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Research Article

Application of n.c.a. 4-[^{18}F]fluorophenol in diaryl ether syntheses of 2-(4-[^{18}F]fluorophenoxy)-benzylamines

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Summary

The availability of no-carrier-added (n.c.a.) 4-[^{18}F]fluorophenol offers the possibility of introducing the 4-[^{18}F]fluorophenoxy moiety into potential radiopharmaceuticals. Besides alkyl–aryl ether synthesis using n.c.a. 4-[^{18}F]fluorophenol the diaryl ether coupling is an attractive synthetic method to enlarge the spectrum of interesting labelling procedures. As examples the syntheses of n.c.a. 2-(4-[^{18}F]fluorophenoxy)-*N*,*N*-dimethylbenzylamine and n.c.a. 2-(4-[^{18}F]fluorophenoxy)-*N*-methylbenzylamine were realized by an Ullmann ether synthesis of corresponding 2-bromobenzoic acid amides using tetrakis(acetonitrile)copper(I) hexafluorophosphate as catalyst and a subsequent reduction of the amides formed. The radiochemical yield of the coupling varied between 5 and 65% based on labelled 4-[^{18}F]fluorophenol. Both compounds are structural analogues of recently published radiotracers for imaging the serotonin reuptake transporter sites (SERT). However, *in vitro* binding assays of both molecules showed only a low affinity towards monoamine transporters.

Key Words: diaryl ether synthesis; radiofluorination; n.c.a. 4-[^{18}F]fluorophenol; 2-(4-[^{18}F]fluorophenoxy)-*N*,*N*-dimethylbenzylamine; SERT

Introduction

The increasing use of positron emission tomography (PET) for basic research and clinical studies demands new labelling strategies using short-lived positron emitters, especially fluorine-18 ($t_{1/2} = 109.7$ min). Several no-carrier-added ^{18}F-labelled aromatic synthons serve as key intermediates in multi-step

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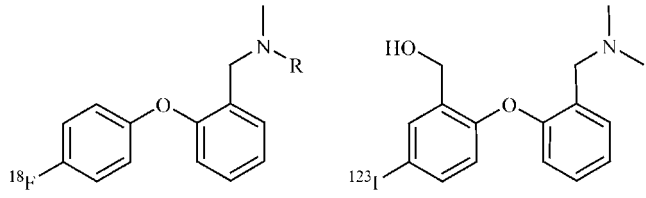
syntheses of radiopharmaceuticals not available via direct nucleophilic substitution. Versatile examples are substituted [^{18}F]fluorobenzaldehydes for the synthesis of aromatic amino acids[1] and neurotransmitter agents[2,3] or [^{18}F]fluorohalobenzenes for organometallic (Grignard or lithium)[4] and palladium-mediated coupling reactions.[5–7] Also, the 4-[^{18}F]fluorophenoxy moiety lends itself to potentially extending the variety of radiotracers and radioligands for PET. It was for example recently shown, that 4-[^{18}F]fluorophenoxyalkanes are readily available via coupling reactions of n.c.a. 4- [^{18}F]fluorophenol with alkylbromides.[8] Besides the synthesis of ^{18}F-labelled alkyl–aryl ethers, however, there is also a need for the preparation of ^{18}F-labelled diaryl ethers.

In this paper, this kind of synthesis is exemplified for the preparation of 2-(4-[^{18}F]fluorophenoxy)-*N*,*N*-dimethylbenzylamine (**[^{18}F]-6**). This compound has structural relations to 5-[^{123}I]iodo-2(2-((dimethylamino)methyl)phenoxybenzyl alcohol ([^{123}I]ODAM)[9] (cf. Scheme 1), which is suitable to visualize the serotonin reuptake transporter (SERT) sites via single photon emission tomography (SPET).[10] For the non-invasive examination of alterations in the serotonergic system, radiolabelled selective serotonin reuptake inhibitors (SSRI) are applied. These pharmaceuticals directly influence this system which is closely related to psychiatric disorders such as depression and other diseases. As an example [^{11}C]R(+)McN5652 is applied for *in vivo* studies of these neurotransporter sites. However, it has only moderate selectivity for SERT relative to other monoamine transporters.[11–13]



[^{18}F]-5 (R = H)
[^{18}F]-6 (R = CH_3)

[^{123}I]ODAM

Scheme 1. Structures of the target molecules [^{18}F]-5, [^{18}F]-6 and [^{123}I]ODAM

The above-mentioned [^{123}I]ODAM belongs to a new class of SERT radiotracers, based on the structure of 5-chloro-2-(2-((dimethylamino)methyl)-phenyl)thio)benzyl alcohol named 403U76. Especially the diaryl ether or thioether derivatives of *N*,*N*-dimethylbenzylamine IDAM,[14,15] ADAM[16] and ODAM[9,10] possess very high affinity and selectivity for SERT.[14] This class of compounds was labelled with iodine-123 and carbon-11 and proved suitable for the examination of the serotonin reuptake system with SPET or PET in

humans.[16,17–21] However, they are not optimum, because on the one hand SPET cannot be quantified and, on the other hand, the regional uptake of these compounds is too slow to be visualized perfectly with the short-lived carbon-11. So far, only a few examples of n.c.a. ^{18}F-derivatives of IDAM directly labelled in an aryl position are reported.[22,23] ^{18}F-Labelled alternatives are desirable for PET examinations due to favourable attributes of this radionuclide with regard to the pharmacokinetics of this class of compounds.

In this paper, the radiosynthesis of 2-(4-[^{18}F]fluorophenoxy)-*N*-methylbenzylamine (**[^{18}F]-5**) and 2-(4-[^{18}F]fluorophenoxy)-*N*,*N*-dimethylbenzylamine (**[^{18}F]-6**) via coupling reactions using the labelling synthon n.c.a. 4-[^{18}F]fluorophenol (**[^{18}F]-7**) is described. Furthermore, their evaluation as SSRI is reported.

Experimental

General

All chemicals were purchased from Aldrich (Steinheim, Germany) and Fluka (Buchs, Switzerland) and used without further purification.

Melting point determinations employed a Mettler FP 61 apparatus and temperatures given are uncorrected. ^{1}H-, ^{13}C- and ^{19}F-NMR spectra were recorded on a BRUKER Avance 200 spectrometer with samples dissolved in $CDCl_3$. All chemical shifts are reported in δ ppm using the signals of the appropriate standard as reference. IR spectra were recorded on a SHIMADZU IR-460 spectrophotometer. Mass spectra were obtained using an FINNIGAN Automass Multi mass spectrometer with an electron beam energy of 70 eV.

Analytical radio-HPLC was performed on a system consisting of a KNAUR pump 6400 and a KNAUR UV/VIS photometer 3060 with a detector wavelength of 254 nm. Sample injection was accomplished by an RHEODYNE injector block 7125. For measurement of radioactivity the outlet of the UV detector was connected to a NaI(Tl) well-type scintillation detector and the recorded data was processed by the software system RAYTEST Ramona MCS (Nuclear Interface, Münster, Germany). Separation of n.c.a. 2-(4-[^{18}F]fluorophenoxy)-*N*,*N*-dimethylbenzylamine and 2-(4-[^{18}F]fluorophenoxy)-*N*-methylbenzylamine was performed using a MULTOSPHERE 120 RP 18 AQ-5 (240 × 4 mm) column (CS-CHROMATROGRAPHIE SERVICE GmbH, Langerwehe, Germany) and a mobile phase consisting of methanol/H_2O (60/40) (v/v) at a flow rate of 2.0 ml/min. Radio TLC was performed on MERCK silica gel plates with solvent system diethyl ether/*n*-hexane in various mixtures. Radio TL-chromatograms were measured on an Instant Imager™ (PACKARD).

Standards and precursors

2-Bromo-N-methylbenzamide (**1**) *and 2-bromo-N,N-dimethylbenzamide* (**2**) were synthesized by the means of an earlier described method.[24] Colourless oils were obtained and yields were 89 and 80%, respectively.

*2-(4-Fluorophenoxy)-N-methylbenzamide (**3**) and 2-(4-fluorophenoxy)-N,N-dimethylbenzamide (**4**)*. A mixture of 1.3 g (5 mmol) of **1** or 1.38 g (5 mmol) of **2**, respectively, 0.56 g (5 mmol) of 4-fluorophenol, 2.61 g (10 mmol) of caesium carbonate and 0.15 g (5 mol%) of tetrakis(acetonitrile)copper(I) hexafluorophosphate $[Cu(MeCN)_4]PF_6$ in toluene was heated under reflux for 12 h. The solvent was removed and the residue purified by flash-chromatography with diethyl ether/*n*-hexane; 4/1 (v/v) as eluent to give 1.14 g (93%) of colourless crystals of **3** and 1.12 g (86%) of colourless crystals of **4**.

3: M.p.: 96–97°C; ^{1}H-NMR (200,13 MHz, $CDCl_3$) in δ: 8.21 (bs, 1 H, (C=O)N**H**), 7.69–6.83 (m, 8 H, Ar-H), 2.75 (t, 3 H, C**H**$_3$); ^{13}C-NMR (50,32 MHz, $CDCl_3$) in δ: 166.41 (C(O)N), 155.17 (C-F), 153.15 (C-O-), 153.10 (C-O-), 132.47 (C-H), 130.97 (C-H), 124.17 (**C**-C(O)N), 121.87 (C-H), 119.01 (C-H, d, J: 6.3 Hz), 117.59 (C-H), 117.13 (C-H, d, J: 19 Hz); ^{19}F-NMR (188,31 MHz, $CDCl_3$) in δ: −119.93; mass spectrum (*m*/*e*): 245 (M^+, 100%).

4: M.p. 83–85°C; ^{1}H-NMR (200,13 MHz, $CDCl_3$) in δ: 7.32 – 6.78 (m, 8 H, Ar-H), 3.03 (s, 3 H, C**H**$_3$), 2.93 (s, 3 H, C**H**$_3$); ^{13}C-NMR (50,32 MHz, $CDCl_3$) in δ: 164.61 (C(O)N), 156.30 (C-F), 155.85 (C-O-), 152.16 (C-O-), 128.99 (C-H), 126.73 (C-H), 123.22 (**C**-C(O)N), 121.56 (C-H), 118.10 (d, C-H, J: 7.6 Hz), 116.50 (C-H), 116.23 (d, C-H, 24 Hz); ^{19}F-NMR (188,31 MHz, $CDCl_3$) in δ: −119.82; mass spectrum (*m*/*e*): 260 (M^+, 96%), 215 (1 0 0), 185 (17), 157 (11).

*2-(4-Fluorophenoxy)-N-methylbenzylamine (**5**) and 2-(4-fluorophenoxy)-N,N-dimethylbenzylamine (**6**)*. Two millimoles of **3** and **4**, respectively, were dissolved in 10 ml water free THF and cooled to 0°C. Ten millilitres of 1 M $BH_3 \cdot THF$ solution were added slowly till the vigorous reaction ceased. The solution was then stirred for 2 h and kept under reflux. The reaction was quenched by adding 1 ml conc. HCl. The solvent was removed under reduced pressure and the residue taken up in 20 ml water. The solution was heated to reflux for further 30 min. The acid solution was extracted three times with 10 ml diethyl ether then neutralized with saturated $NaHCO_3$ solution. After another three extractions with 10 ml diethyl ether the combined organic phases were dried over Na_2SO_4. The solvent was removed whereby 0.45 g (1.95 mmol) of **5** and 0.48 g (1.96 mmol) of **6** were obtained, both of which are colourless oils. The products started decomposing after the extraction and were therefore transferred to their hydrochlorides. For this **5** and **6**, respectively, were dissolved in dry diethyl ether and hydrochloric acid (2 M in diethyl ether) was

added drop wise till no more precipitate formed. The colourless crystals were filtered and dried under reduced pressure.

5: ν_{max} (KBr): 1502, 1602 (RNH_2^+); ^{1}H-NMR (200,13 MHz, $CDCl_3$) in δ: 7.41–6.82 (m, 8 H, Ar-H), 3.83 (s, 2 H, C**H**$_2$), 2.46 (t, 3 H, C**H**$_3$), 1.69 (bs, 1 H, N**H**); ^{13}C-NMR (50,32 MHz, $CDCl_3$) in δ: 155.89 (C-O-), 155.56 (C-F), 154.02 (C-O-), 130.72 (C-H), 130.01 (C-H), 129.58 (**C**-C(O)N), 124.20 (C-H), 119.45 (d, C-H, J: 5.6 Hz), 116.98 (C-H), 116.33 (d, C-H, J: 19 Hz), 49.68 (CH_2), 35.80 (CH_3); ^{19}F-NMR (188,31 MHz, $CDCl_3$) in δ: −120.81; mass spectrum (*m*/*e*): 231 (M^+, 100%), 201 (50).

6: ν_{max} (KBr): 1501, 1687 (R_2NH^+); ^{1}H-NMR (200,13 MHz, $CDCl_3$) in δ: 7.49–6.86 (m, 8 H, Ar-H), 3.53 (s, 2 H, C**H**$_2$), 2.31 (t, 6 H, C**H**$_3$); ^{13}C-NMR (50,32 MHz, $CDCl_3$) in δ: 156.43 (CO-), 155.63 (C-F), 154.15 (C-O-), 131.72 (C-H), 130.47 (C-H), 128.78 (**C**-C(O)N), 124.20 (C-H), 119.71 (d, C-H, J: 8.3), 116.98 (C-H), 116.59 (d, C-H, J: 23 Hz), 57.83 (CH_2), 45.90 ($2 \times CH_3$); ^{19}F-NMR (188,31 MHz, $CDCl_3$) in δ: −121.41; mass spectrum (*m*/*e*): 245 (M^+, 100%), 214 (39), 111 (18).

Radiosyntheses

*4-[^{18}F]Fluorophenol (**[^{18}F]-7**).* The nucleophilic fluorination of (4-(trifluoromethyl)phenyl)-benzoyl-4′-*N*,*N*,*N*-trimethylammonium triflate with n.c.a. [^{18}F]fluoride was carried out as previously described by Ludwig *et al.*[8] After radiofluorination the solvent acetonitrile was removed under reduced pressure and an argon gas flow from the reaction vessel and the residue was dissolved in 2 ml of acetic acid/acetic anhydride (3/2). In total, 0.8 ml of hydrogen peroxide/conc. sulphuric acid (2/1) was added and the mixture heated to 90°C for 10 min. The reaction was quenched by transferring the mixture into a syringe filled with 8 ml of water. This solution was passed through a conditioned Sep-Pak® C18 plus-cartridge (WATERS), washed with 3 ml of water and eluted with 3 ml of diethyl ether. The diethyl ether was removed under reduced pressure and an argon gas flow. In total, 1.5 ml of 5 N NaOH and 0.2 ml of methanol were added to the residue and stirred for 10 min at 90°C. Then the basic reaction mixture was neutralized with 0.7 ml of concentrated hydrogen chloride.

*2-(4-[^{18}F]Fluorophenoxy)-N,N-dimethylbenzamide (**[^{18}F]-4**).* **[^{18}F]-7** was adsorbed on a conditioned Sep-Pak® C18 plus-cartridge (WATERS) and washed with 5 ml of water. The cartridge was stuck onto a glass column (Merck LiChrolut® 65 × 10 mm) filled with 0.5 g of Na_2SO_4 and eluted with 2 ml of diethyl ether into a reaction vessel already containing 1.5 ml of stirred dry toluene. The diethyl ether was carefully removed by an argon gas flow. A typical amount of 14 MBq (400 μCi) in approximately 0.5 ml of toluene was transferred to a sealed reaction vial, containing 4.5 mg (20 μmol) of 2-bromo-

N,*N*-dimethylbenzamide, 15 mg (40 μmol) of caesium carbonate and an excess amount of 20 mg of $[Cu(MeCN)_4]PF_6$. The reaction mixture was stirred for 25 min at 110°C. The toluene solution containing **[^{18}F]-4** and **[^{18}F]-7** was poured on a glass column (15 × 1.5 cm) filled with LiChrolut® RP-18 (40–63 μm) and eluted with diethyl ether/*n*-hexane; 4/1 (v/v) and monitored via radio-TLC (diethyl ether/*n*-hexane; 4/1 (v/v), $R_f = 0.55$). The solvent was removed under reduced pressure to yield dry **[^{18}F]-4**.

*2-(4-[^{18}F]Fluorophenoxy)-N,N-dimethylbenzylamine (**[^{18}F]-6**).* **[^{18}F]-4** was dissolved in 1 ml of THF and transferred by syringe to a sealed reaction vessel. The solution was treated cautiously with 0.5 ml of 1 M $BH_3 \cdot THF$ solution at 0°C and then stirred for 2 min. Solvent and remaining BH_3 were removed under reduced pressure at 80°C and the residue dissolved in methanol/water; 60/40 (v/v). Radio-TLC-analysis of **[^{18}F]-6** was performed with dichloromethane/methanol; 9/1 (v/v) + 0.5% triethylamine as eluent, $R_f = 0.75$. The product was purified for further application via radio-HPLC (LiChrosorb® RP-18 Select B5 (250 × 4 mm) (CS-Chromatographie Service GmbH, Langerwehe, Germany), methanol/water; 60/40 (v/v) + 0.2% CF_3COOH; k' (2-(4-[^{18}F]-fluorophenoxy)-*N*,*N*-dimethylbenzylamine: 5.5, k' (4-[^{18}F]fluorophenol): 15, k' (2-(4-[^{18}F]fluorophenoxy)-*N*,*N*-dimethylbenzamide): 34.

*2-(4-[^{18}F]Fluorophenoxy)-N-methylbenzamide (**[^{18}F]-3**) and 2-(4-[^{18}F]fluorophenoxy)-N-methylbenzamine (**[^{18}F]-5**).* Both compounds were prepared as described above for **[^{18}F]-4** and **[^{18}F]-6**, respectively. Radio-TLC-analysis of **[^{18}F]-3** was performed with diethyl ether/*n*-hexane; 4/1 (v/v) as eluent, $R_f = 0.43$. Radio-TLC-analysis of **[^{18}F]-5** was performed with dichloromethane/methanol; 9/1 (v/v) + 0.5% triethylamine as eluent, $R_f = 0.83$. The product could be purified via radio-HPLC (analogue conditions as above) k' (2-(4- [^{18}F]fluorophenoxy)-*N*-methylbenzylamine): 4.8, k' (2-(4-[^{18}F]fluorophenoxy)-*N*-methylbenzamide): 28.

In vitro binding assays

The preparation of membrane homogenates and the performance of binding assays were carried out as described earlier by Kung *et al.*[15,25]

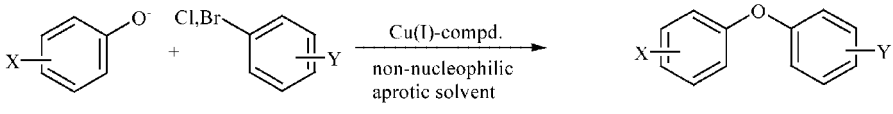
Results and discussion

General

N.c.a. 2-(4-[^{18}F]fluorophenoxy)-*N*,*N*-dimethylbenzylamine (**[^{18}F]-6**) and n.c.a. 2-(4- [^{18}F]fluorophenoxy)-*N*-methylbenzylamine (**[^{18}F]-5**) were chosen as target molecules in order to study the possibilities and limits of diaryl ether syntheses using n.c.a. 4-[^{18}F]fluorophenol (**[^{18}F]-7**). Besides the synthetic aspects, these

compounds were selected because of their structural similarity to the SSRI [*I]ODAM. Differences to the latter are of course the replacement of radioiodine by fluorine-18 and the missing methyl hydroxide substituent in *ortho*-position to the oxygen-bridge (cf. Scheme 1). In order to examine the influence of the changed substitution pattern on the biological properties, the respective affinity to the serotonin, dopamine and norepinephrine transporter system was also examined.

In general, a diaryl ether synthesis is performed in non-nucleophilic aprotic pure solvents or in a melt and in presence of a transition metal-species (e.g. Cu, Pd, Ni) as catalyst. The reaction times vary from 6 to 48 h and the yields from 5 to nearly 100%, depending on the choice of reaction partners and catalysts. Relatively mild reactions of electron deficient haloarenes with electron rich sodium phenolates can be achieved with copper(I)halides as catalysts (cf. Scheme 2). The copper catalyst forms a complex-intermediate and coordinates the nucleophilic aromatic substitution of the phenolate on the haloarene.[26] The choice of the catalyst therefore depends on the substitution pattern of the aromatic compound. In this study a variety of catalysts was applied.



Scheme 2. General conditions for an Ullmann ether synthesis (X = electron releasing substituent; Y = electron withdrawing substituent)

The classical Ullmann ether synthesis has several disadvantages such as elevated reaction temperatures, enormous purification problems, generally low yields and the use of stoichiometric quantities of copper. Recent advances are based on the application of a variety of catalysts, solvents and reaction conditions.[27] A small selection of those procedures was tested in this study for the purpose of performing the coupling reaction with n.c.a. 4-[^{18}F]fluorophenol (**[^{18}F]-7**), however, only with limited success. As an example of a classical coupling reaction pathway[28] a solid-state reaction was chosen but the yields were low and as mentioned above the purification was elaborate. Other conditions have been tested with copper catalysts like CuCl, Cu_2O, CuCl/Cu in various solvents but necessary reaction times were more than one half-life of fluorine-18 (> 2 h) and yields were rather low. As an alternative to copper catalysts triphenylphosphate appeared to be attractive[29] but it turned out that it is limited to coupling reactions where heterocycles are involved. More promising catalysts are palladium compounds and these were successfully used in the form of a combination of a Pd-catalyst and a ligand[30] with respectable yields of up to 60%. However, with more than 14 h the reaction time was still

far too long and this alternative could not further be considered for the n.c.a. radiochemistry of this study. In contrast, the recently suggested catalyst tetrakis(acetonitrile)copper(I) hexafluorophosphate[31] proved very useful for the anticipated coupling to n.c.a. [^{18}F]fluorodiaryl ethers.

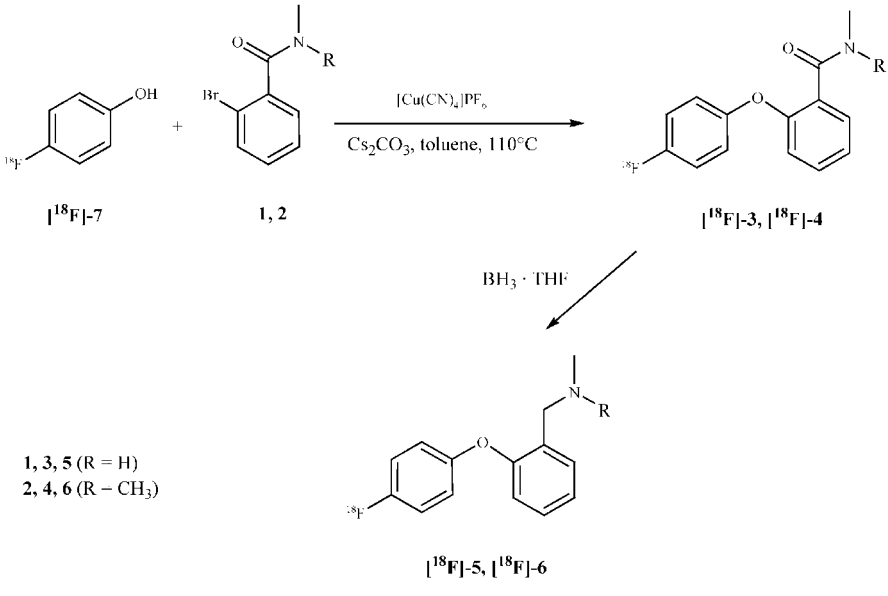
*Preparation of n.c.a. 2-(4-[^{18}F]fluorophenoxy)-N-methylbenzamide (**[^{18}F]-3**) and n.c.a. 2-(4-[^{18}F]fluorophenoxy)-N,N-dimethylbenzamide (**[^{18}F]-4**)*

Preparation of 4-[^{18}F]fluorophenol (**[^{18}F]-7**) was performed using earlier methods[8] with slight modifications. An overall radiochemical yield of $65 \pm 3\%$ could be achieved. This was determined with radio-TLC and radio-HPLC after a reaction time of 60 min. The **[^{18}F]-7** formed, however, had to be removed from the aqueous solution, purified and dried carefully in order to avoid loss of activity. The very basic reaction mixture was neutralised with an estimated equimolar amount of aqueous hydrogen chloride, the product separated by solid phase extraction and dried over Na_2SO_4. The ether was eluted into a reaction vial already containing 2 ml of dry toluene and removed by an argon gas flow.

The caesium salt of **[^{18}F]-7**, as nucleophilic agent, and the 2-bromobenzamides, as electron deficient benzoic systems, were not optimum starting materials for the Ullmann ether synthesis, due to the fact that acid amides are not strong electron withdrawing groups and also that fluorophenolate is not a good nucleophile (cf. Scheme 2). However, an application of the water sensitive tetrakis(acetonitrile)copper(I) hexafluorophosphate catalyst[31] was successful, using toluene or xylene as solvent in a sealed vessel with a reaction temperature of 110°C. This allowed to decrease the reaction time to 25 min. The catalyst is specific for *ortho* substituted benzamides or benzosulphonamides. The strongly variable radiochemical yields of 5–65% relative to labelled **[^{18}F]-7** can be explained by the importance of dryness during the coupling step. Based on about 25 labelling experiments an average radiochemical yield of $32 \pm 14\%$ could be obtained. Very small traces of water could be compensated by an excess amount of the catalyst. But even small amounts of moisture and the resulting decomposition of catalyst seemed to disturb the formation of the reaction-intermediate, which resulted in lower yields. Use of the 2-chlorobenzamides lead to decreased chemical yields and they were not applied for radiochemical reactions; 2-iodobenzamides exhibited comparable chemical and radiochemical yields as the bromo-analogues. Yields have been determined with radio-TLC and radio-HPLC. Higher reaction temperatures did not influence the reaction time; on the other hand, lower temperatures decreased the yield. The purification of the products was performed via column chromatography and all side products and remaining starting materials could be removed.

*Reduction to n.c.a. 2-(4-[18F]fluorophenoxy)-N-methylbenzylamine (**[18F]-5**) and n.c.a. 2-(4-[18F]fluorophenoxy)-N,N-dimethylbenzylamine (**[18F]-6**)*

The reduction of the benzamides **[18F]-3** and **[18F]-4** to n.c.a. 2-(4-[18F]fluorophenoxy)-*N*-methylbenzylamine and n.c.a. 2-(4-[18F]fluorophenoxy)-*N*,*N*-dimethylbenzylamine was carried out using the borane-tetrahydrofuran complex after removing the toluene phase. After 5 min reaction time the reduction was quantitative. For purification the benzylamines were separated via radio-HPLC. The average achievable radiochemical yield was $20 \pm 5\%$ after less than 2 h reaction time. Starting with a typical amount of 135 MBq [18F]fluoride, 14–15 MBq of **[18F]-6** could be obtained after HPLC-purification. **[18F]-5** has been prepared with corresponding yields (Scheme 3).

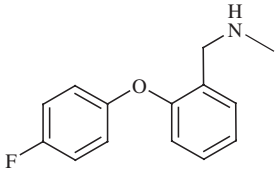
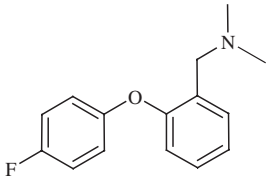
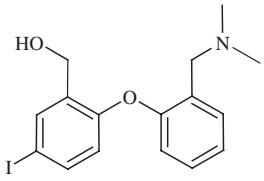


Scheme 3. Synthesis of n.c.a. 2-(4-[18F]fluorophenoxy)-benzylamines [18F]-5 and [18F]-6 via an Ullmann ether synthesis starting with n.c.a. 4-[18F]fluorophenol and corresponding 2-bromobenzamides 1 and 2

Biological evaluation

In vitro binding assays were performed using LLC-PK1 cells over expressing either one of three different types of monoamine transporters (SERT, DAT or NET)[32] to test the binding selectivity of 2-(4-fluorophenoxy)-*N*-methylbenzylamine and 2-(4-fluorophenoxy)-*N*,*N*-dimethylbenzylamine among monoamine transporters using [125I]*N*-(3-iodopropene-2-yl)-2β-carbomethoxy-3β-(4-chlorophenyl) (IPT) as selective ligand for DAT and NET and [125I]IDAM for SERT. The results are summarized in Table 1. The two compounds displayed

Table 1. Inhibition constants of 5, 6 and ODAM[9] (measured against [*I]IDAM[14,15] (SERT) and [*I]IPT (DAT, NET))

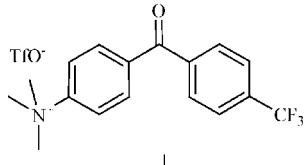
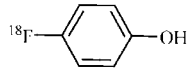
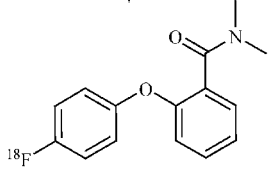
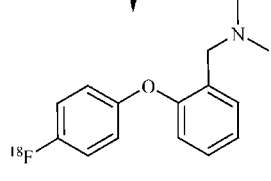
Compound	SERT	K_i(nM) DAT	NET
 **5**	> 400	> 10,000	> 10,000
 **6**	100.53 ± 19.52	3880 ± 50	550 ± 50
 **ODAM**	0.12 ± 0.02	3900 ± 700	20 ± 1.9

only a low inhibition effect on SERT and the other monoamine transporters. Owing to the disappointing low affinity, biodistribution studies of **[^{18}F]-4** and **[^{18}F]-5** were not carried out. The affinities towards other monoamine transporters are comparable to other compounds of this class[10,15,16] and in comparison to the very closely related ODAM the affinity towards DAT is nearly the same and it is even less towards NET.

Conclusion

The diaryl ether synthesis using n.c.a. 4-[^{18}F]fluorophenol (**[^{18}F]-7**) was exemplified by the synthesis of 2-(4-[^{18}F]fluorophenoxy)-*N*-methylbenzylamine (**[^{18}F]-5**) and 2-(4-[^{18}F]fluorophenoxy)-*N*,*N*-dimethylbenzylamine (**[^{18}F]-6**). The best results were obtained using tetrakis(acetonitrile)copper(I) hexafluorophosphate as catalyst for the Ullmann ether synthesis. The major problem of this kind of synthesis is the isolation and drying of the formed n.c.a. 4-[^{18}F]fluorophenol (**[^{18}F]-7**). The catalyst is very sensitive to moisture and therefore absolute dryness of starting material and of the solvent used for the coupling reaction was necessary. Therefore, n.c.a. 4-[^{18}F]fluorophenol was purified by solid phase extraction, dried over Na_2SO_4 and the solvent for elution was removed before commencing the coupling reaction. These steps

were time consuming and not very reliable with the consequence of varying radiochemical yield of the coupling product. Starting from n.c.a. [^{18}F]fluoride five reaction steps, three separations by solid phase extraction and a final HPLC purification were necessary to obtain the product. These conditions together with the reaction time and the radiochemical yields are summarized in Scheme 4. Although the present procedure is not yet convenient for routine production of ^{18}F-labelled radiopharmaceuticals, it was sufficient for preliminary *in vitro* evaluation experiments with the radioligands prepared.

time [min]	RCY [%] (not decay corr.)	compounds	reagents
0			[K⊂2.2.2.] [^{18}F]F, acetonitrile + H_2O_2, H^+ solid phase extraction + NaOH, MeOH, drying (Na_2SO_4)
60	65 (45)		
85	av. 32 (19)		**2**, $CuPF_6(MeCN)_4$, toluene, solid phase extraction
105	20 (11)		BH_3·THF, THF rHPLC

Scheme 4. Preparation of n.c.a. 2-(4-[^{18}F]fluorophenoxy)-*N*,*N*-dimethylbenzylamine ([^{18}F]-6)

Nevertheless, in principle this method shows the possibility of a diaryl ether synthesis to prepare certain radiopharmaceuticals containing an n.c.a. 4-[^{18}F]fluorophenoxy moiety. Furthermore, other catalysts are available for different substitution patterns with favourably adapted reaction conditions[27] and could most likely be applied for other diaryl ether labelling procedures.

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