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

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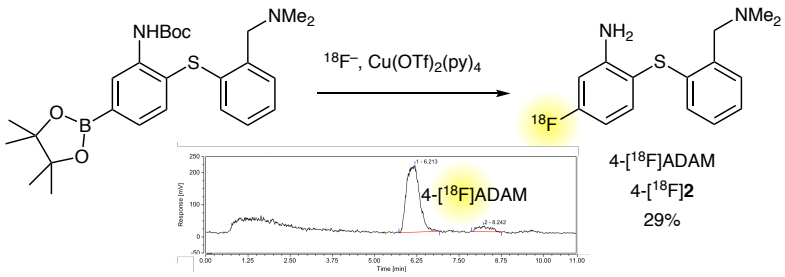

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Serotonin transporters (SERTs) are involved in regulating the concentration of synaptic serotonin and present a good target for many neurologic and psychiatric disorder drugs. Positron Emission Tomography (PET) is a valuable tool in both diagnosis and monitoring treatment therapies for which reason much effort has been 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 was achieved using Pd-catalyzed coupling with thiosalicylic acid and an EDC/HOBt amide coupling in 36% over 4 steps. A novel radiolabelling precursor, the pinacol derived boronic ester was prepared from the bromide using the Miyaura borylation in 27% over 6 steps. Pinacolate was then used for the radiolabelling of 4-[^{18}F]ADAM based on Cu-mediated nucleophilic fluorination in which the presence of oxygen was critical for the reaction. A 1:1 substrate to copper ratio was found to be optimal when the reaction was performed in dimethylacetamide as solvent at 85 °C. Using these conditions 4-[^{18}F]ADAM was prepared in 29±10% (n=6) radiochemical conversion after hydrolysis of the Boc group with HCl. Furthermore, the method was 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 characterized 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 Parkinson's disease affected monkey and human brains.[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**, Figure 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 min. This in turn limits its application to PET centres with an onsite cyclotron. To expand the application, a fluorine-18 analogue with a physical half-life of 110 min was sought.

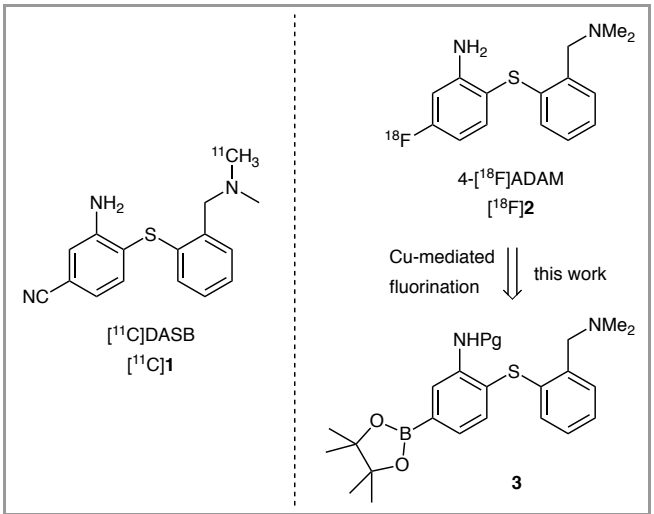


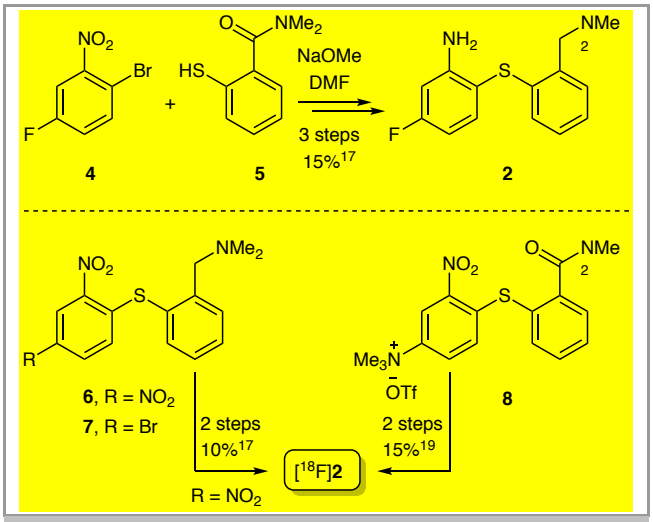
Figure 1 Structures of SERT PET radiotracers: [^{11}C]**1** and 4-[^{18}F]**2** and a novel radiolabelling precursor **3**. Pg – protecting group.

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, due to various reasons, such as challenging chemistry to synthesize 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.

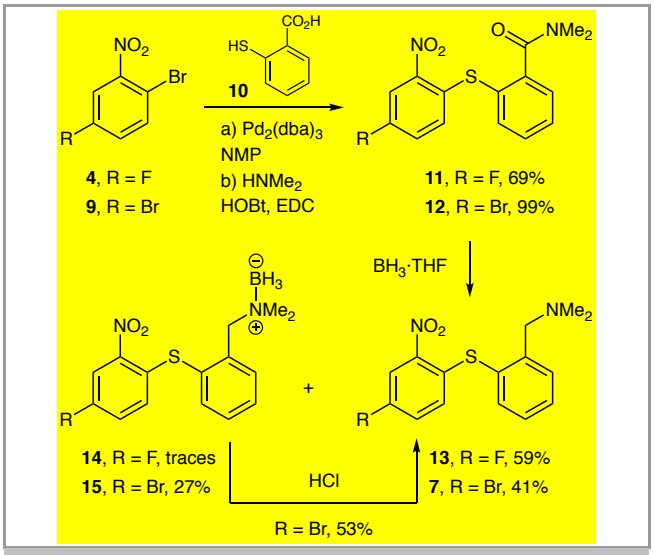
Herein, we report an improved synthesis of **2**, as well as the radiosynthesis of 4-[^{18}F]**2** based on a copper mediated method from the Gouverneur lab[15,16] for the introduction of fluorine-18 into the novel radiolabelling precursor **3** (Figure 1).

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 1).



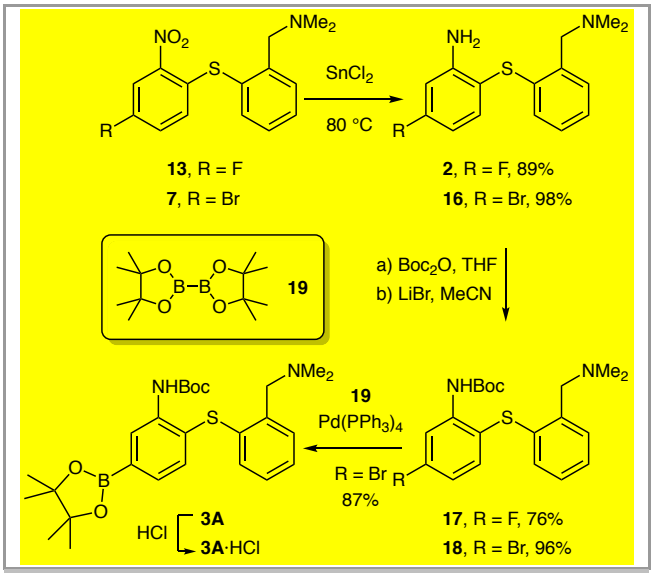
Scheme 1 Previously reported synthesis of **2** and radiosynthesis of 4-[^{18}F]**2** using nitro-, bromo- or trimethylammonium- precursors **6**, **7** and **8**, respectively.

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 desired **2** in 15% over three steps. In the same report, 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 1) with 15% decay corrected radiochemical yield when radiosynthesis was performed manually.[19] In an effort to reproduce the literature synthesis of **2**, we began the synthesis using the same 4-fluorobromide **4** and thiosalicylic acid **10** instead of benzamide **5**, the latter being commercially available only from specialized 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 synthesis route and prepared **2** as depicted in Schemes 2 and 3.



Scheme 2 *En route* **2**: a reproducible synthetic route on gram scale.

To form the thioether we employed the palladium-catalyzed coupling[20] of 4-fluoro-bromide **4** with thiosalicylic acid **10**.



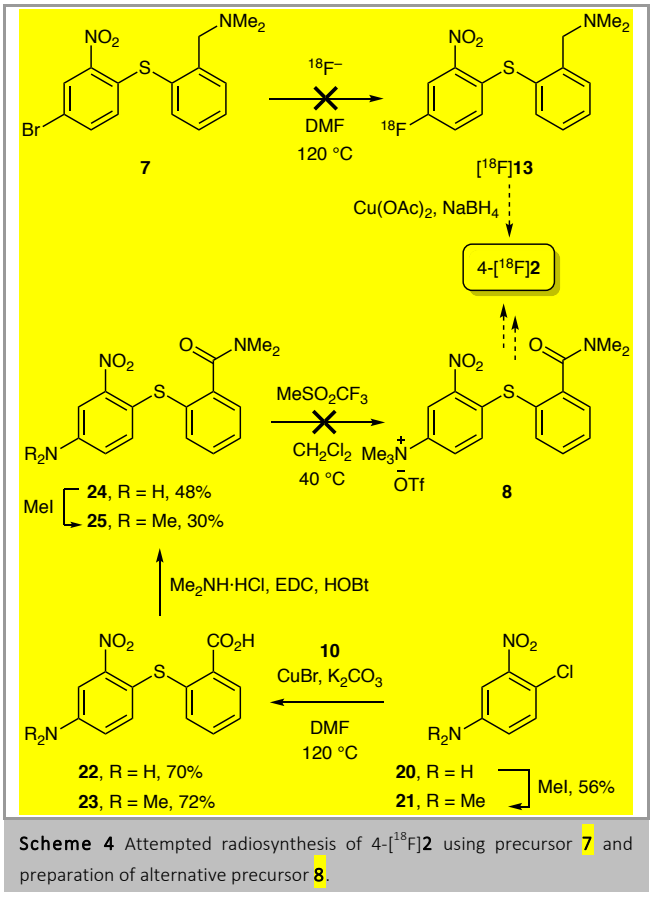
Scheme 3 Completion of gram scale synthesis of **2** and preparation of radiolabelling precursor **3A**.

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 to the desired product amine **13** by heating in 1M

aqueous hydrochloric acid (HCl). The amount of isolated **14** after the borane reduction varied from batch to batch and while the 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 2). In the final step fluoro-analogue **2** was obtained after reduction of the nitro group with the $SnCl_2$ in 89% yield (Scheme 3).

Our improved synthesis of **2** compared favourably with the method published by the Shiue group in 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 analogous synthesis of bromo- precursor **7** (Scheme 2). 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 in 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 catalyzed 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 to amine **7** with 53% yield (Scheme 2).



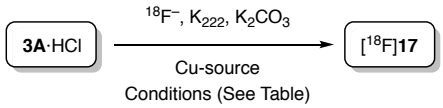
Scheme 4 Attempted radiosynthesis of 4-[^{18}F]**2** using precursor **7** and preparation of alternative precursor **8**.

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 4) which would be converted to 4-[^{18}F]**2** after reduction of the nitro group. Change of base from K_2CO_3 to Cs_2CO_3 and reaction solvent to DMSO had no effect and none of the nitro derivative [^{18}F]**13** was observed. 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 dimethyl amine **25** was synthesized following the modified method of Shiue and co-workers. Copper-mediated coupling of thiosalycilic 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 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** 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 radiosynthesis of 4-[^{18}F]**2** and we envisaged boron pinacolate **3A** (Scheme 3) 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 96% of **18** and finally a palladium catalyzed Miyaura borylation reaction to afford boron pinacolate **3A** (Scheme 3). Pinacol boronic ester **3A** was isolated as a colourless oil and for the ease of handling small amounts of precursor, it was converted to a HCl salt **3A**·HCl. As an unlabeled reference aniline **2** was also protected with Boc to give **17** in 76% yield.

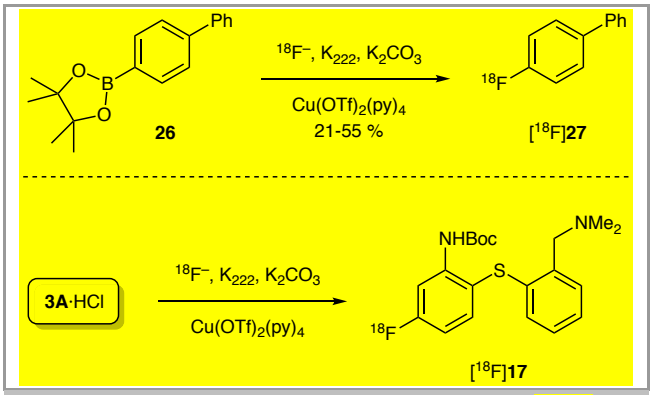
To establish the Gouverneur method in our hands, we first performed the fluorination with biphenyl pinacol boronic ester **26** as a model reaction (Scheme 5) to obtain fluorinated [^{18}F]**27** with 21-55% radiochemical conversion (RCC). When the same reaction conditions were applied to pinacolate **3A**·HCl, an ambiguous result was seen and the radiolabelling product was detected, however the HPLC coinjection with reference **17** showed a mismatch. It was later postulated that the product was likely the free amine with the Boc group being removed; however showing different R_f to **2** due to coordination to copper.

Table 1 Optimisation of 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]



Scheme 5 Gouverneur method for the radiosynthesis of [^{18}F]**27** and [^{18}F]**17**.

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 optimize reaction conditions (Table 1). Gouverneur and co-workers found $Cu(OTf)_2(py)_4$ complex to be the highest yielding. They also determined that the 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 desired product from the fluorination of [^{18}F]**17** were observed when solvent was changed from DMA to DMF (entry 4). The application of initial Gouverneur conditions with $Cu(OTf)_2$ as a catalyst in ester:Cu-complex ratio of 10:1 resulted similarly in no product (entry 5). Finally, the reaction temperature was reduced to 80 °C (entry 6) and once again 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 desired fluorinated product could arise from the chemical form of the boronic ester which was a solid HCl salt.

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 lacked formation of the fluorinated product.

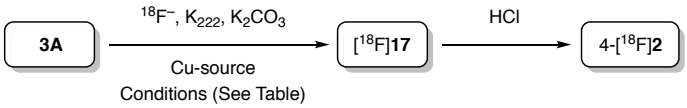
In order to confirm product formation under non-radioactive conditions, **3A** was treated with KF in a model reaction under Gouverneur conditions, and the reaction progress followed by ^{1}H NMR and LCMS. While product was not observed by NMR analysis, LCMS showed a mass ion corresponding to the desired 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, Cu(II)-complex formed after the transmetalation and ligand exchange must be oxidized 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 for which reason the reaction mixtures were sparged with air prior to heating. Further to the requirement of oxidant in the reaction mixture, the Chan-Lam coupling was commonly performed at ambient temperature. Considering that, the reaction was attempted with reduced temperatures compared to the initial 115 °C (Table 2).

These modifications led to 43% RCC to [^{18}F]**17** when the reaction was performed at 85 °C (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 ligand, 11% RCC was observed (entry 6). Reducing reaction temperature to 70 or 40 °C (entries 7 and 9) resulted in reduced RCC 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 4M HCl at 85 °C for 10 min with 90% RCC.

Table 2 Optimisation of 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	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	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 variation of ca. 5 °C was observed. [b] Identity of product could not be determined.

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

Encouraged by the reproducibility of the method we next sought to translate radiosynthesis of 4-[^{18}F]**2** onto an automated synthesizer. 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 to 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 the semipreparative purification. The concentration of non-radioactive 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 optimized the synthesis of unlabelled reference compound **2** (ADAM) and obtained **2** with an overall yield higher than that previously reported. We have successfully optimized 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 using copper mediated nucleophilic fluorination of arenes. As a proof-of-principle we have also demonstrated preparation of 4-[^{18}F]**2** on the automated radiosynthesizer using our optimized reaction conditions. This represents an improvement over the pre-existing radiolabelling methods, which use bromo- or trimethyl ammonium precursors **7** or **8**, respectively and in our hands proved challenging. Further efforts in translating this method to GMP-compliant platform are underway in our laboratory.

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General techniques: 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 method on Thermo Dionex 3000 HPLC system. Preparative chromatographic separations were performed on Material Harvest silica gel 60 (35-75 μm) and reactions followed by TLC analysis using Sigma-Aldrich silica gel 60 plates (2-25 μm) with fluorescent indicator (254 nm) and visualized with UV or potassium permanganate. ^{1}H 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 shift in ppm is quoted relative to residual solvent signals calibrated as follows: **CDCl$_3$** δ_H (C*H*Cl$_3$) = 7.26 ppm, δ_C = 77.2 ppm. Multiplicities in the ^{1}H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintet, m = multiplet, b = 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 Knauer variable wavelength detector and an Eberline radiation detector. Analytical HPLC samples were analyzed by ThermoFisher Scientific Dionex 3000 HPLC system equipped with UV multi-wavelength detector and Bioscan standard radiation detector. The calculation of the RCC was performed as follows: for manual reactions for which radioTLC or the analytical HPLC was used, the RCC represented 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 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.

Procedures

2-((4-Fluoro-2-nitrophenyl)thio)-*N*,*N*-dimethylbenzamide (11). 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 (500 mg, 2.27 mmol, 1 eq) and anhydrous 1-methyl-2-

pyrrolidinone (19 mL) was added and brown solution was treated with triethylamine (2.5 mL, 1.80 g, 18.2 mmol, 8 eq, d=0.726) in one portion and then tris(dibenzylideneacetone)dipalladium(0) (62 mg, 0.07 mmol, 0.03 eq) was added followed by 1,1´-diphenylphosphinoferrocene (151 mg, 0.27 mmol, 0.12 eq) and the resulting brown heterogeneous mixture was sparged with nitrogen over 40 min. After this time thiosalicylic acid (2.8 g, 18.2 mmol, 8 eq) was added in a single portion and brown mixture allowed to heat (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) and the two layers were well shaken and separated. The aqueous phase was extracted with EtOAc (2x80 mL). The combined organic extracts were washed with H_2O (5x80 mL), brine (1x80 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude oily residue which was used without purification for the next step (665 mg, 2.3 mmol, quant.).

To the crude residue (665 mg, 2.3 mmol, 1 eq) anhydrous tetrahydrofuran (42 mL) was added and the mixture was allowed to cool to 0 °C (the ice bath) and it was then treated with dimethylamine hydrochloride salt (203 mg, 2.5 mmol, 1.1 eq). Next, 1-hydroxybenzonitrile (392 mg, 86% pure, 2.5 mmol, 1.1 eq) was added followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC, 870 mg, 4.54 mmol, 2 eq) and finally triethylamine (1.3 mL, 917 mg, 9.08 mmol, 4 eq, 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) and filtered through a celite pad (using a Hirsch funnel) and the filter cake was washed with EtOAc (2x80 mL). The combined filtrates were washed with 1M aq. HCl (2x80 mL), H_2O (2x80 mL), brine (1x80 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give brown oily residue which was purified by column chromatography on a silica gel column (eluting with gradient 100% CH_2Cl_2 to 5% EtOAc in CH_2Cl_2) to afford title compound (502.6 mg, 1.57 mmol, 69%) as pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94-7.86 (m, 1H), 7.62-7.37 (m, 4H), 7.18-7.08 (m, 1H), 7.00-6.90 (m, 1H), 3.04 (s, 3H), 2.85 (s, 3H) ppm. The data were in complete agreement with those previously published.[13,23]

2-((4-Bromo-2-nitrophenyl)thio)-*N*,*N*-dimethylbenzamide (12). 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 (500 mg, 1.77 mmol, 1 eq) and anhydrous 1-methyl-2-pyrrolidinone (15 mL) was added and brown solution was treated with triethylamine (2.0 mL, 1.44 g, 14.2 mmol, 8 eq, d=0.726) in one portion and then tris(dibenzylideneacetone)dipalladium(0) (49 mg, 0.05 mmol, 0.03 eq) was added followed by 1,1´-diphenylphosphinoferrocene (118 mg, 0.21 mmol, 0.12 eq) and the resulting brown heterogeneous mixture was sparged with nitrogen over 30 min. After this time thiosalicylic acid (2.2 g, 14.2 mmol, 8 eq) was added in a single portion and brown mixture allowed to heat (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) and the two layers were well shaken and separated. The aqueous phase was extracted with EtOAc (2x80 mL). The combined organic extracts were washed with H_2O (5x60 mL), brine (1x60 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude oily residue which was used without purification for the next step (630 mg, 1.8 mmol, quant.).

To the crude residue (630 mg, 1.8 mmol, 1 eq) anhydrous tetrahydrofuran (33 mL) was added and the mixture was allowed to cool to 0 °C (the ice bath) and it was then treated with dimethylamine hydrochloride salt (160 mg, 1.96 mmol, 1.1 eq). Next, 1-hydroxybenzonitrile (308 mg, 86% pure, 1.96 mmol, 1.1 eq) was added followed by EDC (682 mg, 3.56 mmol, 2 eq) and finally triethylamine (1.0 mL, 719 mg, 7.12 mmol, 4 eq, 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) and filtered through a celite pad (using a Hirsch funnel) and the filter cake was washed with EtOAc (2x60 mL). The combined filtrates were washed with 1M aq. HCl (2x60 mL), H_2O (2x80 mL), brine (1x80 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give brown oily residue which was purified by column chromatography on a silica gel column (eluting with gradient 100% CH_2Cl_2 to 10% EtOAc in CH_2Cl_2) to afford title compound (673 mg, 1.76 mmol, 99%) as pale yellow oil.

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

MS (ES+) *m/z* 381 and 383 $(M + H)^+$.

HRMS (ESI) *m/z* calcd. for $C_{15}H_{14}BrN_2O_3S$: 380.9903; found: 380.9906. The data were 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 nitrogen atmosphere one neck round bottom flask was charged with 2-((4-fluoro-2-nitrophenyl)thio)-*N*,*N*-dimethylbenzamide (502 mg, 1.57 mmol, 1 eq) and anhydrous tetrahydrofuran (8.7 mL) was added and the yellow solution was allowed to cool to 0 °C (the ice bath) and borane tetrahydrofuran complex (4.7 mL, 4.71 mmol, 3 eq, c=1M) was added dropwise over 1 min and the yellow homogeneous mixture was allowed to heat (oil bath temperature 80 °C) and stir under nitrogen for 2 h. After this time the crude mixture was allowed to cool to ambient temperature and then further to 0 °C (the ice bath) and it was then quenched with 1M aq. HCl which was added until pH of the mixture reached 1. The crude mixture was concentrated *in vacuo* and then diluted with H_2O (15 mL) and the mixture allowed to stand at ambient temperature for 21 h. After this time the mixture was further allowed to heat (oil bath temperature 100 °C) for 1.5 h. Once mixture cooled to ambient temperature saturated aq. $NaHCO_3$ was added to adjust pH to 8 and the mixture was then extracted with CH_2Cl_2 (3x50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give crude mixture as yellow oil which was purified by chromatography on a silica gel column (eluting with gradient 20% to 80% EtOAc in petrol) to afford the title compound (284 mg, 0.93 mmol, 59%) as pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (dm, *J* = 8.4 Hz, 1H), 7.66 (bd, *J* = 7.4 Hz, 1H), 7.58-7.46 (m, 2H), 7.35 (bt, *J* = 7.4 Hz, 1H), 7.12-7.03 (m, 1H), 6.74-6.65 (m, 1H), 3.54 (bs, 2H), 2.19 (bd, *J* = 1.5 Hz, 6H) ppm.

MS (ES+) *m/z* 307 $(M + H)^+$.

HRMS (ESI) *m/z* 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 nitrogen atmosphere one neck round bottom flask was charged with 2-((4-bromo-2-nitrophenyl)thio)-*N*,*N*-dimethylbenzamide (609 mg, 1.6 mmol, 1 eq) and anhydrous tetrahydrofuran (9.0 mL) was added and the yellow solution was allowed to cool to 0 °C (the ice bath) and borane tetrahydrofuran complex (4.8 mL, 4.8 mmol, 3 eq, c=1M) was added dropwise over 1 min and the yellow homogeneous mixture was allowed to heat (oil bath temperature 80 °C) and stir under nitrogen for 2 h. After this time the crude mixture was allowed to cool to ambient temperature and then further to 0 °C (the ice bath) and it was then quenched with 1M aq. HCl which was added until pH of the mixture reached 1. The crude mixture was concentrated *in vacuo* and then diluted with H_2O (15 mL) and the mixture allowed to stand at ambient temperature for 40 h. After this time the mixture was further allowed to heat (oil bath temperature 110 °C) for 1 h. Once mixture cooled to ambient temperature saturated aq. $NaHCO_3$ was added to adjust pH to 8 and the mixture was then extracted with CH_2Cl_2 (3x35 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give crude mixture as yellow oil which was purified by chromatography on a silica gel column (eluting with gradient 20% EtOAc in petrol to 100% EtOAc) to afford the title compound (242 mg, 0.66 mmol, 41%) as pale yellow oil.

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

MS (ES+) *m/z* 367 and 369 $(M + H)^+$.

HRMS (ESI) *m/z* calcd. for $C_{15}H_{16}BrN_2O_2S$: 367.0110; found: 367.0114. The data were 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 (bd, *J* = 2.2 Hz, 1H), 7.77 (dd, *J* = 7.5, 1.7 Hz, 1H), 3.65-3.47 (m, 3H), 7.42 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.37 (d, *J* = 8.7 Hz, 1H), 4.19 (s, 2H), 2.60 (s, 6H) ppm.

MS (ES+) *m/z* 398 and 400 $(M + NH_4)^+$.

HRMS (ESI) *m/z* calcd. for $C_{15}H_{22}BBrN_3O_2S$: 398.0704; found: 398.0702. The data were in complete agreement with those previously published.[23]

1-(2-((4-Bromo-2-nitrophenyl)thio)phenyl)-*N*,*N*-dimethylmethanamine (7). At ambient temperature under nitrogen atmosphere one neck round bottom flask was charged with 1-(2-((4-bromo-2-nitrophenyl)thio)phenyl)-*N*,*N*-dimethylmethanamine borane complex (167 mg, 0.44 mmol, 1 eq) and hydrochloride solution in methanol (3.5 mL, c=1.25M) was added and the resulting yellow homogeneous mixture was allowed to heat (oil bath temperature 90 °C) and stir 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 (3x25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give 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 nitrogen atmosphere one neck flask was charged with 1-(2-((4-fluoro-2-nitrophenyl)thio)phenyl)-*N*,*N*-dimethylmethanamine (284 mg, 0.93 mmol, 1 eq) and ethanol (12.4 mL) was added and the bright yellow solution was further treated with tin(II)chloride dihydrate (2.1 g, 9.3 mmol, 10 eq) in one portion and the heterogeneous mixture was allowed to heat (oil bath temperature 80 °C) and stir 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 oily residue which was allowed to cool to 0 °C (the 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 (2x90 mL). The combined organic extracts were washed with brine (1x90 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give 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* calcd. for $C_{15}H_{18}FN_2S$: 277.1169; found: 277.1171.

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

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

5-Bromo-2-((2-((dimethylamino)methyl)phenyl)thio)aniline (16). At ambient temperature under nitrogen atmosphere one neck flask was charged with 1-(2-((4-bromo-2-nitrophenyl)thio)phenyl)-*N*,*N*-dimethylmethanamine (75 mg, 0.20 mmol, 1 eq) and ethanol (2.7 mL) was added and the bright yellow solution was further treated with tin(II)chloride dihydrate (461 mg, 2.0 mmol, 10 eq) in one portion and the heterogeneous mixture was allowed to heat (oil bath temperature 80 °C) and stir under nitrogen over 2 h. After this time the mixture was allowed to cool to ambient temperature and then concentrated *in vacuo* to give oily residue which was allowed to cool to 0 °C (the 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 (2x25 mL). The combined organic extracts were washed with brine (1x20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give 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 and 339 $(M + H)^+$.

HRMS (ESI) *m/z* calcd. for $C_{15}H_{18}BrN_2S$: 337.0369; found: 337.0371. *Note*: For the purposes of material storage **16** was converted to **16**·HCl, to give crystalline solid.

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

***tert*-Butyl (2-((2-((dimethylamino)methyl)phenyl)thio)-5-fluorophenyl)carbamate (17)**. At ambient temperature under nitrogen atmosphere one neck flask was charged with 2-((2-((dimethylamino)methyl)phenyl)thio)-5-fluoroaniline (50.5 mg, 0.18 mmol, 1 eq) and anhydrous tetrahydrofuran (0.9 mL) was added and pale yellow solution was treated with 4-dimethylaminopyridine (2.2 mg, 0.02 mmol, 0.1 eq) in one portion followed by di-*tert*-butyldicarbonate (120 mg, 0.55 mmol, 3 eq) and the brown heterogeneous mixture was allowed to heat (oil bath temperature 40 °C) and stir 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) and treated with lithium bromide (49 mg, 0.57 mmol, 3.1 eq) and the resulting brown heterogeneous mixture was allowed to heat (oil bath temperature 65 °C) and stir under nitrogen for 8.5 h. After this time the mixture was allowed to cool to ambient temperature and then concentrated to give crude mixture which was purified by the chromatography on a silica gel column (eluting with gradient 20% to 40% EtOAc in petrol with 0.1% Et_3N) to afford the title compound (52.5 mg, 0.14 mmol, 76%) as pale yellow oil.

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

^{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, 2C), 28.4 (3, 3C) ppm.

MS (ES+) *m/z* 377 $(M + H)^+$.

HRMS (ESI) *m/z* 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 nitrogen atmosphere one neck flask was charged with 5-bromo-2-((2-((dimethylamino)methyl)phenyl)thio)aniline (67 mg, 0.2 mmol, 1 eq) and anhydrous tetrahydrofuran (1.0 mL) was added and pale yellow solution was treated with 4-dimethylaminopyridine (2.4 mg, 0.02 mmol, 0.1 eq) in one portion followed by di-*tert*-butyldicarbonate (130 mg, 0.60 mmol, 3 eq) and the brown heterogeneous mixture was allowed to heat (oil bath temperature 40 °C) and stir 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 eq) and the resulting brown heterogeneous mixture was allowed to heat (oil bath temperature 65 °C) and stir under nitrogen for 10 h. After this time the mixture was allowed to cool to ambient temperature and then concentrated to give crude mixture which was purified by the chromatography on a silica gel column (eluting with gradient 20% to 40% EtOAc in petrol with 0.1% Et_3N) to afford the title compound (83.4 mg, 0.19 mmol, 96%) as pale yellow oil.

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

MS (ES+) *m/z* 437 and 439 $(M + H)^+$.

HRMS (ESI) *m/z* 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 nitrogen atmosphere one neck flask was charged with *tert*-butyl (5-bromo-2-((2-((dimethylamino)methyl)phenyl)thio)phenyl)carbamate (93 mg, 0.21 mmol, 1 eq) and 1,4-dioxane (6.8 mL) was added and colourless solution was treated with potassium acetate (63 mg, 0.64 mmol, 3 eq) followed by [1,1´-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (31 mg, 0.04 mmol, 0.2 eq) and 1,1´-bis(diphenylphosphino)ferrocene (47 mg, 0.85 mmol, 0.4 eq) and the resulting orange coloured mixture was sparged with nitrogen for 1 h. After this time bis(pinacolato)diboron (324 mg, 1.28 mmol, 6 eq) was added and the resulting brown heterogeneous mixture was allowed to heat (oil bath temperature 100 °C) and stir under nitrogen for 23.5 h. After this time 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 (2x100 mL). The combined organic extracts were washed with H_2O (3x100 mL), brine (1x100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude mixture as brown oily residue. The residue was purified by chromatography on a silica gel column (eluting with 20% to 40% EtOAc in petrol with 0.1% Et_3N) to afford the title compound (90.5 mg, 0.19 mmol, 87%) as pale yellow oil.

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

^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9 (0), 139.8 (0), 137.84 (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, 2C), 28.5 (3, 2C), 25.2 (3, 2C), 25.1 (3, 3C) ppm. Carbon attached to boron was not observed.

MS (ES+) *m/z* 485 $(M + H)^+$.

HRMS (ESI) *m/z* 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-yl)phenyl)carbamate hydrochloric salt (3A·HCl)**. At ambient temperature under nitrogen atmosphere 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 eq) and methanol (2.3 mL) was added and brown solution was treated with hydrogen chloride solution in methanol (0.31 mL, 0.39 mmol, 1 eq, c=1.25M) dropwise over 1 min and it was allowed to to stir 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, 1H), 8.25 (d, *J* = 1.0 Hz, 1H), 8.21 (bd, *J* = 6.6 Hz, 1H), 7.46 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.48-7.41 (m, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.14 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.09 (d, *J* = 7.8 Hz, 1H), 6.89 (bs, 1H), 4.40 (d, *J* = 3.4 Hz, 2H), 2.77 (d, *J* = 2.8 Hz, 6H), 1.48 (s, 9H), 1.33 (s, 12H) ppm.

4-Chloro-*N*,*N*-dimethyl-3-nitroaniline (21). At ambient temperature under nitrogen atmosphere one neck flask was charged with 40chloro-3-nitroaniline (172 mg, 1 mmol, 1 eq) and anhydrous *N*,*N*´-dimethylformamide (20 mL) was added and brown solution was treated with potassium carbonate (3.6 g, 26 mmol, 26 eq) and finally methyliodide (0.75 mL, 1.7 g, 12 mmol, 12 eq, d=2.28) was added dropwise over 1 min and it was allowed to heat (oil bath temperature 120 °C) for 24 h. After this time the crude mixture was allowed to cool to ambient temperature and it was then poured into H_2O (50 mL) and diluted with CH_2Cl_2 (40 mL) and the two layers were well shaken and separated. The aqueous phase was extracted with CH_2Cl_2 (2x40 mL). The combined organic extracts were washed with H_2O (5x30 mL), brine (1x40 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude mixture as oily residue. The crude reside 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 pale yellow oil.

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

2-((4-Amino-2-nitrophenyl)thio)benzoic acid (22). At ambient temperature under nitrogen atmosphere one neck flask was charged with 4-chloro -3-nitroaniline (1.53 g, 8.9 mmol, 1 eq) and anhydrous *N*,*N*´-dimethylformamide (33 mL) was added and the brown solution was treated with potassium carbonate (2.7 g, 19.5 mmol, 2.2 eq) followed by thiosalycilic acid (1.4 g, 8.9 mmol, 1 eq) and finally copper(I)bromide (1.3 g, 8.9 mmol, 1 eq) and the resulting black heterogeneous mixture was allowed to heat (oil bath temperature 120 °C) and stir for 24 h. After this time the mixture was allowed to cool to ambient temperature and then 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 2M aq. HCl and the aqueous phase was extracted with EtOAc (3x150 mL). The combined organic extracts were washed with H_2O (5x100 mL), brine (1x100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude mixture as an orange solid residue. The residue was purified by chromatography on a silica gel column (eluting with 20% CH_2Cl_2 in EtOAc). Obtained material was insufficiently pure so 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%). Material 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 nitrogen atmosphere one neck flask was charged with 4-chloro-*N*,*N*-dimethyl-3-nitroaniline (112 mg, 0.56 mmol, 1 eq) and anhydrous *N*,*N*´-dimethylformamide (2 mL) was added and the orange solution was treated with potassium carbonate (169 mg, 1.22 mmol, 2.2 eq) followed by thiosalycilic acid (86 mg, 0.56 mmol, 1 eq) and finally copper(I)bromide (80 mg, 0.56 mmol, 1 eq) and the resulting black heterogeneous mixture was allowed to heat (oil bath temperature 120 °C) and stir for 24.5 h. After this time green coloured mixture was allowed to cool to ambient temperature and then diluted with ice cold H_2O (25 mL) and then filtered (using a Hirsch funnel). The pH of the filtrate was adjusted to 2 by 2M aq. HCl and the aqueous phase was extracted with EtOAc (3x40 mL). The combined organic extracts were washed with H_2O (5x25 mL), brine (1x30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude mixture as 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 eq) anhydrous tetrahydrofuran (6.0 mL) was added and the mixture was allowed to cool to 0 °C (the ice bath) and it was then treated with dimethylamine hydrochloride salt (31 mg, 0.38 mmol, 1.1 eq). Next, 1-hydroxybenzonitrile (60 mg, 86% pure, 0.38 mmol, 1.1 eq) was added followed by EDC (132 mg, 0.69 mmol, 2 eq) and finally triethylamine (0.19 mL, 139 mg, 1.38 mmol, 4 eq, 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) and filtered through a celite pad (using a Hirsch funnel) and the filter cake was washed with EtOAc (2x20 mL). The combined filtrates were washed with 1M aq. HCl (2x20 mL), H_2O (2x20 mL), brine (1x25 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give brown oily residue which was purified by column chromatography on a silica gel column (eluting with gradient 100% CH_2Cl_2 to 90% EtOAc in CH_2Cl_2) to afford title compound (52.9 mg, 0.17 mmol, 48%) as pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54-7.29 (m, 5H), 6.90 (d, *J* = 8.7 Hz, 1H), 6.74 (dd, *J* = 8.5, 2.5 Hz, 1H), 3.05 (s, 3H), 2.85 (s, 3H) ppm. The data were 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 eq) anhydrous tetrahydrofuran (7.4 mL) was added and the mixture was allowed to cool to 0 °C (the ice bath) and it was then treated with

dimethylamine hydrochloride salt (36.1 mg, 0.44 mmol, 1.1 eq). Next, 1-hydroxybenzonitrile (70 mg, 86% pure, 0.44 mmol, 1.1 eq) was added followed by EDC (154 mg, 0.8 mmol, 2 eq) and finally triethylamine (0.22 mL, 163 mg, 1.6 mmol, 4 eq, 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) and filtered through a celite pad (using a Hirsch funnel) and the filter cake was washed with EtOAc (3x10 mL). The combined filtrates were washed with 1M aq. HCl (2x20 mL), H_2O (2x20 mL), brine (1x20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give brown oily residue which was purified by column chromatography on a silica gel column (eluting with gradient 100% CH_2Cl_2 to 10% EtOAc in CH_2Cl_2) to afford title compound (42 mg, 0.12 mmol, 30%) as pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.27 (m, 5H), 7.03 (d, *J* = 9.0 Hz, 1H), 6.77 (dd, *J* = 9.0, 2.9 Hz, 1H), 3.06 (s, 3H), 2.98 (s, 6H), 2.86 (s, 3H) ppm. The data were in complete agreement to those previously published.[19]

2-((4-(Dimethylamino)-2-nitrophenyl)thio)-*N*,*N*-dimethylbenzamide (25). At ambient temperature under nitrogen atmosphere one neck flask was charged with 2-((4-amino-2-nitrophenyl)thio)-*N*,*N*-dimethylbenzamide (52 mg, 0.16 mmol, 1 eq) and anhydrous *N*,*N*′-dimethylformamide (3.2 mL) was added and the mixture was treated with potassium carbonate (589 mg, 4.26 mmol, 26 eq) followed by methyliodide (0.12 mL, 279 mg, 1.97 mmol, 12 eq, d=2.28) and the resulting red heterogeneous mixture was allowed to heat (oil bath temperature 120 °C) and stir 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 (2x15 mL). The combined organic extracts were washed with H_2O (5x10 mL), brine (1x15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude mixture which was purified by chromatography on a silica gel column (eluting with a gradient 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 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 (8.8 mg, 0.018 mmol, 1 eq) and Kryptofix (13.7 mg, 0.036 mmol, 2 eq) was added followed by potassium fluoride (spray dried, 2 mg, 0.036 mmol, 2 eq) and anhydrous *N*,*N*′-dimethylformamide (0.5 mL) and brown heterogeneous reaction mixture was allowed to heat (oil bath temperature 110 °C) and stir 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 (2x10 mL) and the combined organic extracts were washed with H_2O (5x8 mL), brine (1x10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude mixture as 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 ion was produced by the $^{18}O(p,n)^{18}F$ nuclear reaction using a GE PETtrace cyclotron (GE Healthcare, Sweden). Amount of 0.7 GBq [^{18}F]fluoride in 2 mL [^{18}O]H_2O was passed through a QMA cartridge (Waters, Sep-pak Light in carbonate form). The trapped [^{18}F]fluoride was eluted with 0.8 mL eluent containing 12 mg Kryptofix 222 (K_{222}) and 2.4 mg K_2CO_3 and dissolved in H_2O/MeCN (1/4, v/v) into 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 2x1 mL of anhydrous MeCN. The complex was then re-dissolved in anhydrous MeCN to reach an activity concentration of 3 MBq/µL. From this 20 µL was taken and added to a 1.5 mL reaction vial containing a magnetic stirrer bar, and 6 mg (0.02 mmol) of **26** (precursor) dissolved in 300 µL dimethylacetamide in the presence of 14 mg (0.02 mmol) $Cu(OTf)_2(Py)_4$. 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 UltraCore 2.5 Å, Super C18, 50x4.6 mm column (eluting with a gradient 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 ion was produced by the $^{18}O(p,n)^{18}F$ nuclear reaction using a GE PETtrace cyclotron (GE Healthcare, Sweden). Amount of 0.7-2 GBq [^{18}F]fluoride in 2 mL [^{18}O]H_2O was passed through a QMA cartridge (Waters, Sep-pak Light in carbonate form). The trapped [^{18}F]fluoride was eluted with 0.8 mL eluent containing 12 mg Kryptofix 222 (K_{222}) and 2.4 mg K_2CO_3 and dissolved in H_2O/MeCN (1/4, v/v) into 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 2x1 mL anhydrous MeCN. The complex was then re-dissolved in anhydrous MeCN to reach an activity concentration of 3 MBq/µL. From this 20 µL was taken and added to a 1.5 mL reaction vial containing a magnetic stirrer bar, and 5-10 mg (0.01-0.02 mmol) **3A**·HCl or **3A** (precursor) dissolved in 300 µL dimethylacetamide in the presence of 7-14 mg (0.01-0.02 mmol) $Cu(OTf)_2(Py)_4$. 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 ion was produced by the $^{18}O(p,n)^{18}F$ nuclear reaction using a GE PETtrace cyclotron (GE Healthcare, Sweden). Amount of 0.7-2 GBq [^{18}F]fluoride in 2 mL [^{18}O]H_2O was passed through a QMA cartridge (Waters, Sep-pak Light in carbonate form). The trapped [^{18}F]fluoride was eluted with 0.8 mL eluent containing 12 mg Kryptofix 222 (K_{222}) and 2.4 mg K_2CO_3 and dissolved in H_2O/MeCN (1/4, v/v) into 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 2x1 mL anhydrous MeCN. The complex was then re-dissolved in anhydrous MeCN to reach an activity concentration of 3 MBq/µL. From this 20 µL was taken and added to a 1.5 mL reaction vial containing a magnetic stirrer bar, and 5 mg (0.01 mmol) **3A** (precursor) dissolved in 300 µL dimethylacetamide in the presence of 7 mg (0.01 mmol) $Cu(OTf)_2(Py)_4$. 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 60 µL of 4M HCl and temperature maintained at 85 °C for another 10 min, which was followed by neutralization with 60 µL 4M NaOH. 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 the HPLC. For the latter, the crude mixture was diluted with 2 equivalents of H_2O 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 UtraCore 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 ion was produced by the $^{18}O(p,n)^{18}F$ nuclear reaction using a GE PETtrace cyclotron (GE Healthcare, Sweden) and the amount of 5.09 GBq of [^{18}F]fluoride in 2.5 mL [^{18}O]H_2O was transferred into the receiving flask of the FXFN module using the stream of N_2. The module was assembled as follows:

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

V2: 2 mL MeCN

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

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

V5: 0.3 mL 4M aq. HCl

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

SPE flask: 30 mL H_2O

Semipreparative HPLC: 100 mM NH_4CO_2H (75%) and MeCN (25%) at 4 mL/min; column: ACE C18, 5 µm, 10x100 mm.

The 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 the flow of He and under vacuum using MeCN from V2. Prior to the addition of Cu-source (from V3) and **3A** (from V4) to the reactor each solution was sparged with air, by bubbling air through the solutions using and external syringe and Vygon tubing. Cu-source was added first and mixture allowed to heat at 85 °C for 1 min after which time the precursor was added and heating continued for further 9 min. From V5 acid was added and heating continued for another 10 min and the mixture was then allowed to cool to 50 °C and then neutralized with base/eluent mixture from V6. The crude mixture was injected onto the semipreparative column and the resulting chromatogram showed 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 non-radioactive ADAM in the sample was determined from the calibration curve.

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Supporting Information

YES

Primary Data

NO

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