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Direct radiofluorination of [^{18}F]MH.MZ for 5-HT$_{2A}$ receptor molecular imaging with PET

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Imaging the serotonin 2A neuroreceptor with positron emission tomography has been carried out with [^{11}C]MDL 100907 and [^{18}F]altanserin for years. Recently, the MDL 100907 analogue [^{18}F]MH.MZ was developed by combining the increased selectivity profile of MDL 100907 and the favourable radiophysical properties of fluorine-18. Here, we want to report the synthesis of [^{18}F]MH.MZ via direct radiofluorination. Unfortunately, the direct radiofluorination did not have any significant benefits over the indirect labelling method. This is mainly because the precursor for the direct labelling approach is not completely stable and slowly decomposes. However, only one HPLC separation is necessary for the direct ^{18}F-nucleophilic labelling procedure, and accordingly, automation is easier.

Keywords: MDL 100907; [^{18}F]MH.MZ; PET; 5-HT$_{2A}$ receptor

Introduction

Serotonin (5-hydroxytryptamine, 5-HT) 2A receptors are of significant clinical interest because of their involvement in the pathophysiology of human diseases such as depression, Alzheimer's disease and schizophrenia.[1] In particular, therapeutic effects of atypical antipsychotics may be attributed to antagonistic effects on these receptors.[2] Stimulation of the 5-HT$_{2A}$ receptor with recreational hallucinogens such as lysergic acid diethylamide elicits hallucinogenic effects.[3]

Positron emission tomography (PET) is widely used as an advanced tool to image cerebral receptors in vivo, where the pharmacological parameters of ligand–neuroreceptor interactions can be quantified. Therefore, in vivo PET studies of cerebral 5-HT$_{2A}$ receptors and occupancy by therapeutic drugs, for example antipsychotics, have provided a significant advance in the understanding of these disorders.

Currently, the 5-HT$_{2A}$ receptor antagonist radiotracers [^{18}F]altanserin (Table 1) and to a lesser extent [^{11}C]MDL 100907 are used as PET tracers to probe the 5-HT$_{2A}$ receptors in vivo.[4] They have high affinity and selectivity for the 5-HT$_{2A}$ receptor (Table 1) and generate good target-to-background ratios in humans. However, both PET radiotracers have limitations; [^{11}C]MDL 100907 displays slow kinetics,[5] whereas in vitro binding of [^{18}F]altanserin lacks 5-HT$_{2A}$ receptor specificity (Table 1) and it gives rise to lipophilic metabolites that cross the blood–brain barrier.[6] Nevertheless, [^{18}F]altanserin is the most commonly used receptor ligand for 5-HT$_{2A}$ receptor imaging. For the reasons given earlier, it would, however, be advantageous to have access to an [^{18}F]MDL 100907 derivative that did not generate lipophilic metabolites.

In an attempt to meet those criteria, [^{18}F]MDL 100907 has been synthesized.[7] However, because of the very low radiochemical yield (RCY) of 2%, this radiotracer is not suitable for clinical studies. We later reported a two-step synthesis of an ^{18}F-labelled analogue of MDL 100907, [^{18}F]MH.MZ (**1**) and its *R*-enantiomer (**2**) (Figure 1) and reported its subsequent evaluation in rodents.[8] In vitro and in vivo studies demonstrated that in rodents, this radioligand combines the high selectivity of MDL 100907 (Table 1) with the superior isotopic properties of [^{18}F]fluorine.[8–11]

The aim of this study was to simplify the two-step labelling procedure of [^{18}F]MH.MZ to a direct radiofluorination approach.

Results

Organic chemistry

The reference compound MH.MZ was synthesised as previously described.[10] The precursor (**5**) was synthesised in a four-step reaction sequence starting with a condensation reaction between (3-((*tert*-butyldiphenylsilyl)oxy)-2-methoxyphenyl)(piperidin-4-yl) methanol (**1**) and *p*-fluorophenylethylbromide in a yield of approximately 75%. The resulting intermediate (**2**) was acylated (yield: 99%) and the *tert*-butyldiphenylsilyl (TBDPS)-protecting group removed by NH_4F (yield: 76%). Finally, ethyleneditosylate was reacted with the phenolic moiety of (**4**) via a Williamson ether synthesis to give **(5)** in a yield of 46% (Scheme 1).

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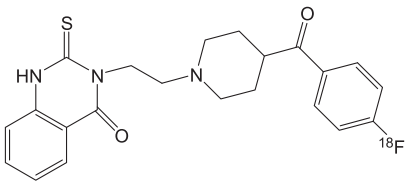
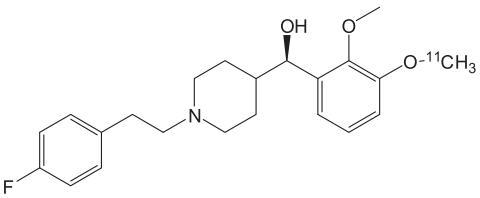
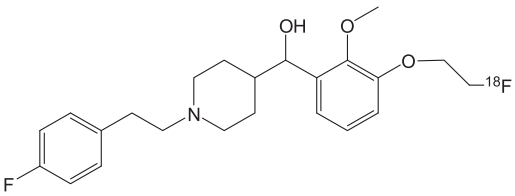
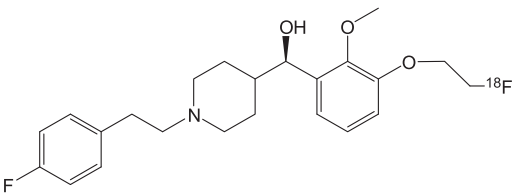
Table 1. Dissociation constants (K_i (nM)) and chemical structures of altanserin, MDL 100907, (*R,S*)-MH.MZ and (*R*)-MH.MZ. Affinities for a large range of receptors are previously published[10,12]

	5-HT_{2A}	D_2/5-HT_{2A} ratio	α_1/5-HT_{2A} ratio	
Altanserin	0.13	~475	~35	
MDL 100907	0.36	~6250	~350	
(*R,S*)-MH.MZ	9.02	> 1100	~35	
(*R*)-MH.MZ	0.72	~3730	~465	

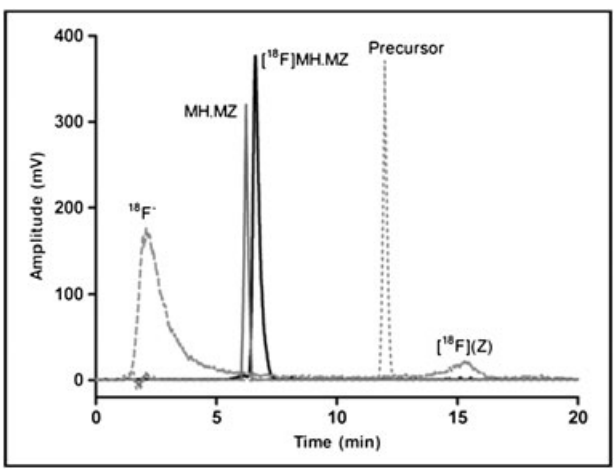


Figure 1. Analytical HPLC diagram of [^{18}F]MH.MZ, [^{18}F](5), MH.MZ and its precursor.

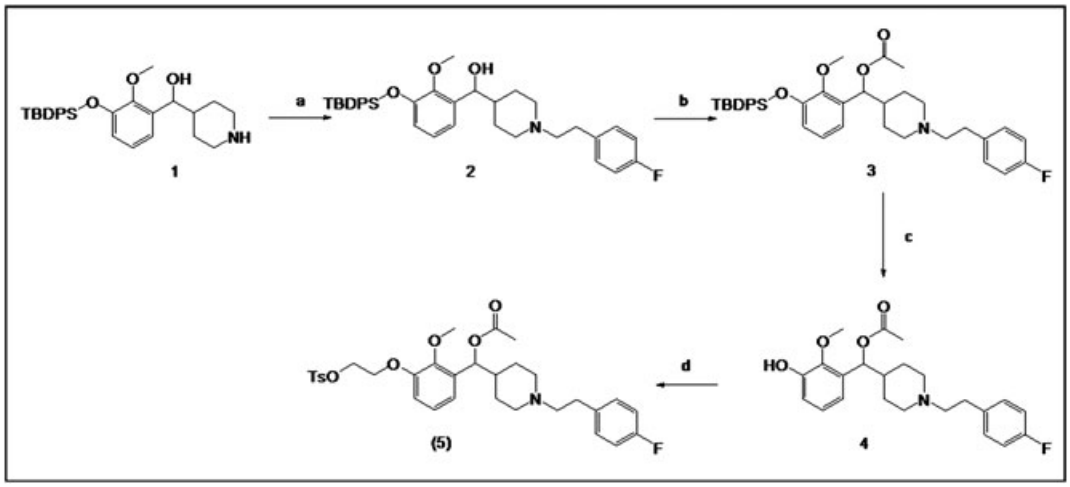
Radiochemistry

Radiolabelling of [^{18}F]MH.MZ was carried out by nucleophilic substitution of [^{18}F]fluoride on (1-(4-fluorophenethyl)piperidin-4-yl)(2-methoxy-3-(2-(tosyloxy)ethoxy)phenyl)methyl acetate (**5**) followed by Zemplen deprotection (Scheme 2). The whole procedure was carried out as a one-pot reaction.

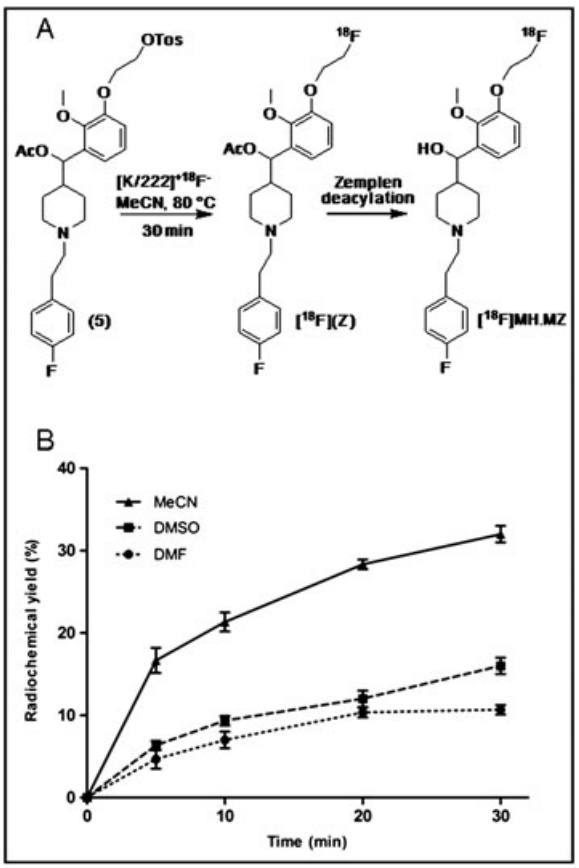
The effect of precursor concentration and reaction solvent on radioactive labelling kinetics was evaluated (Scheme 2). Reaction progress was measured with radio–thin layer chromatography (TLC), and results were verified with analytical HPLC. The optimised reaction conditions (3 mg precursor, 80 °C, 20-min reaction time) gave RCYs of approximately 30%.

The effect of varying temperature was not measured because of a decomposing precursor at 80 °C in dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) (data not shown). Increasing the amount of precursor (3–9 mg) did not significantly change the RCY (data not shown). Finally, Zemplen deacylation of [^{18}F](**Z**) using 0.05 NaOMe at 80 °C for 3 min leads to quantitative deprotection resulting in [^{18}F]MH.MZ.

HPLC purification was carried out as described in the experimental section. The radiochromatogram of the crude product showed a difference in the two retention times of approximately 4 min between the two radioactive compounds, eluting first [^{18}F] fluoride (~2 min) and then [^{18}F]MH.MZ (~6 min). Ultraviolet (UV) absorption at 254 nm indicated that the precursor (**5**) had a retention time of approximately 12 min (Figure 1).



Scheme 1. Reagents and conditions: (a) NaI, *p*-fluorophenylethylbromide, $NaHCO_3$, dimethylformamide, 85 °C, 2 h, 70%; (b) Ac_2O, THF, RT, 99%; (c) NH_4F, MeOH, reflux, 76%; (d) Cs_2CO_3, ethyleneditosylate, MeCN, reflux, 16 h, 46%.



Scheme 2. (A) Nucleophilic ^{18}F-labelling strategy to synthesise [^{18}F]MH.MZ and (B) ^{18}F-labelling kinetics of the intermediate ([^{18}F](**5**)).

The radiosynthesis including HPLC, SepPak® (Waters, Hedehusene Denmark) purification and formulation gave a final injectable solution of [^{18}F]MH.MZ (radiochemical purity > 96%) within 100 min. Specific activities (A_s) were in average 19.8 GBq/μmol (range 0.69–65.9 GBq/μmol). Approximately 25 GBq of [^{18}F] fluorine was used as starting radioactivity, whereby [^{18}F]MH.MZ was obtained as an injectable solution in an overall RCY around 15–20%.

In addition, optimization experiments via microwave (MW) heating were carried out. All experiments were carried out in MeCN, and radioactive labelling kinetics were evaluated and optimised on MW heating mode, temperature and time. MW heating reduced the reaction time to 5 min, whereas RCY was unchanged (Figure 2).

Discussion

We here report a novel approach to synthesise [^{18}F]MH.MZ in a one-step radiochemical approach followed by a Zemplen deprotection reaction in sufficient yield for imaging studies; the best conditions of the nucleophilic substitution included MeCN at 80 °C. MW irradiation has been successfully applied in organic chemistry and radiolabelling. Because of accelerations, higher yields under milder reaction conditions and higher product purities have been reported,[13,14] we tested MW heating as a method to increase RCY for [^{18}F]MH.MZ radiolabelling. This optimised reaction resulted in an RCY of approximately 25%, only slightly lower than that of a conventional heating system, but the reaction time could be reduced by 25 min. No radiolysis was observed for [^{18}F]MH.MZ, but the precursor was sensitive to air, and unless stored at inert conditions, the RCYs dropped. This problem could not be overcome by using a higher precursor

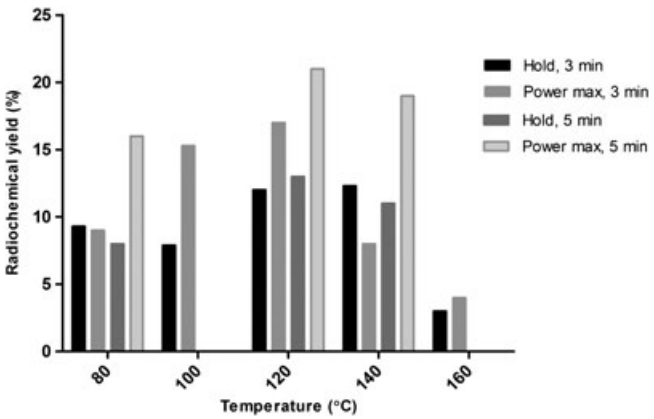


Figure 2. ^{18}F-Labelling kinetics of the intermediate ([^{18}F](**5**)).

concentration. Compared with the two-step labelling procedure of [^{18}F]MH.MZ via [^{18}F]FETos[7], only one HPLC separation is necessary for the direct ^{18}F-nucleophilic labelling procedure, and accordingly, automation would be easier. However, the two-step procedure takes roughly the same time, has similar RCYs and A_s and with a commercial available precursor susceptible to decomposition.

Materials and methods

Chemicals were purchased from ACROS Sport GmbHBenzstr (Renningen, Germany), Fluka, Denmark Sigma-Aldrich (Denmark A/S Copenhagen, Denmark), Tocris Bioscience (Moorend Farm Avenue, Bristol, United Kingdom) or Merck KGaA (Frankfurter Straβe, Darmstadt, Deutschland). Unless otherwise stated, all chemicals were used without further purification. For solid phase extraction, Sep-Pak®-QMA-and Sep-Pak®-C18-cartridges were used. TLC was performed using plates from Merck (silicagel 60 F254 and alumina oxide 60 F254). ^{1}H NMR spectra were recorded using a Bruker AC 300. Chemical shifts are quoted as δ-values (ppm) downfield from tetramethylsilane. Field desorption (FD) mass spectra were recorded using a Finnigan MAT90 spectrometer. Analytical and preparative HPLC were performed on a Dionex (1027 Old York Rd. Ringoes NJ 08551-1054 USA) system consisting of a pump P680A pump, a UVD 170U detector and a Scansys radiodetector. Syntheses were carried out in a commercially available MW oven (CEM LabMate, Corp. 45 Post Irvine, CA, USA). [^{18}F]Fluoride was produced via the ^{18}O(p,n)^{18}F reaction by bombardment of an isotopically enriched [^{18}O]water target with an 11-MeV proton beam in a CTI (Middlebrook, PikeKnoxville, TN, USA) Eclipse cyclotron. All radioactive syntheses were carried out in an automated Scansys radiochemistry module.

Chemistry

*(3-((Tert-butyldiphenylsilyl)oxy)-2-methoxyphenyl)(piperidin-4-yl) methanol (**1**) was synthesised as previously described.[10]*

*(2-Methoxy-3-(t-butyldiphenylsilyloxy)-phenyl)-(1-(2-p-fluorophenylethyl)-piperidine-4-yl)-methanol (**2**)*

The free amine (**1**) (1.5 g, 3.15 mmol), *p*-fluorophenethylbromide (0.64 g, 3.15 mmol), NaI (0.7 g, 4.65 mmol) and $NaHCO_3$ (0.53 g, 6.3 mmol) were dissolved in dry DMF (25 mL) and stirred at 85 °C for 2 h. After evaporation of the solvent, the residue was taken up in NH_4OH (30 mL) and extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Column chromatography (CC) (chloroform/methanol 8:1) yielded (**2**) (1.32 g, 2.21 mmol, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) d [ppm] = 7.732–7.681 (4H, m), 7.416–7.301 (6H, m), 7.156–7.110 (2H, m), 6.969–6.911 (2H, t), 6.787–6.762 (1H, d), 6.642–6.589 (1H, d), 6.418–6.391 1H, d), 4.622–4.595 (1H, d), 3.968 (3H, s), 3.113–3.077 (1H, d), 2.975–2.932 (1H, d), 2.806–2.752 (2H, m), 2.571–2.517 (2H, m), 2.101–1.924 (3H, m), 1.650–1.639 (1H, m), 1.554–1.215 (3H, m), 1.102 (9H, s) MS (FD) *m/z* (% rel Int.): 597.6 (100.0 $[M]^+$); 598.6 (77.39 $[M+1]^+$); 599.6 (24.91 $[M+2]^+$); 595.6.

*(2-Methoxy-3-(t-butyldiphenylsilyloxy)-phenyl)-(1-(2-p-fluorophenylethyl)-piperidine-4-yl)-methyl acetate (**3**)*

To a solution of (**2**) (1.32 g, 2.2 mmol) in dry THF (25 mL), acetic acid anhydride (420 μL, 4.4 mmol) was added dropwise at room temperature. After stirring for 18 h at room temperature, the solution was quenched with H_2O (30 mL), extracted with EtOAc (3 × 40 mL), dried (Na_2SO_4) and evaporated, yielding (**3**) as a colourless oil (1.4 g, 2.18 mmol, 99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm] = 7.665–7.753 (4H, m), 7.268–7.428 (6H, m), 7.118–7.165 (2H, m), 6.946 (2H, t, J = 8.824 Hz), 6.731 (1H, dd, J_1 = 7.721 Hz, J_2 = 1.471 Hz), 6.605 (1H, t, J = 7.721), 6.426 (1H, dd, J_1 = 1.471 Hz, J_2 = 8.089), 5.940 (1H, d, J = 7.354), 3.997 (3H, s), 3.018–3.127 (2H, m), 2.777–2.831 (2H, m), 2.588–2.642 (2H, m), 2.047 (3H, s), 1.955–2.102 (1H, m), 1.677–1.813 (2H, m), 1.423–1.616 (2H, m), 1.239–1.382 (2H, m), 1.102 (9H, s).

*(2-Methoxy-3-hydroxyphenyl)-(1-(2-p-fluorophenylethyl)-piperidine-4-yl)-methyl acetate (**4**)*

A solution of (**3**) (1.4 g, 2.18 mmol) and ammonium fluoride (300 mg, 8 mmol) in dry MeOH was heated under reflux for 30 min. After cooling to room temperature, the solution was evaporated in vacuo, dissolved in H_2O (30 mL), extracted with dichloromethane (DCM) (3 × 50 mL), washed with brine, dried (Na_2SO_4) and evaporated. CC (DCM/MeOH 8:1) afforded (**4**) as colourless crystals (667 mg, 1.66 mmol, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm] = 7.202–7.250 (2H, m), 7.069 (2H, t, J = 8.824 Hz), 6.883 (1H, t, J = 8.089), 6.782 (1H, d, J = 8.089), 6.660 (1H, d, J = 7.721), 5.762 (1H, d, J = 7.721), 3.749 (3H, s), 2.828–3.049 (2H, m), 2.639–2.753 (2H, m), 2.406–2.566 (2H, m), 2.017 (3H, s), 1.883–2.014 (1H, m), 1.609–1.755 (2H, m), 1.114–1.358 (4H, m).

*(2-Methoxy-3-(tosyloxyethyloxy)phenyl)-(1-(2-p-fluorophenylethyl)-piperidine-4-yl)-methyl acetate (**5**)*

A solution of (**4**) (400 mg, 1 mmol), Cs_2CO_3 (390 mg, 1.2 mmol) and ethyleneditosylate (1.85 g, 5 mmol) in dry MeCN (30 mL) was heated under reflux for 16 h. The solvent was removed in vacuo; the residue dissolved in H_2O and extracted with Et_2O. The combined organic phases were washed with brine, dried (Na_2SO_4) and evaporated. CC (DCM/ MeOH 6:1) afforded (**5**) as colourless oil (276 mg, 0.46 mmol, 46%). ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm] = 7.780–7.807 (2H, d, J = 8.089 Hz), 7.314–7.343 (2H, d, J = 8.457), 7.126 (2H, dd, J_1 = 8.457, J_2 = 5.515), 6.839–6.991 (4H, m), 6.724 (1H, dd, J_1 = 8.089, J_2 = 1.471), 5.902 (1H, d, J = 6.986), 4.353–4.385 (2H, m), 4.159–4.188 (2H, m), 3.789 (3H, s), 2.962–3.162 (2H, m), 2.765–2.871 (2H, m), 2.544–2.674 (2H, m), 2.429 (3H, s), 1.981–2.102 (2H, m), 2.044 (3H, s), 1.699–1.872 (2H, m), 1.341–1.652 (3H, m) MS (FD) *m/z* (% rel.Int.): 598.7 (100.0 $[M]^+$), 599.7 (34.2 $[M+1]^+$).

*(3-(2-Fluoroethoxy)-2-methoxyphenyl)(1-(4-fluorophenethyl)piperidin-4-yl)methanol (MH.MZ, (**1**))*

MH.MZ was synthesised as reported by Herth *et al.*[10]

Production of [^{18}F]MH.MZ

To an aqueous [^{18}F]fluoride solution (1400–1600 MBq), Kryptofix®222 (*ABX* GmbH, Heinrich-Glaeser-Strasse, Radeberg, Germany) (15 mg), 15-μL potassium carbonate (1 N) and 1-mL acetonitrile were added. The mixture was dried in a stream of nitrogen at 80 °C. The drying procedure was repeated three times until the reaction mixture was absolutely dry. The dried Kryptofix®222/ [^{18}F]fluoride complex was then dissolved in 1-mL acetonitrile, and 3-mg (1-(4-fluorophenethyl)piperidin-4-yl)(2-methoxy-3-(2-(tosyloxy)ethoxy)phenyl)methyl acetate (**5**, 0.005 mmol)) was added. The resulting solution was heated at 80 °C under stirring in a sealed vial for 25 min. 0.1 mL of a 0.05 M NaOMe solution was added, and the solution was subsequently

cooled to room temperature (RT) by nitrogen cooling. The solution was stirred for further 3 min and then quenched with 3.5 mL of HPLC eluent. Purification of the crude product was accomplished using HPLC (Luna 5 μ C_{18}(2) 100 Å, 250 × 10.00 mm, 5 μm; acetonitrile/buffer (0.25 M NH_4Ac adjusted to pH = 5 with acetic acid) 35:65, flow rate: 6 mL/min, RT: 510 s ([^{18}F]MH.MZ). After diluting the collected HPLC fraction containing [^{18}F]MH.MZ with water, the product was trapped on an activated Sep-Pak®-C18-cartrige and subsequently eluted with 3 mL of ethanol into 12 mL of phosphate-buffered saline.

Determination of radiochemical purity and specific activity

The radiotracer preparation was visually inspected for clarity, absence of colour and particles. Chemical and radiochemical purities were also assessed on this aliquot by TLC and HPLC analysis.

[^{18}F]MH.MZ: Luna 150 × 4.6 mm 5 C_{18}(2) ((0.25 M NH_4Ac adjusted to pH = 5 with acetic acid) 35:65, flow rate: 1 mL/min, RT: [^{18}F]F^- = 2.4 min; [^{18}F]MH.MZ = 6.22 min; the intermediate [^{18}F](**5**) = 15.33 min; precursor (**5**) = 11.98 min; SiO_2-TLC: eluent: $CHCl_3$/MeOH, 8:1, R_f: [^{18}F]MH.MZ: 0.36, R_f: intermediate [^{18}F](**5**): 0.85 and R_f: [^{18}F]fluoride ion: 0.0).

Specific activity (A_s) of the radiotracers were calculated from three consecutive HPLC analyses (average), determined by the area of the UV absorbance peak corresponding to the radiolabelled product on the HPLC chromatogram and compared with a standard curve relating mass to UV absorbance.

Production of [^{18}F]MH.MZ via microwave heating

^{18}F-Labelling kinetics of the intermediate ([^{18}F](5)) of [^{18}F]MH.MZ in MeCN via MW heating: precursor concentration 3 mg/1 mL MeCN; ramp time 120 s; Power max (300 W with cooling); hold (heating until set temperature and hold set temperature).

Conclusion

We developed a method for direct radiofluorination of the 5-HT_{2A} receptor antagonist [^{18}F]MH.MZ and show that the direct does not have any significant benefits over the indirect labelling method. However, only one HPLC separation is necessary for the direct ^{18}F-nucleophilic labelling procedure, and accordingly, automation is easier.

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Conflict of Interest

The authors did not report any conflict of interest.

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