ACS Medicinal Chemistry Letters

Letter

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Radiosynthesis of ^{11}C-Levetiracetam: A Potential Marker for PET Imaging of SV2A Expression

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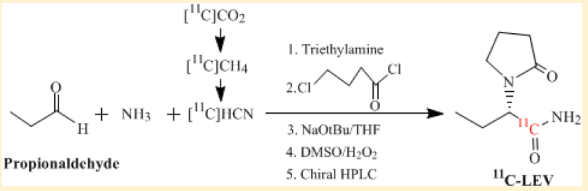
Supporting Information

ABSTRACT: The multistep preparation of ^{11}C-levetiracetam (^{11}C-LEV) was carried out by a one-pot radiosynthesis with 8.3 ± 1.6% (n = 8) radiochemical yield in 50 ± 5.0 min. Briefly, the propionaldehyde was converted to propan-1-imine *in situ* as labeling precursor by incubation with ammonia. Without further separation, the imine was reacted with ^{11}C-HCN to form ^{11}C-aminonitrile. This crude was then reacted with 4-chlorobutyryl chloride and followed by hydrolysis to yield ^{11}C-LEV after purification by chiral high-performance liquid chromatography (HPLC). Both the radiochemical and enantiomeric purities of ^{11}C-LEV were >98%.



KEYWORDS: *Levetiracetam, synaptic vesicle protein 2A, positron emission tomography, carbon-11*

(*S*)-α-Ethyl-2-oxo-1-pyrrolidine acetamide, a pyrrolidone drug named levetiracetam (LEV, UCB Pharma Ltd.), is widely used to treat epilepsy and other central nervous system (CNS) disorders.[1] LEV has been approved by the US Food and Drug Administration since 1999 and more than 90 other countries worldwide for the treatment of epilepsy. This drug has become one of the most successful therapeutics of the newer classes of antiepileptic drugs (AEDs). In addition, mounting evidence have demonstrated that LEV has potential benefits for other psychiatric and neurologic conditions such as Alzheimer's disease, Tourette syndrome, autism, bipolar disorder, and anxiety disorder.[2−6] In the past 10 years, there have been more than 176 clinical trials conducted using LEV in many medical applications.[7] Several beneficial properties of LEV, including potent antiepileptogenic effects, absence of severe adverse effects, and a low potential for drug interactions have indicated that LEV acts via a novel, unique mechanism of action, which is distinct from that of conventional AEDs. Although the precise mechanism of action of LEV has not yet been fully elucidated, synaptic vesicle protein 2A (SV2A) as the binding target for LEV has been identified, based on a strong correlation between the affinity of LEV analogues for the SV2A and their antiseizure potency.[8,9]

SV2A is a member of a family of membrane-bound glycoproteins found on synaptic vesicles of both neurons and endocrine cells. In mammals, this protein family is encoded by three different genes (SV2A, SV2B, and SV2C), of which SV2A is the most abundant and widely expressed product and is critical for proper nervous system function and has been demonstrated to be involved in vesicle trafficking.[10] However, the completely molecular function of SV2A remains elusive, and it is still unknown how LEV interacts with the SV2A to prevent epilepsy.[11]

Positron emission tomography (PET) with specific radioligand has been highly useful to aid proof of concept determinations in CNS drug development.[12] Radiolabeling of drugs with positron-emitting radionuclide (^{11}C or ^{18}F) is a commonly used technique to study the interaction between drugs and their targets, to map neurotransmitter receptor or transporter density in health and disease, and to measure engagement of putative therapeutic targets by potential drugs.[12] Since SV2A has been identified as the binding site of the antiepileptic LEV and with their implication in epilepsy, these make SV2A an interesting therapeutic and imaging target for epileptogenesis and other neurologic disorders. In addition, the widespread distribution of SV2A in brain may provide an opportunity to develop a PET imaging to measure neuronal function in CNS diseases. However, PET imaging of SV2A has rarely been studied because of the lack of an appropriate radiotracer. During our work, another group has reported the

Received: July 14, 2014
Accepted: August 19, 2014
Published: August 19, 2014

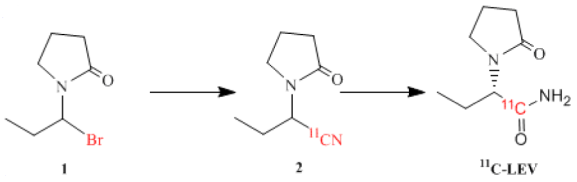
dx.doi.org/10.1021/ml500285t | *ACS Med. Chem. Lett.* 2014, 5, 1152−1155

first PET tracer ^{18}F-UCB-H for imaging SV2A.[13−15] The ^{18}F-UCB-H was obtained from ^{18}F−^{19}F isotope exchange after 150 min or complicated preparation using a four step radiosynthesis process, and then evaluated in the rat using PET imaging. However, in addition to the extremely complex radiochemistry, the selectivity of ^{18}F-UCB-H for SV2A imaging was deduced based on blocking of ^{18}F-UCB-H binding with LEV. This indicates that LEV is the gold standard ligand for binding to SV2A and, as such, is preferable to all other compounds. Although the binding affinity of LEV to SV2A is moderate (pIC_{50} = 6.1), the high selectivity of LEV for SV2A was previously clearly demonstrated using tritium labeling LEV and various preclinical and clinical studies.[8,11] Therefore, the development of labeled LEV for PET imaging is highly desirable and optimal for quantification of SV2A expression *in vivo*.

PET radioligand discovery and development is a long, costly, and well-regulated process, and many radioligands fail to be translated to the clinical arena due to the paucity of pharmacological effects and toxicity data.[16] Despite its short half-life ($t_{1/2}$ = 20.4 min), ^{11}C is one of the most widely used PET radionuclides, especially for CNS radioligand development, because of its favorable physical and biological characteristics and established ^{11}C-PET chemistry.[17] The replacement of one stable ^{12}C atom in a clinically used drug with positron emitting ^{11}C will not alter its chemical and/or biological profile, making a swift translation of PET radioligand from the bench to the bedside possible. Since LEV is the best known ligand binding to SV2A, ^{11}C labeled LEV (^{11}C-LEV) compound, without changing its chemical structure, has the potential to be a radioligand for PET imaging of SV2A expression in human. Therefore, we report here the first design and radiosynthesis of ^{11}C-LEV using a multistep one-pot method.

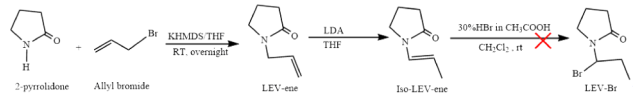
There are several reported methods for the large-scale production of LEV.[18] Generally, these methods involved classical resolution processes and asymmetric syntheses, and some of these methods have their own intrinsic disadvantages. These existing processes, requiring either long reaction time and multiple chromatographic separations or chemical resolution, are not suited for ^{11}C-PET chemistry. According to the chemical structure of LEV and available ^{11}C-PET chemistry toolbox, we first designed a radiosynthetic route shown in Scheme 1.

Scheme 1. Method 1 for Radiosynthesis of ^{11}C-LEV



Initially, we planned to use 1-(1-bromopropyl)pyrrolidin-2-one (LEV-Br, **1**) as radiolabeling precursor. The bromine in the precursor would be replaced with ^{11}C-cyanide, resulting in ^{11}C labeled 2-(2-oxo-1-pyrrolidinyl)butanenitrile **2**, which could be hydrolyzed to yield ^{11}C-LEV after separation by chiral high-performance liquid chromatography (HPLC). Since there is no commercially available LEV-Br, we first tried to synthesize this compound in our laboratory using a straightforward method, shown in Scheme 2. Briefly, *N*-allyl-2-pyrrolidone (LEV-ene)

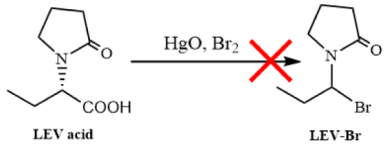
Scheme 2. Straightforward Synthesis of LEV-Br



was prepared by reaction of allyl bromide with 2-pyrrolidone in a tetrahydrofuran (THF) solution of KHMDS at room temperature according to reported methods with minor modifications[19] and then was converted to 1-propenyl-pyrrolidin-2-one (iso-LEV-ene) under basic conditions of lithium diisopropylamide (LDA) in THF.[20] However, iso-LEV-ene failed to produce LEV-Br by reaction with HBr in acetic acid solution according to reported methods.[21]

The failure of the straightforward synthesis of LEV-Br made us look for other methods to prepare LEV-Br. Hundsiecher reaction or its Cristol−Firth modification is a well established reaction for the bromodecarboxylation of organic acid.[22] We tested decarboxylation of commercial (2*S*)-2-(2-oxopyrrolidin-1-yl)butanoic acid (LEV acid) using the Cristol−Firth modification method, shown in Scheme 3, but still failed to

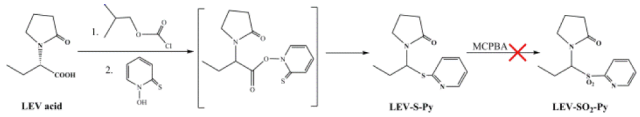
Scheme 3. Synthesis of LEV-Br Using the Cristol−Firth Reaction



produce LEV-Br. The failures of synthesizing LEV-Br using above established methods led us to the conclusion that LEV-Br is unstable in these processes under normal conditions. Indeed, it was reported that LEV-Br analogues are very reactive to air, moisture, and silica gel during purification, and they easily form oligomers and other byproducts under normal conditions.[23]

Beside the Hunsdiecker-type bromodecarboxylation reaction, the Barton decarboxylation protocol via thiohydoxamate ester is another powerful synthetic tool for converting alkyl carboxylic acid residues into a variety of different functionalities.[24] Accordingly, we used this mild decarboxylation method at low temperature to synthesize a new labeling precursor, shown in Scheme 4. We synthesized the compound named LEV-S-Py

Scheme 4. Synthesis of LEV-SO$_2$-Py



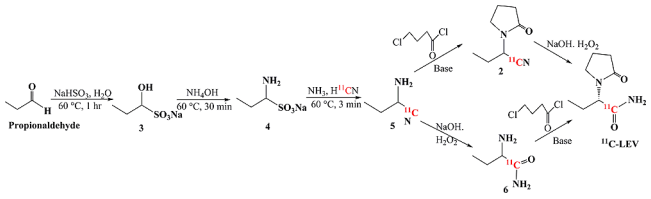
according to reported methods with minor modifications[24] but failed to synthesize the expected compound LEV-SO$_2$-Py, most likely for similar reasons encountered during the synthesis of LEV-Br.

Since we failed to prepare the precursor LEV-Br or LEV-SO$_2$-Py as precursors for radiosynthesis of ^{11}C-LEV using the designed method (Scheme 1), we revisited the common synthetic method of LEV, which was processed by reaction of *S*-aminobutanamide with 4-halobutyryl halide and subsequent cyclization to yield LEV.[18] Indeed, ^{11}C labeled S-amino-butanamide could be produced according to reported radio-

dx.doi.org/10.1021/ml500285t | *ACS Med. Chem. Lett.* 2014, 5, 1152−1155

synthesis of ^{11}C-labeled amino acids.[25] Therefore, we designed another radiosynthetic route of ^{11}C-LEV shown in Scheme 5.

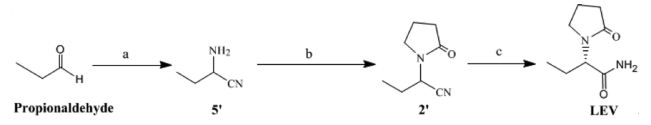
Scheme 5. Method 2 for Radiosynthesis of ^{11}C-LEV



The Bucherer−Strecker synthesis is frequently used and one of the most straightforward methods to prepare ^{11}C-labeled amino acids or amino amide.[25,26] We applied this method to prepare ^{11}C-amnionitrile **5**. Briefly, the bisulfite adduct **3** of propionaldehyde as preprecursor was *in situ* converted to the aminosulfonate **4** as the precursor (reaction with ammonia for 30 min just prior to the end of bombardment (EOB)). The sulfite group of the aminosulfonic salt **4** was replaced by ^{11}C-cyanide to yield ^{11}C-amnionitrile **5** in aqueous solution. The ^{11}C-amnionitrile **5** was followed by reaction with 4-chlorobutyryl chloride in basic conditions to generate compound **2** after removal of water and dried. However, the ^{11}C-amnionitrile **5** is sensitive to high temperature and pH value of aqueous solution, resulting in low radiochemical yield (∼1.0%) of ^{11}C-LEV. Thus, we switched to the hydrolysis of ^{11}C-amnionitrile **5** to ^{11}C-aminobutanamide **6** first and then removed water, followed by reaction with 4-chlorobutyryl chloride in basic conditions, and then separation by chiral HPLC to yield ^{11}C-LEV. Unfortunately, even after this process the radiochemical yield of ^{11}C-LEV was still low (∼1.0%).

The method 2 for the radiosynthesis of ^{11}C-LEV required more than 1 h multistep reactions in two reaction pots, multiple chromatographic separations, and removal of water from compound **5** or **6**, which resulted in the low radiochemical yield (∼1%). Therefore, this method was unsuitable for short half-life of ^{11}C-PET chemistry. We improved this method using a multicomponent reaction to reduce reaction steps and to simplify purifications. We first tested this facile method by the synthesis of standard compound LEV outlined in Scheme 6.

Scheme 6. Synthesis of Standard Compound LEV[a]

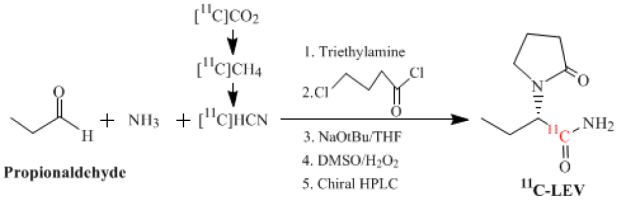


[a]Reagents and conditions: (a) $MgSO_4$, NH_4Cl, NaCN, 7 M NH_3 in MeOH, 0 °C to RT for 4 h. (b) $NaSO_4$, KOH, TBAB, 4-chlorobutyryl chloride, 0 °C to RT for overnight. (c) (i) 95% H_2SO_4, 100 °C for 10 min, (ii) ∼30% NH_3, (iii) chiral HPLC separation; or (i) 0.1 N NaOH, 60 °C for 10 min, (ii) AcOH, (iii) chiral HPLC separation.

Briefly, 2-aminionitrile **5′** was prepared through Strecker-type reaction between an aldehyde, an amine, and a hydrogen cyanide. This multicomponent reaction comprised hydrocyanation of imine generated *in situ* from the aldehyde. The crude aminionitrile **5′** was followed by cyclization reaction with 4-chlorobutyryl chloride to produce 2-(2-oxo-1-pyrrolidinyl)-butanenitrile **2′**, which was hydrolyzed to yield LEV after separation by chiral HPLC.

Using this facile synthesis route of LEV with high yield (total synthesis: 22.7%), we designed a multistep one-pot radiosynthesis of ^{11}C-LEV, shown in Scheme 7. The preprecursor

Scheme 7. Multistep One-Pot Radiosynthesis of ^{11}C-LEV



propionaldehyde was converted to the propan-1-imine *in situ* as radiolabeling precursor by incubating with ammonia in methanol just prior to EOB. ^{11}C-CO_2 produced by cyclotron was trapped and cleared of residual target gas oxygen using a Carbosphere trap. It was then converted to ^{11}C-CH_4 with a hydrogen and nickel catalyst at 360 °C. This ^{11}C-CH_4 gas was further mixed with anhydrous ammonia gas and directed to a platinum wire packed quartz tube placed in the furnace at 1000 °C to yield a mixture of ^{11}C-HCN and ammonia according to a previously reported method.[25] ^{11}C-HCN and ammonia were bubbled into the solution of the crude imine in a reaction vial and formed the desired crude ^{11}C-aminonitrile **5** after 5 min incubation at 0−10 °C. The resulting crude ^{11}C-aminonitrile **5** was directly added with triethylamine, followed by the addition of 4-chlorobutyryl chloride in dichloromethane. The mixed solution was incubated for 5 min at 10−20 °C, followed by the addition of sodium *tert*-butoxide in THF, and incubated for another 5 min at 0−5 °C. The resulting ^{11}C labeled 2-(2-oxo-1-pyrrolidinyl)butanenitrile **2** was treated with the mixture of dimethyl sulfoxide and hydrogen peroxide for basic hydrolysis (3 min at 60 °C) to produce crude racemic ^{11}C-LEV. The enantiomerically pure ^{11}C-LEV (R_t = 9.0 min, >99%) was then isolated from crude mixtures by chiral HPLC separation. The collected product fraction was sterilized by filtration.

The entire synthesis was performed remotely in a closed, lead-lined hot cell using a house-made module for ^{11}C-CO_2 trapping and conversion to ^{11}C-HCN coupled to a module for the synthesis and purification of ^{11}C-LEV. Without any optimization, the radiochemical yield (decay corrected) of ^{11}C-LEV was 8.3 ± 1.6% (n = 8) at the end of synthesis (EOS) based on ^{11}C-HCN radioactivity trapped in the reaction vial (conversion of ^{11}C-CO_2 to ^{11}C-HCN averaged ∼85%). Both the radiochemical and enantiomeric purities of ^{11}C-LEV were more than 98% and the specific activity was more than 17 GBq/μmol at EOS based on HPLC analysis. The total radiosynthesis time was 50 ± 5 min from EOB to the finish of HPLC purification (including 6 min for collection of the ^{11}C-CO_2 and conversion to ^{11}C-HCN). In the final chiral HPLC separation of ^{11}C-LEV, a byproduct, pure R-^{11}C-LEV (t_R = 10.5 min), was also isolated and could be used to determine the stereoselectivity of biochemical processes when compared to ^{11}C-LEV in various *in vivo* and *in vitro* systems. In addition, this novel radiolabeling methodology can be used as a general method for ^{11}C radiolabeling amide molecules including other pyrrolidone drugs (LEV derivatives, such as brivaracetam and seletractam) for *in vivo* PET imaging of SV2A expression.

In conclusion, we designed and developed a novel radiosynthesis of ^{11}C-LEV using a multistep one-pot method. The success of this approach could make ^{11}C-LEV a feasible

dx.doi.org/10.1021/ml500285t | ACS Med. Chem. Lett. 2014, 5, 1152−1155

approach for PET imaging of SV2A expression and facilitate further clinical translation studies.

■ ASSOCIATED CONTENT

Supporting Information

Representative experimental procedures and NMR, MS, and HPLC data for all new test compounds, and micro-PET imaging. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We would like to thank staff members from the Children's Hospital of Michigan PET center for their service and support, and thank Prof. David Crich from Department of Chemistry in Wayne State University for the help of setup of Barton decarboxylation protocol. Dr. Guochao Liao from Wayne State University and Dr. Yongjun Li from Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences are acknowledged for help of chemical analysis and discussion.

■ ABBREVIATIONS

LEV, levetiracetam, (*S*)-α-ethyl-2-oxo-1-pyrrolidine acetamide; SV2A, synaptic vesicle protein 2A; ^{11}C-LEV, ^{11}C-levetiracetam; CNS, central nervous system; AEDs, antiepileptic drugs; PET, positron emission tomography; LEV-ene, *N*-allyl-2-pyrrolidone; THF, tetrahydrofuran; iso-LEV-ene, 1-propenyl-pyrrolidin-2-one; LDA, lithium diisopropylamide; KHMDS, potassium bis(trimethylsilyl)amide; LEV acid, (2*S*)-2-(2-oxopyrrolidin-1-yl)butanoic acid; EOB, end of bombardment; EOS, end of synthesis

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