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Improved Specific Radioactivity of the PET Radioligand [^{11}C]FLB 457 by use of the GE Medical Systems PETtrace MeI MicroLab

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Summary

[^{11}C]FLB 457 is a high affinity dopamine D_2 receptor radioligand that is used for visualisation and quantitation of extrastriatal dopamine D_2 receptors with positron emission tomography (PET). In this study, we report a comparison regarding the specific radioactivity of [^{11}C]FLB 457 obtained by two different methods of synthesising [^{11}C]methyl iodide. In addition, the synthesis of unlabelled FLB 457 and the corresponding desmethyl-precursor, starting from commercially available material, is reported. The first method used for [^{11}C]methyl iodide synthesis was reduction of [^{11}C]CO_2 with lithium aluminium hydride in tetrahydrofuran to [^{11}C]CH_3OH, followed by conversion into [^{11}C]CH_3I with hydrogen iodide. The second, recently developed method uses gas phase halogenation of [^{11}C]CH_4 with iodine. [^{11}C]FLB 457 was labelled with [^{11}C]methyl triflate produced on-line from [^{11}C]methyl iodide. With the first method a specific radioactivity for [^{11}C]FLB 457 of 2100 Ci/mmol (78 GBq/μmol) (n=13) at 40 min after end of bombardment (EOB) was achieved. Using the gas phase method a specific radioactivity of 3400 Ci/mmol (126 GBq/μmol) (n=7) at 40 min EOB could be obtained. The use of the gas phase method also resulted in shorter time for set-up compared to the regular method since no wet chemistry is involved in the preparation of [^{11}C]methyl iodide.

Key words : specific radioactivity, [^{11}C]FLB 457, dopamine D_2 receptors.

Introduction

Dopamine D_2 receptors in extrastriatal brain regions are of central interest in schizophrenia research and in the development of antipsychotic drugs. In order to visualise low-density receptors, such as extrastriatal dopamine D_2 receptors in the human brain (0.5-3.0 pmol g^{-1}), with positron emission tomography (PET) a radioligand with very high affinity is prerequisite (1). FLB 457 [(S)-(-)-5-bromo-*N*-((1-ethyl-2-pyrrolidinyl)methyl)-2,3-dimethoxybenzamide] is a substituted benzamide with

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subnanomolar affinity (K_D = 20 pM) for dopamine D_2 receptors and has recently been developed as a carbon-11 labelled PET radioligand for visualisation of extrastriatal dopamine D_2 receptors (2,3). Equilibrium analysis has been applied in order to calculate the extrastriatal D_2 receptor occupancy in haloperidol and fluphenazine treated patients (3). However, for a reliable use of equilibrium analysis the receptor occupancy by the radioligand should be kept at a minimum level. When receptor densities are low, high specific radioactivity of the radioligand used in the PET investigation is therefore of particular methodological interest.

[^{11}C]FLB 457 ([^{11}C]-**1**) is prepared routinely in our lab by *O*-methylation of the corresponding 2-hydroxy precursor FLB 604 (**5**, previously available from ASTRA, Södertälje, Sweden) using [^{11}C]methyl triflate as the labelled methylating agent (Fig. 1) (4).

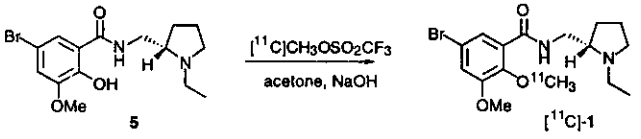

Figure 1 : Preparation of [^{11}C]FLB 457 with [^{11}C]methyl triflate.

[^{11}C]Methyl triflate is regularly prepared from [^{11}C]CO_2 in a three step reaction: [^{11}C]CO_2 is reduced with lithium aluminium hydride (LAH) in tetrahydrofuran (THF) to [^{11}C]methanol which is then converted to [^{11}C]methyl iodide with hydrogen iodide (HI). Subsequently, the [^{11}C]methyl iodide is transformed on-line into [^{11}C]methyl triflate by means of a heated silver triflate column (Fig. 2).

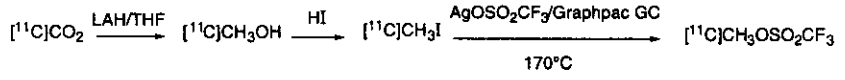

Figure 2 : Synthesis of [^{11}C]methyl triflate with LAH/THF and HI.

A new method of synthesising [^{11}C]methyl iodide has recently been developed (5). The working principle of the new method is a nickel-catalysed reduction of [^{11}C]CO_2 with hydrogen to [^{11}C]methane, which is halogenated in a gas phase reaction with iodine yielding [^{11}C]methyl iodide (Fig. 3).

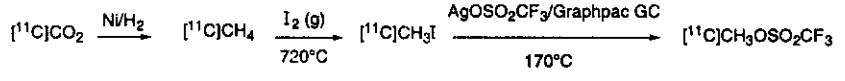

Figure 3 : Gas phase reaction scheme for the synthesis of [^{11}C]methyl triflate from [^{11}C]CO_2.

The absence of wet reagents, such as LAH in THF, is expected to improve the specific radioactivity of the produced [^{11}C]methyl iodide since LAH and THF are considered as being sources of carrier carbon (6). A "black box" (PETtrace MeI MicroLab) producing [^{11}C]methyl iodide from [^{11}C]CO_2 applying the gas phase method is commercially available from General Electrics Medical Systems (GEMS), Uppsala, Sweden. A GEMS PETtrace MeI MicroLab has been installed at the Karolinska Hospital as an integrated part of a fully automatic methylation system (7).

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In this work we report a comparative study of two methods to synthesise [^{11}C]CH_3I regarding the specific radioactivity of the produced [^{11}C]FLB 457. In addition to that, a simple and straightforward synthetic method for the preparation of FLB 457 (**1**) and the corresponding 2-hydroxy-analogue (**5**) is presented.

Results and Discussion

Chemistry

The synthetic approach employed for the synthesis of both FLB 457 (**1**) and its desmethyl-precursor for carbon-11 labelling (**5**) from 5-bromo-2-hydroxy-3-methoxybenzaldehyde (**2**) and (S)-(-)-2-aminomethyl-1-ethylpyrrolidine is based on a previously published method (Fig. 4) (8).

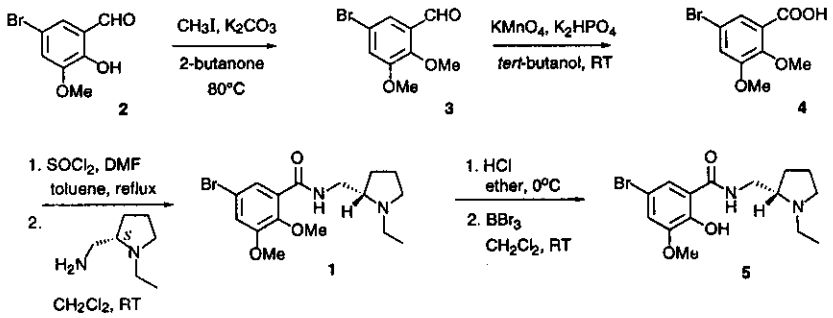

Figure 4 : Synthesis of FLB 457 (**1**) and desmethyl-FLB 457 (**5**).

5-Bromo-2-hydroxy-3-methoxybenzaldehyde (**2**) (commercially available from Aldrich, France) was reacted with methyl iodide and potassium carbonate in 2-butanone at 80°C for 2 hours to give the 2-methoxybenzaldehyde **3** in high yield (93%) (9). Treatment of the aldehyde **3** with potassium permanganate in a mixture of *tert*-butanol and aqueous potassium dihydrogenphosphate yielded the benzoic acid-derivative **4** in 72% yield (10). The substituted benzoic acid **4** was converted into its acid chloride-analogue with $SOCl_2$ in refluxing toluene. Subsequent reaction with (S)-(-)-2-aminomethyl-1-ethylpyrrolidine (commercially available from TCI, Japan) in dichloromethane afforded FLB 457 (**1**) in good yield (75%) (8). Compound **1** was converted into its hydrochloride salt with a solution of HCl in diethylether and then selectively mono-demethylated with boron tribromide in dichloromethane at -20°C to afford FLB 457 (**5**) in high yield (95%) (11). NMR and mass spectrometry analysis confirmed that only one methoxy-group was demethylated while the other was unaffected. 2D NOESY NMR, as recently reported for the desmethyl-derivative of epidepride (11), provided structural evidence for the position of the free phenolic OH-function. The starting material **1** (FLB 457) that was bearing two methoxy-groups clearly showed a correlation peak between one aromatic proton (δ = 7.15 ppm) and the methoxy region (δ = 3.85-4.00 ppm). This proton was therefore attributed to be in 4-position of the aromatic ring. NOESY experiments were run under the same conditions for the product obtained after selective mono-deprotection (**5**), and still showed the above mentioned correlation peak.

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This indicated that proton-4 was neighbouring a methoxy-substituent and therefore attributed the free phenolic OH-group to the 2-position of the aromatic ring.

We intended to use compound **5** for labelling with [^{11}C]methyl triflate under basic conditions. As [^{11}C]methyl triflate presumably reacts with anions, such as bromide, to afford unwanted volatile by-products, we abstained from converting desmethyl-FLB 457 (**5**) into a hydrochloride or hydrobromide salt. It could be stored as the free base for several weeks without degradation.

Radiochemistry

The total synthesis time including purification of the final product was for both methods 30 minutes. The regular method resulted in a mean value of specific radioactivity of 2100 Ci/mmol (78 GBq/μmol) (n=13) at 40 minutes after end of bombardment (EOB) (Fig. 5). The test runs performed on the automated methylation system containing the GEMS PETtrace MeI MicroLab resulted in a mean value of 3400 Ci/mmol (126 GBq/μmol) (n=7) at 40 minutes after EOB (Fig. 5). The 40 min time point was chosen, as formulation of product for administration into the human subject usually takes 10 min from end of synthesis. The productions were performed over the same period of time in order to exclude variations in specific radioactivity originating from the cyclotron.

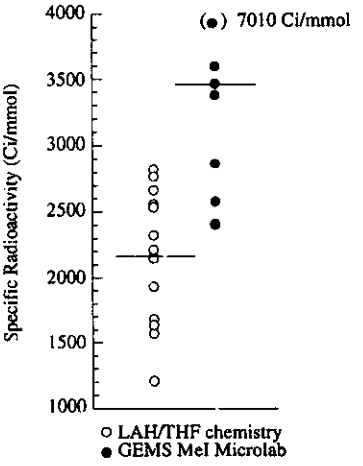

Figure 5 : Specific radioactivity of [^{11}C]FLB 457 at 40 min after EOB. Seven test runs were performed with the new methylation system. These are compared with the regular [^{11}C]FLB 457 production for PET during the same period of time.

The improvement in specific radioactivity with more than 50% using the new method supports the previous finding that LAH and THF are major sources of carrier carbon (6). The exclusion of wet LAH/THF chemistry has not only significantly improved the specific radioactivity but has also shortened the time for set-up since cleaning procedures are simplified. The fast set-up and automatic

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reconditioning of the methyl iodide system makes it suitable as an integrated part of an automatic methylation system.

Experimental

General

Chemistry : 5-Bromo-2-hydroxy-3-methoxybenzaldehyde was purchased from Aldrich, France, and (S)-(-)-2-aminomethyl-1-ethylpyrrolidine from TCI, Japan. Other chemicals were purchased from Aldrich, Fluka or Sigma France unless otherwise stated, and were used without further purification. Analytical TLC was run on pre-coated plates of silica gel 60 F_{254} (Merck). The compounds were localised using an UV-lamp at 254 nm and/or by dipping the TLC-plates into an aqueous $KMnO_4$ solution (1%) and heating on a hot plate. Flash chromatography was conducted on silicagel 63-200 μm (Merck) at 0.3 bars. NMR spectra were recorded on a Bruker AMX 300 MHz apparatus using the hydrogenated residue of the deuteriated solvents (CD_2Cl_2, δ = 5.32 ppm ; DMSO-d_6, δ = 2.51 ppm) and/or TMS as internal standards for ^{1}H NMR as well as the deuteriated solvents (CD_2Cl_2, δ = 53.8 ppm ; DMSO-d_6, δ = 39.7 ppm) and/or TMS as internal standards for ^{13}C NMR. The chemical shifts (δ) are reported in ppm, downfield from TMS (s, t, bs, bt for singlet, triplet, broad singlet and broad triplet respectively). The mass spectra (MS), DCI/NH_4^+, were measured on a Nermag R10-10 apparatus.

Radiochemistry : [^{11}C]CO_2 was produced batchwise using the Scanditronix MC 16 cyclotron at the Karolinska Hospital/Institute by bombardment of a nitrogen gas target with 16 MeV protons in the ^{14}N(p,α)^{11}C reaction. The target gas was irradiated for 40 minutes with a beam intensity of 40 μA. Silver triflate was purchased from Aldrich and Graphpac GC (80–100 mesh) from Alltech. Silver triflate-impregnated graphitized carbon was prepared according to a previously described method (12). The [^{11}C]methyl triflate was trapped at room temperature in a reaction vessel containing 0.5 mg (1.4 μmol) desmethyl-precursor **5**, 300 μL acetone and 6 μL 0.5 M NaOH (2.1 eq). [^{11}C]FLB 457 ([^{11}C]-**1**) was purified using normal-phase semi-preparative HPLC with CH_2Cl_2/CH_3OH/Et_3N (96/4/0.04) (CH_3OH/Et_3N preadjusted to pH 8 with concentrated acetic acid) as the mobile phase with a flow rate of 2.0 mL/min.

Chemistry

5-Bromo-2,3-dimethoxybenzaldehyde (3). To a solution of 5-bromo-2-hydroxy-3-methoxybenzaldehyde (**2**) (3.0 g, 12.99 mmol) in 2-butanone (25 mL), methyl iodide (1.23 mL, 19.5 mmol) and K_2CO_3 (2.70 g 19.5 mmol) were added. The reaction mixture was heated at 80°C for 2 hours and then concentrated to dryness. The residue was taken up in ethyl acetate (50 mL) and washed with 1 M aqueous NaOH and brine, dried over $MgSO_4$, and concentrated to dryness. The residue was purified by flash chromatography (silica gel, heptane/AcOEt 80/20) to afford the title compound as a white powder (2.95 g, 93% yield).

Rf (heptane/AcOEt 1/1) : 0.7-0.8. ^{1}H NMR (CD_2Cl_2, 298.0 K) : δ : 3.90 (s, 3H) ; 3.96 (s, 3H) ; 7.26 (d, J < 3.0 Hz, 1H) ; 7.48 (d, J < 3.0 Hz, 1H) ; 10.32 (s, 1H). ^{13}C NMR (CD_2Cl_2, 298.0 K) : δ :

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56.8 (CH_3) ; 62.6 (CH_3) ; 117.1 (C) ; 121.4 (CH) ; 121.7 (CH) ; 131.0 (C) ; 152.4 (C) ; 154.5 (C) ; 188.9 (CH). MS (DCI/NH_4^+) : $C_9H_9BrO_3$: 264, 262 [M + NH_4^+] ; 247, 245 [M + H^+].

5-Bromo-2,3-dimethoxybenzoic acid (4). To a solution of 5-bromo-2,3-dimethoxybenzaldehyde (**3**) (3.0 g, 12.25 mmol) in *tert*-butanol (100 mL), aqueous $KMnO_4$ (73 mL, 158 g/L, 12.25 mmol, 1 eq.) and aqueous K_2HPO_4 . 3 H_2O (50 mL, 285 g/L, 15.3 mmol, 1.25 eq.) were added. The reaction mixture was stirred under nitrogen for 30 minutes and then concentrated to dryness. The residue was taken up in CH_2Cl_2 (150 mL) and washed with water and brine. The organic layer was dried over $MgSO_4$ and concentrated to dryness. Purification by filtration over silica gel with heptane/AcOEt 50/50 afforded compound **4** as a white powder (2.3 g, 72% yield).

Rf (heptane/AcOEt 1/1) : 0.2-0.3. ^1H NMR (CD_2Cl_2, 298.0 K) : δ : 3.91 (s, 3H) ; 4.04 (s, 3H) ; 7.28 (d, J < 3.0 Hz, 1H) ; 7.74 (d, J < 3.0 Hz, 1H) ; 10.65 (b, $w_{1/2}$ = 30 Hz, 1H). ^{13}C NMR (CD_2Cl_2, 298.0 K) : δ : 56.9 (CH_3) ; 62.6 (CH_3) ; 117.5 (C) ; 120.8 (CH) ; 124.1 (C) ; 126.1 (CH) ; 148.2 (C) ; 153.6 (C) ; 165.1 (C). MS (DCI/NH_4^+) : $C_9H_9BrO_4$: 280, 278 [M + NH_4^+] ; 263, 261 [M + H^+].

*(S)-(-)-5-Bromo-*N*-((1-ethyl-2-pyrrolidinyl)methyl)-2,3-dimethoxybenzamide hydrochloride (1.HCl, FLB 457.HCl).* To a solution of 5-bromo-2,3-dimethoxybenzoic acid (**4**) (2.98 g, 11.4 mmol) in toluene (20 mL), $SOCl_2$ (10 mL, 115 mmol) and 3 drops of DMF were added. The reaction mixture was stirred under nitrogen at 80°C for two hours. The solvent was evaporated under repeated addition of CH_2Cl_2 to obtain the acid chloride as a yellow solid that was not purified any further. The residue was dissolved in CH_2Cl_2 (10 mL) and (S)-(-)-2-aminomethyl-1-ethylpyrrolidine (1.5 g, 11.9 mmol) dissolved in CH_2Cl_2 (10 mL) was added dropwise. The reaction mixture was stirred overnight under nitrogen at ambient temperature. The solvent was removed, the residue redissolved in CH_2Cl_2 and washed with 1 M aqueous NaOH and brine. The organic layer was dried over $MgSO_4$ and concentrated to dryness. The residue was purified by flash chromatography (silica gel, CH_2Cl_2/CH_3OH 9/1) to afford **1** as a yellow powder (3.18 g, 75% yield).

Rf (CH_2Cl_2/CH_3OH 8/2) : 0.7-0.8.

Compound **1** (3.0 g) was dissolved in CH_2Cl_2 and 3.0 M HCl in Et_2O (15 mL) was added. Concentration to dryness yielded the hydrochloride of **1** as a fluffy white solid (2.9 g, 90% yield).

^1H NMR (CD_2Cl_2, 298.0 K) : δ : 1.35 (t, J = 6.0 Hz, 3H) ; 1.70-2.40 (m, 4H) ; 2.75-3.05 (m, 2H) ; 3.15 (m, 1H) ; 3.60-4.05 (m, 4H) ; 3.86 (s, 3H) ; 3.99 (s, 3H) ; 7.15 (d, J < 3.0 Hz, 1H) ; 7.64 (d, J < 3.0 Hz, 1H) ; 8.86 (bt, $w_{1/2}$ = 19 Hz, 1H) ; 12.16 (b, $w_{1/2}$ = 28 Hz, 1H). ^{13}C NMR (CD_2Cl_2, 298.0 K) : δ : 10.8 (CH_3) ; 23.8 (CH_2) ; 29.0 (CH_2) ; 41.7 (CH_2) ; 51.8 (CH_2) ; 54.3 (CH_2) ; 56.8 (CH_3) ; 62.1 (CH_3) ; 67.0 (CH) ; 116.6 (C) ; 119.1 (CH) ; 125.0 (CH) ; 128.0 (C) ; 147.8 (C) ; 154.1 (C) ; 165.4 (C). MS (DCI/NH_4^+) : $C_{16}H_{23}BrN_2O_3$: 373, 371 [M + H^+].

*(S)-(-)-5-Bromo-*N*-((1-ethyl-2-pyrrolidinyl)methyl)-2-hydroxy-3-methoxybenzamide (5).* To a solution of (S)-(-)-5-bromo-*N*-((1-ethyl-2-pyrrolidinyl)methyl)-2,3-dimethoxybenzamide (**1**) hydrochloride (1.5 g, 3.68 mmol) in CH_2Cl_2 (15 mL), cooled to -20°C, BBr_3 in CH_2Cl_2 (1.0 M, 3.68 mL, 3.68 mmol) was added. The reaction mixture was stirred for 2 hours at room temperature, and then concentrated to dryness. The residue was treated with 2 M aqueous NH_4OH and extracted with CH_2Cl_2. Drying of the combined organic layers with Na_2SO_4 and concentration to dryness yielded the

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crude product in the form of a yellow oil. Purification by flash chromatography (silica gel, CH_2Cl_2/CH_3OH 95/5) afforded the title compound **5** as a slightly yellow oil (1.26 g, 95% yield), which was used for the radiolabelling reactions with [^{11}C]methyl triflate.

Rf (CH_2Cl_2/CH_3OH 9/1) : 0.55-0.65. ^{1}H NMR (CD_2Cl_2, 298.0 K) : δ : 1.15 (t, J = 9.0 Hz, 3H) ; 1.50-2.10 (m, 4H) ; 2.30-2.60 (m, 2H) ; 3.00 (m, 1H) ; 3.20-3.75 (m, 3H) ; 3.80 (s, 3H) ; 6.98 (s, 1H) ; 7.39 (s, 1H). ^{13}C NMR (CD_2Cl_2, 298.0 K) : δ : 12.9 (CH_3) ; 23.8 (CH_2) ; 28.6 (CH_2) ; 40.9 (CH_2) ; 49.4 (CH_2) ; 53.9 (CH_2) ; 56.3 (CH_3) ; 64.1 (CH) ; 107.6 (C) ; 117.4 (CH) ; 117.4 (C) ; 121.9 (CH) ; 151.2 (C) ; 153.8 (C) ; 169.2 (C). MS (DCI/NH_4^+) : $C_{15}H_{21}BrN_2O_3$: 359, 357 [M + H$^+$].

Radiochemistry

Preparation of [^{11}C]FLB 457 with regular method. The [^{11}C]CO_2 was trapped in a stainless steel coil cooled with liquid nitrogen before being transferred to the [^{11}C]methyl iodide system. [^{11}C]CH_3I was syn-thesised from [^{11}C]CO_2 utilising a one-pot reaction set-up similar to that reported previously (13). The [^{11}C]methyl triflate was prepared on-line, by sweeping the [^{11}C]CH_3I through a soda glass column (oven temperature: 170°C) containing silver triflate-impregnated graphitized carbon, and trapped in the reaction vessel (4). The product was purified by semi-preparative normal-phase HPLC using a Kontron 420 pump, an automatic sample injector (Type VICI with a 1 mL loop), a Waters μ-Porasil column (300 x 7.8 mm, 10 μm), and a Kontron 432 UV-detector (wavelength: 254 nm) in series with a GM tube for radiation detection.

Preparation of [^{11}C]FLB 457 in automated methylation system. The GEMS MeI PETtrace MicroLab is an integrated part of a fully automated methylation system that has recently been installed at the Karolinska Hospital. The system is fully automatic which restricts the manual work to changing reagents and disposable vials.

The operating procedure of the automated system can briefly be described as follows: Synthesis and formulation of the final product takes place under High Efficiency Particulate Arrestance (HEPA)-filtered air and reagents and solutions are stored in a clean air atmosphere. A PC program has been developed for the control and programming of the system. The user interface gives the operator running information on the synthesis and after completed synthesis all information is printed out. [^{11}C]Methyl iodide is synthesised from [^{11}C]CO_2 using the GEMS PETtrace MeI MicroLab. Reduction of [^{11}C]CO_2 to [^{11}C]CH_4 and subsequent catalytic gas-phase halogenation of [^{11}C]CH_4 with iodine yields [^{11}C]CH_3I, which is converted on-line into [^{11}C]methyl triflate. Methylation with [^{11}C]methyl triflate takes place in a Gilson autosampler, in a reaction vessel containing the precursor, solvent and base. After autoinjection on the built-in HPLC system for purification, the chromatographic process is followed in real time by means of a GM tube that is scanning the HPLC column continuously. Evaporation of solvents after HPLC purification is performed continuously on-line by means of a carburetor. The mobile phase is carburated by a stream of helium and the labelled product is accumulated on a spiral that is heated up to a moderate temperature (70°C). Formulation of the final product is accomplished by flushing the spiral with sterile buffer solution. The formulated radioligand is then collected in a sterile vial. Selfcleaning routines for the autosampler syringe, HPLC system, evaporator and tubing can be executed before, during and after synthesis. The HPLC system

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consists of a Gilson 304 piston pump, an automatic sample injector (Gilson 234 Autoinjector), a Waters μ-Porasil column (300 x 7.8 mm, 10 μm), and a GILSON 118 UV/VIS detector (wavelength: 254 nm) in series with a GM tube for radiation detection.

Conclusion

Two different methods to prepare [^{11}C]methyl iodide were compared in the synthesis of the PET radioligand [^{11}C]FLB 457 in order to improve the specific radioactivity. The method comprising gas phase iodination of [^{11}C]methane clearly afforded a higher mean specific radioactivity, 3400 Ci/mmol versus 2100 Ci/mmol by the standard method. The gas phase halogenation method might be of advantage in the development of future radioligands requiring high specific radioactivity for use in the PET investigation of low-density receptor populations.

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