Synthesis of F-18 Labeled Tolbutamide as Beta-Cells Imaging Agent

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Diabetes mellitus is a major public health problem, affecting ~5% of the population. A reliable method to monitor the progressive loss of beta-cells mass during the silent phase of pre-diabetes will have great impact on the treatment of diabetes mellitus. Tolbutamide is a sulfonylurea agent used to stimulate insulin secretion in type 2 diabetic patients. It binds to a class of molecules known as the ATP-sensitive potassium channels, located at the insulin producing beta-cells of the islets of Langerhans. Therefore, if tolbutamide or its analogues were labeled with a positron emitter, it may serve as a beta-cells imaging agent 1-[(p-Fluorobenzenesulfonyl)]-3-butyl-urea. (p-Fluorotolbutamide) has a similar hypoglycemic potential as tolbutamide. Therefore p-[^{18}F]fluorotolbutamide (1) can be a possible beta-cells imaging agent.

p-[^{18}F]fluorotolbutamide was synthesized via two approaches. Nucleophilic substitution of p-nitrotolbutamide with K[^{18}F]/K2.2.2 in either CH_3CN or DMSO gave a complicated mixture. Compound 1, however, can be prepared by a two-step synthesis. Nucleophilic substitution of p-nitrobenzene-sulfonamide with K[^{18}F]/-K2.2.2 in DMSO at 155°C for 30 minutes gave p-[^{18}F]fluorobenzenesulfonamide in 3.5-7.5% yield. (Fig. 2) Reaction of p-[^{18}F]fluoro benzenesulfonamide with butylisocyanate in the presence of either copper chloride or borontrifluoride etherate complex in CH_3CN (Fig. 3) or DMSO at 80°C for 20 min followed by purification with HPLC (Spherisorb C18, 10x250 mm, CH_3CN/0.1 M NH_4HCO_2, 25/75 with 0.3% CH_3CO_2H, 5 ml/min) gave p-[^{18}F]fluorotolbut-amide in 1-2% yield, in a synthesis time of 100 min from EOB (Fig. 1). In vitro and in vivo evaluation of compound 1 as beta-cells imaging agent and the synthesis of other sulfonylurea receptor ligands with high affinity are under investigation.

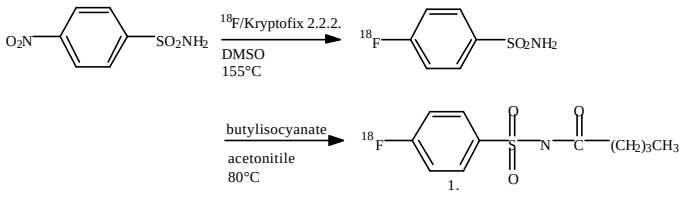

Fig.1: Labeling of p-[^{18}F]fluoro-tolbutamide

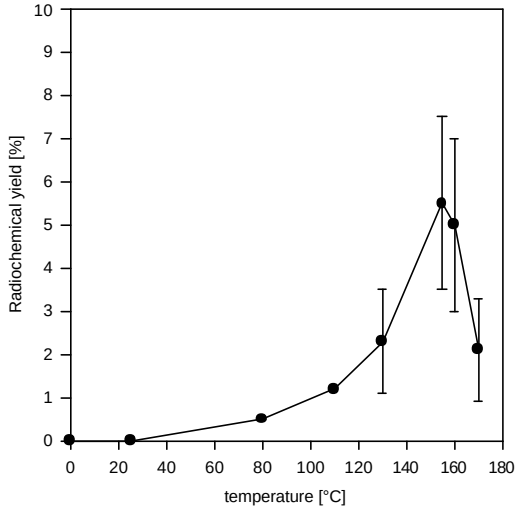

Fig. 2: Temperature dependency of the RCY of 4-[^{18}F]fluorobenzenesulfonamide (*0.5 ml acetonitrile, 4 mg 4-nitrobenzenesulfonamide)*

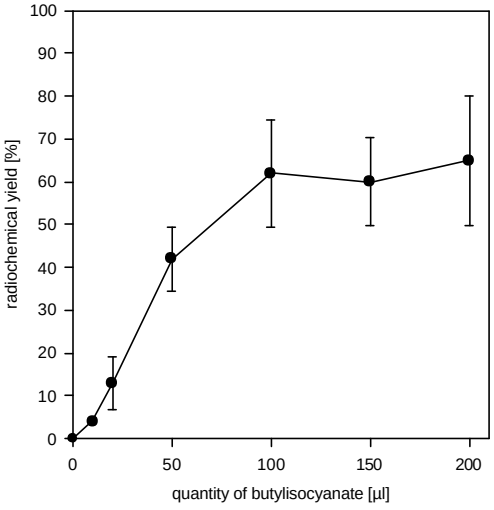

Fig.3: Dependency of the RCY of 4-[^{18}F]fluoro-tolbutamide on the butylisocyanate quantity *(80°C, 20 min)*