Targeting ? -(1,4)-glucosidase in diabetes mellitus type 2: The role of new synthetic coumarins as potent inhibitors

Figueroa-Benavides C.

Matos M.J.

Peñaloza-Amion M.

Veas R.

Valenzuela-Barra G.

Zapata G.

Delogu G.

Uriarte E.

Santana L.

Olea-Azar C.

Delporte C.

Diabetes mellitus type 2 (DMT2) is a metabolic disease characterized by a chronic increase in glycemia that promotes several long-term complications and high mortality. Some enzymes involved in glycaemic control, such as ? -(1,4)-glucosidase, have now been established as novel pharmacological targets. Coumarins have shown benefits in attenuating signs and complications of DMT2, including inhibition of this enzyme. In this work, new synthetic coumarins (bearing different amide and aryl substituents) were studied in vitro as inhibitors of ?-(1,4)-glucosidase. Among them, five molecules proved to be excellent ?-(1,4)-glucosidase inhibitors, being compound 7 (IC 50 = 2.19 μM) about 200 times more potent than acarbose, a drug currently used for the treatment of DMT2. In addition, most of the coumarins presented uncompetitive inhibition for the ?-(1,4)-glucosidase. Molecular docking studies revealed that coumarins bind to the active site of the enzyme in a more external area comparing to the substrate, without interfering with it, and displaying aromatic and hydrophobic interactions, as well as some hydrogen bonds. According to the results, aromatic interactions with two phenylalanine residues, 157 and 177, were the most common among the

studied coumarins. This study is a step forward for the understanding of coumarins as potential anti-diabetic compounds displaying ?-(1,4)-glucosidase inhibition.

Coumarins

Diabetes mellitus

Dmt2

Docking studies

Medicinal chemistry

?-(1,4)-glucosidase inhibition

3 (4 bromothiophen 2 yl) 6 hydroxycoumarin

3 (4 bromothiophen 2 yl) coumarin

4 chloro n (7 hydroxy 4 methoxycoumarin 8 yl)benzamide

acarbose

alpha (1,4) glucosidase

alpha glucosidase

alpha glucosidase inhibitor

antidiabetic agent

coumarin derivative

hydrogen

n (4 hydroxycoumarin 3 yl) 4 methoxybenzamide

n (4 hydroxycoumarin 3 yl)acetamide

n (7 hydroxy 4 methylcoumarin 8 yl) 4 nitrobenzamide

n (7 hydroxy 4 methylcoumarin 8 yl) nicotinamide

n (7 hydroxy 4 methylcoumarin 8 yl)benzamide

phenylalanine

Saccharomyces cerevisiae protein

unclassified drug

coumarin derivative

glucan 1,4 alpha glucosidase

glycosidase inhibitor

Article

chemical interaction

controlled study

drug potency

drug structure

drug synthesis

drug targeting

enzyme active site

enzyme inhibition

hydrogen bond

hydrophobicity

in vitro study

molecular docking

non insulin dependent diabetes mellitus

Saccharomyces cerevisiae

antagonists and inhibitors

chemical structure

chemistry

dose response

enzymology

human

metabolism

non insulin dependent diabetes mellitus

structure activity relation

Coumarins

Diabetes Mellitus, Type 2

Dose-Response Relationship, Drug

Glucan 1,4-alpha-Glucosidase

Glycoside Hydrolase Inhibitors

Humans

Molecular Structure

Structure-Activity Relationship