A Gas Phase Route to $[^{18}\text{F}]{\text{fluoroform}}$ with Limited Molar Activity Dilution

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Positron emission tomography (PET) is an increasingly important molecular imaging modality for drug development1–2, biomedical research3, and medical diagnosis4–6. The value of PET for imaging molecular targets in living animal7 and human8 subjects derives from the development of biochemically specific radiotracers (i.e., radiotracers that are each capable of imaging a single targeted protein, such as a low density neuroreceptor). One of the most useful and widely used radionuclides for labeling such radiotracers is the short-lived positron-emitter, fluorine-18 ($\beta^+ = 97\%$, $t_{1/2} = 109.8\text{ min}$)9,10. Nowadays, fluorine-18 can be produced in very high activities (~500 GBq) as aqueous $[^{18}\text{F}]{\text{fluoride}}$ ion with moderate to high molar activity ($A_m$; where $A_m$ is defined11 as the ratio of the radioactivity of a compound to its mass at a specified time), typically in the 40–400 GBq/μmol range.

Therefore, there has been a surge in the development of methods for the late-stage labeling of PET radiotracers with $[^{18}\text{F}]{\text{fluoride}}$ ion. However, these methods have been confined mostly to labeling monofluorocarbon (C–F) groups12,13.

Substitution of a methyl, chloro, or another substituent in a drug-like molecule with a trifluoromethyl (CF$_3$) group can lead to better pharmaceutical properties and improved metabolic stability14–17. Consequently, a CF$_3$ group regularly appears in many new drugs and drug candidates18–22. Prominent examples include fluoxetine (1; Prozac), celecoxib (2; Celebrex), and leflunomide (3; Arava) (Fig. 1). Because of the role of PET in drug development and a frequent requirement to label drugs and new radiotracers with a positron-emitter, academic groups have pursued the development of methods for labeling CF$_3$ groups with fluorine-1823,24, with the most recent methods being based on generation of $[^{18}\text{F}]{\text{CuCF}}_3$ from $[^{18}\text{F}]{\text{fluoride}}$ ion either directly or via synthesis of $[^{18}\text{F}]{\text{fluoroform}}$ (Fig. 2)25–29. To date, these solution-phase methods of $[^{18}\text{F}]{\text{fluoroform}}$ and $[^{18}\text{F}]{\text{CuCF}}_3$ synthesis have delivered at best only very low to moderate $A_m$ (0.1–32 GBq/μmol), likely due to $[^{18}\text{F}]{\text{fluoride}}$ ion dilution with carrier fluoride ion originating from the difluoro-precursor [difluorohalomethane, methylchlorodifluoroacetate, or (difluoromethyl)(mesityl)(phenyl)-sulfonium salt] under the reaction conditions (Fig. 2). Generally, however, the molar activities that are needed for radiotracers to be used for PET imaging of low-density protein targets are at the high end of the achievable range or ideally even higher. Here we explored the radiosynthesis of $[^{18}\text{F}]{\text{fluoroform}}$ according to a different strategy involving initial installation of the fluorine-18 followed by subsequent gas phase difluorination. We find that carrier dilution with this method is limited to about 3-fold. We
further show that the [18F]fluoroform so produced is useful for preparing a wide range of 18F-trifluoromethylated compounds through diverse radiochemical methods30–32.

We recently reported a robust and efficient method for the radiosynthesis of [11C]fluoroform at very high $A_m$, based on gas phase fluorination of cyclotron-produced [11C]methane with heated cobaltIII fluoride (CoF3)33. We noted that CoF3 has also been used to convert fluoromethane into fluoroform. Therefore, to implement our new strategy for the radiosynthesis of [18F]fluoroform34, we aimed to convert cyclotron-produced [18F]fluoride ion into [18F]fluoromethane for subsequent difluorination over heated CoF3 (Fig. 2). We constructed the apparatus depicted in Fig. 3 for this purpose, except that the indicated gas chromatograph (option B) was introduced in the final stage of our study.

**Figure 1.** Examples of prominent drugs containing trifluoromethyl groups.

**Prior solution phase methods**

Huiban et al. (2013)

\[ ^{18}\text{F}^- \rightarrow \text{ClC}_{2}\text{F}_{5}\text{CO}_{2}\text{Me} \]

\[ \text{CuI, TMEDA} \]

\[ K_2\text{CO}_3, \text{crypt-222} \]

\[ \text{DMF, 150 }^\circ\text{C, 20 min} \]

Ruhl et al. (2014)

\[ ^{18}\text{F}^- \rightarrow \text{CHF}_2 \]

\[ i) \text{CsF, crypt-222} \]

\[ \text{DMF, RT, 10 min} \]

\[ ii) \text{CuBr, DIPEA, 145 }^\circ\text{C, 10 min} \]

Ivashkin et al. (2014)

\[ ^{18}\text{F}^- \rightarrow \text{PhS}^+\text{(CHF}_2\text{)}\text{Mes} \]

\[ \text{TBA}^+, \text{PhCN} \]

van der Born et al. (2014)

\[ ^{18}\text{F}^- \rightarrow \text{CHF}_2 \]

\[ \text{CHF}_2\text{, } K_2\text{CO}_3, \text{crypt-222} \]

\[ \text{MeCN, RT, 10 min} \]

**New gas phase method**

\[ ^{18}\text{F}^- \rightarrow \text{CH}_{3}\text{OMs} \]

\[ \text{K}^+\text{-crypt-222} \]

\[ \text{CH}_3\text{, } ^{18}\text{F}^- \]

\[ \text{280 }^\circ\text{C} \]

\[ \text{CHF}_2\text{, } ^{18}\text{F}^- + 2\text{HF} + 4\text{CoF}_2 \]

**Figure 2.** Methods for the radiosynthesis of [18F]fluoroform or the derivative [18F]CuCF3. Prior methods generate [18F]fluoroform in solution from a difluoro precursor for use in situ or in another solvent. The new method reported here produces [18F]fluoroform in the gas phase from [18F]fluoromethane.
We explored several methods for producing [18F]fluoromethane from cyclotron-produced [18F]fluoride ion and found that the treatment of methyl mesylate with [18F]fluoride ion in DMSO gave an acceptable yield of [18F]fluoromethane (46 ± 18%, n = 140) after only 15 min. This volatile product (b.p. −78.4 °C) was readily released for collection on a trap of Porapak Q in liquid argon (−186 °C) by purging the reaction mixture with helium at low temperature (35 °C). A trap cooled in dry-ice/MeCN (−41 °C) was used to collect any vaporized non-radioactive organic contaminant before the entrapment of the [18F]fluoromethane (Option A). Trapped [18F]fluoromethane was released into a helium stream from the warmed Porapak Q trap, and subsequently passed through Sicapent and then over heated CoF3. The effluent from the CoF3 column was passed through a trap immersed in dry-ice/MeCN to trap any generated acidic species (e.g., potentially HF) and then into either cold ethanol (−72 °C) or DMF to trap the [18F]fluoroform (b.p. −82.1 °C). Pilot experiments confirmed the production of [18F]fluoroform from this process with the CoF3 column operating between 230 and 350 °C.

**Results**

**Production of [18F]fluoroform.** We found that initial conditioning of a newly installed CoF3 column by heating it once to 320 °C while sealed under helium resulted in optimal yields of [18F]fluoroform in subsequent use at lower temperatures. Conditioning of the column before a run and subsequent regeneration are described in Supplementary Information. The temperature-dependence of the conversion of [18F]fluoromethane into [18F]fluoroform was investigated with the flow of carrier helium set at 20 mL/min (Supplementary Figs S3 and S4). Only radioactivity trapped in cold (~−72 °C) ethanol was used to calculate the yield (the breakthrough of radioactivity into a subsequent trap was found to be very low: <2%). Moderate yields of [18F]fluoroform from [18F]fluoromethane were obtained between 280 and 350 °C, with 280 °C appearing optimal (Supplementary Figs S3 and S4).

A single heat-conditioned CoF3 column could be used for a series of [18F]fluoroform productions (Fig. 4). Yield increased appreciably after the first run and was well maintained over at least 12 subsequent runs. The average yield of [18F]fluoroform from [18F]fluoromethane was 35 ± 11% (n = 77) from six different CoF3 columns operated at least a dozen times each. HPLC showed that the only radioactive contaminant was occasionally a very low amount of unchanged [18F]fluoromethane (Supplementary Fig. S7). The six CoF3 columns produced [18F]fluoroform with 98 ± 3% purity (n = 77). This good re-usability implies that the CoF3 is not rapidly and completely decomposed to CoF2 and fluorine at 280 °C. The overall process for producing [18F]fluoroform from [18F]fluoride ion required 60 minutes from the end of a cyclotron irradiation and was thus much less than one half-life of fluorine-18.

**Investigation of carrier dilution in [18F]fluoroform synthesis.** Of major interest was the \( \text{A}_\text{m} \) value that could be achieved for the [18F]fluoroform that was produced from this method. To estimate \( \text{A}_\text{m} \), we converted the [18F]fluoroform into [18F]5 by treatment with benzophenone and t-BuOK in DMF. [18F]5 was obtained in quantitative yield. The accompanying carrier was measured with a radio-HPLC apparatus having an absorbance detector response at \( \lambda \approx 215 \) nm that was calibrated for the injected mass of 5. In parallel, we measured the \( \text{A}_\text{m} \) value of an 18F-labeled tracer ([18F]N-[5-((2,5-S)-2-methyl-4-(6-fluoropyridin-2-yloxy)piperidin-1-yl)methyl]thiazol-2-yl)acetamide; [18F]OGA-1), produced by nuclophilic substitution of an aryl nitro group with [18F]fluoride ion, in order to estimate the \( \text{A}_\text{m} \) value of the starting
cyclotron-produced [18F]fluoride ion. ([18F]OGA-1 was being produced in our laboratory for PET imaging of brain O-GlcNAcase)36. The $A_m$ value of [18F]OGA-1 was taken to be that of the [18F]fluoromethane produced from the same batch of [18F]fluoride ion i.e., we reasonably assumed that neither non-radioactive precursor (OGA-1 precursor or MeOMs) added appreciable carrier in the labeling reactions. The $A_m$ of [18F]fluoroform was found to be about 8.1−fold lower on average than that of [18F]OGA-1 produced from the same stock of [18F]fluoride ion when using the apparatus in Fig. 3 with Option A i.e., with no GC purification (Fig. 5A, Supplementary Table S1).

We considered that some of the lower $A_m$ of [18F]fluoroform relative to that of [18F]OGA-1 might be due to some generation of fluoromethane through pyrolysis and fluorination of low-level organic impurities in the [18F]fluoromethane that reach the CoF$_3$ column. To examine this possibility, we installed a small modular gas chromatograph into the hot-cell to purify the [18F]fluoromethane before entry into the CoF$_3$ column (Fig. 3, option B) and then several times compared the $A_m$ of [18F]fluoroform produced from the generated [18F]fluoroform with that of [18F]OGA-1 from the same batch of [18F]fluoride ion (Fig. 5A). We found that the dilution of $A_m$ was reduced on average from 8.1 to 2.8−fold when GC purification of [18F]fluoromethane was implemented.

From the $A_m$ values and measurements of radioactivity entering and leaving the CoF$_3$ column, we calculated that in the absence of GC purification the average number of moles of carrier fluoroform produced was 2.01 ± 1.56−fold greater than the number of moles of fluoromethane introduced into the CoF$_3$ column. When GC purification was used, this ratio became closer to unity (0.69 ± 0.41−fold) (Fig. 5B, Supplementary Table S4). The latter finding is consistent with our observation that recovery of radioactivity from the CoF$_3$ column was 34%, implying that the rest (66%) was retained on the CoF$_3$ column. The retained activity was not identified but is clearly not [18F]fluoroform or [18F]fluoroform because we had found earlier that no radioactivity adheres to the CoF$_3$ column in the conversion of [11C]methane into [11C]fluoroform33.

To explain our observations on carrier dilution and yield, and the radioactivity retained on the CoF$_3$ column, we postulate that there is exchange of $^{14}$F between [18F]fluoroform and the co-produced two equivalents of HF (Fig. 2), and that all the radioactive HF adheres to the CoF$_3$ column. No radioactivity was ever detected in the depicted HF trap of the apparatus, which is now regarded as redundant. According to our postulate, the yield of [18F]fluoroform from [18F]fluoromethane at equilibrium is expected to be 33% and the carrier dilution 3-fold, which within likely experimental errors, accords with our observations.

Figure 4. Dependence of [18F]fluoroform yield on run number for six different CoF$_3$ columns. Data are mean ± SD ($n = 6$).

Figure 5. (A) Dilution of $A_m$ for the conversion of [18F]fluoromethane into [18F]fluoroform without GC purification (Fig. 3, Option A) and with GC purification (Fig. 3, Option B). (B) Ratio of carrier amount of fluoromethane entering the CoF$_3$ column to that exiting as carrier fluoroform without GC purification and with GC purification.
Most of our runs to produce [18F]fluoroform were performed at varying periods up to several hours after the end of radionuclide production. To benchmark comparisons, all estimated $A_m$ values were decay-corrected to the end of radionuclide production. The maximal molar activity of the [18F]fluoride ion available to us was 336 GBq/µmol and on average was 150 ± 73 GBq/µmol ($n = 10$). We found that [18F]fluoroform could be produced with an $A_m$ up to 163 GBq/µmol with an average of 38 ± 35 GBq/µmol ($n = 20$).

**Trifluoromethylations with [18F]fluoroform.** Treatment of benzophenone (4) with [18F]fluoroform in DMF under basic conditions gave the [18F]2,2,2-trifluoro-1,1-diphenylethan-1-ol ([18F]5) almost quantitatively (Figs 6 and 7), as previously reported 26. This reaction was useful for molar activity estimations. Treatment of methyl benzoate (6) in the presence of t-BuOK with [18F]fluoroform in DMF at RT followed by treatment with acid gave [18F]trifluoroacetylbenzene ([18F]7) in high yield (75%) as a representative of an entirely new 18F-labeled chemotype (Figs 6 and 7).

**Cu(I)-mediated trifluoromethylations with [18F]fluoroform.** We tested the reactivity of the Cu(I) derivative of the [18F]fluoroform from the new method of radiosynthesis on several model substrates with various methods (Fig. 6). We first confirmed the known reactivity of [18F]CuCF$_3$ towards iodoarenes 27. Thus, 1,4-diiodobenzene gave [18F]4-trifluoromethyliodobenzene ([18F]9a), a potentially useful labelling synthon, in high yield (86 ± 12%) (Fig. 7) comparable to that obtained through the same reaction by van der Born et al. (73 ± 6%) 29. This method also gave a previously unknown labeled amino acid ([18F]9b) in moderate yield (53 ± 19%). Similarly, an [18F]-labeled pyrimidine, ([18F]9d), was readily obtained in almost quantitative yield. By use of an iodo precursor, we were able to label the drug leflunomide (3) in moderate yield (36 ± 3%), exceeding that reported by Ivashkin et al. (18%) for the same reaction 27. Finally, we demonstrated that we could label a new radioligand for PET imaging of TSPO ([18F]9c) from an iodo precursor in high non-optimized yield (63 ± 16%).

We also tested the reactivity of [18F]CuCF$_3$ towards arylboronic acids with many previously untested examples. Many substituted arylboronic acids gave the corresponding [18F]-labeled trifluoromethylarenes ([18F]9a, [18F]11a–11l) in excellent yields when treated with [18F]CuCF$_3$ for 2 minutes at room temperature. Our results demonstrated the tolerance of this method for CHO, OH, MeO, Ac, Me, and I substituents (Fig. 7). The very high
yield of $[^{18}F]9a$ from this method (82 ± 13%) was very similar to that which we obtained from an iodo precursor, and far exceeded that previously obtained by van der Born et al. from the same reaction (4 ± 2%)\(^2\)\(^9\). For other examples ($[^{18}F]11a$, $[^{18}F]11d$, $[^{18}F]11f$), our yields were very high (>91%) and in accord with those previously reported\(^2\)\(^9\). The more labile BrCH\(_2\) and AcO substituents were less well tolerated, giving moderate yields under non-optimized conditions. Nonetheless, these examples ($[^{18}F]11g$–$[^{18}F]11i$) show the potential for developing new and useful labeling synthons. The use of a boronic acid precursor gave $[^{18}F]5$-trifluoromethyluracil ($[^{18}F]11k$) in almost quantitative yield.

Figure 7. Yields (mean ± SD, n = 3) of $^{18}$F-labeled trifluoromethyl compounds from diverse substrate classes and $[^{18}F]$fluoroform or its copper(I) derivative measured with HPLC. Radiosynthesis methods are summarized in Fig. 6. Blue text indicates the reaction precursor class.
Finally, the treatment of commercially available ‘wet’ diazonium salts 12a–12e with [18F]CuCF3 gave [18F]11j, and [18F]Br–[18F]13d, respectively, in good to high yields (Fig. 7). The yield of [18F]11j (74 ± 9%) was comparable to that from the use of boronic acid as precursor (85 ± 13%). The yields of [18F]13a–[18F]13c exceeded 86% and compare well with the yields of these labeled compounds from the use of arylboronic acids or aryl iodides as precursors. This new method therefore appeared highly effective for the simple one-pot conversion of arylamines into [18F]trifluoromethylenes.

Discussion
[18F]fluoride ion was produced in useful yield and with limited carrier dilution from cyclotron-produced [18F]fluoride ion by passing [18F]fluoromethane over heated CoF3. Because our results indicate that carrier dilution is limited to about 3-fold in this new method of [18F]fluoride ion production, we expect that [18F]fluoride ion of even higher molar activity could be produced from sources of [18F]fluoride ion of higher molar activity in a directly proportional manner. It would therefore be interesting to see how this method performs with [18F]fluoride ion of much higher A_m as is typically available in some laboratories. A difluorocarbene intermediate has been construed to occur in other methods of [18F]fluoride ion or [18F]CuCF3 synthesis from difluoro precursors and to be a major source of carrier dilution. Prior methods of [18F]fluoride ion/[18F]CuCF3 synthesis may be capable of delivering higher molar activities than so far reported by using much higher levels of starting radioactivity and by limiting the amount of difluorocarbene formation. The radiochemical pathway in our new method for producing [18F]fluoride ion clearly avoids any possibility for carrier dilution from difluorocarbene formation. The radiosynthesis apparatus is considered amenable to automation and remote control to ensure radiation protection for personnel. With this method, the labeling of PET radiotracers at a trifluoromethyl group with usefully high A_m becomes possible. Although the overall yield of [18F]fluoride ion appears modest, the speed, broad scope, and generally high efficiency seen in the many examples of labeling reactions augurs well for useful application of this new method. This is especially so given that very high activities of [18F]fluoride ion can be produced on modern cyclotrons (> 400 GBq). With this method, we now envisage access to an enhanced range of useful and exciting radiotracers for PET based on adapting the known richly diverse chemistry of fluorofom47–49 and its derivatives51–53 for unprecedented 18F-labeling at trifluoromethyl groups. These radiotracers may include chemotypes never previously labeled with fluorine-18.

Materials and Methods
Sources of materials are detailed in Supplementary Information.

Synthesis of [18F]fluoride ion. The apparatus depicted in Fig. 3 was constructed, set-up, and operated as detailed in Supplementary Information. Transfers of radioactivity through the apparatus were monitored with PIN-diode detectors. [18F]fluoride ion was produced on a cyclotron (PETrace; GE) according to the \(^{18}\text{O(}p\text{n})^{18}\text{F}\) reaction by irradiating \(^{18}\text{O}\)-enriched water (3 mL, 98 atom %) with a beam of protons (16.5 MeV; 50 µA) for at least 45 min. [18F]fluoromethane was synthesized within a fully automated apparatus (TRACERLabTM FX2N; GE). Thus, [18F]fluoride ion (1.9–14.8 GBq) in \(^{18}\text{O}\)water (200–400 µL) and a solution (100 µL) containing K_2CO_3 (10 µmol) plus crypt-222 (20 µmol) were loaded into a glass vial. MeCN (2 mL) was added and the solvent was azotropically removed at 88 °C under a stream of nitrogen gas that was vented to vacuum. This step was repeated two more times. A solution of MeOMs (0.1 mmol, 8.5 µL) in anhydrous DMF (1 mL) was then added to the dried [18F]F–K_m–crypt-222 complex, sealed, and heated at 130 °C for 15 min. The reaction vial was then cooled to 35 °C. [18F]fluoromethane (b.p. –78.4 °C) was flushed out of the vial with nitrogen gas (20 mL/min) and into Porapak Q (80–100 mesh; 1 g) contained in a first U-shaped stainless-steel tube (0.069 in i.d.) cooled with liquid argon (–186 °C). The transfer generally required 5 min. The sealed trap was then removed from the cooling bath and measured for radioactivity at RT (20–26 °C) with a dose calibrator. The [18F]fluoromethane was then released into a stream of helium gas (20 mL/min) from the Porapak Q trap through Sicapent (phosphorus pentoxide) and then through a heated column (280 °C) of CoF_3 for a period of 7 to 10 min. The generated [18F]fluoride ion was passed through a trap cooled in dry-ice/McCN (–41 °C) and finally into a glass V-vial containing DMF (0.6–0.8 mL) that was cooled also in a dry-ice/McCN bath. A second U-shaped stainless-steel tube containing Porapak Q (80–100 mesh) was connected to the outlet of the V-shaped glass product vial to retain any breakthrough of radioactive material for measurement.

Trifluoromethylation reactions. Synthesis of [18F]2,2,2-trifluoro-1,1-diphenylethan-1-ol (18F)5). Benzenophene (4; 55 µmol, 9 mg) was put into a 1-mL glass vial with a solution of t-BuOK (0.3 M) in DMF (150 µL) and capped with a septum seal. [18F]fluoromethane in DMF (100–300 µL) was added to the vial, and the mixture was left to react at RT for 5 min.

Synthesis of [18F]trifluoroacetylbenzene (18F)7). 2-Methyl benzene (6; 50 µmol, 7 mg) was put into a 1-mL glass vial with t-BuOK DMF (0.3 M, 50 µL) and capped with a septum seal. [18F]fluoromethane in DMF (100–300 µL) was added, and the mixture was left at RT for 10 min. Hydrochloric acid (37%, 0.1 mL) was added and heated at 60 °C for 5 min. The mixture was quenched with acq. 0.1% TFA/McCN (1:1, v/v) solution and filtered through a PTFE syringe filter (0.2 µm pore size).

[18F]CuCF3 synthesis. CuBr (5 µmol, 0.7 mg) was added to 1-mL glass vial and moved to a glove box (dry nitrogen atmosphere). t-BuOK in DMF (0.3 M, 50 µL) was added to the vial, which was then septum-sealed and removed from the glove box. [18F]fluoromethane in DMF (50–300 µL) was added to the vial, mixed, and left at RT for 1 min. A solution of Et_3N-3HF in DMF (1.64% v/v, 5 mL) was then added. The mixture was mixed thoroughly and allowed to stay at RT for another minute before use in labeling reactions.
Syntheses of $[^{18}F]$trifluoromethylarenes from aryl iodides and $[^{18}F]$CuCF$_3$. Aryl iodide precursor (100 µmol) in DMF (150 µL) was added to a prepared vial of $[^{18}F]$CuCF$_3$ and shaken vigorously. The reaction mixture was heated at 130°C for 5 min, quenched with aq. 0.1% TFA/MeCN (1:1, v/v) solution, and finally filtered through a PTFE syringe filter (0.2 µm pore size).

Syntheses of $[^{18}F]$trifluoromethylarenes from arylboronic acids and $[^{18}F]$CuCF$_3$. Arylboronic acid precursor (50 µmol) in DMF (100 µL) was added to a prepared vial of $[^{18}F]$CuCF$_3$ and shaken vigorously. Air was passed from 10-mL syringe into the vial, and out through a vent needle. The reaction mixture was left at RT for 2 min, quenched with aq. 0.1% TFA/MeCN (1:1, v/v) solution, and finally filtered through a PTFE syringe filter (0.2 µm pore size).

Syntheses of $[^{18}F]$trifluoromethylarenes from aryl diazonium salts and $[^{18}F]$CuCF$_3$. Aryldiazonium salt precursor (50 µmol) in DMF (100 µL) was added to a prepared vial of $[^{18}F]$CuCF$_3$ and shaken vigorously. The reaction mixture was left at RT for 10 min, quenched with aq. 0.1% TFA/MeCN (1:1, v/v) solution, and finally filtered through a PTFE syringe filter (0.2 µm pore size).

Radiochemical analysis. Methods are described in Supplementary Information.

Statistical analyses. Two-tailed unpaired Student’s t-test ($\alpha=0.05$) were used for comparisons between two $\text{A}_{\text{ROI}}$ values (GBq/µmol). Grouped data are presented as mean ± SD. All statistical data were calculated using Prism software v5.02 (GraphPad, San Diego, CA, USA).

Data Availability
All data generated or analysed during this study are included in this published article (and its Supplementary Information Files).

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Author Contributions
B.Y.Y. and M.B.H. created the [18F]fluorocarb synthesis system. B.Y.Y. and S.T. performed [18F]fluorocarb productions and trifluoromethylations. C.L.M. performed other radiolabelling reactions and molar activity measurements. B.Y.Y. and V.W.P. prepared the manuscript. V.W.P. proposed and supervised the project. All authors provided scientific input to the project and reviewed the manuscript.

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