Radiosynthesis of (S)-2-(2-[^{18}F]fluoroethoxy)-4-([3-methyl-1-(2-piperidin-1-yl-phenyl)-butyl-carbamoyl]-methyl)-benzoic acid ([^{18}F]repaglinide)

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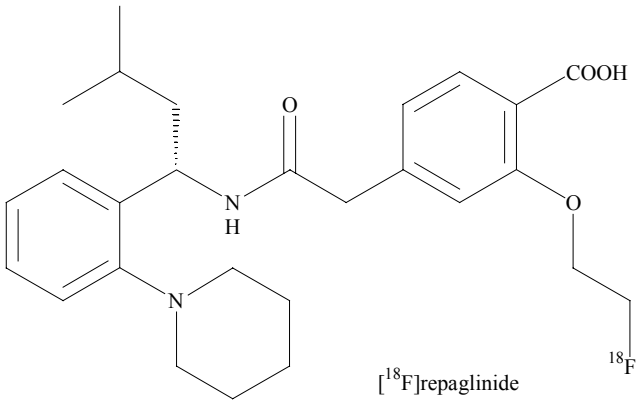
Introduction: Diabetes mellitus comprises a heterogeneous group of disorders characterized by high blood glucose levels. Two major types of diabetes mellitus have been defined: type 1- and type 2 diabetes. Repaglinide is the first member of the carbamoylmethylbenzoic acid chemical family to be used in 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*.



[^{18}F]repaglinide

Aim: The aim was to synthesize the ^{18}F-labeled non-sulfonylurea hypoglycemic agent (S)-2-(2-[^{18}F]fluoro-ethoxy)-4-((3-methyl-1-(2-piperidin-1-yl-phenyl)-butyl-carbamoyl)-methyl)-benzoic acid ([^{18}F]repaglinide), a derivative of the sulfonylurea-receptor (SUR) ligand repaglinide, for the 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.

Radiochemistry: No-carrier-added (NCA) aqueous [^{18}F]fluoride (18000 MBq) prepared by the ^{18}O(p,n)^{18}F nuclear reaction on an enriched water (95 %) target was added to a solution of 1 N K2CO3 (15 µl) and Kryptofix 2.2.2. (10-15 mg) in CH3CN (800 µL). The water was removed by coevaporation to dryness with CH3CN (2 x 1 mL) using a stream of nitrogen at 80°C.

To the dried Kryptofix 2.2.2./[^{18}F]fluoride complex (17000 MBq) in acetonitrile (1 mL) ethylenglycol-1,2-ditosylate (8-10 mg, 20-25 µmol) was added and heated under stirring in a sealed vial for 3 min. Purification of the crude product was accomplished using HPLC (acetonitrile/water, 50:50, flow rate: 5 mL/min rt: 8 min). After diluting the HPLC fraction containing the 2-[^{18}F]fluoroethyltosylate with water (20 mL), the product was loaded on a C18-SepPac cartridge (Waters), dried with nitrogen gas and eluted with tempered (25-30°C) diethyl ether (2 mL) to yield the desired product 2-[^{18}F]fluoroethyltosylate with an activity of 8000 MBq. After evaporation of the diethyl ether in a stream of nitrogen, the 2-[^{18}F]fluoroethyltosylate was taken up in DMSO (150-200 µL).

(S)-2-(2-[^{18}F]Fluoroethoxy)-4-([3-methyl-1-(2-piperidin-1-yl-phenyl)-butylcarbamoyl]-methyl)-benzoic acid

To the precursor (3 mg, 6.8 µmol) dissolved in DMSO (250 µL) 1 N NaOH solution was added (6.8 µL, 6.8 µmol) and the mixture was heated at 150°C for 2 min. A solution of 2-[^{18}F]fluoroethyltosylate (8000 MBq) in DMSO (150–200 µL) was added and stirred in a sealed reaction vessel at 150°C for 10 min. The product was purified with HPLC (acetonitrile/0.1 M acetic acid/sodium acetate buffer (pH = 6) (8/2) (v/v), flow rate 4 mL/min, tr = 10.2 min). After diluting the HPLC fraction containing the product with water (20 mL), it was loaded on a C18-SepPac cartridge (Waters), dried with nitrogen and eluted with methanol (1.5 mL) to yield (S)-2-(2-[^{18}F]fluoroethoxy)-4-([3-methyl-1-(2-piperidin-1-yl-phenyl)-butylcarbamoyl]-methyl)-benzoic acid methyl ester.

1 N NaOH solution was added (100 µL) and stirred in a sealed reaction vessel at 80°C for 35 min. The mixture was neutralized with 1 N HCl (100 µL). The product was purified with HPLC (acetonitrile/0.1 M acetic acid/sodium acetate buffer (pH = 6) (8/2) (v/v), flow rate 4 mL/min, tr = 4.5 min). After diluting the HPLC fraction containing the product with water (20 mL), it was loaded on a C18-SepPac cartridge (Waters), dried with nitrogen and eluted with warm ethanol (1 mL) to yield 1500 MBq of the product. HPLC analysis showed a radiochemical purity of >98%. Radio-TLC analysis confirmed the results (ethylacetate/methanol 9:1, Rf = 0.7). The specific activity of (S)-2-(2-[^{18}F]fluoro-ethoxy)-4-((3-methyl-1-(2-piperidin-1-yl-phenyl)-butyl-carbamoyl)-methyl)-benzoic acid ([^{18}F]repaglinide) was between 50 and 60 GBq/µmol as determined via a UV-calibration curve.