Radiosynthesis of 3-[4-(2-^{18}Fluoro-ethoxy)-phenyl]-2-[(trans-isopropylcyclohexane-carbonyl)-amino]-propionic acid ([^{18}F]nateglinide derivative): a potential pancreatic ß-cell imaging agent with positron Emmission Tomography (PET)

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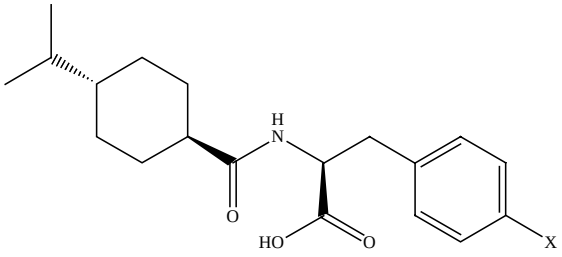
Introduction

Diabetes mellitus comprises a heterogeneous group of disorders characterized by high blood glucose levels. Two major types of diabetes mellitus have been defined: type1 and type 2. Although hyperglycemia is the commen denominator of both types, the etiology and pathophysiology of these syndroms are distinct. Type 1 diabetes 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 in the development of overt hyperglycemia. In type 2 diabetes, 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.
There exists a great medical interest in specific ß-cell imaging agents to quantify and monotoring the β-cell mass in *vivo*.
The aim of this work is to synthesise β-cell-specific positron emitting radiolabeled non-sulfonylurea receptor ligands such as a nateglinide derivative to image the β-cell mass *in vivo* using PET.
Nateglinide belongs to a new chemical class of insulin secretagogues with an insulin release profile which is very different to sulfonylureas like Glyburide.

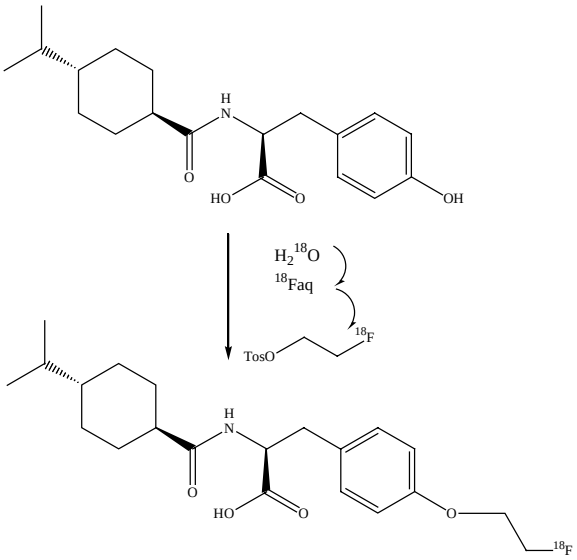


1. X= H Nateglinide
2. X= O-$(CH_2)_2$[^{18}F]F [^{18}F]F Nateglinide
3. X= OH OH Nateglinide

Structure of nateglinide and its derivatives

Results and discussion

The nateglinide analogue was labeled with fluorine-18 for PET studies. The precursor, the OH analogue of nateglinide, was synthesized in multiple steps.
The fluorine-18 labeled compound was synthesized in a two step synthesis by direct nucleophilic substitution of ethylene glycol-1,2-ditosylate with K[^{18}F] / Kryptofix®222 to yield the ^{18}F-fluoroethylating agent 2-[^{18}F]fluoroethyl tosylate, and subsequent reaction with the labeling precursor at 120°C in DMSO. The overall radiochemical yield after HPLC purification was 55% within a total preparation time of 50 min.



Radiosynthesis of [^{18}F]Fluoro-ethoxy- Nateglinide

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