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Azeotropic drying-free aliphatic radiofluorination to produce PET radiotracers in a mixed organic solvent system

Young-Do Kwon[a] , Jeongmin Son[b] , Mijin Yun[a,b] and Joong-Hyun Chun[a] ∗

[a] *Department of Nuclear Medicine, Yonsei University College of Medicine, Seoul 03722, Republic of Korea*

[b] *Department of Nuclear Medicine, Severance Hospital, Yonsei University Health System, Seoul 03722, Republic of Korea*

ABSTRACT

Efficient aliphatic radiofluorination in a mixed organic solvent system was investigated. This method obviates the time-consuming [^{18}F]fluoride drying step routinely required in the preparation of most fluorine-18 positron emission tomography (PET) radiotracers. The [^{18}F]fluoride ions eluted from a QMA (quaternary ammonium anion exchange) cartridge with phase transfer agents were directly mixed in various organic solvents for subsequent radiofluorination. Herein, we report the azeotropic drying-free radiofluorination of aliphatic substrates and demonstrate the viability of hydrated [^{18}F]fluoride ions in a mixed organic solvent system for obtaining useful radiochemical yields (RCYs). This practical and simple method has demonstrated general applicability to the production of established PET tracers as well as to the rapid assessment and chemical optimization of early-stage potential radiotracers.

Keywords: PET, fluorine-18, radiofluorination, PET radiotracer, automation

∗ Corresponding author. Joong-Hyun Chun, Tel.: +82-2-2228-2348; fax: +82-2-312-0578; e-mail: jchun@yuhs.ac

Positron emission tomography (PET) is a molecular imaging technique used to study the dynamics and metabolism of radiotracer distribution in living subjects.[1] The widespread availability of affordable cyclotrons in hospitals allows this technology to be used to diagnose various diseases in their early stages, thus improving overall clinical outcomes. Among the many radionuclides produced by cyclotrons, fluorine-18 is the species of choice as it provides ideal imaging characteristics and a desirable decay pattern.[2] Considering the short half-life ($t_{1/2}$ = 110 min) of fluorine-18, a short radiolabeling time requires reliable PET radiotracer production to introduce fluorine-18 to the target molecule for subsequent imaging studies. The hydration of [^{18}F]fluoride ions is known to have a detrimental effect on the nucleophilicity of fluorine-18, leading to poor overall labeling. In general, cyclotron-produced [^{18}F]fluoride ions are generated by the ^{18}O(p,n)^{18}F nuclear reaction and delivered in their fully hydrated states in [^{18}O]H_2O water. Azeotropic evaporation for the removal of water from cyclotron-produced [^{18}F]fluoride ions is considered to be a crucial step in many ^{18}F-radiotracer preparation procedures. It is, however, both laborious and time-consuming.[3] Excluding this drying step can be advantageous for extensive radiochemistry optimization by allowing the rapid screening of vast chemical libraries against desired target molecules. Significant progress has been made to relieve the burden of this time-consuming process during radiolabeling. Recent efforts have focused on improving radiolabeling efficiency either by varying the [^{18}F]fluoride elution method or by modulating the [^{18}F]fluoride drying process using tetraalkylammonium salts,[4] polymeric solid supports,[5] modulation of bases,[6] ionic liquids,[7] and the addition of protic solvents to the reaction medium.[8] These efforts have been moderately effective in either improving the radiochemical yield (RCY) or enhancing operational convenience; however, some limitations to the application of these methods in commercial modules for complete automation remain, such as elution from QMA in the reverse direction or multiple elutions.[4–7] Although radiofluorination in aqueous medium has

been used to produce [^{18}F]fluoroarenes from [^{18}F]fluoride ions, there are few systematic investigations of aliphatic radiofluorination using hydrated [^{18}F]fluoride ions.[9] In this regard, the exclusion of azeotropic drying boasts several advantages over the conventional full-drying method in terms of time management and the facile automation of PET tracer production.

Herein, we report a convenient radiolabeling method without the need for azeotropic drying through direct use of the [^{18}F]fluoride eluent from QMA in a mixed organic solvent (Fig. 1). This drying-free radiofluorination method can be applied to the production of many PET tracers, and to complement existing labeling protocols.

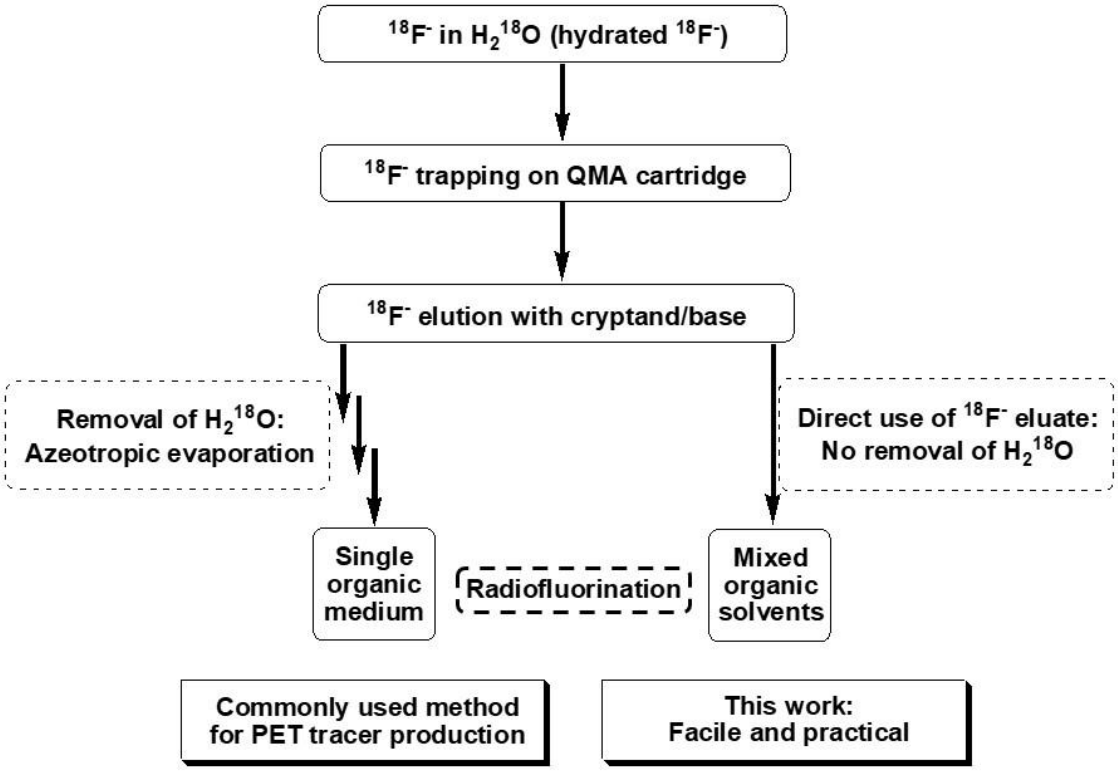
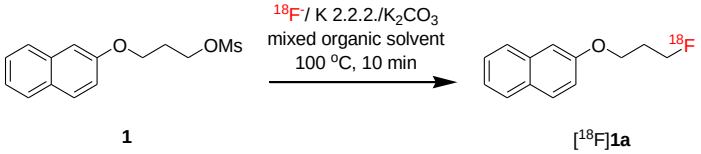


Figure 1. Radiofluorination with [^{18}F]fluoride ions in a mixed organic solvent.

The azeotropic removal of water from cyclotron-produced fluoride ions is a key step in the preparation of many fluorine-18-based radiotracers. The [^{18}F]fluoride ions generated by cyclotrons are delivered in their fully hydrated states. Therefore, the radiolabeling medium inevitably contains water, which may reduce the radiolabeling efficiency. Although uncommon in established radiofluorination procedures, we used a mixed organic solvent system to minimize the effect of residual water from QMA elution. The eluted fluoride ion complex was directly mixed with various organic solvents, including *N*-methyl-2-pyrolidone (NMP), 1,4-dioxane, dimethylsulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), and *N*,*N*-dimethylacetamide (DMA), for use over a broad temperature range and to improve substrate solubility. 3-(Naphthalen-2-yloxy)propyl methanesulfonate (**1**) has been widely used in the assessment of aliphatic fluorination efficiency with protic solvents.[8,10] Therefore, **1** was selected as a model compound to explore the feasibility of aqueous aliphatic radiofluorination in mixed organic solvents with an $^{18}F^-$/K 2.2.2./K_2CO_3 eluent. To determine the labeling efficiency in a mixed organic solvent, model compound **1** was radiofluorinated in different combinations of solvent with [^{18}F]fluoride eluate directly acquired from the QMA cartridge (Table 1).

Table 1. Screening of labeling efficiency in a mixed organic system for azeotropic drying-free radiofluorination.[a]



1 [^{18}F]**1a**

Entry	Solvent[b]	RCY (%)[c]
1	MeCN	20
2	30% DMSO/MeCN	39
3	50% DMSO/MeCN	54
4	70% DMSO/MeCN	76
5	90% DMSO/MeCN	71
6	70% DMF/MeCN	53
7	90% DMF/MeCN	51
8	70% DMA/MeCN	71
9	90% DMA/MeCN	69
10	70% NMP/MeCN	50
11	90% NMP/MeCN	50
12	70% 1,4-Dioxane/MeCN	31
13	90% 1,4-Dioxane/MeCN	56

[a] Reaction conditions: [^{18}F]Fluoride eluate (200 μL of an eluate from the K 2.2.2./K_2CO_3 eluent[11] (1000 μL)), precursor **1** (2 mg), 100 °C, 10 min.
[b] Total reaction volume (2 mL) including the [^{18}F]fluoride eluate (200 μL).
[c] Determined by radio-TLC (average of two runs).

Radiofluorination was initially performed in a DMSO/MeCN solvent system without the azeotropic removal of trace water. Note that a [^{18}F]fluoride eluate acquired under these conditions will inevitably contain a certain amount of water (*ca*. 20 μL water per 1,000 μL eluent) from the K 2.2.2./K_2CO_3 eluent and residual water (*ca*. 84 μL) from the QMA cartridge. One fifth of the eluate was used for each reaction in Table 1, so the amount of water in the reaction medium was as much as 20 μL. Interestingly, aliphatic radiofluorination proceeded in a 30% DMSO/MeCN solvent mixture at 100 °C for 10 minutes, providing the

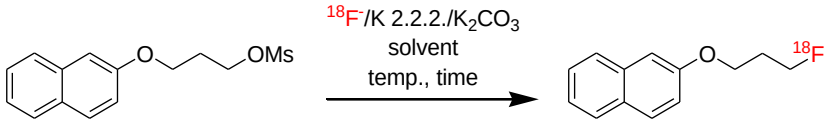
radiofluorinated naphthyl compound [^{18}F]**1a** in a RCY of 39%. Further variations in the DMSO volume (30–90% DMSO volume content in the DMSO/MeCN combination) provided RCYs of 76% and 71% in 70% DMSO and 90% DMSO, respectively. Further screening in different organic solvents (DMF, DMA, 1,4-dioxane, and NMP) resulted in moderate to good RCYs ranging from 31% to 71%. In general, reactions performed in the mixed organic solvents showed higher RCYs than those performed only in MeCN (RCY 20%). From the solvent screening results, 70% DMA/MeCN and 70% DMSO/MeCN mixtures were chosen as ideal organic solvent systems for radiofluorination.

Next, we investigated the [^{18}F]fluoride elution efficiency associated with the volume of phase transfer agent (PTA) solution from QMA (see ESI for details). As the total volume (2 mL) of the reaction solvent can be determined mainly by the portion of eluate volume from PTA containing the $^{18}F^-$/K 2.2.2./K_2CO_3 complex, the optimized volume required to elute the $^{18}F^-$/K 2.2.2./K_2CO_3 complex in MeCN/H_2O was a key factor in this radiofluorination method. It is also necessary to use a limited volume of solvent when PET tracers are intended for production on a commercialized module. Due to the inherent water content in the $^{18}F^-$/K 2.2.2./K_2CO_3 eluent, unnecessarily large volumes of PTA should be avoided to minimize the water content in the reaction medium. Careful measurements revealed that the elution efficiency of the QMA cartridge with K 2.2.2./K_2CO_3 in 600 μL of water-MeCN solvent (12 μL of water plus 588 μL of MeCN) was 86% $^{18}F^-$/K 2.2.2./K_2CO_3 complex (n = 2), which was still useful for radiofluorination. The optimal elution efficiency from the QMA cartridge was not considered in the determination of radiofluorination RCYs.

After establishing the solvent system, other reaction parameters, such as reaction time and temperature, were explored to optimize the fluorination conditions (Table 2). Although longer reaction times would provide higher RCYs for some isotope labeling,

reaction times longer than 20 minutes were not considered in the development of our rapid fluorine-18 radiochemistry model. In addition, temperatures above 150 °C were not considered to avoid the complications associated with the potential precursor degradation and side reactions that often occur at elevated temperatures. A total of 600 µL of K 2.2.2./K_2CO_3 eluent was used for each reaction in Table 2. Consequently, the amount of water in the reaction medium was *ca*. 96 µL (volume of water [*ca*. 12 µL] from the K 2.2.2./K_2CO_3 eluent and residual water [*ca*. 84 µL] from the QMA cartridge). With a higher water content, the RCYs obtained under otherwise identical reaction conditions were lower (Table 2, entry 1 vs. Table 1, entry 4 and 8). From radiofluorination in a mixed organic solvent, [^{18}F]**1a** was obtained in RCYs of 73% and 76% at 140 °C in 70% DMA/MeCN and 70% DMSO/MeCN, respectively. These values were comparable to the previously reported RCYs with use of azeotropically dried [^{18}F]fluoride ions for radiofluorination.[7] Furthermore, it was demonstrated that trace amounts of additional water (0.5–10 volume %) in a mixed organic system can be tolerated when the reaction is run using the optimal conditions for radiofluorination (140 °C, 10 min, and 70% DMSO [or DMA]/MeCN) (see ESI for details).

Table 2. Optimization of radiofluorination conditions in DMA/MeCN and DMSO/MeCN mixed systems.[a]



1 [^{18}F]**1a**

Entry	Temp. (°C)	Time (min)	Solvent (2 mL)	
			70% DMA/MeCN[b]	70% DMSO/MeCN[b]
			RCY (%)[c]	RCY (%)[c]
1	100	10	19	24
2	100	20	25	35
3	120	10	61	55
4	120	20	64	60

5	140	10	73	76
6	140	20	72	72

[a] Reaction conditions: [^{18}F]Fluoride eluate from the K 2.2.2./K_2CO_3 eluent[12] (600 μL), precursor **1** (2 mg).
[b] Total reaction volume (2 mL) including the [^{18}F]fluoride eluate (600 μL).
[c] RCY was determined by radio-TLC (average of two runs).

Based on these preliminary results, the general applicability of the method was evaluated with a broader substrate scope (Fig. 2). These labeling precursors were designed to reflect the structural resemblance often encountered in chemical structures of precursors for aliphatic radiofluorination (see ESI for details). Using the optimal conditions for [^{18}F]**1a**, additional radiofluorination reactions were examined with compounds **2**, **3**, **4**, and **5** to determine the labeling outcomes (Table 3).

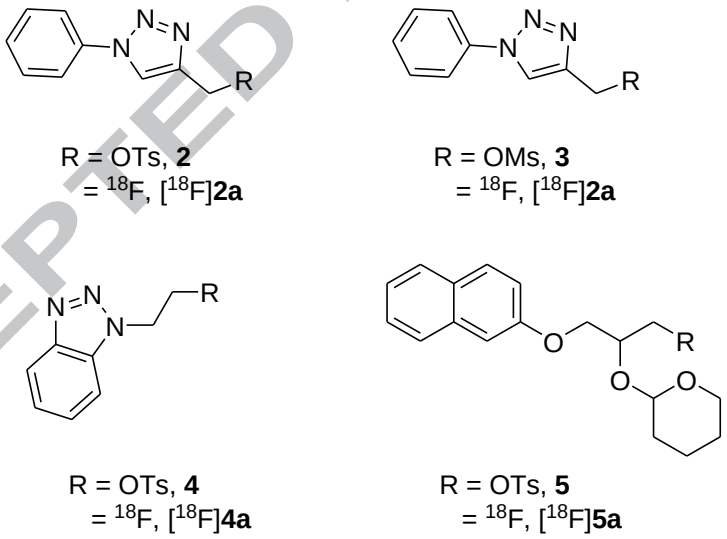


Figure 2. Precursors used to evaluate azeotropic drying-free aliphatic radiofluorination.

Compounds **2** and **3**, which have an aliphatic fluorination site with tosylate and mesylate leaving groups, were used as substrates. RCYs of 5–8% and 28–30% were obtained when compound **2** was radiofluorinated in 70% DMSO/MeCN and 70% DMA/MeCN,

respectively. [^{18}F]**2a** was obtained from **2** with reduced RCY over the temperature range of 120–140 °C in the DMSO mixed system. We later found that the low RCY of [^{18}F]**2a** could be ascribed to the instability of **2** in 70% DMSO/MeCN, as verified by HPLC (UV, 254 nm; data not shown). An alkyl mesylate attached to the triazole ring (**3**) gave higher RCYs than the tosylate leaving group. With an alkyl tosylate directly attached to the benzotriazole nitrogen heteroatom (**4**), aliphatic radiofluorination occurred to afford [^{18}F]fluorobenzotriazole ([^{18}F]**4a**) in RCYs of 23–32% in the DMSO mixed system and 46–52% in the DMA mixed system. Compound **5**, which has a tetrahydropyranyl (-THP) protecting group and an alkyl tosylate connected *via* a glycolic linkage to a naphthalenyl ring, was selected to assess the applicability of the two-step radiofluorination method. This chemical structure, which can be found in PET radiotracers such as the tau PET imaging [^{18}F]THK5351 tracer[13] and hypoxia imaging [^{18}F]FMISO PET tracer,[14] can be used to demonstrate the feasibility of the established two-step reaction, including radiofluorination and deprotection, to afford the [^{18}F]fluorohydrin structure on the PET tracer. Radiofluorinated [^{18}F]**5a** was obtained in a RCY of 28% from the reaction in 70% DMA/MeCN before deprotection. The identity of the protected [^{18}F]**5a** was confirmed by comparison with a nonradioactive standard using radio-HPLC.

Table 3. Azeotropic drying-free aliphatic radiofluorination of various substrates in mixed organic solvent.[a]

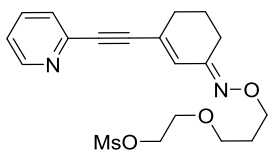
Entry	Temp. (^{o}C)	Time (min)	Solvent[b]	[^{18}F]Fluorinated products, RCY (%)[c]			
				[^{18}F]**2a_1**[d]	[^{18}F]**2a_2**[e]	[^{18}F]**4a**	[^{18}F]**5a**
1	120	10	70% DMSO/MeCN	5	16	23	16
2	120	10	70% DMA/MeCN	28	38	46	12
3	120	20	70% DMSO/MeCN	8	18	32	25
4	120	20	70% DMA/MeCN	27	38	52	18
5	140	10	70% DMSO/MeCN	5	20	26	23
6	140	10	70% DMA/MeCN	30	39	49	28

[a] Reaction conditions: [^{18}F]Fluoride eluate from the K 2.2.2./K_2CO_3 eluent[12] (600 μL), precursor (2 mg).

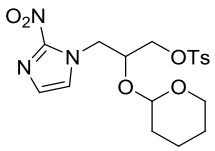
[b] Total reaction volume (2 mL) including the [^{18}F]fluoride eluate (600 μL).
[c] RCY was determined by radio-TLC (average of two runs).
[d] [^{18}F]**2a_1** was produced from compound **2**.
[e] [^{18}F]**2a_2** was produced from compound **3**.

After establishing the relevance of this method for aliphatic PET radiotracer production, the method was extended to demonstrate its usefulness in the established production of clinical PET radiotracers such as [^{18}F]-(*E*)-PSS232, [^{18}F]FMISO, and [^{18}F]fallypride (Table 4).

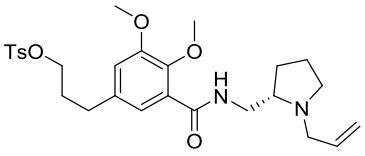
Table 4. Application of azeotropic drying-free radiofluorination to clinical PET tracers.[a]



PSS232 mesyl-precursor



FMISO tosyl-precursor



Fallypride tosyl-precursor

Precursor	Precursor amount (mg)	Temp. (°C)	Time (min)	70% Organic mixed Solvent[b]	
				DMSO	DMA
				RCY (%)[c]	RCY (%)[c]
Mesyl-PSS232	1.0	120	10	13	12
		120	20	15	16
		140	10	22	19
	2.0	140	10	36	-
Tosyl-FMISO	1.0	120	10	9	12
		120	20	12	20
		140	10	15	22
	2.5	140	10	-	46
Tosyl-Fallypride	1.0	120	10	16	15
		120	20	15	16
		140	10	17	17
	2.7	140	10	-	45
	3.0	140	10	-	46[d]
				-	25[e]

[a] [^{18}F]Fluoride eluate from the K 2.2.2./K_2CO_3 eluent[12] (600 µL) was utilized.
[b] Total reaction volume (2 mL) including the [^{18}F]fluoride eluate (600 µL).
[c] RCY was determined by reverse phase radio-HPLC (average of two runs).
[d] Reaction was performed with a GE TRACERlab™ FX_{FN} Pro (average of two runs).
[e] Reaction was performed with a GE TRACERlab™ FX_{FN} (average of two runs) and purified by prep HPLC.

[^{18}F]-(*E*)-PSS232, a recently developed mGlu5 radiotracer,[15] was initially investigated in a mixed organic solvent system. The mesylate precursor was radiolabeled and [^{18}F]-(*E*)-PSS232 was obtained in 22% RCY in 70% DMSO/MeCN. The reaction temperature used here was higher than the reported method, but neither precursor degradation nor thermal (*E*),(*Z*)-isomerization was observed. Surprisingly, increasing the amount of

precursor from 1 to 2 mg provided a higher RCY comparable to the RCY of [^{18}F]-(*E*)-PSS232 obtained in the conventional drying method.[16] When the tosyl-precursor of [^{18}F]FMISO was radiolabeled with [^{18}F]fluoride containing trace amounts of water, [^{18}F]FMISO RCYs of 12–22% were obtained in 70% DMA/MeCN solvent before the deprotection step. The RCY was also significantly improved to 46% when the amount of precursor was increased from 1 to 2.5 mg. In this experiment, deprotection of the -THP group was intentionally omitted only to assess the labeling efficiency in a mixed solvent medium. Careful examination of the UV trace for the reaction revealed no by-product formation caused by the presence of water and the higher reaction temperature compared to the reported method.[14] [^{18}F]Fallypride, used as a D2/D3 receptor imaging PET radiotracer,[17] was selected to demonstrate aliphatic radiofluorination in a mixed organic system. The one-step radiofluorination of the tosyl-fallypride precursor provided a RCY of 45% in 70% DMA/MeCN. Finally, we validated the adaptability of this method by its implementation in commercial radiosynthesizers for the automated production of clinical PET radiotracers. [^{18}F]Fallypride was chosen as a viable clinical PET radiotracer and radiosynthesis was performed using a GE TRACERlab™ FX_{FN} Pro and a GE TRACERlab™ FX_{FN} (GE Healthcare, Madison, WI, USA), which are widely distributed commercial instruments at clinical sites (see ESI for details). Cyclotron-produced [^{18}F]fluoride ions were trapped on a QMA cartridge and released into a reaction vessel with an eluent containing K 2.2.2./K_2CO_3 in MeCN/H_2O (600 μL). The tosyl-fallypride precursor dissolved in DMA (1.4 mL) was introduced to the reaction vessel resulting in an overall 2 mL reaction volume with 70% DMA organic content. The reaction was subsequently performed at 140 °C for 10 minutes without azeotropic drying. After radiofluorination, an aliquot of the reaction mixture was taken and diluted with a 40% MeCN/H_2O solution to analyze the product by radio-HPLC. The automated production of [^{18}F]fallypride matched the RCY value (46%, n = 2) of the

manual batch production in a reaction vessel (45%, n = 2). Preparative HPLC isolation of the resulting [^{18}F]fallypride in a mixed organic solvent validated the use of this method for the large-scale production of PET radiotracers, albeit with somewhat lower RCY (decay-corrected, 25%, n = 2). These radiosyntheses with established radiotracers demonstrate that azeotropic drying-free fluorination can be readily extended to produce PET radiotracers in mixed organic systems, thereby obviating laborious [^{18}F]fluoride drying. These non-drying approaches can be used to replace existing radiotracer production, as well as in the development of PET radiotracers to expedite rapid radiochemistry screening and streamlining production for preclinical studies.

In conclusion, the operationally simple and practical azeotropic drying-free radiofluorination method proved viable for the production of PET tracers with aliphatic fluorination sites. Aliphatic radiofluorination in a mixed organic solvent showed good water tolerance, providing alternative routes to existing labeling methods. This study demonstrated that moderate, though useful, RCYs can be achieved regardless of trace water in a mixed organic solvent. In addition, the mixed organic method enables rapid radiochemistry optimization for early stage PET radiotracer development, which may be useful for PET tracer production in preclinical investigations. The scope and results obtained with this aliphatic radiofluorination methodology can be applied to the streamlined production of aliphatic PET radiotracers, thus simplifying the overall radiopharmaceutical development with automation, which is especially important in clinical settings.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at.

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11. The K 2.2.2./K_2CO_3 eluent (1000 μL) was a solution of K 2.2.2. (12 mg, 32 μmol) and K_2CO_3 (2.2 mg, 16 μmol) in MeCN-H_2O (49:1 v/v; total 1000 μL).

12. The K 2.2.2./K_2CO_3 eluent (600 μL) was a solution of K 2.2.2. (7.2 mg, 19 μmol) and K_2CO_3 (1.3 mg, 9.6 μmol) in MeCN-H_2O (49:1 v/v; 600 μL).

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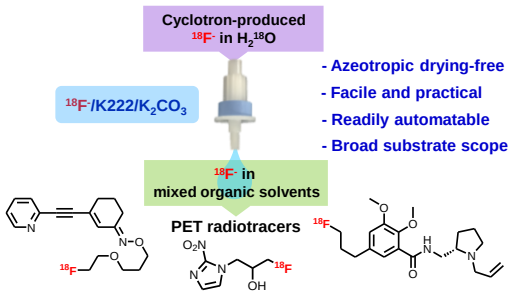
TOC Figure



Highlights

- Azeotropic drying-free radiofluorination in mixed organic solvent.

- Applicability to broad substrate scope for aliphatic radiofluorination.

- Operationally simple and facile automation for preclinical/clinical tracer production.

- Rapid optimization of radiochemistry for newly developed compounds.