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A Resin-Linker-Vector Approach to Radiopharmaceuticals Containing ^{18}F: Application in the Synthesis of *O*-(2-[^{18}F]-Fluoroethyl)-L-tyrosine

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Dedicated to Professor Philip Parsons on the occasion of his 60th birthday

Abstract: A Resin-linker-vector (RLV) strategy is described for the radiosynthesis of tracer molecules containing the radionuclide ^{18}F, which releases the labelled vector into solution upon nucleophilic substitution of a polystyrene-bound arylsulfonate linker with [^{18}F]-fluoride ion. Three model linker-vector molecules **7a–c** containing different alkyl spacer groups were assembled in solution from (4-chlorosulfonylphenyl)alkanoate esters, exploiting a lipase-catalysed chemoselective carboxylic ester hydrolysis in the presence of the sulfonate ester as a key step. The linker-vector systems were attached to aminomethyl polystyrene resin through amide bond formation to give RLVs **8a–c** with acetate, butyrate and hexanoate spacers, which were characterised by using magic-angle spinning (MAS) NMR spectroscopy. On fluoridolysis, the RLVs **8a**,**b** containing the longer spacers were shown to be more effective in the release of the fluorinated model vector (4-fluorobutyl)phenylcarbamic acid *tert*-butyl ester (**9**) in NMR kinetic studies and gave superior radiochemical yields (RCY≈60%) of the ^{18}F-labelled vector. The approach was applied to the synthesis of the radiopharmaceutical *O*-(2-[^{18}F]-fluoroethyl)-L-tyrosine ([^{18}F]-FET), delivering protected [^{18}F]-FET in >90% RCY. Acid deprotection gave [^{18}F]-FET in an overall RCY of 41% from the RLV.

Keywords: amino acids · positron-emission tomography · radiochemistry · radiopharmaceuticals · solid-phase synthesis

Introduction

Positron-emission tomography (PET) is recognised as the most specific and sensitive means of quantitatively imaging molecular pathways and interactions in vivo, having a level of sensitivity unmatched by using other imaging techniques.[1] PET imaging is routinely used in medical diagnostics to locate and assess abnormalities in neurology,[2] cardiology[3] and oncology.[4] Of the radionuclides commonly employed in PET radiotracers, ^{18}F may be considered to possess superior properties in the context of nuclear medicine. For example, ^{18}F emits a relatively low energy positron (up to 0.69 MeV), which has a short path in vivo before its annihilation, giving rise to enhanced resolution in comparison to ^{11}C.[5] The half-life of ^{18}F is 109.8 min, over five times that of ^{11}C, offering more flexibility in radiotracer syntheses and the investigation of biological processes with slower kinetics, in which PET scans can be acquired over periods of several hours.

Despite the longer half-life of ^{18}F, radiotracers incorporating this radionuclide still need to be synthesised, purified, analysed and formulated ready for injection into the subject as rapidly as possible. In radiofluorination, purification of the product is complicated by the use of very large, typically >1000 fold, excess of the labelling precursor. As a consequence, technologies that simplify the isolation and purification of the final radiotracer have been of intense interest to radiochemists.[6] Examples include captive solvent methods,[7] solid-phase extraction (SPE) techniques by using cationic ion-exchange resins, and the use of solid-supported aryl–metal intermediates as substrates for electrophilic fluorination.[8–10] The application of tagged or solid-supported precursors have emerged as technologies to facilitate separation of the labelled product from reaction co-products and the large excess of starting material present in reaction mixtures.[6] For example, Gouverneur and co-workers have described the use of fluorous-tagged sulfonate ester precursors to ^{18}F-labelled radiotracers and ^{18}F-labelled building blocks, in which the fluorous tag allows easy clean up by using fluo-

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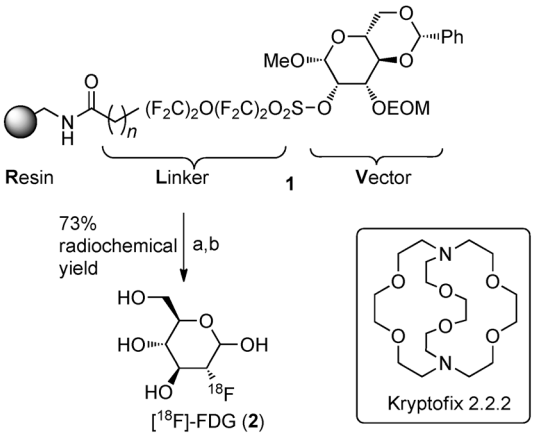
rous solid-phase extraction (FSPE).[11] It was reported that the presence of the fluorous tag caused a decrease in the specific activity of the product compared to a non-fluorous precursor, possibly due to leaching of [^{19}F]-fluoride ion from the tag. Sulfonate-tagged intermediates have been obtained from nucleophilic opening of sultones with [^{18}F]-fluoride ion, enabling removal of the precursor from the polar sulfonate by using reverse-phase SPE.[12]

We introduced an alternative approach, namely, the resin-linker-vector (RLV) strategy, for the synthesis of radiotracers-containing ^{18}F by nucleophilic cleavage of a sulfonate ester linker by using [^{18}F]-fluoride ion.[13] The RLV approach was initially developed for the radiosynthesis of [^{18}F]-2-fluoro-2-deoxy-D-glucose ([^{18}F]-FDG, **2**) utilising a perfluoroalkylsulfonate linker to immobilise a D-mannose derivative on polystyrene resin beads, liberating protected [^{18}F]-FDG into solution upon treatment with [^{18}F]-fluoride ion (Scheme 1). Unreacted precursor and sulfonate by-product



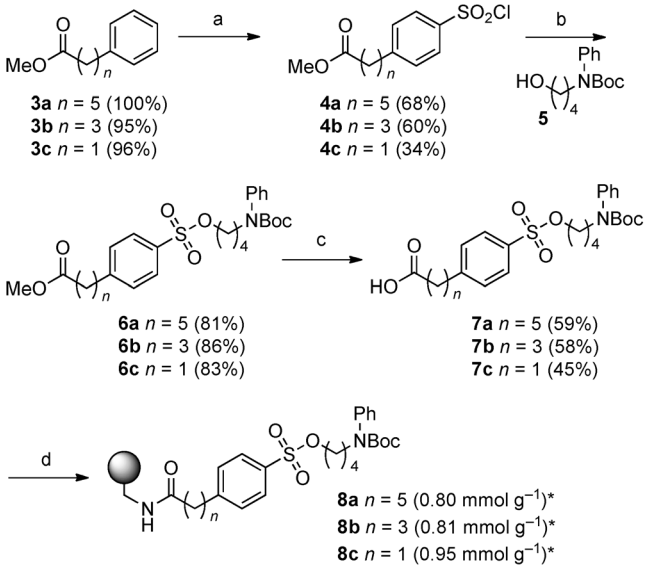
Scheme 1. Radiosynthesis of [^{18}F]-FDG (**2**). Reagents and conditions: a) Kryptofix 2.2.2, K^{18}F, MeCN, reflux, 10 min; b) HCl (6 M), reflux, 10 min.

were retained on the resin and conveniently separated from the product by a simple filtration process.

The radiosynthesis of [^{18}F]-FDG required an RLV system **1** containing an exceptionally reactive "triflate-like" sulfonate linker due to the inherent challenge of nucleophilic substitution with fluoride ion in a sterically encumbered electron-deficient substrate, namely, the 2-position of a protected mannose derivative. However, broader application of the RLV approach would require sulfonate ester linkers with a spectrum of reactivities that match the demands imposed by radiosyntheses of different tracer molecules.[13c,14] Furthermore, polymer-supported precursors are suited in application in automated radiosyntheses. Herein, the development of a model RLV system containing an arylsulfonate linker, suitable for nucleophilic fluoridation, is described. The utility of the optimised resin-linker system was then illustrated by the radiosynthesis of the radiophamacuetical *O*-(2-[^{18}F]-fluoroethyl)-L-tyrosine ([^{18}F]-FET).[15]

Results and Discussion

Linkers based on arylsulfonates were identified as suitable targets based on the widespread application of sulfonate leaving groups in solution [^{18}F]-fluoridation.[5] The length of the spacer between the polystyrene support and reactive centre is important in determining reaction rates in solid-phase synthesis. Therefore, three 4-alkylphenylsulfonate linkers with different alkyl spacers were prepared, commencing by Fischer esterification of commercially available phenylalkanoic acids to give methyl esters **3a–c** (Scheme 2).[16] Chlorosulfonylation of the aryl groups result-

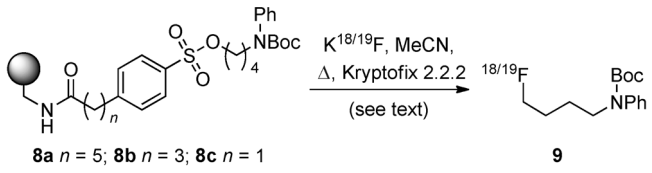


Scheme 2. Synthesis of 4-alkylphenylsulfonate RLVs **8a–c**. Reagents and conditions: a) i) $ClSO_2OH$, CH_2Cl_2, 0 °C to RT; ii) AcCl, MeOH, CH_2Cl_2, 0 °C; b) (4-hydroxybutyl)phenylcarbamic acid *tert*-butyl ester (**5**), Et_3N, DMAP, CH_2Cl_2, RT (reflux for **4c**); c) Novozym 435®, phosphate buffer (pH 7), CH_2Cl_2/acetone, 50 °C; d) aminomethyl polystyrene resin, HOBt, DIC, DMF/CH_2Cl_2. [*] Estimated from sulphur elemental analysis.

ed in partial carboxylate ester cleavage,[17] which was remedied by re-esterification of the crude reaction mixtures leading to improved yields of the desired sulfonyl chlorides **4a–c**. Direct chlorosulfonylation of the free acids was also investigated, but this returned the desired products in comparatively lower yields. The sulfonyl chlorides **4a–c** were then coupled to a model vector molecule, (4-hydroxybutyl)-phenylcarbamic acid *tert*-butyl ester (**5**), to form linker-vector constructs **6a–c**. To complete the synthesis of RLVs **8a–c**, the linker-vector constructs would be coupled to aminomethyl polystyrene resin beads by selective formation of activated carboxylate ester derivatives. Standard conditions for basic hydrolysis of methyl esters were incompatible with the sulfonate ester functionality present in **6a–c**, so chemoselective enzyme-catalysed hydrolysis was applied by using the supported lipase Novozym 435® to return the free acids **7a–c** in acceptable yields (45–59%).[18] The linker-vector systems were then coupled to aminomethyl polystyrene

resin by using carbodiimide coupling conditions to give RLVs **8a–c**. Successful coupling was supported by negative ninhydrin tests, on-bead IR, ^{1}H and ^{13}C NMR spectroscopy. Loadings were estimated by using sulfur elemental analysis.

To confirm that RLVs **8a–c** were suitable substrates for nucleophilic fluoridation, [^{19}F]-fluoridolysis reactions were carried out by using KF and Kryptofix 2.2.2 in CH_3CN at 80 °C (Scheme 3).[19] Purification of the fluorinated product



Scheme 3. Nucleophilic fluoridation of the model RLVs **8a–c**.

[^{19}F]-**9** simply involved filtration of the reaction mixture to remove the resin followed by elution through a short silica plug to remove the Kryptofix 2.2.2. In these experiments, in which a modest excess of [^{19}F]-KF (1.2 equiv) was employed relative to RLVs **8a–c**, the desired fluorinated product [^{19}F]-**9** was the only product obtained in isolated yields of 28, 28 and 27 %, respectively. The yields obtained by using limiting RLV were based upon the loading of the resin obtained from sulfur analysis and were approximately half of those obtained from fluoridolysis by using the linker vectors **6a–c** as substrates. However, subsequent radiochemical experiments were carried out by using a large excess of resin relative to the amount of [^{18}F]-fluoride ion, and given the clean fluorination chemistry observed, were expected to deliver high radiochemical yields. To confirm that unreacted linker vector remained on the resin after reaction with a deficiency of fluoride ion, RLV **8a** was subjected to a series of [^{19}F]-fluoridolysis reactions. It is difficult to directly replicate the conditions typical of radiofluoridation, in which a massive excess of the labelling precursor is employed, and herein 0.25 equivalents of [^{19}F]-KF were used with respect to the RLV to facilitate quantification of the released fluorinated product [^{19}F]-**9**. The fluorinated product [^{19}F]-**9** was obtained over a total of seven cycles, the first five of which gave consistent yields (34, 41, 45, 30, 45, 4 and 7 %, respectively, based on limiting K^{19}F). These results are consistent with the majority of unreacted vector remaining attached to the solid phase through the 4-alkylphenylsulfonate linker.

In view of the time constraints imposed when working with ^{18}F, establishing the relative rates of fluoridolysis for the different linkers is of interest. Towards this end [^{19}F]-fluoridolyses of RLVs **8a–c** were conducted at 40 °C, which gave a rate of product formation that was convenient to establish by ^{19}F NMR spectroscopy through integration against an internal standard (Bn^{19}F). Each reaction was run in duplicate, by using 19 μmol of RLV with 1.5 equiv of K^{19}F to ensure a good level of conversion, and spectra were acquired at 12–15 min intervals periodically removing the samples from the NMR probe to agitate the resin. The results indicate that the rate of cleavage of the fluorinated product improved with alkyl-chain length for the 4-alkylphenylsulfonate linker, which can be attributed to the relatively greater flexibility and "solution-like" character provided by the longer spacers present in RLVs **8a** and **8b** (Figure 1). The

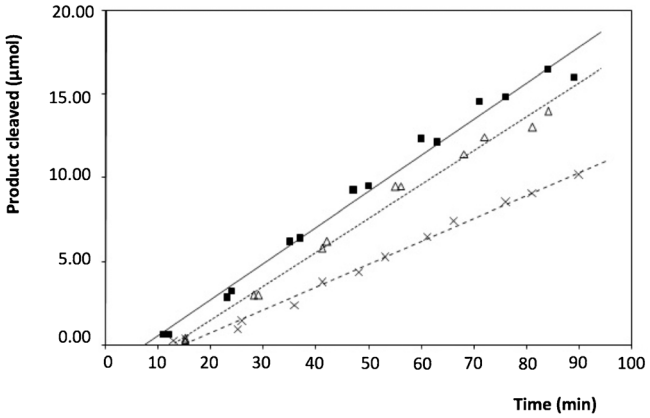


Figure 1. Relative rates of release of the model fluorinated vector [^{19}F]-**9** estimated by using ^{19}F NMR against an internal standard (BnF). Experiments were carried out in duplicate. RLV (19 μmol, BnF (5.3 μmol) in CD_3CN (0.5 mL) at 40 °C. **8a**: ■; **8b**: △; **8c**: ×.

rate of product formation was seen to be slower during the initial 20 min, probably because the RLVs were not preswollen in the reaction solvent and the lack of sample agitation in the NMR probe.

Radiolabelling experiments were carried out manually by using cyclotron-generated [^{18}F]-fluoride with low activity levels (40–150 MBq), RLV **8a–c**, K_2CO_3 and Kryptofix 2.2.2 in CH_3CN with a reaction time of 15 min. Radiochemical yields of the labelled vector [^{18}F]-**9** were established by reverse-phase HPLC analysis of the crude reaction mixture with γ-detection, and/or by using radioTLC (Figure 2). The desired labelled vector [^{18}F]-**9** was formed as the major radiochemical product of the reaction and its identity was confirmed by co-injection of the cold standard [^{19}F]-**9** and HPLC analysis. RLVs **8a** and **8b** containing the longer alkyl spacers resulted in the highest incorporation of [^{18}F]-fluoride (ca. 60 %), whereas RLV **8c** delivered reduced incorporation (40 %). The incorporation for the radiolabelling from

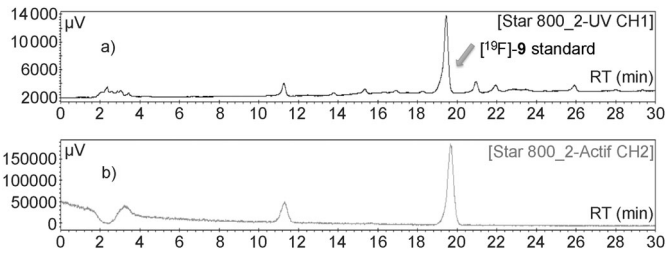
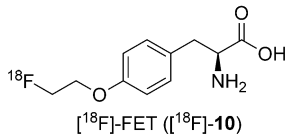


Figure 2. Reverse-phase HPLC analysis of the [^{18}F]-fluoridolysis reaction mixture from RLV **8b**, before Sep-pack filtration. a) UV trace (λ = 254 nm) co-injected with [^{19}F]-**9** (13.3 μg) as a reference. b) Radioactivity trace.

RLV **8a** decreased to 34% when carried out without mechanical stirring, showing good agitation of the polystyrene beads to be important, although care is needed to avoid excessive mechanical damage of the resin beads. Residual RLV was easily removed by filtration and so the analyses were not complicated by the presence of large excesses of unreacted starting material, underscoring the value of the RLV approach in radiosynthesis.

The HPLC analysis of the [^{18}F]-fluoridolysis reaction of RLV **8b** showed three radioactive peaks due to unreacted [^{18}F]-fluoride salts, the [^{18}F]-fluorinated product [^{18}F]-**9**, and an unidentified radioactive by-product (not observed by radioTLC; Figure 2b). The UV trace shows a major peak corresponding to the co-injected [^{19}F]-**9**, and a number of minor UV-active impurities that were not identified due to the very small amounts of material produced (Figure 2a). The formation of significant quantities of eliminated or hydrolysed by-products was excluded by HPLC comparison of the reaction mixture against synthesised samples. However, prolonged heating of RLV **8b** in CH_3CN at 110°C in a sealed vessel, either with or without base, did lead to the formation of *N*-phenylpyrrolidine, which co-eluted with the major UV-active impurity formed during the radiosynthesis. This chemical impurity was not observed at lower temperature (80°C), although no further efforts were made to minimise its formation, because it was produced in a cyclisation side reaction specific to the model RLV system.

Having demonstrated that high levels of [^{18}F] incorporation could be achieved from the RLVs **8a** and **8b** for a model-vector molecule, attention turned to extend the approach to an established radiotracer, the tyrosine derivative *O*-(2-[^{18}F]-fluoroethyl)-L-tyrosine ([^{18}F]-**10**, [^{18}F]-FET, Figure 3). [^{18}F]-FET is promising clinically for imaging of

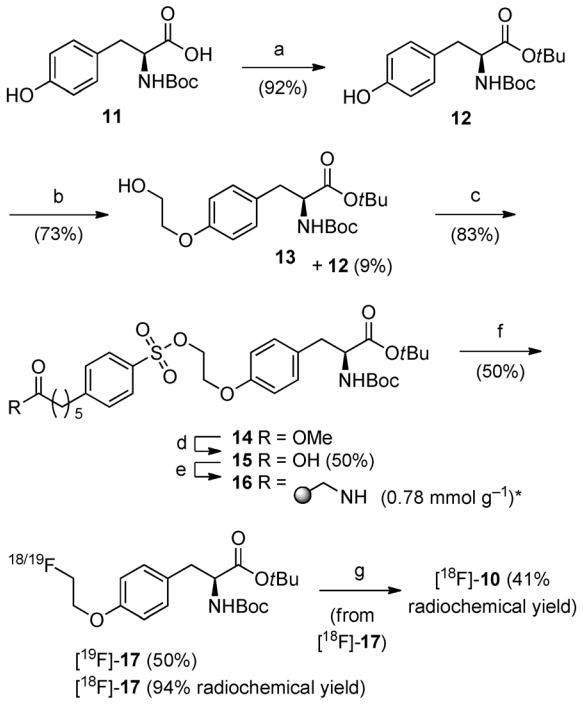


[^{18}F]-FET ([^{18}F]-**10**)

Figure 3. Structure of the radiotracer *O*-(2-[^{18}F]-fluoroethyl)-L-tyrosine ([^{18}F]-FET).

gliomas, through exploitation of active uptake of amino acid derivatives.[15,20] The RLV approach described herein for [^{18}F]-FET will also be more generally applicable to PET tracers containing [^{18}F]-fluoroalkyl groups, which reduces the radiosynthesis time by avoiding the requirement for isolation, purification and further reaction of volatile and/or sensitive radioactive fluoroakylating reagents.[21]

The solid-phase route to FET commenced with the synthesis of the RLV **16** from *N*-(*tert*-butoxycarbonyl)-L-tyrosine (**11**) and the sulfonyl chloride linker **4a** (Scheme 4). First, *N*-Boc tyrosine was protected as its *tert*-butyl ester,[22] followed by phenolic alkylation to give hydroxyethyl derivative **13** in an overall yield of 67%. Alcohol **13** was subsequently *O*-sulfonylated by reaction with the sulfonyl chloride linker **4a**. Enzymatic hydrolysis of the methyl ester functionality and coupling of the free acid to the solid support afforded RLV **16**. [^{19}F]-Fluoridolysis of RLV **16** gave a yield of 50% of protected FET [^{19}F]-**17**, a significant improvement in comparison to the model-fluorinated vector molecule [^{19}F]-**9**.



Scheme 4. Synthesis of [^{19}F] and [^{18}F]-FET. Reagents and conditions: a) 2-bromo-2-methylpropane, K_2CO_3, benzyltriethylammonium chloride (BTEAC), *N,N*-dimethylacetamide (DMAC), 55°C; b) bromoethanol, K_2CO_3, BTEAC, DMF, 50°C; c) sulfonyl chloride **4a**, Et_3N, 4-dimethylaminopyridine (DMAP), CH_2Cl_2; d) Novozym 435®, aqueous phosphate buffer (pH 7), CH_2Cl_2/acetone, 50°C; e) amino methyl polystyrene resin, HOBt, DIC, DMF/CH_2Cl_2; f) KF, Kryptofix 2.2.2, MeCN, 80°C; g) TFA, DCE, 70°C. [*] Estimated from sulphur elemental analysis.

Manually operated radiofluoridolysis of RLV **16** gave a single major radioactive product, which was shown to be protected FET [^{18}F]-**17** from HPLC analysis (UV and γ-detection) of a sample co-injected with authentic [^{19}F]-reference compound. Furthermore, excellent radiochemical yield (94%) and radiochemical purity were realised. Deprotection of the *tert*-butyl ester and *N*-Boc groups from [^{18}F]-**17** was achieved by exposure to trifluoroacetic acid (TFA) in 1,2-dichloroethene (DCE) at 70°C to afford the radiotracer [^{18}F]-FET ([^{18}F]-**10**) with a radiochemical yield of 41 and 97.5% radiochemical purity, the identity of which was confirmed by HPLC analysis against the unlabelled reference [^{19}F]-**10**. In a separate radiolabelling experiment starting with 100 MBq of [^{18}F]-fluoride, the specific activity of HPLC purified protected [^{18}F]-FET was determined to be approximately 0.4 MBq μmol^{-1} by comparison against the reference standard [^{19}F]-**17**. No further optimisation of the deprotection process was carried out although a number of protecting group strategies have been applied in [^{18}F]-FET synthesis.[20]

Conclusion

A RLV strategy has been described for the radiosynthesis of tracer molecules containing the radionuclide ^{18}F, in which the linker has tosylate-like reactivity. The potential for the application of the 4-alkylphenylsulfonate in practical radiosyntheses has been illustrated herein by the synthesis of the radiopharmaceutical [^{18}F]-FET, which is used for imaging of brain tumours. 4-Alkylphenylsulfonate linkers, containing varying spacer lengths, were evaluated for application in the synthesis of a model [^{18}F]-containing radiotracer with longer alkyl linkers ($n=3$ and 5) being more effective. The RLV approach allows facile separation of excess starting material and sulfonate by-product at the end of the radiosynthesis by using a straight forward filtration process, leading to good radiochemical yields in time scales commensurate with practical application in PET imaging. The 4-alkylphenylsulfonate linkers described herein compliment the highly reactive perfluorosulfonate linkers that we reported previously.

Experimental Section

Radiosynthesis of [^{18}F]-FET ([^{18}F]-10): *Step 1 ([^{18}F]-labelling):* Cyclotron-produced [^{18}F]-fluoride was separated from ^{18}O-enriched water by using ion-exchange resin (QMA light, Waters, ABX) after elution with a 1:1 mixture (600 μL) of aqueous potassium carbonate K_2CO_3 (5 mg mL^{-1}) and MeCN. A fraction of the resulting [^{18}F]-fluoride solution [^{18}F]-fluoride (300 mL, 4.83 mCi, 179 MBq) was drawn into a Wheaton vial followed by 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (Kryptofix® K_{222}, 4 mg, 10.6 mmol). No additional K_2CO_3 was used to avoid the presence of excess base. MeCN (1 mL) was added, and the mixture was azeotropically dried under a flow of N_2 at 100 °C. The process was repeated three times in a total time of 15 min. The reaction vessel was cooled to RT, and RLV **16** (30–40 mg) was added followed by MeCN (500 μL). The stirred reaction mixture was heated to 110 °C for 15 min before being cooled and filtered through an acrodisc (syringe filter). The solution containing the protected [^{18}F]-FET ([^{18}F]-**17**) was analysed by radioTLC and reverse-phase HPLC (Phenomenex Luna C18(2) column, 250×4.6 mm, 5 μm, 20 μL loop, 1 mL min^{-1} flow rate, $\lambda=$ 254 nm, eluent MeCN/water, linear gradient 40→95 % MeCN (25 min) then 95 % MeCN (5 min), 30 min total run time). *Step 2 (deprotection):* MeCN was removed under a flow of N_2 and a TFA/DCE mixture (1:2, 1 mL) was added in the reaction vessel. The resulting mixture was stirred at 70 °C for 10 min, cooled to RT followed by the addition of CH_2Cl_2 (5 mL) and passed through a silica-gel cartridge (Sepack normal phase, pre-conditioned with CH_2Cl_2). The cartridge was washed twice with Et_2O/pentane (1:1, 5 mL), and the [^{18}F]-fluorinated product was eluted with warm MeOH (2 mL). The solution containing [^{18}F]-FET ([^{18}F]-**10**) was analysed by reverse-phase HPLC (Phenomenex Luna C18(2) column, 250×4.6 mm, 5 mm, 20 μL loop, 1 mL min^{-1} flow rate, $\lambda=$ 254 nm, eluent MeCN/water, linear gradient from 5→50 % MeCN (25 min) then 50 % MeCN (5 min), 30 min total run time).

Acknowledgements

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