

## Research Article

# [<sup>11</sup>C]methyl iodide from [<sup>11</sup>C]methane and iodine using a non-thermal plasma method

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## Summary

A method and an apparatus for preparing [<sup>11</sup>C]methyl iodide from [<sup>11</sup>C]methane and iodine in a single pass through a non-thermal plasma reactor has been developed. The plasma was created by applying high voltage (400 V/31 kHz) to electrodes in a stream of helium gas at reduced pressure. The [<sup>11</sup>C]methane used in the experiments was produced from [<sup>11</sup>C]carbon dioxide via reduction with hydrogen over nickel. [<sup>11</sup>C]methyl iodide was obtained with a specific radioactivity of  $412 \pm 32$  GBq/ $\mu$ mol within 6 min from approximately 24 GBq of [<sup>11</sup>C]carbon dioxide. The decay corrected radiochemical yield was  $13 \pm 3\%$  based on [<sup>11</sup>C]carbon dioxide at start of synthesis. [<sup>11</sup>C]Flumazenil was synthesized via a *N*-alkylation with the prepared [<sup>11</sup>C]methyl iodide. Copyright © 2006 John Wiley & Sons, Ltd.

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## Introduction

The advances in non-thermal plasma chemistry may open for new methods to convert cyclotron produced <sup>11</sup>C-labelled compounds such as [<sup>11</sup>C]carbon dioxide or [<sup>11</sup>C]methane to other useful precursors. Some applications of non-thermal plasma are surface treatment, fluorescent lightning and flat screens.<sup>1,2</sup> Ozone is produced with non-thermal plasma at industrial scale and complex organic compounds have been synthesized in good yield.<sup>3</sup> Plasma techniques

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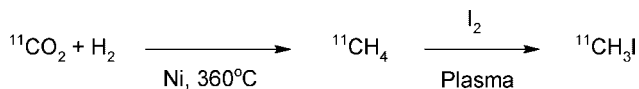
have also been applied in the synthesis of  $^{11}\text{C}$ -labelled compounds.<sup>4,5</sup> Recently, progress has been made in developing methods for the conversion of methane to low-weight hydrocarbons.<sup>6,7</sup> Okumoto *et al.* showed that methane in the presence of oxygen was converted to a variety of products via a single pass through a dielectric barrier discharge plasma reactor.<sup>8</sup> The selectivity of the reaction was approximately 30% with respect to methanol. Methyl iodide was obtained with a selectivity of 95% when oxygen was replaced with iodine.<sup>9</sup> No methylene iodide or iodoform was detected. These findings inspired us to explore the possibility to convert [ $^{11}\text{C}$ ]methane to other useful precursors by use of non-thermal plasma.

[ $^{11}\text{C}$ ]methyl iodide is a useful precursor for incorporating  $^{11}\text{C}$  via methylation of compounds containing oxygen, sulphur and nitrogen nucleophiles or via various type metal mediated methylations.<sup>10–13</sup> Today there are two commonly used production methods for [ $^{11}\text{C}$ ]methyl iodide. In the first, [ $^{11}\text{C}$ ]carbon dioxide is reduced with lithium aluminium hydride in suspension and converted to [ $^{11}\text{C}$ ]methyl iodide with hydriodic acid.<sup>14,15</sup> This method has been modified for example by applying the lithium aluminium hydride suspension as a film on the inner surface of a tubing.<sup>16</sup> The second method utilizes [ $^{11}\text{C}$ ]methane and iodine in a gas phase reaction at  $720^\circ\text{C}$ .<sup>17,18</sup> A relatively low conversion of [ $^{11}\text{C}$ ]methane was increased by trapping the formed [ $^{11}\text{C}$ ]methyl iodide while recirculating the unreacted [ $^{11}\text{C}$ ]methane. Single pass gas-phase systems have been reported to give [ $^{11}\text{C}$ ]methyl iodide in approximately 50% radiochemical yield after optimization of the reaction conditions.<sup>19,20</sup>

In this paper, a method and an apparatus for the iodination of [ $^{11}\text{C}$ ]methane in a single pass through a non-thermal plasma reactor containing iodine vapour to produce [ $^{11}\text{C}$ ]methyl iodide is described.<sup>21</sup>

## Results and discussion

A system was developed based on the chemistry route presented in Scheme 1. [ $^{11}\text{C}$ ]methyl iodide was obtained in  $13 \pm 3\%$  decay corrected radiochemical yield in less than 6 min from [ $^{11}\text{C}$ ]carbon dioxide. Hydrogen and nickel were used in the reduction of [ $^{11}\text{C}$ ]carbon dioxide at  $360^\circ\text{C}$ . The formed [ $^{11}\text{C}$ ]methane was converted to [ $^{11}\text{C}$ ]methyl iodide in the system by a single pass through a non-thermal plasma reactor.



**Scheme 1.** [ $^{11}\text{C}$ ]methyl iodide was prepared from cyclotron-produced [ $^{11}\text{C}$ ]carbon dioxide via nickel catalysed reduction and iodination initiated by electron impact

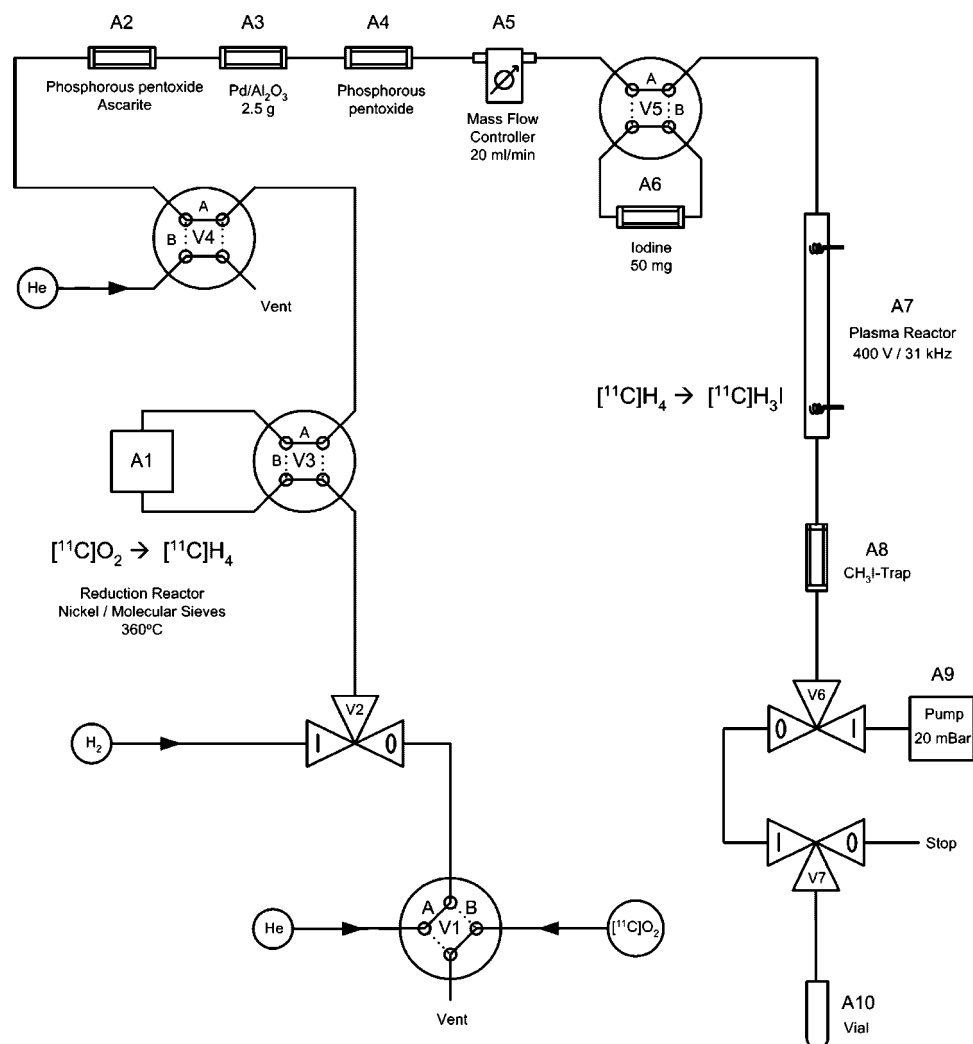
Non-thermal plasma has non-equilibrium properties. While the gas temperature in the plasma may be close to room temperature, the free electrons can reach energies up to 10 eV.<sup>22</sup> The electrons are accelerated in an electric field and collisions with molecules initiate chemical reactions. The non-equilibrium property of non-thermal plasma explains why these reactions can occur at low temperature. To reach the same electron energy with plasma in equilibrium (thermal plasma), the temperature of the gas volume need to be high. In thermal plasma the energy is divided equally between electrons, ions and neutral particles which may lead to breakdown of thermally unstable reactants or product. Although the gas retains low temperature in non-thermal plasma, a mixture of radicals, excited species and ions are formed, often resulting in low product selectivity. This problem may be overcome by selecting proper reagents and reaction conditions as was nicely demonstrated by Okumoto *et al.*<sup>9</sup>

In our experiments glow discharge plasma was utilized. This type of non-thermal plasma is generated by applying a high voltage to electrodes in a gas with low pressure.<sup>22</sup> The plasma was sustained with 400 V AC and the power consumption was lower than 6 W. The reduced pressure enabled homogenous excitation of the gas volume in the reactor which then emitted light. The reactor generated small amounts of heat and the plasma could instantly be turned on or off.

The set-up used in the experiments consisted of two reactors, see Figure 1. [<sup>11</sup>C]carbon dioxide was trapped in the reduction reactor (A1) containing molecular sieves (4 Å 60/80) and nickel powder. Then the reactor was flushed with hydrogen gas before it was closed and heated to 360°C to facilitate the reduction of [<sup>11</sup>C]carbon dioxide to [<sup>11</sup>C]methane.<sup>23</sup> The formed [<sup>11</sup>C]methane was subsequently transferred in a carrier gas and unreacted [<sup>11</sup>C]carbon dioxide was removed by an Ascarite trap (A2). Palladium on aluminium oxide (A3) was used to remove residual hydrogen from the gas. Water produced from the reaction of oxygen with the palladium-hydride was removed on a column containing phosphorous pentoxide (A4).

A mass flow controller (A5) was positioned at the start of the low pressure part which contained the iodine feed (A6), the plasma reactor (A7) and the CH<sub>3</sub>I-trap (A8). A diaphragm vacuum pump (A9) was used to reduce the pressure in the plasma reactor.

[<sup>11</sup>C]methane was transferred to the plasma reactor by passing through the iodine feed, thus mixing with the iodine before entering the plasma reactor. The entrance of iodine in the plasma field was clearly visible as a change from the inherent colour of the carrier gas to a thick white glow. The high-energy electrons in the plasma initiated the reaction which converted [<sup>11</sup>C]methane to [<sup>11</sup>C]methyl iodide. The mechanism of the reaction has not yet been studied.



**Figure 1.** The experimental set-up used in the study

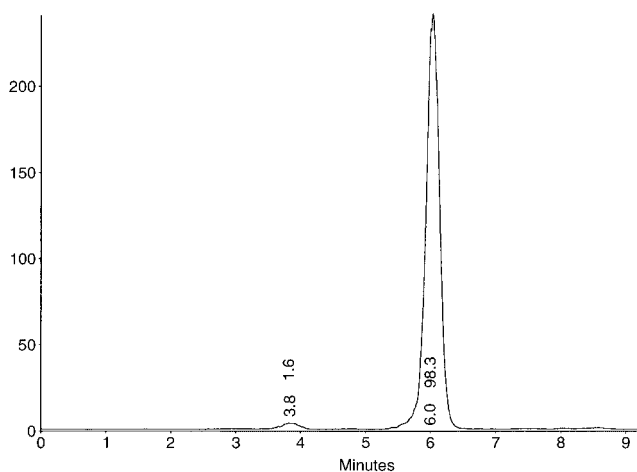
However, we assumed that free radicals of iodine were formed in the plasma reacting with  $[^{11}\text{C}]$ methane. It was not clear if the electron energy was high enough to directly ionize methane.

The formed  $[^{11}\text{C}]$ methyl iodide was trapped on Teflon-tubing immersed in liquid nitrogen. The vacuum pump was disconnected when the entire batch of radioactivity had passed through the plasma reactor and the system was equilibrated to atmospheric pressure by use of the mass flow controller. The Teflon tubing used as the trap was warmed to room temperature to release the  $[^{11}\text{C}]$ methyl iodide which then was transferred by the carrier gas to a vial with dimethylformamide ( $300\ \mu\text{l}$ ) where it was analysed or used in methylation reactions.

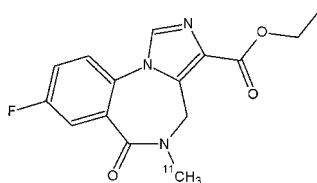
Both neon and helium were tested as carrier gases. Best results were obtained using helium with the vacuum pump operated at 20 mbar and the mass flow through the plasma reactor regulated to 20 ml/min. When using these conditions [<sup>11</sup>C]methyl iodide was obtained with a decay corrected radiochemical yield of  $13 \pm 3\%$  ( $n = 12$ ) based on the amount of [<sup>11</sup>C]carbon dioxide at start of synthesis. The radiochemical purity was  $64 \pm 7\%$  ( $n = 5$ ). By inserting a column with phosphorous pentoxide between the CH<sub>3</sub>I-trap (A8) and the vial (A10), the radiochemical purity was increased to  $88 \pm 7\%$  ( $n = 6$ ). The procedure to convert [<sup>11</sup>C]carbon dioxide and transfer the formed [<sup>11</sup>C]methyl iodide to the vial required less than 6 min. The conversion yield of [<sup>11</sup>C]carbon dioxide to [<sup>11</sup>C]methane was in the order of 90% (Figure 2).

Radionuclide productions using 12 μAh were made when the specific radioactivity of the [<sup>11</sup>C]methyl iodide was determined. 24 GBq of [<sup>11</sup>C]carbon dioxide was transferred to the reduction reactor. In the end of the reaction sequence  $2.0 \pm 0.1$  GBq and  $4.9 \pm 0.6$  nmol of [<sup>11</sup>C]methyl iodide was trapped in acetonitrile at  $-20^{\circ}\text{C}$ . The specific radioactivity was  $412 \pm 32$  GBq/μmol ( $n = 2$ ).

[<sup>11</sup>C]Flumazenil was synthesized via methylation of *N*-desmethyl flumazenil using the produced [<sup>11</sup>C]methyl iodide (Figure 3).<sup>24</sup> After preparative HPLC-purification, [<sup>11</sup>C]flumazenil was obtained in  $12 \pm 3\%$  decay-corrected radiochemical yield based on [<sup>11</sup>C]carbon dioxide ( $n = 3$ ). The [<sup>11</sup>C]methyl iodide was used as received from the CH<sub>3</sub>I-trap. The alkylation reaction proceeded without further purification of the [<sup>11</sup>C]methyl iodide hence neither a phosphorous pentoxide column nor an iodine trap was used.



**Figure 2.** Radiochromatogram obtained with a sample withdrawn from the dimethylformamide solution. A column with phosphorous pentoxide was used to trap impurities. [<sup>11</sup>C]methyl iodide had a retention time of 6.0 min



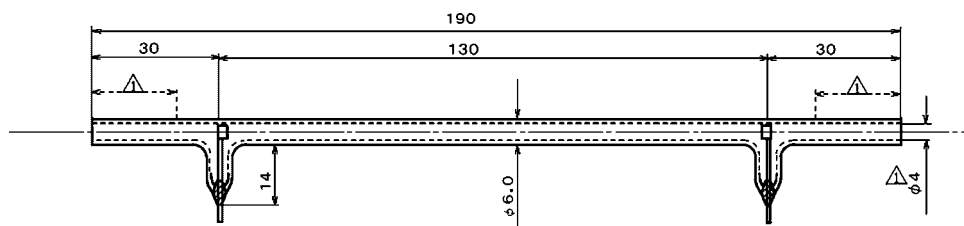
**Figure 3.** [ $^{11}\text{C}$ ]flumazenil

The intensity of the plasma was identified as an important factor when the reaction conditions were optimized. As the pressure was decreased in the reactor, the plasma glow became brighter. However, an increase in the intensity of the plasma clearly favoured the formation of  $^{11}\text{C}$ -labelled polar by-products, observed in the front of the analytical HPLC chromatogram, and to some extent [ $^{11}\text{C}$ ]methylene iodide. The polar products may be derived from reactions with oxygen which efficiently oxidise methane in the plasma environment.<sup>8</sup> The oxygen may have originated from the target gas or from air leakage in the low pressure part of the system.

The formation of [ $^{11}\text{C}$ ]methylene iodide was also dependent on the amount of iodine entering the plasma reactor, which in turn was affected by the flow rate of the carrier gas, the pump pressure, the amount of iodine in the iodine feed and the inner diameter and length of the tubing (peek i.d. 0.5 mm, length 135 mm) connecting the iodine feed with the plasma reactor. Too high iodine concentration resulted in the formation of [ $^{11}\text{C}$ ]methylene iodide.

Other parameters which affected the efficiency of the plasma reaction were the type of carrier gas and the mass flow rate of the carrier gas through the plasma reactor. A low mass flow resulted in deposition of radioactive material in the reactor. A high mass flow lowered the radiochemical yield due to the weakening of the plasma induced by a pressure increase in the reactor. When the carrier gas was changed from helium to neon the radiochemical purity of [ $^{11}\text{C}$ ]methyl iodide was decreased to approximately 50% and several radiochemical by-products were detected although not yet identified. This could be explained by an increase in the electron density of the plasma due to the lower ionization energy of neon.<sup>25</sup>

The flow of the carrier gas at reduced pressure facilitated the release of a sufficient amount of iodine vapours from the source of 50 mg of iodine. The iodine feed was connected to a switch valve. It enabled the disconnection of the iodine from the gas stream and thus reducing the iodine consumption as well as minimizing problems with contamination in the plasma reactor. Iodine deposited on the walls of the reactor during the reaction was removed by running the plasma without the iodine feed in between the experiments. It was possible to run over 30 experiments on a single load of 50 mg of iodine.



**Figure 4. Drawing of the plasma reactor (mm)**

The plasma was created by applying 400 V/31 kHz to the electrodes positioned in the gas stream inside the plasma reactor, shown in Figure 4. The electrodes were made of tungsten and the reactor body was made from quartz glass.

Palladium on solid support is known to efficiently absorb hydrogen gas. The initial experiments were carried out without a hydrogen trap which led to a visible quenching of the plasma glow when the [<sup>11</sup>C]methane was passing through the plasma reactor. The glow plasma was sustained to a high degree when a column with palladium on aluminium oxide was inserted upstream from the plasma reactor. Water which was formed in the reaction between oxygen and the palladium-hydride complex was removed on a column containing phosphorous pentoxide inserted after the hydrogen trap.

Glow discharge plasma was selected for this study due to the uncomplicated and inexpensive reactor and electrical components needed to generate the plasma. The low pressure was favourable for the release of iodine to the reactor. There are several other types of techniques to create non-thermal plasma which is interesting in the context of <sup>11</sup>C-labelling chemistry.<sup>22,26</sup> Dielectric barrier discharge plasma can be sustained at atmospheric pressure.<sup>2</sup> The plasma is generated by applying high voltage pulses to an electrode which is shielded from the grounded electrode by a dielectric barrier, e.g. quartz. Micro-discharges occur in the gas volume in between the electrode and the dielectric barrier. The high voltage pulse can be designed with respect to the application by changing the voltage, frequency and pulse rise time, etc. Two other ways of creating non-thermal plasma is to use microwave discharges and radio-frequency discharges which have the advantage that the reagents entering the plasma are not in contact with the electrodes.

We are now exploring alternative techniques for efficient production of [<sup>11</sup>C]methyl iodide using non-thermal plasma in single-pass and recirculating systems. Especially dielectric discharge plasma is of interest since it allows the ionizing strength of the plasma to be adjusted and to sustain the plasma at atmospheric pressure. The problem associated with leaks and air entering the reactor may be eliminated when using systems operated at atmospheric pressure.

## Conclusion

The feasibility of synthesizing [ $^{11}\text{C}$ ]methyl iodide from [ $^{11}\text{C}$ ]methane and iodine via a reaction initiated by electron impact using a non-thermal plasma reactor has been explored. A small and compact system, easy to automate, was developed which converted [ $^{11}\text{C}$ ]methane to [ $^{11}\text{C}$ ]methyl iodide in a single pass through a non-thermal plasma reactor. 50 mg of iodine was sufficient for over 30 experiments which illustrated that a minute amount of iodine was required for the reaction. The specific radioactivity was satisfactory for many PET-applications. However, the radiochemical yield and purity of the [ $^{11}\text{C}$ ]methyl iodide needs to be improved.

## Experimental

### General

$^{11}\text{C}$  was prepared by the  $^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$  nuclear reaction using 17 MeV protons produced by a Scanditronix MC-17 Cyclotron at Uppsala Imanet AB and obtained as [ $^{11}\text{C}$ ]carbon dioxide. The target gas used was nitrogen (AGA Nitrogen 6.0) containing 0.05% oxygen (AGA Oxygen 4.8). [ $^{11}\text{C}$ ]carbon dioxide was transferred in a stream of nitrogen gas from the cyclotron to the reduction reactor containing a mix of molecular sieves 4 Å 60/80 and nickel powder 50:50 wt%.

*Procedure for converting [ $^{11}\text{C}$ ]carbon dioxide to [ $^{11}\text{C}$ ]methyl iodide using the single pass non-thermal plasma system, Figure 1.*

1. V1 = A, V2 = 0, V3 = A, V4 = B, V5 = A, V6 = 1, V7 = 0, mass flow regulator (A5): 20 ml/min, pump (A9): 20 mbar, the system was flushed with the carrier gas.
2. V2 = 1, the reduction reactor (A1) was flushed for 5 min with  $\text{H}_2$  20 ml/min.
3. V1 = B, V2 = 0, the [ $^{11}\text{C}$ ]carbon dioxide was transferred from the cyclotron to the reduction reactor (A1).
4. V1 = A, V2 = 1, the reactor (A1) was flushed for 2 min with  $\text{H}_2$  20 ml/min.
5. V2 = 0, V3 = B, the reactor (A1) was closed.
6. The reactor (A1) was heated to convert [ $^{11}\text{C}$ ]carbon dioxide to [ $^{11}\text{C}$ ]methane.
7.  $\text{CH}_3\text{I}$ -trap (A8), (teflon tubing i.d. 1.58 mm, o.d. 3.18 mm) was cooled with liquid nitrogen.
8. V4 = A, V5 = B, the plasma reactor (A7) was turned on. The iodine feed (A6) containing 50 mg anhydrous 10 mesh iodine beads 99.999%(Aldrich) was connected.
9. V3 = A, the heating of the reduction reactor (A1) was turned off when it reached 360°C. The reactor was opened and [ $^{11}\text{C}$ ]methane was transferred through the plasma reactor (A7).
10. Paused until [ $^{11}\text{C}$ ]methyl iodide was collected at the  $\text{CH}_3\text{I}$ -trap (A8).
11. V4 = B, V5 = A, V6 = 0, the plasma reactor (A7) was turned off and the pump (A9) was disconnected.



12. Pause until the pressure prior and after the mass flow controller (A5) was equalized.
13. V7 = 1, the CH<sub>3</sub>I-trap (A8) was heated with warm water and the [<sup>11</sup>C]methyl iodide was transferred to the vial (A10).

The following equipment was used in the experiments: valves: V1, V3, V4, V5 EHMA (Vici Valco, US), V2, V6, V7 5300 (Rheodyne, US), mass flow controller MC-100SCCM (Alicat Scientific, US), plasma power supply 400 V, 31 kHz: DC-AC Inverter 24V S24556 (Miyata Elevam, Japan), quartz plasma reactor: OZS-0613 Type B (Miyata Elevam, Japan), vacuum pump N85.3KTDC, (KNF Neuberger, Germany) and PC 2001 Vario (Vacuubrand, Germany). Columns (Omnifit, i.d. 10 mm, length 50 mm), Analytical HPLC was performed on a Beckman system, equipped with a Beckman 126 pump, a Beckman 166 UV detector in series with a Bioscan β<sup>+</sup>-flow count detector and a Waters Spherisorb 5 μm ODS1 column (250 × 4.6 mm). A Gilson 231 was used as auto injector. Purification with preparative HPLC was performed on a similar Beckman system equipped with a Beckman Ultrasphere ODS dp 5 μm column (250 × 10 mm).

#### *Characterization of [<sup>11</sup>C]methyl iodide and determination of specific radioactivity*

[<sup>11</sup>C]methyl iodide was transferred in a stream of helium (20 ml/min) from the CH<sub>3</sub>I-trap to a solution of acetonitrile (400 μl, -20°C). The radioactivity in the vial and the volume of the acetonitrile solution was measured. The concentration of [<sup>11</sup>C]methyl iodide was determined with analytical HPLC using a standard curve: (A) water, 0.1% formic acid; (B) acetonitrile (50:50). Flow 1.0 ml/min. [<sup>11</sup>C]methyl iodide *R<sub>t</sub>* 6.0 min. [<sup>11</sup>C]methylene iodide *R<sub>t</sub>* 8.8 min.

#### *Synthesis of [<sup>11</sup>C]flumazenil*

*N*-desmethyl flumazenil (1.0 mg, 3.5 μmol) was added to a solution of dimethylformamide (250 μl) and dimethyl sulphoxide (60 μl) in a 0.8 ml glass vial equipped with a rubber septum. Potassium hydroxide (0.8 μl, 5 M) was added and the resulting solution was vortexed. The [<sup>11</sup>C]methyl iodide was transferred to the solution in a stream of helium gas (20 ml/min). The vial was heated for 3 min at 75°C. Preparative HPLC: (A) 0.05 M ammonium formate pH 3.5; (B) acetonitrile/water 50/7; (64:36). Flow 4 ml/min. *R<sub>t</sub>* 7.4 min. Analytical HPLC was used to assess the identity and radiochemical purity. (A) 0.05 M ammonium formate pH 3.5; (B) acetonitrile/water 50/7; (60:40). Flow 1.0 ml/min. *R<sub>t</sub>* 8.6 min.

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