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Research Article

Synthesis of fluorine-18-labelled 5- and 6-fluoro-2-pyridinamine

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Summary

A one-pot radiosynthesis method to prepare the new fluorine-18-labelled fluoropyridine derivatives 5-[^{18}F]fluoro-2-pyridinamine and 6-[^{18}F]fluoro-2-pyridinamine in two to three reaction steps was developed. The first step consisted of no-carrier-added nucleophilic aromatic substitution of commercially available halogen-substituted 2-pyridinecarboxamide or 2-pyridinecarbonitrile derivatives with K[^{18}F]F-K_{222} in DMSO at 150–180°C. The [^{18}F]fluoride incorporation yields ranged from 67 to 98% for all studied precursor molecules. It is remarkable that 5-bromo-2-pyridinecarbonitrile gave almost quantitative [^{18}F]fluoride incorporation at the *meta*-position (5-position) of the pyridine ring after only 5 min of heating at 150°C. After base-catalysed hydrolysis of the [^{18}F]fluorinated pyridinecarbonitriles into their corresponding carboxamides, the latter were transformed in a Hofmann-type rearrangement reaction into the respective amines by treatment of crude reaction mixtures with bromine and aqueous base (20–30% conversion yield). Reaction mixtures were purified by reversed-phase semipreparative HPLC followed by strong cation exchange solid-phase extraction to afford 5-[^{18}F]fluoro-2-pyridinamine and 6-[^{18}F]fluoro-2-pyridinamine in non-decay-corrected radiochemical yields of 6–10% in a total synthesis time of 83–112 min. The preparation of 5-[^{18}F]fluoro-2-pyridinamine is one of very few examples demonstrating the feasibility of nucleophilic *meta*-[^{18}F]fluorination of a pyridine derivative. Both 5-[^{18}F]fluoro-2-pyridinamine and 6-[^{18}F]fluoro-2-pyridinamine are new potentially useful radiolabelled synthons for radiopharmaceutical chemistry. Copyright © 2006 John Wiley & Sons, Ltd.

Key Words: fluorine-18; fluoropyridine; no-carrier-added nucleophilic aromatic substitution; *meta*-position; Hofmann rearrangement

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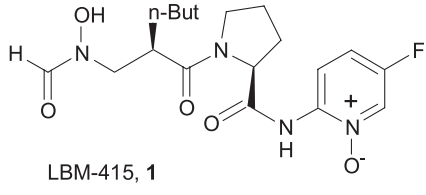
Introduction

The fluoropyridinyl moiety labelled with fluorine-18 (^{18}F, half-life: 109.8 min) is a commonly encountered substituent in radiochemistry for positron emission tomography (PET).[1] The [^{18}F]fluorine is in most cases located in the *ortho*-position (2-position) of the pyridine nitrogen, since this position is well activated for no-carrier-added nucleophilic aromatic substitution with the potassium [^{18}F]fluoride-kryptofix 2.2.2 (K[^{18}F]F-K_{222}) complex.[2] In a recent study, Karramkam *et al.* have compared the reactivity of *ortho*-, *meta*- and *para*-nitropyridine (2-, 3- and 4-nitropyridine) to nucleophilic substitution with [^{18}F]fluoride and obtained good yields for *ortho*- and *para*-[^{18}F]fluoropyridine (70–90%), whereas no reaction was observed for substitution at the *meta*-position.[3] In contrast to *ortho*- and *para*-substitution, nucleophilic [^{18}F]fluorination at the *meta*-position requires an additional electron-withdrawing substituent in the pyridine ring. To our knowledge, only one example of *meta*-[^{18}F]fluorination of a pyridine derivative has been reported in the literature. In this example, the potential MAO-B imaging radiotracer *N*-(2-aminoethyl)-5-[^{18}F]fluoro-2-pyridinecarboxamide was obtained in 35% decay-corrected radiochemical yield by nucleophilic aromatic nitro-for-fluoro substitution.[4]

In our ongoing research program to synthesize ^{18}F-labelled peptide deformylase inhibitors, such as LBM-415 (**1**, Figure 1),[5] we needed to prepare a *meta*-^{18}F-substituted pyridine derivative, i.e. 5-[^{18}F]fluoro-2-pyridinamine ([^{18}F]-**2**, Figure 3), as a radiolabelled intermediate. Here, we report a one-pot method to synthesize [^{18}F]-**2** and its regioisomer 6-[^{18}F]fluoro-2-pyridinamine ([^{18}F]-**3**, Figure 3) in practical radiochemical yields *via* no-carrier-added nucleophilic aromatic substitution of commercially available halogen-substituted 2-pyridinecarboxamide or 2-pyridinecarbonitrile derivatives with K[^{18}F]F-K_{222}, followed by conversion of the carboxamide into the amine function by a Hofmann-type rearrangement reaction.

Results and discussion

Our initial strategy to synthesize the target molecule [^{18}F]-**2** aimed at reacting 5-bromo-2-nitropyridine (**4**) with K[^{18}F]F-K_{222} to obtain 5-[^{18}F]fluoro-2-



LBM-415, **1**

Figure 1. Chemical structure of the peptide deformylase inhibitor LBM-415 (1)

nitropyridine ([18F]-**5**, Figure 2), which we then planned to reduce to the desired amine [18F]-**2**. Unfortunately, the only radiolabelled product that was formed in the substitution reaction – in excellent radiochemical yield of about 85% – was 5-bromo-2-[18F]fluoropyridine ([18F]-**6**, Figure 2) as identified by HPLC co-elution with the commercially available unlabelled reference compound. These results indicate that in the presently employed nucleophilic substitution reaction, the 2-nitro group preferably acted as a leaving group for 18F-substitution rather than as an activating group for substitution at the *meta*-position. We therefore searched for a substrate that possesses an electron-withdrawing substituent in the 2-position that would not be capable of acting as a leaving group in the substitution reaction. Commercially available 5-bromo-2-pyridinecarboxamide (**7**) seemed to meet these requirements. The use of **7** was further supported by the fact that in an earlier published study a carboxamide group has been successfully employed as an activating group for *meta*-18F-substitution of a pyridine derivative.[4]

Derivative **7** was reacted with K[18F]F-K_{222} in dimethylsulphoxide (DMSO) for 20 min at 180°C, which afforded the desired product, i.e. 5-[18F]fluoro-2-pyridinecarboxamide ([18F]-**8**), in an average radiochemical yield of $67 \pm 14\%$ ($n = 9$) (Figure 3). The reaction kinetics shown in Figure 4(A) indicate that heating times longer than 20 min – both at 150 and 180°C – lead to decomposition of the radiolabelled product. Analysis of the crude reaction mixture by HPLC and TLC revealed the presence of a hydrophilic by-product, that was not identical with unreacted [18F]fluoride. In our attempts to identify this hydrophilic product we co-eluted the reaction mixture on HPLC (system B) with two potential, commercially available by-products, i.e. 5-fluoro-2-pyridinecarboxylic acid and 3-fluoropyridine. We assumed that the first compound might be formed by hydrolysis of the carboxamide function as promoted by traces of water contained in the alkaline reaction mixture,[6] whereas the latter compound might be generated by 2-decarboxylation. Interestingly, even though the chromatographic behaviour of the radiolabelled

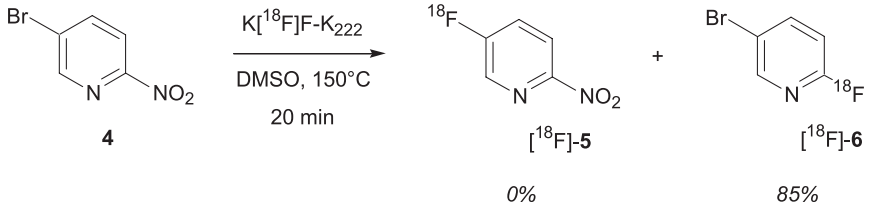


Figure 2. Attempt to synthesize 5-[18F]fluoro-2-nitropyridine ([18F]-5) by reaction of 5-bromo-2-nitropyridine (4) with K[18F]F-K_{222}, which afforded 5-bromo-2-[18F]fluoropyridine ([18F]-6) as the only radiolabelled product

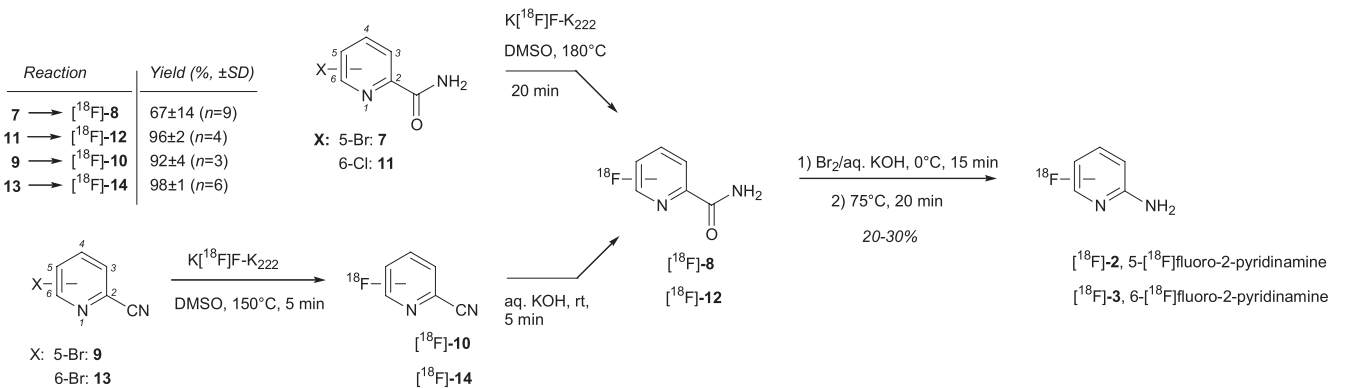


Figure 3. General scheme for the preparation of 5-[^{18}F]fluoro-2-pyridinamine ([^{18}F]-2) and 6-[^{18}F]fluoro-2-pyridinamine ([^{18}F]-3). Mean ($\pm$ standard deviation) radiochemical yields (calculated by TLC analysis) are reported for the nucleophilic substitution reactions

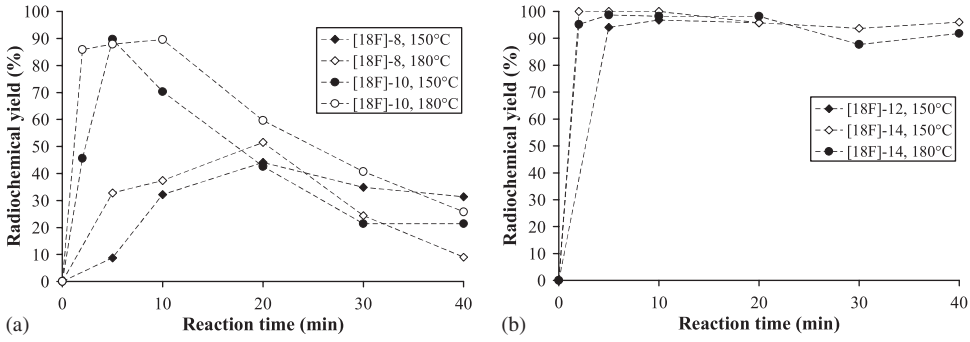


Figure 4. Reaction kinetics for the formation of the *meta*-substituted pyridines 5-[^{18}F]fluoro-2-pyridinecarboxamide ([^{18}F]-8) and 5-[^{18}F]fluoro-2-pyridinecarbonitrile ([^{18}F]-10) (A) and the *ortho*-substituted pyridines 6-[^{18}F]fluoro-2-pyridinecarboxamide ([^{18}F]-12) and 6-[^{18}F]fluoro-2-pyridinecarbonitrile ([^{18}F]-14) (B) by nucleophilic substitution with K[^{18}F]F-K_{222} at two different reaction temperatures (150 and 180°C). Radiochemical yields were calculated by TLC analysis (system B)

by-product pointed to the presence of a carboxylic acid function (prolongation of HPLC retention time when using dilute phosphoric acid instead of water as mobile phase in HPLC system B) the observed by-product was not identical with any of the suspected by-products. We tried to suppress by-product formation by employing less alkaline ^{18}F-fluorination conditions (i.e. the use of potassium oxalate instead of potassium carbonate as a base) that have previously been successfully employed for the ^{18}F-labelling of base-sensitive substrates.[7] In this case, however, we observed that precursor molecule **7** was considerably less reactive to substitution by [^{18}F]fluoride as compared to the standard potassium carbonate system (i.e. about 10% incorporation yield versus 67%).

The reaction solution containing crude [^{18}F]-**8** was then directly treated with an ice-cooled mixture of bromine and aqueous potassium hydroxide to afford the desired amine [^{18}F]-**2** in 20–30% conversion yield based on [^{18}F]-**8** (Figure 3). This type of reaction, which involves the conversion of an amide into an amine containing one fewer carbon upon treatment with bromine in aqueous base, is generally referred to as the Hofmann rearrangement[8] and is commonly employed in preparative organic synthesis.[9,10] Importantly, in the case of our radiosynthesis, the rearrangement reaction was compatible with the reagents of the nucleophilic substitution reaction and could therefore be performed as a one-pot reaction without intermediate purification of the ^{18}F-labelled carboxamide. In the crude reaction mixture, the remainder of radioactivity was distributed between unreacted [^{18}F]-**8** and an unidentified hydrophilic by-product, that comprised about 50% of total radioactivity and

that was presumably identical with the by-product that had already been generated in the nucleophilic substitution reaction. The identity of product [^{18}F]-**2** was confirmed by HPLC co-elution with unlabelled **2**. The crude reaction mixture was then purified by reversed-phase semipreparative HPLC (system C). Pyridinecarboxamide [^{18}F]-**8** and pyridinamine [^{18}F]-**2** co-eluted on the employed HPLC system (Figure 5) and were thus collected in one single fraction. Quantitative separation of [^{18}F]-**8** and [^{18}F]-**2** was achieved by a strong cation exchange (SCX) solid-phase extraction procedure, which afforded radiochemically and chemically pure, no-carrier-added [^{18}F]-**2**. It is important to note that the pseudo-carrier 5-bromo-2-pyridinamine, which was formed by Hofmann rearrangement of precursor pyridinecarboxamide **7**, was removed during the semipreparative HPLC purification of the crude reaction mixture (Figure 5) and therefore not present in purified [^{18}F]-**2**. Starting from 2.1–2.7 GBq of K[^{18}F]F-K$_{222}$, 115–173 MBq of pure [^{18}F]-**2** could be obtained in a total synthesis time of about 110 min (see Table 1).

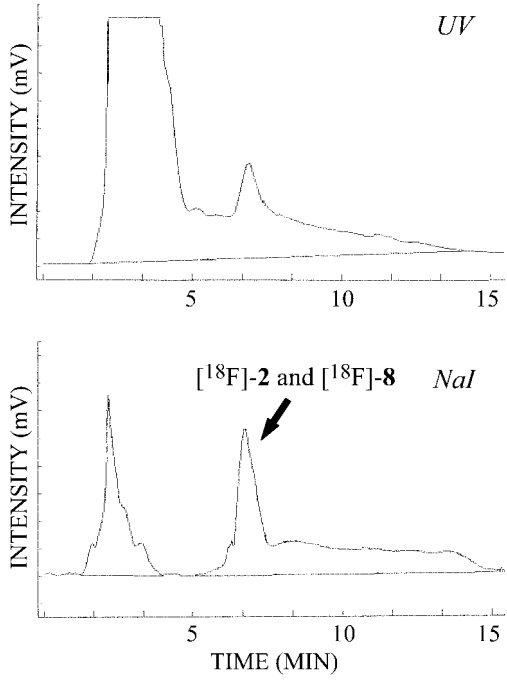


Figure 5. Representative semipreparative HPLC chromatogram for the purification of 5-[^{18}F]fluoro-2-pyridinamine ([^{18}F]-2). A Waters μBondapak C18 column (300 mm × 7.8 mm, 10 μm) was eluted with water/acetonitrile (95/5, v/v) at a flow rate of 6 ml/min (system C). Under the employed HPLC conditions precursor 5-bromo-2-pyridinecarboxamide (7) and the corresponding amine 5-bromo-2-pyridinamine did not elute from the HPLC column

Table 1. Overview of final product amounts (non-decay-corrected) obtained in the preparative syntheses of 5-[^{18}F]fluoro-2-pyridinamine ([^{18}F]-2) and 6-[^{18}F]fluoro-2-pyridinamine ([^{18}F]-3)

Start activity[a] (MBq)	Precursor molecule	Product	Amount of product (MBq)	Synthesis time (min)
2740	**7**	[^{18}F]-**2**	173[b]	112
2130	**7**	[^{18}F]-**2**	115[b]	106
3190	**9**	[^{18}F]-**2**	507[b]	83
2500	**9**	[^{18}F]-**2**	163[b]	100
1360	**11**	[^{18}F]-**3**	119[c]	90
3140	**13**	[^{18}F]-**3**	383[c]	89
3200	**13**	[^{18}F]-**3**	258[c]	89

[a]Start activity is based on the dried K[^{18}F]F-K_{222} complex.
[b]Isolated product.
[c]The amount of [^{18}F]-**3** was calculated by HPLC analysis of semipreparative-HPLC-purified mixtures of [^{18}F]-**3** and [^{18}F]-**12**.

As a second precursor for the synthesis of [^{18}F]-**8** the corresponding pyridinecarbonitrile 5-bromo-2-pyridinecarbonitrile **9** was employed (Figure 3). As can be seen in the reaction kinetics depicted in Figure 4(A), derivative **9** was considerably more reactive to nucleophilic [^{18}F]fluorination than the corresponding pyridinecarboxamide **7**. After only 5 min of heating at both 150 and 180°C the ^{18}F-incorporation was almost quantitative (Figure 3 and Figure 4(A)). These findings underline the strong electron-withdrawing properties of the 2-cyano group in derivative **9**, which make this substituent an excellent activating group for ^{18}F-substitution at the *meta*-position of the pyridine ring. Reaction times longer than 5 min resulted in decomposition of the radiolabelled product into an unidentified hydrophilic by-product. Interestingly, HPLC analysis (system B) revealed that part of the product, i.e. pyridinecarbonitrile [^{18}F]-**10**, was converted into the corresponding pyridinecarboxamide [^{18}F]-**8**, particularly in those cases when reaction times longer than 5 min were chosen. This hydrolysis reaction was desired in view of the subsequent rearrangement reaction (Figure 3) and presumably took place due to traces of water contained in the reaction solvent. We were able to drive this reaction to completion by treating the crude reaction mixture with aqueous potassium hydroxide followed by 5 min of stirring at room temperature. Crude pyridinecarboxamide [^{18}F]-**8** was then transformed, in an analogous way as described before, into pyridinamine [^{18}F]-**2** by reaction with Br_2/aqueous KOH.

The present synthetic pathway was then extended to the preparation of the *ortho*-[^{18}F]fluorinated regioisomer of [^{18}F]-**2**, i.e. 6-[^{18}F]fluoro-2-pyridinamine ([^{18}F]-**3**) (Figure 3). As expected, the employed precursor molecules, that were bearing a halogen leaving group in the *ortho*-position of the pyridine ring,

i.e. 6-chloro-2-pyridinecarboxamide (**11**) and 6-bromo-2-pyridinecarbonitrile (**13**), were better activated for ^{18}F-fluorination than the corresponding *meta*-substituted series (Figure 4(B)). In contrast to the *meta*-substituted series, pyridinecarboxamide **11** appeared to be equally well activated for ^{18}F-substitution as pyridinecarbonitrile **13**, which resulted in almost quantitative incorporation yields after 5 min of heating for both precursor molecules (Figure 3 and Figure 4(B)). In addition to that, we observed less hydrophilic by-product (i.e. $<10\%$ of total radioactivity) on HPLC – even at longer heating times – as compared to the *meta*-[^{18}F]fluorinated compounds, which pointed to a higher chemical stability of the *ortho*-[^{18}F]fluorinated molecules under the employed reaction conditions. The [^{18}F]fluorinated pyridinecarboxamide [^{18}F]-**12**, which was obtained after reaction of **11** with K[^{18}F]F-K_{222}, was converted into target molecule [^{18}F]-**3** by employing the same conditions (i.e. Br_2/aqueous KOH) as for the synthesis of [^{18}F]-**2** (Figure 3). Pyridinamine [^{18}F]-**3**, which co-eluted on HPLC (system B) with unlabelled **3**, was formed in a similar conversion yield (20–30%) based on [^{18}F]-**12** as derivative [^{18}F]-**2**. As an alternative precursor to **11**, pyridinecarbonitrile **13** was reacted with K[^{18}F]F-K_{222} to afford the [^{18}F]fluorinated pyridinecarbonitrile [^{18}F]-**14** in a yield of $98 \pm 1\%$ ($n = 6$) (Figure 3). [^{18}F]-**14** was then hydrolysed with aqueous KOH into the corresponding pyridinecarboxamide [^{18}F]-**12** and subsequently subjected to Hofmann rearrangement conditions to give [^{18}F]-**3** as a product (Figure 3).

As for [^{18}F]-**2**, crude [^{18}F]-**3** was purified by semipreparative HPLC (system C). However, in contrast to the purification of [^{18}F]-**2**, the mixture of pyridinecarboxamide [^{18}F]-**12** and pyridinamine [^{18}F]-**3**, which was collected in one HPLC fraction, could not be resolved by the SCX procedure, which was most likely related to the fact that pyridinamine [^{18}F]-**3** was significantly less basic than the corresponding *meta*-[^{18}F]fluorinated pyridinamine [^{18}F]-**2** (pK_a [^{18}F]-**3**: 4.63 ± 0.13; pK_a [^{18}F]-**2**: 2.44 ± 0.24).[11] Despite this separation problem, the overall radiochemical yield of [^{18}F]-**3**, as calculated by HPLC analysis of unresolved [^{18}F]-**12** and [^{18}F]-**3**, was higher as compared to [^{18}F]-**2** ($6 \pm 1\%$ ($n = 3$) for [^{18}F]-**2** versus $10 \pm 2\%$ ($n = 3$) for [^{18}F]-**3**, Table 1). These higher total radiochemical yields were most likely related to the higher yields obtained in the *ortho*-^{18}F-substitution and/or the better stability of the *ortho*-[^{18}F]fluorinated pyridine derivatives (less hydrophilic by-product formation).

Experimental

General

Chemicals. 5-Bromo-2-pyridinecarboxamide (**7**) was purchased from Aurora Fine Chemicals Ltd. (Graz, Austria), 6-chloro-2-pyridinecarboxamide (**11**) from Chembridge Corporation (San Diego, CA, USA), 6-bromo-2-pyridine-

carbonitrile (**13**) from Chempacific (Baltimore, MD, USA), and 6-fluoro-2-pyridinamine (**3**) and 5-fluoro-2-pyridinecarboxylic acid from Synchem Laborgemeinschaft (Kassel, Germany). All other chemicals were obtained from Sigma-Aldrich Chemie GmbH (Schnelldorf, Germany) or Merck KGaA (Darmstadt, Germany) and used without further purification.

Aqueous [^{18}F]fluoride was produced in a General Electrics PETtrace cyclotron (General Electrics, USA) via the ^{18}O(p,n)^{18}F nuclear reaction by irradiation of a 1.5 ml water target containing 95.9% enriched [^{18}O]water (Hyox^{18}, Rotem Industries, Beer Sheva, Israel) with a 16.5 MeV proton beam.

Analytical procedures. For analytical high performance liquid chromatography (HPLC) a Luna 5μ Phenyl-Hexyl column (150 mm × 4.6 mm) (Phenomenex Ltd., USA) was eluted with a mixture of H_2O (A) and acetonitrile (B) at a flow rate of 1.0 ml/min. The following binary gradient time programs were used:

HPLC system A: 0–3 min, (A:B, v:v) 80:20 isocratic; 3–12 min, (A:B) 80:20–50:50; 12–15 min, (A:B) 50:50 isocratic; 15–16 min, (A:B) 50:50–80:20; 16–17 min, (A:B) 80:20 isocratic.

HPLC system B: 0–7 min, (A:B, v:v) 95:5 isocratic; 7–9 min, (A:B) 95:5–60:40; 9–16 min, (A:B) 60:40 isocratic; 16–17 min, (A:B) 60:40–95:5; 17–19 min, (A:B) 95:5 isocratic.

For detection a Merck Hitachi L-4000 UV detector (wavelength: 254 nm) in series with a Packard Radiomatic Flo-one Beta Flow scintillation analyser (PerkinElmer Life Sciences Inc., Boston, USA) were employed.

For thin layer chromatography (TLC) analysis Merck silica gel 60 F_{254} TLC aluminium sheets (layer thickness: 0.2 mm) were used with one of the following two mobile phases:

TLC system A: ethyl acetate/hexane 50/50 (v/v).

TLC system B: dichloromethane/methanol/triethylamine 90/10/1 (v/v/v).

UV detection was performed using a standard UV lamp at a wavelength of 350 nm. For analysis of radioactive spots a Berthold digital autoradiograph LB 286-20 (Berthold Australia Pty Ltd., Bundoora, Australia) was used.

Radiochemistry

General procedure for the nucleophilic exchange reaction on pyridine derivatives. Aqueous [^{18}F]fluoride ion from the cyclotron target was collected into a 3 ml Wheaton V-vial (Wheaton Science Products, Millville, USA) containing a solution of kryptofix 2.2.2 in acetonitrile (120 mg/ml, 100 μl, 12.0 mg, 32.7 μmol) and a solution of potassium carbonate in water (200 mg/ml, 20 μl, 4.0 mg, 28.9 μmol). The mixture was exposed to a stream of nitrogen and concentrated to dryness at 150°C or 180°C (see below) under repeated addition of acetonitrile (3 × 0.5 ml). To the dried K[^{18}F]F-K_{222} complex, the

respective precursor pyridine derivative (15–20 μmol) dissolved in dimethylsulphoxide (0.5 ml) was added and the resulting solution stirred for 20 min at 150°C (precursor **4**) or for 5 min at 150°C (precursors **9** and **13**) or for 20 min at 180°C (precursors **7** and **11**). An aliquot of the reaction mixture was analysed by TLC and HPLC, whereby TLC analysis was used to estimate the amount of unreacted [^{18}F]fluoride present in the reaction mixture.

Retention times: HPLC system A: precursor **4**: 11–12 min and product [^{18}F]-**6** : 12–13 min; HPLC system B: precursor **7**: 14–15 min and product [^{18}F]-**8**: 12–13 min; precursor **9**: 17–18 min and product [^{18}F]-**10**: 13.5–14.5 min; precursor **11**: 13.5–14.5 min and product [^{18}F]-**12**: 11.5–12.5 min; precursor **13**: 18–19 min and product [^{18}F]-**14**: 14.5–15.5 min. Retention factors (R_f): TLC system A: [^{18}F]fluoride: 0.0; [^{18}F]-**6**: 0.5-0.6. TLC system B: [^{18}F]fluoride: 0.0; [^{18}F]-**8**, [^{18}F]-**10**, [^{18}F]-**12** and [^{18}F]-**14**: 0.5–0.8.

General procedure for the hydrolysis of ^{18}F-labelled pyridinecarbonitriles. The reaction mixture containing crude [^{18}F]-**10** or [^{18}F]-**14**, which was obtained after nucleophilic substitution, was cooled in an ice/water bath. Then potassium hydroxide (5 mg, 89 μmol) in water (200 μl) was added and the solution stirred for 5 min at room temperature. An aliquot of the reaction mixture was analysed by HPLC.

Retention times: HPLC system B: [^{18}F]-**10** (pyridinecarbonitrile): 13.5–14.5 and [^{18}F]-**8** (pyridinecarboxamide): 12–13 min; [^{18}F]-**14** (pyridinecarbonitrile): 14.5–15.5 min and [^{18}F]-**12** (pyridinecarboxamide): 11.5–12.5 min.

General procedure for the Hofmann rearrangement of ^{18}F-labelled pyridinecarboxamides. Bromine (2.0 μl, 39 μmol) was dissolved in a solution of potassium hydroxide (12 mg, 214 μmol) in water (1 ml) and stirred for 15 min in an ice/water bath. This solution was then added to the ice-cooled reaction mixture obtained after nucleophilic substitution or hydrolysis, which resulted in slight but clearly visible gas formation. The reaction mixture was first stirred for 15 min in the ice/water bath and then heated for 20 min at 75°C. An aliquot of the reaction mixture was analysed by HPLC.

Retention times: HPLC system B: [^{18}F]-**8** (pyridinecarboxamide): 12–13 min and [^{18}F]-**2** (pyridinamine): 10–11 min; 5-bromo-2-pyridinecarboxamide (**7**): 14–15 min; 5-bromo-2-pyridinamine: 13.5–14.5 min; [^{18}F]-**12** (pyridinecarboxamide): 11.5–12.5 min and [^{18}F]-**3** (pyridinamine): 12–13 min.

*General procedure for the purification of 5-[^{18}F]fluoro-2-pyridinamine ([^{18}F]-**2**) and 6-[^{18}F]fluoro-2-pyridinamine ([^{18}F]-**3**)*. The purification was performed on a semipreparative HPLC system consisting of a Rheodyne 7010 titanium injector equipped with a Rheodyne 2 ml sample loop mounted on a Besta motor valve (Besta-Technik GmbH, Wilhelmsfeld, Germany), a Jasco 880-PU

HPLC pump (Jasco Corporation, Tokyo, Japan) and a Jasco 875-UV detector (wavelength: 280 nm) in series with a Berthold LB508 C-1 radioactivity detector. A Waters μBondapak C18 column (300 mm × 7.8 mm, 10 μm) (Waters Corporation, Milford, USA) equipped with a Phenomenex SecurityGuard C18 (10 × 10 mm) pre-column was isocratically eluted with a mixture of water and acetonitrile (95/5, v/v) at a flow rate of 6 ml/min (*HPLC system C*). Data were collected on an Axxiom Chromatography 747 chromatography data system (Axxiom Chromatography Inc., Moorpark, USA).

The crude product was siphoned from the reaction vial into the sample loop *via* standard tubing and a disposable 5 ml syringe and injected on to the HPLC system. Since the ^{18}F-labelled pyridinecarboxamides and corresponding pyridinamines co-eluted on this HPLC system (retention time: 6–9 min, Figure 5), both compounds were collected in one fraction. The mixture of pyridinamine [^{18}F]-**2** and pyridinecarboxamide [^{18}F]-**8** was resolved by the following solid-phase extraction procedure: the HPLC fraction was acidified by addition of concentrated phosphoric acid (50 μl), homogenized and then passed over a strong cation exchange cartridge (Isolute 100 mg SCX, International Sorbent Technology Ltd., Hengoed, UK), that had been preconditioned with absolute ethanol (5 ml) and 10 mM aqueous phosphoric acid (10 ml). The pyridinamine [^{18}F]-**2** was retained on the cartridge. The cartridge was washed with water (3 ml) and [^{18}F]-**2** was then eluted with aqueous potassium hydroxide (10 mg/ml, 3 ml). An aliquot of the eluate was analysed by HPLC.

Retention times: HPLC system B: [^{18}F]-**2**: 10–11 min; [^{18}F]-**3**: 12–13 min. Retention factors (R_f): TLC system B: [^{18}F]-**2**: 0.35; [^{18}F]-**3**: 0.5.

Conclusion

We have developed a one-pot synthesis method to prepare no-carrier-added 5-[^{18}F]fluoro-2-pyridinamine ([^{18}F]-**2**) and 6-[^{18}F]fluoro-2-pyridinamine ([^{18}F]-**3**) in practical radiochemical yields of 6–10% (non-decay-corrected). The preparation of [^{18}F]-**2** is one of very few examples demonstrating the feasibility of nucleophilic *meta*-[^{18}F]fluorination of a pyridine derivative. It is remarkable that the use of a 2-cyano-substituted precursor molecule (i.e. 5-bromo-2-pyridinecarbonitrile, **9**) gave almost quantitative *meta*-^{18}F-incorporation after only 5 min of heating at 150°C. Both [^{18}F]-**2** and [^{18}F]-**3** are new potentially useful radiolabelled synthons for radiopharmaceutical chemistry.

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