Journal of the Taiwan Institute of Chemical Engineers 000 (2017) 1–15

Contents lists available at ScienceDirect

Journal of the Taiwan Institute of Chemical Engineers

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

New prospects for the development of selective inhibitors of α-glucosidase based on coumarin-iminothiazolidinone hybrids: Synthesis, *in-vitro* biological screening and molecular docking analysis

Aliya Ibrar[a,*], Sumera Zaib[b], Imtiaz Khan[c,*], Zainab Shafique[b], Aamer Saeed[c], Jamshed Iqbal[b,*]

[a] Department of Chemistry, COMSATS Institute of Information Technology, Abbottabad 22060, Pakistan
[b] Centre for Advanced Drug Research, COMSATS Institute of Information Technology, Abbottabad 22060, Pakistan
[c] Department of Chemistry, Quaid-i-Azam University, Islamabad 45320, Pakistan

ARTICLE INFO

Article history:
Received 21 May 2017
Revised 9 August 2017
Accepted 25 September 2017
Available online xxx

Keywords:
Glucosidase
Thiazolidinone
Heterocycles
Hybridization
Bioactivity
Molecular docking

ABSTRACT

α-Glucosidase inhibitors have extensively been exploited for the effective management of type 2 diabetes and associated complications by significantly reducing the postprandial increase in glucose and plasma insulin levels. In this endeavour, we designed and synthesized a new series of coumarinyl iminothiazolidinone hybrid compounds (**6a–o**) using a one-pot multi-component approach. The hybrid structures were accessed in good chemical yields. The synthesized compounds were tested for their glucosidase inhibitory efficacy using acarbose as a standard inhibitor (IC_{50} = 38.2 ± 0.12 μM). *In-vitro* analysis of the hybrid molecules identified several potential leads for the development of potent glucosidase inhibitors with IC_{50} values in the range of 0.09–0.92 μM with compound **6g** being the most potent drug candidate (IC_{50} = 0.09 ± 0.001 μM). Furthermore, compound **6f** was identified as the lead inhibitor against maltase-glucoamylase with comparable inhibitory efficacy to acarbose with an IC_{50} value of 0.07 ± 0.016 μM. Binding interactions of potent compounds with the key residues in the active site of the glucosidase enzyme were revealed by molecular docking analysis. In summary, these new structural leads based on the hybrid pharmacophores could be developed as potential inhibitors of α-glucosidase for treating postprandial hyperglycemia.

1. Introduction

Diabetes mellitus (DM), a chronic metabolic disease is characterized by high blood sugar levels [1]. The uncontrolled hyperglycemic condition often leads to serious damage to many vital organs in the body including kidneys, heart, and nerves [2,3]. The reduction in blood glucose level and controlling subsequent complications is the key to prevent diabetes mellitus. α-Glucosidase (EC 3.2.1.20), a membrane-bound enzyme from the family of hydrolase enzymes, plays a significant role in the digestion of carbohydrates and glycoprotein processing [4-7]. The inhibition of α-glucosidase can significantly decrease the postprandial hyperglycemia [8], and is thus an attractive therapeutic target for treatment of diabetes [9–11], obesity [12,13] and cancer [14,15]. Several α-glucosidase inhibitors including acarbose, miglitol, and voglibose have been used in clinic for the treatment of diabetes mellitus [16–18]. However, various side effects, such as diarrhea, abdominal and flatulence discomfort [19] invite the scientific community to explore and design new α-glucosidase inhibitors with minimum side effects [20].

Heterocyclic compounds with remarkable ability to act as bioactive pharmacophores has garnered a special attention in the design of biologically active drug candidates in medicinal chemistry arena [21]. Among these heterocycles, five-membered rings incorporating three heteroatoms nitrogen, sulfur and oxygen have proved as privileged structures with broad spectra of biological actions. Thiazolidinone heteroaromatic core is considered as an important moiety with multifaceted profile of diverse pharmacological properties against numerous biological targets [22] contributing greatly to the design of new bioactive molecules [23]. These include anti-HIV [24,25], antiproliferative [26,27], anti-inflammatory [28,29], antimicrobial [30], antitumor [31–33], hypoglycemic [34], anticonvulsant [35], antiviral, anticancer [36] and aldose reductase inhibitory activities [37,38]. Thiazolidinones are also important during the treatment of acute and chronic phases of chigas disease [39]. Fig. 1 summarizes the chemical structures of

* Corresponding authors.
E-mail addresses: aliya@ciit.net.pk (A. Ibrar), ikhanqau@gmail.com (I. Khan), drjamshed@ciit.net.pk (J. Iqbal).

https://doi.org/10.1016/j.jtice.2017.09.041
1876-1070/

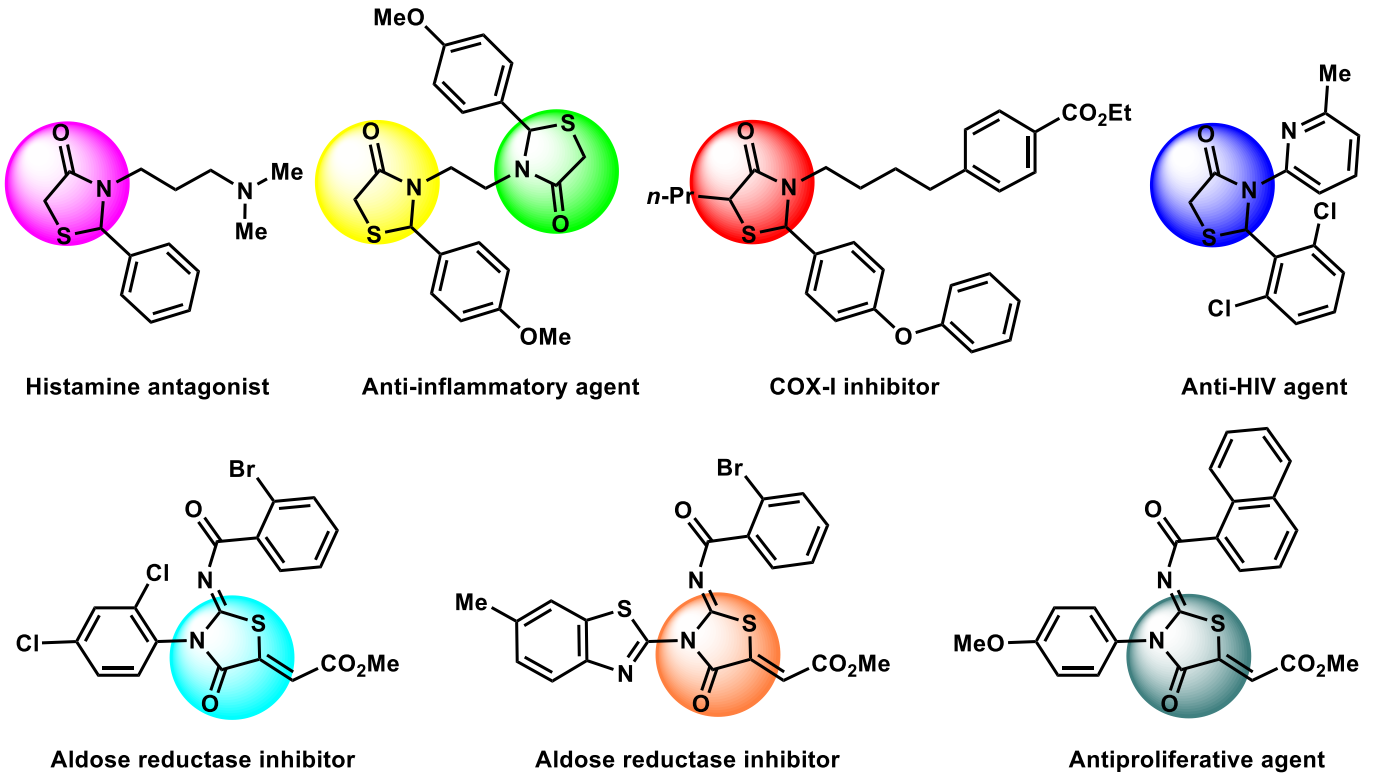

Fig. 1. Representative examples of biologically important thiazolidinone and iminothiazolidinone molecules.

various important thiazolidinone- and iminothiazolidinone-containing compounds with their biological potential.

On the other hand, coumarin compounds are also well known to possess multiple biological functions. These include anti-HIV, antifungal, anti-acetylcholinesterase, antioxidant, antihelmintic, antibacterial, antiviral, antitumor, anticancer, and anticlotting activities, in addition to diverse applications in pharmaceuticals and agrochemicals [40–44]. Recently, the chemical scaffolds incorporating more than one pharmacophores in a single molecule have emerged as lead molecules in the medicinal chemistry research. This pharmacophoric integration approach may help to create new structural entities with improved biological efficacy compared to individual components [45,46].

Coumarin-hybrid compounds have widely been accessed in the literature and found to possess an array of different pharmacological properties. These molecules possess coumarin and other heterocyclic and non-heterocyclic skeletons [47]. We have recently investigated coumarin molecules that are integrated with several other heterocyclic entities with the aim to explore their potent biological function [40,48] (Fig. 2). In view of literature findings and our continued interest in the generation of coumarin-hybrid molecules as potent biological candidates [40,48], we designed and synthesized a new series of coumarinyl iminothiazolidinone hybrids. The synthesized compounds were evaluated for their glucosidase inhibition potential. In addition, molecular docking studies of these compounds have also been carried out to gain further insights into the biological properties.

2. Results and discussion

2.1. Chemistry

The reaction sequence employed for the synthesis of coumarinyl iminothiazolidinones (**6a–o**) is outlined in Scheme 1. Coumarinyl hydrazide (**1**) [48a] was reacted with various aryl isothiocyanates (**2a–o**) [40] in methanol to afford the desired thiosemicarbazides (**3a–o**) [48a] which on subsequent one-pot multi-component reaction involving chloroacetyl chloride (**4**) and 4-flourobenzaldehyde (**5**) under basic conditions delivered coumarinyl iminothiazolidinone products (**6a–o**) in good isolated yields [49]. The structural diversity on this hybrid scaffold was validated by using a range of electron-donating and electron-withdrawing functional groups at the aryl ring attached directly to the thiazolidinone skeleton. The formation of coumarinyl iminothiazolidinone derivatives (**6a–o**) was indicated by IR spectroscopy where distinctive stretching absorptions observed in the range of 3410–3205 and 1629–1601 cm^{-1} were due to N–H and C = N groups, respectively. In ^{1}H NMR spectra, these hybrid compounds showed characteristic signals in the range of 11.48–11.13 ppm, assigned to N–H moiety. ^{13}C NMR spectra also confirmed the presence of C = O functional groups in the range of 172.3–163.2 ppm. The purity of the synthesized products (**6a–o**) was ascertained by elemental analysis.

2.2. Biological activity

2.2.1. Glucosidase isoenzyme inhibition

All the synthesized coumarinyl iminothiazolidinone compounds (**6a–o**) were tested for their glucosidase inhibitory efficacy using acarbose as a standard inhibitor (IC_{50} = 38.2 ± 0.12 μM). *In-vitro* analysis of the hybrid molecules identified several potential leads for the development of potent glucosidase inhibitors. The results of this study are summarized in Table 1. The IC_{50} values of the active derivatives were found in the range of 0.09–0.92 μM. In particular, compound **6g** displayed the highest inhibitory potential (IC_{50} = 0.09 ± 0.001 μM). The identified potent analogue was bestowed with a strong electron-donating methoxy group at the *ortho*-position of the aryl ring attached directly to the thiazolidinone moiety. An inspection of the structure of the hybrid compounds highlights the electronic and steric (in certain cases)

Please cite this article as: A. Ibrar et al., New prospects for the development of selective inhibitors of α-glucosidase based on coumarin-iminothiazolidinone hybrids: Synthesis, *in-vitro* biological screening and molecular docking analysis, Journal of the Taiwan Institute of Chemical Engineers (2017), https://doi.org/10.1016/j.jtice.2017.09.041