ELSEVIER

journal homepage: www.elsevier.com/locate/molstr

Pyrazole-linked thiazolidine-4-carboxylic acid derivatives as potent α-amylase inhibitors: Synthesis, bioactivity, and in silico evaluation

Haider A. Omran [a,b], Dawood S. Abid [a], Ahmed A. Majed [a,*], Huda H. Nameh [c], Aamal A. Al-Mutairi [d,*], Sami A. Al-Hussain [d], Magdi E.A. Zaki [d], Sobhi M. Gomha [e], Islam M. Abdellah [f,g], Ahmed A. Elhenawy [h,i]

[a] College of Education for Pure Sciences, Department of Chemistry, Basrah University, Basrah, Iraq
[b] Education Directorate of Basrah, Ministry of Education, Basrah, Iraq
[c] College of Pharmacy, University of Hilla, Babylon, Iraq
[d] Department of Chemistry, Faculty of Science, Imam Mohammad Ibn Saud Islamic University (IMSIU), Riyadh, Saudi Arabia
[e] Chemistry Department, Faculty of Science, Islamic University of Madinah, Madinah 42351, Saudi Arabia
[f] Department of Chemistry, Faculty of Science, Aswan University, Aswan 81528, Egypt
[g] TESCS Department, Wilson College of Textiles, North Carolina State University, Raleigh, NC, 27606, USA
[h] Chemistry Department, Faculty of Science, Al-Baha University, Al-Baha 65731, Saudi Arabia
[i] Chemistry Department, Faculty of Science, Al-Azhar University, Cairo 11884, Egypt

ARTICLE INFO

Keywords:
Synthesis
Pyrazole-linked thiazolidine
DFT
Docking
ADME/Toxicity

ABSTRACT

The management of type 2 diabetes mellitus (T2DM) necessitates the development of novel and effective therapeutic agents. To this end, a new series of pyrazole-linked thiazolidine-4-carboxylic acid derivatives (**HR.TH$_7$–HR.TH$_{11}$**) was designed, synthesized, and evaluated as potential α-amylase inhibitors. The biological evaluation identified **HR.TH$_7$** (R=H) as the most potent inhibitor, exhibiting an IC_{50} value of 15.1 ± 0.97 μg/mL, a potency directly comparable to the standard drug, Acarbose. To rationalize this finding, molecular docking studies were performed, which revealed key binding interactions within the active site of human α-amylase (PDB: 4BAJ) and provided a structural basis for the observed activity. Density Functional Theory (DFT) calculations further supported the structure-activity relationship. Crucially, comprehensive *in silico* ADME/Toxicity predictions confirmed that the lead compounds, particularly **HR.TH$_7$**, possess a favorable pharmacokinetic profile with high gastrointestinal absorption and a low risk of toxicity. Collectively, these results highlight the significance of the pyrazolyl-thiazolidine scaffold and establish **HR.TH$_7$** as a highly promising lead candidate for the development of novel, orally active antidiabetic agents.

1. Introduction

Diabetes mellitus is currently one of the most prevalent non-communicable metabolic disorders in the world and is categorized into two types: Type 1 is insulin-dependent diabetes mellitus (IDDM) and Type 2 is non-insulin-dependent diabetes mellitus (NIDDM) [1,2]. Type 2 is the most prevalent type of diabetes, affecting approximately 200 million people globally, and due to diet and obesity, this number is expected to gradually increase to 642 million people by 2040 [3,4]. Thus, regulating the blood glucose levels of people with diabetes within the normal range is the most complex task that requires tireless research [5]. Exercise, especially walking, dietary regulation and oral glucose-lowering medications such as peroxisome proliferator-activated receptor agonists, sulfonylureas, thiazolidinediones, biguanides and other drugs such as acarbose [6,7] are the most widely adopted methods for the treatment of diabetes. However, these oral medications have been found to have a negative impact in the long and medium term [8,9]. Recently, research has focused on enzyme inhibitors as potential alternatives to these drugs due to their high selectivity and specialized action on enzymes [10]. Alpha-amylase is one of the most prominent therapeutic targets for non-insulin-dependent type 2 diabetes, due to its ability to hydrolyses alpha-1,4-glycosidic linkages in starch leading to

* Corresponding authors at: College of Education for Pure Sciences, Department of Chemistry, Basrah University, Basrah, Iraq.
E-mail addresses: edupg.ahmed.majed@uobasrah.edu.iq (A.A. Majed), islamabdellah2@aswu.edu.eg (A.A. Al-Mutairi), elhenawy.sci@hotmail.com