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Facile synthesis of new carbon-11 labeled conformationally restricted rivastigmine analogues as potential PET agents for imaging AChE and BChE enzymes

Min Wang, Ji-Quan Wang, Mingzhang Gao, Qi-Huang Zheng*

Department of Radiology, Indiana University School of Medicine, 1345 West 16th Street, L-3 Room 202, Indianapolis, IN 46202, USA

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Abstract

Rivastigmine is a newer-generation inhibitor with a dual inhibitory action on both acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes, and is used for the treatment of AChE- and BChE-related diseases such as brain Alzheimer's disease and cardiovascular disease. New carbon-11 labeled conformationally restricted rivastigmine analogues radiolabeled quaternary ammonium triflate salts, (3a*R*,9b*S*)-1-[^{11}C]methyl-1-methyl-6-(methylcarbamoyloxy)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[g]indolium triflate ([^{11}C]**8**) and (3a*R*,9b*S*)-1-[^{11}C]methyl-1-methyl-6-(heptylcarbamoyloxy)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[g]indolium triflate ([^{11}C]**9**), were designed and synthesized as potential positron emission tomography (PET) agents for imaging AChE and BChE enzymes. The appropriate precursors were labeled with [^{11}C]CH_3OTf through *N*-[^{11}C]methylation, and the target tracers were isolated by solid-phase extraction (SPE) using a cation-exchange CM Sep-Pak cartridge in 40–50% radiochemical yields decay corrected to end of bombardment (EOB), 15–20 min overall synthesis time, and 148–222 GBq/μmol specific activity at EOB.

Keywords: Acetylcholinesterase (AChE); Butyrylcholinesterase (BChE); Positron emission tomography (PET); Rivastigmine; Conformationally restricted analogues; Carbon-11; Imaging

1. Introduction

Central cholinergic systems play an important role in a wide variety of brain functions, including attention, cognition, learning, memory, control of sleep and wakefulness, and many others (Oliveira and Hodges, 2005). Central cholinergic systems are also related to cardiovascular functions like coronary blood flow, cardiac contraction and heart rate (Henning and Sawmiller, 2001). Dysfunctions of central cholinergic systems are associated with various brain and heart diseases such as Alzheimer's disease and coronary heart disease (Gao et al., 2007; Hartmann et al., 2007). The enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) play significant roles in cholinergic dysfunction in which AChE terminates nerve impulse transmission by hydrolyzing the neurotransmitter acetylcholine (ACh) to acetate and choline, and BChE may be involved in the control of ACh release and ACh degradation (Boudinot et al., 2005; Mack and Robitzki, 2000). Both enzymes are likely involved in regulating ACh levels and may represent therapeutic targets for the development of enzyme inhibitors (Leader et al., 2002). To date, the improvement of the central cholinergic function is the only clinical effective approach, and cholinergic dysfunction is treated with AChE inhibitors or the inhibitors with the ability to inhibit BChE in addition to AChE. Rivastigmine as shown in Fig. 1 is a newer-generation inhibitor, which co-inhibits both AChE and BChE, and is used for the treatment of AChE- and BChE-related diseases including brain Alzheimer's disease and cardiovascular disease (Bolognesi et al., 2004; Gottwald and Rozanski, 1999). Both AChE and BChE enzymes also provide attractive targets for the development of enzyme-based imaging agents for biomedical imaging technique positron emission tomography (PET) to study

*Corresponding author. Tel.: +1 317 278 4671; fax: +1 317 278 9711.
E-mail address: qzheng@iupui.edu (Q.-H. Zheng).

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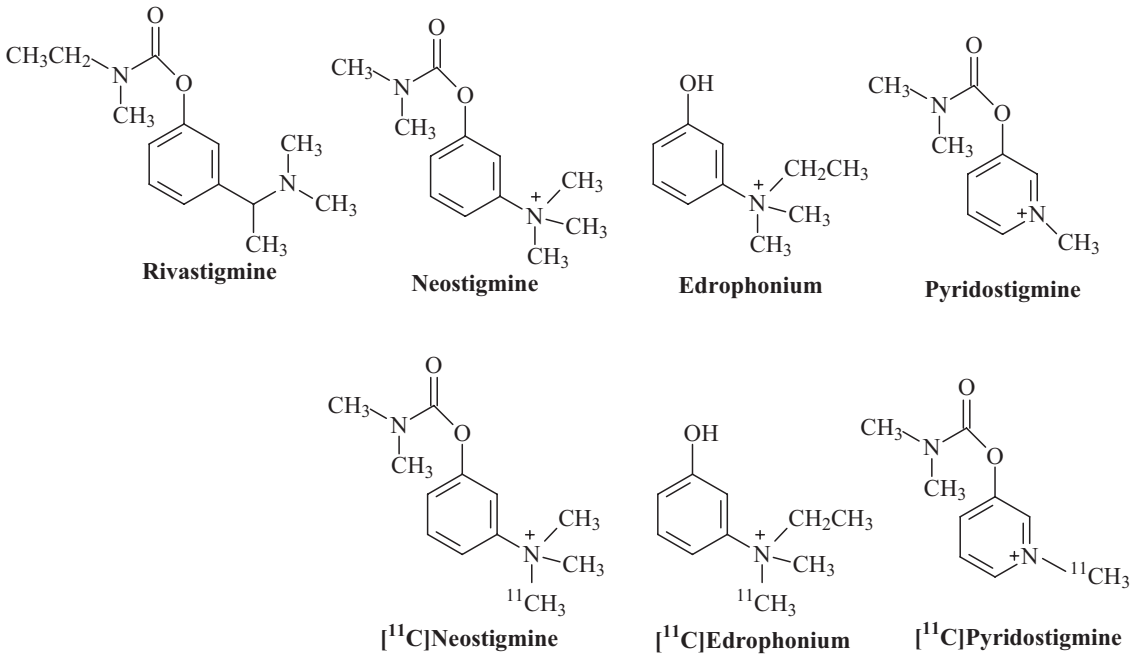

Fig. 1. Chemical structures of rivastigmine, neostigmine, edrophonium and pyridostigmine.

brain and heart diseases. To translate therapeutic agents for diagnostic use, we are interested in the design and synthesis of medical probes. In our previous works, we have directly radiolabeled AChE inhibitors with positron emitting radionuclide carbon-11 and developed [^{11}C]neostigmine, [^{11}C]edrophonium, [^{11}C]pyridostigmine (Fig. 1), and carbon-11 labeled neostigmine, edrophonium and pyridostigmine analogues including [^{11}C]neostigmine metabolite, [^{11}C]edrophonium ethyl analogue, [^{11}C]edrophonium methyl analogue, [^{11}C]*para*-pyridostigmine and [^{11}C]*ortho*-pyridostigmine, for PET imaging of AChE in the heart (Mulholland et al., 1999; Wang et al., 2004, 2005; Zheng et al., 2003). Obviously, these compounds are carbon-11 labeled methylated quaternary ammonium derivatives, and the chemical structure of rivastigmine is very similar to the chemical structure of neostigmine as seen in Fig. 1. Recent findings indicate that in Alzheimer brain, BChE activity rises while AChE activity remains unchanged or declines, and the conformationally restricted rivastigmine analogues have higher in vitro biological activity to AChE and BChE in comparison with the parent compound rivastigmine (Bolognesi et al., 2004). Therefore, the enzyme BChE and the structural modification of BChE inhibitors such as rivastigmine attract more attention (Bolognesi et al., 2004; Leader et al., 2002; Wang et al., 2005), and we turn our effort to the development of PET AChE and BChE imaging agents with a dual inhibitory action on both AChE and BChE. It was our original goal to develop [^{11}C]rivastigmine and its carbon-11 labeled conformationally restricted analogues (tertiary amines) reported in previous work (Bolognesi et al., 2004), and a variety of synthetic approaches were designed and performed for this purpose. However, we were unable to obtain *N*-desmethyl-precursors for radiolabeling via *N*-[^{11}C]methylation with [^{11}C]methyl triflate ([^{11}C]CH_3OTf) (Mock et al., 1999) due to the complexity of their chemical structures and difficulty of the synthesis. As a result of these unsuccessful attempts, we chose to explore an alternative strategy to prepare carbon-11 labeled conformationally restricted rivastigmine analogues (quaternary ammoniums). It has been reported that conformationally restricted quaternary ammonium derivatives of rivastigmine has very similar binding affinity to AChE and BChE in comparison with their tertiary amine derivatives (Bolognesi et al., 2001); moreover, the quaternary ammonium derivatives have a higher affinity with regard to their tertiary amine precursors (Graulich et al., 2005, 2006). In this ongoing study, we report the facile synthesis of new carbon-11 labeled conformationally restricted quaternary ammonium analogues of rivastigmine as potential PET agents for imaging of both AChE and BChE enzymes.

2. Results and discussion

2.1. Chemistry

The synthetic approach for the precursors **6** and **7**, and the *N*-methylated products **8** and **9** as reference standards is outlined in Scheme 1. Commercially available 5-methoxytetralone was conveniently converted to enamine using pyrrolidine and $TiCl_4$ to afford compound **1** in 98% yield. Compound **1** was unstable and used directly for the next step. Cyanoethylation of enamine **1** and consequent hydrolysis gave compound **2** in 80% yield (Cai et al., 1993; Kuhla et al., 1987). Previous work (Bolognesi et al., 2004) has reported that compound **2** was obtained by