Enhanced Copper-Mediated $^{18}$F-Fluorination of Aryl Boronic Esters provides Eight Radiotracers for PET Applications

Sean Preshlock, Samuel Calderwood, Stefan Verhoog, Matthew Tredwell, Mickael Huiban, Antje Hienzsch, Stefan Gruber, Thomas C. Wilson, Nicholas J. Taylor, Thomas Cailly, Michael Schedler, Thomas Lee Collier, Jan Passchier, René Smits, Jan Mollitor, Alexander Hoepping, Marco Mueller, Christophe Genicot, Joël Mercier, Véronique Gouverneur

$^a$ University of Oxford, Chemistry Research Laboratory, 12 Mansfield Road, OX1 3TA Oxford (UK); Email: veronique.gouverneur@chem.ox.ac.uk
$^b$ Imanova, Burlington Danes building Imperial College, London Hammersmith Hospital, Du Cane Road, London W12 0NN (UK)
$^c$ ABX GmbH Heinrich-Glaeser-Strasse 10-14, D-01454 Radeberg (Germany)
$^d$ Normandie University, UNICAEN, CEREM, F-14032 Caen (France)
$^e$ Advion BioSystems, 10 Brown Road, Suite 101, Ithaca, NY 14850 (USA)

$^f$ Global Chemistry, UCB New Medicines, UCB Biopharma sprl, 1420 Braine-L’Alleud (Belgium)

Table of Contents

1 Precursor and Reference Synthesis 2
  1.1 General Experimental Information 2
  1.2 Experimental Procedures and Characterisation 2
  1.3 References 17

2 Radiochemistry 19
  2.1 General Information and Procedures 19
  2.2 Isolation Procedures 21
  2.3 Isolation Radiochemical Yields 27
  2.4 Data from small scale experiments 28
  2.5 Comparison of radiotracer production (with semi-prep HPLC) protocols. 29
  2.6 RadioHPLC Traces 31
  2.7 Specific Activity Calibration Curves 45

3 Novel Compound NMR Spectra 52
1. Precursor and Reference Synthesis

1.1 General Experimental Information

All NMR spectra were recorded on Bruker DPX200, AV400, AVB400, AVCS00, AVB500 and DRX500 spectrometers. Proton and carbon-13 NMR spectra are reported as chemical shifts (δ) in parts per million (ppm) relative to the solvent peak using the Bruker internal referencing procedure (edlock). Fluorine-19 NMR spectra are referenced relative to CFCl$_3$ in CDCl$_3$. Coupling constants (J) are reported in units of hertz (Hz). The following abbreviations are used to describe multiplicities – s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), brs (broad singlet). High resolution mass spectra (HRMS, m/z) were recorded on a Bruker MicroTOF spectrometer using positive electrospray ionization (ESI$^+$) or on a Micromass GCT spectrometer using filed ionization (FI$^+$) or chemical ionization (CI$^+$). Infrared spectra were recorded either as the neat compound or in a solution using a Bruker Tensor 27 FT-IR spectrometer. Absorptions are reported in wavenumbers (cm$^{-1}$) and only peaks of interest are reported. Optical rotations were measured on a PerkinElmer Polarimeter model 341 Specific rotations are reported in $10^{-1}$ deg cm$^2$ g$^{-1}$ and concentrations in g/100 mL. Melting points of solids were measured on a Griffin apparatus and are uncorrected. IUPAC names were obtained using the ACD/I-Lab service. Solvents were purchased from Fisher, Rathburn or Sigma-Aldrich. When anhydrous solvents were required they were purified by expression through an activated alumina column built according to the procedures described by Pangborn and Grubbs. Chemicals were purchased from Acros, Alfa Aesar, Fisher, Fluorochem, Sigma-Aldrich and used as received. Reactions were monitored by thin-layer chromatography (TLC) carried out on Merck Kieselgel 60 F254 plates, silica gel column chromatography was performed over Merck silica gel C60 (40-60 μm).

1.2 Experimental Procedures and Characterisation

3-Fluoro-5-((2-methylthiazol-4-yl)ethynyl)benzonitrile (FMTEB)

1-Chloro-4-(trimethylsilyl)but-3-yn-2-one

Prepared according to literature procedure.$^2$ A solution of bis(trimethylsilyl)acetylene (30 g, 176 mmol) and chloroacetyl chloride (15.4 mL, 194 mmol) in DCM (225 mL) was added dropwise to a suspension of AlCl$_3$ (32.8 g, 246 mmol) in DCM (375 mL) at 0°C over a period of 1 h. The dark brownish-red solution was further stirred for 1 h at 0°C and 1 h at room temperature. After this period the reaction mixture was cooled to 0°C and quenched with 1 M HCl (375 mL). The solution was extracted with DCM (3 x 500 mL), the combined organic layers were washed with H$_2$O (500 mL), NaHCO$_3$ (500 mL), brine (500 mL) and dried over MgSO$_4$. The organic layer was filtered over a silica gel pad and concentrated in vacuum to give a residue that was distilled under high vacuum (vigreux column, BP: 80°C/14 mbar) to afford the product as light yellow oil (22.2 g, 72%).

$^1$H NMR (400 MHz, CDCl$_3$): δ = 4.23 (s, 2H), 0.26 (s, 9H); BP: 80°C (14 mbar). Data consistent with literature values.$^2,3$

2-Methyl-4-((trimethylsilyl)ethynyl)thiazole

Prepared according to literature procedure.$^2$ Thioacetamide (12 g, 160 mmol) was added to a solution of 1-chloro-4-(trimethylsilyl)but-3-yn-2-one (21 g, 123 mmol) in DMF (200 mL) and stirred at room temperature for 16 h. The reaction mixture was diluted with EtOAc (700 mL) and washed with H$_2$O (3
x 500 mL), brine (500 mL) and dried over MgSO₄. The filtrate was concentrated in vacuum and the residue was purified by column chromatography (hexane/EtOAc, 98:2 to 96.5:3.5) to afford the product as reddish-brown oil (17.4 g, 72%).

\( ^1H \text{ NMR} \) (400 MHz, CDCl₃): \( \delta = 7.30 \) (s, 1H), 2.67 (s, 3H), 0.22 (s, 9H); \( ^13C \text{ NMR} \) (100 MHz, CDCl₃): \( \delta = 165.6, 137.0, 123.0, 98.4, 94.6, 19.3, -0.1 \). Data consistent with literature values.⁴

3-Bromo-5-((2-methylthiazol-4-yl)ethynyl)benzonitrile

Prepared according to literature procedure.⁵ 2-Methyl-4-((trimethylsilyl)-ethynyl)thiazole (1.29 g, 6.6 mmol) was dissolved in DMF (15 mL) and then 3,5-dibromobenzonitrile (1.73 g, 6.6 mmol), trans-dichlorobis(triphenylphosphine)palladium (465 mg, 0.6 mmol), CuI (126 mg, 0.6 mmol), and Et₃N (3.7 mL, 26.5 mmol) were added. To this reaction mixture was added dropwise TBAF (7.9 mL, 7.9 mmol; 1 M in THF) over a period of 30 min and the resulting reaction mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with H₂O (50 mL) and extracted with EtOAc (4 x 30 mL). The organic layer was washed with brine (3 x 30 mL), dried over MgSO₄, and concentrated in vacuum. The residue was dissolved in hexane/EtOAc (4:1) and filtered through a small silica-gel column (washed several times) and concentrated in vacuum. The crude product was purified by crystallization from hot hexane/EtOAc (placed in the freezer) to afford the product as a white solid (1.05 g, 52%).

\( ^1H \text{ NMR} \) (400 MHz, CDCl₃): \( \delta = 7.89 \) (s, 1H), 7.74-7.72 (m, 2H), 7.45 (s, 1H), 2.74 (s, 3H); \( ^13C \text{ NMR} \) (100 MHz, CDCl₃): \( \delta = 166.4, 138.6, 135.7, 134.4, 133.5, 126.0, 124.2, 122.9, 116.7, 114.5, 87.3, 85.1, 19.4 \). Data consistent with literature values.⁶

3-((2-Methylthiazol-4-yl)ethynyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile

Nitrogen was bubbled through a mixture of 3-bromo-5-((2-methyl-1,3-thiazol-4-yl)ethynyl)benzonitrile (260.0 mg, 0.86 mmol), bis(pinacolato)diboron (240 mg, 0.94 mmol), potassium acetate (337.0 mg, 3.43 mmol), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (42.0 mg, 0.05 mmol) and N,N-dimethylacetamide (2.6 mL) for 1 h. Then the reaction was heated at 110°C for 40 min, cooled to room temperature and diluted with H₂O (25 mL), and extracted with EtOAc (4 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO₄), filtered, and concentrated in vacuum to give a residue that was dissolve in Et₂O/hexane (5:1) and filtered through a small silica-gel column. The filtrate was concentrated in vacuum and the residue was purified by crystallization from hot MeCN (placed in the freezer) to afford the product as a white solid (117.0 mg, 39%).

\( ^1H \text{ NMR} \) (400 MHz, CD₂Cl₂): \( \delta = 8.16 \) (s, 1H), 8.01 (s, 1H), 7.86 (s, 1H), 7.46 (s, 1H), 2.71 (s, 3H), 1.35 (s, 12H); \( ^13C \text{ NMR} \) (101 MHz, CD₂Cl₂): \( \delta = 166.4, 142.1, 138.1, 137.1, 136.5, 124.1, 123.9, 118.4, 113.0, 86.4, 86.2, 85.2, 25.1, 19.4 \) (note: \( C_{Ar}-B \) was not observed); \( \text{IR (ν, cm}^{-1}) \): 2979, 2232, 1589, 1412, 1371,
1329, 1242, 1143; HRMS (ESI) for C_{18}H_{22}BN_{2}Na_{2}O_{5} [M+Na]^+ requires 373.1153 found 373.1161; MP: 117-119°C.

3-Fluoro-5-((2-methylthiazol-4-yl)ethynyl)benzonitrile

Prepared according to literature procedure.\(^5\) 2-Methyl-4-((trimethylsilyl)ethynyl)-thiazole (300 mg, 1.54 mmol) was dissolved in DMF (6 mL) and then 3-bromo-5-fluorobenzonitrile (307 mg, 1.54 mmol), trans-dichlorobis(triphenyl-phosphine)palladium (108 mg, 0.15 mmol), CuI (29 mg, 0.15 mmol), and Et\(_3\)N (0.86 mL, 6.14 mmol) were added. The reaction mixture was warmed to 60°C and then TBAF (1.8 mL, 1.8 mmol; 1 M in THF) was added dropwise over a period of 10 min and the resulting reaction mixture was stirred at 60°C for 2 h. The reaction mixture was quenched with H\(_2\)O (40 mL) and extracted with EtOAc (4 x 30 mL). The organic layer was washed with brine (30 mL), dried over MgSO\(_4\), filtered and concentrated in vacuum. The residue was purified by column chromatography (hexane/EtOAc, 4:1) to afford the product as white solid (103 mg, 28%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ = 7.62 (t, J = 1.4 Hz, 1H), 7.49-7.45 (m, 2H), 7.34 (ddd, J = 7.9, 2.5, 1.4 Hz, 1H), 3.11 (s, 3H); \(^{13}\)C NMR (101 MHz, CD\(_2\)Cl\(_2\)): δ = 166.4, 162.1 (d, J = 251 Hz), 135.8, 131.3 (d, J = 4 Hz), 126.5 (d, J = 10 Hz), 124.3, 123.3 (d, J = 23 Hz), 119.3 (d, J = 25 Hz), 117.0 (d, J = 3 Hz), 114.5 (d, J = 10 Hz), 87.1, 85.3 (d, J = 3 Hz), 19.4; \(^{19}\)F \(^{1}\)H NMR (376 MHz, CDCl\(_3\)): δ = –109.1 (s, 1F). Data consistent with literature values.\(^5\)

3-Fluoro-5-(pyridin-2-ylethynyl)benzonitrile (FPEB)

3-Bromo-5-(pyridin-2-ylethynyl)benzonitrile

Prepared according to literature procedure.\(^7\) A mixture slurry of 2-ethynylpyridine (0.5 mL, 5.0 mmol), 3,5-dibromobenzonitrile (3.9 g, 15.0 mmol), trans-dichlorobis(triphenyl-phosphine)palladium (350 mg, 0.5 mmol), Cu (475 mg, 2.5 mmol, and PPh\(_3\) (262 mg, 1.0 mmol) in Et\(_3\)N (14.0 mL, 99.9 mmol) was heated in a Schlenk tube at 80°C for 1.5 h. After cooling to room temperature the resulting reaction mixture was diluted with sat. NH\(_4\)Cl (100 mL) and extracted with Et\(_2\)O (3 x 80 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\), filtered and concentrated in vacuum. The residue was dissolve in hexane/EtOAc (4/1) and filtered through a small silica-gel column (washed several times) and concentrated in vacuum. The crude product was purified by crystallization from hot hexane/EtOAc (placed in the freezer) to afford the product as a white solid (852 mg, 60%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ = 8.65 (ddd, J = 4.9, 1.8, 1.0 Hz, 1H), 7.95 (dd, J = 1.9, 1.5 Hz, 1H), 7.80 – 7.76 (m, 2H), 7.73 (td, J = 7.7, 1.8 Hz, 1H), 7.54 (dt, J = 7.8, 1.1 Hz, 1H), 7.31 (ddd, J = 7.7, 4.9, 1.2 Hz, 1H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): δ = 150.4, 142.2, 138.9, 136.4, 134.7, 133.8, 127.6, 125.7, 123.8, 122.9, 116.6, 114.5, 92.0, 84.9. Data consistent with literature values.\(^7\)
3-(Pyridin-2-ylethynyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile

Nitrogen was bubbled through a mixture of 3-bromo-5-(pyridin-2-ylethynyl)benzonitrile (640 mg, 2.26 mmol), bis(pinacolato) diboron (631 mg, 2.49 mmol), potassium acetate (887 mg, 9.04 mmol), dichloro[1,1′-bis(diphenylphosphino)ferrocene]-palladium(II) dichloromethane adduct (111 mg, 0.14 mmol) and N,N-dimethylacetamide (7 mL) for 1 h. Then the reaction was heated at 110°C for 40 min, cooled to room temperature and diluted with H₂O (100 mL), and extracted with EtOAc (4 x 35 mL). The combined organic extracts were washed with brine (35 mL), dried (MgSO₄), filtered, and concentrated in vacuum to give a residue that was dissolve in Et₂O/hexane (5:1) and filtered through a small silica-gel column. The filtrate was concentrated in vacuum and the residue was purified by crystallization from hot MeCN (placed in the freezer) to afford the product as a white solid (332 mg, 45%).

¹H NMR (400 MHz, CD₂Cl₂): δ = 8.65 – 8.56 (m, 1H), 8.21 (s, 1H), 8.04 (t, J = 1.3 Hz, 1H), 7.92 (t, J = 1.6 Hz, 1H), 7.72 (td, J = 7.8 Hz, 1.8, 1H), 7.55 (dd, J = 7.8, 1.5 Hz, 1H), 7.29 (ddd, J = 7.5, 4.9, 1.2 Hz, 1H), 1.35 (s, 12H); ¹³C NMR (126 MHz, CD₂Cl₂): δ = 150.6, 143.1, 142.3, 138.4, 137.4, 136.6, 127.8, 123.7, 118.3, 113.0, 86.4, 85.2, 25.0 (note: C Ar-B was not observed); IR (ν, cm⁻¹): 2979, 2359, 2341, 2233, 1587, 1465, 1430, 1375, 1143; HRMS (ESI) for C₂₀H₁₉BN₂NaO₂ [M+Na]⁺ requires 353.1432 found 353.1432; MP: 107-109°C.

3-Fluoro-5-(pyridin-2-ylethynyl)benzonitrile

A mixture slurry of 2-ethynylpyridine (0.5 mL, 5.0 mmol), 3-dibromo-5-fluorobenzonitrile (3.0 g, 15.0 mmol), trans-dichlorobis(triphenyl-phosphine)palladium (350 mg, 0.5 mmol), CuI (475 mg, 2.5 mmol, and PPh₃ (262 mg, 1.0 mmol) in Et₃N (14.0 mL, 99.9 mmol) was heated in a Schlenk tube at 80°C for 1.5 h. After cooling to room temperature the resulting reaction mixture was diluted with sat. NH₄Cl (100 mL) and extracted with Et₂O (3 x 80 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was dissolved in hexane/EtOAc (4:1) and filtered through a small silica-gel column (washed several times) and concentrated in vacuum. The crude product was purified by crystallization from hot hexane/EtOAc (placed in the freezer) to afford the product as a white solid (684 mg, 62%).

¹H NMR (500 MHz, CDCl₃): δ = 8.66 – 8.54 (m, 1H), 8.21 (s, 1H), 8.04 (t, J = 1.3 Hz, 1H), 7.92 (t, J = 1.6 Hz, 1H), 7.52 (dt, J = 7.8 Hz, 1.1, 1H), 7.49 (ddd, J = 8.7, 2.5, 1.3 Hz, 1H), 7.33 (ddd, J = 7.9, 2.5, 1.3 Hz, 1H), 7.29 (ddd, J = 7.7, 4.8, 1.2 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃): δ = 161.9 (d, J = 252 Hz), 150.4, 142.2, 136.4, 131.5 (d, J = 4 Hz), 127.6, 126.1 (d, J = 10 Hz), 123.8, 123.5 (d, J = 23 Hz), 119.5 (d, J = 25 Hz), 116.8 (d, J = 3 Hz), 114.4 (d, J = 10 Hz), 91.7, 85.1 (d, J = 3 Hz); ¹⁹F NMR (376 MHz, CDCl₃): δ = −108.9. Data consistent with literature values.⁵
Flumazenil

7-Bromo-4-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione

Prepared according to literature procedure. A mixture of 5-bromoisoatiaic anhydride (5.38 g, 22.1 mmol) and sarcosine (1.98 g, 22.1 mmol) in DMSO (50 mL) was heated at 150°C for 5 h, cooled to room temperature and poured into ice water (250 mL). The resulting precipitate was collected by filtration and washed with water (3 x 200 mL) and dried (4.64g, 78%).

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 10.53 (s, 1H), 7.82 (d, $J = 2.3$ Hz, 1H), 7.67 (dd, 8.7, 2.4 Hz, 1H), 7.05 (d, $J = 8.7$ Hz, 1H), 3.88 (s, 2H), 3.11 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 169.5, 165.2, 136.4, 134.5, 132.3, 127.9, 122.9, 115.7, 52.0, 35.9. Data consistent with literature values.

Ethyl 8-bromo-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate

Prepared according to literature procedure. Potassium tert-butoxide (688 mg, 6.13 mmol) was added to a solution of 7-bromo-4-methyl-1H-1,4-benzodiazepin-2,5-diaone (1.5 g, 5.58 mmol) in 150 mL anhydrous THF at 0°C and stirred for 20 min. The reaction mixture was cooled to −35°C and diethylchlorophosphate (1.04 mL, 7.25 mmol) was added slowly. After stirring at 0°C for 30 min, the reaction mixture was cooled to −78°C and ethyl isocyanoacetate (0.67 mL, 6.13 mmol) was added followed by the addition of potassium tert-butoxide (688 mg, 6.13 mmol). After stirring at room temperature for 4 h, the reaction was quenched with a saturated aqueous solution of $K_2CO_3$ and extracted with EtOAc. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated to get a solid residue. This solid residue was treated with ether and the product was precipitated as an off-white solid (418 mg, 21%).

$^1$H NMR (400 MHz, CDCl$_3$): δ = 8.22 (d, $J = 2.2$ Hz, 1H), 7.88 (s, 1H), 7.76 (dd, $J = 8.5, 2.2$ Hz, 1H), 7.32 (d, $J = 8.6$ Hz, 1H), 5.22 (br s, 1H), 4.40 (m, 3H), 3.25 (s, 3H), 1.45 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz): δ 165.0, 162.8, 135.6, 135.5, 135.2, 134.7, 130.9, 130.6, 128.9, 123.3, 122.4, 61.0, 42.2, 35.9, 14.3. Data consistent with literature values.

Ethyl 5-methyl-6-oxo-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydro-4H-benzo[f]imidazo[1,5-a][1,4]diazepine-3-carboxylate

Bispinacol diborane (300 mg, 1.2 mmol), ethyl 8-bromo-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate (363 mg, 1.0 mmol), XPhos-Pd-G2 (4 mg, 5 µmol), XPhos (4.8 mg, 10 µmol) and KOAc (294 mg, 3 mmol) were weighed into an oven dried 25 mL Schlenk flask and purged with N$_2$. 10 mL anhydrous 1,4-dioxane was added and the reaction was stirred at 80°C. After 16 h the reaction was cooled to room temperature and the mixture was evaporated to dryness. The
product was extracted with DCM and loaded onto a short SiO$_2$ column and eluted with DCM/acetone (3:1). Decomposition occurs on the column and the product was purified by trituration with diethyl ether to give a white solid (220 mg, 54%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.51$ (d, $J = 1.3$ Hz, 1H), 8.01 (dd, $J = 8.0$, 1.4 Hz, 1H), 7.90 (s, 1H), 7.40 (d, $J = 8.0$ Hz, 1H), 5.18 (s, 1H), 4.43 (q, $J = 6.9$ Hz, 2H), 4.34 (s, 1H), 3.24 (s, 3H), 1.44 (t, $J = 7.1$ Hz, 3H), 1.35 (s, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 166.8, 163.2, 139.4, 138.7, 135.8, 135.0, 134.0, 128.9, 128.5, 121.1, 84.6, 61.1, 42.5, 35.9, 25.0, 14.5; $^{11}$B NMR (128 MHz, CDCl$_3$): 31.5; HRMS (ESI-TOF) for C$_{21}$H$_{26}$BN$_3$O$_5$ requires m/z = 411.1966, found 411.1960; MP: 204-205°C.

DAA1106

5-Bromo-2-phenoxynitrobenzene

According to a literature procedure,$^{10}$ a mixture of 5-bromo-2-fluoronitrobenzene (4.40 g, 20.0 mmol, 1.00 eq.), phenol (2.07 g, 22.0 mmol, 1.10 eq.) and potassium carbonate (2.76 g, 20.0 mmol, 1.00 eq.) in anhydrous DMF (40 mL) was stirred at 80°C for 3 h. The mixture was concentrated in vacuo and the residue was partitioned between EtOAc and water. The phases were separated and the organic phase was washed with 1 M aqueous HCl and brine. The organic phase was dried (MgSO$_4$), filtered and concentrated in vacuo to afford 5-bromo-2-phenoxynitrobenzene (5.84 g, 19.8 mmol, 99%) as a yellow oil, which was used without further purification.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.08$ (d, $J = 2.3$ Hz, 1H), 7.59 (dd, $J = 8.9$, 2.4 Hz, 1H), 7.40 (t, $J = 7.9$ Hz, 2H), 7.21 (t, $J = 7.4$ Hz, 1H), 7.05 (d, $J = 7.9$ Hz, 2H), 6.89 (d, $J = 8.9$ Hz, 1H). Data consistent with literature values.$^{10}$

5-Bromo-2-phenoxyaniline

According to a literature procedure,$^{10}$ a mixture of 5-bromo-2-phenoxynitrobenzene (5.79 g, 19.7 mmol, 1.00 eq.), Fe powder (3.53 g, 63.0 mmol, 3.20 eq.) and NH$_4$Cl (527 mg, 9.85 mmol, 0.50 eq.) in ethanol (60 mL) and water (20 mL) was stirred at 80°C for 5 h. The mixture was filtered through filter paper to remove Fe. EtOAc and water were added to the filtrate and the phases were separated. The organic layer was washed with water, dried (MgSO$_4$) and filtered. Concentration in vacuo afforded 5-bromo-2-phenoxyaniline (4.40 g, 16.7 mmol, 85%) as a yellow oil, which was used without further purification.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.36 - 7.29$ (m, 2H), 7.11 - 7.06 (m, 1H), 6.99 - 6.94 (m, 3H), 6.81 (dd, $J = 8.5$, 2.3 Hz, 1H), 6.72 (d, $J = 8.5$ Hz, 1H), 3.88 (br s, 2H); MS (ESI$^+$): for C$_{12}$H$_{11}$BrNO$^-$ [M+H]$^+$ requires m/z = 264.0/266.0, found 264.0/266.0. Data consistent with literature values.$^{10}$

N-(5-Bromo-2-phenoxypyphenyl)acetamide

According to a literature procedure,$^{10}$ to a solution of 5-bromo-2-phenoxyaniline (4.16 g, 15.8 mmol, 1.00 eq.) and Et$_3$N (2.85 mL, 20.5 mmol, 1.30 eq.) in anhydrous DCM (30 mL) was added acetyl chloride (1.35 mL, 19.0 mmol, 1.2 eq.) dropwise at 0°C. The mixture was allowed to warm to room temperature and stirred at room temperature for 3 h. The mixture was concentrated in vacuo. The residue was partitioned between EtOAc and water. The phases were separated and the organic phase
was washed with brine, dried (MgSO$_4$), filtered and concentrated in vacuo. Flash column chromatography (15% EtOAc in hexane) afforded N-(5-bromo-2-phenoxyphenyl)acetamide (3.39 g, 11.1 mmol, 70%) as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$): δ = 8.66 (br s, 1H), 7.71 (br s, 1H), 7.38 (t, $J = 7.9$ Hz, 2H), 7.18 (t, $J = 7.4$ Hz, 1H), 7.10 (dd, $J = 8.7$, 2.1 Hz, 1H), 7.01 (d, $J = 8.0$ Hz, 2H), 6.68 (d, $J = 8.7$ Hz, 1H), 2.18 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ = 168.3, 155.9, 144.6, 130.8, 130.1, 126.6, 124.4, 123.4, 118.9, 118.6, 116.5, 24.9; MS (ESI$^+$): for C$_{14}$H$_{13}$BrNO$_2$+ [M+H]$^+$ requires m/z = 306.0/308.0, found 306.0/308.0. Data consistent with literature values.\(^{10}\)

N-(5-Bromo-2-phenoxyphenyl)-N-(2,5-dimethoxybenzyl)acetamide

Based on a literature procedure,\(^{10}\) to a solution of N-(5-bromo-2-phenoxyphenyl)acetamide (3.27 g, 10.7 mmol, 1.00 eq.) in anhydrous DMF (20 mL) was added NaH (60% in mineral oil, 856 mg, 21.4 mmol, 2.00 eq.). The mixture was stirred at room temperature for 1 h. 2,5-Dimethoxybenzyl chloride (2.80 g, 15.0 mmol, 1.4 eq.) was added and the mixture was stirred at room temperature for 2 h. The mixture was poured into water and extracted three times with EtOAc. The combined organic phases were washed with 1M aqueous HCl and brine, dried (MgSO$_4$), filtered and concentrated in vacuo. Flash column chromatography (25% EtOAc in hexane) afforded N-(5-bromo-2-phenoxyphenyl)-N-(2,5-dimethoxybenzyl)acetamide (4.05 g, 8.88 mmol, 83%) as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$): δ = 7.33 (t, $J = 7.8$ Hz, 2H), 7.29 – 7.25 (m, 1H), 7.21 (d, $J = 2.1$ Hz, 1H), 7.14 (t, $J = 7.4$ Hz, 1H), 6.95 (d, $J = 2.8$ Hz, 1H), 6.84 (d, $J = 8.2$ Hz, 2H), 6.77 – 6.65 (m, 3H), 5.05 (d, $J = 14.4$ Hz, 1H), 4.73 (d, $J = 14.4$ Hz, 1H), 3.65 (s, 3H), 3.55 (s, 3H), 1.97 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ = 170.6, 155.5, 153.4, 153.0, 151.7, 134.3, 133.2, 131.8, 129.9, 126.0, 124.4, 119.3, 116.5, 114.4, 113.7, 111.2, 55.7, 55.6, 46.0, 22.2; MS (ESI$^+$): for C$_{23}$H$_{22}$BrNO$_4$+ [M+H]$^+$ requires m/z = 456.1/458.1, found 456.1/458.1. Data consistent with literature values.\(^{10}\)

N-(2,5-Dimethoxybenzyl)-N-(2-phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide

To an oven-dry flask with a magnetic stirrer was added N-(5-bromo-2-phenoxyphenyl)-N-(2,5-dimethoxybenzyl)acetamide (1.44 g, 3.15 mmol, 1.05 eq), bis(pinacolato)diboron (762 mg, 3.00 mmol, 1.00 eq.), Pd(dppf)Cl$_2$ (110 mg, 0.15 mmol, 0.05 eq.) and potassium acetate (882 mg, 9.00 mmol, 3.00 eq). A rubber septum was added, and the flask was evacuated and back-filled with argon three times. Dry, degassed DMF (15 mL) was added. The mixture was heated to 80°C and stirred at this temperature for 18 h. After cooling to room temperature, the mixture was diluted with EtOAc and filtered through a short plug of SiO$_2$, eluting with EtOAc. The crude material was then purified via flash column chromatography (30% EtOAc in pet 40-60) afforded N-(2,5-dimethoxybenzyl)-N-(2-phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide (743 mg, 1.48 mmol, 49% yield) as a white solid.
1H NMR (400 MHz, CDCl₃): δ = 7.61 – 7.55 (m, 2H), 7.32 (t, J = 7.9 Hz, 2H), 7.14 (t, J = 7.4 Hz, 1H), 6.99 (d, J = 3.0 Hz, 1H), 6.84 (d, J = 7.7 Hz, 2H), 6.74 (d, J = 8.6 Hz, 1H), 6.68 (dd, J = 8.9, 3.0 Hz, 1H), 6.62 (d, J = 8.9 Hz, 1H), 4.99 (d, J = 14.5 Hz, 1H), 4.89 (d, J = 14.5 Hz, 1H), 3.63 (s, 3H), 3.50 (s, 3H), 1.97 (s, 3H), 1.32 (s, 6H), 1.31 (s, 6H); 13C NMR (101 MHz, CDCl₃): δ = 171.1, 156.3, 155.4, 153.5, 151.9, 137.0, 135.5, 132.5, 129.8, 126.5, 124.3, 119.7, 116.8, 116.4, 113.7, 111.3, 83.9, 55.7, 55.7, 46.4, 25.0, 24.9, 24.7, 22.3; 11B NMR (128 MHz, CDCl₃) δ 31.2; MS (ESI⁺) for C₉₂H₂₂BNO₆⁺ [M+H⁺] requires m/z = 504.3, found 504.3. Data consistent with literature values.¹¹

**meta-Fluorobenzylguanidine (mFBG)**


To a stirred solution of commercially available [3-{3,3,4,4-tetramethylborolan-1-yl}phenyl]methanaminium chloride (1.00 g, 3.8 mmol) in DCM (10 mL) was added triethylamine (1.00 mL, 7.6 mmol). After 5 minutes stirring, N,N′-bis(tert-butoxycarbonyl)-N′-triflylguanidine (1.45 g, 3.8 mmol) was added before leaving the reaction mixture to stir for 30 min. Upon completion, the excess solvent was removed in vacuo before adding water (50 mL) and extracting the organic layer with DCM (3 × 30 mL). The organic layers were combined, washed with water (2 × 50 mL) and brine (50 mL), dried with MgSO₄, filtered and the solvent removed in vacuo affording tert-butyl-N-[[1E]-{[tert-butoxycarbonyl]imino}[[3-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl]amino]methyl]carbamate as a white solid (1.75 g, 99%).

1H NMR (400 MHz, CDCl₃): δ = 11.54 (bs, 1H), 8.52 (s, 1H), 7.76-7.71 (m, 2H), 7.43 (dt, J = 7.6, 1.4 Hz), 7.35 (t, J = 7.6 Hz), 4.62 (2H, J = 5.1 Hz), 1.52 (s, 9H), 1.46 (s, 9H), 1.34 (s, 12H); 13C NMR (100 MHz, CDCl₃): δ = 163.8, 156.2, 153.3, 136.7, 134.6, 134.3, 131.2, 128.3, 84.0, 83.2, 79.5, 45.2, 28.4, 28.2, 25.0 (note: CAr-B was not observed); IR (ν, cm⁻¹): 2980, 1720, 1639, 1616; HRMS (ESI) for C₂₄H₃₉BN₂O₆ [M+H⁺] requires 476.2926 found 476.2917; MP: 100-101°C.

**tert-Butyl-N-[[1Z]-{bis{[tert-butoxy]carbonyl}amino}{{[3-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl}amino}methylidene]carbamate**

To a round bottom flask was added tert-butyl-N-[[1E]-{[tert-butoxycarbonyl]imino}[[3-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl]amino]methyl)carbamate (0.11 g, 0.23 mmol), di-tert-butyl dicarbonate (0.15 g, 0.69 mmol), dimethylaminopyridine (0.06 mg, 0.46 mmol), triethylamine (0.087 mL, 0.69 mmol) and THF (5 mL). The reaction was then left to stir at room temperature for 2 h. The solvent was then removed in vacuo and the product purified via flash column chromatography (9:1 cyclohexane: EtOAc) gave the title compound tert-butyl-N-[[1Z]-{bis{[tert-butoxy]carbonyl}amino}{{[3-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl}amino}methylidene]carbamate as a colourless oil (0.14 g, 93%).

1H NMR (400 MHz, CDCl₃): δ = 7.78 (s, 1H), 7.69-7.66 (m, 1H), 7.53-7.48 (m, 1H), 7.29 (d, J = 7.5, 1H), 5.03 (s, 2H), 1.48 (s, 9H), 1.45 (s, 18H), 1.38 (s, 9H), 1.32 (s, 12H); 13C NMR (100 MHz, CDCl₃): δ = 157.5, 151.3, 147.4, 144.5, 136.7, 134.3, 133.5, 130.6, 127.7, 83.7, 83.7, 81.9, 50.0, 28.0, 27.9, 27.8, 24.9 (note: C₆-B was not observed); IR (ν, cm⁻¹): 2979, 1806, 1727, 1653, 1127, 1102, 852; HRMS (ESI) for C₃₄H₅₅BN₂O₁₀ [M+H⁺] requires 675.4011 found 675.3996.
tert-Butyl[(Z)-[(3-fluorobenzyl)amino][(tert-butoxycarbonyl)amino]methylidene]carbamate

To a stirred solution of 3-fluorobenzylamine (0.23 mL, 2.00 mmol) in DCM (2 mL) was added triethylamine (0.28 mL, 2.00 mmol). After 5 min stirring, tert-butyl N-[(1E)-[((tert-butoxycarbonyl)amino)((tert-butoxy)carbonyl)amino]methylidene]carbamate (0.75 g, 2.4 mmol) was added before leaving the reaction mixture to stir for 30 min. Upon completion, the excess solvent was removed in vacuo before re-dissolving in Et₂O (10 mL). The organic layer was washed with water (2 × 10 mL) and brine (10 mL) before extraction. The organic layer was dried with MgSO₄ and the solvent removed in vacuo. Purification via column chromatography (hexane/EtOAc, 4:1) afforded the title compound tert-butyl{((Z)-[(3-fluorobenzyl)amino][(tert-butoxycarbonyl)amino]methylidene}carbamate as a white solid (0.66 g, 91%).

1H NMR (400 MHz, CDCl₃): δ = 11.54 (s, 1H), 8.62 (bs, 1H), 7.34-7.27 (m, 1H), 7.11-7.06 (m, 1H), 7.06-7.00 (m, 1H), 4.56 (d, J = 6 Hz, 2H), 1.44 (s, 9H), 1.42 (s, 9H); 13C NMR (400 MHz, CDCl₃): δ = 163.6, 163.0 (d, J = 240 Hz), 156.2, 153.2, 139.9 (d, J = 7 Hz), 130.2 (d, J = 8 Hz), 123.3 (d, J = 3 Hz), 114.7 (d, J = 17 Hz), 114.5 (d, J = 17 Hz), 83.3, 79.5, 44.3 (d, J = 2 Hz), 28.3, 28.1; 19F NMR (376 MHz, CDCl₃): δ = -112.7. IR (ν, cm⁻¹): 2980, 1720, 1639, 1616; HRMS (ESI) for C₁₈H₂₇FN₃O₄ [M+H]⁺ requires 368.1980 found 368.1976; MP: 119-120°C.

tert-Butyl-N-[(1Z)-bis[(tert-butoxycarbonyl)amino]((tert-butoxy)carbonyl)(3-fluorophenyl)methyl]amino)methylidene]carbamate

To a round bottom flask was added, tert-butyl{((Z)-[(3-fluorobenzyl)amino][(tert-butoxycarbonyl)amino]methylidene}carbamate (0.20 g, 0.54 mmol), di-tert-butyl dicarbonate (0.36 g, 1.63 mmol), dimethylaminopyridine (0.13 g, 1.09 mmol), triethylamine (0.21 mL, 1.63 mmol) and THF (5 mL). The reaction was then left to stir at room temperature 17 h. Upon completion, the solvent was removed in vacuo and the product purified via flash column chromatography (cyclohexane:EtOAc, 8:2) affording the title compound tert-butyl-N-[(1Z)-bis[(tert-butoxycarbonyl)amino]((tert-butoxy)carbonyl)(3-fluorophenyl)methyl]amino)methylidene]carbamate as a white powder (0.37 g, 86%).

1H NMR (400 MHz, CDCl₃): δ = 7.24 (td, J = 7.9, 5.9 Hz, 1H), 7.14 (d, J = 7.7 Hz, 1H), 7.12-7.07 (m, 1H), 6.96-6.88 (m, 1H), 5.01 (s, 2H), 1.48 (s, 9H), 1.47 (s, 18H), 1.38 (s, 9H); 13C NMR (100 MHz, CDCl₃): δ = 163.0 (d, J = 245 Hz), 157.4, 151.2, 147.4, 144.6, 140.2 (d, J = 7 Hz), 129.8 (d, J = 8 Hz), 123.3 (d, J = 3 Hz), 114.5 (d, J = 22 Hz), 114.1 (d, J = 21 Hz), 84.1, 84.0, 82.2, 49.8 (d, J = 1 Hz), 28.1, 28.0, 28.0; 19F NMR (376 MHz, CDCl₃): δ = -113.6 ~ -113.7 (m, 1F); IR (ν, cm⁻¹): 2980, 1806, 1725, 1652, 1638, 1123, 1099, 850; HRMS (ESI) for C₂₈H₄₃FN₃O₈ [M+H]⁺ requires 568.3029 found 568.3013; MP: 81-83°C.

1-[(3-Fluorophenyl)methyl]guanidine hydrochloride

To a round bottom flask under an atmosphere of argon was added, tert-butyl{[(Z)-[(3-fluorobenzyl)amino]methylidene}carbamate (0.20 g, 0.54 mmol), di-tert-butyl dicarbonate (0.36 g, 1.63 mmol), dimethylaminopyridine (0.13 g, 1.09 mmol), triethylamine (0.21 mL, 1.63 mmol) and THF (5 mL). The reaction was then left to stir at room temperature 17 h. Upon completion, the solvent was removed in vacuo and the product purified via flash column chromatography (cyclohexane:EtOAc, 8:2) affording the title compound tert-butyl-N-[(1Z)-bis[(tert-butoxycarbonyl)amino]((tert-butoxy)carbonyl)(3-fluorophenyl)methyl]amino)methylidene]carbamate as a white powder (0.37 g, 86%).
**FDOPA**

**Ethyl (S)-2-((tert-butoxycarbonyl)amino)-3-(2-iodo-4,5-dimethoxyphenyl)propanoate**

Title compound was synthesised in four steps from L-DOPA, following the procedure of Stenhagen et al.,12 and ethyl (S)-2-((tert-butoxycarbonyl)amino)-3-(2-iodo-4,5-dimethoxyphenyl)propanoate was isolated as a white solid (3.15 g, 6.60 mmol, 33% yield over four steps).

**Ethyl 2-((tert-butoxycarbonyl)amino)-3-(2-4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl-4,5-dimethoxyphenyl)propanoate**

Prepared according to literature procedure.11 Bis(pinacolato)diboron (698 mg, 2.75 mmol), Pd(dppf)Cl₂·CH₂Cl₂ (102 mg, 0.125 mmol, 0.05 eq.) and potassium acetate (736 mg, 7.5 mmol, 3.0 eq.) were placed in a dry flask under N₂. DMF (15 mL) was added and the mixture purged with argon. Ethyl (S)-2-((tert-butoxycarbonyl)amino)-3-(2-iodo-4,5-dimethoxyphenyl)propanoate (1.20 g, 2.5 mmol, 1.0 eq.) was added and the mixture was heated to 80°C and stirred at this temperature for 18 h. The reaction mixture was allowed to cool to room temperature and brine (20 mL) was added, followed by extraction with Et₂O (3 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried (MgSO₄), filtered and concentrated in vacuo. Silica gel column chromatography (10 – 25% EtOAc in hexane) afforded ethyl 2-((tert-butoxycarbonyl)amino)-3-(2-4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl-4,5-dimethoxyphenyl)propanoate as a white solid (740 mg, 1.54 mmol, 62%).

Two rotamers present at 25 °C in an 81:19 ratio. **1H NMR** (400 MHz, CD₂Cl₂): δ = 7.25 (s, 1H), 6.75 (s, 1H), 5.94 (d, J = 7.9 Hz, 0.81H), 5.37 (br s), 4.28-4.15 (m, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.24-3.13 (m, 2H), 1.38 (s, 6H), 1.37 (s, 6H), 1.34-1.23 (m, 12H); **13C NMR** (100 MHz, CD₂Cl₂): δ = 172.7, 155.5, 151.6, 147.3, 137.9, 118.2, 113.2, 84.0, 78.9, 60.9, 56.5, 55.8, 55.6, 36.6, 28.0, 24.8, 24.4, 14.0. Data consistent with literature values.11
Ethyl (S)-2-((di-tert-butoxycarbonyl)amino)-3-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4,5-dimethoxyphenyl)propanoate

Prepared according to literature procedure.\textsuperscript{11} To a solution of ethyl (S)-2-((tert-butoxycarbonyl)amino)-3-(4,5-dimethoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (240 mg, 0.5 mmol, 1 eq.) in MeCN (2 mL) was added di-tert-butyl dicarbonate (328 mg, 1.5 mmol, 3 eq.), N,N-dimethylaminopyridine (12 mg, 0.1 mmol, 0.2 eq.) and Et\textsubscript{3}N (210 \(\mu\)L, 1.5 mmol, 3 eq.). The mixture was stirred at room temperature under N\textsubscript{2} for 18 h. The solvent was removed \textit{in vacuo}. The residue was dissolved in EtOAc (5 mL) and washed with NH\textsubscript{4}Cl (sat. aq. solution, 5 mL), water (5 mL) and brine (5 mL). The organic extract was dried (MgSO\textsubscript{4}), filtered and concentrated \textit{in vacuo}. Silica gel column chromatography (15 – 25 % EtOAc in hexane) afforded impure ethyl (S)-2-((di-tert-butoxycarbonyl)amino)-3-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4,5-dimethoxyphenyl)propanoate (189 mg) which was purified by preparative reverse phase HPLC to a white solid (153 mg, 53%).

\textsuperscript{1}H NMR (400 MHz, CD\textsubscript{2}Cl\textsubscript{2}): \(\delta\) = 7.22 (s, 1H), 6.56 (s, 1H), 5.18 (dd, \(J\) = 11.2, 3.9 Hz, 1H), 4.21 (m, 2H), 3.95 (dd, \(J\) = 13.4, 3.9, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.05 (dd, \(J\) = 13.4, 11.4, 1H) 1.33 (s, 24H), 1.31 (s, 6H), 1.28 (t, \(J\) = 7.2 Hz, 3H); \textsuperscript{13}C NMR (100 MHz, CD\textsubscript{2}Cl\textsubscript{2}): \(\delta\) = 170.9, 152.7, 151.6, 147.6, 139.3, 119.3, 115.0, 84.0, 82.8, 61.6, 60.9, 56.5, 56.0, 35.6, 28.2, 25.2, 14.7. Data consistent with literature values.\textsuperscript{11}

6-Fluoro-meta-tyrosine (FMT)

Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(3-methoxyphenyl)propanoate

By analogy with a literature procedure,\textsuperscript{13} a solution of (L)-m-tyrosine (800 mg, 4.42 mmol, 1.0 eq.) in a mixture of 1,4-dioxane (9 mL) and 0.5 M aq. NaOH (12 mL) was cooled to 0°C with stirring. Boc\textsubscript{2}O (1.06 g, 4.86 mmol, 1.1 eq.) was added and the mixture was stirred at 0°C for 30 minutes. The solution was concentrated \textit{in vacuo} to 3-5 mL, then cooled to 0°C. EtOAc (9 mL) was added and the mixture was acidified with dilute KHSO\textsubscript{4} solution to pH 2-3. The phases were separated and the aqueous phase was extracted with EtOAc (2 x 15 mL). The combined organic phases were washed with water (2 x 40 mL), dried (MgSO\textsubscript{4}), filtered and concentrated in vacuo. To the crude Boc-protected amino acid was added aceton (30 mL), anhydrous K\textsubscript{2}CO\textsubscript{3} (3.05 g, 22.1 mmol, 5.0 eq.) and MeI (4.26 mL, 9.72 mmol, 2.2 eq.). The mixture was heated to reflux for 8 h. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated to afford crude title compound. Flash column chromatography (15% EtOAc in pet 40-60) afforded methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(3-methoxyphenyl)propanoate (1.08 g, 3.49 mmol, 79% yield over two steps) as a pale yellow oil.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) = 7.20 (t, \(J\) = 7.9 Hz, 1H), 6.79 (dd, \(J\) = 8.2, 2.2 Hz, 1H), 6.71 (d, \(J\) = 7.5 Hz, 1H), 6.67 (br s, 1H), 4.97 (d, \(J\) = 7.0 Hz, 1H), 4.64 – 4.52 (m, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 3.15 – 2.96 (m, 2H), 1.42 (s, 9H); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}): \(\delta\) = 172.3, 159.7, 155.1, 137.5, 129.5, 121.6, 115.0, 112.5, 79.9, 55.1, 54.3, 52.2, 38.3, 28.3. Data consistent with literature values.\textsuperscript{14}
Methyl (S)-3-(2-bromo-5-methoxyphenyl)-2-((tert-butoxycarbonyl)amino)propanoate

To a stirred solution of methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(3-methoxyphenyl)propanoate (800 mg, 2.59 mmol, 1.0 eq.) in DMF (25 mL) was added NBS (507 mg, 2.85 mmol, 1.1 eq.) at room temperature. The mixture was stirred at room temperature for 6 h. The solvent was removed in vacuo to afford crude title compound. Flash column chromatography (20% EtOAc in hexane) afforded methyl (S)-3-(2-bromo-5-methoxyphenyl)-2-((tert-butoxycarbonyl)amino)propanoate (870 mg, 2.24 mmol, 86%) as a white solid.

1H NMR (400 MHz, CDCl3) δ = 7.42 (d, J = 8.7 Hz, 1H), 6.75 (s, 1H), 6.68 (d, J = 9.0 Hz, 1H), 5.06 (d, J = 6.9 Hz, 1H), 4.70 – 4.50 (m, 1H), 3.77 (s, 3H), 3.06 (dd, J = 13.8, 5.7 Hz, 1H), 1.39 (s, 9H); 13C NMR (101 MHz, CDCl3) δ = 172.3, 159.8, 154.9, 136.9, 133.4, 116.8, 115.4, 114.5, 59.4, 53.5, 52.4, 38.7, 28.2. Data consistent with literature values.

Methyl (S)-2-(bis(tert-butoxycarbonyl)amino)-3-(5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate

Into a Schlenk tube under a nitrogen atmosphere was added, (S)-3-(2-bromo-5-methoxyphenyl)-2-((tert-butoxycarbonyl)amino) propanoate (1.14 g, 2.94 mmol), B2pin2 (1.63 g, 6.42 mmol), Pd(dppf)Cl2 (240 mg, 0.32 mmol) and KOAc (0.87 g, 8.86 mmol). The crude mixture was heated to 90°C before addition of degassed toluene (10 mL) was added and the reaction mixture left to stir for 16 h. The reaction was then cooled to room temperature, extracted with EtOAc (30 mL) and filtered through celite. The excess solvent was then removed in vacuo and the crude material partially purified via flash column chromatography (n-Hex: EtOAc 10:1) affording methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate and B2pin2 (1.53g). The crude material was taken directly through to the next step where into a round bottomed flask under a nitrogen atmosphere was added, di-tert-butyldicarbonate (3.83 g, 17.5 mmol), DMAP (1.28 g, 10.5 mmol), triethylamine (2.43 mL, 17.5 mmol) and anhydrous THF (30 mL). The reaction was then left to stir at room temperature for 48 h. Afterwards, the excess solvent was removed in vacuo and the crude material purified via flash column chromatography (n-Hex: EtOAc 10:1) followed by HPLC purification affording methyl (S)-2-(bis(tert-butoxycarbonyl)amino)-3-(5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate as a colourless oil (0.61 g, 1.15 mmol, 38%).

1H NMR (400 MHz, CDCl3): δ = 7.71(d, J = 8.3 Hz, 1H), 6.72 (dd, J = 8.3, 2.5 Hz, 1H), 6.57 (d, J = 2.5 Hz, 1H), 5.30 (dd, J = 11.2, 3.7 Hz, 1H), 4.03 (dd, J = 13.4, 3.7 Hz, 1H), 3.76 (s, 3H), 3.07 (dd, J = 13.3, 11.3, 1H), 1.33 (s, 18H), 1.31 (s 6H), 1.29 (s, 1.29); 13C NMR (100 MHz, CDCl3): δ = 170.9, 161.7, 151.7, 146.8, 138.0, 116.2, 111.7, 83.3, 82.5, 59.9, 55.0, 52.0, 36.0, 27.8, 24.9, 24.8 (note: CAr-B was not observed); IR (v, cm⁻¹): 2978, 2360, 1793, 1747, 1601, 1348, 1142, 859; HRMS (ESI) for C27H42BNNaO9 [M+Na]+ requires 558.2844, found 558.2846.
6-Fluorodopamine (FDA)

1,2-Dimethoxy-4-[(E)-2-nitroethenyl]benzene

To a round bottom flask was added 3,4-dimethoxybenzaldehyde (3.00 g, 18.06 mmol), ammonium acetate (5.00 g, 64.9 mmol), nitromethane (7.02 mL, 130 mmol) and acetic acid (40 mL). The reaction mixture was left to stir at 90°C for 16 h. Upon completion the reaction was cooled to room temperature and water (100 mL) was added to the reaction mixture. The resulting precipitate was collected via filtration affording 1,2-dimethoxy-4-[(E)-2-nitroethenyl]benzene as a dark orange solid (3.09 g, 81%).

1H NMR (400 MHz, CDCl3): δ = 7.97 (d, J = 13.6 Hz, 1H), 7.53 (d, J = 13.6 Hz, 1H), 7.18 (dd, J = 8.3, 2.0 Hz, 1H), 7.01 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H); 13C NMR (100 MHz, CDCl3): δ = 152.8, 149.6, 139.3, 135.2, 124.7, 122.8, 111.4, 110.2, 56.1, 56.0. Data consistent with literature values.

1,2-Dimethoxy-4-(2-nitroethyl)benzene

To a round bottom flask at 0°C was added 1,2-dimethoxy-4-[(E)-2-nitroethenyl]benzene (0.50 g, 2.39 mmol) and ethanol (23 mL). Slowly, sodium borohydride was added in portions (0.24 g, 7.17 mmol). Once added, the reaction was left to stir at 0°C for 1 h before warming to room temperature. After stirring for a further 2 h the solvent was removed in vacuo and the resulting crude solid quenched with ammonium chloride (25 mL). The organic layer was then extracted with EtOAc and washed with water (2 × 20 mL) and brine (20 mL). The organic layer was then dried with MgSO4 and the excess solvent removed in vacuo affording a dark brown oil. Purification via column chromatography (hexane/EtOAc, 10:1) afforded 1,2-dimethoxy-4-(2-nitroethyl)benzene as a yellow oil (0.39 g, 78%).

1H NMR (400 MHz, CDCl3): δ = 6.81 (d, J = 8.1 Hz, 1H), 6.74 (dd, J = 8.1, 2.0 Hz, 1H), 6.70 (d, J = 2.0 Hz, 1H), 4.58 (t, J = 7.4 Hz, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.26 (t, J = 7.4 Hz, 2H); 13C NMR (100 MHz, CDCl3): δ = 149.3, 148.5, 128.2, 120.7, 111.8, 111.6, 76.7, 56.0, 56.0 33.3. Data consistent with literature values.

2-(3,4-Dimethoxyphenyl)ethanaminium chloride

In a round bottom flask were introduced 1,2-dimethoxy-4-(2-nitroethyl)benzene (1.3 g, 5.8 mmol), MeOH (100 mL) and 10% palladium on carbon (65 mg). The flask was connected to a hydrogen balloon and allowed to stir at room temperature for 24h. After completion (TLC monitoring), the solution was filtered on celite, evaporated and dissolved in EtOH (40 mL). HCl (conc., 2 mL) was added and the solution was stirred at room temperature for 15 min. After evaporation of the solution, the crude was dissolved in toluene (50 mL) and evaporated (this operation was repeated 3 times). DCM (40 mL) and pentane (40 mL) were added and filtration of the obtained precipitate afforded 2-(3,4-dimethoxyphenyl)ethanaminium chloride as a white powder (1.18 g, 88%).

1H NMR (400 MHz, CD3OD): δ = 6.94 (d, J = 8.1 Hz, 1H), 6.91 (d, J = 2.0 Hz, 1H), 6.84 (dd, J = 8.1 Hz, J = 2.0 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.18 (t, J = 7.6 Hz, 2H), 2.92 (t, J = 7.6 Hz, 2H) (note: NH3 was not observed); 13C NMR (100 MHz, CD3OD): δ = 150.8, 149.8, 130.6, 122.2, 113.7, 113.4, 56.5, 56.5, 42.1, 34.1; IR (ν, cm⁻¹): 3414, 3166, 2937, 1593, 1516, 1465, 1421, 1261, 1235, 1193, 1157, 1022, 808, 765; HRMS (ESI) for C10H16O2N [M-HCl+H]+ requires 182.1175 found 182.1177; MP: 116-118°C.
**tert-Butyl N-[2-(2-bromo-4,5-dimethoxyphenyl)ethyl]-N-(tert-butoxycarbonyl)carbamate**

In a round bottom flask at 0°C were introduced 2-(3,4-dimethoxyphenyl)ethanaminium chloride (0.85 g, 3.9 mmol), MeCN (85 mL), trifluoroacetic acid (0.72 mL, 9.4 mmol) and N-bromosuccinimide (1.05 g, 4.68 mmol). After stirring for 10 min at 0°C, the reaction was allowed to stir 2 h at room temperature and then Na$_2$S$_2$O$_3$ saturated solution was added (50 mL). The solution was extracted with DCM (3 x 40 mL), dried with MgSO$_4$, filtered and evaporated. The obtained crude material was dissolved in THF (40 mL) under argon and, triethylamine (2.51 mL, 20.5 mmol), 4-dimethylaminopyridine (1.91 g, 15.6 mmol) and di-tert-butyl dicarbonate (4.26 g, 20.5 mmol) were added to the solution. After stirring at room temperature for 16 h, the solution was evaporated and purified by silica gel chromatography (cyclohexane/EtOAc, 9:1) as the eluent. tert-Butyl N-[2-(2-bromo-4,5-dimethoxyphenyl)ethyl]-N-(tert-butoxycarbonyl)carbamate (1.01 g, 56%) was obtained as a yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 6.99$ (s, 1H), 6.69 (s, 1H), 3.84 (s, 3H), 3.84 (s, 3H), 3.80 (t, $J$ = 8.0 Hz, 2H), 2.95 (t, $J$ = 8.0 Hz, 2H), 1.47 (s, 18H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 152.5, 148.5, 148.4, 130.4, 115.6, 114.5, 113.8, 82.3, 56.3, 56.1, 46.2, 35.3, 28.2; IR (v, cm$^{-1}$): 2977, 2934, 1787, 1741, 1695, 1663, 1508, 1441, 1305, 1131, 854; HRMS (ESI) for C$_{20}$H$_{30}$O$_6$N$_7$Br$_2$Na $[M+Na]^+$ requires 482.1148 found 482.1152.

**tert-Butyl N-(tert-butoxycarbonyl)-N-[2-[4,5-dimethoxy-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethyl] carbamate**

In a round bottom flask under argon were introduced tert-butyl N-[2-(2-bromo-4,5-dimethoxyphenyl)ethyl]-N-(tert-butoxycarbonyl)carbamate (0.61 g, 1.32 mmol), bis(pinacolato)diboron (0.67 g, 2.64 mmol), potassium acetate (0.39 g, 3.96 mmol), Pd(dppf)Cl$_2$·CH$_2$Cl$_2$ (52 mg, 5 mol%) and degassed toluene (7 mL). The flask was heated at reflux for 17 h, evaporated and purified by preparative reverse phase HPLC to give tert-Butyl N-(tert-butoxycarbonyl)-N-[2-[4,5-dimethoxy-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethyl] carbamate (0.33 g, 48%) as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.28$ (s, 1H), 6.62 (s, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.83 (t, $J$ = 6.6 Hz, 2H), 3.14 (t, $J$ = 6.6 Hz, 2H), 1.41 (s, 18H), 1.33 (s, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 152.8, 151.1, 146.9, 140.4, 118.4, 113.6, 83.6, 81.9, 56.3, 55.9, 48.5, 34.6, 28.2, 25.1 (note: C$_{Ar}$-B was not observed); IR (v, cm$^{-1}$): 2977, 1785, 1741, 1696, 1390, 1366, 1253, 1136, 859, 766; HRMS (ESI) for C$_{26}$H$_{42}$O$_8$N$_{11}$B$_2$Na $[M+Na]^+$ requires 530.2895 found 530.2897.

**1-Fluoro-4,5-dimethoxy-2-[(E)-2-nitrovinyl]benzene**

To a round bottom flask was added 1-fluoro-3,4-dimethoxybenzaldehyde (1.00 g, 5.4 mmol), ammonium acetate (1.26 g, 32.4 mmol), nitromethane (0.88 mL, 32.4 mmol) and acetic acid (15 mL). The reaction mixture was left to stir at 90°C for 16 h. Upon completion the reaction was cooled to room temperature and water (100 mL) was added to the reaction mixture. The resulting precipitate was collected via filtration affording 1-fluoro-4,5-dimethoxy-2-[(E)-2-nitrovinyl]benzene as a dark orange solid (1.00 g, 82%).
**1-H NMR** (400 MHz, CDCl₃): δ = 8.03 (d, J = 13.7 Hz, 1H), 7.63 (d, J = 13.7 Hz, 1H), 6.87 (d, J = 6.7 Hz, 1H), 6.70 (d, J = 11.8 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H); **13C NMR** (100 MHz, CDCl₃): δ = 157.6 (d, J = 252 Hz), 153.7 (d, J = 10.6 Hz), 146.0 (d, J = 1.7 Hz), 137.1 (d, J = 10.3 Hz), 132.6, 111.1 (d, J = 4.2 Hz), 109.2 (d, J = 13.2 Hz), 100.5 (d, J = 27.9 Hz), 56.5; **19F {1H} NMR** (376 MHz, CDCl₃): δ = -114.5 (s, 1F).

**IR** (ν, cm⁻¹): 1541, 1461, 1222, 1181, 1105, 996, 859; **HRMS** (EI) for C₁₀H₁₀O₄NF₂₃Na [M+Na⁺] requires 250.0486 found 250.0487; MP: 125-127°C.

**1-Fluoro-4,5-dimethoxy-2-(2-nitroethyl)benzene**

To a round bottom flask at 0°C was added, 1-fluoro-4,5-dimethoxy-2-[(E)-2-nitrovinyl]benzene (0.50 g, 2.72 mmol) and ethanol (60 mL). Slowly, sodium borohydride was added in portions (0.31 g, 8.15 mmol). Once added, the reaction was left to stir at 0°C for 1 h before warming to room temperature. After stirring for a further 2 h the solvent was removed in vacuo and the resulting crude solid quenched with ammonium chloride (25 mL). The organic layer was then extracted with EtOAc and washed with water (2 × 20 mL) and brine (20 mL). The organic layer was then dried with MgSO₄ and the excess solvent removed in vacuo affording a dark brown oil. Purification via column chromatography (hexane/EtOAc, 10:1) afforded 1-fluoro-4,5-dimethoxy-2-(2-nitroethyl)benzene as a yellow oil (0.33 g, 64%).

**1-H NMR** (400 MHz, CDCl₃): δ = 6.64 (d, J = 7.0 Hz, 1H), 6.62 (t, J = 7.9 Hz, 1H), 4.58 (t, J = 7.4 Hz, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.26 (t, J = 7.4 Hz, 2H); **13C NMR** (100 MHz, CDCl₃): δ = 155.2 (d, J = 239 Hz), 149.3 (d, J = 9.9 Hz), 145.4 (d, J = 2.4 Hz), 113.0 (d, J = 5.7 Hz), 112.8 (d, J = 17 Hz), 100.2 (d, J = 27.8 Hz), 75.0 (d, J = 1.4 Hz), 56.5, 56.2, 27.1 (d, J = 1.3 Hz); **19F NMR** (376 MHz, CDCl₃): δ = -125.4 (dd, J = 11.1, 7.2, 1F); **IR** (ν, cm⁻¹): 1616, 1518, 1214, 1194, 999, 966, 828; **HRMS** (EI) for C₁₀H₁₂O₄NF₂₃Na [M+Na⁺] requires 252.0643 found 252.0643; MP: 48-50°C.

**2-(2-Fluoro-4,5-dimethoxyphenyl)ethanamine**

In a round bottom flask were introduced 1-fluoro-4,5-dimethoxy-2-(2-nitroethyl)benzene (0.3 g, 1.3 mmol), MeOH (25 mL) and 10% palladium on carbon (13 mg). The flask was connected to a hydrogen balloon and allowed to stir at room temperature for 18 h. After completion (TLC monitoring), the solution was filtered on celite and evaporated to give 2-(2-fluoro-4,5-dimethoxyphenyl)ethanamine (0.22 g, 83%) as a white powder.

**1-H NMR** (400 MHz, CDCl₃): δ = 6.66 (d, J = 7.1 Hz, 1H), 6.61 (d, J = 11.0 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 2.93 (t, J = 6.9 Hz, 2H), 2.71 (t, J = 6.9 Hz, 2H), 1.44 (bs, 2H); **13C NMR** (100 MHz, CDCl₃): δ = 155.4 (d, J = 239 Hz), 149.3 (d, J = 9.9 Hz), 145.4 (d, J = 2.4 Hz), 113.0 (d, J = 5.7 Hz), 112.8 (d, J = 17 Hz), 100.2 (d, J = 27.8 Hz), 75.0 (d, J = 1.4 Hz), 56.5, 56.2, 27.1 (d, J = 1.3 Hz); **19F NMR** (376 MHz, CDCl₃): δ = -125.4 (dd, J = 11.1, 7.2, 1F); **IR** (ν, cm⁻¹): 1616, 1518, 1214, 1194, 999, 966, 828; **HRMS** (EI) for C₁₀H₁₄NO₂F [M⁺] requires 199.1011 found 199.1009; MP: 80-81°C.

**2-(2-Fluoro-4,5-dihydroxyphenyl)ethanaminium bromide**

In a round bottom flask under argon at -60°C were introduced 2-(2-fluoro-4,5-dimethoxyphenyl)ethanamine (0.3 g, 1.3 mmol), MeOH (25 mL) and 10% palladium on carbon (13 mg). The flask was connected to a hydrogen balloon and allowed to stir at room temperature for 18 h. After completion (TLC monitoring), the solution was filtered on celite and evaporated to give 2-(2-fluoro-4,5-dimethoxyphenyl)ethanamine (0.22 g, 83%) as a white powder.

**1-H NMR** (400 MHz, CDCl₃): δ = 6.66 (d, J = 7.1 Hz, 1H), 6.61 (d, J = 11.0 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 2.93 (t, J = 6.9 Hz, 2H), 2.71 (t, J = 6.9 Hz, 2H), 1.44 (bs, 2H); **13C NMR** (100 MHz, CDCl₃): δ = 155.4 (d, J = 239 Hz), 149.3 (d, J = 9.9 Hz), 145.4 (d, J = 2.4 Hz), 114.5 (d, J = 2 Hz), 117.1 (d, J = 18 Hz), 113.4 (d, J = 6 Hz), 100.3 (d, J = 28 Hz), 56.6, 56.2, 42.7, 33.1; **19F NMR** (376 MHz, CDCl₃): δ = -125.8 (dd, J = 11.1, 7.2 Hz); **IR** (ν, cm⁻¹): 1625, 1570, 1515, 1404, 1223, 1192, 1033, 999, 853, 821; **HRMS** (EI) for C₁₀H₁₄NO₄F [M⁺] requires 199.1011 found 199.1009; MP: 80-81°C.
H NMR (400 MHz, CD$_3$OD): $\delta = 6.66 (d, J = 7.5$ Hz, 1H), 6.56 (d, $J = 11.0$ Hz, 1H), 3.09 (t, $J = 7.6$ Hz, 2H), 2.84 (t, $J = 7.7$ Hz, 2H) (note: NH$_3$ was not observed); $^{13}$C NMR (100 MHz, CD$_3$OD): $\delta = 155.8 (d, J = 235$ Hz), 146.7 (d, $J = 11$ Hz), 142.9 (d, $J = 2$ Hz), 117.4 (d, $J = 6$ Hz), 114.0 (d, $J = 17$ Hz), 104.1 (d, $J = 27$ Hz), 41.0, 27.7; $^{19}$F $^{1}H$ NMR (376 MHz, CD$_3$OD): $\delta = -130.6$ (s, 1F); IR (v, cm$^{-1}$): 3224, 2291, 1635, 1526, 1451, 1358, 1295, 1211, 1211, 999, 863; HRMS (ESI) for C$_{8}$H$_{11}$NO$_{2}$F [M-HBr+H$^+$] requires 172.0768 found 172.0766; MP: 174-176°C.

tert-Butyl N-(tert-butoxycarbonyl)-N-{2-[4,5-dimethoxy-2-(fluoro)phenyl]ethyl}carbamate.

To a solution of 2-(2-fluoro-4,5-dimethoxyphenyl)ethanamine (55 mg, 0.28 mmol) in THF (20 mL) under argon, triethylamine (1.53 mL, 1.10 mmol), 4-dimethylaminopyridine (102 mg, 0.84 mmol) and di-tert-butyl dicarbonate (244 mg, 1.14 mmol) were added to the solution. After stirring at room temperature for 16 h, the solution was evaporated and purified by silica gel chromatography ($n$-hexane/EtOAc, 10:3) afforded tert-butyl N-(tert-butoxycarbonyl)-N-{2-[4,5-dimethoxy-2-(fluoro)phenyl]ethyl}carbamate was obtained as a white solid (72 mg, 64%).

$^{1}$H NMR (400 MHz, CDCl$_3$): $\delta = 6.62 (d, J = 7.1$ Hz, 1H), 6.60 (d, $J = 10.9$ Hz, 1H), 3.83 (s, 3H), 3.76 (t, $J = 7.5$ Hz, 2H), 2.84 (t, $J = 7.5$ Hz, 2H), 1.48 (s, 18H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 155.3 (d, J = 238$ Hz), 152.3, 148.4 (d, $J = 10$ Hz), 145.0 (d, $J = 10$ Hz), 143.6 (d, $J = 18$ Hz), 116.0 (d, $J = 6$ Hz), 100.1 (d, $J = 27$ Hz), 82.2, 56.4, 56.1, 46.5, 28.4, 28.0; $^{19}$F $^{1}H$ NMR (376 MHz, CD$_3$OD): $\delta = -125.8$ (s, 1F); IR (v, cm$^{-1}$): 1788, 1744, 1515, 1224, 1134, 1110, 852; HRMS (ESI) for C$_{20}$H$_{30}$NO$_{6}$F$_{2}$Na [M+Na$^+$] requires 422.1949 found 422.1945; MP: 62-64°C.

### References


2. Radiochemistry

2.1 General Experimental Information

General information for radiochemical procedures at the Chemistry Research Laboratory, University of Oxford

$^{18}$F Fluoride was produced by Alliance Medical (UK) via the $^{18}$O(p,n)$^{18}$F reaction and delivered as $^{18}$F fluoride in $^{18}$O-enriched-water. Radiosynthesis and azeotropic drying was performed on a NanoTek microfluidic device (Advion).

General procedure for pre-conditioning of separation cartridge with oxalate counter-ions

A waters Sep-Pak Accell Plus QMA Carbonate Plus Light Cartridge, 46 mg Sorbent per Cartridge, 40 µm Particle Size, 50/pk (Part #186004540 from Waters) or a Chromafix PS-HCO$_3$ $^{18}$F separation cartridge (45 mg) (Product No. 731876 from ABX) was pre-conditioned with 3 mL of a 10 mg/ml K$_2$C$_2$O$_4$(aq) solution followed by 5 mL H$_2$O at a flow rate of 3 mL/min.

General procedure for small scale $^{18}$F fluorination of arenes (University of Oxford)

Radiosynthesis and azeotropic drying was performed on a NanoTek® microfluidic device (Advion). $^{18}$F Fluoride (3.0-4.0 GBq) was separated from $^{18}$O-enriched-water using a Chromafix PS-HCO$_3$ $^{18}$F separation cartridge (45 mg) and subsequently released with 900 µL (in 6 x 150 µL portions) of a solution of K$_2$222/K$_2$CO$_3$ (Kryptofix 222 (15 mg) and K$_2$CO$_3$ (3 mg) in 1 mL of MeCN/H$_2$O, 4:1) into a 5 mL V-vial containing a magnetic stir bar in the concentrator. The solution was dried with five cycles of azeotropic drying with MeCN (5 x 200 µl) under a flow of N$_2$ at 105 °C. The dried $^{18}$FKF/K$_{222}$ residue is redissolved in anhydrous MeCN (500–1000 µL). Small aliquots of this solution of $^{18}$FKF/K$_{222}$ in MeCN (20-30 MBq, 10-40 µL) are dispensed into a V-vial containing Cu(OTf)$_2$(py)$_4$, aryl pinacol boronate and a magnetic stirrer bar. Air was flushed through the reaction vial using a syringe and then DMF (300 µL) was added via syringe. The sealed vial was heated at 110 °C for 20 minutes. The reaction was quenched by addition of water (200 µL). An aliquot was removed for analysis by radioTLC and HPLC for radiochemical conversion and product identity. Analysis was performed using the gradient given below with a Waters Nova-Pak C18 column (4 µm, 3.9 x 150 mm) at a flow rate 1 ml/min.

HPLC gradient: water/MeCN, 1 mL/min, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm
0-1 min (5% MeCN) isocratic
1-10 min (5% MeCN to 95% MeCN) linear increase
10-14 min (95% MeCN) isocratic
14-15 min (95% MeCN to 5% MeCN) linear decrease
15-17 min (5% MeCN) isocratic

Radio-TLC was performed on Merck Kiesegel 60 F254 plates. Analysis was performed using a plastic scintillator/PMT detector.

General information for radiochemical procedures at Imanova

Radiosynthesis were performed on a Synthra fluorination platform. All the chemicals and solvents (including anhydrous solvents) were used directly without further purification.

$^{18}$F Fluoride, produced using a Siemens RDS-111 Eclipse cyclotron equipped with a fluoride target loaded with $^{18}$O-enriched-water, was obtained by means of the $^{18}$O(p,n)$^{18}$F reaction. The $^{18}$F fluoride in $^{18}$O-enriched-water was transferred with a sweep of argon gas from the cyclotron target to the hotcell containing the automated module for radiochemistry. The $^{18}$F fluoride was trapped on an ion exchange cartridge (DW-TRC-L Trap & Release Column) and released into a dried 5 mL Wheaton V-vial using 0.9 mL of a solution consisting of 800 µL of MeCN, 100 µL of a 10 mg/ml K$_2$CO$_3$(aq) solution, 100 µL of a 1 mg/ml K$_2$C$_2$O$_4$(aq) solution and 6.3 mg of kryptofix. The content of the reactor was evaporated a first time (under a stream of argon). The evaporation process was repeated 2 times following the addition of 1 mL of anhydrous MeCN each time. The reaction vessel was cooled down to 30 °C and the atmosphere was renewed with air.
HPLCs (1100 series, Agilent) for quality control were equipped with a binary pump, diode array detector, degasser, column oven and flow cell detector (Berthold sodium iodide detector). Radioactivity was measured using an ion chamber (ISOMED 2000 Dose Calibrator).

**General information for radiochemical procedures at ABX**

$[^{18}\text{F}]$Fluoride was produced with a GE MINI Trace 700 cyclotron via the $^{18}\text{O}(p,n)^{18}\text{F}$ reaction and delivered as $[^{18}\text{F}]$fluoride in $^{18}\text{O}$-enriched-water. Radiosynthesis and azeotropic drying was performed on a NEPTIS® perform synthesizer. $[^{18}\text{F}]$Fluoride (100-300 MBq) was separated from $^{18}\text{O}$-enriched-water by using an anion exchange cartridge (Sep-Pak Light QMA Cartridge, preconditioned, with CO$_3^{2-}$ as counter ions, ABX Prod. No.: K-920) and subsequently released with 800 μL of a solution of K$_{222}$/KH$_2$PO$_4$ (Kryptofix 222 15 mg) and KH$_2$PO$_4$ (4 mg) in 1 mL of MeCN/H$_2$O, 4:1) into the reactor vial. The solution was dried with four cycles of azeotropic drying with MeCN (200 μL) under a flow of N$_2$ at 105 °C.
2.2 Isolation Procedures

**General procedure for the radiosynthesis of [\(^{18}\)F]FMTEB (University of Oxford):** [\(^{18}\)F]Fluoride (3.0-10.0 GBq) was separated from \(^{18}\)O-enriched-water using anion exchange cartridge (see section 2.3) and subsequently released with 900 µL (in 6 x 150 µL portions) of a solution of K\(_{222}/K_{234}CO_3/K_2CO_3\) (kryptofix 222 (6.3 mg), K\(_{234}CO_3\) (1 mg) and K\(_2CO_3\) (0.1 mg) in 1 mL of MeCN/H\(_2O\) 4:1) into a 5 mL V-vial containing a magnetic stir bar in the concentrator. The solution was dried with five cycles of azeotropic drying with MeCN (5 x 200 µL) under a flow of N\(_2\) at 105 °C. The 5 mL vial containing the dried [\(^{18}\)F]K/K\(_{222}\) complex was purged with 30 mL of air using a syringe and then a solution of arylboronate precursor (10.5 mg, 0.03 mmol) and Cu(OTf)\(_2\)(py)\(_4\) (27 mg, 0.04 mmol) in anhydrous DMA (400 µL) was added. The mixture was heated at 120 °C for 20 min in a sealed vial with stirring, after which, the reaction mixture was diluted with 1 mL of 40% MeCN/ 60% 25 mM NH\(_2\)HCOO\(_{aq}\) and loaded directly onto a 2 mL HPLC loop and injected on a semi-Prep HPLC column (Synergi 4µm Hydro-RP 250x10mm) and eluted with 50% MeCN/50% 25 mM NH\(_2\)HCOO (isocratic 4 mL/min) monitoring with UV (254 nm) and radioactive traces.

SA of [\(^{18}\)F]FMTEB in collected fraction was assessed using an analytical Synergi 4µm Hydro-RP 80A, 150 x 4.6 mm with 50% MeCN/50% 25 mM NH\(_2\)HCOO (isocratic 1 mL/min) monitoring with UV (254 nm) and radioactive traces.

**General procedure for the radiosynthesis of [\(^{18}\)F]FPEB (University of Oxford):** [\(^{18}\)F]Fluoride (3.0-10.0 GBq) was separated from \(^{18}\)O-enriched-water using anion exchange cartridge (see section 2.3) and subsequently released with 900 µL (in 6 x 150 µL portions) of a solution of K\(_{222}/K_{234}CO_3/K_2CO_3\) (kryptofix 222 (6.3 mg), K\(_{234}CO_3\) (1 mg) and K\(_2CO_3\) (0.1 mg) in 1 mL of MeCN/H\(_2O\) 4:1) into a 5 mL V-vial containing a magnetic stir bar in the concentrator. The solution was dried with five cycles of azeotropic drying with MeCN (5 x 200 µL) under a flow of N\(_2\) at 105 °C. The 5 mL vial containing the dried [\(^{18}\)F]K/K\(_{222}\) complex was purged with 30 mL of air using a syringe and then a solution of arylboronate precursor (10 mg, 0.03 mmol) and Cu(OTf)\(_2\)(py)\(_4\) (27 mg, 0.04 mmol) in anhydrous DMA (400 µL) was added. The mixture was heated at 120 °C for 20 min in a sealed vial with stirring, after which, the reaction mixture was diluted with 1 mL of 40% MeCN/ 60% 25 mM NH\(_2\)HCOO\(_{aq}\) and loaded directly onto a 2 mL HPLC loop and injected on a semi-Prep HPLC column (Synergi 4µm Hydro-RP 250x10mm) and eluted with 50% MeCN/50% 25 mM NH\(_2\)HCOO (isocratic 4 mL/min) monitoring with UV (254 nm) and radioactive traces.

SA of [\(^{18}\)F]FPEB in collected fraction was assessed using an analytical Synergi 4µm Hydro-RP 80A, 150 x 4.6 mm with 40% MeCN/60% H\(_2O\) (isocratic 1 mL/min) monitoring with UV (254 nm) and radioactive traces.

**General procedure for the radiosynthesis of [\(^{18}\)F]Flumazenil (University of Oxford):** [\(^{18}\)F]Fluoride (3.0-10.0 GBq) was separated from \(^{18}\)O-enriched-water using anion exchange cartridge (see section 2.3) and subsequently released with 900 µL (in 6 x 150 µL portions) of a solution of K\(_{222}/K_{234}CO_3/K_2CO_3\) (kryptofix 222 (6.3 mg), K\(_{234}CO_3\) (1 mg) and K\(_2CO_3\) (0.1 mg) in 1 mL of MeCN/H\(_2O\) 4:1) into a 5 mL V-vial containing a magnetic stir bar in the concentrator. The solution was dried with five cycles of azeotropic drying with MeCN (5 x 200 µL) under a flow of N\(_2\) at 105 °C. The 5 mL vial containing the dried [\(^{18}\)F]K/K\(_{222}\) complex was purged with 30 mL of air using a syringe and then a solution of arylboronate precursor (27 mg, 0.04 mmol) in anhydrous DMA (400 µL) was added. The mixture was heated at 120 °C for 20 min in a sealed vial with stirring, after which, the reaction mixture was diluted with 1 mL of 40% MeCN/ 85% 25 mM NH\(_2\)HCOO\(_{aq}\) and loaded directly onto a 2 mL HPLC loop and injected on a semi-Prep HPLC column (Synergi 4µm Hydro-RP 250x10mm) and eluted with 25% MeCN/75% 25 mM NH\(_2\)HCOO (isocratic 4 mL/min) monitoring with UV (254 nm) and radioactive traces.

SA of [\(^{18}\)F]Flumazenil in collected fraction was assessed using an analytical Synergi 4µm Hydro-RP 80A, 150 x 4.6 mm with 25% MeCN/75% 25 mM NH\(_2\)HCOO (isocratic 1 mL/min) monitoring with UV (254 nm) and radioactive traces.
General procedure for the radiosynthesis of [18F]DAA1106 (University of Oxford): [18F]Fluoride (3.0-10.0 GBq) was separated from 18O-enriched-water using anion exchange cartridge (see section 2.3) and subsequently released with 900 µL (in 6 x 150 µL portions) of a solution of K222/K2CO3/K2CO4 (kryptofix 222 (6.3 mg), K2C2O4 (1 mg) and K2CO3 (0.1 mg) in 1 mL of MeCN/H2O, 4:1) into a 5 mL V-vial containing a magnetic stir bar in the concentrator. The solution was dried with five cycles of azotropic drying with MeCN (5 x 200 µL) under a flow of N2 at 105 °C. The 5 mL vial containing the dried [18F]KF/K222 complex was purged with 30 mL of air using a syringe and then a solution of arylboronate precursor (10 mg, 0.02 mmol) and Cu(OTf)2(py)4 (14 mg, 0.02 mmol) in anhydrous DMF (400 µL) was added. The mixture was heated at 120 °C for 20 min in a sealed vial with stirring, after which, the reaction mixture was diluted with 1 mL of 40% MeCN/ 25 mM NH4HCOO(aq) and loaded directly onto a 2 mL HPLC loop and injected on a semi-Prep HPLC column (Synergi 4 µm Hydro-RP 250x10 mm) and eluted with 60% MeCN/40% 25 mM NH4HCOO (isocratic 4 mL/min) monitoring with UV (254 nm) and radioactive traces.

SA of [18F]DAA1106 in collected fraction was assessed using an analytical Synergi 4 µm Hydro-RP 80A, 150 x 4.6 mm with 60% MeCN/35% H2O (isocratic 1 mL/min) monitoring with UV (254 nm) and radioactive traces.

General procedure for the radiosynthesis of [18F]MFBG (University of Oxford): [18F]Fluoride (3.0-10.0 GBq) was separated from 18O-enriched-water using anion exchange cartridge (see section 2.3) and subsequently released with 900 µL (in 6 x 150 µL portions) of a solution of K222/K2CO3/K2CO4 (kryptofix 222 (6.3 mg), K2C2O4 (1 mg) and K2CO3 (0.1 mg) in 1 mL of MeCN/H2O, 4:1) into a 5 mL V-vial containing a magnetic stir bar in the concentrator. The solution was dried with five cycles of azotropic drying with MeCN (5 x 200 µL) under a flow of N2 at 105 °C. The 5 mL vial containing the dried [18F]KF/K222 complex was purged with 30 mL of air using a syringe and then a solution of arylboronate precursor (13 mg, 0.02 mmol) and Cu(OTf)2(py)4 (14 mg, 0.02 mmol) in anhydrous DMF (400 µL) was added. The mixture was heated at 120 °C for 20 min in a sealed vial with stirring. HI(aq) (57%, 300 µL) was added via syringe and the reaction was stirred at 120 °C for 10 min. The reaction mixture was then allowed to cool to room temperature and partially neutralized with NaOH(aq) (6.75 M, 400 µL) and further diluted with 25 mM NH4HCOO(aq) (800 µL) and filtered before loading onto a 2 mL HPLC loop and injected on a semi-Prep HPLC column (Synergi 4 µm Hydro-RP 250x10 mm) and eluted with 10% MeCN/90% 25 mM NH4HCOO (isocratic 4 mL/min) monitoring with UV (254 nm) and radioactive traces. (Note: Precipitate formed after HI deprotection and led to poor transfer efficiency and loss of activity deposited on the syringe filter prior to loading HPLC.)

SA of [18F]MFBG in collected fraction was assessed using an analytical Synergi 4 µm Hydro-RP 80A, 150 x 4.6 mm with 10% MeCN/90% NH4HCOO (isocratic 1 mL/min) monitoring with UV (254 nm) and radioactive traces.

General procedure for the radiosynthesis of [18F]FDOPA (University of Oxford): [18F]Fluoride (3.0-10.0 GBq) was separated from 18O-enriched-water using anion exchange cartridge (see section 2.3) and subsequently released with 900 µL (in 6 x 150 µL portions) of a solution of K222/K2CO3/K2CO4 (kryptofix 222 (6.3 mg), K2C2O4 (1 mg) and K2CO3 (0.1 mg) in 1 mL of MeCN/H2O, 4:1) into a 5 mL V-vial containing a magnetic stir bar in the concentrator. The solution was dried with five cycles of azotropic drying with MeCN (5 x 200 µL) under a flow of N2 at 105 °C. The 5 mL vial containing the dried [18F]KF/K222 complex was purged with 30 mL of air using a syringe and then a solution of arylboronate precursor (11 mg, 0.02 mmol) and Cu(OTf)2(py)4 (14 mg, 0.02 mmol) in anhydrous DMF (400 µL) was added. The mixture was heated at 120 °C for 20 min in a sealed vial with stirring. The reaction mixture was then diluted into 8 mL of H2O and loaded onto a Sep-Pak® Plus C18 cartridge and washed with two 1 mL portions of H2O. 1 mL of air was then flushed through the cartridge and the product was eluted back into the reaction vial using two 1 mL washes of acetone and then flushing the cartridge with 1 mL air. The acetone was evaporated under a flow of N2 while heated to 120 °C. The dry residue was then redissolved in HI(aq) (57%, 400 µL) and the reaction was stirred at 150 °C for 10 min. The reaction mixture was then allowed to cool to room temperature and partially neutralized with NaOH(aq) (6.75 M, 400 µL) and further diluted with 25 mM NH4HCOO(aq) solution containing 0.2 mg/mL of ascorbic acid (1000 µL) and loaded directly onto a 2 mL HPLC loop and injected on a semi-Prep HPLC column (Synergi 4 µm Hydro-RP 250x10 mm) and eluted with a 50 mM...
AcOH/ 2.5 mM NaOAc buffer containing 0.1 mg/mL ascorbic acid (isocratic 4 mL/min) monitoring with UV (254 nm) and radioactive traces.

SA of [18F]FDOPA in collected fraction was assessed using an analytical Synergi 4µm Hydro-RP 80A, 150 x 4.6 mm with 50 mM AcOH/ 2.5 mM NaOAc buffer containing 0.1 mg/mL ascorbic acid (isocratic 1 mL/min) monitoring with UV (280 nm) and radioactive traces.

General procedure for the radiosynthesis of [18F]FMT (University of Oxford): [18F]Fluoride (3.0-10.0 GBq) was separated from 18O-enriched-water using anion exchange cartridge (see section 2.3) and subsequently released with 900 µL (in 6 x 150 µL portions) of a solution of K222/K2C6O4/K2CO3 (kryptofix 222 (6.3 mg), K2C6O4 (1 mg) and K2CO3 (0.1 mg) in 1 mL of MeCN/H2O, 4:1) into a 5 mL V-vial containing a magnetic stir bar in the concentrator. The solution was dried with five cycles of azeotropic drying with MeCN (5 x 200 µL) under a flow of N2 at 120 °C. The 5 mL vial containing the dried [18F]KF/K222 complex was purged with 30 mL of air using a syringe and then a solution of arylboronate precursor (11 mg, 0.02 mmol) and Cu(OTf)2(py)4 (14 mg, 0.02 mmol) in anhydrous DMF (400 µL) was added. The mixture was heated at 120 °C for 20 min in a sealed vial with stirring. The reaction mixture was then diluted into 8 mL of H2O and loaded onto a Sep-Pak® Plus C18 cartridge and washed with two 1 mL portions of H2O. 1 mL of air was then flushed through the cartridge and the product was eluted back into the reaction vial using two 1 mL washes of acetone and then flushing the cartridge with 1 mL air. The acetone was evaporated under a flow of N2 while heated to 120 °C. The dry residue was then redissolved in HClO4 (6.75 M, 400 µL) and further diluted with 50 mM AcOH/ 2.5 mM NaOAc buffer containing 0.1 mg/mL ascorbic acid (1000 µL) and loaded directly onto a 2 mL HPLC loop and injected on a semi-Prep HPLC column (Synergi 4µm Hydro-RP 250x10mm) and eluted with a 50 mM AcOH/ 2.5 mM NaOAc buffer containing 0.1 mg/mL ascorbic acid (isocratic 4 mL/min) monitoring with UV (254 nm) and radioactive traces.

SA of [18F]FMT in collected fraction was assessed using an analytical Synergi 4µm Hydro-RP 80A, 150 x 4.6 mm with 50 mM AcOH/ 2.5 mM NaOAc buffer containing 0.1 mg/mL ascorbic acid (isocratic 1 mL/min) monitoring with UV (280 nm) and radioactive traces. The enantiomeric purity of [18F]FMT was determined on a separate analytical method. HPLC analysis was performed on Daicel crownpak cr(+) (HClO4 0.01M, isocratic 0.8 mL/min), UV was monitored at 280 nm and radioactive traces.

General procedure for the radiosynthesis of [18F]FDA (University of Oxford): [18F]Fluoride (3.0-10.0 GBq) was separated from 18O-enriched-water using anion exchange cartridge (see section 2.3) and subsequently released with 900 µL (in 6 x 150 µL portions) of a solution of K222/K2C6O4/K2CO3 (kryptofix 222 (6.3 mg), K2C6O4 (1 mg) and K2CO3 (0.1 mg) in 1 mL of MeCN/H2O, 4:1) into a 5 mL V-vial containing a magnetic stir bar in the concentrator. The solution was dried with five cycles of azeotropic drying with MeCN (5 x 200 µL) under a flow of N2 at 120 °C. The 5 mL vial containing the dried [18F]KF/K222 complex was purged with 30 mL of air using a syringe and then a solution of arylboronate precursor (10.1 mg, 0.02 mmol) and Cu(OTf)2(py)4 (14 mg, 0.02 mmol) in anhydrous DMF (400 µL) was added. The mixture was heated at 120 °C for 20 min in a sealed vial with stirring. The reaction mixture was then diluted into 8 mL of H2O and loaded onto a Sep-Pak® Plus C18 cartridge and washed with two 1 mL portions of H2O. 1 mL of air was then flushed through the cartridge and the product was eluted back into the reaction vial using two 1 mL washes of acetone and then flushing the cartridge with 1 mL air. The acetone was evaporated under a flow of N2 while heated to 120 °C. The dry residue was then redissolved in HClO4 (57%, 400 µL) and the reaction was stirred at 150 °C for 10 min. The reaction mixture was then allowed to cool to room temperature and partially neutralized with NaOH (6.75 M, 400 µL) and further diluted with 50 mM AcOH/ 2.5 mM NaOAc buffer containing 0.1 mg/mL ascorbic acid (1000 µL) and loaded directly onto a 2 mL HPLC loop and injected on a semi-Prep HPLC column (Synergi 4µm Hydro-RP 250x10mm) and eluted with a 50 mM AcOH/ 2.5 mM NaOAc buffer containing 0.1 mg/mL ascorbic acid (isocratic 4 mL/min) monitoring with UV (254 nm) and radioactive traces.
SA of [\(^{18}\text{F}\)]FDA in collected fraction was assessed using an analytical Synergi 4µm Hydro-RP 80A, 150 x 4.6 mm with 50 mM AcOH/ 2.5 mM NaOAc buffer containing 0.1 mg/mL ascorbic acid (isocratic 1 mL/min) monitoring with UV (280 nm) and radioactive traces.

Procedure for the radiosynthesis of [\(^{18}\text{F}\)]flumazenil using Cu(OTf)\(_2\)py\(_4\) elution (University of Oxford):

[\(^{18}\text{F}\)]Fluoride (4.0 GBq) was separated from \(^{18}\text{O}\)-enriched-water using a Chromafix PS-HCO\(_3\) \(^{18}\text{F}\) separation cartridge (45 mg) and subsequently released with by 900 µL (in 6 x 150 µL portions) of a solution of 27 mg Cu(OTf)\(_2\)py\(_4\) in 1 mL of MeCN/H\(_2\)O, 1:1 into a 5 mL V-vial containing a magnetic stir bar in the concentrator. The solution was dried with six cycles of azeotropic drying with MeCN (6 x 500 µl) under a flow of N\(_2\) at 120 °C. To the dried [\(^{18}\text{F}\)]KF/K\(_2\text{CO}_3\) complex was added a solution of arylboronate precursor (12 mg, 0.03 mmol) in anhydrous DMF/pyridine (9:1, 400 µL) after which 30 mL of air was flushed through the vial using a syringe. The mixture was heated at 120 °C for 20 min in a sealed vial with stirring, after which, the reaction mixture was diluted with 1 mL of 15% MeCN/ 85% 25 mM NH\(_4\)HCOO(aq) and loaded directly onto a 2 mL HPLC loop and injected on a semi-Prep HPLC column (Synergi 4µm Hydro-RP 250x10mm) and eluted with 25% MeCN/75% 25 mM NH\(_4\)HCOO(isocratic 4 mL/min) monitoring with UV (254 nm) and radioactive traces.

General procedure for the radiosynthesis of [\(^{18}\text{F}\)]FPEB (Imanova):

To the dried [\(^{18}\text{F}\)]fluoride (see section 2.1 for procedure) was added a solution of Cu(OTf)\(_2\)py\(_4\) (27 mg) and precursor (10 mg) in anhydrous DMA (400 µL). The mixture was heated to 120°C for 20 min in a sealed vial with stirring, and then cooled down to 50°C. The crude mixture was diluted with 3 mL of the HPLC mobile phase (35% MeCN/ 65% 100 mM NH\(_4\)HCOO (pH 4)). The resulting solution was loaded onto a semi-prep HPLC for purification. Product was eluted through an Agilent Eclipse XDB C18 column (250 x 9.4 mm, 5 µm) with the HPLC mobile phase at a flow of 6 mL/min. UV (254 nm) and radioactivity traces were monitored and the fraction corresponding to [\(^{18}\text{F}\)]-FPEB was collected.

Analysis was performed on an Agilent Eclipse XDB C18, 150 x 4.6 mm, 5 µm column. The analytical column was eluted at 1 mL/min with 50% MeCN/ 50% 100 mM NH\(_4\)HCOO (pH 4). UV was monitored at 254 nm.

Starting from 12.40 GBq of [\(^{18}\text{F}\)]fluoride, a dose of 666 MBq of [\(^{18}\text{F}\)]-FPEB could be isolated in 90 min. The process was not fully optimised, which explained the long synthesis time required. This corresponds to a 9.5% RCY [dc], or 5.4% RCY [ncd]. SA was 120.8 GBq/µmol. RCP was >99%.

General procedure for the radiosynthesis of [\(^{18}\text{F}\)]flumazenil (Imanova):

To the dried [\(^{18}\text{F}\)]fluoride (see section 2.1 for procedure) was added a solution of Cu(OTf)\(_2\)py\(_4\) (27 mg) and precursor (10 mg) in anhydrous DMA (400 µL). The mixture was heated to 120°C for 20 min in a sealed vial with stirring, and then cooled down to 50°C. The crude mixture was diluted with 3 mL of the HPLC mobile phase (35% MeCN/ 65% 100 mM NH\(_4\)HCOO (pH 4)). The resulting solution was loaded onto a semi-prep HPLC for purification. Product was eluted through an Agilent Eclipse XDB C18 column (250 x 9.4 mm, 5 µm) with the HPLC mobile phase at a flow of 6 mL/min. UV (254 nm) and radioactivity traces were monitored and the fraction corresponding to [\(^{18}\text{F}\)]-Flumazenil was collected.

Analysis was performed on an Agilent Eclipse Plus C18, 250 x 4.6 mm, 5 µm column. The analytical column was eluted at 2 mL/min with 25% MeCN/ 75% 50 mM NH\(_4\)HCOO (pH 8). UV was monitored at 254 nm.

Starting from 25.98 GBq of [\(^{18}\text{F}\)]fluoride, a dose of 5.11 GBq of [\(^{18}\text{F}\)]-Flumazenil could be isolated in 112 min. The process was not fully optimised, which explained the long synthesis time required. This corresponds to a 39.9% RCY [dc], or 19.7% RCY [ncd]. SA was 123.9 GBq/µmol. RCP was >99%.

General procedure for the radiosynthesis of [\(^{18}\text{F}\)]FDOPA (Imanova):

To the dried [\(^{18}\text{F}\)]fluoride (see section 2.1 for procedure) was added a solution of Cu(OTf)\(_2\)py\(_4\) (14 mg) and precursor (12 mg) in anhydrous DMF (400 µL). The mixture was heated to 120°C for 20 min in a sealed vial with stirring, and then cooled down to 50 °C. The crude mixture was transferred to a collection vial containing 22 mL of water. The reaction vessel and delivery lines were rinsed with portions of water and MeCN, which were added to the diluted crude mixture, yielding to a final 30 mL MeCN /water (17/83)
The resulting solution was passed through a SepPak C18 classic cartridge (Waters). The Sep-Pak cartridge was washed with 10 mL of a 15% MeCN solution in water. The radiolabelled products of interest were eluted back in the reaction vessel from the Sep-Pak with 2 mL of MeCN. MeCN was evaporated and HI (57%, 400 µL) was added. The reaction mixture was heated to 150°C for 10 min. The reaction vessel was cooled down to 50 °C and the crude mixture was diluted with 4 mL of the HPLC mobile phase (70 mM NaH$_2$PO$_4$(aq)). The resulting solution was loaded onto a semi-prep HPLC for purification. Product was eluted through a Phenomenex PolymerX RP-1 column (250 x 21.2 mm, 10 µm, 100 Å) with the HPLC mobile phase at a flow of 10 mL/min. UV (254 nm) and radioactivity traces were monitored and the fraction corresponding to $[^{18}F]$-FDOPA was collected.

Analysis was performed on an Agilent Eclipse Plus C18, 250 x 4.6 mm, 5 µm column. The analytical column was eluted at 1 mL/min, with 70 mM NaH$_2$PO$_4$(aq) buffer. UV was monitored at 220 nm and 254 nm. The enantiomeric purity of $[^{18}F]$FDOPA was determined on a separate analytical method. Analysis was performed on a Regis ChiroSil SCA(-), 150 x 4.6 mm, 5 µm column. The analytical column was eluted at 1 mL/min, at 40 °C, with a mixture of 0.01% phosphoric acid buffer and methanol (buffer/methanol = 25/75). UV was monitored at 200 nm.

Starting from 24.96 GBq of $[^{18}F]$fluoride, a dose of 2.18 GBq of $[^{18}F]$FDOPA could be isolated in 146 min. The process was not fully optimised, which explained the long synthesis time required. This corresponds to a 22.0% RCY [dc], or 8.7% RCY [ndc]. SA on that dose could not be assessed due to the presence of an impurity eluting close to the retention time of FDOPA. Further optimisation work on the synthesis and the purification method is required to address this issue. Both radiochemical and enantiomeric purities were >99%, confirming preparation of $[^{18}F]$-6-fluoro-L-FDOPA exclusively.

General procedure for the radiosynthesis of $[^{18}F]$FMT (Imanova): To the dried $[^{18}F]$fluoride was added a solution of Cu(OTf)$_2$(py)$_4$ (15 mg) and precursor (13 mg) in anhydrous DMF (400 µL). The mixture was heated to 120°C for 20 minutes in a sealed vial with stirring, and then cooled down to 50°C. The crude mixture was transferred to a collection vial containing 22 mL of water. The reaction vessel and delivery lines were rinsed with portions of water and MeCN, which were added to the diluted crude mixture, yielding to a final 30 mL MeCN /water (17/83) solution. The resulting solution was passed through a Sep-Pak C18 classic cartridge (Waters). The Sep-Pak cartridge was washed with 10 mL of a 15% MeCN solution in water. The radiolabelled products of interest were eluted back in the reaction vessel from the Sep-Pak with 2 mL of MeCN. MeCN was evaporated and HI (57%, 400 µL) was added. The reaction mixture was heated to 150°C for 10 min. The reaction vessel was cooled down to 50°C and the crude mixture was diluted with 4 mL of the HPLC mobile phase (50 mM AcOH/2.5 mM NaOAc buffer). The resulting solution was loaded onto a semi-prep HPLC for purification. Product was eluted through an Agilent Eclipse XDB C18 column (250 x 9.4 mm, 5 µm) with the HPLC mobile phase at a flow rate of 4 mL/min. UV (254 nm) and radioactivity traces were monitored and the fraction corresponding to $[^{18}F]$FMT was collected.

Analysis was performed on an Agilent Eclipse Plus C18, 250 x 4.6 mm, 5 µm column. The analytical column was eluted at 1 mL/min with an aqueous solution containing 0.1% AcOH and 3% MeOH. UV was monitored at 282 nm.

Starting from 23.22 GBq of $[^{18}F]$fluoride, a dose of 2.39 GBq of $[^{18}F]$FMT could be isolated in 140 min. The process was not fully optimised, which explained the long synthesis time required. This corresponds to a 27.3% RCY [dc], or 10.3% RCY [ndc]. SA was 17.8 GBq/µmol. RCP was >99%.

General procedure for the radiosynthesis of $[^{18}F]$flumazenil (ABX): $[^{18}F]$Fluoride (100-300 MBq) was separated from $^{18}$O-enriched-water by using an anion exchange cartridge (Sep-PAK® Light QMA Cartridge, preconditioned, with CO$_3^-$ as counter ions, ABX Prod. No.: K-920) and subsequently released with 800 µL of a solution of K$_{222}$/KH$_2$PO$_4$ (Kryptofix 222 (15 mg) and KH$_2$PO$_4$ (4 mg) in 1 mL of MeCN/H$_2$O, 4:1) into the reactorvial. The solution was dried with four cycles of azeotropic drying with MeCN (200 µL) under a flow of N$_2$ at 105 °C. A solution of flumazenil pinacol boronate (15 mg, 0.036 mmol) and Cu(OTf)$_2$(py)$_4$ (30 mg, 0.044 mmol, 1.2 eq), dissolved in 1 mL of anhydrous DMA, was added and the vial was heated to 130 °C for 10 min. The reaction was quenched by addition of water (3 mL), the reaction solution was further dissolved with 27 mL of water and trapped on a
preconditioned Sep-Pak tC18 column. The column was washed with water and eluted with 10 mL 27% aqueous MeCN solution into a HPLC loop. Isocratic HPLC was performed on a Waters SunFire™ Prep C18 column (10 µm, 10x250 mm) using 27% aqueous MeCN solution. The product eluted after 15 min with a 15-20% RCY. An aliquot was removed for analysis by radioTLC and HPLC for radiochemical purity and product identity.

Analysis was performed using the following gradient on a Waters X Terra RP18 HPLC column (5 µm, 4.6x250 mm) at a flow rate of 1ml/min. RCP was found to be >99%.
0-2 min 10% MeCN isocratic
2-10 min (10% MeCN to 50% MeCN) linear increase
12-17 min (50% MeCN to 90% MeCN) linear increase
19 min 90% MeCN isocratic
2.3 Isolation Radiochemical Yields

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Run</th>
<th>QMA cartridge</th>
<th>QMA Ion</th>
<th>Cu (mmol)</th>
<th>Sub (mmol)</th>
<th>Solvent</th>
<th>Activity (GBq)</th>
<th>RCY (%)</th>
<th>Synthesis Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[{}\textsuperscript{18}F\textsubscript{]}FMETEB</td>
<td>1</td>
<td>Chromafix</td>
<td>Oxalate</td>
<td>0.04</td>
<td>0.03</td>
<td>DMA</td>
<td>4.0</td>
<td>1.36</td>
<td>34 69</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Chromafix</td>
<td>Oxalate</td>
<td>0.04</td>
<td>0.03</td>
<td>DMA</td>
<td>4.0</td>
<td>0.91</td>
<td>23 67</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.04</td>
<td>0.03</td>
<td>DMA</td>
<td>7.8</td>
<td>1.11</td>
<td>14 72</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.015</td>
<td>DMA</td>
<td>8.3</td>
<td>0.45</td>
<td>5 69</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.015</td>
<td>DMA</td>
<td>7.9</td>
<td>0.18</td>
<td>2 68</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.0075</td>
<td>DMA</td>
<td>9.9</td>
<td>0.20</td>
<td>2 61</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.0075</td>
<td>DMA</td>
<td>9.9</td>
<td>0.20</td>
<td>2 61</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.0075</td>
<td>DMA</td>
<td>9.9</td>
<td>0.20</td>
<td>2 61</td>
</tr>
<tr>
<td>[{}\textsuperscript{18}F\textsubscript{]}FPEB</td>
<td>1</td>
<td>Chromafix</td>
<td>Oxalate</td>
<td>0.04</td>
<td>0.03</td>
<td>DMA</td>
<td>4.0</td>
<td>1.61</td>
<td>41 67</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Chromafix</td>
<td>Oxalate</td>
<td>0.04</td>
<td>0.03</td>
<td>DMA</td>
<td>4.0</td>
<td>1.72</td>
<td>43 67</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.04</td>
<td>0.03</td>
<td>DMA</td>
<td>10.0</td>
<td>0.85</td>
<td>9 61</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.04</td>
<td>0.03</td>
<td>DMA</td>
<td>4.8</td>
<td>0.19</td>
<td>4 79</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.04</td>
<td>0.015</td>
<td>DMA</td>
<td>6.8</td>
<td>0.32</td>
<td>5 62</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.015</td>
<td>DMA</td>
<td>8.8</td>
<td>1.19</td>
<td>15 60</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.015</td>
<td>DMA</td>
<td>9.5</td>
<td>0.41</td>
<td>4 64</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.0075</td>
<td>DMA</td>
<td>9.9</td>
<td>0.20</td>
<td>2 61</td>
</tr>
<tr>
<td>[{}\textsuperscript{18}F\textsubscript{]}Flumazenil</td>
<td>1</td>
<td>Chromafix</td>
<td>Oxalate</td>
<td>0.04</td>
<td>0.03</td>
<td>DMA</td>
<td>4.0</td>
<td>0.73</td>
<td>18 62</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Chromafix</td>
<td>Oxalate</td>
<td>0.04</td>
<td>0.03</td>
<td>DMA</td>
<td>4.0</td>
<td>0.36</td>
<td>9 73</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Chromafix</td>
<td>Oxalate</td>
<td>0.04</td>
<td>0.03</td>
<td>DMA</td>
<td>4.0</td>
<td>0.61</td>
<td>15 64</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Chromafix</td>
<td>Oxalate</td>
<td>0.04</td>
<td>0.03</td>
<td>DMA</td>
<td>4.0</td>
<td>0.58</td>
<td>14 61</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Chromafix</td>
<td>Oxalate</td>
<td>0.04</td>
<td>0.03</td>
<td>DMA</td>
<td>5.8</td>
<td>1.01</td>
<td>17 62</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Waters</td>
<td>Bicarbonate</td>
<td>0.04</td>
<td>0.03</td>
<td>DMF-py</td>
<td>4.0</td>
<td>0.65</td>
<td>16 59</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Waters</td>
<td>Bicarbonate</td>
<td>0.04</td>
<td>0.03</td>
<td>DMF-py</td>
<td>6.3</td>
<td>1.11</td>
<td>17 75</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Waters</td>
<td>Bicarbonate</td>
<td>0.02</td>
<td>0.04</td>
<td>DMF-py</td>
<td>6.5</td>
<td>2.47</td>
<td>38 65</td>
</tr>
<tr>
<td>[{}\textsuperscript{18}F\textsubscript{]}DAA1106</td>
<td>1</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.2</td>
<td>DMF</td>
<td>6.3</td>
<td>0.30</td>
<td>5 81</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.2</td>
<td>DMF</td>
<td>5.5</td>
<td>0.38</td>
<td>7 81</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.2</td>
<td>DMF</td>
<td>6.1</td>
<td>0.59</td>
<td>10 97</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.2</td>
<td>DMF</td>
<td>5.5</td>
<td>1.27</td>
<td>23 80</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.2</td>
<td>DMF</td>
<td>4.9</td>
<td>1.28</td>
<td>26 78</td>
</tr>
<tr>
<td>[{}\textsuperscript{18}F\textsubscript{]}MFBG</td>
<td>1</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.2</td>
<td>DMF</td>
<td>5.5</td>
<td>0.88</td>
<td>16 96</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.2</td>
<td>DMF</td>
<td>4.7</td>
<td>1.18</td>
<td>25 95</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.2</td>
<td>DMF</td>
<td>5.3</td>
<td>1.34</td>
<td>25 98</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.2</td>
<td>DMF</td>
<td>4.2</td>
<td>1.03</td>
<td>24 95</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.2</td>
<td>DMF</td>
<td>5.4</td>
<td>1.04</td>
<td>19 98</td>
</tr>
<tr>
<td>[{}\textsuperscript{18}F\textsubscript{]}FDOPA</td>
<td>1</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.2</td>
<td>DMF</td>
<td>5.5</td>
<td>0.88</td>
<td>16 96</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.2</td>
<td>DMF</td>
<td>4.7</td>
<td>1.18</td>
<td>25 95</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.2</td>
<td>DMF</td>
<td>5.3</td>
<td>1.34</td>
<td>25 98</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.2</td>
<td>DMF</td>
<td>4.2</td>
<td>1.03</td>
<td>24 95</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.2</td>
<td>DMF</td>
<td>5.4</td>
<td>1.04</td>
<td>19 98</td>
</tr>
<tr>
<td>[{}\textsuperscript{18}F\textsubscript{]}FMT</td>
<td>1</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.2</td>
<td>DMF</td>
<td>5.5</td>
<td>0.88</td>
<td>16 96</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.2</td>
<td>DMF</td>
<td>4.7</td>
<td>1.18</td>
<td>25 95</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.2</td>
<td>DMF</td>
<td>4.2</td>
<td>1.03</td>
<td>24 95</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.2</td>
<td>DMF</td>
<td>5.4</td>
<td>1.04</td>
<td>19 98</td>
</tr>
<tr>
<td>[{}\textsuperscript{18}F\textsubscript{]}FDA</td>
<td>1</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.2</td>
<td>DMF</td>
<td>5.5</td>
<td>0.88</td>
<td>16 96</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.2</td>
<td>DMF</td>
<td>5.9</td>
<td>1.45</td>
<td>25 93</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.2</td>
<td>DMF</td>
<td>4.9</td>
<td>1.66</td>
<td>34 96</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Waters</td>
<td>Carbonate</td>
<td>0.02</td>
<td>0.2</td>
<td>DMF</td>
<td>4.6</td>
<td>1.61</td>
<td>24 96</td>
</tr>
</tbody>
</table>

\textsuperscript{a)} 0.04 mmol Cu(ClO\textsubscript{4})\textsubscript{2}py\textsubscript{4} was used instead of Cu(OTf)\textsubscript{2}py\textsubscript{4}.  
\textsuperscript{b)} [{}\textsuperscript{18}F\textsubscript{]}fluoride was eluted from QMA cartridge with Cu(OTf)\textsubscript{2}py\textsubscript{4}.
2.4 Data from small scale experiments

Reoptimization of reaction conditions for electron deficient substrates using 4-\[^{18}\text{F}\]fluoronitobenzene as model substrate. Small aliquots (10-40 µL) of a [\(^{18}\text{F}\)]KF/K\(_{222}\) solution in MeCN were used for reactions. (see General procedure for small scale [\(^{18}\text{F}\)]fluorination)

\[
\text{Cu} \quad \text{Sub} \\
\begin{array}{cccc}
\text{entry} & \text{Solvent} & (\text{mmol}) & (\text{mmol}) & \text{RCC (%)} \\
1 & \text{DMF} & 0.0053 & 0.06 & 14 \pm 2 (n = 4) \\
2 & \text{DMF} & 0.0053 & 0.015 & 14 \pm 2 (n = 4) \\
3 & \text{DMF} & 0.02 & 0.015 & 53 \pm 3 (n = 4) \\
4 & \text{DMF} & 0.04 & 0.015 & 62 \pm 1 (n = 2) \\
5 & \text{DMF} & 0.04 & 0.03 & 70 \pm 5 (n = 5) \\
6 & \text{DMA} & 0.04 & 0.03 & 83 \pm 2 (n = 4) \\
7 & \text{DMA} & 0.03 & 0.02 & 81 \pm 3 (n = 4) \\
\end{array}
\]

Small scale radiolabeling of [\(^{18}\text{F}\)]FMTEB, [\(^{18}\text{F}\)]FPEB and [\(^{18}\text{F}\)]flumazenil. Small aliquots (10-40 µL) of a [\(^{18}\text{F}\)]KF/K\(_{222}\) solution in MeCN were used for reactions.

\[
\text{Cu} \quad \text{Sub} \\
\begin{array}{cccc}
\text{entry} & \text{Solvent} & (\text{mmol}) & (\text{mmol}) & \text{RCC (%)} \\
1 & \text{DMF} & 0.03 & 0.02 & 71\% \pm 2\% (n = 5) \\
2 & \text{DMA} & 0.03 & 0.02 & 66\% \pm 4\% (n = 2) \\
3 & \text{DMF} & 0.03 & 0.02 & 75\% \pm 0\% (n = 2) \\
\end{array}
\]

Reoptimization of reaction conditions for electron rich substrates. Small aliquots (10-40 µL) of a [\(^{18}\text{F}\)]KF/K\(_{222}\) solution in MeCN were used for reactions.
### 2.5 Comparison of radiotracer production (with semi-prep HPLC) protocols.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Radiotracer</th>
<th>This Work RCY (%)</th>
<th>Literature RCY (%)</th>
<th>Methodology (Synthesiser)</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>[n.d.c.]</td>
<td>[d.c.]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>$[^{18}F]$Flumazenil</td>
<td>35 ± 7</td>
<td>54 ± 10</td>
<td>Diaryliodonium Tosylate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Manual)</td>
<td>Moon et al.⁵</td>
</tr>
<tr>
<td>2</td>
<td>$[^{18}F]$FMTEB</td>
<td>29 ± 6</td>
<td>44 ± 9</td>
<td>Microwave/ Diaryliodonium Tosylate</td>
<td>Telu et al.³</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Modified Synthia)³⁵</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>$[^{18}F]$FPEB</td>
<td>13 ± 5</td>
<td>19 ± 6</td>
<td>Spirocyclic Iodonium Ylide</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(GE TRACERlab FX₉₀)</td>
<td>Stephenson et al.⁴</td>
</tr>
<tr>
<td>4</td>
<td>$[^{18}F]$DAA1106</td>
<td>31 ± 1</td>
<td>61 ± 3</td>
<td>CuOTf(MeCN)₉₀/ Diaryliodonium Tetrafluoroborate</td>
<td>Zlatopolskiy et al.⁵</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Manual)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>$[^{18}F]$MFBG</td>
<td>25 ± 2</td>
<td>41 ± 2</td>
<td>Diaryliodonium Triflate</td>
<td>Hu et al.⁶</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(IBA Synthera)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>$[^{18}F]$FDOPA</td>
<td>22 ± 3</td>
<td>40 ± 4</td>
<td>$^{36}$Ar Multi-step</td>
<td>Liebert et al.⁷</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(GE FASTlab)</td>
<td>Lemaire et al.⁸, a</td>
</tr>
<tr>
<td>7</td>
<td>$[^{18}F]$FMT</td>
<td>15 ± 1</td>
<td>30 ± 2</td>
<td>Spirocyclic Iodonium Ylide</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Manual)</td>
<td>Rotstein et al.¹⁰</td>
</tr>
<tr>
<td>8</td>
<td>$[^{18}F]$FDA</td>
<td>29 ± 5</td>
<td>53 ± 9</td>
<td>CuOTf(MeCN)₉₀/ Diaryliodonium Tetrafluoroborate</td>
<td>Zlatopolskiy et al.⁵</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Manual)</td>
<td></td>
</tr>
</tbody>
</table>

a) Both reports give same RCY


2.6 RadioHPLC Traces

Radio-HPLC traces for $^{18}$FFMTEB (University of Oxford)
Radio-HPLC traces of semi-prep HPLC.

The purified product re-injected onto an analytical column overlaid with a UV spectra of an authentic reference sample. Analytical HPLC conditions are listed in the previous section.
Radio-HPLC traces for $[^{18}\text{F}]$FPEB (University of Oxford)
Radio-HPLC traces of semi-prep HPLC.

The purified product re-injected onto an analytical column overlaid with a UV spectra spiked with an authentic reference sample. Analytical HPLC conditions are listed in the previous section.
Radio-HPLC traces for $[^{18}\text{F}]$flumazenil (University of Oxford)

Radio-HPLC traces of semi-prep HPLC.

The purified product re-injected onto an analytical column overlaid with a UV spectra spiked with an authentic reference sample. Analytical HPLC conditions are listed in the previous section.
Radio-HPLC traces for $[^{18}F]$DAA1106 (University of Oxford)

Radio-HPLC traces of semi-prep HPLC.

The purified product re-injected onto an analytical column overlaid with a UV spectra spiked with an authentic reference sample. Analytical HPLC conditions are listed in the previous section.
Radio-HPLC traces for $[^{18}\text{F}]$mFBG (University of Oxford)

Radio-HPLC traces of semi-prep HPLC.

The purified product re-injected onto an analytical column overlaid with a UV spectra spiked with an authentic reference sample. Analytical HPLC conditions are listed in the previous section.
Radio-HPLC traces for $[^{18}F]$FDOPA (University of Oxford)
Radio-HPLC traces of semi-prep HPLC.

The purified product re-injected onto an analytical column overlaid with a UV spectra of an authentic reference sample overlaid. Analytical HPLC conditions are listed in the previous section.
Radio-HPLC traces for $[^{18}F]$FMT (University of Oxford)

Radio-HPLC traces of semi-prep HPLC.

The purified product re-injected onto an analytical column overlaid with a UV spectra spiked with an authentic reference sample. Analytical HPLC conditions are listed in the previous section.
The enantiomeric purity was assessed by injecting the radiotracer alone. Identity of the radiolabelled product was confirmed by comparison with a racemic sample of unlabelled FMT (see chromatograms below).
Radio-HPLC traces for $[^{18}\text{F}]$FDA (University of Oxford)

Radio-HPLC traces of semi-prep HPLC.

The purified product re-injected onto an analytical column overlaid with a UV spectra of an authentic reference sample overlaid. Analytical HPLC conditions are listed in the previous section.
Radiochemical purity was assessed by injecting the radiotracer alone. Identity of the radiolabelled product was confirmed by co-injection with the unlabelled reference standard (see chromatograms below).
Radiochemical purity was assessed by injecting the radiotracer alone. Identity of the radiolabelled product was confirmed by co-injection with the unlabelled reference standard (see chromatograms below).

Radio-HPLC traces [18F]flumazenil (Imanova)
Radio-HPLC traces of semi-prep HPLC.

Radioactivity (Counts/sec)
Radiochemical purity was assessed by injecting the radiotracer alone. Identity of the radiolabelled product was confirmed by co-injection with the unlabelled reference standard (see chromatograms below).
The enantiomeric purity was assessed by injecting the radiotracer alone. Identity of the radiolabelled product was confirmed by comparison with a mixture of unlabelled 6-Fluoro-D-DOPA and 6-Fluoro-L-DOPA reference standards (see chromatograms below).

Sample:

![Sample Chromatogram](image)

Standards:

![Standards Chromatogram](image)
Radiochemical purity was assessed by injecting the radiotracer alone. Identity of the radiolabelled product was confirmed by co-injection with the unlabelled reference standard (see chromatograms below).
2.7 Specific Activity Calibration Curves

Specific Activity measurements (University of Oxford)

Solutions of $^{18}$F-fluoride were delivered to Oxford from external sites, causing an approximately 3h delay from EOB until the beginning of the reaction. The radioactivity of the starting $^{18}$F-fluoride solutions would decrease by nearly two half lives before synthesis began potentially leading to lower specific activities in the isolated products produced. SA activity values obtained were 12-73 GBq/µmol for $^{18}$F-FPEB; 25-86 GBq/µmol for $^{18}$F-FMTEB; 9-28 GBq/µmol for $^{18}$F-flumazenil; 6-37 GBq/µmol for $^{18}$F-DAA 1106; 15-23 GBq/µmol for $^{18}$F-MFBG; 2-32 GBq/µmol for $^{18}$F-FDOPA; 2-3 GBq/µmol for $^{18}$F-FMT; and 4-17 GBq/µmol for $^{18}$F-FDA. A control experiment of the $S_nAr$ reaction on 4-nitrobenzaldehyde gave 4-$^{18}$F-fluorobenzaldehyde as product with a SA of 29 GBq/µmol at our site.

3-Fluoro-5-((2-methylthiazol-4-yl)ethynyl)benzonitrile (FMTEB)

3-Fluoro-5-(pyridin-2-ylethynyl)benzonitrile (FPEB)
meta-Fluorobenzylguanidine (mFBG)

FDOPA
6-Fluoro-meta-tyrosine (FMT)

\[ y = 126.858 \cdot 231.65x \]
\[ R^2 = 0.9960 \]

6-Fluorodopamine (FDA)

\[ y = 546.400 \cdot 340.9x \]
\[ R^2 = 0.9912 \]
Specific Activity Calculations for $[^{18}\text{F}]$FPEB (Imanova)

### FPEB Mass Curve

<table>
<thead>
<tr>
<th>Entry</th>
<th>Volume (µL)</th>
<th>Concentration (µg/mL)</th>
<th>mass (µg)</th>
<th>Area 1</th>
<th>Area 2</th>
<th>Mean Area</th>
<th>SD</th>
<th>%SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>0.05</td>
<td>0.001</td>
<td>0.0739</td>
<td>0.0719</td>
<td>0.073</td>
<td>0.001</td>
<td>1.9%</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>0.2</td>
<td>0.004</td>
<td>0.2164</td>
<td>0.2092</td>
<td>0.213</td>
<td>0.005</td>
<td>2.4%</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>0.5</td>
<td>0.010</td>
<td>0.5041</td>
<td>0.5138</td>
<td>0.509</td>
<td>0.007</td>
<td>1.3%</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>1</td>
<td>0.020</td>
<td>1.0311</td>
<td>1.0475</td>
<td>1.039</td>
<td>0.012</td>
<td>1.1%</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>2.5</td>
<td>0.050</td>
<td>2.6177</td>
<td>2.6361</td>
<td>2.627</td>
<td>0.013</td>
<td>0.5%</td>
</tr>
</tbody>
</table>
### Specific Activity Calculations for $^{18}$F-flumazenil (Imanova)

#### Flumazenil Mass Curve

<table>
<thead>
<tr>
<th>Entry</th>
<th>Volume ($\mu$L)</th>
<th>Concentration ($\mu$g/mL)</th>
<th>mass ($\mu$g)</th>
<th>Area 1</th>
<th>Area 2</th>
<th>Mean Area</th>
<th>SD</th>
<th>%SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>0.05</td>
<td>0.001</td>
<td>0.0478</td>
<td>0.0484</td>
<td>0.048</td>
<td>0.00</td>
<td>0.9%</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>0.2</td>
<td>0.004</td>
<td>0.1393</td>
<td>0.1311</td>
<td>0.135</td>
<td>0.006</td>
<td>4.3%</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>0.5</td>
<td>0.010</td>
<td>0.2725</td>
<td>0.2902</td>
<td>0.281</td>
<td>0.013</td>
<td>4.4%</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>1</td>
<td>0.020</td>
<td>0.5545</td>
<td>0.5690</td>
<td>0.562</td>
<td>0.010</td>
<td>1.8%</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>2.5</td>
<td>0.050</td>
<td>1.3633</td>
<td>1.3476</td>
<td>1.355</td>
<td>0.011</td>
<td>0.8%</td>
</tr>
</tbody>
</table>
Specific Activity Calculations for $^{18}$F-FMT (Imanova)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Volume (µL)</th>
<th>Concentration (µg/mL)</th>
<th>Mass (µg)</th>
<th>Area 1</th>
<th>Area 2</th>
<th>Mean Area</th>
<th>SD</th>
<th>%SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>0.05</td>
<td>0.001</td>
<td>0.0028</td>
<td>0.0051</td>
<td>0.004</td>
<td>0.002</td>
<td>41.2%</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>0.2</td>
<td>0.004</td>
<td>0.0069</td>
<td>0.0078</td>
<td>0.007</td>
<td>0.001</td>
<td>8.7%</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>0.5</td>
<td>0.010</td>
<td>0.0182</td>
<td>0.0181</td>
<td>0.018</td>
<td>0.000</td>
<td>0.4%</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>1</td>
<td>0.020</td>
<td>0.0344</td>
<td>0.0347</td>
<td>0.035</td>
<td>0.000</td>
<td>0.6%</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>2.3</td>
<td>0.047</td>
<td>0.0808</td>
<td>0.0834</td>
<td>0.082</td>
<td>0.002</td>
<td>2.2%</td>
</tr>
</tbody>
</table>
3. Novel Compound NMR Spectra

3-Fluoro-5-((2-methylthiazol-4-yl)ethynyl)benzonitrile (FMTEB)

3-((2-Methylthiazol-4-yl)ethynyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile
3-Fluoro-5-(pyridin-2-yethynyl)benzonitrile (FPEB)

3-(Pyridin-2-yethynyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile
Flumazenil

Ethyl 5-methyl-6-oxo-8-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5,6-dihydro-4H-2,5,10b-triaza-benzo[e]azulene-3-carboxylate
meta-Fluorobenzylguanidine (mFBG)

tert-Butyl-N-[(1E)-{{[tert-butoxy]carbonylimino}({[3-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl}amino)methyl}carbamate
**Tert-Butyl-N-[(1Z)-{bis[(tert-butoxy)carbonyl]amino}][(3-(tert-butoxy)carbonyl){[3-(tetramethyl-1,3,2-
dioxaborolan-2-yl)phenyl]methyl}amino]}methyldene]carbamate**

![Chemical Structure](attachment:image.png)

**NMR Spectra**

- **F1 (ppm)**: 1.32, 1.38, 1.45, 1.48, 2.12, 5.03, 7.26, 7.28, 7.30, 7.49, 7.50, 7.50, 7.51, 7.52, 7.66, 7.68, 7.78
- **F2 (ppm)**: 24.88, 27.76, 27.86, 28.01, 50.03, 76.72, 77.04, 77.36, 81.87, 83.61, 83.67, 83.71, 127.66, 130.62, 133.51, 134.27, 136.72, 144.45, 147.38, 151.28, 157.52
tert-Butyl[(Z)-[3-fluorobenzyl]amino][(tert-butoxycarbonyl)amino]methylidene]carbamate
1-[(3-Fluorophenyl)methyl]guanidine hydrochloride
6-Fluoro-meta-tyrosine (FMT)

Methyl (S)-2-{bis(tert-butoxycarbonyl)amino}-3-{5-methoxy-2-{4,4,5,5-tetramethyl-1,3,2-
dioxaborolan-2-yl}phenyl}propanoate
6-Fluorodopamine (FDA)

2-(3,4-Dimethoxyphenyl)ethanaminium chloride
tert-Butyl N-[2-(2-bromo-4,5-dimethoxyphenyl)ethyl]-N-(tert-butoxycarbonyl)carbamate
tert-Butyl N-(tert-butoxycarbonyl)-N-{2-[4,5-dimethoxy-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethyl}carbamate
1-Fluoro-4,5-dimethoxy-2-[(E)-2-nitrovinyl]benzene

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{\(\text{F}\)} & \quad \text{\(\text{NO}_2\)}
\end{align*}
\]
1-Fluoro-4,5-dimethoxy-2-(2-nitroethyl)benzene
2-(2-Fluoro-4,5-dimethoxyphenyl)ethanamine

[Chemical structure image]

$\delta$ (ppm)

0.93, 0.99

2.35, 2.00, 1.99, 2.95, 3.00

3.83, 3.84

6.60, 6.62, 6.65, 6.67

[Additional spectrum image]
2-(2-Fluoro-4,5-dihydroxyphenyl)ethanaminium bromide
tert-Butyl N-(tert-butoxycarbonyl)-N-{2-[4,5-dimethoxy-2-(fluoro)phenyl]ethyl}carbamate
MeO
F
MeO
\text{NBOc}_2