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One-Step Synthesis of [^{18}F]Fluoro-4-(vinylsulfonyl)benzene: A Thiol Reactive Synthon for Selective Radiofluorination of Peptides

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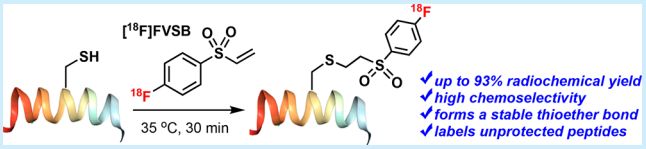
ABSTRACT: Radiolabeled peptide-based molecular imaging probes exploit the advantages of large biologics and small molecules, providing both exquisite selectivity and favorable pharmacokinetic properties. Here, we report an operationally simple and broadly applicable approach for the ^{18}F-fluorination of unprotected peptides via a new radiosynthon, [^{18}F]fluoro-4-(vinylsulfonyl)benzene. This reagent demonstrates excellent chemoselectivity at the cysteine residue and rapid ^{18}F-labeling of a diverse scope of peptides to generate stable thioether constructs.



Radiolabeled peptides are important positron emission tomography (PET) imaging tools due to their selectivity toward overexpressed cell surface receptors of many cancers, which can be exploited for targeting purposes.[1−5] Critical to the continued development of valuable PET probes is the availability of chemical methods to access diverse radiolabeled peptides. Remarkable breakthroughs in ^{18}F-chemistry to afford ^{18}F-labeled peptides with minimal perturbation have unveiled direct synthetic paths toward previously inaccessible radiolabeled peptides.[6−10] Despite recent advances in site-specific radiofluorination, ^{18}F-labeling of peptides is most frequently conducted via conjugation with prosthetic groups.[11−16]

Selective bioconjugation reactions for ^{18}F-labeling of peptides have largely focused around modification of lysine and cysteine side chains.[17,18] Site-selective conjugation via thiol-based chemistry is more desirable when compared to unselective modification of lysine residues, which can produce poorly defined, heterogeneous mixtures of labeled products.[19,20] A powerful tool for site-specific bioconjugation to cysteine and perhaps the most utilized prosthetic group for selective ^{18}F-labeling of peptides is the maleimide-based synthon.[15,21−25] Maleimide-based prosthetic groups (Figure 1A) have garnered persistent popularity due to their fast kinetics and remarkable cysteine chemoselectivity; however, significant limitations exist, the most notable being susceptibility of the succinimidyl thioether linkage to hydrolysis via a retro-Michael reaction.[18,26−28] Furthermore, bioconjugation with maleimide-based prosthetic groups creates stereoisomeric mixtures of *exo*- and *endo*-isomers.[29] In addition, many of these synthons involve three-step syntheses, are obtained in <20% radiochemical yield (RCY), and expend 95−115 min to obtain the HPLC-purified prosthetic group.[22−24]

Several other radiosynthons have been reported for site-selective cysteine conjugation via thiol alkylation (Figure 1). Despite moderate success, bromoacetamides require three step syntheses, azeotropic drying of [^{18}F]fluoride and HPLC purification, resulting in a lengthy production process.[30−32] Reported in 2014, [^{18}F]-(2-(2-(2-fluoroethoxy)ethoxy)-ethylsulfonyl)-ethane ([^{18}F]F-DEG-VS) was utilized to label a neurotensin analogue in moderate yield and maintained in vivo stability with no [^{18}F]fluoride release.[33] More recently, prosthetic groups based on heteroaromatic derivatives provide an alternative class of thiol-reactive synthons with improved stability over maleimides (Figures 1D,E).[34−37] In addition, a new reagent for ^{18}F-trifluoromethylation has demonstrated

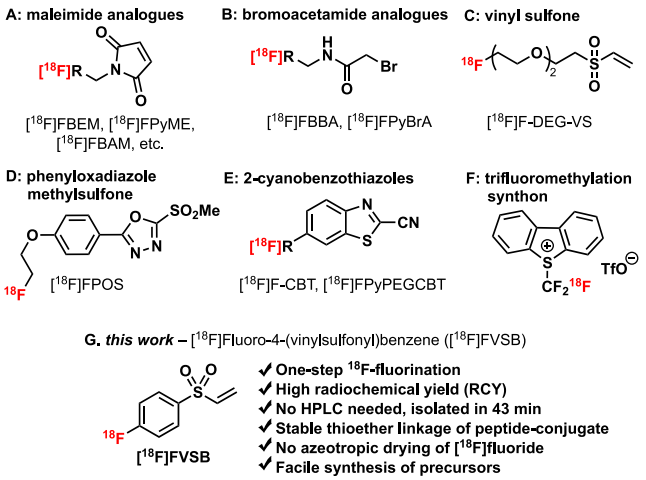


Figure 1. Thiol-reactive radiosynthons for ^{18}F-labeling of cysteine-containing peptides.

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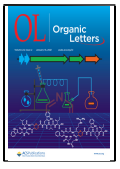

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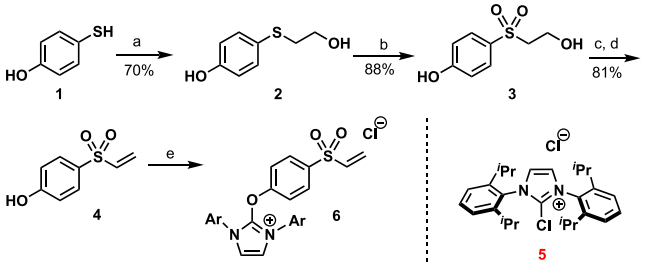
chemoselective ^{18}F-labeling of cysteine-containing peptides, including a [^{18}F]CF_3-amyloid-β fragment (Figure 1F).[10] Despite remarkable advancements, preparation of current thiol-reactive radiosynthons require azeotropic drying of [^{18}F]fluoride and nearly all protocols involve HPLC purification prior to cysteine conjugation. In addition, multistep syntheses or the use of unstable precursors and reagents pose further challenges, resulting in low yields. A robust thiol-reactive synthon that produces a selective and stable linkage while overcoming these limitations offers an attractive alternative approach for peptide ^{18}F-labeling applications.

Here, we report the synthesis and development of [^{18}F]fluoro-4-(vinylsulfonyl)benzene ([^{18}F]FVSB), a new prosthetic group for site-specific conjugation to cysteine residues to afford stable ^{18}F-labeled peptides for applications in PET molecular imaging (Figure 1G). This radiosynthon is prepared in one step, enabled by the deoxyfluorination of a highly stable uronium precursor via a tetrahedral intermediate, and is utilized without azeotropic drying or HPLC purification. Our objective was to provide a readily accessible thiol-reactive synthon for the facile construction of stable, site-specific ^{18}F-labeled peptide conjugates. Critical advantages of a vinyl sulfone motif for cysteine conjugation include the high reactivity with free thiols and the formation of aqueous-stable thioether linkages.[18,38−42] Although reports of vinyl sulfone-functionalized tags toward bioconjugation of peptides and proteins exist, the versatility of this synthon has not been fully explored in the context of ^{18}F-labeling.[41] We designed a vinyl sulfonyl phenol substrate and opted to employ the ^{18}F-deoxyfluorination method reported by Neumann et al.[6] This methodology was chosen due to its robust scope, high radiochemical conversion, use of a stable and accessible precursor, as well as the ability to eliminate azeotropic drying. We anticipated this approach would provide a direct path to a vinyl sulfonyl ^{18}F-arene in a rapid manner.

Preparation of the precursor, uronium **6**, consists of a five-step synthesis and began with commercial thiophenol **1**, which underwent alkylation with bromoethanol followed by oxidation with Oxone to afford sulfone **3** (Scheme 1). Treatment with thionyl chloride and pyridine supplied the chloro intermediate which subsequently underwent elimination under basic conditions to furnish vinyl sulfone **4** in 81% yield. Uronium precursor **6** was obtained upon treatment of phenol **4** with chloroimidazolium chloride and Ag_2CO_3 in chloroform and used after simple filtration with no additional purification.[6]

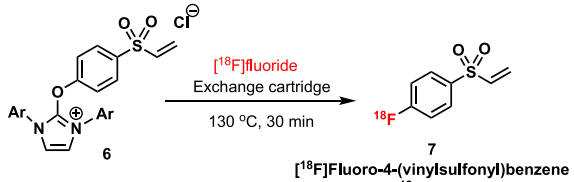
Scheme 1. Preparation of Uronium 6 Precursor[a]



[a]Reagents and conditions: (a) 2-bromoethanol, 1.0 N aq NaOH, MeOH, 23 °C, 21 h; (b) Oxone, MeOH, 23 °C, 2 h; (c) $SOCl_2$, pyridine, CH_2Cl_2, 23 °C, 20 h; (d) Et_3N, THF, 23 °C, 24 h; (e) Ag_2CO_3, **5**, $CHCl_3$, 60 °C, 4.5 h.

The ^{18}F-deoxyfluorination to produce [^{18}F]FVSB **7** began with direct elution of aqueous [^{18}F]fluoride from the anion-exchange cartridge, forgoing the azeotropic drying step of conventional radiofluorination approaches. In this method, aqueous [^{18}F]fluoride was trapped on the cartridge and residual water was removed by flushing with 2-butanone/ethanol (10:1, v/v) and N_2 gas through the cartridge. Uronium complex **6** in a solution of 2-butanone:ethanol was directly passed through the cartridge, without base or additives, to elute the [^{18}F]fluoride. The reaction mixture was directly heated to 130 °C for 30 min and afforded crude [^{18}F]FVSB **7**. Initial optimization focused on the type of anion exchange cartridge and the uronium **6** precursor amounts. [^{18}F]Fluoride elution using a Sep-Pak Accell Plus QMA plus light cartridge was poor, presumably due to excess resin. Improvement in the elution was observed with a custom-made cartridge using 1/16″ PTFE tubing containing 4 mg Biorad MP-1 resin in between two polyethylene frits. Despite moderate elution, inconsistency in the custom cartridges led us to identify a more practical approach that would use a commercial cartridge. Chromafix 30-PS-HCO_3 cartridges were employed which gave sufficiently high elution efficiency using 5 mg of uronium **6** with 94 ± 2% RCY, determined by radio-TLC (Table 1, entry 2). While 3 mg of uronium **6** gave poor [^{18}F]fluoride elution, no improvement in elution efficiency and comparable RCY was obtained when >5 mg of **6** was used (Table 1, entries 1, 3, and 4).

Table 1. Reaction Optimization to Afford [^{18}F]FVSB[a]



entry	precursor (mg)	elution efficiency[b] (%)	RCY[c]
1	3	60 ± 3	88 ± 2[d]
2	5	84 ± 3	94 ± 2[e]
3	7	84 ± 2	97 ± 1[e]
4	9	83 ± 1	96 ± 2[d]

[a]Conditions: precursor, [^{18}F]fluoride (~500 μCi), 10:1 butanone/EtOH (1 mL), 130 °C, 30 min. [b]Determined by dividing the activity eluted from the cartridge by the initial activity loaded on the cartridge. [c]RCY was determined by radio-TLC. Product identity was confirmed by radio-HPLC. [d]n = 2. [e]n = 5. Ar = 2,6-diisopropylphenyl.

We hypothesized that HPLC purification could be avoided and that [^{18}F]FVSB may be promptly utilized for peptide conjugation. We next focused on cartridge purification of [^{18}F]FVSB and screened various commercial cartridges (Table S4). Purification by Oasis HLB plus short LP cartridges resulted in removal of unreacted [^{18}F]fluoride and enabled isolation of [^{18}F]FVSB within 43 min in 46 ± 4% decay-corrected RCY with 85% radiochemical purity (RCP) (Tables S1 and S2, Figures S11 and S12). The molar activity was calculated for HPLC-purified [^{18}F]FVSB and determined to be >2.87 Ci·μmol^{-1} (106.2 GBq·μmol^{-1}). Notably, precursor **6** could be stored at −4 °C for up to 12 months or at room temperature for up to 6 months and used with no discernible loss in quality or RCY.

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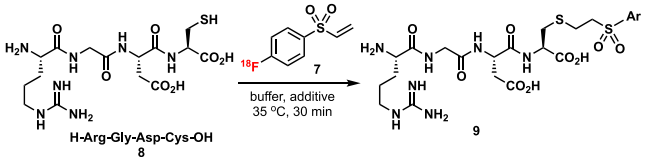
Peptides containing the Arg-Gly-Asp (RGD) sequence display high affinity for integrin $\alpha_v\beta_3$ and are useful for PET molecular imaging of angiogenesis.[43] As such, we initially investigated the bioconjugation of cysteine-containing peptides with [^{18}F]FVSB **7** using the linear tetramer **8**, Arg-Gly-Asp-Cys (RGDC) (Table 2). Conjugate addition of 5 mg of peptide **8**

Table 2. Bioconjugation Optimization[a]



entry	precursor (mg)	buffer	additive	RCY[b] (%)
1	5	borate (pH 8.5)		65 ± 4
2	5	HEPES (pH 7.3)		59 ± 4
3	5	borate (pH 8.5)		70 ± 7[c]
4	5	borate (pH 8.5)		47 ± 5[d]
5	5	borate (pH 8.5)	25% MeOH	86 ± 7
6	5	HEPES (pH 7.3)	75% MeOH	27 ± 1
7	5	borate (pH 8.5)	50% MeOH	90 ± 0
8	**3**	**borate (pH 8.5)**	**50% MeOH**	**89 ± 6**
9	1	borate (pH 8.5)	50% MeOH	79 ± 11

[a]Conditions: ~400−700 μCi **7** per reaction, solvent (500 μL). Reactions performed in duplicate. [b]nonisolated RCY is estimated by radio-HPLC analysis of crude peptide **9**. [c]Reaction temperature = 23 °C. [d]Reaction temperature = 45 °C. Ar = 4-[^{18}F]fluorophenyl.

to [^{18}F]FVSB **7** proceeded in sodium borate (pH 8.5) buffer in 30 min in 65 ± 4% RCY, as determined by radio-HPLC (entry 1). Bioconjugation in HEPES (pH 7.3) buffer afforded peptide conjugate **9** in 59 ± 4% RCY (entry 2). Optimization of the reaction temperature revealed that mild temperatures (23−35 °C) gave highest RCYs and heating to 45 °C decreased the RCY to 47 ± 5% (entries 1, 3, 4 and Table S6).

In many cases, unreacted [^{18}F]FVSB **7** was present after 30 min yet increasing the reaction time is undesirable for PET applications. We sought to push the thiol conjugation to completion by exploring a solvent additive, such as DMF or MeOH, which may enhance peptide solubility (Table S7). With 25% MeOH, ^{18}F-labeled conjugate **9** was obtained in 86 ± 7% RCY in sodium borate buffer (entry 5). Too much methanol was detrimental to the reaction (entry 6), yet 50% MeOH in either buffer afforded ^{18}F-labeled conjugate **9** in 90 ± 0% RCY (entry 7). Comparable RCYs were obtained by lowering the peptide precursor amount to 3 mg (entry 8 and Table S5). Lastly, for labeling precious peptides with limited supply, 1 mg of precursor was sufficient to afford the radiolabeled peptide conjugate in high RCY (entry 9). Although DMF could be used, we opted to employ MeOH because the peptide solubility appeared better in MeOH over DMF and, due to its lower boiling point, MeOH can be readily removed by evaporation.

The optimized bioconjugation conditions were applied to a series of thiol-containing peptides to examine the versatility of [^{18}F]FVSB toward complex substrates which mimic potential PET tracers (Figure 2). The unprotected, linear RGDC peptide **8** readily delivered ^{18}F-construct **9** in 84 ± 8% decay-corrected RCY with exclusive reactivity at the cysteine residue. An analogue of the gastrin-releasing peptide receptor (GRPR) tracer MG11 was successfully conjugated to [^{18}F]FVSB **7** to afford octamer **10** as the single radioactive product in 83 ± 10% RCY.[44] Of note, competitive reactivity with tryptophan was not observed by radio-HPLC, verifying the indole ring of tryptophan is compatible with the labeling protocol (Figure S20).

Cyclic RGD peptides have also garnered sufficient interest as PET tracers prompting us to synthesize cyclic RGDfC analogue **11** which was achieved in 87 ± 2% RCY.[45,46] Due to the recent success in targeting prostate specific membrane antigen (PSMA) for PET imaging of prostate cancer, we applied the approach toward radiolabeling of a PSMA analogue which gave construct **12** in 80 ± 3% RCY.[47] Synthesis of an ^{18}F-labeled neuromedin B analogue **13** was accomplished in 93 ± 1% RCY. Additionally, larger peptides, such as the bombesin analogue **14** containing 14 amino acids was successfully radiolabeled in 55 ± 11% RCY.[48] The presence of unreacted [^{18}F]FVSB in the HPLC trace for analogue **14** suggests that cosolvent systems to increase solubility for larger peptides could remedy the incomplete conversion for specific cases.

To reinforce the compatibility of [^{18}F]FVSB in the presence of other nucleophilic residues, such as histidine or lysine, competition studies were conducted (Figures S25−S29). Competition between *N*-Boc-cysteine and *N*-Boc-lysine with [^{18}F]FVSB yielded, exclusively, the desired cysteine-conjugate addition product in 85 ± 0% RCY, while the lysine-conjugate addition product was not observed (Figure S27). Similarly, competition between *N*-Boc-cysteine and *N*-Boc-histidine afforded the cysteine-conjugate addition product in 88 ± 2% RCY and the histidine-conjugate addition product in only 1 ± 2% RCY (Figure S29). Importantly, these studies reveal the overwhelming predominance for bioconjugation to occur at the cysteine residue, even when histidine or lysine residues are present. Lastly, reactivity toward *N*-terminal amines was evaluated with an RGD peptide lacking a cysteine residue. In this case, with no available thiol, amine conjugation toward [^{18}F]FVSB proceeded in only 6% RCY; therefore, the presence of *N*-terminal free amines is well tolerated and does not impede generation of the desired thiol-conjugated product (Figure S30).

To evaluate the peptide conjugates for stability against elimination of the vinyl sulfone and loss of the radiolabel, peptide **9** was incubated for 1 h at 35 °C in various conditions and the remaining conjugate was calculated by HPLC analysis (Figures S31−34). In aqueous glutathione or in pH 2.6 acetic acid buffer, 97% of conjugate **9** and 0% of [^{18}F]FVSB were observed. In pH 9.5 sodium borate buffer, 82% of conjugate **9** and 5% of [^{18}F]FVSB were observed. These results suggest that, after 1 h, 5% elimination of the vinyl sulfone occurs under basic conditions and no observable elimination occurs under neutral or acidic conditions.

In summary, we report a simple, metal-free approach for ^{18}F-labeling of cysteine containing peptides via a novel prosthetic group, [^{18}F]FVSB. To our knowledge this is the first aryl vinyl sulfone radiosynthon to be reported which can be produced in 43 min in high molar activity and directly used for peptide conjugation without HPLC purification. The robustness of our method is highlighted by the diversity of peptide conjugates that were successfully ^{18}F-labeled in up to 93% RCY. We contend that the [^{18}F]FVSB radiosynthon we report here will offer significant improvement over current strategies for multiple reasons. First, its simplicity—our method is a one-step radiofluorination of a stable precursor that is facile to synthesize and provides [^{18}F]FVSB in high RCY. Second,

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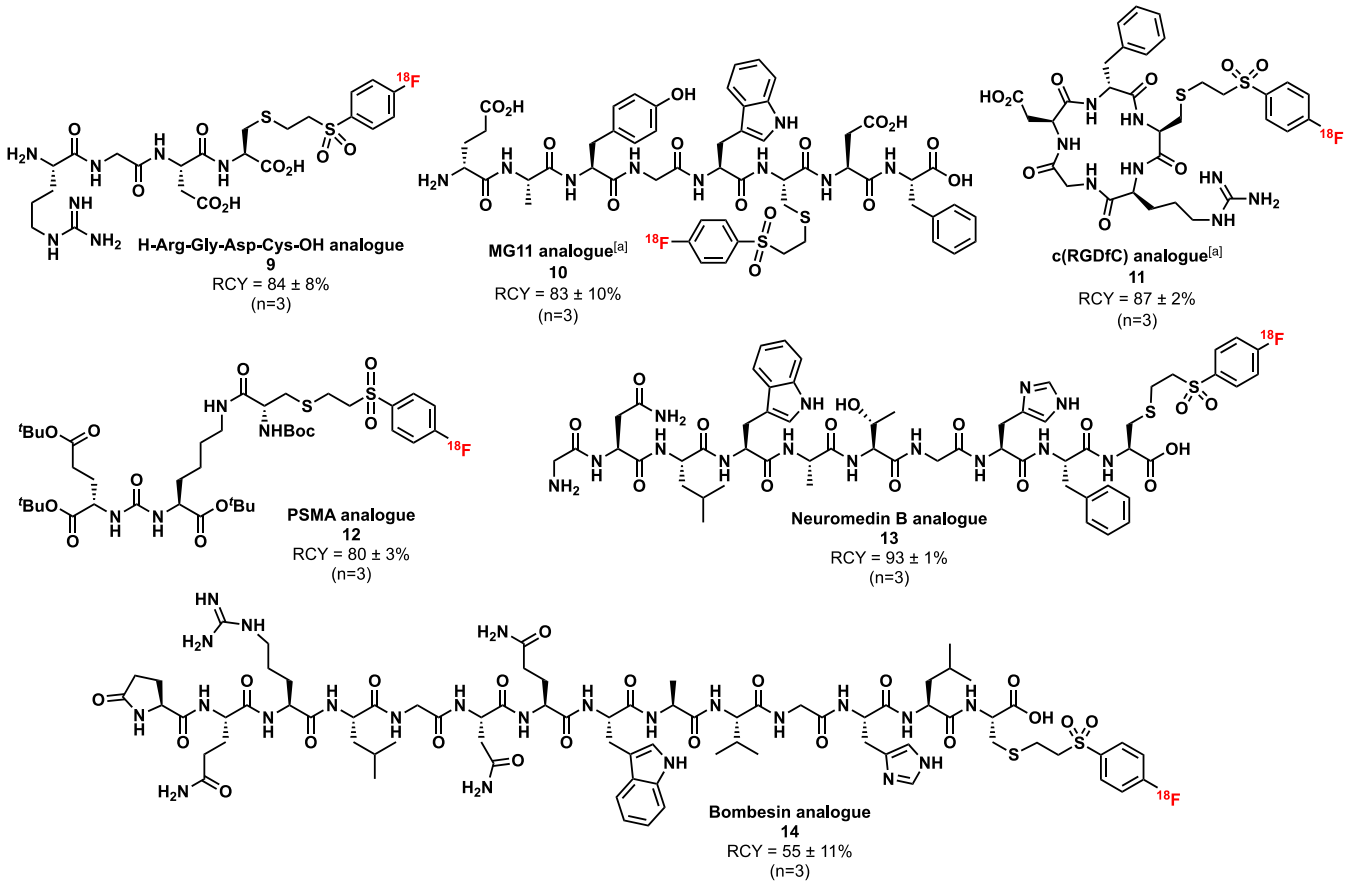

Figure 2. Site-selective ^{18}F-labeling of peptides via cysteine bioconjugation with [^{18}F]fluoro-4-(vinylsulfonyl)benzene. Reaction conditions: peptide (3 mg), **7** (0.5−1.5 mCi), sodium borate buffer pH 8.5 (250 μL), MeOH (250 μL), 35 °C, 30 min. Radiochemical purity (RCP) was determined by radio-HPLC and was calculated by dividing the integrated area of the ^{18}F-labeled product peak by the total integrated area of all ^{18}F-labeled peaks. Identity of each labeled product was confirmed by coinjection with the authentic ^{19}F-reference standard. The decay-corrected radiochemical yield (RCY) was calculated by dividing the final activity of the labeled product by starting [^{18}F]FVSB activity, multiplied by the RCP. [a]5 mg peptide, HEPES buffer pH 7.3 (250 μL), DMF (250 μL).

conjugation to [^{18}F]FVSB yields a highly stable thioether linkage using 2 μmol peptide. Third, and perhaps most crucial, our method eliminates the time-consuming azeotropic drying and HPLC purification steps—a noteworthy benefit for fluorine-18 methodology. Additionally, exclusive reactivity at the cysteine residue in the presence of other nucleophilic residues was demonstrated, confirming the high chemoselectivity of our approach.

Preliminary attempts at automation have been conducted using the ELIXYS FLEX/CHEM radiochemical synthesis module (Sofie Biosciences). Starting with 21 mCi of [^{18}F]fluoride, the automated protocol resulted in an elution efficiency of 82 ± 0% and afforded [^{18}F]FVSB in 63 ± 1% RCY, determined by radio-TLC (n = 2, unoptimized), demonstrating the process can successfully be automated for PET applications. High activity production of [^{18}F]FVSB for protein labeling and PET imaging studies are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04054.

Materials and methods, chemical syntheses, detailed experimental procedures, radiochemical protocols, optimization screens, compound characterization, HPLC traces, and NMR spectra (PDF)

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Author Contributions

[§]G.M. and J.W.M. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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