Synthesis of new ^{18}F-labelled sulfonylurea derivatives for the determination of the beta-cell status in vivo

R. Schirrmacher[1], P. Feilen[3], G. Shiue[2], S. J. Shiue[2], A. Alavi[2], J. Beyer[3], F. Rösch[1]
[1]Institut für Kernchemie, Universität Mainz, D-55128 Mainz; [2]Department of Radiologie, University of Pennsylvania, Philadelphia, PA 19104; [3]Department of Endocrinology and Metabolic Disease, Universität Mainz, D-55131 Mainz

Diabetes mellitus comprises a heterogeneous group of disorders characterized by high blood glucose levels. Two major types of diabetes mellitus have been defined: type 1 (insulin-dependent diabetes mellitus, IDDM), and type 2 (non-insulin-dependent diabetes mellitus, NIDDM). Although hyperglycemia is the common denominator of both IDDM and NIDDM, the etiology and pathophysiology of these syndromes are distinct. IDDM is a chronic autoimmune disease characterized by the selective destruction of insulin-producing β-cells of the islets of Langerhans. When autoimmune destruction affects more than 90% of the β-cell mass, the resulting insulin deficiency culminates into development of overt hyperglycemia. In NIDDM, on the other hand, the pancreatic β-cells are initially intact, and the disease is associated with insulin resistance and loss of β-cell function, and eventual insulin-dependency [1].

The aim of this study was to synthesize β-cell-specific positron emitting radiolabeled sulfonylurea derivatives such as 2-[^{18}F]fluoroethyl-tolbutamide and 2-[^{18}F]fluoroethyl-glibenclamide to image the β-cell mass *in vivo* via positron emission tomography (PET).

Tolbutamide with a K_i of 25-55 µM and glibenclamide with a K_i of 0.7-7 nM are sulfonurea agents used to stimulate insulin secretion in type 2 diabetic patients [2]. We intend to determine the efficacy of these radiolabeled agents in visualizing and quantifying β-cell concentrations in the pancreas of normal non-human primates by PET.

First of all, the ^{19}F-compounds of the described sulfonylurea derivatives were synthesized for testing their ability to stimulate insulin secretion from pig beta-cells. In the case of the tolbutamide derivative the synthesis started from 4-amino-benzensulfonamide, which was converted via diazotation and hydrolysis into 4-hydroxy-benzenesulfonamid. The hydroxy group was then alkylated with 2-fluoro-1-bromoethane under basic conditions and the remaining sulfonamide moiety was coupled with butylisocyanate to yield the desired 2-[^{19}F]fluoroethyl-tolbutamide (fig. 1).

The glibenclamide derivative was obtained by a multistep synthetic route shown in figure 2. Starting from the di-sodium salt of 5-chloro-salicylic acid, 2-fluoro-1-bromoethan was added to yield the fluoroalkylated salicylic acid fluoroethylester which was then cleaved with 2 N NaOH solution to yield the fluoroalkylated salicylic acid derivative. The carboxyl group of this compound was activated via a mixed anhydride for further nucleophilic displacement with 4-(2-aminoethyl) benzenesulfonamide. The resulting compound was reacted with cyclohexylisocyanate and Cu(I) catalysis to give the desired glibenclamide derivative 2-[^{18}F]fluoroethyl-glibenclamide.

The respective labeling precursors for the radiolabeling of the tolbutamide and the glibenclamide were synthesized in a similar manner as shown in figure 2. All compounds were verified with common analytical methods such as ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR, mass spectroscopy and elemental analysis.

Radioactive labeling could easily be achieved by HO-^{18}F-fluoroalkylation of the labeling precursors with 2-[^{18}F]fluoroethyltosylate in DMSO at 80°C in radiochemical yields ranging from 80-90% (fig. 2).

[1] Ronner P et al. Diabetes, 42: 1760-72 (1993)
[2] Gribble F.M. et al. Diabetes , 47: 1412-8 (1998)

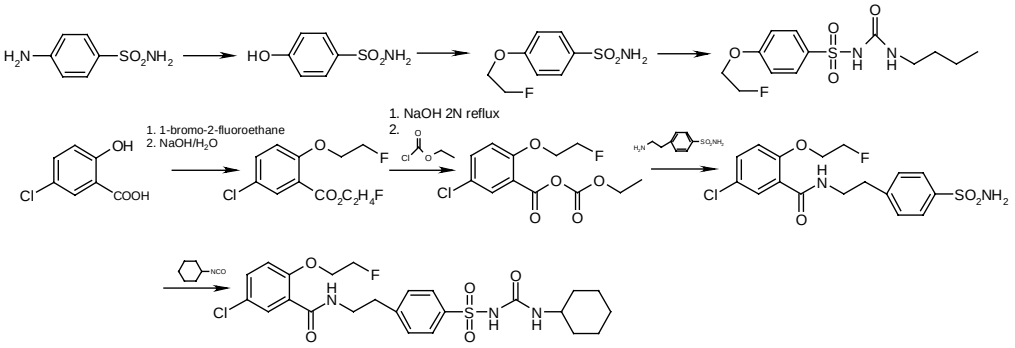

fig. 1: Synthesis of non radioactive standard compounds for *in vitro* testing of insulin inducing effects

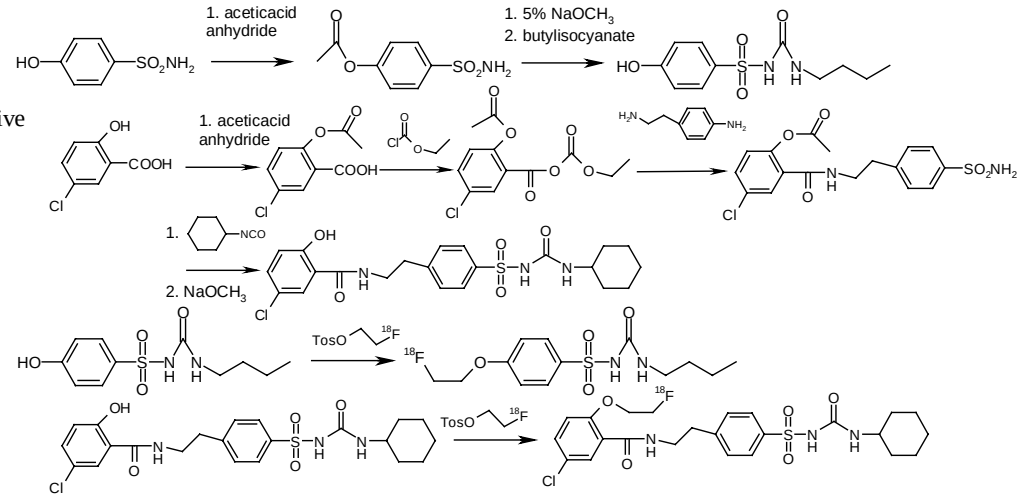

fig. 2: Syntheses of the labeling precursors and their radioactive labeling