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Research Article

4-[^{18}F]fluorophenyl ureas via carbamate-4-nitrophenyl esters and 4-[^{18}F]fluoroaniline

Sebastian Olma, Johannes Ermert* and Heinz H. Coenen
Institut für Nuklearchemie, Forschungszentrum Jülich GmbH, D-52425 Jülich, Germany

Dedicated to Prof. Dr Dr h.c. S. M. Qaim on the occasion of his 65th birthday

Summary

Four different no carrier added (n.c.a.) 4-[^{18}F]fluorophenylurea derivatives are synthesized as model compounds via two alternative routes. In both cases carbamate-4-nitrophenylesters are used as intermediates. Either n.c.a. 4-[^{18}F]fluoroaniline reacts with carbamates of several amines, or the carbamate of n.c.a. 4-[^{18}F]fluoroaniline is formed at first and an amine is added subsequently to yield the urea derivative. The choice of the appropriate way of reaction depends on the possibilities of precursor synthesis.

The radiochemical yields reach up to 80% after 50 min of synthesis time while no radiochemical by-products can be determined. These high yields were possible due to an optimized preparation of n.c.a. 4-[^{18}F]fluoroaniline with a radiochemical yield of up to 90%. From the various ways of its radiosynthesis, the substitution with n.c.a. [^{18}F]fluoride on dinitrobenzene is chosen, using phosphorous acid and palladium black for reduction of the second nitro group. Copyright © 2006 John Wiley & Sons, Ltd.

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Introduction

There is a manifold of urea derivatives in pharmaceutical chemistry, which are found as a structural element in a large variety of biologically active molecules.[1,2] Especially para substituted phenyl ureas (e.g. with halogen) are

*Correspondence to: J. Ermert, Institut für Nuklearchemie, Forschungszentrum Jülich GmbH, D-52425 Jülich, Germany. E-mail: j.ermert@fz-juelich.de

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found quite often.[3,4] Until now, there is no example where these structures are used for the preparation of no-carrier-added (n.c.a.) fluorine-18 labelled analogue or original tracers for diagnostics with positron-emission-tomography (PET). On the other hand, there are several urea derivatives known which are labelled via ^{18}F-fluoroalkylation or ^{18}F-fluoroacylation[5] indicating the interest in this class of compounds. Also, a 4-[^{18}F]fluorophenylguanidine was prepared[6] as an example of a related substance class.

While most known urea derivatives are pharmacologically highly potent, an *in vitro* or *in vivo* application as radiotracer implies a high molar activity of correspondingly ^{18}F-labelled molecules. Therefore, a synthesis without addition of isotopic carrier appears necessary.

In this study here a simple and effective method for the production of para-[^{18}F]fluorophenyl ureas (**[^{18}F]4a–4d**) is described. The strategy followed two alternative pathways to yield these ureas starting from previously prepared 4-[^{18}F]fluoroaniline (**[^{18}F]2**).

Several methods for the preparation of n.c.a. 4-[^{18}F]fluoroaniline can be found in the literature.[6–12] Those general concepts are partially adopted for the procedure developed in this work, whereby the whole radiosynthesis is optimized. In a second step the 4-[^{18}F]fluoroaniline is then either converted into a 4-[^{18}F]fluorophenylcarbamate nitrophenylester (**[^{18}F]3e**) and afterwards reacted with a selected amine in order to yield various asymmetric substituted ureas. Alternatively the 4-[^{18}F]fluoroaniline is reacted directly with a previously synthesized carbamate nitrophenylester (**3a–3d**) under formation of ureas.

Results and discussion

There are many possibilities to prepare urea derivatives on the laboratory scale. The simplest way is to combine an isocyanate compound with an amine.[13,14] In the case of fluorophenyl ureas this method works well. Fluorophenyl isocyanate is commercially available and stable under standard conditions. Further reaction with different amines leads to the correspondingly desired products. A transfer of these results to radiolabelling reactions is not quite simple.

First experiments for this work dealt with isotopic exchange reactions of 4-[^{19}F]fluorophenyl isocyanate with n.c.a. [^{18}F]fluoride. However, they failed even under several harsh conditions tested. This could be expected, since the isocyanate group is obviously not activating the aromatic ring enough for enabling a nucleophilic substitution (Scheme 1).

Therefore, evasion to a multistep synthesis using 4-[^{18}F]fluoroaniline as intermediate became necessary. Generally organic isocyanates can be made from this via a reaction with phosgene or a substitute for this highly toxic gas.

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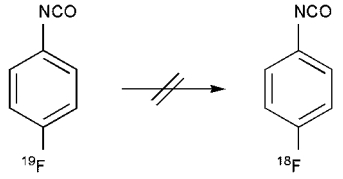
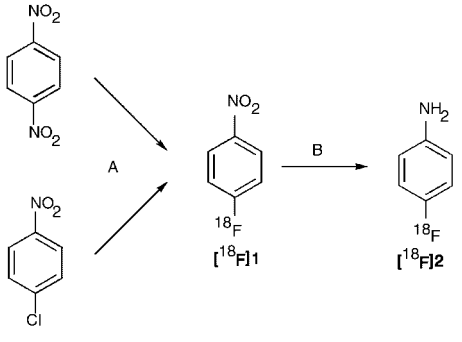


Scheme 1. Direct labelling of 4-fluorophenyl isocyanate failed

N.c.a. 4-[^{18}F]fluoroaniline

As mentioned above, the preparation of n.c.a. 4-[^{18}F]fluoroaniline (**[^{18}F]2**) was described several times before. However, the methods described therein were modified in several aspects. According to Scheme 2 the radiosynthesis starts with dried potassium [^{18}F]fluoride where potassium is complexed with Kryptofix© 2.2.2 in a standard procedure.[15] The precursor is dissolved in DMSO.



Scheme 2. Preparation of para-[^{18}F]fluoroaniline; (A) [K/2.2.2][^{18}F]F, K_2CO_3, DMSO, 120°C, 3 min; (B) Pd black, H_3PO_3, MeOH, reflux, 15 min

Two precursors were tested. 1,4-Dinitrobenzene and 4-chloronitrobenzene lead to very high radiochemical yields after labelling with [^{18}F]fluoride at 120°C for three minutes. The radiochemical yield of **[^{18}F]1** alluded to the dried [^{18}F]fluoride is constantly at least 85% after cartridge purification. The purification is performed on a Waters C18+ cartridge conditioned with ethanol and water. The reaction mixture is diluted with water and passed through the cartridge. Elution of the product is achieved with dry methanol.

Subsequent reduction of the nitro group is the crucial step of this synthesis approach. In order to avoid gaseous hydrogen, seven alternatives were examined in equimolar and n.c.a. radiosyntheses (Table 1). From those, the combination of phosphorous acid and palladium black in methanol at 80°C proved to be the best on the n.c.a. level. The reaction is quantitative within 15 min. The catalyst is filtered off easily, and the inorganic reagent is washed

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Table 1. Methods tested for reduction of 4-fluoronitrobenzene to 4-fluoroaniline

Reduction of 4-fluoronitrobenzene to 4-fluoroaniline

1 2

Equimolar synthesis		n.c.a. Radiosynthesis	
In/acetic acid	Not quantitative	Pd/[NH_4][HCOO]	Not quantitative
Pd/BER[a]	No conversion	$NaBH_4$	No conversion
Pd/hydrazine	Not quantitative	Pd/hydrazine	Complete conversion
$SnCl_2$	Not quantitative	$SnCl_2$	Not quantitative
		NiAc/$NaBH_4$	No conversion
		Pd/H_3PO_3	Complete conversion

[a] BER: borohydride, polymer supported.

out during cartridge purification. For this step, the cartridge used is a Merck Lichrolut EN phase. Fixation is only achieved under alkaline conditions. Afterwards, the charged cartridge is eluted with the solvent of choice for the next reaction step. Referring to the dried [^{18}F]fluoride the radiochemical yield of **[^{18}F]2** is 84 $\pm$ 5% within 30 min of preparation.

Both precursors 1,4-dinitrobenzene and 4-chloronitrobenzene show similar results until this step. Nevertheless, the first molecule seems to be more suitable for further reactions. Reduction of excess 1,4-dinitrobenzene yields 1,4-diaminobenzene which shows a completely different chemical behaviour than 4-fluoroaniline. In contrast, from the excess of the other precursor, 4-chloroaniline is produced. Since it is not easy to separate this completely from 4-[^{18}F]fluoroaniline via HPLC or other quantitative methods, it may lead to a non-isotopic dilution rendering a reduction of the apparent specific activity of the product.

Approaches for n.c.a. 4-[^{18}F]fluorophenyl isocyanate preparation

In order to avoid the synthesis of the isocyanate using phosgene, three alternatives were tested. Diphosgene and triphosgene[16–19] are colourless solids and stable under ambient conditions. One molecule diphosgene releases two, triphosgene three equivalents of phosgene *in situ*. Further, carbonyl diimidazole is a direct substitute for phosgene, where the imidazole units replace the chlorine atoms.[20,21]

These three substances were used in several experiments with n.c.a. 4-[^{18}F]fluoroaniline but no conversion of the free amino group could ever be observed. Tests included different solvents, temperatures and amounts of reagents. Even additional drying of the eluted solution of 4-[^{18}F]fluoroaniline over sodium sulphate resulted in no success (Scheme 3).

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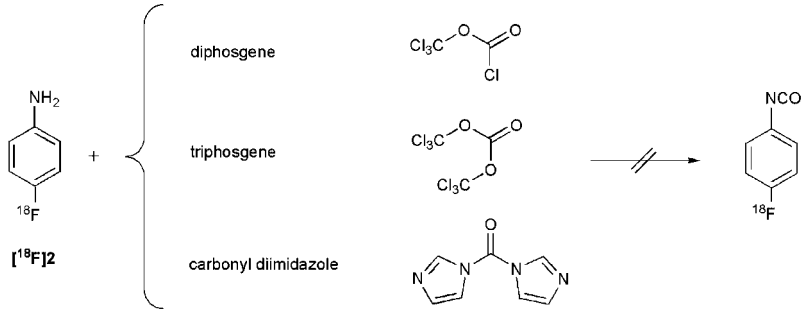
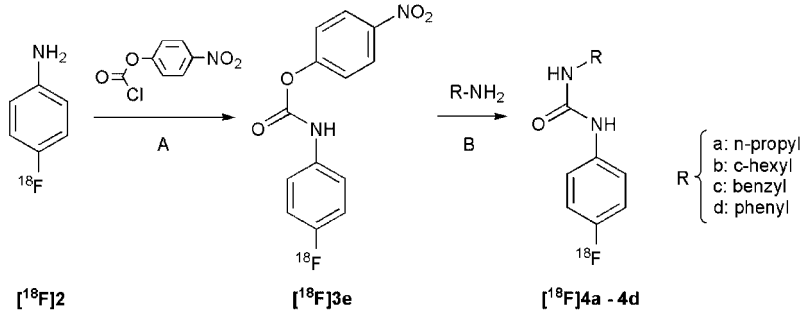


Scheme 3. Approaches of n.c.a. 4-[^{18}F]fluorophenyl isocyanate preparation, performed in chlorinated or etheric solvents at temperatures from 0 to 60°C

*N.c.a. 4-[^{18}F]fluorophenyl carbamate 4-nitrophenylester (**[^{18}F]3e**) and 4-[^{18}F]fluorophenyl urea derivatives (**[^{18}F]4a–4d**)*

Carbamate nitrophenylesters were therefore tested as alternative intermediates. Reactions of amines with 4-nitrophenyl chloroformate lead to carbamate 4-nitrophenylesters.[3,22] These substances are stable under standard conditions and easy to separate. Further reaction with another amine gives disparately substituted ureas. This strategy is well known in organic chemistry and can be applied for the radiosynthesis. Therefore, the n.c.a. **[^{18}F]2** is eluted from the Merck EN-cartridge subsequently passing a cartridge filled with sodium sulphate and kieselguhr powder. After addition of 4-nitrophenyl chloroformate the solution is stirred at room temperature. HPL- and thin layer chromatograms show the conversion to the desired carbamate 4-nitrophenylester (**[^{18}F]3e**) (Scheme 4).



Scheme 4. Preparation of 4-[^{18}F]fluorophenylcarbamate nitrophenyle ester and N-4-[^{18}F]fluorophenyl-N′-substituted ureas; (A) THF, Na_2SO_4-cartridge, (B) THF, △

For conversion to the desired urea, an amino compound of choice is added to the carbamate. After stirring at slightly raised temperatures the urea

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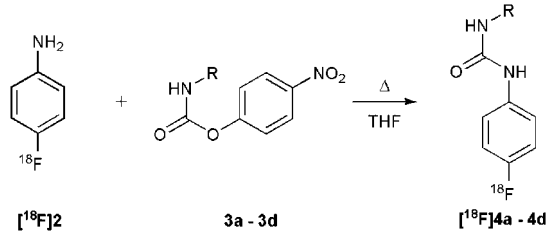
derivative is obtained and can be separated by a further cartridge purification step. The conversion takes place under alkaline conditions. The basicity of aliphatic amines is high enough, so that addition of an excess of it is sufficient. With aromatic amines, however, an assistant base such as ethyl diisopropyl amine is necessary. The yields for labelled fluorophenyl ureas are listed in Table 2.

Table 2. RCY of labelled fluorophenyl urea derivatives via [^{18}F]fluorophenylcarbamate nitrophenyl ester

Amine	Urea	RCY (referring to dry [K ⊂ 2.2.2] [^{18}F]F) (%)
n-Propyl amine	N-4-[^{18}F]fluorophenyl-N′-*n*-propyl urea (**[^{18}F]4a**)	76
c-Hexyl amine	N-4-[^{18}F]fluorophenyl-N′-*c*-hexyl urea (**[^{18}F]4b**)	73
Benzyl amine	N-4-[^{18}F]fluorophenyl-N′-benzyl urea (**[^{18}F]4c**)	82
Aniline[a]	N-4-[^{18}F]fluorophenyl-N′-phenyl urea (**[^{18}F]4d**)	73

Temperature of coupling reaction: 30–40°C.[a] Addition of ethyldiisopropyl amine (ca. 50 µl).

One of these last two steps in the radiosynthesis can be avoided, if it is possible to form the carbamate 4-nitrophenylester of the non-radioactively labelled part of the urea. In this case n.c.a. 4-[^{18}F]fluoroaniline is added to a carbamate (**3a–3d**) and the mixture stirred at 30–40°C to yield the corresponding urea derivative. The temperature is raised to accelerate the conversion. This reaction concept is simpler but it does not work equally effective with all tested amines, respectively, carbamates, as shown in Table 3 and Scheme 5.



Scheme 5. Preparation of N-4-[^{18}F]fluorophenyl-N′-substituted ureas via carbamate 4-nitrophenylesters; (a) THF, △; a–d, see Scheme 4

The 4-fluorophenyl carbamate 4-nitrophenylester (**3e**) is more reactive than some aliphatic compounds, what becomes clear by comparison of the results shown in Tables 2 and 3.

The choice of the right combination is obviously depending on the structure and possibility of synthesis of the desired labelling product.

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Table 3. RCY of labelled fluorophenyl urea derivatives via various carbamate nitrophenyl esters (ureas fixed on a Merck EN cartridge)

Carbamate	Urea	RCY (referring to dry [K ⊂ 2.2.2] [^{18}F]F) (%)
n-Propyl carbamate 4-nitrophenyl ester (**3a**)	N-4-[^{18}F]fluorophenyl-N′-*n*-propyl urea (**[^{18}F]4a**)	< 5
c-Hexyl carbamate 4-nitrophenyl ester (**3b**)	N-4-[^{18}F]fluorophenyl-N′-*c*-hexyl urea (**[^{18}F]4b**)	57 ± 6
Benzyl carbamate 4-nitrophenyl ester (**3c**)	N-4-[^{18}F]fluorophenyl-N′-benzyl urea (**[^{18}F]4c**)	62 ± 5
Phenyl carbamate 4-nitrophenyl ester (**3d**)	N-4-[^{18}F]fluorophenyl-N′-phenyl urea (**[^{18}F]4d**)	74 ± 7

Temperature of coupling reaction: 30–40°C.

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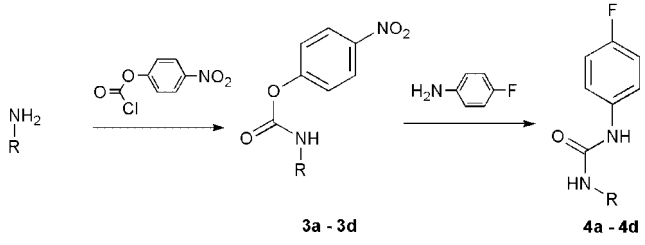
Synthesis of carbamate 4-nitrophenylesters and corresponding 4-fluorophenyl urea derivatives

Syntheses of carbamate 4-nitrophenylesters are well described for many different substances.[22] Nevertheless, some modifications are applied in this work to optimize the results for the individual molecules. Four types of substances were examined.

Benzyl, cyclohexyl and *n*-propyl amine represent several primary aliphatic amines. The reaction of those with 4-nitrophenyl chloroformate takes place in methylene chloride at room temperature and is completed after several hours. As an assistant base ethyl diisopropyl amine is added in equimolar amounts. This base is better suited than triethyl amine, because the formed ammonium salt does not precipitate. The reaction mixture is washed with hydrochloric acid and the precipitated product (**3a–3c**) is recrystallized from iso-propyl alcohol. The yields with all three aliphatic compounds are high, and products are pure after a simple purification procedure (Scheme 6).



Scheme 6. Preparation of carbamate 4-nitrophenylesters and 4-fluorophenyl ureas; a–d, see Scheme 4

In contrast, the conversion of aniline derivatives is not as simple as of aliphatic ones. The rapidly formed carbamate is not stable under alkaline conditions. After a short time, the only product with 4-nitrophenyl chloroformate and an excess of organic bases is bisphenyl urea. Hünigs base, ethyl diisopropyl amine, is used again in equimolar amounts. Cooling of the reaction flask is neccessary. For purification, hydrochloric acid is used again. Further washing, if necessary, is then done by suspending the solid product in diethyl ether.

The four carbamate compounds **3a–3d** described above are reacted in methylene chloride with **2** to give the corresponding urea derivatives. This simple procedure works out very well, except for the *n*-propyl compound (**3a**), where nearly no reaction can be observed.

This finding corresponds to the results of the radiosyntheses where **[^{18}F]-2** does not react with **3a**.

Reaction of *n*-propyl amine with 4-fluorophenyl carbamate nitrophenylester (**3e**), on the other hand, leads to the desired urea with good yields (91%). The

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4-fluorophenyl carbamate nitrophenylester was prepared like the phenyl compound described above.

Experimental

Chemicals

All chemicals are purchased from Merck, KMF, Riedel-de Häen, Fluka or Aldrich in p.a. quality or as otherwise mentioned in the text.

HPLC

The HPLC-System used for standard and product identification consists of a Sykam S1000 pump (constant flow 1 ml/min) and a Phenomenex Bondclone (10 µ C18, 300 × 3.8 mm) column. Detection was done by a Knauer UV detector K2500 at 254 nm and an EG & G Ortec NaI radiodetector with an ACE Mate Amplifier and BIAS supply.

Data acquisition and interpretation was performed via a Raytest Gina box and the corresponding Gina Star software.

Thin layer chromatography

Thin layer chromatography was performed on TLC aluminium roll Silica gel 60 F_{254} from Merck. It was developed with diethyl ether/hexane (volume ratio 1:1) plus 20 µl acetic acid per 5 µl eluent.

Spots were visualized under a Desaga MinUVIS lamp at 254 nm or by heating in a hot air stream after spraying with a solution of 0.45 g ninhydrin in 150 µl ethanol and 3 µl acetic acid.

Radio-TLC plates were measured on a Raytest Mini Gita system equipped with a closed β-counting tube and interpreted with the accordant software.

NMR spectroscopy

^{1}H-, ^{13}C- and ^{19}F-NMR spectra were recorded on a Bruker Avance 200 spectrometer with samples dissolved in solvents mentioned in the text. All shifts are given in δ ppm using the signals of the appropriate solvent as a reference.

Melting points

All melting points were measured in a BÜCHI Melting Point B-540 apparatus and data is corrected.

Organic syntheses

*General method for preparation of alkyl-carbamate nitrophenylesters (***3a**−**3c***)*. In a 100-ml flask 10 mmol of 4-nitrophenyl chloroformate are dissolved in 5 ml dry methylene chloride. 10 mmol of ethyl diisopropyl amine

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and 10 mmol of the accordant alkylamine are dissolved in 5 ml dry dichloromethane and added dropwise. The solution is stirred for 4 h.

The solution is washed with 1 M hydrochloric acid three times. The organic layer is dried over sodium sulphate and evaporated to dryness after filtration.

Recrystallization from iso-propyl alcohol leads to the desired alkyl carbamate 4-nitrophenylester.

*n-Propyl carbamate 4-nitrophenylester (***3a***)*. ^{1}H-NMR (DMSO-d6): (2 H, d, 8.27 ppm Ar-H), (1 H, t, 8.06 ppm N-H), (2 H, d, 7.41 ppm Ar-H), (2 H, q, 3.07 ppm C-H_2), (2 H, q, 1.51 ppm C-H_2), (3 H, t, 0.91 ppm C-H_3)
m.p.: 99.8°C
MS (ESI): $(m+H)/z = 225.2$
Yield: 1.90 g (8.44 mmol; 84%)

*cyclo-Hexyl carbamate 4-nitrophenylester (***3b***)*. ^{1}H-NMR (DMSO-d6): (1 H, s, 8.34 ppm N-H), (2 H, m, 7.40 ppm Ar-H), (2 H, m, 7.09 ppm Ar-H), (1 H, d, 6.03 ppm C-H), (10 H, b, 1.83–1.03 ppm C-H_2)
m.p.: 135.8°C
MS (ESI): $(m+H)/z = 265.1$
Yield: 2.32 g (8.75 mmol; 88%)

*Benzyl carbamate 4-nitrophenylester (***3c***)*. ^{1}H-NMR (DMSO-d6): (1 H, t, 8.62 ppm N-H), (2 H, m, 8.27 ppm Ar-H), (7 H, m, 7.34 ppm Ar-H), (2 H, d, 4.36 ppm C-H_2)
m.p.: 131.0°C
MS (ESI): $(m+H)/z = 295.1$
Yield: 2.80 g (9.5 mmol; 95%)

*General method for preparation of aryl-carbamate nitrophenylesters (***3d**−**3e***)*. In a 100-ml flask 10 mmol of 4-nitrophenyl chloroformate are dissolved in 5 ml dry methylene chloride. The flask is cooled in a water bath. 10 mmol ethyl diisopropyl amine and 10 mmol of the selected aniline derivative are dissolved in 5 ml dry dichloromethane and added dropwise. This solution is stirred for 3 h and afterwards washed three times with 1 M hydrochloric acid. The organic layer is dried over sodium sulphate and evaporated to dryness after filtration. The residue is the analytically pure aryl carbamate 4-nitrophenylester.

*Phenyl carbamate 4-nitrophenylester (***3d***)*. ^{1}H-NMR ($CDCl_3$): (1 H, s, 10.46 ppm N-H), (2 H, d, 8.32 ppm Ar-H), (4 H, m, 7.55 ppm Ar-H), (1 H, t, 7.12 ppm Ar-H)
m.p.: 148.6°C
MS (ESI): $(m+H)/z = 259.3$
Yield: 1.72 g (6.66 mmol; 67%)

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*Fluorophenyl carbamate 4-nitrophenylester (***3e***)*. ^{1}H-NMR ($CDCl_3$): (2 H, d, 8.32 ppm Ar-H), (4 H, m, 7.47 ppm Ar-H), (2 H, m, 7.11 ppm Ar-H), (1 H, b, 7.01 ppm N-H)

m.p.: 157.1°C

MS (ESI): $(m+H)/z = 277.2$

Yield: 2.29 g (8.30 mmol; 83%)

*General method for preparation of fluorophenyl urea derivatives (***4a**−**4d***)*. The corresponding alkyl or aryl carbamate nitrophenyl ester (5 mmol) is dissolved in 5 ml dry THF. After addition of 5 mmol 4-fluoroaniline (or *n*-propylamine) and 5 mmol of ethyl diisopropyl amine the mixture is stirred for several hours at room temperature. The solvent is evaporated under reduced pressure and the residue dissolved in ethyl acetate.

The solution is washed three times with 1 M sodium hydroxide solution and 1 M hydrochloric acid. The organic layer is dried over sodium sulphate and evaporated to dryness after filtration.

*N-Fluorophenyl-N'-n-propyl urea (***4a***)*. Preparation via fluorophenyl carbamate nitrophenyl ester and *n*-propyl amine.

^{1}H-NMR (DMSO-d6): (1 H, s, 8.19 ppm N-H), (2 H, m, 7.30 ppm Ar-H), (2 H, m, 6.88 ppm Ar-H), (1 H, b, 5.90 ppm N-H), (2 H, q, 3.07 ppm C-H_2), (2 H, m, 1.46 ppm C-H_2), (3 H, t, 0.88 ppm C-H_3)

m.p.: 155.0°C

MS (ESI): $(m+H)/z = 197.1$

Yield: 0.90 g (4.57 mmol; 91%)

*N-Fluorophenyl-N'-cyclohexyl urea (***4b***)*. ^{1}H-NMR (DMSO-d6): (1 H, s, 8.31 ppm N-H), (2 H, m, 7.38 ppm Ar-H), (2 H, t, 7.05 ppm Ar-H), (1 H, d, 6.03 ppm N-H), (1 H, b, 3.4 ppm C-H), (5 H, b, 1.83–1.54 ppm C-H_2), (5 H, b, 1.42–1.08 ppm C-H_2)

m.p.: 104.4°C

MS (ESI): $(m+H)/z = 237.2$

Yield: 0.65 g (2.74 mmol; 55%)

*N-Fluorophenyl-N'-benzyl urea (***4c***)*. ^{1}H-NMR (DMSO-d6): (1 H, s, 8.62 ppm N-H), (7 H, m, 7.36 ppm Ar-H), (2 H, t, 7.08 ppm Ar-H), (1 H, t, 6.62 ppm N-H), (2 H, d, 4.31 ppm C-H_2)

m.p.: 179.0°C

MS (ESI): $(m+H)/z = 245.1$

Yield: 1.10 g (4.49 mmol; 90%)

*N-Fluorophenyl-N'-phenyl urea (***4d***)*. ^{1}H-NMR (DMSO-d6): (1 H, d, 8.66 ppm N-H), (4 H, m, 7.48 ppm Ar-H), (2 H, t, 7.30 ppm Ar-H), (2 H, t, 7.13 ppm Ar-H), (1 H, t, 6.97 ppm Ar-H)

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m.p.: 235.0°C
MS (ESI): $(m+H)/z = 231.2$
Yield: 0.96 g (4.15 mmol; 83%)

Radiochemical syntheses

Production of n.c.a. [^{18}F]fluoride. N.c.a. [^{18}F]fluoride is produced via the $^{18}O(p,n)^{18}F$ nuclear reaction by bombardment of an isotopically enriched [^{18}O]water target with a 17 MeV proton beam at the BC 1710 cyclotron (JSW), as described previously.[23]

N.c.a. 4-[^{18}F]fluoroaniline ([**^{18}F**]**1**). The aqueous [^{18}F]fluoride solution (10–50 µl, e.g. 64.2 MBq) is added to 20 mg of Kryptofix 2.2.2. and 26 µl of a 1 M potassium carbonate solution. The mixture is diluted with 0.9 ml of dry acetonitril (< 0.003% H_2O) and transferred via syringe to a 5 ml conical vial (Reactivial) closed with a silicon septum. The solvent is evaporated under a stream of argon at 80°C and 750 mbar. The azeotropic drying is repeated with 1 ml acetonitrile, followed by evaporation of the dry Reactivial for 5 min to 40–50 mbar. The dry cryptate complex (52.9 MBq, reference activity) and approx. 4 mg of 1,4-dinitrobenzene are solubilized in 0.2 ml of dry DMSO. The stirred solution is heated in an oil bath at 120°C for 3 min.

Afterwards the reaction mixture is diluted with 10 ml of water and passed through a Waters C18 + cartridge (500 mg, conditioned with 10 ml of ethanol and 10 ml of water).

The 1,4-[^{18}F]fluoronitrobenzene (**[^{18}F]1**, 45.3 MBq, RCY: 88%) is eluted with 2 ml of methanol into a two necked flask. After addition of approx. 10 mg palladium black and approx. 100 mg phosphorous acid the flask is closed with a plug and a septum. A cannula in the septum is needed for pressure equalization, while the flask is heated under stirring in an oil bath at 60°C for 15 min. The reaction mixture is diluted with 20 ml of a 1 M sodium hydroxide solution and passed through a Merck EN cartridge (500 mg, conditioned with 10 ml of ethanol and 10 ml of a 1 M sodium hydroxide solution). After a synthesis time of 30 min 34.9 MBq (RCY: 82%) of n.c.a. 4-[^{18}F]fluoroaniline (**[^{18}F]2**) are fixed on the cartridge. No radioactive by-products can be determined by radio HPL- or thin layer chromatography.

N.c.a. 4-[^{18}F]fluorophenyl ureas ([**^{18}F**]**4a**−**4d**). **[^{18}F]2** is eluted from the cartridge see above with 2 ml of dry THF and the solution passed through a Merck Lichrolut cartridge filled with a mixture of kieselguhr powder and anhydrous sodium sulphate (volume ratio 1:1, wetted with 2 ml THF).

Urea synthesis via n.c.a. 4-[^{18}F]fluorophenyl carbamate 4-nitrophenylester ([**^{18}F**]**3e**). About 30 mg of 4-nitrophenyl chloroformate are added to the THF

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elution containing n.c.a. 4-[^{18}F]fluoroaniline (**[^{18}F]2**) in a Reactivial. The mixture is stirred at room temperature for 15 min. Afterwards 40 µl of the corresponding amine are added. In the case of aniline addition of an assistance base, e.g. 30 µl Hünigs base, is necessary. After another 15 min of stirring at slightly raised temperature (30–40°C) in an oil bath HPL- and thin layer chromatography show the desired ureas **[^{18}F]4a–4d** as the only radioactive products. Fixing the ureas on a Merck EN cartridge is done after dilution of the reaction mixture with 20 ml of a 1 M sodium hydroxide solution (cartridge conditioned with 10 ml of ethanol and 10 ml of a 1 M sodium hydroxide solution). The radiochemical yields are listed in Table 2.

Synthesis of ureas [^{18}F]**4a**−**4d** *via n.c.a. 4-[*^{18}*F]fluoroaniline and carbamate 4-nitrophenylesters (***3a**–**3d***)*. About 30 mg of the corresponding carbamate-4-nitrophenylester **3a–3d** are added to the THF elution containing n.c.a. 4-[^{18}F]fluoroaniline in a Reactivial. The mixture is stirred at slightly raised temperature for 15 min. After this time, HPL- and thin layer chromatography show the desired ureas **[^{18}F]4b–4d** as the major or exclusive products. Nearly no conversion is observed with the n-propyl derivative **[^{18}F]4a**. The remaining radioactivity signals could be identified in all cases as 4-[^{18}F]fluoroaniline.

Fixing the ureas on a Merck EN cartridge is done after dilution of the reaction mixture with 20 ml of a 1 M sodium hydroxide solution (cartridge conditioned with 10 ml of ethanol and 10 ml of a 1 M sodium hydroxide solution). The radiochemical yields are listed in Table 3.

Conclusion

Phenyl urea derivatives become more and more important in many fields of pharmaceutical chemistry. This work provides two simple routes for production of a variety of n.c.a. 4-[^{18}F]fluorophenyl ureas via 4-[^{18}F]fluoroaniline. Both strategies proceed via carbamate-4-nitrophenyl esters. The choice of the corresponding synthetic pathway depends on the chemical behaviour of the precursor molecules. With radiochemical yields of up to 80% and a synthesis time of 50 min, this concept gives the possibility to adapt the physiological properties of fluorophenyl urea derivatives for radiopharmaceutical applications with positron-emission-tomography .

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