COMPARISON OF TWO SYNTHETIC METHODS TO OBTAIN [^{18}F] N-(2-AMINOETHYL)-5-FLUOROPYRIDINE-2-CARBOXAMIDE, A POTENTIAL MAO-B IMAGING TRACER FOR PET

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Summary

The compound Ro 19-6327, N-(2-aminoethyl)-5-chloropyridine-2-carboxamide, is known to inhibit reversibly and site specifically the enzyme monoamine oxidase B (MAO-B). The ^{123}I-labelled iodo-analogue N-(2-aminoethyl)-5-iodopyridine-2-carboxamide (Ro 43-0463) was investigated successfully in human volunteers by means of SPET (Single Photon Emission Tomography). We developed therefore the synthesis and radiolabelling of the corresponding fluoro-analogue N-(2-aminoethyl)-5-fluoropyridine-2-carboxamide with ^{18}F in order to carry out PET (Positron Emission Tomography) investigations of MAO-B related neuropsychiatric diseases. For this purpose two synthetic approaches leading to the electrophilic and the nucleophilic methods of ^{18}F radiolabelling were undertaken. The nucleophilic approach appeared to be superior when factors such as precursor synthesis, beam time, specific activity and radiochemical purity of the product are considered.

Keywords: MAO-B inhibitor, PET, [^{18}F] N-(2-aminoethyl)-5-fluoropyridine-2-carboxamide, hetero-aromatic nucleophilic fluorination, fluorodestannylation.

Introduction

Monoamine oxidase (MAO) is an enzyme, localized in mitochondrial membranes of neuronal and glial cells of the central nervous system as well as in liver, placenta, intestine, pancreas and thrombocytes. It oxidizes biogenic and exogenous amines (1). The subtype MAO-B is found in human brain, liver and thrombocytes where it acts on phenylethylamine, dopamine, tyramine and tryptamine (2). In some disease conditions such as Morbus Parkinson and Alzheimer's disease

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elevated concentrations of MAO-B have been found in corresponding brain areas (3,4,5,6). The irreversible MAO-B inhibitor L-deprenyl was labelled with ^{11}C (7) to image the MAO-B concentration in the human brain by means of PET. It was shown that the uptake of [^{11}C] L-deprenyl could be blocked by the 100 fold more potent, reversible and specific MAO-B inhibitor N-(2-aminoethyl)-5-chloropyridine-2-carboxamide (Ro 19-6327) (7,8,9). It is known that a change from one halogen to another in the 5-position of Ro 19-6327 has only a negligible influence on its pharmacological behaviour (10). We therefore labelled N-(2-aminoethyl)-5-iodopyridine-2-carboxamide with ^{123}I and successfully performed clinical investigations using SPET (11). Because of our promising SPET data we decided to label N-(2-aminoethyl)-5-fluoropyridine-2-carboxamide with ^{18}F for PET studies of MAO-B related neuropsychiatric diseases and bringing, in addition, the opportunity with this nuclide to deliver the new tracer to other interested PET centres. In this paper, we present a comparison of two successful labelling approaches to [^{18}F] N-(2-t-butylcarbamoylethyl)-5-fluoropyridine-2-carboxamide which further could be hydrolyzed to [^{18}F] N-(2-aminoethyl)-5-fluoropyridine-2-carboxamide.

Experimental

Reagents: 5-Nitro-2-bromopyridine **1** was purchased from Aldrich. Other reagents used were from Fluka, Merck or Baker and of p.a. quality or HPLC grade.

Two high performance liquid chromatography (HPLC) systems were used:

System A (preparative): Consisting of a Waters 510 pump , a Valco 6-port valve with 10 ml loop, a Waters UV detector model 440 (at 254 nm), a Geiger- Müller counter LND 714 with an Eberlein RM-14 instrument and a Knauer column Lichrosorb RP 18, 5 µm, 250x16 mm and 0.06 M H_3PO_4 at 9 ml/min.

System B (analytical): Consisting of a Rheodyne injector with 100 µl loop, a Merck-Hitachi L 6200 pump, a NaI scintillation detector (Scintillation Meter type 540, Mini Instruments Ltd, Burnham on Crouch/UK), a Merck-Hitachi L- 4000 UV detector (at 254 nm), a Merck-Hitachi D-2500 Chroma integrator, a µ-Bondapak C18 column, 5 µm, 300x3.9 mm and CH_3CN/0.1 N NH_4OOCCH_3 (5/95) at 3 ml/min.

Thin layer chromatography (TLC) was performed on silica plates (Kieselgel 60, 0.25 mm layer, 5x20 on glass, Merck) using the indicated solvent mixtures (volume by parts) and analyzed on a

position sensitive detector (Berthold LB-285-AT). MS spectra were recorded on a TRIO 2000 (Fisons, UK) and IR spectra on a Perkin-Elmer 781. The ^{1}H-NMR spectra were recorded on a Gemini 200 (Varian). The melting points were measured on a Büchi 530 instrument and are not corrected.

5-Nitropyridine-2-carbonic acid (2)

To a solution of 11 g (122.8 mmol) CuCN in dry dimethylsulfoxide (DMSO), 17 g (83.7 mmol) of **1** were added and dissolved by slight heating. The solution was heated quickly to 180 °C and kept at this temperature for 5 min. After the reaction the mixture was cooled with running water and extracted once with 500 ml and twice with 250 ml diethylether. The combined extracts were washed twice with 250 ml of 6 M NH_3 solution and twice with 250 ml water. The ether phase was evaporated to dryness and the residue dissolved in 220 ml 6 M HCl. The solution was then refluxed for 90 min. After addition of 500 ml water compound **2** was precipitated, filtered and dried to give 7.5 g (44.61 mmol, 53 %) of a white solid with a melting point of 213.5 °C [literature mp: 214-215 °C (12)]. TLC gave a single spot with R_f value = 0.43 ($CHCl_3$/MeOH/acetic acid 20/20/1).

MS (CI, CH_4), m/e (% relative abundance): 169 (M+1, 100), 151 (5), 124 (17), 78 (5)

IR, cm^{-1}, (KBr): 1705 (C=O), 1610 (C=C), 1525 (NO_2), 1355 (NO_2)

5-Aminopyridine-2-carbonic acid (3)

To 85 ml NH_3 (25%) 1.7 g (10.11 mmol) of **2** were added. The suspension was cooled with ice and H_2S (Merck, zur Synthese) was introduced until **2** was dissolved completely. The solution was then kept boiling (125-135 °C) until sulfur precipitated and the H_2S odor disappeared. The hot solution was filtered, acidified with acetic acid and filtered over charcoal. The filtrate was completely evaporated under vacuum and the slightly green residue was used without any further purification for the next step. The yield was 1.2 g (8.69 mmol, 86 %). TLC of **3** gave a single spot with R_f = 0.17 using $CHCl_3$/MeOH/acetic acid 20/20/1 as mobile phase.

5-Iodopyridine-2-carbonic acid (4)

The total amount of crude product **3** was dissolved in 26 ml water and 4 ml HCl_{conc} were added. A solution of 1 g (14.49 mmol) $NaNO_2$ in 5 ml water was added with stirring to the solution of **3** at a temperature of -5 to 0 °C . After 10 min a solution of 0.1 g urea was added and stirring continued for 15 min at 0 °C. The reaction mixture was then added dropwise at 0 °C to a solution of 5 g KI (30.12 mmol) in 5 ml water. It was then stirred for a further 15 min and the crude product was isolated by suction filtration. The crude product **4** was recrystallized from 10 % KI in water to give 0.8 g (3.21 mmol, 37 %, based on **3**) of a brownish solid with a melting point of 196 °C [literature mp: 197-199 °C (12)]. TLC gave a single spot with R_f = 0.65 using $CHCl_3$/MeOH/acetic acid 20/20/1 as mobile phase.

MS (CI, CH_4), m/e (% relative abundance): 250 (M+1, 100), 232 (90), 204 (10), 77 (10)

IR, cm^{-1}, (KBr): 1695 (C=O), 1553 (C=C), 1420 (C=C), 1003 (C-I)

N-[2-(t-butylcarbamoyl)-ethyl]-5-iodopyridine-2-carboxamide (5)

To a solution of 1.6 g (6.43 mmol) **4** in 250 ml dry tetrahydrofuran (THF), 1.1 g (6.78 mmol) 1,1'-carbamoyldiimidazol (CDI, Fluka, purum) were added. The solution was refluxed for 1 h. After the addition of 1.05 g (6.55 mmol) t-butyl-(2-aminoethyl)-carbamate (Fluka, purum) the reaction mixture was refluxed for 1.5 h. The solvent was removed by vacuum and the crude product purified by column chromatography. A column with 3 cm diameter and 40 cm length was filled with 80 g of 40-60 µm silica gel (Merck) and the compound chromatographed with 75 ml CH_2Cl_2 followed by 500 ml CH_2Cl_2/ethyl acetate 8/2 and 400 ml CH_2Cl_2/ethyl acetate 7/3. Fractions of 75 to 100 ml mobile phase containing the product were collected and evaporated. Compound **5** was obtained as a white solid with a yield of 1.7 g (4.35 mmol, 68 %) and a melting point of 130 °C [literature mp=130-131 °C (13)]. TLC gave a single spot with a R_f value of 0.36 using CH_2Cl_2/ethyl acetate 7/3 as mobile phase.

MS (CI, CH_4), m/e (% relative abundance): 392 (M+1, 70), 376 (5), 364 (25), 336 (65), 318 (15), 292 (100), 274 (35), 262 (15), 249 (10), 232 (5), 204 (5), 78 (5), 57 (45)

IR, cm^{-1}, (KBr): 3370 and 3290 (NH), 1685 (carbamide), 1650 (amide I), 1530 (amide II), 1008 (C-I)

N-[2-(t-butylcarbamoyl)ethyl]-5-trimethylstannylpyridine-2-carboxamide (6)

A solution of 3 g (7.67 mmol) **5** in anhydrous toluene was degassed using nitrogen and 6 g (18.32 mmol) hexamethylditin (Fluka, purum) followed by 0.09 g (0.08 mmol) tetrakis(triphenylphosphin)palladium(0) (Fluka, purum) were added. The mixture was refluxed for 24 h under nitrogen. After cooling to room temperature the solvent was removed under reduced pressure and the residue was mixed with 100 ml hexane and vigorously stirred. Hexane was removed by decantation and **6** was allowed to crystallize to give 1.6 g (3.74 mmol, 49 %) of a slightly yellow solid with a melting point of 58-60 °C. TLC gave a single spot with R_f = 0.44 (hexane/ether/triethylamine, 6/5/9).

The ion peaks appeared with the typical pattern of tin.

MS (EI), m/e (% relative abundance): 427/430 (M^+, 5), 372 (5), 312 (75), 299 (95), 285 (35), 269 (40), 243 (100), 165 (55), 135 (35), 120 (15)

MS (CI, CH_4), m/e (% relative abundance): 430 (M^+, 100), 374 (20), 356 (5), 330 (3), 312 (15), 297 (10), 277 (3), 269 (3), 243 (3), 165 (10), 148 (5), 135 (3), 57 (50)

IR, cm^{-1}, (KBr): 3350 and 3320 (br, NH), 2980 and 2930 (-$Sn(CH_3)_3$), 1690 (carbamide), 1660 (amide I), 1525 (amide II),

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.5 (s, 1H, ArH), δ 8.3 (s, 1H, amide H), δ 8.03 (m, 1H, ArH), δ 7.87 (m, 1H, ArH), δ 4.9 (s, 1H, carbamide H), δ 3.5 (m, 2H, -CH_2-), δ 3.3 (m, 2H, -CH_2-), δ 1.35 (s, 9H, -$C(CH_3)_3$), δ 0.3 (s, 9H, -$Sn(CH_3)_3$)

N-[2-(t-butylcarbamoyl)ethyl]-5-nitropyridine-2-carboxamide (9)

To a solution of 1.08 g (6.42 mmol) of **2** in 250 ml dry THF, 1.1 g (6.78 mmol) 1,1'-carbamoyldiimidazol (CDI, Fluka, purum) were added. The solution was refluxed for 1 h. After the addition of 1.05 g (6.55 mmol) t-butyl-(2-aminoethyl)carbamate (Fluka, purum) the reaction mixture refluxed for 1.5 h. The solvent was removed by vacuum and the crude product purified by column chromatography. A column with 3 cm diameter and 40 cm length was filled with 80 g of 40-60 µm silica gel (Merck) and the compound chromatographed with 75 ml CH_2Cl_2 followed by

500 ml CH_2Cl_2/ethyl acetate 8/2 and 400 ml CH_2Cl_2/ethyl acetate 7/3. Fractions of 75 to 100 ml mobile phase were collected and evaporated. 9 was obtained as a white solid with a yield 1.4 g (4.51 mmol, 70 %) and a mp. of 144 °C. A recrystallization was not necessary. TLC gave a single spot with a R_f value of 0.45 using CH_2Cl_2/ethyl acetate 7/3 as mobile phase.

MS (CI, CH_4), m/e (% relative abundance): 255 (10), 211 (20), 194 (5), 181 (10), 151 (3), 124 (7), 57 (100)

IR, cm^{-1}, (KBr): 3370 (br, NH), 1688 (carbamide), 1662 (amide I), 1603 (C=C), 1530 (br, amide II, NO_2), 1350 (NO_2)

^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.3 (m, 1H, ArH), δ 8.6 (m, 1H, ArH), δ 8.35 (m, 2H, ArH), δ 4.9 (s, 1H, carbamide H), δ 3.6 (m, 2H, $-CH_2-$), δ 3.35 (m, 2H, $-CH_2-$), δ 1.35 (s, 9H, $-C(CH_3)_3$)

[^{18}F] N-[2-(t-butylcarbamoyl)ethyl]-5-fluoropyridine-2-carboxamide (7)

Electrophilic labelling: Using 50 mg 6 in 8 ml freon 79 MBq (mean of 3) of [^{18}F] N-[2-(t-butylcarbamoyl)-ethyl]-5-fluoropyridine-2-carboxamide 7 were obtained after treatment with the irradiated target gas [^{18}F] F_2 in Ne (62 ml, 26 bar, Ne/0.06%F_2, 30 μA, 15 min, activity not measured)[1] at room temperature and purification with 8 ml CH_2Cl_2 over a $Na_2S_2O_3/SiO_2$ (20/80 w/w) omnifit column (1 cm diameter, 10 cm length). The purity of the intermediate 7 was checked with TLC (CH_2Cl_2/ethyl acetate 6/4) and found to be only 55%. The measured R_f value was 0.29 (impurity at 0.67). The whole procedure including target passivation requires about 3 h.

Nucleophilic labelling: [^{18}F] F^- was produced by irradiation of 2.5 ml 98 % enriched [^{18}O] H_2O with 15 μA 17 MeV protons for 2 h. Labelling of 9 with [^{18}F] F^- using the well known FDOPA procedure (12.5 mg 9, 22 mg 2.2.2 kryptofix, 3 mg K_2CO_3, 2.59 GBq [^{18}F] F^-, 0.9 ml DMSO, 20 min, 135 °C, purification over Sep-Pak RP-18), reported in (14, 15), resulted in 587 MBq (mean of

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[1] Target passivation: *1. cycle* - the target is purged 3 times with Ne and 2 times with 1% F_2/Ne and afterwards filled with 1% F_2/Ne up to 20 bars and then the pressure is adjusted with Ne to 26 bars followed by an irradiation for 15 min with 30 μA, *2. cycle* - after emptying, the target is filled again with Ne up to 26 bars and irradiated for 15 min with 30 μA, *3. cycle* - after emptying, the target is filled with 1% F_2/Ne up to 15 bars and the pressure is adjusted with Ne at 26 bars, afterwards the pressure is reduced to 3 bars and again adjusted with Ne to 26 bars and finally irradiated 15 min with 30 μA for labelling use.

[2] **8a: N-(2-aminoethyl)-5-nitro-2-pyridinecarboxamide**

3) nca (no carrier added) 7 (37% yield decay corrected) with 100% purity (TLC: CH_2Cl_2/ethyl acetate 6/4). The measured R_f value was 0.29.

Reference compound 7:

The synthesis of reference compound 7 was achieved by heating at 135 °C 10 mg (0.17 mmol) KF, 55 mg (0.18 mmol) 9 and 65 mg 2.2.2 Kryptofix in 2 mml DMSO. It was used directly for hydrolysis after Sep-Pak purification.

[^{18}F] N-(2-aminoethyl)-5-fluoropyridine-2-carboxamide (8)

Intermediate 7 obtained from the nucleophilic substitution method was hydrolyzed using 1 ml 20 % HCl and heating in a 5 ml sealed conical vial for 10 min at 135 °C. The hydrolyzed final product 8 was neutralized with 2 ml 3 N NaOH and purified using HPLC system A (8: t_r = 35 min; 8a[2]: t_r = 38.5 min). The product fraction was collected and buffered with 0.6 M phosphate buffer to give, after sterile filtration, an isotonic and injectable radiopharmaceutical. Analytical HPLC (system B) revealed a virtually 100 % radiochemical purity. The yield (mean of 3) is 135 MBq 8 EOS which corresponds to 10% decay corrected based on [^{18}F] F^-. The overall preparation time (labelling of 7 to final product 8) including product purification requires 2 h.

Reference compound 8 and 8a:

The total amount of reference compound 7 or 12.5 mg 9 were hydrolyzed and neutralized as described above for use as HPLC reference for compound 8 and 8a respectively. The identity of reference 8 and 8a was confirmed with LC-MS using electrospray as interface (direct flow injection, 0.1 ml/ min, AcCN/H_2O 1/1, 10 µl, 3.6 µg): M+1 8 = 184 and M+1 8a = 211.

Discussion

Nucleophilic fluorination of aromatic systems has been described mainly for substituted phenyl building blocks (16-24) whereas a nucleophilic introduction of ^{18}F into nicotindiethylamide by halogen exchange was reported by Knust et al. in 1982 (25). We decided to apply the electrophilic radiofluorodestannylation method described in the literature (26-30) in comparison with the nucleophilic substitution reaction method described in (14), to gain access to the target molecule

[^{18}F] N-(2-aminoethyl)-5-fluoropyridine-2-carboxamide (**8**) containing the pyridino heteroaromatic system. For this purpose the corresponding precursors **6** and **9** were synthesized according to the scheme shown in Fig. 1. The synthetic route leading to the precursor **6** followed the

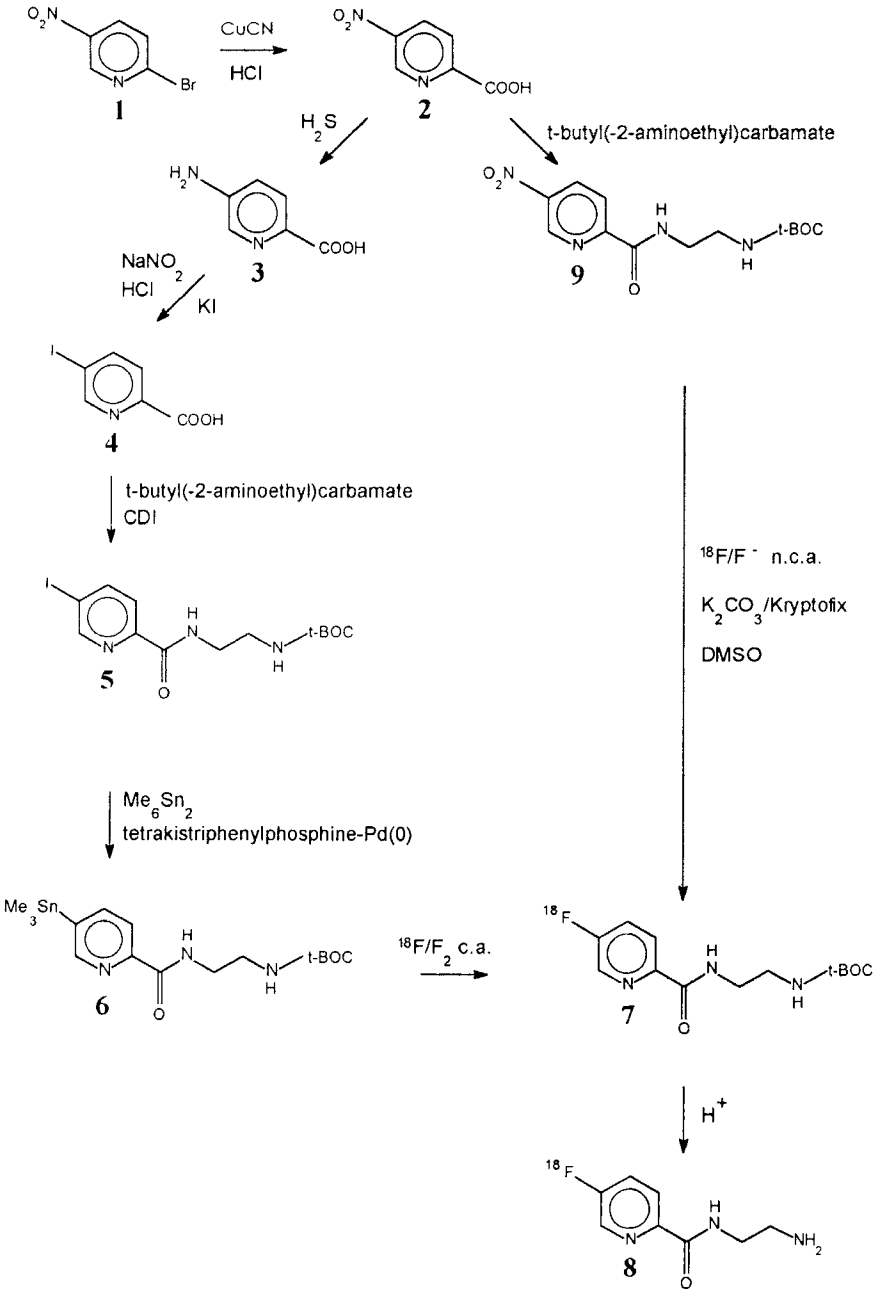

Fig. 1 Synthesis of [^{18}F] N-(2-aminoethyl)-5-fluoropyridine-2-carboxamide **8**.

procedure published by Oehlke et al. (12) up to the intermediate **4**. A crucial step was the reduction of **2** to **3** using H_2S. This resulted in a slurry which was difficult to work up. Compound **5** was synthesized by the CDI supported introduction of the t-Boc protected ethylendiamine side chain (13). We extended the synthesis to **6** by introducing the trimethylstannyl moiety using the approach published by Wilbur et al. (31). **6** was afterwards used as precursor for the electrophilic substitution with fluorine to afford the labelled intermediate **7**.

In general, electron withdrawing groups activate aromatic systems towards nucleophilic substitutions. In the present study, the successful nucleophilic ^{18}F-labelling of the pyridine moiety in position 5 in the synthesis of **7** is caused by the electron-withdrawing effect exerted by the amide substituent.

Both pathways to the labelled intermediate **7** are compared regarding the following aspects:

Synthetic route: Considering the multi-steps involved it is obvious that the synthetic access to precursor **9** is much easier than to precursor **6** (2 compared to 5 steps). In addition the unpleasant reduction of **2** by H_2S to **3** could be avoided.

Labelling: The introduction of [^{18}F] F^- in **9** applying the method described in (14) and (15) results in a 100 % radiochemically pure intermediate with a sufficiently high yield. A further advantage of [^{18}F] F^- is the possibility to produce large amounts of [^{18}F] F^- which can then be dispensed for the parallel labelling of different radiopharmaceuticals, which implies an economical use of available beam time. This aspect is of importance because of our particular technical situation of co-using a 72 MeV cyclotron as a parasite.

The introduction of ^{18}F from [^{18}F] F_2 results in radiochemically impure **7**. The procedure (32) used in producing [^{18}F] F_2 utilizing the ^{20}Ne(p;2pn)^{18}F reaction is time consuming because of the necessary target passivation in advance of each irradiation. In contrast to the nucleophilic procedure, where the obtained [^{18}F] F^- can be dispensed, the available beam time in the case of [^{18}F] F_2 is dedicated only to one product.

Quality: Because of the inherent target chemistry (irradiation of enriched [^{18}O] H_2O) the nca labelled compound **7** is of better quality with a high specific activity. The use of [^{18}F] F_2 allows radiolabelling only under carrier added conditions and low specific activities ranging from 3.7 to 18.5 GBq/mmol are thus obtained. This value is about 20 times smaller than reported by Chirakal et

al. (33) which in part is due to our target volume which is about 5 times larger. Additionally, by using the electrophilic substitution method, labelled by-products have to be expected because of the high chemical reactivity of fluorine gas.

Because of the above described differences in product purity, reliable high yield and nca quality of the product the nucleophilic approach is so attractive that we did not invest in further optimisation of the electrophilic method of labelling, for instance with the widely used [^{18}F] CH_3COOF.

Both labelling methods gave, as expected, the same intermediate **7** as shown with TLC. Reacting compound **9** with "cold" KF afforded after hydrolysis reference compound **8** which corresponds on HPLC with the radioactive labelled **8**. Hydrolysis of **9** gave the 5-nitro by-product **8a** which was used as reference during the separation of **8** from **8a** on HPLC. The chromatographic data and retention values are reported in the experimental section.

Conclusion

The reported analytical data provided by two independent and chemically totally different synthetic approaches prove the successful synthesis of [^{18}F] N-(2-t-butylcarbamoylethyl)-5-fluoropyridine-2-carboxamide **7**. The nucleophilic substitution approach to intermediate **7** merits its implementation as a routine procedure for preparing [^{18}F] N-(2-aminoethyl)-5-fluoropyridine-2-carboxamide **8** because of the above mentioned advantages. Thus, we will now be in a position to evaluate the new product with respect to its future use as a PET tracer for the investigation of MAO-B related neuropsychiatric diseases.

In addition we conclude that nitrogen-containing aromatic systems are also potential substrates for the nca synthesis of ^{18}F-labelled compounds. This possibility will be investigated in more detail in the future.

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