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**Research Article**

# Simultaneous preparation of 16α-[$^{18}$F]fluoroestradiol-sulphamates in an automated module. A high-yield procedure for 16α-[$^{18}$F]fluoroestradiol-17β-sulphamate

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## Summary

After successfully synthesizing 16α-[$^{18}$F]fluoroestradiol-3,17β-disulphamate in an automatic procedure, we studied the conditions for obtaining 16α-[$^{18}$F]fluoroestradiol-monosulphamates in a similar manner. The described procedure can simultaneously provide approximately 3 GBq of 16α-[$^{18}$F]fluoroestradiol-3-sulphamate and 1 GBq of 16α-[$^{18}$F]fluoroestradiol-17β-sulphamate of high radiochemical purity. By treating 16α-[$^{18}$F]fluoroestradiol-3,17β-disulphamate with Kryptofix 2.2.2 and potassium carbonate, 16α-[$^{18}$F]fluoroestradiol-17β-sulphamate also becomes available at high radioactivity. Copyright © 2001 John Wiley & Sons, Ltd.

**Key Words:** fluorine-18; nucleophilic fluorination; sulphamoylation; automated synthesis; PET tracer

## Introduction

Our first steroid tracer for use in positron emission tomography (PET) was 16α-[$^{18}$F]fluoroestradiol ([$^{18}$F]FES), which is considered the PET

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tracer of choice for diagnosing endocrine-dependent breast cancer and breast cancer metastases.[1] A new procedure[2] using 3-O-methoxymethyl-16,17-O-sulphuryl-estra-1,3,5(10)-triene-3,16$\beta$,17$\beta$-triol (cyclic sulphate) as a precursor and non-carrier added (n.c.a.) [$^{18}$F]fluoride as a reagent was modified and then refined to be a reproducible method for preparing [$^{18}$F]FES.[3] By integrating this procedure into a commercially available automatic module, we were able to produce [$^{18}$F]FES of high specific activity and high chemical and radiochemical purity in GBq levels of radioactivity and in a reliable way.[4] Since that time the radiotracer has been used for breast cancer diagnosis in our PET centre.

Later, 16$\alpha$-halogen-estradiol-3,17$\beta$-disulphamates were found to be highly active steroid sulphatase inhibitors.[5] As steroid sulphatase is particularly prevalent in breast cancer tissue, steroids such as 16$\alpha$-fluoroestradiol-3,17$\beta$-disulphamate (FESDS) should be suitable for chemotherapeutic intervention in breast cancer. The use of 16$\alpha$-[$^{18}$F]fluoroestradiol-3,17$\beta$-disulphamate ([$^{18}$F]FESDS), on the other hand, should provide an opportunity of imaging sites of high steroid sulphatase activity. We therefore searched for the conditions to successfully convert [$^{18}$F]FES into [$^{18}$F]FESDS,[6] and worked out a module-assisted one-pot procedure to produce [$^{18}$F]FESDS of first-class quality in GBq amounts.[7] Thus, [$^{18}$F]FES can be made available within 60 min and [$^{18}$F]FESDS within 90 min after the end of bombardment (EOB).

The conditions for producing sulphamates were studied in detail. When estradiol was subjected to sulphamoylation with excess sulphamoyl chloride ($H_2N$–$SO_2Cl$, SCl) in anhydrous acetonitrile and in the presence of solid sodium carbonate as a base, three sulphamates were formed: estradiol-3-sulphamate estradiol-17$\beta$-sulphamate, and estradiol-3,17$\beta$-disulphamate. The same result was found for substituted estradiols. Thus, using 16$\alpha$-fluoroestradiol (FES) as the starting compound, a procedure for producing 16$\alpha$-fluoroestradiol-3-sulphamate (FES3S), 16$\alpha$-fluoroestradiol-17$\beta$-sulphamate (FES17S), and 16$\alpha$-fluoroestradiol-3,17$\beta$-disulphamate (FESDS), and for purifying them by HPLC was elaborated.[8]

In the module-assisted procedure,[7] SCl was applied in high excess relative to n.c.a. [$^{18}$F]FES. The primary product was [$^{18}$F]FESDS, as expected. 16$\alpha$-[$^{18}$F]fluoro-estradiol-3-sulphamate ([$^{18}$F]FES3S) and 16$\alpha$-[$^{18}$F]fluoroestradiol-17$\beta$-sulphamate ([$^{18}$F]FES17S) were obtained at a very low level of radioactivity.

In the first animal experiments [$^{18}$F]FESDS was found to bind strongly to the erythrocytes.[9] Thus, the blood vessels were primarily

imaged. The question whether this applies to both monosulphamates and whether there were also other targets is still unanswered. We therefore carried out modified module-assisted experiments to produce [$^{18}$F]FES3S and [$^{18}$F]FES17S with a good level of radioactivity. In this context FESDS was found to be rather sensitive to alkaline treatment. As a result FES17S was formed. This conversion could provide a new approach to [$^{18}$F]FES17S, which has been insufficiently accessible up to now. We therefore studied the new route.

In previous experiments aimed at producing [$^{18}$F]FES[4] or [$^{18}$F]-FESDS,[6,7] undesirable radioactive polar products were produced in every synthesis. This fact was worth studying because about half the total radioactivity was bound there. Mass spectrometric measurements were therefore carried out.

## Results and discussion

### *Synthesis of [$^{18}$F]FES-monosulphamates*

In non-radioactive experiments we succeeded in preparing FES-monosulphamates by stirring FES in an anhydrous solvent in the presence of a base and excess SCl only at room temperature. The yields increased with the stirring time.[8] The sulphamates were formed in the following descending order: $m$(FESDS) > $m$(FES17S) > $m$(FES3S). On average 25% FES17S and 15% FES3S were obtained. At higher temperatures, the monosulphamates were not formed in noticeable amounts. This result was confirmed by numerous radioactive module-assisted experiments[7] performed at 70°C.

The module made it possible to work with 30°C as the lowest temperature. All the experiments described here were therefore carried out at this temperature.

The results of 10 experiments are compiled in Table 1. The sulphamoylation reaction was carried out while stirring in absolute acetonitrile, using 10–20 mg SCl, within 5 min. Only the base for deprotonating the hydroxy groups (Table 1, column 2) was modified.

Similar to the experiments at 70°C,[6,7] the highest radioactivity (up to 50%) was again found in the polar products. The highest radioactivity for [$^{18}$F]FES-monosulphamates was found when the sulphamoylation was carried out in the presence of a reduced potassium carbonate concentration (condition B in Table 1). Nevertheless, it did not exceed

**Table 1. Distribution of the radioactivity after sulphamoylation of [$^{18}$F]FES with sulphamoyl chloride under different conditions. Solvent: Acetonitrile (1.5 ml). Reagent used: 10–20 mg. Reaction temperature: 30°C. Stirring time: 5 min**

| Expt. | Conditions[a] | Distribution of radioactivity (%)[b] | | | | |
|---|---|---|---|---|---|---|
| | | Polar products | [$^{18}$F]FESDS | [$^{18}$]FES3S | [$^{18}$F]FES17S | [$^{18}$F]FES[c] |
| 1 | A | 45 | 36 | 6 | 2 | 11 |
| 2 | A | 47 | 31 | 7 | 2 | 13 |
| 3 | A | 48 | 35 | 9 | 4 | 4 |
| 4 | B | 40 | 13 | 16 | 9 | 22 |
| 5 | B | 41 | 18 | 15 | 7 | 19 |
| 6 | B[d] | 44 | 27 | 14 | 7 | 8 |
| 7 | B[d] | 37 | 27 | 14 | 6 | 16 |
| 8 | C[e] | 56 | 9 | 8 | 5 | 22 |
| 9 | C | 46 | 15 | 9 | 5 | 25 |
| 10 | D | 43 | 2 | 12 | 4 | 39 |

[a] A – sulphamoylation in presence of 15 mg K222 and 2.77 mg $K_2CO_3$; B – sulphamoylation in presence of 15 mg K222 and 0.46 mg $K_2CO_3$; C – sulphamoylation in presence of 15 mg K222 alone; D – sulphamoylation in absence of any base.
[b] Radioactivity of each peak eluted from the column was measured, decay-corrected and related to the sum of all.
[c] Unconverted [$^{18}$F]FES.
[d] Instead of 0.46 mg $K_2CO_3$ only 0.18 mg had been used.
[e] Instead of 15 mg K222 only 7 mg K222 had been used.

**Table 2. Radioactivities of [$^{18}$F]FES3S and [$^{18}$F]FES17S available at EOS after starting the synthesis with $A_0$ from a 60 min irradiation**

| Expt.[a] | $A_0$ (MBq) | Radioactivity at EOS (MBq) | | |
|---|---|---|---|---|
| | | [$^{18}$F]FESDS | [$^{18}$F]FES3S | [$^{18}$F]FES17S |
| 4 | 52 000 | 3980 | 3080 | 1110 |
| 5 | 58 000 | 4070 | 3000 | 1070 |
| 7 | 46 200 | 4360 | 2350 | 1000 |

[a] Experiment number as in Table 1.

25%. Experiments without a base (condition C) or without a base and Kryptofix (condition D) produced even worse results.

Expts. 4, 5 and 7 of Table 1 started with a high radioactivity level from a 60 min irradiation. The radioactivities of [$^{18}$F]FESDS, [$^{18}$F]FES3S, and [$^{18}$F]FES17S found at the end of synthesis (EOS, about 90 min after EOB) are summarized in Table 2. By starting with a high radioactivity ($A_0 = 40-60$ GBq) and carrying out the following sulphamoylation reaction under condition B of Table 1, the accessible amounts of radioactivity of [$^{18}$F]FES3S and [$^{18}$F]FES17S were about 3 and 1 GBq.

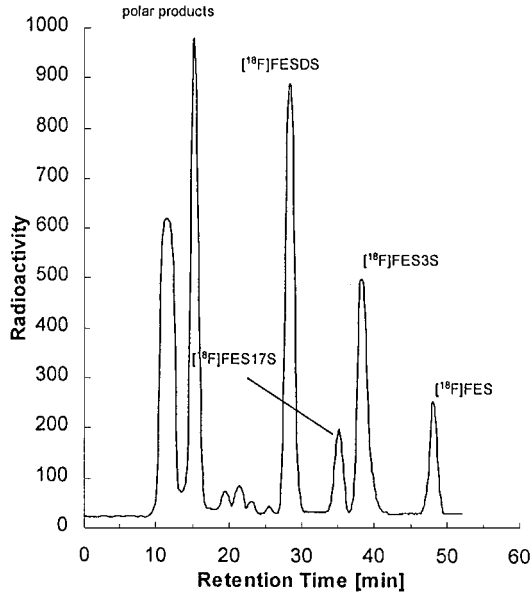


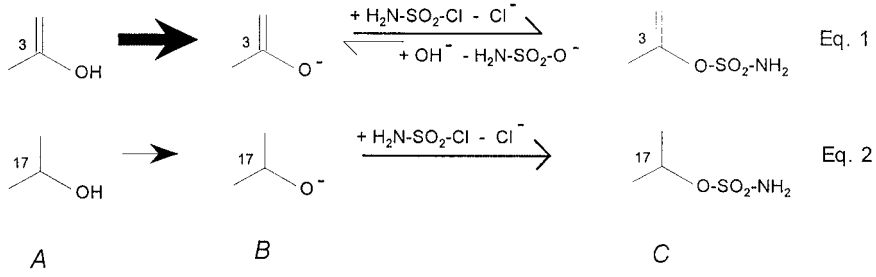

**Figure 1. Radiochromatogram of Expt. 4 of Table 1**

Expt. 4 of Table 1 showed the highest proportions of both [$^{18}$F]FES-monosulphamates. The radiochromatogram of Expt. 4 is illustrated in Figure 1. The retention times found for [$^{18}$F]FESDS, [$^{18}$F]FES17S, [$^{18}$F]FES3S, and for the remaining [$^{18}$F]FES were: 28.2, 34.3, 37.2 and 46.4 min, respectively.

## Different results from the radioactive and non-radioactive reactions

At first sight, it seemed surprising that the proportion of radioactivity for [$^{18}$F]FES3S was greater than that of [$^{18}$F]FES17S in all the experiments mentioned in Table 1, while former non-radioactive sulphamoylation experiments[8] had produced more of the corresponding 17-monosulphamate. However, this is not contradictory as several reactions proceed in parallel depending on the existing equilibria (see the reactions in Scheme 1). The more acidic proton of the phenolic hydroxy group is easily deprotonated (Scheme 1, A $\rightarrow$ B, Equation (1)) and hence 3-monosulphamate is preferentially formed by sulphamoylation (Scheme 1, B $\rightarrow$ C, Equation (1)). This is the case in the rapid radioactive reactions with a high excess of SCl. The non-radioactive experiments, however, were carried out for several hours in the presence




**Scheme 1. Equilibria between hydroxysteroid A , deprotonated hydroxysteroid B, and amidosulphonyloxysteroid C. Equation (1) – Substitution of the proton of the phenolic 3-hydroxy group Equation (2) – Substitution of the proton of the aliphatic 17$\beta$-hydroxy group**

of solid sodium carbonate as a base. During this time, the base split off the 3-amido-sulphonyloxy group from FES3S and FESDS in a reversible reaction (Scheme 1, C $\rightarrow$ A, Equation (1)). Because the 17-amidosulphonyloxy group is less sensitive to sodium carbonate (Scheme 1, C $\not\rightarrow$ A, Equation (2)) and because of the long contact time FES17S is produced in preference to FES3S in the non-radioactive reactions.

## Synthesis of [$^{18}$F]FES17S from [$^{18}$F]FESDS

The sensitivity of the 3-amidosulphonyloxy group to base was confirmed in non-radioactive experiments. FESDS was shown to be quantitatively converted into FES17S, and likewise FES3S into FES. This fact should open the way to a new approach to [$^{18}$F]FES17S at a higher radioactivity level. In order to prove this, we carried out three experiments in which a reaction mixture from the module-assisted procedure[7] was subjected to an additional alkaline treatment before HPLC separation. Only the alkaline conditions were modified to a slight degree in these three experiments. The results are summarized in Table 3. In two cases (Expts. 1 and 2) the alkaline reaction mixture was carefully dried, then heated and stirred. A moderate conversion of [$^{18}$F]FESDS into [$^{18}$F]FES17S took place. The conversion was rather higher however, when careful drying of the alkaline reaction mixture was not performed (Expt. 3). A radiochromatogram is illustrated in Figure 2.

**Table 3. Distribution of the radioactivity after alkaline treatment of [$^{18}$F]FESDS. Solvent: acetonitrile. Reagent: 15 mg K222 and 2.77 mg $K_2CO_3$. Stirring time: 5 min**

| Expt. | Conditions[a] | $A_0$ (MBq) | [$^{18}$F]FES17S (MBq)[b] | Distribution of radioactivity (%)[c] | | | |
|---|---|---|---|---|---|---|---|
| | | | | Polar products | [$^{18}$F]FESDS[d] | [$^{18}$F]FES17S | [$^{18}$F]FES |
| 1 | A | 46 200 | 1160 | 47.5 | 25.0 | 27.4 | 0 |
| 2 | B | 59 000 | 1650 | 44.5 | 23.7 | 19.5 | 12.3 |
| 3 | C | 58 000 | 2580 | 26.1 | 22.7 | 44.5 | 6.5 |

[a] A – Alkaline treatment as described in Experimental. B – Alkaline treatment as described in Experimental, but 90°C in place of 70°C. C – Reaction mixture was not carefully dried as done in A or B.
[b] Decay-corrected to EOS which was 100 min after starting the synthesis.
[c] Radioactivity of the peaks eluted from the column were measured, decay-corrected and related to total radioactivity.
[d] Unconverted [$^{18}$F]FESDS.

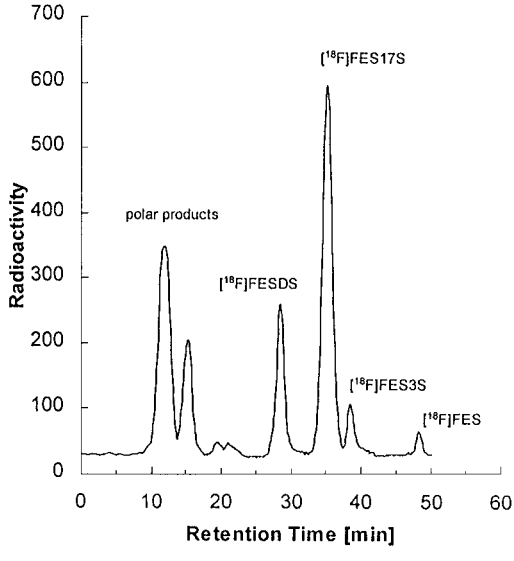



**Figure 2. Radiochromatogram of Expt. 3 of Table 3**

The results are different from the non-radioactive experiments. Figure 2 shows that the [$^{18}$F]FESDS was not completely converted into [$^{18}$F]FES17S by the additional alkaline treatment. But the peak due to [$^{18}$F]FES17S was the highest. Because the starting radioactivity was high (52 GBq), the radioactivity level of [$^{18}$F]FES17S obtained was also

high (2.6 GBq). In this way [$^{18}$F]FES17S can be made accessible for biological experiments on a large scale.

## Mass spectrometric measurements

All the module-assisted experiments to synthesize [$^{18}$F]FES sulphamates provided undesirable polar products at a high radioactivity level (see both figures). Optimization experiments to reduce the loss of radioactivity failed. Up to that point, we only knew that stoichiometric amounts of K222 and potassium carbonate are required to prevent the total conversion of [$^{18}$F]FES into polar products.[6]

K222 is a toxic compound which has to be removed from solutions used for animal experiments. Its separation was accomplished by passing the aqueous solution through a C-18 Sep Pak cartridge.[10] In our semipreparative HPLC separation, the K222 removal must be assumed to take place during elution of the polar products. But to detect traces of K222 is difficult.[11] We searched for a sensitive analytical method and therefore studied the polar products and the other peaks by an LC–MS method.[12] The $ESI^+$ spectrum of the eluate of polar products unequivocally showed the masses $m/z$ 377 and $m/z$ 415. This is doubtless due to K222 ($M = 376$ g/mol) as $(M+H)^+$ and $(M+K)^+$ which was quantitatively eluted with the front of the eluate. No K222 was detected in the eluates of the following peaks. We now know that K222-free sulphamates are eluted in the HPLC separation.

In the $ESI^-$ spectrum of the eluate of the polar products, sulphamoyl acid ($M = 97$ g/mol) and *N*-amidosulphonyl derivatives of FES sulphamates ($m/z$ 446, 525, 604; $\Delta m = 79$) were found with the sulphamoyl acid being formed by hydrolysis of SCl. The *N*-amidosulphonyl derivatives of FES sulphamates were due to reactions of the excess SCl. In an additional experiment, column-purified [$^{18}$F]FESDS was once more treated with K222/$K_2CO_3$ on its own, followed by the usual chromatographic separation. Radioactive polar products were also found here, but they did not contain any steroid as was shown in their $ESI^-$ spectra. Only K222 was found in the $ESI^+$ spectrum. This means that the radioactivity of this eluate cannot be due to polar derivatives of [$^{18}$F]FES-sulphamates. It has to be due to $^{18}$F splitting from the labelled molecules by the alkaline medium. 16α-$^{18}$F labelling is clearly not as stable as expected. In each HPLC purification the split-off [$^{18}$F]fluoride was eluted in the first peak as $(K222+K)^{18}F$.

## Experimental

### *Materials and methods*

The experiments were carried out in an automatically operating module which was also used to produce [$^{18}$F]FES and [$^{18}$F]FESDS. Module and procedure were described in detail elsewhere.[7] The necessary precursor, 3-O-methoxymethyl-16,17-O-sulphuryl-estra-1,3,5(10)-triene-3, 16$\beta$, 17$\beta$-triol (cyclic sulphate), was prepared according to a given procedure.[3] Sulphamoyl chloride (SCl) was prepared from commercial *N*-carbonylsulphamoyl chloride [13] and stored at 5°C under nitrogen. Solvents and reagents (Sigma-Aldrich) were used as supplied. Kryptofix 2.2.2 (K222) was purchased from Merck. [$^{18}$F]HF was produced in an IBA CYCLONE 18/9 cyclotron using enriched [$^{18}$O]$H_2O$ (1.5 ml, 94%) from Chemotrade (Leipzig, Germany). After 60 min irradiation time, the radioactivity at EOB was between 40 and 60 GBq. To separate the final products, an HPLC system (JASCO) was used. It consisted of an injection loop (10 ml), a semipreparative RP column (SP 250/10 Nucleosil 120-7 $C_{18}$, Macherey & Nagel, Germany), a UV/VIS detector and a radioactivity detector. 45% EtOH was used as the eluant at a flow of 1.5 ml/min. To keep check of the purity of the final products, an HPLC system (Hewlett Packard) with a diode array detector, a radioactivity detector and an analytical column ET 125/8/4 Nucleosil 120-5 $C_{18}$ (Macherey & Nagel) were used. Mass spectrometric analyses were carried out on **a** Micromass tandem quadrupole mass spectrometer (Quattro LC) operating in the MS mode and combined with an HPLC system of the 1100 series (Hewlett Packard). The LC-MS method used a Macherey-Nagel NUCLEOSIL 120 C18 column (10 mm × 4 mm) and 50% ethanol as the mobile phase at a flow of 0.25 ml/min. The UV detection of the column eluate was recorded at 216 nm. MS parameters used: detection mode (positive and negative API); cone (40 V); capillary (3.5 kV); desolvation gas flow (763 l/h); nebulizer gas flow (53 l/h); mass range (50–800 amu). The eluate of the polar products which were eluted from the semipreparative HPLC column was collected and lyophilized. The residue was dissolved in 1 ml 50% EtOH.

### *Preparatory operations before starting an automated synthesis*

Before the synthesis the following solutions were prepared:

Solution I: K222 (10 mg) and $K_2CO_3$ (1.85 mg) per ml 86% aqueous MeCN (3 ml)

Solution II: Cyclic sulphate (2 mg) in 1 ml absolute MeCN (freshly prepared solution)

Solution III: 0.1 M hydrochloric MeCN (6 ml), freshly prepared by mixing 9 parts of MeCN and 1 part of 1 M HCl

Solution IV: SCl (10–25 mg) in 1.5 ml absolute MeCN (freshly prepared solution)

Solution V: 22.5% EtOH (4 ml).

Before each synthesis, the module was washed with acetone and dried in an air stream (cleaning program). Five storage vials of the module were filled with the solutions I–V, and a sixth vial with absolute MeCN (12 ml). Then, the starting [$^{18}$F]HF solution was transferred from the cyclotron into the module. After measuring the starting radioactivity $A_0$ at $t = t_0$, the synthesis program was started.

### *Simultaneous synthesis of [$^{18}$F]FES3S and [$^{18}$F]FES17S*

After starting the synthesis program, the following operating steps were automatically carried out:

(1) *Careful drying of the reaction mixture before fluorination*. Addition of solution I (1.5 ml) and MeCN (3 ml) and removing the solvent at 100°C for 4 min. Addition of MeCN (3 ml) alone. Repeat of the drying process.

(2) *Nucleophilic fluorination*. Addition of solution II. Closing the reaction vessel and heating the reaction mixture to 100°C. After 10 min, the reaction mixture was cooled and dried.

(3) *Acidic hydrolysis to remove the protective groups*. Addition of a third of solution III and removing the solvent at 100°C for 3 min. Repeat of the process twice.

(4) *Careful drying of the reaction mixture before sulphamoylation*. Addition of solution I (1.5 ml) and MeCN (2 ml) and removing the solvent at 100°C for 4 min. Addition of MeCN (2 ml) and removing the solvent at 100°C for 4 min. Repeat of the latter process. The temperature was reduced to 30°C.

(5) *Sulphamoylation of the reaction mixture at 30°C*. Addition of solution IV. The temperature was kept at 30°C for 5 min. The reaction mixture was dried.

(6) *Destruction of the excess SCl*. Addition of solution V (1 ml). The reaction mixture was dried.

(7) *Preparation of the HPLC purification*. Addition of solution V (3 ml). After 1 min the solution was transferred into the injection loop.

(8) *HPLC purification*. The solution was injected into the column. The radiochromatogram was observed, and the eluate was fractionated according to the peaks being eluted. The radioactivity of the peaks was measured.

### *Synthesis of [$^{18}$F]FES17S from [$^{18}$F]FESDS*

Before synthesis an additional hose pipe was installed for adding further solutions through the MeCN vial into the reaction vessel. 0.1 M HCl was ready to hand. After starting the synthesis program, the operating steps 1–4 were carried out as before, but the temperature was reduced to 70°C. The synthesis was continued as follows:

(5) *Sulphamoylation of the reaction mixture at 70°C*. Addition of solution IV. The temperature was kept at 70°C for 5 min. The reaction mixture was dried.

(6) *Destruction of the excess SCl*. Addition of solution V (1 ml). The reaction mixture was dried.

(7) *Alkaline treatment of the reaction mixture*. Addition of solution I (1.5 ml) and MeCN (3 ml) through the additional supply pipe into the reaction vessel. The temperature was kept at 70°C for 5 min. The reaction mixture was dried.

(8) *Ensuring an acidic medium for HPLC and preparation of the HPLC purification*. Addition of solution V (3 ml) and 1 ml of 0.1 M HCl through the additional supply pipe into the reaction vessel. Then the solution was transferred into the injection loop.

(9) *HPLC purification*. The solution was injected into the column. The radiochromatogram was observed, and the eluate was fractionated according to the peaks being eluted. The radioactivity of the peaks was measured.

## Conclusion

[$^{18}$F]FES3S and [$^{18}$F]FES17S have been prepared in higher yields than hitherto by modifying the synthesis of [$^{18}$F]FESDS. Both compounds can be produced in GBq amounts in the same automated module as used for [$^{18}$F]FESDS. The radioactivity losses observed in each synthesis as the so-called polar products are mostly due to the alkaline medium necessary for sulphamoylation. As a side effect [$^{18}$F]fluoride is split off from the labelled molecules and is bound by K222 as

$(K222+H)^{18}F$ or $(K222+K)^{18}F$. There is little chance of preventing these radioactivity losses.

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