Mechanism of action of a series of 1,2,3-triazole glyconjugates with hypoglycemic activity: biochemical and docking studies on alpha-glucosidase

Sodero, A.C.R.[1]; Ferreira, S.B.[2,4]; Lima, E.S.[3]; Kaiser, C.R.[4]; Ferreira, V.F.[2]; Silva-Jr, F.P.[1]

[1]Laboratório de Bioquímica de Proteínas e Peptídeos, IOC-FIOCRUZ; [2]Depto. Química Orgânica, Universidade Federal Fluminense; [3]Depto. de Análises Clínicas e Toxicológicas, Universidade Federal do Amazonas; [4]LABRMN, Depto. Química Orgânica, Universidade Federal do Rio de Janeiro.

Type II diabetes mellitus (T2D) is characterized by elevated blood glucose levels or hyperglycaemia, and results from failure of pancreatic β-cells to secrete sufficient insulin to overcome insulin resistance (mainly in liver, adipose and skeletal muscle). Anti-diabetic agents seek to reduce hyperglycaemia and, thus, diminish the elevated risk of micro- and macro-vascular disease in T2D patients. Previously, a series 4-substituted-1,2,3-triazoles conjugated with sugars like D-xylose, D-galactose, D-allose and D-ribose was synthesized and screened for hypoglycemic activity in a mouse model. Methyl-2,3-O-isopropylidene-beta-D-ribofuranoside derivatives were among the most active compounds. A class of drugs in use for treating T2D, typed by the oligosaccharide acarbose, act by inhibiting the alpha-glucosidase activity present in pancreatic secretions and in the brush border of small intestines. Some glycosyl triazoles have been demonstrated as alpha-glucosidase inhibitors, an activity that has been associated with the ability of these compounds to mimic the charge buildup and/or the conformational distortion of the transition state thought to develop in the enzymatic glycosidic bond cleavage. In order to rationalize our previous results and elucidate the mechanism of action of the 1,2,3-triazole glycoconjugates we investigated their interaction with yeast alpha-glucosidase (MAL12) through enzymatic assays and computational docking studies. Activity was measured spectrophometrically by the release of 4-nitrophenol from the 4-nitrophenyl-a-D-glucopiranoside substrate. The 4-(1-cyclohexenyl)-1,2,3-triazole derivative showed 25-fold higher potency as a MAL12 inhibitor as compared to acarbose, with an IC50 of 3.8±0.5 µM. The molecular docking of the inhibitors was carried out in the Molegro v3.0 software using a homology model of MAL12 as the receptor. The binding mode of the most potent alpha-glucosidase inhibitors was characterized by a strong hydrogen bond between the nitrogen atom of the triazole moiety and the Thr207 (carbonyl oxygen) and Glu268 (carboxylate oxygen) residues.

Palavras Chaves: drug design, enzymatic inhibitors, molecular modeling.
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