Enantiospecific synthesis of 2-[^{18}F]fluoro-L-phenylalanine and 2-[^{18}F]fluoro-L-tyrosine by isotopic exchange†

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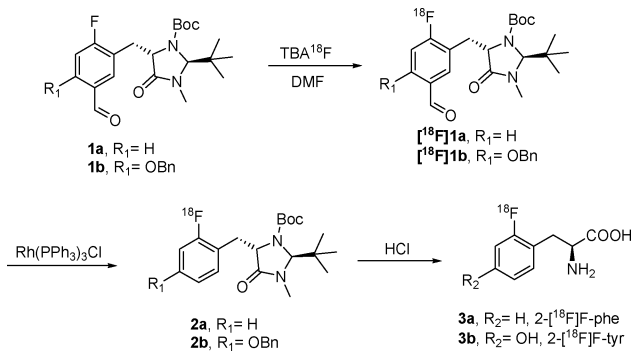
2-[^{18}F]Fluoro-L-phenylalanine and 2-[^{18}F]fluoro-L-tyrosine have been developed as promising radiopharmaceuticals for molecular imaging using positron emission tomography (PET). However, the lack of a convenient radiosynthetic pathway has limited their practical use. In this work a new three-step nucleophilic synthesis of these compounds starting from [^{18}F]fluoride is described. Corresponding precursors (**1a** and **1b**) were ^{18}F-fluorinated by isotopic exchange, followed by the removal of an activating formyl group with $Rh(PPh_3)_3Cl$ and subsequent hydrolysis of protecting groups in acidic medium. All reactions were carried out using both conventional and microwave heating. Conventional heated reactions yielded the desired products 2-[^{18}F]Fphe and 2-[^{18}F]Ftyr in 43% and 49% whereas radiochemical yields of 34% and 43%, respectively, were obtained when they were heated by microwaves. Under optimized conditions the enantiomeric purity was ≥94% for both radiopharmaceuticals.

Introduction

2-[^{18}F]Fluoro-L-phenylalanine (2-[^{18}F]Fphe) **3a** has proven to be a useful radiopharmaceutical for the study of neutral amino acid transport at the blood brain barrier *in vivo* in humans.[1] On the other hand, 2-[^{18}F]fluoro-L-tyrosine (2-[^{18}F]Ftyr) **3b**, unlike other halogenated amino acids, is almost quantitatively incorporated into proteins lending it as interesting tracer for imaging of the protein synthesis *in vivo*.[2] Since the accumulation of 2-[^{18}F]Fphe and 2-[^{18}F]Ftyr enable to distinguish tumours from normal tissue, positron emission tomography (PET) studies of their uptake are of clinical value for the diagnosis of brain tumors.[3,4] In spite of the potential of these compounds the lack of a convenient radiosynthetic methodology for their preparation has limited a wider use in nuclear medicine practice.

Up to now, the synthesis of [^{18}F]fluoroaromatic amino acids have predominantly been performed *via* electrophilic radiofluorination. The electrophilic approach is applicable because many of those compounds have a low toxicity and therefore they can be used in carrier-added (*c.a.*) form.[5] Direct electrophilic synthesis of these tracers was carried out with [^{18}F]F_2 and [^{18}F]AcOF on phenylalanine and tyrosine as well as on O-acetylated tyrosine. However, their radiochemical yield and isomeric purity were not satisfactory.[6] Fluorodemetallation and specially fluorodestannylation have been found most efficient in order to achieve aromatic [^{18}F]fluoroamino acids in routine production. In the case of 2-[^{18}F]Ftyr, *O*,*N*-di-Boc-2-triethylstannyltyrosine ethyl ester has proven to be a suitable precursor for its radiosynthesis.[7] In spite of the success of this method, the electrophilic pathway is limited to relatively low amounts of radioactive product at elevated cost.[8] Furthermore, the electrophilic radiofluorination methodology is not established in every PET centre.

As an alternative, a nucleophilic method for the no-carrier-added (n.c.a.) regiospecific radiofluorination of 2-[^{18}F]Ftyr has been developed.[9] However, the required multi-step and built-up synthesis starting from small benzaldehyde derivatives[10] is technically complex and thus difficult to automate. Recently, a three-step procedure allowed the radiosynthesis of *c.a.* 6-[^{18}F]fluoro-L-DOPA starting from the precursor (2*S*,5*S*)-*tert*-butyl-5-(4-benzyloxy-2-fluoro-formylbenzyl)-2-*tert*-butyl-3-methyl-4-oxoimidazolidine-1-carboxylate **1b** following the sequence: isotopic exchange – Baeyer–Villiger oxidation – hydrolysis.[11] In the work here the reaction sequence has been modified and instead of the Baeyer–Villiger oxidation a decarbonylation reaction using $Rh(PPh_3)_3Cl$ was performed (Scheme 1).



Scheme 1 General radiosynthetic pathway to 2-[^{18}F]Fphe and 2-[^{18}F]Ftyr.

Results and discussion

Radiofluorination

The first step of the radiosynthetic pathway pursued here for labelling of the title compounds is an isotopic ^{18}F-for-^{19}F exchange. Previous work on nucleophilic aromatic ^{18}F-substitution of benzaldehydes using both, model compounds and complex

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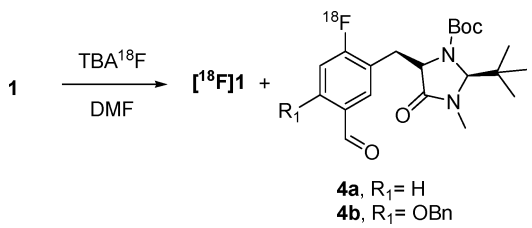
Table 1 Influence of temperature, time and kind of anion activation on the RCY of the isotopic exchange reaction on **1a**[a,b]

Entry	PTC[c]/μmol	Temp °C	10 min		20 min	
			[^{18}F]1a (%)	**4a** (%)	**[^{18}F]1a** (%)	**4a** (%)
1	$TBAHCO_3$ [2.3]	130	28	0	39	0
2	$TBAHCO_3$ [5.2]	130	51	6	57	7
3	$TBAHCO_3$ [8.5]	130	60	10	59	14
4	$TBAHCO_3$ [17.0]	130	61	17	52	30
5	$TBAHCO_3$ [5.2]	150	26	24	—	—
6	$[K222]_2CO_3$ [13.0]	130	26	40	14	50

[a] 1 mL DMF, 15 μmol **1a**, conventional heating (oil bath). [b] SD = ±5%. [c] PTC = phase transfer catalyst for [^{18}F]fluoride activation.

precursors, have shown that the use of DMF as solvent and temperatures above 100 °C gave the best radiochemical yields (RCY).[11,12] Table 1 summarizes the results obtained for the optimization of the labelling conditions for precursor **1a** under conventional heating. Entries 1 to 4 show that an increase of the base concentration led to higher labelling yields; but also the formation of an additional new product was evidenced by both TLC-UV and radio-TLC analyses.

In order to identify the side product a cold experiment was carried out and the new compound was isolated and analyzed by NMR. The ^{1}H spectrum revealed that the new species was the diastereomer **4a** (see Scheme 2), resulting from epimerization in position 5 of the imidazolidinone system. As a further evidence of this statement, the D-enantiomer of [^{18}F]**3a** could be identified at the end of the synthetic procedure *via* comparison of the authentic standard compound using chiral HPLC. The increase of the temperature to 150 °C did not provide better RCY but a diastereomeric 1 : 1 mixture of the compounds **[^{18}F]1a** and **4a** after 10 min. Routine ^{18}F-labeling conditions using Kryptofix2.2.2[13] provides the undesired diastereomer **4a** even as major product.



Scheme 2 Epimerization of **1a,b** during the isotopic exchange reaction.

Based on these results, the conditions described in entry 2 of Table 1 were selected in further experiments for the labelling of precursor **1a** under conventional heating.

Similarly, the labelling reaction with precursor **1b** generates the products **[^{18}F]1b** and **4b** following the trends previously described for the compound **1a**, *i.e.* the fluorine exchange yield increases with the increase of both, the concentration of the base and of the temperature, in detriment of the radiochemical purity. The best RCY of **[^{18}F]1b** was 59% while that of **4b** was 4%. These results were obtained using 15 μmol of precursor, 6.4 μmol of $TBAHCO_3$ and 1 mL of DMF at 130 °C for 10 min.

In an attempt to improve the isotopic exchange process the reaction was performed using microwave heating. Microwave irradiation produces efficient internal heating by direct coupling of microwave energy with the molecules that are present in the reaction mixture creating an inverted temperature gradient compared to conventional thermal heating.[14] Due to these characteristics microwave heated reactions are faster and in some cases more selective than those under conventional heating.

Fig. 1 shows the RCY of compounds [^{18}F]**1a** and **4a** in dependence of the applied microwave power. It can be seen that the total RCY increases with power, however, at about 50 W the undesired diastereomer **4a** starts to appear and its yield increases also with elevated power.

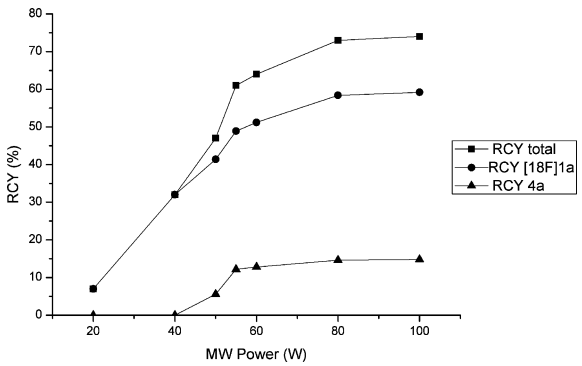


Fig. 1 Dependence of the RCY of [^{18}F]**1a** and **4a** as function of the microwave power. 15 μmol **1a**, $TBAHCO_3$ 5.1 μmol, 1 mL DMF, 1 min.

Table 2 compares the optimized results obtained with the synthesis of **[^{18}F]1a** and **[^{18}F]1b** under conventional and microwave heating. It can be noticed that either conventional or microwave heating produce a similar RCY. The main difference is the reaction time, where the microwave heated reaction is ten times faster than that with heating by oil bath. The RCY of the compounds **[^{18}F]1** are limited due to the occurrence of the diastereomers **4**.

Table 2 Optimized RCY of labelling of **1a,b** by isotopic exchange using both conventional and microwave heating[a]

Entry	Precursor	Heating[b]	Time/min	**[^{18}F]1** (%)	**4** (%)
1	**1a**	CH	10	51	6
2	**1a**	MH	1	42	5
3	**1b**	CH	10	59	4
4	**1b**	MH	1	53	4

[a] SD = ±5% (CH), ±1% (MH). [b] CH: conventional heating (oil bath), MH: microwave heating.

Decarbonylation

The removal of the activating formyl group was performed with $Rh(PPh_3)_3Cl$ (Wilkinson's catalyst). Using this reagent for decarbonylation, however, a stoichiometric reaction is required due to the formation of stable $Rh(PPh_3)_2(CO)Cl$ as secondary product. Optimization studies were carried out using compound **[^{18}F]1a** as starting material under similar conditions as those described by Plenevaux and co-workers for the decarbonylation of **[^{18}F]**fluorobenzaldehydes.[15] Dioxane was used as solvent and the reaction solution was magnetically stirred for 20 min in an oil bath at 150 °C. Since the labeled compound **[^{18}F]1a** is chemically indistinguishable from the precursor **1a** they can not be separated and the amount of the Rh complex was calculated as the equivalent molar quantity of **1a**.

Fig. 2 graphically depicts the obtained results. Using equimolar amounts of starting material and organometallic reagent 64 ± 5% of the desired compound **2a** was observed in the radio-HPLC analysis (System A) as well as 21 ± 7% of the starting material **[^{18}F]1a** and 15 ± 3% of an unknown compound. Increasing the amount of Wilkinson's catalyst to 1.5 eq improved the conversion of the starting material to 99% and a RCY of 85 ± 8% of the desired compound **2a**. Further increase of the amount of catalyst did not cause any improvement.

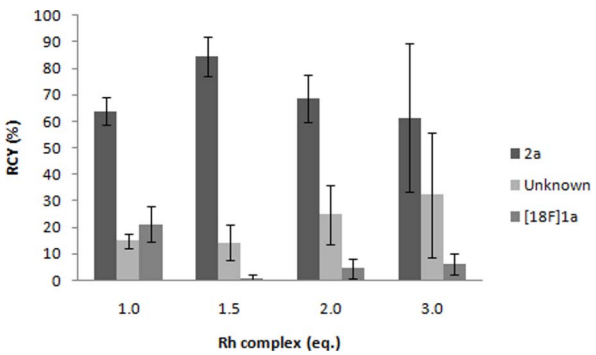


Fig. 2 Radioactivity distribution of **[^{18}F]1a**, **2a** and unknown compound as function of the amount of Rh complex. 15 µmol of **[^{18}F]1a**, 1 mL of dioxane, 20 min.

In 2007 Shen and coworkers published a study dealing with the decarbonylation reaction of poly-substituted [^{18}F]fluorobenzaldehydes with $Rh(PPhe_3)_3Cl$.[12] Also there the formation of an unknown polar compound besides the desired product was observed. They found a relationship between the occurrence of the unknown compound and the kind of solvent, pointing out benzonitrile as the medium of choice for the reaction. Using benzonitrile as solvent at 150 °C the decarbonylation of **[^{18}F]1a** provided a mixture of the starting material and the desired compound **2a** in 40 : 60 proportion while the unknown compound was not detected after 20 min reaction time (Table 3, entry 2). In order to improve the conversion, the temperature was raised to 180 °C. This time 15% of the unknown compound was detected while the conversion of **[^{18}F]1a** was still incomplete (Table 3, entry 3). On the other hand, the use of DMF as solvent produced the unknown compound as major product (Table 3, entry 4).

In further experiments using dioxane as solvent it was observed that a reaction time shorter than 20 min decreases the conversion yields of **[^{18}F]1a** while a longer reaction time increases the yield of the unknown product. The overall best conditions for decarbonylation, however, were those ones described in entry 1 of the Table 3 with an almost quantitative conversion of **[^{18}F]1a** and in total only 15% of other labeled compounds than product **2a**. This could be isolated by use of a silica gel column and a solvent mixture of ethyl acetate in petroleum ether (30%) while the unknown compound remained attached on the stationary phase.

Table 3 Solvent effect on the RCY of the decarbonylation reaction on **[^{18}F]1a**[a,b]

Entry	Solvent	Rh eq.	Temp °C	Unknown (%)	**[^{18}F]1a** (%)	**2a** (%)
1	Dioxane	1.5	150	14	1	85
2	Benzonitrile	2.0	150	—	40	60
3	Benzonitrile	2.0	180	15	18	67
4	DMF	2.0	150	62	16	22

[a] SD = ±5%. [b] 15 µmol **[^{18}F]1a**, 20 min.

A microwave heated version of the decarbonylation reaction was also developed. In this case compound **[^{18}F]1b** was used for the optimization procedure and benzonitrile was preferred over dioxane as solvent since it shows better absorption of microwaves. The reaction was irradiated with 100 W during 50 s. Figure 3 shows the distribution of radioactivity among products formed as function of the amount of Wilkinson's catalyst. In contrast to the conventionally heated reaction both, the conversion of **[^{18}F]1b** and the yield of the desired compound **2b**, increased with the amount of the Rh complex.

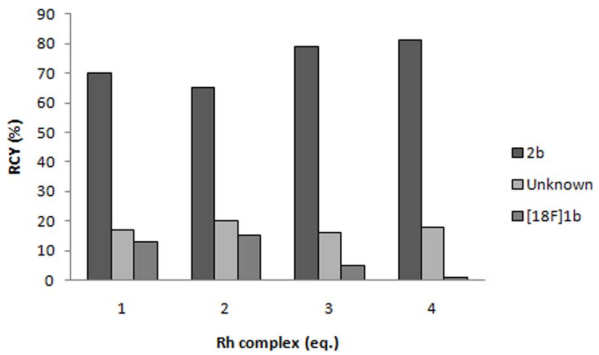


Fig. 3 Radioactivity distribution of **[^{18}F]1b**, **2b** and unknown compound as function of the amount of Rh complex. 15 µmol of **[^{18}F]1b**, 1 mL of benzonitrile, 50 s.

When using 4 equivalents of the Rh complex the desired compounds **2a** and **2b** were obtained in yields of 83 ± 1% and 81 ± 1%, respectively. Although neither the yields nor the selectivity of the microwave heated reactions were better than those by conventional heating. The reproducibility and specially the reaction time was again considerably improved by the change to microwave heating. As with conventional heating again here an optimal reaction time (50 s) was found, with lower RCY at shorter times but increased formation of the unknown product above.

The decarbonylated product was purified using a silica gel cartridge. Due to the higher boiling point of benzonitrile, the solvent was not evaporated but the reaction mixture rather diluted with 5% ethyl acetate in petroleum ether and then passed *via* syringe through the column where the reaction products were

retained. A second portion of the same solvent mixture was used in order to assure the total elution of the benzonitrile. The desired compound **2b** was then eluted with a more polar solvent mixture as described for the elution of **2a**.

Hydrolysis

In previous reports the hydrolysis of imidazolidinones has been carried out with concentrated HI or HBr and temperatures of 200 °C and 150 °C, respectively.[11,16] The need of such harsh conditions is due to the high stability of the amide bond.[17] In this work hydrolysis with all typical mineral acids (HI, HBr and HCl) was performed resulting in quantitative hydrolysis yields at 190 °C during 30 min no matter which acid was used. Several experiments were performed in order to achieve similar results with diluted acids, *e.g.* 1.0 to 7.5 N HCl, however they were unsuccessful. For further experiments concentrated HCl was used and yielded quantitatively the hydrolyzed products.

The microwave heated version of this reaction gave also quantitative yields while saving reaction time when the temperature/time control of the device was used in order to keep the temperature at 140 °C for 20 min. The application of high power microwaves was avoided with HCl because of the rapid generation of overpressure which can lead to the explosion of the reaction vessel.

The conventional heated reactions yielded the desired products 2-[^{18}F]Fphe and 2-[^{18}F]Ftyr in 43% and 49% whereas 34% and 43% RCYs, respectively, were obtained when microwave heating was applied. However, 38 min of total preparation time were saved with the latter. The products were obtained with good enantiomeric purity of ≥ 94%. The *e.e.* achieved for 2-[^{18}F]Fphe was 88% while an *e.e* of 92% was obtained in the case of 2-[^{18}F]Ftyr.

Specific activity

The specific activity in isotopic exchange procedures obtained is a function of both, the quantity of labelling precursor and starting [^{18}F]fluoride activity. Corresponding to the amount of starting material the maximum amount of carrier that can be found in 2-[^{18}F]Fphe and 2-[^{18}F]Ftyr preparations described in this work is 2.8 mg and 3.0 mg, respectively. Using the electrophilic radiofluorination by destannylation it has been reported that batches of 2-[^{18}F]Ftyr can be obtained in activities of 1.41 GBq with a specific activity of around 74 GBq/mmol,[7] which corresponds to a carrier content of approximately 3.8 mg. This amount is bigger than the maximum amount of carrier with the isotopic exchange procedure in development with low starting radioactivity of *ca.* 300 MBq per experiment. Thus, in production runs with >10 GBq of n.c.a. [^{18}F]fluoride, it is expected that the specific activity of the title compounds will still increase several times as compared to those achieved by electrophilic procedures.

Conclusions

A new procedure for the radiosynthesis of 2-[^{18}F]Fphe and 2-[^{18}F]Ftyr has been developed. The three-step approach can be performed either under conventional or microwave heating leading to RCY of over 34% with an enantiomeric excess of >88% for both compounds. This work is the first example of the radiosynthesis of ^{18}F-labeled aromatic amino acids *via* a decarbonylation reaction with $Rh(PPh_3)_3Cl$.

Experimental

General

Dry solvents were purchased from Aldrich and Merck, Germany. All solvents were used without further purification.

Wilkinson's catalyst was purchased from Aldrich, Germany. Hydroiodic and hydrobromic acids were acquired from Merck, Germany. Hydrochloric acid was purchased from KMF Laborchemie Handels GmbH, Germany. The precursors (2*S*,5*S*)-*tert*-butyl 2-*tert*-butyl-5-(2-fluoro-5-formylbenzyl)-3-methyl-4-oxoimidazolidine-1-carboxylate (**1a**) and (2*S*,5*S*)-*tert*-butyl 5-(4-(benzyloxy)-2-fluoro-5-formylbenzyl)-2-*tert*-butyl-3-methyl-4-oxoimidazolidine-1-carboxylate (**1b**) were prepared following a procedure described elsewhere.[18]

Experiments under microwave heating were performed using a CEM Discover (Matthews, USA) single-mode microwave reactor system. Thin layer chromatography (TLC) was performed on precoated plates of silica gel 60 F_{254} (Merck, Germany) and the compounds were detected at 254 nm. Radioactivity on radio-TLC was detected on a Raytest minigita device (Raytest, Germany). High-performance liquid chromatography (HPLC) separations were achieved with a Knauer pump, a Knauer K-2500 UV/VIS detector, a manual Rheodyne injector (20 µL or 1.0 mL loop), and a NaI(Tl) well-type scintillation detector (EG&G Ortec; model 276 Photomultiplier Base) with an ACE Mate Amplifier and BIAS supply (Ortec) for radioactivity detection. Data acquisition and interpretation were performed with Gina software (Raytest Germany).

Chromatographic systems

System A. Analytic HPLC of the ^{18}F-labelled compounds **[^{18}F]1** and **2** was performed with a reverse-phase Kromasil 100–5 C18 column (250–4.6 mm; CS Chromatographieservice GmbH). Elution was performed at a constant flow rate of 1 mL min^{-1} with acetonitrile–water (70 : 30).

System B. Analytic HPLC of 2-[^{18}F]Fphe and 2-[^{18}F]Ftyr was performed with an analytic reverse-phase Synergi 4µ Hydro-RP 80A column (250–4.6 mm; Phenomenex). The mobile phase was aqueous acetic acid (0.1%) used at a flow rate of 1 mL min^{-1}.

System C. Preparative HPLC was carried out with a Synergi 4µ Hydro-RP 80A column (250–10 mm; Phenomenex). The mobile phase was aqueous ethanol (2%), and the flow rate was 4 mL min^{-1}.

System D. The enantiomeric purity of the radiopharmaceuticals was determined by HPLC using a Crownpak CR (1) 5µ column (150–4 mm; Daicel Chemical Industries) and aqueous $HClO_4$ (0.025 M) as eluent at a flow rate of 1 mL min^{-1}. Peak recording was achieved by UV detection at 261 nm.

Radiochemistry

Preparation of TBA^{18}F. N.c.a. [^{18}F]fluoride was produced *via* the ^{18}O(p,n)^{18}F nuclear reaction by bombardment of an isotopically enriched [^{18}O]water target with 17 MeV protons at the JSW cyclotron BC 1710 (FZ Jülich).[19] The produced [^{18}F]fluoride was isolated from the irradiated water through electrochemically supported adsorption on a Sigradur-Anode

(HTW Hochtemperatur-Werkstoffe GmbH) and desorption into 500 mL of pentadistilled water after recovery of the ^{18}O enriched water.[20] An aliquot of the [^{18}F]fluoride solution was added to 17.5–130 µL (2.6–17.0 µmol) of a 0.13 M tetrabutylammonium bicarbonate solution ($TBAHCO_3$)[21] The mixture was diluted with 1.0 mL of dry acetonitrile and transferred *via* syringe to a reaction flask. The solvent was evaporated under a stream of nitrogen at 80 °C and 650 mbar. The azeotropic evaporation was repeated twice with 1.0 mL of acetonitrile and afterwards the vial was evacuated for 5 min at 20–30 mbar.

General procedure for the radiosynthesis of 2-[^{18}F]Fphe and 2-[^{18}F]Ftyr under conventional heating. A solution of 10–15 µmol of the precursor in 1.0 mL DMF was added to the dried residue of TBA^{18}F. The mixture was heated at 130 °C for 10 min. After labelling, the DMF solution was diluted with water (15 mL), and passed through a pre-conditioned LiChrolut RP-18e cartridge (Merck, Germany). The product was eluted from the cartridge with 2.0 mL acetonitrile and then the solvent evaporated at 80 °C and 650 mbar. A solution of 1.5 eq. of Wilkinson's catalyst in 1 mL dioxane was added to the dry residue and the mixture was stirred for 20 min at 150 °C. The dioxane was distilled off, the residue suspended in 1 mL of a solution of ethyl acetate in petroleum ether (30% AcOEt/P.E.) and then filtered through a silica gel plug (650 mg silica gel in a 3 mL polyethylene filtration tube). The reaction vial was washed with an extra portion of the solution (1 mL) and the compound was then eluted with 4 mL of the same mixture. The solvent mixture was evaporated and 250 µL of hydrochloric acid were added and the reaction was heated to 190 °C and stirred for 30 min.

General procedure for the radiosynthesis of 2-[^{18}F]Fphe and 2-[^{18}F]Ftyr under microwave heating. A solution of 10–15 µmol of the precursor in 1.0 mL DMF was added to the dried residue of TBA^{18}F. The mixture was irradiated with 50 W microwaves during 1 min. The purification of the labelled compound was carried out using the same procedure described above. A solution of 4.0 eq. of Wilkinson's catalyst in 1 mL benzonitrile was added and the mixture was irradiated with 100 W microwaves during 50 s. The reaction mixture was diluted with 10 mL of a solution of ethyl acetate in petroleum ether (5% AcOEt–P.E.) and then passed through a silica gel column (see above). The desired compound was then eluted from the column with 5 mL of a solution of 30% AcOEt–P.E. After the solvent mixture was evaporated, 250 µL of hydrochloric acid were added and the reaction mixture was heated with microwaves to 140 °C for 20 min (Ramp: 150 W, 15 s, Hold: 20 min).

Notes and references

1 H. Ito, J. Hatazawa, M. Murakami, S. Miura, H. Iida, P. M. Bloomfield, I. Kanno, H. Fukuda and K. Uemura, *J. Nucl. Med.*, 1995, **35**, 1232–1237.
2 H. H. Coenen, P. Kling and G. Stöcklin, *J. Nucl. Med.*, 1989, **30**, 1367–1372.
3 (*a*) K. Wienhard, K. Herholz, H. H. Coenen, J. Rudolf, P. Kling, G. Stöcklin and W. D. Heiss, *J. Nucl. Med.*, 1991, **32**, 1338–1346; (*b*) I. Rutten, J. Cabay, N. Withofs, C. Lemaire, J. Aerts, V. Baart and R. Hustinx, *J. Nucl. Med.*, 2007, **48**, 720–725.
4 K. Kubota, K. Ishiwata, R. Kubota, S. Yamada, J. Takahashi, Y. Abe, H. Fukuda and T. Ido, *J. Nuc. Med.*, 1996, **37**, 320–325.
5 H. H. Coenen, in *PET Studies on Amino Acid Metabolism and Protein Synthesis*, ed. B. M. Mazoyer, W. D. Heiss and D. Comar, Kluwer Academic Publishers, Dordrecht, 1993, pp. 109.
6 H. H. Coenen, K. Franken, P. Kling and G. Stöcklin, *Int. J. Radiat. Appl. Instrum., Part A*, 1988, **39**, 1243–1250.
7 E. Hess, S. Sichler, A. Kluge and H. H. Coenen, *Appl. Radiat. Isot.*, 2002, **57**, 185–191.
8 E. Hess, G. Blessing, H. H. Coenen and S. M. Qaim, *Appl. Radiat. Isot.*, 2000, **52**, 1431–1440.
9 C. Lemaire, S. Gillet and M. Kameda, *J. Label. Compd. Radiopharm.*, 2001, S857–S859 44(suppl).
10 J. Ermert and H. H. Coenen, *Curr. Radiopharm.*, 2010, **3**, 127–160.
11 F. M. Wagner, J. Ermert and H. H. Coenen, *J. Nucl. Med.*, 2009, **50**, 1724–1729.
12 B. Shen, D. Löffler, K. P. Zeller, M. Übele, G. Reischl and H. J. Machulla, *Appl. Radiat. Isot.*, 2007, **65**, 1227–1231.
13 H. H. Coenen, B. Klatte, A. Knöchel, M. Schüller and G. Stöcklin, *J. Labelled Compd. Radiopharm.*, 1986, **23**, 455–467.
14 C. O. Kappe, *Angew. Chem., Int. Ed.*, 2004, **43**, 6250–6284.
15 A. Plenevaux, C. Lemaire, A. J. Palmer, P. Damhaut and D. Comar, *Int. J. Radiat. Appl. Instrum., Part A*, 1992, **43**, 1035–1040.
16 C. Lemaire, P. Damhaut, A. Plenevaux and D. Comar, *J. Nucl. Chem.*, 1994, **35**, 1996–2002.
17 D. Seebach, A. R. Sting and M. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2708–2748.
18 J. Castillo Meleán, J. Ermert and H. H. Coenen, *Tetrahedron*, 2010, DOI: 10.1016/j.tet.2010.10.036.
19 S. M. Qaim, J. C. Clark, C. Crouzel, M. Guillaume, H. J. Helmecke, B. Nebeling, V. W. Pike and G. Stöcklin, in *Radiopharmaceuticals for PET*, ed. G. Stöcklin, and V. W. Pike, Kluwer Academic Publishers, Dordrecht, 1993, pp. 150–26.
20 K. Hamacher, T. Hirschfelder and H. H. Coenen, *Appl. Radiat. Isot.*, 2002, **56**, 519–523.
21 K. Hamacher and H. H. Coenen, *Appl. Radiat. Isot.*, 2002, **57**, 853–856.