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Synthesis of fluorine-18 labeled sulfonureas as β-cell imaging agents

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Summary

Tolbutamide (**1**) and glyburide (**7**) are hypoglycemic drugs used to stimulate insulin secretion in type 2 diabetic patients. We have synthesized their fluorine-18 labeled analogs, 1-[(4-[^{18}F]fluorobenzenesulfonyl)]-3-butyl]urea (*p*-[^{18}F]fluorotolbutamide, **3a**) and N-{4-[β-(2-[^{18}F]fluoroethoxybenzene carboxamido)ethyl]benzenesulfonyl}-N'-cyclohexylurea (2-[^{18}F]fluoroethoxyglyburide, **6a**) as β-cell imaging agents. Compound **3a** was synthesized via two approaches: One-step synthesis via nucleophilic substitution of *p*-nitrotolbutamide (**2**) with K[^{18}F]/Kryptofix 2.2.2 in either CH_3CN or DMSO gave a complicated mixture; a two-step synthesis via preparation and reaction of 4-[^{18}F]fluorobenzenesulfonamide with butyl isocyanate in the presence of either copper (I) chloride or borontrifluoride etherate complex in CH_3CN followed by HPLC purification yielded compound **3a** in an overall yield of 1-2% with a synthesis time of 120 minutes from EOB. Compound **6a** was synthesized by alkylation of the corresponding hydroxy precursor (**5**) with [^{18}F]fluoroethyl tosylate in DMSO at 120^{0}C for 20 minutes followed by HPLC purification in an overall yield of 5-10 % with a synthesis time of 100 minutes from

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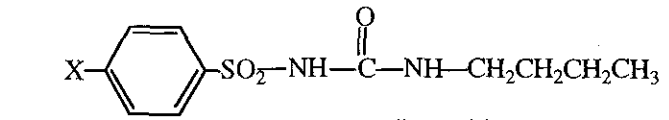
EOB. The lipid/water partition coefficient of compounds **3a** and **6a** was 3.13±0.28, n=6 and 124.33±21.61, n=8, respectively. The feasibility of using these radiotracers as β-cell imaging agents is under evaluation.

Introduction

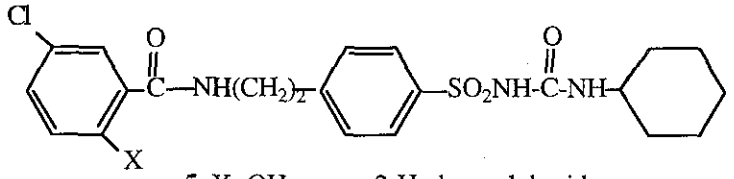
Diabetes mellitus is a major public health problem, affecting ~5% of the population. Diabetes mellitus comprises a heterogeneous group of disorders characterized by high blood glucose levels. Two major types of diabetes mellitus have been defined: Type 1 (insulin-dependent diabetes mellitus, IDDM), and Type 2 (non-insulin-dependent diabetes mellitus, NIDDM). Although hyperglycemia is the common denominator of both IDDM and NIDDM, the etiology and syndromes are distinctly different. Type 1 is a chronic autoimmune disease characterized by the selective destruction of insulin-producing β-cells of the islets of Langerhans, leading to a near total deficiency in insulin secretion. When autoimmune destruction affects more than 90% of the β-cells mass, the resulting insulin deficiency culminates into the development of overt hyperglycemia. Type 2 is the most common form of diabetes, accounting for greater than 90% of patients. It is caused by two physiological defects: resistance to the action of insulin combined with a deficiency in insulin secretion (1, 2). To date, there have been no reported techniques to image the endocrine pancreas. The basis of our inability to image the endocrine pancreas has been due to the unavailability of a marker specific for islet β-cells. 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. In addition, a number of novel strategies for therapy of diabetes mellitus are based on replication of β-cells and islet transplantation. Since we have an on going islet transplantation program (3-5), it is of considerable importance to have a reliable non-invasive method to monitor the progressive loss of β-cells mass during the silent phase of pre-diabetes or transplanted islet mass.

Positron Emission Tomography (PET) coupled with appropriate radiotracers has the unique capability of non-invasively measuring biochemical and metabolic processes. 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 and consequent insulin secretion (6-8). Therefore, if sulfonylureas were labeled with a positron emitter, they may serve as β-cell imaging agents. Tolbutamide (**1**) and glyburide (**7**) are hypoglycemic drugs which bind to sulfonylurea receptor (9-11) in HIT-β cell with a K_i of 25-55 μM (12) and 0.7-7 nM (13), respectively. The fluoro analog, 1-[(*p*-fluorobenzenesulfonyl)]-3-butylurea (**3**), has a similar hypoglycemic potency as tolbutamide (14). Therefore, we have synthesized *p*-[^{18}F]fluorotolbutamide, **3a** and (2-[^{18}F]fluoroethoxyglyburide, **6a** as potential β-cell imaging agents (Figure 1).



1. X=CH_3 Tolbutamide
2. X=NO_2 *p*-Nitrotolbutamide
3. X=F *p*-Fluorotolbutamide



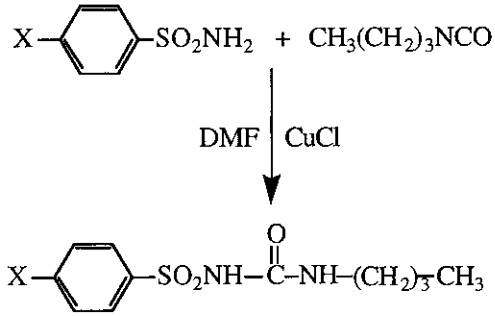
5. X=OH 2-Hydroxyglyburide
6. X=$O(CH_2)_2F$ 2-Fluoroethoxyglyburide
7. X=OCH_3 Glyburide

Fig. 1 Structure of tolbutamide and its analogs

Results and Discussion

Both tolbutamide (**1**) and glyburide (**7**) are hypoglycemic drugs which bind to sulfonylurea receptors with wide ranges of binding affinity. We have labeled the analogs of both compound **1** and compound **7** with fluorine-18 and attempt to use them as β cell imaging agents. Both *p*-nitrotolbutamide (**2**) and *p*-fluorotolbutamide

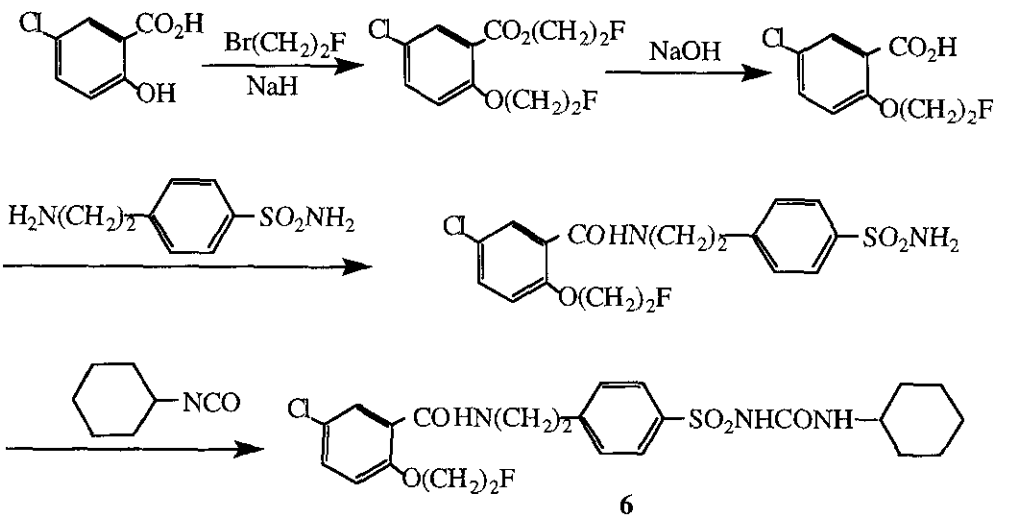
(**3**) were synthesized from the corresponding benzenesulfonamide with butyl isocyanate in the presence of copper (I) chloride (15) in good yield (scheme 1).



Scheme 1. Synthesis of *p*-nitrotolbutamide (**2**) and *p*-fluorotolbutamide (**3**).

N-{4-[β-(2-hydroxy-5-chlorobenzene carboxamido)ethyl]benzenesulfonyl}-N'-cyclohexylurea (**5**) was synthesized in a similar manner as reported in the literature (16) from 4-[β-(2-hydroxy-5-chlorobenzene carboxamido)ethyl]benzene-sulfonamide (**4**) and cyclohexyl isocyanate in the presence of 1N NaOH. Compound **4**, in turn, was synthesized from 5-chlorosalicyclic acid and 4-(2-aminoethyl) benzenesulfonamide. N-{4-[β-(2-fluoroethoxy-5-chlorobenzene carboxamido)ethyl]-benzenesulfonyl}-N'-cyclohexylurea (**6**) was prepared from a multi-step synthesis. Reaction of 5-chlorosalicyclate with bromofluoroethane and sodium hydride followed by deprotection with 5% NaOH solution gave 2-fluoroethoxy-5-chlorobenzonic acid which was converted to 4-[β-(2-fluoroethoxy-5-chlorobenzene carboxamido)ethyl]-benzenesulfonamide. Reaction of this sulfonamide with cyclohexyl isocyanate gave compound **6** in an overall yield of 42% (scheme 2). The identities of these precursors and authentic samples were verified by NMR or elemental analysis.

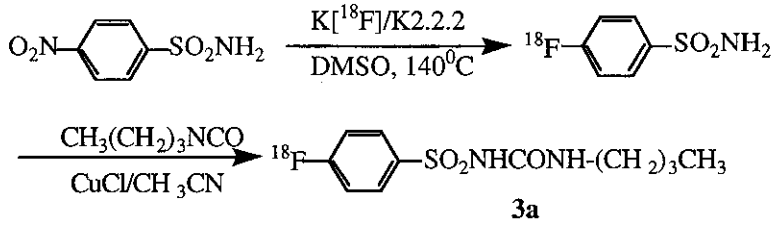
Fluorine-18 labeled fluorotolbutamide (**3a**) was synthesized by two approaches: 1) one step synthesis by direct nucleophilic substitution of p-nitrotolbutamide (**2**) with K[^{18}F]/Kryptofix 2.2.2, and 2) one-pot-two-step synthesis by the preparation of 4-[^{18}F]fluorobenzenesulfonamide followed by the reaction of this intermediate with butyl isocyanate in the presence of either copper (I) chloride (15) or borontrifluoride



Scheme 2. Synthesis of 2-fluoroethoxyglyburide

etherate complex (17) as the catalyst. Direct nucleophilic substitution of p-nitro-tolbutamide with K[^{18}F]/Kryptofix 2.2.2 in either CH_3CN or DMSO at 80-140^{0}C gave a complicated mixture with a very low yield of the desired product. This was not unexpected as the proton in the secondary sulfonamide is very acidic and existed as an anion under the current reaction condition, thus precluded the nucleophilic substitution. This has also been observed in the preparation of other F-18 labeled sulfonamides (18, 19). Protection of the acidic proton in sulfonamide group may improve the product yield of the nucleophilic substitution reaction. On the other hand, the two-step synthesis gave compound **3a** in a useful yield. Reaction of 4-nitrobenzenesulfonamide with K[^{18}F]/Kryptofix 2.2.2 gave 4-[^{18}F]fluorobenzene-sulfonamide in 3-7% yield. Reaction of this intermediate with butyl isocyanate in the presence of either copper (I) chloride or borontrifluoride etherate complex gave compound **3a** in an overall yield of 1-2%. The synthesis time was 120 min from EOB (scheme 3).

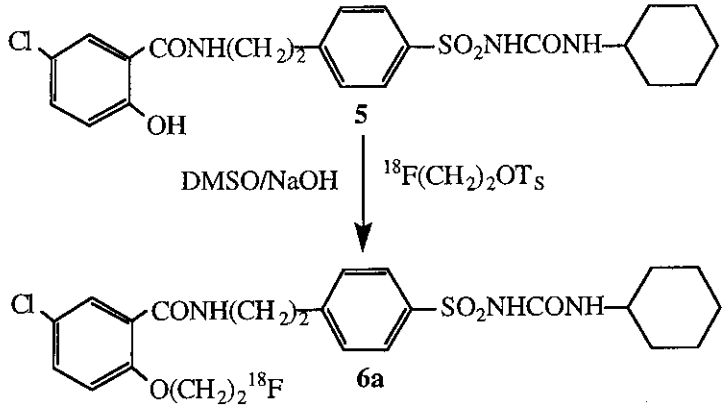
N-{4-[β-(2-[^{18}F]Fluoroethoxy-5-chlorobenzene carboxamido)ethyl]benzene-sulfonyl}-N'-cyclohexylurea (**6a**) was synthesized in two steps. Nucleophilic



Scheme 3. Synthesis of [^{18}F]fluorotolbutamide

substitution of ethylene glycol di-p-tosylate with K[^{18}F]/Kryptofix 2.2.2 gave 1-[^{18}F]fluoro-2-tosylethane in 50% yield. Alkylation of N-{4-[β-(2-hydroxy-5-chlorobenzene carboxamido)ethyl]benzenesulfonyl}-N'-cyclohexylurea (**5**) with 1-[^{18}F]fluoro-2-tosylethane followed by HPLC purification gave compound **6a** in an overall yield of 5-10% yield in a synthesis time of 100 min from EOB (scheme 4). The identities of compound **3a** and compound **6a** were verified by both TLC and HPLC compared to the non-radioactive authentic samples.

The partition coefficients of compound **3a** and compound **6a** were 3.13±0.28 and 124.33±21.61, respectively. The difference in lipophilicity of these two compounds was also evident from their retention times in a C_{18} column. The retention times of compound **3a** and compound **6a** in HPLC ((Phenomenex, Luna 2, C_{18}, 4.6 x 250 mm, CH_3OH:H_2O, 7:3; 1 mL/min) were 5.1 and 15.3 min, respectively. Aside from a great difference in binding affinity to sulfonylurea receptor, the difference in lipophilicity of compounds **3a** and **6a** may also affect their usefulness as β-cell imaging agents.



Scheme 4. Synthesis of 2-[^{18}F]fluoroethoxyglyburide

Experimental

4-Fluorobenzenesulfonamide, 4-nitrobenzenesulfonamide, ethylene glycol di-p-tosylate, 5-chlorosalicyclic acid , ethylchloroformate, 4-(2-aminoethyl)benzene-sulfonamide, butyl isocyanate, cyclohexyl isocyanate, copper(I) chloride and borontrifluoride etherate were purchased from Aldrich Chemical Company (Milwaukee, WI) and used without further purification. C_{18} Sep-Pak cartridges were obtained from Waters Chromatography Division, Millipore Corporation.Radioactivity was determined using a calibrated ion chamber (Capintec CRC-745, Capintec, Inc.) and a sodium iodide well counter (Packard, Gamma Counter 5000 Series, Packard Instrument Company, IL). High performance liquid chromatography (HPLC) analyses were carried out with a Sonntek liquid chromatograph equipped with both u.v. and radioactivity monitors and C_{18} columns. The elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Elemental compositions were within ±0.3% of the calculated values. Melting points were determined on a MEL-Temp II apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker DPX 200 spectrometer. Chemical shifts (δ) are expressed in parts per million relative to internal tetramethylsilane.

Synthesis of precursors and authentic samples:

3-(*p*-Nitrobenzenesulfonyl)-1-butylurea (2). To a solution of 4- nitrobenzene-sulfonamide (1.45 g, 7.18 mmole) and copper (I) chloride (0.84 g, 0.85 mmole) in 10 mL of DMF, 1 mL of butyl isocyanate (8.9 mmole) was added. The solution turned to greenish color immediately. The solution was stirred at room temperature overnight and poured into 100 mL of ice-water. The precipitates were filtered by suction, washed with water and dried to give 1.45 g (67%) of compound **2**, mp149-151^{0}C. The product was recrystallized from MeOH/H_2O, mp. 155-157^{0}C (160-162.5^{0}C (14)). NMR ($CDCl_3$) δ 8.28 (d, J=8.8 Hz, 2H), 8.11 (d, J=8.8 Hz, 2H), 3.57 (br s, 2H), 3.04 (t, J=14Hz, 2H), 1.35 (pent, J=7Hz, 2H), 1.16 (pent, J=7Hz, 2H), 0.80 (t, J=7Hz, 3H).

3-(*p*-Fluorobenzenesulfonyl)-1-butylurea (3). To a solution of 4-fluoro-benzenesulfonamide (0.33 g, 1.89 mmole) and copper (I) chloride (0.023 g, 0.23 mmole) in 5 mL of DMF, 0.4 mL of butyl isocyanate (3.55 mmole) was added. The

solution turned to greenish color immediately. The solution was stirred at room temperature overnight and poured into 100 mL of ice-water. The precipitates were filtered by suction, washed with water and dried to give 0.185 g (36%) of compound **3**, mp 92-94^{0}C. The product was recrystallized from MeOH/H_2O, mp 103-105^{0}C (106-107.5^{0}C (14)). NMR ($CDCl_3$) δ 9.04 (br s, 1H), 7.93 (m, 2H), 7.21 (m, 2H), 6.49 (br s, 1H), 3.20 (t, 2H), 1.45 (pent, 2H), 1.25 (pent, 2H), 0.90 (t, 3H).

4-[β-(2-Hydroxy-5-chlorobenzene carboxamido)ethyl]benzene-sulfonamide (4). To a solution of 5-chlorosalicyclic acid (5.35 g, 0.031 mole) and triethylamine (4.3 mL, 0.031 mole) in 50 mL of acetone, ethylchloroformate (3 mL, 0.031 mole) was added dropwise. The solution turned cloudy. The mixture was stirred at 0^{0}C for 20 minutes and then a suspension of 4-(2-aminoethyl)benzene-sulfonamide (6 g, 0.031 mole) and triethylamine (4.3 mL) in 50 mL of acetone was added. The mixture was stirred at 0^{0}C for one hour and then at room temperature overnight. The precipitates were filtered by suction, washed with acetone, water, 0.2 N HCl, water, acetone and dried to give 2.54 g (23%) of compound **4**, mp 260-262^{0}C; NMR (DMSO-d_6) δ 7.8 (m, 3H), 7.4 (m,4H), 4.08 (t, 2H), 2.95 (t, 2H). The filtrate was evaporated to dryness, suspended in 200 mL of 0.2 N HCl, filtered, washed with water and dried to give 9.28 g of solid which was recrystallized from ethanol to give an additional 0.4 g (4%) of compound **4**, mp 258-260^{0}C. The total yield of compound **4** was 27%. NMR (DMSO-d_6) δ 7.85 (m, 3H), 7.42 (m, 4H), 4.08 (t, 2H), 2.95 (t, 2H).

N-{4-[β-(2-Hydroxy-5-chlorobenzene carboxamido)ethyl]benzene-sulfonyl}-N'-cyclohexylurea (5). To a suspension of compound **4** (225 mg, 0.634 mmole) in 2.3 mL of 1 N NaOH and 2 mL of acetone, cyclohexyl isocyanate (0.5 mL, 3.915 mmole) was added. The mixture was stirred at room temperature overnight, acidified with conc. HCl and filtered by suction. The precipitates were suspended in 10% ammonium hydroxide solution and filtered, washed with water and dried to give 540 mg of white solid which was identified as cyclohexyl carbamic acid, mp 215-217^{0}C. NMR ($CDCl_3$) δ 8.52 (br s, 1H), 3.75 (br s, 1H), 2.16-1.26 (m, 10H). The filtrate was acidified again with conc. HCl, the precipitates were filtered, washed with water and dried to give 240 mg (80%) of compound **5**, mp 178-180^{0}C (183-185^{0}C (20));

NMR (DMSO-d_6) δ 12.46 (s, 1H), 10.30 (s, 1H), 8.95 (s, 1H), 7.85 (m, 3H), 7.42 (m, 4H), 6.9 (d, 1H), 6.34 (d, 1H), 3.54 (m, 2H), 2.94 (m, 2H), 1.59 (m, 5H), 1.08 (m, 5H). Anal. ($C_{22}H_{26}N_3O_5SCl$) C, H, N.

N-{4-[β-(2-Fluoroethoxy-5-chlorobenzene carboxamido)ethyl]benzene-sulfonyl}-N'-cyclohexylurea (6).

Compound **6** was prepared by a multi-step synthesis as follows:

5-Chloro-2-(2-fluoroethoxy)benzoic acid. To a solution of 5-chlorosalicylic acid (2.7 g, 15.64 mmol) in 10 mL of DMF, sodium hydride (60% absorbed on mineral oil,1.26 g, 31.5 mmol) and 1-bromo-2-fluoroethane (4.4 g, 34.67 mmol) were added and the mixture was heated at 80°C for 48 hrs. The solvent was evaporated, the remaining solid was washed with water and purified with flash-chromatography (silica, ethyl acetate:hexane, 95:5). The fractions containing the product (R_f=0.85 on silica gel plates) were collected and the solvent was removed to yield the intermediate 2-fluoroethyl 5-chloro-2-(2-fluoroethoxy) benzoate (3.8 g, 93.4%); NMR (DMSO-d_6) δ 7.5-7.8 (m, 2H), 7.2-7.4 (d, 1H), 4.8 (m, 1H), 4.5-4.6 (m, 3H), 4.4 (m, 2H), 4.2 (dt, 1H). A solution of sodium hydroxide (5%, 80 mL) was added to this compound and the solution was refluxed for 2 hrs. The solution was concentrated and acidified with HCl (2N). The precipitates were filtered by suction and washed with a small amount of ice-water to yield 5-chloro-2-(2-fluoroethoxy)benzoic acid (2.7 g, 80%); NMR (DMSO-d_6) δ 12.9 (s, 1H), 7.4-7.7 (m, 2H), 7.0-7.2 (d, 1H), 4.8 (dt, 1H), 4.6 (dt, 1H), 4.3 (dt, 1H), 4.2 (dt, 1H). Anal. ($C_9H_8O_3ClF$) C, H.

4-[β-(2-(2-Fluoroethoxy-5-chlorobenzene carboxamido)ethyl]benzene-sulfonamide. The title compound was synthesized by a method similar to that used to prepare 4-[β-(2-hydroxylbenzene carboxamido)ethyl]benzenesulfonamide (17) in 65% yield; mp 123^{0}C; NMR (DMSO-d_6) δ 8.2 (t, 1H), 7.1-7.9 (m, 10H), 4.8 (dt, 1H), 4.6 (dt, 1H), 4.4 (dt, 1H), 4.2 (dt, 1H), 3.5 (m, 2H), 2.9 (t, 2H). Anal. ($C_{17}H_{18}N_2O_4SClF$) C, H, N.

N-{4-[β-(2-Fluoroethoxy-5-chlorobenzene carboxamido)ethyl]benzenesulfonyl}-N'-cyclohexylurea (6) A solution of 4-[β-(2-(2-fluoroethoxy-5-chlorobenzene

carboxamido)ethyl]benzenesulfonamide (400.8 mg, 1 mmol), cyclohexyl isocyanate (250.34 mg, 2 mmol) and borontrifluoride-diethyl ether (280 mg) in CH_3CN (10 mL) was stirred at room temperature for 24 hrs. The solvent was evaporated and the remaining solid was purified via flash-chromatography $CHCl_3$/EtOH/NH_3 (25 %) (38:43:19). The fractions containing the product (R_f=0.5 on silica gel plates) were collected, concentrated and acidified with HCl (2N). The precipitates were filtered by suction and washed with water to yield compound **6** as a white solid (420 mg, 82%); mp 141.5^{0}C (dec.); NMR (DMSO-d_6) δ 10.3 (s, 1H), 8.3 (t, 1H), 7.2-7.8 (m, 7H), 6.3 (d, 1H), 4.8 (dt, 1H), 4.6 (dt, 1H), 4.4 (dt, 1H), 4.2 (dt, 1H), 3,6 (m, 2H), 2.9 (t, 2H), 1.4-1.9 (m, 5H), 1.0-1.4 (m, 6H). Anal. ($C_{24}H_{29}N_3O_5SClF$) C, H, N.

Synthesis of 1-[(p-[^{18}F]fluorobenzenesulfonyl)]-3-butylurea (3a). Compound **3a** was synthesized by two methods:

A. One-step synthesis

No-carrier-add (NCA) aqueous [^{18}F]fluoride (0.5 mL) prepared by the ^{18}O(p,n)^{18}F nuclear reaction in a JSW BC 30/15 cyclotron on an enriched water (95+% ^{18}O) target was added to a solution of K_2CO_3/Kryptofix 2.2.2 in a Pyrex vessel. The water was evaporated using a stream of nitrogen at 110^{0}C and coevaporated to dryness with CH_3CN (2 x 0.5 mL). 3-(*p*-nitrobenzenesulfonyl)-1-butylurea (**2**) (4.0 mg in 0.5 mL of DMSO) was added to the dried K[^{18}F] and the solution was heated at 140^{0}C for 20 min and then cooled to room temperature. Water (5 mL) was added and the solution was passed through a C_{18} Sep-Pak. The Sep-Pak was rinsed with an additional 5 mL of water. The combined washings was discarded. The reaction mixture was rinsed out with CH_2Cl_2 (2 x 3 mL), analyzed by both TLC (silica gel, CH_3CN: 0.1 M NH_4HCO_2; 30:70 with 0.3% acetic acid) and HPLC (Spherisorb, C_{18}, 4.6 x 250 mm; CH_3CN: 0.1 M NH_4HCO_2; 30:70 with 0.3% acetic acid; 1.2 mL/min) and showed that only a trace amount of product was produced. Reaction in CH_3CN at 85^{0}C for 30 minutes gave a similar result.

B. Two-step synthesis

A solution of 4-nitrobenzenesulfonamide (4 mg in 0.5 mL of DMSO) was added to the dried K[^{18}F] and the solution was heated at 140^{0}C for 20 min and then cooled to room temperature. Water (5 mL) was added and the solution was passed

through a C_{18} Sep-Pak. The Sep-Pak was rinsed with an additional 5 mL of water. The combined washings was discarded. The reaction mixture was rinsed out with CH_2Cl_2 (2 x 3 mL), dried over K_2CO_3, concentrated and a solution of butyl isocyanate (100 μL) and copper (I) chloride (2 mg) in 0.5 mL of CH_3CN was added. The mixture was heated at 80°C for 20 minutes, cooled to room temperature and injected into a semi-preparative column (Spherisorb, C_{18}, 10 x 250 mm; CH_3CN: 0.1 M NH_4HCO_2; 30:70 with 0.3% acetic acid; 5 mL/min). The fraction containing compound **3a** was collected from 11.5-13.5 min and evaporated to dryness. To the residue 5 mL of normal saline was added and the resulting solution was filtered through a 0.22 μm cellulose acetate membrane filter (Millipore) into a multi-injection vial. The overall radiochemical yield was 1-2% and the synthesis time was 100 minutes from EOB. HPLC analysis (Spherisorb, C_{18}, 4.6 x 250 mm; CH_3CN: 0.1 M NH_4HCO_2; 30:70 with 0.3% acetic acid; 1.2 mL/min) showed that the radiochemical purity was > 99%.

Synthesis of N-{4-[β-(2-[^{18}F]Fluoroethoxybenzene carboxamido)ethyl]-benzenesulfonyl}-N'-cyclohexylurea ([^{18}F]fluoroethoxyglyburide, 6a). Compound **6a** was synthesized by one pot-two-step O-alkylation of compound **5** with 1-[^{18}F]fluoro-2-tosylethane followed by purification with HPLC. Thus, a solution of ethylene glycol di-p-tosylate (5 mg in 0.5 mL of CH_3CN) was added to the dried K[^{18}F] and the solution was heated at 90°C for 20 minutes. Without isolation of 1-[^{18}F]fluoro-2-tosylethane, a solution of compound **5** (2.5 mg in 10 μL of 1N NaOH and 0.3 mL of DMSO) was added and the solution was heated at 90°C for an additional 30 minutes and then cooled to room temperature. Water (5 mL) was added and the solution was passed through a C_{18} Sep-Pak. The Sep-Pak was rinsed with two additional 5 mL water followed by ether (2 x 10 mL). The combined washings were discarded. The crude product **6a** was rinsed out with MeOH (2 x 3 mL), concentrated to ~1.5 mL and injected into HPLC (Phenomenex, Luna 2, C_{18}, 10 x 250 mm, CH_3OH:H_2O, 7:3; 3 mL/min). The fraction containing compound **6a** was collected from 17-22 min and the solvent was evaporated to dryness. To the residue 5 mL of normal saline was added and the resulting solution was filtered through a 0.22 μm cellulose acetate membrane filter (Millipore) into a multi-injection vial. The

radiochemical yield was 5-10% and the synthesis time was 100 minutes from EOB. HPLC analysis (Phenomenex, Luna 2, C_{18}, 4.6 x 250 mm, $CH_3OH:H_2O$, 7:3; 1 mL/min) showed that the radiochemical purity was > 99%.

Determination of partition coefficient of compounds 3a and 6a.

Lipid/water partition coefficients of compounds **3a** and **6a** were measured by adding 5 μL 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 counted in a NaI well counter. The partition coefficient was calculated as (cpm in 1-octanol) / (cpm in pH 7.0 phosphate buffer).

Conclusion

We have synthesized two F-18 labeled sulfonureas, compounds **3a** and **6a,** which bind to sulfonylurea receptor with wide ranges of binding affinity (from μM to nM) in an attempt to use them as β cell imaging agents. This is the first example that a noninvasive method has been proposed to monitor the progressive lose of β-cells mass during the silent phase of pre-diabetes or transplanted islet mass. The feasibility of using sulfonylurea receptor ligands as β-cell imaging agents is under investigation.

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