

Research Article

Radiosynthesis of 1-(4-(2-[¹⁸F]fluoroethoxy)benzenesulfonyl)-3-butyl urea: a potential β -cell imaging agent

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Summary

Tolbutamide (**1**) is a sulfonurea agent used to stimulate insulin secretion in type 2 diabetic patients. Its analogue 1-(4-(2-[¹⁸F]fluoroethoxy)benzenesulfonyl)-3-butyl urea (**3**) was synthesized in overall radiochemical yields of 45% as a potential β -cell imaging agent. Compound **3** was synthesized by ¹⁸F-fluoroalkylation of the corresponding hydroxy precursor (**2**) with 2-[¹⁸F]fluoroethyltosylate in DMF at 120°C for 10 min followed by purification with HPLC in a synthesis time of 50 min. Insulin secretion experiments of the authentic ¹⁹F-standard compound on rat islets showed that the compound has a similar stimulating effect on insulin secretion as that of tolbutamide (**1**). The partition coefficient of compound **3** between octanol/water was determined to be 1.3 ± 0.3 ($n = 5$). Copyright © 2002 John Wiley & Sons, Ltd.

Key Words: ¹⁸F-sulfonureas; β -cell imaging agents; diabetes; ¹⁸F-fluoroalkylation

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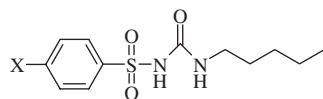
Introduction

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. Although hyperglycemia is the common denominator of both type 1 and type 2, the etiology and pathophysiology of these syndromes are distinct. Type 1 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, 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.^{1,2}

Due to the ongoing efforts in transplanting β -cell mass, there is a great medical interest in specific β -cell imaging agents to quantify the acceptance of transplanted islets in human *in vivo*.^{6–8} Additionally, in the context of type 1 diabetes mellitus the chronic and progressive loss of β -cells due to autoimmune destruction has led to concerted efforts to prevent further loss of β -cells by autoantigen-specific immunotherapy of pre-diabetic patients. Furthermore, the monitoring of β -cell mass during the silent phase of pre-diabetes in diabetes mellitus 2 patients is of special interest. For all these purposes it is of great importance to have a non-invasive method to quantify β -cell mass *in vivo*.

The aim of this study was to synthesize β -cell-specific positron emitting radiolabeled sulfonureas such as tolbutamide (**1**) to image the β -cell mass *in vivo* using positron emission tomography (PET). Sulfonureas are antidiabetic agents which block pancreatic ATP-sensitive potassium channels, located at the insulin producing β -cells of the islets of Langerhans, either directly or via a plasma membrane associated protein, resulting in an increase of intracellular calcium ion concentration and consequent insulin secretion.^{3–5}

Tolbutamide (**1**) is a sulfonurea agent used to stimulate insulin secretion in type 2 diabetic patients.^{9–11} We hypothesize that *in vitro* testing of this class of compounds would provide a strong basis to proceed with *in vivo* studies in a non-human primate model, initially, and in human experiments eventually. 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.



- | | |
|--|---|
| 1. X=CH ₃ | Tolbutamide |
| 2. X=OH | 1-(4-Hydroxybenzenesulfonyl)-3-butyl urea |
| 3. X=O-(CH ₂) ₂ [¹⁸ F]F | 1-(4-(2-[¹⁸ F]fluoroethyl)benzenesulfonyl)-3-butyl urea |

Figure 1. Structure of tolbutamide and its derivatives

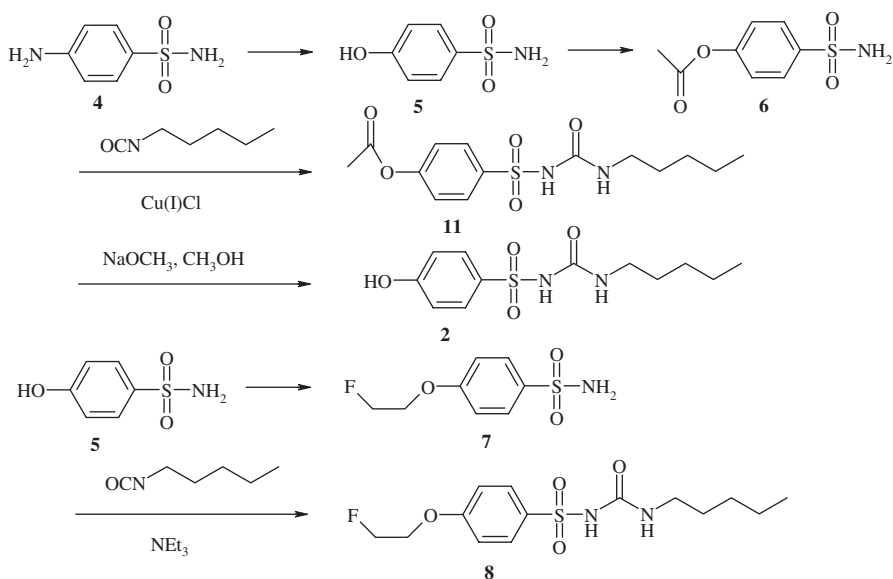
The ¹⁸F-fluoro derivative of tolbutamide, 1-(4-[¹⁸F]fluorobenzenesulfonyl)-3-butyl urea, was synthesized recently in a low overall yield of 1–2%.¹² This low yield makes it difficult to eventually use this radiopharmaceutical routinely in nuclear medicine. To overcome this problem partially, we have synthesized its ¹⁸F-fluoroethoxylated derivative (**3**) (Figure 1) and tested its efficacy in insulin secretion.

Results and discussion

We have labeled the tolbutamide analogue (**3**) with fluorine-18 for PET studies. The precursor 1-(4-(hydroxybenzenesulfonyl)-3-butyl urea (**2**) was synthesized in multiple steps (Scheme 1). Diazotization of 4-aminobenzenesulfonamide (**4**) followed by hydroxylation gave 4-hydroxybenzenesulfonamide (**5**).¹³ Acetylation of compound **5** with acetic anhydride gave compound **6** which prevents the formation of 1-(4-butylcarbamoylbenzenesulfonyl)-3-butyl urea¹⁴ as a by-product in the subsequent step. Reaction of compound **6** with butyl isocyanate in DMF with Cu(I)Cl as a catalyst¹⁵ yielded compound **11** which was de-protected with sodium methoxide in methanol to give the final product (**2**). The overall chemical yield was 58%.

The non-radioactive authentic compound 1-(4-(2-fluoroethoxy)benzenesulfonyl)-3-butyl urea (**8**) was synthesized in a similar manner (Scheme 1). Reaction of compound **5** with 1-bromo-2-fluoroethane in DMF yielded 4-(2-fluoroethoxy)benzenesulfonamide (**7**). Coupling of compound **7** with butyl isocyanate in triethylamine gave (**8**)¹⁶ in an overall chemical yield of 40%. The identity of the compounds was verified by ¹H-NMR as well as elemental analysis and for some compounds additionally by ¹³C-NMR and MS (FD).

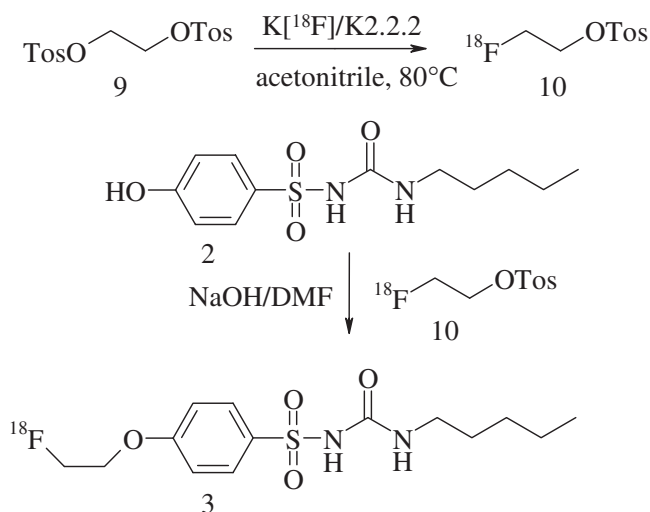
Fluorine-18 labeled compound **3** was synthesized in a two-step synthesis by direct nucleophilic substitution of ethylene glycol-1,2-ditosylate (**9**) with K[¹⁸F]/Kryptofix 2.2.2 to yield the ¹⁸F-fluoroethylating



Scheme 1. Syntheses of the labeling precursor 1-(4-hydroxybenzene)-3-butyl urea (**2**) and the authentic ^{19}F -standard compound **8**

agent 2- ^{18}F]fluoroethyl tosylate (**10**),¹⁷ and subsequent reaction with the labeling precursor (**2**) at 120°C in DMF (Scheme 2). The overall radiochemical yield after HPLC purification was 45% within a total preparation time of 50 min.

In comparison to the recently described compound 1-(4- ^{18}F]fluorobenzenesulfonyl)-3-butyl urea¹² the new compound **3** could be obtained in much higher yields. Due to the nature of nucleophilic aromatic substitution with ^{18}F]fluoride the aromatic system must be activated for obtaining reasonable radiochemical yields. In the case of the previously described two-step synthesis of 1-(4- ^{18}F]fluorobenzenesulfonyl)-3-butyl urea, radioactive labeling was limited by the nucleophilic substitution of the nitro group of 4-nitrobenzenesulfonamide. Reaction with K^{18}F /Kryptofix 2.2.2 gave the corresponding product 4- ^{18}F]fluorobenzenesulfonamide in 3–7% yield. These relatively low yields indicate that the aromatic system is probably not well enough activated or the sulfonamide moiety with its two H-atoms decreases the nucleophilicity of the ^{18}F]fluoride via complexation. All these limitations have no influence on the ^{18}F -fluoroalkylation of phenolic hydroxy groups with 2- ^{18}F]fluoroethyl tosylate because the critical radioactive labeling step has already been performed. Besides, the nucleophilicity of a



Scheme 2. Radiosynthesis of 1-(4-(2-[^{18}F]fluoroethyl)benzenesulfonyl)-3-butyl urea (**3**)

deprotonated phenolic hydroxy function is high and thus guarantees a good radiochemical yield of the corresponding 2-[^{18}F]fluoroethyl phenyl ether.¹⁸

The identity of compound **3** was verified by both TLC and HPLC compared to the non-radioactive authentic samples. *In vitro* experiments showed that compound **8** has a similar stimulating effect on insulin secretion as that of tolbutamide (**1**) itself. The increase of insulin secretion after stimulation with compound **8** was determined to be $183 \pm 50\%$ ($n=6$) and was in the same range as that of the original tolbutamide **1** with $175 \pm 19\%$ ($n=6$). These results indicate that the derivatization of tolbutamide **1** does not affect the binding to the sulfonylurea receptor significantly. The octanol/water partition coefficient of compound **3** was 1.3 ± 0.3 ($n=5$) which is lower than that of the recently reported 1-(4-[^{18}F]fluorobenzenesulfonyl)-3-butyl urea (3.13 ± 0.28) and ^{18}F -fluoroethylated glyburide derivative (124 ± 21.61).¹² The high lipophilicity of these tracers might result in a higher liver uptake and will lead to a difficulty in differentiation between pancreatic and liver radioactivity uptake. A less lipophilic compound such as compound **3** decreases the liver uptake and enhances the imaging quality of β -cell islets in pancreas. The evaluation of compound **8** was performed before the labeling experiments were done.

Experimental

4-Aminobenzenesulfonamide, ethyleneglycol-1,2-ditosylate and butyl isocyanate were purchased from Aldrich Chemical Company (Germany) and used without further purification. Tolbutamide was purchased from Sigma (Germany). Solid phase columns were purchased from Merck (Lichrolut EN). Analytical thin layer chromatography (TLC) was performed using plates from Merck (Silicagel 60 F₂₅₄). High-performance liquid chromatography (HPLC) was performed with a Sycam S1100 system, UV detection was obtained using an UV detector Sycam S3200. NMR spectra were recorded using a Bruker 200-MHz-FT-NMR spectrometer AC 200. Chemical shifts are quoted in δ (ppm) downfield from tetramethylsilane (TMS) as an internal standard. MS spectra were obtained on a Finnigan MAT90 spectrometer. Elemental analyses were performed with an EL2 system (Elementar vario). Melting points were determined on an Electrothermal 9100 apparatus and are uncorrected. Detection of radioactivity was performed using an Instant Imager (Packard Canberra) for radio-TLC and detection of radio-HPLC was performed using an NaI-radiodetector (Packard Canberra). [¹⁸F]fluoride as produced via the ¹⁸O(p,n)¹⁸F reaction was purchased from different institutions. Purification of the labeling precursor 2-[¹⁸F]fluoroethyl tosylate was accomplished using an HPLC column (Lichrosphere RP18-EC5, 250 × 10 mm). Purification of the labeled compound was achieved using an HPLC column (Lichrosphere 100 RP 18-5 μ EC 250 × 4.6 mm).

Syntheses of precursors and authentic samples

4-hydroxybenzenesulfonamide (5)

Sulfanilamide **4** (5 g, 29 mmol), dissolved in a mixture of concentrated sulfuric acid (20 ml) and water (40 ml), was diazotized at 0°C with sodium nitrite (2 g, 29 mmol) in water (20 ml) and then heated on a water-bath until the evolution of nitrogen ceased. After the mixture had been kept overnight at 4°C, the crystals of 4-hydroxybenzenesulfonamide (**5**) were collected. A further quantity of the compound was obtained by exhaustively extracting the filtrate with ether. On recrystallization from water, the sulfonamide was obtained in the form of large yellow needles (4 g, 23.6 mmol, 80%), mp 175°C (176°C¹³).

$^1\text{H-NMR}$ (d_6 -DMSO): (2 H, d, 6.85 ppm), (2 H, s, 7.1 ppm), (2 H, d, 7.6 ppm), (1 H, s, 10.2 ppm); Anal. ($\text{C}_5\text{H}_7\text{NO}_3\text{S}$) C, H, N.

4-acetyloxybenzenesulfonamide (6)

To 4-hydroxybenzenesulfonamide (**5**) (2 g, 11.8 mmol) dissolved in a sodium carbonate solution (pH 8), acetic anhydride (2.55 g, 25 mmol) was added with cooling. After a short while 4-acetyloxybenzenesulfonamide (**6**) was separated and recrystallized from 50% aqueous alcohol (2.1 g, 9.7 mmol, 86%), mp 156°C (158°C¹³). $^1\text{H-NMR}$ (d_6 -DMSO): (3 H, s, 2.3 ppm), (2 H, d, 7.3 ppm), (2 H, s, 7.4 ppm), (2 H, d, 7.85 ppm); Anal. ($\text{C}_8\text{H}_9\text{NO}_4\text{S}$) C, H, N.

1-(4-acetyloxybenzenesulfonyl)-3-butyl urea (11)

4-Acetyloxybenzenesulfonamide (**6**) (0.6 g, 2.8 mmol) was dissolved in DMF (2.5 ml). Butylisocyanate (0.55 g, 5.6 mmol) and copper (I) chloride (20 mg) were added under an argon atmosphere and stirred for 24 h. The crude mixture was poured into ice water (70 ml) under vigorous stirring and hydrochloric acid (2 N) was added until a white solid was precipitating. After drying under vacuum the product was obtained as a white solid (0.8 g, 2.5 mmol, 91%), 156°C (decomposition).

$^1\text{H-NMR}$ (d_6 -DMSO): (3 H, s, 0.8 ppm), (4 H, m, 1.1–1.3 ppm), (3 H, s, 2.3 ppm), (2 H, q, 2.9 ppm), (1 H, t, 6.5 ppm), (2 H, d, 7.35 ppm), (2 H, d, 7.9 ppm), (1 H, s, 10.6 ppm). Elemental analysis ($\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_5\text{S}$) C, H, N.

1-(4-hydroxybenzenesulfonyl)-3-butyl urea (2)

1-(4-Acetyloxybenzenesulfonyl)-3-butyl urea (**11**) (0.8 g, 2.5 mmol) was dissolved in a small amount of methanol (3 ml) and a pH of 8.5 was adjusted using a 1% NaOMe/MeOH solution and was stirred overnight at room temperature. The mixture was added slowly under stirring to a hydrochloric acid/diethyl ether mixture (5%) (10 ml) and the resulting precipitate was filtered, washed with water and dried under vacuum to yield the product nearly quantitatively (0.65 g, 2.3 mmol, 94%), mp 280°C (decomposition).

$^1\text{H-NMR}$ (d_6 -DMSO): (3 H, t, 0.8 ppm), (4 H, m, 1.1–1.3 ppm), (2 H, q, 2.8 ppm), (1 H, t, 5.9 ppm), (2 H, d, 6.7 ppm), (2 H, d, 7.5 ppm), (1 H, s, 10.6 ppm); $^{13}\text{C-NMR}$ (d_6 -DMSO) δ [ppm]: 14, 20, 32, 39, 115, 129,

132, 151, 162; MS (FD): m/z (% relative intensity) 272.6 (100.0, $[M]^+$); Anal. ($C_{11}H_{16}N_2O_4S$) C, H, N.

4-(2-fluoroethoxy)benzenesulfonamide (7)

Elemental sodium (0.132 g, 5.7 mmol) was carefully added to methanol (30 ml) and refluxed until no sodium was left. The sodium methanolate solution was cooled to room temperature and 4-hydroxybenzene sulfonamide (**5**) (1 g, 5.7 mmol) was added and stirred for 30 min. The methanol was evaporated under vacuum and the remaining sodium phenolate was dissolved in DMF (15 ml). Sodium iodide (10 mg) and 1-bromo-2-fluoroethane were added and the mixture was kept at 70°C overnight. The DMF was removed under vacuum (10^{-3} mbar) and the crude product was purified via column chromatography (Si-60, chloroform/methanol/acetone (6/1/1)) to yield (**7**) as a white solid (0.75 g, 3.4 mmol, 59%), mp 132–134°C.

$^1\text{H-NMR}$ (d_6 -DMSO): (1 H, t, 4.2 ppm), (1 H, t, 4.4 ppm), (1 H, t, 4.6 ppm), (1 H, t, 4.9 ppm), (2 H, d, 7.1 ppm), (2 H, s, 7.2 ppm), (2 H, d, 7.75 ppm); Anal. ($C_7H_{10}FNO_3S$) C, H, N.

1-(4-(2-fluoroethoxy)benzenesulfonyl)-3-butyl urea (8)

4-(2-Fluoroethoxy)benzenesulfonamide (**7**) (0.25 g, 1.1 mmol) and butylisocyanate (0.55 g, 5.6 mmol) were added to triethylamine (10 ml) and stirred for 15 h at 90°C. The reaction mixture was cooled to room temperature and poured into DMF (40 ml). Hydrochloric acid (4 ml water/20 μl HCl_{conc}) was added, the precipitating product was filtered and washed with water to give compound **8** as a white solid (0.27 g, 0.85 mmol, 75%), mp 148–149°C.

$^1\text{H-NMR}$ (d_6 -DMSO): (3 H, t, 0.8 ppm), (4 H, m, 1.1–1.3 ppm), (2 H, q, 2.9 ppm), (1 H, t, 4.2 ppm), (1 H, t, 4.4 ppm), (1 H, t, 4.6 ppm), (1 H, t, 4.9 ppm), (1 H, t, 6.4 ppm), (2 H, d, 7.15 ppm), (2 H, d, 7.8 ppm), (1 H, s, 10.4 ppm); $^{13}\text{C-NMR}$ (d_6 -DMSO) δ [ppm]: 14, 20, 32, 39, 68, 82, 115, 129, 132, 151, 162; MS (FD): m/z (% relative intensity) 318.6 (100.0, $[M]^+$); Anal. ($C_{13}H_{19}FN_2O_4S$) C, H, N.

2- ^{18}F fluoroethyltosylate (10)

No-carrier-added (NCA) aqueous [^{18}F]fluoride (540–1100 MBq) prepared by the $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$ nuclear reaction on an enriched water (95%)

target was added to a solution of K_2CO_3 (15 μ l (1 N)) and Kryptofix 2.2.2. (10–15 mg) in CH_3CN (800 μ l). The water was removed using a stream of nitrogen at 80°C and coevaporated to dryness with CH_3CN (2 \times 1 ml).

To the dried Kryptofix 2.2.2/[^{18}F]fluoride (380–750 MBq) complex in acetonitrile (1 ml) ethylenglycol-1,2-ditosylate (**9**) (8–10 mg, 20–25 μ mol) 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, R_t : 8 min). After diluting the HPLC fraction containing the 2-[^{18}F]fluoroethyltosylate with water, the product was loaded on an 18C-Sepac column, dried with nitrogen gas and eluted with 1 ml of tempered (40–50°C) DMF to yield a product activity of 300–600 MBq 2-[^{18}F]fluoroethyltosylate (**10**).

1-(4-(2-[^{18}F]fluoroethoxy)benzenesulfonyl)-3-butyl urea (3)

To 1-(4-hydroxybenzenesulfonyl)-3-butyl urea (**2**) (5 mg, 18.4 μ mol) dissolved in DMF (0.6 ml), sodium hydroxide solution (1 N, 18.4 μ l) was added and the solution was heated at 80°C for at least 3 min. A solution of 2-[^{18}F]fluoroethyltosylate (300–600 MBq) in DMF (300–500 μ l) was added and stirred in a sealed reaction vessel at 120°C for 10 min. The product was purified with HPLC (acetonitrile/water 1:1, flow rate 1 ml/min, t_r : 5.9 min). After diluting the HPLC fraction containing the product with water, it was loaded on a solid phase column (LiChrolut EN, Merck), dried with nitrogen and eluted with 1 ml ethanol to yield 220–440 MBq of the product (**3**). HPLC analysis showed a radiochemical purity of >98%. Radio-TLC analysis confirmed the results (chloroform/methanol/acetone 6:1:1, R_f =0.5). The specific activity of **3** was between 40 and 48.1 GBq/ μ mol as determined via a UV-calibration curve.

Determination of partition coefficient of compound 3

The lipid/water partition coefficient of compound **3** was measured by adding 5 μ l of the compound in saline solution to a 5 ml vial containing 1 ml each of 1-octanol and pH 7.0 phosphate buffer. The vial was capped and vortexed vigorously for 10 min at room temperature. After reaching equilibrium, the organic phase was pipetted out and each phase was analyzed via radio-TLC at an Instant Imager

(Packard Canberra). The partition coefficient was calculated as (cpm in 1-octanol)/(cpm in pH 7.0 phosphate buffer).

Insulin secretion experiments of compound **8** on rat islets

For testing the *in vitro* function of the tolbutamide derivative (**8**) and the original tolbutamide (**1**) a standardized batch stimulation was performed. Adult rat islets were isolated by collagenase digestion and purified by a density gradient.

Lewis rats (Central Animal Facility, University of Mainz), 6–8 weeks old, body weight 250–270 g, were used as islet donors. Rats were anesthetized by intraperitoneal pentobarbital administration (60 mg/kg); a midline abdominal incision was performed; and the pancreas was exposed and injected via the pancreatic duct with Hanks' balanced salt solution (HBSS; Gibco BRL, Long Island, NY) containing 1.7 mg/ml collagenase (Serva PanPlus, Heidelberg, Germany). After the death of the animal, the pancreatic tissue was surgically removed and incubated for 10 min at 37°C in the collagenase solution. Mechanical disruption of the digested pancreatic tissue was achieved by further incubation at 37°C for 10 min in collagenase solution, interrupted every 2 min by shaking for 30 s. The digestion process was stopped by addition of cooled HBSS plus 10% fetal calf serum (4°C). Islet purification was achieved using a discontinuous three-phase Ficoll density gradient (densities: 1.090, 1.077 and 1.040). Islets were cultured in RPMI medium (Biochrom KG, Berlin, Germany) at 37°C. The medium contained 5.1 mmol/l (1 g/l) D-glucose, 25 mmol/l HEPES, 10% fetal calf serum (Greiner Laboratories, Frickenhausen, Germany), 0.2 g/l Glutamax (GibcoBRL, Paisley, Scotland), penicillin, streptomycin (GibcoBRL, Paisley, Scotland) and Ciprobay (Hoechst, Frankfurt, Germany).

For each sample ten islets were picked (equal in size and shape) in a culture insert with a membrane of 12 µm pore size (Millicell PCF, Millipore, France) and incubated in a 24-well culture plate (Falcon Multiwell, Becton Dickinson, USA). First the basal insulin secretion was tested by incubating the islets with normo-glycemic culture media (RPMI 1640 + D-glucose 1 g/l + 10% FCS + P/S) for 1 h at 37°C. After the culture period the media were collected and stored at –20°C. The inserts with islets were transferred to normo-glycemic culture media with several concentrations (2.5, 25 and 250 µg/ml) of the tolbutamide (**1**) and the ¹⁹F-derivative (**8**) and incubated for a stimulation period

Table 1. Insulin secretion of 8, 1 and D-glucose at different concentrations

Compound	Stimulation effect (% \pm SD%) at different concentrations			
	2.5 μ g/ml	25 μ g/ml	250 μ g/ml	3 g/l
1	118 \pm 13	175 \pm 19	120 \pm 8	—
8	127 \pm 15	183 \pm 50	108 \pm 16	—
D-Glucose	—	—	—	297 \pm 30

of 1 h. As a positive control several inserts with islets were cultured with a hyperglycemic culture media (RPMI 1640 D-glucose 3 g/l+10% FCS+P/S) only. For the negative control normo-glycemic culture media (RPMI 1640 D-glucose 1 g/l+10% FCS+P/S) with a diluted solution but with neither compound **1** nor compound **8** was used. The insulin content of each probe was quantified by a rat-insulin ELISA (Merckodia, Sweden). The stimulation effect (in %) was calculated as stimulated insulin secretion divided by basal insulin secretion \times 100 (Table 1).

Conclusion

We have synthesized 1-(4-(2-[18 F]fluoroethoxy)benzenesulfonyl)-3-butyl urea (**3**) in an attempt to use it as a β -cell imaging agent for the non-invasive determination of the progressive loss of β -cell mass during the silent phase of pre-diabetes or transplanted islet mass. The overall yield of the radiosynthesis was 45% within 50 min and the specific activity was determined to be in the range of 40–48 GBq/ μ mol. In comparison to the recently published fluorine-18 labeled tolbutamide and glyburide derivatives, compound **3** is easier to synthesize and gives a better yield. In addition, compound **3** is less lipophilic than fluorine-18 labeled tolbutamide and glyburide which may decrease the liver uptake and could lead to a better resolution for the endocrine pancreatic tissue. The feasibility of using sulfonylurea receptor ligands as β -cell imaging agents is under investigation.

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