Journal of Fluorine Chemistry 283–284 (2025) 110423

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

A simplified GMP-compliant cassette synthesis for ruthenium-mediated ^{18}F-deoxyfluorination of [^{18}F]FPATPP from a phenolic precursor

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ARTICLE INFO

Keywords:
Fluorine-18
PET tracer
GMP
Ruthenium-mediated fluorination
Cassette synthesis
Small molecules
CB1

ABSTRACT

Ruthenium-mediated ^{18}F-deoxyfluorination of phenols is a fairly new, but highly underutilized, labeling method option of tracers for positron emission tomography (PET). Most of the published methods are directed toward peptide syntheses and include extensive preparation steps. This study aimed to simplify ruthenium-mediated ^{18}F-deoxyfluorination of [^{18}F]FPATPP by using the TRASIS AllinOne synthesis platform. This protocol takes minimal preparation time (1 h) and applies a straightforward synthesis that can be used to produce tracers from their electron-rich phenolic precursors bearing protic functional groups such as alcohols and amines. The new simplified cassette method afforded a novel cannabinoid receptor 1 specific tracer [^{18}F]FPATPP with a radiochemical yield of 34 ± 2 %, radiochemical purity of ≥ 97 %, and a molar activity of 620 ± 75 GBq/μmol. The total synthesis time was 55 min. In addition, we developed an attachable accessory compatible with TRASIS AllinOne to enable needle movement to enhance the synthesis yield. Our results broaden the possibilities of a cassette based synthesis development for ^{18}F-labeled molecules and bridge the gap between research and GMP compatible synthesis methods.

1. Introduction

PET is a noninvasive imaging tool that relies on the production of biologically interesting tracer molecules designed to answer diagnostic or academic problems [1]. The injected tracer molecule contains a positron emitting radionuclide (usually a fluorine-18, carbon-11 or gallium-68) which can be detected with PET scanners. Fluorine-18 ($T_{1/2}$=109.8 min) labelling methods mostly utilize nucleophilic substitution in tracer production. Before the labeling, the cyclotron-produced aqueous [^{18}F]fluoride is activated by separating the [^{18}F]fluoride from the aqueous phase. This is carried out using an anion exchange cartridge, an azeotropic distillation step, or a combination of the two and with the assistance of a phase-transfer catalyst. In addition, the precursor molecule requires a good leaving group as well as protecting groups on other, potentially reactive, functional groups in the molecule to ensure specific labeling [2]. Even with the protected precursors the ^{18}F-fluorination of complex molecules and electron rich arenes is difficult using traditional methods.

These limitations have led to the development of alternative methods such as transition metal- mediated fluorination which have gained attention during the last decade [3–7]. Ruthenium-mediated ^{18}F-deoxyfluorination is an attractive method due to the availability of its stable phenol precursors and a wide substrate scope which are able to label electron-rich arenes as well as molecules with protic functional groups such as alcohols and amines, which are otherwise hard to access [7]. Furthermore, the clean reaction profile without major side-products makes the reaction solution relatively easy to purify. The reaction tolerates moisture and does not need a phase transfer catalyst or time-consuming additional drying procedures such as azeotropic distillation. The elution from the anion exchange cartridge is performed with the reaction solution. This protocol can result in a low elution efficiency of [^{18}F]fluoride if the synthesis device does not allow reverse elution from the anion exchange cartridge. Addition of salts increases the elution efficiency, but may affect the radiochemical conversion, and is thus mostly avoided. The best additive options are bis(trimethylneopentylammonium) oxalate, commercially available potassium

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https://doi.org/10.1016/j.jfluchem.2025.110423
Received 13 February 2025; Received in revised form 21 March 2025; Accepted 22 March 2025
Available online 30 March 2025

carbonate, and tetrabutylammonium chloride [8,9]. In the case of molecules containing amides or amines, basic reaction conditions afford better results [9,10].

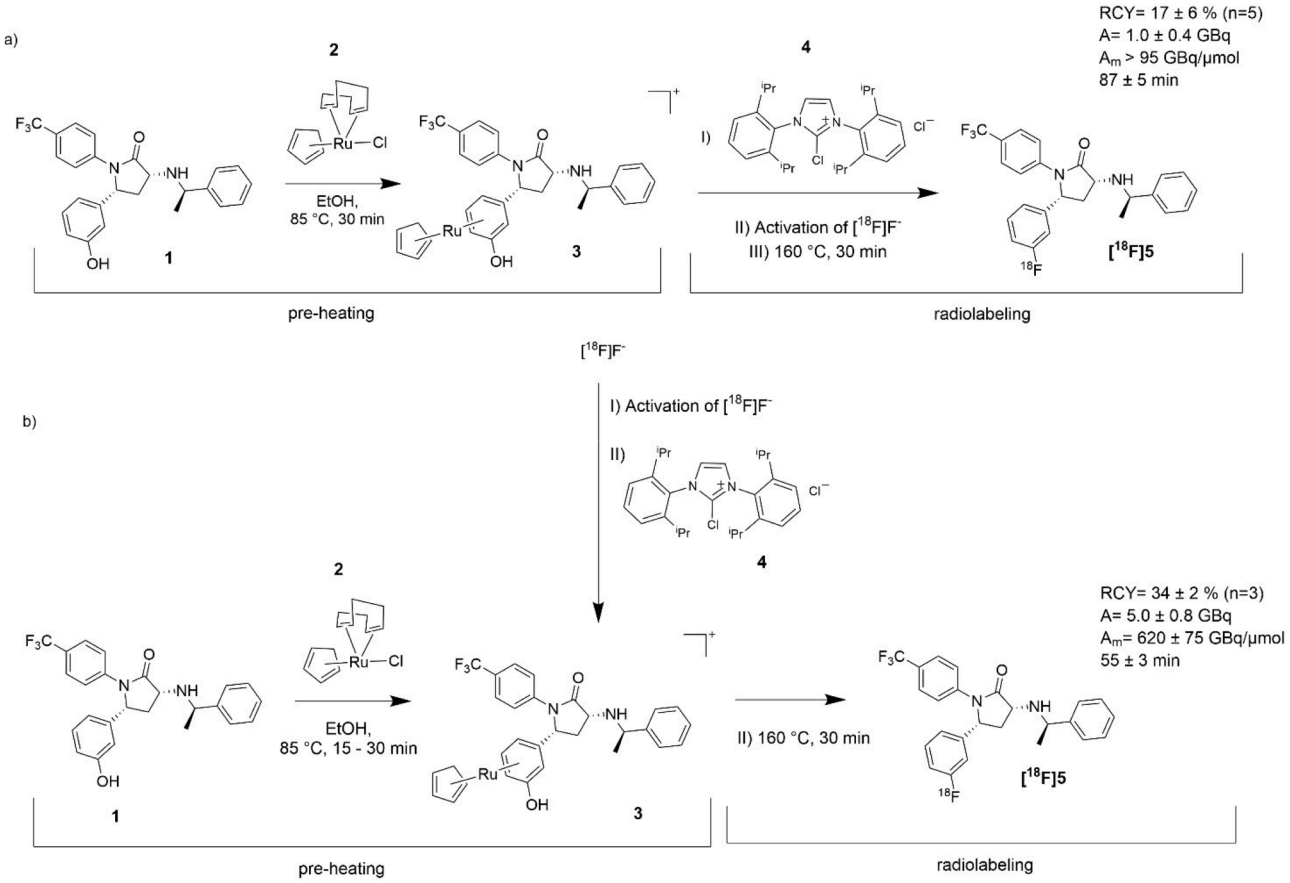
Ruthenium-mediated deoxyfluorination has mainly been used for the direct chemoselective ^{18}F-labelling of peptides as a desirable late-stage fluorination option for labeling with prosthetic groups [7,10,11]. Recently, it has also been used to label other potential tracers such as [^{18}F]Atorvastatin [8] and [^{18}F]EKZ-001 [12]. The Ru-mediated method has been automated using the Synthra GmbH RNplus modular synthesizer with the radiochemical yield of 26 ± 5 % (d.c.) [13], ELIXYS with the radiochemical yield of 15 ± 1 % (d.c.) [10], and TRASIS AllinOne synthesis module with radiochemical yield of 14 ± 4 % [12]. In these methods the ruthenium complexation is done as a separate preparation and stored for varying amounts of time (stable from 4 h to 6 months [8, 10,12]). All methods also reported relatively long synthesis time of 1.5 to 2 h including a deprotection step. We hypothesized that the addition order of the reagents could be changed in order to minimize the manual handling and to overcome the time sensitivity of the coordinated precursor.

Our group reported the synthesis of the novel CB1 specific tracer, (3*R*,5*R*)-5-(3-[^{18}F]fluorophenyl)-3-(((*R*)-1-phenylethyl)amino)-1-(4-(trifluoromethyl)phenyl)-pyrrolidin-2-one ([^{18}F]FPATPP), **[^{18}F] 5** using the Ru-mediated ^{18}F-fluorination with a radiochemical yield of 17 ± 6 % (n = 5) and a molar activity of > 95 GBq/μmol in 87 ± 5 min synthesis time with shelf-life up to 5 h [9] (Scheme 1a). [^{18}F]FPATPP is a novel analog of [^{18}F]FMPEP-d_2 clinical tracer used to study Parkinson's disease. [^{18}F]FMPEP-d_2 suffers from high metabolic defluorination and fairly low synthesis yield combined with a complex synthesis [14]. Our goal was to shorten the synthesis time and simplify the steps to make the Ru-mediated synthesis route the more appealing and accessible choice for clinically relevant tracer production. We chose to automate the synthesis in the TRASIS AllinOne device due to the GMP compliant single-use cassettes. The use of disposable materials mitigates the risk of cross contamination between reactions and makes the synthesis and cleaning procedures of the device straightforward and easily implementable.

2. Results and discussion

2.1. Pre-heating

Coordination of the **1** to the **2** was found to be a crucial step for the synthesis (Scheme 1). No product was detected if the pre-heating for the coordination was omitted. However, the pre-heating time could be reduced from 30 min to 15 min without compromising the radiochemical conversion. Similarly, extending the preheating did not affect the conversion. The elution of [^{18}F]fluoride could be performed with only compound **4** and K_2CO_3 (*aq*) without affecting the radiochemical conversion (Scheme 1b). Thus, the coordination reaction could be performed in the heater of the synthesis device. Since the pre-heated complex **3** was not needed for the elution of the [^{18}F]fluoride and there was no loss of reagents during transfer of the solutions from one vial to another, the amounts of precursor and ruthenium could be reduced. The synthesis was tested with a low amount of reagents **1** (1.0 mg, 2.3 μmol) and **2** (3.7 mg, 13 μmol) which led to a radiochemical conversion of 50 ± 5 % in 20 min (n = 2). However, the need for minimal use of reagents was not deemed necessary for our synthesis because of the good semi-preparative HPLC purification. The amount of **1** was reduced from 3.0 mg (6.8 μmol) to 2.7 mg (6.1 μmol) and of **2** from 6.5 mg (24 μmol) to 6.0 mg (22 μmol).



Scheme 1. (a) Original protocol published by our group [9]. (b) New method with elution to the pre-heating vial (this manuscript).

2.2. Radiolabeling

We found that the original PS-HCO_3^- cartridge could be replaced with a carbonated QMA cartridge (Waters, MA, US). A carbonated QMA cartridge gave a reliable trapping and drying of the [^{18}F]fluoride in an automated device (Table 1, entries 3 and 4). It should be noted that the elution of the [^{18}F]fluoride was reversed to the loading direction and additional losses may occur if the cartridge is not reversed for the elution of the [^{18}F]fluoride. No increase in the conversion was noticed after 20 min with QMA cartridge (Table 1, entries 3 and 4). We screened an alternative reaction solvent of DMSO:MeOH (3:1) (Table 1, entries 2 and 4) which has been shown to improve the reaction yield by other groups [8]. Since high reaction temperature (160°C) was used in the reaction, using methanol caused higher pressure in the reaction vial. Switching to DMSO:MeOH (3:1) from DMSO:CH_3CN (1:1) showed no significant benefits (Table 1, entries 3 and 4). The optimized conditions were activation with QMA Carb. cartridge with DMSO:CH_3CN (1:1) as a reaction solvent and reaction time of 20 min.

2.3. Automated synthesis

The optimized conditions (QMA Carb. cartridge, DMSO:CH_3CN (1:1) as a reaction solvent and reaction time of 20 min) were used when the synthesis was automated on a TRASIS AllinOne synthesis device. The synthesis was initially automated using a commercial reaction vial (RCY= 20 ± 8 %, A(product)= 0.98 ± 0.79 GBq (n = 7)). The preheating solution needed to be added to the vial through the cassette causing reagent losses in the reagent vial, in the transfer lines and on the walls of the reaction vial. The high reaction temperature caused a loss of activity during reaction when using a commercial flat bottom reaction vial. We updated the layout to use a 3.0 ml conical glass vial with 3D printed needle holder to move the needle out of the reaction vial to perform the fluorination reaction more efficiently.

Automated synthesis with optimized conditions doubled the radiochemical yield compared to our original publication [9]. [^{18}F]FPATPP was synthesized with the RCY of 34 ± 2 % (n = 3, decay-corrected; d.c.) from starting activity of 21 ± 2.6 GBq and isolated activity of 5.0 ± 0.8 GBq. Molar activity of the product was 620 ± 75 GBq/μmol. The radiochemical purity of the end product was ≥ 97 %. Lowering the needle only after cooling the vial reduced the reagent and radioactivity losses during reaction and increased the radiochemical yield. The total synthesis, including the purification and formulation of the product, was 55 min. Ruthenium content of the end product was 0.03 ± 0.01 μg/ml (n = 3), which is well below the maximum parenteral daily exposure limit of ruthenium of 10 μg/day [15]. The pH of the product was 5.5. The radiochemical purity of the formulated product after 4 h was 95 % (Fig. S5).

3. Conclusions

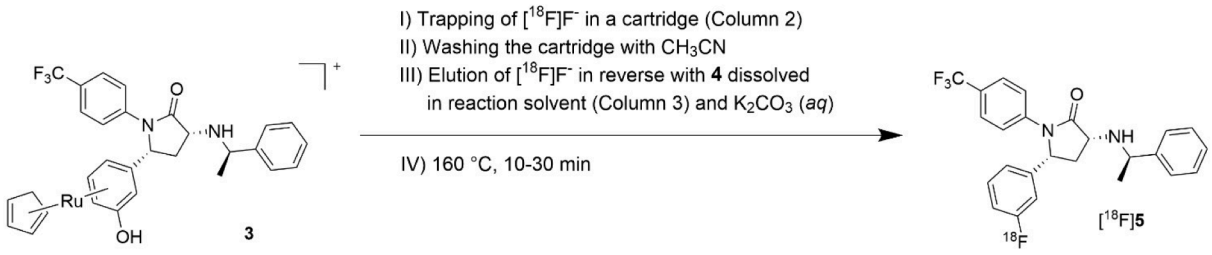
The radiochemical conversion was faster and the radiochemical yield doubled with the method described in this paper. [^{18}F]FPATPP was synthesized with the RCY of 34 ± 2 % (n = 3, decay-corrected; d.c.) with 55 min synthesis time. Molar activity of the product was 620 ± 75 GBq/μmol. The radiochemical purity of the product was ≥ 97 %. In our method, the Ru-complexation is performed during the automated preparation steps and the complex is used immediately. Therefore, there is no need to purify or determine a shelf-life for the complexed intermediate before applying the procedure to novel tracers. This methodology is more suited for cleanroom production. Moreover, our protocol uses only **4** and K_2CO_3 to elute [^{18}F]fluoride from the anion exchange cartridge. As a result the amount of ruthenium and precursor used in the process can be decreased. In addition, the synthesis preparation time is decreased, since the activation of [^{18}F]fluoride and the complexation of the precursor can be done simultaneously. The automated synthesis procedure minimizes the radiation dose of the synthesis operator and using disposable cassettes ensures patient safety for possible clinical application of the method. The general outline of the protocol could be replicated and used to synthesize other ^{18}F-radiolabeled radiopharmaceuticals from phenolic precursors.

4. Materials and methods

4.1. Materials

The precursor, (3*R*,5*R*)-5-(3-hydroxyphenyl)- 3-[(*R*)-1-phenylethylamino]-1-(4-trifluoromethylphenyl)pyrrolidine-2-one was purchased from PharmaSynth AS (Tartu, Estonia). Cyclopentadienyl ruthenium cyclooctadienylchloride, (CpRu(COD)Cl) was prepared according to Ref. [16]. The reference compound (3*R*,5*R*)-5-(3-fluorophenyl)-3-(((*R*)-1-phenylethyl)amino)-1-(4-(trifluoromethyl)phenyl)-pyrrolidin-2-one, was prepared according to Lahdenpohja et al. [9]. Other chemicals were purchased from commercial vendors and used without further handling. Sep-Pak Accell Plus QMA Carbonate Plus Light and Plus Light tC18 SPE cartridges were bought from Waters Corp (Milford, MA, US). Reaction vial (part no. w986Z76), septa, and plastic screw caps were purchased from Thermo Scientific (Waltham, MA, US). Cassette parts were bought from TRASIS (Ans, Belgium).

Table 1
Study on radiochemical conversion (RCC) with different cartridges, solvents and reaction times.



Entry	Cartridge	Reaction solvent	Elution efficiency (%)[a]	[^{18}F]F$^-$ recovery (%)[a]	RCC (%)		
					10 min	20 min	30 min
1	PS-HCO_3^-	DMSO:CH_3CN (1:1)	92 ± 5.7[b]	64 ± 29[b]	21 ± 9.0[c]	54 ± 5.7	66 ± 1.6
2		DMSO:MeOH (3:1)	97 ± 0.4	90 ± 7.2	–	–	50 ± 2.9
3	QMA Carb	DMSO:CH_3CN (1:1)	87 ± 5.1	87 ± 5.1	50 ± 3.9	60 ± 3.6	60 ± 4.0
4		DMSO:MeOH (3:1)	90 ± 4.9	90 ± 4.9	39 ± 7.0[b]	55 ± 3.8[c]	60 ± 5.0

The reaction solvent ratios are vol/vol. If not otherwise noted the n = 3, the radiochemical conversions (RCC) are based on radioHPLC. (a) Eqs. (1) and (2) used for the calculations are explained in 4.2.2, (b) n = 15, c) n = 2.

4.2. Experimental

4.2.1. General

Fluorine-18 (*aq*) was produced via $^{18}O(p,n)^{18}F$ nuclear reaction in the cyclotron with 36 ± 1 μA proton beam and 20 min irradiation time for the automation and 5 min irradiation time for the development tests. The activity was transferred to a collection vial in a lead-shielded hot cell for the synthesis.

The product was analyzed using Luna 5 μm C18, 100 Å, 4.6 × 75 mm analytical HPLC column (Phenomenex, Torrance, CA, US) in Shimadzu analytical HPLC system (Kyoto, Japan). Flow rate 0.95 ml/min; mobile phase 0–15 min, 55 % 0.1 % TFA (*aq*) and 45 % of 0.1 % TFA (*aq*) in CH_3CN.

In the automated synthesis the reaction solution was purified with Luna 10 μm, 110 Å, 10 × 250 mm semi-preparative HPLC column (Phenomenex, Torrance, CA, US) with 8 mL/min flow rate; mobile phase 57/43 1 % TFA (*aq*)/ CH_3CN with ascorbic acid.

Ruthenium content was send to be analyze in a commercial company specialized in metal impurity measurements (Eurofins, Finland) with ICP-MS from three purified and formulated end-products after the decay of the radioactivity.

4.2.2. Equations used for the elution efficiency and [^{18}F]fluoride recovery calculations

The elution efficiency was calculated by dividing the measured activity of the eluted [^{18}F]fluoride by the sum of the activity of the eluted [^{18}F]fluoride and the activity remaining in the cartridge:

$$Elution\ efficiency - \% = \frac{A(reaction\ vial)}{[A(reaction\ vial) + A(cartridge\ after\ elution)]} \times 100 \quad (1)$$

The [^{18}F]fluoride recovery was calculated by dividing the measured activity of the eluted [^{18}F]fluoride by the sum of the activity of the eluted [^{18}F]fluoride, the activity remaining in the cartridge and the unretained [^{18}F]fluoride activity in the loading waste bottle:

$$[^{18}F]Fluoride\ recovery - \% = \frac{A(reaction\ vial)}{[A(reaction\ vial) + A(cartridge\ after\ elution) + A(loading\ waste)]} \times 100 \quad (2)$$

The activities were non-decay-corrected because the measurements of the fractions were done within 5 min.

4.2.3. Development of the protocol

The original protocol used PS-HCO_3^- anion exchange cartridge (Synthra GmbH, Hamburg, German) for the activation of [^{18}F]fluoride. The cartridge is extremely sensitive for any impurities leading to occasional [^{18}F]fluoride (*aq*) trapping problems during the synthesis. Also, it was necessary to adjust the trapping speed to ensure trapping efficiency.

CpRu(COD)Cl (3.0–6.3 mg, 11–24 μmol) and (*3R*,5*R*)-5-(3-hydroxyphenyl)-3-[(*R*)-1-phenyl ethylamino]-1-(4-trifluoromethylphenyl) pyrrolidine-2-one (0.8–3.0 mg, 1.8–6.8 μmol) in 50 μL of EtOH in a 3.0 mL conical glass reaction vial were heated to 90 °C for 0–30 min. [^{18}F]Fluoride (*aq*) (0.3–1.5 GBq) was activated with the PS-HCO_3^- or QMA cartridge, washed with 5 mL of CH_3CN and dried with N_2. [^{18}F]fluoride was eluted from the reversed QMA cartridge into the reaction vial with 1,3-bis(2,6-di-i-propylphenyl)-2-chloroimidazolium chloride (10.0 mg, 22 μmol) in 400 μL of CH_3CN:DMSO (1:1 vol/vol) with 40 μL of K_2CO_3 (45 mg/ml) solution or 400 μL DMSO:MeOH (3:1 vol/vol) with 40 μL of K_2CO_3 (45 mg/ml) solution. The reactor was heated to 160°C for 10–30 min.

4.2.4. Automation

To ensure reproducibility and good radiochemical conversion in the automated environment, we chose a 3.0 ml conical reaction vial with needles instead of using a flat bottom reactor with a fixed line. This set-up allowed us to move the needle out of the solution during the reaction and lower it to the bottom during transfer of solution. To automate the movement of the reaction needle, we designed a needle holder that could be fabricated with a 3D printer, which could be attached to the 10 mL syringe driver and to the reaction needle connection. Movements of the needle holder was performed using the syringe driver. The instructions for the needle holder are shown in the supplementary information. The exhaust needle was not moved, but the exhaust line was controlled with a pinch valve.

4.2.5. Automated synthesis

CpRu(COD)Cl (6.0 mg, 22 μl) and (*3R*,5*R*)-5-(3-hydroxyphenyl)-3-[(*R*)-1-phenylethylamino]-1-(4-trifluoromethylphenyl) pyrrolidine-2-one (2.7 mg, to 6.1 μmol) in EtOH (50 μL) in a 3.0 mL conical glass reaction vial was heated to 90°C for 15 min. Simultaneously, [^{18}F] fluoride (*aq*) was activated with the QMA cartridge, washed in reverse with CH_3CN (5 mL) and dried with N_2. [^{18}F]fluoride was eluted from the reversed QMA cartridge into the reaction vial with 1,3-bis(2,6-di-i-propylphenyl)-2-chloroimidazolium chloride (10.0 mg, 22 μmol) in CH_3CN: DMSO (1:1 vol/vol) (400 μL) containing K_2CO_3 (40 μL of 45 mg/ml aqueous solution, 13 μmol). The reactor was heated to 160°C for 20 min. After the reaction, the reaction vial was cooled to 50°C and the needle lowered to the bottom of the vial using the 3D printed needle holder. The reaction solution was diluted with 0.1 % TFA (*aq*) (1.5 mL) and washed with 3 mL of water. The reaction mix was purified using HPLC. The product fraction corresponding to **[^{18}F] 5** was collected (retention time ~ 13 - 15 min, supplementary material). The collected fraction was transferred into the tC18 SPE cartridge, dried briefly with N_2 flow and washed with water (20 mL) to remove possible residual acetonitrile and TFA (*aq*). **[^{18}F] 5** was formulated by elution with ethanol (1 mL) into a product collection vial and diluted with 0.9 % saline (9 mL). Ascorbic acid was added to the high activity concentrations (> 400 MBq/ml) to prevent radiolysis. The cassette layout is shown in Fig. 1. The detailed reagent placement is shown in the supplementary information. The stability of the end product was tested up to 4 h (Fig. S5). The product was not sterile filtrated, but when needed it can be sterile filtrated using for example Supor Acrodisc 13 sterile filter (Pall Corporation, US).

Abbreviations

PET, positron emission tomography

[^{18}F]FPATPP, (*3R*,5*R*)-5-(3-[^{18}F]fluorophenyl)-3-(((*R*)-1-phenylethyl)amino)-1-(4-(trifluoromethyl)phenyl)-pyrrolidin-2-one

GMP, good manufacturing practise d.c., decay corrected

CB1, cannabinoid 1

[^{18}F]FMPEP-d_2, (*3R*,5*R*)-5-(3-([^{18}F]fluoromethoxy-d_2)phenyl)-3-(((*R*)-1-phenylethyl)amino)-1-(4-(trifluoromethyl)phenyl)pyrrolidin-2-one

A_m, molar activity

K_2CO_3, potassium carbonate

aq, aqueous solution

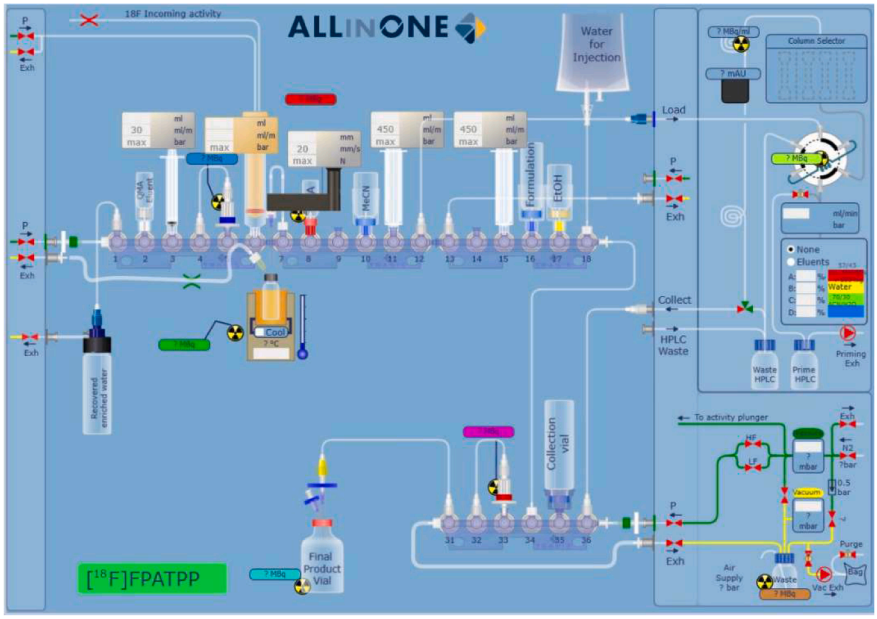


Fig. 1. The cassette layout for [^{18}F]FPATPP synthesis.

HPLC, high performance liquid chromatography
QMA, quaternary ammonium anion exchange
DMSO, dimethyl sulfoxide
MeOH, methanol
CH_3CN, acetonitrile
RCC, radiochemical conversion
RCY, radiochemical yield
CpRu(COD)Cl, cyclopentadienyl ruthenium cyclooctadienylchloride
SPE, solid-phase extraction
TFA, trifluoroacetic acid
A, activity
ICP-MS, inductively coupled plasma mass spectrometry
EtOH, ethanol

CRediT authorship contribution statement

Noora A. Rajala: Writing – original draft, Methodology, Investigation, Formal analysis. **Edla K. Kerminen:** Writing – review & editing, Investigation. **Simo A. Salo:** Writing – review & editing, Investigation. **Melina J.J. Väkiparta:** Writing – review & editing, Investigation. **Anna K. Kirjavainen:** Writing – review & editing, Supervision, Resources, Project administration.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Anna K. Kirjavainen reports financial support was provided by Academy of Finland. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was funded by the Research Council of Finland (grant no. 307924).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2025.110423.

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