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Sulfonyl Fluoride-Based Prosthetic Compounds as Potential ^{18}F Labelling Agents

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Abstract: Nucleophilic incorporation of [^{18}F]F$^-$ under aqueous conditions holds several advantages in radiopharmaceutical development, especially with the advent of complex biological pharmacophores. Sulfonyl fluorides can be prepared in water at room temperature, yet they have not been assayed as a potential means to ^{18}F-labelled biomarkers for PET chemistry. We developed a general route to prepare bifunctional 4-formyl-, 3-formyl-, 4-maleimido- and 4-oxylalkynl-arylsulfonyl [^{18}F]fluorides from their sulfonyl chloride analogues in 1:1 mixtures of acetonitrile, THF, or *t*BuOH and Cs[^{18}F]F/$Cs_2CO_{3(aq.)}$ in a reaction time of 15 min at room temperature. With the exception of 4-*N*-maleimide-benzenesulfonyl fluoride (**3**), pyridine could be used to simplify radiotracer purification by selectively degrading the precursor without significantly affecting observed yields. The addition of pyridine at the start of [^{18}F]fluorination (1:1:0.8 *t*BuOH/$Cs_2CO_{3(aq.)}$/pyridine) did not negatively affect yields of 3-formyl-2,4,6-trimethylbenzenesulfonyl [^{18}F]fluoride (**2**) and dramatically improved the yields of 4-(prop-2-ynyloxy)benzenesulfonyl [^{18}F]fluoride (**4**). The *N*-arylsulfonyl-4-dimethylaminopyridinium derivative of **4** (**14**) can be prepared and incorporates ^{18}F efficiently in solutions of 100% aqueous Cs_2CO_3 (10 mg mL^{-1}). As proof-of-principle, [^{18}F]**2** was synthesised in a preparative fashion [88(±8)% decay corrected ($n=6$) from start-of-synthesis] and used to radioactively label an oxyamino-modified bombesin(6–14) analogue [35(±6)% decay corrected ($n=4$) from start-of-synthesis]. Total preparation time was 105–109 min from start-of-synthesis. Although the ^{18}F-peptide exhibited evidence of proteolytic defluorination and modification, our study is the first step in developing an aqueous, room temperature ^{18}F labelling strategy.

Keywords: acylation · fluorine · peptides · radiopharmaceuticals · sulfonyl fluorides

Introduction

Due to its high sensitivity and spatial resolution, positron emission tomography (PET) has emerged as the premier molecular imaging technique for the in vivo detection and quantification of a variety of human physiological and pathophysiological processes.[1] In the context of disease, PET imaging aims to ease diagnosis and aid in progression analysis, clinical staging and evaluation of treatment response. To this end, PET chemistry has evolved alongside the imaging modality, with continual efforts being made to improve the efficiency and cost of the radiopharmaceutical production process and develop superior functional probes.

The radioisotope ^{18}F, with its low positron emission energy ($E_{\beta+(max)}=0.64$ MeV) and high positron abundance (97%), is often considered the ideal radionuclide in terms of image resolution.[2] However, its intermediate half-life (109.7 min) makes multi-step synthesis a challenging affair, requiring skilled personnel and highly optimised processes. Reactive, anhydrous [^{18}F]F$^-$ is prepared by way of extraction from [^{18}O]H_2O by using anion exchange sorbent, elution with aqueous metal carbonate solution, and repeated azeotropic distillations from acetonitrile. The time required to perform this "dry-down" step negatively affects the overall efficiency of the radiosynthesis protocol. The [^{18}F]fluorination reaction itself typically requires elevated temperatures (80–150 °C), along with the addition of a phase transfer catalyst to enhance the solubility and nucleophilicity of the alkali metal [^{18}F]fluoride in organic solvent.[3] Tetralkylammonium (hydrogen) carbonates[4] or crown ethers[5] can be used, but in terms of anion activation, aminopolyether Kryptofix 2.2.2 cryptand (K2.2.2.) is usually considered the optimal catalyst.[6] However, K2.2.2./M[^{18}F]F complexes are also highly basic and thus incompatible with unprotected hydroxy and amino functional groups. Furthermore, the cryptand is toxic [LD_{50}(rat) = 35(±2) mg kg^{-1} (i.v.)][7] and

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must be carefully removed prior to in vivo use of the radiotracer.

The aforementioned drawbacks become exacerbated when attempting to ^{18}F label sensitive, complex biomolecules. Thus, a number of radiobioconjugate strategies have recently been proposed which do not require C–^{18}F bond formation.[8] Reactions of [^{18}F]F^- with boron to form aryltri-[^{18}F]fluoroborates,[9] with silicon to form triorgano-[^{18}F]fluorosilanes[10,11] and with aluminum to produce aluminum-^{18}F chelates[12] have all been successfully utilised in the preparation of in vivo stable ^{18}F bioconjugates.

Comparatively little interest has been paid to SO_2–^{18}F bond formation in PET chemistry. This is in itself not surprising, as sulfonyl fluorides are known to react with some nucleophilic agents (such as aniline[13] or morpholine[14]) under certain conditions. Compared to arylsulfonyl chlorides, however, arylsulfonyl fluorides are far more resistant to aqueous hydrolysis[15] and in fact readily form from sulfonyl chlorides in mixtures of water and organic co-solvent at room temperature.[16] Because benzenesulfonyl fluorides can be prepared under aqueous conditions, we anticipated that the synthesis of their radioactive versions would not require a time-consuming, high-temperature [^{18}F]F^- "dry-down" step. That sulfonyl [^{18}F]fluorides can be prepared from sulfonyl chlorides in the absence of K2.2.2., can be considered another advantage of this approach.

Reports detailing the synthesis of ^{18}F-labelled arylsulfonyl fluorides are extremely scarce. In 1975, 4-toluenesulfonyl [^{18}F]fluoride (tosyl [^{18}F]fluoride) was synthesised in a carrier-added fashion with the use of reactor-produced K[^{18}F]F.[17] Tosyl [^{18}F]fluoride is commonly thought to be a by-product of nucleophilic aliphatic substitution reactions with *p*-toluenesulfonates and [^{18}F]F^-. However, the only explicit description of this phenomena in the literature was reported by Neal et al., who observed large yet ultimately diminishable radiochemical yields of tosyl [^{18}F]fluoride impurity generated during their synthesis of [^{18}F]fluoromethyl tosylate from bis(tosyloxy) methane.[18] In this work, tosyl [^{18}F]fluoride was synthesised from tosyl chloride in acetonitrile (K2.2.2./K[^{18}F]F/K_2CO_3, 110 °C, 10 min) for use as a radiochemical standard, but no yield was reported.

As noted, sulfonyl fluorides have the potential to react with amine and hydroxy nucleophiles. As such, some alkylsulfonyl and arylsulfonyl fluorides have been found that irreversibly inhibit serine proteases.[19] Notably, phenyl methylsulfonyl fluoride (PMSF) and 4-(2-aminoethyl)benzenesulfonyl fluoride (AEBSF) have found widespread practical use as general, irreversible inhibitors of proteolytic degradation (Figure 1). The mechanism of action involves the sulfonylation of a serine residue inside the enzyme active site through nucleophilic displacement of fluorine.[20,21] However, structure–activity studies have demonstrated that further functionalisation of the aryl ring can significantly attenuate the reactivity of arylsulfonyl fluorides towards serine proteases.[22,23] Furthermore, under physiological conditions the reaction of benzenesulfonyl fluorides with biological nucleophiles is not typically a straightforward process but requires additional neighbouring group interactions to proceed. For instance, only chymotrypsin, and not enzyme precursor chymotrypsinogen, will react with a 20-fold excess of PMSF, and the depletion of PMSF is stoichiometric with respect to enzyme.[20] In another example Baker et al. designed a series of sulfonyl fluoride inhibitors of dihydrofolic reductases and showed that enzyme inhibition did not occur in the absence of a diamino-*s*-triazine ring, the moiety that forms a reversible complex with these enzymes.[24] Thus, inactivation did not depend simply on a bimolecular reaction but required active-site direction to acylate the enzyme and expel the fluorine atom.

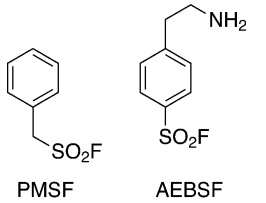


Figure 1. Irreversible protease inhibitors phenyl methylsulfonyl fluoride (PMSF) and 4-(2-aminoethyl) benzenesulfonyl fluoride (AEBSF).

These points considered, we hypothesised that a bifunctional benzenesulfonyl fluoride with appropriate ring substitution could be synthesised that was sufficiently stable in vivo to successfully serve as an easy-to-prepare, ^{18}F-bearing prosthetic for PET targeting ligands. We set out to develop a straightforward protocol for the radiosynthesis preparation of formyl-, maleimido- and alkynyl-bearing benzenesulfonyl [^{18}F]fluorides. Herein we report the synthesis and radiosynthesis of four bifunctional sulfonyl fluorides **1**–**4** (Figure 2)

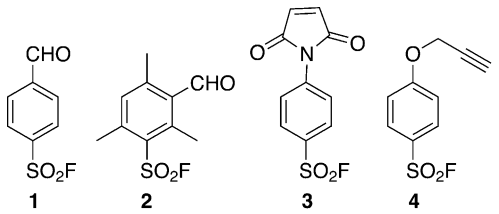


Figure 2. Bifunctional sulfonyl fluorides prepared in this work; F = ^{19}F or ^{18}F. See the Supporting Information for reaction schemes and preparative details.

from their corresponding sulfonyl chloride precursors **5**–**8** (Figure 3). One of these compounds, 3-formyl-2,4,6-trimethylbenzenesulfonyl fluoride (**2**) was chosen for further bioconjugation experiments. Our choice of prosthetic was based on the observed hydrolytic stability of [^{18}F]**2** relative to [^{18}F]**1** (vide infra), and because we anticipated that this formylated arylsulfonyl fluoride could be conjugated to oxyamino- and hydrazino-modified targeting vectors using established, biocompatible carbonyl addition–elimination reactions. This approach has been used previously to efficiently couple 4-[^{18}F]fluorobenzaldehyde to a variety of bioactive peptides of interest in PET receptor imaging.[25] We chose to assess the utility of [^{18}F]**2** as a prosthetic ^{18}F labelling agent using the 9-amino acid neuoropeptide fragment bombesin-(6–14) ([D-Tyr6,βAla11,Thi13,Nle14]BBN(6–14)) as a proof-of-principle targeting vector.

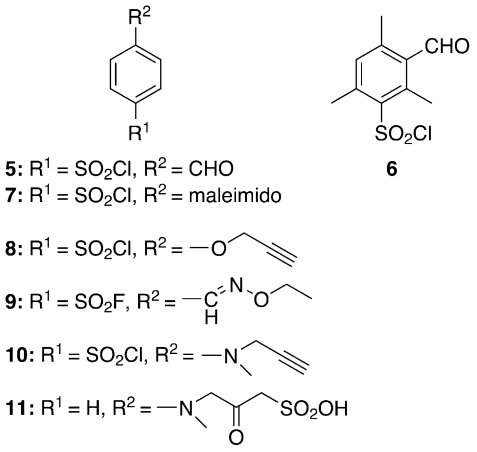


Figure 3. Sulfonyl chloride precursors (**5**–**8**), model oxime compound **9**, desired *sec*-amine **10** and unexpected sulfonic acid **11**. See the Supporting Information for reaction schemes and preparative details.

Table 1. Radiochemical yields by radio-TLC of bifunctional molecules [^{18}F]**1**–[^{18}F]**4** from sulfonyl chloride precursors **5**–**8** at room temperature, before and after pyridine treatment.

Entry	Product	$Cs_2CO_{3(aq.)}$/ co-solvent	Yield [%] before pyridine treatment (+15 min)	Yield [%] after pyridine treatment (+30 min)
1	[^{18}F]**1**	*t*BuOH	93±1[a]	90±2[a]
2	[^{18}F]**1**	THF	96±1[a]	96±1[a]
3	[^{18}F]**1**	MeCN	97±1[b]	90±2[b]
4	[^{18}F]**1**	DMSO	no reaction[b]	no reaction[b]
5	[^{18}F]**1**	$Cs_2CO_{3aq.}$ only	6±1[b]	38±1[b]
6	[^{18}F]**1**	$Cs_2CO_{3aq.}$ only	19±2 (80±1)[b,c]	–
7	[^{18}F]**2**	*t*BuOH	97±1[a]	98±1[a]
8	[^{18}F]**3**	*t*BuOH	28±1[b]	18±2[b]
9	[^{18}F]**3**	THF	72±2[a]	0.6±0.1[a]
10	[^{18}F]**4**	*t*BuOH	29±2[b]	100±1[b]

[a] Average of three traces. [b] Average of four traces. [c] Sampled after addition of DMSO (200 μL), between 15–16 min; errors indicate ±SD.

Results and Discussion

Sulfonyl chloride precursors (Figure 3) were either purchased (**5**), or prepared by direct chlorosulfonylation (**7**,[26] **8**) by using chlorosulfonic acid, or by sulfonylation followed by chlorination with cyanuric chloride[27] (**6**). Bifunctional sulfonyl fluorides **1**, **2** and **4** (Figure 2) were synthesised from their corresponding sulfonyl chlorides (**5**, **6** and **8**, respectively) by using *tert*-butylammonium fluoride (1 M; TBAF) in THF. In the case of formylated compound **2**, pyridine was employed (20 mol%), which was accompanied by an improvement in final yield compared to a similar reaction without pyridine (32 vs. 87%). Maleimide **3** could not be obtained from **7** in acceptable yields by using TBAF/THF, but was prepared in low yields (21%) when **7** was refluxed in 1:1 mixtures of *t*BuOH and aqueous KF. The synthesis and characterisation of ^{19}F standards **1**–**4** and precursors **6**–**8** is described in the Supporting Information section.

To the best of our knowledge, the direct chlorosulfonation of alkylated anilines has never been reported. Despite this, an attempt was made to prepare 4-(methyl(prop-2-ynyl)amino)benzenesulfonyl chloride (**10**, Figure 3) in this fashion. The isolated product after quenching with water was determined to be sulfonic acid **11** (Figure 3, 66% yield, see the Supporting Information). A detailed study was not performed on the mechanistic route to this compound. However, we hypothesise that this compound may form by way of free radical rearrangement of a sulfamic acid intermediate.[28]

Radioactive benzenesulfonyl fluorides [^{18}F]**1**–[^{18}F]**4** were initially prepared in a 1:1 mixture of organic solvent and an aqueous solution of caesium carbonate (10 mg mL^{-1}) at room temperature. Aliquots of the bulk Cs[^{18}F]F/$Cs_2CO_{3(aq.)}$ solution could be used for multiple [^{18}F]fluorination reactions; no azeotropic drying steps were required. After 15 min the reaction mixture was sampled for radio-TLC, then pyridine was added and the reaction was let stand another 15 min. A summary of [^{18}F]fluorination conditions explored are shown in Table 1. The study began with 4-formylbenzenesulfonyl fluoride [^{18}F]**1**, which was produced efficiently by way of halogen exchange from precursor **5** when *t*BuOH was used as co-solvent (Table 1, entry 1). A representative radio-TLC trace of the reaction mixture is shown in Figure 4. Similar results were observed upon synthesis of [^{18}F]**2** from **6** by using identical conditions (Table 1, entry 7, and Figure 4). Hindered protic solvents have recently been identified as an excellent medium for S_N2 [^{18}F]fluorination reactions, presumably because of their capacity to reduce the charge association between Cs^+ and [^{18}F]F^- by hydrogen bonding to the salt and moderately solvating the free fluoride ion.[29] It was also suggested that the enhanced rate of nucleophilic aliphatic [^{18}F]fluorinations with mesylate precursor relative to other leaving groups may be the result of additional hydrogen bonding of *t*BuOH solvent to the sulfonyl moiety. Recently, Kim and Jang[30] prepared a series of

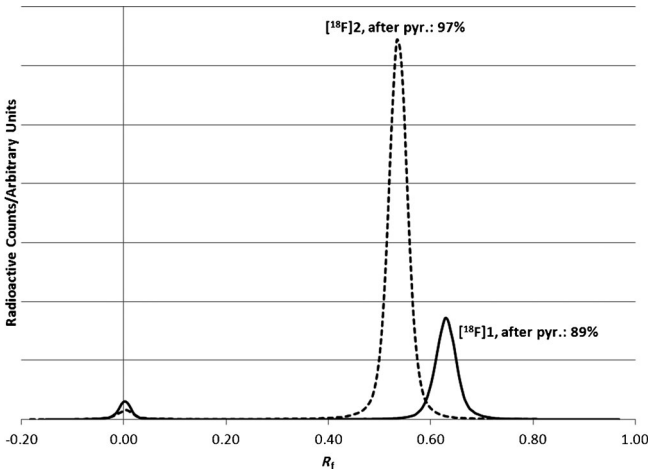


Figure 4. Representative radio-TLCs for the synthesis of [^{18}F]**1** (Table 1, entry 1; ——) and [^{18}F]**2** (Table 1, entry 7; -----), in both cases after pyridine treatment; the vertical scale is linear. Absolute peak height for each trace varies with amount of solvent spotted.

non-radioactive sulfonyl fluorides in a one-pot procedure with *tert*-butylammonium tetra(*tert*-butyl alcohol) fluoride,[31] where sulfonic acid was first converted in situ to sulfonyl chloride with Cl_3CCN and triphenylphosphine. In our case, it is possible that protic *t*BuOH lowers the energy of a S_N1-type sulfonoxy anion transition state; however, the bulk of the literature does not favour this mechanism.[32] We observed excellent radiochemical yields of [^{18}F]**1** even in 1:1 mixtures of THF/$Cs_2CO_{3(aq.)}$ and MeCN/$Cs_2CO_{3(aq.)}$, in which only hydrogen bonding by water is possible (Table 1, entries 2 and 3, respectively).

Polar aprotic solvents, such as DMSO, are essential when utilising K2.2.2./K[^{18}F]F complex, but the presence of DMSO completely inhibits the formation of [^{18}F]**1** under the reported conditions (Table 1, entry 4). The same is true when DMSO is employed and dried K2.2.2./K[^{18}F]F fluoride source is used (data not shown).

It was of significant interest to determine if [^{18}F]**1** could be radiochemically prepared in the absence of organic solvent. However, direct analysis of this reaction by radio-TLC was not expected to provide reliable data, as the product sulfonyl fluoride is not soluble in water. Indeed, observed radiochemical yields from two separate reactions employing only $Cs_2CO_{3(aq.)}$ (10 mg mL^{-1}) as the solvent were found to be low and highly variable (Table 1, entries 5 and 6). Addition of DMSO to the reaction mixture, followed by immediate re-sampling, was associated with a marked increase in the measured radiochemical yield (Table 1, entry 6). As we have shown that sufonyl fluoride formation does not proceed in the presence of DMSO under similar conditions, we attribute this increase in the measured yield to the improved solvation of [^{18}F]**1**.

Apart from sulfonyl fluoride hydrolysis, maleimide-bearing compounds such as **3** and **7** are also susceptible to base-mediated ring opening. This makes them incompatible with typical ^{18}F labelling conditions that utilise alkali salts, K2.2.2. cryptand, and high temperatures.[33] When *t*BuOH was used as a co-solvent under the standard conditions, labelling yields by radio-TLC were low, and decreased slightly after pyridine treatment (Table 1, entry 8). Acceptable yields of [^{18}F]**3** were observed when THF was used as a co-solvent, but the compound degraded almost completely after addition of pyridine (Table 1, entry 9, and Figure 5).

Some arylsulfonyl and arylalkylsulfonyl fluorides have limited stability in buffered solutions.[22,34] For instance, James[34] estimated the inactivation of PMSF based on its ability to inhibit molar equivalents of chymotrypsin in different isotonic buffers. PMSF half-lives in sodium phosphate (pH 7.0), HEPES (pH 7.5), and Tris-HCl (pH 8.0) were found to be 110, 55, and 35 min, respectively (10 mM buffer, 150 mM NaCl, room temperature). Thus, we chose to evaluate the stability of our bifunctional molecules in strong buffer (10% DMSO in 150 mM, pH 7.4 phosphate buffered saline (PBS); Figure 6). Percent stability was assessed based on the relative accumulation of sulfonic acid over time as monitored by HPLC. An inherent error associated with this approach must be acknowledged, as it assumes that the difference in extinction coefficients between the sulfonyl fluorides and their corresponding acids are negligible. Mesitaldehyde analogue **2** was found to be stable in 10% DMSO in PBS [100(±1)% remaining after 2.5 h] but under the same conditions only 1(±1)% of **1** remained. We attribute this difference in stability to an increase in positive charge distribution at the benzene carbon *para* to the aldehyde substituent and α to the sulfur electrophile. Inductive donation of the methyl carbons might also serve to depolarise the α-carbon and stabilise the sulfonyl fluoride towards nucleophilic attack by water. Alkyne-bearing prosthetic **4** exhibited good hydrolytic stability [99(±1)%], but maleimide **3** showed some degradation [90(±5)%]. We also tested compound **9** (Figure 3) as a model of the *para*-oxime linkage, and deemed it to be essentially stable over 2.5 h [97(±3)%].

Pyridine is known to catalyse a number of acylation reactions, including the hydrolysis[35] and methanolysis[36] of ben-

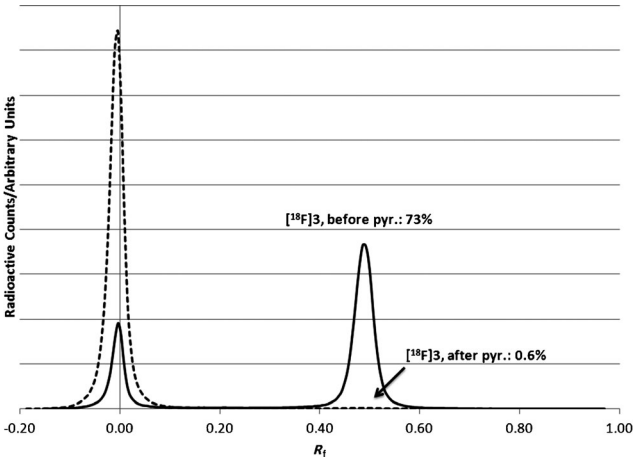


Figure 5. Representative radio-TLCs for the synthesis of [^{18}F]**3** in 1:1 THF/$Cs_2CO_{3(aq.)}$, before (——) and after (-----) pyridine treatment (Table 1, entry 9); the vertical scale is linear. Absolute peak height for each trace varies with amount of solvent spotted.

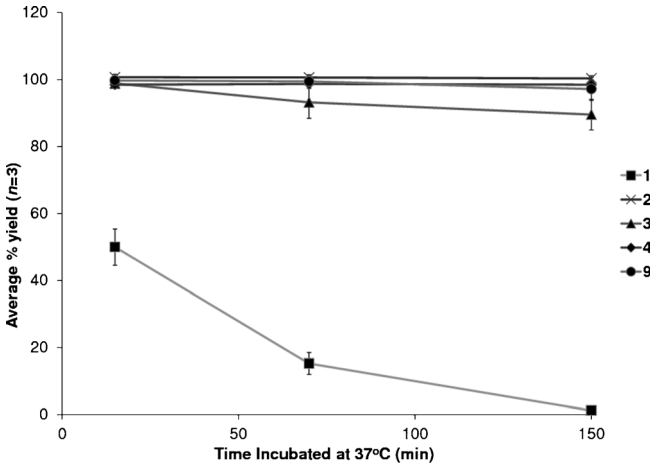


Figure 6. Percent of small molecule prosthetic **1**–**4** and **9** remaining in DMSO (10%) in PBS (pH 7.4, 150 mM) by UV-HPLC (260 nm) versus time. Each data point represents the average of three separate experiments; error bars indicate ±SD.

zenesulfonyl chlorides. In these cases, the mechanism of catalysis has been shown to be nucleophilic. Therefore, it is not surprising that yields of [^{18}F]**4** improved markedly upon addition of pyridine (Table 1, entry 10, and Figure 7), as the

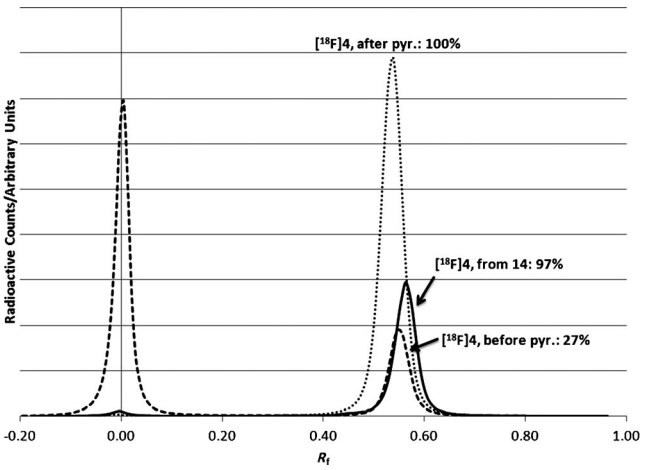
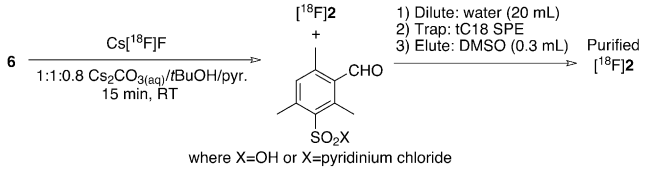


Figure 7. Representative radio-TLCs for the synthesis of [^{18}F]**4** in 1:1 *t*BuOH/$Cs_2CO_{3(aq.)}$, before (-----) and after (•••••) pyridine treatment (Table 1, entry 10). The solid line depicts [^{18}F]**4** as obtained from DMAP salt **14** (Table 2, entry 4); the vertical scale is linear. Absolute peak height for each trace varies with amount of solvent spotted.

formation of a reactive *N*-sulfonylpyridinium chloride ion pair allows for the facile acylation of fluoride with pyridine as the leaving group. Building on this result we improved upon our earlier two-step approach in which the [^{18}F]fluoride and pyridine are added sequentially in favour of a shorter protocol in which all three solvents (*t*BuOH, $Cs_2CO_{3(aq.)}$ and pyridine) are added at the same time. As a result, excellent radiochemical yields of [^{18}F]**4** [99(±1)% by radio-TLC] could be achieved in 15 (versus 30) minutes, with no apparent effect on either chemical or radiochemical purity. This optimised protocol was also deemed acceptable for the preparation of formylated compound [^{18}F]**2** [96(±1)% by radio-TLC]. These yields represent the average of four traces in four separate experiments.

Preparative syntheses of [^{18}F]**2** were carried out (Scheme 1) for use of this compound in later bioconjugation reactions. After purification on a Sep-pak tC18 solid phase extraction (SPE) column, excellent yields from start-of-synthesis (SOS) were obtained [73(±7)% non-decay corrected, 88(±8)% decay corrected, $n=6$]. Total synthesis time was 27–31 min from SOS, or 47–71 min from end-of-bombard-



Scheme 1. Preparative synthesis and purification of prosthetic group [^{18}F]**2**.

ment. Figure 8 shows a typical HPLC trace of [^{18}F]**2** after tC18 SPE purification ($\lambda_{max}=260$ nm). The bulk of the added pyridine was removed ($t_R=3.1$ min). Furthermore, the UV chromatogram reveals little in the way of other

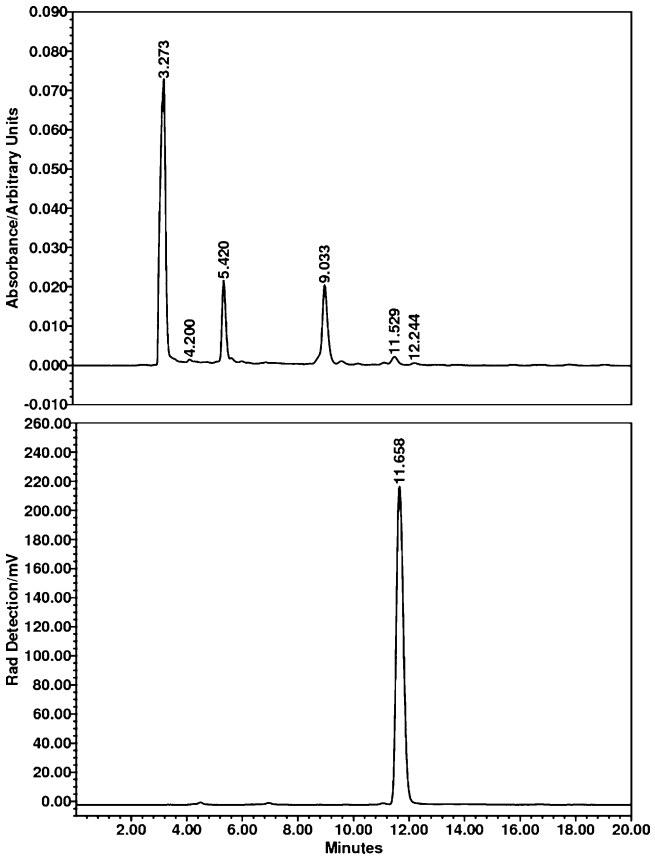
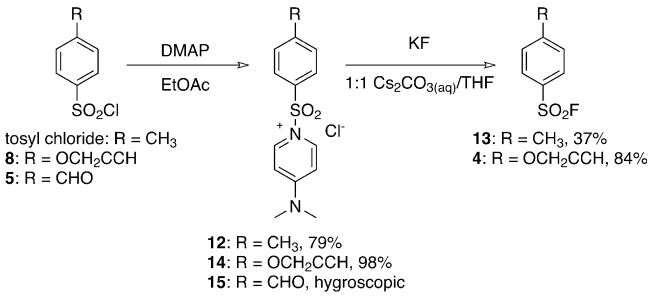


Figure 8. Radio-HPLC (program 4, see the Supporting Information) of [^{18}F]**2** after tC18 SPE purification. Upper trace: UV detection (260 nm, absorbance units); lower trace: radioactive detection (mV).

chemical impurities; this suggests that the SPE step was efficient in separating [^{18}F]**2** from any non-radioactive mesitaldehyde species that might compete with the prosthetic group during subsequent bioconjugations. Under these conditions, the t_R of sulfonyl chloride precursor **6** is 13.7 min and the t_R of sulfonate **16** (see the Supporting Information) is 6.4 min. The apparent specific activity of [^{18}F]**2** prepared in this fashion was estimated to be 105(±2) GBq μmol^{-1} ($n=4$) based on the UV-HPLC signal co-eluting with radiotracer relative to a mass standard curve.

In general, *N*-sulfonylpyridinium chlorides are difficult to isolate under atmospheric conditions, but *N*-sulfonyldialkylaminopyridinium salts are resonance-stabilised and in a few cases have been prepared.[37] Notably, DMAP derivative **12** (Scheme 2) was used to tosylate tyrosine residues on chains A and B of oxidised bovine insulin and human calcitonin at pH 10–11.5.[38] Although 4-dialkylamino substituted pyridines have been used as acylation catalysts for some time,[39] to our knowledge there have been no reports of *N*-sulfonyl-



Scheme 2. Synthesis of benzenesulfonyl fluorides **13** and **4** from *N*-sulfonyldimethylaminopyridinium salts **12** and **14**, respectively. See the Supporting Information for preparative details.

dialkylaminopyridinium salts being used for the synthesis of arylsulfonyl fluorides. However, in light of our observations we synthesised **12** according to published protocol[38] (DMAP, 0 °C, EtOAc) and attempted to fluorinate it with KF in mixtures of 1:1 THF/$Cs_2CO_{3(aq.)}$ (Scheme 2). Qualitative TLC suggested good yields of tosyl fluoride (**13**) in the reaction mixture; we attribute the low recovered yield (37 %) to the reactivity of **13** towards DMAP (and unreacted DMAP salt) during product extraction. Indeed, a bifunctional analogue of **12**, alkynylated DMAP salt **14**, was also synthesised (98 %) and used to prepare **4** in adequate yields (84 %, Scheme 2). The same reaction conditions as those used to prepare **13** were employed, but in this case the work-up was modified. Specifically, the reaction mixture was not diluted with water prior to extraction, and the extract was filtered immediately through silica gel. Unfortunately, an attempt to produce formylated species **15** by the above method resulted in a hygroscopic solid that was very difficult to isolate. Overall, this previously unreported sulfonyl transfer reaction is an attractive alternative to the synthesis of certain sulfonyl fluorides by way of Cl-to-F exchange, which is sometimes sluggish without forcing conditions and often requires careful separation of the two sulfonyl halides.

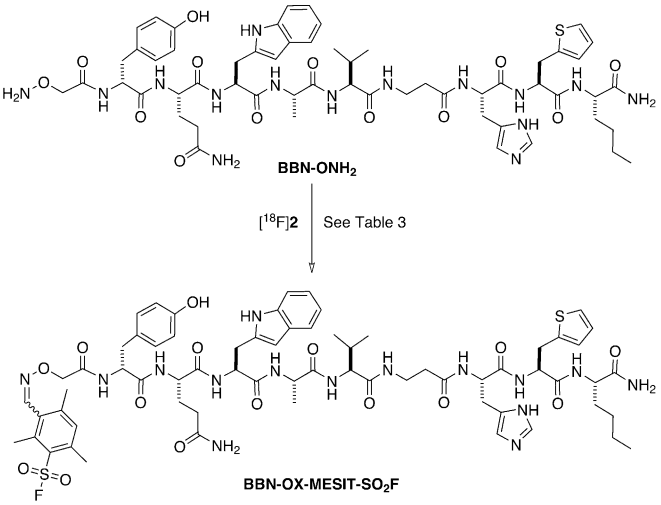
We then set out to prepare [^{18}F]-labelled tosyl fluoride ([^{18}F]**13**) from its *N*-sulfonyldimethylaminopyridinium precursor (**12**). Gratifyingly, excellent yields by radio-TLC were observed in mixtures of THF and $Cs_2CO_{3(aq.)}$ after 15 min at room temperature (Table 2, entry 1). Solvent mixtures composed of 1:1 *t*BuOH/$Cs_2CO_{3(aq.)}$ also work well (Table 2, entry 2). Because salt **12** is water-soluble and exhibits a viable hydrolytic half-life ($t_{1/2}$ = 14.5 h, pH 6.0 at 36 °C),[38] we also attempted to radiolabel under aqueous conditions only (Cs[^{18}F]F/$Cs_2CO_{3(aq.)}$), with excellent radiochemical yields of [^{18}F]**13** observed after quenching with DMSO (Table 2, entry 3). It should be noted however, that in this case the small radioactive peak at the trace origin appears to be a composite of two unresolved peaks, suggesting that a polar radiochemical impurity has formed. We further validated this new ^{18}F labelling approach by converting bifunctional DMAP derivative **14** to [^{18}F]**4** in 1:1 THF/$Cs_2CO_{3(aq.)}$ and 100 % $Cs_2CO_{3(aq.)}$ (Table 2, entries 4 and 5, and Figure 7). In addition, we verified that [^{18}F]**4** could be extracted from the THF/$Cs_2CO_{3(aq.)}$ reaction mixture using the reverse phase SPE method described above. In this fashion, excellent preparative yields of [^{18}F]**4** were achieved (78 % non-decay corrected yield from SOS, 92 % decay corrected).

Table 2. Radiochemical yields by radio-TLC of [^{18}F]**13** and [^{18}F]**4** from *N*-sulfonyldimethylaminopyridinium salts **12** and **14**, respectively.

Entry[a]	Precursor	Product	$Cs_2CO_{3(aq.)}$/ co-solvent	Yield [%] by TLC after 15 min
1	**12**	[^{18}F]**13**	THF	100 ± 1[b]
2	**12**	[^{18}F]**13**	*t*BuOH	99 ± 1[b]
3	**12**	[^{18}F]**13**	$Cs_2CO_{3(aq.)}$	8 ± 1 (98 ± 1)[b,c]
4	**14**	[^{18}F]**4**	THF	96 ± 1[b]
5	**14**	[^{18}F]**4**	$Cs_2CO_{3(aq.)}$	7 ± 1 (97 ± 1)[c,d]

[a] All reactions were conducted for 15 min at room temperature. [b] Average of four traces. [c] Sampled after addition of DMSO (200 μL), between 15–16 min. [d] Average of three traces; errors indicate ± SD.

Certain peptide fragments of the neuropeptide bombesin exhibit a high affinity for gastrin releasing peptide (GRP) receptor, which is overexpressed in a variety of cancers.[40] Modified bombesin analogues have been ^{18}F labelled indirectly by way of *N*-succidimidyl 4-[^{18}F]fluorobenzoate ([^{18}F]SFB),[41] as well as directly from di-*tert*-butylsilyl-[10] and (4-trimethylammonium-3-cyanobenzoyl)-modified[42] precursors. We prepared the 9-amino acid bombesin analogue (amino-oxy acetic) [D-Tyr6,βAla11,Thi13,Nle14]BBN-(6–14) (**BBN-ONH$_2$**; Scheme 3) using standard Fmoc proto-



Scheme 3. Preparation of **BBN-OX-MESIT-SO$_2$F** peptide; F = ^{19}F or ^{18}F.

cols for coupling to formylated sulfonyl fluoride prosthetics, such as **2** (see the Supporting Information). Non-radioactive standard peptide **BBN-OX-MESIT-SO$_2$F** was obtained by mixing of **BBN-ONH$_2$** and aldehyde-bearing prosthetic **2** in DMSO followed by semi-preparative HPLC purification.

Acceptable conjugation yields of radioactive 3-formyl-2,4,6-trimethylbenzenesulfonyl [^{18}F]fluoride ([^{18}F]**2**) to **BBN-ONH$_2$** by way of oxime formation required some optimisation (Scheme 3 and Table 3). As oxime bond formation occurs most rapidly in aqueous solutions at pH 3–5,[43] addi-

Table 3. Parameters tested for the synthesis of **BBN-OX-MESIT-SO$_2$-[^{18}F]F**.

Entry[a]	DMSO/co-solvent (3:1)	t [min]	T	Yield [%] by HPLC
1	DMSO	20	ambient	29
2	MES buffered saline[b]	20	ambient	34
3	5% AcOH	20	ambient	51
4	5% AcOH	30	ambient	52
5	5% AcOH	30	37°C	64

[a] All reactions utilised 0.5 mg precursor peptide (**BBN-ONH$_2$**) and 400 μL total solvent. [b] 100 mM, pH 4.7.

tional test reactions were carried out in the presence of AcOH (5%) and 2-(*N*-morpholino)ethanesulfonic acid (MES) buffered saline (100 mM, pH 4.7). Full preparative radiosynthesis of sulfonyl [^{18}F]fluoride-modified **BBN-OX-MESIT-SO$_2$[^{18}F]F** was eventually carried out according to the parameters outlined in Table 3 (entry 5).

An important requirement for cellular receptor imaging is that the final tracer formulation be reasonably free of functionally similar impurities that might compete with the imaging agent for receptor targets, in vivo. In this case, **BBN-OX-MESIT-SO$_2$[^{18}F]F** was well-separated from precursor **BBN-ONH$_2$** by using the reported HPLC protocol (program 2b; the difference in peptide retention times is ~4.5 min). The radio-peptide was removed from HPLC eluent by way of a second tC18 extraction and formulated in EtOH (10%) in saline. A radio-HPLC trace of the final formulation is shown in Figure 9. The accompanying spectroscopic trace (λ_{max} = 280 nm) failed to detect any measurable amount of UV-absorbing material associated with the ^{18}F-peptide. **BBN-OX-MESIT-SO$_2$[^{18}F]F** was obtained in decay-corrected preparative yields of 35(±6)% (n = 4) from start-of-synthesis. Total synthesis time was 105–109 min from SOS. The distribution coefficient of radioactive peptide **BBN-OX-MESIT-SO$_2$[^{18}F]F** was obtained in the manner described by Wilson et al.[44] The log $D_{[7.4]}$ value was found be 1.91 ± 0.01 (n = 4 measurements).

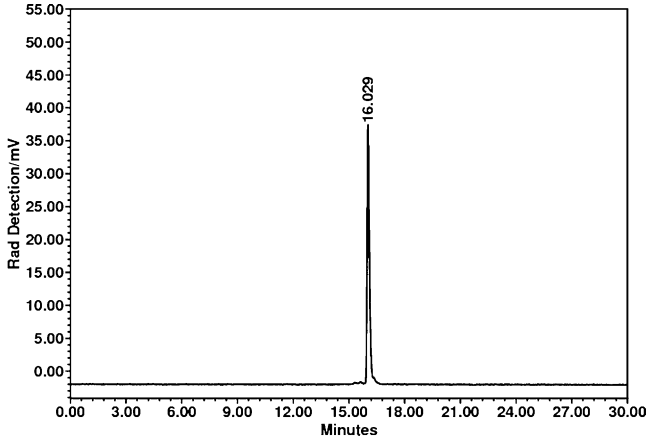


Figure 9. Radio-HPLC (program 2b, see the Supporting Information) of **BBN-OX-MESIT-SO$_2$[^{18}F]F** after final formulation. **BBN-ONH$_2$** precursor elutes at 11.5 min.

The stability of **BBN-OX-MESIT-SO$_2$[^{18}F]F** in DMSO (10%) in murine serum was originally tested by HPLC. After 15, 60 and 120 min at 37°C, a portion of the incubation mixtures were quenched with equal amounts of MeCN, chilled (4°C), centrifuged, and the supernatant was assayed by HPLC. At the 15 min time point, 45–57% of the total radioactivity remained in the precipitate, which suggests that a significant amount of the hydrophobic peptide non-specifically binds to serum protein. After 2 h, control mixtures (10% DMSO in PBS, 37°C, quenched with acetonitrile) appear identical to QC traces of the final formulation. However, **BBN-OX-MESIT-SO$_2$[^{18}F]F** in serum is extensively converted to other radiolabelled metabolites in less than 15 min. As shown in Figure 10, the major decomposition

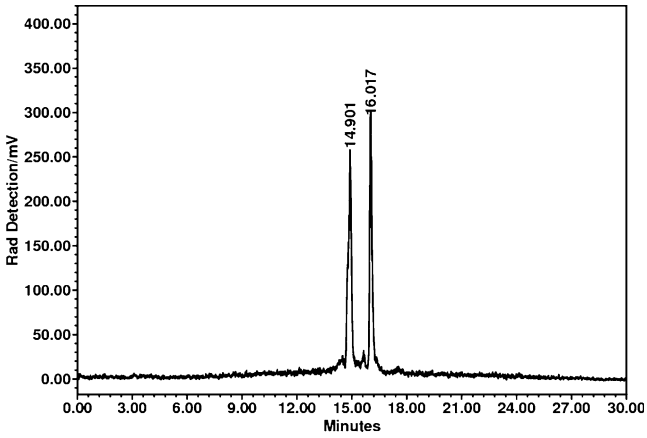


Figure 10. Radio-HPLC (program 2b, see the Supporting Information) of **BBN-OX-MESIT-SO$_2$[^{18}F]F** after incubation in mouse serum (15 min, 37°C). The product ^{18}F-peptide **BBN-OX-MESIT-SO$_2$[^{18}F]F** elutes at 16.0 min, whereas the major decomposition product elutes at 14.9 min.

product (t_R = 14.9 min) constitutes 45(±4)% of the total observed radioactivity (n = 3 separate experiments). Very little or no radioactive signal was observed early in these chromatograms where one would expect to observe free fluoride. In contrast, HPLC traces at 60 and 120 min contain both free fluoride and the product signal, but both peaks are very small relative to the injected activity. Furthermore, the chromatograph baselines are not uniform, indicating that radioactivity is "bleeding" off the HPLC column during the acquisition of these traces. This further suggests that at these time points, defluorination of the radio-peptide is occurring.

These observations highlight the difficulty in assessing the true extent of ^{18}F radiotracer defluorination by way of reverse phase HPLC. This is primarily because [^{18}F]F$^-$ can potentially adsorb onto C18 sorbents and thus be removed from the recorded chromatogram. Thus, we developed a radio-TLC method employing normal phase silica iTLC-SG™ plates (Gelman Sciences) to assess the relative amount of dissolved ^{18}F-peptide after incubation in serum. Using 1:1 MeOH/MES buffered saline as eluent, [^{18}F]F$^-$ in 1:1 MeCN/10% DMSO in mouse serum exhibits an R_f of about 0.1, whereas the R_f of **BBN-OX-MESIT-SO$_2$[^{18}F]F** is

approximately 0.9. It should be noted that individual [^{18}F]-fluorinated peptide degradation products cannot be distinguished with this technique. Thus, the observed radioactivity present at 0.8–1.0 R_f after 15 min in serum [43(±4)% ($n=3$ traces) and 35(±1)% ($n=3$ traces) in two separate experiments] represents only an estimation of the percent remaining of sulfonyl [^{18}F]fluoride-bearing species relative to the total radioactivity in the serum solution.

Summary

Four ^{18}F labelled arylsulfonyl fluorides bearing 4-formyl-, 3-formyl-, 4-maleimido- and 4-oxylalkynl moieties were radiosynthesised in high yields in equal volumes of basic cyclotron target [^{18}O]H_2O and organic co-solvent at room temperature. Preparation of anhydrous K2.2.2./K[^{18}F]F complex was not required. In most cases, sulfonyl chloride precursor could be selectively converted upon addition of pyridine to a reactive *N*-sulfonylpyridinium chloride intermediate. In addition, we synthesised a *N*-sulfonyl-DMAP chloride salt (**14**) and used it to prepare both ^{19}F- and ^{18}F-labelled 4-(prop-2-ynyloxy)benzenesulfonyl fluoride (**4**) in excellent chemical and radiochemical yields.

The in situ degradation of benzenesulfonyl chloride precursor in the presence of pyridine permitted the efficient preparative synthesis of 3-formyl-2,4,6-trimethylbenzenesulfonyl [^{18}F]fluoride ([^{18}F]**2**) without the need for time-consuming HPLC purification of the prosthetic. Compound [^{18}F]**2** was further coupled to an oxyamino-bearing analogue of bombesin (**BBN-OX-MESIT-SO$_2$[^{18}F]F**) via oxime linkage as proof-of-principle. The overall radiosynthesis protocol can be completed in less than 110 min. The sulfonyl fluorinated peptide analogue was found to be stable in DMSO (10%) in PBS over 2 h at physiological temperature and pH. Under similar conditions in mouse serum, however, **BBN-OX-MESIT-SO$_2$[^{18}F]F** showed signs of defluorination. An accurate estimation of the rate of sulfonyl [^{18}F]fluoride hydrolysis was complicated by the fact that enzymatic modification of the ^{18}F-peptide and complexation with serum protein also occurs. The interrelation between these three processes remains to be determined, but further insights might be gleaned through the labelling of alternative targeting vectors.

Experimental Section

Synthesis details and reaction schemes related to the preparation and characterisation of non-radioactive small molecules **1–4**, **6–9**, **11–14** and **16**, along with peptides **BBN-ONH$_2$** and **BBN-OX-MESIT-SO$_2$F**, can be found in the Supporting Information.

Assessing hydrolytic stability of small molecule standards 1–4 and 9 in buffered solution; general procedure: Arylsulfonyl fluoride standards in MeOH (**1**, **3** and **4**) or diethyl ether (**2**, **9**) were prepared (9.8 μM) and aliquots (50 μL) were removed and concentrated in microcentrifuge tubes over a stream of helium. Each aliquot was incubated in PBS (150 mM, pH 7.2, 75 μL) at 37°C for 15, 70 or 150 min. After the appointed time, the sample was diluted with acetonitrile and let stand 15 min, then a portion (75 μL) was injected into HPLC for analysis. HPLC parameters used were as follows: compound **4**, program 1a. Compounds **1** and **3**, program 1b. Compounds **2** and **9**, program 1c (see the Supporting Information). An estimation of percent stability was calculated as follows: absorbance units of the peak of interest/(total absorbance−absorbance units of a blank sample)×100. This approach assumes that the difference in extinction coefficients between a sulfonyl fluoride and its corresponding sulfonic acid is negligible. The experiment was performed three times for each compound.

Preparation of sulfonyl [^{18}F]fluorides for radio-TLC analysis; general procedure: No-carrier-added [^{18}F]F^- was produced by 13 MeV proton bombardment of [^{18}O]H_2O [^{18}O(p,n)^{18}F reaction]. Typical production was 1.5–2.6 GBq of [^{18}F]F^- at end of bombardment for a 10 μA, 5 min irradiation. [^{18}F]Fluoride in [^{18}O]H_2O was immobilised on an anion exchange ^{18}F trap-and-release column (ORTG, Inc), then eluted into a 5 mL conical vial with a solution of caesium carbonate (10 mg mL^{-1}, 400 μL). From this bulk solution, smaller aliquots were removed for further use. An aliquot (100 or 200 μL) of [^{18}F]F^- in aqueous Cs_2CO_3 was pipetted into a reaction vessel containing sulfonyl chloride (**5–8**) or sulfonyl chloride in organic solvent (100 μL; Table 1). Reaction volume was 0.2 mL and precursor concentration was 30 mM. The reaction was shaken and let stand for 15 min, then the reaction mixture was spotted on 3 or 4 TLC plates. The plates were 20 cm long, with the origin at 2 cm. Pyridine (80 μL) was added and the mixture was shaken and let stand for another 15 min before TLC sampling in the same fashion. The TLC eluent was ethyl acetate. Alternately, pyridine (80 μL) was added immediately after addition of [^{18}F]F^- and the reaction sampled after 15 min (Table 2).

Procedure for the purification of [^{18}F]2: An aliquot (100 μL) of [^{18}F]F^- in aqueous Cs_2CO_3 (10 mg mL^{-1}) was pipetted into a reaction vessel containing sulfonyl chloride **6** in *t*BuOH (100 μL). Immediately afterward, pyridine (80 μL) was added and the mixture was vortexed thoroughly and let stand for 15 min. The reaction solution was transferred into an open syringe containing water (20 mL) and immobilised on a Sep-pak© tC18 light column. The column (activated previously with 2 mL EtOH and 6 mL water) was washed with water (5 mL), and dried with air (15 mL). Product benzenesulfonyl [^{18}F]fluoride ([^{18}F]**2**) was eluted from the column with either DMSO (300 μL) for further bioconjugation experiments or acetonitrile (1 mL) for determination of specific activity by HPLC (program 4; see the Supporting Information).

Radiobioconjugate synthesis of BBN-OX-MESIT-SO$_2$[^{18}F]F: Purified [^{18}F]**2** in DMSO (300 μL) was added to **BBN-ONH$_2$** peptide (0.5 mg) in a microcentrifuge tube and AcOH (5%, 100 μL) was added. The reaction mixture was vortexed, centrifuged briefly, and placed in a bed of heated beads (37°C) for 30 min. The ^{18}F-labelled peptide was diluted with water (600 μL) and purified by reverse phase HPLC (program 2b; see the Supporting Information). The collected portion was diluted to 20 mL with water and trapped on Sep-pak© tC18 light column (activated previously with 2 mL EtOH and 6 mL water). The column was washed with water (5 mL) and dried with air (10 mL). **BBN-OX-MESIT-SO$_2$[^{18}F]F** was usually eluted from the column with EtOH (300 μL) and diluted with 0.9% saline solution (2.7 mL). However, for serum stability experiments, the ^{18}F-peptide was eluted from the column with DMSO (400 μL).

Serum stability study: **BBN-OX-MESIT-SO$_2$[^{18}F]F** in DMSO (34.4–44.4 MBq) was diluted 1:9 with fresh mouse serum and heated to 37°C. As control, a second portion of ^{18}F-peptide was treated in an identical fashion with PBS (150 mM, pH 7.2) in place of mouse serum. The samples had aliquots (150–500 μL) removed after 15, 60 and 120 min. The aliquots were quenched with equal amounts of MeCN, chilled at 4°C for 15 min, centrifuged for 3 min (15668 *g*), then the supernate was removed and counted. After being spotted on three separate silica gel plates (iTLC-S, Gelman Sciences; 20 cm), the remainder of the ^{18}F-peptide was assayed by HPLC (program 2b; see the Supporting Information). After drying, radio-TLC was performed by using 1:1 MeOH/MES buffered saline (100 mM, pH 4.7) as mobile phase.

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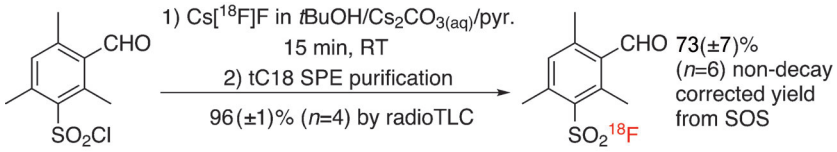
Sulfonyl Fluoride-Based Prosthetic Compounds as Potential ^{18}F Labelling Agents



^{18}F chemistry in water at RT: We have developed a ^{18}F labelling strategy for the synthesis of PET biomarkers in which arylsulfonyl chloride prosthetics are efficiently labelled in basic mixtures of aqueous $[^{18}F]F^-$ and organic solvent at room temperature (see scheme). Pyridine simultaneously catalyses halogen exchange whereas degrading the precursor, and some *N*-sulfonylated DMAP salts can be prepared and fluorinated with ease.