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Introduction

The importance of automated synthesis has long been recognized for increasing reliability and reducing radiation exposure to a chemist in routine preparation of short-lived positron emitting radiopharmaceuticals. Therefore, the development of an automated synthesis system was considered to be essential for starting PET receptor studies using $^{11}$C-labeled radioligands at CYRIC since a rapid operation of synthetic procedures with a large quantity of starting $^{11}$C radioactivity is usually required for synthesis of high specific activity radioligands. Although fully automated operation is the most desirable due to its high reliability, such an automated synthesis system seems to be rather sophisticated as compared with the operation procedures involved in the syntheses of many $^{11}$C-labeled receptor ligands from [$^{11}$C]methyl iodide, if this labeling precursor can be produced with an existing automated synthesis system. On the other hand, remotely-controlled operation is apparently unsuitable for routine preparations. It was consequently expected that a semiautomated synthesis system would be more easily and rapidly established using the automated [$^{11}$C]methyl iodide synthesis system with feedback control. The present report describes the routine preparation of [$^{11}$C]YM-09151-2, a dopamine D2-receptor antagonist, and [$^{11}$C]pyrilamine, a histamine H1-receptor antagonist, from [$^{11}$C]methyl iodide using the semiautomated synthesis system for clinical PET studies at CYRIC.

Materials and Methods

Figure 1 shows the synthetic schemes of [$^{11}$C]YM-09151-2 and [$^{11}$C]pyrilamine from [$^{11}$C]H3l. The original procedure developed for the synthesis of [$^{11}$C]YM-09151-
2) was simplified for rapid operation, and therefore there is no significant difference between the present and previously reported synthetic procedures.3,4) The same procedure was applied to the preparation of [11C]-pyrilamine.5) Figure 2 illustrates a schematic flow chart of the semiautomated system. Pneumatic 3-way PTFE valves, numbered from AV-1 to AV-4 in Fig.2, and a pneumatic 6-way valve are used to control gas and liquid flow. Two motor-driven elevator jacks are employed to remotely move up or down a reaction vessel and a rotary evaporator together with a small radiation sensors. A syringe pump unit for injection and recovery of saline utilizes all disposable, sterile and apyrogenic parts of syringe, 3-way valve and tube for medical use. This unit has another device for stretching the other end of PTFE tubing for transfer of saline to the bottom of a flask only when saline is recovered into a syringe. Also another stretchable tubing device is employed for sampling a collected HPLC eluate in the flask before evaporation to determine specific activity, chemical and radiochemical purities by the end of the synthesis. All the procedure is operated by a programmable controller.

[11C]O₂ is produced by 18 MeV proton irradiation of a nitrogen gas target at 10 μA for an hour. Using the automated system [11C]H₂ is almost quantitatively converted from [11C]O₂ within 9 min after the irradiation. The reaction vessel contains a 500 μl portion of DMF dissolving 2 mg of desmethyl derivative and 2 mg of NaH for [11C]YM-09151-2 or 1.7 mg of desmethyl precursor for [11C]pyrilamine. The HPLC conditions for separation of the reaction products are listed in Table 1.

**Step 1.** The synthesis operation is started from the first step of trapping [11C]methyl iodide in the reaction vessel, corresponding to the last step of [11C]methyl iodide distillation in the automated system, and this step is consequently completed within 9 min after the irradiation when the level of radioactivity at the vessel no longer increases. The reaction vessel is dipped in ice-cold water during the trap of [11C]methyl iodide. Thereafter, the vessel is lifted from the ice bath and warmed for 1 min with the hot blower to complete the reaction.

**Step 2.** A 0.5 ml portion of water is injected into the vessel and the solution is briefly bubbled with He. The resultant clear solution is then transferred with a He flow to a reservoir attached to the inlet port of the HPLC injector.

**Step 3.** The solution in the reservoir is introduced into a 2 ml loop of the injector by drawing it at the loop vent with a syringe, and immediately when the whole sample is drawn into the loop, the injector valve is switched to the injection position.

**Step 4.** Judging from the traces of radioactivity in the HPLC eluate and UV response in a recorder in comparison with the standard retention time of the respective authentic sample listed in Table 1, the radioactive product peak is collected in the evaporator flask
just for 1 min duration to strictly control the amount of the additives inevitably accompanying the HPLC solvent.

**Step 5.** Before starting evaporation a small portion of the collected solution is sampled in a syringe through the stretched PTFE tube for early determining specific activity along with both chemical and radiochemical purities by HPLC. Then the flask is immersed in a hot oil bath heated at 100°C and the entire solvent is evaporated to complete dryness.

**Step 6.** A 10 ml portion of saline is injected into the flask. The flask is briefly rotated to dissolve the residue and the PTFE tube is stretched to the bottom of the flask, and the entire saline is recovered in the syringe again.

**Step 7.** A disposable 3-way valve is turned and the saline solution is injected in a sterile vial through a 0.22 μm membrane filter.

Thus, the product solution can be immediately used for PET studies without delay since quality control by HPLC has been completed by the end of synthesis.

**Results and Discussion**

The preparations of both $[^{11}C]$YM-09151-2 and $[^{11}C]$pyrilamine were completed within 45 min after the irradiation. The overall radiochemical yields for these radioligands were 20 % (corrected for decay and based on the theoretical $^{11}$C production yielded of 640 mCi). Approximately 1 GBq (27 mCi) of human in vivo injectable $[^{11}C]$YM-09151-2 or $[^{11}C]$pyrilamine in 10 ml saline are available at the end of synthesis. These rather low yields are due to a short collection time compared to a product peak width. More than half of the radioactive product was wasted according to the regulations for clinical use of positron emitting radiopharmaceuticals at CYRIC. The chemical and radiochemical purities of both $^{11}$C-labeled receptor ligands, however, are still high enough for PET use. The average specific activity of both products was 37 GBq/μmol (1.0 Ci/μmol) at the end of synthesis. It seems that this value is not so high enough as compared with those reported in the literature.\(^3\)\(^5\) Since a main source of carrier carbons can be attributed to the LiAlH\(_4\)/THF complex for $[^{11}C]$methyl iodide preparations\(^6\) and hence it can be considered that specific activity of the final product inherits primarily that of $[^{11}C]$methyl iodide, the specific activity can be expected to be still improved by simply increasing a beam current.

It is one of the difficulties with rapid and remote operation to prevent a solvent from bumping at evaporation under reduced pressure. When bumping happens just at nearly dryness, the residue is scattered over a flask, and this may lead to an unexpected decrease in a recovery yield with saline. A tube end fixed to the bottom of a flask is sometimes a
cause of bumping. The present system has proven that a stretchable tube is an effective device for prevention of bumping. The same device is also adopted for taking up a sample for saving time usually required for quality control of the final product after the synthesis, and it compensates for a rather long synthesis time in the present system. It has recently been reported that (N-[11C]methyl)sipiperone suffers radiolytic decomposition during an evaporation procedure due to its high specific activity. Fortunately no change in chemical and radiochemical purities was not observed for the present two radioactively receptor ligands before and after solvent evaporation, but it should be always confirmed that no autoradiolysis happens before this sampling method using the stretching device is introduced.

It is expected that all the procedures adopted in the present system can readily be fully automated with feedback control using the state of the art's techniques. However, it should be noted that it is difficult to confirm complete dryness after evaporation of a toxic solvent with an appropriate sensor. In conclusion, the present study has demonstrated that the semiautomated synthesis system can be easily established and flexibly accommodated to many preparations of different 11C-receptor ligands with minor change in reaction and HPLC conditions.

References

<table>
<thead>
<tr>
<th>Radioligand</th>
<th>$[^{11}\text{C}]\text{YM-09151-2}$</th>
<th>$[^{11}\text{C}]\text{pyrilamine}$</th>
</tr>
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<tbody>
<tr>
<td><strong>Column</strong></td>
<td>DELTA PAK C18 100A 15 μ, 25 mm × 10 cm (Waters)</td>
<td>TSK-GEL ODS-80 7.8 mm × 30 cm (Tosoh)</td>
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<tr>
<td>Eluent</td>
<td>CH$_3$CN/0.01M NaH$_2$PO$_4$ (40/60)</td>
<td>CH$_3$CCN/0.1M HCOONH$_4$ (32/68)</td>
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<tr>
<td>Flow rate</td>
<td>12.5 ml/min</td>
<td>7.5 ml/min</td>
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<tr>
<td>Elution time of precursor</td>
<td>6.3 min</td>
<td>7.6 min</td>
</tr>
<tr>
<td>Elution time of product</td>
<td>9.4 min</td>
<td>11.5 min</td>
</tr>
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Fig. 1. Synthetic schemes for $[^{11}\text{C}]$YM-09151-2 and $[^{11}\text{C}]$pyrilamine from $[^{11}\text{C}]$methyl iodide.

Fig. 2. A flow chart of the synthesis system.

(a) automated $[^{11}\text{C}]$methyl iodide synthesis system, (b) syringe pump unit, (c) motor-driven elevator jack, (d) stretching device, (e) hot blower, (f) rotary evaporator, (g) reaction vessel, (h) ice-water bath, (i) oil bath, (j) sample reservoir, (k) glass ball, (l) 100 ml pear-shaped flask, (m) radiation sensor, (n) UV detector, (o) HPLC sample injector, (p) HPLC pump, (q) guard column, (r) HPLC column, (s) sampling syringe, (t) 0.5 ml water, (u) syringe pump, (v) sterile vial, (w) vacuum.