Syntheses of DO2A-Glibenclamide-Derivatives

M. J. Zimny, C. Burchardt, F. Rösch
Institut für Kernchemie, Johannes Gutenberg-Universität, D-55128 Mainz, Germany

Introduction: Diabetes mellitus is a metabolic disease which affects more than 246 million people worldwide or about 6% of world's population. Two major forms of diabetes are known. Diabetes mellitus type 1 shows an absolute deficit of insulin where as diabetes mellitus type 2 describes a relative lack of insulin.
Type 1 is an immune mediated disease which develops mostly from early childhood on. The insulin producing beta-cells of the pancreas are destroyed. However, until the first symptoms occur and the disease is diagnosed more than 80% of the pancreatic cells are already destroyed. At the moment a lot of effort is put into the field of transplantation of beta-cells to those patents. Due to the fact that a human body possesses only a few thousands of those cells, it is hard to control the success of the operation and to control the survival of these cells. Glibenclamide belongs to the class of sulfonylureas and is used for therapy in diabetes mellitus type 2. Sulfonylureas bind to the SUR-subunit of ATP-sensitive potassium-channels. In this way, they influence the insulin disposal of the beta-cells. Glibenclamide has a high binding-affinity to SUR (K_i<10 nM and K_D = 0,05 to 10 nM). Therefore, glibenclamide is an interesting target for imaging the beta-cell mass using PET (positron emission tomography). Recently, several SUR-targeting molecules have been synthesized, but they all suffered from high lipophilicity.[1,2] By attaching a DO2A-chelator to the glibenclamide-targeting molecule the lipophilicity is supposed to drop and at the same time the molecule allows a labeling with the positron-emitting nuclide Gallium-68.

Experimental: Different glibenclamide derivatives and corresponding DO2A-chelators were synthesized.
The syntheses of the glibenclamide derivatives started from 5-bromo- or 5-chloro-hydroxybenzoic acid, respectively.

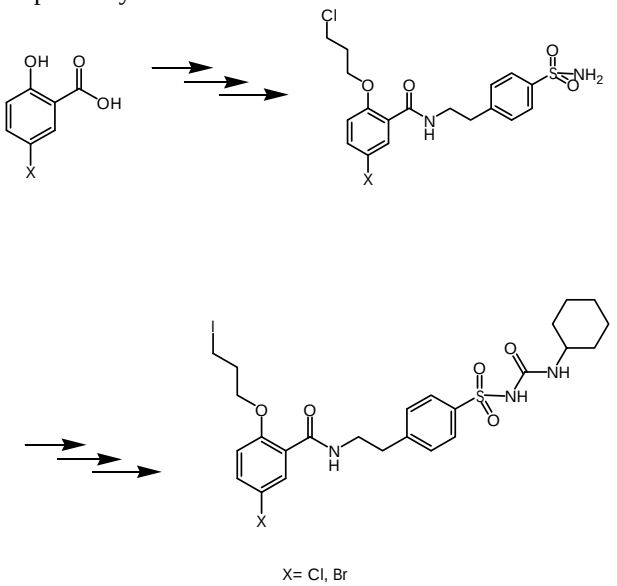

Figure 1. Syntheses of iodopropyl-glibenclamid in 6 steps

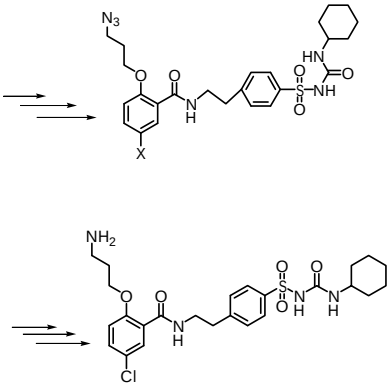

Figure 2. The azid- and aminopropyl derivatives of the glibenclamide

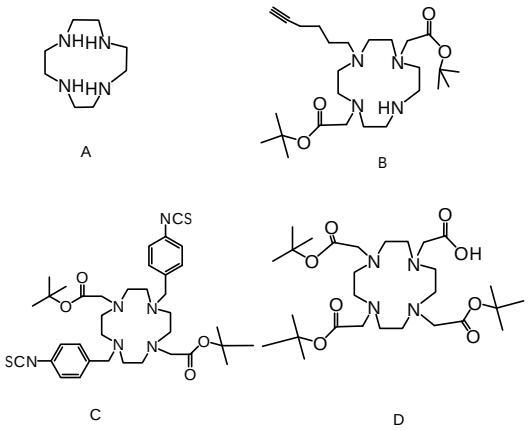

Figure 3. Four different DOTA-chelators for attachment of the glibenclamide derivatives.
A) Cyclen: for iodopropyl-glibenclamide
B) Mono-alkin-Chelator for azid-Glibenclamide
C) DO2A-NCS for aminopropylglibenclamide
D) Tris-DOTA for aminopropylglibenclamide

Results: Different glibenclamide derivatives have been successfully synthesized. Conditions for coupling of these reagents to their appropriate DOTA-chelators will be developed and labeling with Gallium-68 will be performed.

Literatur:
[1] C.-Y. Shiue, A. Schmitz, R. Schirrmacher, G. G. Shiue, A. Alavi, Curr. Med. Chem.– Immun., Endoc. & Metab. Agents, 2004, 4, 271-280
[2] R.Schirrmacher, Dissertation (2004)

Acknowledgment: This work is supported by a PhD scholarship of the Dr. Georg Scheuing Stiftung.