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SHORT NOTE

An updated synthesis of N_1'-([^{11}C]methyl)naltrindole for positron emission tomography imaging of the delta opioid receptor

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A new method for the synthesis of the highly selective delta opioid receptor (DOR) antagonist radiotracer N_1'-([^{11}C]methyl)naltrindole ([^{11}C]MeNTI) is described. The original synthesis required hydrogenation of a benzyl protecting group after ^{11}C-labeling, which is challenging in modern radiochemistry laboratories that tend to be heavily automated and operate according to current good manufacturing practice. To address this challenge, we describe development of a novel MeNTI precursor bearing a methoxymethyl acetal (MOM) protecting group, which is easily removed with HCl, and employ it in an updated synthesis of [^{11}C]MeNTI. The new synthesis is fully automated and validated for clinical use. The total synthesis time is 45 min and provides [^{11}C]MeNTI in good activity yield (49 ± 8 mCi), molar activity (3,926 ± 326 Ci/mmol) and radiochemical purity (97% ± 2%).

KEYWORDS
automation, delta opioid receptor, opioid, opioid imaging, radiochemistry

1 | INTRODUCTION

Opioids exhibit their requisite pharmacological effects through binding to opioid receptors (ORs), which are a group of G-protein-coupled receptors (GPCRs).[1] Distinct ORs are described in the literature: μ ORs (MOR), δ ORs (DOR), κ ORs (KOR), and OR-like 1 (ORL-1, also termed nociceptin opioid peptide [NOP] receptor).[2] Targeting ORs has a very crucial historical role in analgesia, with most historical opioids targeting MORs. However, although MOR agonists are effective analgesics, they also cause euphoric feelings that can lead to addiction. This issue has come to a head during the opioid epidemic that is plaguing the United States (overdoses involving opioids killed nearly 47,000 people in 2018[3]), leading to an urgent need for development of alternative non-addictive analgesics. With this in mind, opioid researchers are increasingly turning to the other ORs as alternatives to MORs.[4] For example, DORs also serve as a target of interest for pain management, as well as treatment of migraine and depression, but with less risk of addiction.[5,6] Key to the development of drugs for these other receptors is a thorough understanding of the entire opioid system,[4] and since the late 1970s/early 1980s, positron emission tomography (PET) imaging has played an important role in opioid research and contributed to our knowledge of opioid pharmacology (for recent reviews of OR imaging, see other studies[7–10]). In recent years, there has been a noticeable growth in OR imaging,[7] due to both the important role ORs play in pharmacology of many systems and disorders and the opioid epidemic.

The PET Center at the University of Michigan has an extensive history in opioid PET imaging, and we currently use [^{11}C]carfentanil (MOR),[11,12] [^{11}C]LY2795050 (KOR),[13,14] and [^{11}C]NOP-1A (ORL-1/NOP)[15,16] in such studies. However, we have never conducted any DOR

PET imaging. The DOR is expressed in the central nervous system (CNS) and the peripheral region. In the CNS, DORs are found in the cerebral cortex, caudate putamen, and the nucleus accumbens.[6] Activation of DORs results in many physiological and behavioral effects including modulation of antinociception, mood, sensory system, motor integration, and cognitive functions.[6,17] In addition, DORs are also present in several immunocompetent cells, which suggests their pivotal role in regulating the immune system.[18] In order to have a complete opioid imaging toolbox available for our clinical collaborators, we were interested in expanding our imaging portfolio to include a radiotracer for DORs. Of the available DOR PET ligands, N_1'-([^{11}C]methyl)naltrindole ([^{11}C]MeNTI) is the most widely used to date.[19] Portoghese and co-workers found that MeNTI is a highly potent DOR antagonist (K_i = 20 pM) that exhibits >700-fold selectivity over MOR, and >3,000 times over KOR.[20] It has been used in PET imaging studies for the localization and quantification of DORs in the human brain and heart,[21–23] as well as for imaging DORs expressed by primary tumors in certain cancer patients.[24] We therefore selected this agent to qualify for clinical use at our institution.

Upon review of existing radiosyntheses of [^{11}C]MeNTI, it became apparent that synthesis of the radiotracer is quite complex and this has perhaps limited widespread adoption of the imaging agent. The first radiosynthesis of [^{11}C]MeNTI was published by Lever et al. in 1995 and involved ^{11}C-methylation of 3-*O*-benzyl-naltrindole precursor with [^{11}C]MeI in dimethylformamide (DMF) under basic conditions.[19] Final deprotection of the benzyl protecting group was accomplished under heterogenous catalytic conditions (10% Pd/C/H_2 or methanolic ammonium formate) to provide [^{11}C]MeNTI in 6% radiochemical yield (RCY) and in a molar activity of 76 GBq/μmol (Figure 1A). When considering technology transfer of this method to our laboratory, we reasoned reductive deprotection of the benzyl group would be particularly difficult with the automated synthesis modules that have become common place in light of current good manufacturing practice (cGMP) regulations introduced since the original [^{11}C]MeNTI synthesis. Although commercial solutions like the H-Cube have simplified hydrogenation reactions in a radiochemistry setting,[25] they are still not widely available. Consistent with our continuing efforts to simplify existing radiosyntheses for routine production of PET radiotracers,[12,26] herein we report a novel MeNTI precursor bearing a methoxymethyl acetal (MOM) protecting group, which can easily be removed with HCl (Figure 1B). We employ this method in an updated synthesis of [^{11}C]MeNTI that is fully automated and validated for clinical use.

2 | EXPERIMENTAL

2.1 | General considerations

Full experimental details for syntheses and radiosyntheses, including copies of nuclear magnetic resonance (NMR) spectra and radio-high-performance liquid chromatography (radio-HPLC) traces, are provided in the supporting information.

2.2 | Synthesis of [^{11}C]MeNTI

[^{11}C]MeNTI was produced using a General Electric (GE) Tracerlab $FX_{C\text{-}Pro}$-automated radiochemistry synthesis module. [^{11}C]CO_2 was produced via ^{14}N(p,α)^{11}C nuclear reaction using a GE PET Trace cyclotron (60-μA beam for 45 min) and converted by standard procedures[27] into carbon-11 labeled [^{11}C]CH_3OTf (~1 Ci). The precursor (MOM-protected NTI (**5**), 1 mg) was dissolved in DMF (100 μl) and TBA-OH (1.0 M in MeOH, 2.1 μl) was added to the reactor. [^{11}C]CH_3OTf was sparged (bubbled) through the reaction solution for 3 min at room temperature (rt) at a rate of 15 ml/min. A 2-M HCl (300 μl) was then added to remove the MOM group, and the reactor was heated at 80°C for 5 min. After this time, the reaction was cooled to 50°C and quenched with 2-M NaOH (400 μl). The crude reaction mixture was purified using semi-preparative HPLC (column: Luna C18 250 × 10 mm–5 μ, flow rate: 4 ml/min, mobile phase: 30% acetonitrile, 10-mM NH_4OAc, 0.2% AcOH). The product peak (t_R ~ 12 min) was collected into 50 ml of water and then loaded onto a C18 Sep-Pak (1 cc). The Sep-Pak was rinsed with water (10 ml), and [^{11}C]MeNTI

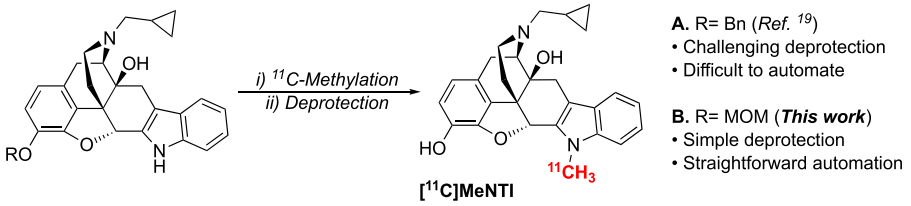


FIGURE 1 (A,B) Strategies for the synthesis of [^{11}C]MeNTI

was eluted with ethanol, USP (0.5 ml) and diluted with saline, USP (9.5 ml). The final product was filtered through a 0.22-μm sterile filter into a sterile dose vial and submitted for quality control testing. The overall synthesis time was 45 min from end-of bombardment (EOB).

2.3 | Quality control testing

Quality control of [^{11}C]MeNTI was conducted according to the guidelines outlined in Chapter <823> of the US Pharmacopeia and previously reported standard procedures.[27,28] HPLC analysis is described in Section 2.3.1. Results for three process verification batches using the new method are summarized in Table 3. Doses met all acceptance criteria confirming their suitability for clinical use and validating the synthesis method for future production.

2.3.1 | HPLC analysis

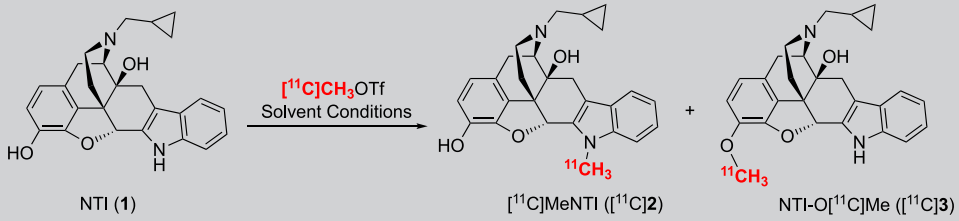
Chemical and radiochemical purity of [^{11}C]MeNTI was analyzed using a Shimadzu LC2010 HPLC equipped with a Bioscan/Eckert and Ziegler radioactivity detector and an ultraviolet (UV) detector (Column: Luna C18 150 × 4.6 mm–5 μ, flow rate: 2 ml/min, mobile phase: 40% MeCN, 10-mM NH_4OAc, 0.2% AcOH, pH 4.4, $t_R \sim 5$ min). Representative HPLC traces are provided in the supporting information.

3 | RESULTS AND DISCUSSION

We first synthesized naltrindole (NTI, 1) and N_1'-methylnaltrindole (MeNTI, **2**) reference standards using a reported Fischer indole synthesis.[29] The synthesis was carried out by condensation of naltrexone with the appropriate phenylhydrazine under mild acidic conditions in water, resulting in NTI (**1**) and MeNTI (**2**) in 98% and 73% yields, respectively (Scheme 1).

Initial work focused on [^{11}C]methylation of NTI (**1**) as it is well known in the literature that sterically crowded tertiary hydroxyl groups at the C-14 position of 4,5-α-epoxymorphinans are unreactive towards alkylating agents.[19] We therefore studied if ^{11}C-methylation of **1** could provide the desired product [^{11}C]MeNTI ([^{11}C]**2**) without protecting the phenol. However, attempts to methylate **1** with [^{11}C]MeOTf did not generate [^{11}C]**2** (Table 1, Entries 1 and 2). Because we have synthesized many ^{11}C-labeled PET imaging agents using loop chemistry, we attempted methylation of **1** in the loop at rt using 3-pentanone as the solvent, but this was also unsuccessful (Table 1, Entry 3). Loop chemistry employing DMF as the solvent was also attempted and did generate [^{11}C]MeNTI but only in trace amounts (Table 1, Entry 4).

TABLE 1 Initial attempts to synthesize [^{11}C]MeNTI



NTI (**1**) [^{11}C]MeNTI ([^{11}C]**2**) NTI-O[^{11}C]Me ([^{11}C]**3**)

Entry	Solvent[a]	Additive	RCY[b] for [^{11}C]2 (%)	RCY[b] for [^{11}C]3 (%)
1.	DMF, rt, 3 min	—	Nd	Nd
2.	DMF, 80°C, 3 min	—	Nd	Nd
3.	3-Pentanone, rt, loop chemistry	—	Multiple peaks observed by RAD detector	Nd
4.	DMF, rt, loop chemistry	—	<1.0	Nd
5.	Ethanol, rt, 3 min	Sat. NH_4Cl	Nd	Nd
6.	DMF, rt, 3 min	TBA-OH	Nd	55

[a]Solvent (100 μl).
[b]The identity of [^{11}C]**2** and [^{11}C]**3** was confirmed by radio-high-performance liquid chromatography (HPLC).
Abbreviations: DMF, dimethylformamide; Nd, not detected; rt, room temperature.

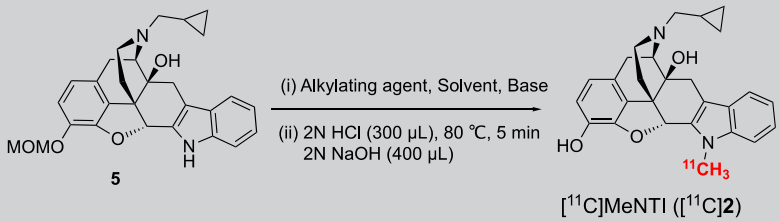


TABLE 2 Automation results for the synthesis on [^{11}C]MeNTI ([^{11}C]**2**)

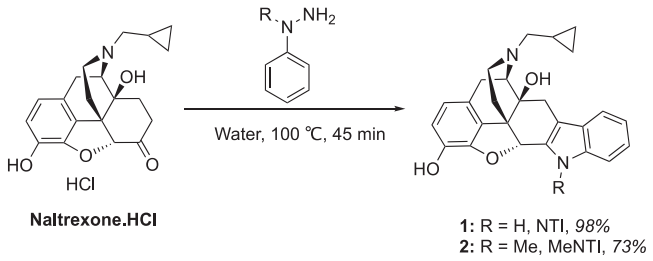
Entry	Solvent	Base	Alkylating agent	RCY (%)
1	DMF, rt	TBA-OH[a]	[^{11}C]MeOTf	70
2	Ethanol, rt	TBA-OH[a]	[^{11}C]MeOTf	Nd
3	DMSO, rt	TBA-OH[a]	[^{11}C]MeOTf	50[b]
4	DMF, rt	NaH[c]	[^{11}C]MeOTf	54
5	DMF, rt	TBA-OH[a]	[^{11}C]MeI	45

[a]TBA-OH (2.2 µl, 1.0 M in methanol).
[b]$n = 2$.
[c]NaH (1.2 mg).
Abbreviations: DMF, dimethylformamide; DMSO, dimethyl sulfoxide; Nd, not detected (product was not formed); rt, room temperature.

TABLE 3 QC data for the process verification batches of [^{11}C]MeNTI ([^{11}C]**2**)

Prerelease QC test	Release criteria	Batch 1	Batch 2	Batch 3
Radiochemical purity	≥95%	95.4	96.3	98.7
Radioactive concentration	≥25 mCi/10 ml batch	54.8	53.0	40.2
MeNTI concentration	Report result	0.66 µg/ml	0.56 µg/ml	0.41 µg/ml
Molar activity	≥1,500 ci/mmol	3,553	4,070	4,155
pH	4.5–7.5	5.0	5.0	5.0
Visual inspection	Clear, colorless, no precipitate	Pass	Pass	Pass
Radiochemical identity	RRT: 0.9–1.1	1.005	0.997	1.024
Radionuclide identity	18.4–22.4 min	19.9	19.6	19.8
Filter membrane integrity test	≥44 psi	47	52	49
Bacterial endotoxin test (initiated prior to release)	<17.5 EU/ml	<2.00	<2.00	<2.00
Residual solvent analysis	Acetone: ≤5,000 µg/ml; MeCN: ≤410 µg/ml; DMF: ≤880 µg/ml; total: ≤10,000 µg/ml	Acetone: 9.0 µg/ml; MeCN: 2.6 µg/ml; DMF: Nd; total: 11.6 µg/ml	Acetone: 10 µg/ml; MeCN: 14 µg/ml; DMF: Nd; total: 24.0 µg/ml	Acetone: 11.5 µg/ml; MeCN: 5.3 µg/ml; DMF: Nd; total: 16.8 µg/ml
Sterility	Sterile	Sterile	Sterile	Sterile

Abbreviations: DMF, dimethylformamide; Nd, not detected; QC, quality control; RRT, relative retention time.



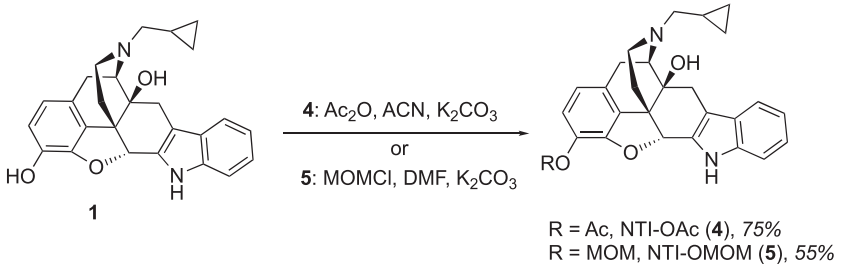
SCHEME 1 Synthesis of naltrindole (NTI) (**1**) and N_1'-methylnaltrindole (MeNTI) (**2**) using Fischer indole condensation

Because NTI has both a phenolic group and a tertiary amine group, it is possible that it has zwitterionic characteristics that can affect methylation. To investigate this possibility, we thought that inclusion of a protic additive (NH_4Cl, 40 μl, 0.05 M in ethanol) in the reaction mixture might promote the reaction, but unfortunately, this was also unsuccessful (Table 1, Entry 5). To improve the RCY, we therefore considered the addition of base to the reaction mixture. *Tetra*-butylammonium hydroxide (TBA-OH, 2.2 μl, 1.0 M in methanol) was included in the loop synthesis of [^{11}C]MeNTI but, unfortunately, HPLC analysis confirmed production of NTI-O[^{11}C]Me ([^{11}C]**3**) as the major product instead due to preferential ^{11}C-methylation of the phenol (Table 1, Entry 6). Consequently, to achieve the yield required for routine clinical production, we moved away from unprotected precursor **1** and instead focused upon developing a new protection strategy compatible with the zwitterionic character of NTI and amenable to cGMP compliant automation.

We initially explored protection of the phenol with an acetate group (Scheme 2). Starting from **1**, NTI-OAc (**4**) was obtained in 75% yield. However, attempts to ^{11}C-methylate **4** ([^{11}C]MeOTf, TBA-OH) revealed that the acetate protecting group was unstable during the radiosynthesis and only NTI-O[^{11}C]Me ([^{11}C]**3**) was formed. To address this, we next decided to protect the phenol with a MOM group because of its stability to basic conditions (Scheme 2). Moreover, the MOM protecting group is easily removed under mild acidic conditions (2-M HCl) making it more attractive than the benzyl group used in the original synthesis that requires either harsh forcing conditions (e.g. conc. HBr) or reduction methods for removal. We treated NTI (**1**) with MOM-Cl in the presence of K_2CO_3, which generated the desired precursor NTI-OMOM (**5**) in 55% yield. In exploratory radiochemistry, a mixture of NTI-OMOM (**5**) and TBA-OH in DMF was sparged with [^{11}C]MeOTf for 3 min at rt and provided the desired labeled intermediate [^{11}C]Me-NTI-OMOM as the major product (confirmed by co-elution with unlabeled Me-NTI-OMOM reference standard in HPLC analysis). Subsequent deprotection with 2-M HCl at 80°C for 5 min provided [^{11}C]MeNTI ([^{11}C]**2**) in 70% RCY, estimated by radio-HPLC (Table 2, Entry 1). In an attempt to develop a greener approach for the synthesis, we also tried to employ a Class 3 solvent instead of DMF.[30] Conducting the labeling in ethanol failed to provide product (Table 2, Entry 2), while using dimethyl sulfoxide (DMSO) gave product in lower (50%) RCY (Table 2, Entry 3). The use of alternative bases (NaH) and ^{11}C-methylating agents ([^{11}C]MeI) was explored (Table 2, Entries 4 and 5), but both of these changes resulted in lower RCYs and complex mixtures. Thus, the use of [^{11}C]MeOTf in DMF for 3 min at rt proved to be the optimal conditions for the preparation of [^{11}C]MeNTI (Table 2, Entry 1).

Lastly, we automated the optimal conditions and validated the process for clinical production. After synthesis and deprotection, [^{11}C]MeNTI was purified by semi-preparative HPLC (column: Luna C18, 5 micron, 250 × 4.6 mm; mobile phase: 30% acetonitrile, 10-mM NH_4OAc, 0.2% acetic acid; flow rate: 4 ml/min), and this chromatographic system gave good separation of [^{11}C]MeNTI (t_R = 12.5–14.5 min) from NTI produced from concomitant deprotection of residual MOM-protected precursor (t_R = 8–10 min). [^{11}C]MeNTI was reformulated using a C18 cartridge, and the final dose was passed through a 0.22-μm Millex GV sterile filter (Millipore) into a sterile dose vial (Hollister-Stier). The total synthesis time was 45 min, and [^{11}C]MeNTI was produced in good activity yield (49 ± 8 mCi), molar activity (3,926 ± 326 Ci/mmol) and radiochemical purity (97 ± 2%), n = 3. Quality control analysis was performed in accordance with the US Pharmacopeia,

SCHEME 2 Synthesis of acetate- and methoxymethyl acetal (MOM)-protected naltrindole (NTI) analogs **4** and **5**



Chapter <823>,[27,28] and confirmed that doses produced using this method are suitable for human use (Table 3). Radiochemical purity and pH of batches were also re-analyzed 1 h post-EOS (end-of-synthesis), confirming that the product was stable and allowing us to assign a 1-h expiration time to doses of [^{11}C]MeNTI.

4 | CONCLUSIONS

In summary, a new method for the radiosynthesis of [^{11}C]MeNTI has been developed. The synthesis utilizes an easily removed MOM protecting group and straightforward chemistry, providing the product in good RCY, molar activity, and purity. The process has been fully automated using a commercially available radiosynthesis module. [^{11}C]MeNTI remains the radiotracer of choice for PET imaging of delta ORs. As such, the straightforward synthesis method described in this paper could facilitate the use of [^{11}C]MeNTI PET to provide a better understanding of the role DORs have in health and neurological disorders and assist in the development of novel DOR-targeted therapeutics.

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CONFLICT OF INTEREST

The authors do not report any conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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