3rd Brazil-France Symposium on Medicinal Chemistry
Maceió/AL | November 12 -14, 2024

# DESIGN, SYNTHESIS, COMPUTATIONAL STUDY AND BIOLOGICAL EVALUATION OF POTENTIAL DPP-4 INHIBITORS

**Mirela I. Sairre (Prof),[1]* Camila S. Oliveira (PG),[1] Simone Q. Pantaleão (Res),[1] Heberth de Paula (Prof),[2] Raquel A. Santos,[3] Ana L. Scott (Prof),[1] Kathia M. Honorio (Prof).[1, 4]***

mirela.sairre@ufabc.edu.br

*[1] Center for Sciences Natural and Human, Federal University of ABC, 09210-170, Santo Andre, SP, Brazil; [2] Center for Exact, Natural and Health Sciences, Federal University of Espírito Santo, 29075-910, Vitoria, ES, Brazil; [3] Laboratory of Genetics and Molecular Biology, University of Franca, 14404-600, Franca, SP, Brazil; [4] School of Arts, Sciences and Humanities, University of S~ao Paulo, 03828-0000, S~ao Paulo, SP, Brazil.*

*Keywords: Diabetes, Dipeptidyl peptidase-IV, Synthesis, Inhibitor*

## ABSTRACT

Background: Diabetes is a metabolic disorder that presents hyperglycemia and vascular complications due to the lack of insulin production or its inadequate use by the body. Dipeptidyl peptidase-4 (DPP-4) is an important biological target related to the treatment of type II diabetes, since DPP-4 inhibitors can lead to an increase in insulin levels and prolonged activity of glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), being effective in glycemic control.[1] From molecular modeling methods, which allow verifying the main contributions of fragments to biological activity, it was possible to obtain a model with structural information and then design new ligands for DPP-4. 1,4-Dihydropyridines (1,4-DHPs) are an important class of organic compounds in medicinal chemistry and are associated with a wide variety of therapeutic effects. 1,4-DHPs can be prepared by the Hantzsch multicomponent reaction (MCR), which involves the condensation of ketoester, aldehyde, and ammonia.

Objectives: This study aims to design and synthesize a series of dihydropyridine compounds to act as DPP-4 ligands, as well as to evaluate their enzymatic activity and toxicity from *in silico* and *in vivo* assays.

Methods: 1,4-DHPs were synthesized according to a new methodology using niobium compounds as catalysts. $^{1}H$ and $^{13}C$ NMR spectra for compound characterization were recorded on a Varian equipamento (500 MHz) using deuterated chloroform as solvent. DPP-4 enzymatic activity was evaluated by luminescent enzyme assay. Human DPP-4 activity was measured using the Promega DPPIV-Glo™ Protease Assay. Among the in silico studies, the physicochemical properties related to the oral bioavailability of the compounds were calculated using SwissADME.

Results and discussion: Based on the computational model, dihydropyridine structural scaffold was proposed as a new DPP-4 ligand. A series of compounds has been prepared via the Hantzsch MCR. The reactions were carried out using ethyl acetoacetate, an aromatic aldehyde, ammonium acetate or enaminonitrile, niobium catalyst and ethanol. Different niobium catalysts (hydrate niobium pentoxide-NBO, hydrate niobium phosphate-NBP, and ammonium niobium oxalate-ANO) were tested. 1,4-DHPs were prepared in a 3-hour reflux reaction with yields ranging from 3-65%. The variation in yield is related to the difficulty of purifying the compounds. Synthetic 1,4-DHPs were subjected to enzymatic inhibition assays, and two compounds showed promising inhibition percentages. However, compared to the reference drug (sitagliptin), a significant difference was observed. The comparison between experimental and predicted values suggests that the model was not suitable for predicting inhibitory potency. Figure 1 represents the synthesis of the ligands and the enzymatic activity results.

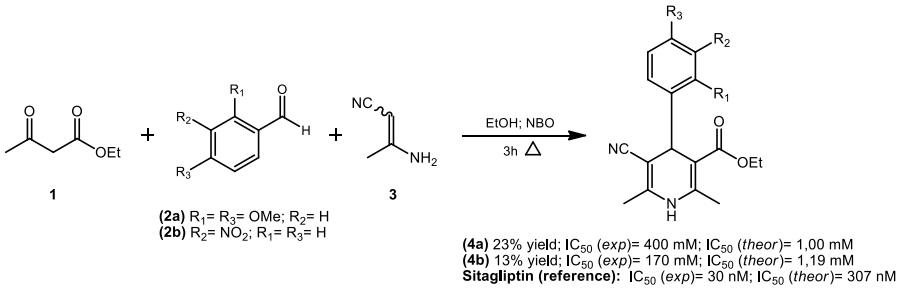


**Figure 1.** Synthesis and enzymatic inhibition

Conclusion: The results suggest that the ligands require structural modifications to achieve suitable activity profiles, but *in silico* and *in vitro* studies may lead to the discovery of a potential DPP-4 inhibitor.

Reference: Pantaleão, S. Q. *et al*. *Biochimie* **2022**, *194*, 43-50.