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Synthesis, labelling and first evaluation of [^{18}F]R91150 as a serotonin 5-HT$_{2A}$ receptor antagonist for PET

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In psychiatric disorders such as anxiety, depression and schizophrenia, 5-HT$_{2A}$ receptors play an important role. In order to investigate them *in vivo* there is an increasing interest in selective and high-affinity radioligands for receptor binding studies using positron emission tomography (PET). Since available radioligands have disadvantages, R91150, which is a selective and high-affinity ligand for 5-HT$_{2A}$ receptors, was labelled with fluorine-18. This was accomplished in six steps via 4-[^{18}F]fluorophenol and 1-(3-bromopropoxy)-4-[^{18}F]fluorobenzene within 190 min starting from no-carrier-added [^{18}F]fluoride. The overall radiochemical yield was 3.8 ± 2% and the specific activity was at least 335 GBq/μmol at the end of the synthesis. First *ex vivo* studies in mice proved the uptake of [^{18}F]R91150 in the brain. Radiometabolite studies revealed no radiometabolites in the brain, whereas in the plasma at least two could be detected 30 min p.i. Further preclinical studies are encouraged to evaluate the potential of this new 5-HT$_{2A}$ ligand as a radiotracer for PET.

Keywords: radiofluorination; 4-[^{18}F]fluorophenol; [^{18}F]R91150; 5-HT$_{2A}$ antagonist; PET

Introduction

Serotonin (5-HT) receptors supposedly play a major role in normal human functions such as sleep and appetite. Dysfunctions in serotonergic transmission, mostly of the 5-HT$_{2A}$ receptor, have been implicated in a great deal of human brain disorders such as anxiety, depression, Alzheimer's disease and schizophrenia.[1–3] For studying the role of those receptors in physiology and pharmacology, there is an increasing interest in high-affinity and selective radiolabelled ligands for *in vivo* receptor binding studies using positron emission tomography (PET) or single photon emission computer tomography (SPECT). For this purpose several radiotracers are being used, among others [^{11}C]MDL 100907 and [^{18}F]altanserin for PET and 5-[^{123}I]I-R91150 for SPECT (cf. Figure 1).

Both MDL 100907 and altanserin bind to the 5-HT$_{2A}$ receptor with high affinity. MDL 100907 exhibits a K_i value of 0.2 nM[4] and a K_D value of 0.56 nM (using [^{3}H]MDL 100907),[5] while altanserin has a K_i of 0.13 nM[6] and a K_D of 0.3 nM.[7] Binding to other 5-HT receptor subtypes is very low for MDL 100907[5] and moderate to low for altanserin.[7] While binding of MDL 100907 to receptors outside the serotonergic system, such as dopaminergic or α-adrenergic receptors, is negligible,[8] this is not the case for altanserin. It shows a relatively high affinity for D_2 (62 nM) and especially for adrenergic-α_1 receptors (4.55 nM).[6,9] Another disadvantage of altanserin is the formation of at least four different metabolites in humans, which may cross the blood–brain-barrier.[9] A shortcoming of [^{11}C]MDL 100907, however, is the short half-life of carbon-11 (20.4 min), which not only requires the availability of a cyclotron on site of the PET scanner but may also impair to achieve a state of reversible binding.[7,10] This should not be a problem with the half-life of fluorine-18 as 109.7 min. In summary, [^{11}C]MDL 100907 is a very specific high-affinity ligand for 5-HT$_{2A}$ receptors with the only disadvantage of the short half-life of carbon-11, while the binding of [^{18}F]altanserin lacks specificity, but due to its availability it is commonly used for 5-HT$_{2A}$ imaging.

For SPECT studies 5-[^{123}I]I-R91150 has been developed. With a K_i value of 0.2 nM and a K_D value of 0.11 nM,[11] it also shows high affinity to 5-HT$_{2A}$ receptors. Its selectivity with regard to other 5-HT receptor subtypes and different receptors is at least a factor of 50 higher.[11–13] Only IC_{50} values and no K_i values are reported[13] for binding affinities to all receptors other than 5-HT$_{2A}$, which makes a direct comparison with altanserin and MDL 100907 difficult. However, MDL 100907 has at least a 300-fold lower affinity for any other receptor type,[8] while for altanserin the selectivity is better or comparable to 5-[^{123}I]I-R91150.[6,9] The radioiodinated compound exhibits rather high non-specific binding and combined with the disadvantages of SPECT vs PET it appears to be a less suitable ligand for 5-HT$_{2A}$ imaging.

The parent compound of 5-[^{123}I]I-R91150 does not bear an iodine atom but does contain a fluorine atom. In a comparative study, the original R91150 exhibited an IC_{50} value of 0.18 vs 0.60 nM of the iodinated compound[13] and has therefore a high affinity for 5-HT$_{2A}$ receptors. A comparison of both compounds

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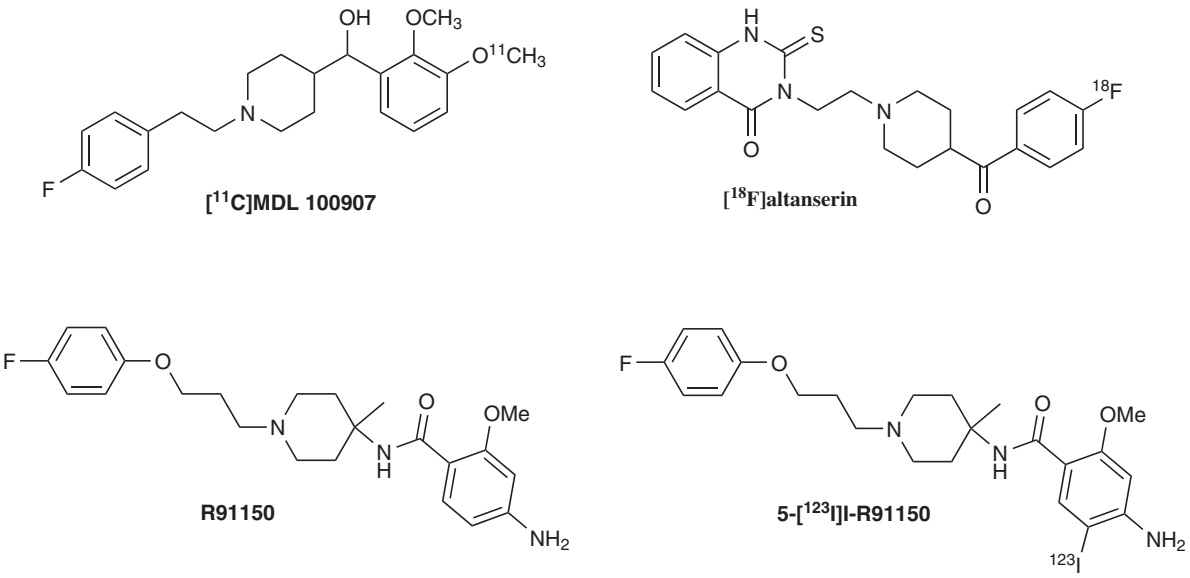

Figure 1. 5-HT_{2A} receptor antagonists.

with regard to binding to other receptors is very favorable for the parent compound.[13] Further, due to its lower lipophilicity less non-selective binding can be expected. Thus, in order to use the advantages of fluorine-18 for PET studies R91150 was radiofluorinated expecting a highly selective ligand with high affinity for 5-HT_{2A} receptors.

The non-labelled compound R91150 as well as the labelling precursors were synthesized. While part of this study was published as an abstract,[14] we report here on the synthetic strategy for labelling of [^{18}F]R91150 via n.c.a. 4-[^{18}F]fluorophenol and on preliminary preclinical data, such as lipophilicity, blood–brain-barrier penetration and metabolism.

Results and discussion

Chemistry

For evaluation studies and the determination of appropriate high-performance liquid chromatography (HPLC) conditions for the identification of radiolabelled compounds, the standard compound R91150 had to be synthesized as well as the corresponding labelling precursors and standard compounds of intermediates occurring in the labelling process. The general synthesis of R91150 as well as of different derivatives such as, for example, 5-I-R91150 is described in a patent by Leysen and Van Daele.[13] However, some reaction steps leading to R91150 could not be reproduced and modifications or even different reactions had to be employed. The total synthesis of R91150 was performed here as depicted in Scheme 1.

In a first step commercially available N-benzyl-piperid-4-one was reacted with methyllithium to get 1-benzyl-4-methyl-piperidin-4-ol (**1**) similar to the literature procedure.[15] As described,[16,17] **1** was converted with acetonitrile and concentrated sulfuric acid to the acetamide derivative N-(1-benzyl-4-methylpiperidin-4-yl)acetamide (**2**) in a Ritter reaction. The next step was deprotection at the nitrogen of the piperidine ring. Because of easier handling debenzylation was conducted using ammonium formate and palladium black instead of hydrogen gas and palladium-on-charcoal (10%) as described earlier.[13] The free base (4-methylpiperidin-4-yl)acetamide (**3**) was directly N-alkylated to N-[1-(3-(4-fluorophenoxy)propyl)-4-methyl-4-piperidinyl]acetamide (**5**) with 1-(3-bromopropoxy)-4-fluorobenzene (**4**) without prior purification. The latter was previously prepared by alkylation of 4-fluorophenol with 1,3-dibromopropane in a 4 M sodium hydroxide solution similar to the literature procedure.[18] The bromo-derivative **4** was preferred over the earlier used 1-(3-chloropropoxy)-4-fluorobenzene[13] because of its greater reactivity in nucleophilic substitutions. For the alkylation at the piperidine NH-group, potassium carbonate and potassium iodide were added and **5** was obtained in a moderate yield of 26%. Lithium hydride for deprotonation of the piperidine NH-group showed no improvement.

For the formation of the benzamide part of R91150, a free amino-group at the 4-position of the piperidine ring was necessary. Similar to the literature procedure,[16] the acetamide **5** was cleaved with concentrated hydrochloric acid at 100°C for 72 h instead of 24 h[13] to get 1-(3-(4-fluorophenoxy)propyl)-4-methylpiperidin-4-amine (**6**). Earlier its condensation to the benzamide was achieved by activating the respective 4-aminobenzoic acid with ethyl chloroformate as a mixed acid anhydride and its subsequent reaction with **6**.[13] However, applying this procedure using 4-amino-2-methoxybenzoic acid, 4-(ethoxycarbonylamino)-2-methoxybenzoic acid was obtained. The mixed acid anhydride was not formed and therefore the subsequent amidation to **6** could not take place. This result is understandable because the amino function is more reactive than the acid function.

In order to avoid an unprotected amino-group on the benzoic acid, a benzamide formation to N-[1-(3-(4-fluorophenoxy)propyl)-4-methyl-piperidin-4-yl]-2-methoxy-4-nitrobenzamide (**7**) was carried out with 2-methoxy-4-nitrobenzoic acid instead, which is commercially available. Furthermore, rather than the formation of the mixed acid anhydride for activation, (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) was used as the coupling reagent. PyBOP is utilized in peptide chemistry and does not form a toxic by-product like (benzotriazol-1-yloxy)tri(dimethylamino)phosphonium hexafluorophosphate (BOP).[19] Using this reaction pathway, **7** was almost quantitatively achieved. However, it could not be

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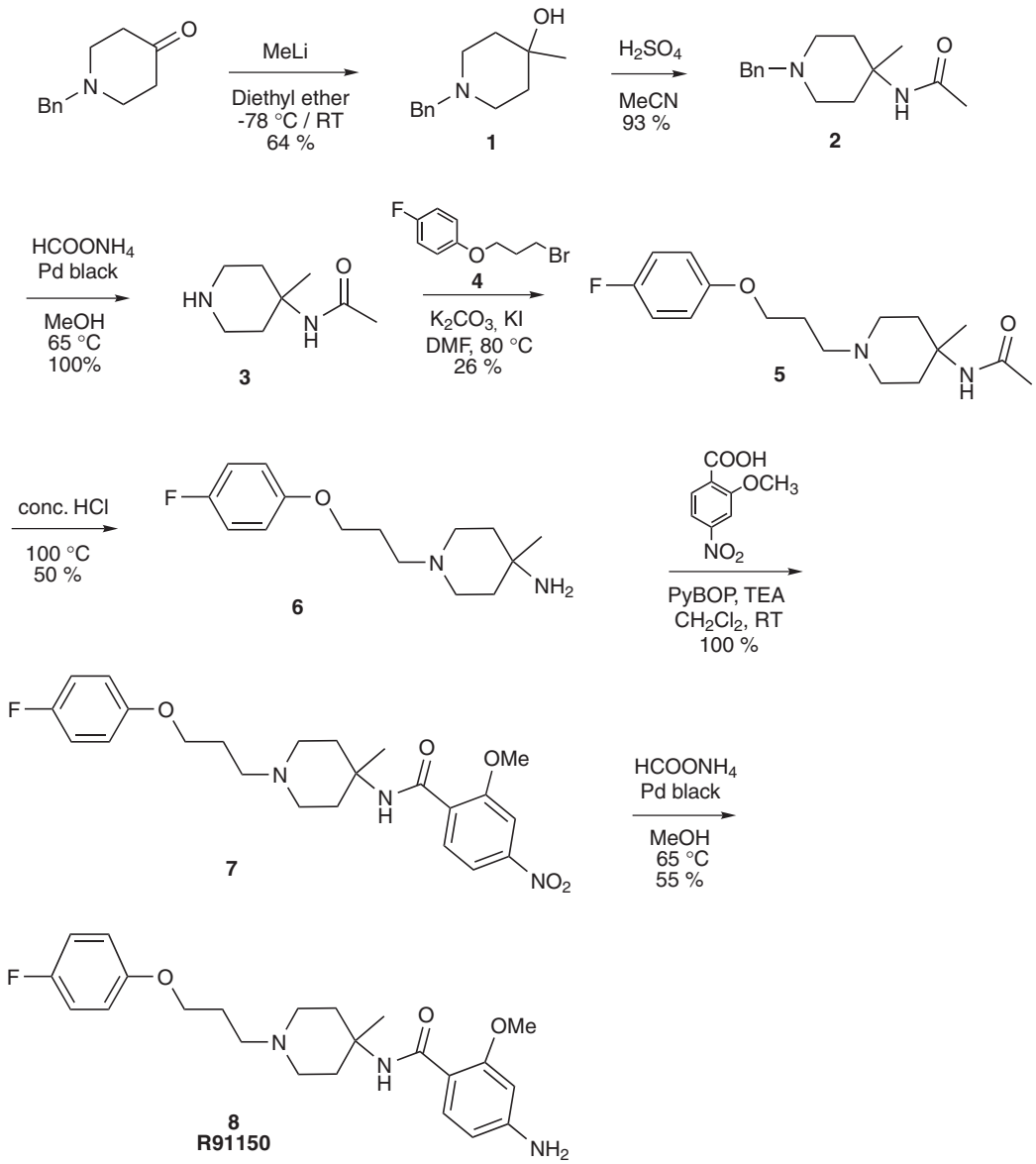

Scheme 1. Synthesis of R91150.

obtained without small impurities from pyrrolidine derivatives after purification by column chromatography, but those could be removed after the next reaction step. Finally the nitro-group in 4-position of the benzamide part was reduced with ammonium formate and palladium black in methanol. Purification gave 4-amino-N-[1-(3-(4-fluorophenoxy)propyl)-4-methylpiperidin-4-yl]-2-methoxy-benzamide (**8**), also known as R91150.

In order to get the labelling precursor and non-radioactive standard compounds of intermediates of the labelling process, a slightly different and more universally applicable concept was chosen to avoid possible side reactions. Instead of primary alkylation at the nitrogen of the piperidine ring, first the formation of the benzamide part was conducted (cf. Scheme 2). For labelling with fluorine-18 it is essential that all functional groups containing acidic protons are derivatized by a suitable protection group. For protection of the amino-group at the benzamide part, the *tert*-butoxycarbonyl (Boc) group was chosen because it is easily cleaved under acidic conditions.[20]

Starting with compound **2** cleavage of the acetamide bond with concentrated hydrochloric acid gave 1-benzyl-4-methylpiperidin-amine (**9**) similar to the literature procedure.[17] For the benzamide formation, 4-(*tert*-butoxycarbonylamino)-2-methoxybenzoic acid (**10**) was synthesized by reducing the nitro-group of commercially available 2-methoxy-4-nitrobenzoic acid with ammonium formate and palladium-on-charcoal (10%).[21] Then the amino-group was protected with di-*tert*-butyl dicarbonate providing the intermediate **10**. The formation of *tert*-butyl 4-(1-benzyl-4-methylpiperidin-4-ylcarbamoyl)-3-methoxyphenylcarbamate (**11**) was achieved similar to the synthesis of **7**. As described above, this compound was also contaminated with pyrrolidine derivatives, but used without further purification in the next reaction step. For getting the free NH-function at the piperidine ring, debenzylation of **11** was performed as described for **3** using ammonium formate and palladium black. Thus, with *tert*-butyl 3-methoxy-4-(4-methylpiperidin-4-ylcarbamoyl)phenylcarbamate (**12**) a versatile usable precursor was obtained.

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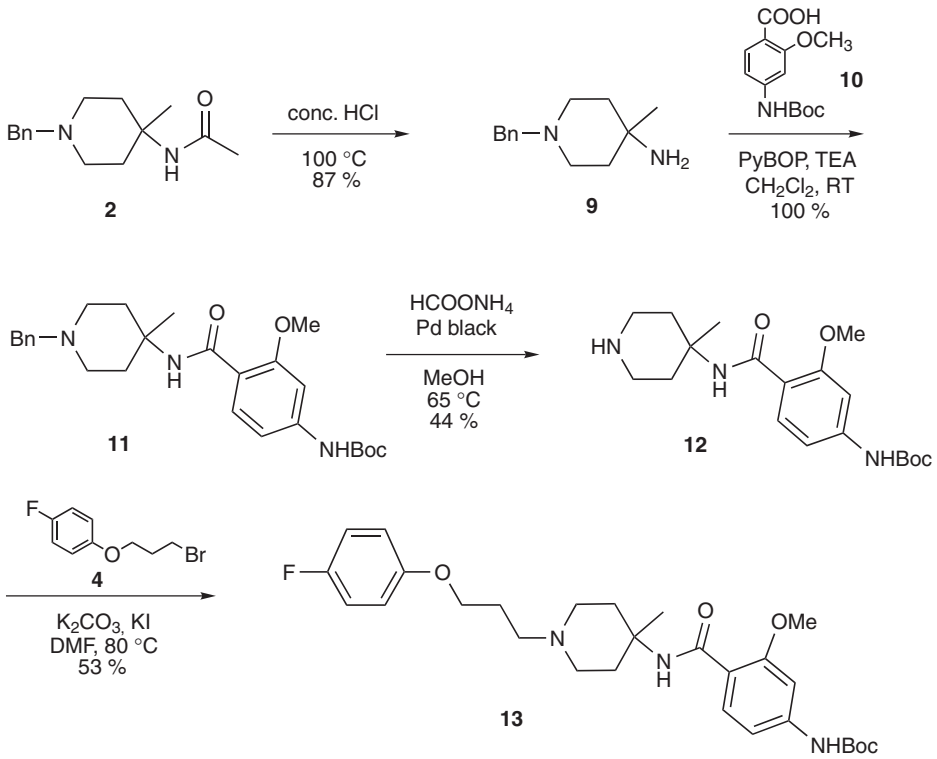

Scheme 2. Syntheses of labelling precursors and standard compounds of R91150.

It proved useful for the alkylation with different phenolarylethers as well as for radioactive labelling using 4-[^{18}F]fluorophenol (**[^{18}F]14**). Reaction of **12** with 1-(3-bromopropoxy)-4-fluorobenzene (**4**) gave the N-Boc protected derivative *tert*-butyl 4-(1-(3-(4-fluorophenoxy)propyl)-4-methylpiperidin-4-ylcarbamoyl)-3-methoxyphenylcarbamate (**13**) in 53% yield, an intermediate of the radiofluorination process. In contrast to the alkylation of (4-methylpiperidin-4-yl)acetamide (**3**), which gave only moderate yields independent of the base used for deprotonation, the nucleophilic substitution of different bromopropyl derivatives with **12** gave good to excellent results.

Since the radiofluorination of R91150 via the synthesis of 4-[^{18}F]fluorophenol (**[^{18}F]14**) as a secondary labelling precursor is a possible way, N,N,N-trimethyl-4-(4-(trifluoromethyl)benzoyl)-phenylammonium trifluoromethylsulfonate (**15**) was prepared, which was shown to be the best precursor for its formation.[22] The preparation was conducted exactly as described earlier[22] aside from the first reaction step to (4-fluorophenyl)-(4-(trifluoromethyl)phenyl)methanone, for which a commercially available fluorophenylmagnesium bromide solution in THF was reacted with 4-trifluoromethylbenzonitrile.

Radiochemistry

For the radiosynthesis of R91150 different synthetic strategies are conceivable. Generally, it is desirable to have only a few radioactive reaction steps. However, given the half-life of fluorine-18 (109.7 min) it is in fact possible to conduct several radioactive reaction steps. This became necessary here since a direct [^{18}F]fluoro-for-nitro exchange on the precursor *tert*-butyl 4-(1-(3-(3-formyl-4-nitrophenoxy)propyl)-4-methylpiperidin-4-ylcarbamoyl)-3-methoxyphenylcarbamate for labelling of R91150 was not successful. Therefore, the more complex labelling procedure via 4-[^{18}F]fluorophenol (**[^{18}F]14**) as a secondary labelling precursor was chosen (cf. Scheme 3).

The preparation of 4-[^{18}F]fluorophenol (**[^{18}F]14**) was adopted from Ludwig *et al.*[22] reproducibly obtaining an overall radiochemical yield (RCY) of 50–69% with a very good radiochemical purity of $>$98% for isolated **[^{18}F]14**. By optimization the overall reaction time for synthesis of **[^{18}F]14** could be reduced by 10–50 min and because all reactions were conducted at the same temperature handling of the procedure was simplified.

The next step on the way to [^{18}F]R91150 (**[^{18}F]8**) was the synthesis of 1-(3-bromopropoxy)-4-[^{18}F]fluorobenzene (**[^{18}F]4**), a compound also described in the literature.[22] The obtained sodium 4-[^{18}F]fluorophenolate was reacted with 1,3-dibromopropane in a two-phase system (sodium hydroxide solution/2-butanone). In HPLC analysis the formation of four different products besides **[^{18}F]4** was observed. One of them was identified as the elimination product 1-(allyloxy)-4-[^{18}F]fluorobenzene (HPLC (condition II, see 'Materials and methods'): $k' = 3.35$), which was formed in varying amounts between 2 and 15%. The yield of **[^{18}F]4** was quite irreproducible under identical reaction conditions (30–80%). The only dependence observed was that reaction times above 20 min resulted in lower yields. For further reaction **[^{18}F]4** had to be purified and isolation by HPLC afforded an RCY of 19–40% (relative to **[^{18}F]14**) and a radiochemical purity of $>$99%.

In order to avoid the time-consuming effort of a HPLC isolation of **[^{18}F]4**, first attempts of an alkylation of the piperidine derivative **12** were made with the non-purified radiofluorinated compound. A great deal of different bases, organic as well as inorganic, were used for deprotonation of **12** with or without the addition of potassium iodide. Whatever base was used, however, the RCY of *tert*-butyl 4-(1-(3-(4-fluorophenoxy)propyl)-4-methylpiperidin-4-ylcarbamoyl)-3-methoxyphenylcarbamate (**[^{18}F]13**) was

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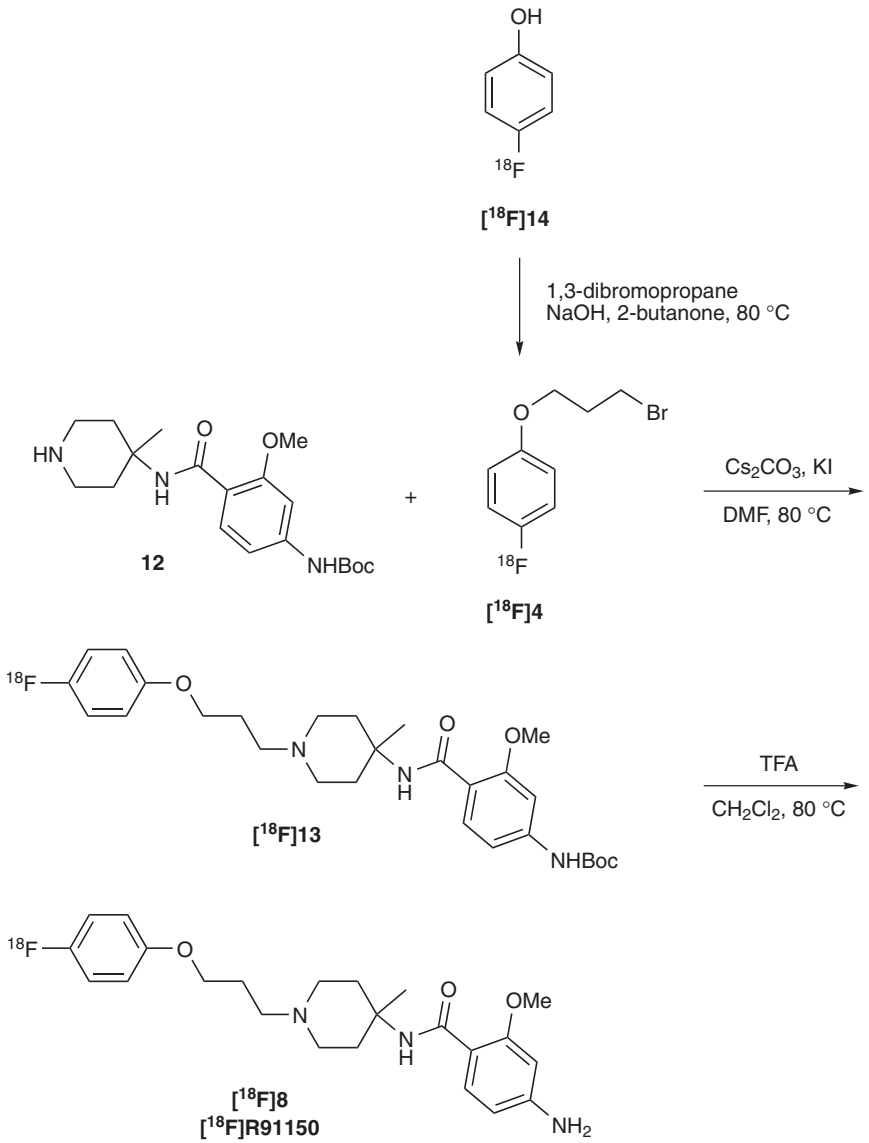

Scheme 3. Radiosynthesis of [^{18}F]R91150 via 4-[^{18}F]fluorophenol and 1-(3-bromopropoxy)-4-[^{18}F]fluorobenzene.

only about 5% as determined by HPLC analysis. However, the use of cesium carbonate/potassium iodide increased the yield to 12% after 10 min reaction time. Raising the reaction temperature above 80°C did not result in higher yields but had a contrary effect.

Because of the very moderate yields the alkylation reaction was then attempted with purified **[^{18}F]4**. In the presence of cesium carbonate/potassium iodide, alkylation resulted in an RCY of 48–68% of **[^{18}F]13** as determined by HPLC analysis (condition I: $k' = 6.24$). This compound was not isolated but deprotected similar to the literature procedure[23] using trifluoroacetic acid (TFA) with almost quantitative yield. Isolation by reversed-phase HPLC gave [^{18}F]R91150 (**[^{18}F]8**) in an RCY of 34–38% (relative to **[^{18}F]4**) with a very good radiochemical purity of >99%. The overall reaction time starting from [^{18}F]fluoride was 190 min and the overall RCY was 1.8–5.7%. [^{18}F]R91150 (**[^{18}F]8**) was obtained with specific activities of at least 335 GBq/μmol end of synthesis as appraised by HPLC using a UV mass calibration curve of non-radioactive R91150 (**8**) for the determination of the carrier content. Even though such a complex reaction procedure including six radioactive steps is not desirable, a reliable radiosynthesis of [^{18}F]R91150 was repetitively possible and sufficient to perform first preclinical evaluation experiments.

Lipophilicity

Using the HPLC method corresponding to the OECD guideline for the testing of chemicals,[24] the lipophilicity of R91150 as well as of altanserin and MDL 100907 was determined. Table 1 gives the $\log D_{7.4}$ values, calculated from HPLC retention times, and a comparison with the available literature data. A comparison of k' values of 5-I-R91150 and R91150 (8 and 2.5, respectively, on a reversed-phase column)[12] is in agreement with a calculation[26] of a 1.27 units higher $\log P$ value for the iodinated analogue; i.e. the original compound is more than 10-fold less lipophilic, suggesting the possibility of lower non-specific binding. The $\log D_{7.4}$ value of 2.53 for R91150 determined here is comparable to MDL 100907, beneficial for its use *in vivo*.

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Table 1. Log $D_{7.4}$ values determined by HPLC and comparison with the literature values

Compound	Log $D_{7.4}$[a]	Literature log *P*
R91150	2.53	–
Altanserin	3.08	3.5[7]
MDL 100907	1.99	1.9–3.8[7,10,25]

[a]SD < 3%.

Biological evaluation

For the affinity as well as the selectivity of R91150 as a 5-HT_{2A} ligand, IC_{50} values are available from the literature.[13] Comparison with 5-I-R91150, which is used as a SPECT ligand, promises better *in vivo* properties for the original compound. Therefore, we conducted first *ex vivo* studies with radiolabelled [^{18}F]R91150 in mice in order to determine the uptake into the brain and the stability of the tracer.

Ex vivo biodistribution

In first studies the *ex vivo* biodistribution of [^{18}F]R91150 (**[^{18}F]8**) in female Navel Medical Research Institute (NMRI) mice was evaluated 30 and 60 min post injection. Brain uptake was 0.54 ± 0.27% ID/g (30 min p.i.) and 1.09 ± 0.17% ID/g (60 min p.i.). The brain to plasma activity ratio, which is a very important factor for possible PET applications, increased from 1.50 (30 min p.i.) to 2.64 (60 min p.i.).

Radiometabolites of [^{18}F]R91150

In addition to the *ex vivo* tissue distribution, the stability of [^{18}F]R91150 (**[^{18}F]8**) in the plasma and the brain of mice 30 min p.i. was examined. Use of acetonitrile as an extraction solvent for the plasma samples ($n = 11$) and the brain homogenates ($n = 2$) resulted in 96 ± 4 and 100 ± 6% recovery of radioactivity, respectively. In plasma, unchanged [^{18}F]R91150 ($R_f = 0.60$) accounted for 64% of the measured radioactivity at that time point. At least two radiometabolites were detected with R_f values of 0.84 and 0.96, indicating their higher polarity, which amounted to 20 and 14% of radioactivity measured in the plasma, respectively. This is a faster metabolism than that of 5-[^{123}I]I-R91150 in man where nearly 80% of the tracer was found unmetabolized in the plasma even after 8 h using radio-HPLC analysis.[27] However, metabolite analysis of 5-[^{123}I]I-R91150 in baboons showed rapid decomposition of the tracer in the plasma, leaving only 24 ± 10% of intact compound 120 min p.i.[28] In the mouse brain, intact [^{18}F]R91150 (**[^{18}F]8**) accounted for > 98% of the radioactivity, indicating that up to 30 min no labelled radiometabolites crossed the blood–brain barrier or were formed in the brain.

Thus, first *ex vivo* studies of [^{18}F]R91150 confirm sufficient *in vivo* uptake into the brain without interference from radiometabolites.

Materials and methods

General

The chemicals were analytical grade or better and were used without further purification (Sigma-Aldrich, Steinheim, Germany). Sep-Pak plus C18, Alumina N and Oasis HLB 1 cc cartridges were purchased from Waters (Eschborn, Germany) and LiChrolut RP-18e cartridges from Merck (Darmstadt, Germany). Analytical TLC was performed on aluminum-backed sheets (Silica gel 60 F_{254}) unless otherwise noted and normal-phase column chromatography was performed using Silica gel 60, both from Merck.

HPLC was performed on the following system from Dionex (Idstein, Germany): an Ultimate 3000 LPG-3400A HPLC pump, an Ultimate 3000 VWD-3100 UV/VIS detector (272 nm), a UCI-50 chromatography interface, an injection valve P/N 8215, analysis of HPLC data with Chromeleon 6.80 software; radioactivity was detected with a Gabi Star NaI(Tl) radioactivity detector from Raytest (Straubenhardt, Germany).

Reversed-phase HPLC was carried out using a Gemini 5 µm C18 110A column, for analytical separations with a dimension of 250 mm × 4.6 mm (flow 1 mL/min) and for semi-preparative applications with 250 mm × 10 mm (flow 5 mL/min) from Phenomenex (Aschaffenburg, Germany). For the separation of ^{18}F-labelled compounds three different conditions were used: (I) isocratic elution with acetonitrile, water and triethylamine (TEA) 60:40:0.1 (v/v/v) at a pH of 9.0 (phosphoric acid); (II) isocratic elution with acetonitrile and water 65:35 (v/v); (III) gradient elution using acetonitrile (0.1% TFA) and water: starting with 10% acetonitrile (0.1% TFA) the gradient was increased to 100% acetonitrile (0.1% TFA) over 20 min and kept there for 5 min.

NMR spectra (^{1}H-400 MHz) were obtained on an Inova 400 MHz spectrometer (Varian, Darmstadt, Germany). Chemical shifts are reported in parts per million, solvent peaks were referenced appropriately. ESI mass spectra were obtained on an Automass Multi III instrument (Thermoquest, Biberach, Germany). HRMS spectra were obtained on an FTICR 'LTQ FT Ultra' (Thermo Fisher Scientific, Dreieich, Germany). Melting points were measured in a Melting Point B-540 apparatus (Büchi Labortechnik GmbH, Essen, Germany).

Chemistry

*1-Benzyl-4-methylpiperidin-4-ol (**1**)*

Similar to the literature procedure[15] N-benzyl-piperid-4-one (5.68 g, 30.0 mmol) was dissolved in dry diethyl ether (60 mL) under an atmosphere of argon and cooled to −78°C. A solution of methyllithium in diethyl ether (1.6 M, 26 mL, 40.0 mmol) was added dropwise. The resulting mixture was stirred for 70 min at room temperature and the reaction terminated by dropwise addition of water (20 mL) under cooling. The water phase was extracted with diethyl ether (3 × 70 mL) and the organic phase dried over Na_2SO_4. After evaporation of the solvent the crude product was purified by silica gel chromatography using 3:1 *n*-hexane:acetone to give **1** (3.95 g, 19.2 mmol) in 64% yield as a yellow oil. Comparison with the literature NMR data[15,17] proved the identity of **1**. ^{1}H NMR ($CDCl_3$): 7.24–7.17 (m, 5H, Bn), 3.54 (s, 2H, CH_2Ph), 2.49 (m, 2H, P2,6), 2.31 (m, 2H, P2,6), 1.61 (m, 2H, P3,5), 1.53 (m, 2H, P3,5), 1.16 (s, 3H, Me). ESIMS: *m/z* (% int.) 206.1 (100) $[M+H]^+$.

*N-(1-Benzyl-4-methylpiperidin-4-yl)acetamide (**2**)*

N-(1-benzyl-4-methylpiperidin-4-yl)acetamide (**2**) was prepared similarly to a previously described procedure.[16,17] 1-Benzyl-4-methylpiperidin-4-ol (**1**) (2.77 g, 13.5 mmol) was dissolved in absolute acetonitrile (20 mL) under an atmosphere of argon and

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cooled to 0°C. To this solution concentrated sulfuric acid (13.4 mL) was added dropwise so that the temperature did not exceed 30°C. After the addition the mixture was stirred at room temperature for 24 h. For termination of the reaction the resulting oil was poured onto ice (100 g) and adjusted to pH 10 with a 50% KOH solution. The water phase was extracted with dichloromethane (4 × 100 mL), dried over Na_2SO_4 and the solvent was evaporated. The resulting yellow solid was levigated with *n*-hexane. Product **2** (3.09 g, 12.5 mmol) was obtained as a yellow solid in 93% yield and its identity verified by comparison with the literature NMR data.[17] ^{1}H NMR ($CDCl_3$): 7.26–7.20 (m, 5H, Bn), 3.45 (s, 2H, CH_2Ph), 2.49 (m, 2H, Pip2,6), 2.31 (m, 2H, Pip2,6), 1.90 (s, 3H, Me_{CO}), 1.61 (m, 2H, Pip3,5), 1.53 (m, 2H, Pip3,5), 1.16 (s, 3H, Me). ESIMS: *m/z* (% int.) 247.1 (100) $[M+H]^+$.

*(4-Methylpiperidin-4-yl)acetamide (**3**)*

Ammonium formate (0.59 g, 9.3 mmol) was dried *in vacuo* (1×10^{-3} mbar) for 30 min. N-(1-benzyl-4-methylpiperidin-4-yl)acetamide (**2**) (0.50 g, 2.0 mmol) was dissolved in absolute methanol (12 mL) under an atmosphere of argon and ammonium formate was added. After the addition of palladium black (0.10 g) the resulting suspension was heated to 65°C and stirred for 1 h. The mixture was filtered (pore width 1.0 μm) and the solvent removed. The product was used without further purification. (4-Methylpiperidin-4-yl)acetamide (**3**) (362 mg) was obtained as a white solid with small impurities in about 100% yield.

*N-[1-(3-(4-Fluorophenoxy)propyl)-4-methyl-4-piperidinyl]-acetamide (**5**)*

(4-Methylpiperidin-4-yl)acetamide (**3**) (360 mg, 2.3 mmol) was dissolved in absolute DMF (4 mL) under an atmosphere of argon and potassium carbonate (320 mg, 2.3 mmol), potassium iodide (380 mg, 2.3 mmol) and 1-(3-bromopropoxy)-4-fluorobenzene (**4**)[18] (630 mg, 2.7 mmol) were added. The suspension was heated to 80°C and stirred for 6 h. After removing the solvent *in vacuo* the residue was taken up in saturated sodium carbonate solution (10 mL) and extracted with dichloromethane (4 × 20 mL). The organic phase was dried over Na_2SO_4 and the solvent evaporated. Purification by silica gel chromatography (4:1 chloroform:methanol) gave **5** (182 mg, 0.59 mmol) in 26% yield as a yellow solid. For comparison with the literature, the melting point of **5** was determined to be 104.3°C (literature: 104–106[29] and 103.4°C[13]). ^{1}H NMR (DMSO-d_6): 7.02 (m, 2H, Ph3,5), 6.85 (m, 2H, Ph2,6), 3.87 (t, 2H, A3; $J = 6.30$), 2.48 (m, 2H, Pip2,6), 2.40 (t, 2H, A1; $J = 7.59$), 2.19 (m, 2H, Pip2,6), 1.97 (m, 2H, Pip3,5), 1.79 (m, 2H, A2), 1.73 (s, 3H, Me_{CO}), 1.40 (m, 2H, Pip3,5), 1.16 (s, 3H, Me). ESIMS: *m/z* (% int.) 309.2 (100) $[M+H]^+$.

*1-(3-(4-Fluorophenoxy)propyl)-4-methylpiperidin-4-amine (**6**)*

1-(3-(4-Fluorophenoxy)propyl)-4-methylpiperidin-4-amine (**6**) was prepared similarly to a previously described procedure[13,29] extending the reaction time to 72 h. Purification by column chromatography (4:1 chloroform:methanol) gave **6** as a yellow oil in 50% yield. ^{1}H NMR (DMSO-d_6): 7.03 (m, 2H, Ph3,5), 6.87 (m, 2H, Ph2,6), 3.89 (t, 2H, A1; $J = 6.52$), 2.45 (m, 2H, Pip2,6), 2.36 (t, 2H, A3; $J = 7.14$), 2.20 (m, 2H, Pip2,6), 1.78 (m, 2H, A2), 1.46 (m, 4H, Pip3,5), 1.07 (s, 3H, Me). ESIMS: *m/z* (% int.) 267.3 (100) $[M+H]^+$.

*N-[1-(3-(4-Fluorophenoxy)propyl)-4-methylpiperidin-4-yl]-2-methoxy-4-nitrobenzamide (**7**)*

2-Methoxy-4-nitrobenzoic acid (130 mg, 0.66 mmol) was dissolved in absolute dichloromethane (6 mL) and TEA (103 μL) under an atmosphere of argon. After 1 min (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) (343 mg, 0.66 mmol) was added and upon 40 min of stirring at room temperature 4-amino-1-(3-(4-fluorophenoxy)propyl)-4-methylpiperidine (**6**) (176 mg, 0.66 mmol), dissolved in absolute dichloromethane (2 mL) and TEA (103 μL), was added dropwise. The resulting solution was stirred for 18 h at room temperature. Then the organic phase was washed successively with water (2 × 10 mL), 5% sodium hydroxide solution (3 × 10 mL) and water (2 × 10 mL). The organic phase was dried over Na_2SO_4 and the solvent evaporated. Purification by column chromatography (4:1 chloroform:methanol) yielded **7** (297 mg) slightly contaminated with pyrrolidine derivatives in about 100% as a yellow oil. The substance was used without further purification.

*4-Amino-N-[1-(3-(4-fluorophenoxy)propyl)-4-methylpiperidin-4-yl]-2-methoxy-benzamide (**8**)*

Ammonium formate (170 mg, 2.70 mmol) was dried *in vacuo* (1×10^{-3} mbar) for 30 min. It was added to a solution of **7** (257 mg, approx. 0.58 mmol) in absolute methanol (4 mL) under an atmosphere of argon and palladium black (30 mg, 0.28 mmol) was added slowly. The suspension was heated to 65°C and stirred for 75 min. After removing the catalyst by filtration, the crude product was adsorbed on silica gel. Column chromatography (4:1 chloroform:methanol) resulted in **8** (132 mg, 0.32 mmol) as a white porous solid in 55% yield. Comparison of the melting point of **8** with the literature (76.1°C, literature: 75.5°C[13]) confirmed the identity. ^{1}H NMR (DMSO-d_6): 7.52 (d, 1H, Ph6′; $J = 8.34$), 7.05 (m, 2H, Ph3,5), 6.87 (m, 2H, Ph2,6), 6.19 (d, 1H, Ph3′; $J = 1.61$), 6.13 (dd, 1H, Ph5′; $J = 8.44$, 1.73), 3.93 (t, 2H, A1; $J = 6.35$), 3.80 (s, 3H, OMe), 2.66 (m, 2H, Pip2,6), 2.48 (t, 2H, A3; $J = 7.24$), 2.21 (m, 2H, Pip2,6), 2.09 (m, 2H, P3,5), 1.83 (m, 2H, A2), 1.51 (m, 2H, Pip3,5), 1.32 (s, 3H, Me). ESIMS: *m/z* (% int.) 416.2 (100) $[M+H]^+$.

*1-Benzyl-4-methyl-piperidin-4-amine (**9**)*

The deacetylation of N-(1-benzyl-4-methylpiperidin-4-yl)acetamide (**2**) was conducted as described for the synthesis of 4-amino-1-(3-fluorophenoxy)propyl-4-methylpiperidine (**6**) and similar to the literature procedure.[17] Compound **2** (800 mg, 3.25 mmol) was heated at 100°C in concentrated hydrochloric acid (8.1 mL) for 94 h. Purification by column chromatography (4:1 chloroform:methanol) gave **9** (580 mg, 2.84 mmol) as a yellow oil in 87% yield. Comparison with the literature NMR data[17] proved the identity of **9**. ^{1}H NMR (DMSO-d_6): 7.35–7.26 (m, 5H, Bn), 3.54 (s, 2H, CH_2Ph), 2.44 (m, 4H, Pip2,6), 1.96 (s, 2H, NH_2), 1.57 (m, 4H, Pip3,5), 1.14 (s, 3H, Me). ESIMS: *m/z* (% int.) 205.1 (98) $[M+H]^+$.

*4-(tert-Butoxycarbonylamino)-2-methoxybenzoic acid (**10**)*

To a solution of 4-amino-2-methoxybenzoic acid[21] (1.54 g, 9.21 mmol) in absolute methanol (15 mL), TEA (1.28 mL,

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9.21 mmol) and di-*tert*-butyl dicarbonate (2.03 g, 9.21 mmol) were added. The mixture was stirred for 7.5 h at room temperature and then the solvent evaporated. Drying *in vacuo* (1×10^{-3} mbar) resulted in **10** (1.83 g, 6.85 mmol) as a beige solid in 74% yield. ^{1}H NMR (DMSO-d_6): 7.51 (d, 1H, Ph6; $J = 8.20$), 7.26 (d, 1H, Ph3; $J = 1.38$), 6.95 (dd, 1H, Ph5; $J = 8.46$, 1.49), 3.69 (s, 3H, OMe), 1.43 (s, 9H, Me_{Boc}). ESIMS: *m/z* (% int.) 268.1 (100) $[M+H]^+$, 212.0 (58) $[M\text{-}tBu+H]^+$, 168.2 (53) $[M\text{-}Boc+H]^+$. HRMS: calculated for $C_{13}H_{18}O_5N_1$: 268.11795, found: 268.11808.

*tert-Butyl 4-(1-benzyl-4-methylpiperidin-4-ylcarbamoyl)-3-methoxyphenylcarbamate (**11**)*

As described for the synthesis of N-[1-(3-(4-fluorophenoxy)propyl)-4-methylpiperidin-4-yl]-2-methoxy-4-nitrobenzamide (**7**), **10** (432 mg, 1.62 mmol), dissolved in absolute dichloromethane (15 mL) and TEA (252 μL), was reacted with PyBOP (842 mg, 1.62 mmol) and subsequently with 1-benzyl-4-methyl-piperidinamine (**9**) (330 mg, 1.62 mmol), dissolved in dichloromethane (15 mL) and TEA (252 μL). Workup and column chromatography (4:1 chloroform:methanol) yielded **11** (771 mg) slightly contaminated with pyrrolidine derivatives as an orange porous solid in about 100%. This product was used without further purification.

*tert-Butyl 3-methoxy-4-(4-methylpiperidin-4-ylcarbamoyl)phenylcarbamate (**12**)*

As described for the synthesis of (4-methylpiperidin-4-yl)acetamide (**3**), *tert*-butyl 4-(1-benzyl-4-methylpiperidin-4-ylcarbamoyl)-3-methoxyphenylcarbamate (**11**) (1.69 g, approx. 3.70 mmol) in absolute methanol (25 mL), ammonium formate (1.11 g, 17.5 mmol) and palladium black (191 mg, 1.79 mmol) were reacted for 3.5 h. Purification by column chromatography (4:1 chloroform:methanol) gave **12** (585 mg, 1.61 mmol) in approximately 44% yield as a white solid. ^{1}H NMR (DMSO-d_6): 7.45 (d, 1H, Ph6′; $J = 8.46$), 7.32 (d, 1H, Ph3′; $J = 1.26$), 7.00 (dd, 1H, Ph5′; $J = 8.55$, 1.30), 3.81 (s, 3H, OMe), 3.08 (m, 2H, Pip2,6), 2.84 (m, 2H, Pip2,6), 2.32 (m, 2H, Pip3,5), 1.42 (s, 9H, Me_{Boc}), 1.66 (m, 2H, Pip3,5), 1.33 (s, 3H, Me). ESIMS: *m/z* (% int.) 364.2 (100) $[M+H]^+$. HRMS: calculated for $C_{19}H_{30}O_4N_3$: 364.22308, found: 364.22305.

*tert-Butyl 4-(1-(3-(4-fluorophenoxy)propyl)-4-methylpiperidin-4-ylcarbamoyl)-3-methoxyphenylcarbamate (**13**)*

As described for the synthesis of N-[1-(3-(4-fluorophenoxy)propyl)-4-methyl-4-piperidinyl]acetamide (**5**), **12** (80 mg, 0.22 mmol) in dry DMF (1 mL), potassium carbonate (30 mg, 0.22 mmol), potassium iodide (36 mg, 0.22 mmol) and 1-(3-bromopropoxy)-4-fluorobenzene (**4**) (80 mg, 0.30 mmol) in absolute DMF (1 mL) were reacted for 17 h. Purification by column chromatography (4:1 chloroform:methanol) gave **13** (60 mg, 0.12 mmol) as an orange porous solid in 53% yield. ^{1}H NMR (DMSO-d_6): 7.63 (d, 1H, Ph6′; $J = 8.62$), 7.34 (d, 1H, Ph3′; $J = 1.20$), 7.04 (m, 2H, Ph3,5), 7.00 (dd, 1H, Ph5′; $J = 8.54$, 1.35), 6.88 (m, 2H, Ph2,6), 3.91 (t, 2H, A3), 3.81 (s, 3H, OMe), 3.48 (m, 2H, A1), 2.61 (m, 2H, Pip2,6), 2.19 (m, 2H, Pip2,6), 2.11 (m, 2H, Pip3,5), 1.84 (m, 2H, A2), 1.50 (m, 2H, Pip3,5), 1.42 (s, 9H, Me_{Boc}), 1.33 (s, 3H, Me). ESIMS: *m/z* (% int.) 516.3 (100) $[M+H]^+$. HRMS: calculated for $C_{28}H_{39}F_1O_5N_3$: 516.28683, found: 516.28706.

*(4-Fluorophenyl)-(4-(trifluoromethyl)phenyl)methanone/N,N,N-trimethyl-4-(4-(trifluoromethyl)benzoyl)phenylammonium trifluoromethylsulfonate (**15**)*

To a solution of 4-fluorophenylmagnesium bromide (15 mL, 1 M in THF, 15.0 mmol) in absolute THF (20 mL) under an atmosphere of argon a solution of 4-trifluoromethylbenzonitrile (2.56 g, 15 mmol) in absolute THF (10 mL) was added dropwise. Then the mixture was heated to 67°C for 6 h. After cooling 1 M sulfuric acid (100 mL) was added and the organic solvent removed *in vacuo*. The residual aqueous phase was extracted with diethyl ether (4×50 mL) and the solvent was evaporated. (4-Fluorophenyl)-(4-(trifluoromethyl)-phenyl)methanone (4.02 g, 15.0 mmol) was obtained as a brownish solid in 100% yield. Spectroscopic data were identical to those reported earlier.[22]

In order to get N,N,N-trimethyl-4-(4-(trifluoromethyl)benzoyl)-phenylammonium trifluoromethylsulfonate (**15**), (4-fluorophenyl)-(4-(trifluoromethyl)phenyl)methanone was first reacted with dimethylamino hydrochloride and then with methyl trifluoromethanesulfonate to give **15** as described.[22]

Radiochemistry

N.c.a. [^{18}F]fluoride was produced via the ^{18}O(p,n)^{18}F nuclear reaction by the bombardment of an isotopically enriched [^{18}O] water target with 17 MeV protons at the JSW cyclotron BC 1710 (FZ Jülich).[30] The [^{18}F]fluoride solution was azeotropically dried as described in the literature by the addition of Kryptofix® 222 and potassium carbonate for anion activation.[22]

*4-[^{18}F]fluorophenol (**[^{18}F]14**)*

The preparation of 4-[^{18}F]fluorophenol (**[^{18}F]14**) was carried out with some modifications of the earlier described procedure.[22]

Labelling: Compound **15** (10 mg, 25.8 μmol) dissolved in dry acetonitrile (1 mL) was added to the dry cryptate of [^{18}F]KF and the mixture stirred for 8 min at 80°C. Then the solvent was evaporated under a stream of argon at 700 mbar.

Oxidation: At 80°C the precipitate was dissolved in a mixture of acetic acid and acetic anhydride (3:2, 2 mL) and hydrogen peroxide (30%, 0.6 mL) and concentrated sulfuric acid (0.5 mL) were slowly added. The mixture was stirred for 10 min before dilution with water (5 mL) and fixation on a conditioned Sep-Pak plus C18 cartridge (Waters). The cartridge was washed with water (5 mL) and dried under a stream of argon. Elution was conducted over a conditioned Sep-Pak plus Alumina N cartridge (Waters) with diethyl ether (4 mL). The solvent was evaporated under a stream of argon at 25°C and 700 mbar.

Hydrolysis: At 80°C aqueous sodium hydroxide (5 M, 0.7 mL) and methanol (0.07 mL) were added into the reaction vial and the solution stirred for 5 min. For further reactions the alkaline phenolate solution was used. For purpose of analysis the mixture was acidified with concentrated hydrochloric acid (350 μL), diluted with water (5 mL), fixed on a conditioned Sep-Pak plus C18 cartridge (Waters) and eluted with acetonitrile (1 mL). Reversed-phase analytical HPLC (condition I) identified the product as 4-[^{18}F]fluorophenol (**[^{18}F]14**) with elution at $k' = 1.65$ and a radiochemical purity of >98%. **[^{18}F]14** was prepared in 50–69% RCY in a reaction time of 50 min.

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*1-(3-Bromopropoxy)-4-[^{18}F]fluorobenzene ([**^{18}F**]**4**)*

The alkylation of **[^{18}F]14** was carried out with some modifications to the previously described procedure.[22] To the alkaline 4-[^{18}F]fluorophenolate solution, a mixture of 2-butanone (2.2 mL) and 1,3-dibromopropane (65 μL, 600 μmol) was added at 80°C and the two-phase system was stirred vigorously for 20 min. Then the mixture was diluted with water (15 mL) and passed through a conditioned LiChrolut RP-18e cartridge (Merck). The cartridge was washed with water (5 mL) and eluted with acetonitrile (1 mL). The solution was injected onto a reversed-phase HPLC (condition II). Elution occurred at $k' = 4.47$. After dilution with water (15 mL), the collected fraction was fixed on a conditioned LiChrolut RP-18e cartridge (Merck), washed with water (5 mL) and eluted through a glass column (LiChrolut 65 × 10 mm, Merck) filled with 4 Å molecular sieves and sodium sulfate (250 mg) with dry DMF (1 mL). Isolation led to the labelled compound **[^{18}F]4** with an RCY of 19–40%, relative to 4-[^{18}F]fluorophenol (**[^{18}F]14**), and a radiochemical purity of >99%.

*tert-Butyl 4-(1-(3-(4-[^{18}F]fluorophenoxy)propyl)-4-methylpiperidin-4-ylcarbamo-yl)-3-methoxyphenylcarbamate (**[^{18}F]13**)/4-amino-N-[1-(3-(4-[^{18}F]fluorophenoxy)propyl)-4-methylpiperidin-4-yl]-2-methoxy-benzamide (**[^{18}F]8**)*

[^{18}F]4 (in 0.7 mL DMF) was added to a suspension of **12** (17 mg, 50 μmol), cesium carbonate (16.3 mg, 50 μmol) and potassium iodide (8.3 mg, 50 μmol) in 50 μL dry DMF under an atmosphere of argon. The mixture was stirred at 80°C for 20 min and after dilution with water (5 mL) passed through a conditioned Sep-Pak plus C18 cartridge (Waters). The cartridge was washed with water (5 mL) and eluted with dichloromethane (1 mL). For analytical purposes aliquots of the reaction mixture were analyzed using reversed-phase HPLC (condition I) identifying **[^{18}F]13** at $k' = 6.24$.

Deprotection was achieved with some modifications to the literature procedure.[23] To the dichloromethane phase, TFA (150 μL) was added and the mixture evaporated to dryness under a gentle stream of argon at 80°C by adding acetonitrile (0.5 mL) after removal of dichloromethane. The residue was dissolved in acetonitrile (0.3 mL) and injected onto a reversed-phase HPLC (condition III). Elution occurred at $k' = 3.71$. After dilution with water (30 mL), the collected fraction was passed through a conditioned Oasis HLB 1 cc cartridge (Waters) and washed with water (5 mL). Elution with ethanol (0.7 mL) led to **[^{18}F]8** in an RCY of 34–48% relative to 1-(3-bromopropoxy)-4-[^{18}F]fluorophenol (**[^{18}F]4**) and a radiochemical purity of >99%. For biological evaluation the ethanol was removed *in vacuo* and **[^{18}F]8** dissolved in physiological saline containing 7% ethanol. [^{18}F]R91150 (**[^{18}F]8**) was prepared in a reaction time of 190 min with an RCY of 1.8–5.7%, relative to [^{18}F]fluoride. The specific activity was at least 335 GBq/μmol (EOS) as determined by HPLC using a UV mass calibration curve of the non-radioactive R91150 (**8**).

Lipophilicity

Using the HPLC method corresponding to the OECD guideline for the testing of chemicals,[24] the lipophilicities were determined using a LiChrospher 100 RP-8 (5 μm) column (Merck). As eluent Soerensen buffer was used (methanol and phosphate buffer 75:25 (v/v) at a pH of 7.4). The retention times for a number of reference compounds (ascorbic acid, benzaldehyde, anisole, toluene, 4-bromoanisole, 4-iodoanisole) with known log *P* values (from −1.67 to 3.24) were determined and the capacity factors k' were calculated. Plotting log k' against log *P* gave the reference curve used to determine the log *P* values of R91150, altanserin and MDL 100907 by their retention times.

Ex vivo studies

Biodistribution

Female Navel Medical Research Institute (NMRI) mice (permission to perform animal experiments 50.203.2-KFA 12/02 for mice) weighing 39 ± 4 g received about 110 kBq [^{18}F]R91150 (**[^{18}F]8**) in a volume of 100 μL physiological saline containing 7% ethanol by tail vein injection. The animals were sacrificed 30 min ($n = 4$) and 60 min ($n = 2$) after tracer injection, the tissues of interest removed, weighed and the radioactivity measured with a gamma-counter.

Radiometabolite analysis

Integrity of the tracer in mice was determined according to an earlier developed procedure.[31] Briefly, blood samples (200 μL each) of mice ($n = 3$) were taken 30 min after tracer injection. Centrifugation (1250 × *g*, 3 min, 18°C) separated the plasma. Plasma aliquots (50 μL each) were mixed with an equal volume of acetonitrile and shaken with a vortex mixer for 2 min. Mouse brains (approx. 500 mg each) were homogenized by a potter in ice cold 0.1 N Tris–HCl buffer, pH 7.4 (1500 μL), for 1 min. Aliquots (500 μL each) were transferred into Eppendorf vials, mixed with an equal volume of acetonitrile and shaken with a vortex mixer for 5 min. After centrifugation (20 800 × *g*, 2 min, 18°C) of the extracts, triplicate samples (5 μL each) of the supernatants were spotted on a TLC plate (SIL G/UV$_{254}$, Macherey-Nagel, Düren, Germany), the plate was developed with methanol, air dried and immediately scanned with an Instant Imager to measure the fluorine-18 activity.

Conclusion

The synthesis of [^{18}F]R91150 (**[^{18}F]8**), a high-affinity antagonist of 5-HT$_{2A}$ receptors, was accomplished by a complex labelling strategy via 4-[^{18}F]fluorophenol (**[^{18}F]14**) and 1-(3-bromopropoxy)-4-[^{18}F]fluorobenzene (**[^{18}F]4**). In a six-step radiosynthesis, [^{18}F]R91150 (**[^{18}F]8**) could be prepared, isolated and formulated within 190 min. The overall RCY was 1.8–5.7% and the specific activity was at least 335 GBq/μmol (EOS). Even though such a complex reaction route is not desirable, the radiofluorinated compound could be synthesized reproducibly and a preliminary pharmacological evaluation conducted.

Ex vivo studies with mice showed sufficient uptake of [^{18}F]R91150 into the brain. Radiometabolite studies in the mouse brain revealed no radiometabolites, whereas in the plasma at least two radiometabolites could be detected 30 min p.i. and here only 64% of the radioactivity accounted for intact [^{18}F]R91150 (**[^{18}F]8**). The results obtained encourage the efforts for an improved radiosynthesis and continued evaluation of this new 5-HT$_{2A}$ antagonist as a radioligand for PET studies.

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