JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Labelled Cpd Radiopharm 2001; **44**: 1013–1023.
DOI: 10.1002/jlcr.523

Research Article

Carbon-11 labelling of MADAM in two different positions: a highly selective PET radioligand for the serotonin transporter

Jari Tarkiainen[1], Johnny Vercouillie[2], Patrick Emond[2], Johan Sandell[1], Jukka hiltunen[3], Yves Frangin[2], Denis Guilloteau[2] and Christer Halldin[1,*]

[1] *Karolinska Institutet, Department of Clinical Neuroscience, Psychiatry Section, Karolinska Hospital, S-17176 Stockholm, Sweden*
[2] *INSERM U316, Université François Rabelais, F-37200 Tours, France*
[3] *MAP Medical Technologies Oy, FIN-00251 Helsinki, Finland*

Summary

Imaging by scintigraphy the serotonin transporter (5-HTT) in the living human brain would be of great value in research on the pathophysiology and treatment of neuropsychiatric disorders such as depression. For that reason, and in order to obtain a selective radiotracer applicable to PET, we report here the carbon-11 labelling of a selective 5-HTT radioligand: *N*, *N*-dimethyl-2-(2-amino-4-methylphenylthio)benzylamine or MADAM in two different positions: [*p*-^{11}C-methyl]MADAM and [*N*-^{11}C-methyl]MADAM. The synthesis of Bu_3Sn-ADAM and *N*-dimethyl-MADAM is described. [*p*-^{11}C-methyl]MADAM was obtained by a Stille coupling reaction between Bu_3Sn-ADAM and [^{11}C]methyl iodide using palladium (0) as a catalyst without (Ia) or with copper chloride as a co-catalyst (Ib). [*N*-^{11}C-methyl]MADAM was obtained by an *N*-methylation reaction between *N*-demethyl-MADAM and [^{11}C]methyl iodide

*Correspondence to: C. Halldin, Karolinska Institutet, Department of Clinical Neuroscience, Psychiatry Section, Karolinska Hospital S-17176 Stockholm, Sweden.

Contract/grant sponsor: Swedish Medical Research Council; Contract/grant number; 12983-01A
Contract/grant sponsor: Karolinska Institutet
Contract/grant sponsor: INSERM-MFR
Contract grant sponsor: The Region Centre (France)
Contract/grant sponsor: European program; Contract/grant number: COST B12

Received 14 August 2001
Revised 3 September 2001
Accepted 12 September 2001

(II). The carbon-11 incorporation yield in [*p*-^{11}C-methyl]MADAM was 10–30% (Ia and Ib) and in [*N*-^{11}C-methyl]MADAM was 75-80% (II). The final product in each case was obtained in 30 min total synthesis time, including HPLC purification and with > 99% radiochemical purity.

Key Words: [^{11}C]MADAM; serotonin transporter; 5-HTT; carbon-11; PET

Introduction

The role of the serotonin transporter (5-HTT) system in psychiatric diseases such as depression[1] and in neurodegenerative disorders such as Alzheimer's and Parkinson's diseases[2,3] can be significant. This transporter modulates extracellular serotonin levels and acts as a site of action of many antidepressant drugs. It would be of a great value to explore the 5-HTT in human brain either by positron emission tomography (PET) or by single-photon emission computed tomography (SPECT) with appropriate radioligands.

Although several compounds have been synthesized possessing high affinity for the 5-HTT *in vitro* none of these are optimal in PET and SPECT due to a lack of selectivity for 5-HTT over the dopamine transporter (DAT) and the norepinephrine transporter (NET). This is the case for [^{11}C](+)McN5652 and certain cocaine derivatives.[4–9] Concerning [^{11}C]citalopram and [^{123}I]5-iodo-6-nitroquipazine they present unsuitable pharmacokinetic properties and a poor signal to noise ratio.[10–12]

Recently, Oya *et al.*[13] described a 403U76 derivative named ADAM (Figure 1), which exhibits *in vitro* high affinity and selectivity for 5-HTT ($Ki_{5\text{-}HTT} = 0.013 \pm 0.003$ nM, $Ki_{DAT} = 840 \pm 100$ nM, $Ki_{NET} = 699 \pm 80$ nM) and is an excellent SPECT tracer for visualisation of 5-HTT. In view of these results we synthesized [^{11}C]ADAM for PET

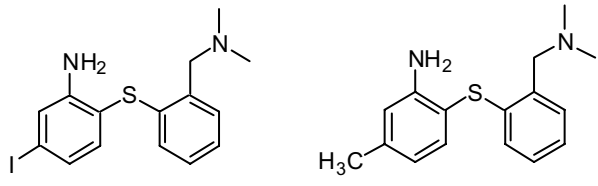

Figure 1. Structures of ADAM and MADAM (6)

examination.[14] However, the relatively slow binding kinetics obtained by [^{11}C]ADAM is not optimal for a PET radioligand.[15] In order to improve its pharmacokinetic properties several radiolabelled analogs of ADAM have been reported including the ^{11}C-methoxy (DAPP) and ^{11}C-cyano (DASB) derivatives[16] that have demonstrated potential for PET visualisation of 5-HTT in the human brain. We have synthesized *N*,*N*-dimethyl-2-(2-amino-4-methylphenylthio)benzylamine (MADAM) which exhibits high affinity and selectivity for 5-HTT ($Ki_{5\text{-}HTT} = 1.65 \pm 0.1$ nM, $Ki_{DAT} = > 10\,\mu$M, $Ki_{NET} = 325 \pm 108$ nM). Labelled with carbon-11, MADAM has potential as a PET radiotracer for visualization of the serotonin transporter in the human brain.

Here, we report the ^{11}C-labelling of MADAM (Figure 1, **6**) in two different positions: in the methyl group of the phenyl ring, *p*-[^{11}C]methyl and of the tertiary amino moiety, N-[^{11}C]methyl. Authentic MADAM compound and the required precursors were synthesized. [^{11}C]Methyl iodide was used in both case precursors subsequently to react in a Stille coupling reaction either with the Bu_3Sn-ADAM precursor using a palladium (0) catalyst with or without copper chloride as co-catalyst or to react in an N-methylation with the *N*-demethyl-MADAM precursor.

Results and discussion

Chemistry

The *N*-demethyl-MADAM precursor (**3**) and the authentic MADAM (**6**) were prepared as outlined in Figure 2 by direct coupling of 4-bromo-3-nitrotoluene with *N*-methyl-2-thiobenzamide and *N*,*N*-dimethyl-2-thiobenzamide, respectively.[14] The amide function was reduced using B_2H_6 in THF, and the nitro group was reduced with $SnCl_2$, hydrochloric acid and methanol, giving *N*-demethyl-MADAM (**3**) and MADAM (**6**). The synthesis of the stannylate precursor of MADAM (**7**) (*N*,*N*-dimethyl-2-(2-amino-4-tri-*n*-butyltinphenylthio)benzylamine) was carried out as previously described.[13]

Radiochemistry

The preparation of [*p*-^{11}C-methyl]MADAM (**8**) was done by a Stille coupling reaction between the tin precursor (**7**) and [^{11}C]methyl iodide

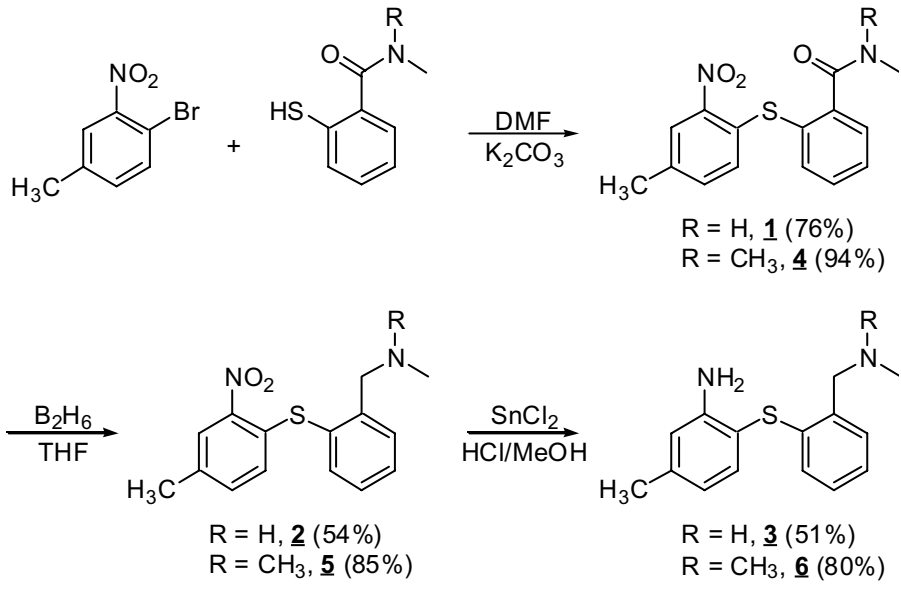

Figure 2. Synthesis of the N-desmethyl-MADAM (3) and MADAM (6)

in DMF. Our attempts using either palladium (0) catalyst with $(o\text{-Tol})_3P$ (Ia, 17) or copper(I) salts as co-catalyst along with palladium (0) catalyst, potassium carbonate and $(o\text{-Tol})_3P$ (Ib, 18) gave relatively low yields (Figure 3). The incorporation yield of C-11 was in both cases in the range of 10–30%. The preparation of [*N*-^{11}C-methyl]MADAM (**9**) was based on an *N*-methylation reaction of its *N*-demethyl precursor (**3**) using [^{11}C]methyl iodide in DMF (Figure 3). The radiochemical yield of C-11 at EOS was in the range of 75–80% using 0.7 mg of precursor **3**. [^{11}C]MADAM was obtained after HPLC purification (Figure 4) with

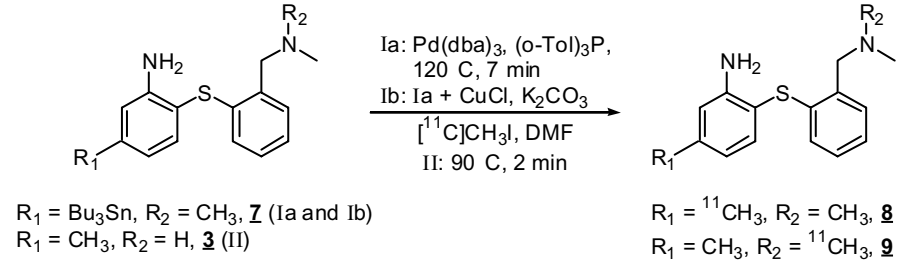

Figure 3. Syntheses (Ia, Ib and II) of [*p*-^{11}C-methyl]MADAM (8) and [N-^{11}C-methyl]MADAM (9) from their precursors 3 and 7, respectively

high radiochemical purity (> 99%) and specific radioactivity between 12 and 18 GBq/μmol at EOS.

Experimental

Chemistry

NMR spectra were recorded on a Bruker DPX Avance 200 spectrometer (200 MHz for ^{1}H, 50.3 MHz for ^{13}C). $CDCl_3$ was used as solvent; chemical shifts are expressed in ppm relative to TMS as an internal standard. Mass spectra were obtained on a CG-MS Hewlett Packard

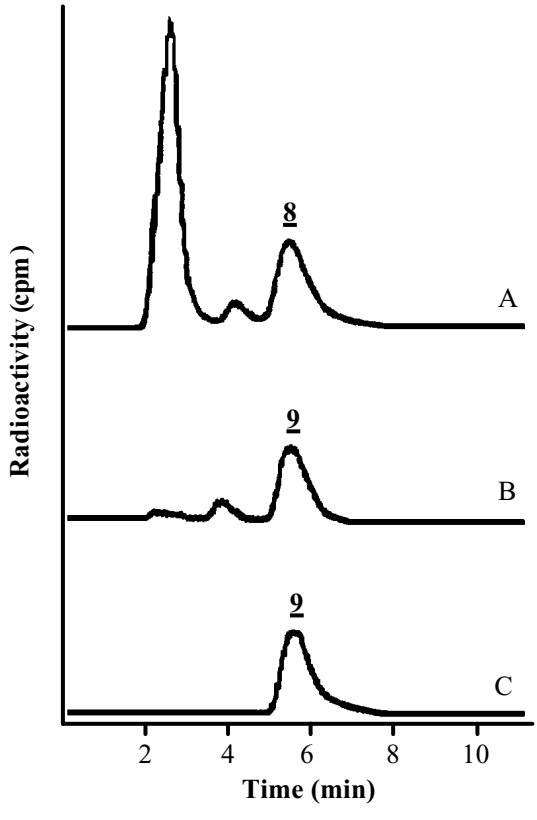

Figure 4. Radiochemical purity control by analytical HPLC. (A) Crude reaction mixture before HPLC-purification from reaction (Ia). (B) Crude reaction mixture before HPLC-purification from reaction (II). (C) After purification from reaction (II)

5989A spectrometer (electronic impact at 70 eV). The thin-layer chromatographic (TLC) analyses were performed using Merck 60F-254 silica gel plates. Flash chromatography was used for routine purification of reaction products using silica gel (230–400 Mesh). Visualisation was accomplished under UV or in an iodine chamber. All chemicals and solvents were of commercial quality and were purified following standard procedures.

*N-methyl-2-(4-methyl-2-nitrophenylthio)benzamide (**1**)*. A mixture of 4-bromo-3-nitrotoluene (5 g, 23.1 mmol), *N*-methyl-2-thiobenzamide (3.86 mg, 23.1 mmol) and K_2CO_3 (3.2 g, 23.1 mmol) in DMF (60 ml) was stirred at 80°C for 6 h. The solution was then poured into cold water (120 ml) and extracted with $CHCl_3$ (2×60 ml). The combined organic fractions were dried, filtered and evaporated to give a brown oil. After flash-chromatography (EtOAc), 5.287 g of pure compound **1** was obtained (76%).

^{1}H NMR: $\delta = 2.38$ (s, 3 H), 2.84 (d, 3 H), 6.54 (m, 1 H), 6.84 (d, 1 H, $^3J = 8.3$ Hz), 7.22 (dd, 1 H, $^3J = 8.4$ Hz, $^4J = 1.4$ Hz), 7.47–7.60 (m, 3 H); 7.78 (dd, 1 H, $^3J = 6.7$ Hz, $^4J = 2.1$ Hz), 8.00 (d, 1 H, $^4J = 1.4$ Hz). ^{13}C NMR: $\delta = 20.4$, 26.5, 125.6, 129.0, 129.6, 129.8, 130.1, 131.1, 133.4, 134.8, 136.5, 136.6, 140.9, 146.0, 168.0. MS (EI): $(m/z) = 302$ (41), 245 (64), 209 (76), 208 (89), 197 (97), 180 (100), 166 (80), 165 (65), 58 (91).

*N-methyl-2-(4-methyl-2-nitrophenylthio)benzylamine (**2**)*. Compound **1** (5 g, 15.8 mmol). was dissolved in anhydrous THF (41 ml) and a solution of 1 M borane complex in distilled THF (41 ml) was added at 0°C under a nitrogen atmosphere. The reaction mixture was refluxed for 5 h and then stirred at room temperature for 17 h. The reaction was cooled and treated with concentrated hydrochloric acid (72 ml), warmed at 70°C for 3 h and concentrated in vacuum. The residue was dissolved in $CHCl_3$ and the precipitate filtered. The solid was diluted in water, basified with NaOH and extracted with $CHCl_3$. The organic phases were dried and the solvent evaporated to give the crude product. After flash-chromatography (EtOAc/MeOH/Et_3N: 8/1/1) compound **2** was obtained in 54% yield.

^{1}H NMR: $\delta = 1.63$ (s, 1 H), 2.40 (s, 3 H), 2.43 (s, 3 H), 3.85 (s, 2 H), 6.63 (d, 1 H, $^3J = 8.3$ Hz), 7.18 (dd, 1 H, $^3J = 8.3$ Hz, $^4J = 1.9$ Hz), 7.39 (td, 1 H, $^3J = 7.4$ Hz, $^3J = 1.4$ Hz), 7.49–7.65 (m, 2 H), 8.11 (d, 1 H, $^4J = 1.9$ Hz). ^{13}C NMR: $\delta = 20.2$, 35.7, 53.3, 125.7, 127.5, 128.3, 129.6,

129.8, 130.3, 134.5, 135.0, 135.3, 137.1, 144.3, 144.6. MS (EI): $(m/z) = 253$ (20), 211 (32), 150 (22), 118 (31), 77 (29), 44 (100), 42 (81).

*N-methyl-2-(2-amino-4-methylphenylthio)benzylamine (**3**)*. Compound **2** (350 mg, 1.21 mmol). was dissolved in 9.7 ml of methanol and 4.8 ml of concentrated HCl. The mixture was cooled at 10°C and $SnCl_2$ (965 mg, 5.1 mmol) was added dropwise and stirred at room temperature overnight. The solution was basified with concentrated NaOH, ethylacetate added and the organic layer was extracted (2 times). Combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The crude material was purified by flash-chromatography (EtOAc/MeOH/Et_3N: 8/1/1) to afford the pure compound **3** in 60% yield.

^{1}H NMR: $\delta = 1.66$ (s, 1 H), 2.35 (s, 3 H), 2.55 (s, 3 H), 3.96 (s, 2 H), 4.26 (s, 2 H), 6.60–6.68 (*m*, 2 H), 6.83–6.88 (m, 1 H), 7.07–7.18 (m, 2 H), 7.29–7.39 (m, 2 H).

^{13}C NMR: $\delta = 21.4$, 36.0, 53.9, 110.7, 115.9, 119.8, 125.1, 126.2, 127.7, 129.2, 136.2, 137.0, 137.3, 141.4, 148.7. MS (EI): $(m/z) = 258$ (36), 212 (23), 151 (55), 150 (38), 120 (100), 44 (48), 42 (37).

*N,N-dimethyl-2-(4-methyl-2-nitrophenylthio)benzamide (**4**)*. A solution of 4-bromo-3-nitrotoluene (3.04 g, 14 mmol), K_2CO_3 (1.94 g, 14 mmol), N,N-dimethyl-2-thiobenzamide (4.00 g, 22 mmol) in DMF (35 ml) was heated at 120°C overnight. After cooling at room temperature, the reaction mixture was poured into cold water and extracted with EtOAc. The solvent was then removed and the residue purified by flash chromatography (EtOAc). Compound **4** was obtained as a yellow solid in 94% yield.

^{1}H NMR: $\delta = 2.37$ (s, 3 H), 2.88 (s, 3 H), 3.07 (s, 3 H), 6.89 (d, 1 H, $^3J = 8.4$ Hz), 7.22 (dd, 1 H, $^3J = 8.4$ Hz, $^4J = 2.0$ Hz), 7.42–7.62 (m, 4 H), 8.20 (d, 1 H, $^4J = 2.0$ Hz). ^{13}C NMR: $\delta = 20.9$, 34.9, 38.9, 125.9, 127.9, 128.6, 130.2, 130.6, 130.9, 134.3, 135.0, 136.5, 137.3, 143.5, 145.8, 169.5. MS: $m/z = 316$ (15), 270 (61); 226 (100), 197 (66), 72 (72), 44 (43).

*N,N-dimethyl-2-(4-methyl-2-nitrophenylthio)benzylamine (**5**)*. To a solution of compound **4** (3.7 g, 11.7 mmol) in THF (29 ml) under a nitrogen atmosphere was added dropwise diborane-THF (1 M, 29 ml, 29 mmol) at 0°C. The mixture was heated to reflux for 5 h, stirred at room temperature overnight and quenched with concentrated HCl. The residue was then dissolved in water, basified with NaOH and extracted

with $CHCl_3$. After evaporation of the solvent, the crude product was purified by flash chromatography (EtOAc/Et_3N: 9/1) in 85% yield.

^1H NMR: $\delta = 2.23$ (s, 6 H), 2.40 (s, 3 H), 3.56 (s, 2 H), 6.63 (d, 1 H, $^3J = 8.3$ Hz,), 7.16 (dd, 1 H, $^3J = 8.3$ Hz, $^4J = 2.0$ Hz), 7.38 (td, 1 H, $^3J = 7.4$ Hz, $^4J = 1.5$ Hz), 7.50 (td, 1 H, $^3J = 7.4$ Hz, $^4J = 1.5$ Hz), 7.56 (dd, 1 H, $^3J = 7.4$ Hz, $^4J = 1.4$ Hz), 7.69 (dd, 1 H, $^3J = 7.4$ Hz, $^4J = 1.4$ Hz), 8.08 (d, 1 H, $^4J = 2.0$ Hz). ^{13}C NMR: $\delta = 20.3$, 45.2 (2C), 61.0, 125.7, 128.1, 128.2, 130.1, 130.3, 130.6, 134.3, 135.2, 135.3, 136.8, 143.5, 145.0. MS: $m/z = 302$ (12), 285 (42), 211 (75), 194 (21), 58 (100), 42 (25).

*N,N-dimethyl-2-(2-amino-4-methylphenylthio)benzylamine (**6**).* To a solution of compound **5** (2.00 g, 6.61 mmol), concentrated HCl (24 ml) and MeOH (49 ml) was added $SnCl_2$ (4.9 g, 25.84 mmol) at below 10°C. The reaction mixture was stirred at room temperature overnight, treated with water (120 ml), basified with NaOH and extracted with EtOAc. After evaporation of the solvent, the residue was purified by flash chromatography (EtOAc/petroleum ether/Et_3N: 5/4.5/0.5) in 80% yield. ^1H NMR: $\delta = 2.34$ (s, 6 H), 2.36 (s, 3 H), 3.62 (s, 2 H), 4.44 (s large, 2 H), 6.60–6.65 (m, 2 H), 6.91 (dd, 1 H, $^3J = 7.3$ Hz, $^4J = 1.6$ Hz), 7.07–7.16 (m, 2 H), 7.27–7.31 (m, 1 H), 7.41 (d, 1 H, $^3J = 8.3$ Hz). ^{13}C NMR: $\delta = 22.0$, 45.8 (2C), 62.8, 112.2, 116.4, 120.0, 125.5, 127.6, 128.4, 130.6, 136.9, 138.0, 138.2, 141.7, 149.6. MS: $m/z = 272$ (M^+, 24), 165 (100), 164 (57), 150 (48), 134 (44), 132 (32), 58 (57), 44 (40).

Radiochemistry

All chemicals were obtained from commercial sources and were of analytical grade. $^{11}CO_2$ was produced batchwise using the Scanditronic MC 16 cyclotron at the Karolinska Hospital/Institute by bombardment of a nitrogen gas target with 16 MeV protons in the $^{14}N(p,\alpha)^{11}C$ reaction. Carbon-11 labelled methyl iodide was synthesised from $^{11}CO_2$ utilising a one-pot reaction set-up similar to that reported previously.[9]

Semi-preparative reversed-phase HPLC was performed using a Waters μ-Bondapak C-18 column (300 × 7.8 mm, 10 μm) and an UV-detector (wavelength = 254 nm) in series with a GM-tube for radiation detection. [*p*-methyl-^{11}C]MADAM (**8**, Ia) was purified by HPLC using acetonitrile and 0.1 M ammonium formate ($\frac{50}{50}$) as the mobile phase with a flow rate of 6 ml/min. [*p*-methyl-^{11}C]MADAM (**8**, Ib) was not purified by semi-preparative system because of discouraging radiochemical yields according to analytical HPLC. [*N*-methyl-^{11}C]MADAM (**9**) was

purified by HPLC using acetonitrile and 0.01 M ammonium formate ($\frac{35}{65}$) as the mobile phase with a flow rate of 8 ml/min. The radiochemical purity of the products was determined by reversed phase HPLC with a Waters μ-Bondapak C-18 column (300 × 3.9 mm, 10 μm) and a UV-detector (wavelength = 234 nm) in series with a Beckman β-flow radiodetector for radiation detection. Acetonitrile and 0.01 M H_3PO_4 ($\frac{30}{70}$) were used as the mobile phase with a flow rate of 2 ml/min. The chemical identity of [*p*-methyl-^{11}C]- and [*N*-methyl-^{11}C] MADAM (**8** and **9**) was determined by co-injection of unlabelled MADAM (**6**).

*Preparation (Ia) of [p-methyl-^{11}C]MADAM (**8**).* Catalysts, tris(dibenzylidene-acetone)dipalladium(0)[$Pd_2(dba)_3$, 0.9 mg,. 1 μmol] and tri(o-tolyl)phosphine [$(o\text{-Tol})_3P$, 1.2 mg, 4 μmol] in 350 μl of *N,N*-dimethylformamide (DMF), were stirred in a N_2 purged dry septum equipped 1.0 ml vial for 10 min. [^{11}C]Methyl iodide was trapped in the solution at room temperature. After trapping the reaction mixture was transferred to a septum equipped 1.0 ml vessel containing 2 mg (3.7 μmol) of precursor **7**. The reaction vessel was heated at 120°C for 7 min. The mobile phase (600 μl) was added prior to injection into the semi-preparative HPLC column. The product fraction was collected after the retention time of 11 min and the mobile phase was evaporated. To the residue was added 8 ml of sterile physiological phosphate buffer (pH = 7.4) solution which was then filtered through a Millipore filter (0.22 μm) yielding a solution which was sterile and free from pyrogens.

*Preparation (Ib) of [p-methyl-^{11}C]MADAM (**8**).* Catalysts, $Pd_2(dba)_3$ (1.7 mg, 1.9 μmol). and $(o\text{-Tol})_3P$ (2.1 mg, 6.9 μmol) in 200 μl of DMF, were stirred in a N_2 purged dry septum equipped 1.0 ml vial for 10 min. The mixture of tin precursor **7** (2.0 mg, 3.7 μmol), CuCl (1.8 mg, 18.2 μmol) and K_2CO_3 (2.1 mg, 15.2 μmol) was prepared in a dry septum equipped 1.0 ml vial without DMF and flushed carefully with N_2 gas for 10 min. [^{11}C]Methyl iodide was trapped at room temperature in the solution containing Pd-catalyst etc. DMF (100 μl) was added just before transferring the trapping solution into the mixture of tin precursor **7** etc. After the addition of the trapping solution the vial was shaken vigorously and heated at 120°C for 7 min. A sample was taken and analysed by HPLC, giving discouraging result.

*Preparation (II) of [N-methyl-^{11}C]MADAM (**9**).* [^{11}C]Methyl iodide was trapped at room temperature in a reaction vessel (1.0 ml) containing the precursor [0.7 mg of the *N*-demethyl-MADAM (**3**)] and DMF (300 μl). The vessel was sealed and heated at 90°C for 2 min. The mobile phase (600 μl) was added prior to injection into the semi-preparative HPLC column. The radioactive fraction containing the methylated radioligand was collected after the retention time of 15 min. After evaporation of the mobile phase the residue was dissolved in 8 ml of sterile physiological phosphate buffer (pH = 7.4) solution and filtered through a Millipore filter (0.22 μm), yielding a solution which was sterile and free from pyrogens.

Acknowledgements

The authors would like to thank Mr Göran Printz for assistance with the radionuclide production, Mr Arsalan Amir and Miss Vilar Marie-Paule for technical assistance. Grants from the Swedish Medical Research Council (12983-01A), Karolinska Institutet, INSERM-MFR, the Région Centre (France) and European program (COST B12) supported this work. We thank SAVIT (Prof. P. Dubois) for chemical analysis.

References

1. Owens MJ, Nemeroff CB. *Clin Chem* 1994; **40**: 288–295.
2. Tejani-Butt SM, Yang J, Pawlyk AC. *Neuro Report* 1995; **6**: 1207–1210.
3. Chinaglia G, Landwehrmayer B, Probst A, Palacios JM. *Neurosci* 1993; **54**: 691–699.
4. Szabo Z, Kao PN, Scheffel U, *et al. Synapse* 1995; **20**: 37–43.
5. Boja JW, Mitchell WM, Patel A, *et al. Synapse* 1992; **12**: 27–36.
6. Scheffel U, Dannals RF, Cline EJ, *et al. Synapse* 1992; **11**: 27–36.
7. Bergström KA, Halldin C, Hall H, *et al. Eur Nucl Med Biol* 1997; **24**: 596–601.
8. Hiltunen J, Åkerman KK, Kuikka JT, *et al. Eur Nucl Med Biol* 1998; **25**: 19–23.
9. Helfenbein J, Sandell J, Halldin C, *et al. Nucl Med Biol* 1999; **26**: 491–499.
10. Jagust WJ, Eberling JL, Roberts JA, *et al. Eur J Pharm* 1993; **242**: 189–193.
11. Jagust WJ, Eberling JL, Biegon A, *et al. J Nucl Med* 1996; **37**: 1207–1214.

12. Hume SP, Pascali C, Pike VW, *et al. Nucl Med Biol*. 1991; **18**: 339–351.
13. Oya S, Choi S-R, Hou C, *et al. Nucl Med Biol* 2000; **27**: 249–254.
14. Vercouillie J, Tarkiainen J, Halldin C, *et al. J labelled Cpd Radiopharm* 2001; **44**: 113–120.
15. Halldin C, Guilloteau D, Tarkiainen J, *et al. J Nucl Med* 2001; **42**: 112.
16. Houle S, Ginovart N, Hussey D, Meyer JH, Wilson AA. *Eur J Nucl Med* 2000; **27**: 1719–1722.
17. Björkman M, Andersson Y, Doi H, *et al. Acta Chem Scand* 1996; **52**: 635–640.
18. Björkman M, Doi H, Resul B, *et al. J labelled Cpd Radiopharm* 2000; **43**: 1327–1334.

