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DO2A-cross-linked sulfonylurea derivatives for the visualisation of the pancreatic β-cell mass in vivo with PET

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Objectives

Diabetes mellitus is a continuously increasing public health problem. A non invasive method for the visualization of the pancreatic β-cell mass would be very helpful for the treatment of diabetes mellitus type 1 patients. For this reason ^{11}C- and ^{18}F-labelled radiotracers of the hypoglycaemic drugs nateglinide, repaglinide and glibenclamide (Fig. 1) have been developed. The major drawback of these compounds was the very high liver uptake, which made the visualization of the β-cell mass impossible. The combination with a macrocyclic chelator affords the labelling with ^{68}Ga and should increase the hydrophilicity and reduce liver uptake.

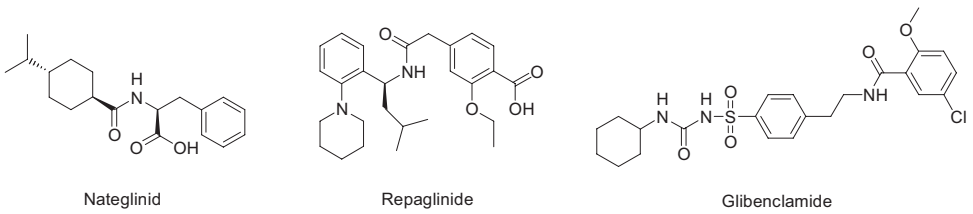

Figure 1: Structural formulas of nateglinid, repaglinide and glibenclamide

Methods

Nateglinide, repaglinide and glibenclamide were modified introducing an iodinated propyl-spacer to attach one or two biomolecules, respectively, to the macrocyclic chelator DO2A. The modified biomolecules and DO2A were synthesized using literature known routes.

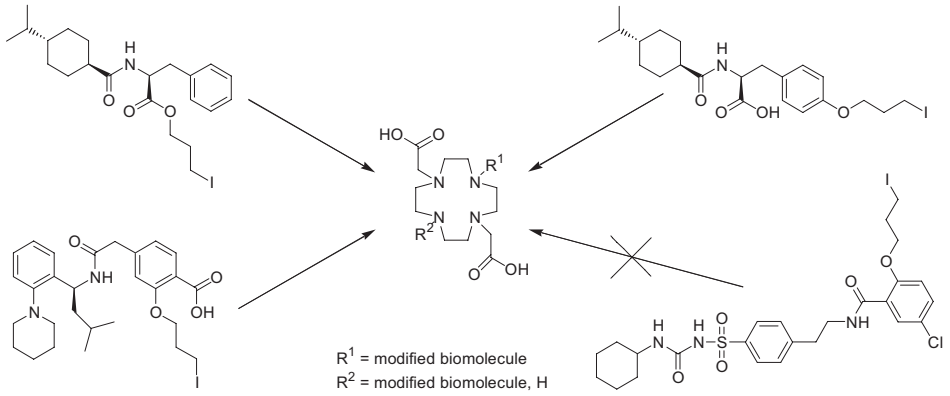

Figure 2: Attachment of the modified nateglinide-, repaglinide- and glibenclamide derivatives to DO2A

Results and conclusion

New nateglinde- and repaglinide-DO2A-conjugates as ^{68}Ga-labelling precursors have been synthesized successfully. With this synthetic strategy is was not possible to attach the modified glibenclamide derivative to DO2A. Systematic ^{68}Ga-labelling and the determination of the SUR1-affinities and the insulin release of the novel derivatives are in progress.