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Synthesis of novel poly-hydroxyl functionalized acridine derivatives as inhibitors of α-Glucosidase and α-Amylase

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ABSTRACT

In this study a novel series of poly-hydroxyl functionalized acridine derivatives (**L_1**–**L_9**) was synthesized and their inhibitory activities against α-Glucosidase (α-Gls) and α-Amylase (α-Amy) were evaluated, spectroscopically. The synthetic compounds consist of three different substructures, including a 4-(4-aminophenoxy) phenyl group (R_3), an acridine moiety (R_2) and a poly-hydroxy chain (R_1). The results indicate that among the synthetic compounds, **L_5** with a chromeno[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine moiety demonstrates the highest inhibitory activity against both yeast and rat α-Gls enzymes. Also, **L_2** with the thioxo-pyrido[2,3-*d*:6,5-*d*′] dipyrimidine moiety plays an important role in the inhibition of yeast α-Gls. In addition, the results may suggest a significant role for the nature of sugar moiety of the synthetic compounds in their inhibitory action against α-Gls. Moreover, in comparison with Acarbose, which is a widely used *anti*-diabetic drug, these compounds show negligible inhibitory activity against pancreatic α-Amy, which is important in the term of their reduced susceptibility for possible development of the intestinal disturbance side effects. Results of this study may suggest these synthetic compounds as novel molecular templates for construction of potentially *anti*-diabetic drugs with the ability for more convenient management of postprandial hyperglycemia.

1. Introduction

Diabetes mellitus is the most common global endocrine disease and its incidence is growing at an alarming rate.[1] This progressive metabolic disorder is characterized by the chronic elevation of serum glucose level, which ultimately leads to micro- and macro-vascular changes, causing damages in several tissues including retina, kidney, nerves and blood vessels.[2] The prolonged elevation of blood glucose in diabetic patients accelerates the rate of non-enzymatic reaction between sugar and long-lived proteins, which subsequently results in formation of protein-bound advanced glycation end products (AGEs).[3] Moreover, chronic hyperglycemia in diabetes mellitus results in the excessive flux of glucose into sorbitol-aldose reductase (SAR) pathway, leading to production and accumulation of intracellular sorbitol in kidney, lens, retina and nerves, which eventually cause the cellular damages.[4] Both of these abnormal metabolic processes have been reported to contribute in the pathological events, leading to development of various diabetic secondary complications.[5] Therefore, the inhibition of aldose reductase, which is the first enzyme in SAR pathway and pharmacological inhibition of AGE formation or disruption of pre-existed AGE-protein cross-links provide significant potential therapeutic approaches towards reducing the severity of diabetes associated complications.[6] However, the incidence of secondary complications in type-II diabetes is known to tightly correlate with postprandial hyperglycemia, which is an indicator of the total glycemic uptake.[7] Therefore, the inhibition of intestinal absorption of sugar, which is not interfering with their metabolism can help to control postprandial hyperglycemia in a non-invasive manner.[8,9] As shown in Fig. 1, the digestion of starch mostly occurs in the lumen of mammalian small intestine by α-Amylase (α-Amy) to yield both linear maltose and branched oligosaccharides such as isomaltose.

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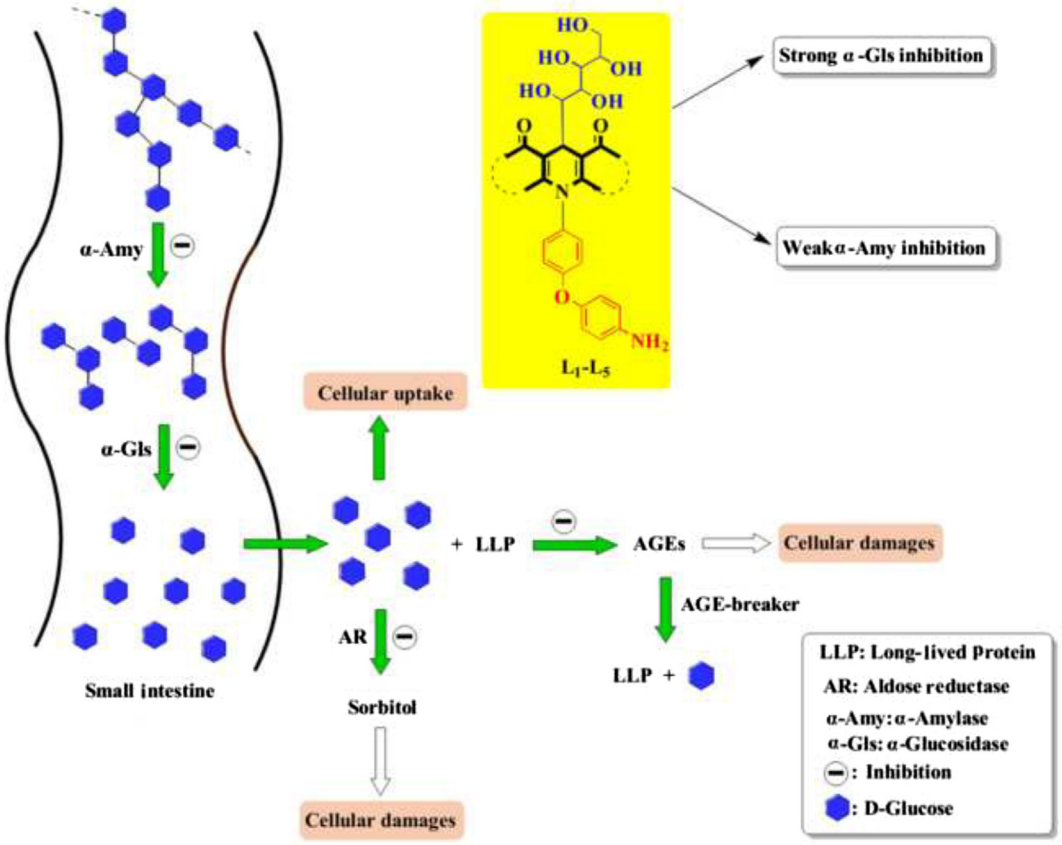

Fig. 1. Schematic representation of major available inhibition sites for reducing the post prandial hyperglycemia and its complications in diabetic patients. Also, the general structure of the synthetic compounds is shown. As indicated, they demonstrate strong and weak inhibitory actions against α-Gls and α-Amy, respectively.

Further digestion of carbohydrates by α-Glucosidase (α-Gls) (EC 3.2.1.20), which is existed in the epithelial mucosa of small intestine releases the absorbable monosaccharides.[10] Therefore, the inhibition of α-Gls is an effective approach in both preventing and treating diabetes through improvement of postprandial hyperglycaemia.[11–13]

The commercial inhibitors of α-Gls (i.e., acarbose, voglibose, miglitol) are currently in use for the treatment of diabetes mellitus. The application of these *anti*-diabetic drugs is associated with the substantial adverse gastrointestinal side effects due to their non-specific inhibition of α-Amy, causing excessive accumulation of undigested carbohydrates in the large intestine.[14–16] Therefore, it is necessary to develop more tolerable α-Gls inhibitors with no or less unfavorable side effects. In this regard, it is desirable to search for compounds with moderate α-Amy inhibitory properties, displaying potent α-Gls inhibition. In this study, the research objective was to synthesis novel poly-hydroxy functionalized acridine (PHFA) derivatives and to assess their inhibitory properties against both α-Gls and α-Amy. The findings in this study may offer strong foundation to develop new and more specific α-Gls inhibitors with potentially therapeutic values for reducing the severity of those secondary complications, which are normally associated with type-II diabetes mellitus.

2. Material and methods

2.1. Materials

Yeast α-Gls (EC.3.2.1.20), porcine pancreatic α-Amy (EC 3.2.1.1) and *para*-nitrophenyl-α-D-Glucopyranoside (pNPG) were purchased from Sigma Aldrich (Gillingham, Dorset, UK) Chemical Company. Other chemicals were purchased from Fluka and Aldrich chemical companies and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance 250 MHz spectrometer in DMSO solution with TMS as an internal standard. Shimadzu GC/MS-QP 1000-EX apparatus; in *m*/*z* (rel%) was used for mass analysis of products. FTIR spectroscopy (Shimadzu FTIR 8300 spectrophotometer) was employed for the compound characterization. Melting points were determined in open capillary tubes in a Barnstead Electrothermal 9100 BZ, circulating oil melting point apparatus. The reaction monitoring was accomplished by TLC on silica gel PolyGram SILG/UV254 plates.

2.2. Methods

2.2.1. General procedure for the synthesis of compounds L_1–L_9

A mixture of sugar (1.0 mmol), diketone (2.0 mmol for identical diketones and 1 mmol for different diketones) 4,4′-oxydianiline (1.0 mmol), and PTSA (0.05 g, 30 mol %) in EtOH (5 mL) was stirred at 50 °C for 12 h. After cooling down to room temperature of the reaction mixture, the precipitate was filtered and washed with ethanol (15 mL) to afford the pure product.

2.2.2. Spectral data for the synthesized compounds

*2.2.2.1. 10-(4-(4-Aminophenoxy)phenyl)-5-((1S,2R,3R,4R)-1,2,3,4,5-pentahydroxypentyl)-5,10-dihydropyrido[2,3-d:6,5-d′]dipyrimidine-2,4,6,8(1H,3H,7H,9H)-tetraone (**L1**).* Yield: 82% (0.48 g); brown solid, mp 139–141 °C. ^{1}H NMR (250 MHz, DMSO-d_6/TMS): 3.27–3.43 (m, 6H), 3.56–3.64 (m, 4H), 3.86 (s, 1H, CH), 4.16 (s, 1H,