Note

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A rapid one-step radiosynthesis of [^{11}C]-*d-threo*-methylphenidate

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Carbon-11 labelled *d-threo*-methylphenidate ([^{11}C]-(1)), a radiopharmaceutical commonly used to image the dopamine transporter, has been labelled in one step using [^{11}C]-methyl triflate. No protection of the nitrogen atom on the piperidine ring of *d-threo*-ritalinic acid · HCl was required, as *O*-methylation was favored over *N*-methylation by performing the methylation in buffered solutions which effectively protonate and protect the amine functionality. The reaction was effectively carried out at room temperature in solution by captive solvent 'LOOP' methods or using conventional glass vials.

Keywords: PET; carbon-11; methyl triflate; methylphenidate

Introduction

d,l-threo-Methylphenidate (Ritalin^{TM}) is often prescribed for the treatment of attention deficit hyperactivity disorder.[1] Carbon-11 labelled *d-threo*-methylphenidate, ((*R*)-methyl 2-phenyl-2-((*R*)-piperidin-2-yl)acetate; [^{11}C]-(**1**)), is an established radiopharmaceutical for imaging the dopamine transporter using positron emission tomography (PET)[2] in both animal and human subjects.[3]

The original syntheses of [^{11}C]-(**1**) utilized the *o*-nitrophenylsulfenyl group (NPS) to protect the nitrogen atom on the piperidine ring of *d-threo*-ritalinic acid, and this precursor (**2**) was reacted with [^{11}C]-iodomethane ([^{11}C]-CH_3I) in the presence of base at 80°C, followed by deprotection with a mixture of HCl and mercaptoacetic acid (Scheme 1, Method A).[4] Method A has been modified to employ the sodium salt of *N*-NPS-ritalinic acid (Na · (**2**)) with a more facile removal of the protecting group (Scheme 1, Method B) and solid phase extraction for the final purification.[5] Another reported preparation of [^{11}C]-(**1**) was accomplished by reacting (**2**) with [^{11}C]-diazomethane at room temperature (Scheme 1, Method C).[6] However, [^{11}C]-CH_2N_2 is not a commonly used [^{11}C]-methylating agent as its present production is low yielding and cumbersome. In contrast, [^{11}C]-methyl triflate ([^{11}C]-CH_3OTf) is an attractive methylating agent that is more reactive than [^{11}C]-CH_3I, is relatively easy to prepare,[7] and is routinely produced in many laboratories worldwide. Herein, we report a fast, one-step radiosynthesis of [^{11}C]-(**1**) from the acid form of the unprotected precursor, *d-threo*-ritalinic acid · HCl (**3**) with [^{11}C]-CH_3OTf, resulting in good yields (Scheme 1, Method D).

Experimental

Samples of (**1**) · HCl and (**3**), as well as *d,l-threo*-methylphenidate · HCl and *d,l-erythro/d,l-threo*-methylphenidate · HCl (chiral HPLC standards), were purchased from JML Biopharm Inc. and used without further purification. All other reagents and solvents were purchased from commercial sources and were used without further purification.

Several reaction conditions were explored to produce (**1**) or [^{11}C]-(**1**) by methylation of (**3**) with CH_3I, [^{11}C]-CH_3I, and [^{11}C]-CH_3OTf. These reactions were performed in DMF or MEK with bases of various strength (as well as in the absence of base), but were inferior to those outlined below (Methods D1–D3), as they gave lower yields and/or more impurities, and were not further pursued.

Radiosynthesis of [^{11}C]-(1) via the 'LOOP' method (Method D1)

Reactions using [^{11}C]-methyl triflate,[7] made via [^{11}C]-methyl iodide,[8] were performed inside an HPLC sample loop[9] following a previously described procedure.[10] Precursor (**3**) (0.5 mg) was dissolved (with vigorous vortexing for ca. 2 min) in a mixture of 72 μL methyl ethyl ketone (MEK) and 8 μL of 0.25 M NaOH/KH_2PO_4 phosphate buffer solution (pH = 7.4; referred hitherto as 'buffer'), followed by loading onto the HPLC loop. After a 5-minute reaction with [^{11}C]-CH_3OTf (reaction time not optimized), the product was purified using a Phemomenex Luna (2) C18 10 μ (250 × 10 mm) column and a mixture of 20:80 CH_3CN/H_2O+0.1 N ammonium formate (pH = 4) as the mobile phase with a flow rate of 7.0 mL/min (λ = 254 nm). No radioactivity was observed after product elution up until 30 min. The purified [^{11}C]-(**1**) was formulated as described previously.[10] At the end of

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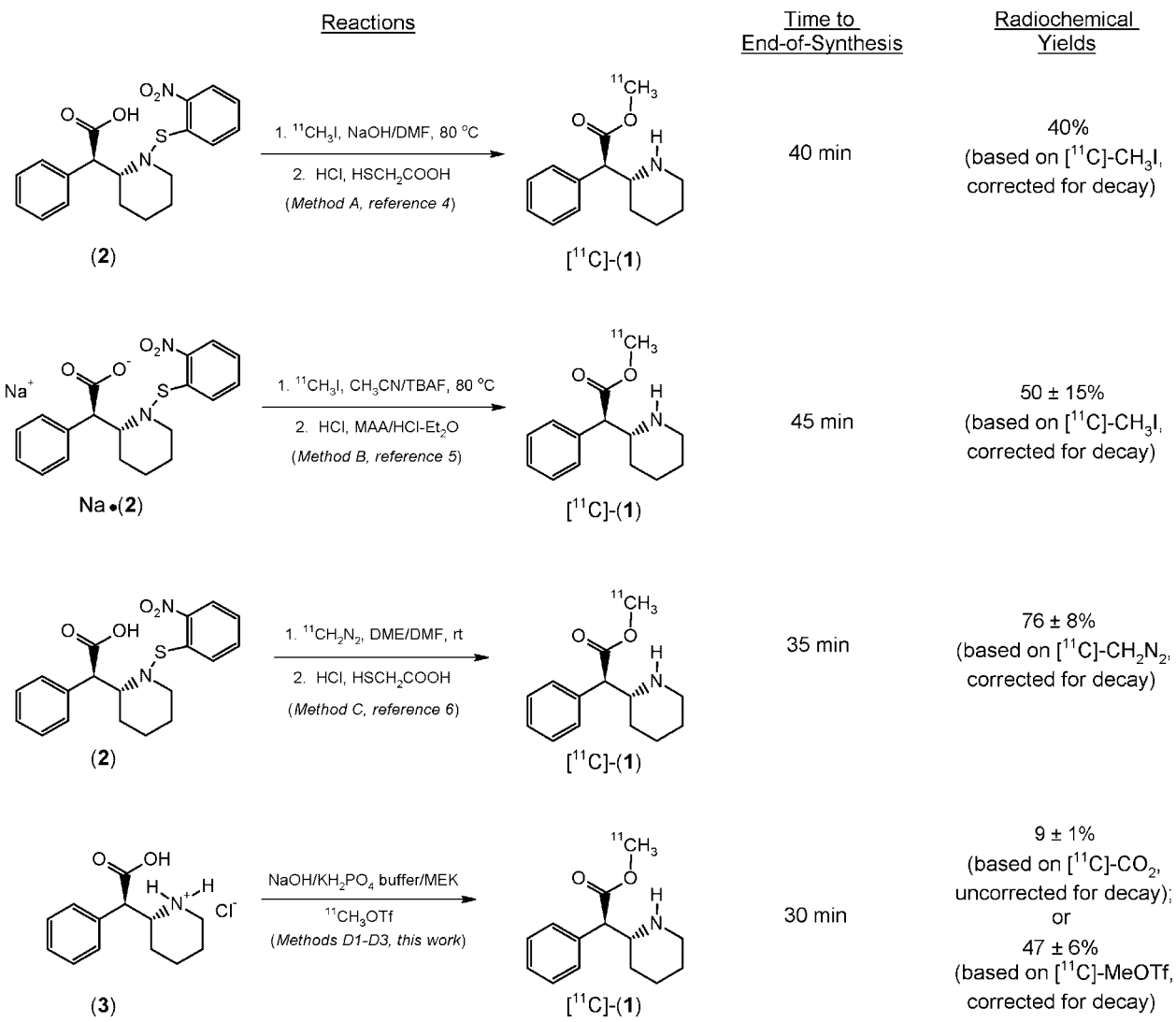

Scheme 1. Radiosynthesis of [^{11}C]-(**1**) by four different methods (Methods A–D).

synthesis (28 min) the final bottle had 2.7 ± 0.4 GBq (73 ± 11 mCi). The radiochemical purity was determined by analytical HPLC using a Phemomenex Prodigy ODS-Prep 10 μ (250 × 4.6 mm) column using a flow rate of 3.0 mL/min using two mobile phases and wavelengths: (1) 20:80 CH_3CN/H_2O + 0.1 N ammonium formate, $\lambda = 254$ nm; (2) 30:70 CH_3CN/H_2O + 0.05N ammonium chloride, $\lambda = 215$ nm. Furthermore, co-injections of [^{11}C]-(**1**) with authentic (**1**) were performed under several other HPLC conditions (columns, wavelengths, mobile phases) to confirm that the *N*-methylated product was not obtained. Enantiomeric purity of [^{11}C]-(**1**) was determined by chiral HPLC using a Chiralcel OD 10 μ (250 × 4.6 mm) column (mobile phase: 96:1.95:1.95:0.1 hexanes/MeOH/EtOH/TFA; flow rate: 1.0 mL/min; $\lambda = 254$ nm) as previously described.[11]

Radiosynthesis of [^{11}C]-(1) in a 'LOOP' using an automated radiofluorination unit (Method D2)

Captive solvent [^{11}C]-methylations were also automated using a GE TRACERlab™ FX_{FN} radiosynthesis module with minor modifications as described by our laboratory.[12] The reaction and separation conditions for the radiosynthesis of [^{11}C]-(**1**) were equivalent to those used for the 'LOOP' method (Method D1; vide supra) with similar synthesis times.

Radiosynthesis of [^{11}C]-(1) in a glass V-vial (Method D3)

[^{11}C]-Methyl triflate was bubbled (N_2 sweep flow of 18 mL/min) into a solution of (**3**) (0.5 mg in 72 μL MEK/8 μL 0.25 M buffer at 20°C) in a 1 mL septum-sealed glass V-vial (vigorously vortexed for 2 min), fitted with a venting needle piercing the septum. After 30–45 s, the reaction mixture was quenched with HPLC buffer (0.6 mL) and purified by semi-preparative HPLC, as described in Method D1. The overall synthesis time was ca. 30 min.

Results and discussion

Clinically useful quantities of [^{11}C]-(**1**) were efficiently and routinely achieved by reactions of (**3**) with [^{11}C]-CH_3OTf (Scheme 1, Method D) in MEK/buffer solutions via 'LOOP' methods (Methods D1 and D2) or in a glass vial (Method D3). Radiochemical yields were found to be highest using the 'LOOP' method (Method D1). After purification by semi-preparative

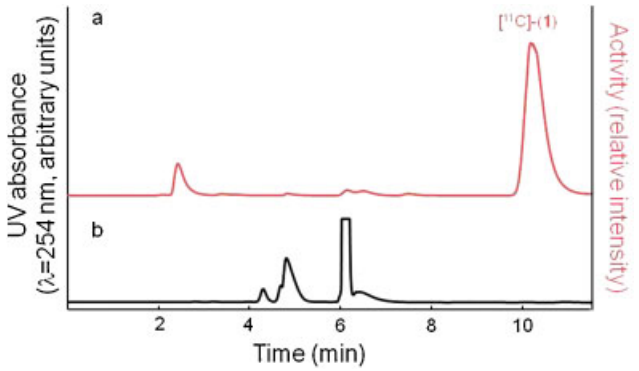

Figure 1. HPLC chromatogram of the purification of [^{11}C]-(**1**), prepared via the 'LOOP' method (Method D1): (a) γ trace (t_R = 10.2 min), and (b) UV trace (λ = 254 nm).

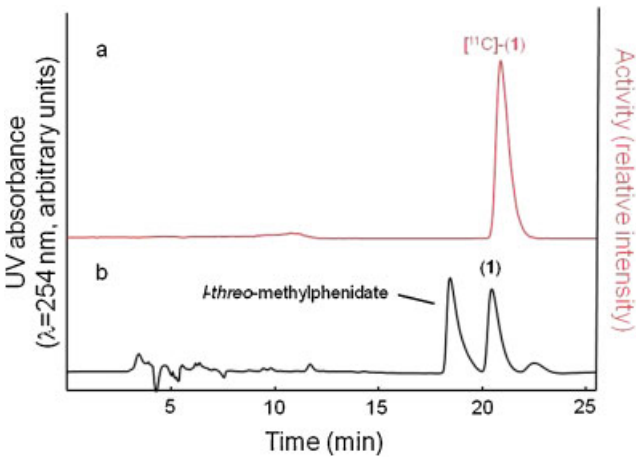

Figure 2. Chiral HPLC chromatogram of purified [^{11}C]-(**1**) (Method D1): (a) γ trace (t_R = 20.0 min), and (b) UV trace (λ = 254 nm; (**1**), t_R = 20.5 min).

HPLC (Figure 1; decay-corrected conversion, 87%), the isolated radiochemical yield of the formulated product was 8.6 ± 1.2% (n = 3, uncorrected for decay, based on production of 31.4 GBq (850 mCi) of [^{11}C]-CO_2), or 47 ± 6% (corrected for decay, based on production of 11.6 GBq (315 mCi) of [^{11}C]-MeOTf), in a synthesis time of 28 min. Specific activity was greater than 110 GBq/μmol (3 Ci/μmol; end-of-synthesis), and the radiochemical purity was >99%. Enantiomeric purity of [^{11}C]-(**1**) was >98% (Figure 2).

Radiosynthesis of [^{11}C]-(**1**) was also performed using a modified GE TRACERlab^{TM} FX_{FN} radiosynthesis module (Method D2),[12] and gave a comparable radiochemical yield (8.5%; n = 1) and specific activity (96 GBq/μmol; 2.6 Ci/μmol) to that achieved using the 'LOOP' method (Method D1), with equivalent radiochemical purity and enantiomeric purity. Clinically useful quantities of [^{11}C]-(**1**) can alternatively be prepared in a conventional glass V-vial (Method D3); however, this method gave lower isolated radiochemical yields of [^{11}C]-(**1**) (4.6 ± 0.7%; n = 2). Method D3 resulted in [^{11}C]-(**1**) with similar specific activity (118 ± 63 GBq/μmol; 3.2 ± 1.7 Ci/μmol), purities, and synthesis time to that of the 'LOOP' methods (Methods D1 and D2).

The original preparation of [^{11}C]-(**1**) using [^{11}C]-CH_3I employed a suitable *N*-protected precursor (**2**),[4] leading to a two-step radiosynthesis: [^{11}C]-methylation (carried out at 80°C in the presence of base), followed by acid deprotection. While alternative syntheses have been reported,[5,6] prior to the present study no attempt has been made to perform the reaction with an unprotected precursor in a single step. We postulate herein that the nitrogen atom in the zwitterionic form of (**3**) is effectively protected, by protonation, via judicious control of the pH of the solution. The use of buffers in radiochemical reactions has been explored.[13,14] Although the pH of mixed solvent/buffer systems cannot be directly measured,[15] reactions of (**3**) with [^{11}C]-CH_3OTf were performed in several mixtures of MEK or DMF with different concentrations of phosphate buffer (0.05–1.0 M, pH = 7.4). In this way, the best condition in our hands (0.5 mg of (**3**), 72 μL MEK, and 8 μL of 0.25 M NaOH/KH_2PO_4 phosphate buffer solution) resulted in clinically useful quantities of [^{11}C]-(**1**), and eliminated the need for elevated temperatures or the use of a protected precursor.

In conclusion, (**3**), and likely several other related compounds, can be directly and efficiently *O*-$^{11}CH_3$ labelled at a carboxylic acid moiety using [^{11}C]-CH_3OTf in appropriately buffered solutions, thereby eliminating the necessity for protecting groups on amine functionalities.

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