RADIOSYNTHESIS AND CHIRAL SEPARATION OF C-11 LABELED BORONOPHENYLALANINE FOR BNCT STUDIES WITH PET

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The overall goal of this research is to combine two powerful methodologies, boron neutron capture therapy (BNCT) and positron emission tomography (PET), to advance the treatment of patients with malignant brain tumors. BNCT is a method to selectively deliver lethal alpha radiation to a tumor through the administration of a boron-10 containing drug, and irradiation of the tumor area with neutrons [1]. L-Boronophenylalanine (L-^{10}BPA) is a boron-10 containing amino acid currently used for BNCT [4]. In order to perform neutron dosimetry, it is essential to determine tumor boron-10 levels in the course of the therapy. PET has the ability to measure the concentration of drugs labeled with positron emitting isotopes in the human body [2]. 2-Fluoro-4-borono-phenylalanine ([^{18}F]FBPA) has been labeled as a surrogate marker for L-BPA for pharmacokinetic studies in brain tumor patients [3]. However, [^{18}F]FBPA is a different drug than L-BPA because it contains a fluorine atom. We report here the labeling of L-BPA with C-11, which has the advantage of being chemically identical to L-BPA. Carbon-11 is also well suited to repeated studies within the same PET scanning session.

Though the Bucherer-Strecker synthesis (Method A) is probably the most straightforward method to prepare C-11 labeled amino acids, it requires harsh reaction conditions [5, 6]. We therefore also investigated the use of the modified procedure reported by Iwata et al. [7] (Method B). This synthesis of [1-^{11}C]amino acids from [^{11}C]cyanide via [^{11}C]aminonitriles uses milder conditions as compared to Method A. [^{11}C]Hydrogen cyanide is produced in a fully automated system. The system is time-based controlled with radiation monitoring for fine-tuning the time-base controls of the software. We have also designed and built a special optical-pressure cell for carrying out the Bucherer-Strecker synthesis under high pressure and high temperature. Phenylacetaldehyde sodium bisulfite adduct (1) was prepared as the starting material and an intermediate, 2-amino-3-phenylpropanenitrile (unlabeled 3), was synthesized to examine each stage of the reaction. Comparative studies to synthesize [^{11}C]phenylalanine using both synthetic methods demonstrated that Method B is more efficient and more suitable for development of a radiosynthesis of [^{11}C]L-BPA. Recently, we applied Method B to synthesize [^{11}C]BPA via the bisulfite adduct of boronophenylacetaldehyde. Aminosulfite (2) was first prepared by a reaction of the bisulfite adduct of boronophenylacetaldehyde (1) with ammonium hydroxide. It was then converted to [^{11}C]aminonitrile (3) by reacting with [^{11}C]HCN. [^{11}C]BPA was obtained after acid hydrolysis of [^{11}C]aminonitrile (3). This one-pot, two-step radiosynthesis afforded [^{11}C]BPA after HPLC purification

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with high radiochemical yields (>50%, not optimized) and high specific activity (2-5 Ci/μmol). This novel approach demonstrated that the presence of the borono group not only survived the reaction conditions but also seemed to improve the yields. We also developed chiral HPLC systems to prepare enantiomerically pure [^{11}C]L-BPA using a similar strategy as we reported previously [8]; that is, to incorporate chiral HPLC separation directly into the radiosythesis of these enantiomerically pure C-11 labeled radiopharmaceuticals. Pharmacokinetic studies in baboon are underway. This new clinical tool, [^{11}C]L-BPA, will allow planning of BNCT in individual patients non-invasively based on direct knowledge of boron-10 concentration in tumors, as well as the investigation of strategies to improve L-BPA tumor uptake in patients, tumor imaging and monitoring tumors after therapy.

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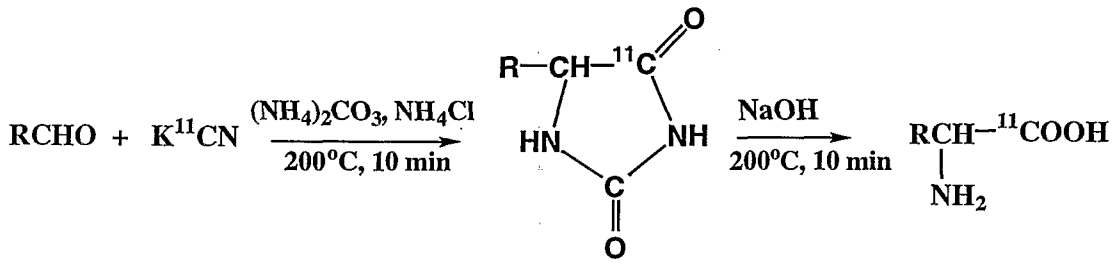
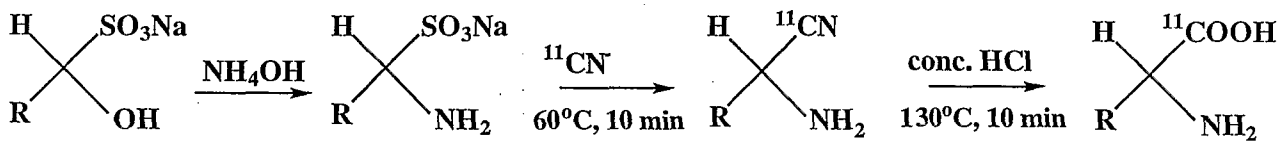
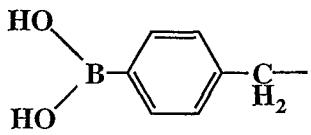
Method A: Bucherer-Strecker Synthesis



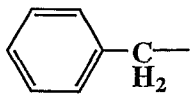
Method B: Modified Bucherer-Strecker Procedure in the Radiosynthesis of [^{11}C]Boronophenylalanine (or [^{11}C]Phenylalanine)



1 2 3

R = 

[^{11}C]BPA

R = 

[^{11}C]Phenylalanine