NOVEL SYNTHESIS OF [^{11}C]GVG (VIGABATRIN) FOR PHARMACOKINETIC STUDIES OF ADDICTION TREATMENT

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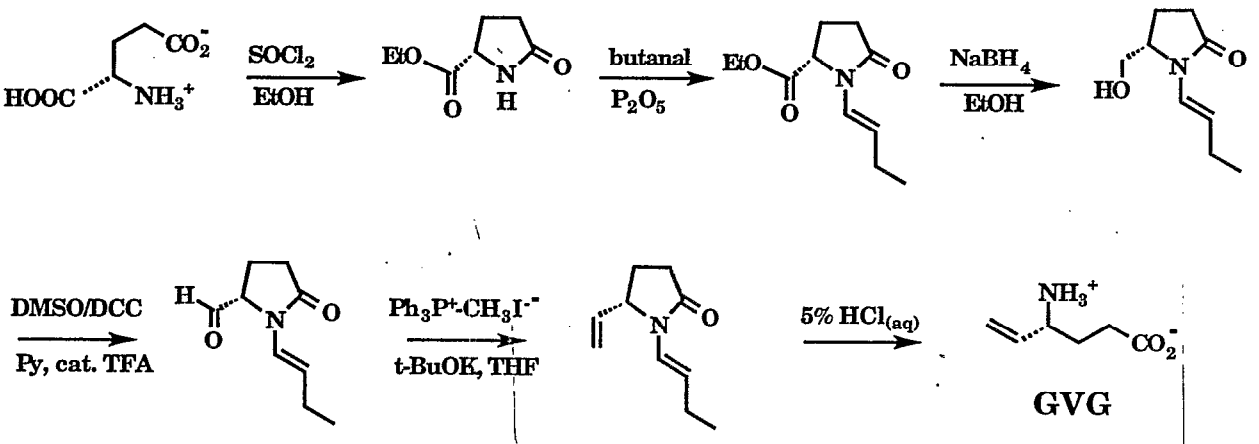
We have shown that gamma vinyl-GABA (GVG, Vigabatrin^{R}), a selective suicide inhibitor of GABA-transaminase (GABA-T), inhibits the effects of cocaine, nicotine, heroin, alcohol and methamphetamine both biochemically (dopamine) and behaviorally in rodents and primates. These data strongly suggest that the use of GVG may represent a new strategy for the treatment of substance abuse [1]. To better understand the mechanism associated with this inhibition and the pharmacokinetics, as well as the potential side effects of this drug, we carried out investigations on developing a radiosynthesis of [^{11}C]GVG for PET studies ($t_{1/2}$ for C-11 = 20 min). Several synthetic routes for the preparation of GVG including radiolabeling with long-lived ^{14}C ($t_{1/2}$ for C-14 = 5730 yr) have been published [2, 3]; however, they are not suitable for C-11 radiosynthesis. For example, a procedure to prepare the key 2-oxopyrrolidine-5-carboxaldehyde precursor that would in principle allow the incorporation of C-11 by employing Wittig condensation with [^{11}C]methyltriphenylphosphonium iodide was not straightforward (Scheme 1) [4, 5, Kihlberg, 1990 #6, 6]. We experienced this in our initial trials and other researchers made similar observations. Difficulties encountered during the isolation of the aldehyde precursor, its instability for storage, as well as the subsequent time-consuming Wittig reaction prompted us to pursue another synthetic pathway.

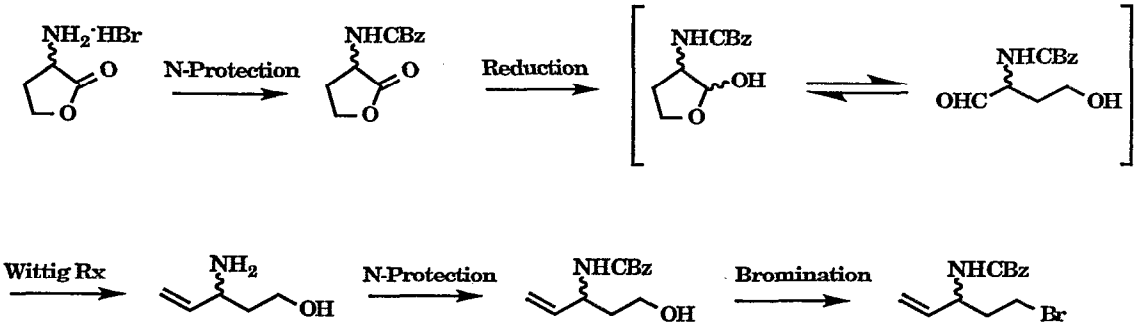
Scheme 1



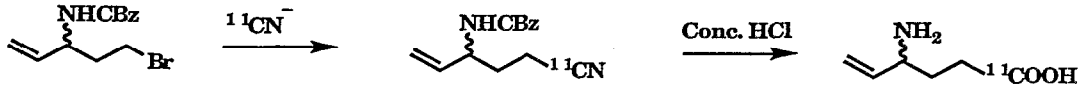
We report here a novel synthetic route to prepare the precursor and to efficiently label GVG with C-11. 5-Bromo-3-(carbobenzyloxy)amino-1-pentene was synthesized in five steps from homoserine lactone (Scheme 2). This was used in a two step radiosynthesis, displacement with [^{11}C]cyanide followed by acid hydrolysis to afford [^{11}C]GVG with high radiochemical yields (> 35%, not optimized) and high specific activity (2-5 Ci/μmol). The [^{11}C]cyanide trapping was achieved at -5^{O} C with a mixture of Kryptofix and K_2CO_3 without using conventional aqueous trapping procedure [7]. At this temperature, the excess NH_3 from the target that may interfere with the synthesis would not be trapped [8]. This procedure would be advantageous to any moisture sensitive radiosynthetic steps, as it was the case for our displacement reaction. When conventional aqueous trapping procedure was used, any trace amount of water left, even after prolonged heating, resulted in either no reaction or extremely low yields for the displacement reaction . The entire synthetic procedure should be extendable to the labeling of the pharmacologically active S- form of GVG when using S-homoserine lactone.

Scheme 2

Synthesis of Precursor:



Radisynthesis of [^{11}C]GVG:



[^{11}C]GVG

PET studies in baboon revealed low brain uptake of [^{11}C]GVG as expected (GABA is also known for its inability to efficiently cross the blood-brain barrier (BBB)), and the uptake was increased following pretreatment with mannitol to open the BBB (Fig. 1). The fact that the radioactivity distributed in a regionally specific manner (prefrontal cortex ≈ retina > occipital cortex > CSF) consistent with the known distribution of GABA-T and suggestive of the specific binding of [^{11}C]GVG in baboon brain [9]. Further investigations are underway.

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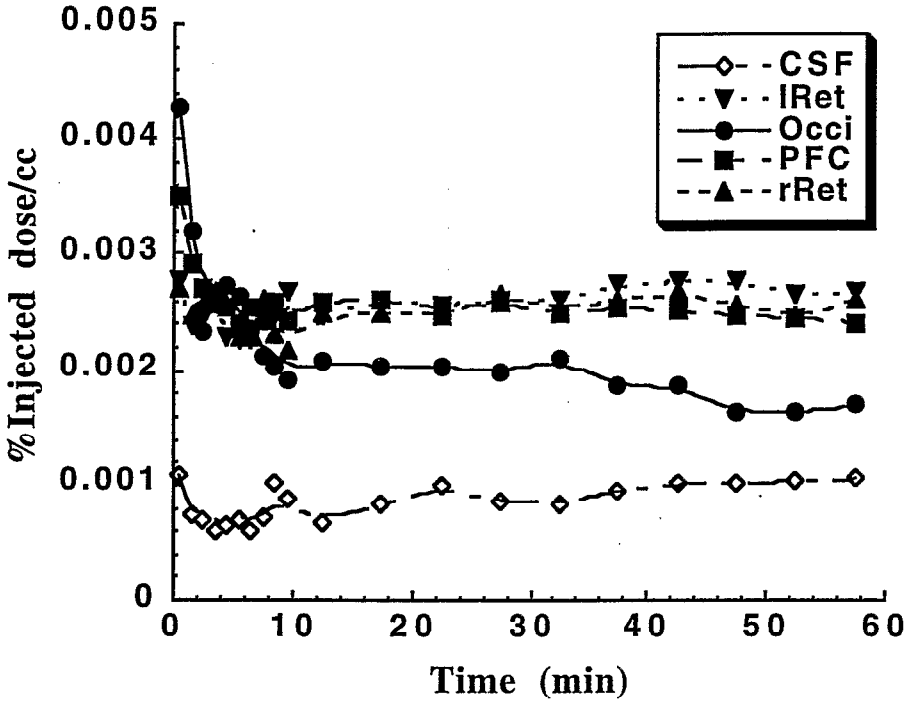

Fig. 1. Regional Activity of [^{11}C]GVG with Mannitol

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