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Fully automated synthesis of the M_1 receptor agonist [^{11}C]GSK1034702 for clinical use on an Eckert & Ziegler Modular Lab system

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ABSTRACT

A fully automated and GMP compatible synthesis has been developed to reliably label the M_1 receptor agonist GSK1034702 with carbon-11. Stille reaction of the trimethylstannyl precursor with [^{11}C]methyl iodide afforded [^{11}C]GSK1034702 in an estimated $10 \pm 3\%$ decay corrected yield. This method utilises the commercially available modular laboratory equipment and provides high purity [^{11}C]GSK1034702 in a formulation suitable for human use.

1. Introduction

M_1 muscarinic acetylcholine receptors (mAChRs) have been suggested to play a role in cognition and therefore represent an attractive drug target for the treatment of cognitive deficits associated with diseases such as Alzheimer's disease and schizophrenia (Caccamo et al., 2009; McArthur et al., 2010). However, the discovery of subtype selective mAChR agonists has been hampered by the high degree of conservation of the orthosteric ACh-binding site among mAChR subtypes (Heinrich et al., 2009). Recently, GSK1034702 was identified as a selective agonist for M_1 mAChRs (Budzik et al., 2007). Knowledge about its *in vivo* distribution in CNS in man at an early stage in the development process has the potential to greatly facilitate the decision as to whether or not to progress the compound into phase 2 A/B studies. Positron emission tomography (PET) can provide a quantitative measure of tissue distribution of a suitably radiolabelled compound. An appropriate chemistry route was identified to radiolabel GSK1034702 with carbon-11 (see Fig. 1). The use of [^{11}C]GSK1034702 in clinical trials depends on the safe and reliable methods for its production. Here we report methods developed for the production and quality control of [^{11}C]GSK1034702.

2. Results and discussion

[^{11}C]GSK1034702 was prepared through a palladium catalysed cross-coupling reaction between GSK1804165A and [^{11}C]CH_3I (Fig. 1) using a modified procedure developed by Björkman et al. (2000). Reacting GSK1804165A with [^{11}C]CH_3I at 130 °C using palladium complex generated in situ from $Pd_2(dba)_3$ and $(o\text{-tolyl})_3P$ (1:4), together with CuCl and K_2CO_3 as co-catalysts, gave the best coupling yield. After reaction, the crude mixture was filtered through an Oasis® cartridge to remove insoluble catalyst particulates. [^{11}C]GSK1034702 was eluted with methanol, diluted with buffer and loaded onto a semi-preparative high performance liquid chromatograph (HPLC) for purification. The collected fraction from HPLC was reformulated through solid phase extraction (SPE) in a 10% ethanol saline solution and passed through a sterile 0.22 μm filter into a sterile, pyrogen free vial. This manufacturing process was fully automated on modular lab equipment from Eckert & Ziegler. The schematic diagram of the setup is depicted in Fig. 2. Typical synthesis provided 1 to 2 GBq (uncorrected) of [^{11}C]GSK1034702 in a total synthesis time of 45 min. This corresponds to a radiochemical yield of $10 \pm 3\%$ ($n=10$), corrected for decay, based on production of 70 GBq of [^{11}C]CO_2.

Specific activities in the range of 4–7 GBq/μmol were obtained at the end of synthesis. Similarly low values were previously reported for this type of chemistry and attributed to side reactions with the methyl groups from the tin derivative precursor (Madsen et al., 2003; Samuelsson and Långström, 2003). It may be possible to increase specific activity of the final product by utilising an alternative tin derivative (e.g. tributyl tin) but the

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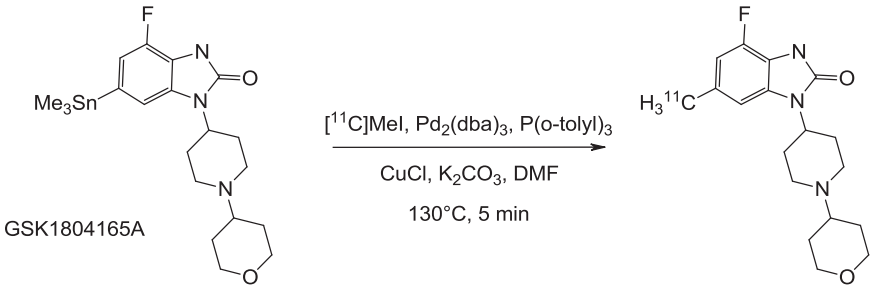

Fig. 1. Synthesis of [^{11}C]GSK1034702.

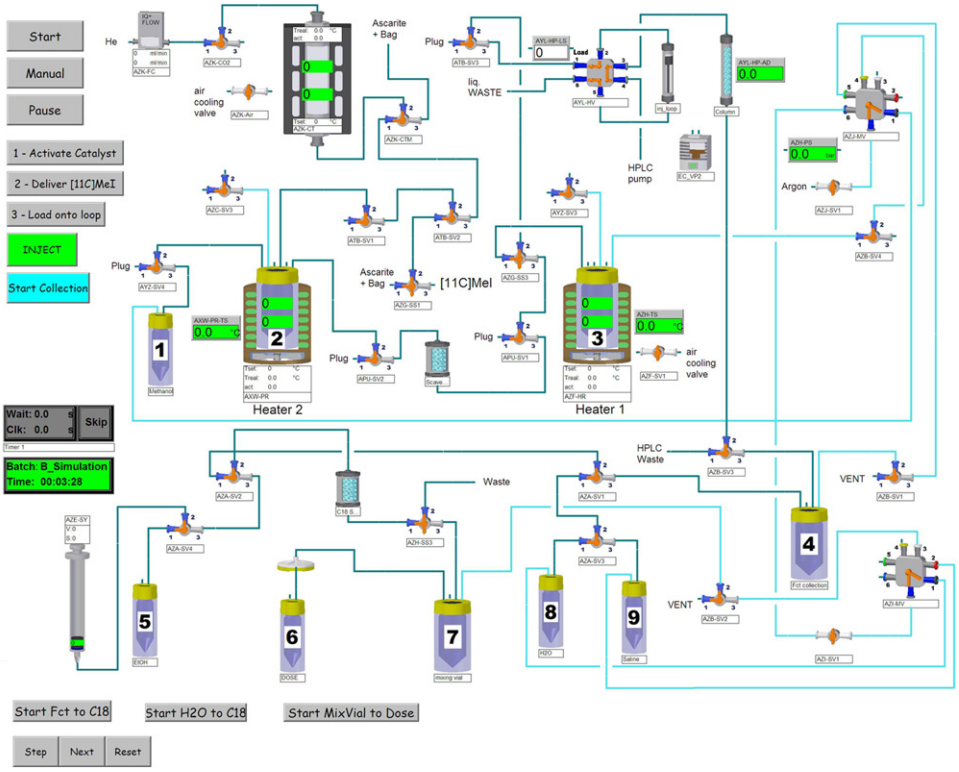

Fig. 2. Diagram of the Eckert & Ziegler setup for the production of [^{11}C]GSK1034702. Vial 1: methanol, vial 2: reaction vessel, vial 3: HPLC buffer (for dilution of crude mixture), vial 4: collected fraction from HPLC, vial 5: ethanol, vial 6: dose, vial 7: mixing vial, vial 8: H_2O, vial 9: saline.

respective tributylstannyl precursor was not available to us for this study.

Quality control showed that manufactured doses were suitable for injection. Set specifications and results from the three validation batches are presented in Table 1. During validation of the manufacturing process of [^{11}C]GSK1034702, potential contamination of manufactured doses with toxic heavy metals like tin (Saxena, 1987; Nicklin and Robson, 1988; Boyer, 1989; Tsangaris and Williams, 1992; Rüdel, 2003) and palladium (Liu et al., 1979; Kielhorn et al., 2002) was of particular interest. Specification for palladium content was derived from the European Medicines Agency (EMEA, 2008) guidance on residues of metal catalysts in medicinal products (2008). The guidance sets the limit to 1 ppm through chronic parenteral exposure (and guideline suggests to use limits from parenteral exposure for any other route than oral administration), but higher concentrations are allowed in case of acute exposure, for example with use of "*contrasting agents, antidotes, or products for diagnostic use*". Unfortunately, the EMEA does not provide data for tin, and in absence of regulatory guidance, specification was derived from the monograph of [^{18}F]FluoroDOPA Injection (British Pharmacopoeia, 2011) whose manufacture also involves the use of a tin derivative PET precursor. In the monograph, specification on the content of tin is set through the content limit of one of the impurities (Impurity A—trimethyl tin chloride). The monograph indicates a "*limit of 0.5 mg/Volume of impurity A*", volume being "*the maximum recommended dose in millilitres*". As various tin-containing impurities may be found in [^{11}C]GSK1034702 batches, this limit was applied to total elemental tin in solution. With a [^{11}C]GSK1034702 maximum volume of 11 mL in this study, the corresponding concentration limit of tin was then set to 27 ppm (Fig. 3). Analysis by inductively coupled plasma optical emission spectrometry (ICP-OES; Abernethy et al., 2010; Raghuram et al., 2010) revealed manufactured doses were containing less than 1 ppm (limit of quantification) of these metals ($n=10$). Very little data are available from literature, but these results proved to be consistent with other manufacturing processes where very low concentrations were reported (<40 ppb as measured by inductively coupled plasma time-of-flight mass spectrometry (Björkman et al., 2000) or atomic absorption spectroscopy (Prabhakaran et al., 2005)).