# Synthesis of (S)-2-(2-[$^{19}$F]fluoroethoxy)-4-([3-methyl-1-(2-piperidin-1-yl-phenyl)-butyl-carbamoyl]-methyl)-benzoic acid ([$^{19}$F]repaglinide) and its analoguous labeling precursor

B. Wängler[1], S. Schneider[2], O. Thews[3], E. Schirrmacher[1], S. Comagic[1], P. Feilen[2], C. Schwanstecher[4], M. Schwanstecher[4], C.-Y. Shiue[5], A. Alavi[5], S. Höhnemann[1], M. Piel[1], F. Rösch[1] and R. Schirrmacher[1]
[1]Institute of Nuclear Chemistry, Johannes Gutenberg-University of Mainz, Fritz Strassmann-Weg 2, D-55128 Mainz, Germany, [2]1. Med. Clinic, Division of Endocrinology and Metabolic Disease, Johannes Gutenberg-University of Mainz, D-55131, Germany, [3]Institute of Physiology and Pathophysiology, Johannes Gutenberg-University Mainz, Germany [4]Institute of Pharmacology and Toxicology, University of Braunschweig, Braunschweig, Germany, [5]Department of Radiology, University of Pennsylvania, Philadelphia, PA 19104, USA

**Introduction:** 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- and type 2 diabetes. Although hyperglycemia is the common denominator of both, type 1- and type 2 diabetes, the etiology and pathophysiology of these syndromes are distinct. Type 1 diabetes 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 the development of overt hyperglycemia. In type 2 diabetes, 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. SURs represent the target for hypoglycemic sulfonylureas, a group of well known antidiabetic agents which have been in clinical use for years, as well as for repaglinide, a novel fast acting prandial glucose regulator with a short plasma half-life (< 1 h). Repaglinide is the first member of the carbamoylmethylbenzoic acid chemical family to be used in a clinical setting, being a new chemical class of insulin secretagogues with an insulin release profile which is very different to sulfonylureas like Glyburide. If biological activity is retained, a $^{18}$F-labeled repaglinide derivative with high specific activity might become a valuable tool for the visualization and quantification of human pancreatic β-cell mass *in vivo*.

**Aim:** The aim was to synthesize $^{19}$F-labeled non-sulfonylurea hypoglycemic agent (S)-2-(2-[$^{19}$F]fluoro-ethoxy)-4-((3-methyl-1-(2-piperidin-1-yl-phenyl)-butyl-carbamoyl)-methyl)-benzoic acid ([$^{19}$F]repaglinide), a derivative of the sulfonylurea-receptor (SUR) ligand repaglinide, as a standard compound for the eventual non-invasive investigation of the sulfonylurea 1 receptor status of pancreatic beta-cells by positron emission tomography (PET) in the context of type 1 and type 2 diabetes with its $^{18}$F-labeled analogue.

**Chemistry:** The syntheses of the $^{19}$F-standard compound **9** for evaluating the biological activity and the labeling precursor **8** for the labeling reaction with 2-[$^{18}$F]fluoroethyltosylate started from 2-hydroxy-4-methyl benzoic acid **1**. The synthetic strategy of Grell et al. for the syntheses of repaglinide and related hypoglycemic benzoic acid derivatives was applied in a modified form (Fig. 1) [1]. Esterfication with methanol and sulfuric acid yielded the corresponding methyl ester **2**. After side chain bromination of **2** with NBS and azo-bis-isobutyronitril (AIBN) as a radical starter, the bromo compound **3** was reacted with NaCN in water using N-benzyltributyl ammonium chloride as a phase catalyst to yield **4**. Hydrolysis of the nitrile moiety was conducted by continuous introduction of gaseous HCl into a methanolic solution. The bis-methyl ester **5** was obtained in high yields and could be selectively cleaved with 2.1 equiv. NaOH to obtain the mono-ester 4-carboxymethyl-2-hydroxy benzoic acid 6. The mono-ester **6** was coupled with (S)-3-methyl-1-[2-(1-piperidinyl)phenyl)-butylamine **7** applying DCC as a coupling agent leading to the final labeling precursor (S)-2-hydroxy-4-((3-methyl-1-(2-piperidin-1-yl-phenyl)-butylcarbamoyl)-methyl) benzoic acid **8**. The following reaction with 1-bromo-2-fluoroethane in acetone led to the methylester protected non-radioactive standard compound **9**.

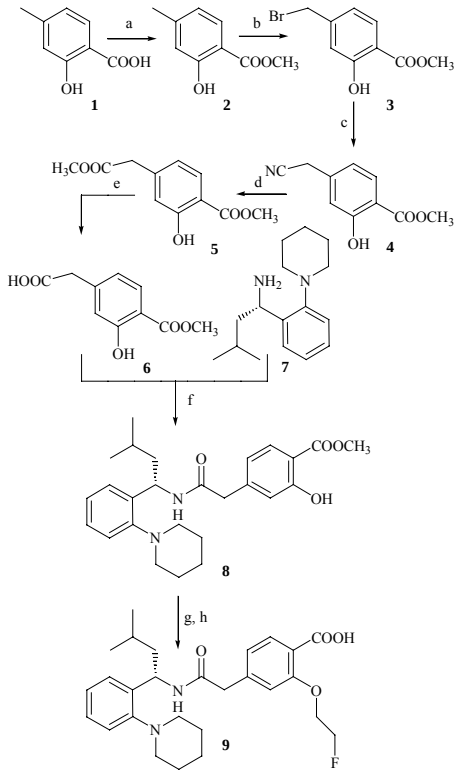


Fig 1: Syntheses of the labeling precursor and the [$^{19}$F]repaglinide standard compound **9** for *in vitro* evaluation. (a) $CH_3OH/H_2SO_4$; (b) NBS/AIBN/$CCl_4$; (c) NaCN/N-benzyltributyl $N^+Cl^-/H_2O$; (d) $HCl/CH_3OH$; (e) NaOH/MeOH; (f) DCC/toluene; (g) 1-bromo-2-fluoroethane/aceton; (h) $NaOH/CH_3OH$

**References:**

[1] Grell W, Hurnaus R, Griss G, Sauter R, Rupprecht E, Mark M, Luger P, Nar H, Wittneben H, Müllert P. Repaglinide and Related Hypoglycemic Benzoic Acid Derivatives. J. Med. Chem. 1998:41:5219-5246.