Review article

A comprehensive review on xanthone derivatives as α-glucosidase inhibitors

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ABSTRACT

α-Glucosidase plays an important role in carbohydrate metabolism and is therefore an attractive therapeutic target for the treatment of diabetes, obesity and other related complications. In the last two decades, considerable interest has been given to natural and synthetic xanthone derivatives in this field of research. Herein, a comprehensive review of the literature on xanthones as inhibitors of α-glucosidase activity, their mechanism of action, experimental procedures and structure-activity relationships have been reviewed for more than 280 analogs. With this overview we intend to motivate and challenge researchers (e.g. chemistry, biology, pharmaceutical and medicinal areas) for the design of novel xanthones as multipotent drugs and exploit the properties of this class of compounds in the management of diabetic complications.

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1. Introduction

9H-Xanthene-9-ones, or simply xanthones, are oxygen-containing heterocyclic compounds known as secondary metabolites of some families of higher plants (especially those of the Guttiferae, Gentianacea, Moraceae, Clusiaceae and Polygonaceae families), and in a few families of fungi, lichens and bacteria [1–3]. Parent xanthone itself (Fig. 1) has not been found as a natural product. However, in 2002, Oldenburg et al. described the occurrence of this compound in crude oils extracted from offshore Norway, possibly formed by oxidation of xanthenes in the reservoir or originated by geochemistry from aromatic precursors [4]. The chemical profile of xanthone nucleus can be highly variable (from...
The anti-diabetic activity of xanthones has also been discussed, but the pancreatic occurrence by a combination of one or more factors that include eight adipose tissue. An alteration in normal glucose homeostasis may endogenous glucose production, primarily in the liver, muscle and decrease their activity. Maintenance of glucose homeostasis is achieved by the hormonal regulation of glucose uptake and decrease hyperglycemia, the brain recognizes it and sends a message glucose levels as part of energy metabolism. Whenever there is Insulin is a pancreatic hormone responsible for regulating blood occurring from de

dabetes. With the evolution of the disease, pancreas can also decrease the body cannot properly use insulin, decreasing the ability to

Fig. 1. Chemical structure and numbering system of the xanthone skeleton.

R¹ to R₈ (Fig. 1), containing hydroxyl, methoxyl, prenyl or glycosyl as simple substituents or appearing as complex units, such as dimers, polycyclic or xanthonolignoid structures [13,5]. In order to compare the description of the compounds along this manuscript, the positions of the substituents from 1 to 8 will be maintained in the xanthone nucleus for all molecules, even in the absence of substituents in some positions of the main skeleton. For more complex structures, the numbering of the substituents will proceed chronologically.

Along the years, several reviews have been focused on the biological properties of xanthone derivatives, namely in the antimicrobial [6–8], anticancer [6-9], anti-inflammatory [6–8], antimarial [6,8,10] and antioxidant activities [6–8,11]. Recently, the anti-diabetic activity of xanthones has also been discussed, but the data remains sparse and/or inconveniently discussed [6,8,11].

Diabetes is a chronic metabolic disorder caused by abnormal carbohydrate metabolism with a consequent hyperglycemia status, occurring from deficiencies in insulin secretion, action, or both. Insulin is a pancreatic hormone responsible for regulating blood glucose levels as part of energy metabolism. Whenever there is hyperglycemia, the brain recognizes it and sends a message through nerve impulses to pancreas and other organs in order to decrease their activity. Maintenance of glucose homeostasis is achieved by the hormonal regulation of glucose uptake and endogenous glucose production, primarily in the liver, muscle and adipose tissue. An alteration in normal glucose homeostasis may occur by a combination of one or more factors that include eight pathophysiological mechanisms: (i) reduced insulin secretion from pancreatic β-cells, (ii) elevated glucagon secretion from pancreatic α-cells, (iii) increased production of glucose in liver, (iv) neurotransmitter dysfunction and insulin resistance in the brain, (v) enhanced lipolysis, (vi) increased renal glucose reabsorption, (vii) reduced incretin effect in the small intestine, and (viii) impaired or diminished glucose uptake in peripheral tissues such as skeletal muscle, adipose tissues and liver, resulting in hyperglycemic condition [12]. This postprandial hyperglycemia can cause severe damage, dysfunction and failure of multiple organs and tissues, with progressive metabolic complications such as neuropathy, retinopathy, nephropathy and cardiovascular diseases [15].

There are three main types of diabetes. Type 1 diabetes, also known as insulin-dependent, is a chronic, autoimmune process that occurs when the immune system attacks the insulin-producing pancreatic β-cells, inducing a loss of ability to produce insulin or a decrease in its production. Type 2 diabetes occurs when the body cannot properly use insulin, decreasing the ability to regulate glucose metabolism, in a mechanism called insulin resistance. With the evolution of the disease, pancreas can also decrease the insulin production - insulin deficiency - leading to hyperglycemia and other related complications. Gestational diabetes, which occurs during the pregnancy, develops when pregnancy hormones block the action of insulin and represent a great risk of morbidity and mortality to mother, fetus and subsequent neonate. Type 2 diabetes is the most common form of diabetes, comprising 80%–90% of all the cases [13–16].

Diabetes is certainly one of the major public health problems, approaching epidemic proportions globally. The remission or cure of diabetes is not yet straightforward, and, until now, there are no effective treatment to modulate this disease. In that sense, several pharmacological approaches have been used to control diabetes. The first line of action include intensive lifestyle modifications combined with oral medication for the treatment of obesity, glycemic control, stimulation of insulin secretion and insulin sensitizers, or the administration of injectable modified insulins [17]. The classes of oral medications currently approved for the treatment of hyperglycemia in type 2 diabetes include a series of biguanides, sulfonylureas, meglitinide, thiazolidinedione (TZD), α-glucosidase inhibitors, dipeptidyl peptidase 4 (DPP-4) inhibitors and sodium-glucose cotransporter (SGLT2) inhibitors [12,18]. Despite the variety of the available drugs, the response and efficacy of the therapy is overly-dependent on the patients [12], inciting several research groups all around the world in the pursuit of novel and broad-spectrum antidiabetic agents. To fulfill this goal, over the years, a great number of heterocyclic compounds, from natural or synthetic origin have been studied, some of them with promising inhibitory effects against one of the main targets of diabetes treatment, the enzyme α-glucosidase [19–23]. In this perspective and due to our undergoing interest in the chemistry of xanthones [24–26], in this comprehensive review, we will provide a systematic survey about the inhibitory profile of a series of natural and synthetic xanthone derivatives against α-glucosidase, establishing, whenever possible, structure-activity relationships. Besides that, it is also our propose to organize and provide useful information about the natural occurrence and isolation of the natural compounds and the currently used methodologies for the evaluation of α-glucosidase inhibitory activity.

1.1. Characterization of human α-glucosidases and their mechanism of action

Starch is the main energy source in human diet. This polysaccharide is synthesized in green plants and it is a mixture of two polymers: amylose (≈ 25%) and amylopectin (≈ 75%), in different amounts and with different characteristics, depending on the botanical origin. Amylose is a linear chain polymer of α-D-glucopyranosyl residues, linked by α-1,4 glycosidic bonds, while amylopectin is a branched glucan of α-D-glucopyranosyl units linked by α-1,4 glycosidic bonds, but with occasional α-1,6-glycosidic bonds, which are responsible for the branching [27,28].

The digestion process of starchy foods to free glucose is called dietary glycogenesis and involves six enzymes, including two α-amylases (salivary and pancreatic) and four mucosal α-glucosidases [N-terminal subunits of maltase-glucosamylase (NtMgAM) and sucrase-isomaltase (NtSI), in the in the domain closest to the membrane anchor; and C-terminal (CtMgAM and CtSI) in the luminal domain], anchored to the brush-border epithelial cells of the small intestine (Fig. 2) [29,30].

The starch digesting enzymes α-amylase, SI and MGAM belong to the class of enzymes known as glycoside hydrolases (GH). This class of enzymes cleave the glycosidic bond between two carbohydrate molecules, commonly found in natural polymers, 10⁴ times faster than the uncatalyzed reaction, making GHs some of the most proficient enzymes. Salivary and pancreatic α-amylases belong to the GH3 family whereas SI and MGAM belong to the GH31 family.

Initially, salivary and pancreatic α-amylases (EC 3.2.1.1) hydrolyze internal α-1,4 glycosidic bonds of amylose, but bypasses the oligosaccharides such as maltose (two glucose molecules) and maltriose (three glucose molecules), while from the hydrolysis of amylopectin, results a range of branched oligosaccharides (which are a mixture of branched glucans and small linear glucans), due to the non-cleavage of α-1,6 bonds or their adjacent α-1,4 glycosidic
bonds. The resultant glucans can be eventually hydrolyzed to glucose in the lumen by the action of both MGAM (EC 3.2.1.20 and 3.2.1.3) and SI (EC 3.2.148 and 3.2.10).

MGAM comprises about 2% of brush-border membrane proteins, being less abundant than SI [31]. However, CtMGAM is the subunit with the highest activity among the above mentioned enzymes [32]. Additionally, in contrast to SI that only exist in intestine, MGAM is also found in kidney, being absent in colon [31]. Unlike SI, whose domains are proteolytically cleaved and can be isolated and assayed separately, MGAM exists as a single polypeptide chain.

SI is expressed in the intestinal brush border and it is responsible for almost all sucrase activity and about 60–80% of maltase activity [33]. This enzyme is mostly localized in the small intestine, although low levels of SI can be found in the colon in early development [34]. SI is a type II membrane glycoprotein which is N-glycosylated in endoplasmic reticulum and then transported to the Golgi apparatus, where it is N- and O-glycosylated [33]. After glycosylation, the enzyme is transported and inserted into the apical membrane of enterocytes as a single, large polypeptide chain and processed by extracellular pancreatic proteases to generate free CtSI and membrane-bound NtSI subunits [35].

Both enzymes (MGAM and SI) can cleave the main α-1,4 glycosidic linkage of glucans, while the CtMGAM and NtSI have additional minor activities on α-1,6 glycosidic branch linkage (Fig. 2). It is important to refer that NtMGAM and NtSI have maximum activity against maltose, while CtMGAM and CtSI prefer glucans up to four glucose residues, through a mechanism that retains the configuration at the anomeric center. In addition, sucrase active site can split sucrase into glucose and fructose [36,37]. Lin et al. reported that mucosal α-glucosidases may also digest starch (granules and gelatinized molecules) directly to free glucose and act with α-amylases at the initial stage of the digestion process [36]. The similarity in the amino acid sequence of SI and MGAM complexes and of their catalytic subunits are around 59% and 40–60%, respectively, and it has been proposed that the shared domain structures arose from duplication and divergence of an ancestral gene, which itself had already undergone tandem gene duplication [27].

Taking into account this knowledge, the inhibition of both α-amylase and α-glucosidase shall delay glucose absorption into the blood, suppressing postprandial hyperglycemia, being these enzymes excellent targets for the treatment of type 2 diabetes.

Currently, four α-glucosidase inhibitors are therapeutically used: acarbose, miglitol, voglibose and emiglitate. Among these, acarbose, the first α-glucosidase inhibitor, introduced into the market in the 1990s, is by far the most prescribed drug. Acarbose, miglitol and voglibose have been the most studied inhibitors, and among them, acarbose originated the best outcomes [38]. However, it is well documented that the use of these inhibitors are associated with serious side-effects such as flatulence, abdominal pain, and diarrhea. These unwanted effects has encouraged researchers

Fig. 2. Schematic diagram of the human digestion process by the digestive enzymes.
towards the discovery of newer and safer second generation of agents [39]. Being aware that none of the commercially available α-glucosidase inhibitors are xanthone-type compounds, the increased number of publications using xanthones in the selected therapeutic target for the management of diabetes complications led us to infer about the importance of this scaffold in this medicinal area.

2. Methodologies used to evaluate the inhibitory effect of xanthones against α-glucosidase activity

The most common assays to evaluate the in vitro inhibitory effect of xanthones against α-glucosidase activity are based on colorimetric enzyme-inhibitor screenings. Currently, the most used method determined spectrophotometrically (400–405 nm) the activity of a yeast culture of Saccharomyces cerevisiae, using as substrate the p-nitrophenyl glucopyranoside (PNPG) and the inhibitors prepared in DMSO or in mixtures with water or phosphate buffer (Table 1). The simplest protocols involve a direct incubation of the three reactants (enzyme, inhibitor and substrate) at 37 °C during 15–30 min and the absorbance is monitored during that period of time [40–44]. Nevertheless, a pre-incubation period of the enzyme and the inhibitors, before the addition of the substrate is also frequently performed, during 5 min [45], 10 min [46,47], 15 min [48–54] and 30 min [55–61]. In these cases, incubations prior the addition of substrate occur also at 37 °C in periods of 5–60 min. Nguyen and coworkers proposed an alternative protocol with a pre-incubation at 28 °C for a period of 10 min, followed by the addition of the substrate to start the reaction and an incubation of the reactional mixture for an additional 30–35 min [62,63]. Another important detail is the use, in some cases, of a basic solution (sodium carbonate 0.1–1 M or sodium hydroxide 2 M) in variable amounts, to stop the reaction, which is especially important for end point absorbance reads. In all the cases, the α-glucosidase activity was determined by measuring the yellow-colored p-nitrophenol (PNP) released from PNPG at 400–405 nm, using a microplate photometer.

A single example of using rat intestinal α-glucosidase was reported by Phoboo et al. [64]. Briefly, a pre-incubation of the inhibitors under study with the enzyme in phosphate buffer, occurs at 25 °C during 10 min. After that, PNPG was added and the reaction mixture was incubated for more 5 min. Before and after incubation, absorbance readings were recorded at 405 nm using a microplate reader (Table 1).

Ichiki et al. published in 2007 an α-glucosidase inhibitory assay using a commercially available enzyme isolated from rice. The protocol is quite different to those previously described, starting with a pre-incubation of the enzyme (1.4 μg/mL) with the tested inhibitors in 2-morpholinoethanesulfonic acid (MES) buffer pH 6.3, at 25 °C, for 15 min. Then, the reaction was initiated by addition of 2 mM PNPG followed by incubation at 70 °C for 90 min and stopped by the addition of 1 M sodium carbonate. The release of PNP was measured spectrophotometrically at 405 nm (Table 1) [65].

The unique report studying the inhibitory effects of a xanthone on α-glucosidase activity, having sucrose as substrate, was published by Li et al. in 2004 [66]. This protocol includes a pre-incubation of the enzyme with the samples, in DMSO, for a period of 5 min. Then, 37 mM of sucrose was added and incubated at 37 °C, for 30 min. The reaction was stopped by heating the reaction mixture at 90–100 °C for 10 min. The formation of glucose was determined using a kit (purchased commercially) for glucose determination [66]. In another study, Ryu et al. also monitored α-glucosidase inhibitory activity using maltose as substrate. In this protocol, the yeast enzyme was incubated in phosphate buffer with maltose and tested inhibitors for 30 min. The absorbance was measured at 540 nm during the 30 min of incubation [44].

The α-glucosidase inhibitory activity was expressed as % inhibition and calculated as follows (Eq. (1)):

\[
\% \text{Inhibition} = \frac{\text{Abs}_{\text{control}} - \text{Abs}_{\text{sample}}}{\text{Abs}_{\text{control}}} \times 100.
\]

where the control represents the assay in which the sample is replaced by the solvent used in its preparation.

In some cases, the IC50 value, defined as the concentration of the sample that inhibits 50% the α-glucosidase activity, was calculated from the dose-inhibition curves.

The use of fluorimetric assays for the determination of α-glucosidase activity inhibition by xanthones was reported only in a couple of papers. Bosman et al. started this protocol by the preparation of an enzyme mixture in phosphate buffer, after an ultrasonic treatment of rat intestinal acetone powder α-glucosidase [67]. The enzyme mixture was diluted to a concentration that provide a fluorescence (FL) of 50,000 arbitrary units (λex 360 nm; λem 460 nm) on release of 4-methylumbelliferone from the substrate, 7-O-α-D-glucopyranosyl-4-methylumbelliferone, after 20 min. A pre-incubation of the enzyme with the tested inhibitors, at 37 °C, was performed during 15 min. Then, the fluorescence was monitored over 30 min after the addition of 1.2 mM of the substrate. The net fluorescence (Net FL) was calculated as the difference between the fluorescence at 30 min and the fluorescence at 0 min. The enzyme activity (%) was calculated by the following equation (Eq. (2)) [67]:

\[
\% \text{Enzyme activity} = \frac{\text{Net FL}_{\text{sample}} - \text{Net FL}_{\text{control}}}{\text{Net FL}_{\text{control}}} \times 100.
\]

Another fluorimetric assay was published by Ryu et al. where the α-glucosidase activity in B16F10 melanoma cells was accessed. B16F10 cell lysates were incubated with the inhibitors under study and the substrate 7-O-α-D-glucopyranosyl-4-methylumbelliferone, in sodium acetate buffer at 37 °C, during 48 h. The reaction was stopped by the addition of 0.4 M of glycine buffer and the fluorescence read immediately (λex 363 nm; λem 444 nm) [68].

Unfortunately, the nature of the enzyme, the concentrations of enzyme and substrate, the times of pre-incubations varies among the authors being difficult to reproduce the assay and even to analyze and/or compare the published data [69–74]. In that sense, we tried our best to systematize the available information about the experimental conditions used in the assays of the inhibitory effect of xanthones against α-glucosidase activity (Table 1).

3. Xanthone derivatives as α-glucosidase inhibitors

To the best of our knowledge, reports on xanthones as inhibitors of α-glucosidase activity have appeared only in the beginning of the 21st century. Since then, several studies addressing the inhibitory properties of a variety of analogs have appeared, highlighting the pharmacological importance of this class of compounds. Thus, we will provide a comprehensive survey on the α-glucosidase inhibitory activity by a series of pure xanthones isolated from natural sources (excluding the effects of the extracts themselves), as well as, by a range of synthetic analogs prepared for this propose, comprising more than 280 derivatives.

Mangiferin, a C-glycosyl xanthone (2-C-β-D-glucopyranosyl-1,3,6,7-tetrahydroxy-9H-xanthen-9-one), is the most abundant natural glycosylated xanthone and widely reported in the literature for their biological activities [75–77]. Several groups dedicate their research to study the inhibitory activity of mangiferin (both from natural or synthetic origin) against α-glucosidases from different
Table 1
Spectrophotometric methodologies used to evaluate the in vitro inhibitory effect of xanthones against α-glucosidase activity.

| Source          | Enzyme            | Samples                          | Pre-incubation* | PNGP   | Incubation | Stop reaction | Absorbance | Ref. |
|-----------------|-------------------|---------------------------------|------------------|--------|------------|---------------|------------|------|
|                 |                   |                                  | Amount (µL) Conc. | Solvent | Temp. (°C) | Time (min) | Amount (µL) Conc. | Temp. (°C) | Time (min) | λ (nm) | Read |
| yeast           | 250 U/mL          | Yeast                            | 250              | 37     | 3          | 15            | Na₂CO₃ 0.1 M | 605 | End point |
| yeast           | 0.1 U/mL          | Yeast                            | 20               | 0.1    | 1          | 37            | Na₂CO₃ 0.2 M | 605 | End point |
| yeast           | 0.2 U/mL          | Yeast                            | 10               | 0.2    | 25         | 37            | Na₂CO₃ 0.1 M | 605 | End point |
| yeast           | 20 U/mL           | Yeast                            | 25               | 20     | 5          | 37            | Na₂CO₃ 0.2 M | 605 | End point |
| yeast           | 0.35 U/mL         | Yeast                            | 50               | 0.35   | 100        | 20            | Na₂CO₃ 1 M | 405 | End point |
| yeast           | 0.6 U/mL          | Yeast                            | 120              | 0.6    | 37         | 20            | Na₂CO₃ 0.2 M | 405 | End point |
| yeast           | 0.2 U/mL          | Yeast                            | 20               | 0.2    | 37         | 20            | Na₂CO₃ 0.2 M | 405 | End point |
| yeast           | 0.4 U/mL          | Yeast                            | 20               | 0.4    | 37         | 20            | Na₂CO₃ 0.2 M | 405 | End point |
| yeast           | 0.1 U/mL          | Yeast                            | 50               | 0.1    | 100        | 20            | Na₂CO₃ 1 M | 405 | End point |
| yeast           | 0.05 U/mL         | Yeast                            | 8                | 0.05   | 20         | 10            | Na₂CO₃ 0.1 M | 405 | End point |
| yeast           | 0.05 U/mL         | Yeast                            | 10               | 0.05   | 20         | 10            | Na₂CO₃ 0.2 M | 405 | End point |
| yeast           | 0.05 U/mL         | Yeast                            | 10               | 0.05   | 20         | 10            | Na₂CO₃ 0.2 M | 405 | End point |
| yeast           | 0.2 U/mL          | Yeast                            | 20               | 0.2    | 37         | 15            | Na₂CO₃ 0.2 M | 405 | End point |
| yeast           | 0.4 U/mL          | Yeast                            | 20               | 0.4    | 37         | 15            | Na₂CO₃ 0.2 M | 405 | End point |
| yeast           | 0.1 U/mL          | Yeast                            | 10               | 0.1    | 37         | 5             | Na₂CO₃ 0.2 M | 405 | End point |
| yeast           | 0.2 U/mL          | Yeast                            | 10               | 0.2    | 37         | 5             | Na₂CO₃ 0.2 M | 405 | End point |

*In pre-incubation period, enzyme and inhibitors are incubated together, before substrate is added.

- No indication about the parameter is given in the reference.
Table 2
Inhibitory effect of mangiferin 2 on α-glucosidases activity.

| Compound source             | Enzyme source          | Inhibitory effect          | Positive control          | Ref. |
|-----------------------------|------------------------|----------------------------|----------------------------|------|
| Roots of Salacia reticulata| sucrase (from rat)     | IC₅₀ = 87 μg/mL           | (data not shown)          | [78] |
|                             | isomaltase (from rat)  | IC₅₀ = 216 μg/mL          | (data not shown)          |      |
|                             | maltase (from rat)     | 42% ± 100 μg/mL          | (data not shown)          |      |
| Roots of Salacia oblonga    | α-glucosidase (yeast-derived) | IC₅₀ = 22.7 μg/mL   | acarbose (IC₅₀ = 53.9 μg/mL) | [39,66] |
| Rhizoma of Anemarrhena asphodeloides | α-glucosidase (from rice) | IC₅₀ = 96.1 μg/mL | acarbose (IC₅₀ = 2.39 μg/mL) | [64] |
| Leaves of Aquilaria sinensis| α-glucosidase (no source indication) | IC₅₀ = 126.5 ± 17.8 μg/mL (299.7 μM) | acarbose (IC₅₀ = 372.0 ± 37.8 μg/mL (576.2 μM) | [69] |
|                            |                       |                            |                            |      |
| Whole plant of iris lycyi and rhizomes of iris unguicularis | α-glucosidase (no source indication) | IC₅₀ = 0.478 ± 0.001 mM | acarbose (IC₅₀ = 1.52 ± 0.004 mM) | [70,79] |
| Whole plant of Swertia kouitchens | α-glucosidase (from Saccharomyces) | IC₅₀ = 296 ± 52 μM | acarbose (IC₅₀ = 627 ± 28 μM) | [48] |
| Whole plant of Swertia mussotii | α-glucosidase (maltase) | IC₅₀ = 13 ± 0.2 μM | acarbose (IC₅₀ = 39.6 ± 0.1 μM) | [71] |
|                            | α-glucosidase (maltase) | IC₅₀ = 13.3 ± 0.1 μM | acarbose (IC₅₀ = 39.8 ± 0.1 μM) | [72] |
|                            | α-glucosidase (mammalian source) | 53% ± 100 μM | acarbose (50% ± 100 μM) | [67] |
| Leaves and stems of Cyclopia genistoides | α-glucosidase (from Saccharomyces) | NA | 1-deoxynojirimycin (79.6% ± 100 μM) | [80] |
| From synthesis              | β-glucosidase (from almonds) | NA | 1-deoxynojirimycin (81.2% ± 100 μM) | [64] |
| From synthesis              | α-glucosidase (from rat intestine) | IC₅₀ = 52171.37 μM | acarbose (IC₅₀ = 18242.3 μM) | [64] |
| From synthesis              | α-glucosidase (no source indication) | IC₅₀ = 85.35 ± 6.39 μg/mL | acarbose (IC₅₀ = 900 μg/mL) | [73] |

* Percentage of inhibition at the highest tested concentration (in superscript).
* In this work, mangiferin 7-O-β-D-glucopyranoside 3 was also isolated and presented an IC₅₀ = 158 μg/mL.
* In this work, isomangiferin (4-C-β-D-glucopyranosyl-1,3,6,7-tetrahydroxy-9H-xanthen-9-one) 4 was also isolated and presented 50% inhibition for 100 μM concentration.
* In this work, isomangiferin 4 was also isolated and presented and IC₅₀ = 76.98 ± 5.18 μg/mL.

Fig. 3. Chemical structure of mangiferin 7-O-β-D-glucopyranoside 3 and isomangiferin 4.

The inhibitory effects of mangiferin 2 against α-glucosidase has been reported since 2001 [78] (Table 2). This xanthone has been isolated in variable amounts and using different extraction techniques from different parts of plants, belonging to families as Celastraceae (Salacia species), Asparagaceae (Anemarrhena species), Thymelaeaceae (Aquilaria species), Iridaceae (Iris species), Gentianaceae (Swertia species), Fabaceae (Cyclopia species), most of them traditionally used for the prevention and treatment of diabetes and obesity. It is not an easy task to make a comparison of results, since the source of the enzyme differ among the studies (yeast [39,48,66], rice [64] or mammalian origin [67,78]), and in some cases, the source of the enzyme is omitted [69–72] or the effect of a positive control is not presented [78]. Nevertheless, in general, the effect of natural mangiferin 2 is higher than the positive control, acarbose. Exceptions are the effects of mangiferin 2 and mangiferin 7-O-β-D-glucopyranoside 3 isolated from rhizoma of Anemarrhena asphodeloides, on the inhibition of α-glucosidase from rice, showing IC₅₀ values of 96.1 μg/mL and 158 μg/mL, respectively, higher than the IC₅₀ of acarbose (IC₅₀ = 2.39 μg/mL) [64]. Interestingly, studies using mangiferin 2 from a synthetic origin, showed no activity in the inhibition of α-glucosidase activity, obtained from yeast [80] and rat intestine [64] or against β-glucosidase isolated from almonds (Table 2) [80]. However, Nian et al. found lower IC₅₀ values for mangiferin 2 and isomangiferin 4 (Fig. 3) (85.35 ± 6.39 μg/mL and 76.98 ± 5.18 μg/mL, respectively) than the positive control acarbose (IC₅₀ = 900 μg/mL) against an α-glucosidase from an unknown source (Table 2) [73].

A series of other xanthones have been isolated from the Gentianaceae family, mainly from plants of the genus Swertia (S. kouitchensis [48], S. corymbosa [74], S. mussotii Franch [71,72,81] and S. bimaculata [52]). Three main types of substituents can be found in their structures, being hydroxyl, methoxyl and glycosyl the most frequent ones, alone or in combination. Most of the isolated compounds 5–64 exhibited moderate to strong α-glucosidase inhibitory properties, as depicted in Table 3. The effect of the positive control, when reported, is listed in the end of each species presented in Table 3. Li et al. published in 2017, a review, which elegantly summarized the chemical constituents and pharmacological activities of Swertia plants, which includes some data on xanthones and their α-glucosidase inhibition [82].

As shown in Table 3, among the compounds isolated from S. kouitchensis 5–24, xanthones 6, 8, 10, 15 and 16 were the most active ones, with IC₅₀ values of 383 ± 18, 360 ± 39, 371 ± 22, 184 ± 23, 126 ± 23 and 451 ± 41 μM, respectively (acarbose, IC₅₀ = 627 ± 28 μM). The presence of a hydroxyl group located at C-1 or C-8 (compounds 10 and 15) seems to be important for the high inhibitory activity against α-glucosidase, while the steric hindrance produced by the diglucoside residue at position C-7 (compounds 13, 20, 22 and 23) lowered the inhibitory activity [48]. Meanwhile, a series of five hydroxylated xanthones were isolated from S. corymbosa, 25–29, and none of them presented a better inhibitory activity (IC₅₀ ranging from 23.2 ± 1.5 to 44.5 ± 1.1 μM) when compared with the positive control, acarbose (IC₅₀ = 15.2 ± 0.6 μM).
Table 3
Inhibitory effect of isolated xanthones 5–64 from the whole plant *Swertia kouitchensis* [48], aerial parts of *Swertia corymbosa* [74], whole parts of *Swertia mussotii* Franch [71,72], overground parts of *Swertia mussotii* Franch [81] and whole parts of *Swertia bimaculata* [52] on α-glucosidase activity.

### Swertia kouitchensis

| Comp. | R₁ | R₂ | R₃ | R₄ | R₅ | IC₅₀ (μM) | Ref. |
|-------|----|----|----|----|----|----------|-----|
| 5     | O-glc (6-1)-xyl | OMe | OMe | H | OH | OMe | 1503 ± 119 [48] |
| 6     | O-glc (6-1)-xyl | OMe | OMe | H | OMe | OMe | 383 ± 18 [48] |
| 7     | O-glc | OMe | OH | H | OH | OMe | 701 ± 51 [48] |
| 8     | O-glc (6-1)-xyl | OMe | OMe | H | OMe | OMe | 360 ± 39 [48] |
| 9     | O-glc (6-1)-xyl | OMe | H | OMe | OMe | OMe | 371 ± 22 [48] |
| 10    | OH | O-glc (6-1)-xyl | OMe | OMe | H | OH | 184 ± 23 [48] |
| 11    | O-glc (6-1)-glic | OMe | H | OMe | H | H | 956 ± 35 [48] |
| 12    | O-glc (6-1)-glic | OMe | H | OMe | H | OH | 693 ± 47 [48] |
| 13    | OH | OMe | H | H | O-glc (2-1)-rha | OH | > 1717 [48] |
| 14    | OH | OMe | H | H | O-glc (2-1)-rha | OH | 714 ± 55 [48] |
| 15    | OH | OMe | H | OH | OMe | OH | 126 ± 23 [48] |
| 16    | O-glc (6-1)-xyl | OMe | H | OMe | H | OH | 451 ± 41 [48] |
| 17    | O-glc (6-1)-xyl | OMe | H | OMe | H | H | 776 ± 46 [48] |
| 18    | O-glc (6-1)-xyl | OMe | H | OMe | OMe | OMe | > 1676 [48] |
| 19    | O-glc (6-1)-glic | OMe | H | OMe | OMe | OH | 801 ± 65 [48] |
| 20    | OH | OMe | OMe | H | O-glc (6-1)-xyl | OH | 1642 ± 97 [48] |
| 21    | OH | OH | OH | OH | OH | OH | 634 ± 33 [48] |
| 22    | OH | OMe | OH | OH | OMe | OMe | 44.5 ± 1 [48] |
| 23    | OH | OMe | H | H | O-glc (2-1)-rha | OH | > 1810 [48] |
| 24    | R₁, R², R³ = OH; R⁴ = glic | OH | H | H | OMe | OH | 1508 ± 116 [48] |

### Swertia corymbosa

| Comp. | R₁ | R₂ | R₃ | R₄ | R₅ | IC₅₀ (μM) | Ref. |
|-------|----|----|----|----|----|----------|-----|
| 25    | OH | OH | OH | H | H | 35.2 ± 0.9 [74] |
| 26    | OH | OH | OH | H | OH | 39.0 ± 1.4 [74] |
| 27    | OH | OH | OH | OH | OH | 23.2 ± 1.5 [74] |
| 28    | OH | OMe | OH | OH | OMe | 44.5 ± 1.1 [74] |
| 29    | OH | OMe | allyl | OH | OMe | 26.3 ± 1.7 [74] |

### Swertia mussotii Franch

| Comp. | R₁ | R₂ | R₃ | R₄ | R₅ | IC₅₀ (μM) | Ref. |
|-------|----|----|----|----|----|----------|-----|
| 30    | OH | OH | OH | OH | OH | 75.8 ± 1.3 [71] |
| 31    | OH | OH | OH | OH | OH | 31.1 ± 0.2 [71] |
| 32    | OH | OH | OH | OH | OH | 31.5 ± 0.4 [71] |
| 33    | OH | OH | OH | OH | OH | 140.4 ± 0.8 [71] |
| 34    | OH | OH | OH | OH | OH | 7.09 ± 0.08 [71] |
| 35    | OH | OH | OH | OH | OH | 7.3 ± 0.2 [72] |
| 36    | OH | OH | OH | OH | OH | 3.5 ± 0.5 [72] |
| 37    | OH | OH | OH | OH | OH | 114.8 ± 2.3 [71] |
| 38    | OH | OH | OH | OH | OH | 134.5 ± 3.0 [72] |
| 39    | OH | OH | OH | OH | OH | 115.0 ± 2.4 [71] |
| 40    | OH | OH | OH | OH | OH | 134.5 ± 3.0 [72] |
| 41    | OH | OH | OH | OH | OH | 114.8 ± 2.3 [71] |
| 42    | OH | OH | OH | OH | OH | 134.5 ± 3.0 [72] |
| 43    | OH | OH | OH | OH | OH | 115.0 ± 2.4 [71] |
| 44    | OH | OH | OH | OH | OH | 134.5 ± 3.0 [72] |
| 45    | OH | OH | OH | OH | OH | 114.8 ± 2.3 [71] |
| 46    | OH | OH | OH | OH | OH | 134.5 ± 3.0 [72] |
| 47    | OH | OH | OH | OH | OH | 114.8 ± 2.3 [71] |
| 48    | OH | OH | OH | OH | OH | 134.5 ± 3.0 [72] |

**Positive control: acarbose**
Table 3 (continued)

| Comp. R1  | R2  | R3  | R4  | R5  | R6  | R7  | R8   | IC50 (µM) | Ref. |
|----------|-----|-----|-----|-----|-----|-----|------|---------|------|
| 49       | OH  | H   | OMe | H   | H   | H   | OH   | 71.6 ± 0.4 | [72] |
| 50       | OH  | H   | OH  | H   | H   | H   | OH   | 173 ± 0.1  | [73] |
| 51       | OH  | H   | OH  | H   | H   | H   | OMe  | 18.1 ± 0.2 | [72] |
| 52       | OH  | H   | OMe | OMe | OH  | H   | H    | 31.8 ± 0.1 | [71] |
| 53       | OH  | H   | OMe | OMe | OMe | H   | H    | 31.8 ± 0.1 | [71] |
| 54       | OH  | H   | OMe | H   | OMe | OMe | H    | 18.0 ± 0.1 | [71] |

Positive control: acarbose

Table 3a

| Comp. R1 | R2  | R3  | R4  | R5  | R6  | R7  | R8   | IC50 (µM) | Ref. |
|----------|-----|-----|-----|-----|-----|-----|------|---------|------|
| 15       | OH  | H   | OMe | H   | OH  | H   | O-glc | 389 ± 23 | [52] |
| 21a      | OH  | H   | OH  | H   | OH  | H   | O-glc | 679 ± 58 | [52] |
| 22a      | OH  | H   | OMe | H   | H   | O-xyl (2-1)-rha | OH | 765 ± 54 | [52] |
| 55       | O-glc (6-1)-xyl | OMe | OMe | OMe | OMe | H   | OH   | 442 ± 47 | [52] |
| 56       | OH  | OMe | OMe | OMe | OMe | H   | O-glc (6-1)-xyl | > 1000 | [52] |
| 57       | O-glc (6-1)-xyl | H   | OMe | OMe | OMe | H   | OH   | 142 ± 17 | [52] |
| 58       | OH  | H   | OMe | OMe | OMe | H   | O-glc (6-1)-xyl | 136 ± 14 | [52] |
| 59       | O-glc (6-1)-xyl | H   | OH  | OMe | OMe | H   | OH   | 417 ± 32 | [52] |
| 60       | O-glc (6-1)-glc | H   | OH  | OMe | OMe | H   | OH   | 478 ± 45 | [52] |
| 61       | O-glc (4-1)-glc | H   | OMe | OMe | OMe | H   | OH   | 258 ± 19 | [52] |
| 62       | OH  | H   | O-glc | OMe | H   | OH   | > 1000 | [52] |
| 63       | O-glc | H   | OH  | OMe | OMe | H   | OH   | 578 ± 39 | [52] |
| 64       | OH  | H   | O-glc | H   | OMe | OMe | H    | > 1000 | [52] |

Positive control: acarbose

**Assays performed on an unknown source of S. mussotii Franch.**

*Assays performed on Saccharomyces cerevisiae.

A–C These compounds were isolated from the signed sources, presenting different IC50 values.

D**In another work, xanthone 22 was also tested and presented an IC50 = 36 μM, with acarbose used as positive control (IC50 = 24 μM) [46].

**[74]** Xanthone 27 along with xanthones 13, 21, 22, 24, and 30–54 were also obtained from whole parts of S. mussotii [71]. The inhibitory effect of compound 27, with its origin, S. corymbosa [74] and S. mussotii [71,72], showing different IC50s, IC50 = 23.2 ± 1.5 μM in the first case and 7.09 ± 0.08 or 7.3 ± 0.2 μM, in the second one. Even more, in the first case, this xanthone was less active than acarbose (IC50 = 15.2 ± 0.6 μM), while in the second one, was more active than the positive control (IC50 = 39.6 ± 0.1 μM). Nevertheless, xanthones 41 and 45 were the most active compounds from whole parts of S. mussotii, with IC50 = 5.42 ± 0.07 and 5.3 ± 0.1 or 5.2 ± 0.3 μM, respectively, that were considerably lower than the IC50 obtained for acarbose (IC50 = 39.6 ± 0.1 μM). The authors also disclosed that, generally, glycosylated xanthones (13, 21, 24 and 30–38) are poor inhibitors of α-glucosidase activity, except for compound 22 which presented an IC50 = 31.1 ± 0.2 μM [71]. Xanthones 31 and 32 isolated from overground parts of S. mussotii Franch displayed no activity, in the tested experimental conditions, in the inhibition of α-glucosidase activity [51]. From the 13 xanthones isolated from S. corymbosa, 21, 22, 55–64, compounds 56, 62 and 64 were ineffective inhibitors against α-glucosidase activity, whilst compounds 57, 58 and 61 were the most promising tested derivatives (IC50 = 142 ± 17, 136 ± 14 and 258 ± 19 μM, respectively), considering the effect of the positive control acarbose (IC50 = 426 ± 45 μM) [52]. On further analysis, it was observed that the presence of a methoxyl group located at C-2 (compounds 55 and 56) produced steric hindrance and lowered the inhibitory activity, when compared with the analogs without substitution at C-2 (compounds 57 and 58). In addition, it is possible to observe that the presence of the O-gluc-(4-1)-glc residue at C-1 (xanthone 61) resulted in relatively more effective inhibitory activity than the respective diglycosides 59 and 60 [52].

Plants of the Garcinia species (Clusiaceae family) are known to possess oxygenated and prenylated xanthones. The structures isolated from different parts of eight species (G. mangostana [44], G. nobilis [54], G. cowa [55], G. xanthochymus [62], G. oblongifolia [63], G. fusca [42], G. paucinervis [45] and G. hanburyi [49]) and their inhibitory activity against α-glucosidase are presented in Table 4. Among the 16 xanthones isolated from the fruit case of G. mangostana 65–80 (IC50 ranging from 1.5 ± 0.1 to 63.5 ± 1.7 μM), only compounds 70 (IC50 = 58.5 ± 0.4 μM), 71 (IC50 = 50.5 ± 2.8 μM), 75 (IC50 = 63.5 ± 1.7 μM) and 80 (IC50 = 45.0 ± 0.2 μM) exhibited IC50 values higher than the obtained for the positive control (1-deoxynojirimycin, IC50 = 39.5 ± 0.5 μM) while α-mangostin 65, mangostingone 67, γ-mangostin 69 and smeathxanthone A 74 reached IC50 values lower than 10 μM (Table 4). These results indicate that the presence of free hydroxyl groups in A and B rings of the xanthone core favors the inhibitory activity of the compounds. Moreover, a comparison of prenyl and prenyl hydrate substitution revealed that prenylation displayed more efficacy for α-glucosidase inhibition (see structures on Table 4: α-mangostin 65, IC50 = 5.0 ± 0.1 μM; mangostingone 67, IC50 = 9.8 ± 0.3 μM vs gargicine D 68, IC50 = 29.9 ± 1.8 μM). The same conclusion was driven by the authors when they used maltose as substrate, instead PNPG in the α-glucosidase inhibitory activity assay, although with less potency (Table 5). Similarly, α-mangostin 65, γ-mangostin 69, gartinan 73 and smeathxanthone A 74 were the more active tested compounds, with IC50 values of 53.3, 17.5, 37.7 and 35.3 μM, respectively, when compared with the positive control 1-deoxynojirimycin (IC50 = 68.8 μM) [44]. In addition, kinetic parameters were determined using the Lineweaver–Burk double-reciprocal-plot method. The kinetic
Table 4
Inhibitory effect of isolated xanthones 65–145 from the fruit case Garcinia mangostana [44], stem bark of Garcinia nobilis [54], young fruits and flowers of Garcinia cowa [55], bark of Garcinia xanthochymus [62], twigs of Garcinia oblongifolia [63], roots of G. fusca [42], leaves of G. paucinervis [43] and from the resin of Garcinia hanburyi [49] on *Saccharomyces cerevisiae* *α*-glucosidase activity.

*Garcinia mangostana*

| R² | R³ | R⁴ | R⁵ | R⁶ | IC₅₀ (μM) |
|----|----|----|----|----|-----------|
| 65 | isopropyl | OH | H | CH₃ | 9.6 ± 0.1 μM |
| 66 | isopropyl | OMe | H | CH₃ | 34.2 ± 2.2 μM |
| 67 | isopropyl | OH | OH | OMe | 14.4 ± 0.1 μM |
| 68 | isopropyl | OH | OH | OMe | 58.5 ± 0.1 μM |
| 69 | isopropyl | OH | H | OH | 49.0 ± 2.8 μM |
| 70 | isopropyl | OH | OH | OMe | 21.0 ± 0.8 μM |
| 71 | isopropyl | OH | OH | OMe | 5.0 ± 1.3 μM |
| 72 | isopropyl | OH | OH | CH₂OH | 6.0 ± 1.1 μM |
| 73 | isopropyl | OH | OH | CH₂OH | 63.5 ± 1.7 μM |

Positive control: 1-deoxynojirimycin (IC₅₀ = 39.5 ± 0.5 μM)

*Garcinia nobilis*

| IC₅₀ (μM) |
|-----------|
| 64 | 145 ± 1.3 μM |
| 65 | 354 ± 2.4 μM |
| 66 | 227 ± 0.5 μM |

Positive control: 1-deoxynojirimycin (IC₅₀ = 441 ± 0.01 μM)

*Garcinia cowa*

| IC₅₀ (μM) |
|-----------|
| 67 | 34.0 ± 0.5 μM |
| 68 | 11.7 ± 0.1 μM |
| 69 | 55.3 ± 0.2 μM |

Positive control: acarbose (IC₅₀ = 8.0 ± 1.7 μM)

*Garcinia xanthochymus*

| IC₅₀ (μM) |
|-----------|
| 102 | 34.2 ± 25.2 μM |
| 103 | 36.7 ± 20.0 μM |
| 104 | 139.3 ± 19.3 μM |

Positive control: acarbose (IC₅₀ = 900 ± 30 μM)
NA: no activity was found.

*E*: These compounds were isolated from the signed sources, presenting different IC₅₀ values.
assays showed that all of the tested compounds are mixed-type inhibitors (Table 5) [44]. Xanthone derivative mangosteneone F [79], isolated from the fruit case of *Garcinia mangostana*, was tested for their inhibitory activity against a range of enzymes. Thus, against α-glucosidase activity (from *Saccharomyces cerevisiae*) showed an IC50 = 210 ± 0.8 μM (positive control 1-deoxynojirimycin, IC50 = 39.5 ± 0.5 μM) [44,68] and against β-glucosidase activity (from almond) presented an IC50 = 212 ± 18 μM, being not active to inhibit the action of enzymes such as α-mannosidase (from jack bean), α-galactosidase (from green coffee bean), β-galactosidase (from bovine liver), α-rhamnosidase (from *Penicillium decumbens*) and α-amylase (from porcine pancreas) [68].

From the 7 xanthones isolated from stem bark of *G. nobilis* (Table 4), 73, 74 and 81–85, the derivatives 83 and 85 were inactive, while the remaining 73, 74, 81, 82 and 84 demonstrated higher inhibitory effects than the standard 1-deoxynojirimycin (IC50 = 441 ± 0.01 μM). The xanthones gartanin 73 (IC50 84 ± 0.2 μM) and 8-hydroxycudranxanthone G 84 (IC50 76 ± 4.1 μM) were the most active compounds [34]. Comparing the data obtained for compounds 73 and 74 isolated from *G. mangostana* and *G. nobilis*, we can state that both xanthones are more active than the positive control of each assay (respectively IC50 = 39.5 ± 0.5 and 441 ± 0.01 μM); however, the reported IC50 values were quite different between the authors being, respectively, of 10.8 ± 0.6 and 6.9 ± 1.1 μM for *G. mangostana* [44] and 84 ± 0.2 and 394 ± 2.4 μM for *G. nobilis* [54] (Table 4).

According to Table 4, among the nineteen xanthones identified in young fruits and flowers of *G. cowa* (65, 66, 76 and 86–101), it was only possible to determine the IC50 value of ten derivatives, α-Mangostin 65 (IC50 78 ± 0.5 μM) and β-mangostin 66 (IC50 87 ± 0.3 μM) exhibited the highest α-glucosidase inhibitory activity, similar to the positive control acarbose (IC50 = 8.0 ± 1.7 μM). The other tested compounds were less effective, with IC50 values ranging from 11.7 ± 0.1 to 55.3 ± 0.2 μM [55]. The 12 xanthones 81 and 102–112 isolated from the bark of *G. xanthochymus* exhibited a strong activity in the inhibition of α-glucosidase, except for compounds 81 and 104 which were inactive in this assay. Subelliptenone F 112 was the most active one (IC50 = 4.1 ± 0.3 μM) whilst IC50 values from 27.5 ± 8.6 to 358.0 ± 50.8 μM were observed for the remaining xanthones, values lower than those obtained for the positive control acarbose (IC50 = 900.0 ± 3.0 μM) [62]. The main feature of derivative 112 is the presence of a 1,4,5,6-tetrahydroxylated substitution pattern (possessing a catechol ring system) and a 1,1-dimethyllallyl moiety at C-2. In the absence of the catechol ring system, the activity decreased, as observed in compounds 103 (IC50 = 36.7 ± 0.0 μM), 107 (IC50 = 85.5 ± 12.8 μM) and 105 (IC50 = 142.3 ± 10.8 μM). Moreover, the 1,1-dimethyllallyl side chain located at C-2 in 1,4,5-trihydroxylated xanthone core (107, IC50 = 85.5 ± 12.8 μM) seemed to enhance the inhibitory activity when compared with the 1,4,5-trihydroxyxanthone 109 (IC50 = 358.0 ± 50.8) [62].

With the exception of compound 113, the isolated compounds from twigs of *G. oblongifolia* 101 and 114–122 were good inhibitors of α-glucosidase activity presenting IC50 values ranging from 1.7 ± 0.5 to 70.3 ± 4.6 μM, significantly lower than the IC50 obtained for acarbose, IC50 = 900 ± 3 μM [63]. Another detail is observed for rubraxanthone 101, that showed an IC50 value of 12.4 ± 2.7 μM [63], lower than that previously reported for this compound isolated from *G. cowa* (IC50 = 23.4 ± 0.9 μM) [44].

Nguyen et al. isolated from the roots of *G. fiscus* a series of ten xanthones 65, 97, 118–120 and 123–127 carrying isoprenyl- or geranyl-type side chains attached to a polyoxygenated xanthone core (Table 4) [42]. All compounds inhibited α-glucosidase activity in a more efficient manner (IC50 values varying from 8.3 ± 1.8 to 168.7 ± 1.5 μM) than the positive control acarbose (IC50 = 214.5 ± 2.3 μM). Fuscatanxones 123 was the most active one with an IC50 value of 8.3 ± 1.8 μM followed by α-mangostin 65 (IC50 = 11.4 ± 2.3 μM). The presence of a prenyl group instead of a geranyl side chain located at C-8 played an important role for a strong α-glucosidase inhibitory activity (65, IC50 = 11.4 ± 2.3 μM < 118, IC50 = 20.7 ± 1.5 μM), whilst the presence of a methoxy group at C-6 decreased the activity (65, IC50 = 11.4 ± 2.3 μM < 125, IC50 = 18.2 ± 1.5 μM). Moreover, xanthone 123, with a hydroxy group at C-6 and an isoprenyl side chain at C-5, showed a higher inhibitory effect than xanthone 124, which has a methoxy group located at C-6 and does not possess the C-5 unit (Table 4) [42].

From the 5 xanthones isolated from the leaves of *G. paucinervis* 128–132, none of them exhibited higher inhibition of α-glucosidase activity than the positive control acarbose (IC50 = 2.88 ± 0.85 μM). Compounds 129 and 131 displayed moderate inhibitory activity with IC50 values of 8.90 ± 3.35 and 29.36 ± 0.81 μM, respectively. The remaining derivatives were ineffective, with IC50 > 100 μM (Table 4) [45].
Apart from the highly diverse number of xanthones already described, 13 caged polypropenylated derivatives 133–145 have been isolated from the resin of *G. hanburyi* with a unique 4-oxatricyclo[4.3.1.014]dec-2-one scaffold and tested for their α-glucosidase inhibitory activity (Table 4). Compounds 133–135 and 137–140 showed inhibitory effects with IC50 values varying from 108.75 ± 6.86 to 282.70 ± 11.60 μM whilst compounds 136 and 141–145 presented IC50 > 300 μM (acarbose, IC50 = 386.1 ± 7.3 μM) [49].

Moreover, a recent review highlighted the pharmacological effects of *Garcinia mangostana* and its xanthones in the control and modification of metabolic syndrome and its related disorders such as obesity, hyperglycemia, dyslipidemia, diabetic and inflammatory complications in experimental *in vitro* and *in vivo* studies [83].

Oxygenated and prenylated xanthones are not restricted to the *Garcinia* species. A wide variety of derivatives have been isolated from other natural sources, which inhibitory effects against α-glucosidase activity are depicted in Table 6 [41,43,47,50,51,53]. Eight xanthones 146–153 have been isolated from the roots of *Crataxylum tricuspidata* and among them seven derivatives have IC50 values ranging from 16.2 ± 0.4 to 52.9 ± 2.1 μM (Table 6) [43]. Xanthone 153 was the most active compound (IC50 16.2 ± 0.4 μM) while the derivative 150 was ineffective at the highest tested concentration (100 μM). Generally, these derivatives are moderate inhibitors when compared to the positive controls used in this assay: voglibose (IC50 = 23.4 μM) and 1-deoxyxojirimycin (IC50 = 3.5 μM). The authors also analyzed the inhibitory kinetic profile of compounds 146–149 and 141–153 using Lineweaver–Burk plots, and showed that all xanthones displayed a mixed type inhibition (Table 7). Moreover, increasing the inhibitor concentration, in a plot of the reaction velocity as a function of the substrate concentration, lowered the slope of the resultant line, which pointed out a reversible inhibitor behavior [43].

A series of eleven hydroxylated and methoxylated xanthones 50, 81 and 154–162 has been isolated from the stem of *Securidaca inappendiculata* and showed, apart from xanthone 161, a strong α-glucosidase inhibition with IC50 values ranging from 3.2 to 77.3 μg/mL (acarbose, IC50 = 735 μg/mL) (Table 6) [50]. Corroborating what was already reported [41,56,60], the authors concluded that the presence of more hydroxyl groups attached to the xanthone nucleus is beneficial to the activity (when compared the higher IC50 value of the compound 81 and 158, which possess two hydroxyl groups, with those of the compounds 50 and 156, with three hydroxyl groups). Nine out of the eleven xanthones inhibited α-glucosidase activity in a noncompetitive reversible manner, evidenced by the intersection of the double reciprocal plots seated on the x axis. On the other hand, the derivative 155 seems to be a competitive reversible inhibitor type [50].

From all the xanthone-type compounds 163–170 isolated from the twigs of *Maclura fruticosa*, none of them exhibited inhibitory activity against α-glucosidase, at the tested experimental conditions (Table 6) [47]. Recently, Li et al. isolated from the root barks of *Cratoxylum cochinense* a series of twelve prenyl-type poly-oxygenated xanthones 65, 69, 127 and 171–179 and tested their α-glucosidase inhibitory activity and kinetic profile [24]. Apart from the derivative 179 (IC50 = 72.2 μM), all xanthones were better inhibitors, with IC50 ranging from 1.7 to 30.7 μM, than the positive control deoxynojirimycin (IC50 = 39.5 μM). The most active xanthones were α-mangostin 65 (IC50 = 5.7 μM), γ-mangostin 69 (IC50 = 1.7 μM) and carotaxoxanthone A 171 (IC50 = 4.8 μM), presenting the derivatives 65 and 69 similar inhibitory effects to those reported when the compounds were isolated from *G. mangostana* (respectively, IC50 = 5.0 ± 0.1 and 1.5 ± 0.1 μM) [44]. According to the obtained results, increasing the number of free hydroxyl groups attached to the xanthone nucleus, favours the inhibitory effect (comparing γ-mangostin 69 with four hydroxyl groups with the other tested compounds which possessed three or two hydroxyl groups). The replacement of a hydroxyl by a methoxy group lowered the inhibitory effect (IC50 γ-mangostin 69 < IC50 α-mangostin 65) (Table 6) [41]. The authors also analyzed the inhibitory kinetic profile of all isolated xanthones using Lineweaver–Burk plots, showing all the compounds a mixed type inhibition (Table 7). Moreover, increasing the concentration of the inhibitor in plots of the initial velocity vs substrate concentrations, results in a decrease of the slope of the line, indicating that these compounds were reversible inhibitors [41].

A group of seven xanthone-type compounds 180–186 isolated from the cultures of *Aspergillus versicolor*, a fungal endophyte of *Huperzia serrate* was screened against their ability to inhibit α-glucosidase activity. Thus, derivative 183 showed a higher efficacy (IC50 = 0.26 mM) than the positive control acarbose (IC50 = 0.38 mM), whilst xanthone 184 (IC50 = 2.98 mM) showed a weak inhibition. However, these results should be carefully analyzed due to the absence of errors associated with the IC50 values. The remaining compounds were completely inactive against α-glucosidase activity, in the tested experimental conditions (Table 6) [53]. A single xanthone 187, isolated from deep-sea-derived fungus *Penicillium oxythegenum* SCSIO 41001, showed a potent inhibitory effect against α-glucosidase activity, presenting an IC50 = 0.04 mM, significantly lower than the positive control acarbose (IC50 = 0.28 mM) (Table 6) [51].

Since 2006, a huge library of xanthone derivatives has been designed and synthesized in order to evaluate their α-glucosidase inhibitory activity. Liu et al. prepared thirty xanthones (derivatives 25, 26, 50 and 188–214) possessing hydroxyl substituents, as well as, their acetoxy and alkoxy derivatives (Table 8) [56]. 1,3,7-Trihydroxyxanthone 50 and 1,3,6,8-tetrahydroxyxanthone 26 with IC50 = 14.7 and 171 μM, respectively, were the most active compounds. The parent xanthone 1 was also tested, but showed no inhibitory effect with an IC50 > 200 μM. According to the results, polyhydroxyxanthones 25, 26, 50 and 188–192 showed higher inhibitory activities than the corresponding acetoxy–193–197 and alkoxyxanthones 198–214. Thus, the presence of hydroxyl groups in the xanthone core was crucial for the inhibitory activity and the efficacy is dependent on the number of hydroxyl groups: tetrahydroxyl (xanthone 26) ≈ trihydroxyl (xanthone 50) > dihydroxyl (xanthones 25, 189 and 190) > monohydroxyl (xanthone 188). In addition, the presence of straight alkyoxyl, heterocyclic or hydroxyalkoxyl side chains located at C-3 (compounds 193–214) was not essential for improving the inhibitory activity of xanthones, these compounds being less actives than the positive control, 1-deoxyxojirimycin (IC50 = 26.4 μM) (Table 8) [56].

One year later, the same group prepared six 1,3-dihydroxybenzoxyxanthones 215–220 and the results showed an enhanced inhibitory activity (IC50 values ranging from 5.8 to 39.9 μM), when compared with 1,3-dihydroxyxanthone 25 (IC50 = 160.8 μM, Table 8) and even better than the positive control, 1-deoxyxojirimycin (IC50 = 26.4 μM), except for xanthones 218 (IC50 = 31.3 μM) and 220 (IC50 = 39.9 μM) (Table 9). The authors postulate that, the extended π-conjugated systems of benzoxan-215–220 play an important role to enhance the inhibitory activity, probably through π-stacking interaction with yeast’s glucosidase [57]. Moreover, the inhibitory and binding mechanisms of 1,3-dihydroxyxanthone 25 and 1,3,7-trihydroxyxanthone 50 towards yeast’s α-glucosidase activity were elucidated by experimental and docking studies, which indicate a non-competitive type of inhibition for both xanthones, with loss of α-helix within the secondary structure of α-glucosidase, an important feature for the inhibitory process [58]. Furthermore, a synergistic effect of these two compounds was observed, suggesting that there may exist
Table 6
Inhibitory effect of isolated xanthones 50, 65, 69, 81, 127 and 146–187 from the roots of *Cudrania tricuspidata* [43], stem of *Securidaca inappendiculata* [50], twigs of *Maclura fruticosa* [47], root barks of *Cratoxylum cochinchinense* [41], cultures of *Aspergillus versicolor* [53], deep-sea-derived fungus *Penicillium chrysogenum* SCSIO 41001 [51] on *Saccharomyces cerevisiae* α-glucosidase activity.

| Compound | Structure | IC_{50} (μM) |
|----------|-----------|--------------|
| **Cudrania tricuspidata** | ![Structure](image1) | 1.7 ± 0.5 μM |
| **Securidaca inappendiculata** | ![Structure](image2) | 3.5 ± 0.3 μM |
| **Maclura fruticosa** | ![Structure](image3) | 3.9 ± 0.3 μM |
| **Cratoxylum cochinchinense** | ![Structure](image4) | 3.5 ± 0.3 μM |
| **Aspergillus versicolor** | ![Structure](image5) | 3.5 ± 0.3 μM |

NA: no activity was found. NT: not tested.

### References

1. [1,7-Dihydroxyxanthone 79 was also isolated from the stem bark of *Harungana madagascariensis* presenting no inhibitory effect, at 800 μM, on Saccharomyces sp. α-glucosidase activity (positive controls used in this assay were deoxyxojirimycin (IC_{50} = 425.6 ± 8.14 μM) and acarbose (IC_{50} = 78 ± 28 μM)) [40].]
Table 7
Kinetic profile of isolated xanthones 146–153 from Cudrania tricuspidata [43] and xanthones 65, 69, 127 and 172–179 from Cratoxylum cochinichinense [41] against Saccharomyces cerevisiae α-glucosidase.

| Comp. | Cudrania tricuspidata | Cratoxylum cochinichinense |
|-------|----------------------|---------------------------|
|       | PNGP K<sub>i</sub> (µM) | Type of inhibition | PNGP K<sub>i</sub> (µM) | Type of inhibition |
| 146   | 31.7                 | mixed                    | 65                |                      |
| 147   | 8.9                  | mixed                    | 69                | 1.4                | mixed |
| 148   | 7.4                  | mixed                    | 127               | 9.9                | mixed |
| 149   | 5.8                  | mixed                    | 171               | 4.2                | mixed |
| 150   | NT                   | NT                        | 172               | 13.4               | mixed |
| 151   | 15.7                 | mixed                    | 173               | 19.2               | mixed |
| 152   | 12.4                 | mixed                    | 174               | 25.1               | mixed |
| 153   | 7.0                  | mixed                    | 175               | 17.7               | mixed |
|       |                      |                           | 176               | 27.2               | mixed |
|       |                      |                           | 177               | 8.2                | mixed |
|       |                      |                           | 178               | 13.0               | mixed |
|       |                      |                           | 179               | 33.9               | mixed |

Positive control: 1-deoxynojirimycin

NT: not tested.

Table 8
Inhibitory effect of synthetic xanthones 1, 25, 26, 50 and 188–214 on baker’s yeast α-glucosidase activity [56].

| Comp. | R<sup>1</sup> | R<sup>2</sup> | R<sup>3</sup> | R<sup>4</sup> | R<sup>5</sup> | R<sup>6</sup> | IC<sub>50</sub> (µM) |
|-------|---------------|---------------|---------------|---------------|---------------|---------------|---------------------|
| 1     | H             | H             | H             | H             | H             | H             | > 200               |
| 25    | OH            | OH            | H             | H             | H             | H             | 160.8               |
| 26    | OH            | OH            | OH            | H             | OH            | H             | 17.1                |
| 50    | OH            | OH            | OH            | H             | OH            | H             | 14.7<sup>a</sup>    |
| 188   | OH            | H             | H             | H             | H             | H             | 177.4               |
| 189   | OH            | H             | H             | H             | OH            | H             | 91.5                |
| 190   | OH            | H             | OH            | H             | H             | H             | 131.4               |
| 191   | OH            | OH            | H             | H             | OH            | H             | 81.8                |
| 192   | OH            | OH            | OH            | H             | H             | H             | 41.5                |
| 193   | OAc           | OAc           | H             | H             | H             | H             | 31.9                |
| 194   | OAc           | H             | H             | H             | H             | H             | > 200               |
| 195   | OAc           | H             | OAc           | H             | H             | H             | 138.9               |
| 196   | OAc           | OAc           | H             | OAc           | H             | H             | 46.5                |
| 197   | OAc           | OAc           | OAc           | H             | OAc           | H             | 49.7                |
| 198   | OH            | OMe           | H             | H             | H             | H             | 172.9               |
| 199   | OH            | OEt           | H             | H             | H             | H             | 110.8               |
| 200   | OH            | OBu           | H             | H             | H             | H             | 130.1               |
| 201   | OH            | Propyl        | H             | H             | H             | H             | 120.9               |
| 202   | OH            | Oheptyl       | H             | H             | H             | H             | 113.8               |
| 203   | OH            | Ooctyl        | H             | H             | H             | H             | 123.7               |
| 204   | OH            | Odecayl       | H             | H             | H             | H             | 115.6               |
| 205   | OH            | OBu           | H             | H             | H             | H             | 98.2                |
| 206   | OH            | Oheptyl       | H             | H             | H             | H             | 66.6                |
| 207   | OH            | Ooctyl        | H             | H             | H             | H             | 53.0                |
| 208   | OH            | Oheptyl       | H             | H             | H             | H             | 115.4               |
| 209   | OH            | Ooctyl        | H             | H             | H             | H             | 61.8                |
| 210   | OH            | OH            | H             | H             | H             | H             | > 200               |
| 211   | OH            | OH            | H             | H             | H             | H             | > 200               |
| 212   | OH            | H             | OH            | H             | H             | H             | 63.5                |
| 213   | OH            | H             | OH            | H             | H             | H             | 132.7               |
| 214   | OH            | H             | OH            | H             | H             | H             | > 200               |

Positive control: 1-deoxynojirimycin

<sup>a</sup> In another work, 1,3,7-trihydroxyxanthone 50 presented an IC<sub>50</sub> = 14.7 ± 1.1 µM, with 1-deoxynojirimycin used as positive control (IC<sub>50</sub> = 26.4 µM) [58].
multiple binding sites in the noncompetitive domain of α-glucosidase [58]. A set of nine 1,3-dihydroxylated (benzo)xanthones bearing nitro, amino and other alkylating substituents were prepared from the corresponding 1,3-dihydroxy (benzo)xanthones and tested towards α-glucosidase activity (positive control 1-deoxynojirimycin (IC50 = 26.4 μM, Table 9) [59]). As previously reported, a higher inhibitory effect was observed for the benzoxanthone derivatives (IC50 = 5.9–67.3 μM) when compared with the xanthone derivatives (IC50 values of 102.3–235.2 μM) [59].

In 2009, Raj et al. reported the inhibitory effects against α-glucosidase by a series of alkylated xanthones bearing prenyl substituents 230 and 232, geranyl 231 and 233, farnesyl 234 and solanesyl substituents 235, and the results are depicted in Table 10 [84]. The variation in the chain length did not affect the inhibitory profile against α-glucosidase, varying from 30.9 to 30.9% of inhibition, at the maximum tested concentration, 100 μM. No information was given by the authors about the use of a positive control.

A group of novel xanthone derivatives 236–247, having one or two hydroxynaphthalene moieties at the C-2 and C-4 positions, at the xanthone core, were synthetized and evaluated for their inhibition of α-glucosidase activity (Table 11) [60]. To establish a structure-activity relationship, the authors compared the IC50 values obtained with those of the previously reported parent

| Comp. | R   | % Inhibition | Comp. | R   | % Inhibition |
|-------|-----|--------------|-------|-----|--------------|
| 230   |     | 31.0         | 232   |     | 42.1         |
| 231   |     | 43.1         | 233   |     | 30.9         |
|       |     |              | 234   |     | 66.2         |
|       |     |              | 235   |     | 34.5         |

*Positive control: 1-deoxynojirimycin [26.4].

In another work, compound 215 presented an IC50 value of 9.3 ± 4 μM, with 1-deoxynojirimycin (IC50 = 26.4 μM) as positive control [57].

Table 9
Inhibitory effect of synthetic compounds 215–229 on baker’s yeast α-glucosidase activity [57,59].

Table 10
Inhibitory effect of synthetic xanthones 230–235 on α-glucosidase activity.*b [84].

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* Positive control: data not shown.

b Percentage of inhibition at the highest tested concentration (100 μM).
compounds [56]. Firstly, and according to the results, the inhibitory effect was augmented with the increasing number of free hydroxyl groups. Second, xanthones 236–239 bearing one \( \beta \)-naphthol group presented a higher inhibitory effect than the corresponding parent compounds (Table 8) [respectively 25 (IC\( _{50} \) = 160.8 \( \mu \)M), 192 (IC\( _{50} \) = 41.5 \( \mu \)M), 26 (IC\( _{50} \) = 17.1 \( \mu \)M) and 247 (IC\( _{50} \) > 200 \( \mu \)M)], whereas compounds 240–242 with two \( \beta \)-naphthol moieties exhibited an even higher inhibition. On the other hand, compounds 243–246 bearing one dihydroxynaphthalenyl group, displayed a lower activity, when compared to their corresponding analogs 236–239, which have one naphthol group. Third, compounds 237–242 and 245 (IC\( _{50} \) ranging from 6.2 to 26.5 \( \mu \)M) were more active than the positive control 1-deoxynojirimycin in 245, while the remaining derivatives showed IC\( _{50} \) > 40 \( \mu \)M. In addition, the authors have made inhibitory kinetics studies using Lineweaver–Burk plots, to evaluate the type of yeast’s \( \alpha \)-glucosidase inhibition. 1,3,6,8-Tetrahydroxyxanthone 26, xanthone 238 and xanthone 245 were used as typical examples, and the results suggested that the analyzed compounds were noncompetitive inhibitors. Moreover, the inhibitory constants (K\( _{i} \)) are reflective of the binding affinity of the inhibitor for the enzyme, constituting a useful tool to compare the activity of the compounds. Thus, the experimental K\( _{i} \) were 62.8 \( \mu \)M for compound 26, 29.2 \( \mu \)M for compound 245, respectively, showing that the compound 238 is the xanthone that better inhibits \( \alpha \)-glucosidase activity [60].

Li et al. also prepared a series of 3-acyloxyxanthones 248–263 through esterification of 1,3-dihydroxyxanthone 25 and screened their biological activity toward \( \alpha \)-glucosidase activity [61]. From the obtained IC\( _{50} \) values listed in Table 12, all of the tested xanthones exhibited enhanced activity (IC\( _{50} \) ranging from 10.6 ± 1.7 to 105.5 ± 1.5 \( \mu \)M) than the precursor xanthone 25 (IC\( _{50} \) = 145.0 ± 15.0 \( \mu \)M) to inhibit \( \alpha \)-glucosidase activity. Moreover, compounds 248–250, 254–258, 260–263 were more effective.

### Table 11
Inhibitory effect of synthetic xanthones 236–247 on baker’s yeast \( \alpha \)-glucosidase activity [60].

| Comp. | R   | IC\( _{50} \) (\( \mu \)M) | Comp. | R   | IC\( _{50} \) (\( \mu \)M) | Comp. | R   | IC\( _{50} \) (\( \mu \)M) |
|-------|-----|----------------|-------|-----|----------------|-------|-----|----------------|
| 236   | H   | 47.7          | 240   | H   | 10.1          | 243   | H   | 75.4          |
| 237   | 6-OH| 10.5          | 241   | 6-OH| 6.2          | 244   | 6-OH| 47.6          |
| 238   | 6-OH| 8.1           | 242   | 7-Me| 6.4          | 245   | 6-OH| 17.4          |
| 239   | 7-Me| 26.5          | 246   | 7-Me| 112.1        | 247   | 7-Me| > 200         |

Positive control: 1-deoxynojirimycin

### Table 12
Inhibitory effect of synthetic xanthones 248–263 on baker’s yeast \( \alpha \)-glucosidase activity\(^a^ \) [61].

| Comp. | R   | IC\( _{50} \) (\( \mu \)M) | Comp. | R   | IC\( _{50} \) (\( \mu \)M) | Comp. | R   | IC\( _{50} \) (\( \mu \)M) |
|-------|-----|----------------|-------|-----|----------------|-------|-----|----------------|
| 248   |     | 36.1 ± 5.3    | 256   |     | 13.3 ± 1.4    | 250   |     | 19.8 ± 2.6    |
| 249   |     | 30.6 ± 7.9    | 257   |     | 23.2 ± 3.9    | 251   |     | 58.2 ± 4.9    |
| 250   |     | 21.6 ± 2.5    | 258   |     | 10.6 ± 1.7    | 252   |     | 42.0 ± 0.1    |
| 251   |     | 46.7 ± 3.2    | 259   |     | 16.6 ± 3.2    | 253   |     | 42.6 ± 0.8    |
| 254   |     | 23.7 ± 2.0    | 258   |     | 21.8 ± 0.6    | 255   |     | 11.6 ± 2.2    |

\(^a^\) Positive control: 1-deoxynojirimycin (IC\( _{50} \) 40 \( \mu \)M).

\(^b^\) In this work, 1,3-dihydroxyxanthone 25 was also tested and presented an IC\( _{50} \) = 145.0 ± 15.0 \( \mu \)M.
than the positive control, 1-deoxyxojirimycin (IC \(_{50} = 40 \mu M\)). A structure activity relationship analysis suggests that the introduction of an additional aromatic moieties, through the acylation of 3-OH position, may represent an efficient way to improve the inhibitory activity against \(\alpha\)-glucosidase. Docking studies were performed to evaluate the binding behavior of the compounds and the results pointed out that the interaction of these xanthones with \(\alpha\)-glucosidase, is favored by \(\pi\)-stacking or hydrophobic effects of the additional aromatic nucleus rather than the H-bonding donor interaction of 3-OH group. Furthermore, the most active compounds 256 (IC \(_{50} = 13.3 \pm 1.4 \mu M\)), 260 (IC \(_{50} = 10.6 \pm 1.7 \mu M\)) and 263 (IC \(_{50} = 11.6 \pm 2.2 \mu M\)) were selected to study the kinetic parameters, determined by Lineweaver–Burk plots. Docking studies, together with the kinetic results, revealed that the 3-arylacyloxyxanthone derivatives act as noncompetitive inhibitors of yeast's \(\alpha\)-glucosidase. The inhibitory constants \(K_i\) were 17.8 \(\mu M\) for compound 256, 13.3 \(\mu M\) for compound 260 and 18.0 \(\mu M\) for compound 263, showing that compound 260 better binds to the enzyme, inhibiting it more efficiently [61].

In order to predict the \(\alpha\)-glucosidase inhibitory activity according to the physical and chemical properties of the bioactive compounds, a series of quantitative structure-activity relationship (QSAR) studies have been performed, providing useful information about the interactions between the enzyme and the potential inhibitors. Thus, in 2008, Liu et al. used a multiple linear regression (MLR) method in combination with the Elimination Stepwise as variable selection algorithm, to establish QSAR models for the 41 xanthones previously described (derivatives 25, 26, 50, 188–193, 195–209, 212, 213 and 215–229). Among 38 typical descriptors analyzed, the three descriptors Hs (number of H-bond forming substituents), Nrt (number of aromatic rings), and S (softness value) on the xanthone nucleus, showed a positive correlation with the inhibitory activity. The accuracy and predictivity of the proposed QSAR model were verified by internal validation [cross-validation by leave-one-out (LOO) and Y-randomization] and test group validation with the studied xanthones. From this study, the authors concluded that the introduction of substituents, capable of H-bond formation, such as hydroxyl and amino groups and/or more aromatic groups coupled to the xanthone core, were requirements for rational design of novel and potent \(\alpha\)-glucosidase inhibitors [59]. One year later, the same xanthones were analyzed through a linear QSAR model developed by a similar MLR method, but applying genetic algorithms to select the appropriate descriptors [85]. The two most important selected descriptors (Van der Waals volumes and elecneutronegativity of atoms and groups) are related to each other, showing that the presence of electron-withdrawing substituents on the aromatic ring result in an unfavorable effect with the electronegativity. In addition, the increase of the aromatic ring number, seems to be a favorable factor to enhance the \(\alpha\)-glucosidase inhibitory potential. The proposed model presented good stability, robustness and predictivity, given by internal and external validation [85]. The authors compared these results with those obtained from a nonlinear QSAR model, using a back-propagation neural network method, and concluded that Van der Waals volumes were the most important independent variable on the \(\alpha\)-glucosidase inhibitory effect [86]. Two more studies were reported concerning QSAR models for the xanthones 25, 26, 50, 188–193, 195–209, 212, 213 and 215–229: i) Moorthy et al. which used V life MDS (Molecular Design Site) and Statistica software and verified that hydrophilic, polar and/or electron negative groups, which are responsible for hydrogen bonding and interaction with the enzyme, are favorable for the inhibitory potential [67] and ii) Masand et al. which used a k-cluster analysis to infer that the presence of 7-OH substituent and the increase of aromatic rings in the xanthone skeleton, increase the \(\alpha\)-glucosidase inhibitory activity [88].

Q SAR studies using linear free energy relationship model of Hansch were conducted on the 25 xanthones already described (25, 26, 50, 188–193, 195–209, 212, 213). These studies were performed using steric and topological indices parameters along with the appropriate dummy variables. Multi-regression analysis suggested that denser and bulkier groups are beneficial for the inhibitory potential. In addition, acetoxy groups at C-2 and hydroxyl groups at C-4 enhanced while the presence of hydrogen at C-2 lowered the \(\alpha\)-glucosidase inhibitory effect. Cross-validation analysis using LOO method confirmed the validity of the models [89].

Saqib et al. tested the known 41 xanthones 25, 26, 50, 188–193, 195–209, 212, 213 and 215–229 in three-dimensional quantitative structure-activity relationship (3D-QSAR) studies, in order to provide information about the 3D structural features for \(\alpha\)-glucosidase inhibitors [90]. These studies include Comparative Molecular Field Analysis (CoMFA) and Comparative Molecular Similarity Indices Analysis (CoMSIA). Models with good predictive abilities were generated with the cross validated \(r^2\) values for CoMFA and CoMSIA being 0.580 and 0.610, respectively. The conventional \(r^2\) values were 0.949 each for both CoMFA and CoMSIA models. Moreover, for docking based alignment of the compounds, a homology model of human \(\alpha\)-glucosidase was used and the most active compound (216) was the template for the remaining structures, in order to align all compounds, prior to QSAR studies. The results gave an idea about the bioactive conformations that these inhibitors adopt within the \(\alpha\)-glucosidase active site. Further, mapping of contours onto the active site validated each other in terms of residues involved with reference to respective contours [90]. Recently, Zheng et al. performed a similar docking-assisted 3D-DSAR studies on 54 xanthones (the already reported xanthones 25, 26, 50, 188–193, 195–209, 212, 213, 215–229 plus xanthones 236–246, bearing naphthol groups) as \(\alpha\)-glucosidase inhibitors [91]. Here, CoMFA and CoMSIA approaches were also used to construct 3D-QSAR models and the bioactive conformations were analyzed by docking studies and optimized by the homology modeled structure of \(\alpha\)-glucosidase. Several robust 3D-QSAR models were established and confirmed externally. Increasing the number of aromatic rings and addition of H-bond acceptor substituents located at C-3, play an important role in the enhancing of the inhibitory effectiveness of the tested xanthones. These structural modifications were consistent with the interaction improvements between the ligand and \(\alpha\)-glucosidase [91]. Molecular docking studies were also applied to evaluate plausible binding modes of mangiferin 2 to \(\alpha\)-glucosidase. The results showed that mangiferin bonds to both allosteric and orthosteric sites by \(\pi\)-\(\pi\) interactions. In addition, the difference in the fitness value found for the docking at the allosteric site (68.11) with that in the orthosteric site (59.11) is in agreement with a noncompetitive type of inhibition [92].

A docking-based virtual screening of 189 xanthone derivatives was performed by Lakehal et al. to provide insights into their binding mechanism toward NtMGAM. From binding mode analysis, 20 top-scoring xanthones [see structures 176 (Table 6) and 264–282 (Table 13)] revealed that sulfonamide xanthone derivatives showed favorable binding affinity in comparison with miglitol, used as positive control. These binding affinities are due to significant H-bonding interactions of the xanthone substituents with key catalytic residues of NtMGAM [93].

4. Conclusions

The current review has provided insights into the potential inhibitory effect of several xanthones, covering more than 280 natural and synthetic derivatives, against one of the main therapeutic target for diabetes, the enzyme \(\alpha\)-glucosidase. The comparison of results is difficult due to the variability of the experimental
conditions found among the different studies, namely in what concerns the nature of the enzyme, concentration of enzyme and substrate, incubation times, etc. Therefore, in this review a detailed description of the enzyme was provided, as well as, a survey on the techniques and the main experimental conditions that can be found in this type of assays. Undoubtedly, the results pointed out for a wide range of active compounds, and a structure activity relationship was performed whenever possible. To provide a deep insight into the correlation between the analyzed structures and their inhibitory profile, a series of QSAR models have been applied and discussed. Based on this statements, xanthones are undeniably a class of heterocyclic compounds with a privileged motif as α-glucosidase inhibitors that deserve special attention for future investigations in the pursuit for novel and improved anti-diabetic agents.

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