditions were carried out under inert atmosphere (nitrogen) and using oven-dried glassware (152 °C). NMR (1H, 13C, 19F and 11B) spectra were acquired on a 600 MHz Bruker Avance III HD, a 400 MHz Bruker Avance II or a Bruker AC200. Samples were measured at 300 K, except for the Bruker AC200, in which samples were measured at 293 K. Chemical shift (δ) are expressed in parts per million and referenced to residual solvent peak and internal standards for 19F and 11B. The resonance multiplicity is abbreviated as follows or combinations thereof: s (singlet), bs (broad singlet), d (doublet), t (triplet), p (quintet) and m (multiplet). All 13C and 19F NMR spectra were measured with proton decoupling. Thin-layer chromatography (TLC) was run on silica plated aluminum sheets (Silica gel 60 F254) from Merck and the spots were visualized by ultraviolet light at 254 nm, by anisaldehyde and/or by potassium permanganate staining. Flash column chromatography was carried out manually on silica gel 60 (0.040–0.063 mm). Preparative high-performance liquid chromatography (HPLC) was performed on a Thermo Scientific Dionex 3000 UltiMate instrument connected to a Thermo Scientific Dionex 3000 Diode Array Detector using a Gemini-NX 5µ RP C18 column (250 × 21.2 mm) with UV detection at 254 and 280 nm. Mobile phase A (MP A): 0.1% trifluoroacetic acid (TFA) in water (v/v). Mobile phase B (MP B): 0.1% TFA, 10% water in ACN (v/v/v). Flow rate: 20 mL/min. Gradient: 0–100% MP B; 30–35 min, 100% MP B. High resolution mass spectrometry (HRMS) was performed as matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF). Analyses were performed in positive ion mode with ionization on a ThermoQExactive Orbitrap mass spectrometer (Thermo Scientific) equipped with an AP-SMALDI 10 ion source (TransmitMIT) and operated with mass resolving power 140,000 at m/z 200 and lock-mass for internal mass calibration. Samples were dissolved in a matrix consisting of 2,5-dihydroxybenzoic acid (20 mg) in MeOH (1 mL). Melting points were measured on an IA9100 digital melting point apparatus from Electrothermal and are uncorrected.

The following reference compounds were commercially available: fluoroethylamine (2), 1-(azidomethyl)-4-fluorobenzene (11), 1-azido-4-fluorobenzene (12), (4-fluorophenyl)methanamine (14) and 4-fluoroaniline (15).

**1-Azido-2-fluoroethane (1)**

![N3F](image)

Azide 1 was synthesized according to Denk et al. with minor modifications.[1] 2-Fluorethanol (1.0 g, 15.6 mmol) in dry pyridine (5 mL) was cooled to 0 °C and treated dropwise with a solution of p-toluenesulfonyl chloride (5.95 g, 31.2 mmol) in dry pyridine (8 mL). The mixture was stirred at 0 °C for 3 h and thereafter poured onto ice, which caused the product to precipitate. Extraction with EtOAc, washing of the organic phase with aqueous 2 M HCl, saturated Na2CO3 solution and brine, followed by drying over Na2SO4 and removal of the solvent yielded crude 2-fluoroethyl-4-methylbenzenesulfonate as colorless liquid. The tosylate was dissolved in dry DMF (10 mL) and NaN3 (1.1 g, 16.9 mmol) was added to the solution, which was stirred for 48 h at room temperature. The formed solids were filtered off and a pale-yellow solution containing 1 (8.1 g, 74%) was afforded as investigated by 1H NMR. 1 free of DMF was obtained by heating a mixture of 2-azidoethyl 4-nitrobenzenesulfonate (136 mg, 0.5 mmol), Kryptofix-222 (136 mg, 0.47 mmol) and anhydrous
potassium fluoride (30 mg, 0.5 mmol) in CD$_3$CN (1.5 mL) to 80 °C for 10 min using a laboratory microwave. After cooling to room temperature vacuum (10 mbar) was applied and volatiles were collected in a trap cooled with liquid nitrogen resulting in a solution of 1 in CD$_3$CN. $^1$H NMR (400 MHz, MeCN-$d_3$) $\delta$ 4.57 (dt, $J = 47.6, 4.7$ Hz, 2H), 3.53 (dt, $J = 28.9, 4.7$ Hz, 2H). $^{13}$C NMR (50.32 MHz, MeCN-$d_3$) $\delta$ 83.8 (d, $J = 166.8$ Hz), 51.9 (d, $J = 19.3$ Hz). $^{19}$F NMR (376.5 MHz, MeCN-$d_3$) $\delta$ = -223.2.

2-Azidoethyl 4-nitrobenzenesulphonate (I, precursor in the radiosynthesis of $[^{18}$F]$^1$)

Azide I was synthesized according to Denk et al. with minor modifications,[1] 2-Azidoethanol (2.0 g, 23 mmol) and Et$_3$N (6.58 mL, 47 mmol) in dry DCM (20 mL) were cooled to 0 °C and p-nitrobenzenesulfonyl chloride (10.4 g, 47 mmol) in dry DCM (30 mL) was added within 20 min. The mixture was allowed to reach room temperature and stirred for additional 2 h. The mixture was diluted with DCM and washed with aqueous 2 M HCl and brine, dried over Na$_2$SO$_4$, filtered off and concentrated under reduced pressure. The crude product was purified by flash column chromatography using EtOAc in heptane (10→20%) and subsequent recrystallization from toluene to afford I (3.93 g, 63%) as pale yellow crystals. Melting point 80–82 °C. $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 8.42 (dt, $J = 8.8, 2.0$ Hz, 2H), 8.14 (dt, $J = 8.8, 2.3$ Hz, 2H), 4.27 (t, $J = 5.3$ Hz, 2H), 3.55 (t, $J = 4.9$ Hz, 2H). $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 150.8, 141.2, 129.2, 124.5, 69.2, 68.8, 50.8, 23.80. HRMS m/z (MALDI-TOF) calculated for C$_{15}$H$_{30}$N$_{7}$O$_{6}$SNa$: 396.1199, found: 396.1198 [M+Na]$^+$.

2-(2-(2-(2-Azidoethoxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulphonate (3)

Azide 5 was synthesized according to Dao et al. [2]. Tetraethylene glycol di(p-toluenesulphonate) (4.87 g, 9.69 mmol) was dissolved in EtOH (60 mL) and Na$_2$S$_2$O$_4$ (630 mg, 9.69 mmol) was added. The mixture was heated to reflux overnight (15 h) and thereafter poured on ice-water (~150 mL). The phases were separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried over MgSO$_4$, filtered off and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using a gradient of EtOAc in heptane (30%→60%) as eluent to afford 3 (1.7 g, 47%) as a colorless oil. TLC R$_f$ = 0.27 (50% EtOAc in heptane). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.80 (d, $J = 8.3$ Hz, 2H), 7.34 (d, $J = 8.0$ Hz, 2H), 4.15 (t, $J = 5.0$ Hz, 2H), 3.77–3.55 (m, 12H), 3.38 (t, $J = 5.1$ Hz, 2H), 2.44 (s, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 144.9, 133.2, 130.0, 128.1, 124.5, 69.2, 68.8, 50.8, 21.80. HRMS m/z (MALDI-TOF) calculated for C$_{15}$H$_{30}$N$_{7}$O$_{6}$SNa$: 396.1199, found: 396.1198 [M+Na]$^+$.

1-Azido-2-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)ethane (4)

Tetra-n-butylammonium fluoride (1.96 g, 7.01 mmol) was added to a solution of 3 (2.31g, 5.83 mmol) in dry MeCN (20 mL). The mixture was heated to reflux overnight and thereafter concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using EtOAc in heptane (50%) as eluent to afford 4 (1.27 g, 96%) as a colorless oil. TLC R$_f$ = 0.39 (60% EtOAc in heptane). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.65–4.59 (m, 1H), 4.53–4.46 (m, 1H), 3.81–3.77 (m, 1H), 3.73–3.61 (m, 1H), 3.38 (t, $J = 5.1$ Hz, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 83.3 (d, $J = 169.0$ Hz), 71.0–70.2, 50.9. $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ 14.19. HRMS m/z (MALDI-TOF) calculated for C$_{16}$H$_{30}$FN$_{7}$O$_{6}$Na$: 222.1248, found: 222.1252 [M+H]$^+$.
2-(2-(2-Fluoroethoxy)ethoxy)ethoxy)ethan-1-amine (5)

A solution of 4 (712 mg, 3.22 mmol) and PPh₃ (1.27 g, 4.83 mmol) in dry THF (16 mL) was stirred at room temperature overnight under nitrogen atmosphere. Thereafter, the mixture was treated with water (~10 mL) and stirred at room temperature for 1.5 h, before it was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using 7N NH₃/MeOH in DCM (10%) as eluent to afford 5 (534 mg, 85%) as a pale yellow oil. TLC Rf = 0.36 (10% 7N NH₃/MeOH in DCM).

1H NMR (400 MHz, CDCl₃) δ 4.63–4.58 (m, 1H), 4.51–4.44 (m, 1H), 3.81–3.74 (m, 1H), 3.72–3.58 (m, 9H), 3.49 (t, J = 5.2 Hz, 2H), 2.84 (t, J = 5.2 Hz, 2H), 1.44 (bs, 2H).

13C NMR (101 MHz, CDCl₃) δ 83.2 (d, J = 168.9 Hz), 73.4, 70.9–70.3, 41.8. 19F NMR (376 MHz, CDCl₃) δ 14.21.

HRMS m/z (MALDI-TOF) calculated for C₈H₁₈FNO₃+: 196.1343, found 196.1349 [M+H]+.

2,5-Dioxopyrrolidin-1-yl 4-(6-(pyrimidin-2-yl)-1,2,4,5-tetrazin-3-yl)benzoate (6)

Tetrazine 6 was synthesized according to Beckmann et al. with minor modifications.[3] Hydrazine monohydrate (1.2 mL, 34 mmol) was added dropwise to a mixture of 4-cyanobenzoic acid (1.0 g, 6.8 mmol) and pyrimidine-2-carbonitrile (715 mg, 6.80 mmol) in EtOH (3 mL). The mixture was heated to reflux overnight at 85 °C. After cooling to room temperature, the orange precipitate was filtered off and washed with EtOH (1.4 mL). In order to remove the 3,6-di(pyrimidin-2-yl)-1,2,4,5-tetrazine by-product, acetone (6 mL) was added to the filtrate and the mixture was heated to reflux for 30 min. The solids were filtered off from the warm solution. The filtrate was suspended in acetic acid (12 mL) and isopentyl nitrite (0.5 mL, 3.4 mmol) was added drop wise, while the color changed from orange to purple. The mixture was stirred overnight, the precipitation was filtered off and later recrystallized from acetic acid. The product was then precipitated from acetic acid by addition of diethyl ether (19.3 mL), filtered off and dried under vacuum to afford a carboxylic acid tetrazine intermediate (500 mg) as a purple solid, which was used in the next step without further purification. N-Hydroxy succinimide (310 mg, 2.70 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (518 mg, 2.70 mmol) were added to a suspension of tetrazine (500 mg, 1.78 mmol) in dry DMSO:pyridine (19:1, 19 mL). The mixture was heated at 40 °C for 2.5 h and thereafter at room temperature overnight. The solvent was removed, and DCM and water were added to the residue. The phases were separated, and the aqueous phase was extracted with DCM. The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using EtOAc as eluent to afford 6 (170 mg, 25%) as a pink solid. Melting point (decomposition) 245–247 °C. TLC Rf = 0.30 (EtOAc). 1H NMR (600 MHz, CDCl₃) δ 9.16 (d, J = 4.8 Hz, 2H), 8.91 (d, J = 8.1 Hz, 2H), 8.41 (d, J = 8.1 Hz, 2H), 7.62 (t, J = 4.9 Hz, 1H), 2.95 (s, 4H) 13C NMR (151 MHz, CDCl₃) δ 169.1, 163.9, 163.5, 161.4, 159.5, 158.7, 137.1, 131.6, 129.4, 129.1, 122.8, 25.9. HRMS m/z (MALDI-TOF) calculated for C₁₇H₁₄N₇O₄+: 378.0945, found: 378.0952 [M+H]+.
**N-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)ethyl)-4-(6-(pyrimidin-2-yl)-1,2,4,5-tetrazin-3-yl)benzamide (7)**

Amide formation was performed with inspiration from literature procedure.[3] A solution of amine (49 mg, 0.3 mmol) in dry DMSO:pyridine (1.6 mL, 18:1) was added to 6 (80 mg, 0.2 mmol) in dry DMSO:pyridine (4.9 mL, 18:1) over the course of 4h at 50 °C. The mixture was thereafter stirred at room temperature overnight. The solvent was removed and the residue was dissolved in DCM, washed with water and brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by preparative HPLC (Rt = 14.47 min) to afford 7 (74 mg, 81%) as a purple solid. Melting point 117 – 119 °C. TLC Rf = 0.18 (5% MeOH in DCM).

**1H NMR (600 MHz, CDCl₃)** δ 9.18 (d, J = 4.9 Hz, 2H), 8.82 (d, J = 8.4 Hz, 2H), 8.07 (d, J = 8.4 Hz, 2H), 7.65 (t, J = 4.9 Hz, 1H), 7.24 (t, J = 4.7 Hz, 1H), 4.58 – 4.54 (m, 1H), 4.51 – 4.46 (m, 1H), 3.78 – 3.65 (m, 14H).

**13C NMR (151 MHz, CDCl₃)** δ 167.5, 164.2, 163.1, 159.3, 158.6, 138.5, 134.2, 129.2, 128.4, 122.9, 83.2 (d, J = 169.1 Hz), 70.9 – 70.4, 69.7, 40.4.

**19F NMR (376 MHz, CDCl₃)** δ -75.73.

**HRMS m/z (MALDI-TOF) calculated for C₂₁H₂₄F₇NO₄⁺:** 458.1946, found: 458.1959 [M+H]+.

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**N-(2-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)ethyl)phenylthiourea (8)**

A solution of 5 (105 mg, 0.54 mmol) and Et₃N (97 µL, 0.7 mmol) in dry DCM (2 mL) was stirred at room temperature for 30 min before benzoyl chloride (64 µL, 0.54 mmol) was added. The mixture was stirred at room temperature overnight. Water and DCM were added, and the phases were separated. The aqueous phase was extracted with DCM. The combined organic phases were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using a gradient of MeOH in DCM (0→3%) as eluent to afford 8 (149 mg, 92%) as a pale-yellow oil. TLC Rf = 0.26 (3% MeOH in DCM) ¹H NMR (600 MHz, CDCl₃) δ 7.82 – 7.78 (m, 2H), 7.51 – 7.47 (m, 1H), 7.45 – 7.39 (m, 2H), 6.75 (bs, 1H), 4.57 – 4.54 (m, 1H), 4.49 – 4.46 (m, 1H), 3.81 – 3.56 (m, 15H).

**13C NMR (151 MHz, CDCl₃)** δ 167.6, 134.8, 131.5, 128.6, 127.2, 83.3 (d, J = 169.1 Hz), 71.0 – 70.4, 70.0, 40.0. **19F NMR (376 MHz, CDCl₃)** δ 14.38. HRMS m/z (MALDI-TOF) calculated for C₁₅H₂₂FNO⁺: 300.1605, found: 300.1604 [M+H]+.

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**1-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)ethyl)-3-phenylthiourea (9)**

Synthesis of thiourea 9 was performed with inspiration from literature.[4] Phenyl isothiocyanate (100 µL, 0.53 mmol) was added to a solution of 5 (103 mg, 0.53 mmol) in dry toluene (4 mL). The mixture was stirred at room temperature for 3 h. The solvent was removed, and the crude product was purified by flash column chromatography on silica gel using a gradient of EtOAc in heptane (25→100%) as eluent to afford 9 (156 mg, 89%) as a white solid. Melting point <40 °C. TLC Rf = 0.16 (60% EtOAc in heptane). ¹H NMR (600 MHz,
N-Benzyl-2-(2-(2-fluoroethoxy)ethoxy)ethoxy)ethan-1-amine (10)

Reductive alkylation was carried out as described by Herth et al with modifications.[5] Benzaldehyde (106 µL, 1.05 mmol) and Et3N (146 µL, 1.05 mmol) were added to a solution of 5 (102 mg, 0.52 mmol) in EtOH (5 mL). The mixture was heated to reflux in a sealed vial for 48 h, cooled to room temperature and NaBH4 (40 mg, 1.05 mmol) was added. The mixture was stirred at room temperature overnight. The solvent was removed, and water and EIOAc were added to the residue. The phases were separated, and the aqueous phase was extracted with EIOAc. The combined organic phases were washed with brine, dried over Na2SO4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using a gradient of MeOH in DCM (0→2%) with 0.5% NH3 as eluent to afford 10 (93 mg, 63%) as a colorless oil. TLC Rf = 0.29 (2% 7N NH3/MeOH in DCM). 1H NMR (600 MHz, CDCl3) δ 7.35–7.29 (m, 4 H), 7.25–7.21 (m, 1H), 4.59–4.56 (m, 1H), 4.52–4.48 (m, 1H), 3.81 (s, 2H), 3.76–3.69 (m, 1H), 3.68–3.63 (m, 6H), 3.63–3.58 (m, 4H), 2.81 (t, J = 5.2 Hz, 2H), 1.90 (bs, 1H). 13C NMR (151 MHz, CDCl3) δ 140.4, 128.5, 128.3, 127.0, 83.3 (d, J = 169.0 Hz), 70.95–70.46, 54.0, 48.8. 19F NMR (376 MHz, CDCl3) δ 14.23. HRMS m/z (MALDI-TOF) calculated for C15H24FNO3+: 286.1813, found: 286.1816 [M+H]+.

2-(4-(Azidomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (II, precursor in the radiosynthesis of [18F]11)

Synthesis of I was carried out based on methods described in the literature.[6] 4-Bromomethylphenylboronic acid pinacol ester (122 mg, 0.41 mmol) and NaN3 (35 mg, 0.54 mmol) were dissolved in DMF (5 mL) and stirred overnight at room temperature. Water and EIOAc were added and the phases were separated. The organic layer was washed with water, dried over Na2SO4 and concentrated under reduced pressure to afford II (86 mg, 81%) as colorless oil. TLC Rf = 0.58 (33% EIOAc in heptane). 1H NMR (600 MHz, CDCl3) δ 7.83 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 4.35 (s, 2H), 1.35 (s, 12H). 13C NMR (151 MHz, CDCl3) δ 138.4, 135.4, 129.1, 127.6, 84.1, 54.9, 25.0. 11B NMR (128 MHz, CDCl3) δ 30.63.

1 Overlapping with solvent signal.
4(4,4,5,5-Tetramethyl-1,3,2-dioxaborolane-2-yl)phenyl azide (III, precursor in the radiosynthesis of $[^{18}F]$12)

Synthesis of II was carried out based on methods described in the literature.[6] Tert-Butyl nitrite (200 µL, 1.50 mmol) in MeCN (0.8 mL) was added drop wise to a solution of 4-aminophenylboronic acid pinacol ester (120 mg, 0.55 mmol) in MeCN (1.8 mL). The mixture was stirred at 0°C for 5 min under nitrogen atmosphere. Trimethylsilyl azide (170 µL, 1.21 µmol) in MeCN (0.8 mL) was added drop wise to the mixture. After 15 min of stirring, TLC (50% EtOAc in heptane) showed full consumption of 4-aminophenylboronic acid pinacol ester. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel using a gradient of EtOAc in heptane (10%→50%) as eluent to afford III (95 mg, 71%) as a brown oil. TLC Rf = 0.72 (25% EtOAc in heptane). $^1$H NMR (600 MHz, CDCl$_3$) δ 7.79 (d, $J = 8.4$ Hz, 2H), 7.02 (d, $J = 8.4$ Hz, 2H), 1.34 (s, 12H). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 143.0, 136.6, 125.6, 118.5, 84.0, 25.0. $^{11}$B NMR (128 MHz, CDCl$_3$) δ 30.62.

4-Azidophenol (IV)

Azide IV was synthesized as described by Kwok et al. [7]. Conc. HCl (3.2 mL, 39 mmol) was added slowly to a suspension of 4-aminophenol (2.00 g, 18.3 mmol) in water (20 mL). The mixture was stirred vigorously in an ice-bath for 20 min. Thereafter, an ice-cold solution of NaNO$_2$ (1.26 g, 18.3 mmol) in water (10 mL) was added drop wise, while keeping the temperature in the reaction mixture below 5 °C. After complete addition the mixture was stirred for 10 min, before a solution of NaN$_3$ (1.19 g, 18.3 mmol) in water (20 mL) was added drop wise from an addition funnel. The mixture was stirred for an additional 10 min in an ice-bath and then at room temperature for 2 h. EtOAc was added and the phases were separated. The aqueous phase was extracted with EtOAc and the combined organic phases were washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using a gradient of EtOAc in heptane (20%→80%) as eluent to afford crude IV (2.00 g, 81%) as a black oil that was used to synthesize 13 without any further purification steps.

3-Fluoropropyl-4-methylbenzenesulfonate (V)

The synthesis of V was performed as previously described by van Wieringen et al. [8], with some modifications. Tetrabutylammonium fluoride in THF (2.6 mL, 2.6 mmol, 1 M) was mixed with MeCN (3 mL) and the solvents were removed under reduced pressure. The residue was dissolved in MeCN (3 mL) and once again concentrated under reduced pressure. This procedure was repeated 3 times, after which tetrabutylammonium fluoride residue was dissolved MeCN (2 mL) and added to a solution of 1,3-propanediol bistosylate (994 mg, 2.6 mmol) in MeCN (5 mL). The mixture was heated to reflux overnight, thereafter cooled down to room temperature. Water and EtOAc were added and the phases were separated. The organic phase was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was
purified by flash column chromatography on silica gel using a gradient of EtOAc in heptane (20→100%) as eluent to afford V (239 mg, 39%) as an yellow oil. TLC Rf = 0.55 (50% EtOAc in heptane). 1H NMR (600 MHz, CDCl3) δ 7.80 (d, J = 8.4 Hz, 2H), 7.41–7.32 (m, 2H), 4.52 (t, J = 5.7 Hz, 1H), 4.44 (t, J = 5.7 Hz, 1H), 4.16 (t, J = 6.2 Hz, 2H), 2.45 (s, 3H), 2.04 (dp, J = 25.9, 5.9 Hz, 2H). 13C NMR (151 MHz, CDCl3) δ 145.1, 133.0, 130.1, 128.1, 79.7 (d, J = 25.9 Hz, 1H), 2.45 (s, 3H), 2.04 (dp, J = 25.9, 5.9 Hz, 2H). HRMS m/z (MALDI-TOF) calculated for C10H16FNO3SNa+: 255.0461, found: 255.0463 [M+Na]+.

1-Azido-4-(3-fluoropropoxy)benzene (13)

O-Alkylation towards 13 was carried out with inspiration from literature. [9] Tetrabutylammonium hydroxide (278 mg of 40 mass% methanolic solution, 0.43 mmol) was added to a solution of azide IV (68 mg, 0.50 mmol) in MeCN (1.5 mL). The solvent was removed under reduced pressure and the residue was dissolved in MeCN (1 mL), thereafter once again concentrated under reduced pressure before a solution of V (100 mg, 0.43 mmol) in MeCN (1 mL). The mixture was stirred overnight at room temperature. Water and EtOAc were added and the phases were separated. The organic layer was washed with water, dried over Na2SO4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using EtOAc in heptane (25%) as eluent to afford 13 (43 mg, 44%) as an orange oil. TLC Rf = 0.68 (25% EtOAc in heptane). 1H NMR (400 MHz, DMSO-d6) δ 7.07–7.02 (m, 2H), 7.02–6.97 (m, 2H), 4.66 (t, J = 5.9 Hz, 1H), 4.54 (t, J = 5.9 Hz, 1H), 4.05 (t, J = 6.3 Hz, 2H), 2.17–2.02 (m, 2H). 13C NMR (151 MHz, CDCl3) δ 156.3, 132.7, 120.2, 115.9, 80.8 (d, J = 164.7 Hz), 64.1 (d, J = 5.2 Hz), 30.6 (d, J = 20.2 Hz). 19F NMR (376 MHz, CDCl3) δ 14.82.

4-(3-Fluoropropoxy)aniline (16)

4-Nitrophenol (63 mg, 0.5 mmol) was added to a solution of MeCN (0.7 mL) and tetrabutylammonium hydroxide (303 mg of 40 mass% methanolic solution, 0.47 mmol). Upon the dissolution of 4-nitrophenol, the solvent was removed under reduced pressure, the residue was dissolved in MeCN (2.5 mL) and once again concentrated under reduced pressure. The residue was dissolved in MeCN (3 mL) and added to a solution of IV (100 mg, 0.43 mmol) in MeCN (1 mL). The mixture was stirred for 48 h at room temperature. Water and EtOAc were added and the phases were separated. The organic phase was washed with water, dried over Na2SO4 and concentrated under reduced pressure yielding in (1-(3-fluoropropoxy)-4-nitrobenzene), which was used in the next step without further purification. In a next step, crude (1-(3-fluoropropoxy)-4-nitrobenzene) was dissolved in EtOH (6 mL) and flushed with nitrogen. Pd/C (9 mg, 10 wt%) was added and the mixture was saturated with hydrogen gas. The mixture was stirred under hydrogen atmosphere for 4 h. The solution was filtered through celite® and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using EtOAc in heptane (50%) as eluent to afford 16 (39 mg, 51%) as a brown oil. TLC Rf = 0.33 (50% EtOAc in heptane). 1H NMR (600 MHz, CDCl3) δ 6.78–6.72 (m, 2H), 6.69–6.60 (m, 2H), 4.67 (t, J = 5.8 Hz, 1H), 4.60 (t, J = 5.8 Hz, 1H), 4.02 (t, J = 6.1 Hz, 2H), 3.45–3.40 (bs, 2H), 2.13 (dp, J = 25.9, 6.0 Hz, 2H). 13C NMR (151 MHz, CDCl3) δ 152.1, 140.3, 116.5, 115.9, 81.1 (d, J = 164.0 Hz), 64.4 (d, J = 5.4 Hz), 30.7 (d, J = 19.9 Hz). 19F NMR (376 MHz, CDCl3) δ 15.13. HRMS m/z (MALDI-TOF) calculated for C9H12FNO3: 170.0976, found: 170.098 [M+H]+.
**N-(2-Fluoroethyl)benzamide (17)**

To a suspension of 2-fluoroethylamine hydrochloride (76 mg, 0.76 mmol) in DMF/dioxane (4 mL, 1:1) was added Et$_3$N (0.5 mL, 6.7 mmol) and benzoyl chloride (50 µL, 0.42 mmol). Mixture was stirred for 4 h at room temperature. Water and EtOAc were added and the phases were separated. The organic phase was washed with water, aqueous HCl (1% v/v) and water, dried over Na$_2$SO$_4$ and concentrated under reduced pressure to afford 17 (43 mg, 62%) as pale yellow oil. TLC R$_f$ = 0.77 (10% 7N NH$_3$/MeOH in DCM). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.84–7.75 (m, 2H), 7.58–7.48 (m, 1H), 7.48–7.44 (m, 2H), 6.50 (bs, 1H), 4.67 (t, $J$ = 4.8 Hz, 1H), 4.55 (t, $J$ = 4.8 Hz, 1H), 3.85–3.80 (m, 1H), 3.78–3.73 (m, 1H). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 167.8, 134.3, 131.9, 128.8, 127.1, 83.0 (d, $J$ = 21.5 Hz). HRMS m/z (MALDI-TOF) calculated for C$_9$H$_9$FNO+: 168.0819, found: 168.0824 [M+H]$^+$. 

**N-(4-Fluorobenzyl)benzamide (18)**

To a solution of benzoyl chloride (80 µL, 0.7 mmol) and 4-fluorobenzylamine (90 µL, 0.80 mmol) in acetone (1 mL) was added Et$_3$N (150 µL, 1.07 mmol) and the mixture was stirred for 8 h at room temperature. Water and DCM were added and the phases were separated. The organic phase was washed with water, aqueous HCl (0.3M) and water, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using a gradient of EtOAc in heptane (20–50%) as eluent to afford 18 (56 mg, 36%) as pale yellow crystals. Melting point 115–117 °C. TLC R$_f$ = 0.29 (17% EtOAc in heptane). $^1$H NMR (600 MHz, CDCl$_3$) δ 7.80–7.77 (m, 2H), 7.53–7.47 (m, 1H), 7.46–7.41 (m, 2H), 7.36–7.29 (m, 2H), 7.03 (t, $J$ = 8.6 Hz, 2H), 6.43 (bs, 1H), 4.61 (d, $J$ = 5.7 Hz, 1H). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 167.5, 162.4 (d, $J$ = 245.9 Hz), 134.4, 134.2 (d, $J$ = 3.3 Hz), 131.8, 129.7 (d, $J$ = 8.1 Hz), 128.8, 127.1, 115.8 (d, $J$ = 21.5 Hz), 43.5. $^{19}$F NMR (376 MHz, CDCl$_3$) δ -114.84. HRMS m/z (MALDI-TOF) calculated for C$_{14}$H$_{12}$FNO+: 230.0976, found: 230.0978 [M+H]$^+$. 

**N-(4-Fluorophenyl)benzamide (19)**

A solution of 4-fluoroaniline (0.17 mL, 1.80 mmol) and Et$_3$N (0.3 mL, 2.16 mmol) in dry DCM (12 mL) was stirred at room temperature for 30 min before benzoyl chloride (0.23 mL, 1.98 mmol) was added. The mixture was stirred at room temperature overnight. Water and DCM were added and the phases were separated. The aqueous phase was extracted with DCM. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using EtOAc in heptane (50%) as eluent to afford 19 (360 mg, 93%) as a colorless solid. Melting point 184–186 °C. TLC R$_f$ = 0.21 (20% EtOAc in heptane). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.90–7.83 (m, 2H), 7.79 (bs, 1H), 7.66–7.53 (m, 3H), 7.52–7.45 (m, 2H), 7.13–7.00 (m, 2H). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 165.8, 159.7 (d, $J$ = 243.8 Hz), 134.9, 134.0 (d, $J$ = 2.8 Hz), 132.1, 129.0, 127.1, 122.2 (d, $J$ = 8.0 Hz), 115.9 (d, $J$ = 22.6 Hz). $^{19}$F NMR (376 MHz, CDCl$_3$) δ -117.62. HRMS m/z (MALDI-TOF) calculated for C$_{13}$H$_{10}$FNO+: 216.0819, found: 216.0823 [M+H]$^+$. 
Benzoyl chloride (14 µL, 0.1 mmol) was added to a solution of 16 (20 mg, 0.12 mmol) and Et₃N (18 µL, 0.2 mmol) in THF (0.8 mL) at 0°C. The mixture was stirred under nitrogen atmosphere for 2 h. Additional benzoyl chloride (80 µL of 10 µL/mL solution in THF, 0.007 mmol) was added and the mixture was again stirred for 1 h. Precipitated triethylammonium chloride was removed by filtration through celite® and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using a gradient of EtOAc in heptane (20→60%) as eluent to afford 20 (21 mg, 64%) as a white amorphous solid. Melting point 142–144 °C. TLC Rₜ = 0.57 (50% EtOAc in heptane). 'H NMR (600 MHz, CDCl₃) δ 7.89–7.84 (m, 2H), 7.76 (bs, 1H), 7.58–7.51 (m, 3H), 7.50–7.44 (m, 2H), 6.91 (d, J = 8.9 Hz, 2H), 4.69 (t, J = 5.8 Hz, 1H), 4.62 (t, J = 5.8 Hz, 1H), 4.10 (t, J = 6.1 Hz, 2H), 2.17 (dp, J = 26.0, 6.0 Hz, 2H). 'C NMR (151 MHz, CDCl₃) δ 165.7, 155.9, 135.2, 131.9, 131.3, 128.9, 127.1, 122.2, 115.1, 80.9 (d, J = 164.5 Hz), 64.0 (d, J = 5.3 Hz), 30.6 (d, J = 20.2 Hz). 'F NMR (376 MHz, CDCl₃) δ 14.97. HRMS m/z (MALDI-TOF) calculated for C₁₆H₁₆FNO₂⁺: 274.1238, found: 274.1233 [M+H]⁺.
2. Radiochemistry

**General information**

\[^{18}\text{F}]\text{Fluoride was produced via the (p,n)-reaction in a cyclotron (CTI Siemens and Scanditronix, Rigshospitalet, Denmark) by irradiating }^{18}\text{O}_2\text{H}_2\text{O with a 11 MeV proton beam. All QMA anion exchange cartridges (Sep-Pak Accell Plus QMA Plus Light, chloride form, Waters) were washed with EtOH (20 mL) and water (20 mL) and dried with air before use. All C18 cartridges (Sep-Pak C18 Plus Light and Sep-Pak C18 Plus Short types) were washed with 50% EtOH in water (10 mL) and dried with air before use. Automated syntheses were performed on a Scansys Laboratorieteknik synthesis module. Dry THF and MeCN used in the radiosyntheses were purchased from Sigma Aldrich. Analytical HPLC was performed on a Dionex system connected to a P680A pump, a UVD 170U detector and a Scansys radiodetector. The HPLC system was controlled by Chromeleon 6.8 software. Radio-TLC plates were imaged on a Packard InstantImager and analyzed by Optiquant software. Identity of all radiolabeled compounds was confirmed by co-elution with \[^{19}\text{F}]\text{-references on radio-HPLC and radio-TLC (see Table S1 and Table S2). For }^{18}\text{F}\text{1, co-elution on TLC was not performed due to the volatility of this compound. RCC values reported are determined by radio-TLC. Radiochemical yields (RCYs) are decay corrected to the start of synthesis.**

**General procedure for the preparation of anhydrous }^{18}\text{F}\text{fluoride for radiolabeling**

Irradiated \[^{18}\text{O}]\text{water containing }^{18}\text{F}\text{ was passed through an anion exchange resin cartridge (Sep-Pak Accell Plus QMA Plus Light, chloride form). }^{18}\text{F}\text{Fluoride trapped on the QMA was then eluted with an aliquot (0.6 mL unless stated otherwise) of eluting solution (19 mg/mL 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane and 5 mg/mL K}_2\text{CO}_3\text{ in 96% methanol unless stated otherwise) into a 4 mL glass vial. The resulting mixture was then gently evaporated to dryness at 100 °C under nitrogen flow. When the solvents evaporated, dry MeCN (0.5 mL) was added to the vial and also evaporated. Addition of acetonitrile with subsequent evaporation was repeated twice.**

**Supplementary information on the establishment of the Staudinger reduction procedure**

Supplementary Figure S1 shows radio-HPLC traces for a representative 2-step Staudinger reduction of \[^{18}\text{F}]\text{4 to }^{18}\text{F}\text{5 at different time-points. While the reaction of azide }^{18}\text{F}\text{4 with PPh}_3\text{ readily produced a hydrophobic product }^{18}\text{F}\text{IP with a retention time of 4.6 min (possibly – the iminophosphorane adduct), further conversion of that product into amine }^{18}\text{F}\text{5 upon water addition proceeded slowly. However, quantitative conversion to }^{18}\text{F}\text{5 could be achieved by the addition of NaOH (2 mM) to the reaction mixture.**

**HPLC method used:** Luna C18(2) 5 µ 150 x 4.6 mm column. Mobile phase A (MP A): 0.1% trifluoroacetic acid (TFA) in water (v/v). Mobile phase B (MP B): 0.1% TFA in ACN (v/v). Flow rate: 1.5 mL/min. Gradient: 0-0.5 min, 30% MP B; 0.5-7 min, 30→100% MP B; 7-8 min, 100% MP B; 8-9 min, 100→30% MP B; 9-9.5 min – 30% MP B.
Preparation of $^{18}$F-labeled azides

1-Azido-2-(2-(2-[18F]fluoroethoxy)ethoxy)ethoxy)ethane ([18F]4)

Synthesis of [18F]4 was performed on an automated synthesis module. [18F]Fluoride was recovered from irradiated [18O]water and dried as described in the General Procedure. To the dried residue containing [18F]fluoride, azide 3 (3 mg) in DMSO (0.5 mL) was added. The mixture was heated at 120 °C for 10 min, cooled down to 80 °C, diluted with water (3 mL) and purified by semi-preparative HPLC using a Luna 5µ C18(2) (100Å 250x10 mm) column with a water/MeCN/TFA mixture (70/30/0.1 v/v/v) as eluent. The flow rate was 4 mL/min. HPLC fraction containing [18F]4 (retention time 13.3 min) was diluted with water (50 mL) and loaded on a Sep-Pak C18 Plus Short cartridge. The cartridge was dried with a nitrogen flow for 2 min and eluted with dry MeCN or dry THF (1 mL in both cases). Radiochemical purity of [18F]4 was determined by radio-TLC (10% 7N NH3/MeOH in DCM, Rf = 0.88, RCP >95%). Isolated radioactivity amounts of [18F]4 were in the order of 3 GBq, which corresponds to an average RCY of about 27-36%.

1-Azido-2-[18F]fluoroethane ([18F]1)

Synthesis of [18F]1 was performed manually. [18F]Fluoride was recovered from irradiated [18O]water and dried as described in the general procedure above. To the dried residue containing [18F]fluoride, 2-azidoethyl-4-nitrobenzenesulfonate (2 mg) in dry MeCN (0.5 mL) was added. The reaction vial was connected via a polypropylene line to a 0.9 mL distillation vial containing dry MeCN (0.5 mL), as illustrated in Figure S2. Nitrogen was bubbled through the reaction mixture, while the reaction vial was heated to 90 °C, until all MeCN was collected in the distillation vial. Distillation vial content was then diluted with water (10 mL) and loaded on a Sep-Pak C18 Plus Light cartridge. The cartridge was dried with a nitrogen flow for 2 min and eluted with dry MeCN (1 mL). Radiochemical purity of [18F]1 was determined by radio-HPLC (RCP >95%). Radio-TLC confirmed the absence of non-volatile labeled impurities in 2-[18F]1-azido-2-fluoroethane. Isolated radioactivity amounts of [18F]1 were in the order of 9–150 MBq, which corresponds to an average RCY of 28±6% (n=5).
Figure S2. Distillation of $[^{18}F]$1-azido-2-fluoroethane

1-(Azidomethyl)-4-$[^{18}F]$fluorobenzene ($[^{18}F]$11)

Synthesis of $[^{18}F]$11 was performed on the automated synthesis module (ScanSys, Denmark). $[^{18}F]$Fluoride was recovered from irradiated $[^{18}O]$water and dried as described General Procedure with the following modification: to elute $[^{18}F]$fluoride from the QMA cartridge, tetrabutylammonium mesylate (3 mg) in MeCN/water (1/1 v/v, 1 mL total volume) was used. To the dried residue containing $[^{18}F]$fluoride, a solution of II (1 mg), copper (II) triflate (7 mg) and pyridine (40 µL) in dry DMF (0.96 mL) was added. The reaction mixture was heated for 10 min at 110 °C, then cooled to 80 °C, diluted with water (4 mL) and injected onto a semi-preparative HPLC on a Luna 5µ C18(2) (100Å 250x10 mm) column using water/acetonitrile/TFA (50/50/0.1 v/v/v) as eluent. The flow rate was 6 mL/min. The HPLC fraction containing $[^{18}F]$11 (retention time 10.0 min) was diluted with water (50 mL) and loaded on a Sep-Pak C18 Plus Light cartridge. The cartridge was dried with nitrogen and eluted with dry MeCN (1 mL). Radiochemical purity of $[^{18}F]$11 was determined by radio-TLC (16% EtOAc in hexane, $R_f = 0.78$, RCP >95%). Isolated radioactivity amounts of $[^{18}F]$11 were in the order of 100–200 MBq, which corresponds to an average RCY of about 7%.

1-Azido-4-$[^{18}F]$fluorobenzene ($[^{18}F]$12)

$[^{18}F]$12 was prepared using the same procedure as used for $[^{18}F]$11, with the following modifications: Precursor III (1 mg) was used instead. The retention time of $[^{18}F]$12 on the semi-preparative HPLC column was 10.8 min. Radiochemical purity of $[^{18}F]$12 was determined by radio-TLC (20% EtOAc in hexane, $R_f = 0.88$, RCP >95%). Isolated radioactivity amounts of $[^{18}F]$12 were in the order of 100–200 MBq, which corresponds to an average RCY of about 2%.

3-(4-Azidophenoxy)propyl $[^{18}F]$fluoride ($[^{18}F]$13)

Synthesis of $[^{18}F]$13 was performed manually. $[^{18}F]$Fluoride was recovered from irradiated $[^{18}O]$water and dried as described in the general procedure. To the dried residue containing $[^{18}F]$fluoride, 3-(4-azidophenoxy)propyl methanesulfonate (1 mg) in dry MeCN (1 mL) was added. The mixture was heated for at 120 °C for 5 min, then left to cool down at room temperature for 2 min. Afterward, this mixture was diluted with water (10 mL) and loaded on a Sep-Pak C18 Plus Light cartridge. The cartridge was dried with a nitrogen flow for 2 min and eluted with dry MeCN (1 mL). Radiochemical purity of $[^{18}F]$13 was determined by radio-TLC (33% EtOAc in hexane, $R_f = 0.86$, RCP >80%). Isolated radioactivity amounts of $[^{18}F]$13 were in the order of 9–150 MBq, which corresponds to an average RCY of 44±15% (n=3).

General procedures for the Staudinger reduction and amine acylation, particular procedures for the preparation of N-(2-(2-((2-[18]F)fluoroethoxy)ethoxy)ethoxy)ethyl)-4-(6-(pyrimidin-2-yl)-1,2,4,5-tetrazin-3-yl)benzamid (18F)7, 1-(2-(2-(2-[18]F)fluoroethoxy)ethoxy)ethoxy)ethyl)-3-phenylthiourea (18F)9, N-benzyl-2-(2-((2-[18]F)fluoroethoxy)ethoxy)ethoxy)ethanol-1-amine (18F)10, and for the automated two-step
synthesis of N-(2-(2-(2-[18F]Fluoroethoxy)ethoxy)ethoxy)ethyl)benzamide ([18F]8) from azide [18F]4 are provided in the Experimental Section of the main text.
### Analytical Radio-HPLC and Radio-TLC data

**Table S1. Analytical radio-HPLC data summary**

| Compound | Gradient / Retention time / Retention factor |
|----------|---------------------------------------------|
| $[^{18}F]1$ | Gradient 2: 4.21 min $k$ 2.08 |
| $[^{18}F]2$ | Gradient 2: 1.37 min $k$ 0 |
| $[^{18}F]4$ | Gradient 1: 4.00 min $k$ 1.96 |
| $[^{18}F]5$ | Gradient 2: 5.42 min $k$ 2.41 |
| $[^{18}F]6$ | Gradient 1: 1.35 min $k$ 0 |
| $[^{18}F]7$ | Gradient 2: 1.6–2.1 min $^c$ $k$ 0–0.33 |
| $[^{18}F]8$ | Gradient 1: 4.85 min $k$ 2.59 |
| $[^{18}F]9$ | Gradient 2: 4.80 min $k$ 2.56 |
| $[^{18}F]10$ | Gradient 2: 5.59 min $k$ 2.56 |
| $[^{18}F]11$ | Gradient 2: 6.28 min $k$ 2.97 |
| $[^{18}F]12$ | Gradient 2: 4.89 min $k$ 2.11 |
| $[^{18}F]13$ | Gradient 2: 4.56 min $k$ 2.77 |
| $[^{18}F]14$ | Gradient 3: 6.47 min $k$ 3.90 |
| $[^{18}F]15$ | Gradient 2: 8.01 min $k$ 4.72 |
| $[^{18}F]16$ | Gradient 2: 4.08 min $k$ 1.91 |
All analytical radio-HPLC was performed on Luna C18(2) 5 µ (150 × 4.6 mm) columns eluted with mixtures of 0.1% TFA in water (mobile phase A, MP A) and 0.1% TFA in acetonitrile (mobile phase B, MP B). All percentages mentioned are volume/volume (v/v) percentages. Total elution flow was 1.5 mL/min for all gradients. Four gradients were used. Gradient 1: 0-5 min, 25% MP B; 5-6 min, 25→100% MP B; 6-9 min, 100% MP B; 9-9.5 min, 100→25% MP B; 9.5-10 min – 25% MP B. Gradient 2: 0-1 min, 10% MP B; 1-7 min, 10→80% MP B; 7-8 min, 80→100% MP B, 8-10 min, 100% MP B; 10-11 min, 100→10% MP B; 11-12 min – 10% MP B. Gradient 3: 0-0.5 min, 30% MP B; 0.5-8 min, 30→100% MP B; 8-9.5 min, 100% MP B; 9.5-10 min, 100→50% MP B; 10-10.5 min – 30% MP B. Gradient 4: 0-5 min, 50% MP B; 5-5.5 min, 50→100% MP B; 5.5-9 min, 100% MP B; 9-9.5 min, 100→50% MP B; 9.5-10 min – 50% MP B. Retention times are given for the radioactive peak. Under conditions of Gradient 2, [18F]4 is eluted as 3 overlapping peaks within the mentioned retention time range. Relative contribution of each peak appears to be dependent on the solvent mixture in which [18F]4 is dissolved.

Table S2. Analytical radio-TLC data summary

| Compound | Systema | Rf  |
|----------|---------|-----|
| [18F]1   | no datab | 0.74 |
| [18F]2   | System 1: | 0.44 |
| [18F]4   | System 1: | 0.88 |
| [18F]5   | System 1: | 0.29 |
| [18F]7   | System 1: | 0.74 |
| ![18F]8 | System 1: 0.61 |
| ![18F]9 | System 1: 0.77 |
| ![18F]10 | System 1: 0.46 |
| ![18F]11 | System 4: 0.77 |
| ![18F]12 | System 3: 0.87 |
| ![18F]13 | System 2: 0.86 |
| ![18F]14 | System 1: 0.53 |
| ![18F]15 | System 3: 0.26 |
| ![18F]16 | System 2: 0.28 |
| ![18F]17 | System 1: 0.77 |
| ![18F]18 | System 4: 0.29 |
| ![18F]19 | System 3: 0.39 |
| ![18F]20 | System 2: 0.51 |

Four solvent systems were used for radio-TLC. System 1: 10% 7N NH\(_3\)/MeOH in DCM; System 2: 33% EtOAc in hexane, System 3: 20% EtOAc in hexane, System 4: 16% EtOAc in hexane. \( \text{R}_f \) of \([^{18}\text{F}]1\) could not be determined due to the volatility of this compound.
3. Analytical HPLC Spectra

1-Azido-2-$^{[18]F}$fluoroethane ($[^{18}F]1$), gamma trace

1-Azido-2-fluoroethane (1), 220 nm trace

$[^{18}F]$Fluoroethylamine ($[^{18}F]2$), gamma trace

No UV trace could be obtained for fluoroethylamine (2) because of the low absorption of this compound in the UV range. Identity of $[^{18}F]$fluoroethylamine was confirmed by co-elution with unlabeled fluoroethylamine (2, taken as hydrochloride salt) on TLC.
1-Azido-2-(2-(2-[\textsuperscript{18}F]fluoroethoxy)ethoxy)ethoxy)ethane ([\textsuperscript{18}F]4), gamma trace

1-Azido-2-(2-(2-\textsuperscript{18}Ffluoroethoxy)ethoxy)ethoxy)ethane (4), 220 nm trace

2-(2-(2-\textsuperscript{18}FFluoroethoxy)ethoxy)ethoxy)ethan-1-amine ([\textsuperscript{18}F]5), gamma trace

No UV trace could be obtained for 2-(2-(2-\textsuperscript{18}Ffluoroethoxy)ethoxy)ethoxy) ethan-1-amine (5) because of the low absorption of this compound in the UV range. Identity of [\textsuperscript{18}F]5 was confirmed by co-elution with unlabeled 5 on TLC.
\[N-(2-(2-(2-\{^{18}\text{F}\}\\text{fluoroethoxy})ethoxy)ethoxy)ethyl\)-4-(6-(pyrimidin-2-yl)-1,2,4,5-tetrazin-3-yl) (\[^{18}\text{F}\]7), gamma trace\]

\[N-(2-(2-(2-\{^{18}\text{F}\}\\text{fluoroethoxy})ethoxy)ethoxy)ethyl\)-4-(6-(pyrimidin-2-yl)-1,2,4,5-tetrazin-3-yl) (7), 254 nm trace\]

\[N-(2-(2-(2-\{^{18}\text{F}\}\\text{fluoroethoxy})ethoxy)ethoxy)ethyl)benzamide (\[^{18}\text{F}\]8), gamma trace\]

\[N-(2-(2-(2-\{^{18}\text{F}\}\\text{fluoroethoxy})ethoxy)ethoxy)ethyl)benzamide (8), 254 nm trace\]
1-(2-(2-(2-[18F]Fluoroethoxy)ethoxy)ethoxy)ethyl)-3-phenylthiourea ([18F]9), gamma trace

1-(2-(2-(2-Fluoroethoxy)ethoxy)ethoxy)ethyl)-3-phenylthiourea (9), 254 nm trace

N-Benzyl-2-(2-(2-[18F]fluoroethoxy)ethoxy)ethoxy)ethan-1-amine ([18F]10), gamma trace

N-Benzyl-2-(2-(2-fluoroethoxy)ethoxy)ethoxy)ethan-1-amine (10), 208 nm trace
1-(Azidomethyl)-4-[\textsuperscript{18}F]fluorobenzene ([\textsuperscript{18}F]11), gamma trace

1-(Azidomethyl)-4-fluorobenzene (11), 254 nm trace

1-Azido-4-[\textsuperscript{18}F]fluorobenzene ([\textsuperscript{18}F]12), gamma trace

1-Azido-4-fluorobenzene (12), 254 nm trace
1-Azido-4-(3-[\text{\textsuperscript{18}}F]\text{fluoropropoxy})benzene, ([\text{\textsuperscript{18}}F]13), gamma trace

1-Azido-4-(3-fluoropropoxy)benzene (13), 254 nm trace

(4-[\text{\textsuperscript{18}}F]\text{Fluorophenyl})methanamine ([\text{\textsuperscript{18}}F]14), gamma trace

(4-Fluorophenyl)methanamine (14), 254 nm trace
4-[^18]FFluoroaniline ([^18]F15), gamma trace

4-Fluoroaniline (15), 254 nm trace

4-(3[^18]Ffluoropropoxy)aniline ([^18]F16), gamma trace

4-(3-Fluoropropoxy)aniline (16), 254 nm trace
$N-(2-[^{18}\text{F}]\text{Fluoroethyl})\text{benzamide}$ ([$^{18}\text{F}$]17), gamma trace

$N-(2-\text{Fluoroethyl})\text{benzamide}$ (17), 254 nm trace

$N-(4-[^{18}\text{F}]\text{Fluorobenzyl})\text{benzamide}$ ([$^{18}\text{F}$]18), gamma trace

$N-(4-\text{Fluorobenzyl})\text{benzamide}$ (18), 254 nm trace
$N$-(4-$[^{18}\text{F}]$Fluorophenyl)benzamide $[^{18}\text{F}]19$, gamma trace

$N$-(4-Fluorophenyl)benzamide (19), 254 nm trace

$N$-(4-(3-$[^{18}\text{F}]$Fluoropropyl)oxyphenyl)benzamide $[^{18}\text{F}]20$, gamma trace

$N$-(4-(3-Fluoropropyl)oxyphenyl)benzamide (20), 254 nm trace
4. NMR spectra

2-(2-(2-Azidoethoxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (3)
1-Azido-2-(2-(2-fluoroethoxy)ethoxy)ethane (4)
2-(2-(2-(2-Fluoroethoxy)ethoxy)ethoxy)ethan-1-amine (5)
2,5-Dioxopyrrolidin-1-yl 4-(6-(pyrimidin-2-yl)-1,2,4,5-tetrazin-3-yl)benzoate (6)
N-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)ethyl)-4-(6-(pyrimidin-2-yl)-1,2,4,5-tetrazin-3-yl)benzamide (7)
N-(2-(2-(2-Fluoroethoxy)ethoxy)ethoxy)ethyl)benzamide (8)
1-(2-(2-(2-Fluoroethoxy)ethoxy)ethoxy)ethyl)-3-phenylthiourea (9)
N-Benzyl-2-(2-(2-fluoroethoxy)ethoxy)ethoxy)ethan-1-amine (10)
2-(4-(Azidomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (II)
4(4,4,5,5-Tetramethyl-1,3,2-dioxaborolane-2-yl)phenyl azide (III)
3-Fluoropropyl-4-methylbenzenesulfonate (V)

$\text{H NMR} \quad \text{O} \quad \text{O} \quad \text{F} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H}$

$\text{C NMR}$

$\text{H NMR}$

$\text{C NMR}$
1-Azido-4-(3-fluoropropoxy)benzene (13)
4-(3-Fluoropropoxy)aniline (16)
N-(2-Fluoroethyl)benzamide (17)
N-(4-Fluorobenzyl)benzamide (18)
N-(4-Fluorophenyl)benzamide (19)

1H NMR

19F NMR
$N$-(4-(3-Fluoropropyl)oxyphenyl)benzamide (20)

$\text{1H NMR}$

$\text{1J C NMR}$
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