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Highly Efficient Synthesis of [^{11}C]PE2I, a Selective Radioligand for the Quantification of the Dopamine Transporter using PET

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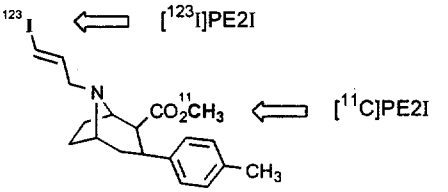
Summary

PE2I ((E)-N-(3-iodoprop-2-enyl)-2β-carbomethoxy-3β-(4'-tolyl) nortropane) is a cocaine derivative belonging to a new generation of selective dopamine transporter inhibitors. Labelled with iodine-123 (half-life : 13.1 hours), PE2I has been dedicated to the diagnostics of neurodegenerative diseases such as Parkinson's disease in humans using single photon emission computed tomography. Labelled with carbon-11 (half-life : 20.4 minutes), it can be used in the absolute quantification of the dopamine transporter (DAT) using the high-resolution, sensitive and non-invasive quantitative imaging technique PET (positron emission tomography). In this paper, the radiosynthesis of carbon-11 labelled PE2I was investigated and oriented towards the preparation of multi milliCuries of radiotracer. Typically, 200 to 300 mCi (7.4-11.1 GBq) of [^{11}C]PE2I were routinely obtained within 25 minutes of radiosynthesis (including HPLC purification) with specific radioactivities ranging from 0.8 to 1.2 Ci/μmol (29.6-44.4 GBq/μmol). Based on the preliminary PET experiments, it can be assumed that this radioligand would permit quantification of the DAT using PET and mathematical compartmental ligand-transporter models.

Key Words : PE2I, carbon-11, positron emission tomography, PET, dopamine transporter

Introduction

PE2I (**1**, (E)-N-(3-iodoprop-2-enyl)-2β-carbomethoxy-3β-(4'-tolyl) nortropane (1)) and its bromo analogue PE2Br (2) are cocaine derivatives belonging to a new generation of selective dopamine transporter inhibitors (1-6). Labelled with iodine-123 (half-life : 13.1 hours), PE2I ([^{123}I]-**1**) has been dedicated to the diagnostics of neurodegenerative diseases such as Parkinson's disease in humans using the imaging technique single photon emission computed tomography (7,8).



Due to its chemical structure, this compound can also be labelled with carbon-11 (9,10), a positron-emitting isotope (half-life : 20.4 minutes). It can therefore be used in the absolute quantification of dopamine transporter (DAT)

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in the brain using the high-resolution, sensitive and quantitative imaging technique PET (positron emission tomography). Mathematical compartmental ligand-transporter models using a kinetic approach based on a multi-injection protocol can be used in order to analyze and fit the PET time-concentration curves (11). A typical multi-injection protocol requires the preparation at a given time of large amounts of labelled tracer.

In this paper, the radiosynthesis of carbon-11 labelled PE2I ([^{11}C]-**1**) has been investigated and oriented towards the preparation of hundreds of milliCuries of radiotracer. Preliminary PET curves obtained in a *Papio anubis* baboon following a single injection of a tracer dose of [^{11}C]PE2I ([^{11}C]-**1**) are also presented.

Results and discussion

Radiochemistry

PE2I (**1**) was labelled with carbon-11 at its methyl ester function from the corresponding carboxylic acid precursor **2** and the highly efficient methylation reagent [^{11}C]methyl triflate.

[^{11}C]Methyl triflate was prepared according to a literature procedure from [^{11}C]methyl iodide using silver triflate (12). [^{11}C]Methyl iodide was prepared from [^{11}C]carbon dioxide using the well-known two step, one pot protocol, consisting of the trapping of [^{11}C]CO_2 and conversion into [^{11}C]methanol ($LiAlH_4$) followed by iodination using aqueous HI giving [^{11}C]methyl iodide (13).

$$[^{11}C]CO_2 \xrightarrow[\text{then } H_2O]{LiAlH_4/THF} [^{11}C]CH_3OH \xrightarrow{\text{aq. HI}} [^{11}C]CH_3I \xrightarrow[150\text{-}200°C]{AgOTf} [^{11}C]CH_3OTf$$

On average, about 750 mCi (27.75 GBq) of [^{11}C]CH_3OTf is routinely obtained in our laboratory in 7 to 8 minutes after the end of the bombardment (EOB) in 80% decay-corrected yield (960 mCi or 35.52 GBq, at EOB), based on starting [^{11}C]CO_2 (1.20 Ci or 44.40 GBq, at EOB).

Reaction of the desmethyl-compound **2** hydrochloride with [^{11}C]methyl triflate employing the standard conditions that have so far been used in our laboratory for the routine radiosynthesis of [^{11}C]raclopride for example, yielded [^{11}C]PE2I in unusual low yield : The conditions used were the following : (1) trapping at room temperature of the [^{11}C]methyl triflate in 300 µL of acetone (solvent) containing 0.4-0.6 mg of precursor (**2**, hydrochloride, 0.9-1.3 µmol) and 5 µL of a 1M solution of TMBA (benzyltrimethylammonium hydroxide) in EtOH (5 µmol) ; (2) concentration to dryness of the reaction mixture (at 105°C, using a helium stream) ; (3) taking up the crude with 0.5 mL of the HPLC mobile phase and (4) HPLC purification. From an average production batch of 960 mCi (or 35.52 GBq, at EOB) of [^{11}C]CH_3OTf, only 20 to 30 mCi of [^{11}C]PE2I could be synthesized in 30 minutes after EOB (Yield, decay-corrected and based on [^{11}C]methyl triflate : 6-9%).

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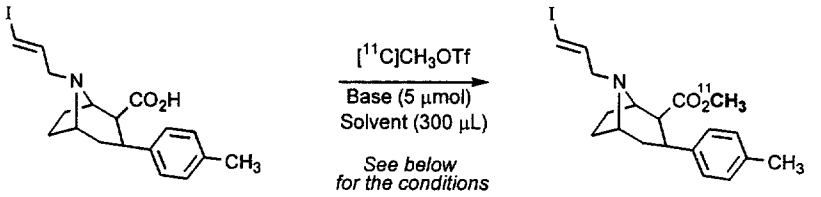
Using DMF as the solvent (300 µL) and only a slight modification of the procedure (no concentration to dryness of the reaction mixture after the [^{11}C]methyl triflate trapping) significantly increases the yield : 12-20%, providing 40 to 70 mCi of [^{11}C]PE2I (111 to 194 mCi, decay-corrected for EOB) in about 30 minutes synthesis time. However, using DMF as the solvent affected the HPLC resolution, which may give rise to less pure [^{11}C]PE2I. The replacement of the base TMBA (5 µL of a 1M solution of TMBA in EtOH, 5 µmol) by NaOH (2 µL of a 2.5M solution of NaOH in water, 5 µmol) did not affect the yield (Yield, decay-corrected and based on [^{11}C]methyl triflate : 15-20%).



Nor-PE2I (**2**)
0.9-1.3 µmol

PE2I (**1**)

Precursor	Solvent	Base	Yield §	Protocol
HCl salt	acetone	TMBA	6-9%	a,b,c,d
HCl salt	DMF	TMBA	12-20%	a,c & d
HCl salt	DMF	NaOH	15-20%	a,c & d
free base	acetone	NaOH	49-74% #	a,b,c,d

Conditions : (a) [^{11}C]methyl triflate trapping at room temperature for 2-3 min ; (b) Concentration to dryness of the reaction mixture (at 105°C, using a helium stream) ; (c) Taking up the crude with 0.5 mL of the HPLC mobile phase and (d) HPLC purification.

§ : decay-corrected, based on [^{11}C]methyl triflate ; # : and occasionally up to 95%.

Based on previous observations in our laboratory regarding the often poor labelling of hydrochloride or hydrobromide salts of a precursor (14-16), the free base of compound **2** was prepared (see experimental for details).

Reaction of the desmethyl-compound **2** (0.4-0.6 mg, as the free base, 0.9-1.3 µmol) with [^{11}C]methyl triflate in acetone (300 µL) containing 2 µL of a 5M solution of NaOH in water (10 µmol) yielded [^{11}C]PE2I in very high yield : The conditions used were identical to those described above : (1) trapping at room temperature of the [^{11}C]methyl triflate ; (2) concentration to dryness of the reaction mixture (at 105°C, using a helium stream) ; (3) taking up the crude with 0.5 mL of the HPLC mobile phase and (4) HPLC purification. Typically, 200 to 300 mCi (7.4-11.1 GBq) of [^{11}C]PE2I ([^{11}C]-**1**) were routinely obtained within 25 minutes of radiosynthesis (including HPLC purification). Occasionally, up to 380 mCi (14.1 GBq) were obtained. Based on a decay-corrected average production batch of 960 mCi (35.52 GBq) of [^{11}C]CH_3OTf, the decay-corrected yields for these radiosyntheses are 49-74% (up to 95%).

The specific radioactivities at the end of the synthesis range from 0.8 to 1.2 Ci/µmol (29.6-44.4 GBq/µmol).

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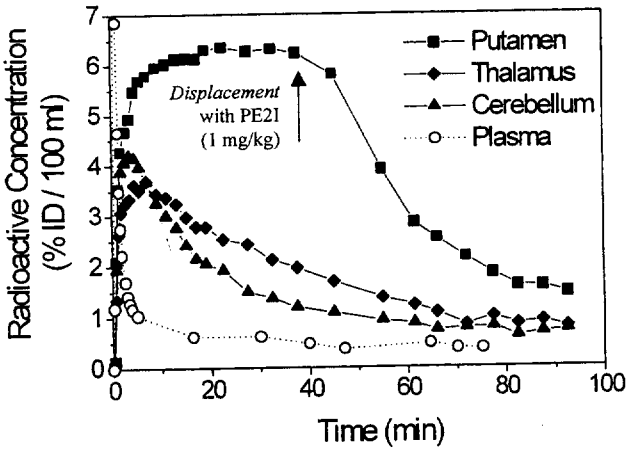
These highly efficient productions permit the preparation of 3 syringes, each containing 5 mCi (185 MBq) of radiotracer at their time of injection (usually 10, 50 and 90 minutes respectively after the end of synthesis).

Brain PET study in Papio anubis baboon

Kinetics of the tracer in cerebral structures and in plasma following a single injection of tracer are shown below. Typical decay-corrected time-activity curves obtained in several brain structures after i.v. administration of a tracer dose of [^{11}C]PE2I (5.6 mCi or 207.2 MBq ; i.e. 7.5 nmol ; close symbols) are represented. Unlabelled PE2I (1 mg/kg) was injected i.v., 40 minutes after tracer injection. Plasma kinetics are also displayed (open symbols). Values are expressed in % ID/100 mL of tissue (% of injected dose per 100 mL of tissue).



After injection of [^{11}C]PE2I, there was a rapid appearance of radioactivity in the whole of the brain. The time course of radioactivity showed a rapid accumulation in the caudate nucleus and putamen, reaching a plateau at about 6% ID/100 mL, 10 minutes after injection. In the thalamus and cerebellum radioactivity concentrations were maximal at 5 minutes post injection (p.i.) at a level of 3.5% and 4.0% ID/100 mL respectively and decreased progressively during the PET study to 1.7% and 1.0% ID/100 mL respectively at 40 minutes post injection. Radioactivity in the thalamus remained slightly higher than radioactivity in the cerebellum. The thalamus to cerebellum radioactivity concentration ratios were 1.7 after 40 minutes. Mainly because of the continuous wash-out from the cerebellum, the caudate nucleus to cerebellum, and putamen to cerebellum radioactivity concentration ratios increased from 2 at 10 minutes p.i. to 5.0 and 5.4 and respectively at 40 minutes p.i.

Displacement with unlabelled PE2I (1 mg/kg, at 40 minutes post injection) induced a rapid wash-out of the radioactivity in the caudate nucleus and putamen. In these structures, the ratios decreased rapidly and reached 2.2 and 2.0 respectively. A small and rather slow radioactive displacement induced by the injection of unlabelled PE2I was also observed in the thalamus while no displacement was observed in the cerebellum.

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Experimental

General

PE2I (**1**, (E)-N-(3-iodoprop-2-enyl)-2β-carbomethoxy-3β-(4'-tolyl) nortropane) and its desmethyl labelling precursor **2** were kindly provided by Prof. D. Guilloteau (INSERM 316 - Laboratoire de Biophysique Médicale et Pharmaceutique, Faculté de Pharmacie, Tours, France) and Dr L. Mauclaire (CIS Bio International, Gif-sur-Yvette, France). Other chemicals were purchased from Aldrich, Fluka or Sigma (France) and were used without further purification.

HPLCs : **A** : Equipment : HPLCs were run on Waters systems equipped with a 510 pump, 440 UV detector or 481 & 486 UV-multiwavelength detectors ; the effluent was also monitored for radioactivity with a Geiger-Müller counter ; column : semipreparative C-18 Zorbax® SB, Hewlett Packard (250 x 9.4 mm) ; porosity : 5 μm ; conditions: isocratic elution with : MeCN / water / TEA : 85 / 15 / 0.1 ; flow rate : 6.0 mL/min ; temperature : RT ; UV detection at λ : 254 nm ; **B** : Equipment : HPLC system consisted of two Shimadzu (Kyoto, Japan) LC-10AS pumps, a 2.6 mL mixing chamber, a Valco injector (model C6W ; Vici Valco Instruments, Tx, USA) with a 1 mL loop, a UV detector (Shimadzu SPD-10A) operated at 254 nm and a radioisotope detector (Berthold, Wildbad, Germany ; model LB 506, 500 μl cell). A Berthold LB 5035 pump was used to add liquid scintillator (Quickszint Flow 302 ; Zinsser Analytic, Frankfurt, Germany) to the eluent at a flow rate of 6.0 mL/min, just before the radioactivity detector. The data acquisition and handling were done on a PC using the software Winflow (vers. 1.21, JMBS Developments, Grenoble, France) ; column : analytical C-18, μBondapak®, Waters (300 x 3.9 mm) ; porosity : 5 μm ; conditions : gradient elution from 20% acetonitrile in 0.01M aq. phosphoric acid up to 90% in 7 min ; flow rate before addition of the liquid scintillator : 2.0 mL/min ; temperature : RT ; UV detection at λ : 254 nm.

Specific radioactivity was determined as follows : The area of the UV absorbance peak corresponding to the radiolabelled product was measured on the HPLC chromatogram and compared to a standard curve relating mass to UV absorbance.

Animal subjects : All animal-use procedures were in strict accordance with the recommendations of the EEC (86/609/CEE) and the French National Committee (décret 87/848) for the care and use of laboratory animals.

Preparation of [^{11}C]CO_2

[^{11}C]CO_2 was produced by irradiation of an ultrapure N60 Air Liquide N_2 target with a 20 MeV proton beam (30 μA) *via* the ^{14}N[p,α]^{11}C nuclear reaction on a CGR-MeV 520 cyclotron (54000 μC in 30 minutes). After being separated from the target gas by trapping at -186°C (liquid argon), the [^{11}C]CO_2 was released from the trap by simply raising the latter to room temperature and using nitrogen as vector gas.

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Preparation of [^{11}C]CH_3OTf

[^{11}C]CO_2 was converted into [^{11}C]CH_3OH by reduction at room temperature with a 1.0M THF solution of lithium aluminium hydride (5 μL) in THF (50 μL), followed by concentration (evaporation of solvent) and hydrolysis (50 μL of deionized water). The [^{11}C]MeOH was distilled using a flow of nitrogen gas (heating block at 105°C) into 1 mL of an aqueous 57% HI solution. The [^{11}C]CH_3I thus synthesized was continuously swept away by a flow of nitrogen gas (heating block at 165°C), passed through a P_2O_5 guard and converted into [^{11}C]CH_3OTf by passing through a glass column (internal diameter : 5 mm, length : 33 cm), heated at 200°C and containing silver triflate impregnated graphitized carbon (200 mg). [^{11}C]CH_3OTf was then trapped at room temperature into the reaction flask, containing the solvent, the base and the precursor. On average, about 750 mCi (27.75 GBq) of [^{11}C]CH_3OTf is routinely obtained in our laboratory in 7 to 8 minutes after EOB in 80% decay-corrected yield (960 mCi or 35.52 GBq, EOB), based on starting [^{11}C]CO_2 (1.20 Ci or 44.40 GBq, EOB).

Preparation of [^{11}C]PE2I

[^{11}C]CH_3OTf was trapped at room temperature in a reaction vessel containing 0.4-0.6 mg of the desmethyl-precursor **2** (hydrochloride or salt-free base*, 0.9-1.3 μmol) dissolved in a mixture of 5-10 μmol of the base used (for TMBA, 5 μL of a 1M solution of TMBA in EtOH ; for NaOH, 2 μL of a 2.5M solution of NaOH in water) and 300 μL of the solvent used (acetone or DMF). Trapping of [^{11}C]CH_3OTf was monitored using an ionisation-chamber probe. When the reading had reached its maximum (2 to 3 minutes usually), the reaction mixture was concentrated to dryness (at 105°C, using a helium stream). The crude was then taken up with 0.5 mL of the HPLC mobile phase and was injected onto the column (HPLC A ; retention time : 6.5 to 7.5 min). Typically, 200 to 300 mCi (7.4-11.1 GBq) of [^{11}C]PE2I ([^{11}C]-**1**) with a radiochemical- and chemical purity of more than 95% were routinely obtained within 25 minutes of radiosynthesis (including HPLC purification) with specific radioactivities of 800-1400 mCi/μmol (29.6-51.8 GBq/μmol).

* Compound **2** (25 mg, as its HCl salt) was dissolved in diluted aqueous ammonia (200 μL of aq. 28% NH_4OH in 5 mL water) and then extracted with diethylether (three times 15 mL). The organic layers were combined, washed once with brine (10 mL), dried over anhydrous sodium sulphate and concentrated to dryness to give 20 mg of salt-free base desmethyl-precursor which were divided into 0.4 to 0.6 mg aliquots and stored for future labelling.

Formulation of [^{11}C]PE2I ([^{11}C]-1)

Formulation of labelled product for i.v. injection was effected as follows : (1) HPLC solvent removal by evaporation ; (2) taking up the residue, while heating gently (45°C), in 5 mL of physiological saline; (3) filtration on a 0.22 μm Millipore filter. Injection in PET experiments was done within 15 minutes after End Of Synthesis.

Quality control of [^{11}C]PE2I ([^{11}C]-1)

As demonstrated by HPLC analysis (HPLC A and HPLC B), the radiolabelled product was found to be > 95% chemically and radiochemically pure and also co-eluted with a sample of authentic PE2I (**1**) (HPLC A ; retention time : 6.5 to 7.5 min ; HPLC B ; retention time : 6.0 to 6.5 min). The preparation was shown to be free of non-radioactive precursor and radiochemically stable for at least 180 min.

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Positron Emission Tomography using [^{11}C]PE2I ([^{11}C]-1)

PET studies of the brain distribution and -kinetic of [^{11}C]PE2I were carried out in an adult Papio anubis baboon. The Animal was anesthetized with ketamine, intubated and artificially respired with 1-1.5% isoflurane, 67% N_2O, 33% O_2 (controlled by an Ohmeda OAV 7710 ventilator). The tidal volume was adjusted to achieve stable end-tidal carbon dioxide tension between 38-40 mmHg. The baboon's head was fixed in the tomograph using a custom-designed stereotaxic headholder and positioned in the scanner gantry for axial plane acquisition.

Brain distribution experiments were performed with an ECAT 953B/31 tomograph (CTI/Siemens, Knoxville). A transmission scan (^{68}Ge rods, 15 minutes) was recorded to correct for γ-ray attenuation. The image acquisition started at the intravenous injection of [^{11}C]PE2I (5.6 mCi; with a specific radioactivity of 750 mCi/μmol) and lasted 100 minutes. Arterial blood samples were withdrawn from a femoral artery at designated times to follow plasma [^{11}C]PE2I kinetics. Blood and plasma radioactivity was measured in a γ-counter and the blood-plasma time-activity curves were corrected for carbon-11 decay from the beginning of the PET acquisition.

Regions of interest (ROI) for anatomical structures such as caudate nucleus, putamen, thalamus and cerebellum were delineated on PET images. The concentration of radioactivity in each ROI was determined on each sequential scan and expressed as percent of the injected dose per 100 ml of tissue (% ID / 100 ml).

Displacement with unlabelled PE2I (1 mg/kg) was performed 40 minutes after injection of the tracer.

Conclusion

In this paper, the radiosynthesis of carbon-11 labelled PE2I ([^{11}C]-**1**), a new tracer for DAT exploration by PET, was investigated and oriented towards the preparation of multi milliCuries of radiotracer. Large amounts of [^{11}C]PE2I (typically, 200 to 300 mCi (7.4-11.1 GBq)) were routinely obtained within 25 minutes of radiosynthesis (including HPLC purification) with specific radioactivities ranging from 0.8 to 1.2 Ci/μmol (29.6-44.4 GBq/μmol). The high efficiencies of these radiosyntheses will allow quantification of the DAT using kinetic approaches based on multi-injection protocols.

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References

1. Emond P., Garreau L., Chalon S., Boazi M., Caillet M., Bricard J., Frangin Y., Mauclaire L., Besnard J.-C. and Guilloteau D. - *J. Med. Chem.* 40: 1366-1372 (1997).
2. Helfenbein J., Emond P., Loc'h C., Bottlaender M., Ottaviani M., Guilloteau D., Mazière B., Frangin Y., Chalon S. - *J. Label. Compounds Radiopharm.*, 42: 581-588 (1999),
3. Guilloteau D., Emond P., Baulieu J.L., Garreau L., Frangin Y., Pourcelot L., Mauclaire L., Besnard J.C. and Chalon S. - *Nucl. Med. Biol.* 25: 331-337 (1998).
4. Chalon S., Emond P., Bodard S., Vilar M.P., Thiercelin C., Besnard J.C. and Guilloteau D. - *Synapse* 31: 134-139 (1999).
5. Hall H., Halldin C., Guilloteau D., Chalon S., Emond P., Besnard J., Farde L. and Sedvall G. - *Neuroimage* 9: 108-116 (1999).
6. Helfenbein J., Loc'h C., Coulon C., Emond P., Guenther I., Ottaviani M., Fuseau C., Chalon S., Bottlaender M., Frangin Y., Guilloteau D., Mazière B. - *Life Sci.* 65: 2715-2726 (1999).
7. Kuikka J.T., Baulieu J.L., Hiltunen J., Halldin C., Bergstrom K.A., Farde L., Emond P., Chalon S., Yu M., Nikula T., Laitinen T., Karhu J., Tupala E., Hallikainen T., Kolehmainen V., Mauclaire L., Maziere B., Tiihonen J. and Guilloteau D. - *Eur. J. Nucl. Med.* 25: 531-534 (1998).
8. Kuikka J.T., Tupala E., Bergstrom J., Hiltunen J., Tiihonen J., Chalon S., Garreau L., Emond P., Zimmer L., Vilar M.P., Besnard J.C. and Guilloteau D. - *J. Pharmacol Exp. Ther.* 291: 648-654 (1999).
9. Lundkvist C., Halldin H., Guilloteau D., Olsson H., Karlsson P., Chalon S., Emond P., Frangin Y., Hall H., Swahn C.G. and Farde L. - *J. Label. Compounds Radiopharm.*, 40: 580-582 (1997), *abstract of the XIIth International Symposium on Radiopharmaceutical Chemistry, Uppsala, Sweden (June 15-19, 1997).*
10. Halldin C., Guilloteau D., Okubo Y., Lundkvist C., Olsson H., Karlsson P., Chalon S., Emond P., Swahn C.-G. and Farde L. - *J. Nucl. Med.* 39: 118 (1998), *abstract of the 45th Annual Meeting of the Society of Nuclear Medicine (USA), Toronto, Ontario, Canada (June 7-11, 1998).*
11. Delforge J., Pappata S., Millet P., Samson B., Bendriem B., Jobert A., Crouzel C. and Syrota A. - *J. Cereb. Blood Flow Metab.* 15: 284-300 (1995).
12. Jewett D.M. - *Appl. Radiat. Isot.* 43: 1383-1385 (1992).
13. Crouzel C., Langstrom B., Pike V.W. and Coenen H.H. - *Appl. Radiat. Isot.* 38: 601 (1987).
14. Langer O., Halldin C., Dollé F., Swahn C.-G., Olsson H., Karlsson P., Hall H., Sandell J., Lundkvist C., Vaufrey F., Loc'h C., Crouzel C., Mazière B. and Farde L. - *Nucl. Med. Biol.* 26: 509-518 (1999).
15. Langer O., Någren K., Dollé F., Lundkvist C., Sandell J., Swahn C.-G., Vaufrey F., Crouzel C., Mazière B. and Halldin C. - *J. Label. Compounds Radiopharm.* 42: 1183-1193 (1999).
16. Sandell J., Langer O., Larsen P., Dollé F., Vaufrey F., Demphel S., Crouzel C. and Halldin C. - *J. Label. Compounds Radiopharm.* (1999), in press.

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