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Research Article

N-Arylation of indoles with 4-[^{18}F]fluoroiodobenzene: synthesis of ^{18}F-labelled σ_2 receptor ligands for positron emission tomography (PET)

Frank R. Wüst* and Torsten Kniess
Institut für Bioanorganische und Radiopharmazeutische Chemie, FZ-Rossendorf e.V., Dresden, Germany

Summary

The palladium-mediated *N*-arylation of indoles with 4-[^{18}F]fluoroiodobenzene as a novel radiolabelling method has been developed. Optimized reaction conditions were elaborated by variation of different catalyst systems (CuI/1,2-diamines and $Pd_2(dba)_3$/phosphine ligands), bases and solvents in the reaction of indole with 4-[^{18}F]fluoroiodobenzene. Optimized reaction conditions ($Pd_2(dba)_3$/(2-(dicyclohexyl-phosphino)-2′-(*N*,*N*-dimethylamino)-biphenyl, NaOBu^t, toluene, 100°C for 20 min) were applied for the synthesis of ^{18}F-labelled σ_2 receptor ligands **[^{18}F]-11** and **[^{18}F]-13** which were obtained in 91 and 84% radiochemical yields, respectively. Copyright © 2004 John Wiley & Sons, Ltd.

Key Words: *N*-arylation; 4-[^{18}F]fluoroiodobenzene; σ_2 ligands

Introduction

N-Arylindoles are central structural motifs in many drugs and other pharmaceutically important compounds. Popular examples of pharmaceuticals with a *N*-arylindole moiety comprise antipsychotic drugs,[1] melatonin receptor MT_1 agonists[2] and angiotensin II-1 antagonists.[3] Moreover, numerous *N*-arylindoles bearing a 4-fluorophenyl group are among the highest affinity and most selective σ_2 receptor ligands reported in the literature.[4,5]

Sigma receptors represent a distinct class of receptor proteins consisting of two subtypes, termed σ_1 and σ_2.[6] They are found in the central nervous system as well as in various peripheral tissues such as liver, kidney, and endocrine

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*Correspondence to: F. R. Wüst, Institute of Bioinorganic and Radiopharmaceutical Chemistry, FZ-Rossendorf, PF 51 01 19, 01314 Dresden, Germany. E-mail: f.wuest@fz-rossendorf.de

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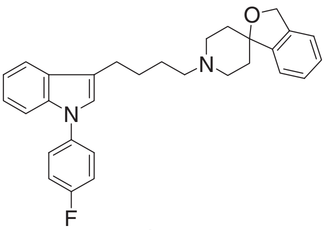
organs. Furthermore, recent findings also imply σ_2 receptors in the induction of cell death consistent with apoptosis.[7] However, the exact functional role of σ_2 receptors is not yet clearly defined. Over the last decade several studies have shown an overexpression of both σ receptor subtypes in many human and non-human tumours, including those of the breast, lung, colon, brain, and prostate.[7–9] The particularly high expression of σ_2 receptors in rapidly proliferating tumour cells and the need for a more defined characterization of their functional role have prompted research on σ_2 receptors as potential targets for non-invasive diagnostic imaging techniques such as positron emission tomography (PET).[9]

PET is a powerful imaging methodology in biomedical research which provides functional information of physiological, biochemical and pharmacological processes *in vivo*.[10,11] PET uses compounds labelled with short-lived positron emitting radioisotopes such as ^{11}C ($t_{1/2}=20.4\,min$), ^{13}N ($t_{1/2}=9.9\,min$), ^{15}O ($t_{1/2}=2\,min$) and ^{18}F ($t_{1/2}=109.6\,min$). Chemistry with short-lived positron emitters differs significantly from conventional chemistry, and the special features encountered in organic chemistry with short-lived positron emitters such as ^{11}C and ^{18}F have been reviewed recently.[11]

For *in vivo* PET imaging of receptor proteins like σ_2 receptors an appropriate compound should primarily be labelled with ^{11}C or ^{18}F at high specific radioactivity. Hence, radiolabelled σ_2 receptor ligands may serve as molecular probes to assess the proliferative status of certain tumour entities and to study the distinct functional role of σ_2 receptors *in vivo* by means of PET.

The fluorine atom in the 4-fluorophenyl part found in a series of high affinity and selective σ_2 receptor ligands such as Lu 28-179 represents a potential site for isotopic substitution with ^{18}F (Figure 1). Thus, the isotopic labelling with ^{18}F will lead to a PET radiotracer indistinguishable from the parent compound, which can be used as a molecular probe to study biochemical processes associated with σ_2 receptors *in vivo*.

Direct incorporation of ^{18}F as readily available [^{18}F]fluoride into the phenyl ring of the *N*-aryl moiety is not feasible since the aromatic ring is not sufficiently activated for nucleophilic aromatic substitution with [^{18}F]fluoride.



Lu 28-179

Figure 1. High affinity and selective σ_2 receptor ligand Lu 28-179

An alternative route for the introduction of ^{18}F into an aryl moiety comprises the utilization of ^{18}F-labelled prosthetic groups such as 4-[^{18}F]fluorohalobenzenes. In this connection especially 4-[^{18}F]fluoroiodobenzene is ideally suited for the selective introduction of a 4-[^{18}F]fluorophenyl group into various molecules via transition metal-mediated cross-coupling reactions.

Recently we have described a convenient synthesis of 4-[^{18}F]fluoroiodobenzene via thermal decomposition of symmetrical iodonium salts in the presence of no-carrier-added [^{18}F]fluoride.[12,13] We and other groups have successfully applied 4-[^{18}F]fluoroiodobenzene as a useful ^{18}F-labelling precursor in several C–C bond-forming reactions, such as Sonogashira[12] and Stille reactions.[13–16] Moreover, 4-[^{18}F]fluoroiodobenzene can also be used in cross-coupling reaction involving heteroatoms. The first application of an *N*-arylation reaction in ^{18}F chemistry was exemplified by the synthesis of the selective 5-HT$_{2A}$ receptor ligand [^{18}F]RP 62203 via palladium-assisted *N*-arylation of the piperazine moiety with 4-[^{18}F]bromofluorobenzene (Figure 2).[17]

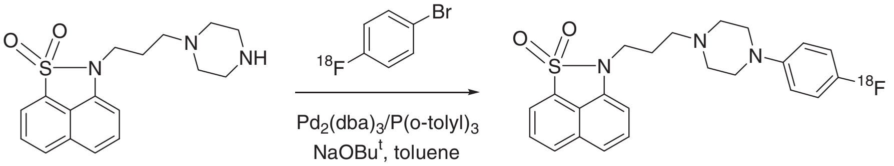
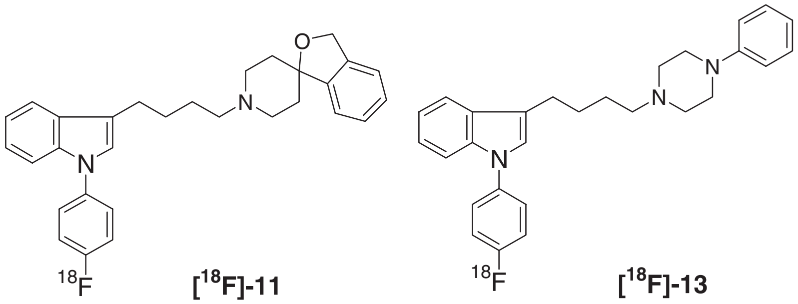


Figure 2. Synthesis of 5-HT$_{2A}$ receptor ligand [^{18}F]RP 62203

In recent years several research groups have demonstrated very efficient synthetic methods for the preparation of *N*-arylated compounds including indoles.[18–21] The reported palladium mediated[22,23] and copper-mediated[24,25] reactions of several aryl halide electrophiles with indoles gave the corresponding *N*-aryl-substituted indoles in high yields under mild reaction conditions. These approaches represent a major breakthrough in the formation of *N*-arylindoles in terms of a more general route when compared with other methods such as Fischer indole synthesis and Ullmann-type couplings. However, the transition-mediated *N*-arylation of indoles has not been adapted yet to organic chemistry with the short-lived positron emitter ^{18}F for the synthesis of PET radiotracers.

In this paper we describe the synthesis of two σ_2 selective ligands via *N*-arylation of the indole moiety with 4-[^{18}F]fluoroiodobenzene. The reaction conditions were optimized by using the reaction of indole **1** with 4-[^{18}F]fluoroiodobenzene as a model reaction, and optimized reaction conditions were applied for the synthesis of ^{18}F-labelled σ_2 receptor ligands **[^{18}F]-11** and **[^{18}F]-13** (Figure 3).



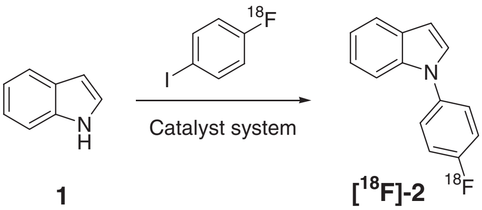
[^{18}F]-11 **[^{18}F]-13**

Figure 3. ^{18}F-labelled σ_2 receptor ligands [^{18}F]-11 and [^{18}F]-13

Results and discussion

Typically, *N*-arylations of indoles are carried out upon completion during a 12–24 h reaction time period while using almost equimolar amounts of indoles and aryl halides or triflates as the coupling partners.[22–25] However, direct application of these reaction conditions for palladium- and copper-catalysed *N*-arylations of indoles as reported in the literature is not possible when 4-[^{18}F]fluoro-iodobenzene is used as the electrophile in the amination reaction.

The short half-life of ^{18}F ($t_{1/2} = 109.6\,\text{min}$) prevents such long reaction times and the use of submicromolar amounts of ^{18}F-labelled compounds, as typically found in the synthesis of PET radiotracers, results in an extraordinary stoichiometrical relation between labelled and unlabelled reagents in the coupling reaction. Therefore, one has to develop an appropriate radiosynthesis route considering the short half-life of ^{18}F and the submicromolar amounts of ^{18}F-labelled species. For that purpose we set up the reaction of indole with 4-[^{18}F]fluoroiodobenzene to give 1-(4-[^{18}F]fluorophenyl)-1*H*-indole **[^{18}F]-2** as a model reaction (Figure 4) in order to optimize reaction conditions by screening different catalyst systems, bases and solvents.



1 **[^{18}F]-2**

Figure 4. *N*-arylation of indole with 4-[^{18}F]fluoroiodobenzene

The radiochemical yield of the desired 1-(4-[^{18}F]fluorophenyl)-1*H*-indole **[^{18}F]-2**, which was determined by radio-HPLC, refers to the percentage of radioactivity area of the desired product **[^{18}F]-2** relative to the total radioactivity area. The results are given in Table 1.

Table 1. *N*-Arylation of indole with [^{18}F]fluoroiodobenzene

Entry	Catalyst system	Base	Solvent[c]	Radiochemical yield (%)[a,b]
1	CuI/*trans* 1,2-diaminocyclohexane	K_3PO_4	THF/toluene	0
2	CuI/*trans* 1,2-diaminocyclohexane	K_3PO_4	Toluene	0
3	CuI/ethylendiamine	K_3PO_4	THF/toluene	7
4	CuI/ethylendiamine	K_3PO_4	Toluene	36
5	$Pd_2(dba)_3$/Xantphos	$NaOBu^t$	THF	5
6	$Pd_2(dba)_3$/Xantphos	$KOBu^t$	THF	6
7	$Pd_2(dba)_3$/Xantphos	$NaOBu^t$	THF/toluene	13
8	$Pd_2(dba)_3$/Xantphos	Cs_2CO_3	THF/toluene	0
9	$Pd_2(dba)_3$/Xantphos	K_3PO_4	THF/toluene	16
10	$Pd_2(dba)_3$/Xantphos	$NaOBu^t$	Toluene	28
11	$Pd_2(dba)_3$/2-(dicyclohexyl-phosphino) -2′-(*N*,*N*-dimethylamino)-biphenyl	$NaOBu^t$	THF/toluene	22
12	$Pd_2(dba)_3$/2-(dicyclohexyl-phosphino) -2′-(*N*,*N*-dimethylamino)-biphenyl	$NaOBu^t$	DMF	0
13	$Pd_2(dba)_3$/2-(dicyclohexyl-phosphino) -2′-(*N*,*N*-dimethylamino)-biphenyl	$NaOBu^t$	Toluene	25 (10 min), 69 (20 min) 71 (30 min), 70 (60 min)
14	$Pd_2(dba)_3$/2-(dicyclohexyl-phosphino) -2′-(*N*,*N*-dimethylamino)-biphenyl	$NaOBu^t$	Toluene	3[d]
15	$Pd_2(dba)_3$/2-(dicyclohexyl-phosphino) -2′-(*N*,*N*-dimethylamino)-biphenyl	$NaOBu^t$	Toluene	70[e]

[a] Radiochemical yield determined by radio-HPLC representing the percentage of radioactivity area of cross-coupled product [^{18}F]-2 related to the total radioactivity area.
[b] All reactions were conducted at 100°C for 30 min.
[c] Solvents in a 1:1 mixture.
[d] Reaction was carried out at 65°C.
[e] Reaction was carried out at 140°C.

In a first set of reactions we studied several copper-mediated reactions for the synthesis of 1-(4-[^{18}F]fluorophenyl)-1*H*-indole **[^{18}F]-2** (entry 1–4). The use of copper catalysts consisting of CuI and a 1,2-diamine ligand were found to be very efficient for the amidation of aryl halides and the *N*-arylation of nitrogen heterocycles.[24,25]

In our experiments we used K_3PO_4 exclusively as the base as it is known to be the best base in the performance of copper-mediated *N*-arylations.[24]

Trans-1,2-diaminocyclohexane (entry 1 and 2) and ethylendiamine (entry 3 and 4) were used as 1,2-diamine ligands. In the case of *trans*-1,2-diaminocyclohexane as bidentate ligand for copper chelation no product formation was observed, neither using a 1:1 mixture of THF/toluene nor pure toluene as the solvent (entry 1 and 2). On the other hand, the use of ethylendiamine gave 7% of the desired product **[^{18}F]-2** when a mixture of THF/toluene was used (entry 3). The radiochemical yield could further be increased to 36% when the reaction was carried out in pure toluene as the solvent (entry 4).

In the following reactions (entry 5–15) we investigated several palladium-based catalyst systems in the reaction of indole with 4-[^{18}F]fluoroiodobenzene. First (entry 5–10) we used $Pd_2(dba)_3$ and Xantphos as catalyst system while varying the base and the solvent. The system Pd/Xantphos has been shown in the literature to promote several C–N bond forming processes in good to excellent yields while displaying good functional group compatibility.[26,27] When $NaOBu^t$ (entry 5) and $KOBu^t$ (entry 6) were used as bases and THF as the solvent only low radiochemical yields of 5 and 6%, respectively, could be obtained. The radiochemical yield could be increased to 13% when a 1:1 mixture of THF/toluene was used (entry 7). Thus, a 1:1 mixture of THF and toluene is a superior solvent to the use of THF alone. In entries 7–9 we studied the effect of different bases, namely $NaOBu^t$, Cs_2CO_3 and K_3PO_4, on the radiochemical yield while using a 1:1 mixture of THF/toluene as the solvent. The obtained radiochemical yields clearly show a significant effect of the base on the reaction. When $NaOBu^t$ (entry 7) or K_3PO_4 (entry 9) is used as the base, 13 and 16% of *N*-4-[^{18}F]fluorophenylindole could be detected in the reaction mixture. On the other hand, no product formation was found when Cs_2CO_3 was used as the base (entry 8). The finding that $NaOBu^t$ and K_3PO_4 are suitable bases is consistent with results reported in the literature dealing with various *N*-arylation reactions.[22,24] The beneficial effect of pure toluene as the solvent of choice was demonstrated in entry 10. The radiochemical yield could further be increased to 28% by using $Pd_2(dba)_3$/Xantphos as the catalyst system, $NaOBu^t$ as the base and pure toluene as the solvent.

In another set of reactions involving palladium-based catalyst systems (entry 11–15) we tested 2-(dicyclohexyl-phosphino)-2′-(*N*,*N*-dimethylamino)-biphenyl as an electron-rich phosphine ligand. Several electron-rich phosphines were demonstrated to be excellent ligands in many palladium-mediated *N*-arylation reactions.[22,28] As we have learnt from the reactions employing the catalyst system $Pd_2(dba)_3$/Xantphos (entry 5–10), $NaOBu^t$ seems to be the base of choice. Thus, in the following set of reactions (entry 11–15) we further studied the effect of different solvents on the radiochemical yield while using $NaOBu^t$ as the base. The use of a 1:1 mixture of THF/toluene (entry 11) gave 22% of the desired product. This result reflects the superior properties of 2-(dicyclohexyl-phosphino)-2′-(*N*,*N*-dimethylamino)-biphenyl as phosphine ligand in the catalyst system when compared to Xantphos (entry 7, 13%). No product formation was observed when the polar solvent DMF was tested (entry 12).

On the other hand, we were very pleased to find a radiochemical yield of 71% when toluene was used as the solvent (entry 13). This finding further confirms toluene as the solvent of choice in the *N*-arylation of indole **1** with 4-[^{18}F]fluoroiodobenzene as already observed in entry 4 and 10. So far all reactions were carried out for 30 min. However, optimization of reaction time is a very important aspect in the synthesis of ^{18}F-labelled compounds. For this purpose we determined the radiochemical yield dependent on the reaction time after 10, 20, 30 and 60 min (entry 13). Cross-coupled product **[^{18}F]-2** was formed in 25% after 10 min, and the radiochemical yield could be increased significantly to 69% after 20 min. Extension of the reaction time to 30 and 60 min did not further improve the radiochemical yield, being 71 and 70%, respectively.

The effect of temperature on the radiochemical yield was studied as shown in entry 14 and 15. Lowering the reaction temperature to 65°C (entry 14) was accompanied by a drastic decrease of radiochemical yield and only 3% of the desired product was formed. On the other hand, performance of the reaction at 140°C did not further improve radiochemical yield of product **[^{18}F]-2** when compared with the reaction at 100°C (entry 15 vs 13).

In conclusion, we optimized the reaction conditions by screening different catalyst systems, bases, and solvents, enabling rapid cross-coupling of indole with [^{18}F]fluoroiodobenzene.

The found optimized reaction conditions ($Pd_2(dba)_3$/(2-(dicyclohexylphosphino)-2′-(*N*,*N*-dimethylamino)-biphenyl, NaOBu^t, toluene, 100°C for 20 min) were now applied to the synthesis of ^{18}F-labelled σ_2-receptor ligands by the reaction of indoles **10** and **12** with 4-[^{18}F]fluoroiodobenzene.

The synthesis of labelling precursors **10** and **12** and the synthesis of reference compounds **11** and **13** is depicted in Figure 5.

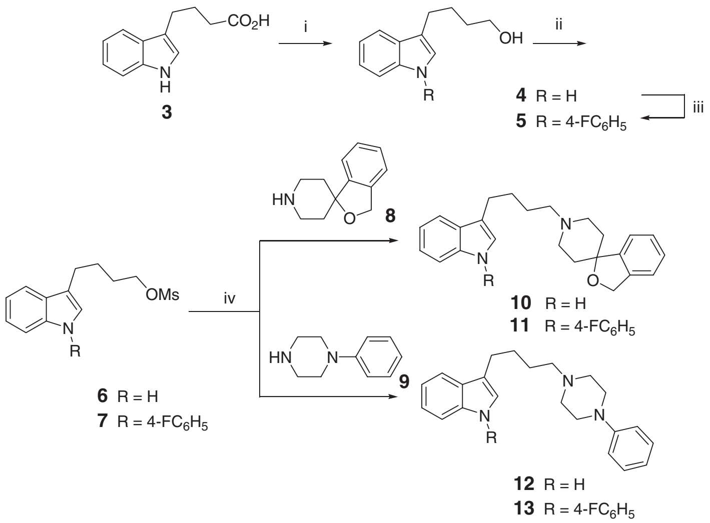
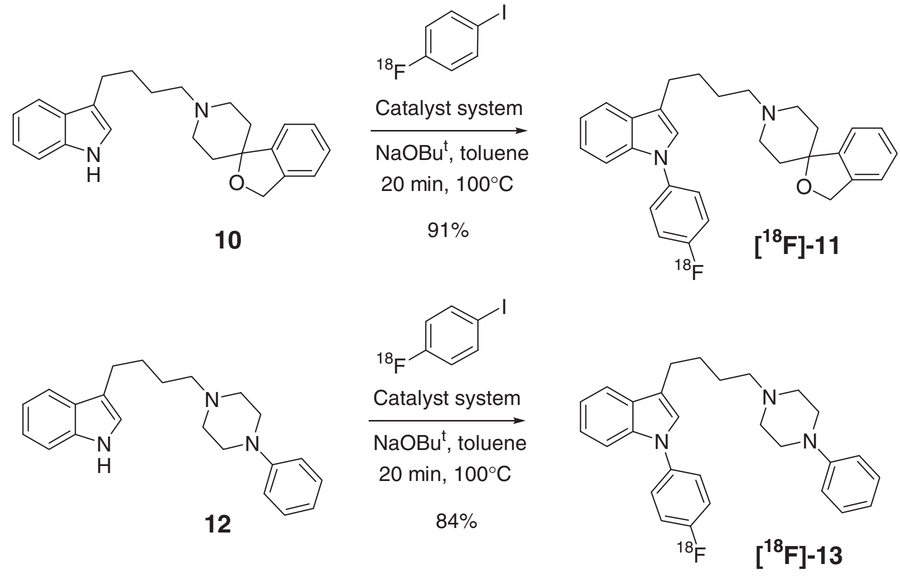


Figure 5. Synthesis of labelling precursors (10 and 12) and reference compounds (11 and 13). Reagents and conditions: (i) $LiAlH_4$, THF, 0°C-r.t.; (ii) MsCl, TEA, CH_2Cl_2, 0°C; (iii) 4-fluoroidobenzene, CuI, ZnO, K_2CO_3 NMP, 160°C; (iv) amine 8 or 9, Na_2CO_3, acetone, r.t.

The synthesis started with reduction of commercially available 4-(3-indolyl)-butyric acid **3** by means of $LiAlH_4$ to give the corresponding alcohol **4** in 57% yield. 4-(1*H*-Indol-3-yl)-1-butanol **4** was converted into methanesulfonate ester **6** followed by *N*-alkylation reactions with amines **8**[29] and **9** to give labelling precursors **10** and **12** in 59 and 67% yield, respectively, for the two steps. For the synthesis of reference compounds **11** and **13** alcohol **4** was subjected to an Ullmann arylation reaction with 4-fluoroiodobenzene to give 1-(4-fluorophenyl)-substituted compound **5**[4] in 44% yield prior to conversion into methanesulfonate ester **7**. *N*-alkylation was carried out using the same procedure as was used for the synthesis of labelling precursors **10** and **12** using amines **8**[29] and **9**. Following this procedure reference compounds **11** and **13** could be obtained in 52 and 62% yield relative to methanesulfonate ester **7**.

The radiolabelling of sigma-2 receptor ligands **[^{18}F]-11** and **[^{18}F]-13** via *N*-arylation with 4-[^{18}F]fluoroiodobenzene is depicted in Figure 6.



Catalyst system: $Pd_2(dba)_3$/2-(dicyclohexyl-phosphino)-2'-(N,N-dimethylamino)-biphenyl

Figure 6. Radiolabelling of σ_2 receptor ligands [^{18}F]-11 and [^{18}F]-13 via *N*-arylation with 4-[^{18}F]fluoroiodobenzene

Starting from labelling precursors **10** and **12** the desired compounds **[^{18}F]-11** and **[^{18}F]-13** could be obtained in excellent radiochemical yields of 91 and 84%, respectively, relative to 4-[^{18}F]fluoroiodobenzene.

In summary, we have developed a convenient radiolabelling method for the synthesis of 4-[^{18}F]fluorophenyl-substituted indoles via *N*-arylation with 4-[^{18}F]fluoroiodobenzene. Optimized reaction conditions were obtained by screening different catalyst systems, bases and solvents, and the effectiveness of the reaction was demonstrated by the radiosynthesis of two sigma-2 receptor ligands **[^{18}F]-11** and **[^{18}F]-13**. This novel radiosynthesis method further expands the arsenal of ^{18}F-labelled PET radiotracers to compounds exhibiting a 4-[^{18}F]fluorophenyl-substituted indole motif.

Experimental

General

^{1}H-NMR spectra were recorded on a Varian Inova-400 spectrometer at 400 MHz. Chemical shifts (δ) were determined relative to the solvent and converted to the TMS scale. Mass spectra were obtained on a Quattro/LC mass spectrometer (Micromass) by electrospray ionization. Flash chromatography was conducted according to Still *et al.*[30] using MERCK silica gel (mesh size 230–400 ASTM). Thin-layer chromatography (TLC) was performed on Merck silica gel F-254 plastic plates, with visualization under UV (254 nm).

All chemicals were obtained from commercial suppliers of reagent grade and used without further purification. 4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-butanol **5**[4] and amine **8**[29] were prepared according to literature procedures.

Chemical synthesis

4-(1H-Indol-3-yl)-1-butanol **4**. A suspension of indole **3** (2.5 g, 12.3 mmol) in THF (40 ml) was cooled to 0°C. $LiAlH_4$ (20 ml, 20 mmol, 1 M in THF) was added at such rate that the temperature was kept below 30°C. The reaction mixture was warmed up to room temperature and stirring continued for an additional 4 h. After cooling to 0°C water (20 ml) and 4 M NaOH (20 ml) were added carefully. The resulting suspension was filtered to remove inorganic salts. CH_2Cl_2 (100 ml) was added and the solution thoroughly washed with water. The CH_2Cl_2 layer was evaporated to yield 1.3 g (57%) of compound **4**, which was directly used without further purification. ^{1}H-NMR ($CDCl_3$) δ 1.66 (m, 2H, CH_2), 1.79 (m, 2H, CH_2), 2.80 (t, $J = 7.3$ Hz, 2H, CH_2), 3.66 (t, $J = 6.6$ Hz, 2H, CH_2), 6.94 (s, 1H), 7.13 (m, 1H, Ar-H), 7.20 (m, 1H, Ar-H), 7.33 (d, $J = 8.0$ Hz, 1H, Ar-H), 7.62 (d, $J = 7.8$ Hz, 1H, Ar-H), 8.10 (bs, 1H). LRMS (ESI positive) 190 [M + H].

General procedure for the synthesis of methansulfonates **6** *and* **7**. A solution of alcohol **4** or **5** (3.2 mmol) in CH_2Cl_2 (10 ml) was treated with triethylamine (0.7 ml) and methanesulfonylchloride (4.2 mmol) at 0°C. Stirring was continued for 30 min at 0°C and for one additional hour at room temperature. Water (25 ml) was added to the reaction mixture and the aqueous layer was extracted several times with CH_2Cl_2. After drying the organic layer the solvent was evaporated to give the desired methanesulfonate esters **6** or **7**, which were used without further purification.

4-(1H-Indol-3-yl)butyl Methanesulfonate **6**. Yield: 96%. ^{1}H-NMR ($CDCl_3$) δ 1.84 (m, 4H, CH_2), 2.82 (m, 2H, CH_2), 2.95 (s, 3H, CH_3), 4.24 (m, 2H, CH_2), 6.99 (s, 1H), 7.12 (m, 1H, Ar-H), 7.20 (m, 1H, Ar-H), 7.36 (d, J = 8.1 Hz, 1H, Ar-H), 7.59 (d, J = 7.7 Hz, 1H, Ar-H), 8.05 (bs, 1H). LRMS (ESI positive) 268 [M + H].

4-[1-(4-Fluorophenyl)-1H-Indol-3-yl]butyl methanesulfonate **7**. Yield: 92%. ^{1}H-NMR ($CDCl_3$) δ 1.89 (m, 4H, CH_2), 2.87 (m, 2H, CH_2), 2.98 (s, 3H, CH_3), 4.28 (m, 2H, CH_2), 7.10 (s, 1H), 7.16–7.24 (m, 4H, Ar-H), 7.43–7.48 (m, 3H, Ar-H), 7.66 (d, J = 7.0 Hz, 1H, Ar-H). LRMS (ESI positive) 362 [M + H].

General procedure for the N-alkylation of methansulfonates **6** *and* **7** *with amines* **8** *and* **9** *to give compounds* **10**, **11**, **12** *and* **13**. Amine **8**[29] or **9** (10 mmol) and Na_2CO_3 (4.7 mmol) were placed with water (2.5 ml) in a flask. Mesylate **6** or **7** in acetone (15 ml) was added to the amine/Na_2CO_3 slurry while stirring. The mixture was stirred overnight at 50°C. 10% $NaHCO_3$-solution was added and the mixture extracted with ethyl acetate. After removal of the solvent the residue was purified by flash-chromatography (10% MeOH/$CHCl_3$).

1′-[4-(1H-Indol-3-yl)-1-butyl]spiro[isobenzofuran-1(3H),4′-piperidine] **10**. Yield: 59%. ^{1}H-NMR ($CDCl_3$) δ 1.66 (m, 2H, CH_2), 1.76 (m, 4H, CH_2), 2.00 (td, J = 12.9, 4.2 Hz, 2H, CH_2), 2.38 (t, J = 10.9 Hz, 2H, CH_2), 2.48 (m, 2H, CH_2), 2.80 (t, J = 7.3 Hz, 2H, CH_2), 2.88 (m, 2H, CH_2), 5.07 (s, 2H, CH_2), 6.99 (s, 1H), 7.12 (m, 2H, Ar-H), 7.20 (m, 2H, Ar-H), 7.27 (m, 2H, Ar-H), 7.36 (d, J = 8.1 Hz, 1H, Ar-H), 7.59 (d, J = 7.7 Hz, 1H, Ar-H), 7.98 (bs, 1H). LRMS (ESI positive) 361 [M + H].

1′-[4-[1-(4-Fluorophenyl)-1H-indol-3-yl]-1-butyl]spiro[isobenzofuran-1(3h),4′-piperidine] **11**. Yield: 52%. ^{1}H-NMR ($CDCl_3$) δ 1.71 (m, 2H, CH_2), 1.79 (m, 4H, CH_2), 2.05 (m, 2H, CH_2), 2.42 (m, 2H, CH_2), 2.51 (m, 2H, CH_2), 2.85 (t, J = 7.0 Hz, 2H, CH_2), 2.91 (m, 2H, CH_2), 5.07 (s, 2H, CH_2), 7.10 (s, 1H), 7.15 (m, 1H, Ar-H), 7.17 (m, 1H, Ar-H), 7.18–7.22 (m, 4H, Ar-H), 7.26–7.29 (m, 2H, Ar-H), 7.43–7.47 (m, 3H, Ar-H), 7.66 (d, J = 7.3 Hz, 1H). LRMS (ESI positive) 455 [M + H].

3-[4-(4-Phenyl-1-piperazinyl)-1-butyl]-1H-indole **12**. Yield: 67%. ^{1}H-NMR ($CDCl_3$) δ 1.68 (m, 2H, CH_2), 1.80 (m, 2H, CH_2), 2.48 (m, 2H, CH_2), 2.64 (m, 4H, CH_2), 2.83 (t, J = 7.3 Hz, 2H, CH_2), 3.24 (m, 4H, CH_2), 6. 89 (t, J = 7.3 Hz, 1H, Ar-H), 6.96 (m, 2H, Ar-H), 6.97 (s, 1H), 7.15 (m, 1H, Ar-H), 7.21 (m, 1H, Ar-H), 7.65 (d, J = 7.7 Hz, 1H), 8.13 (bs, 1H). LRMS (ESI positive) 334 [M + H].

1-(4-Fluorophenyl)-3-[4-(4-phenyl-1-piperazinyl)-1-butyl]-1H-indole **13**. Yield: 62%. ^{1}H-NMR ($CDCl_3$) δ 1.71 (m, 2H, CH_2), 1.80 (m, 2H, CH_2), 2.52 (m, 2H, CH_2), 2.67 (m, 4H, CH_2), 2.85 (t, $J = 6.9$ Hz, 2H, CH_2), 3.28 (m, 4H, CH_2), 6.88 (t, $J = 7.3$ Hz, 1H, Ar-H), 6.94 (m, 2H, Ar-H), 7.10 (s, 1H), 7.15–7.22 (m, 4H, Ar-H), 7.26–7.29 (m, 2H, Ar-H), 7.43–7.47 (m, 3H, Ar-H), 7.65 (d, $J = 7.7$ Hz, 1H, Ar-H). LRMS (ESI positive) 428 [M + H].

Radiochemical synthesis

No-carrier-added aqueous [^{18}F]fluoride ion was produced in a IBA CYCLONE 18/9 cyclotron by irradiation of [^{18}O]H_2O via the ^{18}O(p,n)^{18}F nuclear reaction. Synthesis of 4-[^{18}F]fluoroiodobenzene was performed in an automated nucleophilic fluorination module (Nuclear Interface, Münster) as described by Wüst and Kniess.[12,13]

Radio-HPLC analyses were carried out with a SUPELCOSIL LC-18S column (4.6 × 250 mm, 5 μm) column using an indicated isocratic eluent (CH_3CN/0.1 M NH_4-formiate) from a gradient pump L2500 (Merck, Hitachi) with a flow rate of 1 ml/min. The products were monitored by an UV detector L4500 (Merck, Hitachi) at 254 nm and by γ-detection with a scintillation detector GABI (X-RAYTEST).

Optimization of N-arylation of indole **1** *with 4-[^{18}F]fluoroiodobenzene via copper-mediated reaction (entries 1–4)*

To a vial containing indole **1** (7 mg, 60 μmol), CuI (3 mg, 15 μmol), 1,2-diamine (5 μl) and K_3PO_4 (10 mg, 47 μmol) in THF or toluene (0.5 ml) was added 4-[^{18}F]fluoroiodobenzene (15–35 MBq in 0.5 ml of toluene). The sealed reaction vial was heated at 100°C for 30 min. Aliquots (50 μl) were taken and after dilution with acetonitrile the samples were subjected to radio-HPLC analysis.

Optimization of N-arylation of indole **1** *with 4-[^{18}F]fluoroiodobenzene via palladium-mediated reactions (entries 5–15)*

To a vial containing indole **1** (7 mg, 60 μmol), $Pd_2(dba)_3$ (3 mg, 15 μmol), phosphine ligand (5 mg), the base (10 mg) in THF, DMF or toluene (0.5 ml) was added 4-[^{18}F]fluoroiodobenzene (15–35 MBq in 0.5 ml of THF, DMF or toluene). The sealed reaction vial was heated (65, 100 and 140°C) for 10, 20, 30 or 60 min. Aliquots (50 μl) were taken and after dilution with acetonitrile the samples were subjected to radio-HPLC analysis.

1-(4-[^{18}F]Fluorophenyl)-1H-indole **[^{18}F]-2**. HPLC-analysis: CH_3CN/0.1 M NH_4-formiate (70/30), $t_R = 6.8$ min.

Radiosynthesis of 1′-[4-[1-(4-[^{18}F]Fluorophenyl)-1H-indol-3-yl]-1-butyl]spiro[iso-benzofuran-1(3H),4′-piperidine] **[^{18}F]-11** *and 1-(4-[^{18}F]fluorophenyl)-3-[4-(4-phenyl-1-piperazinyl)-1-butyl]-1H-indole* **[^{18}F]-13** *using optimized reaction conditions*

To a vial containing labelling precursors **10** or **12** (7 mg), $Pd_2(dba)_3$ (4 mg, 3.75 μmol), $NaOBu^t$ (9 mg, 83 μmol) and 2-(dicyclohexyl-phosphino)-2′-(*N*,*N*-di-methylamino)-biphenyl (3 mg, 7.6 μmol) in 0.5 ml of toluene was added 4-[^{18}F]fluoroiodobenzene (50 MBq in 0.5 ml toluene). The sealed reaction vial was heated at 65°C for 20 min and aliquots (50 μl) were taken for radio-HPLC analysis after dilution with acetonitrile.

1′-[4-[1-(4-[^{18}F]Fluorophenyl)-1H-Indol-3-yl]-1-butyl]spiro[isobenzofuran-1(3H), 4′-piperidine] **[^{18}F]-11**. Yield: 91% (relative to 4-[^{18}F]fluoroiodobenzene). HPLC-analysis: CH_3CN/0.1 M NH_4-formiate (70/30), $t_R = 9.6$ min.

1-(4-[^{18}F]Fluorophenyl)-3-[4-(4-phenyl-1-piperazinyl)-1-butyl]-1H-indole [^{18}F]-13. Yield: 84% (relative to 4-[^{18}F]fluoroiodobenzene). HPLC-analysis: CH_3CN/0.1 M NH_4-formiate (70/30), $t_R = 10.3$ min.

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References

1. Andersen K, Liljefors T, Hyttel J, Perregaard J. *J Med Chem* 1996; **39**: 3723–3738.
2. Spadoni G, Balsamini C, Bedini A, Diamantini G, Di Giacomo B, Tontini A, Tarzia G, Mor M, Plazzi PV, Rivara S, Nonno R, Pannacci M, Lucini V, Fraschini F, Stankov BM. *J Med Chem* 1998; **41**: 3624–3634.
3. Stabler SR, Jahangir. *Synth Commun* 1994; **24**: 123–127.
4. Perregaard J, Moltzen EK, Meier E, Sanchez C. *J Med Chem* 1995; **38**: 1998–2008.
5. Sanchez C, Arnt J, Costall B, Kelly ME, Meier E, Naylor RJ, Perregaard J. *J Pharmacol Exp Ther* 1997; **283**: 1323–1332.
6. Su TP. *Eur J Biochem* 1991; **200**: 633–642.
7. Crawford KW, Bowen WD. *Cancer Res* 2002; **62**: 313–322.
8. Vilner BJ, John CS, Bowen WD. *Cancer Res* 1995; **55**: 408–413.
9. Wheeler KT, Wang LM, Wallen CA, Childers SR, Cline JM, Keng PC, Mach RH. *Br J Cancer* 2000; **82**: 1223–1232.
10. McCarthy TJ, Schwarz SW, Welch MJ. *J Chem Educ* 1994; **71**: 830–836.
11. Langström B, Kihlberg T, Bergström M, Antoni G, Björkman M, Forngren BH, Forngren T, Hartvig P, Markides K, Yngve U, Ögren M. *Acta Chem Scand* 1999; **53**: 651–669.

12. Wüst F, Kniess T. *J Label Compd Radiopharm* 2003; **46**: 699–713.
13. Wüst F, Kniess T. *J Label Compd Radiopharm* 2004; **47**: 457–468.
14. Allain-Barbier L, Lasne MC, Perrio-Huard C, Moreau B, Barré L. *Acta Chem Scand* 1998; **52**: 480–489.
15. Forngren T, Andersson Y, Lamm B, Langström B. *Acta Chem Scand* 1998; **52**: 475–479.
16. Marriére E, Rouden J, Tadino V, Lasne MC. *Org Lett* 2000; **2**: 1121–1124.
17. Marriére E, Chazalviel L, Dhilly M, Toutain J, Perrio C, Dauphin F, Lasne MC. *J Label Compd Radiopharm* 1999; **42**: S69–S71.
18. Mann G, Hartwig JF, Driver MS, Fernandez-Rivas C. *J Am Chem Soc* 1998; **120**: 827–828.
19. Wolfe JP, Wagaw S, Marcoux J-F, Buchwald SL. *Acc Chem Res* 1998; **31**: 805–818.
20. Wolfe JP, Tomori H, Sadighi JP, Yin J, Buchwald SL. *J Org Chem* 2000; **65**: 1158–1174.
21. Urgaonkar S, Nagarajan M, Verkade JGL. *J Org Chem* 2003; **68**: 452–459.
22. Old DW, Harris MC, Buchwald SL. *Org Lett* 2000; **2**: 1403–1406.
23. Grasa GA, Viciu MS, Huang J, Nolan SP. *J Org Chem* 2001; **66**: 7729–7737.
24. Antilla JC, Klapars A, Buchwald SL. *J Am Chem Soc* 2002; **124**: 11684–11688.
25. Klapars A, Antilla JC, Huang X, Buchwald SL. *J Am Chem Soc* 2001; **123**: 7727–7729.
26. Kranenburg M, van der Burgt YEM, Kamer PCJ, van Leuwen PWNM. *Organòmetallics* 1995; **14**: 3081–3089.
27. Yin J, Buchwald SL. *J Am Chem Soc* 2002; **124**: 6043–6048.
28. Wolfe JP, Tomori H, Sadighi JP, Yin J, Buchwald SL. *J Org Chem* 2000; **656**: 1158–1174.
29. Kubota H, Fujii M, Ikeda K, Takeuchi M, Shibanuma T, Isomura Y. *Chem Pharm Bull* 1998; **46**: 351–354.
30. Still WC, Kahn M, Mitra A. *J Org Chem* 1978; **43**: 2923–2925.
31. Phelps ME. *Proc Natl Acad Sci* 2000; **97**: 9226–9233.