Synthesis of a sugar-conjugated sulfonurea derivative: A possible new concept for β-cells imaging with PET using ^{18}F-labelled analogues in the future

A. Korobeinikov, R. Schirrmacher, F. Rösch
Institut für Kernchemie, Johannes Gutenberg–Universität, Fritz-Straßmann-Weg 2, 55128 Mainz

Diabetes mellitus, better known as "diabetes", is a chronic disease associated with abnormally high levels of the sugar glucose in the blood. There are two main types of the disease: insulin-dependent diabetes mellitus (IDDM, type 1), and non-insulin-dependent diabetes mellitus (NIDDM, type 2). IDDM is an autoimmune disease characterized by destruction of pancreatic β-cells being responsible for insulin secretion. It causes absolute insulin deficiency. NIDDM is associated with defects of insulin action (insulin resistance) and insulin secretion although pancreatic β-cells are remain intact [1].

This study is the continuation of our experiments of ^{18}F-labelled sulfonylurea derivatives synthesis [2,3]. Some of the sulfonylurea derivatives, such as tolbutamide and glibenclamide, are used as pharmacological agents for stimulating insulin secretion [4]. Binding of these compounds to β-cells receptors might allow to use ^{18}F-labelled sulfonylurea derivatives for visualizing and quantifying β-cells concentrations *in vivo* via positron emission tomography (PET).

The current aim of our experimental work is the synthesis of a non-labelled conjugate from the original glibenclamide and glucose which are connected via an alkyl group. According to our intention the sugar group has to decrease rather high lipophilicity of fluoroglibenclamide (lg P = 2) to lower accumulation of the imaging agent in non-aimed organs such as a liver. If this conjugate proves to have a lower lipophilicity than the original glibenclamide, the concept will be transferred to analogous ^{18}F-labelled compounds.

The synthesis of sugar-conjugated glibenclamide is shown in figure 1. After the amino group protection by acetylation the starting material 4-amino-5-chloro-2-methoxybenzoic acid (**1**) is coupled to p-(β-aminoethyl)-benzenesulfonamide with formation of 4-[β-(2-methoxy-4-acetylamino-5-chloro-benzenecarboxamido)ethyl]benzene-sulfonamide (**3**). The resulting compound is reacted with cyclohexyl isocyanate by using CuCl as a catalyst to yield the sulfonylurea (**4**). This step of the synthesis is followed by removing the protection group from the sulfonylurea amino group. Currently we have synthesized N-{4-[β-(2-methoxy-4-amino-5-chloro-benzenecarboxamido)ethyl]-benzenesulfonyl}-N'-cyclohexylurea (**5**) with free amino group. In the future we intend to attach a protected glucose to **5** with aid of a preliminary alkylation of the amino group. The last step of the synthesis is supposed to be a deprotection of the sugar rest.

After completing the synthesis the desired compound (**8**) will be evaluated in insulin-secretion experiments.

[1] Ronner P et al. Diabetes, 42: 1760-72 (1993).
[2] Shiue G.G., Schirrmacher R. et al. J. Labelled Cpd. Radiopharm., 44: 127-139 (2001).
[3] Schirrmacher R., Weber M. et al. J. Labelled Cpd. Radiopharm., (2002, submitted).
[4] Ashcroft S, Ashcroft F. Biochimica et Biophisica Acta, 1175: 45-59 (1992).

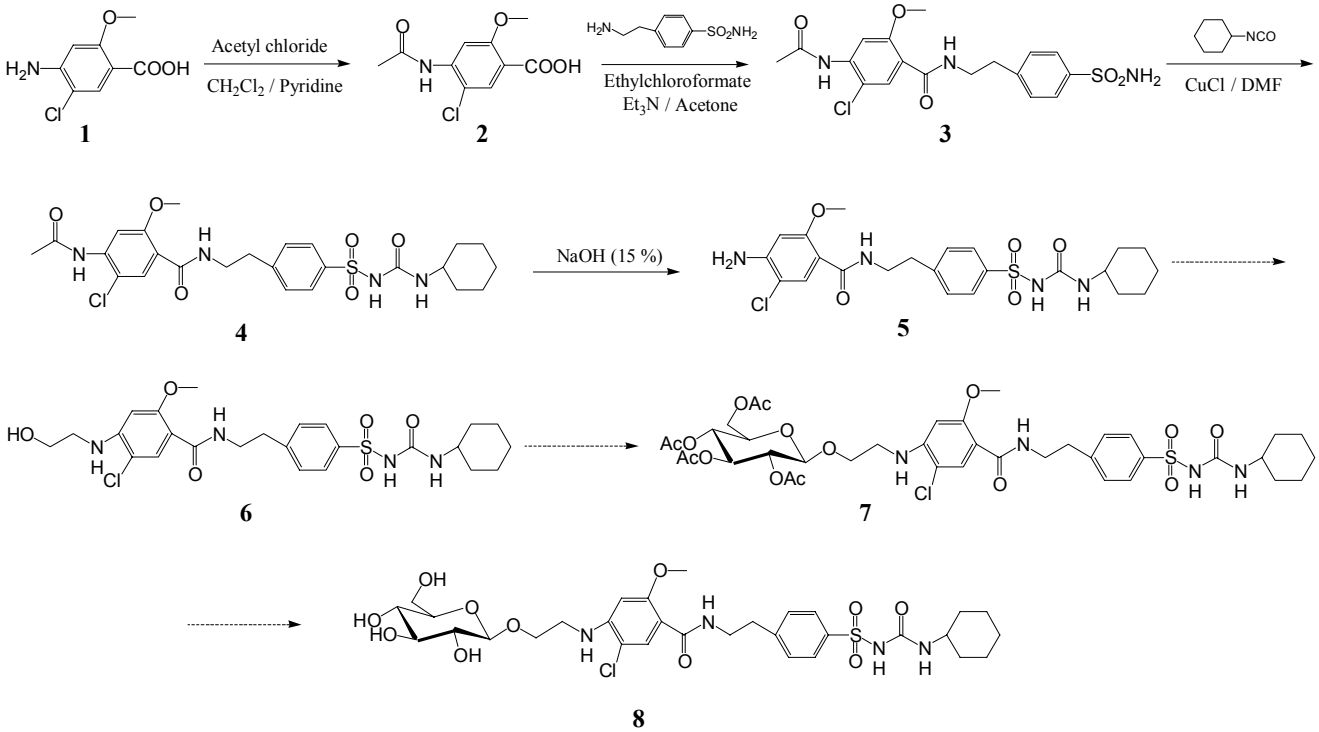

Fig. 1: Synthesis of sugar-conjugated glibenclamide