SYNTHESIS OF [^{11}C]-S21007 A NOVEL 5HT$_3$ PARTIAL AGONIST AS A POTENTIAL TRACER FOR PET STUDIES.

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SUMMARY

A novel selective and partial agonist S21007 (IC_{50} =1nM), for 5HT$_3$ receptor studies in positron emission tomography, has been labelled with [^{11}C]benzyl iodide in 40-50% radiochemical yield and 200-700mCi/μmol in 60 min synthesis time.

Key Words : carbon-11, [^{11}C]benzyl iodide, 5HT$_3$ receptor, PET

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INTRODUCTION

5HT$_3$ receptors have been the focus of much research during the last decade. The presence of these receptors has been demonstrated in many neuronal tissues, both in the periphery and in the CNS. The identification of selective agonists and antagonists for this receptor subtype has allowed the discovery of several important new therapeutic applications as the inhibition of pain, migraine, cytotoxic and radiation-induced emesis and treatment of psychoses and anxiety. The first 5HT$_3$ antagonist labelled with a β+ emitter atom was [^{11}C]MDL72222. The PET studies which have been performed with it in the brain of baboon (distribution, kinetics and binding) have established that it was not a good radioligand to detect a specific binding, due to its high lipophilicity (1). Since, other radioligands have been developed, but their affinities for 5HT$_3$ receptors PET studies have not been demonstrated (2,3).Among a series of tricyclic piperazine derivatives synthetized, S21007 has been described as a novel selective and partial agonist which possesses a good affinity for 5HT$_3$ receptors (IC_{50} = 1nM) versus others 5HT subtypes studied where IC_{50} > 1μM (4). We report here the radiosynthesis of [^{11}C]S21007.

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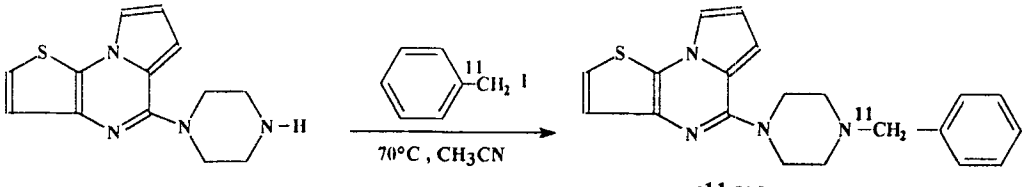
RESULTS AND DISCUSSION

The radiosynthesis of [^{11}C]S21007 has been performed by N-alkylation of **2** with [^{11}C]benzyl iodide in CH_3CN at 70°C for 5min (scheme1). For routine purposes, large amounts of initial radioactivity are required and to avoid excessive cumulative radiation doses, a robotic system has been developped to label S21007. The radiosynthesis by this apparatus was problematic. The production system consists of three units (Fig.1) and the key step was the purification and isolation of [^{11}C]benzyl iodide by a Sep-pak C18 followed by a pass through an anhydrous column to dry and obtain it with a pH range between 6-8. It has occured to us that a pH inferior to 6 inhibit the alkylation reaction and a pH superior to 8 ,with added base (KOH) in the reactor vessel, disturb the phase normal HPLC purification.In fact, when we control before HPLC and by radioTLC the percent of alkylation (50-60%), in the presence of added base, this last fails to 20-40% after HPLC and we obtain a no identified by-product which results on a decomposition of [^{11}C]S21007 onto the column. In the absence of base, the alkylation reaction is less efficient but [^{11}C]S21007 was isolated by HPLC with a radiochemical yield of 40-50%, without decomposition. To avoid this problem, we have tested a reverse phase HPLC (HAMILTON PRP1 eluent : CH_3CN/Phosphate buffer KH_2PO_4) and the alkylation has been performed with KOH, but if we take in consideration the rapid decay of ^{11}C ($t_{1/2}$=20.4min), the time to remove the solvents before formulation is too long by this purification system and [^{11}C]S21007 was isolated in 30-40% based on [^{11}C]benzyl iodide.In conclusion, it is preferable to use a phase normal HPLC and although the alkylation reaction occurs more slowly in the absence of base the average isolated radiochemical yield of [^{11}C]S21007 was 40-50% (uncorrected decay) based on [^{11}C]benzyl iodide,with a good correlation between radioTLC control and HPLC purification. The total synthesis time was 60min and the average specific activity was 200-700mCi/μmole at the end of the synthesis. Radiochemical purities were greater than 98%.



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SCHEME 1: Synthesis of [^{11}C]S21007

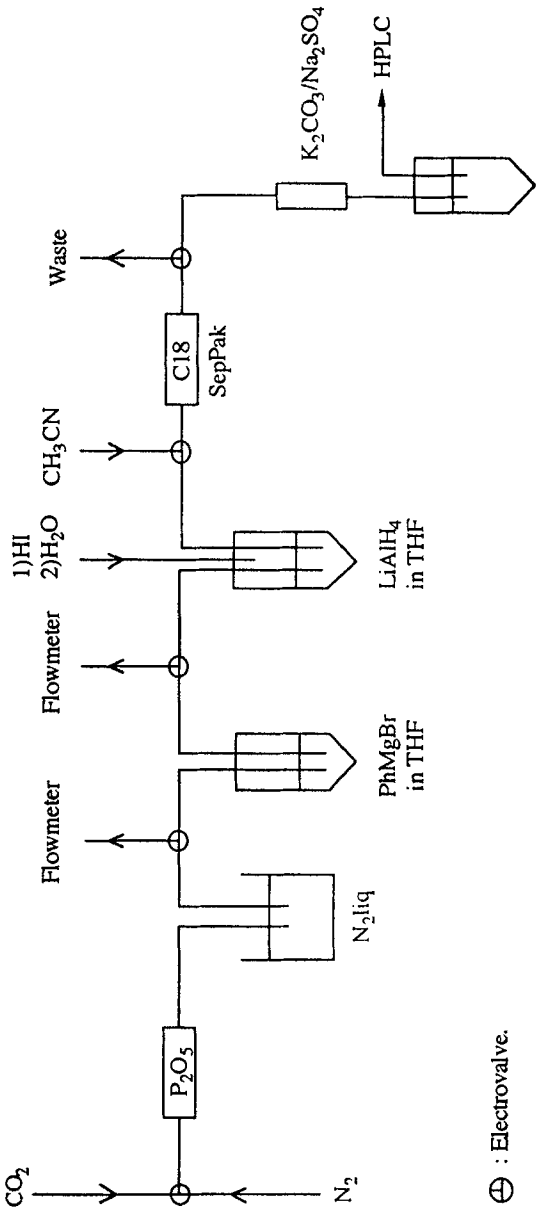

Fig.1 : Set up of the [11C] S21007 production.

EXPERIMENTAL

Preparation of phenylmagnesium bromide solution

Phenylmagnesium bromide (1M) was freshly prepared in a reaction vessel containing magnesium turnings (125mg) and bromobenzene (625μL) in THF ($5cm^3$). The mixture is gently stirred under nitrogen during one hour.

Preparation of [^{11}C]benzyl iodide

[^{11}C]benzyl iodide was prepared with some modifications of a described method (5). [^{11}C] carbon dioxide was produced by 16MeV proton bombardment of a nitrogen gas target using a 325CGR-MeV biomedical cyclotron. After the bombardment, [^{11}C]CO_2 was trapped in a stainless steel coil cooled in liquid nitrogen. After removing of the cooling bath, [^{11}C]CO_2 was carried by a stream of nitrogen in a 1M solution of phenylmagnesium bromide in THF (0.5mL) and the reaction vessel was kept at room temperature for 1 min. This mixture transferred to the second reactor was reduced with $LiAlH_4$ (1M) solution in THF (300μL) then evaporated to dryness at 140°C. After cooling of the reactor, hydriodic acid (0.6mL, 57% in water) was slowly added and the solution was heated at 140°C for 5 min. The acid solution was loaded onto an activated Sep Pak C_{18} cartridge via a nitrogen gas stream. The Sep Pak was washed with 20mL of water and dryied. [^{11}C]benzyl iodide was eluted off the cartridge with 3mL CH_3CN, then passed through an anhydrous column of Na_2SO_4 / K_2CO_3 (1.8g, 60/40, w/w) and collected in a 10mL vial containing the N-nor S21007 precursor.

Synthesis of [^{11}C]S21007

The above solution containing [^{11}C]benzyl iodide was evaporated to a residual volume (1.5mL) and mixed with N-nor S21007 (4mg) previously dissolved in 0.5mL CH_3CN. The solution was heated at 70°C for 5min. The reaction mixture was injected onto the HPLC column (Waters μ porasil ; 7.8 mm x 30 cm), eluted with a mobile phase of CH_2Cl_2 / solB (solB : EtOH/H_2O/$EtNH_2$ 96/2/2, v/v/v) (99/1, v/v) at 4mL/min. The effluent from the column was monitored both with an UV detector (λ:265nm) associated to an on-line radioactivity detector. The radioactive peak corresponding to [^{11}C]S21007 (t_R = 8min) was collected and the solvent evaporated to dryness under a nitogen gas stream. The residue was dissolved in a mixture of physiological saline solution/ethanol (80/20 ; v/v) and filtered through a sterile 0.22μm Waters Millipore filter.

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