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Design, synthesis, *in vitro, in vivo and in silico* pharmacological characterization of antidiabetic *N*-Boc-L-tyrosine-based compounds☆

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ABSTRACT

In this study, we synthesized five *N*-Boc-L-tyrosine-based analogues to glitazars. The *in vitro* effects of compounds **1–5** on protein tyrosine phosphatase 1B (PTP-1B), peroxisome proliferator-activated receptor alpha and gamma (PPARα/γ), glucose transporter type-4 (GLUT-4) and fatty acid transport protein-1 (FATP-1) activation are reported in this paper. Compounds **1** and **3** were the most active in the *in vitro* PTP-1B inhibition assay, showing IC_{50}s of approximately 44 μM. Treatment of adipocytes with compound **1** increased the mRNA expression of PPARγ and GLUT-4 by 8- and 3-fold, respectively. Moreover, both compounds (**1** and **3**) also increased the relative mRNA expression of PPARα (by 8-fold) and FATP-1 (by 15-fold). Molecular docking studies were performed in order to elucidate the polypharmacological binding mode of the most active compounds on these targets. Finally, a murine model of hyperglycemia was used to evaluate the *in vivo* effectiveness of compounds **1** and **3**. We found that both compounds are orally active using an exploratory dose of 100 mg/kg, decreasing the blood glucose concentration in an oral glucose tolerance test and a non-insulin-dependent diabetes mellitus murine model. In conclusion, we demonstrated that both molecules showed strong *in vitro* and *in vivo* effects and can be considered polypharmacological antidiabetic candidates.

1. Introduction

Type 2 diabetes mellitus (T2DM), a chronic metabolic disease, affects the quality of life of individuals worldwide and is characterized by increased blood glucose concentrations (> 120 mg/dL or > 7 mM) caused by a deficiency in insulin production by the pancreas or by the inactivation of some proteins involved in the insulin signaling pathway (insulin resistance) [1,2]. In addition, it is well known that diabetic patients often show high plasma triglyceride concentrations [3,4] which leads to the development atherosclerotic vascular disease, increasing worldwide mortality [5,6]. Currently, experimental T2DM drug discovery is focused on compounds with insulin-sensitizing activity that acts *via* several mechanisms. Some of them are mediated by peroxisome-proliferator activated receptors, which include 3 different subtypes of nuclear receptors: PPARα, PPARγ, and PPARδ [7]. Every isoform controls tissue-specific target proteins that act as lipid sensors. The activation of PPARα reduces triglycerides by increasing fatty acid transport protein-1 (FATP-1) which is expressed in some insulin-sensitive tissues and increases the cellular uptake of long chain fatty acids [8], showing beneficial, preventative effects on cardiovascular risks [9]. Furthermore, PPARγ activation in muscle and adipose tissue causes insulin sensitization by increasing glucose transporter type 4 (GLUT4) expression, which is one of the proteins involved in the insulin signaling pathway [10,11]. Indeed, it has been widely demonstrated that increased translocation and activation of GLUT-4 is essential for increased glucose uptake and improved glucose homeostasis in murine models

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