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P-015 Preparation of the C-11 labelled SERT tracers NS9531, NS9762 and NS6417 on a GE FX-C Pro module using C-11 methyl triflate.

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Objectives: NS9531, NS9762 and NS6417 are highly selective, low nanomolar affinity SERT inhibitors. They have previously been labelled with C-11 using C-11 methyl iodide and used in a pre-clinical evaluation [1]. Precursor tailing into product fraction on preparative HPLC led to substantial amounts of precursors in the final products (up to 10 μg injected mass). The objectives of this study were to: evaluate if reduced precursor amounts could be used when labelling with C-11 methyl triflate, to evaluate alternative preparative HPLC methods, and to evaluate SPE procedures to replace evaporation of HPLC solvent in the final formulation of the products.
Methods: C-11 methyl triflate (MT) was reacted with 0.2 mg of des-methyl-precursors in 0.2 mL of acetone for 1 min. at 60 °C. For the NS6417 fumarate precursor, 0.5 μL of pentamethylpiperidine in 50 μL of MeOH was added before reaction with MT. C-11 labelled NS9531 and NS9762 were purified by HPLC on a Gemini C18 column using mixtures of CH_3CN in 50 mM H_3PO_4. C-11 labelled NS6417 was purified by HPLC on a Luna-C18 column using a mixture of CH_3CN in 70 mM NaH_2PO_4, pH 2.5. The purified products were after dilution with water formulated into ethanol / buffer solutions using Strata-X, Strata C18-E or Sep-Pak C-18 light columns.

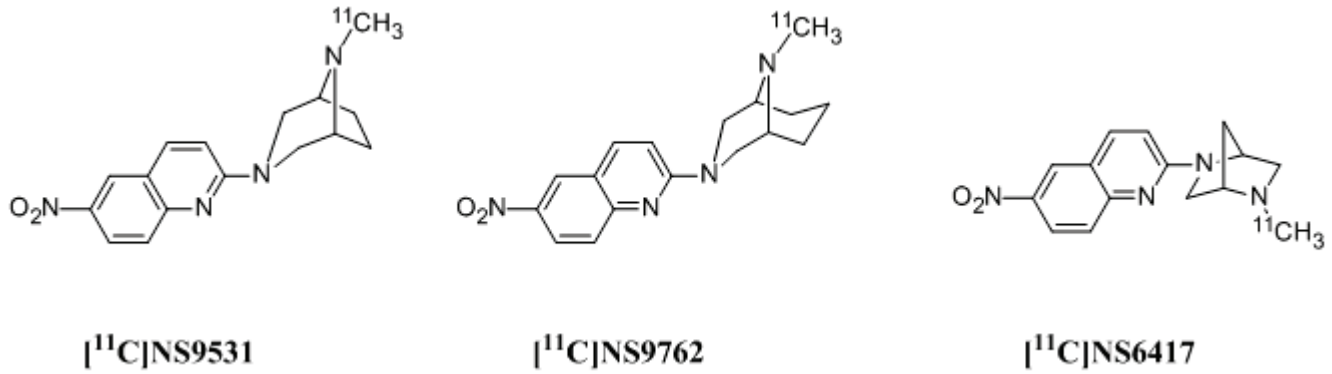

Figure 1. Structure of the three C-11 labelled SERT inhibitors.

Results: The use of MT gave a high radiochemical yield, more than 80%, in the methylation of NS9531 and NS9762 precursors. For the NS6417 precursor, a radiochemical yield of 65% was obtained. A good separation of des-methyl precursors and C-11 labelled products were obtained on HPLC. The reduced amount of precursor, 0.2 mg versus the previously reported 1.0 mg [1], resulted in less than 0.5 μg of precursor in the final product solutions, calculated for a 300 MBq injection at 20 min EOS. Formulations on Strata columns were fast (4-5 min.) and the total time for preparation of C-11 labelled products from EOB was 30 to 35 min. Total yield was 1.5-3 GBq, with a specific radioactivity of 20-60 GBq/ mol.
Conclusions: The use of C-11 methyl triflate enables preparation of C-11 labelled NS9531, NS9762 and NS6417 in high yields and with low amounts of residual precursor after HPLC purification. The proposed SPE formulations are fast and easy to automate on the GE FX-C Pro system.
References: [1] Bender D, et al. (2008) NeuroImage, 41 (Suppl. 2), T88.