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PRACTITIONER PROTOCOL - SYNTHESIS

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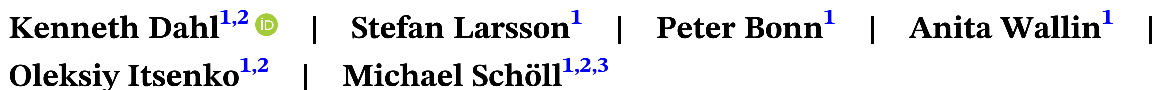
Good manufacturing procedure production of [^{18}F]SynVesT-1, a radioligand for in vivo positron emission tomography imaging of synaptic vesicle glycoprotein 2A



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[^{18}F]SynVesT-1 (also known as [^{18}F]SDM-8 or [^{18}F]MNI-1126) is a potent and selective synaptic vesicle glycoprotein 2 (SV2A) positron emission tomography (PET) imaging agent. In order to fulfill the increasing clinical demand of an ^{18}F-labeled SV2A PET ligand, we have developed a fully automated procedure to provide a sterile and pyrogen-free good manufacturing procedure (GMP)-compliant product of [^{18}F]SynVesT-1 suitable for clinical studies in humans. [^{18}F]SynVesT-1 is synthesized via a rapid copper-mediated radiofluorination protocol. The procedure was developed and established on a commercially available module, TracerMaker (ScanSys Laboratorieteknik ApS, Copenhagen, Denmark), a synthesis platform originally developed to conduct carbon-11 radiochemistry. From ~130 GBq (end-of-bombardment), our newly developed procedure enabled us to prepare [^{18}F]SynVesT-1 in an isolated radioactivity yield of 14,220 ± 800 MBq ($n = 3$), which corresponds to a radiochemical yield (RCY) of 19.5 ± 0.5%. The radiochemical purity (RCP) and enantiomeric purity of each of the final formulated batches exceeded 98%. The overall synthesis time was 90 min and the molar activity was 330 ± 60 GBq/μmol (8.9 ± 1.6 Ci/μmol). The produced [^{18}F]SynVesT-1 was stable over 8 h at room temperature and is suitable for in vivo PET imaging studies in human subjects.

KEYWORDS

fluorination, fluorine-18, PET, radiochemistry, SV2A

1 | INTRODUCTION

Synaptic vesicle glycoprotein 2 (SV2A) is a transmembrane protein expressed ubiquitously in secretory vesicles in the human brain, and dysfunction of SV2A has been implicated in a wide range of neurologic disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), epilepsy, autism, stroke, and traumatic brain injury, as well as psychiatric disorders such as schizophrenia and depression.[1–8] Thus, positron emission tomography (PET) neuroimaging of SV2A has tremendous potential to be utilized as an early-stage biomarker for AD, PD, and other neurodegenerative disorders. A number of PET radioligands have been reported and applied for PET in

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human subjects, including [^{11}C]UCB-J,[9] [^{11}C]UCB-A,[10] [^{18}F]UCB-H,[11] [^{18}F]SynVesT-1,[12] and [^{18}F]SynVesT-2.[13] The fluorine-18-labeled radioligand [^{18}F]SynVesT-1 (also known as [^{18}F]SDM-8 or [^{18}F]MNI-1126), developed by the Yale PET Center,[14] has shown the most favorable in vivo characteristics including high brain uptake, fast and reversible binding kinetics, SV2A specificity, high specific binding signals, and excellent reproducibility in the measurement of quantitative kinetic parameters.[12,14,15] The goal of the current work was to enable large-scale production of [^{18}F]SynVesT-1 to meet the increasing clinical demand for a ^{18}F-labeled SV2A PET imaging agent. Herein, we report the fully automated radiosynthesis of [^{18}F]SynVesT-1 performed according to good manufacturing procedure (GMP) using a commercially available module (TracerMaker, ScanSys Laboratorieteknik ApS, Copenhagen, Denmark) and its comprehensive validation for routine human use.

2 | PROCEDURE

All chemicals and reagents were obtained from commercial vendors and used as received without further purification.

2.1 | Production of non-carrier added [^{18}F]fluoride

[^{18}F]Fluoride ([^{18}F]F^{-}) was produced via the standard ^{18}O(p,n)^{18}F nuclear reaction, by irradiating cyclotron target containing [^{18}O]water with a proton beam (16.4 meV) of 65 μA for 40 min (PETtrace 800 cyclotron, GE, Uppsala, Sweden). The typical amount of [^{18}F]F^{-} produced was approximately 130 GBq (3.5 Ci).

2.2 | Radiosynthesis of [^{18}F]SynVesT-1

Only small modifications to the original [^{18}F]SynVesT-1 synthesis protocol presented by Li et al.[14] were made to better fit our synthesis module. A schematic diagram of the TracerMaker radiosynthesis module used for the synthesis of [^{18}F]SynVesT-1 is shown in Figure 1. The in-house developed sequence for [^{18}F]SynVesT-1 includes all key production steps: (i) trap and release of cyclotron produced [^{18}F]F^{-} using an ion-exchange cartridge, (ii) azeotropic drying of [^{18}F]F^{-}, followed by (iii) copper-mediated ^{18}F-fluorination of the Me_3Sn-SDM-8 precursor compound (Scheme 1), (iv) high-performance liquid chromatography (HPLC) purification, and (v) formulation of the final product. A more detailed

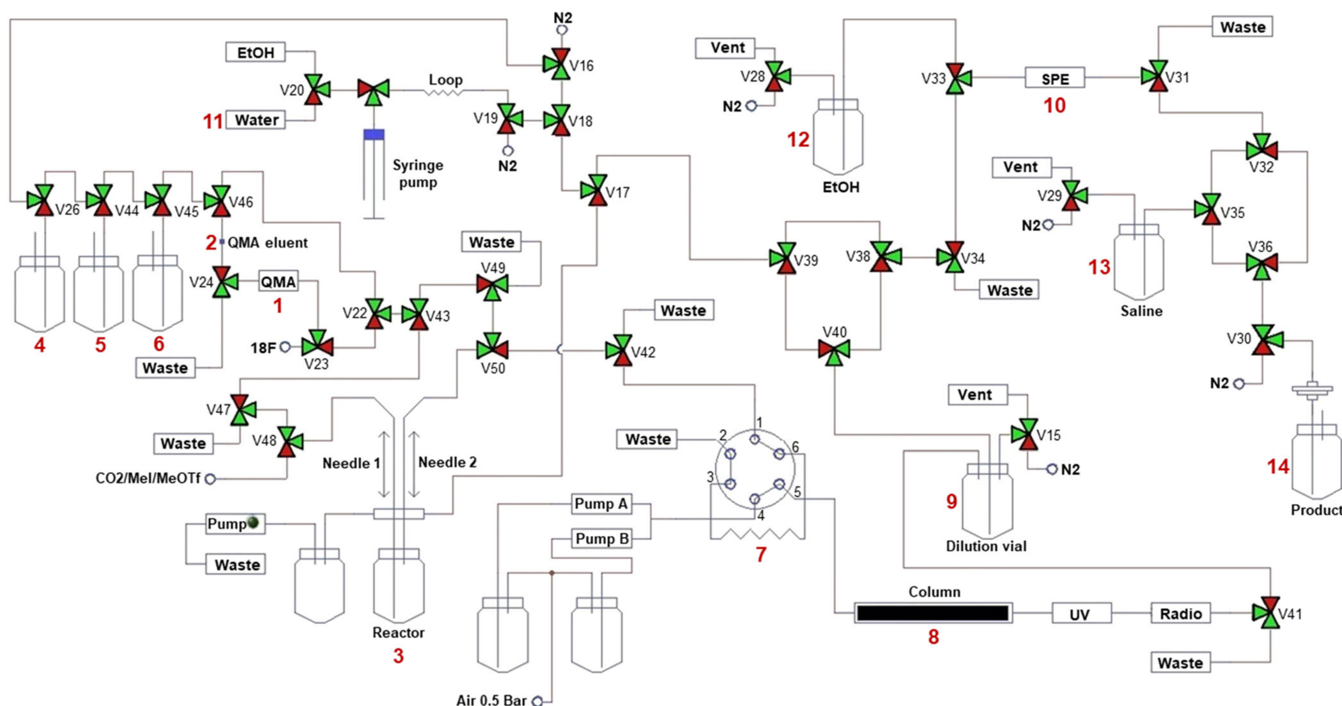
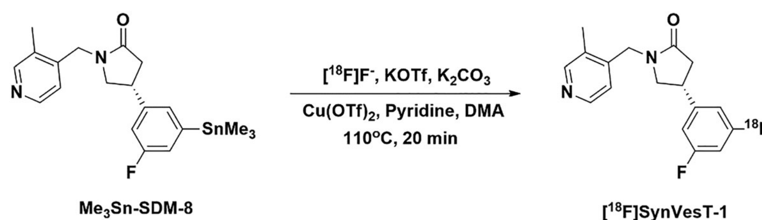


FIGURE 1 Schematic diagram of TracerMaker module used for synthesis of [^{18}F]SynVesT-1

SCHEME 1 Radiosynthesis of [18F]SynVesT-1



description follows, with bold numerals referring to Figure 1.

1. At the end of bombardment, aqueous [18F]fluoride ([18F]F$^-$, ~130 GBq) was transferred from the target by helium gas (6.0, AGA) via valves V23 and V24 over a pre-activated (10 ml of potassium triflate [90 mg/ml] and 10 ml of 18 MΩ water, followed by 30 ml of air using a plastic syringe) Sep-Pak Accell Plus QMA Carbonate Light Cartridge (**1**, Waters). [18F]F$^-$ was quantitively trapped on the QMA cartridge, and [18O]water was recovered in a recovery vial.
2. The trapped [18F]F$^-$ was eluted using 600 μl of an eluting solution (4.5 mg of KOTf, 50 μg of K_2CO_3, 300 μl of 18 MΩ water, 300 μl of acetonitrile, vial **2**) into the reactor vial **3** (4 ml, Chromacol) using N_2 gas (6.0, AGA) flow. The nitrogen gas was regulated with a mass-flow controller.
3. The [18F]F$^-$ mixture in the reactor vial **3** was dried azeotropically for 15 min at 125°C under continuous N_2 flow (200 ml/min) supplied via needle 1, with needle 2 serving as the exhaust line. As this module does not have a vacuum pump, two portions (1 ml each) of acetonitrile from vial **4** were added at 5 and 10 min. This was done to ensure the complete removal of water from the reaction vessel. Further, the temperature was increased to 140°C under N_2 flow for another 3 min. The reaction vial was finally cooled down to 70°C prior to the next step.
4. The precursor solution (2.0 mg of Me_3Sn-SDM-8 [Pharmasynth Radiopharmaceuticals, Estonia], 5 mg of $Cu(OTf)_2$ [98%, P/N: 283673, Sigma-Aldrich], 10 μl of pyridine [99.5%, P/N: 1.09728.0100, Merck], dissolved in 700 μl of *N,N*-dimetylacetamide [anhydrous, 99.8%, P/N: 271012, Sigma-Aldrich]) preloaded into vial **6** was transferred to the reaction vial **3** using the syringe pump. It is worth noting that no special precautions in terms of precursor preparation conditions were necessary. The precursor and catalyst were weighed out in a glass vial (4 ml, Chromacol, same as the reactor vial) at ambient laboratory conditions.
5. The reactor was sealed and heated to 110°C for 20 min. After the labeling reaction, the reactor was cooled to 70°C prior to the next step.
6. The crude reaction mixture was then diluted with 2 ml of 200:800:0.5, acetonitrile:0.1 M of ammonium formate:acetic acid, which was added from vial **5** using the syringe pump.
7. The content of reactor vial **3** was delivered to the HPLC loop (**7**, total volume of 5 ml) using the syringe pump. The solution was then injected to a semi-preparative HPLC column (**8**, Gemini 5 μm NX-C18, 250 × 10 mm, Phenomenex). The separation was performed using isocratic conditions with acetonitrile/0.1 M of ammonium formate/acetic acid (300:700:0.5) as a mobile phase at a flow rate of 5 ml/min. The elution was monitored by UV (λ = 254 nm), and a radioactivity detector connected in series.
8. A typical semi-preparative HPLC chromatogram is displayed in Figure 2. The fraction containing the desired product, [18F]SynVesT-1 with retention time approximately 22 min, was collected into a dilution vial (**9**), which was preloaded with 30 ml of sterile water.
9. The diluted fraction was then transferred via V40, V38, V34, V33, and V31 over a pre-activated (10 ml of ethanol and 10 ml of sterile water) Sep-Pak tC18 Plus short Cartridge (**10**, Waters). [18F]SynVesT-1 was thus trapped on the cartridge, which was immediately washed with 10 ml of sterile water from reservoir **11** using the syringe pump and later dried with N_2 gas for 30 s.
10. Using 1.0 ml of ethanol, preloaded into vial **12**, [18F]SynVesT-1 was released from the cartridge into mixing vial **13** that had been preloaded with 15 ml of saline (0.9% NaCl, pH 4.5–7.0).
11. Finally, the formulated product was delivered using N_2 gas into the sterile product vial **14** via a sterilizing-grade filter (0.22 μm Cathivex-GV filter, Millipore). Typical product volume was about 16 ml, approximately 6% ethanol in saline.
12. After each synthesis, the system was cleaned with three different solvents (water, ethanol, and acetonitrile) using an automated cleaning procedure, which was also validated.

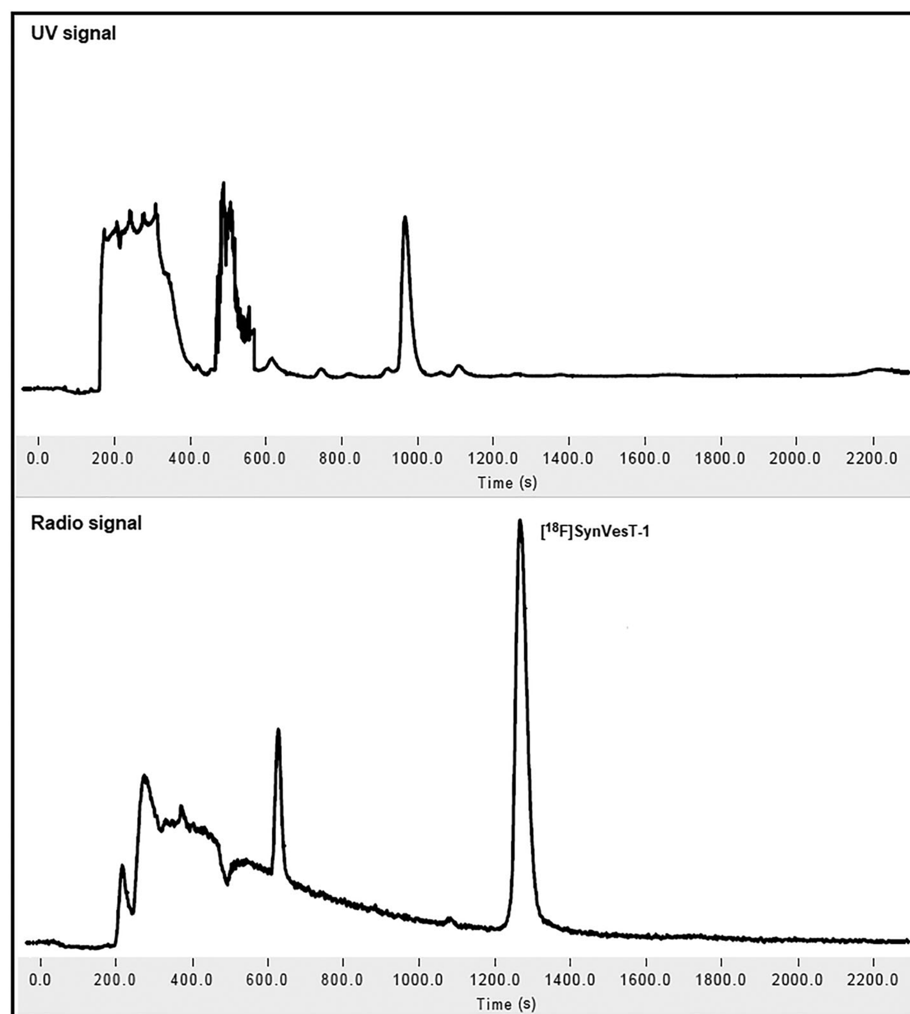


FIGURE 2 Semi-preparative high-performance liquid chromatography (HPLC) trace (300:700:0.5 acetonitrile:0.1 M of ammonium formate:acetic acid, at a flow rate of 5 ml/min, Gemini, NX-C18, 250 × 10 mm i.d., 5 μm) of a typical radiosynthesis of [^{18}F]SynVesT-1. Retention time of [^{18}F]SynVesT-1 was approximately 22 min (1300 s).

2.3 | Quality control

Release criteria and quality control (QC) results from three productions of [^{18}F]SynVesT-1 are presented in Table 1. All the QC tests were performed using in-house validated analytical methods.

Chromatographic methods were developed for testing the key quality characteristics: radiochemical purity (RCP), chemical purity, enantiomerical purity, product identity, stability, and residual solvents. Chemical purity and RCP were determined by analytical radio-HPLC using Thermo Scientific Ultimate System equipped with a quaternary pump, autosampler, ultraviolet detector, and a radiodetector (Berthold fLUMO detector). RCP analysis was performed on an analytical column (ACE 3, C18, 150 × 3.0 mm i.d., 3 μm) by gradient elution, with acetonitrile:10 mM of ammonium formate (with 0.5% acetic acid) as the mobile phase (flow rate = 600 μl/min). Retention time of the labeled product [^{18}F]SynVesT-1 was 4.5 min (Figure 3). Stability (shelf life) of [^{18}F]SynVesT-1 after 8 h was measured by radio-HPLC as described above. Enantiomeric purity analysis was performed on a chiral analytical column (LUX, Cellulose-1, 150 × 4.6 mm i.d., 5 μm) with 350:650 acetonitrile:10 mM of ammonium formate (with 0.5% acetic acid) as the mobile phase (flow rate = 1.5 ml/min). Retention time of the SynVesT-1 ((*R*)-SDM-8) reference and (*S*)-SDM-8 was 7.7 and 6.9 min, respectively (Figure 4). A complementary RCP test was done using thin-layer chromatography (TLC) using Silica gel TLC strips (TLC Silica gel 60, Merck) eluted with a mobile phase of 800:200 (v/v) acetonitrile:water, and the radioactivity was detected using a Radio TLC scanner (miniGita, Elysia-Raytest). The retardation factor (R_f) for ^{18}F was approximately 0–0.1 and R_f 0.65–0.75 for [^{18}F]SynVesT-1 (Figure 5).

Residual solvent levels were analyzed using a gas chromatograph (GC, Trace 1310, Thermo Scientific) equipped with a flame ionization detector, a TG-624 column (30 m, 0.32 mm i.d., 1.8 μm of film), and an autoinjector.

TABLE 1 Results from three productions of [^{18}F]SynVesT-1 using the TracerMaker module

Test	Specifications	Batch 1	Batch 2	Batch 3
Radioactivity per batch	Not specified	13,880 MBq	13,830 MBq	14,950 MBq
Radiochemical yield (%)	Not specified	19.6%	19.0%	20.0%
Appearance	Clear and free from particles	Pass	Pass	Pass
pH	4.5–8.0	5.0	5.0	5.0
Molar activity (by HPLC)	55.5 GBq/μmol	270 GBq/μmol	381 GBq/μmol	332 GBq/μmol
Product identity (by radio-HPLC)	[R_t radiopeak − R_t UV] = 0.01–0.05 min	0.02 min	0.02 min	0.03 min
Radiochemical purity (by radio-HPLC)	≥95%	100%	99.9%	100%
Enantiomerical purity (radio-HPLC)	≥95%	98.8%	98.8%	98.7%
Radiochemical purity (by radio-TLC)	≥95%	99.7%	99.6%	99.8%
Stability, 8 h (radio-HPLC)	≥95%	100%	100%	100%
Bacterial endotoxins	<17.5 EU/ml	<0.5 EU/ml	<0.5 EU/ml	<0.5 EU/ml
Filter integrity	≥3.5 bar	4.1 bar	4.0 bar	4.1 bar
Radionuclidic identity	105–115 min	109 min	107.6 min	107 min
Residual DMA	≤1090 ppm	n.d.	n.d.	n.d.
Residual acetonitrile	≤410 ppm	n.d.	n.d.	n.d.
Residual pyridine	≤200 ppm	n.d.	n.d.	n.d.
Ethanol content	≤10%	3.6%	3.6%	4.0%

Abbreviations: DMA, *N,N*-dimethylacetamide; HPLC, high-performance liquid chromatography; n.d., not detected; TLC, thin-layer chromatography.

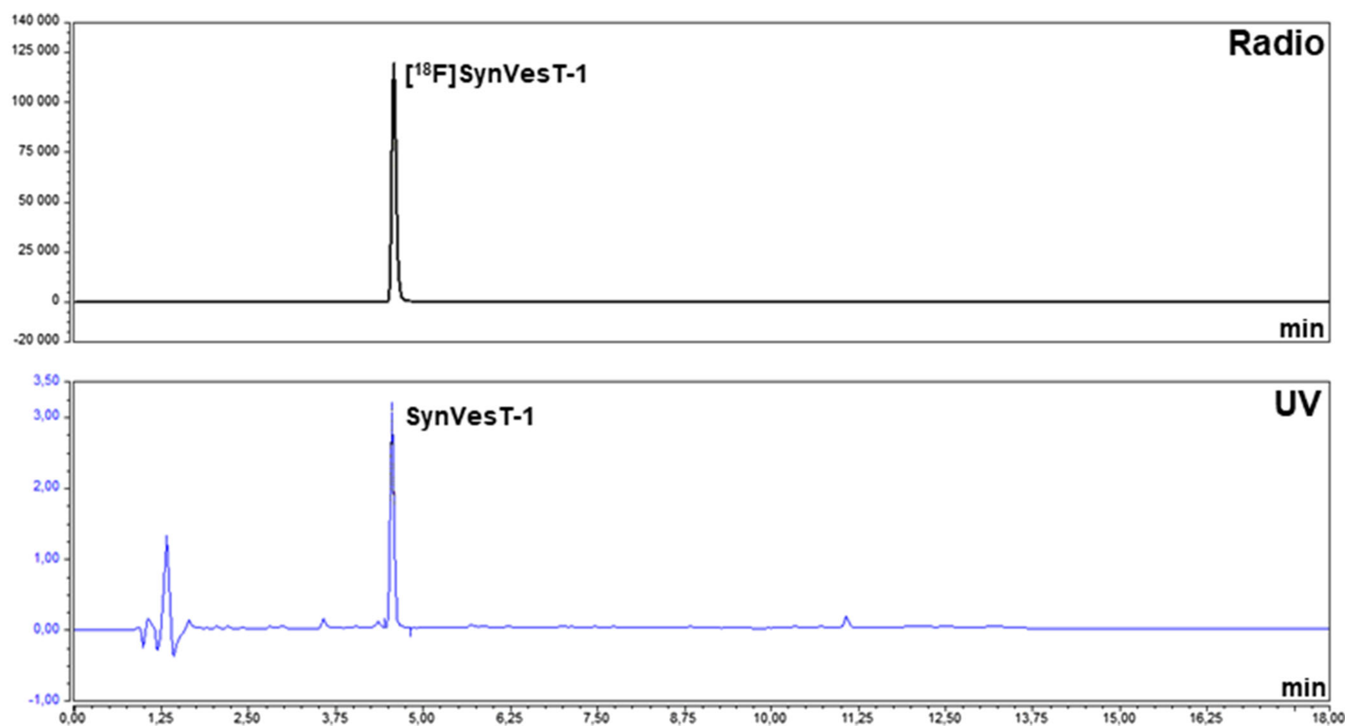


FIGURE 3 Analytical high-performance liquid chromatography (HPLC) chromatogram using reversed phase column (ACE 3, C18, 150 × 3.0 mm i.d., 3 μm) at a flow rate of 600 μl/min (acetonitrile:10 mM of ammonium formate; with 0.5% acetic acid). Gradient method starting at 350:650 (v/v) to 800:200 after 10 min, hold 800:200 for 2.5 min, go back down to 350:650 at 12.5 min, and hold the composition until the end of method (18 min). Radioactivity (top) and UV (λ = 261 nm; bottom). [^{18}F]SynVesT-1 eluted at 4.5 min under these conditions.

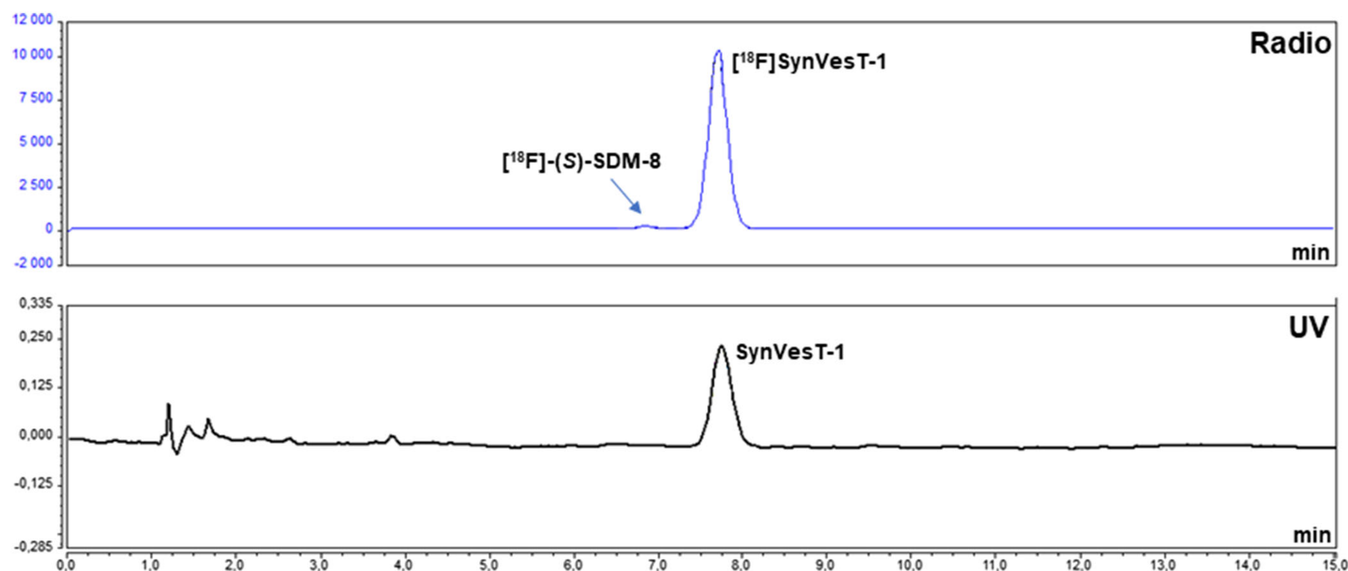


FIGURE 4 Analytical chiral high-performance liquid chromatography (HPLC) chromatogram (350:650, acetonitrile:10 mM of ammonium formate; with 0.5% acetic acid) at a flow rate of 1.5 ml/min using a LUX Cellulose-1 column (150 × 4.6 mm i.d., 5 μm). Radioactivity (top) and UV (λ = 261 nm; bottom). [^{18}F]SynVesT-1 eluted at 7.7 min and [^{18}F](*S*)-SDM-8 at 6.8 min under these conditions.

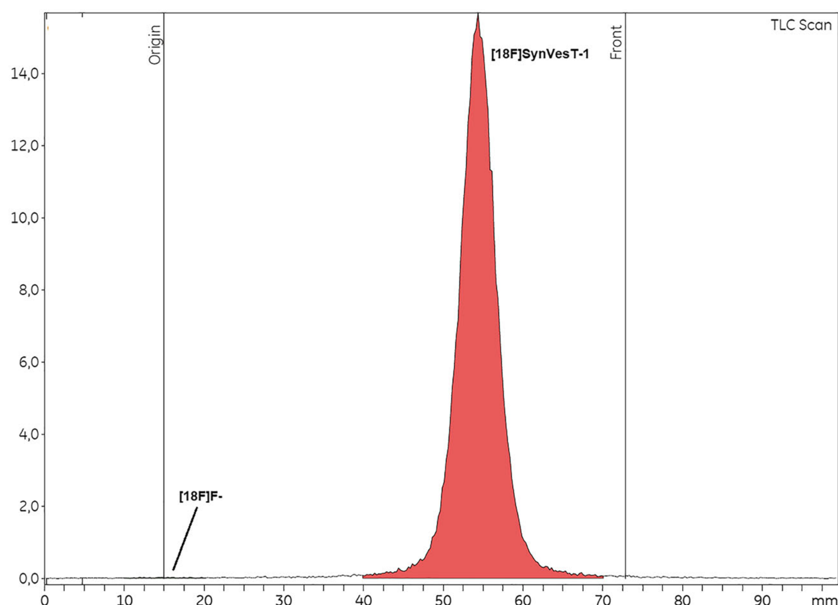


FIGURE 5 Radio thin-layer chromatography (TLC) using silica gel plates and 80:20 (v/v) acetonitrile:water as the mobile phase. The retardation factor (R_f) for [^{18}F]SynVesT-1 using these conditions was 0.65–0.75.

Appearance was checked by visual inspection behind a lead-shielded window. Common methods were used to perform tests such as radionuclide identity by half-life measurement using dose calibrator (Comecer) and pH defemination by strips (MQuant, Merck). Bacterial endotoxin tests were performed by chromogenic LAL-test method (Endosafe-Nextgen PTS, Charles River), and the filter integrity was tested by a bubble point method using a pressure gage (Integrity Test Kit for small volume devices, Millipore).

3 | RESULTS AND DISCUSSION

Radiosynthesis of [^{18}F]SynVesT-1 was automated using the commercially available TracerMaker synthesis module platform, which was originally developed to conduct carbon-11 radiochemistry and predominantly ^{11}C-methylation labeling reactions. As such, the system layout had to undergo changes to accommodate a unit for the initial [^{18}F]F^{-} concentration step using an ion-exchange cartridge. This was easy to accomplish

because the module contains an ample number of valves that can be freely connected to build a desired configuration. Hence, after the changes, the synthesis module is still fully suitable for performing ^{11}C-labeling reactions with [^{11}C]carbon dioxide, [^{11}C]methyl iodide, and [^{11}C]methyl triflate. Some technical features of the system were found useful in fine-tuning the trap-release and preparation of [^{18}F]fluoride before labeling reaction. These include the unique reactor system design with two motor-driven needles and a mass-flow controller for gases. Disposable glass reactor vials added an extra convenience as they do not require cleaning.

With regard to the production protocol, small adjustments were made to the original [^{18}F]SynVesT-1 synthesis conditions published by Li et al. in order to accommodate them to the new commercial radiosynthesis unit. For example, the volume used to elute [^{18}F]F$^-$ from the ion-exchange cartridge was reduced from 1.0 ml to 600 μl. This change hade minimal effect on the [^{18}F]F$^-$ efficiency (>95%), while in turn simplifying the following azeotropic drying step as well as reduced the amount of base used for the base-sensitive ^{18}F-fluorination reaction.

In brief, radiolabeling was performed in a single step by copper-mediated radiofluorination reaction of the Me_3Sn-SDM-8 precursor compound in the presence of pyridine using azeotropically dried potassium [^{18}F]fluoride ([^{18}F]KF) dissolved in anhydrous *N,N*-dimethylacetamide. Heating the reactor to 110°C for 20 min proved to be adequate to provide radiochemical yields comparable with those reported earlier.[14] The crude product solution was further purified by a semi-preparative chromatography. The chromatographic fraction containing the product was collected and diluted with sterile water and finally reformulated using SPE to produce [^{18}F]SynVesT-1 in a reproducible decay-corrected radiochemical yield of 19.5 ± 0.5% ($n = 3$, relative to [^{18}F]F$^-$ delivered to the module). Using the above described conditions, [^{18}F]SynVesT-1 could be obtained with over 99% radiochemical purity and enantiomeric purity of 98.8%. The molar activity (A_m) averaged to 330 ± 60 GBq/μmol (8.9 ± 1.6 Ci/μmol, $n = 3$) at the end of synthesis. The overall synthesis time was 90 min from the end of bombardment to having the finished product in a vial. Although additional optimization may further improve the yield, typical final product activities (13.5–15 GBq, 365–405 mCi) were sufficient for multiple human PET investigations. QC analysis was performed on the formulated product solutions, and the obtained results met all acceptance criteria for the product (Table 1).

4 | CONCLUSION

A fully automated production sequence of [^{18}F]SynVesT-1 was developed using a commercially available radiosynthesis module, TracerMaker (ScanSys Laboratorieteknik ApS). The decay-corrected radiochemical yield was around 20% and the radiochemical purity was greater than 99%. Overall, the protocol reliably provides a pharmaceutical grade solution of [^{18}F]SynVesT-1 suitable for clinical studies.

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DATA AVAILABILITY STATEMENT

The data that support the findings of the study are available from the corresponding authors upon reasonable request.

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