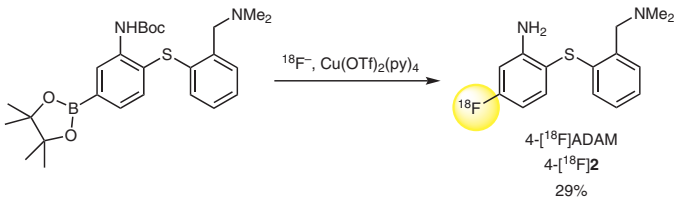
Synthesis S. Milicevic Sephton et al. Special Topic

Preparation of the Serotonin Transporter PET Radiotracer 2-({2-[(Dimethylamino)methyl]phenyl}thio)-5-[^{18}F]fluoroaniline (4-[^{18}F]ADAM): Probing Synthetic and Radiosynthetic Methods

Selena Milicevic Sephton*
Xiaoyun Zhou
Stephen Thompson
Franklin I. Aigbirhio

Molecular Imaging Chemistry Laboratory, Wolfson Brain Imaging Centre, Department of Clinical Neurosciences, University of Cambridge, Cambridge Biomedical Campus, Cambridge CB2 0SZ, UK
sms96@cam.ac.uk

Published as part of the Special Topic *Halogenation methods (with a view towards radioimaging applications)*

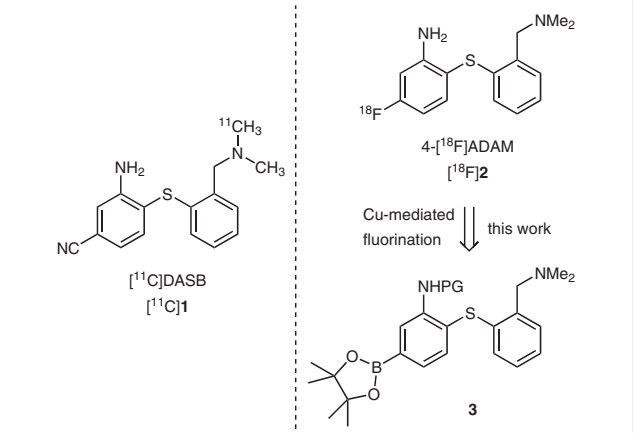


Received: 26.06.2019
Accepted after revision: 25.07.2019
Published online: 21.08.2019
DOI: 10.1055/s-0039-1690522; Art ID: ss-2019-c0355-st

Abstract Serotonin transporters (SERTs) are involved in regulating the concentration of synaptic serotonin and present a good target for many neurologic and psychiatric disorder drugs. Positron-emission tomography (PET) is a valuable tool in both diagnosis and monitoring treatment therapies, and hence much effort is being given to developing suitable PET agents for imaging SERT. Our interest in applying the fluorine-18 analogue 4-[^{18}F]ADAM for imaging SERT prompted the development of an improved synthetic route to access unlabelled ADAM. This is achieved using Pd-catalysed coupling with thiosalicylic acid and an EDC/HOBt amide coupling in 36% yield over 4 steps. A novel radiolabelling precursor, the pinacol-derived boronic ester, is prepared from the bromide using the Miyaura borylation and is obtained in 27% yield over 6 steps. Pinacolate is then used for the radiolabelling of 4-[^{18}F]ADAM based on Cu-mediated nucleophilic fluorination in which the presence of oxygen is critical for the reaction. A 1:1 substrate to copper ratio is found to be optimal when the reaction is performed in dimethylacetamide at 85 °C. Using these conditions, 4-[^{18}F]ADAM is prepared in 29 ± 10% (n = 6) radiochemical conversion after hydrolysis of the Boc group with HCl. Furthermore, the method is successfully automated to afford 4-[^{18}F]ADAM in 10% radiochemical conversion.

Key words 4-[^{18}F]ADAM, serotonin transporter, copper-mediated fluorination, ^{18}F-radiolabelling, PET imaging

The serotonin transporter (SERT) is an oligomeric protein which controls the concentration of synaptic serotonin by regulating reuptake of serotonin in the synaptic cleft.[1] Deregulation of SERT function or expression consequently leads to alterations in serotonergic neurotransmission, which has been observed in some neurologic and psychiatric disorders.[2] For instance, depression is characterised by the decrease of serotonergic neurotransmission.[3] Similarly, positron-emission tomography (PET) and single-photon emission computed tomography (SPECT) studies have shown a reduction in SERT density in monkey and human brains affected by Parkinson's disease.[4–8] Owing to the role SERT has in some neurologic and psychiatric disorders, significant efforts have been made in developing PET radiotracers for non-invasive imaging of SERT in vivo.[2] Of these radiotracers the most widely applied is [^{11}C]*N*,*N*-dimethyl-2-(2-amino-4-cyanophenylthio)benzylamine ([^{11}C]DASB, [^{11}C]**1**) (Scheme 1),[9,10] which in human studies showed a direct correlation between radioactivity uptake and the distribution of SERT. A study of patients with depression indicated an 80% reduction in radioactivity uptake under blocking conditions with citalopram and fluoxetine.[3] While [^{11}C]**1** is a suitable radiotracer for the measurement of SERT density showing favourable binding kinetics, a major disadvantage is due to its carbon-11 radiolabel with a short physical half-life of 20 minutes. This in turn limits its application to PET centres with an on-site cyclotron. To expand the application, a fluorine-18 analogue with a physical half-life of 110 minutes was sought.



Scheme 1 Structures of SERT PET radiotracers: [^{11}C]**1** and 4-[^{18}F]**2** and a novel radiolabelling precursor **3**. PG = protecting group

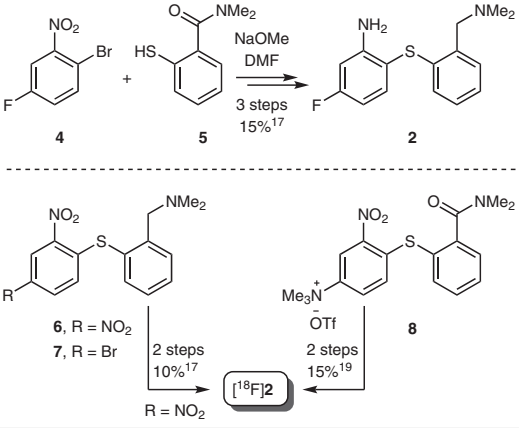
Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Although several candidates were investigated[11,12] in vivo in human subjects, to date, no fluorine-18 PET radiotracer for imaging SERT has seen widespread use. This has been due to various reasons, such as challenging chemistry to synthesise the precursor and radiochemistry to incorporate the radioisotope.

An ongoing study in our laboratory required a SERT PET imaging agent with a fluorine-18 radiolabel. Based on the reports of rodent,[1,8,13] non-human primate[14] and initial human studies,[11] we selected an analogue of **1**, 2-({2-[(dimethylamino)methyl]phenyl}thio)-5-[^{18}F]fluoroaniline (4-[^{18}F]ADAM, 4-[^{18}F]**2**) as a potential PET radiotracer of interest.

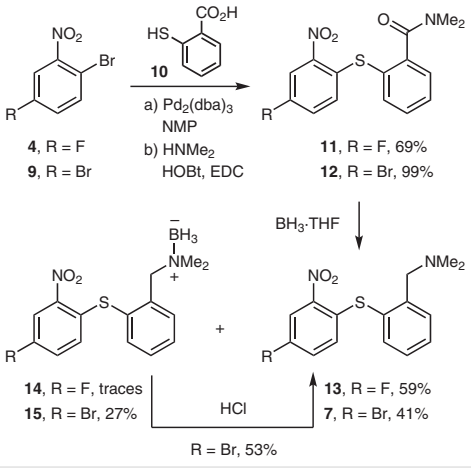
Herein, we report an improved synthesis of **2**, as well as the radiosynthesis of 4-[^{18}F]**2** based on a copper-mediated method from the Gouverneur lab[15,16] for the introduction of fluorine-18 into the novel radiolabelling precursor **3** (Scheme 1).

The synthesis of **2** has been previously reported[13,17] as well as the radiolabelling to access 4-[^{18}F]**2** from either nitro,[17,18] bromo[17] or trimethylammonium[19] precursors **6**, **7** or **8**, respectively (Scheme 2).



Scheme 2 Previously reported synthesis of **2** and radiosynthesis of 4-[^{18}F]**2** using nitro, bromo or trimethylammonium precursors **6**, **7** and **8**, respectively

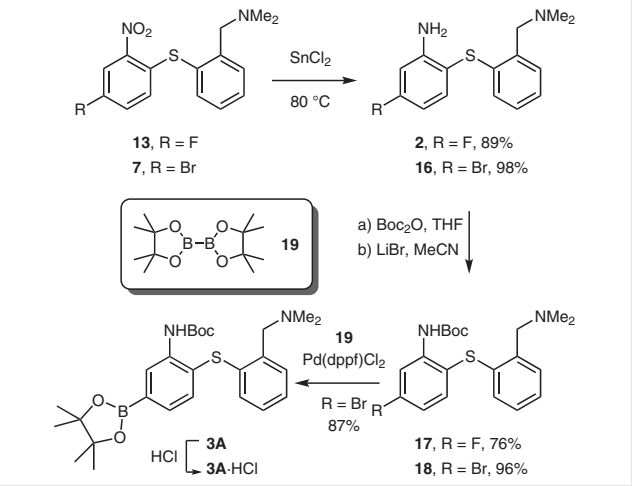
In the report from the Shiue group,[17] the synthesis of **2** commenced with the condensation of 4-fluorobromide **4** with thiophenol **5** to form the desired thioether in 58% yield. This was followed by the borane reduction of the amide group in 25% yield and subsequent quantitative reduction of the nitro group using $SnCl_2$ to afford the desired product **2** in 15% yield over three steps. In the same report, the authors used both nitro (**6**) and bromo (**7**) precursors to provide 4-[^{18}F]**2** in 5–10% radiochemical yield. The radiolabelling process was also automated by the Shiue group;[13,18] however, this did not have a beneficial effect on the radiochemical yield. Using precursor **6** in an automated protocol afforded 4-[^{18}F]**2** in 1.7% decay-corrected radiochemical yield. The same research group published the radiosynthesis of 4-[^{18}F]**2** using an improved radiolabelling precursor **8** (Scheme 2) with 15% decay-corrected radiochemical yield when radiosynthesis was performed manually.[19] In an effort to reproduce the literature preparation of **2**, we began the synthesis using the same 4-fluorobromide **4** and thiosalicylic acid (**10**) instead of thiophenol **5**, the latter being commercially available only from specialised suppliers. Thiosalicylic acid (**10**) has previously been used successfully for the formation of the desired thioether[13] and was available commercially at a very low cost. In our hands the substitution worked sluggishly and repeatedly gave inseparable black tars. For this reason, we sought an improved synthetic route and prepared **2** as depicted in Schemes 3 and 4.



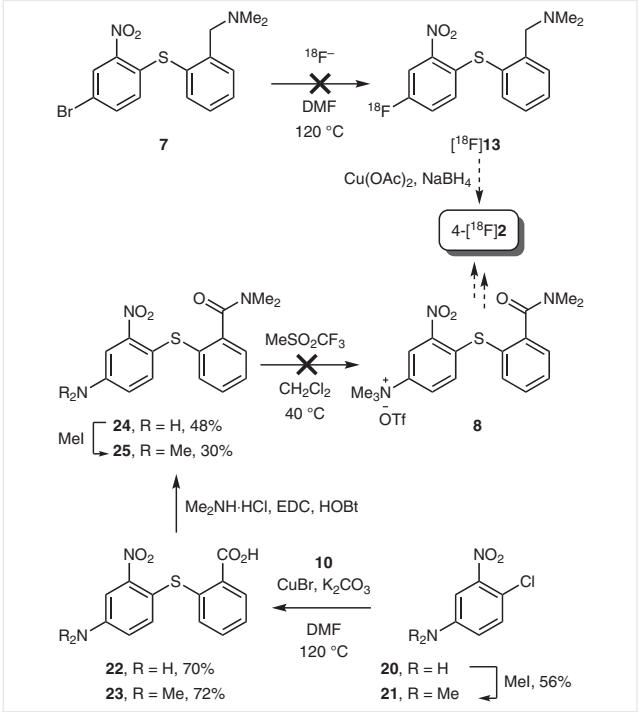
Scheme 3 *En route* to compound **2**: a reproducible synthetic route on gram scale

To form the thioether we employed the palladium-catalysed coupling[20] of 4-fluorobromide **4** with thiosalicylic acid (**10**).

Without purification the crude mixture was further reacted under amide coupling conditions using EDC/HOBt to afford amide **11** in 69% yield over two steps. The amide functionality in **11** was reduced with borane in 59% yield, following the method from the Shiue group.[17] An amine-borane complex **14** was commonly isolated as a by-product in agreement with the observations from the Shiue report. Complex **14** could easily be converted into the desired product, amine **13**, by heating in 1 M aqueous hydrochloric acid (HCl). The amount of isolated **14** after the borane reduction varied from batch to batch, and while extended treatment with hot HCl prior to work-up showed a reduction in the isolated yield of **14**, it did not eliminate the formation of **14** completely (Scheme 3). In the final step, fluoro analogue **2** was obtained in 89% yield after reduction of the nitro group with $SnCl_2$ (Scheme 4).



Scheme 4 Completion of the gram-scale synthesis of **2** and preparation of radiolabelling precursor **3A**



Scheme 5 Attempted radiosynthesis of 4-[^{18}F]**2** using precursor **7** and preparation of alternative precursor **8**

Our improved synthesis of **2** compared favourably with the method published by the Shiue group, and gave an increased overall yield of 36% despite an extra synthetic step. With reference compound **2** in hand, we next turned our attention to the preparation of an appropriate radiolabelling precursor.

Using our newly established synthetic route to **2**, we began the analogous synthesis of bromo precursor **7** (Scheme 3). Bromo precursor **7** was chosen over the nitro precursor **6** for reasons of speculated poor selectivity between the two nitro groups in **6** during the aromatic nucleophilic fluorination. Furthermore, the nitro group at the *ortho* position was more reactive as demonstrated by the higher radiochemical yield of the *ortho* analogue (3.9% vs 1.7% obtained for 4-[^{18}F]**2**) reported by the Shiue group.[13] Analogous to the synthesis of **2**, bromobenzene **9** was coupled to thiosalicylic acid (**10**) in a palladium-catalysed reaction and the crude mixture was similarly treated with EDC/HOBt to yield 99% of amide **12**. Borane reduction of the amide in **12** afforded precursor **7** in 41% yield. In agreement with our previous observations, borane-amine complex **15** was isolated in 27% yield and then converted into amine **7** with 53% yield (Scheme 3).

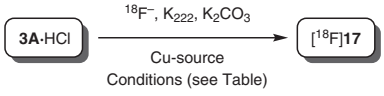
Following the reported radiosynthesis conditions, aromatic nucleophilic substitution was attempted with bromo precursor **7**, only to fail to produce any of the desired fluorinated intermediate [^{18}F]**13** (Scheme 5), which would be converted into 4-[^{18}F]**2** after reduction of the nitro group. A change of the base from K_2CO_3 to Cs_2CO_3 and replacing the reaction solvent with DMSO had no effect and none of the nitro derivative [^{18}F]**13** was observed. The failure to radiolabel 4-[^{18}F]**2** using the bromo precursor **7** prompted us to attempt the radiosynthesis with trimethylammonium precursor **8**, which was reported to give a better radiochemical yield.[19] In our hands however, precursor **8** could not be formed. Tertiary dimethylamine **25** was synthesised following the modified method of Shiue and co-workers.[19] Copper-mediated coupling of thiosalicylic acid (**10**) and aniline **20** afforded thioether **22** in 70% yield. Acid **22** then underwent EDC/HOBt amide coupling to yield 48% of amide **24**, which was subsequently methylated to give **25**. Alternatively, aniline **20** was methylated first to give **21** in 56% yield and then coupled to afford 72% of thioether **23**. This was followed by amide coupling with dimethylamine to yield **25**. Numerous attempts to further methylate **25** with methyl trifluoromethanesulfonate failed to yield any of the quaternary ammonium precursor **8**. Instead, decomposition of the starting material was observed.

Since established methods for the formation of 4-[^{18}F]**2** proved challenging, it was deemed beneficial to develop an improved radiosynthesis. For this, we explored copper-mediated nucleophilic fluorination methodology from the Gouverneur group.[15] First published in 2014, the method was based on fluorination of pinacol aryl boronic esters using nucleophilic [^{18}F]fluoride in the presence of $Cu(OTf)_2(py)_4$ and showed good functional group tolerability as well as versatility towards both electron-poor and electron-rich arenes. In the subsequent report,[16] the Gouverneur group published an extension of the application of the method to electron-deficient fluoroarenes and demonstrated this on several previously low-yielding PET radiotracers (e.g., [^{18}F]FPEB, [^{18}F]flumazenil). The Gouverneur method presented an appealing alternative for the radio-

synthesis of 4-[^{18}F]**2** and we envisaged boron pinacolate **3A** (Scheme 4) as a suitable radiolabelling precursor. Pinacolate **3A** was easily accessible from bromide **7** in just three steps: reduction of the nitro group with $SnCl_2$ in 98% yield followed by a one-pot, two-step method for the installation of the Boc protecting group on the aniline to give a 96% yield of **18**. Finally, a palladium-catalysed Miyaura borylation reaction afforded boron pinacolate **3A** (Scheme 4). Pinacol boronic ester **3A** was isolated as a colourless oil, and for the ease of handling small amounts of this precursor, it was converted into the HCl salt **3A**·HCl. As an unlabelled reference, aniline **2** was also protected with Boc to give **17** in 76% yield.

To establish the Gouverneur method in our hands, we first performed the fluorination with biphenyl pinacol boronic ester **26** as a model reaction (Scheme 6) to obtain fluorinated [^{18}F]**27** with 21–55% radiochemical conversion (RCC). When the same reaction conditions were applied to pinacolate **3A**·HCl, an ambiguous result was seen and the radiolabelling product was detected, however, the HPLC co-injection with reference **17** showed a mismatch. It was later postulated that the product was likely the free amine with the Boc group having been removed; however, showing a different R_f to **2** due to coordination to copper.

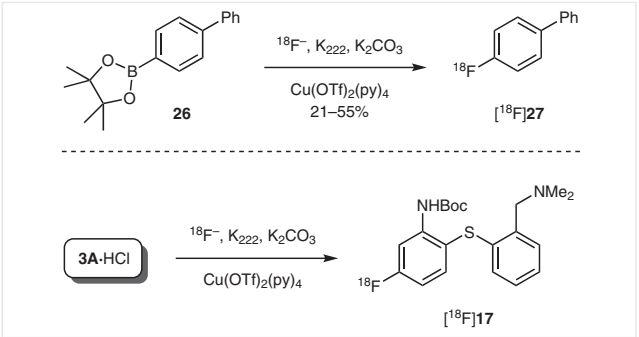
Table 1 Optimisation of the Reaction Conditions for the Radiolabelling of 4-[^{18}F]**2** Based on the Gouverneur Copper-Mediated Nucleophilic Fluorination Using **3A**·HCl



Entry	**3A**·HCl (mg)	Cu source	**3A**·HCl/Cu	Solvent	Temp (°C)	Time (min)	[^{18}F]**17** (% RCC)
1	10	$Cu(OTf)_2(py)_4$	1:1.5	DMA	115	30	<1
2	10	$Cu(OTf)_2(py)_4$	1:1	DMA	115	30	<1
3	10	$Cu(OTf)_2(py)_4$	1:0.5	DMA	115	30	<1
4	10	$Cu(OTf)_2(py)_4$	1:1	DMF	115	40	<1
5	5	$Cu(OTf)_2$	1:0.1	DMA	115	50	0
6	5	$Cu(OTf)_2(py)_4$	1:1	DMA	80	50	0

It has been established that in the presence of $Cu(OTf)_2$, the aniline Boc-protecting group can become labile.[21]

In an effort to understand the outcome of the initial radiolabelling reaction with **3A**·HCl, we conducted a series of manual reactions in order to optimise the reaction conditions (Table 1). Gouverneur and co-workers found the $Cu(OTf)_2(py)_4$ complex to be the highest yielding. They also determined that a ratio of pinacol boronic ester to Cu-complex of at least 10:1 is required for a successful reaction.[15] However, subsequently[16] the effect of the ratio of ester to Cu-complex was shown to be substrate dependent, thus further directing our investigation towards the determination of this effect. In the case of **3A**·HCl the amount of Cu-complex had very little effect (entries 1–3). Similarly, only trace amounts of the desired product from the fluorination of [^{18}F]**17** were observed when the solvent was changed from DMA to DMF (entry 4). The application of the initial Gouverneur conditions with $Cu(OTf)_2$ as the catalyst in an ester/Cu-complex ratio of 1:0.1 similarly resulted in no product (entry 5). Finally, the reaction temperature was reduced to 80 °C (entry 6), but once again the procedure failed to yield any [^{18}F]**17**. Surprised by these results, but encouraged that trace amounts of product did form, we speculated that the difficulty in forming meaningful amounts of the desired fluorinated product could arise from the chemical form of the boronic ester which was a solid HCl salt.



Scheme 6 The Gouverneur method for the radiosynthesis of [^{18}F]**27** and [^{18}F]**17**

The next series of Cu-mediated nucleophilic fluorinations was conducted with **3A** as the free base (Table 2). Using the same conditions as with **3A·HCl** (entry 1) no product was observed. Similarly, application of $Cu(OTf)_2$ as a Cu source (entry 2) or portionwise addition of $Cu(OTf)_2(py)_4$ (entry 3) also failed to give the fluorinated product.

In order to confirm product formation under non-radioactive conditions, **3A** was treated with KF in a model reaction under Gouverneur conditions, and the reaction progress followed by ^{1}H NMR and LCMS. While a product was not observed by NMR analysis, LCMS showed a mass ion corresponding to the desired product, thus suggesting the presence of trace amounts of **17** in the reaction mixture.

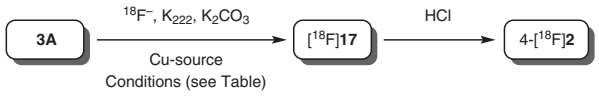
With the aim of achieving higher yields, we needed to consider the mechanism of the reaction. While the mechanism of the radioactive reaction has not been studied, the method was based on the known Chan–Lam coupling.[22] For the reductive elimination to occur, the Cu(II) complex formed after the transmetalation and ligand exchange must be oxidised to Cu(III), for which the presence of oxygen is needed. It is possible that the reductive elimination occurs from a Cu(II) complex by reducing it to Cu(0), however, this is energetically more demanding. Thus the presence of oxygen in the reaction mixture makes the reaction more facile, and hence the reaction mixtures were sparged with air pri-

or to heating. Further to the requirement of an oxidant in the reaction mixture, the Chan–Lam coupling was commonly performed at ambient temperature. Taking this into consideration, the reaction was attempted with reduced temperatures compared to the initial 115 °C (Table 2).

These modifications led to a 43% RCC to [^{18}F]**17** when the reaction was performed at 85 °C (Table 2, entry 4). When DMF was used instead of DMA the RCC decreased to 11% (entry 5). Using $Cu(OTf)_2$ as a source of copper with added pyridine as a ligand, an 11% RCC was observed (entry 6). Reducing the reaction temperature to 70 °C or 40 °C (entries 7 and 9) resulted in reduced RCCs of 22% and 1%, respectively. Similarly using only 1 mg of **3A** afforded only trace amounts of [^{18}F]**17** (entry 8).

To complete the radiosynthesis of 4-[^{18}F]**2**, Boc-protected [^{18}F]**17** was hydrolysed using 4 M HCl at 85 °C for 10 minutes with 90% RCC (Table 2).

Table 2 Optimisation of the Reaction Conditions for the Radiolabelling of 4-[^{18}F]**2** Based on the Gouverneur Copper-Mediated Nucleophilic Fluorination Using Free Base **3A**



Entry	**3A** (mg)	Cu source	**3A**/Cu	Solvent	Temp (°C)[a]	Time (min)	[^{18}F]**17** (% RCC)
1	10	$Cu(OTf)_2(py)_4$	1:1.5	DMA	115	30	0
2	10	$Cu(OTf)_2$	1:0.1	DMA	115	50	0
3	5	$Cu(OTf)_2(py)_4$	1:0.5:0.5[c]	DMA	115	50	0
4	5	$Cu(OTf)_2(py)_4$	1:1	DMA	85	50	43
5	5	$Cu(OTf)_2(py)_4$	1:1	DMF	85	50	11[b]
6	5	$Cu(OTf)_2$, py	1:1:2[d]	DMF	85	50	11[b]
7	5	$Cu(OTf)_2(py)_4$	1:1	DMA	70	30	22
8	1	$Cu(OTf)_2(py)_4$	1:1	DMA	70	30	<1
9	5	$Cu(OTf)_2(py)_4$	1:1	DMA	40	30	<1

[a] For temperatures below 100 °C a variation of ca. 5 °C was observed.
[b] The identity of the product could not be determined.
[c] overall ratio **3A**/Cu was 1:1, but the addition of the Cu-complex was done in two equal portions.
[d] The ratio depicted is **3A**:Cu:py.

Further to co-injection of the product with the reference material, confirmation of product formation was warranted when the hydrolysis was performed under analogous non-radioactive reaction conditions and the progress followed by ^{1}H NMR and LCMS to show complete consumption of **17**. With these optimised conditions in hand, radiolabelling using novel pinacolate precursor **3A** was repeated and afforded the desired fluorinated product 4-[^{18}F]**2** with 29 ± 10% (n = 6) RCC.

Encouraged by the reproducibility of the method we next sought to translate the radiosynthesis of 4-[^{18}F]**2** onto an automated synthesiser. For this purpose, we employed a GE Tracerlab FXFN (see the Supporting information) as a modular platform. While keeping the amounts of required fluoride drying reagents (e.g., K_{222} and K_2CO_3) the same as those used in manual radiosynthetic runs, the amounts of precursor and Cu source were doubled. Although the reaction concentration changed, the ratio of **3A** to Cu source was preserved, thus affording 4-[^{18}F]**2** in 10% RCC after semi-preparative purification. The concentration of cold ADAM in the sample was 32 μg/mL in agreement with other similar radioactive fluorinations on this scale in our laboratory.

In conclusion, we have optimised the synthesis of unlabelled reference compound **2** (ADAM) and obtained it with an overall yield higher than that previously reported. We have successfully optimised the radiochemical reaction conditions to reproducibly prepare 4-[^{18}F]**2** in good RCC from the boron pinacolate **3A** based on a new application of the method developed by the Gouverneur group[15,16] using copper-mediated nucleophilic fluorination of arenes. As a proof-of-principle, we have also demonstrated the preparation of 4-[^{18}F]**2** on an automated radiosynthesiser using our optimised reaction conditions. This represents an improvement over the pre-existing radiolabelling methods, which use bromo or trimethylammonium precursors **7** or **8**, respectively, and which in our hands proved challenging. Further efforts in translating this method to a good manufacturing practice (GMP)-compliant platform are underway in our laboratory.

All reactions requiring anhydrous conditions were conducted in oven-dried glass apparatus under an atmosphere of inert gas. All chemicals and anhydrous solvents were purchased from Aldrich or Alfa Aesar and used as received unless otherwise noted. Triethylamine was distilled over P_2O_5 and then stored over KOH prior to use. Reported density values are for ambient temperature. Purity of compounds was ≥95% as determined by analytical HPLC on a Thermo Dionex 3000 HPLC system. Preparative chromatographic separations were performed on Material Harvest silica gel 60 (35–75 μm) and reactions were followed by TLC analysis using Sigma-Aldrich silica gel 60 plates (2–25 μm) with fluorescent indicator (254 nm), and visualised with UV or potassium permanganate. ^{1}H NMR spectra were recorded in Fourier transform mode at the field strength specified on Bruker Avance III FT-NMR spectrometers (300 MHz). Spectra were obtained from the specified deuterated solvents in 5 mm diameter tubes. Chemical shifts in ppm are quoted relative to residual solvent signals calibrated as follows: $CDCl_3$, δ_H ($CHCl_3$) = 7.26, δ_C = 77.2. Multiplicities in the ^{1}H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad; coupling constants are reported in Hz. Numbers in parentheses following carbon atom chemical shifts refer to the number of attached hydrogen atoms as revealed by the DEPT/HSQC spectral editing technique. LRMS mass spectra as well as HRMS were obtained from the EPSRC Mass Spectrometry Service at the University of Swansea. Ion mass/charge (*m*/*z*) ratios are reported as values in atomic

mass units. The radio-TLC was performed on DC-Fertigfolien ALUGRAM® SIL G/UV$_{254}$ (Macherey-Nagel, Germany) plates with a specified mobile phase. Plate analysis was carried out using an image plate scanner (DÜRR MEDICAL - CR 35 BIO, Germany). The automated radiosynthesis was performed on a GE Healthcare FX$_{FN}$ TRACERlab. Semi-preparative purification of radiolabelled material was performed on a Merck-Hitachi L6200A system equipped with a Knauer variable wavelength detector and an Eberline radiation detector. Analytical HPLC samples were analysed with a ThermoFisher Scientific Dionex 3000 HPLC system equipped with a UV multi-wavelength detector and a Bioscan standard radiation detector. The calculation of the radiochemical conversion (RCC) was performed as follows: for manual reactions for which radioTLC or analytical HPLC was used, the RCC represents the percentage of the peak area of the product observed over the total peak area of all radioactive peaks present, including unreacted fluoride and any other observed radioactive species. This value was not decay-corrected. For the automated radiosynthesis the RCC was calculated in the same way, only this time the value was obtained from the semi-preparative HPLC trace. The material was not formulated. The manual reactions were performed in small reaction vessels and the [^{18}F]fluoride absorbed onto the reaction vessel was under the detectable levels.

2-[(4-Fluoro-2-nitrophenyl)thio]-*N*,*N*-dimethylbenzamide (11)

An oven-dried one-neck flask was allowed to cool to ambient temperature under vacuum and backfilled with nitrogen. At ambient temperature under nitrogen, it was then charged with 1-bromo-4-fluoro-2-nitrobenzene (**4**) (500 mg, 2.27 mmol, 1 equiv) and anhydrous 1-methyl-2-pyrrolidinone (19 mL) was added. The obtained brown solution was treated with triethylamine (2.5 mL, 1.80 g, 18.2 mmol, 8 equiv, d = 0.726) in one portion and then tris(dibenzylideneacetone)dipalladium(0) (62 mg, 0.07 mmol, 0.03 equiv) was added followed by 1,1′-bis(diphenylphosphino)ferrocene (151 mg, 0.27 mmol, 0.12 equiv) and the resulting brown heterogeneous mixture was sparged with nitrogen over 40 min. After this time, thiosalicylic acid (**10**) (2.8 g, 18.2 mmol, 8 equiv) was added in a single portion and the brown mixture heated (oil bath temperature: 85 °C) for 28 h. After this time, the mixture was allowed to cool to ambient temperature and then diluted with H_2O (100 mL) and EtOAc (80 mL). The two layers were well-shaken, separated and the aqueous phase extracted with EtOAc (2 × 80 mL). The combined organic extracts were washed with H_2O (5 × 80 mL), brine (80 mL), dried ($MgSO_4$) and concentrated in vacuo to give a crude oily residue (665 mg, 2.3 mmol, quant.) that was used without purification in the next step.

To the crude residue (665 mg, 2.3 mmol, 1 equiv) was added anhydrous tetrahydrofuran (42 mL) and the mixture was cooled to 0 °C (ice bath) and then treated with dimethylamine hydrochloride salt (203 mg, 2.5 mmol, 1.1 equiv). Next, 1-hydroxybenzonitrile (392 mg, 86% pure, 2.5 mmol, 1.1 equiv) was added followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) (870 mg, 4.54 mmol, 2 equiv) and finally triethylamine (1.3 mL, 917 mg, 9.08 mmol, 4 equiv, d = 0.726) was added via syringe, and the resulting green–brown heterogeneous mixture was allowed to stir under nitrogen at ambient temperature over 30 h. After this time, the crude mixture was diluted with EtOAc (100 mL), filtered through a Celite pad (using a Hirsch funnel) and the filter cake was rinsed with EtOAc (2 × 80 mL). The combined filtrates were washed with 1 M aq HCl (2 × 80 mL), H_2O (2 × 80 mL), brine (1 × 80 mL), dried ($MgSO_4$) and concentrated in vacuo to give a brown oily residue that was purified by column chromatography on a silica gel column (gradient elution: 100% CH_2Cl_2 to 5% EtOAc in CH_2Cl_2) to afford the title compound (502.6 mg, 1.57 mmol, 69%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94–7.86 (m, 1 H), 7.62–7.37 (m, 4 H), 7.18–7.08 (m, 1 H), 7.00–6.90 (m, 1 H), 3.04 (s, 3 H), 2.85 (s, 3 H).

The data are in complete agreement with those previously published.[13,23]

2-[(4-Bromo-2-nitrophenyl)thio]-*N*,*N*-dimethylbenzamide (12)

An oven-dried one-neck flask was allowed to cool to ambient temperature under vacuum and backfilled with nitrogen. At ambient temperature under nitrogen, it was then charged with 1,4-dibromo-2-nitrobenzene (**9**) (500 mg, 1.77 mmol, 1 equiv) and anhydrous 1-methyl-2-pyrrolidinone (15 mL) was added. The obtained brown solution was treated with triethylamine (2.0 mL, 1.44 g, 14.2 mmol, 8 equiv, d = 0.726) in one portion and then tris(dibenzylideneacetone)dipalladium(0) (49 mg, 0.05 mmol, 0.03 equiv) was added followed by 1,1′-bis(diphenylphosphino)ferrocene (118 mg, 0.21 mmol, 0.12 equiv) and the resulting brown heterogeneous mixture was sparged with nitrogen over 30 min. After this time, thiosalicylic acid (**10**) (2.2 g, 14.2 mmol, 8 equiv) was added in a single portion and the brown mixture heated (oil bath temperature: 85 °C) for 21 h. After this time, the mixture was allowed to cool to ambient temperature and then diluted with H_2O (100 mL) and EtOAc (80 mL). The two layers were well-shaken, separated and the aqueous phase was extracted with EtOAc (2 × 80 mL). The combined organic extracts were washed with H_2O (5 × 60 mL), brine (1 × 60 mL), dried ($MgSO_4$) and concentrated in vacuo to give a crude oily residue (630 mg, 1.8 mmol, quant.) that was used without purification in the next step.

To the crude residue (630 mg, 1.8 mmol, 1 equiv) was added anhydrous tetrahydrofuran (33 mL) and the mixture was cooled to 0 °C (ice bath) and then treated with dimethylamine hydrochloride salt (160 mg, 1.96 mmol, 1.1 equiv). Next, 1-hydroxybenzonitrile (308 mg, 86% pure, 1.96 mmol, 1.1 equiv) was added followed by EDC (682 mg, 3.56 mmol, 2 equiv) and finally triethylamine (1.0 mL, 719 mg, 7.12 mmol, 4 equiv, d = 0.726) was added via syringe, and the resulting green–brown heterogeneous mixture was allowed to stir under nitrogen at ambient temperature over 30 h. After this time, the crude mixture was diluted with EtOAc (60 mL), filtered through a Celite pad (using a Hirsch funnel) and the filter cake was rinsed with EtOAc (2 × 60 mL). The combined filtrates were washed with 1 M aq HCl (2 × 60 mL), H_2O (2 × 80 mL), brine (1 × 80 mL), dried ($MgSO_4$) and concentrated in vacuo to give a brown oily residue that was purified by column chromatography on a silica gel column (gradient elution: 100% CH_2Cl_2 to 10% EtOAc in CH_2Cl_2) to afford the title compound (673 mg, 1.76 mmol, 99%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31 (d, J = 2.2 Hz, 1 H), 7.62–7.54 (m, 2 H), 7.52–7.40 (m, 3 H), 6.81 (d, J = 8.8 Hz, 1 H), 3.04 (s, 3 H), 2.85 (s, 3 H).

MS (ES+): m/z = 381 (^{79}Br) $[M + H]^+$, 383 (^{81}Br) $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{14}BrN_2O_3S$: 380.9903; found: 380.9906.

The data are in complete agreement with those previously published.[23]

1-{2-[(4-Fluoro-2-nitrophenyl)thio]phenyl}-*N*,*N*-dimethylmethanamine (13) and 1-{2-[(4-Fluoro-2-nitrophenyl)thio]phenyl}-*N*,*N*-dimethylmethanamine Borane Complex (14)

At ambient temperature under a nitrogen atmosphere, a one-neck round-bottom flask was charged with 2-[(4-fluoro-2-nitrophenyl)thio]-*N*,*N*-dimethylbenzamide (**11**) (502 mg, 1.57 mmol, 1 equiv) and anhydrous tetrahydrofuran (8.7 mL) was added. The resulting yellow solution was allowed to cool to 0 °C (ice bath) and borane tetrahy-

drofuran complex (4.7 mL, 4.71 mmol, 3 equiv, *c* = 1 M) was added dropwise over 1 min and the yellow homogeneous mixture was heated (oil bath temperature: 80 °C) and stirred under nitrogen for 2 h. After this time, the crude mixture was allowed to cool to ambient temperature and then further to 0 °C (ice bath). It was then quenched with 1 M aq HCl which was added until the pH of the mixture reached 1. The crude mixture was concentrated in vacuo, diluted with H_2O (15 mL) and then allowed to stand at ambient temperature for 21 h. After this time, the mixture was heated (oil bath temperature: 100 °C) for 1.5 h. Once the mixture had cooled to ambient temperature, saturated aq $NaHCO_3$ was added to adjust the pH to 8 and the mixture was then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give a crude mixture as a yellow oil, purification of which by chromatography on a silica gel column (gradient elution: 20% to 80% EtOAc in petrol) afforded the title compound **13** (284 mg, 0.93 mmol, 59%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (dm, *J* = 8.4 Hz, 1 H), 7.66 (br d, *J* = 7.4 Hz, 1 H), 7.58–7.46 (m, 2 H), 7.35 (br t, *J* = 7.4 Hz, 1 H), 7.12–7.03 (m, 1 H), 6.74–6.65 (m, 1 H), 3.54 (br s, 2 H), 2.19 (br d, *J* = 1.5 Hz, 6 H).

MS (ES+): *m*/*z* = 307 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{16}FN_2O_2S$: 307.0911; found: 307.0910.

The data were in complete agreement with those previously published.[23] Borane complex **14** was in this instance isolated in trace amounts only.

1-{2-[(4-Bromo-2-nitrophenyl)thio]phenyl}-*N*,*N*-dimethylmethanamine (7) and 1-{2-[(4-Bromo-2-nitrophenyl)thio]phenyl}-*N*,*N*-dimethylmethanamine Borane Complex (15)

At ambient temperature under a nitrogen atmosphere, a one-neck round-bottom flask was charged with 2-[(4-bromo-2-nitrophenyl)thio]-*N*,*N*-dimethylbenzamide (**12**) (609 mg, 1.6 mmol, 1 equiv) and anhydrous tetrahydrofuran (9.0 mL) was added. The resulting yellow solution was allowed to cool to 0 °C (ice bath) and borane tetrahydrofuran complex (4.8 mL, 4.8 mmol, 3 equiv, *c* = 1 M) was added dropwise over 1 min and the yellow homogeneous mixture was heated (oil bath temperature: 80 °C) and stirred under nitrogen for 2 h. After this time, the crude mixture was allowed to cool to ambient temperature and then further to 0 °C (ice bath). It was then quenched with 1 M aq HCl which was added until the pH of the mixture reached 1. The crude mixture was concentrated in vacuo, diluted with H_2O (15 mL) and then allowed to stand at ambient temperature for 40 h. After this time, the mixture was heated (oil bath temperature: 110 °C) for 1 h. Once the mixture had cooled to ambient temperature, saturated aq $NaHCO_3$ was added to adjust the pH to 8 and the mixture was then extracted with CH_2Cl_2 (3 × 35 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give a crude mixture as a yellow oil, purification of which by chromatography on a silica gel column (gradient elution: 20% EtOAc in petrol to 100% EtOAc) afforded the title compound **7** (242 mg, 0.66 mmol, 41%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 2.2 Hz, 1 H), 7.67 (br d, *J* = 7.4 Hz, 1 H), 7.57–7.47 (m, 2 H), 7.41–7.32 (m, 2 H), 6.55 (d, *J* = 8.7 Hz, 1 H), 3.54 (s, 2 H), 2.20 (s, 6 H).

MS (ES+): *m*/*z* = 367 (^{79}Br) $[M + H]^+$, 369 (^{81}Br) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{16}BrN_2O_2S$: 367.0110; found: 367.0114.

The data are in complete agreement with those previously published.[23]

Borane complex **15** (167 mg, 0.44 mmol, 27%) was also isolated.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.40 (br d, *J* = 2.2 Hz, 1 H), 7.77 (dd, *J* = 7.5, 1.7 Hz, 1 H), 3.65–3.47 (m, 3 H), 7.42 (dd, *J* = 8.7, 2.2 Hz, 1 H), 6.37 (d, *J* = 8.7 Hz, 1 H), 4.19 (s, 2 H), 2.60 (s, 6 H).

MS (ES+): *m*/*z* = 398 (^{79}Br) $[M + NH_4]^+$, 400 (^{81}Br) $[M + NH_4]^+$.

HRMS (ESI): *m*/*z* $[M + NH_4]^+$ calcd for $C_{15}H_{22}BBrN_3O_2S$: 398.0704; found: 398.0702.

The data are in complete agreement with those previously published.[23]

1-{2-[(4-Bromo-2-nitrophenyl)thio]phenyl}-*N*,*N*-dimethylmethanamine (7)

At ambient temperature under a nitrogen atmosphere, a one-neck round-bottom flask was charged with 1-{2-[(4-bromo-2-nitrophenyl)thio]phenyl}-*N*,*N*-dimethylmethanamine borane complex (**15**) (167 mg, 0.44 mmol, 1 equiv) and a solution hydrogen chloride in methanol (3.5 mL, *c* = 1.25 M) and the resulting yellow homogeneous mixture was heated (oil bath temperature: 90 °C) and stirred for 19 h. After this time, the mixture was allowed to cool to ambient temperature and then concentrated in vacuo. The yellow residue was diluted with H_2O (10 mL) and the pH of the mixture was adjusted to 8 using saturated aq $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give a yellow oily residue which was purified by chromatography on a silica gel column (50% EtOAc/petrol) to afford the title compound (85.1 mg, 0.23 mmol, 53%).

2-({2-[(Dimethylamino)methyl]phenyl}thio)-5-fluoroaniline (2)

At ambient temperature under a nitrogen atmosphere, a one-neck flask was charged with 1-{2-[(4-fluoro-2-nitrophenyl)thio]phenyl}-*N*,*N*-dimethylmethanamine (**13**) (284 mg, 0.93 mmol, 1 equiv) and ethanol (12.4 mL). The resulting bright yellow solution was further treated with tin(II)chloride dihydrate (2.1 g, 9.3 mmol, 10 equiv) in one portion and the heterogeneous mixture was heated (oil bath temperature: 80 °C) and stirred under nitrogen over 2.5 h. After this time, the mixture was allowed to cool to ambient temperature and then concentrated in vacuo to give an oily residue. The residue was cooled to 0 °C (ice bath) and then treated with 5% aq NaOH (32 mL) and the resulting white heterogeneous mixture was allowed to stir open to the air for 7 h. The mixture was then diluted with H_2O (90 mL) and EtOAc (90 mL) and the two layers were well shaken and separated. The aqueous phase was extracted with EtOAc (2 × 90 mL). The combined organic extracts were washed with brine (1 × 90 mL), dried ($MgSO_4$) and concentrated in vacuo to give a pale brown oily residue (229.1 mg, 0.83 mmol, 89%) which was used for the next step without purification.

MS (ES+): *m*/*z* = 277 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{18}FN_2S$: 277.1169; found: 277.1171.

Note: For the purposes of material storage, **2** was converted into **2**·HCl to give a crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.36 (br s, 1 H), 7.80–7.70 (m, 1 H), 7.35–7.20 (m, 2 H), 6.85–6.79 (m, 1 H), 6.56–6.39 (m, 3 H), 4.36 (s, 2 H), 2.89 (s, 6 H).

5-Bromo-2-({2-[(dimethylamino)methyl]phenyl}thio)aniline (16)

At ambient temperature under a nitrogen atmosphere, a one-neck flask was charged with 1-{2-[(4-bromo-2-nitrophenyl)thio]phenyl}-*N*,*N*-dimethylmethanamine (**7**) (75 mg, 0.20 mmol, 1 equiv) and etha-

nol (2.7 mL). The resulting bright yellow solution was further treated with tin(II)chloride dihydrate (461 mg, 2.0 mmol, 10 equiv) in one portion and the heterogeneous mixture was heated (oil bath temperature: 80 °C) and stirred under nitrogen over 2 h. After this time, the mixture was allowed to cool to ambient temperature and then concentrated in vacuo to give an oily residue. The residue was cooled to 0 °C (ice bath) and then treated with 5% aq NaOH (6.8 mL) and the resulting white heterogeneous mixture was allowed to stir open to the air for 3 h. The mixture was then diluted with H_2O (25 mL) and EtOAc (25 mL) and the two layers were well shaken and separated. The aqueous phase was extracted with EtOAc (2 × 25 mL). The combined organic extracts were washed with brine (1 × 20 mL), dried ($MgSO_4$) and concentrated in vacuo to give a pale brown oily residue (67.9 mg, 0.20 mmol, 98%) which was used for the next step without purification.

MS (ES+): m/z = 337 (^{79}Br) $[M + H]^+$, 339 (^{81}Br) $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{18}BrN_2S$: 337.0369; found: 337.0371.

Note: For the purposes of material storage **16**, was converted into **16**·HCl to give a crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.48 (br s, 1 H), 7.82–7.70 (m, 1 H), 7.30–7.23 (m, 1 H), 7.13 (d, J = 8.2 Hz, 1 H), 7.00 (d, J = 1.6 Hz, 1 H), 6.92–6.84 (m, 3 H), 4.36 (s, 2 H), 2.88 (s, 6 H).

tert-Butyl [2-({2-[(Dimethylamino)methyl]phenyl}thio)-5-fluorophenyl]carbamate (17)

At ambient temperature under a nitrogen atmosphere, a one-neck flask was charged with 2-({2-[(dimethylamino)methyl]phenyl}thio)-5-fluoroaniline (**2**) (50.5 mg, 0.18 mmol, 1 equiv) and anhydrous tetrahydrofuran (0.9 mL). The resulting pale yellow solution was treated with 4-dimethylaminopyridine (2.2 mg, 0.02 mmol, 0.1 equiv) in one portion followed by di-*tert*-butyldicarbonate (120 mg, 0.55 mmol, 3 equiv) and the brown heterogeneous mixture was heated (oil bath temperature: 40 °C) and stirred for 15.5 h. The mixture was allowed to cool to ambient temperature and then concentrated in vacuo. The oily residue was diluted with anhydrous acetonitrile (1.8 mL), treated with lithium bromide (49 mg, 0.57 mmol, 3.1 equiv) and the resulting brown heterogeneous mixture was heated (oil bath temperature: 65 °C) and stirred under nitrogen for 8.5 h. After this time, the mixture was allowed to cool to ambient temperature and then concentrated to give a crude mixture which was purified by chromatography on a silica gel column (gradient elution: 20% to 40% EtOAc in petrol with 0.1% Et_3N) to afford the title compound (52.5 mg, 0.14 mmol, 76%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (dd, J = 11.7, 2.8 Hz, 1 H), 7.97 (s, 1 H), 7.52 (dd, J = 8.5, 6.4 Hz, 1 H), 7.31–7.24 (m, 1 H), 7.16–7.04 (m, 2 H), 6.78–6.70 (m, 2 H), 3.58 (s, 2 H), 2.33 (s, 6 H), 1.46 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.4 (0, d, J = 246 Hz), 152.6 (0), 142.9 (0, d, J = 12.5 Hz), 138.8 (1, d, J = 9.7 Hz), 137.0 (0), 137.0 (0), 130.6 (1), 128.4 (1), 127.8 (1), 126.0 (1), 115.0 (0, d, J = 3.3 Hz), 110.1 (1, d, J = 22.2 Hz), 107.0 (1, d, J = 28.6 Hz), 81.3 (0), 62.6 (2), 45.3 (3, 2 C), 28.4 (3, 3 C).

MS (ES+): m/z = 377 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{26}FN_2O_2S$: 377.1694; found: 377.1692.

tert-Butyl [5-Bromo-2-({2-[(dimethylamino)methyl]phenyl}thio)phenyl]carbamate (18)

At ambient temperature under a nitrogen atmosphere, a one-neck flask was charged with 5-bromo-2-({2-[(dimethylamino)methyl]phenyl}thio)aniline (**16**) (67 mg, 0.2 mmol, 1 equiv) and anhydrous tetrahydrofuran (1.0 mL). The resulting pale yellow solution was treated with 4-dimethylaminopyridine (2.4 mg, 0.02 mmol, 0.1 equiv) in one portion followed by di-*tert*-butyldicarbonate (130 mg, 0.60 mmol, 3 equiv) and the brown heterogeneous mixture was heated (oil bath temperature: 40 °C) and stirred for 16 h. The mixture was allowed to cool to ambient temperature and then concentrated in vacuo. The oily residue was diluted with anhydrous acetonitrile (2.0 mL) and treated with lithium bromide (54 mg, 0.62 mmol, 3.1 equiv) and the resulting brown heterogeneous mixture was heated (oil bath temperature: 65 °C) and stirred under nitrogen for 10 h. After this time, the mixture was allowed to cool to ambient temperature and then concentrated to give a crude mixture which was purified by chromatography on a silica gel column (gradient elution: 20% to 40% EtOAc in petrol with 0.1% Et_3N) to afford the title compound (83.4 mg, 0.19 mmol, 96%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.45 (d, J = 2.1 Hz, 1 H), 7.86 (s, 1 H), 7.37 (d, J = 8.2 Hz, 1 H), 7.30–7.23 (m, 1 H), 7.17–7.05 (m, 3 H), 6.80 (dd, J = 7.1, 2.0 Hz, 1 H), 3.56 (s, 2 H), 2.31 (s, 6 H), 1.46 (s, 9 H).

MS (ES+): m/z = 437 (^{79}Br) $[M + H]^+$, 439 (^{81}Br) $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{26}BrN_2O_2S$: 437.0893; found: 437.0894.

tert-Butyl [2-({2-[(Dimethylamino)methyl]phenyl}thio)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (3A)

At ambient temperature under a nitrogen atmosphere, a one-neck flask was charged with *tert*-butyl [5-bromo-2-({2-[(dimethylamino)methyl]phenyl}thio)phenyl]carbamate (**18**) (93 mg, 0.21 mmol, 1 equiv) and 1,4-dioxane (6.8 mL). The resulting colourless solution was treated with potassium acetate (63 mg, 0.64 mmol, 3 equiv) followed by [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (31 mg, 0.04 mmol, 0.2 equiv) and 1,1′-bis(diphenylphosphino)ferrocene (47 mg, 0.85 mmol, 0.4 equiv) and the obtained orange coloured mixture was sparged with nitrogen for 1 h. After this time, bis(pinacolato)diboron **19** (324 mg, 1.28 mmol, 6 equiv) was added and the resulting brown heterogeneous mixture was heated (oil bath temperature: 100 °C) and stirred under nitrogen for 23.5 h. After this time, the obtained black mixture was allowed to cool to ambient temperature and then diluted with H_2O (100 mL) and EtOAc (100 mL), and the two layers were well shaken and separated. The aqueous phase was extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with H_2O (3 × 100 mL), brine (1 × 100 mL), dried ($MgSO_4$) and concentrated in vacuo to give a crude mixture as a brown oily residue. The residue was purified by chromatography on a silica gel column (gradient elution: 20% to 40% EtOAc in petrol with 0.1% Et_3N) to afford the title compound (90.5 mg, 0.19 mmol, 87%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.49 (br s, 1 H), 7.56 (s, 1 H), 7.45–7.44 (m, 1 H), 7.44 (d, J = 1.1 Hz, 1 H), 7.29 (dd, J = 7.6, 1.5 Hz, 1 H), 7.12 (td, J = 7.3, 1.4 Hz, 1 H), 7.05 (td, J = 7.7, 1.8 Hz, 1 H), 6.81 (dd, J = 7.6, 1.3 Hz, 1 H), 3.56 (s, 2 H), 2.30 (s, 6 H), 1.44 (s, 9 H), 1.33 (s, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.9 (0), 139.8 (0), 137.8 (0), 136.4 (0, d, J = 0.02 Hz), 135.6 (1), 130.4 (1), 129.5 (1), 128.9 (1), 128.3 (1), 126.2 (1), 125.9 (1), 124.8 (0, d, J = 0.01 Hz), 84.2 (0), 83.7 (0), 80.6 (0), 62.6 (2), 45.4 (3, 2 C), 28.5 (3, 2 C), 25.2 (3, 2 C), 25.1 (3, 3 C); the carbon attached to boron was not observed.

MS (ES+): m/z = 485 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{26}H_{38}BN_2O_4S$: 484.2676; found: 484.2669.

tert-Butyl [2-({2-[(Dimethylamino)methyl]phenyl}thio)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-ylphenyl]carbamate Hydrochloric Salt (3A·HCl)

At ambient temperature under a nitrogen atmosphere, a one-neck flask was charged with *tert*-butyl [2-({2-[(dimethylamino)methyl]phenyl}thio)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (189 mg, 0.39 mmol, 1 equiv) (**3A**) and methanol (2.3 mL). The resulting brown solution was treated with a solution of hydrogen chloride in methanol (0.31 mL, 0.39 mmol, 1 equiv, c = 1.25 M) dropwise over 1 min and then stirred for 30 min. After this time, the crude mixture was concentrated in vacuo and the brown residue was further diluted with Et_2O and allowed to crystallise. The crystals were filtered, washed with ice-cold Et_2O and dried in air to afford the title compound (64.8 mg, 0.12 mmol, 32%) as needle-like crystals.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.68 (s, 1 H), 8.25 (d, J = 1.0 Hz, 1 H), 8.21 (br d, J = 6.6 Hz, 1 H), 7.46 (dd, J = 7.8, 1.0 Hz, 1 H), 7.48–7.41 (m, 1 H), 7.33 (t, J = 7.8 Hz, 1 H), 7.14 (dd, J = 7.9, 0.9 Hz, 1 H), 7.09 (d, J = 7.8 Hz, 1 H), 6.89 (br s, 1 H), 4.40 (d, J = 3.4 Hz, 2 H), 2.77 (d, J = 2.8 Hz, 6 H), 1.48 (s, 9 H), 1.33 (s, 12 H).

4-Chloro-*N*,*N*-dimethyl-3-nitroaniline (21)

At ambient temperature under a nitrogen atmosphere, a one-neck flask was charged with 4-chloro-3-nitroaniline (172 mg, 1 mmol, 1 equiv) and anhydrous *N*,*N*′-dimethylformamide (20 mL). The resulting brown solution was treated with potassium carbonate (3.6 g, 26 mmol, 26 equiv) and then methyl iodide (0.75 mL, 1.7 g, 12 mmol, 12 equiv, d = 2.28) was added dropwise over 1 min and the mixture was heated (oil bath temperature: 120 °C) for 24 h. After this time, the crude mixture was allowed to cool to ambient temperature, poured into H_2O (50 mL) and diluted with CH_2Cl_2 (40 mL). The two layers were well shaken, separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic extracts were washed with H_2O (5 × 30 mL), brine (1 × 40 mL), dried ($MgSO_4$) and concentrated in vacuo to give a crude oily residue. The crude residue was purified by chromatography on a silica gel column (eluting with 50% CH_2Cl_2/petrol) to afford the title compound (112.1 mg, 0.56 mmol, 56%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (d, J = 9.0 Hz, 1 H), 7.09 (d, J = 3.0 Hz, 1 H), 6.77 (dd, J = 9.0, 3.0 Hz, 1 H), 3.00 (s, 6 H).

2-[(4-Amino-2-nitrophenyl)thio]benzoic Acid (22)

At ambient temperature under a nitrogen atmosphere, a one-neck flask was charged with 4-chloro-3-nitroaniline (1.53 g, 8.9 mmol, 1 equiv) and anhydrous *N*,*N*′-dimethylformamide (33 mL). The resulting brown solution was treated with potassium carbonate (2.7 g, 19.5 mmol, 2.2 equiv) followed by thiosalicylic acid (**10**) (1.4 g, 8.9 mmol, 1 equiv) and copper(I) bromide (1.3 g, 8.9 mmol, 1 equiv). The obtained black heterogeneous mixture was heated (oil bath temperature: 120 °C) and stirred for 24 h. After this time, the mixture was allowed to cool to ambient temperature, diluted with ice-cold H_2O (100 mL) and then filtered through a Celite pad (using a Hirsch funnel). The pH of the filtrate was adjusted to 2 by adding 2 M aq HCl and the aqueous phase was extracted with EtOAc (3 × 150 mL). The combined organic extracts were washed with H_2O (5 × 100 mL), brine (1 × 100 mL), dried ($MgSO_4$) and concentrated in vacuo to give a crude orange solid residue. The residue was purified by chromatography on a silica gel column (eluting with 20% CH_2Cl_2 in EtOAc). The obtained material was insufficiently pure so a second column was performed (eluting with 10% CH_2Cl_2 in EtOAc with 0.1% HCO_2H) to afford the title compound (1.82 g, 6.3 mmol, 70%). The product could not be isolated in pure form even after several attempted crystallisations. ^{1}H NMR data were in complete agreement with those previously published.[19]

2-{[4-(Dimethylamino)-2-nitrophenyl]thio}benzoic Acid (23)

At ambient temperature under a nitrogen atmosphere, a one-neck flask was charged with 4-chloro-*N*,*N*-dimethyl-3-nitroaniline (112 mg, 0.56 mmol, 1 equiv) (**21**) and anhydrous *N*,*N*′-dimethylformamide (2 mL). The resulting orange solution was treated with potassium carbonate (169 mg, 1.22 mmol, 2.2 equiv) followed by thiosalicylic acid (**10**) (86 mg, 0.56 mmol, 1 equiv) and copper(I) bromide (80 mg, 0.56 mmol, 1 equiv). The obtained black heterogeneous mixture was heated (oil bath temperature: 120 °C) and stirred for 24.5 h. After this time, the resulting green coloured mixture was allowed to cool to ambient temperature, diluted with ice-cold H_2O (25 mL) and then filtered through a Celite pad (using a Hirsch funnel). The pH of the filtrate was adjusted to 2 by adding 2 M aq HCl and the aqueous phase was extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with H_2O (5 × 25 mL), brine (1 × 30 mL), dried ($MgSO_4$) and concentrated in vacuo to give an orange solid residue (128.1 mg, 0.40 mmol, 72%). The crude mixture was used for the next step without further purification.

2-[(4-Amino-2-nitrophenyl)thio]-*N*,*N*-dimethylbenzamide (24)

To the crude residue **22** (100 mg, 0.34 mmol, 1 equiv) was added anhydrous tetrahydrofuran (6.0 mL) and the mixture was allowed to cool to 0 °C (ice bath) and then treated with dimethylamine hydrochloride salt (31 mg, 0.38 mmol, 1.1 equiv). Next, 1-hydroxybenzonitrile (60 mg, 86% pure, 0.38 mmol, 1.1 equiv) and EDC (132 mg, 0.69 mmol, 2 equiv) were added. Triethylamine (0.19 mL, 139 mg, 1.38 mmol, 4 equiv, d = 0.726) was added via syringe and the resulting green–brown heterogeneous mixture was allowed to stir under nitrogen at ambient temperature over 20.5 h. After this time, the crude mixture was diluted with EtOAc (20 mL), filtered through a Celite pad (using a Hirsch funnel) and the filter cake was rinsed with EtOAc (2 × 20 mL). The combined filtrates were washed with 1 M aq HCl (2 × 20 mL), H_2O (2 × 20 mL), brine (1 × 25 mL), dried ($MgSO_4$) and concentrated in vacuo to give a brown oily residue which was purified by column chromatography on a silica gel column (gradient elution: 100% CH_2Cl_2 to 90% EtOAc in CH_2Cl_2) to afford the title compound (52.9 mg, 0.17 mmol, 48%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54–7.29 (m, 5 H), 6.90 (d, J = 8.7 Hz, 1 H), 6.74 (dd, J = 8.5, 2.5 Hz, 1 H), 3.05 (s, 3 H), 2.85 (s, 3 H).

The data are in complete agreement with those previously published.[19]

2-{[4-(Dimethylamino)-2-nitrophenyl]thio}-*N*,*N*-dimethylbenzamide (25)

To the crude residue **23** (128 mg, 0.40 mmol, 1 equiv) was added anhydrous tetrahydrofuran (7.4 mL) and the mixture was allowed to cool to 0 °C (ice bath) and then treated with dimethylamine hydrochloride salt (36.1 mg, 0.44 mmol, 1.1 equiv). Next, 1-hydroxybenzonitrile (70 mg, 86% pure, 0.44 mmol, 1.1 equiv) and EDC (154 mg, 0.8 mmol, 2 equiv) were added. Triethylamine (0.22 mL, 163 mg, 1.6 mmol, 4 equiv, d = 0.726) was added via syringe and the resulting green–brown heterogeneous mixture was allowed to stir under nitrogen at ambient temperature over 22 h. After this time, the crude mixture was diluted with EtOAc (10 mL), filtered through a Celite pad (using a Hirsch funnel) and the filter cake was rinsed with EtOAc (3 × 10

mL). The combined filtrates were washed with 1 M aq HCl (2 × 20 mL), H_2O (2 × 20 mL), brine (1 × 20 mL), dried ($MgSO_4$) and concentrated in vacuo to give a brown oily residue which was purified by column chromatography on a silica gel column (gradient elution: 100% CH_2Cl_2 to 10% EtOAc in CH_2Cl_2) to afford the title compound (42 mg, 0.12 mmol, 30%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.27 (m, 5 H), 7.03 (d, *J* = 9.0 Hz, 1 H), 6.77 (dd, *J* = 9.0, 2.9 Hz, 1 H), 3.06 (s, 3 H), 2.98 (s, 6 H), 2.86 (s, 3 H).

The data are in complete agreement with those previously published.[19]

2-{[4-(Dimethylamino)-2-nitrophenyl]thio}-*N*,*N*-dimethylbenzamide (25)

At ambient temperature under a nitrogen atmosphere, a one-neck flask was charged with 2-[(4-amino-2-nitrophenyl)thio]-*N*,*N*-dimethylbenzamide (**24**) (52 mg, 0.16 mmol, 1 equiv) and anhydrous *N*,*N*′-dimethylformamide (3.2 mL). The resulting mixture was treated with potassium carbonate (589 mg, 4.26 mmol, 26 equiv) followed by methyl iodide (0.12 mL, 279 mg, 1.97 mmol, 12 equiv, *d* = 2.28) and the resulting red heterogeneous mixture was heated (oil bath temperature: 120 °C) and stirred for 37 h. After this time, the mixture was allowed to cool to ambient temperature and then diluted with H_2O (10 mL) and EtOAc (15 mL) and the two layers were well shaken and separated. The aqueous phase was extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed with H_2O (5 × 10 mL), brine (1 × 15 mL), dried ($MgSO_4$) and concentrated in vacuo to give a crude mixture which was purified by chromatography on a silica gel column (gradient elution: 100% CH_2Cl_2 to 20% EtOAc in CH_2Cl_2) to afford the title compound (29.7 mg, 0.08 mmol, 52%).

tert-Butyl [2-({2-[(Dimethylamino)methyl]phenyl}thio)-5-fluorophenyl]carbamate (17)

At ambient temperature open to air, a one-neck flask was charged with *tert*-butyl [2-({2-[(dimethylamino)methyl]phenyl}thio)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (**3A**) (8.8 mg, 0.018 mmol, 1 equiv) and Kryptofix (13.7 mg, 0.036 mmol, 2 equiv), followed by potassium fluoride (spray-dried, 2 mg, 0.036 mmol, 2 equiv) and anhydrous *N*,*N*′-dimethylformamide (0.5 mL). The resulting brown heterogeneous reaction mixture was heated (oil bath temperature: 110 °C) and stirred over 15 h. After this time, the reaction mixture was allowed to cool to ambient temperature and then diluted with H_2O (10 mL) and EtOAc (10 mL) and the two layers were well shaken and separated. The aqueous phase was extracted with EtOAc (2 × 10 mL) and the combined organic extracts were washed with H_2O (5 × 8 mL), brine (1 × 10 mL), dried ($MgSO_4$) and concentrated in vacuo to give a crude mixture as a yellow oily residue. The residue was analysed by ^{1}H NMR and LCMS.

MS (ES+): *m*/*z* = 377 $[M + H]^+$.

4-[^{18}F]Fluoro-1,1′-biphenyl ([^{18}F]27)

[^{18}F]Fluoride ions were produced by the ^{18}O(p,n)^{18}F nuclear reaction using a GE PETtrace cyclotron (GE Healthcare, Sweden). [^{18}F]fluoride (0.7 GBq) in [^{18}O]H_2O (2 mL) was passed through a QMA cartridge (Waters, Sep-pak Light in carbonate form). The trapped [^{18}F]fluoride was eluted with an eluent (0.8 mL) containing Kryptofix 222 (K_{222}) (12 mg) and K_2CO_3 (2.4 mg) dissolved in H_2O/MeCN (1:4, v/v) in a 5 mL V-vial. The solution was dried at 120 °C under a N_2 flow. The [^{18}F]KF/K_{222} complex was dried two more times with anhydrous MeCN (2 × 1 mL). The complex was then re-dissolved in anhydrous MeCN to reach an activity concentration of 3 MBq/μL. An aliquot of this solution (20 μL) was taken and added to a 1.5 mL reaction vial containing a magnetic stir bar and precursor **26** (6 mg, 0.02 mmol) dissolved in dimethylacetamide (300 μL) in the presence of $Cu(OTf)_2(py)_4$ (14 mg, 0.02 mmol). Air (10 mL) was bubbled through the reaction mixture after which the reaction vial was sealed and heated at 115 °C for 20 min. The reaction mixture was analysed by HPLC analysis using an UltraCore 2.5 Å, Super C18, 50 × 4.6 mm column (gradient elution: 5% to 95% aqueous MeCN).

tert-Butyl (2-{[2-(dimethylamino)methyl]phenyl}thio)-5-([^{18}F]fluorophenyl)carbamate (4-[^{18}F]17)

[^{18}F]Fluoride ions were produced by the ^{18}O(p,n)^{18}F nuclear reaction using a GE PETtrace cyclotron (GE Healthcare, Sweden). [^{18}F]fluoride (0.7–2 GBq) in [^{18}O]H_2O (2 mL) was passed through a QMA cartridge (Waters, Sep-pak Light in carbonate form). The trapped [^{18}F]fluoride was eluted with an eluent (0.8 mL) containing Kryptofix 222 (K_{222}) (12 mg) and K_2CO_3 (2.4 mg) dissolved in H_2O/MeCN (1:4, v/v) in a 5 mL V-vial. The solution was dried at 120 °C under a N_2 flow. The [^{18}F]KF/K_{222} complex was dried two more times with anhydrous MeCN (2 × 1 mL). The complex was then re-dissolved in anhydrous MeCN to reach an activity concentration of 3 MBq/μL. An aliquot of this solution (20 μL) was taken and added to a 1.5 mL reaction vial containing a magnetic stir bar and precursor **3A**·HCl or **3A** (5–10 mg, 0.01–0.02 mmol) dissolved in dimethylacetamide (300 μL) in the presence of $Cu(OTf)_2(Py)_4$ (7–14 mg 0.01–0.02 mmol). Air (10 mL) was bubbled through the reaction mixture after which the reaction vial was sealed and heated at 85–115 °C for up to 50 min. Aliquots were collected and analysed to obtain the radiochemical conversion by radio-TLC (mobile phase: 40% EtOAc/hexane with 0.2% Et_3N).

2-({2-[(Dimethylamino)methyl]phenyl}thio)-5-[^{18}F]fluoroaniline (4-[^{18}F]2)

[^{18}F]Fluoride ions were produced by the ^{18}O(p,n)^{18}F nuclear reaction using a GE PETtrace cyclotron (GE Healthcare, Sweden). [^{18}F]fluoride (0.7–2 GBq) in [^{18}O]H_2O (2 mL) was passed through a QMA cartridge (Waters, Sep-pak Light in carbonate form). The trapped [^{18}F]fluoride was eluted with an eluent (0.8 mL) containing Kryptofix 222 (K_{222}) (12 mg) and K_2CO_3 (2.4 mg) and dissolved in H_2O/MeCN (1:4, v/v) in a 5 mL V-vial. The solution was dried at 120 °C under a N_2 flow. The [^{18}F]KF/K_{222} complex was dried two more times with anhydrous MeCN (2 × 1 mL). The complex was then re-dissolved in anhydrous MeCN to reach an activity concentration of 3 MBq/μL. An aliquot of this solution (20 μL) was taken and added to a 1.5 mL reaction vial containing a magnetic stir bar and precursor **3A** (5 mg, 0.01 mmol) dissolved in dimethylacetamide (300 μL) in the presence of $Cu(OTf)_2(Py)_4$ (7 mg, 0.01 mmol). Air (10 mL) was bubbled through the reaction mixture after which the reaction vial was sealed and heated at 85 °C for 10 min. Upon completion of the reaction, to the mixture was added 4 M HCl (60 μL) and the temperature maintained at 85 °C for another 10 min, which was followed by neutralisation with 4 M NaOH (60 μL). Aliquots were collected for analysis of the radiochemical conversion by radio-TLC (mobile phase: 40% EtOAc/hexane with 0.2% Et_3N) as well as by HPLC. For the latter, the crude mixture was diluted with H_2O (2 equiv) and filtered through a 0.02 μm filter (Anotop 10, GE Healthcare, Germany) before the injection. The HPLC analysis was conducted using an analytical HPLC column (ACE UltraCore 2.5 Å Super C18, 2.5 μm, 4.6 × 50 mm) at a flow rate of 1 mL/min using the following gradient: 80% 100 mM NH_4CO_2H in MeCN, 0–4 min; 60% 100 mM NH_4CO_2H in MeCN, 5–7 min; 30% 100 mM NH_4CO_2H in MeCN, 8–10 min; 80% 100 mM NH_4CO_2H in MeCN, 11 min.

Automated Radiosynthesis of 2-({2-[(Dimethylamino)methyl]phenyl}thio)-5-[^{18}F]fluoroaniline (4-[^{18}F]2)

[^{18}F]Fluoride ions were produced by the ^{18}O(p,n)^{18}F nuclear reaction using a GE PETtrace cyclotron (GE Healthcare, Sweden). [^{18}F]fluoride (5.09 GBq) in [^{18}O]H_2O (2.5 mL) was transferred into the receiving flask of the FXFN module using a stream of N_2. The module was assembled as follows:

V1: a solution (0.8 mL) of Kryptofix (K_{222}) (12 mg) and K_2CO_3 (2.4 mg) in H_2O/MeCN (1:4).

V2: MeCN (2 mL).

V3: $Cu(OTf)_2(py)_4$ (14 mg) in DMA (0.3 mL) (blue solution).

V4: **3A** (11 mg) in DMA (0.3 mL).

V5: 4 M aq HCl (0.3 mL).

V6: 4 M aq NaOH (0.3 mL) and HPLC eluent (3 mL).

SPE flask: H_2O (30 mL).

Semi-preparative HPLC: 100 mM NH_4CO_2H (75%) and MeCN (25%) at 4 mL/min; column: ACE C18, 5 µm, 10 × 100 mm.

Aqueous [^{18}F]fluoride was passed through a QMA cartridge (Waters, Sep-pak Light in carbonate form) and eluted with a Kryptofix solution from V1 into the reactor. The solution was azeotropically dried at 95 °C under a flow of He and under vacuum using MeCN from V2. Prior to the addition of the Cu-source (from V3) and **3A** (from V4) to the reactor, each solution was sparged with air by bubbling air through the solutions using an external syringe and Vygon tubing. The Cu-source was added first and the mixture allowed to heat at 85 °C for 1 min, after which time the precursor was added and heating was continued for a further 9 min. The acid from V5 was added and heating was continued for another 10 min. The mixture was allowed to cool to 50 °C and then neutralised with the base/eluent mixture from V6. The crude mixture was injected into the semi-preparative column and the resulting chromatogram showed a 10% radiochemical yield for 4-[^{18}F]**2**. The identity of the product was confirmed by co-injection on the analytical HPLC. The concentration of cold ADAM in the sample was determined from the calibration curve.

Funding Information

This work was in part funded by an internal grant from the Behavioural and Clinical Neuroscience Institute (BCNI), University of Cambridge.

Acknowledgment

Dr. Lindsay McMurray (WBIC) is acknowledged for many useful discussions on the non-radioactive synthesis of ADAM. Dr. Bianca Jupp (BCNI) is acknowledged for suggesting the [^{18}F]ADAM radiotracer for application in drug addiction in vivo studies. Dr. Mark Sephton (CRL) is acknowledged for proofreading the manuscript.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690522.

References

(1) Ma, K. H.; Huang, W. S.; Kuo, Y. Y.; Peng, C. J.; Liou, N. H.; Liu, R. S.; Hwang, J. J.; Liu, J. C.; Chen, H. J.; Shiue, C. Y. *Neuroimage* **2009**, *45*, 687.
(2) Sephton, S. M.; Ametamey, S. M. *Positron Emission Tomography Agents*, In *Molecular Imaging Techniques: New Frontiers*; Gazeau, F., Ed.; Future Medicine: London, **2013**, DOI 10.4155/ebo.12.504.
(3) Brust, P.; Hesse, S.; Muller, U.; Szabo, Z. *Curr. Psychiatry Rev.* **2006**, *2*, 111.
(4) Kim, S. E.; Choi, J. Y.; Choe, Y. S.; Choi, Y.; Lee, W. Y. *J. Nucl. Med.* **2003**, *44*, 870.
(5) Li, I.-H.; Huang, W.-S.; Yeh, C.-B.; Liao, M.-H.; Chen, C.-C.; Shen, L.-H.; Liu, J.-C.; Ma, K.-H. *Nucl. Med. Biol.* **2009**, *36*, 605.
(6) Kerenyi, L.; Ricaurte, G. A.; Schretlen, D. J.; McCann, U.; Varga, J.; Mathews, W. B.; Ravert, H. T.; Dannals, R. F.; Hilton, J.; Wong, D. F.; Szabo, Z. *Arch. Neurol.* **2003**, *60*, 436.
(7) Guttman, M.; Boileau, I.; Warsh, J.; Saint-Cyr, J. A.; Ginovart, N.; McCluskey, T.; Houle, S.; Wilson, A.; Mundo, E.; Rusjan, P.; Meyer, J.; Kish, S. J. *Eur. J. Neurol.* **2007**, *14*, 523.
(8) Weng, S.-J.; Shiue, C.-Y.; Huang, W.-S.; Cheng, C.-Y.; Huang, S.-Y.; Li, I.; Tao, C.-C.; Chou, T.-K.; Liao, M.-H.; Chang, Y.-P.; Ma, K.-H. *Cell Transplant.* **2013**, *22*, 1295.
(9) Houle, S.; Ginovart, N.; Hussey, D.; Meyer, J. H.; Wilson, A. A. *Eur. J. Nucl. Med.* **2000**, *27*, 1719.
(10) Wilson, A. A.; Ginovart, N.; Schmidt, M.; Meyer, J. H.; Threlkeld, P. G.; Houle, S. *J. Med. Chem.* **2000**, *43*, 3103.
(11) Huang, W.-S.; Huang, S.-Y.; Ho, P.-S.; Ma, K.-H.; Huang, Y.-Y.; Yeh, C.-B.; Liu, R.-S.; Cheng, C.-Y.; Shiue, C.-Y. *Eur. J. Nucl. Med. Mol. Imaging* **2013**, *40*, 115.
(12) Hesse, S.; Brust, P.; Mäding, P.; Becker, G.-A.; Patt, M.; Seese, A.; Sorger, D.; Zessin, J.; Meyer, P. M.; Lobsien, D.; Laudi, S.; Habermann, B.; Füchtner, F.; Luthardt, J.; Bresch, A.; Steinbach, J.; Sabri, O. *Eur. J. Nucl. Med. Mol. Imaging* **2012**, *39*, 1001.
(13) Huang, Y. Y.; Huang, W. S.; Ma, K. H.; Chou, T. K.; Kuo, Y. Y.; Cheng, C. Y.; Shiue, C. Y. *Appl. Radiat. Isot.* **2012**, *70*, 2298.
(14) Chen, Y.-A.; Huang, W.-S.; Lin, Y.-S.; Cheng, C.-Y.; Liu, R.-S.; Wang, S.-J.; Li, I.-H.; Huang, S.-Y.; Shiue, C.-Y.; Chen, C.-Y.; Ma, K.-H. *Nucl. Med. Biol.* **2012**, *39*, 279.
(15) Tredwell, M.; Preshlock, S. M.; Taylor, N. J.; Gruber, S.; Huiban, M.; Passchier, J.; Mercier, J.; Génicot, C.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2014**, *53*, 7751.
(16) Preshlock, S.; Calderwood, S.; Verhoog, S.; Tredwell, M.; Huiban, M.; Hienzsch, A.; Gruber, S.; Wilson, T. C.; Taylor, N. J.; Cailly, T.; Schedler, M.; Collier, T. L.; Passchier, J.; Smits, R.; Mollitor, J.; Hoepping, A.; Mueller, M.; Genicot, C.; Mercier, J.; Gouverneur, V. *Chem. Commun.* **2016**, *52*, 8361.
(17) Shiue, G. G.; Fang, P.; Shiue, C.-Y. *Appl. Radiat. Isot.* **2003**, *58*, 183.
(18) Peng, C. J.; Huang, Y. Y.; Huang, W. S.; Shiue, C. Y. *Appl. Radiat. Isot.* **2008**, *66*, 625.
(19) Huang, Y.-Y.; Huang, W.-S.; Chu, T.-C.; Shiue, C.-Y. *Appl. Radiat. Isot* **2009**, *67*, 1063.
(20) Blakemore, P. R.; Kilner, C.; Milicevic, S. D. *J. Org. Chem.* **2005**, *70*, 373.
(21) Evans, V.; Mahon, M. F.; Webster, R. L. *Tetrahedron* **2014**, *70*, 7593.
(22) Lam, P. Y.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941.
(23) Shiue, G. G.; Fang, P.; Shiue, C. Y. *Appl. Radiat. Isot.* **2003**, *58*, 183.