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Radiosynthesis and quality control of [^{11}C]TASP457 as a clinically useful PET ligand for imaging of histamine H_3 receptors in human brain

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ABSTRACT

Introduction: Recently, 6-[(1-cyclobutylpiperidin-4-yl)oxy]-1-(6-[^{11}C]methoxypyridin-3-yl)-3,4-dihydroquinolin-2(1*H*)-one ([^{11}C]TASP457, [^{11}C]**2**) has been developed as a novel PET ligand for histamine H_3 receptors in brain. [^{11}C]**2** is potentially suitable for imaging H_3 receptors in rat and monkey brains, which has motivated us to perform first-in-human study of [^{11}C]**2** for qualifying H_3 receptors in human brain. In this paper, we report an efficient radiosynthesis of [^{11}C]**2** to obtain sufficient radioactivity and high quality for clinical application.
Methods: In manual synthesis, we optimized the reaction conditions of desmethyl precursor **1**, which contains a 2-hydroxypyridine moiety, with [^{11}C]MeI or [^{11}C]MeOTf. After optimization, we performed automated synthesis and quality control of [^{11}C]**2**.
Results: Bubbling [^{11}C]MeOTf into a heated mixture of precursor **1** and cesium carbonate in DMF at 100 °C for 90 s produced [^{11}C]**2** with decay-corrected radiochemical yields of (based on [^{11}C]CO_2) 7.9 ± 1.8% (n = 78). The specific activity of [^{11}C]**2** was 156 ± 52 GBq/μmol (n = 78) at the end of synthesis. The total synthesis time was approximately 35 min from the end of bombardment. All the quality control results of [^{11}C]**2** were in compliance with our in-house quality control/assurance specifications.
Conclusion: We radiosynthesized [^{11}C]TASP457 ([^{11}C]**2**) with sufficient amounts of radioactivity and high quality for clinical usefulness. This radioligand is being used for PET assessment of H_3 receptors in human brain in our facility.
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1. Introduction

Histaminergic neurotransmission is involved in numerous pathologies of the central nervous system, such as sleep, addiction, depression, schizophrenia, pain, and neurodegeneration, for example in Alzheimer's and Parkinson's diseases [1]. Histamine H_3 receptors have been reported to play a role in the synthesis and regulation of release of histamine, and are widely expressed in the mammalian brain, with the highest density expressed in the areas involved with cognitive processes and arousal [2].

Molecular imaging is an advancing technology that allows for visualization of interactions between molecular probes and biological targets. Positron emission tomography (PET), in particular, is a useful modality that enables *in vivo* biological information to be obtained in a noninvasive manner using a variety of radioligands [3,4]. Since 1994, several PET ligands for imaging of H_3 receptors have been synthesized and evaluated [5–12]. The carbodithioate analog *S*-[^{11}C]methylthioperamide was the first reported H_3-targeting PET ligand [6], but the brain uptake of this radioligand demonstrated a high level of nonspecific binding [6]. As the first reported ^{18}F-labeled H_3 ligand, the imidazolylbenzophenone analog [^{18}F]FUB272 showed low and non-specific binding in brain [7]. On the other hand, because non-imidazole-based H_3 receptor antagonists seemed to be more promising clinical candidates as drugs with higher target selectivity than the previous imidazole analogs, pharmacophores in the development of PET ligands have been converted to non-imidazole analogs. The first reported non-imidazole-based radioligand was derived from the benzylmorpholine analog JNJ-10181457 [8]. Followed by the JNJ compound, some promising PET ligands for H_3 receptors have been reported [9–12]. Among them, [^{11}C]GSK189254 [9] and [^{11}C]MK-8278 [10], both belonging to non-imidazole analogs, have recently been developed and used for clinical studies of H_3 receptors in human brain (Fig. 2). [^{11}C]GSK189254 has an extremely high affinity for H_3 receptors, but has slow brain kinetics that limits the accuracy and precision of PET quantification of H_3 density in human brain [9]. [^{11}C]MK-8278 has shown large test–retest variability especially in the high density H_3 regions of human

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brain [10]. Therefore, a novel PET ligand with more suitable pharmacokinetics and better binding characteristics is required for imaging and assessment of H_3 receptors in clinical research.

More recently, we have labeled a new class of non-imidazole H_3 receptor ligands and evaluated their potentials for PET imaging of brain H_3 receptors *in vivo*. Among these radioligands, 6-[(1-cyclobutylpiperidin-4-yl)oxy]-1-(6-[^{11}C]methoxypyridin-3-yl)-3,4-dihydroquinolin-2(1*H*)-one ([^{11}C]TASP457 or [^{11}C]TASP0410457, [^{11}C]**2**) (Fig. 1) showed high binding affinity for H_3 receptors (IC_{50} = 2.34 nM for rat and 1.80 nM for monkey) and high selectivity for compared to other receptors (IC_{50} = 379 nM for σ_1 and 1000 nM for adrenergic α_{2c} receptors) [13]. Radioligand [^{11}C]**2** has shown to be suitable for PET imaging of H_3 receptors in rat and monkey brains, as it offered robust quantitative measurement of H_3 receptor binding throughout the H_3-enriched brain regions [13]. These results have motivated us to translate [^{11}C]**2** for the first-in-human study in our facility [14].

In this paper, we report an efficient synthesis of [^{11}C]**2** that provides with sufficient radioactivity for clinical research use that routinely meets our quality control and release criteria.

2. Materials and methods

Desmethyl precursor 6-[(1-cyclobutylpiperidin-4-yl)oxy]-1-(6-hydroxypyridin-3-yl)-3,4-dihydroquinolin-2(1*H*)-one (**1**, Fig. 2), 6-[(1-cyclobutylpiperidin-4-yl)oxy]-1-(6-methoxypyridin-3-yl)-3,4-dihydroquinolin-2(1*H*)-one (TASP457, TASP0410457, **2**, Fig. 1), and *N*-methylated byproduct 6-[(1-cyclobutylpiperidin-4-yl)oxy]-1-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-3,4-dihydroquinolin-2(1*H*)-one (**3**, Fig. 2) were synthesized and kindly supplied from Taisho Pharmaceutical (Tokyo, Japan). Commercially available reagents and organic solvents were purchased from Sigma-Aldrich (St. Louis, MI, USA) and Wako Pure Chemical Industries (Osaka, Japan) without further purification. Injection water and sodium phosphate corrective injection (0.5 mol/L) were purchased from Otsuka Pharmaceutical Factory (Naruto, Tokushima, Japan). Semi-preparative HPLC was performed using a Jasco HPLC system (Jasco, Tokyo, Japan). Analytical HPLC was performed using the Jasco HPLC system or a Waters HPLC system (Milford, MA, USA). The ^{11}C radioactivity was produced using a cyclotron (CYPRIS HM-18; Sumitomo Heavy Industries, Tokyo, Japan).

2.1. Radiolabeling of **1** by manual synthesis using [^{11}C]methyl iodide

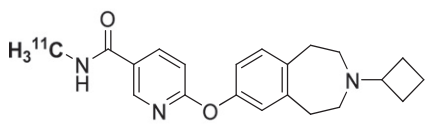
[^{11}C]Carbon dioxide ([^{11}C]CO_2) was produced using the ^{14}N(p,α)^{11}C nuclear reaction in a 0.01% oxygen-containing nitrogen gas with 18 MeV proton beams (15.8 MeV on target). Following the bombardment process, [^{11}C]CO_2 was transferred to a reaction vessel containing a 50 mmol/L solution of lithium aluminium hydride in tetrahydrofuran (500 μL) at a temperature in the range −10 to −15 °C. The resulting solution was concentrated to dryness and a 57% solution of hydriodic acid (400 μL) was added to the vessel. The mixture was then heated for 150 °C to produce [^{11}C]methyl iodide ([^{11}C]MeI). The [^{11}C]MeI was purified by passing it through a small column filled with Ascarite and phosphorus pentoxide, and collected in a reaction vial containing a solution of **1** (1.0 mg) and base in *N*,*N*-dimethylformamide (DMF, 300 μL) at a flow rate of 30 mL/min at room temperature. The reaction mixture was then heated at 100 °C for 3 min, followed by addition of water (100 μL) to terminate the reaction. The detailed reaction conditions are showed in Table 1. Aliquots of the reaction mixtures were analyzed by reverse-phase HPLC using an X-terra C-18 column (4.6 mm i.d. × 150 mm, 5 μm, Waters). A flow rate of 1 mL/min was used with an isocratic mobile phase (acetonitrile/50 mmol/L phosphoric acid (25/75, *v*/v)). The absorbance was monitored at a wavelength of 254 nm. The identity of reaction products was confirmed by co-injection of unlabeled sample **2** or **3** with the corresponding reaction mixture.

2.2. Radiolabeling of **1** by manual synthesis using [^{11}C]methyl triflate

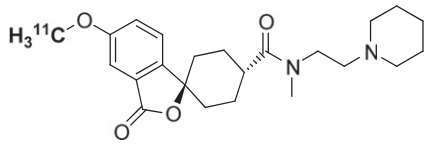
[^{11}C]Methyl triflate ([^{11}C]MeOTf) for radiosynthesis was prepared from [^{11}C]MeI as previously described [15]. Briefly, [^{11}C]MeOTf was generated by the reaction of fresh [^{11}C]MeI with silver triflate in an on-line flow-through process at 150 °C under a N_2 gas flow of 30 mL/min. Reaction condition surveys of [^{11}C]**2** were carried out according to the same procedures with [^{11}C]MeI. The detailed reaction conditions are showed in Table 2. Aliquots of the reaction mixtures were analyzed by reverse-phase HPLC.

2.3. Automated production of [^{11}C]**2** by remote-controlled synthesis

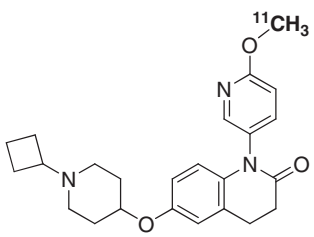
[^{11}C]MeOTf was synthesized using an automated synthesis system developed in house [16]. The produced [^{11}C]MeOTf was transferred



[^{11}C]GSK189254



[^{11}C]MK8278



[^{11}C]TASP457 ([^{11}C]2)

Fig. 1. Chemical structures of PET ligands for imaging histamine H_3 receptors in human brain.

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