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# An efficient one-step radiosynthesis of [$^{18}$F] FE-PE2I, a PET radioligand for imaging of dopamine transporters

Vladimir Stepanov,[a*] Raisa Krasikova,[a,b] Liina Raus,[c,d] Olavi Loog,[c] Jukka Hiltunen,[c] and Christer Halldin[a]

**The aim of this study was to develop a direct fluorination method for the preparation of [$^{18}$F]-(*E*)-*N*-(3-iodoprop-2-enyl)-2$\beta$-carbofluoroethoxy-3$\beta$-(4′-methyl-phenyl)nortropane ([$^{18}$F]FE-PE2I (VI). The synthesis procedure relies on the conventional Kryptofix-mediated nucleophilic $^{18}$F-substitution of the tosylate group in the precursor, TsOE-PE2I (V). Out of reaction conditions tested, the highest fluorination efficiency was obtained in dimethyl sulfoxide at 140°C. The reaction mixture was purified by semi-preparative HPLC, followed-up by a standard Sep-Pak SPE procedure. On average, 1.0 GBq of [$^{18}$F]FE-PE2I was produced from 5-min irradiation at 35 μA (dimethyl sulfoxide, 5 min/140°C). Decay-uncorrected yield of the product after HPLC purification and formulation was in the order of 20%. Specific radioactivity of [$^{18}$F]FE-PE2I at 15 min after EOS was 3.3–5.1 Ci/μmol ($n = 3$); radiochemical purity was >98% ($n = 4$). This direct nucleophilic fluorination strategy is well suited for the automation of the entire synthesis of [$^{18}$F]FE-PE2I in a modern PET synthesizer for human PET application. In addition, the $^{18}$F-incorporation rate into TsOE-PE2I was evaluated using radio-thin layer chromatography (TLC) and radio-HPLC. The suggested HPLC method (ACE 5 C18-HL column and acetonitrile/0.1 M $NH_4CO_2$ (80:20)) was found to be suitable for evaluation of 'free' $^{18}$F-fluoride in the reaction mixture; in addition, this method allowed the detection of three radiolabelled by-products that were not discernable with the TLC approach. Therefore, we conclude that the HPLC approach may serve as a good alternative to traditional radio-TLC technique as it provides more detailed information about the fluorination process in the reaction kinetics or optimization studies.**

**Keywords:** FE-PE2I; single-step; tosylate; dopamine transporter; PET chemistry; F-18

## Introduction

The dopamine transporter (DAT) is a transmembrane protein typically localized at the synaptic junctions and is responsible for the regulation of extracellular levels of dopamine. Molecular imaging techniques allow evaluating the DAT density changes in the progression of Parkinson's disease and in the course of other various central nervous system disorders (for a recent review, see[1]). From several radioligands available for PET imaging of DAT-binding sites in the brain, the tropane analog *N*-(3-iodoprop-2E-enyl)-2b-carbomethoxy-3b-(4-methyl-phenyl) nortropane labeled with carbon-11 ([$^{11}$C]PE2I) is considered a 'text-book' tracer because of its high affinity and specificity for DAT, along with good blood–brain barrier penetration.[2–7] The potential limitations of [$^{11}$C]PE2I for accurate *in vivo* quantification are relatively slow kinetics with the late peak equilibrium and formation of at least one radiometabolite that crosses the blood–brain barrier.[8] More recently, a fluorine-18 labeled analog of PE2I, [$^{18}$F]-(*E*)-*N*-(3-iodoprop-2-enyl)-2$\beta$-carbofluoroethoxy-3$\beta$-(4′-methyl-phenyl)nortropane ([$^{18}$F]FE-PE2I) has been developed[9–11] (Figure 1).

The direct comparison between the [$^{18}$F]FE-PE2I and [$^{11}$C]PE2I shows that [$^{18}$F]FE-PE2I displays faster kinetics and more favorable metabolism than [$^{11}$C]PE2I.[11] The analyses with the input function of the parent compound and its radiometabolite show that the bias in $BP_{ND}$ was much lower for [$^{18}$F]FE-PE2I (<10% in the caudate and putamen) than for [$^{11}$C]PE2I (40–60% in the caudate and putamen) and suggested that the lower formation of the radiometabolite would make [$^{18}$F]FE-PE2I more suitable for the DAT quantification, because the radiometabolite is likely to have some affinity for the DAT; in DAT-rich regions, kinetic analysis would require a four-tissue compartment model with eight rate constants, which would significantly complicate quantification.[9–11] Also, with [$^{11}$C]PE2I, the late peak equilibrium and slow kinetics result in long imaging times that can also pose a problem in some circumstances, such as imaging patients with Parkinson's disease.[11] Compared with carbon-11, the use of fluorine-18 is advantageous for several reasons – lower positron energy results in higher intrinsic resolution in the PET image, whereas the relatively long half-life (110 min) allows for a widespread clinical availability through remote-site delivery of the radioligand from centralized cyclotron facilities. For the first evaluation studies, the [$^{18}$F]FE-PE2I was prepared via alkylation of its acid precursor with [$^{18}$F]fluoroethyl bromide in a two-step

[a]*Karolinska Institutet, Department of Clinical Neuroscience, Stockholm, Sweden*

[b]*Institute of Human Brain, Russian Academy of Science, St.-Petersburg, Russia*

[c]*PharmaSynth AS, Tartu, Estonia*

[d]*Institute of Chemistry, University of Tartu, Tartu, Estonia*

**Correspondence to: Vladimir Stepanov, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden.*
*E-mail: vladimir.stepanov@ki.se*

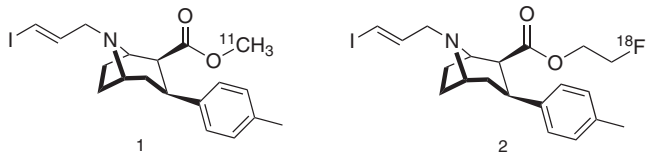



**Figure 1.** Structures of [$^{11}$C]PE2I (1) and [$^{18}$F]FE-PE2I (**2**).

method.[9,10] Despite an acceptable radiochemical yield (7%, EOS) and good radiochemical purity (>95%), this two-step two-pot synthesis procedure is considered to be practically inconvenient. Direct nucleophilic radiofluorination is generally a better method in the sense of both production yield and time, and is readily adaptable into fully automated $^{18}$F-fluorination systems – because a one-step synthesis can be implemented even in the simplest commercially available module, whereas two-step reaction with a distillation sequence would be difficult to implement. In this paper, we report for the first time a direct fluorination method for the preparation of [$^{18}$F]FE-PE2I suitable for a rapid and easy to automate production of the radioligand for use in human studies. The synthesis procedure relies on conventional Kryptofix-mediated nucleophilic $^{18}$F-substitution of TsO group in a tosylated derivative of PE2I-TsOE-PE2I.

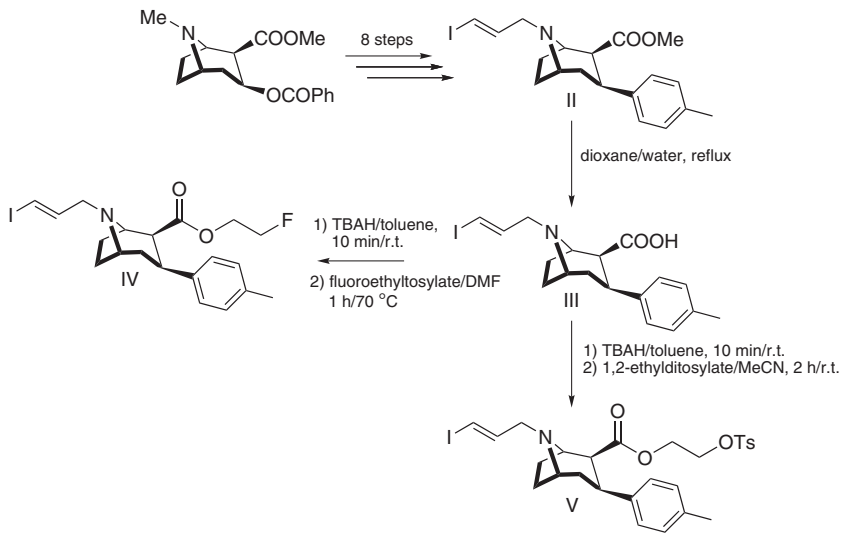
## Experimental

### Reagents and instrumentation

All reagents and solvents were acquired from Sigma-Aldrich, St. Louis, MO, USA, and used as received without further purification. Acetonitrile (for DNA synthesis, max 10 ppm $H_2O$) was bought from Merck (Darmstadt, Germany). Solid-phase extraction cartridges (Sep-Pak QMA light, Sep-Pak tC18 Plus) were purchased from Waters Corp., Milford, MA, USA. Column chromatography was performed on silica gel (60 Å, 70–230 mesh, Sigma-Aldrich). NMR spectra were recorded on a Bruker Avance II 200 spectrometer (Billerica, MA, USA) at 298 K using $CDCl_3$ as a solvent and tetramethylsilane as internal standard. HPLC analysis of TsOE-PE2I, FE-PE2I and related compounds were performed on a Waters X-Bridge C18 column (4.6 × 250 mm) with Kontron (Poway, CA, USA) HPLC system (UV absorbance at 220 nm) using $CH_3CN$/0.1% TFA in $H_2O$ 50/50 or 60/40 as an eluent. Semi-preparative HPLC purification system consisted of a pump (Knauer, Smartline Pump 100 (Berlin, Germany)), an automatic sample injector (Rheodyne-type) equipped with a 2 ml loop; UV detector from Knauer, Smartline UV Detector 2500 and a gamma-radioactivity PIN diode detector (Caroll & Ramsey Associates, Berkeley, CA, USA) to monitor the effluent radioactivity. Radioanalytical HPLC system included a pump (LaChrom Model L-7100, Merck-Hitachi), UV detector (LaChrom model L-7400), a D-7000 interface and a Beckman $\beta$-flow radiodetector (Model 170). ACE 5 C18-HL column (4.6 × 250 mm) was used for radiochemical purity determination and incorporation rate analysis. The system was controlled by Merck-Hitachi Chromatography Data Station Software D-7000 (version 4.1). Thin layer chromatography (TLC) analyses were run on precoated Kiesel gel 60 F254 (Merck) glass plates; radioactivity spots were detected using an automatic radio-TLC scanner (Raytest GmBH, Germany).

*Preparation of TsOE-PE2I (2-(tosyloxy)ethyl-8-[(2E)*-3-iodoprop-2-en-1-yl]-3-(4-methyl-phenyl)-8-azabicyclo[3.2.1]octane-2-carboxylate): **V** (Scheme 1)

This compound was prepared from desmethyl-PE2I in analogy (with and addition of an extra synthetic step described in the following paragraph) to a previously published method.[12] Briefly, 40% tetrabutyl ammonium hydroxide solution in $H_2O$ (0.518 g, 0.788 mmol) was added to the stirred suspension of desmethyl-PE2I (**III**) (0.268 g, 0.652 mmol) in toluene (5 ml). The mixture was stirred 10 min at room temperature and then concentrated at reduced pressure. Toluene (5 ml) was added to the residue, and the solution was reconcentrated. The yellowish residue was then dissolved in $CH_3CN$ (8 ml) and the obtained solution was added dropwise over the period of 35 min into the solution of 1,2-ethylditosylate (1.093 g, 2.95 mmol) in $CH_3CN$ (25 ml). After a 2-h reaction at room temperature, the mixture was concentrated at reduced pressure. The residue was purified sequentially by column chromatography using two different systems: (i) EtOAc/hexane 2/1 + 2.5% $Et_3N$; (ii) EtOAc/hexane 1/4 and EtOAc/hexane 1/1 + 1% $Et_3N$) to give after drying in vacuum tosylethyl-PE2I (0.233 g, 0.382 mmol, 54%) as a colorless semi-solid. Purity of **V** by HPLC was 98%. TsOE-PE2I (**V**) is stable for significant periods if kept in the dark and refrigerated – no difference in precursor purity and performance in the labeling procedure was observed after 9 months of storage. $^1$H NMR (200 MHz, $CDCl_3$) δ ppm 1.55–2.15 (m, 5 H), 2.29 (s, 3 H), 2.46 (s, 3 H), 2.42–2.58 (m, 1 H), 2.60–3.07 (m, 4 H), 3.37 (br s, 1 H), 3.56 (br s, 1 H), 4.00–4.15 (m, 4 H), 6.10–6.52 (m, 2 H), 7.09 (q, 4 H) (ABq, 4 H, $\Delta\delta_{AB}$ = 6.9 Hz, $J_{AB}$ = 8.6 Hz), 7.34 (d, 2 H, J = 8.0 Hz), 7.78 (d, 2 H, J = 8.4 Hz). $^{13}$C NMR (50 MHz, $CDCl_3$) δ ppm 21.0, 21.9, 25.9, 26.2, 33.6, 34.0, 52.6, 58.0, 60.8, 61.0, 63.0, 67.9, 127.1, 128.0, 128.7, 129.9, 133.2, 135.4, 139.6, 144.5, 144.9, 170.9.




**Scheme 1.** Route to the synthesis of tosylated precursor, TsOE-PE2I (**V**) and FE-PE2I (**IV**).

*Preparation of FE-PE2I (2-fluoroethyl 8-[(2E)*-3-iodoprop-2-en-1-yl]-3-(4-methylphenyl)-8-azabicyclo[3.2.1]octane-2-carboxylate): **IV** (Scheme 1)

This compound was prepared from desmethyl-PE2I in analogy (with some modifications) to a previously published method.[13] Briefly, 40% tetrabutyl ammonium hydroxide solution in $H_2O$ (0.198 g, 0.305 mmol) was added to the stirred suspension of desmethyl-PE2I (**III**) (0.102 g, 0.248 mmol) in toluene (2.5 ml). The mixture was stirred 20 min at room temperature and then concentrated at reduced pressure. Toluene (1 ml) was added to the residue, and the solution was reconcentrated. To the yellowish residue were added dimethylformamide (DMF) (1 ml) and then fluoroethyltosylate (1.093 g, 2.95 mmol) in DMF (0.5 ml). The mixture was stirred for 15 min at room temperature and then for 1 h at 70°C. After cooling the reaction, the mixture was poured into a mixture of saturated $NaHCO_3$ solution (10 ml) and $H_2O$ (10 ml), and extracted with EtOAc (20 ml + 2 × 10 ml). The combined organic layers were washed with $H_2O$ (20 ml) and brine (20 ml), dried over $MgSO_4$ and concentrated at reduced pressure. The residue was purified by column chromatography (EtOAc/hexane 1/2) to give fluoroethyl-PE2I (0.085 g, 0.186 mmol, 75%) as colorless oil. Purity of **IV** by HPLC was 98%. $^1$H NMR (200 MHz, $CDCl_3$) δ ppm 1.55–2.15 (m, 5 H), 2.29 (s, 3 H), 2.48–2.60 (m, 1 H), 2.64–3.10 (m, 4 H), 3.41 (br s, 1 H), 3.68 (m, 1 H), 3.98–4.70 (m, 4 H), 6.14–6.58 (m, 2 H), 7.11 (q, 4 H) (4 H, $\Delta\delta_{AB}$ = 13.3 Hz, $J_{AB}$ = 8.2 Hz). $^{13}$C NMR (50 MHz, $CDCl_3$) δ ppm 21.0, 25.9, 26.1, 33.7, 34.1, 52.6, 58.1, 61.0, 62.5, 62.88, 62.92, 79.8, 83.2, 127.2, 128.7, 135.4, 139.7, 144.4, 171.1.

*Radiosynthesis of [$^{18}$F]FE-PE2I (Scheme 2)*

Aqueous [$^{18}$F]fluoride was produced via the $^{18}$O(p,n)$^{18}$F nuclear reaction using a General Electric Medical Systems PETtrace cyclotron in a silver fluorine-18 water target. The radionuclide was transferred from the target by means of helium flow (in a 1.5-ml bolus of [$^{18}$O]$H_2O$) and trapped on a QMA light Sep-Pak cartridge (bicarbonate form) to remove [$^{18}$O]$H_2O$. [$^{18}$F]fluoride was then eluted into the reaction vessel using 2 ml of acetonitrile/water (96/4 v/v) containing 9.8 mg of Kryptofix 2.2.2 and 1.8 mg of potassium carbonate. The solvents were evaporated by heating at 140°C under a stream of nitrogen (100 ml/min). With the use of this method, azeotropic distillation with additional acetonitrile was not required to produce reactive [$^{18}$F]fluoride.[14] To the dried [$^{18}$F]fluoride, complex 0.9–1.0 mg of **V** dissolved in 600 µl of solvent were added. The reaction mixture was heated for 5 min at 90°C (acetonitrile (MeCN)) or 140°C (DMF, dimethyl sulfoxide (DMSO)) in the sealed 5-ml V-shaped reaction vial without stirring. The reaction was quenched by addition of 1.5 ml of water. The crude product was injected directly onto semi-preparative HPLC and purified on a Waters µBondapak C18 column (10 µ, 125 A, 7.8 × 300 mm) under the following conditions: 0–5 min: $H_2O$, 4 ml/min; 6–25 min, MeCN : $H_2O$ : TEA 650:350:1, 6 ml/min, UV 230 nm. The desired fraction ($R_t$ [$^{18}$F]FE-PE2I 15–17 min) was collected into a vial containing 50 ml of water and 70 mg of sodium ascorbate. The resulting solution was pushed through Sep-Pak tC18 Plus Short cartridge previously conditioned by rinsing it with 10 ml of ethanol and 15 ml of water. After trapping of the product, the cartridge was rinsed with 10 ml of distilled water, and the product was then eluted with 1.0 ml of EtOH and collected in a sterile receiving vial prefilled with 8 ml of sterile Phosphate buffered saline. Finally, the product was passed through a sterile filter (0.22 µm pore size, Millipore) in a particle-free aseptic environment. The [$^{18}$F]FE-PE2I (**2**) was analyzed by analytical radio-HPLC under following conditions: column ACE 5 C18-HL, 5 µm, 4.6 × 250 mm, MeCN : 0.1M $NH_4CO_2$ 80:20, flow 2 ml/min, UV 234 nm. The identity of **2** was confirmed by a co-injection with an authentic nonradioactive standard, FE-PE2I (**IV**). The same HPLC conditions were used to monitor the course of $^{18}$F-fluorination in optimization experiments; the samples were taken at 5, 10, 15 and 25 min reaction times and analyzed also by radio-TLC (EtOAc : Hexane 1:1).

## Results and discussion

Scheme 1 describes the synthesis of the tosylated precursor, TsOE-PE2I (**V**). This compound was synthesized starting from cocaine in eight steps (not all shown), with overall yield of 4.6% and purity of 97% (by HPLC) according to previously published procedures for the desmethyl-PE2I with some modifications.[12] The nonradioactive fluorinated analog **IV** was also prepared in a similar way using a slightly modified published method.[13]

Scheme 2 presents the radiosynthesis of [$^{18}$F]FE-PE2I via Kryptofix-mediated direct nucleophilic fluorination of tosylated precursor **V**.

In optimization studies, radiofluorination of **V** was investigated in three different solvents and various temperatures; the course of the reaction was monitored at time intervals of 5, 10, 15 and 25 min (Figure 2). In addition to radio-TLC analysis that is considered to be a general practice for evaluation of the $^{18}$F-incorporation rates into precursor structure, we developed the HPLC method allowing detection of unbounded [$^{18}$F]fluoride as well as other $^{18}$F-labeleled products. With the use of the ACE 5 C18-HL column and MeCN : 0.1M $NH_4CO_2$ (80:20) as a mobile phase, the desired labeled product 2 ($R_t$ 5.3 min.) and three labeled by-products (not identified) were well resolved (Figure 3). For the same sample of reaction mixture, radio-TLC analysis showed the presence of only two peaks: unbonded [$^{18}$F]fluoride with $R_f$ = 0.02 and the product peak with $R_f$ 0.7, which was not resolved from by-products (Figure 4). Varying composition of TLC-developing solvent did not result in the improved resolution.

From a direct comparison of two analytical techniques (Table 1), we may conclude that the suggested HPLC method is

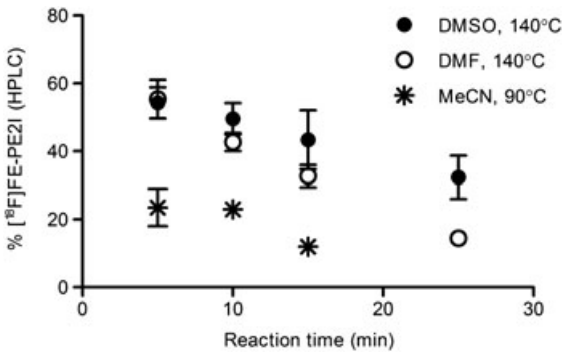
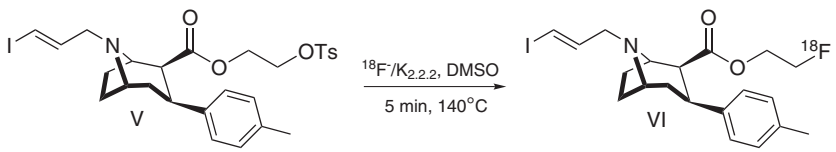



**Figure 2.** Fluorination efficiency of (**V**) under various reaction conditions.




**Scheme 2.** Radiosynthesis of [$^{18}$F]FE-PE2I.

a suitable way for the evaluation of fluorination efficiency, allowing detection of all radiolabeled components presented in the reaction mixture. This method is very practical and fast, and it is less laborious compared with radio-TLC. In our optimization study, both methods showed similar trend in the efficiency of fluorination (Table 1). The incorporation rates were somewhat overestimated with the use of radio-TLC because it was difficult to separate the target compound **2** from labeled by-products that contributed to the peak area. From three different solvents, the fluorination yields in MeCN at 90°C were much lower than that in DMSO or DMF at 140°C. From the current results, the yield in DMSO was slightly higher than in DMF; therefore, DMSO was used as preferred solvent in preparative runs. The 5-min reaction time seemed to be optimal, giving the highest incorporation rates. Radiochemical yields declined up to 20–30% for reaction time of 20 min (Figure 2) because of the formation of fluorinated by-products detected via the HPLC analysis (Figure 3). It is noteworthy that the radiofluorination reaction works with a moderately low amount of precursor **V** (1 mg), as might be demanded by a need to conserve expensive precursor in radiopharmaceutical production.

On average, 1.0 GBq of [$^{18}$F]FE-PE2I was produced from 5-min irradiation at 35 μA (DMSO, 5 min/140°C). Decay-uncorrected yield of the product after HPLC purification and formulation was in the order of 20%, with total synthesis time of 70 min. Specific radioactivity of [$^{18}$F]FE-PE2I (15 min after EOS) was 3.3–5.1 Ci/μmol ($n = 3$), and radiochemical purity was >98% ($n = 4$). No significant radiolysis of the product was observed after 2 h at room temperature in a formulation containing 11% v/v of ethanol in PBS.

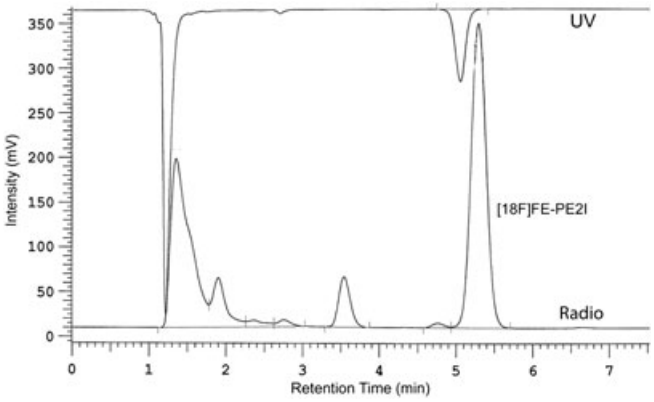



**Figure 3.** Representative chromatogram from the HPLC analysis of the products from a nucleophilic fluorination of **V** in dimethyl sulfoxide, 5 min, 140°C; co-injection with reference **IV**.

## Conclusions

The synthesis of radiolabelled analog of PE2I, [$^{18}$F]FE-PE2I, via direct $^{18}$F-nucleophilic substitution of the tosyl group of precursor **V** with [$^{18}$F]fluoride has been developed. The suggested synthesis procedure provides the radioligand in good yield, high purity and high specific radioactivity, and is well suited for the automation of the entire synthesis process in the modern synthesizers for human PET application. Compared with the previously described procedures, the overall yield of the reaction was improved more than 2 times – 20% vs 7% yield uncorrected for decay, while the overall length of the synthesis was decreased by 20–25%.[9] The radio-HPLC method suggested within the course of this work for evaluation of radiofluorination efficiency of tosylated precursor **V** may serve as a good alternative to traditional radio-TLC technique and provides more detailed information about the fluorination process. This method may be useful in the performance of the reaction kinetics or optimization studies using various aliphatic substrates.

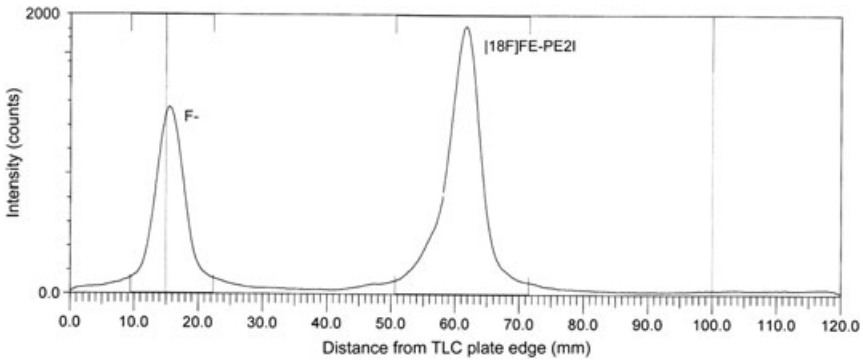



**Figure 4.** Radio-TLC analysis of the products from a nucleophilic fluorination of **V** in dimethyl sulfoxide, 5 min, 140°C.

**Table 1.** Results from the radiofluorinations of **V** in various solvents at 5 min reaction time

| Solvent | Reaction temperature, °C | $^{18}$F-incorporation rate (TLC) | % of product (HPLC) |
|---|---|---|---|
| MeCN | 90 | (20 ± 6) ($n = 3$) | (24 ± 8) ($n = 2$) |
| DMSO | 140 | (73 ± 7) ($n = 4$) | (61 ± 7) ($n = 6$) |
| DMF | 140 | (66 ± 11) ($n = 3$) | (55 ± 8) ($n = 3$) |

TLC, thin layer chromatography; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; MeCN, acetonitrile.

## Acknowledgements

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## Conflict of Interest

The authors did not report any conflict of interest.

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