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[^{11}C]GR103545: novel one-pot radiosynthesis with high specific activity

Nabeel B. Nabulsi[a,*], Ming-Qiang Zheng[a], Jim Ropchan[a], David Labaree[a], Yu-Shin Ding[a], Laura Blumberg[b], Yiyun Huang[a]

[a]*Department of Diagnostic Radiology, PET Center, Yale School of Medicine, PO Box 208048, New Haven, CT 06520-8048, USA*
[b]*Pfizer Global R&D, Groton, CT 06340, USA*

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Abstract

Introduction: GR103545 is a potent and selective kappa-opioid receptor agonist. Previous studies in non-human primates demonstrated favorable properties of [^{11}C]GR103545 as a positron emission tomography tracer for in vivo imaging of cerebral kappa-opioid receptor. Nonetheless, advancement of [^{11}C]GR103545 to imaging studies in humans was hampered by difficulties of its multiple-step radiosynthesis, which produces a final product with low specific activity (SA), which in turn could induce undesirable physiological side effects resulting from the mass associated with an injected amount of radioactivity. We report herein an alternative radiosynthesis of [^{11}C]GR103545 with higher SA and radiochemical yields.

Methods: The TRACERLab FXC automated synthesis module was used to carry out the two-step, one-pot procedure. In the first step, the desmethoxycarbonyl precursor was converted to the carbamic acid intermediate desmethyl-GR103545 via transcarboxylation with the zwitterionic carbamic complex, 1,8-diazabicyclo[5.4.0]undec-7-ene–carbon dioxide, in the presence and/or absence of cesium carbonate and tetrabutylammonium triflate. In the second step, the intermediate was radiolabeled at the carboxyl oxygen with [^{11}C]methyl trifluoromethanesulfonate to give [^{11}C]GR103545.

Results: This novel synthesis produced [^{11}C]GR103545 with ≥90% chemical and radiochemical purities and an SA of 290.45±99.9 MBq/nmol at the end of synthesis (n=26). Injectable radioactivity was 1961±814 GBq/μmol with 43 min of average synthesis time from the end of beam.

Conclusion: We have developed a practical one-pot method for the routine production of [^{11}C]GR103545 with reliably high SA and radiochemical yield, thus allowing the advancement of this radiotracer to imaging applications in humans.

Keywords: PET; Kappa-Opioid; [^{11}C]GR103545; Radiosynthesis; Carbamate; DBU

1. Introduction

Two and a half decades have passed since it was shown that opioid receptors (ORs) could be labeled in vivo, with the first successful positron emission tomography (PET) study done in 1985 using the mu-OR agonist [^{11}C]carfentanil [1]. ORs are widely distributed in the central nervous system and peripheral sensory and autonomic nerves, and PET studies offer a non-invasive method to investigate in vivo the function or dysfunction of the different ORs in relation to neurobiology and neuropsychiatric disorders [2]. Several selective kappa-OR (κ-OR) agonist and antagonist ligands have since been developed [3–5], but only a few have advanced to clinical trials in humans [6,7]. GR89696, (±)-methyl 4-[(3,4-dichlorophenyl)acetyl]-3-(pyrrolidin-1-ylmethyl)piperazine-1-carboxylate, is a potent κ-OR agonist, and its ^{11}C-labeled form, [^{11}C]GR89696, has been assessed as a potential PET imaging agent [8,9]. Furthermore, [^{11}C]GR103545, the active *R*-enantiomer of [^{11}C]GR89696, has also been synthesized and shown to display favorable properties as a PET imaging radiotracer for κ-OR in the brain of non-human primates [10,11]. It has exhibited high binding affinity with fast uptake and clearance rates. Its binding distribution is similar to the known central nervous system regional distribution of κ-ORs in humans [10]. However, its advancement to imaging applications in humans was hampered by the radiolabeling method, which generally gives [^{11}C]GR103545 not only in

* Corresponding author. Tel.: +1 203 785 2474; fax: +1 203 785 2994.
E-mail address: nabeel.nabulsi@yale.edu (N.B. Nabulsi).

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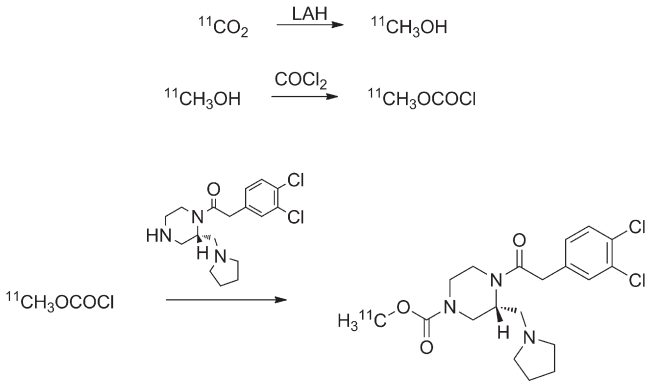


Scheme 1. Multiple-step synthesis of [^{11}C]GR103545 [9,11].

low and variable radiochemical yields (RCYs) but also in relatively low specific activity (SA) (69.3–75.5 MBq/nmol; 2–2.6 mCi/nmol) [9,11]. Following the published procedure (Scheme 1), we were unsuccessful in labeling [^{11}C]GR103545 in SA high enough for imaging studies in humans.[1] It is well established that opioid agonists are powerful analgesics and can induce undesirable physiological effects even when given at doses of micrograms that are relevant in PET imaging experiments. For example, in the case of [^{11}C]carfentanil, undesirable physiological effects were noted in early imaging experiments in humans, and injected mass of carfentanil has been limited to <0.03 μg/kg in subsequent human PET studies (Frost JJ. Personal communication) [1]. Similarly, GR103545, a potent, selective κ-OR agonist, has been shown to cause dysphoria and sedation at the microgram dose level [7,12]. Thus, it is essential to find a reliable radiosynthetic method that produces [^{11}C]GR103545 in acceptable RCY and, more importantly, in high SA, in order to successfully advance [^{11}C]GR103545 to imaging applications in humans, so that the mass associated with an injected amount of radioactivity can be held to a level that does not elicit undesirable physiological side effects. We report here our findings in the search for such a method.

GR103545 contains a methyl carbamate group, and the original radiosynthesis of [^{11}C]GR103545 employed a three-step procedure, starting with [^{11}C]CO_2, to construct the methyl carbamate functionality (Scheme 1). We envisioned an alternative synthetic approach toward this functionality by using carbon-11 methylation of a carbamic acid intermediate (Scheme 2).

In PET radiochemistry, carbon-11 methylation by nucleophilic substitution with [^{11}C]methyl iodide ([^{11}C]CH_3I) or [^{11}C]methyl trifluoromethanesulfonate ([^{11}C]methyl triflate; [^{11}C]CH_3OTf) is a favored method for incorporating a carbon-11 nuclide into a molecule. The simplicity of this reaction has rendered it the most widely used procedure for the synthesis of a large number of ^{11}C-labeled radiotracers via *N*-, *O*-, or *S*-methylation with carbon-11 [13,14]. In our laboratory, we routinely carry out these carbon-11 methylations to produce a wide range of radiopharmaceuticals in good yields and high SA by the gas-phase transformation of [11]CO_2 via [^{11}C]CH_4 to [^{11}C]CH_3I (or onward to [^{11}C]CH_3OTf) [15]. Therefore, it was expected that the approach depicted in Scheme 2 would lead to high-SA [^{11}C]GR103545. The requisite carbamic acid intermediate in turn can be constructed through two ways: direct carboxylation by CO_2 [16,17] or transcarboxylation via fixated CO_2. Transcarboxylation with the 1,8-diazabicyclo [5.4.0]undec-7-ene–carbon dioxide (DBU–CO_2) zwitterionic carbamic complex has been used to prepare urethanes [18], carbonates and carbamates [19,20], as well as carboxylation of active methylene compounds [21].

2. Experimental procedure

2.1. Materials and methods

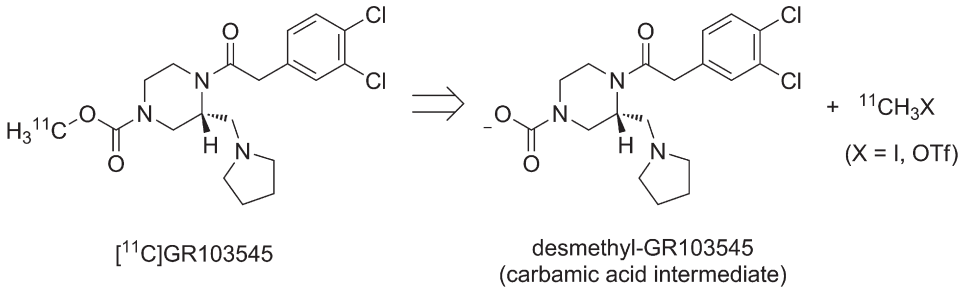
Reagents and solvents were purchased from commercial sources (Sigma-Aldrich, Fisher Scientific, Merck or J.T. Baker) and were used without further purification. Both the desmethoxycarbonyl precursor (**1**) and reference standard (GR103545) were obtained from the National Institute of Mental Health's Chemical Synthesis and Drug Supply Program. The DBU–CO_2 carbamic complex was prepared according to the literature [20].

Radiosynthesis of [^{11}C]GR103545 was carried out using a TRACERLab FXC automated synthesizer (GE Healthcare, Chalfont St. Giles, United Kingdom). [^{11}C]CH_3OTf was produced from [^{11}C]CO_2 as previously described [22]. Purification of [^{11}C]GR103545 was done by reversed-phase semi-preparative HPLC using a Phenomenex Prodigy C18 ODS(3) column (10 μm, 250×10 mm), eluting at a flow rate of 4 ml/min under isocratic conditions with a mobile phase composed of 35:65 (v/v) acetonitrile/0.1 M ammonium formate solution. Quality control analyses were carried out using a Shimadzu LC-20AT Prominence HPLC system equipped with an SPD-M20A photo diode array detector or an SPD-20A UV/Vis detector (230 nm) operating in series with a Bioscan Flow-Count gamma detector [HPLC column: Phenomenex Gemini C18 (110 Å, 5 μm, 4.6×250 mm); mobile phase: 32:68 (v/v) acetonitrile/0.1 M ammonium formate solution; flow rate: 2 ml/min].

2.2. Synthesis of [^{11}C]GR103545

DBU–CO_2 (1.2–2.5 equivalents) was weighed out and added to the reaction vial of the FXC module that contained a solution of compound **1** (0.5–3 mg) in anhydrous DMF (0.3 ml), with or without cesium carbonate and tetrabutylammonium triflate (Cs_2CO_3/TBATf) (1–3 molar equivalents each). The resulting heterogeneous mixture was vortexed for 5 min. The reaction vial was then placed in the FXC module, and [^{11}C]CH_3OTf was bubbled through the

[1] Our average RCY and SA (n=15) were 673.4±444 MBq and 32.19±15.91 MBq, respectively (18.2±12 mCi and 0.87±0.43 mCi/nmol).



Scheme 2. Retrosynthesis plan for radiolabeling of [^{11}C]GR103545 via *O*-methylation with carbon-11 of the carbamic acid intermediate compound **2**.

heterogeneous mixture at 0°C or at ambient temperature until activity peaked. The mixture was warmed to 25°C, allowed to stand for 5 min, diluted with 1 ml of deionized water and loaded onto the semi-preparative HPLC for purification. The product fraction eluting between 13 and 15 min was collected, diluted with 0.8% aqueous ascorbic acid (USP) solution (50 ml) and loaded onto a Waters Classic C18 Sep-Pak cartridge. The Sep-Pak cartridge was washed with of 0.1% aqueous ascorbic acid solution (10 ml), dried with a stream of helium for about 2 min and eluted with 1 ml of ethanol (USP), followed by 3 ml of 0.1% ascorbic acid in USP saline, into the FXC's product vessel pre-charged with 7 ml of 0.1% ascorbic acid in USP saline and 200 µl of 4.2% sodium bicarbonate solution, USP. The combined product in ethanolic saline was passed through a sterile 0.22-µm membrane filter (33 mm, MILLEX-GV, Millipore) into a sterile assembly comprising of a 1-ml QC vial connected to a vented 10-ml dose vial. Analytical HPLC analysis of the final product confirmed average chemical and radiochemical purities of >99% and 94.5%±1.7%, respectively, for radiolabeling in the presence of Cs_2CO_3/TBATf (n=15), and >99% and 93.3%±0.1%, respectively, for radiolabeling without Cs_2CO_3/TBATf (n=11) (Fig. 1). Identity of the tracer was confirmed by a co-injection of the tracer with the reference standard GR103545. SA was determined by counting an aliquot of the product in a dose calibrator for radioactivity amount, performing HPLC analysis of the aliquot and determining the mass of GR103545 associated with the injection by comparing the corresponding UV area with a standard curve relating UV area with mass.

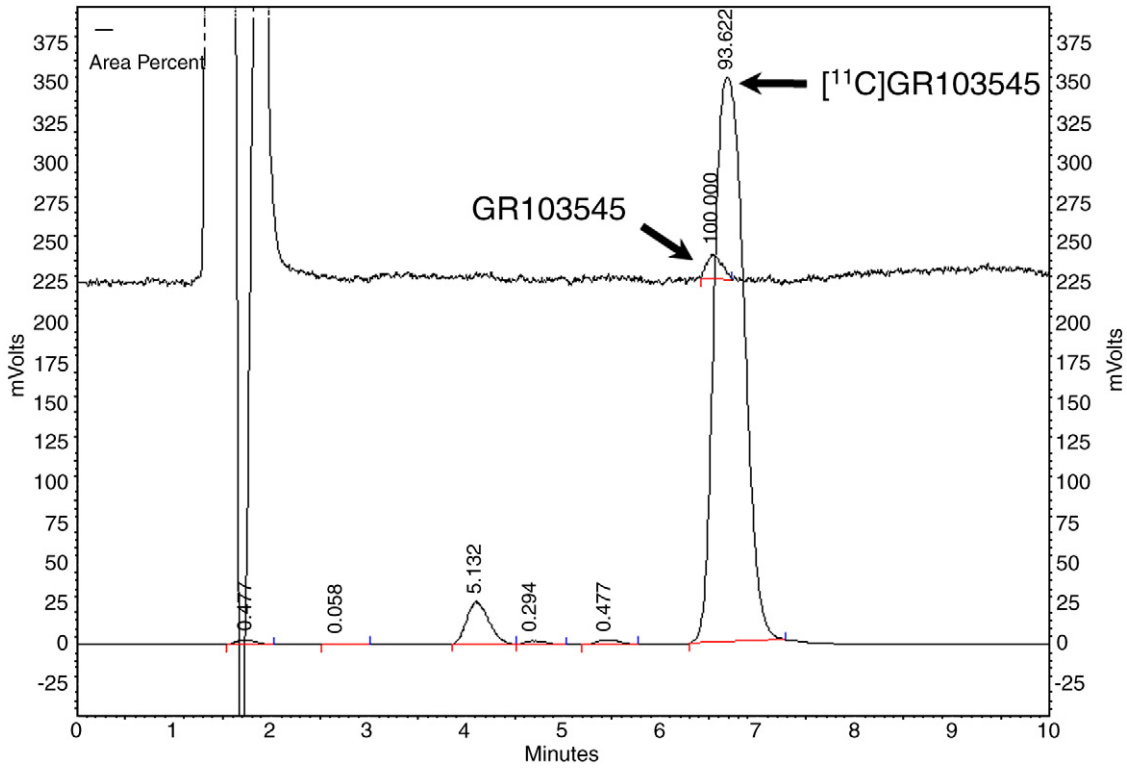
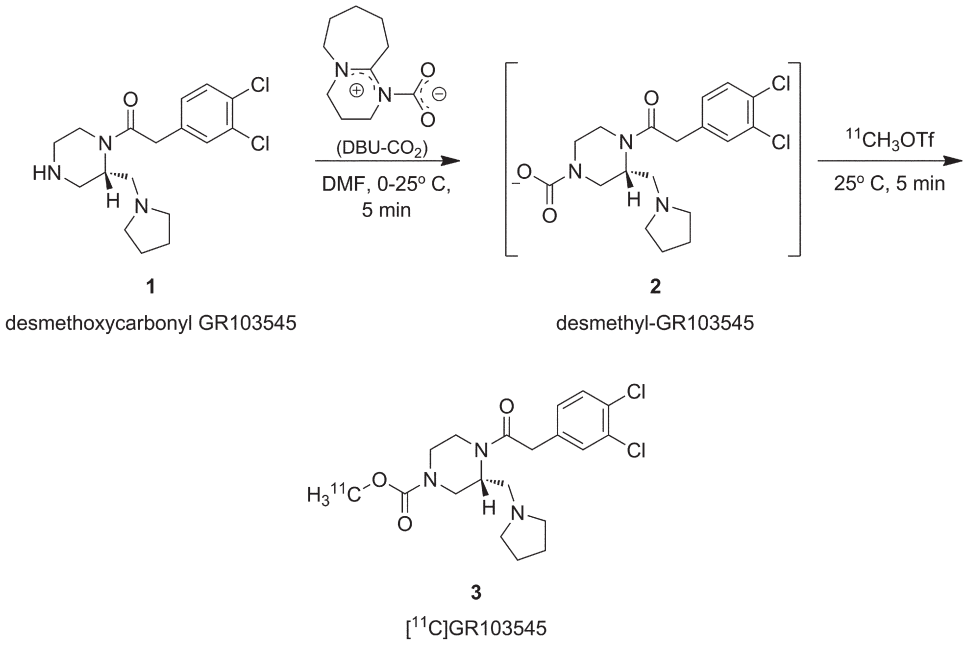


Fig. 1. Representative UV (top) and gamma (bottom) chromatograms from a typical HPLC analysis of the final [^{11}C]GR103545 product solution.



Scheme 3. Radiosynthesis of [^{11}C]GR103545 via *O*-methylation with carbon-11 of the carbamic acid intermediate compound **2**.

3. Results

Scheme 3 outlines our new and efficient approach for radiolabeling [^{11}C]GR103545. All radiosyntheses were carried on a TRACERLab FXC automated synthesizer. In total, 26 experiments were performed under two radiolabeling conditions: about half of the syntheses (n=15) were carried out in the presence of Cs_2CO_3/TBATf, and the remainder (n=11) was carried out without Cs_2CO_3/TBATf. The combined SA for both labeling conditions was 290.45±99.9 MBq (7.85±2.7 mCi/nmol) at the end of synthesis. Furthermore, both labeling conditions yielded a combined injectable radioactivity of 1961±814 MBq (53±22 mCi) after about 43 min from the end of beam, with combined radiochemical and chemical purities of >93% and >99%, respectively. Results from these experiments are summarized in Table 1. As pointed out earlier, the requisite carbamic acid intermediate, desmethyl GR103545-carbamate (**2**), was prepared in situ via a transcarboxylation reaction involving compound **1** and the DBU–CO_2 complex [20]. Reactions and applications using DBU have been widely reported in the literature [21,23–29].

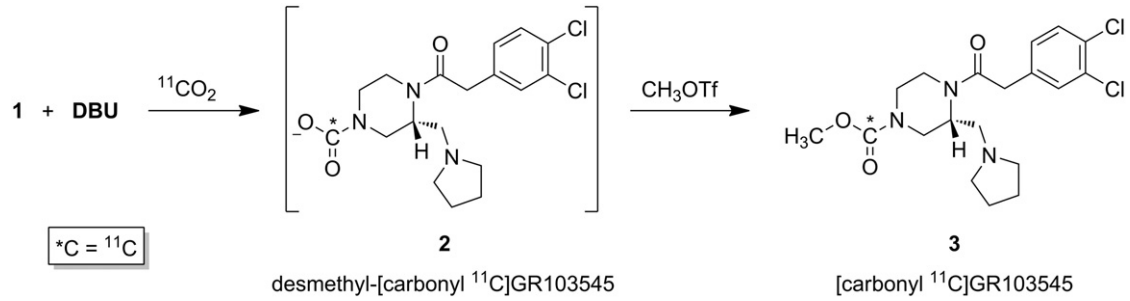
4. Discussion

Organic carbamates are used in many applications, ranging from synthesis of polyurethanes, pesticides and fungicides, in addition to medicinal drugs and other important synthetic intermediates [30]. They have traditionally been prepared using hazardous and toxic reagents, such as phosgene and isocyanate intermediates, as well as carbon monoxide [31]. We first carried out the radiosynthesis of [^{11}C]GR103545 using the phosgene approach as reported in the original literature. As shown in Table 1, yields were low and SA was not much better than what have been reported previously. Presence of trace amounts of methanol in dichloromethane and that of trace amounts of methyl chloroformate in phosgene contribute to lowering the SA.

Table 1
RCY and SA of [^{11}C]GR103545 by different methods

	DBU–CO_2	DBU–CO_2 & Cs_2CO_3 + TBATf	Literature method[a]
n	11	15	15
Yield [MBq (mCi)][b]	1517±814 (41±22)	2405±814 (65±22)	666±444 (18±12)
% RCY[c]	5.4±1.5	8.2±2.5	–
SA [MBq/nmol (mCi/nmol)]	259±118.4 (7.0±3.2)	321.9±81.4 (8.7±2.2)	32.19±0.43 (0.87±0.43)

[a] Radiolabeling was carried out in our laboratory using a device built in-house.
[b] Average beam conditions: 40 min of bombardment with a beam current of 50 μA.
[c] Decay-uncorrected, based on trapped [^{11}C]CH_3OTf at the end of synthesis.



Scheme 4. Radiosynthesis of [^{11}C-carbonyl]GR103545 [48].

Alternatively, direct reactions with carbon dioxide have been reported as an inexpensive and harmless way for the synthesis of carbamates [16,17]. However, these reactions take several days and yields are poor, as equilibrium usually favors the reactants. Meanwhile, the concept of chemical activation of carbon dioxide by fixation for its consumption and removal from the atmosphere has evolved to efficiently utilize CO_2 in various important chemical reactions [32,33]. With the aid of organometallic compounds, CO_2 fixation has been achieved by use of alcohols and amines, in addition to a variety of other compounds, such as unsaturated hydrocarbons and alkylene oxides [34].

In a departure from the usual methods, formation of *N*-alkylcarbamates has been reported during the course of alkylating secondary amines with alkyl halides and alkyl mesylates in the presence of inorganic carbonates as bases [35–37]. In one report, formation of the carbamate was attributed to CO_2 generated in situ from neutralizing of the carbonate base.

N-Alkylcarbamates are also efficiently synthesized through transcarboxylation and *O*-alkylation-coupled reactions using the DBU–CO_2 complex [19,20]. This method is very efficient such that in one report the solvent's intrinsic CO_2 concentration was sufficient to bring about formation of cyclic carbamates in the presence of DBU [23]. We found that CO_2 fixation as the DBU–CO_2 zwitterionic carbamic complex is very efficient in bringing about in situ transformation of compound **1** to the requisite carbamic acid intermediate compound **2**, under mild conditions, for subsequent *O*-methylation with carbon-11 to give [^{11}C]GR103545 in high SA. This DBU–CO_2 complex is a stable white powder with a reported melting point of 38°C–39°C [20]. DBU–CO_2 carbamic acid complex was stored in a freezer at −8°C to −10°C and used for 13 months. We have not determined its shelf life beyond this period, nor have we determined it shelf life when stored at ambient temperatures.

The efficiency of DBU–CO_2 for carboxylation of compound **1** is demonstrated through the short 5-min transcarboxylation period. We did not quantify the yield of compound **2**, nor have we performed extensive optimization for the radiosynthesis procedure. All syntheses were carried out using approximately 1.2–2.5 equivalents of DBU–CO_2. The DBU–CO_2 carbamic complex was weighed out and then added to the reaction vial of the automated synthesis module containing 0.5–3 mg of compound **1** in 300 μl of anhydrous DMF, either pre-chilled in ice water or at ambient temperature and in the presence or absence of Cs_2CO_3/TBATf. The resulting heterogeneous solution was then mixed well for 5 min using a vortex mixer in order to facilitate the generation of the requisite compound **2**. Afterwards, the reaction vial was placed in the automated synthesis module for subsequent radiolabeling with [^{11}C]CH_3OTf. The carbon-11 labeling agent was trapped at 0°C or at ambient temperature until radioactivity peaked. The resulting mixture was allowed to stand for 5 min at ambient temperature and then purified by semi-preparative HPLC followed by solid-phase extraction and formulation of the product. The average radiosynthesis time was 43 min from the end of bombardment.

As pointed out above, about half of the radiosyntheses were carried out with the addition of 1–3 molar equivalents each of Cs_2CO_3 and TBATf. There was no significant difference in the SA of [^{11}C]GR103545 when labeling was done in the presence or absence of Cs_2CO_3 and the quaternary amine: 321.9±81.4 MBq/nmol (8.7±2.2 mCi/nmol) and 259±118.4 MBq/nmol (7.0±3.2 mCi/nmol), respectively. However, the RCY was significantly higher when labeling was conducted in the presence of Cs_2CO_3/TBATf: 2405±814 MBq (65±22 mCi) in the final product vial vs. 1517±814 MBq (41±22 mCi) when Cs_2CO_3 and TBATf were absent. Although DBU carbamic anions exhibit enhanced nucleophilicity toward S_N2-type reaction due to the greater charge separation of the carbamic anion and delocalization of the DBU cation[2] [38], one can speculate that exchange of the DBU cation with cesium further improves the nucleophilicity of the carbamic anion due to the

[2] For instance, the reaction of benzoic acid with ethyl iodide for 1 h at room temperature in the presence of DBU gives the corresponding ester in 95% yield, whilst this reaction under the same conditions using triethylamine as the base gave only 1% of the ester. In this case, the enhanced reactivity is due to the greater charge delocalization of the DBU cation vis-à-vis the localized triethylammonium charge. In the former case, increased charge separation of the ion pair enhances the nucleophilicity of the carboxylate oxygen due to increasing the ground state energy of the ion pair. Conversely, the tight ion pair of triethylammonium salt lowers the ground state energy of the ion pair (cf. Ono et al. [38]).

"cesium effect" [39,40]. This greater reactivity in turn is largely due to the enhanced solubilization of the Cs^+ ion, leading to what is known as the "naked anion" [39]. The quaternary ammonium salt is added to prevent direct *N*-methylation of compound **1** [41,42].

5. Conclusions

We have developed a one-pot method for the automated radiosynthesis of the κ-OR tracer [^{11}C]GR103545 with high SA under mild conditions and in good yield via *O*-methylation with carbon-11 of compound **2**. This carbamic intermediate was prepared in situ by a transcarboxylation reaction between compound **1** and DBU–CO_2 zwitterionic carbamic complex. The method is highly efficient and reproducible, yielding [^{11}C]GR103545 in approximately nine times greater SA and four times higher yield than the original phosgene method. To further demonstrate the efficiency of our approach, we also radiolabeled [^{11}C]GR103545 by an analogous method that was reported recently [43]. It involves Cs_2CO_3-promoted direct carboxylation of compound **1** followed by *O*-methylation with carbon-11 of the resulting carbamic acid **2**. The RCYs (based on isolated product) were similar, but our method produced [^{11}C]GR103545 in about five times higher SA. More importantly, formation of the requisite carbamic intermediate compound **2** in the direct carboxylation method required bubbling of CO_2 for at least 1 h. In clear contrast, our approach is superior in that it only requires 5 min to produce the carbamic ion compound **2** through transcarboxylation. Another significant application is that our transcarboxylation method allows placement of the radiolabel in more than one place, as in the synthesis of the alternative [^{11}C]GR103545 analog, [^{11}C-carbonyl]GR103545 (Scheme 4). Syntheses of this and other [^{11}C-carbonyl]carbamates were reported via the transient immobilization of [^{11}C]CO_2 with DBU in situ and subsequent carbon-11 transcarboxylation followed by *O*-alkylation [44,45].

Acknowledgments

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